

THIRD GENERATION OF REOXIDANT FOR OSMIUM: EXTENSION AND NOVEL APPLICATIONS

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Declaration

The work described in this thesis is entirely my own, except where I have either acknowledged help from a named person or given reference to a published source. Text taken from another source will be enclosed in quotation marks and a reference given.

Cedric Kofi Aurélien Callens

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Abstract

Third Generation of Reoxidant for Osmium: Extension and novel Applications

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This thesis describes the development of new osmium-mediated methodologies providing novel applications through the use of a third generation of reoxidant for osmium.

Chapter 1 The introduction

- Summary of past and present methodologies towards the synthesis of the 1,2 amino alcohol motif.

Chapter 2 Intramolecular processes

- The studies of the tethered aminohydroxylation (TA) of amide and urea derivatives are being investigated.

Chapter 3 Investigations towards an intermolecular process

- The transposition of the TA methodology to an intermolecular process and the requirements involved are discussed. The role of acetamide is being investigated.

Chapter 4 Successful transition to an intermolecular process

- Amino acid derivatives became for the first time possible nitrogen sources and were efficiently employed through osmium-mediated reaction to afford interesting biological scaffolds.

Chapter 5 Experimental

- Full experimental procedures and characterisation of compounds are reported.

References

- A complete list of citations employed in the previous five chapters is provided.

Appendix

- Full documentation of X-ray crystal structures, key NMR spectra and HPLC traces is provided.

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To the one and only person that put up with my perfect character during these past seven years, finding the correct words would not be an easy task. A la Dame émut du soir, mtj.K.

CCK

Abbreviations and Acronyms used in this Thesis

Å	Ångstrom	DIBAL-H	di- <i>iso</i> -butylaluminium
AA	asymmetric		hydride
	aminohydroxylation	DMAP	4-(dimethyl)aminopyridine
Ac	acetyl	DMF	<i>N,N</i> -dimethylformamide
AD	asymmetric dihydroxylation	DMP	Dess-Martin periodinane
AIBN	2,2'-azobisisobutyronitrile	DMSO	dimethylsulfoxide
aq.	aqueous solution	DMTMM	4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium
AQN	anthraquinone		chloride
Ar	aromatic group		
atm	atmosphere pressure		
Bn	benzyl	<i>dr</i>	diastereomeric ratio
Boc	<i>tert</i> -butoxycarbonyl	EDCI	<i>N</i> -(3-dimethylaminopropyl)- <i>N'</i> -ethylcarbodiimide
b.p.	boiling point		
br	broad		hydrochloride
Bu	butyl	EDG	electron donating group
Bz	benzoyl	<i>ee</i>	enantiomeric excess
C	Celsius	eq.	equivalents
cat.	Catalytic	ESI	electrospray ionisation
Cbz	carboxy benzyl	Et	ethyl
cm ⁻¹	wavenumbers	EWG	electron withdrawing group
conc.	concentrated	g	grams
CSA	<i>RS</i> -camphor-10-sulfonic acid	h	hour(s)
C ₆ D ₆	deuterated benzene	HATU	O-(7-Azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium
CDCl ₃	deuterated chloroform		hexafluorophosphate
CDI	1,1'-carbonyldiimidazole		
(CD ₃) ₂ CO	deuterated acetone		
DBI	dibromoisocyanuric acid	HBTU	O-Benzotriazole- <i>N,N,N',N'</i> -tetramethyl-uronium-hexafluoro-phosphate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene	HOMO	highest occupied molecular orbital
DEPT	distortionless enhanced polarization transfer	<i>hν</i>	irradiation with light
DHQ	dihydroquinyl	HPLC	high performance liquid chromatography
DHQD	dihydroquinidyl		

HRMS	high resolution mass spectrometry - accurate mass spectrometry	Ph	phenyl
		Phth	phthalimide
		pH	$-\log_{10}[\text{H}_3\text{O}^+]$
Hz	Hertz	PHAL	phthalaziny
<i>i</i>	<i>iso</i>	PIFA	phenyliodinebis- (trifluoroacetate)
Im	imidazole		
IR	<i>infra</i> red	pK _a	$-\log_{10}K_a$
<i>J</i>	coupling constant	ppm	parts per million
K	kelvin	PPTS	pyridinium <i>para</i> - toluenesulfonate
KHMDS	potassium hexamethyldisilazide	Pr	propyl
L	litre / generic ligand	PTC	phase transfer catalysis
LDA	lithium di- <i>iso</i> -propylamide	PTSA	<i>para</i> -toluenesulfonic acid
LHMDS	lithium hexamethyldisilazide	pyr	pyridine- pyrazine
LUMO	lowest unoccupied molecular orbital	R	generic alkyl group
		<i>rs</i>	regioselectivity ratio
M	molecular ion- metal- molar solution, mol·L ⁻¹	RSM	recovered starting material
		rt	room temperature
Me	methyl	δ	chemical shift
CD ₃ OD	deuterated methanol	SiO ₂	silica gel
min	minute(s)	sat.	saturated solution
mL	millilitres	SM	starting material
mol	mole	<i>t/tert</i>	tertiary
m.p.	melting point	TA	tethered aminohydroxylation
Ms	methanesulfonyl	TFA	trifluoroacetic acid
MS	mass spectrometry - molecular sieves	THF	tetrahydrofuran
<i>m/z</i>	mass to charge ratio	TLC	thin layer chromatography
NaH	sodium hydride	TMEDA	<i>N,N,N',N'</i> - tetramethylethylenediamine
NaHCO ₃	sodium hydrogen carbonate		
Na ₂ SO ₃	sodium sulphite	Ts	<i>para</i> -toluenesulfonyl
NBS	<i>N</i> -bromosuccinimide	UV	ultraviolet
NMM	4-methylmorpholine	X	generic leaving group
NMR	nuclear magnetic resonance	$[\alpha]_D^{25}$	specific rotation
NOESY	nuclear Overhauser effect spectroscopy	ν_{max}	infrared absorption
PG	generic protecting group	Z	number of molecules in the unit cell

Chapter 1
Introduction

1. Introduction: the 1,2-amino alcohol motif

The importance of the 1,2-amino alcohol motif is illustrated by its occurrence in a vast range of natural products, bioactive compounds and chiral reagents used in stereoselective syntheses, as depicted in Figure 1.

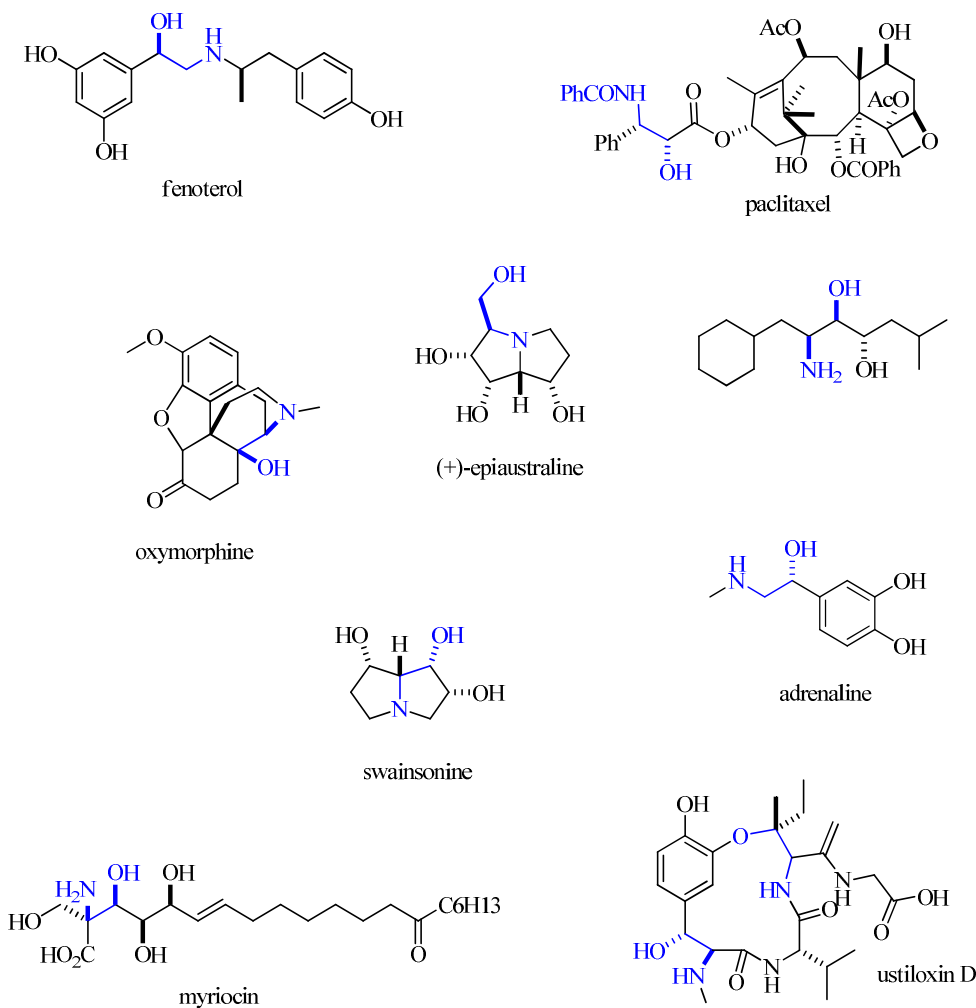


Figure 1 - Examples of compounds bearing the 1,2-amino alcohol moiety

- Fenoterol is an asthma medication designed to open up the airways to the lungs. It is classed as an adrenergic β -2 agonist that is used as a bronchodilator and tocolytic.¹
- Myriocin is an immunosuppressor and antibiotic, which prevents the biosynthesis of sphingosine, a cell membrane lipid.²
- Swainsonine is an indolizine alkaloid; it is a potent inhibitor of Golgi α -mannosidase II, an immunomodulator and a potential chemotherapy drug.³

- Paclitaxel, commonly known as Taxol, is a mitotic inhibitor interfering with microtubules and is mostly used to treat patients with lung, ovarian, breast, head and neck cancer.⁴
- Epiaustraline is a glycosidase inhibitor. These are involved in the degradation of carbohydrates and the processing of glycoproteins and glycolipids in both eukaryotic and prokaryotic cells. These glyco-molecules are important for energy production, cell wall fortification, cell recognition and other key processes.

An examination of the best selling drugs 2009 revealed that this pharmacore was present 27 times out of 200 top pharmaceutical products.⁵

1.1 Vicinal 1,2-amino alcohol motif

The synthesis of this moiety can be approached from several angles and in recent years numerous reviews have attempted to compile an exhaustive list of such procedures (Figure 2).⁶

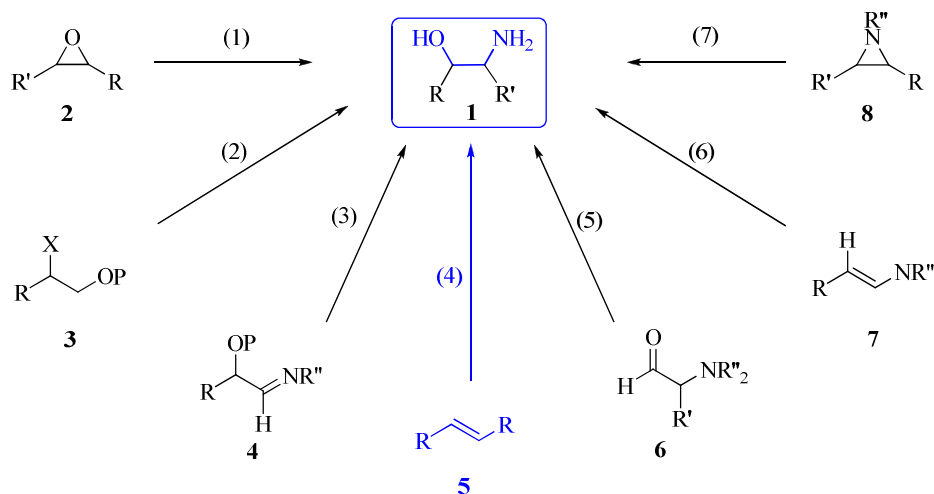


Figure 2 - Approaches for the synthesis of vicinal 1,2-amino alcohol motif 1

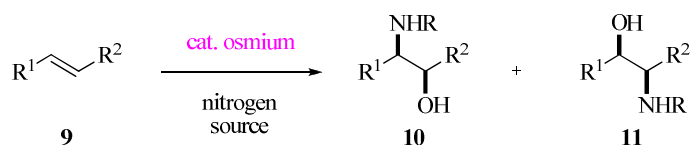
- (1) Opening of epoxide **2**.⁷
- (2) Nucleophilic substitution.
- (3) Imine formation and subsequent reduction.
- (4) Aminohydroxylation of alkene **5**
- (5) Aldehyde **6** reduction.⁸
- (6) Addition of oxygen to an enamine.⁹
- (7) Opening of aziridine **8**.¹⁰

Figure 2 summarises most of the common routes to amino alcohols employed throughout the years. However well studied this motif has been, the direct conversion of an alkene to a vicinal 1,2-amino

alcohol, namely the aminohydroxylation (or oxyamination) reaction, has gained particular attention in recent years and research in this area remains highly prolific. We have recently published a review of novel procedures developed in the last decade using this particular approach, with metal-promoted and metal free procedures being well represented.¹¹ For a more comprehensive account on the diverse methodologies available, the review by Donohoe *et al.* should be consulted.

1.2 Osmium-mediated aminohydroxylation of an alkene

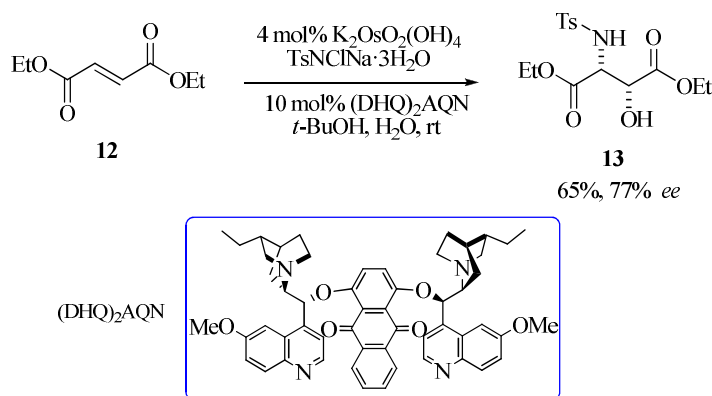
The stereospecific vicinal aminohydroxylation of alkenes developed by Sharpless *et al.* was a key discovery and its widespread use over the years has clearly highlighted this methodology over others: one reason for this success being the ease with which the substrates, namely alkenes, can be accessed.¹² The reaction outcome is the result of an addition of nitrogen and oxygen across a double bond, promoted by an osmium-based catalyst (Scheme 1).¹³



Scheme 1 - Regioselectivity issue

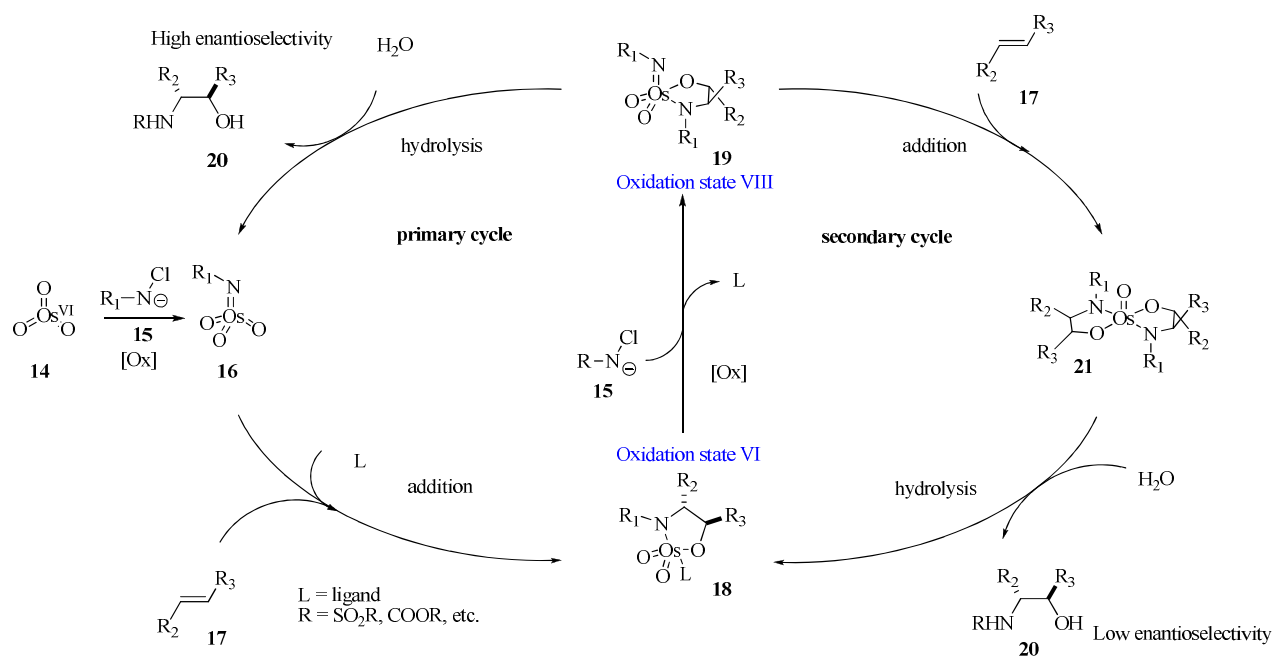
The main difference with the well-known dihydroxylation procedure is the regioselectivity of the reaction, with unsymmetrical substrates providing two possible products **10** and **11**, as illustrated in Scheme 1.

This one-pot synthesis of vicinal 1,2-amino alcohols has evolved considerably throughout the years and one major breakthrough has been the introduction of enantiocontrol resulting from the use of chiral tertiary amine ligands belonging to the cinchona alkaloid family (Scheme 2).¹²



Scheme 2 - Enantioselective aminohydroxylation

Submitting symmetrical fumarate **12** to a catalytic amount of osmium and an enantiopure ligand afforded amino alcohol **13** derivative in good yield and enantioselectivity. In general, this improvement enabled access to vicinal 1,2-amino alcohols in high yield and enantioselectivities from simple alkenes. The proposed mechanism for the aminohydroxylation is analogous to the asymmetric dihydroxylation reaction.¹⁴ In a similar manner, two catalytic cycles have been postulated and the addition process has finally been depicted as a [3+2] cycloaddition following recent computational studies by Strassner *et al.* (Scheme 3).¹⁵



Scheme 3 - Aminohydroxylation reaction mechanism

The primary cycle begins with oxidation of the Os^{VI} species **14** by nitrogen source **15** to deliver imidotrioxosmium(VIII) species **16**. A subsequent ligand-mediated cycloaddition reaction to

alkene **17** generates azaglycolate(VI) complex **18**. This reaction proceeds with enantio- and regioselectivities enforced by the chiral ligand and occurs in a *syn* stereospecific manner. Intermediate **18** is then oxidised by the nitrogen source to afford **19** and subsequent hydrolysis ends the primary catalytic cycle, providing vicinal amino alcohol **20** as well as the initial imidoosmium **16**. As previously reported, the amount of water present in the medium plays a crucial role in determining the rate of hydrolysis. Indeed, if the hydrolysis step is slow, oxidised azaglycolate species **19** can undergo an addition to a second alkene **17** to give bis(azaglycolate)osmium species(VI) **21** (Scheme 3). This novel species **21** then enters the ligand-free secondary cycle. In this cycle, low enantio- and regioselectivities are obtained as the ligand cannot coordinate to the metal centre during the cycloaddition reaction. It was the discovery of the prerequisite for water that enabled access to a catalytic asymmetric version of the reaction.

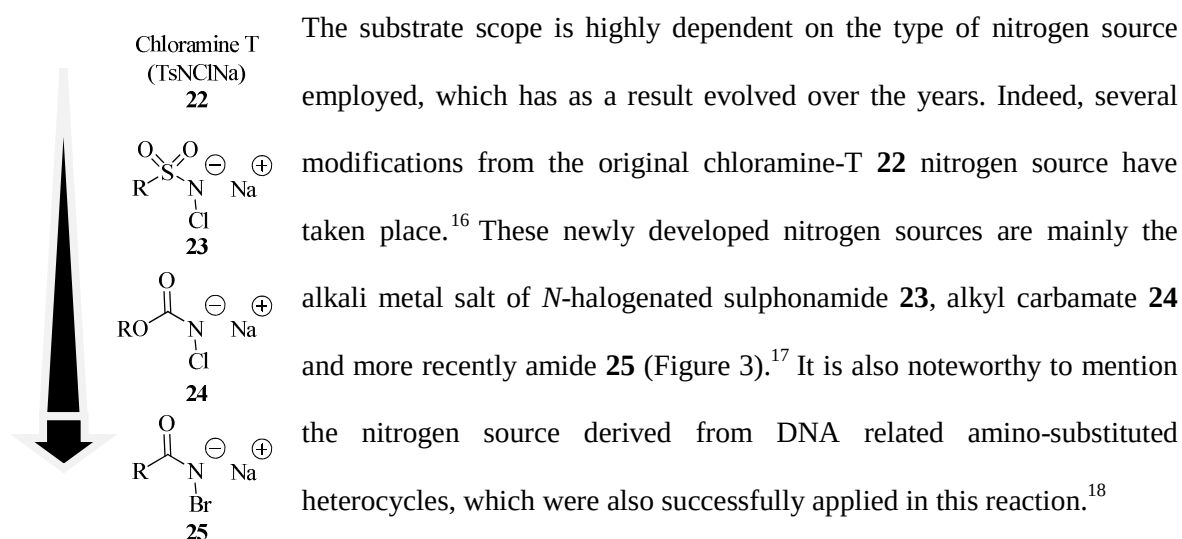
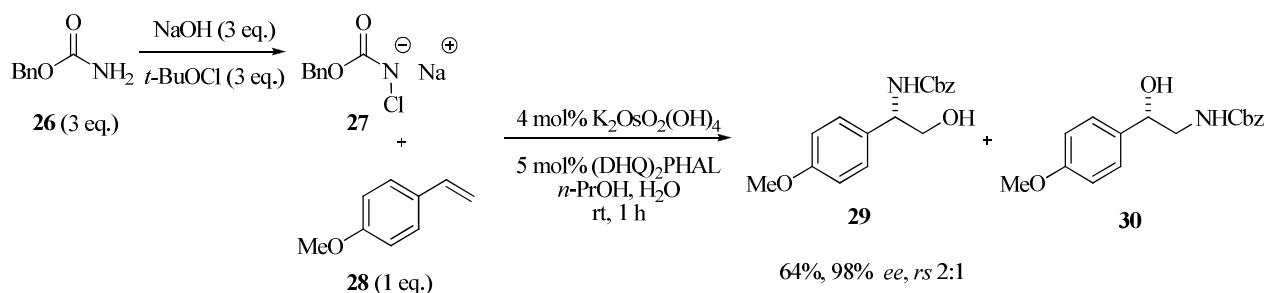


Figure 3 - Evolution of the nitrogen source

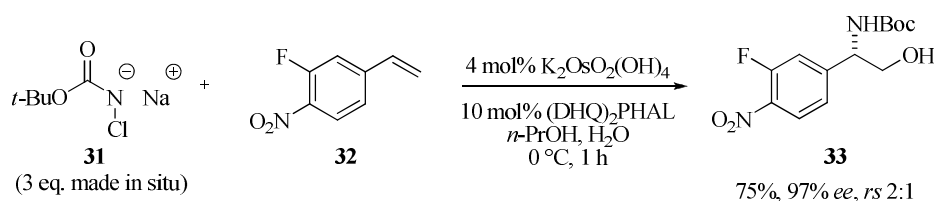
A typical procedure uses *t*-butyl hypochlorite in the presence of sodium hydroxide to generate *N*-halocarbamate reoxidant **27** *in situ*, as depicted in Scheme 4.



Scheme 4 - Representative example of an aminohydroxylation procedure

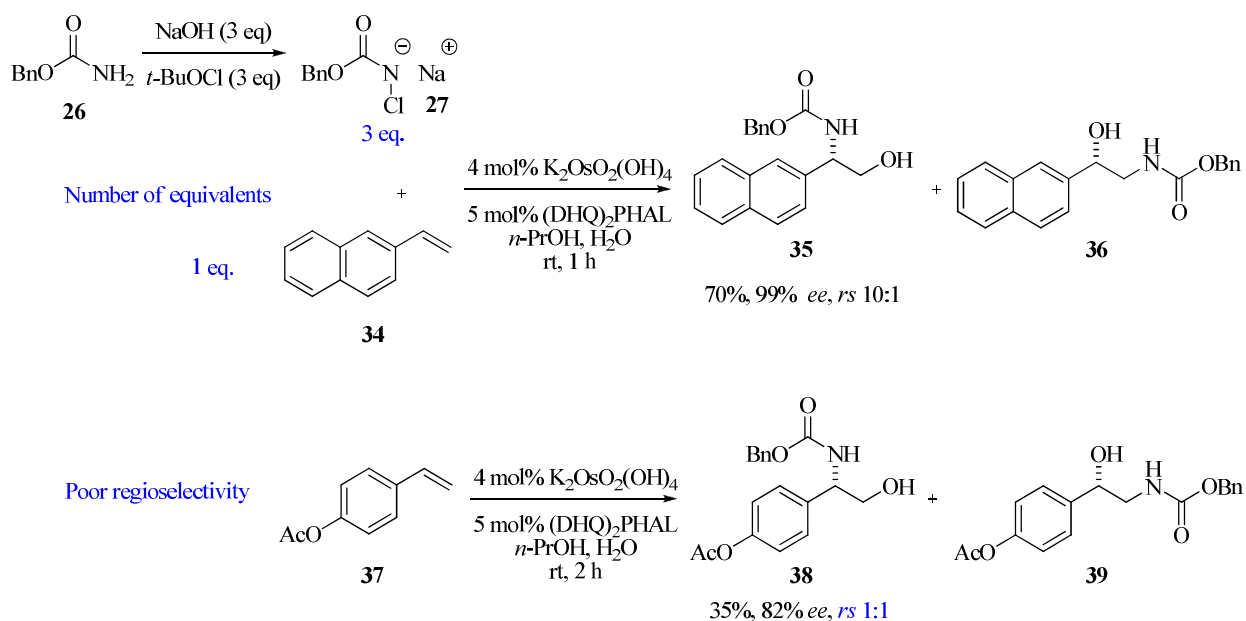
Carbamate **26** was activated *in situ* to provide **27**. The generated *N*-chlorocarbamate **27** in the presence of catalytic osmium enabled the aminohydroxylation of 4-methoxystyrene **28** in good yield, with excellent enantiopurity.

As previously mentioned, the reactivity of the nitrogen source dictates the nature of substrates that are compatible with the methodology. For instance, *N*-halogenated sulphonamide sources **23** would be mainly limited to electron poor olefins while *N*-halogenated carbamates **24** and amide **25** have a broader range of reactivity towards both electron rich and poor alkenes.¹⁷ Furthermore, carbamates as nitrogen sources became especially useful due to their use as orthogonal protecting groups and relative ease of deprotection under reductive (Cbz), acidic (Boc) and nucleophilic (Teoc) conditions (Scheme 5).¹⁹



Scheme 5 - Representative example of a Boc-protected carbamate nitrogen source

Boger *et al.* employed this strategy towards the synthesis of teicoplanin aglycon, using Boc-protected carbamate nitrogen source **31** to react with 4-nitrostyrene derivative **32**.²⁰ Although the carbamate aminohydroxylation procedure developed by Sharpless *et al.* has contributed to turning this reaction into a key component in the organic chemist's toolbox, this process has a few drawbacks. Firstly, the need for a large excess (more than three equivalents) of nitrogen source **27** limited its value and the use of more complex carbamates (Scheme 6). Secondly, the difficulty in predicting and achieving good levels of regioselectivity was hampering its widespread employment.

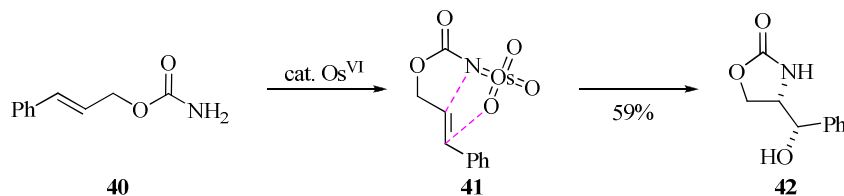


Scheme 6 - Issues linked to the aminohydroxylation reaction

Indeed, the regioselectivity has been revealed over the years to be heavily influenced by the solvent system in which the reaction is conducted, the nature of the ligand and finally the nature of the nitrogen source employed.²¹

1.3 Origins and development of the Tethered Aminohydroxylation (TA)

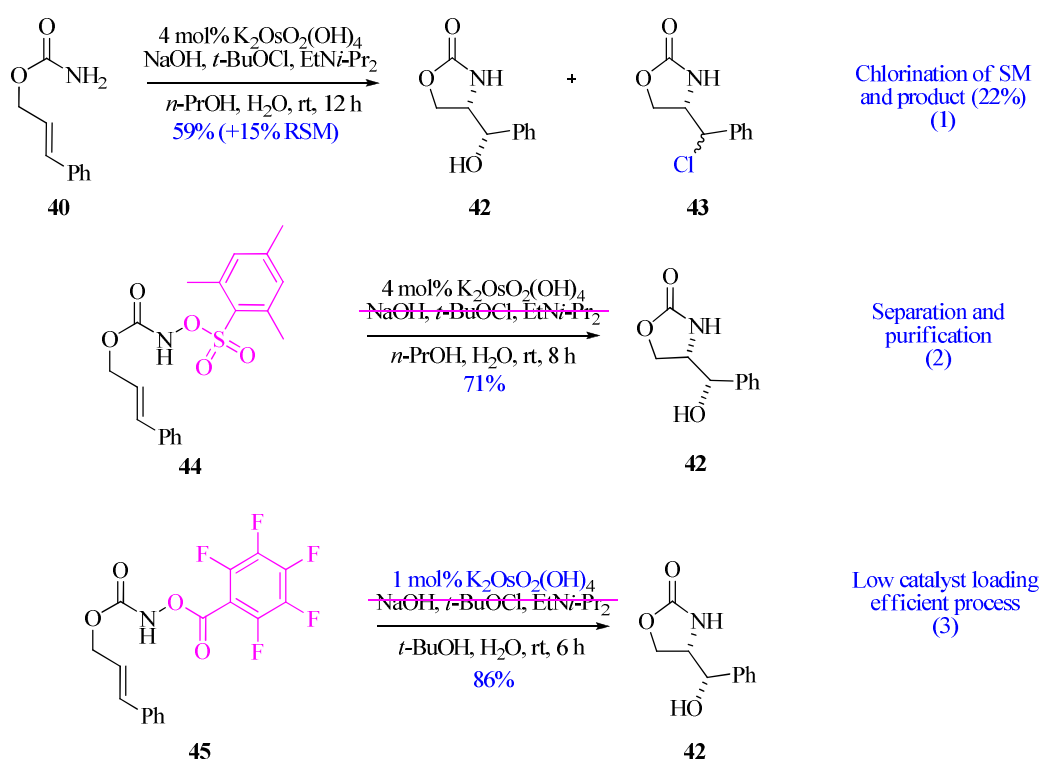
It was with this problem in mind that Donohoe *et al.* decided to tether the nitrogen source to the substrate. Indeed, this substrate modification allowed a completely regioselective process to take place, providing a novel and simple way of controlling the 1,2-amino alcohol motif. Furthermore, the oxidant for osmium being built within the substrate, no excess reagent would be required (Scheme 7).



Scheme 7 - Representative example of the TA procedure

Submitting cinnamyl carbamate **40** to a catalytic amount of osmium afforded exclusively five-membered oxazolidinone **42** in a good 59% yield with complete regioselectivity. In the last decade,

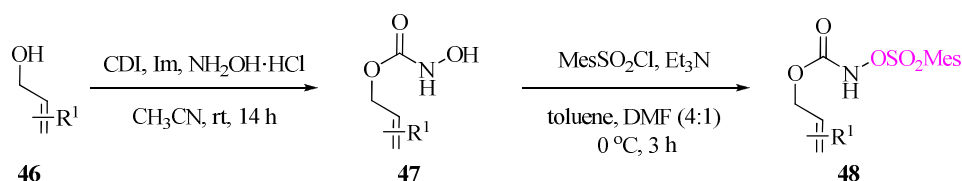
this procedure has been successfully applied to allylic and homoallylic alcohols, providing the desired cyclic carbamates **42** with complete regioselectivity.²² In a similar manner to the nitrogen source employed by Sharpless *et al.* the nature of the tethered oxidant has inevitably evolved during these past few years to its current third generation level, as depicted in Scheme 8.



Scheme 8 - Evolution of the tethered oxidant for the intramolecular aminohydroxylation

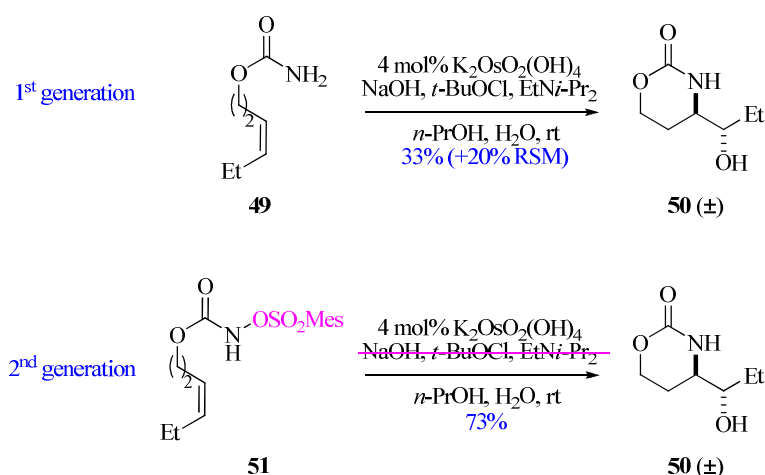
The first generation source used *t*-butyl hypochlorite in the presence of sodium hydroxide, similar to the conditions developed by Sharpless *et al.*, to activate the substrate *in situ*, often resulting in the formation of side products. These stemmed from chlorination of the alkene starting material **40** leading to chlorinated by-products **43** (Scheme 8, (1)). Moreover, modest yields were generally obtained and the reaction conversion never reached completion. Consequently, this limited the substrate scope to electron poor alkenes, which were inert towards competitive chlorination. Finally, the general instabilities of those *N*-chlorocarbamate reagents prepared *in situ* contributed to reduce its wide application.²³ The second generation based on a sulphonamide linker **44**, solved most of these initial problems and increased the reaction rate and overall yield (by an average of 25%) as

illustrated in Scheme 8, (2). Its two step synthesis was straightforward and its stability greatly improved (air stable, Scheme 9).²⁴



Scheme 9 - General synthesis of second generation tethered reoxidant

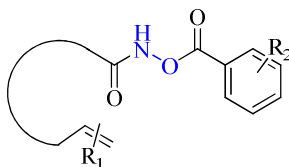
The major improvement associated with the sulphonamide linker was the efficiency of the process under basic catalytic reaction conditions. Indeed, there was no requirement for the addition of an external base or chlorinating agent, one of the Achilles heel of the first version (Scheme 10).



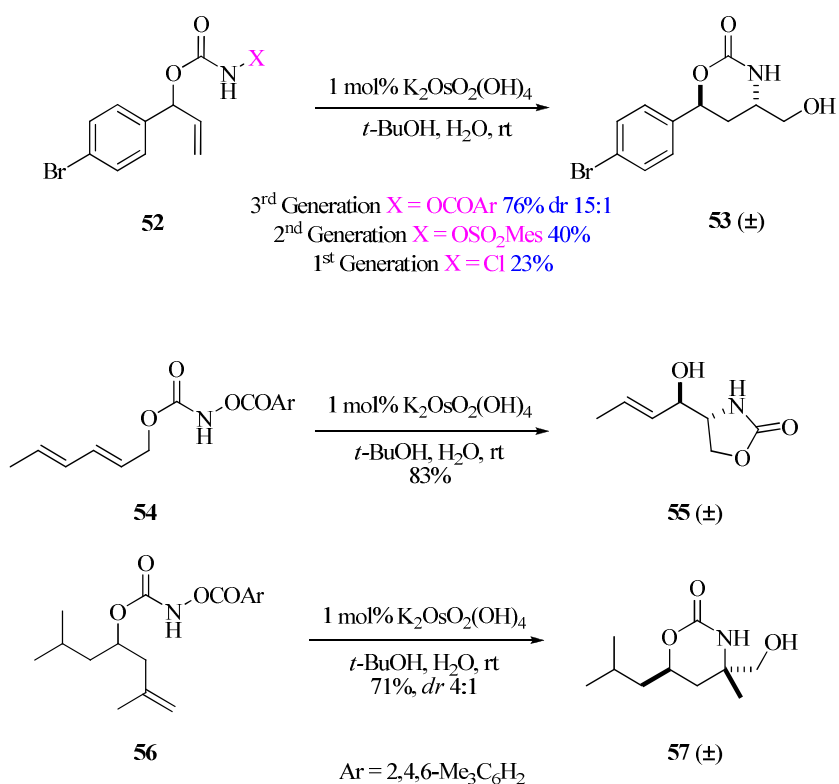
Scheme 10 - Efficiency of TA improved via sulphonamide linker

Oxazolidinone **50** was synthesised with a 40% yield increase when second generation reoxidant **51** was employed. However, the acidity of the medium linked to the gradual release of the sulphonic acid during the reaction, limited its use to a smaller range of substrates. This protocol was also impeded with challenging purification of the desired product **50**.

Finally, based on a similar substrate strategy used by Lebel *et al.* during her prospect of rhodium catalysed aziridination, tethering this key acylated hydroxylamine structure to allylic alcohol substrates led to the current third generation of oxidant for osmium (Figure 4).²⁵

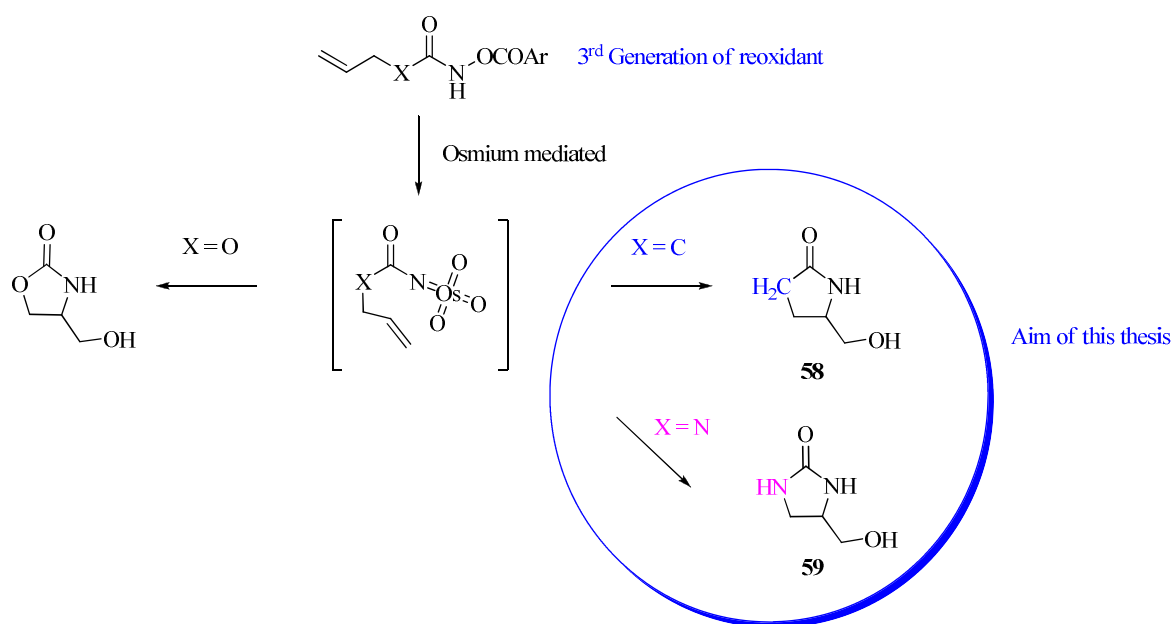
**Figure 4** - Key acylated hydroxylamine bond

This last version combined both the stability of the reoxidant built within the substrate (air stable) and the efficient and clean osmium catalysed aminohydroxylation process. Its facile synthetic preparation and base free conditions extended the scope of the tethered aminohydroxylation (TA), providing access to a large range of stereochemically well defined 1,2-amino alcohols from acyclic, cyclic, allylic and homoallylic precursors.²⁶ These oxazolidinones were obtained with complete regioselectivity and in good yields (Scheme 11).

**Scheme 11** - Representative examples of the TA procedure

1.4 Project aim-Preliminary results

The initial aim of the project was to extend the scope of this methodology to amides and ureas, thus accessing the valuable synthetic and biological scaffolds of hydroxyl lactams **58** and hydroxyl urea moieties **59** respectively, using this 3rd generation of reoxidant (Scheme 12).²⁷

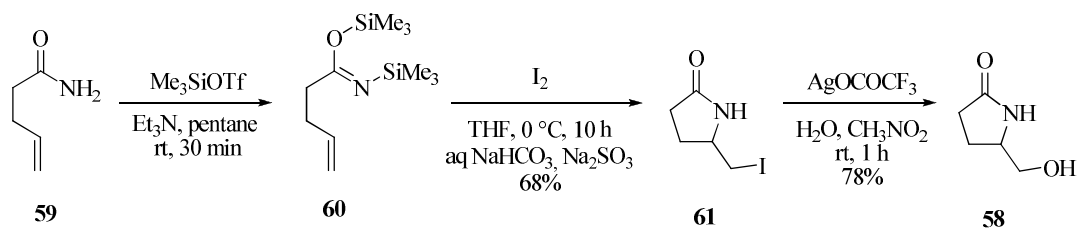


Scheme 12 -Initial aim of this thesis/osmium-mediated methodologies

1.4.1 Hydroxyl lactam synthesis-literature precedence

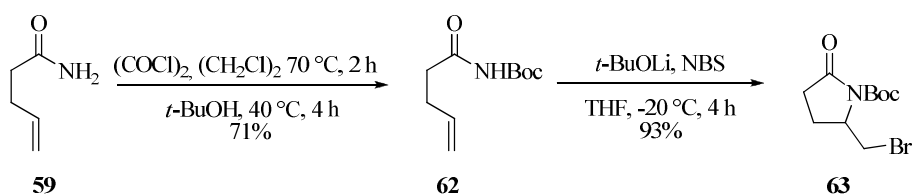
Few methodologies were available in 2007 for the generation of motifs such as **58**. For instance, only two procedures were reported for the synthesis of racemic compound **58**, which is nowadays sold at \$364 per gram!²⁸ Both of these methodologies involved multi-step sequences.

In 1986, Knapp *et al.* suggested the initial synthesis of iodolactam derivatives before displacement of iodide to afford hydroxyl lactams. The synthesis of **58** started from commercially available pent-4-enamide **59**, which was further reacted with trimethylsilyl triflate, followed by subsequent iodination of intermediate **60**. The resulting iodo-derivative **61** was then treated with silver trifluoroacetate in aqueous nitromethane to yield the desired hydroxyl lactam moiety **58** as illustrated in Scheme 13.²⁹



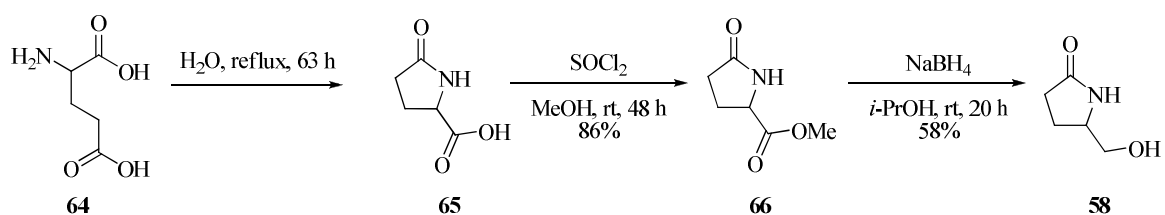
Scheme 13 - Representative example of iodolactamisation

This halogen-mediated procedure to provide hydroxyl lactam was improved by Corey *et al.* as they found that the bromoderivative avoided the use of trimethylsilyl triflate, an expensive and moisture sensitive reagent (Scheme 14).³⁰



Scheme 14 - Representative example of bromolactamisation

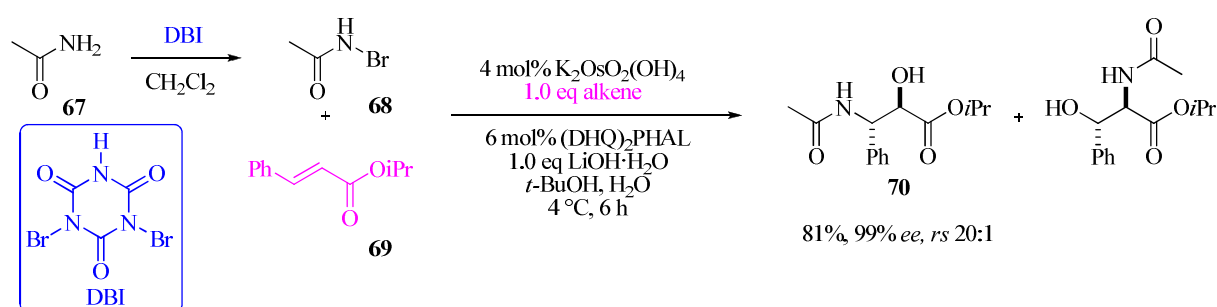
Pent-4-enamide **59** was first reacted with oxalyl chloride to form *in situ* the corresponding isocyanate which was subsequently treated with *t*-butanol to afford Boc-protected amide **62**. Lithium *t*-butoxide mediated deprotonation in the presence of *N*-bromosuccinimide afforded derivative **63** in 93% yield. Subsequent displacement of the bromine and Boc deprotection afforded the desired product **58**. The need for stoichiometric iodine or strong base in both cases, combined with the multi-step procedures required to access such motifs rendered these routes less attractive. Another approach, developed as early as 1914, consisted of refluxing glutamic acid **64** in water to afford carboxylic acid **65**. Treatment of the latter with thionyl chloride in methanol yielded ester **66** in 86% yield. Subsequent reduction with sodium borohydride led to desired compound **58** in three steps as illustrated in Scheme 15.³¹

Scheme 15 - Synthesis of **58** from glutamic amino acid **64**

This last methodology was inherently limited to the formation of five-membered rings. Consequently, it was envisaged that access to these hydroxyl lactam derivatives through the one step catalytic osmium-mediated methodology would be extremely beneficial.

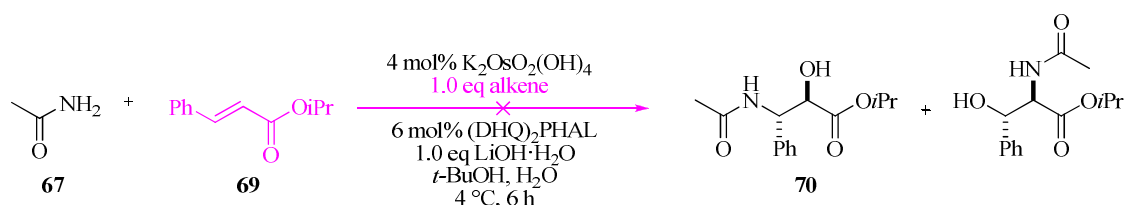
1.4.2 Hydroxyl lactams-preliminary results

As mentioned previously, pioneering studies by Sharpless *et al.* have shown that primary amides could be used as nitrogen sources *via* preactivation with dibromoisocyanuric acid, which is a mild brominating agent (Scheme 16).^{17e-f}



Scheme 16-Aminoxyhydroxylation of preactivated amide **68**

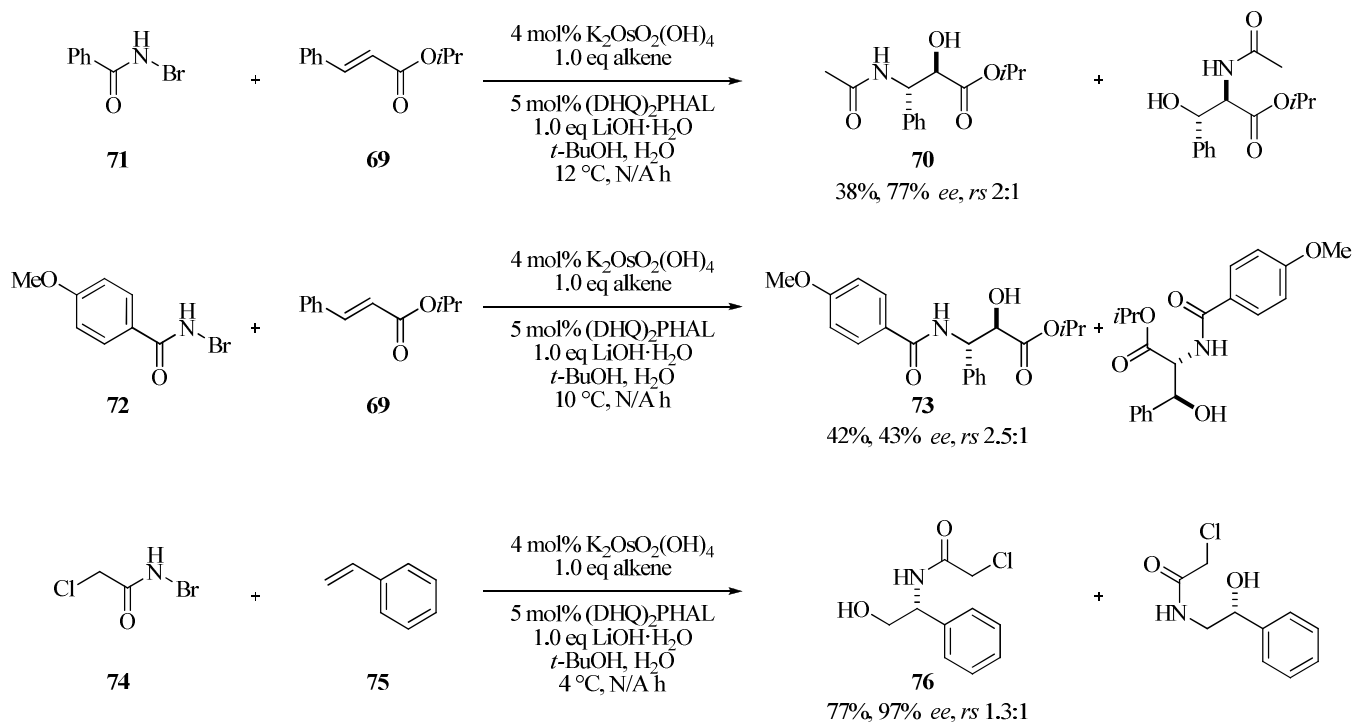
The difficulty of generating *in situ* *N*-bromoacetamide species meant that their synthesis was required in a step prior to the actual aminoxyhydroxylation reaction. Active *N*-bromoacetamide species **68** underwent an efficient aminoxyhydroxylation process leading to enantiopure 1,2-amino alcohol derivative **70** in excellent yield and regioselectivity. It is noteworthy that subjecting isopropyl cinnamate to the reaction without preactivating amide **67** resulted in complete recovery of both starting material **67** and **69** (Scheme 17).



Scheme 17 - Activation is essential for primary amide to act as nitrogen source and reoxidant

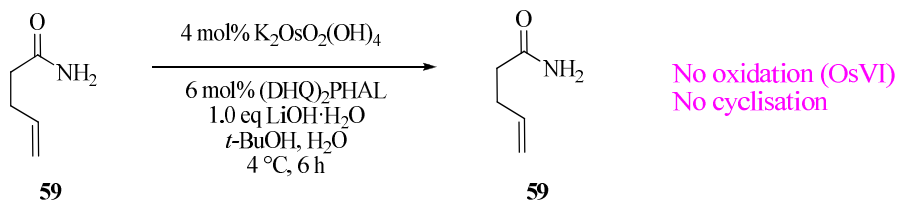
Commercially available *N*-bromoacetamide has thus increased the applicability of this methodology. However, most *N*-bromocarboxamide precursors are unstable and need to be stored under vacuum at low temperature. Moreover, a critical control of both temperature (to avoid

decomposition) and concentration of the reaction mixture are essential for reliable reproducibility.^{16,17} Finally, the moderate to low regioselectivity obtained was also a problem when bulky *N*-bromocarboxamides were submitted to the reaction conditions (Scheme 18).



Scheme 18 - Reactivity and regioselectivity issues with hindered *N*-bromocarboxamides

Following a similar approach to the tethered aminohydroxylation of allylic alcohols, we were interested in carrying out this reaction in an intramolecular fashion, *i.e.* with a substrate having a pendant alkene in order to control the regioselectivity. In a test experiment, pent-4-enamide **54** was directly submitted to osmium catalysed conditions without activation (Scheme 19).

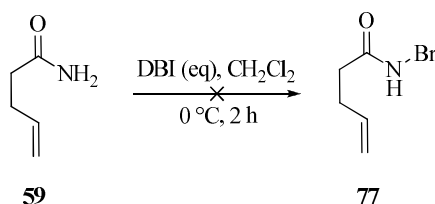


Scheme 19 - Control experiment

As expected, no reaction occurred and complete recovery of starting material **59** was observed.

Following the same procedure developed for primary amides in the intermolecular methodology of

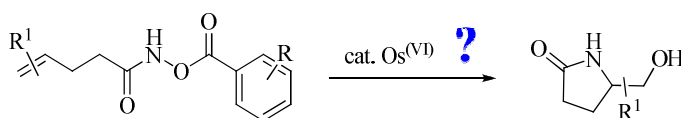
Sharpless *et al.*, **59** was then subjected to DBI in dichloromethane to afford *N*-bromocarboxamide **77** (Scheme 20).



Scheme 20 - Bromination of pent-4-enamide **59**

However, using the initial DBI conditions previously mentioned did not provide *N*-bromocarboxamide **77** but a rather complex mixture of overoxidised products. Indeed, analysis of the ^1H NMR spectrum of the crude material revealed complete disappearance of the characteristic signals of the terminal alkene, confirming this unwanted bromination. Lowering the temperature and number of equivalents of DBI were counterproductive as mixtures of several products were consistently produced.

Herein, the viability of performing TA reactions of amides that have been preactivated using the third generation of *N*-O reoxidant for osmium, so as to circumvent the problems of alkene bromination, was considered (Scheme 21).

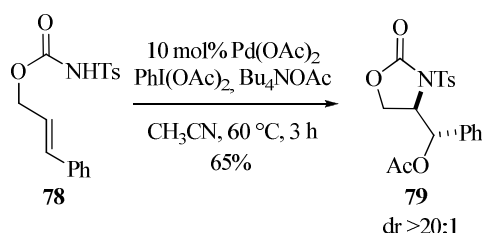


Scheme 21 - Extending the scope of the TA for amide derivatives

1.5 Diverse methodologies for the aminohydroxylation reaction

As mentioned previously, diverse methodologies are available nowadays for the aminohydroxylation process and the review by Donohoe *et al.* should be consulted for more detailed applications.¹¹ For an overall overview, only a few examples are depicted in the following schemes.

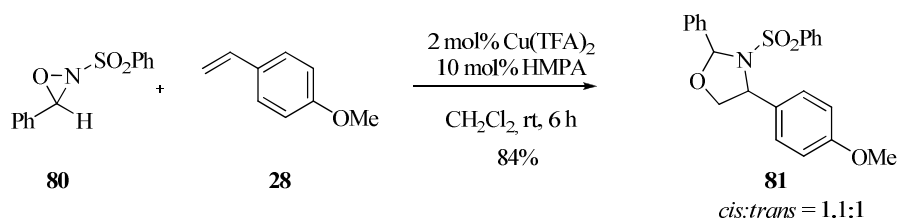
In 2005, Sorensen *et al.* reported an *intramolecular* aminohydroxylation using a catalytic source of palladium(II) in combination with an iodine(III) reoxidant (Scheme 22).³²



Scheme 22 - Representative example of palladium(II)-catalysed reaction

Under the catalytic conditions outlined in Scheme 22, cinnamyl tosylcarbamate **78** afforded in a good 65% yield, five-membered oxazolidinone derivative **79**. Although this procedure was highly diastereoselective for *anti* stereospecific addition across alkenes, it was hampered by the various levels of regioselectivity for non-tethered substrates.

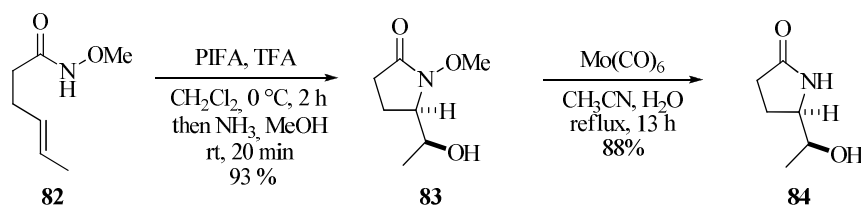
A copper version of the *intermolecular* aminohydroxylation was reported in 2007 by Yoon *et al.* The reaction is catalysed by copper(II) and proceeds *via* the addition of the *N*-O bond of *N*-sulfonyl oxaziridine **75** onto an olefin (Scheme 23).³³



Scheme 23 - Representative example of copper(II)-catalysed reaction

Submitting 4-methoxystyrene **28** to catalytic amounts of copper(II) in combination with oxaziridine **80** afforded (phenylsulfonyl)oxazolidine derivative **81** in an excellent 84% yield with complete regioselectivity. A broad range of alkenes were found to be suitable substrates and this methodology enabled access to diverse 1,2-amino alcohol derivatives, controlling both the regio and enantioselectivity when a chiral ligand was employed.³⁴ However, the main limitation of this methodology was the general lack of stereospecificity as illustrated in Scheme 23.

Finally, Wardrop *et al.* published a successful metal free *intramolecular* aminohydroxylation in 2010, using trifluoroacetic acid in combination with iodine(III) as a reoxidant (Scheme 24).³⁵



Scheme 24 - Representative example of metal free procedure for the synthesis of **84**

(*E*)-*N*-Methoxyhex-4-enamide **82** underwent an efficient cyclisation and subsequent ammonia methanolysis afforded compound **83** in an excellent 93% yield. Wardrop's methodology enabled the formation of five- to eight-membered hydroxyl lactams in good to excellent yields. This procedure was also highly diastereoselective for *anti* stereospecific addition across alkenes, but was hampered by the scope of its precursors affording in several cases modest levels of regioselectivity. Moreover, the need for stoichiometric loadings of molybdenum hexacarbonyl in refluxing aqueous acetonitrile-in order to remove the methoxy group and yield hydroxyl lactam **84**-constituted another drawback.

Therefore, a general, high yielding protocol allowing a broad range of substrates to be employed is still required. While other complementary aminohydroxylation reactions based on metals have emerged, it is reasonable to highlight that none can so far match the *syn* stereospecificity and functional group tolerance offered by osmium.

Results and discussions

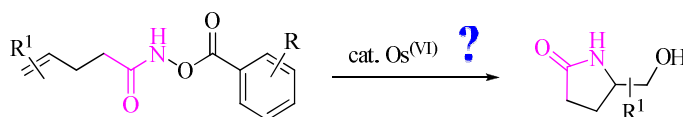
Chapter 2

Intramolecular processes - Tethered aminohydroxylation

2. Intramolecular processes - Tethered aminohydroxylation

2.1 Osmium-catalysed amide series: the use of a carbon tether

As mentioned in the introduction, the aim of this project was to access valuable hydroxyl lactam scaffolds in one step using an osmium catalysed procedure (Scheme 25).

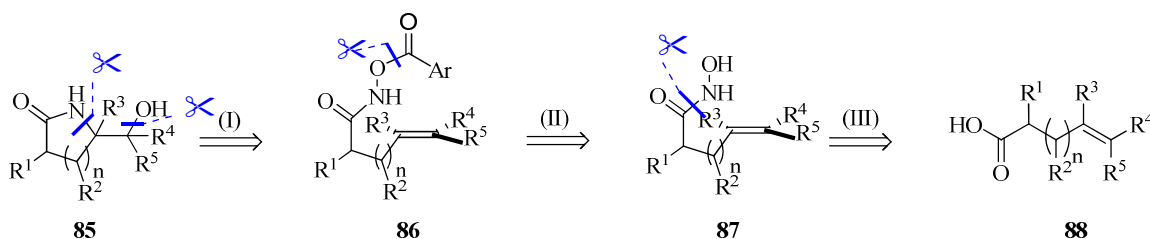


Scheme 25 - Extending the scope of the TA for amide derivatives

To explore the feasibility of this approach, a retrosynthetic analysis was carried out.

2.1.1 Retrosynthesis

The analysis involved three disconnections leading to unsaturated carboxylic acids **88** (Scheme 26).



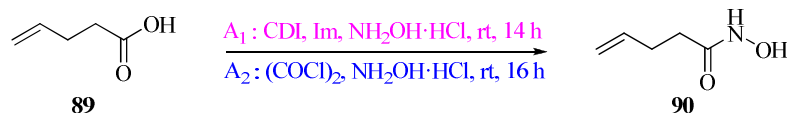
Scheme 26 - Retrosynthetic analysis

Starting with hydroxyl lactam **85**, the first disconnection (I) would come from the tethered aminohydroxylation providing **86** intermediate bearing the reoxidant function as well as a pendant alkene. Further disconnection (II) would lead to hydroxamic acid **87** which in turn would come from unsaturated carboxylic acids **88** (disconnection (III), whether n = 0, 1 or 2).

2.1.2 Synthesis of the hydroxamic acids - Disconnection (III)

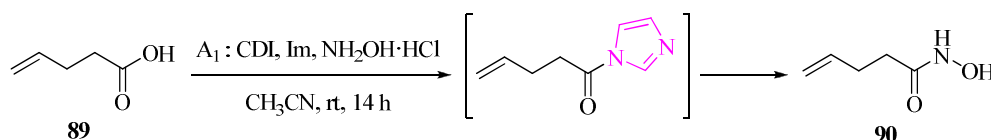
The carboxylic acids **88** that were required were either commercially available or readily accessible *via* common organic reactions described later on in the following sections.

Starting from a carboxylic acid, two synthetic procedures were considered in order to access hydroxamic derivatives **87** depending on whether the carboxylic acids **88** bore acid or base labile functionalities as described in Scheme 27, using pent-4-enoic acid **89** as a test substrate.



Scheme 27 - Developed procedures for the one-pot hydroxamic acid synthesis

Using the conditions outlined in Scheme 27, both procedures started with activation of the carboxylic acid, either with 1,1'-carbodiimidazole (CDI) (A_1) or oxalyl chloride (A_2). Procedure A_1 was based on previous work in the group (Table 1, entry 1) and an optimisation using pent-4-enoic acid **89** was carried out in order to employ fewer equivalents of CDI.³⁶



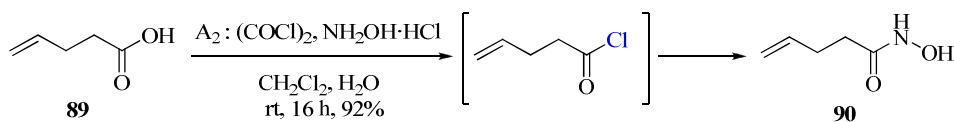
Entry	CDI/Hydroxylamine/Imidazole	Yield of 90
1	2:5:4	92% ¹
2	2:4:3	91% ¹
3	1.5:3:2	94% ¹
4	1:2:1	82% + 15% (89) ²

¹Isolated yield, ²Ratio of compounds determined from the ¹H NMR spectrum of the crude material

Table 1 - Procedure A_1 optimisation

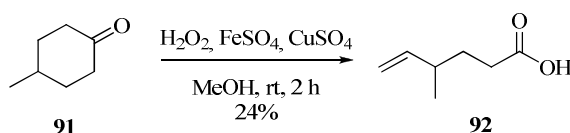
However, the reaction proved to be capricious with 15% of pent-4-enoic acid **89** recovered when an equimolar amount of coupling reagent was used (Table 1, entry 4). It was then concluded that the best yielding conditions that resulted in complete conversion were achieved with entry 3.

Regarding procedure A_2 (Scheme 28), the reaction started first with the formation of an acyl chloride followed by the addition of a saturated solution of hydroxylamine hydrochloride.³⁷

Scheme 28 - Representative example for Procedure A₂

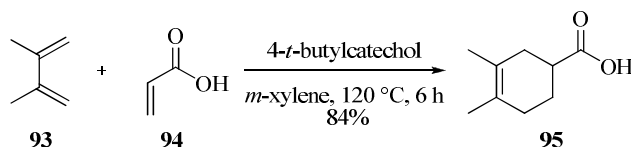
It was anticipated that since the nitrogen of hydroxylamine is more nucleophilic than the oxygen, the desired hydroxamic acid structure **90** would be obtained. Indeed, all compounds synthesised either *via* procedure A₁ or A₂ presented a characteristic IR spectroscopy stretch of the carbonyl ranging between 1645 and 1657 cm^{-1} relating better to parent amides (1630-1690 cm^{-1}) than to esters (1735-1750 cm^{-1}). Furthermore, an X-ray crystal structure obtained from subsequent acylation of a derivative of hydroxamic acid **90** as described in following Section 2.1.3 confirmed unambiguously the correct structure of these acid derivatives. Both procedures A₁ and A₂ were applied to a wide range of unsaturated carboxylic acids as depicted in Scheme 37, page 33.

As previously mentioned, the unsaturated carboxylic acids employed for the synthesis of these hydroxamic acids were either commercially available or readily accessible *via* common organic reactions. For instance, precursors of compounds **90**, **108**, **119** and **120** were synthesised following Fenton's radical procedure employing a combination of iron and copper salt to afford the required carboxylic acids (Scheme 29).



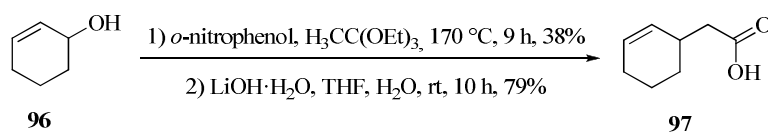
Scheme 29 - Representative example of Fenton's radical procedure

In general, the yields using this procedure were low, yet sufficient to produce enough material for the hydroxamic acid syntheses. In each case, the characteristic ^1H NMR spectrum signals around 5.0 and 5.9 ppm of the terminal olefin protons were observed. Another example was carried out with compound **125** precursor, the product of a Diels-Alder cycloaddition reaction as depicted in Scheme 30. 3,4-Dimethylcyclohex-3-ene-1-carboxylic acid **95** was obtained in an excellent 84% yield from 2,3-dimethyl-1,3-butadiene **93** and acrylic acid **94**.



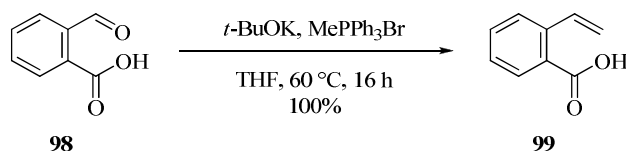
Scheme 30 - Synthesis of **95** via a Diels-Alder cycloaddition reaction

Regarding the synthesis of compounds **118** and **126** precursors, it involved a [3,3]-sigmatropic Johnson-Claisen rearrangement followed by subsequent saponification of the resulting esters in order to afford the desired unsaturated carboxylic acids (Scheme 31).



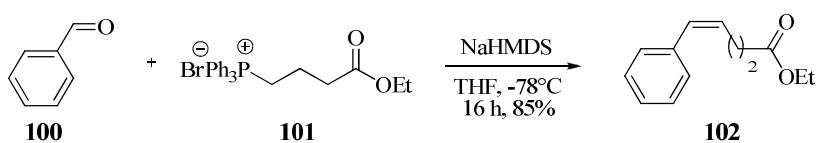
Scheme 31 - Representative example of the Johnson-Claisen rearrangement

Cyclohex-2-en-1-ylacetic acid **97** was then obtained in 30% yield over two steps. The alkene protons signals at 5.8 and 5.6 ppm on the ^1H NMR spectrum confirmed its structure. Finally, the precursors of compounds **114**, **115**, **116**, **117** and **124** were all produced *via* a Wittig olefination reaction as depicted in Scheme 32.



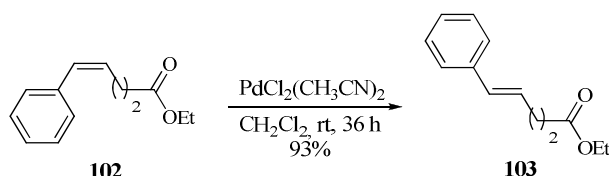
Scheme 32 - Representative example of a Wittig olefination reaction

Out of the examples carried out, the syntheses of compound **112** and **113** were of interest involving an isomerisation of **114** and **115** catalysed by palladium(II). First, compounds **114** and **115** precursors synthesis started from benzaldehyde **100** *via* a Wittig reaction involving a non-stabilised phosphonium ylide as described in Scheme 33.



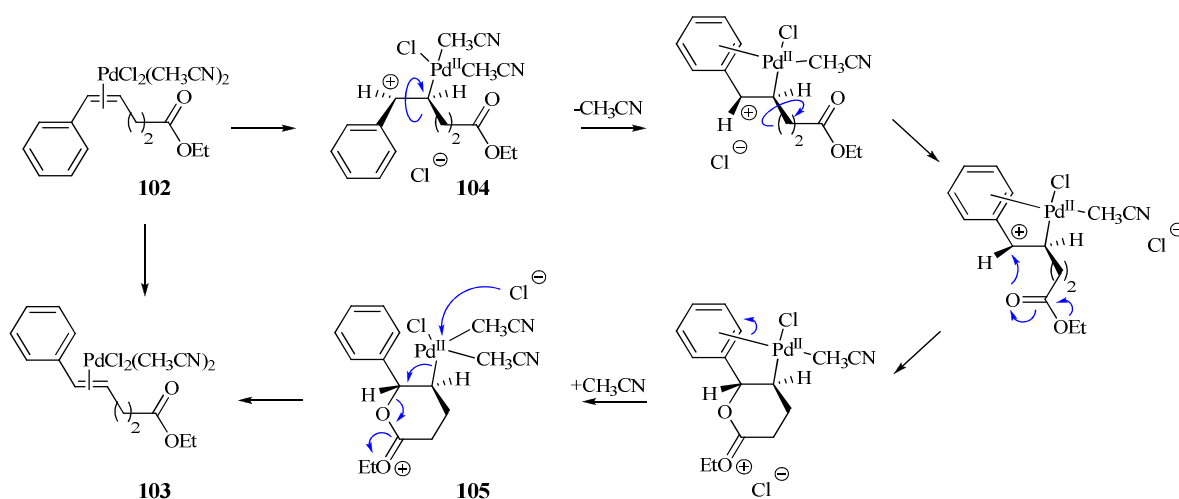
Scheme 33 - Synthesis of ethyl (4Z)-5-phenylpent-4-enoate **102**

In all cases, the alkene coupling constant between 11.6 and 12.8 Hz was indicative of the *cis*-stereochemistry of the newly formed double bond. Then, for instance, **102** was submitted in dichloromethane to a source of palladium(II) to afford ethyl (4*E*)-5-phenylpent-4-enoate (*J* 15.9 Hz) **103** in an excellent 93% yield (Scheme 34).



Scheme 34 - Representative example of palladium-catalysed isomerisation of **102**

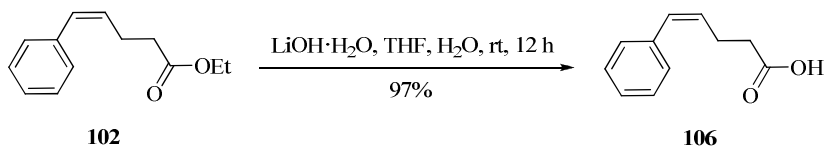
In all cases, the alkene coupling constant between 15.7 and 15.9 Hz was indicative of the *trans*-stereochemistry of the newly formed double bond. This isomerisation process, although not fully understood, was reported to transpire through palladium intermediate **104** (Scheme 35).³⁸



Scheme 35 - Proposed isomerisation mechanism with palladium(II)

Spencer *et al.* suggested the formation of carbocation species **104** from the interaction of **102** double bond with $\text{PdCl}_2(\text{CH}_3\text{CN})_2$.³⁹ Subsequent rotation around the carbon-carbon bond and regeneration of the catalyst through the nucleophilic attack of chlorine ion **105** would end the isomerisation process. Another postulated mechanism would involve *trans* addition of $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ onto **102** alkene bond followed by rotation and *syn* β -elimination to regenerate the catalyst. Both mechanisms are supported by previous studies demonstrating that $\text{PdCl}_2(\text{CH}_3\text{CN})_2$

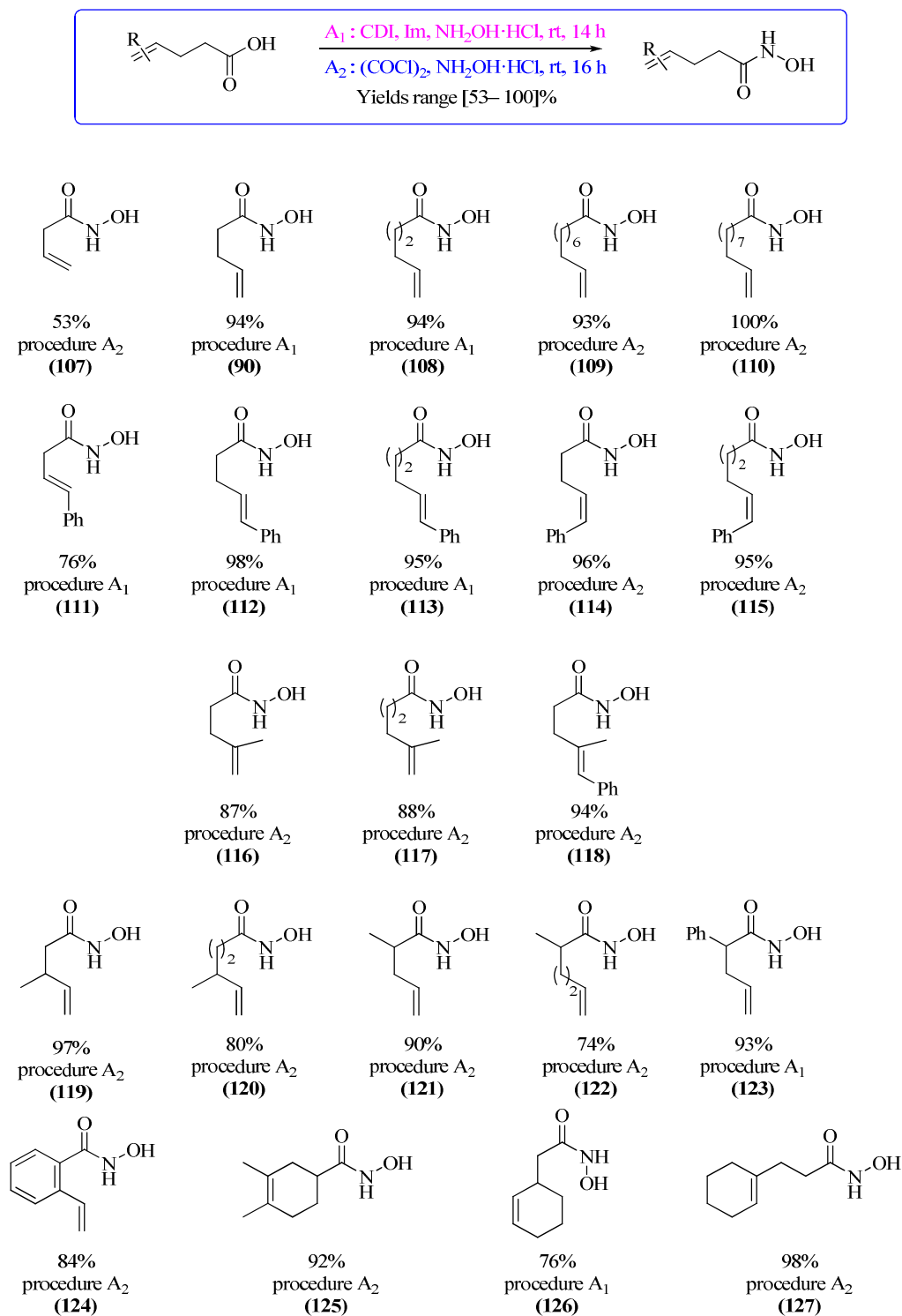
forms olefin complexes resulting in the lowering of the alkene torsional barrier.⁴⁰ Finally, all synthesised esters afforded the respective carboxylic acids after saponification reaction (Scheme 36).



Scheme 36 - Representative example of saponification procedure

All details regarding the procedures employed for the synthesis of these carboxylic acids can be found in the Experimental section, Chapter 5.

Substrate scope



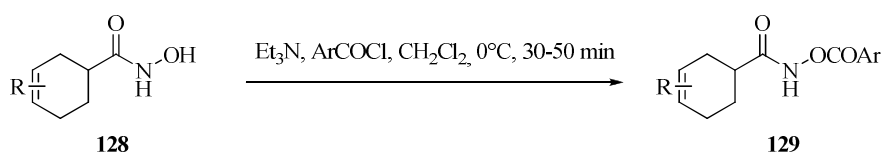
Scheme 37 - Summary of the synthesised hydroxamic acids

Whilst procedure A₁ proved to be useful for acid-sensitive compounds, procedure A₂ gave superior yield and an easier work-up. Purification of these compounds by column chromatography proved to

be capricious and not compulsory since they were produced in good purity (above 95%). Hence, the hydroxamic acids were taken to the subsequent acylation step without further purification.

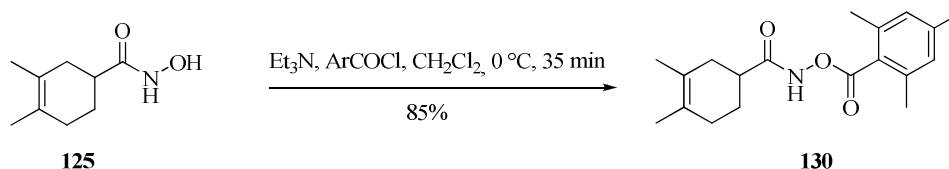
2.1.3 Acylation of the hydroxamic acids - Disconnection (II)

According to literature precedent on the study of hydroxamic acids, the reaction was conducted in an aprotic polar solvent, in the presence of an organic base and at low temperature as detailed in Scheme 38.⁴¹



Scheme 38 - Procedure applied for the acylation of hydroxamic acid derivatives

Aprotic solvents do not favour hydrogen bonding and carrying out the reaction at low temperature should minimise any possible isomerisation.⁴¹ The first deprotonation to occur would then be of the oxygen of hydroxamic acid **125** enabling the formation of the desired acylated compound **130**.



Scheme 39 - Representative example

Consequently, conducting the reaction with **125** in dichloromethane at 0 °C, using triethylamine as the base, yielded the desired product **130** in less than an hour in an excellent 85% yield (Scheme 39). The swiftness of this reaction even at low temperature was one of the advantages of this procedure. The correct structure assignment of product **130** was confirmed by the **NH signal peak** on the ¹H NMR spectrum at 10.5 ppm, the **IR spectroscopy stretch of the carbonyl of the hydroxamic derivative** at 1645 cm⁻¹ closer to amides (1630-1690 cm⁻¹) than esters (1735-1750 cm⁻¹) and finally by the study of the relevant X-ray crystal structure (Figure 5).

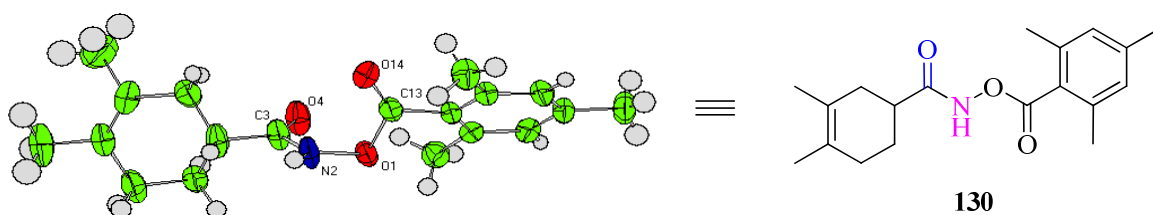
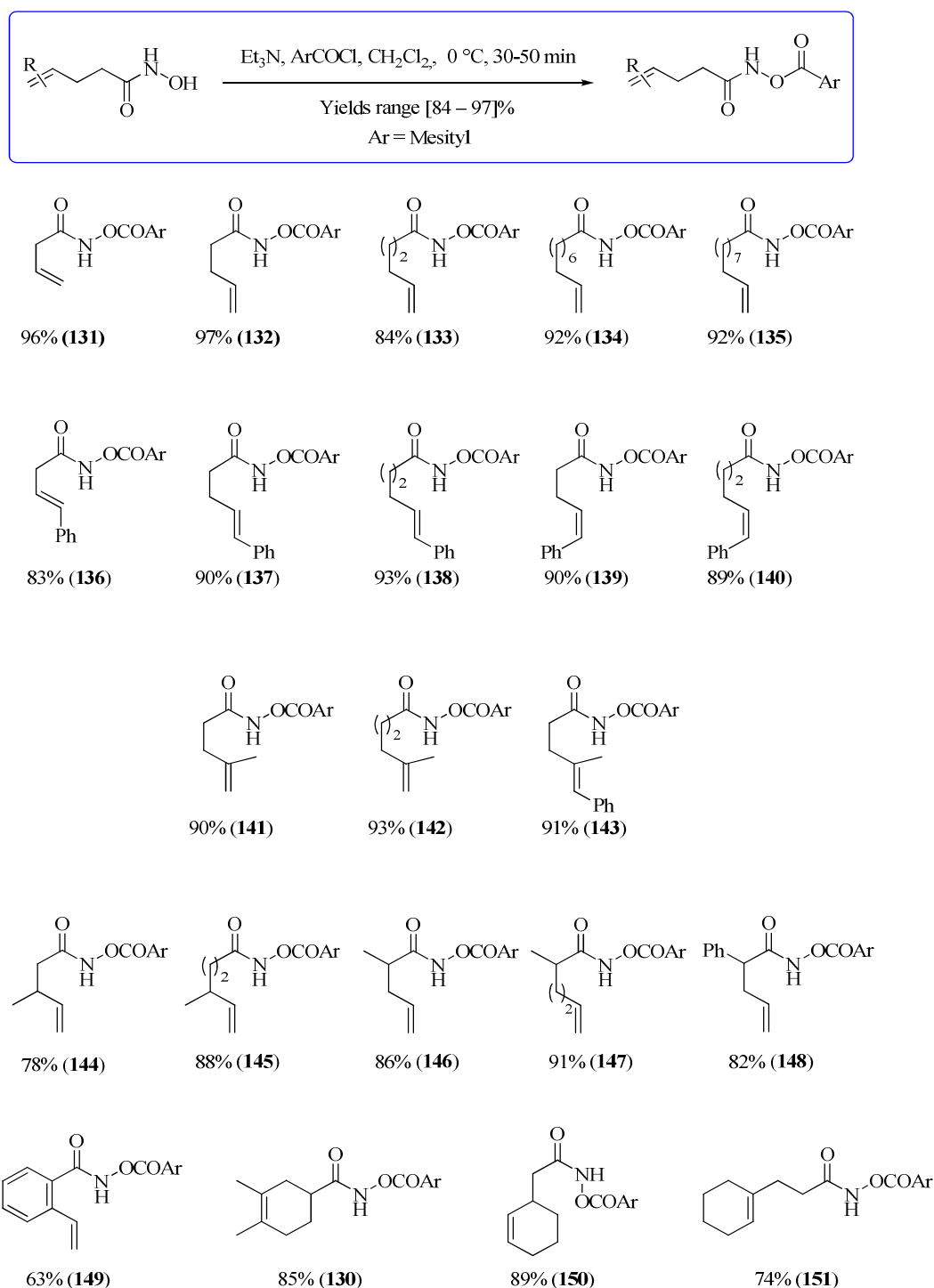


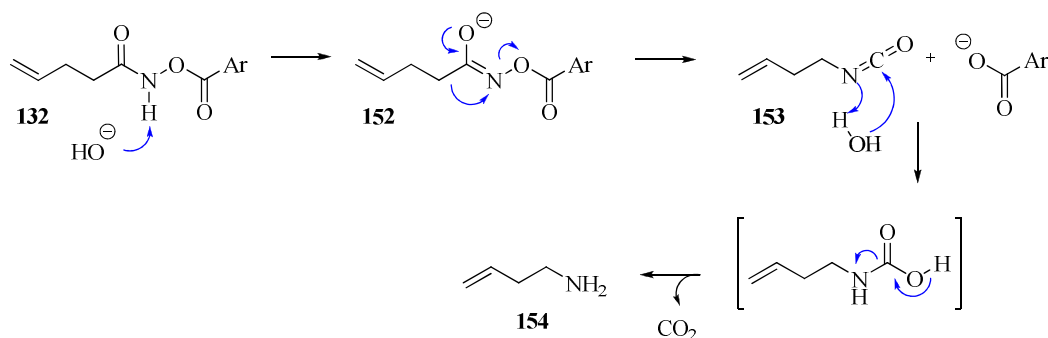
Figure 5 - Correct structure assignment confirmed by X-ray crystal analysis

Regarding the rest of acylated hydroxamic acid derivatives, the correct structure assignment was established partly with their carbonyl stretch in the IR spectroscopy ranging between 1669 and 1672 cm^{-1} and the characteristic NH signal peak on their ^1H NMR spectrum ranging from 9.5 to 11 ppm. These similar spectroscopic data were in complete accordance with compound **130**, which had been formally identified by X-ray crystal structure. The results of the acylation experiment are listed in Scheme 40.

Substrate scope

**Scheme 40** - Summary of the synthesised precursors for the tethered aminohydroxylation

It is important to note that the specific use of an organic base in this procedure was critical. Indeed, homoallylic amine **154**, the product of a Lossen rearrangement, was observed when an inorganic base such as lithium hydroxide was employed. This rendered the medium too alkaline favouring a Lossen rearrangement as depicted in Scheme 41.⁴²

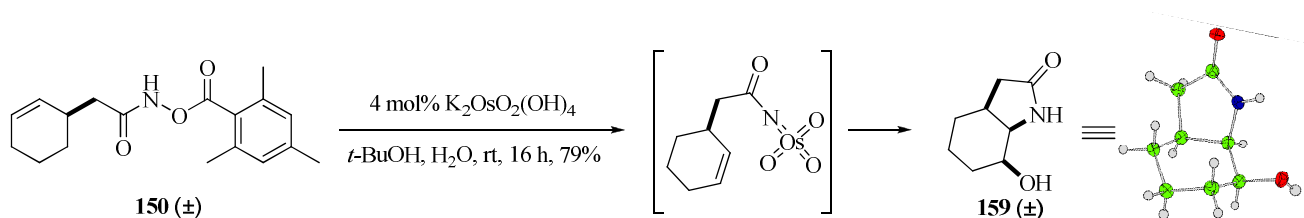


Scheme 41 - Lossen rearrangement mechanism

The first step of this well described side reaction involved deprotonation of *O*-acyl hydroxamate **132** at the nitrogen position. It was envisaged that alkali intermediate **152** was unstable under the conditions outlined and underwent a concerted rearrangement to afford isocyanate **153**. Subsequent hydrolysis afforded homoallylic amine **154**. Furthermore, this side reaction was also observed and favoured when more electron withdrawing aryl groups (Ar = C₆F₅) were used as acylating reagents. Therefore, 2,4,6-trimethyl and 2,4,6-trichlorobenzyl chloride were selected as reagent of choice.⁴³

2.1.4 Tethered Aminohydroxylation (TA) of amide derivatives - Disconnection (I)

With our precursors in hand, the tethered aminohydroxylation was first run using 4 mol% of the non-volatile potassium osmate K₂OsO₂(OH)₄ (Scheme 42).

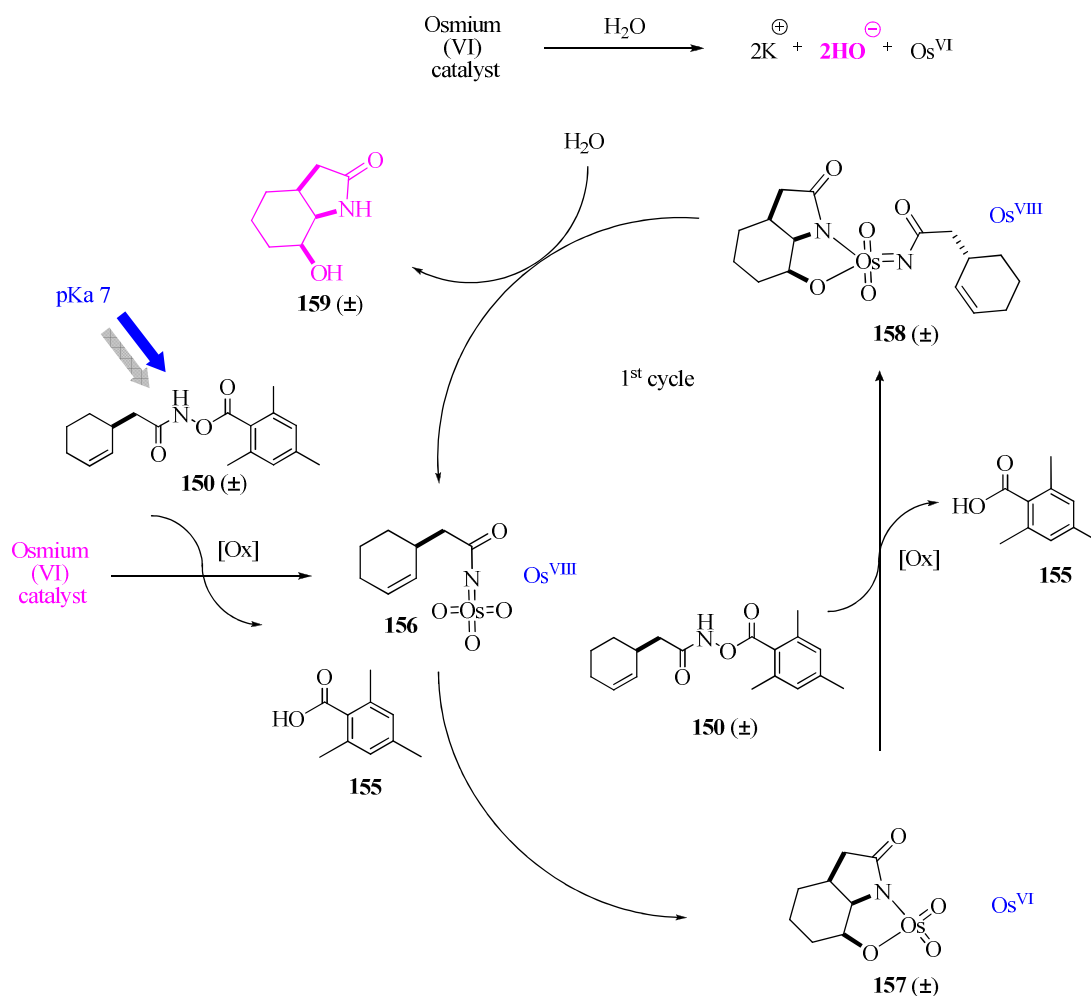


Scheme 42 - One example of the TA procedure

Pleasingly, the TA reaction of racemic **150** proceeded efficiently affording **159** in an excellent 79% yield. The complete disappearance of the alkene protons signals in the ¹H NMR spectrum as well as the correct *m/z* (ESI⁺) 156 of product **159** corroborated its synthesis. Moreover, the relative stereochemistry of 2*H*-indol-2-one **159** was proven unambiguously by X-ray crystal structure analysis, clearly highlighting the *syn* stereospecific nature of the oxidation process.

With the reoxidant tethered to the substrate (the hydroxylamine bond acts as the oxidising agent), this meant that the reaction did not require any external additives or need to be under an inert atmosphere.

Previous studies have classified these mono-acylated hydroxamic acids as rather weak acids ($\text{pK}_a \sim 7$).⁴⁴ When potassium osmate is dissolved in water, two molecules of hydroxide ions are released (Scheme 43). Hence, upon addition of a solution of potassium osmate, this catalytic amount of base was enough to deprotonate species **150**, thus enabling the oxidation of Os^{VI} to Os^{VIII} and facilitating the entry to the catalytic cycle. Imidotrioxoosmium(VIII) species **156** then underwent a cycloaddition reaction to generate azaglycolate(VI) complex **157**. This reaction proceeded with complete regioselectivity.



Scheme 43 - Proposed mechanism for the tethered aminohydroxylation reaction

157 intermediate was then oxidised by nitrogen source **150** to afford **158** and subsequent hydrolysis ended the primary catalytic cycle providing the desired vicinal 1,2-amino alcohol **159** as well as initial imidoosmium **156**. The latter carried on the catalytic cycle. The existence of a secondary cycle operating in the tethered aminohydroxylation reaction as described in Section 1.3 remained to be proven. Furthermore, it was noted that upon addition of potassium osmate to the reaction mixture, a distinctive colour change from colourless to brown was observed (Figure 6).

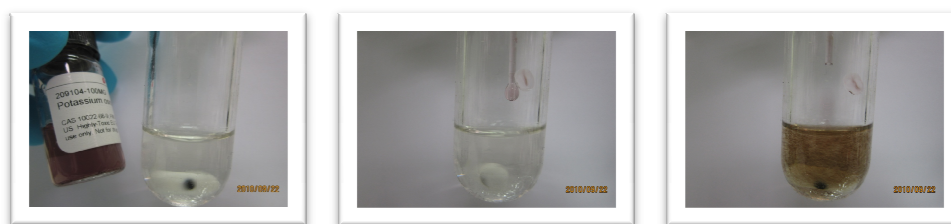
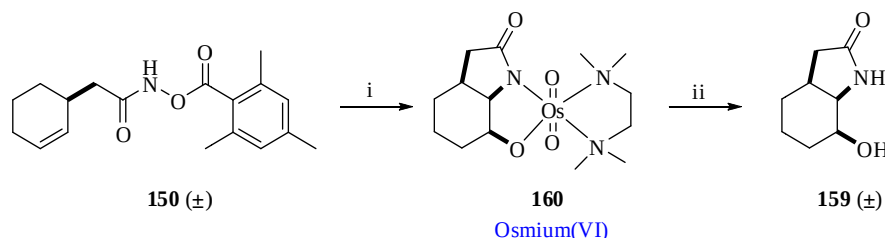


Figure 6 - Colour change over addition of the first drop (< 2 seconds)

This observation was most likely the result of a change in the osmium oxidation state from osmium(VI) to osmium(VIII).

To our knowledge, no azaglycolate osmate **157** ester derived from an amide has ever been described in the literature. Hence, being able to trap out an Os^{VI} intermediate **160** (generated in a model stoichiometric oxidation using tetramethylethylenediamine (TMEDA) as a stabilizing ligand) was significant and strongly supported the *syn*-stereospecific proposed mechanism as depicted in Scheme 44. The diagnostic $\text{Os}=\text{O}$ stretch at 842 cm^{-1} in the IR spectroscopic spectrum was in accordance with previously reported spectroscopic data.⁴⁵



Reagents and conditions: i) $\text{K}_2\text{OsO}_2(\text{OH})_4$, TMEDA, *t*-BuOH, H_2O , rt, 30 h, 43%; ii) Na_2SO_3 , H_2O , 40 °C, 24 h, 100%.

Scheme 44 - Isolation of 2-Cyclohex-2-en-1-yl-N-[(mesitylcarbonyl)oxy]acetamide **160** coordinating to Os^{VI}

As expected, **160** was transformed into product **159** in a separate hydrolysis experiment with identical spectral data to those previously reported (Scheme 44). Gratifyingly, **160** proved to be

crystalline and orange crystals were grown of sufficient quality to enable analysis by X-ray diffraction. The X-ray crystal structure of **160** further confirmed that the osmium metal was chelated by TMEDA and the newly formed hydroxyl lactam (Figure 7). This result was in accordance with a *syn* addition most likely due to a concerted process.

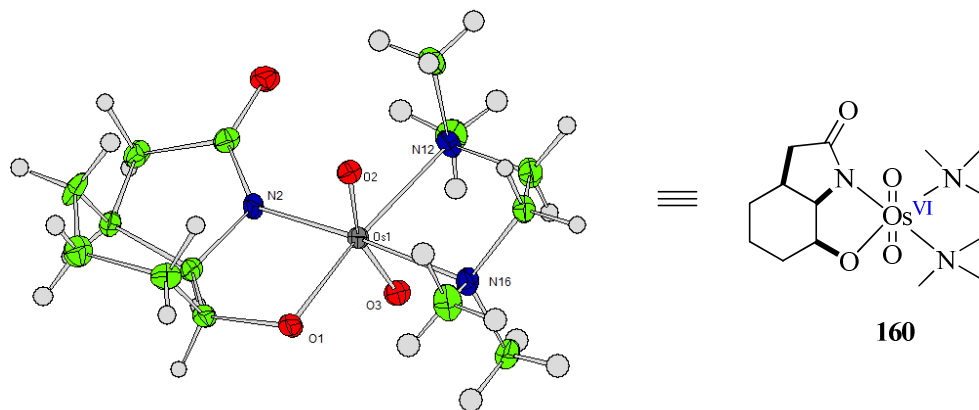
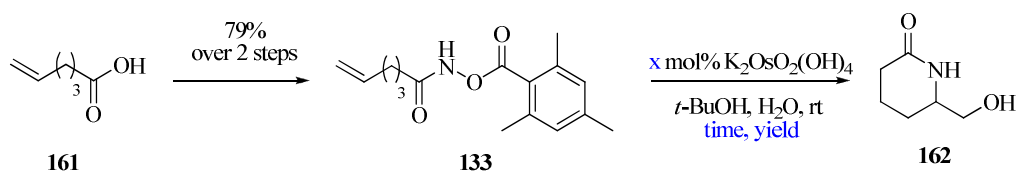


Figure 7 - X-ray crystal structure of **160**

After performing this mechanistic investigation and in an effort to render this methodology even more applicable for large scale synthesis, investigations to reach a more desirable 1 mol% loading of a catalyst were carried out.

2.1.5 Optimisation of the TA procedure with lower catalyst loadings study

Precursor **133** obtained from hex-5-enoic acid **161** was chosen for this optimisation (Table 2).



Entry	Catalyst $\text{K}_2\text{OsO}_2(\text{OH})_4$	Conditions	Yield ¹ of 162
		$t\text{-BuOH}$, H_2O (3:1) 25 mL · mmol ⁻¹	
1	4 mol%	rt, 4 h	83%
2	1 mol%	rt, 48 h	25%

¹Isolated yield

Table 2 - Optimisation using **133** as a test substrate

Although the reaction proceeded completely with 4 mol% of potassium osmate to afford the desired product **162** in an excellent 83% yield (spectroscopic data were consistent with those reported in the literature), decreasing the amount of catalyst to 1 mol% resulted in a low yield, extended reaction time and recovery of unreacted precursor **133** (entry 2). Starting with the initial conditions outlined in entry 1, several parameters were examined in order to increase the turnover of this reaction when using as low as 1 mol% of catalyst. These were the solvent media, the pH of the medium, the addition of ligand, the temperature and the osmium catalyst. The optimisation was carried out with 1 or 2 mol% of potassium osmate unless stated otherwise. All the yields quoted in this optimisation process were from isolated product after column chromatography purification. The first criterion that was investigated was the solvent in which the reaction was conducted.

2.1.5.1 Solvent media investigation

2.1.5.1.1 Concentration parameter

Hypothesis: The initial conditions, which were inefficient for low catalyst loading, required 25 mL of solvent for 1 mmol of reoxidant **133**. Moreover, these dilution conditions were not feasible on large scale synthesis.⁴³ Thus, it was postulated that decreasing the total volume of solvent might have a positive impact on the process reactivity with low catalyst loading. The ratio between the co-solvents was also considered in order to improve the hydrolysis step, see Scheme 43 (Table 3).

133 **162**

Entry	Dilution	<i>t</i> -BuOH, H ₂ O (3:1)	<i>t</i> -BuOH, H ₂ O (1:1)
1	25 mL · mmol ⁻¹	47% (25% ¹)	45%
2	5 mL · mmol ⁻¹	58% (28% ¹)	59%

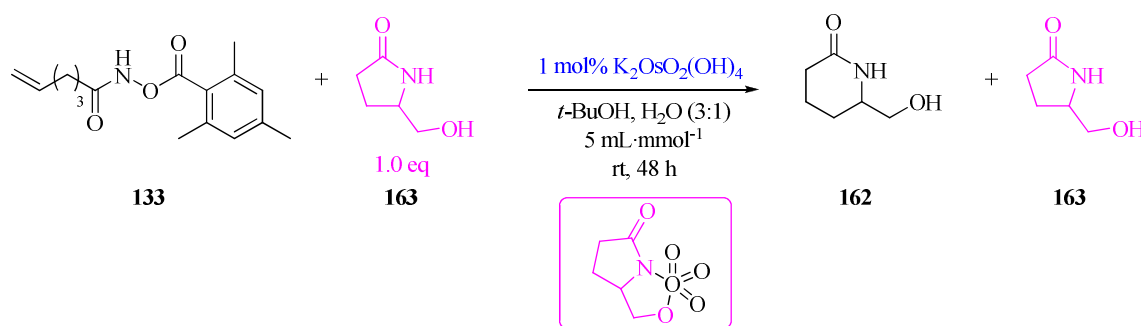
¹Reaction with 1 mol% of catalyst halted after 48h and purified

Table 3 - Investigation of the dilution parameter

Results: Conducting the reaction with higher concentration of substrate gave higher yield. However, increasing the ratio of water did not promote hydrolysis h₁.

2.1.5.1.2 Substrate inhibition

Hypothesis: The reaction depicted in Scheme 45 was carried out to verify whether the gradual formation of product **162** (similar to an enzyme/substrate inhibition) and thus its increasing concentration in the medium prevented further starting material **133** from reacting with the osmium catalyst. This type of inhibition is sensitive to the solvent and concentration in which the reaction is conducted.⁴⁶ In the designed experiment, it was postulated that no formation of **162** would occur with full recovery of reoxidant starting material **133**. This hypothesis was tested with the addition of one equivalent of **163** during a cross-experiment to be able to distinguish the outcome (Scheme 45).

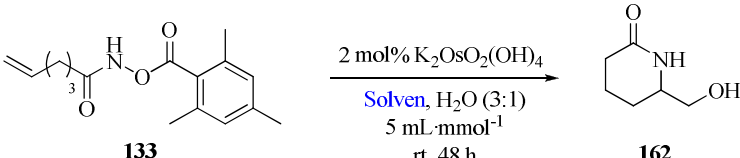


Scheme 45 - Substrate inhibition experiment

Results: This product inhibition hypothesis was discarded as **162** was afforded in 29% yield (versus 28% without the addition of **163**) with recovery of both pyrrolidin-2-one **163** and starting material **133**.

2.1.5.1.3 Solvent effect

Hypothesis: Regarding the solvent effect, it was envisaged that the solubility of either starting material **133** or product **162** might interfere with the reactivity of the catalyst. The solvents considered were capable of solubilising both **133** and **162** but at various concentrations (Table 4).

					
Solvent ratio (3:1)	<i>t</i>-BuOH, H₂O	THF, H₂O	Et₂O, H₂O	CH₃CN, H₂O	H₂O
Yield of 162	58%	45%	34%	68% (31%¹)	No reaction

¹Reaction with 1 mol% of catalyst halted after 48h and purified

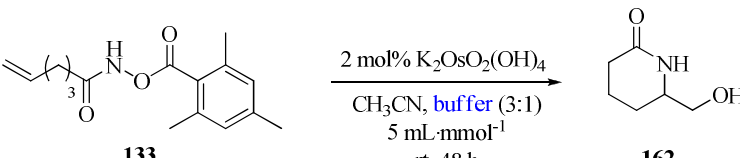
Table 4 - Investigation of the solvent effect

Results: This screening determined that acetonitrile and *t*-butanol were the best yielding solvents. Although *t*-butanol has been described in previous literature studies to increase the rate of the catalytic cycle, acetonitrile gave a higher yield and was chosen for the next set of experiments.⁴⁷

2.1.5.2 Influence of the pH parameter on the medium

Another parameter considered was the pH of the reaction mixture. Indeed, past studies pinpointed this factor as an important one in the aminohydroxylation process.⁴⁸

Hypothesis: Potassium osmate when dissolved in water liberates two molecules of hydroxide ions and osmium(VI). The measured pH of the reaction mixture at the beginning was close to 8 as expected and dropped to 5 a few hours later. This was likely the result of the gradual release of carboxylic acid **155** in the medium (Table 5). Based on this observation, two buffered solution at pH 8 and 5 were employed in the tethered aminohydroxylation in order to investigate whether the carboxylate resulting from **155** interfered with the catalyst, consequently halting the conversion process.

				
pH	Control experiment	5 (Buffer)	8 (Buffer)	1
Yield of 162	68% (31% ¹)	45%	47%	23%

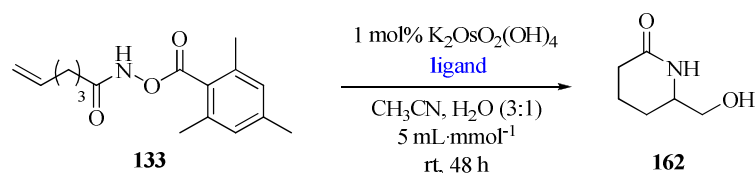
¹Reaction with 1 mol% of catalyst halted after 48h and purified

Table 5 - Investigation of the pH parameter

Results: It was concluded following these results that setting the pH of the medium using a buffer far from improving the yield, impaired the outcome. Therefore, the moderate conversion obtained in the control experiment was not the consequence of the carboxylic acid **155** interfering with the osmium catalyst.

2.1.5.3 Influence of ligands

Hypothesis: The use of a ligand has previously, in the aminohydroxylation and TA reaction of allylic alcohols, helped to improve the catalytic turnover.⁴³ By coordinating to the metal, the ligand enhanced the reactivity of imidoosmium intermediate **156** prompting a faster cycloaddition reaction (see Scheme 43). It was envisaged that if degradation of the catalyst was responsible for not driving the reaction to completion, increasing the rate of the reaction by using ligands might counterbalance this effect (Table 6). Moreover, using triethylamine or Hünig's base as ligand would result in a faster deprotonation of starting material **133**, improving the oxidation rate of osmium(VI). The reaction mixture was carried out with 1 mol% of the catalyst and the reaction stopped after 48 h.



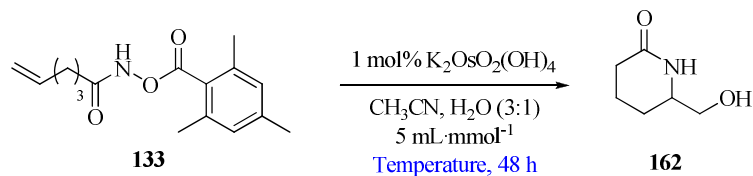
Ligand	No ligand	Hünig's base	Triethylamine	2,3 Sodium Tosyldiaminopropionate 164	Sodium citrate
Yield of 162	31%	30%	26%	29%	27%

Table 6 - Ligand effect on the osmium catalysed process

Results: Frustratingly, no improvement was observed with the use of ligand. These series of experiments indicated that another means to increase the catalyst turnover would be required if higher conversion was to be achieved. Consequently, the next factor to be considered was the temperature at which the reaction was carried out.

2.1.5.4 Influence of the temperature parameter

Hypothesis: In the first instance, optimising the outcome at room temperature was attempted as it would have been highly beneficial for large scale applications. However, since every procedure modification so far failed to reach completion, heating the reaction was considered a possibility at this stage (Table 7). Furthermore, increasing the temperature might facilitate the oxidation step as well as the hydrolysis of **158** (see Scheme 43).



Temperature	Control experiment, rt	40 °C	60 °C	110 °C	170 °C
Yield of 162	31%	44%	41%	31% ¹	decomposition

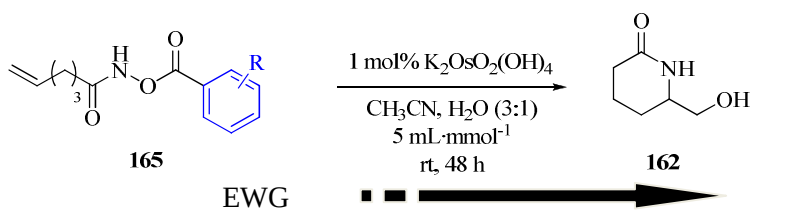
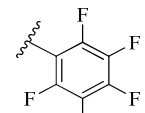
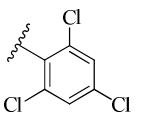
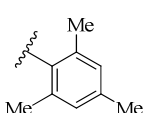
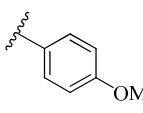
¹Microwave radiation were used for 30 min. Conducting the reaction for another 30 min did not improve the yield.

Table 7 - Temperature effect on the osmium catalysed process

Results: Gratifyingly, increasing the temperature did improve the yield but only to a certain extent. As anticipated, a higher temperature decomposed the osmium catalyst and consequently, the nature of the osmium reoxidant was investigated as next parameter.

2.1.5.5 Nature of the reoxidant.⁴⁴

Hypothesis: It was envisaged that substitution on the aryl moiety with electron donating (ED) or electron withdrawing (EW) group could promote an increase or decrease of hydroxamic acid derivative **165**'s pKa; and therefore could facilitate the oxidation of osmium(VI) to osmium(VIII). Steric hindrance (especially at the *ortho* position) and the stability of the resulting carboxylate might also have a noticeable impact on the process (Table 8).

				
Precursors for the Tethered Aminohydroxylation (165)				
	166	167	133	168
Yield of 162	24%	33%	31%	18%

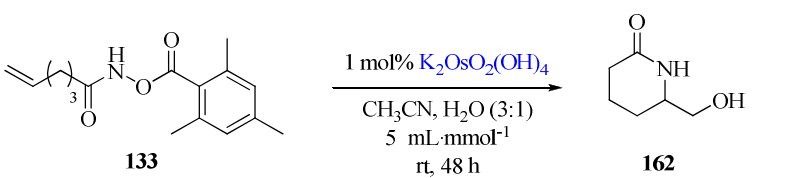
Average of 3 runs for each reaction

Table 8 - Nature of the aryl group on the reoxidant

Results: 2,4,6-trisubstituted aryls gave the best yields in this series. Moreover, the trend for moderate EDG or EWG to be more suitable as aryl substituent could be explained since a strong EWG facilitated the decomposition of the reoxidant (see Section 2.1.4, Scheme 43); while a strong EDG would slow down the deprotonation of the reoxidant by increasing the pKa resulting in a slower oxidation step.

2.1.5.6 Influence of the osmium catalyst source

The source of the osmium catalyst was investigated next (Table 9).

						
Osmium source	OsO ₄	AD-mix β	OsCl ₃	K ₂ OsO ₂ (OH) ₄ Sigma-Aldrich, 98% 2-month old	K ₂ OsO ₂ (OH) ₄ VWR 97% new bottle	K ₂ OsO ₂ (OH) ₄ Sigma-Aldrich 98% new bottle
Yield of 162	33%	15%	29%	24%	26%	31%

¹Microwave radiations were used for 30 min. Conducting the reaction for another 30 min did not improve the yield.

Table 9 - Influence of the osmium catalyst source

Results: Interestingly, the yield obtained with a fresh source of potassium osmate differed from a two month old source. After careful experimental manipulation, the best yields were obtained when the catalyst gave a limpid purple solution when dissolved in water (Figure 8, picture on the left).

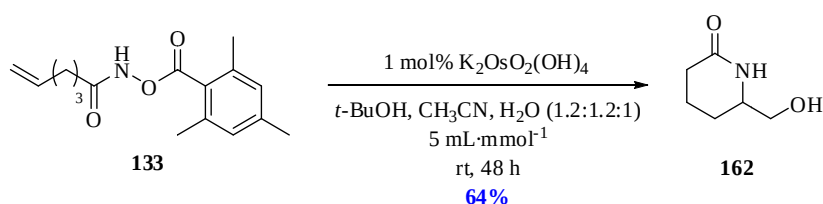


Figure 8 - Quality of the catalyst source

The solid residue observed (Figure 8, picture on the right) after water dissolution of an old source of potassium osmate was most likely contamination by osmium dioxide Os^{IV} which is a black solid insoluble in water.⁴⁹ Its presence might stem from disproportion of potassium osmate Os^{VI} affording osmium dioxide Os^{IV} and osmium tetroxide Os^{VIII} corroborating the moderate quality of the two-month old catalyst.⁵⁰

2.1.5.7 Tripartite solvent system

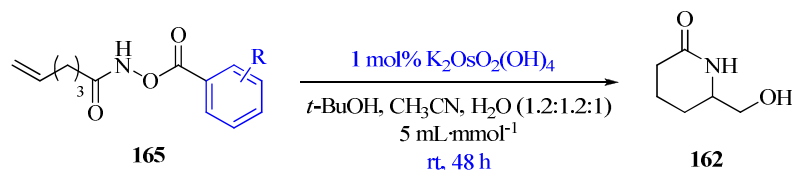
Based on the literature and past studies, *t*-butanol has been described as a solvent capable of accelerating the turnover of the reaction in osmium-mediated processes and acetonitrile has been employed to afford higher yield although in longer reaction time.⁴⁷ It was proposed that these effects could be explained as better solvation of the osmium catalyst due to hydrogen bondings in the case of *t*-butanol and an improved solubility of reoxidant **133** in the case of acetonitrile. Therefore, to examine the hypothesis of a possible solvent synergy, the decision was taken to use a tripartite solvent system in combination with fresh potassium osmate (Scheme 46).



Scheme 46 - Tripartite solvent system

Pleasingly, the result of this solvent combination was an outstanding improvement in the reactivity (from 25% to 62%) compared to the conditions used at the beginning of this optimisation. Although the hypothesis formulated revealed to be judicious, this solvent cooperative effect would need further studies to be fully understood.

With these unique conditions in hand, all the key results previously obtained for each parameter were investigated once more (Table 10).



Modified parameter			Scale-up (x 3)	40 °C	5 days	Reverse addition ³	2 mol% K ₂ OsO ₂ (OH) ₄
Yield of 162 ¹	60%	63% ²	60%	64%	61%	65%	78%

¹Sigma-Aldrich new bottle, 5 mL·mmol⁻¹

²Robustness of the reaction checked (given yield was the average of 3 reactions)

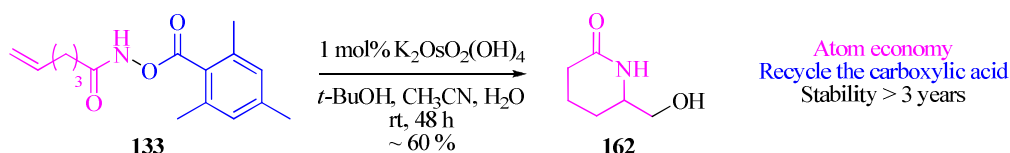
³Starting material **133** was added over 2 h with a syringe pump to the aqueous potassium osmate solution.

Table 10 - Tripartite solvent system-Final screening

Examination of these results did not reveal anymore synergies between the parameters investigated.

2.1.5.8 Conclusion of the optimisation process

These results ended the optimisation process and highlighted the fact that the TA for this series was efficient without additives which also had implications for waste and cost minimization for large scale applications (Table 11).



Atom economy
Recycle the carboxylic acid
Stability > 3 years

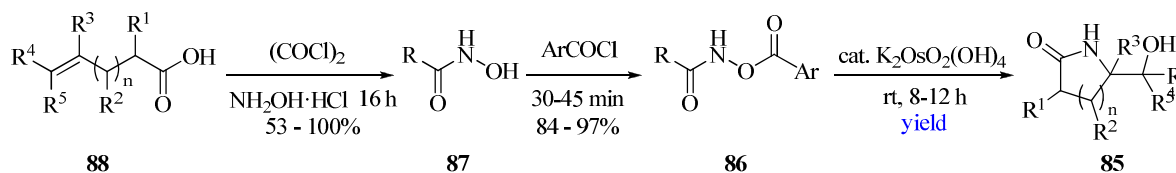
Conditions	Catalyst 1 mol% K ₂ OsO ₂ (OH) ₄	Conditions	Yield of 162
Initial	<i>t</i> -BuOH, H ₂ O (3:1) 25 mL·mmol ⁻¹	rt, 4 h	25%
Optimised	<i>t</i> -BuOH, CH ₃ CN, H ₂ O (1.2:1.2:1) 5 mL·mmol ⁻¹	rt, 48 h	63%

Table 11 - Summary of the optimisation

The reaction was now robust and scalable. Moreover, unreacted starting material **133** could easily be recovered after purification, which raised the potential of this reaction on an industrial scale with a low loading of 1 mol% of a non-volatile catalyst.

2.1.6 Substrate scope

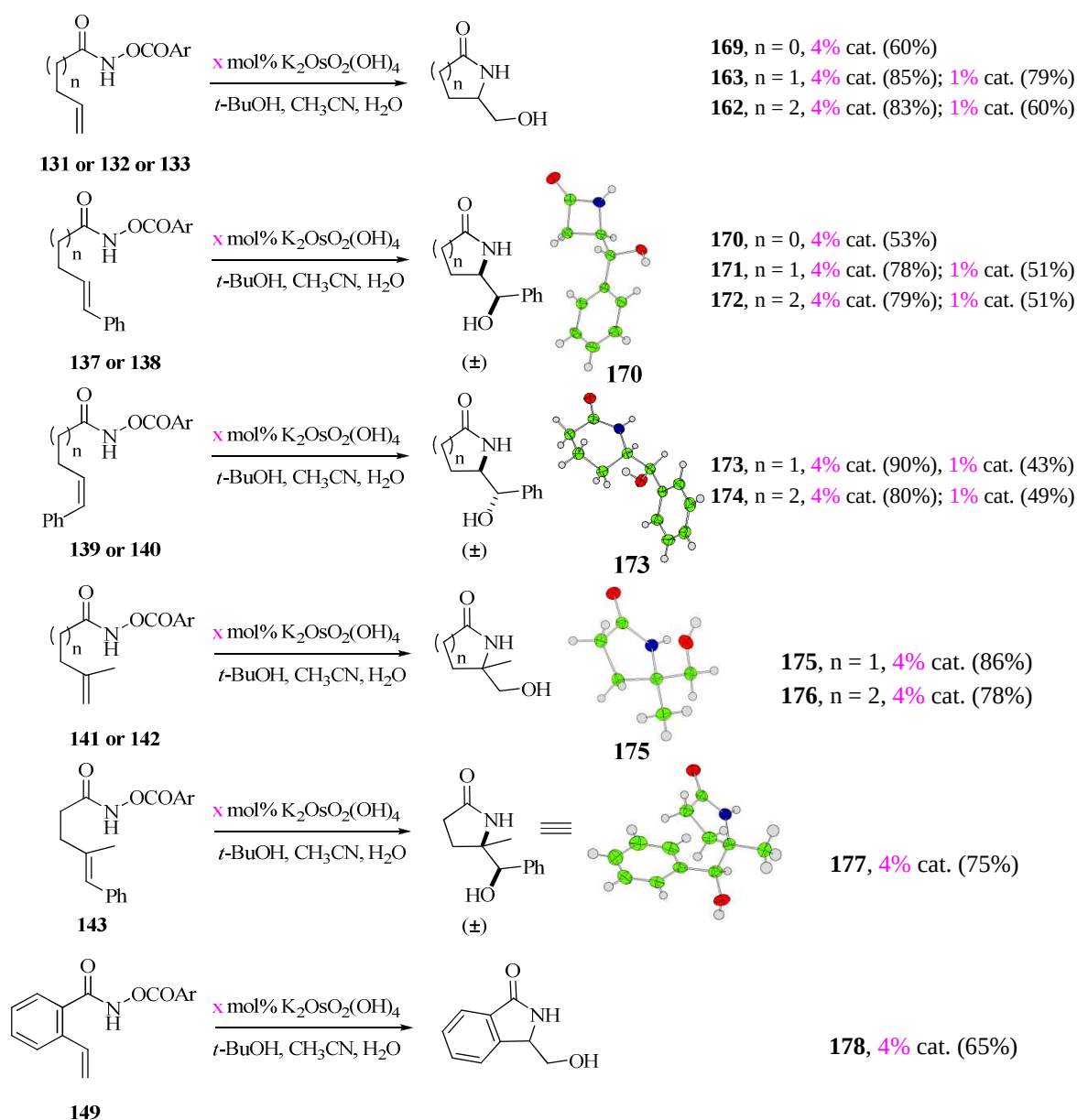
With precursors **86** easily available in excellent yield over a two step procedure, the osmium based tethered aminohydroxylation of amide was successfully applied to a wide range of substrates (Scheme 47).



Scheme 47 - Overview of the methodology - 24 examples
(R equals a side chain containing an alkene)

This efficient and convenient process is capable of forming β -lactams ($n=0$), pyrrolidinones ($n=1$) and piperidinones ($n=2$) as depicted in Scheme 48. Each reaction gave essentially a single product.

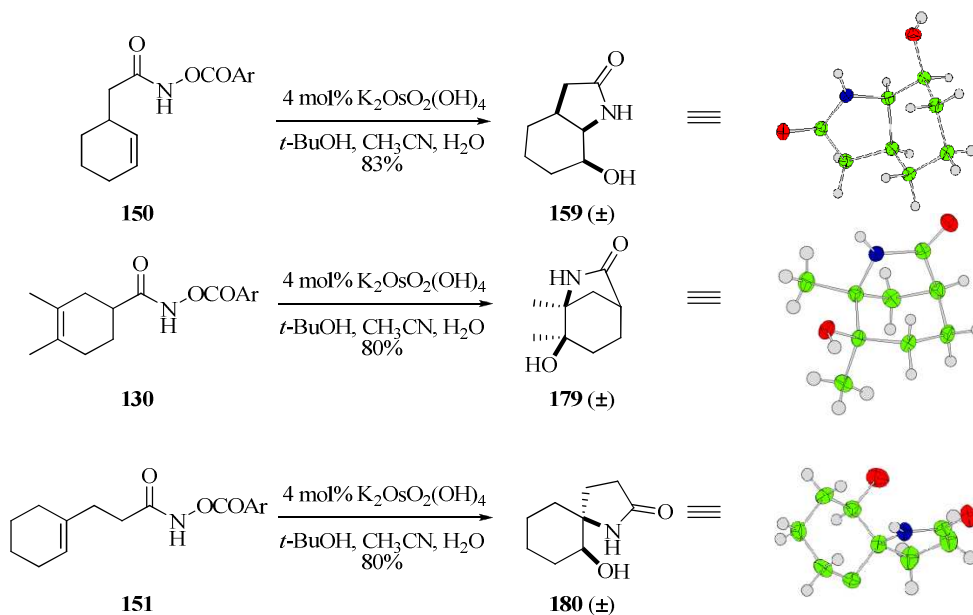
All products obtained had a characteristic carbonyl IR stretch inherent to amide functionality in the range of 1645 to 1664 cm^{-1} (1729 cm^{-1} for **170**). Furthermore, the structures of novel compounds **170**, **171**, **172**, **173** and **174** have been unambiguously determined by X-ray crystal analysis. Hence, the reaction was both stereospecific (X-ray crystal structures had confirmed the *syn* addition process across the alkene) and regiospecific (tethering the reoxidant to the pendant alkene defined the final position of the nitrogen across the alkene).



Scheme 48 - Acyclic substrates and X-ray crystal structures of some products

This methodology also enabled the construction of quaternary centre (**175**, **176** and **177**) when conducting the reaction with 1,1'-substituted alkene precursors **141**, **142** and **143**. Once more, crystallographic analysis proved unambiguously structure **175** and **177**, where the nitrogen of the newly synthesised lactam is part of the quaternary centre. These examples showcased the versatility of the TA reaction of amides, as both products could be further employed to access tertiary chiral amines after subsequent carbonyl reduction.⁵¹

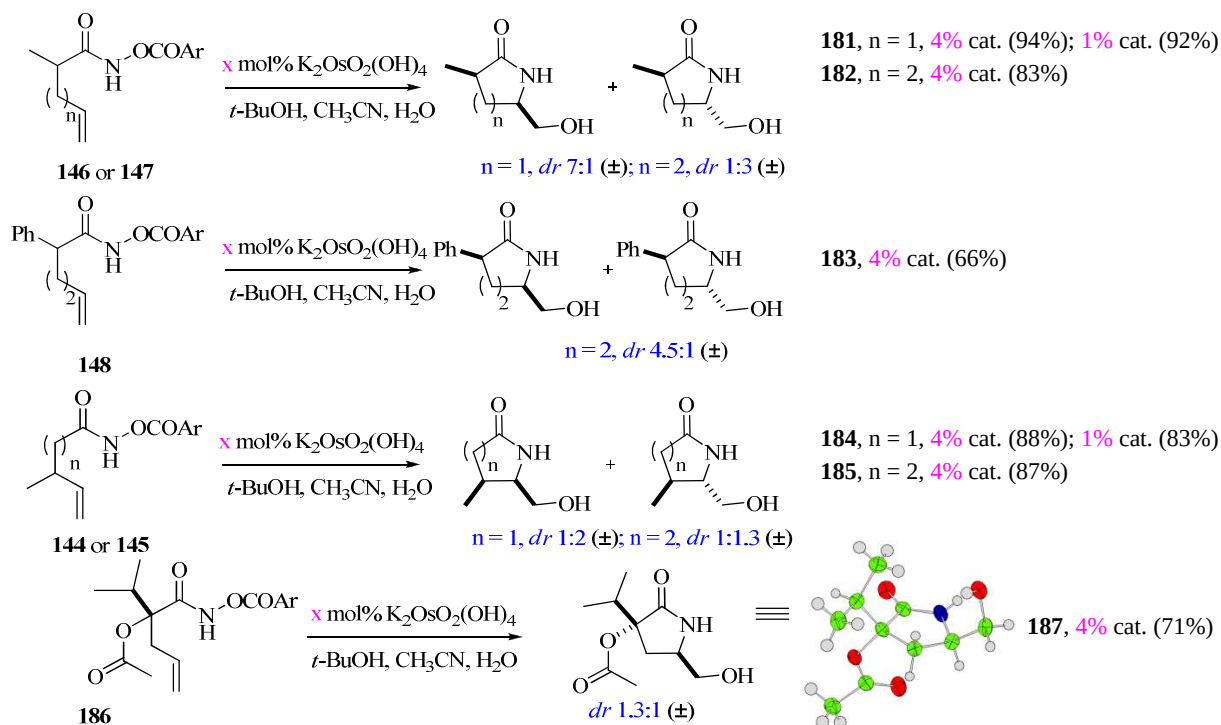
The scope of the methodology was also illustrated with cyclic alkenes **130**, **150** and **151** as suitable substrates as depicted in Scheme 49; the results clearly display the diastereoselective nature of the TA reaction.



Scheme 49 - Reactions of cyclic alkene substrates

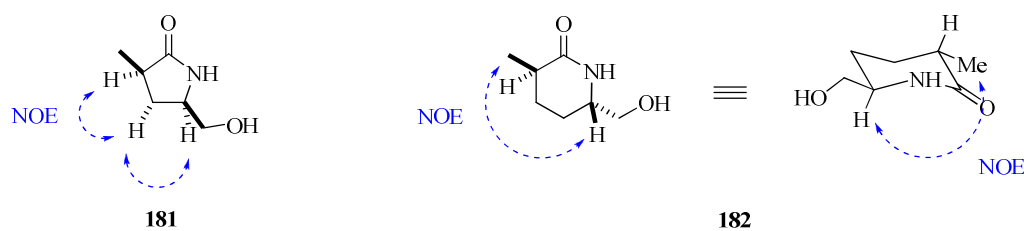
Bicyclic or even spiro-cyclic compounds were accessible through this highly efficient reaction. The relative stereochemistry of **159**, **179** and **180** were all confirmed unambiguously from the analysis of their X-ray crystal structures.

Finally, to complete the study, several substrates with various substitutions pattern on the backbone of the unsaturated carboxylic acids were tested in order to assert the level of acyclic diastereoselectivity achievable. A series of chiral acids were converted into the oxidation precursors and subjected to the TA reaction (Scheme 50).



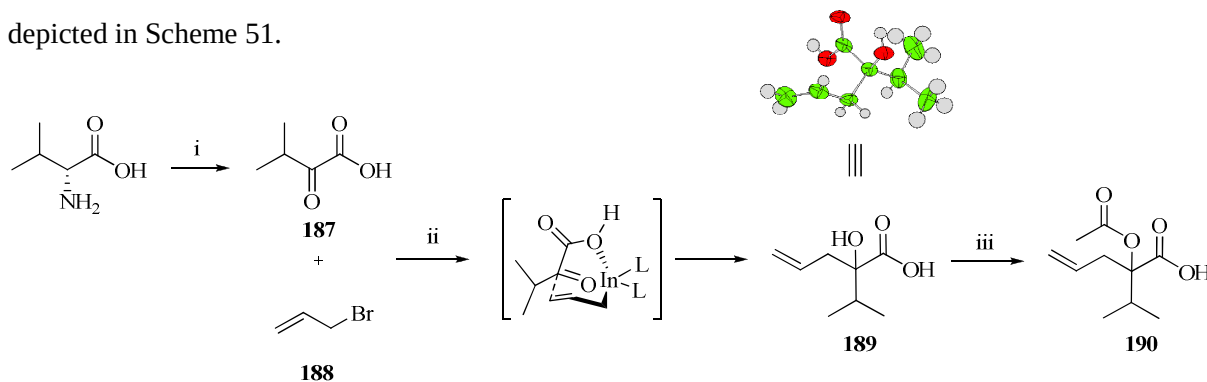
Scheme 50 - Diastereoselectivity study

Early studies showed that a methyl group adjacent to the carbonyl function gave moderate levels of diastereoselectivity for the *cis*-1,3-disubstituted pyrrolidinones **181** and *trans*-piperidinones **182**. The correct stereochemical assignment was made *via* NOESY experiments when possible and the rest assigned by analogy (Figure 9, see Annexe 1).

Figure 9 - Correct assignment by NOESY experiment for **181** and **182**

Exchanging this methyl substituent with phenyl in the alpha position to the carbonyl group provided a similar selectivity (see Scheme 50). However, moving the stereodirecting methyl group to an allylic position was not as successful and compounds **144** and **145** were formed with little selectivity (Scheme 50). After examination of these results, it was rationalised that steric hindrance was the main factor leading to this outcome. In addition to the scope of this methodology, the

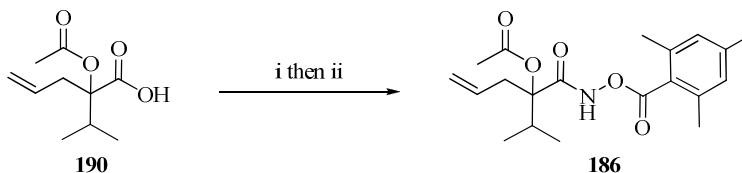
reaction conducted with **186** bearing a quaternary centre provided an interesting starting point for further studies on a highly substituted substrate. An elegant approach was employed en route to precursor **186** that underwent the tethered aminohydroxylation in 71% yield; this approach is depicted in Scheme 51.



Reagents and conditions: i) TFAC, 80°C, 30 min, 130°C, 30 min, NaOH (aq) 2 h, 88%; ii) Allyl bromide, In, THF-H₂O, 30°C, 16 h, 66%; iii) Acetyl chloride, CH₂Cl₂, rt, 16 h, 75%.

Scheme 51 - Indium-catalysed allylic mediated reaction

With **187** available from L-valine (analysis of ¹³C NMR spectrum confirmed the presence of the ketone signal at 198 ppm and the carboxylic acid signal at 169 ppm), an aqueous indium-mediated reaction was conducted to deliver **189**, which underwent subsequent acetylation to afford **190** in excellent yield.⁵² Carboxylic acid **189** structure was confirmed by X-ray crystallography analysis.



Reagents and conditions: i) (COCl)₂, CH₂Cl₂, NH₂OH·HCl, Na₂CO₃, rt, 12 h, then ii) 2,4,6-trimethylbenzoyl chloride, Et₃N, CH₂Cl₂, 0 °C, 35 min, 68% over two steps.

Scheme 52 - Synthesis of **186**

Compound **190** was then subjected to procedure A₁ (see Section 2.1.2) and subsequent acylation afforded **186** in 68% yield over two steps (Scheme 52). The characteristic 10.5 ppm NH signal in the ¹H NMR spectrum in conjunction with the IR spectroscopic stretch of the carbonyl function at 1684 cm⁻¹ were further evidence of its structure (see Section 2.1.3).

Consequently, mono-, di-, tri- and tetra-substituted alkenes were viable substrates through this methodology as well as terminal and internal alkenes.

2.1.7 Application to the synthesis of natural product cores

One noticeable advantage of this osmium based procedure was the complexity of some targets produced at the very last step through the TA reaction. To further highlight the potential of this methodology in accessing natural product templates, the focus was made on the synthesis of stemona alkaloids. Their roots and leaves are being used in traditional Chinese, Japanese and Thai medicines to treat respiratory disease and parasitic infestations. Besides, they also act as insecticides with antifeedent and repellent activities and are mainly used against the cotton leafworm and mosquitoes larvae providing a potential solution against the vectors of malaria (Figure 10).⁵³

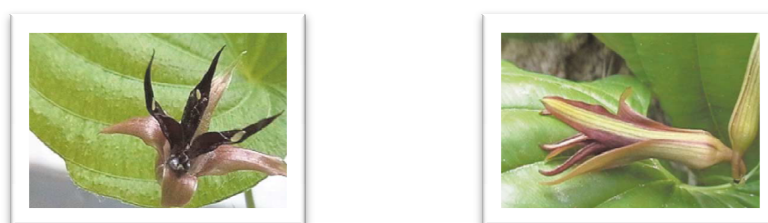
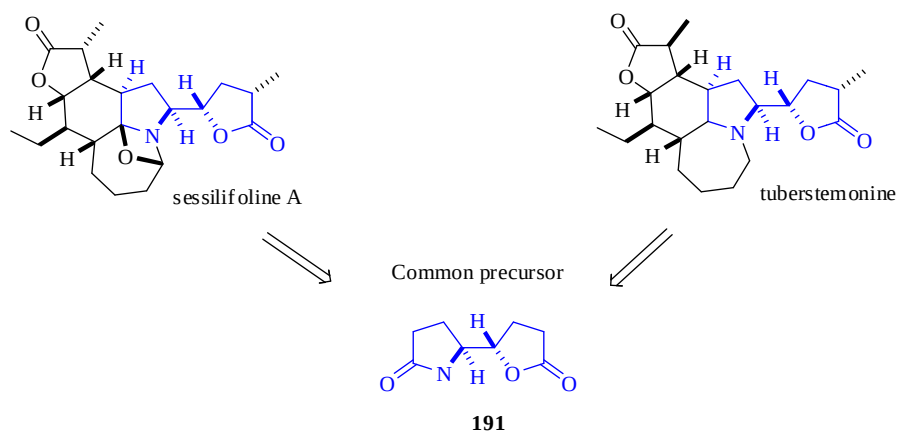
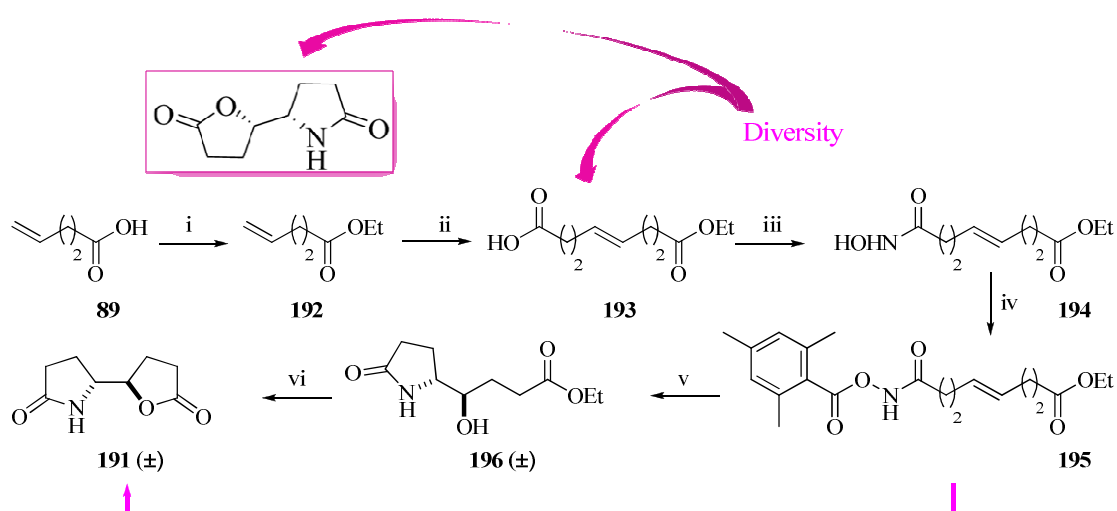


Figure 10 - Stemona alkaloids



Scheme 53 - Natural products isolated from stemona species

Therefore, sessilifoline A and tuberstemoninol were appealing targets for employing the current methodology and it was envisaged that both alkaloids could be synthesised from a common synthetic precursor **191** (Scheme 53). Indeed, this lactam-lactone **191** bicyclic system was accessible through the TA reaction and its synthesis has been carried out as a test of the current methodology (Scheme 54).

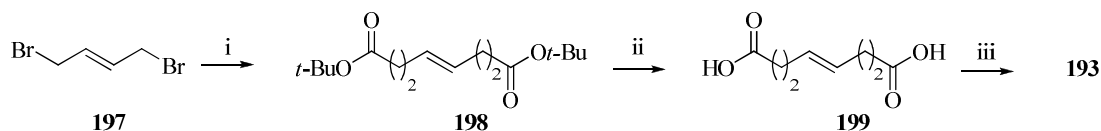


Reagents and conditions: i) (COCl)₂, EtOH, Et₂O, rt, 12 h, 94%; ii) pent-4-enoic acid, Grubbs II, CH₂Cl₂, 40 °C, 12 h, 51%, (*E*:*Z* ratio 8:1); iii) (COCl)₂, CH₂Cl₂, NH₂OH·HCl, Na₂CO₃, rt, 12 h, 78%; iv) 2,4,6-trimethylbenzoyl chloride, Et₃N, CH₂Cl₂, 0 °C, 35 min, 92%; v) 4 mol% K₂OsO₂(OH)₄, *t*-BuOH, CH₃CN, H₂O, rt, 14 h, 90%, vi) TFA, *t*-BuOH, CH₃CN, H₂O, rt, 10 h, 100%.

Scheme 54 - 31% overall yield for the synthesis of **191**

After cross-metathesis reaction between a large excess of hex-5-enoic acid **89** and one equivalent of ethyl pent-4-enoate **192**, alkene **193** was obtained in a moderate 51% yield with a good *E*:*Z* ratio of 8 to 1 (as determined by ¹H NMR spectrum analysis of the crude material). If these stemona alkaloids were picked in a lead generation stage, one could easily diversify the plausible toxicophore through the cross-metathesis step. **193** was then converted into the oxidation precursor **195** in 72% yield over two steps followed by the tethered aminohydroxylation which afforded compound **196** in an excellent 90% yield. IR spectroscopic analysis revealed the expected stretches for the amide (1681 cm⁻¹) and the ester (1728 cm⁻¹) functionalities. Then **196**, in the presence of a catalytic amount of trifluoroacetic acid, cyclised in a 5-*exo-trig* manner to give the desired lactam-lactone core **191** quantitatively as a colourless solid. The disappearance of the ester signal in the ¹H NMR spectrum as well as the observed shift in the IR spectroscopic stretch of the ester to 1772 cm⁻¹ were conclusive evidence regarding the correct structure assignment. This process was also carried out in a pseudo one-pot approach adding at the end of the TA reaction step, a catalytic amount of TFA. The overall yield in five steps for the synthesis of **191** was 31%.

An alternative approach to obtain compound **193** was through a three step sequence starting with commercially available 1,4-dibromobutene **197** to afford compound **193** in 38% yield as the sole *E* isomer (the alkene coupling constant of 15.2 Hz in this molecule was indicative of the *trans*-nature of alkene, Scheme 55).



Reagents and conditions: i) *t*-BuOCOME, LDA, THF, -78 °C, 10 h, 80%; ii) TFA, CH₂Cl₂, rt, 6 h, 92%; iii) (COCl)₂, EtOH, Et₂O, rt, 12 h, 53%.

Scheme 55 - Alternative approach for the synthesis of **193**

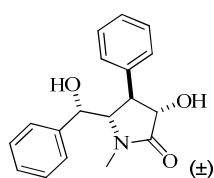
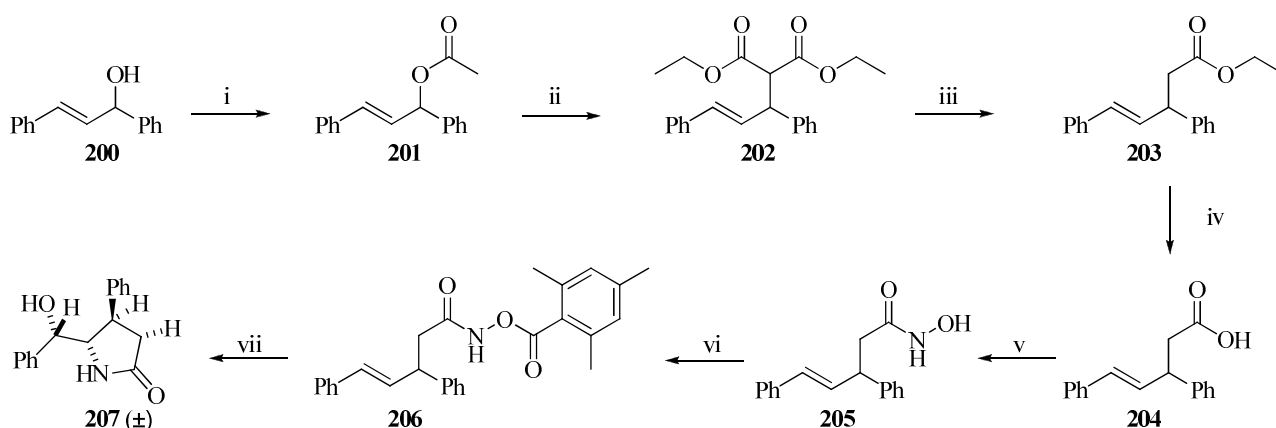


Figure 11

Another example highlighting the versatility of this methodology was the synthesis of a simplified analogue of epineoclausenamide (Figure 11), which among other benefits, provides significant protection against hepatotoxicity.⁵⁴



Reagents and conditions: i) Ac₂O, Et₃N, CH₂Cl₂, rt, 2 h, 84%; ii) [(Ph)₃P]₂PdCl₂, dppp, NaCH(COOEt)₂, rt, 10 h, 88%; iii) H₂O, DMSO, LiCl, reflux, 5 h, 67%; iv) NaOH, 60 °C, 4 h, 69%; v) (COCl)₂, CH₂Cl₂, NH₂OH·HCl, Na₂CO₃, rt, 16 h, 89%; vi) 2,4,6-trimethylbenzoyl chloride, Et₃N, CH₂Cl₂, 0 °C, 55 min, 71%; vii) 4 mol% K₂OsO₂(OH)₄, *t*-BuOH, CH₃CN, H₂O, rt, 22 h, 71%.

Scheme 56 - 15% overall yield for the core structure **207** of epineoclausenamide

From commercially available 1,3-diphenyl allyl alcohol **200**, only seven steps were required to access the core structure **207** of epineoclausenamide (Scheme 56). The readily obtained acylated product **201** was submitted to a Tsuji-Trost reaction to afford compound **202** in an excellent 88% yield. Analysis of ¹H NMR spectrum confirmed the presence of the diester moiety. Subsequent

Krapcho decarbonylation furnished compound **203**, which was then saponified to afford compound **204** (Spectroscopic data were consistent with those reported in the literature). Then, the current methodology applied to **204** afforded compound **205** in two steps with an overall 60% yield. The NH signal at 9.51 ppm in addition to the IR spectroscopic stretch of 1669 cm^{-1} of the carbonyl moiety were conclusive regarding its structure (see Section 2.1.3). Finally, through the TA reaction, the desired core structure of epinoclausenamide **207** was produced in 71% yield with high diastereoselectivity. Finally, NOESY experiment and X-ray crystal structure analysis confirmed unambiguously the relative stereochemistry of **207** (Figure 12).

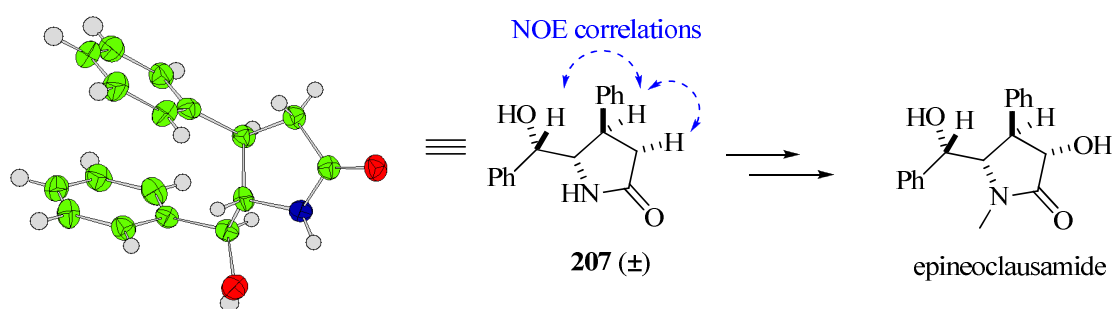
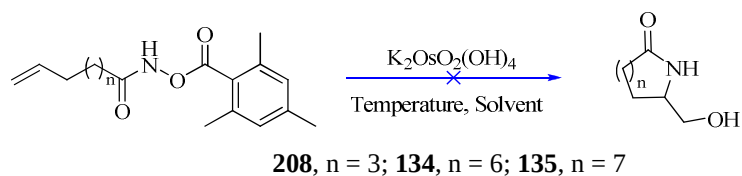


Figure 12 - X-ray crystal structure of **207**

It is noteworthy to mention that both enantiomers of epinoclausenamide should be easily accessible using chiral ligands during the palladium coupling step.

2.1.8 Conclusion and future work

The current methodology developed was limited to the synthesis of 4, 5- and 6-membered ring hydroxyl lactams. Indeed, the synthesis of 7, 10- or 11-membered ring was yet to be successful with only a trace of product observed (< 5%) in all cases (Scheme 57).

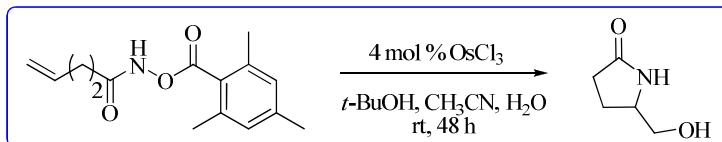


Scheme 57 - Unsuccessful attempts to synthesise medium to large rings

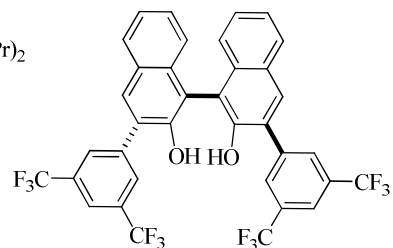
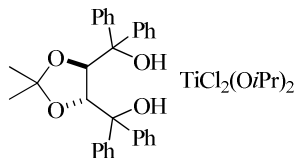
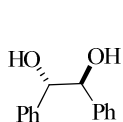
Moreover, the TA methodology bore one important limitation, which was the difficulty to render the process enantioselective. Initially, a screening was conducted on pent-4-enoic derivative **89**

(Scheme 58): chiral ligands belonging to the cinchona family, ligands known to block the secondary cycle, chiral transfer agents and even chiral 1,2-amino alcohols were tested.⁵⁵ Thanks to a chiral HPLC using an OD column at 215 nm, the splitting and distinct separation of the two enantiomers was achievable.

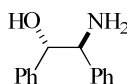
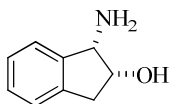
Ligand Screening



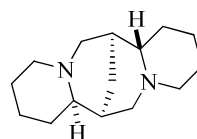
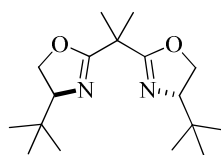
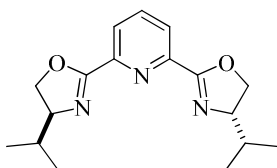
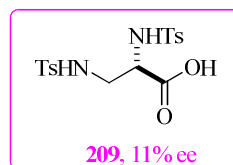
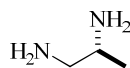
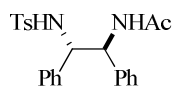
1, 2-Diols



1, 2-Amino alcohols

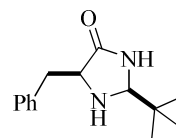
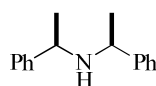
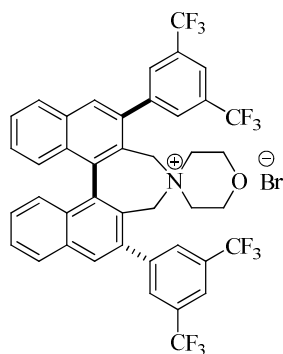


1, 2-Diamines

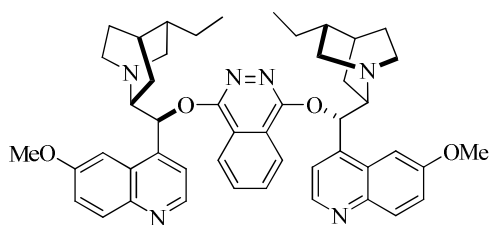


Pincer ligand

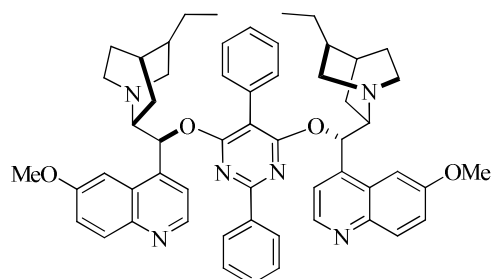
Phase transfer agent



Secondary amines



cinchona family

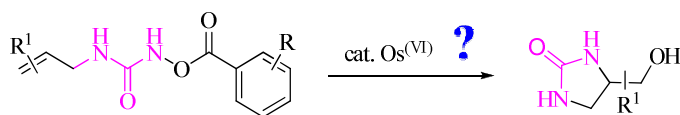


Scheme 58 - Screening of chiral ligands resulting in racemic product

Disappointingly, the outcome of the screening was negative except for **209** which induced a weak enantiomeric excess (average of three runs). The structure of **209** was familiar and related well to TMEDA that was used to coordinate and trap out a key osmium intermediate (see Section 2.1.4). With this result in hand, the design of a chiral ligand specific to the TA own characteristics became evident: being an intramolecular process, the elected ligand should be strong enough to bind to the osmium metal and weak enough to release the newly synthesised 1,2-amino alcohol product. Further studies would be required to synthesise such a ligand.

2.2 Osmium-catalysed urea series: the use of a nitrogen tether

With the successful application of this third generation of reoxidant for osmium to the amide series (see Section 2.1), it was decided to further extend the scope to the urea derivatives (Scheme 59).

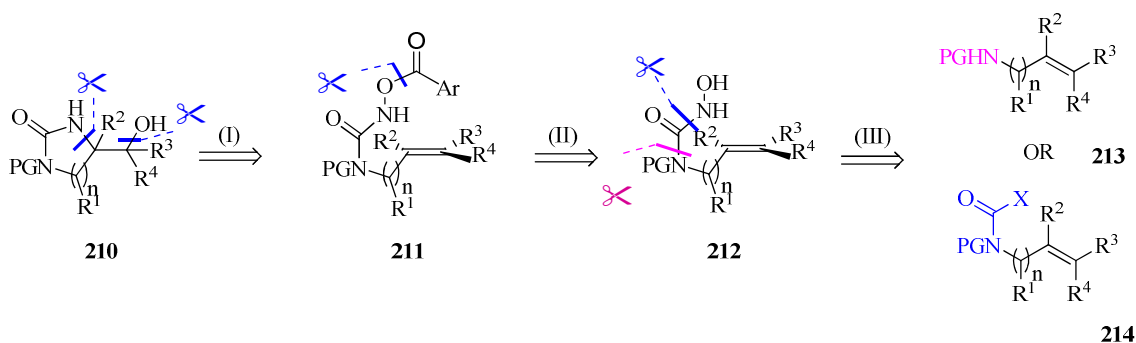


Scheme 59 - Extending the scope of the TA for urea derivatives

Although not often present in Nature, this urea motif would give access to versatile compounds and add an extra tool for the organic chemist. To explore the feasibility of this approach, a retrosynthetic analysis was carried out.

2.2.1 Retrosynthesis

This retrosynthesis also involved three main disconnections.



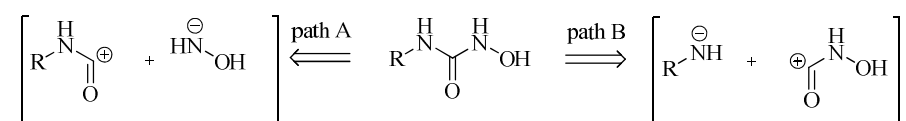
Scheme 60 - Retrosynthetic analysis

Starting with hydroxyl urea **210**, the first disconnection (I) would come from the tethered aminohydroxylation providing **211** intermediate bearing the reoxidant function as well as a pendant alkene. Further disconnection (II) would lead to 1-allyl-3-hydroxyurea derivatives **212**. It was anticipated that two possibilities emerged for the introduction of the *N*-hydroxy urea moiety (disconnection III, Scheme 60) affording either **unsaturated amines 213** or their **preactivated species 214**.

Allylic or homoallylic amines **213** were either commercially available or readily accessible via common organic reactions such as the Overman rearrangement, the Tsuji-Trost reaction or even by simple nucleophilic substitution.⁵⁶

2.2.2 Synthesis of the *N*-hydroxy urea moiety - Disconnection (III)

Two potential disconnections considered (path A and B) would relate to the reagent equivalents depicted in Scheme 61.



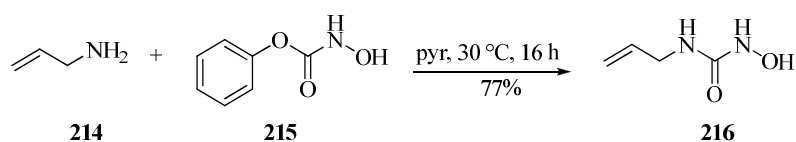
Scheme 61 - Proposed synthons for the synthesis of **212** moiety

2.2.2.1 Investigation towards Route A

Initially, route A was investigated. It was anticipated that **213** amines would require preactivation prior to their reaction with a hydroxylamine derivative (Scheme 61). However, it became rapidly evident that this two-step procedure and the necessity to use reactive reagents such as triphosgene would be difficult to improve. Moreover, these reagents limited the functionalities on the amines substrates **213**. The lack of significant results directed the research towards route B where early experiments were encouraging.

2.2.2.2 Investigation towards Route B

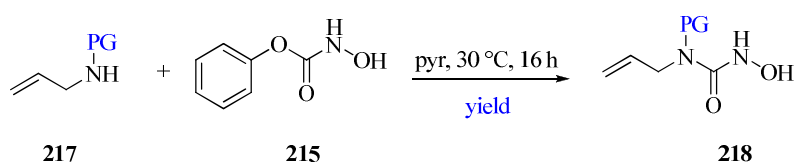
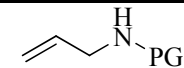
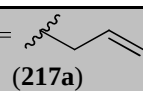
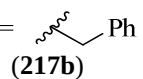
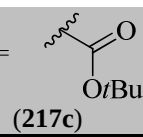
Research into the introduction of *N*-hydroxyurea motif has been limited to a handful of publications. Furthermore, a literature search on a one pot procedure using unsaturated amines resulted in one hit.⁵⁷



Scheme 62 - Initial conditions

Repeating the literature procedure for the primary allylic amine **214** in the presence of phenylhydroxycarbamate **215** employing pyridine as the solvent did provide analogous results

affording **216** in a good 77% yield (Scheme 62).⁵⁷ The spectroscopic data of **216** were consistent with those reported in the literature. Phenylhydroxycarbamate **215** was synthesised from commercially available phenylchloroformate and hydroxylamine chloride (see Experimental section, Chapter 5 for detailed procedure). With this procedure available, the screening of secondary protected amines **217** was investigated in order to expand the scope of viable substrates (Table 12).

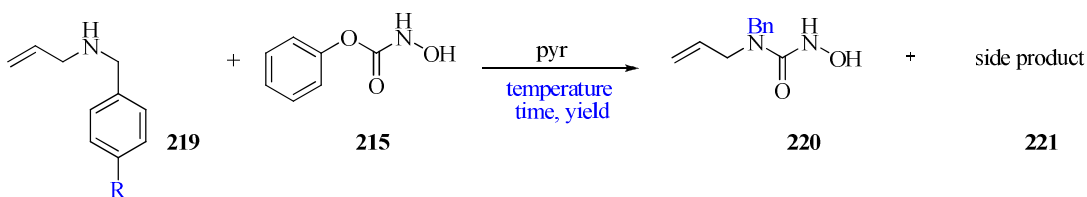
		
217	215	218
Entry		Yield of 218 ¹
1	PG =  (217a)	30% (218a)
2	PG =  (217b)	Traces of desired product ²
3	PG =  (217c)	No reaction ²

¹Isolated yield, ²Recovery of starting material **217**

Table 12 - Protecting group screening

However, the reaction gave poor yields with recovery of starting material **217** when secondary amines having an allyl, benzyl or Boc protecting group were employed. This disappointing result was anticipated for entry 3 where the steric hindrance and electron withdrawing effect of the carbamate would deactivate the nucleophilicity of the amine substrate **214**.

In an effort to improve this outcome and thus to expand the methodology substrate scope, it was postulated that an increase of the reaction temperature (above 30 °C) would favour the formation of the desired *N*-hydroxyurea **218**. Initial investigations were conducted on *N*-benzyl allylic amine **219** as it was rationalised that tuning the electronic nature of the aromatic group could influence positively the process (Table 13).



Entry	Compounds	Conditions		
		30 °C, 16 h	60 °C, 24 h	Reflux, 12 h
1	219a (R = H)	traces of desired product	(ratio 2:1:1)	(ratio 2:2:1)
2	219b (R = NO ₂)	product	desired product 220 (40%)	desired product 220 (30%)
3	219c (R = Br)	for R = Br, 11% (220c)	side product 221	side product 221
4	219d (R = OMe)		recovery of 219	recovery of 219

General conditions: pyridine (1 mL·mmol⁻¹), 1 eq. phenylhydroxycarbamate **215**

Table 13 - Exploiting the temperature and substrate influence

All the reactions set in this series thus far were eminently amenable to the sole formation of *N*-hydroxyurea derivative **220**. However, the strategy of increasing the temperature and tuning the electronic nature of substrate **219** to promote the reaction was met with partial success as the desired *N*-hydroxyurea derivative **220** was obtained with concomitant side product **221** formation. Furthermore, complete conversion of *N*-benzyl allylic amine **219** to **220** was never achieved with partial recovery of starting material.

In an effort to better understand the process, investigations to identify this undesired side product **221** were carried out. Initially, NMR spectroscopy data were analysed. Analysis of the ¹H NMR spectrum revealed the presence of (CH₃CHXCH₂-) and (PhCH₂-) residues confirmed by a ¹H-¹H COSY experiment. Furthermore, it was suggested that side product **221** had the urea motif embedded in his structure with a distinct 164.8 ppm signal in the ¹³C NMR spectrum and a 1717 cm⁻¹ stretch in the IR spectroscopy spectrum. Moreover, the result of an HSQC experiment was in accordance with previously reached conclusion regarding the presence of (CH₃CHXCH₂-) and (PhCH₂-) residues. Interestingly, the value obtained by mass spectroscopy measure *m/z* (ESI⁺) was 206, the exact molecular weight of the expected *N*-hydroxyurea **220**. Taking all this information into account, it was rationalised that the side product **221** structure was of 1-benzyl-3-hydroxy-4-methylimidazolidin-2-one as depicted in Figure 13.

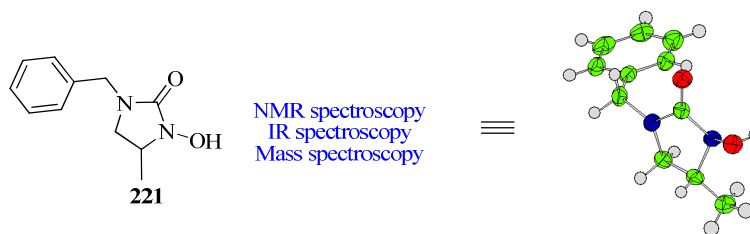
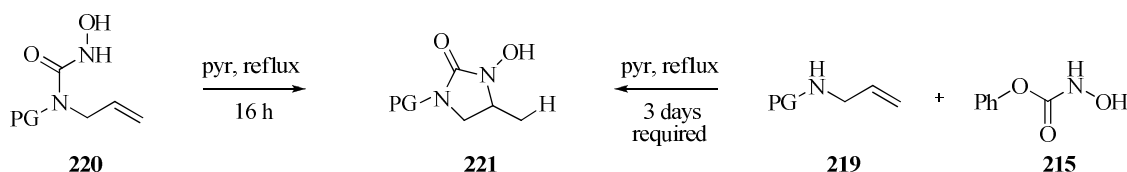


Figure 13 - Suggested side product **221** structure

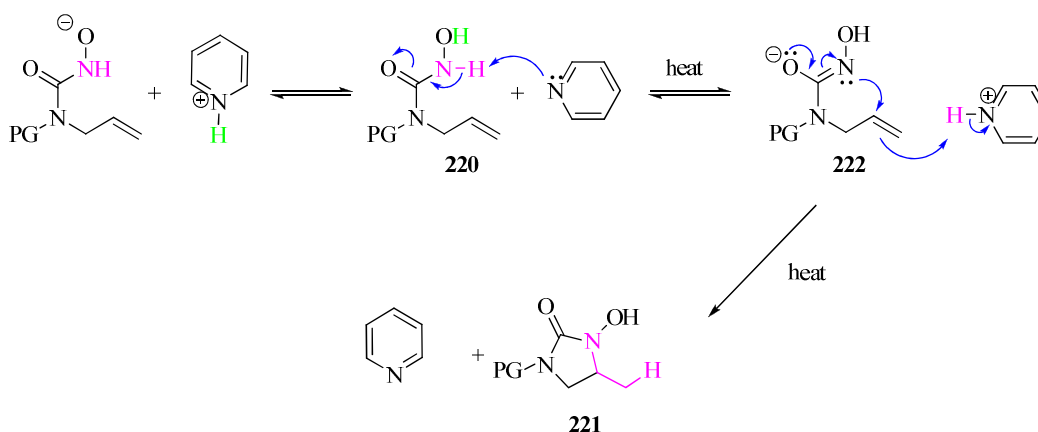
However, this proposed structure has never been reported in the literature and still bore uncertainty especially regarding the *N*-hydroxy motif. After exhaustive efforts, a suitable solvent system was found and enabled the growth of crystals of sufficient quality to perform a crystallographic analysis. Most gratifyingly, the resulted X-ray structure was in accordance with imidazolidinone structure **221**.

Interest arose from the discovery of this unexpected compound. It was then postulated that for this side reaction to proceed, it required the initial formation of **220**. Therefore, in order to establish whether imidazolidinone **221** stemmed directly from the starting material **219** or **220**, two experiments were conducted (Scheme 63).



Scheme 63 - Synthetic origin of **221**

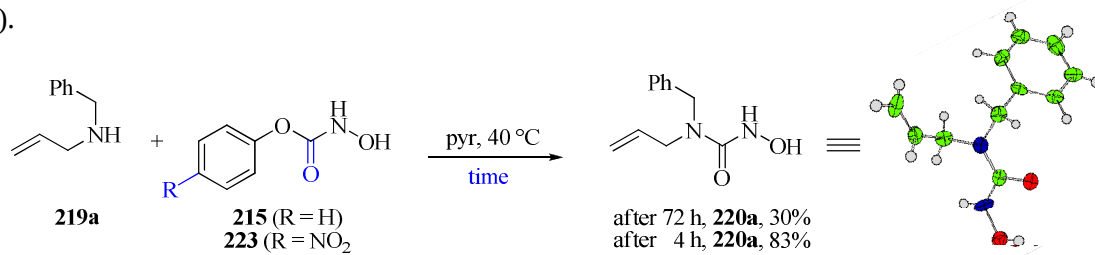
Building on these results, it was concluded that **221** did originate from initially desired product **220** and a proposed mechanism depicted in Scheme 64 was postulated.



Scheme 64 - Proposed pyridine catalysed hydroamination mechanism

It was postulated that since heating was compulsory for side product **221** to be produced, the reaction would be driven forward when deprotonation of **220** occurred at the **nitrogen position**. Upon deprotonation, a subsequent 5-*exo-trig* cyclisation onto the pendant alkene could then be suggested from intermediate **222** leading to imidazolidinone **221**. Therefore, **221** might be synthesized in what could formally be described as a pyridine-catalysed hydroamination reaction. Literature investigations on similar substrates led to a unique complementary gold-catalysed procedure.⁵⁸

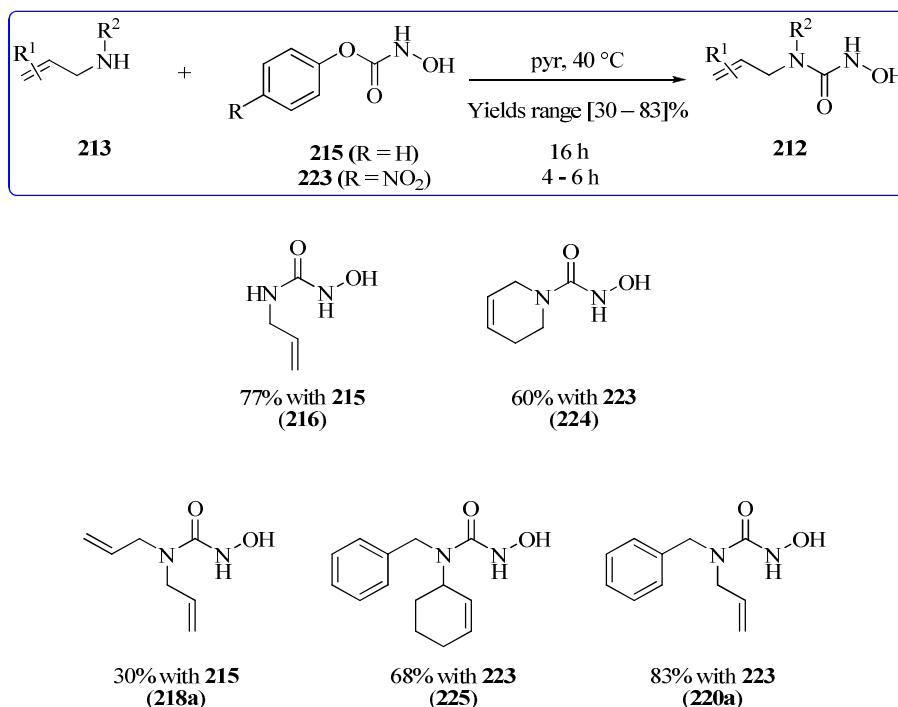
As it became apparent that the formation of this imidazolidinone side product would be difficult to avoid upon conducting the reaction at elevated temperature, it was postulated that tuning the reactivity of phenylhydroxycarbamate reagent **215** was worth investigating. Indeed, it was rationalised that increasing the electrophilicity of the hydroxycarbamate carbonyl centre **215** would enable the reaction to be conducted at lower temperature preventing any side product formation (Scheme 65).



Scheme 65 - Exploiting the reactivity of the *p*-nitrohydroxycarbamate **220a**

Finally, using the conditions outlined in Scheme 65, the introduction of the *N*-hydroxyurea motif proceeded in very good yields when the *p*-nitro derivative of phenylhydroxycarbamate **223** was employed (see Experimental section, Chapter 5 for its detailed synthesis). The correct structure assignment of product **220a** was confirmed by the NH peak on the ¹H NMR spectrum at 7.94 ppm, the IR spectroscopy stretch of the carbonyl of this urea derivative at 1651 cm⁻¹ and finally by the study of the relevant X-ray crystal structure. It is noteworthy that even with a prolonged stirring (> 3 days), the control experiment (R = H) failed to reach total conversion with no sign of side-product **221a**.

This procedure was successfully applied to several allylic amines **213** as depicted in Scheme 66.

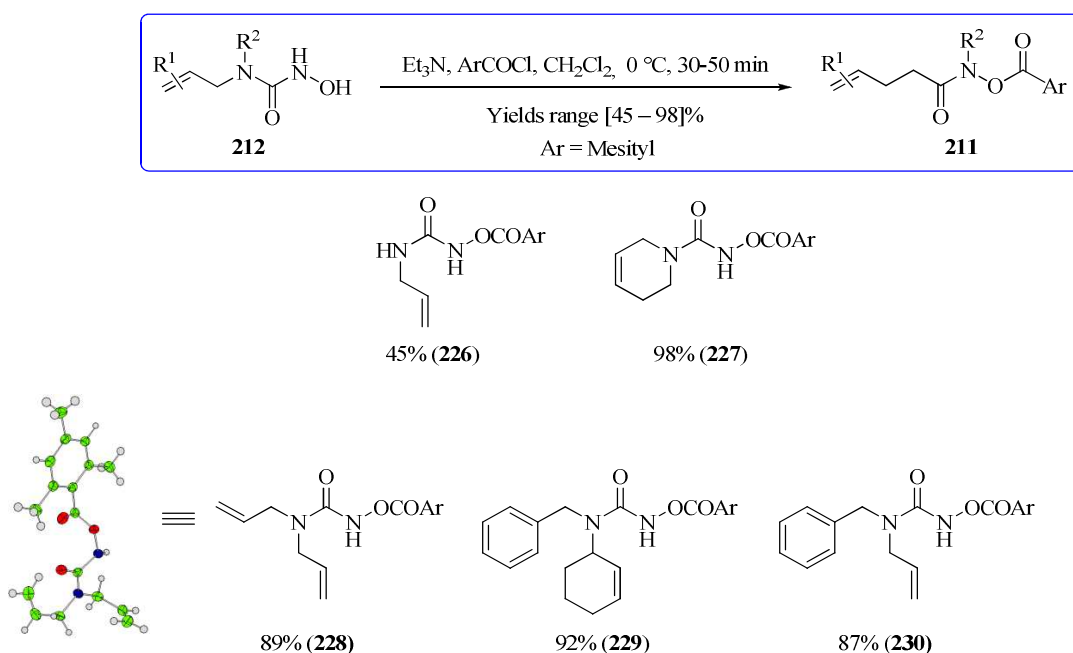
Substrate scope**Scheme 66** - Summary of the synthesised *N*-hydroxy urea derivatives

Regarding urea derivatives **212**, in each case the correct structure assignment was established partly with their carbonyl stretch in the IR spectroscopy spectrum ranging between 1660 and 1653 cm⁻¹ and the characteristic NH signal peak on their ¹H NMR spectrum ranging from 7.5 to 7.8 ppm. These spectroscopic data were in complete accordance with compound **220a**, which had been identified by an X-ray crystal structure. Hence, these urea derivatives **212** were taken to the subsequent acylation step.

2.2.3 Acylation of the *N*-hydroxy urea derivatives - Disconnection (II)

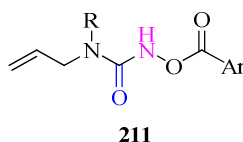
Using the similar protocol established for the amide series, acylation of these *N*-hydroxy urea derivatives **212** was efficient and excellent yields were delivered (Scheme 67).

Substrate scope



Scheme 67 - Summary of the precursors synthesised for the tethered aminohydroxylation

Regarding the acylated urea derivatives **211**, the correct structure assignment was established partly by their **carbonyl stretch** in the IR spectroscopy ranging between 1673 and 1684 cm^{-1} and the characteristic **NH signal peak** on their ^1H NMR spectrum ranging from 8.5 to 8.8 ppm. These similar spectroscopic data were in complete accordance with compound **228**, which had been identified by an X-ray crystal structure.

Figure 14 - Correct assignment of acylated N-hydroxy urea derivatives **211**

2.2.4 Tethered Aminohydroxylation (TA) of urea derivatives - Disconnection (I)

With those acylated N-hydroxy urea derivatives **211** in hand, the tethered aminohydroxylation was investigated (Table 14).

Entry	Compound	R	R ₁	Conversion ¹	Isolated yield
1	226	Allyl	H	No reaction	
2	227			100%	No isolated product
3	228	Allyl	Allyl	100%	~68% (1:1) ² (232)
4	229		Benzyl	No reaction	
5	230	Benzyl	Allyl	85%	~49% (1:1.5) ² (233)

¹The conversion was determined from the ¹H NMR spectrum of the crude material

²Isolated mixture of two products, yield corrected after identification of by product

Table 14 - Substrate scope investigation in the tethered aminohydroxylation

Initially, it was observed that the complete consumption (entry 2, 3 and 4) *via* the TA reaction of these acylated *N*-hydroxy urea derivatives **211** was twice as fast as the amide series halving the reaction time when employing as low as 1 mol% of potassium osmate. It was envisaged that oxidative species **236** involved in the catalytic cycle was more electron rich than **234** and **235** facilitating the [3+2] cycloaddition onto the alkene (Figure 15).

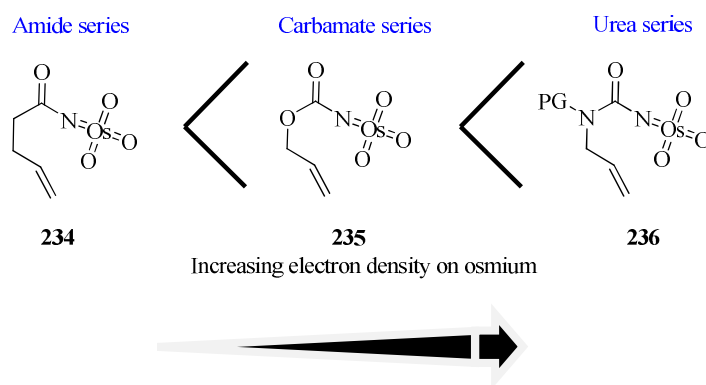
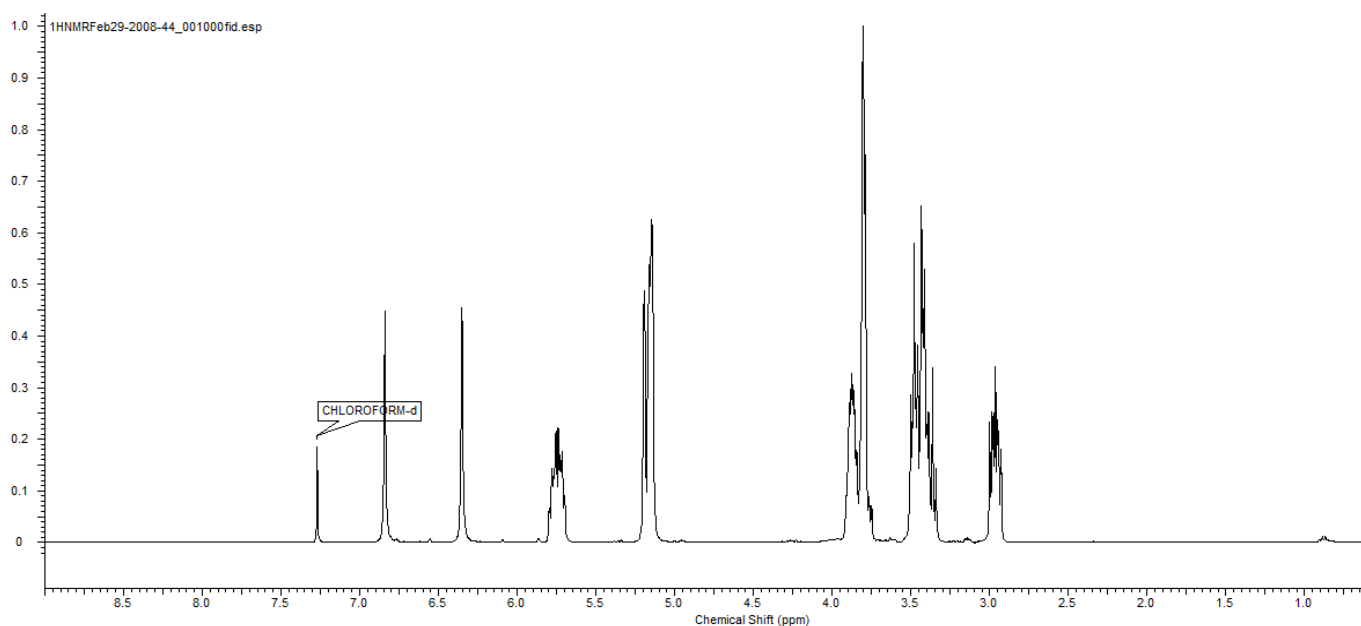


Figure 15 - Reactivity related to the electronic nature of the osmium intermediate

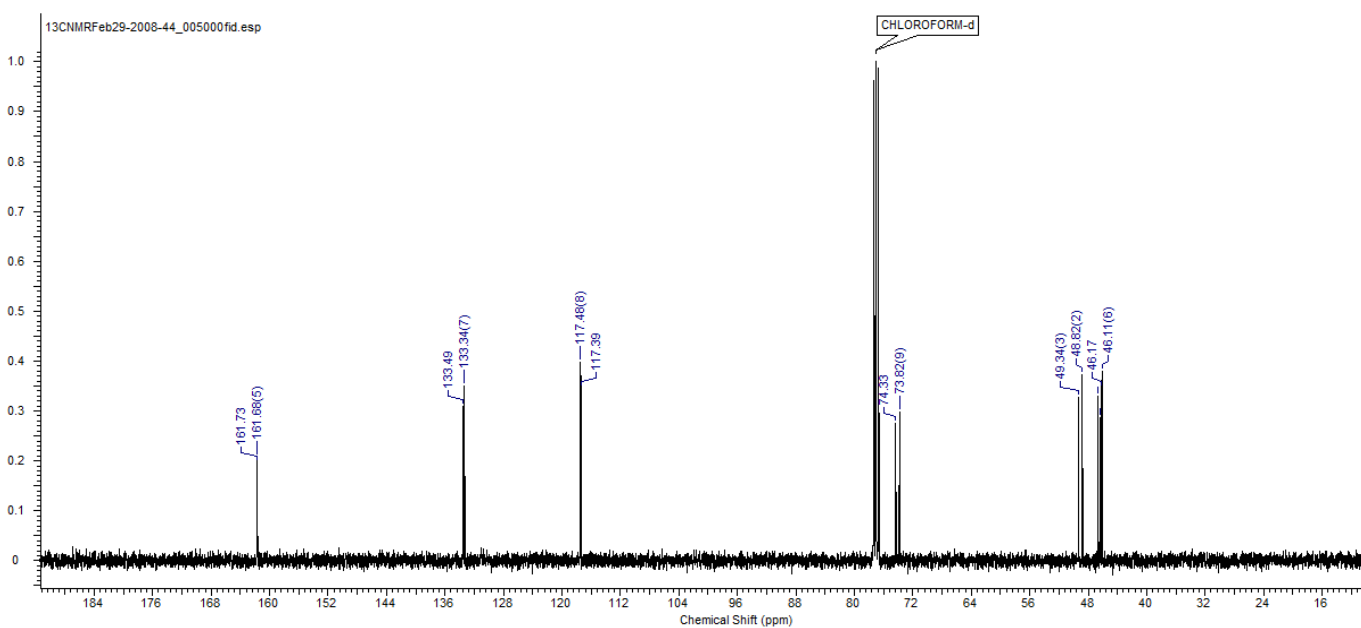
However, examination of Table 14 revealed several limitations for this series. The reactivity in this series was hampered by the narrow window of tolerated protecting group present on precursors **211**.

Indeed, while urea precursor **226** bearing an unprotected NH bond (Table 14, entry 1) failed to react under the standard TA conditions, sterically challenging derivative **229** (Table 14, entry 4) also stalled the process with complete recovery of starting material in both cases. It was postulated for entry 1 that the lone pair of the unprotected secondary nitrogen of **226**, by coordinating to the osmium catalyst in the key intermediate **236** would prevent a correct orbital alignment to occur. This hypothesis was partly confirmed when its protection afforded the desired product (Table 14, entry 3 and 5). Furthermore, in each instance, the synthesis of **232** and **233** required a difficult silica chromatographic separation. Indeed, their high hydrophilicity became an inherent problem in the purification of this series. Another problem arose with the actual identification of the products obtained. The exact yields for entry 3 and 5 could not be ascertained due to an unidentified side product **231**, which ran closely to the desired products **232** and **233**, leading to their contaminations in a ratio determined by the analysis of the ^1H NMR after column chromatography. The value obtained by mass spectroscopy measure m/z (ESI^+) indicated in each case the presence of compound **232** and **233** respectively but their complete isolation proved to be difficult. In an effort to better understand the process, investigations to identify side product **231** were carried out. Initially, NMR spectroscopy data were analysed (Figure 16 and 17).



δ_{H} (400 MHz, CDCl_3) 6.84 (1H, s), 6.35 (1 H, s), 5.68-5.81 (1H, m), 5.09-5.23 (2H, m), 3.87 (1H, m), 3.80 (2H, m), 3.45-3.54 (1H, m), 3.37-3.45 (2H, m), 2.91-3.03 (1H, m)

Figure 16 - ^1H NMR spectroscopy of **232** mixture



δ_{C} (100 MHz, CDCl_3) 161.73, 161.68, 133.5, 133.3, 117.5, 117.4, 74.3, 73.8, 49.3, 48.8, 46.6, 46.4, 46.2, 46.1

Figure 17 - ^{13}C NMR spectroscopy of **232** mixture

Upon analysis of the ^1H and ^{13}C NMR spectra obtained for **232** in deuterated chloroform, it became evident that structure wise, both products **231** and **232** were closely related. Indeed, all peaks were doubled in both spectra. It was then suggested that rotamers could account for these twin sets of

signals.⁵⁹ Another possibility envisaged was dimer adducts resulting from strong hydrogen bonding between two parent molecules as depicted in Figure 18.⁶⁰

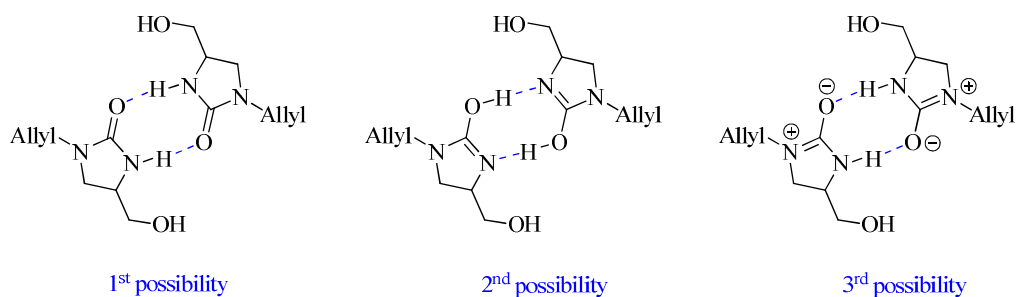


Figure 18 - Hydrogen pairing adduct

Eventually, our last hypothesis not to be protracted for this NMR observation was the dimerisation of the desired hydroxyl urea **232**. This would also account for a reasonable explanation regarding the presence of these twin sets of peaks. In order to explore these rationales, several spectroscopic analyses including *infra* red and mass were carried out. Unfortunately, the incapacity to explicitly determine the structure of this side product through NMR analysis, led to a thorough column chromatography purification cycle including several recrystallisations in order to finally obtain the side product in pure form but small quantity. Performing an X-ray crystallographic analysis to determine the exact structure was highly desirable and after exhaustive efforts, X-ray quality crystals of the co-product could finally be grown.

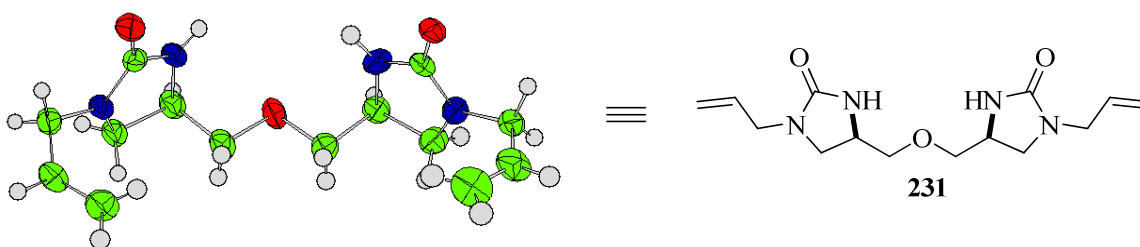
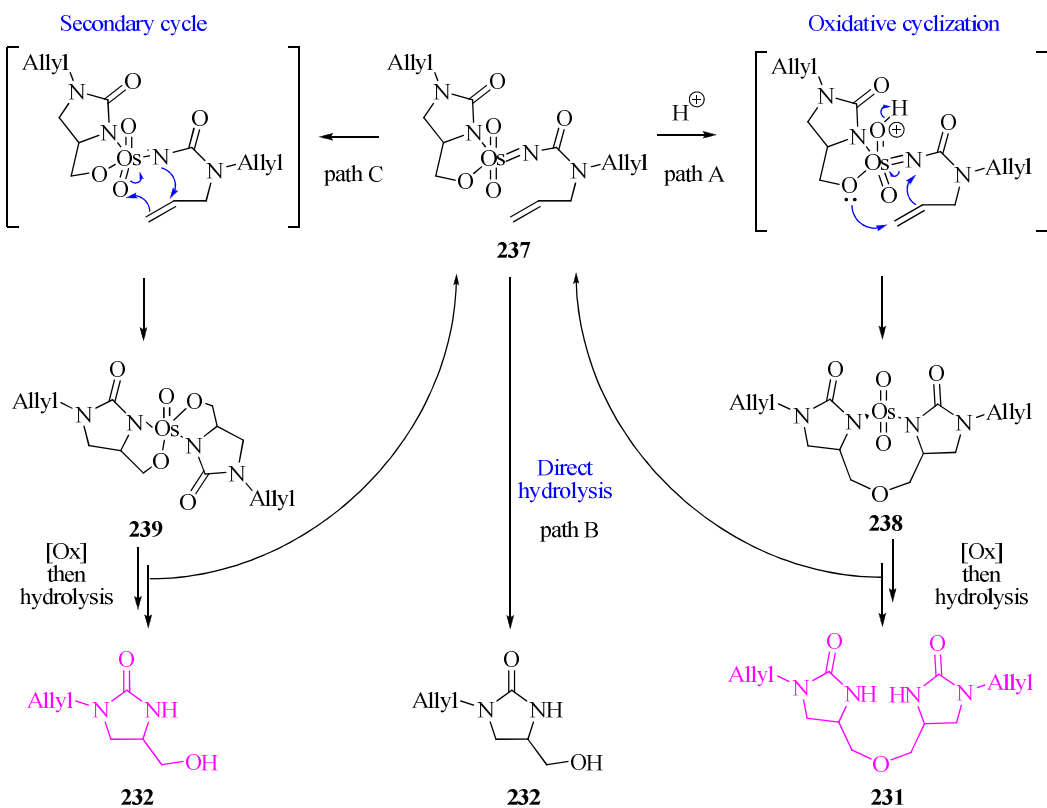


Figure 19 - X-ray crystal structure of **231**

Most gratifyingly, the resulting X-ray crystal structure analysis formerly identified the side product as the dimer of **232** validating one of our hypotheses (Figure 19). However, the ratio of diastereomers of **231** could not be determined and remained to be fully investigated. Furthermore, full spectroscopic characterisation of compound **232** would require more material isolation.

Building on these results, it was speculated that **231** might originate from intermediate **238** and a proposed mechanism depicted in Scheme 68 was postulated.



Scheme 68 - Plausible pathway for the formation of the dimer **231**

It was suggested that the formation of dimer **231** could be the result of an osmium oxidative cyclisation (path A) promoted by the acidity of the carboxylic acid released during the reaction. Intermediate **238** would then undergo hydrolysis to afford **231**. This oxidative cyclisation process has been extensively described in recent papers.⁶¹ Nevertheless, this pathway would be in competition either with the direct hydrolysis (path B) of **237** or with a second tethered aminohydroxylation process leading to intermediate **239** (path C) before subsequent hydrolysis.

2.2.5 Conclusion and future work

A route into cyclic hydroxyl urea framework was explored with varying degree of success. Although the access to acylated *N*-hydroxy urea **211**, precursors for the osmium catalysed step, was rendered possible in two steps starting with unsaturated amines **213**, the tethered aminohydroxylation of these was hampered by dimerisation of the desired product and its isolation. It is important to stress that further investigations would need to be carried out in order to favour

the formation of **232** over its dimer for the aminohydroxylation of urea derivatives to become a viable process. At this stage, the lack of control of the TA reaction with the dimer **231** formation, as well as the difficulty to isolate **232** as a single compound are critical issues.

It is noteworthy that efforts during the introduction of the *N*-hydroxy urea moiety led to the discovery of an unprecedented side reaction that would surely find applications in the near future.

2.3 Conclusion for intramolecular processes

The tethered aminohydroxylation of amide derivatives have successfully been applied to access valuable hydroxyl lactam scaffolds in one step using an osmium based procedure.⁶² This process was made possible *via* the use of the third generation of reoxidant for osmium based on a key hydroxylamine bond. The latter has demonstrated its utility to promote an efficient oxidation of osmium(VI) to osmium(VIII) leading to valuable scaffolds from easily accessible starting material. Furthermore, the wide range of viable alkene substrates expanded the potential applications of this methodology. Nevertheless, the method suffers from the lack of significant results when exploiting chiral reagents for enantioselective oxidations and future work should focus on the asymmetric variant.

Although this procedure was not as successful in the urea series, this reaction has potential and it was encouraging to formally identify by X-ray diffraction an unexpected dimer product, which may have use in the future.

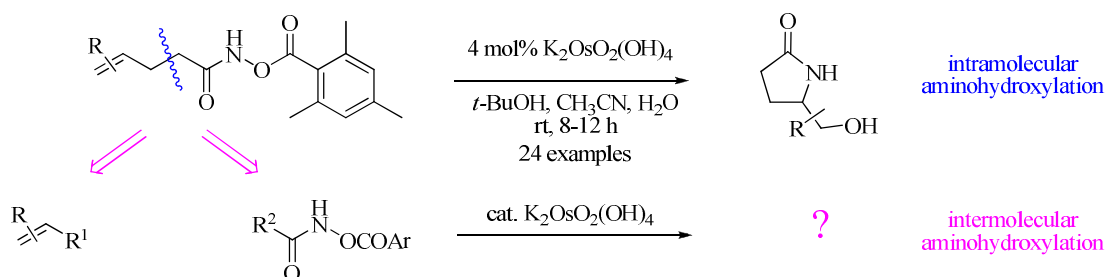
During the course of this study, examination of these acylated hydroxyenamides as nitrogen source precursors revealed at least one point of expansion: being shelf stable and easy to handle contrary to *N*-bromoamides (see Introduction), they should find applications in the intermolecular aminohydroxylation reaction. This is addressed in the following chapter.

Chapter 3

Investigations towards an intermolecular process

3. Investigations towards an intermolecular process

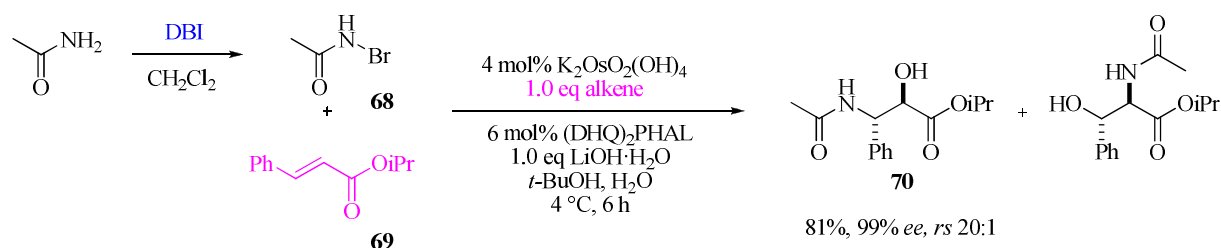
To further expand the scope of this novel type of reoxidant for osmium, an attempt to carry out the aminohydroxylation reaction in an intermolecular fashion was investigated (Scheme 69).



Scheme 69 - Investigations towards an intermolecular process

3.1 Introduction

Exploiting the key results obtained for amide derivatives in the tethered aminohydroxylation (see Section 2.1.6), the next step was to compare its efficiency against the acetamide version used by Sharpless *et al.* in 1997. In their studies, primary amides needed to be preactivated (as the *N*-bromoderivative) for the reaction to proceed.^{17e,f} This operation was achieved through the use of dibromoisocyanuric acid (DBI) acting as a mild brominating agent in dichloromethane (Scheme 70).



Scheme 70 - *N*-bromoacetamide as a nitrogen source

The osmium-catalysed reaction of *N*-bromoacetamide **68** with isopropyl cinnamate **69** afforded **70** as the major regioisomer in excellent yield and enantioselectivity. However, the main drawback of this procedure, as previously mentioned, were the difficulty in purifying the *N*-bromoamide reagents and the critical storage conditions required to avoid their degradation (air and light

sensitive). Finding an alternate solution is therefore desirable and the answer could be delivered through our third generation of reoxidant. Indeed, these had a proven shelf-life stability of at least three years (Figure 20).

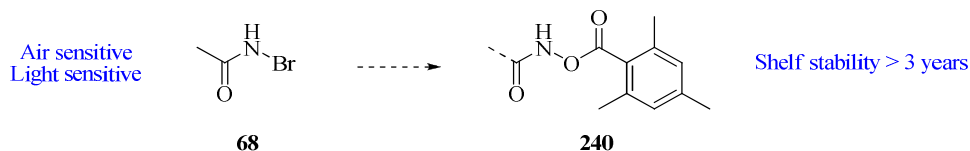
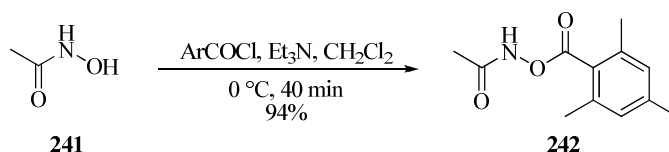


Figure 20 - Alternates to *N*-bromoacetamide **68**

Additionally, the substitution tolerated on the nitrogen source might be greatly expanded. To this end, **242** was synthesised in order to explore this rationale (Scheme 71).



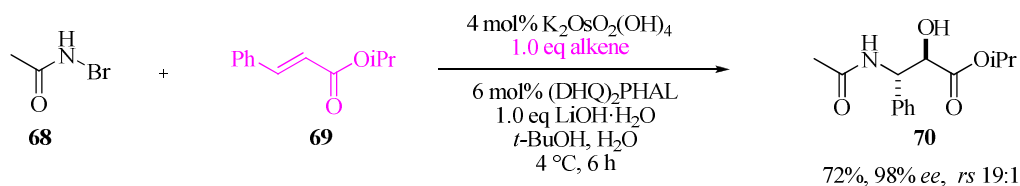
Scheme 71 - Synthesis of **242**

Following the procedure established in Chapter 1, commercially available *N*-hydroxyamide **241** was acetylated to afford product **242** in an excellent 94% yield. The characteristic 9.29 ppm NH signal in the ¹H NMR spectrum in conjunction with the IR spectroscopic stretch of the carbonyl at 1657 cm⁻¹ were further evidence of its structure (see Section 2.1.3).

3.2 Preliminary results

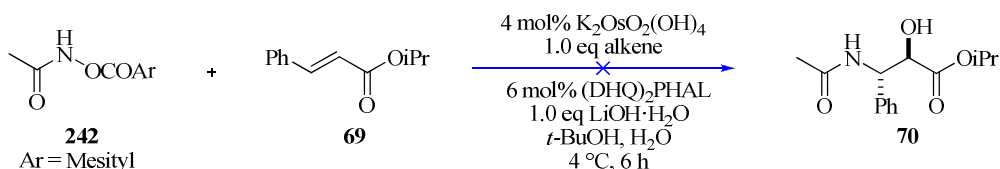
3.2.1 *N*-bromoacetamide methodology

In order to compare the reactivity of these two reoxidants, the decision was taken to reproduce first the experiment using the conditions outlined in Scheme 70, employing *N*-bromoacetamide **68** as the nitrogen source (Scheme 72).



Scheme 72 - Attempts to reproduce the *N*-bromoacetamide methodology

As expected, 1,2-amino alcohol **70** was obtained in good yield albeit lower than the one reported. It was understood that strict temperature control was important to achieve reproducibility. In a subsequent experiment, **242** was submitted in place of *N*-bromoacetamide **68** to determine whether our reoxidant could act as a surrogate in the intermolecular aminohydroxylation (Scheme 73).

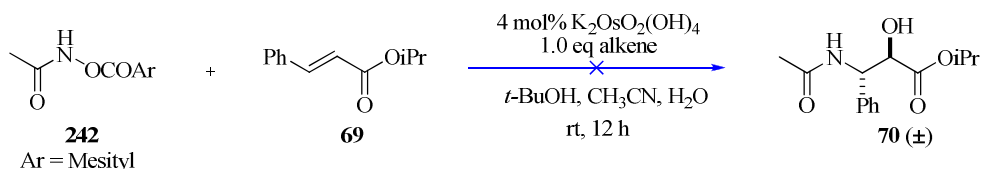


Scheme 73 - Initial attempt with **242**

Surprisingly, this initial attempt resulted in the recovery of both starting materials **69** and **242** with only traces of **70** isolated. Moreover, conducting the reaction at room temperature did not improve the result. It was then envisaged to carry out the reaction under the tethered aminohydroxylation experimental conditions to ensure that no obvious solution was missed.

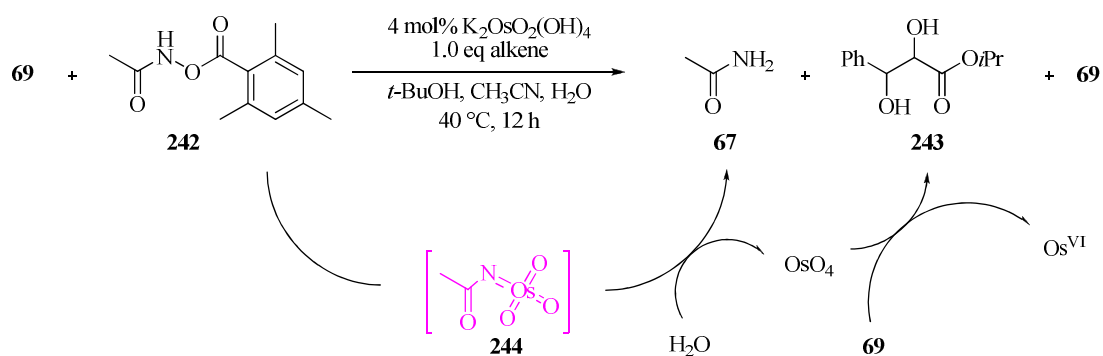
3.2.2 Tethered Aminohydroxylation experimental conditions

Employing the tripartite solvent system in conjunction with potassium osmate ligand free conditions (see Section 2.1.5.7), **242** was subjected to this intramolecular process as depicted in Scheme 74.



Scheme 74 - Attempt under the TA experimental conditions

The reaction again failed to yield any desired amino alcohol **70** with recovery of **69** and **242**. Whilst increasing the temperature to 40 °C did not improve the outcome, two side products were identified: acetamide **67** and dihydroxylated alkene **243** (spectroscopic data were consistent with those reported in the literature). It was rationalised that their origin stemmed respectively from the hydrolysis of imidoosmium **244** and subsequent osmium tetroxide mediated dihydroxylation of isopropyl cinnamate **69** (Scheme 75).

Scheme 75 - Possible origin for **67** and **243** formation

These series of experiments highlighted the stark contrast of reactivity between the two reoxidants **68** and **242**. In order to identify the causes of this reactivity, a structural comparison was established (Figure 21).

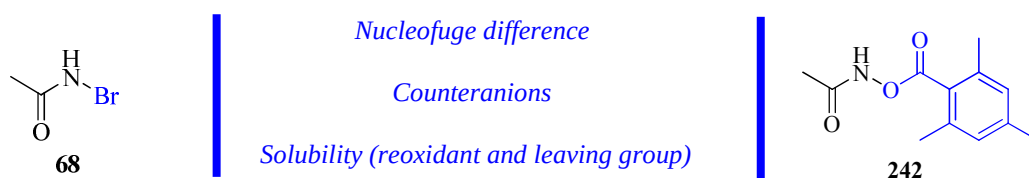
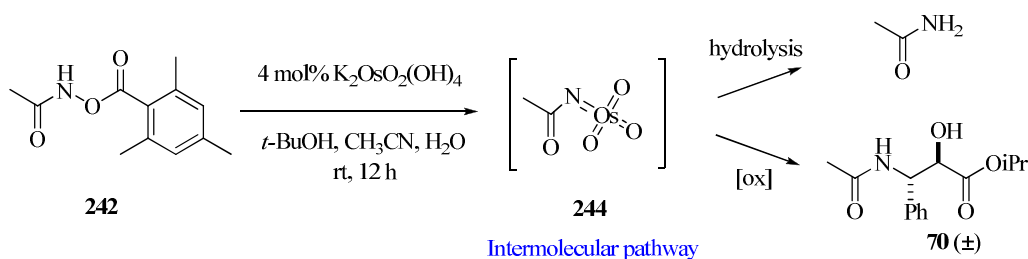


Figure 21 - Possible key parameters explaining different reactivity

As depicted in Figure 21, the most evident difference was the *leaving group* characteristic. Hence, the following study aimed at identifying the reasons for this lack of reactivity and ways to overturn this result.

3.3 Investigations towards a viable intermolecular process

Based on previous studies, it was rationalised that within the *intramolecular* process, the hydroxyamination of alkenes was a favoured process thanks to the tethered link. Furthermore, the reoxidant being built within the substrate meant that no external additives were required and the reaction could proceed only with a catalytic amount of base to initiate the oxidation process, key for the catalytic cycle initiation (see Section 1.3). However, in an *intermolecular* process, after this catalytic amount of base released from potassium osmate has deprotonated the *N*-acylated product **242**, the entropy advantage of the alkene being spatially close to osmium intermediate **244** is lost. Consequently, the competition between the oxidation reaction of isopropyl cinnamate by **244** and the hydrolysis of intermediate **244** would be enhanced (Scheme 76).

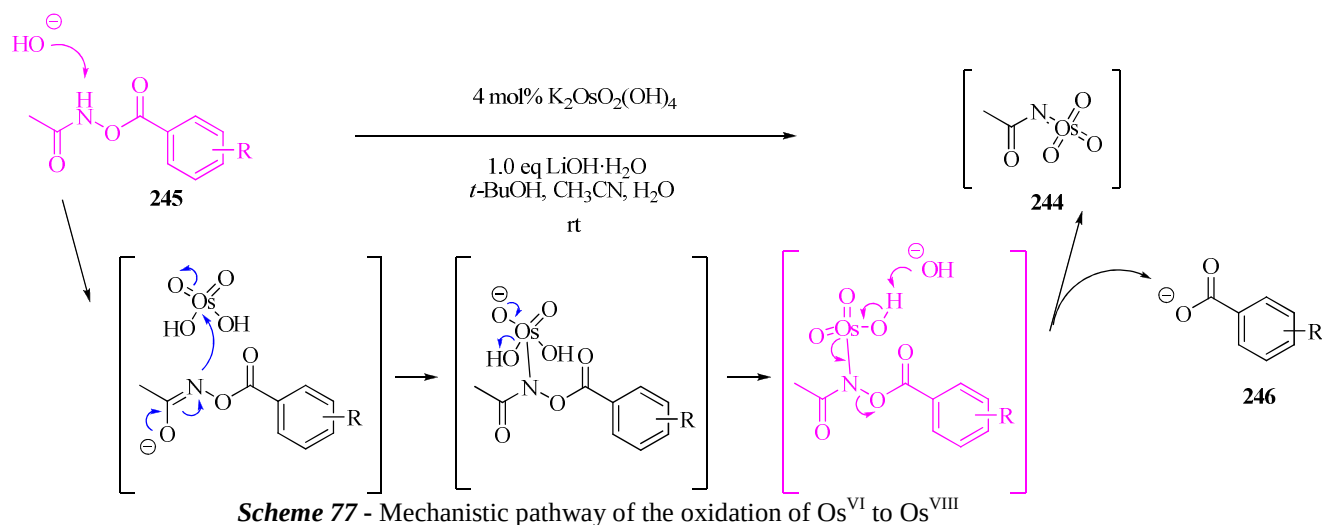


Scheme 76 - Absence of tethered alkene favours hydrolysis of **244**

If this hypothesis was confirmed, this would suggest a slower oxidation process of the alkene, *i.e.* the rate determining step of the reaction. Moreover, for the next studies to be similar to the conditions developed by Sharpless *et al.* one equivalent of base was added

3.3.1 Investigations into the reoxidant reactivity

It was envisaged that the electronic nature of the nucleofuge was an important parameter (Scheme 77).



Scheme 77 - Mechanistic pathway of the oxidation of Os^{VI} to Os^{VIII}

Indeed, the oxidation of osmium(VI) to osmium(VIII) could be influenced by two factors: the pK_a of N -acylated hydroxamic acid **245** and the stability of released carboxylate **246**. Therefore, by increasing the electron deficiency of the aromatic moiety, it was postulated that deprotonation of **245** would be facilitated. Moreover, the stability of the resulting carboxylate **246** would also be increased favouring consequently the overall oxidation process. Hence, precursors **247** and **248** were synthesised in order to explore this rationale (Figure 22).

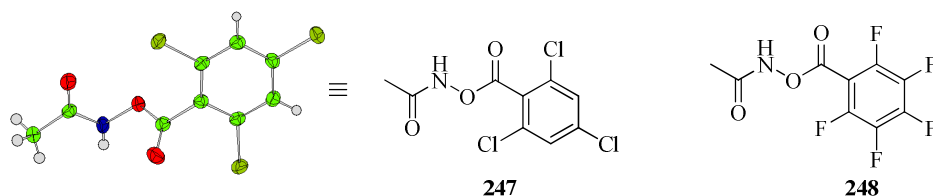
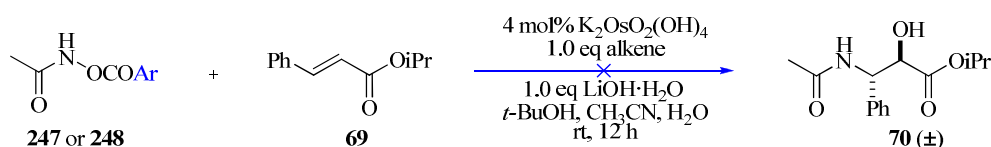


Figure 22 - Synthesis of more reactive precursors

Both compounds **247** and **248** showcased the characteristic *NH* signal peaks at 9.41 and 9.62 ppm as well as the IR spectroscopic stretch of the carbonyl moiety around 1650 cm^{-1} . Moreover, an X-ray crystal structure obtained for the 2,4,6-trichloroderivative **247** further confirmed their correct structure assignment.

However, it was also anticipated that increasing the electrodeficiency of the aromatic moiety could favour the background Lossen rearrangement reaction as previously mentioned in Section 2.1.3 (Scheme 78).

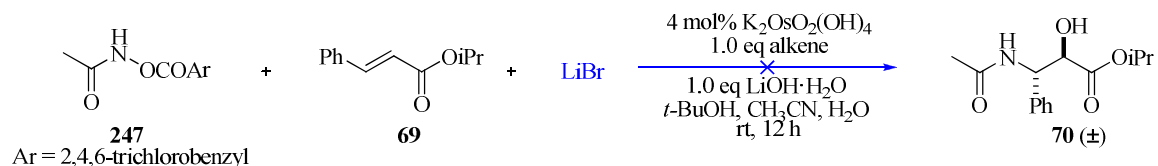


Scheme 78 - Screening with more reactive precursors

As a result, carrying out the reaction with **248** ended in complete destruction of the amide derivative and recovery of the isopropyl cinnamate **69**. Although, **247** derivative gave similar results than 2,4,6-trimethyl derivative **242** with only traces of **70** obtained, there was a noticeable difference regarding the rate of oxidation if the colour change (from 20 to 10 min) was assumed to be a good indicator of the osmium oxidation status (see Section 2.1.4). For that reason, **247** was used as a standard in the following set of experiments.

3.3.2 Investigation into the importance of the counterion

In a control experiment, one equivalent of lithium bromide was added to **247** to ensure that the bromide ion did not have any hidden benefits and was not playing any crucial role in the aminohydroxylation process (Scheme 79).

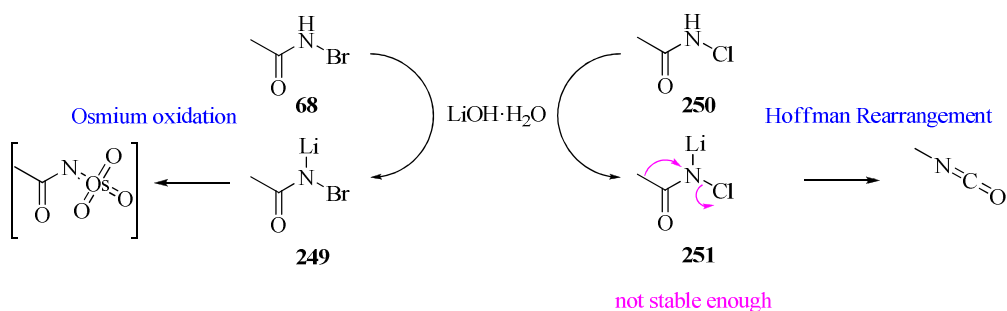


Scheme 79 - Possible active role played by bromine ions

As expected, this reaction failed to reach completion and only traces of **70** were isolated discarding any hidden benefits in the presence of bromine anions in the catalytic cycle. Therefore, another parameter was investigated.

3.3.3 Investigation into the external base

In their studies, Sharpless *et al.* have reported that the stability of an alkali metal salt of an *N*-halogenated amide was intimately related to the halogen considered (Scheme 80).

Scheme 80 - Reported stability of *N*-halogenacetamide salts

Indeed, when one equivalent of an inorganic base was employed to produce *N*-lithio, *N*-bromoacetamide intermediate **249**, subsequent oxidation of osmium was possible. However, for *N*-chloroacetamide **251** employing the same conditions resulted in no oxidation as a competitive Hoffman rearrangement took place.¹ Based on this observation and the knowledge that these amide derivatives **245** were prone to undergo a Lossen rearrangement, a screening to replace lithium hydroxide with an organic base was carried out. Indeed, rendering the medium less alkaline should slow down the background Lossen side reaction in favour of the osmium oxidation as explained in Section 2.1.5.5 (Figure 23).

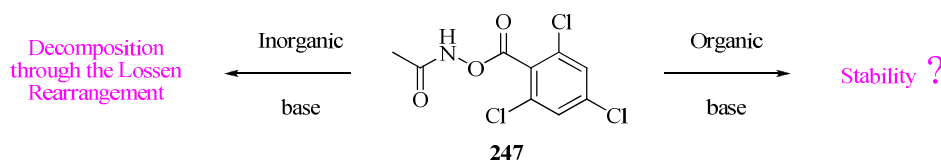
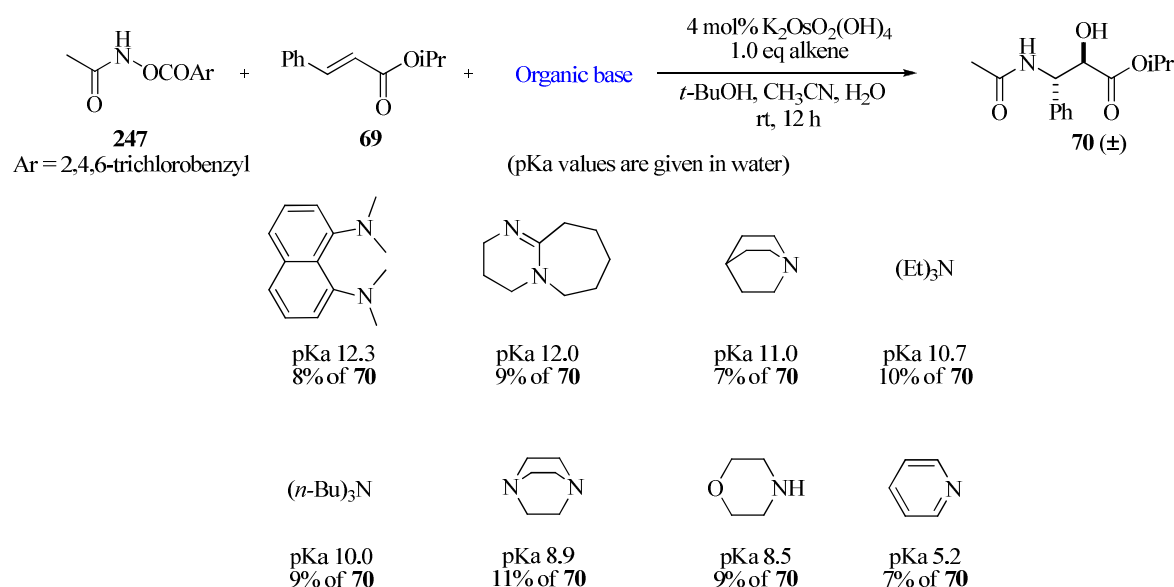


Figure 23 - Research into the use of an organic base

To explore this hypothesis, a screen was conducted varying the basicity of the organic bases employed as depicted in Scheme 81.



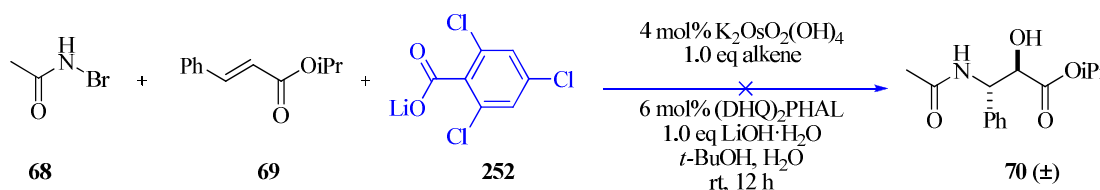
Scheme 81 - Screening of organic base

Upon examination of this screening result, it was decided to stop any further studies as more appealing hypotheses were prioritised.

3.3.4 Investigation of the pH parameter

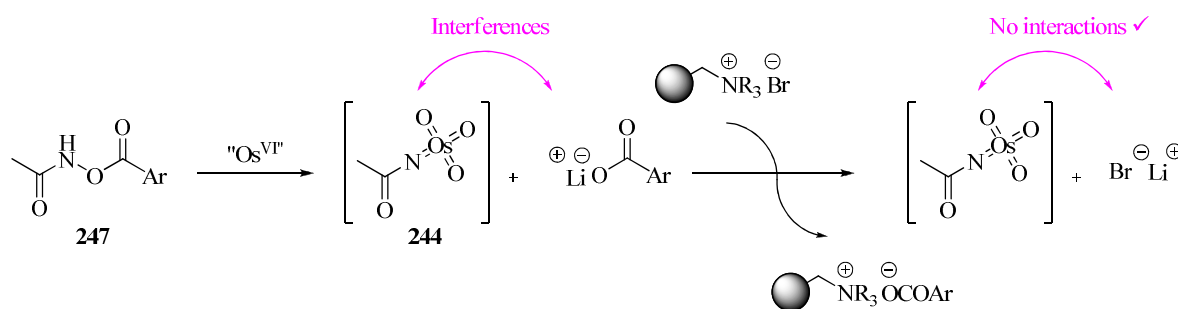
Using *N*-bromoacetamide **68** as precursor in the methodology published by Sharpless *et al.*, bromide ions were released during the osmium oxidation process and proofs were obtained of their non-interference in the subsequent mechanistic steps (see Section 1.4.2). However in the current methodology, using **247** as the nitrogen source, the gradual release of carboxylic acid lowered the pH from an 8 value to 5 or 4 measured after a few hours depending of the choice of the reoxidant used (**242** or **247**). It was thus proposed that the low reactivity observed could be linked to interferences of the resulting carboxylate with the osmium catalyst. In order to assess this

hypothesis, one equivalent of lithium 2,4,6-trichlorobenzoate **252** was added to the efficient *N*-bromoacetamide protocol (Scheme 82).



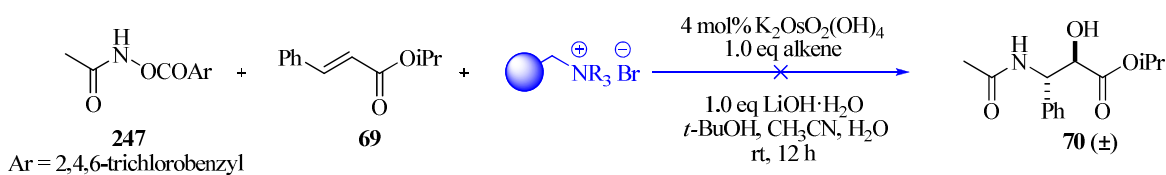
Scheme 82 - Addition of one equivalent of carboxylate salt

Interestingly, no product **70** was obtained. It was consequently envisaged to employ quaternary ammonium anion exchange resins that should theoretically scavenge carboxylate and release bromine anions when employing reoxidant **247** (Scheme 83).



Scheme 83 - Possible existence of interferences

If successful, this would provide essential insight into the catalytic cycle. Therefore, the reaction employing **247** as the nitrogen source was carried out in the presence of such resins (Scheme 84).



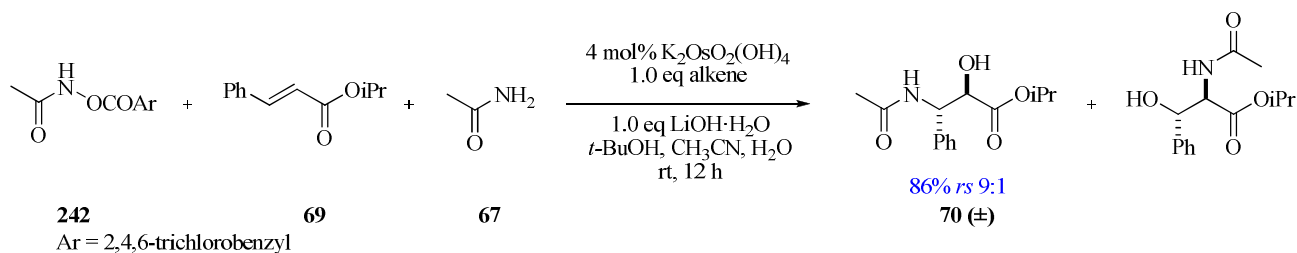
Scheme 84 - Addition of anion exchange resins

Unfortunately, this hypothesis did not seem to be conclusive as no reaction was observed. Another aspect of the specific reactivity of these *N*-bromoamide species was then focused on.

3.4 Acetamide, a key parameter not to be neglected

Through the description of the several *N*-bromoamide syntheses, Sharpless *et al.* added the following remark in what would become a key footnote for the success of this methodology “Unexpectedly, we found that when the non-recrystallized *N*-bromoamide containing several percents of the primary amide starting material is used, the reaction is more reliable”. In recent years, further studies have highlighted the need of at least one equivalent of acetamide for smooth execution of the aminohydroxylation process. These investigations by Wut *et al.* were carried out to enable the suppression of diol formation and to increase the yield of the amino alcohol product.² Furthermore, this addition of a substoichiometric amount of acetamide has also been reported in industrial processes as a method to enhance the yield.³ Nevertheless, the exact role of acetamide is still to be determined.

A decision was taken to try it in our system (Scheme 85).



Scheme 85 - Successful intermolecular reaction

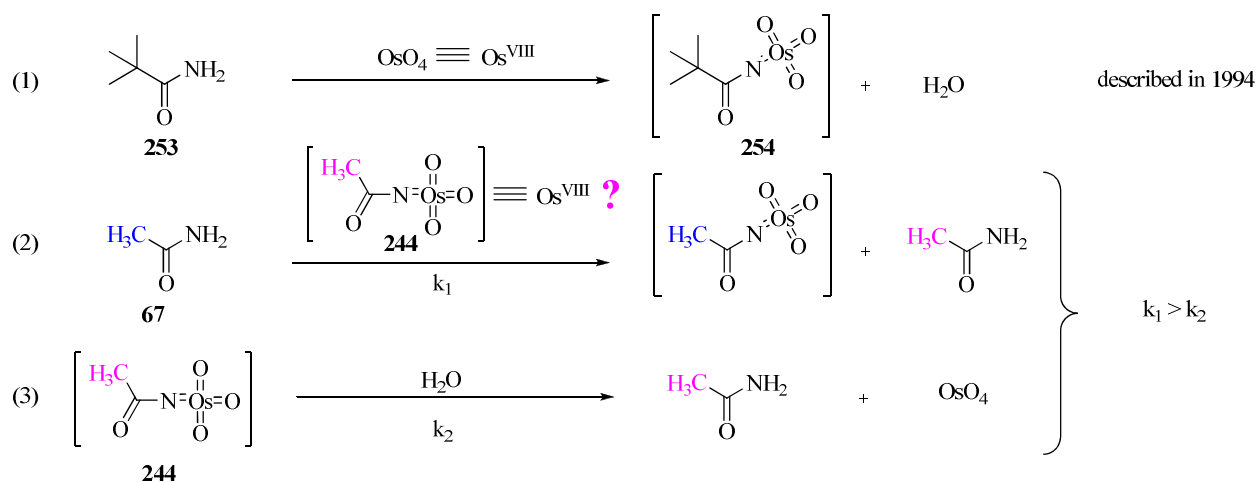
Pleasingly, adding one equivalent of acetamide to the system using **247** as the reoxidant gave the desired product **70** in excellent yield and good regioselectivity (9:1). Spectroscopic data were consistent with those reported in the literature.

From this key result, three hypotheses were envisaged in order to understand the role of acetamide in the aminohydroxylation reaction.

3.5 Determination of the role of acetamide

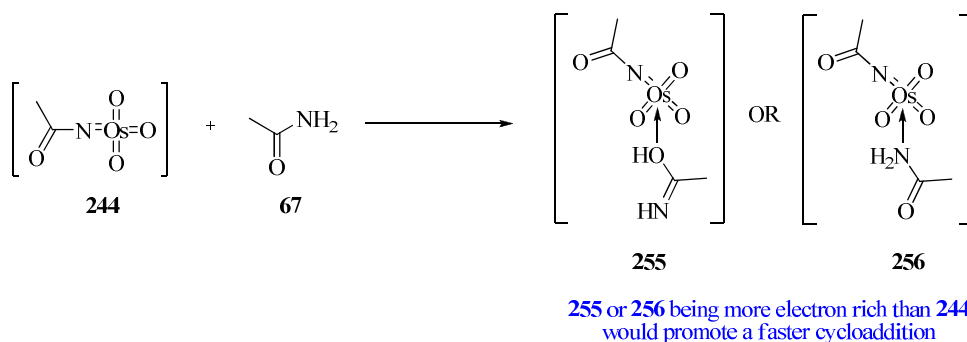
Firstly, it was postulated that the addition of acetamide could enable the regeneration of the key reoxidant imidoosmium complex **244** in the same manner as the condensation described by

Svendsen *et al.* (Scheme 86, equation 1) where *t*-butyl amide **253** was reacted with a stoichiometric amount of osmium tetroxide.⁴ A similar reaction could then be envisaged where acetamide would react with an equivalent of osmium(VIII) **244** (equation 2), competing then with the hydrolysis of the imidoosmium intermediate **244** as described in equation 3.



Scheme 86 - Possible condensation to regenerate the active catalyst

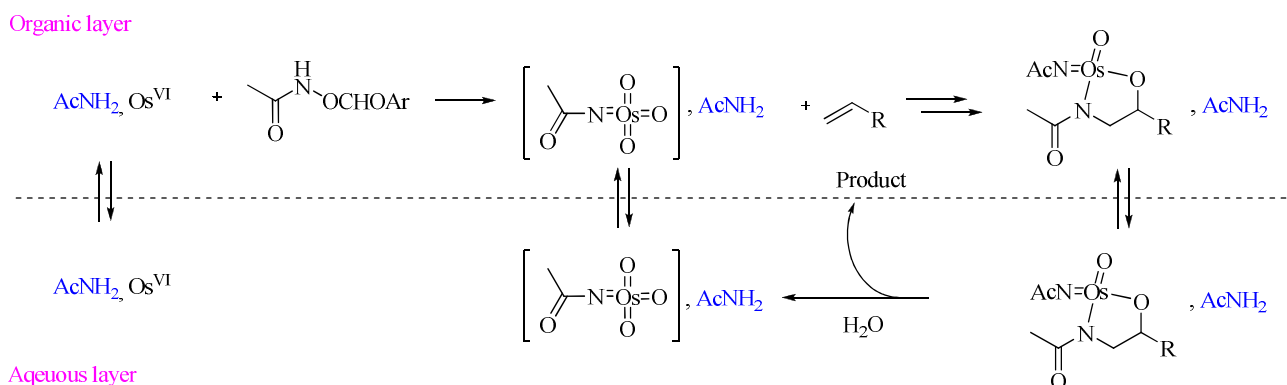
The second hypothesis envisaged was that by coordinating to the osmium metal as a ligand, acetamide could increase the electron density on imidoosmium intermediate **244**. This would result in a faster addition onto the alkene, counterbalancing the decomposition of the catalyst over time (Scheme 87).



Scheme 87 - Electronic nature of the catalyst species favoured higher catalytic rate

Finally, the last hypothesis formulated was that acetamide played the role of a saturating and phase transfer agent. Indeed, acetamide is soluble in both aqueous and organic solvent employed in the aminohydroxylation. The oxidation of osmium(VI) to osmium(VIII) would then be facilitated. Moreover, by saturating the aqueous phase, therefore decelerating the hydrolysis of imido complex

244 (see Scheme 86, equation 3), acetamide **67** would also favour the addition of aqueous soluble active catalyst species **244** onto the alkene (Scheme 88).

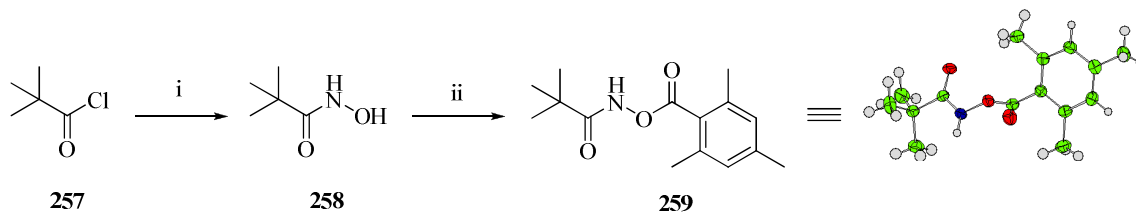


Scheme 88 - Acetamide (AcNH_2) as phase transfer agent

In order to assess those three hypotheses, several experiments were conducted on two substrates: vinyl naphthalene **34** and isopropyl cinnamate **69**, both of which have been well studied in the aminohydroxylation of alkenes.

3.5.1 Results and discussion

To assess the first hypothesis, *N*-(2,4,6-trimethylbenzoyloxy)pivalamide **259** was synthesized (Scheme 89).



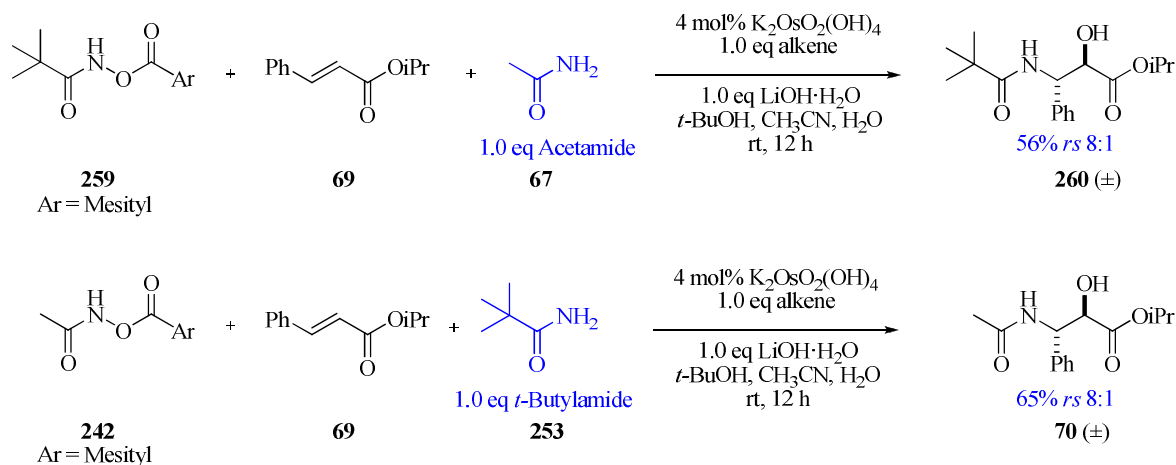
Reagents and conditions: i) $\text{NH}_2\text{OH} \cdot \text{HCl}$, CH_2Cl_2 , H_2O , rt, 16 h, 93%; ii) 2,4,6-trimethylbenzoyl chloride, Et_3N , CH_2Cl_2 , 0°C , 45 min, 89%.

Scheme 89 - Synthesis and X-ray structure of **259**

Starting with pivaloyl acyl chloride **257**, *N*-hydroxypivalamide **258** was synthesised in nearly quantitative manner and subsequent acylation afforded **259** in an excellent 89% yield. Analysis of the X-ray crystal structure of **259** unambiguously confirmed its structure.

On the basis that regeneration of imidoosmium intermediate **244** took place during the reaction, performing a cross-over experiment should lead to a mixture of product (acetyl **242** and *t*-butyl **259**

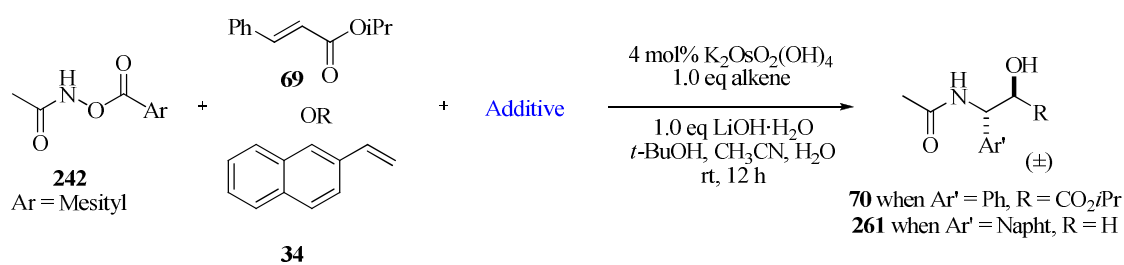
derivatives) in both cases (Scheme 90). As an important remark, *t*-butylamide **253** was not as soluble as acetamide under these conditions.



Scheme 90 - Cross-over experiments

The hypothesis of acetamide acting as regenerator of imidoosmium complex **244** was discarded when in both cases only one product originating from the reoxidant was identified and isolated. Spectroscopic data of **260** were consistent with those reported in the literature. Its correct structure assignment was established by comparison with compound **70** data (see Experimental section, Chapter 5 for details).

In order to assess the veracity of acetamide acting as a ligand or saturating agent hypotheses, several additives were screened as detailed in Table 15.



Entry	Substrates	Additive	Yield ¹ (%)	<i>rs</i> ²
1	69	None	No reaction	
2	34	None	No reaction	
3	69	AcNH ₂ (67)	86 (70)	9:1
4	34	AcNH ₂ (67)	74 (261)	3:1
4	69	MeSO ₂ NH ₂ (262)	84 (70)	8:1

5	34	MeSO ₂ NH ₂ (262)	70 (261)	2:1
6	69	AcNHOH (241)	No reaction	
7	34	AcNHOH (241)	No reaction	

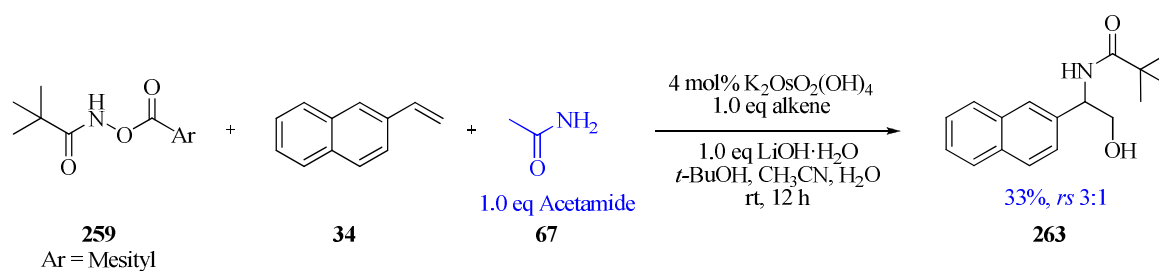
¹Isolated yield, ²Ratio of compounds determined from the ¹H NMR spectrum of the crude material

Table 15 - Final additive screening

Gratifyingly, using acetamide (entry 3 and 4), both alkenes were oxidised in good yield compared to no reaction without (entry 1 and 2). Analysis of the results obtained for the addition of acetamide **67** (entry 1) and *N*-hydroxyacetic acid **241** (entry 6) supported the concept of a phase transfer type implication. Indeed, *N*-hydroxyacetic acid **241** although soluble in water displayed low organic solvent solubility. Furthermore, in the likelihood of *N*-hydroxyacetic acid **241** coordinating to the osmium metal through the reaction course, this would establish that only one of the previously stated conditions is necessary but not sufficient for the reaction to proceed. On the contrary, the addition of sulfonamide **262**, both soluble in organic and aqueous solvents (entry 3) displayed similar good results as acetamide confirming the idea of both a saturating and phase transfer type agent. Therefore, the results obtained tended to accept a combination of ligand and saturating agent hypothesis.

3.6 Solubility of reoxidant

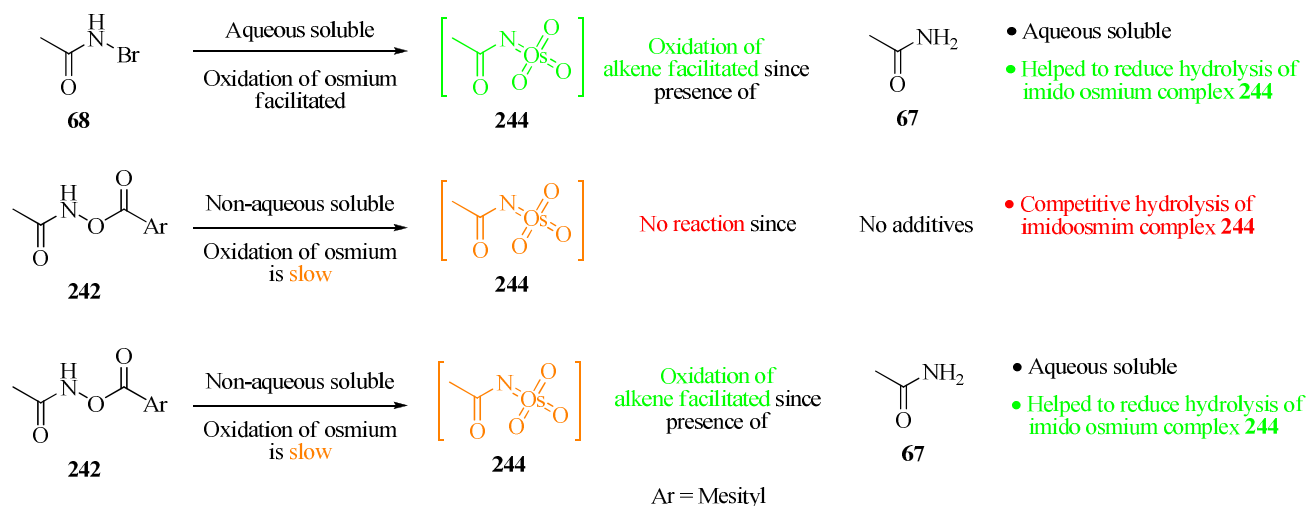
The reported aminohydroxylation of alkenes employing *N*-bromo-*t*-butylamide was described as sluggish and only gave traces of the amino alcohol products in the methodology developed by Sharpless *et al.*. However, by using **259** as the reoxidant in combination with acetamide, a good yield was obtained for activated alkene (see Scheme 90) and a moderate yield for non-activated substrate (Scheme 91).



Scheme 91 - Sterically hindered reoxidant

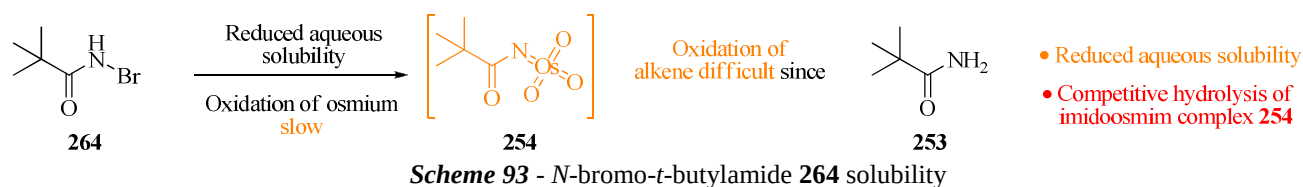
The assignment of the major regioisomer was established via ^1H - ^1H COSY NMR experiment and confirmed with comparison of acetamide derivative **70**. It was this outcome that highlighted the key difference between the use of *N*-bromoamides and our current methodology: their aqueous solubility.

Indeed, it was postulated that *N*-bromoacetamide **68** being soluble in water, the oxidation of osmium(VI) was fast but the hydrolysis of the resulting imidoosmium complex **244** slow due to the “several percents” of acetamide acting as a saturating agent (Scheme 92). The highly efficient aminohydroxylation of imidoosmium complex **244** onto the considered alkene could then take place. Furthermore, since our reoxidant **242** is insoluble in water, the oxidation of osmium(VI) is only facilitated by the addition of one equivalent of a phase transfer agent, *i.e.* acetamide (see Section 3.3).



Scheme 92 - Solubility as key parameter in both methodologies

Therefore, this solubility factor could also explain the poor reactivity of *N*-bromo-*t*-butylamide **264** in Sharpless *et al.* methodology. *N*-bromo-*t*-butylamide **264** being less soluble in water than *N*-bromoacetamide **68**, the oxidation of osmium would be slower. Moreover, *t*-butylamide being twelve times less soluble in water than acetamide, the “several percents” carried out through its synthesis would not be able to act as an efficient saturating agent as in the acetamide case and would not be able to slow down the hydrolysis of **244**.⁵ This would result in poor yield (Scheme 93).



3.7 Conclusion

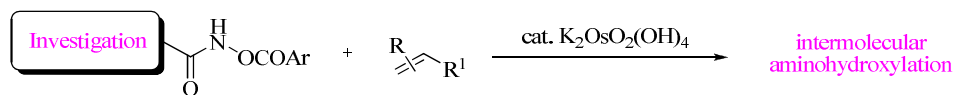
In conclusion, the use of shelf stable and convenient amide derivative **240** using our 3rd generation of osmium reoxidant for the intermolecular aminohydroxylation process has become a viable process. Moreover, employing hindered amide derivative **259** as nitrogen source was also made possible for the first time albeit moderate regioselectivity and yield were obtained. Further investigations would be required for their widespread use. Nevertheless, it was by understanding the initial unreactivity of our amide derivative **242** that the key role of acetamide in the aminohydroxylation might have been solved. Further studies were conducted in order to extend the scope of substrates, which when activated with our 3rd generation of reoxidant would result in an efficient aminohydroxylation reaction in an intermolecular manner. This is addressed in the following chapter.

Chapter 4

***A successful transition to an intermolecular
aminohydroxylation process***

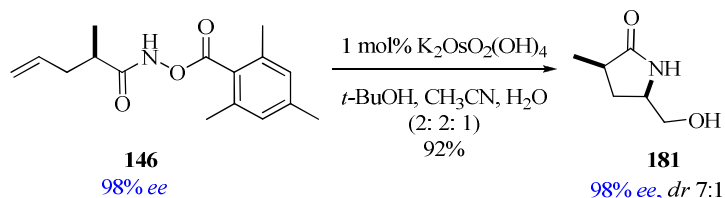
4. A successful transition to an intermolecular aminohydroxylation process

Following the results obtained for acetamide derivative **242**, where imidoosmium intermediate **244** aqueous solubility was responsible for the poor reactivity observed (see Section 3.6), it was envisaged to investigate novel substrates for the intermolecular process (Scheme 94).



Scheme 94 - Investigations towards an intermolecular process

As discussed in Section 2.1.8, the main drawback of the tethered aminohydroxylation (TA) methodology was the difficulty to turn this process into an enantioselective one. However, submitting an enantiopure substrate (**146** was synthesized *via* Evans oxazolidinone chiral auxiliary, see Experimental section; Chapter 5), no loss of enantiomeric excess at the methyl centre was observed in hydroxyl lactam **181** (Scheme 95).



Scheme 95 - Tethered aminohydroxylation of enantiopure **146**

This result outlined the use of osmium under the TA conditions as mild and which do not cause epimerisation adjacent to the carbonyl group. Taking all these information into account, it was decided to search for a substrate, enantiopure and preferably readily available (*i.e.* from the chiral pool) that would provide useful products in terms of core structure and biological activities when submitted to this osmium methodology (Figure 24).

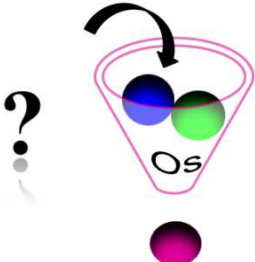
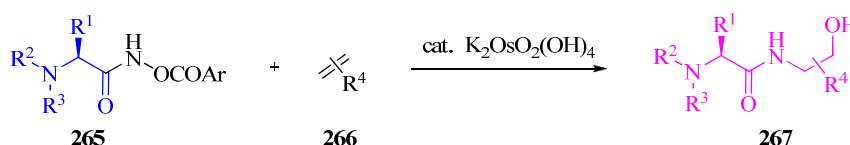
- Enantiopure
 - Readily available
 - Useful products
- 

Figure 24 - Novel substrate characteristics required

It appeared that the ideal candidates were amino acids. Indeed, the outcome of this reaction would be adduct **267** containing both an 1,2-aminodiols unit as well as the corresponding amino acid moiety (Scheme 96).

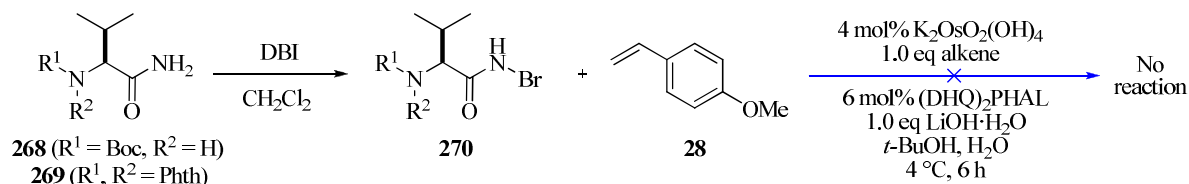


Scheme 96 - Amino acids as interesting substrates

It was envisaged that by screening several amino acids **265** and modifying the substitution of alkene **266** employed, this reaction would extend the scope of osmium-catalysed methodology.⁶⁸

4.1 Amino acids as a nitrogen source

In a preliminary control experiment, protected L-valine derivatives **268** and **269** were subjected to Sharpless *et al.*'s methodology developed for primary amides (see Section 3.1), using 4-methoxystyrene **28** as the alkene test substrate. After bromination of amino amides **268** or **269** and subsequent work-up procedure, the resulting intermediate **270** was directly submitted to the conditions depicted in Scheme 97.



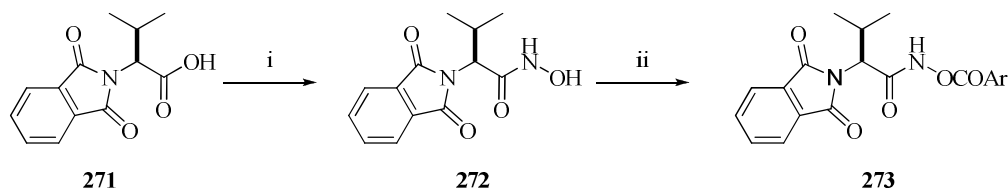
Scheme 97 - Amino amide preactivated with DBI as possible nitrogen source

As expected with hindered amides (see Section 3.6), the reaction did not proceed and no product was obtained. It was then envisaged to synthesise amino acid derivatives **265** bearing this 3rd generation of reoxidant for osmium.

4.1.1 Synthesis of protected L-valine precursor

Three methodologies were developed for this purpose and are detailed below:

- The first procedure based on the protocol developed during the TA of amide (see Section 2.1.2) was the most convenient and scalable process (Scheme 98).



Reagents and conditions: i) (COCl)₂, NH₂OH·HCl, CH₂Cl₂, H₂O, rt, 12 h, 90%, ii) 2,4,6-trimethylbenzoyl chloride, CH₂Cl₂, Et₃N, 0 °C, 1 h, 72%.

Scheme 98 - 1st protocol for the synthesis of L-valine precursor **273**

Starting from easily accessible phthalimide-protected L-valine **271**, intermediate **272** was synthesised in 90% yield (spectroscopic data were in accordance with those reported in the literature).⁶⁹ Subsequent acylation afforded the desired product **273**, which structure was unambiguously determined by X-ray crystallographic analysis (Figure 24).

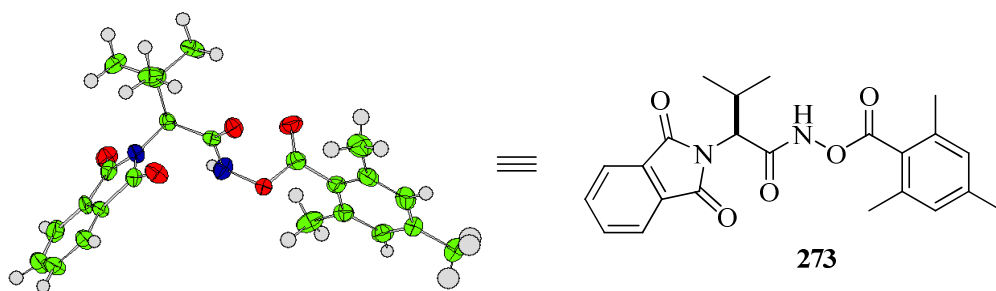
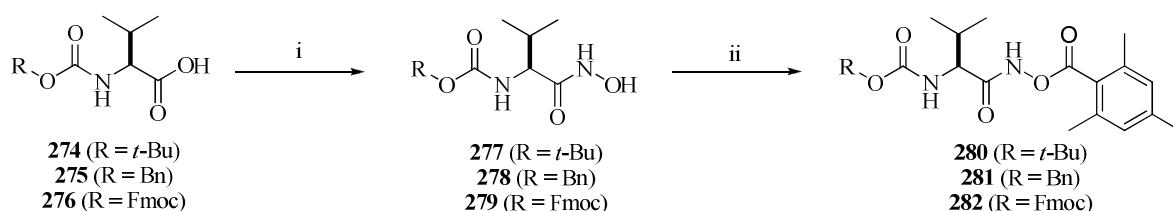


Figure 24 - X-ray crystal structure of **273**

This procedure took place without significant racemisation as the enantiomeric purity of reoxidant **273** was assessed using a chiral OD HPLC column and revealed to be of 94% *ee* upon comparison to authentic racemic standards (see Appendix 2 for HPLC traces). After recrystallisation in a co-

mixture of hexane and ethyl acetate, **273** was obtained with an enantiomeric excess of 98% *ee*. This first protocol was only applied to phthalimide protected amino acids.

- The second methodology developed enabled access to mono protected L-valine derivatives. Boc, Cbz, Fmoc derivatives were synthesised in a two-step procedure. Firstly, commercially available protected L-valine derivatives (**274**, **275** and **276**) were reacted with ethyl-3-(3'-dimethylaminopropyl)-carbodiimide (EDCI·HCl) coupling reagent in the presence of pentafluorophenol in dichloromethane. This allowed the formation of the respective ester in high yield and a facile purification of the resulting urea by-product stemming from the coupling reagent. Further reaction of the crude material in dichloromethane with an aqueous hydroxylamine solution provided the desired hydroxamic acid derivatives (**277**, **278** and **279**) in high yield. Spectroscopic data of compounds **277**, **278** and **279** were consistent with those reported in the literature. The last step was the acylation procedure (see Section 2.1.3) to afford the corresponding mono-protected L-valine derivatives **280**, **281** and **282** in moderate to excellent yields (Scheme 99).

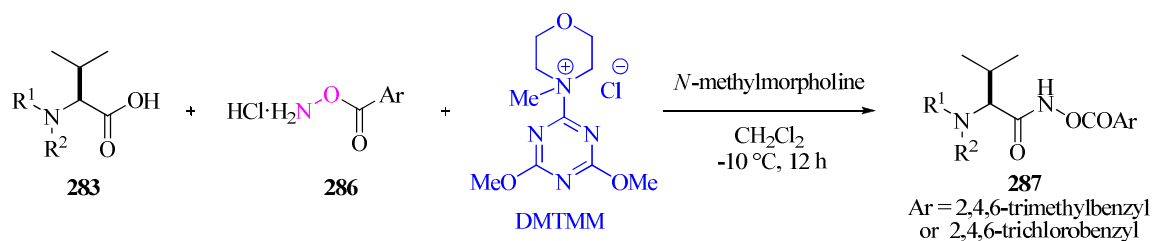


Reagents and conditions: i) EDCI·HCl, CH₂Cl₂, pentafluorophenol, aq. NH₂OH, rt, 14 h, (78%, 76%, 62% respectively); ii) 2,4,6-trimethylbenzoyl chloride, CH₂Cl₂, Et₃N, 0 °C, 1 h, (91%, 89%, 71% respectively).

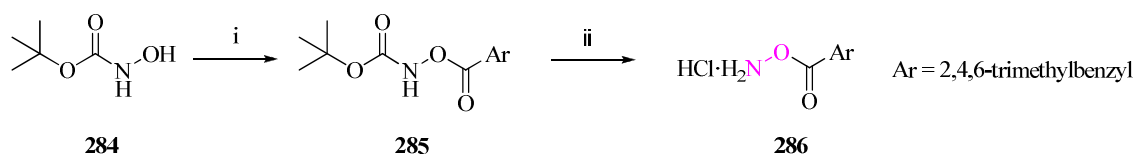
Scheme 99 - 2nd protocol for the synthesis of L-valine precursor **280**, **281** and **282**

In each case, the characteristic *NH* signal between 9.76 and 11.07 ppm in the ¹H NMR spectrum as well as the signal at 6.87 ppm of the two aromatic protons of the acyl moiety confirmed the correct synthesis of mono protected L-valine precursors. This procedure being used in common amino acid synthesis, no epimerisation was expected.⁷⁰ Indeed, examination of the enantiomeric purity of reoxidant **273** synthesised through this procedure revealed to be of 95% *ee*.

- Finally, the last procedure developed gave access in one step to reoxidant derivatives **287** from readily available amino acids **283** in combination with amine **286** (Scheme 100).



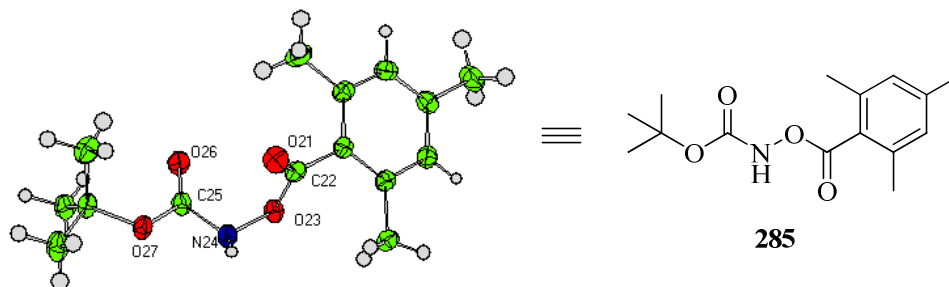
Amine **286** synthesis started with commercially available *N*-Boc-hydroxylamine **284**. Acylation and subsequent Boc deprotection in acidic medium afforded **286** in excellent yield (Scheme 101).



Reagents and conditions: i) 2,4,6-trimethylbenzoyl chloride, CH₂Cl₂, Et₃N, 0 °C, 1 h, 92%; ii) 4M HCl in dioxane, 0 °C, 6 h, CH₂Cl₂, 100%.

Scheme 101 - Synthesis of amine **286**

The structure of intermediate **285** was unambiguously determined by X-ray crystallography analysis (Figure 25).



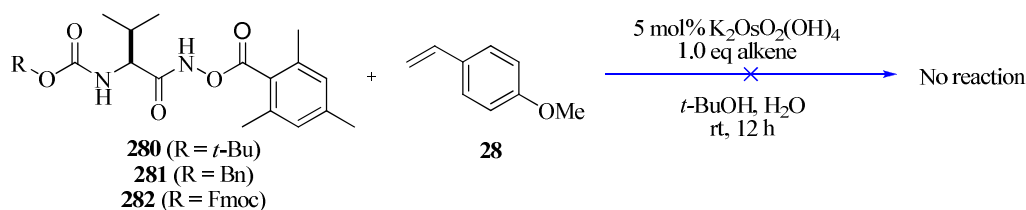
This coupling procedure was only successful when 4-(3,5-dimethoxyphenyl)-4-methylmorpholin-4-ium chloride (DMTMM) coupling reagent was employed. Indeed, out of the screening conducted for this procedure, DMTMM was the only coupling agent to afford the desired product in high yield: common reagents such as HBTU, HATU, EDCI·HCl as well as the direct formation of the acyl chloride in neutral conditions using 1-chloro-*N*, *N*,2-trimethyl-1-propenylamine (Ghosez reagent) all failed to provide good yields.⁷¹ This procedure could be employed for both mono and doubly protected amino acids but was essentially developed for base and acid sensitive substrates.

DMTMM reagent gave no racemisation in the products, but was less convenient to use on a large scale. Upon formation of these reoxidant precursors **265**, the stage was set for the osmium-mediated process.

4.2 Osmium-catalysed reaction

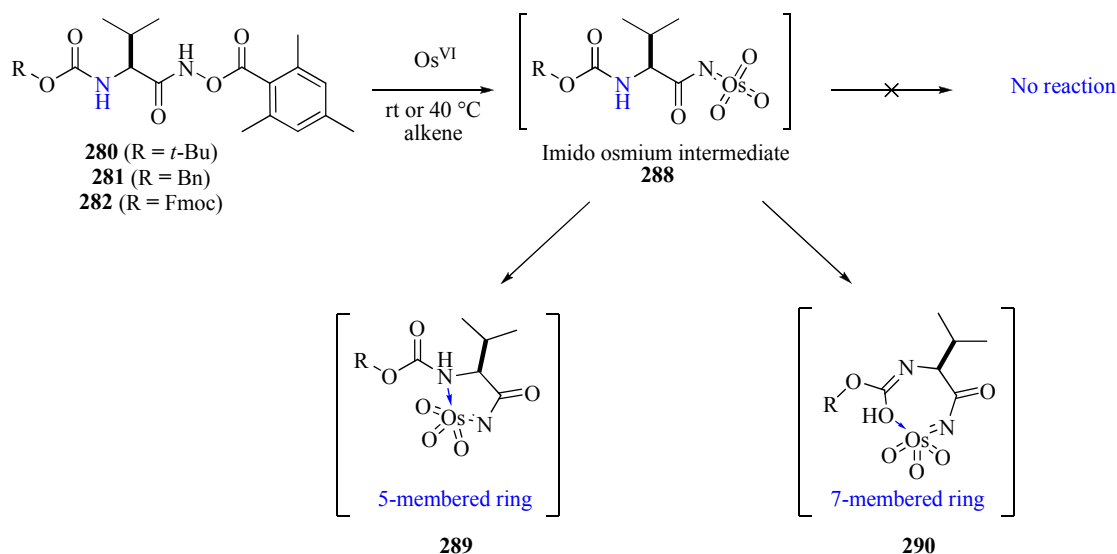
4.2.1 Mono-protected L-valine precursors

With our precursors in hand, the tethered aminohydroxylation was first run using 5 mol% of the non-volatile potassium osmate $\text{K}_2\text{OsO}_2(\text{OH})_4$ (Scheme 102).



Scheme 102 - Aminohydroxylation of mono-protected L-valine precursors

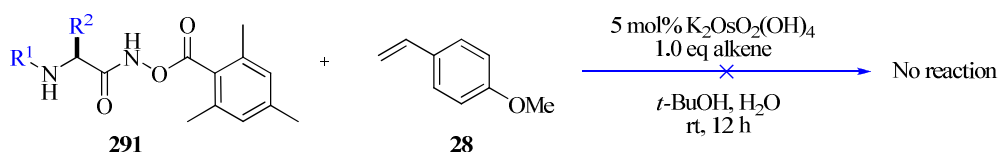
As described in Section 2.2.4, the [presence of mono-protected amine](#) completely shut down the catalytic process. Increasing the temperature and the addition of catalytic amount of cinchona ligands also failed to promote the reaction. The necessity of doubly protecting this function for the reaction to proceed as explained in the next section, supported the existence of an analogous osmium intermediate model where the secondary amine strongly coordinated to the metal (Scheme 103).



Scheme 103 - Possible coordination model to osmium

It was rationalised that these adducts could possibly have derived from a 5 or 7-membered ring intermediate **289** or **290** respectively.

In an effort to break these adducts, several protected amino acids were tested (Table 16).



Entry	Compounds	Amino acid derivative R ²	Protecting group R ¹	Yield ¹
1	280	<i>i</i> Pr (L-Valine)	<i>t</i> -Bu (Boc)	No reaction
2	291a	Me (L-Alanine)	<i>t</i> -Bu (Boc)	No reaction
3	281	<i>i</i> Pr (L-Valine)	Bn (Cbz)	No reaction
4	291b	PhCH ₂ (L-Phenyl)	Bn (Cbz)	No reaction

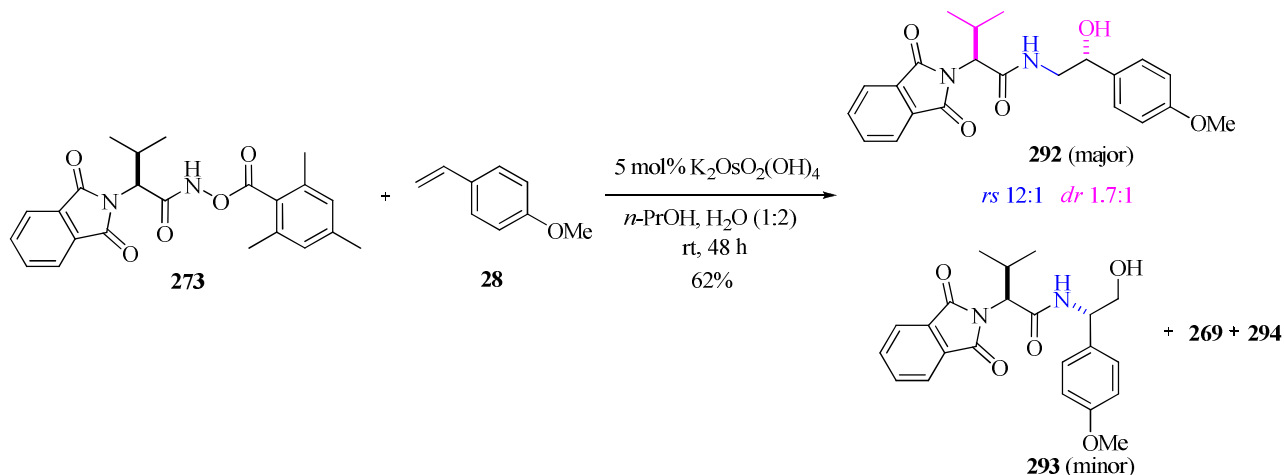
¹Conversion determined from the ¹H NMR spectrum of the crude material

Table 16 - Possible use of steric hindrance for breaking osmium adduct

Synthesis of compound **291a** and **291b** was carried out following the pentafluorophenol procedure (see Section 4.1.1) and full characterisation can be found in the Experimental section, Chapter 5. However, steric hindrance modulation was inefficient as no desired product was isolated with complete recovery of reoxidant starting material **291**.

4.2.2 Doubly-protected L-valine precursors

As mentioned previously, the reaction was only successful when phthalimide protected L-valine derivative **273** was employed. To the best of our knowledge, this is the first time that amino acids are used as nitrogen source in the aminohydroxylation reaction (Scheme 104).



Scheme 104 - Successful aminohydroxylation process using **273** as reoxidant

From this first successful reaction, both regioisomers **292** and **293** were isolated. The correct regioisomer assignment after isolation was determined by ^1H - ^1H COSY experiment between the NH peak at 7.27 ppm and the CH_2 protons. Furthermore, **292** and **293** structures were unambiguously determined by X-ray crystallographic analysis (Figure 26).

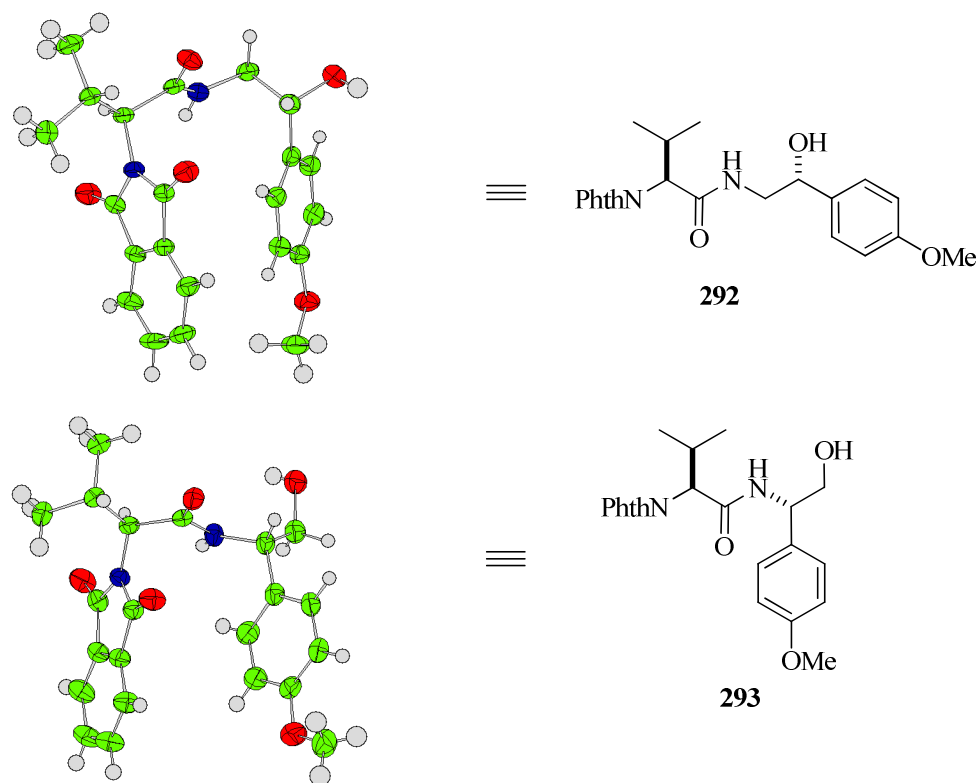


Figure 26 - X-ray crystal structure of **292** and **293**

Both regioselectivity (*rs* 12:1) and diastereoselectivity (*dr* 1.7:1) were determined by ^1H NMR spectrum analysis of the crude material. Regarding the diastereoselectivity of **292**, the ratio was established between the chiral hydroxyl group (R) or (S) and the alkyl chain of L-amino acid derivative **271** as depicted in Scheme 104. The diastereoselectivity ratio within the minor regioisomer **293** was not determined. In the following result and discussions, the product drawn always refers to the major regio- and diastereoisomer unless stated otherwise.

This unprecedented achievement was however hampered by the formation of two noticeable side products **269** (20%) and **294** (18%). Careful isolation and characterization enabled the identification of amide **269** and 1,2 styrenediol **294** (Figure 27). Their spectroscopic data were consistent with those reported in the literature (see Experimental section, Chapter 5).

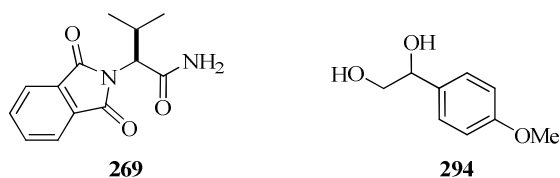
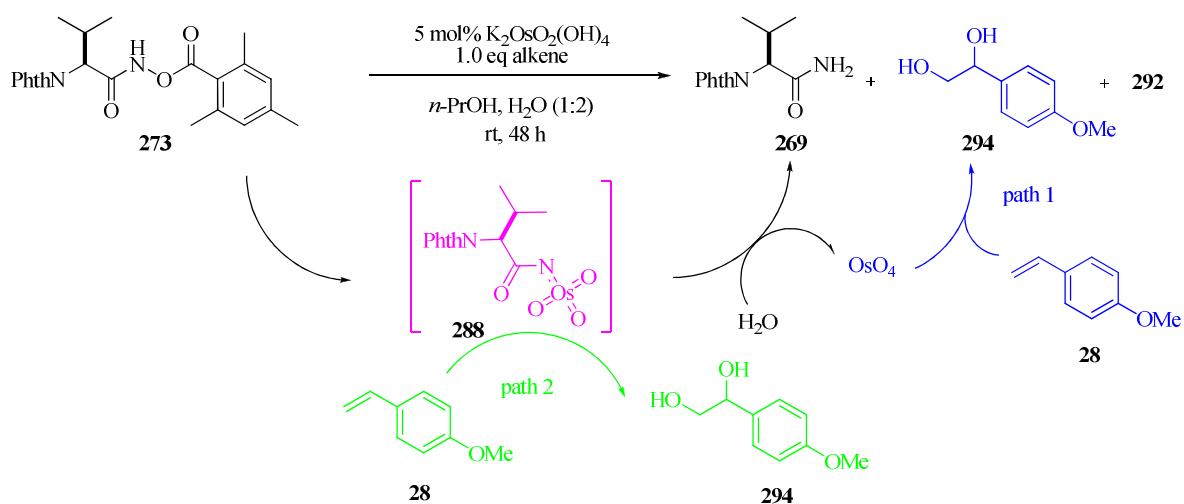


Figure 27 - Identification of side products **269** and **294**

As previously discussed in Section 3.2.2, the origin of these products was closely associated with the hydrolysis of imidoosmium intermediate **288** followed by dihydroxylation of alkene **28** by osmium tetroxide (see Scheme 105, path 1). It was also envisaged that bulky intermediate **288** could oxidise **28** resulting in the formation of 1,2-styrenediol **294** as depicted in path 2.



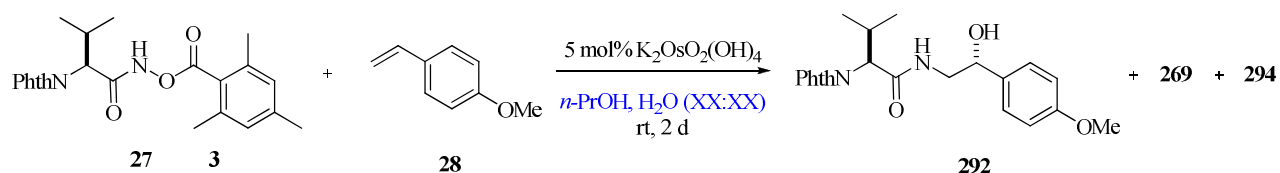
Scheme 105 - Possible explanation regarding side products **269** and **294** formation

Based on previous studies linked to osmium reactivity (see Section 3.3), it was then rationalised that two possible factors could prevent this background reaction: the amount of water present in the process and the type of solvent used.

4.2.3 Solvent media investigation

4.2.3.1 Influence of the amount of water

Hypothesis: It was envisaged that finding the optimal ratio of water to *n*-propanol should impact the formation of amide **269** and 1,2-styrenediol **294** based on previous work carried out in Section 2.5.1 (Table 17).



Entry	$n\text{-PrOH}$, H_2O (Ratio)	Yield of (292) ¹	rs ²	dr ²	Yield of (269) ¹	Yield of (294) ¹
1	1:1	69%	12:1	1.7:1	11%	10%
2	2:1	75%	14.5:1	1.5:1	7%	6%
3	4:1	81%	14:1	1.7:1	traces	
4	1:3	58%	7:1	1.5:1	21%	19%
5	1:7	10% ³	6.5:1	1.5:1	22%	19%
6	0:1	No reaction ⁴				

¹Isolated yield, ²Determined from the ^1H NMR spectrum of the crude material, ³Solubility issue leading to recovery of

starting material **273**, ⁴Complete recovery of starting material **273**

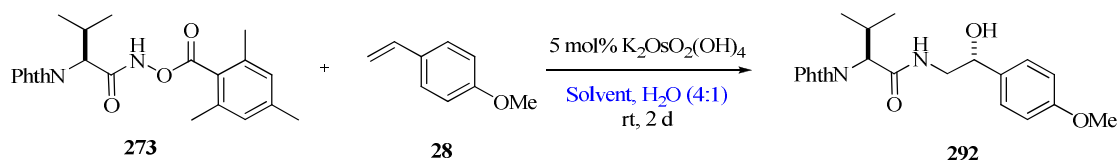
Table 17- Influence of the amount of water

Results: Decreasing the concentration of water in the medium reduced the formation of amide **269** and diol **294** resulting from the hydrolysis of the active osmium intermediate **288** (Scheme 105). Moreover, it was observed that an increase in the water concentration had a negative impact on the regioselectivity while the diastereoselectivity was untouched. A possible explanation for this outcome could be the formation of hydrophobic pockets in the aqueous media affecting the usually steric driven selectivity of the aminohydroxylation process.

It was then concluded that the best yielding conditions were achieved with entry 3 and this ratio was chosen for the next set of experiments.

4.2.3.2 Influence of the co-organic solvent

Hypothesis: A screen for the best combination of solvent capable of solvating both starting material **273** and osmium catalyst was carried out (Table 18).



Entry	Solvent, H ₂ O (4:1)	Yield of (292) ¹	<i>rs</i> ²	<i>dr</i> ²
1	Dichloromethane	No reaction ³		
2	Toluene	No reaction ³		
3	Diethyl ether	52%	7:1	2:1
4	Acetonitrile	56%	22:1	1.7:1
5	Acetone	67%	16:1	1.8:1
6	<i>t</i> -Butanol, Acetonitrile	74%	16:1	1.8:1
7	<i>n</i> -Propanol	81%	14:1	1.7:1
8	<i>t</i> -Butanol	87%	14:1	1.7:1
9	Tetrahydrofuran	91%	33:1	1.9:1

¹Isolated yield, ²Determined from the ¹H NMR spectrum of the crude material

³Solubility issue leading to recovery of starting material **273**

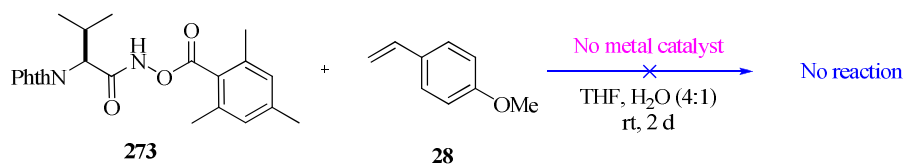
Table 18 - Screening of co-organic solvent

Results: It was observed that using a water miscible organic solvent improved the yields while the diastereoselectivity remained untouched. The best yielding conditions were achieved with entry 9 employing tetrahydrofuran as co-solvent and was selected for the rest of the study.

This optimisation (Table 17 and 18) led to the formation of **292** in both excellent yield and regioselectivity. The high regioselectivity achieved could be dictated by steric interactions between bulky imidoosmium intermediate **288** and styrene **28** spatial position.

Although an excellent yield and high regioselectivity were obtained using L-valine derivative **273** as reoxidant, the poor diastereoselectivity remained an issue for a complete organic synthetic use. This is addressed in the following section.

It is noteworthy to pinpoint that a control experiment where **273** was subjected to 4-methoxystyrene **28** without addition of osmium catalyst was conducted before further studies (Scheme 106).



Scheme 106 - Osmium free control reaction

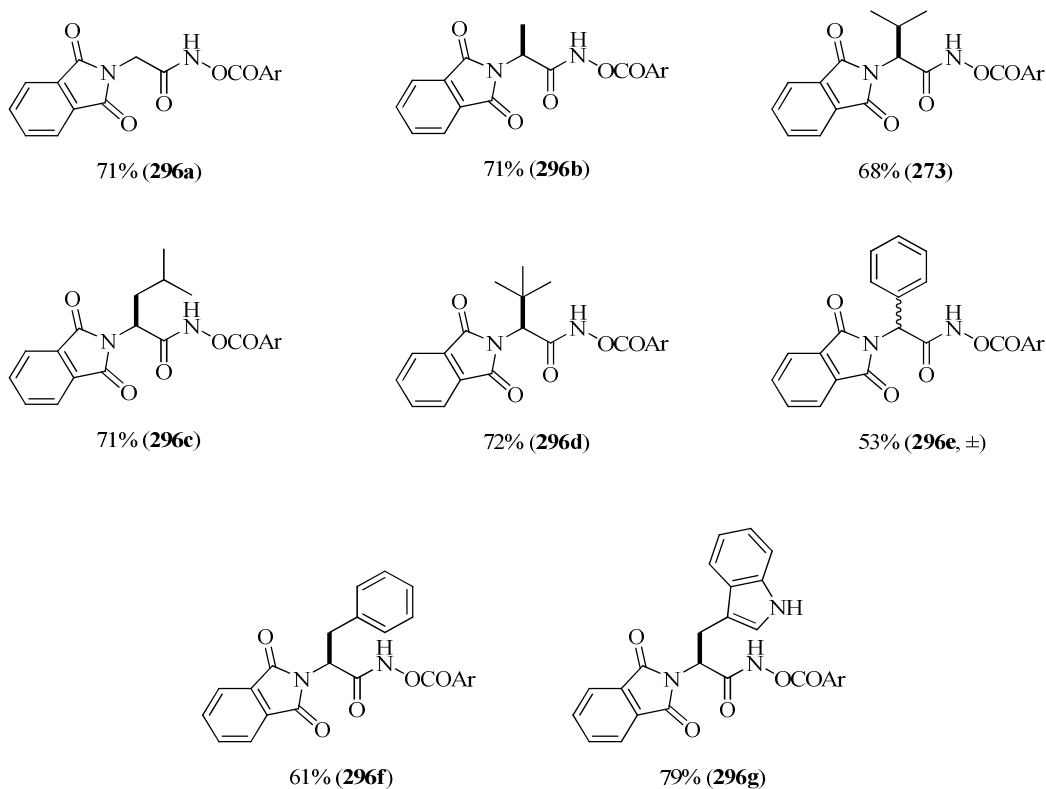
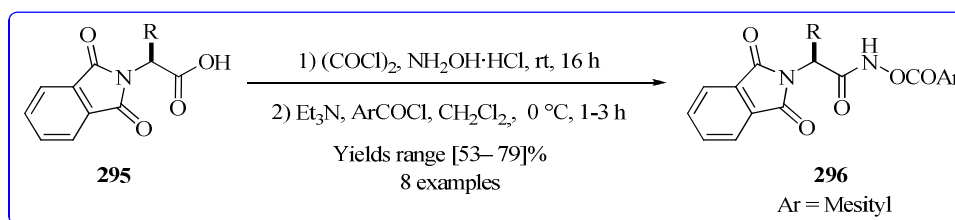
No reaction occurred even upon heating the reaction mixture up to 40 °C. As expected, the presence of osmium metal catalyst is essential for the methodology to succeed.

4.3 Investigation toward improving the diastereoselectivity

4.3.1 Screening of amino acids

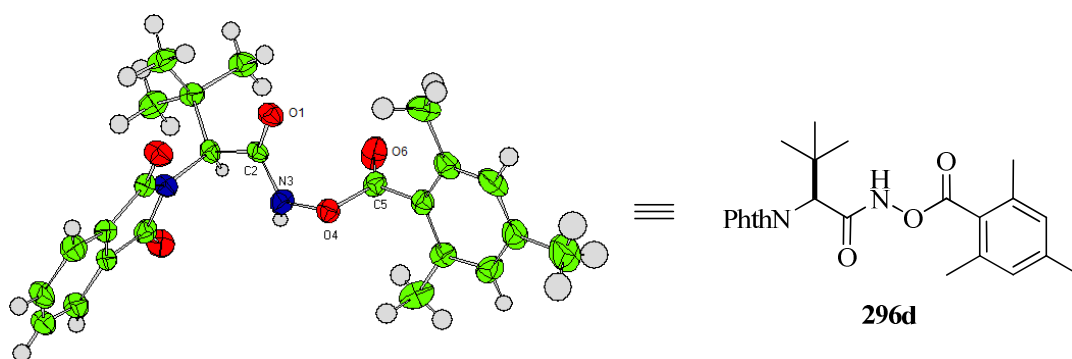
In an effort to improve the diastereoselectivity, different amino acid derivatives **296** were examined. Indeed, it was envisaged that steric hindrance from their alkyl chains might influence the diastereoselectivity. All precursors depicted in Scheme 107 were synthesised as previously described in Section 4.1.1 (see Experimental section, Chapter 5 for more details).

Substrate scope



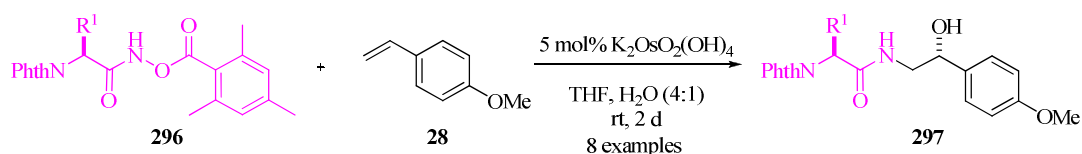
Scheme 107 - Summary of the synthesised amino acid precursors

Analysis of their spectroscopic data displayed the expected NH signal ranging between 9.58 and 11.08 ppm in their ^1H NMR spectrum. Furthermore, every derivative presented a characteristic IR spectroscopy stretch of the carbonyl ranging between 1611 and 1670 cm^{-1} . These data were in complete accordance with substrates **273** and **296d**, which were formerly indentified by X-ray crystallographic analysis (Figure 28).

Figure 28 - X-ray crystal structure of **296d**

Assessment of the enantiomeric purity of L-alanine reoxidant derivative **296b** was also assessed using a chiral OD HPLC column and revealed to be of 98% *ee* upon comparison to authentic racemic standards (see Appendix 2 for HPLC traces). It was then rationalised that compounds **296c**, **296d**, **296f** and **296g** would not undergo any epimerisation and no further tests were carried out; except for α -phenylglycine derivative **296e**, which displayed complete epimerisation through this protocol.

The results of this screening are depicted in Table 19.



Entry	Reoxidant (296)	Amino acid	Yield ¹ of (297)	<i>rs</i> ²	<i>dr</i> ²
1	296a	glycine	72% (297a)	5:1	N/A
2	296b	L-alanine	86% (297b)	14:1	1.2:1
3	273	L-valine	91% (292)	33:1	1.9:1
4	296c	L-leucine	83% (297c)	12:1	2:1
5	296d	L- <i>t</i> -butylleucine	67% (297d)	16:1	1.8:1
(6)	296e	L- α -phenylglycine	56% (297e)	8:1	2:1
7	296f	L-phenylalanine	74% (297f)	23:1	1.8:1
8	296g	L-tryptophan	No reaction ³		

¹Isolated yield, ²Determined from the ¹H NMR spectrum of the crude material

³Solubility issue leading to recovery of starting material **296g**

Table 19 - Screening of amino acid precursors **296**

All compounds synthesised presented a characteristic IR spectroscopy stretch of the carbonyl ranging between 1612 and 1684 cm^{-1} inherent of amides. Moreover, subsequent oxidation of the products as described in following Section 4.7 was conducted. Unfortunately, testing different amino acid precursors was unsuccessful regardless of the bulk of the alkyl group used. Although the regioselectivity fluctuated slightly, the diastereoselectivity remained unaffected at a disappointing low 2:1 ratio. Attempt to further improve the diastereoselectivity with entry 3 by conducting the reaction at 5°C was ineffective as no reaction was observed with complete recovery of reoxidant **273**.

Hence, it was envisaged in view of these results that the addition of an external additive might be necessary to achieve an increase in diastereoselectivity.

4.3.2 Screening of additives

In order to improve the diastereoselectivity of the reaction, a ligand screening was conducted (Table 20). By adding a catalytic amount of enantiopure ligand, it was postulated that the creation of a chiral pocket involving imidoosmium intermediate **288** would occur. This stereochemically well defined pocket would then hinder one approach to alkene substrate **28** leading to high diastereoselective aminohydroxylation process. The elected ligands for this initial screening all belonged to the cinchona family as their relevance to osmium reactivity has been proven in past studies (see Section 1.2).



Entry	Ligand	rs^1	dr^1
1	No ligand	20:1	1.3:1
2	Quinuclidine	25:1	1.5:1
3	(DHQ) ₂ PYR	2.5:1	1:1.25
4	(DHQ) ₂ PHAL	1:1.6	1:2
5	(DHQD) ₂ PHAL	3:1	2.6:1
6	(DHQ) ₂ AQN	6.5:1	1:1.3
7	(DHQD) ₂ AQN	13:1	15:1

¹Determined from the ¹H NMR spectrum of the crude material

Table 20 - Screening of enantiopure ligand

As anticipated, a noticeable difference between these results prompted a more detailed analysis. Indeed, intriguingly the diastereoselectivity differed quite drastically between PHAL and AQN core structures (entry 5, 7 and Figure 29) with the latter giving the best result. In addition, the DHQ and DHQD also played an important role suggesting a critical spatial position of both the **tertiary amine** and the **ethyl group** (entry 6, 7 and Figure 29) towards osmium catalyst. Finally, entry 2 confirmed the need for chirality to implement any good levels of diastereoselectivity.

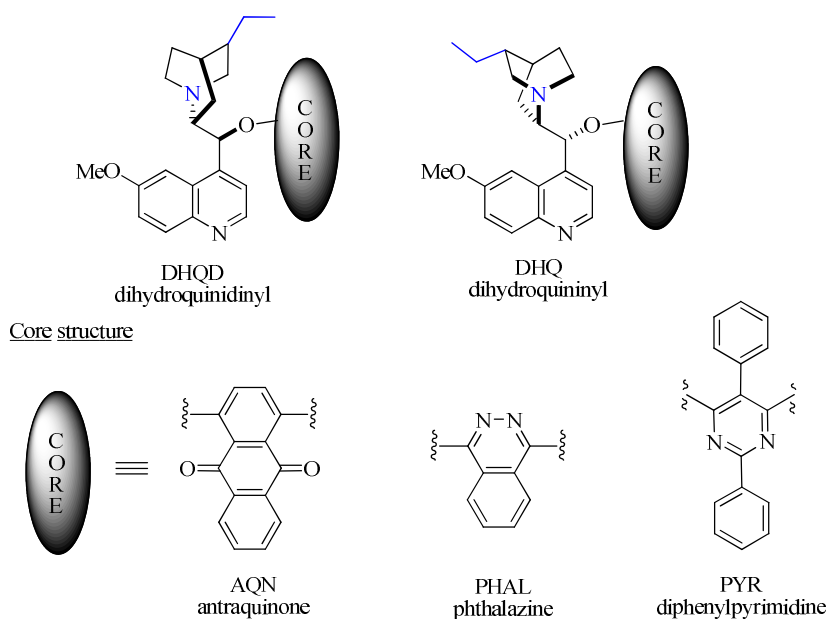


Figure 29 - Structural difference between the ligands employed

Taken all this information into account, the following osmium catalytic transition state model was proposed.

4.4 Possible transition state model

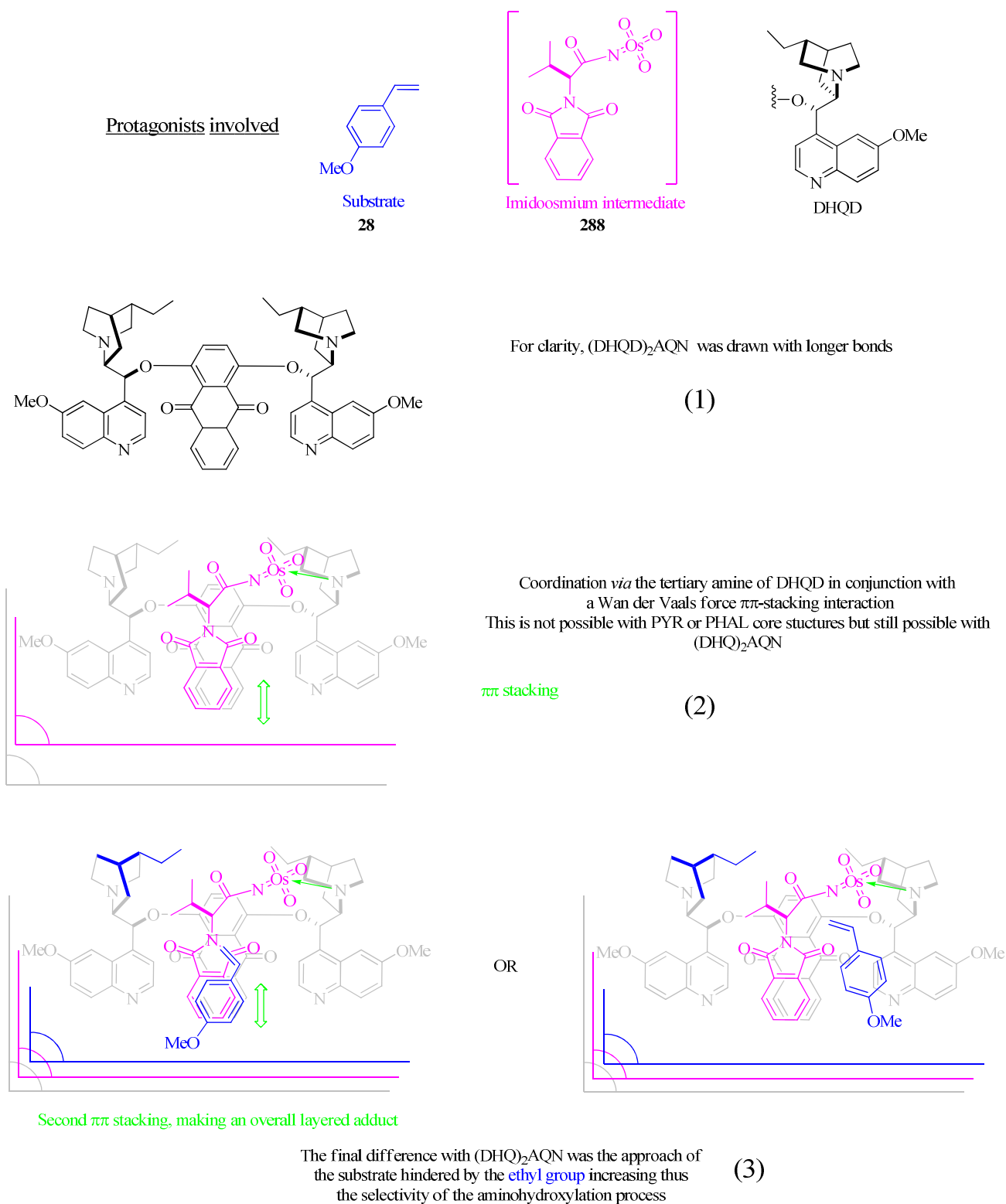
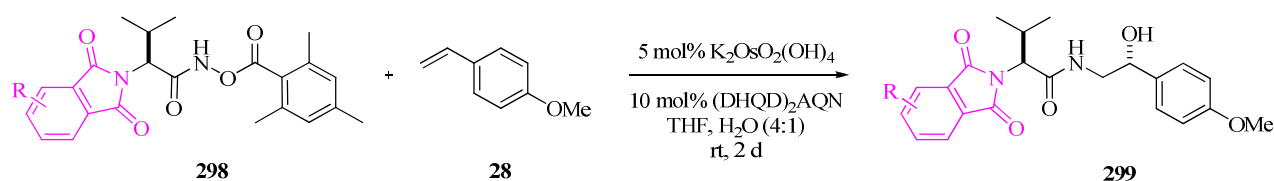


Figure 30 - Possible transition state model

Indeed, relying on previous studies (see Section 1.2), it was envisaged that imidoosmium complex **288** would be coordinated by the tertiary amine of DHQD enabling a $\pi\pi$ -stacking to take place between the phthalimide group of the reoxidant and the anthraquinone core as depicted in Step (1) of Figure 30. AQN contrary to the PYR or PHAL cores, would be the best fit for a possible $\pi\pi$ -stacking interaction. Consequently, the only possibility for a ligand to bind simultaneously to osmium metal, interacting at the same time with the phthalimido group of imidoosmium intermediate **288** would be by using either (DHQD)₂AQN or (DHQ)₂AQN ligand (Step (2)). In the DHQ ligand derivative one of the two described interactions would be weaker due to spatial hindrance but still possible. Eventually, substrate **28** being an aromatic alkene; an additional hydrophobic effect, *i.e.* $\pi\pi$ -stacking could be involved (Step (3)). Therefore, one approach in this sandwich pocket is favoured for an efficient cycloaddition to occur. This approach is further influenced by the spatial arrangement of the ethyl group of DHQD resulting in this high diastereoselectivity observed.

4.4.1 Influence of the phthalimide group on the $\pi\pi$ -stacking

In order to support the catalytic model proposed in Figure 30, a structural investigation on the imidoosmium **288** protecting group was carried out. The procedure employed for the synthesis of compounds **298a** and **298b** as well as their full spectroscopic characterisation can be found in the Experimental section, Chapter 5 (Table 21).



Entry	Reoxidant	Modification	Yield of 299 ¹	<i>rs</i> ²	<i>dr</i> ²
1	273		89% (292)	13:1 (20:1) ³	15:1 (1.3:1) ³
2	298a		63% (299a)	7.5:1 (20:1) ³	2.3:1 (1.9:1) ³
3	298b		75% (299b)	9:1 (17:1) ³	3.5:1 (1.4:1) ³

¹Isolated yield, ²Determined from the ^1H NMR spectrum of the crude material, ³Reaction carried out with no ligand

Table 21 - Investigations towards the $\pi\pi$ -stacking interaction

Reported spectroscopic data of product **299a** and **299b** were in accordance with compound **296d** formerly identified by X-ray crystallography analysis (see Section 2.1.3). Regarding their enantiopurity, it was rationalised that no significant racemisation would occur (see Section 4.3.1). Both structural modifications to the initial phthalimide protecting group (Table 21, entry 1) resulted in a net decrease in diastereoselectivity as expected. Indeed, tetrachloro substituted derivative **298a** would disrupt any $\pi\pi$ -interaction with the anthraquinone core of $(\text{DHQD})_2\text{AQN}$ according to our depicted model. Furthermore, by extending the aromatic system in **298b**, difficulty to accommodate this substrate in the the chiral pocket would lead to poor diastereoselectivity (Figure 31).

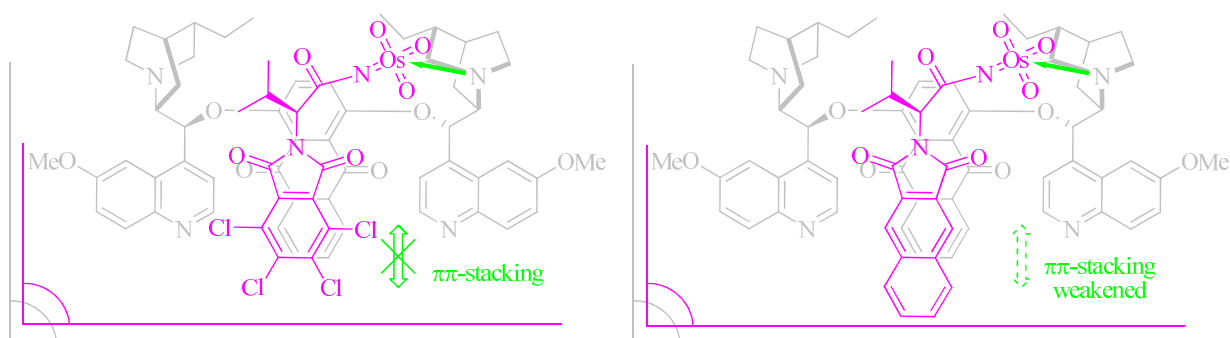


Figure 31 - Description of $\pi\pi$ -stacking interference

These experiments further supported the transition state model proposed.

4.4.2 Amino acid modifications

In addition to these last results, it was rationalised that the use of D-valine would result in a poor diastereoselectivity due to mismatch interactions within the chiral pocket. If positive, this hypothesis would further support our transition state model (Table 22).



Entry	Compound	Amino acid	Ligand	Yield ¹ of 301	rs^2	dr^2
1	273	L-valine	(DHQ) ₂ AQN	72%	6.5:1	1:1.3
2	273	L-valine	(DHQD) ₂ AQN	89%	13:1	15:1
3	300a	D-valine	(DHQ) ₂ AQN	63%	12:1	1:4.8
4	300b	D-valine	(DHQD) ₂ AQN	55%	6:1	1.6:1
5	300c	(±)-valine	(DHQD) ₂ AQN	64%	9:1	1.7:1

¹Isolated yield, ²Determined from the ¹H NMR spectrum of the crude material

Table 22 - Influence of chirality of the amino acids

The synthesis of D-valine derivative **300a** was confirmed with spectroscopic data in accordance with L-valine derivative **273** and opposite and equal $[\alpha]_D^{25}$. Its enantiopurity of 95% *ee* was confirmed by HPLC analysis. The low diastereoselectivity obtained with either ligand confirmed the mismatch interactions occurring (entry 3 and 4). This overall result was equally obtained when the phthalimide protected racemic valine (entry 5) was tested.

These experiments further supported the transition state model proposed.

4.5 Biological interest

The vast majority of α and β adrenergic agonists fall into distinctive chemical categories among which the phenethylamine: adrenaline being the hormone in the blood and noradrenaline the neurotransmitter (Figure 32).

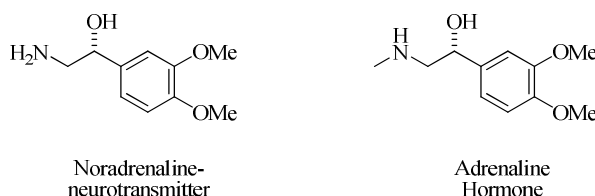


Figure 32 - Phenethylamine derivatives

The relative stereochemistry of these natural messengers matched perfectly with product **292** obtained through the osmium based methodology. Therefore, employing this methodology would lead in one step to well define enantiopure substrates, which would greatly facilitate the finding of antagonist or agonist binders in the very stereochemically sensitive neurotransmission process for example.⁷² Indeed, the high regioselectivity obtained complementary to past procedures, gave access to valuable phenethylamine derivatives which in combination with amino acids already used for instance in blood-brain barrier drug targeting therapy could help identifying a new set of biologically active compounds.^{17e, 21a, 73}

4.6 Scope of the methodology

The scope of this methodology was illustrated by the diverse substrates tolerated when treated with L-valine derivative **273**. All of the substrates tested were commercially available (Scheme 108).

The term *rs* referred to the major regioisomer obtained and the term *dr* referred to the ratio between the chiral hydroxyl group (R) or (S) and the alkyl chain of the amino acid derivative as mentioned previously.

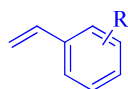
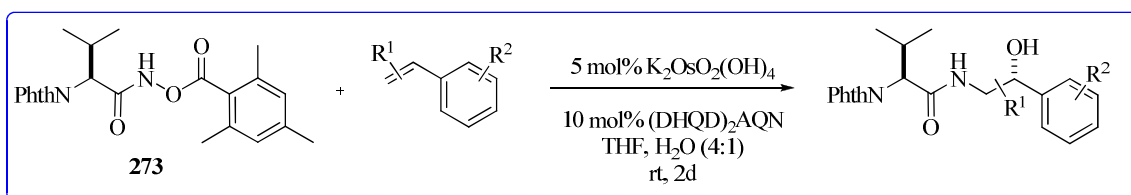
4.6.1 Aromatic alkenes

The structure assignment of all products was established by X-ray crystallographic analysis when possible (**292**, **302**, **304** and **312**) and by subsequent oxidation of the products as described in following Section 4.7.

Examining the reactivity of alkenes (Scheme 108), it was observed that electron rich substrates (entry 2 and 3) were prone to a more efficient aminohydroxylation process than unsubstituted styrene (entry 1) leading to the desired product in high yield and excellent diastereoselectivity. Although a net decrease of the reactivity was observed for very electron poor alkenes (entry 6), the reaction still proceeded for moderately electron poor alkenes (entry 2, 4 and 5) in moderate to excellent diastereoselectivity. In these last examples, both reoxidant and starting alkene were recovered during the reaction work-up procedure.

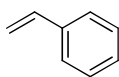
Having the proposed model for the transition state in mind (see Figure 30), entries 7, 9 and 10 were tested. An attempt to compare steric and to increase the $\pi\pi$ -stacking effects of the substrate using a naphthalene derivative did not improve the diastereoselectivity. Similar result was obtained with compound **309** displaying possible torsion angle within the catalyst pocket.

Substrate scope

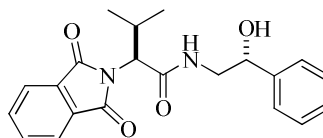


a) 10 mol% (DHQD)₂AQN
b) No ligand
c) 10 mol% (DHQ)₂AQN

Entry (1)



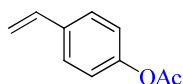
75%_a, *rs* 15:1 *dr* 13:1
80%_a, *rs* 20:1 *dr* 1.5:1
68%_c, *rs* 6.6:1 *dr* 1:1.4



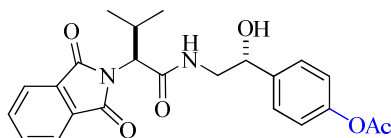
(302)



Entry (2)

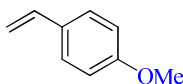


78%_a, *rs* 12:1 *dr* 8:1
80%_a, *rs* 13:1 *dr* 1.5:1
69%_a, *rs* 6.3:1 *dr* 1:2

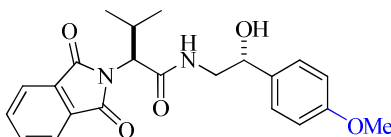


(303)

Entry (3)



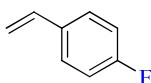
89%_a, *rs* 13:1 *dr* 15:1
91%_a, *rs* 33:1 *dr* 1.9:1
72%_c, *rs* 6.5:1 *dr* 1:1.3



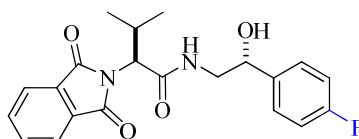
(304)



Entry (4)

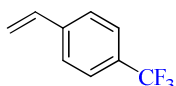


79%_a, *rs* 17:1 *dr* 6.2:1
81%_a, *rs* 15:1 *dr* 2:1
71%_c, *rs* 15:1 *dr* 1.3:1

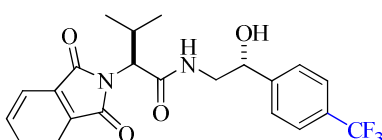


(305)

Entry (5)

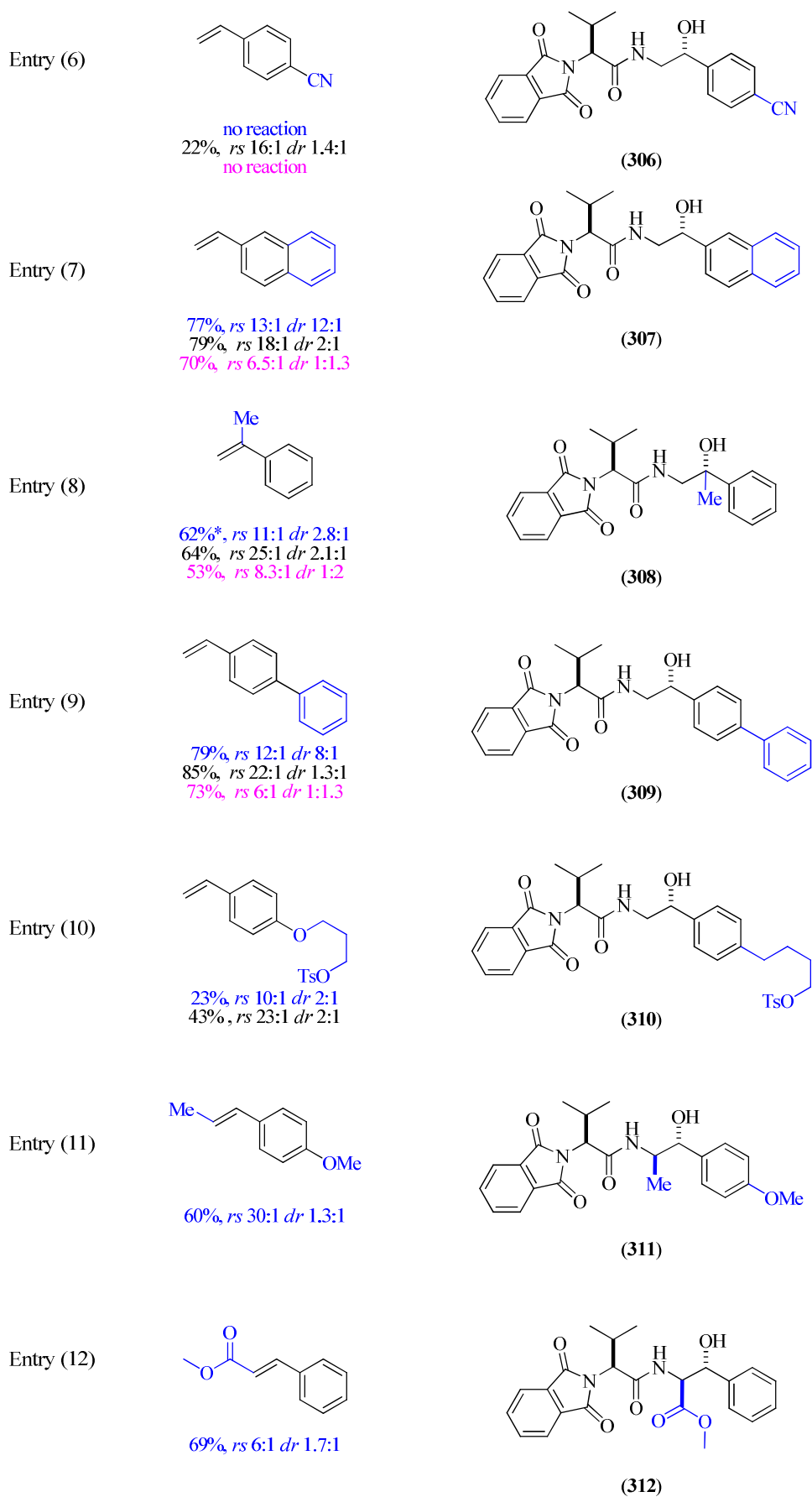


50%_a, *rs* 12:1 *dr* 11:1
56%_a, *rs* 19:1 *dr* 1.5:1
46%_c, *rs* 4:1 *dr* 1:1.4



(306)

Scheme 108 - Substrate scope



Scheme 108 - Substrate scope (continued)

Examining the substitution tolerated on the alkene, 1,1'-substituted substrate (entry 8) enabled the formation of a quaternary centre in a moderately stereocontrolled manner. Tertiary alcohol **308** albeit obtained with low diastereoselectivity remained an attractive result in the prospect of creating quaternary centre through this methodology. Its structure determination was carried out through ^1H - ^1H COSY experiment analysis with the NH signal only coupling with the CH_2 protons. Furthermore, the 7.23 ppm signal of the NH amide was in the same range with all the previous examples. The stereochemistry at the newly formed stereogenic centre is assumed to be that as shown (*i.e.* under control exerted by the chiral ligands). Moreover, ^1H NMR spectroscopic data were compared with a similar product present in the literature.⁷⁴

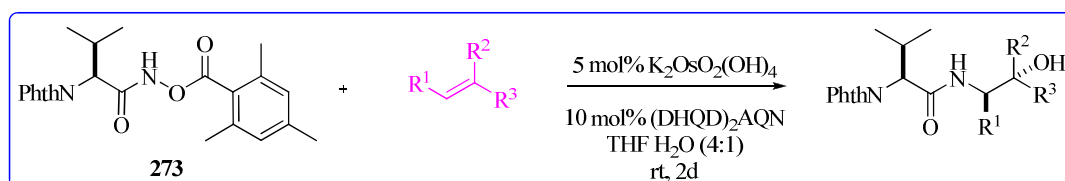
Upon comparison of entry 3 and 11, it became evident that, although good conversion was achieved, non-activated 1,2-substituted alkenes were not viable substrates in the styrene pattern with low diastereoselectivity observed. As for activated 1,2-substituted alkene (entry 12), the low regioselectivity was the main stumbling block.

Finally, in order to ensure that our transition state model (see Section 4.4) was applicable to other substrates regardless of their electronic nature, terminal alkenes having displayed good diastereoselectivity employing $(\text{DHQD})_2\text{AQN}$ as the chiral ligand (entry 1 to 9) were screened with its $(\text{DHQ})_2\text{AQN}$ counterpart. The low level of diastereoselectivity obtained was anticipated and in accordance with the hypothesis formulated as the use of $(\text{DHQ})_2\text{AQN}$ could only overturn the facial bias of the system to a small degree.

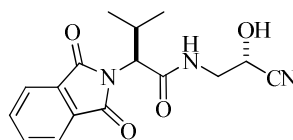
4.6.2 Non-aromatic alkenes

This methodology was also applicable to aliphatic alkenes as depicted in Scheme 109. It is important to stress out that the conditions applied to these non-aromatic substrates were not optimised due to time restrictions. These results remained of particular interest as explained later on.

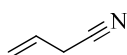
Substrate scope



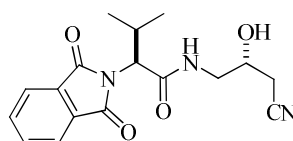
66%, *rs* 15:1 *dr* 4:1



(313)



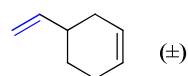
75%, *rs* 2.5:1 *dr* 7:1



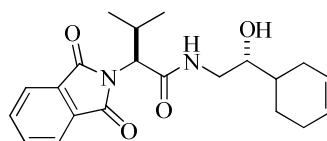
(314)



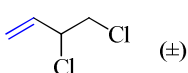
no reaction



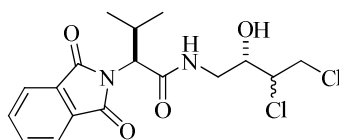
8%, r_s 100:0 dr 3:1


$$(\pm) \quad (315)$$

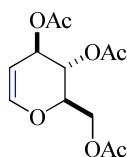
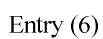
Selectivity of terminal over internal alkene



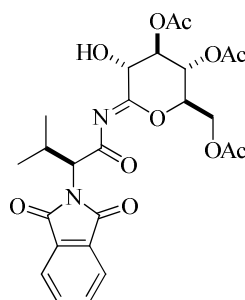
79%, *rs* 17:1 *dr* 6.2:1


$$(\pm) \text{ (316)}$$

Further fonctionnalisation possible



21%, r_s 100:1 dr 16:1



(317)

Creation of an aminoacid-sugar adduct

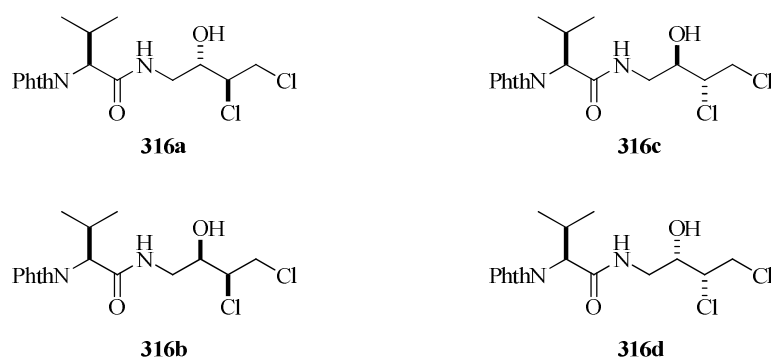
Scheme 109 - Substrate scope for non-aromatic alkenes

The correct structure assignment for each product was established after thorough spectroscopic analysis detailed in the Experimental section, Chapter 5. However, the determination of the major

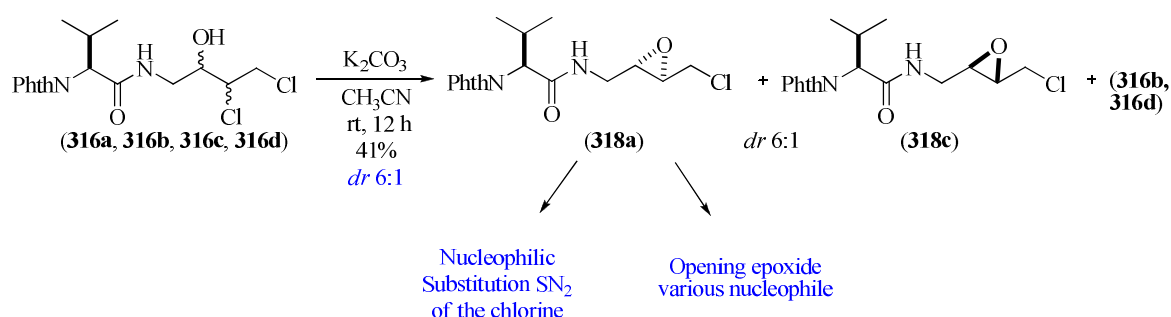
diastereomer of these products remained uncertain and was assigned by analogy to the styrene series (when (DHQD)₂AQN was employed) lacking X-ray crystal structures.

Entry 1 displayed excellent regioselectivity and moderate diastereoselectivity. It was envisaged that the nitrile group π orbitals were in conjugation with the π -system of the alkene enhancing its reactivity towards the imidoosmium intermediate **288**. This could also result in good interactions with the phthalimide group. Upon comparison of the diastereoselectivity between entry 1 and 2, it was postulated that the presence of an extra carbon broke the rigidity of the former substrate enabling a better fitting within the chiral pocket. However, this added flexibility was also responsible for a loss in regioselectivity. The addition of an extra electron withdrawing group completely shut down the reactivity of 1,1' disubstituted alkene (entry 3) compared to entry 1. It was rationalised that the benefit of the conjugated π -system observed for acrylonitrile lowering the LUMO of the alkene was lost explaining its low reactivity. Although entry 4 demonstrated selectivity in favour of a terminal alkene over an internal one, the poor yield stressed the need for activated aliphatic alkene to obtain an applicable process. Analysis of **315** ¹H NMR spectrum confirmed the presence of internal alkene protons at 5.65 ppm as well as the complete disappearance of the terminal alkene protons signals.

In this series, two entries deserved to be highlighted. Indeed, entry 5 showcased the facile access to more complex structure from straightforward functionalisation. Starting with racemic 3,4-dichlorobut-1-ene, the aminohydroxylation employing phthalimide protected L-valine derivative **273** as nitrogen source afforded compound **316** in a good 79% yield with excellent regioselectivity and moderate diastereoselectivity. As expected, four diastereomers were observed in the NMR spectroscopic data of the crude material and the diastereomer ratio given is between (**316a**, **316d**) and (**316b**, **316c**) (Figure 33).

**Figure 33** - Four diastereomers obtained

It was postulated that submitting this mixture of compounds to basic conditions would result in a kinetic resolution with selective epoxide formation for only **316a** and **316c** (Scheme 110).

**Scheme 110** - Williamson epoxide synthesis of **318**

This hypothesis was successful affording compounds **318** (*dr* 6:1) in an excellent 41% yield after column chromatography separation from **316b** and **316d**. Further functionalisation could involve the opening of the epoxide with various nucleophiles and substitution of the chlorine.

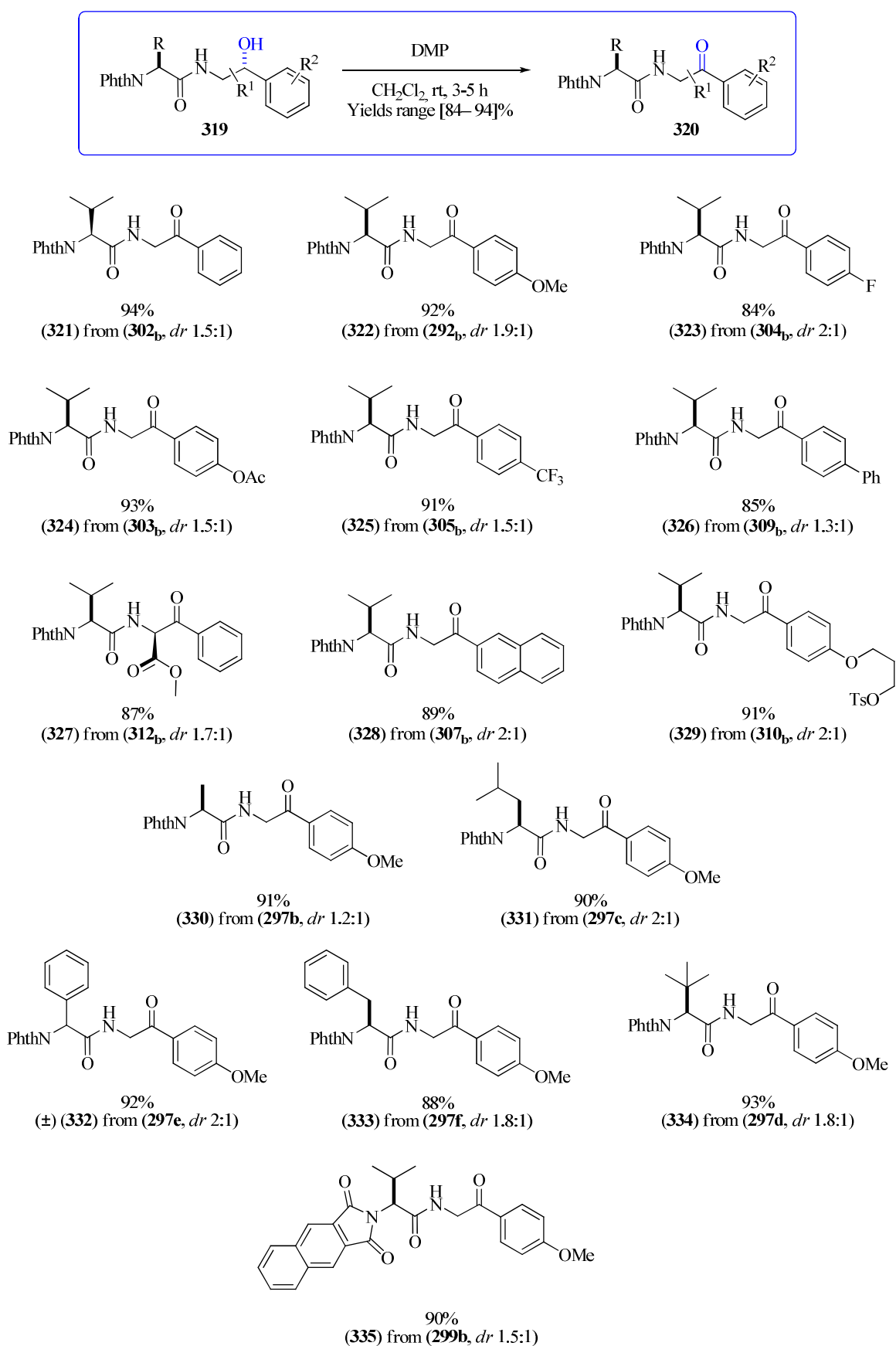
The second key example (see Scheme 109, entry 6) showcased the conjugation of biomolecules under aqueous conditions: amino acid-sugar adduct **317** was accessed in high diastereoselectivity and complete regioselectivity albeit in low yield. It was rationalised that this outcome was mainly due to the steric bulk of alkene substrate dictating the low reactivity but high selectivity of the process. Its correct structure assignment was determined by analysis of NMR spectrum with a key interaction of the NH signal of the amide with the anomeric proton at 5.72 ppm. Furthermore, its 76.2 ppm value in the ^{13}C NMR spectrum matched typically the range where non-anomeric carbons in monosaccharides are found (60 - 85 ppm).⁷⁵

As depicted in Scheme 108 and 109, the scope of this methodology employing amino acids as nitrogen source is broad.

4.7 Investigation towards the correct diastereo and regioisomer assignment

In addition to the three X-ray structures obtained in this series, the oxidation of several final compounds in the non-ligand experiments was carried out (see Scheme 108, (b) experiment). Using Dess-Martin reagent in dichloromethane proved to be efficient and this process was carried out on 15 examples (Scheme 111). In all cases, this oxidation resulted in the isolation of one unique product in excellent yield. Spectroscopic data analysis of the IR stretch of the carbonyl between 1712 and 1769 cm^{-1} in conjunction with one set of peak between 191.5 and 192.7 ppm in the ^{13}C NMR spectrum confirmed the structure of the resulting ketone **320**.

Substrate scope



Scheme 111 - Oxidation of the aminohydroxylation reaction product

These results supported the fact that the compounds isolated after the aminohydroxylation process were indeed diastereomers **319** and not regioisomers. Moreover, regarding the correct regioisomer assignment of these diastereomers, analysis of ^1H NMR spectra after oxidation reaction displayed no aldehyde signal but a very distinctive ABX type system in ketone derivatives **320** as depicted in Figure 34.

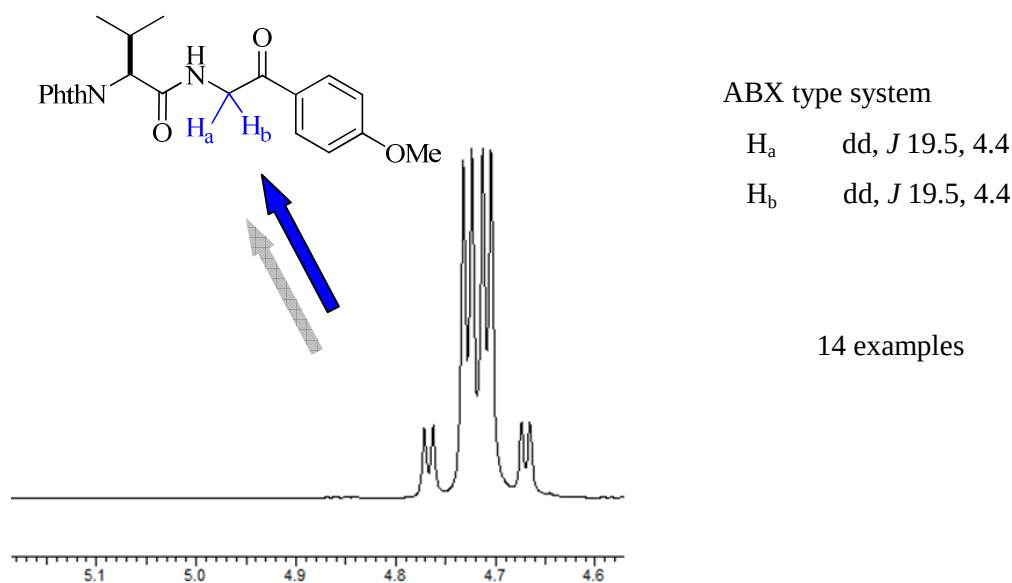
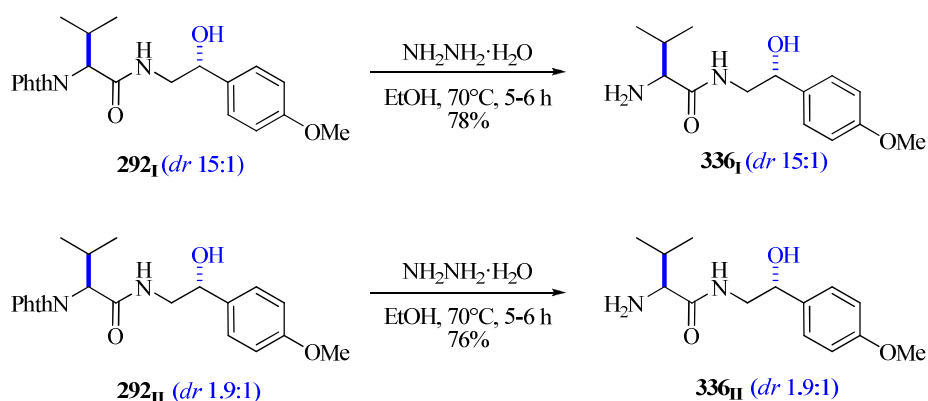


Figure 34 - Representative example of doublet of doublet observed for **322**

4.8 Investigation towards the phthalimide deprotection

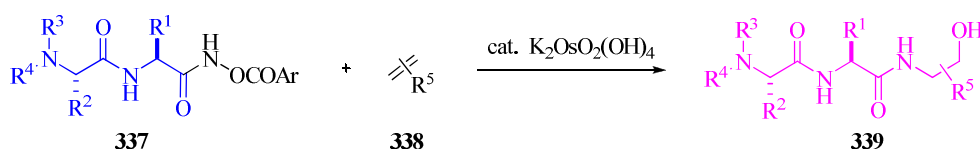
The deprotection of the phthalimide group has been described in several procedures containing fragile chiral products.⁷⁶ It was envisaged to employ sodium borohydride or methylamine as reagents but eventually, hydrazine monohydrate was chosen due to the nature of the by-product produced, facilitating subsequent purification. It was rationalised that conducting this deprotection experiment starting with two different ratio of diastereomers **292_I** and **292_{II}** and obtaining the same respective ratio with **292_I** and **292_{II}** would ensure that no epimerisation occurred when employing this methodology (Scheme 112).



Refluxing starting material **292** in ethanol with 1.5 equivalent of hydrazine monohydrate resulted in complete deprotection of the phthalimide group to afford the desired product **336** in high yield. Spectroscopic data analysis of product **336** revealed an IR stretch of 1656 cm^{-1} inherent to amide moiety with a broad singlet peak at 2.5 ppm in the ^1H NMR spectrum in accordance with the presence of primary amine NH_2 . Finally, complete disappearance of the phthalimide group signals in the NMR spectra of **336** supported the correct structure assignment. The retention of the diastereomer ratio for both experiments ensured that no epimerisation occurred. Even submitting compound **292**_I with six equivalents of hydrazine monohydrate at 60°C for a week afforded **336** in 72% with no noticeable epimerization.

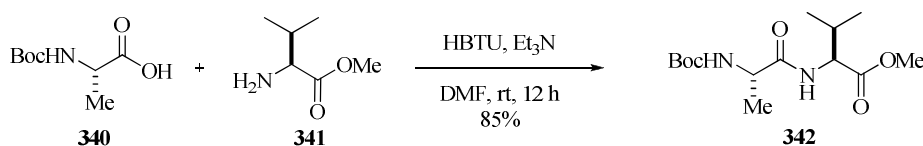
4.9 Investigations towards extending the scope to dipeptide derivatives

Following the success obtained with amino acid derivatives **265**, the methodology was pushed forward aiming to extend its scope to dipeptide derivatives **337** as depicted in Scheme 113.



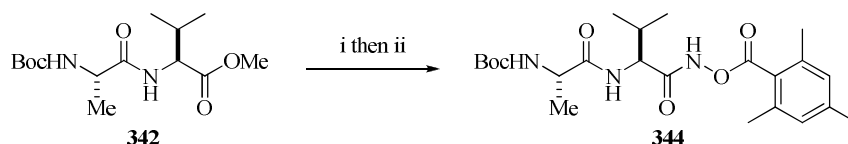
An initial attempt was conducted with 4-methoxystyrene **28** and Boc-protected dipeptide derivative **344** as depicted in the next page. Synthesis of Boc-protected dipeptide derivative **344** started first with the coupling of commercially available Boc-L-alanine **340** with L-valine methyl ester **341**

using *O*-benzotriazole-*N,N,N',N'*-tetramethyluroniumhexafluorophosphate (HBTU) as reagent (Scheme 114).



Scheme 114 - Synthesis of dipeptide **342**

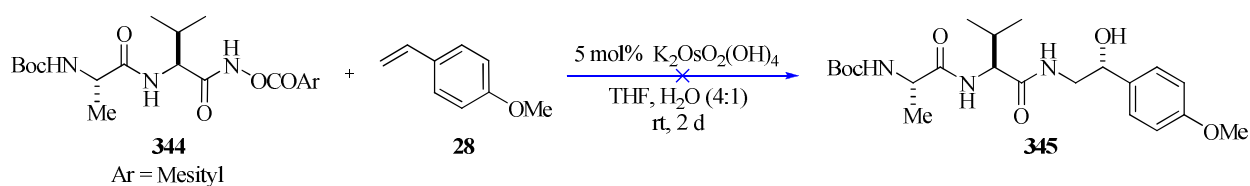
Spectroscopic data of resulting dipeptide **342** obtained in 85% yield were consistent with those reported in the literature. Subsequent saponification of **342** furnished quantitatively carboxylic acid **343**, which was further functionalised to produce reoxidant **344** in 63% yield over two steps (Scheme 115). Spectroscopic data of **344** were consistent with previously synthesised amino acid derivatives and full characterisation can be found in the Experimental section, Chapter 5.



Reagents and conditions: i) LiOH·H₂O, THF, H₂O, rt, 10 h, 100%; ii) *N*-methylmorpholine, **286**, DMTMM, CH₂Cl₂, -10 °C, 12 h, 63%.

Scheme 115 - Synthesis of dipeptide derivative **344**

The osmium-mediated aminohydroxylation of Boc-protected dipeptide derivative **344** with 4-methoxystyrene **28** was then carried out (Scheme 116).



Scheme 116 - Aminohydroxylation using **344** as nitrogen source

The reaction negative outcome (same result were obtained with the addition of a catalytic amount of ligand with the reaction being conducted at 40 °C) with recovery of both starting material **28** and **344** prompted several hypotheses as to understand and circumvent this unreactivity (Figure 35).

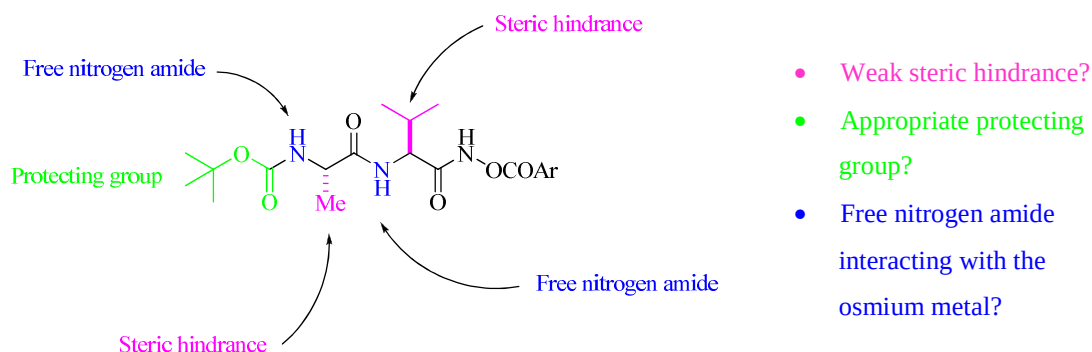


Figure 35 - Investigations towards the unreactivity of derivative **344**

According to previous studies (see Section 2.2.4), protecting the free **NH amide** would be sensible as a first option. However, it was rationalised that synthesising dipeptide derivatives **346**, where the first amino acid was mono-protected with a facile cleavable group would be unpractical and tedious if a broad substrate methodology was to be discovered (Figure 36).

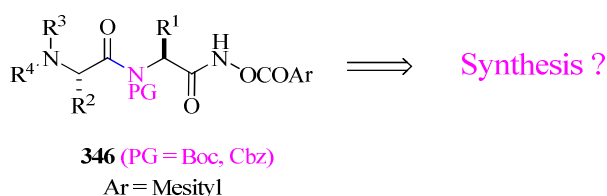
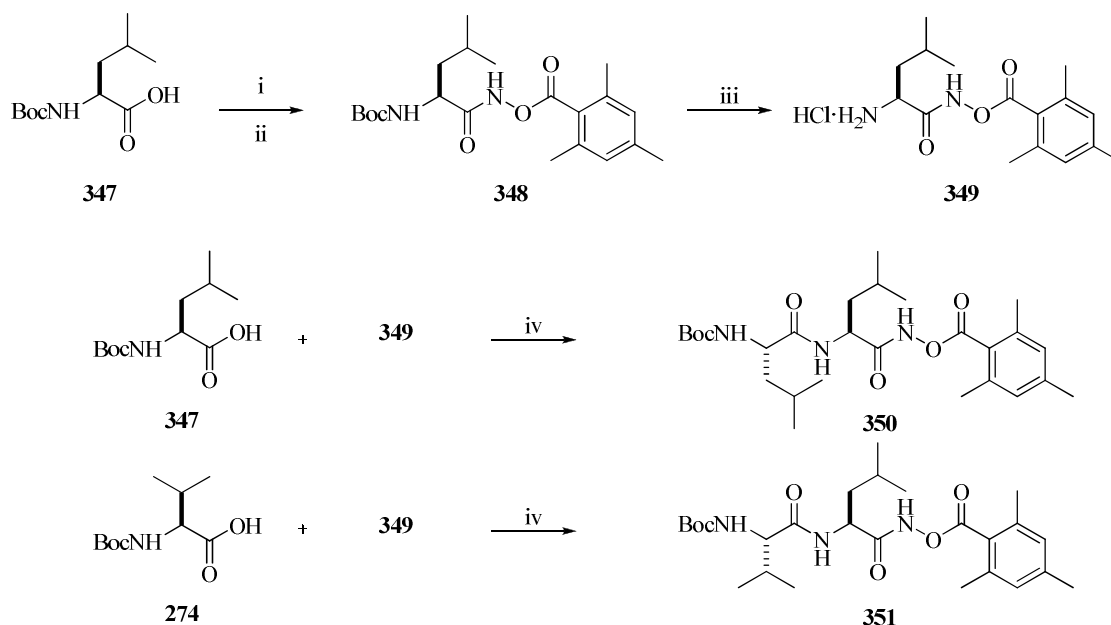


Figure 36 - Difficult synthesis of **346**

Therefore, the two other options were first considered.

4.9.1 Influence of the steric hindrance factor

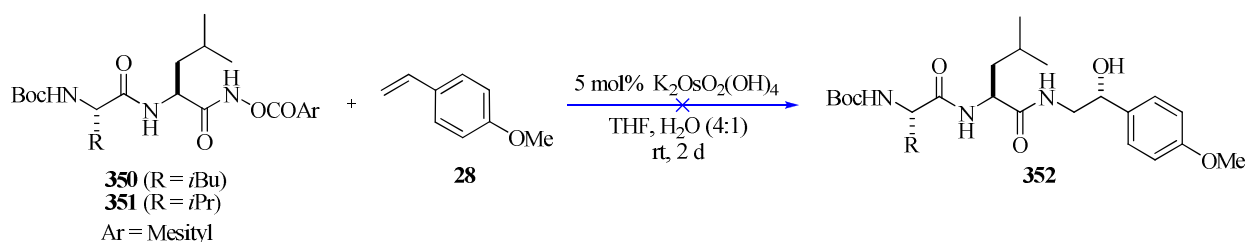
In order to assess this hypothesis, **350** and **351** were synthesised using DMTMM as coupling reagent and previously synthesised amine **349** as coupling partner (Scheme 117).



Reagents and conditions: i) EDCI·HCl, CH₂Cl₂, pentafluorophenol, aq. NH₂OH, rt, 14 h, 89%, ii) 2,4,6-trimethylbenzoyl chloride, CH₂Cl₂, Et₃N, 0 °C, 1 h, 81%; iii) 4M HCl in dioxane, 0 °C, 6 h, CH₂Cl₂, 100%; iv) *N*-methylmorpholine, DMTMM, CH₂Cl₂, 0 °C, 10 h, 70% (**350**) and 65% (**351**)

Scheme 117 - Synthesis of dipeptide derivative **350** and **351**

Structure identification of **349**, **350** and **351** was established through the analysis of their spectroscopic data which were consistent with previously reported compounds (see Experimental section, Chapter 5 for more details). It was envisaged that the alkyl chain of L-leucine amino acid present in **350** would provide additional steric hindrance compared to **344**. This bulked position would interfere with any possible adduct whilst formation of imidoosmium intermediate and promote the aminohydroxylation process (Scheme 118).



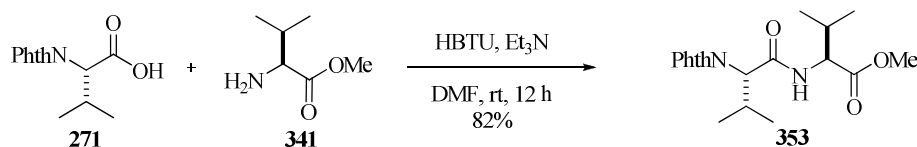
Scheme 118 - Aminohydroxylation using **350** and **351** as nitrogen source

Unfortunately, discouraging results were obtained where no traces of product **352** were detected. Heating up the reaction proved to be ineffective.

The possibility of Boc-dipeptide derivatives **350** and **351** bearing non-appropriate protecting groups (see Figure 36 in Section 4.2.1) was then envisaged and further investigated.

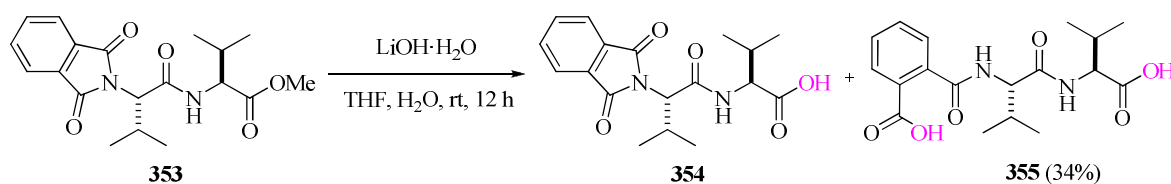
4.9.2 Influence of the protecting group of the terminal amino acid

To this end, compound **353** was synthesised from corresponding phthalimide protected L-valine **271** and L-valine methyl ester **341** (Scheme 119).



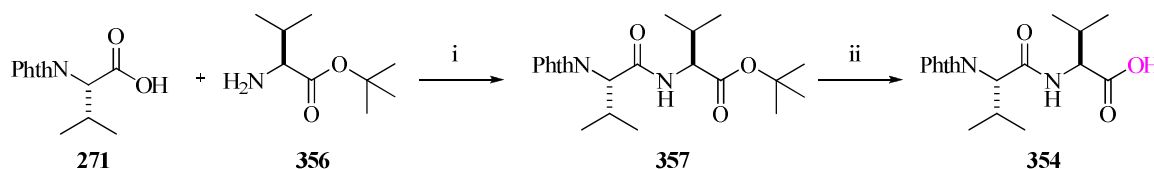
Scheme 119 - Synthesis of dipeptide **353**

Spectroscopic data of the resulting dipeptide **353** obtained in 82% yield were consistent with those reported in the literature. **353** was then submitted to a saponification procedure. Surprisingly, the desired carboxylic acid **343** was heavily contaminated with what revealed to be diacid **355**. Partial hydrolysis of the phthalimide protecting group was responsible for its formation as depicted in Scheme 120.



Scheme 120 - Unexpected hydrolysis of the phthalimide group

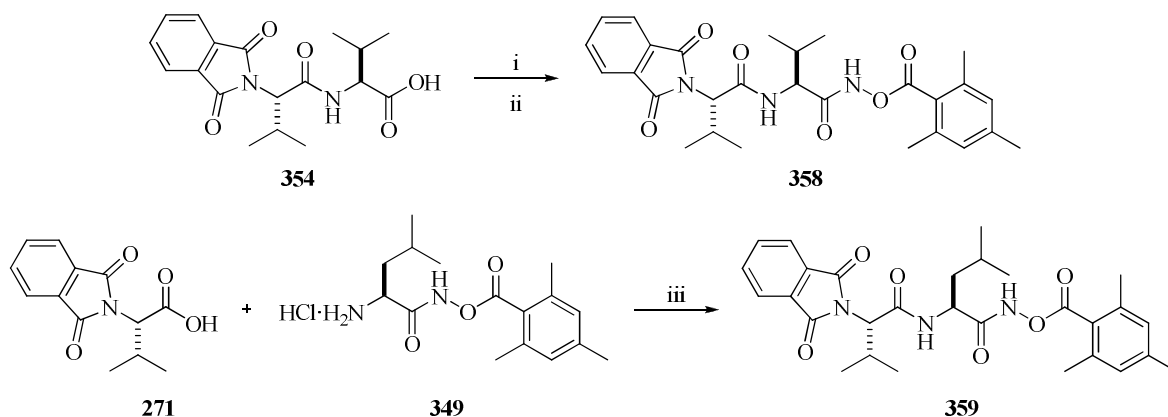
Compound **355** structure was confirmed by mass spectroscopic data of its sodium adduct m/z (ESI⁺) at 387 and by the identification of two peaks at 175.1 and 174.9 ppm in the ¹³C NMR. This problem was circumvented by reacting **271** with L-valine *t*-butyl ester **356**. Deprotection of **357** in acidic medium afforded **354** in a quantitative manner (Scheme 121).



Reagents and conditions: i) HBTU, DMF, Et₃N, rt, 12 h, 71%, ii) TFA, CH₂Cl₂, 0 °C, 2 h, 100%.

Scheme 121 - Successful synthesis of **354**

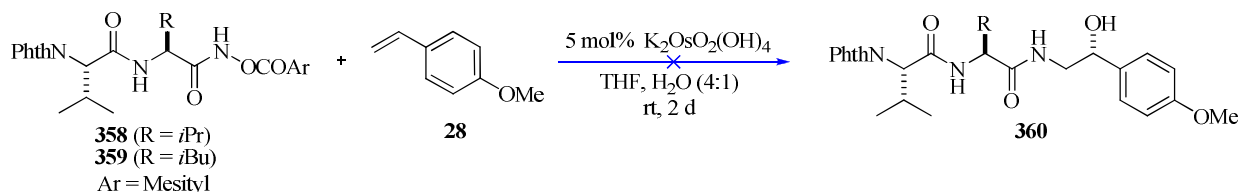
354 was then converted in 66% yield to reoxidant **358** demonstrating the required characteristic spectroscopic data (see Experimental section, Chapter 5 for more details). In a parallel experiment, **359** was also synthesised from phthalimide protected acid **271** with **349** as depicted in Scheme 122.



Reagents and conditions: i) $(\text{COCl})_2$, $\text{NH}_2\text{OH}\cdot\text{HCl}$, CH_2Cl_2 , H_2O , rt, 12 h then ii) 2,4,6-trimethylbenzoyl chloride, CH_2Cl_2 , Et_3N , 0 °C, 1 h, 66% over two steps; iii) *N*-methylmorpholine, DMTMM, CH_2Cl_2 , 0 °C, 10 h, 68%.

Scheme 122 - Synthesis of dipeptide derivatives **358** and **359**

Frustratingly, both attempts appeared to be counterproductive as both experiments yielded no product but only recovery of starting material (Scheme 123).



Scheme 123 - Aminohydroxylation using **358** and **359** as nitrogen source

As previously observed, heating up the reaction proved to be ineffective. However, traces of amide side product. **361** were identified in this case (Figure 37).

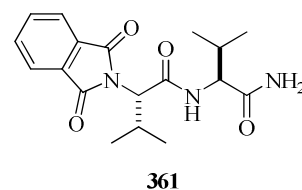
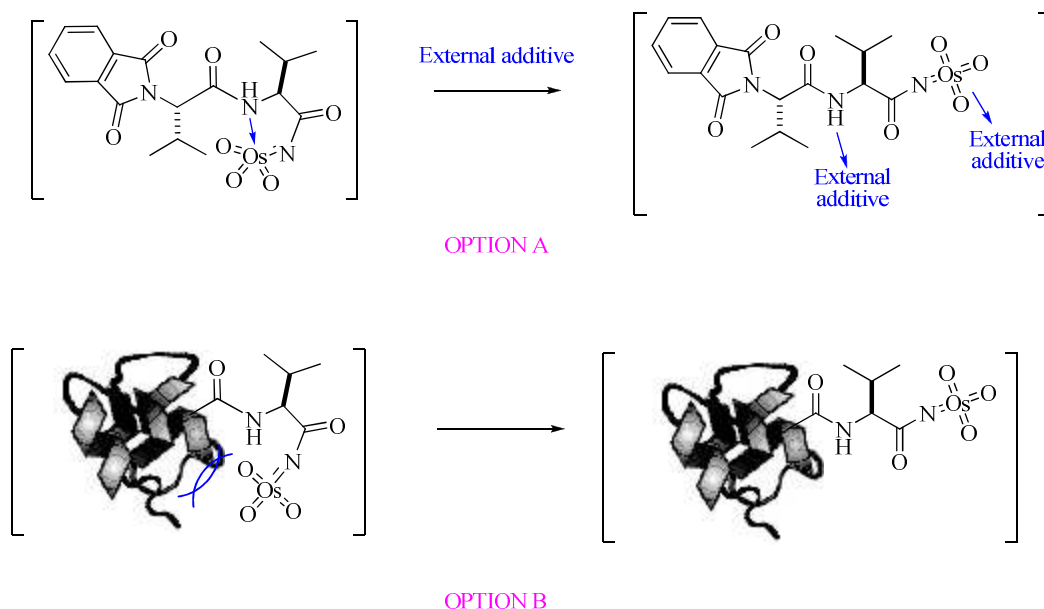


Figure 37 - Amide side product **361**

4.10 Conclusion and future work

To conclude, extending the methodology with dipeptide derivatives **337** would most likely require an external additive capable of breaking any adduct resulting from self-coordination of the imidoosmium intermediate (Scheme 124, option A). Another possible solution envisaged would be

to attempt the aminohydroxylation reaction with a larger polypeptide chain attached, possibly in its tertiary structure that could prevent any coordination of the free NH amide to the osmium metal (Scheme 124, option B).



Scheme 124- Additional additive⁷⁷

Finally, it would be important as a proof of concept to synthesise compound **362** or **363** and to submit it to the aminohydroxylation procedure to assess the actual limitation of this methodology (Figure 38).

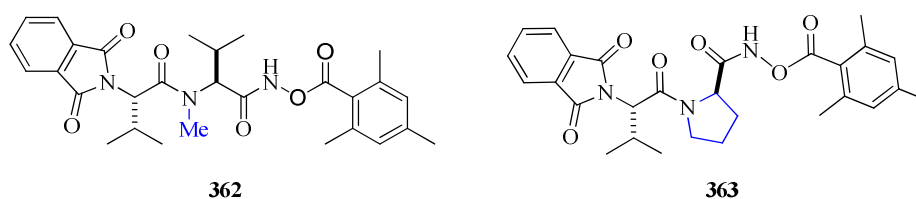
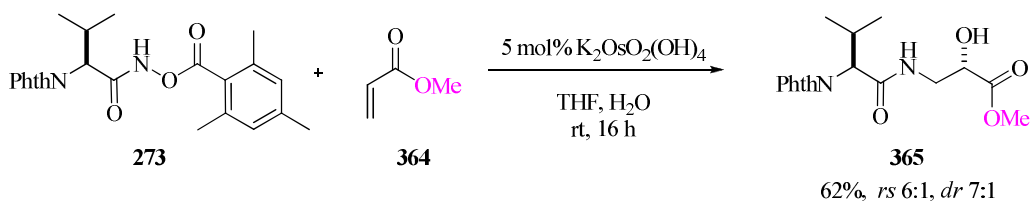
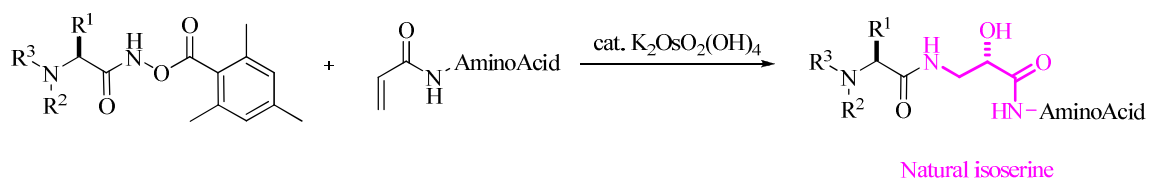


Figure 38 - Aminohydroxylation using **362** and **363** as nitrogen source

Another aspect worth investigating would be the generation of a new fundamental way of making peptide bonds. Indeed, early experiments afforded promising results when L-valine derivative **273** was reacted with methyl acrylate ester **364** providing the corresponding compound **365** in good yield and moderate diastereoselectivity (Scheme 125).⁷⁸

**Scheme 125** - Acrylate ester as viable substrate

Creating natural and unnatural polypeptides chains easily with a simple aqueous procedure would certainly be welcomed as depicted in Scheme 126.

**Scheme 126** - Polypeptide aqueous synthesis

Finally, employing the methodology described for amino acids as a tool in natural product synthesis should find applications in the synthesis of cyclopeptide alkaloids.⁷⁹

Chapter 5
Experimental Section

5. EXPERIMENTAL SECTION

5.1 General Experimental

Tetrahydrofuran, dichloromethane, acetonitrile, toluene, benzene and diethyl ether were purified prior to use by filtration through two activated alumina columns (grade: DD-2, Alcoa – THF; activated basic aluminium oxide, Brockmann I, standard grade, ~ 150 mesh, 58 Å, Aldrich – dichloromethane, acetonitrile, toluene, diethyl ether).⁸⁰ Reagents obtained from Acros, Aldrich, Avocado, Fluka and Lancaster fine chemicals suppliers were used directly as supplied or following purification according to procedures described by Perrin and Armarego.⁸¹ All non-aqueous reactions were carried out under an atmosphere of argon using oven- or flame- dried glassware. Syringes and needles, for the transfer of moisture sensitive reagents, were oven-dried and cooled in a dessicator over self-indicating silica gel.

Flash column chromatography was carried out according to the method of Still using silica gel 60 (0.040-0.063 mm) (Merck) using head pressure by means of head bellows.⁸² Thin layer chromatography was performed on commercially available pre-coated aluminium-backed plates (0.25 mm silica gel with fluorescent indicator UV254). Compounds were visualised either by the quenching of UV fluorescence or by staining with a potassium permanganate, ammonium molybdate, or vanillin solution.

¹H NMR spectra were recorded on a Bruker AC200 (200 MHz), Bruker AVANCE AV400 (400 MHz), Bruker DPX400 (400 MHz) or on a Bruker AVANCE AV500 (500 MHz) spectrometer in CDCl₃, (CD₃)₂CO, C₆D₆ or (CD₃)₂SO. Signal positions were recorded in ppm with the abbreviations s, d, dd, t, dt, td, q, quint, sxt, ddt, dddd, br and m denoting singlet, doublet, double doublet, triplet, doublet of triplets, triplet of doublets, quartet, quintet, sextuplet, double doublet of triplet, double doublet of double doublet, broad and multiplet respectively. ¹³C NMR spectra were recorded on a Bruker AVANCE AV400 (100 MHz) or on a Bruker AVANCE AV500 (125 MHz) spectrometer. All NMR chemical shifts were referenced to residual solvent peaks. All coupling constants, *J*, are quoted in Hz. Signals in both the ¹H and ¹³C spectra were assigned with the aid of COSY (correlated spectroscopy), HMQC (heteronuclear multiple-quantum correlation) and HMBC (heteronuclear multiple-bond correlation).

Infra-red spectra were recorded on a Bruker Tensor 27 FTIR spectrometer. Spectra were analysed as thin films between NaCl plates. Absorption maxima are quoted in wavenumbers (cm^{-1}).

Mass spectra (m/z) under the conditions of electrospray ionisation (ESI) were recorded on a Fisons Platform II. Accurate mass (HRMS) data were recorded under conditions of ESI on a Micromass LCT (resolution = 5000 FWHM) using a lock-spray source. The lock-mass used for calibration was tetraoctylammonium bromide in positive ion and sodium dodecyl sulfate in negative ion. m/z and HRMS data were recorded under conditions of electron impact ionisation (EI) on a Micromass GCT (resolution = 7000 FWHM).

Optical rotations were recorded on a Perkin Elmer 241 polarimeter (using the sodium D line, 589 nm) and $[\alpha]_D^{25}$ are given in units of $10^{-1} \cdot \text{deg} \cdot \text{dm}^2 \cdot \text{g}^{-1}$.

Melting points were obtained using a Leica VMTG heated-stage microscope or Griffin melting point apparatus with a mercury thermometer, and are uncorrected.

The result of ACD/IUPAC Name v8.05 was obtained using the ACD/I-Lab service.

“Petrol” refers to the fraction boiling in the range 40-60 °C unless otherwise stated.

Crystals of **130**, **159**, **160**, **170**, **171**, **172**, **173**, **174**, **175**, **177**, **179**, **180**, **187**, **189**, **207**, **228**, **220a**, **221**, **247**, **259**, **285**, **292**, **293**, **296d**, **302** and **312** were grown by slow evaporation. Single crystal X-ray diffraction data were collected using graphite monochromated Mo K α radiation ($\lambda = 0.71073$ Å) on an Enraf-Nonius KappaCCD diffractometer. The diffractometer was equipped with a Cryostream N₂ open-flow cooling device, and the data were collected at 150(2) K.⁸³ Series of ω -scans were performed in such a way as to cover a sphere of data to a maximum resolution of 0.77 Å. Cell parameters and intensity data were processed using the DENZO-SMN package.⁸⁴ The structures of were all solved by direct methods⁸⁵ and refined by full-matrix least squares on F^2 using the CRYSTALS suite.⁸⁶ Intensities were corrected for absorption effects by the multi-scan method, based on multiple scans of identical and Laue equivalent reflections. All non-hydrogen atoms were refined with anisotropic displacement parameters.

Special recommendation for the osmium catalysis: several sources of potassium osmate were used, and Sigma-Aldrich material gave the best results. However if possible, the direct synthesis of potassium osmate dihydrate is highly recommended for better quality results (see general procedure section).

5.2 General Procedures

Synthesis of Potassium Osmate dihydrate $\text{K}_2\text{OsO}_2(\text{OH})_4$

Osmium tetroxide is extremely toxic and must be handled with utmost care. Residues containing osmium must be viewed as potential sources of this dangerous compound. The hazard is reduced by storage of osmium wastes in contact with alkaline aqueous ethanol

In a fumehood, 1 g ampule of Osmium tetroxide (4.0 mmol) is opened by scoring it and touching with the molten tip of a glass rod. It is dropped into a 150 mL Erlenmeyer flask containing 10 g of potassium hydroxide in 43 mL of water. The mixture is stirred gently until all the osmium tetroxide has dissolved (10-15 min). With the addition of 10 mL of absolute ethanol, the dark-brown solution becomes opaque and violet in colour. The solution then clears as the potassium osmate salt precipitates. After 5 min of gentle stirring, 19 mL of absolute ethanol is added. The precipitate is collected using a sintered glass filter (medium frit) and fragments of the glass vials are removed with forceps and washed carefully with ethanol to recover any adhering product. The yield, after washing with ethanol and diethyl ether and air drying, is 1.28 g of $\text{K}_2\text{OsO}_2(\text{OH})_4$ (94%). The light purple powder is stored under an argon filled vial at rt.

Procedure A: Formation of *N*-hydroxy carbamates

Procedure A1

N,N'-Carbonyl diimidazole (1.5 eq.) was added to a solution of the carboxylic acid (1.0 eq.) in acetonitrile (8 mL•mmol⁻¹) and stirred under argon at room temperature until TLC indicated complete consumption of the carboxylic acid (typically after 1 h 30 - 2 h). Imidazole (4.0 eq.) and hydroxylamine hydrochloride (5.0 eq.) were successively added and stirring continued until TLC showed complete consumption of the adduct (generally after 12 h - 16 h). After halving the reaction solvent, the residue was acidified to pH 2 with 3 M aqueous HCl. The extraction of the aqueous phase was carried out with ethyl acetate (3 x 10 mL•mmol⁻¹). The organic phase was separated, was washed with brine (10 mL•mmol⁻¹), dried over Na_2SO_4 , filtered and the solvent was removed under reduced pressure to give the crude product which was used directly in the next step.

Procedure A2

To a solution of the carboxylic acid (1.0 eq.) in dichloromethane (15 mL•mmol⁻¹) under argon at 0 °C, was added three drops of *N,N'*-Dimethylformamide followed by the dropwise addition of freshly distilled oxalyl chloride (2.0 eq.). After completion of the addition, the reaction mixture was stirred for 1 h. The reaction mixture was then concentrated *in vacuo*, and redissolved in diethyl

ether ($15 \text{ mL} \cdot \text{mmol}^{-1}$) affording a heterogenous mixture. Hydroxylamine hydrochloride (1.2 eq.) and anhydrous sodium carbonate (2.4 eq.) were added successively to the reaction mixture, and it was left to stir for 15 min. Then distilled water ($1.5 \text{ mL} \cdot \text{mmol}^{-1}$) was added (cautious, rapid gas evolution) followed 5 min later by the same amount of distilled water ($1.5 \text{ mL} \cdot \text{mmol}^{-1}$). The reaction mixture became cloudy and was stirred (for typically 16 h) until TLC indicated complete consumption of starting material. The reaction mixture was then acidified to pH 1 with a 3 M aqueous HCl solution and extracted with ethyl acetate ($2 \times 6 \text{ mL} \cdot \text{mmol}^{-1}$). The organic phase was separated, washed with brine ($6 \text{ mL} \cdot \text{mmol}^{-1}$), dried over Na_2SO_4 , filtered and the solvent was removed under reduced pressure. The residue was redissolved in dichloromethane ($15 \text{ mL} \cdot \text{mmol}^{-1}$) and reconcentrated *in vacuo* to afford the desired product which was used in the next step without further purification.

Procedure B: Mesitylation of *N*-hydroxy carbamates

To a suspension of substrate (1.0 mmol) in dichloromethane ($10 \text{ mL} \cdot \text{mmol}^{-1}$) cooled to 0°C , was added freshly distilled triethylamine (1.0 eq.) followed by dropwise addition of 2-mesityleneacetyl chloride (0.8 eq.). The reaction was maintained at 0°C until TLC indicated complete consumption of starting material (typically 30-50 min). The reaction mixture was concentrated *in vacuo* to a few mL and the residue was purified by flash column chromatography, eluting with dichloromethane to give the desired product.

Procedure C: Tethered Aminohydroxylation of *N*-[(mesitylcarbonyl)oxy]enamide

To a stirred solution of *N*-[(mesitylcarbonyl)oxy]enamide (1.0 eq.) in acetonitrile ($2.3 \text{ mL} \cdot \text{mmol}^{-1}$) was added *t*-butanol ($2.3 \text{ mL} \cdot \text{mmol}^{-1}$) at room temperature. The reaction mixture was stirred until a homogenous solution was obtained (use of sonicator recommended). To the reaction mixture was then added dropwise a solution of $\text{K}_2\text{OsO}_2(\text{OH})_4$ (0.04 eq. or 0.01 eq.) in water ($1.75 \text{ mL} \cdot \text{mmol}^{-1}$). The reaction was stirred at room temperature for 4-12 h (4 mol % catalyst) up to 48 h (1 mol % catalyst). After TLC indicated that the reaction had ceased, anhydrous Na_2SO_3 (ca. 80 mg/mg of osmium catalyst) was added and the reaction was stirred for another 30 min. The reaction mixture was concentrated onto silica *in vacuo* and purified by flash column chromatography (on a 0.5 mmol scale, 5 g of SiO_2 , elution with 50-60 mL of ethyl acetate/acetic acid 9.8:0.2 followed by 80 mL of ethyl acetate/methanol 9.5:0.5) to give the desired product.

Procedure D: Formation of phthalimide protected amino acids

To the neat carboxylic acid (1.0 eq.) under argon at rt, was added phthalic anhydride (1.1 eq.). After completion of the addition, the reaction mixture was heated at 150 °C and stirred for 5 h. The reaction mixture was then cooled down to 80 °C and cyclohexane was added very cautiously *via* the condenser. The reaction mixture was refluxed for 1 h. Upon cooling down, the solid was collected and dried under high vacuum for 1 h to afford the desired phthalimide protected amino acid.⁸⁷

Procedure E: Formation of *N*-hydroxy-alkanamide followed by subsequent acylationProcedure E₁

To a solution of the carboxylic acid (1.0 eq.) in dichloromethane (15 mL/mmol) under argon at 0 °C, was added three drops of *N,N'*-dimethylformamide followed by the dropwise addition of freshly distilled oxalyl chloride (2.0 eq.). After completion of the addition, the reaction mixture was stirred for 1 h at rt. The reaction mixture was then concentrated *in vacuo at rt*, and redissolved under argon in diethyl ether (15 mL•mmol⁻¹) affording a heterogenous mixture. Hydroxylamine hydrochloride (1.2 eq.) and anhydrous sodium carbonate (2.4 eq.) were added successively to the reaction mixture, and it was left to stir for 15 min. Then distilled water (1.5 mL•mmol⁻¹) was added (cautious, rapid gas evolution) followed 5 min later by the same amount of distilled water (1.5 mL•mmol⁻¹). The reaction mixture became cloudy and was stirred (for typically 12 h) until TLC indicated complete consumption of starting material. The reaction mixture was then acidified to pH 1 with a 3 M aqueous HCl solution and extracted with ethyl acetate (2 x 6 mL•mmol⁻¹). The organic phase was separated, washed with brine (6 mL•mmol⁻¹), dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure. The residue was redissolved in dichloromethane (15 mL•mmol⁻¹) and reconcentrated *in vacuo* to afford the desired product which was used in the next step without further purification. To a suspension of substrate (1.0 mmol) in dichloromethane (10 mL•mmol⁻¹) cooled to 0 °C, was added freshly distilled triethylamine (1.0 eq.) followed by dropwise addition of 2-mesityleneacetyl chloride (0.8 eq.). The reaction was maintained at 0 °C until TLC indicated complete consumption of starting material (typically 50-90 min). The reaction mixture was concentrated *in vacuo* to a few mL and the residue was purified by flash column chromatography, eluting with dichloromethane/methanol (100:0 to 9:1) to give the desired product.

Procedure E₂

To a solution of the carboxylic acid (1.0 eq.) in dichloromethane (15 mL•mmol⁻¹) under argon at 0 °C, was added *N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (1.0 eq.) followed by the addition of pentafluorophenol (1.2 eq.). After completion of the addition, the reaction

mixture was stirred for 6 h. The reaction mixture was then washed with a saturated solution of ammonium chloride ($3 \times 1.5 \text{ mL} \cdot \text{mmol}^{-1}$), separated, dried over Na_2SO_4 and filtered. To the resulting solution under argon was added a hydroxylamine solution (50 wt. % in H_2O ; 1.2 eq.) dropwise. The reaction mixture became cloudy and was stirred (for typically 4-6 h) until TLC indicated complete consumption of starting material. The reaction mixture was then concentrated *in vacuo*, and the residue triturated vigorously in lukewarm hexane ($3 \times 15 \text{ mL} \cdot \text{mmol}^{-1}$) to afford the desired product which was used in the next step without further purification. To a suspension of substrate (1.0 mmol) in dichloromethane ($10 \text{ mL} \cdot \text{mmol}^{-1}$) cooled to 0°C , was added freshly distilled triethylamine (1.0 eq.) followed by dropwise addition of 2-mesityleneacetyl chloride (0.8 eq.). The reaction was maintained at 0°C until TLC indicated complete consumption of starting material (typically 50-90 min). The reaction mixture was concentrated *in vacuo* to a few mL and the residue was purified by flash column chromatography, eluting with dichloromethane/methanol (100:0 to 9:1) to give the desired product.

Procedure F: Direct AminoAcid coupling using DMTMM as coupling agent

To a solution of the carboxylic acid (1.0 eq.) in dichloromethane ($15 \text{ mL} \cdot \text{mmol}^{-1}$) under argon at 0°C , was added freshly prepared 4-(3,5-dimethoxyphenyl)-4-methylmorpholin-4-ium chloride (DMTMM) (1.0 eq.).⁸⁸ After completion of the addition, the reaction mixture was stirred vigorously for 10 h at 0°C . To the reaction mixture was then added *O*-(2,4,6-trimethylbenzoyl)hydroxylammonium chloride (1.2 eq.) followed by the dropwise addition of *N*-methylmorpholin (1.2 eq.). The reaction mixture was stirred vigorously for another 10 h letting the reaction mixture warmed to rt. The reaction mixture was then washed with 1 N aqueous CuSO_4 solution ($3 \times 1.5 \text{ mL} \cdot \text{mmol}^{-1}$) and concentrated *in vacuo* **at rt** to a few mL. The residue was purified by flash column chromatography, eluting with dichloromethane/methanol (100:0 to 9:1) to give the desired product.

Procedure G: Aminohydroxylation of styrene derivative

To a stirred solution of styrene (1.0 eq.) in tetrahydrofuran ($9.1 \text{ mL} \cdot \text{mmol}^{-1}$) was added (*S*)-2-(1,3-dioxoisindolin-2-yl)-3-*Alkyl-N*-(2,4,6-trimethylbenzoyloxy)*alkanamide* (1.1 eq.), followed by $(\text{DHQD})_2\text{AQN}$ (0.10 eq.) at room temperature. The reaction mixture was stirred for 5 minutes until a homogenous solution was obtained (use of sonicator recommended). To the reaction mixture was then added dropwise a solution of $\text{K}_2\text{OsO}_2(\text{OH})_4$ (0.05 eq.) in distilled water ($2.2 \text{ mL} \cdot \text{mmol}^{-1}$). The reaction was stirred vigorously at room temperature for 48 h. After TLC indicated that the reaction had ceased, anhydrous Na_2SO_3 (ca. 80 mg/mg of osmium catalyst) was added and the reaction was stirred for another 30 min. The reaction mixture was extracted with ethyl acetate

(3 x 6 mL•mmol⁻¹), separated, dried over Na₂SO₄ and filtered. It was then concentrated *in vacuo* and purified by flash column chromatography (typically on a 0.23 mmol scale, 30 g of SiO₂ used in a 15 mm glass column, elution with Dichloromethane/Methanol 200:0 to 100:1, vaniline used as TLC dip) to give the desired product.

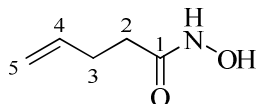
Procedure H: Oxidation of the resulting aminoalcohol

To a stirred solution of the aminoalcohol (1.0 eq.) in dichloromethane (1 mL•mmol⁻¹) under argon was added Dess-Martin reagent (1.05 eq.). The reaction mixture was stirred at rt until TLC indicated complete consumption of starting material (typically 3-5 h). The reaction mixture was then concentrated *in vacuo* to a few mL and the residue was purified by flash column chromatography, eluting with dichloromethane/methanol (100:0 to 100:1) to give the desired product.

5.3 Experimental Details

5.3.1 Chapter 2 – Characterisation Data

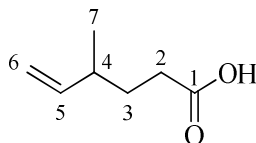
N-Hydroxypent-4-enamide (**90**)



Pent-4-enoic acid **89** (1.0 g, 10.0 mmol) was subjected to General Procedure A₁ to give the title compound **90** (1.1 g, 9.4 mmol, 94%) as a beige solid.

m.p. 70-72 °C; **v_{max}** (thin film)/cm⁻¹ 3211br, 3081br, 2918m, 1642s, 1538w, 1447m, 1112m, 1062m, 986m, 916m; **δ_H** (400 MHz, CDCl₃) 5.66-5.92 (1H, ddt, *J* 16.9, 10.3, 6.4, C(4)H), 4.97-5.17 (2H, m, C(5)H₂), 2.39 (2H, t, *J* 6.3, C(2)H₂), 2.21-2.32 (2H, m, C(3)H₂); **δ_C** (100 MHz, CDCl₃) 171.4 (C(1)O), 136.3 (C(4)H), 116.0 (C(5)H₂), 32.2 (C(2)H₂), 29.3 (C(3)H₂); **m/z** (ESI) 114 ([M-H]⁻, 100%); **HRMS** (ESI) C₅H₉NO₂ requires [M-H]⁻ 114.0555, found 114.0561 (+1.99 ppm).

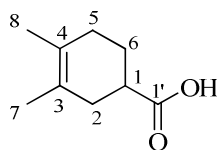
4-Methylhex-5-enoic acid (**92**)



Hydrogen peroxide (2 eq., 10 mL, 102 mmol) was added over 2 min at room temperature to a stirred solution of 4-methylcyclohexanone **91** (1 eq., 6.2 mL, 51 mmol) in methanol (0.22 mL•mmol⁻¹). After 15 min, the reaction mixture was added over 5 min to a stirred solution of ferrous sulphate (1.0 eq., 14 g, 51 mmol) and cupric sulphate (1.0 eq., 12.7 g, 51 mmol) in water (100 mL) maintaining the reaction mixture at room temperature. Upon the addition, the reaction mixture turned dark brown. It was stirred an additional hour. The aqueous phase was separated and extracted with diethyl ether (3 x 30 mL). The organic phase and ether extracts were washed with a saturated aqueous NaHCO₃ solution (3 x 30 mL). The alkaline extract were acidified with 3 M aqueous HCl and extracted with diethyl ether (3 x 30 mL). Removal of the solvent at reduced pressure gave the title compound **92** (1.56 g, 12.2 mmol, 24%) as a yellow oil.⁸⁹

δ_H (400 MHz, CDCl₃) 11.14 (1H, br s, OH), 5.64 (1H, ddd, *J* 17.4, 9.9, 7.8, C(5)H), 4.94-5.04 (2H, m, C(6)H₂), 2.26-2.44 (2H, m, C(2)H₂), 2.10-2.22 (1H, m, C(4)H), 1.53-1.75 (2H, m, C(3)H₂), 1.02 (3H, d, *J* 6.8, C(7)H₃); **δ_C** (100 MHz, CDCl₃) 180.6 (C(1)O), 143.2 (C(5)H), 113.9 (C(6)H₂), 37.4 (C(4)H), 32.0 (C(2)H₂), 31.0 (C(3)H₂), 20.2 (C(7)H₃).

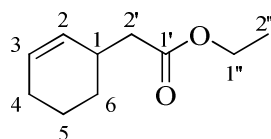
Spectroscopic data were consistent with those reported in the literature.⁹⁰

3,4-Dimethylcyclohex-3-ene-1-carboxylic acid (95)

To acrylic acid **94** (1 eq., 0.34 mL, 5 mmol) was added 4-*tert*-butylcatechol (0.00045 eq. ~1 mg) and *m*-xylene (0.4 mL•mmol⁻¹) followed by the addition of 2,3-dimethyl-1,3-butadiene **93** (1.04 eq., 0.59 mL, 5.2 mmol) at room temperature. The reaction mixture was then heated at 120 °C for 2 to 4 h. The reaction mixture was cooled down and put directly on the column chromatography (eluting with dichloromethane/methanol 9.5:0.5). Purification furnished the title compound **95** (649 mg, 4.2 mmol, 84%) as a white solid.

δ_{H} (400 MHz, CDCl₃) 12.35 (1H, br s, OH), 2.49-2.60 (1H, m, C(1)H), 2.15-2.28 (1H, m, C(2)H_a), 2.09-2.18 (1H, m, C(2)H_b), 1.94-2.06 (3H, m, C(5)H₂, C(6)H_a), 1.63-1.72 (1H, m, C(6)H_b), 1.62 (3H, s, C(7)H₃), 1.60 (3H, s, C(8)H₃); δ_{C} (100 MHz, CDCl₃) 182.9 (C(1')O), 125.3 (C(4)), 123.7 (C(3)), 40.1 (C(1)H), 33.4 (C(2)H₂), 30.3 (C(5)H₂), 25.5 (C(6)H₂), 18.9 (C(7)H₃), 18.8 (C(8)H₃).

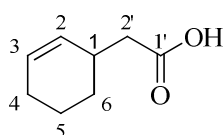
Spectroscopic data were consistent with those reported in the literature.⁹¹

Ethyl cyclohex-2-en-1-ylacetate

To cyclohex-2-enol **96** (1.0 eq., 995 mg, 10.1 mmol) and *o*-nitrophenol (0.03 eq., 45 mg, 0.31 mmol) was added triethylorthoacetate (2.8 eq., 5.3 mL, 28.7 mmol) and the reaction mixture was heated at 170 °C removing ethanol continuously. After 9 h, the reaction mixture was distilled to give the title compound (654 mg, 3.80 mmol, 38%) as a colourless oil.

δ_{H} (400 MHz, CDCl₃) 5.65-5.81 (1H, m, C(3)H), 5.48-5.61 (1H, m, C(2)H), 4.14 (2H, q, *J* 7.2, C(1'')H₂), 2.49-2.69 (1H, m, C(1)H), 2.27 (2H, dd, *J* 7.5, 3.1, C(2')H₂), 1.91-2.04 (2H, m, C(4)H₂), 1.48-1.89 (4H, m, C(5)H₂, C(6)H₂), 1.26 (3H, t, *J* 7.2, C(2'')H₃); δ_{C} (126 MHz, CDCl₃) 173.2 (C(1')O), 129.9 (C(3)H), 128.4 (C(2)H), 60.4 (C(1'')H₂), 41.1 (C(2')H₂), 32.3 (C(1)H), 29.7 (C(6)H₂), 25.2 (C(4)H₂), 21.5 (C(5)H₂), 14.2 (C(2'')H₃).

Spectroscopic data were consistent with those reported in the literature.⁹²

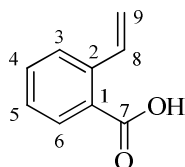
Cyclohex-2-en-1-ylacetic acid (97)

To ethyl cyclohex-2-en-1-ylacetate (1.0 eq., 654 mg, 3.80 mmol) dissolved in ethanol (0.45 mL•mmol⁻¹) was added a 1 M aqueous LiOH (5 mL•mmol⁻¹). The reaction mixture was stirred until TLC indicated complete consumption of starting material. The reaction mixture was extracted with diethyl ether (3 x 20 mL). The aqueous phase was then acidified to pH 1 with 3 M aqueous HCl and extracted with ethyl acetate (3 x 20 mL). The organic phase was dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure to give the title compound **97** (422 mg, 3.01 mmol, 79%) as a colourless oil.

δ_{H} (400 MHz, CDCl₃) 5.70-5.78 (1H, m, C(3)H), 5.57 (1H, dd, *J* 7.3, 1.8, C(2)H), 2.60 (1H, m, C(1)H), 2.34 (2H, m, C(2')H₂), 1.95-2.04 (2H, m, C(4)H₂), 1.82-1.91 (1H, m, C(6)H_a), 1.67-1.77 (1H, m, C(5)H_a), 1.51-1.64 (1H, m, C(6)H_b), 1.31 (1H, m, C(5)H_b); δ_{C} (125 MHz, CDCl₃) 179.5 (C(1')O), 129.8 (C(3)H), 128.4 (C(2)H), 40.6 (C(2')H₂), 31.9 (C(1)H), 28.7 (C(6)H₂), 25.0 (C(4)H₂), 20.9 (C(5)H₂).

Spectroscopic data were consistent with those reported in the literature.⁹³

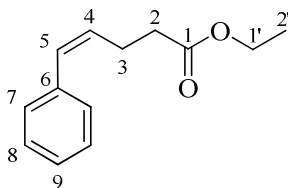
2-Vinylbenzoic acid (**99**)



To a solution of methylphenylphosphonium bromide salt (1.6 eq., 11 g, 31 mmol) in THF (1.44 mL•mmol⁻¹) at room temperature was added dropwise a solution of potassium *tert*-butoxide (2.3 eq., 5 g, 44.6 mmol) in THF (0.5 mL•mmol⁻¹). The reaction mixture was stirred for 90 min, before dropwise addition of a solution of 2-carboxybenzaldehyde **98** (1.0 eq., 2.9 g, 19.4 mmol) in THF (0.2 mL•mmol⁻¹). Upon complete addition, the reaction mixture was heated at 60 °C and stirring was continued for 16 h (beige slurry). The reaction mixture was concentrated *in vacuo* affording a beige solid. This solid was redissolved in ethyl acetate, and washed thoroughly with saturated aqueous NaHCO₃ solution (3 x 50 mL). The aqueous layer was then acidified to pH 1 with 3 M aqueous HCl and extracted with ethyl acetate (3 x 30 mL). The organic phase was dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure to give the title compound **99** (3.0 g, 20.0 mmol, 100%) as a white solid.

δ_{H} (400 MHz, CDCl₃) 12.11 (1H, br s, OH), 8.10 (1H, dd, *J* 7.8, 1.3, C(6)H), 7.66-7.72 (1H, m, C(4)H), 7.61-7.65 (1H, m, C(3)H), 7.51-7.58 (1H, m, C(5)H), 7.33-7.42 (1H, m, C(8)H), 5.71 (1H, dd, *J* 17.3, 1.4, C(9)H_a), 5.42 (1H, dd, *J* 11.1, 1.4, C(9)H_b); δ_{C} (100 MHz, CDCl₃) 173.2 (C(7)O), 140.6 (C(2)), 136.1 (C(8)H), 133.2 (C(4)H), 131.4 (C(6)H), 130.8 (C(3)H), 127.6 (C(5)H), 127.5 (C(1)), 116.8 (C(9)H₂).

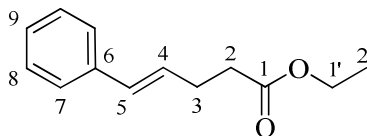
Spectroscopic data were consistent with those reported in the literature.⁹⁴

Ethyl (4Z)-5-phenylpent-4-enoate (102)

To a solution of 3-(Ethoxycarbonyl)propyltriphenylphosphonium bromide **101** (1.0 eq., 2.2 g, 4.8 mmol) in THF (12 mL•mmol⁻¹) was added dropwise NaHMDS (0.9 eq, 4.3 mL, 4.3 mmol) at -78 °C. The reaction mixture was kept at -78 °C for 1 h 30. Benzaldehyde **100** (0.8 eq, 0.4 mL, 3.8 mmol) was added dropwise at -78 °C. The reaction mixture was stirred and allowed to warm to room temperature for 16 h. The reaction mixture was quenched in icy water and extracted with ethyl acetate (3 x 30 mL). The organic phase was dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure to give a brown oil. Purification by flash column chromatography (SiO₂, eluting with petrol 40-60/diethyl ether 9:1) furnished the title compound **102** (657 mg, 3.2 mmol, 85%) as a yellowish oil.

δ_{H} (400 MHz, CDCl₃) 7.11-7.51 (5H, m, C(7)H, C(8)H, C(9)H), 6.48 (1H, d, *J* 11.6, C(5)H), 5.64 (1H, dt, *J* 11.6, 7.1, C(4)H), 4.11 (2H, q, *J* 7.2, C(1')H₂), 2.56-2.79 (2H, m, C(2)H₂), 2.32-2.53 (2H, m, C(3)H₂), 1.25 (3H, t, *J* 7.2, C(2')H₃); δ_{C} (100 MHz, CDCl₃) 173.5 (C(1)O), 137.1 (C(6)), 131.0 (C(5)H), 128.8 (C(4)H), 128.5 (C(8)H), 127.3 (C(9)H), 126.0 (C(7)H), 60.4 (C(1')H₂), 33.7 (C(2)H₂), 28.3 (C(3)H₂), 14.2 (C(2')H₃).

Spectroscopic data were consistent with those reported in the literature.⁹⁵

Ethyl (4E)-5-phenylpent-4-enoate (103)

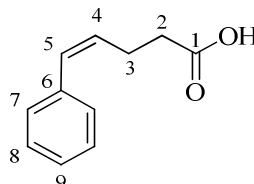
To a solution of compound **102** (1.0 eq., 500 mg, 2.45 mmol) in dichloromethane (2.5 mL•mmol⁻¹) was added bis(acetonitrile)dichloropalladium(II) catalyst (0.10 eq., 64 mg, 0.245 mmol) at room temperature. The reaction mixture was stirred for 36 h, then filtered through a short pad of celite. The filtrate was dried over Na₂SO₄ and the solvent was removed under reduced pressure to give an orange oil. Purification by flash column chromatography (SiO₂, eluting with gradient petrol 40-60/ethyl acetate 1:0 to 6:4) furnished the title compound **103** (465 mg, 2.28 mmol, 93%) as a yellowish oil.

δ_{H} (400 MHz, CDCl₃) 7.34 (4H, m, C(7)H, C(8)H), 7.20-7.26 (1H, m, C(9)H), 6.46 (1H, d, *J* 15.9, C(5)H), 6.24 (1H, dt, *J* 15.9, 6.6, C(4)H), 4.18 (2H, q, *J* 7.2, C(1')H₂), 2.53-2.61 (2H, m, C(2)H₂), 2.47-2.53 (2H, m, C(3)H₂), 1.29 (3H, t, *J* 7.2, C(2')H₃); δ_{C} (100 MHz, CDCl₃) 173.3 (C(1)O), 137.2

(C(6)), 130.8 (C(5)H), 128.4 (C(4)H), 128.3 (C(8)H), 127.0 (C(9)H), 125.9 (C(7)H), 60.2 (C(1')H₂), 33.9 (C(2)H₂), 28.2 (C(3)H₂), 14.1 (C(2')H₃).

Spectroscopic data were consistent with those reported in the literature.⁹⁶

(4Z)-5-Phenylpent-4-enoic acid (**106**)

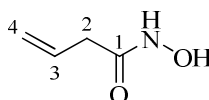


To compound **102** (1.0 eq., 500 mg, 2.45 mmol) dissolved in methanol (0.45 mL•mmol⁻¹) was added a 2 M aqueous LiOH (5 mL•mmol⁻¹). The reaction mixture was stirred until TLC indicated complete consumption of starting material. The reaction mixture was extracted with diethyl ether (3 x 30 mL). The aqueous phase was then acidified to pH 1 with 3 M aqueous HCl and extracted with ethyl acetate (3 x 30 mL). The organic phase was dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure to give the title compound **106** (420 mg, 2.38 mmol, 97%) as a white solid.

δ_{H} (400 MHz, CDCl₃) 11.12 (1H, br s, OH), 7.18-7.46 (5H, m, C(7)H, C(8)H, C(9)H), 6.52 (1H, d, *J* 11.6, C(5)H), 5.67 (1H, dt, *J* 11.6, 7.1, C(4)H), 2.71 (4H, m, C(2)H₂, C(3)H₂); δ_{C} (100 MHz, CDCl₃) 179.3 (C(1)O), 137.6 (C(6)), 131.2 (C(5)H), 129.0 (C(4)H), 128.3 (C(8)H), 127.4 (C(9)H), 126.3 (C(7)H), 33.8 (C(2)H₂), 28.1 (C(3)H₂).

Spectroscopic data were consistent with those reported in the literature.⁹⁷

N-[(Mesitylcarbonyl)oxy]but-3-enamide (**107**)

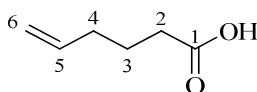


But-3-enoic acid (507 mg, 5.89 mmol) was subjected to General Procedure A₂ to furnish the title compound **107** (315 mg, 3.12 mmol, 53%) as a colourless solid.

δ_{H} (400 MHz, CD₃OD) 6.67-6.82 (1H, m, C(3)H), 5.28-5.37 (2H, m, C(4)H₂), 2.75 (1H, d, *J* 8.7, C(2)H₂); δ_{C} (100 MHz, CD₃OD) 168.1 (C(1)O), 129.9 (C(3)H), 120.1 (C(4)H₂), 38.6 (C(2)H₂).

Spectroscopic data were consistent with those reported in the literature.⁹⁸

Hex-5-enoic acid



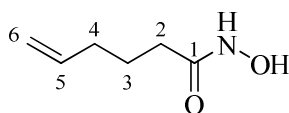
Hydrogen peroxide (2 eq., 10 mL, 102 mmol) was added over 2 min at room temperature to a stirred solution of cyclohexanone (1 eq., 5.1 mL, 51 mmol) in methanol (0.22 mL•mmol⁻¹). After

15 min, the reaction mixture was added over 5 min to a stirred solution of ferrous sulphate (1.0 eq., 14 g, 51 mmol) and cupric sulphate (1.0 eq., 12.7 g, 51 mmol) in water (100 mL) maintaining the reaction mixture at room temperature. Upon the addition, the reaction mixture turned dark brown. It was stirred for an additional hour. The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The combined organic phases were washed with 2 M aqueous NaOH (3 x 50 mL). The alkaline extract were acidified with 2 M aqueous H₂SO₄ and extracted with diethyl ether (3 x 50 mL). Removal of the solvent under reduced pressure gave the title compound (7.6 g, 67 mmol, 33%) as an orange oil.⁹⁹

δ_{H} (400 MHz, CDCl₃) 5.72-5.84 (1H, ddt, J 17.0, 10.2, 6.7, C(5)H), 4.97-5.09 (2H, m, C(6)H₂), 2.37 (2H, t, J 7.6, C(2)H₂), 2.12 (2H, m, C(4)H₂), 1.75 (2H, dq, J 7.6, 7.4, C(3)H₂); δ_{C} (100 MHz, CDCl₃) 180.3 (C(1)O), 137.4 (C(5)H), 115.5 (C(6)H₂), 33.3 (C(2)H₂), 32.9 (C(4)H₂), 23.7 (C(3)H₂).

Spectroscopic data were consistent with those reported in the literature.¹⁰⁰

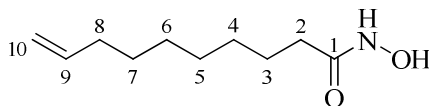
***N*-Hydroxyhex-5-enamide (108)**



Hex-5-enoic acid (1.8 g, 15.8 mmol) was subjected to General Procedure A₁ to give the title compound **108** (1.9 g, 14.8 mmol, 94%) as a yellow-orange oil.

ν_{max} (thin film)/cm⁻¹ 3411br, 1641s, 912w; δ_{H} (400 MHz, CDCl₃) 10.20 (2H, br s, OH, NH), 5.73-5.87 (1H, ddt, J 16.9, 10.3, 6.8, C(5)H), 4.89-5.07 (2H, m, C(6)H₂), 2.12 (2H, t, J 7.3, C(2)H₂), 2.05 (2H, m, C(4)H₂), 1.68 (2H, quint, J 7.3, C(3)H₂); δ_{C} (100 MHz, CDCl₃) 171.0 (C(1)O), 138.8 (C(5)H), 115.3 (C(6)H₂), 33.6 (C(4)H₂), 32.4 (C(2)H₂), 25.3 (C(3)H₂); m/z (ESI) 128 ([M-H]⁻, 100%); **HRMS** (ESI) C₆H₁₀NO₂ requires [M-H]⁻ 128.0717, found 128.0714 (+2.03 ppm).

***N*-Hydroxydec-9-enamide (109)**

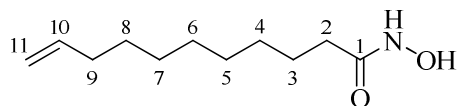


Caproic acid (1.70 g, 10.0 mmol) was subjected to General Procedure A₂ to give the title compound **109** (1.72 g, 9.3 mmol, 93%) as a beige solid.

m.p. 51-53 °C; ν_{max} (thin film)/cm⁻¹ 3262br, 2918br, 2849br, 1643s, 1467m, 1423m 1122w, 992w, 914m, 549m; δ_{H} (400 MHz, (CD)₃CO) 10.29 (1H, br s, NH), 8.58 (1H, br s, OH), 5.68-5.91 (1H, ddt, J 17.0, 10.3, 6.7, C(9)H), 4.94-5.02 (1H, m, C(10)H_a), 4.88-4.93 (1H, m, C(10)H_b), 2.13 (2H, t, J 7.5, C(2)H₂), 2.00-2.07 (2H, m, C(8)H₂), 1.54-1.64 (2H, m, C(7)H₂), 1.34-1.43 (2H, m, C(3)H₂), 1.26-1.33 (6H, m, C(4)H₂, C(5)H₂, C(6)H₂); δ_{C} (100 MHz, (CD)₃CO) 171.8 (C(1)O), 139.9

($\underline{C}(9)H$), 114.9 ($\underline{C}(10)H_2$), 34.6 ($\underline{C}(8)H_2$), 33.4 ($\underline{C}(2)H_2$), 30.1-30.0-29.9 ($\underline{C}(4)H_2$, $\underline{C}(5)H_2$, $\underline{C}(6)H_2$), 29.8 ($\underline{C}(3)H_2$), 26.5 ($\underline{C}(7)H_2$); m/z (ESI⁻) 184 ([M-H]⁻, 100%), 369 ([2M-H]⁻, 80); **HRMS** (ESI⁺) $C_{10}H_{19}NO_2$ requires [M+Na]⁺ 208.1308, found 208.1312 (-2.08 ppm).

***N*-Hydroxyundec-10-enamide (110)**

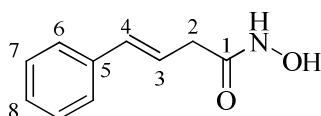


10-Undecenoic acid (1.8 g, 10.0 mmol) was subjected to General Procedure A₂ to give the title compound **110** (2.1 g, 100%) as a white solid.

δ_H (400 MHz, $CDCl_3$) 9.51 (2H, br s, $\underline{NH}$, $\underline{OH}$), 5.72-5.86 (1H, ddt, J 17.1, 10.2, 6.7, $\underline{C}(10)H$), 4.86-5.03 (2H, m, $\underline{C}(11)H_2$), 2.13 (2H, t, J 7.6, $\underline{C}(2)H_2$), 2.02 (2H, m, $\underline{C}(9)H_2$), 1.53-1.64 (2H, m, $\underline{C}(8)H_2$), 1.31-1.40 (2H, m, $\underline{C}(3)H_2$), 1.26 (8H, m, $\underline{C}(4)H_2$, $\underline{C}(5)H_2$, $\underline{C}(6)H_2$, $\underline{C}(7)H_2$); δ_C (100 MHz, $CDCl_3$) 172.4 ($\underline{C}(1)O$), 139.3 ($\underline{C}(10)H$), 114.4 ($\underline{C}(11)H_2$), 34.0 ($\underline{C}(2)H_2$), 33.2 ($\underline{C}(9)H_2$), 29.62-29.55-29.41-29.36 ($\underline{C}(4)H_2$, $\underline{C}(5)H_2$, $\underline{C}(6)H_2$, $\underline{C}(7)H_2$), 29.2 ($\underline{C}(8)H_2$), 25.8 ($\underline{C}(3)H_2$).

Spectroscopic data were consistent with those reported in the literature.¹⁰¹

(3*E*)-*N*-Hydroxy-4-phenylbut-3-enamide (111)

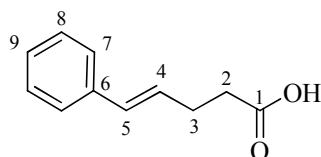


(3*E*)-4-phenylbut-3-enoic acid (1.01 g, 6.22 mmol) was subjected to General Procedure A₁ to give (3*E*)-*N*-hydroxy-4-phenylbut-3-enamide **111** (942 mg, 4.71 mmol, 76%) as a beige solid.

δ_H (400 MHz, $(CD_3)_2CO$) 10.21 (1H, br s, $\underline{NH}$), 8.89 (1H, br s, $\underline{OH}$), 7.30-7.39 (2H, m, $\underline{C}(6)H$), 7.29-7.34 (1H, m, $\underline{C}(7)H$), 7.22-7.28 (1H, m, $\underline{C}(8)H$), 6.59 (1H, d, J 15.9, $\underline{C}(4)H$), 6.32-6.38 (1H, m, $\underline{C}(3)H$), 3.31 (2H, d, J 7.4, $\underline{C}(2)H_2$); δ_C (100 MHz, $(CD_3)_2CO$) 169.4 ($\underline{C}(1)O$), 136.6 ($\underline{C}(4)H$), 134.9 ($\underline{C}(5)$), 128.9 ($\underline{C}(7)H$), 128.2 ($\underline{C}(3)H$), 126.4 ($\underline{C}(6)H$), 121.9 ($\underline{C}(8)H$), 37.3 ($\underline{C}(2)H_2$).

Spectroscopic data were consistent with those reported in the literature.¹⁰²

(4*E*)-5-Phenylpent-4-enoic acid



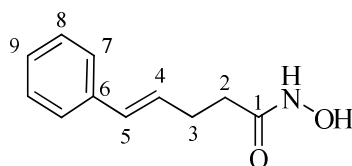
To compound **103** (1.0 eq., 465 mg, 2.28 mmol) dissolved in ethanol (0.45 mL•mmol⁻¹) was added a 2 M aqueous NaOH (5 mL•mmol⁻¹). The reaction mixture was stirred until TLC indicated complete consumption of starting material (typically 25 h). The reaction mixture was extracted with diethyl ether (3 x 20 mL). The aqueous phase was then acidified to pH 1 with 3 M aqueous

HCl and extracted with ethyl acetate (3 x 20 mL). The organic phase was dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure to give the title compound (392 mg, 2.22 mmol, 96%) as a beige solid.

δ_{H} (400 MHz, CDCl₃) 7.29-7.41 (4H, m, C(7)H, C(8)H), 7.21-7.28 (1H, m, C(9)H), 6.48 (1H, d, *J* 15.7, C(5)H), 6.24 (1H, dt, *J* 15.7, 6.5, C(4)H), 2.57 (4H, m, C(2)H₂, C(3)H₂); δ_{C} (100 MHz, CDCl₃) 179.8 (C(1)O), 137.5 (C(6)), 131.5 (C(5)H), 128.8 (C(4)H), 128.3 (C(8)H), 127.5 (C(9)H), 126.4 (C(7)H), 34.1 (C(2)H₂), 28.2 (C(3)H₂).

Spectroscopic data were consistent with those reported in the literature.¹⁰³

(4E)-N-Hydroxy-5-phenylpent-4-enamide (112)

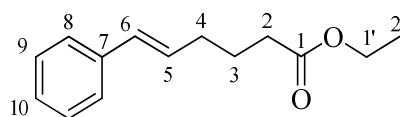


(4E)-5-Phenylpent-4-enoic acid (310 mg, 1.77 mmol) was subjected to General Procedure A₁ to give the title compound **112** (335 mg, 1.75 mmol, 98%) as a white solid.

m.p. 98-100 °C; ν_{max} (thin film)/cm⁻¹ 3286br, 2800br, 1723m, 1655s, 1599m, 1423m, 1234m, 951m, 735m, 681m; δ_{H} (400 MHz, (CD₃)₂CO) 10.15 (1H, br s, NH), 8.70 (1H, br s, OH), 7.29-7.37 (2H, m, C(7)H), 7.23-7.26 (2H, m, C(8)H), 7.12-7.18 (1H, m, C(9)H), 6.36-6.44 (1H, m, C(5)H), 6.17-6.27 (1H, m, C(4)H), 2.45 (2H, m, C(3)H₂), 2.23 (2H, t, *J* 7.3, C(2)H₂); δ_{C} (100 MHz, (CD₃)₂CO) 170.4 (C(1)O), 138.5 (C(6)), 131.5 (C(5)H), 129.8 (C(4)H), 129.4 (C(8)H), 127.9 (C(9)H), 126.9 (C(7)H), 32.6 (C(2)H₂), 29.0 (C(3)H₂); **m/z** (ESI⁻) 382 ([2M-H]⁻, 100%), 190 ([M-H]⁻, 80); **HRMS** (ESI⁺) C₁₁H₁₃NO₂ requires [M+Na]⁺ 214.0838, found 214.0837 (+0.85 ppm).

This product has previously being synthesized but no full characterisation was reported.¹⁰⁴

Ethyl (5E)-6-phenylhex-5-enoate

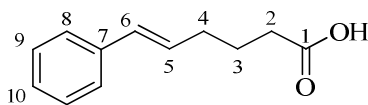


To a solution of ethyl (5Z)-6-phenylhex-5-enoate (1.0 eq., 1.3 g, 4 mmol) in dichloromethane (2.5 mL•mmol⁻¹) was added bis(acetonitrile)dichloropalladium(II) catalyst (0.12 eq., 120 mg, 0.46 mmol) at room temperature. The reaction mixture was stirred for 36 h, then filtered through a short pad of celite. The filtrate was dried over Na₂SO₄ and the solvent was removed under reduced pressure to give an orange oil. Purification by flash column chromatography (SiO₂, eluting with gradient petrol 40-60/ethyl acetate 1:0 to 6:4) furnished the title compound (800 mg, 3.60 mmol, 91%) as a yellowish oil.

δ_{H} (400 MHz, CDCl_3) 7.28-7.38 (4H, m, C(8)H, C(9)H), 7.21 (1H, t, J 7.1, C(10)H), 6.41 (1H, d, J 15.9, C(6)H), 6.20 (1H, dt, J 15.9, 6.9, C(5)H), 4.14 (2H, q, J 7.1, C(1')H₂), 2.37 (2H, t, J 7.5, C(2)H₂), 2.27 (2H, m, C(4)H₂), 1.83 (2H, quint, J 7.5, C(3)H₂), 1.26 (3H, t, J 7.1, C(2')H₃); δ_{C} (100 MHz, CDCl_3) 173.3 (C(1)O), 137.2 (C(7)), 130.4 (C(6)H), 129.2 (C(5)H), 128.1 (C(9)H), 126.6 (C(10)H), 125.6 (C(8)H), 59.9 (C(1')H₂), 33.3 (C(2)H₂), 32.0 (C(4)H₂), 24.2 (C(3)H₂), 13.9 (C(2')H₃).

Spectroscopic data were consistent with those reported in the literature.¹⁰⁵

(5E)-6-Phenylhex-5-enoic acid

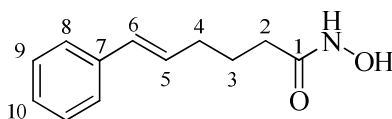


To ethyl (5E)-6-phenylhex-5-enoate (1.0 eq., 464 mg, 2.13 mmol) dissolved in ethanol (0.45 mL•mmol⁻¹) was added a 2 M aqueous NaOH (5 mL•mmol⁻¹). The reaction mixture was stirred until TLC indicated complete consumption of starting material (typically 25 h). The reaction mixture was extracted with diethyl ether (3 x 20 mL). The aqueous phase was then acidified to pH 1 with 3 M aqueous HCl and extracted with ethyl acetate (3 x 20 mL). The organic phase was dried over Na_2SO_4 , filtered and the solvent was removed under reduced pressure to give the title compound (393 mg, 2.07 mmol, 97%) as a yellowish oil.

δ_{H} (400 MHz, CDCl_3) 7.29-7.41 (4H, m, C(8)H, C(9)H), 7.23 (1H, t, J 7.1, C(10)H), 6.44 (1H, d, J 15.9, C(6)H), 6.21 (1H, dt, J 15.9, 6.9, C(5)H), 2.44 (2H, t, J 7.3, C(2)H₂), 2.31 (2H, m, C(4)H₂), 1.86 (2H, quint, J 7.3, C(3)H₂); δ_{C} (100 MHz, CDCl_3) 179.9 (C(1)O), 137.1 (C(7)), 130.6 (C(6)H), 128.9 (C(5)H), 128.1 (C(9)H), 126.7 (C(10)H), 125.6 (C(8)H), 33.0 (C(2)H₂), 31.9 (C(4)H₂), 23.8 (C(3)H₂).

Spectroscopic data were consistent with those reported in the literature.¹⁰⁶

(5E)-N-Hydroxy-6-phenylhex-5-enamide (113)

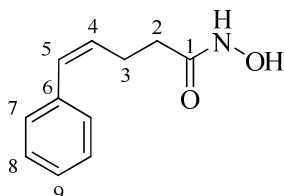


(5E)-6-Phenylhex-5-enoic acid (350 mg, 1.84 mmol) was subjected to General Procedure A₁ to give the title compound **113** (360 mg, 1.75 mmol, 95%) as a beige solid.

m.p. 79-81 °C; ν_{max} (thin film)/cm⁻¹ 3208br, 2932br, 1723m, 1633s, 1493m, 1448m, 1277w, 969m, 741m, 693m; δ_{H} (400 MHz, CDCl_3) 7.51 (1H, br s, NH), 7.25-7.36 (4H, m, C(8)H, C(9)H), 7.20 (1H, m, C(10)H), 7.19 (1H, br s, OH), 6.38 (1H, d, J 15.7, C(6)H), 6.09-6.22 (1H, dt, J 15.7, 6.8,

C(5)H), 2.15-2.32 (4H, m, C(2)H₂, C(4)H₂), 1.77-1.85 (2H, m, C(3)H₂); δ_c (100 MHz, CDCl₃) 171.3 (C(1)O), 137.0 (C(7)), 130.6 (C(6)H), 128.9 (C(5)H), 128.2 (C(8)H), 126.7 (C(10)H), 125.6 (C(9)H), 33.0 (C(2)H₂), 31.8 (C(4)H₂), 24.5 (C(3)H₂); m/z (ESI⁻) 409.6 ([2M-H]⁻, 100%), 204 ([M-H]⁻, 90); **HRMS** (ESI⁺) C₁₂H₁₅NO₂ requires [M+Na]⁺ 228.0995, found 228.0992 (+1.12 ppm).

(4Z)-N-Hydroxy-5-phenylpent-4-enamide (144)

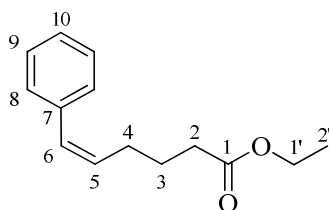


Compound **106** (430 mg, 2.44 mmol) was subjected to General Procedure A₂ to give the title compound **114** (449 mg, 2.35 mmol, 96%) as a beige solid.

m.p. 76-84 °C; $\nu_{\max}$ (thin film)/cm⁻¹ 3190br, 1634s, 1073w, 951m, 770w, 698m; δ_H (400 MHz, CDCl₃) 7.15-7.38 (5H, m, C(7)H, C(8)H, C(9)H), 6.47 (1H, d, *J* 11.5, C(5)H), 5.57 (1H, dt, *J* 11.5, 7.1, C(4)H), 2.66 (2H, m, C(3)H₂), 2.25 (2H, t, *J* 7.3, C(2)H₂); δ_c (100 MHz, CDCl₃) 171.5 (C(1)O), 137.3 (C(6)), 133.7 (C(5)H), 130.2 (C(4)H), 128.54 (C(8)H), 128.48 (C(9)H), 126.1 (C(7)H), 33.7 (C(2)H₂), 28.0 (C(3)H₂); m/z (ESI⁺) 405 ([2M+Na]⁺, 100%), 192 ([M+H]⁺, 70), 255 ([M+CH₃CN+Na]⁺, 50), 214 ([M+Na]⁺, 40); **HRMS** (ESI⁺) C₁₁H₁₃NO₂ requires [M+Na]⁺ 214.0837, found 214.0837 (+0.47 ppm).

This product has previously being synthesized but no full characterisation was reported.¹⁰⁴

Ethyl (5Z)-6-phenylhex-5-enoate

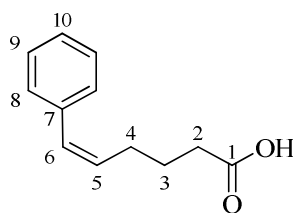


To a solution of 1-(4-Ethoxycarbonyl)butyltriphenylphosphonium bromide (1.0 eq, 4 g, 8.5 mmol) in THF (15 mL•mmol⁻¹) was added dropwise NaHMDS (1.05 eq, 8.9 mL, 8.9 mmol) at -78 °C. The reaction mixture was kept at -78 °C for 1 h 30. Benzaldehyde (0.8 eq, 0.7 mL, 7.2 mmol) was added dropwise at -78 °C. The reaction mixture was stirred and allowed to warm to room temperature for 16 h. The reaction mixture was quenched in icy water and extracted with ethyl acetate (3 x 50 mL). The organic phase was dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure to give a brown oil. Purification by flash column chromatography (SiO₂, eluting with petrol 40-60/diethyl ether 9:1) furnished the title compound (1.3 g, 5.96 mmol, 83%) as a yellowish oil.

δ_{H} (400 MHz, CDCl_3) 7.34-7.42 (2H, m, C(8)H), 7.28-7.34 (2H, m, C(9)H), 7.23-7.28 (1H, m, C(10)H), 6.51 (1H, d, J 11.6, C(6)H), 5.69 (1H, dt, J 11.6, 7.3, C(4)H), 4.14 (2H, q, J 7.1, C(1')H₂), 2.33-2.48 (4H, m, C(2)H₂, C(4)H₂), 1.84 (2H, quint, J 7.5, C(3)H₂), 1.29 (3H, t, J 7.1, C(2')H₃); δ_{C} (100 MHz, CDCl_3) 173.5 (C(1)O), 137.5 (C(7)), 131.7 (C(6)H), 129.7 (C(5)H), 128.5 (C(9)H), 128.2 (C(10)H), 126.6 (C(8)H), 60.4 (C(1')H₂), 33.8 (C(2)H₂), 27.9 (C(4)H₂), 25.1 (C(3)H₂), 14.2 (C(2')H₃).

Spectroscopic data were consistent with those reported in the literature.¹⁰⁷

(5Z)-6-Phenylhex-5-enoic acid

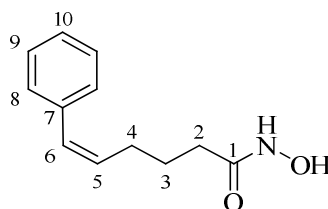


To ethyl (5Z)-6-phenylhex-5-enoate (1.0 eq., 345 mg, 1.58 mmol) dissolved in ethanol (0.45 mL•mmol⁻¹) was added a 2 M aqueous NaOH (5 mL•mmol⁻¹). The reaction mixture was stirred until TLC indicated complete consumption of starting material. The reaction mixture was extracted with diethyl ether (3 x 20 mL). The aqueous phase was then acidified to pH 1 with 3 M aqueous HCl and extracted with ethyl acetate (3 x 20 mL). The organic phase was dried over Na_2SO_4 , filtered and the solvent was removed under reduced pressure to give the title compound (280 mg, 1.47 mmol, 93%) as a colourless oil.

δ_{H} (400 MHz, CDCl_3) 7.26-7.40 (4H, m, C(8)H, C(9)H), 7.22-7.26 (1H, m, C(10)H), 6.50 (1H, d, J 11.6, C(6)H), 5.66 (1H, dt, J 11.7, 7.3, C(5)H), 2.41 (4H, m, C(2)H₂, C(4)H₂), 1.83 (2H, m, C(3)H₂); δ_{C} (100 MHz, CDCl_3) 179.7 (C(1)O), 137.0 (C(7)), 131.0 (C(6)H), 129.6 (C(5)H), 128.4 (C(9)H), 127.8 (C(8)H), 126.3 (C(10)H), 33.2 (C(2)H₂), 27.5 (C(4)H₂), 24.4 (C(3)H₂).

Spectroscopic data were consistent with those reported in the literature.¹⁰⁸

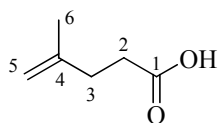
(5Z)-N-Hydroxy-6-phenylhex-5-enamide (115)



(5Z)-6-Phenylhex-5-enoic acid (300 mg, 1.58 mmol) was subjected to General Procedure A₂ to give the title compound **115** (310 mg, 1.51 mmol, 95%) as a beige solid.

m.p. 72-73 °C; ν_{max} (thin film)/ cm^{-1} 3199br, 2925w, 1774s, 1665br s, 1540s, 1418m, 1172m, 1021w, 917w, 651w; δ_{H} (400 MHz, CDCl_3) 7.33 (1H, t, J 7.5, C(10)H), 7.19-7.28 (4H, m, C(8)H, C(9)H), 7.1 (1H, br s, OH), 6.44 (1H, d, J 11.4, C(6)H), 5.52-5.64 (1H, m, C(5)H), 2.28-2.36 (2H, m, C(2)H), 2.06-2.13 (2H, m, C(4)H), 1.69-1.80 (2H, m, C(3)H); δ_{C} (100 MHz, CDCl_3) 171.7 (C(1)O), 137.6 (C(7)), 131.6 (C(6)H), 130.2 (C(5)H), 129.0 (C(9)H), 128.5 (C(8)H), 127.0 (C(10)H), 32.5 (C(2)H₂), 28.0 (C(4)H₂), 25.8 (C(3)H₂); m/z (ESI) 409 ([2M-H]⁺, 100%), 204 ([M-H]⁺, 90); **HRMS** (ESI) $\text{C}_{12}\text{H}_{15}\text{NO}_2$ requires [M-H]⁺ 204.1030, found 204.1034 (-2.13 ppm).

4-Methylpent-4-enoic acid

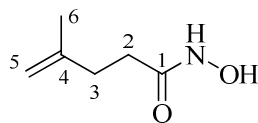


To a solution of methylphenylphosphonium bromide salt (3.2 eq., 22 g, 62 mmol) in THF (1.44 mL•mmol⁻¹) at room temperature was added dropwise a solution of potassium *tert*-butoxide (4.6 eq., 10 g, 45 mmol) in THF (0.5 mL•mmol⁻¹). The reaction mixture was stirred for 90 min, before dropwise addition of a solution of levulinic acid (1.0 eq., 2.0 mL, 19.5 mmol) in THF (0.2 mL•mmol⁻¹). Upon complete addition, the reaction mixture was heated at 60 °C and stirring was continued for 16 h (beige slurry). The reaction mixture was concentrated *in vacuo* affording a beige solid. This solid was redissolved in ethyl acetate (50 mL), and washed thoroughly with a saturated aqueous NaHCO_3 solution (3 x 50 mL). The aqueous layer was then acidified to pH 1 with 3 M aqueous HCl and extracted with ethyl acetate (3 x 30 mL). The organic phase was dried over Na_2SO_4 , filtered and the solvent was removed under reduced pressure to give a pale yellow oil. Purification by flash column chromatography (SiO_2 , eluting with dichloromethane/methanol 9.5:0.5) furnished the title compound (560 mg, 4.9 mmol, 11%) as a colourless oil. Starting material recovered (4 g, 35 mmol).

δ_{H} (400 MHz, CDCl_3) 11.01-11.77 (1H, m, OH), 4.62-4.82 (2H, m, C(5)H), 2.47-2.55 (2H, m, C(3)H), 2.33 (2H, t, J 7.7, C(2)H), 1.74 (3H, s, C(6)H); δ_{C} (100 MHz, CDCl_3) 180.3 (C(1)O), 143.9 (C(4)), 110.7 (C(5)H₂), 32.7 (C(3)H₂), 32.4 (C(2)H₂), 22.7 (C(6)H₃).

Spectroscopic data were consistent with those reported in the literature.¹⁰⁹

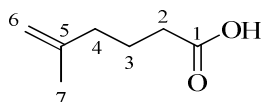
N-Hydroxy-4-methylpent-4-enamide (116)



4-Methylpent-4-enoic acid (560 mg, 4.9 mmol) was subjected to General Procedure A₂ to give the title compound **116** (550 mg, 4.3 mmol, 87%) as a colourless gum.

$\nu_{\max}$ (thin film)/cm⁻¹ 3210br, 2916br, 1651s, 1537m, 1447m, 1077m, 1033m, 1007m, 890s; δ_{H} (400 MHz, (CD₃)₂CO) 10.15 (1H, br s, NH), 8.75 (1H, br s, OH), 4.57-4.85 (2H, m, C(5)H₂), 2.15-2.40 (4H, m, C(2)H₂, C(3)H₂), 1.74 (3H, s, C(6)H₃); δ_{C} (100 MHz, (CD₃)₂CO) 170.9 (C(1)O), 145.7 (C(4)), 111.0 (C(5)H₂), 34.1 (C(2)H₂), 32.1 (C(3)H₂), 22.8 (C(6)H₃); m/z (ESI) 128 ([M-H]⁻, 100%); **HRMS** (ESI) C₆H₁₁NO₂ requires [M-H]⁻ 128.0717, found 128.0718 (-0.62 ppm).

5-Methylhex-5-enoic acid

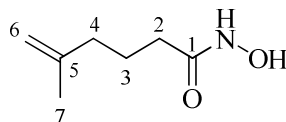


To a solution of methylphenylphosphonium bromide salt (3.0 eq., 19 g, 54 mmol) in THF (1.44 mL•mmol⁻¹) at room temperature was added dropwise a solution of potassium *tert*-butoxide (4.3 eq., 8.1 g, 72 mmol) in THF (0.5 mL•mmol⁻¹). The reaction mixture was stirred for 90 min, before dropwise addition of a solution of 4-acetylbutyric acid (1.0 eq., 2 mL, 18 mmol) in THF (0.2 mL•mmol⁻¹). Upon complete addition, the reaction mixture was heated at 60 °C and stirring was continued for 24 h (yellow slurry). Acetic acid (0.22 mL•mmol⁻¹) was added. The reaction mixture was filtered. Removal of the solvent at reduced pressure gave an orange oil. This oil was redissolved in ethyl acetate (50 mL) and washed thoroughly with a saturated NaHCO₃ aqueous solution (3 x 50 mL). The aqueous layer was then acidified to pH 1 with 3 M aqueous HCl and extracted with ethyl acetate (3 x 20 mL). The organic phase was dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure to give a pale yellow oil. Purification by flash column chromatography (SiO₂, eluting with dichloromethane/methanol 100:1) furnished the title compound (205 mg, 1.6 mmol, 9%) as a colourless oil. Starting material recovered (1.7 g, 13 mmol).

δ_{H} (400 MHz, CDCl₃) 11.34 (1H, br s, OH), 4.75 (1H, s, C(6)H_a), 4.70 (1H, s, C(6)H_b), 2.36 (2H, t, *J* 7.5, C(2)H₂), 2.07 (2H, t, *J* 7.5, C(4)H₂), 1.79 (2H, quint, *J* 7.5, C(3)H₂), 1.72 (3H, s, C(7)H₃); δ_{C} (100 MHz, CDCl₃) 180.8 (C(1)O), 144.8 (C(5)), 111.1 (C(6)H₂), 37.2 (C(4)H₂), 33.7 (C(2)H₂), 22.7 (C(3)H₂), 22.4 (C(7)H₃).

Spectroscopic data were consistent with those reported in the literature.¹¹⁰

N-Hydroxy-5-methylhex-5-enamide (117)

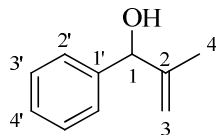


5-Methylhex-5-enoic acid (205 mg, 1.60 mmol) was subjected to General Procedure A₂ to give the title compound **117** (201 mg, 1.40 mmol, 88%) as a pale yellow oil.

$\nu_{\max}$ (thin film)/cm⁻¹ 3214br, 2937br, 1650s, 1531m, 1453s, 1375m, 1084m, 1043w, 986w, 889s, δ_{H} (400 MHz, (CD₃)₂CO) 10.38 (1H, br s, NH), 8.87 (1H, br s, OH), 4.69 (1H, s, C(6)H_a), 4.67 (1H, s, C(6)H_b), 2.13 (2H, t, *J* 7.5, C(2)H₂), 2.01 (2H, t, *J* 7.6, C(4)H₂), 1.69-1.78 (2H, m, C(3)H₂), 1.69

(3H, m, C(7)H₃); δ_c (100 MHz, (CD₃)₂CO) 171.7 (C(1)O), 145.9 (C(5)), 111.0 (C(6)H₂), 37.8 (C(4)H₂), 32.9 (C(2)H₂), 24.0 (C(3)H₂), 22.6 (C(7)H₃); m/z (ESI⁺) 142 ([M-H]⁺, 100%); **HRMS** (ESI⁺) C₇H₁₃NO₂ requires [M+Na]⁺ 166.0838, found 166.0838 (+0.39 ppm).

2-Methyl-1-phenylprop-2-en-1-ol

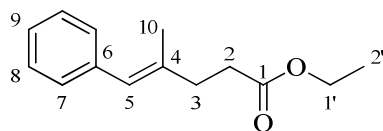


To benzaldehyde **100** (1.0 eq., 1.06 g, 10 mmol) dissolved in THF (2.5 mL•mmol⁻¹) at -78 °C was added dropwise a solution of isopropenylmagnesium bromide (1.2 eq., 24 mL, 12 mmol). The reaction mixture was stirred at -78 °C for 1 h 30. TLC showed complete consumption of starting material. The reaction mixture was quenched in icy water and solid NH₄Cl was added. The reaction mixture was stirred for 15 min and extracted with ethyl acetate (3 x 30 mL). The organic phase was dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure to give the title compound (1.36 g, 9.3 mmol, 93%) as a colourless oil.

δ_H (400 MHz, CDCl₃) 7.27-7.42 (5H, m, C(2')H, C(3')H, C(4')H), 5.22 (1H, s, C(3)H_a), 5.09 (1H, d, *J* 2.8, C(1)H), 4.97 (1H, s, C(3)H_b), 3.00 (1H, d, *J* 2.8, OH), 1.63 (3H, s, C(4)H₃); δ_c (100 MHz, CDCl₃) 146.9 (C(2)), 142.2 (C(1')), 128.4 (C(3')H), 127.6 (C(4')H), 126.6 (C(2')H), 111.2 (C(3)H₂), 77.7 (C(1)H), 18.3 (C(4)H₃).

Spectroscopic data were consistent with those reported in the literature.¹¹¹

Ethyl (4E)-4-methyl-5-phenylpent-4-enoate



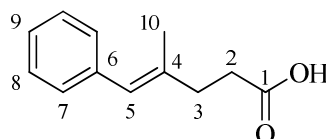
To 2-methyl-1-phenylprop-2-en-1-ol (1 eq., 1.36 g, 9.2 mmol) dissolved in *m*-xylene (4 mL•mmol⁻¹) was added triethylorthoacetate (2.0 eq., 3.4 mL, 18.4 mmol), followed by the addition of propionic acid (0.05 eq., 0.03 mL, 0.46 mmol). The reaction mixture was heated at 140 °C until TLC showed total consumption of starting material (usually 4 h). The reaction mixture was washed successively with a saturated aqueous NaHCO₃ solution (30 mL), distilled water (30 mL) and brine (30 mL). The organic phase was dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure to give a yellowish oil. Purification by flash column chromatography (SiO₂, eluting with gradient petrol 40-60/ethyl acetate 1:0 to 8:2) furnished the title compound (1.5 g, 6.9 mmol, 75%) as a colourless oil.

$\nu_{\max}$ (thin film)/cm⁻¹ 3023w, 1735s, 1491w, 1444w, 1178m, 1155m, 1096w, 1051w, 917w, 742w, 699m; δ_H (400 MHz, CDCl₃) 7.30-7.36 (2H, m, C(8)H), 7.18-7.26 (3H, m, C(7)H, C(9)H), 6.32 (1H, s, C(5)H), 4.17 (2H, q, *J* 7.2, C(1')H₂), 2.51-2.56 (4H, m, C(2)H₂, C(3)H₂), 1.89 (3H, s,

C(10)H₃), 1.28 (3H, t, *J* 7.2, C(2')H₃); δ_{C} (100 MHz, CDCl₃) 173.2 (C(1)O), 138.1 (C(4)), 137.0 (C(6)), 128.8 (C(8)H), 128.0 (C(7)H), 126.0 (C(9)H), 125.6 (C(5)H), 60.4 (C(1')H₂), 35.6 (C(2)H₂), 33.1 (C(3)H₂), 17.6 (C(10)H₃), 14.3 (C(2')H₃); *m/z* (ESI⁺) 282 ([M+H]⁺, 100%), 282 ([M+Na+CH₃CN]⁺, 80); **HRMS** (ESI⁺) C₁₄H₁₈O₂ requires [M+H]⁺ 241.1199, found 241.1197 (+0.93 ppm).

Spectroscopic data were consistent with those reported in the literature.¹¹²

(4E)-4-Methyl-5-phenylpent-4-enoic acid

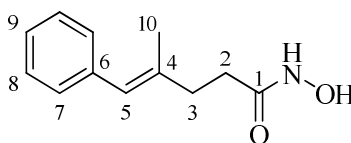


To ethyl (4E)-4-methyl-5-phenylpent-4-enoate (1.0 eq., 1.4g, 6.4 mmol) dissolved in ethanol (0.45 mL•mmol⁻¹) was added a 2 M aqueous NaOH (5 mL•mmol⁻¹). The reaction mixture was stirred until TLC indicated complete consumption of starting material (typically 16 h). The reaction mixture was extracted with diethyl ether (2 x 15 mL). The aqueous phase was then acidified to pH 1 with 3 M aqueous HCl and extracted with ethyl acetate (2 x 30 mL). The organic phase was dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure to give the title compound (1.12 g, 5.9 mmol, 92%) as a yellowish oil.

δ_{H} (400 MHz, CDCl₃) 7.41 (2H, t, *J* 7.2, C(8)H), 7.27-7.35 (3H, m, C(7)H, C(9)H), 6.41 (1H, s, C(5)H), 2.65-2.74 (2H, m, C(2)H₂), 2.57-2.63 (2H, m, C(3)H₂), 1.97 (3H, s, C(10)H₃); δ_{C} (100 MHz, CDCl₃) 179.9 (C(1)O), 138.1 (C(4)), 136.7 (C(6)), 128.9 (C(8)H), 128.1 (C(7)H), 126.2 (C(9)H), 125.9 (C(5)H), 35.2 (C(2)H₂), 33.0 (C(3)H₂), 17.7 (C(10)H₃).

Spectroscopic data were consistent with those reported in the literature.¹¹³

(4E)-N-Hydroxy-4-methyl-5-phenylpent-4-enamide (118)

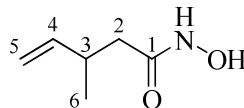


(4E)-4-Methyl-5-phenylpent-4-enoic acid (1.10 g, 5.8 mmol) was subjected to General Procedure A₂ to give the title compound **118** (1.12 g, 5.46 mmol, 94%) as a white solid.

m.p. 75-76 °C; ν_{max} (thin film)/cm⁻¹ 3208br, 2914br, 1645s, 1491m, 1444m, 1075m, 1027w, 741m, 699s; δ_{H} (400 MHz, (CD₃)₂CO) 10.50 (1H, br s, NH), 9.14 (1H, br s, OH), 7.31 (2H, t, *J* 7.3, C(8)H), 7.22-7.26 (2H, m, C(7)H), 7.18 (1H, t, *J* 7.2, C(9)H), 6.32 (1H, s, C(5)H), 2.45-2.57 (2H, m, C(2)H₂), 2.34-2.44 (2H, m, C(3)H₂), 1.85 (3H, s, C(10)H₃); δ_{C} (100 MHz, (CD₃)₂CO) 171.5 (C(1)O), 139.4 (C(4)), 138.5 (C(6)), 130.0 (C(8)H), 129.2 (C(7)H), 127.2 (C(9)H), 126.7 (C(5)H₂),

37.3 ($\underline{C}(2)H_2$), 32.6 ($\underline{C}(3)H_2$), 18.3 ($\underline{C}(10)H_3$); **m/z** (ESI⁺) 204 ([M-H]⁺, 100%), 409 ([2M-H]⁺, 50); **HRMS** (ESI⁺) C₁₂H₁₅NO₂ requires [M+Na]⁺ 228.0995, found 228.0995 (-0.18 ppm).

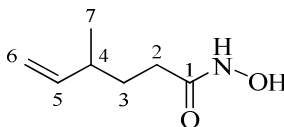
N-Hydroxy-3-methylpent-4-enamide (119)



3-Methyl-4-pentenoic acid (1.0 g, 8.8 mmol) was subjected to General Procedure A₂ to give the title compound **119** (1.12 g, 8.6 mmol, 97%) as a beige solid.

m.p. 54-56 °C; **v_{max}** (thin film)/cm⁻¹ 3210br, 1645s, 1377w, 1111w, 1042m, 995m, 916m, 676w; **δ_H** (400 MHz, (CD₃)₂CO) 10.52 (1H, br s, NH), 9.43 (1H, br s, OH), 5.85 (1H, ddd, *J* 17.3, 10.4, 6.9, C(4)H), 4.94-5.12 (2H, m, C(5)H₂), 2.73 (2H, m, C(3)H₂), 2.11-2.32 (2H, m, C(2)H₂), 1.08 (3H, d, *J* 6.7, C(6)H₃); **δ_C** (100 MHz, (CD₃)₂CO) 170.1 ($\underline{C}(1)O$), 143.2 ($\underline{C}(4)H$), 113.2 ($\underline{C}(5)H_2$), 39.8 ($\underline{C}(2)H_2$), 34.8 ($\underline{C}(3)H$), 19.3 ($\underline{C}(6)H_3$); **m/z** (ESI⁺) 128 ([M-H]⁺, 100%); **HRMS** (ESI⁺) C₆H₁₁NO₂ requires [M+Na]⁺ 152.0682, found 152.0677 (+3.53 ppm).

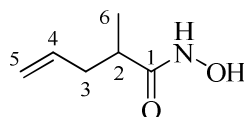
N-Hydroxy-4-methylhex-5-enamide (120)



Compound **92** (500 mg, 3.9 mmol) was subjected to General Procedure A₂ to give the title compound **120** (446 mg, 3.1 mmol, 80%) as a pale yellowish oil.

v_{max} (thin film)/cm⁻¹ 3442br, 1642s, 742m; **δ_H** (400 MHz, (CD₃)₂CO) 10.56 (1H, br s, NH), 8.42 (1H, br s, OH), 5.65 (1H, ddd, *J* 17.4, 10.0, 7.7, C(5)H), 4.88-5.00 (2H, m, C(6)H₂), 2.07-2.16 (3H, m, C(4)H, C(2)H₂), 1.52-1.65 (2H, m, C(3)H₂), 0.97 (3H, d, *J* 6.8, C(7)H₃); **δ_C** (100 MHz, (CD₃)₂CO) 171.7 ($\underline{C}(1)O$), 144.3 ($\underline{C}(5)H$), 113.7 ($\underline{C}(6)H_2$), 37.9 ($\underline{C}(4)H$), 32.7 ($\underline{C}(3)H_2$), 31.0 ($\underline{C}(2)H_2$), 20.3 ($\underline{C}(7)H_3$); **m/z** (ESI⁺) 142 ([M-H]⁺, 100%); **HRMS** (ESI⁺) C₇H₁₃NO₂ requires [M+Na]⁺ 166.0838, found 166.0837 (+1.04 ppm).

N-Hydroxy-2-methylpent-4-enamide (121)

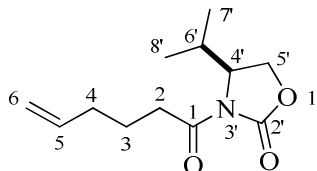


2-Methyl-4-pentenoic acid (1.1 g, 10.0 mmol) was subjected to General Procedure A₂ to give the title compound **121** (1.15 g, 8.9 mmol, 90%) as a beige solid.

m.p. 69-70 °C; **v_{max}** (thin film)/cm⁻¹ 3213br, 1643s, 1458m, 1375w, 1111w, 1021m, 994w, 917m, 622w; **δ_H** (400 MHz, (CD₃)₂CO) 10.36 (1H, br s, NH), 9.36 (1H, br s, OH), 5.66-5.79 (1H, m,

C(4)H), 4.93-5.06 (2H, m, C(5)H₂), 2.28-2.39 (2H, m, C(3)H₂), 2.05-2.15 (1H, m, C(2)H), 1.08 (3H, d, *J* 6.6, C(6)H₃); δ_c (100 MHz, (CD₃)₂CO) 174.2 (C(1)O), 136.6 (C(4)H), 116.7 (C(5)H₂), 37.8 (C(2)H), 38.5 (C(3)H₂), 17.5 (C(6)H₃); *m/z* (ESI⁺) 128 ([M-H]⁺, 100%); **HRMS** (ESI⁺) C₆H₁₁NO₂ requires [M+Na]⁺ 152.0682, found 152.0675 (+4.62 ppm).

(4S)-3-Hex-5-enoyl-4-isopropyl-1,3-oxazolidin-2-one

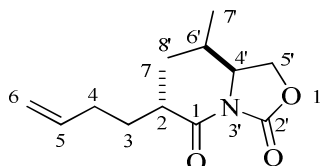


To a solution of hex-5-ynoic acid (1.0 eq., 0.25 mL, 2.1 mmol) in THF (3 mL•mmol⁻¹) was added *i*Pr₂Net (1.3 eq., 0.48 mL, 2.8 mmol) and pivaloyl chloride (1.1 eq., 0.29 mL, 2.3 mmol) at -78 °C. The resulting mixture was stirred for 15 min at -78 °C, allowed to warm up to room temperature and stirred for 16 h. The above suspension was added *via canula* to a solution of (S)-(-)-4-benzyl-2-oxazolidinone treated previously with *n*-Buli (1.2 eq., 1.6 mL, 2.6 mmol) in THF (2.5 mL•mmol⁻¹) at -78°C. After 15 min at -78 °C, the reaction mixture was warmed to room temperature for 2 h. The reaction mixture was quenched with a saturated aqueous NH₄Cl solution (10 mL) and extracted with ethyl acetate (2 x 20 mL). The organic phase was removed under reduced pressure. The residue was dissolved in 5 mL of ethyl acetate and washed with a saturated aqueous NaHCO₃ solution (5 mL). The organic phase was dried over Na₂SO₄, filtered and the solvent removed under reduced pressure to give the title compound (319 mg, 1.42 mmol) as a colourless oil.

δ_H (400 MHz, CDCl₃) 5.72-5.88 (1H, m, C(5)H), 4.92-5.08 (2H, m, C(6)H₂), 4.42 (1H, dd, *J* 7.8, 3.5, C(4')H), 4.16-4.31 (2H, m, C(5')H₂), 2.80-3.04 (2H, m, C(2)H₂), 2.26-2.48 (1H, m, C(6')H), 1.98-2.18 (2H, m, C(4)H₂), 1.64-1.86 (2H, m, C(3)H₂), 0.89-0.93 (3H, d, *J* 6.8, C(7')H₃), 0.84-0.88 (3H, d, *J* 6.8, C(8')H₃); δ_c (100 MHz, CDCl₃) 173.1 (C(1)O), 154.1 (C(2')O), 137.8 (C(5)H), 115.3 (C(6)H₂), 63.3 (C(5')H₂), 58.4 (C(4')H), 34.8 (C(2)H₂), 33.0 (C(4)H₂), 28.4 (C(6')H), 23.5 (C(3)H₂), 18.0 (C(7')H₃), 14.6 (C(8')H₃).

Spectroscopic data were consistent with those reported in the literature.¹¹⁴

(4S)-4-Isopropyl-3-[(2S)-2-methylhex-5-enoyl]-1,3-oxazolidin-2-one

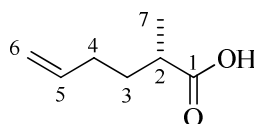


To a solution of NaHMDS (1.4 eq., 2.0 mL, 2.0 mmol) in THF (1 mL•mmol⁻¹) was added dropwise a solution of (4S)-3-hex-5-enoyl-4-isopropyl-1,3-oxazolidin-2-one (1.0 eq., 319 mg, 1.42 mmol) in THF (1 mL•mmol⁻¹) at -78 °C. After stirred at -78 °C for 1 h, the reaction mixture was treated with

iodomethane (5 eq., 0.5 mL, 7.0 mmol) and stirred for additional 3 h at -78°C. The reaction was quenched with acetic acid (0.1 mL) and warmed to room temperature. Water (20 mL) was added and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure to give a yellow oil. Purification by flash column chromatography (SiO₂, eluting with petrol 40-60/ethyl acetate 9:1) furnished the title compound (230 mg, 0.96 mmol, 68%) as a yellowish oil.

$[\alpha]_D^{23} + 10.7$ ($c = 1.0$, dichloromethane); $\nu_{\max}$ (thin film)/cm⁻¹ 3077m, 2966br, 2934br, 1779s, 1698s, 1461m, 1385s, 1300m, 1242m, 1201m, 1057w, 993w, 965w, 911w; δ_H (400 MHz, CDCl₃) 5.70 (1H, ddt, J 17.0, 10.2, 6.8, C(5)H), 4.82-4.95 (2H, m, C(6)H₂), 4.37 (1H, ddd, J 8.0, 3.5, 3.5, C(4')H), 4.11-4.22 (2H, m, C(5')H₂), 3.61-3.72 (1H, m, C(2)H), 2.19-2.33 (1H, m, C(6')H), 1.94-2.02 (2H, m, C(4)H₂), 1.72-1.83 (1H, m, C(3)H_a), 1.34-1.44 (1H, m, C(3)H_b), 1.13 (3H, d, J 6.8, C(7)H₃), 0.84 (1H, d, J 6.3, C(7')H₃), 0.79 (1H, d, J 7.1, C(8')H₃); δ_C (100 MHz, CDCl₃) 176.8 (C(1)O), 153.5 (C(2')O), 138.0 (C(5)H), 114.8 (C(6)H₂), 63.1 (C(5')H₂), 58.3 (C(4')H), 37.1 (C(2)H), 32.0 (C(3)H₂), 31.5 (C(4)H₂), 28.4 (C(6')H), 17.86 (C(7)H), 17.84 (C(7')H₃), 14.6 (C(8')H₃); m/z (ESI⁺) 303 ([M+CH₃CN+Na]⁺, 100%), 501 ([2M+Na]⁺, 50), 262 ([M+Na]⁺, 40), 240 ([M+H]⁺, 20); **HRMS** (ESI⁺) C₁₃H₂₁NO₃ requires [M+Na]⁺ 262.1414, found 262.1405 (+3.47 ppm).

(2S)-2-Methylhex-5-enoic acid



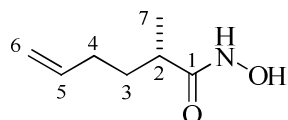
To a solution of (4S)-4-isopropyl-3-[(2S)-2-methylhex-5-enoyl]-1,3-oxazolidin-2-one (1.0 eq., 230 mg, 0.96 mmol) in THF (4 mL•mmol⁻¹) and water (1 mL•mmol⁻¹) under argon at 0 °C is added hydrogen peroxide (4.10⁻³ eq., 0.4 mL, 3.8.10⁻³ mmol) gradually over a period of 15 min. Lithium hydroxide hydrate (1.7.10⁻³ eq., 66 mg, 1.6.10⁻³ mmol) in water (1 mL•mmol⁻¹) is added. The reaction mixture was stirred for 3 h after which Na₂SO₃ (4.10⁻³ eq., 479 mg, 3.8.10⁻³ mmol) in water (3 mL•mmol⁻¹) was added slowly. The reaction mixture was stirred for another 20 min. THF was removed under reduced pressure. The aqueous phase was then washed with dichloromethane (2 x 5 mL) and acidified to pH 2 with 3 M aqueous HCl. The aqueous phase was then extracted with diethyl ether (3 x 10 mL). The organic phase was dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure to give the title compound (110 mg, 0.86 mmol, 89%) as a yellowish oil.

δ_H (400 MHz, CDCl₃) 11.59 (1H, br s, OH), 5.64-5.96 (1H, ddt, J 17.0, 10.3, 6.7, C(5)H), 4.86-5.13 (2H, m, C(6)H₂), 2.49 (1H, sxt, J 7.0, C(2)H), 2.11 (2H, q, J 7.5, C(4)H₂), 1.75-1.87 (1H, m, C(3)H_a), 1.46-1.58 (1H, m, C(3)H_b), 1.19 (3H, d, J 7.5, C(7)H₃); δ_C (100 MHz, CDCl₃) 183.1

($\underline{C}(1)O$), 137.3 ($\underline{C}(5)H$), 114.9 ($\underline{C}(6)H_2$), 38.4 ($\underline{C}(2)H$), 32.1 ($\underline{C}(4)H_2$), 30.9 ($\underline{C}(3)H_2$), 16.4 ($\underline{C}(7)H_3$).

Spectroscopic data were consistent with those reported in the literature.¹¹⁵

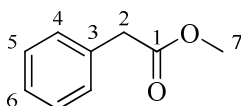
(2S)-N-Hydroxy-2-methylhex-5-enamide (122)



Compound (2S)-2-methylhex-5-enoic acid (110 mg, 0.86 mmol) was subjected to General Procedure A₂ to give the title compound **122** (91 mg, 0.64 mmol, 74%) as a beige solid.

$[\alpha]_D^{23} + 34.5$ ($c = 1.0$, dichloromethane); **m.p.** 78-80 °C; $\nu_{\max}$ (thin film)/cm⁻¹ 3194br, 2926br, 1631s, 1539m, 1462m, 1375m, 1038br, 954m, 918m, 640br; δ_H (400 MHz, (CD₃)₂CO) 10.27 (1H, br s, $\underline{NH}$), 8.07 (1H, br s, $\underline{OH}$), 5.69-5.85 (1H, ddt, J 17.0, 10.2, 6.6, $\underline{C}(5)H$), 4.86-5.05 (2H, m, $\underline{C}(6)H_2$), 2.20-2.35 (1H, m, $\underline{C}(2)H$), 2.00 (1H, q, J 7.2, $\underline{C}(4)H_2$), 1.63-1.75 (1H, m, $\underline{C}(3)H_a$), 1.35-1.49 (1H, m, $\underline{C}(3)H_b$), 1.08 (1H, d, J 6.8, $\underline{C}(7)H_3$); δ_C (100 MHz, (CD₃)₂CO) 174.8 ($\underline{C}(1)O$), 139.2 ($\underline{C}(5)H$), 115.4 ($\underline{C}(6)H_2$), 37.9 ($\underline{C}(2)H$), 34.0 ($\underline{C}(3)H_2$), 32.4 ($\underline{C}(4)H_2$), 18.4 ($\underline{C}(7)H_3$); **m/z** (ESI⁺) 166 ([M+Na]⁺, 100%); **HRMS** (ESI⁺) C₇H₁₃NO₂ requires [M+Na]⁺ 166.0839, found 166.0842 (+1.04 ppm).

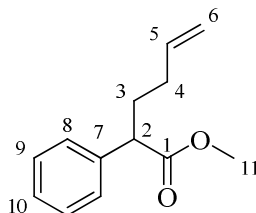
Methyl 2-phenylacetate



To a solution of phenylacetic acid (1.0 eq., 5.0 g, 37 mmol) in methanol (80 mL) under a stream of argon at 0 °C was added dropwise thionyl chloride (1.1 eq., 3.0 mL, 42 mmol). After completion of the addition, the reaction mixture was stirred vigorously for 14 h at rt. The reaction mixture was then concentrated *in vacuo* to give the title compound (5.6 g, 37 mmol, 100%) as a colourless oil.

δ_H (400 MHz, CDCl₃) 7.27-7.39 (5H, m, $\underline{C}(4)H$, $\underline{C}(5)H$, $\underline{C}(6)H$), 3.71 (3H, s, $\underline{C}(7)H_3$), 3.66 (2H, s, $\underline{C}(2)H_2$); δ_C (100 MHz, CDCl₃) 171.9 ($\underline{C}(1)O$), 133.9 ($\underline{C}(3)$), 129.1 ($\underline{C}(4)H$), 128.5 ($\underline{C}(5)H$), 127.0 ($\underline{C}(6)H$), 51.9 ($\underline{C}(2)H_2$), 41.1 ($\underline{C}(7)H_3$).

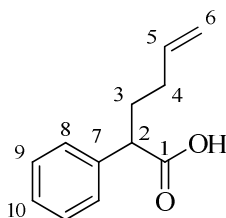
Spectroscopic data were consistent with those reported in the literature.¹¹⁶

Methyl 2-phenylhex-5-enoate

To sodium hydride (1.5 eq., 400 mg, 10 mmol as a 60% suspension in oil) in *N,N'*-dimethylformamide (30 mL) under argon at 0 °C was added dropwise a solution of methyl 2-phenylacetate (1.0 eq., 1.0 g, 6.7 mmol) in *N,N'*-dimethylformamide (2 mL). After completion of the addition, the reaction mixture was stirred vigorously for 30 min until no more gas evolution was observed. Then to the reaction mixture still at 0 °C was added dropwise a solution of 4-bromo-1-butene (1.1 eq., 0.75 mL, 7.4 mmol) in *N,N'*-dimethylformamide (2 mL). After completion of the addition, the reaction mixture was stirred vigorously for 2 h at 0 °C. The resulting yellow suspension was quenched with a saturated aqueous ammonium chloride solution (50 mL), diluted with water (300 mL) and extracted with dichloromethane (3 x 15 mL). The organic layer was dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure to give an orange oil which was purified by chromatography on silica eluting with a petrol:ethyl acetate gradient (90:10 to 80:20) to give the title compound (602 mg, 3.0 mmol, 44%) as a colourless oil.

δ_{H} (400 MHz, CDCl₃) 7.28-7.43 (5H, m, C(8)H, C(9)H, C(10)H), 5.67-5.98 (1H, m, C(5)H), 5.07 (1H, m, C(6)H_a), 5.00 (1H, m, C(6)H_b), 3.67 (3H, s, C(11)H₃), 3.57-3.70 (1H, m, C(2)H), 2.12-2.34 (1H, m, C(3)H_a), 2.05 (2H, m, C(4)H₂), 1.81-1.98 (1H, m, C(3)H_b); δ_{C} (100 MHz, CDCl₃) 174.2 (C(1)O), 138.8 (C(7)), 137.4 (C(5)H), 128.5 (C(8)H), 127.8 (C(9)H), 127.1 (C(10)H), 115.3 (C(6)H₂), 51.8 (C(11)H₃), 50.6 (C(2)H), 32.9 (C(4)H₂), 31.4 (C(3)H₂).

Spectroscopic data were consistent with those reported in the literature.¹¹⁷

2-Phenylhex-5-enoic acid

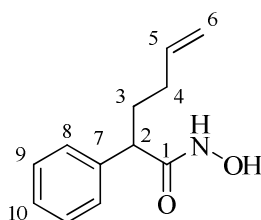
To a solution of methyl 2-phenylhex-5-enoate (1.0 eq., 333 mg, 1.63 mmol) in tetrahydrofuran (2 mL) under argon at rt was added water (20 mL) followed by the dropwise addition of a 0.25 N aqueous sodium hydroxide solution (8 mL). After completion of the addition, the reaction mixture was stirred vigorously (for typically 12 h) until TLC indicated complete consumption of starting

material. The reaction mixture was then acidified to pH 1 with a 3 M aqueous HCl solution and extracted with diethyl ether (3 x 50 mL). The organic phase was separated, washed with brine (3 x 5 mL), dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure to give the title compound (300 mg, 1.58 mmol, 97%) as a colourless oil.

δ_{H} (400 MHz, CDCl₃) 11.93 (1H, br s, OH), 7.28-7.42 (5H, m, C(8)H, C(9)H, C(10)H), 5.81 (1H, ddt, *J* 16.9, 10.4, 6.6, 6.6, C(5)H), 5.04-5.08 (1H, m, C(6)H_a), 5.02 (1H, s, C(6)H_b), 3.63 (1H, t, *J* 7.6, C(2)H), 2.15-2.30 (1H, m, C(3)H_a), 2.07 (2H, dd, *J* 6.6, C(4)H₂), 1.86-1.99 (1H, m, C(3)H_b); δ_{C} (100 MHz, CDCl₃) 180.5 (C(1)O), 138.1 (C(7)), 137.3 (C(5)H), 128.7 (C(8)H), 128.1 (C(9)H), 127.5 (C(10)H), 115.6 (C(6)H₂), 50.7 (C(2)H), 31.9 (C(3)H₂), 31.3 (C(4)H₂).

Spectroscopic data were consistent with those reported in the literature.¹¹⁸

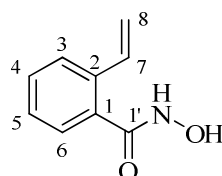
***N*-Hydroxy-2-phenylhex-5-enamide (123)**



2-Phenylhex-5-enoic acid (300 mg, 1.58 mmol) was subjected to General Procedure A₁ to give the title compound **123** (304 mg, 1.48 mmol, 93%) as a colourless solid.

m.p. 50-51 °C; ν_{max} (thin film)/cm⁻¹ 3224br s, 2927br m, 1735w, 1642br s, 1494m, 1454m, 1261w, 1032m, 913m, 747m, 698m; δ_{H} (400 MHz, (CD₃)₂CO) 10.50 (1H, br s, NH), 8.92 (1H, br s, OH), 7.16-7.46 (5H, m, C(8)H, C(9)H, C(10)H), 5.81 (1H, ddt, *J* 17.0, 10.3, 6.4, 6.4, C(5)H), 4.89-5.07 (2H, m, C(6)H₂), 3.47 (1H, t, *J* 7.6, C(2)H), 2.06-2.25 (1H, m, C(3)H_a), 1.91-2.07 (2H, m, C(4)H₂), 1.73-1.87 (1H, m, C(3)H_b); δ_{C} (100 MHz, (CD₃)₂CO) 171.7 (C(1)O), 141.1 (C(7)), 138.8 (C(5)H), 129.2 (C(8)H), 128.7 (C(9)H), 127.8 (C(10)H), 115.5 (C(6)H₂), 49.1 (C(2)H), 33.4 (C(3)H₂), 32.3 (C(4)H₂); **m/z** (ESI⁻) 204 ([M-H]⁻, 100%); **HRMS** (ESI⁺) C₁₂H₁₅NO₂ requires [M+Na]⁺ 228.0995, found 228.0996 (-0.52 ppm).

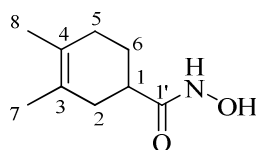
***N*-Hydroxy-2-vinylbenzamide (124)**



Compound **99** (1.0 g, 6.8 mmol) was subjected to General Procedure A₂ to give the title compound **124** (933 mg, 5.7 mmol, 84%) as a pink-beige solid.

m.p. 113-114 °C; $\nu_{\max}$ (thin film)/cm⁻¹ 3210br, 1619s, 1530m, 1330m, 1167m, 1024w, 903w, 767w; δ_{H} (400 MHz, (CD₃)₂CO) 10.50 (1H, br s, NH), 8.70 (1H, br s, OH), 7.71 (1H, d, *J* 7.8, C(6)H), 7.45 (1H, t, *J* 7.5, C(5)H), 7.40 (1H, m, C(4)H), 7.29-7.35 (1H, m, C(3)H), 7.08 (1H, dd, *J* 17.7, 11.1, C(7)H), 5.79 (1H, d, *J* 17.7, C(8)H_a), 5.27 (1H, d, *J* 11.1, C(8)H_b); δ_{C} (100 MHz, (CD₃)₂CO) 167.8 (C(1')O), 137.4 (C(2)), 135.3 (C(7)H), 134.2 (C(1)), 131.4 (C(4)H), 129.0 (C(5)H), 128.7 (C(3)H), 126.6 (C(6)H), 116.6 (C(8)H₂); ***m/z*** (ESI⁺) 162 ([M-H]⁺, 100%); **HRMS** (ESI⁺) C₉H₉NO₂ requires [M+Na]⁺ 186.0525, found 186.0523 (+1.14 ppm).

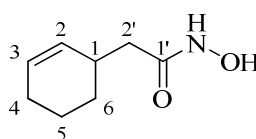
***N*-Hydroxy-3,4-dimethylcyclohex-3-ene-1-carboxamide (125)**



Compound **95** (355 mg, 2.3 mmol) was subjected to General Procedure A₂ to give the title compound **125** (360 mg, 2.1 mmol, 92%) as a white solid.

m.p. 120-121 °C; $\nu_{\max}$ (thin film)/cm⁻¹ 3251br, 2907br, 1633s, 1542w, 1441m, 1077w, 1027w; δ_{H} (400 MHz, (CD₃)₂CO) 10.17 (1H, br s, NH), 8.85 (1H, br s, OH), 2.29-2.41 (1H, m, C(1)H), 2.16-2.29 (1H, m, C(2)H_a), 1.98-2.11 (1H, m, C(2)H_b), 1.85-1.98 (2H, m, C(5)H₂), 1.72-1.82 (1H, m, C(6)H_a), 1.62-1.69 (1H, m, C(6)H_b), 1.61 (6H, s, C(7)H₃, C(8)H₃); δ_{C} (100 MHz, (CD₃)₂CO) 174.6 (C(1')O), 125.5 (C(4)), 124.6 (C(3)), 39.3 (C(1)H), 34.7 (C(2)H₂), 31.7 (C(5)H₂), 27.0 (C(6)H₂), 18.9 (C(7)H₃), 18.8 (C(8)H₃); ***m/z*** (ESI⁺) 361 ([2M+Na]⁺, 100%), 170 ([M+H]⁺, 70); **HRMS** (ESI⁺) C₉H₁₅NO₂ requires [M+Na]⁺ 192.0995, found 192.0993 (+1.22 ppm).

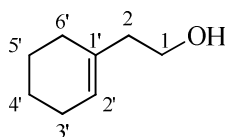
2-Cyclohex-2-en-1-yl-*N*-hydroxyacetamide (126)



Compound **97** (421 mg, 3.0 mmol) was subjected to General Procedure A₁ to give the title compound **126** (402 mg, 2.6 mmol, 76%) as a beige solid.

m.p. 46-47 °C; $\nu_{\max}$ (thin film)/cm⁻¹ 2930br, 1627s, 1033w, 978w, 678w, 614w; δ_{H} (400 MHz, CDCl₃) 8.20-8.41 (2H, br s, NH, OH), 5.70-5.81 (1H, m, C(3)H), 5.53 (1H, m, C(2)H), 2.64 (1H, m, C(1)H), 2.04-2.23 (2H, m, C(2')H₂), 1.99 (2H, m, C(4)H₂), 1.83 (1H, m, C(6)H_a), 1.48-1.76 (2H, m, C(5)H₂), 1.20-1.34 (1H, m, C(6)H_b); δ_{C} (126 MHz, CDCl₃) 168.5 (C(1')O), 137.9 (C(3)H), 128.9 (C(2)H), 39.5 (C(2')H₂), 32.4 (C(1)H), 28.7 (C(5)H₂), 25.0 (C(6)H₂), 20.9 (C(4)H₂); ***m/z*** (ESI⁺) 309 ([2M-H]⁺, 100%), 154 ([M-H]⁺, 90); **HRMS** (ESI⁺) C₈H₁₃NO₂ requires [M-H]⁺ 154.0874, found 154.0877 (-1.99 ppm).

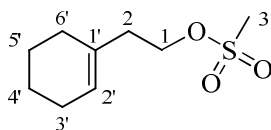
Spectroscopic data were consistent with those reported in the literature.¹¹⁹

2-Cyclohexenylethanol

To a solution of methyl 2-cyclohexenylacetate (1.0 eq., 12.5 g, 82 mmol) in diethyl ether (100 mL) at 0 °C was added a suspension of lithium aluminium hydride (1.0 M in THF, 44 mL) over 30 min. The reaction mixture was stirred for 3 h and diluted with diethyl ether (80 mL). Caution addition of water at 0 °C and subsequent extraction afforded after the solvent was removed under reduced pressure a dark oil. Purification by flash column chromatography (SiO₂, eluting with petrol 40-60 °C/ethyl acetate 9:1) furnished 2-cyclohexenylethanol (5.1 g, 40.5 mmol, 49%) as a colourless oil.

δ_{H} (400 MHz, CDCl₃) 5.53 (1H, br s, C(2')H), 3.44-3.87 (2H, m, C(1)H₂), 2.22 (2H, m, C(2)H₂), 2.02 (2H, br s, C(3')H₂), 1.95 (2H, br s, C(6')H₂), 1.41-1.79 (4H, m, C(4')H₂, C(5')H₂); δ_{C} (100 MHz, CDCl₃) 134.0 (C(1')), 124.3 (C(2')H), 60.1 (C(1)H₂), 41.1 (C(2)H₂), 27.9 (C(6')H₂), 25.2 (C(3')H₂), 22.8 (C(5')H₂), 22.3 (C(4')H₂).

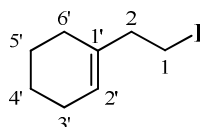
Spectroscopic data were consistent with those reported in the literature.¹²⁰

2-Cyclohexenylethyl methanesulfonate

To a solution of 2-cyclohexenylethanol (1.0 eq., 5.1 g, 40.5 mmol) in pyridine (52 mL) at 0 °C was added dropwise mesyl chloride (1.2 eq., 3.8 mL, 48.6 mmol) and the resulting reaction mixture was stirred at 5 °C for 24 h. Further dilution with dichloromethane (100 mL) and after subsequent washed with a saturated solution of aqueous NaHCO₃ (2 x 20 mL) and with brine (3 x 50 mL), the organic phase was dried over Na₂SO₄, filtered and removed under reduced pressure to afford an oil. Purification by flash column chromatography (SiO₂, eluting with petrol 40-60 °C/ethyl acetate 8:2) furnished 2-cyclohexenylethyl methanesulfonate (7.0 g, 34.3 mmol, 85%) as a colourless oil.

δ_{H} (400 MHz, CDCl₃) 5.52 (1H, br s, C(2')H), 4.28 (2H, t, *J* 6.9, C(1)H₂), 3.00 (3H, s, C(3)H₃), 2.38 (2H, t, *J* 6.9, C(2)H₂), 1.87-2.04 (4H, m, C(4')H₂, C(6')H₂), 1.59-1.69 (2H, m, C(4')H₂), 1.51-1.59 (2H, m, C(5')H₂); δ_{C} (100 MHz, CDCl₃) 132.2 (C(1')), 124.7 (C(2')H), 68.6 (C(1)H₂), 37.45 (C(3)H₃), 36.9 (C(2)H₂), 28.3 (C(6')H₂), 25.2 (C(3')H₂), 22.7 (C(5')H₂), 22.1 (C(4')H₂).

Spectroscopic data were consistent with those reported in the literature.¹²¹

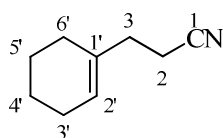
1-(2-Iodoethyl)cyclohex-1-ene

To a solution of 2-cyclohexenylethyl methanesulfonate (1.0 eq., 7.0 g, 34.3 mmol) in acetone (100 mL) at rt, was added sodium iodide (3.0 eq., 15.4 g, 103 mmol). The resulting reaction mixture was refluxed for 24 h in the dark. Subsequent dilution with diethyl ether (80 mL) and successive washes with a saturated solution of aqueous NaHCO_3 (2 x 20 mL) and with brine (3 x 50 mL), afforded the organic phase, which was dried over Na_2SO_4 , filtered and removed under reduced pressure to afford an oil. Purification by flash column chromatography (SiO_2 , eluting with petrol 40-60 °C) furnished 1-(2-Iodoethyl)cyclohex-1-ene (4.9 g, 20.9 mmol, 61%) as a colourless oil that gradually turned pink.

δ_{H} (400 MHz, CDCl_3) 5.48 (1H, br s, C(2') $\underline{\text{H}}$), 3.22 (2H, t, J 7.7, C(1) $\underline{\text{H}}_2$), 2.50 (2 H, t, J 7.7, C(2) $\underline{\text{H}}_2$), 1.96-2.04 (2H, m, C(4') $\underline{\text{H}}_2$), 1.93 (2H, br s, C(6') $\underline{\text{H}}_2$), 1.59-1.68 (2H, m, C(4') $\underline{\text{H}}_2$), 1.51-1.59 (2H, m, C(5') $\underline{\text{H}}_2$); δ_{C} (100 MHz, CDCl_3) 136.4 ($\underline{\text{C}}$ (1')), 123.8 ($\underline{\text{C}}$ (2')H), 42.3 ($\underline{\text{C}}$ (2) H_2), 27.6 ($\underline{\text{C}}$ (6') H_2), 25.4 ($\underline{\text{C}}$ (3') H_2), 22.8 ($\underline{\text{C}}$ (5') H_2), 22.2 ($\underline{\text{C}}$ (4') H_2), 5.0 ($\underline{\text{C}}$ (1) H_2).

Spectroscopic data were consistent with those reported in the literature.¹²¹

3-Cyclohexenylpropanenitrile

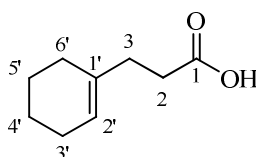


To a solution of 1-(2-iodoethyl)cyclohex-1-ene (1.0 eq., 4.9 g, 20.9 mmol) in acetonitrile (30 mL) at rt, was added sodium cyanide (4.0 eq., 4.1 g, 83.8 mmol). The resulting reaction mixture was refluxed for 72 h. Subsequent dilution with diethyl ether (100 mL) and successive washes with a saturated solution of aqueous NaHCO_3 (2 x 20 mL) and with brine (3 x 50 mL), afforded the organic phase, which was dried over Na_2SO_4 , filtered and removed under reduced pressure to afford an oil. Purification by flash column chromatography (SiO_2 , eluting with petrol 40-60 °C/ethyl acetate 7:3) furnished 3-cyclohexenylpropanenitrile (2.7 g, 19.8 mmol, 95%) as a colourless oil.

δ_{H} (400 MHz, CDCl_3) 5.52 (1H, br s, C(2') $\underline{\text{H}}$), 2.42 (2H, t, J 7.7, C(2) $\underline{\text{H}}_2$), 2.20-2.31 (2H, m, C(3) $\underline{\text{H}}_2$), 2.00 (2H, m, C(6') $\underline{\text{H}}_2$), 1.91 (2H, br s, C(3') $\underline{\text{H}}_2$), 1.58-1.68 (2H, m, C(5') $\underline{\text{H}}_2$), 1.50-1.58 (2H, m, C(4') $\underline{\text{H}}_2$); δ_{C} (100 MHz, CDCl_3) 133.9 ($\underline{\text{C}}$ (1')), 123.8 ($\underline{\text{C}}$ (2')H), 119.7 ($\underline{\text{C}}$ (1)), 33.2 ($\underline{\text{C}}$ (3) H_2), 27.7 ($\underline{\text{C}}$ (6') H_2), 24.9 ($\underline{\text{C}}$ (3') H_2), 22.5 ($\underline{\text{C}}$ (5') H_2), 22.0 ($\underline{\text{C}}$ (4') H_2), 15.9 ($\underline{\text{C}}$ (2) H_2).

Spectroscopic data were consistent with those reported in the literature.¹²¹

3-Cyclohexenylpropanoic acid

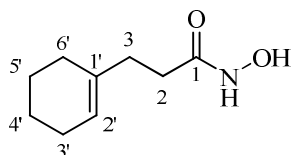


To a solution of 3-cyclohexenylpropanenitrile (1.0 eq., 2.6 g, 19.2 mmol) in a mixture of ethanol (20 mL) and water (20 mL) at rt, was added potassium hydroxide (4.4 eq., 4.7 g, 84.5 mmol). The resulting reaction mixture was heated at 85 °C for 18 h. Subsequent dilution with diethyl ether (100 mL) was followed by the slow addition a 6 M aqueous HCl solution (75 mL). Separation and further extraction with diethyl ether (100 mL) afforded the organic phase, which was dried over Na₂SO₄, filtered and removed under reduced pressure to afford 3-Cyclohexenylpropanoic acid (2.5 g, 16.3 mmol, 85%) as an orange oil which was not further purified.

δ_{H} (400 MHz, CDCl₃) 11.73 (1H, br s, OH), 5.43 (1H, br s, C(2')H), 2.43-2.46 (2H, m, C(2)H₂), 2.20-2.31 (2H, m, C(3)H₂), 1.94-2.03 (2H, m, C(6')H₂), 1.92 (2 H, br s, C(4')H₂), 1.47-1.67 (4H, m, C(4')H₂, C(5')H₂); δ_{C} (100 MHz, CDCl₃) 180.3 (C(1)O), 135.7 (C(1')), 121.6 (C(2')H), 32.6 (C(3)H₂), 32.5 (C(2)H₂), 28.2 (C(6')H₂), 25.1 (C(3')H₂), 22.8 (C(5')H₂), 22.3 (C(4')H₂).

Spectroscopic data were consistent with those reported in the literature.¹²¹

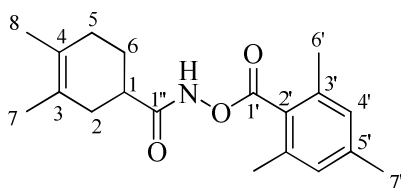
3-(Cyclohex-1-en-1-yl)-N-hydroxypropanamide (127)



3,4-Dimethylcyclohex-3-ene-1-carboxylic acid (1.18 g, 7.66 mmol) was subjected to General Procedure A₂ to give 3-(Cyclohex-1-en-1-yl)-N-hydroxypropanamide **127** (1.28 g, 7.57 mmol, 98%) as a beige solid.

m.p. 87-89 °C; ν_{max} (thin film)/cm⁻¹ 3340br, 2921m, 1665s, 1442w, 1239s, 1155s, 1043s, 839m, 729m; δ_{H} (400 MHz, (CD₃)₂CO) 10.17 (1H, br s, NH), 8.95 (1H, br s, OH), 5.40 (1H, br s, C(2')H), 2.20 (4H, br s, C(2)H₂, C(3)H₂), 1.93 (4H, br s, C(3')H₂, C(6')H₂), 1.45-1.66 (4H, m, C(4')H₂, C(5')H₂); δ_{C} (100 MHz, (CD₃)₂CO) 171.1 (C(7)O), 137.3 (C(1')), 122.0 (C(2')H), 34.3 (C(3)H₂), 32.1 (C(2)H₂), 28.8 (C(6')H₂), 25.8 (C(3')H₂), 23.7 (C(5')H₂), 23.2 (C(4')H₂); *m/z* (ESI⁺) 192 ([M+Na]⁺, 100%); **HRMS** (ESI⁺) C₉H₁₅NO₂ requires [M+Na]⁺ 192.0995, found 192.0993 (-0.95 ppm).

N-[(Mesitylcarbonyl)oxy]-3,4-dimethylcyclohex-3-ene-1-carboxamide (130)

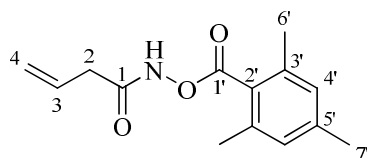


N-Hydroxy-3,4-dimethylcyclohex-3-ene-1-carboxamide **125** (330 mg, 1.95 mmol) was subjected to General Procedure B to furnish the title compound **130** (520 mg, 1.65 mmol, 85%) as a colourless solid.

m.p. 131-132 °C; $\nu_{\max}$ (thin film)/cm⁻¹ 3193br, 2915br, 2360m, 1776s, 1668s, 1611m, 1454m, 1232s, 1157m, 1041s, 851w, 733w; δ_{H} (400 MHz, CDCl₃) 9.46 (1H, br s, NH), 6.86 (2H, s, C(4')H), 2.52 (1H, m, C(1)H), 2.37 (6H, s, C(6')H₃), 2.35 (1H, m, C(2)H_a), 2.29 (3H, s, C(7')H₃), 2.06-2.16 (1H, m, C(2)H_b), 1.92-2.05 (3H, m, C(5)H₂, C(6)H_a), 1.70-1.84 (1H, m, C(6)H_b), 1.62 (6H, s, C(7)H₃, C(8)H₃); δ_{C} (100 MHz, CDCl₃) 174.8 (C(1')O), 168.5 (C(1'')O), 141.0 (C(5')), 137.0 (C(3')), 128.9 (C(4')H), 126.9 (C(2')), 125.7 (C(4)), 124.0 (C(3)), 39.6 (C(1)H), 34.2 (C(2)H₂), 31.1 (C(5)H₂), 26.4 (C(6)H₂), 21.5 (C(7')H₃), 20.2 (C(6')H₃), 19.2 (C(7)H₃), 19.1 (C(8)H₃); **m/z** (ESI⁺) 631 ([2M+H]⁺, 100%), 653 ([2M+Na]⁺, 50), 316 ([M+H]⁺, 30); **HRMS** (ESI⁺) C₁₉H₂₅NO₃ requires [M+Na]⁺ 338.1727, found 338.1732 (-1.71 ppm).

Single Crystal X-ray Diffraction Data for 130: C₁₉H₂₅N₁O₃, M_r = 315.41, monoclinic (P1 21/c 1), a = 14.5795(2) Å, b = 9.26180(10) Å, c = 13.4334(2) Å, α = 90 °C, β = 102.8400(6) °C, γ = 90 °C, V = 1768.59(4) Å³, Z = 4, μ = not measured D_{calc} = 1.185, T = 150(2) K, 30743 reflections collected, 2288 independent [R(int) = 0.028], R₁ = 0.0669, wR₂ = 0.0723 [I > 3σ(I)].

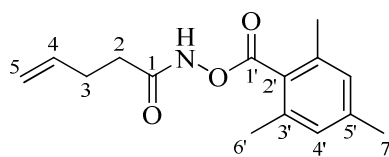
N-[(Mesitylcarbonyl)oxy]but-3-enamide (**131**)



N-Hydroxybut-3-enamide **107** (109 mg, 1.08 mmol) was subjected to General Procedure B to furnish the title compound **131** (257 mg, 1.04 mmol, 96%) as a colourless solid.

m.p. 86-88 °C; $\nu_{\max}$ (thin film)/cm⁻¹ 2966br, 1777s, 1674s, 1427w, 1233s, 1158s, 1041s, 987s, 926w, 851w; δ_{H} (400 MHz, CDCl₃) 9.64 (1H, br s, NH), 6.87 (2H, s, C(4')H), 5.97 (1H, ddt, J 17.1, 10.1, 7.0, C(3)H), 5.24-5.33 (2H, m, C(4)H₂), 3.14 (2H, d, J 7.0, C(2)H₂), 2.37 (6H, s, C(6')H₃), 2.29 (3H, s, C(7')H₃); δ_{C} (100 MHz, CDCl₃) 169.1 (C(1')O), 168.2 (C(1'')O), 141.1 (C(5')), 136.9 (C(3')), 129.7 (C(3)H), 128.9 (C(4')H), 126.7 (C(2')), 120.5 (C(4)H₂), 38.5 (C(2)H₂), 21.5 (C(7')H₃), 20.2 (C(6')H₃); **m/z** (ESI⁺) 311 ([M+CH₃CN+Na]⁺, 100%), 517 ([2M+Na]⁺, 80); **HRMS** (ESI⁺) C₁₄H₁₇NO₃ requires [M+Na]⁺ 270.1101, found 270.1094 (+2.31 ppm).

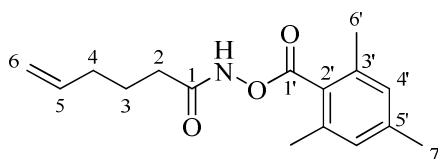
N-[(Mesitylcarbonyl)oxy]pent-4-enamide (**132**)



N-Hydroxypent-4-enamide **90** (196 mg, 1.70 mmol) was subjected to General Procedure B to furnish the title compound **132** (438 mg, 1.68 mmol, 97%) as a colourless solid.

m.p. 72-73 °C; **v_{max}** (thin film)/cm⁻¹ 3190br, 2977br, 1776s, 1672br, 1611w, 1448m, 1233s, 1158s, 1050br, 916m, 851m, 732w; **δ_H** (400 MHz, CDCl₃) 10.24 (1H, br s, NH), 6.84 (2H, s, C(4')H), 5.66-5.93 (1H, m, C(4)H), 4.86-5.19 (2H, m, C(5)H₂), 2.35-2.47 (4H, m, C(2)H₂, C(3)H₂), 2.35 (6H, s, C(6')H₃), 2.27 (3H, s, C(7')H₃); **δ_C** (100 MHz, CDCl₃) 170.7 (C(1')O), 167.7 (C(1)O), 140.5 (C(5')), 136.4 (C(4)H), 136.1 (C(3')), 128.4 (C(4')H), 126.6 (C(2')), 115.7 (C(5)H₂), 31.9 (C(2)H₂), 28.8 (C(3)H₂), 21.0 (C(7')H₃), 19.7 (C(6')H₃); **m/z** (ESI⁻) 521 ([2M-H]⁻, 100%), 260 ([M-H]⁻, 70); **HRMS** (ESI⁺) C₁₅H₁₉NO₃ requires [M+Na]⁺ 284.1257 found 284.1254 (+1.18 ppm).

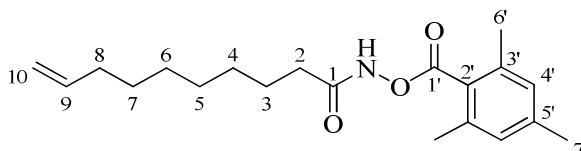
N-[(Mesitylcarbonyl)oxy]hex-5-enamide (**133**)



N-Hydroxyhex-5-enamide **108** (491 mg, 3.80 mmol) was subjected to General Procedure B to furnish the title compound **133** (880 mg, 3.19 mmol, 84%) as a colourless solid.

m.p. 63-64 °C; **v_{max}** (thin film)/cm⁻¹ 3191br, 2956br, 1776s, 1671br, 1612w, 1456w, 1233s, 1158m, 1040br, 851w; **δ_H** (400 MHz, CDCl₃) 9.11 (1H, br s, NH), 6.89 (2H, s, C(4')H), 5.72-5.86 (1H, ddt, *J* 17.0, 10.3, 6.7, C(5)H), 5.04 (2H, dd, *J* 16.4, 10.4, C(6)H₂), 2.38 (6H, s, C(6')H₃), 2.33 (2H, t, *J* 7.5, C(2)H₂), 2.30 (3H, s, C(7')H₃), 2.15 (2H, m, C(4)H₂), 1.84 (2H, quint, *J* 7.5, C(3)H₂); **δ_C** (100 MHz, CDCl₃) 171.4 (C(1')O), 167.9 (C(1)O), 140.6 (C(5')), 137.4 (C(5)H), 136.5 (C(3')), 128.5 (C(4')H), 126.6 (C(2')), 115.5 (C(6)H₂), 32.8 (C(2)H₂), 32.0 (C(4)H₂), 24.0 (C(3)H₂), 21.1 (C(7')H₃), 19.8 (C(6')H₃); **m/z** (ESI⁻) 549 ([2M-H]⁻, 100%), 274 ([M-H]⁻, 50); **HRMS** (ESI⁻) C₁₆H₂₁NO₃ requires [M-H]⁻ 274.1449 found 274.1444 (+1.62 ppm).

N-[(Mesitylcarbonyl)oxy]dec-9-enamide (**134**)

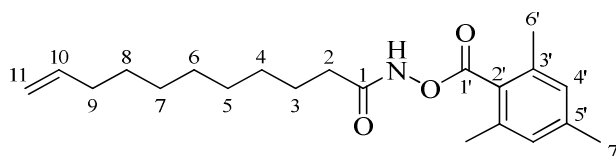


Compound **109** (1.56 g, 8.4 mmol) was subjected to General Procedure B to furnish the title compound **134** (2.30 g, 7.0 mmol, 92%) as a colourless solid.

m.p. 51 -53 °C; **v_{max}** (thin film)/cm⁻¹ 3262br, 2918br, 2849br, 1643s, 1467m, 1423m 1122w, 992w, 914m, 549m; **δ_H** (400 MHz, (CD)₃CO) 10.70 (1H, br s, NH), 6.82 (2H, s, C(4')H), 5.72-5.86 (1H, m, C(9)H), 4.90-5.04 (2H, m, C(10)H₂), 2.35 (6H, s, C(6')H₃), 2.26-2.31 (2H, m, C(2)H₂), 2.25 (3H, s, C(7')H₃), 1.97-2.06 (2H, m, C(8)H₂), 1.61-1.72 (2H, m, C(7)H₂), 1.29-1.40 (2H, m, C(3)H₂), 1.23-1.29 (6H, m, C(4)H₂, C(5)H₂, C(6)H₂); **δ_C** (100 MHz, (CD)₃CO) 171.8 (C(1')O),

167.8 ($\underline{C}(1)O$), 140.4 ($\underline{C}(5')$), 139.0 ($\underline{C}(9)H$), 136.6 ($\underline{C}(3')$), 128.6 ($\underline{C}(4')H$), 127.0 ($\underline{C}(2')$), 114.3 ($\underline{C}(10)H_2$), 33.8 ($\underline{C}(8)H_2$), 32.9 ($\underline{C}(2)H_2$), 29.0-29.2-29.3 ($\underline{C}(4)H_2$, $\underline{C}(5)H_2$, $\underline{C}(6)H_2$), 28.9 ($\underline{C}(3)H_2$), 25.4 ($\underline{C}(7)H_2$), 21.2 ($\underline{C}(7')H_3$), 19.9 ($\underline{C}(6')H_3$); **m/z** (ESI⁺) 661 ([2M-H]⁺, 100%), 992 ([3M-H]⁺, 70), 330 ([M-H]⁺, 50); **HRMS** (ESI⁺) C₂₀H₂₉NO₃ requires [M+Na]⁺ 354.2040, found 354.2041 (-0.44 ppm).

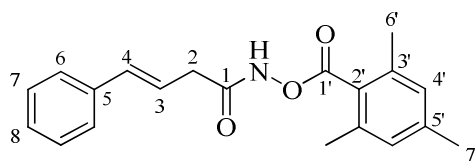
N-[(Mesitylcarbonyl)oxy]undec-10-enamide (135)



Compound **110** (1.7 g, 8.5 mmol) was subjected to General Procedure B to furnish the title compound **135** (2.4 g, 7.0 mmol, 92%) as a colourless oil.

v_{max} (thin film)/cm⁻¹ 3182br, 2927br, 2855s, 1777s, 1670s, 1612m, 1459m, 1233s, 1158m, 1041br, 909m, 850m; **δ_H** (400 MHz, CDCl₃) 10.22 (1H, br s, NH), 6.83 (2H, s, C(4')H), 5.74-5.85 (1H, ddt, *J* 17.1, 10.3, 6.7, C(10)H), 4.90-5.02 (2H, m, C(11)H₂), 2.35 (6H, s, C(6')H₃), 2.24-2.30 (5H, m, C(2)H₂, C(7')H₃), 1.99-2.06 (2H, m, C(9)H₂), 1.62-1.71 (2H, m, C(8)H₂), 1.22-1.40 (10H, m, C(3)H₂, C(4)H₂, C(5)H₂, C(6)H₂, C(7)H₂); **δ_C** (100 MHz, CDCl₃) 171.7 ($\underline{C}(1')O$), 168.0 ($\underline{C}(1)O$), 140.7 ($\underline{C}(5')$), 139.2 ($\underline{C}(10)H$), 136.7 ($\underline{C}(3')$), 128.7 ($\underline{C}(4')H$), 127.0 ($\underline{C}(2')$), 114.3 ($\underline{C}(11)H_2$), 33.9 ($\underline{C}(2)H_2$), 33.0 ($\underline{C}(9)H_2$), 29.5-29.4-29.3-29.2 ($\underline{C}(4)H_2$, $\underline{C}(5)H_2$, $\underline{C}(6)H_2$, $\underline{C}(7)H_2$), 29.0 ($\underline{C}(8)H_2$), 25.4 ($\underline{C}(3)H_2$), 21.3 ($\underline{C}(7')H_3$), 20.0 ($\underline{C}(6')H_3$); **m/z** (ESI⁺) 689 ([2M-H]⁺, 100%), 344 ([M-H]⁺, 50); **HRMS** (ESI⁺) C₂₁H₃₁NO₃ requires [M+Na]⁺ 368.2196, found 368.2194 (+0.49 ppm).

(3E)-N-[(Mesitylcarbonyl)oxy]-4-phenylbut-3-enamide (136)

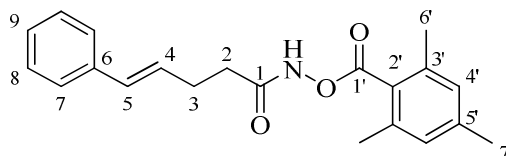


Compound **111** (747 mg, 4.22 mmol) was subjected to General Procedure B to furnish the title compound **136** (1.13 g, 3.50 mmol, 83%) as a white solid.

m.p. 118-120 °C; **v_{max}** (thin film)/cm⁻¹ 3162br, 2960br, 1773s, 1669s, 1611w, 1496w, 1251s, 1158m, 1038m, 986m, 968m, 849w, 692w; **δ_H** (400 MHz, CDCl₃) 9.22 (1H, br s, NH), 7.38-7.43 (2H, m, C(6)H), 7.34 (1H, t, *J* 7.6, C(7)H), 7.24-7.30 (1H, m, C(8)H), 6.89 (2H, s, C(4')H), 6.63 (1H, d, *J* 15.8, C(4)H), 6.30-6.40 (1H, m, C(3)H), 3.33 (2H, d, *J* 7.3, C(2)H₂), 2.39 (6H, s, C(6')H₃), 2.31 (3H, s, C(7')H₃); **δ_C** (100 MHz, CDCl₃) 169.2 ($\underline{C}(1')O$), 168.3 ($\underline{C}(1)O$), 141.2 ($\underline{C}(5')$), 137.0 ($\underline{C}(3')$), 136.6 ($\underline{C}(4)H$), 135.5 ($\underline{C}(5)$), 128.9 ($\underline{C}(7)H$), 128.9 ($\underline{C}(4')H$), 128.2 ($\underline{C}(3)H$), 126.7 ($\underline{C}(6)H$), 126.6 ($\underline{C}(2')$), 120.6 ($\underline{C}(8)H$), 38.0 ($\underline{C}(2)H_2$), 21.5 ($\underline{C}(7')H_3$), 20.3 ($\underline{C}(6')H_3$); **m/z** (ESI⁺)

322 ($[M-H]^-$, 100%); **HRMS** (ESI^+) $C_{20}H_{21}NO_3$ requires $[M+Na]^+$ 346.1414, found 346.1421 (-2.00 ppm).

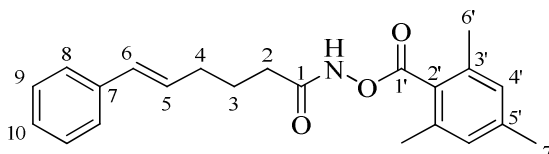
(4E)-N-[(Mesitylcarbonyl)oxy]-5-phenylpent-4-enamide (137)



(4E)-N-Hydroxy-5-phenylpent-4-enamide **112** (318 mg, 1.66 mmol) was subjected to General Procedure B to furnish the title compound **137** (510 mg, 1.51 mmol, 90%) as a colourless solid.

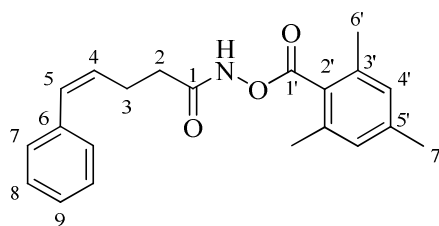
m.p. 93-95 °C; ν_{max} (thin film)/ cm^{-1} 3185br, 2961br, 1773s, 1669s, 1494m, 1447m, 1232s, 1157s, 1047m, 744m, 693m; δ_H (400 MHz, $CDCl_3$) 9.72 (1H, br s, NH), 7.34-7.38 (2H, m, C(7) H), 7.30-7.42 (2H, m, C(8) H), 7.19-7.25 (1H, m, C(9) H), 6.88 (2H, s, C(4') H), 6.48 (1H, d, J 15.6, C(5) H), 6.25 (1H, dt, J 15.6, 7.1, C(4) H), 2.65 (2H, m, C(3) H_2), 2.50 (2H, t, J 7.1, C(2) H_2), 2.38 (6H, s, C(6') H_3), 2.30 (3H, s, C(7') H_3); δ_C (100 MHz, $CDCl_3$) 171.0 ($\underline{C(1')O}$), 168.3 ($\underline{C(1)O}$), 141.0 ($\underline{C(5')}$), 137.4 ($\underline{C(6)}$), 136.9 ($\underline{C(3')}$), 131.6 ($\underline{C(5)H}$), 128.9 ($\underline{C(7)H}$), 128.7 ($\underline{C(4')H}$), 128.1 ($\underline{C(4)H}$), 127.4 ($\underline{C(9)H}$), 126.8 ($\underline{C(2')}$), 126.3 ($\underline{C(8)H}$), 32.9 ($\underline{C(2)H_2}$), 28.5 ($\underline{C(3)H_2}$), 21.4 ($\underline{C(7')H_3}$), 20.2 ($\underline{C(6')H_3}$); **m/z** (ESI^-) 673 ($[2M-H]^-$, 100%), 336 ($[M-H]^-$, 50); **HRMS** (ESI^+) $C_{21}H_{23}NO_3$ requires $[M+Na]^+$ 360.1570, found 360.1567 (+0.98 ppm).

(5E)-N-[(Mesitylcarbonyl)oxy]-6-phenylhex-5-enamide (138)



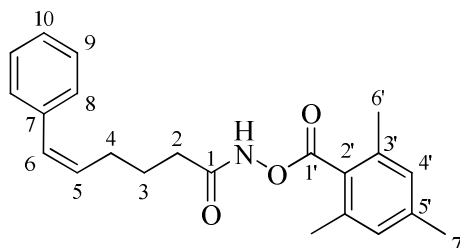
(5E)-N-Hydroxy-6-phenylhex-5-enamide **113** (310 mg, 1.51 mmol) was subjected to General Procedure B to furnish the title compound **138** (445 mg, 1.27 mmol, 93%) as a colourless solid.

m.p. 63-65 °C; ν_{max} (thin film)/ cm^{-1} 3230br, 2956br, 1775s, 1678s, 1380m, 1232s, 1158s, 1037m, 851w, 742w; δ_H (400 MHz, $CDCl_3$) 9.94 (1H, br s, NH), 7.35 (2H, m, C(9) H), 7.29-7.33 (2H, m, C(8) H), 7.22-7.23 (1H, m, C(10) H), 6.87 (2H, s, C(4') H), 6.43 (1H, d, J 15.9, C(6) H), 6.19 (1H, dt, J 15.9, 6.9, C(5) H), 2.33-2.44 (8H, m, C(4) H_2 , C(6') H_3), 2.24-2.34 (5H, m, C(2) H_2 , C(7') H_3), 1.91 (2H, quint, J 7.4, C(3) H_2); δ_C (100 MHz, $CDCl_3$) 171.2 ($\underline{C(1')O}$), 168.8 ($\underline{C(1)O}$), 140.5 ($\underline{C(5')}$), 137.3 ($\underline{C(7)}$), 136.5 ($\underline{C(3')}$), 130.7 ($\underline{C(5)H}$), 129.2 ($\underline{C(6)H}$), 128.4 ($\underline{C(8)H}$), 128.3 ($\underline{C(4')H}$), 126.8 ($\underline{C(10)H}$), 126.6 ($\underline{C(2')}$), 125.8 ($\underline{C(9)H}$), 32.01 ($\underline{C(2)H_2}$), 31.92 ($\underline{C(4)H_2}$), 24.4 ($\underline{C(3)H_2}$), 21.0 ($\underline{C(7')H_3}$), 19.8 ($\underline{C(6')H_3}$); **m/z** (ESI^-) 701 ($[2M-H]^-$, 100%), 350 ($[M-H]^-$, 80); **HRMS** (ESI^+) $C_{22}H_{25}NO_3$ requires $[M+Na]^+$ 374.1727 found 374.1725 (+0.49 ppm).

(4Z)-N-[(Mesitylcarbonyl)oxy]-5-phenylpent-4-enamide (139)

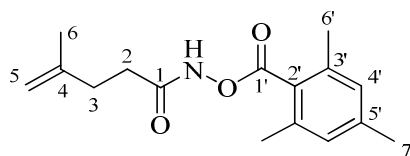
(4Z)-N-Hydroxy-5-phenylpent-4-enamide **114** (430 mg, 2.25 mmol) was subjected to General Procedure B to furnish the title compound **139** (681 mg, 2.02 mmol, 90%) as a colourless solid.

m.p. 74-75 °C; ν_{max} (thin film)/cm⁻¹ 3191br, 2962br, 1775s, 1670s, 1611w, 1493m, 1447m, 1233s, 1158s, 1037m, 851m, 770w, 700m; δ_{H} (400 MHz, CDCl₃) 9.45 (1H, br s, NH), 7.19-7.49 (5H, m, C(7)H, C(8)H, C(9)H), 6.91 (2H, s, C(4')H), 6.54 (1H, d, *J* 11.5, C(5)H), 5.69 (1H, dt, *J* 11.6, 7.1, C(4)H), 2.70-2.89 (2H, m, C(3)H), 2.38-2.52 (8H, m, C(2)H, C(6')H), 2.33 (3H, s, C(7')H); δ_{C} (100 MHz, CDCl₃) 170.5 (C(1')O), 167.8 (C(1)O), 140.6 (C(5')), 136.9 (C(6)), 136.5 (C(3')), 130.3 (C(5)H), 129.7 (C(7)H), 128.6 (C(4')H), 128.5 (C(4)H), 128.1 (C(9)H), 126.7 (C(8)H), 126.5 (C(2')), 32.7 (C(2)H₂), 23.9 (C(3)H₂), 21.1 (C(7')H₃), 19.8 (C(6')H₃); **m/z** (ESI⁺) 673 ([2M-H]⁺, 100%), 336 ([M-H]⁺, 70); **HRMS** (ESI⁺) C₂₁H₂₃NO₃ requires [M+Na]⁺ 360.1570, found 360.1570 (-0.04 ppm).

(5Z)-N-[(Mesitylcarbonyl)oxy]-6-phenylhex-5-enamide (140)

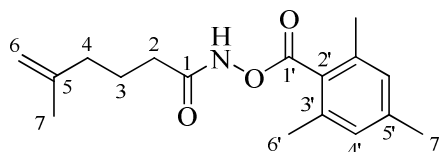
(5Z)-N-Hydroxy-6-phenylhex-5-enamide **115** (310 mg, 1.51 mmol) was subjected to General Procedure B to furnish the title compound **140** (425 mg, 1.21 mmol, 89%) as a colourless oil.

ν_{max} (thin film)/cm⁻¹ 3196br, 2955br, 1774s, 1670s, 1611w, 1494m, 1232s, 1158m, 1035br, 851m, 770w, 700m; δ_{H} (400 MHz, CDCl₃) 9.40 (1H, br s, NH), 7.31-7.39 (2H, m, C(9)H), 7.20-7.31 (3H, m, C(8)H, C(10)H), 6.87 (2H, s, C(4')H), 6.43 (1H, d, *J* 11.6, C(6)H), 5.64 (1H, dt, *J* 11.6, 7.3, C(5)H), 2.34-2.47 (8H, m, C(4)H, C(6')H), 2.26-2.34 (5H, m, C(2)H, C(7')H), 1.87 (2H, quint, *J* 7.3, C(3)H); δ_{C} (100 MHz, CDCl₃) 171.5 (C(1')O), 168.2 (C(1)O), 140.9 (C(5')), 137.6 (C(7)), 136.9 (C(3')), 131.6 (C(5)H), 130.1 (C(6)H), 128.9 (C(8)H), 128.8 (C(4')H), 127.2 (C(10)H), 126.88 (C(9)H), 126.84 (C(2')), 32.5 (C(2)H₂), 28.0 (C(4)H₂), 25.4 (C(3)H₂), 21.4 (C(7')H₃), 20.2 (C(6')H₃); **m/z** (ESI⁺) 701 ([2M-H]⁺, 100%), 350 ([M-H]⁺, 70); **HRMS** (ESI⁺) C₂₂H₂₅NO₃ requires [M+Na]⁺ 374.1727 found 374.1723 (+1.11 ppm).

***N*-[*(Mesitylcarbonyl)*oxy]-4-methylpent-4-enamide (141)**

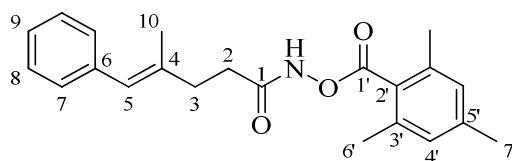
Compound **116** (421 mg, 3.26 mmol) was subjected to General Procedure B to furnish the title compound **141** (644 mg, 2.34 mmol, 90%) as a colourless solid.

m.p. 65-67 °C; **v_{max}** (thin film)/cm⁻¹ 3192br, 2969br, 1776s, 1672s, 1448br, 1233s, 1158s, 1035 br, 892m, 851m, 733w, 604w; **δ_H** (400 MHz, CDCl₃) 10.29 (1H, br s, NH), 6.83 (2H, s, C(4')H), 4.69-4.77 (2H, m, C(5)H₂), 2.41-2.48 (2H, m, C(2)H₂), 2.37-2.41 (2H, m, C(3)H₂), 2.34 (6H, s, C(6')H₃), 2.27 (3H, s, C(7')H₃), 1.72 (3H, s, C(6)H₃); **δ_C** (100 MHz, CDCl₃) 170.6 (C(1')O), 167.4 (C(1)O), 143.3 (C(5')), 140.1 (C(4)), 136.1 (C(3')), 128.0 (C(4')H), 126.3 (C(2')), 110.2 (C(5)H₂), 32.1 (C(2)H₂), 30.7 (C(3)H₂), 21.9 (C(6)H₃), 20.7 (C(7')H₃), 19.4 (C(6')H₃); **m/z** (ESI⁻) 549 ([2M-H]⁻, 100%), 274 ([M-H]⁻, 50); **HRMS** (ESI⁺) C₁₆H₂₁NO₃ requires [M+Na]⁺ 298.1414, found 298.1412 (+0.55 ppm).

***N*-[*(Mesitylcarbonyl)*oxy]-5-methylhex-5-enamide (142)**

N-Hydroxy-5-methylhex-5-enamide **117** (198 mg, 1.38 mmol) was subjected to General Procedure B to furnish the title compound **142** (295 mg, 1.02 mmol, 93%) as a colourless oil.

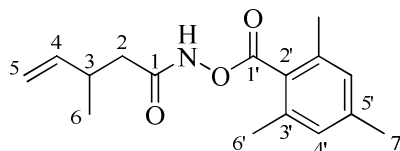
v_{max} (thin film)/cm⁻¹ 3192br, 2965br, 1776s, 1671s, 1612m, 1453m, 1233s, 1158s, 1036br, 890m, 851m; **δ_H** (400 MHz, CDCl₃) 9.64 (1H, br s, NH), 6.86 (2H, s, C(4')H), 4.74 (1H, s, C(6)H_a), 4.70 (1H, s, C(6)H_b), 2.36 (6H, s, C(6')H₃), 2.25-2.33 (5H, m, C(2)H₂, C(7')H₃), 2.07 (2H, t, *J* 7.5, C(4)H₂), 1.85 (2H, quint, *J* 7.5, C(3)H₂), 1.71 (3H, s, C(7)H₃); **δ_C** (100 MHz, CDCl₃) 171.6 (C(1')O), 168.3 (C(1)O), 144.8 (C(5')), 141.0 (C(5)), 136.9 (C(3')), 128.8 (C(4')H), 126.9 (C(2')), 111.1 (C(6)H₂), 37.1 (C(4)H₂), 32.4 (C(2)H₂), 22.9 (C(3)H₂), 22.4 (C(7)H₃), 21.4 (C(7')H₃), 20.2 (C(6')H₃); **m/z** (ESI⁻) 577 ([2M-H]⁻, 100%), 288 ([M-H]⁻, 70); **HRMS** (ESI⁺) C₁₇H₂₃NO₃ requires [M+H]⁺ 290.1751, found 290.1751 (-0.15 ppm).

***(4E)*-N-[*(Mesitylcarbonyl)*oxy]-4-methyl-5-phenylpent-4-enamide (143)**

Compound **118** (460 mg, 2.24 mmol) was subjected to General Procedure B to furnish the title compound **143** (572 mg, 1.63 mmol, 91%) as a colourless oil. Correct alkene geometry proven by NOESY experiment.

$\nu_{\max}$ (thin film)/ cm^{-1} 3218br, 2964br, 1773s, 1669s, 1612s, 1491m, 1446m, 1233s, 1158s, 1033br, 851m, 739m, 699m; δ_{H} (400 MHz, CDCl_3) 10.31 (1H, br s, NH), 7.30-7.42 (5H, m, C(7) $\underline{\text{H}}$, C(8) $\underline{\text{H}}$, C(9) $\underline{\text{H}}$), 6.92 (2H, s, C(4') $\underline{\text{H}}$), 6.41 (1H, s, C(5) $\underline{\text{H}}$), 2.59-2.71 (4H, m, C(2) $\underline{\text{H}}$, C(3) $\underline{\text{H}}$), 2.47 (6H, s, C(6') $\underline{\text{H}}$), 2.36 (3H, s, C(7') $\underline{\text{H}}$), 1.94 (3H, d, J 1.5, C(10) $\underline{\text{H}}$); δ_{C} (100 MHz, CDCl_3) 170.8 ($\underline{\text{C}}$ (1')O), 167.8 ($\underline{\text{C}}$ (1)O), 140.5 ($\underline{\text{C}}$ (5')), 137.8 ($\underline{\text{C}}$ (4)), 136.4 ($\underline{\text{C}}$ (6)), 136.3 ($\underline{\text{C}}$ (3')), 128.6 ($\underline{\text{C}}$ (4')H), 128.5 ($\underline{\text{C}}$ (5)H), 127.9 ($\underline{\text{C}}$ (8)H), 126.5 ($\underline{\text{C}}$ (2')), 125.9 ($\underline{\text{C}}$ (7)H), 125.8 ($\underline{\text{C}}$ (9)H), 35.4 ($\underline{\text{C}}$ (2) $\underline{\text{H}}$), 31.5 ($\underline{\text{C}}$ (3) $\underline{\text{H}}$), 21.0 ($\underline{\text{C}}$ (7') $\underline{\text{H}}$), 19.8 ($\underline{\text{C}}$ (6') $\underline{\text{H}}$), 17.4 ($\underline{\text{C}}$ (10) $\underline{\text{H}}$); m/z (ESI $^-$) 701 ($[\text{2M-H}]^-$, 100%), 350 ($[\text{M-H}]^-$, 60); **HRMS** (ESI $^+$) $\text{C}_{22}\text{H}_{25}\text{NO}_3$ requires $[\text{M+Na}]^+$ 374.1727, found 374.1724.1751 (+0.78 ppm).

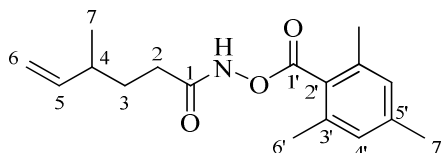
N-[(Mesitylcarbonyl)oxy]-3-methylpent-4-enamide (**144**)



N-Hydroxy-3-methylpent-4-enamide **119** (900 mg, 6.98 mmol) was subjected to General Procedure B to furnish the title compound **144** (1.35 g, 4.90 mmol, 78%) as a colourless solid.

m.p. 46-48 °C; $\nu_{\max}$ (thin film)/ cm^{-1} 3188br, 2965br, 1776s, 1669s, 1612m, 1457m, 1379w, 1233s, 1158m, 1037br, 988s, 916m, 850m, 734w; δ_{H} (400 MHz, CDCl_3) 10.53 (1H, br s, NH), 6.82 (2H, s, C(4') $\underline{\text{H}}$), 5.75 (1H, ddd, J 17.2, 10.4, 6.8, C(4) $\underline{\text{H}}$), 5.03 (1H, dd, J 17.2, 1.4, C(5) $\underline{\text{H}}$), 4.95 (1H, dd, J 10.4, 1.4, C(5) $\underline{\text{H}}$), 2.69-2.82 (1H, m, C(3) $\underline{\text{H}}$), 2.35 (6H, s, C(6') $\underline{\text{H}}$), 2.28-2.34 (1H, m, C(2) $\underline{\text{H}}$), 2.26 (3H, s, C(7') $\underline{\text{H}}$), 2.17-2.24 (1H, m, C(2) $\underline{\text{H}}$), 1.06 (3H, d, J 6.8, C(6) $\underline{\text{H}}$); δ_{C} (100 MHz, CDCl_3) 169.9 ($\underline{\text{C}}$ (1')O), 167.5 ($\underline{\text{C}}$ (1)O), 141.9 ($\underline{\text{C}}$ (4)H), 140.3 ($\underline{\text{C}}$ (5')), 136.3 ($\underline{\text{C}}$ (3')), 128.3 ($\underline{\text{C}}$ (4')H), 126.7 ($\underline{\text{C}}$ (2')), 113.4 ($\underline{\text{C}}$ (5) $\underline{\text{H}}$), 39.5 ($\underline{\text{C}}$ (2) $\underline{\text{H}}$), 34.1 ($\underline{\text{C}}$ (3)H), 20.9 ($\underline{\text{C}}$ (7') $\underline{\text{H}}$), 19.7 ($\underline{\text{C}}$ (6') $\underline{\text{H}}$), 19.0 ($\underline{\text{C}}$ (6) $\underline{\text{H}}$); m/z (ESI $^-$) 128 ($[\text{M-H}]^-$, 100%); **HRMS** (ESI $^+$) $\text{C}_{16}\text{H}_{21}\text{NO}_3$ requires $[\text{M+Na}]^+$ 298.1414, found 298.1415 (-0.35 ppm).

N-[(Mesitylcarbonyl)oxy]-4-methylhex-5-enamide (**145**)

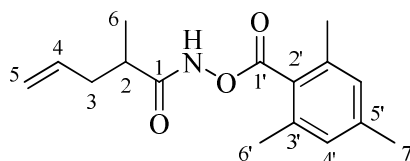


Compound **120** (368 mg, 2.57 mmol) was subjected to General Procedure B to furnish the title compound **145** (537 mg, 1.86 mmol, 88%) as a yellowish gum.

$\nu_{\max}$ (thin film)/ cm^{-1} 3191br, 2962s, 2929s, 2867m, 1776s, 1671s, 1612m, 1455m, 1378w, 1233s, 1158s, 1045s, 994m, 948w, 915w, 851w, 679w, 602w; δ_{H} (400 MHz, CDCl_3) 10.66 (1H, br s, NH),

6.80 (2H, s, C(4')H), 5.60 (1H, ddd, J 17.4, 9.9, 7.8, C(5)H), 4.88-5.01 (2H, m, C(6)H₂), 2.34 (6H, s, C(6')H₃), 2.24 (5H, m, C(2)H₂, C(7')H₃), 2.04-2.17 (1H, m, C(4)H), 1.57-1.77 (2H, m, C(3)H₂), 0.97 (3H, d, J 6.8, C(7)H₃); δ_c (100 MHz, CDCl₃) 171.7 (C(1')O), 167.7 (C(1)O), 143.3 (C(5)H), 140.4 (C(5')), 136.5 (C(3')), 128.5 (C(4')H), 127.0 (C(2')), 113.7 (C(6)H₂), 37.4 (C(4)H), 31.6 (C(3)H₂), 30.7 (C(2)H₂), 21.1 (C(7)H₃), 20.1 (C(7')H₃), 19.9 (C(6')H₃); m/z (ESI⁻) 577 ([2M-H]⁻, 100%), 288 ([M-H]⁻, 80); **HRMS** (ESI⁺) C₁₇H₂₃NO₃ requires [M+Na]⁺ 312.1570, found 312.1572 (-0.49 ppm).

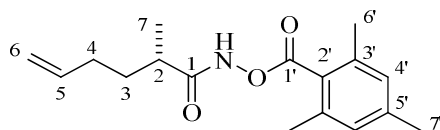
***N*-[*(Mesitylcarbonyl)oxy*]-2-methylpent-4-enamide (146)**



Compound **121** (960 mg, 7.44 mmol) was subjected to General Procedure B to furnish the title compound **146** (1.59 g, 5.78 mmol, 86%) as a colourless solid.

m.p. 95-96 °C; $\nu_{\max}$ (thin film)/cm⁻¹ 3191br, 2976br, 1777s, 1671s, 1611m, 1457m, 1380w, 1233s, 1157m, 1027br, 986m, 851m, 734m; δ_H (400 MHz, CDCl₃) 10.88 (1H, br s, NH), 6.81 (2H, s, C(4')H), 5.69-5.82 (1H, m, C(4)H), 4.99-5.11 (2H, m, C(5)H₂), 2.50-2.56 (1H, m, C(2)H), 2.42-2.50 (1H, m, C(3)H_a), 2.37 (6H, s, C(6')H₃), 2.24 (3H, s, C(7')H₃), 2.15-2.22 (1H, m, C(3)H_b), 1.19 (3H, d, J 6.8, C(6)H₃); δ_c (100 MHz, CDCl₃) 174.1 (C(1')O), 167.3 (C(1)O), 140.1 (C(5')), 136.2 (C(4)H), 134.8 (C(3')), 128.1 (C(4')H), 126.7 (C(2')), 116.8 (C(5)H₂), 37.7 (C(2)H), 37.2 (C(3)H₂), 20.8 (C(7')H₃), 19.5 (C(6')H₃), 16.8 (C(6)H₃); m/z (ESI⁻) 549 ([2M-H]⁻, 100%), 274 ([M-H]⁻, 60); **HRMS** (ESI⁺) C₁₆H₂₁NO₃ requires [M+Na]⁺ 298.1414, found 298.1415 (-0.39 ppm).

***(2S)*-N-[*(Mesitylcarbonyl)oxy*]-2-methylhex-5-enamide (147)**

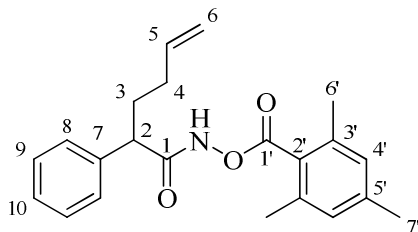


Compound **122** (91.5 mg, 0.64 mmol) was subjected to General Procedure B to give the title compound **147** (133 mg, 0.46 mmol, 91%) as a colourless oil.

$[\alpha]_D^{23} + 24.7$ ($c = 1.0$, dichloromethane); $\nu_{\max}$ (thin film)/cm⁻¹ 3443br, 1775w, 1643 br, 1232w, 1157w, 1025w; δ_H (400 MHz, CDCl₃) 8.95 (1H, br s, NH), 6.89 (2H, s, C(4')H), 5.71-5.87 (1H, ddt, J 17.1, 10.2, 6.7, C(5)H), 4.97-5.14 (2H, m, C(6)H₂), 2.40 (7H, br s, C(2)H, C(6')H₃), 2.30 (3H, s, C(7')H₃), 2.12-2.21 (2H, m, C(4)H₂), 1.84-1.95 (1H, m, C(3)H_a), 1.52-1.65 (1H, m, C(3)H_b), 1.27 (3H, d, J 6.8, C(7)H₃); δ_c (100 MHz, CDCl₃) 170.5 (C(1')O), 167.9 (C(1)O), 140.5 (C(5')), 137.5 (C(5)H), 136.4 (C(3')), 128.3 (C(4')H), 126.2 (C(2')), 115.2 (C(6)H₂), 37.1 (C(2)H), 32.4 (C(3)H₂), 31.0 (C(4)H₂), 20.9 (C(7')H₃), 19.7 (C(6')H₃), 17.4 (C(7)H₃); m/z (ESI⁻) 288 ([M-H]⁻,

100%), 577 ([2M-H]⁻, 50); **HRMS** (ESI⁻) C₁₇H₂₃NO₃ requires [M-H]⁻ 288.1605 found 288.1606 (-0.15 ppm).

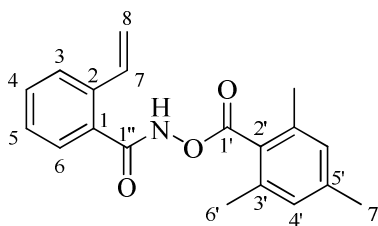
2-Phenyl-*N*-(2,4,6-trimethylbenzoyloxy)hex-5-enamide (**148**)



Compound **123** (304 mg, 1.48 mmol) was subjected to General Procedure B to furnish the title compound **148** (427 mg, 1.21 mmol, 82%) as a colourless oil.

$\nu_{\max}$ (thin film)/cm⁻¹ 3198br s, 2949br s, 1776s, 1670br s, 1611m, 1495m, 1454m, 1379w, 1232s, 1157s, 1033br s, 913w, 850w, 732w, 698m; δ_{H} (500 MHz, CDCl₃) 8.94 (1H, br s, NH), 7.37 (4H, m, C(8)H, C(9)H), 7.32 (1H, td, *J* 8.6, 4.5, C(10)H), 6.87 (2H, s, C(4')H), 5.80 (1H, ddt, *J* 16.9, 10.2, 6.6, 6.6, C(5)H), 4.99-5.10 (2H, m, C(6)H), 3.56 (1H, t, *J* 7.3, C(2)H), 2.36 (7H, br s, C(3)H, C(6')H), 2.29 (3H, s, C(7')H), 2.09 (2H, td, *J* 7.3, 6.6, C(4)H), 1.92-2.02 (1H, m, C(3)H); δ_{C} (125 MHz, CDCl₃) 171.8 (C(1')O), 167.9 (C(1)O), 140.8 (C(7)), 138.2 (C(5)H), 137.5 (C(5')), 136.8 (C(3')), 129.0 (C(4')H), 128.6 (C(8)H), 128.1 (C(9)H), 127.7 (C(10)H), 126.4 (C(2')), 115.7 (C(6)H₂), 49.2 (C(2)H), 32.0 (C(3)H₂), 31.2 (C(4)H₂), 21.2 (C(7')H₃), 20.0 (C(6')H₃); *m/z* (ESI⁻) 350 ([M-H]⁻, 100%); **HRMS** (ESI⁻) C₂₂H₂₅NO₃ requires [M-H]⁻ 350.1762, found 350.1755 (-1.01 ppm).

N-[(Mesitylcarbonyl)oxy]-2-vinylbenzamide (**149**)

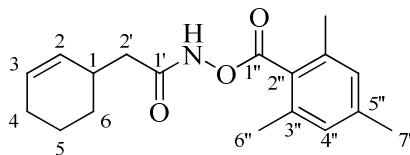


Compound **124** (900 mg, 5.52 mmol) was subjected to General Procedure B to furnish the title compound **149** (1.07 g, 3.48 mmol, 63%) as a colourless solid.

m.p. 135-137 °C; $\nu_{\max}$ (thin film)/cm⁻¹ 3184br, 1767s, 1656s, 1493w, 1231m, 1158w, 1020w, 984w, 909w, 773w; δ_{H} (400 MHz, CDCl₃) 9.17 (1H, br s, NH), 7.63-7.69 (2H, m, C(6)H, C(3)H), 7.50 (1H, t, *J* 7.6, C(5)H), 7.35 (1H, t, *J* 7.6, C(4)H), 7.19 (1H, dd, *J* 17.4, 11.1, C(7)H), 6.92 (2H, s, C(4')H), 5.80 (1H, d, *J* 17.4, C(8)H), 5.44 (1H, d, *J* 11.1, C(8)H), 2.44 (6H, s, C(6')H), 2.32 (3H, s, C(7')H); δ_{C} (100 MHz, CDCl₃) 171.1 (C(1')O), 168.5 (C(1''O)), 141.3 (C(5')), 137.4 (C(2)), 137.2 (C(3')), 134.2 (C(7)H), 131.7 (C(4)H), 130.9 (C(1)), 129.0 (C(4')H), 128.5 (C(5)H), 128.0

($\underline{C}(3)H$), 126.8 ($\underline{C}(6)H$), 126.6 ($\underline{C}(2')$), 117.9 ($\underline{C}(8)H_2$), 21.6 ($\underline{C}(7')H_3$), 20.4 ($\underline{C}(6')H_3$); **m/z** (ESI⁻) 617 ([2M-H]⁻, 100%), 308 ([M-H]⁻, 100%); **HRMS** (ESI⁺) C₁₉H₁₉NO₃ requires [M+Na]⁺ 332.1257, found 332.1248 (+2.75 ppm).

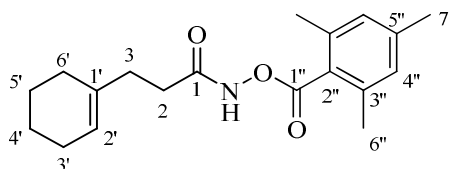
2-Cyclohex-2-en-1-yl-*N*-[(mesitylcarbonyl)oxy]acetamide (**150**)



Compound **126** (390 mg, 2.52 mmol) was subjected to General Procedure B to furnish the title compound **150** (590 mg, 1.96 mmol, 89%) as a colourless solid.

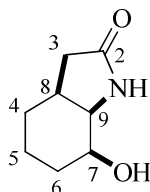
m.p. 102-104 °C; $\nu_{\max}$ (thin film)/cm⁻¹ 2927br, 1776s, 1667s, 1608w, 1237s, 1158m, 1035s, 987m, 850w; δ_H (400 MHz, CDCl₃) 9.11 (1H, br s, NH), 6.88 (2H, s, C(4'')H), 5.73-5.81 (1H, m, C(3)H), 5.62 (1H, dd, *J* 10.0, 1.4, C(2)H), 2.66-2.78 (1H, m, C(1)H), 2.39 (6H, s, C(6'')H₃), 2.30 (5H, m, C(2')H₂, C(7'')H₃), 1.97-2.03 (2H, m, C(4)H₂), 1.87-1.95 (1H, m, C(6)H_a), 1.71-1.77 (1H, m, C(5)H_a), 1.53-1.64 (1H, m, C(5)H_b), 1.28-1.39 (1H, m, C(6)H_b); δ_C (126 MHz, CDCl₃) 170.5 ($\underline{C}(1'')O$), 168.2 ($\underline{C}(1')O$), 140.5 ($\underline{C}(5'')$), 136.4 ($\underline{C}(3)H$), 129.4 ($\underline{C}(3'')$), 128.4 ($\underline{C}(2)H$), 128.3 ($\underline{C}(4'')H$), 126.2 ($\underline{C}(2'')$), 39.2 ($\underline{C}(2')H_2$), 31.9 ($\underline{C}(1)H$), 28.4 ($\underline{C}(5)H_2$), 24.7 ($\underline{C}(6)H_2$), 20.9 ($\underline{C}(4)H_2$), 20.6 ($\underline{C}(7'')H_3$), 19.6 ($\underline{C}(6'')H_3$); **m/z** (ESI⁻) 602 ([2M-H]⁻, 100%), 300 ([M-H]⁻, 50); **HRMS** (ESI⁻) C₁₈H₂₃NO₃ requires [M-H]⁻ 300.1605, found 300.1604 (+0.35 ppm).

3-(Cyclohex-1-en-1-yl)-*N*-[(mesitylcarbonyl)oxy]propanamide (**151**)



Compound **127** (1.16 g, 6.86 mmol) was subjected to General Procedure B to furnish the title compound **151** (1.31 g, 5.08 mmol, 74%) as a white solid.

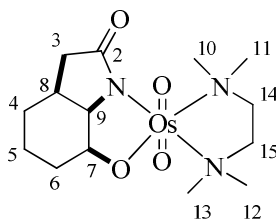
m.p. 98-100 °C; $\nu_{\max}$ (thin film)/cm⁻¹ 3187br, 2927br, 1776s, 1668s, 1612m, 1447m, 1232s, 1158s, 1047s, 1010s, 850m, 733m; δ_H (400 MHz, CDCl₃) 9.95 (1H, br s, NH), 6.84 (2H, s, C(4'')H), 5.45 (1H, br s, C(2')H), 2.29-2.44 (10H, m, C(2)H₂, C(3)H₂, C(6'')H₃), 2.28 (3H, s, C(7'')H₃), 1.86-2.00 (4H, m, C(3')H₂, C(6')H₂), 1.48-1.65 (4H, m, C(4')H₂, C(5')H₂); δ_C (100 MHz, CDCl₃) 170.9 ($\underline{C}(1'')O$), 167.5 ($\underline{C}(1')O$), 140.2 ($\underline{C}(5'')$), 136.1 ($\underline{C}(3'')$), 135.4 ($\underline{C}(1')H$), 128.1 ($\underline{C}(4'')H$), 126.3 ($\underline{C}(2'')$), 121.7 ($\underline{C}(2')H$), 32.5 ($\underline{C}(3)H_2$), 31.1 ($\underline{C}(2)H_2$), 27.7 ($\underline{C}(6')H_2$), 24.7 ($\underline{C}(3')H_2$), 22.4 ($\underline{C}(5')H_2$), 21.9 ($\underline{C}(4')H_2$), 20.7 ($\underline{C}(7'')H_3$), 19.4 ($\underline{C}(6'')H_3$); **m/z** (ESI⁻) 314 ([M-H]⁻, 100%), 629 ([2M-H]⁻, 50); **HRMS** (ESI⁺) C₁₉H₂₅NO₃ requires [M+NH₄+CH₃CN]⁺ 374.2438, found 374.2438 (+0.08 ppm).

(3aR*, 7R*, 7aS*)-7-Hydroxyoctahydro-2H-indol-2-one (159)

Compound **159** (119 mg, 0.39 mmol) was subjected to General Procedure C to give the title compound **150** (50.2 mg, 0.32 mmol, 83% with 4 mol % of the catalyst used) as a colourless solid.

m.p. 45-47 °C; $\nu_{\max}$ (thin film)/cm⁻¹ 3281br, 2934br, 1681s, 1307w, 1054w; δ_{H} (400 MHz, CDCl₃) 7.08 (1H, br s, NH), 5.86 (1H, br s, OH), 3.86 (1H, t, *J* 4.5, C(9)H), 3.74 (1H, ddd, *J* 10.7, 4.0, 3.9, C(7)H), 2.45 (1H, dd, *J* 16.0, 6.7, C(3)H_a), 2.30-2.39 (1H, m, C(8)H), 2.01-2.05 (1H, m, C(3)H_b), 1.64-1.74 (2H, m, C(5)H_a, C(6)H_a), 1.54-1.62 (1H, m, C(4)H_a), 1.41-1.52 (1H, m, C(6)H_b), 1.12-1.28 (2H, m, C(4)H_b, C(5)H_b); δ_{C} (100 MHz, CDCl₃) 179.8 (C(2)O), 69.7 (C(7)H), 58.8 (C(9)H), 39.8 (C(3)H₂), 35.1 (C(8)H), 28.6 (C(6)H₂), 27.2 (C(4)H₂), 21.6 (C(5)H₂); **m/z** (ESI⁺) 333 ([2M+Na]⁺ 100%), 311 ([2M+H]⁺ 90), 488 ([3M+Na]⁺ 60), 197 ([M+H+CH₃CN]⁺ 50), 219 ([M+Na+CH₃CN]⁺ 45), 156 ([M+H]⁺, 50); **HRMS** (ESI⁺) C₈H₁₃NO₂ requires [M+Na]⁺ 178.0838 found 178.0837 (+0.77 ppm).

Single Crystal X-ray Diffraction Data for 159: C₈H₁₃NO₂, H₂O, M_r = 173.21, monoclinic (P1 21/c 1), *a* = 4.97490(10) Å, *b* = 7.86990(10) Å, *c* = 22.0125(5) Å, α = 90 °C, β = 95.2915(8) °C, γ = 90 °C, *V* = 858.16(3) Å³, *Z* = 4, μ = not measured *D*_{calc} = 1.341, *T* = 150(2) K, 10581 reflections collected, 1954 independent [*R*(int) = 0.025], *R*₁ = 0.0434, *wR*₂ = 0.0966 [*I* > 3σ(*I*)].

Osmate ester (160)

TMEDA (1.0 eq., 15 μL, 0.1 mmol) was added to a solution of compound **150** (1.0 eq., 30 mg, 0.1 mmol) in water (0.2 mL), acetonitrile (0.7 mL) and *t*-butanol (0.7 mL). The reaction mixture was stirred for 5 min then a solution of potassium osmate (1.0 eq., 37 mg, 0.1 mmol) in water (0.4 mL) was added. The reaction mixture was stirred for 30 h and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, eluting with dichloromethane: methanol 20:1) furnished the title compound **160** (21.2 mg, 0.04 mmol, 43%) as a brown solid.

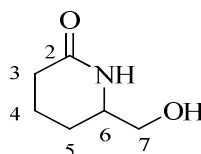
m.p. (decomp.) 155-158 °C; $\nu_{\max}$ (thin film)/cm⁻¹ 3366v, 2925s, 2853m, 1635s, 1459m, 1402m, 1369m, 1331w, 1312w, 1296w, 1267w, 1245w, 1128w, 1049w, 1020w, 991w, 959w, 842s, 802m, 664m, 592m; δ_{H} (200 MHz, CDCl₃) 4.09 (1H, t, *J* 5.2, C(9)H), 3.90-4.01 (1H, m, C(7)H), 3.25-3.37 (2H, m, C(14)H_a, C(15)H_a), 3.21 (3H, s, C(10)H₃), 3.09 (3H, s, C(11)H₃), 2.94 (3H, s,

C(12)H₃), 2.64-2.87 (7H, m, C(3)H_a, C(8)H, C(13)H₃, C(14)H_b, C(15)H_b), 2.28 (1H, d, *J* 15.1, C(3)H_b), 1.63-1.73 (3H, m, C(4)H_a, C(5)H_a, C(6)H_a), 0.98-1.49 (3H, m, C(4)H_b, C(5)H_b, C(6)H_b); δ_c (125 MHz, CDCl₃) 183.7 (C(2)O), 82.8 (C(7)H), 73.5 (C(9)H), 64.7 (C(15)H₂), 63.1 (C(14)H₂), 53.4 (C(13)H₃), 52.3 (C(12)H₃), 49.5 (C(10)H₃), 49.0 (C(11)H₃), 42.5 (C(3)H₂), 34.9 (C(8)H), 28.7 (C(4)H₂), 27.3 (C(5)H₂), 21.8 (C(6)H₂); *m/z* (ESI⁺) 494 ([M+H]⁺, 100%), 557 ([M+CH₃CN+H]⁺, 80), 985 ([2M+H]⁺, 50); **HRMS** (ESI⁺) C₁₄H₂₇N₃O₄Os requires [M+Na]⁺ 513.1476, 514.1481, 515.1509, 516.1509, 517.1538, found 513.1475, 514.1483, 515.1496, 516.1504, 517.1534 (+0.95 ppm).

Single Crystal X-ray Diffraction Data for 160: C₁₄H₂₇N₃O₄Os₁, *M_r* = 491.59, monoclinic (C 1 c 1), *a* = 11.2229(2) Å, *b* = 22.1408(4) Å, *c* = 7.34520(10) Å, α = 90 °C, β = 116.1764(9) °C, γ = 90 °C, *V* = 1637.98(5) Å³, *Z* = 4, μ = not measured *D*_{calc} = 1.993, *T* = 150(2) K, 3657 reflections collected, 3599 independent [*R*(int) = 0.014], *R*₁ = 0.0230, *wR*₂ = 0.0584 [*I*>3sigma(*I*)].

Hex-5-enoic acid (161) see page 145

6-(Hydroxymethyl)piperidin-2-one (162)



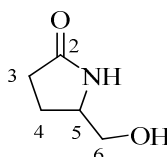
Compound **133** (268 mg, 0.90 mmol) was subjected to General Procedure C to give the title compound **162** (104 mg, 0.80 mmol, 83% with 4 mol % of the catalyst used) as a white powder.

Compound **133** (330 mg, 1.20 mmol) was subjected to General Procedure C to give the title compound **162** (92.6 mg, 0.72 mmol, 60% with 1 mol % of the catalyst used) as a white powder.

δ_H (400 MHz, CDCl₃) 7.37 (1H, br s, NH), 4.56 (1H, br s, OH), 3.64 (1H, dd, *J* 10.7, 2.6, C(7)H_a), 3.45-3.54 (1H, m, C(6)H), 3.42 (1H, dd, *J* 10.7, 2.6, C(7)H_b), 2.32-2.42 (1H, m, C(3)H_a), 2.18-2.30 (1H, m, C(3)H_b), 1.84-1.94 (1H, m, C(4)H_a), 1.76-1.84 (1H, m, C(5)H_a), 1.63-1.76 (1H, m, C(5)H_b), 1.28-1.40 (1H, m, C(4)H_b); δ_c (100 MHz, CDCl₃) 173.6 (C(2)O), 66.3 (C(7)H₂), 55.1 (C(6)H), 31.5 (C(3)H₂), 24.6 (C(5)H₂), 19.8 (C(4)H₂).

Spectroscopic data were consistent with those reported in the literature.¹²²

5-(Hydroxymethyl)pyrrolidin-2-one (163)



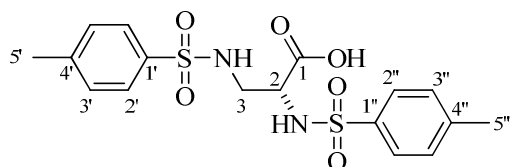
Compound **132** (161 mg, 0.62 mmol) was subjected to General Procedure C to give the title compound **163** (60.1 mg, 0.53 mmol, 85% with 4 mol % of the catalyst used) as a colourless solid.

Compound **132** (313 mg, 1.20 mmol) was subjected to General Procedure C to give the title compound **163** (109 mg, 0.94 mmol, 79% with 1 mol % of the catalyst used) as a colourless solid.

δ_{H} (400 MHz, CDCl_3) 7.45 (1H, br s, NH), 4.53 (1H, br s, OH), 3.75-3.84 (1H, m, $\text{C}(5)\text{H}$), 3.66 (1H, dd, J 11.1, $\text{C}(6)\text{H}_a$), 3.40-3.48 (1H, m, $\text{C}(6)\text{H}_b$), 2.26-2.42 (2H, m, $\text{C}(3)\text{H}_2$), 2.10-2.21 (1H, m, $\text{C}(4)\text{H}_a$), 1.72-1.83 (1H, m, $\text{C}(4)\text{H}_b$); δ_{C} (100 MHz, CDCl_3) 179.7 ($\text{C}(2)\text{O}$), 66.0 ($\text{C}(6)\text{H}_2$), 56.8 ($\text{C}(5)\text{H}$), 30.6 ($\text{C}(3)\text{H}_2$), 22.9 ($\text{C}(4)\text{H}_2$).

Spectroscopic data were consistent with those reported in the literature.¹²³

N-[(4-Methylphenyl)sulfonyl]-3-[[4-(4-methylphenyl)sulfonylamino]-D-alanine (164)

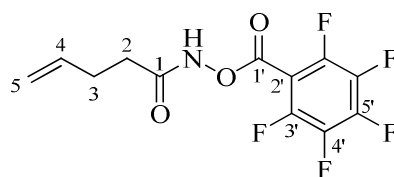


In a three-necked round-bottom flask equipped with a pH electrode was added D-2,3-diaminopropionic acid monohydrochloride (1 eq., 1 g, 7.1 mmol), dioxane ($1.7 \text{ mL} \cdot \text{mmol}^{-1}$) and distilled water ($6.6 \text{ mL} \cdot \text{mmol}^{-1}$). A dropping funnel containing a 1 M aqueous NaOH was also fitted on the flask. The pH was adjusted to 9. An ice bath was placed under the flask and solid *p*-toluenesulfonic chloride (2.2 eq., 2.98 g, 15.6 mmol) was added portionwise over 10 min with vigorous stirring. The reaction mixture was kept at pH 9 for 6 h by titration with 1 M aqueous NaOH. Finally more *p*-toluenesulfonic chloride (0.4 eq., 0.6 g, 3.2 mmol) was added. Stirring was continued with pH monitoring for 3 h and stirred for 16 h reaching room temperature (pH $\sim$ 6). 1 M aqueous NaOH was added until all unreacted sulfonic chloride in the middle was suspended. The reaction mixture was filtered. The pH of the filtrate was adjusted to 4 with 1 M aqueous HCl. The white precipitated obtained was filtered, washed with cooled distilled water (30 mL) and dried for 16 h in the oven to give the title compound **164** (2.1 g, 5.07 mmol, 71%).

δ_{H} (400 MHz, $(\text{CD}_3)_2\text{SO}$) 7.59 (4H, d, J 7.96, $\text{C}(2')\text{H}$, $\text{C}(2'')\text{H}$), 7.34 (4H, d, J 7.96, $\text{C}(3')\text{H}$, $\text{C}(3'')\text{H}$), 3.51 (1H, t, J 6.3, $\text{C}(2)\text{H}$), 2.71-2.87 (2H, m, $\text{C}(3)\text{H}_2$), 2.38 (3H, s, $\text{C}(5')\text{H}_3$), 2.36 (3H, s, $\text{C}(5'')\text{H}_3$); δ_{C} (100 MHz, $(\text{CD}_3)_2\text{SO}$) 171.3 ($\text{C}(1)\text{O}$), 143.6 ($\text{C}(4')$), 143.5 ($\text{C}(4'')$), 138.4 ($\text{C}(1')$), 137.8 ($\text{C}(1'')$), 130.5 ($\text{C}(2')\text{H}$), 130.3 ($\text{C}(2'')\text{H}$), 127.4 (br, $\text{C}(3')\text{H}$, $\text{C}(3'')\text{H}$), 55.9 ($\text{C}(2)\text{H}$), 45.6 ($\text{C}(3)\text{H}_2$), 21.8 (br, $\text{C}(5')\text{H}_3$, $\text{C}(5'')\text{H}_3$).

Spectroscopic data were consistent with those reported in the literature.¹²⁴

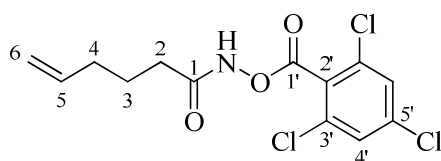
N-[(Pentafluorobenzoyl)oxy]pent-4-enamide (166)



Compound **90** (196 mg, 1.70 mmol) was subjected to General Procedure B to furnish the title compound **166** (176 mg, 0.57 mmol, 33%) as a yellowish oil.

$\nu_{\max}$ (thin film)/ cm^{-1} 3184br, 2952br, 1783s, 1680s, 1654s, 1525s, 1503s, 1422m, 1329m, 1182m, 1081s, 1003s, 909w, 795w; δ_{H} (400 MHz, CDCl_3) 9.54 (1H, br s, NH), 5.76-5.93 (1H, m, C(4) $\underline{\text{H}}$), 5.02-5.13 (2H, m, C(5) $\underline{\text{H}}_2$), 2.45 (4H, m, C(2) $\underline{\text{H}}_2$, C(3) $\underline{\text{H}}_2$); δ_{C} (100 MHz, CDCl_3) 170.7 ($\underline{\text{C}}$ (1)O), 156.1 ($\underline{\text{C}}$ (1')O), 146.2 (m, $\underline{\text{C}}$ (3')F), 145.5 (m, $\underline{\text{C}}$ (3')F), 144.2 (m, $\underline{\text{C}}$ (5')F), 142.2 (m, $\underline{\text{C}}$ (4')F), 141.9 (m, $\underline{\text{C}}$ (5')F), 138.5 (m, $\underline{\text{C}}$ (4')F), 136.0 ($\underline{\text{C}}$ (4)H), 116.4 ($\underline{\text{C}}$ (5) $\underline{\text{H}}_2$), 32.0 ($\underline{\text{C}}$ (2) $\underline{\text{H}}_2$), 28.7 ($\underline{\text{C}}$ (3) $\underline{\text{H}}_2$); δ_{F} (377 MHz, CDCl_3) $^{-135.0}$ (m, C(3') $\underline{\text{E}}$), $^{-145}$ (m, C(5') $\underline{\text{E}}$), $^{-159.7}$ (m, C(4') $\underline{\text{E}}$); m/z (ESI $^{-}$) 308 ([M-H] $^{-}$, 100%); **HRMS** (ESI $^{+}$) $\text{C}_{12}\text{H}_8\text{F}_5\text{NO}_3$ requires [M+Na] $^{+}$ 332.0317 found 332.0310 (+2.02 ppm).

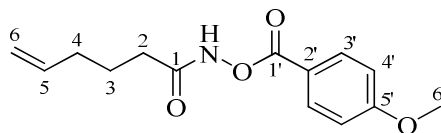
N-[(2,4,6-trichlorobenzoyl)oxy]hex-5-enamide (**167**)



Compound **90** (247 mg, 1.91 mmol) was subjected to General Procedure B to furnish the title compound **167** (352 mg, 1.04 mmol, 61%) as a colourless solid.

m.p. 79-81 °C; $\nu_{\max}$ (thin film)/ cm^{-1} 3155br, 2940br, 1792s, 1675s, 1578m, 1550m, 1372w, 1235m, 1096m, 1036s, 822w, 807w; δ_{H} (400 MHz, CDCl_3) 9.33 (1H, br s, NH), 7.39 (2H, s, C(4') $\underline{\text{H}}$), 5.65-5.87 (1H, ddt, J 17.0, 10.2, 6.8, C(5) $\underline{\text{H}}$), 4.94-5.19 (2H, m, C(6) $\underline{\text{H}}_2$), 2.36 (2H, t, J 7.2, C(2) $\underline{\text{H}}_2$), 2.15 (2H, m, C(4) $\underline{\text{H}}_2$), 1.84 (2H, quint, J 7.3, C(3) $\underline{\text{H}}_2$); δ_{C} (100 MHz, CDCl_3) 162.6 ($\underline{\text{C}}$ (1)O), 154.8 ($\underline{\text{C}}$ (1')O), 138.2 ($\underline{\text{C}}$ (2')), 137.7 ($\underline{\text{C}}$ (5)H), 133.9 ($\underline{\text{C}}$ (3')), 128.8 ($\underline{\text{C}}$ (5')), 128.6 ($\underline{\text{C}}$ (4')H), 116.1 ($\underline{\text{C}}$ (6) $\underline{\text{H}}_2$), 33.2 ($\underline{\text{C}}$ (2) $\underline{\text{H}}_2$), 32.3 ($\underline{\text{C}}$ (4) $\underline{\text{H}}_2$), 23.7 ($\underline{\text{C}}$ (3) $\underline{\text{H}}_2$); m/z (ESI $^{+}$) 336, 338 ([M+H] $^{+}$, 100%); **HRMS** (ESI $^{+}$) $\text{C}_{13}\text{H}_{12}\text{Cl}_3\text{NO}_3$ requires [M+Na] $^{+}$ 357.9775, 359.9747, 361.9720 found 357.9763, 359.9742, 361.9725 (+3.22 ppm).

N-[(4-Methoxybenzoyl)oxy]hex-5-enamide (**168**)

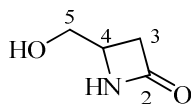


Compound **90** (850 mg, 6.58 mmol) was subjected to General Procedure B to furnish the title compound **168** (100 mg, 0.37 mmol, 6%) as a colourless oil.

$\nu_{\max}$ (thin film)/ cm^{-1} 3187br, 2938br, 1763s, 1673 br s, 1607s, 1511s, 1253s, 1170s, 1028m, 915w, 846m, 761m, 693w; δ_{H} (400 MHz, CDCl_3) 9.83 (1H, br s, NH), 7.87-8.12 (2H, m, C(3') $\underline{\text{H}}$), 6.90 (2H, m, C(4') $\underline{\text{H}}$), 5.60-5.87 (1H, ddt, J 17.0, 10.3, 6.7, C(5) $\underline{\text{H}}$), 4.83-5.19 (2H, m, C(6) $\underline{\text{H}}_2$), 3.71-4.00 (3H, s, C(6') $\underline{\text{H}}_3$), 2.25-2.37 (2H, m, C(2) $\underline{\text{H}}_2$), 2.09 (2H, m, C(4) $\underline{\text{H}}_2$), 1.70-1.83 (2H, m, C(3) $\underline{\text{H}}_2$);

δ_{C} (100 MHz, CDCl_3) 177.9 ($\underline{\text{C}}(1')\text{O}$), 164.6 ($\underline{\text{C}}(5')$), 164.3 ($\underline{\text{C}}(1)\text{O}$), 137.6 ($\underline{\text{C}}(5)\text{H}$), 132.2 ($\underline{\text{C}}(3')\text{H}$), 118.7 ($\underline{\text{C}}(2')$), 115.6 ($\underline{\text{C}}(6)\text{H}_2$), 114.0 ($\underline{\text{C}}(4')\text{H}$), 55.5 ($\underline{\text{C}}(6')\text{H}_3$), 32.9 ($\underline{\text{C}}(4)\text{H}_2$), 32.1 ($\underline{\text{C}}(2)\text{H}_2$), 23.7 ($\underline{\text{C}}(3)\text{H}_2$); m/z (ESI^+) 327 ($[\text{M}+\text{CH}_3\text{CN}+\text{Na}]^+$, 100), 549 ($[\text{2M}+\text{Na}]^+$, 90), 286 ($[\text{M}+\text{Na}]^+$, 60); **HRMS** (ESI^+) $\text{C}_{14}\text{H}_{17}\text{NO}_3$ requires $[\text{M}+\text{Na}]^+$ 286.1050, found 286.1048 (+0.65 ppm).

4-(Hydroxymethyl)azetidin-2-one (169)

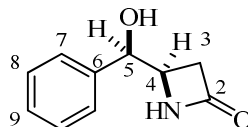


Compound **131** (201 mg, 0.81 mmol) was subjected to General Procedure C and heated at 50°C for 16 h to give the title compound **169** (49.5 mg, 0.49 mmol, 60% with 4 mol % of the catalyst used) as a colourless solid.

δ_{H} (400 MHz, CDCl_3) 6.70 (1H, br s, $\underline{\text{NH}}$), 3.73-3.95 (2H, m, $\underline{\text{C}}(5)\underline{\text{H}}_2$), 3.54-3.70 (1H, m, $\underline{\text{C}}(4)\underline{\text{H}}$), 3.33 (1H, br s, $\underline{\text{OH}}$), 2.92-3.08 (1H, m, $\underline{\text{C}}(3)\underline{\text{H}}_a$), 2.66-2.83 (1H, m, $\underline{\text{C}}(3)\underline{\text{H}}_b$); δ_{C} (100 MHz, CDCl_3) 169.7 ($\underline{\text{C}}(2)\text{O}$), 64.1 ($\underline{\text{C}}(5)\text{H}_2$), 49.2 ($\underline{\text{C}}(4)\text{H}$), 39.5 ($\underline{\text{C}}(3)\text{H}_2$).

Spectroscopic data were consistent with those reported in the literature.¹²⁵

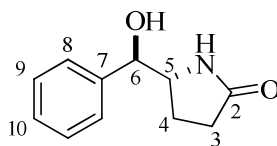
(4*R**)-4-[(*R**)-Hydroxy(phenyl)methyl]azetidin-2-one (170)



Compound **137** (316 mg, 0.98 mmol) was subjected to General Procedure C and heated at 40°C for 48 h to give the title compound **170** (92.2 mg, 0.52 mmol, 53% with 4 mol % of the catalyst used) as a colourless solid.

m.p. 110-112 °C; ν_{max} (thin film)/ cm^{-1} 3383br, 1729s, 1453w, 1413w, 1193m, 1039w, 1025w, 701m; δ_{H} (400 MHz, CD_3OD) 7.26-7.44 (5H, m, $\underline{\text{C}}(7)\underline{\text{H}}$, $\underline{\text{C}}(8)\underline{\text{H}}$, $\underline{\text{C}}(9)\underline{\text{H}}$), 4.60 (1H, d, J 6.8, $\underline{\text{C}}(5)\underline{\text{H}}$), 3.79 (1H, ddd, J 6.8, 4.8, 2.4, $\underline{\text{C}}(4)\underline{\text{H}}$), 2.74-2.83 (1H, m, $\underline{\text{C}}(3)\underline{\text{H}}_a$), 2.64-2.70 (1H, m, $\underline{\text{C}}(3)\underline{\text{H}}_b$); δ_{C} (100 MHz, CD_3OD) 171.0 ($\underline{\text{C}}(2)\text{O}$), 142.7 ($\underline{\text{C}}(6)$), 129.6 ($\underline{\text{C}}(8)\text{H}$), 129.1 ($\underline{\text{C}}(9)\text{H}$), 127.7 ($\underline{\text{C}}(7)\text{H}$), 77.1 ($\underline{\text{C}}(5)\text{H}$), 54.1 ($\underline{\text{C}}(4)\text{H}$), 40.3 ($\underline{\text{C}}(3)\text{H}_2$); m/z (ESI^+) 241 ($[\text{M}+\text{CH}_3\text{CN}+\text{Na}]^+$, 100%), 377 ($[\text{2M}+\text{Na}]^+$, 30), 219 ($[\text{M}+\text{CH}_3\text{CN}+\text{H}]^+$, 20); **HRMS** (ESI^+) $\text{C}_{10}\text{H}_{11}\text{NO}_2$ requires $[\text{M}+\text{Na}]^+$ 200.0682, found 200.0684 (-1.25 ppm).

Single Crystal X-ray Diffraction Data for 170: $\text{C}_{10}\text{H}_{11}\text{NO}_2$, $M_r = 177.20$, monoclinic (P1 21/c 1), $a = 12.3541(2)$ Å, $b = 5.50880(10)$ Å, $c = 13.1359(2)$ Å, $\alpha = 90^\circ$, $\beta = 100.0534(9)^\circ$, $\gamma = 90^\circ$, $V = 880.25(3)$ Å³, $Z = 4$, μ = not measured $D_{\text{calc}} = 1.337$, $T = 150(2)$ K, 9041 reflections collected, 2003 independent [$R(\text{int}) = 0$], $R_1 = 0.0755$, $wR_2 = 0.1150$ [$I > 3\sigma(I)$].

(5*R)-5-[(*R**)-Hydroxy(phenyl)methyl]pyrrolidin-2-one (171)**

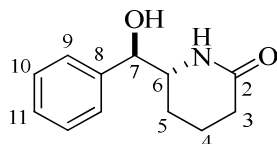
Compound **137** (340 mg, 1.01 mmol) was subjected to General Procedure C to give the title compound **171** (151 mg, 0.79 mmol, 78% with 4 mol % of the catalyst used) as a colourless solid.

Compound **137** (273 mg, 0.81 mmol) was subjected to General Procedure C to give the title compound **171** (78.3 mg, 0.41 mmol, 51% with 1 mol % of the catalyst used) as a colourless solid.

δ_{H} (400 MHz, CD_3OD) 7.33-7.43 (4H, m, C(8)H, C(9)H), 7.27-7.33 (1H, m, C(10)H), 4.50 (1H, d, J 6.8, C(6)H), 3.87-3.94 (1H, m, C(5)H), 2.07-2.31 (2H, m, C(3)H₂), 1.79-2.04 (2H, m, C(4)H₂); δ_{C} (100 MHz, CD_3OD) 181.3 (C(2)O), 142.3 (C(7)), 129.4 (C(9)H), 128.9 (C(10)H), 127.9 (C(8)H), 77.9 (C(6)H), 61.9 (C(5)H), 31.0 (C(3)H₂), 23.8 (C(4)H₂).

Spectroscopic data were consistent with those reported in the literature.¹²⁶

Single Crystal X-ray Diffraction Data for 171: $\text{C}_{11}\text{H}_{13}\text{NO}_2$, $M_r = 191.23$, monoclinic (P1 21/n 1), $a = 5.60930(10)$ Å, $b = 23.6664(4)$ Å, $c = 7.60370(10)$ Å, $\alpha = 90^\circ$, $\beta = 109.9111(8)^\circ$, $\gamma = 90^\circ$, $V = 949.07(3)$ Å³, $Z = 4$, $\mu =$ not measured $D_{\text{calc}} = 1.338$, $T = 150(2)$ K, 9925 reflections collected, 2135 independent [$R(\text{int}) = 0.024$], $R_1 = 0.0452$, $wR_2 = 0.0989$ [$I > 3\sigma(I)$].

(6*R)-6-[(*R**)-Hydroxy(phenyl)methyl]piperidin-2-one (172)**

Compound **138** (280 mg, 0.80 mmol) was subjected to General Procedure C to give the title compound **172** (130 mg, 0.63 mmol, 79% with 4 mol % of the catalyst used) as a colourless solid.

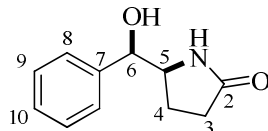
Compound **138** (182 mg, 0.52 mmol) was subjected to General Procedure C to give the title compound **172** (54.4 mg, 0.27 mmol, 51% with 1 mol % of the catalyst used) as a colourless solid.

m.p. 124-126 °C; ν_{max} (thin film)/cm⁻¹ 3381br, 1597s, 1436w, 1302w, 1329w, 1059w, 702m; δ_{H} (400 MHz, CDCl_3) 7.28-7.41 (5H, m, C(9)H, C(10)H, C(11)H), 7.07 (1H, br s, NH), 4.51 (1H, br s, OH), 4.34 (1H, d, J 8.6, C(7)H), 3.43 (1H, dt, J 9.5, 4.4, C(6)H), 2.27-2.40 (1H, m, C(3)H_a), 2.14-2.27 (1H, m, C(3)H_b), 1.79 (1H, m, C(4)H_a), 1.46-1.62 (1H, m, C(5)H_a), 1.33-1.43 (1H, m, C(5)H_b), 1.18-1.28 (1H, m, C(4)H_b); δ_{C} (100 MHz, CDCl_3) 172.4 (C(2)O), 140.5 (C(8)), 128.2 (C(10)H), 128.0 (C(11)H), 126.4 (C(9)H), 77.6 (C(7)H), 58.3 (C(6)H), 30.8 (C(3)H₂), 24.6 (C(5)H₂), 19.3 (C(4)H₂); **m/z** (ESI^+) 638 ($[\text{3M}+\text{Na}]^+$, 100%), 433 ($[\text{2M}+\text{Na}]^+$, 70), 411 ($[\text{M}+\text{H}]^+$, 70); **HRMS** (ESI^+) $\text{C}_{12}\text{H}_{15}\text{NO}_2$ requires $[\text{M}+\text{Na}]^+$ 228.0995, found 228.0995 (-0.19 ppm).

Single Crystal X-ray Diffraction Data for 172: $\text{C}_{12}\text{H}_{15}\text{NO}_2$, $M_r = 205.26$, monoclinic (P1 21/c 1), $a = 6.11250(10)$ Å, $b = 15.5663(3)$ Å, $c = 11.1621(2)$ Å, $\alpha = 90^\circ$, $\beta = 99.2961(8)^\circ$, $\gamma = 90^\circ$, $V =$

1048.11(3) Å³, Z = 4, μ = not measured D_{calc} = 1.301, T = 150(2) K, 14007 reflections collected, 2370 independent [R(int) = 0.024], R_1 = 0.0443, wR_2 = 0.0924 [I > 3 σ (I)].

(5*R)-5-[(*S**)-Hydroxy(phenyl)methyl]pyrrolidin-2-one (173)**



Compound **139** (300 mg, 0.89 mmol) was subjected to General Procedure C to give the title compound **173** (153 mg, 0.80 mmol, 90% with 4 mol % of the catalyst used) as a colourless solid.

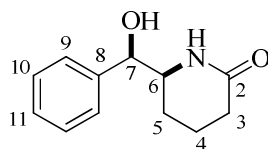
Compound **139** (367 mg, 1.09 mmol) was subjected to General Procedure C to give the title compound **173** (90.0 mg, 0.47 mmol, 43% with 1 mol % of the catalyst used) as a colourless solid.

δ_{H} (400 MHz, CDCl₃) 7.29-7.42 (5H, m, C(8)H, C(9)H, C(10)H), 6.38 (1H, br s, NH), 4.68 (1H, d, J 5.1, C(6)H), 3.89 (1H, m, C(5)H), 3.48 (1H, br s, OH), 1.95-2.26 (4H, m, C(3)H₂, C(4)H₂); δ_{C} (100 MHz, CDCl₃) 181.3 (C(2)O), 142.3 (C(7)), 129.4 (C(9)H), 128.9 (C(10)H), 127.9 (C(8)H), 77.9 (C(6)H), 61.9 (C(5)H), 31.0 (C(3)H₂), 23.8 (C(4)H₂).

Spectroscopic data were consistent with those reported in the literature.¹²⁶

Single Crystal X-ray Diffraction Data for 173: C₁₁H₁₃NO₂, M_r = 191.23, monoclinic (P1 21/c 1), a = 18.0508(4) Å, b = 6.27090(10) Å, c = 9.1222(2) Å, α = 90 °C, β = 100.9990(9) °C, γ = 90 °C, V = 1013.62(4) Å³, Z = 4, μ = not measured D_{calc} = 1.253, T = 150(2) K, 16667 reflections collected, 2305 independent [R(int) = 0.037], R_1 = 0.0581, wR_2 = 0.1061 [I > 3 σ (I)].

(6*R)-6-[(*S**)-Hydroxy(phenyl)methyl]piperidin-2-one (174)**



Compound **140** (204 mg, 0.58 mmol) was subjected to General Procedure C to give the title compound **174** (95.1 mg, 0.46 mmol, 80% with 4 mol % of the catalyst used) as a colourless solid.

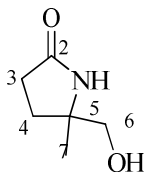
Compound **140** (141 mg, 0.40 mmol) was subjected to General Procedure C to give the title compound **174** (40.2 mg, 0.20 mmol, 49% with 1 mol % of the catalyst used) as a colourless solid.

m.p. 55-56 °C; ν_{max} (thin film)/cm⁻¹ 3305br, 2950br, 1650s, 1451w, 1410w, 1329w, 1065w, 911w, 713m; δ_{H} (400 MHz, CDCl₃) 7.28-7.41 (5H, m, C(9)H, C(10)H, C(11)H), 6.31 (1H, br s, NH), 4.59 (1H, d, J 5.3, C(7)H), 3.76 (1H, br s, OH), 3.60 (1H, dt, J 9.5, 4.7, C(6)H), 2.21-2.32 (1H, m, C(3)H_a), 2.05-2.19 (1H, m, C(3)H_b), 1.72-1.88 (2H, m, C(4)H_a, C(5)H_a), 1.51-1.65 (1H, m, C(5)H_b), 1.38-1.51 (1H, m, C(4)H_b); δ_{C} (100 MHz, CDCl₃) 173.6 (C(2)O), 140.2 (C(8)), 128.9 (C(10)H), 128.5 (C(11)H), 127.2 (C(9)H), 76.1 (C(7)H), 58.4 (C(6)H), 31.6 (C(3)H₂), 23.7

($\underline{C}(5)H_2$), 19.6 ($\underline{C}(4)H_2$); m/z (ESI⁺) 638 ([3M+Na]⁺, 100%), 433 ([2M+Na]⁺, 70), 411 ([M+H]⁺, 60); **HRMS** (ESI⁺) C₁₂H₁₅NO₂ requires [M+Na]⁺ 228.0995, found 228.0997 (-0.75 ppm).

Single Crystal X-ray Diffraction Data for 174: C₁₂H₁₅NO₂, 0.5(H₂O), M_r = 214.26, triclinic (P -1), a = 6.02820(10) Å, b = 12.9201(2) Å, c = 14.5745(2) Å, α = 90.8275(6) °C, β = 93.8444(6) °C, γ = 100.0136(8) °C, V = 1114.93(3) Å³, Z = 4, μ = not measured D_{calc} = 1.276, T = 150(2) K, 9069 reflections collected, 5054 independent [R(int) = 0.022], R₁ = 0.0542, wR₂ = 0.1015 [I>3σ(I)].

5-(Hydroxymethyl)-5-methylpyrrolidin-2-one (175)

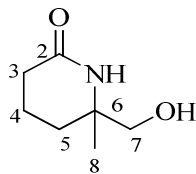


Compound **141** (385 mg, 1.40 mmol) was subjected to General Procedure C to give the title compound **175** (155 mg, 1.20 mmol, 86%) as a colourless solid.

m.p. 82-83 °C; $\nu_{\max}$ (thin film)/cm⁻¹ 3350br, 1674s, 1672s, 1419w, 1388w, 1057m, 638w; δ_H (400 MHz, CDCl₃) 7.43 (1H, br s, NH), 4.80 (1H, t, *J* 6.1, OH), 3.32-3.47 (2H, m, C(6) $\underline{H}_2$), 2.26-2.48 (2H, m, C(3) $\underline{H}_2$), 2.04 (1H, ddd, *J* 12.9, 9.9, 6.5, C(4) $\underline{H}_a$), 1.74 (1H, ddd, *J* 12.9, 9.9, 6.5, C(4) $\underline{H}_b$), 1.19 (3H, s, C(7) $\underline{H}_3$); δ_C (100 MHz, CDCl₃) 178.8 ($\underline{C}(2)O$), 69.3 ($\underline{C}(6)H_2$), 61.1 ($\underline{C}(5)$), 31.0 ($\underline{C}(3)H_2$), 30.2 ($\underline{C}(4)H_2$), 24.1 ($\underline{C}(7)H_3$); m/z (ESI⁻) 128 ([M-H]⁻, 100%), 257 ([2M-H]⁻, 70); **HRMS** (ESI⁺) C₆H₁₁NO₂ requires [M+Na]⁺ 152.0682, found 152.0678 (+2.88 ppm).

Single Crystal X-ray Diffraction Data for 175: C₆H₁₁NO₂, M_r = 177.20, monoclinic (P1 21/c 1), a = 8.6393(2) Å, b = 5.20040(10) Å, c = 14.3361(4) Å, α = 90 °C, β = 90.8101(12) °C, γ = 90 °C, V = 644.03(3) Å³, Z = 4, μ = not measured D_{calc} = 1.332, T = 150(2) K, 7135 reflections collected, 1454 independent [R(int) = 0], R₁ = 0.0485, wR₂ = 0.0869 [I>3σ(I)].

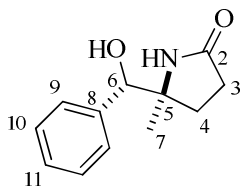
6-(Hydroxymethyl)-6-methylpiperidin-2-one (176)



Compound **142** (143 mg, 0.49 mmol) was subjected to General Procedure C to give the title compound **176** (54.7 mg, 0.38 mmol, 78% with 4 mol % of the catalyst used) as a colourless solid.

δ_H (400 MHz, CDCl₃) 7.06 (1H, br s, NH), 4.45 (1H, br s, OH), 3.42 (2H, s, C(7) $\underline{H}_2$), 2.16-2.38 (2H, m, C(3) $\underline{H}_2$), 1.74-1.84 (2H, m, C(5) $\underline{H}_2$), 1.63-1.72 (1H, m, C(4) $\underline{H}_a$), 1.46-1.55 (1H, m, C(4) $\underline{H}_b$), 1.20 (3H, s, C(8) $\underline{H}_3$); δ_C (100 MHz, CDCl₃) 172.9 ($\underline{C}(2)O$), 69.8 ($\underline{C}(7)H_2$), 55.8 ($\underline{C}(6)$), 30.6 ($\underline{C}(3)H_2$), 29.8 ($\underline{C}(5)H_2$), 24.5 ($\underline{C}(8)H_3$), 16.7 ($\underline{C}(4)H_2$).

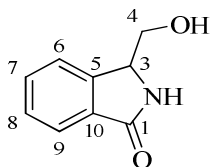
Spectroscopic data were consistent with those reported in the literature.¹²⁷

(5*R)-5-[(*R**)-Hydroxy(phenyl)methyl]-5-methylpyrrolidin-2-one (177)**

Compound **143** (182 mg, 0.52 mmol) was subjected to General Procedure C to give the title compound **177** (80.1 mg, 0.39 mmol, 75% with 4 mol % of the catalyst used) as a colourless oil.

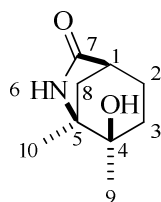
m.p. 159-161 °C; ν_{max} (thin film)/cm⁻¹ 3422br, 2520m, 2097w, 1650s, 1453m, 1399m, 1049m; δ_{H} (400 MHz, CH₃OD) 7.38-7.44 (2H, m, C(10)H), 7.25-7.36 (3H, m, C(9)H, C(11)H), 4.55 (1H, s, C(6)H), 2.35 (1H, ddd, *J* 13.1, 9.7, 3.9, C(3)H_a), 2.05-2.16 (1H, m, C(4)H_a), 1.78-1.90 (1H, m, C(4)H_b), 1.62-1.74 (1H, m, C(3)H_b), 1.02 (1H, s, C(7)H₃); δ_{C} (100 MHz, CH₃OD) 180.8 (C(2)O), 142.6 (C(8)), 129.2 (C(9)H), 128.97-128.95 (C(10)H, C(11)H), 80.2 (C(6)H), 65.0 (C(5)), 32.3 (C(4)H₂), 31.2 (C(3)H₂), 25.7 (C(7)H₃); **m/z** (ESI) 204 ([M-H]⁻, 100%), 409 ([2M-H]⁻, 60); **HRMS** (ESI⁺) C₁₂H₁₅NO₂ requires [M+H]⁺ 206.1176, found 206.1176 (-0.06 ppm).

Single Crystal X-ray Diffraction Data for 177: C₁₂H₁₅NO₂, *M_r* = 205.26, trigonal (R -3), *a* = 22.3219(4) Å, *b* = 22.3219(4) Å, *c* = 12.1112(3) Å, α = 90 °C, β = 90 °C, γ = 120 °C, *V* = 5226.13(19) Å³, *Z* = 18, μ = not measured *D_{calc}* = 1.174, *T* = 150(2) K, 2635 reflections collected, 2635 independent [*R*(int) = 0], *R*₁ = 0.0548, *wR*₂ = 0.1077 [*I* > 3σ(*I*)].

3-(Hydroxymethyl)isoindolin-1-one (178)

Compound **149** (150 mg, 0.48 mmol) was subjected to General Procedure C to give the title compound **178** (51 mg, 0.31 mmol, 65% with 4 mol % of the catalyst used) as a colourless solid.

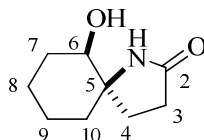
m.p. 141-142 °C; ν_{max} (thin film)/cm⁻¹ 3299br, 1678s, 1470w, 1069w, 745w; δ_{H} (400 MHz, CD₃OD) 7.77 (1H, d, *J* 7.6, C(9)H), 7.61 (2H, m, C(7)H, C(8)H), 7.46-7.54 (1H, m, C(6)H), 4.67 (1H, t, *J* 5.4, C(3)H), 3.88 (1H, dd, *J* 11.2, 5.4, C(4)H_a), 3.68 (1H, dd, *J* 11.2, 5.4, C(4)H_b); δ_{C} (100 MHz, CD₃OD) 173.7 (C(1)O), 147.1 (C(5)), 134.0 (C(10)), 133.7 (C(7)H), 130.0 (C(9)H), 124.9 (C(8)H), 124.8 (C(6)H), 65.4 (C(4)H₂), 60.9 (C(3)H); **m/z** (ESI⁺) 327 ([2M+H]⁺, 100%), 349 ([2M+Na]⁺, 90), 512 ([3M+Na]⁺, 70) 164 ([M+H]⁺, 50); **HRMS** (ESI⁺) C₉H₉NO₂ requires [M+Na]⁺ 186.0525, found 186.0525 (+0.25 ppm).

(4R*, 5S*)-4-Hydroxy-4,5-dimethyl-6-azabicyclo[3.2.1]octan-7-one (179)

Compound **130** (220 mg, 0.70 mmol) was subjected to General Procedure C to give the title compound **179** (94.4 mg, 0.56 mmol, 80% with 4 mol % of the catalyst used) as a colourless solid.

m.p. 150-151 °C; ν_{max} (thin film)/ cm^{-1} 3392br, 2941m, 2360m, 1683s, 1195w, 605w; δ_{H} (400 MHz, CD_3OD) 2.28-2.24 (1H, m, C(1) $\underline{H}$), 1.87-1.94 (1H, m, C(8) $\underline{H}_a$), 1.82-1.87 (1H, m, C(2) $\underline{H}_a$), 1.73-1.80 (1H, m, C(3) $\underline{H}_a$), 1.66-1.73 (1H, m, C(8) $\underline{H}_b$), 1.63-1.66 (1H, m, C(2) $\underline{H}_b$), 1.57-1.63 (1H, m, C(3) $\underline{H}_b$), 1.30 (3H, s, C(9) $\underline{H}_3$), 1.27 (3H, s, C(10) $\underline{H}_3$); δ_{C} (100 MHz, CD_3OD) 182.1 ($\underline{C}(7)\text{O}$), 73.9 ($\underline{C}(4)$), 66.1 ($\underline{C}(5)$), 43.8 ($\underline{C}(1)\text{H}$), 43.0 ($\underline{C}(8)\text{H}_2$), 37.4 ($\underline{C}(3)\text{H}_2$), 25.1 ($\underline{C}(2)\text{H}_2$), 24.1 ($\underline{C}(9)\text{H}_3$), 19.5 ($\underline{C}(10)\text{H}_3$); **m/z** (ESI^+) 530 ($[\text{3M}+\text{Na}]^+$, 100%), 361 ($[\text{2M}+\text{Na}]^+$, 80), 339 ($[\text{2M}+\text{H}]^+$, 70), 170 ($[\text{M}+\text{H}]^+$, 20); **HRMS** (ESI^+) $\text{C}_9\text{H}_{15}\text{NO}_2$ requires $[\text{M}+\text{Na}]^+$ 192.0995, found 192.0997 (-1.15 ppm).

Single Crystal X-ray Diffraction Data for 179: $\text{C}_9\text{H}_{15}\text{NO}_2$, M_r = 169.22, monoclinic (C 1 2/c 1), a = 18.3496(3) Å, b = 9.3578(2) Å, c = 11.8645(2) Å, α = 90 °C, β = 120.0222(9) °C, γ = 90 °C, V = 1763.94(6) Å³, Z = 8, μ = not measured D_{calc} = 1.274, T = 150(2) K, 10482 reflections collected, 2009 independent [$R(\text{int})$ = 0.029], R_1 = 0.0472, wR_2 = 0.0854 [$I > 3\sigma(I)$].

(5R*, 6R*)-6-Hydroxy-1-azaspiro[4.5]decan-2-one (180)

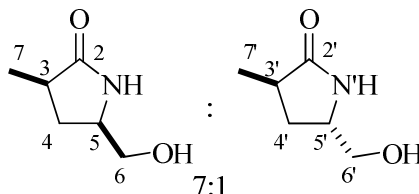
Compound **151** (370 mg, 1.05 mmol) was subjected to General Procedure C to give the title compound **180** (142 mg, 0.84 mmol, 80% with 4 mol % of the catalyst used) as a white solid.

m.p. 131-133 °C; ν_{max} (thin film)/ cm^{-1} 3242br, 2935s, 2863m, 1680s, 1454m, 1416m, 1391m, 1345m, 1296m, 1256m, 1157w, 1068m, 1000m, 865s, 730m, 655m, 616m; δ_{H} (400 MHz, CDCl_3) 7.94 (1H, br s, $\underline{\text{NH}}$), 4.12 (1H, br s, $\underline{\text{OH}}$), 3.36 (1H, m, C(6) $\underline{H}$), 2.39-2.51 (1H, m, C(3) $\underline{H}_a$), 2.22-2.34 (1H, m, C(4) $\underline{H}_a$), 2.07-2.19 (1H, m, C(4) $\underline{H}_b$), 1.61-1.79 (4H, m, C(3) $\underline{H}_b$, C(7) $\underline{H}_a$, C(8) $\underline{H}_a$, C(10) $\underline{H}_a$), 1.35-1.53 (4H, m, C(8) $\underline{H}_b$, C(9) $\underline{H}_2$, C(10) $\underline{H}_b$), 1.20-1.33 (1H, m, C(7) $\underline{H}_b$); δ_{C} (400 MHz, CDCl_3) 179.1 ($\underline{C}(2)\text{O}$), 74.5 ($\underline{C}(6)\text{H}$), 63.5 ($\underline{C}(5)$), 36.4 ($\underline{C}(10)\text{H}$), 30.8 ($\underline{C}(4)\text{H}_2$), 30.5 ($\underline{C}(8)\text{H}_2$), 30.4 ($\underline{C}(3)\text{H}_2$), 22.7 ($\underline{C}(7)\text{H}_2$), 21.7 ($\underline{C}(9)\text{H}_2$); **m/z** (ESI^-) 168 ($[\text{M}-\text{H}]^-$, 100); **HRMS** (ESI^+) $\text{C}_9\text{H}_{15}\text{NO}_2$ requires $[\text{M}+\text{Na}]^+$ 192.0995, found 192.0998 (-1.48 ppm).

Single Crystal X-ray Diffraction Data for 180: $\text{C}_9\text{H}_{15}\text{N}_1\text{O}_2$, M_r = 169.22, triclinic (P -1), a = 7.51050(10) Å, b = 10.56470(10) Å, c = 12.0602(2) Å, α = 114.0433(6) °C, β = 90.0214(6) °C, γ =

89.9751(7) °C, $V = 873.91(2) \text{ \AA}^3$, $Z = 4$, $\mu = \text{not measured}$ $D_{\text{calc}} = 1.286$, $T = 150(2) \text{ K}$, 7233 reflections collected, 3752 independent [$R(\text{int}) = 0$], $R_1 = 0.0928$, $wR_2 = 0.2122$ [$I > 3\sigma(I)$].

5-(Hydroxymethyl)-3-methylpyrrolidin-2-one (**181**)



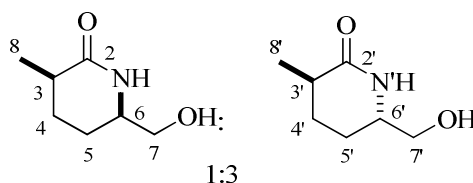
Compound **146** (325 mg, 1.18 mmol) was subjected to General Procedure C to give the title compound **181** (143 mg, 1.11 mmol, 94% with 4 mol % of the catalyst used) as a colourless solid.

Compound **146** (325 mg, 1.18 mmol) was subjected to General Procedure C to give the title compound **181** (141 mg, 1.09 mmol, 92% with 1 mol % of the catalyst used) as a colourless solid.

δ_{H} (400 MHz, CDCl_3) 7.59 (1H, br s, NH), 7.50 (1H, br s, N'H), 4.91 (1H, br s, OH), 3.56-3.75 (2H, m, C(5)H , C(6)H_a), 3.35 (1H, dd, J 11.4, 7.6, C(6)H_b), 2.40-2.52 (1H, m, C(3)H), 2.21-2.32 (1H, m, C(4)H_a), 1.93-2.02 (1H, m, C(4)H_b), 1.75 (1H, ddd, J 13.0, 8.1, 8.0, C(4')H_b), 1.19-1.32 (1H, m, C(4')H_b), 1.11 (3H, J 7.3, C(7)H_3); δ_{C} (100 MHz, CDCl_3) 182.1 (C(2)O), 181.4 (C(2')O), 66.2 (C(6)H_2), 65.9 (C(6')H_2), 55.2 (C(5)H), 54.6 (C(5')H), 36.6 (C(3)H), 35.9 (C(3')H), 31.9 (C(4)H_2), 31.6 (C(4')H_2), 16.2 (C(7)H_3), 16.8 (C(7')H_3).

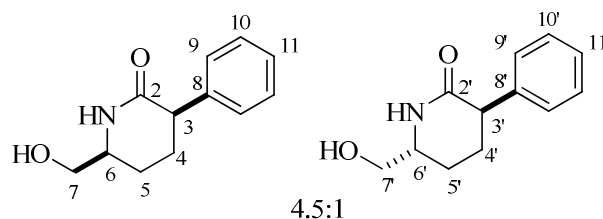
Spectroscopic data were consistent with those reported in the literature.¹²⁸

(3R, 6R)-6-(Hydroxymethyl)-3-methylpiperidin-2-one (**182**)



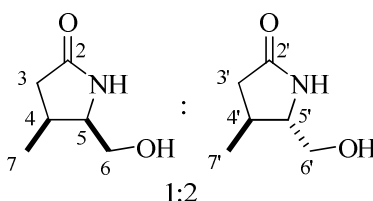
Compound **147** (133 mg, 0.46 mmol) was subjected to General Procedure C to give the title compound **182** (54.3 mg, 0.38 mmol, 83% with 4 mol % of the catalyst used) as a colourless oil.

$[\alpha]_{\text{D}}^{23} + 2.1$ ($c = 1.0$, dichloromethane); ν_{max} (thin film)/ cm^{-1} 3384br, 2935br, 2873br, 1644s, 1472w, 1416w, 1300w, 1056w, 644w; δ_{H} (400 MHz, CDCl_3) 6.90 (1H, br s, N'H), 3.68 (1H, J 10.7, 2.9, C(7')H_a), 3.50-3.61 (1H, m, C(6')H), 3.38-3.47 (1H, m, C(7')H_b), 3.26 (1H, br s, O'H), 2.22-2.35 (1H, m, C(3')H), 1.93-2.06 (1H, m, C(4')H_a), 1.80-1.90 (1H, m, C(5')H_a), 1.44-1.58 (1H, m, C(4')H_b), 1.30-1.44 (1H, m, C(5')H_b), 1.24 (3H, d, J 7.1, C(8')H_3); δ_{C} (100 MHz, CDCl_3) 176.2 (C(2')O), 66.3 (C(7')H_2), 55.4 (C(6')H), 36.1 (C(3')H), 28.6 (C(4')H_2), 24.5 (C(5')H_2), 16.9 (C(8')H_3); m/z (ESI^+) 309 ($[\text{2M}+\text{Na}]^+$, 100%), 207 ($[\text{M}+\text{CH}_3\text{CN}+\text{Na}]^+$, 40), 144 ($[\text{M}+\text{H}]^+$, 15); **HRMS** (ESI^+) $\text{C}_7\text{H}_{13}\text{NO}_2$ requires $[\text{M}+\text{Na}]^+$ 166.0838, found 166.0838 (+0.57 ppm).

(3*R,6*S**)-6-(Hydroxymethyl)-3-phenylpiperidin-2-one (183)**

Compound **183** (299 mg, 0.85 mmol) was subjected to General Procedure C to give the title compound **148** (115 mg, 0.56 mmol, 66% with 4 mol % of the catalyst used) as a beige solid.

m.p. 118-120 °C; ν_{max} (thin film)/cm⁻¹ 3284br s, 2942br m, 1648br s, 1494w, 1138w, 1052w, 753w, 700m; δ_{H} (400 MHz, CDCl₃) 7.54 (1H, s, N'H), 7.45 (1H, s, NH), 7.29-7.40 (4H, m, C(10)H, C(10')H), 7.16-7.29 (6H, m, C(9)H, C(11)H, C(9')H, C(11')H), 4.56 (2H, br s, OH, O'H), 3.72 (1H, t, *J* 5.1, C(3')H), 3.42-3.58 (5H, m, C(3)H, C(6)H, C(7)H_a, C(6')H, C(7')H_a), 3.32 (1H, m, C(7')H_b), 3.16-3.29 (1H, m, C(7)H_b), 2.03-2.25 (2H, m, C(4)H_a, C(4')H_a), 1.71-1.97 (2H, m, C(3)H_a, C(4)H_b, C(3')H_a), 1.54-1.65 (1H, m, C(3')H_b), 1.35-1.53 (1H, m, C(3)H_b); δ_{C} (100 MHz, CDCl₃) 173.9 (C(1)O), 173.6 (C(1')O), 141.0 (C(8)), 140.8 (C(8')), 128.44 (C(9)H), 128.40 (C(9')H), 128.3 (C(10)H), 128.1 (C(10')H), 126.7 (C(11)H), 126.6 (C(11')H), 65.7 (C(7')H₂), 65.6 (C(7)H₂), 55.1 (C(6)H), 54.6 (C(6')H), 48.5 (C(3)H), 46.8 (C(3')H), 29.7 (C(5)H₂), 27.9 (C(5')H₂), 24.1 (C(4)H₂); 20.1 (C(4') H₂); *m/z* (ESI⁺) 204 ([M-H]⁺, 100%); **HRMS** (ESI⁺) C₂₂H₂₅NO₃ requires [M-H]⁺ 204.1025, found 204.1023 (+0.86 ppm).

5-(Hydroxymethyl)-4-methylpyrrolidin-2-one (184)

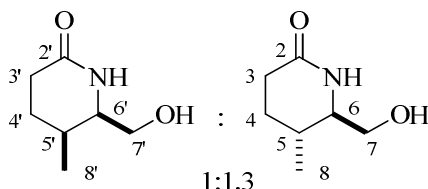
Compound **144** (319 mg, 1.16 mmol) was subjected to General Procedure C to give the title compound **184** (132 mg, 1.02 mmol, 88% with 4 mol % of the catalyst used) as a colourless oil.

Compound **144** (300 mg, 1.09 mmol) was subjected to General Procedure C to give the title compound **184** (117 mg, 0.90 mmol, 83% with 1% of the catalyst used) as a colourless oil.

ν_{max} (thin film)/cm⁻¹ 3321br, 2965m, 2933m, 1670br, 1426m, 1314m, 1276m, 1083m, 668br; δ_{H} (400 MHz, CDCl₃) 7.50 (1H, br s, NH), 7.47 (1H, br s, N'H), 4.98 (2H, br s, OH, O'H), 3.56-3.68 (3H, m, C(6')H_a, C(6)H_a), 3.50-3.58 (1H, m, C(5')H), 3.40 (1H, dd, *J* 11.5, 6.9, C(6)H_b), 3.28 (1H, td, *J* 6.2, 3.0, C(5)H), 2.52-2.64 (1H, m, C(4')H), 2.47 (1H, dd, *J* 16.9, 8.6, C(3)H_a), 2.34 (1H, dd, *J* 16.7, 8.7, C(3')H_b), 2.07-2.18 (1H, m, C(4)H), 2.03 (1H, dd, *J* 16.7, 8.7, C(3')H_a), 1.93 (1H, m, C(3)H_b), 1.07 (1H, d, *J* 6.8, C(7)H₃), 1.02 (1H, d, *J* 7.1, C(7')H₃); δ_{C} (100 MHz, CDCl₃) 179.2 (C(2')O), 178.5 C(2)O), 64.6 (C(6')H₂), 64.0 (C(6)H₂), 62.4 (C(5')H), 59.1 (C(5)H), 38.9 (C(3)H₂),

38.6 ($\underline{C}(3')\text{H}_2$), 31.5 ($\underline{C}(4')\text{H}$), 31.1 ($\underline{C}(4)\text{H}$), 19.3 ($\underline{C}(7)\text{H}_3$), 14.5 ($\underline{C}(7')\text{H}_3$); m/z (ESI^+) 281 ($[\text{2M}+\text{Na}]^+$, 100%), 193 ($[\text{M}+\text{CH}_3\text{CN}+\text{Na}]^+$, 70), 130 ($[\text{M}+\text{H}]^+$, 65), 171 ($[\text{M}+\text{CH}_3\text{CN}+\text{H}]^+$, 60); **HRMS** (ESI^+) $\text{C}_6\text{H}_{11}\text{NO}_2$ requires $[\text{M}+\text{Na}]^+$ 152.0682, found 152.0680 (+1.41 ppm).

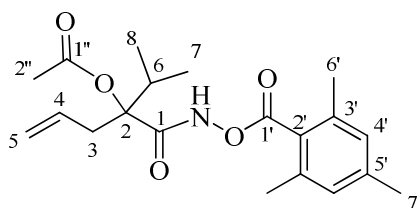
6-(Hydroxymethyl)-5-methylpiperidin-2-one (185)



Compound **145** (367 mg, 1.27 mmol) was subjected to General Procedure C to give the title compound **185** (157 mg, 1.10 mmol, 87% with 4 mol % of the catalyst used) as a yellow oil.

ν_{max} (thin film)/ cm^{-1} 3387br, 2963m, 2935m, 1635br, 1478m, 1411m, 1360w, 1330w, 1232w, 1086w, 1060m, 1034w; δ_{H} (400 MHz, CDCl_3) 7.31 (1H, br s, $\text{N}'\text{H}$), 7.27 (1H, br s, NH), 4.83 (2H, br s, OH , $\text{O}'\text{H}$), 3.71 (1H, dd, J 11.2, 2.7, $\text{C}(7)\underline{\text{H}}_a$), 3.52-3.61 (1H, m, $\text{C}(7')\underline{\text{H}}_a$), 3.40-3.48 (2H, m, $\text{C}(6')\underline{\text{H}}$, $\text{C}(7')\underline{\text{H}}_b$), 3.35 (1H, dd, J 11.2, 2.7, $\text{C}(7)\underline{\text{H}}_b$), 2.97-3.04 (1H, m, $\text{C}(6)\underline{\text{H}}$), 2.14-2.34 (3H, m, $\text{C}(5)\underline{\text{H}}$, $\text{C}(3)\underline{\text{H}}_2$), 1.95-2.05 (1H, m, $\text{C}(5')\underline{\text{H}}$), 1.59-1.76 (4H, m, $\text{C}(3')\underline{\text{H}}_2$, $\text{C}(4')\underline{\text{H}}_2$), 1.38-1.56 (2H, m, $\text{C}(4)\underline{\text{H}}_2$), 0.95 (1H, d, J 6.3, $\text{C}(8)\underline{\text{H}}_3$), 1.07 (1H, d, J 7.1, $\text{C}(8')\underline{\text{H}}_3$); δ_{C} (100 MHz, CDCl_3) 172.8 ($\underline{C}(2)\text{O}$), 172.5 ($\underline{C}(2')\text{O}$), 63.5 ($\underline{C}(7)\text{H}_2$), 62.7 ($\underline{C}(7')\text{H}_2$), 60.3 ($\underline{C}(6)\text{H}$), 57.1 ($\underline{C}(6')\text{H}$), 30.2 ($\underline{C}(3)\text{H}_2$), 28.9 ($\underline{C}(5)\text{H}$), 28.1 ($\underline{C}(4)\text{H}_2$), 27.9 ($\underline{C}(3')\text{H}_2$), 27.6 ($\underline{C}(5')\text{H}$), 26.0 ($\underline{C}(4')\text{H}_2$), 17.5 ($\underline{C}(8)\text{H}_3$), 13.0 ($\underline{C}(8')\text{H}_3$); m/z (ESI^+) 309 ($[\text{2M}+\text{Na}]^+$, 100%), 452 ($[\text{3M}+\text{Na}]^+$, 75), 287 ($[\text{2M}+\text{H}]^+$, 70), 207 ($[\text{M}+\text{CH}_3\text{CN}+\text{Na}]^+$, 30), 144 ($[\text{M}+\text{H}]^+$, 30), 185 ($[\text{M}+\text{CH}_3\text{CN}+\text{H}]^+$, 20); **HRMS** (ESI^+) $\text{C}_7\text{H}_{13}\text{NO}_2$ requires $[\text{M}+\text{Na}]^+$ 166.0838, found 166.0834 (+2.61 ppm).

2-Methyl-3-(2,4,6-trimethylbenzoyloxycarbamoyl)hex-5-en-3-yl acetate (186)

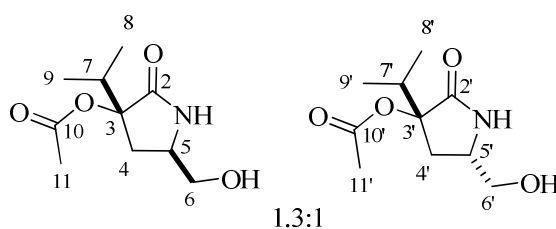


Compound **190** (350 mg, 1.75 mmol) was subjected to General Procedure A₁ & B to furnish the title compound **186** (430 mg, 1.19 mmol, 68%) as a colourless oil.

ν_{max} (thin film)/ cm^{-1} 3279br w, 2879br w, 1780m, 1744m, 1684m, 1643m, 1577w, 1457br m, 1373m, 1226br s, 1141m, 1076m, 1037m, 851w, 703w; δ_{H} (400 MHz, CDCl_3) 9.66 (1H, s, NH), 6.65-7.00 (2H, s, $\text{C}(4')\underline{\text{H}}$), 5.68-5.84 (1H, m, $\text{C}(4)\underline{\text{H}}$), 5.10-5.21 (2H, m, $\text{C}(5)\underline{\text{H}}_2$), 3.20 (1H, dd, J 14.4, 7.3, $\text{C}(3)\underline{\text{H}}_a$), 3.09 (1H, dd, J 14.4, 7.3, $\text{C}(3)\underline{\text{H}}_b$), 2.74-2.88 (1H, m, $\text{C}(2)\underline{\text{H}}$), 2.41 (6H, s,

C(6')H₃), 2.31 (3H, s, C(7')H₃), 2.16 (3H, s, C(2'')H₃), 1.11 (3H, d, *J* 6.8, C(7)H₃), 1.08 (3H, d, *J* 6.8, C(8)H₃); δ_c (100 MHz, CDCl₃) 168.5 (C(1')O), 167.74 (C(1'')O), 167.72 (C(1)O), 140.9 (C(5')), 136.8 (C(3')), 131.9 (C(4)H), 128.6 (C(4')H), 126.4 (C(2')), 119.4 (C(5)H₂), 91.7 (C(2)), 37.4 (C(3)H₂), 33.4 (C(6)H), 22.1 (C(2'')H₃), 21.2 (C(7')H₃), 20.0 (C(6')H₃), 17.5 (C(7)H₃), 17.3 (C(8)H₃); *m/z* (ESI⁺) 360 ([M-H]⁺, 100%); **HRMS** (ESI⁺) C₂₀H₂₇NO₅ requires [M+Na]⁺ 384.1781, found 384.1780 (+2.0 ppm).

5-(Hydroxymethyl)-3-isopropyl-2-oxopyrrolidin-3-yl acetate (**187**)

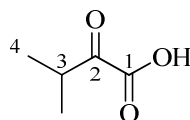


Compound **186** (50 mg, 0.14 mmol) was subjected to General Procedure C to give the title compound **187** (22 mg, 0.10 mmol, 71% with 4 mol % of the catalyst used) as a colourless oil.

$\nu_{\max}$ (thin film)/cm⁻¹ 3291br m, 2934br w, 1739s, 1682s, 1561m, 1457br m, 1324m, 1259m, 1113w, 1065m, 1035m, 858w, 721m; δ_H (400 MHz, CDCl₃) 7.00 (1H, br s, NH), 6.84 (1H, br s, N'H), 4.01-4.11 (1H, m, C(5)H), 3.56-3.77 (4H, m, C(6)H_a, C(5')H, C(6')H₂), 3.45 (1H, m, C(6)H_b), 2.85 (1H, br s, OH), 2.12-2.34 (2H, m, C(4)H_a, C(4')H_a), 2.09 (8H, m, C(7)H, C(7')H, C(11)H₃, C(11')H₃), 1.94 (2H, m, C(4)H_b, C(4')H_b), 1.06 (3H, d, *J* 6.6, C(8')H₃), 1.01 (3H, d, *J* 6.7, C(8)H₃), 0.96 (3H, d, *J* 6.6, C(9')H₃), 0.89 (3H, d, *J* 6.7, C(9)H₃); δ_c (100 MHz, CDCl₃) 175.1 (C(2)O), 174.8 (C(2')O), 170.9 (C(10)O), 170.7 (C(10')O), 85.49 (C(3')), 85.44 (C(3)), 65.2 (C(6)H₂), 64.9 (C(6')H₂), 53.3 (C(5)H), 52.9 (C(5')H), 33.9 (C(7')H), 33.4 (C(7)H), 28.9 (br s, C(4)H₂, C(4')H₂), 21.3 (C(11')H₃), 21.1 (C(11)H₃), 16.9 (C(8)H₃), 16.10 (C(8')H₃), 16.07 (C(9')H₃), 16.0 (C(9)H₃); *m/z* (ESI⁺) 214 ([M-H]⁺, 100%); **HRMS** (ESI⁺) C₁₀H₁₇NO₄ requires [M+Na]⁺ 238.1050, found 238.1055 (-2.3 ppm).

Single Crystal X-ray Diffraction Data for 187: C₁₀H₁₇N₁O, *M_r* = 215.21, triclinic (P -1), *a* = 6.0621(2) Å, *b* = 7.9355(3) Å, *c* = 12.1691(6) Å, α = 88.8233(16) °C, β = 81.5421(17) °C, γ = 69.842(2) °C, *V* = 543.28(4) Å³, *Z* = 2, μ = not measured *D_{calc}* = 1.316, *T* = 150(2) K, 8688 reflections collected, 2473 independent [*R*(int) = 0], *R*₁ = 0.0662, *wR*₂ = 0.0783 [*I* > 3σ(*I*)].

3-Methyl-2-oxobutanoic acid

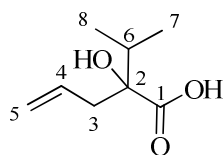


To L-valine (1.0 eq., 10 g, 85 mmol) under argon at rt was added trifluoroacetic anhydride (16 mL). After completion of the addition, the reaction mixture was heated at 80 °C and stirred for 30 min. The reaction mixture was then heated at 130 °C and stirred for another 30 min. The reaction mixture was then cooled down, vacuumed down to a few mL and the residue diluted with diethyl ether (50 mL). The organic phase was washed with a 5% aqueous NaHCO₃ solution (3 x 5 mL), dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure to afford a yellow oil. Purification by distillation (40 mbar, 80-90 °C) gave the oxazolone as a colourless oil (19.2 g) that was stirred with a 2.2 M aqueous sodium hydroxide solution (50 mL) for 12 h at rt. The resulting reaction mixture was acidified with a 3 M aqueous HCl solution and extracted with diethyl ether (3 x 30 mL). The organic phase was dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure to give the title compound (8.7 g, 75 mmol, 88%) as colourless oil.

δ_{H} (400 MHz, CDCl₃) 10.87 (1H, br. s, OH), 3.35 (1H, dt, *J* 13.9, 6.9, C(3)H), 1.16 (6H, d, *J* 6.9, C(4)H₃); δ_{C} (100 MHz, CDCl₃) 198.1 (C(2)O), 169.0 (C(1)O), 32.6 (C(3)H), 17.3 (C(4)H₃).

Spectroscopic data were consistent with those reported in the literature.¹²⁹

2-Hydroxy-2-isopropylpent-4-enoic acid (**189**)



To a solution of 3-methyl-2-oxobutanoic acid (1.0 eq., 2.5 g, 21.8 mmol) in tetrahydrofuran (31 mL) and water (15 mL) under argon at rt was added allyl bromide (1.5 eq., 2.8 mL, 21.8 mmol). After completion of the addition, the reaction mixture was heated at 30 °C and stirred for 36 h. The reaction mixture was acidified with a 3 M aqueous HCl solution and extracted with diethyl ether (3 x 50 mL). The organic phase was dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure to afford a yellow oil. Purification by chromatography on silica eluting with petrol:diethyl ether (80:20 + drops of acetic acid) gave **189** (2.29 g, 14.4 mmol, 66%) as a colourless oil that crashed out overnight.

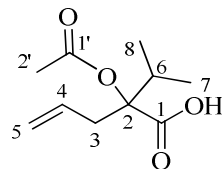
δ_{H} (400 MHz, CDCl₃) 5.69-5.85 (1H, m, C(4)H), 5.03-5.20 (2H, m, C(5)H₂), 2.54 (1H, dd, *J* 13.7, 6.3, C(3)H_a), 2.43 (1H, dd, *J* 13.7, 6.3, C(3)H_b), 2.04 (1H, spt, *J* 6.8, C(6)H), 0.98 (3H, d, *J* 6.9, C(7)H₃), 0.91 (3H, d, *J* 6.9, C(8)H₃); δ_{C} (100 MHz, CDCl₃) 180.6 (C(1)O), 132.2 (C(4)H), 119.3 (C(5)H₂), 80.2 (C(2)), 41.2 (C(3)H₂), 34.9 (C(6)H), 17.3 (C(7)H₃), 15.8 (C(8)H₃).

Spectroscopic data were consistent with those reported in the literature.¹³⁰

Single Crystal X-ray Diffraction Data for 189: C₈H₁₄O₃, M_r = 158.20, orthorhombic (P b c a), a = 14.2514(3) Å, b = 11.4679(2) Å, c = 22.8055(6) Å, α = 90 °C, β = 90 °C, γ = 90 °C, V =

3727.19(14) Å³, Z = 16, μ = not measured D_{calc} = 1.128, T = 150(2) K, 28736 reflections collected, 2288 independent [R(int) = 0.033], R_1 = 0.0564, wR_2 = 0.1137 [$I > 3\sigma(I)$].

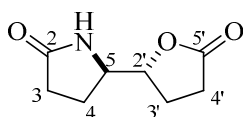
2-Acetoxy-2-isopropylpent-4-enoic acid (**190**)



To a solution of **189** (1.0 eq., 471 mg, 3.0 mmol) in dichloromethane (20 mL) under argon at rt was added dropwise acetyl chloride (3.0 eq., 0.64 mL, 9.0 mmol). After completion of the addition, the reaction mixture was stirred vigorously at rt for 16 h. The reaction mixture was acidified with a 1 N aqueous HCl solution and stirred for 10 min. The organic layer was separated, dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure to give **190** (452 mg, 2.3 mmol, 75%) as a colourless oil.

ν_{max} (thin film)/cm⁻¹ 3259br s, 2912br w, 1732s, 1716s, 1378m, 1265w, 1119w, 1061m, 787m, 710m; δ_{H} (400 MHz, CDCl₃) 10.24 (1H, br s, OH), 5.64-5.82 (1H, m, C(4)H), 5.01-5.18 (2H, m, C(5)H₂), 3.12 (1H, dd, J 15.3, 7.3, C(3)H_a), 2.78 (1H, dd, J 15.3, 7.3, C(3)H_b), 2.25 (1H, spt, J 6.9, C(6)H), 2.08 (3H, s, C(2')H₃), 1.03 (3H, d, J 6.8, C(7)H₃), 0.99 (3H, d, J 6.8, C(8)H₃); δ_{C} (100 MHz, CDCl₃) 176.1 (C(1')O), 170.0 (C(1)O), 132.0 (C(4)H), 119.0 (C(5)H₂), 84.7 (C(2)), 35.3 (C(3)H₂), 32.9 (C(6)H), 21.0 (C(2')H₃), 16.9 (C(7)H₃); 16.8 (C(8)H₃); m/z (ESI) 199 ([M-H]⁻, 100%); **HRMS** (ESI) C₁₀H₁₆O₄ requires [M-H]⁻ 199.0970, found 199.0971 (+0.74 ppm).

(5R*)-5-[(2R*)-5-Oxotetrahydrofuran-2-yl]pyrrolidin-2-one (**191**)

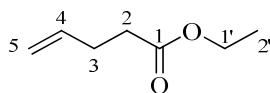


Compound **195** (116 mg, 0.32 mmol) was subjected to General Procedure C. Before the addition of Na₂O₃, 70.0 μ L of TFA was added and the reaction mixture was stirred for 5h. After TLC indicated that the reaction had ceased, anhydrous Na₂SO₃ (ca. 80 mg/mg of osmium catalyst) was added and the reaction was stirred for another 30 min. The reaction mixture was concentrated onto silica *in vacuo* and purified by flash column chromatography (on a 0.5 mmol scale, 5 g of SiO₂, elution with 50-60 mL of Ethyl acetate/Acetic acid 9.8:0.2 followed by 80 mL of Ethyl acetate/Methanol 9.5:0.5) to give the title compound **191** (47.6 mg, 0.28 mmol, 88% with 4 mol % of the catalyst used) as a colourless solid.

Compound **195** (303 mg, 0.84 mmol) was subjected to the same procedure above to give the title compound **191** (122 mg, 0.72 mmol, 86% with 1 mol % of the catalyst used) as a colourless solid. ^{19}F NMR indicated no trace of TFA salt.

m.p. 130-133 °C; ν_{max} (thin film)/ cm^{-1} 3369br, 2955m, 1766s, 1678s, 1133m, 1033m, 842m, 803m; δ_{H} (400 MHz, CDCl_3) 4.48 (1H, q, J 7.2, C(2')H), 3.69-3.87 (1H, m, C(5)H), 2.50-2.66 (2H, m, C(4')H₂), 2.16-2.49 (4H, m, C(3)H₂, C(3')H₂), 1.80-2.10 (2H, m, C(4)H₂); δ_{C} (100 MHz, CD_3OD) 181.7 (C(5')O), 179.8 (C(2)O), 85.1 (C(2')H), 59.5 (C(5)H), 31.1 (C(3)H₂), 29.4 (C(4')H₂), 25.3 (C(3')H₂), 24.2 (C(4)H₂); **m/z** (ESI^+) 361 ($[\text{2M}+\text{Na}]^+$, 100%), 339 ($[\text{2M}+\text{H}]^+$, 45), 233 ($[\text{M}+\text{CH}_3\text{CN}+\text{Na}]^+$, 45), 211 ($[\text{M}+\text{CH}_3\text{CN}+\text{H}]^+$, 25), 192 ($[\text{M}+\text{Na}]^+$, 15), 170 ($[\text{M}+\text{H}]^+$, 5); **HRMS** (ESI^+) $\text{C}_8\text{H}_{11}\text{NO}_3$ requires $[\text{M}+\text{Na}]^+$ 192.0631, found 192.0630 (+0.71 ppm).

Ethyl pent-4-enoate (192)

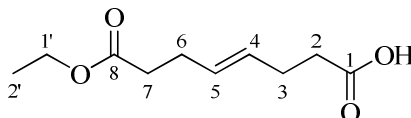


To a solution of pent-4-enoic acid (1 eq., 10 g, 100 mmol) in dichloromethane (50 mL•mmol⁻¹) under argon at 0 °C was added 3 drops of DMF followed by the dropwise addition of oxalyl chloride (2 eq., 17 mL, 200 mmol). After 1 h, the reaction mixture was concentrated *in vacuo* and the residue redissolved in diethyl ether (50 mL•mmol⁻¹). Ethanol (2 eq., 20 mL, 200 mmol) was then added dropwise and the reaction mixture stirred for 2 h (no more starting material by TLC). The reaction mixture was concentrated *in vacuo* (caution, b.p. of the product is 140 °C at P_{atm}) to give the title compound **192** (12.1 g, 94 mmol, 94%) as a yellowish oil.

δ_{H} (400 MHz, CDCl_3) 5.66-5.79 (1H, m, C(4)H), 4.87-5.00 (2H, m, C(5)H₂), 4.04 (2H, q, J 7.1, C(1')H₂), 2.24-2.34 (4H, m, C(2)H₂, C(3)H₂), 1.29 (3H, t, J 7.1, C(2')H₃); δ_{C} (100 MHz, CDCl_3) 172.3 (C(1)O), 136.1 (C(4)H), 114.8 (C(5)H₂), 59.7 (C(1')H₂), 32.9 (C(3)H₂), 28.3 (C(2)H₂), 13.3 (C(2')H₃).

Spectroscopic data were consistent with those reported in the literature.¹³¹

(4E)-8-Ethoxy-8-oxooct-4-enoic acid (193)

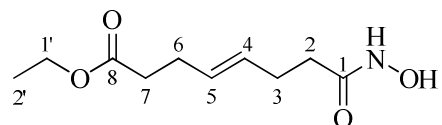


To pent-4-enoic (1 eq., 0.36 mL, 3.5 mmol) was added ethyl pent-4-enoate (10.0 eq., 4.5 g, 35 mmol), Grubbs 2nd generation (0.05 eq., 150 mg, 0.15 mmol) and dichloromethane (2.9 mL•mmol⁻¹). Argon was bubbled through the reaction for 20 min. The reaction mixture was reflux for 16 h until TLC showed total consumption of the acid. The reaction mixture was then filtered through a pad of celite and was concentrated *in vacuo*. Purification by flash column chromatography (SiO_2 ,

eluting with gradient petrol 40-60/ethyl acetate 1:0 to 8:2) furnished the title compound **193** (360 mg, 1.8 mmol, 51%) as a colourless oil (ratio E/Z 6:1).

$\nu_{\max}$ (thin film)/cm⁻¹ 3210br, 1651s, 1447s, 1077m, 1007m, 981m, 890s; δ_{H} (400 MHz, CDCl₃) 11.01 (1H, br s, OH), 5.44 (2H, br s, C(4)H, C(5)H), 4.08 (2H, q, *J* 7.2, C(1')H), 2.22-2.40 (8H, m, C(2)H, C(3)H, C(6)H, C(7)H), 1.21 (3H, t, *J* 7.2, C(2')H); δ_{C} (100 MHz, CDCl₃) 179.2 (C(1)O), 173.3 (C(8)O), 129.6 (C(4)H), 129.0 (C(5)H), 60.4 (C(1')H₂), 34.1 (C(3)H₂), 33.9 (C(6)H₂), 27.8 (C(7)H₂), 27.4 (C(2)H₂), 14.2 (C(2')H₃); *m/z* (ESI⁺) 199 ([M-H]⁻, 100%), 399 ([2M-H]⁻, 90); **HRMS** (ESI⁺) C₁₀H₁₆O₄ requires [M+Na]⁺ 223.0941, found 223.0940 (+0.45 ppm).

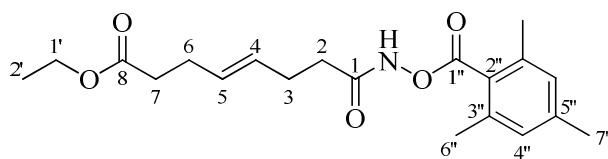
Ethyl (4E)-8-(hydroxyamino)-8-oxooct-4-enoate (**194**)



Compound **193** (ratio E/Z 6:1) (240 mg, 1.2 mmol) was subjected to General Procedure A₂ to give the title compound **194** (201 mg, 0.93 mmol, 78%) as a colourless oil (ratio E/Z 7:1).

$\nu_{\max}$ (thin film)/cm⁻¹ 3197br, 2919br, 1732br, 1651br, 1447m, 1374m, 1261m, 1183m, 1096m, 1058m, 1036m, 973m, 858w; δ_{H} (400 MHz, (CD₃)₂CO) 10.31 (1H, br s, NH), 9.09 (1H, br s, OH), 5.45-5.49 (2H, br s, C(4)H, C(5)H), 4.07 (2H, q, *J* 7.1, C(1')H), 2.13-2.36 (8H, m, C(2)H, C(3)H, C(6)H, C(7)H), 1.20 (3H, t, *J* 7.1, C(2')H); δ_{C} (100 MHz, (CD₃)₂CO) 173.2 (C(8)O), 170.9 (C(1)O), 130.3 (C(4)H), 130.2 (C(5)H), 60.6 (C(1')H₂), 34.5 (C(3)H₂), 33.2 (C(6)H₂), 29.1 (C(7)H₂), 28.5 (C(2)H₂), 14.6 (C(2')H₃); *m/z* (ESI⁺) 453 ([2M+Na]⁺, 100%), 238 ([M+Na]⁺, 70), 279 ([M+Na+CH₃CN]⁺, 50); **HRMS** (ESI⁺) C₁₀H₁₇NO₄ requires [M+Na]⁺ 238.1050, found 238.1048 (+0.68 ppm).

Ethyl (4E)-8-[(mesitylcarbonyl)oxy]amino}-8-oxooct-4-enoate (**195**)

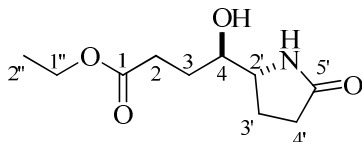


Compound **194** (469 mg, 2.18 mmol) was subjected to General Procedure B to give the title compound **195** (559 mg, 1.55 mmol, 92%) as a colourless oil.

$\nu_{\max}$ (thin film)/cm⁻¹ 3212br, 2980br, 2858br, 1775s, 1733s, 1612w, 1446m, 1374w, 1234s, 1158s, 1046m, 852w, 732w; δ_{H} (400 MHz, CDCl₃) 9.71 (1H, br s, NH), 6.86 (2H, s, C(4'')H), 5.51 (2H, br s, C(4)H, C(5)H), 4.11 (2H, q, *J* 7.1, C(1')H), 2.16-2.52 (17H, m, C(2)H, C(3)H, C(6)H, C(7)H, C(6'')H, C(7'')H), 1.23 (3H, t, *J* 7.1, C(2')H); δ_{C} (100 MHz, CDCl₃) 173.0 (C(8)O), 170.4 (C(1'')O), 167.5 (C(1)O), 140.2 (C(5'')), 136.1 (C(3'')), 129.6 (C(4)H), 128.8 (C(5)H), 128.1 (C(4'')H), 126.3 (C(2'')), 60.0 (C(1')H₂), 33.6 (C(6)H₂), 32.5 (C(7)H₂), 27.4 (C(2)H₂), 27.3

($\underline{C}(3)H_2$), 20.7 ($\underline{C}(7'')H_3$), 19.4 ($\underline{C}(6'')H_3$), 13.8 ($\underline{C}(2')H_3$); **m/z** (ESI⁻) 721 ([2M-H]⁻, 100%), 360 ([M-H]⁻, 60); **HRMS** (ESI⁺) C₂₀H₂₇NO₅ requires [M+Na]⁺ 384.1781, found 384.1775 (+1.75 ppm).

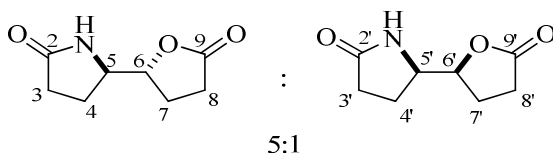
Ethyl (4*R**)-4-hydroxy-4-[(2*S**)-5-oxopyrrolidin-2-yl]butanoate (**196**)



Compound **195** (ratio E/Z 8:1) (265 mg, 0.74 mmol) was subjected to General Procedure C to give the title compound **196** (144 mg, 0.66 mmol, 90% with 4 mol % of the catalyst used) as a colourless oil (syn:anti 8:1).

v_{max} (thin film)/cm⁻¹ 3369br, 2982w, 2935w, 1728s, 1681s, 1421w, 1376w, 1269m, 1180m, 1080w, 1028w; **δ**_H (200 MHz, CDCl₃) 6.95 (1H, br s, NH), 4.14 (2H, q, *J* 7.1, C(1'')H₂), 3.49-3.62 (1H, m, C(2')H), 3.34-3.47 (1H, m, C(4')H), 2.51 (2H, t, *J* 7.0, C(2)H₂), 2.37 (2H, t, *J* 7.9, C(4')H₂), 2.01-2.29 (1H, m, C(3')H_a), 1.74-1.94 (2H, m, C(3')H_b, C(3)H_a), 1.52-1.74 (1H, m, C(3)H_b), 1.26 (3H, t, *J* 7.2, C(2'')H₃); **δ**_C (50 MHz, CDCl₃) 179.8 ($\underline{C}(1)O$), 174.4 ($\underline{C}(5')O$), 74.8 ($\underline{C}(4)H$), 61.0 ($\underline{C}(1'')H_2$), 60.5 ($\underline{C}(2')H$), 31.0 ($\underline{C}(4')H_2$), 30.8 ($\underline{C}(2)H_2$), 28.6 ($\underline{C}(3)H_2$), 24.1 ($\underline{C}(3')H_2$), 14.7 ($\underline{C}(2'')H_3$); **m/z** (ESI⁺) 668 ([3M+Na]⁺, 100%), 431 ([2M+H]⁺, 80), 453 ([2M+Na]⁺, 70), 216 ([M+H]⁺, 40), 883 ([4M+Na]⁺, 30), 279 ([M+CH₃CN+Na]⁺, 30), 238 ([M+Na]⁺, 25); **HRMS** (ESI⁺) C₁₀H₁₇NO₄ requires [M+Na]⁺ 238.1050, found 238.1050 (-0.20 ppm).

5-(5-Oxotetrahydrofuran-2-yl)pyrrolidin-2-one (**191**)

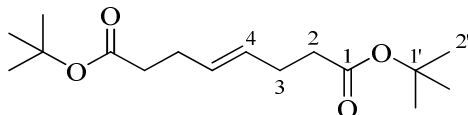


To compound **196** (ratio E/Z 8:1) (70 mg, 0.33 mmol) in *t*-butanol (0.9 mL), acetonitrile (0.9 mL) and water (0.7 mL) was added 3 drops of TFA. The reaction mixture was stirred for 10 h. The reaction mixture was concentrated *in vacuo* to give the title compound **191** (56 mg, 100%) as a colourless solid (anti:syn 5:1). ¹⁹F indicated no trace of TFA salt.

m.p. 130⁻¹³³ °C; **v**_{max} (thin film)/cm⁻¹ 3253w, 2939w, 1772s, 1687s, 1269w, 1189m, 1147w, 1040w, 984w; **δ**_H (400 MHz, CDCl₃) 7.63 (1H, br s, N'H), 7.41 (1H, br s, NH), 4.40-4.45 (1H, m, C(6')H), 4.36-4.43 (1H, m, C(6)H), 3.83-3.90 (1H, m, C(5')H), 3.70-3.77 (1H, m, C(5)H), 2.49-2.65 (4H, m, C(8)H₂, C(8')H₂), 2.19-2.47 (8H, m, C(3)H₂, C(3')H₂, C(7)H_a, C(7')H_a, C(4)H_a, C(4')H_a), 1.92-2.04 (2H, m, C(7)H_b, C(7')H_b), 1.82-1.92 (2H, m, C(4)H_b, C(4')H_b); **δ**_C (100 MHz, CDCl₃) 179.2 ($\underline{C}(9)O$, $\underline{C}(9')O$), 176.75 ($\underline{C}(2)O$), 176.73 ($\underline{C}(2')O$), 82.8 ($\underline{C}(6)H$), 81.7 ($\underline{C}(6')H$), 57.8 ($\underline{C}(5)H$), 56.8 ($\underline{C}(5')H$), 29.9 ($\underline{C}(3)H_2$), 29.8 ($\underline{C}(3')H_2$), 28.6 ($\underline{C}(8')H_2$), 28.4 ($\underline{C}(8)H_2$), 24.3 ($\underline{C}(7)H_2$), 23.8 ($\underline{C}(7')H_2$), 23.0 ($\underline{C}(4)H_2$), 22.7 ($\underline{C}(4')H_2$); **m/z** (ESI⁺) 361 ([2M+Na]⁺, 100%), 339 ([2M+H]⁺,

85), 530 ($[3M+Na]^+$, 65), 233 ($[M+CH_3CN+Na]^+$, 63) 211 ($[M+CH_3CN+H]^+$, 50), 192 ($[M+Na]^+$, 45), 170 ($[M+H]^+$, 30); **HRMS** (ESI^+) $C_8H_{11}NO_3$ requires $[M+Na]^+$ 192.0631, found 192.0631 (-0.16 ppm).

(E)-di-tert-Butyl oct-4-enedioate (198)

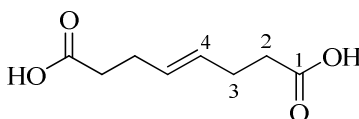


To freshly distilled diisopropylamine (2.7 eq., 3.6 mL, 25 mmol) in tetrahydrofuran (10 mL) at -78 °C was added *n*-butyllithium (2.7 eq., 15.5 mL, 25 mmol) dropwise for 40 min. *tert*-Butyl acetate (2.5 eq., 3.6 mL, 24 mmol) in tetrahydrofuran (10 mL) was then added over 20 min and the reaction mixture left to stir for another hour. To the reaction at -78 °C was added 1,4-dibromobutene **197** (1.0 eq., 9.3 mL, 9.6 mmol) in tetrahydrofuran (30 mL) over 30 min and the reaction mixture was allowed to warm to room temperature and stirred for 10 h. A mixture of brine (30 mL) and water (30 mL) was carefully added and the resulting mixture was extracted with ethyl acetate (3 x 80 mL). The organic phase was dried over Na_2SO_4 , filtered and the solvent was removed under reduced pressure to give a yellow oil. Purification by flash column chromatography (SiO_2 , eluting with gradient petrol 40-60/ethyl acetate 1:0 to 9:1) furnished the title compound **198** (2.2 g, 7.7 mmol, 80%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 5.42 (2H, br s, C(4)H), 2.23 (8H, s, C(2)H₂, C(3)H₂), 1.41 (18H, s, C(2')H₃); δ_C (100 MHz, $CDCl_3$) 172.4 (C(1)O), 129.3 (C(4)H), 80.0 (C(1')), 35.3 (C(3)H₂), 28.0 (C(2')H₃), 27.9 (C(2)H₂).

Spectroscopic data were consistent with those reported in the literature.¹³²

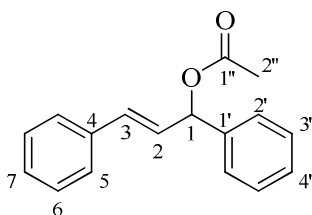
(E)-Oct-4-enedioic acid (199)



To compound **198** (1.0 eq., 2.1 g, 7.5 mmol) in dichloromethane (20 mL) at 0 °C was added carefully trifluoroacetic acid (20 mL) and the reaction mixture was stirred at rt until TLC showed total consumption of the acid (typically 1 h). The reaction mixture was then washed with 0.1 M aqueous HCl (50 mL) and the organic phase was dried over Na_2SO_4 filtered and was concentrated *in vacuo* to furnish the title compound **199** (1.2 g, 6.9 mmol, 92%) as a white solid.

δ_H (400 MHz, CD_3OD) 5.52 (2H, br s, C(4)H), 2.32 (4H, m, C(2)H₂), 2.28 (4H, m, C(3)H₂); δ_C (100 MHz, CD_3OD) 177.1 (C(1)O), 130.8 (C(4)H), 35.0 (C(3)H₂), 29.0 (C(2)H₂).

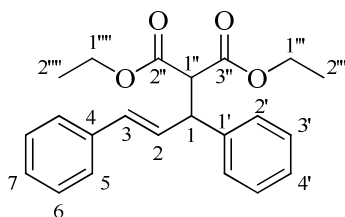
Spectroscopic data were consistent with those reported in the literature.¹³³

(2E)-1,3-Diphenylprop-2-en-1-yl acetate (201)

To 1,3 diphenyl allyl alcohol (1.0 eq., 5.0 g, 23.7 mmol) dissolved in dichloromethane was added triethylamine under argon. The reaction mixture was cooled to 0 °C and acetic anhydride (3.0 eq, 4.5 mL, 71.1 mmol) was added dropwise. The reaction mixture was allowed to stir for 36 h at room temperature. The organic layer was washed with saturated aqueous NaHCO₃ solution (50 mL), water (50 mL) and brine (50 mL). It was dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure to give an orange oil. Purification by flash column chromatography (SiO₂, eluting with petrol 40-60/ethyl acetate 9:1) furnished the title compound **201** (5.0 g, 19.8 mmol, 84%) as a colourless oil.

δ_{H} (400 MHz, CDCl₃) 7.28-7.52 (10H, m, C(2')H, C(3')H, C(4')H, C(5)H, C(6)H, C(7)H), 6.71 (1H, d, *J* 15.7, C(3)H), 6.53 (1H, d, *J* 6.9, C(1)H), 6.38-6.47 (1H, dd, *J* 15.7, 6.9, C(2)H), 2.19 (3H, s, C(2'')H₃); δ_{C} (100 MHz, CDCl₃) 169.9 (C(1'')O), 139.2 (C(4)), 136.1 (C(1')), 132.5 (C(3)H), 128.53 (C(6)H), 128.48 (C(3')H), 128.07 (C(7)H), 127.96 (C(2)H), 127.4 (C(4')H), 126.9 (C(5)H), 126.6 (C(2')H), 76.0 (C(1)H), 21.2 (C(2'')H₃).

Spectroscopic data were consistent with those reported in the literature.¹³⁴

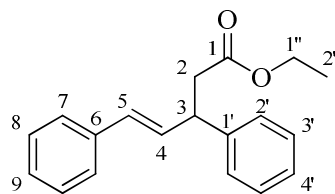
Diethyl [(2E)-1,3-diphenylprop-2-en-1-yl]malonate (202)

1,3-Bis(diphenylphosphino)propane (0.10 eq., 163 mg, 0.396 mmol) and dichloro(bis)triphenylpalladium (0.05 eq., 139 mg, 0.198 mmol) were placed in a flask purged with argon. Compound **201** in THF (4 mL•mmol⁻¹) was added. The resulting solution was stirred at 0 °C for 5 min, and a solution of sodium dimethyl malonate was added at 0 °C. The solution of sodium dimethyl malonate was prepared by slow addition of dimethyl malonate (1.6 eq., 0.73 mL, 6.3 mmol) to a suspension of 60% NaH (0.9 eq., 278 mg, 5.4 mmol) in mineral oil in THF (4 mL•mmol⁻¹) at 0 °C. The mixture was kept stirring at room temperature for 20 h, hydrolysed with 100 mL of water and extracted with ether (4 x 80 mL). The organic phase was washed with brine (80 mL), dried over Na₂SO₄, filtered and the solvent removed under reduced pressure to give the title compound **202** (1.11 g, 3.48 mmol, 88%) as a colourless oil.

δ_{H} (400 MHz, CDCl_3) 7.21-7.38 (10H, m, C(2') $\underline{\text{H}}$, C(3') $\underline{\text{H}}$, C(4') $\underline{\text{H}}$, C(5) $\underline{\text{H}}$, C(6) $\underline{\text{H}}$, C(7) $\underline{\text{H}}$), 6.49-6.55 (1H, d, J 15.9, C(3) $\underline{\text{H}}$), 6.33-6.42 (1H, dd, J 15.9, 8.6, C(2) $\underline{\text{H}}$), 4.31 (1H, dd, J 10.9, 8.6, C(1) $\underline{\text{H}}$), 4.20 (2H, q, J 7.1, C(1'') $\underline{\text{H}}_2$), 3.94-4.04 (3H, m, C(1'') $\underline{\text{H}}$, C(1''') $\underline{\text{H}}_2$), 1.23 (3H, t, J 7.2, C(2''') $\underline{\text{H}}_3$), 1.03 (3H, t, J 7.2, C(2''') $\underline{\text{H}}_3$); δ_{C} (100 MHz, CDCl_3) 167.4 (C(2'')O), 167.0 (C(3'')O), 139.9 (C(4)), 136.4 (C(1')), 131.3 (C(3')H), 128.9 (C(2')H), 128.24 (C(6)H), 128.06 (C(3')H), 127.6 (C(5)H), 127.1 (C(7)H), 126.7 (C(4')H), 125.9 (C(2')H), 61.2 (C(1'')H₂), 61.0 (C(1'')H₂), 57.4 (C(1'')H), 48.8 (C(1')H), 13.7 (C(2'')H₂), 13.4 (C(2'')H₂).

Spectroscopic data were consistent with those reported in the literature.¹³⁵

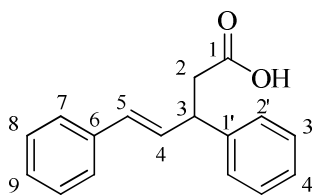
Ethyl-(4E)-3,5-diphenylpent-4-enoate (203)



To a stirred solution of **202** (1.0 eq., 780 mg, 2.43 mmol) and water (0.17 mL•mmol⁻¹) in DMSO (12 mL•mmol⁻¹) was added LiCl (2.2 eq., 224 mg, 5.35 mmol). The reaction mixture was heated at reflux for 2 h and cooled to room temperature. Saturated aqueous NH_4Cl (67 mL) was added and the aqueous phase was extracted with ether (3 x 67 mL). The combined organic layers were dried over Na_2SO_4 , filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography (SiO_2 , eluting with petrol 40-60/diethyl ether 85:15) furnished the title compound **203** (458 mg, 1.64 mmol, 67%) as a yellow oil.

ν_{max} (thin film)/cm⁻¹ 3027m, 2980m, 2360m, 1733s, 1494m, 1452m, 1370m, 1251m, 1154br, 1031m, 966m, 746s, 697s; δ_{H} (400 MHz, CDCl_3) 7.21-7.41 (10H, m, C(2') $\underline{\text{H}}$, C(3') $\underline{\text{H}}$, C(4') $\underline{\text{H}}$, C(7) $\underline{\text{H}}$, C(8) $\underline{\text{H}}$, C(9) $\underline{\text{H}}$), 6.49 (1H, d, J 15.9, C(5) $\underline{\text{H}}$), 6.40 (1H, dd, J 15.9, 7.1, C(4) $\underline{\text{H}}$), 4.05-4.20 (3H, m, C(3) $\underline{\text{H}}$, C(1'') $\underline{\text{H}}_2$), 2.80-2.94 (2H, m, C(2') $\underline{\text{H}}_2$), 1.21 (3H, t, J 7.1, C(2'') $\underline{\text{H}}_3$); δ_{C} (100 MHz, CDCl_3) 172.0 (C(1')O), 142.8 (C(6)), 137.3 (C(1'')), 132.2 (C(5)H), 130.3 (C(4)H), 128.9 (C(8)H), 128.7 (C(3')H), 127.8 (C(7)H), 127.6 (C(9)H), 127.0 (C(4')H), 126.5 (C(2')H), 60.7 (C(1'')H₂), 45.4 (C(3)H), 41.0 (C(2')H₂), 14.5 (C(2'')H₃); m/z (ESI⁺) 583 ([2M+Na]⁺, 100%), 344 ([M+CH₃CN+Na]⁺, 60), 281 ([M+H]⁺, 55); **HRMS** (ESI⁺) $\text{C}_{19}\text{H}_{20}\text{O}_2$ requires [M+H]⁺ 303.1356, found 303.1357 (-0.41 ppm).

(4E)-3,5-diphenylpent-4-enoic acid (204)

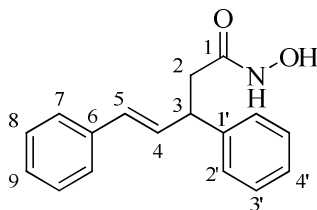


To compound **203** (1.0 eq., 458 mg, 1.64 mmol) dissolved in ethanol ($0.45 \text{ mL} \cdot \text{mmol}^{-1}$) was added a 2 M aqueous NaOH ($5 \text{ mL} \cdot \text{mmol}^{-1}$). The reaction mixture was heated at 60°C and stirred until TLC indicated complete consumption of starting material. The reaction mixture was extracted with diethyl ether ($3 \times 30 \text{ mL}$). The aqueous phase was then acidified to pH 1 with 3 M aqueous HCl and extracted with ethyl acetate ($3 \times 30 \text{ mL}$). The organic phase was dried over Na_2SO_4 , filtered and the solvent was removed under reduced pressure to give the title compound **204** (284 mg, 1.12 mmol, 69%) as a white solid.

m.p. $120\text{--}121^\circ \text{C}$ (lit. 118°C); δ_{H} (400 MHz, CDCl_3) 11.02 (1H, br s, OH), 7.20–7.48 (10H, m, $\text{C}(2')\text{H}$, $\text{C}(3')\text{H}$, $\text{C}(4')\text{H}$, $\text{C}(7)\text{H}$, $\text{C}(8)\text{H}$, $\text{C}(9)\text{H}$), 6.52 (1H, d, J 15.9, $\text{C}(5)\text{H}$), 6.41 (1H, dd, J 15.9, 7.1, $\text{C}(4)\text{H}$), 4.10 (1H, q, J 7.3, $\text{C}(3)\text{H}$), 2.87–3.00 (2H, m, $\text{C}(2)\text{H}_2$); δ_{C} (100 MHz, CDCl_3) 178.2 ($\text{C}(1)\text{O}$), 142.2 ($\text{C}(6)$), 136.9 ($\text{C}(1')$), 131.6 ($\text{C}(4)\text{H}$), 130.2 ($\text{C}(5)\text{H}$), 128.7 ($\text{C}(8)\text{H}$), 128.4 ($\text{C}(3')\text{H}$), 127.5 ($\text{C}(7)\text{H}$), 127.4 ($\text{C}(9)\text{H}$), 126.8 ($\text{C}(4')\text{H}$), 126.2 ($\text{C}(2')\text{H}$), 44.5 ($\text{C}(3)\text{H}$), 40.3 ($\text{C}(2)\text{H}_2$).

Spectroscopic data were consistent with those reported in the literature.¹³⁶

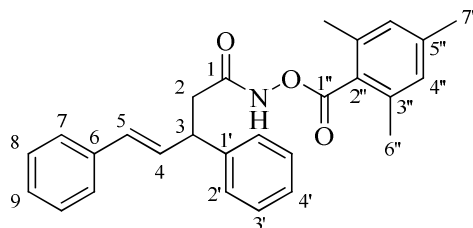
(4E)-N-Hydroxy-3,5-diphenylpent-4-enamide (205)



Compound **204** (284 mg, 1.13 mmol) was subjected to General Procedure A₂ to give the title compound **205** (267 mg, 1.02 mmol, 89%) as a white solid.

m.p. $45\text{--}47^\circ \text{C}$; ν_{max} (thin film)/ cm^{-1} 3223br, 2920br, 1651 br s, 1494m, 1452m, 1257m, 1063m, 1030m, 968m, 746s, 697s; δ_{H} (400 MHz, $(\text{CD}_3)_2\text{CO}$) 10.60 (1H, br s, NH), 8.91 (1H, br s, OH), 7.04–7.51 (10H, m, $\text{C}(2')\text{H}$, $\text{C}(3')\text{H}$, $\text{C}(4')\text{H}$, $\text{C}(7)\text{H}$, $\text{C}(8)\text{H}$, $\text{C}(9)\text{H}$), 6.48–6.57 (2H, m, $\text{C}(4)\text{H}$, $\text{C}(5)\text{H}$), 4.12–4.19 (1H, m, $\text{C}(3)\text{H}$), 2.63–2.81 (2H, m, $\text{C}(2)\text{H}_2$); δ_{C} (100 MHz, $(\text{CD}_3)_2\text{CO}$) 169.4 ($\text{C}(1)\text{O}$), 143.6 ($\text{C}(6)$), 137.9 ($\text{C}(1')$), 132.9 ($\text{C}(5)\text{H}$), 130.4 ($\text{C}(4)\text{H}$), 129.1 ($\text{C}(3')\text{H}$), 129.0 ($\text{C}(8)\text{H}$), 128.2 ($\text{C}(2')\text{H}$), 127.7 ($\text{C}(9)\text{H}$), 127.1 ($\text{C}(4')\text{H}$), 126.8 ($\text{C}(7)\text{H}$), 45.7 ($\text{C}(3)\text{H}$), 39.3 ($\text{C}(2)\text{H}_2$). **m/z** (ESI) 266 ($[\text{M}-\text{H}]^-$, 100%), 533 ($[\text{2M}-\text{H}]^-$, 65); **HRMS** (ESI⁺) $\text{C}_{17}\text{H}_{17}\text{NO}_2$ requires $[\text{M}+\text{Na}]^+$ 290.1151, found 290.1148 (+1.15 ppm).

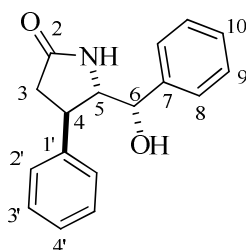
(4E)-N-[(Mesitylcarbonyl)oxy]-3,5-diphenylpent-4-enamide (206)



Compound **205** (268 mg, 1.00 mmol) was subjected to General Procedure B to give the title compound **206** (294 mg, 0.71 mmol, 71%) as a colourless oil.

$\nu_{\max}$ (thin film)/cm⁻¹ 3186br, 3027br, 1774s, 1669s, 1611m, 1494m, 1452m, 1233s, 1158s, 1048br, 986br, 910w, 851w, 744s, 698s; δ_{H} (400 MHz, CDCl₃) 9.51 (1H, br s, NH), 7.20-7.40 (10H, m, C(2')H, C(3')H, C(4')H, C(7)H, C(8)H, C(9)H), 6.86 (2H, s, C(4'')H), 6.49 (1H, d, *J* 15.8, C(5)H), 6.42 (1H, dd, *J* 15.8, 6.9, C(4)H), 4.19 (1H, q, *J* 6.9, C(3)H), 2.74-2.89 (2H, m, C(2)H), 2.34 (6H, s, C(6'')H), 2.30 (3H, s, C(7'')H); δ_{C} (100 MHz, CDCl₃) 168.8 (C(1'')O), 167.5 (C(1')O), 141.8 (C(6)), 140.4 (C(2'')), 136.6 (C(1')), 136.2 (C(3'')), 131.0 (C(5)H), 130.3 (C(4)H), 128.4 (C(8)H), 128.2 (C(4'')H), 128.0 (C(3')H), 127.2 (C(7)H), 127.0 (C(9)H), 126.6 (C(4')H), 126.1 (C(2'')), 125.9 (C(2')H), 44.3 (C(3)H), 39.2 (C(2)H₂), 20.8 (C(7'')H₃), 19.5 (C(6'')H₃); *m/z* (ESI⁻) 825 ([2M-H]⁻, 100%), 412 ([M-H]⁻, 98); **HRMS** (ESI⁺) C₂₇H₂₇NO₃ requires [M+Na]⁺ 436.1883, found 436.1884 (-0.25 ppm).

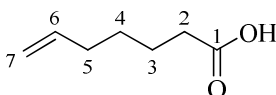
(4R*, 5S*)-5-[(S*)-Hydroxy(phenyl)methyl]-4-phenylpyrrolidin-2-one (207)



Compound **206** (269 mg, 0.65 mmol) was subjected to General Procedure C to give the title compound **207** (123 mg, 0.46 mmol, 71% with 4 mol % of the catalyst used) as a white powder.

m.p. 177-178 °C; $\nu_{\max}$ (thin film)/cm⁻¹ 3345br, 3029br, 1678s, 1494w, 1454w, 1419m, 1379w, 1349w, 1289w, 1255w, 1079w, 1057w, 1022w, 797w, 696m; δ_{H} (400 MHz, CDCl₃) 7.09-7.36 (8H, m, C(2')H, C(3')H, C(8)H, C(9)H), 6.95-6.99 (2H, m, C(4')H, C(10)H), 4.62 (1H, d, *J* 6.3, C(6)H), 3.85 (1H, dd, *J* 6.3, 4.3, C(5)H), 3.37 (1H, ddd, *J* 9.5, 5.0, 4.3, C(4)H), 2.62 (1H, dd, *J* 17.4, 9.5, C(3)H), 2.25 (1H, dd, *J* 17.4, 5.0, C(3)H); δ_{C} (100 MHz, CDCl₃) 179.8 (C(2)O), 145.3 (C(7)), 142.0 (C(1')), 129.6 (C(9)H), 127.3 (C(3')H), 128.9 (C(10)H), 128.1 (C(8)H), 127.63 (C(2')H), 127.58 (C(4')H), 77.2 (C(6)H), 69.7 (C(5)H), 42.6 (C(4)H), 39.8 (C(3)H₂); *m/z* (ESI⁻) 266 ([M-H]⁻, 100%), 533 ([2M-H]⁻, 55); **HRMS** (ESI⁺) C₁₇H₁₇NO₂ requires [M+H]⁺ 268.1332, found 268.1328 (+1.64 ppm).

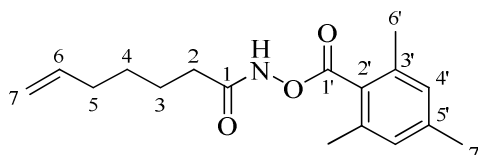
Single Crystal X-ray Diffraction Data for 207: C₁₇H₁₇NO₂, M_r = 267.33, monoclinic (C 1 2/c 1), a = 32.8860(12) Å, b = 6.0205(3) Å, c = 14.9007(7) Å, α = 90 °C, β = 109.973(2) °C, γ = 90 °C, V = 2772.7(2) Å³, Z = 8, μ = not measured D_{calc} = 1.281, T = 150(2) K, 5251 reflections collected, 3027 independent [R(int) = 0.086], R₁ = 0.0985, wR₂ = 0.1163 [I > 3σ(I)].

Hept-6-enoic acid

Hydrogen peroxide (2 eq., 5 mL, 40 mmol) was added over 2 min at room temperature to a stirred solution of cycloheptanone (1 eq., 2.36 mL, 20 mmol) in methanol (0.22 mL•mmol⁻¹). After 15 min, the reaction mixture was added over 5 min to a stirred solution of ferrous sulphate (1 eq., 5.56 g, 20 mmol) and cupric sulphate (1 eq., 5.0 g, 20 mmol) in water (50 mL) maintaining the reaction mixture at room temperature. Upon the addition, the reaction mixture turned dark brown. It was stirred for an additional hour. The aqueous phase was separated and extracted with diethyl ether (3 x 50 mL). The combined organic phases were washed with 2 M aqueous NaOH solution (3 x 50 mL). The alkaline extract were acidified with 2 M aqueous H₂SO₄ and extracted with diethyl ether (3 x 50 mL). Removal of the solvent at reduced pressure gave the title compound (600 mg, 6.2 mmol, 23%) as an orange oil.

δ_{H} (400 MHz, CDCl₃) 5.68-5.93 (1H, ddt, *J* 17.0, 10.2, 6.6, C(6)H), 4.89-5.13 (2H, m, C(7)H₂), 2.38 (2H, t, *J* 7.3, C(2)H₂), 2.09 (2H, m, C(5)H₂), 1.61-1.79 (2H, m, C(4)H₂), 1.35-1.54 (2H, m, C(3)H₂); δ_{C} (100 MHz, CDCl₃) 180.3 (C(1)O), 137.8 (C(6)H), 115.1 (C(7)H₂), 33.8 (C(2)H₂), 33.1 (C(5)H₂), 28.4 (C(4)H₂), 23.9 (C(3)H₂).

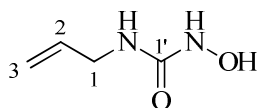
Spectroscopic data were consistent with those reported in the literature.¹³⁷

***N*-[(Mesitylcarbonyl)oxy]hept-6-enamide (208)**

Hept-6-enoic acid (803 mg, 6.27 mmol) was subjected to General Procedure A₂ and B to furnish the title compound **208** (1.27 g, 4.40 mmol, 70% over 2 steps) as a colourless oil.

ν_{max} (thin film)/cm⁻¹ 3543br, 2743br, 1776s, 1681s, 1584s, 1505br, 1496br, 1198s, 1130s, 1038s, 993m, 812m, 740w, 630w; δ_{H} (400 MHz, CDCl₃) 9.28 (1H, br s, NH), 7.39 (2H, s, C(4')H), 5.73-5.85 (1H, m, C(6)H), 4.92-5.06 (2H, m, C(7)H₂), 2.37 (6H, s, C(6')H₃), 2.30-2.35 (2H, m, C(2)H₂), 2.29 (3H, s, C(7')H₃), 2.04-2.09 (2H, m, C(5)H₂), 1.73 (2H, quint, *J* 7.6, C(3)H₂), 1.46 (2H, quint, *J* 7.6, C(4)H₂); δ_{C} (100 MHz, CDCl₃) 171.9 (C(1')O), 168.2 (C(1)O), 140.8 (C(5')), 138.2 (C(6)H), 136.6 (C(3')), 128.6 (C(4')H), 126.5 (C(2')), 114.8 (C(7)H₂), 33.3 (C(5)H₂), 32.7 (C(2)H₂), 28.43 (C(4)H₂), 28.41 (C(3)H₂), 21.2 (C(6')H₃), 19.9 (C(7')H₃); *m/z* (ESI) 577 ([2M-H]⁻, 100%), 288 ([M-H]⁻, 60); **HRMS** (ESI) C₁₇H₂₃NO₃ requires [M-H]⁻ 288.1605, found 288.1604 (-0.04 ppm).

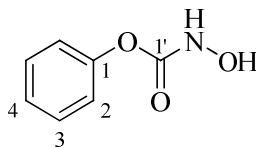
***N*-[(4-Methylphenyl)sulfonyl]-3-[[4-(4-methylphenyl)sulfonyl]amino]-D-alanine (209) see p178 compound 164**

1-Allyl-3-hydroxyurea (214)

To allylic amine (1 eq., 371 mg, 6.5 mmol) dissolved in pyridine (1.67 mL•mmol⁻¹) was added phenyl hydroxycarbamate (1 eq., 634 mg, 6.5 mmol) at room temperature under argon. The reaction mixture was heated at 30 °C and stirred for 12 h. The reaction mixture was concentrated *in vacuo* and the residue purified by flash column chromatography (SiO₂, eluting with gradient petrol 40-60/ethyl acetate 8:2 to 2:8) to give the title compound **214** (581 mg, 5.01 mmol, 77%) as a colourless solid.

δ_{H} (400 MHz, CD₃OD) 5.87 (1H, ddt, *J* 16.8, 10.9, 5.4, C(2)H), 5.12-5.26 (2H, m, C(3)H), 3.83 (2H, d, *J* 5.3, C(1)H); δ_{C} (100 MHz, CD₃OD) 164.3 (C(1')O), 136.6 (C(2)H), 115.2 (C(3)H₂), 47.4 (C(1)H₂).

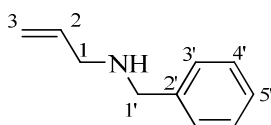
Spectroscopic data were consistent with those reported in the literature.¹³⁸

Phenyl hydroxycarbamate (215)

To hydroxylamine chloride (1.25 eq., 6.9 g, 100 mmol) and solid NaHCO₃ (2.2 eq., 14.8 g, 176 mmol) in water (1.1 mL•mmol⁻¹) cooled down to 0 °C was added dropwise a solution of *p*-phenylchloroformate (1 eq., 10.4 mL, 80 mmol) in dichloromethane (0.8 mL•mmol⁻¹). The reaction mixture was allowed to stir for 1 h at room temperature. The reaction mixture was then diluted with water (0.7 mL•mmol⁻¹), dichloromethane (0.7 mL•mmol⁻¹) and ethyl acetate (0.7 mL•mmol⁻¹). The organic phase was separated, washed with brine (50 mL), dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure to give the title compound **215** (10 g, 65 mmol, 81%) as a white solid.

δ_{H} (400 MHz, CDCl₃) 7.53 (1H, br s, NH), 7.40 (2H, t, *J* 7.6, C(3)H), 7.28 (1H, m, C(4)H), 7.12-7.23 (2H, m, C(2)H), 6.10 (1H, br s, OH); δ_{C} (100 MHz, CDCl₃) 156.4 (C(1')O), 151.6 (C(1)), 129.8 (C(3)H), 125.5 (C(4)H), 121.8 (C(2)H).

Spectroscopic data were consistent with those reported in the literature.¹³⁹

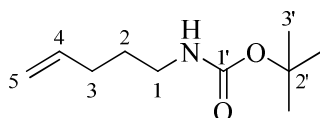
***N*-Benzylprop-2-en-1-amine (217b)**

To a solution of benzaldehyde (1 eq., 1.6 mL, 16 mmol) in acetonitrile (1.25 mL•mmol⁻¹), allylamine (3 eq., 3.6 mL, 48 mmol) was added and the resulting solution was stirred at room temperature for 1 h. Sodium cyanoborohydride (1.5 eq., 1.5 g, 24 mmol) was added followed 25 min later by acetic acid (2 eq., 1.8 mL, 32 mmol). The resulting turbid solution was stirred at room temperature until no more starting material by TLC (typically 12h). To the reaction mixture was added dichloromethane (7.5 mL•mmol⁻¹). It was washed with 1 M aqueous KOH (2 x 6.5 mL•mmol⁻¹). The organic phases were gathered, dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure to give the title compound **217b** (1.7 g, 11.5 mmol, 72%) as a pale yellowish oil.

δ_{H} (400 MHz, CDCl₃) 7.35 (4H, m, C(3')H, C(4')H), 7.23-7.31 (1H, m, C(5')H), 5.96 (1H, ddt, *J* 16.9, 10.7, 6.1, C(2)H), 5.19 (2H, dd, *J* 16.9, 10.7, C(3)H₂), 3.81 (2H, s, C(1')H₂), 3.30 (2H, d, *J* 6.1, C(1)H₂), 1.39 (1H, br s, NH); δ_{C} (100 MHz, CDCl₃) 140.5 (C(2')), 137.1 (C(2)H), 128.7 (C(3')H), 128.4 (C(4')H), 127.2 (C(5')H), 116.4 (C(3)H₂), 53.5 (C(1')H₂), 52.0 (C(1)H₂).

Spectroscopic data were consistent with those reported in the literature.¹⁴⁰

tert-Butyl pent-4-en-1-ylcarbamate (217c)

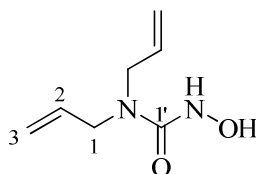


A flame-dried flask under argon was charged with a solution of 4-pentenylamine (1 eq., 681 mg, 8.0 mmol). Di-*tert*-butyldicarbonate (1.5 eq., 2.6 g, 12 mmol) was added to the solution and the resulting mixture was stirred for 4 h. 1 M aqueous NaOH solution (6.3 mL•mmol⁻¹) was added. The biphasic mixture was vigorously stirred for 12 h. The layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic phases were dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure to give the title compound **217c** (1.3 g, 7.0 mmol, 88%) as a yellowish oil.

δ_{H} (400 MHz, CDCl₃) 5.58-6.03 (1H, m, C(4)H), 4.86-5.20 (2H, m, C(5)H₂), 4.53 (1H, br s, NH), 3.14 (2H, m, C(1)H₂), 1.94-2.24 (2H, m, C(3)H₂), 1.55-1.67 (2H, m, C(2)H₂), 1.45 (9H, s, C(3')H₃); δ_{C} (100 MHz, CDCl₃) 156.2 (C(1')O), 137.7 (C(4)H), 115.2 (C(5)H₂), 80.1 (C(2')), 39.8 (C(3)H₂), 30.4 (C(2)H₂), 29.3 (C(1)H₂), 28.4 (C(3')H₃).

Spectroscopic data were consistent with those reported in the literature.¹⁴¹

N,N-Diallyl-N'-hydroxyurea (218a)

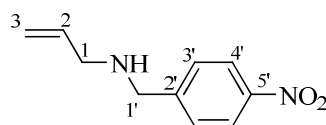


To *N,N'*-di-2-propen-1-yl-urea (1 eq., 1.0 g, 6.5 mmol) dissolved in pyridine (1.67 mL•mmol⁻¹) was added phenyl hydroxycarbamate (1 eq., 634 mg, 6.5 mmol) at room temperature under argon. The reaction mixture was heated at 30 °C and stirred for 12 h. The reaction mixture was concentrated *in vacuo* and the residue purified by flash column chromatography (SiO₂, eluting with gradient petrol 40-60/ethyl acetate 8:2 to 2:8) to give the title compound **218a** (309 mg, 1.97 mmol, 30%) as a yellow oil.

ν_{max} (thin film)/cm⁻¹ 3256br, 1653s, 1475m, 1253m, 924m; δ_{H} (400 MHz, CDCl₃) 7.68 (1H, br s, NH), 7.15 (1H, br s, OH), 5.69-5.83 (2H, ddt, *J* 16.6, 11.0, 5.4, C(2)H), 5.12-5.26 (4H, m, C(3)H), 3.84 (4H, d, *J* 5.4, C(1)H); δ_{C} (100 MHz, CDCl₃) 161.1 (C(1')O), 132.5 (C(2)H), 117.1 (C(3)H₂), 48.6 (C(1)H₂); *m/z* (ESI⁺) 155 ([M-H]⁺, 100%); **HRMS** (ESI⁺) C₇H₁₂N₂O₂ requires [M+Na]⁺ 179.0791, found 179.0791 (-0.05 ppm).

For compound 219a see p 201, compound 217b

N-(4-Nitrobenzyl)prop-2-en-1-amine (219b)

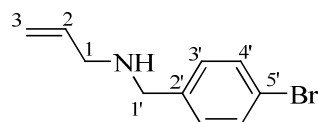


To a solution of 4-nitrobenzaldehyde (1 eq., 1.2 g, 8.0 mmol) in acetonitrile (1.25 mL•mmol⁻¹), allylamine (3 eq., 18 mL, 24 mmol) was added and the resulting solution was stirred at room temperature for 1 h. Sodium cyanoborohydride (1.5 eq., 754 mg, 12 mmol) was added followed 25 min later by acetic acid (2 eq., 0.92 mL, 16 mmol). The resulting turbid solution was stirred at room temperature until no more starting material by TLC (typically 12 h). To the reaction mixture was added dichloromethane (7.5 mL•mmol⁻¹). It was washed with 1 M aqueous KOH (2 x 6.5 mL•mmol⁻¹). The organic phases were gathered, dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure to give the title compound **219b** (605 mg, 3.2 mmol, 40%) as a yellow oil.

δ_{H} (400 MHz, CDCl₃) 8.19 (2H, d, *J* 8.6, C(4')H), 7.52 (2H, d, *J* 8.6, C(3')H), 5.78-6.04 (1H, m, C(2)H), 5.08-5.29 (2H, m, C(3)H), 3.91 (2H, s, C(1')H), 3.29 (2H, d, *J* 6.0, C(1)H), 1.45 (1H, br s, NH); δ_{C} (100 MHz, CDCl₃) 158.3 (C(2')), 148.2 (C(4')H), 136.5 (C(2)H), 128.8 (C(3')H), 123.7 (C(5')), 116.7 (C(3)H₂), 52.4 (C(1)H₂), 51.8 (C(1')H₂).

Spectroscopic data were consistent with those reported in the literature.¹⁴²

N-(4-Bromobenzyl)prop-2-en-1-amine (219c)

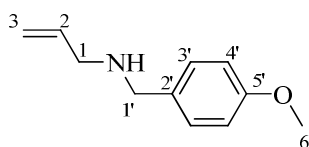


To a solution of 4-bromobenzaldehyde (1 eq., 1.48 g, 8.0 mmol) in acetonitrile ($1.25 \text{ mL} \cdot \text{mmol}^{-1}$), allylamine (3 eq., 18 mL, 24 mmol) was added and the resulting solution was stirred at room temperature for 1 h. Sodium cyanoborohydride (1.5 eq., 754 mg, 12 mmol) was added followed 25 min later by acetic acid (2 eq., 0.92 mL, 16 mmol). The resulting turbid solution was stirred at room temperature until no more starting material by TLC (typically 12 h). To the reaction mixture was added dichloromethane ($7.5 \text{ mL} \cdot \text{mmol}^{-1}$). It was washed with 1 M aqueous KOH ($2 \times 6.5 \text{ mL} \cdot \text{mmol}^{-1}$). The organic phases were gathered, dried over Na_2SO_4 , filtered and the solvent was removed under reduced pressure to give the title compound **219c** (1.06 g, 4.7 mmol, 59%) as a colourless oil.

δ_{H} (400 MHz, CDCl_3) 7.45 (2H, d, J 8.3, C(4') $\underline{\text{H}}$), 7.21 (2H, d, J 8.3, C(3') $\underline{\text{H}}$), 5.76-6.04 (1H, m, C(2') $\underline{\text{H}}$), 5.07-5.27 (2H, m, C(3) $\underline{\text{H}}_2$), 3.75 (2H, s, C(1') $\underline{\text{H}}_2$), 3.26 (2H, d, J 5.9, C(1) $\underline{\text{H}}_2$), 1.40 (1H, br s, NH); δ_{C} (100 MHz, CDCl_3) 139.3 ($\underline{\text{C}}(2')$), 136.7 ($\underline{\text{C}}(2)\text{H}$), 131.1 ($\underline{\text{C}}(4')\text{H}$), 129.6 ($\underline{\text{C}}(3')\text{H}$), 120.4 ($\underline{\text{C}}(5')$), 116.4 ($\underline{\text{C}}(3)\text{H}_2$), 52.5 ($\underline{\text{C}}(1)\text{H}_2$), 51.4 ($\underline{\text{C}}(1')\text{H}_2$).

Spectroscopic data were consistent with those reported in the literature.¹⁴³

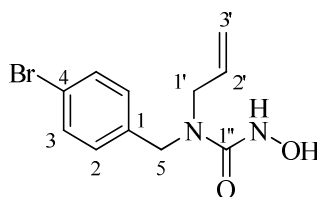
***N*-(4-Methoxybenzyl)prop-2-en-1-amine (219d)**



To a solution of *p*-anisaldehyde (1 eq., 0.97 mL, 8.0 mmol) in acetonitrile ($1.25 \text{ mL} \cdot \text{mmol}^{-1}$), allylamine (3 eq., 18 mL, 24 mmol) was added and the resulting solution was stirred at room temperature for 1 h. Sodium cyanoborohydride (1.5 eq., 754 mg, 12 mmol) was added followed 25 min later by acetic acid (2 eq., 0.92 mL, 16 mmol). The resulting turbid solution was stirred at room temperature until no more starting material by TLC (typically 12 h). To the reaction mixture was added dichloromethane ($7.5 \text{ mL} \cdot \text{mmol}^{-1}$). It was washed with 1 M aqueous KOH ($2 \times 6.5 \text{ mL} \cdot \text{mmol}^{-1}$). The organic phases were gathered, dried over Na_2SO_4 , filtered and the solvent was removed under reduced pressure to give the title compound **219d** (430 mg, 2.4 mmol, 30%) as a colourless oil.

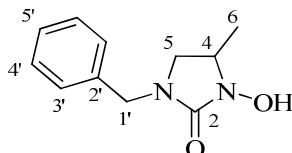
δ_{H} (400 MHz, CDCl_3) 7.20-7.30 (2H, m, C(3') $\underline{\text{H}}$), 6.87 (2H, d, J 8.6, C(4') $\underline{\text{H}}$), 5.82-6.06 (1H, m, C(2') $\underline{\text{H}}$), 5.06-5.28 (2H, m, C(3) $\underline{\text{H}}_2$), 3.81 (3H, s, C(6') $\underline{\text{H}}_3$), 3.74 (2H, s, C(1') $\underline{\text{H}}_2$), 3.27 (2H, d, J 6.0, C(1) $\underline{\text{H}}_2$), 1.39 (1H, br s, NH); δ_{C} (100 MHz, CDCl_3) 159.4 ($\underline{\text{C}}(2')$), 137.3 ($\underline{\text{C}}(2)\text{H}$), 130.8 ($\underline{\text{C}}(5')$), 130.2 ($\underline{\text{C}}(3')\text{H}$), 117.0 ($\underline{\text{C}}(4')\text{H}$), 114.5 ($\underline{\text{C}}(3)\text{H}_2$), 53.4 ($\underline{\text{C}}(1)\text{H}_2$), 52.3 ($\underline{\text{C}}(1')\text{H}_2$).

Spectroscopic data were consistent with those reported in the literature.¹⁴³

N-Allyl-N-(4-bromobenzyl)-N'-hydroxyurea (220c)

To compound **219c** (1 eq., 500 mg, 2.21 mmol) dissolved in pyridine (1.67 mL•mmol⁻¹) was added phenyl hydroxycarbamate (1 eq., 339 mg, 2.21 mmol) at room temperature under argon. The reaction mixture was heated at 30°C and stirred for 16 h. The reaction mixture was concentrated *in vacuo* and the residue purified by flash column chromatography (SiO₂, eluting with gradient petrol/ethyl acetate 8:2 to 2:8) to give the title compound **220c** (60 mg, 0.21 mmol, 11%) as a yellow oil.

v_{max} (thin film)/cm⁻¹ 3263br, 2918br, 1667s, 1488s, 1403s, 1250m, 1070w, 1011m, 926m, 795m; **δ**_H (400 MHz, CDCl₃) 7.72 (1H, br s, NH), 7.43 (2H, d, *J* 8.3, C(3)H), 7.23 (1H, br s, OH), 7.12 (2H, d, *J* 8.3, C(2)H), 5.64-5.77 (1H, m, C(2')H), 5.14-5.25 (2H, m, C(3')H), 4.44 (2H, s, C(5)H), 3.77 (2H, d, *J* 5.3, C(1')H); **δ**_C (100 MHz, CDCl₃) 162.0 (C(1'')O), 136.1 (C(1)), 132.6 (C(2')H), 132.1 (C(3)H), 129.6 (C(2)H), 121.8 (C(4)), 118.2 (C(3')H₂), 49.9 (C(5)H₂), 49.0 (C(1')H₂); **m/z** (ESI⁺) 569-571-573 ([2M+H]⁺, 100%), 285-287 ([M+H]⁺, 90); **HRMS** (ESI⁺) C₁₁H₁₃BrN₂O₂ requires [M+Na]⁺ 307.0053, 309.0033, found 307.0052, 309.0034 (+0.24 ppm).

1-Benzyl-3-hydroxy-4-methylimidazolidin-2-one (221)

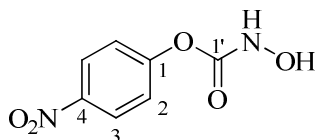
To compound **219a** (1 eq., 294 mg, 2 mmol) dissolved in pyridine (1.67 mL•mmol⁻¹) was added phenyl hydroxycarbamate (1 eq., 306 mg, 2 mmol) at room temperature under argon. The reaction mixture was heated at reflux for 72 h. The reaction mixture was concentrated *in vacuo* and the residue purified by flash column chromatography (SiO₂, eluting with gradient petrol 40-60/ethyl acetate 8:2 to 2:8) to give the title compound **221** (235 mg, 0.82 mmol, 41%) as a white solid.

m.p. 133-134 °C; **v**_{max} (thin film)/cm⁻¹ 3221br, 2931br, 2360w, 1717s, 1485s, 1445s, 1358m, 1258m, 1029m, 912w, 762m, 702s, 636m; **δ**_H (400 MHz, CDCl₃) 9.32 (1H, br s, OH), 7.26-7.36 (3H, m, C(4')H, C(5')H), 7.22-7.26 (2H, m, C(3')H), 4.46 (1H, d, *J* 14.7, C(1')H_a), 4.31 (1H, d, *J* 14.7, C(1')H_b), 3.54-3.66 (1H, m, C(4)H), 3.26 (1H, t, *J* 8.2, C(5)H_a), 2.74 (1H, t, *J* 9.1, C(5)H_b), 1.31 (3H, d, *J* 6.1, C(6)H₃); **δ**_C (100 MHz, CDCl₃) 164.8 (C(2)O), 135.8 (C(2')), 128.6 (C(4')H), 128.0 (C(3')H), 127.6 (C(5')H), 55.2 (C(4)H), 47.9 (C(1')H₂), 47.6 (C(5)H₂), 16.6 (C(6)H₃); **m/z**

(ESI⁺) 413 ([2M+H]⁺, 100%), 641 ([3M+Na]⁺, 90), 435 ([2M+Na]⁺, 70), 207 ([M+H]⁺, 50); **HRMS** (ESI⁺) C₁₁H₁₄N₂O₂ requires [M+Na]⁺ 229.0947, found 229.0947 (+0.11 ppm).

Single Crystal X-ray Diffraction Data for 221: C₂₂H₂₈N₄O₄, M_r = 412.49, triclinic (P -1), a = 9.3933(3) Å, b = 10.5472(3) Å, c = 11.1850(3) Å, α = 89.9798(14) °C, β = 90.0100(14) °C, γ = 102.5009(12) °C, V = 1081.86(5) Å³, Z = 2, μ = not measured D_{calc} = 1.266, T = 150(2) K, 8878 reflections collected, 3741 independent [R(int) = 0.051], R₁ = 0.0916, wR₂ = 0.1674 [I>3σ(I)].

4-Nitrophenyl hydroxycarbamate (223)

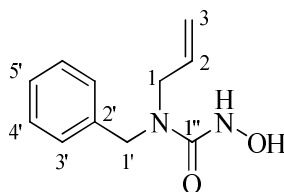


To hydroxylamine chloride (1.25 eq., 1.08 g, 15.5 mmol) and solid NaHCO₃ (2.2 eq., 2.3 g, 27.3 mmol) in water (1.1 mL•mmol⁻¹) cooled down to 0 °C was added dropwise a solution of *p*-nitrophenylchloroformate (1 eq., 2.5 g, 12.4 mmol) in dichloromethane (0.8 mL•mmol⁻¹). The reaction mixture was allowed to stir for 1 h at room temperature. The reaction mixture was then diluted with water (0.7 mL•mmol⁻¹), dichloromethane (0.7 mL•mmol⁻¹) and ethyl acetate (0.7 mL•mmol⁻¹). The organic phase was separated, washed with brine (30 mL) solution, dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure to give the title compound **223** (1.6 g, 8.01 mmol, 65%) as a white solid.

δ_H (400 MHz, CDCl₃) 9.76 (1H, br s, NH), 8.54-9.17 (1H, br s, OH), 8.23 (2H, d, *J* 9.1, C(3)H), 7.40 (2H, d, C(2)H); δ_C (100 MHz, CDCl₃) 163.9 (C(1)), 163.7 (C(1')O), 145.2 (C(4)), 126.3 (C(2)H), 116.0 (C(3)H).

Spectroscopic data were consistent with those reported in the literature.¹⁴⁴

N-Allyl-*N*-benzyl-*N'*-hydroxyurea (220a)

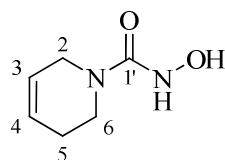


To *N*-benzylprop-2-en-1-amine **219a** (1 eq., 194 mg, 1.32 mmol) dissolved in pyridine (1.67 mL•mmol⁻¹) was added **223** (2 eq. 527 mg, 2.64 mmol) at room temperature under argon. The reaction mixture was heated at 40 °C and stirred until TLC indicated complete consumption of the starting material (typically after 4 h). The reaction mixture was concentrated *in vacuo* and the residue purified by flash column chromatography (SiO₂, eluting with gradient petrol 40-60/ethyl acetate 8:2 to 2:8) to give the title compound **220a** (226 mg, 1.09 mmol, 83%) as a white solid.

m.p. 86-87 °C; $\nu_{\max}$ (thin film)/cm⁻¹ 3259br, 1651s, 1495s, 1250m, 1033v, 926m, 670m; δ_{H} (400 MHz, CDCl₃) 7.94 (1H, br s, NH), 7.19-7.35 (5H, m, C(3')H, C(4')H, C(5')H), 5.72 (1H, ddt, *J* 16.5, 10.9, 5.6, C(2)H), 5.12-5.23 (2H, m, C(3)H₂), 4.48 (2H, s, C(1')H₂), 3.81 (2H, d, *J* 5.4, C(1)H₂); δ_{C} (100 MHz, CDCl₃) 162.0 (C(1'')O), 137.0 (C(2')), 132.8 (C(2)H), 129.0 (C(3')H), 127.8 (C(5')H), 127.7 (C(4')H), 117.9 (C(3)H₂), 50.1 (C(1')H₂), 49.0 (C(1)H₂); **m/z** (ESI⁺) 435 ([2M+Na]⁺, 100%), 207 ([M+H]⁺, 60); **HRMS** (ESI⁺) C₁₁H₁₄N₂O₂ requires [M+Na]⁺ 229.0947, found 229.0951 (-1.34 ppm).

Single Crystal X-ray Diffraction Data for 220a: C₁₁H₁₄N₂O₂, *M_r* = 206.24, monoclinic (P2₁ 2₁ 2₁), *a* = 7.79790(10) Å, *b* = 10.1302(2) Å, *c* = 26.8506(6) Å, α = 90 °C, β = 90 °C, γ = 90 °C, *V* = 2121.04(7) Å³, *Z* = 8, μ = not measured *D_{calc}* = 1.292, *T* = 150(2) K, 4822 reflections collected, 1842 independent [*R*(int) = 0.053], *R*₁ = 0.0750, *wR*₂ = 0.1123 [*I*>3σ(*I*)].

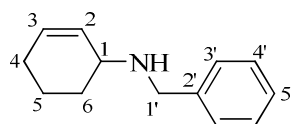
***N*-Hydroxy-3,6-dihydropyridine-1(2*H*)-carboxamide (224)**



1,2,3,6-tetrahydro-pyridine (250 mg, 3.0 mmol) was subjected to General Procedure with **223** to give the title compound **224** (257 mg, 1.8 mmol, 60%) as a white crystalline solid.

m.p. 103⁻¹04 °C; $\nu_{\max}$ (thin film)/cm⁻¹ 3243br, 2918w, 1609s, 1520m, 1282w, 1263w, 1007w, 654m; δ_{H} (400 MHz, CDCl₃) 7.74 (1H, br s, NH), 7.52 (1H, br s, OH), 5.85 (1H, ddd, *J* 8.1, 4.0, 2.0, C(4)H), 5.59-5.68 (1H, m, C(3)H), 3.80-3.88 (2H, m, C(2)H₂), 3.48 (2H, t, *J* 5.7, C(6)H₂), 2.12-2.20 (2H, m, C(5)H₂); δ_{C} (100 MHz, CDCl₃) 161.4 (C(1')O), 125.8 (C(4)H), 123.4 (C(3)H), 43.0 (C(2)H₂), 40.1 (C(6)H₂), 24.9 (C(5)H₂); **m/z** (ESI⁺) 307 ([2M+Na]⁺, 100%), 206 ([M+CH₃CN+Na]⁺, 80), 143 ([M+H]⁺, 60); **HRMS** (ESI⁺) C₆H₁₀N₂O₂ requires [M+Na]⁺ 165.0634, found 165.0630 (+2.97 ppm).

***N*-Benzylcyclohex-2-en-1-amine**



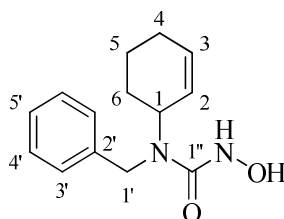
To benzylamine (1.2 eq., 1.3 mL, 12 mmol) in acetonitrile (3.0 mL•mmol⁻¹) was added solid K₂CO₃ (3.5 eq., 4.8 g, 35 mmol). The reaction mixture was stirred for 5 min followed by the addition of 3-bromocyclohexene (1 eq., 1.15 mL, 10 mmol). The reaction mixture gradually turned from a white to a brown heterogenous solution. After 16 h, the reaction mixture was concentrated *in vacuo* to afford a beige gum. A solution of 1 M aqueous NaOH (4 mL•mmol⁻¹) is added, and the residue extracted with dichloromethane (3 x 20 mL). The organic layer was dried over Na₂SO₄, filtered and

the solvent was removed under reduced pressure to give a black oil. Purification by flash column chromatography (SiO₂, eluting with a gradient from petrol 40-60/ethyl acetate 10/1 to 4/1) furnished the title compound (1.4 g, 7.3 mmol, 61%) as a colourless oil.

δ_{H} (400 MHz, CDCl₃) 7.31-7.41 (4H, m, C(3')H, C(4')H), 7.23-7.30 (1H, m, C(5')H), 5.73-5.84 (2H, m, C(2)H, C(3)H), 3.87 (2H, dd, J 19.0, 5.2, C(1')H₂), 3.24 (1H, m, C(1)H), 2.03 (2H, td, J 5.1, 2.8, C(4)H₂) 1.89-1.97 (1H, m, C(6)H_a), 1.73-1.83 (1H, m, C(5)H_a), 1.47-1.65 (2H, m, C(5)H_b, C(6)H_b), 1.28 (1H, br s, NH); δ_{C} (100 MHz, CDCl₃) 140.8 (C(2')), 130.0 (C(2)H), 129.0 (C(5')H), 128.4 (C(3')H), 128.2 (C(4')H), 126.9 (C(3)H), 52.4 (C(1)H), 51.1 (C(1')H₂), 29.6 (C(6)H₂), 25.4 (C(4)H₂), 20.3 (C(5)H₂).

Spectroscopic data were consistent with those reported in the literature.¹⁴⁵

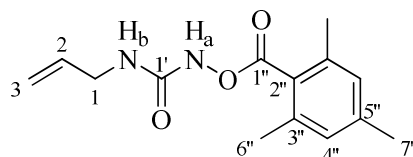
N-Benzyl-*N*-cyclohex-2-en-1-yl-*N'*-hydroxyurea (**225**)



N-Benzylcyclohex-2-en-1-amine (500 mg, 2.67 mmol) was subjected to General Procedure with **223** give the title compound **225** (450 mg, 1.8 mmol, 68%) as yellow solid.

m.p. 98-99 °C; ν_{max} (thin film)/cm⁻¹ 3246br, 2933m, 2360w, 2341w, 2360m, 2341m, 1650s-br, 1496m, 1433m, 990w, 934w, 728m; δ_{H} (400 MHz, CDCl₃) 7.92 (1H, br s, NH), 7.30-7.36 (2H, m, C(4')H), 7.23-7.29 (3H, m, C(3')H, C(5')H), 6.98 (1H, br s, OH), 5.88-5.96 (1H, m, C(2)H), 5.52 (1H, m, C(3)H), 4.74-4.85 (1H, m, C(1)H), 4.48 (1H, d, J 16.9, C(1')H_a), 4.29 (1H, d, J 16.9, C(1')H_b), 1.89-2.06 (3H, m, C(4)H₂, C(6)H_a), 1.72-1.81 (1H, m, C(5)H_a), 1.50-1.68 (2H, m, C(5)H_b, C(6)H_b); δ_{C} (100 MHz, CDCl₃) 162.1 (C(1')O), 137.8 (C(2')), 133.0 (C(2)H), 129.1 (br, C(3')H, C(4')H), 127.8 (C(5')H), 126.5 (C(3)H), 53.5 (C(1)H), 47.4 (C(1')H₂), 27.6 (C(6)H₂), 24.7 (C(4)H₂), 21.5 (C(5)H₂); **m/z** (ESI⁻) 245 ([M-H]⁻, 100%); **HRMS** (ESI⁺) C₁₄H₁₈N₂O₂ requires [M+Na]⁺ 269.1260, found 269.1258 (+1.11 ppm).

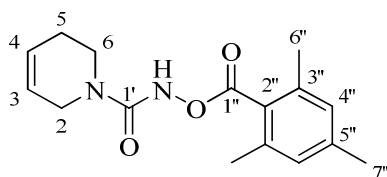
N-Allyl-*N'*-(mesitylcarbonyl)oxy]urea (**226**)



N-Allyl-*N'*-hydroxyurea (174 mg, 1.50 mmol) was subjected to General Procedure B to furnish the title compound **226** (160 mg, 0.61 mmol, 45%) as a colourless solid.

m.p. 81-82 °C; $\nu_{\max}$ (thin film)/cm⁻¹ 3304br, 2922m, 1762s, 1680s, 1539m, 1233m, 1160m, 1046m, 852w; δ_{H} (400 MHz, CDCl₃) 8.86 (1H, br s, NH_a), 6.91 (2H, s, C(4'')H), 5.76-5.92 (1H, m, C(2')H), 5.54 (1H, br s, NH_b), 5.10-5.25 (2H, m, C(3')H), 3.91 (2H, m, C(1')H), 2.33 (6H, s, C(6'')H), 2.32 (3H, s, C(7'')H); δ_{C} (100 MHz, CDCl₃) 167.9 (C(1'')O), 158.3 (C(1')O), 141.3 (C(5'')), 136.5 (C(3'')), 134.1 (C(2')H), 128.9 (C(4'')H), 127.0 (C(2'')), 117.0 (C(3')H₂), 42.6 (C(1')H₂), 21.5 (C(7'')H₃), 20.1 (C(6'')H₃); **m/z** (ESI⁺) 523 ([2M-H]⁺, 100%), 261 ([M-H]⁺, 80); **HRMS** (ESI⁺) C₁₄H₁₈N₂O₃ requires [M+Na]⁺ 285.1210, found 285.1209 (+0.22 ppm).

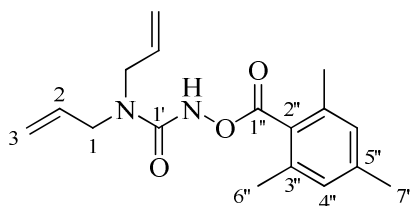
N-[(Mesitylcarbonyl)oxy]-3,6-dihydropyridine-1(2*H*)-carboxamide (227)



Compound **224** (250 mg, 1.76 mmol) was subjected to General Procedure B to furnish the title compound **227** (398 mg, 1.38 mmol, 98%) as a colourless solid.

m.p. 125-127 °C; $\nu_{\max}$ (thin film)/cm⁻¹ 3216br, 2922br, 1764s, 1673s, 1502m, 1449m, 1414m, 1237s, 1160s, 1049s, 1008m, 852m, 732m, 657m; δ_{H} (400 MHz, CDCl₃) 8.46 (1H, br s, NH), 6.89 (2H, s, C(4'')H), 5.91 (1H, ddd, *J* 8.1, 4.0, 2.1, C(4')H), 5.63-5.77 (1H, m, C(3')H), 3.94-4.08 (2H, m, C(2')H), 3.61 (2H, t, *J* 5.7, C(6')H), 2.41 (6H, s, C(6'')H), 2.30 (3H, s, C(7'')H), 2.20-2.27 (2H, m, C(5')H); δ_{C} (100 MHz, CDCl₃) 170.1 (C(1'')O), 157.4 (C(1')O), 140.8 (C(5'')), 136.9 (C(3'')), 128.8 (C(4'')H), 127.3 (C(2'')), 125.9 (C(4')H), 123.4 (C(3')H), 43.5 (C(2')H₂), 40.6 (C(6')H₂), 24.9 (C(5')H₂), 21.4 (C(7'')H₃), 20.2 (C(6'')H₃); **m/z** (ESI⁺) 287 ([M-H]⁺, 100%), 575 ([2M-H]⁺, 70); **HRMS** (ESI⁺) C₁₆H₂₀N₂O₃ requires [M+Na]⁺ 311.1366, found 311.1369 (-0.87 ppm).

N,N-Diallyl-*N'*-[(mesitylcarbonyl)oxy]urea (228)



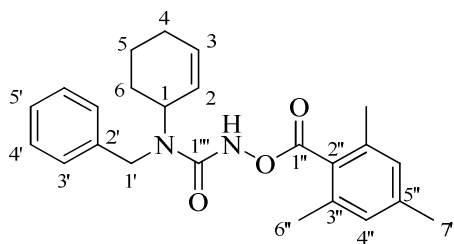
Compound **218a** (268 mg, 1.72 mmol) was subjected to General Procedure B to furnish the title compound **228** (465 mg, 1.53 mmol, 89%) as a colourless solid.

m.p. 107-108 °C; $\nu_{\max}$ (thin film)/cm⁻¹ 3208br, 1762s, 1674s, 1471m, 1235m, 1158m, 1034s, 852w; δ_{H} (400 MHz, CDCl₃) 8.47 (1H, br s, NH), 6.88 (2H, s, C(4'')H), 5.81-5.92 (2H, m, C(2')H), 5.26-5.37 (4H, m, C(3')H), 3.98 (4H, d, *J* 5.3, C(1')H), 2.41 (6H, s, C(6'')H), 2.29 (3H, s, C(7'')H); δ_{C} (100 MHz, CDCl₃) 170.0 (C(1'')O), 157.9 (C(1')O), 140.8 (C(5'')), 137.0 (C(3'')), 133.0 (C(2')H),

128.8 ($\underline{C}(4'')$ H), 127.3 ($\underline{C}(2'')$), 118.0 ($\underline{C}(3)$ H₂), 49.5 ($\underline{C}(1)$ H₂), 21.5 ($\underline{C}(7'')$ H₃), 20.3 ($\underline{C}(6'')$ H₃); **m/z** (ESI⁻) 301 ([M-H]⁻, 100%); **HRMS** (ESI⁺) C₁₇H₂₂N₂O₃ requires [M+Na]⁺ 325.1523, found 325.1516 (+1.91 ppm).

Single Crystal X-ray Diffraction Data for 228: C₁₇H₂₂N₂O₃, M_r = 302.37, monoclinic (P1 21/c 1), a = 9.0000(2) Å, b = 20.1778(4) Å, c = 9.5533(2) Å, α = 90 °C, β = 108.3390(8) °C, γ = 90 °C, V = 1646.77(6) Å³, Z = 4, μ = not measured D_{calc} = 1.220, T = 150(2) K, 15902 reflections collected, 3741 independent [R(int) = 0.027], R₁ = 0.0745, wR₂ = 0.1253 [I > 3σ(I)].

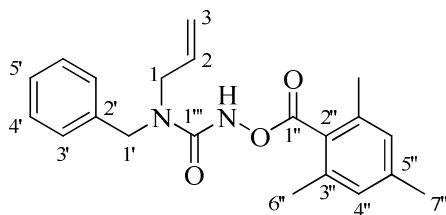
***N*-Benzyl-*N*-cyclohex-2-en-1-yl-*N'*-[(mesitylcarbonyl)oxy]urea (229)**



Compound **225** (262 mg, 1.06 mmol) was subjected to General Procedure B to furnish the title compound **229** (346 mg, 0.88 mmol, 92%) as a colourless solid.

m.p. 65-66 °C; **v_{max}** (thin film)/cm⁻¹ 3257br, 3028m, 2931s, 1759s, 1684s, 1611m, 1453v, 1236s, 1159m, 1030m, 955w, 911w, 730s; **δ_H** (400 MHz, CDCl₃) 8.25 (1H, br s, NH), 7.36-7.44 (4H, m, C(3'')H, C(4'')H), 7.32 (1H, t, *J* 6.6, C(5'')H), 6.86 (2H, s, C(4'')H), 5.98 (1H, dd, *J* 9.9, 2.5, C(2'')H), 5.63 (1H, m, C(3'')H), 4.78-5.00 (1H, m, C(1'')H), 4.64 (1H, d, *J* 17.1 C(1')H_a), 4.46 (1H, d, *J* 17.1, C(1')H_b), 2.38 (6H, s, C(6'')H₃), 2.29 (3H, s, C(7'')H₃), 1.95-2.08 (3H, m, C(4'')H₂, C(6'')H₂), 1.74-1.88 (1H, m, C(5'')H_a), 1.65 (2H, m, C(6'')H_b, C(5'')H_b); **δ_C** (100 MHz, CDCl₃) 169.3 (C(1'')O), 157.8 (C(1'')O), 140.0 (C(5'')), 137.1 (C(2'')), 136.3 (C(3'')), 132.7 (C(4'')H), 128.6 (C(2'')H), 128.1 (C(4'')H), 127.2 (C(5'')H), 127.1 (C(3'')H), 126.7 (C(2'')), 126.0 (C(3'')H), 53.3 (C(1'')H), 47.1 (C(1'')H₂), 27.1 (C(6'')H₂), 24.2 (C(4'')H₂), 21.0 (C(5'')H₂), 20.8 (C(7'')H₃), 19.6 (C(6'')H₃); **m/z** (ESI⁺) 393 ([M+H]⁺, 100%), 415 ([M+Na]⁺, 50), 785 ([2M+H]⁺, 50%); **HRMS** (ESI⁺) C₂₄H₂₈N₂O₃ requires [M+Na]⁺ 415.1991, found 415.1992 (+0.73 ppm).

***N*-Allyl-*N*-benzyl-*N'*-[(mesitylcarbonyl)oxy]urea (230)**

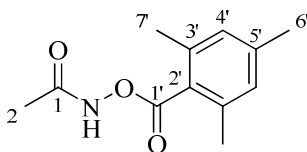


Compound **220a** (215 mg, 1.04 mmol) was subjected to General Procedure B to furnish the title compound **230** (288 mg, 0.81 mmol, 87%) as a colourless solid.

m.p. 113-115 °C; ν_{max} (thin film)/ cm^{-1} 3234br, 2922w, 2360w, 1762s, 1683s-br, 1496m, 1470v, 1233s, 1160m, 1032m, 923w, 851w, 700m; δ_{H} (400 MHz, CDCl_3) 8.48 (1H, br s, NH), 7.23-7.50 (5H, m, C(3') $\underline{H}$, C(4') $\underline{H}$, C(5') $\underline{H}$), 6.89 (2H, s, C(4'') $\underline{H}$), 5.78-5.92 (1H, m, C(2) $\underline{H}$), 5.28-5.41 (2H, m, C(3) $\underline{H}_2$), 4.61 (2H, s, C(1') $\underline{H}_2$), 3.95 (2H, d, J 5.1, C(1) $\underline{H}_2$), 2.42 (6H, s, C(6'') $\underline{H}_3$), 2.30 (3H, s, C(7'') $\underline{H}_3$); δ_{C} (100 MHz, CDCl_3) 170.1 ($\underline{\text{C}}$ (1'')O), 158.2 ($\underline{\text{C}}$ (1''')O), 140.8 ($\underline{\text{C}}$ (5'')), 137.0 ($\underline{\text{C}}$ (2'')), 136.8 ($\underline{\text{C}}$ (3'')), 132.6 ($\underline{\text{C}}$ (2)H), 129.1 ($\underline{\text{C}}$ (4'')H), 128.8 ($\underline{\text{C}}$ (3')H), 128.0 ($\underline{\text{C}}$ (4')H), 127.9 ($\underline{\text{C}}$ (5')H), 127.22 ($\underline{\text{C}}$ (2'')), 118.0 ($\underline{\text{C}}$ (3) H_2), 50.5 ($\underline{\text{C}}$ (1') H_2), 49.2 ($\underline{\text{C}}$ (1) H_2), 21.5 ($\underline{\text{C}}$ (7'') H_3), 20.3 ($\underline{\text{C}}$ (6'') H_3); **m/z** (ESI⁻) 351 ([M-H]⁻, 100%); **HRMS** (ESI⁺) $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_3$ requires [M+Na]⁺ 375.1679, found 375.1670 (+2.55 ppm).

5.3.2 Chapter 3 – Characterisation Data

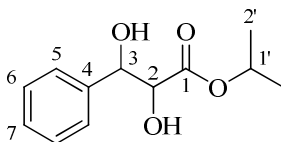
N-(2,4,6-Trimethylbenzoyloxy)acetamide (**242**)



N-Hydroxyacetamide **240** (1.2 g, 16 mmol) was subjected to General Procedure B to furnish the title compound **242** (3.3 g, 15 mmol, 94%) as a white solid.

δ_{H} (400 MHz, $(\text{CD}_3)_2\text{O}$) 9.29 (1H, br s, NH), 6.89 (2H, s, $\text{C}(4')\text{H}_2$), 2.37 (6H, s, $\text{C}(7')\text{H}_3$), 2.30 (3H, s, $\text{C}(6')\text{H}_3$), 2.13 (3H, s, $\text{C}(2')\text{H}_3$); δ_{C} (100 MHz, $(\text{CD}_3)_2\text{O}$) 172.9 ($\underline{\text{C}}(1')\text{O}$), 168.0 ($\underline{\text{C}}(1)\text{O}$), 140.7 ($\underline{\text{C}}(5')$), 136.5 ($\underline{\text{C}}(3')$), 128.6 ($\underline{\text{C}}(4')\text{H}$), 126.5 ($\underline{\text{C}}(3')$), 21.1 ($\underline{\text{C}}(6')\text{H}_3$), 19.8 ($\underline{\text{C}}(7')\text{H}_3$), 19.6 ($\underline{\text{C}}(2')\text{H}_3$). Spectroscopic data were consistent with those reported in the literature.¹⁴⁶

Isopropyl 2,3-dihydroxy-3-phenylpropanoate (**243**)

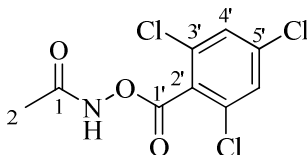


To a solution of potassium osmate (0.05 eq., 7.6 mg, $1.05 \cdot 10^{-3}$ mmol) in water (0.6 mL) was added compound **69** (1.0 eq., 78 mg, 0.41 mmol) and compound **242** (1.1 eq., 127 mg, 0.45 mmol) at rt. in a mixture of *t*-butanol (1.1 mL) and acetonitrile (1.1 mL). After the reaction mixture was stirred for 15 min, it was heated at 40 °C and stirred for 12 h. The reaction mixture was then concentrated onto silica *in vacuo* and purified by flash column chromatography (on a 0.5 mmol scale, 5 g of SiO_2 , elution with 50-60 mL of Ethyl acetate/Acetic acid 9.8:0.2 followed by 80 mL of Ethyl acetate/Methanol 9.5:0.5) to furnish the side product **243** (21 mg, 0.09 mmol, 22%) as a colourless solid.

δ_{H} (400 MHz, CDCl_3) 7.25-7.46 (5H, m, $\text{C}(5)\text{H}$, $\text{C}(6)\text{H}$, $\text{C}(7)\text{H}$), 5.09 (1H, m, $\text{C}(1')\text{H}$), 4.98-4.92 (1H, m, $\text{C}(3)\text{H}$), 4.35 (1H, d, J 3.1, $\text{C}(2)\text{H}$), 3.21 (1H, br s, OH), 2.80 (1H, br s, OH), 1.23-1.26 (6H, m, $\text{C}(2')\text{H}_3$); δ_{C} (100 MHz, CDCl_3) 172.5 ($\underline{\text{C}}(1)\text{O}$), 141.0 ($\underline{\text{C}}(4)$), 128.5 ($\underline{\text{C}}(6)\text{H}$), 128.2 ($\underline{\text{C}}(7)\text{H}$), 126.9 ($\underline{\text{C}}(5)\text{H}$), 75.27 ($\underline{\text{C}}(3)\text{H}$), 75.21 ($\underline{\text{C}}(2)\text{H}$), 70.5 ($\underline{\text{C}}(1')\text{H}$), 22.19 ($\underline{\text{C}}(2')\text{H}_{3a}$), 22.10 ($\underline{\text{C}}(2')\text{H}_{3b}$).

Spectroscopic data were consistent with those reported in the literature.¹⁴⁷

N-(2,4,6-Trichlorobenzoyloxy)acetamide (**247**)

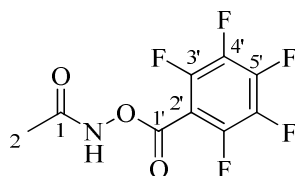


N-Hydroxyacetamide **240** (2.0 g, 27 mmol) was subjected to General Procedure B to furnish the title compound **247** (6.2 g, 22 mmol, 82%) as a colourless solid.

m.p. 153-155 °C; $\nu_{\max}$ (thin film)/cm⁻¹ 3230br m, 2971s, 1771m, 1660s, 1612w, 1464m, 1367w, 1240m, 1161w, 1033s, 964w, 732m; δ_{H} (400 MHz, CDCl₃) 9.41 (1H, br s, NH), 7.40 (2H, s, C(4')H₂), 2.16 (3H, s, C(2)H₃); δ_{C} (100 MHz, CDCl₃) 162.5 (C(1)O), 162.3 (C(1')O), 140.7 (C(5')), 133.6 (C(3')), 128.3 (C(4')H), 125.2 (C(2')), 19.9 (C(2)H₃); **m/z** (ESI⁻) 279, 281, 283 ([M-H]⁻, 100%); **HRMS** (ESI⁺) C₉H₆Cl₃NO₃ requires [M+Na]⁺ 303.9305, 305.9276, 307.9247, found 303.9309, 305.9281, 307.9247 (-1.2 ppm).

Single Crystal X-ray Diffraction Data for 247: C₉H₆Cl₃NO₃, M_r = 282.51, monoclinic (P 1 21/n 1), a = 3.93520(10) Å, b = 33.1639(6) Å, c = 8.3121(2) Å, α = 90 °C, β = 92.2252(8) °C, γ = 90 °C, V = 1083.97(4) Å³, Z = 4, μ = not measured D_{calc} = 1.731, T = 150(2) K, 12943 reflections collected, 2462 independent [R(int) = 0], R₁ = 0.0514, wR₂ = 0.0800 [I > 3σ(I)].

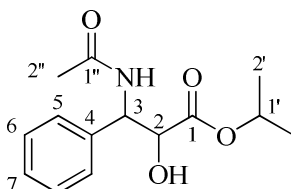
N-(Perfluorobenzoyloxy)acetamide (**248**)



N-Hydroxyacetamide **240** (1.6 g, 21.0 mmol) was subjected to General Procedure B to furnish the title compound **248** (2.7 g, 10.1 mmol, 48%) as a colourless oil.

$\nu_{\max}$ (thin film)/cm⁻¹ 3224br s, 2950s, 1763s, 1658s, 1609m, 1478m, 1224s, 1149s, 1038m, 1009m, 928w, 887m, 809w, 734w; δ_{H} (400 MHz, CDCl₃) 9.62 (1H, br s, NH), 2.14 (3H, s, C(2)H₃); δ_{C} (100 MHz, CDCl₃) 168.6 (C(1)O), 157.6 (C(1')O), 147.3 (C(3')F), 144.8 (C(5')F), 139.2 (C(4')F), 99.6 (C(2')), 19.4 (C(2)H₃); **m/z** (ESI⁺) 292 ([M+Na]⁺, 100%); **HRMS** (ESI⁺) C₉H₄F₅NO₃ requires [M+Na]⁺ 292.0004, found 292.0003 (+0.3 ppm).

Isopropyl 3-acetamido-2-hydroxy-3-phenylpropanoate (**70**)



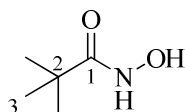
To a solution of potassium osmate (0.05 eq., 7.6 mg, 1.05·10⁻³ mmol) and lithium hydroxide monohydrate (1.1 eq., 19 mg, 0.45 mmol) in water (0.6 mL) was added acetamide (1.1 eq., 25 mg, 0.45 mmol). After the reaction mixture was stirred for 15 min, compound **69** (1.0 eq., 78 mg, 0.41 mmol) and compound **247** (1.1 eq., 127 mg, 0.45 mmol) were added at rt in a mixture of *t*-butanol (1.1 mL) and acetonitrile (1.1 mL). The reaction mixture was stirred for 12 h. Work-up and

purification were subjected to General Procedure C to furnish the title compound **70** (81 mg, 0.35 mmol, 86%, *rs* 9:1) as a colourless solid.

δ_{H} (400 MHz, CDCl_3) 7.02-7.62 (5H, m, C(5)H, C(6)H, C(7)H), 6.66 (1H, d, *J* 9.3, NH), 5.53 (1H, dd, *J* 9.3, 2.1, C(3)H), 4.89-5.21 (1H, m, C(1')H), 4.45 (1H, d, *J* 2.2, C(2)H), 1.94 (3H, s, C(2'')H), 1.26 (6H, m, C(2')H); δ_{C} (100 MHz, CDCl_3) 176.9 (C(1'')O), 172.3 (C(1)O), 139.0 (C(4)), 128.6 (C(6)H), 127.7 (C(7)H), 126.8 (C(5)H), 73.3 (C(2)H), 70.9 (C(1')H), 54.0 (C(3)H), 27.6 (br s, C(2')H).

Spectroscopic data were consistent with those reported in the literature.¹⁴⁸

***N*-Hydroxypivalamide (258)**

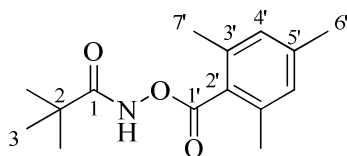


Pivalic acyl chloride (1.0 g, 8.3 mmol) was subjected to General Procedure A₁ to furnish the title compound **258** (900 mg, 7.7 mmol, 93%) as a white solid.

δ_{H} (400 MHz, $(\text{CD}_3)_2\text{O}$) 10.24 (1H, br s, OH), 8.72 (1H, br s, NH), 1.24 (9H, s, C(3)H); δ_{C} (100 MHz, $(\text{CD}_3)_2\text{O}$) 176.9 (C(1)O), 38.8 (C(2)), 27.2 (C(3)H).

Spectroscopic data were consistent with those reported in the literature.¹⁴⁹

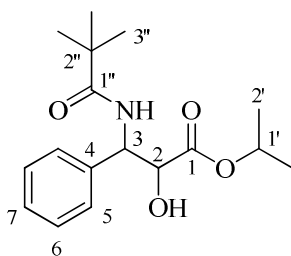
***N*-(2,4,6-Trimethylbenzoyloxy)pivalamide (259)**



Compound **258** (850 mg, 7.3 mmol) was subjected to General Procedure B to furnish the title compound **259** (1.53 g, 5.8 mmol, 89%) as a colourless solid.

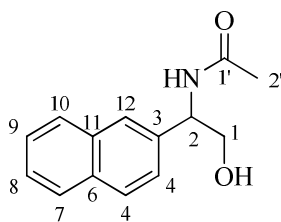
m.p. 140-141 °C; ν_{max} (thin film)/ cm^{-1} 3232br s, 2970s, 1776s, 1665s, 1612m, 1481br s, 1236s, 1156s, 1043s, 1016s, 944m, 847m, 813w, 734w; δ_{H} (400 MHz, CDCl_3) 9.44 (1H, s, NH), 6.86 (2H, s, C(4')H), 2.39 (6H, s, C(7')H), 2.28 (3H, s, C(6')H), 1.32 (9H, s, C(3)H); δ_{C} (100 MHz, CDCl_3) 177.1 (C(1)O), 168.5 (C(1')O), 140.8 (C(2')), 137.0 (C(3')), 128.8 (C(4')H), 126.9 (C(5')), 38.9 (C(2)), 27.5 (C(3)H), 21.4 (C(6')H), 20.2 (C(7')H); **m/z** (ESI⁺) 262 ([M-H]⁺, 100%); **HRMS** (ESI⁺) $\text{C}_{15}\text{H}_{21}\text{NO}_3$ requires [M+Na]⁺ 286.1414, found 286.1416 (-1.1 ppm).

Single Crystal X-ray Diffraction Data for 259: $\text{C}_{15}\text{H}_{21}\text{NO}_3$, $M_r = 263.34$, monoclinic (P -1), $a = 9.0141(2)$ Å, $b = 9.9620(2)$ Å, $c = 17.7080(3)$ Å, $\alpha = 74.1500(7)$ °C, $\beta = 83.7142(7)$ °C, $\gamma = 83.6747(7)$ °C, $V = 1515.13(5)$ Å³, $Z = 4$, μ = not measured $D_{\text{calc}} = 1.154$, $T = 150(2)$ K, 6892 reflections collected, 6887 independent [$R(\text{int}) = 0.026$], $R_1 = 0.0876$, $wR_2 = 0.1380$ [$I > 3\sigma(I)$].

Isopropyl 2-hydroxy-3-phenyl-3-pivalamidopropanoate (260)

To a solution of potassium osmate (0.05 eq., 7.6 mg, $1.05 \cdot 10^{-3}$ mmol) and lithium hydroxide monohydrate (1.1 eq., 19 mg, 0.45 mmol) in water (0.6 mL) was added acetamide (1.1 eq., 25 mg, 0.45 mmol). After the reaction mixture was stirred for 15 min, compound **69** (1.0 eq., 78 mg, 0.41 mmol) and compound **259** (1.1 eq., 127 mg, 0.45 mmol) were added at rt in a mixture of *t*-butanol (1.1 mL) and acetonitrile (1.1 mL). The reaction mixture was stirred for 12 h. Work-up and purification were subjected to General Procedure C to furnish the title compound **70** (70 mg, 0.23 mmol, 56%, *rs* 8:1) as a colourless oil.

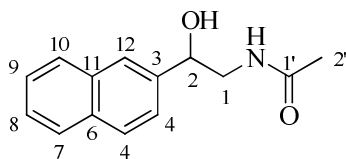
ν_{max} (thin film)/ cm^{-1} 3352br s, 2965s, 1737s, 1639s, 1513br s, 1361m, 1288s, 1207s, 1105s, 913w, 701m; δ_{H} (400 MHz, CDCl_3) 7.34 (4H, m, C(5)H, C(6)H), 7.28 (1H, m, C(7)H), 6.58 (1H, d, *J* 8.8, NH), 5.52 (1H, d, *J* 9.1, C(3')H), 4.99-5.15 (1H, m, C(1')H), 4.48 (1H, br s, C(2')H), 3.38 (1H, br s, OH), 1.29 (9H, s, C(3'')H), 1.20 (6H, s, C(2'')H); δ_{C} (100 MHz, CDCl_3) 177.5 (C(1'')O), 172.5 (C(1')O), 139.0 (C(4)), 128.6 (C(6)H), 127.6 (C(7)H), 126.7 (C(5)H), 73.3 (C(2')H), 70.8 (C(1')H), 53.8 (C(3')H), 38.8 (C(2'')H), 29.5 (C(3'')H₃), 27.5 (br s, C(2'')H₃); *m/z* (ESI⁺) 342 ([M+Cl]⁺, 100%); **HRMS** (ESI⁺) $\text{C}_{17}\text{H}_{25}\text{NO}_4$ requires [M+Na]⁺ 330.1676, found 330.1675 (+0.13 ppm).

Isopropyl 3-acetamido-2-hydroxy-3-(naphthalen-2-yl)propanoate (262)

To a solution of potassium osmate (0.05 eq., 7.6 mg, $1.05 \cdot 10^{-3}$ mmol) and lithium hydroxide monohydrate (1.1 eq., 19 mg, 0.45 mmol) in water (0.6 mL) was added acetamide (1.1 eq., 25 mg, 0.45 mmol). After the reaction mixture was stirred for 15 min, compound **34** (1.0 eq., 63 mg, 0.41 mmol) and compound **242** (1.1 eq., 127 mg, 0.45 mmol) were added at rt in a mixture of *t*-butanol (1.1 mL) and acetonitrile (1.1 mL). The reaction mixture was stirred for 12 h. Work-up and purification were subjected to General Procedure C to furnish the title compound **262** (69 mg, 0.30 mmol, 74%, *rs* 2:1) as a colourless solid.

Major Regioisomer δ_{H} (400 MHz, CDCl_3) 7.77-7.89 (3H, m, C(5)H, C(7)H, C(10)H), 7.73 (1H, s, C(12)H), 7.44-7.53 (2H, m, C(8)H, C(9)H), 7.38 (1H, d, *J* 8.3, C(4)H), 6.52 (1H, d, *J* 6.6, NH), 5.14-5.25 (1H, m, C(2')H), 3.94 (2H, m, C(1')H), 2.06 (3H, s, C(2'')H); δ_{C} (100 MHz, CDCl_3)

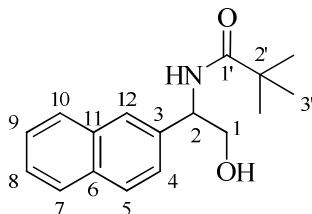
169.6 ($\underline{C}(1')\text{O}$), 136.3 ($\underline{C}(3)$), 133.3 ($\underline{C}(11)$), 132.9 ($\underline{C}(6)$), 128.8 ($\underline{C}(5)\text{H}$), 127.9 ($\underline{C}(7)\text{H}$), 127.7 ($\underline{C}(10)\text{H}$), 126.5 ($\underline{C}(12)\text{H}$), 126.2 ($\underline{C}(9)\text{H}$), 125.5 ($\underline{C}(4)\text{H}$), 124.7 ($\underline{C}(8)\text{H}$), 66.3 ($\underline{C}(2)\text{H}$), 56.0 ($\underline{C}(1)\text{H}_2$), 23.3 ($\underline{C}(2')\text{H}_3$).



Minor Regioisomer δ_{H} (400 MHz, CDCl_3) 7.76-7.85 (4H, m, $\underline{C}(5)\text{H}$, $\underline{C}(7)\text{H}$, $\underline{C}(10)\text{H}$, $\underline{C}(12)\text{H}$), 7.47 (2H, m, $\underline{C}(8)\text{H}$, $\underline{C}(9)\text{H}$), 7.43 (1H, d, J 8.6, $\underline{C}(4)\text{H}$), 6.21 (1H, br s, NH), 4.92-5.01 (1H, m, $\underline{C}(2)\text{H}$), 3.72 (1H, ddd, J 13.9, 6.4, 2.9, $\underline{C}(1)\text{H}_a$), 3.31-3.44 (1H, m, $\underline{C}(1)\text{H}_b$), 1.95 (3H, s, $\underline{C}(2')\text{H}_3$); δ_{C} (100 MHz, CDCl_3) 171.8 ($\underline{C}(1')\text{O}$), 139.1 ($\underline{C}(3)$), 133.2 ($\underline{C}(11)$), 133.0 ($\underline{C}(6)$), 128.3 ($\underline{C}(5)\text{H}$), 127.9 ($\underline{C}(7)\text{H}$), 127.6 ($\underline{C}(10)\text{H}$), 126.2 ($\underline{C}(12)\text{H}$), 126.0 ($\underline{C}(9)\text{H}$), 124.6 ($\underline{C}(4)\text{H}$), 123.7 ($\underline{C}(8)\text{H}$), 73.6 ($\underline{C}(2)\text{H}$), 47.5 ($\underline{C}(1)\text{H}_2$), 23.0 ($\underline{C}(2')\text{H}_3$).

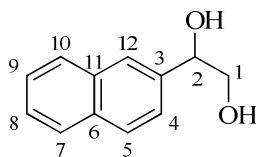
Spectroscopic data were consistent with those reported in the literature.¹⁴⁸

Isopropyl 2-hydroxy-3-(naphthalen-2-yl)-3-pivalamidopropanoate (263)



To a solution of potassium osmate (0.05 eq., 7.6 mg, $1.05 \cdot 10^{-3}$ mmol) and lithium hydroxide monohydrate (1.1 eq., 19 mg, 0.45 mmol) in water (0.6 mL) was added acetamide (1.1 eq., 25 mg, 0.45 mmol). After the reaction mixture was stirred for 15 min, compound **34** (1.0 eq., 63 mg, 0.41 mmol) and compound **259** (1.1 eq., 119 mg, 0.45 mmol) were added at rt in a mixture of *t*-butanol (1.1 mL) and acetonitrile (1.1 mL). The reaction mixture was stirred for 12 h. Work-up and purification were subjected to General Procedure C to furnish the title compound **263** (37 mg, 0.14 mmol, 33%, *rs* 3:1) as a colourless solid.

δ_{H} (400 MHz, CDCl_3) 7.76-7.89 (3H, m, $\underline{C}(5)\text{H}$, $\underline{C}(7)\text{H}$, $\underline{C}(10)\text{H}$), 7.72 (1H, s, $\underline{C}(12)\text{H}$), 7.42-7.55 (3H, m, $\underline{C}(4)\text{H}$, $\underline{C}(8)\text{H}$, $\underline{C}(9)\text{H}$), 6.51 (1H, d, J 6.1, NH), 5.18 (1H, m, $\underline{C}(2)\text{H}$), 3.87-4.02 (2H, m, $\underline{C}(1)\text{H}_2$), 1.30 (9H, s, $\underline{C}(3')\text{H}_3$); δ_{C} (100 MHz, CDCl_3) 179.1 ($\underline{C}(1')\text{O}$), 136.7 ($\underline{C}(3)$), 133.3 ($\underline{C}(11)$), 132.9 ($\underline{C}(6)$), 128.8 ($\underline{C}(5)\text{H}$), 127.8 ($\underline{C}(7)\text{H}$), 127.6 ($\underline{C}(10)\text{H}$), 126.3 ($\underline{C}(12)\text{H}$), 126.1 ($\underline{C}(9)\text{H}$), 125.3 ($\underline{C}(4)\text{H}$), 124.6 ($\underline{C}(8)\text{H}$), 66.5 ($\underline{C}(1)\text{H}_2$), 55.8 ($\underline{C}(2)\text{H}$), 38.8 ($\underline{C}(2')$), 29.6 ($\underline{C}(3')\text{H}_3$); m/z (ESI) 270 ($[\text{M}-\text{H}]^-$, 100%); **HRMS** (ESI) $\text{C}_{17}\text{H}_{21}\text{NO}_2$ requires $[\text{M}+\text{Na}]^+$ 294.1465, found 294.1463 (+0.45 ppm).

1-(Naphthalen-2-yl)ethane-1,2-diol

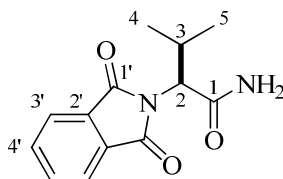
1-(Naphthalen-2-yl)ethane-1,2-diol was isolated as a side product in 24% yield during compound **263** synthesis.

δ_{H} (400 MHz, CDCl_3) 7.79-7.84 (4H, m, C(5)H, C(7)H, C(10)H, C(12)H), 7.42-7.52 (3H, m, C(4)H, C(8)H, C(9)H), 4.98-5.01 (1H, m, C(2)H), 3.75-3.91 (2H, m, C(1)H₂), 2.66 (1H, d, J 3.1, OH), 2.14 (1H, m, OH); δ_{C} (100 MHz, CDCl_3) 139.9 (C(3)), 133.4 (C(11)), 132.7 (C(6)), 128.8 (C(5)H), 127.7 (C(7)H), 127.6 (C(10)H), 126.2 (C(12)H), 126.1 (C(9)H), 125.4 (C(4)H), 124.5 (C(8)H), 73.7 (C(2)H), 67.3 (C(1)H₂).

Spectroscopic data were consistent with those reported in the literature.¹⁵⁰

5.3.3 Chapter 4 – Characterisation Data

(S)-2-(1,3-Dioxoisindolin-2-yl)-3-methylbutanamide (269)

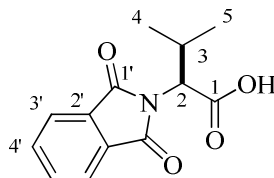


To a solution of phthalimide-protected L-valine **271** (1.0 eq., 1.0 g, 4.0 mmol) in dichloromethane (40 mL) under argon at 0 °C, was added three drops of *N,N'*-dimethylformamide followed by the dropwise addition of freshly distilled oxalyl chloride (2.0 eq., 1.0 g, 8.0 mmol). After completion of the addition, the reaction mixture was stirred for 1 h at rt. The reaction mixture was then concentrated *in vacuo* **at rt**, and redissolved under argon in diethyl ether (40 mL) affording a heterogeneous mixture. Aqueous ammonia (1.3 eq.) was added dropwise to the reaction mixture, and it was left to stir for 12 h. The reaction mixture was then extracted with ethyl acetate (2 x 60 mL). The organic phase was separated, washed with brine (60 mL), dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography, eluting with dichloromethane/methanol (100:0 to 9:1) to give the title compound **269** (768 mg, 3.1 mmol, 78%) as a white solid.

δ_{H} (400 MHz, CDCl₃) 7.88 (2H, dd, *J* 5.3, 3.1, C(3')H), 7.77 (2H, dd, *J* 5.4, 3.0, C(4')H), 6.92 (1H, br s, NH_a), 5.80 (1H, br s, NH_b), 4.41 (1H, d, *J* 11.3, C(2)H), 2.76-2.92 (1H, m, C(3)H), 1.14 (3H, d, *J* 6.6, C(4)H₃), 0.87 (3H, d, *J* 6.5, C(5)H₃); δ_{C} (100 MHz, CDCl₃) 171.1 (C(1)O), 168.4 (C(1')), 134.5 (C(4')H), 131.3 (C(2')), 123.7 (C(3')H), 62.9 (C(2)H), 27.6 (C(3)H), 19.7 (C(4)H₃), 19.4 (C(5)H₃).

Spectroscopic data were consistent with those reported in the literature.¹⁵¹

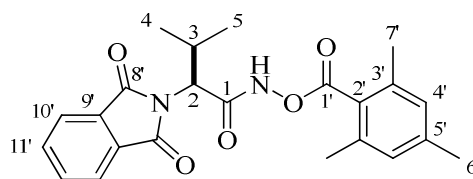
(S)-2-(1,3-Dioxoisindolin-2-yl)-3-methylbutanoic acid (271)



L-valine (3.0 g, 14.1 mmol) was subjected to General Procedure D to furnish the title compound **271** (3.2 g, 13.1 mmol, 93%) as a colourless solid.

δ_{H} (400 MHz, CD₃OD) 7.85 (2H, dd, *J* 5.8, 3.3, C(3')H), 7.81 (2H, dd, *J* 5.8, 3.3, C(4')H), 4.53 (1H, d, *J* 8.1, C(2)H), 2.62-2.75 (1H, m, C(3)H), 1.13 (3H, d, *J* 6.8, C(4)H₃), 0.88 (3H, d, *J* 6.8, C(5)H₃); δ_{C} (100 MHz, CD₃OD) 172.4 (C(1)O), 169.7 (C(1')O), 136.2 (C(4')H), 133.3 (C(2')), 124.9 (C(3')H), 59.1 (C(2)H), 30.1 (C(3)H), 22.1 (C(4)H₃), 20.4 (C(5)H₃).

Spectroscopic data were consistent with those reported in the literature.¹⁵²

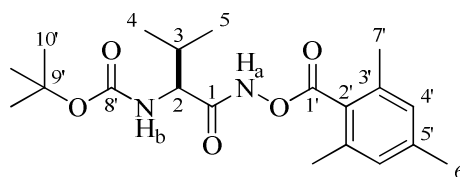
(S)-2-(1,3-Dioxoisindolin-2-yl)-3-methyl-N-(2,4,6-trimethylbenzoyloxy)butanamide (273)

Phthalimide-protected L-valine **271** (1.00 g, 4.06 mmol) was subjected to General Procedure E₁ to furnish the title compound **273** (1.13 g, 2.76 mmol, 68%) as a colourless solid (HPLC showed 94% ee).

Phthalimide-protected L-valine **271** (1.00 g, 4.06 mmol) was subjected to General Procedure E₂ to furnish the title compound **273** (1.11 g, 2.72 mmol, 67%) as a colourless solid (HPLC showed 95% ee).

Phthalimide-protected L-valine **271** (1.00 g, 4.06 mmol) was subjected to General Procedure G to furnish the title compound **273** (1.06 g, 2.60 mmol, 64%) as a colourless solid (HPLC showed 98% ee).

$[\alpha]_D^{25} - 15.1$ ($c = 0.6$, chloroform); **m.p.** 129-131 °C; $\nu_{\max}$ (thin film)/cm⁻¹ 3282br, 2968m, 1778br s, 1714br s, 1611m, 1580m, 1427br m, 1233m, 1157m, 1069br m, 948w, 887w, 732br m; δ_H (400 MHz, CDCl₃) 10.61 (1H, s, NH), 7.81 (2H, dd, J 5.4, 2.8, C(10')H), 7.69 (2H, dd, J 5.4, 2.8, C(11')H), 6.80 (2H, s, C(4')H), 4.58 (1H, d, J 11.4, C(2)H), 2.88-3.02 (1H, m, C(3)H), 2.32 (6H, s, C(7')H₃), 2.22 (3H, s, C(6')H₃), 1.19 (3H, d, J 6.6, C(4)H₃), 0.87 (3H, d, J 6.6, C(5)H₃); δ_C (100 MHz, CDCl₃) 168.2 (C(8')O), 167.3 (C(1')O), 166.1 (C(1)O), 140.4 (C(5')), 136.5 (C(9')), 134.4 (C(11')H), 130.9 (C(3')), 128.3 (C(4')H), 126.4 (C(2')), 123.6 (C(10')H), 60.7 (C(2)H), 27.5 (C(3)H), 20.9 (C(6')H₃), 19.7 (C(7')H₃), 19.5 (C(4)H₃), 19.2 (C(5)H₃); **m/z** (ESI⁺) 431 ([M+Na]⁺, 70%), 839 ([2M+Na]⁺, 100); **HRMS** (ESI⁺) C₂₃H₂₄N₂O₅ requires [M+Na]⁺ 431.1577, found 431.1578 (-2.37 ppm).

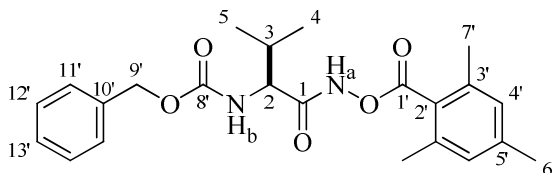
(S)-tert-butyl-3-methyl-1-oxo-1-(2,4,6-trimethylbenzoyloxyamino)butan-2-ylcarbamate (280)

Boc-protected-L-valine (1.07 g, 4.92 mmol) was subjected to General Procedure E₂ to furnish the title compound **280** (1.32 g, 3.49 mmol, 71%) as a white solid.

$[\alpha]_D^{25} - 32.3$ ($c = 0.6$, chloroform); **m.p.** 124-125 °C; $\nu_{\max}$ (thin film)/cm⁻¹ 3299br, 2975m, 1779m, 1674br s, 1520m, 1367m, 1297w, 1158m, 1016m, 993w; δ_H (400 MHz, CDCl₃) 11.07 (1H, br, NH_a), 6.79 (2H, s, C(4')H), 5.79 (1H, d, J 9.1, NH_b), 4.23 (1H, t, J 8.5, C(2)H), 2.31 (6H, s, C(7')H₃), 2.25 (3H, s, C(6')H₃), 2.10-2.22 (2H, m, C(3)H), 1.33-1.47 (9H, s, C(10')H₃), 1.08 (3H, d, J 6.6, C(4)H₃), 1.06 (3H, d, J 6.6, C(5)H₃); δ_C (100 MHz, CDCl₃) 169.2 (C(1')O), 167.0 (C(1)O),

156.2 ($\underline{C}(8')\text{O}$), 140.0 ($\underline{C}(5')$), 136.4 ($\underline{C}(3')$), 128.2 ($\underline{C}(4')\text{H}$), 127.0 ($\underline{C}(2')$), 80.0 ($\underline{C}(9')$), 57.6 ($\underline{C}(2)\text{H}$), 31.0 ($\underline{C}(3)\text{H}$), 28.2 ($\underline{C}(10')\text{H}_3$), 21.0 ($\underline{C}(6')\text{H}_3$), 19.6 ($\underline{C}(7')\text{H}_3$), 18.9 ($\underline{C}(4)\text{H}_3$), 18.3 ($\underline{C}(5)\text{H}_3$); m/z (ESI^-) 377 ($[\text{M}-\text{H}]^-$, 100%), 755 ($[\text{2M}-\text{H}]^-$, 40); **HRMS** (ESI^+) $\text{C}_{20}\text{H}_{30}\text{N}_2\text{O}_5$ requires $[\text{M}+\text{Na}]^+$ 401.2047, found 401.2047 (+2.6 ppm).

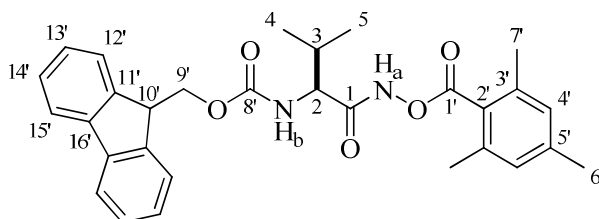
(S)-benzyl-3-methyl-1-oxo-1-(2,4,6-trimethylbenzoyloxyamino)butan-2-ylcarbamate (281)



Cbz-protected-L-valine (1.94 g, 7.74 mmol) was subjected to General Procedure E₂ to furnish the title compound **281** (2.04 g, 4.95 mmol, 64%) as a white solid.

$[\alpha]_{\text{D}}^{25}$ – 25.5 ($c = 1.6$, chloroform); **m.p.** 160–161 °C; ν_{max} (thin film)/ cm^{-1} 3290br, 3175br, 1776m, 1692br s, 1538m, 1289m, 1248m, 1232m, 1037m, 739w; δ_{H} (400 MHz, CDCl_3) 10.49 (1H, br, NH_a), 7.33 (5H, br s, $\underline{C}(11')\text{H}$, $\underline{C}(12')\text{H}$, $\underline{C}(13')\text{H}$), 6.85 (2H, s, $\underline{C}(4')\text{H}$), 5.69 (1H, d, J 8.8, NH_b), 5.14 (1H, d, J 11.9, $\underline{C}(9')\text{H}_a$), 5.06 (1H, d, J 11.9, $\underline{C}(9')\text{H}_b$), 4.23 (1H, t, J 7.8, $\underline{C}(2)\text{H}$), 2.35 (6H, s, $\underline{C}(7')\text{H}_3$), 2.29 (3H, s, $\underline{C}(6')\text{H}_3$), 2.13–2.27 (1H, m, $\underline{C}(3)\text{H}$), 1.08 (3H, d, J 6.6, $\underline{C}(4)\text{H}_3$), 1.05 (3H, d, J 6.6, $\underline{C}(5)\text{H}_3$); δ_{C} (100 MHz, CDCl_3) 169.1 ($\underline{C}(1')\text{O}$), 167.5 ($\underline{C}(2)\text{O}$), 156.8 ($\underline{C}(8')\text{O}$), 140.6 ($\underline{C}(5')$), 136.6 ($\underline{C}(3')$), 135.8 ($\underline{C}(13')\text{H}$), 128.9 ($\underline{C}(10')$), 128.5 ($\underline{C}(4')\text{H}$), 128.2 ($\underline{C}(12')\text{H}$), 128.0 ($\underline{C}(11')\text{H}$), 126.7 ($\underline{C}(2')$), 67.4 ($\underline{C}(9')\text{H}_2$), 58.2 ($\underline{C}(2)\text{H}$), 30.9 ($\underline{C}(3)\text{H}$), 21.2 ($\underline{C}(6')\text{H}_3$), 19.8 ($\underline{C}(7')\text{H}_3$), 19.1 ($\underline{C}(4)\text{H}_3$), 18.2 ($\underline{C}(5)\text{H}_3$); m/z (ESI^+) 435 ($[\text{M}+\text{Na}]^+$, 70%), 847 ($[\text{2M}+\text{Na}]^+$, 95); **HRMS** (ESI^+) $\text{C}_{23}\text{H}_{28}\text{N}_2\text{O}_5$ requires $[\text{M}+\text{Na}]^+$ 435.1890, found 435.1881 (+2.31 ppm).

(S)-(9H-fluoren-9-yl)methyl 3-methyl-1-oxo-1-(2,4,6-trimethylbenzoyloxyamino)butan-2-ylcarbamate (282)

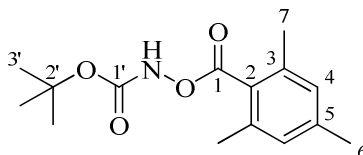


Fmoc-protected-L-valine (967 mg, 2.85 mmol) was subjected to General Procedure E₂ to furnish the title compound **282** (685 mg, 1.37 mmol, 44%) as a colourless solid.

$[\alpha]_{\text{D}}^{25}$ – 85.4 ($c = 0.4$, chloroform); **m.p.** 156–158 °C; ν_{max} (thin film)/ cm^{-1} 3286br, 3192br, 1778w, 1673br s, 1539w, 1449w, 1294w, 1082w, 1004w; δ_{H} (500 MHz, CDCl_3) 9.76 (1H, br, NH_a), 7.77 (2H, d, J 7.3, $\underline{C}(15')\text{H}$), 7.59 (2H, t, J 7.3, $\underline{C}(12')\text{H}$), 7.40 (2H, t, J 7.3, $\underline{C}(14')\text{H}$), 7.28–7.36 (2H, m, J 7.3, $\underline{C}(13')\text{H}$), 6.87 (2H, s, $\underline{C}(4')\text{H}$), 5.42 (1H, d, J 8.2, NH_b), 4.35–4.60 (2H, m, $\underline{C}(9')\text{H}_2$), 4.24 (1H, dd, J 6.6, 6.0, $\underline{C}(10')\text{H}$), 4.10 (1H, m, $\underline{C}(3)\text{H}$), 2.33–2.41 (6H, s, $\underline{C}(7')\text{H}_3$), 2.30 (3H, s, $\underline{C}(6')\text{H}_3$),

2.16-2.27 (1H, m, C(3)H), 1.06 (6H, m, C(4)H₃, C(5)H₃); δ_{C} (125 MHz, CDCl₃) 169.2 (C(1')O), 167.5 (C(1)O), 156.7 (C(8')O), 143.7 (C(11')), 141.3 (C(16')), 140.8 (C(5')), 136.7 (C(3')), 128.6 (C(4')H), 128.4 (C(2')), 127.8 (C(14')H), 127.1 (C(13')H), 125.0 (C(12')H), 120.0 (C(15')H), 67.4 (C(9')H₂), 58.3 (C(2)H), 47.1 (C(10')H), 30.4 (C(3)H), 21.2 (C(6')H₃), 20.0 (C(7')H₃), 19.2 (C(4)H₃), 18.1 (C(5)H₃); m/z (ESI⁺) 523 ([M+ Na]⁺, 100%); **HRMS** (ESI⁺) C₃₀H₃₂N₂O₅ requires [M+Na]⁺ 523.2227, found 523.2214 (+2.2 ppm).

***tert*-Butyl 2,4,6-trimethylbenzoyloxycarbamate (285)**



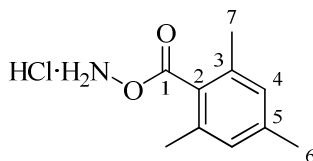
N-Boc hydroxylamine **284** (5.0 g, 37.5 mmol) was subjected to General Procedure B to furnish the title compound **285** (9.7 g, 34.6 mmol, 92%) as a colourless solid.

δ_{H} (400 MHz, CDCl₃) 8.09 (1H, s, NH), 6.89 (2H, s, C(4)H₂), 2.38 (6H, s, C(7)H₃), 2.30 (3H, s, C(6)H₃), 1.54 (9H, s, C(3')H₃); δ_{C} (100 MHz, CDCl₃) 169.3 (C(1)O), 155.6 (C(1')O), 140.8 (C(5)), 136.7 (C(3)), 128.7 (C(4)H₂), 126.7 (C(2)), 83.3 (C(2')), 28.1 (C(3')H₃), 21.4 (C(6)H₃), 20.0 (C(7)H₃).

Spectroscopic data were consistent with those reported in the literature.¹⁵³

Single Crystal X-ray Diffraction Data for 285: C₁₅H₂₁N₁O₄, M_r = 279.34, monoclinic (P 1 21/a 1), a = 10.06900(10) Å, b = 11.07300(10) Å, c = 27.8200(3) Å, α = 90 °C, β = 99.4877(5) °C, γ = 90 °C, V = 3059.34(5) Å³, Z = 8, μ = not measured D_{calc} = 1.213, T = 150(2) K, 13103 reflections collected, 4767 independent [$R(\text{int})$ = 0.022], R_1 = 0.0439, wR_2 = 0.0917 [$I > 3\sigma(I)$].

***O*-(2,4,6-Trimethylbenzoyl)hydroxylamine hydrochloride salt (286)**

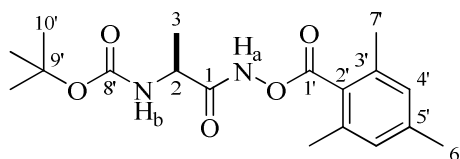


To compound **285** (3.0 g, 10.7 mmol) dissolved in dichloromethane (5 mL) was added dropwise at 0 °C at solution of 4 M HCl in dioxane (6 mL) and the reaction mixture was vigorously stirred until TLC indicated complete consumption of the starting material (typically 6 h). The solvent was removed under reduced pressure to give the title compound **286** (2.31 g, 10.7 mmol, 100%) as a white solid.

δ_{H} (400 MHz, CDCl₃) 8.49 (2H, br s, NH₂), 6.90 (2H, s, C(4)H), 2.31 (3H, s, C(6)H₃), 2.30 (6H, s, C(7)H₃); δ_{C} (100 MHz, CDCl₃) 169.7 (C(1)O), 141.3 (C(5)), 136.6 (C(3)), 128.9 (C(4)H₂), 124.3 (C(2)), 21.2 (C(6)H₃), 19.8 (C(7)H₃).

Spectroscopic data were consistent with those reported in the literature.¹⁴⁶

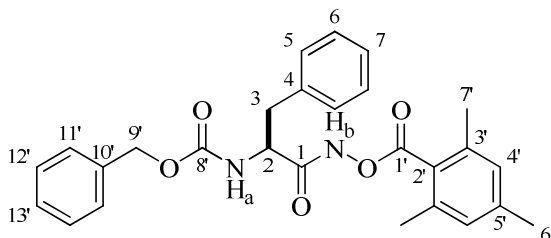
(S)-tert-Butyl 1-oxo-1-(2,4,6-trimethylbenzoyloxyamino)propan-2-ylcarbamate (291a)



Boc-protected-L-alanine (997 mg, 4.9 mmol) was subjected to General Procedure E₂ to furnish the title compound **291a** (1.05 g, 3.0 mmol, 61%) as a colourless oil.

$[\alpha]_D^{25}$ – 28.3 (c = 0.8, chloroform); $\nu_{\max}$ (thin film)/cm⁻¹ 3226br s, 2980s, 1777s, 1682br s, 1612m, 1517s, 1314m, 1234m, 1158m, 1095s, 981s, 912w, 852w, 733m; δ_H (400 MHz, CDCl₃) 10.53 (1H, br s, NH_a), 6.86 (2H, s, C(4')H), 5.36 (1H, d, J 6.8, NH_b), 4.43 (1H, br s, C(2)H), 2.33-2.42 (6H, s, C(7')H₃), 2.28 (3H, s, C(6')H₃), 1.47 (12H, br s, C(3)H₃, C(10')H₃); δ_C (100 MHz, CDCl₃) 170.6 (C(1')O), 167.6 (C(1)O), 156.1 (C(8')O), 140.5 (C(5')), 136.6 (C(3')), 128.5 (C(4')H), 126.7 (C(2')), 80.8 (C(9')), 47.4 (C(2)H), 28.3 (C(10')H₃), 21.1 (C(6')H₃), 19.8 (C(7')H₃), 17.4 (C(3)H₃); m/z (ESI⁺) 373 ([M+Na]⁺, 100%), 723 ([2M+Na]⁺, 40); **HRMS** (ESI⁺) C₁₈H₂₆N₂O₅ requires [M+Na]⁺ 373.1734, found 373.1740 (+1.2 ppm).

(S)-Benzyl 1-oxo-3-phenyl-1-(2,4,6-trimethylbenzoyloxyamino)propan-2-ylcarbamate (291b)

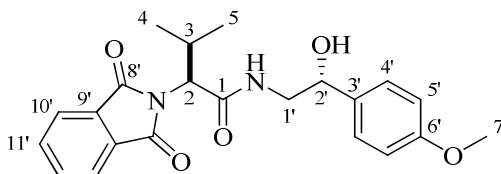


CBz-protected-L-phenylalanine (642 mg, 2.15 mmol) was subjected to General Procedure E₂ to furnish the title compound **291b** (653 mg, 1.42 mmol, 66%) as a white solid.

$[\alpha]_D^{25}$ – 4.7 (c = 3.3, chloroform); **m.p.** 132-133 °C; $\nu_{\max}$ (thin film)/cm⁻¹ 3299br w, 3194w, 1777m, 1674s, 1585m, 1454w, 1318w, 1262m, 1231w, 1157w, 1042m, 850w, 746m, 697m; δ_H (400 MHz, CDCl₃) 10.48 (1H, br s, NH_a), 7.14-7.43 (10H, m, C(5)H, C(6)H, C(7)H, C(11')H, C(12')H, C(13')H), 6.85 (2H, s, C(4')H), 5.83 (1H, d, J 8.3, NH_b), 4.96-5.17 (2H, m, C(9')H₂), 4.75 (1H, d, J 6.6, C(2)H), 3.26 (1H, dd, J 13.5, 7.0, C(3)H_a), 3.11 (1H, dd, J 13.5, 7.0, C(3)H_b), 2.34 (6H, s, C(7')H₃), 2.30 (3H, s, C(6')H₃); δ_C (100 MHz, CDCl₃) 168.8 (C(1')O), 167.3 (C(1)O), 156.5 (C(8')O), 140.5 (C(5')), 136.6 (C(3')), 135.9 (C(10')), 135.8 (C(4)), 129.3 (C(5)H), 128.6 (C(4')H), 128.44 (C(6)H), 128.41 (C(12')H), 128.1 (C(13')H), 127.9 (C(11')H), 127.0 (C(7)H), 126.6 (C(2')), 67.3 (C(9')H₂), 53.9 (C(2)H), 38.2 (C(3)H₂), 21.1 (C(6')H₃), 19.8 (C(7')H₃); m/z (ESI⁺) 483

$[\text{M}+\text{Na}]^+$, 100%); **HRMS** (ESI^+) $\text{C}_{27}\text{H}_{28}\text{N}_2\text{O}_5$ requires $[\text{M}+\text{Na}]^+$ 483.1891, found 483.1890 (+0.3 ppm).

(S)-2-(1,3-Dioxoisindolin-2-yl)-N-((R)-2-hydroxy-2-(4-methoxyphenyl)ethyl)-3-methylbutanamide (292)

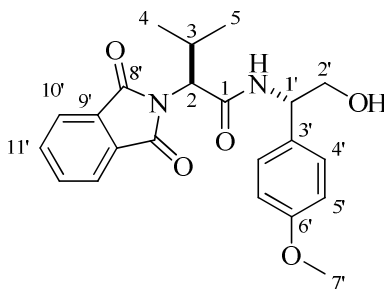


Compound **28** (31 mg, 0.23 mmol) and compound **273** (102 mg, 0.25 mmol) were subjected to General Procedure G to furnish the title compound **292** (81 mg, 0.21 mmol, 89%, *rs* 13:1, *dr* 15:1) as a colourless solid.

$[\alpha]_{\text{D}}^{25}$ – 23.7 ($c = 1.7$, chloroform); **m.p.** 110–112 °C; ν_{max} (thin film)/ cm^{-1} 3351br, 2961m, 1773m, 1708s, 1670m, 1590m, 1518s, 1459m, 1390s, 1241m, 1065m, 957w, 722m; δ_{H} (400 MHz, CDCl_3) 7.84 (2H, dd, J 5.6, 3.0, C(10') $\underline{\text{H}}$), 7.76 (2H, dd, J 5.6, 3.0, C(11') $\underline{\text{H}}$), 7.27 (1H, t, J 5.6, $\underline{\text{NH}}$), 7.22 (2H, d, J 8.6, C(4') $\underline{\text{H}}$), 6.74 (2H, d, J 8.6, C(5') $\underline{\text{H}}$), 4.75–4.85 (1H, m, C(2') $\underline{\text{H}}$), 4.39 (1H, d, J 11.4, C(2) $\underline{\text{H}}$), 3.71 (3H, s, C(7') $\underline{\text{H}}$), 3.64 (1H, ddd, J 13.8, 7.1, 4.3, C(1') $\underline{\text{H}}$), 3.41 (1H, ddd, J 13.8, 7.1, 4.3, C(1') $\underline{\text{H}}$), 3.35 (1H, d, J 3.5, $\underline{\text{OH}}$), 2.73–2.85 (1H, m, C(3) $\underline{\text{H}}$), 1.06 (3H, d, J 6.6, C(4) $\underline{\text{H}}$), 0.83 (3H, d, J 6.6, C(5) $\underline{\text{H}}$); δ_{C} (100 MHz, CDCl_3) 170.1 ($\underline{\text{C}}$ (1)O), 168.3 ($\underline{\text{C}}$ (8')O), 159.0 ($\underline{\text{C}}$ (6')), 134.4 ($\underline{\text{C}}$ (11')H), 133.7 ($\underline{\text{C}}$ (3')), 131.3 ($\underline{\text{C}}$ (9')), 126.9 ($\underline{\text{C}}$ (5')H), 123.6 ($\underline{\text{C}}$ (10')H), 113.7 ($\underline{\text{C}}$ (4')H), 72.9 ($\underline{\text{C}}$ (2')H), 62.8 ($\underline{\text{C}}$ (2)H), 55.1 ($\underline{\text{C}}$ (7') $\underline{\text{H}}$), 47.3 ($\underline{\text{C}}$ (1') $\underline{\text{H}}$), 27.5 ($\underline{\text{C}}$ (3)H), 19.8 ($\underline{\text{C}}$ (4) $\underline{\text{H}}$), 19.4 ($\underline{\text{C}}$ (5) $\underline{\text{H}}$); **m/z** (ESI^+) 419 ($[\text{M}+\text{Na}]^+$, 100%), 815 ($[2\text{M}+\text{Na}]^+$, 70); **HRMS** (ESI^+) $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_5$ requires $[\text{M}+\text{Na}]^+$ 419.1577, found 419.1576 (–0.7 ppm).

Single Crystal X-ray Diffraction Data for 292: $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_5$, $M_r = 396.43$, monoclinic ($R -3$), $a = 19.9255(6)$ Å, $b = 5.5134(2)$ Å, $c = 20.1945(7)$ Å, $\alpha = 90^\circ$, $\beta = 115.5269(16)^\circ$, $\gamma = 90^\circ$, $V = 2001.95(12)$ Å³, $Z = 4$, μ = not measured $D_{\text{calc}} = 1.315$, $T = 150(2)$ K, 3317 reflections collected, 3317 independent [$R(\text{int}) = 0$], $R_1 = 0.0374$, $wR_2 = 0.0855$ [$I > 3\sigma(I)$].

(S)-2-(1,3-Dioxoisindolin-2-yl)-N-((S)-2-hydroxy-1-(4-methoxyphenyl)ethyl)-3-methylbutanamide (293)

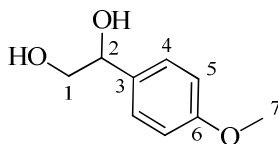


Compound **28** (31 mg, 0.23 mmol) and compound **273** (102 mg, 0.25 mmol) were subjected to General Procedure G to furnish the title compound **293** (8 mg, 0.02 mmol, 9%, *rs* 1:6.5, *dr* N/A) as a colourless solid.

$[\alpha]_D^{25} - 20.8$ ($c = 0.5$, chloroform); **m.p.** 159-161 °C; $\nu_{\max}$ (thin film)/ cm^{-1} 3349br, 2965m, 1777m, 1712s, 1663m, 1612w, 1585m, 1514s, 1467m, 1385s, 1248m, 1070m, 1034w, 721m; δ_{H} (400 MHz, CDCl_3) 7.87 (2H, dd, J 5.3, 3.1, C(10')H), 7.76 (2H, dd, J 5.3, 3.1, C(11')H), 7.65 (1H, d, J 7.0, NH), 7.20 (2H, d, J 8.5, C(4')H), 6.85 (2H, d, J 8.5, C(5')H), 4.86-5.14 (1H, m, C(1')H), 4.48 (1H, d, J 11.3, C(2')H), 3.86 (1H, t, J 5.8, C(2')H_a), 3.78 (3H, s, C(7')H₃), 2.78-3.02 (1H, m, C(3')H), 2.47 (1H, t, J 5.8, C(2')H_b), 1.16 (3H, d, J 6.6, C(4')H₃), 0.88 (3H, d, J 6.6, C(5')H₃); δ_{C} (100 MHz, CDCl_3) 169.2 (C(1)O), 168.6 (C(8')O), 159.2 (C(6')), 134.5 (C(11')H), 131.3 (C(9')), 130.7 (C(3')), 127.9 (C(4')H), 123.8 (C(10')H), 114.3 (C(5')H), 66.8 (C(7')H₃), 63.3 (C(2')H), 55.5 (C(1')H), 55.3 (C(7')H₃), 27.9 (C(3')H), 19.7 (C(4')H₃), 19.5 (C(5')H₃); **m/z** (ESI^+) 419 ($[\text{M}+\text{Na}]^+$, 100%), 815 ($[\text{2M}+\text{Na}]^+$, 80); **HRMS** (ESI^+) $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_5$ requires $[\text{M}+\text{Na}]^+$ 419.1577, found 419.1573 (+1.8 ppm).

Single Crystal X-ray Diffraction Data for 293: $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_5$, $M_r = 396.43$, orthorhombic ($R -3$), $a = 5.3136(1) \text{ \AA}$, $b = 19.4044(6) \text{ \AA}$, $c = 20.0409(6) \text{ \AA}$, $\alpha = 90^\circ$, $\beta = 90^\circ$, $\gamma = 90^\circ$, $V = 2066.36(10) \text{ \AA}^3$, $Z = 4$, $\mu =$ not measured $D_{\text{calc}} = 1.274$, $T = 150(2) \text{ K}$, 2878 reflections collected, 2878 independent [$R(\text{int}) = 0$], $R_1 = 0.0384$, $wR_2 = 0.0851$ [$I > 3\sigma(I)$].

1-(4-Methoxyphenyl)ethane-1,2-diol (294)

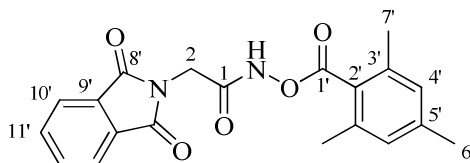


Compound **294** was isolated in % yield during the synthesis of **292** in the conditions stated in Chapter 4.

δ_{H} (400 MHz, CDCl_3) 7.31 (2H, d, J 8.3, C(5)H), 6.90 (2H, d, J 8.3, C(4)H), 4.73-4.75 (1H, m, C(2')H), 3.81 (3H, s, C(7')H₃), 3.62-3.74 (2H, m, C(1')H₂), 2.52 (1H, br s, OH), 2.23 (1H, br s, OH); δ_{C} (100 MHz, CDCl_3) 159.2 (C(6)), 132.5 (C(3)), 127.3 (C(4)H), 113.8 (C(5)H), 74.3 (C(2)H), 68.1 (C(7)H₃), 55.3 (C(1)H₂).

Spectroscopic data were consistent with those reported in the literature.¹⁵⁴

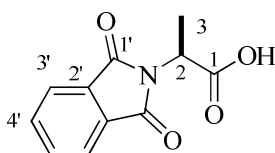
2-(1,3-Dioxoisindolin-2-yl)-N-(2,4,6-trimethylbenzoyloxy)acetamide (296a)



Commercially available phthalimide-protected glycine (1.25 g, 5.72 mmol) was subjected to General Procedure E₁ to furnish the title compound **296a** (1.52 g, 4.06 mmol, 71%) as a white solid.

m.p. 189-191 °C; ν_{max} (thin film)/cm⁻¹ 3238br, 2962m, 1775s, 1710br, 1616m, 1432m, 1285m, 1227m, 1151m, 1029w, 851s, 729w; δ_{H} (400 MHz, CDCl₃) 9.62 (1H, br s, NH), 7.91 (2H, dd, *J* 5.6, 3.0, C(10')H), 7.77 (2H, dd, *J* 5.6, 3.0, C(11')H), 6.88 (2H, s, C(4')H), 4.55 (2H, s, C(2)H), 2.37 (6H, s, C(7')H₃), 2.30 (3H, s, C(6')H₃); δ_{C} (100 MHz, CDCl₃) 169.8 (C(1')O), 167.6 (C(8')O), 164.9 (C(1)O), 141.1 (C(5')), 136.9 (C(3')), 134.4 (C(11')H), 131.9 (C(9')), 128.7 (C(4')H), 126.3 (C(2')), 123.8 (C(10')H), 38.8 (C(2)H₂), 21.2 (C(6')H₃), 20.1 (C(7')H₃); **m/z** (ESI⁺) 389 ([M+Na]⁺, 100%); **HRMS** (ESI⁺) C₂₀H₁₈N₂O₅ requires [M+Na]⁺ 389.1108, found 389.1110 (+0.8 ppm).

(S)-2-(1,3-Dioxoisindolin-2-yl)propanoic acid

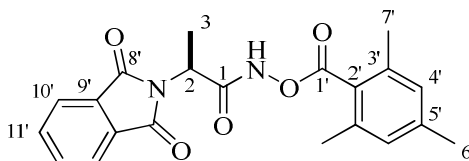


L-alanine (5.0 g, 56.1 mmol) was subjected to General Procedure D to furnish the title compound (11.6 g, 52.7 mmol, 94%) as a white solid.

δ_{H} (400 MHz, (CD₃)₂CO) 9.08-11.14 (1H, br s, OH), 7.82-7.92 (4H, m, C(3')H, C(4')H), 5.01 (1H, q, *J* 7.3, C(2)H), 1.70 (3H, d, *J* 7.3, C(3)H₃); δ_{C} (100 MHz, (CD₃)₂CO) 171.3 (C(1)O), 167.9 (C(1')O), 135.2 (C(4')H), 132.7 (C(2')), 123.9 (C(3')H), 47.8 (C(2)H), 15.3 (C(3)H₃).

Spectroscopic data were consistent with those reported in the literature.¹⁵⁵

(S)-2-(1,3-Dioxoisindolin-2-yl)-N-(2,4,6-trimethylbenzoyloxy)propanamide (296b)

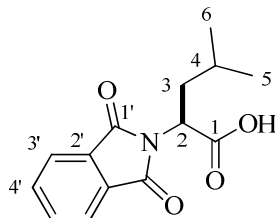


Phthalimide-protected L-alanine (1.25 g, 5.72 mmol) was subjected to General Procedure E₁ to furnish the title compound **296b** (1.52 g, 4.06 mmol, 71%) as a colourless solid.

$[\alpha]_{\text{D}}^{25} + 16.0$ (*c* = 0.1, chloroform); **m.p.** 148-149 °C; ν_{max} (thin film)/cm⁻¹ 3241br, 2965m, 2924m, 2558s, 1777s, 1715br, 1610m, 1436m, 1385s, 1294m, 1231m, 1157s, 1033m, 855s, 721m; δ_{H} (400 MHz, CDCl₃) 10.43 (1H, br s, NH), 7.81-7.93 (2H, m, C(10')H), 7.75 (2H, dd, *J* 5.3, 2.9, C(11')H), 6.86 (2H, s, C(4')H), 5.10-5.22 (1H, m, C(2)H), 2.40 (3H, s, C(6')H₃), 2.36 (6H, s, C(7')H₃), 1.83 (3H, d, *J* 5.3, C(3)H₃); δ_{C} (100 MHz, CDCl₃) 168.3 (C(1')O), 167.7 (C(8')O), 167.7 (C(1)O), 140.8 (C(5')), 136.8 (C(3')), 134.4 (C(11')H), 131.6 (C(9')), 128.6 (C(4')H), 126.2 (C(2')), 123.7 (C(10')H), 48.3 (C(2)H), 20.2 (C(6')H₃), 20.0 (C(7')H₃), 15.3 (C(3)H₃); **m/z** (ESI⁺) 403 ([M+Na]⁺,

96%), 783 ($[2M+Na]^+$, 94%); **HRMS** (ESI^+) $C_{21}H_{20}N_2O_5$ requires $[M+Na]^+$ 403.1264, found 403.1261 (+0.7 ppm).

(S)-2-(1,3-Dioxoisindolin-2-yl)-4-methylpentanoic acid

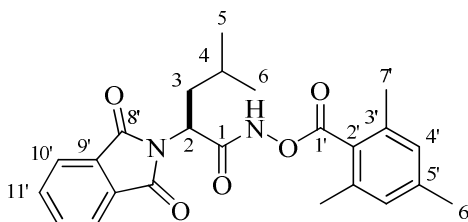


L-leucine (5.0 g, 38.1 mmol) was subjected to General Procedure D to furnish the title compound (9.2 g, 35.1 mmol, 92%) as a white solid.

δ_H (400 MHz, CD_3OD) 7.74-7.92 (4H, m, C(3')H, C(4')H), 4.85-4.94 (1H, m, C(2')H), 2.23-2.38 (1H, m, C(3')H_a), 1.86-1.98 (1H, m, C(3')H_b), 1.36-1.53 (1H, m, C(4')H), 0.83-0.98 (6H, m, C(5')H₃, C(6')H₃); δ_C (100 MHz, CD_3OD) 173.1 (C(1')O), 169.3 (C(1')O), 135.8 (C(4')H), 133.0 (C(2')), 124.5 (C(3')H), 51.8 (C(2')H), 38.4 (C(3')H₂), 26.4 (C(4')H), 23.7 (C(5')H₃), 21.5 (C(6')H₃).

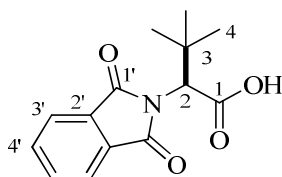
Spectroscopic data were consistent with those reported in the literature.¹⁵⁵

(S)-2-(1,3-Dioxoisindolin-2-yl)-4-methyl-N-(2,4,6-trimethylbenzoyloxy)pentanamide (296c)



Phthalimide-protected L-leucine (508 mg, 1.94 mmol) was subjected to General Procedure E₁ to furnish the title compound **296c** (582 mg, 1.38 mmol, 71%) as a colourless solid.

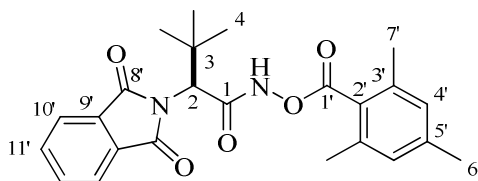
$[\alpha]_D^{25} + 12.9$ ($c = 0.1$, chloroform); **m.p.** 130-132 °C; ν_{max} (thin film)/ cm^{-1} 3264br, 2961m, 1777br s, 1714br s, 1611m, 1469s, 1384br s, 1233m, 1157m, 1040br m, 987w, 948w, 911w, 721m; δ_H (400 MHz, $CDCl_3$) 10.15 (1H, s, NH), 7.87 (2H, dd, J 5.1, 3.1, C(10')H), 7.75 (2H, dd, J 5.1, 3.1, C(11')H), 6.85 (2H, s, C(4')H), 5.13 (1H, dd, J 12.6, 5.3, C(2')H), 2.39-2.50 (1H, m, C(3')H_a), 2.35 (6H, s, C(7')H₃), 2.28 (3H, s, C(6')H₃), 1.99 (1H, ddd, J 12.6, 9.2, 5.3, C(3')H_b), 1.45-1.61 (1H, m, C(4')H), 0.96 (6H, dd, J 6.4, 1.9, C(5')H₃, C(6')H₃); δ_C (100 MHz, $CDCl_3$) 169.4 (C(1')O), 168.1 (C(8')O), 167.6 (C(1')O), 140.7 (C(5')), 136.8 (C(3')), 134.5 (C(11')H), 131.4 (C(9')), 128.5 (C(4')H), 126.3 (C(2')), 123.8 (C(10')H), 60.0 (C(2')H), 37.5 (C(3')H₂), 25.0 (C(4')H), 22.9 (C(5')H₃), 21.3 (C(6')H₃), 21.1 (C(6')H₃), 20.0 (C(7')H₃); **m/z** (ESI^+) 445 ($[M+Na]^+$, 80%), 867 ($[2M+Na]^+$, 80); **HRMS** (ESI^+) $C_{24}H_{26}N_2O_5$ requires $[M+Na]^+$ 445.1734, found 445.1735 (-2.26 ppm).

(S)-2-(1,3-Dioxoisindolin-2-yl)-3,3-dimethylbutanoic acid

L-*tert*-butylglycine (3.5 g, 26.7 mmol) was subjected to General Procedure D to furnish the title compound (6.8 g, 26.1 mmol, 98%) as a white solid.

δ_{H} (400 MHz, $(\text{CD}_3)_2\text{CO}$) 7.79-7.95 (4H, m, C(3')H, C(4')H), 4.63 (1H, s, C(2)H), 1.16 (9H, s, C(4)H₃); δ_{C} (100 MHz, $(\text{CD}_3)_2\text{CO}$) 169.2 (C(1')O), 168.6 (C(1')O), 135.4 (C(4')H), 132.5 (C(2')), 124.1 (C(3')H), 59.9 (C(2)H), 36.0 (C(3)), 28.2 (C(4)H₃).

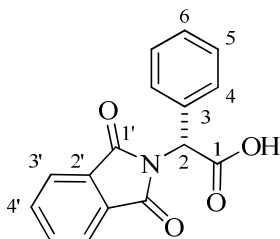
Spectroscopic data were consistent with those reported in the literature.¹⁵⁵

(S)-2-(1,3-Dioxoisindolin-2-yl)-3,3-dimethyl-N-(2,4,6-trimethylbenzoyloxy)butanamide (296d)

Phthalimide-protected L-*t*-butylglycine (1.73 g, 6.61 mmol) was subjected to General Procedure E₁ to furnish the title compound **296d** (2.01 g, 4.76 mmol, 72%) as a colourless solid.

$[\alpha]_{\text{D}}^{25} + 17.5$ ($c = 0.2$, chloroform); **m.p.** 151-153 °C; ν_{max} (thin film)/cm⁻¹ 3251br, 2965br, 2255w, 1776br s, 1713br s, 1611s, 1469s, 1381br, 1352br, 1233s, 1158s, 1084m, 990m, 910w, 772m; δ_{H} (400 MHz, CDCl_3) 11.08 (1H, s, NH), 7.75-7.84 (2H, m, C(10')H), 7.68 (2H, dd, J 4.5, 3.3, C(11')H), 6.79 (2H, s, C(4')H), 4.97 (1H, s, C(2)H), 2.33 (6H, s, C(7')H₃), 2.22 (3H, s, C(6')H₃), 1.18 (9H, s, C(4)H₃); δ_{C} (100 MHz, CDCl_3) 168.7 (C(1')O), 167.1 (C(8')O), 165.2 (C(1)O), 140.3 (C(5')), 136.4 (C(11')H), 134.5 (C(3')), 130.7 (C(9')), 128.3 (C(4')H), 126.4 (C(2')), 123.6 (C(10')H), 63.15 (C(2)H), 36.3 (C(3)), 27.7 (C(4)H₃), 20.9 (C(6')H₃), 19.7 (C(7')H₃); **m/z** (ESI) 421 ([M-H]⁻, 100%), 843 ([2M-H]⁻, 60); **HRMS** (ESI⁺) $\text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_5$ requires [M+Na]⁺ 445.1734, found 445.1742 (-1.94 ppm).

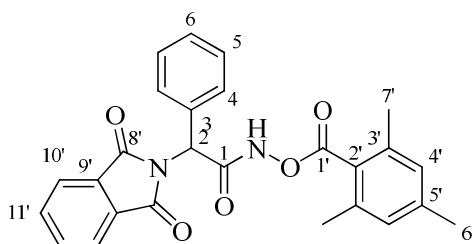
Single Crystal X-ray Diffraction Data for 296d: $\text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_5$, $M_r = 491.59$, orthorhombic (P 21 21), $a = 5.8398(2)$ Å, $b = 10.8763(3)$ Å, $c = 35.0638(12)$ Å, $\alpha = 90$ °C, $\beta = 90$ °C, $\gamma = 90$ °C, $V = 2227.09(12)$ Å³, $Z = 4$, μ = not measured $D_{\text{calc}} = 1.260$, $T = 150(2)$ K, 4956 reflections collected, 4956 independent [$R(\text{int}) = 0.000$], $R_1 = 0.0631$, $wR_2 = 0.0904$ [$I > 3\sigma(I)$].

(S)-2-(1,3-Dioxoisindolin-2-yl)-2-phenylacetic acid

D- α -phenylglycine (5.00 g, 33.1 mmol) was subjected to General Procedure D to furnish the title compound (8.3 g, 29.4 mmol, 89%) as a white solid.

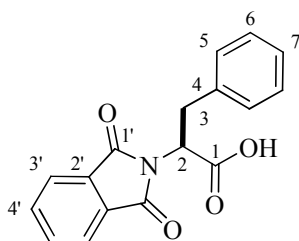
δ_{H} (400 MHz, $(\text{CD}_3)_2\text{CO}$) 7.82-7.94 (4H, m, C(3')H, C(4)H), 7.60 (2H, m, C(4')H), 7.30-7.40 (3H, m, C(5)H, C(6)H), 6.08 (1H, s, C(2)H); δ_{C} (100 MHz, $(\text{CD}_3)_2\text{CO}$) 169.7 (C(1)O), 168.2 (C(1')O), 136.5 (C(3)), 135.8 (C(4')H), 123.9 (C(2')), 130.9 (C(5)H), 129.33 (C(4)H), 129.27 (C(6)H), 124.5 (C(3')H), 56.6 (C(2)H).

Spectroscopic data were consistent with those reported in the literature.¹⁵⁵

($\pm$)-(R)-2-(1,3-Dioxoisindolin-2-yl)-2-phenyl-*N*-(2,4,6-trimethylbenzoyloxy)acetamide (296e)

Phthalimide-protected D- α -phenylglycine (440 mg, 1.57 mmol) was subjected to General Procedure E₁ to furnish the title compound **296e** (367 mg, 0.83 mmol, 53%) as a white solid.

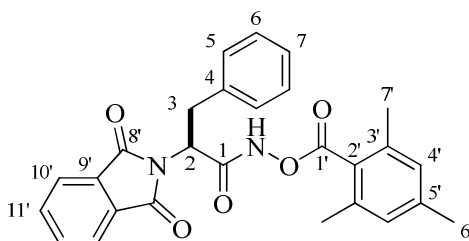
$[\alpha]_{\text{D}}^{25}$ has epimerised;¹⁵⁶ **m.p.** 158-160 °C; ν_{max} (thin film)/ cm^{-1} 3285br, 2922w, 1772s, 1717s, 1611w, 1468m, 1383s, 1231m, 1157w, 1109w, 1048w, 721m; δ_{H} (400 MHz, CDCl_3) 9.58 (1H, br s, NH), 7.78-7.93 (2H, m, C(10')H), 7.64-7.78 (4H, m, C(4)H, C(11')H), 7.33-7.47 (3H, m, C(5)H, C(6)H), 6.86 (2H, s, C(4')H), 6.17 (1H, s, C(2)H), 2.37 (6H, s, C(7')H₃), 2.28 (3H, s, C(6')H₃); δ_{C} (100 MHz, CDCl_3) 167.8 (C(1')O), 167.4 (C(8')O), 165.2 (C(1)O), 140.8 (C(5')), 136.8 (C(11')H), 134.3 (C(3')), 133.3 (C(3)), 131.5 (C(9')), 129.5 (C(4)H), 129.4 (C(6)H), 129.3 (C(4')H), 128.5 (C(5)H), 126.1 (C(2')), 123.7 (C(10')H), 56.4 (C(2)H), 21.1 (C(6')H₃), 19.9 (C(7')H₃); **m/z** (ESI) 441 ($[\text{M}-\text{H}]^-$, 100%); **HRMS** (ESI) $\text{C}_{26}\text{H}_{22}\text{N}_2\text{O}_5$ requires $[\text{M}-\text{H}]^-$ 441.1456, found 441.1456 (-0.18 ppm).

(S)-2-(1,3-Dioxoisindolin-2-yl)-3-phenylpropanoic acid

L-phenylglycine (3.5 g, 21.1 mmol) was subjected to General Procedure D to furnish the title compound (5.6 g, 19.1 mmol, 90%) as a white solid.

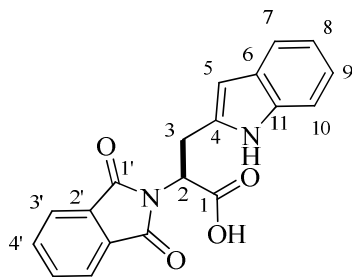
δ_{H} (400 MHz, $(\text{CD}_3)_2\text{CO}$) 7.79 (4H, s, C(3')H, C(5)H), 6.94-7.38 (5H, m, C(4')H, C(6)H, C(7)H), 5.25 (1H, m, C(2)H), 3.44-3.70 (2H, m, C(3)H₂); δ_{C} (100 MHz, $(\text{CD}_3)_2\text{CO}$) 174.5 (C(1')O), 167.5 (C(1')O), 136.0 (C(4')H), 134.1 (C(2')), 131.5 (C(5)H), 128.8 (C(3')H), 128.6 (C(6)H), 127.0 (C(7)H), 124.1 (C(3')H), 53.0 (C(2)H), 34.4 (C(3)H₂).

Spectroscopic data were consistent with those reported in the literature.¹⁵⁷

(S)-2-(1,3-Dioxoisindolin-2-yl)-3-phenyl-*N*-(2,4,6-trimethylbenzoyloxy)propanamide (296f)

Phthalimide-protected L-phenylalanine (696 mg, 2.34 mmol) was subjected to General Procedure X to furnish the title compound **296f** (652 mg, 1.43 mmol, 61%) as a white solid.

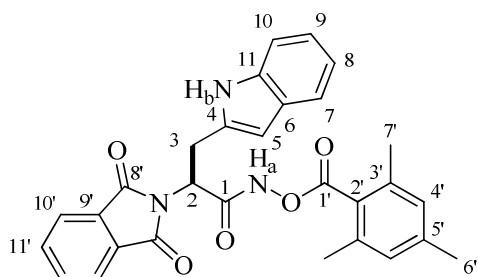
$[\alpha]_{\text{D}}^{25}$ – 69.1 ($c = 0.1$, chloroform); **m.p.** 210-212 °C; ν_{max} (thin film)/ cm^{-1} 3201br, 2975w, 1779s, 1717s, 1670s, 1496w, 1377s, 1355w, 1171w, 717m; δ_{H} (400 MHz, CDCl_3) 10.14 (1H, br s, NH), 7.74-7.82 (2H, m, C(10')H), 7.69 (2H, dd, J 4.9, 2.9, C(11')H), 7.08-7.24 (5H, m, C(5)H, C(6)H, C(7)H), 6.87 (2H, s, C(4')H), 5.32 (1H, dd, J 10.9, 6.1, C(2)H), 3.54-3.74 (2H, m, C(3)H₂), 2.37 (6H, s, C(7')H₃), 2.29 (3H, s, C(6')H₃); δ_{C} (100 MHz, CDCl_3) 167.9 (C(8')O), 167.6 (C(1')O), 166.8 (C(1')O), 140.9 (C(5')), 136.9 (C(3')), 135.8 (C(4)), 134.4 (C(11')H), 131.1 (C(9')), 128.9 (C(5)H), 128.7 (C(6)H), 128.6 (C(4')H), 127.1 (C(7)H), 126.2 (C(2')), 123.7 (C(10')H), 54.7 (C(2)H), 34.8 (C(3)H₂), 21.2 (C(6')H₃), 20.0 (C(7')H₃); **m/z** (ESI^+) 479 ($[\text{M}+\text{Na}]^+$, 90%), 935 ($[\text{2M}+\text{Na}]^+$, 100); **HRMS** (ESI^+) $\text{C}_{27}\text{H}_{24}\text{N}_2\text{O}_5$ requires $[\text{M}+\text{Na}]^+$ 479.1577, found 479.1578 (–0.24 ppm).

(S)-2-(1,3-Dioxoisindolin-2-yl)-3-(1H-indol-2-yl)propanoic acid

L-tryptophan (5.1 g, 25.1 mmol) was subjected to General Procedure D to furnish the title compound (8.1 g, 24.3 mmol, 97%) as a beige solid.

δ_{H} (400 MHz, $(\text{CD}_3)_2\text{SO}$) 13.37 (1H, br s, OH), 10.77 (1H, br s, NH), 7.75-7.83 (9H, m, $\text{C}(4)\text{H}_3$), 7.52 (1H, d, J 8.0, $\text{C}(4)\text{H}_3$), 7.28 (1H, d, J 8.0, $\text{C}(4)\text{H}_3$), 7.07 (1H, d, J 2.0, $\text{C}(4)\text{H}_3$), 6.98 (1H, t, J 8.1, $\text{C}(4)\text{H}_3$), 6.94 (1H, t, J 8.1, $\text{C}(4)\text{H}_3$), 5.15 (1H, m, $\text{C}(4)\text{H}_3$), 3.56-3.59 (2H, m, $\text{C}(4)\text{H}_3$); δ_{C} (100 MHz, $(\text{CD}_3)_2\text{SO}$) 171.0 ($\text{C}(1)\text{O}$), 168.6 ($\text{C}(1')\text{O}$), 136.4 ($\text{C}(11)$), 135.5 ($\text{C}(4)$), 134.0 ($\text{C}(4')\text{H}$), 127.1 ($\text{C}(2')$), 123.5 ($\text{C}(6)$), 123.4 ($\text{C}(3')\text{H}$), 121.1 ($\text{C}(9)\text{H}$), 119.6 ($\text{C}(8)\text{H}$), 118.0 ($\text{C}(7)\text{H}$), 111.4 ($\text{C}(10)\text{H}$), 109.6 ($\text{C}(5)\text{H}$), 52.7 ($\text{C}(2)\text{H}$), 24.2 ($\text{C}(3)\text{H}_2$).

Spectroscopic data were consistent with those reported in the literature.¹⁵⁸

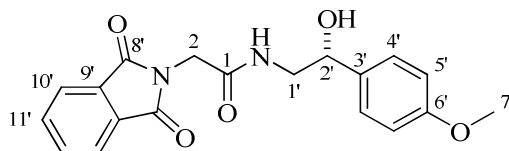
(S)-2-(1,3-Dioxoisindolin-2-yl)-3-(1H-indol-2-yl)-N-(2,4,6-trimethylbenzoyloxy)propanamide (296g)

Phthalimide-protected L-tryptophan (1.0 g, 3.0 mmol) was subjected to General Procedure E₁ to furnish the title compound **296g** (1.2 g, 2.4 mmol, 79%) as a yellowish solid.

$[\alpha]_{\text{D}}^{25}$ - 22.9 (c = 0.9, chloroform); **m.p.** 167-169 °C; ν_{max} (thin film)/ cm^{-1} 2959w, 1775m, 1715s, 1517m, 1383s, 1233m, 1158m, 1087w, 1056w, 877w, 718m; δ_{H} (400 MHz, CDCl_3) 10.17 (1H, br s, NH_a), 8.16 (1H, br s, NH_b), 7.77 (2H, dd, J 5.4, 3.1, $\text{C}(10')\text{H}$), 7.66 (2H, dd, J 5.4, 3.1, $\text{C}(11')\text{H}$), 7.63 (1H, m, $\text{C}(9)\text{H}$), 7.27 (1H, d, J 8.1, $\text{C}(10)\text{H}$), 7.10-7.17 (1H, m, $\text{C}(8)\text{H}$), 7.08 (1H, d, J 2.3, $\text{C}(7)\text{H}$), 6.89 (1H, s, $\text{C}(5)\text{H}$), 6.86 (2H, s, $\text{C}(4')\text{H}$), 5.45 (1H, dd, J 9.1, 7.1, $\text{C}(2)\text{H}$), 3.73-3.90 (2H, m, $\text{C}(3)\text{H}_2$), 2.35 (6H, s, $\text{C}(7')\text{H}_3$), 2.29 (3H, s, $\text{C}(6')\text{H}_3$); δ_{C} (100 MHz, CDCl_3) 169.9 ($\text{C}(1')\text{O}$), 168.0 ($\text{C}(8')\text{O}$), 167.5 ($\text{C}(1)\text{O}$), 140.8 ($\text{C}(5')$), 136.8 ($\text{C}(3')$), 136.2 ($\text{C}(11)$), 135.6 ($\text{C}(4)$), 134.3 ($\text{C}(11')\text{H}$), 131.4 ($\text{C}(9')$), 128.6 ($\text{C}(4')\text{H}$), 128.4 ($\text{C}(6)$), 123.6 ($\text{C}(10')\text{H}$), 123.1 ($\text{C}(2')$), 122.3 ($\text{C}(9)\text{H}$), 119.7 ($\text{C}(8)\text{H}$), 118.4 ($\text{C}(7)\text{H}$), 111.2 ($\text{C}(10)\text{H}$), 110.0 ($\text{C}(5)\text{H}$), 53.7 ($\text{C}(2)\text{H}$), 25.4

($\underline{\text{C}}(3)\text{H}_2$), 21.2 ($\underline{\text{C}}(6')\text{H}_3$), 20.0 ($\underline{\text{C}}(7')\text{H}_3$); **m/z** (ESI⁻) 494 ([M-H]⁻, 100%); **HRMS** (ESI⁺) $\text{C}_{29}\text{H}_{25}\text{N}_3\text{O}_5$ requires [M+Na]⁺ 518.1686 found 518.1684 (+0.1 ppm).

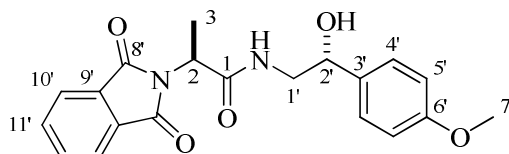
(R)-2-(1,3-Dioxoisindolin-2-yl)-N-(2-hydroxy-2-(4-methoxyphenyl)ethyl)acetamide (297a)



Compound **28** (31 mg, 0.23 mmol) and compound **296a** (92 mg, 0.25 mmol) were subjected to General Procedure G to furnish the title compound **297a** (59 mg, 0.17 mmol, 72%, *rs* 5:1) as a colourless solid.

$[\alpha]_{\text{D}}^{25} - 34.8$ ($c = 0.8$, acetone); **m.p.** 198-202 °C; ν_{max} (thin film)/cm⁻¹ 3330br, 2923w, 1804w, 1773br s, 1650s, 1539w, 1511m, 1417m, 1245m, 1114w, 1029m, 953w, 735m; δ_{H} (200 MHz, (CD₃)₂CO) 7.89 (4H, m, C(10')H, C(11')H), 7.59 (1H, br s, NH), 7.30 (2H, d, *J* 8.7, C(4')H), 6.87 (2H, d, *J* 8.7, C(5')H), 4.72 (1H, dt, *J* 7.9, 4.1, C(2')H), 4.57 (1H, d, *J* 3.9, OH), 4.36 (2H, s, C(2)H), 3.77 (3H, s, C(7')H), 3.38-3.58 (1H, m, C(1')H_a), 3.15-3.37 (1H, m, C(1')H_b); δ_{C} (100 MHz, (CD₃)₂CO) 170.4 ($\underline{\text{C}}(1)\text{O}$), 167.9 ($\underline{\text{C}}(8')\text{O}$), 155.5 ($\underline{\text{C}}(6')$), 136.7 ($\underline{\text{C}}(3')$), 135.7 ($\underline{\text{C}}(11')\text{H}$), 133.8 ($\underline{\text{C}}(9')$), 128.5 ($\underline{\text{C}}(4')\text{H}$), 124.4 ($\underline{\text{C}}(10')\text{H}$), 114.8 ($\underline{\text{C}}(5')\text{H}$), 73.3 ($\underline{\text{C}}(2')\text{H}$), 55.9 ($\underline{\text{C}}(7')\text{H}_3$), 48.9 ($\underline{\text{C}}(1')\text{H}_2$), 41.5 ($\underline{\text{C}}(2)\text{H}_2$); **m/z** (ESI⁻) 353 ([M-H]⁻, 100%); **HRMS** (ESI⁺) $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_5$ requires [M+Na]⁺ 377.1108, found 377.1109 (-0.4 ppm).

(S)-2-(1,3-Dioxoisindolin-2-yl)-N-((R)-2-hydroxy-2-(4-methoxyphenyl)ethyl)propanamide (297b)

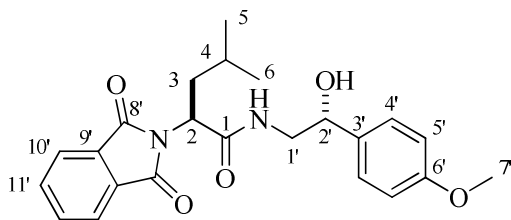


Compound **28** (31 mg, 0.23 mmol) and compound **296b** (95 mg, 0.25 mmol) were subjected to General Procedure G to furnish the title compound **297b** (68 mg, 0.18 mmol, 79%, *rs* 14:1, *dr* 6:1) as a colourless gum.

$[\alpha]_{\text{D}}^{25} - 40.4$ ($c = 0.8$, chloroform); ν_{max} (thin film)/cm⁻¹ 3384br, 1777w, 1712s, 1663br m, 1612m, 1538m, 1513s, 1387br s, 1247s, 1174m, 1031m, 832w; δ_{H} (400 MHz, CDCl₃) 7.89 (2H, dd, *J* 5.5, 2.9, C(10')H), 7.78 (2H, dd, *J* 5.5, 2.9, C(11')H), 7.27-7.33 (2H, m, C(5')H), 6.86 (2H, d, *J* 8.6, C(4')H), 6.52 (1H, t, *J* 5.3, NH), 4.91-5.00 (1H, m, C(2)H), 4.85 (1H, dd, *J* 8.1, 3.3, C(2')H), 3.81 (3H, s, C(7')H), 3.73 (1H, ddd, *J* 13.9, 7.6, 3.3, C(1')H_a), 3.35 (1H, ddd, *J* 13.9, 7.6, 3.3, C(1')H_b), 3.15 (1H, br s, OH), 1.72 (3H, d, *J* 7.3, C(3)H); δ_{C} (100 MHz, CDCl₃) 169.9 ($\underline{\text{C}}(1)\text{O}$), 167.8

($\underline{C}(8')\text{O}$), 159.2 ($\underline{C}(6')$), 134.3 ($\underline{C}(11')\text{H}$), 133.6 ($\underline{C}(3')$), 131.8 ($\underline{C}(9')$), 127.0 ($\underline{C}(4')\text{H}$), 123.6 ($\underline{C}(10')\text{H}$), 113.9 ($\underline{C}(5')\text{H}$), 72.5 ($\underline{C}(2')\text{H}$), 55.2 ($\underline{C}(7')\text{H}_3$), 49.3 ($\underline{C}(2)\text{H}$), 47.4 ($\underline{C}(1')\text{H}_2$), 15.2 ($\underline{C}(3)\text{H}_3$); m/z (ESI^+) 391 ($[\text{M}+\text{Na}]^+$, 100%), 759 ($[\text{2M}+\text{Na}]^+$, 96); **HRMS** (ESI^+) $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_5$ requires $[\text{M}+\text{Na}]^+$ 391.1264, found 391.1259 (+2.2 ppm).

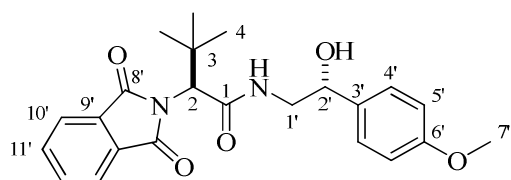
(S)-2-(1,3-Dioxoisindolin-2-yl)-N-((R)-2-hydroxy-2-(4-methoxyphenyl)ethyl)-4-methylpentanamide (297c)



Compound **28** (31 mg, 0.23 mmol) and compound **296c** (106 mg, 0.25 mmol) were subjected to General Procedure G to furnish the title compound **297c** (77 mg, 0.19 mmol, 81%, *rs* 12:1, *dr* 4:1) as a colourless oil.

$[\alpha]_{\text{D}}^{25}$ – 20.6 ($c = 0.3$, chloroform); ν_{max} (thin film)/ cm^{-1} 3360br, 2959s, 1773s, 1713br s, 1682s, 1612m, 1513w, 1386s, 1248m, 1174w, 1073m, 912w, 722s; δ_{H} (400 MHz, CDCl_3) 7.87 (2H, dd, J 5.4, 3.1, $\underline{C}(10')\text{H}$), 7.76 (2H, dd, J 5.4, 3.1, $\underline{C}(11')\text{H}$), 7.21–7.30 (2H, m, $\underline{C}(5')\text{H}$), 6.82 (2H, d, J 8.6, $\underline{C}(4')\text{H}$), 6.57 (1H, br s, NH), 4.92 (1H, dd, J 11.4, 5.1, $\underline{C}(2)\text{H}$), 4.81 (1H, dd, J 8.1, 3.3, $\underline{C}(2')\text{H}$), 3.76 (3H, br s, $\underline{C}(7')\text{H}_3$), 3.62–3.73 (1H, m, $\underline{C}(1')\text{H}_a$), 3.25–3.39 (1H, m, $\underline{C}(1')\text{H}_b$), 2.27–2.39 (1H, m, $\underline{C}(3)\text{H}_a$), 1.76–1.92 (1H, m, $\underline{C}(3)\text{H}_b$), 1.38–1.53 (1H, m, $\underline{C}(4)\text{H}$), 1.20–1.36 (1H, m, OH), 0.82–1.00 (6H, m, $\underline{C}(5)\text{H}_3$, $\underline{C}(6)\text{H}_3$); δ_{C} (125 MHz, CDCl_3) 170.3 ($\underline{C}(1)\text{O}$), 168.2 ($\underline{C}(8')\text{O}$), 159.2 ($\underline{C}(6')$), 134.3 ($\underline{C}(11')\text{H}$), 133.6 ($\underline{C}(3')$), 131.6 ($\underline{C}(9')$), 127.0 ($\underline{C}(5')\text{H}$), 123.6 ($\underline{C}(10')\text{H}$), 113.9 ($\underline{C}(4')\text{H}$), 72.8 ($\underline{C}(2')\text{H}$), 55.2 ($\underline{C}(7')\text{H}_3$), 53.1 ($\underline{C}(2)\text{H}$), 47.5 ($\underline{C}(1')\text{H}_2$), 37.5 ($\underline{C}(3)\text{H}_2$), 25.2 ($\underline{C}(4)\text{H}$), 23.1 ($\underline{C}(5)\text{H}_3$), 21.3 ($\underline{C}(6)\text{H}_3$); m/z (ESI^+) 433 ($[\text{M}+\text{Na}]^+$, 55%), 843 ($[\text{2M}+\text{Na}]^+$, 90); **HRMS** (ESI^+) $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_5$ requires $[\text{M}+\text{Na}]^+$ 433.1734, found 433.1727 (+1.71 ppm).

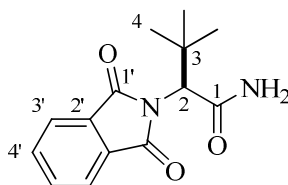
(S)-2-(1,3-dioxoisindolin-2-yl)-N-((R)-2-hydroxy-2-(4-methoxyphenyl)ethyl)-3,3-dimethylbutanamide (297d)



Compound **28** (31 mg, 0.23 mmol) and compound **296d** (106 mg, 0.25 mmol) were subjected to General Procedure G to furnish the title compound **297d** (62 mg, 0.15 mmol, 64%, *rs* 9:1, *dr* 10:1) as a colourless solid.

$[\alpha]_D^{25} - 8.9$ ($c = 1.0$ chloroform); **m.p.** 151-153 °C; $\nu_{\max}$ (thin film)/ cm^{-1} 3382br, 1773m, 1711br s, 1512m, 1382m, 1247m, 1085w, 719m; δ_{H} (400 MHz, CDCl_3) 7.88 (2H, dd, J 5.3, 3.1, C(10')H), 7.79 (2H, dd, J 5.3, 3.1, C(11')H), 7.70 (1H, br s, NH), 7.25 (2H, d, J 8.6, C(5')H), 6.77 (2H, d, J 8.6, C(4')H), 4.79-4.86 (2H, m, C(2)H, C(2')H), 3.72 (3H, s, C(7')H₃), 3.57-3.66 (1H, m, C(1')H_a), 3.43-3.53 (1H, m, C(1')H_b), 3.32 (1H, d, J 3.9, OH), 1.13 (9H, s, C(4)H₃); δ_{C} (100 MHz, CDCl_3) 169.5 (C(8')O), 169.0 (C(1)O), 159.0 (C(6')), 134.5 (C(11')H), 133.8 (C(3')), 131.2 (C(9')), 126.9 (C(5')H), 123.8 (C(10')H), 113.7 (C(4')H), 73.5 (C(2')H), 65.2 (C(2)H), 55.2 (C(7')H₃), 47.7 (C(1')H₂), 36.1 (C(3)), 28.3 (C(4)H₃); **m/z** (ESI⁺) 409 ([M-H]⁺, 100%); **HRMS** (ESI) $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_5$ requires [M-H]⁺ 409.1769, found 409.1769 (-0.44 ppm).

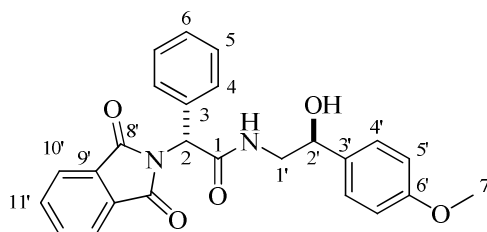
(S)-2-(1,3-Dioxoisindolin-2-yl)-3,3-dimethylbutanamide



(S)-2-(1,3-Dioxoisindolin-2-yl)-3,3-dimethylbutanamide was obtained in 8% yield during the synthesis of **297d**.

$[\alpha]_D^{25} + 13.9$ ($c = 0.8$, chloroform); **m.p.** 196-201 °C; $\nu_{\max}$ (thin film)/ cm^{-1} 3336br w, 1797w, 1714s, 1665m, 1382m, 1350w, 1329w, 1101w, 1086w, 897w, 722m; δ_{H} (400 MHz, CDCl_3) 7.90 (2H, dd, J 5.3, 3.1, C(3')H), 7.78 (2H, dd, J 5.3, 3.2, C(4')H), 7.11-7.48 (1H, br s, NH_a), 5.66 (1H, br s, NH_b), 4.84 (1H, s, C(2)H), 1.17 (9H, s, C(4)H₃); δ_{C} (100 MHz, CDCl_3) 170.1 (C(1)O), 169.0 (C(1')), 134.6 (C(4')H), 131.2 (C(2')), 123.8 (C(3')H), 65.2 (C(2)H), 36.0 (C(3)), 28.3 (C(4)H₃); **m/z** (ESI) 259 ([M-H]⁺, 100%); **HRMS** (ESI⁺) $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_3$ requires [M+Na]⁺ 283.1053 found 283.1055 (+0.8 ppm).

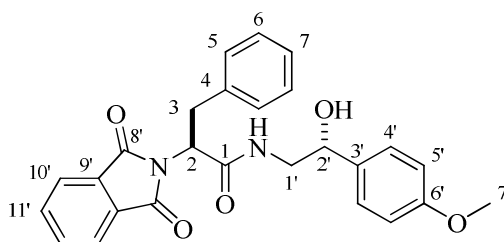
(±)-(R)-2-(1,3-dioxoisindolin-2-yl)-N-((S)-2-hydroxy-2-(4-methoxyphenyl)ethyl)-2-phenylacetamide (297e)



Compound **28** (31 mg, 0.23 mmol) and compound **296e** (111 mg, 0.25 mmol) were subjected to General Procedure G (without ligand) to furnish the title compound **297e** (56 mg, 0.13 mmol, 56%, *rs* 8:1, *dr* 2:1) as a colourless oil.

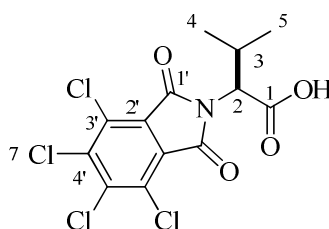
$[\alpha]_D^{23}$ racemised; $\nu_{\max}$ (thin film)/ cm^{-1} 3470br, 1771m, 1716s, 1684s, 1612m, 1513m, 1425br s, 1247m, 1201w, 1176w, 1114w, 1074w, 911w, 721s; δ_{H} (400 MHz, CDCl_3) 7.81-7.89 (2H, m, C(10')H), 7.68-7.76 (2H, C(11')H), 7.64 (1H, d, J 7.1, NH), 7.53 (2H, d, J 5.3, C(4')H), 7.32-7.44 (3H, m, C(5')H, C(6')H), 7.21-7.29 (2H, m, C(4')H), 6.80-6.89 (2H, m, C(5')H), 6.10-6.22 (1H, m, OH), 5.91 (1H, d, J 11.6, C(2')H), 4.90 (1H, dd, J 7.6, 4.3, C(2')H), 3.72-3.85 (3H, m, C(7')H₃), 3.39-3.59 (1H, m, C(1')H_a), 3.16 (1H, ddd, J 13.6, 8.1, 4.8, C(1')H_b); δ_{C} (100 MHz, CDCl_3) 169.3 (C(1)O), 167.8 (C(8')O), 159.1 (C(6')), 134.5 (C(3')), 134.2 (C(11')H), 131.7 (C(9')), 129.6 (C(6)H), 129.3 (C(4')H), 129.20 (C(4)H), 129.15 (C(5)H), 127.1 (C(3')), 123.6 (C(10')H), 113.8 (C(5')H), 71.8 (C(2')H), 57.9 (C(2)H), 55.2 (C(7')H₃), 47.9 (C(1')H₂); m/z (ESI^+) 453 ($[\text{M}+\text{Na}]^+$, 55%), 883 ($[\text{2M}+\text{Na}]^+$, 90); **HRMS** (ESI^+) $\text{C}_{25}\text{H}_{22}\text{N}_2\text{O}_5$ requires $[\text{M}+\text{Na}]^+$ 453.1421, found 453.1414 (+1.56 ppm).

(S)-2-(1,3-Dioxoisindolin-2-yl)-N-((R)-2-hydroxy-2-(4-methoxyphenyl)ethyl)-3-phenylpropanamide (297f)



Compound **28** (31 mg, 0.23 mmol) and compound **296f** (114 mg, 0.25 mmol) were subjected to General Procedure G to furnish the title compound **297f** (71 mg, 0.16 mmol, 68%, *rs* 8:1, *dr* 6:1) as a colourless solid.

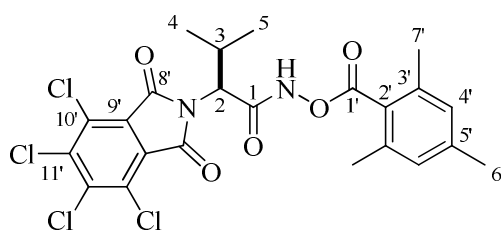
$[\alpha]_D^{25}$ – 55.3 (c = 1.0, chloroform); **m.p.** 121-123 °C; $\nu_{\max}$ (thin film)/ cm^{-1} 3383br, 1775w, 1714s, 1661br m, 1612w, 1538br m, 1513m, 1384s, 1248s, 1072w, 953w, 720m; δ_{H} (400 MHz, CDCl_3) 7.78 (2H, dd, J 5.4, 3.2, C(10')H), 7.71 (2H, dd, J 5.4, 3.2, C(11')H), 7.25 (2H, d, J 8.5, C(5')H), 7.05-7.22 (5H, m, C(5')H, C(6')H, C(7')H), 6.82 (2H, d, J 8.5, C(4')H), 6.50 (1H, br s, NH), 5.11 (1H, dd, J 10.2, 6.3, C(2')H), 4.73-4.83 (1H, m, C(2')H), 3.73-3.81 (3H, m, C(7')H₃), 3.68 (1H, ddd, J 13.8, 7.4, 3.8, C(1')H_a), 3.44-3.63 (2H, m, C(3')H), 3.66 (1H, ddd, J 13.8, 7.4, 3.8, C(1')H_b), 2.77 (1H, d, J 3.8, OH); δ_{C} (100 MHz, CDCl_3) 169.3 (C(1)O), 167.9 (C(8')O), 159.3 (C(6')), 136.5 (C(4)), 134.3 (C(11')H), 133.5 (C(3')), 131.4 (C(9')), 128.9 (C(5)H), 128.7 (C(6)H), 127.0 (br, C(4')H, C(7)H), 123.5 (C(10')H), 113.9 (C(5')H), 72.7 (C(2')H), 55.8 (C(2)H), 55.2 (C(7')H₃), 47.4 (C(1')H₂), 34.8 (C(3)H₂); m/z (ESI^+) 467 ($[\text{M}+\text{Na}]^+$, 60%), 911 ($[\text{2M}+\text{Na}]^+$, 100); **HRMS** (ESI^+) $\text{C}_{26}\text{H}_{24}\text{N}_2\text{O}_5$ requires $[\text{M}+\text{Na}]^+$ 467.1577, found 467.1566 (+2.34 ppm).

(S)-3-Methyl-2-(4,5,6,7-tetrachloro-1,3-dioxoisindolin-2-yl)butanoic acid

L-valine (4.4 g, 37.5 mmol) was subjected to General Procedure D to furnish the title compound (4.61 g, 11.9 mmol, 32%) as a colourless solid.

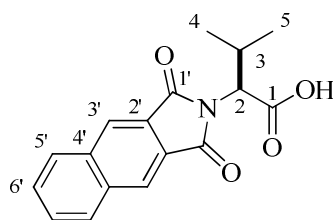
δ_{H} (400 MHz, $(\text{CD}_3)_2\text{CO}$) 4.64 (1H, d, J 8.0, C(2) $\underline{\text{H}}$), 2.72-2.74 (1H, m, C(2) $\underline{\text{H}}_3$), 1.24 (3H, d, J 6.9, C(4) $\underline{\text{H}}_3$), 0.99 (3H, d, J 6.9, C(4) $\underline{\text{H}}_3$); δ_{C} (100 MHz, $(\text{CD}_3)_2\text{CO}$) 169.5 ($\underline{\text{C}}(1)\text{O}$), 163.9 ($\underline{\text{C}}(1')\text{O}$), 140.2 ($\underline{\text{C}}(4')$), 130.1 ($\underline{\text{C}}(2')$), 128.9 ($\underline{\text{C}}(3')$), 58.9 ($\underline{\text{C}}(2)\text{H}$), 28.8 ($\underline{\text{C}}(3)\text{H}$), 21.2 ($\underline{\text{C}}(4)\text{H}_3$), 19.6 ($\underline{\text{C}}(5)\text{H}_3$).

Spectroscopic data were consistent with those reported in the literature¹⁵⁹

(S)-3-Methyl-2-(4,5,6,7-tetrachloro-1,3-dioxoisindolin-2-yl)-N-(2,4,6-trimethylbenzoyloxy)butanamide (298a)

(S)-3-Methyl-2-(4,5,6,7-tetrachloro-1,3-dioxoisindolin-2-yl)butanoic acid (1.3 g, 3.25 mmol) was subjected to General Procedure E₁ to furnish the title compound **298a** (1.61 g, 2.96 mmol, 91%) as a yellow gum.

$[\alpha]_{\text{D}}^{25} - 94.3$ ($c = 1.2$, chloroform); ν_{max} (thin film)/ cm^{-1} 3285br w, 2968w, 1780m, 1724s, 1611w, 1470w, 1386m, 1372m, 1346m, 1330w, 1299w, 1231w, 1043m, 989w, 738m; δ_{H} (400 MHz, CDCl_3) 10.02 (1H, br s, $\underline{\text{NH}}$), 6.85 (2H, s, C(4') $\underline{\text{H}}$), 4.55 (1H, d, J 11.4, C(2) $\underline{\text{H}}$), 2.74-3.19 (1H, m, C(3) $\underline{\text{H}}$), 2.35 (6H, s, C(7') $\underline{\text{H}}_3$), 2.29 (3H, s, C(6') $\underline{\text{H}}_3$), 1.22 (3H, d, J 6.5, C(4) $\underline{\text{H}}_3$), 0.91 (3H, d, J 6.5, C(5) $\underline{\text{H}}_3$); δ_{C} (100 MHz, CDCl_3) 165.7 ($\underline{\text{C}}(1')\text{O}$), 164.0 ($\underline{\text{C}}(1)\text{O}$), 163.6 ($\underline{\text{C}}(8')\text{O}$), 140.9 ($\underline{\text{C}}(5')$), 140.8 ($\underline{\text{C}}(11')$), 136.8 ($\underline{\text{C}}(3')$), 130.2 ($\underline{\text{C}}(9')$), 128.6 ($\underline{\text{C}}(4')\text{H}$), 126.8 ($\underline{\text{C}}(10')$), 126.2 ($\underline{\text{C}}(2')$), 61.3 ($\underline{\text{C}}(2)\text{H}$), 27.3 ($\underline{\text{C}}(3)\text{H}$), 21.2 ($\underline{\text{C}}(6')\text{H}_3$), 20.0 ($\underline{\text{C}}(7')\text{H}_3$), 19.7 ($\underline{\text{C}}(4)\text{H}_3$), 19.4 ($\underline{\text{C}}(5)\text{H}_3$); m/z (ESI^+) 567, 569 ($[\text{M}+\text{Na}]^+$, 100%); **HRMS** (ESI^+) $\text{C}_{23}\text{H}_{20}\text{Cl}_4\text{N}_2\text{O}_5$ requires $[\text{M}+\text{Na}]^+$ 567.0019, 568.0052, 568.9992, 570.0023, 570.9961, 571.9993 (six peaks) found 567.0018, 568.0069, 568.9982, 570.0021, 570.9971, 571.9988 (-0.1 ppm).

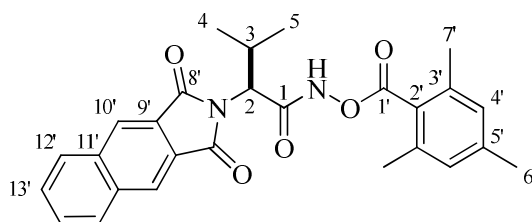
(S)-2-(1,3-Dioxo-1H-benzo[f]isoindol-2(3H)-yl)-3-methylbutanoic acid

L-valine (1.5 g, 12.8 mmol) was subjected to General Procedure D to furnish the title compound (2.7 g, 9.2 mmol, 72%) as a colourless solid.

δ_{H} (400 MHz, CDCl_3) 8.38 (2H, s, C(3')H), 8.08 (2H, dd, J 6.1, 3.3, C(5')H), 7.70-7.75 (2H, dd, J 6.1, 3.3, C(6')H), 4.71 (2H, d, J 8.5, C(2)H), 2.77-2.79 (1H, m, C(3)H), 1.19 (3H, d, J 6.8, C(4)H₃), 0.93 (3H, d, J 6.8, C(5)H₃); δ_{C} (100 MHz, CDCl_3) 173.74 (C(1)O), 167.4 (C(1')O), 135.4 (C(4')), 130.2 (C(6')H), 129.3 (C(5')H), 127.1 (C(2')), 125.2 (C(3')H), 57.8 (C(2)H), 28.5 (C(3)H), 21.4 (C(4)H₃), 20.0 (C(5)H₃).

Spectroscopic data were consistent with those reported in the literature.¹⁶⁰

Single Crystal X-ray Diffraction Data for (S)-2-(1,3-dioxo-1H-benzo[f]isoindol-2(3H)-yl)-3-methylbutanoic acid: $\text{C}_{17}\text{H}_{15}\text{N}_1\text{O}_4$, $M_r = 297.31$, monoclinic (P 1 21/c 1), $a = 11.4597(2)$ Å, $b = 6.0083(2)$ Å, $c = 11.6452(3)$ Å, $\alpha = 90$ °C, $\beta = 117.2212(11)$ °C, $\gamma = 90$ °C, $V = 713.01(3)$ Å³, $Z = 2$, $\mu =$ not measured $D_{\text{calc}} = 1.385$, $T = 150(2)$ K, 13103 reflections collected, 3138 independent [$R(\text{int}) = 0$], $R_1 = 0.0425$, $wR_2 = 0.0748$ [$I > 3\sigma(I)$].

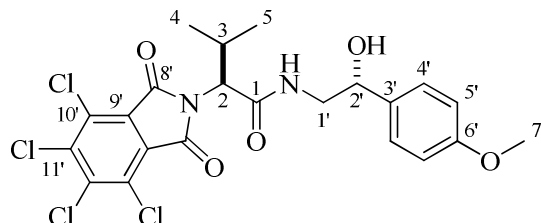
(S)-3-Methyl-2-(4,5,6,7-tetrachloro-1,3-dioxoisindolin-2-yl)-N-(2,4,6-trimethylbenzoyloxy)butanamide (298b)

(S)-2-(1,3-Dioxo-1H-benzo[f]isoindol-2(3H)-yl)-3-methylbutanoic acid (1.0 g, 3.4 mmol) was subjected to General Procedure E₁ to furnish the title compound **298b** (1.1 g, 2.3 mmol, 68%) as a colourless gum.

$[\alpha]_{\text{D}}^{25} + 16.4$ ($c = 3.9$, chloroform); ν_{max} (thin film)/cm⁻¹ 3266 br w, 2967br s, 1769s, 1714s, 1637w, 1424m, 1372m, 1233m, 1158m, 1100m, 1046m, 989w, 851w, 766m; δ_{H} (400 MHz, CDCl_3) 10.74 (1H, br s, NH), 8.32 (2H, s, C(10')H), 7.99 (2H, dd, J 6.1, 3.3, C(12')H), 7.68 (2H, dd, J 6.2, 3.2, C(13')H), 6.83 (2H, s, C(4')H), 4.70 (1H, d, J 11.6, C(2)H), 2.92-3.09 (1H, m, C(3)H), 2.38 (6H, s, C(7')H₃), 2.26 (3H, s, C(6')H₃), 1.25 (3H, d, J 6.6, C(4)H₃), 0.92 (3H, d, J 6.3, C(5)H₃); δ_{C} (100 MHz, CDCl_3) 168.1 (C(8')O), 167.6 (C(1')O), 166.3 (C(1)O), 140.6 (C(5')), 136.7 (C(3')), 135.4 (C(11')), 130.3 (C(13')H), 129.5 (C(12')H), 128.5 (C(4')H), 126.5 (C(2')), 126.5 (C(9')), 125.5

($\underline{C}(10')\text{H}$), 61.3 ($\underline{C}(2)\text{H}$), 27.8 ($\underline{C}(3)\text{H}$), 21.1 ($\underline{C}(6')\text{H}_3$), 19.9 ($\underline{C}(7')\text{H}_3$), 19.7 ($\underline{C}(4)\text{H}_3$), 19.3 ($\underline{C}(5)\text{H}_3$); m/z (ESI $^-$) 457 ($[\text{M}-\text{H}]^-$, 100%); **HRMS** (ESI $^+$) $\text{C}_{27}\text{H}_{26}\text{N}_2\text{O}_5$ requires $[\text{M}+\text{Na}]^+$ 457.1769 found 457.1770 (-0.17 ppm).

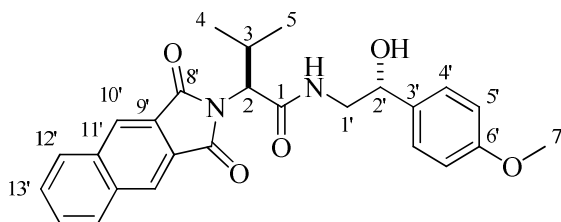
(S)-N-((R)-2-Hydroxy-2-(4-methoxyphenyl)ethyl)-3-methyl-2-(4,5,6,7-tetrachloro-1,3-dioxoisindolin-2-yl)butanamide (299a)



Compound **28** (31 mg, 0.23 mmol) and compound **298a** (137 mg, 0.25 mmol) were subjected to General Procedure G to furnish the title compound **299a** (77 mg, 0.14 mmol, 63%, *rs* 8:1, *dr* 2.6:1) as a yellow solid.

$[\alpha]_D^{25}$ - 13.5 ($c = 0.7$, chloroform); **m.p.** 90-91 °C; ν_{max} (thin film)/ cm^{-1} 3373br s, 2966w, 1778w, 1720s, 1663m, 1584m, 1539s, 1513s, 1464s, 1388s, 1248s, 1200m, 1175m, 1091m, 1034m, 910m, 832w, 738s; δ_{H} (400 MHz, CDCl_3) 7.14-7.22 (2H, m, $\underline{C}(4')\text{H}$), 6.91-6.98 (1H, m, $\underline{NH}$), 6.65-6.75 (2H, m, $\underline{C}(5')\text{H}$), 4.81 (1H, dd, J 6.6, 3.3, $\underline{C}(2')\text{H}$), 4.34 (1H, d, J 11.1, $\underline{C}(2)\text{H}$), 3.69 (4H, m, $\underline{C}(1')\text{H}_a$, $\underline{C}(7')\text{H}_3$), 3.62-3.74 (1H, m, $\underline{C}(1')\text{H}_b$), 3.34-3.48 (1H, m, $\underline{OH}$), 2.79 (1H, m, $\underline{C}(3)\text{H}$), 1.07 (3H, d, J 6.3, $\underline{C}(4)\text{H}_3$), 0.83 (3H, d, J 6.3, $\underline{C}(5)\text{H}_3$); δ_{C} (100 MHz, CDCl_3) 169.3 ($\underline{C}(1)\text{O}$), 163.5 ($\underline{C}(8')\text{O}$), 158.9 ($\underline{C}(6')$), 140.6 ($\underline{C}(11')$), 133.4 ($\underline{C}(3')$), 129.9 ($\underline{C}(9')$), 127.0 ($\underline{C}(10')$), 126.8 ($\underline{C}(4')\text{H}$), 113.6 ($\underline{C}(5')\text{H}$), 72.7 ($\underline{C}(2')\text{H}$), 63.2 ($\underline{C}(2)\text{H}$), 55.2 ($\underline{C}(7')\text{H}_3$), 47.2 ($\underline{C}(1')\text{H}_2$), 27.1 ($\underline{C}(3)\text{H}$), 19.8 ($\underline{C}(4)\text{H}_3$), 19.4 ($\underline{C}(5)\text{H}_3$); m/z (ESI $^+$) 555, 557 ($[\text{M}+\text{Na}]^+$, 100%); **HRMS** (ESI $^+$) $\text{C}_{21}\text{H}_{20}\text{Cl}_4\text{N}_2\text{O}_2$ requires $[\text{M}+\text{Na}]^+$ 555.0013, found 555.0016 (6 peaks)(-0.8 ppm).

(S)-2-(1,3-Dioxo-1H-benzo[f]isoindol-2(3H)-yl)-N-((R)-2-hydroxy-2-(4-methoxyphenyl)ethyl)-3-methylbutanamide (299b)

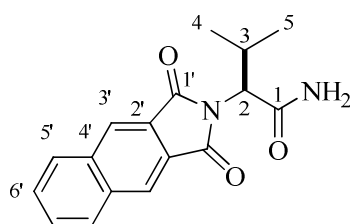


Compound **28** (31 mg, 0.23 mmol) and compound **298b** (115 mg, 0.25 mmol) were subjected to General Procedure G to furnish the title compound **299b** (77 mg, 0.14 mmol, 75%, *rs* 10:1, *dr* 4:1) as a colourless gum.

$[\alpha]_D^{25}$ + 5.4 ($c = 1.1$, chloroform); ν_{max} (thin film)/ cm^{-1} 3357br m, 2966m, 1766s, 1705s, 1667m, 1611m, 1538m, 1514s, 1464m, 1372s, 1359s, 1344s, 1247s, 1100m, 1034m, 907w, 767s, 735s; δ_{H}

(400 MHz, CDCl₃) 8.30 (2H, s, C(10')H), 8.05 (2H, dd, *J* 6.0, 3.1, C(12')H), 7.71 (2H, dd, *J* 6.0, 3.1, C(13')H), 7.33-7.49 (1H, m, NH), 7.22 (2H, d, *J* 8.3, C(5')H), 6.64-6.76 (2H, m, C(4')H), 4.79-4.88 (1H, m, C(2')H), 4.47 (1H, d, *J* 11.2, C(2)H), 3.63-3.72 (1H, m, C(1')H_a), 3.57 (3H, s, C(7')H₃), 3.37-3.49 (1H, m, C(1')H_b), 2.77-2.92 (1H, m, C(3)H), 1.02-1.14 (3H, m, C(4)H₃), 0.85 (3H, d, *J* 6.6, C(5)H₃); δ_c (100 MHz, CDCl₃) 170.2 (C(1)O), 168.0 (C(8')O), 158.9 (C(6')), 135.5 (C(11')), 133.7 (C(3')), 130.3 (C(13')H), 129.4 (C(4')H), 126.8 (C(12')H), 126.7 (C(9')), 125.3 (C(10')H), 113.6 (C(5')H), 72.9 (C(2')H), 63.1 (C(2)H), 54.9 (C(7')H₃), 47.4 (C(1')H₂), 27.5 (C(3)H), 19.8 (C(4)H₃), 19.4 (C(5)H₃); *m/z* (ESI⁻) 445 ([M-H]⁻, 100%); **HRMS** (ESI⁺) C₂₆H₂₆N₂O₅ requires [M+Na]⁺ 469.1734 found 469.1725 (+2.0 ppm).

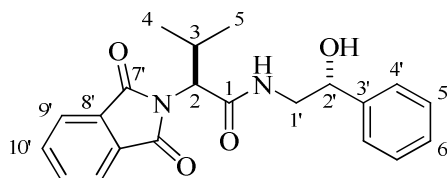
(S)-2-(1,3-Dioxo-1*H*-benzo[*f*]isoindol-2(3*H*)-yl)-3-methylbutanamide



(S)-2-(1,3-Dioxo-1*H*-benzo[*f*]isoindol-2(3*H*)-yl)-3-methylbutanamide was obtained in 12% yield during the synthesis of **299b**

[α]_D²⁵ + 10.9 (*c* = 0.2, chloroform); **m.p.** 198-199 °C; $\nu_{\max}$ (thin film)/cm⁻¹ 3342br w, 1799w, 1716s, 1661m, 1679m, 1329w, 1086w, 987w, 897w 875w, 729m; δ_H (400 MHz, CDCl₃) 8.38 (2H, s, C(3')H), 8.09 (2H, dd, *J* 6.1, 3.3, C(5')H), 7.74 (2H, dd, *J* 6.2, 3.2, C(6')H), 7.06 (1H, br s, NH_a), 5.52 (1H, br s, NH_b), 4.51 (1H, d, *J* 11.4, C(2)H), 2.91 (1H, dq, *J* 18.1, 6.6, C(3)H), 1.18 (3H, d, *J* 6.6, C(4)H₃), 0.90 (3H, d, *J* 6.6, C(5)H₃); δ_c (100 MHz, CDCl₃) 170.2 (C(1)O), 168.2 (C(1')), 135.6 (C(4')), 130.4 (C(6')H), 129.6 (C(5')H), 126.8 (C(2')), 125.4 (C(3')H), 63.3 (C(2)H), 27.6 (C(3)H), 19.8 (C(4)H₃), 19.4 (C(5)H₃); *m/z* (ESI⁻) 295 ([M-H]⁻, 100%); **HRMS** (ESI⁺) C₁₇H₁₆N₂O₃ requires [M+Na]⁺ 319.1053 found 319.1056 (-1.2 ppm).

(S)-2-(1,3-Dioxoisindolin-2-yl)-*N*-((*R*)-2-hydroxy-2-phenylethyl)-3-methylbutanamide (302)



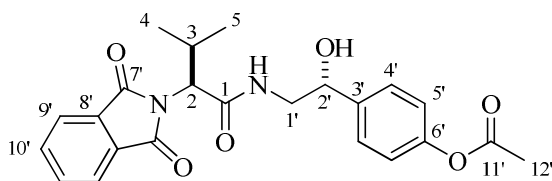
Styrene (24 mg, 0.23 mmol) and compound **273** (102 mg, 0.25 mmol) were subjected to General Procedure G to furnish the title compound **302** (63 mg, 0.17 mmol, 75%, *rs* 15:1, *dr* 13:1) as a colourless foam.

[α]_D²⁵ +24.5 (*c* = 1.0, chloroform); $\nu_{\max}$ (thin film)/cm⁻¹ 3362br, 1771m, 1708s, 1546m, 1387m, 1218w, 1073m, 725m; δ_H (500 MHz, CDCl₃) 7.85 (2H, dd, *J* 5.4, 3.1, C(9')H), 7.77 (2H, dd, *J* 5.4,

3.1, C(10')H), 7.25-7.34 (3H, m, C(4')H, NH), 7.20 (2H, t, *J* 7.6, C(5')H), 7.06-7.14 (1H, *J* 7.6, C(6')H), 4.82-4.92 (1H, m, C(2')H), 4.40 (1H, d, *J* 11.3, C(2)H), 3.70 (1H, ddd, *J* 14.0, 6.2, 3.2, C(1')H_a), 3.38-3.49 (2H, m, C(1')H_b, OH), 2.71-2.84 (1H, m, C(3)H), 1.06 (3H, d, *J* 6.6, C(4)H₃), 0.84 (3H, d, *J* 6.6, C(5)H₃); δ_{C} (125 MHz, CDCl₃) 170.4 (C(1)O), 168.3 (C(7')O), 141.5 (C(3')), 134.4 (C(10')H), 131.3 (C(8')), 128.3 (C(5')H), 127.6 (C(6')H), 125.6 (C(4')H), 123.7 (C(9')H), 73.5 (C(2')H), 62.9 (C(2)H), 47.5 (C(1')H₂), 27.6 (C(3)H), 19.7 (C(4)H₃), 19.4 (C(5)H₃); *m/z* (ESI⁺) 389 ([M+Na]⁺, 100%); **HRMS** (ESI⁺) C₂₁H₂₂N₂O₄ requires [M+Na]⁺ 389.1472, found 389.1483 (+1.2 ppm).

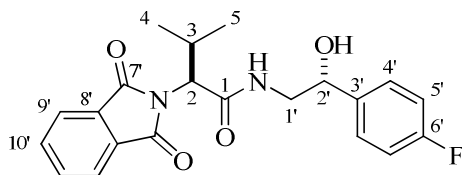
Single Crystal X-ray Diffraction Data for 302: C₂₁H₂₂N₂O₄, M_r = 366.42, monoclinic (R -3), *a* = 5.4234(3) Å, *b* = 11.1965(5) Å, *c* = 15.7831(9) Å, α = 90 °C, β = 96.6243(19) °C, γ = 90 °C, *V* = 952.00(9) Å³, *Z* = 4, μ = not measured *D*_{calc} = 1.278, *T* = 150(2) K, 2196 reflections collected, 2196 independent [*R*(int) = 0], *R*₁ = 0.0358, *wR*₂ = 0.0844 [*I* > 3σ(*I*)].

4-((*R*)-2-((*S*)-2-(1,3-Dioxoisindolin-2-yl)-3-methylbutanamido)-1-hydroxyethyl)phenyl acetate (303)



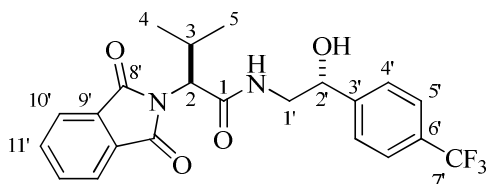
4-Acetoxystyrene (37 mg, 0.23 mmol) and compound **273** (102 mg, 0.25 mmol) were subjected to General Procedure G to furnish the title compound **303** (76 mg, 0.18 mmol, 78%, *rs* 12:1, *dr* 8:1) as a colourless oil.

[α]_D²⁵ – 12.4 (*c* = 0.4, chloroform); ν_{max} (thin film)/cm^{–1} 3361br, 2965w, 1763m, 1713s, 1661m, 1539m, 1508m, 1424m, 1266br m, 1165m, 1123w, 1070w, 730m; δ_{H} (400 MHz, CDCl₃) 7.85 (2H, dd, *J* 5.3, 3.0, C(9')H), 7.76 (2H, dd, *J* 5.3, 3.0, C(10')H), 7.33 (3H, d, *J* 8.3, C(5')H, NH), 6.96 (2H, d, *J* 8.3, C(4')H), 4.75-4.92 (1H, m, C(2')H), 4.41 (1H, d, *J* 11.1, C(2)H), 3.64 (1H, ddd, *J* 13.8, 6.9, 4.8, C(1')H_a), 3.55 (1H, m, *J* 3.0, OH), 3.39 (1H, ddd, *J* 13.8, 6.9, 4.8, C(1')H_b), 2.71-2.85 (1H, m, C(3)H), 2.27 (3H, s, C(12')H₃), 1.05 (3H, d, *J* 6.6, C(4)H₃), 0.84 (3H, d, *J* 6.6, C(5)H₃); δ_{C} (100 MHz, CDCl₃) 170.3 (C(1)O), 169.34 (C(11')O), 168.3 (C(7')O), 149.9 (C(6')), 139.2 (C(3')), 134.4 (C(10')H), 131.2 (C(8')), 126.7 (C(4')H), 123.7 (C(9')H), 121.4 (C(5')H), 72.9 (C(2')H), 62.8 (C(2)H), 47.5 (C(1')H₂), 27.6 (C(3)H), 21.1 (C(12')H₃), 19.8 (C(4)H₃), 19.4 (C(5)H₃); *m/z* (ESI⁺) 447 ([M+Na]⁺, 100%), 871 ([2M+Na]⁺, 100); **HRMS** (ESI⁺) C₂₃H₂₄N₂O₆ requires [M+Na]⁺ 447.1527, found 447.1530 (–0.8 ppm).

(S)-2-(1,3-Dioxoisindolin-2-yl)-N-((R)-2-(4-fluorophenyl)-2-hydroxyethyl)-3-methylbutanamide (305)

4-Fluorostyrene (28 mg, 0.23 mmol) and compound **273** (102 mg, 0.25 mmol) were subjected to General Procedure G to furnish the title compound **305** (66 mg, 0.18 mmol, 79%, *rs* 17:1, *dr* 6:1) as a colourless oil.

$[\alpha]_{\text{D}}^{25}$ – 22.7 ($c = 0.2$, chloroform); ν_{max} (thin film)/ cm^{-1} 3362br, 2967w, 1770w, 1713s, 1662m, 1540w, 1509m, 1385m, 1222m, 1070m, 837w, 719m; δ_{H} (400 MHz, CDCl_3) 7.85 (2H, dd, J 5.4, 2.9, C(9')H), 7.78 (2H, dd, J 5.4, 2.9, C(10')H), 7.19–7.36 (3H, m, C(5')H, NH), 6.81–6.93 (2H, m, C(4')H), 4.84–4.92 (1H, m, C(2')H), 4.40 (1H, d, J 11.3, C(2)H), 3.60–3.74 (1H, m, C(1')H_a), 3.34–3.47 (1H, m, C(1')H_b), 2.70–2.85 (1H, m, C(3)H), 1.03–1.11 (3H, m, C(4)H₃), 0.84 (3H, d, J 6.6, C(5)H₃); δ_{C} (100 MHz, CDCl_3) 170.6 (C(1)O), 168.4 (C(7)O), 137.3 (C(8')), 134.6 (C(10')H), 131.3 (C(5')H), 127.3 (C(3')), 127.2 (C(6')), 123.7 (C(9')H), 115.2 (C(4')H), 72.9 (C(2')H), 62.8 (C(2)H), 47.3 (C(1')H₂), 27.6 (C(3)H), 19.7 (C(4)H₃), 19.4 (C(5)H₃); m/z (ESI⁺) 385 ([M+H]⁺, 70%), 407 ([M+Na]⁺, 90); **HRMS** (ESI⁺) $\text{C}_{21}\text{H}_{21}\text{FN}_2\text{O}_4$ requires [M+Na]⁺ 407.1378, found 407.1379 (–0.3 ppm).

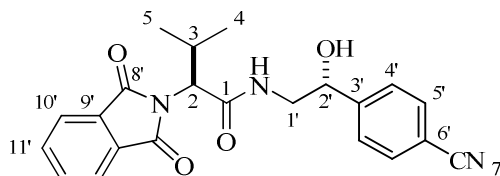
(S)-2-(1,3-Dioxoisindolin-2-yl)-N-((R)-2-hydroxy-2-(4-(trifluoromethyl)phenyl)ethyl)-3-methylbutanamide (306)

4-Trifluoromethylstyrene (40 mg, 0.23 mmol) and compound **273** (102 mg, 0.25 mmol) were subjected to General Procedure G to furnish the title compound **306** (52 mg, 0.12 mmol, 50%, *rs* 12:1, *dr* 11:1) as a colourless oil.

$[\alpha]_{\text{D}}^{25}$ – 11.2 ($c = 0.3$, chloroform); ν_{max} (thin film)/ cm^{-1} 3383br, 2932w, 1775w, 1714s, 1661m, 1612w, 1585br m, 1384m, 1248m, 1032w, 720m; δ_{H} (400 MHz, CDCl_3) 7.86 (2H, dd, J 5.5, 3.1, C(10')H), 7.79 (2H, dd, J 5.5, 3.1, C(11')H), 7.40–7.48 (4H, m, C(4')H, C(5')H), 7.36 (1H, t, J 5.1, NH), 4.98 (1H, m, C(2')H), 4.43 (1H, d, J 11.4, C(2)H), 3.81 (1H, d, J 4.4, OH), 3.76 (1H, ddd, J 14.1, 6.3, 3.1, C(1')H_a), 3.45 (1H, ddd, J 14.1, 6.3, 3.1, C(1')H_b), 2.69–2.81 (1H, m, C(3)H), 1.06 (3H, d, J 6.7, C(4)H₃), 0.84 (3H, d, J 6.7, C(5)H₃); δ_{C} (100 MHz, CDCl_3) 171.1 (C(1)O), 168.4 (C(8')O), 145.6 (C(3')), 134.6 (C(11')H), 131.1 (C(9')), 129.9 (C(6')), 126.0 (br, C(4')H, C(5')H), 125.2 (q, J 3.8, C(7')F₃), 123.8 (C(10')H), 73.3 (C(2')H), 62.9 (C(2)H), 47.6 (C(1')H₂), 27.7

($\underline{\text{C}}(3)\text{H}$), 19.7 ($\underline{\text{C}}(4)\text{H}_3$), 19.4 ($\underline{\text{C}}(5)\text{H}_3$); m/z (ESI^+) 457 ($[\text{M}+\text{Na}]^+$, 80%), 891 ($[2\text{M}+\text{Na}]^+$, 100); **HRMS** (ESI^+) $\text{C}_{22}\text{H}_{21}\text{F}_3\text{N}_2\text{O}_4$ requires $[\text{M}+\text{Na}]^+$ 457.1346, found 457.1340 (+1.6 ppm).

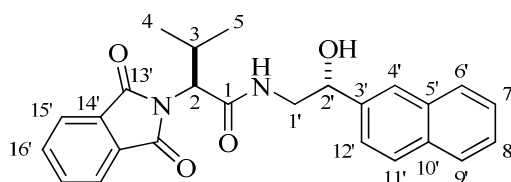
(S)-N-((R)-2-(4-Cyanophenyl)-2-hydroxyethyl)-2-(1,3-dioxisoindolin-2-yl)-3-methylbutanamide (306)



4-Cyanostyrene (30 mg, 0.23 mmol) and compound **273** (115 mg, 0.25 mmol) were subjected to General Procedure G to furnish the title compound **306** (27 mg, 0.05 mmol, 22%, *rs* 16:1, *dr* 1.4:1) as a colourless oil.

$[\alpha]_{\text{D}}^{25}$ - 16.0 ($c = 0.2$, chloroform); ν_{max} (thin film)/ cm^{-1} 3339br w, 2960m, 1771w, 1762s, 1703m, 1662m, 1538m, 1567w, 1532m, 1464m, 1371m, 1361s, 1339m, 1229m, , 1034m, 989w, 952w, 731m; δ_{H} (400 MHz, CDCl_3) 7.85-7.92 (4H, m, C(10') $\underline{\text{H}}$), 7.78-7.84 (2H, m, C(11') $\underline{\text{H}}$), 7.48-7.54 (2H, m, C(4') $\underline{\text{H}}$), 7.43-7.47 (2H, m, C(5') $\underline{\text{H}}$), 7.36 (1H, t, J 5.4, NH), 4.95-5.01 (1H, m, C(2') $\underline{\text{H}}$), 4.41 (1H, m, C(2) $\underline{\text{H}}$), 3.38-3.49 (2H, m, C(1') $\underline{\text{H}}_2$), 2.67-2.81 (3H, m, C(3) $\underline{\text{H}}$), 1.06 (3H, m, C(4) $\underline{\text{H}}_3$), 0.84 (3H, m, C(5) $\underline{\text{H}}_3$); δ_{C} (100 MHz, CDCl_3) 170.9 ($\underline{\text{C}}(1)\text{O}$), 168.4 ($\underline{\text{C}}(8')\text{O}$), 147.1 ($\underline{\text{C}}(3')$), 134.8 ($\underline{\text{C}}(11')\text{H}$), 132.0 ($\underline{\text{C}}(5')\text{H}$), 131.2 ($\underline{\text{C}}(9')$), 126.5 ($\underline{\text{C}}(4')\text{H}$), 123.8 ($\underline{\text{C}}(10')\text{H}$), 118.6 ($\underline{\text{C}}(7')$), 111.2 ($\underline{\text{C}}(6')$), 72.8 ($\underline{\text{C}}(2')\text{H}$), 62.7 ($\underline{\text{C}}(2)\text{H}$), 47.4 ($\underline{\text{C}}(1')\text{H}_2$), 27.6 ($\underline{\text{C}}(3)\text{H}$), 19.8 ($\underline{\text{C}}(4)\text{H}_3$), 19.4 ($\underline{\text{C}}(5)\text{H}_3$); m/z (ESI^+) 414 ($[\text{M}+\text{Na}]^+$, 100%), 805 ($2[\text{M}+\text{Na}]^+$, 80); **HRMS** (ESI^+) $\text{C}_{22}\text{H}_{21}\text{N}_3\text{O}_4$ requires $[\text{M}+\text{Na}]^+$ 414.1424 found 414.1417 (+2.1 ppm).

(S)-2-(1,3-Dioxisoindolin-2-yl)-N-((R)-2-hydroxy-2-(naphthalen-2-yl)ethyl)-3-methylbutanamide (307)

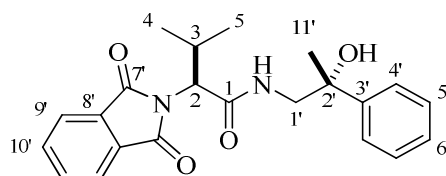


Vinylnaphthalene **34** (35 mg, 0.23 mmol) and compound **273** (102 mg, 0.25 mmol) were subjected to General Procedure G to furnish the title compound **307** (75 mg, 0.18 mmol, 77%, *rs* 13:1, *dr* 12:1) as a colourless solid.

$[\alpha]_{\text{D}}^{25}$ - 15.5 ($c = 2.3$, chloroform); **m.p.** 186-188 °C; ν_{max} (thin film)/ cm^{-1} 3356br, 2964w, 1770w, 1711s, 1661m, 1540w, 1384m, 1070m, 820w, 728m; δ_{H} (400 MHz, CDCl_3) 7.79 (1H, s, C(11') $\underline{\text{H}}$), 7.64-7.75 (7H, m, C(4') $\underline{\text{H}}$, C(6') $\underline{\text{H}}$, C(9') $\underline{\text{H}}$, C(15') $\underline{\text{H}}$, C(16') $\underline{\text{H}}$), 7.32-7.43 (3H, m, C(7') $\underline{\text{H}}$, C(8') $\underline{\text{H}}$, C(12') $\underline{\text{H}}$), 5.06 (1H, m, C(2') $\underline{\text{H}}$), 4.40 (1H, d, J 11.4, C(2) $\underline{\text{H}}$), 3.71-3.89 (2H, m, C(1') $\underline{\text{H}}_2$, OH), 3.47-

3.59 (1H, m, C(1') $\underline{H}_b$), 2.66-2.81 (1H, m, C(3) $\underline{H}$), 1.03 (3H, d, J 6.6, C(4) $\underline{H}_3$), 0.80 (3H, d, J 6.6, C(5) $\underline{H}_3$); δ_c (100 MHz, CDCl₃) 170.7 (C(1)O), 168.3 (C(13')O), 138.9 (C(3')), 134.4 (C(16')H), 133.1 (C(10')), 132.8 (C(5')), 131.1 (C(14')), 128.1 (C(6')H), 127.8 (C(11')H), 127.5 (C(9')H), 126.1 (C(7')H), 125.8 (C(4')H), 124.5 (C(8')H), 123.6 (C(15')H), 123.6 (C(12')H), 73.7 (C(2')H), 63.0 (C(2)H), 47.6 (C(1')H₂), 27.6 (C(3)H), 19.6 (C(4)H₃), 19.4 (C(5)H₃); m/z (ESI⁻) 415 ([M-H]⁻, 100%); **HRMS** (ESI⁺) C₂₅H₂₄N₂O₄ requires [M+CH₃OH+Na]⁺ 471.1890, found 471.1890 (+1.86 ppm).

(S)-2-(1,3-Dioxoisindolin-2-yl)-N-((R)-2-hydroxy-2-phenylpropyl)-3-methylbutanamide (308)

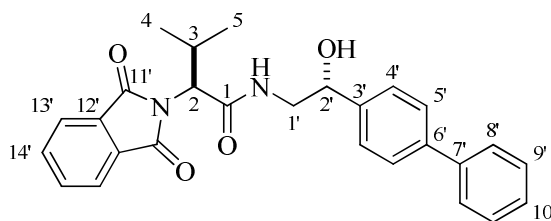


α -Methylstyrene (27 mg, 0.23 mmol) and compound **273** (102 mg, 0.25 mmol) were subjected to General Procedure G to furnish the title compound **308** (54 mg, 0.14 mmol, 62%, *rs* 11:1, *dr* 3:1) as a colourless oil.

Only the signals of the major diastereomer **308** are detailed below

$[\alpha]_D^{25} + 7.8$ ($c = 1.5$, chloroform); $\nu_{\max}$ (thin film)/cm⁻¹ 3359br, 2969m, 1769m, 1713s, 1659s, 1542m, 1468m, 1385s, 1071m, 912w, 721m; δ_H (400 MHz, CDCl₃) 7.80-7.88 (2H, m, C(9') $\underline{H}$), 7.73-7.80 (2H, m, C(10') $\underline{H}$), 7.33-7.42 (2H, m, C(4') $\underline{H}$), 7.17 (1H, t, J 7.6, $\underline{NH}$), 6.90-7.14 (3H, m, C(5') $\underline{H}$, C(6') $\underline{H}$), 4.22-4.37 (1H, m, C(2) $\underline{H}$), 3.63-3.75 (1H, m, C(1') $\underline{H}_a$), 3.47-3.60 (1H, m, C(1') $\underline{H}_b$), 3.35 (1H, br s, $\underline{OH}$), 2.58-2.75 (1H, m, C(3) $\underline{H}$), 1.56 (3H, s, C(11') $\underline{H}_3$), 0.98 (3H, d, J 6.5, C(4) $\underline{H}_3$), 0.72-0.82 (3H, d, J 6.5, C(5) $\underline{H}_3$); δ_c (100 MHz, CDCl₃) 170.6 (C(1)O), 168.2 (C(7')O), 145.3 (C(3')), 134.3 (C(10')H), 131.2 (C(8')), 127.9 (C(5')H), 126.6 (C(6')H), 124.8 (C(4')H), 123.7 (C(9')H), 75.3 (C(2')H), 63.0 (C(2)H), 51.6 (C(1')H₂), 28.1 (C(3)H), 27.4 (C(11')H₃), 19.5 (C(4)H₃), 19.3 (C(5)H₃); m/z (ESI⁻) 379 ([M-H]⁻, 100%); **HRMS** (ESI⁺) C₂₂H₂₄N₂O₄ requires [M+Na]⁺ 403.1628, found 403.1629 (-0.2 ppm).

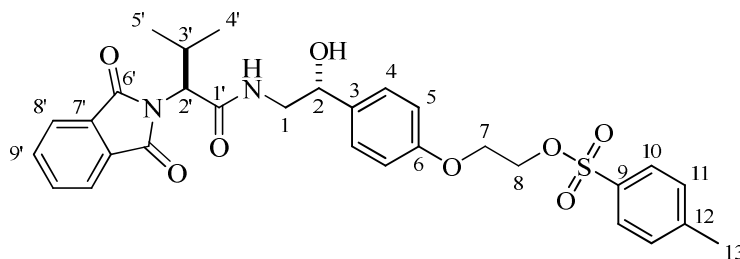
(S)-N-((R)-2-(Biphenyl-4-yl)-2-hydroxyethyl)-2-(1,3-dioxoisindolin-2-yl)-3-methylbutanamide (309)



4-Vinyl-1,1'-biphenyl (41 mg, 0.23 mmol) and compound **273** (102 mg, 0.25 mmol) were subjected to General Procedure G to furnish the title compound **309** (80 mg, 0.18 mmol, 79%, *rs* 12:1, *dr* 8:1) as a colourless oil.

$[\alpha]_D^{25}$ – 14.8 (*c* = 0.9, chloroform); $\nu_{\max}$ (thin film)/cm⁻¹ 3362br, 2929w, 1770w, 1712s, 1662m, 1537m, 1468w, 1384s, 1333w, 1070m, 729m; δ_H (400 MHz, CDCl₃) 7.78 (2H, dd, *J* 5.5, 3.1, C(13')H), 7.63 (2H, dd, *J* 5.5, 3.1, C(14')H), 7.45-7.56 (2H, m, C(4')H), 7.29-7.46 (7H, m, C(5')H, C(8')H, C(9')H, C(10')H), 4.94 (1H, ddd, *J* 6.5, 4.1, 3.5, C(2')H), 4.42 (1H, d, *J* 11.3, C(2)H), 3.78 (1H, ddd, *J* 14.2, 6.5, 3.2, C(1')H_a), 3.56 (1H, d, *J* 4.1, OH), 3.43-3.53 (1H, m, C(1')H_b), 2.71-2.86 (1H, m, C(3)H), 1.07 (3H, d, *J* 6.5, C(4)H₃), 0.84 (3H, d, *J* 6.5, C(5)H₃); δ_C (100 MHz, CDCl₃) 170.6 (C(1)O), 168.4 (C(11')O), 140.57 (C(3')), 140.55 (C(7')), 140.3 (C(6')), 134.4 (C(14')H), 131.1 (C(12')), 128.7 (C(9')H), 127.3 (C(10')H), 127.0 (br, C(5')H, C(8')H), 126.1 (C(4')H), 123.6 (C(13')H), 73.4 (C(2')H), 63.0 (C(2)H), 47.5 (C(1')H₂), 27.6 (C(3)H), 19.7 (C(4)H₃), 19.4 (C(5)H₃); *m/z* (ESI⁻) 441 ([M-H]⁻, 100%); **HRMS** (ESI⁻) C₂₇H₂₆N₂O₄ requires [M-H]⁻ 441.1819, found 441.1820 (+0.02 ppm).

2-(4-((*R*)-2-((*S*)-2-(1,3-Dioxoisindolin-2-yl)-3-methylbutanamido)-1-hydroxyethyl)phenoxy)ethyl 4-methylbenzenesulfonate (310)

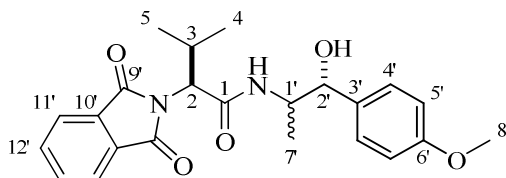


2-(4-Vinylphenoxy)ethyl 4-methylbenzenesulfonate (31 mg, 0.23 mmol) and compound **273** (102 mg, 0.25 mmol) were subjected to General Procedure G (no ligand used) to furnish the title compound **310** (57 mg, 0.10 mmol, 43%, *rs* 23:1, *dr* 2:1) as a colourless solid.

$[\alpha]_D^{25}$ – 5.0 (*c* = 0.9, chloroform); *m.p.* 143-144 °C; $\nu_{\max}$ (thin film)/cm⁻¹ 3374br w, 2965w, 1769w, 1713s, 1664m, 1611m, 1537m, 1512s, 1384s, 1357s, 1292m, 1176s, 1070m, 930m, 732m; δ_H (400 MHz, CDCl₃) 7.72-7.90 (6H, m, C(11)H, C(8')H, C(9')H), 7.35 (2H, d, *J* 7.9, C(5)H), 7.29-7.33 (1H, m, NH), 7.11-7.22 (2H, m, C(10)H), 6.57-6.65 (2H, m, C(4)H), 4.76-4.83 (1H, m, C(2)H), 4.38 (1H, d, *J* 11.3, C(2')H), 4.28-4.35 (2H, m, C(8)H₂), 3.97-4.10 (2H, m, C(7)H₂), 3.56-3.70 (1H, m, C(1)H_a), 3.33-3.44 (1H, m, C(1)H_b), 2.71-2.84 (1H, m, C(3')H), 2.38-2.50 (3H, s, C(13)H₃), 1.00-1.11 (3H, m, C(4')H₃), 0.82 (3H, d, *J* 6.3 C(5')H₃); δ_C (100 MHz, CDCl₃) 170.3 (C(1')O), 168.4 (C(6')O), 157.3 (C(6)), 145.0 (C(12)), 134.6 (C(9')H), 134.4 (C(3)), 132.5 (C(9)), 129.9 (C(11)H), 126.8 (C(4)H), 123.7 (C(8')H), 114.2 (C(5)H), 72.9 (C(2)H), 68.1 (C(8)H₂), 65.2 (C(7)H₂), 62.8 (C(2')H), 47.4 (C(1)H₂), 27.5 (C(3')H), 21.6 (C(13)H₃), 19.7 (C(4')H₃), 19.4

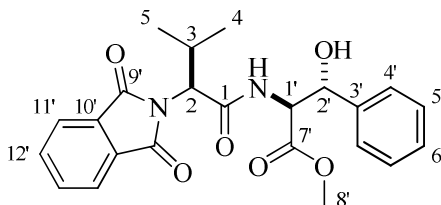
($\underline{C}(5')\text{H}_3$); m/z (ESI^+) 603 ($[\text{M}+\text{H}]^+$, 100%); **HRMS** (ESI^+) $\text{C}_{30}\text{H}_{32}\text{N}_2\text{O}_8\text{S}$ requires $[\text{M}+\text{Na}]^+$ 603.1772 found 603.1772 (+0.5 ppm).

(S)-2-(1,3-Dioxoisindolin-2-yl)-N-((R)-1-hydroxy-1-(4-methoxyphenyl)propan-2-yl)-3-methylbutanamide (311)



(*E*)-1-methoxy-4-(prop-1-en-1-yl)benzene (34 mg, 0.23 mmol) and compound **273** (102 mg, 0.25 mmol) were subjected to General Procedure G to furnish the title compound **311** (58 mg, 0.14 mmol, 61%, *rs* 30:1, *dr* 1.3:1) as a colourless gum. Identified by COSY starting with NH signal $[\alpha]_{\text{D}}^{25}$ - 28.6 ($c = 0.3$, chloroform); ν_{max} (thin film)/ cm^{-1} 3355br w, 2931w, 1771w, 1712s, 1658m, 1612w, 1585m, 1513m, 1467w, 1384s, 1248m, 1177w, 1070m, 1034w, 719s; δ_{H} (400 MHz, CDCl_3) one diastereomer 7.87 (2H, m, C(11') $\underline{\text{H}}$), 7.66-7.81 (2H, m, C(12') $\underline{\text{H}}$), 7.24 (1H, d, J 8.6, C(4') $\underline{\text{H}}$), 6.81 (2H, d, J 8.6, C(5') $\underline{\text{H}}$), 4.85 (1H, dd, J 8.2, 4.4, C(2') $\underline{\text{H}}$), 4.35 (1H, d, J 11.6, C(2) $\underline{\text{H}}$), 3.95-4.07 (1H, m, C(1') $\underline{\text{H}}$), 3.75 (3H, s, C(8') $\underline{\text{H}}_3$), 2.65-2.85 (1H, m, C(3) $\underline{\text{H}}$), 0.74-1.23 (9H, m, C(4) $\underline{\text{H}}_3$, C(5) $\underline{\text{H}}_3$, C(7') $\underline{\text{H}}_3$); δ_{C} (100 MHz, CDCl_3) 168.4 ($\underline{\text{C}}(9')\text{O}$), 167.7 ($\underline{\text{C}}(1)\text{O}$), 159.5 ($\underline{\text{C}}(6')$), 135.6 ($\underline{\text{C}}(3')$), 134.5 ($\underline{\text{C}}(12')\text{H}$), 131.3 ($\underline{\text{C}}(10')$), 127.9 ($\underline{\text{C}}(4')\text{H}$), 123.7 ($\underline{\text{C}}(11')\text{H}$), 114.1 ($\underline{\text{C}}(5')\text{H}$), 71.4 ($\underline{\text{C}}(2')\text{H}$), 63.4 ($\underline{\text{C}}(2)\text{H}$), 55.2 ($\underline{\text{C}}(8')\text{H}_3$), 52.0 ($\underline{\text{C}}(1')\text{H}$), 27.9 ($\underline{\text{C}}(3)\text{H}$), 19.5 ($\underline{\text{C}}(4)\text{H}_3$), 17.5 ($\underline{\text{C}}(5)\text{H}_3$), 15.6 ($\underline{\text{C}}(7')\text{H}_3$); m/z (ESI^-) 409 ($[\text{M}-\text{H}]^-$, 100%); **HRMS** (ESI^+) $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_5$ requires $[\text{M}+\text{Na}]^+$ 433.1734 found 433.1731 (+0.9 ppm).

(2S,3R)-Methyl-2-((S)-2-(1,3-dioxoisindolin-2-yl)-3-methylbutanamido)-3-hydroxy-3-phenylpropanoate (312)



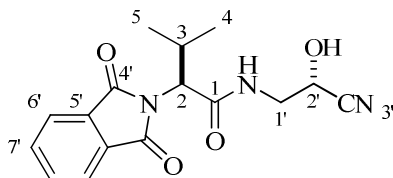
Methyl cinnamate (37 mg, 0.23 mmol) and compound **273** (115 mg, 0.25 mmol) were subjected to General Procedure G to furnish the title compound **312** (67 mg, 0.16 mmol, 69%, *rs* 6:1, *dr* 1.7:1) as a colourless solid.

$[\alpha]_{\text{D}}^{25}$ - 13.5 ($c = 0.7$, chloroform); ν_{max} (thin film)/ cm^{-1} 3332br w, 2965w, 1718w, 1713br s, 1678m, 1546m, 1379m, 1272m, 1228m, 1076w, 989w, 915w, 726m; δ_{H} (400 MHz, CDCl_3) 7.88 (2H, dd, J 5.3, 3.1, C(11') $\underline{\text{H}}$), 7.77 (2H, dd, J 5.3, 3.1, C(12') $\underline{\text{H}}$), 7.33-7.46 (3H, m, C(5') $\underline{\text{H}}$, C(6') $\underline{\text{H}}$), 7.18-7.26 (2H, m, C(4') $\underline{\text{H}}$), 7.07-7.17 (1H, m, NH), 5.41 (1H, m, C(2') $\underline{\text{H}}$), 4.82 (1H, dd, J 9.0, 2.7,

C(1')H), 4.39 (1H, d, *J* 2.7, OH), 4.32 (1H, d, *J* 11.6, C(2)H), 3.68 (3H, s, C(8')H₃), 2.62-2.80 (1H, m, C(3)H), 0.78 (3H, d, *J* 6.6, C(4)H₃), 0.71 (3H, d, *J* 6.6, C(5)H₃); δ_c (100 MHz, CDCl₃) 170.5 (C(7')O), 169.1 (C(9')O), 168.3 (C(1)O), 139.6 (C(3')), 134.4 (C(12')H), 131.3 (C(10')), 128.5 (C(4')H), 128.3 (C(6')H), 127.8 (C(5')H), 123.7 (C(11')H), 74.7 (C(2')H), 63.0 (C(2)H), 58.2 (C(1')H), 52.6 (C(8')H₃), 27.4 (C(3)H), 19.30 (C(4)H₃), 19.26 (C(5)H₃); *m/z* (ESI⁺) 447 ([M+Na]⁺, 100%); **HRMS** (ESI⁺) C₂₃H₂₄N₂O₆ requires [M+Na]⁺ 447.1527 found 447.1522 (+1.1 ppm).

Single Crystal X-ray Diffraction Data for 312: C₂₃H₂₄N₂O₆, M_r = 424.45, monoclinic (P 1 21 1), a = 10.6230(4) Å, b = 7.4925(3) Å, c = 13.4324(7) Å, α = 90 °C, β = 103.1765(18) °C, γ = 90 °C, V = 1040.98(8) Å³, Z = 2, μ = not measured D_{calc} = 1.354, T = 150(2) K, 27855 reflections collected, 2535 independent [R(int) = 0], R₁ = 0.0753, wR₂ = 0.1023 [I > 3sigma(I)].

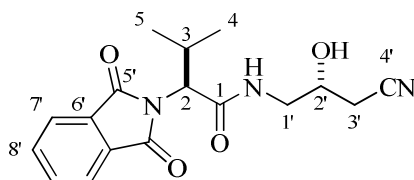
(S)-N-((S)-2-Cyano-2-hydroxyethyl)-2-(1,3-dioxoisindolin-2-yl)-3-methylbutanamide (313)



Acrylonitrile (13 mg, 0.23 mmol) and compound **273** (102 mg, 0.25 mmol) were subjected to General Procedure G to furnish the title compound **313** (48 mg, 0.15 mmol, 66%, *rs* 15:1, *dr* 4:1) as a colourless gum.

[α]_D²⁵ + 15.2 (*c* = 0.9, chloroform); $\nu_{\max}$ (thin film)/cm⁻¹ 3332br m, 2964m, 1770w, 1712s, 1659m, 1503m, 1358s, 1016m, 794m; δ_H (400 MHz, CDCl₃) 7.85-7.94 (2H, m, C(6')H), 7.74-7.85 (3H, m, NH, C(7')H), 5.10 (1H, d, *J* 7.3, OH), 4.66 (1H, br s, C(2')H), 4.44-4.55 (1H, m, C(2)H), 3.76-3.86 (1H, m, C(1')H_a), 3.50 (1H, m, C(1')H_b), 2.74-2.95 (1H, m, C(3)H), 1.16 (1H, d, *J* 6.6, C(5)H₃), 0.88 (3H, d, *J* 6.6, C(4)H₃); δ_c (100 MHz, CDCl₃) 172.3 (C(1)O), 68.5 (C(4')O), 134.7 (C(7')H), 131.1 (C(5')), 123.9 (C(6')H), 118.0 (C(3')), 62.6 (C(2)H), 62.1 (C(2')H), 44.6 (C(1')H₂), 28.0 (C(3)H), 19.7 (C(4)H₃), 19.4 (C(5)H₃); *m/z* (ESI⁺) 338 ([M+Na]⁺, 100%), 653 ([2M+Na]⁺, 60); **HRMS** (ESI⁺) C₁₆H₁₇N₃O₄ requires [M+Na]⁺ 338.1111 found 338.1111 (+0.0 ppm).

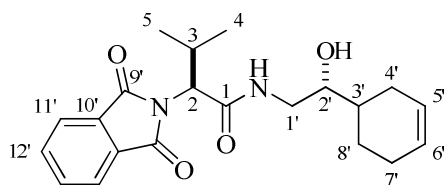
(S)-N-((R)-3-Cyano-2-hydroxypropyl)-2-(1,3-dioxoisindolin-2-yl)-3-methylbutanamide (314)



But-3-enenitrile (16 mg, 0.23 mmol) and compound **273** (102 mg, 0.25 mmol) were subjected to General Procedure G to furnish the title compound **314** (57 mg, 0.17 mmol, 75%, *rs* 2.5:1, *dr* 7:1) as a colourless gum.

$[\alpha]_D^{25} + 4.8$ ($c = 1.0$, chloroform); $\nu_{\max}$ (thin film)/ cm^{-1} 3359br m, 2967br w, 1770m, 1714s, 1662m, 1538s, 1468m, 1385s, 1071s, 889w, 718m; δ_{H} (400 MHz, CDCl_3) 7.88 (2H, dd, J 5.2, 3.0, C(7') $\underline{\text{H}}$), 7.78 (2H, dd, J 5.2, 3.0, C(8') $\underline{\text{H}}$), 7.49 (1H, t, J 5.4, NH), 4.47 (1H, d, J 10.9, C(2') $\underline{\text{H}}$), 4.08 (1H, m, C(2') $\underline{\text{H}}$), 3.48-3.61 (1H, m, C(1') $\underline{\text{H}}_{\text{a}}$), 3.29-3.45 (1H, m, C(1') $\underline{\text{H}}_{\text{b}}$), 2.74-2.89 (1H, m, C(3') $\underline{\text{H}}$), 2.53 (2H, d, J 5.8, C(3') $\underline{\text{H}}_2$), 1.76 (1H, s, OH), 1.11 (3H, d, J 6.6, C(4') $\underline{\text{H}}_3$), 0.87 (3H, d, J 6.6, C(5') $\underline{\text{H}}_3$); δ_{C} (100 MHz, CDCl_3) 171.1 ($\underline{\text{C}}$ (1')O), 168.5 ($\underline{\text{C}}$ (5')O), 134.6 ($\underline{\text{C}}$ (8')H), 131.2 ($\underline{\text{C}}$ (6')H), 123.8 ($\underline{\text{C}}$ (7')H), 117.2 ($\underline{\text{C}}$ (3') $\underline{\text{H}}_2$), 67.4 ($\underline{\text{C}}$ (2')H), 62.3 ($\underline{\text{C}}$ (2')H), 45.3 ($\underline{\text{C}}$ (1') $\underline{\text{H}}_2$), 27.8 ($\underline{\text{C}}$ (3') $\underline{\text{H}}_2$), 23.5 ($\underline{\text{C}}$ (3')H), 19.9 ($\underline{\text{C}}$ (4') $\underline{\text{H}}_3$), 19.4 ($\underline{\text{C}}$ (5') $\underline{\text{H}}_3$); m/z (ESI $^-$) 328 ($[\text{M}-\text{H}]^-$, 100%); **HRMS** (ESI $^+$) $\text{C}_{17}\text{H}_{19}\text{N}_3\text{O}_4$ requires $[\text{M}+\text{Na}]^+$ 352.1268 found 352.1268 (-0.5 ppm).

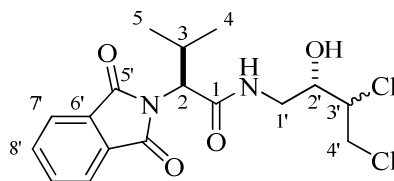
($\pm$)-(2*S)-*N*-((2*R**)-2-(Cyclohex-2-enyl)-2-hydroxyethyl)-2-(1,3-dioxoisindolin-2-yl)-3-methylbutanamide (315)**



4-Vinylcyclohex-1-ene (25 mg, 0.23 mmol) and compound **273** (102 mg, 0.25 mmol) were subjected to General Procedure G to furnish the title compound **315** (7 mg, 0.02 mmol, 8%, *rs* 30:1, *dr* 3:1) as a colourless oil.

$[\alpha]_D^{25} + 10.3$ ($c = 0.5$, chloroform); $\nu_{\max}$ (thin film)/ cm^{-1} 3356br m, 2917m, 1770w, 1715s, 1654m, 1541w, 1467w, 1383m, 1287w, 1123m, 1071m; δ_{H} (400 MHz, CDCl_3) 7.88 (2H, dd, J 5.1, 3.1, C(11') $\underline{\text{H}}$), 7.77 (2H, dd, J 5.1, 3.1, C(12') $\underline{\text{H}}$), 7.34 (1H, m, NH), 5.65 (2H, br s, C(5') $\underline{\text{H}}$, C(6') $\underline{\text{H}}$), 4.45 (1H, d, J 11.3, C(2') $\underline{\text{H}}$), 4.18-4.27 (1H, m, C(2') $\underline{\text{H}}$), 3.55-3.65 (1H, m, C(1') $\underline{\text{H}}_{\text{a}}$), 3.24-3.35 (1H, m, C(1') $\underline{\text{H}}_{\text{b}}$), 2.75-2.91 (1H, m, C(3') $\underline{\text{H}}$), 2.25-2.39 (1H, m, C(3') $\underline{\text{H}}$), 1.85-2.17 (4H, m, C(4') $\underline{\text{H}}_2$, C(7') $\underline{\text{H}}_2$), 1.54-1.75 (2H, m, C(8') $\underline{\text{H}}_2$), 0.84-0.95 (6H, m, C(4') $\underline{\text{H}}_3$, C(5') $\underline{\text{H}}_3$); δ_{C} (100 MHz, CDCl_3) 169.9 ($\underline{\text{C}}$ (1')O), 168.5 ($\underline{\text{C}}$ (9')O), 134.5 ($\underline{\text{C}}$ (12')H), 131.3 ($\underline{\text{C}}$ (5')H), 130.9 ($\underline{\text{C}}$ (10')H), 128.8 ($\underline{\text{C}}$ (6')H), 123.7 ($\underline{\text{C}}$ (11')H), 75.0 ($\underline{\text{C}}$ (2')H), 63.0 ($\underline{\text{C}}$ (2')H), 43.9 ($\underline{\text{C}}$ (1') $\underline{\text{H}}_2$), 38.7 ($\underline{\text{C}}$ (3')H), 27.7 ($\underline{\text{C}}$ (4') $\underline{\text{H}}_2$), 24.9 ($\underline{\text{C}}$ (7') $\underline{\text{H}}_2$), 23.0 ($\underline{\text{C}}$ (8') $\underline{\text{H}}_2$), 19.8 ($\underline{\text{C}}$ (4') $\underline{\text{H}}_3$), 19.5 ($\underline{\text{C}}$ (5') $\underline{\text{H}}_3$); m/z (ESI $^-$) 369 ($[\text{M}-\text{H}]^-$, 100%); **HRMS** (ESI $^+$) $\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_4$ requires $[\text{M}+\text{Na}]^+$ 393.1785 found 393.1788 (-0.4 ppm).

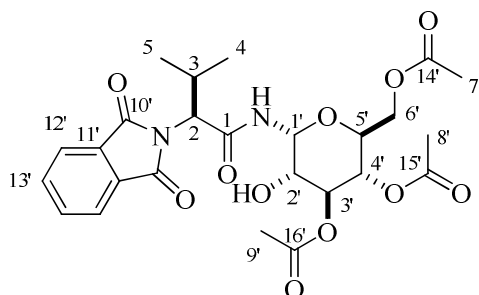
($\pm$)-(S*)-*N*-((S*)-3,4-Dichloro-2-hydroxybutyl)-2-(1,3-dioxoisindolin-2-yl)-3-methylbutanamide (316)



3,4-Dichlorobut-1-ene (29 mg, 0.23 mmol) and compound **273** (102 mg, 0.25 mmol) were subjected to General Procedure G to furnish the title compound **316** (47 mg, 0.12 mmol, 53%, *rs* 30:1, *dr* 8:1 between the 2 main diastereomers) as a colourless gum.

$\nu_{\max}$ (thin film)/cm⁻¹ 3362br m, 2936w, 1712s, 1687m, 1542m, 1384m, 1070m, 976w, 854w, 729m; δ_{H} (400 MHz, CDCl₃) 7.88 (2H, dd, *J* 5.4, 3.2, C(7')H), 7.77 (2H, dd, *J* 5.4, 3.2, C(8')H), 7.46 (1H, t, *J* 5.4, NH), 4.46 (1H, d, *J* 11.3, C(2)H), 4.15-4.26 (1H, m, C(2')H), 4.05 (1H, m, C(3')H), 3.91 (1H, dd, *J* 11.1, 8.4, C(4')H_a), 3.75 (1H, dd, *J* 11.1, 5.4, C(4')H_b), 3.61 (1H, ddd, *J* 14.1, 7.1, 5.4, C(1')H_a), 3.40 (1H, ddd, *J* 14.1, 7.1, 5.4, C(1')H_b), 2.73-2.88 (1H, m, C(3)H), 1.12 (3H, d, *J* 6.6, C(4)H₃), 0.87 (3H, d, *J* 6.6, C(5)H₃); δ_{C} (100 MHz, CDCl₃) 170.5 (C(1)O), 168.5 (C(5')O), 134.6 (C(8')H), 131.2 (C(6')), 123.8 (C(7')H), 69.2 (C(2')H), 63.0 (C(3')H), 62.8 (C(2)H), 44.2 (C(4')H₂), 43.8 (C(1')H₂), 27.8 (C(3)H), 19.8 (C(4)H₃), 19.5 (C(5)H₃); *m/z* (ESI) 385 ([M-H]⁻, 100%); HRMS (ESI) C₁₇H₂₀Cl₂N₂O₄ requires [M-H]⁻ 385.0727, 387.0701 found 385.0726, 387.0696 (+0.61 ppm).

(2S,3S,4S,5S,6R)-2-(Acetoxymethyl)-6-((S)-2-(1,3-dioxoisindolin-2-yl)-3-methylbutanamido)-5-hydroxytetrahydro-2H-pyran-3,4-diyl diacetate (317)

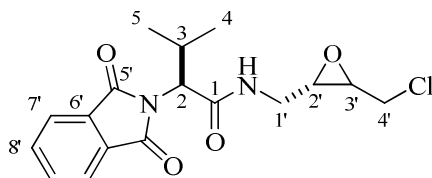


(2S,3R,4S)-2-(Acetoxymethyl)-3,4-dihydro-2H-pyran-3,4-diyl diacetate (64 mg, 0.23 mmol) and compound **273** (102 mg, 0.25 mmol) were subjected to General Procedure G to furnish the title compound **317** (47 mg, 0.05 mmol, 21%, *rs* 30:1, *dr* 16:1) as a colourless oil.

$[\alpha]_{\text{D}}^{25} + 44.2$ (*c* = 0.6, chloroform); $\nu_{\max}$ (thin film)/cm⁻¹ 3357br w, 2976m, 1749s, 1715s, 1530m, 1385s, 1369s, 1311m, 1233s, 1145m, 1069m, 1039m, 980w, 720w; δ_{H} (400 MHz, CDCl₃) 8.37 (1H, d, *J* 7.3, NH), 7.91 (2H, dd, *J* 5.4, 3.2, C(12')H), 7.78 (2H, dd, *J* 5.4, 3.2, C(13')H), 5.72 (1H, dd, *J* 7.3, 5.0, C(1')H), 5.18 (1H, t, *J* 9.0, C(3')H), 5.01 (1H, t, *J* 9.0, C(4')H), 4.52 (1H, d, *J* 11.3, C(2)H), 4.28 (1H, dd, *J* 12.2, 5.5, C(6')H_a), 4.12 (1H, dd, *J* 12.3, 2.5, C(6')H_b), 3.88-4.03 (2H, m, C(2')H, C(5')H), 2.78-2.95 (1H, m, C(3)H), 2.74 (1H, d, *J* 5.7, OH), 2.11 (3H, s, C(7')H₃), 2.09 (3H, s, C(8')H₃), 2.06 (3H, s, C(9')H₃), 1.13 (3H, d, *J* 6.6, C(4)H₃), 0.89 (3H, d, *J* 6.6, C(5)H₃); δ_{C} (100 MHz, CDCl₃) 171.3 (C(14')O), 170.7 (C(15')O), 169.9 (C(16')O), 169.5 (C(1)O), 168.7 (C(10')O), 134.7 (C(13')H), 131.2 (C(11')), 124.0 (C(12')H), 76.2 (C(1')H), 73.6 (C(3')H), 69.0 (C(5')H), 68.8 (C(4')H), 67.9 (C(2')H), 63.7 (C(4')H), 62.0 (C(2)H), 28.2 (C(3)H), 20.8 (C(7')H₃),

20.70 ($\underline{C}(8')\text{H}_3$), 20.67 ($\underline{C}(9')\text{H}_3$), 19.39 ($\underline{C}(4)\text{H}_3$), 19.36 ($\underline{C}(5)\text{H}_3$); **m/z** (ESI⁺) 533 ($[\text{M}-\text{H}]^+$, 100%); **HRMS** (ESI⁺) $\text{C}_{25}\text{H}_{30}\text{N}_2\text{O}_{11}$ requires $[\text{M}+\text{Na}]^+$ 557.1742 found 557.1740 (+1.3 ppm).

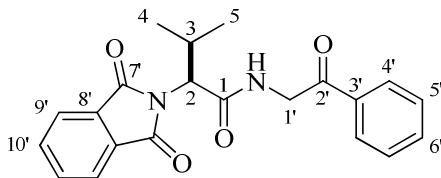
(2S)-N-(((2S)-3-(Chloromethyl)oxiran-2-yl)methyl)-2-(1,3-dioxisoindolin-2-yl)-3-methylbutanamide (318)



To a solution of compound **316** (20 mg, 0.05 mmol) in dichloromethane (5 mL) under argon was added a catalytic amount of lithium hydroxide monohydrate. The reaction mixture was stirred until TLC indicated complete consumption of starting material. The reaction mixture was diluted in dichloromethane (5 mL), washed with brine (2 x 1 mL), dried over Na_2SO_4 and filtered. It was then concentrated *in vacuo* and purified by flash column chromatography in a pipette to furnish the title compound **318** (7 mg, 0.02 mmol, 41%, *dr* 6:1) as a white solid.

$[\alpha]_{\text{D}}^{25} + 15.3$ ($c = 1.3$, chloroform); **m.p.** 164-165 °C; ν_{max} (thin film)/ cm^{-1} 3355br m, 2926br w, 1773w, 1712s, 1662m, 1545m, 1468m, 1385s, 1071m, 901w, 732m, 718m; δ_{H} (400 MHz, CDCl_3) 7.89 (2H, dd, J 5.4, 3.1, $\underline{C}(7')\text{H}$), 7.79 (2H, dd, J 5.4, 3.1, $\underline{C}(8')\text{H}$), 7.45-7.56 (1H, m, $\underline{NH}$), 4.51 (1H, m, $\underline{C}(3')\text{H}$), 4.48 (1H, d, J 11.3, $\underline{C}(2)\text{H}$), 3.87-4.00 (3H, m, $\underline{C}(2')\text{H}$, $\underline{C}(4')\text{H}_2$), 3.75 (1H, m, $\underline{C}(1')\text{H}_a$), 3.55 (1H, m, $\underline{C}(1')\text{H}_b$), 2.76-2.88 (1H, m, $\underline{C}(3)\text{H}$), 1.12 (3H, d, J 6.6, $\underline{C}(4)\text{H}_3$), 0.88 (3H, d, J 6.6, $\underline{C}(5)\text{H}_3$); δ_{C} (100 MHz, CDCl_3) 172.2 ($\underline{C}(1)\text{O}$), 168.4 ($\underline{C}(5')\text{O}$), 134.7 ($\underline{C}(8')\text{H}$), 131.2 ($\underline{C}(6')$), 123.9 ($\underline{C}(7')\text{H}$), 72.6 ($\underline{C}(2')\text{H}$), 62.5 ($\underline{C}(2)\text{H}$), 61.3 ($\underline{C}(3')\text{H}$), 46.6 ($\underline{C}(4')\text{H}_2$), 44.2 ($\underline{C}(1')\text{H}_2$), 27.9 ($\underline{C}(3)\text{H}$), 19.8 ($\underline{C}(4)\text{H}_3$), 19.4 ($\underline{C}(5)\text{H}_3$); **m/z** (ESI⁺) 349 ($[\text{M}-\text{H}]^+$, 80%); **HRMS** (ESI⁺) $\text{C}_{17}\text{H}_{19}\text{ClN}_2\text{O}_4$ requires $[\text{M}-\text{H}]^+$ 349.0955, 351.0929 found 349.0957, 351.0943 (+1.3 ppm).

(S)-2-(1,3-Dioxisoindolin-2-yl)-3-methyl-N-(2-oxo-2-phenylethyl)butanamide (321)

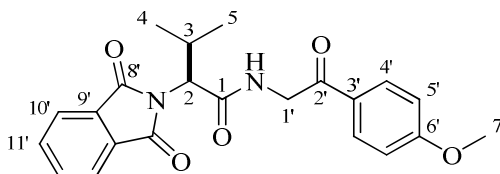


Compound **302_b** (*dr* 1.5:1, 35 mg, 0.10 mmol) was subjected to General Procedure H to furnish the title compound **321** (33 mg, 0.09 mmol, 94%) as a colourless oil.

$[\alpha]_{\text{D}}^{25} - 11.1$ ($c = 0.6$, chloroform); ν_{max} (thin film)/ cm^{-1} 2966br, 1769w, 1714br s, 1672m, 1528m, 1384m, 1357m, 1223w, 1070w, 757m; δ_{H} (400 MHz, CDCl_3) 7.96 (2H, d, J 7.6, $\underline{C}(4')\text{H}$), 7.91 (2H, dd, J 5.3, 3.0, $\underline{C}(9')\text{H}$), 7.85 (1H, br s, $\underline{NH}$), 7.76 (2H, dd, J 5.3, 3.0, $\underline{C}(10')\text{H}$), 7.61 (1H, t, J 7.3, $\underline{C}(6')\text{H}$), 7.48 (2H, dd, J 7.6, 7.3, $\underline{C}(5')\text{H}$), 4.81 (1H, dd, J 19.8, 4.4, $\underline{C}(1')\text{H}_a$), 4.74 (1H, dd, J 19.8, 4.4, $\underline{C}(1')\text{H}_b$), 4.53 (1H, d, J 11.1, $\underline{C}(2)\text{H}$), 2.83-3.15 (1H, m, $\underline{C}(3)\text{H}$), 1.15 (3H, d, J 6.6, $\underline{C}(4)\text{H}_3$),

0.91 (3H, d, J 6.6, C(5) $\underline{H}_3$); δ_{C} (100 MHz, CDCl_3) 193.7 (C(2')O), 169.0 (C(1)O), 168.4 (C(7')O), 134.4 (C(10')H), 134.0 (C(3')), 131.4 (C(6')H), 128.9 (C(8')), 127.9 (br, C(4')H, C(5')H), 123.7 (C(9')H), 62.7 (C(2)H), 46.6 (C(1')H₂), 27.6 (C(3)H), 19.9 (C(4)H₃), 19.5 (C(5)H₃); m/z (ESI⁺) 363 ([M-H]⁻, 100%); **HRMS** (ESI⁺) C₂₁H₂₀N₂O₄ requires [M+Na]⁺ 387.1315, found 387.1307 (+2.6 ppm).

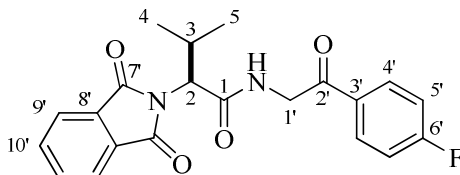
(S)-2-(1,3-Dioxoisindolin-2-yl)-N-(2-(4-methoxyphenyl)-2-oxoethyl)-3-methylbutanamide (322)



Compounds **292_b** (*dr* 2:1, 35 mg, 0.09 mmol) was subjected to General Procedure H to furnish the title compound **322** (32 mg, 0.08 mmol, 92%) as a colourless oil.

$[\alpha]_{\text{D}}^{25}$ – 15.1 (c = 0.6, chloroform); ν_{max} (thin film)/cm⁻¹ 2931w, 1714s, 1667m, 1601m, 1485w, 1384s, 1357w, 1238w, 1173w, 723m; δ_{H} (500 MHz, CDCl_3) 7.94 (2H, d, J 8.6, C(5') $\underline{H}$), 7.90 (2H, dd, J 5.4, 3.0, C(10') $\underline{H}$), 7.85 (1H, br s, NH), 7.75 (2H, dd, J 5.4, 3.0, C(11') $\underline{H}$), 6.94 (2H, d, J 8.6, C(4') $\underline{H}$), 4.75 (1H, dd, J 19.5, 4.4, C(1') $\underline{H}_a$), 4.69 (1H, dd, J 19.5, 4.4, C(1') $\underline{H}_b$), 4.52 (1H, d, J 11.0, C(2) $\underline{H}$), 3.87 (3H, s, C(7') $\underline{H}_3$), 2.91-3.04 (1H, m, C(3) $\underline{H}$), 1.14 (3H, d, J 6.6, C(4) $\underline{H}_3$), 0.90 (3H, d, J 6.6, C(5) $\underline{H}_3$); δ_{C} (125 MHz, CDCl_3) 192.1 (C(2')O), 168.9 (C(1)O), 168.3 (C(8')O), 164.2 (C(6')), 134.3 (C(11')H), 131.4 (C(9')), 130.2 (C(4')H), 127.4 (C(3')), 123.7 (C(10')H), 114.1 (C(5')H), 62.7 (C(2)H), 55.5 (C(7')H₃), 46.3 (C(1')H₂), 27.6 (C(3)H), 20.0 (C(4)H₃), 19.5 (C(5)H₃); m/z (ESI⁺) 393 ([M-H]⁻, 100%); **HRMS** (ESI⁺) C₂₂H₂₂N₂O₅ requires [M+Na]⁺ 417.1421, found 417.1423 (-0.72 ppm).

(S)-2-(1,3-Dioxoisindolin-2-yl)-N-(2-(4-fluorophenyl)-2-oxoethyl)-3-methylbutanamide (323)

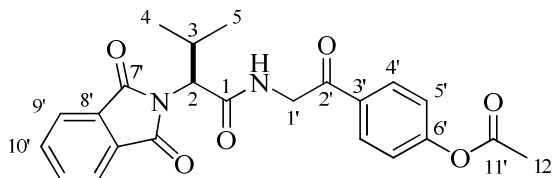


Compound **304_b** (*dr* 2:1, 31 mg, 0.09 mmol) was subjected to General Procedure H to furnish the title compound **323** (27 mg, 0.07 mmol, 84%) as a colourless oil.

$[\alpha]_{\text{D}}^{25}$ + 1.9 (c = 1.1, chloroform); ν_{max} (thin film)/cm⁻¹ 2967w, 1769w, 1714s, 1676s, 1598m, 1509m, 1384m, 1357m, 1230m, 1070w, 888w, 734m; δ_{H} (400 MHz, CDCl_3) 7.94-8.05 (2H, m, C(4') $\underline{H}$), 7.82-7.95 (3H, m, C(9') $\underline{H}$, NH), 7.72 (2H, dd, J 5.4, 3.0, C(10') $\underline{H}$), 7.16 (2H, t, J 8.5, C(5') $\underline{H}$), 4.78 (1H, dd, J 19.8, 4.3, C(1') $\underline{H}_a$), 4.69 (1H, dd, J 19.8, 4.3, C(1') $\underline{H}_b$), 4.52 (1H, d, J 11.3, C(2) $\underline{H}$), 2.88-3.04 (1H, m, C(3) $\underline{H}$), 1.14 (3H, d, J 6.6, C(4) $\underline{H}_3$), 0.90 (3H, d, J 6.6, C(5) $\underline{H}_3$); δ_{C} (100

MHz, CDCl₃) 192.2 ($\underline{C}(2')\text{O}$), 169.1 ($\underline{C}(1)\text{O}$), 168.4 ($\underline{C}(7')\text{O}$), 167.5 ($\underline{C}(6')\text{F}$), 134.4 ($\underline{C}(10')\text{H}$), 130.7 ($\underline{C}(8')$), 130.6 ($\underline{C}(4')\text{H}$), 123.8 ($\underline{C}(9')\text{H}$), 116.2 ($\underline{C}(5')\text{H}$), 62.8 ($\underline{C}(2)\text{H}$), 46.5 ($\underline{C}(1')\text{H}_2$), 27.6 ($\underline{C}(3)\text{H}$), 19.9 ($\underline{C}(4)\text{H}_3$), 19.5 ($\underline{C}(5)\text{H}_3$); **m/z** (ESI⁺) 405 ([M+Na]⁺, 90%), 787 ([2M+Na]⁺, 100); **HRMS** (ESI⁺) C₂₁H₁₉FN₂O₄ requires [M+Na]⁺ 405.1221, found 405.1210 (+3.0 ppm).

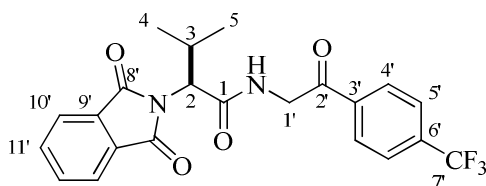
(S)-4-(2-(2-(1,3-Dioxoisindolin-2-yl)-3-methylbutanamido)acetyl)phenyl acetate (324)



Compound **303_b** (*dr* 1.5:1, 34 mg, 0.08 mmol) was subjected to General Procedure H to furnish the title compound **324** (31 mg, 0.07 mmol, 93%) as a colourless oil.

$[\alpha]_{\text{D}}^{25}$ – 9.0 (*c* = 0.9, chloroform); ν_{max} (thin film)/cm⁻¹ 2966w, 1761w, 1714s, 1673m, 1599w, 1527w, 1384m, 1196m, 1164m, 1124w, 912w, 721m; δ_{H} (400 MHz, CDCl₃) 8.00 (2H, d, *J* 8.6, C(4')H), 7.84-7.93 (3H, m, C(9')H, NH), 7.76 (2H, d, *J* 5.5, 3.1, C(10')H), 7.23 (2H, d, *J* 8.6, C(5')H), 4.79 (1H, dd, *J* 19.8, 4.3, C(1')H_a), 4.72 (1H, dd, *J* 19.8, 4.3, C(1')H_b), 4.52 (1H, d, *J* 11.3, C(2)H), 2.88-3.04 (1H, m, C(3)H), 2.33 (3H, s, C(12')H₃), 1.14 (3H, d, *J* 6.7, C(4)H₃), 0.90 (3H, d, *J* 6.7, C(5)H₃); δ_{C} (100 MHz, CDCl₃) 192.5 ($\underline{C}(2')\text{O}$), 169.4 ($\underline{C}(11')\text{O}$), 168.7 ($\underline{C}(1)\text{O}$), 168.3 ($\underline{C}(7')\text{O}$), 155.0 ($\underline{C}(6')$), 134.4 ($\underline{C}(10')\text{H}$), 131.3 ($\underline{C}(8')$), 129.6 ($\underline{C}(5')\text{H}$), 127.9 ($\underline{C}(3')$), 123.7 ($\underline{C}(9')\text{H}$), 122.1 ($\underline{C}(4')\text{H}$), 116.2 ($\underline{C}(5')\text{H}$), 62.6 ($\underline{C}(2)\text{H}$), 46.6 ($\underline{C}(1')\text{H}_2$), 27.6 ($\underline{C}(3)\text{H}$), 21.1 ($\underline{C}(12')\text{H}_3$), 19.8 ($\underline{C}(4)\text{H}_3$), 19.4 ($\underline{C}(5)\text{H}_3$); **m/z** (ESI⁻) 421 ([M-H]⁻, 100%); **HRMS** (ESI⁺) C₂₃H₂₂N₂O₆ requires [M+Na]⁺ 445.1370, found 445.1359 (+2.2 ppm).

(S)-2-(1,3-Dioxoisindolin-2-yl)-3-methyl-N-(2-oxo-2-(4-(trifluoromethyl)phenyl)ethyl)butanamide (325)

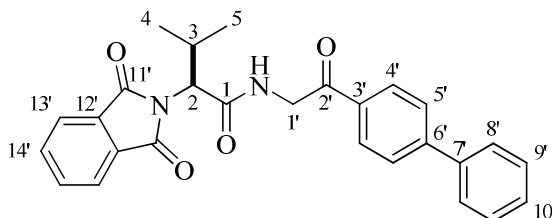


Compound **305_b** (34 mg, 0.08 mmol) was subjected to General Procedure H to furnish the title compound **325** (31 mg, 0.07 mmol, 91%) as a colourless oil.

$[\alpha]_{\text{D}}^{25}$ – 13.4 (*c* = 0.5, chloroform); ν_{max} (thin film)/cm⁻¹ 2968w, 1769w, 1715s, 1681s, 1530m, 1468m, 1384s, 1325s, 1170m, 1129s, 1067s, 989w, 828w, 718m; δ_{H} (400 MHz, CDCl₃) 8.07 (2H, d, *J* 8.3, C(4')H), 7.91 (2H, dd, *J* 5.3, 3.0, C(10')H), 7.87 (1H, t, *J* 4.2, NH), 7.74-7.80 (3H, m, C(5')H, C(11')H), 4.83 (1H, dd, *J* 19.8, 4.5, C(1')H_a), 4.76 (1H, dd, *J* 19.8, 4.5, C(1')H_b), 4.54 (1H, d, *J* 11.1, C(2)H), 2.85-3.08 (1H, m, C(3)H), 1.15 (3H, d, *J* 6.6, C(4)H₃), 0.91 (3H, d, *J* 6.6, C(5)H₃); δ_{C} (100 MHz, CDCl₃) 193.1 ($\underline{C}(2')\text{O}$), 169.2 ($\underline{C}(1)\text{O}$), 168.4 ($\underline{C}(8')\text{O}$), 134.5 ($\underline{C}(11')\text{H}$),

133.2 ($\underline{C}(3')$), 131.4 ($\underline{C}(9')$), 129.3 ($\underline{C}(5')\text{H}$), 128.3 ($\underline{C}(4')\text{H}$), 126.0 (q, J 3.7, $\underline{C}(7')\text{F}_3$), 123.8 ($\underline{C}(10')\text{H}$), 62.8 ($\underline{C}(2)\text{H}$), 46.9 ($\underline{C}(1')\text{H}_2$), 27.7 ($\underline{C}(3)\text{H}$), 19.9 ($\underline{C}(4)\text{H}_3$), 19.5 ($\underline{C}(5)\text{H}_3$); m/z (ESI⁺) 431 ([$\text{M}-\text{H}$]⁻, 100%); **HRMS** (ESI⁺) $\text{C}_{22}\text{H}_{19}\text{F}_3\text{N}_2\text{O}_4$ requires [$\text{M}+\text{Na}$]⁺ 455.1189, found 455.1177 (+2.9 ppm).

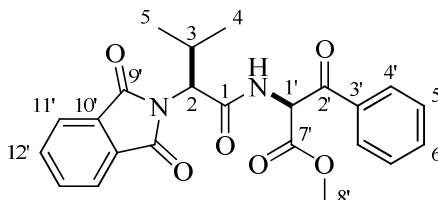
(S)-N-(2-(Biphenyl-4-yl)-2-oxoethyl)-2-(1,3-dioxoisindolin-2-yl)-3-methylbutanamide (326)



Compound **309b** (33 mg, 0.07 mmol) was subjected to General Procedure H to furnish the title compound **326** (28 mg, 0.06 mmol, 85%) as a colourless oil.

$[\alpha]_{\text{D}}^{25} - 8.2$ ($c = 0.9$, chloroform); ν_{max} (thin film)/ cm^{-1} 2966w, 1769w, 1714s, 1673s, 1604m, 1525m, 1384m, 1357m, 1229w, 1070w, 795w, 723m; δ_{H} (500 MHz, CDCl_3) 7.98-8.14 (2H, m, $\underline{C}(4')\text{H}$), 7.84-7.97 (3H, m, $\underline{C}(13')\text{H}$, $\underline{\text{NH}}$), 7.76 (2H, dd, J 5.5, 3.1, $\underline{C}(14')\text{H}$), 7.69-7.73 (2H, m, $\underline{C}(5')\text{H}$), 7.60-7.65 (2H, m, $\underline{C}(8')\text{H}$), 7.46-7.51 (2H, m, $\underline{C}(9')\text{H}$), 7.38-7.44 (1H, m, $\underline{C}(10')\text{H}$), 4.84 (1H, dd, J 19.5, 4.4, $\underline{C}(1')\text{H}_a$), 4.78 (1H, dd, J 19.5, 4.4, $\underline{C}(1')\text{H}_b$), 4.54 (1H, d, J 11.0, $\underline{C}(2)\text{H}$), 2.91-3.08 (1H, m, $\underline{C}(3)\text{H}$), 1.16 (3H, d, J 6.6, $\underline{C}(4)\text{H}_3$), 0.92 (3H, d, J 6.6, $\underline{C}(5)\text{H}_3$); δ_{C} (125 MHz, CDCl_3) 193.3 ($\underline{C}(2')\text{O}$), 169.1 ($\underline{C}(1)\text{O}$), 168.4 ($\underline{C}(11')\text{O}$), 146.7 ($\underline{C}(6')$), 139.5 ($\underline{C}(7')$), 134.4 ($\underline{C}(14')\text{H}$), 133.1 ($\underline{C}(3')$), 131.4 ($\underline{C}(12')$), 129.0 ($\underline{C}(4')\text{H}$), 128.5 ($\underline{C}(9')\text{H}$), 128.4 ($\underline{C}(10')\text{H}$), 127.5 ($\underline{C}(5')\text{H}$), 127.3 ($\underline{C}(8')\text{H}$), 123.8 ($\underline{C}(13')\text{H}$), 62.8 ($\underline{C}(2)\text{H}$), 46.7 ($\underline{C}(1')\text{H}_2$), 27.7 ($\underline{C}(3)\text{H}$), 20.0 ($\underline{C}(4)\text{H}_3$), 19.5 ($\underline{C}(5)\text{H}_3$); m/z (ESI⁺) 463 ([$\text{M}+\text{Na}$]⁺, 50%), 903 ([$2\text{M}+\text{Na}$]⁺, 100); **HRMS** (ESI⁺) $\text{C}_{27}\text{H}_{24}\text{N}_2\text{O}_4$ requires [$\text{M}+\text{Na}$]⁺ 463.1628, found 463.1617 (+2.8 ppm).

(S)-Methyl-2-((S)-2-(1,3-dioxoisindolin-2-yl)-3-methylbutanamido)-3-oxo-3-phenylpropanoate (327)

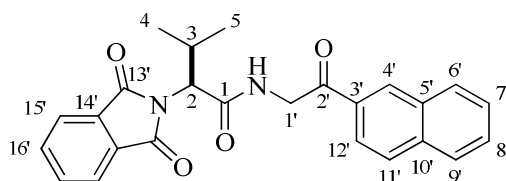


Compound **312b** (*dr* 1.7:1, 42 mg, 0.1 mmol) was subjected to General Procedure H to furnish the title compound **327** (37 mg, 0.09 mmol, 87%) as a colourless oil.

$[\alpha]_{\text{D}}^{25} + 18.1$ ($c = 1.3$, chloroform); ν_{max} (thin film)/ cm^{-1} 3334br w, 2965w, 1712br s, 1520m, 1385s, 1282m, 1239m, 1070m, 1048w, 914w, 889w, 722m; δ_{H} (400 MHz, CDCl_3) 8.00 (1H, d, J 4.9, $\underline{\text{NH}}$), 7.85 (2H, dd, J 5.5, 3.1, $\underline{C}(11')\text{H}$), 7.74 (2H, dd, J 5.5, 3.1, $\underline{C}(12')\text{H}$), 7.32-7.40 (5H, m,

C(4')H, C(5')H, C(6')H), 6.22 (1H, d, *J* 4.9, C(1')H), 4.46 (1H, d, *J* 11.4, C(2)H), 3.78 (3H, s, C(8')H), 2.96 (1H, m, C(3)H), 1.13 (3H, d, *J* 6.6, C(4)H₃), 0.87 (3H, d, *J* 6.6, C(5)H₃); δ_c (100 MHz, CDCl₃) 188.1 (C(2')O), 168.6 (C(7')O), 168.4 (C(9')O), 159.9 (C(1'O)), 134.5 (C(12')H), 132.6 (C(3')), 131.2 (C(10')), 129.4 (C(4')H), 129.2 (C(6')H), 128.6 (C(5')H), 123.8 (C(11')H), 62.7 (C(2)H), 59.9 (C(1')H), 53.1 (C(8')H₃), 27.9 (C(3)H), 19.6 (C(4)H₃), 19.5 (C(5)H₃); *m/z* (ESI⁺) 421 ([M-H]⁻, 100%); **HRMS** (ESI⁺) C₂₃H₂₂N₂O₆ requires [M+Na]⁺ 445.1370 found 445.1358 (+2.5 ppm).

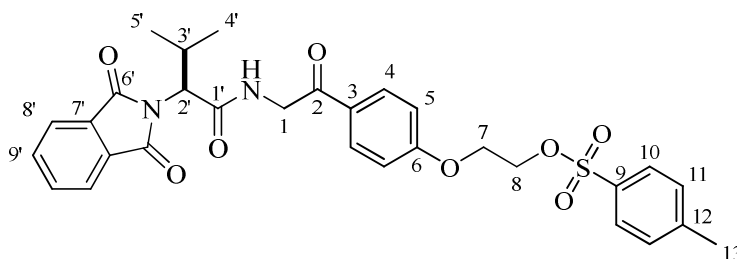
(S)-2-(1,3-Dioxoisindolin-2-yl)-3-methyl-N-(2-(naphthalen-2-yl)-2-oxoethyl)butanamide (328)



Compound **307_b** (*dr* 2:1, 32 mg, 0.08 mmol) was subjected to General Procedure H to furnish the title compound **328** (29 mg, 0.07 mmol, 89%) as a colourless oil.

$[\alpha]_D^{25}$ – 8.6 (*c* = 1.1, chloroform); $\nu_{\max}$ (thin film)/cm⁻¹ 2929w, 1769w, 1714br s, 1670s, 1597m, 1524m, 1469m, 1385s, 1359s, 1189m, 1070m, 943w, 727s; δ_H (400 MHz, CDCl₃) 8.47 (1H, s, C(4')H), 7.99 (1H, dd, *J* 8.6, 1.5, C(12')H), 7.91-7.96 (2H, m, C(6')H, NH), 7.83-7.91 (4H, m, C(9')H, C(11')H, C(15')H), 7.74 (2H, dd, *J* 5.3, 3.0, C(16')H), 7.51-7.64 (2H, m, C(7')H, C(8')H), 4.94 (1H, dd, *J* 19.6, 4.4, C(1')H_a), 4.87 (1H, dd, *J* 19.6, 4.4, C(1')H_b), 4.56 (1H, d, *J* 11.4, C(2)H), 2.92-3.07 (1H, m, C(3)H), 1.16 (3H, d, *J* 6.6, C(4)H₃), 0.91 (3H, d, *J* 6.6, C(5)H₃); δ_c (100 MHz, CDCl₃) 193.6 (C(2')O), 169.0 (C(1'O)), 168.3 (C(13')O), 135.9 (C(10')), 134.3 (C(16')H), 132.3 (C(5')), 131.6 (C(4')H), 131.4 (C(14')), 129.9 (C(6')H), 129.6 (C(3')), 128.9 (C(11')H), 128.7 (C(8')H), 127.8 (C(9')H), 127.0 (C(7')H), 123.7 (C(12')H), 123.2 (C(15')H), 62.7 (C(2)H), 46.7 (C(1')H₂), 27.6 (C(3)H), 19.9 (C(4)H₃), 19.5 (C(5)H₃); *m/z* (ESI⁺) 437 ([M+Na]⁺, 40%), 851 ([2M+Na]⁺, 100); **HRMS** (ESI⁺) C₂₅H₂₂N₂O₄ requires [M+Na]⁺ 437.1472, found 437.1464 (+2.2 ppm).

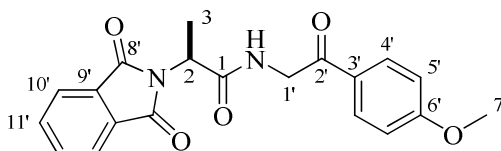
(S)-2-(4-(2-(2-(1,3-Dioxoisindolin-2-yl)-3-methylbutanamido)acetyl)phenoxy)ethyl-4-methylbenzenesulfonate (329)



Compound **310b** (*dr* 2:1, 35 mg, 0.06 mmol) was subjected to General Procedure H to furnish the title compound **329** (32 mg, 0.05 mmol, 91%) as a colourless oil.

$[\alpha]_D^{25} - 12.5$ ($c = 0.4$, chloroform); $\nu_{\max}$ (thin film)/ cm^{-1} 3373br m, 2966s, 1769s, 1711s, 1611m, 1512m, 1384m, 1248m, 1176s, 1071m, 1021m, 915br m, 816m, 730s; δ_{H} (400 MHz, CDCl_3) 7.69–8.00 (9H, m, C(10)H, C(11)H, C(8')H, C(9')H, NH), 7.35 (2H, d, J 8.4, C(4)H), 6.83 (2H, d, J 8.4, C(5)H), 4.71 (2H, m, C(1)H₂), 4.52 (1H, d, J 11.2, C(2')H), 4.31–4.44 (2H, m, C(8)H₂), 4.16–4.28 (2H, m, C(7)H₂), 2.84–3.11 (1H, m, C(3')H), 2.45 (3H, s, C(13)H₃), 1.14 (3H, d, J 6.6, C(4')H₃), 0.90 (3H, d, J 6.6, C(5')H₃); δ_{C} (100 MHz, CDCl_3) 192.1 (C(2)O), 169.0 (C(1')O), 162.4 (C(6)), 145.1 (C(12)), 134.4 (C(9')H), 132.7 (C(3)), 131.4 (C(9)), 130.2 (C(5)H), 129.9 (C(11)H), 128.0 (C(10)H), 123.7 (C(8')H), 114.5 (C(4)H), 67.6 (C(8)H₂), 65.6 (C(7)H₂), 62.7 (C(2')H), 46.3 (C(1)H₂), 27.6 (C(3')H), 21.7 (C(13)H₃), 20.0 (C(4')H₃), 19.5 (C(5')H₃); m/z (ESI^+) 601 ($[\text{M}+\text{H}]^+$, 100%); **HRMS** (ESI^+) $\text{C}_{30}\text{H}_{30}\text{N}_2\text{O}_8\text{S}$ requires $[\text{M}+\text{Na}]^+$ 601.1615 found 601.1118 (+1.4 ppm).

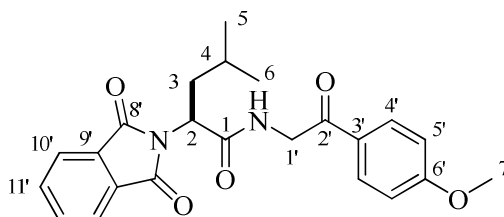
(S)-2-(1,3-Dioxoisindolin-2-yl)-N-(2-(4-methoxyphenyl)-2-oxoethyl)propanamide (330)



Compound **297b** (*dr* 1.2:1, 32 mg, 0.09 mmol) was subjected to General Procedure H to furnish the title compound **330** (29 mg, 0.08 mmol, 91%) as a colourless oil.

$[\alpha]_D^{25} + 14.4$ ($c = 0.7$, chloroform); $\nu_{\max}$ (thin film)/ cm^{-1} 2926br, 1777w, 1715s, 1668m, 1601m, 1513w, 1387m, 1356m, 1235m, 1173m, 1022w, 912w, 722m; δ_{H} (400 MHz, CDCl_3) 7.93 (2H, d, J 8.8, C(4')H), 7.89 (2H, dd, J 5.4, 3.0, C(10')H), 7.75 (2H, dd, J 5.4, 3.0, C(11')H), 7.11 (1H, br s, NH), 6.96 (2H, d, J 8.8, C(5')H), 5.04 (1H, q, J 7.3, C(2)H), 4.73 (2H, d, J 4.0, C(1')H₂), 3.88 (3H, s, C(7')H₃), 1.79 (3H, d, J 7.3, C(3)H₃); δ_{C} (100 MHz, CDCl_3) 192.1 (C(2')O), 169.1 (C(1)O), 167.7 (C(8')O), 164.3 (C(6')), 134.2 (C(11')H), 131.9 (C(9')), 130.3 (C(4')H), 127.2 (C(3')), 123.6 (C(10')), 114.1 (C(5')H), 55.5 (C(7')H₃), 49.2 (C(2)H), 46.3 (C(1')H₂), 15.3 (C(3)H₃); m/z (ESI^-) 365 ($[\text{M}-\text{H}]^-$, 100%); **HRMS** (ESI^+) $\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}_5$ requires $[\text{M}+\text{Na}]^+$ 389.1108, found 389.1102 (+1.7 ppm).

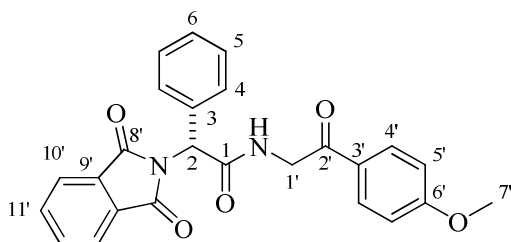
(S)-2-(1,3-Dioxoisindolin-2-yl)-N-(2-(4-methoxyphenyl)-2-oxoethyl)-4-methylpentanamide (331)



Compounds **297c** (*dr* 2:1, 31 mg, 0.08 mmol) was subjected to General Procedure H to furnish the title compound **331** (28 mg, 0.07 mmol, 90%) as a colourless oil.

$[\alpha]_D^{25} - 19.3$ ($c = 0.7$, chloroform); $\nu_{\max}$ (thin film)/ cm^{-1} 2959w, 1774w, 1714s, 1667m, 1600m, 1514m, 1384m, 1261m, 1173m, 721m; δ_{H} (400 MHz, CDCl_3) 7.85-7.99 (4H, m, C(4')H, C(10')H), 7.76 (2H, dd, J 5.3, 3.1, C(11')H), 7.23 (1H, br s, NH), 6.96 (2H, d, J 8.7, C(5')H), 5.02 (1H, dd, J 12.8, 4.9, C(2)H), 4.72 (2H, d, J 3.9, C(1')H₂), 3.89 (3H, s, C(7')H₃), 2.41-2.55 (1H, m, C(3)H_a), 1.93 (1H, ddd, J 12.8, 9.7, 4.9, C(3)H_b), 1.42-1.56 (1H, m, C(4)H), 0.97 (6H, dd, J 5.9, 5.9, C(5)H₃, C(6)H₃); δ_{C} (100 MHz, CDCl_3) 192.1 (C(2')O), 169.3 (C(1)O), 168.2 (C(8')O), 164.3 (C(6')), 134.3 (C(11')H), 131.7 (C(9')), 130.3 (C(4')H), 127.2 (C(3')), 123.7 (C(10')H), 114.1 (C(5')H), 55.5 (C(7')H₃), 52.9 (C(2)H), 46.3 (C(1')H₂), 37.5 (C(3)H₂), 25.3 (C(4)H), 23.2 (C(5)H₃), 21.2 (C(6)H₃); m/z (ESI⁺) 407 ([M-H]⁺, 100%); **HRMS** (ESI⁺) $\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_5$ requires $[\text{M}+\text{Na}]^+$ 431.1577, found 431.1571 (+1.4 ppm).

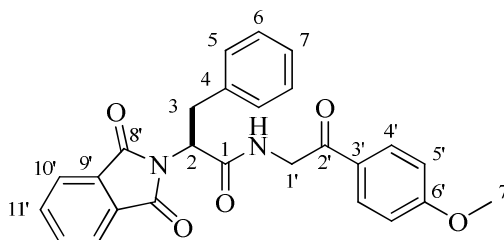
(±)-(R)-2-(1,3-dioxoisindolin-2-yl)-N-(2-(4-methoxyphenyl)-2-oxoethyl)-2-phenylacetamide (332)



Compound **297e** (34 mg, 0.08 mmol) was subjected to General Procedure H to furnish the title compound **332** (31 mg, 0.07 mmol, 92%) as a colourless oil.

$[\alpha]_D^{23}$ racemised; $\nu_{\max}$ (thin film)/ cm^{-1} 2920w, 1771w, 1716br s, 1671m, 1600m, 1513m, 1385m, 1359w, 1242w, 1173m, 895w, 721m; δ_{H} (400 MHz, CDCl_3) 7.81-8.02 (4H, m, C(4')H, C(10')H), 7.59-7.79 (4H, m, C(4)H, C(11')H), 7.33-7.54 (3H, m, C(5)H, C(6)H), 6.78-7.05 (3H, m, C(5')H, NH), 6.00 (1H, s, C(2)H), 4.80 (1H, dd, J 19.6, 4.1, C(1')H_a), 4.73 (1H, dd, J 19.6, 4.1, C(1')H_b), 3.87 (3H, s, C(7')H₃); δ_{C} (100 MHz, CDCl_3) 191.8 (C(2')O), 167.7 (C(8')O), 167.2 (C(1)O), 164.3 (C(6')), 134.6 (C(3)), 134.1 (C(11')H), 131.9 (C(9')), 130.2 (C(6)H), 129.7 (C(4')H), 129.31 (C(4)H), 129.29 (C(5)H), 127.2 (C(3')), 123.6 (C(10')H), 114.1 (C(5')H), 57.9 (C(2)H), 55.5 (C(7')H₃), 46.4 (C(1')H₂); m/z (ESI⁺) 451 ([M+Na]⁺, 85%), 879 ([2M+Na]⁺, 100); **HRMS** (ESI⁺) $\text{C}_{25}\text{H}_{20}\text{N}_2\text{O}_5$ requires $[\text{M}+\text{Na}]^+$ 451.1264, found 451.1259 (+1.1 ppm).

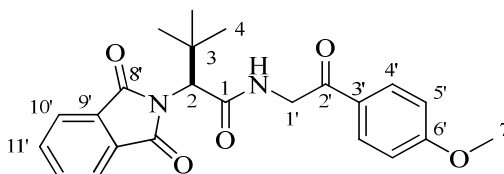
(S)-2-(1,3-Dioxisoindolin-2-yl)-N-(2-(4-methoxyphenyl)-2-oxoethyl)-3-phenylpropanamide (333)



Compound **297f** (*dr* 1.8:1, 32 mg, 0.07 mmol) was subjected to General Procedure H to furnish the title compound **333** (28 mg, 0.06 mmol, 88%) as a colourless oil.

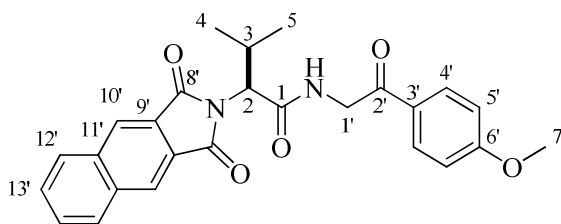
$[\alpha]_{\text{D}}^{25} - 79.4$ ($c = 0.8$, chloroform); ν_{max} (thin film)/ cm^{-1} 2932br, 1775w, 1715s, 1667m, 1600m, 1513m, 1384s, 1358m, 1239m, 1173m, 1088w, 988w, 720m; δ_{H} (400 MHz, CDCl_3) 7.94 (2H, d, J 8.9, C(4')H), 7.81 (2H, dd, J 5.4, 3.1, C(10')H), 7.70 (2H, dd, J 5.4, 3.1, C(11')H), 7.06-7.23 (6H, m, C(5)H, C(6)H, C(7)H, NH), 6.96 (2H, d, J 8.9, C(5')H), 5.23 (1H, t, J 8.9, C(2)H), 4.75 (2H, d, J 3.9, C(1')H₂), 3.89 (3H, s, C(7')H₃), 3.63 (2H, d, J 8.7, C(3)H₂); δ_{C} (125 MHz, CDCl_3) 191.9 (C(2')O), 168.4 (C(8')O), 167.9 (C(1)O), 164.3 (C(6')), 136.6 (C(4)), 134.2 (C(11')H), 131.4 (C(9')), 130.3 (C(4')H), 128.9 (C(5)H), 128.6 (C(6)H), 127.2 (C(3')), 126.9 (C(7)H), 123.6 (C(10')H), 114.2 (C(5')H), 55.6 (C(2)H), 55.5 (C(7')H₃), 34.8 (C(3)H₂); m/z (ESI^+) 465 ($[\text{M}+\text{Na}]^+$, 100%), 907 ($[\text{2M}+\text{Na}]^+$, 80); **HRMS** (ESI^+) $\text{C}_{26}\text{H}_{22}\text{N}_2\text{O}_5$ requires $[\text{M}+\text{Na}]^+$ 465.1421, found 465.1414 (+1.6 ppm).

(S)-2-(1,3-Dioxisoindolin-2-yl)-N-(2-(4-methoxyphenyl)-2-oxoethyl)-3,3-dimethylbutanamide (334)



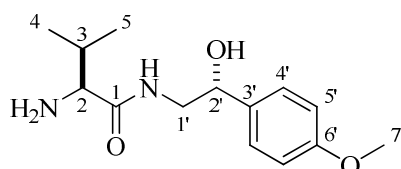
Compound **297d** (*dr* 2.5:1, 35 mg, 0.09 mmol) was subjected to General Procedure H to furnish the title compound **334** (33 mg, 0.08 mmol, 93%) as a colourless oil

$[\alpha]_{\text{D}}^{25} + 5.5$ ($c = 0.4$, chloroform); ν_{max} (thin film)/ cm^{-1} 3356br, 2961w, 1773w, 1716s, 1666br m, 1601m, 1514m, 1380br m, 1329m, 1262m, 1172m, 1030w, 988w, 719m; δ_{H} (500 MHz, CDCl_3) 8.12 (1H, br s, NH), 7.88-8.01 (4H, m, C(4')H, C(10')H), 7.77 (2H, dd, J 5.4, 2.8, C(11')H), 6.95 (2H, d, J 8.8, C(5')H), 4.91 (1H, s, C(2)H), 4.82 (1H, dd, J 19.2, 4.4, C(1')H_a), 4.69 (1H, dd, J 19.2, 4.4, C(1')H_b), 3.88 (3H, s, C(7')H₃), 1.21 (9H, s, C(4)H₃); δ_{C} (125 MHz, CDCl_3) 192.1 (C(2')O), 168.9 (C(1)O), 168.0 (C(8')O), 164.2 (C(6')), 134.4 (C(11')H), 131.4 (C(9')), 130.2 (C(4')H), 127.5 (C(3')), 123.8 (C(10')H), 114.1 (C(5')H), 64.6 (C(2)H), 55.5 (C(7')H₃), 46.5 (C(1')H₂), 36.2 (C(3)), 28.4 (C(4)H₃); m/z (ESI^+) 431 ($[\text{M}+\text{Na}]^+$, 95%), 839 ($[\text{2M}+\text{Na}]^+$, 100); **HRMS** (ESI^+) $\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_5$ requires $[\text{M}+\text{Na}]^+$ 431.1577, found 431.1577 (+0.09 ppm).

(S)-2-(1,3-Dioxo-1H-benzof[isoindol-2(3H)-yl)-N-(2-(4-methoxyphenyl)-2-oxoethyl)-3-methylbutanamide (335)

Compound **299b** (*dr* 1.4:1,77 mg, 0.17 mmol) was subjected to General Procedure H to furnish the title compound **335** (67 mg, 0.15 mmol, 90%) as a colourless oil.

$[\alpha]_D^{25} + 13.0$ ($c = 2.7$, chloroform); $\nu_{\max}$ (thin film)/ cm^{-1} 3355br w, 2966w, 1766m, 1706s, 1669s, 1601m, 1515m, 1443w, 1423w, 1357br m, 1264m, 1239m, 1172m, 1101m, 909w, 833w, 767m, 732m; δ_{H} (400 MHz, CDCl_3) 8.37 (2H, s, C(10')H), 8.06 (2H, dd, J 6.1, 3.2, C(12')H), 7.99 (1H, br s, NH), 7.93 (2H, d, J 8.9, C(4')H), 7.70 (2H, dd, J 6.1, 3.2, C(13')H), 6.93 (2H, d, J 8.9, C(5')H), 4.77 (1H, dd, J 19.4, 4.4, C(1')H_a), 4.70 (1H, dd, J 19.4, 4.4, C(1')H_b), 4.60 (1H, d, J 11.1, C(2)H), 3.85 (3H, s, C(7')H₃), 2.92-3.11 (1H, m, C(3)H), 1.16 (3H, d, J 6.5, C(4)H₃), 0.92 (3H, d, J 6.5, C(5)H₃); δ_{C} (125 MHz, CDCl_3) 192.1 (C(2')O), 169.0 (C(1)O), 168.1 (C(8')O), 164.1 (C(6')), 135.5 (C(11')), 130.3 (C(13')H), 130.2 (C(12')H), 129.4 (C(4')H), 127.4 (C(3')), 126.9 (C(9')), 125.3 (C(10')H), 114.0 (C(5')H), 62.9 (C(2)H), 55.5 (C(7')H₃), 46.3 (C(1')H₂), 27.6 (C(3)H), 20.0 (C(4)H₃), 19.5 (C(5)H₃); m/z (ESI⁻) 479 ([M-H]⁻, 100%); **HRMS** (ESI⁺) $\text{C}_{26}\text{H}_{24}\text{N}_2\text{O}_5$ requires [M+Na]⁺ 476.1577 found 476.1571 (+1.7 ppm).

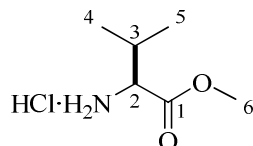
(S)-2-Amino-N-((R)-2-hydroxy-2-(4-methoxyphenyl)ethyl)-3-methylbutanamide (336)

To compound **292** (136 mg, 0.34 mmol) in absolute ethanol at rt under argon was added dropwise hydrazine monohydrate (1.5 eq.). The reaction mixture was heated at 70 °C until TLC indicated complete consumption of starting material (typically 5-6 h). The reaction mixture was concentrated *in vacuo* to a few mL **at rt** and the residue was purified by flash column chromatography, eluting with dichloromethane/methanol/aq. ammoniac (100:0:1 drop to 9:1:1 drop) to furnish the title compound **336** (71.4 mg, 0.27 mmol, 78%) as a colourless solid.

$[\alpha]_D^{25} - 30.8$ ($c = 0.2$, methanol); **m.p.** 131-132 °C; $\nu_{\max}$ (thin film)/ cm^{-1} 3423br, 1656s, 1051m, 1026m, 1006m, 824m, 762m; δ_{H} (400 MHz, CDCl_3) 7.71 (1H, br s, NH), 7.30 (2H, d, J 8.6, C(5')H), 6.89 (2H, d, J 8.6, C(4')H), 4.81 (1H, dd, J 7.8, 3.2, C(2')H), 3.81 (3H, s, C(7')H₃), 3.53-3.63 (1H, m, C(1')H_a), 3.46 (1H, ddd, J 13.8, 7.8, 5.6, C(1')H_b), 3.27 (1H, br s, C(2)H), 2.07-2.45 (3H, br s, OH, NH₂), 0.99 (3H, d, J 6.8, C(4)H₃), 0.83 (3H, d, J 6.8, C(5)H₃); δ_{C} (100 MHz,

CD₃OD) 177.2 (C(1)O), 160.9 (C(6')), 135.9 (C(3')), 128.6 (C(4')H), 114.9 (C(5')H), 73.4 (C(2')H), 61.8 (C(2)H), 55.8 (C(7')H₃), 47.8 (C(1')H₂), 33.4 (C(3)H), 19.9 (C(4)H₃), 17.8 (C(5)H₃); **m/z** (ESI⁺) 267 ([M+H]⁺, 95%), 533 ([2M+H]⁺, 100); **HRMS** (ESI⁺) C₁₄H₂₂N₂O₃ requires [M+H]⁺ 267.1703, found 267.1702 (+2.4 ppm).

(S)-Methyl 2-amino-3-methylbutanoate hydrochloride (341)

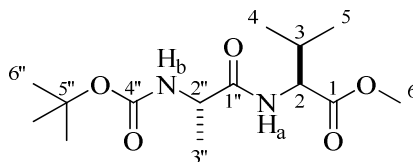


To a solution of L-valine (1.0 eq., 5.0 g, 42.7 mmol) in methanol (50 mL) at 0 °C under argon was added dropwise thionyl chloride (1.0 eq., 3.4 mL, 42.7 mmol). **Caution, exothermic reaction.** The reaction mixture was stirred at rt for 12 h then concentrated *in vacuo* to give the title compound **341** (42.7 mmol, 100%) as a white solid

δ_H (400 MHz, (CD₃)₂SO) 8.78 (2H, s, NH₂), 3.92 (1H, m, C(2)H), 3.78 (3H, s, C(6)H₃), 1.76 (3H, d, *J* 6.7, C(4)H₃), 1.68 (3H, d, *J* 6.7, C(4)H₃); **δ_C** (100 MHz, (CD₃)₂SO) 174.1 (C(1)O), 52.3 (C(2)H), 51.9 (C(6)H₃), 20.0 (C(4)H₃), 19.9 (C(5)H₃).

Spectroscopic data were consistent with those reported in the literature.¹⁶¹

(S)-Methyl 2-((S)-2-(tert-butoxycarbonylamino)propanamido)-3-methylbutanoate (342)



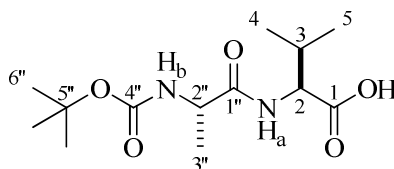
To a solution of compound **340** (1.0 eq., 189 mg, 1.0 mmol) and compound **341** (1.0 eq., 167 mg, 1.0 mmol) in *N,N*-dimethylformamide (5 mL) under argon at rt, was added dropwise triethylamine (2.0 eq., 202 mg, 2.0 mmol) followed by the addition of a solution of *O*-benzotriazole-*N,N,N',N'*-tetramethyluroniumhexafluorophosphate (1.0 eq. 379 mg, 1.0 mmol) in *N,N'*-dimethylformamide (5 mL) (syringe pump 1mL·min⁻¹). After completion of the addition, the reaction mixture was stirred vigorously for 12 h at rt. The reaction mixture was then washed with brine (3 x 100 mL) and concentrated *in vacuo* to a few mL. The residue was purified by flash column chromatography, eluting with ethyl acetate/petrol gradient (100:0 to 70:30) to give the title compound **342** as a colourless gum (272 mg, 0.85 mmol, 85%).

δ_H (400 MHz, CDCl₃) 6.75 (1H, br s, NH_a), 5.14 (1H, d, *J* 7.1, NH_b), 4.50 (1H, dd, *J* 7.9, 5.1, C(2'')H), 4.19 (1H, br s, C(2)H), 3.71 (3H, s, C(6)H₃), 2.09-2.28 (1H, m, C(3)H), 1.42 (9H, s, C(6'')H₃), 1.33 (3H, d, *J* 7.9, C(3'')H₃), 0.91 (3H, d, *J* 6.8, C(4)H₃), 0.88 (3H, d, *J* 6.8, C(5)H₃); **δ_C** (100 MHz, CDCl₃) 172.6 (C(1'')O), 172.2 (C(1)O), 155.5 (C(4'')O), 80.0 (C(5'')), 57.0 (C(2)H),

52.0 ($\underline{C}(6)H_3$), 49.9 ($\underline{C}(2'')H$), 31.5 ($\underline{C}(3)H$), 28.2 ($\underline{C}(6'')H_3$), 18.9 (br s, $\underline{C}(4)H_3$, $\underline{C}(5)H_3$), 17.6 ($\underline{C}(3'')H_3$).

Spectroscopic data were consistent with those reported in the literature.¹⁶²

(S)-2-((S)-2-(tert-Butoxycarbonylamino)propanamido)-3-methylbutanoic acid (343)

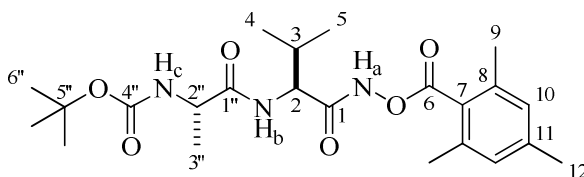


To a solution of compound **342** (1.0 eq., 658 mg, 2.2 mmol) in a mixture of tetrahydrofuran (45 mL) and water (15 mL) under argon at 0 °C was added lithium hydroxide monohydrate (1.1 eq., 100 mg, 2.4 mmol). The reaction mixture was stirred until TLC indicated complete consumption of starting material (12 h). The reaction mixture was then acidified to pH 1 with a 3 M aqueous HCl solution and extracted with diethyl ether (3 x 50 mL). The organic phase was separated, washed with brine (20 mL), dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure to give the title compound **343** as a white solid (quantitative).

δ_H (400 MHz, CDCl₃) 8.48-9.43 (1H, br s, $\underline{OH}$), 6.79-7.21 (1H, m, $\underline{NH_a}$), 5.47 (1H, br s, $\underline{NH_b}$), 4.55 (1H, dd, J 7.5, 4.7, $\underline{C}(2'')H$), 3.70-4.11 (1H, m, $\underline{C}(2)H$), 2.03-2.42 (1H, m, $\underline{C}(3)H$), 1.42 (9H, s, $\underline{C}(6'')H_3$), 1.34 (3H, d, J 7.5, $\underline{C}(3'')H_3$), 0.94 (3H, d, J 6.8, $\underline{C}(4)H_3$), 0.90 (3H, d, J 6.8, $\underline{C}(5)H_3$); δ_C (100 MHz, CDCl₃) 172.6 ($\underline{C}(1'')O$), 171.2 ($\underline{C}(1)O$), 155.4 ($\underline{C}(4'')O$), 80.1 ($\underline{C}(5'')$), 57.2 ($\underline{C}(2)H$), 52.1 ($\underline{C}(6)H_3$), 49.9 ($\underline{C}(2'')H$), 31.4 ($\underline{C}(3)H$), 28.3 ($\underline{C}(6'')H_3$), 18.9 (br s, $\underline{C}(4)H_3$, $\underline{C}(5)H_3$), 17.5 ($\underline{C}(3'')H_3$).

Spectroscopic data were consistent with those reported in the literature.¹⁶³

tert-Butyl (S)-1-((S)-3-methyl-1-oxo-1-(2,4,6-trimethylbenzoyloxyamino)butan-2-ylamino)-1-oxopropan-2-ylcarbamate (344)

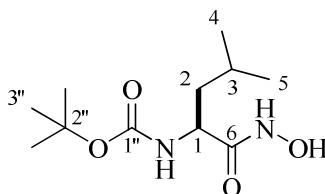


Compound **343** (890 mg, 2.9 mmol) was subjected to General Procedure F to furnish the title compound **344** (820 mg, 1.8 mmol, 63%) as a colourless oil.

$[\alpha]_D^{25}$ - 3.1 (c = 3.0, chloroform); ν_{max} (thin film)/cm⁻¹ 3277br m, 2975s, 1779m, 1682s, 1652br s, 1612m, 1517br m, 1454m, 1367m, 1234m, 1166s, 1032s, 851w, 738w; δ_H (400 MHz, CDCl₃) 10.93 (1H, br s, $\underline{NH_a}$), 7.20-7.52 (1H, m, $\underline{NH_b}$), 6.60-7.04 (2H, s, $\underline{C}(10)H$), 5.41 (1H, br s, $\underline{NH_c}$), 4.49 (1H, m, $\underline{C}(2'')H$), 4.29 (1H, br s, $\underline{C}(2)H$), 2.36 (6H, s, $\underline{C}(9)H_3$), 2.28 (3H, s, $\underline{C}(12)H_3$), 1.43 (10H, m, $\underline{C}(3)H$, $\underline{C}(6'')H_3$), 1.38 (3H, d, J 6.9, $\underline{C}(3'')H_3$), 1.07 (3H, d, J 6.6, $\underline{C}(4)H_3$), 1.03 (3H, d, J

6.6, C(5)H₃); δ_{C} (100 MHz, CDCl₃) 173.4 (C(1'')O), 168.4 (C(6)O), 167.3 (C(1)O), 155.6 (C(4'')O), 140.4 (C(11)), 136.6 (C(8)), 128.5 (C(10)H), 126.9 (C(7)), 80.4 (C(5'')), 56.5 (C(2)H), 50.4 (C(2'')H), 30.4 (C(3)H), 28.2 (C(6'')H₃), 21.2 (C(12)H₃), 21.1 (C(4)H₃), 20.1 (C(3'')H₃), 19.9 (C(9)H₃), 19.1 (C(5)H₃); m/z (ESI⁺) 472 ([M+Na]⁺, 100%); **HRMS** (ESI⁺) C₂₃H₃₅N₃O₆ requires [M+Na]⁺ 472.2418, found 472. 2416 (+0.8 ppm).

(S)-tert-Butyl 1-(hydroxyamino)-4-methyl-1-oxopentan-2-ylcarbamate

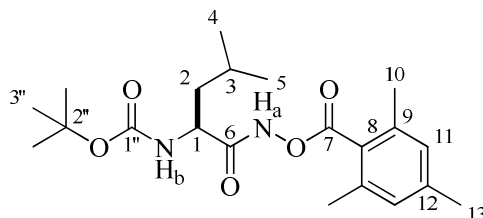


Boc-protected L-leucine (5.9 g, 25.7 mmol) was subjected to General Procedure E₂ to furnish (S)-tert-Butyl 1-(hydroxyamino)-4-methyl-1-oxopentan-2-ylcarbamate (5.6 g, 22.9 mmol, 89%) as a white solid.

δ_{H} (400 MHz, (CD₃)₂CO) 10.23 (1H, br s, NH₂OH), 6.06 (1H, d, J 7.3, NH), 4.12 (1H, m, C(1)H), 1.50-1.88 (3H, m, C(2)H₂, C(3)H), 1.43 (9H, s, C(3'')H₃), 0.74-1.10 (6H, m, C(4)H₃, C(5)H₃); δ_{C} (100 MHz, (CD₃)₂CO), 170.2 (C(7)O), 160.1 (C(6)O), 71.0 (C(2'')), 51.0 (C(1)H), 41.5 (C(2)H₂), 28.4 (C(3'')H₃), 23.1 (C(3)H), 22.0 (C(5)H₃), 21.9 (C(6)H₃).

Spectroscopic data were consistent with those reported in the literature (cas 156706-53-5)¹⁶⁴

(S)-tert-Butyl 4-methyl-1-oxo-1-(2,4,6-trimethylbenzoyloxyamino)pentan-2-ylcarbamate (348)

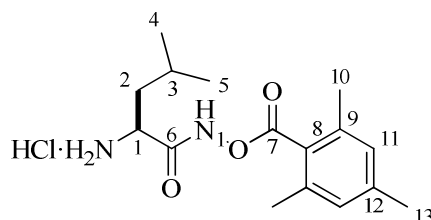


(S)-tert-Butyl 1-(hydroxyamino)-4-methyl-1-oxopentan-2-ylcarbamate (4.7 g, 19.0 mmol) was subjected to General Procedure B to furnish the title compound **348** (6.0 g, 15.4 mmol, 81%) as a white solid.

$[\alpha]_{\text{D}}^{25}$ – 39.2 (c = 1.6, chloroform); **m.p.** 117-118 °C; ν_{max} (thin film)/cm⁻¹ 3212br s, 2960br s, 1779s, 1669s, 1612m, 1531s, 1455m, 1392m, 1367m, 1157m, 1039s, 948m, 850s, 739s; δ_{H} (400 MHz, CDCl₃) 11.08 (1H, br s, NH_a), 6.78 (2H, s, C(11)H), 5.73 (1H, d, J 8.3, NH_b), 4.22-4.67 (1H, m, C(1)H), 2.29 (6H, s, C(10)H₃), 2.25 (3H, s, C(13)H₃), 1.63-1.88 (3H, m, C(2)H₂, C(3)H), 1.43 (9H, s, C(3'')H₃), 0.97 (6H, m, C(5)H₃, C(6)H₃); δ_{C} (100 MHz, CDCl₃) 170.4 (C(7)O), 167.2 (C(6)O), 156.2 (C(1'')O), 140.0 (C(12)), 136.4 (C(9)), 128.2 (C(11)H), 127.0 (C(8)), 80.2 (C(2'')), 50.4 (C(1)H), 41.0 (C(2)H₂), 28.2 (C(3'')H₃), 24.5 (C(3)H), 22.7 (C(5)H₃), 21.9 (C(6)H₃), 21.0

($\underline{C}(13)H_3$), 19.6 ($\underline{C}(10)H_3$); m/z (ESI⁺) 391 ([M-H]⁺, 100%); **HRMS** (ESI⁺) C₂₁H₃₂N₂O₅ requires [M+Na]⁺ 415.2202, found 415.2203 (+1.0 ppm).

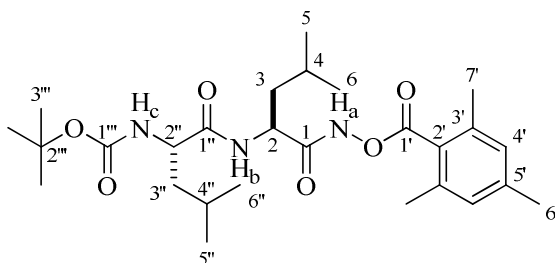
(S)-2-amino-4-methyl-N-(2,4,6-trimethylbenzoyloxy)pentanamide hydrochloride salt (349)



To a solution of compound **348** (1.0 eq., 900 mg, 2.3 mmol) in dichloromethane (20 mL) at rt under argon was added a solution of 4M HCl in dioxane (3.0 eq., 1.7 mL, 6.9 mmol). The reaction mixture was stirred until TLC indicated complete consumption of starting material (typically 2-3 h). The solvent was removed under reduced pressure *at rt* to give the title compound **349** as a colorless foam (100%).

[α]_D²⁵ – 4.7 ($c = 3.3$, chloroform); $\nu_{\max}$ (thin film)/cm⁻¹ 2960br s, 1779br s, 1695br s, 1612s, 1505br s, 1370m, 1232s, 1157s, 1121m, 1045br s, 889m, 872m, 851m, 733s; δ_H (400 MHz, CDCl₃) 8.36 (1H, br s, N¹H), 6.38-6.93 (2H, m, C(11)H), 4.49 (1 H, br s, C(1)H), 2.27 (6H, br s, C(10)H₃), 2.21 (3H, br s, C(13)H₃), 1.86 (3H, br s, C(2)H₃, C(3)H₃), 0.89 (6H, m, C(4)H₃, C(5)H₃); δ_C (100 MHz, CDCl₃) 167.0 ($\underline{C}(7)O$), 166.4 ($\underline{C}(6)O$), 140.2 ($\underline{C}(12)$), 136.3 ($\underline{C}(9)$), 128.2 ($\underline{C}(11)H$), 126.2 ($\underline{C}(8)$), 50.7 ($\underline{C}(1)H$), 40.2 ($\underline{C}(2)H_2$), 23.9 ($\underline{C}(3)H$), 22.4 ($\underline{C}(4)H_3$), 21.8 ($\underline{C}(13)H_3$), 20.9 ($\underline{C}(5)H_3$); m/z (ESI⁺) 291 ([M-H]⁺, 100%); **HRMS** (ESI⁺) C₁₆H₂₄N₂O₃ requires [M+Na]⁺ 315.1679, found 315.1677 (+0.9 ppm).

***tert*-Butyl (S)-4-methyl-1-((S)-4-methyl-1-oxo-1-(2,4,6-trimethylbenzoyloxyamino)pentan-2-ylamino)-1-oxopentan-2-ylcarbamate (350)**

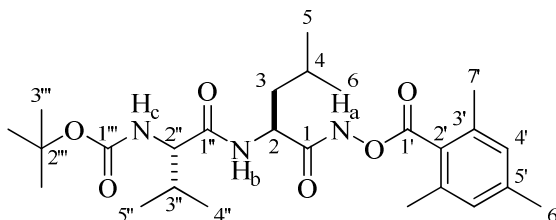


To a solution of compound **347** (1.0 eq., 88 mg, 0.38 mmol) in dichloromethane (5 mL) under argon at 0 °C, was added freshly prepared 4-(3,5-dimethoxyphenyl)-4-methylmorpholin-4-ium chloride (DMTMM) (1.0 eq., 92 mg, 0.38 mmol)¹⁶⁵. After completion of the addition, the reaction mixture was stirred vigorously for 10 h at 0 °C. To the reaction mixture was then added compound

349 (1.2 eq., 150 mg, 0.46 mmol) followed by the dropwise addition of *N*-methylmorpholin (1.2 eq., 47 mg, 0.46 mmol). The reaction mixture was stirred vigorously for another 10 h letting the reaction mixture warmed to rt. The reaction mixture was then washed with 1M aqueous CuSO₄ solution (3 x 1 mL) and concentrated *in vacuo* at rt to a few mL. The residue was purified by flash column chromatography, eluting with dichloromethane/methanol (100:0 to 9:1) to give the title compound **350** as a colourless oil (135 mg, 0.27 mmol, 70%).

$[\alpha]_D^{25}$ – 10.2 (*c* = 0.3, chloroform); $\nu_{\max}$ (thin film)/cm⁻¹ 3260br s, 2959br s, 1780m, 1682br s, 1650br s, 1523m, 1366m, 1232m, 1158m, 1044m, 1025m, 850w, 733m; δ_H (400 MHz, CDCl₃) 10.70 (1H, br s, NH_a), 7.12 (1H, d, *J* 6.3, NH_b), 6.84 (2H, s, C(4')H), 5.25 (1H, d, *J* 4.5, NH_c), 4.66 (1H, d, *J* 5.8, C(2)H), 4.20 (1H, br s, C(2'')H), 2.35 (6H, s, C(7')H₃), 2.27 (3H, s, C(6')H₃), 1.47–1.88 (6H, m, C(3)H₂, C(4)H, C(3'')H₂, C(4')H), 1.43 (9H, s, C(3'')H₃), 0.81–1.00 (12H, m, C(5)H₃, C(6)H₃, C(5'')H₃, C(6'')H₃); δ_C (100 MHz, CDCl₃) 173.5 (C(1'')O), 169.4 (C(1')O), 167.3 (C(1)O), 156.0 (C(1'')O), 140.4 (C(5')), 136.6 (C(3')), 128.4 (C(4')H), 126.9 (C(2')), 80.3 (C(2'')), 53.2 (C(2'')H), 49.4 (C(2)H), 40.7 (C(3'')H₂), 39.8 (C(3)H₂), 28.2 (C(3'')H₃), 24.6 (C(4'')H), 24.5 (C(4)H), 22.8 (C(5'')H₃), 22.7 (C(6'')H₃), 21.9 (br s, C(5)H₃, C(6)H₃), 21.2 (C(6')H₃), 19.9 (C(7')H₃); *m/z* (ESI⁺) 528 ([M+Na]⁺, 100%); HRMS (ESI⁺) C₂₇H₄₃N₃O₆ requires [M+Na]⁺ 528.3044, found 528.3035 (+1.8 ppm).

tert-Butyl (S)-3-methyl-1-((S)-4-methyl-1-oxo-1-(2,4,6-trimethylbenzoyloxyamino)pentan-2-ylamino)-1-oxobutan-2-ylcarbamate (351)

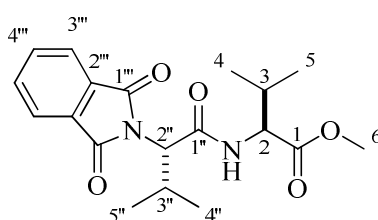


To a solution of compound **274** (1.0 eq., 413 mg, 1.9 mmol) in dichloromethane (10 mL) under argon at 0 °C, was added freshly prepared 4-(3,5-dimethoxyphenyl)-4-methylmorpholin-4-ium chloride (DMTMM) (1.0 eq., 460 mg, 1.9 mmol).¹⁶⁵ After completion of the addition, the reaction mixture was stirred vigorously for 10 h at 0 °C. To the reaction mixture was then added compound **349** (1.2 eq., 749 mg, 2.3 mmol) followed by the dropwise addition of *N*-methylmorpholin (1.2 eq., 233 mg, 2.3 mmol). The reaction mixture was stirred vigorously for another 10 h letting the reaction mixture warmed to rt. The reaction mixture was then washed with 1M aqueous CuSO₄ solution (3 x 3 mL) and concentrated *in vacuo* at rt to a few mL. The residue was purified by flash column chromatography, eluting with dichloromethane/methanol (100:0 to 9:1) to give the title compound **351** as a colourless oil (606 mg, 1.2 mmol, 65%).

$[\alpha]_D^{25}$ – 39.6 (*c* = 0.8, chloroform); $\nu_{\max}$ (thin film)/cm⁻¹ 3257br s, 2962s, 1781s, 1683s, 1649s, 1520s, 1391m, 1367m, 1299m, 1233s, 1158s, 1042s, 1020s, 878w, 733m; δ_H (400 MHz, CDCl₃)

10.39 (1H, br s, NH_a), 6.86 (2H, s, C(4') $\underline{\text{H}}$), 6.64 (1H, d, J 6.3, NH_b), 5.13 (1H, d, J 7.3, NH_c), 4.64 (1H, d, J 6.3, C(2'') $\underline{\text{H}}$), 3.95 (1H, t, J 6.9, C(2) $\underline{\text{H}}$), 2.36 (6H, s, C(7') $\underline{\text{H}}_3$), 2.29 (3H, s, C(6') $\underline{\text{H}}_3$), 2.18 (1H, dd, J 11.9, 6.1, C(3'') $\underline{\text{H}}$), 1.80-1.91 (1H, m, C(4) $\underline{\text{H}}$), 1.61-1.78 (2H, m, C(3) $\underline{\text{H}}_2$), 1.45 (9H, s, C(3'') $\underline{\text{H}}_3$), 0.53-1.23 (12H, m, C(5) $\underline{\text{H}}_3$, C(6) $\underline{\text{H}}_3$, C(4'') $\underline{\text{H}}_3$, C(5'') $\underline{\text{H}}_3$); δ_{C} (100 MHz, CDCl_3) 172.9 (C(1'')O), 169.3 (C(1')O), 167.2 (C(1)O), 156.0 (C(1'')O), 140.4 (C(5')), 136.6 (C(3')), 128.5 (C(4') $\underline{\text{H}}$), 126.9 (C(2')), 80.0 (C(2'')), 60.2 (C(2'') $\underline{\text{H}}$), 49.4 (C(2) $\underline{\text{H}}$), 40.1 (C(3) $\underline{\text{H}}_2$), 30.7 (C(3'') $\underline{\text{H}}$), 28.3 (C(3'') $\underline{\text{H}}_3$), 24.6 (C(4) $\underline{\text{H}}$), 22.8 (C(5) $\underline{\text{H}}_3$), 22.7 (C(6) $\underline{\text{H}}_3$), 22.1 (C(4'') $\underline{\text{H}}_3$), 21.2 (C(5'') $\underline{\text{H}}_3$), 19.8 (C(7') $\underline{\text{H}}_3$), 19.2 (C(6') $\underline{\text{H}}_3$); m/z (ESI^+) 514 ($[\text{M}+\text{Na}]^+$, 100%); **HRMS** (ESI^+) $\text{C}_{26}\text{H}_{41}\text{N}_3\text{O}_6$ requires $[\text{M}+\text{Na}]^+$ 514.2888, found 514.2878 (+1.8 ppm).

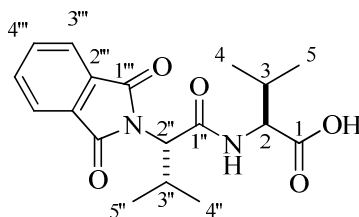
(S)-Methyl 2-((S)-2-(1,3-dioxoisindolin-2-yl)-3-methylbutanamido)-3-methylbutanoate (353)



To a solution of compound **271** (1.0 eq., 2.2 g, 8.0 mmol) and compound **341** (1.0 eq., 2.5 g, 8.9 mmol) in *N,N*-dimethylformamide (40 mL) under argon at rt, was added dropwise triethylamine (2.1 eq., 1.9 g, 18.7 mmol) followed by the addition of a solution of *O*-benzotriazole-*N,N,N',N'*-tetramethyluroniumhexafluorophosphate (1.1 eq. 4.1 g, 11.4 mmol) in *N,N'*-dimethylformamide (40 mL) (syringe pump $1\text{ mL} \cdot \text{min}^{-1}$). After completion of the addition, the reaction mixture was stirred vigorously for 12 h at rt. The reaction mixture was then washed with brine (3 x 100 mL) and concentrated *in vacuo* to a few mL. The residue was purified by flash column chromatography, eluting with ethyl acetate/petrol gradient (100:0 to 70:30) to give the title compound **353** as a colourless gum (2.4 g, 6.6 mmol, 82%).

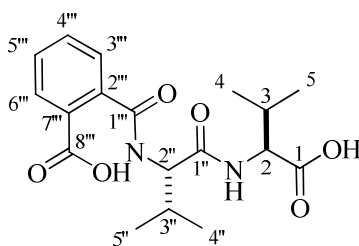
δ_{H} (400 MHz, CDCl_3) 7.90 (2H, d, J 2.8, C(3'') $\underline{\text{H}}$), 7.77 (2H, d, J 2.8, C(4'') $\underline{\text{H}}$), 7.51 (1H, d, J 7.8, NH), 4.50-4.59 (1H, m, C(2) $\underline{\text{H}}$), 4.47 (1H, d, J 10.9, C(2'') $\underline{\text{H}}$), 3.65 (3H, s, C(6) $\underline{\text{H}}_3$), 2.89 (1H, m, C(3'') $\underline{\text{H}}$), 2.13-2.30 (1H, m, C(3) $\underline{\text{H}}$), 1.09-1.18 (3H, m, C(4'') $\underline{\text{H}}_3$), 0.92-1.03 (6H, m, C(4) $\underline{\text{H}}_3$, C(5) $\underline{\text{H}}_3$), 0.88 (3H, d, J 6.3, C(5'') $\underline{\text{H}}_3$); δ_{C} (100 MHz, CDCl_3) 172.0 (C(1)O), 168.9 (C(1'')O), 168.5 (C(1'')O), 134.4 (C(4'') $\underline{\text{H}}$), 131.4 (C(2'')), 123.7 (C(3'') $\underline{\text{H}}$), 63.4 (C(2'') $\underline{\text{H}}$), 57.2 (C(2) $\underline{\text{H}}$), 52.0 (C(6) $\underline{\text{H}}_3$), 30.9 (C(3) $\underline{\text{H}}$), 27.8 (C(3'') $\underline{\text{H}}$), 19.8 (C(4'') $\underline{\text{H}}_3$), 19.5 (C(4) $\underline{\text{H}}_3$), 19.1 (C(5'') $\underline{\text{H}}_3$), 17.7 (C(5) $\underline{\text{H}}_3$).

Spectroscopic data were consistent with those reported in the literature.¹⁶⁶

(S)-2-((S)-2-(1,3-Dioxoisindolin-2-yl)-3-methylbutanamido)-3-methylbutanoic acid (354)

To a solution of compound **357** (1.0 eq., 1.2 g, 2.9 mmol) in dichloromethane (20 mL) under argon at 0 °C was added dropwise trifluoroacetic acid (1 mL). The reaction mixture was stirred until TLC indicated complete consumption of starting material (typically 1-2 h). The reaction mixture was then concentrated *in vacuo* to give the title compound **353** as a colourless gum (quantitative).

$[\alpha]_D^{25} + 49.6$ ($c = 0.5$, chloroform); $\nu_{\max}$ (thin film)/ cm^{-1} 3331br w, 2968w, 1778w, 1712s, 1660w, 1546w, 1386m, 1170m, 1070w, 720w; δ_{H} (400 MHz, CDCl_3) 10.65 (H, br s, OH), 8.09 (1H, d, J 8.6, NH), 7.89 (2H, dd, J 5.4, 3.2, $\text{C}(3'')\text{H}$), 7.79 (2H, dd, J 5.4, 3.2, $\text{C}(4'')\text{H}$), 4.50-4.60 (2H, m, $\text{C}(2'')\text{H}$, $\text{C}(2'')\text{H}$), 2.77-2.92 (1H, m, $\text{C}(3'')\text{H}$), 2.24-2.41 (1H, m, $\text{C}(3'')\text{H}$), 1.11 (3H, d, J 6.6, $\text{C}(4'')\text{H}_3$), 1.03 (6H, t, J 7.2, $\text{C}(4'')\text{H}_3$, $\text{C}(5'')\text{H}_3$), 0.88 (3H, d, J 6.6, $\text{C}(5'')\text{H}_3$); δ_{C} (100 MHz, CDCl_3) 176.3 ($\text{C}(1'')\text{O}$), 171.7 ($\text{C}(1''')\text{O}$), 168.8 ($\text{C}(1''')\text{O}$), 134.9 ($\text{C}(4'')\text{H}$), 130.9 ($\text{C}(2'')\text{H}$), 124.0 ($\text{C}(3'')\text{H}$), 62.8 ($\text{C}(2'')\text{H}$), 57.7 ($\text{C}(2'')\text{H}$), 30.5 ($\text{C}(3'')\text{H}$), 28.2 ($\text{C}(3'')\text{H}$), 19.32 ($\text{C}(4'')\text{H}_3$), 19.28 ($\text{C}(5'')\text{H}_3$), 19.0 ($\text{C}(4'')\text{H}_3$), 17.4 ($\text{C}(5'')\text{H}_3$); m/z (ESI^+) 369 ($[\text{M}+\text{Na}]^+$, 100%); **HRMS** (ESI^+) $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_5$ requires $[\text{M}+\text{Na}]^+$ 369.1421, found 369.1412 (+2.7 ppm).

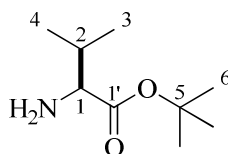
2-((S)-1-((S)-1-Carboxy-2-methylpropylamino)-3-methyl-1-oxobutan-2-ylcarbonyl)benzoic acid (355)

To a solution of compound **353** (1.0 eq., 1.3 g, 3.6 mmol) in a mixture of tetrahydrofuran (66 mL) and water (33 mL) under argon at 0 °C was added lithium hydroxide monohydrate (1.1 eq., 167 mg, 4.0 mmol). The reaction mixture was stirred until TLC indicated complete consumption of starting material (12 h). The reaction mixture was then acidified to pH 1 with a 3 M aqueous HCl solution and extracted with diethyl ether (3 x 100 mL). The organic phase was separated, washed with brine (50 mL), dried over Na_2SO_4 , filtered and the solvent was removed under reduced pressure to give the title compound **355** as a white solid (446mg, 1.2 mmol, 34%).

$[\alpha]_D^{25} - 41.3$ ($c = 0.5$, chloroform); **m.p.** 195-201 °C $\nu_{\max}$ (thin film)/ cm^{-1} 3331br s, 3322 br w, 2965w, 1779m, 1715s, 1668m, 1528w, 1392m, 1172m, 1070w, 963w, 847w, 725w; δ_{H} (400 MHz, CDCl_3) 9.71 (2H, br s, OH , OH), 7.91 (1H, d, J 8.6, NH), 7.81-7.87 (2H, m, $\text{C}(3'')\text{H}$, $\text{C}(6'')\text{H}$), 7.70-

7.78 (2H, m, C(4'')H, C(5'')H), 4.38-4.53 (2H, m, C(2'')H, C(2')H), 2.77-2.90 (1H, m, C(3')H), 2.17-2.32 (1H, m, C(3'')H), 1.07 (3H, d, J 6.6, C(4'')H₃), 0.96 (6H, t, J 6.9, C(4)H₃, C(5)H₃), 0.83 (3H, d, J 6.6, C(5'')H₃); δ_c (100 MHz, CDCl₃) 175.1 (C(8'')O), 174.9 (C(1')O), 170.9 (C(1'')O), 168.6 (C(1''')O), 134.7 (C(5''')H), 134.6 (C(4''')H), 131.0 (C(2''')H), 130.9 (C(7''')H), 123.8 (br s, C(3''')H), C(6''')H), 62.7 (C(2'')H), 57.6 (C(2')H), 30.4 (C(3')H), 27.9 (C(3'')H), 19.4 (C(4'')H₃), 19.2 (C(5'')H₃), 18.9 (C(4')H₃), 17.3 (C(5')H₃); m/z (ESI⁺) 387 ([M+Na]⁺, 100%); **HRMS** (ESI⁺) C₁₈H₂₄N₂O₆ requires [M+Na]⁺ 387.1527, found 387.1524 (-0.9 ppm).

(S)-tert-Butyl 2-amino-3-methylbutanoate (356)

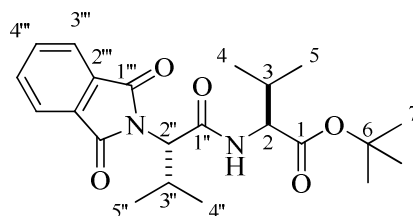


To a solution of L-valine (1.0 eq., 1.0 g, 8.5 mmol) in *tert*-butyl acetate (20 mL) at 0 °C under argon was added dropwise perchloric acid (1.5 eq., 0.7 mL, 12.8 mmol). **Caution, see COSSH assessment.** The reaction mixture was stirred at rt for 12 h then washed with water (40 mL) and a 1N aqueous HCl solution (21 mL). The resultant aqueous solution was adjusted to pH 9 by addition of a 10% aqueous K₂CO₃ solution, and then extracted with dichloromethane (3 x 50 mL). The combined organic phases were dried with Na₂SO₄, filtered and concentrated *in vacuo* at rt to give an oil. This was purified by flash chromatography on silica gel, using an ethyl acetate/petrol gradient (1:1 to 3:1) to give the title compound **356** (1.3 g, 7.7 mmol, 90%) as a colourless oil.

δ_H (400 MHz, CDCl₃) 3.14 (1H, d, J 4.8, C(1')H), 1.97 (1H, dq, J 11.9, 6.8, C(2')H), 1.44 (9H, s, C(6)H₃), 1.37 (2H, s, NH₂), 0.95 (3H, d, J 6.8, C(4)H₃), 0.87 (3H, d, J 6.8, C(4)H₃); δ_c (100 MHz, CDCl₃) 174.8 (C(1')O), 80.7 (C(5)), 60.3 (C(1')H), 32.1 (C(2')H), 28.0 (C(6)H₃), 19.2 (C(4)H₃), 16.9 (C(5)H₃).

Spectroscopic data were consistent with those reported in the literature.¹⁶⁷

(S)-tert-Butyl 2-((S)-2-(1,3-dioxisoindolin-2-yl)-3-methylbutanamido)-3-methylbutanoate (357)

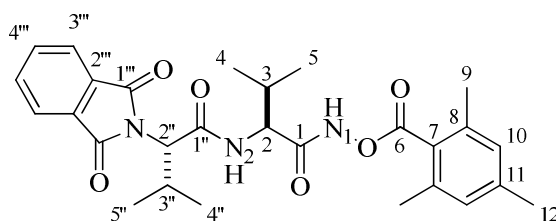


To a solution of compound **271** (1.0 eq., 1.96 g, 11.3 mmol) and compound **356** (1.0 eq., 2.80 g, 11.3 mmol) in *N,N*-dimethylformamide (50 mL) under argon at rt, was added dropwise triethylamine (1.1 eq., 1.26 g, 11.4 mmol) followed by the addition of a solution of *O*-benzotriazole-*N,N,N',N'*-tetramethyluroniumhexafluorophosphate (1.1 eq. 4.71 g, 11.4 mmol) in

N,N-dimethylformamide (50 mL) (syringe pump 1 mL · min⁻¹). After completion of the addition, the reaction mixture was stirred vigorously for 12 h at rt. The reaction mixture was then washed with brine (3 x 100 mL) and concentrated *in vacuo* to a few mL. The residue was purified by flash column chromatography, eluting with ethyl acetate/petrol gradient (100:0 to 70:30) to give the title compound **357** as a colourless gum (3.22 g, 8.0 mmol, 71%).

$[\alpha]_{\text{D}}^{25} + 45.8$ ($c = 0.5$, chloroform); ν_{max} (thin film)/cm⁻¹ 3347br s, 2967s, 1778w, 1713s, 1682m, 1532m, 1468m, 1385br s, 1152s, 1070m, 909w, 847w, 729m; δ_{H} (400 MHz, CDCl₃) 7.89 (2H, dd, J 5.6, 3.0, C(3'')H), 7.76 (2H, dd, J 5.6, 3.0, C(4'')H), 7.41 (1H, d, J 8.3, NH), 4.46 (1H, d, J 11.4, C(2'')H), 4.41 (1H, dd, J 8.5, 4.4, C(2')H), 2.78-2.98 (1H, m, C(3'')H), 2.06-2.31 (1H, m, C(3')H), 1.38 (9H, s, C(7)H₃), 1.13 (3H, d, J 6.6, C(4'')H₃), 0.95 (6H, t, J 6.9, C(4)H₃, C(5)H₃), 0.87 (3H, d, J 6.6, C(5'')H₃); δ_{C} (100 MHz, CDCl₃) 170.3 (C(1'')O), 168.7 (C(1')O), 168.4 (C(1'')O), 134.4 (C(4'')H), 131.4 (C(2'')), 123.7 (C(3'')H), 81.7 (C(6)), 63.3 (C(2'')H), 57.7 (C(2')H), 31.2 (C(3')H), 27.9 (C(7)H₃), 27.8 (C(3'')H), 19.9 (C(4'')H₃), 19.6 (C(5'')H₃), 19.0 (C(4)H₃), 17.6 (C(5)H₃); m/z (ESI⁺) 425 ([M+Na]⁺, 100%); **HRMS** (ESI⁺) C₂₂H₃₀N₂O₅ requires [M+Na]⁺ 425.2047, found 425.2038 (+2.5 ppm).

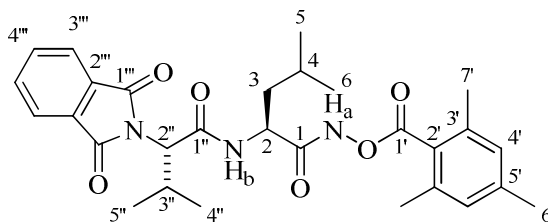
(S)-2-(1,3-Dioxoisindolin-2-yl)-3-methyl-*N*-((S)-3-methyl-1-oxo-1-(2,4,6-trimethylbenzoyloxyamino)butan-2-yl)butanamide (358)



Compound **354** (1.5 g, 4.2 mmol) was subjected to General Procedure F to furnish the title compound **358** (1.4 g, 2.7 mmol, 66%) as a white solid.

$[\alpha]_{\text{D}}^{25} - 23.2$ ($c = 2.0$, chloroform); **m.p.** 86-87 °C; ν_{max} (thin film)/cm⁻¹ 3283br w, 2966w, 1778m, 1716s, 1656s, 1537br w, 1468w, 1383s, 1233w, 1156w, 1035m, 728m; δ_{H} (400 MHz, CDCl₃) 10.21 (1H, br s, N¹H), 7.83 (2H, dd, J 5.2, 3.2, C(3'')H), 7.70 (2H, dd, J 5.2, 3.2, C(4'')H), 7.65 (1H, d, J 8.6, N²H), 6.80 (2H, s, C(10)H), 4.50 (1H, d, J 11.1, C(2'')H), 4.39 (1H, t, J 8.3, C(2')H), 2.81-2.97 (1H, m, C(3'')H), 2.27-2.37 (1H, m, C(3')H), 2.25 (9H, s, C(9)H₃, C(12)H₃), 1.13 (3H, d, J 6.6, C(4'')H₃), 1.06 (6H, d, J 6.8, C(4)H₃, C(5)H₃), 0.88 (3H, d, J 6.6, C(5'')H₃); δ_{C} (100 MHz, CDCl₃) 170.1 (C(6)O), 168.8 (C(1')O), 168.5 (C(1'')O), 167.3 (C(1')O), 140.4 (C(11)), 136.8 (C(8)), 134.3 (C(4'')H), 131.3 (C(2'')), 128.4 (C(10)H), 126.6 (C(7)), 123.7 (C(3'')), 62.8 (C(2'')H), 56.4 (C(2')H), 29.4 (C(3')H), 27.8 (C(3'')H), 21.1 (C(4'')H₃), 19.8 (C(9)H₃), 19.7 (C(5'')H₃), 19.39 (C(12)H₃), 19.36 (C(4)H₃), 18.3 (C(5)H₃); m/z (ESI⁺) 531 ([M+Na]⁺, 100%); **HRMS** (ESI⁺) C₂₈H₃₃N₃O₆ requires [M+Na]⁺ 531.2262, found 531.2245 (+2.3 ppm).

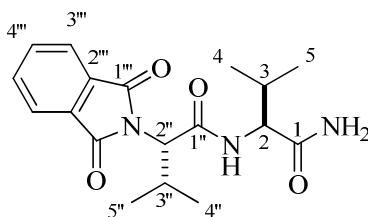
(S)-2-((S)-2-(1,3-Dioxoisindolin-2-yl)-3-methylbutanamido)-4-methyl-N-(2,4,6-trimethylbenzoyloxy)pentanamide (359)



To a solution of compound **271** (1.0 eq., 470 mg, 1.9 mmol) in dichloromethane (10 mL) under argon at 0 °C, was added freshly prepared 4-(3,5-dimethoxyphenyl)-4-methylmorpholin-4-ium chloride (DMTMM) (1.0 eq., 460 mg, 1.9 mmol).¹⁶⁵ After completion of the addition, the reaction mixture was stirred vigorously for 10 h at 0 °C. To the reaction mixture was then added compound **349** (1.2 eq., 749 mg, 2.3 mmol) followed by the dropwise addition of *N*-methylmorpholin (1.2 eq., 233 mg, 2.3 mmol). The reaction mixture was stirred vigorously for another 10 h letting the reaction mixture warmed to rt. The reaction mixture was then washed with 1 M aqueous CuSO₄ solution (3 x 3 mL) and concentrated *in vacuo* at rt to a few mL. The residue was purified by flash column chromatography, eluting with dichloromethane/methanol (100:0 to 9:1) to give the title compound **359** as a colourless oil (673 mg, 1.3 mmol, 68%).

[α]_D²⁵ – 21.2 (*c* = 3.8, chloroform); ν_{max} (thin film)/cm⁻¹ 3214br s, 2961s, 1778s, 1718s, 1659s, 1538br m, 1468m, 1383br s, 1232m, 1157m, 1069m, 1019m, 912w, 850w, 719m; δ_{H} (500 MHz, CDCl₃) 10.19 (1H, s, NH_a), 7.81 (2H, dd, *J* 5.5, 3.0, C(3'')H), 7.69 (2H, dd, *J* 5.5, 3.0, C(4'')H), 7.58 (1H, d, *J* 8.2, NH_b), 6.77 (2H, s, C(4')H), 4.58-4.67 (1H, m, C(2)H), 4.50 (1H, d, *J* 11.3, C(2'')H), 2.86 (1H, dq, *J* 18.0, 6.6, C(3'')H), 2.23 (3H, s, C(6')H₃), 2.21 (6H, s, C(3'')H), 1.78-1.91 (1H, m, C(4)H), 1.68-1.78 (2H, m, C(3)H₂), 1.12 (3H, d, *J* 6.6, C(4'')H₃), 0.97 (3H, d, *J* 6.1, C(5)H₃), 0.92 (3H, d, *J* 6.1, C(6)H₃), 0.87 (3H, d, *J* 6.6, C(5'')H₃); δ_{C} (125 MHz, CDCl₃) 170.4 (C(1')O), 169.5 (C(1'')O), 168.5 (C(1'')O), 167.3 (C(1)O), 140.4 (C(5')), 136.7 (C(3')), 134.3 (C(4'')H), 131.3 (C(2'')), 128.4 (C(4')H), 126.5 (C(2')), 123.6 (C(3'')H), 62.6 (C(2')H), 49.0 (C(2)H), 38.7 (C(3)H₂), 27.7 (C(3'')H), 24.7 (C(4)H), 22.7 (C(5)H₃), 21.9 (C(6)H₃), 21.1 (C(4'')H₃), 19.8 (C(7')H₃), 19.7 (C(4'')H₃), 19.3 (C(6')H₃); *m/z* (ESI⁺) 544 ([M+Na]⁺, 100%); HRMS (ESI⁺) C₂₉H₃₅N₃O₆ requires [M+Na]⁺ 544.2424, found 544.2426 (+0.4 ppm).

(S)-N-((S)-1-Amino-3-methyl-1-oxobutan-2-yl)-2-(1,3-dioxoisindolin-2-yl)-3-methylbutanamide (361)



Compound **361** was obtained as a white solid in 9% following the synthesis attempt of **360**.

$[\alpha]_D^{25} + 8.0$ ($c = 0.2$, chloroform); **m.p.** 187-188 °C; $\nu_{\max}$ (thin film)/ cm^{-1} 3442br w, 3278br w, 2956br w, 1767s, 1709s, 1675s, 1651s, 1377m, 1078w, 709m; δ_{H} (500 MHz, CDCl_3) 7.84-7.94 (2H, m, C(3'') $\underline{H}$), 7.77 (2H, dd, J 5.5, 3.0, C(4'') $\underline{H}$), 7.37 (1H, d, J 8.4, NH), 6.03 (1H, br s, NH_a), 5.34 (1H, br s, NH_b), 4.47 (1H, d, J 11.0, C(2'') $\underline{H}$), 4.27 (1H, dd, J 8.4, 6.1, C(2') $\underline{H}$), 2.79-2.92 (1H, m, C(3'') $\underline{H}$), 2.23-2.30 (1H, m, C(3') $\underline{H}$), 1.14 (3H, d, J 6.6, C(4'') $\underline{H}_3$), 1.00 (-H, m, C(4') $\underline{H}_3$, C(5') $\underline{H}_3$), 0.89 (3H, d, J 6.6, C(5'') $\underline{H}_3$); δ_{C} (125 MHz, CDCl_3) 172.7 ($\underline{\text{C}}(1)\text{O}$), 169.2 ($\underline{\text{C}}(1'')\text{O}$), 168.4 ($\underline{\text{C}}(1''')\text{O}$), 134.5 ($\underline{\text{C}}(4'')\text{H}$), 131.3 ($\underline{\text{C}}(2'')$), 123.8 ($\underline{\text{C}}(3'')\text{H}$), 62.7 ($\underline{\text{C}}(2'')\text{H}$), 58.4 ($\underline{\text{C}}(2')\text{H}$), 30.0 ($\underline{\text{C}}(3')\text{H}$), 27.8 ($\underline{\text{C}}(3'')\text{H}$), 20.0 ($\underline{\text{C}}(4'')\text{H}_3$), 19.5 ($\underline{\text{C}}(4')\text{H}_3$), 19.4 ($\underline{\text{C}}(5'')\text{H}_3$), 17.9 ($\underline{\text{C}}(5')\text{H}_3$); **m/z** (ESI^+) 368 ($[\text{M}+\text{Na}]^+$, 90%), 713 ($[\text{2M}+\text{Na}]^+$, 100%); **HRMS** (ESI^+) $\text{C}_{18}\text{H}_{23}\text{N}_3\text{O}_4$ requires $[\text{M}+\text{Na}]^+$ 368.1581, found 368.1579 (+0.5 ppm).

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***Appendix 1 - NMRs for
stereochemical determination***

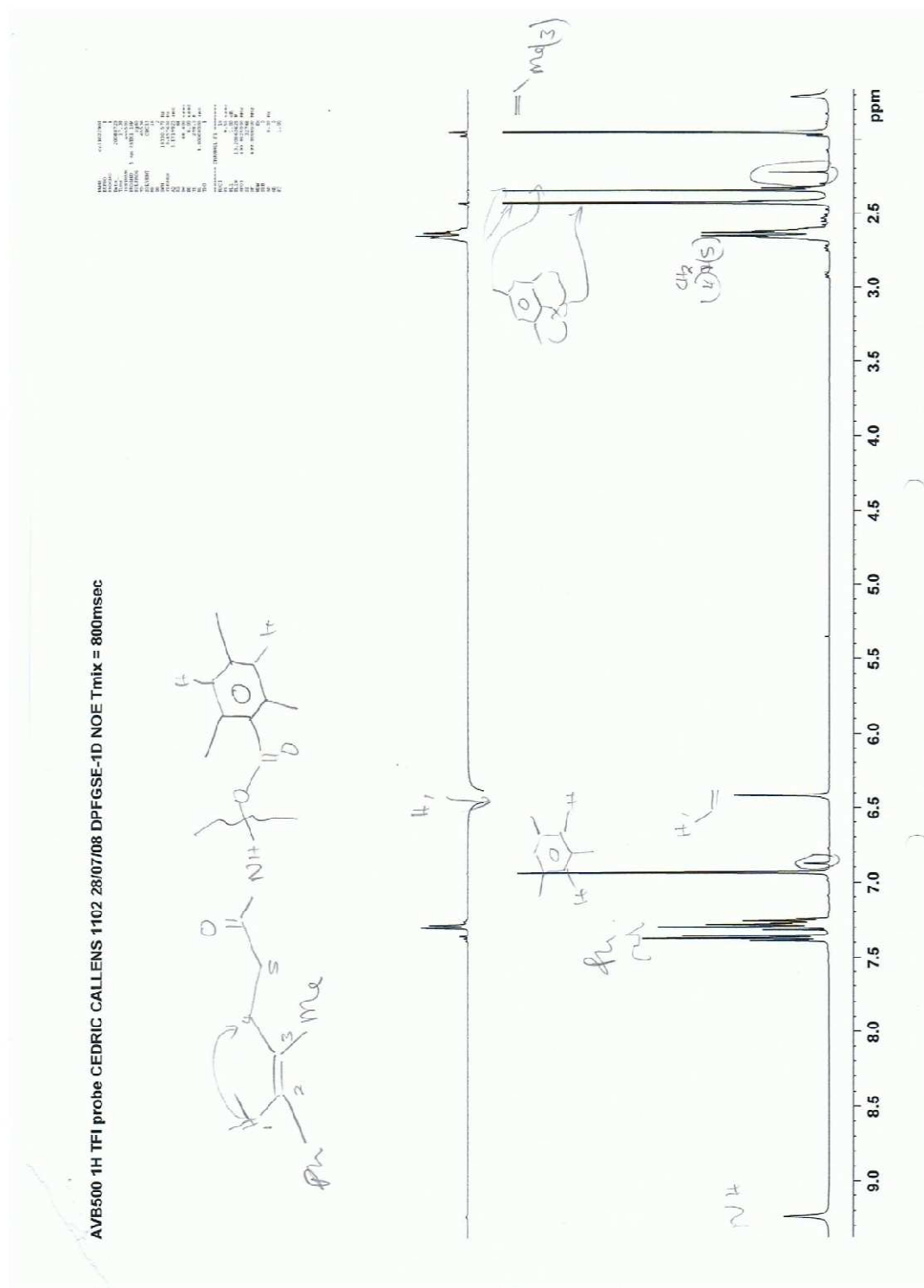


Figure 39 - NOESY experiment for the *E* geometry determination of compound 143

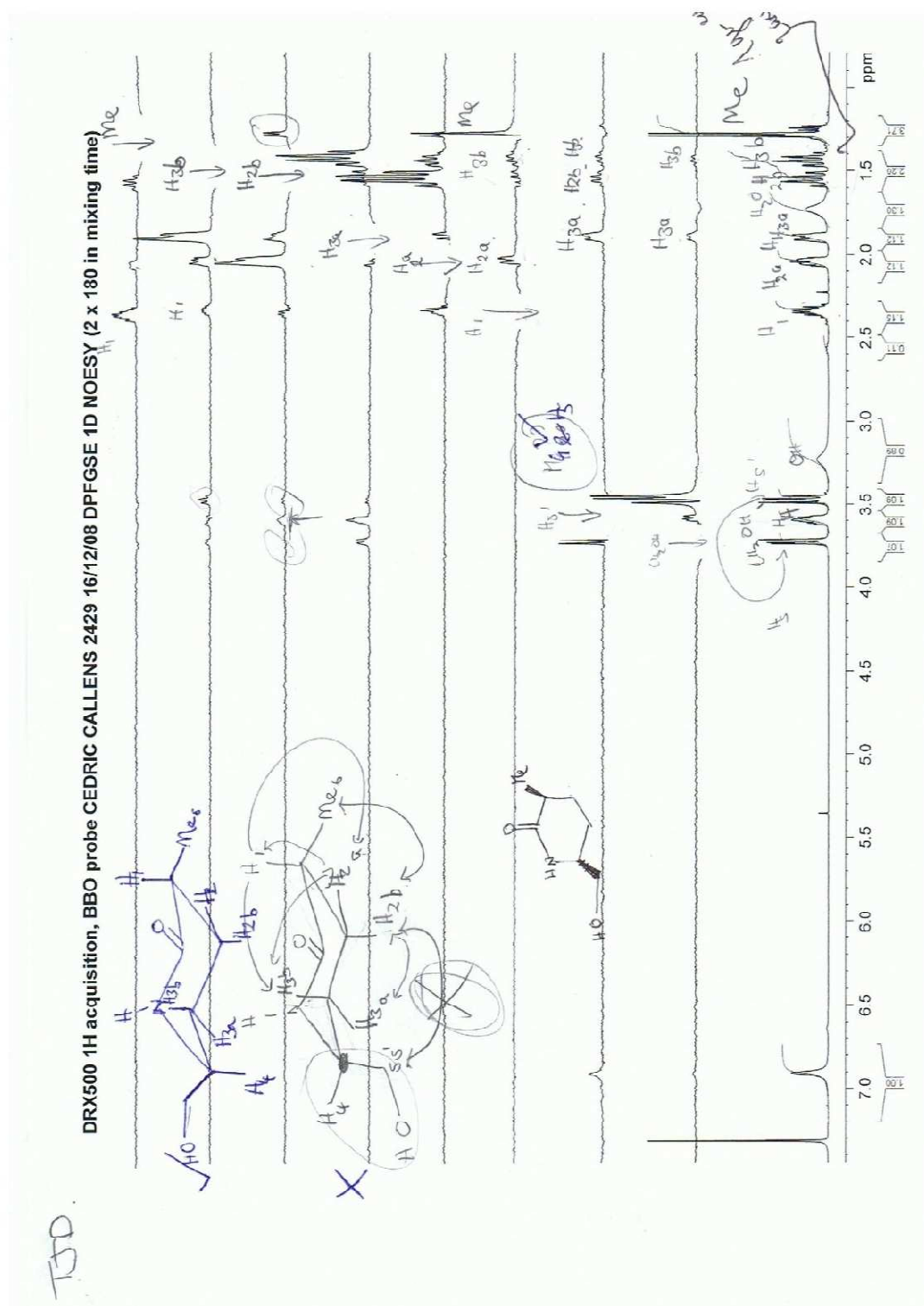


Figure 40 - 1D NOESY experiment for the *dr* determination of compound **182**

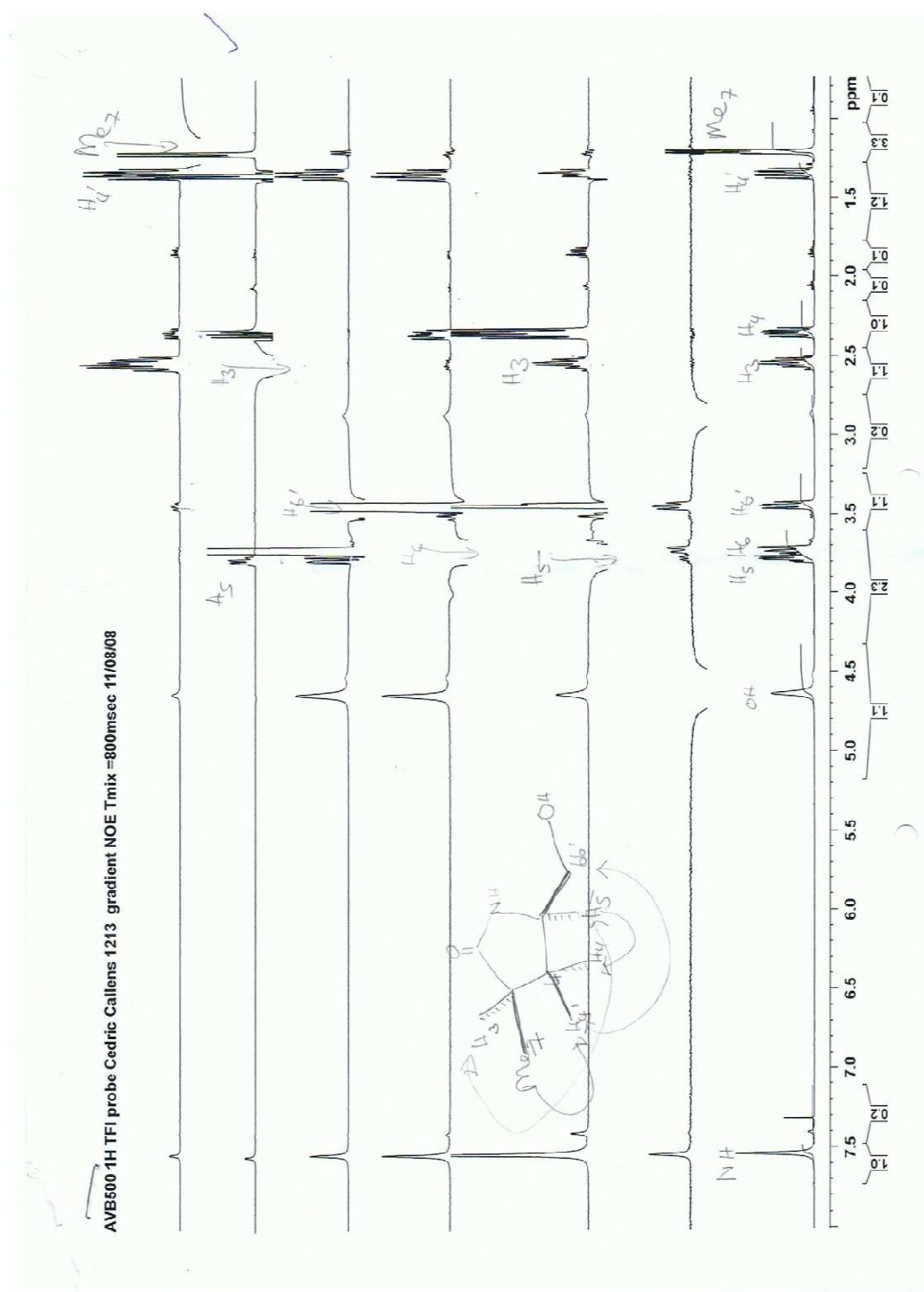


Figure 42 - 1D NOESY experiment for the *dr* determination of compound **181**

Appendix 2 - HPLC chromatography

Screening for enantiopurity - see Section 2.1.8

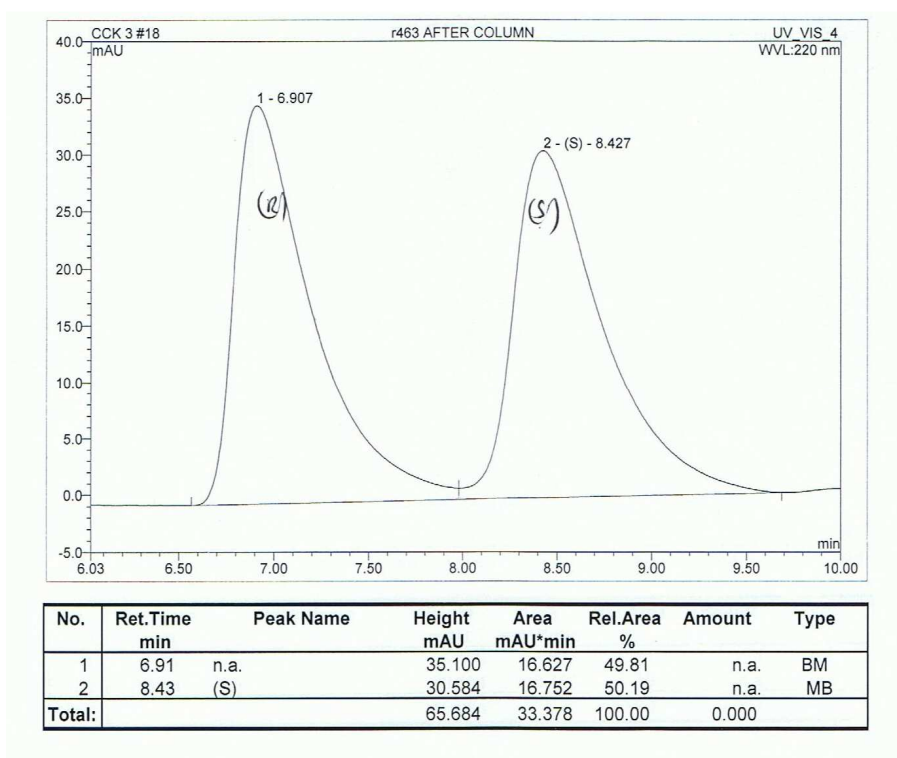


Figure 43 - Racemic mixture of 162

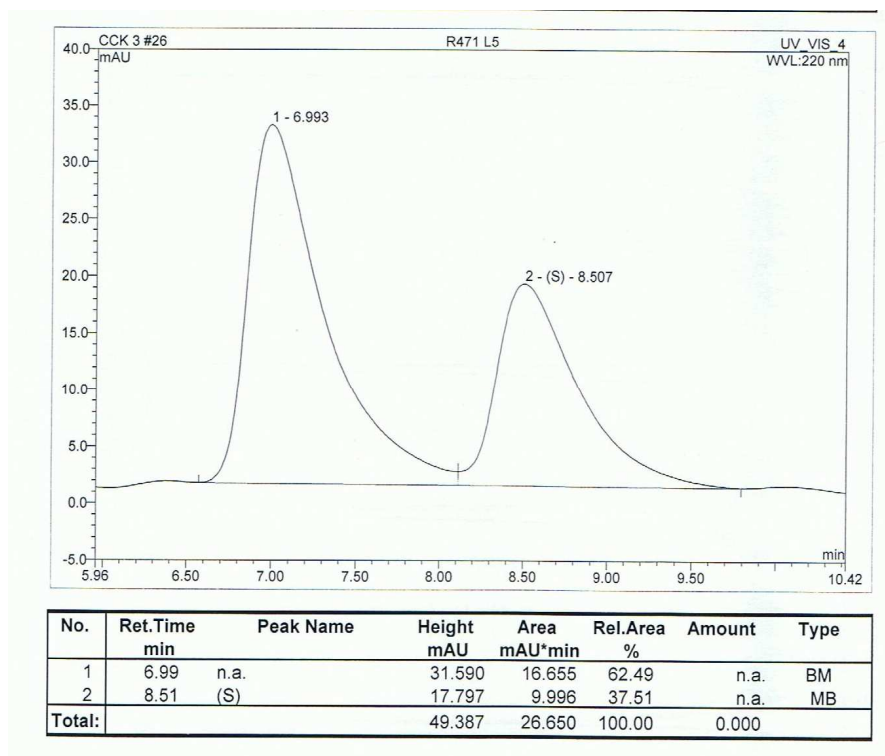


Figure 44 - 11% ee obtained from the use of 164

Assessment of the methodology employed
towards possible epimerisation- see Section 4.2.2

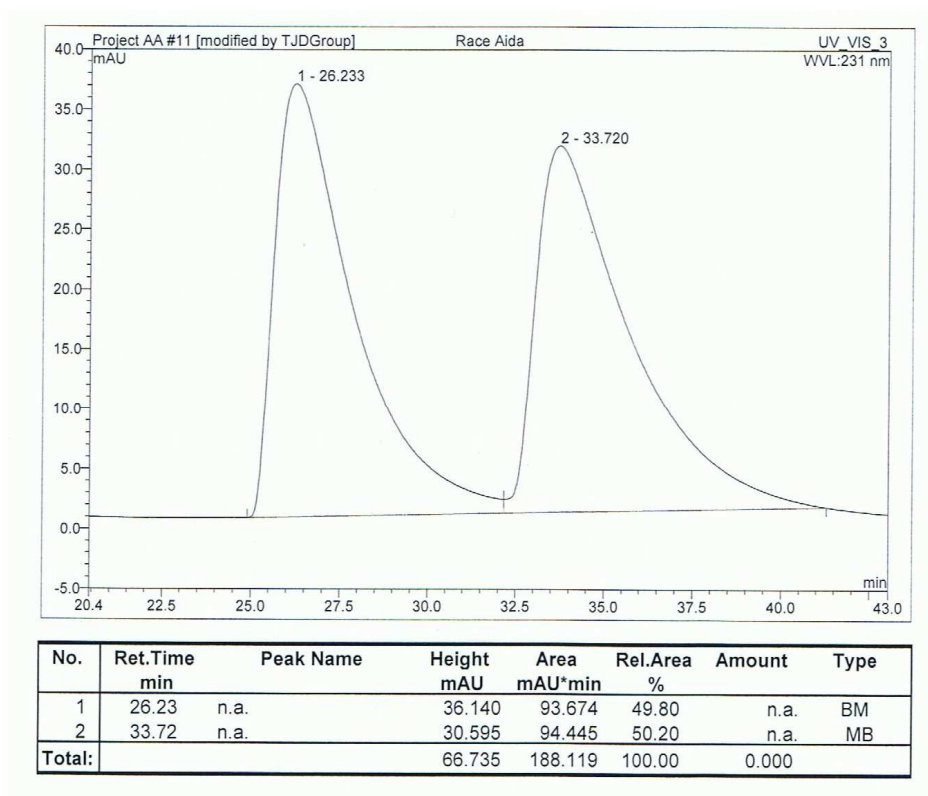


Figure 45 - Racemic phthalimide protected L-valine reoxidant 273

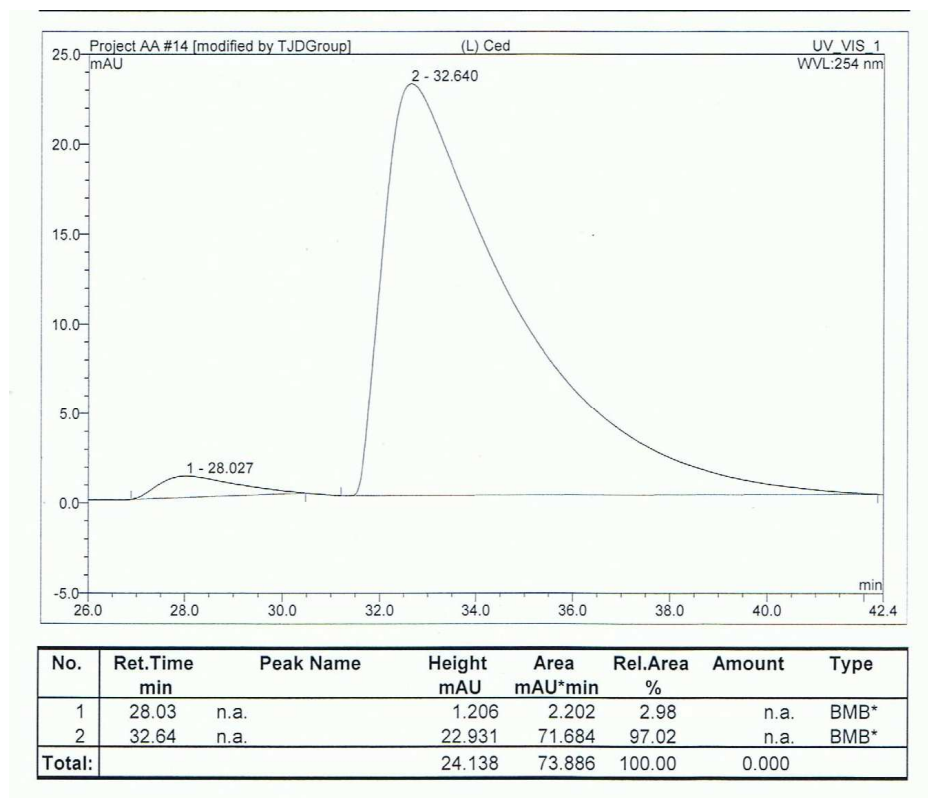


Figure 46 - Phthalimide protected L-valine reoxidant 273
synthesised from General Procedure E₁, 94% ee

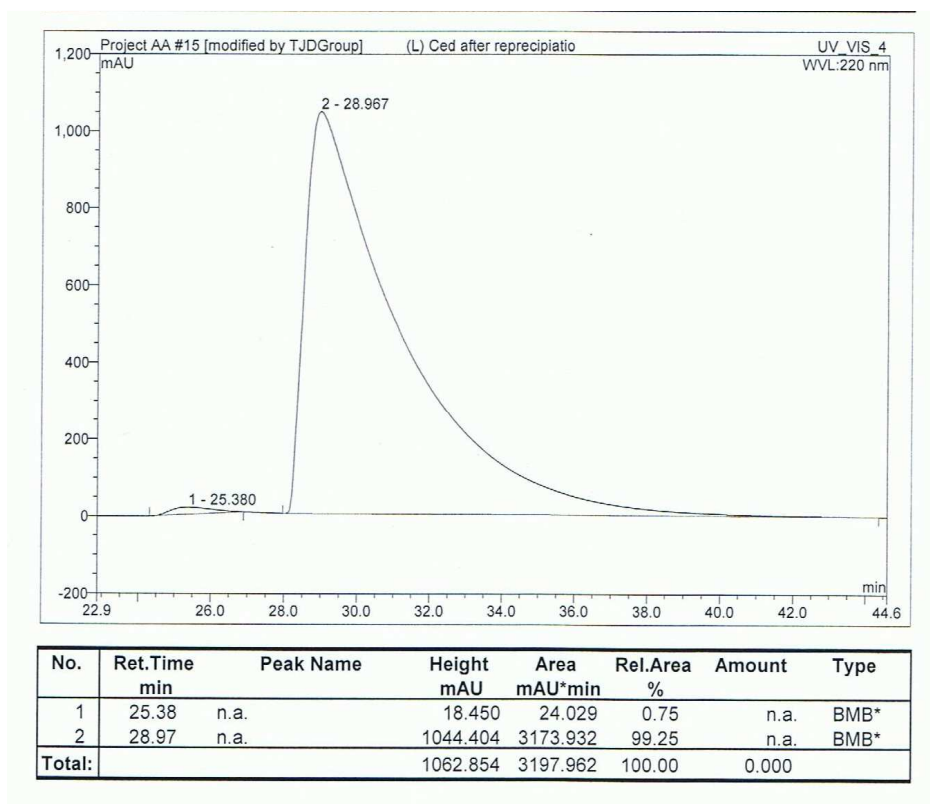


Figure 47 - Phthalimide protected L-valine reoxidant **273**
synthesised from General Procedure F, 98% *ee*

Assessment of the methodology employed
towards possible epimerisation- see Section 4.2.2

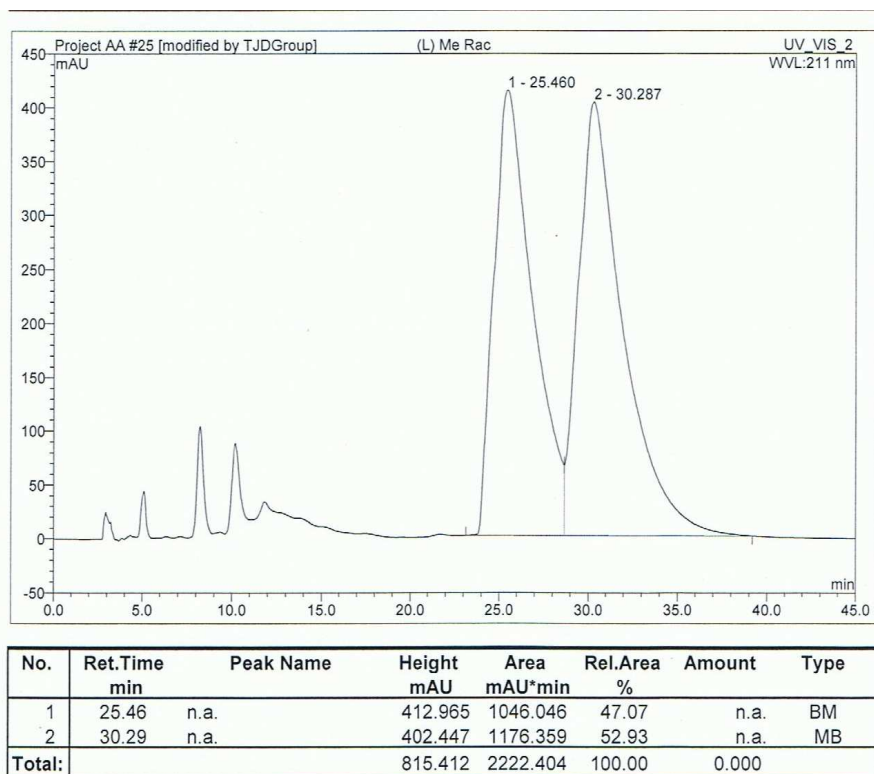


Figure 48 - Racemic phthalimide protected L-alanine reoxidant **296b**

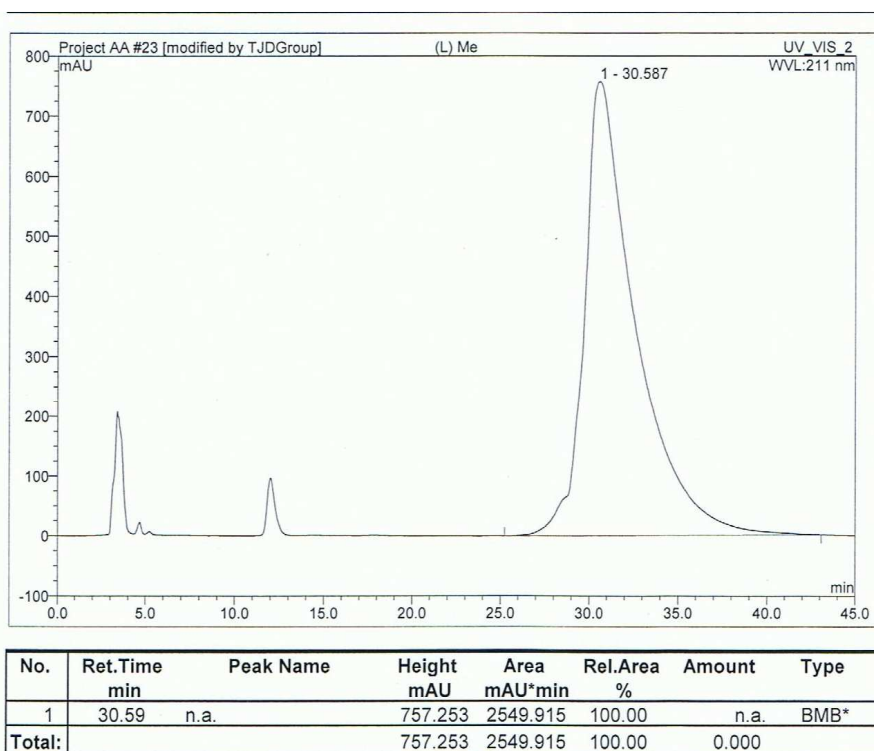
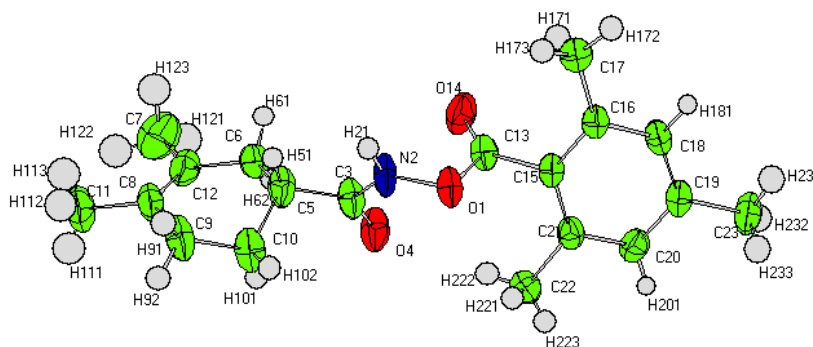


Figure 49 - Phthalimide protected L-alanine reoxidant **296b**
synthesised from General Procedure E₁ - 100% ee

Appendix 3 - X-ray Crystal Structure

Single-crystal X-ray diffraction report for compound **130** (Datablock: 0260109)

Crystal of **130** were grown and run by Callens Cédric from dichloromethane and petrol 40-60 °C. A single crystal having dimensions approximately **0.24 x 0.41 x 0.43 mm** was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150 K in a stream of cold N₂ using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoK_α radiation, $\lambda = 0.71073$ Å). Intensity data were processed using the DENZO-SMN package.¹

Examination of the systematic absences of the intensity data showed the space group to be **P 2/c**. The structure was solved in this space group using the direct-methods program SIR92,² which located all non-hydrogen atoms. The H atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. Subsequent full-matrix least-squares refinement was carried out against F² using the CRYSTAL program suite.³ Coordinates and anisotropic thermal parameters were refined for all non-hydrogen atoms, and the hydrogens were refined with riding constraints. A modified statistical weighting scheme was applied. Refinement converged satisfactorily to give **R = 0.06690**, **wR = 0.0723**.

Attached is a thermal ellipsoid plot (CAMERON) at 50% probability. A summary of crystallographic data is given below, as are full lists of atomic coordinates, anisotropic thermal parameters and those bond lengths and angles not concerning H atoms.

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- (2) A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr.* **1994**, 27, 435.
- (3) P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout, D. J. Watkin, *J. Appl. Crystallogr.* **2003**, 36, 1487.

Crystal identification	CCK 0260109
Chemical formula	C ₁₉ H ₂₅ N ₁ O ₃
Formula weight	315.41
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	P 2/c
<i>a</i> (Å)	14.5795(2)
<i>b</i> (Å)	9.26180(10)
<i>c</i> (Å)	13.4334(2)
α (°)	90
β (°)	102.8400(6)
γ (°)	90
Cell volume (Å ³)	1768.59(4)
<i>Z</i>	4
Calculated density (Mg/m ³)	1.185
Absorption coefficient (mm ⁻¹)	0.079
<i>F</i> ₀₀₀	680
Crystal size (mm)	0.24 × 0.41 × 0.43
Description of crystal	Colourless plate
Absorption correction	multi-scan
Transmission coefficients (min,max)	0.95, 0.98
θ range for data collection (°)	5.16 ≤ θ ≤ 27.37
Index ranges	-18 ≤ <i>h</i> ≤ 18, -11 ≤ <i>k</i> ≤ 11, -17 ≤ <i>l</i> ≤ 17
Reflections measured	30743
Unique reflections	3969
<i>R</i> _{int}	0.028
Observed reflections (<i>I</i> > -2σ(<i>I</i>))	2288
Refinement method	Full-matrix least-squares on <i>F</i>
Parameters refined	203
Weighting scheme	Modified Sheldrick
Goodness of fit	1.1081
<i>R</i>	0.0669
<i>wR</i>	0.0723
Residual electron density (min,max) (eÅ ⁻³)	-0.28, 0.59

Table 1: Crystal data and refinement details

Atom	x	y	z	U _{equiv}
O(1)	0.40357(12)	0.49862(19)	0.34831(14)	0.0497
N(2)	0.47510(15)	0.4708(2)	0.2955(2)	0.0561
C(3)	0.52541(18)	0.5807(3)	0.2719(2)	0.0531
O(4)	0.51033(14)	0.70614(18)	0.29290(18)	0.0638
C(5)	0.6056(2)	0.5340(3)	0.2247(3)	0.0575
C(6)	0.60582(19)	0.6165(3)	0.1295(2)	0.0567
C(7)	0.6973(2)	0.6188(3)	0.0951(2)	0.0597
C(8)	0.77608(19)	0.5655(3)	0.1533(3)	0.0581
C(9)	0.7795(2)	0.5066(4)	0.2579(3)	0.0714
C(10)	0.6988(2)	0.5584(4)	0.3040(3)	0.0650
C(11)	0.8690(2)	0.5622(5)	0.1209(4)	0.0943
C(12)	0.6922(3)	0.6864(5)	-0.0042(3)	0.0983
C(13)	0.32337(17)	0.5568(3)	0.2876(2)	0.0460
O(14)	0.31446(15)	0.5721(3)	0.19850(16)	0.0703
C(15)	0.25342(16)	0.5903(3)	0.34990(19)	0.0409
C(16)	0.16115(17)	0.5387(3)	0.3136(2)	0.0449
C(17)	0.1354(2)	0.4407(4)	0.2223(2)	0.0623
C(18)	0.09349(18)	0.5782(3)	0.3667(2)	0.0513
C(19)	0.11372(18)	0.6671(3)	0.4519(2)	0.0505
C(20)	0.20562(18)	0.7147(3)	0.4865(2)	0.0484

C(21)	0.27663(17)	0.6770(3)	0.43752(18)	0.0427
C(22)	0.37470(18)	0.7329(3)	0.4810(2)	0.0552
C(23)	0.0376(2)	0.7133(4)	0.5053(3)	0.0696

Table 2: Atomic coordinates and equivalent isotropic thermal parameters ($\text{\AA}^2$) of non-hydrogen atoms

Atom	x	y	z	U_{iso}
H(51)	0.6014	0.4313	0.2117	0.0729
H(62)	0.5915	0.7172	0.1367	0.0654
H(61)	0.5584	0.5738	0.0767	0.0684
H(92)	0.8389	0.5431	0.3026	0.0886
H(91)	0.7984	0.4012	0.2646	0.0865
H(101)	0.7033	0.6667	0.3168	0.0835
H(102)	0.6969	0.5065	0.3713	0.0828
H(112)	0.9001	0.4694	0.1399	0.1459
H(111)	0.9090	0.6413	0.1536	0.1457
H(113)	0.8562	0.5736	0.0478	0.1453
H(122)	0.7564	0.7133	-0.0133	0.1516
H(121)	0.6520	0.7728	-0.0118	0.1517
H(123)	0.6635	0.6154	-0.0569	0.1520
H(172)	0.0723	0.4031	0.2170	0.0923
H(171)	0.1359	0.4956	0.1620	0.0926
H(173)	0.1820	0.3632	0.2262	0.0926
H(181)	0.0317	0.5442	0.3443	0.0595
H(201)	0.2207	0.7738	0.5450	0.0570
H(223)	0.3720	0.8164	0.5233	0.0812
H(222)	0.4068	0.7552	0.4266	0.0802
H(221)	0.4100	0.6592	0.5234	0.0813
H(233)	0.0581	0.7133	0.5767	0.1082
H(232)	0.0179	0.8099	0.4854	0.1084
H(231)	-0.0161	0.6525	0.4870	0.1080
H(21)	0.4811	0.3847	0.2749	0.0738

Table 3: Atomic coordinates and isotropic thermal parameters ($\text{\AA}^2$) of hydrogen atoms

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(1)	0.0401(10)	0.0453(10)	0.0701(12)	0.0139(9)	0.0259(9)	0.0096(8)
N(2)	0.0439(12)	0.0393(11)	0.0976(19)	0.0037(12)	0.0421(13)	0.0066(10)
C(3)	0.0439(14)	0.0353(13)	0.088(2)	0.0029(13)	0.0313(14)	0.0021(11)
O(4)	0.0618(12)	0.0342(10)	0.1095(17)	-0.0043(10)	0.0492(12)	0.0001(9)
C(5)	0.0542(16)	0.0342(13)	0.096(2)	-0.0056(14)	0.0427(16)	-0.0063(12)
C(6)	0.0419(15)	0.0658(18)	0.0619(18)	-0.0089(15)	0.0102(13)	0.0084(13)
C(7)	0.0643(19)	0.0525(16)	0.0718(19)	-0.0132(14)	0.0355(16)	-0.0110(14)
C(8)	0.0420(15)	0.0565(16)	0.083(2)	-0.0125(15)	0.0298(15)	-0.0056(13)
C(9)	0.0458(16)	0.070(2)	0.106(3)	0.0081(19)	0.0317(17)	0.0088(15)
C(10)	0.0523(17)	0.072(2)	0.076(2)	0.0197(17)	0.0257(15)	0.0106(15)
C(11)	0.057(2)	0.109(3)	0.130(3)	-0.031(3)	0.051(2)	-0.018(2)
C(12)	0.1166	0.1055	0.0801	0.0075	0.0376	0.0102
C(13)	0.0408(14)	0.0444(14)	0.0562(17)	0.0080(12)	0.0180(12)	0.0030(11)
O(14)	0.0635(13)	0.1042(18)	0.0502(12)	0.0105(12)	0.0277(10)	0.0162(12)
C(15)	0.0363(13)	0.0444(13)	0.0454(14)	0.0080(11)	0.0164(11)	0.0073(11)
C(16)	0.0394(13)	0.0494(14)	0.0480(14)	0.0038(12)	0.0145(11)	0.0057(11)
C(17)	0.0528(17)	0.0694(19)	0.0664(19)	-0.0125(16)	0.0168(14)	-0.0040(15)
C(18)	0.0342(13)	0.0617(16)	0.0602(17)	0.0024(14)	0.0155(12)	0.0018(12)
C(19)	0.0442(15)	0.0585(16)	0.0542(16)	0.0045(13)	0.0226(12)	0.0071(12)
C(20)	0.0511(15)	0.0554(16)	0.0416(14)	0.0016(12)	0.0166(12)	0.0052(12)
C(21)	0.0382(13)	0.0510(14)	0.0403(13)	0.0099(11)	0.0119(10)	0.0049(11)
C(22)	0.0441(14)	0.0687(18)	0.0526(16)	-0.0017(14)	0.0104(12)	-0.0043(13)

C(23)	0.0599(18)	0.082(2)	0.079(2)	-0.0052(18)	0.0399(16)	0.0055(16)
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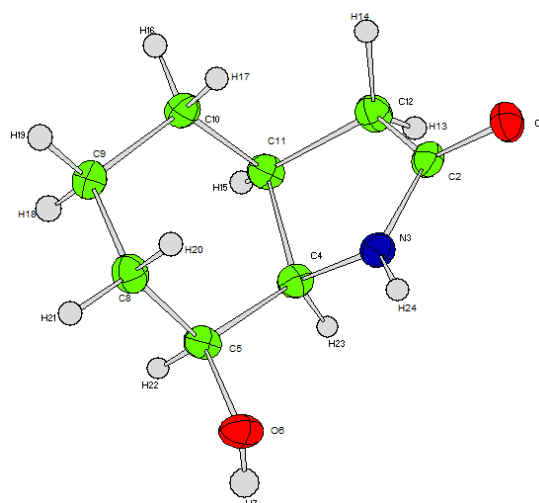
Table 4: Anisotropic thermal parameters ($\text{\AA}^2$)

O(1) - N2	1.409(3)	C(9) - C(10)	1.524(4)
O(1) - C(13)	1.378(3)	C(13) - O(14)	1.183(3)
N(2) - C(3)	1.333(3)	C(13) - C(15)	1.489(3)
N(2) - H(21)	0.855	C(15) - C(16)	1.409(4)
C(3) - O(4)	1.227(3)	C(15) - C(21)	1.403(4)
C(3) - C(5)	1.512(4)	C(16) - C(17)	1.504(4)
C(5) - C(6)	1.490(4)	C(16) - C(18)	1.389(4)
C(5) - C(10)	1.546(5)	C(18) - C(19)	1.387(4)
C(6) - C(7)	1.506(4)	C(19) - C(20)	1.389(4)
C(7) - C(8)	1.332(4)	C(19) - C(23)	1.510(4)
C(7) - C(12)	1.460(5)	C(20) - C(21)	1.389(3)
C(8) - C(9)	1.498(5)	C(21) - C(22)	1.511(4)
C(8) - C(11)	1.513(4)	/	

Table 5: Bond lengths ($\text{\AA}$) Note – C-H atoms have been excluded

N(2) - O(1) - C(13)	113.5(2)	O(1) - C(13) - O(14)	122.3(2)
O(1) - N(2) - C(3)	119.2(2)	O(1) - C(13) - C(15)	110.2(2)
N(2) - C(3) - O4	122.1(2)	O(14) - C(13) - C(15)	127.5(2)
N(2) - C(3) - C(5)	113.5(2)	C(13) - C(15) - C(16)	117.0(2)
O(4) - C(3) - C(5)	124.2(2)	C(13) - C(15) - C(21)	121.6(2)
C(3) - C(5) - C(6)	111.3(2)	C(16) - C(15) - C(21)	121.3(2)
C(3) - C(5) - C(10)	108.2(3)	C(15) - C(16) - C(17)	122.3(2)
C(6) - C(5) - C(10)	110.3(2)	C(15) - C(16) - C(18)	117.7(2)
C(5) - C(6) - C(7)	116.2(2)	C(17) - C(16) - C(18)	120.0(2)
C(6) - C(7) - C(8)	121.4(3)	C(16) - C(18) - C(19)	122.4(3)
C(6) - C(7) - C(12)	114.7(3)	C(18) - C(19) - C(20)	118.5(2)
C(8) - C(7) - C(12)	123.8(3)	C(18) - C(19) - C(23)	121.0(3)
C(7) - C(8) - C(9)	122.0(3)	C(20) - C(19) - C(23)	120.5(3)
C(7) - C(8) - C(11)	123.3(3)	C(19) - C(20) - C(21)	121.8(3)
C(9) - C(8) - C(11)	114.7(3)	C(15) - C(21) - C(20)	118.4(2)
C(8) - C(9) - C(10)	113.5(3)	C(15) - C(21) - C(22)	123.5(2)
C(5) - C(10) - C(9)	108.3(3)	C(20) - C(21) - C(22)	118.1(2)

Table 6: Bond angles ($^\circ$ C) Note – H atoms have been excluded

Single-crystal X-ray diffraction report for compound **159** (Datablock: 0040808)

Crystal of **159** were grown and run by Callens Cédric from dichloromethane and petrol 40-60 °C. A single crystal having dimensions approximately **0.28 x 0.32 x 0.40 mm** was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150 K in a stream of cold N₂ using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoK_α radiation, $\lambda = 0.71073$ Å). Intensity data were processed using the DENZO-SMN package.¹

Examination of the systematic absences of the intensity data showed the space group to be **P 1 21/c 1**. The structure was solved in this space group using the direct-methods program SIR92,² which located all non-hydrogen atoms. The H atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. Subsequent full-matrix least-squares refinement was carried out against F² using the CRYSTAL program suite.³ Coordinates and anisotropic thermal parameters were refined for all non-hydrogen atoms, and the hydrogens were refined with riding constraints. A modified statistical weighting scheme was applied. Refinement converged satisfactorily to give **R = 0.0389**, **wR = 0.0949**.

Attached is a thermal ellipsoid plot (CAMERON) at 50% probability. A summary of crystallographic data is given below, as are full lists of atomic coordinates, anisotropic thermal parameters and those bond lengths and angles not concerning H atoms.

Comments: A network of hydrogen bonding is the result of the presence of a molecule of water per compound.

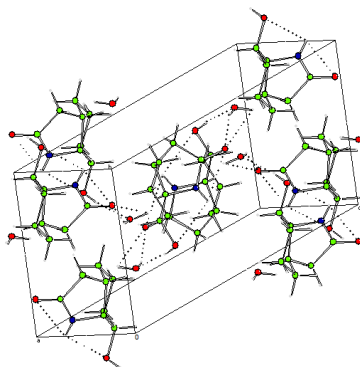


Figure 1. Hydrogen bondings

References

- (1) Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, 276, 307.
- (2) A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli *J. Appl. Crystallogr.* **1994**, 27, 435.
- (3) P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout, D. J. Watkin, *J. Appl. Crystallogr.* **2003**, 36, 1487.

Crystal identification	CCK 0040808
Chemical formula	C ₈ H ₁₅ N ₁ O ₃
Formula weight	173.21
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	P 1 21/c 1
<i>a</i> (Å)	4.97490(10)
<i>b</i> (Å)	7.86990(10)
<i>c</i> (Å)	22.0125(5)
α (°)	90
β (°)	95.2915(8)
γ (°)	90
Cell volume (Å ³)	858.16(3)
<i>Z</i>	4
Calculated density (Mg/m ³)	1.341
Absorption coefficient (mm ⁻¹)	0.102
<i>F</i> ₀₀₀	376
Crystal size (mm)	0.28 × 0.32 × 0.40
Description of crystal	Colourless needle
Absorption correction	multi-scan
Transmission coefficients (min,max)	0.89, 0.97
θ range for data collection (°)	5.1 ≤ θ ≤ 27.49
Index ranges	-6 ≤ <i>h</i> ≤ 6, -9 ≤ <i>k</i> ≤ 10, -28 ≤ <i>l</i> ≤ 28
Reflections measured	3783
Unique reflections	1957
<i>R</i> _{int}	0.025
Observed reflections (<i>I</i> > -3 σ (<i>I</i>))	1954
Refinement method	Full-matrix least-squares on <i>Fsqd</i>
Parameters refined	10581
Weighting scheme	Modified Sheldrick
Goodness of fit	1.0088
<i>R</i>	0.0389
<i>wR</i>	0.0949
Residual electron density (min,max) (eÅ ⁻³)	-0.20, 0.30

Table 1: Crystal data and refinement details

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{equiv}
O(1)	0.04947(17)	0.72572(11)	0.50227(4)	0.0248
C(2)	0.2100(2)	0.69503(15)	0.46360(5)	0.0198
N(3)	0.23439(19)	0.54502(12)	0.43578(4)	0.0204
C(4)	0.4637(2)	0.54066(14)	0.39831(5)	0.0191
C(5)	0.4213(2)	0.42239(14)	0.34335(5)	0.0199
O(6)	0.34467(17)	0.25635(10)	0.36212(4)	0.0254
C(8)	0.2177(2)	0.48881(16)	0.29376(6)	0.0236
C(9)	0.3033(3)	0.66514(16)	0.27398(6)	0.0258
C(10)	0.3088(2)	0.78858(15)	0.32747(5)	0.0232
C(11)	0.4959(2)	0.73147(14)	0.38288(5)	0.0206
C(12)	0.4142(2)	0.81713(15)	0.44129(5)	0.0222
O(25)	0.15842(17)	0.60528(11)	0.11163(4)	0.0271

Table 2: Atomic coordinates and equivalent isotropic thermal parameters (Å²) of non-hydrogen atoms

Atom	x	y	z	U _{iso}
H(7)	0.4857	0.2007	0.3702	0.0401
H(13)	0.5737	0.8297	0.4718	0.0277
H(14)	0.3321	0.9356	0.4343	0.0272
H(15)	0.6959	0.7563	0.3780	0.0264
H(16)	0.3564	0.9057	0.3146	0.0284
H(17)	0.1226	0.7999	0.3400	0.0274
H(18)	0.4800	0.6533	0.2582	0.0319
H(19)	0.1800	0.7053	0.2411	0.0318
H(20)	0.0395	0.4983	0.3101	0.0287
H(21)	0.2051	0.4147	0.2591	0.0285
H(22)	0.5981	0.4160	0.3257	0.0238
H(23)	0.6251	0.5004	0.4239	0.0239
H(24)	0.1533	0.4585	0.4443	0.0255

Table 3: Atomic coordinates and isotropic thermal parameters ($\text{\AA}^2$) of hydrogen atoms

Atom	U ₁₁	U ₂₂	U ₃₃	U ₂₃	U ₁₃	U ₁₂
O(1)	0.0277(5)	0.0266(5)	0.0211(4)	-0.0010(3)	0.0078(3)	0.0003(3)
C(2)	0.0200(5)	0.0222(6)	0.0169(5)	0.0019(4)	0.0001(4)	0.0008(4)
N(3)	0.0222(5)	0.0179(5)	0.0218(5)	0.0018(4)	0.0062(4)	-0.0021(4)
C(4)	0.0158(5)	0.0194(5)	0.0222(6)	0.0018(4)	0.0027(4)	0.0004(4)
C(5)	0.0181(5)	0.0173(5)	0.0254(6)	-0.0001(4)	0.0071(4)	-0.0015(4)
O(6)	0.0247(4)	0.0167(4)	0.0357(5)	0.0024(3)	0.0082(4)	-0.0010(3)
C(8)	0.0239(6)	0.0240(6)	0.0230(6)	-0.0022(4)	0.0030(5)	-0.0025(5)
C(9)	0.0322(6)	0.0250(6)	0.0207(6)	0.0028(5)	0.0053(5)	0.0019(5)
C(10)	0.0279(6)	0.0196(6)	0.0229(6)	0.0036(4)	0.0073(5)	0.0014(5)
C(11)	0.0190(5)	0.0188(5)	0.0247(6)	-0.0003(4)	0.0060(4)	-0.0026(4)
C(12)	0.0231(6)	0.0206(6)	0.0232(6)	-0.0022(4)	0.0033(4)	-0.0030(4)
O(25)	0.0263(5)	0.0288(5)	0.0265(5)	0.0013(4)	0.0035(3)	0.0015(4)

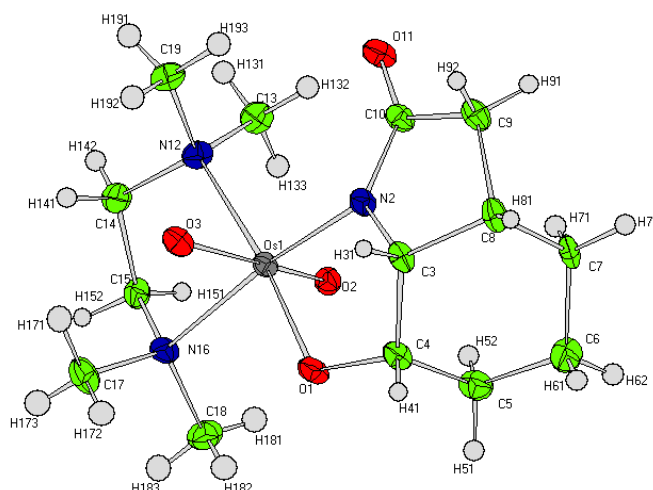
Table 4: Anisotropic thermal parameters ($\text{\AA}^2$)

O(1) – C(2)	1.2434(14)	C(5) – C(8)	1.5123(16)
C(2) – N(3)	1.3406(15)	O(6) – H(7)	0.832
C(2) – C(12)	1.5128(16)	C(8) – C(9)	1.5268(17)
N(3) – C(4)	1.4683(14)	C(9) – C(10)	1.5246(17)
N(3) – H(24)	0.822	C(10) – C(11)	1.5321(17)
C(4) – C(5)	1.5256(16)	C(11) – C(12)	1.5392(16)
C(4) – C(11)	1.5512(15)	O(25) – H(26)	0.840
C(5) – O(6)	1.4327(13)	O(25) – H(27)	0.845

Table 5: Bond lengths ($\text{\AA}$) Note – C-H atoms have been excluded

O(1) - C(2) - N(3)	125.08(11)	O(6) - C(5) - C(8)	110.18(9)
O(1) - C(2) - C(12)	126.29(11)	C(5) - C(8) - C(9)	109.51(10)
N(3) - C(2) - C(12)	108.62(9)	C(8) - C(9) - C(10)	110.15(10)
C(2) - N(3) - C(4)	112.64(9)	C(9) - C(10) - C(11)	113.22(10)
N(3) - C(4) - C(5)	113.71(9)	C(10) - C(11) - C(4)	113.00(9)
N(3) - C(4) - C(11)	101.64(9)	C(10) - C(11) - C(12)	110.40(9)
C(5) - C(4) - C(11)	115.25(9)	C(4) - C(11) - C(12)	101.57(9)
C(4) - C(5) - O(6)	110.41(9)	C(11) - C(12) - C(2)	103.30(9)
C(4) - C(5) - C(8)	113.32(9)	H(26) - O(25) - H(27)	106.8

Table 6: Bond angles ($^\circ$ C) Note – H atoms have been excluded

Single-crystal X-ray diffraction report for compound **160** (Datablock: 0181208)

Crystal of **160** were grown and run by Callens Cédric from dichloromethane and petrol 40-60 °C. A single crystal having dimensions approximately **0.15 x 0.17 x 0.48 mm** was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150 K in a stream of cold N₂ using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoK_α radiation, $\lambda = 0.71073$ Å). Intensity data were processed using the DENZO-SMN package.¹

Examination of the systematic absences of the intensity data showed the space group to be **C c**. The structure was solved in this space group using the direct-methods program SIR92,² which located all non-hydrogen atoms. The H atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. Subsequent full-matrix least-squares refinement was carried out against F² using the CRYSTAL program suite.³ Coordinates and anisotropic thermal parameters were refined for all non-hydrogen atoms, and the hydrogens were refined with riding constraints. A modified statistical weighting scheme was applied. Refinement converged satisfactorily to give **R = 0.0230**, **wR = 0.0584**.

Attached is a thermal ellipsoid plot (CAMERON) at 50% probability. A summary of crystallographic data is given below, as are full lists of atomic coordinates, anisotropic thermal parameters and those bond lengths and angles not concerning H atoms.

References

- (1) Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, 276, 307.
- (2) A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr.* **1994**, 27, 435.
- (3) P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout, D. J. Watkin, *J. Appl. Crystallogr.* **2003**, 36, 1487.

Crystal identification	CCK 0181208
Chemical formula	C ₁₄ H ₂₇ N ₃ O ₄ Os ₁
Formula weight	419.59
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	C c
<i>a</i> (Å)	11.2229(2)
<i>b</i> (Å)	22.1408(4)
<i>c</i> (Å)	7.34520(10)
α (°)	90
β (°)	116.1764(9)
γ (°)	90
Cell volume (Å ³)	1637.98(5)
<i>Z</i>	4
Calculated density (Mg/m ³)	1.993
Absorption coefficient (mm ⁻¹)	7.806
<i>F</i> ₀₀₀	960
Crystal size (mm)	0.15 × 0.17 × 0.48
Description of crystal	Orange block
Absorption correction	multi-scan
Transmission coefficients (min,max)	0.19, 0.31
θ range for data collection (°)	5.18 ≤ θ ≤ 27.56
Index ranges	-14 ≤ <i>h</i> ≤ 14, -28 ≤ <i>k</i> ≤ 27, -9 ≤ <i>l</i> ≤ 9
Reflections measured	3657
Unique reflections	3599
<i>R</i> _{int}	0.014
Observed reflections (<i>I</i> > 3 σ (<i>I</i>))	3599
Refinement method	Full-matrix least-squares on <i>Fsqd</i>
Parameters refined	201
Weighting scheme	Modified Sheldrick
Goodness of fit	0.9496
<i>R</i>	0.0230
<i>wR</i>	0.0584
Residual electron density (min,max) (eÅ ⁻³)	-1.16, 2.46

Table 1: Crystal data and refinement details

Atom	x	y	z	<i>U</i> _{equiv}
Os(1)	0.11044(10)	0.621430(5)	0.21615(14)	0.0134
N(2)	0.2386(4)	0.6327(2)	0.0997(7)	0.0160
C(3)	0.3180(5)	0.5793(3)	0.1161(8)	0.0158
C(4)	0.3387(5)	0.5458(2)	0.3087(8)	0.0181
C(5)	0.4537(5)	0.5691(2)	0.4999(8)	0.0241
C(6)	0.5784(6)	0.5773(3)	0.4686(9)	0.0279
C(7)	0.5527(6)	0.6233(2)	0.2990(10)	0.0251
C(8)	0.4411(5)	0.6032(3)	0.0980(8)	0.0196
C(9)	0.3821(5)	0.6580(2)	-0.0428(8)	0.0202
C(10)	0.2667(6)	0.6784(3)	0.0001(8)	0.0173
O(11)	0.2125(4)	0.72786(16)	-0.0501(6)	0.0228
N(12)	-0.0285(4)	0.7012(2)	0.1042(6)	0.0188
C(13)	0.0377(5)	0.7589(2)	0.1921(8)	0.0221
C(14)	-0.1361(5)	0.6893(3)	0.1663(9)	0.0225
C(15)	-0.0812(6)	0.6609(3)	0.3750(9)	0.0195
N(16)	-0.0165(5)	0.6015(3)	0.3748(7)	0.0181
C(17)	-0.1179(6)	0.5537(3)	0.2730(10)	0.0257
C(18)	0.0633(6)	0.5826(3)	0.5879(8)	0.0278
C(19)	-0.0888(5)	0.7086(3)	-0.1204(8)	0.0258
O(1)	0.2177(4)	0.54873(16)	0.3305(6)	0.0199

O(2)	0.1943(3)	0.66696(15)	0.4299(5)	0.0175
O(3)	-0.0138(4)	0.58690(16)	0.0068(5)	0.0192

Table 2: Atomic coordinates and equivalent isotropic thermal parameters ($\text{\AA}^2$) of non-hydrogen atoms

Atom	x	y	z	U_{iso}
H(31)	0.2687	0.5538	0.0015	0.0218
H(41)	0.3576	0.5036	0.2914	0.0242
H(52)	0.4292	0.6092	0.5338	0.0314
H(51)	0.4711	0.5399	0.6108	0.0304
H(62)	0.6489	0.5923	0.5937	0.0322
H(61)	0.6087	0.5403	0.4372	0.0321
H(71)	0.5203	0.6607	0.3349	0.0325
H(72)	0.6283	0.6324	0.2693	0.0304
H(81)	0.4737	0.5741	0.0307	0.0250
H(91)	0.4473	0.6910	-0.0098	0.0258
H(92)	0.3522	0.6469	-0.1833	0.0256
H(132)	0.1065	0.7672	0.1490	0.0374
H(131)	-0.0252	0.7925	0.1500	0.0374
H(133)	0.0796	0.7556	0.3411	0.0364
H(142)	-0.1805	0.7272	0.1662	0.0297
H(141)	-0.2010	0.6622	0.0663	0.0301
H(151)	-0.0202	0.6874	0.4726	0.0248
H(152)	-0.1538	0.6547	0.4108	0.0246
H(172)	-0.0754	0.5154	0.2793	0.0450
H(171)	-0.1660	0.5652	0.1323	0.0458
H(173)	-0.1792	0.5503	0.3309	0.0460
H(182)	0.1076	0.5460	0.5849	0.0438
H(181)	0.1268	0.6138	0.6593	0.0440
H(183)	0.0046	0.5747	0.6489	0.0444
H(192)	-0.1259	0.6704	-0.1844	0.0404
H(191)	-0.1583	0.7389	-0.1620	0.0406
H(193)	-0.0210	0.7208	-0.1588	0.0405

Table 3: Atomic coordinates and isotropic thermal parameters ($\text{\AA}^2$) of hydrogen atoms

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Os(1)	0.01476(10)	0.01300(10)	0.01477(10)	-0.00021(16)	0.00865(6)	0.00017(15)
N(2)	0.0164(19)	0.0184(19)	0.018(2)	0.0001(16)	0.0118(16)	0.0012(15)
C(3)	0.018(2)	0.016(2)	0.018(2)	-0.0058(17)	0.0122(19)	-0.0032(17)
C(4)	0.0209(19)	0.014(2)	0.025(2)	0.0004(16)	0.0153(17)	0.0012(16)
C(5)	0.027(2)	0.020(3)	0.025(2)	0.0020(19)	0.0119(18)	-0.0009(19)
C(6)	0.022(2)	0.028(3)	0.032(3)	0.003(2)	0.010(2)	0.001(2)
C(7)	0.014(2)	0.033(3)	0.028(3)	0.0022(18)	0.0087(19)	-0.0092(18)
C(8)	0.017(2)	0.018(2)	0.028(2)	-0.0055(17)	0.0135(17)	-0.0029(16)
C(9)	0.023(2)	0.022(2)	0.021(2)	-0.0030(17)	0.0143(19)	-0.0048(17)
C(10)	0.021(2)	0.018(2)	0.016(3)	-0.0018(18)	0.011(2)	-0.0031(17)
O(11)	0.0285(19)	0.0177(16)	0.027(2)	0.0030(14)	0.0166(16)	-0.0004(13)
N(12)	0.0204(19)	0.0187(17)	0.0193(17)	0.0017(14)	0.0105(15)	0.0051(13)
C(13)	0.023(3)	0.018(2)	0.026(3)	-0.0005(18)	0.013(2)	0.0043(17)
C(14)	0.019(2)	0.024(3)	0.026(2)	0.005(2)	0.012(2)	0.0043(18)
C(15)	0.015(3)	0.021(2)	0.023(2)	0.001(2)	0.009(2)	0.0017(18)
N(16)	0.019(2)	0.021(2)	0.0187(19)	0.0040(17)	0.0130(16)	0.0023(16)
C(17)	0.023(3)	0.026(3)	0.035(3)	-0.001(2)	0.019(2)	-0.003(2)
C(18)	0.026(3)	0.037(3)	0.023(2)	0.010(2)	0.0130(19)	0.008(2)
C(19)	0.026(3)	0.030(3)	0.0181(19)	0.0056(19)	0.0065(19)	0.002(2)
O(1)	0.0231(16)	0.0142(15)	0.0292(19)	0.0046(14)	0.0176(14)	0.0028(12)
O(2)	0.0162(16)	0.0159(16)	0.0198(15)	0.0000(11)	0.0074(13)	-0.0006(12)

O(3)	0.0237(17)	0.0179(17)	0.0207(15)	-0.0026(13)	0.0141(12)	-0.0019(12)
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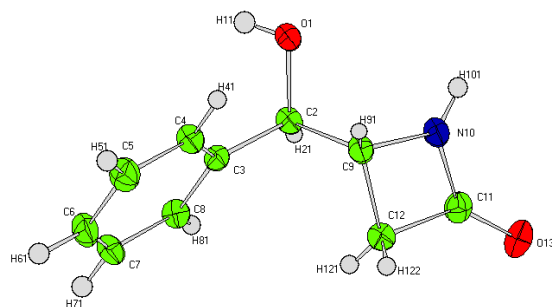
Table 4: Anisotropic thermal parameters ($\text{\AA}^2$)

Os(1) - N(2)	1.987(4)	C(6) - C(7)	1.535(8)
Os(1) - N(12)	2.258(4)	C(7) - C(8)	1.521(8)
Os(1) - N(16)	2.247(5)	C(8) - C(9)	1.541(8)
Os(1) - O(1)	1.963(4)	C(9) - C(10)	1.530(7)
Os(1) - O(2)	1.750(3)	C(10) - O(11)	1.227(7)
Os(1) - O(3)	1.732(4)	N(12) - C(13)	1.475(7)
N(2) - C(3)	1.453(7)	N(12) - C(14)	1.492(7)
N(2) - C(10)	1.364(7)	N(12) - C(19)	1.490(7)
C(3) - C(4)	1.522(8)	C(14) - C(15)	1.513(8)
C(3) - C(8)	1.538(7)	C(15) - N(16)	1.503(8)
C(4) - C(5)	1.518(7)	N(16) - C(17)	1.492(8)
C(4) - O(1)	1.438(6)	N(16) - C(18)	1.480(7)
C(5) - C(6)	1.526(8)	/	

Table 5: Bond lengths ($\text{\AA}$) Note – C-H atoms have been excluded

N(2) - Os(1) - N(12)	105.01(18)	N(2) - Os(1) - N(16)	173.27(19)
N(2) - Os(1) - N(16)	173.27(19)	N(12) - Os(1) - N(16)	81.30(17)
N(12) - Os(1) - N(16)	81.30(17)	C(5) - C(6) - C(7)	110.2(5)
N(2) - Os(1) - O(1)	82.19(18)	C(6) - C(7) - C(8)	111.9(4)
N(12) - Os(1) - O(1)	172.79(15)	C(3) - C(8) - C(7)	113.8(5)
N(16) - Os(1) - O(1)	91.51(17)	C(3) - C(8) - C(9)	101.1(4)
N(2) - Os(1) - O(2)	96.24(19)	C(7) - C(8) - C(9)	110.3(4)
N(12) - Os(1) - O(2)	83.55(16)	C(8) - C(9) - C(10)	104.3(4)
N(16) - Os(1) - O(2)	82.00(17)	C(9) - C(10) - N(2)	107.9(5)
O(1) - Os(1) - O(2)	95.90(16)	C(9) - C(10) - O11	123.7(5)
N(2) - Os(1) - O(3)	97.22(19)	N(2) - C(10) - O11	128.4(5)
N(12) - Os(1) - O(3)	82.31(17)	Os(1) - N(12) - C(13)	112.6(3)
N(16) - Os(1) - O(3)	85.83(17)	Os(1) - N(12) - C(14)	105.8(3)
O(1) - Os(1) - O(3)	96.86(17)	C(13) - N(12) - C(14)	109.8(4)
O(2) - Os(1) - O(3)	162.57(17)	Os(1) - N(12) - C(19)	113.1(3)
Os(1) - N(2) - C(3)	113.3(3)	C(13) - N(12) - C(19)	106.6(4)
Os(1) - N(2) - C(10)	135.0(4)	C(14) - N(12) - C(19)	108.9(4)
C(3) - N(2) - C(10)	111.7(4)	N(12) - C(14) - C(15)	111.1(4)
N(2) - C(3) - C(4)	108.1(4)	C(14) - C(15) - N(16)	110.1(5)
N(2) - C(3) - C(8)	104.7(5)	Os(1) - N(16) - C(15)	104.2(4)
C(4) - C(3) - C(8)	118.2(5)	Os(1) - N(16) - C(17)	113.4(3)
C(3) - C(4) - C(5)	114.4(4)	C(15) - N(16) - C(17)	111.1(4)
C(3) - C(4) - O(1)	108.5(4)	Os(1) - N(16) - C(18)	112.2(3)
C(5) - C(4) - O(1)	109.9(4)	C(15) - N(16) - C(18)	108.3(4)
C(4) - C(5) - C(6)	111.3(5)	C(17) - N(16) - C(18)	107.5(5)
N(2) - Os(1) - N(12)	105.01(18)	C(4) - O(1) - Os(1)	114.9(3)

Table 6: Bond angles ($^\circ$) Note – H atoms have been excluded

Single-crystal X-ray diffraction report for compound **170** (Datablock: 0200109)

Crystal of **170** were grown and run by Callens Cédric from dichloromethane and petrol 40-60 °C. A single crystal having dimensions approximately **0.20 x 0.36 x 0.50 mm** was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150 K in a stream of cold N₂ using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoK α radiation, $\lambda = 0.71073$ Å). Intensity data were processed using the DENZO-SMN package.¹

Examination of the systematic absences of the intensity data showed the space group to be **P 2/c**. The structure was solved in this space group using the direct-methods program SIR92,² which located all non-hydrogen atoms. The H atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. Subsequent full-matrix least-squares refinement was carried out against F² using the CRYSTAL program suite.³ Coordinates and anisotropic thermal parameters were refined for all non-hydrogen atoms, and the hydrogens were refined with riding constraints. A modified statistical weighting scheme was applied. Refinement converged satisfactorily to give **R = 0.0460**, **wR = 0.1039**.

Attached is a thermal ellipsoid plot (CAMERON) at 50% probability. A summary of crystallographic data is given below, as are full lists of atomic coordinates, anisotropic thermal parameters and those bond lengths and angles not concerning H atoms.

References

- (1) Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, 276, 307.
- (2) A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr.* **1994**, 27, 435.
- (3) P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout, D. J. Watkin, *J. Appl. Crystallogr.* **2003**, 36, 1487.

Crystal identification	CCK 0200109
Chemical formula	C ₁₀ H ₁₁ N ₁ O ₂
Formula weight	177.20
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	P 2/c
<i>a</i> (Å)	12.3541(2)
<i>b</i> (Å)	5.50880(10)
<i>c</i> (Å)	13.1359(2)
α (°)	90
β (°)	100.0534(9)
γ (°)	90
Cell volume (Å ³)	880.25(3)
<i>Z</i>	4
Calculated density (Mg/m ³)	1.337
Absorption coefficient (mm ⁻¹)	0.094
<i>F</i> ₀₀₀	376
Crystal size (mm)	0.20 × 0.36 × 0.50
Description of crystal	Colourless plate
Absorption correction	multi-scan
Transmission coefficients (min,max)	0.89, 0.98
θ range for data collection (°)	5.32 ≤ θ ≤ 27.48
Index ranges	-15 ≤ <i>h</i> ≤ 16, -6 ≤ <i>k</i> ≤ 7, -17 ≤ <i>l</i> ≤ 16
Reflections measured	9041
Unique reflections	2003
<i>R</i> _{int}	0
Observed reflections (<i>I</i> > -2σ(<i>I</i>))	2002
Refinement method	Full-matrix least-squares on <i>Fsqd</i>
Parameters refined	118
Weighting scheme	Modified Sheldrick
Goodness of fit	0.9367
<i>R</i>	0.0755
<i>wR</i>	0.1150
Residual electron density (min,max) (eÅ ⁻³)	-0.46, 0.44

Table 1: Crystal data and refinement details

Atom	x	y	z	<i>U</i> _{equiv}
O(1)	0.88962(8)	0.5454(2)	0.84642(8)	0.0278
C(2)	0.84111(12)	0.3090(3)	0.84807(11)	0.0243
C(3)	0.73858(12)	0.2838(3)	0.76617(10)	0.0219
C(4)	0.65579(12)	0.4579(3)	0.75476(11)	0.0266
C(5)	0.56126(13)	0.4310(3)	0.68057(12)	0.0323
C(6)	0.54923(14)	0.2280(4)	0.61802(12)	0.0346
C(7)	0.63066(14)	0.0532(3)	0.62886(12)	0.0330
C(8)	0.72553(13)	0.0808(3)	0.70250(11)	0.0273
C(9)	0.81205(12)	0.2774(3)	0.95473(11)	0.0244
N(10)	0.90574(10)	0.2415(3)	1.04018(9)	0.0288
C(11)	0.87126(12)	0.0257(3)	1.06937(11)	0.0256
C(12)	0.77288(13)	0.0219(3)	0.98125(12)	0.0271
O(13)	0.90619(9)	-0.1109(2)	1.14135(8)	0.0330

Table 2: Atomic coordinates and equivalent isotropic thermal parameters (Å²) of non-hydrogen atoms

Atom	x	y	z	<i>U</i> _{iso}
H(21)	0.8949	0.1789	0.8406	0.0308

H(41))	0.6660	0.5998	0.7988	0.0321
H(51)	0.5040	0.5538	0.6735	0.0408
H(61)	0.4835	0.2098	0.5668	0.0420
H(71)	0.6231	-0.0883	0.5838	0.0398
H(81)	0.7844	-0.0400	0.7072	0.0337
H(91)	0.7620	0.4119	0.9701	0.0274
H(122)	0.6997	0.0164	1.0055	0.0336
H(121)	0.7780	-0.1048	0.9314	0.0327
H(11)	0.9047	0.5601	0.7822	0.0417
H(101)	0.9627	0.3346	1.0665	0.0363

Table 3: Atomic coordinates and isotropic thermal parameters ($\text{\AA}^2$) of hydrogen atoms

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(1)	0.0294(6)	0.0315(7)	0.0214(5)	-0.0015(5)	0.0014(4)	-0.0099(5)
C(2)	0.0238(8)	0.0254(9)	0.0226(7)	-0.0014(6)	0.0014(6)	-0.0032(7)
C(3)	0.0224(7)	0.0242(8)	0.0193(7)	0.0020(6)	0.0038(6)	-0.0032(6)
C(4)	0.0277(8)	0.0276(9)	0.0239(8)	-0.0026(7)	0.0024(6)	-0.0026(7)
C(5)	0.0240(8)	0.0399(11)	0.0315(9)	0.0032(8)	0.0009(6)	0.0004(8)
C(6)	0.0293(9)	0.0473(12)	0.0245(8)	0.0014(8)	-0.0027(6)	-0.0093(8)
C(7)	0.0413(10)	0.0336(10)	0.0226(8)	-0.0068(7)	0.0008(7)	-0.0113(8)
C(8)	0.0310(8)	0.0272(9)	0.0236(7)	-0.0006(7)	0.0040(6)	-0.0032(7)
C(9)	0.0245(8)	0.0273(9)	0.0203(7)	-0.0013(6)	0.0011(6)	-0.0020(7)
N(10)	0.0278(7)	0.0355(9)	0.0215(6)	0.0013(6)	-0.0004(5)	-0.0080(6)
C(11)	0.0256(8)	0.0311(9)	0.0216(7)	-0.0004(7)	0.0084(6)	0.0008(7)
C(12)	0.0275(8)	0.0280(9)	0.0249(8)	0.0008(7)	0.0022(6)	-0.0045(7)
O(13)	0.0357(6)	0.0402(8)	0.0241(6)	0.0077(5)	0.0077(5)	0.0079(6)

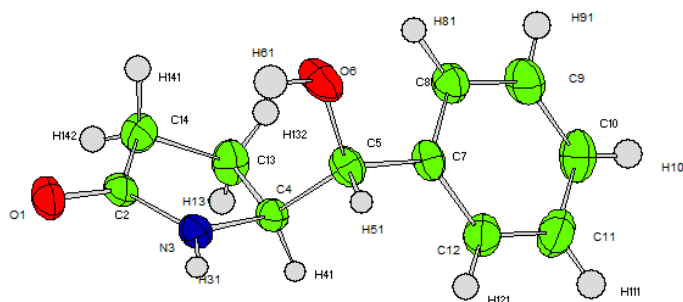
Table 4: Anisotropic thermal parameters ($\text{\AA}^2$)

O(1) - C(2)	1.4349(18)	C(6) - C(7)	1.382(2)
O(1) - H(11)	0.899	C(7) - C(8)	1.392(2)
C(2) - C(3)	1.5183(19)	C(9) - N(10)	1.4783(18)
C(2) - C(9)	1.516(2)	C(9) - C(12)	1.548(2)
C(3) - C(4)	1.391(2)	N(10) - C(11)	1.341(2)
C(3) - C(8)	1.389(2)	N(10) - H(101)	0.890
C(4) - C(5)	1.392(2)	C(11) - C(12)	1.525(2)
C(5) - C(6)	1.380(2)	C(11) - O(1)3	1.2261(19)
C(8) - C(9)	1.516(4)	C(19) - C(20)	1.529(4)
C(9) - C(10)	1.523(4)	C(20) - C(21)	1.522(4)

Table 5: Bond lengths ($\text{\AA}$) Note – C-H atoms have been excluded

O(1). C(2) - C(3)	111.80(12)	C(7) - C(8) - C(3)	120.11(15)
O(1) - C(2) - C(9)	106.57(12)	C(2) - C(9) - N(10)	115.91(12)
C(3) - C(2) - C(9)	109.97(12)	C(2) - C(9) - C(12)	116.51(13)
C(2) - C(3) - C(4)	121.33(13)	N(10) - C(9) - C(12)	86.64(11)
C(2) - C(3) - C(8)	119.68(14)	C(9) - N(10) - C(11)	95.18(12)
C(4) - C(3) - C(8)	118.97(13)	N(10) - C(11) - C(12)	92.62(12)
C(3) - C(4) - C(5)	120.88(15)	N(10) - C(11) - O13	132.66(15)
C(4) - C(5) - C(6)	119.54(16)	C(12) - C(11) - O13	134.71(15)
C(5) - C(6) - C(7)	120.16(15)	C(9) - C(12) - C(11)	85.39(11)
C(6) - C(7) - C(8)	120.34(15)	/	

Table 6: Bond angles ($^\circ$) Note – H atoms have been excluded



Attached is a thermal ellipsoid plot (CAMERON) at 50% probability. A summary of crystallographic data is given below, as are full lists of atomic coordinates, anisotropic thermal parameters and those bond lengths and angles not concerning H atoms.

- (1) Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, 276, 307.
- (2) A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr.* **1994**, 27, 435.
- (3) P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout, D. J. Watkin, *J. Appl. Crystallogr.* **2003**, 36, 1487.

Crystal identification	CCK 0020808
Chemical formula	C ₁₁ H ₁₃ N ₁ O ₂
Formula weight	191.23
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	P 1 21/a 1
<i>a</i> (Å)	9.1222(2)
<i>b</i> (Å)	6.27090(10)
<i>c</i> (Å)	18.0508(4)
α (°)	90
β (°)	100.9987(9)
γ (°)	90
Cell volume (Å ³)	1013.62(4)
<i>Z</i>	4
Calculated density (Mg/m ³)	1.253
Absorption coefficient (mm ⁻¹)	0.087
<i>F</i> ₀₀₀	408
Crystal size (mm)	0.20 × 0.38 × 0.48
Description of crystal	Colourless plate
Absorption correction	multi-scan
Transmission coefficients (min,max)	0.89, 0.98
θ range for data collection (°)	5.16 ≤ θ ≤ 27.49
Index ranges	-11 ≤ <i>h</i> ≤ 11, -8 ≤ <i>k</i> ≤ 8, -23 ≤ <i>l</i> ≤ 23
Reflections measured	16667
Unique reflections	2487
<i>R</i> _{int}	0.037
Observed reflections (<i>I</i> > -3 σ (<i>I</i>))	2305
Refinement method	Full-matrix least-squares on <i>Fsqd</i>
Parameters refined	127
Weighting scheme	Modified Sheldrick
Goodness of fit	0.9369
<i>R</i>	0.0429
<i>wR</i>	0.0986
Residual electron density (min,max) (eÅ ⁻³)	-0.27, 0.29

Table 1: Crystal data and refinement details

Atom	x	y	z	<i>U</i> _{equiv}
O(1)	0.13651(10)	0.64814(16)	-0.02856(5)	0.0395
C(2)	0.15192(13)	0.6568(2)	0.04135(7)	0.0298
N(3)	0.22189(11)	0.51108(17)	0.08878(5)	0.0285
C(4)	0.23318(13)	0.55948(19)	0.16873(6)	0.0266
C(5)	0.14726(14)	0.3978(2)	0.20763(7)	0.0318
O(6)	-0.00800(10)	0.40736(19)	0.17852(5)	0.0495
C(7)	0.17575(14)	0.4386(2)	0.29166(7)	0.0310
C(8)	0.07478(15)	0.5472(2)	0.32659(7)	0.0362
C(9)	0.10778(17)	0.5855(3)	0.40392(7)	0.0435
C(10)	0.24111(18)	0.5175(3)	0.44654(8)	0.0479
C(11)	0.34249(18)	0.4105(3)	0.41207(8)	0.0488
C(12)	0.31005(16)	0.3723(2)	0.33527(8)	0.0414
C(13)	0.17407(16)	0.7895(2)	0.16739(7)	0.0377
C(14)	0.09767(16)	0.8315(2)	0.08643(7)	0.0389

Table 2: Atomic coordinates and equivalent isotropic thermal parameters (Å²) of non-hydrogen atoms

Atom	x	y	z	U _{iso}
H(41)	0.3389	0.5538	0.1947	0.0326
H(51)	0.1860	0.2518	0.1980	0.0379
H(81)	0.0185	-0.5918	0.2972	0.0438
H(91)	0.0349	0.6604	0.4265	0.0523
H(101)	0.2649	0.5447	0.5000	0.0578
H(111)	0.4360	0.3645	0.4420	0.0568
H(121)	0.3786	0.3003	0.3115	0.0504
H(131)	0.2593	0.8897	0.1815	0.0485
H(132)	0.1085	0.8071	0.2019	0.0481
H(142)	0.1209	0.9693	0.0693	0.0486
H(141)	-0.0136	0.8175	0.0798	0.0496
H(31)	0.2628	0.3966	0.0731	0.0376
H(61)	-0.0255	0.3905	0.1291	0.0752

Table 3: Atomic coordinates and isotropic thermal parameters ($\text{\AA}^2$) of hydrogen atoms

Atom	U ₁₁	U ₂₂	U ₃₃	U ₂₃	U ₁₃	U ₁₂
O(1)	0.0389(5)	0.0539(6)	0.0249(5)	0.0038(4)	0.0040(4)	-0.0119(4)
C(2)	0.0227(6)	0.0384(7)	0.0287(6)	0.0033(5)	0.0056(4)	-0.0071(5)
N(3)	0.0292(5)	0.0322(6)	0.0255(5)	-0.0015(4)	0.0084(4)	0.0008(4)
C(4)	0.0251(6)	0.0312(6)	0.0235(6)	-0.0012(5)	0.0047(4)	-0.0007(5)
C(5)	0.0369(7)	0.0308(7)	0.0288(6)	-0.0029(5)	0.0095(5)	-0.0058(5)
O(6)	0.0358(5)	0.0844(8)	0.0290(5)	-0.0092(5)	0.0082(4)	-0.0241(5)
C(7)	0.0384(7)	0.0280(6)	0.0276(6)	0.0015(5)	0.0090(5)	-0.0053(5)
C(8)	0.0373(7)	0.0415(8)	0.0301(7)	-0.0009(5)	0.0069(5)	-0.0029(6)
C(9)	0.0538(9)	0.0472(9)	0.0317(7)	-0.0061(6)	0.0135(6)	0.0013(7)
C(10)	0.0648(10)	0.0515(9)	0.0257(7)	-0.0010(6)	0.0040(6)	-0.0019(8)
C(11)	0.0527(9)	0.0553(10)	0.0350(7)	0.0086(7)	-0.0002(6)	0.0073(7)
C(12)	0.0476(8)	0.0423(8)	0.0353(7)	0.0055(6)	0.0108(6)	0.0084(6)
C(13)	0.0519(8)	0.0290(7)	0.0333(7)	0.0003(5)	0.0106(6)	0.0023(6)
C(14)	0.0399(7)	0.0401(8)	0.0379(7)	0.0080(6)	0.0100(5)	0.0087(6)

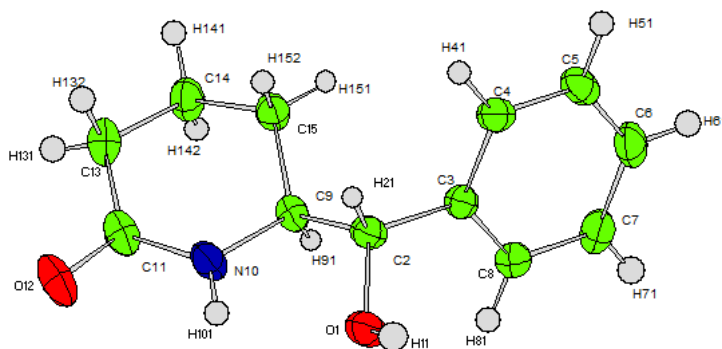
Table 4: Anisotropic thermal parameters ($\text{\AA}^2$)

O(1) – C(2)	1.2440(14)	O(6) – H(61)	0.882
C(2) – N(3)	1.3290(16)	C(7) – C(8)	1.3895(19)
C(2) – C(14)	1.5040(19)	C(7) – C(12)	1.3877(19)
N(3) – C(4)	1.4590(14)	C(8) – C(9)	1.3917(18)
C(4) – C(5)	1.5316(16)	C(9) – C(10)	1.377(2)
C(4) – C(13)	1.5382(18)	C(10) – C(11)	1.383(2)
N(3) – H(31)	0.880	C(11) – C(12)	1.3822(19)
C(5) – O(6)	1.4148(16)	C(13) – C(14)	1.5173(18)
C(5) – C(7)	1.5110(17)		

Table 5: Bond lengths ($\text{\AA}$) Note –C-H atoms have been excluded

O(1) - C(2) - N(3)	124.82(12)	C(5) - C(7) - C(8)	122.45(11)
O(1) - C(2) - C(14)	126.54(12)	C(5) - C(7) - C(12)	118.86(12)
N(3) - C(2) - C(14)	108.64(10)	C(8) - C(9) - C(10)	118.65(12)
C(2) - N(3) - C(4)	115.39(10)	C(7) - C(8) - C(9)	120.29(13)
N(3) - C(4) - C(5)	111.72(10)	C(9) - C(10) - C(11)	119.61(13)
N(3) - C(4) - C(13)	102.78(9)	C(10) - C(11) - C(12)	120.13(14)
C(5) - C(4) - C(13)	114.79(10)	C(7) - C(12) - C(11)	120.92(13)
C(4) - C(5) - O(6)	111.43(10)	C(4) - C(13) - C(14)	105.86(10)
C(4) - C(5) - C(7)	110.06(10)	C(13) - C(14) - C(2)	104.85(10)
O(6) - C(5) - C(7)	109.51(10)		

Table 6: Bond angles ($^\circ$ C) Note – H atoms have been exclude

Single-crystal X-ray diffraction report for compound **172** (Datablock: 0050808)

Crystal of **172** were grown and run by Callens Cédric from dichloromethane and petrol 40-60 °C. A single crystal having dimensions approximately **0.24 x 0.28 x 0.44 mm** was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150 K in a stream of cold N₂ using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoK α radiation, $\lambda = 0.71073$ Å). Intensity data were processed using the DENZO-SMN package.¹

Examination of the systematic absences of the intensity data showed the space group to be **P 1 21/c 1**. The structure was solved in this space group using the direct-methods program SIR92,² which located all non-hydrogen atoms. The H atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. Subsequent full-matrix least-squares refinement was carried out against F² using the CRYSTAL program suite.³ Coordinates and anisotropic thermal parameters were refined for all non-hydrogen atoms, and the hydrogens were refined with riding constraints. A modified statistical weighting scheme was applied. Refinement converged satisfactorily to give **R = 0.0392**, **wR = 0.0891**.

Attached is a thermal ellipsoid plot (CAMERON) at 50% probability. A summary of crystallographic data is given below, as are full lists of atomic coordinates, anisotropic thermal parameters and those bond lengths and angles not concerning H atoms.

References

- (1) Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, 276, 307.
- (2) A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr.* **1994**, 27, 435.
- (3) P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout, D. J. Watkin, *J. Appl. Crystallogr.* **2003**, 36, 1487.

Crystal identification	CCK 0050808
Chemical formula	C ₁₂ H ₁₅ N ₁ O ₂
Formula weight	205.26
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	P 1 21/c 1
<i>a</i> (Å)	6.11250(10)
<i>b</i> (Å)	15.5663(3)
<i>c</i> (Å)	11.1621(2)
α (°)	90
β (°)	95.2915(8)
γ (°)	90
Cell volume (Å ³)	1048.11(3)
<i>Z</i>	4
Calculated density (Mg/m ³)	1.301
Absorption coefficient (mm ⁻¹)	0.089
<i>F</i> ₀₀₀	440
Crystal size (mm)	0.24 × 0.28 × 0.44
Description of crystal	Colourless plate
Absorption correction	multi-scan
Transmission coefficients (min,max)	0.94, 0.98
θ range for data collection (°)	5.56 ≤ θ ≤ 27.46
Index ranges	-7 ≤ <i>h</i> ≤ 7, -20 ≤ <i>k</i> ≤ 20, -14 ≤ <i>l</i> ≤ 14
Reflections measured	14007
Unique reflections	2442
<i>R</i> _{int}	0
Observed reflections (<i>I</i> > -3 σ (<i>I</i>))	2370
Refinement method	Full-matrix least-squares on <i>F</i> _{sqr}
Parameters refined	136
Weighting scheme	Modified Sheldrick
Goodness of fit	0.9619
<i>R</i>	0.0392
<i>wR</i>	0.0891
Residual electron density (min,max) (eÅ ⁻³)	-0.20, 0.30

Table 1: Crystal data and refinement details

Atom	x	y	z	<i>U</i> _{equiv}
O(1)	1.09782(12)	0.70192(6)	0.46615(8)	0.0376
C(2)	0.86564(17)	0.68963(7)	0.46365(10)	0.0284
C(3)	0.74709(17)	0.66719(7)	0.33781(9)	0.0277
C(4)	0.52919(17)	0.69275(7)	0.29850(10)	0.0313
C(5)	0.41970(19)	0.66918(8)	0.18405(11)	0.0363
C(6)	0.5269(2)	0.62085(8)	0.10725(10)	0.0388
C(7)	0.7441(2)	0.59543(9)	0.14521(11)	0.0419
C(8)	0.85343(19)	0.61829(8)	0.25968(10)	0.0355
C(9)	0.84400(17)	0.61694(7)	0.55407(9)	0.0270
N(10)	0.99739(16)	0.63462(6)	0.66648(8)	0.0338
C(11)	0.9686(2)	0.61842(7)	0.78038(10)	0.0336
O(12)	1.11337(16)	0.63794(6)	0.86783(8)	0.0455
C(13)	0.7548(2)	0.57731(8)	0.80022(10)	0.0379
C(14)	0.6107(2)	0.54332(8)	0.68577(10)	0.0354
C(15)	0.61104(18)	0.60643(7)	0.58179(9)	0.0294

Table 2: Atomic coordinates and equivalent isotropic thermal parameters (Å²) of non-hydrogen atoms

Atom	x	y	z	U _{iso}
H(21)	0.7999	0.7423	0.4928	0.0332
H(41)	0.4544	0.7266	0.3518	0.0383
H(51)	0.2670	0.6879	0.1579	0.0438
H(61)	0.4507	0.6051	0.0279	0.0469
H(71)	0.8180	0.5615	0.0922	0.0523
H(81)	1.0065	0.6004	0.2867	0.0429
H(91)	0.8934	0.5617	0.5190	0.0320
H(132)	0.6727	0.6214	0.8363	0.0463
H(131)	0.7898	0.5307	0.8594	0.0463
H(141)	0.4593	0.5330	0.7019	0.0427
H(142)	0.6697	0.4871	0.6625	0.0415
H(152)	0.5563	0.6638	0.6034	0.0359
H(151)	0.5134	0.5862	0.5075	0.0340

Table 3: Atomic coordinates and isotropic thermal parameters ($\text{\AA}^2$) of hydrogen atoms

Atom	U ₁₁	U ₂₂	U ₃₃	U ₂₃	U ₁₃	U ₁₂
O(1)	0.0249(4)	0.0449(5)	0.0415(5)	0.0093(4)	0.0006(3)	-0.0041(3)
C(2)	0.0236(5)	0.0301(5)	0.0310(5)	0.0032(4)	0.0027(4)	0.0005(4)
C(3)	0.0257(5)	0.0303(5)	0.0273(5)	0.0061(4)	0.0043(4)	-0.0003(4)
C(4)	0.0272(5)	0.0320(6)	0.0349(6)	0.0081(4)	0.0058(4)	0.0016(4)
C(5)	0.0283(5)	0.0397(6)	0.0385(6)	0.0156(5)	-0.0016(4)	-0.0029(5)
C(6)	0.0432(7)	0.0452(7)	0.0258(5)	0.0097(5)	-0.0007(5)	-0.0079(5)
C(7)	0.0464(7)	0.0528(8)	0.0275(6)	0.0016(5)	0.0095(5)	0.0041(6)
C(8)	0.0295(5)	0.0471(7)	0.0304(6)	0.0048(5)	0.0064(4)	0.0058(5)
C(9)	0.0280(5)	0.0271(5)	0.0244(5)	0.0002(4)	-0.0004(4)	0.0023(4)
N(10)	0.0294(5)	0.0377(5)	0.0311(5)	0.0044(4)	-0.0049(4)	-0.0028(4)
C(11)	0.0414(6)	0.0270(5)	0.0291(5)	-0.0025(4)	-0.0046(4)	0.0048(4)
O(12)	0.0524(5)	0.0415(5)	0.0351(5)	-0.0064(4)	-0.0160(4)	0.0043(4)
C(13)	0.0492(7)	0.0403(6)	0.0235(5)	0.0003(5)	0.0033(5)	0.0000(5)
C(14)	0.0400(6)	0.0369(6)	0.0281(5)	0.0043(5)	0.0022(4)	-0.0064(5)
C(15)	0.0301(5)	0.0318(5)	0.0253(5)	0.0004(4)	0.0014(4)	-0.0019(4)

Table 4: Anisotropic thermal parameters ($\text{\AA}^2$)

O(1) – C(2)	1.4279(12)	C(7) – C(8)	1.3893(17)
O(1) – H(11)	0.869	C(9) – N(10)	1.4660(13)
C(2) – C(3)	1.5137(14)	C(9) – C(15)	1.5141(15)
C(2) – C(9)	1.5361(14)	N(10) – C(11)	1.3354(15)
C(3) – C(4)	1.3914(14)	N(10) – H(101)	0.882
C(3) – C(8)	1.3947(16)	C(11) – O(12)	1.2446(13)
C(4) – C(5)	1.3923(16)	C(11) – C(13)	1.5036(18)
C(5) – C(6)	1.3827(19)	C(13) – C(14)	1.5243(15)
C(6) – C(7)	1.3842(18)	C(14) – C(15)	1.5208(15)

Table 5: Bond lengths ($\text{\AA}$) Note – C-H atoms have been excluded

O(1) - C(2) - C(3)	111.98(9)	C(2) - C(9) - N(10)	108.24(8)
O(1) - C(2) - C(9)	106.06(8)	C(2) - C(9) - C(15)	113.42(8)
C(3) - C(2) - C(9)	111.13(8)	N(10) - C(9) - C(15)	109.75(8)
C(2) - C(3) - C(4)	121.12(10)	C(9) - N(10) - C(11)	127.95(10)
C(2) - C(3) - C(8)	120.30(9)	N(10) - C(11) - O(12)	120.94(12)
C(4) - C(3) - C(8)	118.55(10)	N(10) - C(11) - C(13)	118.16(10)
C(3) - C(4) - C(5)	120.51(11)	O(12) - C(11) - C(13)	120.89(11)
C(4) - C(5) - C(6)	120.43(10)	C(11) - C(13) - C(14)	114.99(9)
C(5) - C(6) - C(7)	119.53(11)	C(13) - C(14) - C(15)	110.10(9)
C(6) - C(7) - C(8)	120.22(12)	C(14) - C(15) - C(9)	110.05(9)
C(3) - C(8) - C(7)	120.74(11)		

Table 6: Bond angles ($^\circ$ C) Note – H atoms have been excluded

Crystal identification	CCK 0030808
Chemical formula	C ₁₁ H ₁₃ N ₁ O ₂
Formula weight	191.23
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	P 1 21/a 1
<i>a</i> (Å)	5.60930(10)
<i>b</i> (Å)	23.6664(4)
<i>c</i> (Å)	7.60370(10)
α (°)	90
β (°)	109.9111(8)
γ (°)	90
Cell volume (Å ³)	949.07(3)
<i>Z</i>	4
Calculated density (Mg/m ³)	1.338
Absorption coefficient (mm ⁻¹)	0.092
<i>F</i> ₀₀₀	408
Crystal size (mm)	0.26 × 0.33 × 0.45
Description of crystal	Colourless plate
Absorption correction	multi-scan
Transmission coefficients (min,max)	0.88, 0.98
θ range for data collection (°)	5.16 ≤ θ ≤ 27.48
Index ranges	-7 ≤ <i>h</i> ≤ 7, -30 ≤ <i>k</i> ≤ 29, -9 ≤ <i>l</i> ≤ 9
Reflections measured	9925
Unique reflections	4060
<i>R</i> _{int}	0.024
Observed reflections (<i>I</i> > -3 σ (<i>I</i>))	2135
Refinement method	Full-matrix least-squares on <i>Fsqd</i>
Parameters refined	127
Weighting scheme	Modified Sheldrick
Goodness of fit	0.9760
<i>R</i>	0.0416
<i>wR</i>	0.0971
Residual electron density (min,max) (eÅ ⁻³)	-0.20, 0.39

Table 1: Crystal data and refinement details

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{equiv}
O(1)	-0.33123(16)	0.52218(4)	-0.12608(11)	0.0233
C(2)	-0.2822(2)	0.55123(5)	0.01794(16)	0.0191
N(3)	-0.06815(19)	0.54878(4)	0.16620(13)	0.0221
C(4)	-0.0430(2)	0.59580(5)	0.29723(16)	0.0227
C(5)	-0.3195(2)	0.61381(5)	0.25453(17)	0.0241
C(6)	-0.4510(2)	0.59669(5)	0.05098(16)	0.0217
C(7)	0.0918(2)	0.57956(5)	0.50003(16)	0.0223
O(8)	0.32970(17)	0.55622(4)	0.51163(12)	0.0283
C(9)	0.1181(2)	0.63179(5)	0.62168(16)	0.0205
C(10)	0.2928(2)	0.67404(5)	0.62354(17)	0.0238
C(11)	0.3227(2)	0.72076(5)	0.74025(18)	0.0270
C(12)	0.1782(3)	0.72578(5)	0.85581(18)	0.0281
C(13)	-0.0006(2)	0.68483(6)	0.85037(17)	0.0276
C(14)	-0.0314(2)	0.63805(5)	0.73371(17)	0.0237

Table 2: Atomic coordinates and equivalent isotropic thermal parameters (Å²) of non-hydrogen atoms

Atom	x	y	z	U _{iso}
H(41)	0.0618	0.6275	0.2652	0.0262
H(51)	-0.3330	0.6538	0.2759	0.0295
H(52)	-0.3916	0.5927	0.3357	0.0289
H(61)	-0.4556	0.6275	-0.0339	0.0267
H(62)	-0.6243	0.5826	0.0259	0.0266
H(71)	-0.0125	0.5500	0.5368	0.0259
H(101)	0.3947	0.6702	0.5445	0.0294
H(111)	0.4462	0.7489	0.7423	0.0323
H(121)	0.2050	0.7569	0.9395	0.0325
H(131)	-0.1047	0.6884	0.9264	0.0328
H(141)	-0.1519	0.6097	0.7313	0.0278
H(31)	0.0534	0.5265	0.1722	0.0278
H(81)	0.3938	0.5440	0.6219	0.0429

Table 3: Atomic coordinates and isotropic thermal parameters ($\text{\AA}^2$) of hydrogen atoms

Atom	U ₁₁	U ₂₂	U ₃₃	U ₂₃	U ₁₃	U ₁₂
O(1)	0.0235(4)	0.0264(4)	0.0177(4)	-0.0032(3)	0.0040(3)	0.0019(3)
C(2)	0.0200(5)	0.0196(5)	0.0176(5)	0.0015(4)	0.0063(4)	0.0002(4)
N(3)	0.0210(5)	0.0246(5)	0.0181(5)	-0.0025(4)	0.0035(4)	0.0067(4)
C(4)	0.0241(6)	0.0224(6)	0.0196(6)	-0.0018(4)	0.0049(5)	0.0019(4)
C(5)	0.0238(6)	0.0257(6)	0.0203(6)	-0.0035(5)	0.0041(5)	0.0063(5)
C(6)	0.0213(6)	0.0210(6)	0.0204(6)	0.0002(4)	0.0038(4)	0.0035(4)
C(7)	0.0224(6)	0.0225(6)	0.0198(6)	-0.0010(4)	0.0044(4)	0.0032(4)
O(8)	0.0255(5)	0.0358(5)	0.0205(4)	-0.0005(4)	0.0039(4)	0.0113(4)
C(9)	0.0194(5)	0.0217(5)	0.0162(5)	0.0005(4)	0.0006(4)	0.0029(4)
C(10)	0.0230(6)	0.0278(6)	0.0197(6)	0.0020(5)	0.0060(5)	0.0006(5)
C(11)	0.0285(6)	0.0221(6)	0.0266(6)	0.0026(5)	0.0044(5)	-0.0028(5)
C(12)	0.0351(7)	0.0214(6)	0.0236(6)	-0.0026(5)	0.0046(5)	0.0049(5)
C(13)	0.0279(6)	0.0325(7)	0.0226(6)	-0.0007(5)	0.0090(5)	0.0054(5)
C(14)	0.0213(6)	0.0264(6)	0.0214(6)	0.0012(5)	0.0046(5)	-0.0004(4)

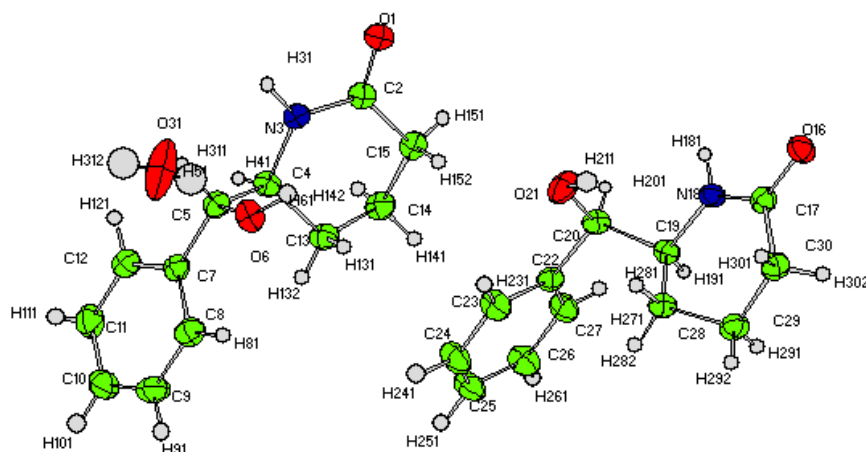
Table 4: Anisotropic thermal parameters ($\text{\AA}^2$)

O(1) – C(2)	1.2420(14)	C(7) – C(9)	1.5208(16)
C(2) – N(3)	1.3395(15)	O(8) – H(81)	0.843
C(2) – C(6)	1.5093(16)	C(9) – C(10)	1.3966(17)
N(3) – C(4)	1.4681(15)	C(9) – C(14)	1.3916(17)
N(3) – H(31)	0.851	C(10) – C(11)	1.3918(18)
C(4) – C(5)	1.5329(17)	C(11) – C(12)	1.3886(19)
C(4) – C(7)	1.5176(16)	C(12) – C(13)	1.3851(19)
C(5) – C(6)	1.5251(16)	C(13) – C(14)	1.3920(18)
C(7) – O(8)	1.4187(14)		

Table 5: Bond lengths ($\text{\AA}$) Note –C-H atoms have been excluded

O(1) - C(2) - N(3)	125.72(11)	C(4) - C(7) - C(9)	108.88(9)
O(1) - C(2) - C(6)	125.34(10)	O(8) - C(7) - C(9)	112.61(9)
N(3) - C(2) - C(6)	108.91(10)	C(7) - C(9) - C(10)	120.68(11)
C(2) - N(3) - C(4)	112.94(9)	C(7) - C(9) - C(14)	120.34(11)
N(3) - C(4) - C(5)	102.14(9)	C(10) - C(9) - C(14)	118.97(11)
N(3) - C(4) - C(7)	113.39(10)	C(9) - C(10) - C(11)	120.47(11)
C(5) - C(4) - C(7)	113.81(10)	C(10) - C(11) - C(12)	120.12(12)
C(4) - C(5) - C(6)	104.23(9)	C(11) - C(12) - C(13)	119.59(12)
C(5) - C(6) - C(2)	104.14(9)	C(12) - C(13) - C(14)	120.46(12)
C(4) - C(7) - O(8)	107.12(9)	C(13) - C(14) - C(9)	120.32(11)

*Note – H atoms have been excluded Table 6: Bond angles ($^\circ$)

Single-crystal X-ray diffraction report for compound **174** (Datablock: 0100808)

Crystal of **174** were grown and run by Callens Cédric from dichloromethane and petrol 40-60 °C. A single crystal having dimensions approximately **0.30 x 0.32 x 0.36 mm** was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150 K in a stream of cold N₂ using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoK α radiation, $\lambda = 0.71073$ Å). Intensity data were processed using the DENZO-SMN package.¹

Examination of the systematic absences of the intensity data showed the space group to be **P-1**. The structure was solved in this space group using the direct-methods program SIR92,² which located all non-hydrogen atoms. The H atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. Subsequent full-matrix least-squares refinement was carried out against F² using the CRYSTAL program suite.³ Coordinates and anisotropic thermal parameters were refined for all non-hydrogen atoms, and the hydrogens were refined with riding constraints. A modified statistical weighting scheme was applied. Refinement converged satisfactorily to give **R = 0.0402**, **wR = 0.0962**.

Attached is a thermal ellipsoid plot (CAMERON) at 50% probability. A summary of crystallographic data is given below, as are full lists of atomic coordinates, anisotropic thermal parameters and those bond lengths and angles not concerning H atoms.

Comments: A network of hydrogen bondings is the result of the presence of water in the cell.

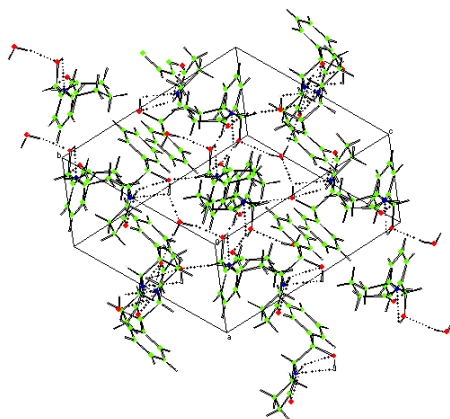


Figure 1. Hydrogen bondings

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- (3) P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout, D. J. Watkin, *J. Appl. Crystallogr.* **2003**, 36, 1487.

Crystal identification	CCK 0100808
Chemical formula	C ₁₂ H ₁₆ N ₁ O _{2.5}
Formula weight	214.26
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Triclinic
Space group	P -1
a (Å)	6.02820(10)
b (Å)	12.9201(2)
c (Å)	14.5745(2)
α (°)	90.8275(6)
β (°)	93.8444(6)
γ (°)	100.0136(8)
Cell volume (Å ³)	1114.93(3)
Z	4
Calculated density (Mg/m ³)	1.276
Absorption coefficient (mm ⁻¹)	0.086
F ₀₀₀	460
Crystal size (mm)	0.30 × 0.32 × 0.36
Description of crystal	Colourless block
Absorption correction	multi-scan
Transmission coefficients (min,max)	0.97, 0.97
θ range for data collection (°)	5.20 ≤ θ ≤ 27.47
Index ranges	-7 ≤ h ≤ 7, -15 ≤ k ≤ 16, -18 ≤ l ≤ 18
Reflections measured	9069
Unique reflections	5054
R _{int}	0.022
Observed reflections (I > -3σ(I))	4175
Refinement method	Full-matrix least-squares on Fsqd
Parameters refined	281
Weighting scheme	Modified Sheldrick
Goodness of fit	0.9426
R	0.0402
wR	0.0962
Residual electron density (min,max) (eÅ ⁻³)	-0.36, 0.22

Table 1: Crystal data and refinement details

Atom	x	y	z	U _{equiv}
O(1)	1.28284(15)	0.55713(8)	0.50911(7)	0.0286
C(2)	1.2263(2)	0.46330(11)	0.48284(10)	0.0251
N(3)	1.16359(18)	0.43981(9)	0.39408(8)	0.0259
C(4)	1.0834(2)	0.33533(11)	0.35133(10)	0.0259
C(5)	0.8850(2)	0.34263(11)	0.28058(10)	0.0265
O(6)	0.69043(16)	0.36551(8)	0.32115(7)	0.0326
C(7)	0.8220(2)	0.24159(11)	0.22376(9)	0.0264
C(8)	0.6264(2)	0.16953(12)	0.23602(11)	0.0330
C(9)	0.5762(3)	0.07635(13)	0.18389(12)	0.0391
C(10)	0.7203(3)	0.05344(13)	0.12022(11)	0.0398
C(11)	0.9158(3)	0.12393(13)	0.10770(11)	0.0397
C(12)	0.9651(3)	0.21763(12)	0.15858(10)	0.0335
C(13)	1.0244(2)	0.25381(11)	0.42421(10)	0.0299
C(14)	1.2092(2)	0.26820(12)	0.50256(10)	0.0312
C(15)	1.2204(2)	0.37503(11)	0.54946(10)	0.0285
O(16)	0.76081(16)	0.47295(8)	1.06001(7)	0.0329
C(17)	0.7011(2)	0.39433(11)	1.00696(9)	0.0266
N(18)	0.82908(18)	0.37370(9)	0.94040(8)	0.0261
C(19)	0.7821(2)	0.28221(11)	0.87675(9)	0.0252
C(20)	0.8885(2)	0.31134(11)	0.78546(10)	0.0264

O(21)	0.8005(2)	0.39379(8)	0.74159(7)	0.0391
C(22)	0.8588(2)	0.21489(11)	0.72185(10)	0.0250
C(23)	0.7059(3)	0.20205(12)	0.64550(11)	0.0334
C(24)	0.6772(3)	0.11212(13)	0.58998(11)	0.0390
C(25)	0.8016(3)	0.03365(13)	0.60923(11)	0.0376
C(26)	0.9559(3)	0.04579(12)	0.68491(11)	0.0355
C(27)	0.9837(2)	0.13563(12)	0.74038(10)	0.0308
C(28)	0.5302(2)	0.24105(12)	0.86546(10)	0.0288
C(29)	0.4372(2)	0.22317(12)	0.95934(10)	0.0314
C(30)	0.4775(2)	0.32423(12)	1.01693(10)	0.0315
O(31)	0.4903(3)	0.49317(13)	0.20211(9)	0.0726

Table 2: Atomic coordinates and equivalent isotropic thermal parameters ($\text{\AA}^2$) of non-hydrogen atoms

Atom	x	y	z	U_{iso}
H(41)	1.2062	0.3166	0.3162	0.0307
H(51)	0.9411	0.4004	0.2377	0.0311
H(81)	0.5248	0.1845	0.2804	0.0391
H(91)	0.4416	0.0287	0.1925	0.0455
H(101)	0.6864	-0.0121	0.0843	0.0477
H(111)	1.0164	0.1071	0.0651	0.0489
H(121)	1.0994	0.2672	0.1487	0.0403
H(131)	0.8830	0.2639	0.4492	0.0355
H(132)	1.0075	0.1826	0.3954	0.0358
H(141)	1.1781	0.2121	0.5482	0.0374
H(142)	1.3534	0.2644	0.4772	0.0371
H(151)	1.3516	0.3926	0.5932	0.0342
H(152)	1.0840	0.3729	0.5831	0.0352
H(191)	0.8598	0.2260	0.9019	0.0293
H(201)	1.0538	0.3356	0.8021	0.0296
H(231)	0.6226	0.2560	0.6319	0.0411
H(241)	0.5719	0.1045	0.5374	0.0477
H(251)	0.7793	-0.0300	0.5706	0.0454
H(261)	1.0429	-0.0087	0.6991	0.0434
H(271)	1.0879	0.1429	0.7926	0.0371
H(281)	0.4556	0.2930	0.8321	0.0354
H(282)	0.5027	0.1742	0.8290	0.0345
H(291)	0.5128	0.1702	0.9908	0.0355
H(292)	0.2735	0.1949	0.9527	0.0363
H(301)	0.3625	0.3662	0.9992	0.0377
H(302)	0.4693	0.3095	1.0822	0.0386
H(312)	0.5607	0.4865	0.1548	0.1214
H(211)	0.7107	0.4221	0.7730	0.0609
H(31)	1.1688	0.4933	0.3571	0.0314
H(61)	0.7231	0.3965	0.3747	0.0501
H(311)	0.5430	0.4605	0.2448	0.1213
H(181)	0.9552	0.4174	0.9359	0.0318

Table 3: Atomic coordinates and isotropic thermal parameters ($\text{\AA}^2$) of hydrogen atoms

Atom	U ₁₁	U ₂₂	U ₃₃	U ₂₃	U ₁₃	U ₁₂
O(1)	0.0238(5)	0.0277(6)	0.0348(6)	-0.0023(4)	0.0040(4)	0.0053(4)
C(2)	0.0162(6)	0.0278(8)	0.0321(8)	-0.0004(6)	0.0037(5)	0.0058(5)
N(3)	0.0242(6)	0.0248(6)	0.0288(6)	0.0036(5)	0.0027(5)	0.0043(5)
C(4)	0.0244(7)	0.0243(7)	0.0295(7)	-0.0015(6)	0.0013(6)	0.0060(6)
C(5)	0.0260(7)	0.0265(8)	0.0279(7)	0.0036(6)	0.0027(6)	0.0068(6)
O(6)	0.0283(5)	0.0386(6)	0.0329(6)	-0.0040(5)	-0.0007(4)	0.0132(4)
C(7)	0.0267(7)	0.0267(8)	0.0265(7)	0.0050(6)	-0.0007(6)	0.0070(6)
C(8)	0.0277(8)	0.0338(9)	0.0374(8)	0.0034(7)	0.0028(6)	0.0043(6)
C(9)	0.0352(8)	0.0318(9)	0.0466(10)	0.0045(7)	-0.0037(7)	-0.0023(7)
C(10)	0.0535(10)	0.0290(9)	0.0355(9)	-0.0016(7)	-0.0058(7)	0.0068(7)
C(11)	0.0492(10)	0.0397(10)	0.0320(8)	-0.0013(7)	0.0074(7)	0.0110(8)
C(12)	0.0335(8)	0.0330(9)	0.0332(8)	0.0023(7)	0.0062(6)	0.0021(6)
C(13)	0.0298(7)	0.0248(8)	0.0351(8)	0.0031(6)	-0.0024(6)	0.0060(6)
C(14)	0.0302(8)	0.0293(8)	0.0350(8)	0.0054(6)	-0.0012(6)	0.0086(6)
C(15)	0.0243(7)	0.0325(8)	0.0293(8)	0.0028(6)	0.0018(6)	0.0063(6)
O(16)	0.0300(5)	0.0359(6)	0.0310(6)	-0.0065(5)	0.0059(4)	0.0000(4)
C(17)	0.0251(7)	0.0287(8)	0.0258(7)	0.0023(6)	0.0006(6)	0.0047(6)
N(18)	0.0208(6)	0.0264(7)	0.0291(6)	-0.0028(5)	0.0027(5)	-0.0019(5)
C(19)	0.0253(7)	0.0230(7)	0.0270(7)	-0.0005(6)	-0.0003(6)	0.0041(5)
C(20)	0.0240(7)	0.0240(7)	0.0312(8)	0.0007(6)	0.0032(6)	0.0036(6)
O(21)	0.0553(7)	0.0302(6)	0.0377(6)	0.0090(5)	0.0190(5)	0.0175(5)
C(22)	0.0217(7)	0.0246(7)	0.0286(7)	0.0010(6)	0.0031(5)	0.0028(5)
C(23)	0.0328(8)	0.0318(8)	0.0366(8)	-0.0010(7)	-0.0059(6)	0.0118(6)
C(24)	0.0395(9)	0.0399(10)	0.0358(9)	-0.0060(7)	-0.0135(7)	0.0088(7)
C(25)	0.0438(9)	0.0294(8)	0.0383(9)	-0.0082(7)	-0.0053(7)	0.0068(7)
C(26)	0.0372(8)	0.0305(8)	0.0406(9)	-0.0026(7)	-0.0048(7)	0.0139(7)
C(27)	0.0271(7)	0.0324(8)	0.0323(8)	-0.0028(6)	-0.0052(6)	0.0066(6)
C(28)	0.0261(7)	0.0272(8)	0.0310(8)	0.0003(6)	0.0012(6)	-0.0010(6)
C(29)	0.0253(7)	0.0323(8)	0.0344(8)	0.0046(6)	0.0022(6)	-0.0012(6)
C(30)	0.0254(7)	0.0362(9)	0.0322(8)	0.0019(7)	0.0054(6)	0.0017(6)
O(31)	0.0894(11)	0.1114(13)	0.0431(8)	0.0296(8)	0.0287(7)	0.0786(10)

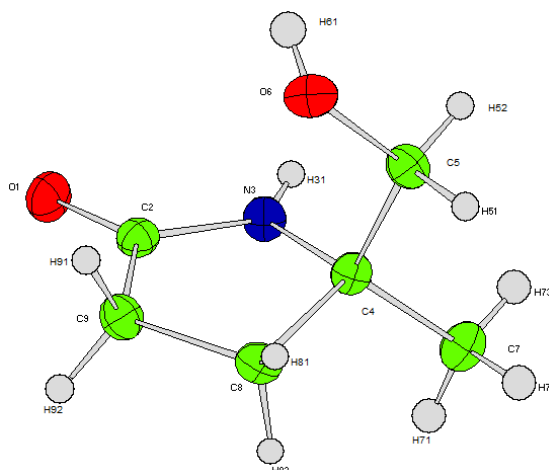
Table 4: Anisotropic thermal parameters (Å²)

O(1) – C(2)	1.2481(17)	C(17) – N(18)	1.3311(18)
C(2) – N(3)	1.3386(18)	C(17) – C(30)	1.5045(19)
C(2) – C(15)	1.506(2)	N(18) – C(19)	1.4680(17)
N(3) – C(4)	1.4671(17)	N(18) – H(181)	0.871
N(3) – H(31)	0.880	C(19) – C(20)	1.539(2)
C(4) – C(5)	1.5426(19)	C(19) – C(28)	1.5163(19)
C(4) – C(13)	1.522(2)	C(20) – O(21)	1.4128(17)
C(4) – H(41)	0.989	C(20) – C(22)	1.5202(19)
C(5) – O(6)	1.4218(17)	O(21) – H(211)	0.857
C(5) – C(7)	1.513(2)	C(22) – C(23)	1.386(2)
O(6) – H(61)	0.866	C(22) – C(27)	1.392(2)
C(7) – C(8)	1.393(2)	C(23) – C(24)	1.385(2)
C(7) – C(12)	1.391(2)	C(24) – C(25)	1.383(2)
C(8) – C(9)	1.391(2)	C(25) – C(26)	1.383(2)
C(9) – C(10)	1.376(2)	C(26) – C(27)	1.384(2)
C(10) – C(11)	1.383(2)	C(28) – C(29)	1.519(2)
C(11) – C(12)	1.387(2)	C(29) – C(30)	1.516(2)
C(13) – C(14)	1.5265(19)	O(31) – H(312)	0.845
C(14) – C(15)	1.520(2)	O(2) – H(311)	0.833
O(16) – C(17)	1.2538(17)		

Table 5: Bond lengths (Å) Note – C-H atoms have been excluded-

O(1) - C(2) - N(3)	119.82(13)	O(16) - C(17) - N(18)	121.09(12)
O(1) - C(2) - C(15)	121.44(12)	O(16) - C(17) - C(30)	119.33(12)
N(3) - C(2) - C(15)	118.72(12)	N(18) - C(17) - C(30)	119.55(12)
C(2) - N(3) - C(4)	127.61(12)	C(17) - N(18) - C(19)	126.10(11)
N(3) - C(4) - C(5)	108.49(11)	N(18) - C(19) - C(20)	109.53(11)
N(3) - C(4) - C(13)	110.73(11)	N(18) - C(19) - C(28)	110.11(11)
C(5) - C(4) - C(13)	113.58(11)	C(20) - C(19) - C(28)	113.61(11)
C(4) - C(5) - O(6)	113.42(11)	C(19) - C(20) - O(21)	112.48(11)
C(4) - C(5) - C(7)	110.27(11)	C(19) - C(20) - C(22)	110.13(11)
O(6) - C(5) - C(7)	109.35(11)	O(21) - C(20) - C(22)	110.70(11)
C(5) - C(7) - C(8)	122.02(13)	C(20) - C(22) - C(23)	121.67(13)
C(5) - C(7) - C(12)	119.64(13)	C(20) - C(22) - C(27)	120.16(12)
C(8) - C(7) - C(12)	118.32(14)	C(23) - C(22) - C(27)	118.16(13)
C(7) - C(8) - C(9)	120.48(14)	C(22) - C(23) - C(24)	120.62(14)
C(8) - C(9) - C(10)	120.49(15)	C(23) - C(24) - C(25)	120.74(14)
C(9) - C(10) - C(11)	119.67(15)	C(24) - C(25) - C(26)	119.22(14)
C(10) - C(11) - C(12)	120.06(15)	C(25) - C(26) - C(27)	119.89(14)
C(7) - C(12) - C(11)	120.97(14)	C(22) - C(27) - C(26)	121.36(13)
C(4) - C(13) - C(14)	110.11(12)	C(19) - C(28) - C(29)	109.78(12)
C(13) - C(14) - C(15)	109.17(12)	C(28) - C(29) - C(30)	111.23(12)
C(14) - C(15) - C(2)	113.21(12)	C(29) - C(30) - C(17)	114.95(12)

Table 6: Bond angles (° C) Note – H atoms have been excluded

Single-crystal X-ray diffraction report for compound **175** (Datablock: 0120808)

Crystal of **175** were grown and run by Callens Cédric from dichloromethane and petrol 40-60 °C. A single crystal having dimensions approximately **0.18 x 0.20 x 0.44 mm** was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150 K in a stream of cold N₂ using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoK α radiation, $\lambda = 0.71073$ Å). Intensity data were processed using the DENZO-SMN package.¹

Examination of the systematic absences of the intensity data showed the space group to be **P 1 21/c 1**. The structure was solved in this space group using the direct-methods program SIR92,² which located all non-hydrogen atoms. The H atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. Subsequent full-matrix least-squares refinement was carried out against F² using the CRYSTAL program suite.³ Coordinates and anisotropic thermal parameters were refined for all non-hydrogen atoms, and the hydrogens were refined with riding constraints. A modified statistical weighting scheme was applied. Refinement converged satisfactorily to give **R = 0.0377**, **wR = 0.0838**.

Attached is a thermal ellipsoid plot (CAMERON) at 50% probability. A summary of crystallographic data is given below, as are full lists of atomic coordinates, anisotropic thermal parameters and those bond lengths and angles not concerning H atoms.

References

- (1) Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, 276, 307.
- (2) A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr.* **1994**, 27, 435.
- (3) P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout, D. J. Watkin, *J. Appl. Crystallogr.* **2003**, 36, 1487.

Crystal identification	CCK 0120808
Chemical formula	C ₆ H ₁₁ N ₁ O ₂
Formula weight	129.16
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	P 1 21/c 1
<i>a</i> (Å)	8.6393(2)
<i>b</i> (Å)	5.2004(1)
<i>c</i> (Å)	14.3361(4)
α (°)	90
β (°)	90.8101(12)
γ (°)	90
Cell volume (Å ³)	644.03(3)
<i>Z</i>	4
Calculated density (Mg/m ³)	1.332
Absorption coefficient (mm ⁻¹)	0.100
<i>F</i> ₀₀₀	280
Crystal size (mm)	0.18 × 0.20 × 0.44
Description of crystal	Colourless plate
Absorption correction	Semi-empirical from equivalent reflections
Transmission coefficients (min,max)	0.90, 0.98
θ range for data collection (°)	5.4 ≤ θ ≤ 27.4
Index ranges	-11 ≤ <i>h</i> ≤ 11, 0 ≤ <i>k</i> ≤ 6, 0 ≤ <i>l</i> ≤ 18
Reflections measured	7135
Unique reflections	2766
<i>R</i> _{int}	0.026
Observed reflections (<i>I</i> > -3 σ (<i>I</i>))	1454
Refinement method	Full-matrix least-squares on <i>Fsqd</i>
Parameters refined	82
Weighting scheme	Modified Sheldrick
Goodness of fit	0.9792
<i>R</i>	0.0377
<i>wR</i>	0.0838
Residual electron density (min,max) (eÅ ⁻³)	-0.29, 0.30

Table 1: Crystal data and refinement details

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{equiv}
O(1)	0.69442(10)	1.12126(17)	0.41937(6)	0.0261
C(2)	0.73340(13)	0.9976(2)	0.48970(8)	0.0189
N(3)	0.69518(11)	1.05329(18)	0.57752(6)	0.0193
C(4)	0.75167(13)	0.8722(2)	0.64879(8)	0.0181
C(5)	0.61957(13)	0.7038(2)	0.68398(8)	0.0214
O(6)	0.54925(9)	0.55345(16)	0.61212(6)	0.0240
C(7)	0.82295(15)	1.0137(2)	0.73165(8)	0.0251
C(8)	0.87147(13)	0.7131(2)	0.59359(8)	0.0205
C(9)	0.83279(14)	0.7585(2)	0.49036(8)	0.0222

Table 2: Atomic coordinates and equivalent isotropic thermal parameters (Å²) of non-hydrogen atoms

Atom	x	y	z	U _{iso}
H(51)	0.6625	0.5828	0.7319	0.0257
H(52)	0.5408	0.8154	0.7145	0.0255
H(72)	0.8615	0.8893	0.7783	0.0370
H(71)	0.9094	1.1205	0.7115	0.0366
H(73)	0.7458	1.1245	0.7614	0.0370
H(82)	0.9748	0.7770	0.6088	0.0221
H(81)	0.8646	0.5298	0.6098	0.0236
H(92)	0.9258	0.7869	0.4525	0.0266
H(91)	0.7723	0.6187	0.4640	0.0272
H(31)	0.6381	1.1818	0.5907	0.0239
H(61)	0.4735	0.6361	0.5889	0.0386

Table 3: Atomic coordinates and isotropic thermal parameters ($\text{\AA}^2$) of hydrogen atoms

Atom	U ₁₁	U ₂₂	U ₃₃	U ₂₃	U ₁₃	U ₁₂
O(1)	0.0288(5)	0.0282(5)	0.0214(4)	0.0053(4)	0.0013(3)	0.0041(4)
C(2)	0.0178(5)	0.0185(6)	0.0204(6)	0.0007(5)	0.0004(4)	0.0026(4)
N(3)	0.0226(5)	0.0147(5)	0.0205(5)	0.0007(4)	0.0004(4)	0.0040(4)
C(4)	0.0204(6)	0.0151(5)	0.0187(5)	0.0009(4)	0.0007(4)	0.0022(4)
C(5)	0.0218(6)	0.0203(6)	0.0221(6)	0.0003(5)	0.0026(4)	0.0009(5)
O(6)	0.0212(4)	0.0176(4)	0.0331(5)	0.0028(3)	0.0022(3)	0.0003(3)
C(7)	0.0286(6)	0.0237(6)	0.0229(6)	0.0013(5)	0.0033(5)	0.0003(5)
C(8)	0.0194(6)	0.0177(6)	0.0245(6)	0.0026(5)	0.0014(4)	0.0023(5)
C(9)	0.0234(6)	0.0206(6)	0.0225(6)	0.0013(5)	0.0026(5)	0.0015(5)

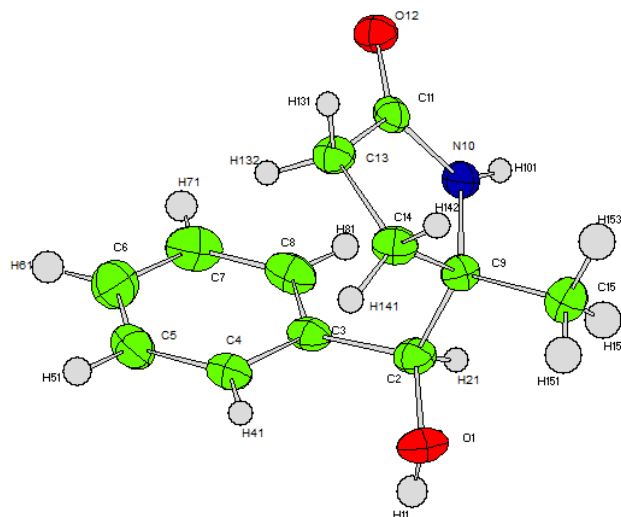
Table 4: Anisotropic thermal parameters ($\text{\AA}^2$)

O(1) – C(2)	1.2386(13)	C(4) – C(5)	1.5298(16)
C(2) – N(3)	1.3377(14)	C(4) – C(7)	1.5203(15)
C(2) – C(9)	1.5111(16)	C(4) – C(8)	1.5506(15)
N(3) – C(4)	1.4681(14)	C(5) – C(6)	1.4226(14)
N(3) – H(31)	0.853	C(8) – C(9)	1.5308(15)

Table 5: Bond lengths ($\text{\AA}$) Note C–H atoms have been excluded

O(1) – C(2) – N(3)	125.86(11)	N(3) – C(4) – C(8)	101.81(8)
O(1) – C(2) – C(9)	125.47(10)	C(5) – C(4) – C(8)	111.69(9)
N(3) – C(2) – C(9)	108.67(9)	C(7) – C(4) – C(8)	113.02(9)
C(2) – N(3) – C(4)	115.59(9)	C(4) – C(5) – O(6)	112.87(9)
N(3) – C(4) – C(5)	110.77(9)	C(4) – C(8) – C(9)	105.85(9)
N(3) – C(4) – C(7)	111.11(9)	C(8) – C(9) – C(2)	104.42(9)
C(5) – C(4) – C(7)	108.37(9)		

Table 6: Bond angles ($^\circ$ C) Note – H atoms have been excluded

Single-crystal X-ray diffraction report for compound **177** (Datablock: 0110808)

Crystal of **177** were grown and run by Callens Cédric from dichloromethane and petrol 40-60 °C. A single crystal having dimensions approximately **0.16 x 0.50 x 0.50 mm** was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150 K in a stream of cold N₂ using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoK α radiation, $\lambda = 0.71073$ Å). Intensity data were processed using the DENZO-SMN package.¹

Examination of the systematic absences of the intensity data showed the space group to be **R -3**. The structure was solved in this space group using the direct-methods program SIR92,² which located all non-hydrogen atoms. The H atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. Subsequent full-matrix least-squares refinement was carried out against F² using the CRYSTAL program suite.³ Coordinates and anisotropic thermal parameters were refined for all non-hydrogen atoms, and the hydrogens were refined with riding constraints. A modified statistical weighting scheme was applied. Refinement converged satisfactorily to give **R = 0.0427**, **wR = 0.1033**.

Attached is a thermal ellipsoid plot (CAMERON) at 50% probability. A summary of crystallographic data is given below, as are full lists of atomic coordinates, anisotropic thermal parameters and those bond lengths and angles not concerning H atoms.

References

- (1) Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, 276, 307.
- (2) A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr.* **1994**, 27, 435.
- (3) P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout, D. J. Watkin, *J. Appl. Crystallogr.* **2003**, 36, 1487.

Crystal identification	CCK 0110808
Chemical formula	C ₁₂ H ₁₂ N ₁ O ₂
Formula weight	205.26
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Trigonal
Space group	R -3
<i>a</i> (Å)	22.3219(4)
<i>b</i> (Å)	22.3219(4)
<i>c</i> (Å)	12.1112(3)
α (°)	90
β (°)	90
γ (°)	120
Cell volume (Å ³)	5226.13(19)
<i>Z</i>	18
Calculated density (Mg/m ³)	1.174
Absorption coefficient (mm ⁻¹)	0.080
<i>F</i> ₀₀₀	1980
Crystal size (mm)	0.16 × 0.50 × 0.50
Description of crystal	Colourless plate
Absorption correction	multi-scan
Transmission coefficients (min,max)	0.88, 0.99
θ range for data collection (°)	5 ≤ θ ≤ 27
Index ranges	-28 ≤ <i>h</i> ≤ 28, -28 ≤ <i>k</i> ≤ 28, -13 ≤ <i>l</i> ≤ 15
Reflections measured	13172
Unique reflections	138
<i>R</i> _{int}	0
Observed reflections (<i>I</i> > -3 σ (<i>I</i>))	2635
Refinement method	Full-matrix least-squares on <i>Fsqd</i>
Parameters refined	136
Weighting scheme	Modified Sheldrick
Goodness of fit	0.9526
<i>R</i>	0.0427
w <i>R</i>	0.1033
Residual electron density (min,max) (eÅ ⁻³)	-0.25, 0.36

Table 1: Crystal data and refinement details

Atom	x	y	z	U _{equiv}
O(1)	0.41696(5)	0.45366(5)	0.32851(8)	0.0396
C(2)	0.49033(7)	0.49171(7)	0.32982(11)	0.0318
C(3)	0.52205(6)	0.45427(6)	0.27074(10)	0.0288
C(4)	0.48581(7)	0.40605(6)	0.18850(11)	0.0311
C(5)	0.51647(8)	0.37481(7)	0.13045(12)	0.0391
C(6)	0.58369(9)	0.39098(8)	0.15388(14)	0.0454
C(7)	0.61976(8)	0.43781(8)	0.23680(14)	0.0450
C(8)	0.58930(7)	0.46913(7)	0.29558(12)	0.0367
C(9)	0.51189(7)	0.56359(7)	0.27916(11)	0.0318
N(10)	0.58752(6)	0.60697(5)	0.28568(9)	0.0303
C(11)	0.62092(6)	0.61501(6)	0.19111(10)	0.0263
O(12)	0.68482(5)	0.64689(5)	0.17922(7)	0.0308
C(13)	0.56881(6)	0.57924(7)	0.10007(10)	0.0300
C(14)	0.49937(7)	0.56085(7)	0.15329(11)	0.0329
C(15)	0.47792(9)	0.59801(8)	0.34210(15)	0.0500

Table 2: Atomic coordinates and equivalent isotropic thermal parameters (Å²)
of non-hydrogen atoms

Atom	x	y	z	U_{iso}
H(21)	0.5072	0.5002	0.4078	0.0339
H(41)	0.4406	0.3951	0.1742	0.0347
H(51)	0.4915	0.3418	0.0742	0.0454
H(61)	0.6041	0.3691	0.1137	0.0565
H(71)	0.6659	0.4484	0.2555	0.0544
H(81)	0.6145	0.5021	0.3533	0.0417
H(131)	0.5800	0.6099	0.0380	0.0347
H(132)	0.5708	0.5378	0.0785	0.0349
H(142)	0.4871	0.5961	0.1344	0.0403
H(141)	0.4617	0.5154	0.1285	0.0401
H(153)	0.4975	0.6458	0.3175	0.0720
H(152)	0.4845	0.5963	0.4211	0.0736
H(151)	0.4271	0.5728	0.3259	0.0713
H(11)	0.4051	0.4195	0.3723	0.0558
H(101)	0.6086	0.6226	0.3498	0.0348

Table 3: Atomic coordinates and isotropic thermal parameters ($\text{\AA}^2$) of hydrogen atoms

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(1)	0.0315(5)	0.0376(5)	0.0414(6)	0.0114(4)	0.0100(4)	0.0112(4)
C(2)	0.0320(6)	0.0318(7)	0.0231(6)	0.0024(5)	0.0028(5)	0.0096(5)
C(3)	0.0293(6)	0.0250(6)	0.0242(6)	0.0066(5)	-0.0004(5)	0.0077(5)
C(4)	0.0288(6)	0.0272(6)	0.0300(7)	0.0029(5)	-0.0037(5)	0.0085(5)
C(5)	0.0459(8)	0.0293(7)	0.0370(7)	-0.0006(6)	-0.0024(6)	0.0151(6)
C(6)	0.0503(9)	0.0410(8)	0.0507(9)	0.0054(7)	0.0059(7)	0.0271(7)
C(7)	0.0348(7)	0.0439(8)	0.0562(10)	0.0102(7)	-0.0031(7)	0.0197(7)
C(8)	0.0343(7)	0.0316(7)	0.0351(7)	0.0034(6)	-0.0097(6)	0.0095(6)
C(9)	0.0311(7)	0.0285(6)	0.0298(7)	-0.0003(5)	0.0054(5)	0.0103(5)
N(10)	0.0324(6)	0.0271(5)	0.0226(5)	-0.0033(4)	0.0017(4)	0.0083(4)
C(11)	0.0318(6)	0.0208(5)	0.0242(6)	0.0015(4)	0.0009(5)	0.0115(5)
O(12)	0.0289(5)	0.0316(5)	0.0276(5)	0.0037(4)	0.0002(4)	0.0119(4)
C(13)	0.0316(6)	0.0312(6)	0.0219(6)	0.0031(5)	-0.0003(5)	0.0116(5)
C(14)	0.0304(6)	0.0316(6)	0.0334(7)	0.0047(5)	-0.0006(5)	0.0131(5)
C(15)	0.0508(9)	0.0403(8)	0.0572(10)	-0.0011(7)	0.0191(8)	0.0216(7)

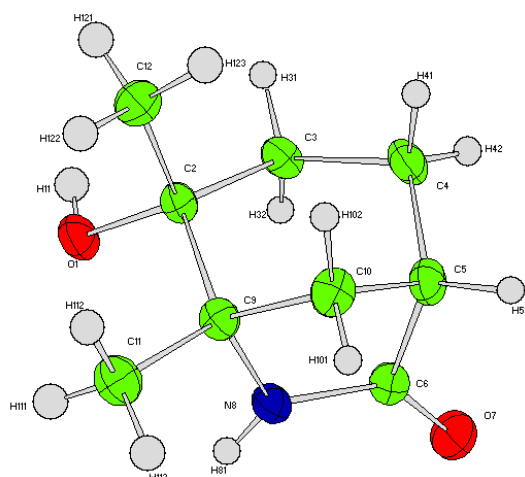
Table 4: Anisotropic thermal parameters ($\text{\AA}^2$)

O(1) – C(2)	1.4187(16)	C(7) – C(8)	1.390(2)
O(1) – H(11)	0.855	C(9) – N(10)	1.4694(17)
C(2) – C(3)	1.5179(19)	C(9) – C(14)	1.5456(19)
C(2) – C(9)	1.5524(18)	C(9) – C(15)	1.5259(19)
C(3) – C(4)	1.3907(18)	N(10) – C(11)	1.3290(16)
C(3) – C(8)	1.3987(19)	N(10) – H(101)	0.884
C(4) – C(5)	1.388(2)	C(11) – O(12)	1.2437(15)
C(5) – C(6)	1.386(2)	C(11) – C(13)	1.5092(17)
C(6) – C(7)	1.381(2)	C(13) – C(14)	1.5330(18)

Table 5: Bond lengths ($\text{\AA}$) Note C–H atoms have been excluded

O(1) - C(2) - C(3)	112.44(10)	C(2) - C(9) - N(10)	108.67(11)
O(1) - C(2) - C(9)	106.43(11)	C(2) - C(9) - C(14)	113.11(11)
C(3) - C(2) - C(9)	113.20(10)	N(10) - C(9) - C(14)	101.80(10)
C(2) - C(3) - C(4)	120.86(12)	C(2) - C(9) - C(15)	110.34(11)
C(2) - C(3) - C(8)	120.59(12)	C(14) - C(9) - C(15)	112.77(12)
C(4) - C(3) - C(8)	118.53(13)	C(9) - N(10) - C(11)	115.14(10)
C(3) - C(4) - C(5)	120.64(13)	N(10) - C(11) - O(12)	125.63(11)
C(4) - C(5) - C(6)	120.46(14)	N(10) - C(11) - C(13)	109.04(10)
C(5) - C(6) - C(7)	119.44(15)	O(12) - C(11) - C(13)	125.33(11)
C(6) - C(7) - C(8)	120.42(14)	C(11) - C(13) - C(14)	104.07(10)
C(3) - C(8) - C(7)	120.48(13)	C(14) - C(9) - C(15)	105.40(10)

Table 6: Bond angles (° C) Note – H atoms have been excluded

Single-crystal X-ray diffraction report for compound **179** (Datablock: 0060808)

Crystal of **179** were grown and run by Callens Cédric from dichloromethane and petrol 40-60 °C. A single crystal having dimensions approximately **0.12 x 0.16 x 0.24 mm** was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150 K in a stream of cold N₂ using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoK α radiation, $\lambda = 0.71073$ Å). Intensity data were processed using the DENZO-SMN package.¹

Examination of the systematic absences of the intensity data showed the space group to be **C 1 2/c 1**. The structure was solved in this space group using the direct-methods program SIR92,² which located all non-hydrogen atoms. The H atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. Subsequent full-matrix least-squares refinement was carried out against F² using the CRYSTAL program suite.³ Coordinates and anisotropic thermal parameters were refined for all non-hydrogen atoms, and the hydrogens were refined with riding constraints. A modified statistical weighting scheme was applied. Refinement converged satisfactorily to give **R = 0.0364**, **wR = 0.0813**.

Attached is a thermal ellipsoid plot (CAMERON) at 50% probability. A summary of crystallographic data is given below, as are full lists of atomic coordinates, anisotropic thermal parameters and those bond lengths and angles not concerning H atoms.

References

- (1) Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, 276, 307.
- (2) A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr.* **1994**, 27, 435.
- (3) P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout, D. J. Watkin, *J. Appl. Crystallogr.* **2003**, 36, 1487.

Crystal identification	CCK 060808
Chemical formula	C ₉ H ₁₅ N ₁ O ₂
Formula weight	169.22
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	C 1 2/c 1
a (Å)	18.3496(3)
b (Å)	9.3578(2)
c (Å)	11.8645(2)
α (°)	90
β (°)	120.0222(9)
γ (°)	90
Cell volume (Å ³)	1763.94(6)
Z	8
Calculated density (Mg/m ³)	1.274
Absorption coefficient (mm ⁻¹)	0.090
F ₀₀₀	736
Crystal size (mm)	0.12 × 0.16 × 0.24
Description of crystal	Colourless block
Absorption correction	multi-scan
Transmission coefficients (min,max)	0.95, 0.99
θ range for data collection (°)	5.13 ≤ θ ≤ 27.48
Index ranges	-23 ≤ h ≤ 23, -12 ≤ k ≤ 11, -15 ≤ l ≤ 15
Reflections measured	10482
Unique reflections	2009
R _{int}	0.029
Observed reflections (I > -3σ(I))	1658
Refinement method	Full-matrix least-squares on Fsqd
Parameters refined	109
Weighting scheme	Modified Sheldrick
Goodness of fit	0.9426
R	0.0364
wR	0.0962
Residual electron density (min,max) (eÅ ⁻³)	-0.36, 0.28

Table 1: Crystal data and refinement details

Atom	x	y	z	U _{equiv}
O(1)	0.43989(5)	0.09153(9)	0.56719(8)	0.0268
C(2)	0.39416(7)	0.20871(12)	0.48314(10)	0.0210
C(3)	0.30328(7)	0.15978(12)	0.38818(11)	0.0234
C(4)	0.25698(7)	0.24861(13)	0.26332(11)	0.0268
C(5)	0.31401(7)	0.27903(12)	0.20524(11)	0.0254
C(6)	0.35452(7)	0.13824(12)	0.20190(11)	0.0238
O(7)	0.32494(5)	0.04929(10)	0.11262(8)	0.0331
N(8)	0.42639(6)	0.12528(10)	0.31590(9)	0.0217
C(9)	0.43956(7)	0.24429(12)	0.40556(10)	0.0212
C(10)	0.39080(8)	0.36213(12)	0.30564(11)	0.0264
C(11)	0.53317(7)	0.27251(14)	0.49215(12)	0.0302
C(12)	0.39499(8)	0.33375(14)	0.56709(12)	0.0309

Table 2: Atomic coordinates and equivalent isotropic thermal parameters (Å²) of non-hydrogen atoms

Atom	x	y	z	U_{iso}
H(31)	0.2716	0.1605	0.4342	0.0289
H(32)	0.3072	0.0590	0.3647	0.0280
H(41)	0.2388	0.3399	0.2823	0.0305
H(42)	0.2059	0.1953	0.2001	0.0309
H(51)	0.2827	0.3223	0.1186	0.0285
H(101)	0.4256	0.3977	0.2692	0.0320
H(102)	0.3757	0.4434	0.3437	0.0315
H(113)	0.5581	0.2900	0.4376	0.0449
H(112)	0.5423	0.3565	0.5462	0.0453
H(111)	0.5619	0.1902	0.5480	0.0439
H(123)	0.3563	0.4099	0.5144	0.0456
H(122)	0.4515	0.3755	0.6177	0.0462
H(121)	0.3775	0.2985	0.6277	0.0450
H(81)	0.4572	0.0495	0.3396	0.0281
H(11)	0.4069	0.0502	0.5875	0.0423

Table 3: Atomic coordinates and isotropic thermal parameters ($\text{\AA}^2$) of hydrogen atom

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(1)	0.0218(4)	0.0306(5)	0.0272(4)	0.0110(3)	0.0115(4)	0.0065(3)
C(2)	0.0191(5)	0.0214(5)	0.0198(5)	0.0027(4)	0.0078(4)	0.0035(4)
C(3)	0.0178(5)	0.0249(6)	0.0261(6)	0.0015(5)	0.0100(5)	0.0012(4)
C(4)	0.0192(5)	0.0285(6)	0.0259(6)	0.0010(5)	0.0061(5)	0.0066(5)
C(5)	0.0270(6)	0.0234(6)	0.0202(5)	0.0033(4)	0.0077(5)	0.0065(5)
C(6)	0.0233(6)	0.0253(6)	0.0214(5)	-0.0003(5)	0.0103(5)	0.0018(4)
O(7)	0.0319(5)	0.0356(5)	0.0257(4)	-0.0095(4)	0.0099(4)	0.0023(4)
N(8)	0.0201(5)	0.0213(5)	0.0221(5)	-0.0006(4)	0.0093(4)	0.0035(4)
C(9)	0.0204(5)	0.0196(5)	0.0218(5)	-0.0019(4)	0.0091(5)	-0.0018(4)
C(10)	0.0321(6)	0.0196(6)	0.0263(6)	0.0015(5)	0.0137(5)	-0.0003(5)
C(11)	0.0214(6)	0.0344(7)	0.0313(6)	-0.0044(5)	0.0106(5)	-0.0074(5)
C(12)	0.0313(6)	0.0342(7)	0.0260(6)	-0.0059(5)	0.0134(5)	0.0013(5)
O(1)	0.0218(4)	0.0306(5)	0.0272(4)	0.0110(3)	0.0115(4)	0.0065(3)
C(2)	0.0191(5)	0.0214(5)	0.0198(5)	0.0027(4)	0.0078(4)	0.0035(4)
C(3)	0.0178(5)	0.0249(6)	0.0261(6)	0.0015(5)	0.0100(5)	0.0012(4)
C(4)	0.0192(5)	0.0285(6)	0.0259(6)	0.0010(5)	0.0061(5)	0.0066(5)
C(5)	0.0270(6)	0.0234(6)	0.0202(5)	0.0033(4)	0.0077(5)	0.0065(5)
C(6)	0.0233(6)	0.0253(6)	0.0214(5)	-0.0003(5)	0.0103(5)	0.0018(4)
O(7)	0.0319(5)	0.0356(5)	0.0257(4)	-0.0095(4)	0.0099(4)	0.0023(4)
N(8)	0.0201(5)	0.0213(5)	0.0221(5)	-0.0006(4)	0.0093(4)	0.0035(4)
C(9)	0.0204(5)	0.0196(5)	0.0218(5)	-0.0019(4)	0.0091(5)	-0.0018(4)
C(10)	0.0321(6)	0.0196(6)	0.0263(6)	0.0015(5)	0.0137(5)	-0.0003(5)
C(11)	0.0214(6)	0.0344(7)	0.0313(6)	-0.0044(5)	0.0106(5)	-0.0074(5)
C(12)	0.0313(6)	0.0342(7)	0.0260(6)	-0.0059(5)	0.0134(5)	0.0013(5)

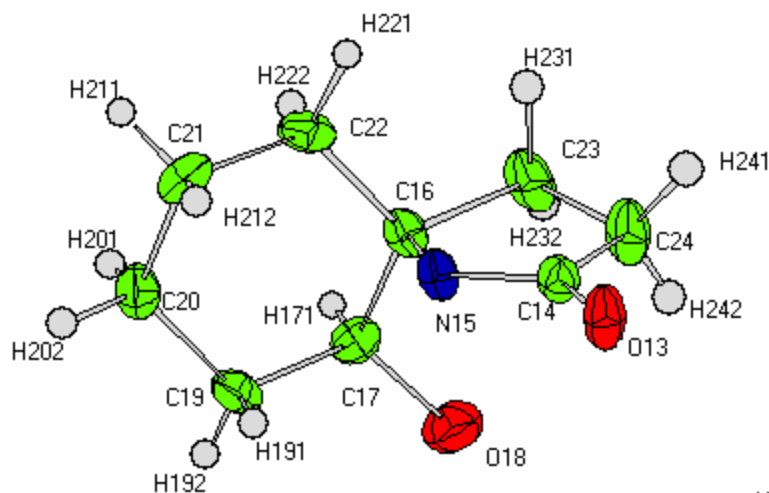
Table 4: Anisotropic thermal parameters ($\text{\AA}^2$)

O(1) – C(2)	1.4365(13)	C(5) – C(10)	1.3311(18)
O(1) – H(11)	0.848	C(6) – O(7)	1.5045(19)
C(2) – C(3)	1.5427(15)	C(6) – N(8)	1.4680(17)
C(2) – C(9)	1.5555(15)	N(8) – C(9)	0.871
C(2) – C(12)	1.5318(16)	N(8) – H(81)	1.539(2)
C(3) – C(4)	1.5323(16)	C(9) – C(10)	1.5163(19)
C(4) – C(5)	1.5403(17)	C(9) – C(11)	1.4128(17)
C(5) – C(6)	1.5230(16)		

Table 5: Bond lengths ($\text{\AA}$) Note – C-H atoms have been excluded

O(1) - C(2) - C(3)	108.84(9)	C(5) - C(6) - O(7)	126.36(10)
O(1) - C(2) - C(9)	105.93(8)	C(5) - C(6) - N(8)	107.36(9)
C(3) - C(2) - C(9)	109.55(9)	O(7) - C(6) - N(8)	126.21(11)
O(1) - C(2) - C(12)	108.63(9)	C(6) - N(8) - C(9)	112.52(9)
C(3) - C(2) - C(12)	110.92(9)	C(2) - C(9) - N(8)	108.81(9)
C(9) - C(2) - C(12)	112.78(9)	C(2) - C(9) - C(10)	109.43(9)
C(2) - C(3) - C(4)	114.77(9)	N(8) - C(9) - C(10)	99.41(8)
C(3) - C(4) - O(5)	111.14(9)	C(2) - C(9) - C(11)	113.32(9)
C(4) - C(5) - C(6)	107.55(9)	N(8) - C(9) - C(11)	109.93(9)
C(4) - C(5) - C(10)	108.28(9)	C(10) - C(9) - C(11)	114.95(10)
C(6) - C(5) - C(10)	100.90(9)	C(9) - C(10) - C(5)	100.97(9)

Table 6: Bond angles (° C) Note – H atoms have been excluded

Single-crystal X-ray diffraction report for compound **180** (Datablock: 0191208)

Crystal of **180** were grown and run by Callens Cédric from dichloromethane and petrol 40-60 °C. A single crystal having dimensions approximately **0.48 x 0.48 x 0.48 mm** was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150 K in a stream of cold N₂ using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoK α radiation, $\lambda = 0.71073$ Å). Intensity data were processed using the DENZO-SMN package.¹

Examination of the systematic absences of the intensity data showed the space group to be **P -1**. The structure was solved in this space group using the direct-methods program SIR92,² which located all non-hydrogen atoms. The H atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. Subsequent full-matrix least-squares refinement was carried out against F² using the CRYSTAL program suite.³ Coordinates and anisotropic thermal parameters were refined for all non-hydrogen atoms, and the hydrogens were refined with riding constraints. A modified statistical weighting scheme was applied. Refinement converged satisfactorily to give **R = 0.0928**, **wR = 0.2122**.

Attached is a thermal ellipsoid plot (CAMERON) at 50% probability. A summary of crystallographic data is given below, as are full lists of atomic coordinates, anisotropic thermal parameters and those bond lengths and angles not concerning H atoms.

References

- (1) Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, 276, 307.
- (2) A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr.* **1994**, 27, 435.
- (3) P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout, D. J. Watkin, *J. Appl. Crystallogr.* **2003**, 36, 1487.

Crystal identification	CCK 0191208
Chemical formula	C ₉ H ₁₅ N ₁ O ₂
Formula weight	169.22
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Triclinic
Space group	P -1
<i>a</i> (Å)	7.51050(10)
<i>b</i> (Å)	10.56470(10)
<i>c</i> (Å)	12.0602(2)
α (°)	114.0433(6)
β (°)	90.0214(6)
γ (°)	89.9751(7)
Cell volume (Å ³)	873.91(2)
<i>Z</i>	4
Calculated density (Mg/m ³)	1.286
Absorption coefficient (mm ⁻¹)	0.090
<i>F</i> ₀₀₀	368
Crystal size (mm)	0.48 × 0.48 × 0.48
Description of crystal	Colourless block
Absorption correction	multi-scan
Transmission coefficients (min,max)	0.96, 0.99
θ range for data collection (°)	5.11 ≤ θ ≤ 27.51
Index ranges	-9 ≤ <i>h</i> ≤ 9, -13 ≤ <i>k</i> ≤ 13, -15 ≤ <i>l</i> ≤ 15
Reflections measured	7233
Unique reflections	3955
<i>R</i> _{int}	0
Observed reflections (<i>I</i> > -2 σ (<i>I</i>))	3752
Refinement method	Full-matrix least-squares on <i>Fsqd</i>
Parameters refined	218
Weighting scheme	Modified Sheldrick
Goodness of fit	1.0483
<i>R</i>	0.0928
<i>wR</i>	0.2122
Residual electron density (min,max) (eÅ ⁻³)	-0.38, 1.12

Table 1: Crystal data and refinement details

Atom	x	y	z	U _{equiv}
O(1)	0.2855(3)	0.5961(2)	1.06207(17)	0.0348
C(2)	0.2775(3)	0.5860(3)	0.9565(2)	0.0258
N(3)	0.3956(3)	0.5207(2)	0.87025(19)	0.0245
C(4)	0.3643(3)	0.5298(3)	0.7529(2)	0.0243
C(5)	0.5029(4)	0.6235(3)	0.7310(2)	0.0279
O(6)	0.4783(3)	0.7595(2)	0.8211(2)	0.0444
C(7)	0.6895(3)	0.5627(3)	0.7228(3)	0.0294
C(8)	0.7004(4)	0.4178(3)	0.6205(3)	0.0330
C(9)	0.5578(4)	0.3236(3)	0.6341(3)	0.0329
C(10)	0.3730(4)	0.3876(3)	0.6476(2)	0.0298
C(11)	0.1724(4)	0.5875(4)	0.7698(3)	0.0380
C(12)	0.1358(4)	0.6474(4)	0.9040(3)	0.0380
O(13)	0.7854(3)	0.9038(2)	0.93771(17)	0.0352
C(14)	0.7774(3)	0.9139(3)	1.0435(2)	0.0254
N(15)	0.8953(3)	0.9796(2)	1.12995(19)	0.0244
C(16)	0.8641(3)	0.9702(3)	1.2467(2)	0.0245
C(17)	1.0027(4)	0.8764(3)	1.2687(2)	0.0272
O(18)	0.9784(3)	0.7407(2)	1.1791(2)	0.0437
C(19)	1.1893(3)	0.9368(3)	1.2771(3)	0.0297
C(20)	1.2004(4)	1.0819(3)	1.3795(3)	0.0325

C(21)	1.0574(4)	1.1767(3)	1.3658(3)	0.0327
C(22)	0.8730(4)	1.1125(3)	1.3523(2)	0.0303
C(23)	0.6723(4)	0.9120(4)	1.2297(3)	0.0377
C(24)	0.6354(4)	0.8525(4)	1.0957(3)	0.0380

Table 2: Atomic coordinates and equivalent isotropic thermal parameters ($\text{\AA}^2$) of non-hydrogen atoms

Atom	x	y	z	U_{iso}
H(51)	0.4764	0.6244	0.6518	0.0336
H(72)	0.7177	0.5597	0.8006	0.0365
H(71)	0.7728	0.6208	0.7036	0.0363
H(81)	0.8173	0.3772	0.6194	0.0393
H(82)	0.6863	0.4230	0.5418	0.0391
H(91)	0.5869	0.3101	0.7076	0.0385
H(92)	0.5632	0.2333	0.5632	0.0381
H(101)	0.2632	0.3321	0.6592	0.0351
H(102)	0.3466	0.4012	0.5744	0.0360
H(111)	0.1619	0.6560	0.7376	0.0493
H(112)	0.0875	0.5110	0.7282	0.0492
H(122)	0.1475	0.7485	0.9364	0.0470
H(121)	0.0187	0.6240	0.9229	0.0464
H(171)	0.9768	0.8768	1.3488	0.0339
H(191)	1.2727	0.8773	1.2942	0.0363
H(192)	1.2155	0.9398	1.1990	0.0362
H(202)	1.3164	1.1221	1.3789	0.0387
H(201)	1.1877	1.0765	1.4586	0.0380
H(211)	1.0618	1.2666	1.4354	0.0381
H(212)	1.0858	1.1905	1.2942	0.0383
H(222)	0.8470	1.0983	1.4251	0.0368
H(221)	0.7637	1.1678	1.3396	0.0358
H(231)	0.5899	0.9906	1.2716	0.0482
H(232)	0.6618	0.8433	1.2617	0.0484
H(241)	0.5184	0.8740	1.0764	0.0463
H(242)	0.6467	0.7523	1.0627	0.0469
H(31)	0.4859	0.4793	0.8837	0.0312
H(151)	0.9855	1.0218	1.1175	0.0312
H(61)	0.5758	0.7943	0.8581	0.0617
H(181)	1.0677	0.6974	1.1923	0.0629

Table 3: Atomic coordinates and isotropic thermal parameters ($\text{\AA}^2$) of hydrogen atoms

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(1)	0.0327(11)	0.0503(13)	0.0215(9)	0.0146(9)	0.0044(7)	0.0160(9)
C(2)	0.0221(12)	0.0302(13)	0.0239(12)	0.0099(10)	-0.0015(9)	0.0044(9)
N(3)	0.0194(10)	0.0354(12)	0.0221(10)	0.0152(9)	-0.0003(8)	0.0075(8)
C(4)	0.0200(11)	0.0338(14)	0.0221(12)	0.0146(11)	-0.0022(9)	0.0033(9)
C(5)	0.0336(14)	0.0245(13)	0.0267(13)	0.0116(11)	-0.0013(10)	-0.0006(10)
O(6)	0.0408(12)	0.0300(11)	0.0538(14)	0.0084(10)	-0.0134(10)	-0.0011(9)
C(7)	0.0229(12)	0.0320(14)	0.0326(14)	0.0124(12)	-0.0017(10)	-0.0067(10)
C(8)	0.0291(14)	0.0405(16)	0.0267(13)	0.0111(12)	0.0042(10)	0.0074(11)
C(9)	0.0463(17)	0.0234(13)	0.0246(13)	0.0052(11)	-0.0037(11)	0.0011(11)
C(10)	0.0300(13)	0.0361(15)	0.0244(13)	0.0133(11)	-0.0083(10)	-0.0106(11)
C(11)	0.0235(13)	0.060(2)	0.0380(16)	0.0280(15)	-0.0029(11)	0.0092(13)
C(12)	0.0299(14)	0.0524(19)	0.0314(15)	0.0168(14)	-0.0003(11)	0.0186(13)
O(13)	0.0321(11)	0.0511(13)	0.0227(10)	0.0154(9)	-0.0043(7)	-0.0161(9)
C(14)	0.0221(12)	0.0292(13)	0.0235(12)	0.0093(10)	0.0010(9)	-0.0044(9)
N(15)	0.0196(10)	0.0354(12)	0.0216(10)	0.0151(9)	0.0004(8)	-0.0075(8)
C(16)	0.0196(11)	0.0355(14)	0.0226(12)	0.0160(11)	0.0019(9)	-0.0033(10)

C(17)	0.0339(14)	0.0221(12)	0.0270(13)	0.0113(10)	0.0011(10)	0.0003(10)
O(18)	0.0406(12)	0.0301(11)	0.0514(14)	0.0071(10)	0.0096(10)	0.0006(9)
C(19)	0.0221(12)	0.0338(14)	0.0337(14)	0.0143(12)	0.0017(10)	0.0067(10)
C(20)	0.0284(13)	0.0397(16)	0.0270(13)	0.0113(12)	-0.0035(10)	-0.0065(11)
C(21)	0.0464(17)	0.0229(13)	0.0249(13)	0.0057(11)	0.0038(11)	-0.0012(11)
C(22)	0.0297(13)	0.0366(15)	0.0248(13)	0.0127(11)	0.0084(10)	0.0098(11)
C(23)	0.0234(13)	0.059(2)	0.0361(16)	0.0251(15)	0.0030(11)	-0.0094(12)
C(24)	0.0305(14)	0.0525(19)	0.0308(15)	0.0167(14)	0.0001(11)	-0.0188(13)

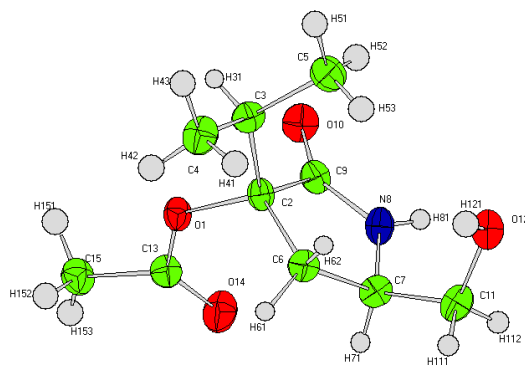
Table 4: Anisotropic thermal parameters ($\text{\AA}^2$)

O(1) – C(2)	1.235(3)	C(11) – C(12)	1.504(4)
C(2) – N(3)	1.326(3)	O(13) – C(14)	1.238(3)
C(2) – C(12)	1.513(4)	C(14) – N(15)	1.328(3)
N(3) – C(4)	1.476(3)	C(14) – C(24)	1.512(4)
N(3) – H(31)	0.857	N(15) – C(16)	1.470(3)
C(4) – C(5)	1.532(4)	N(15) – H(151)	0.858
C(4) – C(10)	1.524(4)	C(16) – C(17)	1.533(4)
C(4) – C(11)	1.546(4)	C(16) – C(22)	1.525(4)
C(5) – O(6)	1.417(3)	C(16) – C(23)	1.547(4)
C(5) – C(7)	1.528(4)	C(17) – O(18)	1.412(3)
O(6) – H(61)	0.858	C(17) – C(19)	1.526(4)
C(7) – C(8)	1.528(4)	O(18) – H(181)	0.862
C(8) – C(9)	1.516(4)	C(19) – C(20)	1.529(4)
C(9) – C(10)	1.523(4)	C(20) – C(21)	1.522(4)

Table 5: Bond lengths ($\text{\AA}$) Note – C-H atoms have been excluded

O(1) - C(2) - N(3)	125.1(2)	O(13) - C(14) - N(15)	125.1(2)
O(1) - C(2) - C(12)	126.4(2)	O(13) - C(14) - C(24)	126.3(2)
N(3) - C(2) - C(12)	108.5(2)	N(15) - C(14) - C(24)	108.6(2)
C(2) - N(3) - C(4)	115.4(2)	C(14) - N(15) - C(16)	115.3(2)
N(3) - C(4) - C(5)	110.9(2)	N(15) - C(16) - C(17)	111.0(2)
N(3) - C(4) - C(10)	111.4(2)	N(15) - C(16) - C(22)	111.4(2)
C(5) - C(4) - C(10)	108.3(2)	C(17) - C(16) - C(22)	108.2(2)
N(3) - C(4) - C(11)	101.4(2)	N(15) - C(16) - C(23)	101.6(2)
C(5) - C(4) - C(11)	114.2(2)	C(17) - C(16) - C(23)	113.9(2)
C(10) - C(4) - C(11)	110.6(2)	C(22) - C(16) - C(23)	110.8(2)
C(4) - C(5) - O(6)	107.7(2)	C(16) - C(17) - O(18)	107.8(2)
C(4) - C(5) - C(7)	110.6(2)	C(16) - C(17) - C(19)	110.6(2)
O(6) - C(5) - C(7)	115.9(2)	O(18) - C(17) - C(19)	115.9(2)
C(5) - C(7) - C(8)	111.0(2)	C(17) - C(19) - C(20)	111.0(2)
C(7) - C(8) - C(9)	111.1(2)	C(19) - C(20) - C(21)	111.1(2)
C(8) - C(9) - C(10)	111.9(2)	C(20) - C(21) - C(22)	111.7(2)
C(4) - C(10) - C(9)	111.8(2)	C(16) - C(22) - C(21)	112.0(2)
C(4) - C(11) - C(12)	106.4(2)	C(16) - C(23) - C(24)	106.5(2)
C(2) - C(12) - C(11)	104.9(2)	C(14) - C(24) - C(23)	104.8(2)

Table 6: Bond angles ($^\circ$ C) Note – H atoms have been excluded

Single-crystal X-ray diffraction report for compound **187** (Datablock: 0330509)

Crystal of **187** were grown and run by Callens Cédric from dichloromethane and petrol 40-60 °C. A single crystal having dimensions approximately **0.06 x 0.20 x 0.50 mm** was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150 K in a stream of cold N₂ using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoK_α radiation, $\lambda = 0.71073$ Å). Intensity data were processed using the DENZO-SMN package.¹

Examination of the systematic absences of the intensity data showed the space group to be **P -1**. The structure was solved in this space group using the direct-methods program SIR92,² which located all non-hydrogen atoms. The H atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. Subsequent full-matrix least-squares refinement was carried out against F² using the CRYSTAL program suite.³ Coordinates and anisotropic thermal parameters were refined for all non-hydrogen atoms, and the hydrogens were refined with riding constraints. A modified statistical weighting scheme was applied. Refinement converged satisfactorily to give **R = 0.0662**, **wR = 0.1053**.

Attached is a thermal ellipsoid plot (CAMERON) at 50% probability. A summary of crystallographic data is given below, as are full lists of atomic coordinates, anisotropic thermal parameters and those bond lengths and angles not concerning H atoms.

References

- (1) Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, 276, 307.
- (2) A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr.* **1994**, 27, 435.
- (3) P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout, D. J. Watkin, *J. Appl. Crystallogr.* **2003**, 36, 1487.

Crystal identification	CCK 0330509
Chemical formula	C ₁₀ H ₁₇ N ₁ O ₄
Formula weight	215.25
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Triclinic
Space group	P -1
<i>a</i> (Å)	6.0621(2)
<i>b</i> (Å)	7.9355(3)
<i>c</i> (Å)	12.1691(6)
α (°)	88.8233(16)
β (°)	81.5421(17)
γ (°)	69.842(2)
Cell volume (Å ³)	543.28(4)
<i>Z</i>	2
Calculated density (Mg/m ³)	1.316
Absorption coefficient (mm ⁻¹)	0.101
<i>F</i> ₀₀₀	232
Crystal size (mm)	0.06 × 0.20 × 0.50
Description of crystal	Colourless plate
Absorption correction	multi-scan
Transmission coefficients (min,max)	0.91, 0.99
θ range for data collection (°)	5.24 ≤ θ ≤ 27.54
Index ranges	-7 ≤ <i>h</i> ≤ 7, -10 ≤ <i>k</i> ≤ 10, -15 ≤ <i>l</i> ≤ 15
Reflections measured	8688
Unique reflections	2473
<i>R</i> _{int}	0.000
Observed reflections (<i>I</i> > -3 σ (<i>I</i>))	1818
Refinement method	Full-matrix least-squares on <i>Fsqd</i>
Parameters refined	137
Weighting scheme	Modified Sheldrick
Goodness of fit	0.9496
<i>R</i>	0.0662
<i>wR</i>	0.0662
Residual electron density (min,max) (eÅ ⁻³)	-0.29, 0.33

Table 1: Crystal data and refinement details

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{equiv}
O(1)	0.2778(2)	0.17127(18)	0.37639(11)	0.0267
C(2)	0.1758(3)	0.1920(3)	0.27262(15)	0.0236
C(3)	0.2112(3)	-0.0016(3)	0.23910(16)	0.0270
C(4)	0.0566(4)	-0.0799(3)	0.32053(18)	0.0352
C(5)	0.1685(4)	-0.0206(3)	0.12040(17)	0.0357
C(6)	-0.0808(3)	0.3245(3)	0.28407(16)	0.0267
C(7)	-0.0750(3)	0.4850(3)	0.21161(17)	0.0279
N(8)	0.1642(3)	0.4218(2)	0.14849(13)	0.0284
C(9)	0.3126(3)	0.2745(3)	0.18518(16)	0.0255
O(10)	0.5293(2)	0.2057(2)	0.15333(11)	0.0334
C(11)	-0.2650(4)	0.5464(3)	0.13623(18)	0.0326
O(12)	-0.2398(2)	0.41467(19)	0.05349(11)	0.0325
C(13)	0.3138(3)	0.3122(3)	0.42123(16)	0.0271
O(14)	0.2556(3)	0.4599(2)	0.38442(13)	0.0407
C(15)	0.4354(4)	0.2565(3)	0.52092(17)	0.0346

Table 2: Atomic coordinates and equivalent isotropic thermal parameters ($\text{\AA}^2$) of non-hydrogen atoms

Atom	x	y	z	U_{iso}
H(31)	0.3797	-0.0712	0.2433	0.0303
H(43)	0.1084	-0.2091	0.3066	0.0540
H(42)	0.0700	-0.0557	0.3973	0.0551
H(41)	-0.1080	-0.0252	0.3090	0.0547
H(51)	0.1967	-0.1468	0.1042	0.0532
H(52)	0.2735	0.0186	0.0680	0.0539
H(53)	0.0046	0.0489	0.1145	0.0537
H(61)	-0.1434	0.3651	0.3621	0.0315
H(62)	-0.1780	0.2649	0.2558	0.0320
H(71)	-0.0912	0.5877	0.2611	0.0322
H(112)	-0.2542	0.6553	0.0962	0.0385
H(111)	-0.4247	0.5793	0.1841	0.0382
H(153)	0.4752	0.3540	0.5482	0.0537
H(152)	0.3351	0.2258	0.5792	0.0548
H(151)	0.5765	0.1494	0.5041	0.0548
H(121)	-0.3088	0.3472	0.0819	0.0521
H(81)	0.2052	0.4788	0.0914	0.0356

Table 3: Atomic coordinates and isotropic thermal parameters ($\text{\AA}^2$) of hydrogen atoms

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(1)	0.0302(8)	0.0279(8)	0.0267(8)	0.0035(6)	-0.0107(6)	-0.0134(6)
C(2)	0.0229(10)	0.0292(11)	0.0225(10)	0.0033(8)	-0.0079(8)	-0.0123(8)
C(3)	0.0230(10)	0.0264(11)	0.0332(11)	-0.0012(9)	-0.0066(8)	-0.0094(8)
C(4)	0.0403(13)	0.0300(12)	0.0423(13)	0.0060(10)	-0.0112(10)	-0.0193(10)
C(5)	0.0390(13)	0.0364(13)	0.0350(12)	-0.0030(10)	-0.0093(10)	-0.0155(10)
C(6)	0.0250(10)	0.0284(11)	0.0287(11)	0.0013(9)	-0.0053(8)	-0.0115(9)
C(7)	0.0249(11)	0.0268(11)	0.0332(11)	0.0015(9)	-0.0045(8)	-0.0106(9)
N(8)	0.0283(9)	0.0336(10)	0.0283(9)	0.0095(8)	-0.0075(7)	-0.0160(8)
C(9)	0.0239(11)	0.0316(12)	0.0257(11)	0.0007(9)	-0.0066(8)	-0.0142(9)
O(10)	0.0229(8)	0.0416(9)	0.0395(9)	0.0040(7)	-0.0046(6)	-0.0161(7)
C(11)	0.0288(11)	0.0306(12)	0.0400(13)	0.0075(10)	-0.0103(9)	-0.0107(9)
O(12)	0.0333(8)	0.0373(9)	0.0340(8)	0.0077(7)	-0.0097(6)	-0.0195(7)
C(13)	0.0289(11)	0.0278(12)	0.0284(11)	0.0012(9)	-0.0060(9)	-0.0139(9)
O(14)	0.0553(10)	0.0315(10)	0.0447(9)	0.0079(7)	-0.0225(8)	-0.0211(8)
C(15)	0.0434(13)	0.0344(13)	0.0319(12)	0.0010(10)	-0.0125(10)	-0.0181(10)

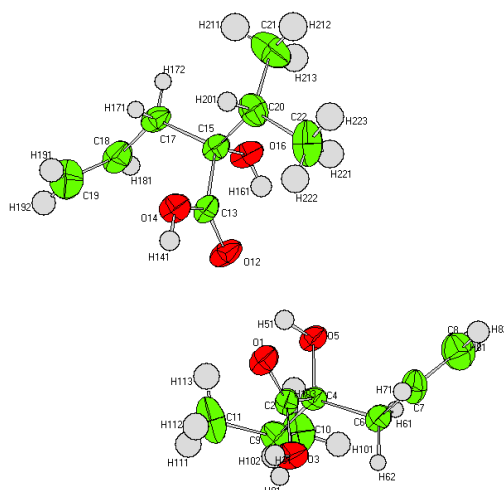
Table 4: Anisotropic thermal parameters ($\text{\AA}^2$)

O(1) - C(2)	1.468(2)	C(7) - C(11)	1.520(3)
O(1) - C(13)	1.351(2)	N(8) - C(9)	1.322(3)
C(2) - C(3)	1.532(3)	N(8) - H(81)	0.873
C(2) - C(6)	1.536(3)	C(9) - O(10)	1.241(2)
C(2) - C(9)	1.528(3)	C(11) - O(12)	1.420(3)
C(3) - C(4)	1.533(3)	O(12) - H(121)	0.828
C(3) - C(5)	1.524(3)	C(13) - O(14)	1.200(2)
C(6) - C(7)	1.542(3)	C(13) - C(15)	1.492(3)
C(7) - N(8)	1.460(2)	/	

Table 5: Bond lengths ($\text{\AA}$) Note – C-H atoms have been excluded

C(2) - O(1) - C(13)	119.74(15)	C(6) - C(7) - N(8)	103.28(15)
O(1) - C(2) - C(3)	102.98(15)	C(6) - C(7) - C(11)	115.27(16)
O(1) - C(2) - C(6)	113.41(15)	N(8) - C(7) - C(11)	111.99(16)
C(3) - C(2) - C(6)	115.68(15)	C(2) - C(9) - N(8)	109.68(16)
O(1) - C(2) - C(9)	110.04(14)	C(2) - C(9) - O(10)	123.22(18)
C(3) - C(2) - C(9)	111.03(16)	N8 - C(9) - O(10)	127.06(18)
C(6) - C(2) - C(9)	103.83(16)	C(7) - C(11) - O12	112.87(17)
C(2) - C(3) - C(4)	111.52(16)	O(1) - C(13) - O(14)	123.82(18)
C(2) - C(3) - C(5)	112.89(17)	O(1) - C(13) - C(15)	110.35(17)
C(4) - C(3) - C(5)	110.39(16)	O(14) - C(13) - C(15)	125.82(18)
C(2) - C(6) - C(7)	106.63(15)	/	

Table 6: Bond angles (° C) Note – H atoms have been excluded

Single-crystal X-ray diffraction report for compound **189** (Datablock: 0340609)

Crystal of **189** were grown and run by Callens Cédric from dichloromethane and petrol 40-60 °C. A single crystal having dimensions approximately **0.12 x 0.42 x 0.47 mm** was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150 K in a stream of cold N₂ using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoK α radiation, $\lambda = 0.71073$ Å). Intensity data were processed using the DENZO-SMN package.¹

Examination of the systematic absences of the intensity data showed the space group to be **P b c a**. The structure was solved in this space group using the direct-methods program SIR92,² which located all non-hydrogen atoms. The H atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. Subsequent full-matrix least-squares refinement was carried out against F² using the CRYSTAL program suite.³ Coordinates and anisotropic thermal parameters were refined for all non-hydrogen atoms, and the hydrogens were refined with riding constraints. A modified statistical weighting scheme was applied. Refinement converged satisfactorily to give **R = 0.0564**, **wR = 0.1137**.

Attached is a thermal ellipsoid plot (CAMERON) at 50% probability. A summary of crystallographic data is given below, as are full lists of atomic coordinates, anisotropic thermal parameters and those bond lengths and angles not concerning H atoms.

References

- (1) Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, 276, 307.
- (2) A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr.* **1994**, 27, 435.
- (3) P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout, D. J. Watkin, *J. Appl. Crystallogr.* **2003**, 36, 1487.

Crystal identification	CCK 0340609
Chemical formula	C ₈ H ₁₄ O ₃
Formula weight	158.20
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Orthorhombic
Space group	P b c a
<i>a</i> (Å)	14.2514(3)
<i>b</i> (Å)	11.4679(2)
<i>c</i> (Å)	22.8055(6)
α (°)	90
β (°)	90
γ (°)	90
Cell volume (Å ³)	3727.19(14)
<i>Z</i>	16
Calculated density (Mg/m ³)	1.128
Absorption coefficient (mm ⁻¹)	0.085
<i>F</i> ₀₀₀	1376
Crystal size (mm)	0.12 × 0.42 × 0.47
Description of crystal	Colourless block
Absorption correction	multi-scan
Transmission coefficients (min,max)	0.90, 0.99
θ range for data collection (°)	5.24 ≤ θ ≤ 27.47
Index ranges	-18 ≤ <i>h</i> ≤ 18, -14 ≤ <i>k</i> ≤ 11, -29 ≤ <i>l</i> ≤ 29
Reflections measured	28736
Unique reflections	4215
<i>R</i> _{int}	0.033
Observed reflections (<i>I</i> > 3 σ (<i>I</i>))	2288
Refinement method	Full-matrix least-squares on <i>Fsqd</i>
Parameters refined	199
Weighting scheme	Modified Sheldrick
Goodness of fit	0.9775
<i>R</i>	0.0564
<i>wR</i>	0.1137
Residual electron density (min,max) (eÅ ⁻³)	-0.21, 0.18

Table 1: Crystal data and refinement details

Atom	x	y	z	<i>U</i> _{equiv}
O(1)	0.73056(11)	0.58539(11)	0.65288(6)	0.0436
C(2)	0.76842(14)	0.58025(16)	0.60577(9)	0.0328
O(3)	0.78816(11)	0.67114(11)	0.57251(6)	0.0469
C(4)	0.80060(14)	0.46623(15)	0.57767(8)	0.0309
O(5)	0.76810(10)	0.37255(10)	0.61298(6)	0.0391
C(6)	0.75569(15)	0.45227(18)	0.51734(8)	0.0374
C(7)	0.65220(16)	0.46597(19)	0.51766(9)	0.0459
C(8)	0.59208(19)	0.3839(2)	0.50502(12)	0.0647
C(9)	0.90931(15)	0.46542(18)	0.57520(11)	0.0469
C(10)	0.94756(18)	0.3505(2)	0.55121(12)	0.0613
C(11)	0.95194(18)	0.4910(2)	0.63484(13)	0.0702
O(12)	0.77290(11)	0.33712(12)	0.73276(6)	0.0472
C(13)	0.73087(15)	0.33502(17)	0.77898(9)	0.0362
O(14)	0.71109(11)	0.42785(11)	0.81064(6)	0.0449
C(15)	0.69472(15)	0.22247(15)	0.80612(8)	0.0362
O(16)	0.72560(11)	0.12815(11)	0.77007(6)	0.0457
C(17)	0.73941(15)	0.20688(18)	0.86699(8)	0.0406
C(18)	0.84336(17)	0.2144(2)	0.86625(10)	0.0501
C(19)	0.8933(2)	0.2935(3)	0.89268(13)	0.0745
C(20)	0.58664(16)	0.22476(19)	0.80848(11)	0.0508

C(21)	0.5461(2)	0.1069(2)	0.82886(15)	0.0800
C(22)	0.5436(2)	0.2624(3)	0.75050(13)	0.0781

Table 2: Atomic coordinates and equivalent isotropic thermal parameters ($\text{\AA}^2$) of non-hydrogen atoms

Atom	x	y	z	U_{iso}
H(62)	0.7879	0.5109	0.4893	0.0440
H(61)	0.7703	0.3739	0.5027	0.0442
H(71)	0.6285	0.5399	0.5283	0.0557
H(81)	0.6140	0.3053	0.4946	0.0782
H(82)	0.5248	0.4010	0.5064	0.0789
H(91)	0.9257	0.5287	0.5490	0.0562
H(102)	1.0167	0.3516	0.5496	0.0906
H(103)	0.9262	0.2880	0.5787	0.0894
H(101)	0.9241	0.3347	0.5120	0.0912
H(111)	1.0211	0.4886	0.6313	0.1045
H(112)	0.9328	0.5690	0.6478	0.1040
H(113)	0.9306	0.4290	0.6630	0.1050
H(171)	0.7131	0.2675	0.8932	0.0483
H(172)	0.7208	0.1300	0.8813	0.0490
H(181)	0.8753	0.1578	0.8439	0.0610
H(192)	0.9606	0.2922	0.8897	0.0902
H(191)	0.8617	0.3527	0.9150	0.0901
H(201)	0.5698	0.2845	0.8378	0.0597
H(212)	0.4796	0.1099	0.8303	0.1190
H(211)	0.5716	0.0844	0.8668	0.1192
H(213)	0.5641	0.0495	0.7998	0.1185
H(223)	0.4759	0.2586	0.7536	0.1165
H(222)	0.5638	0.3422	0.7398	0.1171
H(221)	0.5653	0.2088	0.7203	0.1160
H(51)	0.7670	0.3886	0.6474	0.0596
H(161)	0.7426	0.1502	0.7375	0.0686
H(141)	0.7310	0.4872	0.7952	0.0682
H(31)	0.7697	0.7325	0.5889	0.0699

Table 3: Atomic coordinates and isotropic thermal parameters ($\text{\AA}^2$) of hydrogen atoms

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(1)	0.0709(11)	0.0261(8)	0.0338(9)	-0.0038(6)	-0.0005(8)	0.0035(7)
C(2)	0.0448(12)	0.0222(11)	0.0316(12)	0.0002(9)	-0.0069(10)	0.0001(9)
O(3)	0.0743(11)	0.0166(7)	0.0498(9)	0.0015(7)	0.0093(8)	0.0035(7)
C(4)	0.0445(12)	0.0162(9)	0.0319(11)	0.0024(8)	0.0003(9)	-0.0009(8)
O(5)	0.0681(10)	0.0199(7)	0.0292(8)	0.0007(6)	0.0004(7)	-0.0036(6)
C(6)	0.0541(13)	0.0262(10)	0.0320(11)	-0.0011(9)	-0.0009(10)	0.0005(9)
C(7)	0.0544(14)	0.0377(13)	0.0456(13)	-0.0076(10)	-0.0124(11)	0.0056(11)
C(8)	0.0584(16)	0.0618(16)	0.0740(18)	0.0002(14)	-0.0094(14)	0.0048(13)
C(9)	0.0463(13)	0.0306(11)	0.0637(15)	-0.0004(11)	-0.0016(11)	0.0025(10)
C(10)	0.0557(15)	0.0558(15)	0.0723(18)	-0.0145(13)	-0.0045(13)	0.0149(12)
C(11)	0.0543(16)	0.0593(16)	0.097(2)	-0.0274(15)	-0.0259(15)	0.0105(13)
O(12)	0.0820(12)	0.0284(8)	0.0313(9)	0.0028(6)	0.0061(8)	0.0019(7)
C(13)	0.0558(14)	0.0250(11)	0.0278(12)	-0.0011(9)	-0.0045(10)	0.0049(9)
O(14)	0.0707(11)	0.0207(7)	0.0432(9)	-0.0034(6)	0.0040(7)	0.0018(7)
C(15)	0.0556(13)	0.0227(11)	0.0305(11)	-0.0040(9)	0.0029(10)	0.0026(9)
O(16)	0.0806(11)	0.0231(8)	0.0334(8)	-0.0019(6)	0.0121(7)	0.0031(7)
C(17)	0.0609(15)	0.0295(11)	0.0314(11)	0.0016(9)	0.0051(10)	0.0020(10)
C(18)	0.0641(16)	0.0465(14)	0.0397(13)	0.0012(11)	-0.0049(12)	0.0069(12)
C(19)	0.0731(19)	0.082(2)	0.0687(19)	-0.0051(16)	-0.0097(15)	0.0003(16)
C(20)	0.0520(14)	0.0416(13)	0.0588(15)	-0.0114(11)	-0.0017(12)	-0.0019(10)

C(21)	0.0672(18)	0.0670(18)	0.106(2)	-0.0071(17)	0.0088(17)	-0.0218(15)
C(22)	0.0710(18)	0.082(2)	0.081(2)	-0.0172(16)	-0.0272(16)	0.0106(16)

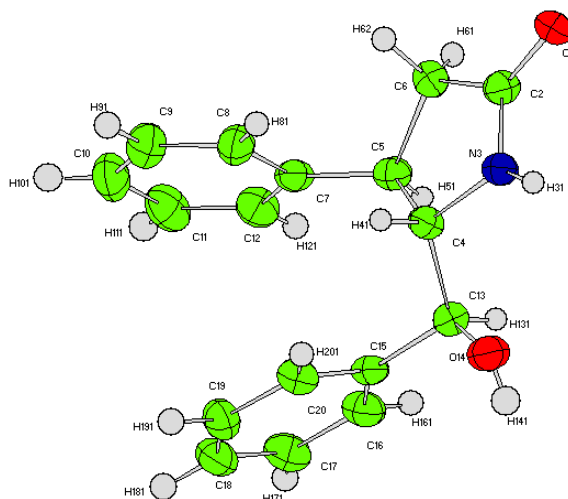
Table 4: Anisotropic thermal parameters ($\text{\AA}^2$)

O(1) - C(2)	1.204(2)	O(12) - C(13)	1.213(2)
C(2) - O(3)	1.319(2)	C(13) - O(14)	1.317(2)
C(2) - C(4)	1.527(3)	C(13) - C(15)	1.521(3)
O(3) - H(31)	0.839	O(14) - H(141)	0.817
C(4) - O(5)	1.420(2)	C(15) - O(16)	1.428(2)
C(4) - C(6)	1.526(3)	C(15) - C(17)	1.538(3)
C(4) - C(9)	1.550(3)	C(15) - C(20)	1.542(3)
O(5) - H(51)	0.806	O(16) - H(161)	0.821
C(6) - C(7)	1.483(3)	C(17) - C(18)	1.484(3)
C(7) - C(8)	1.305(3)	C(18) - C(19)	1.301(3)
C(9) - C(10)	1.527(3)	C(20) - C(21)	1.541(3)
C(9) - C(11)	1.518(3)	C(20) - C(22)	1.520(4)

Table 5: Bond lengths ($\text{\AA}$) Note – C-H atoms have been excluded

O(1) - C(2) - O(3)	124.75(17)	O(12) - C(13) - O(14)	124.50(18)
O(1) - C(2) - C(4)	123.46(17)	O(12) - C(13) - C(15)	122.53(17)
O(3) - C(2) - C(4)	111.79(17)	O(14) - C(13) - C(15)	112.97(17)
C(2) - C(4) - O(5)	108.17(15)	C(13) - C(15) - O(16)	107.70(15)
C(2) - C(4) - C(6)	110.02(16)	C(13) - C(15) - C(17)	109.01(16)
O(5) - C(4) - C(6)	107.17(15)	O(16) - C(15) - C(17)	107.70(16)
C(2) - C(4) - C(9)	108.70(16)	C(13) - C(15) - C(20)	109.76(17)
O(5) - C(4) - C(9)	110.00(16)	O(16) - C(15) - C(20)	109.93(17)
C(6) - C(4) - C(9)	112.69(17)	C(17) - C(15) - C(20)	112.60(17)
C(4) - C(6) - C(7)	113.68(17)	C(15) - C(17) - C(18)	113.35(17)
C(6) - C(7) - C(8)	125.1(2)	C(17) - C(18) - C(19)	125.6(2)
C(4) - C(9) - C(10)	112.02(18)	C(15) - C(20) - C(21)	111.7(2)
C(4) - C(9) - C(11)	111.48(19)	C(15) - C(20) - C(22)	112.2(2)
C(10) - C(9) - C(11)	110.16(19)	C(21) - C(20) - C(22)	111.1(2)

Table 6: Bond angles ($^\circ$ C) Note – H atoms have been excluded

Single-crystal X-ray diffraction report for compound **207** (Datablock: 0130808)

Crystal of **207** were grown and run by Callens Cédric from dichloromethane and petrol 40-60 °C. A single crystal having dimensions approximately **0.10 x 0.20 x 0.28 mm** was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150 K in a stream of cold N₂ using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoK_α radiation, $\lambda = 0.71073$ Å). Intensity data were processed using the DENZO-SMN package.¹

Examination of the systematic absences of the intensity data showed the space group to be **P 2₁/c**. The structure was solved in this space group using the direct-methods program SIR92,² which located all non-hydrogen atoms. The H atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. Subsequent full-matrix least-squares refinement was carried out against F² using the CRYSTAL program suite.³ Coordinates and anisotropic thermal parameters were refined for all non-hydrogen atoms, and the hydrogens were refined with riding constraints. A modified statistical weighting scheme was applied. Refinement converged satisfactorily to give **R = 0.0523**, **wR = 0.0988**.

Attached is a thermal ellipsoid plot (CAMERON) at 50% probability. A summary of crystallographic data is given below, as are full lists of atomic coordinates, anisotropic thermal parameters and those bond lengths and angles not concerning H atoms.

References

- (1) Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, 276, 307.
- (2) A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr.* **1994**, 27, 435.
- (3) P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout, D. J. Watkin, *J. Appl. Crystallogr.* **2003**, 36, 1487.

Crystal identification	CCK 0130808
Chemical formula	C ₁₇ H ₁₇ N ₁ O ₂
Formula weight	267.33
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	P 2/c
<i>a</i> (Å)	32.8860(12)
<i>b</i> (Å)	6.0205(3)
<i>c</i> (Å)	14.9007(7)
α (°)	90
β (°)	109.973(2)
γ (°)	90
Cell volume (Å ³)	2772.7(2)
<i>Z</i>	8
Calculated density (Mg/m ³)	1.281
Absorption coefficient (mm ⁻¹)	0.084
<i>F</i> ₀₀₀	1136
Crystal size (mm)	0.10 × 0.20 × 0.28
Description of crystal	Colourless plate
Absorption correction	multi-scan
Transmission coefficients (min,max)	0.97, 0.99
θ range for data collection (°)	5.27 ≤ θ ≤ 27.41
Index ranges	-42 ≤ <i>h</i> ≤ 42, -7 ≤ <i>k</i> ≤ 7, -19 ≤ <i>l</i> ≤ 19
Reflections measured	5251
Unique reflections	181
<i>R</i> _{int}	0
Observed reflections (<i>I</i> > -2σ(<i>I</i>))	3521
Refinement method	Full-matrix least-squares on <i>F</i> _{sqr}
Parameters refined	136
Weighting scheme	Modified Sheldrick
Goodness of fit	0.9021
<i>R</i>	0.0523
<i>wR</i>	0.0988
Residual electron density (min,max) (eÅ ⁻³)	-0.41, 0.40

Table 1: Crystal data and refinement details

Atom	x	y	z	U _{equiv}
O(1)	0.24158(5)	1.0178(2)	0.41576(10)	0.0373
C(2)	0.21616(8)	0.9635(4)	0.45742(14)	0.0331
N(3)	0.21529(6)	1.0487(3)	0.53938(11)	0.0340
C(4)	0.17904(7)	0.9725(3)	0.56627(14)	0.0309
C(5)	0.16256(7)	0.7635(3)	0.50411(13)	0.0314
C(6)	0.18128(7)	0.7928(4)	0.42247(14)	0.0361
C(7)	0.11437(7)	0.7289(4)	0.47006(14)	0.0321
C(8)	0.08581(8)	0.8903(4)	0.41730(15)	0.0382
C(9)	0.04173(8)	0.8562(4)	0.38458(16)	0.0472
C(10)	0.02456(9)	0.6597(4)	0.40370(17)	0.0501
C(11)	0.05222(9)	0.4976(4)	0.45583(18)	0.0485
C(12)	0.09643(8)	0.5324(4)	0.48834(16)	0.0405
C(13)	0.19119(7)	0.9258(3)	0.67322(14)	0.0326
O(14)	0.20959(5)	1.1268(2)	0.72176(10)	0.0402
C(15)	0.15145(7)	0.8550(4)	0.69493(13)	0.0306
C(16)	0.14842(8)	0.6457(4)	0.73179(14)	0.0384
C(17)	0.11093(9)	0.5811(4)	0.74781(16)	0.0427
C(18)	0.07629(8)	0.7207(4)	0.72661(15)	0.0433
C(19)	0.07861(8)	0.9304(4)	0.69002(16)	0.0411
C(20)	0.11607(8)	0.9958(4)	0.67505(14)	0.0353

Table 2: Atomic coordinates and equivalent isotropic thermal parameters ($\text{\AA}^2$) of non-hydrogen atoms

Atom	x	y	z	U_{iso}
H(41)	0.1571	1.0894	0.5480	0.0352
H(51)	0.1777	0.6350	0.5412	0.0343
H(61)	0.1926	0.6589	0.4072	0.0422
H(62)	0.1586	0.8544	0.3661	0.0429
H(81)	0.0964	1.0261	0.4048	0.0439
H(91)	0.0231	0.9706	0.3510	0.0540
H(101)	-0.0060	0.6404	0.3822	0.0581
H(111)	0.0407	0.3614	0.4673	0.0602
H(121)	0.1156	0.4219	0.5229	0.0502
H(131)	0.2137	0.8118	0.6914	0.0361
H(161)	0.1721	0.5479	0.7451	0.0451
H(171)	0.1105	0.4352	0.7745	0.0529
H(181)	0.0504	0.6758	0.7376	0.0521
H(191)	0.0542	1.0312	0.6745	0.0498
H(201)	0.1183	1.1422	0.6548	0.0429
H(31)	0.2322	1.1536	0.5670	0.0379
H(141)	0.2186	1.0961	0.7775	0.0577

Table 3: Atomic coordinates and isotropic thermal parameters ($\text{\AA}^2$) of hydrogen atoms

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(1)	0.0351(10)	0.0492(10)	0.0324(8)	0.0006(7)	0.0178(7)	-0.0018(8)
C(2)	0.0336(15)	0.0383(14)	0.0273(12)	0.0018(10)	0.0101(11)	0.0032(11)
N(3)	0.0328(12)	0.0435(12)	0.0271(10)	-0.0041(8)	0.0121(9)	-0.0067(9)
C(4)	0.0314(14)	0.0341(13)	0.0293(11)	0.0005(10)	0.0134(10)	0.0009(11)
C(5)	0.0368(15)	0.0307(13)	0.0275(12)	0.0025(10)	0.0122(11)	0.0032(11)
C(6)	0.0315(15)	0.0440(15)	0.0339(13)	-0.0023(10)	0.0126(11)	-0.0020(11)
C(7)	0.0368(16)	0.0359(14)	0.0252(11)	-0.0027(10)	0.0126(11)	-0.0027(11)
C(8)	0.0328(16)	0.0424(15)	0.0372(13)	0.0037(11)	0.0091(11)	-0.0027(12)
C(9)	0.0393(18)	0.0525(17)	0.0471(15)	0.0032(12)	0.0115(13)	0.0032(13)
C(10)	0.0340(17)	0.0599(19)	0.0568(16)	-0.0107(14)	0.0159(13)	-0.0083(14)
C(11)	0.0507(19)	0.0420(16)	0.0605(16)	-0.0057(13)	0.0289(14)	-0.0113(14)
C(12)	0.0452(18)	0.0364(14)	0.0436(14)	0.0009(11)	0.0198(12)	-0.0004(12)
C(13)	0.0309(15)	0.0386(14)	0.0277(11)	0.0005(10)	0.0092(10)	0.0009(11)
O(14)	0.0440(11)	0.0467(10)	0.0298(8)	-0.0015(7)	0.0123(7)	-0.0086(8)
C(15)	0.0353(15)	0.0358(13)	0.0219(11)	-0.0006(10)	0.0112(10)	-0.0003(11)
C(16)	0.0463(17)	0.0386(15)	0.0343(13)	0.0060(11)	0.0191(12)	0.0093(12)
C(17)	0.0545(19)	0.0383(15)	0.0424(14)	0.0011(11)	0.0255(13)	-0.0032(13)
C(18)	0.0437(18)	0.0522(17)	0.0406(14)	-0.0059(12)	0.0230(13)	-0.0105(13)
C(19)	0.0343(15)	0.0486(16)	0.0429(13)	0.0049(12)	0.0165(12)	0.0072(12)
C(20)	0.0416(16)	0.0335(14)	0.0343(12)	0.0009(10)	0.0175(11)	-0.0002(11)

Table 4: Anisotropic thermal parameters ($\text{\AA}^2$)

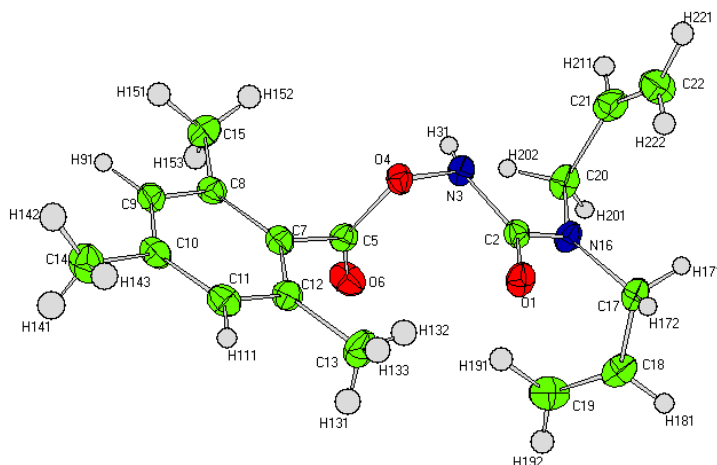
O(1) – C(2)	1.243(2)	C(9) – C(10)	1.382(3)
C(2) – N(3)	1.334(2)	C(10) – C(11)	1.379(3)
C(2) – C(6)	1.495(3)	C(11) – C(12)	1.382(3)
N(3) – C(4)	1.455(3)	C(13) – O(14)	1.433(2)
N(3) – H(31)	0.848	C(13) – C(15)	1.511(3)
C(4) – C(5)	1.547(3)	O(14) – H(141)	0.802
C(4) – C(13)	1.531(3)	C(15) – C(16)	1.392(3)
C(5) – C(6)	1.550(3)	C(15) – C(20)	1.387(3)
C(5) – C(7)	1.504(3)	C(16) – C(17)	1.389(3)
C(7) – C(8)	1.393(3)	C(17) – C(18)	1.363(3)
C(7) – C(12)	1.390(3)	C(18) – C(19)	1.388(3)

C(8) – C(9)	1.378(3)	C(18) – C(20)	1.382(3)
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Table 5: Bond lengths (Å) Note – C-H atoms have been excluded

O(1) - C(2) - N(3)	125.8(2)	C(8) - C(9) - C(10)	120.6(2)
O(1) - C(2) - C(6)	125.00(18)	C(9) - C(10) - C(11)	119.0(3)
N(3) - C(2) - C(6)	109.23(19)	C(10) - C(11) - C(12)	120.2(2)
C(2) - N(3) - C(4)	114.00(17)	C(7) - C(12) - C(11)	121.8(2)
N(3) - C(4) - C(5)	104.11(16)	C(4) - C(13) - O(14)	106.57(16)
N(3) - C(4) - C(13)	113.41(18)	C(4) - C(13) - C(15)	109.71(17)
C(5) - C(4) - C(13)	112.79(16)	O(14) - C(13) - C(15)	112.15(16)
C(4) - C(5) - C(6)	103.04(16)	C(13) - C(15) - C(16)	121.6(2)
C(4) - C(5) - C(7)	115.35(18)	C(13) - C(15) - C(20)	120.3(2)
C(6) - C(5) - C(7)	113.97(17)	C(16) - C(15) - C(20)	118.0(2)
C(5) - C(6) - C(2)	105.54(17)	C(15) - C(16) - C(17)	120.6(2)
C(5) - C(7) - C(8)	121.5(2)	C(16) - C(17) - C(18)	120.5(2)
C(5) - C(7) - C(12)	121.4(2)	C(17) - C(18) - C(19)	119.9(2)
C(8) - C(7) - C(12)	117.1(2)	C(18) - C(19) - C(20)	119.6(2)
C(7) - C(8) - C(9)	121.4(2)	C(15) - C(20) - C(19)	121.3(2)

Table 6: Bond angles (° C) Note – H atoms have been excluded

Single-crystal X-ray diffraction report for compound **228** (Datablock: 0230109)

Crystal of **228** were grown and run by Callens Cédric from dichloromethane and petrol 40-60 °C. A single crystal having dimensions approximately **0.20 x 0.20 x 0.20 mm** was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150 K in a stream of cold N₂ using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoK α radiation, $\lambda = 0.71073$ Å). Intensity data were processed using the DENZO-SMN package.¹

Examination of the systematic absences of the intensity data showed the space group to be **P 2/c**. The structure was solved in this space group using the direct-methods program SIR92,² which located all non-hydrogen atoms. The H atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. Subsequent full-matrix least-squares refinement was carried out against F² using the CRYSTAL program suite.³ Coordinates and anisotropic thermal parameters were refined for all non-hydrogen atoms, and the hydrogens were refined with riding constraints. A modified statistical weighting scheme was applied. Refinement converged satisfactorily to give **R = 0.0745**, **wR = 0.1253**.

Attached is a thermal ellipsoid plot (CAMERON) at 50% probability. A summary of crystallographic data is given below, as are full lists of atomic coordinates, anisotropic thermal parameters and those bond lengths and angles not concerning H atoms.

References

- (1) Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, 276, 307.
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- (3) P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout, D. J. Watkin, *J. Appl. Crystallogr.* **2003**, 36, 1487.

Crystal identification	CCK 0230109
Chemical formula	C ₁₇ H ₂₂ N ₂ O ₃
Formula weight	302.37
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	P 2/c
<i>a</i> (Å)	9.0000(2)
<i>b</i> (Å)	20.1778(4)
<i>c</i> (Å)	9.5533(2)
α (°)	90
β (°)	108.3390(8)
γ (°)	90
Cell volume (Å ³)	1646.77(6)
<i>Z</i>	4
Calculated density (Mg/m ³)	1.220
Absorption coefficient (mm ⁻¹)	0.084
<i>F</i> ₀₀₀	648
Crystal size (mm)	0.20 × 0.20 × 0.20
Description of crystal	Colourless block
Absorption correction	multi-scan
Transmission coefficients (min,max)	0.98, 0.99
θ range for data collection (°)	5.18 ≤ θ ≤ 27.45
Index ranges	-11 ≤ <i>h</i> ≤ 11, -26 ≤ <i>k</i> ≤ 25, -12 ≤ <i>l</i> ≤ 12
Reflections measured	15902
Unique reflections	3743
<i>R</i> _{int}	0.027
Observed reflections (<i>I</i> > 3 σ (<i>I</i>))	3741
Refinement method	Full-matrix least-squares on <i>Fsqd</i>
Parameters refined	200
Weighting scheme	Modified Sheldrick
Goodness of fit	0.9435
<i>R</i>	0.0745
<i>wR</i>	0.1253
Residual electron density (min,max) (eÅ ⁻³)	-0.47, 0.51

Table 1: Crystal data and refinement details

Atom	x	y	z	<i>U</i> _{equiv}
O(1)	0.34352(14)	0.72881(6)	0.78095(12)	0.0277
C(2)	0.31816(18)	0.76392(8)	0.87663(16)	0.0213
N(3)	0.42686(15)	0.76814(6)	1.01802(14)	0.0221
O(4)	0.54216(12)	0.71727(5)	1.04580(12)	0.0234
C(5)	0.48770(18)	0.65602(8)	1.06934(16)	0.0225
O(6)	0.35463(13)	0.64626(6)	1.06448(14)	0.0320
C(7)	0.61675(18)	0.60612(8)	1.10366(18)	0.0238
C(8)	0.71040(18)	0.59744(8)	1.25035(17)	0.0240
C(9)	0.82396(19)	0.54790(8)	1.28012(19)	0.0267
C(10)	0.84394(19)	0.50712(8)	1.1700(2)	0.0291
C(11)	0.7502(2)	0.51787(8)	1.0257(2)	0.0305
C(12)	0.6359(2)	0.56729(8)	0.98921(18)	0.0269
C(13)	0.5353(2)	0.57676(10)	0.83125(19)	0.0366
C(14)	0.9604(2)	0.45096(10)	1.2059(2)	0.0416
C(15)	0.6886(2)	0.63943(9)	1.37284(18)	0.0309
N(16)	0.19170(15)	0.80324(7)	0.85275(14)	0.0237
C(17)	0.08017(19)	0.80873(8)	0.70415(17)	0.0266
C(18)	-0.0612(2)	0.76545(9)	0.67792(19)	0.0321
C(19)	-0.0806(2)	0.71877(10)	0.7666(2)	0.0400
C(20)	0.1625(2)	0.84534(8)	0.96601(18)	0.0268

C(21)	0.2359(2)	0.91255(9)	0.9787(2)	0.0329
C(22)	0.3105(2)	0.93745(10)	0.8927(2)	0.0405

Table 2: Atomic coordinates and equivalent isotropic thermal parameters ($\text{\AA}^2$) of non-hydrogen atoms

Atom	x	y	z	U_{iso}
H(91)	0.8894	0.5406	1.3804	0.0295
H(111)	0.7623	0.4907	0.9485	0.0367
H(133)	0.5951	0.5704	0.7642	0.0554
H(132)	0.4904	0.6199	0.8120	0.0550
H(131)	0.4510	0.5454	0.8040	0.0560
H(143)	1.0044	0.4436	1.1264	0.0600
H(142)	1.0430	0.4586	1.2958	0.0601
H(141)	0.9108	0.4104	1.2183	0.0603
H(151)	0.7720	0.6332	1.4649	0.0463
H(152)	0.6873	0.6858	1.3479	0.0475
H(153)	0.5917	0.6295	1.3900	0.0476
H(171)	0.0461	0.8558	0.6909	0.0300
H(172)	0.1329	0.7983	0.6308	0.0305
H(181)	-0.1442	0.7732	0.5875	0.0377
H(191)	-0.0002	0.7102	0.8573	0.0479
H(192)	-0.1743	0.6932	0.7408	0.0484
H(201)	0.0496	0.8509	0.9401	0.0316
H(202)	0.1998	0.8225	1.0610	0.0318
H(211)	0.2252	0.9389	1.0564	0.0387
H(221)	0.3540	0.9811	0.9104	0.0466
H(222)	0.3222	0.9112	0.8122	0.0461
H(31)	0.4065	0.7863	1.0861	0.0287

Table 3: Atomic coordinates and isotropic thermal parameters ($\text{\AA}^2$) of hydrogen atoms

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(1)	0.0367(7)	0.0287(6)	0.0196(6)	-0.0002(5)	0.0115(5)	0.0070(5)
C(2)	0.0245(8)	0.0209(7)	0.0196(7)	0.0022(6)	0.0086(6)	-0.0001(6)
N(3)	0.0242(7)	0.0229(7)	0.0196(7)	-0.0004(5)	0.0076(5)	0.0060(5)
O(4)	0.0213(6)	0.0226(6)	0.0262(6)	0.0037(4)	0.0073(4)	0.0031(4)
C(5)	0.0253(8)	0.0246(8)	0.0182(7)	-0.0011(6)	0.0078(6)	-0.0013(6)
O(6)	0.0263(6)	0.0283(6)	0.0444(7)	-0.0005(5)	0.0156(5)	-0.0011(5)
C(7)	0.0238(8)	0.0216(8)	0.0263(8)	0.0010(6)	0.0085(7)	-0.0007(6)
C(8)	0.0242(8)	0.0232(8)	0.0251(8)	0.0006(6)	0.0085(7)	-0.0045(6)
C(9)	0.0244(8)	0.0235(8)	0.0293(9)	0.0051(7)	0.0045(7)	-0.0028(6)
C(10)	0.0262(8)	0.0219(8)	0.0393(10)	0.0022(7)	0.0103(7)	-0.0003(7)
C(11)	0.0347(9)	0.0242(8)	0.0344(9)	-0.0034(7)	0.0135(8)	0.0020(7)
C(12)	0.0280(8)	0.0261(8)	0.0266(8)	-0.0005(7)	0.0087(7)	-0.0012(7)
C(13)	0.0428(11)	0.0398(10)	0.0255(9)	-0.0016(8)	0.0084(8)	0.0076(8)
C(14)	0.0372(10)	0.0326(10)	0.0527(12)	0.0034(9)	0.0107(9)	0.0088(8)
C(15)	0.0311(9)	0.0350(10)	0.0255(9)	-0.0013(7)	0.0074(7)	-0.0001(7)
N(16)	0.0247(7)	0.0270(7)	0.0188(6)	-0.0005(5)	0.0059(5)	0.0055(6)
C(17)	0.0270(8)	0.0299(9)	0.0206(8)	0.0023(6)	0.0043(7)	0.0056(7)
C(18)	0.0272(9)	0.0391(10)	0.0274(9)	-0.0050(8)	0.0051(7)	0.0030(8)
C(19)	0.0401(11)	0.0411(11)	0.0394(11)	-0.0069(8)	0.0133(9)	-0.0072(9)
C(20)	0.0285(8)	0.0313(9)	0.0219(8)	0.0009(7)	0.0099(7)	0.0081(7)
C(21)	0.0345(9)	0.0310(9)	0.0290(9)	-0.0070(7)	0.0038(7)	0.0070(8)
C(22)	0.0400(11)	0.0301(9)	0.0469(11)	-0.0003(8)	0.0072(9)	-0.0018(8)

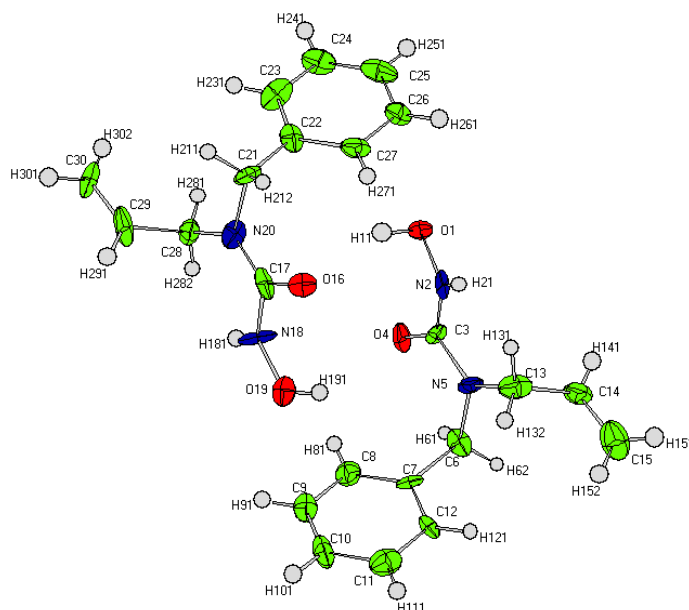
Table 4: Anisotropic thermal parameters ($\text{\AA}^2$)

O(1) - C(2)	1.2331(18)	C(9) - C(10)	1.391(2)
C(2) - N(3)	1.399(2)	C(10) - C(11)	1.388(2)
C(2) - N(16)	1.347(2)	C(10) - C(14)	1.508(2)
N(3) - O(4)	1.4238(16)	C(11) - C(12)	1.396(2)
N(3) - H(31)	0.816	C(12) - C(13)	1.508(2)
O(4) - C(5)	1.3740(19)	N(16) - C(17)	1.462(2)
C(5) - O(6)	1.2001(19)	N(16) - C(20)	1.463(2)
C(5) - C(7)	1.494(2)	C(17) - C(18)	1.498(2)
C(7) - C(8)	1.401(2)	C(18) - C(19)	1.315(3)
C(7) - C(12)	1.399(2)	C(20) - C(21)	1.497(2)
C(8) - C(9)	1.393(2)	C(21) - C(22)	1.313(3)
C(8) - C(15)	1.507(2)	/	

Table 5: Bond lengths ($\text{\AA}$) Note – C-H atoms have been excluded

O(1) - C(2) - N(3)	120.95(14)	C(9) - C(10) - C(11)	118.40(15)
O(1) - C(2) - N(16)	123.82(14)	C(9) - C(10) - C(14)	121.24(16)
N(3) - C(2) - N(16)	115.13(13)	C(11) - C(10) - C(14)	120.32(16)
C(2) - N(3) - O(4)	112.54(12)	C(10) - C(11) - C(12)	121.97(16)
N(3) - O(4) - C(5)	113.73(11)	C(7) - C(12) - C(11)	117.86(15)
O(4) - C(5) - O(6)	122.97(14)	C(7) - C(12) - C(13)	121.89(15)
O(4) - C(5) - C(7)	110.46(13)	C(11) - C(12) - C(13)	120.25(15)
O(6) - C(5) - C(7)	126.55(15)	C(2) - N(16) - C(17)	119.63(13)
C(5) - C(7) - C(8)	119.04(14)	C(2) - N(16) - C(20)	123.75(13)
C(5) - C(7) - C(12)	118.98(14)	C(17) - N(16) - C(20)	116.49(13)
C(8) - C(7) - C(12)	121.91(15)	N(16) - C(17) - C(18)	113.93(14)
C(7) - C(8) - C(9)	117.76(15)	C(17) - C(18) - C(19)	126.02(16)
C(7) - C(8) - C(15)	121.50(14)	N(16) - C(20) - C(21)	114.12(14)
C(9) - C(8) - C(15)	120.74(14)	C(20) - C(21) - C(22)	126.54(17)
C(8) - C(9) - C(10)	122.08(15)	/	

Table 6: Bond angles ($^\circ$ C) Note – H atoms have been excluded

Single-crystal X-ray diffraction report for compound **220a** (Datablock: 0250109)

Crystal of **220a** were grown and run by Callens Cédric from dichloromethane and petrol 40-60 °C. A single crystal having dimensions approximately **0.12 x 0.20 x 0.20 mm** was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150 K in a stream of cold N₂ using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoK α radiation, $\lambda = 0.71073$ Å). Intensity data were processed using the DENZO-SMN package.¹

Examination of the systematic absences of the intensity data showed the space group to be **P 2₁ 2₁ 2₁**. The structure was solved in this space group using the direct-methods program SIR92,² which located all non-hydrogen atoms. The H atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. Subsequent full-matrix least-squares refinement was carried out against F² using the CRYSTAL program suite.³ Coordinates and anisotropic thermal parameters were refined for all non-hydrogen atoms, and the hydrogens were refined with riding constraints. A modified statistical weighting scheme was applied. Refinement converged satisfactorily to give **R = 0.0750, wR = 0.1123**.

Attached is a thermal ellipsoid plot (CAMERON) at 50% probability. A summary of crystallographic data is given below, as are full lists of atomic coordinates, anisotropic thermal parameters and those bond lengths and angles not concerning H atoms.

References

- (1) Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, 276, 307.
- (2) A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr.* **1994**, 27, 435.
- (3) P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout, D. J. Watkin, *J. Appl. Crystallogr.* **2003**, 36, 1487.

Crystal identification	CCK 0250109
Chemical formula	C ₁₁ H ₁₄ N ₂ O ₂
Formula weight	206.24
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Orthorhombic
Space group	C c
<i>a</i> (Å)	7.79790(10)
<i>b</i> (Å)	10.1302(2)
<i>c</i> (Å)	26.8506(6)
α (°)	90
β (°)	90
γ (°)	90
Cell volume (Å ³)	2121.04(7)
<i>Z</i>	8
Calculated density (Mg/m ³)	1.292
Absorption coefficient (mm ⁻¹)	0.090
<i>F</i> ₀₀₀	880
Crystal size (mm)	0.12 × 0.20 × 0.20
Description of crystal	Colourless plate
Absorption correction	multi-scan
Transmission coefficients (min,max)	0.98, 0.99
θ range for data collection (°)	5.25 ≤ θ ≤ 27.48
Index ranges	-10 ≤ <i>h</i> ≤ 10, -13 ≤ <i>k</i> ≤ 13, -34 ≤ <i>l</i> ≤ 34
Reflections measured	4822
Unique reflections	2758
<i>R</i> _{int}	0.053
Observed reflections (<i>I</i> > -3 σ (<i>I</i>))	1842
Refinement method	Full-matrix least-squares on <i>F</i> ²
Parameters refined	271
Weighting scheme	Modified Sheldrick
Goodness of fit	0.8934
<i>R</i>	0.0750
<i>wR</i>	0.1123
Residual electron density (min,max) (eÅ ⁻³)	-1.35, 0.44

Table 1: Crystal data and refinement details

Atom	x	y	z	U _{equiv}
O(119)	-0.0674(7)	0.3605(4)	0.54320(17)	0.0353
N(118)	-0.1087(8)	0.2980(4)	0.4980(2)	0.0333
C(117)	0.0101(9)	0.3010(6)	0.4620(2)	0.0291
O(116)	0.1334(5)	0.3803(4)	0.46348(16)	0.0295
N(120)	-0.0125(8)	0.2197(5)	0.42215(19)	0.0307
C(121)	0.1031(9)	0.2346(6)	0.3792(2)	0.0318
C(122)	0.0289(10)	0.3241(5)	0.3406(2)	0.0295
C(127)	0.0471(11)	0.4617(6)	0.3430(2)	0.0353
C(126)	-0.0266(11)	0.5422(7)	0.3070(3)	0.0388
C(125)	-0.1159(12)	0.4898(8)	0.2683(3)	0.0418
C(124)	-0.1422(11)	0.3595(10)	0.2649(3)	0.0426
C(123)	-0.0680(11)	0.2740(6)	0.3009(2)	0.0369
C(128)	-0.1516(9)	0.1214(6)	0.4175(3)	0.0319
C(129)	-0.0796(12)	-0.0156(6)	0.4220(3)	0.0423
C(130)	-0.0825(9)	-0.1022(6)	0.3857(3)	0.0431
O(16)	-0.1340(5)	0.6202(4)	0.53541(16)	0.0315
C(17)	-0.0106(8)	0.7002(6)	0.5382(2)	0.0246
N(18)	0.1110(9)	0.7028(4)	0.5009(2)	0.0328
O(19)	0.0661(6)	0.6373(4)	0.45671(17)	0.0327
N(20)	0.0108(8)	0.7803(5)	0.5772(2)	0.0297
C(21)	-0.1008(9)	0.7667(6)	0.6210(2)	0.0332

C(22)	-0.0253(9)	0.6762(5)	0.6608(2)	0.0269
C(23)	0.0659(11)	0.7258(7)	0.6999(3)	0.0340
C(24)	0.1366(11)	0.6452(10)	0.7345(3)	0.0418
C(25)	0.1197(10)	0.5072(7)	0.7302(3)	0.0451
C(26)	0.0214(10)	0.4562(6)	0.6915(3)	0.0423
C(27)	-0.0489(12)	0.5406(5)	0.6569(2)	0.0343
C(28)	0.1441(8)	0.8800(6)	0.5822(3)	0.0383
C(29)	0.0761(12)	1.0168(6)	0.5793(3)	0.0450
C(30)	0.0847(9)	1.1051(6)	0.6138(3)	0.0503

Table 2: Atomic coordinates and equivalent isotropic thermal parameters ($\text{\AA}^2$) of non-hydrogen atoms

Atom	x	y	z	U_{iso}
H(1211)	0.2081	0.2700	0.3913	0.0368
H(1212)	0.1185	0.1463	0.3643	0.0361
H(1271)	0.1102	0.4996	0.3696	0.0417
H(1261)	-0.0119	0.6334	0.3099	0.0493
H(1251)	-0.1635	0.5433	0.2441	0.0507
H(1241)	-0.2082	0.3214	0.2390	0.0576
H(1231)	-0.0841	0.1816	0.2980	0.0418
H(1281)	-0.2364	0.1330	0.4442	0.0451
H(1282)	-0.2044	0.1319	0.3842	0.0458
H(1291)	-0.0292	-0.0402	0.4519	0.0565
H(1301)	-0.0429	-0.1879	0.3920	0.0550
H(1302)	-0.1276	-0.0803	0.3540	0.0547
H(211)	-0.1165	0.8548	0.6355	0.0388
H(212)	-0.2107	0.7318	0.6100	0.0381
H(231)	0.0796	0.8175	0.7033	0.0426
H(241)	0.1955	0.6797	0.7611	0.0440
H(251)	0.1665	0.4523	0.7540	0.0536
H(261)	0.0065	0.3652	0.6883	0.0502
H(271)	-0.1131	0.5054	0.6301	0.0435
H(281)	0.2037	0.8716	0.6140	0.0365
H(282)	0.2286	0.8632	0.5563	0.0372
H(291)	0.0174	1.0393	0.5499	0.0481
H(302)	0.1358	1.0821	0.6445	0.0563
H(301)	0.0394	1.1908	0.6089	0.0572
H(181)	0.1853	0.7676	0.4990	0.0401
H(1191)	-0.0878	0.4371	0.5361	0.0486
H(191)	0.0862	0.5559	0.4582	0.0528
H(1181)	-0.1664	0.2290	0.5021	0.0409

Table 3: Atomic coordinates and isotropic thermal parameters ($\text{\AA}^2$) of hydrogen atoms

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(119)	0.042(3)	0.035(2)	0.029(3)	-0.005(2)	-0.004(3)	-0.001(3)
N(118)	0.028(3)	0.031(3)	0.041(3)	0.000(3)	0.002(3)	-0.010(4)
C(117)	0.020(4)	0.033(4)	0.034(4)	0.008(4)	0.002(4)	0.003(4)
O(116)	0.023(3)	0.028(2)	0.037(3)	0.001(2)	0.000(3)	-0.001(3)
N(120)	0.030(4)	0.039(3)	0.024(3)	-0.001(3)	0.005(3)	-0.010(3)
C(121)	0.032(4)	0.028(3)	0.035(4)	0.000(3)	0.000(4)	0.014(4)
C(122)	0.022(4)	0.036(3)	0.031(4)	-0.001(3)	0.008(4)	-0.012(4)
C(127)	0.032(4)	0.035(4)	0.039(5)	-0.014(4)	0.014(4)	-0.009(4)
C(126)	0.043(5)	0.030(3)	0.043(5)	0.017(4)	0.001(5)	0.007(4)
C(125)	0.032(5)	0.063(6)	0.030(4)	0.007(5)	0.003(4)	0.008(6)
C(124)	0.036(5)	0.047(6)	0.045(5)	-0.018(5)	-0.010(4)	-0.007(5)
C(123)	0.041(5)	0.034(4)	0.036(4)	0.004(3)	0.010(4)	-0.007(4)
C(128)	0.028(4)	0.024(4)	0.044(5)	-0.004(4)	0.003(4)	-0.014(4)
C(129)	0.051(6)	0.043(4)	0.033(5)	0.000(4)	-0.007(4)	-0.006(5)

C(130)	0.036(4)	0.036(3)	0.057(6)	0.003(4)	-0.008(5)	0.013(5)
O(16)	0.029(3)	0.028(2)	0.037(3)	0.003(2)	-0.003(3)	-0.005(3)
C(17)	0.030(4)	0.016(3)	0.028(4)	0.002(3)	-0.007(4)	0.007(4)
N(18)	0.044(4)	0.036(4)	0.018(3)	-0.012(3)	0.001(3)	-0.006(4)
O(19)	0.043(3)	0.023(2)	0.032(3)	0.001(2)	0.001(3)	0.001(3)
N(20)	0.025(4)	0.025(3)	0.039(3)	-0.007(3)	-0.001(3)	0.000(3)
C(21)	0.024(4)	0.045(4)	0.031(4)	-0.004(4)	0.010(4)	-0.013(5)
C(22)	0.026(4)	0.031(3)	0.024(4)	-0.003(3)	0.004(4)	0.009(4)
C(23)	0.022(5)	0.041(4)	0.039(5)	-0.012(4)	-0.007(5)	0.001(4)
C(24)	0.032(5)	0.069(6)	0.025(4)	0.013(5)	-0.001(4)	0.002(5)
C(25)	0.044(4)	0.042(5)	0.050(5)	0.016(5)	0.003(4)	0.008(5)
C(26)	0.051(5)	0.040(4)	0.036(3)	-0.011(4)	0.020(5)	-0.007(4)
C(27)	0.041(5)	0.042(4)	0.020(5)	0.009(4)	-0.006(4)	-0.008(4)
C(28)	0.039(4)	0.052(4)	0.025(4)	-0.006(3)	0.002(4)	0.001(4)
C(29)	0.053(6)	0.029(4)	0.054(5)	0.017(4)	-0.020(5)	-0.011(5)
C(30)	0.049(5)	0.025(3)	0.077(6)	-0.001(4)	-0.009(5)	-0.015(4)

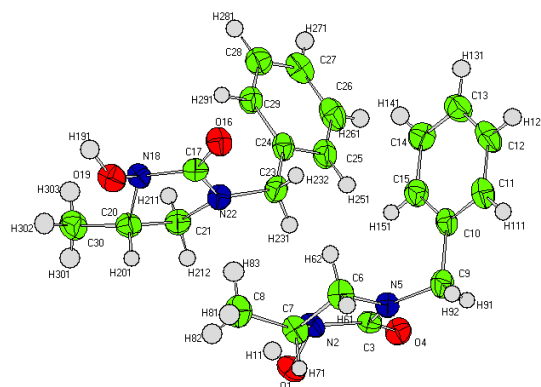
Table 4: Anisotropic thermal parameters ($\text{\AA}^2$)

O(119) - N(118)	1.407(6)	O(16) - C(17)	1.260(7)
O(119) - H(1191)	0.815	C(17) - N(18)	1.378(8)
N(118) - C(117)	1.339(9)	C(17) - N(20)	1.336(7)
N(118) - H(1181)	0.839	N(18) - O(19)	1.405(6)
C(117) - O(116)	1.253(7)	N(18) - H(181)	0.877
C(117) - N(120)	1.362(7)	O(19) - H(191)	0.840
N(120) - C(121)	1.471(7)	N(20) - C(21)	1.469(7)
N(120) - C(128)	1.477(7)	N(20) - C(28)	1.456(7)
C(121) - C(122)	1.494(7)	C(21) - C(22)	1.525(7)
C(122) - C(127)	1.402(7)	C(22) - C(23)	1.364(8)
C(122) - C(123)	1.403(8)	C(22) - C(27)	1.390(7)
C(127) - C(126)	1.390(9)	C(23) - C(24)	1.354(10)
C(126) - C(125)	1.360(10)	C(24) - C(25)	1.408(11)
C(125) - C(124)	1.339(12)	C(25) - C(26)	1.391(10)
C(124) - C(123)	1.420(9)	C(26) - C(27)	1.376(9)
C(128) - C(129)	1.502(8)	C(28) - C(29)	1.486(8)
C(129) - C(130)	1.310(9)	C(29) - C(30)	1.289(8)

Table 5: Bond lengths ($\text{\AA}$) Note – C-H atoms have been excluded

O119 - N(118) - C(117)	117.0(5)	O(16) - C(17) - N(20)	122.1(6)
N(118) - C(117) - O116	121.5(6)	N(18) - C(17) - N(20)	118.1(6)
N(118) - C(117) - N(120)	117.6(6)	C(17) - N(18) - O(19)	115.6(6)
O116 - C(117) - N(120)	120.8(6)	C(17) - N(20) - C(21)	119.8(6)
C(117) - N(120) - C(121)	118.3(6)	C(17) - N(20) - C(28)	125.7(6)
C(117) - N(120) - C(128)	124.7(6)	C(21) - N(20) - C(28)	114.4(5)
C(121) - N(120) - C(128)	117.0(5)	N(20) - C(21) - C(22)	112.9(5)
N(120) - C(121) - C(122)	111.6(5)	C(21) - C(22) - C(23)	121.3(6)
C(121) - C(122) - C(127)	122.1(6)	C(21) - C(22) - C(27)	119.3(7)
C(121) - C(122) - C(123)	121.1(5)	C(23) - C(22) - C(27)	119.4(7)
C(127) - C(122) - C(123)	116.7(7)	C(22) - C(23) - C(24)	121.2(7)
C(122) - C(127) - C(126)	120.6(7)	C(23) - C(24) - C(25)	120.3(9)
C(127) - C(126) - C125	121.0(7)	C(24) - C(25) - C(26)	118.7(8)
C(126) - C125 - C124	121.0(9)	C(25) - C(26) - C(27)	119.6(6)
C125 - C124 - C(123)	119.6(9)	C(22) - C(27) - C(26)	120.7(7)
N(120) - C(128) - C129	110.0(5)	N(20) - C(28) - C(29)	112.8(5)
C(128) - C129 - C130	123.6(8)	C(28) - C(29) - C(30)	126.2(7)
O(16) - C(17) - N(18)	119.7(6)	/	

Table 6: Bond angles ($^\circ$ C) Note – H atoms have been excluded

Single-crystal X-ray diffraction report for compound **221** (Datablock: 0300209)

Crystal of **221** were grown and run by Callens Cédric from dichloromethane and petrol 40-60 °C. A single crystal having dimensions approximately **0.10 x 0.18 x 0.18 mm** was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 293 K in a stream of cold N₂ using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoK α radiation, $\lambda = 0.71073$ Å). Intensity data were processed using the DENZO-SMN package.¹

Examination of the systematic absences of the intensity data showed the space group to be **P -1**. The structure was solved in this space group using the direct-methods program SIR92,² which located all non-hydrogen atoms. The H atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. Subsequent full-matrix least-squares refinement was carried out against F² using the CRYSTAL program suite.³ Coordinates and anisotropic thermal parameters were refined for all non-hydrogen atoms, and the hydrogens were refined with riding constraints. A modified statistical weighting scheme was applied. Refinement converged satisfactorily to give **R = 0.0916**, **wR = 0.1674**.

Attached is a thermal ellipsoid plot (CAMERON) at 50% probability. A summary of crystallographic data is given below, as are full lists of atomic coordinates, anisotropic thermal parameters and those bond lengths and angles not concerning H atoms.

References

- (1) Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, 276, 307.
- (2) A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr.* **1994**, 27, 435.
- (3) P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout, D. J. Watkin, *J. Appl. Crystallogr.* **2003**, 36, 1487.

Crystal identification	CCK 0300209
Chemical formula	C ₂₂ H ₂₈ N ₄ O ₄
Formula weight	412.49
Temperature (K)	293
Wavelength (Å)	0.71073
Crystal system	Triclinic
Space group	P -1
<i>a</i> (Å)	9.3933(3)
<i>b</i> (Å)	10.5472(3)
<i>c</i> (Å)	11.1850(3)
α (°)	89.9798(14)
β (°)	90.0100(14)
γ (°)	102.5009(12)
Cell volume (Å ³)	1081.86(5)
<i>Z</i>	2
Calculated density (Mg/m ³)	1.266
Absorption coefficient (mm ⁻¹)	0.089
<i>F</i> ₀₀₀	440
Crystal size (mm)	0.20 × 0.20 × 0.20
Description of crystal	Colourless block
Absorption correction	multi-scan
Transmission coefficients (min,max)	0.98, 0.99
θ range for data collection (°)	5.24 ≤ θ ≤ 27.52
Index ranges	-12 ≤ <i>h</i> ≤ 12, -13 ≤ <i>k</i> ≤ 13, -14 ≤ <i>l</i> ≤ 14
Reflections measured	8878
Unique reflections	4916
<i>R</i> _{int}	0.051
Observed reflections (<i>I</i> > -3 σ (<i>I</i>))	3741
Refinement method	Full-matrix least-squares on <i>Fsqd</i>
Parameters refined	272
Weighting scheme	Modified Sheldrick
Goodness of fit	0.9946
<i>R</i>	0.0916
<i>wR</i>	0.1674
Residual electron density (min,max) (eÅ ⁻³)	-0.40, 0.52

Table 1: Crystal data and refinement details

Atom	x	y	z	<i>U</i> _{equiv}
O(1)	0.3468(3)	1.0040(2)	0.43232(19)	0.0430
N(2)	0.4380(3)	1.0295(3)	0.3309(2)	0.0342
C(3)	0.5394(4)	1.1470(3)	0.3378(3)	0.0333
O(4)	0.6032(3)	1.1923(2)	0.4304(2)	0.0418
N(5)	0.5608(3)	1.1976(3)	0.2276(2)	0.0357
C(6)	0.4743(4)	1.1110(4)	0.1403(3)	0.0425
C(7)	0.3542(4)	1.0309(4)	0.2196(3)	0.0398
C(8)	0.2854(5)	0.8996(4)	0.1739(3)	0.0506
C(9)	0.6837(4)	1.3011(3)	0.1947(3)	0.0404
C(10)	0.8137(4)	1.2536(3)	0.1472(3)	0.0365
C(11)	0.9006(4)	1.3246(4)	0.0588(3)	0.0442
C(12)	1.0224(4)	1.2834(4)	0.0169(3)	0.0512
C(13)	1.0584(4)	1.1724(4)	0.0608(4)	0.0507
C(14)	0.9719(4)	1.1015(4)	0.1477(4)	0.0497
C(15)	0.8508(4)	1.1423(3)	0.1904(3)	0.0404
O(16)	0.6031(3)	0.6921(2)	0.0698(2)	0.0416
C(17)	0.5397(4)	0.6465(3)	0.1620(3)	0.0337
N(18)	0.4381(3)	0.5300(3)	0.1694(2)	0.0331
O(19)	0.3470(3)	0.5037(3)	0.0677(2)	0.0438
C(20)	0.3545(4)	0.5318(4)	0.2805(3)	0.0398

C(21)	0.4743(4)	0.6108(4)	0.3597(3)	0.0418
N(22)	0.5609(3)	0.6973(3)	0.2724(2)	0.0360
C(23)	0.6837(4)	0.8009(3)	0.3051(3)	0.0412
C(24)	0.8137(4)	0.7535(3)	0.3527(3)	0.0362
C(25)	0.9005(4)	0.8251(4)	0.4413(3)	0.0450
C(26)	1.0220(4)	0.7839(4)	0.4832(3)	0.0521
C(27)	1.0583(4)	0.6728(4)	0.4392(3)	0.0506
C(28)	0.9716(4)	0.6017(4)	0.3525(3)	0.0478
C(29)	0.8511(4)	0.6423(3)	0.3094(3)	0.0406
C(30)	0.2855(5)	0.3996(4)	0.3259(3)	0.0512

Table 2: Atomic coordinates and equivalent isotropic thermal parameters ($\text{\AA}^2$) of non-hydrogen atoms

Atom	x	y	z	U_{iso}
H(61)	0.4321	1.1572	0.0780	0.0546
H(62)	0.5354	1.0543	0.1052	0.0540
H(71)	0.2753	1.0820	0.2313	0.0492
H(81)	0.2318	0.9085	0.0997	0.0755
H(82)	0.2178	0.8533	0.2353	0.0754
H(83)	0.3626	0.8507	0.1575	0.0753
H(91)	0.7156	1.3541	0.2680	0.0509
H(92)	0.6493	1.3553	0.1314	0.0508
H(111)	0.8763	1.4013	0.0275	0.0544
H(121)	1.0809	1.3332	-0.0427	0.0615
H(131)	1.1425	1.1451	0.0305	0.0617
H(141)	0.9968	1.0232	0.1777	0.0629
H(151)	0.7901	1.0950	0.2517	0.0496
H(201)	0.2761	0.5824	0.2685	0.0489
H(212)	0.4324	0.6578	0.4221	0.0537
H(211)	0.5349	0.5532	0.3946	0.0529
H(231)	0.6479	0.8558	0.3668	0.0517
H(232)	0.7158	0.8522	0.2318	0.0518
H(251)	0.8769	0.9024	0.4726	0.0554
H(261)	1.0811	0.8339	0.5427	0.0625
H(271)	1.1419	0.6455	0.4698	0.0606
H(281)	0.9959	0.5230	0.3228	0.0599
H(291)	0.7905	0.5945	0.2482	0.0495
H(301)	0.2349	0.4098	0.4019	0.0764
H(303)	0.3638	0.3514	0.3400	0.0765
H(302)	0.2162	0.3548	0.2650	0.0764
H(11)	0.3704	0.9367	0.4627	0.0652
H(191)	0.3646	0.4353	0.0358	0.0661

Table 3: Atomic coordinates and isotropic thermal parameters ($\text{\AA}^2$) of hydrogen atoms

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(1)	0.0381(14)	0.0570(17)	0.0321(13)	0.0070(11)	0.0079(11)	0.0064(12)
N(2)	0.0318(16)	0.0456(18)	0.0226(14)	0.0027(12)	0.0026(12)	0.0031(14)
C(3)	0.0324(19)	0.038(2)	0.0300(19)	0.0001(15)	0.0022(15)	0.0093(16)
O(4)	0.0469(15)	0.0463(16)	0.0297(13)	-0.0073(11)	-0.0022(11)	0.0046(12)
N(5)	0.0394(17)	0.0359(17)	0.0301(16)	0.0006(12)	0.0007(13)	0.0045(13)
C(6)	0.047(2)	0.046(2)	0.0326(19)	0.0038(16)	-0.0099(16)	0.0056(18)
C(7)	0.039(2)	0.048(2)	0.0303(18)	0.0044(16)	-0.0061(16)	0.0058(17)
C(8)	0.054(2)	0.051(3)	0.044(2)	-0.0011(18)	-0.0093(19)	0.004(2)
C(9)	0.048(2)	0.032(2)	0.039(2)	0.0048(15)	0.0019(17)	0.0024(17)
C(10)	0.037(2)	0.036(2)	0.0303(18)	-0.0016(15)	-0.0012(15)	-0.0037(16)
C(11)	0.044(2)	0.042(2)	0.041(2)	0.0051(17)	-0.0018(17)	-0.0032(18)
C(12)	0.041(2)	0.064(3)	0.040(2)	0.0018(19)	0.0055(18)	-0.008(2)

C(13)	0.038(2)	0.060(3)	0.052(2)	-0.008(2)	0.0014(18)	0.004(2)
C(14)	0.048(2)	0.047(2)	0.055(2)	-0.0035(19)	-0.0010(19)	0.0098(19)
C(15)	0.043(2)	0.037(2)	0.039(2)	0.0045(16)	0.0033(17)	0.0037(17)
O(16)	0.0473(15)	0.0446(15)	0.0302(13)	0.0058(11)	0.0014(11)	0.0039(12)
C(17)	0.0343(19)	0.039(2)	0.0298(19)	0.0011(15)	-0.0015(15)	0.0124(16)
N(18)	0.0324(16)	0.0416(18)	0.0226(14)	-0.0031(12)	-0.0025(12)	0.0025(13)
O(19)	0.0388(14)	0.0586(17)	0.0328(13)	-0.0078(11)	-0.0097(11)	0.0077(12)
C(20)	0.041(2)	0.045(2)	0.0316(18)	-0.0041(16)	0.0065(16)	0.0066(17)
C(21)	0.050(2)	0.044(2)	0.0288(18)	-0.0055(16)	0.0080(16)	0.0045(18)
N(22)	0.0404(17)	0.0351(17)	0.0312(16)	-0.0002(12)	-0.0011(13)	0.0056(13)
C(23)	0.046(2)	0.034(2)	0.041(2)	-0.0050(16)	-0.0007(17)	0.0034(17)
C(24)	0.040(2)	0.034(2)	0.0302(18)	0.0031(15)	0.0001(15)	-0.0014(16)
C(25)	0.046(2)	0.042(2)	0.041(2)	-0.0049(17)	0.0011(18)	-0.0036(18)
C(26)	0.042(2)	0.066(3)	0.040(2)	-0.0031(19)	-0.0059(18)	-0.007(2)
C(27)	0.040(2)	0.059(3)	0.050(2)	0.009(2)	-0.0012(18)	0.004(2)
C(28)	0.044(2)	0.045(2)	0.054(2)	0.0037(19)	0.0010(19)	0.0092(19)
C(29)	0.040(2)	0.038(2)	0.042(2)	-0.0029(16)	-0.0024(16)	0.0027(17)
C(30)	0.053(2)	0.052(3)	0.045(2)	0.0015(18)	0.0084(19)	0.002(2)

Table 4: Anisotropic thermal parameters ($\text{\AA}^2$)

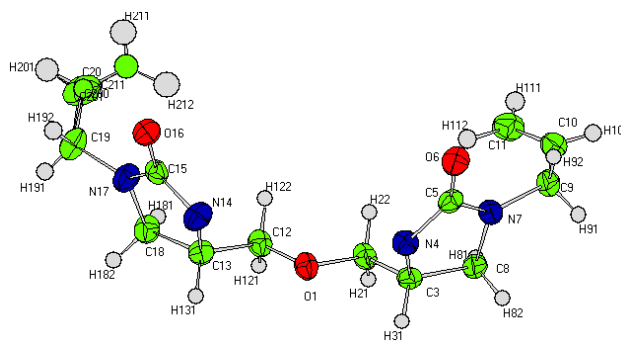
O(1) - N(2)	1.412(3)	O(16) - C(17)	1.236(4)
O(1) - H(11)	0.858	C(17) - N(18)	1.386(4)
N(2) - C(3)	1.393(4)	C(17) - N(22)	1.343(4)
N(2) - C(7)	1.474(4)	N(18) - O(19)	1.414(3)
C(3) - O(4)	1.239(4)	N(18) - C(20)	1.472(4)
C(3) - N(5)	1.341(4)	O(19) - H(191)	0.853
N(5) - C(6)	1.458(4)	C(20) - C(21)	1.530(5)
N(5) - C(9)	1.454(4)	C(20) - C(30)	1.493(5)
C(6) - C(7)	1.536(5)	C(21) - N(22)	1.458(4)
C(7) - C(8)	1.487(5)	N(22) - C(23)	1.453(4)
C(9) - C(10)	1.513(5)	C(23) - C(24)	1.513(5)
C(10) - C(11)	1.393(5)	C(24) - C(25)	1.396(5)
C(10) - C(15)	1.382(5)	C(24) - C(29)	1.383(5)
C(11) - C(12)	1.390(6)	C(25) - C(26)	1.388(6)
C(12) - C(13)	1.378(6)	C(26) - C(27)	1.379(6)
C(13) - C(14)	1.378(5)	C(27) - C(28)	1.379(5)
C(14) - C(15)	1.386(5)	C(28) - C(29)	1.381(5)

Table 5: Bond lengths ($\text{\AA}$) Note – C-H atoms have been excluded

O(1) - N(2) - C(3)	113.2(2)	O(16) - C(17) - N(18)	125.2(3)
O(1) - N(2) - C(7)	112.2(3)	O(16) - C(17) - N(22)	126.5(3)
C(3) - N(2) - C(7)	107.6(3)	N(18) - C(17) - N(22)	108.3(3)
N(2) - C(3) - O(4)	124.8(3)	C(17) - N(18) - O(19)	113.4(2)
N(2) - C(3) - N(5)	108.5(3)	C(17) - N(18) - C(20)	107.8(3)
O(4) - C(3) - N(5)	126.6(3)	O(19) - N(18) - C(20)	112.3(3)
C(3) - N(5) - C(6)	110.6(3)	N(18) - C(20) - C(21)	99.4(3)
C(3) - N(5) - C(9)	123.9(3)	N(18) - C(20) - C(30)	113.6(3)
C(6) - N(5) - C(9)	123.0(3)	C(21) - C(20) - C(30)	115.5(3)
N(5) - C(6) - C(7)	101.6(3)	C(20) - C(21) - N(22)	101.4(3)
C(6) - C(7) - N(2)	99.4(3)	C(21) - N(22) - C(17)	110.6(3)
C(6) - C(7) - C(8)	115.6(3)	C(21) - N(22) - C(23)	123.1(3)
N(2) - C(7) - C(8)	114.0(3)	C(17) - N(22) - C(23)	123.8(3)
N(5) - C(9) - C(10)	114.0(3)	N(22) - C(23) - C(24)	113.9(3)
C(9) - C(10) - C(11)	119.5(3)	C(23) - C(24) - C(25)	119.3(3)
C(9) - C(10) - C(15)	121.9(3)	C(23) - C(24) - C(29)	121.9(3)
C(11) - C(10) - C(15)	118.6(3)	C(25) - C(24) - C(29)	118.8(3)
C(10) - C(11) - C(12)	119.8(4)	C(24) - C(25) - C(26)	119.6(4)
C(11) - C(12) - C(13)	121.0(4)	C(25) - C(26) - C(27)	121.1(4)

C(12) - C(13) - C14	119.2(4)	C(26) - C(27) - C(28)	119.2(4)
C(13) - C14 - C(15)	120.1(4)	C(27) - C(28) - C(29)	120.2(4)
C14 - C(15) - C(10)	121.2(3)	C(24) - C(29) - C(28)	121.1(3)

* **Table 6: Bond angles (° C)** Note – H atoms have been excluded

Single-crystal X-ray diffraction report for compound **231** (Datablock: 0550510)

Crystal of **231** were grown and run by Callens Cédric from dichloromethane and petrol 40-60 °C. A single crystal having dimensions approximately **0.16 x 0.18 x 0.20 mm** was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150 K in a stream of cold N₂ using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoK_α radiation, $\lambda = 0.71073$ Å). Intensity data were processed using the DENZO-SMN package.¹

Examination of the systematic absences of the intensity data showed the space group to be **P -1**. The structure was solved in this space group using the direct-methods program SIR92,² which located all non-hydrogen atoms. The H atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. Subsequent full-matrix least-squares refinement was carried out against F² using the CRYSTAL program suite.³ Coordinates and anisotropic thermal parameters were refined for all non-hydrogen atoms, and the hydrogens were refined with riding constraints. A modified statistical weighting scheme was applied. Refinement converged satisfactorily to give **R = 0.0687**, **wR = 0.1203**.

Attached is a thermal ellipsoid plot (CAMERON) at 50% probability. A summary of crystallographic data is given below, as are full lists of atomic coordinates, anisotropic thermal parameters and those bond lengths and angles not concerning H atoms.

References

- (1) Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, 276, 307.
- (2) A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr.* **1994**, 27, 435.
- (3) P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout, D. J. Watkin, *J. Appl. Crystallogr.* **2003**, 36, 1487.

Crystal identification	CCK 0550510
Chemical formula	C ₁₄ H ₂₀ N ₄ O ₃
Formula weight	292.34
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Triclinic
Space group	P -1
<i>a</i> (Å)	8.9148(2)
<i>b</i> (Å)	8.9148(2)
<i>c</i> (Å)	10.8120(3)
α (°)	70.6891(12)
β (°)	66.5632(11)
γ (°)	76.5531(15)
Cell volume (Å ³)	755.69(4)
<i>Z</i>	2
Calculated density (Mg/m ³)	1.285
Absorption coefficient (mm ⁻¹)	0.092
<i>F</i> ₀₀₀	312
Crystal size (mm)	0.16 × 0.18 × 0.20
Description of crystal	Colourless block
Absorption correction	multi-scan
Transmission coefficients (min,max)	0.92, 0.99
θ range for data collection (°)	5.11 ≤ θ ≤ 27.48
Index ranges	-11 ≤ <i>h</i> ≤ 10, -11 ≤ <i>k</i> ≤ 11, -14 ≤ <i>l</i> ≤ 14
Reflections measured	5838
Unique reflections	3442
<i>R</i> _{int}	0.022
Observed reflections (<i>I</i> > -3 σ (<i>I</i>))	2440
Refinement method	Full-matrix least-squares on <i>Fsqd</i>
Parameters refined	191
Weighting scheme	Modified Sheldrick
Goodness of fit	0.9891
<i>R</i>	0.0687
<i>wR</i>	0.1203
Residual electron density (min,max) (eÅ ⁻³)	-0.44, 1.07

Table 1: Crystal data and refinement details

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{equiv}
O(1)	0.4951(2)	0.2632(2)	0.86752(17)	0.0333
C(2)	0.3586(3)	0.2400(3)	0.9949(3)	0.0326
C(3)	0.2715(3)	0.1134(3)	0.9998(3)	0.0310
N(4)	0.2057(3)	0.1603(3)	0.8859(2)	0.0325
C(5)	0.0399(3)	0.2068(3)	0.9342(3)	0.0290
O(6)	-0.0462(2)	0.2683(2)	0.86125(19)	0.0398
N(7)	-0.0143(2)	0.1711(2)	1.0767(2)	0.0313
C(8)	0.1150(3)	0.0859(3)	1.1312(3)	0.0328
C(9)	-0.1857(3)	0.1813(3)	1.1645(3)	0.0349
C(10)	-0.2324(3)	0.2996(3)	1.2461(3)	0.0385
C(11)	-0.1439(4)	0.4100(3)	1.2204(3)	0.0472
C(12)	0.5809(3)	0.3885(3)	0.8462(3)	0.0326
C(13)	0.7136(3)	0.4071(3)	0.7037(3)	0.0313
N(14)	0.6451(3)	0.4556(3)	0.5917(2)	0.0374
C(15)	0.6732(3)	0.6032(3)	0.5125(2)	0.0293
O(16)	0.6202(2)	0.6781(2)	0.41626(18)	0.0355
N(17)	0.7709(3)	0.6562(3)	0.5543(2)	0.0380
C(18)	0.8155(3)	0.5405(3)	0.6668(3)	0.0363
C(19)	0.8460(4)	0.7991(3)	0.4797(3)	0.0420
C(20)	0.7626(5)	0.9382(4)	0.5343(4)	0.0624

C(21)	0.6272(6)	0.9524(5)	0.6269(5)	0.0815
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Table 2: Atomic coordinates and equivalent isotropic thermal parameters ($\text{\AA}^2$) of non-hydrogen atoms

Atom	x	y	z	U_{iso}
H(21)	0.3990	0.2073	1.0748	0.0412
H(22)	0.2831	0.3400	0.9974	0.0407
H(31)	0.3491	0.0140	0.9947	0.0386
H(81)	0.1161	0.1315	1.2032	0.0402
H(82)	0.0969	-0.0265	1.1725	0.0408
H(91)	-0.2074	0.0760	1.2297	0.0420
H(92)	-0.2520	0.2091	1.1037	0.0430
H(101)	-0.3361	0.2913	1.3228	0.0491
H(111)	-0.1828	0.4813	1.2785	0.0601
H(112)	-0.0396	0.4152	1.1434	0.0594
H(121)	0.6322	0.3614	0.9197	0.0399
H(122)	0.5048	0.4886	0.8483	0.0404
H(131)	0.7874	0.3050	0.7026	0.0386
H(181)	0.7873	0.5835	0.7475	0.0457
H(182)	0.9362	0.5035	0.6331	0.0456
H(191)	0.9586	0.7770	0.4837	0.0529
H(192)	0.8555	0.8234	0.3817	0.0524
H(201)	0.8163	1.0304	0.4979	0.0795
H(211)	0.5987	1.0547	0.6459	0.0992
H(212)	0.5635	0.8621	0.6717	0.0993

Table 3: Atomic coordinates and isotropic thermal parameters ($\text{\AA}^2$) of hydrogen atoms

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(1)	0.0295(9)	0.0403(10)	0.0277(9)	-0.0084(8)	-0.0068(7)	-0.0064(8)
C(2)	0.0269(13)	0.0428(15)	0.0268(13)	-0.0071(11)	-0.0097(10)	-0.0040(11)
C(3)	0.0299(13)	0.0305(13)	0.0291(13)	-0.0042(10)	-0.0120(11)	0.0003(10)
N(4)	0.0340(11)	0.0356(12)	0.0301(11)	-0.0087(9)	-0.0142(9)	-0.0026(9)
C(5)	0.0344(14)	0.0242(12)	0.0319(13)	-0.0043(10)	-0.0163(11)	-0.0061(10)
O(6)	0.0403(11)	0.0461(11)	0.0372(11)	-0.0017(8)	-0.0228(9)	-0.0096(8)
N(7)	0.0290(11)	0.0365(12)	0.0270(11)	-0.0049(9)	-0.0120(9)	-0.0022(9)
C(8)	0.0314(13)	0.0339(14)	0.0303(14)	-0.0020(11)	-0.0131(11)	-0.0041(11)
C(9)	0.0271(13)	0.0379(14)	0.0373(14)	-0.0059(11)	-0.0103(11)	-0.0068(11)
C(10)	0.0341(14)	0.0381(15)	0.0356(15)	-0.0077(12)	-0.0089(12)	0.0010(12)
C(11)	0.0492(18)	0.0395(16)	0.0517(18)	-0.0178(14)	-0.0155(15)	0.0015(13)
C(12)	0.0284(13)	0.0404(14)	0.0312(14)	-0.0082(11)	-0.0125(11)	-0.0062(11)
C(13)	0.0325(13)	0.0352(14)	0.0274(13)	-0.0052(10)	-0.0149(11)	-0.0030(11)
N(14)	0.0488(14)	0.0385(12)	0.0288(12)	-0.0001(9)	-0.0223(10)	-0.0095(10)
C(15)	0.0256(12)	0.0354(13)	0.0227(12)	-0.0081(10)	-0.0055(10)	-0.0007(10)
O(16)	0.0406(10)	0.0384(10)	0.0269(9)	-0.0031(8)	-0.0162(8)	-0.0033(8)
N(17)	0.0419(13)	0.0378(12)	0.0370(13)	0.0008(10)	-0.0210(10)	-0.0122(10)
C(18)	0.0367(14)	0.0420(15)	0.0304(14)	-0.0033(12)	-0.0150(11)	-0.0083(12)
C(19)	0.0543(18)	0.0396(15)	0.0316(15)	-0.0042(12)	-0.0126(13)	-0.0169(13)
C(20)	0.086(3)	0.0474(19)	0.0427(19)	-0.0025(15)	-0.0242(19)	0.0015(18)
C(21)	0.080(3)	0.070(3)	0.087(3)	-0.018(2)	-0.038(3)	0.017(2)

Table 4: Anisotropic thermal parameters ($\text{\AA}^2$)

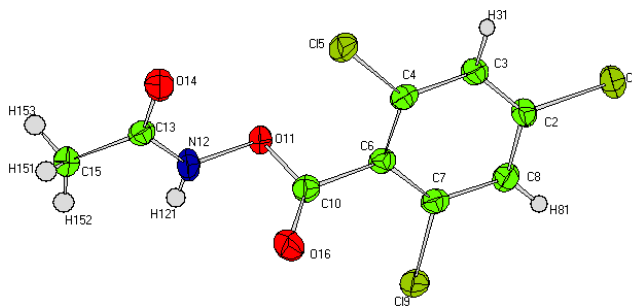
O(1) - C(2)	1.420(3)	C(10) - C(11)	1.312(4)
O(1) - C(12)	1.426(3)	C(12) - C(13)	1.507(3)
C(2) - C(3)	1.510(4)	C(13) - N(14)	1.464(3)
C(3) - N(4)	1.467(3)	C(13) - C(18)	1.540(4)

C(3) - C(8)	1.542(3)	N(14) - C(15)	1.353(3)
N(4) - C(5)	1.370(3)	C(15) - O(16)	1.242(3)
C(5) - O(6)	1.231(3)	C(15) - N(17)	1.360(3)
C(5) - N(7)	1.365(3)	N(17) - C(18)	1.447(3)
N(7) - C(8)	1.450(3)	N(17) - C(19)	1.442(3)
N(7) - C(9)	1.443(3)	C(19) - C(20)	1.489(4)
C(9) - C(10)	1.497(4)	C(20) - C(21)	1.235(5)

Table 5: Bond lengths (Å) Note – C-H atoms have been excluded

C(2) - O(1) - C(12)	112.79(19)	O(1) - C(12) - C(13)	106.9(2)
O(1) - C(2) - C(3)	107.5(2)	C(12) - C(13) - N(14)	112.0(2)
C(2) - C(3) - N(4)	111.8(2)	C(12) - C(13) - C(18)	112.2(2)
C(2) - C(3) - C(8)	111.4(2)	N(14) - C(13) - C(18)	102.8(2)
N(4) - C(3) - C(8)	102.5(2)	C(13) - N(14) - C(15)	111.9(2)
C(3) - N(4) - C(5)	110.5(2)	N(14) - C(15) - O(16)	125.9(2)
N(4) - C(5) - O(6)	125.7(2)	N(14) - C(15) - N(17)	108.9(2)
N(4) - C(5) - N(7)	108.7(2)	O(16) - C(15) - N(17)	125.3(2)
O(6) - C(5) - N(7)	125.7(2)	C(15) - N(17) - C(18)	112.3(2)
C(5) - N(7) - C(8)	111.9(2)	C(15) - N(17) - C(19)	124.0(2)
C(5) - N(7) - C(9)	124.1(2)	C(18) - N(17) - C(19)	122.8(2)
C(8) - N(7) - C(9)	122.4(2)	C(13) - C(18) - N(17)	103.3(2)
C(3) - C(8) - N(7)	102.42(19)	N(17) - C(19) - C(20)	116.6(3)
N(7) - C(9) - C(10)	113.3(2)	C(19) - C(20) - C(21)	128.3(4)
C(9) - C(10) - C11	125.1(3)	-	-

Table 6: Bond angles (° C) Note – H atoms have been excluded

Single-crystal X-ray diffraction report for compound **247** (Datablock: 0370609)

Crystal of **247** were grown and run by Callens Cédric from dichloromethane and petrol 40-60 °C. A single crystal having dimensions approximately **0.08 x 0.10 x 0.14 mm** was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150 K in a stream of cold N₂ using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoK α radiation, $\lambda = 0.71073$ Å). Intensity data were processed using the DENZO-SMN package.¹

Examination of the systematic absences of the intensity data showed the space group to be **P 2₁**. The structure was solved in this space group using the direct-methods program SIR92,² which located all non-hydrogen atoms. The H atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. Subsequent full-matrix least-squares refinement was carried out against F² using the CRYSTAL program suite.³ Coordinates and anisotropic thermal parameters were refined for all non-hydrogen atoms, and the hydrogens were refined with riding constraints. A modified statistical weighting scheme was applied. Refinement converged satisfactorily to give **R = 0.0514**, **wR = 0.0800**.

Attached is a thermal ellipsoid plot (CAMERON) at 50% probability. A summary of crystallographic data is given below, as are full lists of atomic coordinates, anisotropic thermal parameters and those bond lengths and angles not concerning H atoms.

References

- (1) Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, 276, 307.
- (2) A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr.* **1994**, 27, 435.
- (3) P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout, D. J. Watkin, *J. Appl. Crystallogr.* **2003**, 36, 1487.

Crystal identification	CCK 0370609
Chemical formula	C ₉ H ₆ Cl ₃ N ₁ O ₃
Formula weight	282.51
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	P 2/n
<i>a</i> (Å)	3.93520(10)
<i>b</i> (Å)	33.1639(6)
<i>c</i> (Å)	8.3121(2)
α (°)	90
β (°)	92.2252(8)
γ (°)	90
Cell volume (Å ³)	1083.97(4)
<i>Z</i>	4
Calculated density (Mg/m ³)	1.731
Absorption coefficient (mm ⁻¹)	0.833
<i>F</i> ₀₀₀	568
Crystal size (mm)	0.16 × 0.18 × 0.20
Description of crystal	Colourless plate
Absorption correction	multi-scan
Transmission coefficients (min,max)	0.88, 0.94
θ range for data collection (°)	5.21 ≤ θ ≤ 27.50
Index ranges	-5 ≤ <i>h</i> ≤ 5, -38 ≤ <i>k</i> ≤ 43, -10 ≤ <i>l</i> ≤ 10
Reflections measured	12943
Unique reflections	2462
<i>R</i> _{int}	0.030
Observed reflections (<i>I</i> > -3 σ (<i>I</i>))	2462
Refinement method	Full-matrix least-squares on <i>Fsqd</i>
Parameters refined	145
Weighting scheme	Modified Sheldrick
Goodness of fit	0.9749
<i>R</i>	0.0514
<i>wR</i>	0.0800
Residual electron density (min,max) (eÅ ⁻³)	-0.42, 0.38

Table 1: Crystal data and refinement details

Atom	x	y	z	U _{equiv}
Cl(1)	0.31821(15)	0.489957(16)	0.78506(7)	0.0364
C(2)	0.1898(5)	0.53859(6)	0.7328(2)	0.0270
C(3)	0.0682(5)	0.56367(6)	0.8502(2)	0.0277
C(4)	-0.0290(5)	0.60263(6)	0.8062(2)	0.0261
Cl(5)	-0.19743(15)	0.633177(16)	0.95165(6)	0.0332
C(6)	-0.0038(5)	0.61686(6)	0.6489(2)	0.0242
C(7)	0.1112(5)	0.58976(6)	0.5340(2)	0.0262
C(8)	0.2104(5)	0.55077(6)	0.5747(3)	0.0287
Cl(9)	0.13680(15)	0.603697(16)	0.33415(6)	0.0339
C(10)	-0.1067(5)	0.65877(6)	0.6002(2)	0.0268
O(11)	0.0860(4)	0.68621(4)	0.68431(17)	0.0294
N(12)	0.0071(5)	0.72610(5)	0.6376(2)	0.0342
C(13)	-0.1554(5)	0.74928(6)	0.7409(2)	0.0260
O(14)	-0.2502(4)	0.73689(4)	0.87104(18)	0.0363
C(15)	-0.2134(6)	0.79149(6)	0.6819(3)	0.0297
O(16)		0.66697(5)	0.4992(2)	0.0429

Table 2: Atomic coordinates and equivalent isotropic thermal parameters ($\text{\AA}^2$) of non-hydrogen atoms

Atom	x	y	z	U_{iso}
H(31)	0.0437	0.5547	0.9572	0.0324
H(81)	0.2866	0.5334	0.4963	0.0350
H(151)	-0.4445	0.7992	0.6943	0.0474
H(153)	-0.0760	0.8098	0.7437	0.0455
H(152)	-0.1609	0.7943	0.5732	0.0463
H(121)	0.0733	0.7344	0.5465	0.0416

Table 3: Atomic coordinates and isotropic thermal parameters ($\text{\AA}^2$) of hydrogen atoms

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Cl(1)	0.0483(4)	0.0248(3)	0.0361(3)	0.0040(2)	0.0027(3)	0.0055(2)
C(2)	0.0302(12)	0.0219(10)	0.0289(11)	0.0027(8)	0.0004(9)	-0.0012(9)
C(3)	0.0334(12)	0.0257(11)	0.0240(10)	0.0026(8)	0.0016(9)	-0.0058(9)
C(4)	0.0286(11)	0.0273(11)	0.0225(10)	-0.0030(8)	0.0011(9)	-0.0039(9)
Cl(5)	0.0454(3)	0.0300(3)	0.0246(3)	-0.0041(2)	0.0069(2)	0.0014(2)
C(6)	0.0241(11)	0.0248(10)	0.0236(10)	-0.0008(8)	-0.0012(8)	-0.0029(8)
C(7)	0.0280(11)	0.0281(11)	0.0224(10)	-0.0003(8)	-0.0007(9)	-0.0048(9)
C(8)	0.0331(12)	0.0255(11)	0.0275(11)	-0.0032(9)	0.0025(9)	-0.0008(9)
Cl(9)	0.0505(4)	0.0299(3)	0.0216(3)	0.0003(2)	0.0049(2)	-0.0019(2)
C(10)	0.0305(12)	0.0266(11)	0.0235(10)	-0.0003(8)	0.0044(9)	0.0000(9)
O(11)	0.0402(9)	0.0189(7)	0.0290(8)	0.0000(6)	-0.0003(7)	0.0009(6)
N(12)	0.0578(13)	0.0183(9)	0.0273(9)	0.0023(7)	0.0133(9)	0.0047(8)
C(13)	0.0287(11)	0.0259(11)	0.0231(10)	-0.0020(8)	-0.0006(9)	-0.0029(9)
O(14)	0.0516(10)	0.0307(9)	0.0277(8)	0.0021(7)	0.0132(7)	0.0015(7)
C(15)	0.0324(12)	0.0253(11)	0.0314(11)	-0.0010(9)	0.0011(9)	0.0022(9)
O(16)	0.0477(10)	0.0342(9)	0.0454(10)	0.0025(8)	-0.0162(8)	0.0057(8)

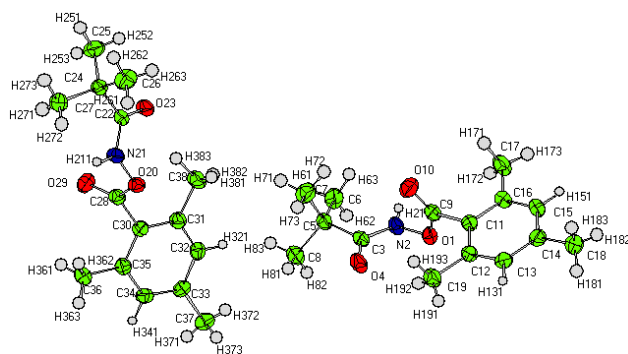
Table 4: Anisotropic thermal parameters ($\text{\AA}^2$)

Cl(1) - C(2)	1.740(2)	C(7) - Cl(9)	1.731(2)
C(2) - C(3)	1.382(3)	C(10) - O(11)	1.361(2)
C(2) - C(8)	1.380(3)	C(10) - O(16)	1.188(2)
C(3) - C(4)	1.392(3)	O(11) - N(12)	1.409(2)
C(4) - Cl(5)	1.729(2)	N(12) - C(13)	1.334(3)
C(4) - C(6)	1.397(3)	N(12) - H(121)	0.856
C(6) - C(7)	1.399(3)	C(13) - O(14)	1.229(2)
C(6) - C(10)	1.499(3)	C(13) - C(15)	1.498(3)
C(7) - C(8)	1.389(3)	/	

Table 5: Bond lengths ($\text{\AA}$) Note – C-H atoms have been excluded

Cl(1) - C(2) - C(3)	119.12(15)	C(6) - C(7) - Cl(9)	121.05(16)
Cl(1) - C(2) - C(8)	118.81(16)	C(8) - C(7) - Cl(9)	117.14(16)
C(3) - C(2) - C(8)	122.06(19)	C(7) - C(8) - C(2)	118.57(19)
C(2) - C(3) - C(4)	118.19(19)	C(6) - C(10) - O(11)	109.99(17)
C(3) - C(4) - Cl(5)	117.98(16)	C(6) - C(10) - O(16)	125.22(19)
C(3) - C(4) - C(6)	122.02(19)	O(11) - C(10) - O(16)	124.74(19)
Cl(5) - C(4) - C(6)	119.97(16)	C(10) - O(11) - N(12)	111.95(15)
C(4) - C(6) - C(7)	117.29(18)	O(11) - N(12) - C(13)	118.01(17)
C(4) - C(6) - C(10)	122.51(18)	N(12) - C(13) - O(14)	122.92(19)
C(7) - C(6) - C(10)	120.16(17)	N(12) - C(13) - C(15)	113.49(18)
C(6) - C(7) - C(8)	121.80(18)	O(14) - C(13) - C(15)	123.59(19)

Table 6: Bond angles ($^\circ$ C) Note – H atoms have been excluded

Single-crystal X-ray diffraction report for compound **259** (Datablock: 0270209)

Crystal of **259** were grown and run by Callens Cédric from dichloromethane and petrol 40-60 °C. A single crystal having dimensions approximately **0.18 x 0.22 x 0.50 mm** was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150 K in a stream of cold N₂ using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoK α radiation, $\lambda = 0.71073$ Å). Intensity data were processed using the DENZO-SMN package.¹

Examination of the systematic absences of the intensity data showed the space group to be **P -1**. The structure was solved in this space group using the direct-methods program SIR92,² which located all non-hydrogen atoms. The H atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. Subsequent full-matrix least-squares refinement was carried out against F² using the CRYSTAL program suite.³ Coordinates and anisotropic thermal parameters were refined for all non-hydrogen atoms, and the hydrogens were refined with riding constraints. A modified statistical weighting scheme was applied. Refinement converged satisfactorily to give **R = 0.0876**, **wR = 0.1380**.

Attached is a thermal ellipsoid plot (CAMERON) at 50% probability. A summary of crystallographic data is given below, as are full lists of atomic coordinates, anisotropic thermal parameters and those bond lengths and angles not concerning H atoms.

References

- (1) Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, 276, 307.
- (2) A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr.* **1994**, 27, 435.
- (3) P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout, D. J. Watkin, *J. Appl. Crystallogr.* **2003**, 36, 1487.

Crystal identification	CCK 0270209
Chemical formula	C ₁₅ H ₂₁ N ₁ O ₃
Formula weight	263.34
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Triclinic
Space group	P -1
<i>a</i> (Å)	9.0141(2)
<i>b</i> (Å)	9.9620(2)
<i>c</i> (Å)	17.7080(3)
α (°)	74.1500(7)
β (°)	83.7142(7)
γ (°)	83.6747(7)
Cell volume (Å ³)	1515.13(5)
<i>Z</i>	4
Calculated density (Mg/m ³)	1.154
Absorption coefficient (mm ⁻¹)	0.080
<i>F</i> ₀₀₀	568
Crystal size (mm)	0.16 × 0.18 × 0.20
Description of crystal	Colourless plate
Absorption correction	multi-scan
Transmission coefficients (min,max)	0.97, 0.99
θ range for data collection (°)	5.13 ≤ θ ≤ 27.50
Index ranges	-11 ≤ <i>h</i> ≤ 11, -12 ≤ <i>k</i> ≤ 12, 0 ≤ <i>l</i> ≤ 22
Reflections measured	6892
Unique reflections	6892
<i>R</i> _{int}	0.026
Observed reflections (<i>I</i> > 3 σ (<i>I</i>))	6887
Refinement method	Full-matrix least-squares on <i>Fsqd</i>
Parameters refined	344
Weighting scheme	Modified Sheldrick
Goodness of fit	0.9280
<i>R</i>	0.0876
<i>wR</i>	0.1380
Residual electron density (min,max) (eÅ ⁻³)	-0.46, 0.38

Table 1: Crystal data and refinement details

Atom	x	y	z	<i>U</i> _{equiv}
O(1)	0.92139(12)	0.10175(11)	0.16241(6)	0.0316
N(2)	1.04410(15)	0.06272(14)	0.20928(8)	0.0322
C(3)	1.08081(18)	0.15817(16)	0.24362(10)	0.0304
O(4)	1.02631(14)	0.27985(12)	0.22466(8)	0.0419
C(5)	1.19153(19)	0.10614(17)	0.30659(10)	0.0324
C(6)	1.2679(2)	-0.03987(19)	0.30830(12)	0.0454
C(7)	1.1005(2)	0.1019(2)	0.38550(11)	0.0497
C(8)	1.3098(2)	0.2114(2)	0.29162(12)	0.0438
C(9)	0.78601(19)	0.09703(17)	0.20759(10)	0.0324
O(10)	0.77586(15)	0.06571(15)	0.27769(7)	0.0478
C(11)	0.66047(18)	0.13308(17)	0.15516(9)	0.0307
C(12)	0.60759(19)	0.27261(17)	0.12495(9)	0.0318
C(13)	0.48422(19)	0.29942(18)	0.08067(10)	0.0346
C(14)	0.41417(19)	0.19233(19)	0.06621(10)	0.0362
C(15)	0.4718(2)	0.05527(19)	0.09613(10)	0.0384
C(16)	0.59356(19)	0.02204(17)	0.14156(10)	0.0344
C(17)	0.6495(2)	-0.12790(19)	0.17794(13)	0.0465
C(18)	0.2767(2)	0.2236(2)	0.02070(12)	0.0481
C(19)	0.6778(2)	0.38971(19)	0.14265(12)	0.0439
O(20)	1.00641(12)	0.48007(11)	0.67821(6)	0.0312

N(21)	0.94765(16)	0.45697(14)	0.75713(8)	0.0328
C(22)	0.92718(17)	0.32514(16)	0.79873(9)	0.0274
O(23)	0.95509(14)	0.22647(11)	0.76892(7)	0.0361
C(24)	0.85528(19)	0.30968(17)	0.88278(10)	0.0312
C(25)	0.8974(2)	0.1622(2)	0.93272(11)	0.0473
C(26)	0.6856(2)	0.3306(2)	0.87619(12)	0.0501
C(27)	0.9034(3)	0.4166(2)	0.92093(11)	0.0508
C(28)	1.16149(19)	0.46788(16)	0.67056(10)	0.0306
O(29)	1.23430(14)	0.44050(14)	0.72584(7)	0.0428
C(30)	1.21571(18)	0.49746(16)	0.58570(9)	0.0291
C(31)	1.18785(19)	0.40843(17)	0.54052(10)	0.0328
C(32)	1.24423(19)	0.43855(18)	0.46226(10)	0.0342
C(33)	1.32531(18)	0.55406(17)	0.42750(10)	0.0326
C(34)	1.35124(19)	0.63987(17)	0.47399(10)	0.0332
C(35)	1.29774(18)	0.61410(17)	0.55290(10)	0.0318
C(36)	1.3272(2)	0.71258(19)	0.60017(11)	0.0438
C(37)	1.3807(2)	0.5870(2)	0.34173(10)	0.0409
C(38)	1.1000(2)	0.28128(19)	0.57463(11)	0.0457

Table 2: Atomic coordinates and equivalent isotropic thermal parameters ($\text{\AA}^2$) of non-hydrogen atoms

Atom	x	y	z	U_{iso}
H(61)	1.3410	-0.0629	0.3473	0.0678
H(62)	1.3186	-0.0373	0.2568	0.0675
H(63)	1.1948	-0.1096	0.3227	0.0677
H(71)	1.1694	0.0691	0.4275	0.0743
H(73)	1.0550	0.1958	0.3848	0.0738
H(72)	1.0223	0.0374	0.3932	0.0735
H(83)	1.3764	0.1829	0.3341	0.0669
H(82)	1.3688	0.2124	0.2412	0.0674
H(81)	1.2626	0.3039	0.2913	0.0667
H(131)	0.4463	0.3950	0.0597	0.0399
H(151)	0.4264	-0.0193	0.0856	0.0465
H(173)	0.6036	-0.1913	0.1561	0.0711
H(172)	0.7587	-0.1411	0.1673	0.0708
H(171)	0.6265	-0.1524	0.2348	0.0719
H(182)	0.2683	0.1499	-0.0038	0.0707
H(181)	0.2793	0.3094	-0.0196	0.0710
H(183)	0.1864	0.2262	0.0568	0.0712
H(191)	0.6467	0.4791	0.1067	0.0687
H(192)	0.7842	0.3752	0.1392	0.0689
H(193)	0.6427	0.3948	0.1951	0.0686
H(251)	0.8464	0.1497	0.9862	0.0673
H(253)	1.0062	0.1478	0.9356	0.0686
H(252)	0.8653	0.0931	0.9090	0.0674
H(262)	0.6320	0.3135	0.9288	0.0728
H(261)	0.6579	0.4267	0.8469	0.0728
H(263)	0.6531	0.2669	0.8488	0.0735
H(273)	0.8603	0.3958	0.9755	0.0785
H(271)	1.0119	0.4100	0.9194	0.0789
H(272)	0.8656	0.5108	0.8927	0.0779
H(321)	1.2257	0.3782	0.4307	0.0420
H(341)	1.4065	0.7198	0.4509	0.0380
H(363)	1.3555	0.7987	0.5657	0.0679
H(361)	1.4084	0.6709	0.6341	0.0678
H(362)	1.2390	0.7318	0.6332	0.0682
H(371)	1.4820	0.6169	0.3336	0.0613
H(372)	1.3837	0.5046	0.3213	0.0610
H(373)	1.3142	0.6606	0.3107	0.0609

H(382)	1.1342	0.2093	0.5476	0.0721
H(383)	1.1121	0.2427	0.6302	0.0719
H(381)	0.9928	0.3081	0.5685	0.0731
H(21)	1.0800	-0.0241	0.2205	0.0413
H(211)	0.9358	0.5271	0.7772	0.0403

Table 3: Atomic coordinates and isotropic thermal parameters ($\text{\AA}^2$) of hydrogen atoms

Atom	U₁₁	U₂₂	U₃₃	U₂₃	U₁₃	U₁₂
O(1)	0.0310(6)	0.0306(6)	0.0357(6)	-0.0125(5)	-0.0056(5)	-0.0015(5)
N(2)	0.0326(7)	0.0245(7)	0.0429(8)	-0.0128(6)	-0.0112(6)	0.0015(6)
C(3)	0.0330(9)	0.0239(8)	0.0362(9)	-0.0110(7)	-0.0006(7)	-0.0047(7)
O(4)	0.0478(8)	0.0220(6)	0.0603(8)	-0.0138(6)	-0.0182(6)	0.0000(5)
C(5)	0.0350(9)	0.0297(9)	0.0350(9)	-0.0112(7)	-0.0042(7)	-0.0051(7)
C(6)	0.0511(12)	0.0345(10)	0.0516(12)	-0.0108(8)	-0.0185(9)	0.0051(8)
C(7)	0.0512(12)	0.0601(13)	0.0384(11)	-0.0140(9)	0.0001(9)	-0.0082(10)
C(8)	0.0424(11)	0.0401(10)	0.0517(11)	-0.0118(9)	-0.0088(9)	-0.0113(8)
C(9)	0.0352(9)	0.0265(8)	0.0371(10)	-0.0111(7)	-0.0022(7)	-0.0039(7)
O(10)	0.0446(8)	0.0652(9)	0.0328(7)	-0.0097(6)	-0.0039(6)	-0.0087(7)
C(11)	0.0302(9)	0.0328(9)	0.0298(8)	-0.0099(7)	0.0005(7)	-0.0048(7)
C(12)	0.0340(9)	0.0314(9)	0.0305(9)	-0.0091(7)	-0.0006(7)	-0.0045(7)
C(13)	0.0397(10)	0.0313(9)	0.0307(9)	-0.0056(7)	-0.0009(7)	-0.0025(7)
C(14)	0.0346(9)	0.0401(10)	0.0330(9)	-0.0068(8)	-0.0045(7)	-0.0050(8)
C(15)	0.0379(10)	0.0376(10)	0.0430(10)	-0.0124(8)	-0.0065(8)	-0.0101(8)
C(16)	0.0343(9)	0.0313(9)	0.0381(9)	-0.0095(7)	-0.0015(7)	-0.0055(7)
C(17)	0.0455(11)	0.0331(10)	0.0643(13)	-0.0141(9)	-0.0150(10)	-0.0047(8)
C(18)	0.0474(11)	0.0483(11)	0.0473(11)	-0.0039(9)	-0.0166(9)	-0.0083(9)
C(19)	0.0523(12)	0.0322(9)	0.0505(11)	-0.0126(8)	-0.0118(9)	-0.0058(8)
O(20)	0.0362(7)	0.0282(6)	0.0285(6)	-0.0077(5)	0.0025(5)	-0.0041(5)
N(21)	0.0443(8)	0.0250(7)	0.0300(7)	-0.0118(6)	0.0084(6)	-0.0071(6)
C(22)	0.0269(8)	0.0241(8)	0.0324(8)	-0.0087(7)	-0.0034(6)	-0.0036(6)
O(23)	0.0495(7)	0.0238(6)	0.0375(7)	-0.0133(5)	0.0014(5)	-0.0055(5)
C(24)	0.0362(9)	0.0278(8)	0.0305(8)	-0.0090(7)	-0.0005(7)	-0.0054(7)
C(25)	0.0641(13)	0.0371(10)	0.0363(10)	-0.0044(8)	-0.0003(9)	-0.0032(9)
C(26)	0.0385(11)	0.0670(14)	0.0413(11)	-0.0123(10)	0.0070(9)	-0.0046(10)
C(27)	0.0778(15)	0.0448(11)	0.0352(10)	-0.0164(9)	0.0016(10)	-0.0195(10)
C(28)	0.0349(9)	0.0250(8)	0.0326(9)	-0.0094(7)	-0.0009(7)	-0.0030(7)
O(29)	0.0423(7)	0.0527(8)	0.0329(7)	-0.0094(6)	-0.0057(6)	-0.0038(6)
C(30)	0.0299(8)	0.0279(8)	0.0294(8)	-0.0079(7)	-0.0026(7)	-0.0008(6)
C(31)	0.0350(9)	0.0312(9)	0.0326(9)	-0.0096(7)	-0.0010(7)	-0.0040(7)
C(32)	0.0376(9)	0.0352(9)	0.0321(9)	-0.0127(7)	-0.0032(7)	-0.0032(7)
C(33)	0.0305(9)	0.0335(9)	0.0304(9)	-0.0050(7)	-0.0044(7)	0.0040(7)
C(34)	0.0327(9)	0.0295(9)	0.0340(9)	-0.0021(7)	-0.0031(7)	-0.0029(7)
C(35)	0.0326(9)	0.0277(8)	0.0356(9)	-0.0084(7)	-0.0069(7)	-0.0005(7)
C(36)	0.0565(12)	0.0348(10)	0.0438(11)	-0.0131(8)	-0.0056(9)	-0.0119(9)
C(37)	0.0435(11)	0.0428(10)	0.0331(10)	-0.0071(8)	0.0016(8)	-0.0021(8)
C(38)	0.0605(13)	0.0394(10)	0.0424(11)	-0.0178(8)	0.0067(9)	-0.0190(9)

Table 4: Anisotropic thermal parameters ($\text{\AA}^2$)

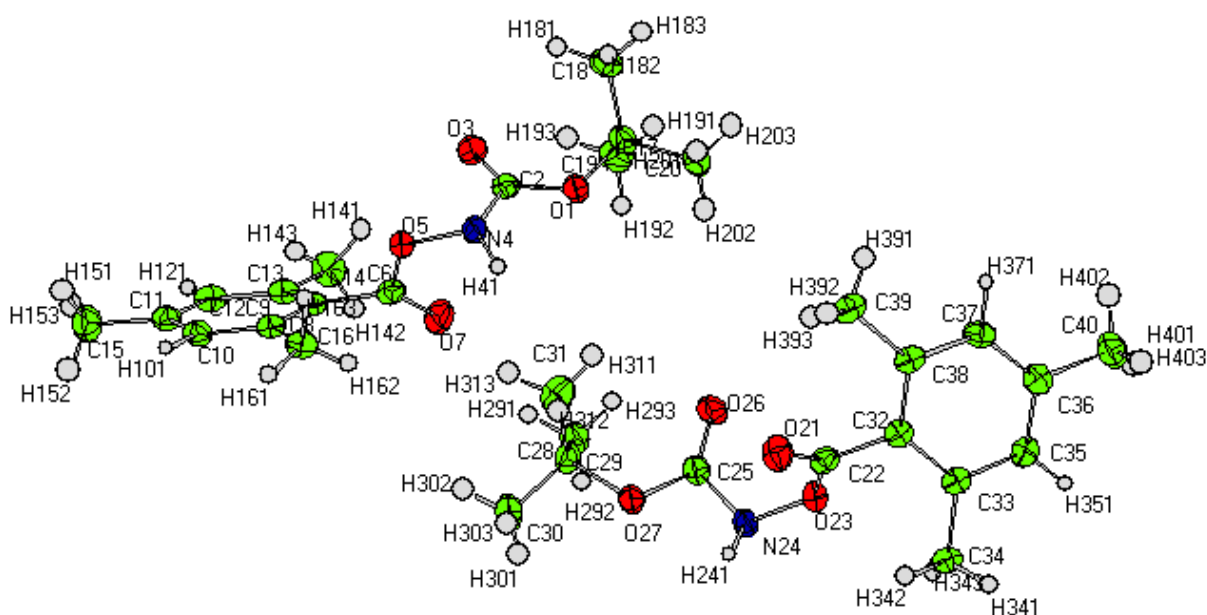
O(1 - N2)	1.4119(17)	O(20) - N(21)	1.4056(16)
O(1) - C(9)	1.382(2)	O(20) - C(28)	1.385(2)
N(2) - C(3)	1.3463(19)	N(21) - C(22)	1.340(2)
N(2) - H(21)	0.867	N(21) - H(211)	0.858
C(3) - O(4)	1.2273(19)	C(22) - O(23)	1.2281(18)
C(3) - C(5)	1.524(2)	C(22) - C(24)	1.531(2)
C(5) - C(6)	1.533(2)	C(24) - C(25)	1.525(2)
C(5) - C(7)	1.533(2)	C(24) - C(26)	1.534(3)
C(5) - C(8)	1.529(2)	C(24) - C(27)	1.529(2)
C(9) - O(10)	1.190(2)	C(28) - O(29)	1.191(2)

C(9) - C(11)	1.493(2)	C(28) - C(30)	1.488(2)
C(11) - C(12)	1.396(2)	C(30) - C(31)	1.404(2)
C(11) - C(16)	1.403(2)	C(30) - C(35)	1.400(2)
C(12) - C(13)	1.391(2)	C(31) - C(32)	1.386(2)
C(12) - C(19)	1.505(2)	C(31) - C(38)	1.515(2)
C(13) - C(14)	1.391(2)	C(32) - C(33)	1.392(2)
C(14) - C(15)	1.387(3)	C(33) - C(34)	1.391(2)
C(14) - C(18)	1.510(3)	C(33) - C(37)	1.504(2)
C(15) - C(16)	1.389(2)	C(34) - C(35)	1.391(2)
C(16) - C(17)	1.510(2)	C(35) - C(36)	1.513(2)

Table 5: Bond lengths (Å) Note – C-H atoms have been excluded

N2 - O(1) - C(9)	112.00(12)	O(20) - N(21) - C(22)	118.27(12)
O(1) - N(2) - C(3)	116.81(13)	N(21) - C(22) - O(23)	121.56(14)
N(2) - C(3) - O(4)	120.88(15)	N(21) - C(22) - C(24)	115.02(13)
N(2) - C(3) - C(5)	116.38(14)	O(23) - C(22) - C(24)	123.23(14)
O(4) - C(3) - C(5)	122.74(14)	C(22) - C(24) - C(25)	108.98(14)
C(3) - C(5) - C(6)	113.07(13)	C(22) - C(24) - C(26)	105.95(13)
C(3) - C(5) - C7	106.03(14)	C(25) - C(24) - C(26)	109.73(15)
C(6) - C(5) - C7	109.51(15)	C(22) - C(24) - C(27)	112.71(13)
C(3) - C(5) - C8	108.45(14)	C(25) - C(24) - C(27)	109.34(15)
C(6) - C(5) - C8	109.75(15)	C(26) - C(24) - C(27)	110.05(16)
C7 - C(5) - C8	109.94(14)	O(20) - C(28) - O(29)	1
O(1) - C(9) - O(10)	123.33(16)	O(20) - C(28) - C(30)	109.62(14)
O(1) - C(9) - C(11)	109.66(14)	O(29) - C(28) - C(30)	127.92(15)
O(10) - C(9) - C(11)	126.99(16)	C(28) - C(30) - C(31)	120.52(14)
C(9) - C(11) - C(12)	120.33(14)	C(28) - C(30) - C(35)	118.27(14)
C(9) - C(11) - C(16)	117.60(15)	C(31) - C(30) - C(35)	121.20(14)
C(12) - C(11) - C(16)	121.97(15)	C(30) - C(31) - C(32)	118.24(15)
C(11) - C(12) - C(13)	117.81(15)	C(30) - C(31) - C(38)	122.25(15)
C(11) - C(12) - C(19)	121.03(15)	C(32) - C(31) - C(38)	119.50(14)
C(13) - C(12) - C(19)	121.11(15)	C(31) - C(32) - C(33)	122.18(15)
C(12) - C(13) - C(14)	122.01(16)	C(32) - C(33) - C(34)	118.09(15)
C(13) - C(14) - C(15)	118.36(16)	C(32) - C(33) - C(37)	121.04(15)
C(13) - C(14) - C(18)	121.07(16)	C(34) - C(33) - C(37)	120.86(15)
C(15) - C(14) - C(18)	120.55(16)	C(33) - C(34) - C(35)	122.07(15)
C(14) - C(15) - C(16)	122.18(16)	C(30) - C(35) - C(34)	118.22(14)
C(11) - C(16) - C(15)	117.65(16)	C(30) - C(35) - C(36)	122.08(15)
C(11) - C(16) - C(17)	120.59(16)	C(34) - C(35) - C(36)	119.69(15)
C(15) - C(16) - C(17)	121.72(15)	O(23) - C(22) - C(24)	123.23(14)
N(21) - O(20) - C(28)	112.54(12)	/	

Table 6: Bond angles (° C) Note – H atoms have been excluded

Single-crystal X-ray diffraction report for compound **285** (Datablock: 0680211)

Crystal of **285** were grown by Callens Cédric and run by David Baker from dichloromethane and petrol 40-60 °C. A single crystal having dimensions approximately **0.12 x 0.20 x 0.50 mm** was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150 K in a stream of cold N₂ using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoK α radiation, λ = 0.71073 Å). Intensity data were processed using the DENZO-SMN package.¹

Examination of the systematic absences of the intensity data showed the space group to be **P 2₁/a**. The structure was solved in this space group using the direct-methods program SIR92,² which located all non-hydrogen atoms. The H atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. Subsequent full-matrix least-squares refinement was carried out against F² using the CRYSTAL program suite.³ Coordinates and anisotropic thermal parameters were refined for all non-hydrogen atoms, and the hydrogens were refined with riding constraints. A modified statistical weighting scheme was applied. Refinement converged satisfactorily to give **R = 0.0439**, **wR = 0.0917**.

Attached is a thermal ellipsoid plot (CAMERON) at 50% probability. A summary of crystallographic data is given below, as are full lists of atomic coordinates, anisotropic thermal parameters and those bond lengths and angles not concerning H atoms.

References

- (1) Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, 276, 307.
- (2) A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr.* **1994**, 27, 435.
- (3) P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout, D. J. Watkin, *J. Appl. Crystallogr.* **2003**, 36, 1487.

Crystal identification	CCK 0680211
Chemical formula	C ₁₅ H ₂₁ N ₁ O ₄
Formula weight	279.34
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	P 21/a
<i>a</i> (Å)	10.06900(10)
<i>b</i> (Å)	11.07300(10)
<i>c</i> (Å)	27.8200(3)
α (°)	90
β (°)	99.4877(5)
γ (°)	90
Cell volume (Å ³)	3059.34(5)
<i>Z</i>	8
Calculated density (Mg/m ³)	1.213
Absorption coefficient (mm ⁻¹)	0.088
<i>F</i> ₀₀₀	1200
Crystal size (mm)	0.18 × 0.20 × 0.50
Description of crystal	Colourless prism
Absorption correction	multi-scan
Transmission coefficients (min,max)	0.98, 0.99
θ range for data collection (°)	5.20 ≤ θ ≤ 27.48
Index ranges	-13 ≤ <i>h</i> ≤ 13, -14 ≤ <i>k</i> ≤ 14, -36 ≤ <i>l</i> ≤ 36
Reflections measured	13103
Unique reflections	6933
<i>R</i> _{int}	0.022
Observed reflections (<i>I</i> > -3 σ (<i>I</i>))	4767
Refinement method	Full-matrix least-squares on <i>Fsqd</i>
Parameters refined	362
Weighting scheme	Modified Sheldrick
Goodness of fit	0.9883
<i>R</i>	0.0439
<i>wR</i>	0.0917
Residual electron density (min,max) (eÅ ⁻³)	-0.23, 0.27

Table 1: Crystal data and refinement details

Atom	x	y	z	U _{equiv}
O(1)	0.89895(10)	0.22272(10)	0.73319(4)	0.0301
C(2)	0.84572(14)	0.23604(14)	0.68636(5)	0.0267
O(3)	0.73054(10)	0.26049(10)	0.66923(4)	0.0344
N(4)	0.94327(12)	0.20818(12)	0.65873(4)	0.0273
O(5)	0.91022(10)	0.24331(9)	0.60950(3)	0.0264
C(6)	0.91825(14)	0.36671(14)	0.60253(5)	0.0266
O(7)	0.94816(12)	0.43563(10)	0.63561(4)	0.0391
C(8)	0.88128(14)	0.39438(13)	0.54971(5)	0.0248
C(9)	0.94812(14)	0.33738(13)	0.51553(5)	0.0251
C(10)	0.90503(15)	0.36248(14)	0.46645(5)	0.0284
C(11)	0.79868(15)	0.44024(14)	0.45073(6)	0.0290
C(12)	0.73748(15)	0.49785(14)	0.48560(6)	0.0300
C(13)	0.77742(15)	0.47772(13)	0.53509(6)	0.0277
C(14)	0.70639(17)	0.54200(16)	0.57144(6)	0.0396
C(15)	0.75098(19)	0.46092(17)	0.39730(6)	0.0425
C(16)	1.06556(15)	0.25326(14)	0.53001(6)	0.0302
C(17)	0.81204(15)	0.23124(15)	0.77151(6)	0.0308
C(18)	0.70909(16)	0.13062(15)	0.76422(6)	0.0354
C(19)	0.75185(18)	0.35707(16)	0.77087(6)	0.0407
C(20)	0.91231(17)	0.21015(18)	0.81789(6)	0.0424

O(21)	1.33292(12)	0.57190(10)	0.85551(4)	0.0389
C(22)	1.32775(14)	0.63700(14)	0.88954(5)	0.0275
O(23)	1.31082(10)	0.76026(9)	0.88456(3)	0.0277
N(24)	1.29958(12)	0.80209(12)	0.83622(4)	0.0281
C(25)	1.17629(15)	0.77694(14)	0.80809(5)	0.0270
O(26)	1.07824(10)	0.74410(11)	0.82451(4)	0.0356
O(27)	1.18511(10)	0.80294(10)	0.76204(4)	0.0311
C(28)	1.06422(15)	0.79730(15)	0.72336(5)	0.0302
C(29)	0.95976(16)	0.88688(15)	0.73469(6)	0.0334
C(30)	1.12165(17)	0.83785(19)	0.67877(6)	0.0430
C(31)	1.01382(18)	0.66860(16)	0.71796(7)	0.0427
C(32)	1.33352(14)	0.60448(13)	0.94154(5)	0.0256
C(33)	1.42721(14)	0.66061(13)	0.97767(5)	0.0262
C(34)	1.53353(15)	0.74610(14)	0.96557(6)	0.0318
C(35)	1.42182(15)	0.63382(14)	1.02606(5)	0.0294
C(36)	1.32691(16)	0.55527(14)	1.03947(6)	0.0306
C(37)	1.23923(16)	0.49809(14)	1.00276(6)	0.0314
C(38)	1.24014(15)	0.52019(14)	0.95375(6)	0.0290
C(39)	1.14011(18)	0.45777(17)	0.91543(6)	0.0423
C(40)	1.32014(19)	0.53353(17)	1.09233(6)	0.0432

Table 2: Atomic coordinates and equivalent isotropic thermal parameters ($\text{\AA}^2$) of non-hydrogen atoms

Atom	x	y	z	U_{iso}
H(101)	0.9507	0.3241	0.4420	0.0359
H(121)	0.6643	0.5545	0.4751	0.0374
H(143)	0.6260	0.5802	0.5536	0.0635
H(142)	0.7656	0.6046	0.5876	0.0631
H(141)	0.6842	0.4850	0.5962	0.0630
H(153)	0.6713	0.5094	0.3918	0.0700
H(152)	0.8184	0.4977	0.3817	0.0697
H(151)	0.7249	0.3854	0.3817	0.0694
H(161)	1.1203	0.2503	0.5048	0.0503
H(162)	1.1190	0.2795	0.5615	0.0491
H(163)	1.0307	0.1710	0.5353	0.0496
H(183)	0.6621	0.1329	0.7930	0.0562
H(182)	0.7541	0.0515	0.7639	0.0559
H(181)	0.6409	0.1437	0.7343	0.0567
H(191)	0.7091	0.3645	0.8008	0.0621
H(192)	0.8242	0.4178	0.7726	0.0625
H(193)	0.6828	0.3693	0.7418	0.0628
H(203)	0.8604	0.2107	0.8459	0.0672
H(202)	0.9813	0.2761	0.8217	0.0669
H(201)	0.9573	0.1294	0.8156	0.0675
H(291)	0.8859	0.8889	0.7071	0.0543
H(293)	0.9218	0.8605	0.7643	0.0544
H(292)	0.9999	0.9704	0.7392	0.0542
H(302)	1.0475	0.8376	0.6512	0.0670
H(301)	1.1602	0.9194	0.6851	0.0684
H(303)	1.1890	0.7791	0.6740	0.0676
H(313)	0.9481	0.6628	0.6871	0.0672
H(311)	0.9713	0.6436	0.7460	0.0669
H(312)	1.0908	0.6157	0.7146	0.0672
H(341)	1.6105	0.7511	0.9923	0.0523
H(342)	1.5673	0.7203	0.9348	0.0513
H(343)	1.4946	0.8284	0.9595	0.0518
H(351)	1.4867	0.6727	1.0521	0.0373
H(371)	1.1747	0.4398	1.0115	0.0414
H(391)	1.0718	0.4171	0.9312	0.0685

H(392)	1.1858	0.3988	0.8974	0.0695
H(393)	1.0963	0.5193	0.8922	0.0688
H(402)	1.2388	0.4869	1.0955	0.0701
H(403)	1.3985	0.4891	1.1091	0.0705
H(401)	1.3134	0.6091	1.1101	0.0698
H(241)	1.3739	0.7858	0.8219	0.0372
H(41)	1.0279	0.2269	0.6720	0.0377

Table 3: Atomic coordinates and isotropic thermal parameters ($\text{\AA}^2$) of hydrogen atoms

Atom	U ₁₁	U ₂₂	U ₃₃	U ₂₃	U ₁₃	U ₁₂
O(1)	0.0205(5)	0.0452(7)	0.0248(6)	0.0048(5)	0.0043(4)	0.0016(5)
C(2)	0.0216(8)	0.0299(8)	0.0284(8)	0.0027(6)	0.0031(6)	-0.0027(6)
O(3)	0.0182(6)	0.0516(7)	0.0328(6)	0.0054(5)	0.0030(4)	0.0023(5)
N(4)	0.0194(6)	0.0392(8)	0.0226(6)	0.0033(5)	0.0011(5)	-0.0006(5)
O(5)	0.0264(5)	0.0289(6)	0.0233(5)	0.0014(4)	0.0029(4)	-0.0029(4)
C(6)	0.0211(7)	0.0282(9)	0.0311(8)	-0.0040(7)	0.0057(6)	-0.0019(6)
O(7)	0.0487(7)	0.0356(7)	0.0318(6)	-0.0086(5)	0.0028(5)	-0.0060(5)
C(8)	0.0229(7)	0.0232(8)	0.0287(8)	-0.0018(6)	0.0052(6)	-0.0047(6)
C(9)	0.0223(7)	0.0223(8)	0.0312(8)	-0.0019(6)	0.0056(6)	-0.0034(6)
C(10)	0.0303(8)	0.0265(8)	0.0299(8)	-0.0031(6)	0.0093(6)	-0.0033(7)
C(11)	0.0297(8)	0.0247(8)	0.0321(8)	0.0018(6)	0.0041(6)	-0.0053(7)
C(12)	0.0248(8)	0.0239(8)	0.0410(9)	0.0033(7)	0.0048(7)	0.0017(6)
C(13)	0.0249(8)	0.0231(8)	0.0360(9)	-0.0022(6)	0.0080(6)	-0.0023(6)
C(14)	0.0400(10)	0.0372(10)	0.0435(10)	-0.0051(8)	0.0125(8)	0.0081(8)
C(15)	0.0468(10)	0.0452(11)	0.0337(9)	0.0044(8)	0.0017(8)	0.0007(8)
C(16)	0.0259(8)	0.0298(9)	0.0364(9)	0.0003(7)	0.0092(7)	0.0032(7)
C(17)	0.0263(8)	0.0397(9)	0.0279(8)	0.0035(7)	0.0095(6)	0.0016(7)
C(18)	0.0287(8)	0.0387(10)	0.0400(9)	0.0087(8)	0.0089(7)	0.0018(7)
C(19)	0.0445(10)	0.0397(10)	0.0398(10)	-0.0014(8)	0.0126(8)	0.0002(8)
C(20)	0.0360(9)	0.0627(12)	0.0287(9)	0.0061(8)	0.0060(7)	-0.0051(9)
O(21)	0.0492(7)	0.0353(7)	0.0330(6)	-0.0085(5)	0.0092(5)	0.0024(5)
C(22)	0.0214(7)	0.0302(9)	0.0306(8)	-0.0039(7)	0.0036(6)	0.0013(6)
O(23)	0.0301(6)	0.0307(6)	0.0223(5)	0.0010(4)	0.0042(4)	0.0047(5)
N(24)	0.0242(7)	0.0390(8)	0.0216(6)	0.0027(5)	0.0054(5)	0.0021(6)
C(25)	0.0236(8)	0.0321(9)	0.0260(8)	0.0017(6)	0.0062(6)	0.0051(6)
O(26)	0.0231(6)	0.0514(7)	0.0336(6)	0.0083(5)	0.0084(5)	0.0017(5)
O(27)	0.0224(5)	0.0471(7)	0.0239(6)	0.0038(5)	0.0040(4)	0.0006(5)
C(28)	0.0241(8)	0.0407(9)	0.0245(8)	-0.0002(7)	0.0001(6)	0.0036(7)
C(29)	0.0296(8)	0.0389(9)	0.0311(8)	0.0029(7)	0.0037(7)	0.0051(7)
C(30)	0.0354(9)	0.0658(13)	0.0275(9)	0.0027(8)	0.0045(7)	0.0085(9)
C(31)	0.0395(10)	0.0416(11)	0.0455(10)	-0.0075(8)	0.0027(8)	0.0034(8)
C(32)	0.0236(7)	0.0239(8)	0.0291(8)	-0.0006(6)	0.0040(6)	0.0039(6)
C(33)	0.0231(8)	0.0224(8)	0.0324(8)	-0.0008(6)	0.0029(6)	0.0034(6)
C(34)	0.0254(8)	0.0315(9)	0.0376(9)	0.0003(7)	0.0027(7)	-0.0039(7)
C(35)	0.0307(8)	0.0253(8)	0.0303(8)	-0.0015(6)	-0.0003(6)	0.0020(7)
C(36)	0.0331(8)	0.0257(8)	0.0330(9)	0.0033(7)	0.0057(7)	0.0055(7)
C(37)	0.0290(8)	0.0260(8)	0.0399(9)	0.0039(7)	0.0078(7)	-0.0003(7)
C(38)	0.0251(8)	0.0253(8)	0.0358(9)	-0.0019(7)	0.0032(6)	0.0006(6)
C(39)	0.0381(10)	0.0428(11)	0.0450(10)	-0.0066(8)	0.0036(8)	-0.0131(8)
C(40)	0.0540(11)	0.0433(11)	0.0326(9)	0.0070(8)	0.0078(8)	-0.0004(9)

Table 4: Anisotropic thermal parameters ($\text{\AA}^2$)

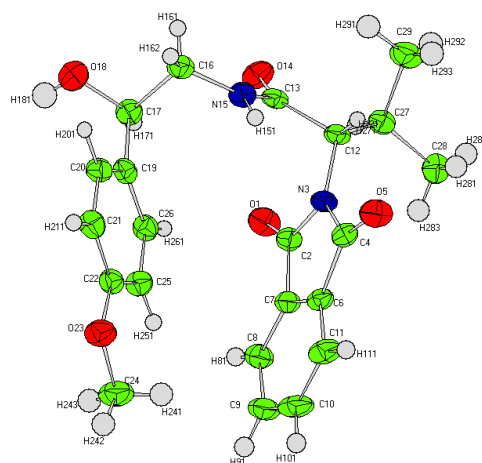
O(1) - C(2)	1.3328(18)	O(21) - C(22)	1.1978(18)
O(1) - C(17)	1.4895(17)	C(22) - O(23)	1.3796(19)
C(2) - O(3)	1.2096(17)	C(22) - C(32)	1.483(2)
C(2) - N(4)	1.3783(19)	O(23) - N(24)	1.4090(15)
N(4) - O(5)	1.4098(15)	N(24) - C(25)	1.3824(19)
N(4) - H(41)	0.895	N(24) - H(241)	0.921

O(5) - C(6)	1.3843(18)	C(25) - O(26)	1.2101(18)
C(6) - O(7)	1.1952(18)	C(25) - O(27)	1.3303(18)
C(6) - C(8)	1.487(2)	O(27) - C(28)	1.4871(17)
C(8) - C(9)	1.402(2)	C(28) - C(29)	1.516(2)
C(8) - C(13)	1.404(2)	C(28) - C(30)	1.520(2)
C(9) - C(10)	1.391(2)	C(28) - C(31)	1.512(2)
C(9) - C(16)	1.507(2)	C(32) - C(33)	1.405(2)
C(10) - C(11)	1.387(2)	C(32) - C(38)	1.406(2)
C(11) - C(12)	1.387(2)	C(33) - C(34)	1.508(2)
C(11) - C(15)	1.502(2)	C(33) - C(35)	1.388(2)
C(12) - C(13)	1.387(2)	C(35) - C(36)	1.388(2)
C(13) - C(14)	1.510(2)	C(36) - C(37)	1.388(2)
C(17) - C(18)	1.513(2)	C(36) - C(40)	1.503(2)
C(17) - C(19)	1.518(2)	C(37) - C(38)	1.387(2)
C(17) - C(20)	1.520(2)	C(38) - C(39)	1.508(2)

Table 5: Bond lengths (Å) Note – C-H atoms have been excluded

C(2) - O(1) - C(17)	120.24(11)	O(21) - C(22) - O(23)	122.46(14)
O(1) - C(2) - O(3)	127.94(14)	O(21) - C(22) - C(32)	128.70(15)
O(1) - C(2) - N(4)	108.16(12)	O(23) - C(22) - C(32)	108.82(12)
O(3) - C(2) - N(4)	123.75(14)	C(22) - O(23) - N(24)	114.22(11)
C(2) - N(4) - O(5)	113.84(11)	O(23) - N(24) - C(25)	113.42(11)
N(4) - O(5) - C(6)	113.48(11)	N(24) - C(25) - O(26)	123.99(14)
O(5) - C(6) - O(7)	122.39(14)	N(24) - C(25) - O(27)	107.78(12)
O(5) - C(6) - C(8)	109.32(12)	O(26) - C(25) - O(27)	128.09(14)
O(7) - C(6) - C(8)	128.28(14)	C(25) - O(27) - C(28)	120.74(11)
C(6) - C(8) - C(9)	120.48(13)	O(27) - C(28) - C(29)	109.59(12)
C(6) - C(8) - C(13)	118.36(13)	O(27) - C(28) - C30	101.65(12)
C(9) - C(8) - C(13)	121.16(14)	C(29) - C(28) - C30	110.28(13)
C(8) - C(9) - C(10)	117.96(14)	O(27) - C(28) - C31	109.44(13)
C(8) - C(9) - C16	122.70(13)	C(29) - C(28) - C31	113.85(13)
C(10) - C(9) - C16	119.32(13)	C30 - C(28) - C31	111.34(14)
C(9) - C(10) - C(11)	122.20(14)	C(22) - C(32) - C(33)	120.29(13)
C(10) - C(11) - C(12)	118.28(14)	C(22) - C(32) - C(38)	118.47(13)
C(10) - C(11) - C(15)	120.70(14)	C(33) - C(32) - C(38)	121.20(14)
C(12) - C(11) - C(15)	121.02(14)	C(32) - C(33) - C(34)	122.39(13)
C(11) - C(12) - C(13)	122.04(14)	C(32) - C(33) - C(35)	122.39(13)
C(8) - C(13) - C(12)	118.26(13)	C(34) - C(33) - C(35)	119.55(13)
C(8) - C(13) - C(14)	121.90(14)	C(33) - C(35) - C(36)	122.22(14)
C(12) - C(13) - C(14)	119.82(14)	C(35) - C(36) - C(37)	118.09(14)
O(1) - C(17) - C(18)	109.14(12)	C(35) - C(36) - C(40)	120.51(15)
O(1) - C(17) - C(19)	109.28(12)	C(37) - C(36) - C(40)	121.41(15)
C(18) - C(17) - C(19)	114.26(13)	C(36) - C(37) - C(38)	122.45(14)
O(1) - C(17) - C(20)	102.21(12)	C(32) - C(38) - C(37)	117.89(14)
C(18) - C(17) - C(20)	110.21(14)	C(32) - C(38) - C(39)	121.94(14)
C(19) - C(17) - C(20)	111.04(14)	C(37) - C(38) - C(39)	120.14(14)

Table 6: Bond angles (° C) Note – H atoms have been excluded

Single-crystal X-ray diffraction report for compound **292** (Datablock: 0510410)

Crystal of **292** were grown and run by Callens Cédric from dichloromethane and petrol 40-60 °C. A single crystal having dimensions approximately **0.18 x 0.20 x 0.50 mm** was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150 K in a stream of cold N₂ using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoK_α radiation, $\lambda = 0.71073$ Å). Intensity data were processed using the DENZO-SMN package.¹

Examination of the systematic absences of the intensity data showed the space group to be **C 21**. The structure was solved in this space group using the direct-methods program SIR92,² which located all non-hydrogen atoms. The H atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. Subsequent full-matrix least-squares refinement was carried out against F² using the CRYSTAL program suite.³ Coordinates and anisotropic thermal parameters were refined for all non-hydrogen atoms, and the hydrogens were refined with riding constraints. A modified statistical weighting scheme was applied. Refinement converged satisfactorily to give **R** = 0.0517, **wR** = **0.0855**.

Attached is a thermal ellipsoid plot (CAMERON) at 50% probability. A summary of crystallographic data is given below, as are full lists of atomic coordinates, anisotropic thermal parameters and those bond lengths and angles not concerning H atoms.

References

- (1) Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, 276, 307.
- (2) A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr.* **1994**, 27, 435.
- (3) P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout, D. J. Watkin, *J. Appl. Crystallogr.* **2003**, 36, 1487.

Crystal identification	CCK 0510410
Chemical formula	C ₂₂ H ₂₄ N ₂ O ₅
Formula weight	396.44
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	C 21
<i>a</i> (Å)	19.9255(6)
<i>b</i> (Å)	5.5134(2)
<i>c</i> (Å)	20.1945(7)
α (°)	90
β (°)	115.5269(16)
γ (°)	90
Cell volume (Å ³)	2001.95(12)
<i>Z</i>	4
Calculated density (Mg/m ³)	1.315
Absorption coefficient (mm ⁻¹)	0.094
<i>F</i> ₀₀₀	840
Crystal size (mm)	0.18 × 0.20 × 0.50
Description of crystal	Colourless prism
Absorption correction	multi-scan
Transmission coefficients (min,max)	0.95, 0.99
θ range for data collection (°)	5.11 ≤ θ ≤ 27.48
Index ranges	-25 ≤ <i>h</i> ≤ 25, -5 ≤ <i>k</i> ≤ 7, -26 ≤ <i>l</i> ≤ 25
Reflections measured	4016
Unique reflections	4013
<i>R</i> _{int}	0.000
Observed reflections (<i>I</i> > 3 σ (<i>I</i>))	2350
Refinement method	Full-matrix least-squares on <i>Fsqd</i>
Parameters refined	263
Weighting scheme	Modified Sheldrick
Goodness of fit	0.9493
<i>R</i>	0.0517
<i>wR</i>	0.0855
Residual electron density (min,max) (eÅ ⁻³)	-0.25, 0.26

Table 1: Crystal data and refinement details

Atom	x	y	z	<i>U</i> _{equiv}
O(1)	0.55989(7)	-0.1136(3)	0.72816(8)	0.0405
C(2)	0.58084(9)	0.0422(3)	0.69931(9)	0.0282
N(3)	0.53799(8)	0.2361(3)	0.65937(8)	0.0287
C(4)	0.57903(10)	0.3903(4)	0.63491(9)	0.0286
O(5)	0.55497(7)	0.5715(3)	0.59899(7)	0.0419
C(6)	0.65424(9)	0.2811(3)	0.66246(9)	0.0286
C(7)	0.65494(9)	0.0720(4)	0.70001(9)	0.0289
C(8)	0.71746(10)	-0.0722(4)	0.73220(10)	0.0360
C(9)	0.78114(10)	0.0053(5)	0.72593(11)	0.0439
C(10)	0.78111(11)	0.2184(4)	0.68895(12)	0.0448
C(11)	0.71767(11)	0.3599(4)	0.65644(11)	0.0391
C(12)	0.46009(9)	0.2798(4)	0.64487(9)	0.0281
C(13)	0.45423(9)	0.2967(3)	0.71871(9)	0.0277
O(14)	0.42249(7)	0.1437(3)	0.73860(7)	0.0383
N(15)	0.48589(8)	0.4961(3)	0.75754(8)	0.0321
C(16)	0.49188(9)	0.5421(4)	0.83053(9)	0.0332
C(17)	0.55727(10)	0.4074(4)	0.88986(10)	0.0351
O(18)	0.55108(8)	0.4610(3)	0.95588(8)	0.0524
C(19)	0.63219(10)	0.4807(3)	0.89375(9)	0.0294
C(20)	0.66558(10)	0.7019(4)	0.92500(9)	0.0315

C(21)	0.73546(10)	0.7596(4)	0.93224(10)	0.0327
C(22)	0.77430(9)	0.5995(4)	0.90834(9)	0.0298
O(23)	0.84511(7)	0.6733(3)	0.92058(7)	0.0402
C(24)	0.88920(11)	0.5071(5)	0.90083(12)	0.0483
C(25)	0.74188(10)	0.3840(4)	0.87533(10)	0.0323
C(26)	0.67080(10)	0.3272(3)	0.86857(10)	0.0313
C(27)	0.40525(9)	0.0955(4)	0.59240(10)	0.0351
C(28)	0.42332(12)	0.0369(5)	0.52798(10)	0.0453
C(29)	0.32677(11)	0.2016(5)	0.56490(12)	0.0514

Table 2: Atomic coordinates and equivalent isotropic thermal parameters ($\text{\AA}^2$) of non-hydrogen atoms

Atom	x	y	z	U_{iso}
H(81)	0.7168	-0.2201	0.7586	0.0474
H(91)	0.8259	-0.0897	0.7474	0.0548
H(101)	0.8276	0.2712	0.6876	0.0541
H(111)	0.7179	0.5047	0.6308	0.0488
H(121)	0.4482	0.4414	0.6212	0.0356
H(161)	0.4451	0.4869	0.8338	0.0413
H162)	0.5019	0.7165	0.8416	0.0417
H(171)	0.5491	0.2237	0.8835	0.0446
H(201)	0.6390	0.8135	0.9422	0.0370
H(211)	0.7576	0.9135	0.9533	0.0416
H(242)	0.9382	0.5928	0.9146	0.0742
H(241)	0.8635	0.4724	0.8472	0.0743
H(243)	0.8973	0.3530	0.9310	0.0745
H(251)	0.7681	0.2728	0.8569	0.0390
H(261)	0.6480	0.1754	0.8460	0.0391
H(271)	0.4096	-0.0564	0.6220	0.0437
H(282)	0.3823	-0.0609	0.4919	0.0704
H(281)	0.4258	0.1955	0.5046	0.0699
H(283)	0.4721	-0.0505	0.5468	0.0700
H(292)	0.2906	0.0787	0.5350	0.0770
H(291)	0.3193	0.2426	0.6091	0.0770
H(293)	0.3259	0.3451	0.5349	0.0776
H(151)	0.5134	0.5851	0.7419	0.0405
H(181)	0.5783	0.3495	0.9885	0.0832

Table 3: Atomic coordinates and isotropic thermal parameters ($\text{\AA}^2$) of hydrogen atoms

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(1)	0.0359(8)	0.0374(8)	0.0503(8)	0.0130(7)	0.0206(6)	-0.0024(6)
C(2)	0.0257(8)	0.0281(10)	0.0323(9)	0.0008(8)	0.0138(7)	-0.0015(8)
N(3)	0.0217(7)	0.0320(9)	0.0350(8)	0.0051(7)	0.0147(6)	0.0006(6)
C(4)	0.0301(9)	0.0281(10)	0.0327(9)	0.0002(8)	0.0183(7)	-0.0022(8)
O(5)	0.0422(8)	0.0368(8)	0.0536(8)	0.0156(7)	0.0273(6)	0.0046(7)
C(6)	0.0254(9)	0.0317(11)	0.0333(9)	-0.0057(8)	0.0169(7)	-0.0044(8)
C(7)	0.0235(8)	0.0321(11)	0.0318(8)	-0.0037(8)	0.0125(7)	0.0005(8)
C(8)	0.0285(10)	0.0377(12)	0.0393(10)	-0.0057(9)	0.0123(8)	0.0032(8)
C(9)	0.0231(9)	0.0562(15)	0.0489(12)	-0.0147(11)	0.0124(8)	0.0031(9)
C(10)	0.0266(10)	0.0534(14)	0.0615(13)	-0.0171(12)	0.0257(9)	-0.0079(10)
C(11)	0.0341(10)	0.0412(12)	0.0515(12)	-0.0083(10)	0.0275(9)	-0.0103(9)
C(12)	0.0198(8)	0.0328(10)	0.0335(9)	0.0044(8)	0.0132(7)	0.0025(7)
C(13)	0.0180(8)	0.0308(10)	0.0346(9)	0.0030(7)	0.0118(7)	0.0008(7)
O(14)	0.0398(8)	0.0379(8)	0.0474(8)	-0.0026(6)	0.0285(6)	-0.0105(6)
N(15)	0.0276(8)	0.0359(9)	0.0353(8)	0.0012(7)	0.0159(6)	-0.0068(7)
C(16)	0.0254(9)	0.0383(11)	0.0360(9)	-0.0029(9)	0.0134(7)	-0.0006(8)
C(17)	0.0308(10)	0.0424(12)	0.0343(10)	0.0046(9)	0.0160(8)	-0.0005(9)
O(18)	0.0453(9)	0.0750(13)	0.0425(8)	0.0061(8)	0.0243(7)	0.0035(8)
C(19)	0.0268(9)	0.0314(10)	0.0271(9)	0.0048(7)	0.0091(7)	-0.0002(8)

C(20)	0.0313(10)	0.0287(10)	0.0334(10)	0.0008(8)	0.0129(8)	0.0058(8)
C(21)	0.0331(10)	0.0278(10)	0.0331(9)	-0.0031(8)	0.0102(7)	-0.0037(8)
C(22)	0.0258(8)	0.0329(11)	0.0300(9)	0.0025(8)	0.0115(7)	-0.0018(8)
O(23)	0.0308(7)	0.0439(9)	0.0485(8)	-0.0071(6)	0.0195(6)	-0.0092(6)
C(24)	0.0337(10)	0.0590(15)	0.0590(13)	-0.0057(12)	0.0263(10)	-0.0021(10)
C(25)	0.0315(10)	0.0320(11)	0.0352(10)	-0.0024(8)	0.0160(8)	-0.0014(8)
C(26)	0.0297(9)	0.0310(11)	0.0307(9)	-0.0029(8)	0.0106(7)	-0.0027(8)
C(27)	0.0235(9)	0.0456(13)	0.0354(9)	-0.0034(9)	0.0118(7)	-0.0033(8)
C(28)	0.0403(11)	0.0579(15)	0.0364(10)	-0.0038(10)	0.0152(9)	-0.0004(11)
C(29)	0.0258(10)	0.0708(17)	0.0527(12)	-0.0129(12)	0.0121(9)	-0.0019(10)

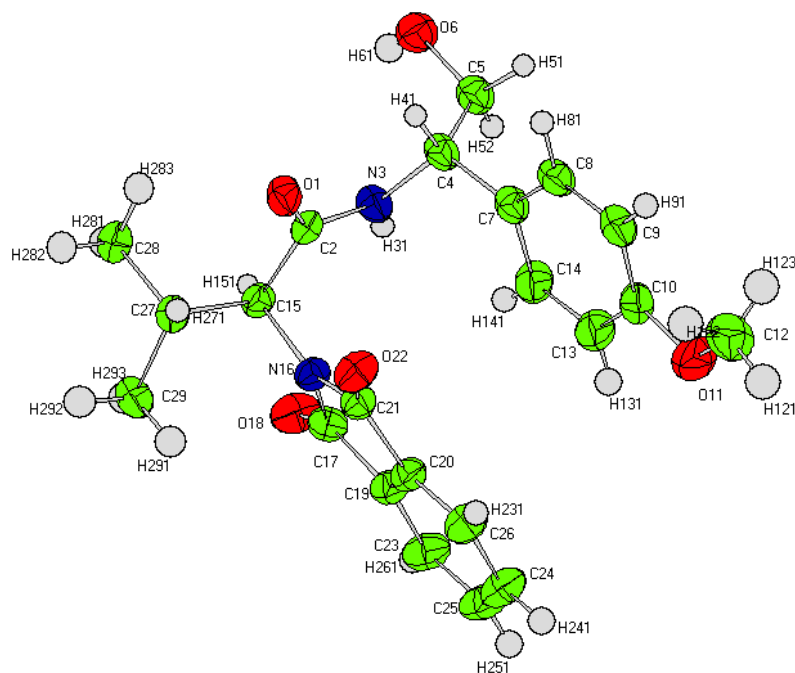
Table 4: Anisotropic thermal parameters ($\text{\AA}^2$)

O(1) - C(2)	1.208(2)	N(15) - C(16)	1.449(2)
C(2) - N(3)	1.389(2)	N(15) - H(151)	0.889
C(2) - C(7)	1.480(2)	C(16) - C(17)	1.529(3)
N(3) - C(4)	1.408(2)	C(17) - O(18)	1.422(2)
N(3) - C(12)	1.470(2)	C(17) - C(19)	1.515(2)
C(4) - O(5)	1.206(2)	O(18) - H(181)	0.893
C(4) - C(6)	1.483(2)	C(19) - C(20)	1.402(3)
C(6) - C(7)	1.377(3)	C(19) - C(26)	1.380(2)
C(6) - C(11)	1.390(2)	C(20) - C(21)	1.374(2)
C(7) - C(8)	1.382(3)	C(21) - C(22)	1.390(3)
C(8) - C(9)	1.395(3)	C(22) - O(23)	1.385(2)
C(9) - C(10)	1.392(3)	C(22) - C(25)	1.379(3)
C(10) - C(11)	1.386(3)	O(23) - C(24)	1.440(3)
C(12) - C(13)	1.548(2)	C(25) - C(26)	1.399(3)
C(12) - C(27)	1.533(3)	C(27) - C(28)	1.527(3)
C(13) - O(14)	1.221(2)	C(27) - C(29)	1.532(3)
C(13) - N(15)	1.340(2)	-	-

Table 5: Bond lengths ($\text{\AA}$) Note – C-H atoms have been excluded

O(1) - C(2) - N(3)	124.99(15)	C(12) - C(13) - O(14)	122.67(17)
O(1) - C(2) - C(7)	128.68(17)	C(12) - C(13) - N(15)	113.66(15)
N(3) - C(2) - C(7)	106.31(15)	O(14) - C(13) - N(15)	123.65(16)
C(2) - N(3) - C(4)	111.34(14)	C(13) - N(15) - C(16)	123.39(15)
C(2) - N(3) - C(12)	125.02(15)	N(15) - C(16) - C(17)	112.40(15)
C(4) - N(3) - C(12)	123.64(15)	C(16) - C(17) - O(18)	104.16(15)
N(3) - C(4) - O(5)	124.79(16)	C(16) - C(17) - C(19)	113.51(15)
N(3) - C(4) - C(6)	105.62(15)	O(18) - C(17) - C(19)	112.17(15)
O(5) - C(4) - C(6)	129.60(16)	C(17) - C(19) - C(20)	121.40(17)
C(4) - C(6) - C(7)	108.37(14)	C(17) - C(19) - C(26)	120.69(17)
C(4) - C(6) - C(11)	130.56(18)	C(20) - C(19) - C(26)	117.88(16)
C(7) - C(6) - C(11)	121.06(17)	C(19) - C(20) - C(21)	120.82(17)
C(2) - C(7) - C(6)	108.35(15)	C(20) - C(21) - C(22)	120.41(17)
C(2) - C(7) - C(8)	129.35(18)	C(21) - C(22) - O(23)	115.37(16)
C(6) - C(7) - C(8)	122.30(16)	C(21) - C(22) - C(25)	120.00(16)
C(7) - C(8) - C(9)	116.9(2)	O(23) - C(22) - C(25)	124.63(16)
C(8) - C(9) - C(10)	121.13(19)	C(22) - O(23) - C(24)	117.40(16)
C(9) - C(10) - C(11)	121.22(18)	C(22) - C(25) - C(26)	118.92(17)
C(6) - C(11) - C(10)	117.4(2)	C(25) - C(26) - C(19)	121.91(17)
N(3) - C(12) - C(13)	109.23(13)	C(12) - C(27) - C(28)	111.69(15)
N(3) - C(12) - C(27)	113.94(15)	C(12) - C(27) - C(29)	108.04(17)
C(13) - C(12) - C(27)	112.24(14)	C(28) - C(27) - C(29)	110.53(16)

Table 6: Bond angles ($^\circ$ C) Note – H atoms have been excluded

Single-crystal X-ray diffraction report for compound **293** (Datablock: 0520510)

Crystal of **293** were grown and run by Callens Cédric from dichloromethane and petrol 40-60 °C. A single crystal having dimensions approximately **0.16 x 0.20 x 0.50 mm** was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150 K in a stream of cold N₂ using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoK α radiation, $\lambda = 0.71073$ Å). Intensity data were processed using the DENZO-SMN package.¹

Examination of the systematic absences of the intensity data showed the space group to be **P 2₁ 2₁ 2₁**. The structure was solved in this space group using the direct-methods program SIR92,² which located all non-hydrogen atoms. The H atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. Subsequent full-matrix least-squares refinement was carried out against F² using the CRYSTAL program suite.³ Coordinates and anisotropic thermal parameters were refined for all non-hydrogen atoms, and the hydrogens were refined with riding constraints. A modified statistical weighting scheme was applied. Refinement converged satisfactorily to give **R = 0.0516**, **wR = 0.0851**.

Attached is a thermal ellipsoid plot (CAMERON) at 50% probability. A summary of crystallographic data is given below, as are full lists of atomic coordinates, anisotropic thermal parameters and those bond lengths and angles not concerning H atoms.

References

- (1) Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, 276, 307.
- (2) A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr.* **1994**, 27, 435.
- (3) P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout, D. J. Watkin, *J. Appl. Crystallogr.* **2003**, 36, 1487.

Crystal identification	CCK 0520510
Chemical formula	C ₂₂ H ₂₄ N ₂ O ₅
Formula weight	396.44
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Orthorhombic
Space group	P 21 21 21
<i>a</i> (Å)	5.31360(10)
<i>b</i> (Å)	19.4044(6)
<i>c</i> (Å)	20.0409(6)
α (°)	90
β (°)	90
γ (°)	90
Cell volume (Å ³)	2066.36(10)
<i>Z</i>	4
Calculated density (Mg/m ³)	1.274
Absorption coefficient (mm ⁻¹)	0.091
<i>F</i> ₀₀₀	840
Crystal size (mm)	0.16 × 0.20 × 0.50
Description of crystal	Colourless prism
Absorption correction	multi-scan
Transmission coefficients (min,max)	0.94, 0.99
θ range for data collection (°)	5.15 ≤ θ ≤ 27.50
Index ranges	-6 ≤ <i>h</i> ≤ 6, -24 ≤ <i>k</i> ≤ 25, -25 ≤ <i>l</i> ≤ 26
Reflections measured	4674
Unique reflections	2679
<i>R</i> _{int}	0.000
Observed reflections (<i>I</i> > 3 σ (<i>I</i>))	3473
Refinement method	Full-matrix least-squares on <i>Fsqd</i>
Parameters refined	263
Weighting scheme	Modified Sheldrick
Goodness of fit	0.9845
<i>R</i>	0.0516
<i>wR</i>	0.0851
Residual electron density (min,max) (eÅ ⁻³)	-0.18, 0.23

Table 1: Crystal data and refinement details

Atom	x	y	z	<i>U</i> _{equiv}
O(1)	0.2022(3)	0.53252(8)	0.80537(7)	0.0398
C(2)	0.3706(4)	0.49663(10)	0.78141(10)	0.0301
N(3)	0.5479(3)	0.46566(9)	0.81721(8)	0.0359
C(4)	0.5389(4)	0.45631(11)	0.88986(10)	0.0360
C(5)	0.8001(4)	0.46289(12)	0.91875(11)	0.0408
O(6)	0.8968(3)	0.53119(8)	0.91451(7)	0.0470
C(7)	0.4256(4)	0.38696(11)	0.90868(10)	0.0357
C(8)	0.2839(4)	0.37997(12)	0.96622(10)	0.0390
C(9)	0.1667(5)	0.31831(12)	0.98340(10)	0.0411
C(10)	0.1946(5)	0.26165(12)	0.94231(11)	0.0442
O(11)	0.0811(4)	0.19884(9)	0.95244(8)	0.0630
C(12)	-0.1000(6)	0.19461(16)	1.00471(13)	0.0656
C(13)	0.3456(5)	0.26678(13)	0.88602(12)	0.0512
C(14)	0.4592(5)	0.32808(12)	0.86943(11)	0.0459
C(15)	0.3850(4)	0.48280(10)	0.70575(10)	0.0325
N(16)	0.3399(3)	0.40878(8)	0.69498(8)	0.0318
C(17)	0.4989(4)	0.36671(11)	0.65619(10)	0.0366
O(18)	0.6811(3)	0.38749(9)	0.62580(8)	0.0501
C(19)	0.3989(4)	0.29594(11)	0.66198(10)	0.0354
C(20)	0.1881(4)	0.29776(11)	0.70267(10)	0.0341

C(21)	0.1462(4)	0.37029(11)	0.72354(10)	0.0334
O(22)	-0.0200(3)	0.39368(8)	0.75836(8)	0.0444
C(23)	0.0561(5)	0.23874(12)	0.71834(12)	0.0449
C(24)	0.1398(5)	0.17710(12)	0.69102(12)	0.0505
C(25)	0.3487(5)	0.17518(12)	0.64950(13)	0.0527
C(26)	0.4818(5)	0.23464(12)	0.63442(13)	0.0476
C(27)	0.2095(4)	0.53013(11)	0.66550(10)	0.0385
C(28)	0.3173(6)	0.60323(12)	0.66653(12)	0.0508
C(29)	0.1769(6)	0.50496(13)	0.59383(11)	0.0536

Table 2: Atomic coordinates and equivalent isotropic thermal parameters ($\text{\AA}^2$) of non-hydrogen atoms

Atom	x	y	z	U_{iso}
H(41)	0.4328	0.4945	0.9084	0.0444
H(52)	0.9170	0.4303	0.8967	0.0481
H(51)	0.7856	0.4505	0.9668	0.0470
H(81)	0.2668	0.4192	0.9940	0.0464
H(91)	0.0655	0.3149	1.0221	0.0512
H(121)	-0.1756	0.1492	1.0032	0.0991
H(122)	-0.2246	0.2299	0.9997	0.0987
H(123)	-0.0124	0.2015	1.0464	0.0986
H(131)	0.3700	0.2269	0.8592	0.0613
H(141)	0.5612	0.3315	0.8302	0.0558
H(151)	0.5587	0.4922	0.6916	0.0391
H(231)	-0.0886	0.2412	0.7456	0.0541
H(241)	0.0548	0.1359	0.7010	0.0631
H(251)	0.4015	0.1326	0.6321	0.0644
H(261)	0.6218	0.2334	0.6067	0.0574
H(271)	0.0419	0.5320	0.6874	0.0482
H(282)	0.2014	0.6333	0.6439	0.0756
H(281)	0.4760	0.6036	0.6443	0.0759
H(283)	0.3387	0.6179	0.7123	0.0756
H(292)	0.0593	0.5366	0.5715	0.0811
H(291)	0.1071	0.4587	0.5941	0.0808
H(293)	0.3398	0.5056	0.5709	0.0808
H(31)	0.6653	0.4435	0.7960	0.0438
H(61)	0.9842	0.5347	0.8796	0.0702
H(41)	0.4328	0.4945	0.9084	0.0444
H(52)	0.9170	0.4303	0.8967	0.0481

Table 3: Atomic coordinates and isotropic thermal parameters ($\text{\AA}^2$) of hydrogen atoms

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(1)	0.0460(9)	0.0373(9)	0.0361(8)	0.0008(7)	0.0011(7)	0.0142(8)
C(2)	0.0327(12)	0.0234(10)	0.0343(11)	0.0015(8)	0.0007(10)	0.0010(10)
N(3)	0.0390(10)	0.0402(10)	0.0287(9)	-0.0036(8)	0.0014(8)	0.0121(9)
C(4)	0.0404(13)	0.0395(13)	0.0280(10)	-0.0018(9)	-0.0008(9)	0.0110(11)
C(5)	0.0442(13)	0.0430(14)	0.0353(11)	-0.0014(10)	-0.0013(10)	0.0068(12)
O(6)	0.0548(10)	0.0474(10)	0.0389(8)	-0.0021(7)	0.0054(7)	-0.0046(9)
C(7)	0.0370(12)	0.0391(13)	0.0312(11)	0.0002(9)	-0.0018(9)	0.0102(11)
C(8)	0.0427(13)	0.0441(15)	0.0304(11)	-0.0037(10)	-0.0031(10)	0.0096(11)
C(9)	0.0424(14)	0.0493(15)	0.0316(12)	0.0033(10)	0.0008(10)	0.0072(12)
C(10)	0.0543(15)	0.0383(14)	0.0399(13)	0.0062(11)	-0.0044(12)	0.0066(12)
O(11)	0.0890(15)	0.0486(11)	0.0514(10)	0.0029(8)	0.0098(10)	-0.0131(11)
C(12)	0.077(2)	0.0731(19)	0.0469(15)	0.0061(13)	0.0048(15)	-0.0187(17)
C(13)	0.0729(18)	0.0387(14)	0.0418(14)	-0.0038(11)	0.0034(14)	0.0115(14)
C(14)	0.0579(16)	0.0402(14)	0.0395(13)	-0.0001(10)	0.0087(12)	0.0125(13)
C(15)	0.0366(12)	0.0277(11)	0.0333(11)	0.0017(9)	0.0027(10)	-0.0030(9)
N(16)	0.0343(10)	0.0292(10)	0.0318(9)	-0.0028(7)	0.0033(8)	-0.0005(8)
C(17)	0.0351(13)	0.0408(13)	0.0338(12)	-0.0045(10)	0.0015(11)	0.0001(11)

O(18)	0.0488(10)	0.0510(11)	0.0505(9)	-0.0106(8)	0.0199(9)	-0.0104(9)
C(19)	0.0341(12)	0.0334(12)	0.0386(12)	-0.0055(9)	-0.0004(10)	0.0013(10)
C(20)	0.0342(12)	0.0291(12)	0.0389(11)	-0.0023(9)	-0.0012(11)	0.0010(10)
C(21)	0.0336(12)	0.0325(12)	0.0342(11)	-0.0002(9)	0.0011(10)	-0.0008(10)
O(22)	0.0409(9)	0.0388(9)	0.0535(9)	-0.0050(7)	0.0147(8)	0.0022(8)
C(23)	0.0422(14)	0.0382(13)	0.0543(14)	-0.0019(11)	0.0045(12)	-0.0037(11)
C(24)	0.0505(15)	0.0335(13)	0.0675(16)	-0.0060(11)	-0.0004(14)	-0.0039(12)
C(25)	0.0543(16)	0.0369(14)	0.0669(16)	-0.0175(12)	-0.0031(14)	0.0049(13)
C(26)	0.0435(14)	0.0427(14)	0.0567(15)	-0.0150(11)	0.0036(12)	0.0030(12)
C(27)	0.0465(13)	0.0334(12)	0.0356(11)	0.0048(10)	-0.0032(10)	-0.0022(11)
C(28)	0.0717(17)	0.0359(13)	0.0449(13)	0.0076(10)	-0.0055(14)	-0.0037(13)
C(29)	0.0702(18)	0.0523(16)	0.0384(13)	0.0076(11)	-0.0126(13)	-0.0083(14)

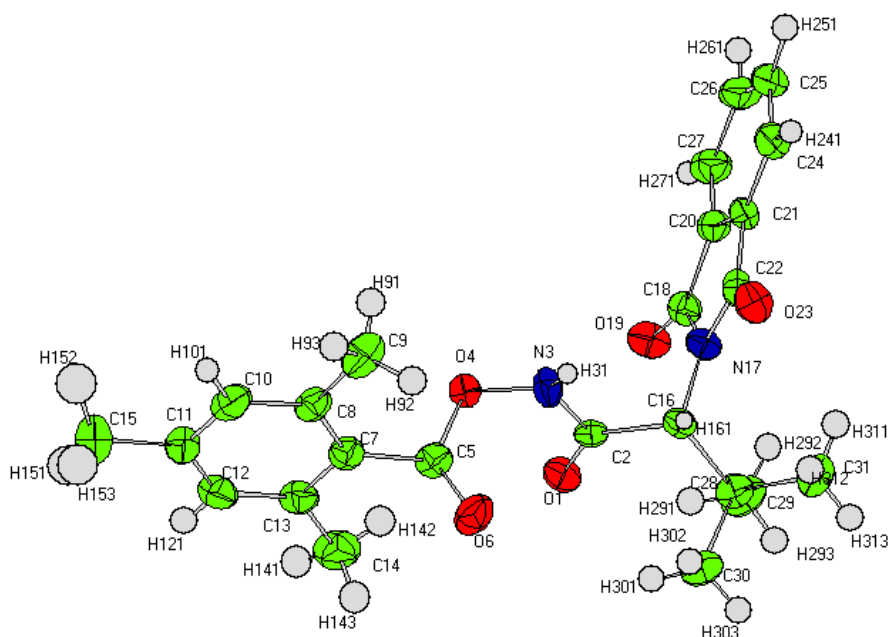
Table 4: Anisotropic thermal parameters ($\text{\AA}^2$)

O(1) - C(2)	1.231(2)	C(15) - N(16)	1.472(2)
C(2) - N(3)	1.328(3)	C(15) - C(27)	1.537(3)
C(2) - C(15)	1.542(3)	N(16) - C(17)	1.409(3)
N(3) - C(4)	1.468(2)	N(16) - C(21)	1.394(3)
N(3) - H(31)	0.868	C(17) - O(18)	1.213(3)
C(4) - C(5)	1.509(3)	C(17) - C(19)	1.477(3)
C(4) - C(7)	1.522(3)	C(19) - C(20)	1.386(3)
C(5) - O(6)	1.424(3)	C(19) - C(26)	1.383(3)
O(6) - H(61)	0.843	C(20) - C(21)	1.485(3)
C(7) - C(8)	1.384(3)	C(20) - C(23)	1.379(3)
C(7) - C(14)	1.399(3)	C(21) - O(22)	1.214(3)
C(8) - C(9)	1.392(3)	C(23) - C(24)	1.389(3)
C(9) - C(10)	1.382(3)	C(24) - C(25)	1.388(4)
C(10) - O(11)	1.375(3)	C(25) - C(26)	1.387(3)
C(10) - C(13)	1.388(3)	C(27) - C(28)	1.530(3)
O(11) - C(12)	1.425(3)	C(27) - C(29)	1.527(3)
C(13) - C(14)	1.375(3)	-	-

Table 5: Bond lengths ($\text{\AA}$) Note – C-H atoms have been excluded

O(1) - C(2) - N(3)	124.10(18)	C(15) - N(16) - C(17)	123.28(17)
O(1) - C(2) - C(15)	121.20(18)	C(15) - N(16) - C(21)	125.64(17)
N(3) - C(2) - C(15)	114.68(18)	C(17) - N(16) - C(21)	111.01(16)
C(2) - N(3) - C(4)	124.67(18)	N(16) - C(17) - O(18)	124.28(19)
N(3) - C(4) - C(5)	109.89(17)	N(16) - C(17) - C(19)	106.25(18)
N(3) - C(4) - C(7)	111.58(17)	O(18) - C(17) - C(19)	129.5(2)
C(5) - C(4) - C(7)	110.08(17)	C(17) - C(19) - C(20)	108.26(18)
C(4) - C(5) - O(6)	112.81(18)	C(17) - C(19) - C(26)	130.8(2)
C(4) - C(7) - C(8)	120.55(19)	C(20) - C(19) - C(26)	120.9(2)
C(4) - C(7) - C(14)	122.19(19)	C(19) - C(20) - C(21)	108.11(18)
C(8) - C(7) - C(14)	117.3(2)	C(19) - C(20) - C(23)	121.60(19)
C(7) - C(8) - C(9)	122.3(2)	C(21) - C(20) - C(23)	130.3(2)
C(8) - C(9) - C(10)	119.2(2)	C(20) - C(21) - N(16)	106.36(18)
C(9) - C(10) - O(11)	124.8(2)	C(20) - C(21) - O(22)	128.7(2)
C(9) - C(10) - C(13)	119.3(2)	N(16) - C(21) - O(22)	124.94(19)
O(11) - C(10) - C(13)	115.9(2)	C(20) - C(23) - C(24)	117.5(2)
C(10) - O(11) - C(12)	117.1(2)	C(23) - C(24) - C(25)	121.1(2)
C(10) - C(13) - C(14)	120.8(2)	C(24) - C(25) - C(26)	121.1(2)
C(7) - C(14) - C(13)	121.0(2)	C(25) - C(26) - C(19)	117.8(2)
C(2) - C(15) - N(16)	107.81(15)	C(15) - C(27) - C(28)	108.65(19)
C(2) - C(15) - C(27)	112.46(17)	C(15) - C(27) - C(29)	111.80(19)
N(16) - C(15) - C(27)	114.03(17)	C(28) - C(27) - C(29)	110.59(18)

Table 6: Bond angles ($^\circ$ C) Note – H atoms have been excluded

Single-crystal X-ray diffraction report for compound **296d** (Datablock: 0500410)

Crystal of **296d** were grown and run by Callens Cédric from dichloromethane and petrol 40-60 °C. A single crystal having dimensions approximately **0.12 x 0.18 x 0.50 mm** was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150 K in a stream of cold N₂ using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoK_α radiation, $\lambda = 0.71073$ Å). Intensity data were processed using the DENZO-SMN package.¹

Examination of the systematic absences of the intensity data showed the space group to be **P 2₁ 2₁ 2₁**. The structure was solved in this space group using the direct-methods program SIR92,² which located all non-hydrogen atoms. The H atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. Subsequent full-matrix least-squares refinement was carried out against F² using the CRYSTAL program suite.³ Coordinates and anisotropic thermal parameters were refined for all non-hydrogen atoms, and the hydrogens were refined with riding constraints. A modified statistical weighting scheme was applied. Refinement converged satisfactorily to give **R = 0.0655**, **wR = 0.0886**.

Attached is a thermal ellipsoid plot (CAMERON) at 50% probability. A summary of crystallographic data is given below, as are full lists of atomic coordinates, anisotropic thermal parameters and those bond lengths and angles not concerning H atoms.

References

- (1) Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, 276, 307.
- (2) A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr.* **1994**, 27, 435.
- (3) P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout, D. J. Watkin, *J. Appl. Crystallogr.* **2003**, 36, 1487.

Crystal identification	CCK 0500410
Chemical formula	C ₂₄ H ₂₆ N ₂ O ₅
Formula weight	422.48
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Orthorhombic
Space group	P 21 21 21
<i>a</i> (Å)	5.8398(2)
<i>b</i> (Å)	10.8763(3)
<i>c</i> (Å)	35.0638(12)
α (°)	90
β (°)	90
γ (°)	90
Cell volume (Å ³)	2227.09(12)
<i>Z</i>	4
Calculated density (Mg/m ³)	1.260
Absorption coefficient (mm ⁻¹)	0.089
<i>F</i> ₀₀₀	896
Crystal size (mm)	0.12 × 0.18 × 0.50
Description of crystal	Colourless prism
Absorption correction	multi-scan
Transmission coefficients (min,max)	0.94, 0.99
θ range for data collection (°)	5.12 ≤ θ ≤ 27.47
Index ranges	-7 ≤ <i>h</i> ≤ 7, -13 ≤ <i>k</i> ≤ 14, -45 ≤ <i>l</i> ≤ 45
Reflections measured	75157
Unique reflections	4956
<i>R</i> _{int}	0.060
Observed reflections (<i>I</i> > -3 σ (<i>I</i>))	3184
Refinement method	Full-matrix least-squares on <i>Fsqd</i>
Parameters refined	281
Weighting scheme	Modified Sheldrick
Goodness of fit	0.9443
<i>R</i>	0.0655
<i>wR</i>	0.0886
Residual electron density (min,max) (eÅ ⁻³)	-0.53, 0.46

Table 1: Crystal data and refinement details

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{equiv}
O(1)	0.3833(3)	0.16752(16)	0.36313(6)	0.0375
C(2)	0.2473(4)	0.2481(2)	0.35481(8)	0.0278
N(3)	0.0818(4)	0.2904(2)	0.37878(7)	0.0371
O(4)	0.0476(3)	0.23244(16)	0.41405(5)	0.0350
C(5)	-0.0503(5)	0.1168(3)	0.41135(9)	0.0360
O(6)	-0.0832(4)	0.0673(2)	0.38151(6)	0.0543
C(7)	-0.1064(4)	0.0712(3)	0.45018(8)	0.0357
C(8)	-0.2891(5)	0.1235(3)	0.46984(8)	0.0371
C(9)	-0.4230(5)	0.2301(3)	0.45382(9)	0.0520
C(10)	-0.3467(5)	0.0745(3)	0.50509(9)	0.0469
C(11)	-0.2260(6)	-0.0213(3)	0.52144(9)	0.0536
C(12)	-0.0430(6)	-0.0703(3)	0.50141(10)	0.0547
C(13)	0.0193(5)	-0.0265(3)	0.46588(9)	0.0444
C(14)	0.2185(6)	-0.0815(3)	0.44384(10)	0.0594
C(15)	-0.2944(9)	-0.0693(3)	0.56025(11)	0.0925
C(16)	0.2424(5)	0.3213(2)	0.31734(8)	0.0286
N(17)	0.3269(3)	0.44656(19)	0.32484(6)	0.0306
C(18)	0.5217(5)	0.4783(2)	0.34584(8)	0.0331
O(19)	0.6589(3)	0.40610(17)	0.35909(6)	0.0418
C(20)	0.5185(5)	0.6142(2)	0.34941(8)	0.0331

C(21)	0.3198(5)	0.6578(2)	0.33287(8)	0.0345
C(22)	0.1916(5)	0.5518(3)	0.31762(8)	0.0348
O(23)	0.0060(3)	0.54773(17)	0.30230(6)	0.0447
C(24)	0.2648(6)	0.7809(3)	0.33348(9)	0.0453
C(25)	0.4211(6)	0.8596(3)	0.35117(10)	0.0539
C(26)	0.6206(6)	0.8161(3)	0.36729(10)	0.0533
C(27)	0.6732(5)	0.6920(3)	0.36691(9)	0.0466
C(28)	0.3496(4)	0.2584(3)	0.28205(8)	0.0355
C(29)	0.6103(4)	0.2488(3)	0.28427(9)	0.0479
C(30)	0.2435(5)	0.1304(3)	0.27816(9)	0.0442
C(31)	0.2842(5)	0.3352(3)	0.24714(9)	0.0471

Table 2: Atomic coordinates and equivalent isotropic thermal parameters ($\text{\AA}^2$) of non-hydrogen atoms

Atom	x	y	z	U_{iso}
H(93)	-0.5775	0.2266	0.4631	0.0775
H(92)	-0.4242	0.2251	0.4260	0.0771
H(91)	-0.3507	0.3076	0.4620	0.0775
H(101)	-0.4705	0.1078	0.5183	0.0560
H(121)	0.0388	-0.1361	0.5123	0.0664
H(141)	0.3132	-0.1281	0.4613	0.0892
H(143)	0.1614	-0.1365	0.4241	0.0887
H(142)	0.3094	-0.0168	0.4321	0.0894
H(151)	-0.1789	-0.1270	0.5689	0.1361
H(153)	-0.4390	-0.1118	0.5578	0.1360
H(152)	-0.3084	-0.0029	0.5782	0.1362
H(161)	0.0788	0.3321	0.3105	0.0344
H(241)	0.1255	0.8098	0.3223	0.0544
H(251)	0.3897	0.9441	0.3529	0.0644
H(261)	0.7217	0.8715	0.3787	0.0641
H(271)	0.8062	0.6625	0.3782	0.0559
H(293)	0.6624	0.2044	0.2619	0.0694
H(292)	0.6769	0.3315	0.2842	0.0699
H(291)	0.6544	0.2053	0.3076	0.0697
H(303)	0.2882	0.0935	0.2541	0.0637
H(302)	0.0777	0.1366	0.2793	0.0636
H(301)	0.2984	0.0794	0.2992	0.0643
H(313)	0.3427	0.2960	0.2244	0.0694
H(312)	0.1186	0.3430	0.2457	0.0700
H(311)	0.3523	0.4186	0.2497	0.0696
H(31)	-0.0378	0.3249	0.3688	0.0444

Table 3: Atomic coordinates and isotropic thermal parameters ($\text{\AA}^2$) of hydrogen atoms

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(1)	0.0350(11)	0.0331(11)	0.0444(13)	0.0031(10)	-0.0041(9)	0.007(1)
C(2)	0.0272(14)	0.0253(15)	0.0309(16)	-0.0054(12)	-0.0034(12)	-0.0036(13)
N(3)	0.0360(13)	0.0411(15)	0.0342(15)	0.0123(11)	0.0040(11)	0.0083(11)
O(4)	0.0403(11)	0.0329(11)	0.0319(11)	0.0023(9)	0.0013(9)	0.0005(9)
C(5)	0.0299(15)	0.0397(18)	0.038(2)	-0.0048(15)	-0.0003(14)	-0.0053(13)
O(6)	0.0641(14)	0.0623(14)	0.0366(14)	-0.0111(12)	0.0046(11)	-0.0258(12)
C(7)	0.0354(16)	0.0363(18)	0.0353(18)	-0.0039(14)	-0.0003(13)	-0.0071(14)
C(8)	0.0369(17)	0.0413(18)	0.0331(18)	-0.0074(14)	-0.0032(14)	-0.0041(14)
C(9)	0.0399(17)	0.074(2)	0.0424(19)	-0.0076(18)	-0.0052(14)	0.0090(17)
C(10)	0.0479(18)	0.051(2)	0.041(2)	-0.0138(16)	0.0075(15)	-0.0084(17)
C(11)	0.080(3)	0.043(2)	0.038(2)	-0.0008(16)	0.0077(19)	-0.012(2)
C(12)	0.086(2)	0.0304(19)	0.047(2)	0.0007(16)	-0.0067(19)	0.0045(18)
C(13)	0.055(2)	0.0354(18)	0.043(2)	-0.0051(15)	-0.0045(16)	-0.0047(16)
C(14)	0.066(2)	0.050(2)	0.062(2)	-0.0069(17)	0.0000(19)	0.0165(19)
C(15)	0.158(4)	0.069(3)	0.051(3)	0.011(2)	0.023(3)	-0.009(3)

C(16)	0.0253(14)	0.0262(15)	0.0342(17)	-0.0006(13)	-0.0040(13)	-0.0037(12)
N(17)	0.0266(12)	0.0269(13)	0.0383(15)	0.0010(11)	-0.0062(10)	0.0018(11)
C(18)	0.0289(16)	0.0334(17)	0.0369(18)	0.0006(13)	0.0025(14)	-0.0025(14)
O(19)	0.0329(11)	0.0379(12)	0.0547(14)	-0.0016(10)	-0.0110(10)	0.0038(9)
C(20)	0.0342(17)	0.0308(16)	0.0345(17)	-0.0025(13)	0.0045(13)	-0.0023(13)
C(21)	0.0435(18)	0.0274(17)	0.0326(18)	0.0039(13)	0.0085(14)	0.0010(14)
C(22)	0.0363(17)	0.0390(18)	0.0292(16)	0.0075(14)	0.0046(13)	0.0035(15)
O(23)	0.0391(12)	0.0469(12)	0.0482(14)	0.0074(10)	-0.0077(10)	0.0071(11)
C(24)	0.057(2)	0.0360(19)	0.0429(19)	0.0037(15)	0.0105(16)	0.0049(17)
C(25)	0.081(3)	0.0305(19)	0.050(2)	-0.0013(16)	0.023(2)	-0.0009(18)
C(26)	0.069(2)	0.037(2)	0.053(2)	-0.0130(17)	0.0122(19)	-0.0141(17)
C(27)	0.047(2)	0.042(2)	0.051(2)	-0.0080(16)	0.0037(16)	-0.0063(15)
C(28)	0.0294(15)	0.0390(18)	0.0382(18)	-0.0050(14)	-0.0025(12)	-0.0011(14)
C(29)	0.0316(16)	0.062(2)	0.050(2)	-0.0147(17)	0.0034(14)	0.0045(16)
C(30)	0.0433(18)	0.0459(19)	0.043(2)	-0.0125(15)	-0.0052(15)	-0.0010(16)
C(31)	0.048(2)	0.059(2)	0.0338(19)	-0.0013(16)	0.0012(15)	0.0024(16)

Table 4: Anisotropic thermal parameters ($\text{\AA}^2$)

O(1) - C(2)	1.218(3)	C(16) - N(17)	1.473(3)
C(2) - N(3)	1.361(3)	C(16) - C(28)	1.546(4)
C(2) - C(16)	1.537(4)	N(17) - C(18)	1.398(3)
N(3) - O(4)	1.402(3)	N(17) - C(22)	1.414(3)
N(3) - H(31)	0.867	C(18) - O19	1.215(3)
O(4) - C(5)	1.385(3)	C(18) - C(20)	1.483(4)
C(5) - O(6)	1.192(3)	C(20) - C(21)	1.382(4)
C(5) - C(7)	1.486(4)	C(20) - C(27)	1.381(4)
C(7) - C(8)	1.392(4)	C(21) - C(22)	1.475(4)
C(7) - C(13)	1.404(4)	C(21) - C(24)	1.376(4)
C(8) - C(9)	1.507(4)	C(22) - O(23)	1.211(3)
C(8) - C10	1.387(4)	C(24) - C(25)	1.397(4)
C(10) - C(11)	1.382(4)	C(25) - C(26)	1.379(5)
C(11) - C(12)	1.386(5)	C(26) - C(27)	1.385(4)
C(11) - C15	1.512(5)	C(28) - C(29)	1.528(4)
C(12) - C(13)	1.382(4)	C(28) - C(30)	1.530(4)
C(13) - C(14)	1.519(4)	C(28) - C(31)	1.530(4)

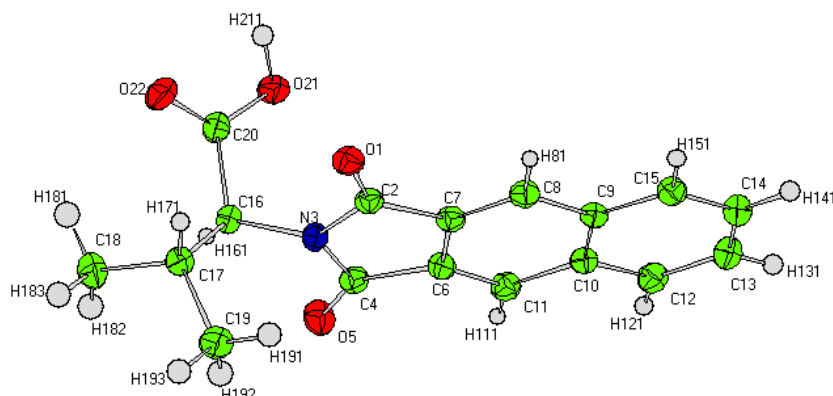
Table 5: Bond lengths ($\text{\AA}$) Note – C-H atoms have been excluded

O(1) - C(2) - N(3)	123.9(3)	C(16) - N(17) - C(18)	126.5(2)
O(1) - C(2) - C(16)	126.1(2)	C(16) - N(17) - C(22)	122.0(2)
N(3) - C(2) - C(16)	109.9(2)	C(18) - N(17) - C(22)	110.4(2)
C(2) - N(3) - O(4)	119.6(2)	N(17) - C(18) - O(19)	125.3(2)
N(3) - O(4) - C(5)	114.0(2)	N(17) - C(18) - C(20)	106.3(2)
O(4) - C(5) - O(6)	122.4(3)	O(19) - C(18) - C(20)	128.3(3)
O(4) - C(5) - C(7)	109.4(2)	C(18) - C(20) - C(21)	108.5(2)
O(6) - C(5) - C(7)	128.2(3)	C(18) - C(20) - C(27)	129.8(3)
C(5) - C(7) - C(8)	119.1(3)	C(21) - C(20) - C(27)	121.7(3)
C(5) - C(7) - C(13)	119.8(3)	C(20) - C(21) - C(22)	108.0(2)
C(8) - C(7) - C(13)	121.1(3)	C(20) - C(21) - C(24)	121.6(3)
C(7) - C(8) - C(9)	121.9(3)	C(22) - C(21) - C(24)	130.3(3)
C(7) - C(8) - C(10)	118.0(3)	C(21) - C(22) - N(17)	106.5(2)
C(9) - C(8) - C(10)	120.1(3)	C(21) - C(22) - O(23)	130.1(3)
C(8) - C(10) - C(11)	122.4(3)	N(17) - C(22) - O(23)	123.4(3)
C(10) - C(11) - C(12)	118.3(3)	C(21) - C(24) - C(25)	116.7(3)
C(10) - C(11) - C15	119.9(3)	C(24) - C(25) - C(26)	121.6(3)
C(12) - C(11) - C15	121.8(3)	C(25) - C(26) - C(27)	121.2(3)
C(11) - C(12) - C(13)	121.8(3)	C(26) - C(27) - C(20)	117.2(3)
C(7) - C(13) - C(12)	118.5(3)	C(16) - C(28) - C(29)	113.1(2)
C(7) - C(13) - C(14)	119.9(3)	C(16) - C(28) - C(30)	108.1(2)

C(12) - C(13) - C(14)	121.6(3)	C(29) - C(28) - C(30)	110.2(3)
C(2) - C(16) - N(17)	108.7(2)	C(16) - C(28) - C(31)	107.3(2)
C(2) - C(16) - C(28)	116.6(2)	C(29) - C(28) - C(31)	109.1(3)
N(17) - C(16) - C(28)	114.6(2)	C(30) - C(28) - C(31)	108.9(2)

Table 6: Bond angles (°C) Note – H atoms have been excluded

Single-crystal X-ray diffraction report for (S)-2-(1,3-Dioxo-1H-benzo[f]isoindol-2(3H)-yl)-3-methylbutanoic acid (Datablock: 0590910)



Crystal of **(S)-2-(1,3-Dioxo-1H-benzo[f]isoindol-2(3H)-yl)-3-methylbutanoic acid** were grown and run by Callens Cédric from dichloromethane and petrol 40-60 °C. A single crystal having dimensions approximately **0.18 x 0.24 x 0.26 mm** was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 293 K in a stream of cold N₂ using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoK_α radiation, $\lambda = 0.71073$ Å). Intensity data were processed using the DENZO-SMN package.¹

Examination of the systematic absences of the intensity data showed the space group to be **P 2₁/n**. The structure was solved in this space group using the direct-methods program SIR92,² which located all non-hydrogen atoms. The H atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. Subsequent full-matrix least-squares refinement was carried out against F² using the CRYSTAL program suite.³ Coordinates and anisotropic thermal parameters were refined for all non-hydrogen atoms, and the hydrogens were refined with riding constraints. A modified statistical weighting scheme was applied. Refinement converged satisfactorily to give **R = 0.0425**, **wR = 0.0748**.

Attached is a thermal ellipsoid plot (CAMERON) at 50% probability. A summary of crystallographic data is given below, as are full lists of atomic coordinates, anisotropic thermal parameters and those bond lengths and angles not concerning H atoms.

References

- (1) Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, 276, 307.
- (2) A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr.* **1994**, 27, 435.
- (3) P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout, D. J. Watkin, *J. Appl. Crystallogr.* **2003**, 36, 1487.

Crystal identification	CCK 0590910
Chemical formula	C ₁₇ H ₁₅ N ₁ O ₄
Formula weight	297.31
Temperature (K)	293
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	P 21/c
<i>a</i> (Å)	11.4597(2)
<i>b</i> (Å)	6.0083(2)
<i>c</i> (Å)	11.6452(3)
α (°)	90
β (°)	117.2212(11)
γ (°)	90
Cell volume (Å ³)	713.01(3)
<i>Z</i>	2
Calculated density (Mg/m ³)	1.385
Absorption coefficient (mm ⁻¹)	0.099
<i>F</i> ₀₀₀	312
Crystal size (mm)	0.18 × 0.24 × 0.26
Description of crystal	Colourless bloc
Absorption correction	multi-scan
Transmission coefficients (min,max)	0.98, 0.98
θ range for data collection (°)	5.17 ≤ θ ≤ 27.50
Index ranges	-14 ≤ <i>h</i> ≤ 14, -7 ≤ <i>k</i> ≤ 7, -15 ≤ <i>l</i> ≤ 14
Reflections measured	13103
Unique reflections	6933
<i>R</i> _{int}	0.022
Observed reflections (<i>I</i> > -3 σ (<i>I</i>))	3138
Refinement method	Full-matrix least-squares on <i>Fsqd</i>
Parameters refined	200
Weighting scheme	Modified Sheldrick
Goodness of fit	0.9793
<i>R</i>	0.0425
<i>wR</i>	0.0748
Residual electron density (min,max) (eÅ ⁻³)	-0.18, 0.19

Table 1: Crystal data and refinement details

Atom	x	y	z	U _{equiv}
O(1)	0.04433(10)	0.0530(2)	0.18621(10)	0.0261
C(2)	-0.01745(14)	0.1663(3)	0.22741(14)	0.0217
N(3)	0.02587(12)	0.3696(2)	0.28771(12)	0.0219
C(4)	-0.06279(15)	0.4660(3)	0.32648(14)	0.0226
O(5)	-0.04466(11)	0.6409(2)	0.38303(12)	0.0310
C(6)	-0.17596(14)	0.3105(3)	0.27998(14)	0.0221
C(7)	-0.14738(14)	0.1269(3)	0.22161(14)	0.0214
C(8)	-0.23550(15)	-0.0404(3)	0.16528(14)	0.0232
C(9)	-0.36008(14)	-0.0252(3)	0.16479(13)	0.0224
C(10)	-0.39018(15)	0.1645(3)	0.21990(14)	0.0231
C(11)	-0.29416(15)	0.3343(3)	0.27962(15)	0.0243
C(12)	-0.51672(15)	0.1826(3)	0.21269(15)	0.0279
C(13)	-0.60780(15)	0.0182(3)	0.15632(16)	0.0327
C(14)	-0.57705(16)	-0.1719(3)	0.10452(16)	0.0319
C(15)	-0.45609(15)	-0.1915(3)	0.10782(15)	0.0262
C(16)	0.13596(14)	0.4917(3)	0.28795(14)	0.0238
C(17)	0.27240(15)	0.4062(3)	0.38488(15)	0.0269
C(18)	0.37141(17)	0.5959(3)	0.42107(18)	0.0384
C(19)	0.26899(17)	0.3111(4)	0.50434(16)	0.0367
C(20)	0.11934(14)	0.5040(3)	0.15006(15)	0.0265

O(21)	-0.00642(10)	0.5213(2)	0.06263(10)	0.0311
O(22)	0.20908(11)	0.5013(3)	0.12375(11)	0.0410

Table 2: Atomic coordinates and equivalent isotropic thermal parameters ($\text{\AA}^2$) of non-hydrogen atoms

Atom	x	y	z	U_{iso}
H(81)	-0.2158	-0.1666	0.1236	0.0285
H(111)	-0.3148	0.4645	0.3178	0.0273
H(121)	-0.5375	0.3186	0.2477	0.0343
H(131)	-0.6943	0.0327	0.1527	0.0402
H(141)	-0.6421	-0.2884	0.0637	0.0378
H(151)	-0.4344	-0.3214	0.0688	0.0321
H(161)	0.1275	0.6520	0.3105	0.0286
H(171)	0.2974	0.2812	0.3375	0.0339
H(183)	0.4613	0.5378	0.4802	0.0587
H(182)	0.3464	0.7136	0.4666	0.0586
H(181)	0.3727	0.6602	0.3409	0.0580
H(193)	0.3593	0.2785	0.5712	0.0550
H(192)	0.2304	0.4280	0.5391	0.0561
H(191)	0.2139	0.1743	0.4824	0.0555
H(211)	-0.0087	0.5198	-0.0147	0.0475

Table 3: Atomic coordinates and isotropic thermal parameters ($\text{\AA}^2$) of hydrogen atoms

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(1)	0.0260(5)	0.0289(6)	0.0255(6)	-0.0026(5)	0.0137(5)	0.0036(5)
C(2)	0.0219(7)	0.0239(8)	0.0188(7)	0.0025(6)	0.0090(6)	0.0016(6)
N(3)	0.0211(6)	0.0223(7)	0.0236(6)	-0.0020(5)	0.0115(5)	-0.0021(5)
C(4)	0.0229(7)	0.0238(8)	0.0223(7)	0.0004(6)	0.0114(6)	0.0015(6)
O(5)	0.0315(6)	0.0261(6)	0.0373(7)	-0.0088(5)	0.0175(5)	-0.0032(5)
C(6)	0.0226(7)	0.0224(8)	0.0207(7)	-0.0003(6)	0.0095(6)	-0.0009(7)
C(7)	0.0214(7)	0.0227(8)	0.0196(7)	0.0012(6)	0.0090(6)	0.0018(6)
C(8)	0.0252(8)	0.0226(8)	0.0214(7)	0.0015(6)	0.0103(6)	0.0016(6)
C(9)	0.0223(7)	0.0257(8)	0.0178(7)	0.0016(6)	0.0079(6)	-0.0004(6)
C(10)	0.0223(7)	0.0270(8)	0.0199(7)	0.0007(7)	0.0096(6)	-0.0012(7)
C(11)	0.0255(7)	0.0256(8)	0.0235(7)	-0.0019(7)	0.0127(6)	0.0008(7)
C(12)	0.0262(8)	0.0331(10)	0.0271(8)	-0.0015(7)	0.0144(7)	-0.0002(7)
C(13)	0.0254(8)	0.0435(11)	0.0315(8)	-0.0009(8)	0.0150(7)	-0.0054(8)
C(14)	0.0296(8)	0.0371(10)	0.0287(8)	-0.0013(8)	0.0132(7)	-0.0087(8)
C(15)	0.0293(8)	0.0254(9)	0.0230(8)	0.0006(7)	0.0112(6)	-0.0036(7)
C(16)	0.0215(7)	0.0268(8)	0.0245(7)	0.0004(7)	0.0117(6)	-0.0041(7)
C(17)	0.0228(8)	0.0336(9)	0.0233(8)	0.0001(7)	0.0098(6)	-0.0022(7)
C(18)	0.0270(8)	0.0487(13)	0.0345(10)	0.0011(9)	0.0098(7)	-0.0091(8)
C(19)	0.0301(9)	0.0485(12)	0.0273(9)	0.0076(8)	0.0094(7)	-0.0017(9)
C(20)	0.0236(7)	0.0293(9)	0.0266(8)	0.0023(7)	0.0115(6)	-0.0035(7)
O(21)	0.0267(6)	0.0425(8)	0.0223(5)	0.0044(6)	0.0096(5)	-0.0006(6)
O(22)	0.0302(6)	0.0652(10)	0.0324(6)	0.0046(7)	0.0186(5)	-0.0073(7)

Table 4: Anisotropic thermal parameters ($\text{\AA}^2$)

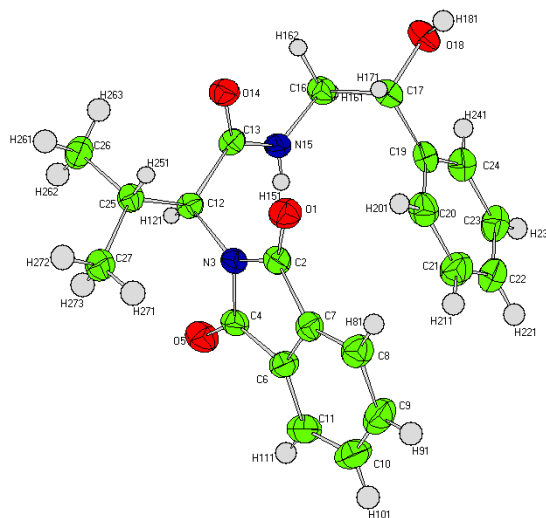
O(1) - C(2)	1.2269(18)	C(10) - C(11)	1.426(2)
C(2) - N(3)	1.383(2)	C(10) - C(12)	1.418(2)
C(2) - C(7)	1.478(2)	C(12) - C(13)	1.367(2)
N(3) - C(4)	1.4112(18)	C(12) - H(121)	0.989
N(3) - C(16)	1.4581(18)	C(13) - C(14)	1.410(3)
C(4) - O(5)	1.206(2)	C(14) - C(15)	1.374(2)
C(4) - C(6)	1.485(2)	C(16) - C(17)	1.539(2)

C(6) - C(7)	1.411(2)	C(16) - C(20)	1.530(2)
C(6) - C(11)	1.360(2)	C(17) - C(18)	1.525(2)
C(7) - C(8)	1.362(2)	C(17) - C(19)	1.521(2)
C(8) - C(9)	1.428(2)	C(20) - O(21)	1.3349(18)
C(9) - C(10)	1.426(2)	C(20) - O(22)	1.2000(18)
C(9) - C(15)	1.407(2)	O(21) - H(211)	0.890

Table 5: Bond lengths (Å) Note – C-H atoms have been excluded

O(1) - C(2) - N(3)	123.44(13)	C(10) - C(9) - C(15)	118.80(13)
O(1) - C(2) - C(7)	129.99(15)	C(9) - C(10) - C(11)	119.97(13)
N(3) - C(2) - C(7)	106.55(13)	C(9) - C(10) - C(12)	119.08(14)
C(2) - N(3) - C(4)	112.41(12)	C(11) - C(10) - C(12)	120.94(15)
C(2) - N(3) - C(16)	123.68(12)	C(10) - C(11) - C(6)	118.14(15)
C(4) - N(3) - C(16)	122.82(13)	C(10) - C(12) - C(13)	120.56(16)
N(3) - C(4) - O(5)	124.24(14)	C(12) - C(13) - C(14)	120.37(15)
N(3) - C(4) - C(6)	105.16(13)	C(13) - C(14) - C(15)	120.24(16)
O(5) - C(4) - C(6)	130.58(14)	C(9) - C(15) - C(14)	120.91(16)
C(4) - C(6) - C(7)	108.14(12)	N(3) - C(16) - C(17)	114.94(13)
C(4) - C(6) - C(11)	129.60(15)	N(3) - C(16) - C(20)	109.27(12)
C(7) - C(6) - C(11)	122.07(15)	C(17) - C(16) - C(20)	112.52(12)
C(2) - C(7) - C(6)	107.68(13)	C(16) - C(17) - C(18)	109.35(14)
C(2) - C(7) - C(8)	130.52(15)	C(16) - C(17) - C(19)	110.72(13)
C(6) - C(7) - C(8)	121.66(13)	C(18) - C(17) - C(19)	110.81(14)
C(7) - C(8) - C(9)	118.32(14)	C(16) - C(20) - O(21)	112.14(12)
C(8) - C(9) - C(10)	119.78(14)	C(16) - C(20) - O(22)	123.89(13)
C(8) - C(9) - C(15)	121.40(15)	O(21) - C(20) - O(22)	123.96(14)

Table 6: Bond angles (° C) Note – H atoms have been excluded

Single-crystal X-ray diffraction report for compound **302** (Datablock: 0560910)

Crystal of **302** were grown and run by Callens Cédric from dichloromethane and petrol 40-60 °C. A single crystal having dimensions approximately **0.12 x 0.40 x 0.50 mm** was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150 K in a stream of cold N₂ using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoK_α radiation, $\lambda = 0.71073$ Å). Intensity data were processed using the DENZO-SMN package.¹

Examination of the systematic absences of the intensity data showed the space group to be **P 2₁/c**. The structure was solved in this space group using the direct-methods program SIR92,² which located all non-hydrogen atoms. The H atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. Subsequent full-matrix least-squares refinement was carried out against F² using the CRYSTAL program suite.³ Coordinates and anisotropic thermal parameters were refined for all non-hydrogen atoms, and the hydrogens were refined with riding constraints. A modified statistical weighting scheme was applied. Refinement converged satisfactorily to give **R = 0.0422, wR = 0.0844**.

Attached is a thermal ellipsoid plot (CAMERON) at 50% probability. A summary of crystallographic data is given below, as are full lists of atomic coordinates, anisotropic thermal parameters and those bond lengths and angles not concerning H atoms.

References

- (1) Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, 276, 307.
- (2) A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr.* **1994**, 27, 435.
- (3) P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout, D. J. Watkin, *J. Appl. Crystallogr.* **2003**, 36, 1487.

Crystal identification	CCK 0560910
Chemical formula	C ₂₁ H ₂₂ N ₂ O ₄
Formula weight	366.42
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	P 21/c
<i>a</i> (Å)	5.4234(3)
<i>b</i> (Å)	11.1965(5)
<i>c</i> (Å)	15.7831(9)
α (°)	90
β (°)	96.6243(19)
γ (°)	90
Cell volume (Å ³)	2066.36(10)
<i>Z</i>	2
Calculated density (Mg/m ³)	1.278
Absorption coefficient (mm ⁻¹)	0.089
<i>F</i> ₀₀₀	388
Crystal size (mm)	0.12 × 0.40 × 0.50
Description of crystal	Colourless plate
Absorption correction	multi-scan
Transmission coefficients (min,max)	0.95, 0.99
θ range for data collection (°)	5.11 ≤ θ ≤ 27.45
Index ranges	-7 ≤ <i>h</i> ≤ 7, -13 ≤ <i>k</i> ≤ 14, -20 ≤ <i>l</i> ≤ 20
Reflections measured	4192
Unique reflections	2413
<i>R</i> _{int}	0.000
Observed reflections (<i>I</i> > -3 σ (<i>I</i>))	2413
Refinement method	Full-matrix least-squares on <i>Fsqd</i>
Parameters refined	246
Weighting scheme	Modified Sheldrick
Goodness of fit	1.0118
<i>R</i>	0.0422
<i>wR</i>	0.0844
Residual electron density (min,max) (eÅ ⁻³)	-0.17, 0.14

Table 1: Crystal data and refinement details

Atom	x	y	z	U _{equiv}
O(1)	1.1096(4)	0.31283(19)	0.27272(12)	0.0421
C(2)	0.9351(5)	0.2971(2)	0.21899(17)	0.0323
N(3)	0.7377(4)	0.2197(2)	0.22798(13)	0.0301
C(4)	0.5656(5)	0.2195(3)	0.15431(17)	0.0333
O(5)	0.3789(4)	0.15983(19)	0.14484(13)	0.0438
C(6)	0.6624(5)	0.3062(3)	0.09425(17)	0.0358
C(7)	0.8832(5)	0.3530(2)	0.13378(18)	0.0346
C(8)	1.0132(6)	0.4382(3)	0.0946(2)	0.0446
C(9)	0.9129(7)	0.4759(3)	0.0133(2)	0.0557
C(10)	0.6970(6)	0.4276(3)	-0.0263(2)	0.0524
C(11)	0.5664(6)	0.3408(3)	0.01338(18)	0.0453
C(12)	0.7207(5)	0.1424(2)	0.30198(16)	0.0302
C(13)	0.7509(5)	0.2194(2)	0.38336(17)	0.0298
O(14)	0.9200(3)	0.20688(18)	0.44131(11)	0.0378
N(15)	0.5714(4)	0.3013(2)	0.38567(13)	0.0305
C(16)	0.5562(5)	0.3816(2)	0.45755(18)	0.0339
C(17)	0.6862(5)	0.5008(2)	0.44667(17)	0.0340
O(18)	0.6551(3)	0.56687(18)	0.52236(12)	0.0409
C(19)	0.5814(5)	0.5661(2)	0.36710(17)	0.0338
C(20)	0.6945(5)	0.5610(3)	0.29324(19)	0.0423

C(21)	0.5929(6)	0.6181(3)	0.2189(2)	0.0503
C(22)	0.3770(6)	0.6824(3)	0.2195(2)	0.0491
C(23)	0.2622(6)	0.6884(3)	0.2923(2)	0.0462
C(24)	0.3619(5)	0.6310(2)	0.36597(19)	0.0399
C(25)	0.9007(5)	0.0362(2)	0.30536(17)	0.0333
C(26)	0.8258(6)	-0.0551(3)	0.36928(19)	0.0456
C(27)	0.9033(6)	-0.0207(3)	0.21760(19)	0.0486

Table 2: Atomic coordinates and equivalent isotropic thermal parameters ($\text{\AA}^2$) of non-hydrogen atoms

Atom	x	y	z	U_{iso}
H(81)	1.1628	0.4696	0.1219	0.0532
H(91)	0.9949	0.5339	-0.0151	0.0650
H(101)	0.6368	0.4541	-0.0818	0.0649
H(111)	0.4179	0.3084	-0.0124	0.0551
H(121)	0.5520	0.1103	0.2954	0.0347
H(161)	0.3814	0.3983	0.4614	0.0399
H(162)	0.6328	0.3419	0.5098	0.0401
H(171)	0.8656	0.4859	0.4431	0.0399
H(201)	0.8421	0.5193	0.2939	0.0510
H(211)	0.6723	0.6123	0.1685	0.0611
H(221)	0.3078	0.7217	0.1693	0.0612
H(231)	0.1098	0.7302	0.2909	0.0551
H(241)	0.2836	0.6362	0.4162	0.0483
H(251)	1.0686	0.0660	0.3268	0.0396
H(261)	0.9582	-0.1146	0.3775	0.0673
H(262)	0.6703	-0.0922	0.3470	0.0667
H(263)	0.8081	-0.0168	0.4243	0.0668
H(272)	1.0218	-0.0865	0.2224	0.0720
H(273)	0.7377	-0.0508	0.1983	0.0716
H(271)	0.9508	0.0388	0.1770	0.0721
H(181)	0.7878	0.6031	0.5348	0.0595
H(151)	0.4622	0.3081	0.3419	0.0384

Table 3: Atomic coordinates and isotropic thermal parameters ($\text{\AA}^2$) of hydrogen atoms

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(1)	0.0382(12)	0.0454(13)	0.0410(12)	0.0012(10)	-0.0031(10)	-0.0022(10)
C(2)	0.0283(16)	0.0330(16)	0.0346(17)	-0.0031(14)	-0.0009(14)	0.0072(14)
N(3)	0.0306(12)	0.0290(12)	0.0294(13)	-0.0018(11)	-0.0021(10)	-0.0004(11)
C(4)	0.0360(16)	0.0327(16)	0.0299(16)	-0.0046(13)	-0.0016(12)	0.0086(15)
O(5)	0.0393(12)	0.0471(12)	0.0432(12)	-0.0061(10)	-0.0031(9)	-0.0050(11)
C(6)	0.0425(18)	0.0363(17)	0.0286(16)	0.0026(13)	0.0041(13)	0.0076(14)
C(7)	0.0360(16)	0.0324(15)	0.0361(16)	-0.0003(13)	0.0076(13)	0.0069(14)
C(8)	0.0462(18)	0.0442(19)	0.0443(19)	0.0033(16)	0.0097(14)	0.0010(16)
C(9)	0.074(3)	0.046(2)	0.051(2)	0.0139(17)	0.0216(18)	0.0091(19)
C(10)	0.062(2)	0.059(2)	0.0362(18)	0.0088(17)	0.0031(16)	0.014(2)
C(11)	0.0498(19)	0.051(2)	0.0344(19)	-0.0020(15)	0.0014(15)	0.0094(16)
C(12)	0.0331(15)	0.0302(16)	0.0272(15)	0.0014(12)	0.0036(11)	-0.0013(12)
C(13)	0.0310(15)	0.0295(15)	0.0290(16)	0.0038(12)	0.0041(13)	0.0017(13)
O(14)	0.0393(11)	0.0400(12)	0.0327(11)	-0.0014(9)	-0.0022(9)	0.0118(9)
N(15)	0.0339(13)	0.0305(12)	0.0259(12)	-0.0009(10)	-0.0023(9)	0.0046(11)
C(16)	0.0324(16)	0.0347(17)	0.0341(16)	-0.0044(13)	0.0015(12)	0.0031(12)
C(17)	0.0310(16)	0.0373(17)	0.0336(17)	-0.0064(13)	0.0037(12)	-0.0014(13)
O(18)	0.0372(11)	0.0424(12)	0.0425(12)	-0.0132(10)	0.0020(9)	-0.0053(10)
C(19)	0.0337(16)	0.0263(15)	0.0418(17)	-0.0053(13)	0.0058(13)	-0.0034(13)
C(20)	0.0431(17)	0.0376(17)	0.048(2)	-0.0040(15)	0.0121(15)	0.0041(14)
C(21)	0.060(2)	0.0465(19)	0.046(2)	0.0050(16)	0.0143(16)	0.0056(17)
C(22)	0.062(2)	0.0343(18)	0.049(2)	0.0071(14)	-0.0005(16)	0.0033(16)
C(23)	0.0482(19)	0.0336(18)	0.057(2)	0.0041(15)	0.0043(16)	0.0063(14)

C(24)	0.0404(18)	0.0336(17)	0.0462(18)	-0.0009(15)	0.0077(14)	0.0008(15)
C(25)	0.0382(16)	0.0292(15)	0.0330(16)	-0.0009(12)	0.0064(12)	0.0053(13)
C(26)	0.062(2)	0.0329(16)	0.0430(19)	0.0064(14)	0.0125(15)	0.0067(15)
C(27)	0.070(2)	0.0366(17)	0.0404(19)	-0.0004(14)	0.0125(15)	0.0147(16)

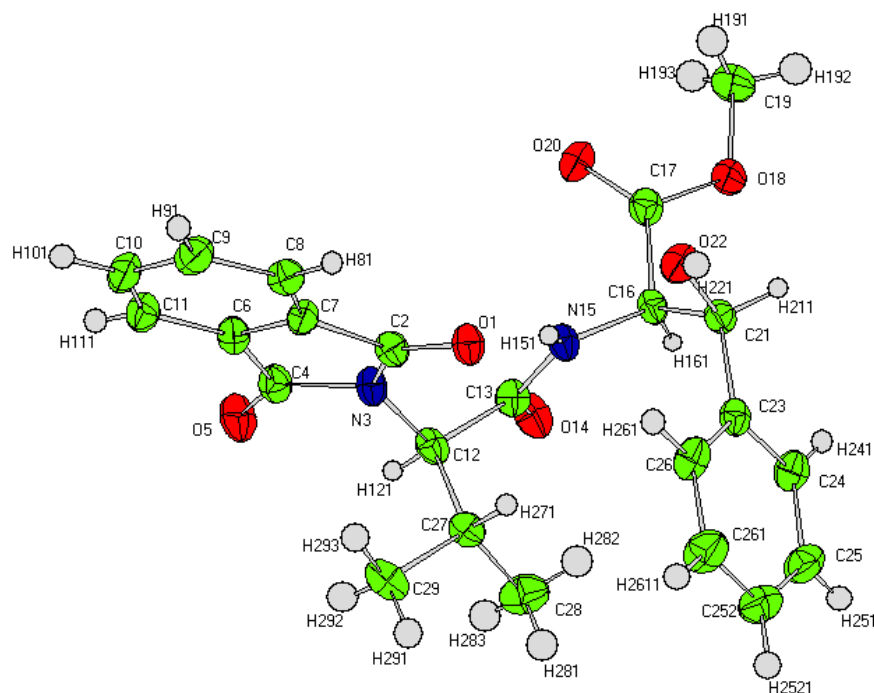
Table 4: Anisotropic thermal parameters ($\text{\AA}^2$)

O(1) - C(2)	1.209(3)	C(13) - O(14)	1.226(3)
C(2) - N(3)	1.398(3)	C(13) - N(15)	1.341(3)
C(2) - C(7)	1.481(4)	N(15) - C(16)	1.457(3)
N(3) - C(4)	1.405(3)	N(15) - H(151)	0.860
N(3) - C(12)	1.465(3)	C(16) - C(17)	1.528(4)
C(4) - O(5)	1.208(3)	C(17) - O(18)	1.432(3)
C(4) - C(6)	1.494(4)	C(17) - C(19)	1.507(4)
C(6) - C(7)	1.388(4)	O(18) - H(181)	0.830
C(6) - C(11)	1.377(4)	C(19) - C(20)	1.380(4)
C(7) - C(8)	1.375(4)	C(19) - C(24)	1.393(4)
C(8) - C(9)	1.400(5)	C(20) - C(21)	1.393(4)
C(9) - C(10)	1.373(5)	C(21) - C(22)	1.376(4)
C(10) - C(11)	1.394(5)	C(22) - C(23)	1.370(4)
C(10) - H(101)	0.947	C(23) - C(24)	1.383(4)
C(11) - H(111)	0.932	C(25) - C(26)	1.524(4)
C(12) - C(13)	1.540(4)	C(25) - C(27)	1.526(4)
C(12) - C(25)	1.536(4)	-	-

Table 5: Bond lengths ($\text{\AA}$) Note – C-H atoms have been excluded

O(1) - C(2) - N(3)	124.5(2)	C(9) - C(10) - C(11)	121.4(3)
O(1) - C(2) - C(7)	128.8(3)	C(10) - C(11) - C(6)	117.1(3)
N(3) - C(2) - C(7)	106.7(2)	N(3) - C(12) - C(13)	108.9(2)
C(2) - N(3) - C(4)	111.1(2)	N(3) - C(12) - C(25)	112.8(2)
C(2) - N(3) - C(12)	124.5(2)	C(13) - C(12) - C(25)	113.5(2)
C(4) - N(3) - C(12)	124.2(2)	C(12) - C(13) - O(14)	123.8(2)
N(3) - C(4) - O(5)	124.8(3)	C(12) - C(13) - N(15)	113.5(2)
N(3) - C(4) - C(6)	106.0(2)	O(14) - C(13) - N(15)	122.7(2)
O(5) - C(4) - C(6)	129.2(2)	C(13) - N(15) - C(16)	123.3(2)
C(4) - C(6) - C(7)	108.0(2)	N(15) - C(16) - C(17)	112.5(2)
C(4) - C(6) - C(11)	130.4(3)	C(16) - C(17) - O(18)	104.9(2)
C(7) - C(6) - C(11)	121.7(3)	C(16) - C(17) - C(19)	112.5(2)
C(2) - C(7) - C(6)	108.2(2)	O(18) - C(17) - C(19)	112.0(2)
C(2) - C(7) - C(8)	130.4(3)	C(17) - C(19) - C(20)	121.5(2)
C(6) - C(7) - C(8)	121.4(3)	C(17) - C(19) - C(24)	120.2(2)
C(7) - C(8) - C(9)	117.1(3)	C(20) - C(19) - C(24)	118.3(3)
C(8) - C(9) - C(10)	121.3(3)	C(19) - C(20) - C(21)	121.4(3)

Table 6: Bond angles ($^\circ$ C) Note – H atoms have been excluded

Single-crystal X-ray diffraction report for compound **312** (Datablock: 0620910)

Crystal of **312** were grown and run by Callens Cédric from dichloromethane and petrol 40-60 °C. A single crystal having dimensions approximately **0.18 x 0.20 x 0.36 mm** was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150 K in a stream of cold N₂ using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoK_α radiation, $\lambda = 0.71073$ Å). Intensity data were processed using the DENZO-SMN package.¹

Examination of the systematic absences of the intensity data showed the space group to be **P 2₁/c**. The structure was solved in this space group using the direct-methods program SIR92,² which located all non-hydrogen atoms. The H atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. Subsequent full-matrix least-squares refinement was carried out against F² using the CRYSTAL program suite.³ Coordinates and anisotropic thermal parameters were refined for all non-hydrogen atoms, and the hydrogens were refined with riding constraints. A modified statistical weighting scheme was applied. Refinement converged satisfactorily to give **R = 0.0753**, **wR = 0.1023**.

Attached is a thermal ellipsoid plot (CAMERON) at 50% probability. A summary of crystallographic data is given below, as are full lists of atomic coordinates, anisotropic thermal parameters and those bond lengths and angles not concerning H atoms.

References

- (1) Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, 276, 307.
- (2) A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr.* **1994**, 27, 435.
- (3) P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout, D. J. Watkin, *J. Appl. Crystallogr.* **2003**, 36, 1487.

Crystal identification	CCK 0620910
Chemical formula	C ₂₃ H ₂₄ N ₂ O ₆
Formula weight	424.45
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	P 21/c
<i>a</i> (Å)	10.6230(4)
<i>b</i> (Å)	7.4925(3)
<i>c</i> (Å)	13.4324(7)
α (°)	90
β (°)	103.1765(18)
γ (°)	90
Cell volume (Å ³)	1040.98(8)
<i>Z</i>	2
Calculated density (Mg/m ³)	1.354
Absorption coefficient (mm ⁻¹)	0.099
<i>F</i> ₀₀₀	448
Crystal size (mm)	0.18 × 0.24 × 0.26
Description of crystal	Colourless block
Absorption correction	multi-scan
Transmission coefficients (min,max)	0.90, 0.98
θ range for data collection (°)	5.20 ≤ θ ≤ 27.45
Index ranges	-13 ≤ <i>h</i> ≤ 13, -9 ≤ <i>k</i> ≤ 8, -17 ≤ <i>l</i> ≤ 17
Reflections measured	27855
Unique reflections	2535
<i>R</i> _{int}	0.051
Observed reflections (<i>I</i> > -3 σ (<i>I</i>))	2535
Refinement method	Full-matrix least-squares on <i>Fsqd</i>
Parameters refined	280
Weighting scheme	Modified Sheldrick
Goodness of fit	0.9102
<i>R</i>	0.0753
<i>wR</i>	0.1023
Residual electron density (min,max) (eÅ ⁻³)	-0.47, 0.49

Table 1: Crystal data and refinement details

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{equiv}
O(1)	0.7210(2)	0.4443(3)	0.40517(17)	0.0293
O(2)	0.7517(2)	0.3781(4)	-0.02036(16)	0.0345
O(3)	0.8809(2)	0.2955(4)	0.12877(17)	0.0405
O(4)	0.6219(2)	-0.0319(3)	0.18345(17)	0.0338
O(5)	0.6632(2)	0.6089(3)	0.16692(18)	0.0312
O(6)	0.8284(2)	-0.1286(3)	0.51130(18)	0.0378
N(7)	0.7567(3)	0.1395(4)	0.4314(2)	0.0260
C(8)	0.7754(3)	0.3271(4)	0.0772(2)	0.0271
N(9)	0.6702(3)	0.2579(4)	0.2177(2)	0.0253
C(10)	0.8759(3)	0.3299(5)	0.5536(2)	0.0267
C(11)	0.7761(3)	0.3206(5)	0.4557(2)	0.0259
C(12)	1.0064(3)	0.1253(5)	0.6719(3)	0.0335
C(13)	0.5783(3)	0.4940(4)	0.1003(2)	0.0251
C(14)	0.3460(3)	0.4000(5)	0.0513(3)	0.0308
C(15)	0.6483(3)	0.0920(5)	0.2453(2)	0.0266
C(16)	0.4455(3)	0.4773(4)	0.1239(2)	0.0251
C(17)	0.2250(3)	0.3753(5)	0.0714(3)	0.0368
C(18)	0.9130(3)	0.1579(4)	0.5837(2)	0.0274
C(19)	0.8337(3)	0.0323(5)	0.5089(3)	0.0286
C(20)	0.6491(3)	0.3145(4)	0.1121(2)	0.0232

C(21)	0.5160(3)	0.1265(5)	0.3779(2)	0.0286
C(22)	1.0188(3)	0.4446(5)	0.7001(3)	0.0357
C(23)	1.0576(3)	0.2710(6)	0.7296(3)	0.0378
C(24)	0.4029(4)	0.0360(6)	0.3050(3)	0.0447
C(25)	0.9274(3)	0.4775(5)	0.6098(3)	0.0309
C(26)	0.4209(3)	0.5306(5)	0.2166(3)	0.0348
C(27)	0.5117(4)	0.0951(5)	0.4890(3)	0.0392
C(28)	0.6468(3)	0.0628(4)	0.3571(2)	0.0258
C(29)	0.8625(3)	0.3915(6)	-0.0657(3)	0.0443
C(261)	0.2989(3)	0.5075(6)	0.2357(3)	0.0422
C(171)	0.2019(3)	0.4276(6)	0.1643(3)	0.0430

Table 2: Atomic coordinates and equivalent isotropic thermal parameters ($\text{\AA}^2$) of non-hydrogen atoms

Atom	x	y	z	U_{iso}
H(121)	1.0342	0.0093	0.6894	0.0396
H(131)	0.5694	0.5335	0.0294	0.0300
H(141)	0.3602	0.3695	-0.0135	0.0368
H(171)	0.1586	0.3208	0.0236	0.0439
H(201)	0.5943	0.2259	0.0706	0.0279
H(211)	0.5086	0.2537	0.3640	0.0344
H(221)	1.0551	0.5401	0.7418	0.0431
H(231)	1.1194	0.2499	0.7910	0.0448
H(242)	0.4031	0.0660	0.2343	0.0665
H(243)	0.4101	-0.0911	0.3146	0.0667
H(241)	0.3223	0.0793	0.3215	0.0667
H(251)	0.9045	0.5924	0.5871	0.0377
H(261)	0.4884	0.5813	0.2662	0.0424
H(272)	0.5769	0.1687	0.5332	0.0582
H(271)	0.5292	-0.0295	0.5066	0.0593
H(273)	0.4255	0.1242	0.4980	0.0587
H(281)	0.6522	-0.0659	0.3684	0.0307
H(292)	0.8324	0.4301	-0.1365	0.0668
H(293)	0.9056	0.2773	-0.0615	0.0667
H(291)	0.9207	0.4768	-0.0278	0.0671
H(91)	0.6802	0.3421	0.2644	0.0300
H(1711)	0.1206	0.4127	0.1769	0.0521
H(2611)	0.2823	0.5475	0.2972	0.0515
H(51)	0.6661	0.6782	0.2152	0.0513

Table 3: Atomic coordinates and isotropic thermal parameters ($\text{\AA}^2$) of hydrogen atoms

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(1)	0.0363(12)	0.0215(12)	0.0287(12)	0.0026(10)	0.0042(10)	0.0037(11)
O(2)	0.0278(11)	0.0489(16)	0.0283(12)	0.0083(11)	0.0096(9)	0.0045(11)
O(3)	0.0273(12)	0.0526(17)	0.0380(13)	0.0090(13)	0.0001(10)	0.0036(12)
O(4)	0.0530(15)	0.0204(12)	0.0278(12)	-0.0027(10)	0.0087(11)	-0.0032(12)
O(5)	0.0314(12)	0.0227(12)	0.0360(13)	-0.0041(11)	0.0007(10)	-0.0042(11)
O(6)	0.0505(16)	0.0202(14)	0.0401(15)	0.0065(11)	0.0050(12)	0.0046(11)
N(7)	0.0321(14)	0.0199(15)	0.0242(14)	0.0019(12)	0.0026(12)	0.0033(12)
C(8)	0.0301(17)	0.0218(17)	0.0279(17)	0.0015(15)	0.0038(13)	0.0015(15)
N(9)	0.0317(14)	0.0204(15)	0.0225(13)	0.0003(11)	0.0037(11)	-0.0003(12)
C(10)	0.0233(15)	0.0308(19)	0.0244(16)	0.0028(15)	0.0023(12)	0.0027(15)
C(11)	0.0300(16)	0.0245(18)	0.0233(16)	-0.0011(15)	0.0065(13)	-0.0004(15)
C(12)	0.0295(17)	0.037(2)	0.0330(19)	0.0066(17)	0.0060(15)	0.0079(17)
C(13)	0.0278(15)	0.0228(18)	0.0239(16)	0.0029(14)	0.0043(13)	-0.0025(14)
C(14)	0.0311(17)	0.0326(19)	0.0268(17)	-0.0027(15)	0.0025(14)	0.0024(15)
C(15)	0.0300(17)	0.0206(17)	0.0296(17)	-0.0020(14)	0.0073(14)	0.0025(14)

C(16)	0.0294(15)	0.0182(16)	0.0255(16)	0.0018(14)	0.0018(12)	0.0017(13)
C(17)	0.0273(17)	0.037(2)	0.042(2)	-0.0016(17)	0.0005(15)	-0.0037(16)
C(18)	0.0291(16)	0.0285(19)	0.0239(17)	0.0022(14)	0.0048(14)	0.0046(15)
C(19)	0.0310(17)	0.028(2)	0.0272(17)	0.0028(15)	0.0067(14)	0.0049(15)
C(20)	0.0289(15)	0.0202(16)	0.0196(15)	0.0011(14)	0.0034(12)	-0.0024(14)
C(21)	0.0305(16)	0.0266(17)	0.0293(17)	0.0022(15)	0.0078(14)	-0.0016(15)
C(22)	0.0288(17)	0.041(2)	0.036(2)	-0.0003(17)	0.0045(15)	-0.0001(18)
C(23)	0.0264(17)	0.055(3)	0.0295(18)	0.0055(18)	0.0013(14)	0.0051(17)
C(24)	0.0372(19)	0.047(2)	0.050(2)	-0.007(2)	0.0104(18)	-0.0084(19)
C(25)	0.0285(16)	0.0309(19)	0.0330(19)	0.0021(16)	0.0061(14)	-0.0004(15)
C(26)	0.0332(18)	0.037(2)	0.0312(18)	-0.0033(16)	0.0008(14)	0.0043(16)
C(27)	0.051(2)	0.034(2)	0.038(2)	0.0048(17)	0.0198(17)	-0.0028(18)
C(28)	0.0356(17)	0.0174(16)	0.0235(16)	0.0006(13)	0.0046(13)	-0.0054(14)
C(29)	0.0372(19)	0.058(3)	0.042(2)	0.008(2)	0.0180(17)	0.0009(19)
C(171)	0.0292(17)	0.054(3)	0.046(2)	0.002(2)	0.0106(16)	0.0019(19)
C(261)	0.0336(18)	0.059(3)	0.0351(19)	-0.0083(19)	0.0091(15)	0.0052(19)

Table 4: Anisotropic thermal parameters ($\text{\AA}^2$)

O(1) - C(11)	1.217(4)	C(12) - C18	1.383(5)
O(2) - C(8)	1.333(4)	C(12) - C(23)	1.377(6)
O(2) - C(29)	1.447(4)	C(13) - C(16)	1.520(4)
O(3) - C(8)	1.199(4)	C(13) - C(20)	1.532(4)
O(4) - C(15)	1.235(4)	C(14) - C(16)	1.390(4)
O(5) - C(13)	1.410(4)	C(14) - C(17)	1.385(5)
O(5) - H(51)	0.827	C(15) - C(28)	1.521(4)
O(6) - C(19)	1.208(4)	C(16) - C(26)	1.388(5)
N(7) - C(11)	1.400(4)	C(17) - C(171)	1.383(5)
N(7) - C(19)	1.418(4)	C(18) - C(19)	1.490(5)
N(7) - C(28)	1.469(4)	C(21) - C(24)	1.525(5)
C(8) - C(20)	1.521(4)	C(21) - C(27)	1.523(5)
N(9) - C(15)	1.333(4)	C(21) - C(28)	1.554(4)
N(9) - C(20)	1.448(4)	C(22) - C(23)	1.395(6)
N(9) - H(91)	0.879	C(22) - C(25)	1.392(5)
C(10) - C(11)	1.491(4)	C(26) - C(261)	1.388(5)
C(10) - C18	1.381(5)	C(171) - C(261)	1.375(5)
C(10) - C(25)	1.380(5)	-	-

Table 5: Bond lengths ($\text{\AA}$) Note – C-H atoms have been excluded

C(8) - O(2) - C(29)	116.4(2)	C(14) - C(16) - C(26)	118.8(3)
C(11) - N(7) - C(19)	110.4(3)	C(14) - C(17) - C(171)	120.2(3)
C(11) - N(7) - C(28)	126.1(3)	C(12) - C(18) - C(10)	121.1(3)
C(19) - N(7) - C(28)	120.9(3)	C(12) - C(18) - C(19)	130.6(3)
O(2) - C(8) - O(3)	124.5(3)	C(10) - C(18) - C(19)	108.2(3)
O(2) - C(8) - C(20)	109.8(2)	C(18) - C(19) - N(7)	106.3(3)
O(3) - C(8) - C(20)	125.7(3)	C(18) - C(19) - O(6)	129.5(3)
C(15) - N(9) - C(20)	123.2(3)	N(7) - C(19) - O(6)	124.2(3)
C(11) - C(10) - C(18)	108.2(3)	C(13) - C(20) - C(8)	111.1(3)
C(11) - C(10) - C(25)	129.3(3)	C(13) - C(20) - N(9)	108.7(3)
C(18) - C(10) - C(25)	122.4(3)	C(8) - C(20) - N(9)	111.7(2)
C(10) - C(11) - N(7)	106.8(3)	C(24) - C(21) - C(27)	111.5(3)
C(10) - C(11) - O(1)	127.7(3)	C(24) - C(21) - C(28)	110.7(3)
N(7) - C(11) - O(1)	125.6(3)	C(27) - C(21) - C(28)	110.9(3)
C(18) - C(12) - C(23)	117.2(4)	C(23) - C(22) - C(25)	121.0(4)
O(5) - C(13) - C(16)	114.1(3)	C(22) - C(23) - C(12)	121.8(3)
O(5) - C(13) - C(20)	104.0(2)	C(22) - C(25) - C(10)	116.5(3)
C(16) - C(13) - C(20)	111.3(2)	C(16) - C(26) - C(261)	120.3(3)
C(16) - C(14) - C(17)	120.6(3)	C(21) - C(28) - C(15)	110.1(3)
N(9) - C(15) - O(4)	122.7(3)	C(21) - C(28) - N(7)	111.3(2)

N(9) - C(15) - C(28)	116.8(3)	C(15) - C(28) - N(7)	115.4(3)
O(4) - C(15) - C(28)	120.3(3)	C(17) - C(171) - C(26)1	119.6(3)
C(13) - C(16) - C(14)	118.7(3)	C(26) - C(26)1 - C(171)	120.6(3)
C(13) - C(16) - C(26)	122.5(3)	-	-

Table 6: Bond angles (° C) Note – H atoms have been excluded