

The Tethered Aminohydroxylation of Allylic Carbamates

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For mum and dad

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Abstract

The Tethered Aminohydroxylation of Allylic Carbamates

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The osmium-mediated aminohydroxylation reaction is a powerful oxidation that introduces a hydroxyl group and a protected amino group in a *syn* relationship across an olefinic double bond. This study concerns one approach to controlling the regioselectivity of this oxidation.

Introduction I

The mechanism, scope and limitations of the aminohydroxylation reaction are discussed, with particular attention to the asymmetric version, providing a background from which the newly developed methodology has emerged.

Results and Discussion I

Development of the reaction

This section concerns the original attempts to perform the tethered aminohydroxylation reaction, and early process optimisation to maximise the yield of aminohydroxylated product produced.

Scope of the reaction

This section details the results of the TA reaction as applied to further allylic carbamates demonstrating the applicability of the reaction to other olefinic geometries. The diastereoselectivity of the reaction in cyclic and acyclic systems is reported, and a model to explain the observed results discussed. Also covered within are the syntheses of the various substrates and proof of the stereochemistry of the products.

Mechanistic investigations

Work involving attempts to isolate a catalytic intermediate from the reaction is described. A crystal structure of this intermediate is discussed.

Introduction II

The isolation and physiological properties of the antibiotic compound hygromycin A are described. Prior synthetic routes towards this compound are discussed.

Results and Discussion II

Three approaches towards the aminocyclitol unit of hygromycin A, employing the tethered aminohydroxylation reaction, are outlined. Two of these allow for potential future development and completion of the synthesis.

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Abbreviations used in this thesis

AA	asymmetric aminohydroxylation	ee	enantiomeric excess
AAA	asymmetric allylic alkylation	eq.	Equivalents
Ac	acetyl	ES	electrospray ionisation
Ad	adenine	Et	ethyl
AD	asymmetric dihydroxylation	FI	field ionisation
ADDP	1,1'-(azodicarbonyl) dipiperidine	g	gram
AE	asymmetric epoxidation	GC	gas chromatography
aq.	aqueous	H	hours
AQN	anthraquinonyl	Het	generic heterocycle
Ar	aromatic group	HMPA	hexamethylphosphoric triamide
Bn	benzyl	HPLC	high performance liquid chromatography
Boc	<i>tert</i> -butyloxycarbonyl	HRMS	high-resolution mass spectrometry
Bu	butyl	Hz	Hertz
Bus	<i>tert</i> -butylsulfonyl	<i>i</i>	iso
C	Celsius	IND	indolinyll
CAN	ceric ammonium nitrate	IR	infra-red
Cat.	catalyst/catalytic	KHMDS	potassium hexamethyldisilazide
CI	chemical ionisation	L	litre/ligand
CBz	benzyloxycarbonyl	LCMS	liquid chromatography mass spectrometry
CLB	chlorobenzoate	LDA	lithium diisopropylamide
conc.	Concentrated	lit.	literature
DBAD	di- <i>tert</i> -butyl diazadicarboxylate	M	molar
DBU	1,8-diazabicyclo [5.4.0]undec-7-ene	Me	methyl
DCC	dicyclohexyl carbodiimide	min	minutes
de	diastereomeric excess	mol	mole
dec.	decomposed	MOM	methoxymethyl
DEAD	diethyl azadicarboxylate	mp	melting point
DHQ	dihydroquinyl	Ms	methanesulfonyl
DHQD	dihydroquinidyl	MS	mass spectrometry
DIAD	diisopropyl azadicarboxylate	m/z	mass-to-charge ratio
DIBAL	diisobutyl aluminium hydride	NBS	<i>N</i> -bromosuccinimide
DMAP	<i>N,N</i> -dimethyl aminopyridine	NMO	<i>N</i> -methylmorpholine- <i>N</i> - oxide
DMF	dimethylformamide	NMR	nuclear magnetic resonance
DMP	dimethoxypropane	nOe	nuclear Overhauser effect
DMSO	dimethylsulfoxide	PG	protecting group
		Ph	phenyl
		pH	-log ₁₀ [H ₃ O ⁺]
		PHAL	phthalazinyl
		PHN	phenanthryl
		PMB	<i>para</i> -methoxy benzyloxy

ppm	parts per million	temp.	temperature
PPTS	pyridinium <i>para</i> -toluenesulfonate	TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy radical
Pr	propyl	TeoC	trimethylsilyl
psi	pounds per square inch	TES	ethyloxycarbonyl
PTC	phase transfer catalysis	Tf	triethylsilyl
PYR	diphenylpyrimidyl	TFA	trifluoromethylsulfonyl
R	generic alkyl group	THAB	trifluoroacetic acid
R_f	retention fraction	THF	tetrahexylammonium bromide
rt	room temperature	THP	tetrahydrofuran
sat.	saturated	TLC	tetrahydropyranyl
SM	starting material		thin layer chromatography
<i>t</i>	tertiary	TMEDA	<i>N,N,N',N'</i> -tetramethyl ethylenediamine
TA	tethered aminohydroxylation	TMS	trimethylsilyl
TBA	tetrabutylammonium	Ts	<i>para</i> -toluenesulfonyl
TBDPS	<i>tert</i> -butyldiphenylsilyl	W	Watts
TBS	<i>tert</i> -butyl dimethylsilyl	X	generic atom or group
		[α]	specific rotation

Introduction I

Osmium-mediated aminohydroxylation

1.1 Osmium oxides in organic synthesis

1.1.1 Osmium tetroxide

Osmium tetroxide, OsO_4 , is the highest oxidation state oxide of the group 8 metal, osmium. It has found particular synthetic utility in the oxidation of carbon-carbon double bonds to *syn* 1,2-diols.¹ Within this sphere of chemistry, it provides a mild alternative to oxidation with other transition metal oxides, such as manganese and ruthenium oxides, which often result in over-oxidation. In addition, the introduction of a chiral cinchona alkaloid ligand to osmium tetroxide has enabled this reaction to give a single enantiomer.² This development, which earned its creator K. B. Sharpless the Nobel Prize for Chemistry in 2001, forms one of the most potent reactions available to the synthetic chemist.

Due to the volatility, high toxicity and expense of OsO_4 ,³ it is desirable to use the reagent in sub-stoichiometric quantities. The Sharpless asymmetric dihydroxylation protocol reduces the amount required to catalytic (often 1 mol % or less) quantities, but in addition the introduction of an *in situ* precursor to OsO_4 has been established.

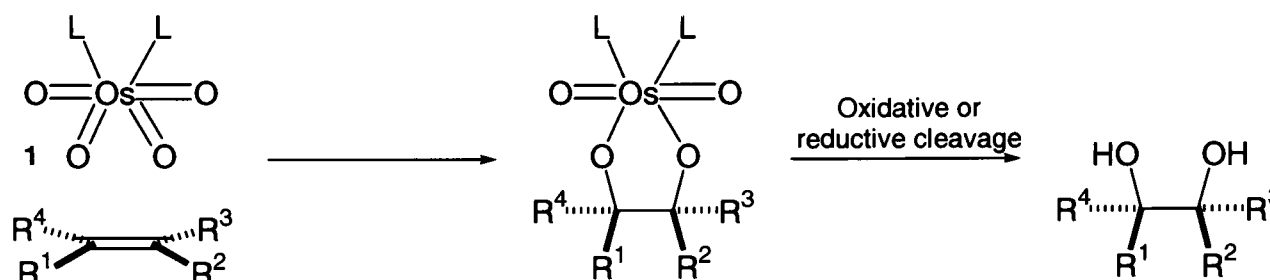
1.1.2 Potassium osmate

Potassium osmate dihydrate, $\text{K}_2\text{OsO}_2(\text{OH})_4$ or $\text{K}_2\text{OsO}_4 \cdot 2\text{H}_2\text{O}$, is a purple, crystalline solid. Like osmium tetroxide, it is commercially available. It is non-volatile, and as such represents a lesser hazard than osmium tetroxide itself. On hydrolysis it liberates 1 mole of water, 2 moles of potassium hydroxide and 1 mole of ' OsO_3 '. This Os(VI) species can then be oxidised by cheaper, stoichiometric oxidants to give an Os(VIII) complex that represents the active oxidant in the course of the dihydroxylation reaction.

1.1.3 Dihydroxylation with osmium tetroxide

The dihydroxylation of olefins using osmium tetroxide was first reported by Makowka.⁴ The mechanism of the reaction (scheme 1) was somewhat elucidated by

Criegee, who also discovered the acceleration of the rate by the addition of an amine ligand.^{5, 6}

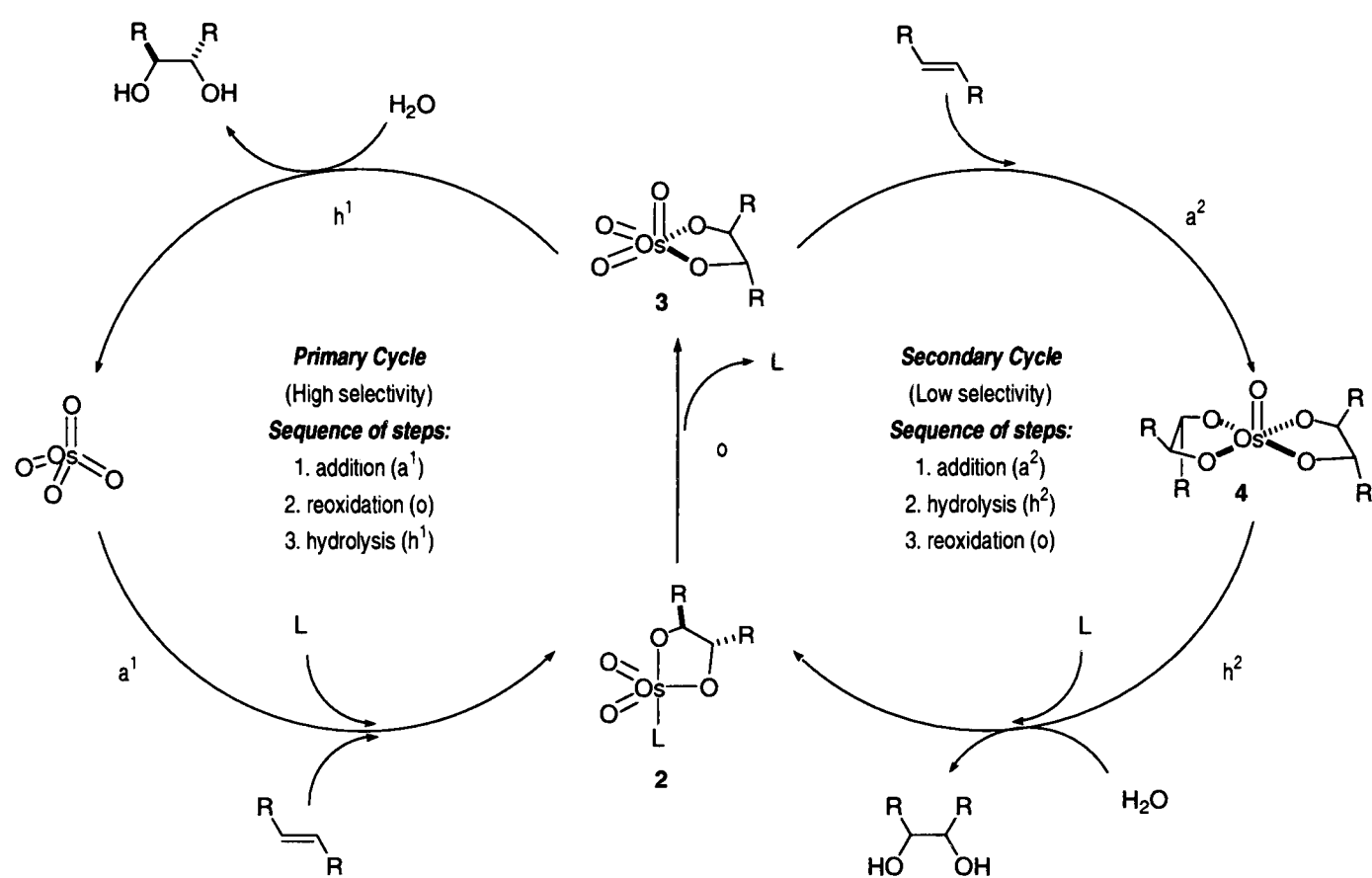


Scheme 1 Dihydroxylation via an osmaglycolate. L=e.g pyridine

Over the following years, efforts were made by several groups to enforce a catalytic regime on the reaction. Hoffman^{7, 8} and Milas^{9, 10} initially used aggressive reoxidants, and the conditions were over time ameliorated through the discovery of *tert*-butyl hydroperoxide¹¹ and subsequently, *N*-methyl-morpholine-*N*-oxide (NMO).¹² This last set of conditions was discovered by researchers at the Upjohn Company and as such has become well known by that name. Subsequently, this system has been adapted to incorporate the use of homochiral amine ligands to promote an *asymmetric* dihydroxylation.

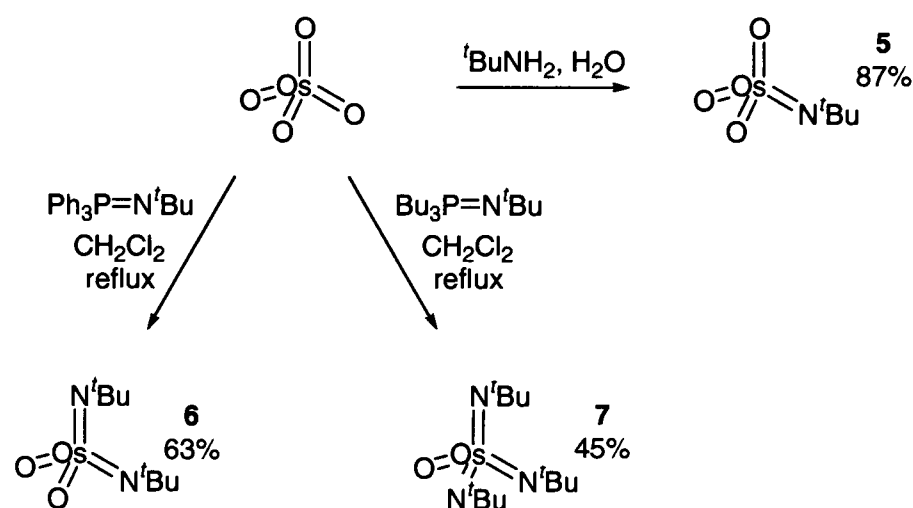
In the catalytic system, an entwined two-cycle process is operational (scheme 2). The accepted first catalytic cycle involves first the addition of an OsO₄.ligand complex 1 across an olefinic double bond to give the glycolate osmate ester 2. Reoxidation of this diester by NMO (in the Upjohn system) gives complex 3, which is then hydrolysed to liberate the diol product and regenerate the OsO₄.ligand complex 1.

In the course of his studies on the system, Sharpless observed the action of a competing second cycle.¹³ If a second molecule of olefin reacts with the reoxidised complex 3 *before* hydrolysis can occur, a bisglycolate ester 4 is formed. This addition occurs in the absence of the chiral ligand and thus produces diols with low or no enantioselectivity.



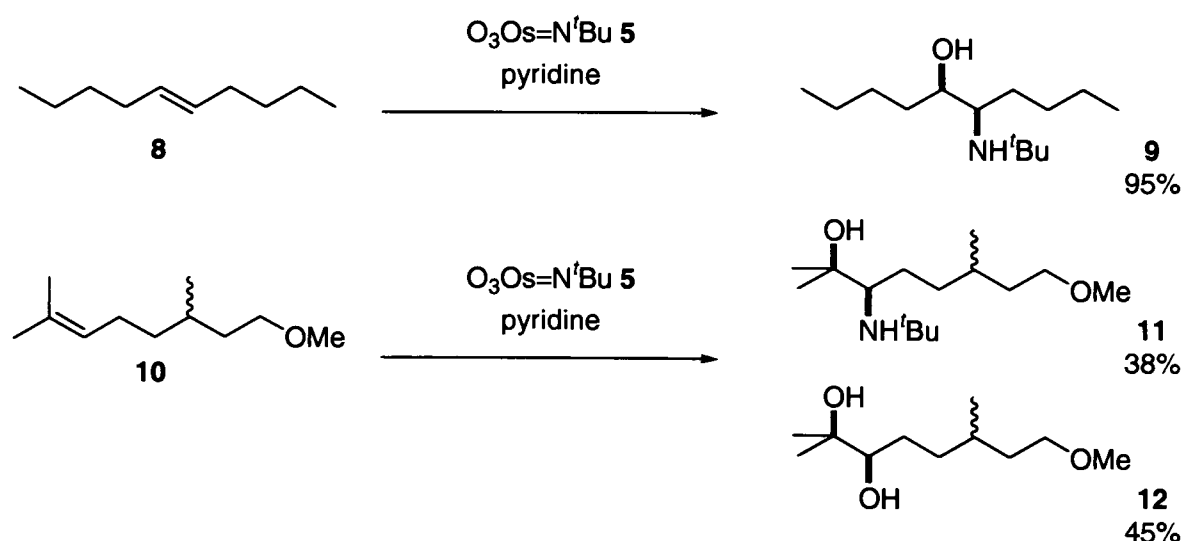
Scheme 2 The twin catalytic cycles operating in the Upjohn dihydroxylation

1.2 Other osmium complexes: aminohydroxylation and diamination



Scheme 3 Formation of imido-osmium complexes

Early in his work utilising osmium tetroxide, Sharpless investigated the possibility of ligands other than oxo attached to osmium. By treatment of aqueous osmium tetroxide with *tert*-butylamine, the azatrioxosmium complex **5** was obtained in 87% yield (scheme 3).¹⁴ This 18-electron complex is isoelectronic with osmium tetroxide, and behaves similarly with regard to oxidation of olefins. As such alkene **8** was oxidised to aminoalcohol **9** on treatment with the azatrioxosmium species (scheme 4).

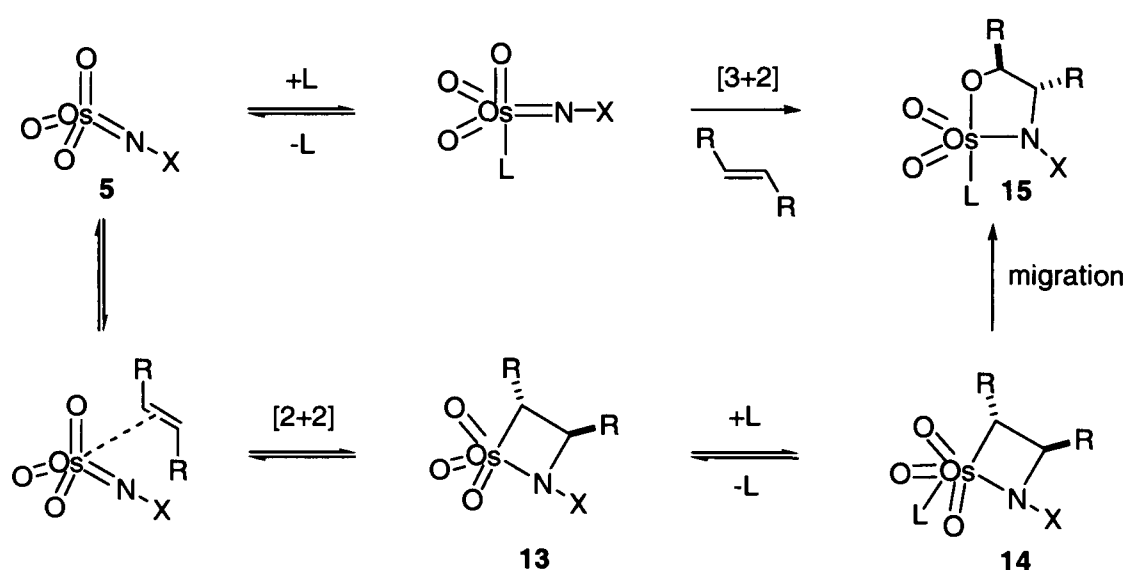


Scheme 4 Aminohydroxylation using $\text{O}_3\text{Os}=\text{N}^t\text{Bu}$

In some instances, considerable amounts of diol were produced either with, or instead of, the intended aminoalcohol product. It was proposed that this was due to unfavourable steric interactions between the bulky *tert*-butyl substituent on nitrogen and the olefin. In fact, it was remarkable that the nitrogen was delivered at all. Subsequent

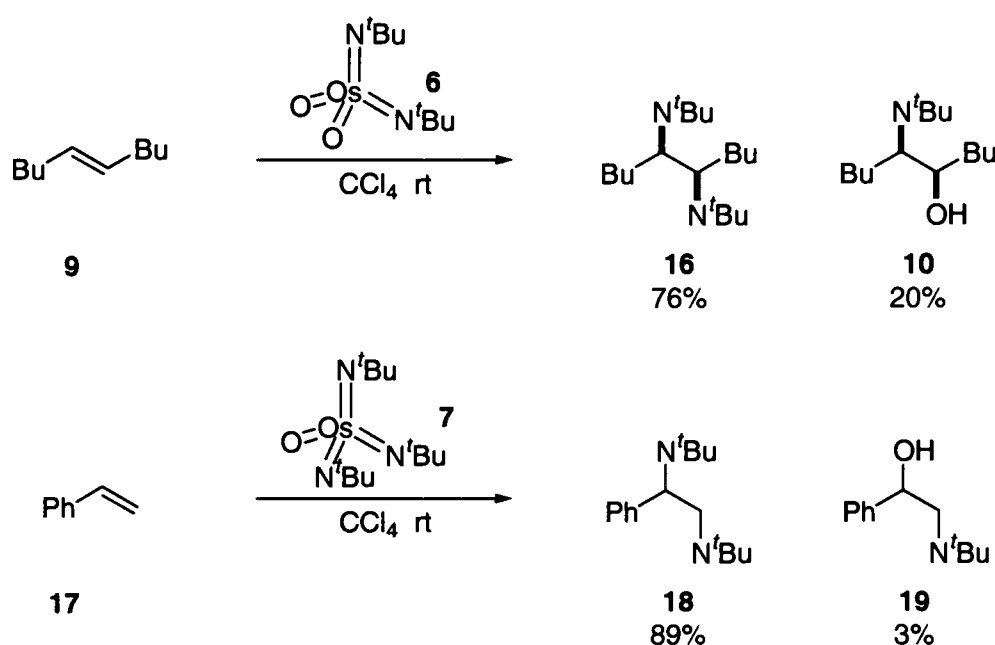
efforts were made to reduce the size of the nitrogen substituent. However, only tertiary amines were compatible nitrogen sources for the formation of these complexes. Sharpless' early investigations were thus restricted to the use of *tert*-butylamine and adamantylamine.

The mechanism of addition of complex **5** to an alkene is also thought to parallel that of OsO₄ in dihydroxylation. As such, it has inherited the controversy surrounding it. Sharpless' preferred mechanism involves an initial [2+2] cycloaddition to give the osamazetidine **13**, either preceded or followed by ligand coordination to give **14** (scheme 5). Subsequent migration gives the azaglycolate **15**. Alternatively, the mechanism may proceed *via* the Criegee mechanism for dihydroxylation, namely by a [3+2] cycloaddition in the presence of the ligand to give the azaglycolate directly.



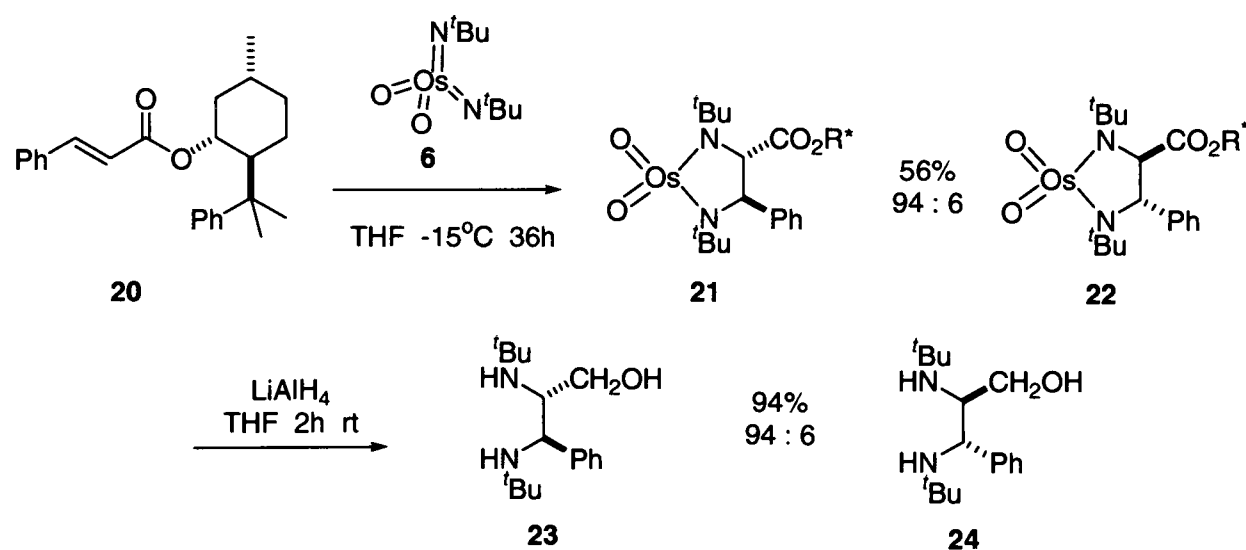
Scheme 5 Proposed mechanisms for aminohydroxylation

The diimido- and triimido-osmium species **6** and **7** can be similarly formed by reaction of OsO₄ with *tert*-alkyl phosphinimines (scheme 3).¹⁵ Again these are restricted to formation from tertiary amines. These exhibit similar reactivity towards alkenes to the monoimido complex. Surprisingly, given the steric bulk of the aza ligands, the nitrogen substituents are transferred preferentially to an olefinic substrate, resulting in a diaminated compound on hydrolysis (scheme 6).



Scheme 6 Diamination of alkenes with imido-osmium complexes

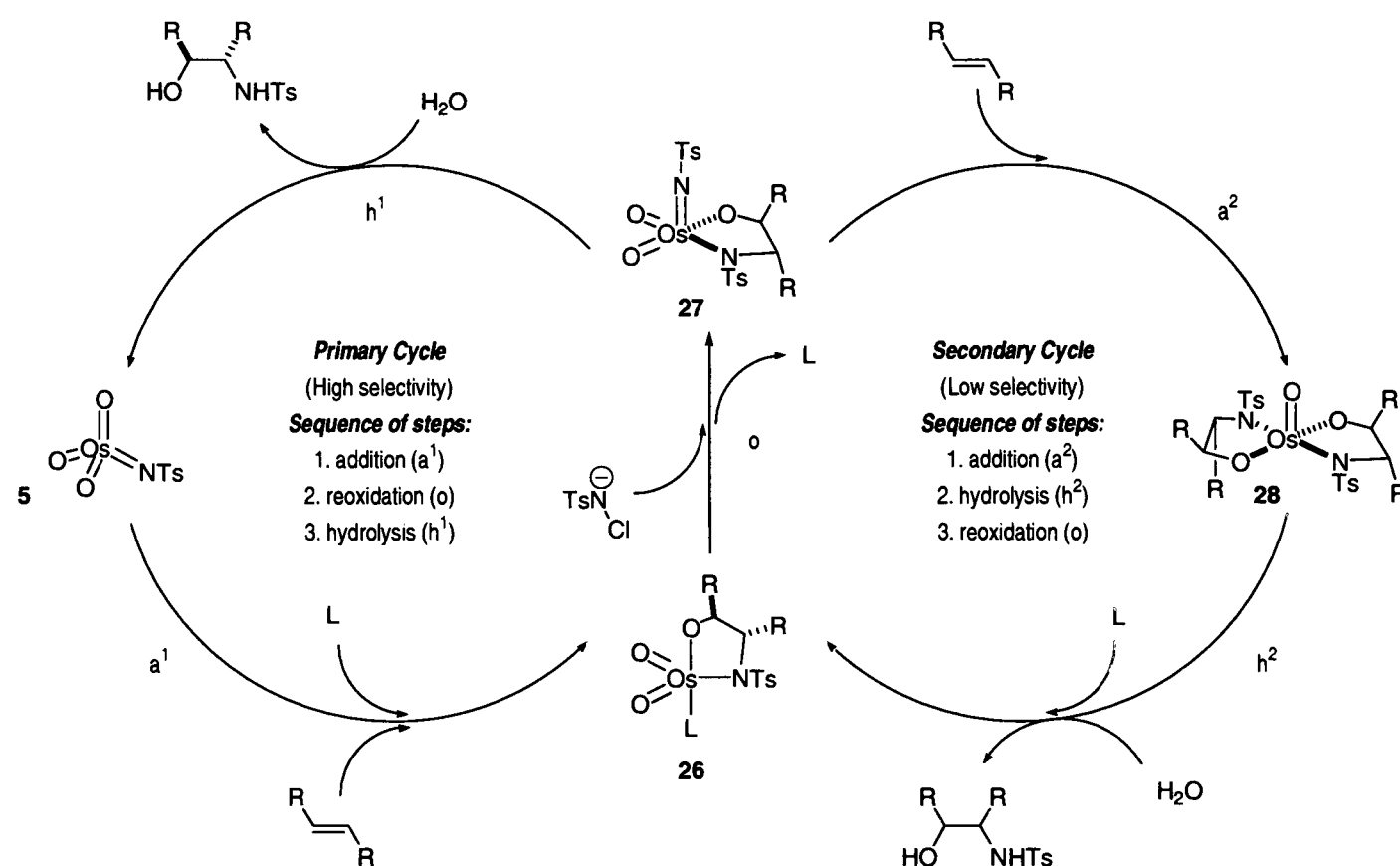
Unfortunately, due to the harsh conditions required for the formation of the aza-osmium species by refluxing with a phosphinimine, these reagents were not suitable for a catalytic procedure. In addition, the restriction of protecting groups for the nitrogen to tertiary alkyl groups meant that synthetically this reaction was not particularly attractive. Ongoing attempts have been made to render this reaction stereoselective, notable success being achieved by the use of 8-phenylmenthol as a chiral auxiliary in the asymmetric diamination of α,β -unsaturated esters.¹⁶

Scheme 7 The first asymmetric diamination. R^{*} = 8-phenylmenthyl

1.3 Early catalytic aminohydroxylation

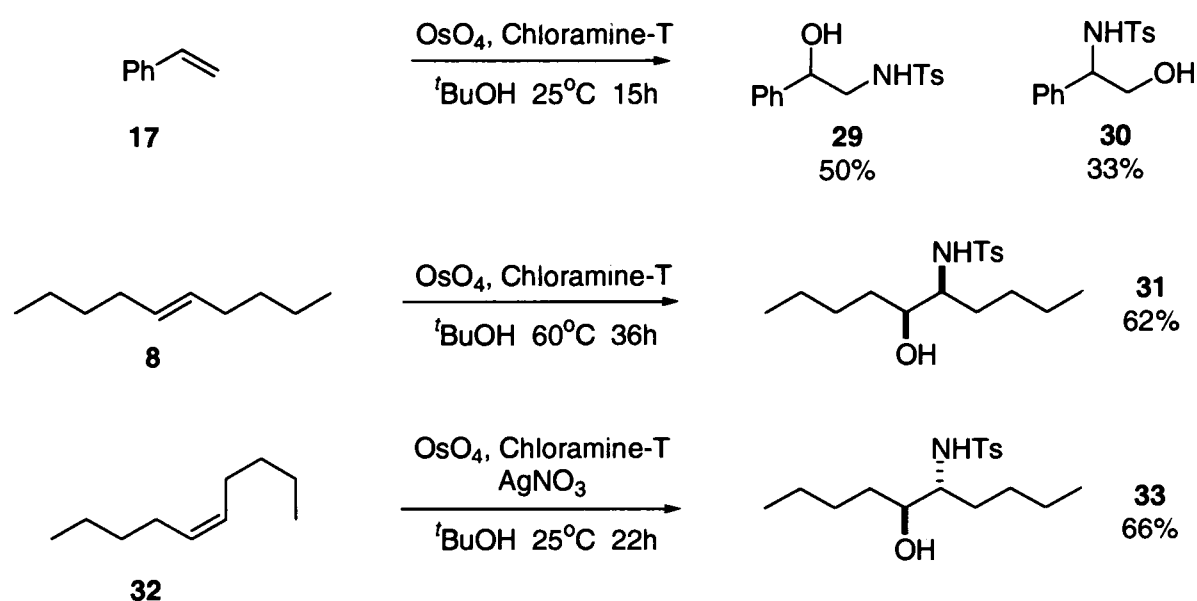
Sharpless recognised the potential of the aminohydroxylation reaction, but was well aware of its limitations. He sought a milder means for formation of an aza-osmium oxidant that would lend itself to a catalytic system. Such an oxidant was discovered in Chloramine-T **25**.¹⁷ This chloro-sodio-sulfonamide was thought to oxidise Os (VI) (specifically, OsO_3) to Os (VIII), thus allowing the oxidation of olefins.

1.3.1 Aminohydroxylation with sulfonamide nitrogen sources



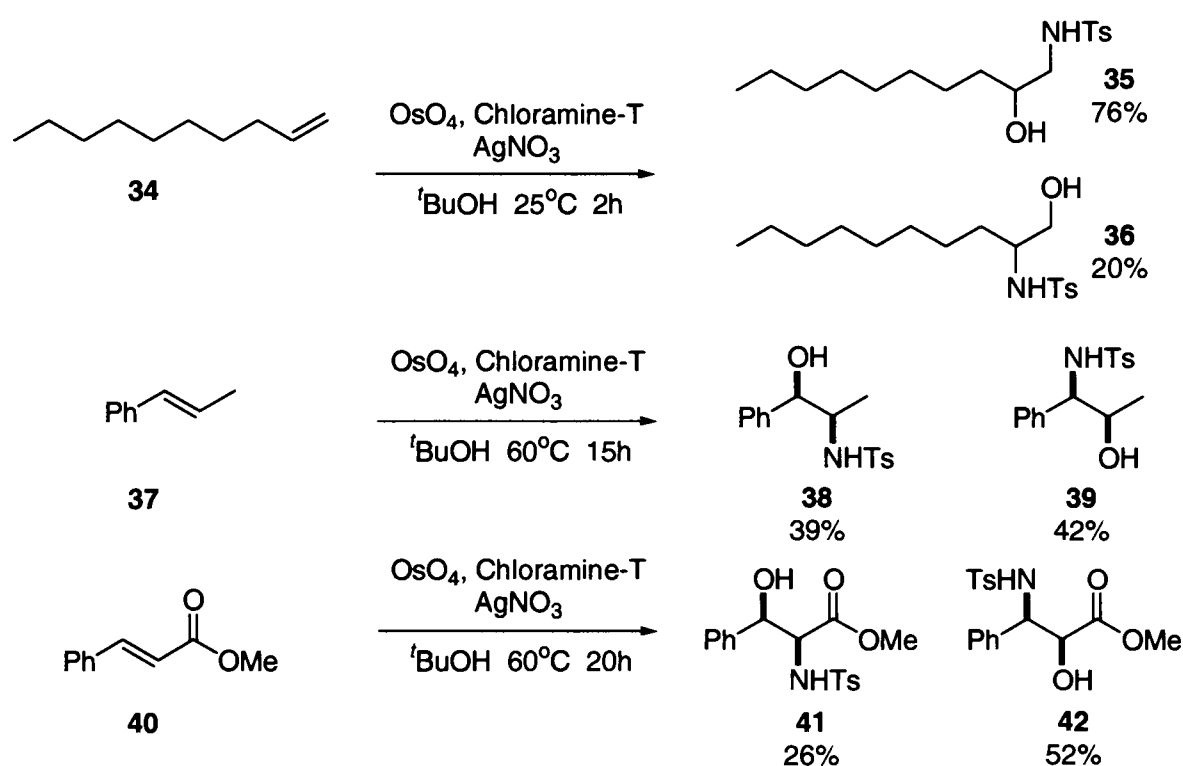
Scheme 8 Catalytic cycles for aminohydroxylation

A number of olefins were oxidised, incorporating most substitution patterns; yields varied, but were usually in the range 60-90% (scheme 9). The process was often inhibited by the chloride ion released on oxidation of the Os (VI) species. This could be counteracted by the addition of AgNO_3 to precipitate out the chloride as AgCl . Unfortunately this procedure was unsuitable for a range of substrates, as silver ion also seemed to have a detrimental effect, particularly with more substituted olefins. Thus Sharpless devised two procedures: one with and one without AgNO_3 . Which was superior varied with substrate and with no discernable pattern.



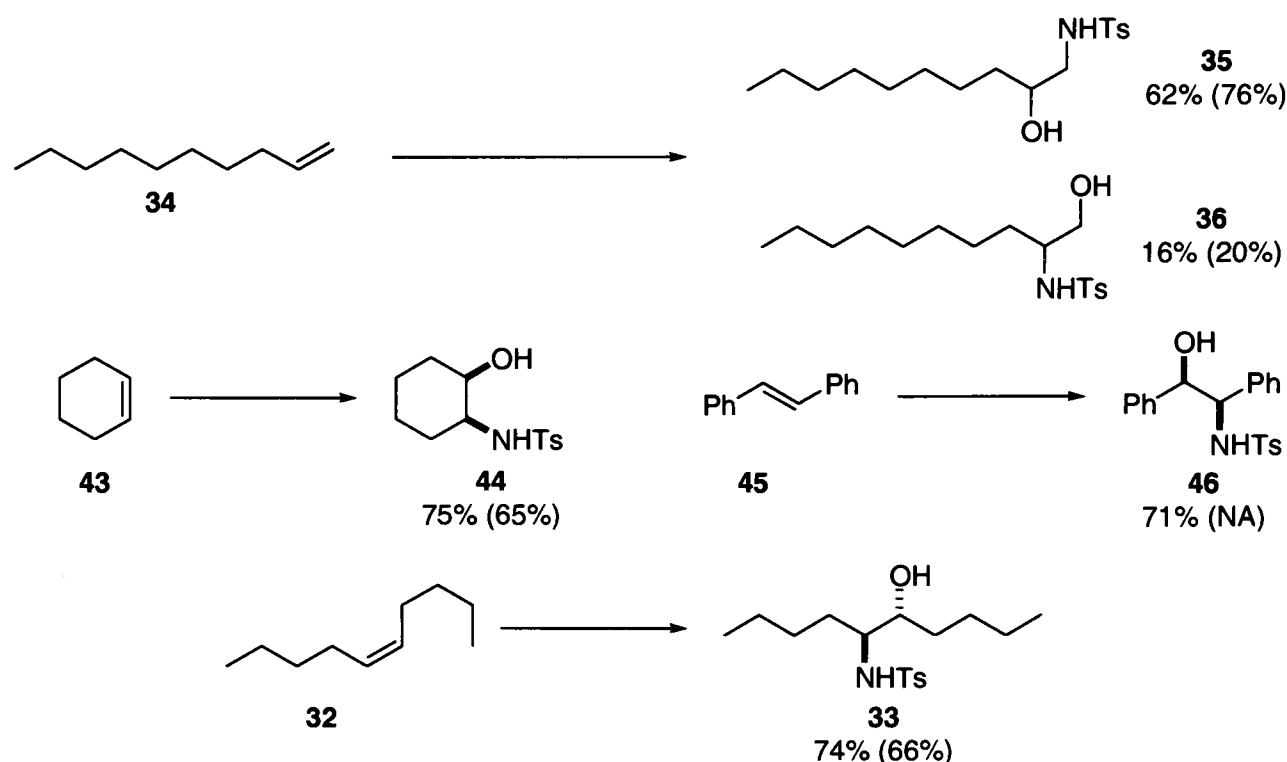
Scheme 9 The first catalytic aminohydroxylations

The substrate scope was expansive but by no means all encompassing. In particular, steric encumbrance around the double bond seemed to preclude reaction (e.g. with 1-phenylcyclohexene and cholesteryl acetate). Tetrasubstituted olefins were inert. The regioselectivities were noticeably diminished compared to the stoichiometric variant. Presumably the lower steric bulk of the sulfonamide group gave the oxidant greater reactivity, but at the same time exerting less control with respect to the regiochemical outcome.



Scheme 10 Catalytic aminohydroxylation has lower regioselectivity than stoichiometric aminohydroxylation

Further improvements were observed when the reaction was carried out under phase-transfer catalysis (PTC) conditions, again to alleviate problems associated with the use of silver ions.¹⁸ The procedure was superior to that including AgNO_3 , improving yields and allowing the aminohydroxylation of a number of previously unsuccessful substrates (e.g. stilbene **45**, scheme 11). Even so, the most highly functionalised olefins remained unreactive.



Scheme 11 Improved yields under PTC conditions. Previous best yields are in brackets. *Reagents and conditions* OsO_4 , Chloramine-T, BnEt_3NCl , $\text{CHCl}_3\text{-H}_2\text{O}$, 60°C

A number of aryl sulfonamide sources were investigated, by varying the sulfonamide substituent.¹⁸ Only two were commercially available: Chloramine-T and Chloramine-B (phenyl). Others were prepared *in situ* by treatment of the parent sulfonamide with Chlorox (a commercial bleach solution of sodium hypochlorite). The yields were uniform for both the preformed chloramines and the *in situ* generated salt. In addition, a range of aryl sulfonamides proved efficacious for the reaction. Of those tested, only *p*-methoxy and 2,5-dimethoxy-substituted aromatics failed to effect aminohydroxylation, assumed to be due to the instability of the chloramine salts.

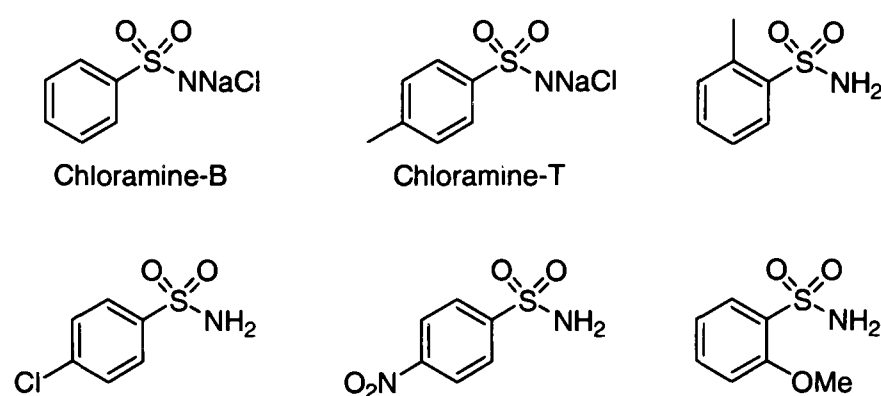
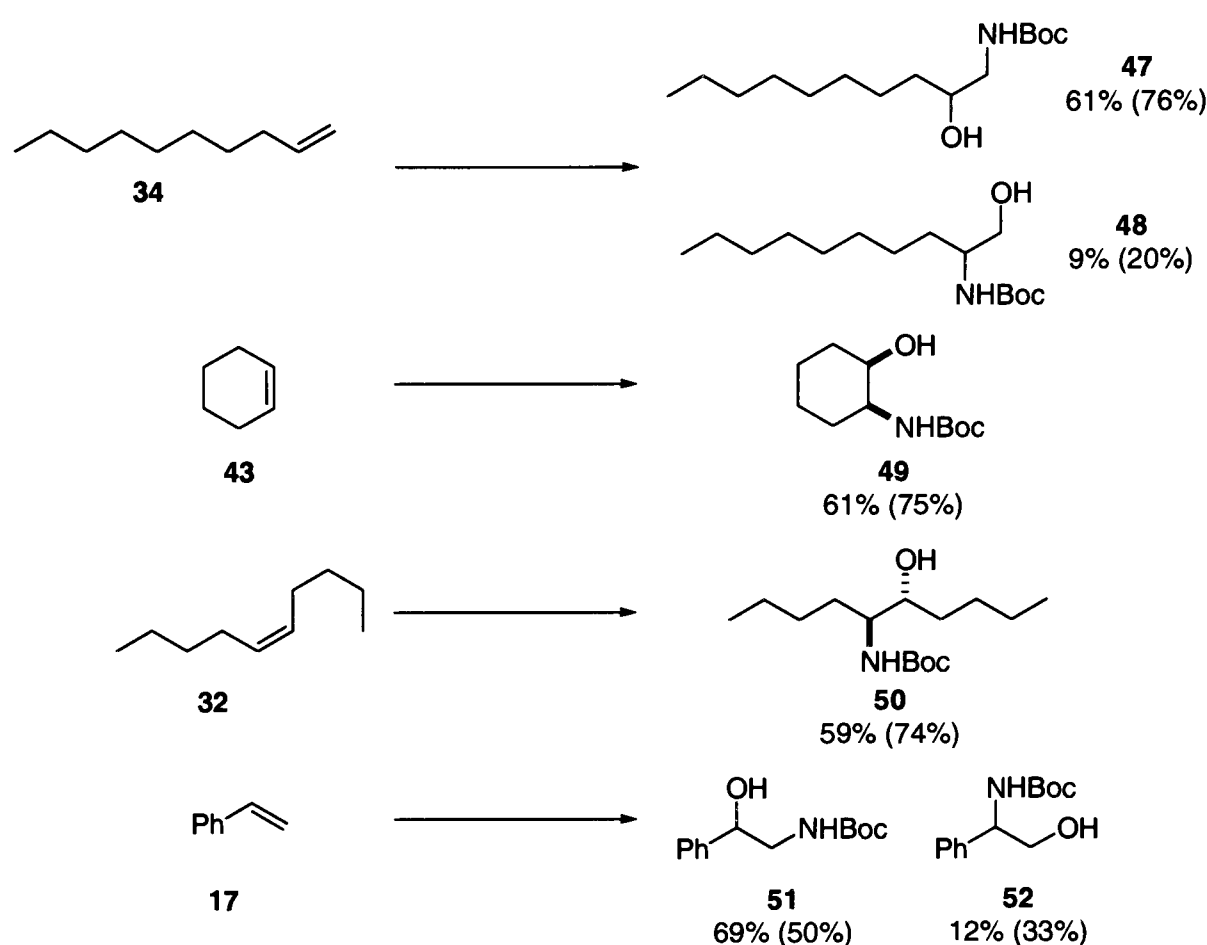


Figure 1 Sulfonamides used in early aminohydroxylations

The sulfonamide work had shown that the reaction could be made catalytic in osmium, but the problem of removing the nitrogen protecting group remained. Cleavage of a sulfonamide linkage frequently requires harsh reductive conditions, such as LiAlH_4 or sodium in ammonia (Birch conditions). In the context of a more complicated synthesis this is not often practical.

1.3.2 Aminohydroxylation with carbamate nitrogen sources

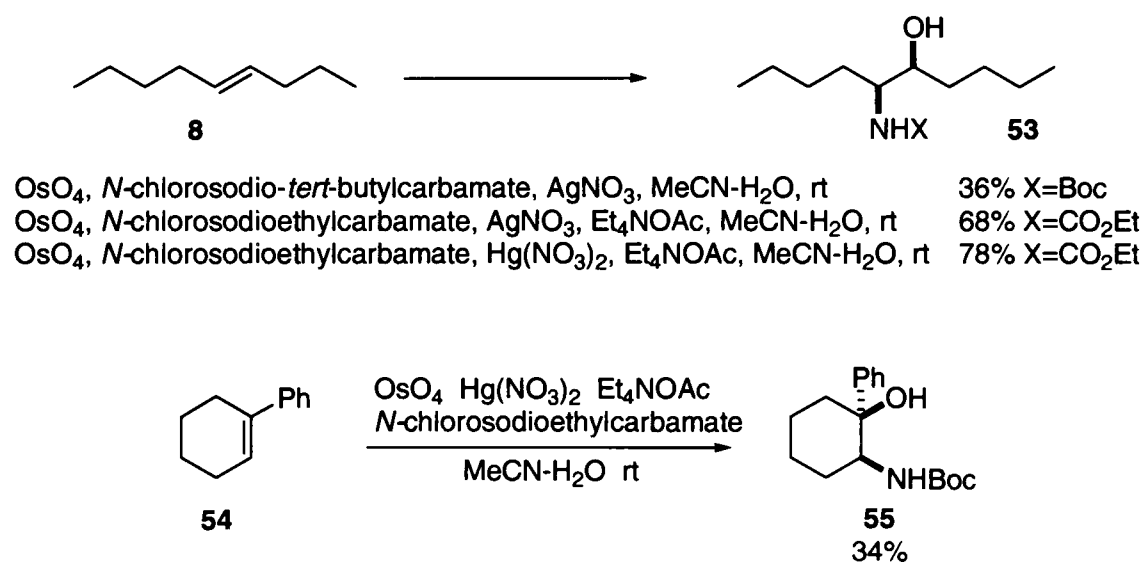
Carbamates were investigated as potential nitrogen sources for precisely this reason. The linkages are much easier to cleave, and the number of carbamates available for use was much greater, allowing tailoring of protecting group to the circumstances. Initial results were disappointing, indicating little or no turnover in the reaction. It was reasoned that as before, free chloride in the reaction mixture was impairing the process, and so the silver salts were used in preference.¹⁹ The result of this change was to enhance turnover to useful rates, allowing access for the first time to carbamate-protected aminoalcohols directly from an olefinic precursor (scheme 12).



Scheme 12 Early carbamate variant aminohydroxylations (best Chloramine-T yields in brackets)

Reagents and conditions OsO_4 (1 mol%), *N*-chlorosodio-*tert*-butylcarbamate, AgNO_3 , $\text{MeCN-H}_2\text{O}$, rt

The yields were lower than optimised sulfonamide variant aminohydroxylations, although adjustment again to PTC conditions improved the yield of aminohydroxylated product from *E*-5-decene **8** from 36% to 68% (scheme 13). Further studies identified the addition of Et_4NOAc as enhancing the reactivity of the metal salts. A screen of a variety of different metals identified mercury salts as the most effective.²⁰



Scheme 13 Gradual improvements to the aminohydroxylation protocol

Under these conditions the oxidations of *E*-5-decene **8** and stilbene **45** were both moderately improved, and obtained in shorter times. In addition previously unreactive substrates (e.g. 1-phenylcyclohexene **54**, 34% yield) were successfully oxidised. An *in situ* preparation of the chlorosodiocarbamate was advocated. A scale-up of the preparation of these salts had discovered a rapid decomposition that was ‘vigorous but not explosive’.²⁰ Reports varied on the stability of these compounds but the recommended procedure involved the use of the crude salts in a one-pot procedure, and transmetallation to silver or mercury as before.

Despite these promising advances, the reaction was overshadowed at this stage of its development by the faster-evolving and more powerful processes, the asymmetric epoxidation (AE)²¹ and asymmetric dihydroxylation (AD).²

1.4 Asymmetric dihydroxylation

Because of its close relation to the process of aminohydroxylation, the development of the AD merits some discussion. The advances in the methodology would later impact on the aminohydroxylation reaction.

It had been noted earlier by Criegee⁶ that amine additives to the dihydroxylation reaction mixture could effect an increase in rate. Indeed other groups had attempted to utilise the chelation of amines to osmium to produce a stoichiometric asymmetric dihydroxylation.²²⁻²⁷

Sharpless discovered that chiral cinchona alkaloids such as quinine were good ligands for osmium.² After a series of screening studies he arrived at a modified form that was able to both accelerate the rate and impart absolute stereocontrol on the reaction. Even more pleasing was the fact that two pseudo-enantiomers were available (figure 2). Thus access to either enantiomer of the oxidised product was possible. The ligands were also compatible with the established Upjohn oxidation conditions.

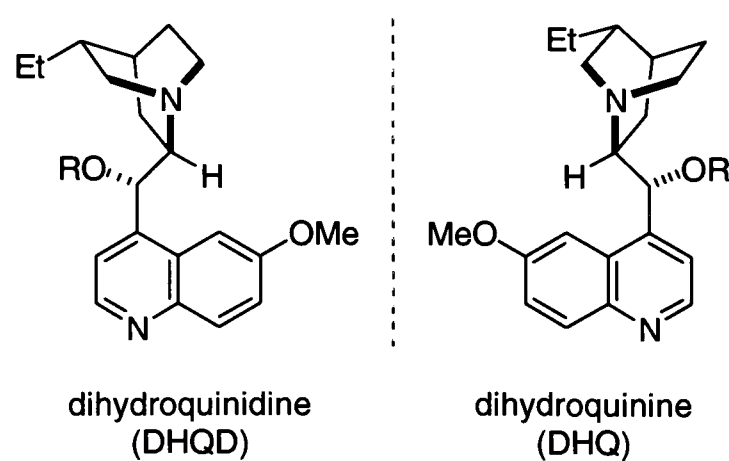


Figure 2 Monodentate cinchona-based chiral amines

The initial results were disappointingly poor. While turnover was appreciable, the enantioselectivities were far from perfect, attributed to the intrusion of the second cycle (*vide supra*, section 1.1.3). Three modifications were made that considerably remedied this.

- The addition of methanesulfonamide greatly increased the rate of hydrolysis of the osmaglycolate ester. While this promoted turnover in the primary cycle, it also allowed the reactions to be run at 0°C, which enhanced the enantioselectivity.
- The reactions were conducted in a biphasic system so that oxidation and hydrolysis occur apart in different phases, limiting the formation of the bisglycolate diester.
- Modification of the cinchona ligands to incorporate a spacer group, and subsequently a second alkaloid unit (so-called ‘*second-generation*’ ligands, figure 3) brought a notable enhancement of enantioselectivity.

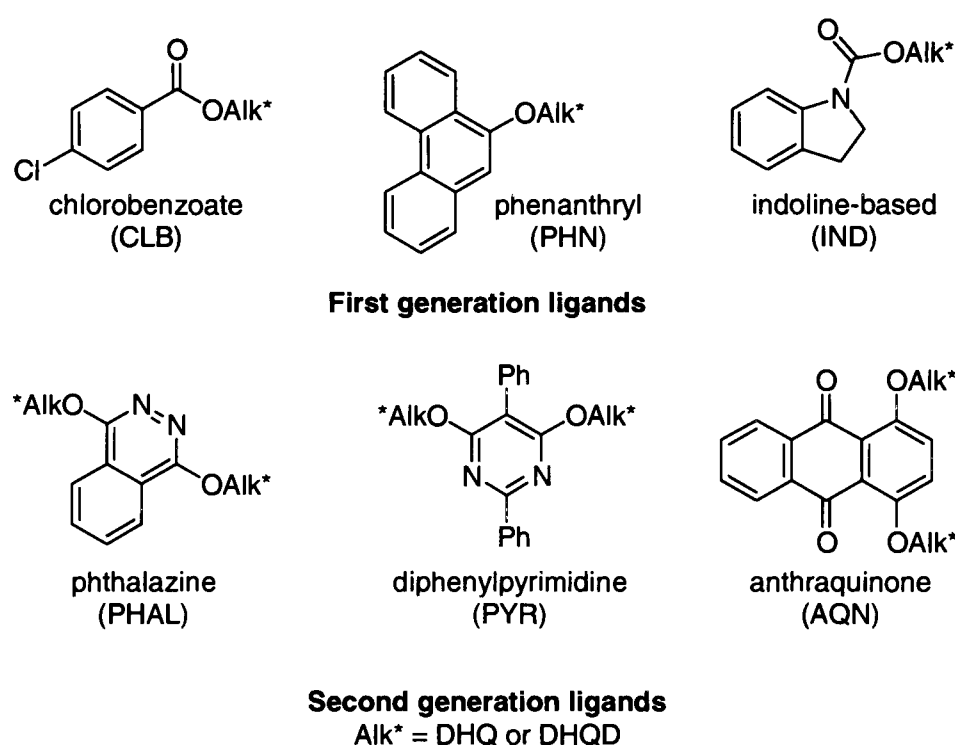


Figure 3 First and second generation Sharpless ligands for asymmetric dihydroxylation

Despite the reliability and success brought about by these changes in concert, the reaction is still highly dependent on olefin geometry. A comprehensive study of olefinic geometries and their behaviour in the AD reaction has been carried out, allowing judicious choice of ligand for the substrate (table 1).

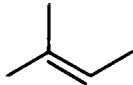
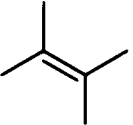
Alkene						
Preferred ligand	PYR/PHAL	PHAL	PHAL	IND	PHAL	PYR/PHAL
ee range	30-97%	70-97%	90-100%	20-80%	90-99%	20-97%

Table 1 Optimum catalysts for the various olefin geometries

Prediction of the absolute stereochemical outcome is possible by the use of the Sharpless mnemonic (figure 4). The rectangle is a crude representation of the catalyst's binding pocket. The southwest corner is an 'attractive' area, in which π -stacking residues and bulky alkyl substituents on the substrate are preferentially located. The SE corner is the most sterically demanding area; if a vinylic hydrogen is present, it will almost certainly be located here to minimise repulsive interactions. The remaining two corners are successively less sterically encumbered, and dictate substrate orientation accordingly.

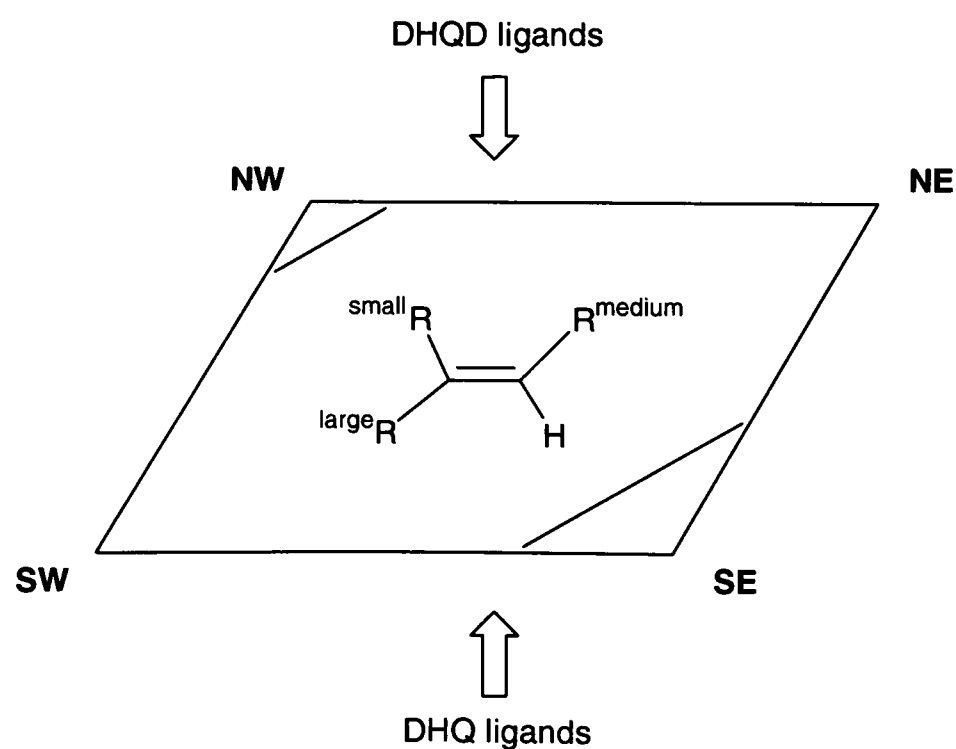


Figure 4 Mnemonic for prediction of absolute stereochemistry of asymmetric dihydroxylation

From this consideration, it can be seen that the better the fit into this pocket, the higher will be the enantiomeric excess. Empirically, 1,2-*trans* disubstituted olefins fit this pattern very well; tri-, tetra- and especially 1,2-*cis* disubstituted olefins do not. In addition, high ee's are achieved when the substrate has aromatic substituents.

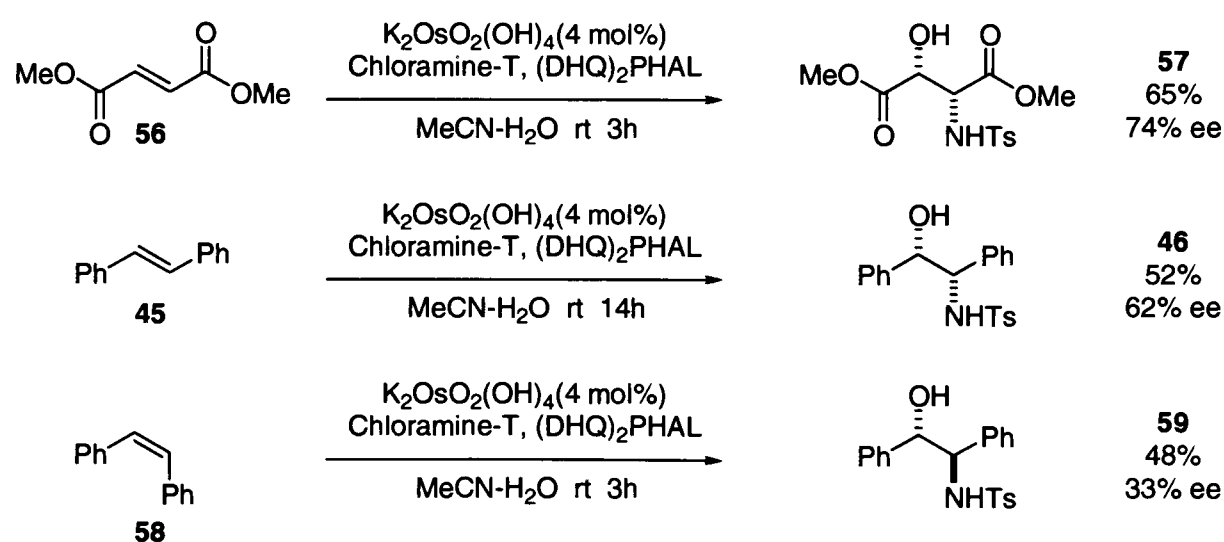
The absolute stereochemical outcome is determined by the choice of alkaloid. From the mnemonic, dihydroquinine (DHQ) derivative will oxidise from the bottom face; dihydroquinidine (DHQD) derivatives from the top.

1.5 Asymmetric Aminohydroxylation

The development of the AD reaction, in tandem with Sharpless' other notable asymmetric transformation, the asymmetric epoxidation, occupied the group for the best part of fifteen years. In 1995, with the AD well established and broadly utilised, Sharpless turned his attention back to the aminohydroxylation process he had addressed in the late 1970's.

1.5.1 Sulfonamide nitrogen sources in the AA

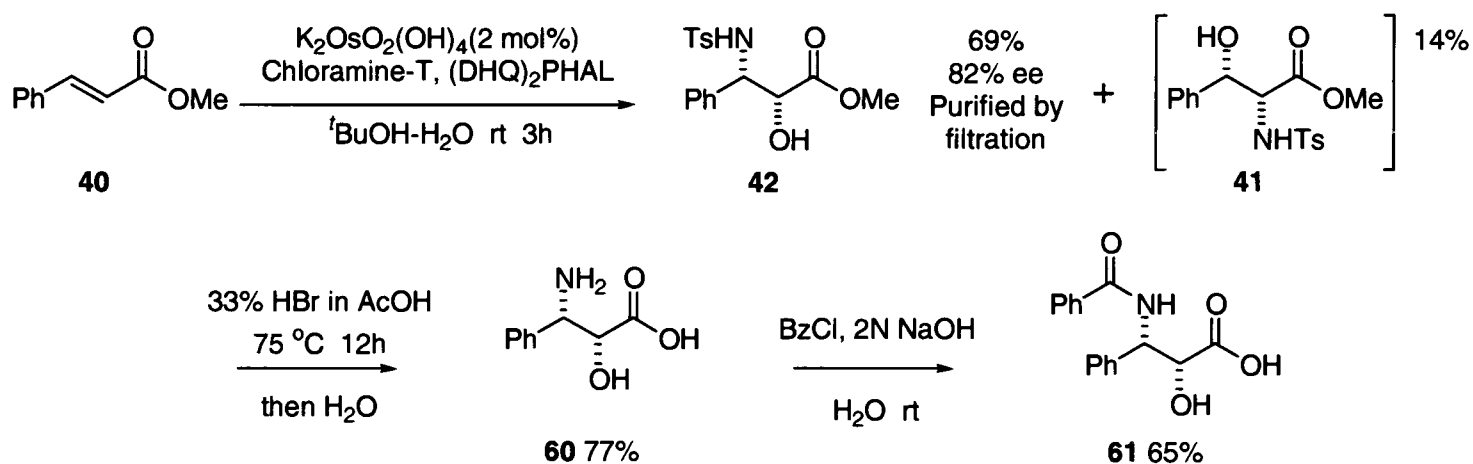
Applying what had been learnt from the development of the AD, the cinchona alkaloid ligands were incorporated into the sulfonamide variant of the aminohydroxylation. Extensive modification of the reaction conditions eventually led to a suitable procedure.²⁸ Turnovers were moderate to good, and diol formation was avoided, and for the first time appreciable levels of enantiocontrol were observed (scheme 14). Sharpless drew the analogy to the initial successes with the AD, and predicted further improvements. This first success was made greater by its application to a synthesis of the taxol side-chain (scheme 15).²⁹



Scheme 14 The first asymmetric aminohydroxylations (AA)

The sense of enantioselectivity observed was found to be completely consistent with the Sharpless mnemonic (*vide supra*, figure 4). Thus asymmetric dihydroxylation of *trans*-stilbene with $(\text{DHQ})_2\text{PHAL}$ gives the (S,S)-diol with >99.5% ee, while the AA using the same ligand also gives the (S,S) enantiomer, albeit in only 62% ee.

While the ee's were good at up to 80%, they were not yet up to the levels seen in the AD reaction. Equally, the levels of regiocontrol observed in the reaction were not particularly high. The steric demands imposed by the use of a bulky cinchona alkaloid ligand had improved the regioselectivity in a number of cases, but the levels were still not high. Removal of the sulfonamide protecting group still also required harsh conditions.



Scheme 15 Taxol side-chain synthesis by Sharpless *et al.*

The seemingly simple substitution of the tolyl group for methyl led to the development of 'Chloramine-M' – the chloro-sodio salt of methanesulfonamide.³⁰ Initially in MeCN-H₂O solvent systems, the rates were much improved. However, these were sacrificed on moving to a preferred ⁿPrOH-H₂O system in order to optimise yields and enantioselectivities, which were much improved compared to the Chloramine-T protocol (table 2). In addition, removal of the sulfonamide by-product was made easier by the water-solubility of methanesulfonamide. It is strange, given the specific inclusion of methanesulfonamide as a rate-enhancer in most AD processes, that Sharpless does not comment on the possibility of a similar role within the AA.

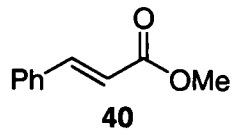
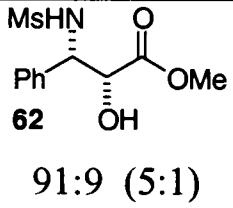
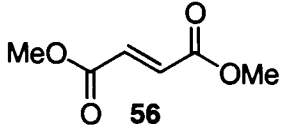
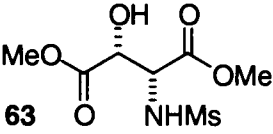
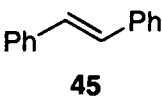
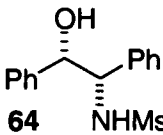
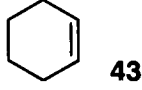
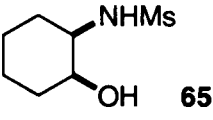
<i>Alkene</i>	<i>Major product (regiomeric ratio)</i>	<i>Yield (%)</i>	<i>ee (%)</i>	<i>Time (h)</i>
 40	 62 91:9 (5:1)	65 (69)	95 (82)	3 (3)
 56	 63	76 (65)	95 (77)	2 (3)
 45	 64	71 (52)	75 (62)	16 (14)
 43	 65	49 (64)	63 (45)	18 (6)

Table 2 Improvements in the AA using Chloramine-M (Chloramine-T results in brackets) *Reagents and conditions:* K₂OsO₂(OH)₄ (4 mol%), (DHQ)₂PHAL, Chloramine-M, ⁿPrOH-H₂O (1:1), rt

While these superior rates were obviously desirable, this investigation illustrated the fine balance of factors affecting the outcome of the AA reaction. The rate of reaction was found to be both substrate and solvent dependent. Temperature also had to be finely controlled to maintain an appreciable rate of reaction while minimising the formation of glycol by dihydroxylation. Finally the ligand proved to have a crucial effect. While operating as a ligand in the Chloramine-T system, the ligand actually slowed down the rate. For Chloramine-M it was necessary to have the ligand present to see appreciable turnover, an example of ligand-accelerated catalysis.

The generally superior enantioselectivity obtained using Chloramine-M was attributed to its smaller size, and hence lower steric repulsion and a ‘better fit’ (*sic.*) within the catalyst’s binding pocket. Within these homogeneous systems, however, the impact of the second cycle must be considered. This intrudes when a second addition of olefin occurs before hydrolysis of the azaglycolate. The lower steric bulk of

Chloramine-M, coupled with lower hydrophobicity, means that hydrolysis of the azaglycolate osmate esters should also be faster. While this would speed hydrolysis in both cycles, if it were sufficiently fast, turnover in the enantioselective primary cycle would be favoured. The strong ligand dependence of the rate of reaction would suggest that this is the case.

The removal of the sulfonamide protection remained an aggressive procedure, however. Other sulfonamides ($\text{Me}_3\text{SiCH}_2\text{CH}_2\text{SO}_2\text{NH}_2$, *p*-nitrophenylsulfonamide and *tert*-butylsulfonamide) were investigated because of their ease of removal. The nosyl chloramine salts were unfortunately unreliable in the AA, while the *tert*-butylsulfonamide (Bus) was not tested under asymmetric conditions.³¹ These studies were curtailed when another avenue of research yielded results.

1.5.2 Carbamate nitrogen sources in the AA

Appreciation of the effect of reducing the size of the substituent on nitrogen led Sharpless back to the carbamate variant of the aminohydroxylation. Movement away from the sulfonamides would not only reduce the size of the nitrogen substituent, but also introduce a much more readily cleaved protecting group.

Carbamates were reinvestigated as nitrogen sources, utilising conditions directly taken from the sulfonamide variant. ‘The result was spectacular’.³² The yields rose dramatically from previous carbamate aminohydroxylations, and ee’s comparable to those seen in the AD were observed (table 3). In addition, within the narrow scope of substrates oxidised, the regioselectivities were also high, though not numerically quoted.

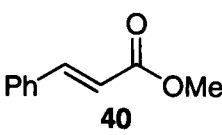
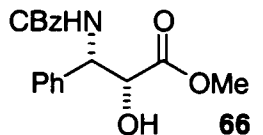
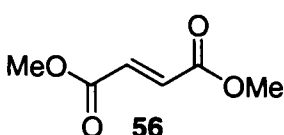
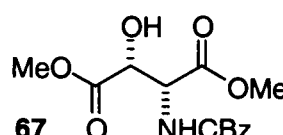
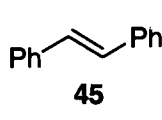
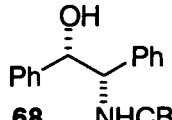
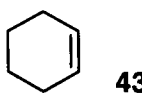
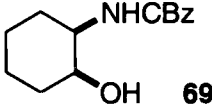
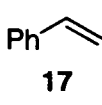
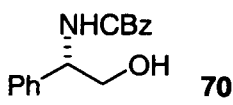
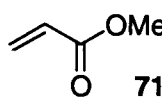
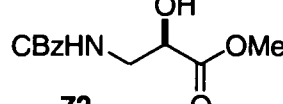
<i>Alkene</i>	<i>Major product</i>	<i>Yield (%)</i>	<i>ee (%)</i>	<i>Time (h)</i>
 40	 66	65 (65)	94 (95)	0.6 (3)
 56	 67	55 (76)	94 (95)	2 (2)
 45	 68	92 (71)	91 (75)	3 (16)
 43	 69	51 (49)	63 (63)	2 (18)
 17	 70	60 (NA)	93 (NA)	1.5 (NA)
 71	 72	89 (NA)	84 (NA)	0.8 (NA)

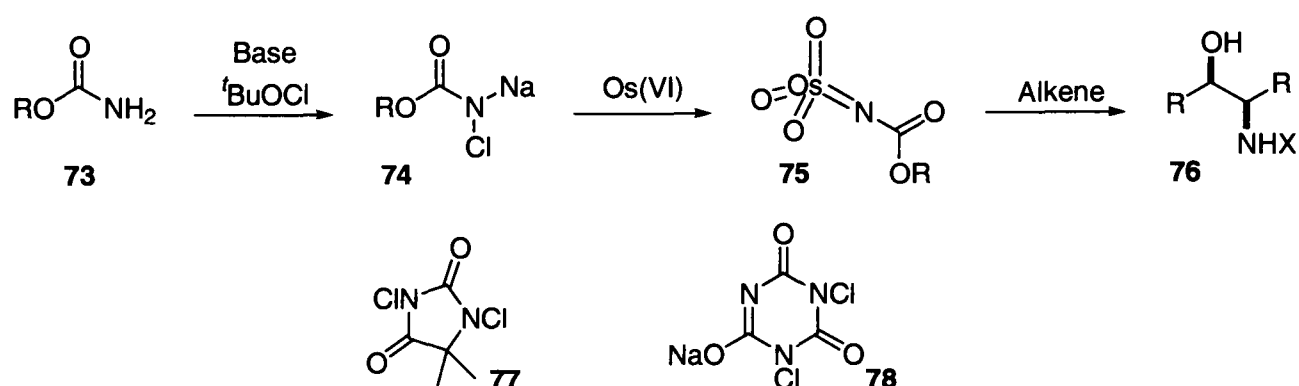
Table 3 Improvements in the AA using benzyl carbamate. (Chloramine-M results in brackets)

Reagents and conditions: $\text{K}_2\text{OsO}_2(\text{OH})_4$ (4 mol%), $(\text{DHQ})_2\text{PHAL}$, BnOCONH_2 , NaOH , $t\text{BuOCl}$, $n\text{PrOH-H}_2\text{O}$ (1:1), 0 °C/rt

Sharpless attributes this improvement over previous carbamate variants to two factors: the use of the sodium salt and primarily, the increased amount of water present. Originally, the hydrolysis of the azaglycolate intermediates was frustratingly slow. The discovery that these changes, when coupled, resulted in a much more powerful oxidation system was, by the group's own admission, fortuitous. Nevertheless, the key problem had been solved and real advances could now be made.

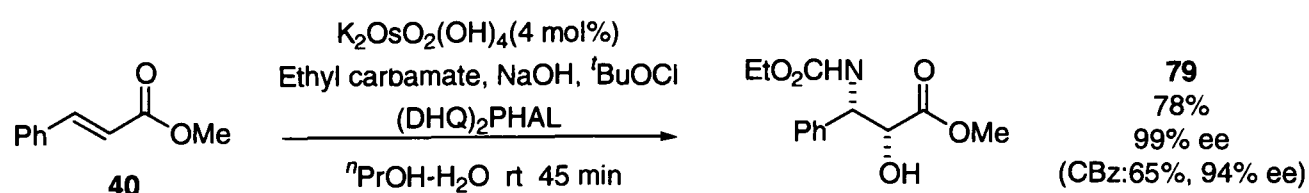
Originally the sodium salts had been synthesised and then transmetallated to either silver or mercury for the reaction.^{19, 20} Now that the original sodium salt was desired, the reaction could be carried out in one pot, also obviating any need for isolation of the

potentially explosive carbamate salts. The carbamates **73** are deprotonated by the base and chlorinated by modified bleach (*tert*-butyl hypochlorite). Subsequent deprotonation gives the *N*-chlorosodiocarbamate **74**, which is believed to act as a reoxidant (scheme 16). While *tert*-butyl hypochlorite is suitable for small-scale reactions, two solid chlorine sources have been discovered that are more appropriate for large-scale reactions: 1,3-dichloro-5,5-dimethylhydantoin **77** and the sodium salt of dichloroisocyanuric acid **78**.³³ Both are commercially available, shelf-stable for long periods and efficient chlorinating agents as both chlorines are available for oxidation. The carbamate was still required to be in threefold excess relative to the olefin, which meant chromatography as a purification method could be tricky and tedious. Where the products were crystalline, and particularly when insoluble in the reaction mixture, recrystallisation was the method of choice for obtaining pure material.



Scheme 16 One-pot aminohydroxylation using carbamate nitrogen sources

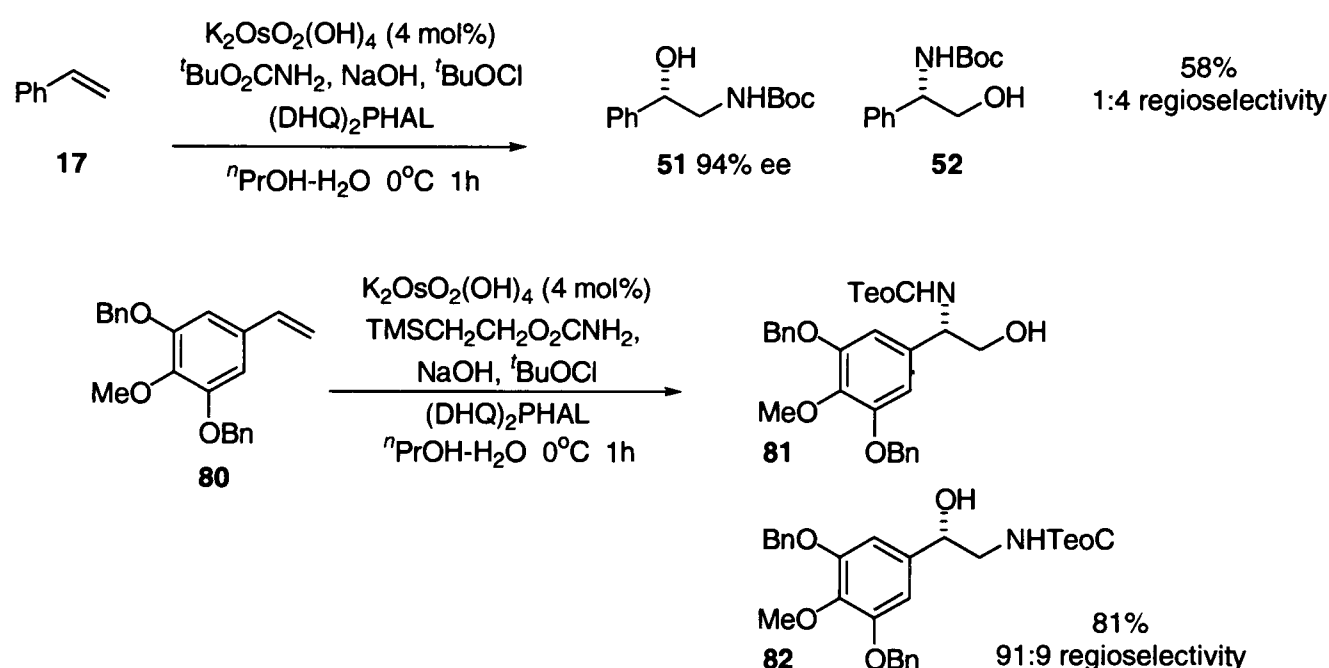
The benzyl carbamate series was the first investigated, and would be synthetically useful because of the ease of removal of the protecting group by hydrogenolysis. It was noted that ethyl carbamate was superior to benzyl carbamate in a number of instances.³²



Scheme 17 Ethyl carbamate is superior to benzyl carbamate

As with the sulfonamide variant, the reaction proved sensitive to a variety of reaction conditions, although less so than its predecessor. In addition, the alkyl group of

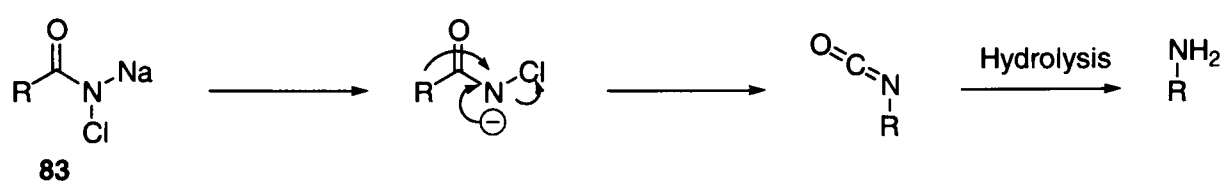
the carbamate could be varied, be it to influence the regioselectivity or to adjust the cleavage conditions to be more compatible with synthetic endeavours. Sharpless had addressed benzyl carbamate (reductive removal) and ethyl carbamate (basic).³² Further work had identified *tert*-butyl carbamate (acidic cleavage)³⁴ and trimethylsilylethyl carbamate (TeoC, nucleophilic fluoride)³⁵ as suitable substitutes. TeoC, while not commercially available, has given the best published results of the carbamate variant to date.



Scheme 18 Other carbamate-based nitrogen sources

1.5.3 Amide nitrogen sources in the AA

Buoyed by the success of the carbamate variant, Sharpless went on to investigate the possibility of introducing other nitrogen protecting groups. A large number of potentially useful nitrogen sources were amides. Ordinarily these would be precluded from the reaction due to the formation, either *in situ* or prior to reaction, of the *N*-chloro-*N*-sodio-carboxamide derivative **83**. These compounds are well known to rapidly undergo Hofmann rearrangement to the corresponding isocyanates and amines (scheme 19).³⁶ This can be avoided by the use of the bromo-derivative instead, and by running the reaction at a reduced temperature of 4°C . Initially, *N*-bromoacetamide was used as it was commercially available and introduced an easily removed acetate group on the nitrogen.³⁷



Scheme 19 Hofmann rearrangement

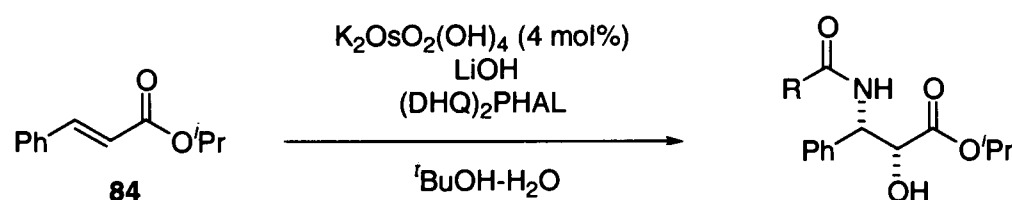
Indeed, the smooth reactivity of these compounds was such that the nitrogen source could be employed in lower quantities: 1.1 equivalents compared to (typically) three for the other variants, resulting in simplified purification. The yields remained high, but the ee's were noticeably lower. As with the two previous versions, solvent and ligand effects could be used in parallel to influence, if not control, the regioselectivity of the process (*vide infra*, section 1.7.4). In particular, a curiosity of this variant was the reversal of inherent regiochemical bias of styrene substrates when compared to the carbamate variant. The former showed a preference for the formation of the benzylic amine, the latter in favour of the benzylic alcohol (table 4).

<i>Alkene</i>	<i>Major product</i>	<i>Regioselectivity</i>	<i>Yield (%)</i>	<i>ee (%)</i>
84	85	>20:1	81	99
45	86	>20:1	50	94
87	88	>20:1	46	89
17	89	6:1	55	88

Table 4 Amide variant results. Reagents and conditions: $\text{K}_2\text{OsO}_2(\text{OH})_4$ (4 mol %), $(\text{DHQ})_2\text{PHAL}$, *N*-bromoacetamide, $\text{LiOH}\cdot\text{H}_2\text{O}$ or KOH , $^t\text{PrOH}\cdot\text{H}_2\text{O}$ or $\text{MeCN}\cdot\text{H}_2\text{O}$, 4 °C

A greater range of amides was exploited by Sharpless in a later study.³⁸ He comments that, unlike the earlier sulfonamide and carbamate variants, *in situ* chlorination is not an option due to competing Hofmann rearrangement. *N*-

bromoacetamide was used as a pre-brominated reagent. Sharpless investigated a broader range of amides by adopting this approach and pre-brominating using the mild reagent dibromoisocyanuric acid, affording the *N*-bromoamide in high yield (typically 90-99%).



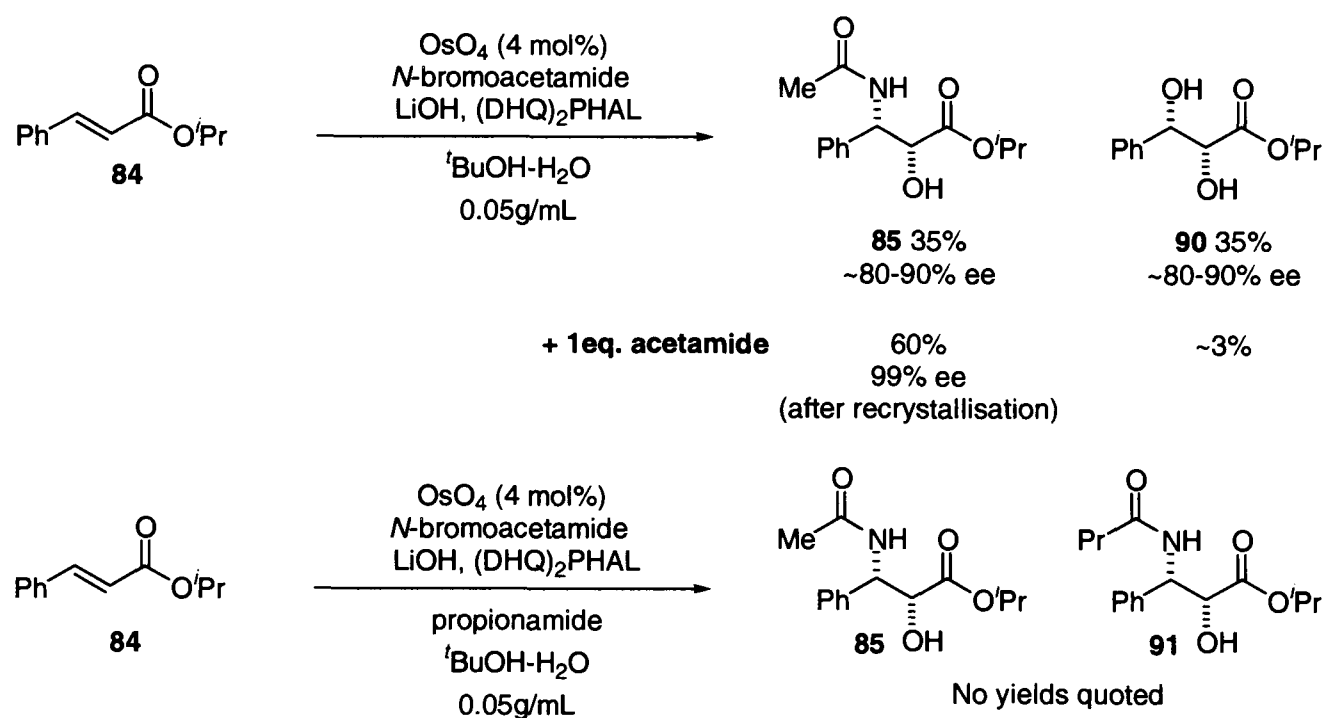
<i>N</i> -Bromoamide	<i>T</i> (°C)	Yield (%)	<i>ee</i> (%)	Regioselectivity
	4	94	95	21:1
	10	75	95	23:1
	4	76	93	12:1
	4	71	80	20:1
	4	38	77	2:1
	0	42	43	2.5:1

Table 5 Investigation of different amide nitrogen sources

The effect of substitution on the amide was investigated in a model case: the AA of isopropyl cinnamate. Moderate steric encumbrance did not have a marked effect on the yield of the reaction, although the enantioselectivity was impaired as bulkier reagents were used. The most hindered amides (*tert*-butyl carboxamide, adamantyl amide) gave low yields. Aromatic amides were also deemed to be much less effective nitrogen sources than aliphatic amides (table 5).

The electronic nature of the amide was of crucial importance. While electron-deficient amides were less prone to Hofmann rearrangement, they also reacted more slowly in the AA and reactions had to run at a slightly warmed temperature (10 °C). However, amides that were too electron-deficient showed a propensity for diol formation, presumably due to accelerated hydrolysis of the imido-osmium species. In contrast, electron-rich amides both undergo the AA and rearrange rapidly, meaning that lower temperatures are of benefit.

The success of the amide variant attracted the pharmaceutical industry. In the course of a semi-synthesis of paclitaxel, Wuts and co-workers had cause to scale up the aminohydroxylation of isopropyl cinnamate to produce 200g of product.³⁹ The high dilutions used in most AA reactions were not suitable and thus the reaction was run at a much higher concentration. Unfortunately, running the reaction ten times more concentrated led to considerable diol formation. The problem was remedied by the addition of acetamide to the reaction mixture (scheme 20).



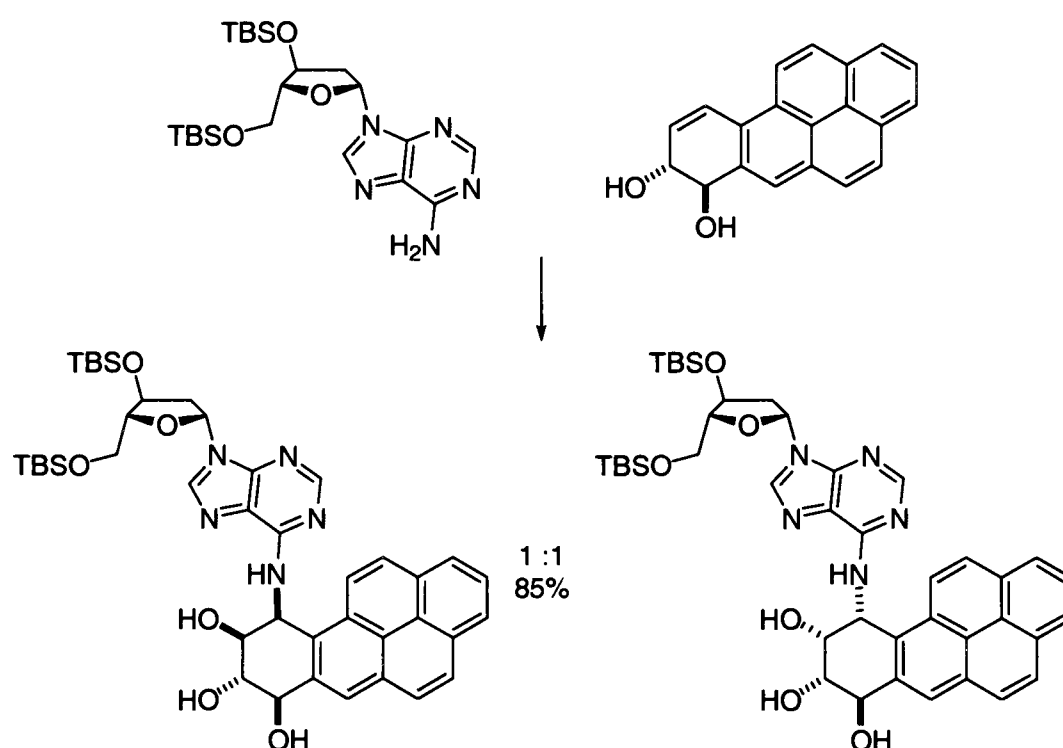
Scheme 20 Addition of acetamide allows higher concentrations to be used

The exact role of the amide in suppressing diol formation and/or promoting aminohydroxylation is uncertain. Rate acceleration in dihydroxylation by methanesulfonamide is a common observation, but in this system methanesulfonamide had no effect. Propionamide was an adequate substitute for acetamide, but trifluoroacetamide, pivalamide and urea completely shut down reactivity – no turnover

of substrate was observed at all. The use of propionamide led to the formation of some propionyl aminoalcohol. This may suggest bromine exchange between amides, or possibly transamidation after the oxidation event.

1.5.4 Other nitrogen sources in the AA

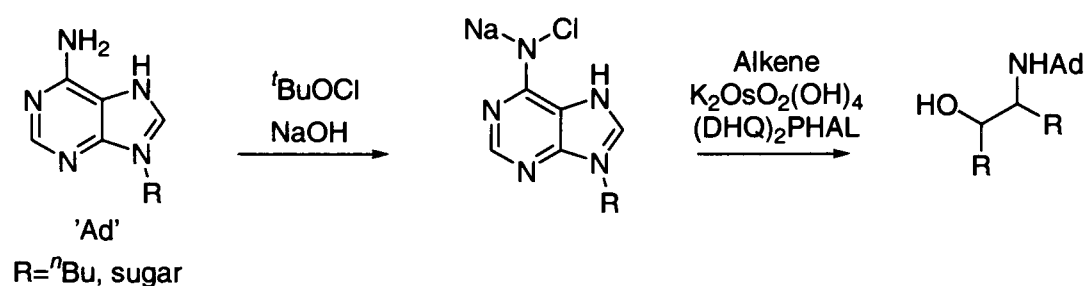
Sharpless pursued further nitrogen sources with the goal of making the AA reaction as versatile as possible. Two more papers were published detailing protocols for the use of heteroaromatic amines as nitrogen sources. The application of this is obvious: very few commercial drugs do not incorporate heteroaromatic rings somewhere.



Scheme 21 Jerina's use of adenosides *Reagents and conditions:* $\text{K}_2\text{OsO}_2(\text{OH})_4$, $(\text{DHQD})_2\text{PHAL}$, NaOH , $t\text{-BuOCl}$, $n\text{-PrOH-H}_2\text{O}$, 3h, rt

Initially, a breakthrough in the laboratories of Jerina had allowed, through rigorous control of reaction conditions, adenine derivatives to be used as the nitrogen source (scheme 21).⁴⁰ While careful selection of solvent and temperature was nothing new, it was discovered that rigorous exclusion of oxygen from the system suppressed the numerous side-reactions also observed under standard conditions, notably ring-chlorination.

The reactions were sluggish, even at elevated temperatures. Interestingly, the addition of a Sharpless chiral ligand led to rate acceleration in these systems but did not impart absolute stereocontrol.⁴¹ The substituent at the 9-position of adenosine was found to have no effect on the outcome of the reaction, but the use of adenosine sugars meant that a 1:1 mixture of diastereomeric products was formed (table 6). Separation of these by chromatography and removal of the sugar would then give them in enantiopure form.



Alkene	R	Product	Yield (%)	Diastereoselectivity
			65	1:1
	Bu		79	NA
	Bu		75	NA
			71	1:1

Table 6 Aminohydroxylation using adenosine derivatives

Other heterocycles do not suffer from this lack of enantiocontrol in the AA. Application of Jerina's conditions to a number of amino-substituted heterocycles led to the formation of a number of aminoalcohols with good ee's (table 7).⁴² As with the adenine derivatives, exclusion of moisture from the system proved imperative in minimising ring chlorination by electrophilic aromatic substitution. Once the chlorination had occurred, deprotonation could be carried out in water, provided the

base was kept in slight deficit and the reaction was kept under an inert atmosphere. The choice of co-solvent was restricted to short-chain primary alcohols, presumably required to assist hydrolysis of the osmium azaglycolate intermediate.

As with the standard variants of the AA, the size of the nitrogen substituent appeared to be highly significant with regard to the enantioselectivity. Smaller heterocycles (especially 2-aminopyrimidine) gave the highest ee values; lower values were obtained with methyl-substituted heterocycles. In addition, there appeared to be a modest ee advantage for having a less electron-withdrawing substituent on nitrogen.

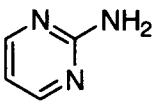
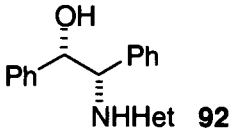
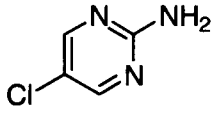
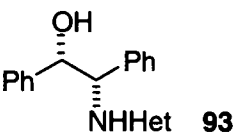
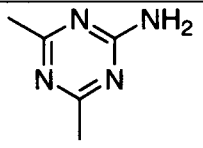
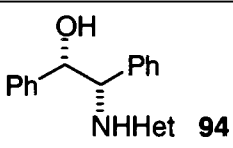
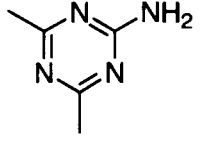
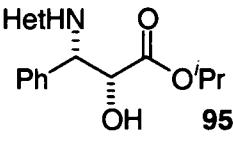
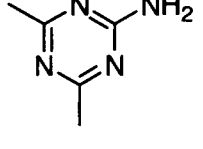
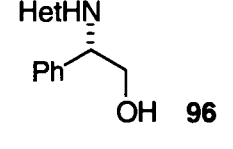
<i>Heterocycle</i>	<i>Product</i>	<i>Yield (%)</i>	<i>ee (%)</i>	<i>Regioselectivity</i>
	 92	45	97	NA
	 93	60	56	NA
	 94	86	87	NA
	 95	97	99	>20:1
	 96	74	86	5:1

Table 7 AA using amino-substituted heterocycles. *Reagents and conditions:* $\text{K}_2\text{OsO}_2(\text{OH})_4$, (5 mol%), $(\text{DHQ})_2\text{PHAL}$, NaOH , $t\text{BuOCl}$, $n\text{PrOH-H}_2\text{O}$, 12h, rt

1.6 Substrate variations in the AA

1.6.1 1,2 Disubstituted olefins in the AA

Disubstituted olefins are by far the most important class of alkenes. Early examples showed them to be viable substrates for the reaction, but it was not until the advent of the asymmetric variant of the reaction that these substrates really came to the fore.⁴³ The first (sulfonamide variant) AA reactions were conducted using a number of disubstituted olefins: - stilbenes, cinnamates and crotonates.²⁸ From these early results it seemed that both *cis* and *trans* disubstituted olefins would be viable substrates. In particular, and in contrast to the AD, electron-deficient olefins were amongst the fastest reacting substrates.

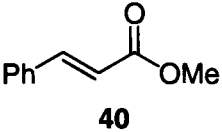
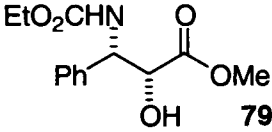
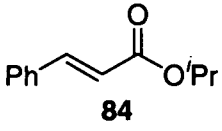
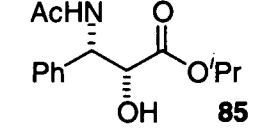
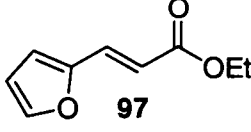
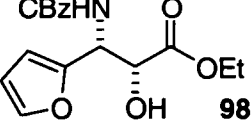
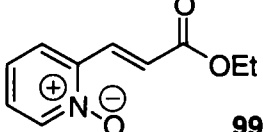
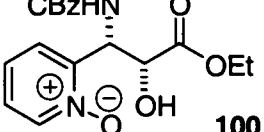
<i>Alkene</i>	<i>Major product</i>	<i>Yield(%)</i>	<i>ee (%)</i>	<i>Regioselectivity</i>
 40	 79	78	99	>20:1
 84	 85	81	99	>20:1
 97	 98	62	87	7:1
 99	 100	80	79	2.3:1

Table 8 Asymmetric aminohydroxylation of cinnamates

When the sulfonamide variant of the AA was surpassed by the carbamate variant, particularly in terms of enantioselectivity, any trend that existed became more pronounced. The cinnamates stood out as reacting rapidly, giving high yields and for

the first time uniformly topping 90% ee.³² Exchange of the aryl group for a variety of other heterocycles allowed access to a greater variety of aromatic scaffolds.^{44, 45}

By contrast no such enhancement was seen in acyclic *cis* disubstituted olefins, exemplified by their prolonged absence in the literature. The yields were consistently much lower, and the enantioselectivities were much poorer than one would associate with Sharpless chemistry (table 9). Cyclic *cis* olefins were better, but not exceptional substrates. Other deviations from the cinnamate template showed similar, if less marked and predictable, detriments. The loss of the aryl group, in particular, was accompanied by a drop in ee.

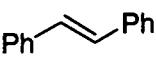
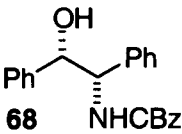
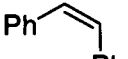
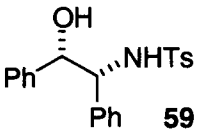
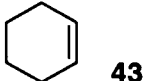
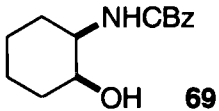
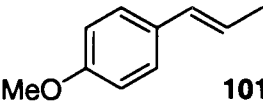
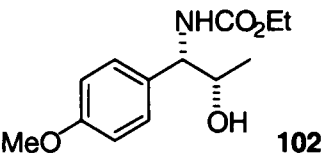
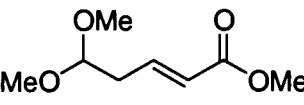
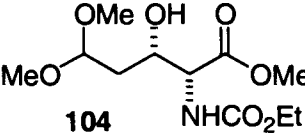
<i>Alkene</i>	<i>Major product</i>	<i>Yield (%)</i>	<i>ee (%)</i>	<i>Regioselectivity</i>
 45	 68	92	91	NA
 58	 59	57	50	NA
 43	 69	51	63	NA
 101	 102	81	98	5:1
 103	 104	93	78	1.3:1

Table 9 Less successful disubstituted olefins in the AA

Presuming that the cinnamic acid skeleton had unique features, Sharpless went on to investigate other derivatives, with the hope of finding other pockets of exceptional

reactivity. While cinnamates gave high yields, enantioselectivities and regioselectivities (*vide infra*), cinnamides⁴⁶ and cinnamic acids⁴⁷ themselves gave racemic material under AA conditions. In the AD reaction these substrates gave exceptional enantiocontrol, further underlining that the similarities between the AA and the AD are only superficial.

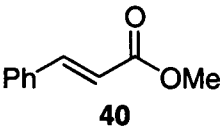
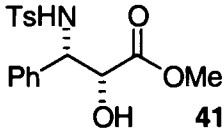
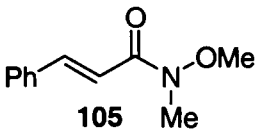
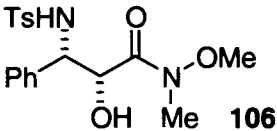
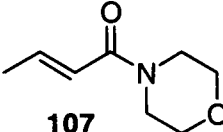
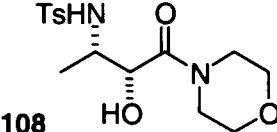
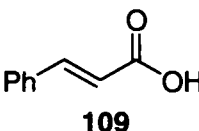
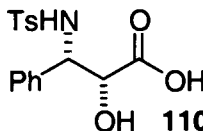
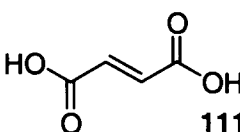
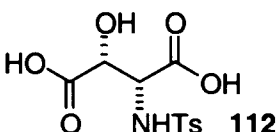
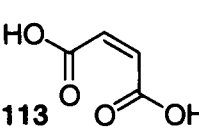
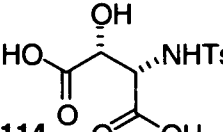
<i>Alkene</i>	<i>Major product</i>	<i>Catalyst/ Chloramine (mol%)</i>	<i>Time (h)</i>	<i>Yield (%)</i>	<i>Regioselectivity</i>
 40	 41	4.0 / 3.0	3	64	'High'
 105	 106	1.0 / 1.2	1	93	7.3 : 1
 107	 108	0.5 / 1.0	10	97	1.4 : 1
 109	 110	1.0 / 1.0	10	96	1.6 : 1
 111	 112	0.2 / 1.0	6	98	NA
 113	 114	1.0 / 1.0	12	88	NA

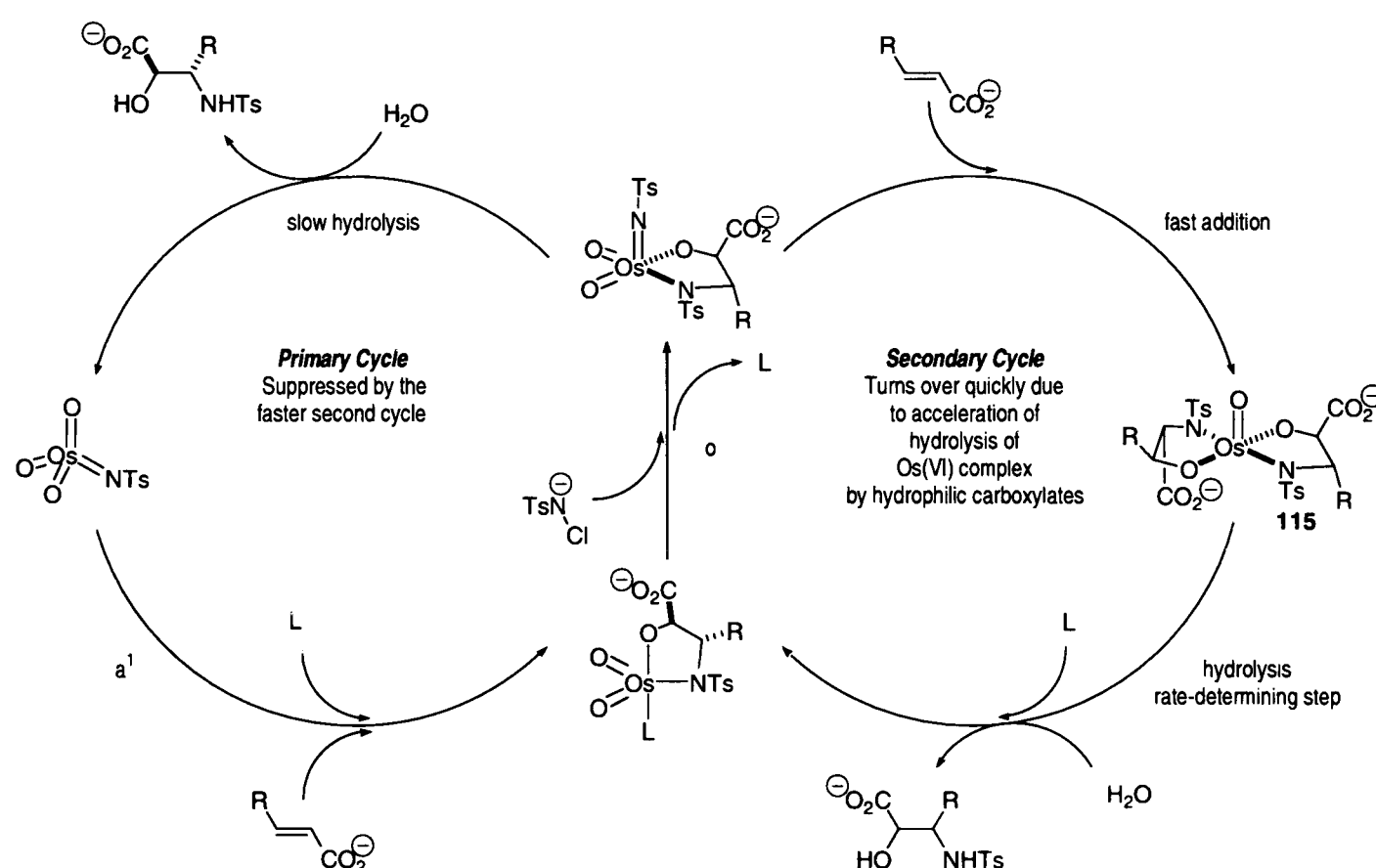
Table 10 α,β -Unsaturated amides and acids are highly reactive in the AA

The cinnamides and cinnamic acids did, however, represent a pocket of heightened reactivity in the AA. In the absence of some form of ligand-accelerated catalysis, most substrates were oxidised slowly and afforded high proportions of diol. By contrast, the cinnamides and cinnamic acids reacted more rapidly than other substrates, allowing for the use of lower osmium catalyst and nitrogen source loadings (table 10).

A range of α,β -unsaturated carboxylic acids were subjected to AA conditions and also found to be oxidised with high rates and yields, while affording racemic material. The reactions involving acids can in fact be run in water with no organic co-solvent, again assisting hydrolysis. This high rate of reaction, even in the absence of ligands, allows the reactions to be run at much higher concentrations than would otherwise be possible, greatly simplifying scale-up procedures. It should be noted that the inclusion of maleic acid in these results represents a rare example of an acyclic *cis* substituted olefin in the recent literature.

1.6.2 Second-cycle catalysis of the AD and AA

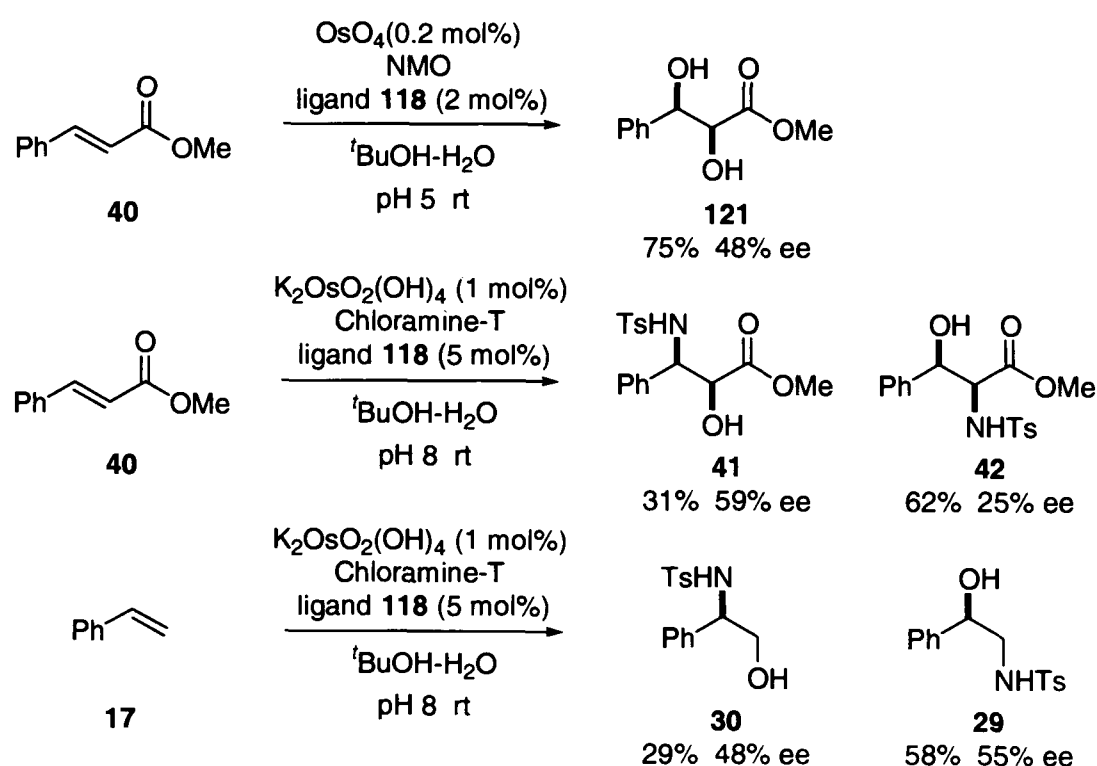
The resting state of the osmium catalyst, under homogeneous conditions, is at the bisglycolate (in dihydroxylation) or bisazaglycolate ester **115**. The observations that the reactions with acids run very quickly in homogeneous conditions, while giving racemic material, suggests that this oxidation is dominated by the second cycle (scheme 22). It is proposed that the carboxylate units accelerate hydrolysis of the bisazaglycolate by creating a more hydrophilic environment at the vacant coordination site of the osmium.⁴⁷



Scheme 22 Catalytic cycle for carboxylic acid substrates

Sharpless recognised that this phenomenon presented an opportunity to control the enantioselectivity of both dihydroxylation and aminohydroxylation through the second catalytic cycle. By introducing a chiral ligand that would bind to osmium in a fashion analogous to that in a glycolate ester, the process could be deliberately driven through the second cycle, but subjected to an asymmetric environment on oxidation.⁴⁹

Even the relatively simple tartaric acid showed some asymmetric induction, albeit only to a small degree and when present in 25 mol%. In order to improve the ee's, vicinal hydroxysulfonamides were used since they have higher binding constants for osmium and should remain bound to the metal for longer. These were easily accessible from the corresponding olefins *via* the AA. The study found that, while all the ligands tested were excellent at improving the *yield* of reaction, the stereo-induction was highly variable according to the substitution of the aminoalcohol (table 11). Sulfonamides were all very similar, but amides noticeably poorer. The benzylic amine was found to give greater enantioselectivity than the benzylic alcohol. *N*-tosyl threonine was found to be an adequate substitute for other synthetic aminoalcohols. The sense of selectivity was solely dependent on the configuration of the centre α to the acid. The best ee's were obtained using the *para*-nitrocinnamic acid ligand **118**, and this was tested against other substrates in both second-cycle AD and AA processes (scheme 23).



Scheme 23 Second cycle AD and AA reactions

1.6.3 Primary olefins in the AA

Work involving the use of stoichiometric $\text{O}_3\text{Os}=\text{NR}$ complexes quickly identified primary olefins as being the most reactive under the reaction conditions.¹⁴ This seemed counterintuitive, given that OsO_4 itself reacts much more quickly with polysubstituted olefins. At that time this was the only known oxidant to behave in this way. This was ascribed to the high steric bulk of the nitrogen substituent, although this failed to account for the delivery of nitrogen in preference to oxygen despite this being statistically less likely. Pyridine was the solvent of choice for these early reactions, and under these conditions both styrene and 1-decene were oxidised with complete chemo- (for the aminoalcohol) and regioselectivity (for the terminal amine).

Surprisingly, with the move towards catalytic aminohydroxylation, and the sulfonamides in particular, the yields of aminoalcohol from primary olefins were low.²⁸ In particular, Sharpless notes that while styrenes represent some of the best substrates for the AD reaction, in the early sulfonamide variant of the AA the yields were low and enantioselectivities moderate at best.

Fortunately, the styrene systems are much more reactive under the carbamate variant.³² Instantly Sharpless noticed the potential of this reaction, and published the synthesis of an extensive library of arylglycines by this method (table 12).⁵⁰ Sharpless also investigated systematically the effect that the ligand/solvent combination had on the regioselectivity of the process (*vide infra*, section 1.7.4).

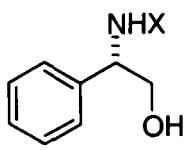
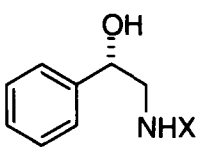
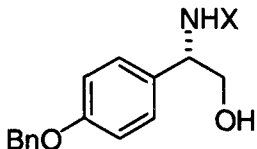
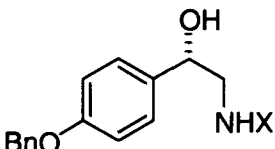
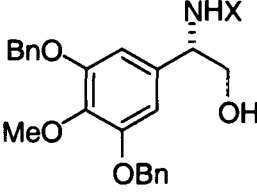
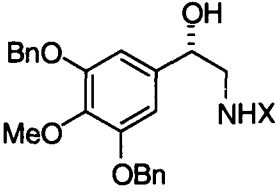
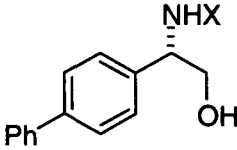
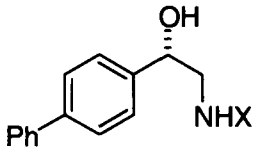
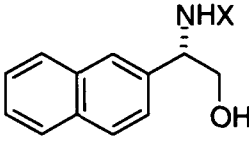
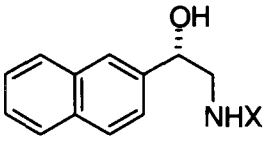
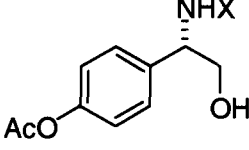
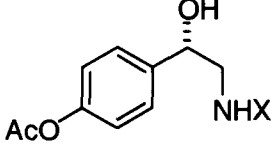
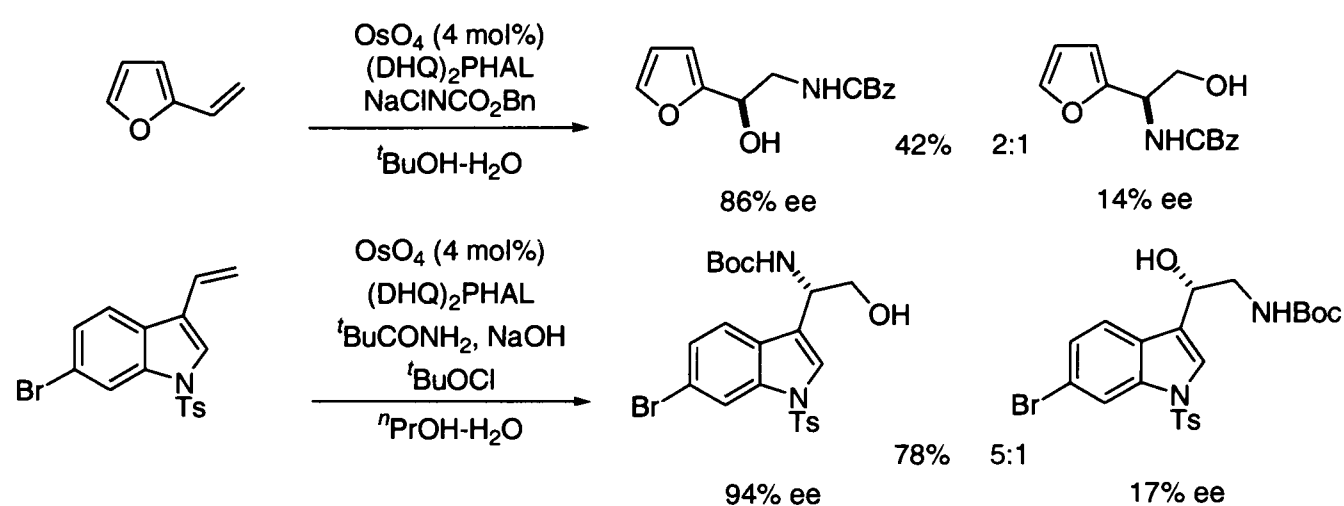
<i>Product A</i>	<i>Product B</i>	<i>Ratio A:B (X)</i>	<i>Yield A (%)</i>	<i>ee A (%)</i>
		55:45 (CBz)	40	93
		88:12 (CBz) 83:17 (Boc)	76 68	97 99
		88:12 (CBz) 89:11 (Boc) 91:9 (TeoC)	68 70 81	91 98 98
		91:9 (CBz)	70	74
		91:9 (CBz) 88:12 (Boc) 86:14 (TeoC)	71 70 76	94 98 97
		50:50 (CBz)	42	83

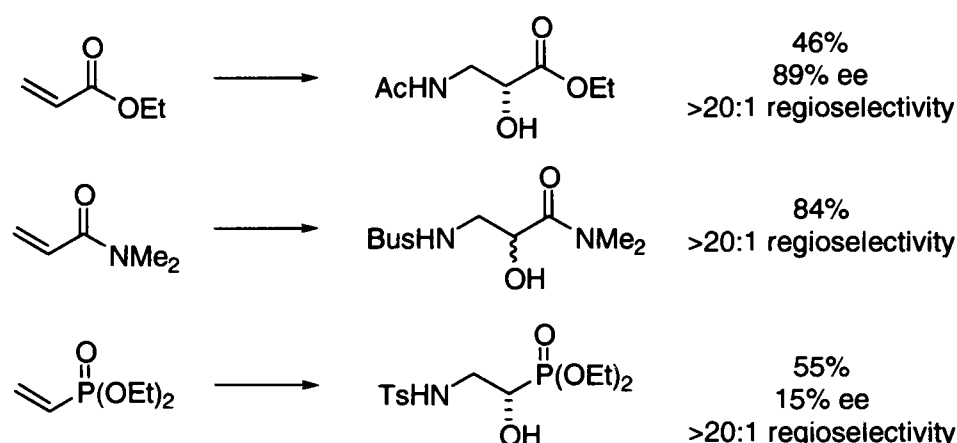
Table 12 Oxidation of styrenes in the carbamate AA

Within all of these studies, amongst others, it became apparent that ethyl carbamate and *tert*-butyl carbamate were generally superior to benzyl carbamate with respect to both yield and enantioselectivity. The best regioselectivities were obtained using TeoC carbamate, although the benzylic amine was the major regioisomer in all cases. This could be reversed by switching to the amide variant, where the opposite was true (*vide infra*).³⁷ This became necessary when it was discovered that the ee's of the benzylic alcohols are considerably lower than those of the benzylic amines formed by the carbamate procedure.



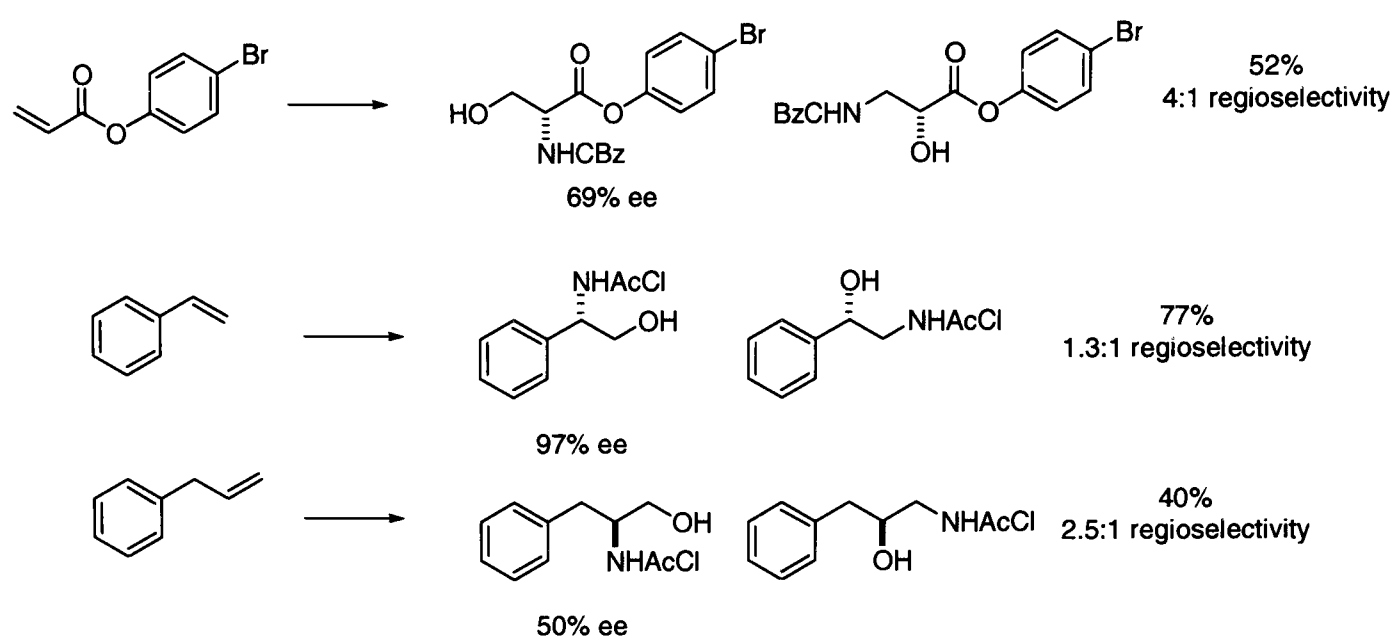
Scheme 24 AA of vinyl heterocycles

Closely related olefins also underwent the AA, showing similar trends with respect to regio- and enantioselectivity. Vinyl heterocycles have been aminohydroxylated in good yields by O'Doherty,^{51, 52} while Jiang has investigated vinyl indoles (scheme 24).⁵³ Acrylates,³⁷ acrylamides³¹ and α,β -unsaturated phosphonates⁵⁴ have also been oxidised, with impressive levels of regiocontrol (scheme 25). Primary olefins generally seem to have a preference for forming the primary amine, presumably arising from steric considerations. The presence of an aryl group can disrupt this considerably, however (scheme 26 and *vide infra*, section 1.7.3).⁵⁵



Scheme 25 Primary olefins in the AA

The remarkable decline in all relevant areas of the reaction on moving from styrene to its homologated counterpart is obvious.³⁸ The inferiority of non-conjugated olefins in the AA does indeed seem to be a general phenomenon (*vide infra*).



Scheme 26 Aryl groups have an effect on the regioselectivity of oxidation

1.6.4 1,1 Disubstituted olefins in the AA

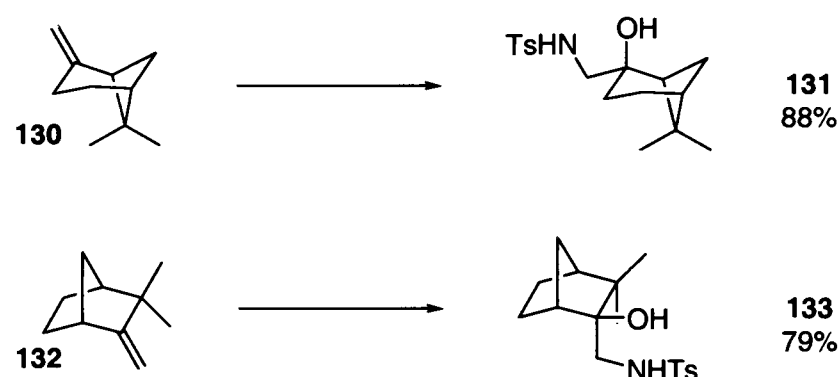
A much understudied class of olefins, 1,1 disubstituted alkenes have also shown unusual reactivity under AA conditions. Much of Sharpless' recent work has concerned cinnamic acid derivatives, because of their general high reactivity and selectivity. Early oxidations, however, had embraced 1,1 disubstituted olefins. They showed, as most substrates did with the sterically demanding $\text{O}_3\text{Os}=\text{N}^t\text{Bu}$ system, complete preference for forming the terminal amine.¹⁴

Alkene	Major product	Yield (%)	dr
 122	 123	88	88:12
 124	 125	71	98:2
 126	 127	71	92:8
 128	 129	23	>99:1

Table 13 Aminohydroxylation of Baylis-Hillman olefins *Reagents and conditions*: $\text{K}_2\text{OsO}_2(\text{OH})_4$ (1 mol%), Chloramine-T (1.2 eq.), MeCN- H_2O (1:1), rt

When the AA came to prominence in 1996, these substrates all but disappeared from the literature. The inference is that, as with *cis* olefins, these are generally poor substrates. One notable exception is that of Baylis-Hillman olefins. These highly functionalised synthetic manifolds exhibit similar ligand-independent reactivity to α,β -unsaturated acids and amides.⁵⁶ Yields of aminoalcohol are high, even in the absence of chiral ligand (table 13).

The most notable feature of these substrates is the high diastereoselectivity observed in most systems. Even with a methyl group (substrate 122) the *syn* isomer is favoured in a ratio of about 7:1. Further substitution, in particular branching of the R group, means the diastereoselection approaches total. This high level of reactivity and stereocontrol is unique to the free alcohol: alkylated analogues did not show the same reactivity, while acetylated versions gave lower stereocontrol.



Scheme 27 β -Pinene and camphene are completely diastereoselective substrates for aminohydroxylation *Reagents and conditions:* OsO₄ (1 mol%), Chloramine-T (1.25 eq.), ^tBuOH-H₂O (1:1), reflux

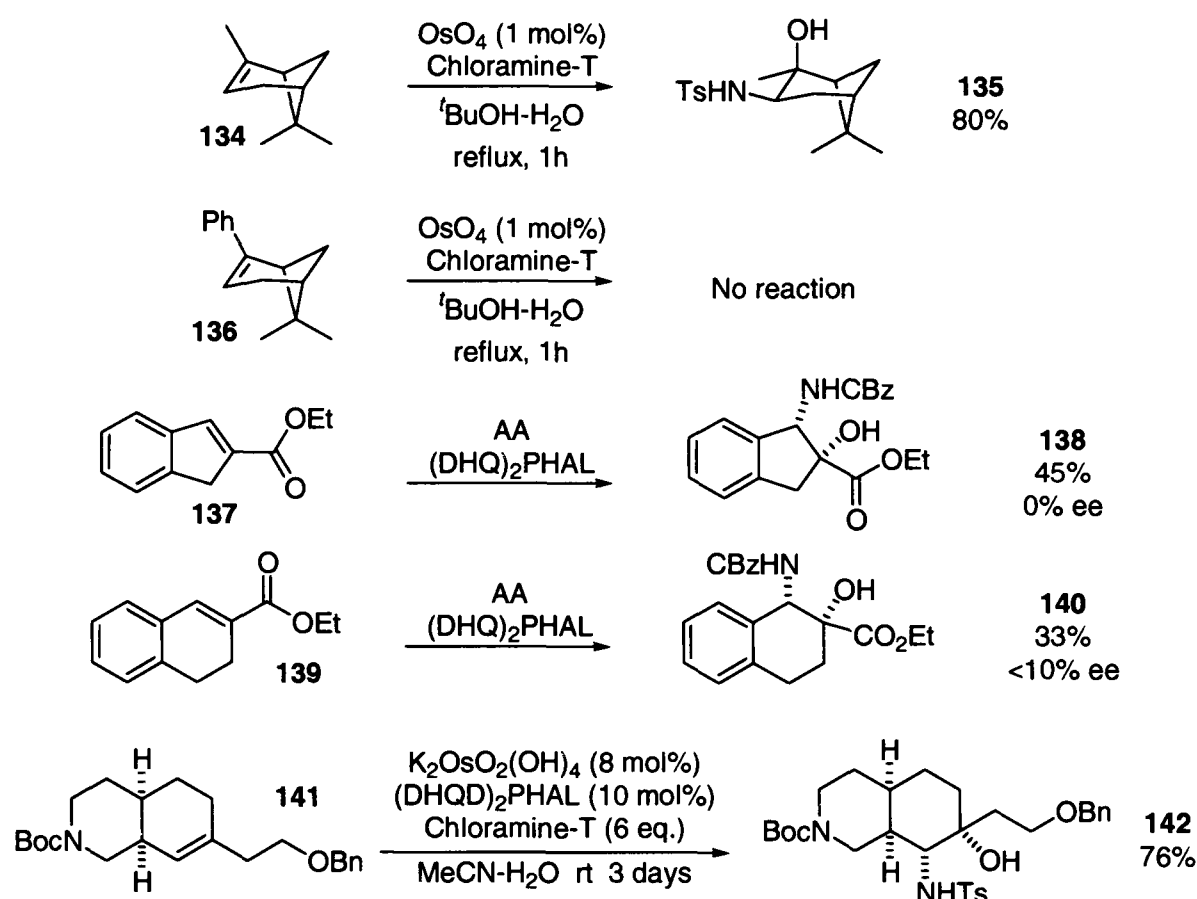
In conformationally rigid systems, such as β -pinene and camphene, the reaction is completely diastereoselective, with oxidation occurring from the less hindered face of the double bond.⁵⁷ These substrates were less reactive than Baylis-Hillman olefins, again demonstrating the unique reactivity of the latter. The regioselectivity of all these ligand-independent systems is completely in favour of the primary amine, indicating a very large steric differentiation of the two ends of the double bond.

There are, however, no examples in the literature of *enantioselective* aminohydroxylations of 1,1-disubstituted olefins. The complete failure of the two

examples below (137 and 139, scheme 28) suggests that a different approach will be required for these and more highly substituted systems.^{58, 59}

1.6.5 Tri- and tetrasubstituted olefins in the AA

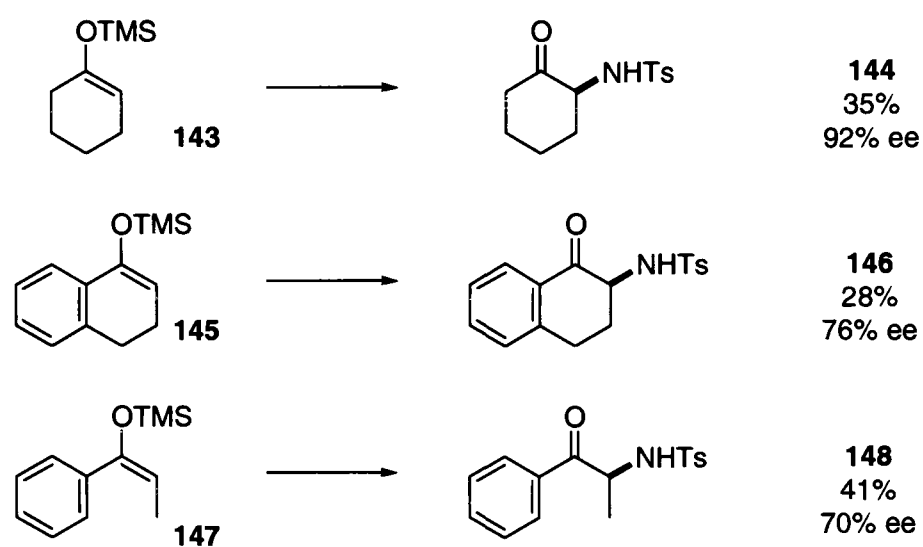
These final classes have been grouped together for their notable absence among the many papers published in this area. The earliest stoichiometric aminohydroxylations did incorporate these substrates, albeit with low yield, but since the advent of the less potent asymmetric catalytic protocol these substrates have largely remained inert. A few examples are scattered throughout the literature, although no trialkyl-substituted olefins have given any enantioselectivity (scheme 28). The often-sluggish nature of these reactions is clearly seen in the oxidation of 141, where high catalyst loadings and extended reaction times are required.⁶⁰ The reaction is also sensitive to the alkene substituents, as seen in the two α -pinene substrates 134 and 136.⁵⁷



Scheme 28 Aminohydroxylation of trisubstituted olefins

The only examples of enantioselective aminohydroxylation of these classes of are in the oxidation of silyl enol ethers.⁶¹ Aminohydroxylation of these substrates gives the α -

sulfonaminoketones in moderate yield. The process is again highly regioselective, favouring the β -amine. The low yields are attributed to difficulties encountered during work-up.



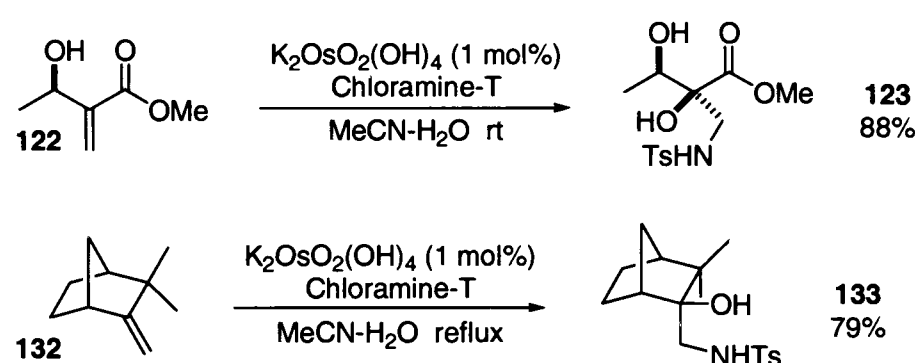
Scheme 29 Aminohydroxylation of silyl enol ethers *Reagents and conditions:* OsO₄ (1 mol%), DHQD-CLB, Chloramine-T (2.5 eq.), ^tBuOH-H₂O (1:1), rt

1.7 – Regioselectivity of the AA

The AA has now reached a point in its development whereby various factors are now much better understood. The chemoselectivity has been improved to the point that in most cases no diol is formed at all. In the more important olefinic classes the enantioselectivity approaches total, and the development of a number of ligands means that access to either enantiomer is possible. Thus the single greatest challenge remaining for the aminohydroxylation reaction is control of the regioselectivity. Even in cases where the product is virtually enantiomerically pure, the regioselectivity can be remarkably poor. This complicates purification procedures considerably, as the regioisomers formed can be difficult to separate by column chromatography. Crystallisation is a useful alternative, but applies largely to the sulfonamide variant, and is not always possible.

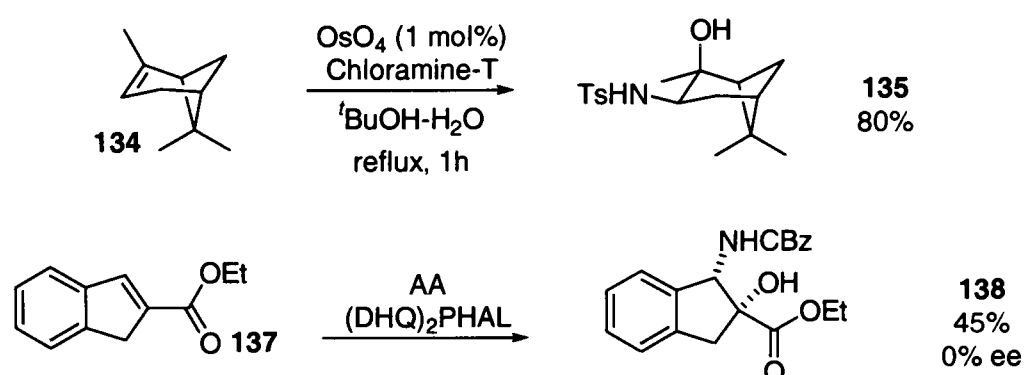
1.7.1 Effect of alkene substitution on regioselectivity

The most clearly defined trend in influencing the regioselectivity of the aminohydroxylation process is the substitution pattern of the double bond. The most extreme class is that of 1,1-disubstituted olefins. In this instance one end of the alkene is clearly more hindered than the other, and in every reported case the nitrogen is delivered to this less-substituted end (scheme 30).^{56, 57}



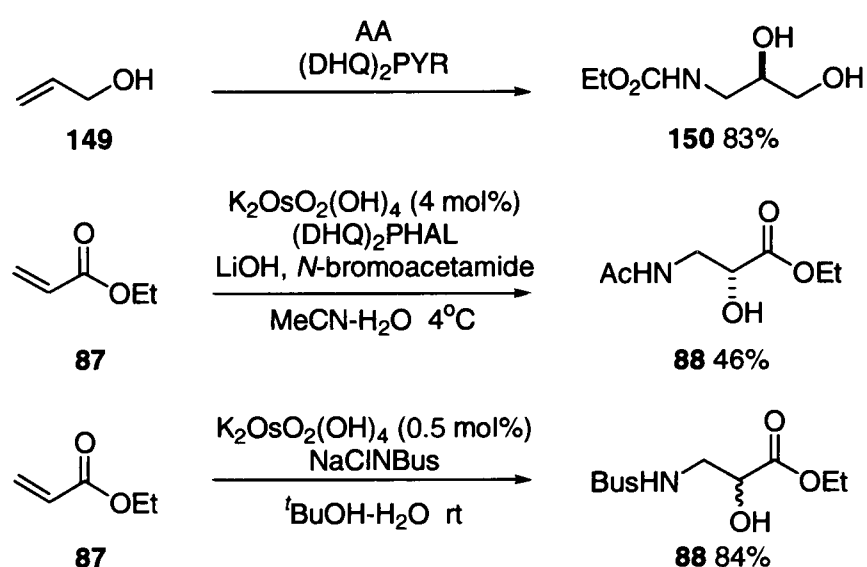
Scheme 30 Complete regioselectivity in aminohydroxylation of 1,1 disubstituted olefins

More highly substituted systems also show this pattern (scheme 31).^{57, 58}



Scheme 31 Complete regioselectivity in aminohydroxylation of trisubstituted olefins

As do many mono-substituted olefins (scheme 32):^{31, 37, 62}

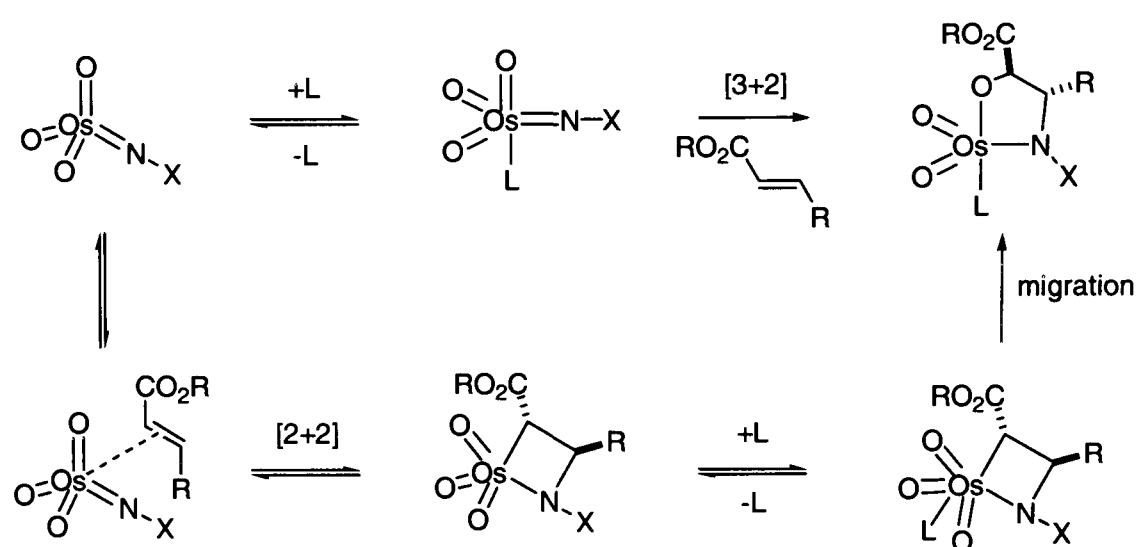


Scheme 32 Highly selective primary olefins in the AA

This observation can be simply rationalised on the basis of the greater steric encumbrance of the substituted imidoosmium grouping ($\text{Os}=\text{NR}$) compared to the unsubstituted oxaoosmium linkage ($\text{Os}=\text{O}$). Importantly, this preference is shown in the presence or absence of a chiral ligand.

1.7.2 Effect of alkene polarisation on regioselectivity

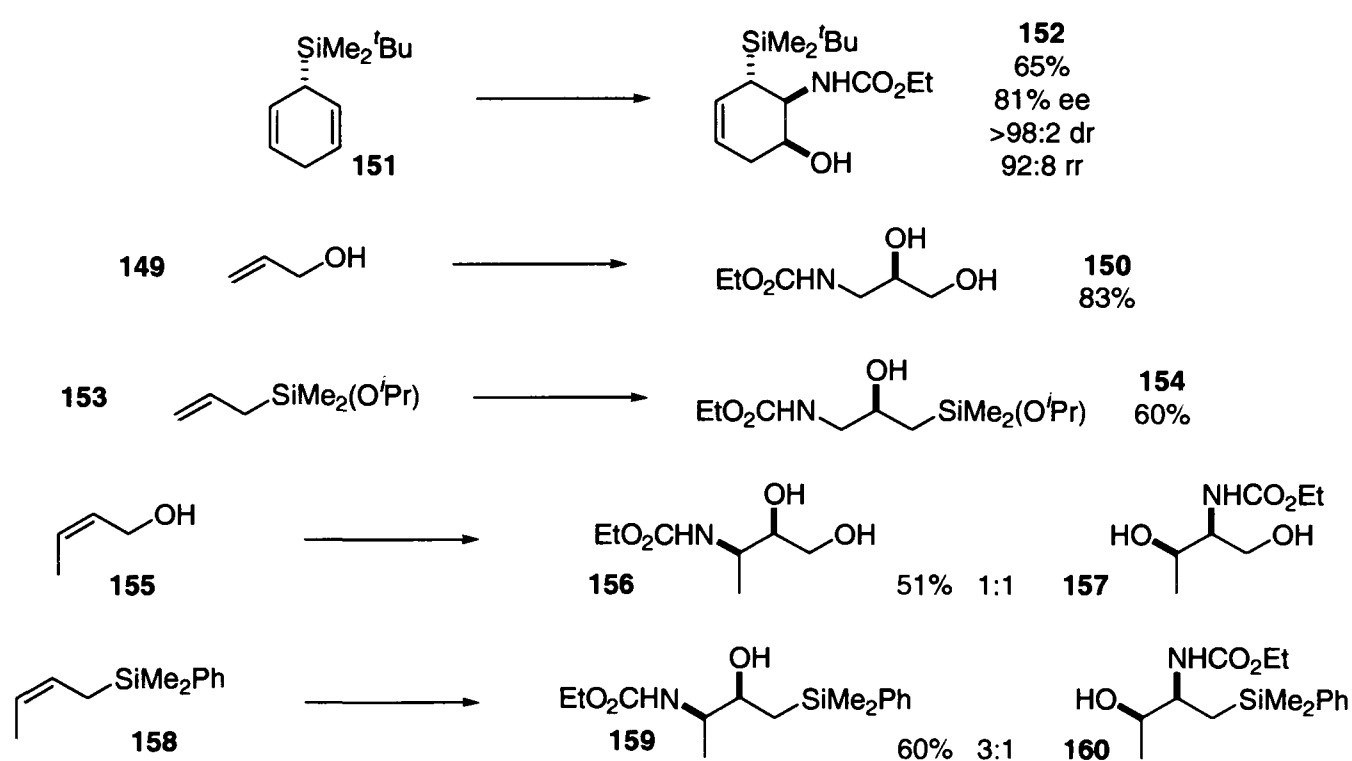
In the case of alkene **87** above (scheme 32), it is possible that the preference for nitrogen delivery to the terminal end of the double bond arises from polarisation. Though the exact nature of the argument varies according to which oxidation mechanism is preferred ($[3+2]$ vs. $[2+2]$), the suggestion is that the imidoosmium grouping is more nucleophilic than $\text{Os}=\text{O}$ and thus adds to the most electron-deficient end of the alkene. (scheme 33).



Scheme 33 Addition of nitrogen to the more electrophilic terminus

This would seem particularly plausible if the [2+2] mechanism were operating, as there would be steric clashes between the substrate and the bulky osmium metal. However, this does not account for the considerable reversals of selectivity when AQN ligands are used instead of PHAL (*vide infra*, section 1.7.4).

Electronic effects were also used to explain the unusual result obtained by Landais in scheme 34.⁶² The nitrogen in this example has again been added to the more electron-deficient end of the alkene **151**. Unfortunately, this was not a general phenomenon, as illustrated by the acyclic examples **153-158**.⁶³

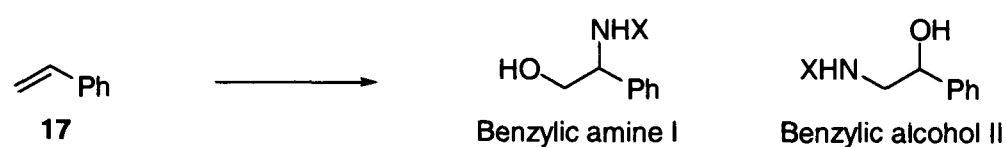


Scheme 34 Landais AA of allyl silanes *Reagents and conditions*: $\text{K}_2\text{OsO}_2(\text{OH})_4$ (4 mol%), $(\text{DHQ})_2\text{PYR}$, EtOCONH_2 , NaOH , $t\text{BuOCl}$, $i\text{PrOH-H}_2\text{O}$ (1:1), rt

The crotyl silyl substrate **158** demonstrates addition of the nitrogen to the more nucleophilic, not electrophilic end of the double bond. The complete regioselection for substrates **149** and **153** would suggest that the substitution pattern is a more dominant factor in determining regioselectivity, although other factors should be considered (*vide infra*).

The aminohydroxylation of silyl enol ethers (*vide supra*, scheme 29) is another example showing the relative influences of polarisation and substitution on regioselectivity.⁶¹ The nitrogen in these examples has clearly been added to the more nucleophilic end of the olefin, but importantly away from the bulky trimethylsilyl group. Consideration of all these examples suggests that alkene polarisation plays a relatively minor role in influencing the regiochemistry of aminohydroxylation.

1.7.3 Ligand-substrate interactions: PHAL ligands



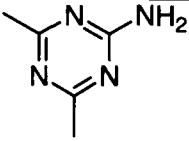
<i>X</i>	<i>Ligand</i>	<i>Yield (%)</i>	<i>Ratio I:II</i>
Ts ¹⁷	None	83	1:1.5
Boc ¹⁹	None	81	1:5.7
CBz ³²	PHAL	73	1.2:1
Boc ³⁴	PHAL	73	4:1
EtO ₂ C ⁶⁴	PHAL	67	1.9:1
AcCl ³⁸	PHAL	77	1.3:1
 42	PHAL	74	5:1

Table 14 Influence of ligand on regioselectivity of styrene aminohydroxylation *Reagents and conditions* K₂OsO₂(OH)₄ (4 mol%), ligand, nitrogen source NaCINX, ⁿPrOH-H₂O/ⁿBuOH-H₂O/MeCN-H₂O

Possibly the most startlingly profound influence on regioselectivity is that imparted by the interaction of the olefin substrate with the chiral cinchona alkaloid ligand in the catalyst system used in the AA process. The earliest, and most clear-cut examples of this are in the oxidation of styrenes. The early, non-asymmetric aminohydroxylations gave predominantly, though not exclusively, the benzylic alcohol when styrene was oxidised. It is almost universally the case that when styrene is aminohydroxylated in the presence of PHAL ligands, the reverse regiochemical trend is observed i.e. the benzylic amine is favoured (table 12).

Sharpless' library of arylglycines, produced by aminohydroxylation of a variety of styrene substrates illustrates this very clearly.⁵⁰ While styrene itself still has a modest preference for formation of the benzylic amine (55:45), most other styrenes oxidised under the same conditions give a much-improved ratio in favour of the benzylic amine (figure 5). Of the nineteen styrenes oxidised, only three showed no selectivity at all.

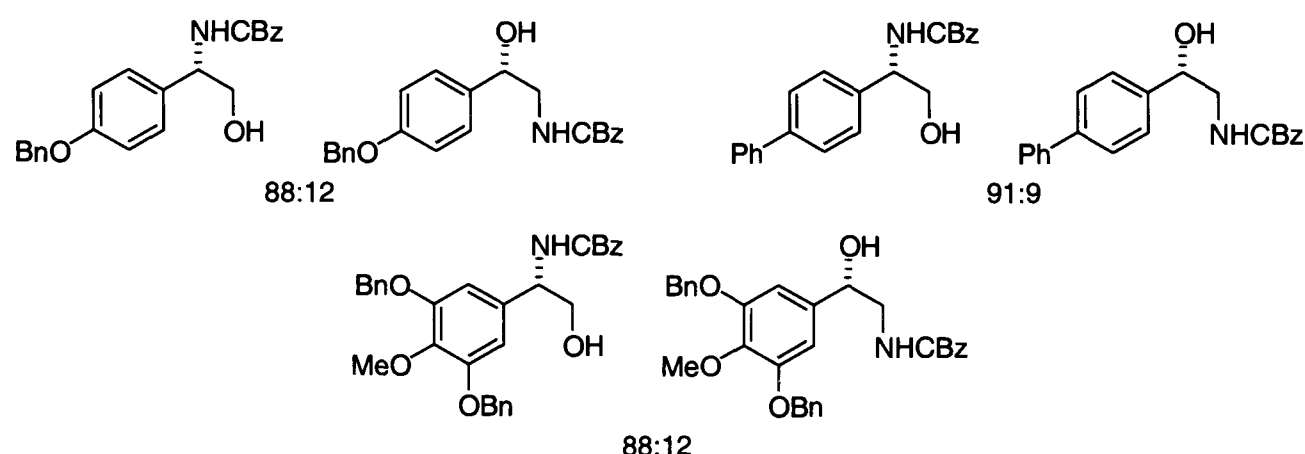
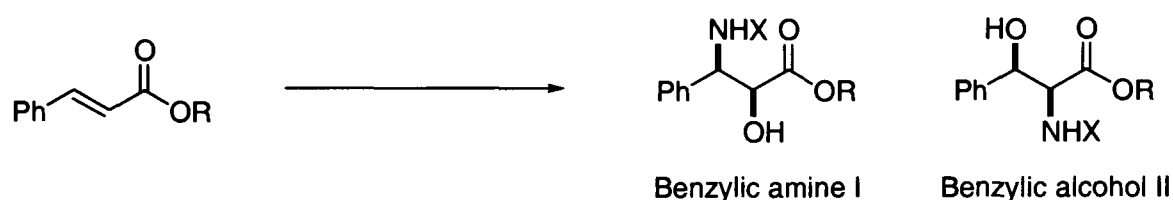


Figure 5 Styrene AA with PHAL ligands favours the benzylic amine

This trend is also seen with the cinnamates. This time, while methyl cinnamate was oxidised under racemic conditions to give a 2:1 mixture of benzylic amine to benzylic alcohol, the ratios are exaggerated by performing the oxidation under asymmetric conditions (table 15).



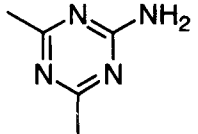
<i>R</i>	<i>X</i>	<i>Ligand</i>	<i>Yield (%)</i>	<i>Ratio I:II</i>
Me	Ts	None	78 ¹⁷	2:1
Me	Ts	PHAL	83 ²⁸	5:1
Me	Ms	PHAL	65 ³⁰	10:1
Me	CBz	PHAL	65 ³²	1:0
Me	EtO ₂ C	PHAL	78 ³²	1:0
^{<i>i</i>} Pr	Ac	PHAL	81 ³⁷	>20:1
^{<i>i</i>} Pr		PHAL	97 ⁴²	>20:1

Table 15 Influence of ligand on regioselectivity of cinnamate aminohydroxylation *Reagents and conditions* K₂OsO₂(OH)₄ (4 mol%), ligand, nitrogen source NaClNX, ^{*n*}PrOH-H₂O/^{*n*}BuOH-H₂O/MeCN-H₂O

This preference in the cinnamate series cannot be explained by a simple steric argument: neither end of the double bond is appreciably more hindered than the other. As has been shown already, it seems unlikely that the modest influence alkene polarisation has on regioselectivity could account for it either. Thus the ligand itself must be playing some important role in determining the regiochemical outcome.

Models of the ligand-catalyst complex have suggested that it forms in solution a U-shaped binding pocket.⁶⁵ It is from this model that the mnemonic for the AD reaction derives (*vide supra*, section 1.4). The important structural features are the aromatic cleft at the top of the diagram, the space at the lower edge that is open to solvent and the distorted trigonal bipyramidal osmium metal (figure 6).⁶⁶ This incorporates three equatorial oxo ligands, with a quinuclidine nitrogen occupying one axial position and the imidoosmium linkage the other.

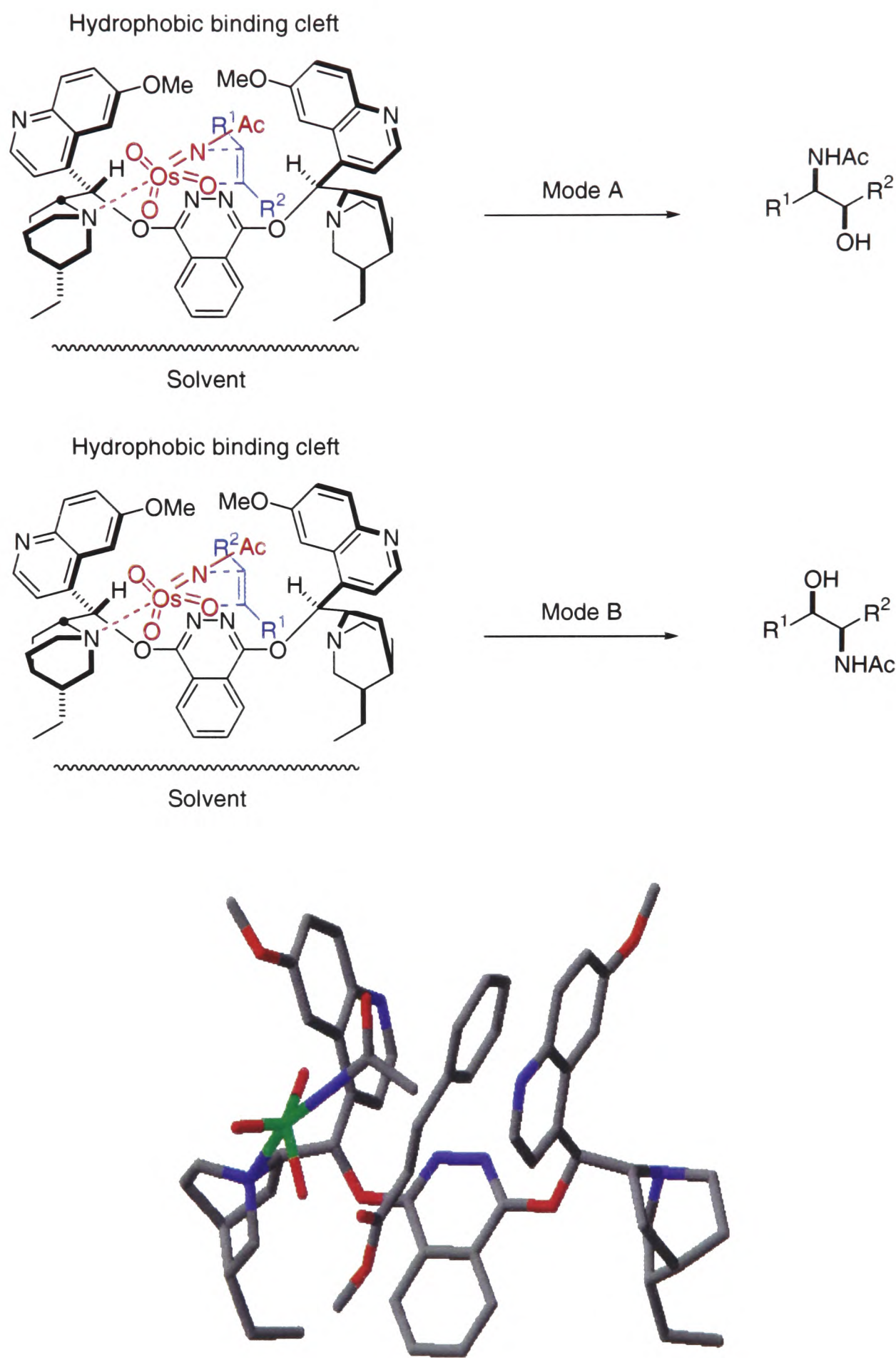


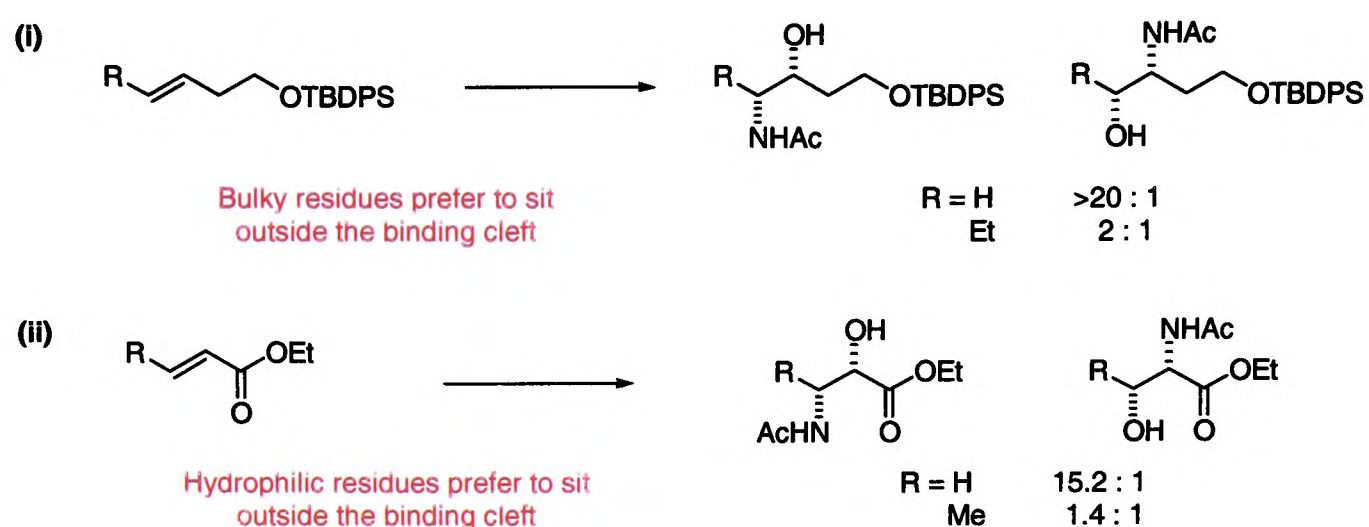
Figure 6 (DHQD)₂PHAL ligand binding pocket model for aminohydroxylation

In order for oxidation to occur, the substrate must adopt one of two ‘docked’ conformations, A or B. These would then directly lead to the formation of the two regioisomers. Three main factors determine which is preferred:

- The binding cleft defined by the methoxyquinoline rings is small and narrow, thus small substituents are favoured sterically, and aromatic substituents by consideration of π - π interactions.
- Larger substituents will preferentially be located outside of the binding cleft.
- The solvent outside of the binding cleft is invariably polar, and usually 50% water. Thus hydrophilic substituents are located outside of the binding pocket.

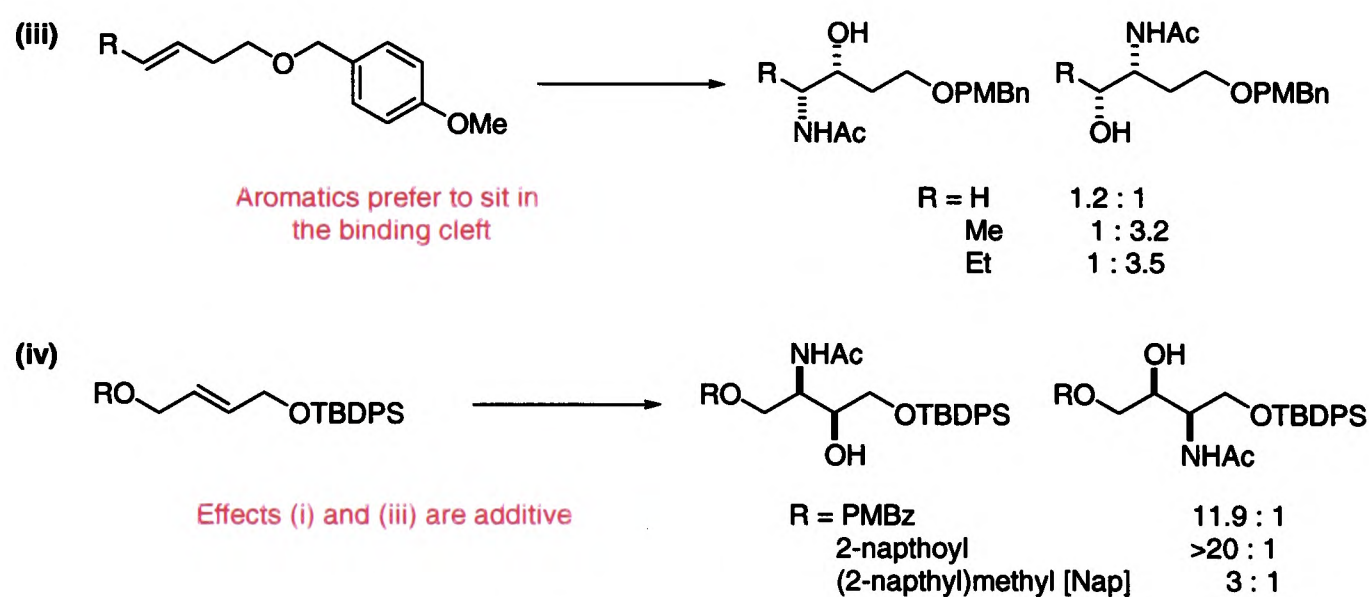
Considering the cinnamates, it is clear that these fit this model well. All cinnamates possess an aryl group at one end of the double bond. This would be expected to sit favourably within the binding pocket, maximising π -stacking interactions with the methoxyquinoline units. The ester group at the other end, while not appreciably bulkier, is much more hydrophilic and therefore comfortably located outside the cleft (figure 6). The styrenes should also fit this pattern, but not as well as the cinnamates. The difference in steric bulk between the two ends clearly still plays a major role in determining regiochemistry, even when the ligand-substrate interactions are considered.

If this pattern hold true for all olefins, it should in theory be possible to direct the regiochemistry of oxidation by judicious choice of protecting groups. Both Janda and Panek have adopted this approach. Janda, who originally applied the ligand binding pocket model to the AA, systematically explored the extent to which this could be exploited.⁶⁷ Firstly, Janda presented evidence for each of the factors mentioned above. In scheme 35 (i), the very bulky silyl group sits outside the pocket, and thus high regioselectivity results. If the other terminus is even slightly increased in size, the regioselectivity decreases dramatically. In scheme 35 (ii), the hydrophilic ester now sits outside the binding pocket, again giving a high level of selectivity. Substitution of any kind reduces this considerably.



Scheme 35 Ligand-substrate interactions can dictate regiochemistry *Reagents and conditions:* $\text{K}_2\text{OsO}_2(\text{OH})_4$ (5 mol%), $(\text{DHQD})_2\text{PHAL}$, *N*-bromoacetamide, $\text{LiOH} \cdot \text{H}_2\text{O}$, $t\text{BuOH} \cdot \text{H}_2\text{O}$ (2:1), 0°C

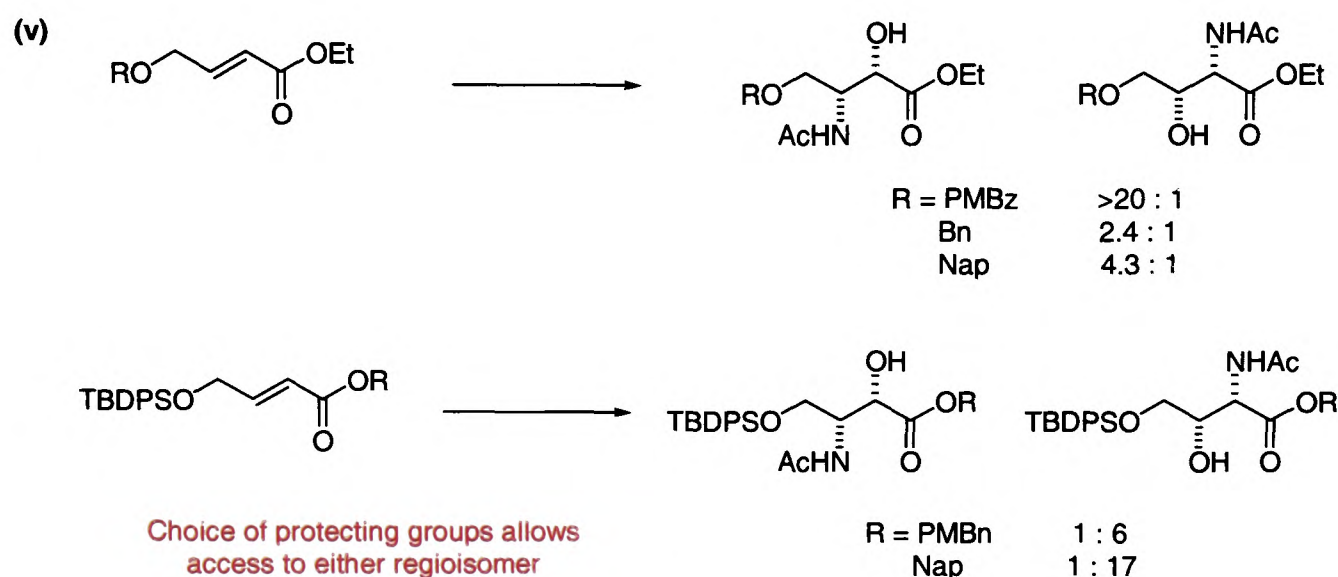
The third series demonstrates the influence of aromatic groups (scheme 36). While the *para*-methoxybenzyl group is bulkier than hydrogen, the regiomer ratio is considerably poorer than the corresponding examples in scheme 35. As substitution at the other end is introduced, the selectivity is overturned. While this shows that aromatic groups do indeed prefer to sit within the binding cleft, it also shows that these effects are additive. As such, if substrates are 'matched' at either end of a double bond, regioselectivity of aminohydroxylation should be high.



Scheme 36 Ligand-substrate interactions can dictate regiochemistry *Reagents and conditions:* $\text{K}_2\text{OsO}_2(\text{OH})_4$ (5 mol%), $(\text{DHQD})_2\text{PHAL}$, *N*-bromoacetamide, $\text{LiOH} \cdot \text{H}_2\text{O}$, $t\text{BuOH} \cdot \text{H}_2\text{O}$ (2:1), 0°C

Thus in scheme 36 (iv), where a bulky group is present at one end of the alkene and an aromatic group at the other, the selectivity is much improved over all earlier disubstituted examples. By extending the π -surface the effect can be increased. Interestingly, the replacement of the carbonyl by methylene results in a much less

regioselective process, presumably due to increased freedom of rotation and therefore increased effective steric bulk of the aromatic portion. Finally, Janda showed that the same substrate could be made selective in either direction by the correct alignment of the protecting groups (scheme 37).



Scheme 37 Ligand-substrate interactions can dictate regiochemistry *Reagents and conditions:* $K_2OsO_2(OH)_4$ (5 mol%), $(DHQD)_2PHAL$, *N*-bromoacetamide, $LiOH \cdot H_2O$, $tBuOH-H_2O$ (2:1), $0^\circ C$

Janda's proposals were supported further by other related examples. Cinnamic acids and cinnamides, substrates that by all accounts should show high regioselectivity, do not show anywhere near the levels exhibited by the cinnamates (figure 7).^{46, 47} Because it is assumed these processes take place in the second cycle, and hence in the absence of the chiral ligand, they cannot be influenced by the factors listed above.

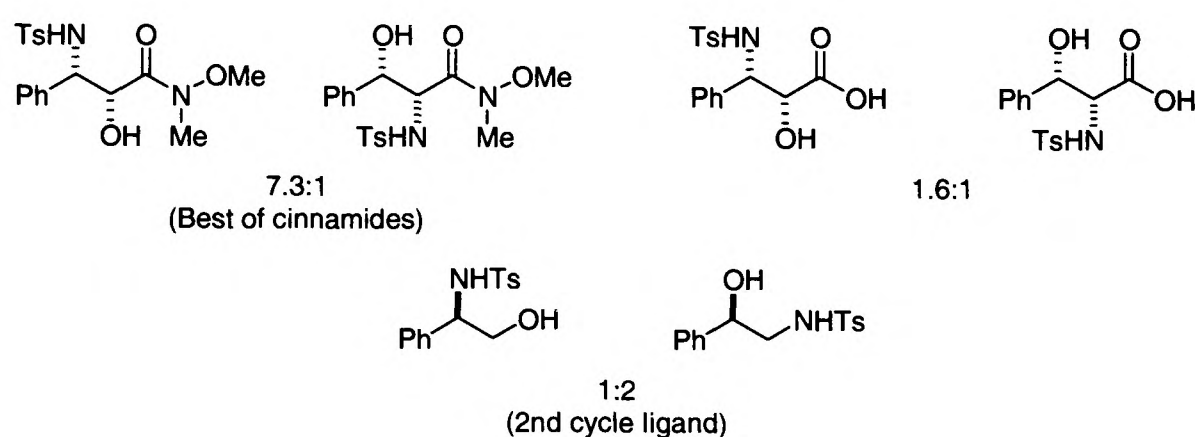
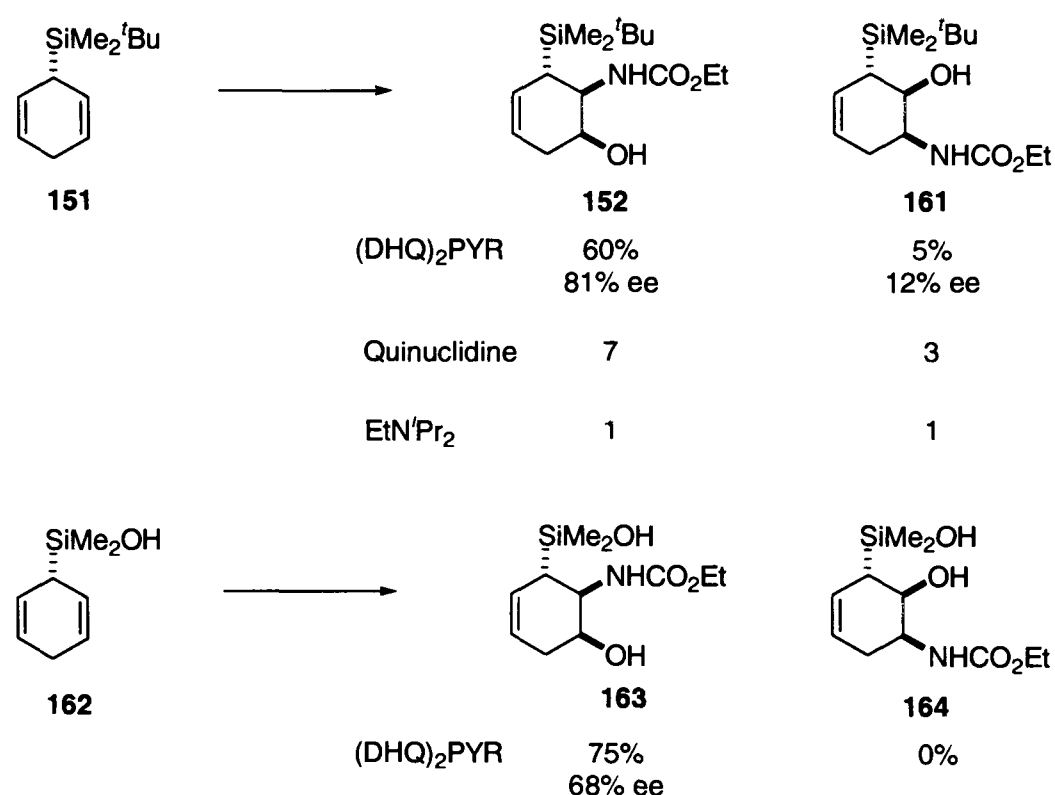


Figure 7 Ligand independent processes have lower regioselectivities

Processes deliberately driven into the second cycle also demonstrate this loss of ligand-based regiocontrol. The aminohydroxylation of styrene under second cycle conditions gives predominantly the benzylic alcohol (figure 7).⁴⁹ This is more akin to

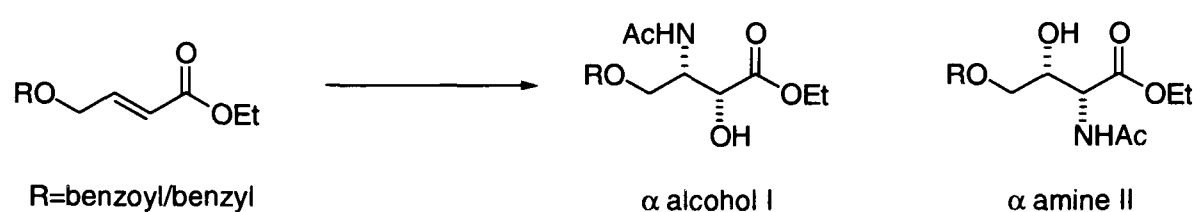
the ligand-independent process than the ligand-dependent oxidation, where the opposite regioisomer is favoured.

A third observation is that the minor regioisomer is sometimes formed with a much lower ee, as might be expected from the substrate being oxidised largely away from the chiral environment of the binding pocket (substrate **151**, scheme 38).⁶³ The lower regioselectivities obtained using achiral ligands in this system show the strength of the directing effects. In addition, the coupling of steric bulk with hydrophilicity by the introduction of a hydroxyl group (substrate **162**) managed to heighten the already exceptional selectivity to remove any of the undesired regiomer.⁶²



Scheme 38 Oxidation of allyl silanes demonstrating ligand effects *Reagents and conditions:* K₂OsO₂(OH)₄ (4 mol%), ligand, EtOCONH₂, ^tBuOCl, NaOH, ⁿPrOH-H₂O (1:1), rt

A refinement of Janda's model was made by Ojima, studying the aminohydroxylation of a number of differently protected 4-hydroxy-2-butenates.⁶⁸ His results are summarised in table 16. Simply put, he notes that for benzoyl-protected substrates, greater levels of regioselectivity were achieved when electron-donating substituents were located in the *para* position on the aryl ring. When the hydroxyl is benzyl-protected, exactly the reverse trend is true. This is borne out by Hammett plots of his results.



Substrate	R	Ratio I:II	Yield (%)	Dipole (debye)
	4-OMe	25:1	74	3.72
	4-H	9:1	65	1.91
	4-Br	6.6:1	71	2.03
	4-NO ₂	4:1	78	5.15
	2-OMe	5.8:1	49	2.37
	4-OMe	1.2:1	76	2.91
	4-H	1.3:1	66	1.91
	4-Br	2.9:1	84	2.16
	4-NO ₂	11:1	65	7.37

Table 16 Ojima's investigation of dipole-dipole interactions *Reagents and conditions:* K₂OsO₂(OH)₄ (4 mol%), (DHQ)₂PHAL, *N*-bromoacetamide, LiOH·H₂O, ^tBuOH-H₂O (1:1), 0°C

His explanation for these trends, and for the outlying *ortho*-methoxy substituted substrate, cites dipole-dipole interactions within the ligand binding pocket as the cause. Essentially, the key features are the two methoxyquinoline rings of the ligand, themselves possessing an inherent dipole. These are complementarily aligned in the binding pocket (figure 8). When the substrate 'docks', aromatic residues will try to align themselves against one or the other of these dipoles.

Thus the most favourable interactions between ligand and substrate will be when the substrate has itself a large aromatic dipole. In the benzoyl series, an electron-withdrawing group is already present, thus *para*-electron-donating groups create the largest dipole and the most favourable interaction with the ligand (figure 9, (i)).

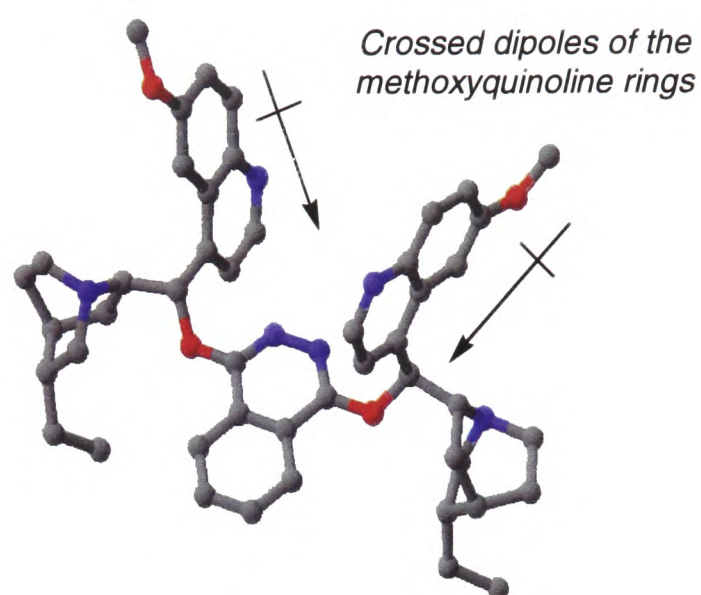


Figure 8 Methoxyquinoline dipoles of (DHQD)₂PHAL

Conversely, the benzyl series possesses an electron-donating group in every case. *Para*-electron withdrawing groups therefore maximise the dipole-dipole interactions, which this time are with the right-hand methoxyquinoline-ring (figure 9, (ii)). The anomalous *ortho*-methoxy result now makes sense: the push-pull substituents are not in concert.

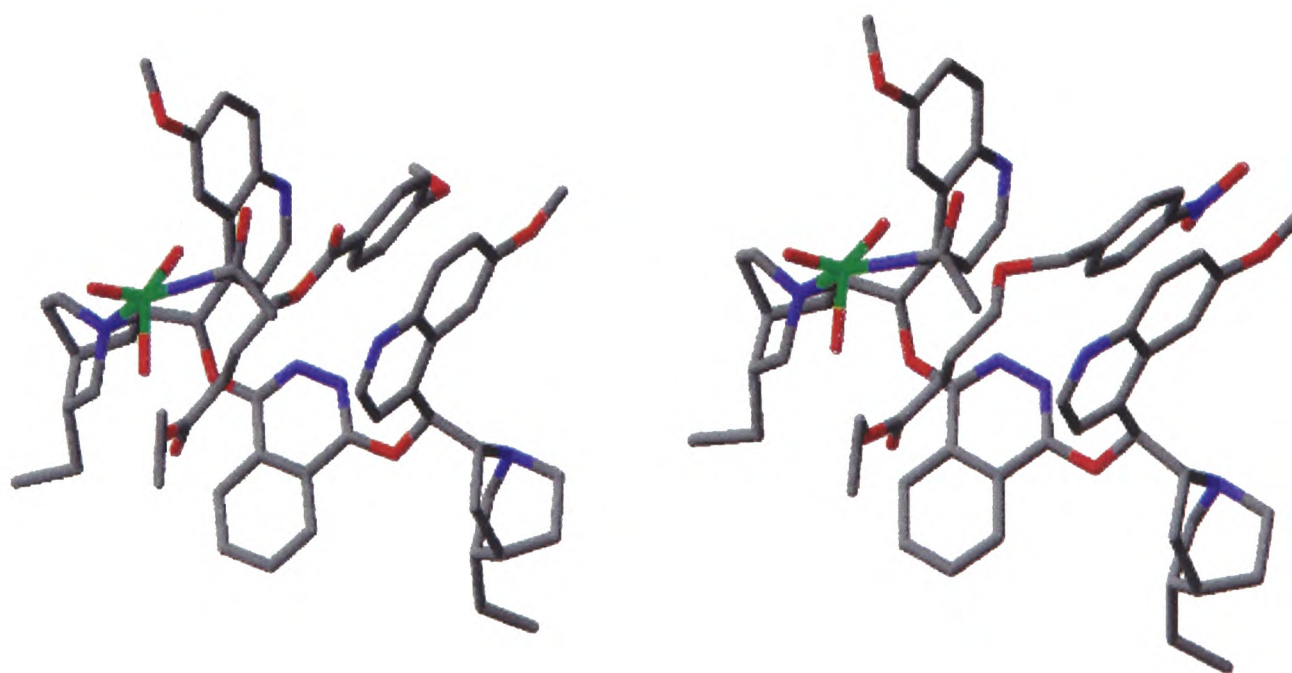


Figure 9 Dipole aligned substrate docking (i) *para*-methoxybenzoyl; (ii) *para*-nitrobenzyl

However, if the regioselectivity were directly proportional to the dipole moment (table 16), then the *para*-nitrobenzoyl protected substrate should give a high level of regiocontrol, which it does not. Thus, this dipole-dipole interaction seems to be quite a small effect.

1.7.4 Ligand-substrate interactions: AQN ligands

One interesting, and particularly useful, observation came from Sharpless' laboratories. When the relatively new anthraquinone (AQN) linked ligands were employed in the AA, the usual sense of regioselectivity was reversed, while the sense of stereoselection (DHQ vs. DHQD) remained the same (table 17).^{50, 69}

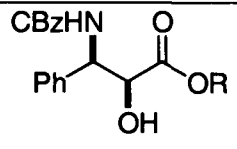
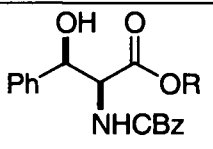
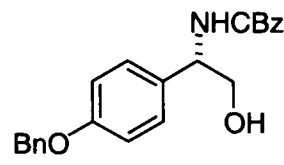
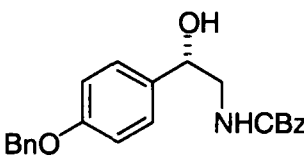
<i>Product A</i>	<i>Product B</i>	<i>Ligand</i>	<i>Cosolvent</i>	<i>Ratio A:B</i>
		PHAL	ⁿ PrOH	100:0
		AQN	ⁿ PrOH	21:79
		PHAL	ⁿ PrOH	88:12
		AQN	ⁿ PrOH	33:66
		AQN	MeCN	25:75

Table 17 Reversal of regioselection in the AA of cinnamates with AQN ligands

This strategy was not applicable to all substrates. Electron-deficient cinnamates gave at best 1:1 mixtures of regioisomers and were often contaminated with diol. While the regiochemistry of oxidation of styrenes was reliable, the enantiomeric excesses of these regioreversed products were drastically reduced, sometimes to 0% ee. The regioselectivity of aminohydroxylation of styrenes could also be reversed by switching to the amide variant. *N*-bromoacetamide as nitrogen source gave the benzylic alcohol as the major regioisomer.³⁷ Coupling this process with the use of AQN ligands, and variations in solvent enhanced this reversal to significant levels, while maintaining high levels of enantiocontrol (table 18).

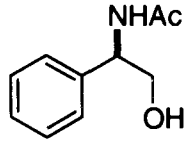
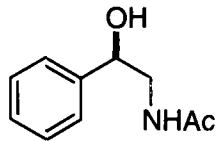
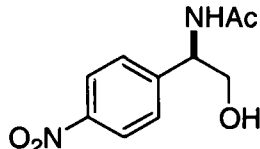
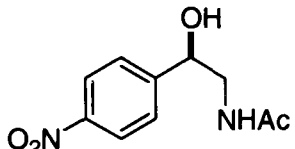
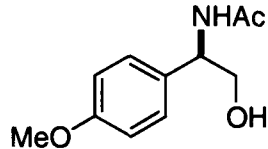
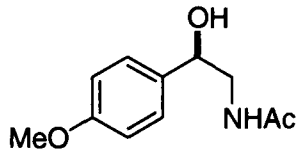
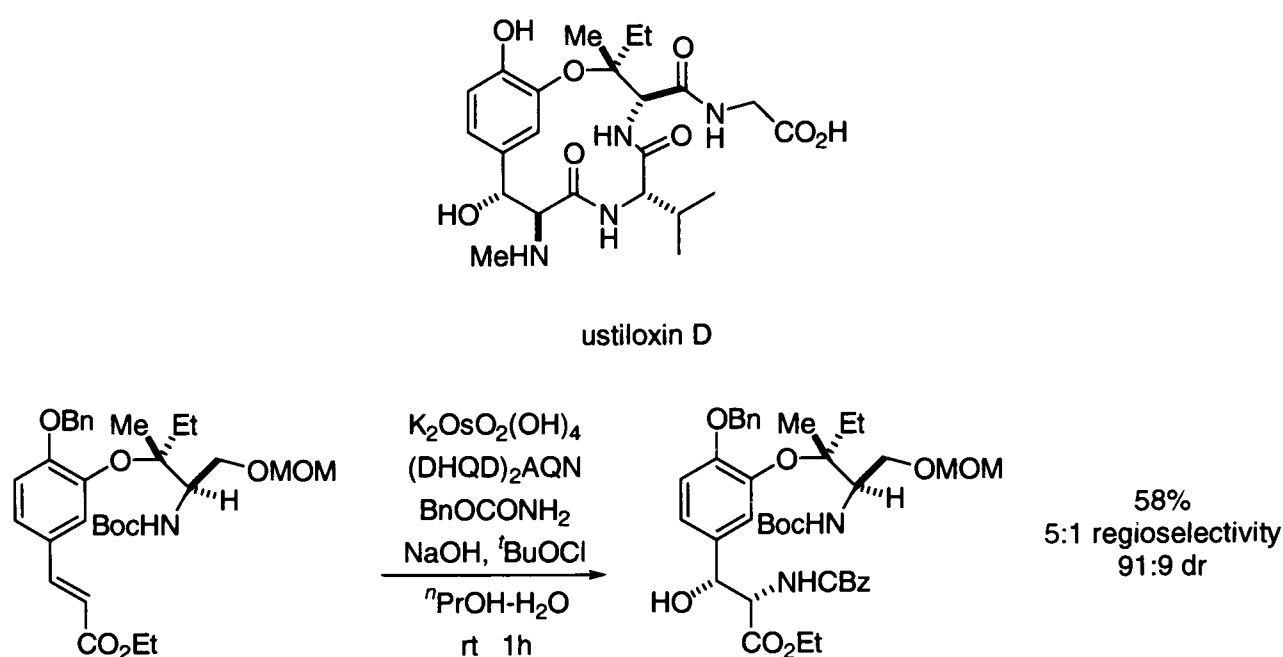
<i>Product A</i>	<i>Product B</i>	<i>Ligand</i>	<i>Cosolvent</i>	<i>Ratio A:B</i>
		PHAL	ⁿ PrOH	1.1:1
		PHAL	MeCN	1:6.1
		AQN	MeCN	1:13
		PHAL	ⁿ PrOH	1.4:1
		PHAL	MeCN	1:2
		AQN	MeCN	1:4
		PHAL	ⁿ PrOH	2.5:1
		PHAL	MeCN	1:2.4
		AQN	MeCN	1:9

Table 18 Reversal of regioselection in the AA of styrenes

The success of this approach for styrenes is such that simply adapting the conditions can produce either regioisomer:⁴³

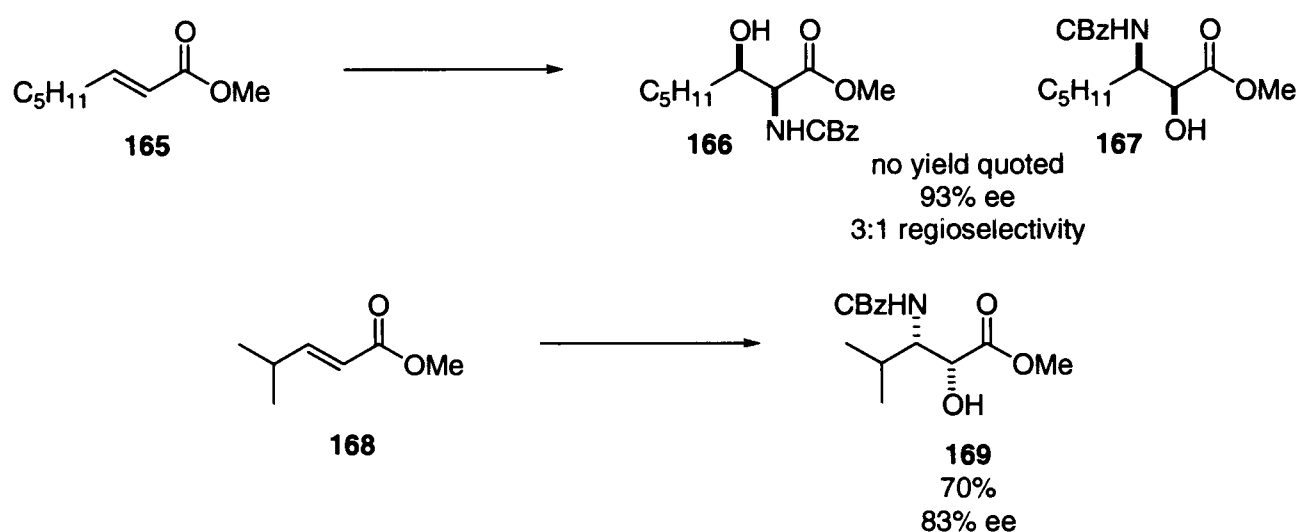
- *Benzylic amine* – use carbamate variant, PHAL ligands and ⁿPrOH-H₂O
- *Benzylic alcohol* – use acetamide, AQN ligands and MeCN-H₂O

The exact reasoning for this strange reversal of regioselectivity is uncertain. It seems likely, based on the explanations for selectivity in PHAL systems, that the AQN ligand simply has a different catalyst-ligand binding pocket shape. This could account for a difference in regiocontrol without significantly affecting enantioselectivity. This ligand-controlled approach has been used in a number of cases, most notably by Madeleine Joullé in the first total synthesis of ustiloxin D (scheme 39).⁷⁰



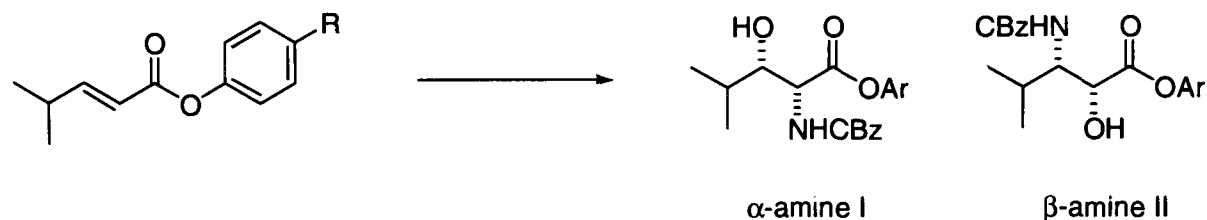
Scheme 39 Regioreversed AA as a key step in Jouille's synthesis of ustiloxin D

James Panek, in the course of his synthetic studies towards a total synthesis of (+)-lactacystin, required access to 3-hydroxyleucine in enantiopure form. Despite similar literature precedent in the oxidation of **165** (scheme 40),⁶⁹ oxidation of **168** using AQN ligands did not reverse the regioselectivity obtained using PHAL ligands.⁵⁵

Scheme 40 Failure of AQN to reverse regioselectivity *Reagents and conditions:* $K_2OsO_2(OH)_4$ (4 mol%), (DHQ)₂AQN or (DHQD)₂AQN, BnOCONH₂, NaOH, *t*BuOCl, *n*PrOH-H₂O, rt

Inspired by Janda's earlier work, Panek looked to aryl esters as a potential means of obtaining the correct regioisomer. Even the phenol ester gave a significant amount of regioreversed product (table 19). A Hammett study was conducted to determine if the electronic nature of the aryl group would have any influence.⁵⁵ The results suggested that more electron-donating substituents generally led to greater

enantioselectivity. In addition, halogenated aryl groups displayed a separate linear trend to other substituted aryl esters, suggesting a subtly different mode of binding (figure 9).



<i>R</i>	<i>Ratio I:II</i>	<i>Yield (%)</i>	<i>ee A (%)</i>
H	1:1	100	10
Me	4:1	66	16
OMe	5:1	66	30
CN	1.4:1	86	3
F	3:1	79	96
Cl	5:1	70	89
Br	7:1	69	87
Cl	1:2.5 (PHAL)	-	-

Table 19 Panek's aminohydroxylation of aryl esters *Reagents and conditions:* K₂OsO₂(OH)₄ (4 mol%), (DHQ)₂AQN, BnOCONH₂, NaOH, ^tBuOCl, ⁿPrOH-H₂O (1:1), rt

Investigation of the most electron withdrawing groups, particularly nitro-, was precluded because of the ease of saponification of the esters. Most of the aryl esters used proved susceptible to saponification to some degree. This was lessened by the use of OsO_4 in place of $\text{K}_2\text{OsO}_2(\text{OH})_4$. Basic hydrolysis was then not required to liberate the Os (VI) species and so the amount of base could be reduced.

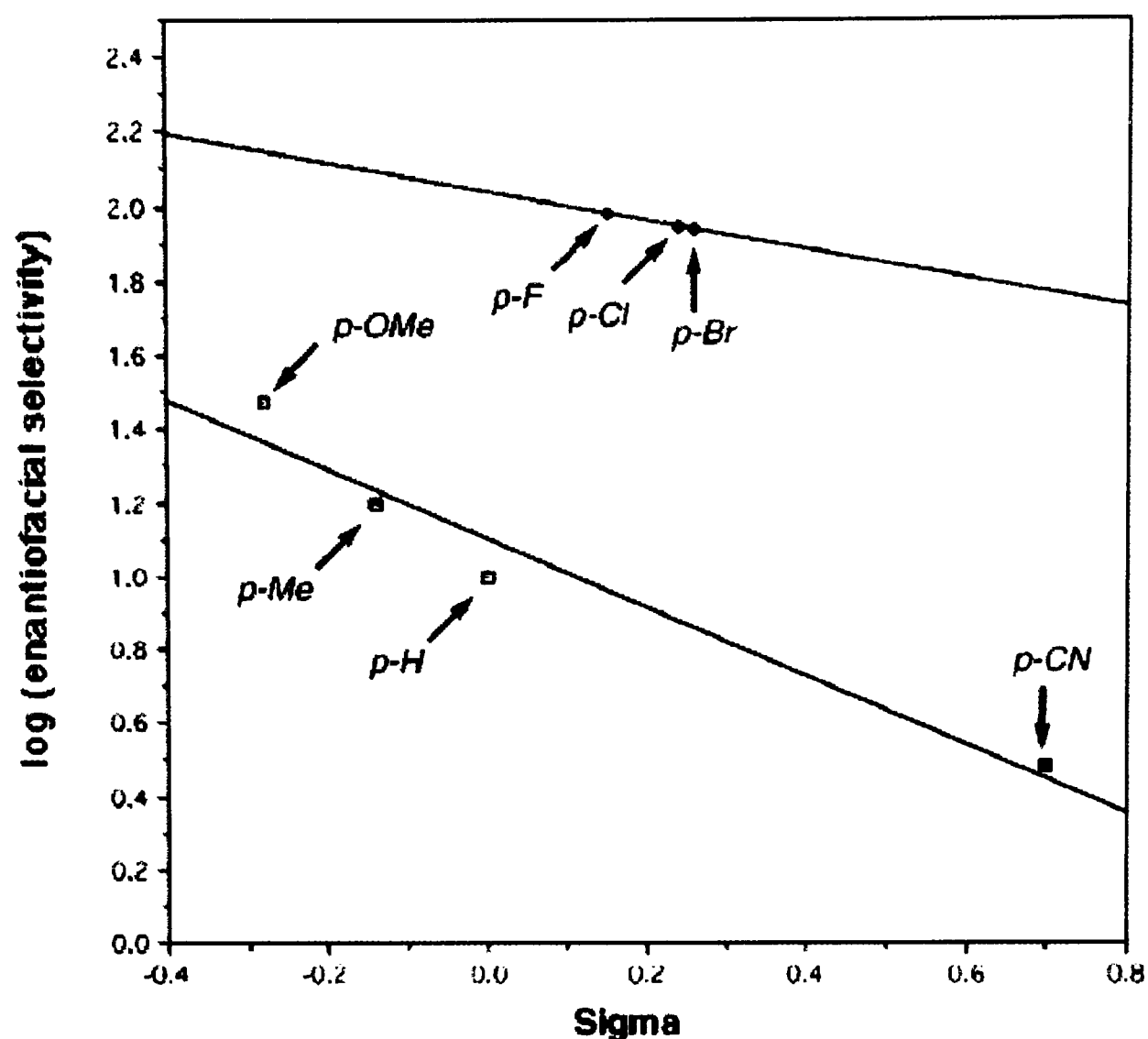
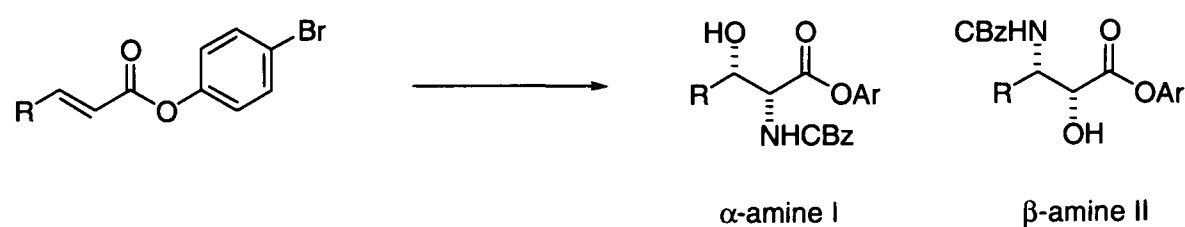


Figure 9 Hammett plot for aminohydroxylation of substituted aryl esters

The final result in table 19 shows that the AQN ligand was required to attain this level of regiocontrol. Attempts to extend this methodology to a broader range of substrates led to highly varied results (table 20). While substrate **170** showed extremely high regioselectivity under these conditions, the crotonate esters gave essentially no selectivity. This again demonstrates the sensitivity of this reaction to substitution around the double bond.



<i>R</i>	<i>Ratio I:II</i>	<i>Yield (%)</i>	<i>ee (%)</i>
H	4:1	65	69
Me	1:1	80	2
^{<i>i</i>} Pr	7:1	69	87
Cl(CH ₂) ₃ 170	>20:1	53	82

Table 20 Application of Panek's methodology to other substrates *Reagents and conditions:* K₂OsO₂(OH)₄ (4 mol%), (DHQ)₂AQN, BnOCONH₂, NaOH, ^{*t*}BuOCl, ^{*n*}PrOH-H₂O (1:1), rt

1.7.5 Effect of reaction pH on regioselectivity

One peculiar influence on regioselectivity is that of pH. Hergenrother and co-workers required access to a number of 1-aryl-2-aminoethanol derivatives and had identified the aminohydroxylation of styrenes as a viable route.⁷¹ While the amide variant had proved the most effective access to these regioisomers for Sharpless, carbamate protection was desired, and reaction conditions were varied to achieve that aim.

Regioreversed carbamate variant aminohydroxylation of styrenes using AQN ligands led to much reduced enantioselectivity. Hergenrother was surprised to find that by maintaining the pH between 7.5 and 8.5 not only was the inherent regioselectivity reversed to be in favour of the benzylic alcohol. In addition, the products were now obtained with moderate ee's.

Coupling this observation with the use of AQN ligands improved the situation still further, giving a 10:1 ratio of regioisomers and good ee's. Further studies incorporated reaction concentration. It was found that at higher concentrations, yields of aminoalcohol were reduced with a concomitant increase in diol formation, as had been previously observed by Wuts (*vide supra*, section 1.5.3).

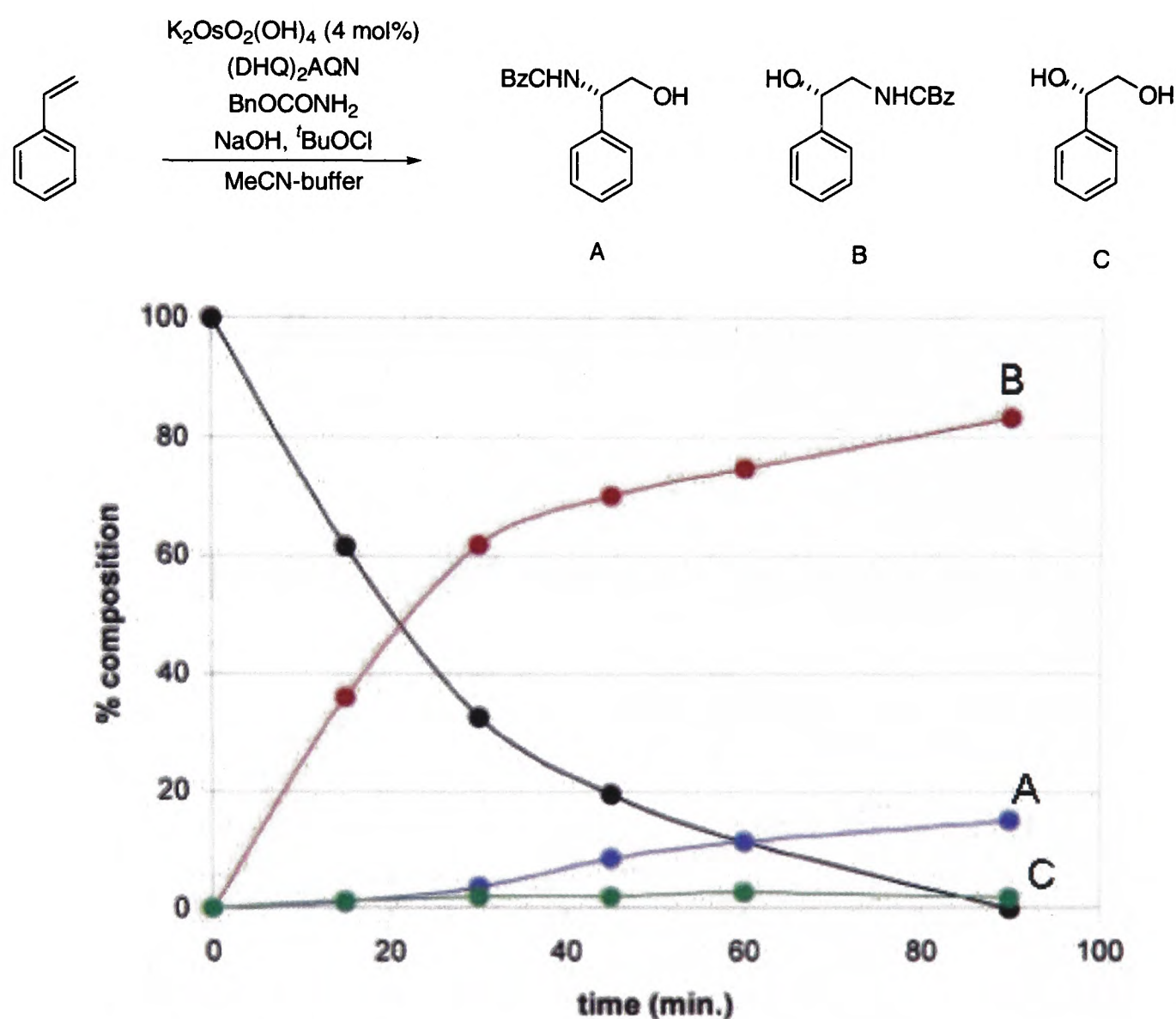


Figure 10 pH dependent AA of styrene and variation of composition of the reaction mixture with time

Hergenrother also noted another strange effect. The reaction profile (figure 10) shows that formation of the benzylic alcohol is much quicker than formation of the benzylic amine. However if the reaction is ‘doped’ at the outset with some of the benzylic amine product A, the regioselectivity of the reaction is much reduced, from 10:1 to 1.6:1. The benzylic alcohol B showed no such autocatalysis.

Temperature was the final variable explored. While the temperature of reaction had no large effect on the outcome of the reaction, by increasing the temperature to 40°C the rate was much improved, meaning the reactions ran to completion in the space of a few minutes. Clearly, despite having a broad grasp on the reaction, much more research is required to fully understand what is an intricate and highly sensitive catalytic cycle.

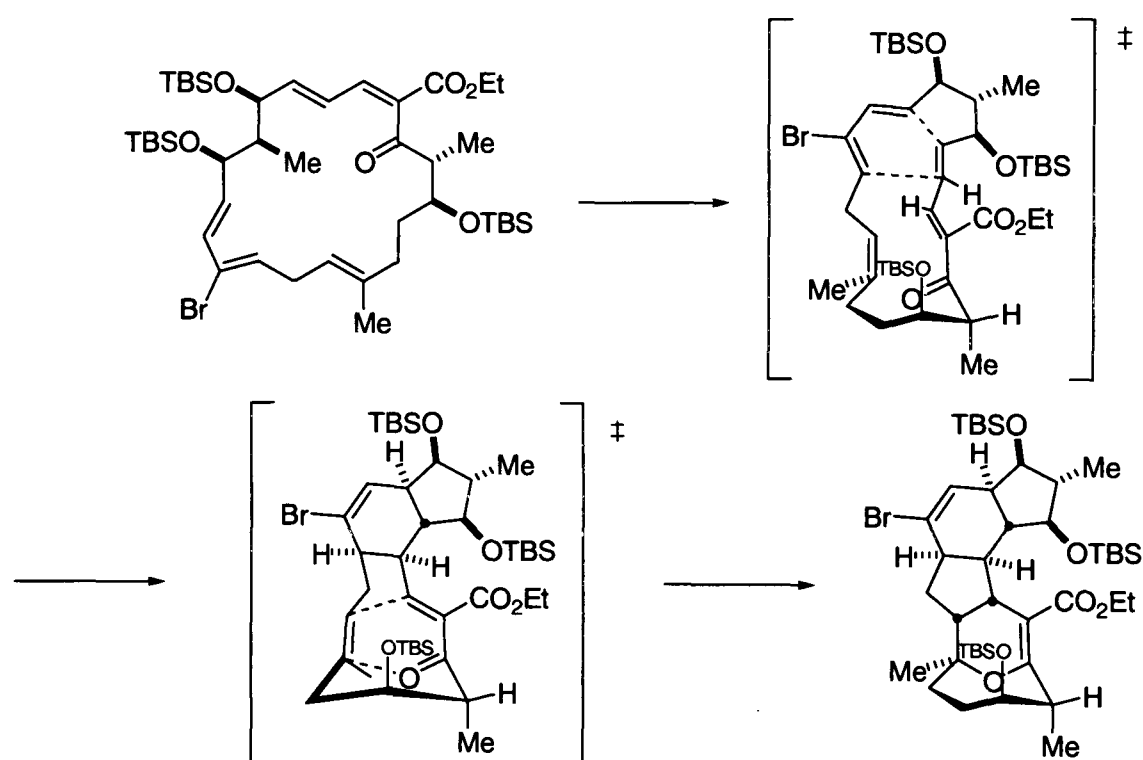
Results and Discussion I

The tethered aminohydroxylation (TA) reaction

2.1 Outline of the research

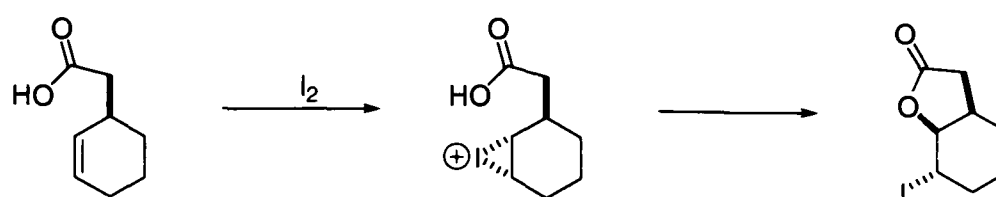
While advances have been made with respect to control of the regioselectivity of the AA, no single method as yet gives a reliable prediction for the regiochemical outcome. Therefore, it seemed useful to develop a method that would give complete confidence in the prediction of product distribution.

One highly successful means of controlling the regiochemical outcome of a reaction is *via* the use of an intramolecular tether. This tactic was first used by Stork, and is common within synthetic chemistry. For example, Evans' synthesis of (-)-FR182877 involves an intramolecular Diels-Alder reaction cascade (scheme 41).⁷²



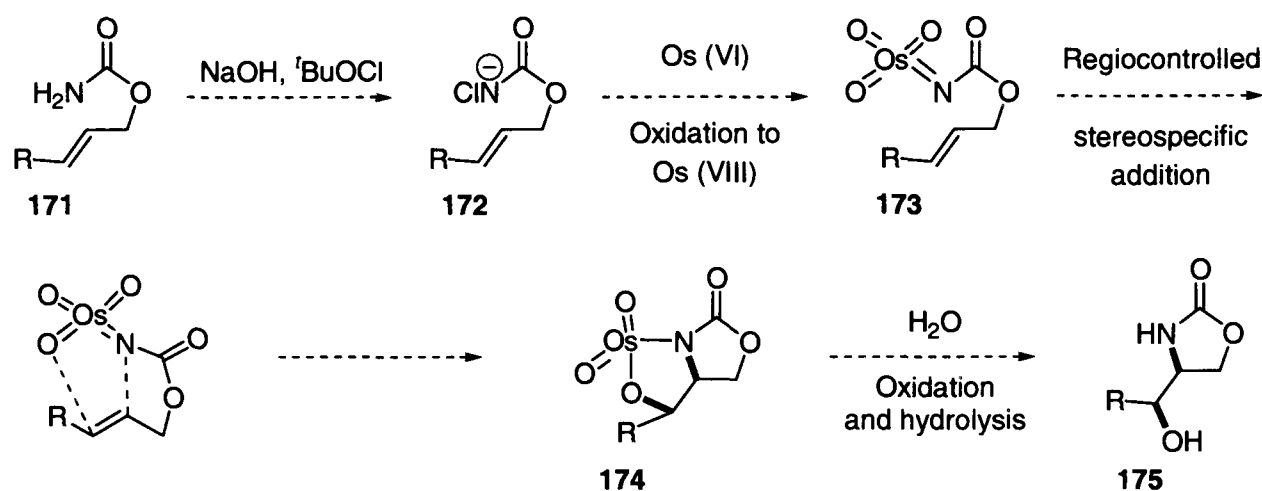
Scheme 41 Tethered Diels-Alder reaction in Evans' synthesis of (-)-FR182877

Perhaps more commonly, iodolactonisation gives control over the regiochemistry of opening an iodonium ion (scheme 42).⁷³



Scheme 42 Halolactonisation is a tethered regiospecific process

Based on these foundations, a proposal was made for a tethered approach to the aminohydroxylation reaction. If the nitrogen source were tethered in some way to the olefin (e.g. as in allylic carbamate **171**, scheme 43), oxidation of Os (VI) by this nitrogen source would give a transition metal complex **173**. This contains a double bond that could then be oxidised by the Os (VIII) species. The resulting osmate ester **174** would then be hydrolysed to give a product **175**.



Scheme 43 Proposed intermediates in a tethered aminohydroxylation

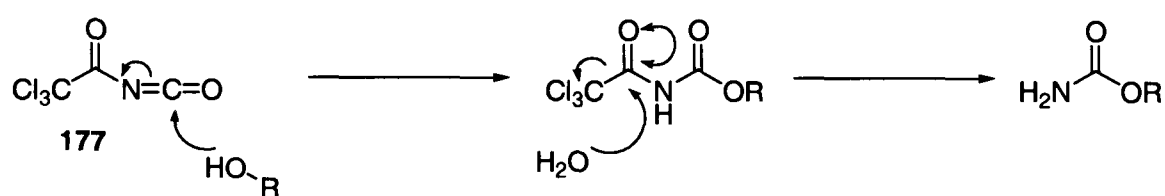
By virtue of the tether, the oxidation should occur with complete regioselectivity, to give solely the five-membered oxazolidinone **175** as the geometry of the 5,5 fused system formed is less strained than the corresponding bridged system formed if the regioreversed addition occurs. In addition, it could be reasonably expected that the oxidation will occur in a stereospecific manner, adding the heteroatoms in a *syn* fashion across the double bond as empirically all analogous Os (VIII) oxidants behave this way. This would mean the formation of both a single regio- and diastereomer of the product.

2.2 – Development of the Tethered Aminohydroxylation (TA) of primary carbamates⁷⁴

2.2.1 *trans*-Cinnamyl carbamate 176

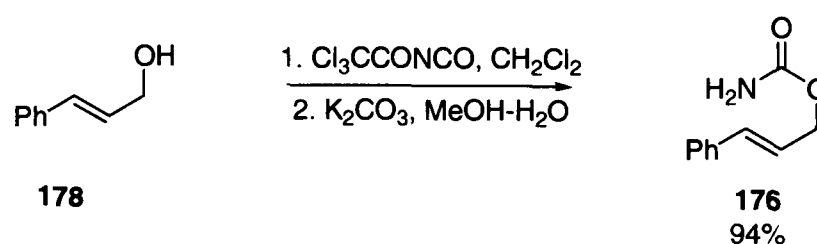
In order to test the hypothesis, cinnamyl carbamate **176** was chosen as a first substrate. The hope was that its similarity to the bulk of Sharpless' successful examples would assist, while equally it was easily available from commercial materials.

The formation of a primary carbamate from an alcohol typically involves addition to an isocyanate, followed by basic cleavage. The literature includes a number of methods for this, including the use of isocyanic acid and chlorosulfanyl isocyanate. Our reagent of choice was trichloroacetyl isocyanate **177** (scheme 44). Kočovský had introduced this in 1982 as an alternative to earlier procedures that required harsher cleavage of the R group from nitrogen.⁷⁵



Scheme 44 Formation of a carbamate from an alcohol using trichloroacetyl isocyanate

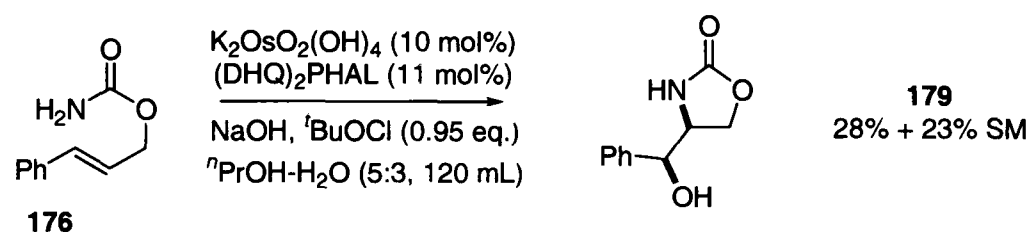
Thus, treatment of cinnamyl alcohol **178** with trichloroacetyl isocyanate in dichloromethane at 0°C gave a smooth reaction, resulting in complete conversion to the trichloroacetyl carbamate. The mixture was simply concentrated, the residue redissolved in methanol and basified with potassium carbonate, again at 0°C. Within a few hours, all of the intermediate had been cleaved, and isolation gave cinnamyl carbamate **176** that was essentially pure by ¹H NMR spectroscopy (scheme 45, 94%).



Scheme 45 Synthesis of *trans*-cinnamyl carbamate

This procedure gave, in almost all cases, clean and efficient conversion of alcohol to carbamate, and so in most cases further purification was not required. Most of the carbamates synthesised were crystalline, and so where material of the highest purity was necessary, recrystallisation using petrol-chloroform mixtures furnished crystals of good quality.

With the substrate in hand, the aminohydroxylation could now be investigated. The reaction conditions were based on the firm foundation of Sharpless' carbamate variant AA,³⁴ with necessary adjustments. Due to the restriction of only one equivalent of nitrogen source present, by virtue of the tether, it was necessary to adjust the amounts of NaOH and *t*BuOCl accordingly. The original attempts at the reaction used 10 mol% of potassium osmate and 11 mol% of a chiral ligand, (DHQ)₂PHAL. In addition, the reaction was performed in dilute solution to minimise the chance of intermolecular aminohydroxylation. As a convenient amount of material, 100-200 mg (0.6-1.1 mmol) of starting material was used in each reaction.



Scheme 46 Aminohydroxylation using cinnamyl carbamate 176

The substrate **176** was first dissolved in *n*PrOH, often used as a co-solvent for the carbamate AA. This was treated with an aqueous solution of NaOH, then with neat *t*BuOCl. At this stage the solution was a pale yellow colour. The ligand was added as a solution in *n*PrOH, followed by an aqueous solution of potassium osmate. Instantly a colour change was observed with the pale yellow solution turning a deep shade of green, then very quickly returning to yellow. Over a period of 90 minutes this solution darkened to a green colour, finally becoming black and opaque. TLC analysis of the reaction mixture, in neat ethyl acetate, showed the presence of some starting material, staining blue, accompanied by a spot of increased polarity (*R*_f 0.45) that stained yellow in anisaldehyde. Work up involved addition of an aqueous solution of sodium sulfite, routinely added to reactions involving osmium to ensure the metal is reduced to a low oxidation state. Separation of the organic and aqueous layers proved difficult. The

black colour observed towards the end of the reaction, presumably some insoluble form of Os (IV),¹⁸ permeated both layers and made judgement of phase boundaries difficult. This situation was improved by dilution of the mixture with ethyl acetate, then washing with brine. On addition of the brine the layers clearly partitioned, although some of the black residue was inevitably present in the organic layer. The aqueous layer was extracted several times with ethyl acetate, and the collected organics concentrated to give a black residue. This was suspended in acetone and concentrated onto silica. Column chromatography using petrol-ethyl acetate mixtures yielded starting material **176** (23%) and a white crystalline product **179** (28%).

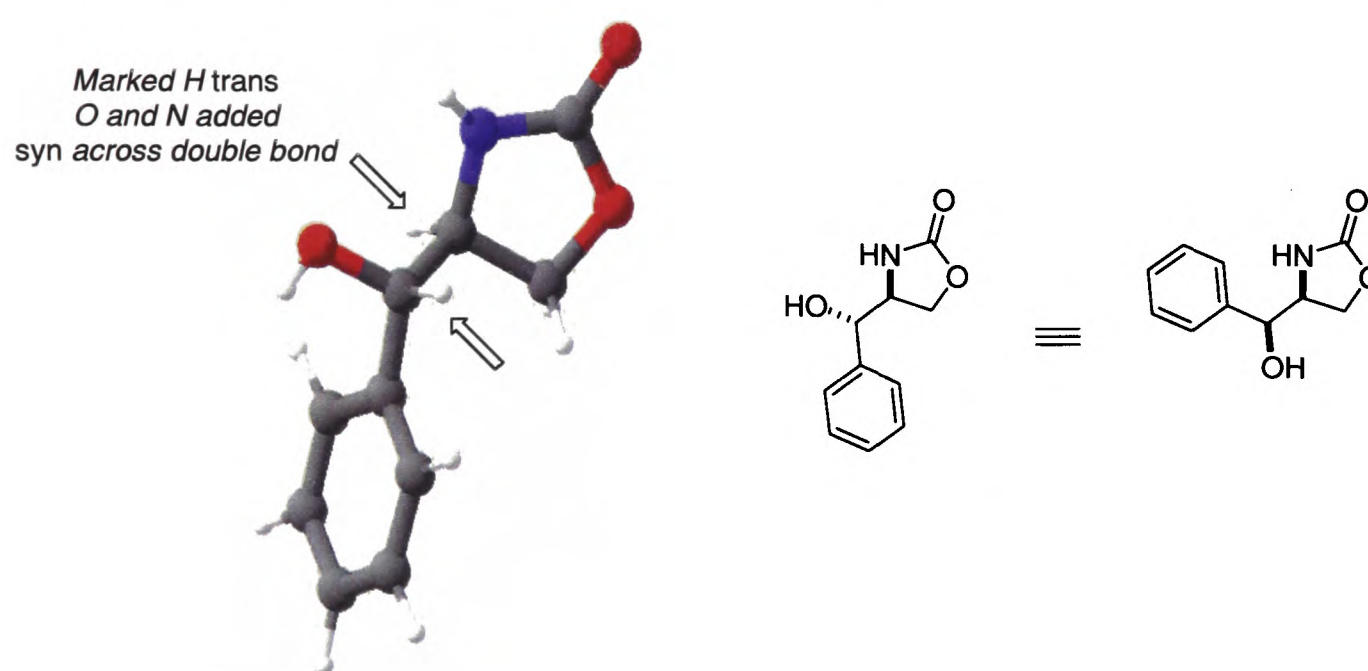


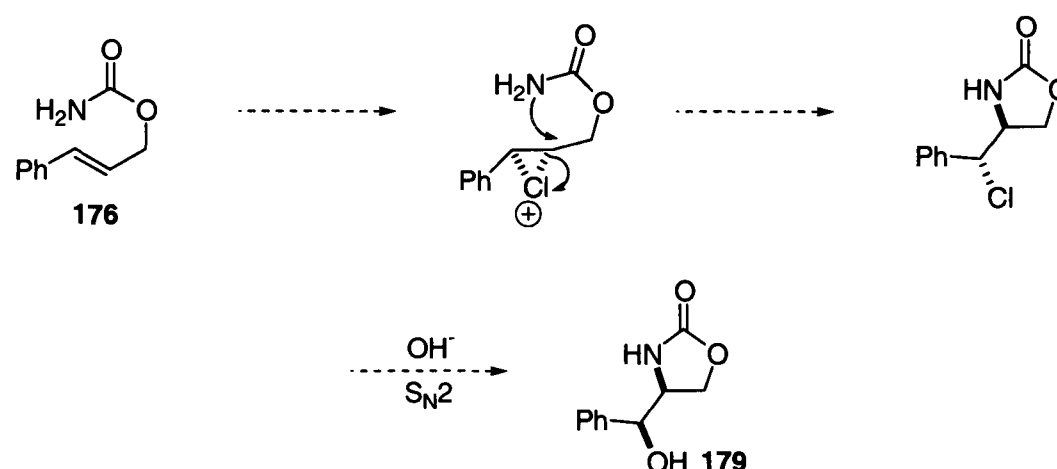
Figure 11 Crystal structure of **179** shows *syn* addition across the double bond

The ^1H NMR spectrum of the new product clearly showed that oxidation of the double bond had occurred. The olefinic signals were no longer present, and had been replaced by an additional two signals between 4 and 4.6 ppm. The broad signal corresponding to the carbamate NH_2 protons had shifted further downfield, and now integrated only to one proton, highly suggestive that the oxazolidinone **179** had formed as expected. Mass spectral and IR data was consistent with the proposed structure, but the relative stereochemistry was not unambiguously determined until a crystal structure was obtained (figure 11).

2.2.2 Control experiments

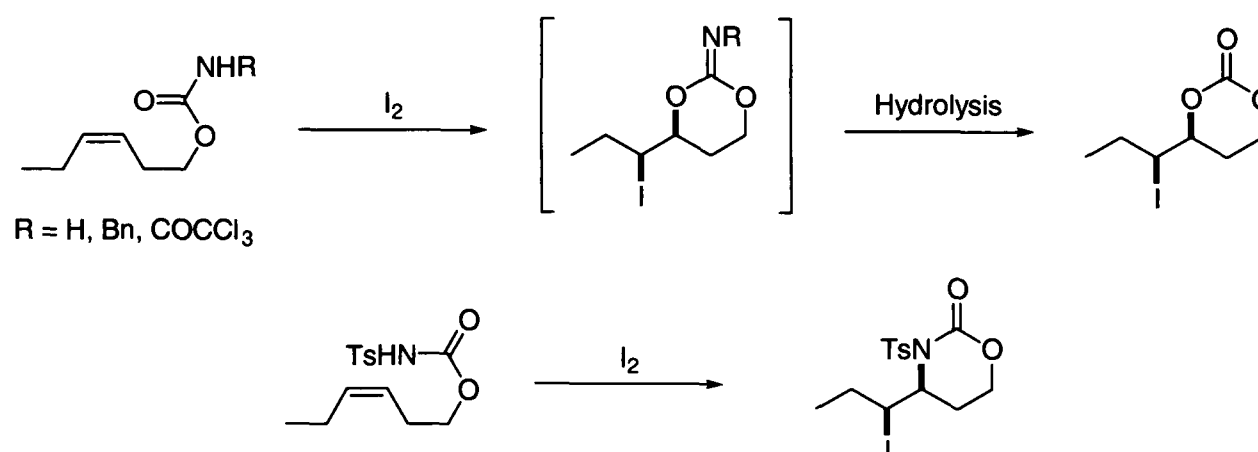
This result was obviously very encouraging. The oxidation had occurred, albeit in low yield, and the only major impurity isolated after chromatography had been recovered starting material. This was in stark contrast to the intermolecular version of the reaction, where isolation of the desired isomer would involve separation from both the other regiomer product *and* excess carbamate.³²

A concern at this early stage was that the reaction did not require the osmium catalyst to occur. Another plausible mechanism is outlined in scheme 47, involving chlorination of the double bond by *t*-BuOCl. Subsequent ring opening by nitrogen, and hydroxide displacement of the chlorine would give the same product.



Scheme 47 Possible chloronium ion involvement in the reaction

This seemed unlikely: ring-forming reactions of this type typically cyclise primarily through oxygen unless the availability of the nitrogen lone-pair is significantly reduced (scheme 48).⁷⁶

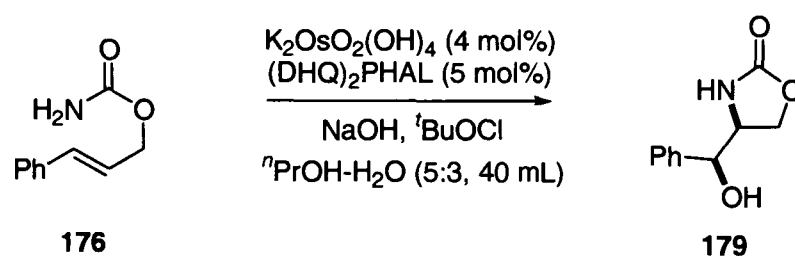


Scheme 48 Competing modes of cyclisation

Treatment of **176** with NaOH and *t*BuOCl did not afford any of the cyclised product **179**. Repetition of the experiment, but including (DHQ)₂PHAL, gave the same result. The starting material was recovered in both cases, but not quantitatively (typically ~90%). TLC analysis of the reaction mixtures had identified a spot of slightly lower polarity. Unfortunately attempts to isolate this material proved fruitless. Nevertheless, these control experiments had shown that the osmium catalyst was crucial for formation of the oxazolidinone.

2.2.3 Improvements to the reaction protocol

Concerned by the high dilution of the original experiment, the reaction was repeated, but concentrated threefold. The amount of potassium osmate and the ligand were also reduced, more closely imitating Sharpless AA conditions. Gratifyingly turnover was improved, giving 40% of product with a concomitant fall in the amount of recovered starting material (table 21). The reaction otherwise proceeded exactly as before.

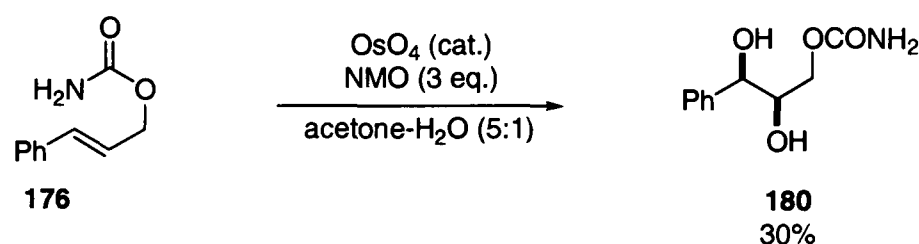


<i>NaOH</i> (eq.)	<i>t</i> BuOCl (eq.)	Time (h)	Yield (%)	SM (%)
0.95	0.95	16	40	11
0.95	1.5	16	22	-
1.5	1.5	16	-	-
0.95	0.5 ^a	16	25 ^b	16

Table 21 Early adjustments to the reaction protocol (a) 1,3-dichloro-5,5-dimethylhydantoin used as Cl source; (b) In addition to product, 15% of dihydroxylated carbamate was isolated

A number of minor adjustments to the reaction were made from this point, attempting to identify areas of improvement. Increased amounts of base or chlorinating agent led to more complicated mixtures of products, presumably arising from chlorination and/or isomerisation. Substitution of *tert*-butyl hypochlorite for the commercially available solid 1,3-dichloro-5,5-dimethylhydantoin³³ **77** gave a lower

yield of product, but interestingly also gave an appreciable amount of diol from dihydroxylation. The identity of the diol was confirmed by comparison with an authentic sample obtained by Upjohn dihydroxylation of **176** (scheme 49).



Scheme 49 Upjohn dihydroxylation of *trans*-cinnamyl carbamate

The single biggest improvement in yield came when the work-up procedure was examined in more detail. Previously the organic layers had been dried with magnesium sulfate, but on inspection the sulfate residue was grey in colour. Re-extraction of this afforded a small but significant amount of product. To avoid this problem, the work-up was omitted completely. Unfortunately, the product obtained post-column was grey, suggesting that it was still contaminated by osmium residues. Sharpless has mentioned this as an occasional problem in both asymmetric dihydroxylation and aminohydroxylation reactions.¹⁸ A compromise was made, simply omitting the drying agent, and adding solid sodium sulfite rather than a saturated aqueous solution. This slight modification improved the yield to 62%, accompanied by 12% recovered starting material.

Attempts were made to completely consume the starting material. Increasing the reaction time to 96 hours did not alter the yield significantly, suggesting that the catalyst was already inactive at 16 hours. In actuality, the reaction appears to be almost at completion when it turns black, verifying that the dark colour is due to low oxidation state osmium compounds precipitating out of solution. Further confirmation of this was attained by addition of further base and chlorinating agent either before or after the reaction had turned black, with a complicated mixture of products again formed.

2.2.4 Enantioselectivity in the TA

With the tethered aminohydroxylation (TA) now functioning well, the optical rotation of the product was measured. Disappointingly, several samples all gave specific rotations of zero. GC on a chiral column confirmed that these samples were indeed racemic (appendix I). The racemic standard for the assay was obtained by performing the reaction in the absence of a Sharpless cinchona alkaloid ligand. While the reaction was considerably slower, and the yield lower, the reaction clearly functioned without a ligand for osmium. In an attempt to get some sense of asymmetric induction, other chiral ligands were employed. Neither of the other commercially available Sharpless ligands gave any enantioselectivity. Furthermore, these ligands did not exhibit the level of efficiency that (DHQ)₂PHAL had achieved, as manifested in lower yields (table 22).

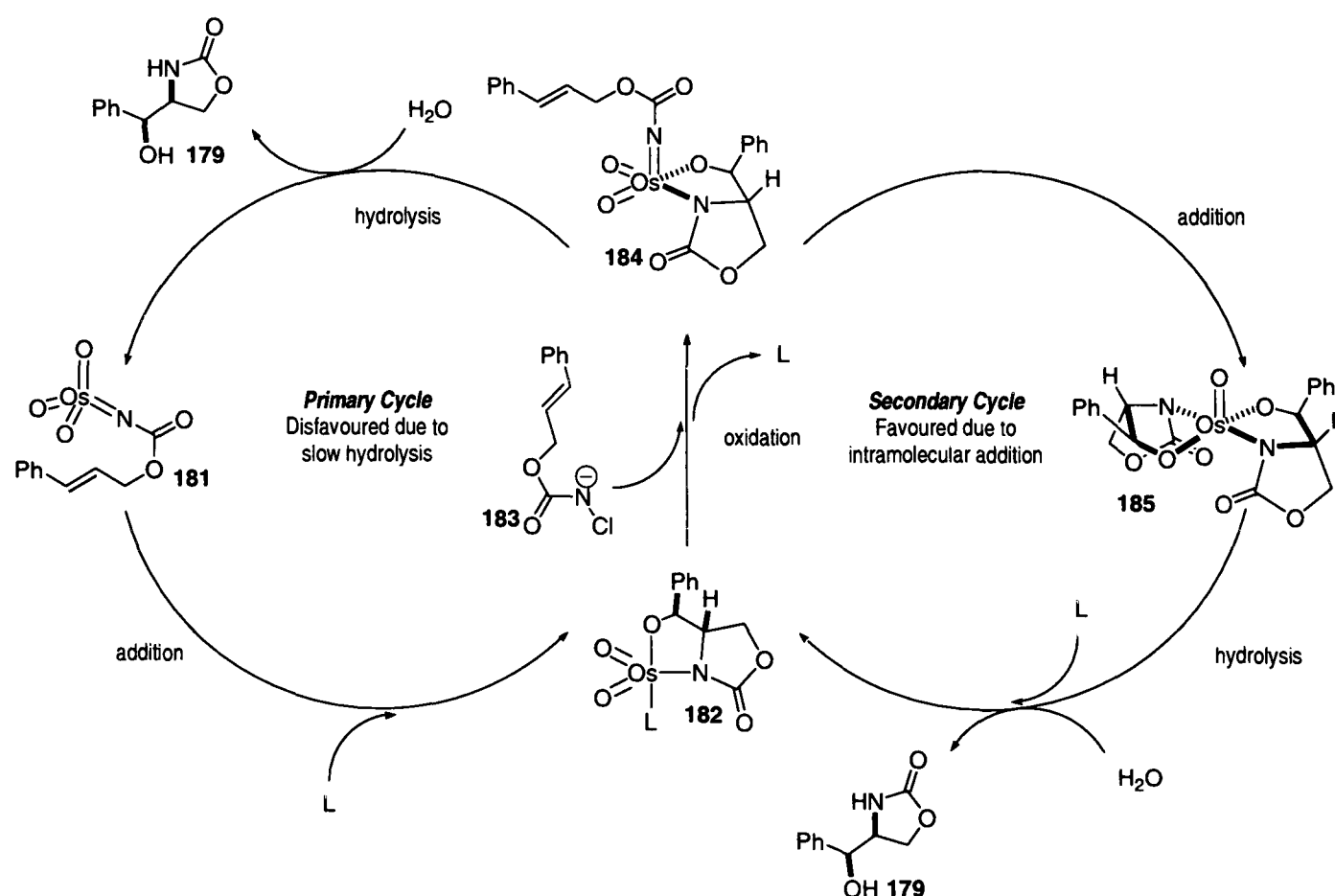
<i>Ligand</i>	<i>Mol %</i>	<i>Time (h)</i>	<i>Yield (%)</i>	<i>SM (%)</i>
(DHQ) ₂ PHAL	5	16	62	12
	15	16	54	14
(DHQ) ₂ PYR	5	96	29	40
(DHQ) ₂ AQN	5	16	30	48
None	-	144	42	23
Quinuclidine	10	96	18	51
EtN ^{<i>i</i>} Pr ₂	5	16	59	23
	50	16	51	30

Table 22 Ligand screen for the aminohydroxylation of cinnamyl carbamate *Reagents and conditions:* K₂OsO₂(OH)₄ (4 mol%), NaOH (0.95 eq.), ^{*t*}BuOCl (0.95 eq.), ligand, ^{*n*}PrOH-H₂O (5:3), rt. All reactions carried out on 200mg substrate.

As the expensive chiral ligands were not providing enantiomerically enriched material, cheaper achiral substitutes were sought. Quinuclidine is a ligand often added to dihydroxylation reactions so this was examined. The yield immediately fell. Increasing the amount of quinuclidine present to one equivalent virtually shut down the reaction. This seemed strange, given that one group has used it as a ligand in the carbamate variant AA without this effect.⁶³ Their report also described the use of

Hünig's base, and in our hands this gave a much more satisfactory result (table 22). The amount of Hünig's base was increased to 0.5 equivalents, and gave a similar result although the product was contaminated to a small degree by the excess amine.

The lack of enantioselectivity can be attributed in this instance to the intrusion of the second catalytic cycle. Entry into the non-selective cycle is achieved by a second oxidative addition to an olefin occurring before hydrolysis of the product has occurred (scheme 50). In the case of this tethered aminohydroxylation, the second addition is an intramolecular event (compound **184**). As such it can be expected to be rapid, and certainly faster than the hydrolysis step, which Sharpless has quoted as being rate-limiting.³²

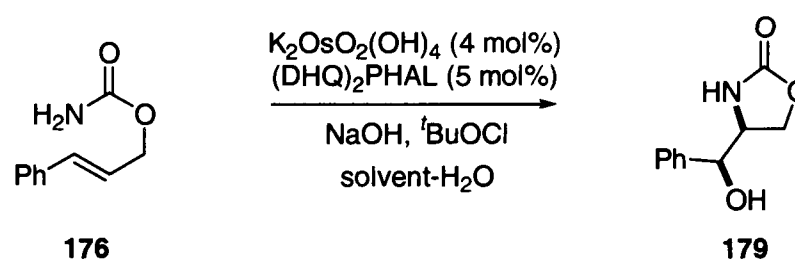


Scheme 50 Catalytic cycle for the tethered aminohydroxylation

That rate-acceleration is observed when the cinchona ligands are used, while no enantioselectivity ensues, is a strange but not unprecedented observation. The same effect occurs when adenine derivatives are used in the AA, with no explanation given.⁴¹

2.2.5 Choice of solvent

The AA reaction and early racemic variants have been reported in a number of different solvents.⁴³ With process optimisation in mind, the TA of cinnamyl carbamate was performed in a number of water-cosolvent mixes to see if better results were observed (table 23).



<i>Cosolvent</i>	<i>Ratio</i>	<i>Volume (mL)</i>	<i>Yield (%)</i>	<i>SM (%)</i>
<i>n</i> PrOH	5:3	40	59	23
	8:3	11	50	27
	20:1	27.5	0	-
<i>t</i> BuOH	5:3	40	45	38
MeCN	5:3	40	44	15
None	-	40	0	69
CH ₂ Cl ₂	5:3	40	0	87
Pyridine	5:3	40	0	90

Table 23 Variation of cosolvent in the TA of cinnamyl carbamate. Reactions were carried out on 200mg of substrate

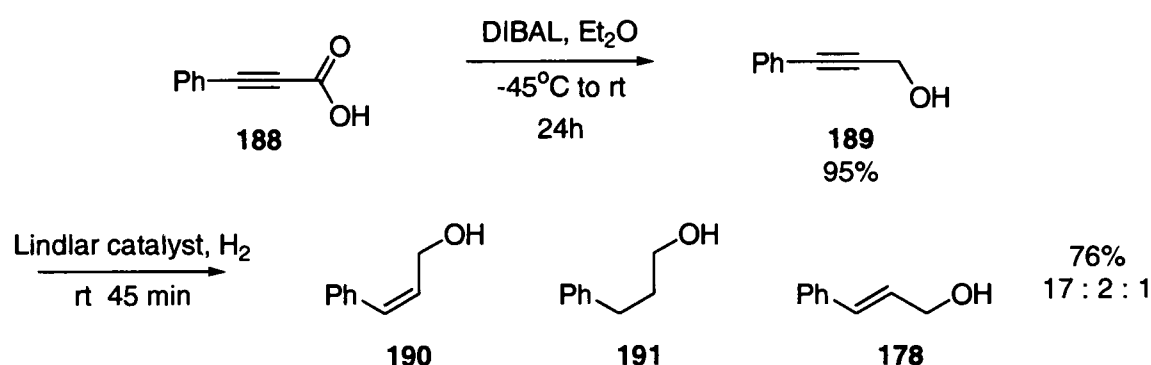
Disappointingly, none improved on the propanol-water mix already in use. It appeared that concentrating the solution did not have a large adverse effect on the yield, while *tert*-butanol proved an adequate substitute for propanol. Reducing the amount of water present in the system reduced turnover to essentially zero, presumably because hydrolysis was not occurring. In that instance, the solution remained a yellow colour, indicating that the osmium was still in solution, bound to the product. Excluding the cosolvent altogether again completely shut down the catalytic cycle, though this is probably due to the insolubility of the carbamate in water. The same is true of the biphasic systems involving dichloromethane and pyridine.

2.3 – TA of other terminal carbamates

2.3.1 *cis*-Cinnamyl carbamate 187

The stereochemistry of addition across the double bond in *trans*-cinnamyl carbamate 176 had been shown to be *syn*, as is the case with all osmium oxide oxidations. In order to prove the stereospecificity of the reaction, the geometric isomer of the test substrate was synthesised and subjected to the same conditions.

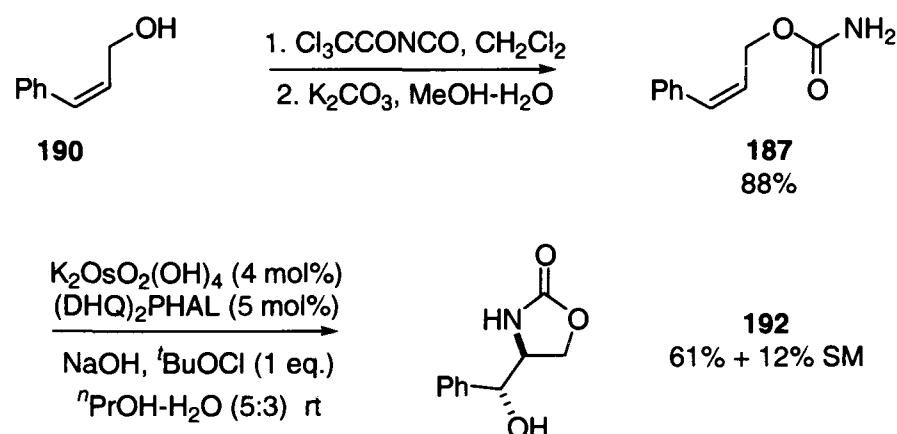
The *cis* double bond was to come from hydrogenation of the corresponding alkyne (scheme 51). The propargylic alcohol 189 was produced by DIBAL reduction of phenylpropionic acid 188, according to literature procedure.⁷⁷ This method gave a good yield of the product (71-95%), but was always contaminated with a small amount of *trans*-cinnamyl alcohol 178. Careful chromatography (30% EtOAc – petrol) was required to separate them.



Scheme 51 Synthesis of *cis*-cinnamyl alcohol 190

Hydrogenation of the alkyne was initially attempted using nickel boride,⁷⁸ as it was feared that Lindlar hydrogenation would give some over-reduced material. Unfortunately, the nickel boride procedure gave a low yield, and ironically was contaminated with saturated material (5:1). Lindlar hydrogenation proved more successful, and the easier protocol meant that this became the method of choice. The product obtained after filtration through celite also contained some saturated alcohol, but in a much reduced amount compared to the nickel boride procedure (product:saturated:*trans* 17:2:1). Attempts were made at purification at this stage but it proved easier to transform the mixture of alcohols to their corresponding carbamates, then recrystallise the mixture from chloroform-petrol to obtain 187 as needles (>98:2

cis:saturated). The *J* values for coupling between the alkene protons was 12 Hz, much reduced from the 16 Hz coupling seen in *trans*-cinnamyl carbamate **176**.



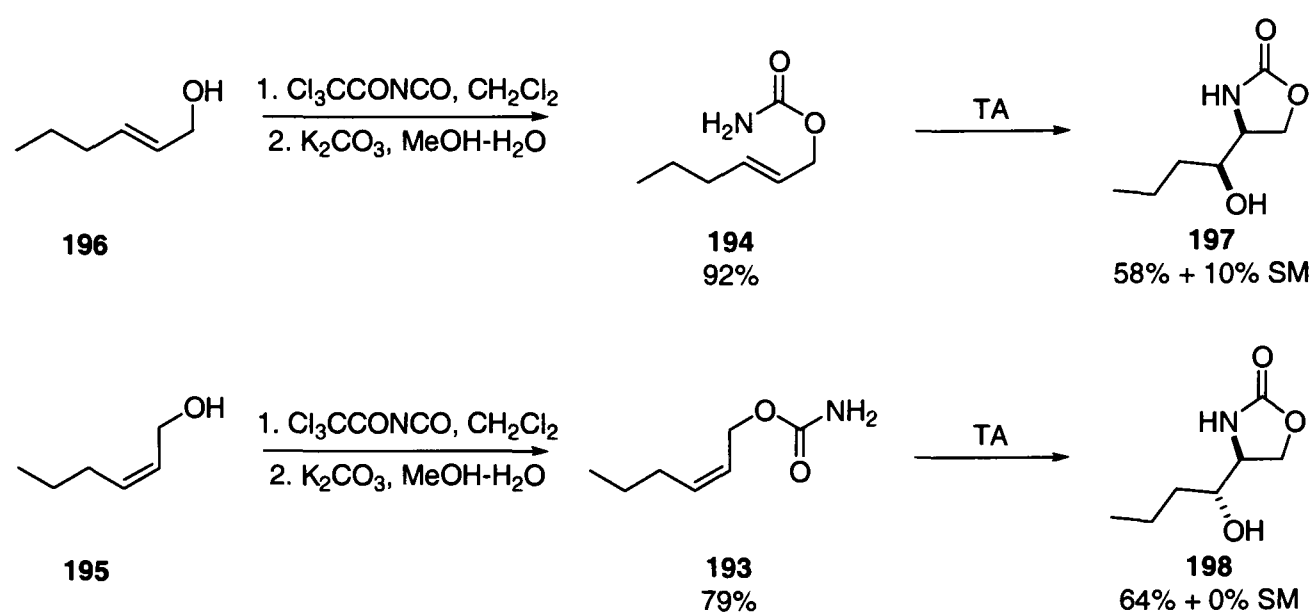
Scheme 52 Synthesis and TA of *cis*-cinnamyl carbamate **187**

TA of **187** was carried out exactly as for *trans*-cinnamyl carbamate, affording the product oxazolidinone **192** again as a white crystalline solid (scheme 52). This diastereomer of the product had previously been synthesised by Knapp, but unfortunately not fully characterised.⁷⁹ The ¹H NMR spectra correlated exactly, and in addition the melting points were the same (139-141°C; lit. 140-142°C).

That only a single diastereomer of the oxazolidinone resulted from each TA shows that the aminohydroxylation is stereospecific – one isomer of the substrate gives one diastereomer; the other isomer of substrate gives the other diastereomer. Importantly, this result also shows the validity of the TA for *cis*-substituted olefins. The AA did not tolerate these substrates well, particularly acyclic *cis* olefins. Thus this methodology gives complete regiocontrol in the oxidation event and has expanded the substrate scope of the aminohydroxylation reaction.

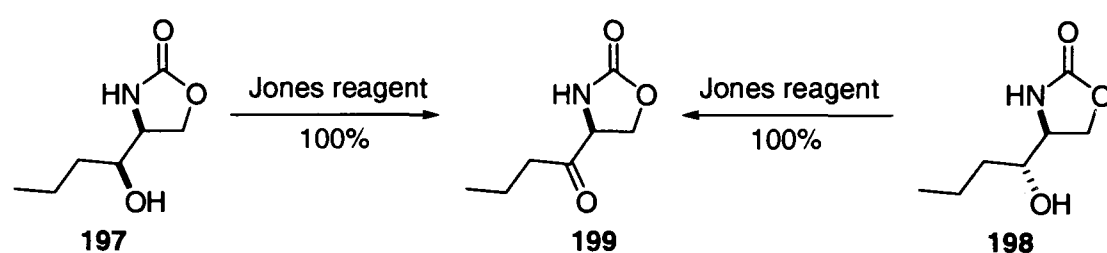
2.3.2 *Cis*- and *trans*-2-hexenyl carbamates **193** and **194**

To further illustrate the scope of the reaction, another pair of geometric isomers were synthesised and subjected to the TA. Both *cis*- **195** and *trans*-2-hexenol **196** are commercially available. The carbamates were synthesised as described previously (section 2.2), and the TA itself gave results similar to that for the cinnamyl carbamates (scheme 53).



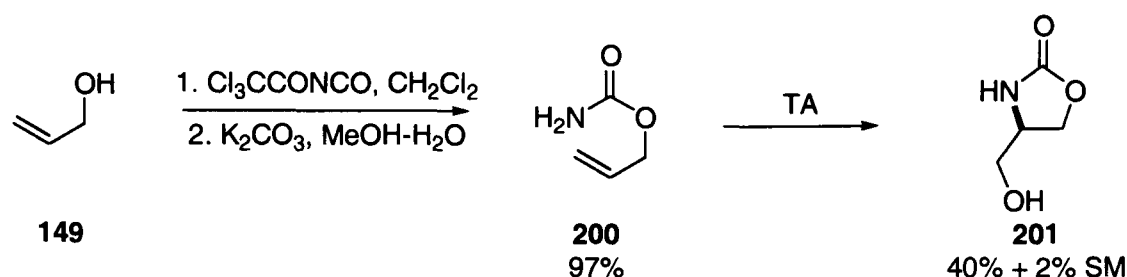
Scheme 53 Synthesis and TA of hexenyl carbamates *TA reagents and conditions:* $\text{K}_2\text{OsO}_2(\text{OH})_4$ (4 mol%), EtN^iPr_2 (5 mol%), NaOH (1 eq.), $^t\text{BuOCl}$ (1 eq.), $^n\text{PrOH-H}_2\text{O}$ (5:3), rt

Again, the products obtained after the TA reaction were diastereomeric, due to the stereospecific addition across the double bond. The isolated yields are identical, within error, for each isomer, although no starting material could be isolated from the TA of **193**. Thus aliphatic *cis* double bonds are also viable substrates for the reaction. The identity of oxazolidinone **198** was confirmed by correlation to literature ^1H and ^{13}C NMR data.⁸⁰ While diastereomeric **197** was not a known compound, confirmation of its structure was obtained by Jones oxidation of both **197** and **198** to the same ketone **199** (scheme 54).



Scheme 54 Jones oxidation of diastereomeric hydroxyoxazolidinones

2.3.3 Allyl carbamate 200

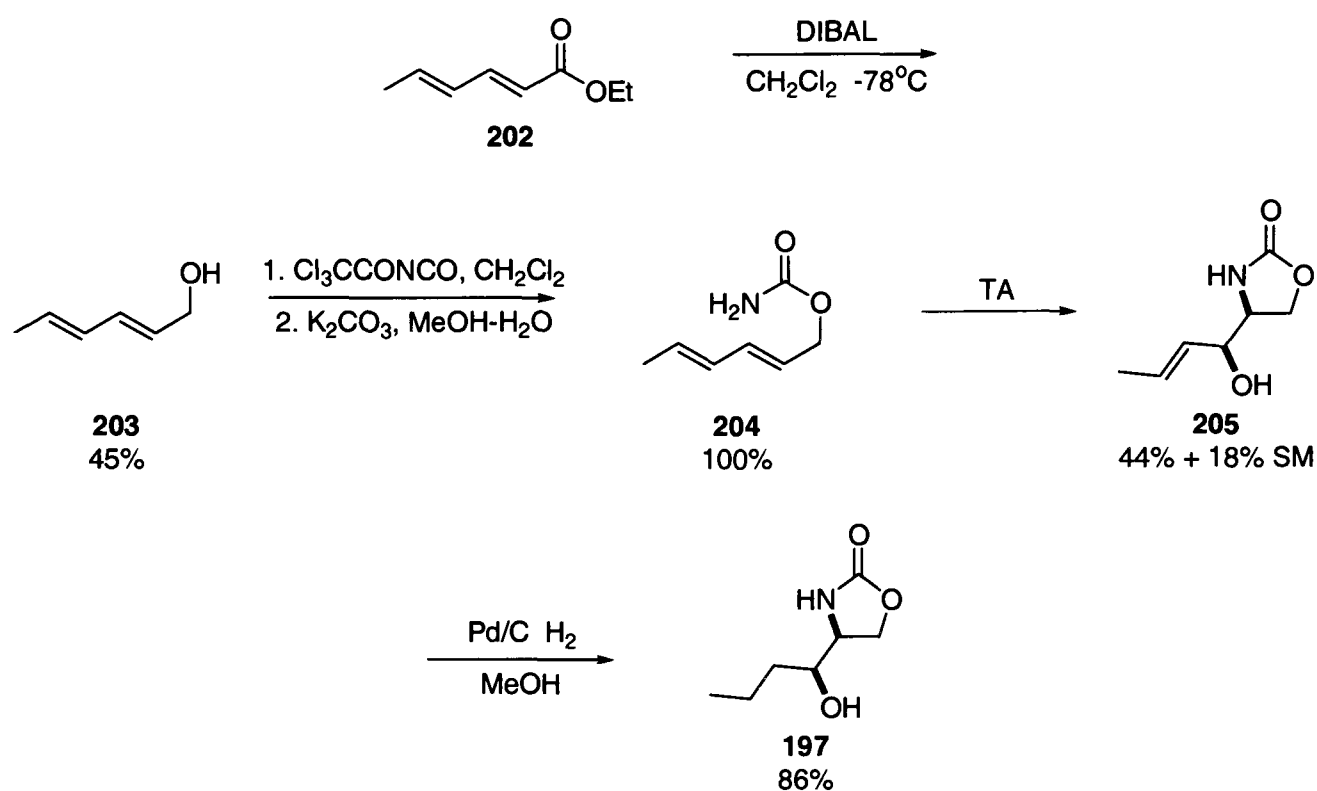


Scheme 55 Synthesis and TA of allyl carbamate *TA reagents and conditions*: $\text{K}_2\text{OsO}_2(\text{OH})_4$ (4 mol%), EtN^iPr_2 (5 mol%), NaOH (1 eq.), $t\text{BuOCl}$ (1 eq.), $n\text{PrOH-H}_2\text{O}$ (5:3), rt

The parent terminal carbamate, allyl carbamate **200**, was also subjected to the TA (scheme 55). It was synthesised from the parent alcohol as described before, using trichloroacetyl isocyanate. The TA, however, was disappointing. It proved difficult to visualise the polar product on the TLC plates, but even so the isolated yield of 40% seemed low. Attempts to re-extract what product there may have been in the aqueous layer led to only small amounts of material. Product NMR data matched that of literature precedent.⁸¹ This reaction is notable for its reversal of the inherent selectivity bias of the substrate. Allyl alcohol gives solely the protected terminal amine in the AA (*vide supra*, scheme 34).⁶²

2.3.4 Sorbyl carbamate 204

The final example of terminal carbamates in the TA was sorbyl carbamate. It was chosen to illustrate the chemoselectivity of the oxidation. Due to the tether, addition should occur solely across the allylic double bond and not its conjugated partner. It was synthesised by DIBAL reduction of ethyl sorbate **202** (scheme 56) to give alcohol **203**. The carbamate **204** was then prepared as previously described.



Scheme 56 Synthesis and TA of sorbyl carbamate **204** *TA reagents and conditions:* $\text{K}_2\text{OsO}_2(\text{OH})_4$ (4 mol%), EtN^iPr_2 (5 mol%), NaOH (1 eq.), $^t\text{BuOCl}$ (1 eq.), $^n\text{PrOH-H}_2\text{O}$ (5:3), rt

The low yield obtained from the TA of **204** was surprising. Given the structural similarity to the hexenyl carbamate **194**, a similar result had been anticipated. No trace of oxidation of the distal double bond could be found, at least confirming that the transformation is chemoselective. Confirmation of the structure was obtained by hydrogenation of the double bond to give oxazolidinone **197**, previously synthesised *via* the TA (*vide supra*), with all data correlating exactly.

The brief selection of examples, collected together for convenience in table 24, show that the aminohydroxylation can be made completely regioselective by tethering the nitrogen source to the double bond. This tethered aminohydroxylation (TA) is also stereospecific with respect to the addition across the double bond, and chemoselective for the proximal allylic double bond in allylic systems.

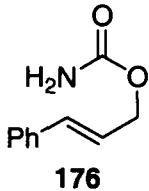
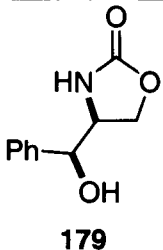
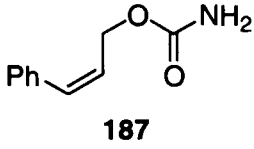
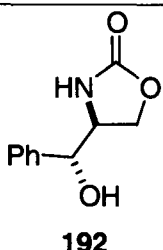
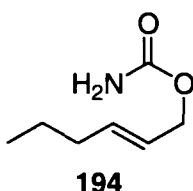
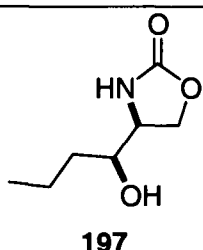
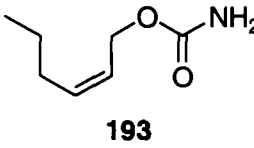
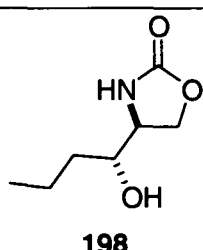
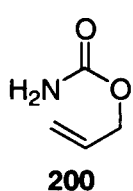
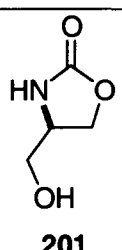
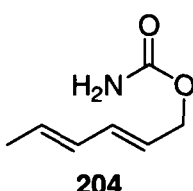
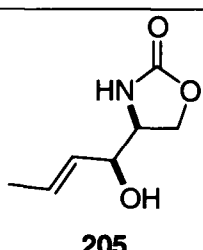
Substrate	Product	Ligand	Yield (%)	SM (%)
 176	 179	(DHQ) ₂ PHAL	62	12
		EtN ⁱ Pr ₂	59	23
 187	 192	(DHQ) ₂ PHAL	-	-
		EtN ⁱ Pr ₂	61	12
 194	 197	(DHQ) ₂ PHAL	54	8
		EtN ⁱ Pr ₂	58	10
 193	 198	(DHQ) ₂ PHAL	60	10
		EtN ⁱ Pr ₂	64	0
 200	 201	(DHQ) ₂ PHAL	43	0
		EtN ⁱ Pr ₂	40	2
 204	 205	(DHQ) ₂ PHAL	41	25
		EtN ⁱ Pr ₂	44	18

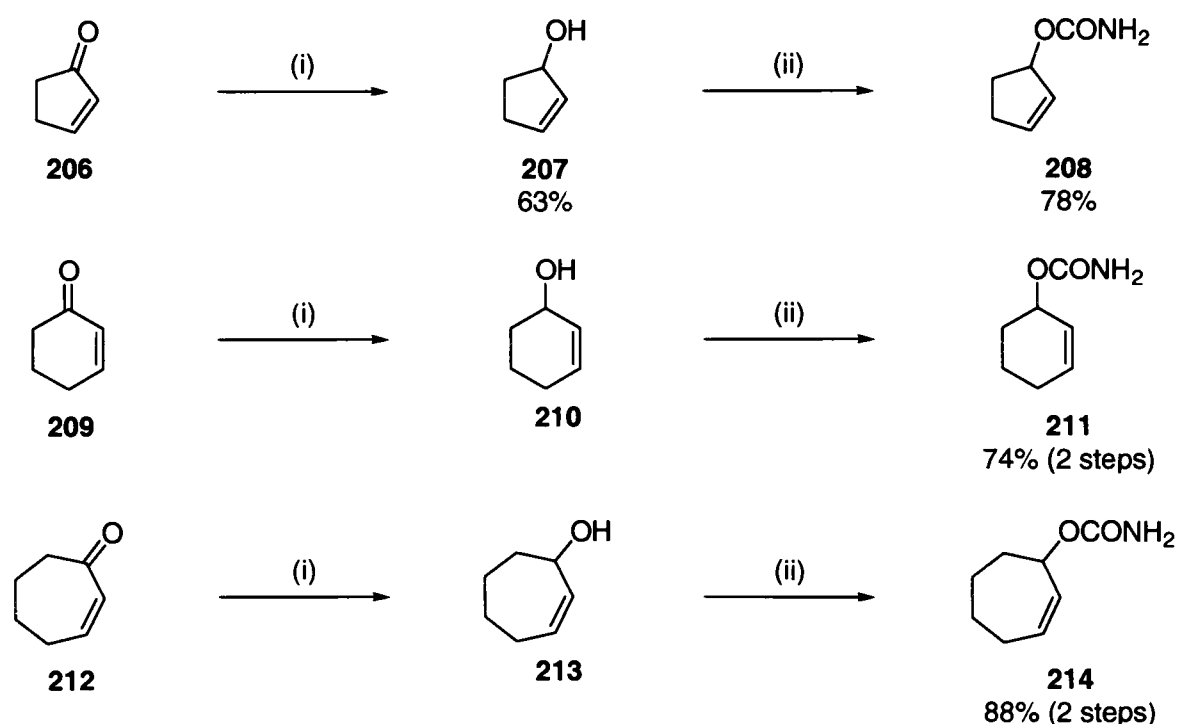
Table 24 Collected results of TA on terminal carbamates *Reagents and conditions* K₂OsO₂(OH)₄ (4 mol%), ligand (5 mol%), NaOH (1 eq.), ⁱBuOCl (1 eq.), ⁿPrOH-H₂O (5:3), rt; (–) denotes no entry.

2.4 – Cyclic Diastereocontrol in the TA⁸²

With the protocol for the reaction established, the scope of the reaction was explored further. The lack of enantioselectivity in the TA when using chiral ligands for the osmium catalyst meant that the issue of diastereoselectivity took on a heightened importance. The first chiral substrates investigated were cyclic secondary carbamates.

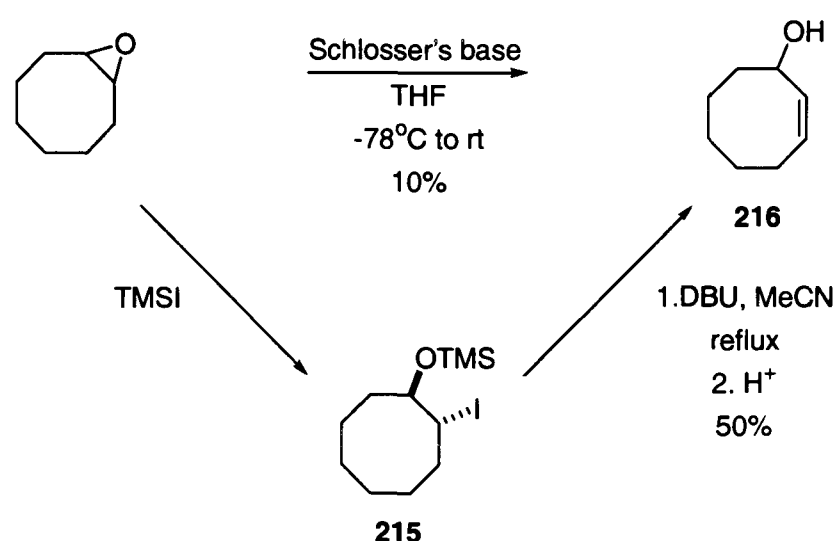
2.4.1 TA of unsubstituted alicyclic allylic carbamates

A homologous series of unsaturated cyclic carbamates were synthesised to investigate the effect ring size had on the diastereoselectivity of oxidation. The five-, six-, and seven-membered ring carbamates **208**, **211** and **214** were accessible from the corresponding enones *via* Luche reduction^{83, 84} and carbamation with trichloroacetyl isocyanate (scheme 57).



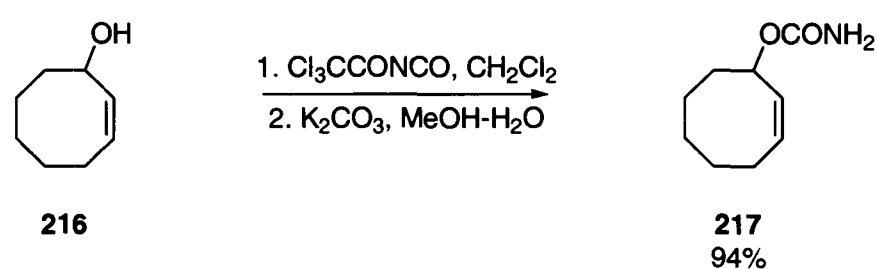
Scheme 57 Preparation of cyclic TA substrates *Reagents and conditions* (i) NaBH₄, CeCl₃·7H₂O, MeOH, 0°C, 12h; (ii) (a) Cl₃CCONCO, CH₂Cl₂, 0°C, 2h (b) K₂CO₃, MeOH-H₂O, 0°C to rt, 4-16h

The corresponding enone for the eight-membered ring was not commercially available, so another route was sought. Cyclooctene oxide can be isomerised under basic conditions to give the allylic alcohol (scheme 58).⁸⁵



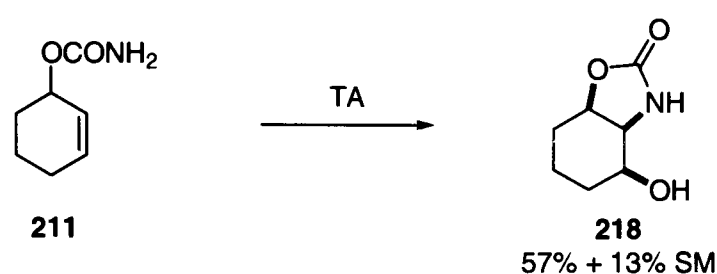
Scheme 58 Synthesis of cyclooctenyl alcohol 216

Using strong bases (LDA, potassium *tert*-butoxide or Schlosser's base, a mixed base containing both), this route was largely unsatisfactory, as the product was obtained in poor yield and was difficult to separate from unreacted starting material. A superior route involved the use of trimethylsilyl iodide to open the epoxide under Lewis acidic conditions, followed by elimination of the iodide **215** with DBU to give the allylic silyl ether.⁸⁶ Acidic workup gave the allylic alcohol **216** in a much-improved 50% yield. This material was also notably purer after column chromatography than that obtained by basic isomerisation. Treatment of **216** with trichloroacetyl isocyanate gave the allylic carbamate **217** (94%, scheme 59). This material was recrystallised from petrol-chloroform before use to remove residual trace impurities from the isomerisation step.



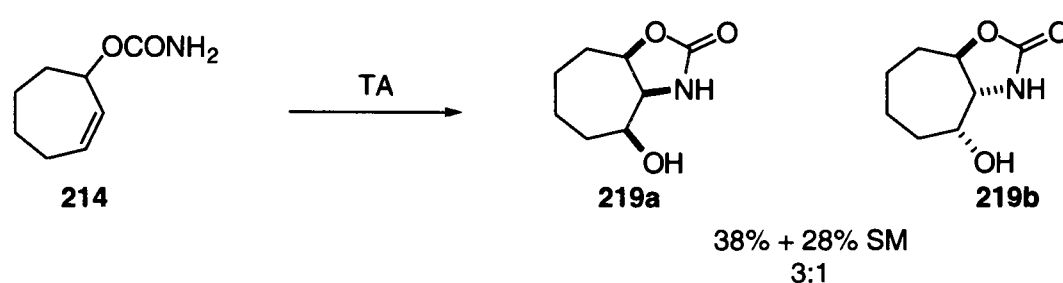
Scheme 59 Preparation of cyclooctenyl carbamate 217

The TA reactions were initially carried out using the best conditions established for the terminal carbamates. The six-membered ring showed the best diastereoselectivity, with only the all *syn* isomer **218** isolated in addition to recovered starting carbamate (scheme 60).



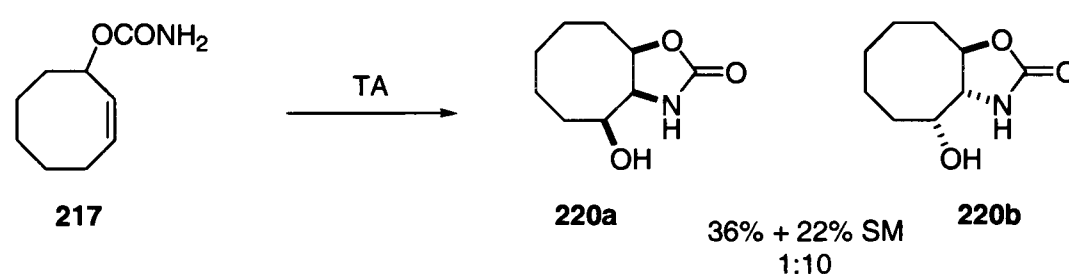
Scheme 60 TA of cyclohexenyl carbamate *Reagents and conditions* $K_2OsO_2(OH)_4$ (4 mol%), EtN^iPr_2 (5 mol%), $tBuOCl$ (1 eq.), $NaOH$ (1 eq.), $nPrOH-H_2O$ (5:3), rt

The seven-membered ring showed the same sense of selectivity, albeit in a reduced 3:1 *syn-syn* **219a**:*syn-anti* **219b** ratio.



Scheme 61 TA of cycloheptenyl carbamate *Reagents and conditions* $K_2OsO_2(OH)_4$ (4 mol%), EtN^iPr_2 (5 mol%), $tBuOCl$ (1 eq.), $NaOH$ (1 eq.), $nPrOH-H_2O$ (5:3), rt

The greater flexibility in the eight-membered ring leads to a strong 10:1 preference for the *syn-anti* isomer **220b**.



Scheme 62 TA of cyclooctenyl carbamate *Reagents and conditions* $K_2OsO_2(OH)_4$ (4 mol%), EtN^iPr_2 (5 mol%), $tBuOCl$ (1 eq.), $NaOH$ (1 eq.), $nPrOH-H_2O$ (5:3), rt

2.4.2 Proof of stereochemistry of **218**, **219** and **220**

Not wishing to assume the stereochemistry of the products, each of the oxazolidinones was identified separately. Most straightforwardly, the structure of the crystalline six-membered oxazolidinone **218** was solved by X-ray crystallography, clearly showing the all-*syn* relationship of the three heteroatoms around the ring (figure 12).

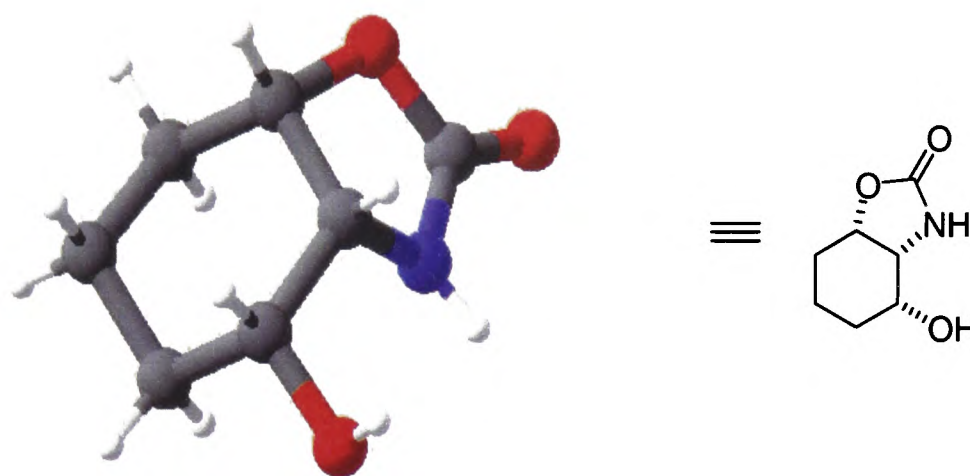
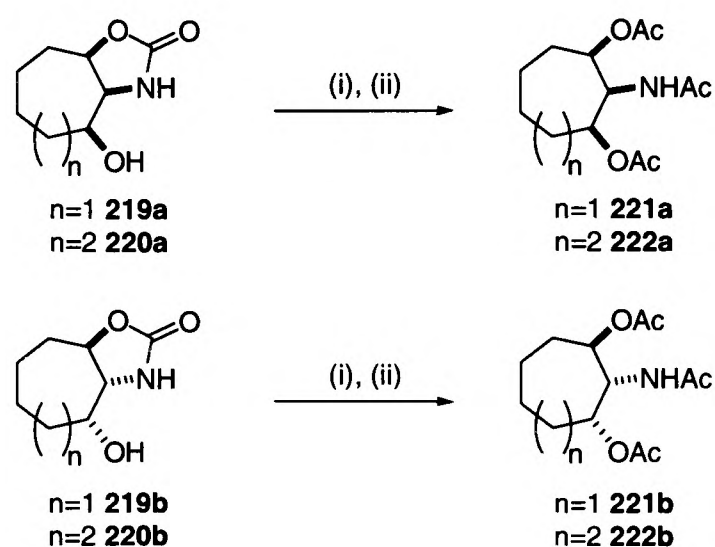


Figure 12: X-ray crystal structure of oxazolidinone 218

The seven- and eight-membered ring compounds **219** and **220** were not so easily elucidated. While the compounds were crystalline, they were not separable by chromatography or recrystallisation, and when attempts were made to grow crystals, laminates of unsuitably thin plates were formed. A number of derivatives were synthesised but initially none provided crystals of suitable quality for analysis (*vide infra*).

The relative stereochemistry of the isomers was proven in the first instance by symmetry. Basic cleavage of the oxazolidinone mixture, followed by peracetylation gave a mixture of two triacetates (scheme 63). Making the reasonable assumption that *syn* addition has occurred across the double bond, the two possible isomers of the product give either the *meso*-triacetate **221/222a** or the chiral triacetate **221/222b**.



Scheme 63 Cleavage-peracetylation of oxazolidinone mixtures *Reagents and conditions* (i) aq. NaOH, MeOH, reflux; (ii) Ac₂O, pyridine, rt

The seven-membered ring gave a 3:1 mixture of triacetates. Partial separation was achieved by column chromatography, isolating a pure sample of the major isomer. Both ^1H and ^{13}C NMR spectra showed that this must be the *meso*-triacetate **221a** (figure 13), by virtue of the reduced number of observed signals due to the symmetry of the compound.

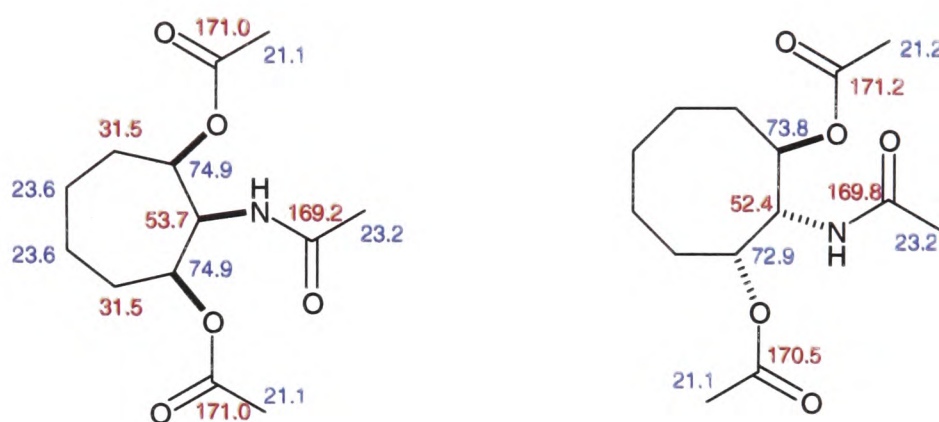
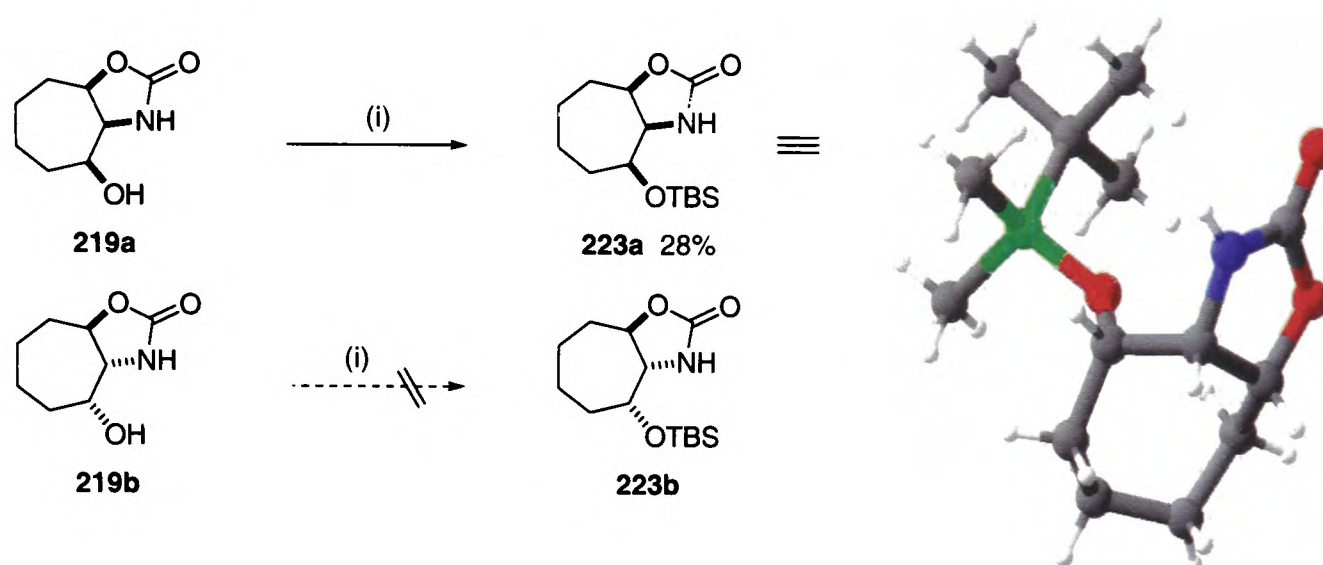


Figure 13 ^{13}C NMR data for 221a and 222b

Treatment of the eight-membered ring oxazolidinone to the same conditions gave exclusively the *syn-anti* triacetate **222b**. It was assumed that the small amount of the *meso*-isomer was lost during the course of the reaction and purification. Further confirmation of the identity of **221a** was obtained serendipitously. A series of derivatisation experiments had been performed in an attempt to cleanly separate the diastereomeric oxazolidinones **219a** and **219b**. One of these, formation of the *tert*-butyldimethylsilyl ethers **223a** and **223b**, did not proceed to completion. Instead a kinetic resolution occurred whereby only the all *syn* diastereomer formed the silyl ether **223a** (scheme 64). Separation of this compound from unreacted starting material was facile and furnished **223a** as a crystalline solid. A crystal of suitable quality for X-ray diffraction experiments was obtained, and the structure proposed from the symmetry considerations confirmed. As a final proof, **223a** was also converted into the triacetate **221a** by basic cleavage and peracetylation (50%).

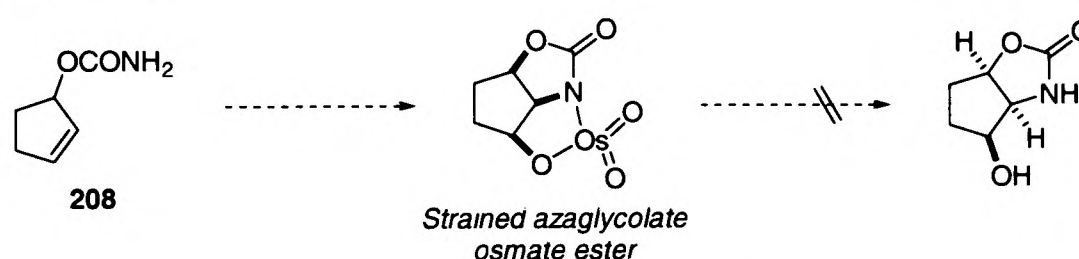


Scheme 64 TBS kinetic resolution of seven-membered oxazolidinones and crystal structure of 223a

Reagents and conditions TBSCl (1.1 eq.), imidazole (2.2 eq.), DMAP, CH₂Cl₂

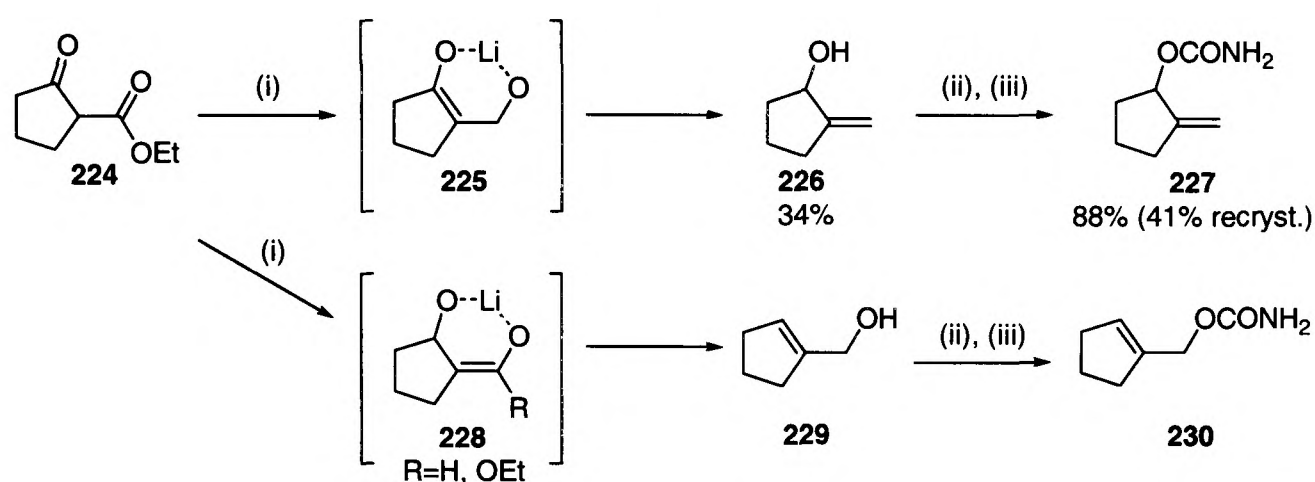
2.4.3 Failed TA of cyclopentenyl carbamate 208

The five-membered ring carbamate **208** did not give any product under these conditions. The reaction was heated to try and force turnover but as the temperature was increased the result was a more complicated mixture of unidentifiable products and less recovered starting material. It seems likely that the failure of this carbamate to undergo the TA is due to strain in the postulated osmate ester intermediate 5,5,5 ring system (scheme 65).



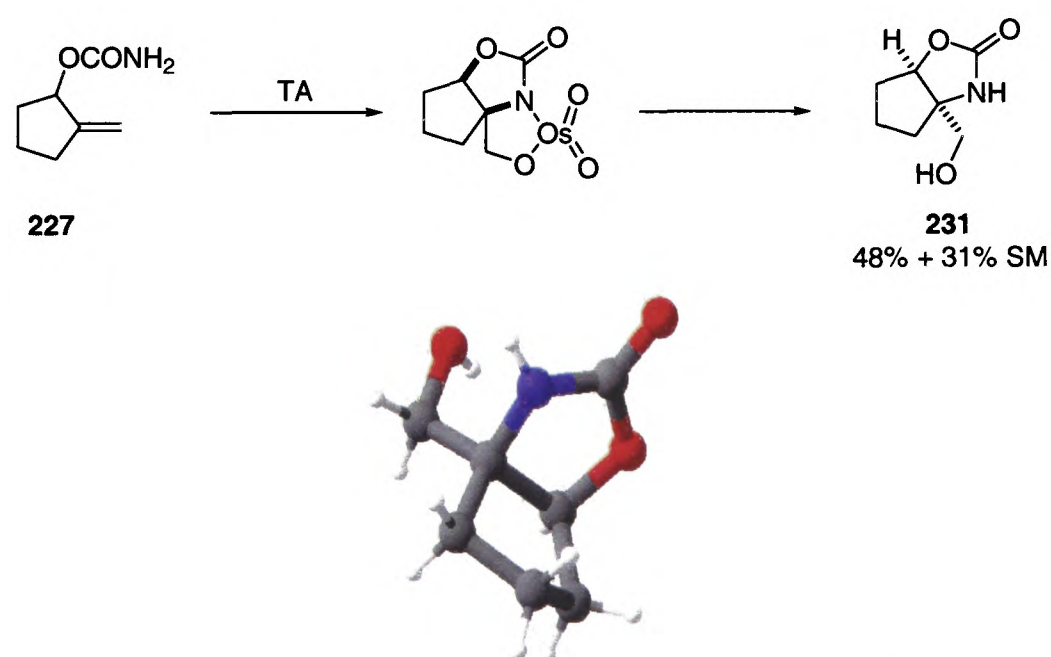
Scheme 65 Failed TA of cyclopentenylcarbamate 208

By reducing the ring strain, five-membered ring systems should become viable substrates. Thus synthesis of carbamate **227**, with an exocyclic double bond, was attempted (scheme 66). Literature precedent for synthesis of the parent allylic alcohol involves LiAlH₄ reduction of the β -keto-ester **224**.⁸⁷



Scheme 66 Preparation of substrate **227** with exocyclic double bond *Reagents and conditions* (i) LiAlH_4 , Et_2O , reflux; (ii) Cl_3CCONCO , CH_2Cl_2 ; (iii) K_2CO_3 , $\text{MeOH-H}_2\text{O}$, 0°C

The starting material **224** exists in a partially enolised form. Reduction of one enolate **225** leads to the desired exocyclic product **226**. The other enolate affords the endocyclic double bond **229**. The alcohol was inevitably contaminated with some of this material. Kgelrohr distillation removed most of the unwanted alcohol **229**, but some always remained. Recrystallisation of a mixture of carbamates **227** and **230** gave the desired carbamate free from its isomer.



Scheme 67 TA of carbamate **227** and crystal structure of **231** *Reagents and conditions* $\text{K}_2\text{OsO}_2(\text{OH})_4$ (4 mol%), $(\text{DHQ})_2\text{PHAL}$ (5 mol%), $t\text{BuOCl}$ (1 eq.), NaOH (1 eq.), $n\text{PrOH-H}_2\text{O}$ (5:3), rt

TA of carbamate **227** proceeded exactly as predicted to give the 5,5-bicyclic oxazolidinone **231** (scheme 67). The supposition that strain in the osmate ester was precluding reaction for carbamate **208** is supported by this result. Crystallisation of the

product was possible by boundary diffusion between chloroform and acetone and the identity of the product confirmed by X-ray analysis.

2.4.4 Improvement to the reaction protocol for cyclic substrates

An important distinction between the protocol for substrate **227** and the prior examples was the return to using (DHQ)₂PHAL as the ligand. The somewhat disappointing yields obtained with the seven- and eight-membered substrates had encouraged experimentation with reaction conditions. Pleasingly simply changing the ligand back to one of Sharpless' seemed to remedy the situation (table 25). However, a subsequent modification returned the yields when using Hünig's base to similar efficiencies (*vide infra*, section 2.4.7).

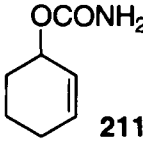
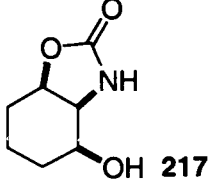
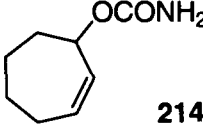
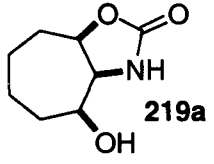
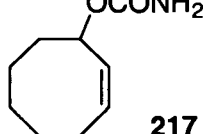
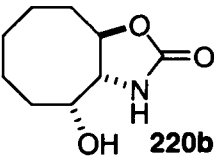
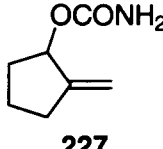
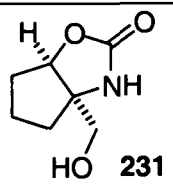
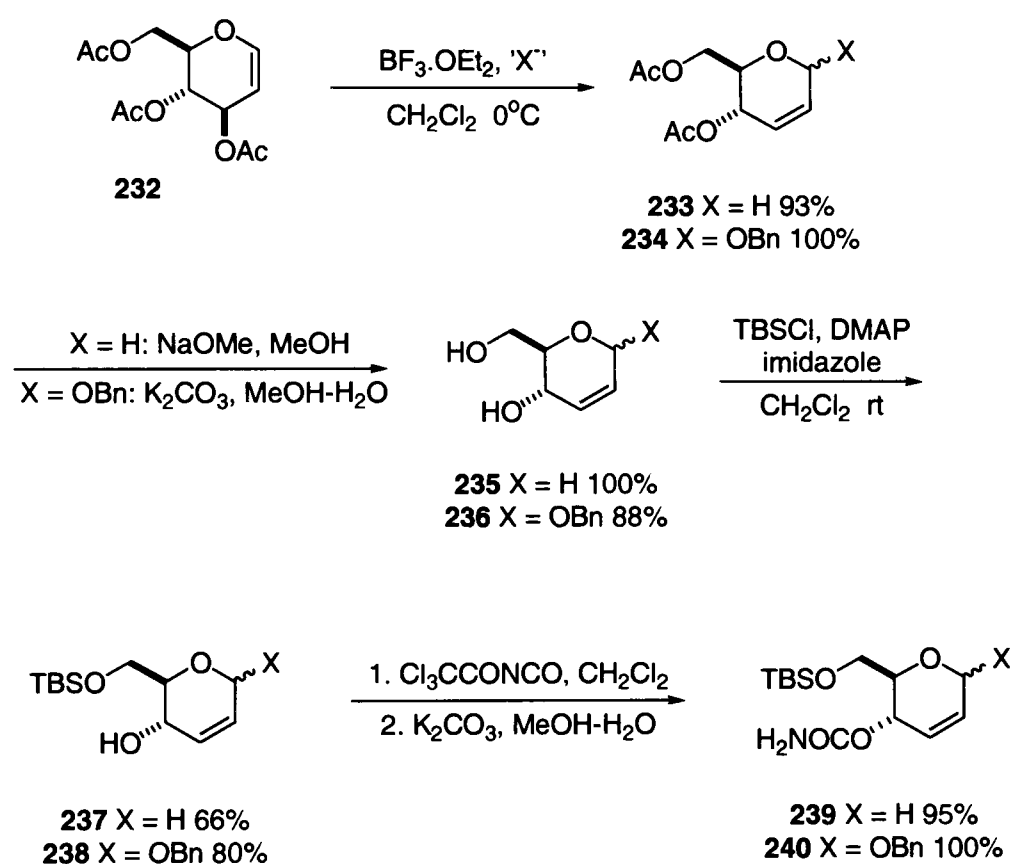
Substrate	Major product	Ligand	Yield (%)	SM (%)
 211	 217	EtN ^{<i>i</i>} Pr ₂	57	13
		(DHQ) ₂ PHAL	61	11
 214	 219a	EtN ^{<i>i</i>} Pr ₂	38	28
		(DHQ) ₂ PHAL	58	16
 217	 220b	EtN ^{<i>i</i>} Pr ₂	36	22
		(DHQ) ₂ PHAL	58	20
 227	 231	(DHQ) ₂ PHAL	48	31

Table 25 Improvement in TA yields using (DHQ)₂PHAL *Reagents and conditions* K₂OsO₂(OH)₄ (4 mol%), ligand (5 mol%), ^{*t*}BuOCl (1 eq.), NaOH (1 eq.), ^{*n*}PrOH-H₂O (5:3), rt

2.4.5 TA of carbohydrate-derived carbamates

The initial results from the cyclic carbamate series had shown that six-membered rings gave complete regiocontrol *and* stereocontrol in the TA. With this in mind it was decided to explore more substituted systems, in an attempt to ascertain the functional group tolerance of the reaction and to illustrate its utility.

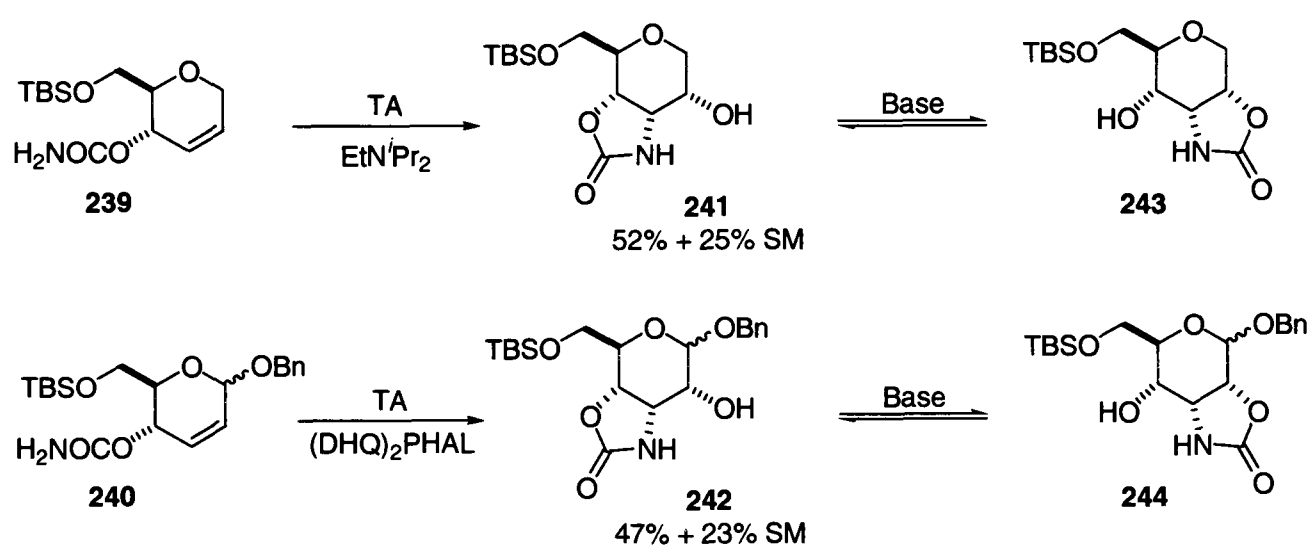
The carbohydrate-based allylic alcohol **237** had been used previously in the Donohoe group to study hydrogen bond directed dihydroxylation.⁸⁸ This compound was expensive to make in large quantities, due mainly to the hydride nucleophile source for the Ferrier rearrangement, triethylsilane (scheme 68, X=H). As the studies using sugars progressed, larger amounts of material were required and so the cheaper substitute **238** was synthesised instead using benzyl alcohol (scheme 68, X=OBn).⁸⁹



Scheme 68 Synthesis of sugar-based carbamates **239** and **240**; 'X' = Et₃SiH (series a) or BnOH (series b)

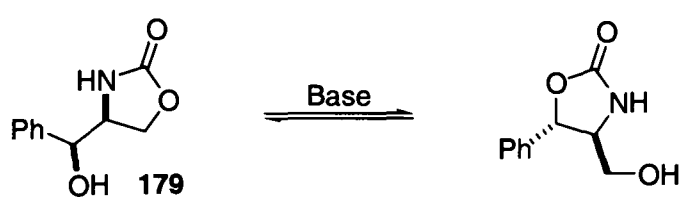
Both compounds were synthesised using literature routes, employing the same basic sequence of transformations. Starting from commercially available tri-*O*-acetyl-D-glucal **232**, Ferrier rearrangement with boron trifluoride and a nucleophile gave the diacetates **233** or **234**. Both acetates were cleaved under basic conditions, and subsequent selective primary hydroxyl protection as the *tert*-butyldimethylsilyl ether

furnished the allylic alcohol precursors **237** or **238**. Carbamation under standard conditions afforded the carbamate **239** or **240**. TA of carbamate **239** on first appearance worked smoothly. TLC analysis of the crude reaction mixture indicated two spots, corresponding to starting carbamate and product. The ^1H NMR spectrum of the isolated product had two very similar sets of signals, in an approximate 7:1 ratio. Repetition of the experiment led to varying amounts of the mystery impurity. It was suspected that it was most likely arising from base-catalysed isomerisation of the oxazolidinone (scheme 69).



Scheme 69 Base-catalysed isomerisation of oxazolidinone products *Reagents and conditions* $\text{K}_2\text{OsO}_2(\text{OH})_4$ (4 mol%), ligand (5 mol%), NaOH (1 eq.), $t\text{BuOCl}$ (1 eq.), $n\text{PrOH-H}_2\text{O}$ (5:3), rt

Treatment of a clean sample of oxazolidinone **241** with sodium hydroxide in propanol gave a 1:1 mixture of starting material and the newly-formed oxazolidinone **243**, lending credence to the fact that excess base was responsible. The same occurred when oxazolidinone **179** was treated with base (scheme 70), and also with compound **240**, although made more complicated by a mixture of anomers. Cooling of the TA reaction mixture to 0°C removed all traces of isomerisation, although yields of product were much reduced (13-17%). Using $(\text{DHQ})_2\text{PHAL}$ as the ligand gave less isomerisation, but did not prevent it completely.



Scheme 70 Base-catalysed isomerisation of oxazolidinone **179**

2.4.6 General improvement to the TA reaction protocol

Success in eliminating isomerisation was achieved by ensuring that the base was not in excess, and preferably in a slight deficit in the case of sensitive oxazolidinones. Potassium osmate itself liberates two moles of hydroxide and this was taken into account. Thus when using 4 mol% of potassium osmate the amount of base added was reduced to 0.92 equivalents. Yields of product were immediately improved; to the extent that Hünig's base could again be used as the ligand (table 26). The reaction of carbamates **214** and **240** were performed on scales up to 8 mmol with no detrimental effect on yield.

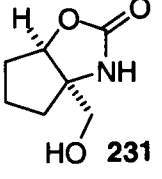
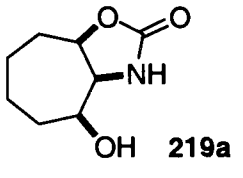
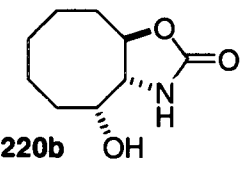
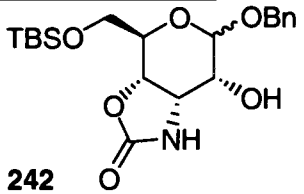
<i>Product</i>	<i>Base (eq.)</i>	<i>Ligand</i>	<i>Yield (%)</i>	<i>SM (%)</i>
 231	1.0	(DHQ) ₂ PHAL	48	31
	0.92	EtN ^t Pr ₂	51	28
 219a	1.0	EtN ^t Pr ₂	38	28
	1.0	(DHQ) ₂ PHAL	58	16
	0.92	EtN ^t Pr ₂	69	10
	0.92	(DHQ) ₂ PHAL	69	13
 220b	1.0	EtN ^t Pr ₂	36	22
	1.0	(DHQ) ₂ PHAL	26	28
	0.92	EtN ^t Pr ₂	55	20
	0.92	(DHQ) ₂ PHAL	58	20
 242	1.0	(DHQ) ₂ PHAL	47	23
	0.92	EtN ^t Pr ₂	53	24
	0.92	(DHQ) ₂ PHAL	65	10

Table 26 Improvements to TA protocol using strictly 1 equivalent of base *Reagents and conditions* K₂OsO₂(OH)₄ (4 mol%), ligand (5 mol%), NaOH, ^tBuOCl (1 eq.), ⁿPrOH-H₂O (5:3), rt

2.4.7 Proof of stereochemistry of carbohydrates

The stereochemistry of both **241** and **242** was taken to be analogous, by virtue of their identical origins. Proof of stereochemistry of **242** was achieved by nOe studies on

the tetraacetate derivative **245** (figure 14). Study of the coupling constants of the same compound did not give a clear picture, due to the unfortunate overlap of the signals from C³H and C⁴H.

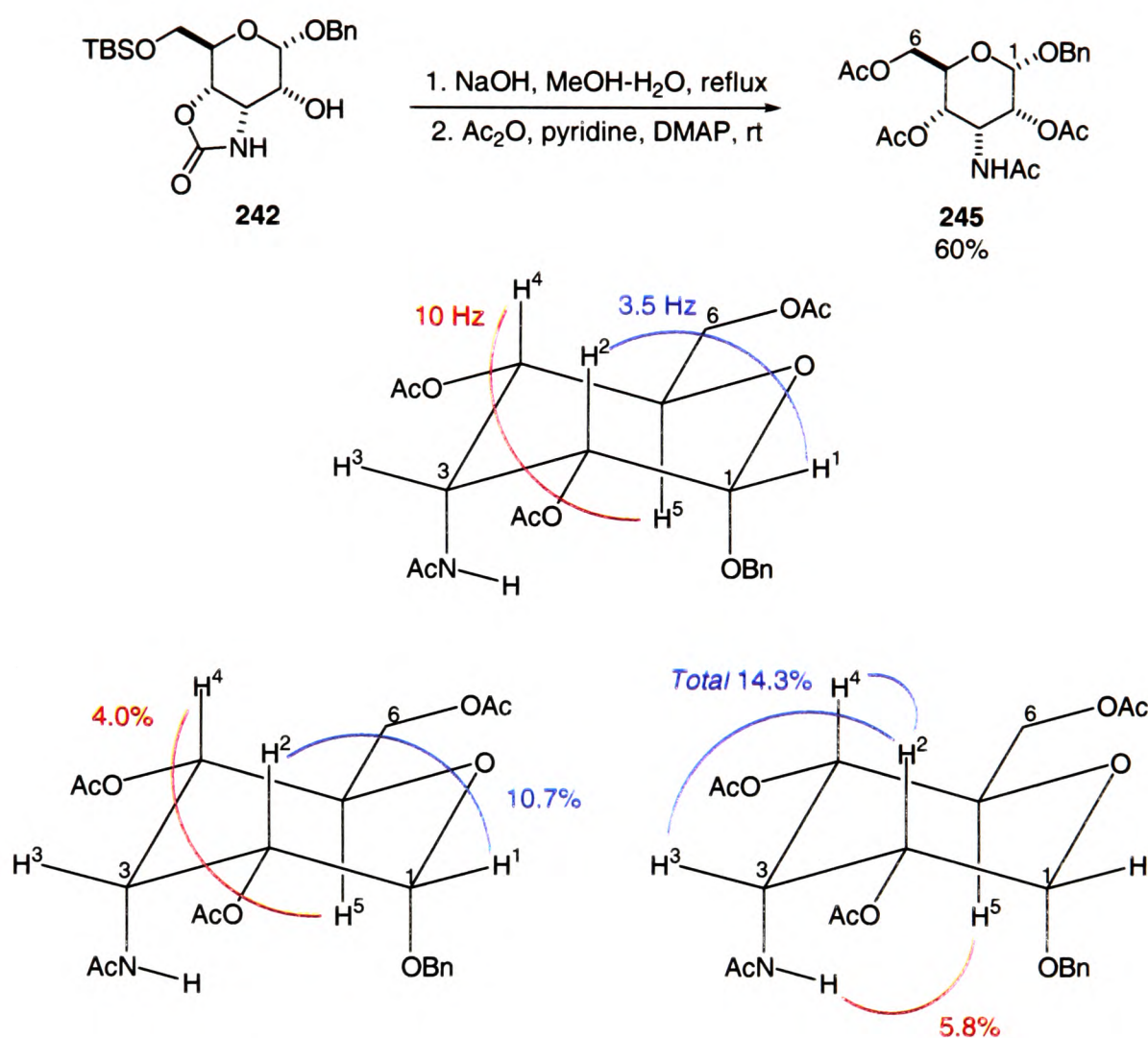


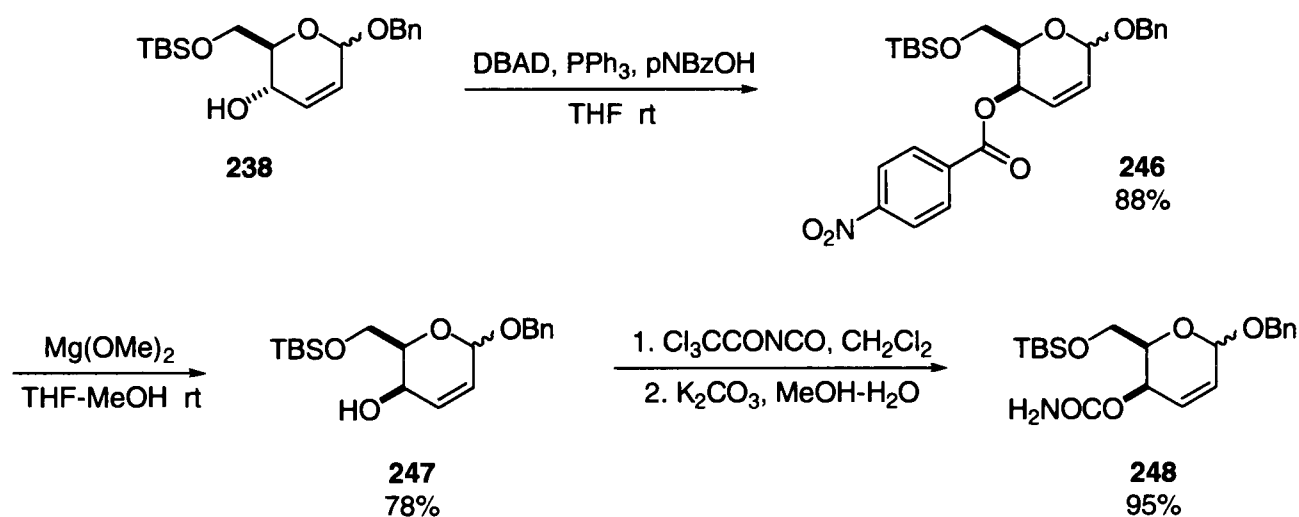
Figure 14 Coupling constants and nOe's for tetraacetate **245**; data shown on separate diagrams for clarity

H⁵ has three coupling constants: 10, 4.5 and 2.5 Hz. Two of these are to the diastereotopic pair of protons on C⁶. Given the magnitude of the largest coupling, and comparing it to the only known gauche coupling in the molecule, it seems likely that it is a transdiaxial coupling and that the stereochemistry across C⁴-C⁵ is as shown. This would be no surprise, these centres deriving directly from tri-*O*-acetyl-D-glucal. H² has no such large coupling, which is consistent with the proposed structure. The nuclear Overhauser effect studies on tetraacetate **245** were not straightforward to interpret. Again the overlapping signals from H³ and H⁴ meant that accurate determination of a diaxial nOe between H² and H⁴ was not possible. However the enhancement to the overlapping signal was considerable (14.3%). This is larger than any of the other enhancements, as can be seen in figure 14. The value obtained is also roughly equal to

the combined nOe's of H²-H¹ (gauche, 10.7%) and H⁵-NH (pseudo-diaxial, 5.8%). It can be inferred, therefore, that the enhancement is not entirely due to the H²-H³ interaction, and so both H² and H⁴ must be axial. Finally the shape of the H³-H⁴ multiplet changes in the difference spectrum. When H⁵ is irradiated, the multiplet corresponding to H³ and H⁴ is a different shape to that in both the natural spectrum and that in the spectrum when H² is irradiated. This shows that there is no enhancement to H³ from H⁵, and in addition again suggests enhancements to both H³ and H⁴ from H². The weight of these many observations in concert is highly consistent with the proposed structure.

2.4.8 TA of axially locked carbamate 248

Both of the carbohydrate substrates utilised had featured the carbamate locked in an equatorial position. It was not clear whether an axial carbamate would be able to react or not. Thus carbamate **248** was synthesised (scheme 71).⁹⁰ Taking alcohol **238** and subjecting it to Mitsunobu conditions gave the benzoate **246**, which was cleaved using magnesium methoxide as a mild base, avoiding any cleavage of the silyl ether. The alcohol **247** was then converted to the carbamate **248** under standard conditions.



Scheme 71 Preparation of the axially locked carbamate 248

The benzyloxy substituent would prefer to sit in an axial position to maximise the anomeric effect between itself and the ring oxygen. This would also place the carbamate in an axial position. TA of this compound proved unsuccessful. The normal colour changes associated with the reaction were observed, with the exception that the

mixture did not turn black, instead remaining a yellow-orange colour. Surprisingly, only 28% of the starting material was recovered, with no other major products isolated.

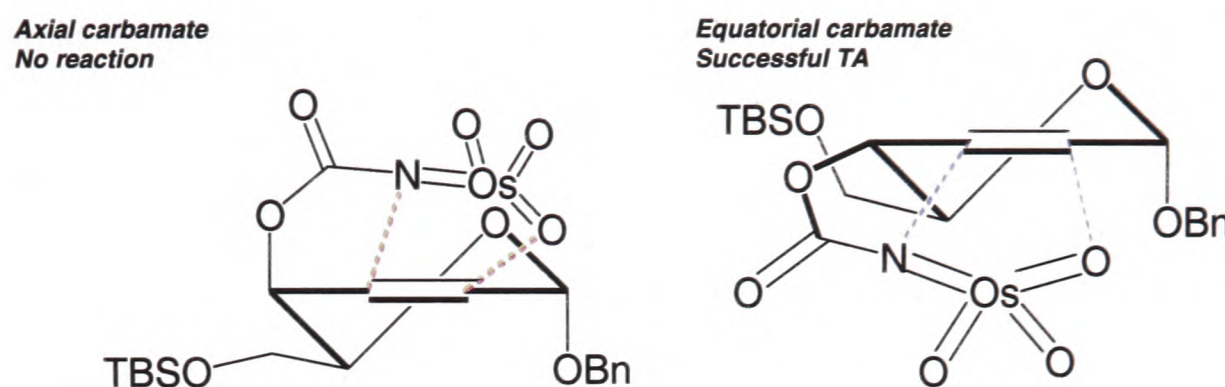
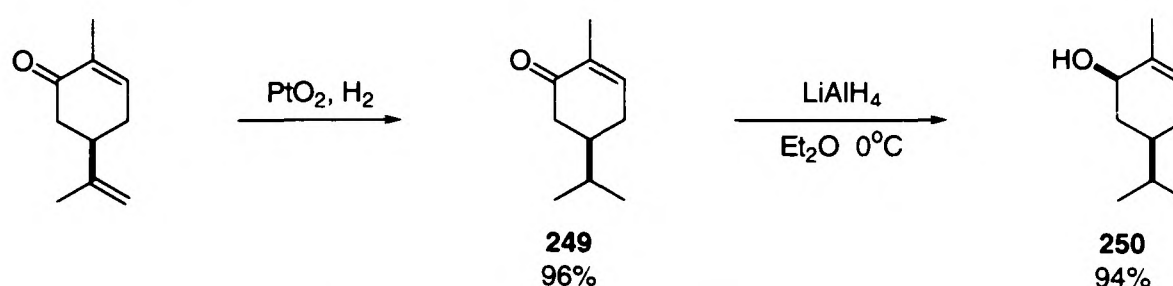


Figure 15 Conformation of equatorial and axial carbamates in the TA

The requirement for an *equatorial* carbamate is believed to be geometric in origin. The Os=N=C linkage is believed to be linear, based on crystallographic evidence from the literature.⁹¹ When the carbamate is axial, the N=Os=O linkage cannot be aligned so that there is orbital overlap for oxidation. The linearity of the complex means it protrudes past the end of the double bond. In contrast, an equatorial carbamate can rotate the osmium complex into a reactive conformation, and thus oxidation can occur.

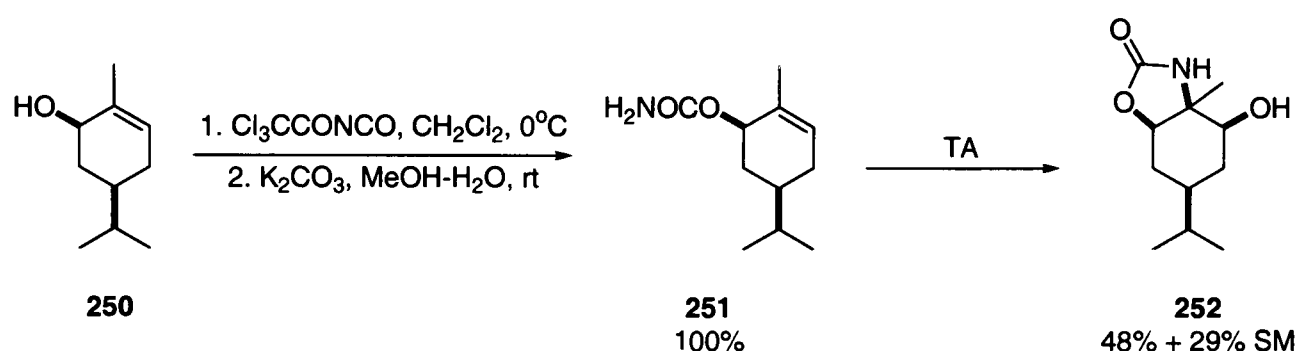
2.4.9 TA of terpene carbamate 251

The use of (DHQ)₂PHAL as a ligand for the TA had raised the question of kinetic resolution *via* matched and mismatched pathways. The lack of enantioselectivity in achiral examples suggested that no such resolution should occur. The substrate chosen for these experiments was derived from carvone. Previous researchers in the Donohoe group had synthesised allylic alcohol **250** for studies on directed dihydroxylation.⁹² The material was synthesised as described in scheme 72.



Scheme 72 Synthesis of allylic alcohol 250

Carbamate **251** was synthesised as described previously (100%), and subjected to a test reaction using the improved TA conditions mentioned above. The expected product **252** was obtained as an oil in 48% yield. Notably this transformation is on a trisubstituted olefin and this produces a quaternary centre.



Scheme 73 Preparation and TA of carbamate **251** *TA Reagents and conditions* $\text{K}_2\text{OsO}_2(\text{OH})_4$ (4 mol%), EtN^iPr_2 (5 mol%), NaOH (0.92 eq.), $^t\text{BuOCl}$ (1 eq.), $^n\text{PrOH-H}_2\text{O}$ (5:3), rt

2.4.10 Kinetic studies for TA of carbamate **251**

The reaction was repeated a number of times, varying the ligand used. The reaction was closely followed, and the time for the reaction to go black noted (table 27). This point generally represents the cessation of turnover and denotes an approximate time to completion. From the table it is immediately apparent that with the exception of quinuclidine, the choice of ligand is unimportant. There does not appear to be any difference in rate between Hünig's base and the Sharpless ligands. Crucially, the two pseudo-enantiomers of the Sharpless ligand do not give different rates, ruling out any suggestion of matched/mismatched kinetics. As before, quinuclidine shows a decelerating effect upon the reaction (*vide supra*, section 2.2.4).

<i>Ligand</i>	<i>Mol %</i>	<i>Time to black (h)</i>	<i>Yield (%)</i>	<i>SM (%)</i>
None	-	5.5	43	37
EtN ^t Pr ₂	5	2.5	48	29
	100	-	45	17
(DHQ) ₂ PHAL	5	2.3	55	25
(DHQD) ₂ PHAL	5	2.5	46	29
Quinuclidine	5	>7.0	35	40
	100	-	6	74

Table 27 Investigation of rate of reaction *Reagents and conditions* K₂OsO₂(OH)₄ (4 mol%), ligand, NaOH (0.92 eq.), ^tBuOCl (1 eq.), ⁿPrOH-H₂O (5:3), rt

2.4.11 Conclusion to cyclic diastereocontrol

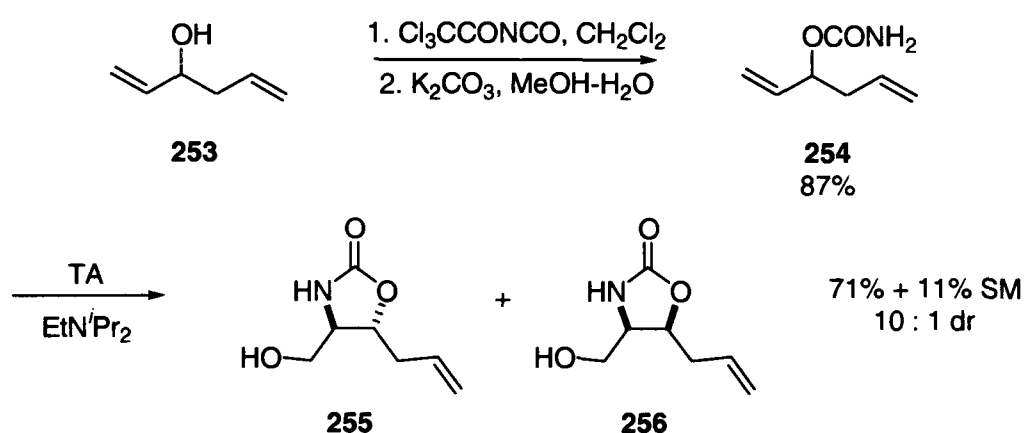
The studies on cyclic carbamates expanded the scope of the TA considerably. The complete control of diastereoselectivity in six-membered ring systems is in keeping with the aims of the project, developing an aminohydroxylation that has a predictable outcome. Kinetic studies on carbamate **176** have further shown that Sharpless ligands play a rate-accelerating role without stereochemical induction. The geometric nuances of the reaction have been shown in the failure to react of the five-membered ring carbamate **208** and the axially locked carbamate **248**. Other functionalised examples (**239** and **240**) have illustrated the utility of this reaction for carbohydrate synthesis.

2.5 Acyclic Diastereocontrol in the TA

The issue of diastereoselectivity in acyclic systems is often more complicated than in the corresponding cyclic cases. Each of the different substitution patterns of the alkene was investigated.

2.5.1 TA of 1-Vinyl-but-3-enyl carbamate **254**

Primary olefins were the first to be studied. The diene **253** is commercially available. Carbamation under standard conditions gave **254** in 87% yield. The TA proceeded smoothly, and in good yield to give a 10:1 mixture of diastereomers **255** and **256** (scheme 74).

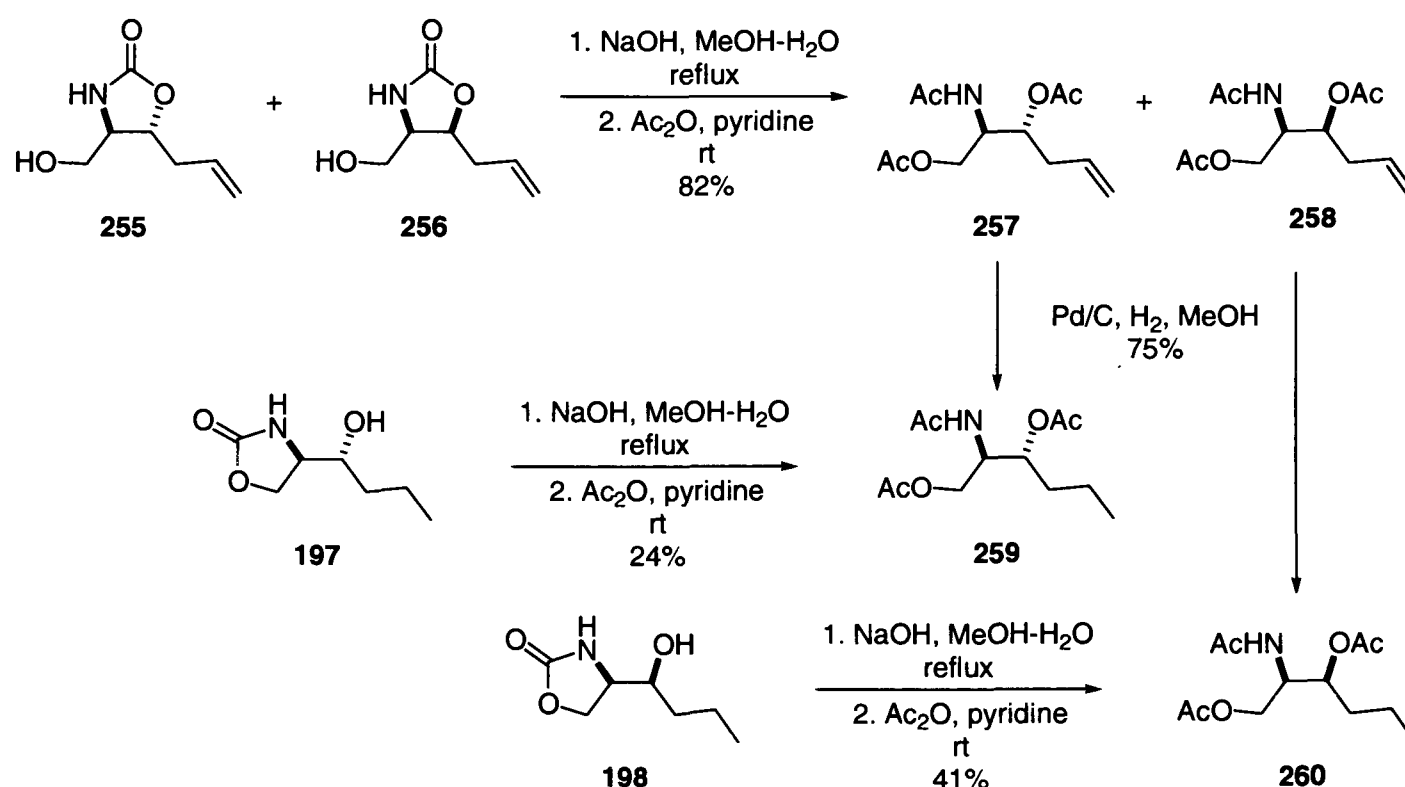


Scheme 74 TA of primary olefins proceeds with excellent diastereoselectivity *TA Reagents and conditions* $\text{K}_2\text{OsO}_2(\text{OH})_4$ (4 mol%), EtN^iPr_2 (5 mol%), NaOH (0.92 eq.), $^t\text{BuOCl}$ (1 eq.), $^n\text{PrOH-H}_2\text{O}$ (5:3), rt

The excellent diastereoselectivity bode well for further examples. In addition, this substrate showed a complete kinetic preference for oxidation of the allylic bond over the homoallylic double bond. This was as expected, from consideration of intramolecular processes such as halolactonisation. The addition across the allylic alkene can be considered a 5-exo-trig process, compared to 6-exo-trig for the homoallylic alkene.

Proof of the stereochemistry of the diastereomers was difficult. The diastereomers were exceptionally difficult to separate, both for the oxazolidinones **255**

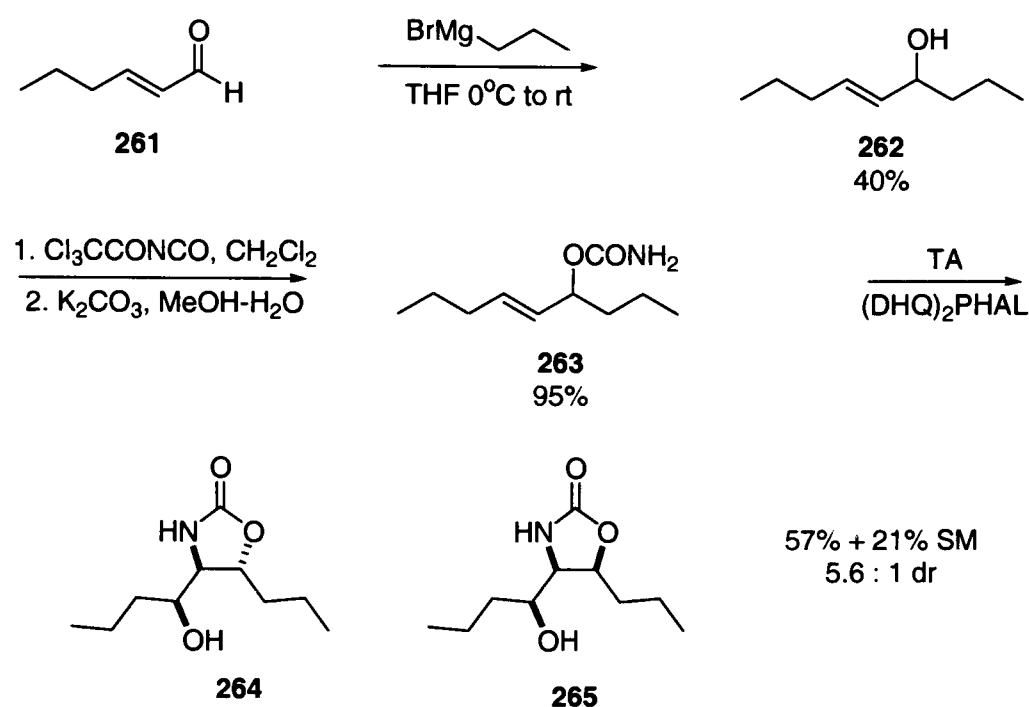
and **256** and for numerous derivatives. Ultimately proof of stereochemistry was obtained by correlation to a common intermediate (scheme 75). Basic cleavage of the oxazolidinone followed by peracetylation provided a mixture of triacetates **257** and **258**. Hydrogenation gave triacetates **259** and **260**, which were separable. These triacetates were also synthesised from the diastereomeric oxazolidinones **197** and **198**, available from the early TA studies (*vide supra*, section 2.3.2). Comparison of ^1H and ^{13}C NMR spectra showed that the major isomer from the diene TA (**255**) gave the same triacetate as the oxazolidinone from the *trans*-hexenyl carbamate (**197**). This means that the major product oxazolidinone **255** arises from a *syn* sense of addition.

Scheme 75 Proof of stereochemistry of oxazolidinones **255** and **256**

2.5.2 TA of *cis* and *trans* 1-Propyl-hex-2-enyl carbamate **263** and **268**

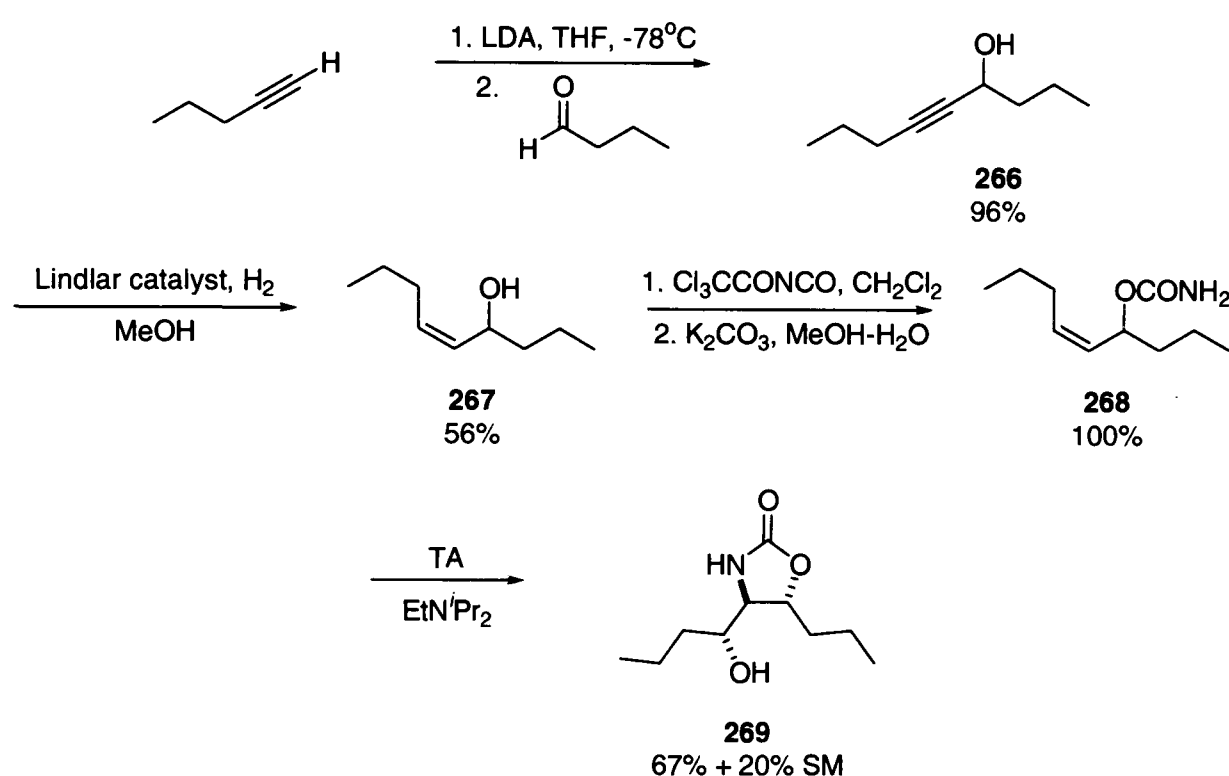
The TA of chiral 1,2 disubstituted olefins are strongly linked and will be discussed together. Synthesis of the *trans* nonenyl carbamate **263** began from the *trans* aldehyde **261** (scheme 76). Reaction with freshly prepared propyl magnesium bromide gave the allylic alcohol **262** in 40% yield.⁹³ Subsequent carbamation proceeded uneventfully and in 95% yield to give carbamate **263**. The TA itself gave a respectable

57% yield. A 6:1 mixture of diastereomers was formed, a lower selectivity than that observed for the primary olefin **254**.



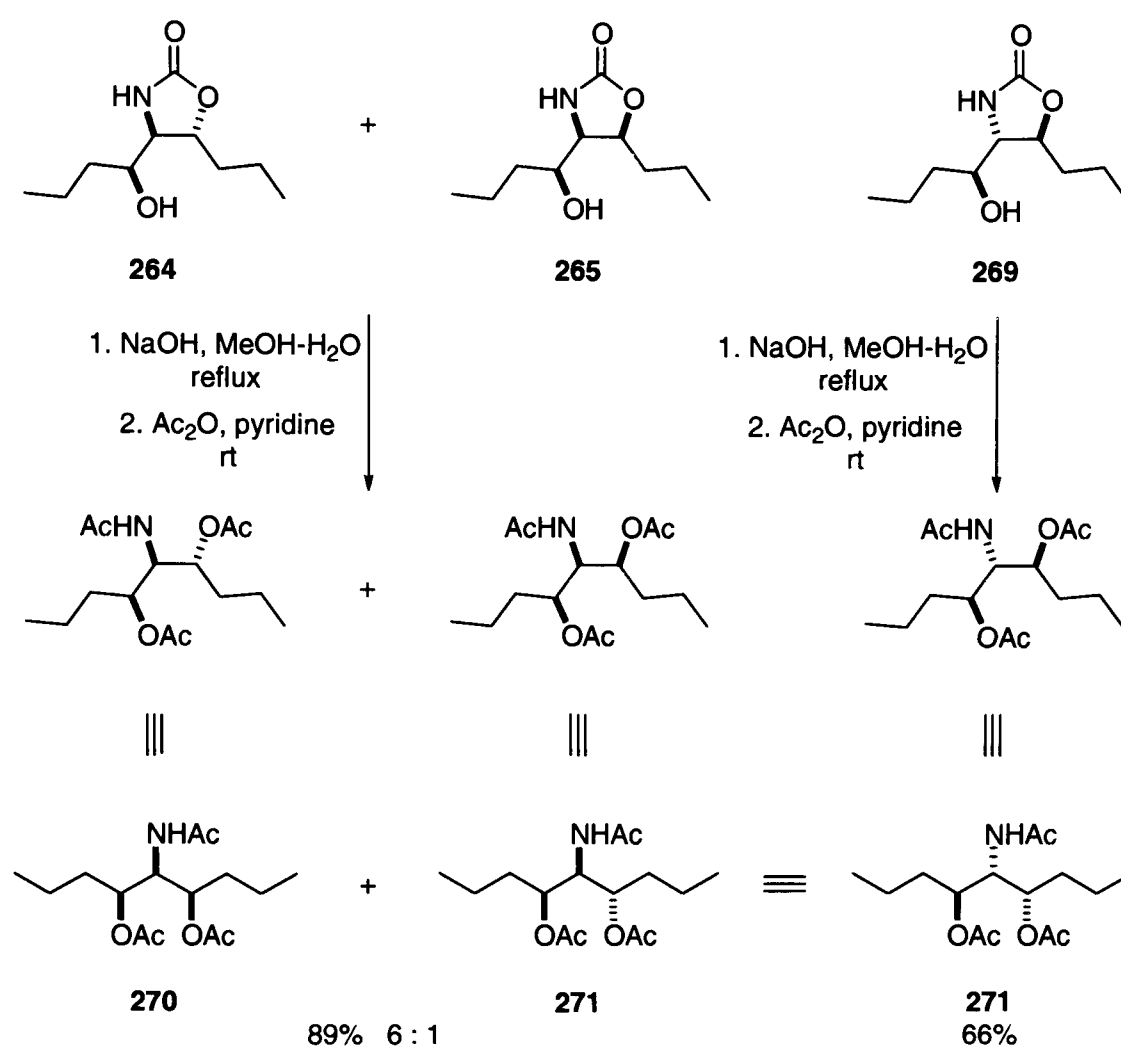
Scheme 76 Synthesis and TA of *trans*-nonenyl carbamate **263** TA Reagents and conditions $\text{K}_2\text{OsO}_2(\text{OH})_4$ (4 mol%), $(\text{DHQ})_2\text{PHAL}$ (5 mol%), NaOH (0.92 eq.), $t\text{-BuOCl}$ (1 eq.), $n\text{-PrOH-H}_2\text{O}$ (5:3), rt

The *cis*-isomer **268** could not be synthesised using this route. Attempts to isolate the *cis*-aldehyde from oxidations of the corresponding alcohol were unsuccessful, leading to varying amounts of *trans*-aldehyde. Instead, the double bond was installed *via* addition of 1-pentyne to butanal (scheme 77, 96%). LDA rather than $n\text{-BuLi}$ was used to deprotonate the alkyne to prevent butyl addition to the aldehyde.



Scheme 77 Synthesis and TA of *trans*-nonenyl carbamate **268** TA Reagents and conditions $\text{K}_2\text{OsO}_2(\text{OH})_4$ (4 mol%), EtN^iPr_2 (5 mol%), NaOH (0.92 eq.), $t\text{BuOCl}$ (1 eq.), $n\text{PrOH-H}_2\text{O}$ (5:3), rt

Lindlar hydrogenation of the nonyne **266** gave the *cis* allylic alcohol **267**. The yield was poor for this transformation (56%), due to the care required in avoiding saturation of the alkyl chain. The reaction was stopped at five-minute intervals and a sample withdrawn for TLC and NMR analysis. Generally it proved impossible to reduce alkyne **266** cleanly before saturation of the double bond began to occur. Thus, the reaction was worked up when the first traces saturated material appeared. Carbamation of the alcohol was quantitative. Again contrary to experiences from the AA, the reaction of an aliphatic *cis* double bond worked very well, giving a good yield (67%) of a single diastereomer of the oxazolidinone **269**. The dramatic improvement in diastereoselectivity for *cis* substrates over *trans* is highly indicative of a process where 1,3 allylic strain plays a key role (*vide infra*, section 2.5.5).



Scheme 78 Proof of stereochemistry of 264, 265 and 269 by symmetry

Proof of the stereochemistry of the oxazolidinones **264**, **265**, and **269** was obtained from the triacetates **270** and **271** (scheme 78). Knowing that Os (VIII) addition across the double bond is *syn* in all cases, the relative stereochemistry of the nitrogen and hydroxyl centre is known. As with the seven- and eight-membered ring products **219** and **220** above, the triacetates can therefore be either symmetrical (*meso*-triacetate **270**) or not (triacetate **271**). The mixture of oxazolidinones obtained from oxidation of the *trans*-isomer **263** gave a separable mixture of triacetates. The major product was the symmetrical triacetate **270**, which again derives from a *syn* sense of addition. Oxazolidinone **269** gave the other triacetate **271**, confirming a preference for *syn* addition.

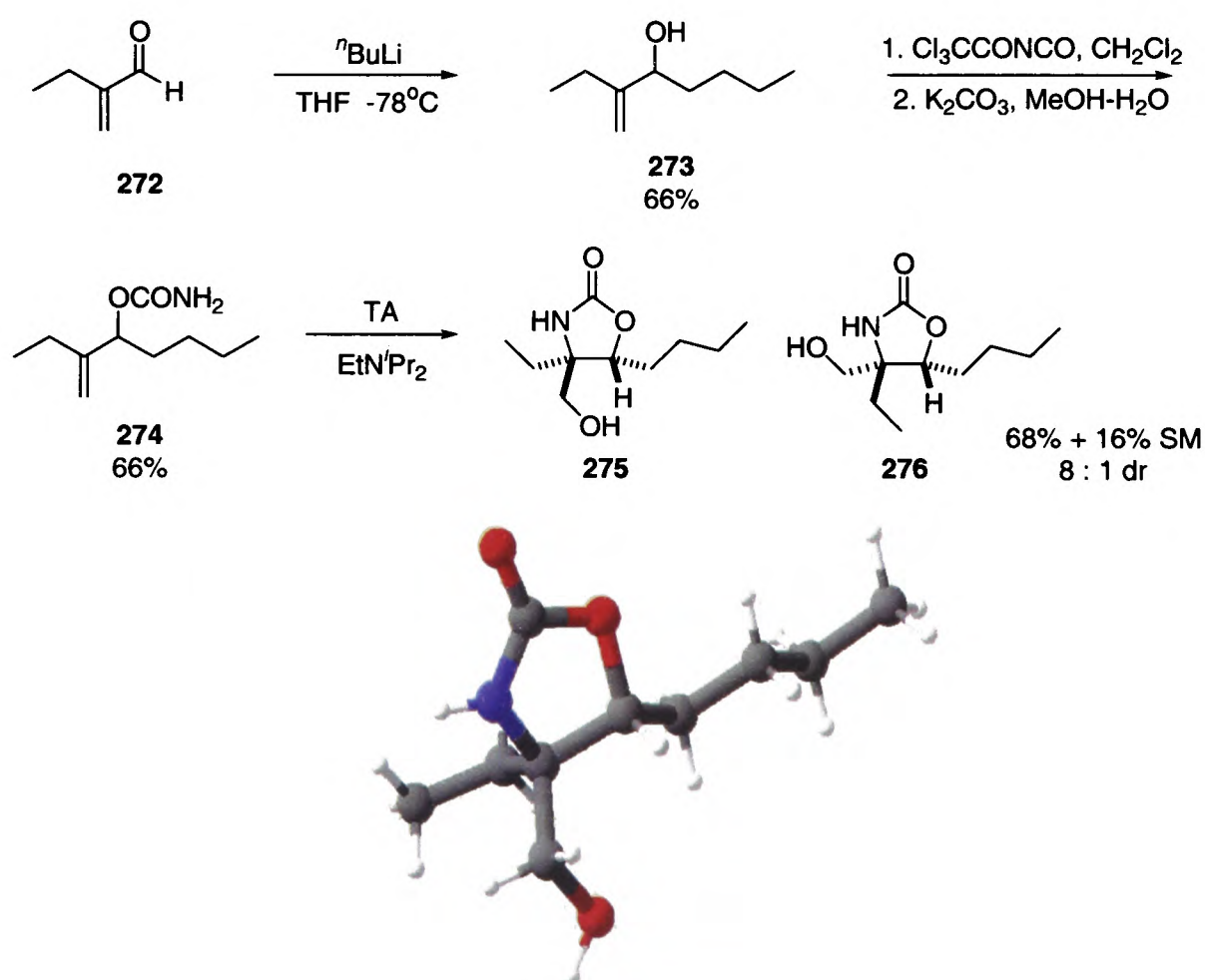
The scope for improvement in the level of selectivity shown by carbamate **263** prompted studies into the effect of temperature on the diastereomeric outcome. The reaction was repeated, at both lower and higher temperatures (table 28). Unusually, the diastereoselectivity was greater at higher temperatures, although the increase was modest and accompanied by a fall in yield. At lower temperatures a greater proportion

of the *anti* diastereomer was formed. This unusual temperature dependence could be explained by differing entropies of activation, whereby the conformation that has the larger entropy is more favoured.^{94, 95}

Temp. (°C)	264:265	Yield (%)	SM (%)
0	3.8:1	51	38
20	5.6:1	57	21
40	5:1	63	32
70	7:1	23	45

Table 28 Effect on temperature on diastereoselectivity of TA of carbamate 263 *Reagents and conditions* K₂OsO₂(OH)₄ (4 mol%), (DHQ)₂PHAL (5 mol%), NaOH (0.92 eq.), ^tBuOCl (1 eq.), ⁿPrOH-H₂O (5:3)

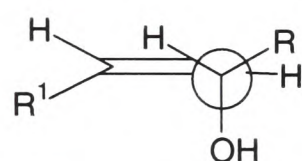
2.5.3 TA of 1-(1'-Methylene-propyl)-pentyl carbamate 274



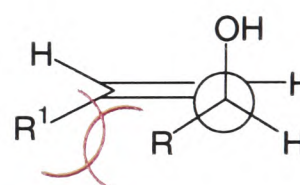
Scheme 79 Synthesis and TA of carbamate 274; crystal structure of 275 *TA Reagents and conditions* K₂OsO₂(OH)₄ (4 mol%), EtNⁱPr₂ (5 mol%), NaOH (0.92 eq.), ^tBuOCl (1 eq.), ⁿPrOH-H₂O (5:3), rt

1,1 disubstituted olefins typically give poor diastereoselectivity in substrate-directed reactions.⁹⁶ Carbamate **274** was produced by *n*-butyl lithium addition to aldehyde **272**, and subsequent carbamation of the allylic alcohol **273** (scheme 79). The TA again gave a good yield of oxidised product, and a good level of diastereoselection (8:1) in favour of the *syn-syn* isomer **275**. This represents an unusually high level of *syn* stereocontrol in acyclic systems. 1,1 disubstituted olefins do not typically give high levels of *syn* selectivity due to the more prominent influence of $A^{[1,2]}$ strain over $A^{[1,3]}$ (figure 16). The crystal structure of the major isomer was obtained by crystallisation from chloroform. (scheme 79).

1,2 *cis* disubstituted olefins

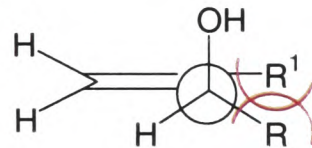


syn - minimises $A^{[1,3]}$ strain

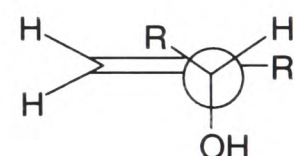


anti - disfavoured

1,1 disubstituted olefins



syn - disfavoured

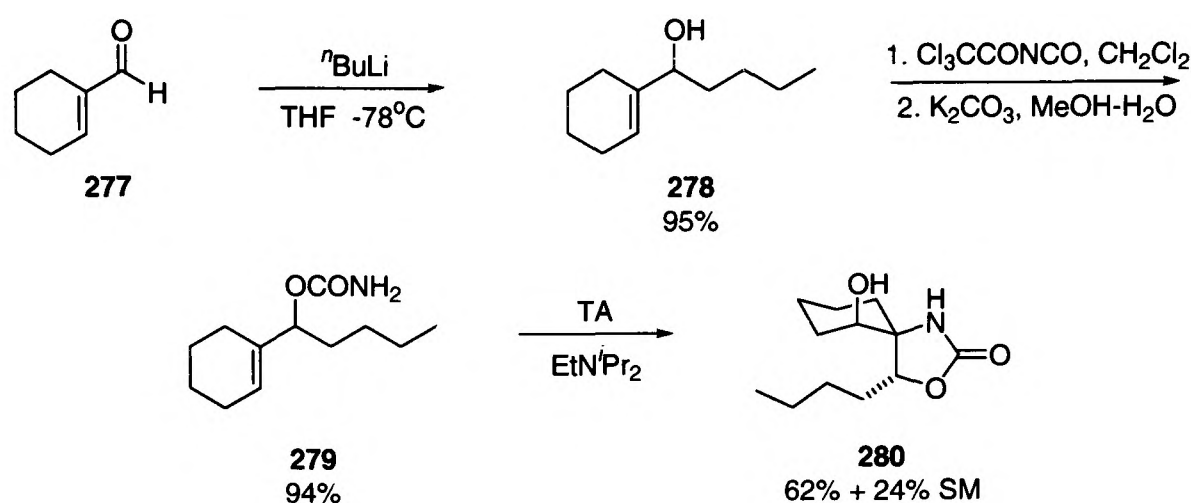


anti - minimises $A^{[1,2]}$ strain

Figure 16 Preferred conformations of *cis*- and 1,1-disubstituted olefins based on minimising allylic strain

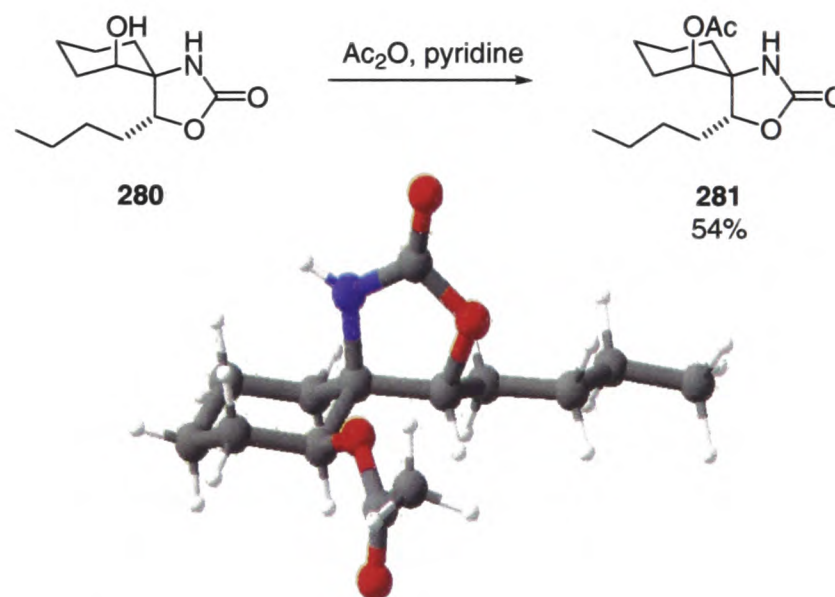
2.5.4 TA of 1-Cyclohexen-1-yl-pentyl carbamate **279**

A single trisubstituted olefin was also subjected to the TA (scheme 80). Addition of *n*BuLi to cyclohexenecarboxaldehyde **277** furnished the allylic alcohol **278** in excellent yield. Carbamation of **278** was also highly successful, giving the TA substrate **279** in 94% yield. The TA itself was highly selective, with the oxazolidinone **280** formed in a >10:1 ratio with its diastereomer (62%).



Scheme 80 Synthesis and TA of carbamate 279 *TA Reagents and conditions* $\text{K}_2\text{OsO}_2(\text{OH})_4$ (4 mol%), EtN^iPr_2 (5 mol%), NaOH (0.92 eq.), $^t\text{BuOCl}$ (1 eq.), $^t\text{PrOH-H}_2\text{O}$ (5:3), rt

Assignment of the structure of **280** was made by X-ray crystallography. A number of derivatives and the product **280** itself were all crystallised from a variety of solvents but failed to give crystals suitable for analysis. Eventually the monoacetate **281** was found to give good crystals on slow evaporation from an acetone solution. The crystal structure (scheme 81) again shows that *syn* addition has occurred.



Scheme 81 Synthesis and crystal structure of monoacetate 281

2.5.5 A model for selectivity in the TA of acyclic carbamates

The high levels of *syn* selectivity observed in the TA of chiral acyclic carbamates cannot be explained solely by the minimisation of allylic strain as depicted in figure 16. As mentioned above, the impact of 1,2 allylic strain would mean that for 1,1 disubstituted olefins, greater amounts of the *anti* product should be observed. In the

case of substrate **274**, the selectivity is 8:1 in favour of the *syn* product. Thus a different model is required to explain the stereochemistry.

An earlier observation led us to refine our model. The Os=N=C linkage is believed to be linear, based on crystallographic evidence.⁹¹ If this is the case, the carbamate tether must sit at a much greater angle from the π -system in order for the orbital geometries to be aligned for oxidation (figure 17 and figure 15, *vide supra*).

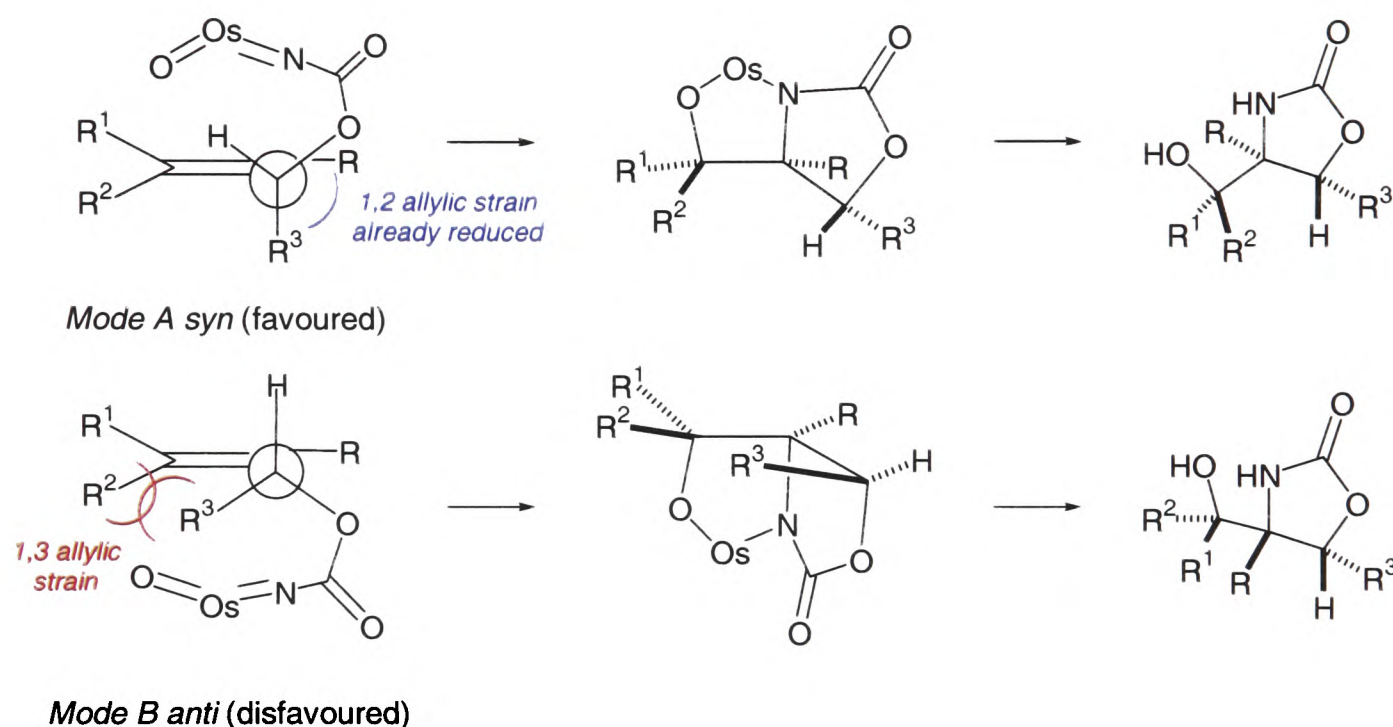


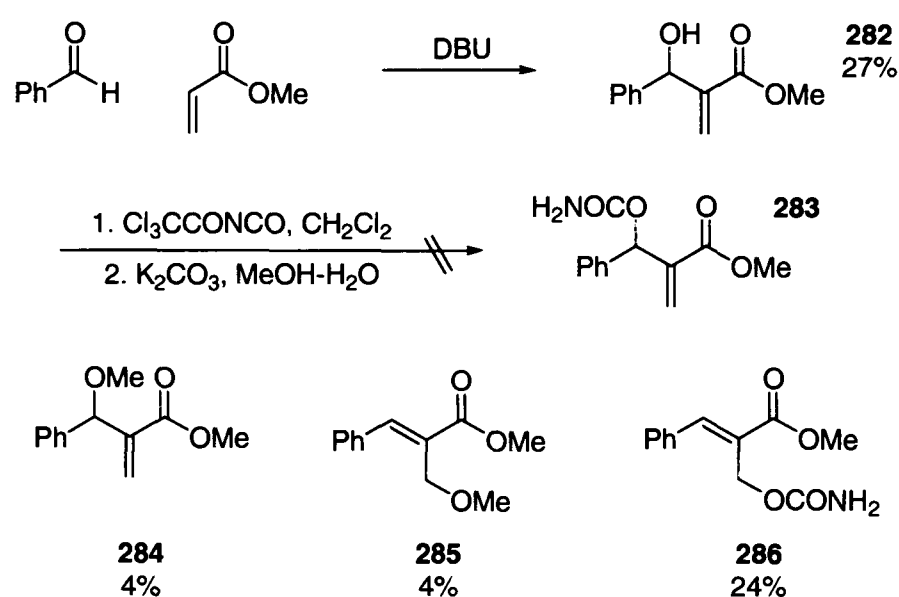
Figure 17 Revised model for selectivity in the TA of acyclic carbamates (other Os ligands omitted for clarity)

Modelling studies suggest that this angle is likely to be about 150° . The two postulated reactive conformations are depicted in figure 17. From a consideration of 1,3 allylic strain, mode A is preferred by virtue of placing the smaller hydrogen in the 'inside' allylic position rather than the bulkier alkyl group R^3 , as in mode B. Thus as observed, *cis* double bonds would be expected to give greater levels of stereocontrol. The position of R^3 is also relevant when considering 1,2 allylic strain. Because in mode A it lies approximately orthogonal to the plane of the π -system, the interaction between R^3 and R is already greatly reduced. Thus the impact of *gem* substituents is also reduced. This is manifested in the high levels of *syn* selectivity seen in 1,1 disubstituted olefins. A final consideration is the rate of oxidation. In the favoured conformation A, the incoming oxidant must oxidise from the same π -face as the 'inside' allylic hydrogen. This could be expected to be faster than oxidation in the disfavoured

conformation B, where the incoming oxidant must now oxidise from the same π -face as the bulkier ‘inside’ alkyl group R^2 .

2.5.6 Failed TA attempts

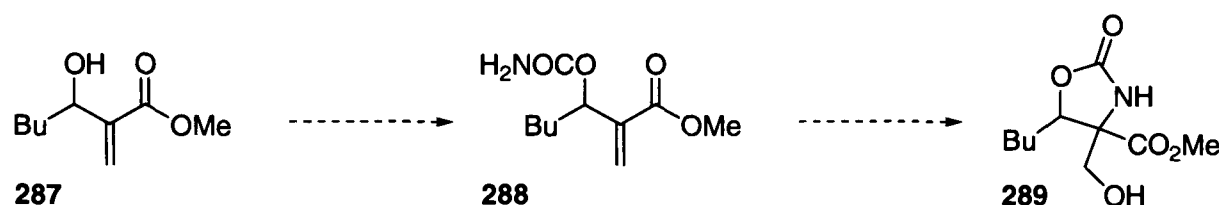
In the course of the acyclic studies, a number of desired substrates proved problematic, either failing to react under TA conditions or rearranging before being subjected to TA conditions. The first of these was the Baylis-Hillman substrate **283**. The alcohol **282** was synthesised following a literature procedure from Aggarwal, using DBU as the nucleophilic catalyst (scheme 82). The reaction was slow, taking six hours to give a yield of 17% and 3 days to give a yield of 27%. Nevertheless this provided enough material to attempt carbamation.



Scheme 82 Attempted synthesis of carbamate **283** and resulting products

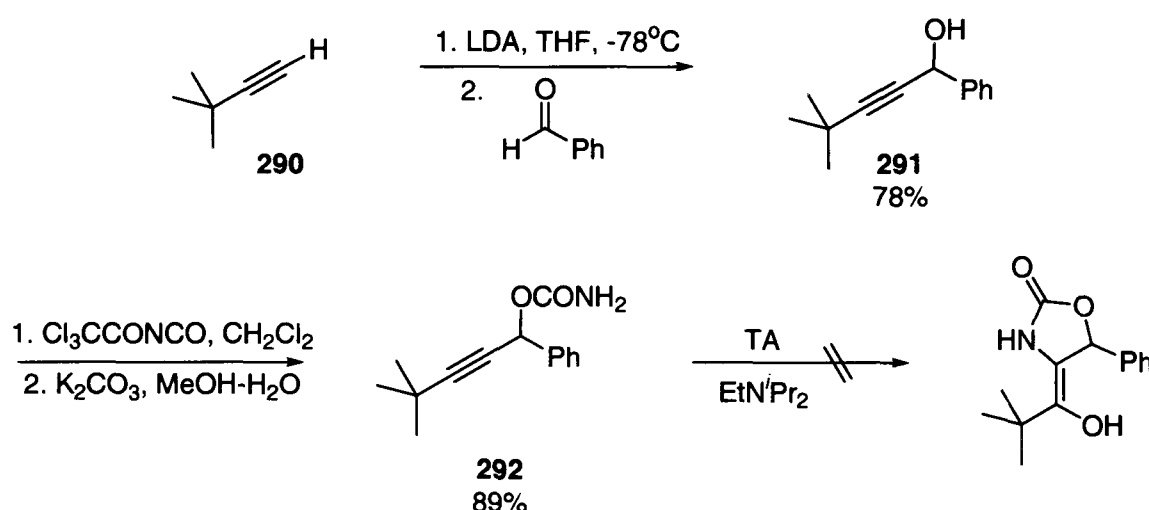
On subjection to the usual carbamation procedure, a mixture of products resulted. Three spots were visible by TLC, two very close-running (R_f 0.68 in 10% EtOAc – petrol) and one of much higher polarity (R_f 0.1 in 10% EtOAc – petrol). The former two spots were a mixture of isomers **284** and **285**, arising by some process of addition and elimination. The lower-running spot was the isomerised carbamate **286**, presumably favoured over the desired **283** by virtue of the extended conjugation. This was disappointing, especially as the TA would give the regioisomeric product to the intermolecular aminohydroxylation as performed by Sharpless (*vide supra*, section 1.6.4). This area of research was not pursued further. It is possible that the benzylic

nature of the alcohol assisted the rearrangement process, and other Baylis-Hillman adducts (e.g **288**, scheme 83) may prove more suitable.



Scheme 83 Potentially successful Baylis-Hillman substrate for the TA

If the TA were performed on an acetylene, the resultant product would be an enol which would likely tautomerise to the ketone (scheme 84). Carbamate **292** was synthesised by addition of alkyne **290** to benzaldehyde (78%), followed by carbamation with trichloroacetyl isocyanate (89%).



Scheme 84 Failed TA of propargylic carbamate **292** TA Reagents and conditions $\text{K}_2\text{OsO}_2(\text{OH})_4$ (4 mol%), EtN^iPr_2 (5 mol%), NaOH (0.92 eq.), $t\text{BuOCl}$ (1 eq.), $n\text{PrOH-H}_2\text{O}$ (5:3), rt

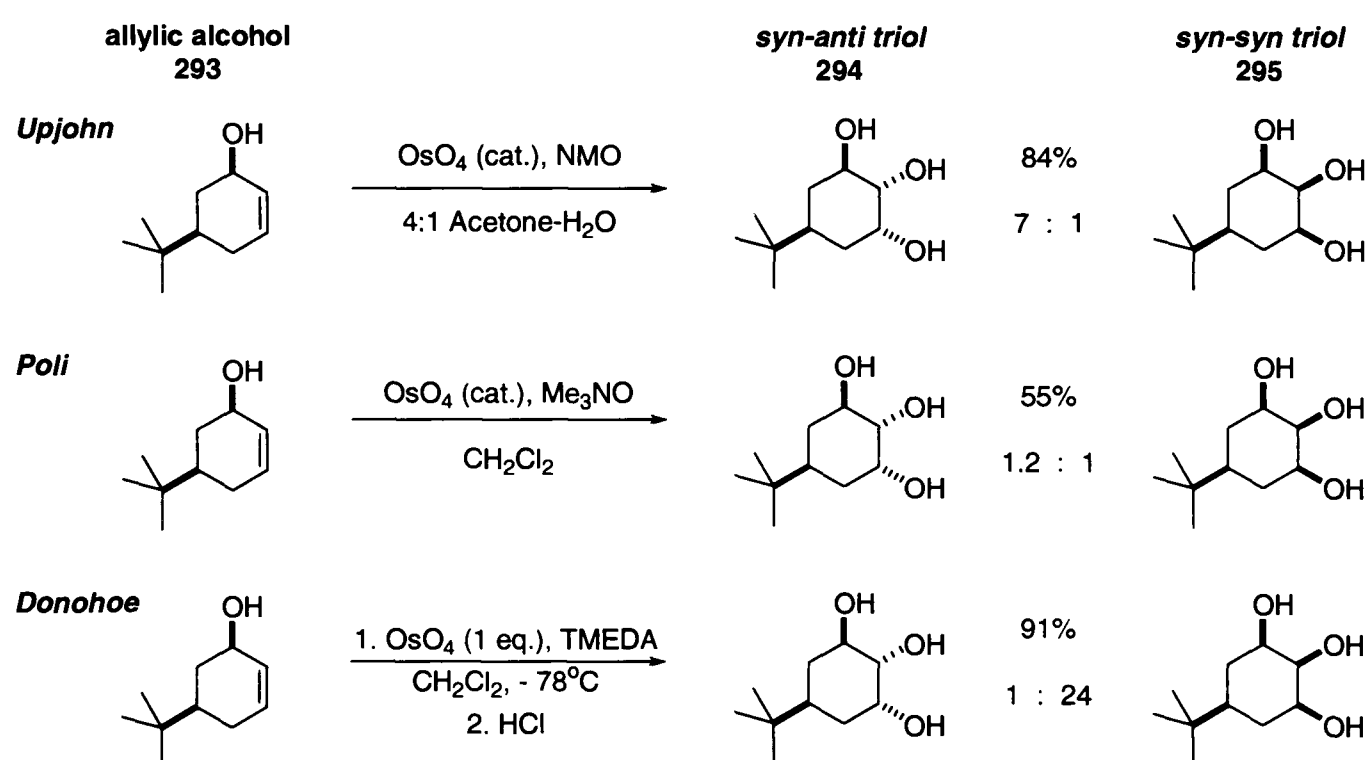
Unfortunately, TA of substrate **292** proved unsuccessful. The reaction showed the usual colour changes from colourless to green and rapidly to yellow, but then turned black within a few minutes. The crude ^1H NMR spectrum only showed starting material of which 80% was recovered by chromatography. Dihydroxylation of triple bonds with osmium tetroxide is a slow process, thought to be due to the electron-rich nature of the alkyne.

2.6 – Isolation of a catalytic intermediate

The previous sections have shown the development of the TA reaction into a useful synthetic tool and its scope in terms of the systems in which it can be employed.⁹⁷ To elucidate better the nature of the catalytic intermediates of the reaction, it was decided to intercept the reaction earlier along the catalytic cycle.

2.6.1 TMEDA directed dihydroxylation of allylic alcohols⁹⁸

Previous work in the Donohoe group had led to the development of a protocol for the formation of *syn-syn* triol units from a corresponding allylic alcohol. Under standard Upjohn dihydroxylation conditions, cyclohexenol **293** gives a 7:1 mixture of the *syn-anti* triol **294** and the all *syn* triol **295** (scheme 85).⁹⁹ This can be rationalised on the basis of steric interactions. The incoming osmium tetroxide reagent is bulky and therefore prefers to oxidise from the opposite face to the hydroxyl group.



Scheme 85 Dihydroxylation of cyclohexenol **293** under protic, aprotic and directed conditions

When the reaction is conducted in an aprotic solvent, such as dichloromethane, this ratio of products is much reduced. Under conditions discovered by Poli,¹⁰⁰ using trimethylamine-*N*-oxide as the stoichiometric reoxidant, the amount of *syn-syn* triol **295** was greatly increased, though it was still the minor product (1.2:1, *syn-anti*:*syn-syn*).

This is attributed to hydrogen-bonding interactions between the hydroxyl proton and an oxo ligand on the incoming oxidant. These interactions direct, to a degree, the oxidation to occur on the same face of the double bond as the hydroxyl group (figure 18).

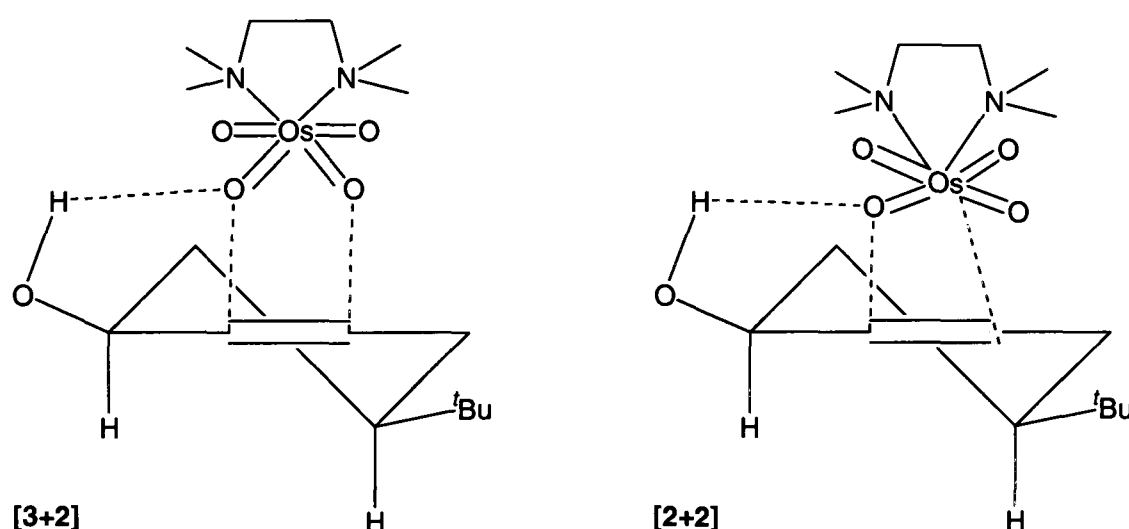
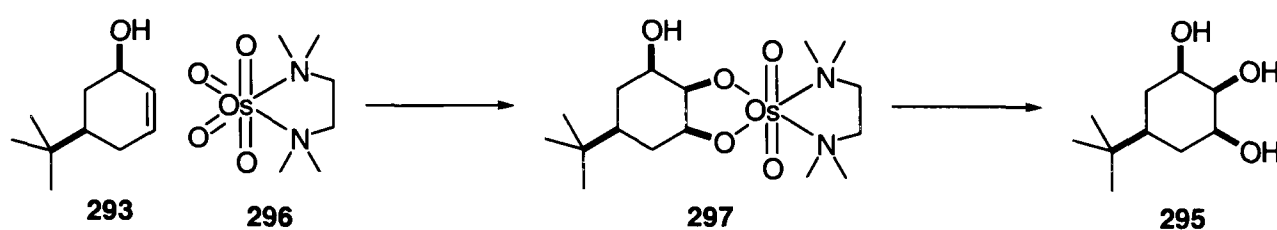


Figure 18 Proposed transition states for hydrogen-bond directed dihydroxylation

Donohoe dramatically enhanced this effect by the addition to the reaction mixture of tetramethylethylenediamine (TMEDA).⁸⁸ TMEDA is a bidentate chelating diamine and an exceptional ligand for osmium. It binds to osmium tetroxide, forming an extremely electron-rich 20-electron complex **296**. This complex is a better hydrogen-bond acceptor than OsO_4 itself, and thus the interaction between substrate **293** and the incoming oxidant **296** is much stronger. The effect is to completely reverse the selectivity of dihydroxylation to give, after acidic cleavage, almost exclusively the *syn-syn* triol **295** (scheme 86).



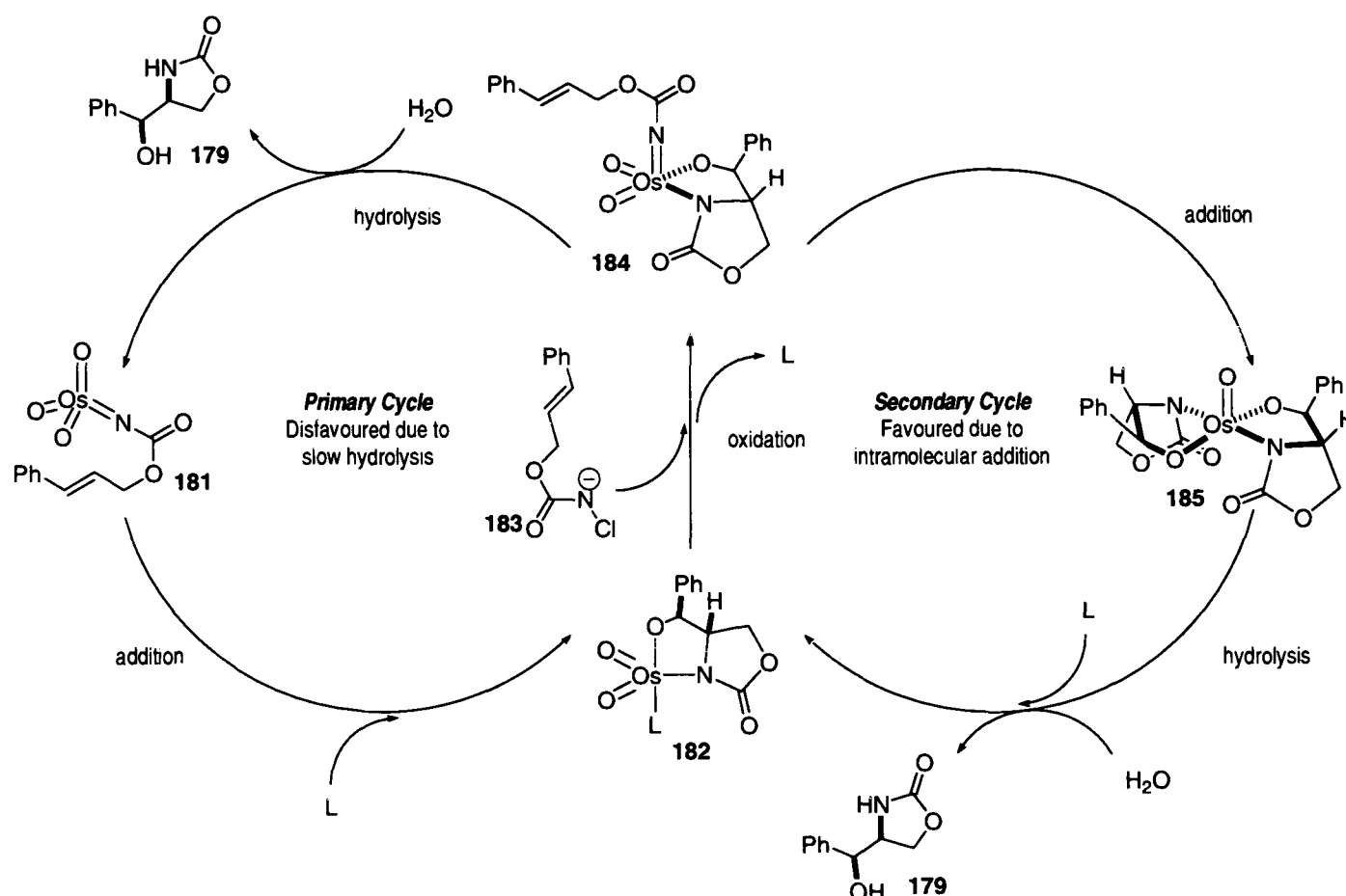
Scheme 86 Osmylation of cyclohexenol **293** and cleavage of osmate diester **297**

A notable feature of this methodology is a requirement for stoichiometric osmium tetroxide, and a cleavage step following oxidation. The 18-electron osmate diester **297** formed from addition of the reagent **296** across the double bond is retardant to hydrolysis, and as such has to date not been made catalytic in transition metal. To cleave the osmaglycolate **297**, a subsequent step must be employed, using either acidic

conditions (conc. HCl), basic conditions (aq. sodium sulfite) or neutral conditions (ethylene diamine). Yields for this cleavage step were high and can be carried out in the same pot, so the inconvenience of this step is minimised.

2.6.2 TA incorporating TMEDA as a ligand⁸²

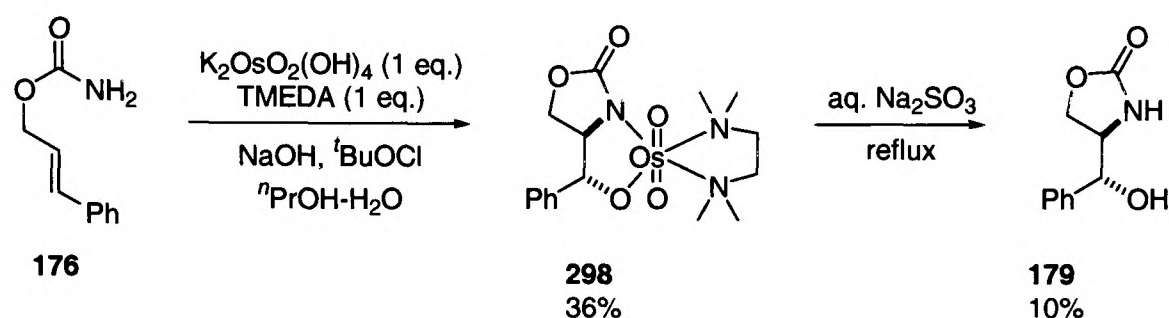
The stability of TMEDA osmate esters was an attractive attribute for studies on catalytic intermediates in the TA. The azaglycolate osmate esters formed are known to be more resistant to hydrolysis than the glycolates formed from dihydroxylation, as exemplified by Sharpless' unsuccessful early attempts to make the carbamate variant of the AA catalytic.



Scheme 87 Catalytic cycle for the tethered aminohydroxylation

It was envisaged that introduction of TMEDA to the TA would result in complex 182 (L = TMEDA) being resistant to hydrolysis and thus potentially isolable. To this end, the TA of *trans*-cinnamyl carbamate was revisited. The conditions were adjusted so as to maximise the chances of both formation and isolation of the product osmate ester. Water was not added to the system, as hydrolysis was no longer a

required step. Stoichiometric TMEDA was added in place of catalytic Hünig's base. Finally, one equivalent of potassium osmate was used.



Scheme 88 Trapping of osmate ester intermediate **298** from TA and cleavage to oxazolidinone **179**

The reaction was unsuccessful. It became immediately apparent that the lack of water in the system caused solubility problems for both sodium hydroxide and potassium osmate. Without the aid of an aqueous basic solution, the transition metal salt was simply suspended in the reaction mixture. The reaction was repeated, this time introducing a small amount of water to solubilise both the base and potassium osmate (scheme 88). A brown solution resulted. The reaction was stirred overnight, then concentrated and purified directly by column chromatography ($\text{MeOH} - \text{CH}_2\text{Cl}_2$ mixtures). A polar, orange material was isolated after column chromatography.

The product **298** was a red-orange solid that grew as dendritic crystals on evaporation. The ^1H NMR showed four distinct methyl peaks between 2.87 and 3.31 ppm, belonging to the TMEDA ligand. There were five aromatic protons, indicating the presence of a phenyl group, and four separate signals from 4.17 to 4.96 ppm belonging to the backbone hydrogens as indicated in figure 19. ^{13}C NMR and mass spectral data also corresponded with the proposed structure, including a matching isotope pattern for osmium in the high-resolution mass spectrum.

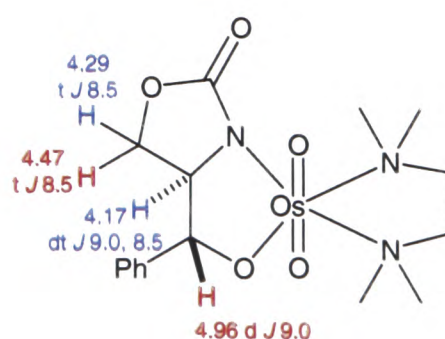
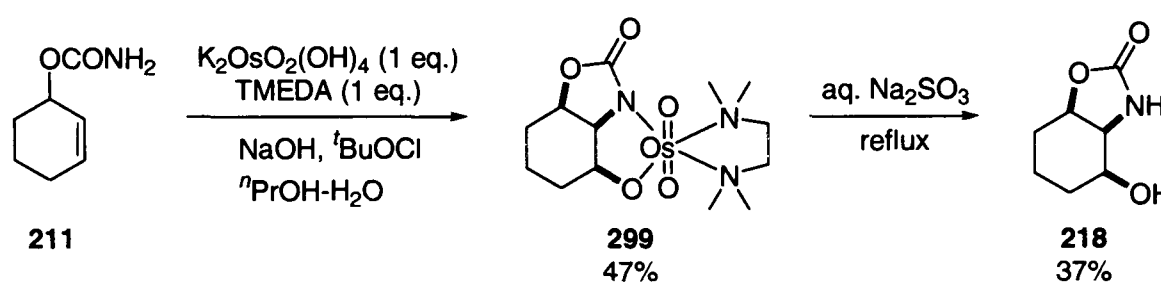


Figure 19 Selected ^1H NMR data for osmate ester **298**

Confirmation of the structure of **298** was obtained by cleavage of the ester using refluxing aqueous sodium sulfite to obtain the oxazolidinone **179**. The yield for this step was poor (10%), presumably due to hydrolysis of the oxazolidinone to give the corresponding aminodiol.

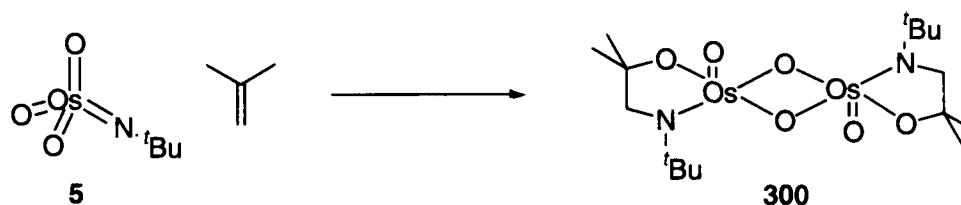
Thus an intermediate had been isolated, confirming at least in part the proposal for the catalytic cycle. Disappointingly however, and despite the obvious crystalline nature of **298**, attempts to grow a crystal for X-ray analysis proved fruitless. Consistently the dendritic nature of the crystal packing made for uselessly thin crystals.



Scheme 89 Synthesis and cleavage of azaglycolate osmate ester **299**

A second osmate ester was therefore synthesised in an attempt to provide crystals. Cyclohexenyl carbamate **211** was subjected to the same conditions as **176**, to give after chromatography 47% of the osmate ester **299** (scheme 89). This could be hydrolysed with refluxing aqueous sodium sulfite to give the oxazolidinone **218**, proving its structure.

This time, crystals were successfully grown, and we were able to obtain what is only the second azaglycolate osmate ester crystal structure. Importantly, however, this is the first to be isolated from a *catalytic* system, and is the first to show stereochemistry with respect to the addition. The only prior example (scheme 90) resulted from the addition of stoichiometric $\text{O}_3\text{Os}=\text{N}^t\text{Bu}$ **5** across isobutylene.¹⁰¹



The structure of **299** shows three key features. The first is the TMEDA ligand chelating the osmium metal centre. The second is the *syn* arrangement of the three heteroatoms around the ring, exactly as in the oxazolidinone product. The third and most important is the direct linkage between the nitrogen of the carbamate and the osmium metal. This indicates that, as proposed, the nitrogen has been involved in oxidation of the metal at some stage in the catalytic cycle.

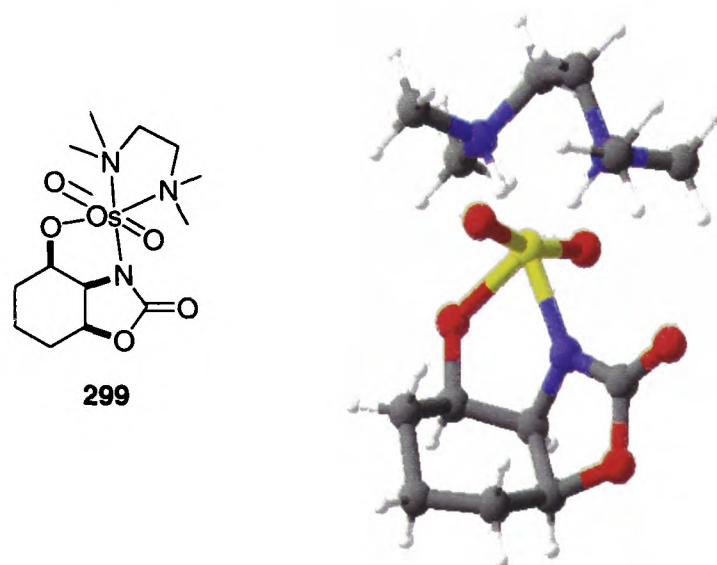
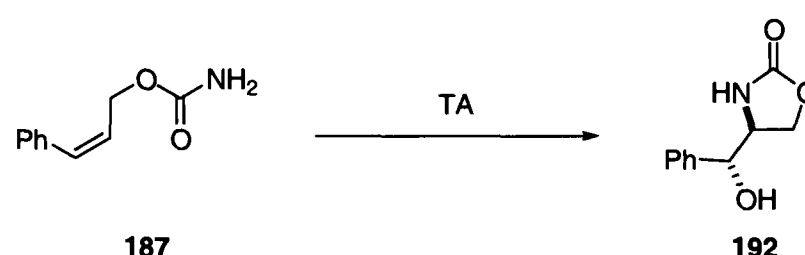


Figure 20 Crystal structure of osmate ester **299**

2.7 – Second cycle catalysis of the TA

As mentioned earlier (section 1.6.2), Sharpless has recently developed a number of so-called second cycle ligands for catalysis of dihydroxylation and aminohydroxylation.^{48, 49} Given the lack of enantioselectivity in the TA using commercially available Sharpless ligands, it was decided to attempt the reaction using these alternatives.

Sharpless details the use of a number of *N*-tosyl aminoalcohols to attain moderate levels of asymmetric induction in the AA. These studies only incorporated one of these – *N*-tosyl threonine **120**. In addition to the use of these enantiopure second-cycle ligands, sodium citrate had been employed as a racemic alternative, and this was also tried. The first substrate to be examined was *cis*-cinnamyl carbamate **187**. The reaction conditions were identical to the established protocol (section 2.4.7), with the alteration that instead of 5 mol% of Hünig's base, 20 mol% of the second-cycle catalyst was added. The results are outlined in table 29.



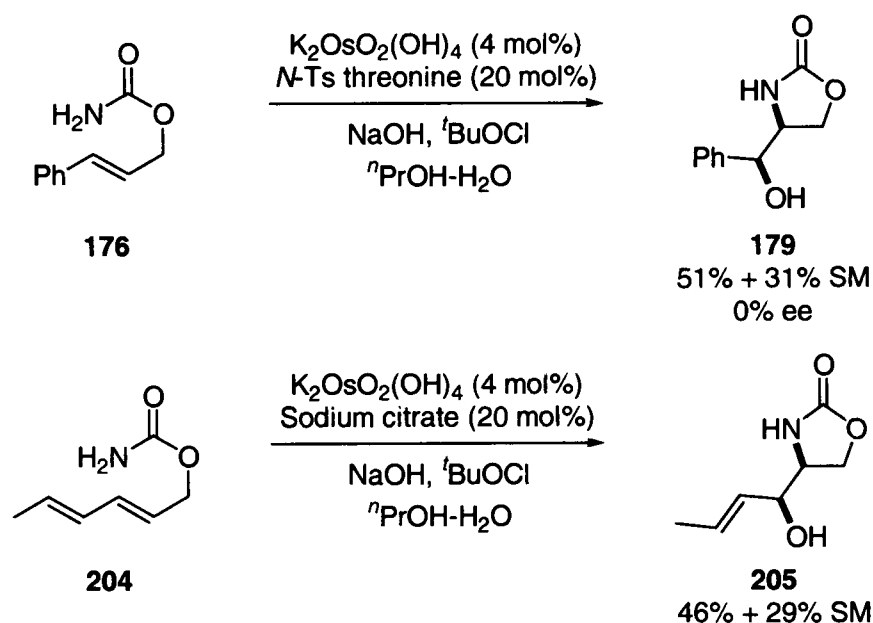
Ligand	Mol %	Yield (%)	SM (%)	ee (%)
EtN ^{<i>i</i>} Pr ₂	5	61	12	0
Sodium citrate	20	74	11	0
<i>N</i> -tosyl threonine	20	54	20	0

Table 29 Use of second-cycle ligands in the TA of *cis*-cinnamyl carbamate **187** K₂OsO₂(OH)₄ (4 mol%), EtN^{*i*}Pr₂ (5 mol%), NaOH (1 eq.), ^{*t*}BuOCl (1 eq.), ^{*n*}PrOH-H₂O (5:3), rt

Hünig's base gave a 61% yield of the oxazolidinone **192**. *N*-tosyl threonine gave a similar yield, but the best was achieved by sodium citrate, affording 74% of the product. Increased amounts of Hünig's base led to contamination of the product. Other

improvements were also evident in the use of sodium citrate. The reaction mixture did not go black at the end of turnover, instead remaining a bright orange colour. While this made the crude assessment of the end of turnover difficult, it did entail a simpler and notably cleaner workup procedure, without the usual difficulties in visualising the partition. *N*-tosyl threonine also gave a simpler work-up, although in this instance the final colour of the solution was a deep orange-red.

Encouraged by the results, other substrates were also tried using these ligands (scheme 91). *Trans*-cinnamyl carbamate **176** gave an unimproved 51% yield using **120** as the ligand, while surprisingly did not seem to give any product with sodium citrate. This is suspected to be anomalous, although time constraints on this area of the project have meant that this reaction has not yet been repeated. Sorbyl carbamate **204** also underwent the TA using sodium citrate, though again no improvement in yield was seen compared to the TA using Hünig's base.



Scheme 91 TA of primary carbamates using second-cycle ligands

The enantiomeric excess of the material obtained from the *N*-tosyl threonine reactions was determined using chiral HPLC. As can be seen from the traces in appendix I, all material obtained was racemic. Clearly the benefits of second-cycle catalysis seem, at this point, to be in the simplicity they lend to the protocol. Sodium citrate is a white crystalline solid and as such is easier to handle than Hünig's base. In addition the work-up is simplified by the removal of the insoluble black residues associated with low oxidation state osmium complexes. Further work is required to determine whether this approach can impart absolute stereocontrol on the reaction.

Introduction II

Hygromycin A

3.1 – Applications of the AA reaction

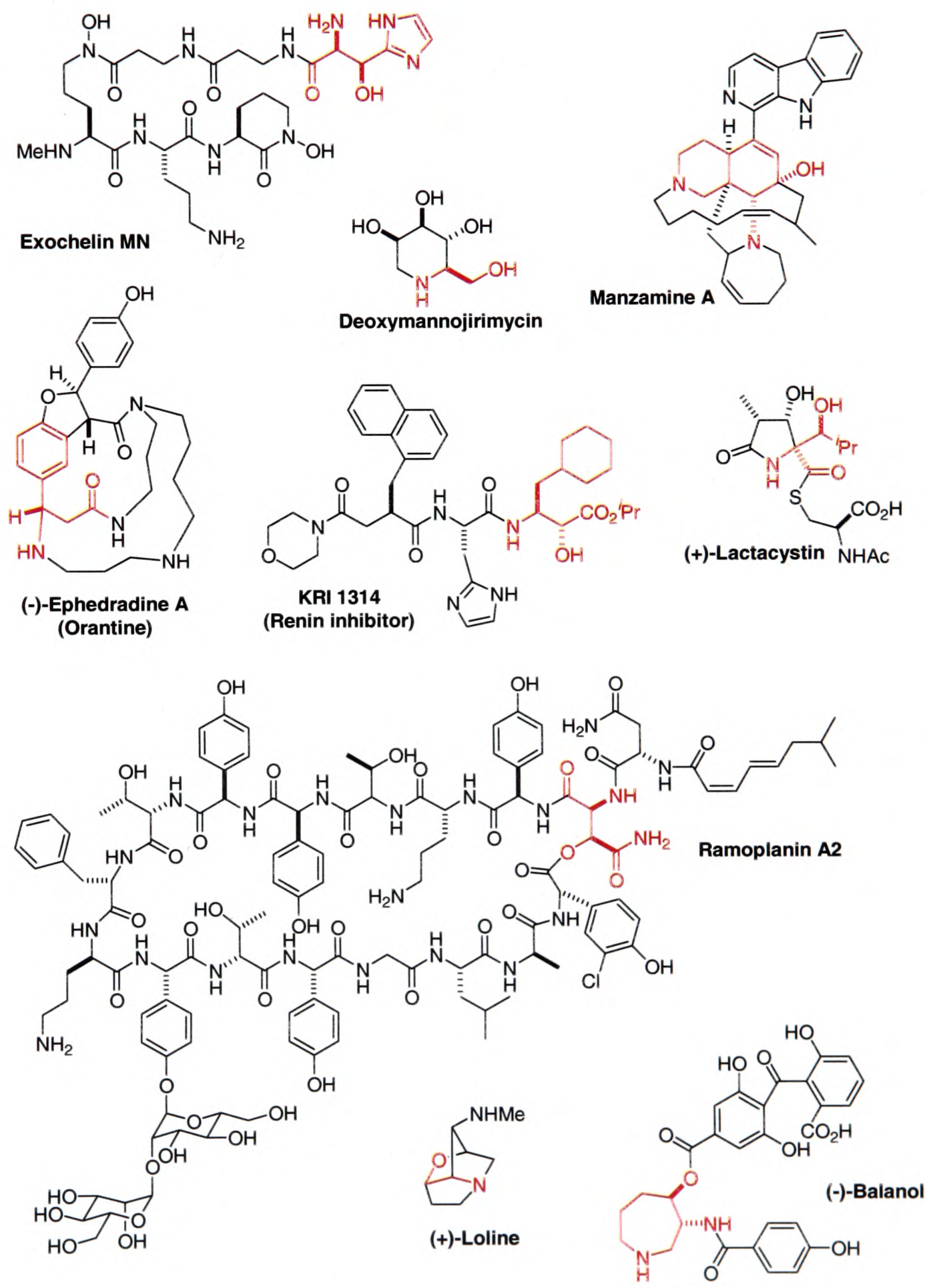
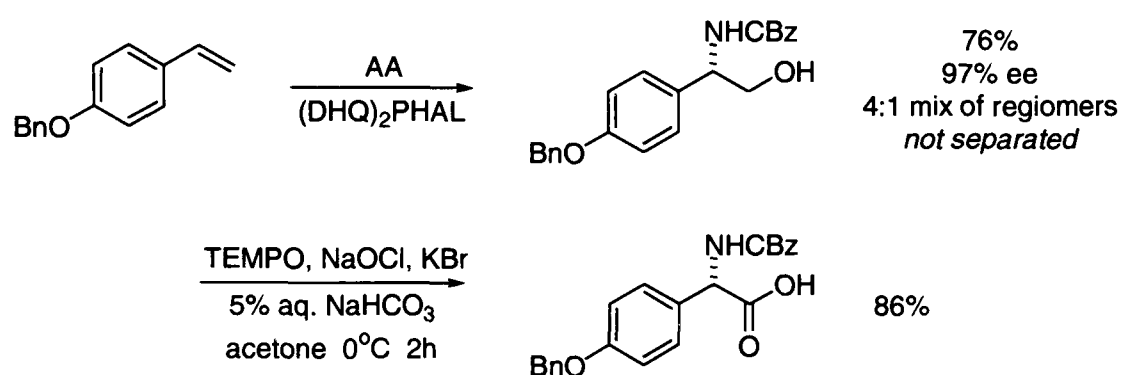


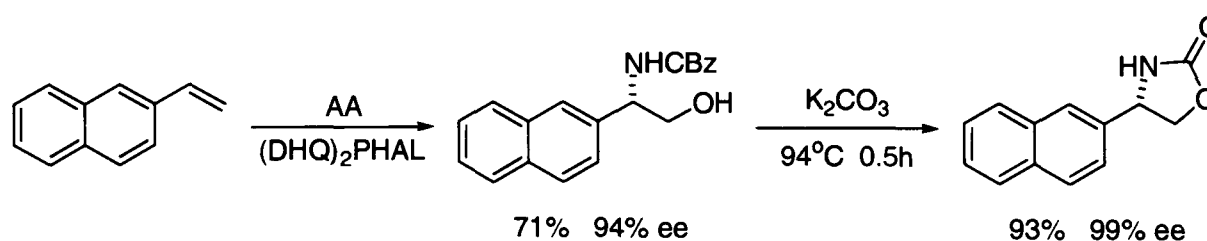
Figure 21 The AA in total synthesis

The asymmetric aminohydroxylation obviously has great synthetic utility as a stereospecific oxidation, and has duly found its way into a number of total syntheses of natural products. Figure 21 shows numerous natural products whose syntheses, or approaches towards, have included the AA at some stage.^{60, 102-107} The key fragment of lactacystin, as synthesised by Panek, has been mentioned earlier (section 1.7.4),^{55, 108} as have the total synthesis of ustiloxin D by Jouillé^{70, 109} and Sharpless' rapid, large-scale synthesis of the taxol side-chain.²⁹ Boger's total synthesis of ramoplanin A2 incorporates a non-proteinogenic amino acid, 3-hydroxyasparagine.¹¹⁰



Scheme 92 Sharpless' brief synthesis of arylglycines

Sharpless has applied the AA to the synthesis of unnatural arylglycines (scheme 92).⁵⁰ Aminohydroxylation of a substituted styrene, followed by TEMPO/bleach oxidation to the acid gave rapid access to the products in enantiopure form. Styrenes also formed the basis for Li's synthesis of novel Evans-type auxiliaries (scheme 93).¹¹¹ Aminohydroxylation in this instance was followed by neat basic cyclisation to give the oxazolidinones directly.



Scheme 93 New Evans' auxiliaries via the AA

Han and Janda pursued their protecting group directing approach, applying it to the synthesis of a number of chiral building blocks. Among them were aminobutanetriols,¹¹² polyhydroxypiperidines¹¹³ and diaminobutanoic acids.¹¹⁴

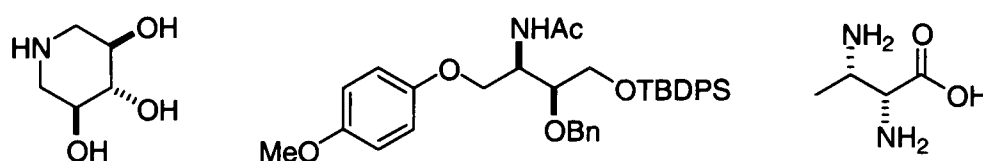


Figure 22 Chiral building blocks assembled by Han and Janda

The diversity of structure evident in the published syntheses reflects the utility of the AA as a synthetic tool. It was our hope that the TA would be as useful; to demonstrate this, a synthesis of the natural product hygromycin A was undertaken.

3.2 – Isolation and SAR of hygromycin A

Hygromycin A is an antibiotic first isolated from the fermentation broth of *Streptomyces hygroscopicus* in 1953.¹¹⁵⁻¹¹⁹ It was quickly identified as having a broad spectrum of activity against both Gram-positive and Gram-negative bacteria.^{115, 116} Its mode of action is peptidyl transferase inhibition, sharing a binding site on the ribosome with chloramphenicol.¹²⁰ More recent studies have shown that it also has hemagglutination inactivation activity,¹²¹ plus high antitreponemal activity.^{122, 123} This has led to renewed interest in hygromycin A as a treatment for swine dysentery, a mucohemorrhagic disease of economic importance to pig farmers.

A series of semi-synthetic modifications to hygromycin A were published by a group from Pfizer in the mid-90's.¹²⁴⁻¹²⁸ A pharmacophore model was developed, arising from the structure-activity relationships they investigated. The highlights of their studies are presented in figure 23. The most surprising result was that the loss of the furanoside unit was not necessarily detrimental to the activity.¹²⁹ Replacement of the sugar by an allyl group was in fact sufficient to maintain the activity, making further studies simpler. In addition, this would remove the complication of hygromycin A naturally occurring as a mixture of epimers at C-4. The aminocyclitol appeared to be critical for the activity of the compound. Systematic removal of functionality indicated that the C-2 and C-5 hydroxyls, in particular, were of crucial importance.^{125, 126} Methylation of these positions led to a drop in activity. The methylene acetal, in addition to being the symmetry-breaking element of the aminocyclitol, is essential for restricting the conformation of the unit.

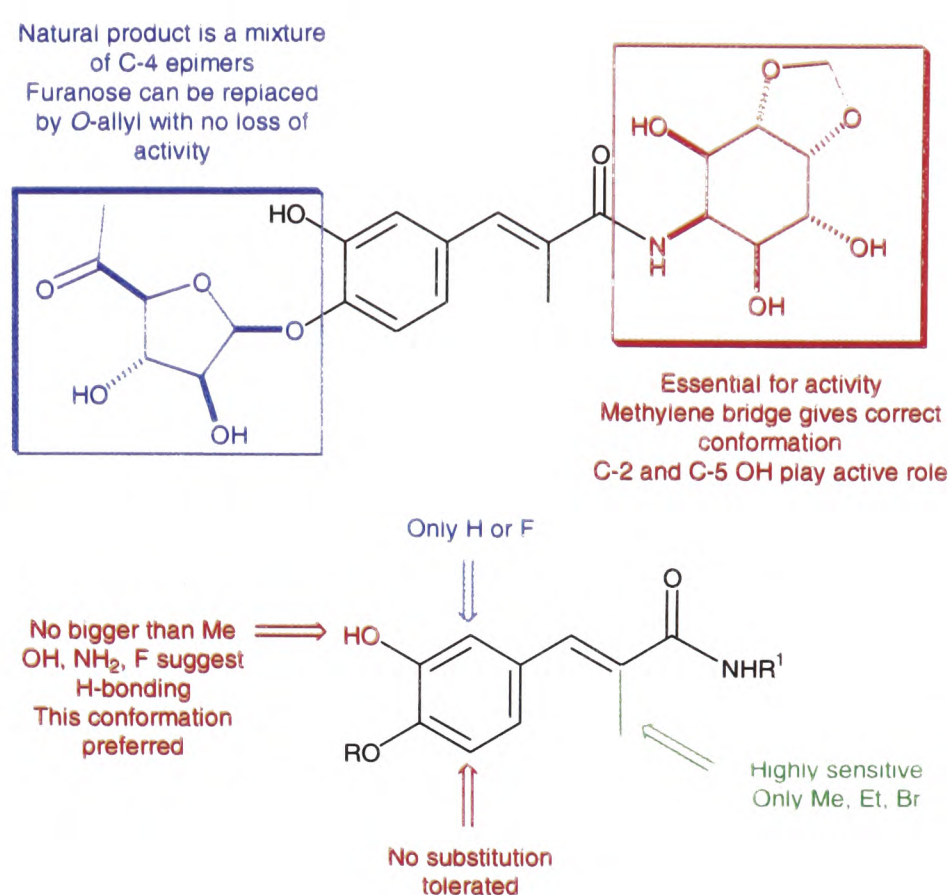


Figure 23 SAR summary for hygromycin A

The aryl linker portion is actually remarkably sensitive to substitution. The C-2 and C-5 positions offered little scope for variation without significant loss of activity,¹²⁷ while the methyl substituent on the benzylic double bond could only be moderately increased in size.¹²⁴ Most interesting was the substitution of C-3. The natural activity was only retained if a hydroxyl or free amine was positioned there. In addition, the synthesis of rotationally constrained analogues had shown that the depicted arrangement was preferred.¹²⁸ These in conjunction pointed to the presence of hydrogen bonding to the C-3 substituent.

3.3 – Ogawa's synthesis of hygromycin A

To date, there has been only one total synthesis of hygromycin A, completed by Seiichiro Ogawa and co-workers in 1989.^{130, 131} The key disconnections (figure 24) involve breakage of the amide bond and the anomeric linkage in the furanoside unit. The aromatic linker fragment was to be introduced as a vanillin derivative. The furanoside and aminocyclohexitol would be derived from D-glucose.

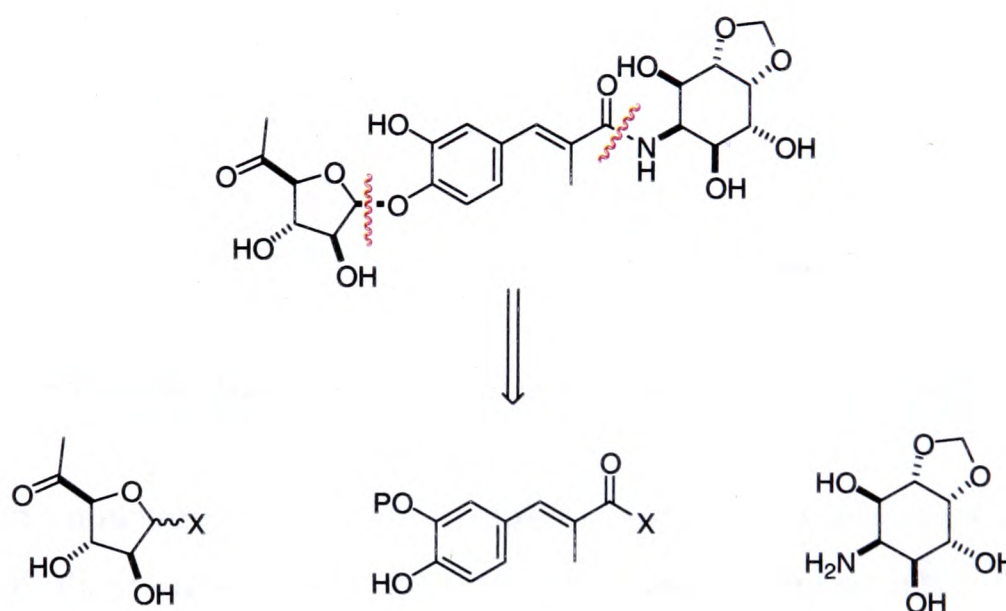
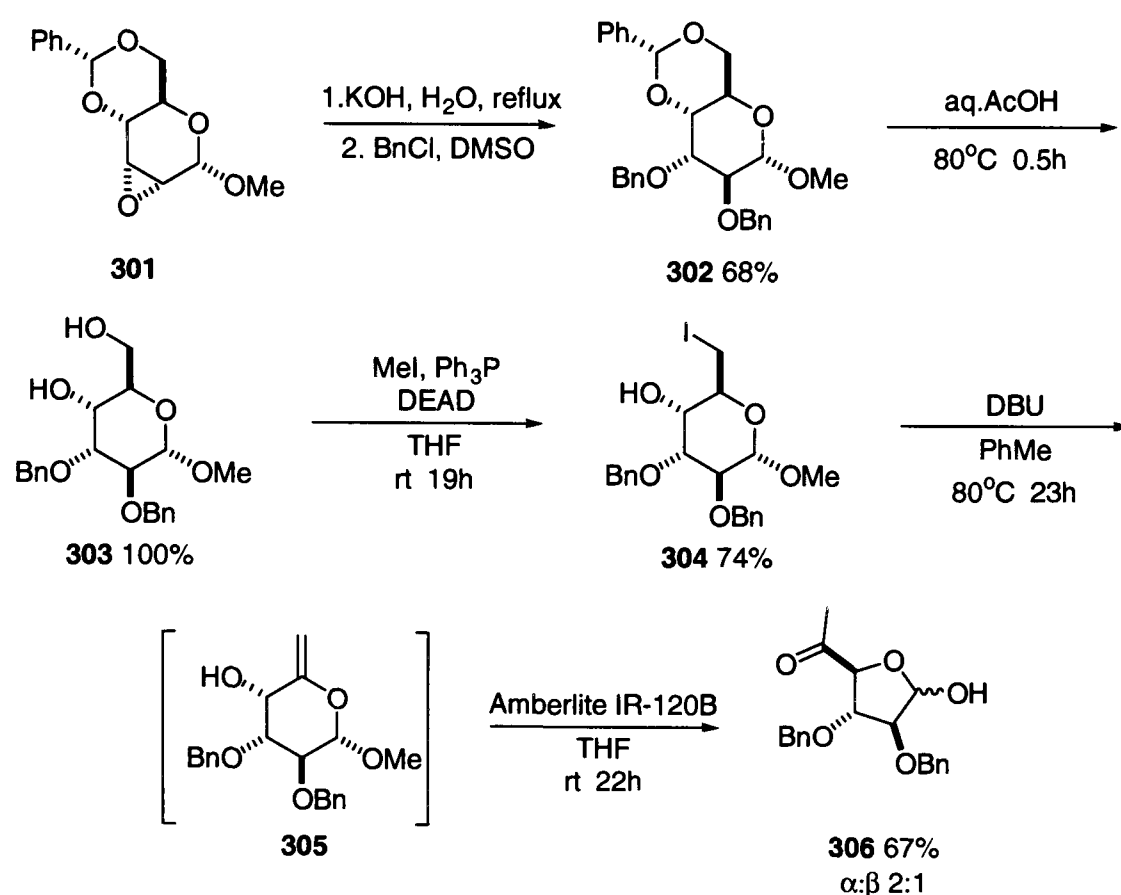


Figure 24 Disconnection of hygromycin A

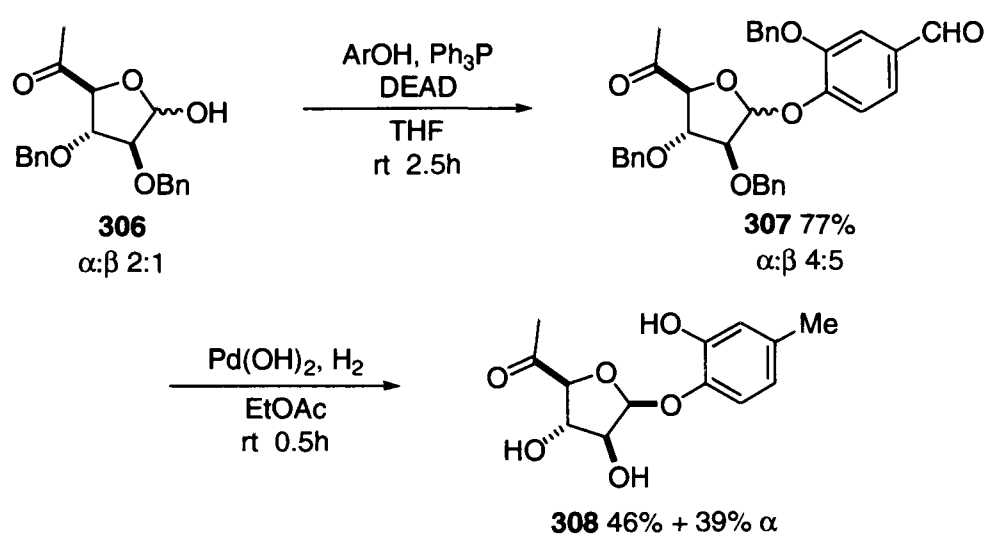
3.3.1 Synthesis of furanoside 313

Borrowing heavily from earlier work by Takahashi and Nakajima, Ogawa first began the synthesis starting from the known compound **301**.¹³² The epoxide was opened selectively with potassium hydroxide, then benzylated *in situ* to give the bis-benzyl ether **302** (scheme 94, 68%). Deprotection of the benzylidene acetal with aqueous acetic acid proceeded quantitatively to give diol **303**, which was iodinated at the primary centre under Mitsunobu conditions in 74% yield. This was eliminated with DBU to give the sugar precursor **305**, which was hydrolysed directly to obtain the furanoside **306** as a 2:1 mixture of anomers (67%).



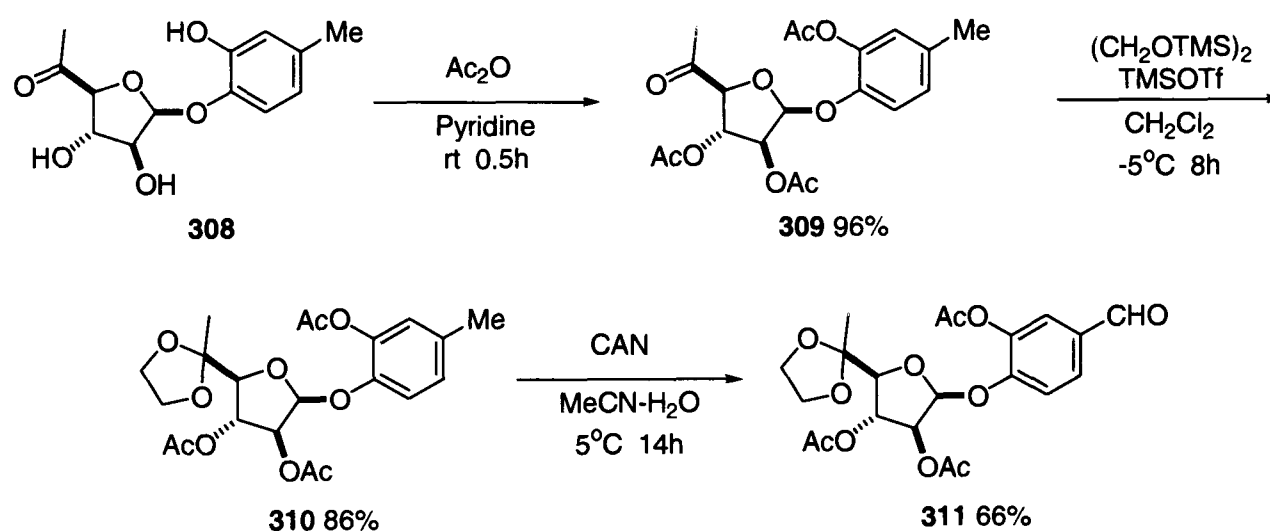
Scheme 94 Ogawa's synthesis of the furanoside and aromatic linker

Again employing Mitsunobu conditions, and using a monoprotected catechol accomplished the installation of the anomeric linker (scheme 95). The anomers remained inseparable by chromatography at this stage, so the condensate was obtained as a mixture (α : β 4:5, 77% combined yield). Removal of the three benzyl groups was accompanied by an unfortunate reduction of the aldehyde that proved unavoidable under all standard hydrogenolysis conditions. The deprotected and reduced anomers were separable at this stage, allowing access to the pure, desired β anomer in 46% yield, with 39% of the α anomer.



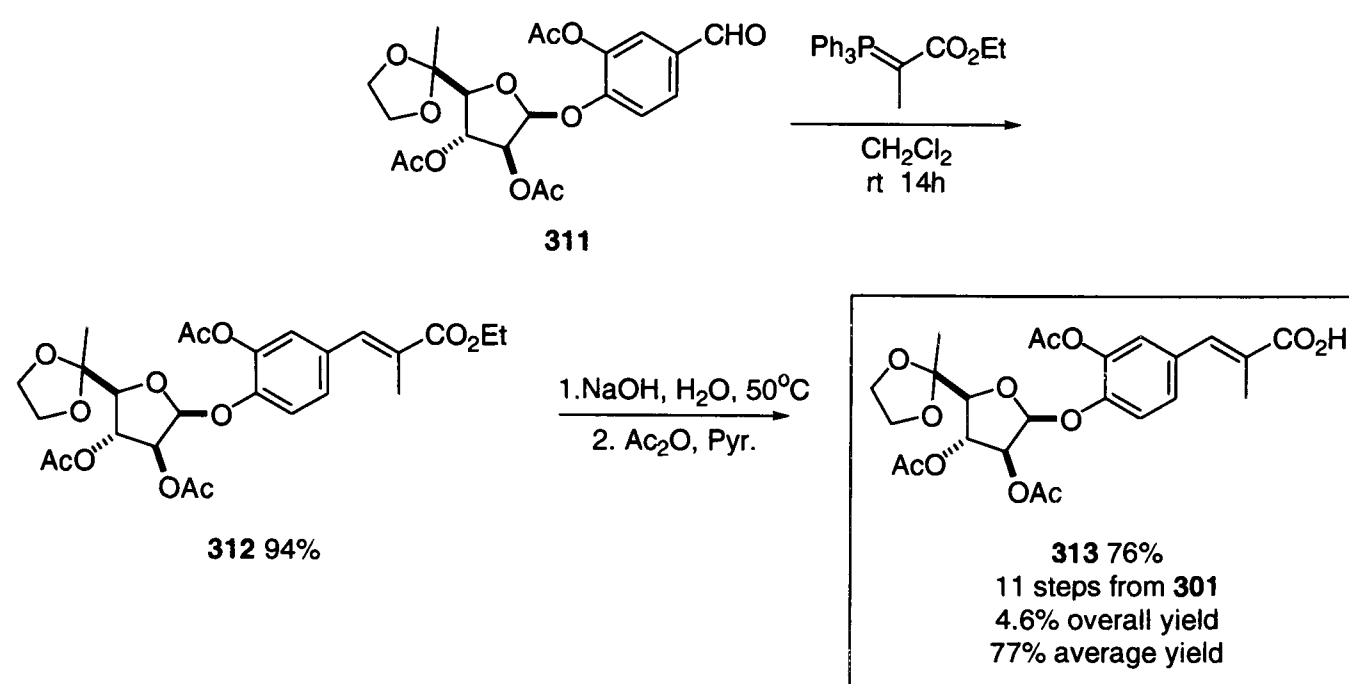
Scheme 95 Ogawa's synthesis of the furanoside and aromatic linker

Peracetylation of the β anomer gave triacetate **309** (scheme 96, 96%), followed by attempted oxidation of the aryl methyl group. Using ceric ammonium nitrate and regenerating the formyl group at this stage proved low yielding (30-35%). It was reasoned that the methyl ketone moiety was interfering with this process and so was protected. Standard acidic conditions for the introduction of the acetal led to decomposition of the substrate, but Noyori's conditions granted success, affording the ketal **310** in 86% yield.¹³³ Subsequent CAN oxidation of the benzylic methyl group to the aldehyde **311** proceeded in 66% yield, almost twice that observed for the unprotected ketone.



Scheme 96 Ogawa's synthesis of the furanoside and aromatic linker

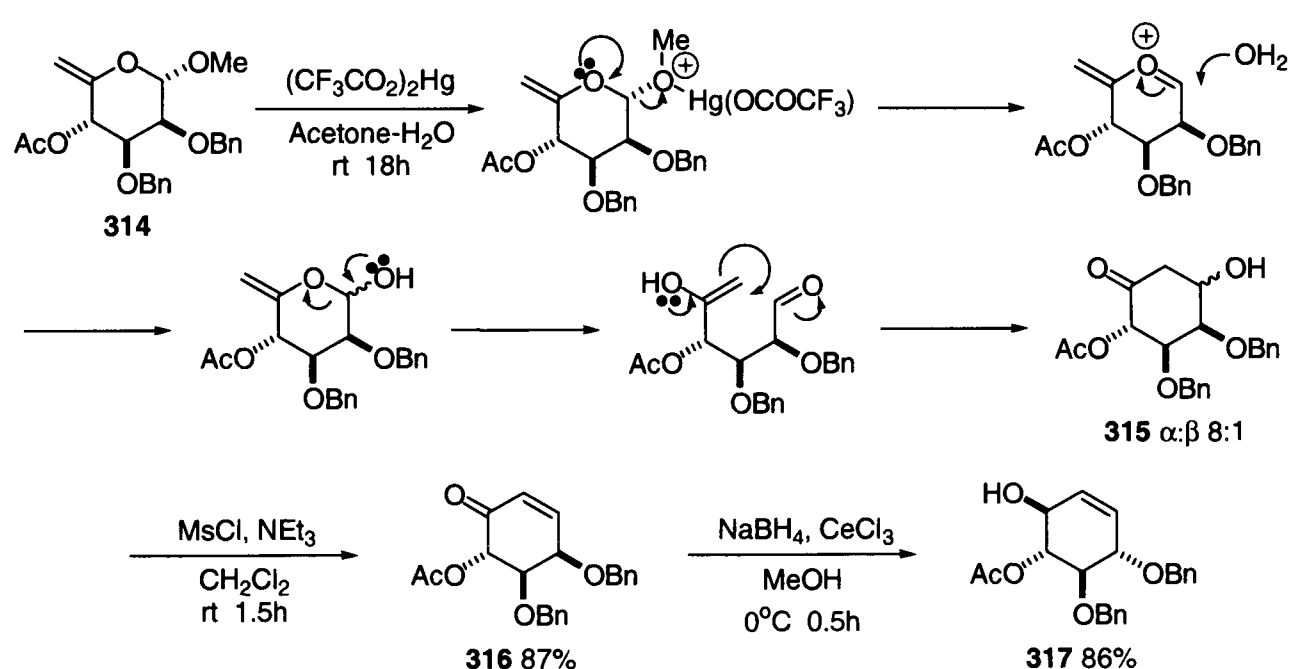
Elaboration of the linker fragment was accomplished by a stabilised Wittig olefination using $\text{Ph}_3\text{P}=\text{C}(\text{Me})\text{CO}_2\text{Et}$ (scheme 97). Only the *E* isomer was formed, giving the ester **312** (95%). To obtain the acid required for coupling, the ester was saponified with NaOH, and then reacetylated (Ac_2O , pyridine) to give **313** in 76% yield.



Scheme 97 Ogawa's synthesis of the furanoside and aromatic linker

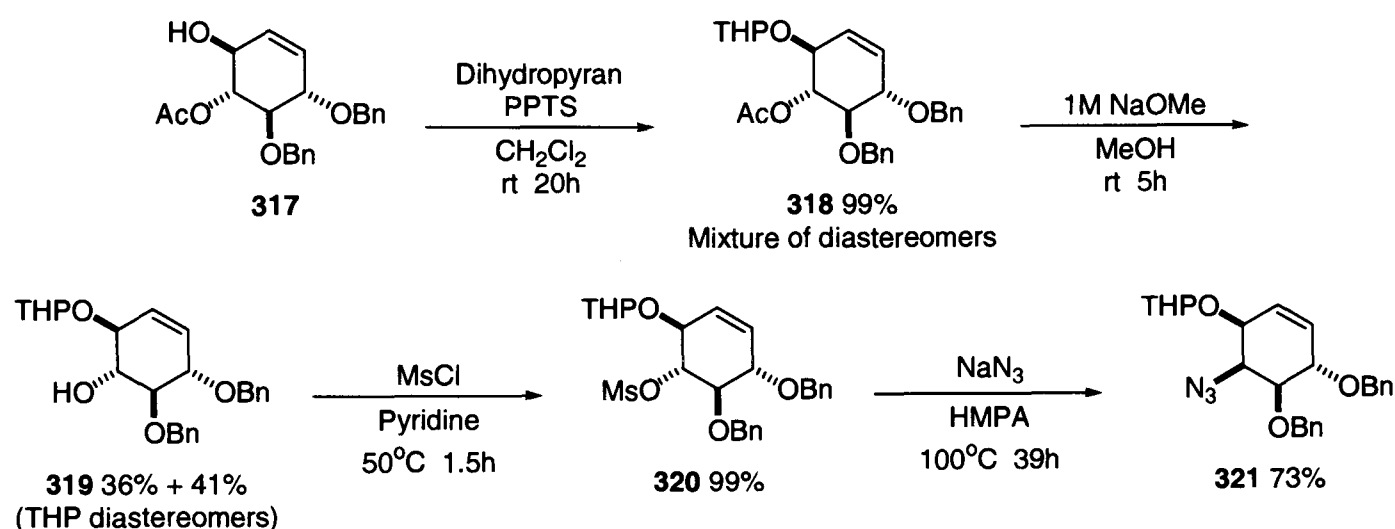
3.3.2 Synthesis of aminocyclohexitol 327

Again starting from glucose, Ogawa used literature precedent to arrive at the methylenated compound **314** in 7 steps and 40% overall yield.¹³⁴ Ferrier rearrangement (scheme 98) using mercuric trifluoroacetate allowed mutarotation to give a mixture of isomers of the hydroxy-ketone **315**.¹³⁵ Without isolation, the alcohol of **315** was eliminated *via* mesylation to give the enone **316** in 87% overall yield. 1,2 reduction of the ketone under Luche conditions occurred with complete stereoselectivity giving 86% of **317**.⁸⁴



Scheme 98 Ferrier rearrangement of 314

Protection of the free hydroxyl as the tetrahydropyranyl ether **318** (99% and removal of the acetate (77%) gave access to a mixture of diastereomers **319**, arising from the introduction of the THP ether. They were separated at this stage to simplify product analysis in future steps, which all gave virtually identical yields for each diastereomer. Introduction of the requisite nitrogen was achieved by first converting the free alcohol to the mesylate **320** (99%), and then displacing with azide in HMPA (73%). Problems were then encountered on trying to introduce the remaining oxygen atoms *via* dihydroxylation.



Scheme 99 Ogawa's synthesis of the aminocyclohexitol

It was expected that the axial conformation of the azido group would be enough to encourage predominant dihydroxylation with OsO_4 from the α -face. Treatment of **321** with OsO_4 and *N*-methylmorpholine-*N*-oxide in *tert*-butanol-THF-water oxidised preferentially from the β -face to give the undesired isomer as the major product (figure 25).

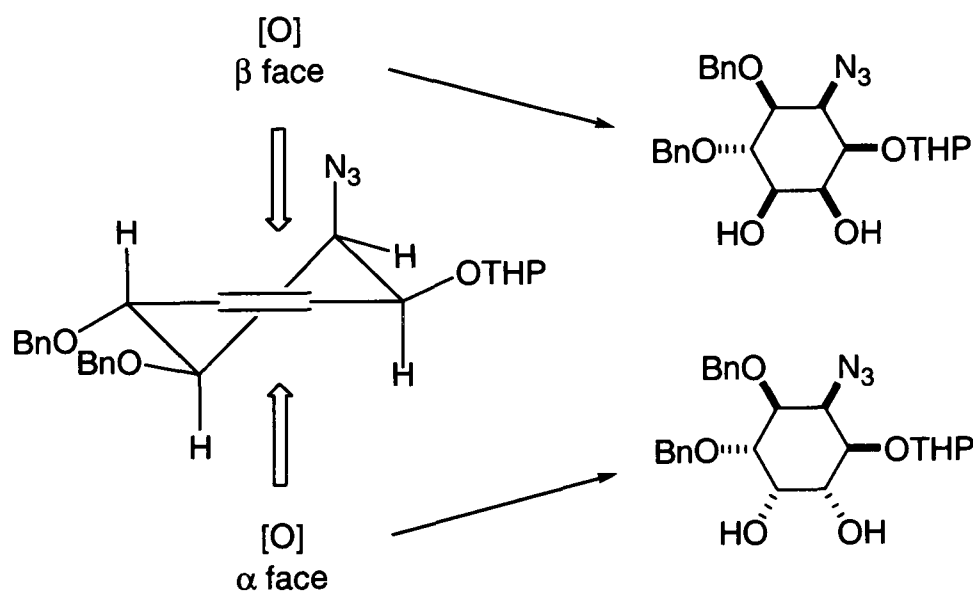
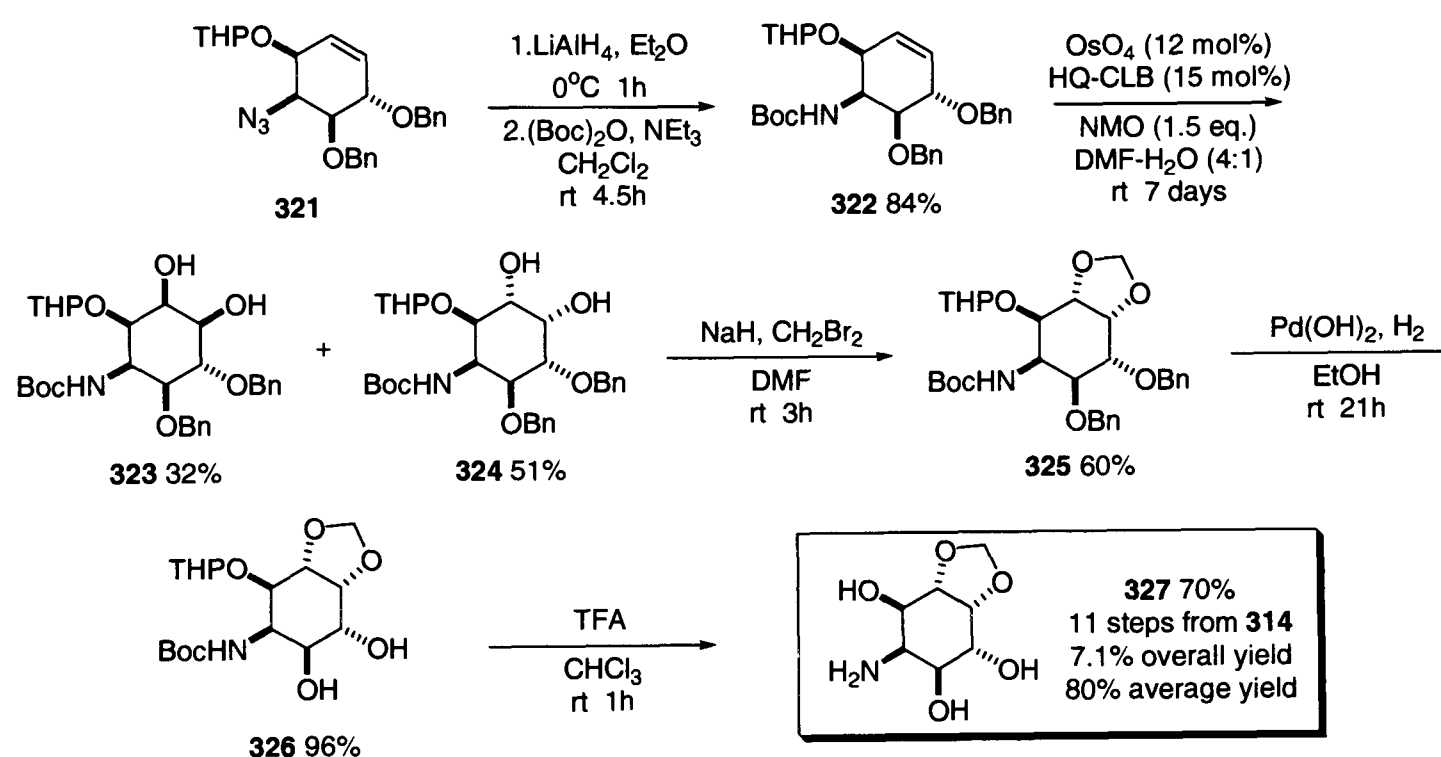


Figure 25 Dihydroxylation of the cyclohexene system

The azide was therefore converted to the bulkier Boc-protected amine **322** to enhance this effect. Unfortunately this had only a minor effect on the observed selectivity. A screen of many solvents and ligands for the reaction eventually discovered DMF-water and the Sharpless ligand hydroquinine 4-chlorobenzoate as giving an improved 62:38 ratio of isomers, now in favour of oxidation from the α -face (scheme 100). At the time of this synthesis, the second-generation Sharpless ligands had not been invented, and it is not known whether these would be of benefit in this system.



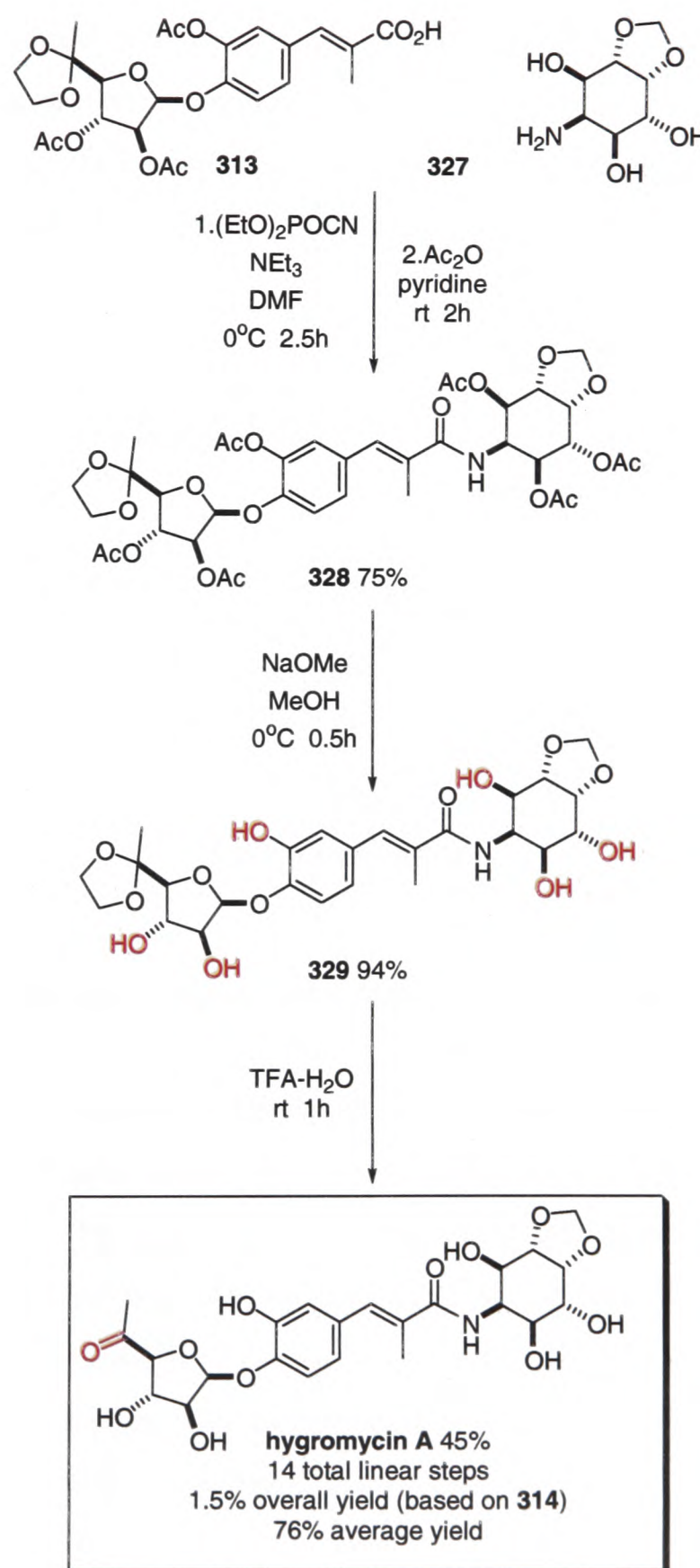
Scheme 100 Ogawa's synthesis of the aminocyclohexitol

Introduction of the methylene acetal was performed using sodium hydride in DMF, giving 60% of **325**. Subsequent removals of the benzyl groups by hydrogenolysis (Pearlman's catalyst, 96%) and of the Boc and THP ether by acid (70%) gave the Hygromycin A aminocyclitol **327**.

3.3.3 Final steps of the synthesis

The completion of the synthesis required the formation of the amide bond between the aminocyclitol and linker portions. It was found that while DCC coupling was unsuccessful in this instance, application of Shiori's protocol using

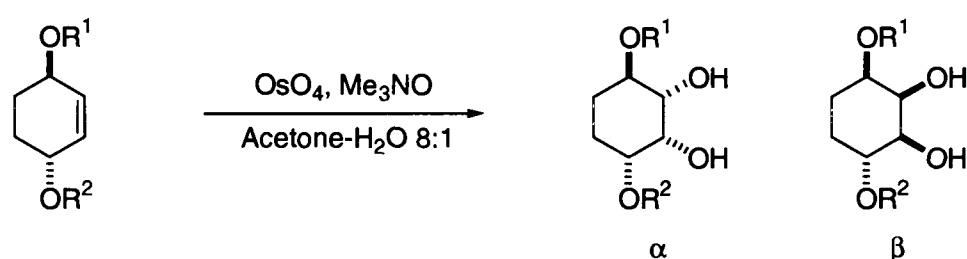
diethylcyanophosphonate and triethylamine gave the amide **328** in 75% after peracetylation.¹³⁶ Final isolation of the natural product was accomplished by removal of the purification-simplifying acetates (sodium methoxide, 94%) and the ketal (TFA, 45%). The synthesis had produced hygromycin A in an overall yield of 1.5%, an average yield of 76% and a total of 14 linear steps.



Scheme 101 Completion of Ogawa's synthesis

3.4 – Arjona's formal synthesis of hygromycin A

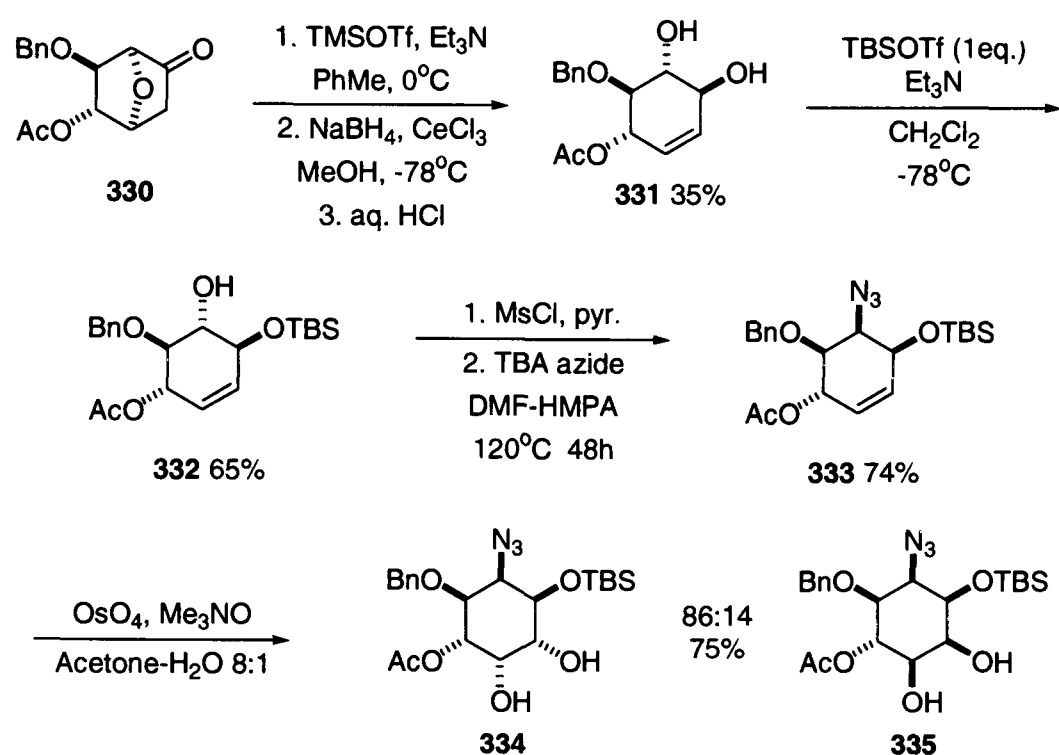
A subsequent discovery, by Arjona and co-workers, showed that the electronic nature of the allylic substituents in these cyclohexene systems could influence the facial bias of dihydroxylation (table 30).¹³⁷ Through utilisation of one bulky substituent (R^1) and another strongly electron-withdrawing substituent (R^2), direction to the same face as R^2 could be influenced to be as high as ~10:1. By this means, Arjona showed that the dihydroxylation of a similarly protected cyclohexene could be made more selective than Ogawa had managed. He managed access to such a differentially protected derivative by starting from the known compound **330** (scheme 102).¹³⁸



R^1	R^2	$\alpha:\beta$
TBS	Me	50:50
TBS	H	80:20
TBS	Bz	80:20
TBS	3,5-dinitrobenzoate	93:7

Table 30 Electronic influences on the diastereoselectivity of dihydroxylation

Compound **330** can be synthesised in six steps from furan.¹³⁹ The correct stereochemistry of the four chiral centres was established by ring opening of **330** with trimethylsilyl triflate. The silyl ether resulting from this transformation proved too unstable to isolate, and so was reduced directly under Luche conditions to give **331** in an overall 35% yield. Selective protection of the allylic hydroxyl gave the requisite silyl ether **332**. The nitrogen was introduced by an S_N2 displacement of mesylate, as Ogawa had done, to give the azide **333** (74% for two steps).



Scheme 102 Arjona's formal synthesis of the aminocyclitol

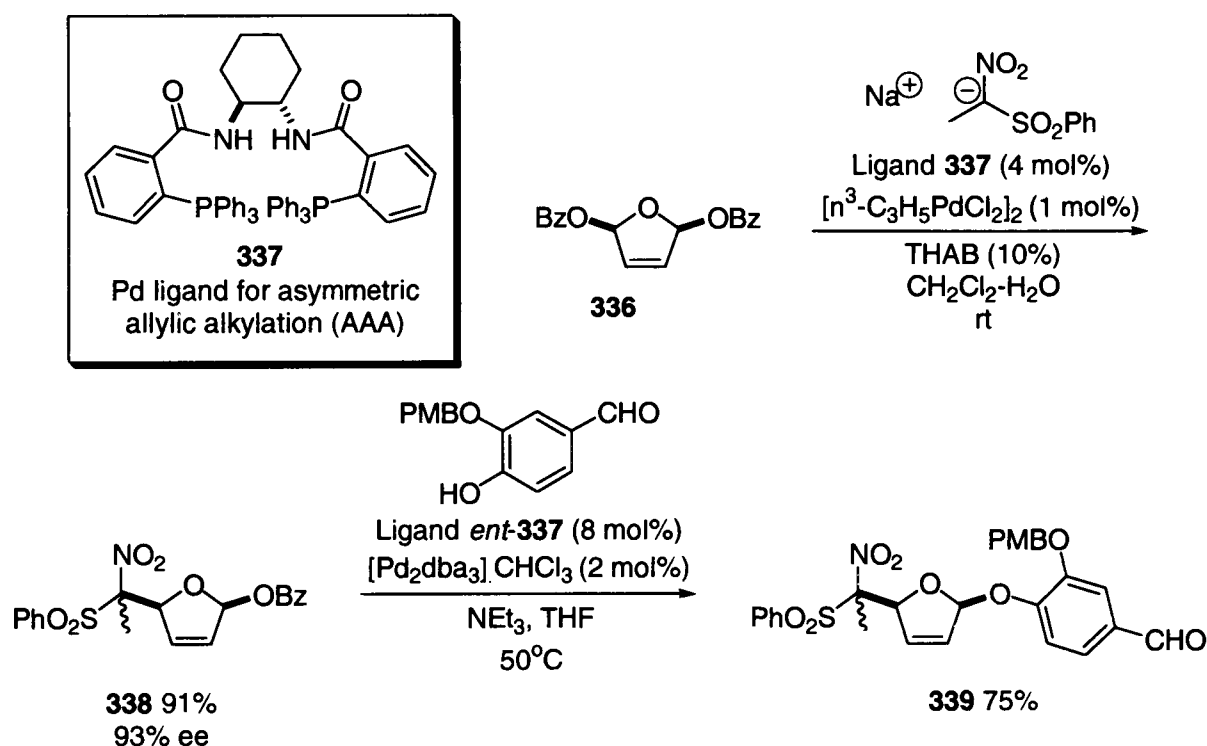
This azide is directly analogous to compound **321** in Ogawa's synthesis, but under the same dihydroxylation conditions gives a much improved 86:14 ratio of diastereomeric diols **334** and **335** (cf. 62:38 for **321**). However, the subsequent protecting group manipulation required to complete the synthesis does not feature the same direct nature of Ogawa's synthesis, so greater control in the dihydroxylation is not as beneficial as might first appear.

3.5 – Trost's Synthesis of *epi-hygromycin A*

3.5.1 Synthesis of furanoside 344

Barry Trost, in a study that was a showcase for his asymmetric allylic alkylation (AAA) methodology, undertook a synthesis of hygromycin A. He successfully employed his AAA reaction in synthesising both chiral fragments, but was only able to access the C-2 *epi*-analogue.^{140, 141} Nevertheless, the synthesis is impressive, particularly in the rapid and high yielding assembly of the furanoside and linker portion. In his published work on the subject, Trost is very candid about related, but ultimately unsuccessful, routes towards the targets. For brevity, only the final versions will be discussed in full here.

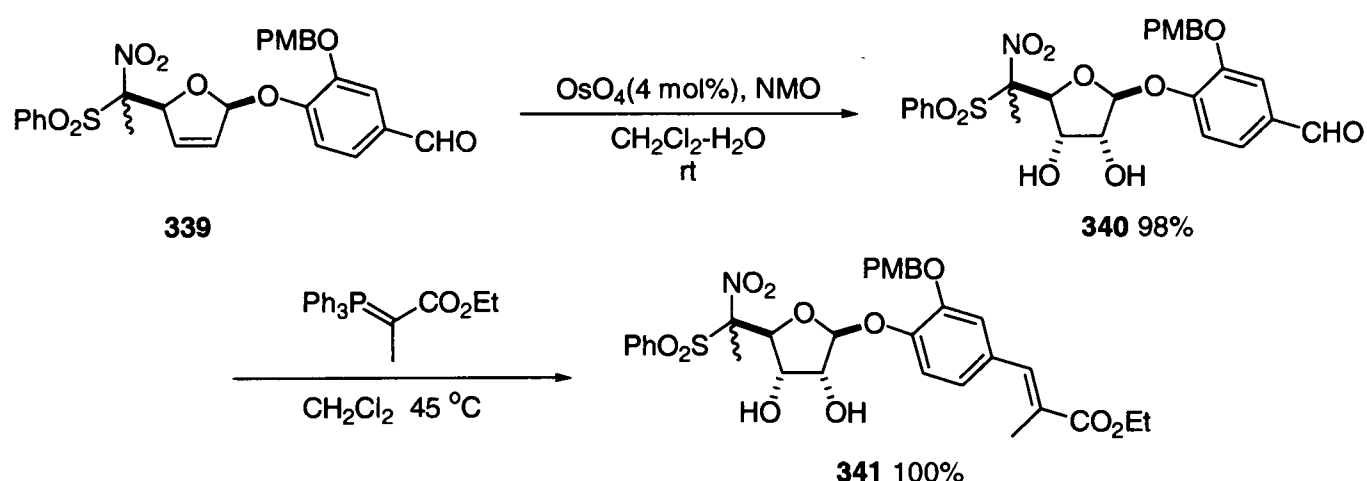
The synthesis of the furanoside unit begins with compound **336**, synthesised directly from furan by treatment with lead tetrabenzoate in 76% yield (scheme 103). The *meso* dicarbonate is then desymmetrised by Trost's own asymmetric allylic alkylation.¹⁴²⁻¹⁴⁴ Application of this to the dicarbonate **336** allows access to the masked ketone derivative **338**, in an excellent 91% yield and with 93% ee.



Scheme 103 Trost's synthesis of the *epi*-furanoside and aromatic linker

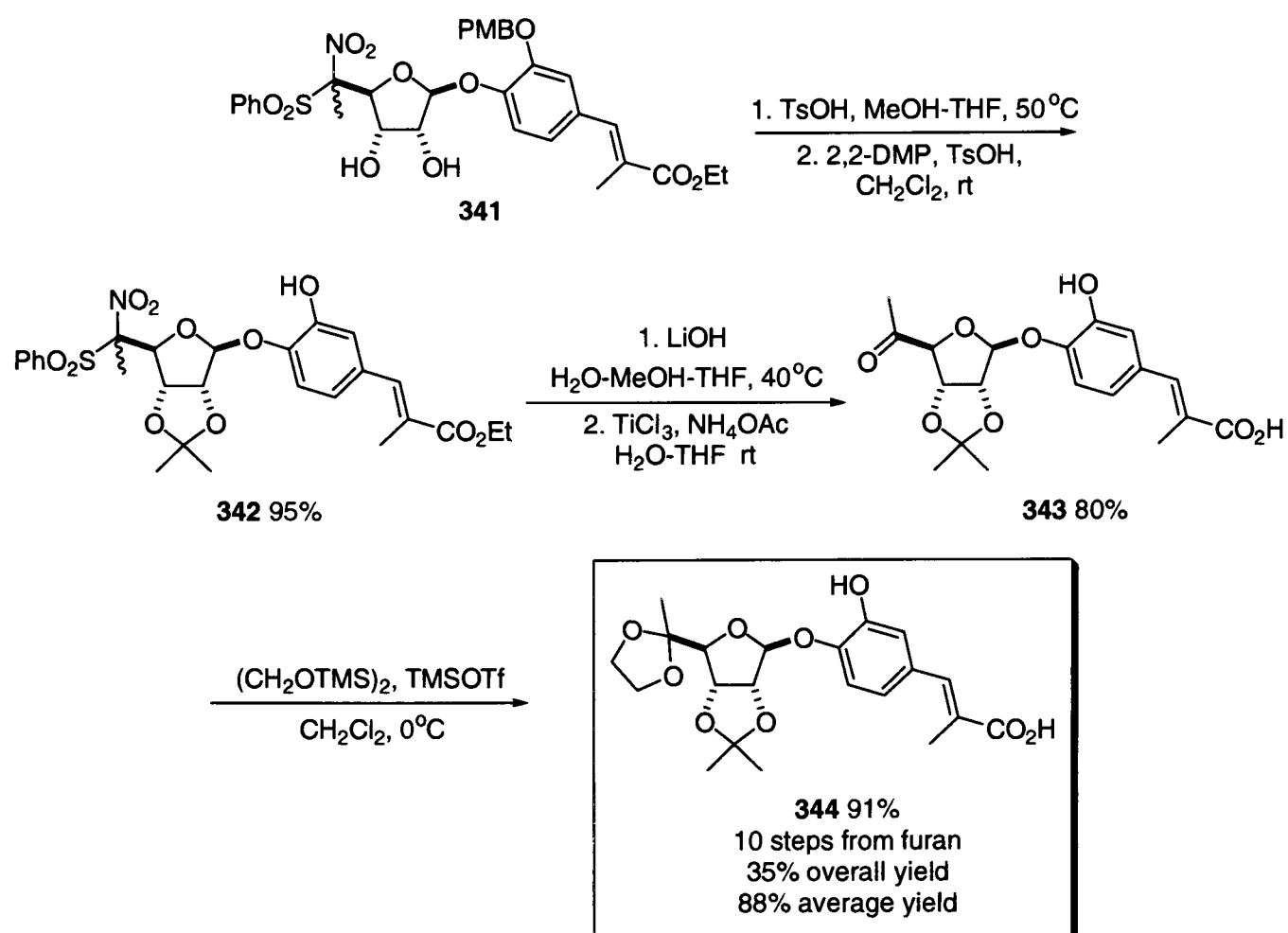
Attempts to establish the anomeric linkage proved problematic. In particular the reaction was quite slow, so a 'matched' chiral ligand was again used, as they prove more reactive. Other variables had to be optimised also, involving adaptation of the palladium source and increasing the temperature. The optimised conditions eventually gave the installed anomeric unit in a yield of 75%. Notably the complete stereocontrol at this centre was much better than had been previously achieved by Ogawa (~2:1, *vide supra*).

Dihydroxylation of the double bond proved uneventful and completely diastereoselective (98%). Prior studies into converting this *cis*-diol unit into the natural *trans* relationship had been fruitless, and it was decided to proceed with a synthesis of the *epi*-analogue. The establishment of *trans* diol linkages across C3-C4 of heterocyclic systems is a common problem, for which no general satisfactory solution exists. The linker fragment was elaborated in identical fashion to Ogawa, employing Wittig methodology to give the alkene **341** quantitatively.



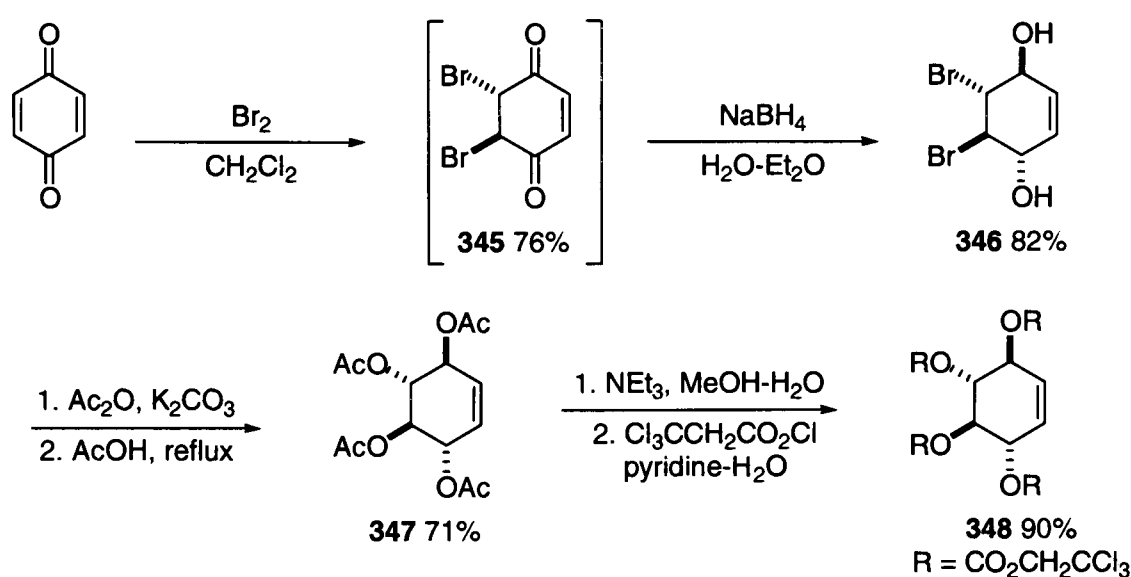
Scheme 104 Trost's synthesis of the *epi*-furanoside and aromatic linker

Removal of the *para*-methoxybenzyl protecting group from the linker with tosic acid, followed by protection of the diol as the acetonide gave **342** (95% for two steps). This allowed saponification of the ester (LiOH) and revealing the latent ketone with titanium trichloride gave the coupling precursor **343** (80%). Attempted coupling at this stage failed due to epimerisation at C-4 of the furanoside. The ketone was protected as Ogawa had done, using Noyori's conditions.¹³³ The ethylene ketal **344** proved more amenable to the coupling reaction (*vide infra*).

Scheme 105 Trost's synthesis of the *epi*-furanoside and aromatic linker

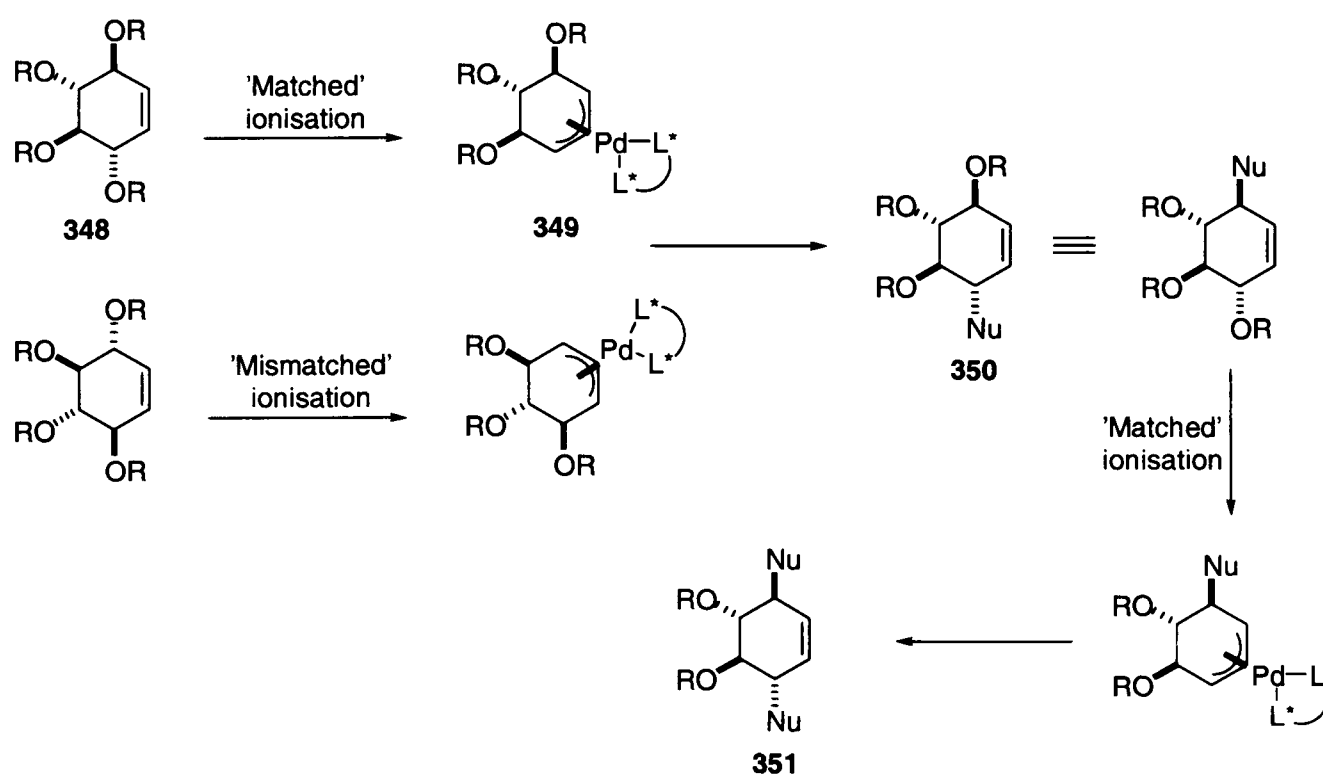
3.5.2 Synthesis of aminocyclitol **327**

Trost's paper on his synthesis of the aminocyclitol incorporates two distinct routes. As mentioned before, only the superior route will be discussed here. The key starting material is the racemic conduritol B derivative **348**, which was available in 6 steps from benzoquinone, by a modification of a known literature procedure.¹⁴⁵ The product **347** of this procedure was converted into the tetracarboxylate **348**. The slightly unusual choice of protecting group was so that selective cleavage could be effected after the desymmetrisation step.



Scheme 106 Trost's synthesis of the aminocyclitol

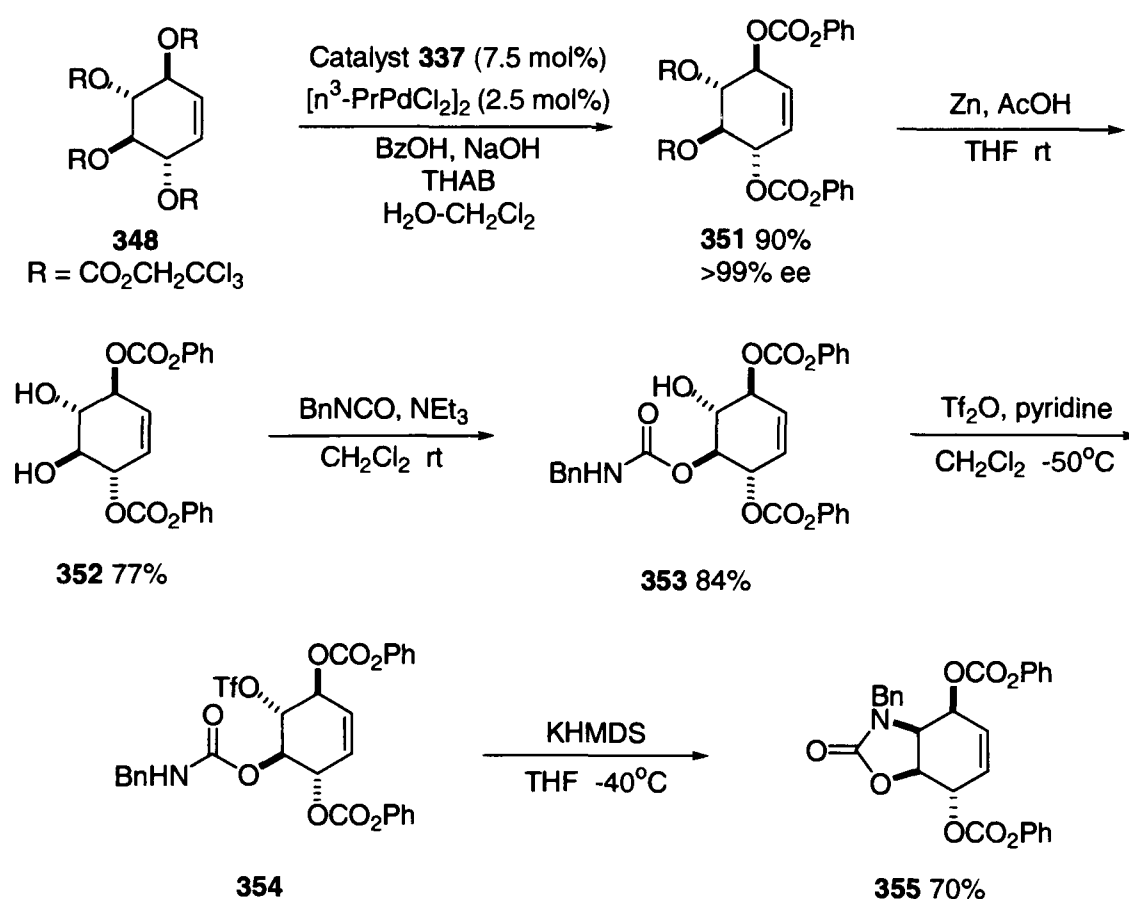
Asymmetric allylic alkylation of the tetracarbonate gave, in 90% yield, enantiomerically pure **351** via a dynamic kinetic resolution. The reaction proceeds as shown in scheme 107. The 'matched' ionisation step occurs faster than the 'mismatched', thus the AAA occurs faster on one enantiomer than the other. Due to the C_2 symmetry of the substrate, the product **350** also has a suitable 'matched' allylic substituent available for the reaction. Thus this is substituted as well, and at 50% conversion the reaction mixture comprises enantiomerically pure starting material **348** and disubstituted product **351**.



Scheme 107 Dynamic kinetic resolution of a racemic conduritol B derivative

If the reaction is allowed to proceed further, the slower 'mismatched' AAA will occur on the tetracarboxylate, giving the same *meso*-complex **349** as was obtained by the 'matched' step. The same sense of stereochemical induction gives the same product as before, and so both enantiomers are ultimately converted to the same enantiomer of the product.

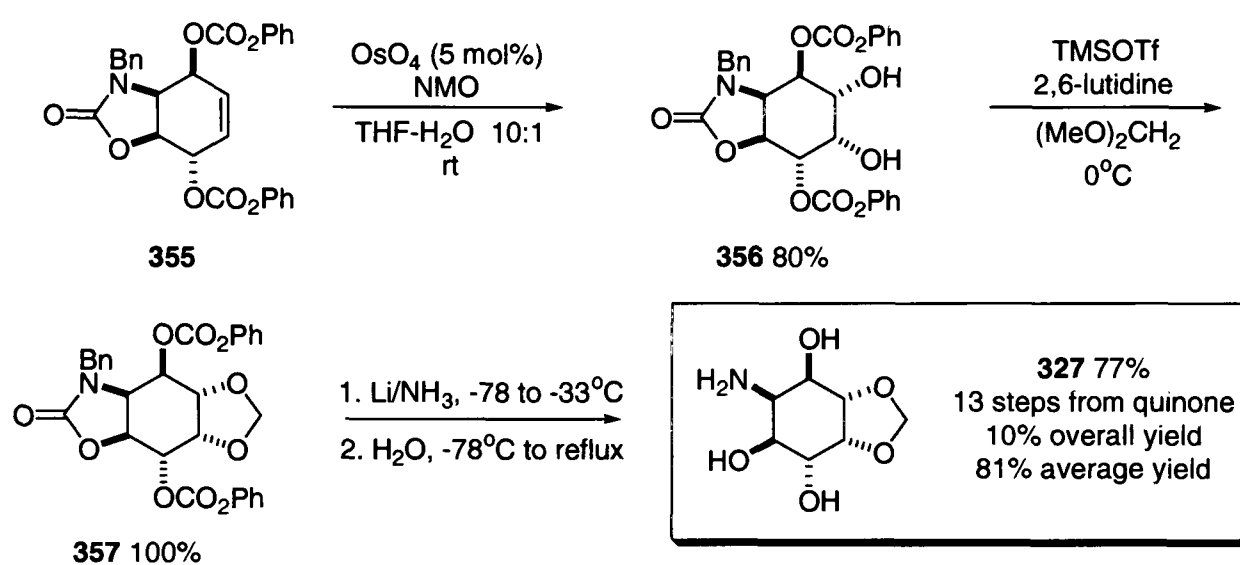
Deprotection of the trichloroethyl carbonate groups in the presence of the newly installed benzoates was achieved using activated zinc in acetic acid (77%, scheme 108). Attempts to install the nitrogen by cyclisation of a suitable carbamate had led to problems due to competing side-reactions. The key to the solution was found by chance, in the discovery that carbamation of the diol with benzyl isocyanate led exclusively to the monocarbamate **353** in good yield. The reactive triflate derivative **354** was needed to promote smooth cyclisation, but the oxazolidinone **355** was obtained in 70% over the two steps.



Scheme 108 Trost's synthesis of the aminocyclitol

Dihydroxylation with OsO₄ occurred with high diastereoselectivity (>10:1, scheme 109). The often-difficult formation of the methylene acetal was achieved under strong Lewis acid conditions. Treatment of the diol **356** with 2,6-lutidine and

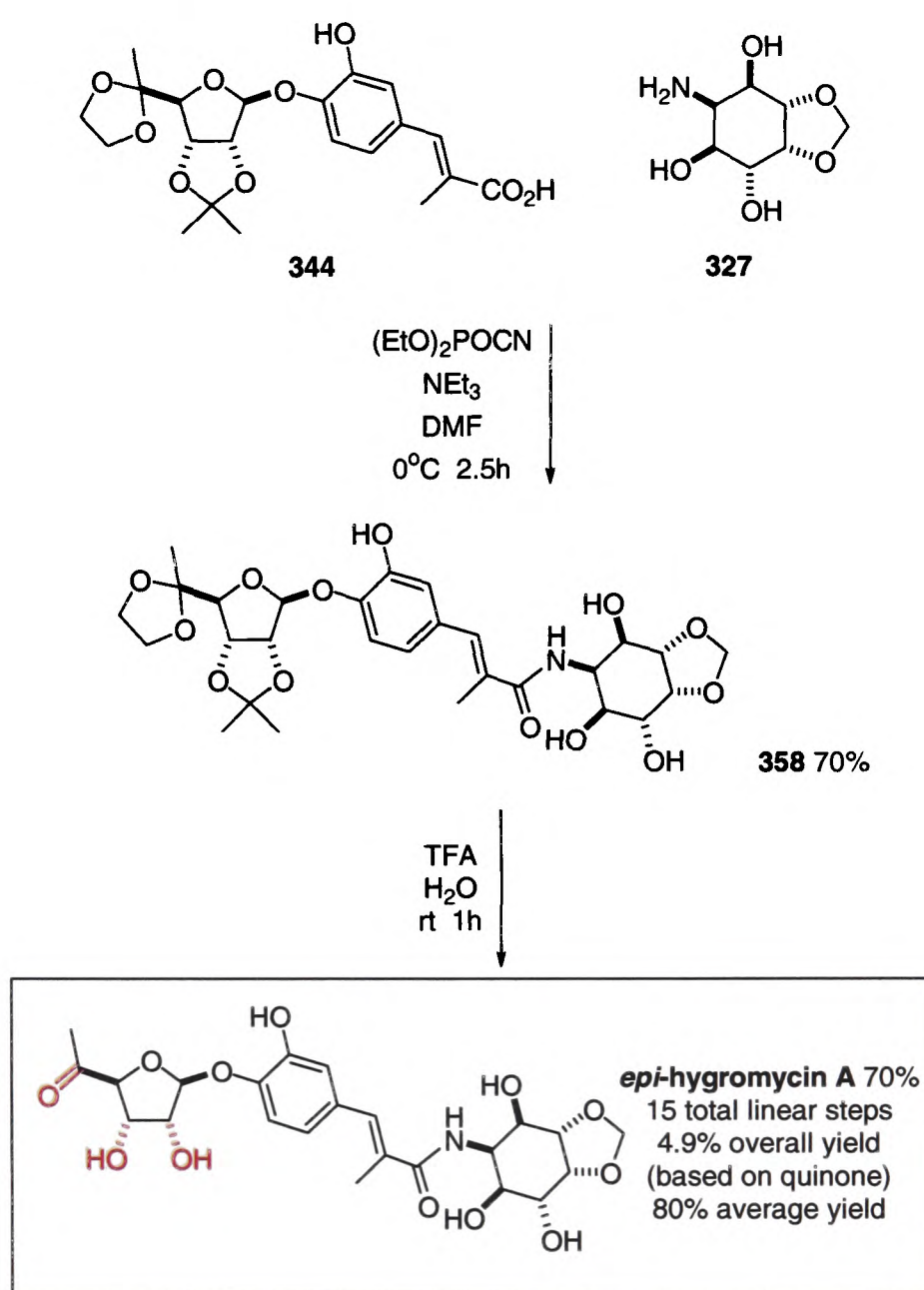
trimethylsilyl triflate in dimethoxymethane gave the methylene acetal **357** in quantitative yield. The final deprotections were achieved in a single step by lithium-ammonia reduction of the benzyl group, followed by an aqueous quench and warming to reflux. Ion-exchange chromatography gave the aminocyclitol **327** in 10% overall yield. In addition, this route allows easy access to either enantiomer of the product.



Scheme 109 Trost's synthesis of the aminocyclitol

3.5.3 Final steps of the synthesis

The final two steps of Trost's synthesis were straightforward (scheme 110). Coupling of the two major fragments was accomplished using diethylcyanophosphonate, giving the protected product **358**. The ethylene ketal and the diol were unmasked using trifluoroacetic acid, giving C-2 *epi*-Hygromycin A in 50% yield.



Scheme 110 Final steps of Trost's synthesis

Results and Discussion II

Approaches towards a total synthesis of hygromycin A

4.1 Disconnection of hygromycin A aminocyclitol

The aminocyclitol of hygromycin A **327** lends itself naturally to synthesis *via* the tethered aminohydroxylation. The *syn-syn* aminodiols motif can be synthesised with complete regio- and diastereocontrol as has been seen for six-membered ring systems already (*vide supra*, section 2.4). Some form of dihydroxylation could install the methylene acetal protected diol unit. The presence of an additional hydroxyl group *syn* to this pair might allow direction of this oxidation to the correct face of the double bond.

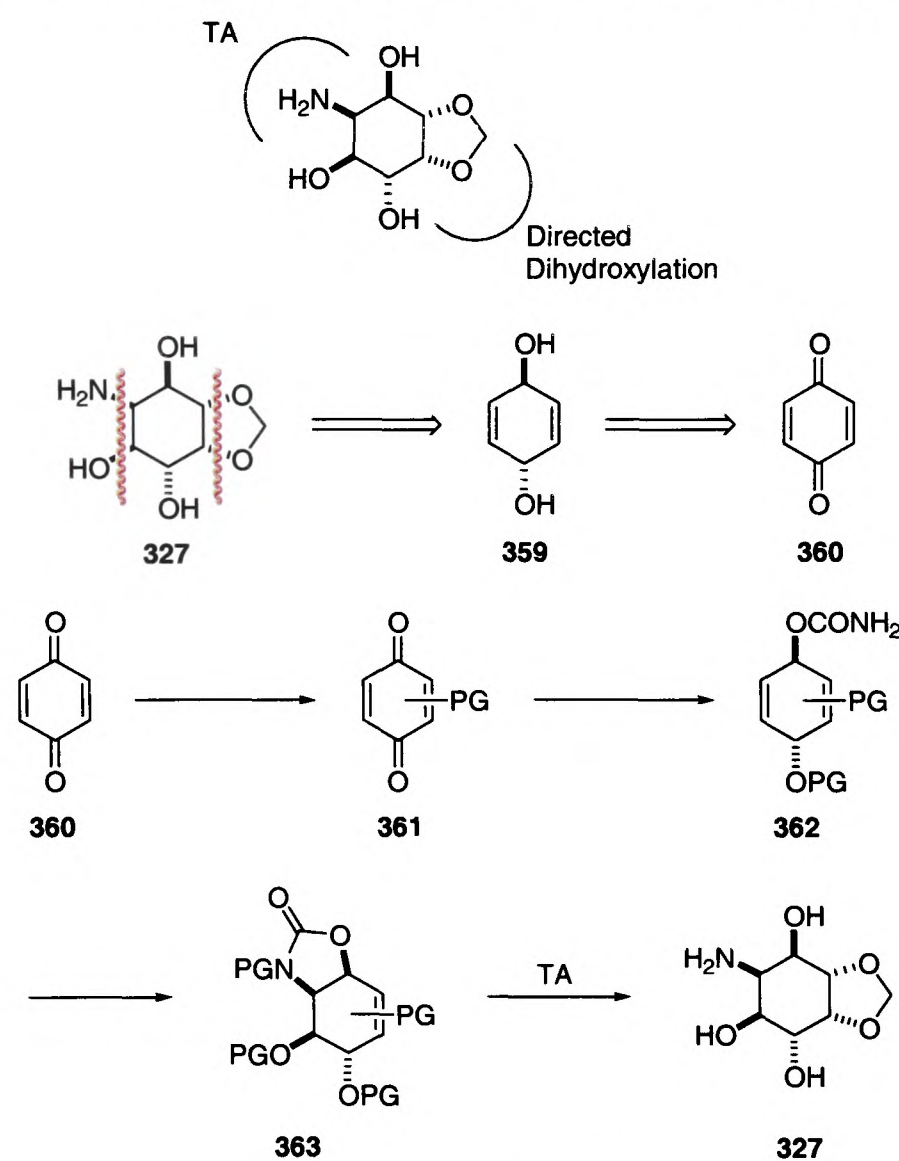
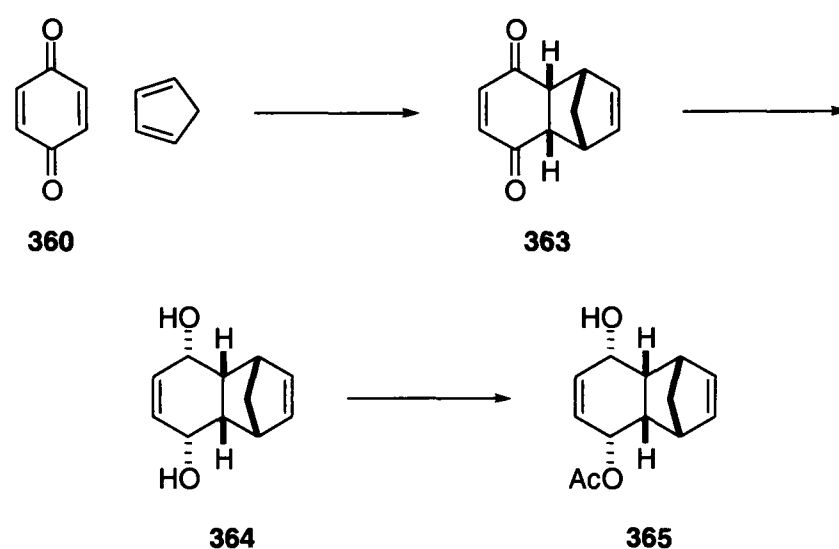


Figure 26 Disconnection of hygromycin A aminocyclitol incorporating tethered aminohydroxylation

A logical disconnection of the aminocyclitol, therefore, involves removal of these two moieties to give the *trans*-dienediol **359** (figure 26). This could derive from *para*-benzoquinone **360** *via* an appropriate reduction-inversion sequence. In the forward sense, desymmetrisation of an intermediate such as **361** could give an enantiopure TA precursor **362**. Tethered aminohydroxylation followed by a deprotection – oxidation sequence produces the target **327**.

4.2 First synthetic strategy

The initial search for a suitable protecting group for one of the benzoquinone double bonds made the pleasing discovery that compound **363** (scheme 111) is commercially available.¹⁴⁶ Alternatively it could be simply prepared from a Diels-Alder reaction of benzoquinone **360** and cyclopentadiene.¹⁴⁷ More pleasing still was that enzymatic desymmetrisation of the *meso*-diol **364** had been reported in the literature.¹⁴⁸¹⁴⁹ Inversion of the free hydroxyl of the monoacetate **365** would establish the *trans* relationship of the synthon **362**.



Scheme 111 Known transformations form the first steps of the synthesis

4.2.1 Synthesis of diol **364**

The sequence commences with the Diels-Alder reaction of benzoquinone **360** and cyclopentadiene (scheme 112).¹⁴⁷ The reaction is notable for its production of solely the *endo* diastereomer of the product, arising from secondary orbital overlap of the enones and the diene (figure 27).

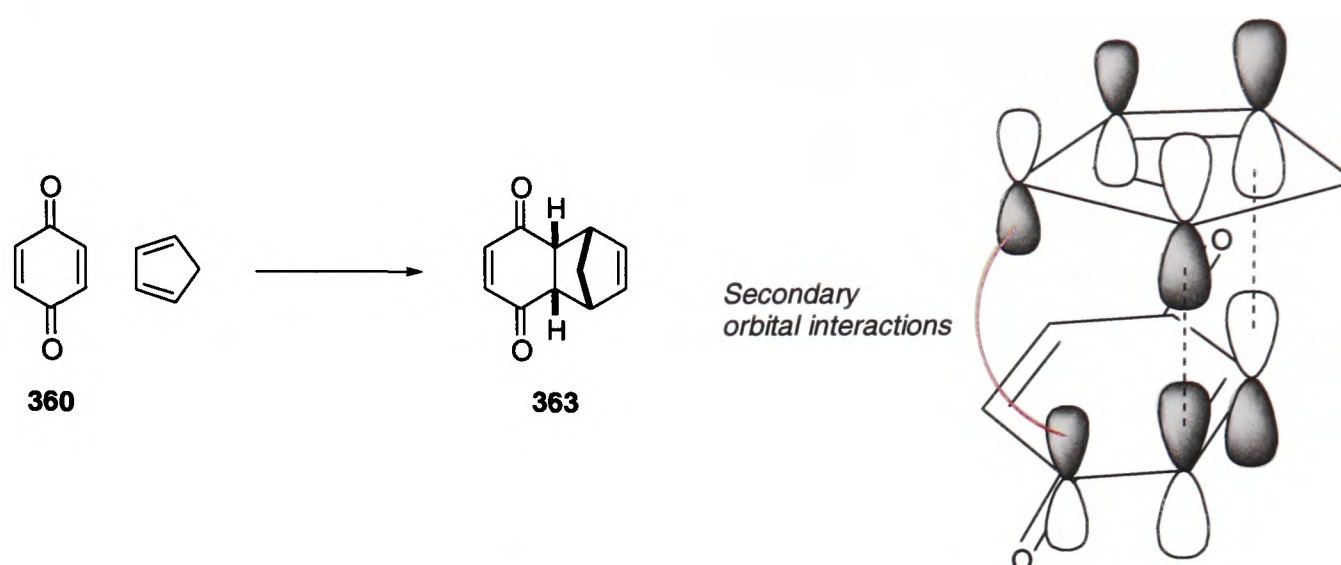
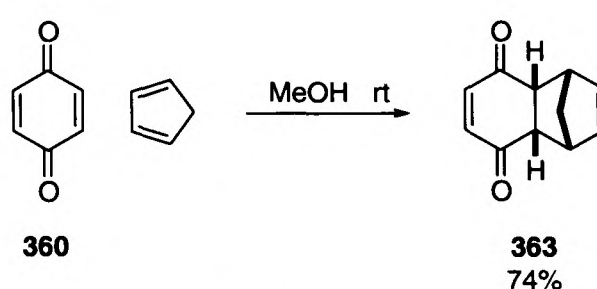


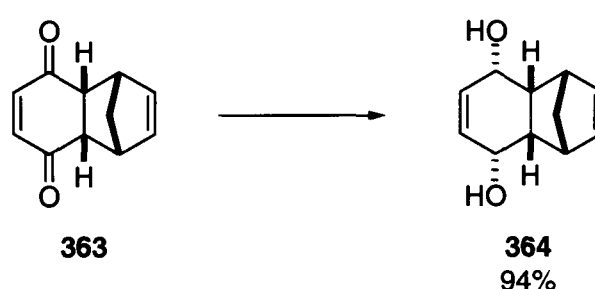
Figure 27 Secondary orbital interactions promote the *endo* transition state for the Diels-Alder reaction

This was a literature procedure, although strict adherence to the reported protocol caused significant problems. Most notably, the concentration of the methanolic solution of benzoquinone mentioned therein seemed unlikely. The procedure involved dissolving 243g of the quinone in 0.4 litres of cold methanol. Attempts to get even a quarter of this amount of quinone into solution failed, leaving a sludge of undissolved quinone crystals at the bottom of the flask, creating additional problems with stirring.



Scheme 112 Diels-Alder reaction of benzoquinone and cyclopentadiene

The reaction was therefore carried out in a more dilute solution (0.37 M compared to Marchand's 5.6 M), and at room temperature rather than 0°C. At the end of the reaction the mixture was separated into portions, which were individually cooled to -78°C and filtered. The red-brown needles of 363 were washed and collected. A second batch was obtained by concentration of the filtrates and a second filtration at -78°C. The yield was not as high as that reported in the literature (74% vs. 94%), but given the inexpensive nature of the starting materials, and the knowledge that the adduct could be bought this was deemed acceptable. All data matched literature values.

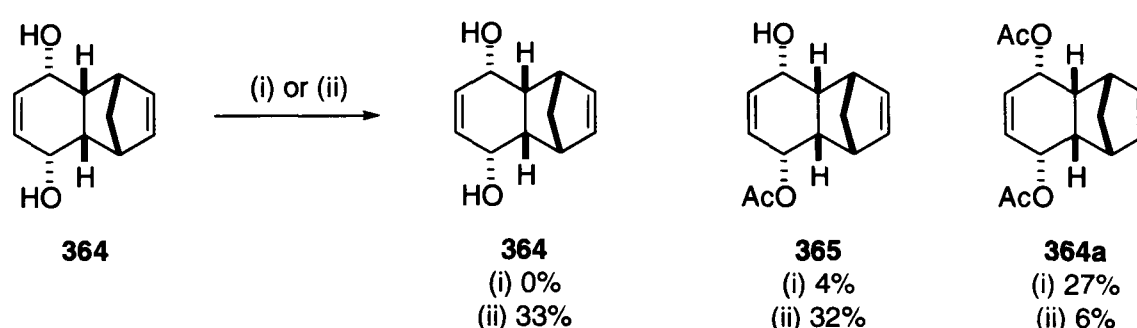


Scheme 113 Luche reduction of dienone **363** *Reagents and conditions* NaBH_4 (2 eq.), $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (0.5eq.), MeOH, 0°C

Reduction of the dienone was performed under Luche conditions, as reported in the literature.¹⁵⁰ On large scales the work-up procedure was made difficult by the viscous aqueous layer containing cerium salts. Extraction of the diol **364** with ether was performed portion-wise on the reaction mixture. The poor solubility of the product in most solvents (e.g. CH_2Cl_2 , EtOAc) had initially led to reduced isolated yields.¹⁵¹ ^1H NMR spectra in d^6 -DMSO of crude samples of **364** matched literature values and generally no further purification was employed.

4.2.2 Monoacetylation of diol **364** to racemic acetate **365**

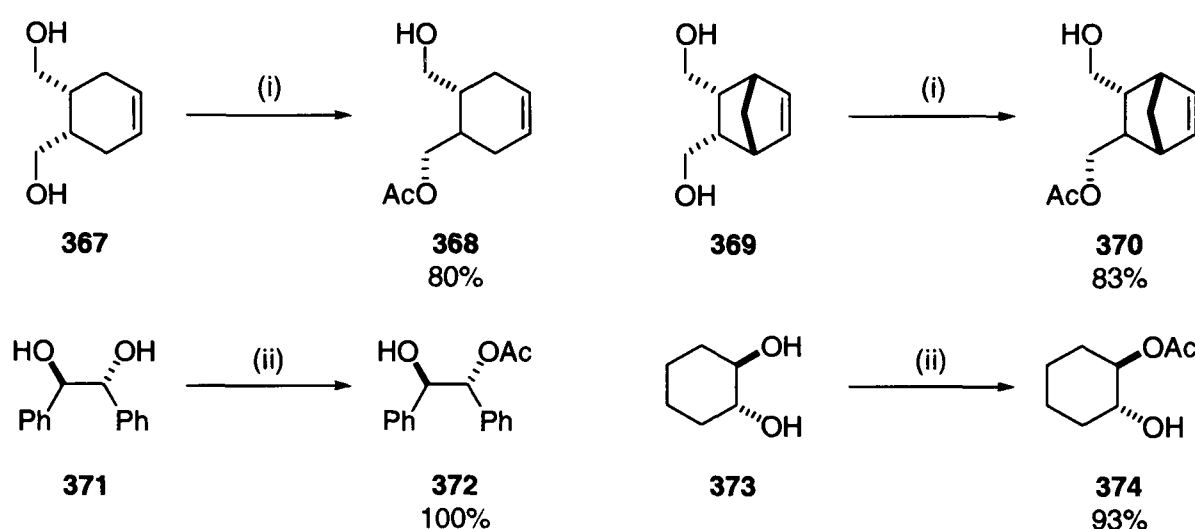
For the elucidation of the synthesis, enantiopure material was not required and so a method for producing racemic monoacetate **365** was sought. The key problem with monoacetylation of symmetrical diols is that very often the rates of acetylation of both the starting diol and the monoacetate are very similar. Thus most attempts result in a statistical mixture of starting material, monoacetate and diacetates. This was very much in evidence in the early attempts, involving the use of strictly one equivalent of acetic anhydride in pyridine. Low yields of monoacetate **365** were obtained, with greater proportions of diacetate **364a** and diol **364**. This is attributed to the poor solubility of the diol.



Scheme 114 Monoacetylation of diol **364** *Reagents and conditions* (i) Ac_2O (1 eq.), pyridine, rt; (ii) (a) $n\text{BuLi}$, THF, -78°C to rt, (b) AcCl (1 eq.)

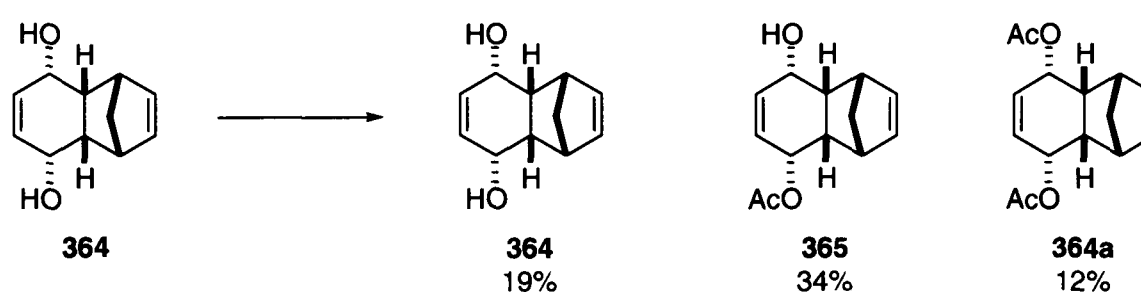
Superior yields were obtained using butyl lithium and acetyl chloride. With these reagents in THF, between 25% and 38% of **365** was isolated. The diol showed much improved solubility in this solvent. A small (~5%) amount of diacetate was formed, with 30-40% of the diol **364**. Attempts to drive this reaction further by lengthening the reaction time resulted in greater amounts of diacetate **364a** at the expense of starting material.

Recent papers by Clarke have discussed this problem.^{152, 153} Treatment of symmetrical diols with an excess of acetic anhydride in the presence of a catalytic amount of a lanthanide salt produces, in good yield, the corresponding monoacetates (scheme 115).



Scheme 115 Clarke monoacetylation of symmetrical diols *Reagents and conditions* (i) Ac_2O (10 eq.), $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (10 mol%), THF, rt; (ii) Ac_2O (10 eq.), $\text{YbCl}_3 \cdot 7\text{H}_2\text{O}$ (10 mol%), THF, rt

Encouraged by this finding, the same conditions were applied to the *meso*-1,4-diol **364**. Disappointingly, overnight the reaction only produced 18% of the monoacetate **365**, with 47% of the recovered diol **364**. Ytterbium chloride and cerium chloride appeared to give similar results. Scale-up of the reaction, and an increased reaction time (4 days) afforded 34% of **365**, with 12% diacetate **364a** and 19% recovered diol **364** (scheme 116).



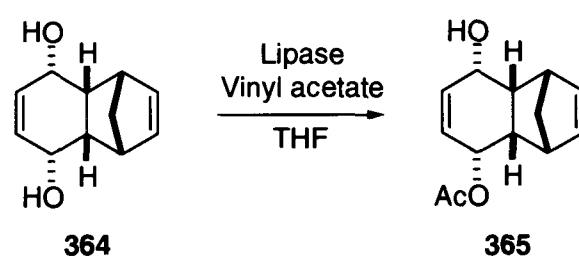
Scheme 116 Clarke acetylation of diol **364** *Reagents and conditions* Ac_2O (10 eq.), $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (10 mol%),

While there were no improvements on the butyl lithium procedure, the simplicity of the protocol made it more attractive. In addition, work-up was aided by the insolubility of the diol **364** in chloroform. The starting material could be recovered before chromatography of the products by simply washing away the mono- and diacetates.

4.2.3 Enzymatic desymmetrisation of diol **364**

Ultimately the synthesis was to be made enantioselective, and as such a means for producing enantiopure **365** was necessary. Work by Ogasawara had involved desymmetrisation of **364** using a solid-supported enzyme for access to a number of chiral building blocks.¹⁴⁹

The enzyme used by Ogasawara was not easily obtainable, and so alternatives were sought. A number of lipases are commercially available, with varying turnover numbers. A small screening study was performed to determine the most effective. Ten enzymes were screened in all. All of the reactions were performed on 350 mg of diol **364** in 10 mL of THF. Ten equivalents of vinyl acetate were used as the irreversible acetate donor. After five days a sample of each reaction was extracted and filtered. The composition of the crude mixture was determined by LCMS (table 31).



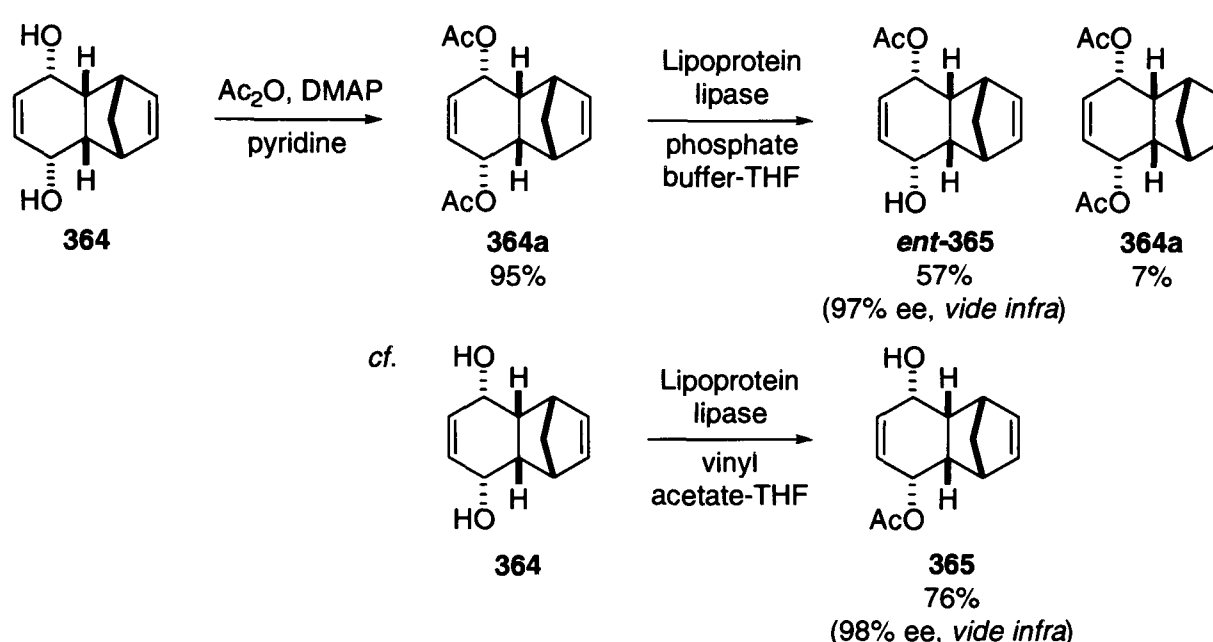
<i>Enzyme Origin</i>	<i>Fluka #</i>	<i>Turnover Number (U)</i>	<i>Quantity Q (mg)</i>	<i>U × Q</i>	<i>Acetate 365 (%)</i>	<i>SM 364 (%)</i>
Aspergillus niger	84205	1	100	100	0	100
Candida antarctica	62299	3	50	150	10	90
Candida cylindracea	62316	2	1000	2000	10	90
Mucor mehei	62298	1	100	100	0	100
Pseudomonas cepacia	62309	50	100	5000	25	75
Pseudomonas fluorescens	62312	40	50	2000	31	69
Rhizopus arrhizus	62305	0.002	1000	2	0	100
Rhizopus niveus	62310	0.0025	1000	2500	~10 ^a	~90 ^a
Hog pancreas	62300	-	-	-	22	78
Pseudomonas species (lipoprotein)	62336	1400	35	49000	100	0

Table 31 Enzyme screen for the monoacylation of 364 *Reagents and conditions* Enzyme, vinyl acetate (10 eq.), THF, rt, 5 days; (a) Approximate LCMS values. Accurate measurement was not possible due to broadened peaks

Four of the screened enzymes gave turnovers greater than 20%. Of these, the lipoprotein lipase from *Pseudomonas* species clearly gave the best result, with solely monoacetate discernable by LCMS after five days. This enzyme is also the most closely related to that used by Ogasawara. The turnover number, U, is a guide to the efficiency of the enzyme, and is always listed for 1 mg of enzyme, though not necessarily for the same reaction. The product UQ of the quantity of enzyme added to the reaction (Q) and the turnover number can therefore be compared directly to the amount of acetate formed. To a good approximation, the enzymes with the highest UQ values achieved the best turnovers.

The four most promising reactions were filtered to remove the enzyme. The starting material was reclaimed by washing out the acetate **365** with chloroform, and purified acetate **365** obtained after column chromatography. The isolated yields for the enzymes from *Pseudomonas cepacia* (24%), *Pseudomonas fluorescens* (31%) and hog pancreas (15%) were inferior to that from the lipoprotein lipase (76%). This enzyme was therefore chosen for future reactions. Scale-up of the reaction to 25 mmol entailed an increased reaction time (12 days) but a marginally improved yield (83%, 98% e.e, *vide infra*, section 4.2.4).

Not knowing at this stage in which order the TA and dihydroxylation would be performed in the final synthesis, enzymatic synthesis of the enantiomer of **364** was also performed. The diacetate **364a** had been isolated from earlier monoacetylation studies, and was also freshly synthesised as in scheme 117. Treatment of **364a** with the lipoprotein lipase in a phosphate buffer – THF mixture gave, after stirring for eight days, 57% of the enantiomeric monoacetate **365**.

Scheme 117 Synthesis and desymmetrisation of diacetate 364a to produce *ent*-365

The enantiomeric excesses of the monoacetates **365** could not be determined at this stage. Attempted chiral HPLC studies failed to cleanly separate the enantiomers, with the added problem that the compounds possessed only a weak chromophore. The rotations of both samples were measured, and were comparable at +93.3 ($c = 1.0$, CHCl_3 , 20°C) and -92.2 ($c = 1.0$, CHCl_3 , 20°C). Comparison to Ogasawara's literature values initially suggests that these are wildly different. One paper quotes +72.2 ($c = 1.0$, CHCl_3 , 30°C)¹⁵⁴. While the temperature is different, the large discrepancy in rotations is evident. However, comparison of Ogasawara's literature values across a series of papers reveals inconsistencies (table 32).^{148, 149, 151}

Reference	Rotation	c	Temperature ($^\circ\text{C}$)
148	+71.7	2.2	26
148	-70.6	0.2	30
149	+70.05	1.02	30
154	+72.20	1.00	31
151	-68.8	0.96	27

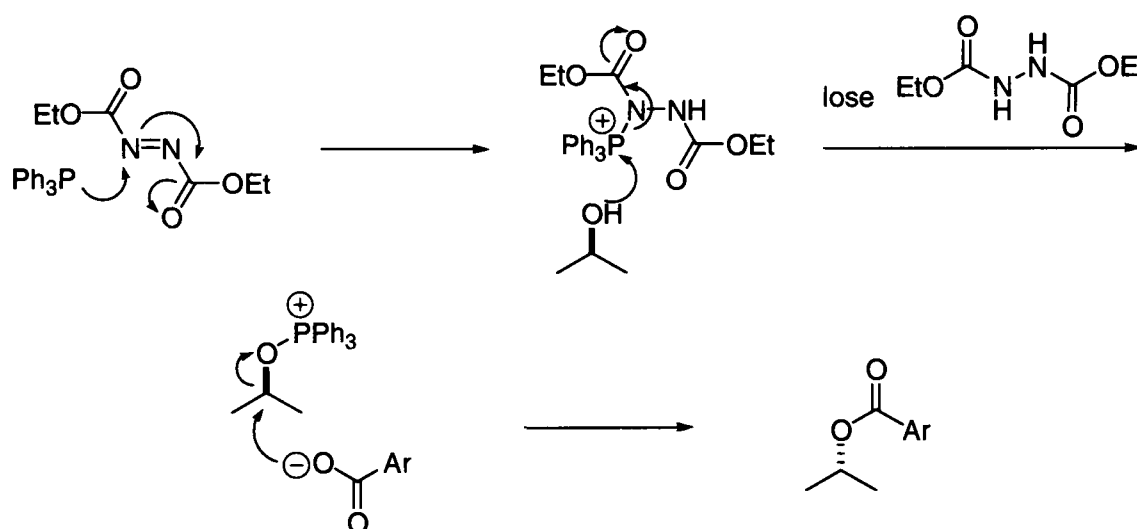
Table 32 Ogasawara's reported rotations for acetate **365**. Chloroform was used as solvent.

The seeming independence of rotation from concentration seems unlikely. While this raised obvious concerns, especially given the failure of HPLC to allow

determination of enantiomeric excess, fears were allayed when the next step provided material more suitable for chiral HPLC analysis.

4.2.4 Mitsunobu inversion of the hydroxyl centre of acetate 365

To establish the *trans* relationship of the 1,4-hydroxyl centres, some form of inversion of one of the centres was required. Acetate is not an excellent leaving group, so attention was turned to inversion of the free hydroxyl centre. The Mitsunobu reaction is an excellent method for achieving this through a one-pot conversion to a leaving group (scheme 118), and subsequent displacement with an introduced nucleophile, typically a carboxylic acid, phenol or phthalimide.¹⁵⁵

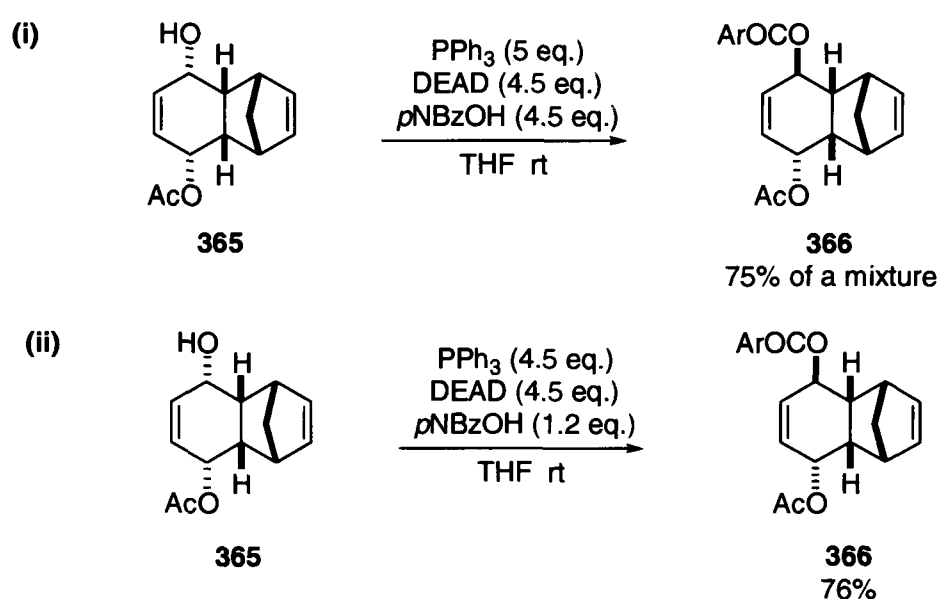


Scheme 118 Mitsunobu inversion of a hydroxyl centre

The free hydroxyl centre in monoacetate **365** points to the concave face of the molecule. While this would in theory slow the formation of the oxygen-phosphorus bond, attack by the nucleophile will then occur from the convex face and should therefore be feasible.

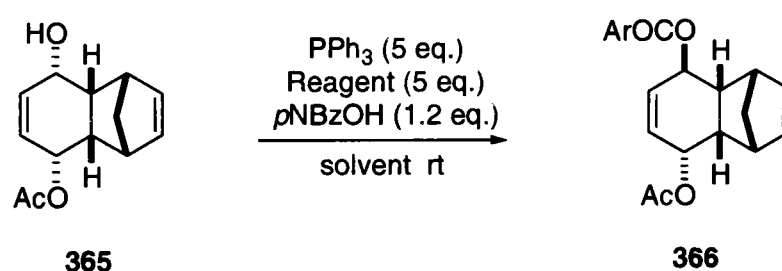
The first attempts were made using benzoic acid as the nucleophile. While some of the benzoate product was isolated, the yield was poor and the material not pure. Specifically, it appeared that some isomerisation had occurred. Within the ¹H NMR spectrum more than one set of benzoate peaks were visible. The alkene region also clearly contained more than one set of peaks.

Martin has reported improved yields in the Mitsunobu reaction using *para*-nitrobenzoic acid as the nucleophile.¹⁵⁶ Switching to these conditions gave a similar result, with the alkene region again cluttered with signals from more than one compound (scheme 119). Norbornene systems are known to undergo rearrangement in acidic conditions, and it was believed that the acid nucleophile was enough to prompt isomerisation *via* the non-classical 7-norbornyl cation.¹⁵⁷ The amount of acid added was reduced from five equivalents to 1.2 equivalents, with the isolated product clearly purer than before, and the product ¹H NMR signals now distinct from those of the trace isomerised impurities.



Scheme 119 Mitsunobu reaction of 365 is acid-sensitive

The putative isomerisation also seemed to be sensitive to the time of the reaction. Less of the impurities were seen when the reaction was closely monitored and worked-up as soon on completion, usually within 45-60 minutes. For the best results, the product would be purified as soon as possible to minimise contact with any reagent that might be promoting isomerisation. Further optimisation was performed by trying different azodicarboxylate reagents, in each of two different solvents, THF and dichloromethane. All the reactions were carried out on 0.45 mmol of the acetate 365, and under an atmosphere of nitrogen. Table 33 shows the results. The reagent 1,1'-(azodicarbonyl)dipiperidine (ADDP) proved completely ineffectual in this system. Often this reagent requires more reactive phosphines (e.g. PBu₃, PMe₃) for successful reaction.¹⁵⁸ Dichloromethane was a poor solvent, giving increased amounts of isomerisation compared to THF. Both diethylazodicarboxylate (DEAD) and di-*tert*-butyldiazodicarboxylate (DBAD) were effective reagents.



<i>Solvent</i>	<i>Reagent</i>	<i>Yield (%)</i>	<i>Isomerisation?</i>
THF	DEAD	64	N
	DBAD	78	N
	ADDP	0	-
CH ₂ Cl ₂	DEAD	61	Y
	DBAD	55	Y
	ADDP	0	-

Table 33 Screening for Mitsunobu reaction of acetate 365

Further experimentation discovered that while DBAD and DEAD had both performed well in this study, DBAD gave more consistent results. In addition DBAD is a bright yellow solid and therefore easier to handle than the orange liquid DEAD. The drawback is that the di-*tert*-butylbiscarbamate by-product is very difficult to separate from the product **366** by chromatography. Its presence is easy to detect, with a strong singlet at 1.5 ppm. Use of diisopropyl azodicarboxylate (DIAD) did not give yields as high as DBAD, while also isomerisation seemed more prevalent.

Another problem with the reaction was the triphenylphosphine oxide by-product. Usually this can be precipitated out of solution and filtered off. However, attempts to achieve this also precipitated product out of solution. Thus, to simplify chromatography, the equivalents of phosphine (and DBAD) were reduced to 1.5. This led to no significant drop in recovered mass, but a small increase in the amount of isomerisation was noticeable. Fortunately, recrystallisation of columned **366** from hot methanol successfully removed both the isomerised material *and* the DBAD-derived by-product. In addition, slow crystallisation from methanol gave large crystals suitable for X-ray analysis. The crystal structure of **366** clearly shows the established *trans*-relationship of the two protected hydroxyl groups (figure 28).

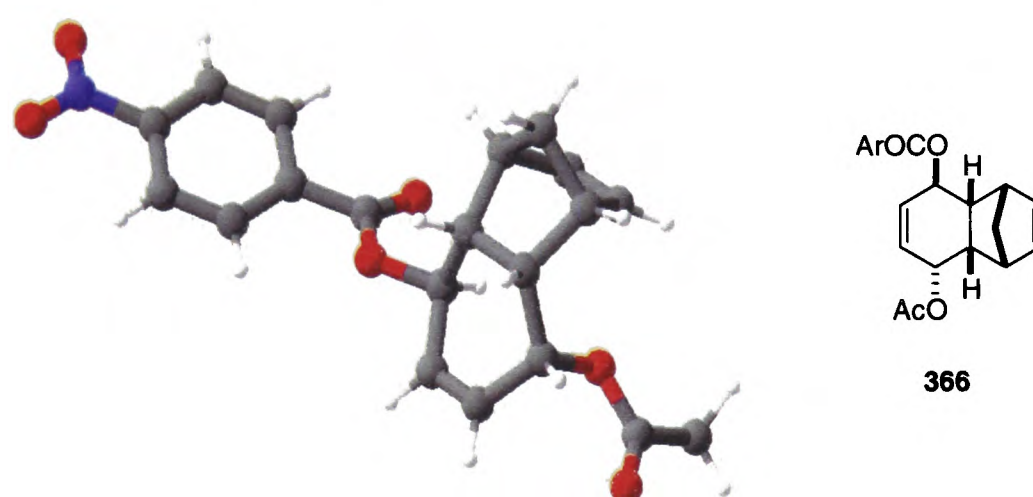
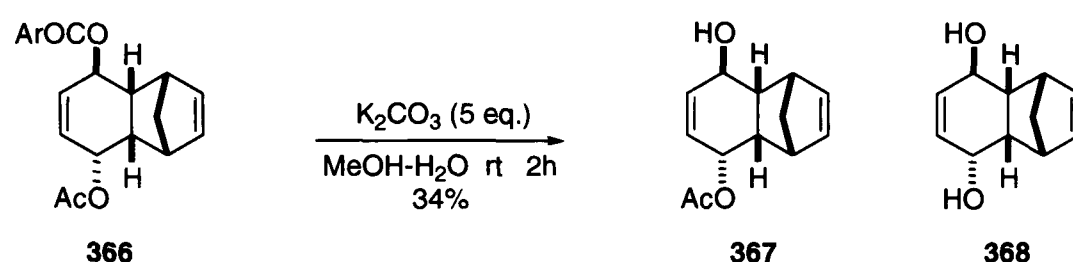


Figure 28 Crystal structure of Mitsunobu product 366 showing *trans* relationship of 1,4 - hydroxyl groups

The benzoate **366** was also amenable to chiral HPLC, allowing more accurate determination of the enantiomeric excess. Samples of **366** synthesised from both **365** and *ent*-**365** were analysed (appendix I). Pleasingly, both samples gave material of very high ee (98% and 97%, respectively). While both samples had been recrystallised, this result had been suggested by less successful HPLC separations on the acetate **365**. Both enantiomeric series were available in equally pure form.

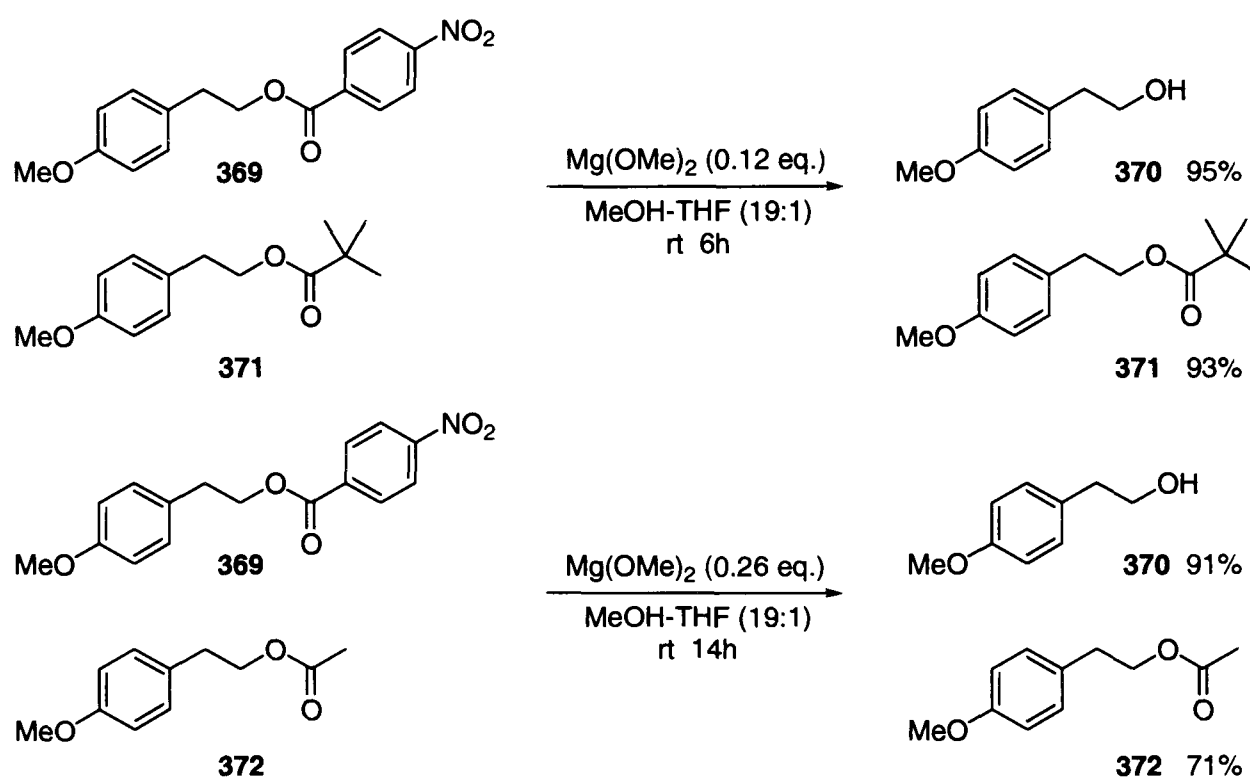
4.2.5 Cleavage of benzoate ester of 366

With the necessary stereochemical arrangement of the existing functional groups now established, the next step was to install the carbamate in readiness for the TA. Cleavage of the *para*-nitrobenzoate would be straightforward, but in order to minimise by-products ideally the acetate protection on the *endo* hydroxyl group would remain intact. It was hoped that with **366**, the positioning of the acetate within the concave face of the molecule would slow hydrolysis of this ester and grant a degree of selectivity. Strong bases were therefore avoided. Treatment of **366** with potassium carbonate in aqueous methanol gave a mixture of products by TLC (scheme 120). Isolation of the major products suggested a mixture of the cleaved benzoate **367** and the diol **368**. Milder conditions were then sought.



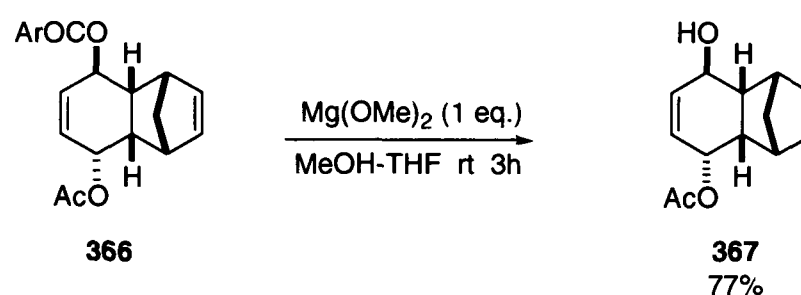
Scheme 120 Potassium carbonate cleavage of benzoate 366

Magnesium methoxide is a base reported to be very selective in the cleavage of esters.^{159, 160} In kinetic competition experiments benzoates were cleanly and selectively cleaved in the presence of pivalates (scheme 121). In the presence of acetates, good levels of selectivity for cleavage of the benzoate were achieved with careful monitoring of the reaction.



Scheme 121 Magnesium methoxide deprotection of benzoates

Initially there was no success in the selective ester cleavage reaction. While the benzoate had obviously been cleaved the ^1H NMR spectrum of the isolated product was contaminated with a number of unidentified peaks. The source of this contamination was again suspected to be acid-mediated isomerisation. Acid had been employed in the work-up to neutralise excess methoxide. On small scales this step was omitted, and on large scales great care was taken to not acidify the mixture.

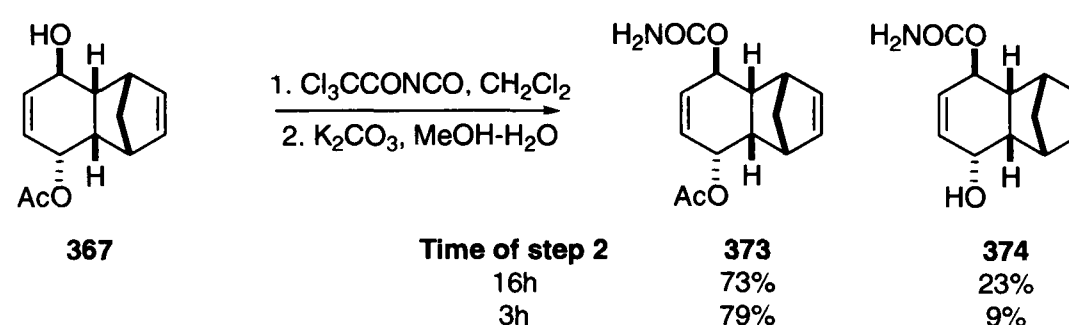


Scheme 122 Selective deprotection of 366 using magnesium methoxide

Yields were now much improved, the major contaminant of the reaction being methyl *para*-nitrobenzoate. On a larger 2.5mmol scale, the benzoate **366** was taken through to this step without recrystallisation. Chromatography now allowed the product **367** to be isolated free from the DBAD impurity residual from the Mitsunobu reaction.

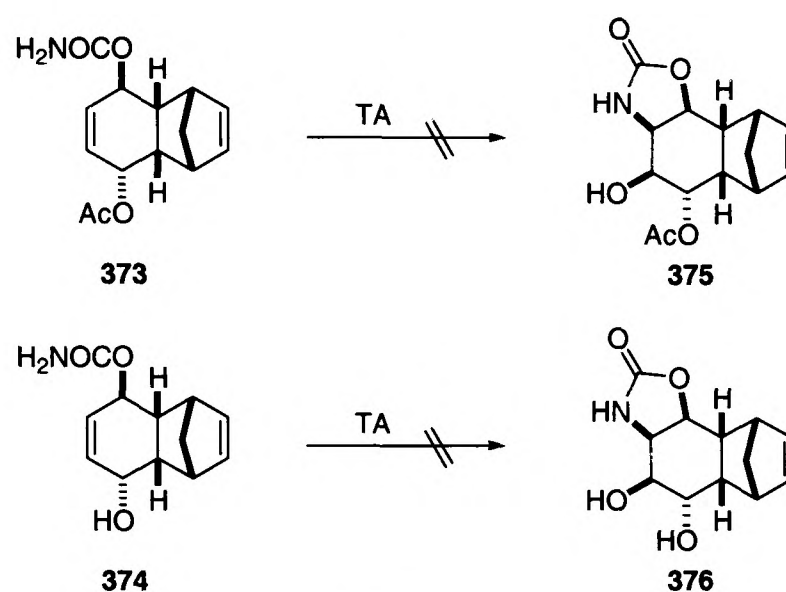
4.2.6 Synthesis and TA of carbamate 373

With the allylic alcohol in hand, the TA substrate **373** could now be synthesised. Subjection of **367** to standard carbamation conditions gave a mixture of the desired carbamate **373** (73%) and 23% of **374**, arising from cleavage of the acetate in the second step of the reaction (scheme 123). This second carbamate was contaminated with an unidentified impurity. This impurity was also present when the reaction was repeated, but using sodium hydroxide in place of potassium carbonate to try to obtain solely **374**. More careful monitoring of the second step, and work-up as soon as all of the intermediate had been consumed gave a marginally improved yield of **373** of 79%.



Scheme 123 Carbamation of allylic alcohol 367

Both of these carbamates are valid TA substrates, and so were both subjected to TA conditions (scheme 124). Unfortunately, neither afforded the expected product. Both ^1H NMR spectra of the crude product were complicated, suggesting a multicomponent mixture.



Scheme 124 Attempted TA of carbamates **373** and **374** *Reagents and conditions* $\text{K}_2\text{OsO}_2(\text{OH})_4$ (4 mol%), EtN^iPr_2 (5 mol%), NaOH (0.92 eq.), $t\text{BuOCl}$ (1 eq.), $n\text{PrOH-H}_2\text{O}$ (5:3), rt

Subjection of monoacetate **365** to TA conditions did not effect any major changes. The starting material was recovered almost in its entirety, with a very small amount of an unidentified impurity. The TA of carbamate **373** was repeated, omitting the work-up procedure. 56% of the starting carbamate was recovered.

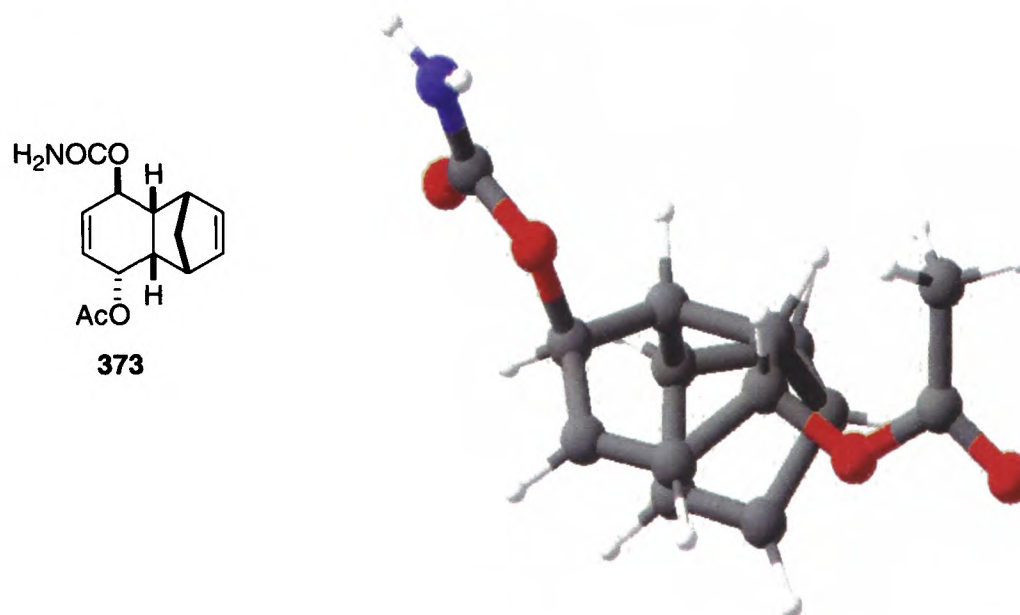


Figure 29 MM-2 model of carbamate **373** showing the pseudo-axial conformation of the carbamate

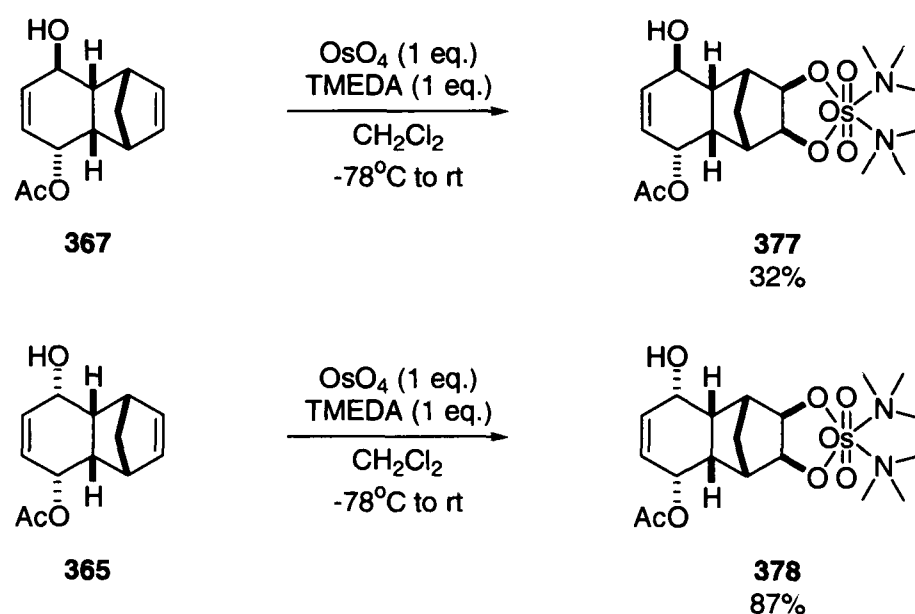
The lack of a clean TA reaction in this instance is believed to be due to geometric constraints. The carbamate in **373** is pseudo-axial, and the rigid nature of the compound is such that it cannot achieve a reactive pseudo-equatorial conformation (figure 29 and figure 15, *vide supra*).

4.3 Second synthetic strategy

The flexibility in the acetylation of *meso*-diol **364** allows the synthesis of either enantiomeric series, and thus the order of oxidations required to install the necessary heteroatoms around the ring could be in either order. With this in mind, a route performing dihydroxylation first was attempted as a second strategy.

4.3.1 OsO₄ – TMEDA oxidation of monoacetates **364** and **367**

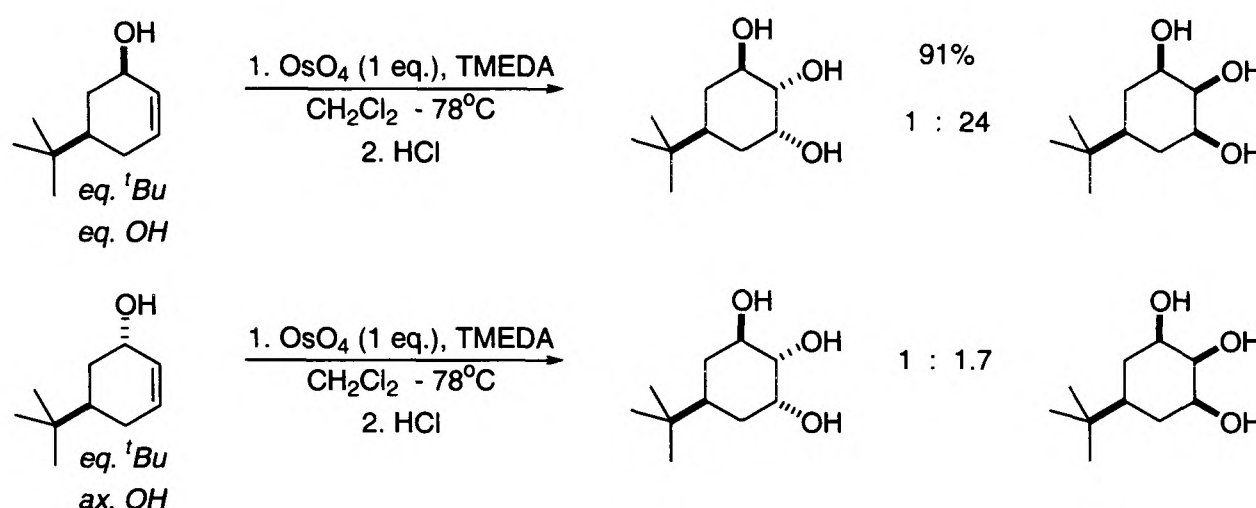
The starting points for this strategy were the isomeric monoacetates **365** and **367**. Both have two double bonds, so there was an issue of regioselectivity of the dihydroxylation. To try to bias this selection, the reactions were performed first using stoichiometric OsO₄ and TMEDA.⁸⁸ It was hoped that the presence of an allylic alcohol would allow directed dihydroxylation.



Scheme 125 OsO₄ – TMEDA oxidation of acetates **365** and **367**

At first surprisingly, both acetates **365** and **367** provided the distal osmate esters **378** and **377** respectively. This might be expected for the *endo* isomer **365**, where hydrogen-bond direction would involve delivery of the osmium tetroxide oxidant from the more hindered concave face of the molecule. Oxidation could then be expected to occur more rapidly on the more electron-rich double bond. The lack of a directing effect in **367** can be reasoned as for the failure of the TA in the same substrate. TMEDA direction in cyclic systems only works effectively if the directing group can

adopt an equatorial configuration (scheme 126), as axial substituents pose a greater steric barrier to the incoming oxidant.¹⁶¹



Scheme 126 Requirement for equatorial alcohol in directed dihydroxylation

The identity of **377** and **378** was elucidated simply by interpretation of the ¹H NMR and COSY spectra. The presence of two allylic protons with electron-withdrawing groups immediately inferred the regioselectivity of the oxidation. In addition, the *gem*-protons on the methylene bridge were now in markedly different environments. This would be expected if the osmate ester were situated as in **377** and **378**.

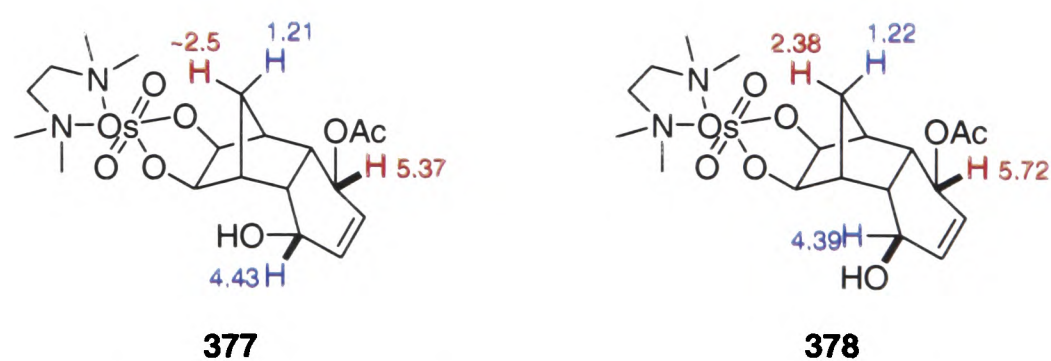
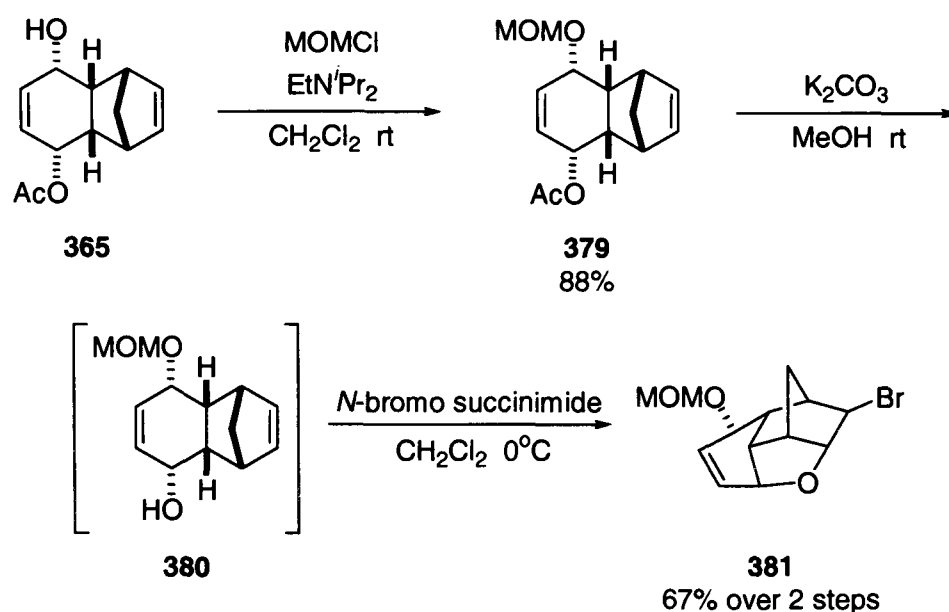


Figure 30 Selected ¹H NMR data for osmate esters 377 and 378

4.3.2 Protection of distal double bond

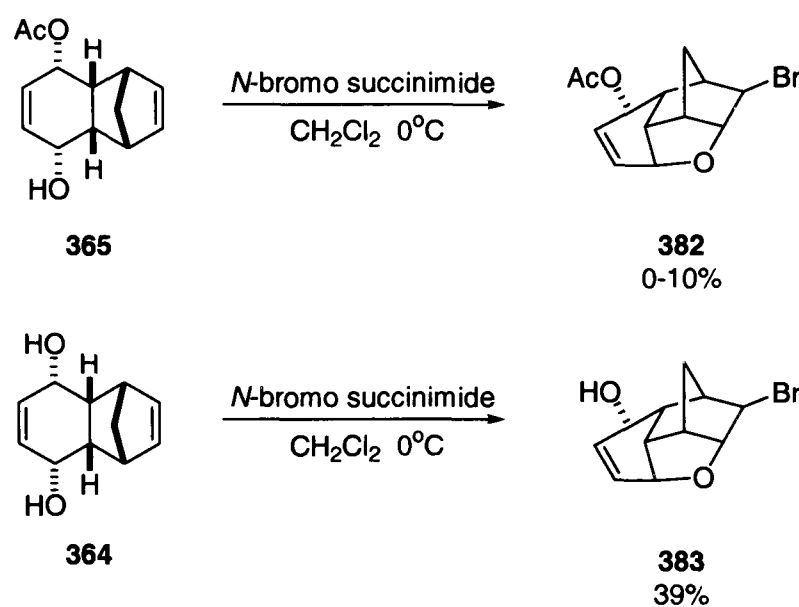
Clearly for this initial dihydroxylation route to be viable, the distal double bond must be protected in some way so that it is not dihydroxylated in addition to or in preference to the required allyl system. Ogasawara has had similar problems in his studies on the system. One solution was to treat alcohol **380** with *N*-bromosuccinimide

(NBS), forming the cage structure **381** (scheme 127).¹⁶² This was later deprotected using zinc metal and acetic acid.



Scheme 127 Ogasawara protection of distal double bond

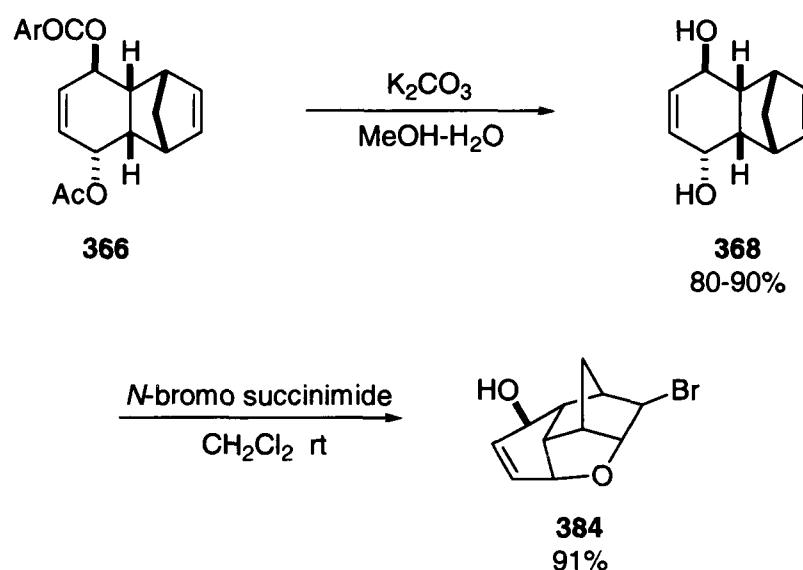
Obviously only *endo* alcohols will react in this way. Treatment of both **365** and **364** with NBS led to the formation of the desired THFs, but in poor yields.



Scheme 128 Poor-yielding NBS cyclisation of alcohols **364** and **365**

The failure of the acetate **365** was no great surprise. Ogasawara has gone to some lengths to avoid performing the reaction on that substrate (scheme 127).¹⁵⁴ A myriad of products were formed. Products resulting from α -bromination are the likeliest contaminants. The diol **364** was more disappointing. The reaction consistently

formed a second spot on the TLC plate that by ^1H NMR was clearly a mixture of several compounds.

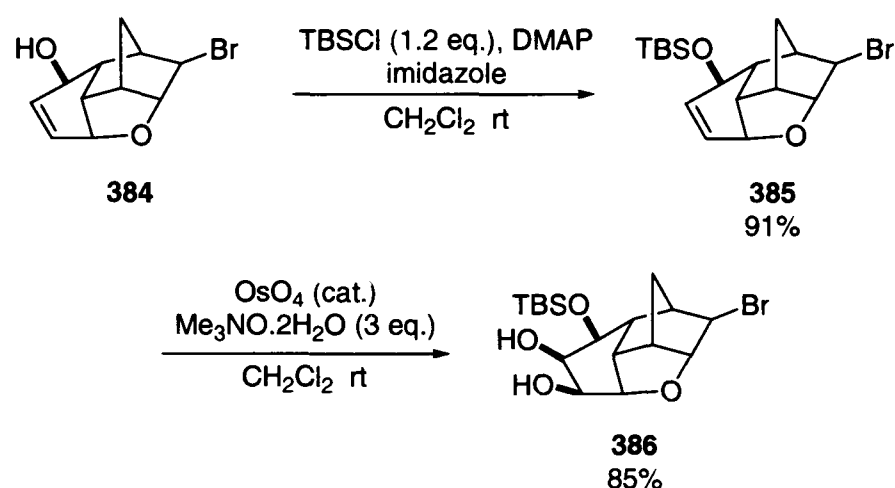


Scheme 129 Synthesis and NBS cyclisation of *trans*-diol **368**

The *trans*-diol **368** would also be a valid substrate for this reaction. Conceptually this route is simply an alteration to the order of steps necessary to establish the correct stereochemistry around the ring. **368** is formed by basic cleavage of the diester **366** (scheme 129). Extended reaction times (~1-2 days) or elevated temperatures were necessary using potassium carbonate as base. NBS cyclisation of **368** proceeded much more smoothly than for the earlier substrates, giving a 91% yield of the bromo ether **384**.

4.3.3 Dihydroxylation of the cage structure

While installation of the requisite diol unit across the double bond would be facile, future discrimination of the three hydroxyl groups would be difficult. Thus allylic alcohol **384** was first protected as its *tert*-butyl dimethylsilyl ether **385** (scheme 130). Dihydroxylation with catalytic osmium tetroxide gave a good yield of the diol **386**. The oxidation occurred from the convex face with complete stereospecificity, owing to the biased structure of **385**.



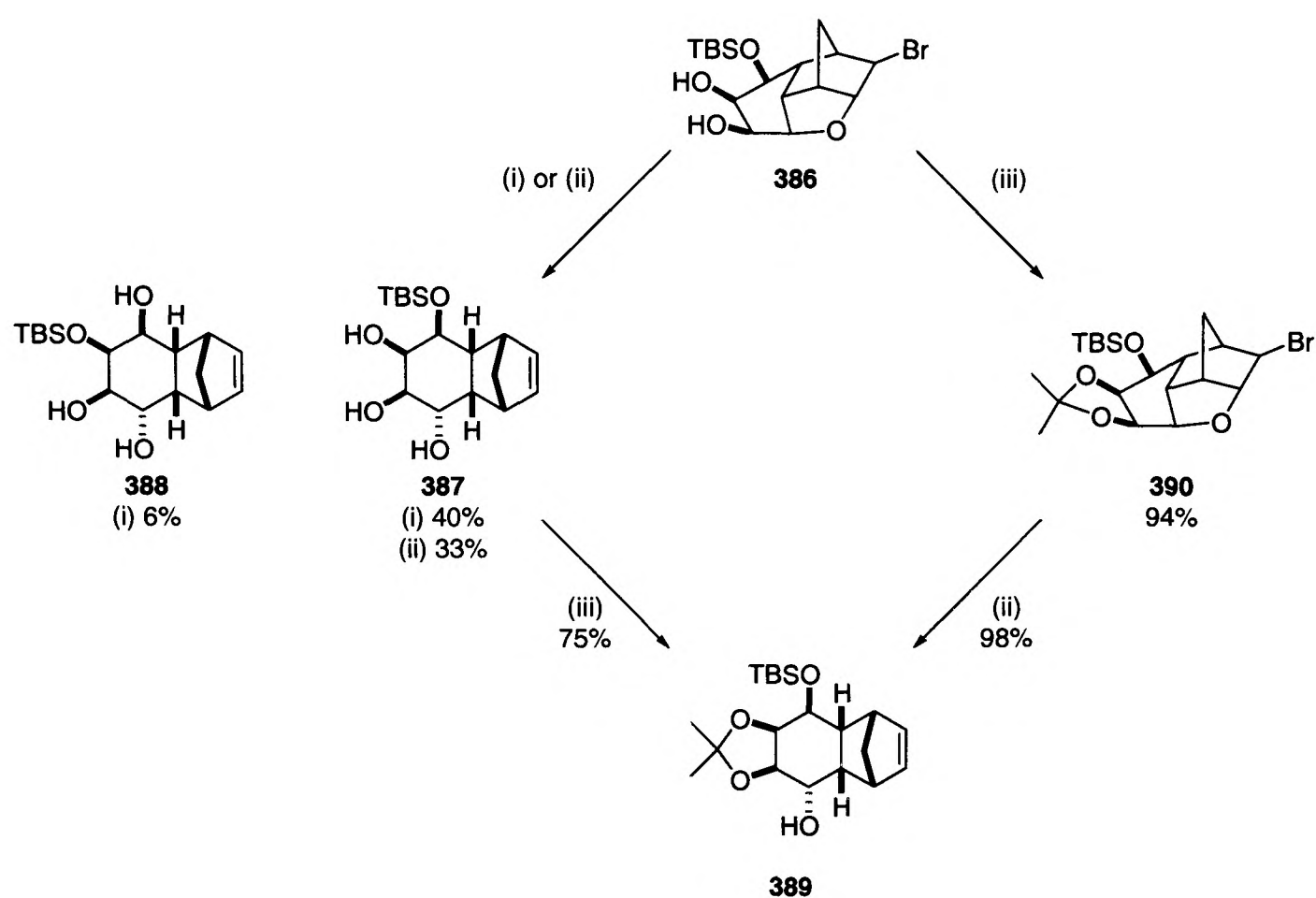
Scheme 130 Silyl protection of 384 and dihydroxylation of 385

4.3.4 Synthesis of acetonide 389

The diol unit introduced in the dihydroxylation step is protected by the methylene acetal in the final product. Owing to the difficulties in the installation of this protecting group, acetonide protection was initially chosen as a substitute. Formation of these acetals is straightforward and high yielding.

Opening of the bromo-THF protecting group was also necessary, in order to expose the double bond required for a retro-Diels-Alder reaction. This could be performed either in advance of acetonide protection, or subsequently (scheme 131). Two sets of conditions were employed for opening of the THF. Ogasawara quotes the use of zinc metal and acetic acid in refluxing methanol.¹⁵⁴ Under these conditions the diol **386** was converted to the triol **387**. The acetonide could be installed across the *syn* hydroxyl groups with 2,2-dimethoxypropane and catalytic tosic acid (75%). The ring-opening reaction also produced a minor (6%) product, believed to be **388** in which the TBS group has migrated.

Disappointed by the low yield for the first of these steps, the order was reversed. Formation of the acetonide **390** proceeded in excellent yield (94%). Concern over the stability of the acetonide in refluxing acidic solution led to the use of Birch conditions to open the THF. The reaction was remarkably clean, requiring only extraction from the aqueous quench and no further purification. Unfortunately the application of these conditions to the diol **386** did not improve the yield.



Scheme 131 Synthesis of acetonide **389** *Reagents and conditions* (i) Zn (8 eq.), AcOH (cat.), MeOH, reflux; (ii) (a) Na (5 eq.), NH₃, THF, -78°C (b) aq. NH₄Cl, rt; (iii) TsOH (cat.), 2,2-dimethoxypropane, acetone, rt

The crystal structures of acetonides **389** and **390** are displayed in figure 31. Both show the stereochemistry of the oxygen atoms around the ring. These were now established in the same configuration as in the final product **327**.

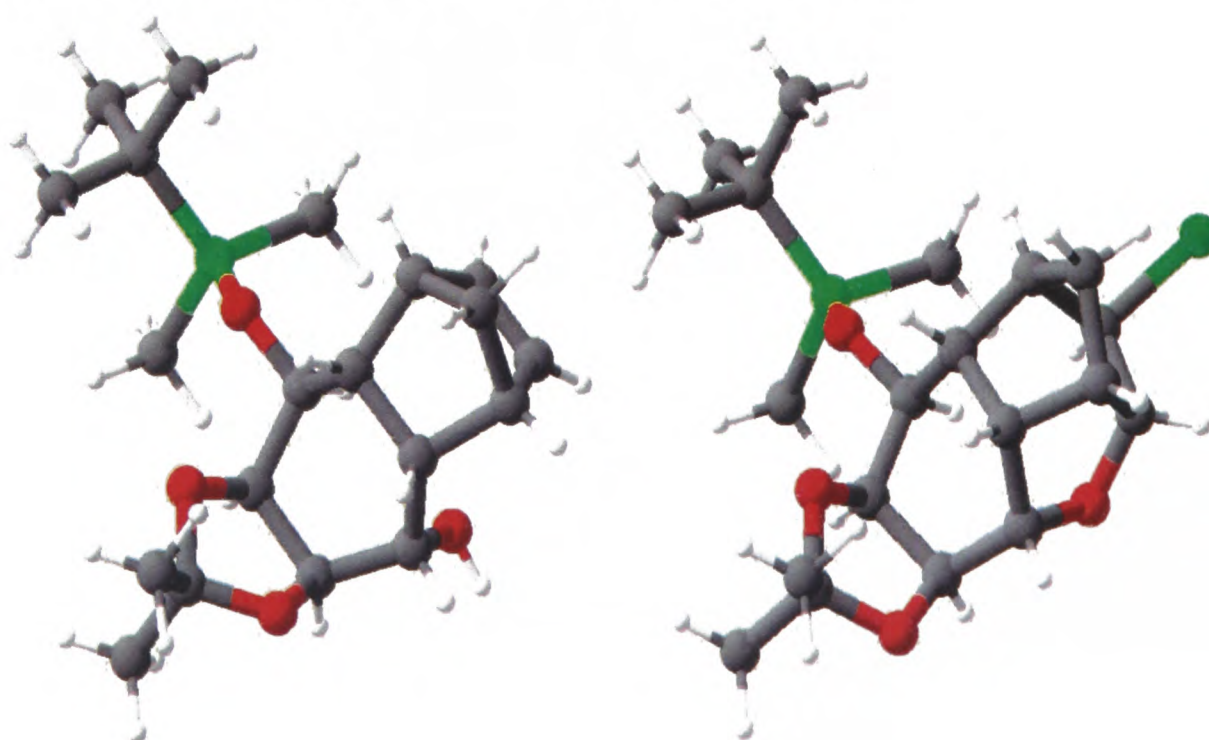
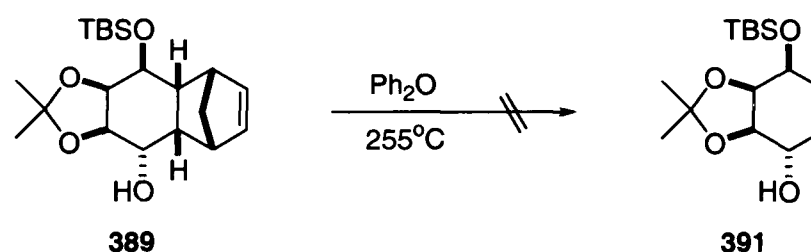


Figure 31 Crystal structures of acetonides **389** and **390**

4.3.5 Attempted retro-Diels-Alder reaction of acetonide 389

With acetonide **389** in hand, the retro-Diels-Alder reaction could be attempted.¹⁵⁴ A solution of **389** in diphenyl ether was heated to 255°C for one hour. TLC analysis of the mixture is difficult, particularly on small scales, as a minimum volume of solvent was necessary so measurement of the temperature with an internal thermometer was possible. The reaction mixture was filtered through silica, and the solvent washed off with petrol, with the products later eluted with ethyl acetate.

After one hour, only starting material was observed in the ¹H spectrum of the collected and concentrated column fractions. This was resubjected to the reaction conditions for a further eight hours, at which point no starting material was observed by ¹H NMR. No olefinic signals were present in the ¹H spectrum, thus the reaction had not proceeded as expected (*vide infra*).



Scheme 132 Failed retro-Diels-Alder reaction of acetonide **389**

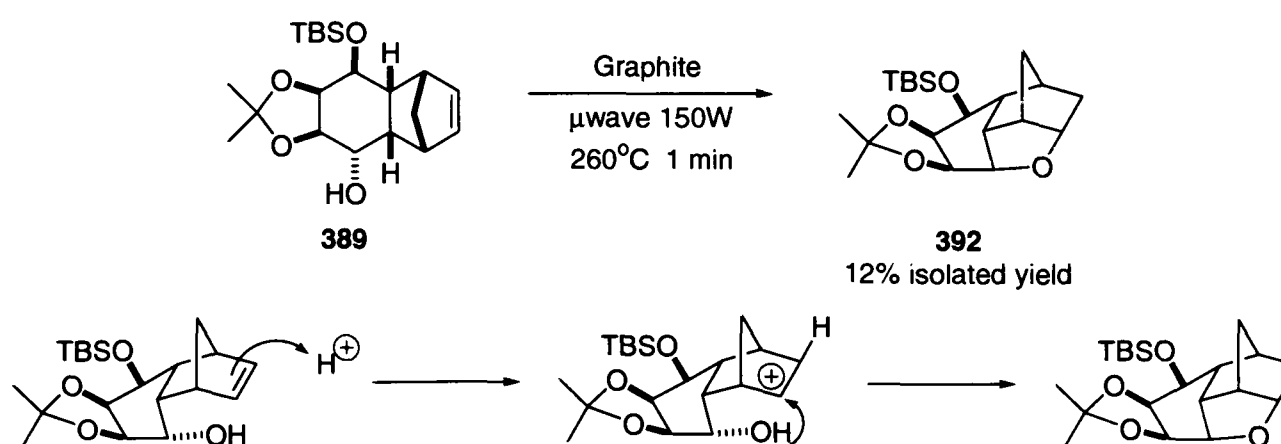
The long reaction time, at such high temperature, mean that many alternative reactions may be possible. In an attempt to minimise side-reactions, the retro-Diels-Alder reaction was performed in a microwave. A number of protocols exist for microwave reactions.¹⁶³ They can be performed neat,¹⁶⁴ in solvent or on a number of solid-supports.¹⁶⁵⁻¹⁶⁷ The most notable of these solid supports is graphite.^{168, 169} Under microwave irradiation, graphite heats up extremely quickly, due primarily to its high thermal conductivity, or more specifically its low specific heat capacity.¹⁷⁰

The reaction was attempted a number of times under microwave conditions. All runs were using 30 mg of **389**, and either 170 mg of the solid support or 1 mL of solvent. The microwave was irradiating with a power of 150 W. Other conditions for each reaction are summarised in table 34.

Reaction no.	Support/solvent	Time (min)	T_{max} ($^{\circ}C$)	P_{max} (psi)
1	Graphite	1	262	3
2	Graphite	5	263	3
3	Graphite	10	260	3
4	Neat	1	-	-
5	Silica	1	170	4
6	Basic Al_2O_3	1	115	-
7	Neutral Al_2O_3	1	141	3
8	1,4 dioxane	1	105	10
9	1,4-dioxane	20	-	-
10	Water	20	-	-

Table 34 Summary of conditions for microwave-assisted retro-Diels-Alder reaction. No entry indicates the value was not measured.

Reactions 4 through 10 all returned unreacted starting material, contaminated with an unknown impurity. The reactions performed on graphite were the most interesting. All three cleanly returned a product that contained no olefinic protons, but had features similar to those of the caged THF compounds. Purification of the material by chromatography, and careful inspection of the 1H NMR and mass spectra identified the unknown as **392**. Its formation is likely to be due to adventitious acid in the reaction promoting cyclisation as in scheme 133. This unknown was the same product as formed under standard thermal conditions.



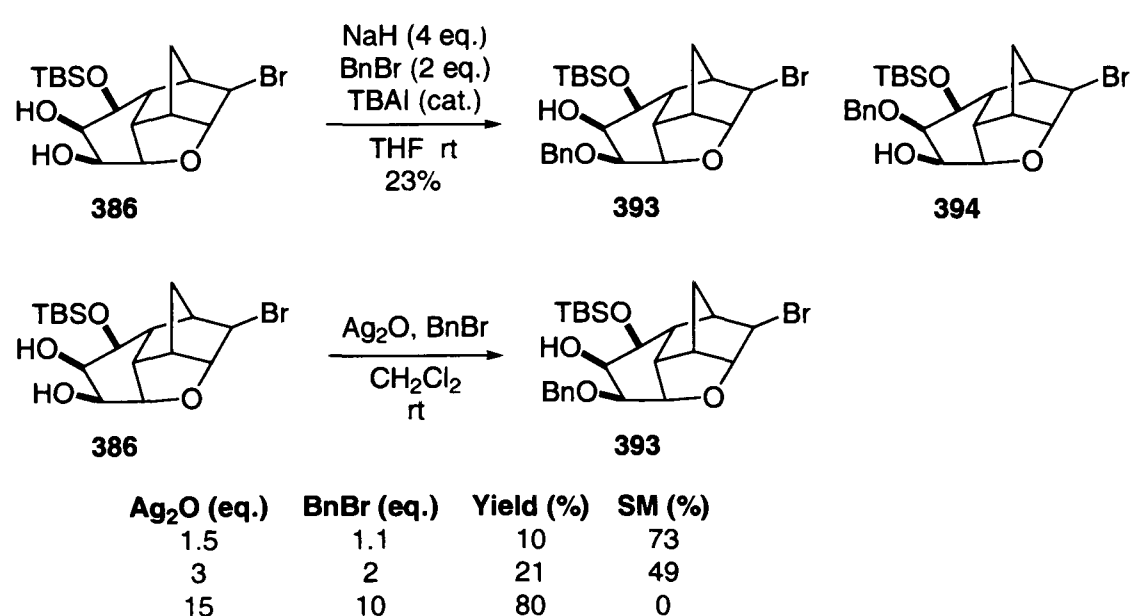
Scheme 133 Outcome of attempted retro-Diels-Alder reaction and mechanism for formation of 392

Repetition of the reaction in diphenyl ether, with the inclusion of sodium hydrogen carbonate to remove any acid present, simply led to recovered starting material. Thus it seemed that the thermal barrier to the reaction was simply too high to be achieved in this manner.

4.3.6 Alternative retro-Diels-Alder substrates

It was postulated that the acetonide was prohibiting the reaction. All literature examples of similar substrates undergoing retro-Diels-Alder chemistry did not contain a similar cyclic acetal.^{154, 171, 172} Thus two separate series of compounds involving acyclic protection were synthesised. Benzyl protection was chosen for its ease of removal, and methoxymethyl (MOM) protection was chosen with a view to later installation of the methylene acetal by intramolecular trans-acetalisation.

The benzyl-protected series was begun by benzylation of diol **386**. Attempts to produce the bis-benzyl compound failed, producing only a mixture of the two monobenzylated compounds **393** and **394** (scheme 134). Monobenzylation was deemed sufficient for our requirements. A recent paper has described the efficient monobenzylation of diols using benzyl bromide in the presence of silver oxide.¹⁷³

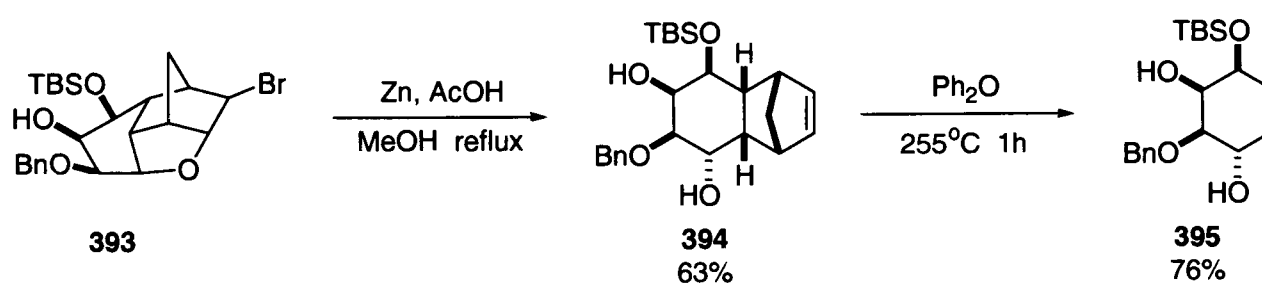


Scheme 134 Benzylation of diol **386**

Treatment of diol **386** with 1.5 equivalents of silver oxide and 1.1 equivalents of benzyl bromide led to a small, but significant, 10% yield of monobenzylated product,

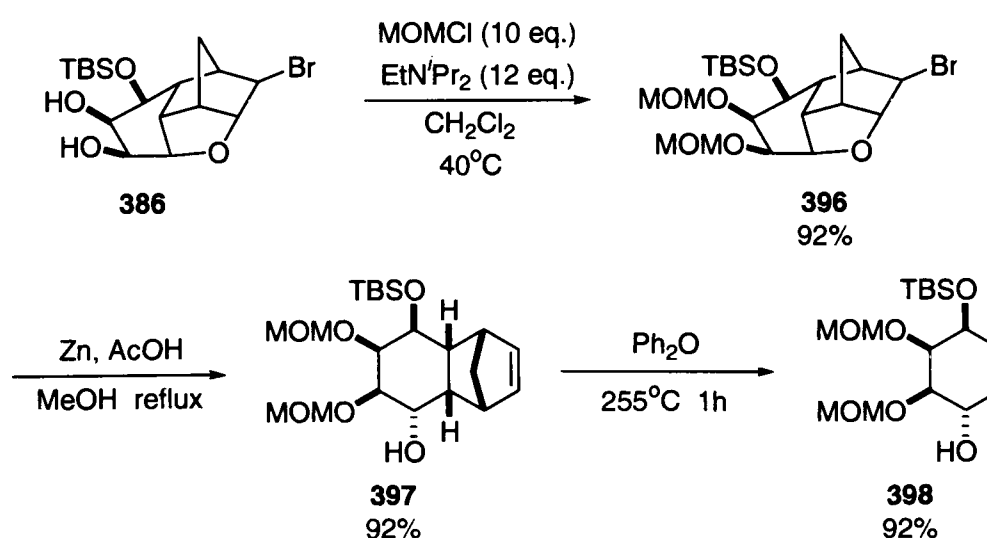
with 79% recovered starting material. Importantly the benzylation had been completely selective, producing only one of the possible regioisomers. Gradual increments in the amount of silver oxide and benzyl bromide used eventually gave a 80% yield of the monobenzyl compound **393**.

Birch conditions for the ring opening of the THF were avoided, to preclude reduction of the benzyl group. Zinc-acetic acid cleavage furnished the alcohol **394** in 63% yield (scheme 135). Pleasingly, and as postulated, this tricyclic compound *did* undergo a retro-Diels-Alder reaction to give the protected conduritol B compound **395**.



Scheme 135 Synthesis and successful retro-Diels-Alder of **394**

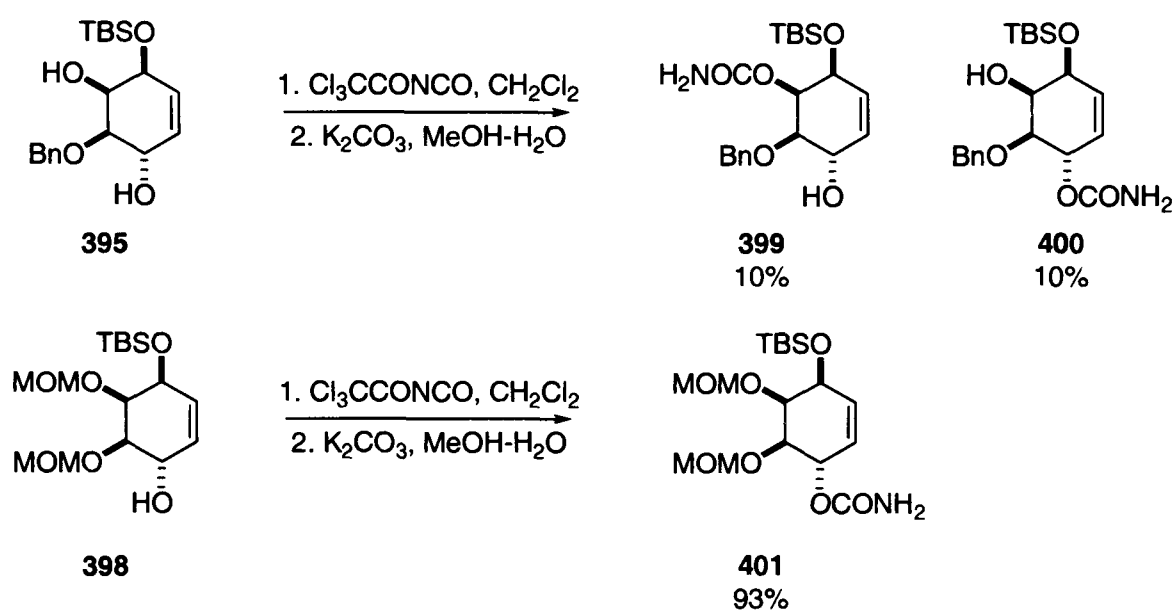
Synthesis of the MOM series was uneventful (scheme 136). Treatment of diol **386** with methoxymethyl chloride and Hünig's base gave the bis-MOM compound **396**. Birch conditions for the THF ring opening gave a poor 36% yield, but the zinc – acetic acid procedure gave a superior 92% yield of the alcohol **397**. Again, simple thermal conditions effected the retro-Diels-Alder reaction, to give **398** in 92% yield.



Scheme 136 Synthesis of bis-MOM conduritol B **398**

4.3.7 Carbamation and TA of 395 and 398

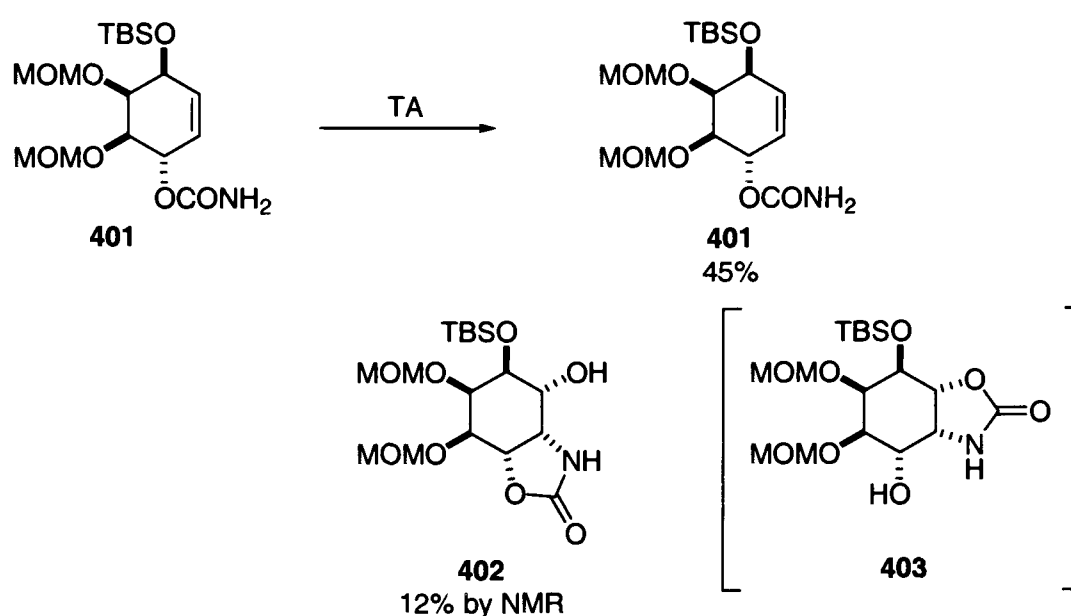
Both of the allylic alcohols were subjected to the standard carbamation procedure. While the bis-MOM alcohol **398** cleanly gave the desired carbamate **401** in 93% yield, the benzylated compound **395** gave a mixture of carbamates. The steric bulk of the TBS group and the benzyl group was not enough to preclude reaction at the alcohol they surrounded.



Scheme 137 Carbamation of 395 and 398

The TA was then performed on the bis-MOM carbamate **401**. Initial analysis was promising. TLC indicated the formation of a new spot at lower R_f , and the ^1H NMR spectrum of the crude product showed the presence of a new broad peak at 5.2 ppm, suggestive of the formation of an oxazolidinone. However the integration of that spectrum suggested that the ratio of starting material to product was about 4:1.

Attempts to isolate the product only succeeded in producing small (~3%) amounts of material that was obviously not pure by ^1H NMR spectroscopy. GC - mass spectral analysis of this sample detected a compound with the same mass as **402** as the major component. It is possible that oxazolidinone migration accounts for the impurity in the mixture.



Scheme 138 TA of carbamate **401** gives a poor yield *Reagents and conditions* $\text{K}_2\text{OsO}_2(\text{OH})_4$ (4 mol%), EtN^iPr_2 (5 mol%), NaOH (0.92 eq.), $^t\text{BuOCl}$ (1 eq.), $^n\text{PrOH-H}_2\text{O}$ (5:3), rt/45°C

The poor yield was discouraging. As the carbamate **401** should have an equatorial arrangement (figure 32) it should be geometrically suitable for reaction to take place. The reaction clearly *can* occur, but either slowly or disfavourably and thus it would appear that more subtle effects are operating in this system.

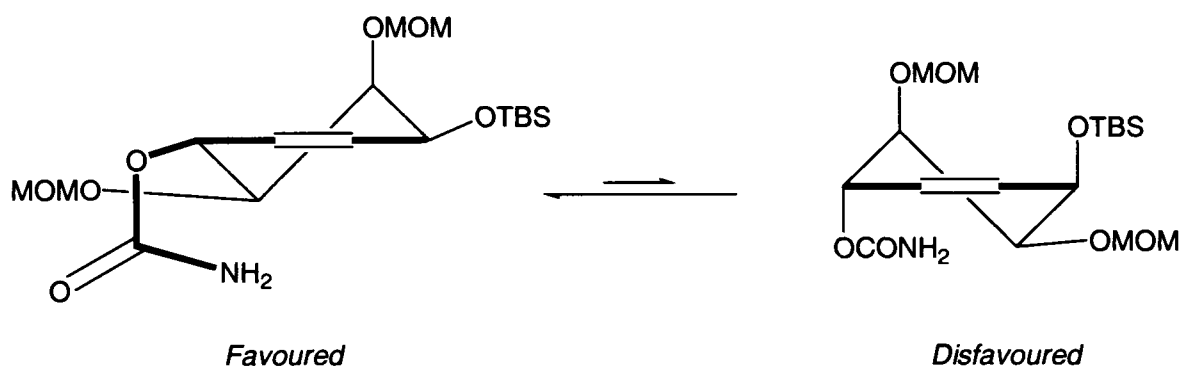
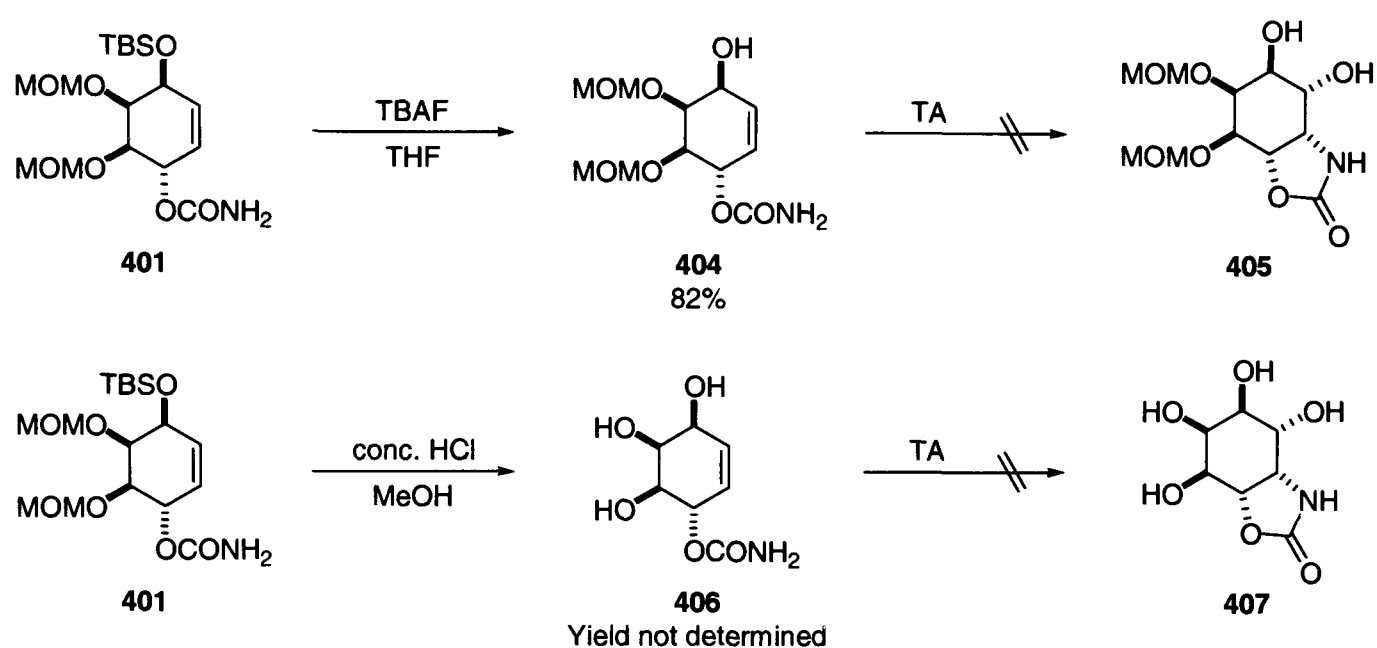


Figure 32 The favoured conformation of **401** should have an equatorial carbamate

Elevated temperature (45°C) or an increase in the catalyst loading to 50% did not produce significantly greater proportions of product. Removal of the TBS group gave the alcohol **404**, which it was hoped would be less hindered and allow a more successful TA (scheme 139). This was not the case, with reactions at both room temperature and at 45°C predominantly returning starting material. The ^1H NMR spectra of the reactions hinted that the reaction may have occurred to some small degree, but no isolable amounts of product were isolated.



Scheme 139 TA of deprotected derivatives was also unsuccessful *TA reagents and conditions* $\text{K}_2\text{OsO}_2(\text{OH})_4$ (4 mol%), EtN^iPr_2 (5 mol%), NaOH (0.92 eq.), $t\text{BuOCl}$ (1 eq.), $n\text{PrOH-H}_2\text{O}$ (5:3), $\text{rt}/45^\circ\text{C}$

Removal of all protecting groups from **401** was accomplished by treatment with concentrated hydrochloric acid (scheme 139). TA of this compound also gave mostly recovered starting material, with only a suggestion that some product had been formed in the ^1H NMR spectrum. Further studies into the effect of conformation on the outcome of the reaction were curtailed when another avenue yielded results.

4.4 Third synthetic strategy

The previous route had involved the protection of the distal double bond of **367** as the bromo-THF derivative **384**. This compound too contains an allylic alcohol that could be used to install nitrogen and oxygen atoms of the target *via* the TA. The earlier attempt to use this hydroxyl to tether the nitrogen source had met with failure, due to its pseudo-axial conformation. In contrast, the ethereal linkage of **384** acts as a ‘drawstring’, imposing greater strain throughout the molecule and pulling the alcohol closer to an equatorial position (figure 33). If the model predicted above (section 2.5.5) is correct, this may be enough of a change in conformation to permit the TA to occur.

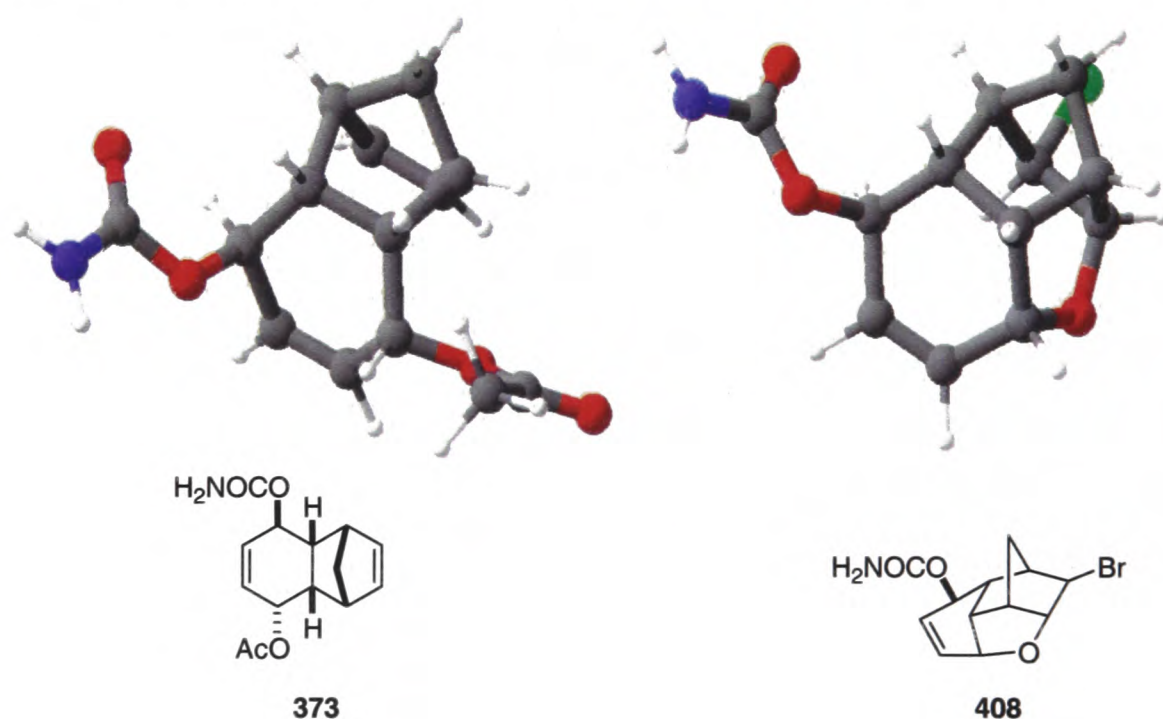
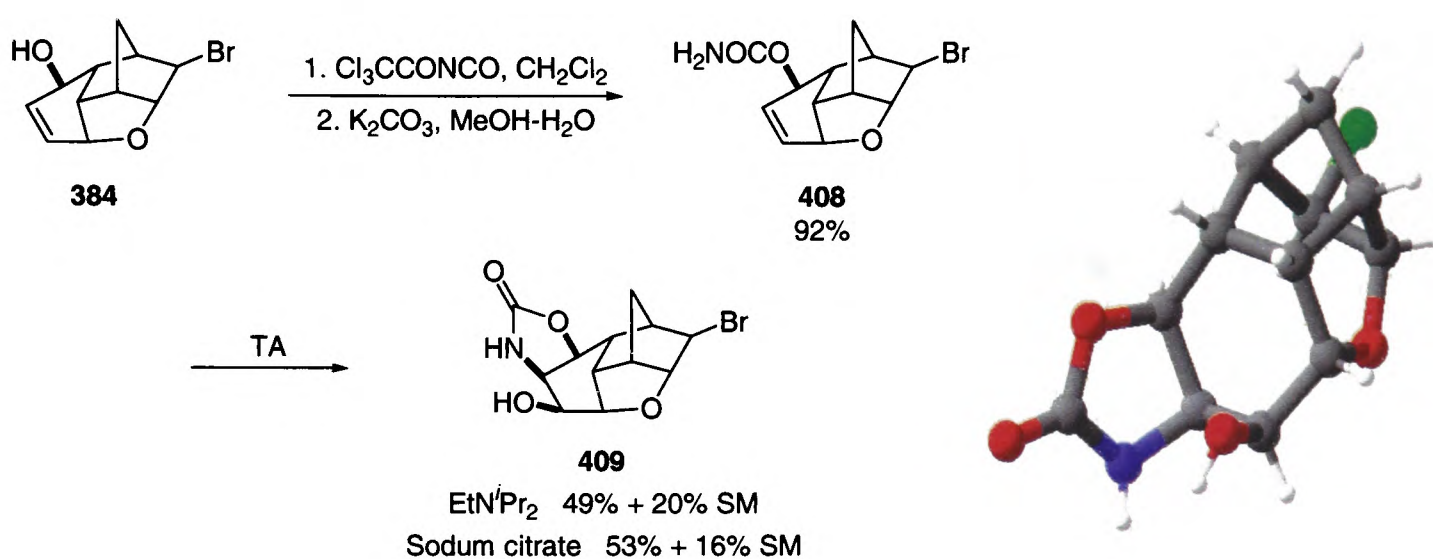


Figure 33 Models of carbamates 373 and 408 showing the effect of the THF linkage on the conformation of the carbamate tether

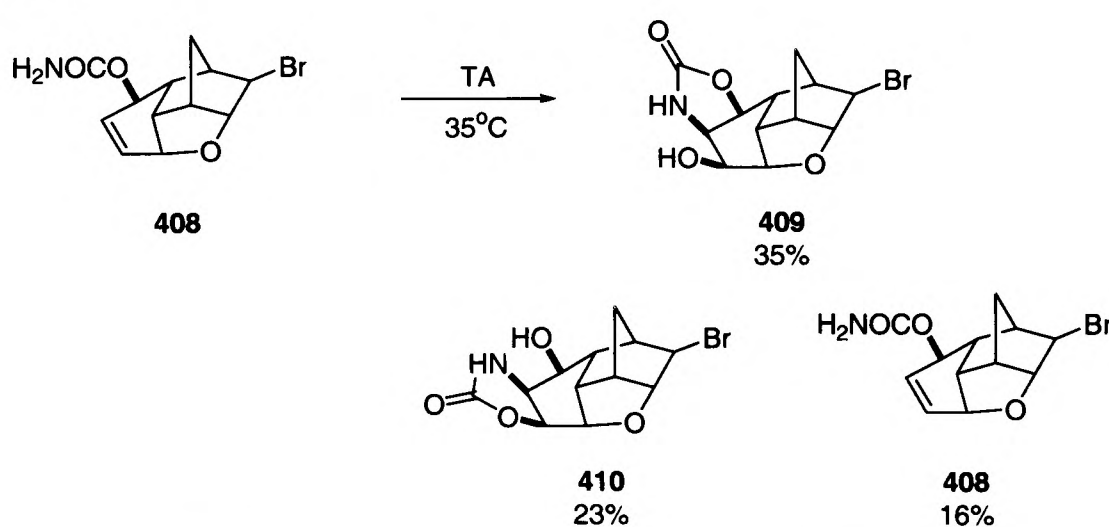
4.4.1 Synthesis and TA of carbamate 408

Carbamation of **384** was performed under standard conditions, to give **408** in 92% yield (scheme 140). The TA was then undertaken, using Hünig's base as the ligand. Pleasingly, the reaction proceeded well, affording the crystalline TA product **409** (49%), along with 20% recovered **408**. The product **409** was insoluble in most solvents with pyridine being the most effective. Crystallisation of **409** from pyridine allowed X-ray analysis to confirm the structure.



Scheme 140 Synthesis and TA of carbamate **408** and crystal structure of **409**. *TA reagents and conditions* K₂OsO₂(OH)₄ (4 mol%), EtNⁱPr₂ (5 mol%) or sodium citrate (20 mol%), NaOH (0.92 eq.), ^tBuOCl (1 eq.), ⁿPrOH-H₂O (5:3), 0°C

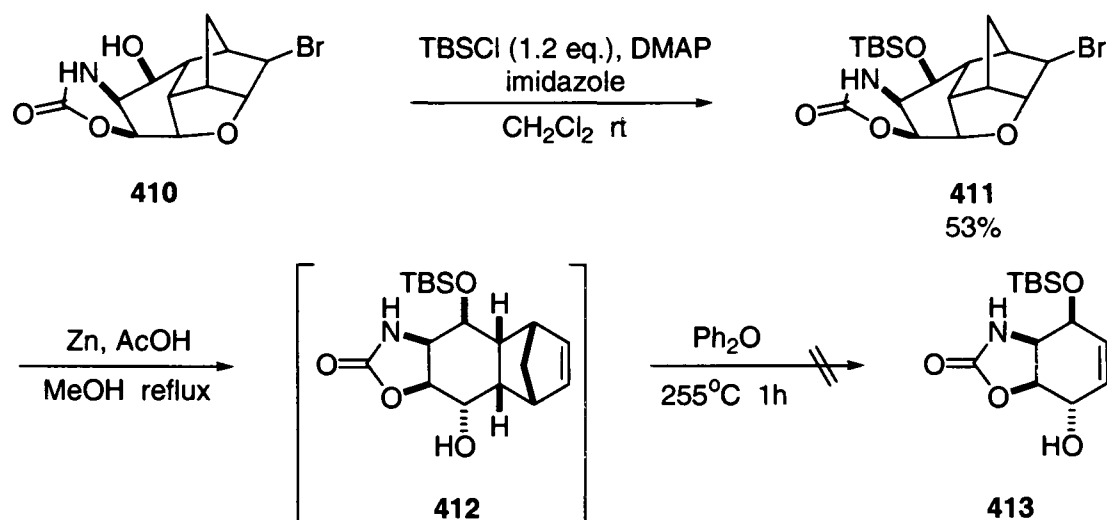
The recently developed use of sodium citrate in the TA (*vide supra*, section 2.7) had given hope that the yield could be enhanced further. Unfortunately, the use of this ligand did not lead to any significant improvement in yield, although work-up was simplified. Performing this reaction at a high ambient temperature (35°C), a notable amount of a second product was formed (scheme 141). Isolation and analysis of this compound showed it to be the isomerised oxazolidinone **410**. Future TA reactions of **408** would be conducted at 0°C, resulting in a 5-10% drop in yield but removing isomerisation.



Scheme 141 Higher temperatures induce isomerisation in the TA of **408**

Attempts to incorporate this isomerised material into the synthesis were unsuccessful. Subjection of the oxazolidinone to basic conditions led to an equilibrium

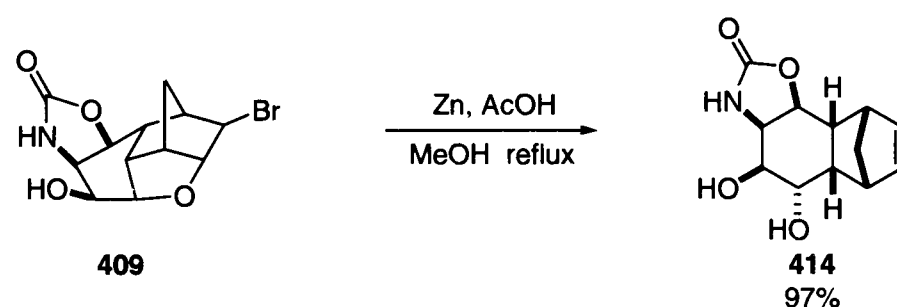
mixture of **409** and **410** (~1:1). As with the acetone **389** (*vide supra*, section 4.3.5), heating compound **412** did not effect a retro-Diels-Alder reaction.



Scheme 142 Isomerised oxazolidinone does not undergo retro-Diels-Alder chemistry

4.4.2 Synthesis of protected cyclohexenes **416**, **418** and **420**

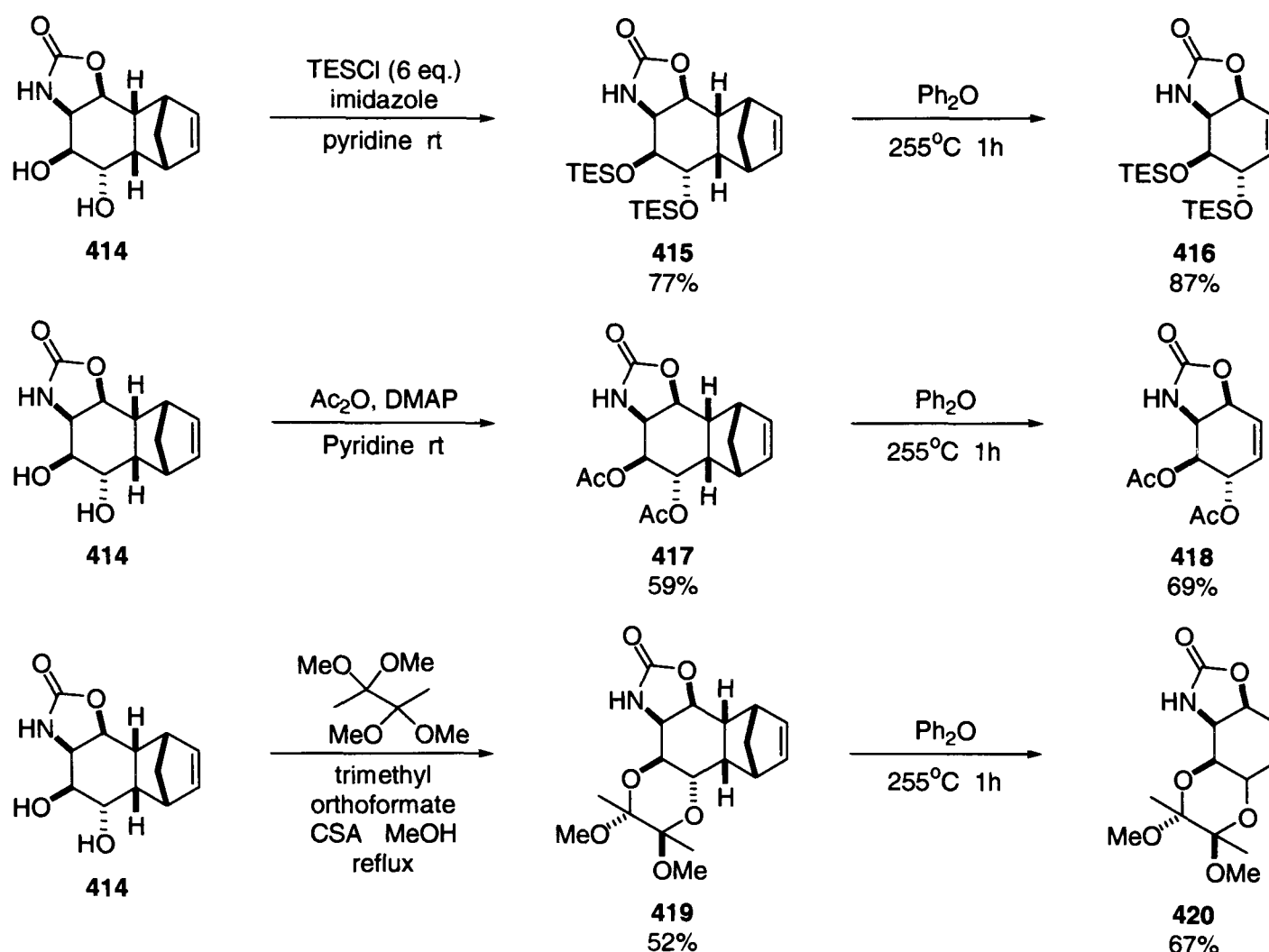
Continuation of the sequence from the TA product entailed zinc-acetic acid cleavage of the THF ether, which gave diol **414** in an excellent 97% yield (scheme 143). The product was again insoluble in most solvents, with the exception of pyridine.



Scheme 143 Zinc – acetic acid opening of THF in TA product **409**

Protection of the diol prior to performing the retro-Diels-Alder reaction would reduce the polarity of the product and make purification more straightforward. Thus three different derivatives of **414** were synthesised. The triethylsilyl group was chosen solely to reduce the polarity of the product. Acetates were used to attempt to influence the diastereoselectivity of the subsequent dihydroxylation (*vide infra*). The bispoke acetal was used to try and restrict the conformation of the molecule and accentuate any facial preference in the dihydroxylation step.¹⁷⁴

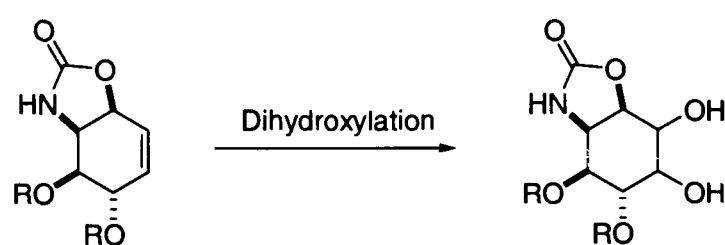
All the protection reactions worked smoothly, but only in moderate yield (scheme 144). Tetramethoxybutane was synthesised according to a literature protocol, which claimed greater success in the installation of the bis-acetal by transacetalisation than by direct formation from the diketone.¹⁷⁵ The retro-Diels-Alder reactions were all performed under standard thermal conditions, in diphenyl ether at 255°C. Compounds **415** and **420** have not been fully characterised to date.



Scheme 144 Synthesis of protected cyclohexenes **416**, **418** and **420**

4.4.3 Dihydroxylation of cyclohexenes **416**, **418** and **420**

The final key step is installation of the last two oxygen atoms, which are protected as the methylene acetal in the final product. All three protected cyclohexenes were subjected to dihydroxylation conditions as described in table 35.



Reaction conditions	 421	 422	 423
Upjohn	-	20% (2:1) (49% SM)	-
Poli ^a	42% (1:1)	67% (1.8:1)	63% (1.5:1)
AD: (DHQ) ₂ AQN	0% (22% SM)	0%	-
AD: (DHQD) ₂ AQN	-	(57% SM)	-
AD: (DHQ) ₂ PYR	0%	-	-

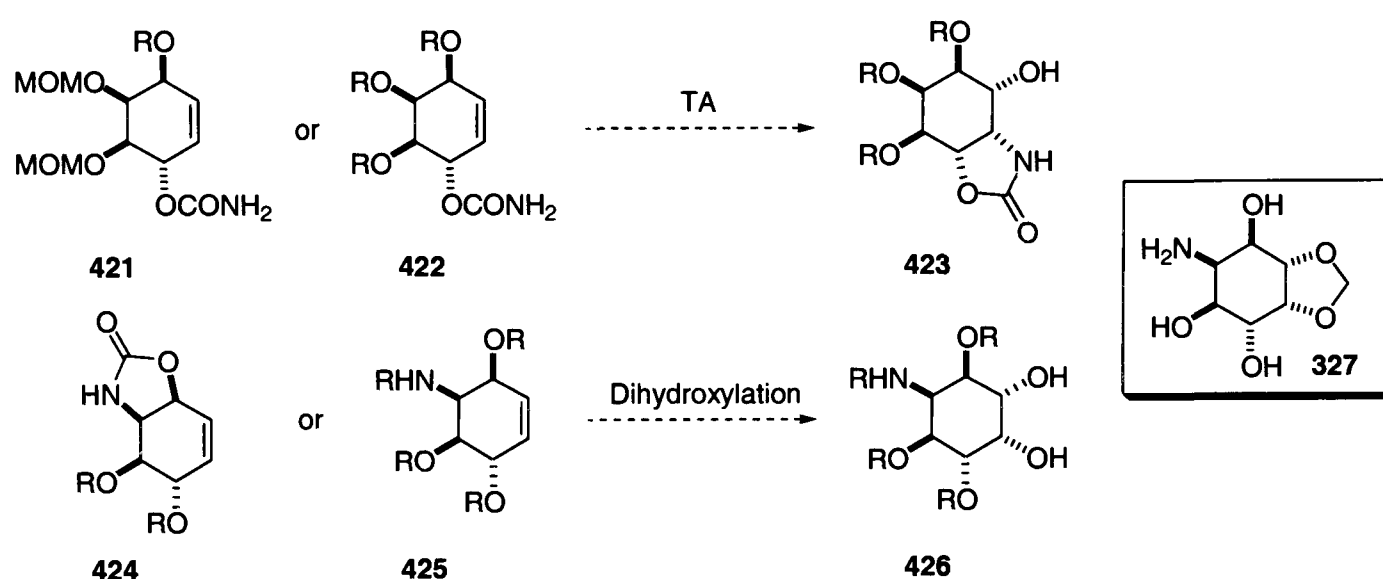
Table 35 Yields and diastereomeric ratios for dihydroxylations of 416, 418 and 420 under various conditions ^a*Poli conditions* OsO₄ (cat.), Me₃NO.2H₂O (3 eq.), quinuclidine, CH₂Cl₂ (-) denotes no reaction has been performed

Disappointingly, none of the derivatives gave particularly high selectivities. The electron-poor nature of the double bond also makes the dihydroxylations slow. Frustratingly, the use of Sharpless AD chemistry to try and impose stereoselectivity on the reaction was unsuccessful, presumably due to the hindered nature of the substrates.

The selectivities closely resemble those obtained by Ogawa in the total synthesis of hygromycin A (*vide supra*, section 3.3.2).^{130, 131} In that instance, his best selectivity was 2:1 in favour of the desired stereoisomer. Tentatively the stereochemistry of the major isomers is ascribed as the same. Arjona was able to enhance that selectivity by choice of protecting group, noting that electron-withdrawing allylic substituents would direct the oxidation to the same face.¹³⁸ In the above systems, there is an electron-withdrawing group in the oxazolidinone, thus the electronic bias is for the undesired isomer. Time constraints have prevented further investigation to determine protecting groups that would grant better diastereoselectivity.

4.5 – Conclusion

Approaches towards the aminocyclitol fragment of hygromycin A have led to two synthetic routes with promise for future development and completion of the synthesis. Adjustment of the conformation of **421** (scheme 145) should allow tethered aminohydroxylation to install the final heteroatoms around the cyclohexene ring. The attractiveness of this route is the complete diastereoselectivity of both key oxidative steps.



Scheme 145 Future work to complete the synthesis of **327**

The second involves tethered aminohydroxylation earlier in the synthetic sequence, and requires adjustment of the protecting groups used so as to bias the dihydroxylation of cyclohexene **424** in favour of the desired stereoisomer of the diol **426**. Installation of the methylene acetal and deprotection will then afford the aminocyclohexitol **327**.

Experimental section

5.1 – General Experimental

THF was dried prior to use by distillation from sodium-benzophenone ketyl under an atmosphere of argon. DCM was dried prior to use by distillation from calcium hydride under an atmosphere of argon. Petrol refers to the fraction of petroleum ether boiling between 40 and 60°C. Diisopropylamine, ethyldiisopropylamine and triethylamine were both dried by stirring over and distilling from calcium hydride (at reduced pressure where necessary). Diisopropylamine was stored over 4Å molecular sieves. Triethylamine and ethyldiisopropylamine were stored over calcium hydride granules. 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 Armerego.¹⁷⁶ All non-aqueous reactions were carried out under an atmosphere of argon using oven-dried glassware.

Flash column chromatography was carried out according to the method of Still¹⁷⁷ with silica gel 60 (0.040-0.063 mm) (Merck) using head pressure by means of head bellows. Thin layer chromatography was performed on commercially available pre-coated aluminium-backed plates (Merck silica Kieselgel 60F₂₅₄). Spots were made visible either by the quenching of UV fluorescence, or by staining with a potassium permanganate solution or an anisaldehyde solution.

Analytical HPLC was used for the determination of enantiomeric excess, e.e., using a Waters 600E System Controller, a Waters 991 Photodiode Array detector and a Daicel Chiralpak AD column.

Elemental analyses were carried out in the microanalytical laboratory in the Chemistry Department of the University of Manchester. Melting points were obtained using a Reichert Kofler heated-stage microscope and are uncorrected.

Proton NMR spectra were recorded using Varian Inova 300 (300 MHz), Varian Inova 500 (500 MHz) and Bruker DQX 400 (400 MHz) Fourier transform spectrometers. Carbon NMR spectra were recorded using Varian Inova 300 (75 MHz) and Bruker DQX 400 (100 MHz) instruments. Chemical shifts (δ) are quoted in parts per million (ppm) relative to tetramethylsilane ($\delta = 0.00$). Coupling constants, J , are quoted in Hz and are quoted in the same order as the splitting pattern. The abbreviations s, d, t, q, sp, br and m denote singlet, doublet, triplet, quartet, septet, broad

and multiplet respectively. Where a mixture of diastereomers can be seen in the spectrum, the resonance for each diastereomer is quoted with the fraction of the overall integral for the proton(s) concerned attributable to that diastereomer. Carbon NMR spectra were recorded with broad band proton decoupling.

Infrared spectra were recorded on a Perkin Elmer Paragon 1000 or an ATI Mattson Genesis series FTIR spectrophotometer and analysed either as thin films between NaCl plates or as solutions in chloroform. Absorption maxima (ν_{max}) are quoted in wavenumbers (cm^{-1}) to 4 significant figures and only structurally significant peaks are quoted.

Mass spectra (m/z) were recorded on a Micromass 500 OAT spectrometer under chemical ionisation conditions (CI), using NH_3 as the ionising source, or on a VG Platform instrument under electrospray (ES) ionisation conditions. Accurate mass (HRMS) was recorded on a Micromass 500 OAT. Values are quoted as a ratio of mass to charge in Daltons.

Optical rotations were recorded on a Perkin Elmer 241 polarimeter (using the sodium D line; 589 nm) and $[\alpha]_{\text{D}}$ values are given in units of $10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$. Solution concentrations are quoted in units of $10^{-2} \text{ g mL}^{-1}$.

5.2 – General Procedures

Preparation of *tert*-Butyl hypochlorite¹⁷⁸

A 5% aqueous NaOCl solution (500 mL) was prepared from a stock bleach preparation and cooled to less than 10 °C. The fumehood lights were switched off, and a solution of *t*-BuOH (37 mL) in glacial acetic acid (25 mL) was added in one portion. The mixture was allowed to stir for 3 minutes. The reaction mixture was separated and the organic layer washed with 10% aqueous Na₂CO₃ solution (50 mL) and water (50 mL). The product was dried (CaCl₂) and filtered to yield *tert*-butyl hypochlorite as a yellow liquid. The product was stored below 4 °C in the dark over CaCl₂.

General Carbamate Formation Procedure⁷⁵

Trichloroacetyl isocyanate (1.2 eq.) was added dropwise to a solution of the alcohol (1 eq.) in dry CH₂Cl₂ (1.5 mL/mmol) at 0 °C. After stirring for 2 h, or until TLC showed no starting material present, the mixture was concentrated under reduced pressure and the residue dissolved in MeOH (2 mL/mmol). This solution was cooled to 0 °C and an aqueous K₂CO₃ solution (3 eq., 0.5 mL/mmol) was added. The cooling bath was removed and the mixture allowed to stir for 4 h, by which time TLC showed complete conversion. The MeOH was evaporated under reduced pressure and the aqueous residue was extracted with CH₂Cl₂. The combined organics were dried (MgSO₄), filtered and concentrated under reduced pressure to yield the crude carbamate, which was purified by column chromatography or recrystallisation if necessary.

General Tethered Aminohydroxylation Procedure

A fresh, aqueous solution of NaOH (80 μM, 0.9 eq.) was prepared. All but a few drops of this was added in one portion to a magnetically stirred solution of the allylic carbamate (1 eq.) in *n*-PrOH (12 mL/mmol). The solution was allowed to stir for 5 minutes, then *tert*-butyl hypochlorite (1 eq.) was added. The mixture was again allowed to stir for 5 minutes. To this was then added the ligand (either EtN^{*i*}Pr₂ or (DHQ)₂PHAL) (5 mol %) in one portion. The mixture was allowed to stir for a further

5 minutes before the final addition of a solution of potassium osmate (4 mol%) in the remainder of the NaOH solution made previously. The reaction was followed by TLC until the solution turned black, which denoted the end of turnover. The reaction was quenched by the addition of Na₂SO₃ (500 mg), and allowed to stir for 30 minutes. The mixture was extracted with EtOAc, and the organic layer washed with brine. The organic layer was then collected and concentrated under reduced pressure. The crude product was purified by column chromatography.

General Luche Reduction Procedure⁸³

The enone was dissolved in MeOH (10 mL/g enone) and cerium chloride heptahydrate added (1.48 g/10 mL solvent). The stirred solution was cooled to 0 °C and sodium borohydride (1.1 eq.) was added in 100 mg portions. The viscous mixture was stirred vigorously for 18 h. The reaction was quenched with water and extracted with CH₂Cl₂. The extracts were dried (MgSO₄) and concentrated under reduced pressure to yield the crude alcohol. The crude product was purified by column chromatography.

General Aza-glycolate Osmate Ester Preparation Procedure

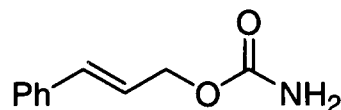
A fresh, aqueous solution of NaOH (0.9 eq.) was prepared using minimal water to dissolve the solid. This was added in one portion to a magnetically stirred solution of the allylic carbamate (1 eq.) in *n*-PrOH (12 mL/mmol). The solution was allowed to stir for 5 minutes, then *tert*-butyl hypochlorite (1 eq.) was added. The mixture was again allowed to stir for 5 minutes. A solution of potassium osmate (1 eq.) in a small amount of the NaOH solution was added and the mixture allowed to stir for a further 5 minutes before the final addition of TMEDA (1 eq.). The reaction mixture was allowed to stir overnight, and then the solvents were removed under reduced pressure. The crude product was purified by column chromatography.

General oxazolidinone cleavage – peracetylation procedure

The oxazolidinone was dissolved in MeOH (5 mL/mmol). An aqueous solution of NaOH (10 eq., 2.5 mL/mmol) was added and the mixture heated at reflux for 16 h. The reaction mixture was concentrated, and redissolved in pyridine (2 mL/mmol). Acetic

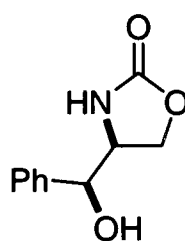
anhydride (1 mL/mmol) and DMAP (cat.) were added and the mixture stirred for 6 h. The reaction was diluted with aqueous CuSO₄, and extracted with EtOAc. The combined organic extracts were concentrated, and the residue purified by column chromatography.

5.3 – Experimental details for chapters 2.2-2.3

***trans*-Cinnamyl carbamate 176¹⁷⁹**

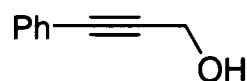
trans-Cinnamyl alcohol **178** (4.0 g, 30 mmol) was subjected to the general carbamate formation procedure, affording the carbamate **176** without purification as an off-white solid (5.0 g, 94%).

¹H NMR δ_{H} (300 MHz; CDCl₃) 7.44-7.28 (5 H, m, ArH), 6.69 (1 H, d, *J* 16.0, ArCH), 6.33 (1 H, dt, *J* 16.0 and 6.5, CH₂CH), 4.85 (2 H, br s, NH₂) and 4.78 (2 H, dd, *J* 6.5 and 1.0, CH₂).

(1'*RS*, 4*RS*)-4-[1'-Hydroxyphenylmethyl]-oxazolidin-2-one 179¹⁸⁰

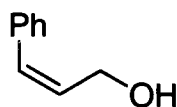
trans-Cinnamyl carbamate **176** (200 mg, 1.1 mmol) was subjected to the general tethered aminohydroxylation procedure, using EtN^{*i*}Pr₂ as the ligand. Purification of the crude compound by column chromatography (EtOAc - petrol, 60:40) afforded the oxazolidinone **179** as a white crystalline solid (135 mg, 62%).

*R*_f (EtOAc) 0.44; m.p. 142-143 °C; **IR** ν_{max} (CHCl₃) 3366 (OH), 3230 (NH) and 1730 (C=O); **¹H NMR** δ_{H} (500 MHz; CDCl₃) 7.43-7.35 (5 H, m, ArH), 5.54 (1 H, br s, NH), 4.63 (1 H, dd, *J* 7.5 and 3.5, PhCH), 4.23 (1 H, t, *J* 9.0, CH_AH_BO), 4.12 (1 H, dd, *J* 9.0, 5.5, CH_AH_BO), 4.06 (1 H, m, CHNH) and 2.48 (1 H, d, *J* 3.5, OH); **¹³C NMR** δ_{C} (CDCl₃) 159.0 (C=O), 139.1, 129.2, 126.5 (Aryl C), 76.3 (ArCH), 66.4 (CH₂O), 58.0 (CHNH); **MS** *m/z* (CI) 211 (MNH₄⁺) and 194 (100%, MH⁺); **HRMS (CI)** Found: MH⁺, 194.0816. C₁₀H₁₂NO₃⁺ requires *M*, 194.0817.

3-Phenyl-prop-2-yn-1-ol 189⁷⁷

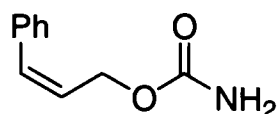
A solution of DIBAL-H in hexane (1 M, 34 mL, 34 mmol) was added to a solution of phenylpropionic acid **188** (1.0 g, 6.8 mmol) in Et₂O (20 mL) at –50 °C. The solution was allowed to warm to room temperature and stirred for 25 h, by which time TLC indicated no remaining starting material. The reaction mixture was cooled to 0 °C, and ice was added until the mixture solidified. A 10% aqueous solution of sulphuric acid was added until the solid had dissolved. The mixture was extracted with Et₂O (2 × 50 mL), dried (MgSO₄) and concentrated *in vacuo*. Column chromatography (EtOAc – petrol 10:90) afforded the alcohol **189** as an oil (660 mg, 74%).

¹H NMR δ_{H} (300 MHz; CDCl₃) 7.50-7.47 (2 H, m, ArH), 7.37-7.30 (3 H, m, ArH), 4.55 (2 H, d, *J* 5.0, CH₂O), 1.83 (1 H, d, *J* 5.0, OH).

***cis*-Cinnamyl alcohol 190⁷⁸**

Lindlar catalyst (100 mg) was added to a solution of 3-phenyl-prop-2-yn-1-ol **189** (600 mg, 4.6 mmol) in MeOH (10 mL). The resulting suspension was stirred under H₂ for 45 minutes, by which time TLC showed no starting material present. The reaction mixture was filtered through celite and the filtrate concentrated *in vacuo* to yield the alcohol **190** as an oil in a 10:1 ratio of *cis:trans* isomers, with some saturated material (540 mg, 88%). The product was carried forward without purification.

¹H NMR δ_{H} (300 MHz; CDCl₃) 7.42-7.24 (5 H, m, ArH), 6.62 (1 H, d, *J* 12.0, PhCH), 5.92 (1 H, dt, *J* 12.0 and 6.5, CH₂CH), 4.49 (2 H, d, *J* 6.5, CH₂) and 1.56 (1 H, br s, OH).

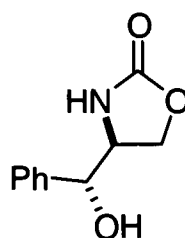
***cis*-Cinnamyl carbamate 187**

cis-Cinnamyl alcohol **190** (790 mg, 5.9 mmol) was subjected to the general carbamate formation procedure, affording the *carbamate* **187** as a white solid (920 mg, 88%, 10:1

cis:trans). Recrystallisation twice from petrol – CHCl₃ gave the carbamate as white needles (490 mg, 98:2 *cis:trans*).

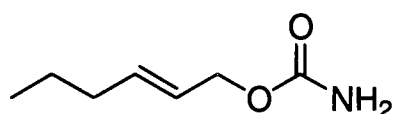
R_f (EtOAc) 0.71; m.p. 73 °C; **IR** $\nu_{\max}$ (CHCl₃) 3423, 3386 (NH₂), 1720 (C=O) and 1596 (NH₂); **¹H NMR** δ_H (300 MHz; CDCl₃) 7.43-7.25 (5 H, m, ArH), 6.70 (1 H, d, J 12.0, PhCH), 5.86 (1 H, dt, J 12.0 and 6.5, CH₂CH) and 4.89 (4 H, dd and br s, J 6.5 and 2.0, CH₂ and NH₂); **¹³C NMR** δ_C (CDCl₃) 156.7 (C=O), 136.0, 132.7 (CH=CH), 128.7, 128.3, 127.4, 126.1 (4 × Aryl C) and 62.0 (CH₂); **MS** m/z (CI) 195 (MNH₄⁺), 178 (MH⁺), 134 (MH⁺ – CONH₂) and 117 (100%, MH⁺ – OCONH₂); **HRMS (CI)** Found MH⁺, 177.0787. C₁₀H₁₂NO₂⁺ requires M , 177.0790.

(1'SR, 4RS)-4-[1'-Hydroxyphenylmethyl]-oxazolidin-2-one 192⁷⁹



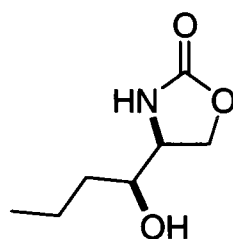
cis-Cinnamyl carbamate **187** (200 mg, 1.1 mmol) was subjected to the general tethered aminohydroxylation procedure, using EtN^{*i*}Pr₂ as the ligand. Purification of the crude compound by column chromatography (EtOAc - petrol, 60:40) afforded the oxazolidinone **192** as a white crystalline solid (130 mg, 61%).

R_f (EtOAc) 0.34; m.p. 139-141 °C (lit.⁷⁹ 140-142 °C); **IR** $\nu_{\max}$ (CHCl₃) 3385 (NH and OH), 2952, 2923, 2853 (CH), 1802 and 1715 (C=O); **¹H NMR** δ_H (300 MHz; CDCl₃) 7.45-7.40 (5 H, m, ArH), 5.02 (1 H, br s, NH), 4.73 (1 H, dd, J 6.5 and 2.5, PhCH), 4.57-4.46 (2 H, m, CH₂O), 4.04 (1 H, m, CHNH) and 2.54 (1 H, d, J 2.5, OH); **¹³C NMR** δ_C (CDCl₃) 161.6 (C=O), 138.6 (4° Aryl C), 128.5, 128.3, 126.5 (3 × Aryl C), 73.7, 67.1, 57.0; **MS** m/z (CI) 211 (MNH₄⁺) and 194 (100%, MH⁺); **HRMS (CI)** Found MH⁺, 194.0822. C₁₀H₁₂NO₃⁺ requires M , 194.0817.

(2E) - Hexenyl carbamate 194

(2E) - Hexenyl alcohol **196** (1.0 g, 10 mmol) was subjected to the general carbamate formation procedure, affording the *carbamate* **194** without purification as a white solid (1.3 g, 92%).

R_f (EtOAc) 0.74; m.p. 43–45 °C; **IR** $\nu_{\max}$ (CHCl₃) 3432, 3332 (NH₂), 1687 (C=O) and 1613 (NH₂); **¹H NMR** δ_H (400 MHz; CDCl₃) 5.77 (1 H, dtt, J 15.0, 7.0 and 1.0, CHPr), 5.57 (1 H, dtt, J 15.0, 6.5 and 1.0, CHCHPr), 4.85 (2 H, br s, NH₂), 4.50 (2 H, dt, J 6.5 and 1.0, CH₂O), 2.03 (2 H, qd, J 7.0 and 1.0, CH₂Et), 1.41 (2 H, sextet, J 7.0, MeCH₂) and 0.90 (3 H, t, J 7.0, Me); **¹³C NMR** δ_C (CDCl₃) 156.9 (C=O), 136.2 (CHPr), 124.2 (CHCH₂O), 66.9 (CH₂O), 34.3 (CH₂Et), 22.0 (MeCH₂) and 14.6 (CH₃); **MS** m/z (CI) 161 (100%, MNH₄⁺), 144 (MH⁺), 100 (MH⁺ – CONH₂) and 83 (MH⁺ – OCONH₂); **HRMS (CI)** Found MH⁺, 144.1025. C₇H₁₄NO₂⁺ requires M , 144.1024

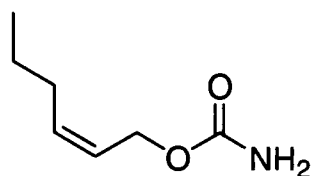
(1'RS, 4RS)-4-[1'-Hydroxybutyl]-oxazolidin-2-one 197

(2E) - Hexenyl carbamate **194** (200 mg, 1.4 mmol) was subjected to the general tethered aminohydroxylation procedure, using EtN^{*i*}Pr₂ as the ligand. Purification of the crude compound by column chromatography (EtOAc - petrol, 60:40) afforded the *oxazolidinone* **197** as a white crystalline solid (130 mg, 58%).

R_f (EtOAc) 0.35; m.p. 71–74 °C; **IR** $\nu_{\max}$ (CHCl₃) 3425 (br, OH, NH), 2961, 2934, 2873 (CH) and 1740 (C=O); **¹H NMR** δ_H (300 MHz; CDCl₃) 6.70 (1 H, br s, NH), 4.48 (1 H, t, J 8.5, CH_AH_BO), 4.23 (1 H, dd, J 8.5 and 5.5, CH_AH_BO), 3.81 (1 H, dt, J 9.0 and 5.5, CHNH), 3.58–3.48 (2 H, m, CHOH), 1.59 (1 H, m, MeCH₂CH_AH_B), 1.49–1.30 (3 H, m, MeCH₂CH_AH_B) and 0.98 (3 H, t, J 7.0, CH₃); **¹³C NMR** δ_C (CDCl₃) 160.8 (C=O), 72.6 (CH₂OR), 67.4 (CHNH), 57.3 (CHOH), 35.1, 18.6 (MeCH₂CH₂) and 13.8 (CH₃); **MS**

m/z (CI) 177 (MNH_4^+) and 160 (100%, MH^+); **HRMS (CI)** Found MH^+ , 160.0974. $\text{C}_7\text{H}_{14}\text{NO}_3^+$ requires M 160.0974.

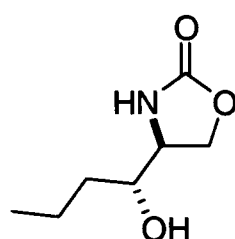
(2Z) - Hexenyl carbamate 193



(2Z) - Hexenyl alcohol **197** (1.0 g, 10 mmol) was subjected to the general carbamate formation procedure, affording the *carbamate* **193** without purification as a yellow oil (1.1 g, 79%).

R_f (EtOAc) 0.74; **IR** ν_{max} (film) 3468, 3348 (NH_2), 3023, 2960, 2932, 2872 (CH), 1723 (C=O) and 1602 (NH_2); **$^1\text{H NMR}$** δ_{H} (300 MHz; CDCl_3) 5.73-5.54 (2 H, m, CH=CH), 4.67 (4 H, d and br s, CH_2O and NH_2), 2.12 (2 H, q, J 7.5, CHCH_2Et), 1.44-1.35 (2 H, m, MeCH_2) and 0.95 (3 H, t, J 7.5, CH_3); **$^{13}\text{C NMR}$** δ_{C} (CDCl_3) 157.2 (C=O), 135.9 (CHPr), 123.6 (CHCH_2O), 60.9 (CH_2O), 29.4 (CH_2Et), 22.5 (MeCH_2) and 13.5 (CH_3); **MS** m/z (CI) 161 (100%, MNH_4^+), 144 (MH^+) and 83 ($\text{MH}^+ - \text{OCONH}_2$); **HRMS (CI)** Found MH^+ , 144.1027. $\text{C}_7\text{H}_{14}\text{NO}_2^+$ requires M 144.1024.

(1'SR, 4RS)-4-[1'-Hydroxybutyl]-oxazolidin-2-one 198⁸⁰

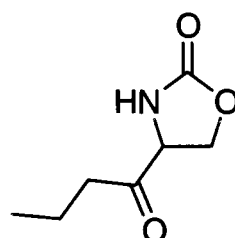


(2Z) - Hexenyl carbamate **193** (200 mg, 1.4 mmol) was subjected to the general tethered aminohydroxylation procedure, using EtN^iPr_2 as the ligand. Purification of the crude compound by column chromatography (EtOAc - petrol, 60:40) afforded the oxazolidinone **198** as a white crystalline solid (140 mg, 64%).

R_f (EtOAc) 0.33; m.p. 72-75 °C; **IR** ν_{max} (CHCl_3) 3305 (br, OH, NH), 2961, 2933, 2874 (CH) and 1746 (C=O); **$^1\text{H NMR}$** δ_{H} (300 MHz; CDCl_3) 6.63 (1 H, br s, NH), 4.47 (1 H, dd, J 8.5 and 5.5, $\text{CH}_\text{A}\text{H}_\text{B}\text{O}$), 4.42 (1 H, t, J 8.5, $\text{CH}_\text{A}\text{H}_\text{B}\text{O}$), 3.87 (1 H, m, CHNH), 3.74 (1 H, m, CHOH), 3.51 (1 H, d, J 4.0, OH), 1.54 (1 H, m, $\text{MeCH}_2\text{CH}_\text{A}\text{H}_\text{B}$), 1.44-1.29 (3

H, m, $\text{MeCH}_2\text{CH}_A\text{H}_B$) and 0.97 (3 H, m, CH_3); **^{13}C NMR** $\delta_{\text{C}}(\text{CDCl}_3)$ 161.0 (C=O), 70.7 (CH_2OR), 65.6 (CHNH), 56.9 (CHOH), 34.1 (MeCH_2CH_2), 18.8 (MeCH_2CH_2) and 13.8 (CH_3); **MS** m/z (CI) 177 (MNH_4^+) and 160 (100%, MH^+); **HRMS (CI)** Found MH^+ , 160.0973. $\text{C}_7\text{H}_{14}\text{NO}_3^+$ requires M 160.0974.

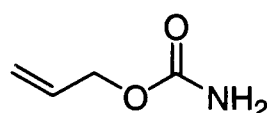
(4*RS*)-Butyryl-oxazolidin-2-one **199**



(1'*SR*,4*RS*)-4-[1'-Hydroxybutyl]-oxazolidin-2-one **198** (30 mg, 0.19 mmol) was dissolved in acetone (1 mL) and cooled to 0 °C. A solution of Jones' reagent (4 eq.) in acetone (10 cm³/cm³ reagent) was added over 5 min. Upon obtaining a red-brown colour signifying the end-point, *i*-PrOH was added dropwise until a deep green colour was obtained. The mixture was extracted with ether (2 × 15 mL) and the organics successively washed with H₂O (5 mL), sat. aq. NaHCO₃ (5 mL) and brine (5 mL). The extracts were dried (MgSO₄) and concentrated under reduced pressure, yielding the *ketone* (30 mg, 100%) without purification as a white solid.

m.p. 65-66 °C; **IR** ν_{max} (CHCl_3) 3289 (br, NH), 2967 (CH), 1756 (Oxazolidinone C=O) and 1724 (Ketone C=O); **^1H NMR** $\delta_{\text{H}}(300 \text{ MHz}; \text{CDCl}_3)$ 6.77 (1 H, br s, NH), 4.56 (1 H, t, J 8.5, $\text{CH}_A\text{H}_B\text{O}$), 4.37-4.27 (2 H, m, CHNH and $\text{CH}_A\text{H}_B\text{O}$), 2.46 (2 H, td, J 7.0 and 4.0, CH_2CO), 1.58 (2 H, sextet, J 7.0, MeCH_2) and 0.87 (3 H, t, J 7.0, CH_3); **^{13}C NMR** $\delta_{\text{C}}(\text{CDCl}_3)$ 206.8 (Ketone C=O), 159.5 (Oxazolidinone C=O), 66.2 (CH_2O), 59.7 (CHNH), 40.5 (COCH_2), 16.4 (MeCH_2) and 13.5 (CH_3); **MS** m/z (CI) 175 (100%, MNH_4^+) and 158 (MH^+); **HRMS (CI)** Found MH^+ , 158.0818. $\text{C}_7\text{H}_{12}\text{NO}_3^+$ requires M 158.0817.

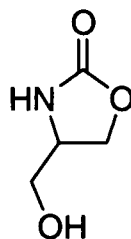
Allyl carbamate **200**⁸¹



Allyl alcohol **149** (0.87 g, 15 mmol) was subjected to the general carbamate formation procedure, affording the carbamate **200** without purification as a colourless oil (1.5 g, 97%).

^1H NMR δ_{H} (300 MHz; CDCl_3) 5.96 (1 H, ddt, J 17.0, 10.5 and 5.5, CHCH_2), 5.36 (1 H, dq, J 17.0 and 1.5, $\text{CH}_\text{A}\text{H}_\text{B}\text{CH}$), 5.26 (1 H, dq, J 10.5 and 1.5, $\text{CH}_\text{A}\text{H}_\text{B}\text{CH}$), 4.89 (2 H, br s, NH_2) and 4.60 (2 H, dt, J 5.5 and 1.5, OCH_2).

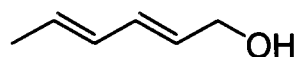
(4*RS*)-Hydroxymethyl-oxazolidin-2-one **201**¹⁸¹



Allyl carbamate **200** (200 mg, 2.0 mmol) was subjected to the general tethered aminohydroxylation procedure, using EtN^iPr_2 as the ligand. Purification of the crude compound by column chromatography (EtOAc) afforded the oxazolidinone **201** as a white crystalline solid (93 mg, 40%).

R_f (EtOAc) 0.14; m.p. 77-83 °C (lit.^x 77-81 °C); **IR** ν_{max} (Nujol) 3331, 3239 (NH, OH), 2952, 2853, 2923 (CH) and 1730 (C=O); **^1H NMR** δ_{H} (300 MHz; D_2O) 4.43 (1 H, t, J 9.0, Ring $\text{CH}_\text{A}\text{H}_\text{B}\text{O}$), 4.17 (1 H, dd, J 9.0 and 5.0, Ring $\text{CH}_\text{A}\text{H}_\text{B}\text{O}$), 3.94 (1 H, m, CHNH), 3.55 (1 H, dd, J 12.0 and 4.0, $\text{CH}_\text{A}\text{H}_\text{B}\text{O}$) and 3.46 (1 H, dd, J 12.0 and 4.5, $\text{CH}_\text{A}\text{H}_\text{B}\text{O}$); **^{13}C NMR** δ_{C} (D_2O) 162.0 (C=O), 67.6 (CH_2OR), 62.1 (CHNH), 53.4 (CH_2OH); **MS** m/z (CI) 135 (100%, MNH_4^+), 119 and 118 (MH^+); **HRMS (CI)** Found MH^+ , 118.0506. $\text{C}_4\text{H}_8\text{NO}_3^+$ requires M 118.0504.

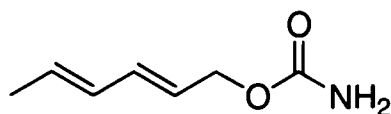
Sorbyl alcohol **203**¹⁸²



A solution of DIBAL-H in hexane (1 M, 31 mL, 31 mmol) was added to a solution of ethyl sorbate **202** (2.00 g, 14 mmol) in dichloromethane at -78 °C. The mixture was stirred for 1 h. Ethanol (40 mL) and saturated aqueous Na_2SO_4 (20 mL) were added sequentially and the mixture was allowed to warm to room temperature. The reaction mixture was filtered through celite and the filtrate concentrated *in vacuo*. Column chromatography (EtOAc – petrol, 1:9) afforded the alcohol **203** as an oil (626 mg, 45%).

^1H NMR δ_{H} (300 MHz; CDCl_3) 6.25 (1 H, dd, J 15.0 and 10.5), 6.10 (1 H, ddd, J 15.0, 10.5 and 1.5), 5.81-5.70 (2 H, m), 4.19 (2 H, d, J 6.0, CH_2), 1.80 (3 H, d, J 7.0, CH_3) and 1.40 (1 H, br s, OH).

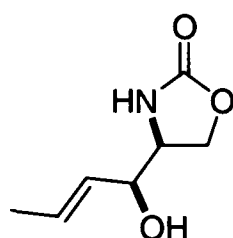
Sorbyl carbamate **204**



Sorbyl alcohol **203** (0.60 g, 6.1 mmol) was subjected to the general carbamate formation procedure, affording the *carbamate* **204** without purification as a yellow solid (0.68 g, 79%).

R_f (EtOAc) 0.74; m.p. 84-85 °C; **IR** ν_{max} (CHCl_3) 3504, 3864 (NH_2), 1725 (C=O) and 1586 (NH_2); **^1H NMR** δ_{H} (300 MHz; CDCl_3) 6.28 (1 H, dd, J 15.5 and 10.5, C^5H), 6.08 (1 H, ddd, J 15.0, 10.5 and 1.5, C^4H), 5.78 (1 H, dq, J 15.0 and 6.5, C^5H), 5.66 (1 H, dt, J 15.5, 6.5, C^2H), 4.89 (2 H, br s, NH_2), 4.59 (2 H, d, J 6.5, CH_2O) and 1.79 (3 H, d, J 6.5, CH_3); **^{13}C NMR** δ_{C} (CDCl_3) 156.8 (C=O), 134.5, 131.1, 130.3, 123.9 ($4 \times \text{CH}$), 65.5 (CH_2O) and 18.0 (CH_3); **MS** m/z (CI) 141 (MH^+) and 81 (100%, $\text{MH}^+ - \text{OCONH}_2$); **HRMS (CI)** Found MH^+ , 141.0788. $\text{C}_7\text{H}_{12}\text{NO}_2^+$ requires M 141.0790.

(1'*RS*, 2'*E*, 4*RS*)-4-[1'-Hydroxy-but-2'-enyl]-oxazolidin-2-one **205**



Sorbyl carbamate **204** (200 mg, 1.4 mmol) was subjected to the general tethered aminohydroxylation procedure, using EtN^iPr_2 as the ligand. Purification of the crude compound by column chromatography (EtOAc – petrol, 60:40) afforded the *oxazolidinone* **205** as an oil (91 mg, 41%).

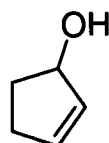
R_f (EtOAc) 0.39; **IR** ν_{max} (film) 3319 (br, OH, NH), 2973, 2917, (CH) and 1729 (C=O); **^1H NMR** δ_{H} (300 MHz; CDCl_3) 6.78 (1 H, br s, NH), 5.83 (1 H, dq, J 15.5 and 6.5, MeCH), 5.40 (1 H, dd, J 15.5 and 5.5, MeCHCH), 4.38 (1 H, t, J 9.0, $\text{CH}_\text{A}\text{H}_\text{BO}$), 4.15 (1 H, dd, J 9.0 and 5.5, $\text{CH}_\text{A}\text{H}_\text{BO}$), 4.01 (2 H, br s, OH and CHNH), 3.81 (1 H, dd, J 14.0

and 6.5, *CHOH*) and 1.74 (3 H, dd, *J* 6.5 and 1.5, CH_3); **^{13}C NMR** $\delta_{\text{C}}(\text{CDCl}_3)$ 160.3 ($\text{C}=\text{O}$), 130.8 ($\text{C}_\text{A}=\text{C}_\text{B}$), 128.4 ($\text{C}_\text{A}=\text{C}_\text{B}$), 74.7, 66.8, 56.9 and 17.8 (CH_3); **MS** *m/z* (CI) 175 (MNH_4^+) and 158 (100%, MH^+); **HRMS (CI)** Found MH^+ , 158.0819. $\text{C}_7\text{H}_{12}\text{NO}_3^+$ requires *M* 158.0817.

Further confirmation of the identity of the oxazolidinone **205** was obtained by hydrogenation, yielding the previously synthesised oxazolidinone **197**. Palladium on charcoal (catalytic) was added to a stirred solution of (1'*RS*, 2'*E*, 4*RS*)-4-[1'-Hydroxy-but-2'-enyl]-oxazolidin-2-one **205** (34 mg, 0.22 mmol) in MeOH (15 mL). The resulting suspension was stirred under H_2 for 1 h. The reaction mixture was filtered through celite and concentrated *in vacuo* to yield the oxazolidinone **197** as a white solid (30 mg, 86%). The spectral data were identical to that of the previously synthesised material.

5.4 – Experimental details for chapter 2.4

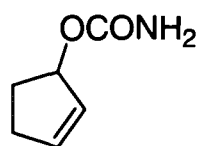
Cyclopenten-2-ol **207**¹⁸³



Cyclopenten-2-one **206** (1.0 g, 12 mmol) was subjected to the general Luche reduction procedure, affording the alcohol **207** without purification as an oil (640 mg, 63%).

¹H NMR δ_{H} (200 MHz; CDCl₃) 5.99 (1 H, m, CH_A=CH_B), 5.85 (1 H, m, CH_A=CH_B), 4.89 (1 H, br m, CHOH), 2.50 (1 H, m, allylic CH_AH_B), 2.36-2.29 (2 H, m, allylic CH_AH_B and CH_AH_B), 1.73 (1 H, m, CH_AH_B) and 1.44 (1 H, m, OH).

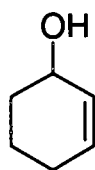
Cyclopent-2-enyl carbamate **208**



Cyclopenten-2-ol (640 mg, 7.7 mmol) was subjected to the general carbamate formation procedure, affording the *carbamate* **208** as an off-white solid (760 mg, 78%).

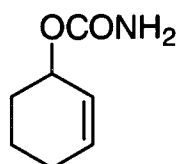
Recrystallisation from petrol – CHCl₃ gave the carbamate as white needles (410 mg, 42%).

*R*_f (EtOAc) 0.56; m.p. 93-95 °C; **IR** ν_{max} (CHCl₃) 3420, 3327 (NH₂), 1683 (C=O) and 1613 (NH₂); **¹H NMR** δ_{H} (400 MHz; CDCl₃) 6.10 (1 H, m, CH₂CH=CH), 5.84 (1 H, dq, *J* 6.0 and 2.0, CHORCH), 5.65 (1 H, m, CHOR), 4.74 (2 H, br s, NH₂), 2.53 (1 H), 2.36-2.24 (2 H) and 1.84 (1 H) (all m, CH₂CH₂); **¹³C NMR** δ_{C} (CDCl₃) 157.2 (C=O), 137.5, 129.5 (CH=CH), 81.0 (CHOR), 31.0 (allylic CH₂) and 29.9 (CH₂CHOR); **MS** *m/z* (CI) 145 (MNH₄⁺) and 84 (100%, MH⁺ – CONH₂); **HRMS (CI)** Found MNH₄⁺, 145.0979. C₆H₁₃N₂O₂⁺ requires *M* 145.0977.

Cyclohexen-2-ol 210¹⁸³

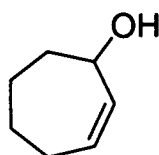
Cyclohexen-2-one **209** (2.0 g, 21 mmol) was subjected to the general Luche reduction procedure, affording the alcohol **210** without purification as an oil (2.04 g, 100%).

¹H NMR δ_{H} (300 MHz; CDCl₃) 5.88 (1 H, dtd, J 10.0, 3.5 and 1.0, CH=CHOH), 5.78 (1 H, ddd, J 10.0, 4.0 and 2.0, CH=CHCH₂), 4.23 (1 H, br s, CHOH) and 2.11-1.53 (7 H, m, CH₂CH₂CH₂ and OH).

Cyclohex-2-enyl carbamate 211

Crude cyclohexen-2-ol **210** (2.2 g, 22 mmol) was subjected to the general carbamate formation procedure, affording the *carbamate* **211** as a white solid (2.2 g, 74%).

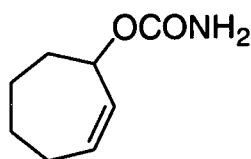
R_{f} (EtOAc) 0.70; m.p. 106-108 °C; **IR** ν_{max} (CHCl₃) 3424, 3387 (NH₂) and 1678 (C=O); **¹H NMR** δ_{H} (300 MHz; CDCl₃) 5.98 (1 H, dtd, J 10.0, 3.5 and 1.0, H₂CCH=CH), 5.76 (1 H, ddt, J 10.0, 4.0 and 2.0, CHCHOR), 5.19 (1 H, ddt, J 6.0, 3.5 and 1.5, CHOR), 4.78 (2 H, br s, NH₂) and 2.17-1.59 (6 H, m, CH₂CH₂CH₂); **¹³C NMR** δ_{C} (CDCl₃) 156.9 (C=O), 132.4 (C_A=C_B), 125.8 (C_A=C_B), 68.6 (CHOR), 28.4 (CH₂CHOR), 24.8 and 18.7 (CH₂CH₂); **MS** m/z (CI) 142 (MH⁺) and 98 (100%, MH⁺ – CONH₂); **Elemental analysis** Found: C, 59.3; H, 7.78; N, 9.6. C₇H₁₁NO₂ requires C, 59.6; H, 7.85; N, 9.9.

Cyclohepten-2-ol 213⁹²

Cyclohepten-2-one **212** (410 mg, 3.8 mmol) was subjected to the general Luche reduction procedure, affording the alcohol **213** without purification as an oil (370 mg, 88%).

$^1\text{H NMR}$ δ_{H} (400 MHz; CDCl_3) 5.75 (2 H, m, $\text{CH}=\text{CH}$), 4.40 (1 H, m, CHOH), 2.15 (1 H, m), 2.02 (1 H, m), 1.95 (1 H, m), 1.87 (1 H, m), 1.71-1.54 (3 H, m), 1.50 (1 H, br s, OH) and 1.39 (1 H, m).

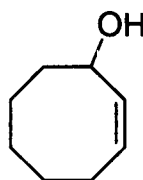
Cyclohept-2-enyl carbamate **214**



Crude cyclohepten-2-ol (1.0 g, 9.1 mmol) was subjected to the general carbamate formation procedure, affording the *carbamate* **214** as a white solid (1.2 g, 81%).

R_f (EtOAc) 0.67; m.p. 84-85 °C; **IR** ν_{max} (CHCl_3) 3440, 3321 (NH_2), 1684 ($\text{C}=\text{O}$) and 1609 (NH_2); **$^1\text{H NMR}$** δ_{H} (400 MHz; CDCl_3) 5.81 (1 H, m, $\text{CH}_2\text{CH}=\text{CH}$), 5.67 (1 H, dddd, J 11.5, 3.0, 2.0 and 1.0, $\text{CH}=\text{CHOR}$), 5.29 (1 H, m, CHOR), 4.85 (2 H, br s, NH_2), 2.19 (1 H), 2.08 (1 H), 1.96-1.85 (2 H), 1.73-1.1.58 (3 H) and 1.38 (1 H) (all m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$); **$^{13}\text{C NMR}$** δ_{C} (CDCl_3) 156.9 ($\text{C}=\text{O}$), 134.0 ($\text{C}_\text{A}=\text{C}_\text{B}$), 131.2 ($\text{C}_\text{A}=\text{C}_\text{B}$), 75.1 (CHOR), 33.1 (CH_2CHOR), 28.5, 26.6 and 26.5 ($\text{CH}_2\text{CH}_2\text{CH}_2$); **MS** m/z (CI) 173 (MNH_4^+) and 112 (100%, $\text{MH}^+ - \text{CONH}_2$); **HRMS (CI)** Found MNH_4^+ , 173.1294. $\text{C}_8\text{H}_{17}\text{N}_2\text{O}_2$ requires M 173.1290.

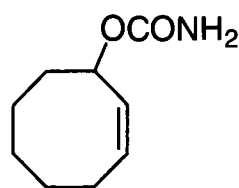
Cyclooct-2-enol **216**¹⁸⁴



Cyclooctene oxide (500 mg, 4.0 mmol) was dissolved in MeCN (10 mL) and cooled to 0 °C. DBU (1.2 g, 1.2 mL, 7.9 mmol) was added, followed by dropwise addition of iodotrimethylsilane (870 mg, 4.4 mmol). The solution was allowed to stir for 15 minutes and then heated at reflux for 25 h. The solution was concentrated to dryness, diluted with brine and extracted with Et_2O . The combined organic extracts containing the TMS ether were shaken with HCl (1 M) to give the crude product. Column chromatography (1:9, acetone – petrol) afforded the alcohol **216** as an oil (250 mg, 50%).

^1H NMR δ_{H} (200 MHz; CDCl_3) 5.61 (2 H, m, $\text{CH}=\text{CH}$), 4.66 (1 H, m, CHOH), 2.27-2.10 (2 H, m), 1.91 (1 H, m), 1.68-1.37 (8 H, m) ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$ and OH).

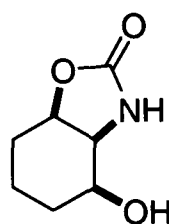
Cyclooct-2-enyl carbamate **217**



Crude cyclooct-2-enol **216** (250 mg, 2.0 mmol) was subjected to the general carbamate formation procedure, affording the *carbamate* **217** as a white solid (320 mg, 94%).

R_f (EtOAc) 0.51; m.p. 49-51 °C; **IR** ν_{max} (CHCl_3) 3477, 3351 (NH_2), 2928, 2857 (CH), 1709 ($\text{C}=\text{O}$) and 1601 (NH_2); **^1H NMR** δ_{H} (400 MHz; CDCl_3) 5.64 (1 H, m, $\text{CH}_2\text{CH}=\text{CH}$), 5.56-5.46 (2 H, m, $\text{CH}=\text{CHCHOR}$), 4.85 (2 H, br s, NH_2), 2.26 (1 H, tddd, J 13.0, 9.0, 4.0 and 1.0, $\text{CH}_\text{A}\text{H}_\text{B}\text{CH}=\text{CH}$), 2.10 (1 H, m, $\text{CH}_\text{A}\text{H}_\text{B}\text{CH}=\text{CH}$), 1.94 (1 H, m), 1.67 (1 H, m) and 1.61-1.34 (6 H, m) ($\text{CH}_2\text{CH}_2\text{CH}_2$); **^{13}C NMR** δ_{C} (CDCl_3) 156.7 ($\text{C}=\text{O}$), 130.9 ($\text{C}_\text{A}=\text{C}_\text{B}$), 129.4 ($\text{C}_\text{A}=\text{C}_\text{B}$), 73.1 (CHOR), 35.3 (CH_2CHOR), 28.7, 26.3, 25.7 and 23.2 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$); **MS** m/z (CI) 187 (MNH_4^+) and 126 (100%, $\text{MH}^+ - \text{CONH}_2$); **HRMS (CI)** Found MNH_4^+ , 187.1452. $\text{C}_9\text{H}_{19}\text{N}_2\text{O}_2$ requires M 187.1447.

(3*SR*, 4*SR*, 8*RS*)-4-Hydroxy-hexahydro-benzooxazol-2-one **218**



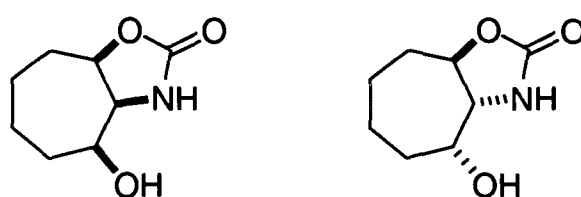
Cyclohex-2-enyl carbamate **211** (200 mg, 1.4 mmol) was subjected to the general tethered aminohydroxylation procedure, using $(\text{DHQ})_2\text{PHAL}$ as the ligand. Purification of the crude compound by column chromatography (EtOAc) afforded the *oxazolone* **218** as a white crystalline solid (140 mg, 61%).

R_f (EtOAc) 0.17; m.p. 81-83 °C; **IR** ν_{max} (CHCl_3) 3399 (br, OH, NH) and 1746 ($\text{C}=\text{O}$); **^1H NMR** δ_{H} (400 MHz; CDCl_3) 6.36 (1 H, s, NH), 4.70 (1 H, dt, J 7.0 and 5.0, CHOR), 3.95 (1 H, dd, J 7.0 and 4.5, CHNH), 3.75 (1 H, d, J 4.5, OH), 3.86 (1 H, dq, J 8.5 and 4.5, CHOH), 1.87-1.78 (3 H, m), 1.76-1.62 (2 H, m), 1.33 (1 H, m) ($\text{CH}_2\text{CH}_2\text{CH}_2$); **^{13}C**

NMR δ_{C} (CDCl₃) 161.3 (C=O), 76.3, 66.9 (CHOR and CHNR), 55.8 (CHOH), 26.5, 25.7 (CHCHOR and CHCHNR) and 15.6 (CH₂CH₂CH₂); **MS** m/z (CI) 175 (MNH₄⁺) and 158 (100%, MH⁺); **HRMS (CI)** Found MH⁺, 158.0822. C₇H₁₂NO₃ requires M 158.0817.

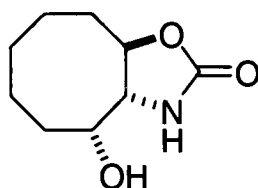
(3*RS*, 4*RS*, 9*SR*)-4-Hydroxy-octahydro-cycloheptaoxazol-2-one 219a

(3*RS*, 4*RS*, 9*RS*)-4-Hydroxy-octahydro-cycloheptaoxazol-2-one 219b



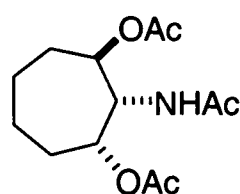
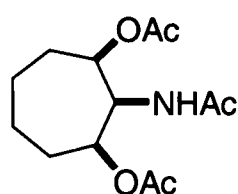
Cyclohept-2-enyl carbamate **214** (1.2 g, 8.0 mmol) was subjected to the general tethered aminohydroxylation procedure, using EtN^{*i*}Pr₂ as the ligand. Purification of the crude compound by column chromatography (EtOAc) afforded the *oxazolones* **219a** and **219b** as a white solid (950 mg, 3:1, 69%).

R_f (EtOAc) 0.20; **IR** ν_{max} (CHCl₃) 3326 (br, OH and NH), 2933, 2863 (CH) and 1738 (C=O); **¹H NMR** δ_{H} (400 MHz; CDCl₃); 6.66 (0.75 H, br s, *major* NH), 6.54 (0.25 H, br s, *minor* NH), 4.86 (0.75 H, ddd, J 10.0, 7.5 and 3.0, *major* CHOCO), 4.80 (0.25 H, m, *minor* CHOCO), 4.13 (0.25 H, td, J 5.5 and 3.0, *minor* CHNH), 4.08 (0.75 H, dd, J 6.5 and 3.0, *major* CHNH), 3.86 (0.75 H, d, J 10.0, *major* CHOH), 3.76 (0.25 H, ddd, J 10.5, 3.0 and 1.0, *minor* CHOH), 3.68 (0.75 H, br s, *major* OH), 3.59 (0.25 H, br s, *minor* OH), 2.22 (1 H, m, CH_AH_BCHOCO), 1.88 (1 H, m, CH_AH_BCHOH), 1.82-1.56 (4 H, m) and 1.46-1.35 (2 H, m) (remaining methylene H); **¹³C NMR** δ_{C} (CDCl₃) 160.8, 160.1(C=O), 77.7, 76.3, 71.9, 64.8, 63.0, 60.2 (CHOH, CHNH and CHOCO), 34.8, 32.3, 30.5, 29.9, 25.4, 24.3, 22.2 and 20.3 (CH₂CH₂CH₂CH₂); **MS** m/z (CI) 189 (MNH₄⁺) and 172 (100%, MH⁺); **HRMS (CI)** Found MH⁺, 172.0975. C₈H₁₄NO₃ requires M 172.0974.

(3*RS*, 4*RS*, 9*SR*)-4-Hydroxy-octahydro-cycloheptaoxazol-2-one 220b

Cyclooct-2-enyl carbamate **217** (250 mg, 1.5 mmol) was subjected to the general tethered aminohydroxylation procedure, using (DHQ)₂PHAL as the ligand. Purification of the crude compound by column chromatography (EtOAc) afforded the *oxazolidinone* **220b** as a white crystalline solid (160 mg, 58%).

R_f (EtOAc) 0.16; m.p. 136-137 °C; **IR** $\nu_{\max}$ (CHCl₃) 3312 (br, OH and NH), 2932, 2864 (CH) and 1745 (C=O); **¹H NMR** δ_H (400 MHz; CDCl₃); 6.91 (1 H, br s, NH), 4.95 (1 H, ddd, J 11.0, 8.5 and 4.5, CHOCO), 4.06 (1 H, d, J 3.0, OH), 3.95 (1 H, dd, J 7.0 and 2.5, CHOH), 3.85 (1 H, dd, J 8.5 and 1.0, CHNH), 2.17 (1 H, m), 1.88 (1 H, m), 1.72 (3 H, m), 1.59 (4 H, m) and 1.36 (1 H, m) (methylene CH₂); **¹³C NMR** δ_C (CDCl₃) 160.3 (C=O), 76.5, 67.3, 61.5, (CHOH, CHNH and CHOCO), 33.8, 29.4, 26.5, 21.5 and 19.4 (CH₂CH₂CH₂CH₂CH₂); **MS** m/z (CI) 203 (MNH₄⁺) and 186 (100%, MH⁺); **HRMS (CI)** Found MH⁺, 186.1130. C₉H₁₆NO₃ requires M 186.1130.

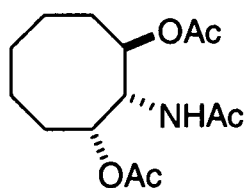
(1*RS*, 2*sr*, 3*SR*)-2-acetylamino-1,3-diacetoxycycloheptane 221a**(1*RS*, 3*RS*)-2-acetylamino-1,3-diacetoxycycloheptane 221b**

Oxazolones **219a** and **219b** (110 mg, 0.61 mmol) were subjected to the general oxazolidinone cleavage - peracetylation procedure. Purification of the crude compound by column chromatography (50% EtOAc – petrol) afforded the *triacetates* **221a** and **221b** as a white solid (110 mg, 3:1, 69%).

R_f (EtOAc) 0.23; m.p. 105-110 °C; **IR** $\nu_{\max}$ (CHCl₃) 3326 (br, NH), 2940, 2869 (CH), 1732 and 1659 (C=O); **¹H NMR** δ_H (400 MHz; CDCl₃); 6.70 (0.75 H, d, J 9.0, *major* NH), 6.09 (0.25 H, d, J 9.0, *minor* NH), 5.03 (1.75 H, m, *major/minor* CHOAc), 4.94 (0.25 H, ddd, J 9.0, 7.0 and 4.5, *minor* CHOAc), 4.45 (0.75 H, dt, J 9.0 and 3.0, *major* CHNH), 4.25 (0.25 H, td, J 9.0 and 2.0, *minor* CHNH), 2.06 (0.75 H, s, *minor* OAc),

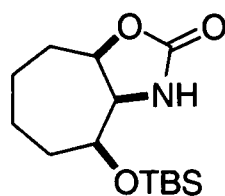
2.02 (4.5 H, s, $2 \times$ major OAc), 1.98 (0.75 H, s, *minor* OAc), 1.92 (2.25 H, s, *major* NHAc), 1.89 (0.75 H, s, *minor* NHAc) and 1.74-1.59 (8 H, m, methylene protons); ^{13}C NMR $\delta_{\text{C}}(\text{CDCl}_3)$ 171.1 (*minor* C=O), 171.0 (*major* C=O), 170.4, 169.7 ($2 \times$ *minor* C=O), 169.2 (*major* C=O), 75.1 (*minor* CHOAc), 74.9 (*major* CHOAc), 74.0 (*minor* CHOAc), 56.1 (*minor* CHNH), 53.6 (*major* CHNH), 31.6 (*minor* CH₂), 31.5 (*major* CH₂), 29.0 (*minor* CH₂), 23.6 (*major* CH₂), 23.2 (2 peaks, $2 \times$ *major/minor* OAc), 22.6, 21.8 (*minor* CH₂), 21.2, 21.1 and 21.0 ($3 \times$ *major/minor* OAc); **MS** m/z (CI) 272 (100%, MH^+), 211 ($\text{M}^+ - \text{OAc}$) and 151 ($\text{M}^+ - 2 \times \text{OAc}$); **HRMS (CI)** Found MH^+ , 272.1495. $\text{C}_{13}\text{H}_{22}\text{NO}_5$ requires M 272.1498.

(1*RS*, 3*RS*)-2-acetylamino-1,3-diacetoxycyclooctane 222b



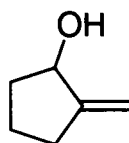
Oxazolone **220b** (91 mg, 0.57 mmol) was subjected to the general oxazolidinone cleavage - peracetylation procedure. Purification of the crude compound by column chromatography (50% EtOAc – petrol) afforded the *triacetate* **222b** as an oil (100 mg, 64%).

R_f (EtOAc) 0.21; **IR** ν_{max} (film) 3285 (br, NH), 3076, 2937, 2869 (CH), 1732 and 1659 (C=O); ^1H NMR $\delta_{\text{H}}(400 \text{ MHz}; \text{CDCl}_3)$ 6.03 (1 H, d, J 9.0, NH), 5.09-5.01 (2 H, m, $2 \times$ CHOAc), 4.55 (1 H, td, J 7.5 and 2.0, CHNH), 2.02 (3 H, s), 1.97 (3 H, s), 1.89 (3 H, s) ($3 \times$ Ac) and 1.74-1.58 (10 H, m, methylene protons); ^{13}C NMR $\delta_{\text{C}}(\text{CDCl}_3)$ 171.2, 170.5, 169.8 ($3 \times$ C=O), 73.8, 72.9 ($2 \times$ CHOAc), 52.4 (CHNH), 30.4, 29.8, 27.3, 23.4 (methylene C), 23.2 (Ac), 22.0 (methylene C), 21.2 and 21.1 ($2 \times$ Ac); **MS** m/z (CI) 286 (100%, MH^+), 226 ($\text{M}^+ - \text{OAc}$) and 165 ($\text{M}^+ - 2 \times \text{OAc}$); **HRMS (CI)** Found MH^+ , 286.1660. $\text{C}_{14}\text{H}_{24}\text{NO}_5$ requires M 286.1654.

(3*RS*, 4*RS*, 9*SR*)-4-(*tert*-Butyldimethylsilyloxy)-octahydro-cycloheptaoxazol-2-one 223

Oxazolones **221a/b** (50 mg, 0.29 mmol), imidazole (43 mg, 0.64 mmol) and DMAP (catalytic) were dissolved in CH₂Cl₂ (5 mL). TBSCl (48 mg, 0.32 mmol) was added and the mixture stirred at room temperature for 15 h. Water (5 mL) was added and the mixture extracted with CH₂Cl₂ (3 × 20 mL). The organic extracts were dried (MgSO₄) and concentrated. Column chromatography (2:3, petrol – EtOAc) afforded the *silyl ether* **223** as a white crystalline solid (16 mg, 19%).

R_f (EtOAc) 0.59; m.p. 101-104 °C; **IR** $\nu_{\max}$ (CHCl₃) 3486 (br, NH), 2928, 2855 (CH) and 1745 (C=O); **¹H NMR** δ_H (400 MHz; CDCl₃); 5.38 (1 H, br s, NH), 4.82 (1 H, ddd, J 18.5, 16.0 and 5.5, CHOCO), 3.89 (1H, dd, J 18.5 and 5.0, CHNH), 3.78 (1 H, ddd, J 18.5, 5.5 and 3.0, CHOTBS), 2.22 (1H, m, CH_AH_BCHOCO), 1.94-1.62 (4 H, m, methylene CH₂), 1.56-1.26 (3 H, m, methylene CH₂), 0.89 (9 H, s, CMe₃), 0.07 (3 H, s) and 0.06 (3 H, s) (SiMe₂); **¹³C NMR** δ_C (CDCl₃) 159.0 (C=O), 95.7 (CHOCO), 73.5 (CHOTBS), 60.6 (CHNH), 33.1, 30.3 (methylene C), 25.7 (CMe₃), 25.3, 22.2 (methylene C), 17.9 (CMe₃), -4.7 and -5.1 (SiMe₂); **MS** m/z (CI) 303 (MNH₄⁺), 286 (100%, MH⁺) and 228 (M – ^tBu); **HRMS (CI)** Found MNH₄⁺, 303.2107. C₁₄H₃₁N₂O₃Si requires M 303.2104.

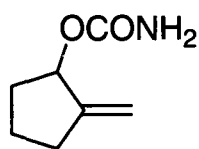
2-Methylene cyclopentanol 226⁸⁷

Dry ether (100 mL) was added carefully to lithium aluminium hydride (2.4 g, 64 mmol) in a round-bottomed flask cooled to -78 °C. A solution of 2-carbethoxycyclopentanone **224** (5.0 g, 32 mmol) in ether was added dropwise. When the effervescence had subsided, the mixture was refluxed at 50 °C for 16 h, by which time no starting material remained by TLC. A 1:1 solution of ethyl acetate and 10% aqueous citric acid was added dropwise with cooling to the reaction mixture. When the effervescence had subsided, a further 100 mL of 10% aqueous citric acid solution was added, and the mixture allowed to warm to room temperature with stirring. The organic layer was

separated and the aqueous layer extracted with EtOAc. The combined organic extracts were dried over MgSO_4 , filtered and concentrated. The crude product was purified by Kugelrohr distillation, affording the alcohol **226** as an oil, b.p. 91-95 °C at 12 mmHg (lit. 85-86 °C at 68 mmHg)⁸⁷ (550 mg, 18%).

^1H NMR δ_{H} (400 MHz; CDCl_3) 5.14 (1 H, d, J 1.5, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 5.02 (1 H, d, J 1.5, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 4.43 (1 H, m, CHOH), 2.46 (1 H, m, allylic $\text{CH}_\text{A}\text{H}_\text{B}$), 2.31 (1 H, m, allylic $\text{CH}_\text{A}\text{H}_\text{B}$), 1.95 (1 H), 1.83 (1 H) and 1.68-1.58 (2 H) (all m, CH_2CH_2).

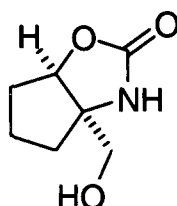
2-Methylene cyclopentyl carbamate **227**



2-Methylene cyclopentanol **226** (550 mg, 5.6 mmol) was subjected to the general carbamate formation procedure, affording the *carbamate* **227** as a white solid (670 mg, 85%). Recrystallisation from petrol – CHCl_3 gave the carbamate as white flakes (330 mg, 41%).

R_f (EtOAc) 0.63; m.p. 68 °C (dec.); **IR** ν_{max} (CHCl_3) 3410, 3327 (NH_2) and 1682 ($\text{C}=\text{O}$); **^1H NMR** δ_{H} (400 MHz; CDCl_3) 5.34 (1 H, m, CHOR), 5.19 (1 H, t, J 1.0, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 5.09 (1 H, dd, J 1.0 and 0.5, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 4.89 (2 H, br s, NH_2), 2.44 (1 H, m, allylic $\text{CH}_\text{A}\text{H}_\text{B}$), 2.29 (1 H, m, allylic $\text{CH}_\text{A}\text{H}_\text{B}$), 2.02 (1 H, m, $\text{CH}_\text{A}\text{H}_\text{B}\text{CHOR}$), 1.85-1.62 (3 H, m, $\text{CH}_2\text{CH}_\text{A}\text{H}_\text{B}\text{CHOR}$); **^{13}C NMR** δ_{C} (CDCl_3) 157.0 ($\text{C}=\text{O}$), 150.3 ($\text{R}_2\text{C}=\text{CH}_2$), 110.1 ($\text{R}_2\text{C}=\text{CH}_2$), 77.2 (CHOR), 33.0 (CH_2CHOR), 30.6 and 22.4 (CH_2CH_2); **MS** m/z (CI) 159 (100%, MNH_4^+), 142 (MH^+) and 81 ($\text{MH}^+ - \text{OCONH}_2$); **HRMS (CI)** Found MNH_4^+ , 159.1138. $\text{C}_7\text{H}_{15}\text{N}_2\text{O}_2^+$ requires M 159.1134.

(3aSR, 7aSR)-3a-Hydroxymethyl-hexahydro-cyclopentaoxazol-2-one **231**

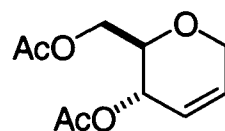


2-Methylene cyclopentyl carbamate **227** (190 mg, 1.3 mmol) was subjected to the general tethered aminohydroxylation procedure, using EtN^iPr_2 as the ligand.

Purification of the crude compound by column chromatography (EtOAc) afforded the oxazolone **231** as a white crystalline solid (100 mg, 51%).

R_f (EtOAc) 0.10; m.p. 133-135 °C; **IR** $\nu_{\max}$ (Nujol) 3223 (br, OH and NH) and 1716 (C=O); **$^1\text{H NMR}$** δ_{H} (400 MHz; D_2O) 4.75 (1 H, m, CHOR), 3.60 (1 H, d, J 12.0, $\text{CH}_\text{A}\text{H}_\text{B}\text{OH}$), 3.43 (1 H, d, J 12.0, $\text{CH}_\text{A}\text{H}_\text{B}\text{OH}$), 1.87 (1 H), 1.72-1.58 (4 H) and 1.40 (1 H) (all m, $\text{CH}_2\text{CH}_2\text{CH}_2$); **$^{13}\text{C NMR}$** δ_{C} (D_2O) 161.9 (C=O), 85.6 (CHOR), 70.7 (CNR), 64.6 (CHOH), 35.2, 33.6 (CH_2CHOR and $\text{CH}_2\text{CRNR}'$) and 22.6 ($\text{CH}_2\text{CH}_2\text{CH}_2$); **MS** m/z (CI) 175 (MNH_4^+) and 158 (100%, MH^+); **HRMS (CI)** Found MH^+ , 158.0821. $\text{C}_7\text{H}_{12}\text{NO}_3$ requires M 158.0817.

(2R, 3S)-2-Acetoxymethyl-3,6-dihydro-2H-pyran-3-ol acetate 233¹⁸⁵

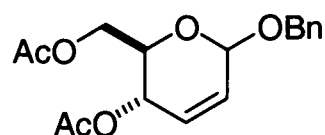


Tri-*O*-acetyl-D-glucal **232** (5.5 g, 20 mmol) and triethylsilane (3.9 mL, 24 mmol) were dissolved in CH_2Cl_2 (70 mL) and cooled to 0 °C. $\text{BF}_3 \cdot \text{OEt}_2$ (1.7 mL, 20 mmol) was added dropwise and the solution stirred for 30 minutes. The reaction was quenched with 10% aqueous NaHCO_3 (10 mL) and diluted with ether (250 mL). The organic extracts were washed with water and brine, then dried (MgSO_4) and concentrated to afford the diacetate **233** as an oil (4.0 g, 93%).

$^1\text{H NMR}$ δ_{H} (300 MHz; CDCl_3) 5.98 (1 H, ddd, J 10.5, 4.0 and 2.0, C^3H), 5.80 (1 H, dq, J 10.5 and 2.0, C^4H), 5.30 (1 H, m, CHOAc), 4.29-4.18 (4 H, m, CH_2O and CH_2OAc), 3.77 (1 H, m, CHOR), 2.14 (3 H, s) and 2.12 (3 H, s) ($2 \times \text{OAc}$).

(2*R*, 3*S*, 6*R*)-2-Acetoxymethyl-6-benzyloxy-3,6-dihydro-2*H*-pyran-3-ol acetate
234 α

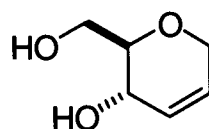
(2*R*, 3*S*, 6*S*)-2-Acetoxymethyl-6-benzyloxy-3,6-dihydro-2*H*-pyran-3-ol acetate
234 β ⁸⁹



Tri-*O*-acetyl-D-glucal **232** (2.0 g, 7.4 mmol) and benzyl alcohol (0.84 mL, 8.1 mmol) were dissolved in CH₂Cl₂ (30 mL) and cooled to 0 °C. BF₃·OEt₂ (90 μL, 0.37 mmol) was added dropwise and the solution stirred for 2 h. The reaction was quenched with 10% aqueous NaHCO₃ (10 mL) and diluted with ether (100 mL). The organic extracts were washed with water and brine, then dried (MgSO₄) and concentrated to afford the inseparable anomeric diacetates **234 α** and **234 β** as an oil (2.5 g, 5:1, 100%).

¹H NMR δ_H (400 MHz; CDCl₃) 7.38-7.30 (5 H, m, ArH), 6.01-5.99 (0.34 H, m, *minor* C⁴H=C⁵H), 5.89 (0.83 H, ddd, *J* 10.0, 1.0 and 0.5, *major* C⁵H), 5.80 (0.83 H, ddd, *J* 10.5, 2.5 and 1.5, *major* C⁴H), 5.30 (0.83 H, dq, *J* 9.5 and 1.5, *major* CHOAc), 5.22-5.20 (0.34 H, m, *minor* CHOAc and CHOBn), 5.15 (0.83 H, m, *major* CHOBn), 4.90 (0.17 H, d, *J* 11.5, *minor* CH_AH_BPh), 4.82 (0.83 H, d, *J* 11.5, *major* CH_AH_BPh), 4.63 (0.17 H, d, *J* 11.0, *minor* CH_AH_BPh), 4.61 (0.83 H, d, *J* 12.0, *major* CH_AH_BPh), 4.32-4.11 (3 H, m, CHCH₂OSi), 2.11 (3 H, 2 × s, *major/minor* OAc), 2.10 and 2.09 (3 H, 2 × s, *major/minor* OAc).

(2*R*, 3*S*)-2-Hydroxymethyl-3,6-dihydro-2*H*-pyran-3-ol **235**¹⁸⁵

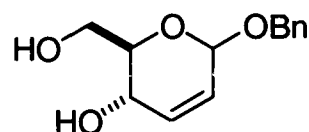


Diacetate **233** (4.0 g, 19 mmol) and NaOMe (500 mg, 9.3 mmol) were dissolved in MeOH (20 mL) and stirred at room temperature for 1 h, by which time no starting material remained by TLC. The mixture was concentrated to afford the diol **235** as an orange oil (2.4 g, 100%).

¹H NMR δ_{H} (300 MHz; CDCl₃) 5.92-5.83 (2 H, m, olefinic H), 4.25-4.23 (3 H, m, allylic H), 3.94 (1 H, dd, J 11.5 and 4.0, CH_AH_BOH), 3.84 (1 H, dd, J 11.5 and 6.0, CH_AH_BOH), 3.39 (1 H, m, C⁶H) and 1.90 (2 H, br s, 2 $\times$ OH).

(2*R*, 3*S*, 6*R*)-2-Hydroxymethyl-6-benzyloxy-3,6-dihydro-2*H*-pyran-3-ol 236 α

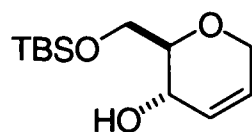
(2*R*, 3*S*, 6*S*)-2-Hydroxymethyl-6-benzyloxy-3,6-dihydro-2*H*-pyran-3-ol 236 β ¹⁸⁶



Diacetate **234** (2.5 g, 7.4 mmol) and K₂CO₃ (510 mg, 3.7 mmol) were dissolved in MeOH (30 mL) and water (15 mL) and stirred at room temperature for 3 h, by which time no starting material remained by TLC. The mixture was concentrated to afford the diols **236 α** and **236 β** as an orange oil (1.50 g, 8:1, 88%).

¹H NMR δ_{H} (400 MHz; CDCl₃) 7.38-7.28 (5 H, m, ArH), 6.01 (0.11 H, dq, J 10.5 and 1.5, *minor* C⁵H), 5.95 (0.89 H, dt, J 10.0 and 1.5, *major* C⁵H), 5.81 (0.11 H, dt, J 10.5 and 2.0, *minor* C⁴H), 5.77 (0.89 H, ddd, J 10.0, 3.0 and 2.0, *major* C⁴H), 5.25 (0.11 H, q, J 1.5, *minor* CHOBn), 5.09 (0.89 H, t, J 1.5, *major* CHOBn), 4.86 (0.11 H, d, J 12.0, *minor* CH_AH_BPh), 4.77 (0.89 H, d, J 11.5, *major* CH_AH_BPh), 4.69 (0.22 H, br s, 2 $\times$ *minor* OH), 4.65 (0.11 H, d, J 12.0, *minor* CH_AH_BPh), 4.61 (0.89 H, d, J 12.0, *major* CH_AH_BPh), 4.20 (1 H, t, J 7.0, allylic CHOH), 3.88-3.80 (2 H, m), 3.75-3.68 (1 H, m) (CHCH₂OH), 2.60 (0.89 H, d, J 7.0, *major* OH) and 2.29 (br s, 0.89 H, *major* OH).

(2*R*, 3*S*)-2-(*tert*-Butyldimethylsilyloxy)methyl-3,6-dihydro-2*H*-pyran-3-ol 237¹⁸⁷

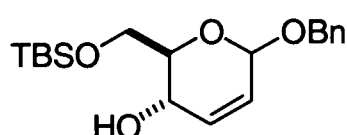


Crude diol **235** (2.4 g, 19 mmol) and imidazole (2.2 g, 33 mmol) were dissolved in CH₂Cl₂ (70 mL). TBSCl (4.2 g, 27 mmol) was added to the solution and the mixture stirred overnight. When all starting diol had been consumed, as determined by TLC, water (60 mL) was added and the mixture extracted with CH₂Cl₂ (3 $\times$ 50 mL). The organic extracts were dried (MgSO₄) and concentrated. Column chromatography (2:1, petrol - EtOAc) afforded the alcohol as an oil (3.1 g, 66%).

¹H NMR δ_H (200 MHz; CDCl₃) 5.82 (2 H, s, olefinic H), 4.15-4.11 (1 H, m, CHOH), 4.06-4.03 (2 H, m, CH₂OR), 3.96 (1 H, dd, *J* 10.0 and 5.0, CH_AH_BOSi), 3.73 (1 H, dd, *J* 10.0 and 8.0, CH_AH_BOSi), 3.38 (1 H, td, *J* 8.0 and 5.0, CHOR), 3.10 (1 H, d, *J* 3.0, OH), 0.92 (9 H, s, ^{*t*}Bu) and 0.12 (6 H, s, SiMe₂).

(2*R*, 3*S*, 6*R*)-2-(*tert*-Butyldimethylsilanyloxy)methyl-6-benzyloxy-3,6-dihydro-2*H*-pyran-3-ol 238 α

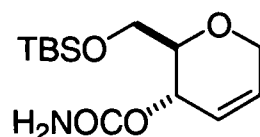
(2*R*, 3*S*, 6*S*)-2-(*tert*-Butyldimethylsilanyloxy)methyl-6-benzyloxy-3,6-dihydro-2*H*-pyran-3-ol 238 β ¹⁸⁶



Crude diol **236** (1.5 g, 6.5 mmol), imidazole (970 mg, 14 mmol) and DMAP (catalytic) were dissolved in CH₂Cl₂ (30 mL). TBSCl (1.1 g, 7.1 mmol) was added to the solution and the mixture stirred overnight. When all starting diol had been consumed, as determined by TLC, water (20 mL) was added and the mixture extracted with CH₂Cl₂ (3 × 40 mL). The organic extracts were dried (MgSO₄) and concentrated. Column chromatography (2:1, petrol - EtOAc) afforded the alcohols **238 α** and **238 β** as an oil (1.8 g, 5:1, 80%).

¹H NMR δ_H (400 MHz; CDCl₃) 7.39-7.27 (5 H, m, ArH), 6.01 (0.17 H, ddd, *J* 10.0, 2.5 and 1.5, *minor* C⁵H), 5.96 (0.83 H, dt, *J* 10.5 and 1.5, *major* C⁵H), 5.80 (0.17 H, m, *minor* C⁴H), 5.77 (0.83 H, dt, *J* 10.5 and 2.5, *major* C⁴H), 5.24 (0.17 H, dd, *J* 2.5 and 1.0, *minor* CHOBn), 5.05 (0.83 H, dt, *J* 2.5 and 1.0, *major* CHOBn), 4.84 (0.17 H, d, *J* 11.0, *minor* CH_AH_BPh), 4.78 (0.83 H, d, *J* 12.0, *major* CH_AH_BPh), 4.61 (1 H, d, *J* 12.0, CH_AH_BPh), 4.30 (0.17 H, m, *minor* CHOH), 4.20 (0.83 H, m, *major* CHOH), 3.97 (0.17 H, dd, *J* 9.5 and 5.0, *minor* CH_AH_BOSi), 3.86-3.66 (2.83 H, m, *major* CH_AH_BOSi, CH_AH_BOSi and CHCH₂OSi), 2.92 (0.17 H, d, *J* 3.5, *minor* OH), 2.85 (0.83 H, d, *J* 3.5, *major* OH), 0.92 (9 H, s, CMe₃) and 0.12 (6 H, s, SiMe₂).

(2*R*, 3*S*)-6-(*tert*-Butyldimethylsilanyloxy)methyl-3,6-dihydro-2*H*-pyran-3-ol carbamate **239**

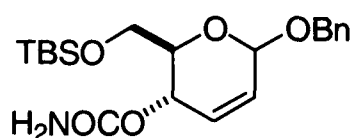


Alcohol **237** (800 mg, 3.2 mmol) was subjected to the general carbamate formation procedure, affording the *carbamate* **239** as a pale yellow solid (870 mg, 95%).

R_f (EtOAc) 0.68; m.p. 100-102 °C; $[\alpha]_D +76.0$ (c 0.7 in CH₂Cl₂); **IR** $\nu_{\max}$ (CHCl₃) 3455, 3353 (NH₂) and 1716 (C=O); **¹H NMR** δ_H (400 MHz; CDCl₃) 5.93 (1 H, ddd, J 10.5, 4.0 and 2.5, C=CHCH₂), 5.82 (1 H, ddd, J 10.5, 4.5 and 2.0, CHOCONH₂), 5.11 (1 H, m, CHOR), 4.80 (2 H, br s, NH₂), 4.20-4.18 (2 H, m, allylic CH₂OR), 3.81 (1 H, dd, J 11.5 and 3.0, CH_AH_BOSi), 3.74 (1 H, dd, J 11.5 and 6.0, CH_AH_BOSi), 3.56 (1 H, ddd, J 7.5, 6.0 and 3.0, CHCH₂OSi), 0.90 (9 H, s, ^tBu) and 0.08 (6 H, s, SiMe₂); **¹³C NMR** δ_C (CDCl₃) 156.1 (C=O), 129.6 (C_A=C_B), 124.6 (C_A=C_B), 77.0 (CHOCO), 66.1 (CHOR), 64.8 (CH₂OR), 63.3 (CH₂OSi), 25.9 (CMe₃), 18.4 (CMe₃), -5.3 and -5.4 (SiMe₂); **MS** m/z (ESI) 310 (100%, MNa⁺) and 288 (MH⁺); **HRMS (ES)** Found MH⁺, 288.1640. C₁₃H₂₆NO₄Si requires M 288.1631.

(2*R*, 3*S*, 6*R*)-6-(*tert*-Butyldimethylsilanyloxy)methyl-6-benzyloxy-3,6-dihydro-2*H*-pyran-3-ol carbamate **240α**

(2*R*, 3*S*, 6*S*)-6-(*tert*-Butyldimethylsilanyloxy)methyl-6-benzyloxy-3,6-dihydro-2*H*-pyran-3-ol carbamate **240β**

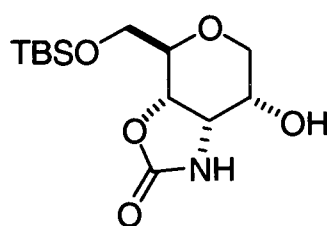


Alcohol **238** (1.1 g, 3.1 mmol) was subjected to the general carbamate formation procedure, affording the carbamates **240α** and **240β** as an oil (1.3 g, 5:1, 100%).

R_f (Et₂O) 0.42; $[\alpha]_D +66.4$ (c 0.8 in CH₂Cl₂); **IR** $\nu_{\max}$ (film) 3464, 3355 (NH₂), 2929, 2857 (CH) and 1716 (C=O); **¹H NMR** δ_H (400 MHz; CDCl₃) 7.39-7.29 (5 H, m, ArH), 6.07 (0.17 H, ddd, J 10.5, 4.0 and 2.0, *minor* C⁵H), 5.97 (0.83 H, ddd, J 10.0, 2.0 and 1.0, *major* C⁵H), 5.94 (0.17 H, ddd, J 10.0, 2.0 and 1.0, *minor* C⁴H), 5.84 (0.83 H, ddd, J 10.0, 3.0 and 2.0, *major* C⁴H), 5.17 (1 H, m, *major/minor* CHOBn), 5.12 (1 H, m,

major/minor CHOCO), 4.87 (0.17 H, d, J 11.5, minor CH_AH_BPh), 4.85 (0.83 H, d, J 11.5, major CH_AH_BPh), 4.71 (2 H, br s, NH_2), 4.62 (0.17 H, d, J 12.0, minor CH_AH_BPh), 4.59 (0.83 H, d, J 11.5, major CH_AH_BPh), 4.00 (0.83 H, m, major $CHCH_2OSi$), 3.93 (0.17 H, m, minor $CHCH_2OSi$), 3.84-3.72 (2 H, m, CH_2OSi), 0.92 (9 H, s, CMe_3), 0.10 (3 H) and 0.10 (3 H) ($SiMe_2$); ^{13}C NMR $\delta_c(CDCl_3)$ 157.2, 156.4 ($2 \times C=O$), 137.8, 136.3 ($2 \times 4^\circ$ aryl), 130.0 (2 peaks), 128.6, 128.4 (2 peaks), 128.2 (2 peaks), 128.1 (2 peaks), 127.9, 127.8 (2 peaks), 127.6, 126.7 (all sp^2), 93.8, 93.3 ($2 \times CHOCO$), 76.2, 70.0 ($COBn$), 69.9, 69.4 (CH_2Ph), 66.2, 64.9 ($CHCH_2OSi$), 63.1, 62.9 (CH_2OSi), 26.0, 25.9 (CMe_3), 18.5, 18.3 (CMe_3), -5.2, -5.3 (3 peaks) ($SiMe_2$); **MS** m/z (ESI) 416 (MNa^+) and 411 (100%, MNH_4^+); **HRMS (ES)** Found MNa^+ , 416.1870. $C_{20}H_{31}NO_5NaSi$ requires M 416.1869.

(3a*S*, 4*R*, 7*S*, 8a*S*)-4-(*tert*-Butyl-dimethyl-silanyloxymethyl)-7-hydroxy-hexahydro-pyran-[4,3-*d*]-oxazol-2-one **241**

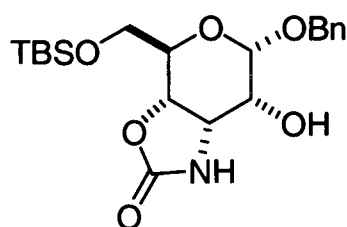


Carbamate **239** (150 mg, 0.52 mmol) was subjected to the general tethered aminohydroxylation procedure, using $(DHQ)_2PHAL$ as the ligand. Purification of the crude compound by column chromatography (60:40, EtOAc – petrol) afforded the *oxazolone* **241** as a white crystalline solid (78 mg, 50%).

R_f (EtOAc) 0.38; m.p. 153 °C; $[\alpha]_D +35.2$ (c 0.8 in CH_2Cl_2); **IR** ν_{max} ($CHCl_3$) 3297 (br, OH, NH), 1753 ($C=O$) and 1723; 1H NMR δ_H (400 MHz; $CDCl_3$) 6.22 (1 H, br s, NH), 4.62 (1 H, dd, J 7.5 and 7.0, CHOCO), 4.29 (1 H, dd, J 7.0 and 4.0, CHNR), 3.97 (1 H, m, CHOH), 3.93 (1 H, dd, J 11.0 and 1.0, CH_AH_BOR), 3.88 (1 H, dd, J 11.5 and 2.5, CH_AH_BOSi), 3.76 (1 H, dd, J 11.5 and 4.0, CH_AH_BOR), 3.57 (1 H, dd, J 11.0 and 9.0, CH_AH_BOR), 3.52 (1 H, ddd, J 8.0, 4.5 and 2.5, $CHCH_2OSi$), 3.43 (1 H, br s, OH), 0.90 (9 H, s, tBu) and 0.08 (3 H, s, $SiMe_2$), 0.08 (3 H, s, $SiMe_3$); ^{13}C NMR $\delta_c(CDCl_3)$ 160.4 ($C=O$), 76.6, 72.2 (CHOR and CNR), 66.4, 64.6, 63.3 (C^3 , C^4 and C^6), 54.8 (COSi), 26.0 (CMe_3), 18.5 (CMe_3) and -5.3 (2 peaks, $SiMe_2$); **MS** m/z (ESI) 326 (100%, MNa^+),

321 (MNH_4^+) and 304 (MH^+); **HRMS (ES)** Found MH^+ , 304.1571. $\text{C}_{13}\text{H}_{26}\text{NO}_5\text{Si}$ requires M 304.1580.

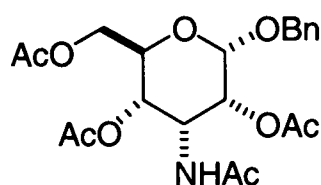
(3a*S*, 4*R*, 6*S*, 7*S*, 8a*S*)-4-(*tert*-Butyl-dimethyl-silanyloxymethyl)-6-benzyloxy-7-hydroxy-hexahydro-pyran-[4,3-*d*]-oxazol-2-one **242**



Carbamate **240** (790 mg, 2.0 mmol) was subjected to the general tethered aminohydroxylation procedure, using $(\text{DHQ})_2\text{PHAL}$ as the ligand. Purification of the crude compound by column chromatography (1:1, EtOAc – petrol) afforded the *oxazolone* **242** as a white crystalline solid (540 mg, 65%).

R_f (Et_2O) 0.06; m.p. 131-133 °C; $[\alpha]_D +87.2$ (c 0.8 in CH_2Cl_2); **IR** ν_{max} (CHCl_3) 3385 (br, OH, NH) and 1717 (br, C=O); **^1H NMR** δ_{H} (400 MHz; CDCl_3) 7.36-7.28 (5 H, m, ArH), 6.28 (1 H, br s, NH), 4.87 (1 H, d, J 4.0, CHOBn), 4.82 (1 H, d, J 12.0, $\text{CH}_\text{A}\text{H}_\text{B}\text{Ph}$), 4.63 (1 H, m, CHOCO), 5.58 (1 H, d, J 11.5, $\text{CH}_\text{A}\text{H}_\text{B}\text{Ph}$), 4.06 (1 H, ddd, J 8.5, 4.5 and 2.0, CHCH_2OSi), 4.00 (1 H, dd, J 8.0 and 4.5, CHNH), 3.89 (1 H, q, J 4.0, CHOH), 3.81 (1 H, dd, J 12.0 and 2.5, $\text{CH}_\text{A}\text{H}_\text{B}\text{OSi}$), 3.74 (1 H, dd, J 11.5 and 5.0, $\text{CH}_\text{A}\text{H}_\text{B}\text{OSi}$), 3.30 (1 H, d, J 4.0, OH), 0.91 (9 H, s, CMe_3), 0.09 (3 H, s) and 0.08 (3 H, s) (SiMe_2); **^{13}C NMR** δ_{C} (CDCl_3) 159.8 (C=O), 136.8, 128.5, 128.1, 128.0 ($4 \times$ aryl C), 94.9 (COBn), 71.4, 69.5 (CH_2Ph), 69.2, 65.7, 63.0 (CH_2OSi), 52.8, 25.9 (CMe_3), 184 (CMe_3) –5.30 and –5.33 (SiMe_2); **MS** m/z (ESI) 432 (MNa^+), 427 (MNH_4^+) and 410 (100%, MH^+); **HRMS (ES)** Found MH^+ , 410.1996. $\text{C}_{20}\text{H}_{32}\text{NO}_6\text{Si}$ requires M 410.1999.

(2*S*, 3*S*, 4*R*, 5*R*, 6*S*)-3,5-Diacetoxy-4-acetylamino-6-benzyloxy-tetrahydro-pyran-2-methyl acetate **245**



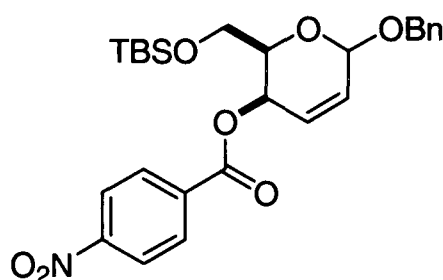
Oxazolone **242** (100 mg, 0.24 mmol) was subjected to the general oxazolidinone cleavage - peracetylation procedure. Purification of the crude compound by column

chromatography (40% EtOAc – petrol) afforded the *tetraacetate* **245** as a yellow oil (63 mg, 60%).

R_f (40% EtOAc – petrol) 0.13; $[\alpha]_D +90.8$ (c 0.5 in MeOH); **IR** $\nu_{\max}$ (film) 3415 (NH), 1747 (C=O) and 1682 (Aryl CH); **$^1\text{H NMR}$** δ_H (400 MHz; CDCl_3) 7.42-7.33 (5 H, m, ArH), 6.89 (1 H, d, J 8.5, NH), 5.09 (1 H, d, J 3.5, CHOBn), 4.95 (1 H, dd, J 4.0 and 3.5, C^2H), 4.89-4.83 (2 H, m, C^3H and C^4H), 4.80 (1 H, d, J 11.5, $\text{CH}_\text{A}\text{H}_\text{B}\text{Ph}$), 4.58 (1 H, d, J 11.5, $\text{CH}_\text{A}\text{H}_\text{B}\text{Ph}$), 4.24-4.16 (2 H, m, CH_2OAc), 4.03 (1 H, ddd, J 10.0, 4.5 and 2.5, C^5H), 2.09 (3 H, s), 2.05 (3 H, s), 1.97 (3 H, s) and 1.93 (3 H, s) ($4 \times \text{Ac}$); **$^{13}\text{C NMR}$** δ_C (CDCl_3) 170.7, 170.6, 169.6, 169.5 ($4 \times \text{C=O}$), 136.5 (4° aryl C), 128.8, 128.5, 127.8 ($3 \times$ aryl C), 96.0 (COBn), 70.4 (CH_2Ph), 66.5 (C^4), 66.1 (C^2), 64.3 (C^5), 62.2 (CH_2OAc), 47.7 (C^3), 23.5, 20.8 and 20.7 (2 peaks) ($4 \times \text{Ac}$); **MS** m/z (CI) 437 (MH^+) and 329 (100%, $\text{M}^+ - \text{OBn}$); **HRMS (CI)** Found MH^+ , 438.1768. $\text{C}_{21}\text{H}_{28}\text{NO}_9$ requires M 438.1764.

(2*R*, 3*R*, 6*R*)-6-benzyloxy-2-(tert-butyl-dimethyl-silanyloxymethyl)-3,6-dihydro-2H-pyran-3-yl 4-nitro benzoate 246 α

(2*R*, 3*R*, 6*S*)- 6-benzyloxy-2-(tert-butyl-dimethyl-silanyloxymethyl)-3,6-dihydro-2H-pyran-3-yl 4-nitro benzoate 246 β



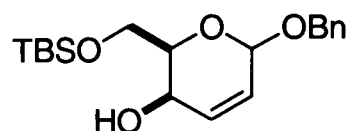
The alcohol **238** (770 mg, 2.2 mmol), 4-nitrobenzoic acid (440 mg, 2.6 mmol) and PPh_3 (860 mg, 3.3 mmol) were dissolved in THF under argon. Di-tert-butyl azodicarboxylate (760 mg, 3.3 mmol) was added in one portion and the mixture stirred until TLC indicated no starting material was present (45 minutes). The mixture was concentrated and the product purified by column chromatography (10% EtOAc – petrol) to afford the *benzoate* as a yellow solid (950 mg, 88%).

R_f (20% EtOAc – petrol) 0.68; m.p. 92-93 $^\circ\text{C}$; $[\alpha]_D -135$ (c = 1.55, CH_2Cl_2); **IR** $\nu_{\max}$ (CHCl_3) 2932, 2886, 2859 (CH) and 1725 (C=O); **$^1\text{H NMR}$** δ_H (400 MHz; CDCl_3) 8.28

(4 H, AA'BB', benzoate CH), 7.37 (5 H, m, phenyl CH), 6.29 (1 H, ddd, J 10.0, 5.5 and 1.0, $C_4H=C_5H$), 6.11 (1 H, dd, J 10.0 and 3.0, $C_4H=C_5H$), 5.33 (1 H, dd, J 5.5 and 2.5, $CHOCOAr$), 5.21 (1 H, dd, J 3.0 and 1.0, anomeric CH), 4.84-4.67 (2 H, AB q, $PhCH_AH_B$), 4.36 (1 H, td, J 6.5 and 2.5, $CHCH_2OSi$), 3.81 (1 H, dd, J 10.0 and 7.0, $TBSOCH_AH_B$), 3.74 (1 H, dd, J 10.0 and 6.5), 0.83 (9 H, s, CMe_3), 0.02 (3 H, s, $SiMe_AMe_B$) and -0.07 (3 H, s, $SiMe_AMe_B$); **^{13}C NMR** δ_C ($CDCl_3$) 163.9 ($C=O$), 150.6 (CNO_2), 137.7, 135.5 ($2 \times 4^\circ$ aryl C), 131.3 (C^5), 130.8, 128.5, 128.1, 127.9 (aryl C), 125.2 (C^4), 123.6 (aryl C), 93.2 (anomeric C), 70.0 (CH_2Ph), 69.3 ($CHCH_2OSi$), 64.3 ($CHOCOAr$), 61.5 (CH_2OSi), 25.7 (CMe_3), 18.1 (CMe_3), -5.5 and -5.6 ($SiMe_2$); **MS** m/z (FI) 500 (MH^+), 442 ($M-Bu^+$, 100%) and 334 ($M-OCOAr^+$); **HRMS (CI)** Found ($M - OBn$) $^+$, 392.1530. $C_{19}H_{26}NO_6Si$ requires M 392.1529.

(2*R*, 3*R*, 6*R*)-6-Benzyloxy-2-(tert-butyl-dimethyl-silanyloxymethyl)-3,6-dihydro-2H-pyran-3-ol 247 α

(2*R*, 3*R*, 6*S*)-6-Benzyloxy-2-(tert-butyl-dimethyl-silanyloxymethyl)-3,6-dihydro-2H-pyran-3-ol 247 β



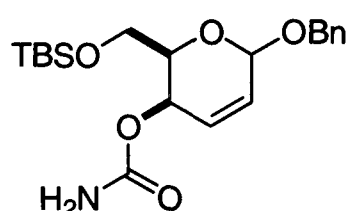
The benzoate **246** (520 mg, 1.0 mmol) was dissolved in THF – MeOH (10:1, 10 mL) and a solution of magnesium methoxide (10% in MeOH, 1.1 mL, 1.0 mmol) was added in one portion. The reaction was stirred for 2 h, by which time TLC indicated no starting material was present. The reaction was concentrated and the product purified by column chromatography (10% EtOAc – petrol) to afford the *alcohols* **247 α** and **247 β** as an oil (280 mg, 78%).

R_f (20% EtOAc – petrol) 0.31; $[\alpha]_D -76$ ($c = 1.42$, CH_2Cl_2); **IR** ν_{max} (film) 3457 (OH), 2929 and 2856 (CH); **1H NMR** δ_H (400 MHz; $CDCl_3$) 7.38-7.27 (5 H, m, aryl CH), 6.16 (1 H, ddd, J 10.0, 5.5 and 1.0, $C^4H=C^5H$), 5.92 (1 H, ddd, J 10.0, 3.5 and 1.0, $C^4H=C^5H$), 5.11 (1 H, d, J 3.5, anomeric CH), 4.81-4.59 (2 H, AB q, $PhCH_AH_B$), 4.11 (1 H, td, J 6.0 and 2.0, $CHOH$), 3.91-3.81 (3 H, m, $CHCH_2OSi$), 2.35 (1 H, br s, OH), 0.94 (9 H, s, CMe_3) and 0.13 (2 peaks, 6 H, $SiMe_2$); **^{13}C NMR** δ_C ($CDCl_3$) 137.9 (4° aryl C), 129.8, 128.4 (2 peaks), 128.2, 127.7 (aryl C and $C^4=C^5$), 93.4 (anomeric C), 71.0 ($CHOH$), 69.6 ($PhCH_2$), 62.8, 61.8 ($CHCH_2OSi$), 25.9 (CMe_3), 18.3 (CMe_3), -5.3 and $-$

5.4 (SiMe₂); **MS** *m/z* (FI) 351 (MH⁺), and 293 (M – Bu⁺, 100%); **HRMS (FI)** Found MH⁺, 351.1977. C₁₉H₃₀O₄Si requires *M* 351.1992.

(2*R*, 3*R*, 6*R*)-6-benzyloxy-2-(tert-butyl-dimethyl-silanyloxymethyl)-3,6-dihydro-2H-pyran-3-yl carbamate 248α

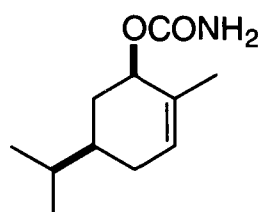
(2*R*, 3*R*, 6*S*)-6-benzyloxy-2-(tert-butyl-dimethyl-silanyloxymethyl)-3,6-dihydro-2H-pyran-3-yl carbamate 248β



Alcohol **247** (210 mg, 0.60 mmol) was subjected to the general carbamate formation procedure, affording the carbamates **248α** and **248β** as a white solid (220 mg, 95%).

m.p. 74-76 °C; [α]_D -53 (c = 1.39, CH₂Cl₂); **IR** *v*_{max} (CHCl₃) 3344 (NH₂), 2953, 2928, 2857 (CH) and 1716 (C=O); **¹H NMR** δ_H(400 MHz; CDCl₃) 7.38-7.27 (5 H, m, aryl H), 6.19 (1 H, ddd, *J* 10.0, 5.5 and 1.0, C⁴H=C⁵H), 6.02 (1 H, dd, *J* 10.0 and 3.0, C⁴H=C⁵H), 5.13 (1 H, dd, *J* 3.0 and 1.0, anomeric CH), 5.01 (2 H, br s, NH₂), 4.96 (1 H, dd, *J* 5.5 and 3.0, CHOCO), 4.83-4.62 (2 H, AB q, CH₂Ph), 4.26 (1 H, td, *J* 6.5 and 2.5, CHCH₂OSi), 3.79 (1 H, dd, *J* 10.5 and 6.5, CH_AH_BOSi), 3.71 (1 H, dd, *J* 10.5 and 7.0, CH_AH_BOSi), 0.91 (9 H, s, CMe₃), 0.09 and 0.08 (SiMe₂); **¹³C NMR** δ_C(CDCl₃) 156.0 (C=O), 137.6 (4° aryl C), 130.4 (C⁵), 128.4, 128.2, 127.8 (Aryl C), 126.2 (C⁴), 93.0 (anomeric C), 69.9 (CHCH₂OSi), 69.7 (CH₂Ph), 63.4 (CHOCO), 61.7 (CH₂OSi), 25.8 (CMe₃), 18.2 (CMe₃), -5.4 and -5.5 (SiMe₂); **MS** *m/z* (FI) 394 (MH⁺), 336 (100%, M – 'Bu⁺) and 275; **HRMS (CI)** Found (M – OBn)⁺, 286.1475. C₁₃H₂₄NO₄Si requires *M* 286.1475.

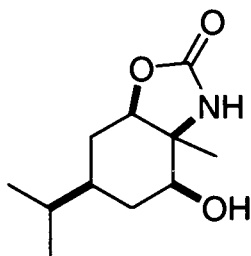
(1*R*, 5*R*)-5-Isopropyl-2-methyl-cyclohex-2-enyl carbamate 251



Carvotanacetol **250** (500 mg, 3.2 mmol) was subjected to the general carbamate formation procedure, affording the carbamate **251** as a white solid (620 mg, 99%).

R_f (EtOAc) 0.66; m.p. 86-88 °C; $[\alpha]_D +31.2$ (c 0.8 in CH_2Cl_2); **IR** ν_{max} (CHCl_3) 3435, 3332 (NH_2), 1687 ($\text{C}=\text{O}$) and 1611 (NH_2); **$^1\text{H NMR}$** δ_{H} (400 MHz; CDCl_3) 5.56 (1 H, m, $\text{C}=\text{CH}$), 5.29 (1 H, m, CHOR), 4.79 (2 H, br s, NH_2), 2.15 (1 H, ddt, J 12.0, 6.0 and 2.0, $\text{C}^6\text{H}_\text{A}\text{H}_\text{B}$), 1.98 (1 H, m, $\text{C}^4\text{H}_\text{A}\text{H}_\text{B}$), 1.76 (1 H, m, $\text{C}^4\text{H}_\text{A}\text{H}_\text{B}$), 1.66 (3 H, t, J 1.0, $\text{C}=\text{CMe}$), 1.56-1.46 (2 H, m, CHMe_2 and CH^iPr), 1.26 (1 H, dt, J 12.0 and 10.0, $\text{C}^6\text{H}_\text{A}\text{H}_\text{B}$) and 0.88 (6 H, dd, J 6.5 and 5.0 CHMe_2); **$^{13}\text{C NMR}$** δ_{C} (CDCl_3) 157.2 ($\text{C}=\text{O}$), 133.2 ($\text{C}_\text{A}=\text{C}_\text{B}$), 126.0 ($\text{C}_\text{A}=\text{C}_\text{B}$), 74.3 (CHOR), 39.2, 33.0, 32.0, 28.7, 19.6, 19.3 and 18.6; **MS** m/z (EI) 197 (100%, M^+); **HRMS (EI)** Found M^+ , 197.1417. $\text{C}_{11}\text{H}_{19}\text{NO}_2$ requires M 197.1416.

(3a*S*, 4*S*, 6*R* 8a*R*)-4-Hydroxy-6-isopropyl-3a-methyl-hexahydro-benzooxazol-2-one
252

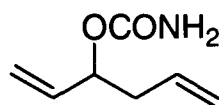


Carbamate **251** (200 mg, 1.0 mmol) was subjected to the general tethered aminohydroxylation procedure, using $(\text{DHQ})_2\text{PHAL}$ as the ligand. Purification of the crude compound by column chromatography (60:40, EtOAc – petrol) afforded the oxazolone **252** as a yellow oil (120 mg, 55%).

R_f (EtOAc) 0.33; $[\alpha]_D -30.3$ (c 0.8 in CH_2Cl_2); **IR** ν_{max} (film) 3324 (br, OH, NH) and 1737 ($\text{C}=\text{O}$); **$^1\text{H NMR}$** δ_{H} (400 MHz; CDCl_3) 5.68 (1 H, br s, NH), 4.28 (1 H, ddd, J 9.0, 6.5 and 1.0, CHOR), 3.58 (1 H, dd, J 12.5 and 5.0, CHOH), 2.74 (1 H, br s, OH), 2.02 (1 H, m, $\text{C}^7\text{H}_\text{A}\text{H}_\text{B}$), 1.81 (1 H, m, $\text{C}^5\text{H}_\text{A}\text{H}_\text{B}$), 1.54 (1 H, heptet, J 7.0, CHMe_2), 1.43 (3 H, s, CNRMe), 1.56-1.10 (2 H, m, $\text{C}^5\text{H}_\text{A}\text{H}_\text{B}$ and $\text{C}^7\text{H}_\text{A}\text{H}_\text{B}$), 1.18 (1 H, m, CH^iPr), 0.89 (6 H, dd, J 7.0 and 3.0, CMe_2); **$^{13}\text{C NMR}$** δ_{C} (CDCl_3) 159.5 ($\text{C}=\text{O}$), 82.5, 73.2 (CHOR and CMeNR), 60.8 (CHOH), 36.2, 32.5, 32.1, 31.2, 25.0, 19.5 and 19.4 (CMe_2); **MS** m/z (CI) 214 (100%, MH^+) and 170 ($\text{M}^+ - ^i\text{Pr}$); **HRMS (CI)** Found MH^+ , 214.1444. $\text{C}_{11}\text{H}_{20}\text{NO}_3$ requires M 214.1443.

5.5 – Experimental details for chapter 2.5

1-Vinyl-but-3-enyl carbamate **254**



1-Vinyl-but-3-enol **253** (1.1 g, 11 mmol) was subjected to the general carbamate formation procedure, affording the *carbamate* **254** as an oil (1.4 g, 87%).

R_f (EtOAc) 0.78; **IR** $\nu_{\max}$ (film) 3478, 3351 (NH₂), 3081, 3013, 2937 (CH), 1722 (C=O), 1643 (C=C) and 1601 (NH₂); **¹H NMR** δ_H (300 MHz; CDCl₃) 5.86-5.72 (2 H, m), 5.30-5.08 (5 H, m) (2 $\times$ CH=CH₂ and CHOCO), 4.74 (2 H, br s, NH₂) and 2.41 (2 H, t, J 6.5, C²H₂); **¹³C NMR** δ_C (CDCl₃) 156.1 (C=O), 136.1, 133.1 (C² and C⁵), 117.8, 116.4 (C¹ and C⁶), 74.4 (C⁴), 38.8 (C³); **MS** m/z (CI) 159 (100%, MNH₄⁺) and 142 (MH⁺); **HRMS (CI)** Found MNH₄⁺, 159.1136. C₇H₁₅N₂O₂ requires M 159.1134.

5-(*RS*)-Allyl-4-(*RS*)-hydroxymethyl-oxazolidin-2-one **255**

5-(*SR*)-Allyl-4-(*RS*)-hydroxymethyl-oxazolidin-2-one **256**



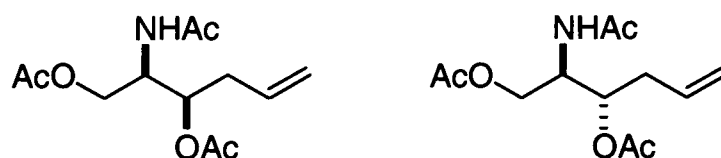
1-Vinyl-but-3-enyl carbamate **254** (570 mg, 4.0 mmol) was subjected to the general tethered aminohydroxylation procedure, using EtN^tPr₂ as the ligand. Purification of the crude compound by column chromatography (50:50, EtOAc – petrol) afforded the *oxazolidinones* **255** and **256** as an oil (450 mg, 9:1, 71%).

R_f (EtOAc) 0.25; **IR** $\nu_{\max}$ (film) 3334 (br, OH, NH) and 1735 (C=O); **¹H NMR** δ_H (400 MHz; CDCl₃) 6.98-6.96 (1 H, 2 br s, NH), 5.84-5.70 (1 H, *minor* m and *major* ddt, J 17.0, 10.5 and 7.0, CH₂=CH), 5.21-5.11 (2 H, m, CH₂=CH), 4.70 (0.1 H, dt, J 8.5 and 5.5, *minor* CHOCO), 4.61 (1 H, br s, OH), 4.43 (0.9 H, m, *major* CHOCO), 3.83 (0.1 H, m, *minor* CHNH), 3.71-3.55 (2 H, m, CH₂OH), 3.50-3.48 (0.9 H, br m, *major* CHNH), 2.63-2.55 (0.2 H, m, *minor* CH₂), 2.53-2.39 (1.8 H, m, *major* CH₂); **¹³C NMR** δ_C (CDCl₃) 160.6 (*minor* C=O), 160.3 (*major* C=O), 132.8 (*minor* CH=CH₂), 131.2

(*major* CH=CH₂), 119.6 (*major* CH=CH₂), 118.3 (*minor* CH=CH₂), 78.8 (*minor* CHOCO), 78.0 (*major* CHOCO), 63.1 (*major* CHOH), 60.7 (*minor* CHOH), 58.5 (*major* CHNH), 56.6 (*minor* CHNH), 38.7 (*major* CH₂) and 33.2 (*minor* CH₂); **MS** *m/z* (CI) 175 (MNH₄⁺) and 158 (100%, MH⁺); **HRMS (CI)** Found MH⁺, 158.0816. C₇H₁₂NO₃ requires *M* 158.0817.

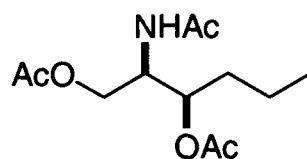
(2*RS*, 3*RS*)-3-Acetoxy-2-acetylamino-hex-5-enyl acetate 257

(2*RS*, 3*SR*)-3-Acetoxy-2-acetylamino-hex-5-enyl acetate 258



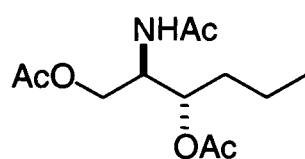
Oxazolidinones **255** and **256** (95 mg, 0.61 mmol) were subjected to the general oxazolidinone cleavage - peracetylation procedure. Purification of the crude compound by column chromatography (50% EtOAc – petrol) afforded the *triacetates* **257** and **258** as an oil (94 mg, 60%).

R_f (EtOAc) 0.33; **IR** ν_{max} (film) 3297 (br, NH), 3079, 2981 (CH), 1732 and 1682 (C=O); **¹H NMR** δ_{H} (400 MHz; CDCl₃); 6.13 (0.1 H, br d, *J* 9.0, *minor* NH), 5.80 (0.9 H, br d, *J* 9.0, *major* NH), 5.75-5.64 (1 H, m, *minor* CH=CH₂), 5.10-5.01 (2.9 H, m, CH=CH₂ and *major* CHOAc), 4.93 (0.1 H, m, *minor* CHOAc), 4.44-4.36 (1 H, m, CHNH), 4.23 (0.1 H, dd, *J* 11.5 and 6.0, *minor* CH₂OAc), 4.04-3.96 (1.9 H, m, *major* CH₂OAc), 2.30 (2 H, t, *J* 7.0, C⁴H₂), 2.04, 2.03 (2 peaks), 2.02, 2.00 and 1.96 (all s, Ac); **¹³C NMR** δ_{C} (CDCl₃) 174.1, 170.7, 170.5, 170.2, 170.1, 170.0 (C=O), 132.7 (*minor* CH=CH₂), 132.3 (*major* CH=CH₂), 118.8 (*major* CH=CH₂), 118.4 (*minor* CH=CH₂), 72.3 (*minor* CHOAc), 71.4 (*major* CHOAc), 63.1 (*major* CH₂OAc), 60.3 (*minor* CH₂OAc), 50.1 (*minor* CHNHAc), 49.6 (*major* CHNHAc), 35.9 (*minor* CH₂), 35.8 (*major* CH₂), 23.1 (2 peaks), 20.9, 20.8 and 20.7 (2 peaks) (Ac); **MS** *m/z* (CI) 275 (MNH₄⁺), 258 (100%, MH⁺) and 198 (M⁺ - OAc); **HRMS (CI)** Found MNH₄⁺, 275.1605. C₁₂H₂₃N₂O₅ requires *M* 275.1607.

(2*RS*, 3*RS*)-3-Acetoxy-2-acetylamino-hexyl acetate 259

Oxazolidinone **197** (250 mg, 1.6 mmol) was subjected to the general oxazolidinone cleavage - peracetylation procedure. Purification of the crude compound by column chromatography (30% EtOAc – petrol) afforded the *triacetate* **259** as an oil (96 mg, 24%).

IR $\nu_{\max}$ (film) 3288 (NH), 1740 and 1658 (C=O); **$^1\text{H NMR}$** δ_{H} (400 MHz; CDCl_3) 5.72 (1 H, br d, J 9.0, NH), 5.07 (1 H, ddd, J 8.0, 5.5 and 3.0, CHOAc), 4.39 (1 H, dtd, J 10.0, 6.5 and 3.5, CHNH), 4.04 (1 H, dd, J 11.5 and 6.0, $\text{CH}_\text{A}\text{H}_\text{B}\text{OAc}$), 4.00 (1 H, dd, J 11.5 and 6.0, $\text{CH}_\text{A}\text{H}_\text{B}\text{OAc}$), 2.06 (3 H, s, Ac), 2.04 (3 H, s, Ac), 2.01 (3 H, s, Ac), 1.61-1.44 (2 H, m, C^4H_2), 1.32 (2 H, hextet, J 7.5, C^5H_2) and 0.89 (3 H, t, J 7.5, C^6H_3); **$^{13}\text{C NMR}$** δ_{C} (CDCl_3) 171.2, 170.8, 170.6 (C=O), 72.5 (CHOAc), 63.7 (CH_2OAc), 50.5 (CHNH), 33.7 (C^4), 23.6, 21.3, 21.1 ($3 \times \text{Ac}$), 18.8 (C^5) and 14.1 (C^6); **MS** m/z (CI) 260 (MH^+) and 200 ($\text{M}^+ - \text{OAc}$); **HRMS (CI)** Found MH^+ , 260.1486. $\text{C}_{12}\text{H}_{22}\text{NO}_5$ requires M 260.1498.

(2*RS*, 3*SR*)-3-Acetoxy-2-acetylamino-hexyl acetate 260

Oxazolidinone **198** (100 mg, 0.63 mmol) was subjected to the general oxazolidinone cleavage - peracetylation procedure. Purification of the crude compound by column chromatography (30% EtOAc – petrol) afforded the *triacetate* **260** as an oil (64 mg, 39%).

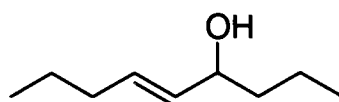
IR $\nu_{\max}$ (film) 3287 (NH), 2963, 2937, 2876 (CH), 1753 and 1662 (C=O); **$^1\text{H NMR}$** δ_{H} (400 MHz; CDCl_3) 5.92 (1 H, br d, J 9.0, NH), 4.93 (1 H, dt, J 8.5 and 5.0, CHOAc), 4.38 (1 H, dtd, J 9.0, 5.5 and 4.0, CHNH), 4.24 (1 H, dd, J 11.5 and 6.0, $\text{CH}_\text{A}\text{H}_\text{B}\text{OAc}$), 4.06 (1 H, dd, J 11.5 and 4.5, $\text{CH}_\text{A}\text{H}_\text{B}\text{OAc}$), 2.07 (3 H, s, Ac), 2.06 (3 H, s, Ac), 2.00 (3 H, s, Ac), 1.66-1.51 (2 H, m, C^4H_2), 1.41-1.25 (2 H, m, C^5H_2) and 0.91 (3 H, t, J 7.0, C^6H_3); **$^{13}\text{C NMR}$** δ_{C} (CDCl_3) 171.3, 171.2, 170.2 (C=O), 73.9 (CHOAc), 63.0

(CH₂OAc), 50.9 (CHNH), 33.9 (C⁴), 23.3, 21.3, 21.2 (3 × Ac), 19.0 (C⁵) and 14.1 (C⁶);

MS *m/z* (CI) 260 (MH⁺) and 200 (MH⁺ – OAc); **HRMS (CI)** Found MH⁺, 260.1507.

C₁₂H₂₂NO₅ requires *M* 260.1498.

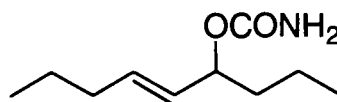
(5E)-Nonen-4-ol 262^{93, 188}



Iodine (1 crystal) was added to a suspension of magnesium turnings (0.59 g, 24 mmol) in THF (20 mL) and the mixture stirred for 1 h. A solution of n-propyl bromide (2.9 g, 24 mmol) in THF (80 mL) was added dropwise over 30 minutes then the mixture heated at reflux for 2 h (solution becomes colourless, heating continued until most of the magnesium had disappeared). This solution was then cooled to 0 °C and a solution of *E*-hex-2-enal **261** (2.0g, 20 mmol) in THF (50 mL) was added dropwise over 1 h (the solution becomes yellow over this time). The mixture was allowed to warm to room temperature and stirred for 1 h. Dilute H₂SO₄ (10% aqueous, 30 mL) was added dropwise to quench the reaction mixture, which was then extracted with Et₂O. The ethereal extracts were washed with saturated K₂CO₃ solution and brine, dried (MgSO₄), filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (5:95 EtOAc – petrol) to afford the alcohol **262** as an oil (1.1 g, 40%).

¹H NMR δ_H(400 MHz; CDCl₃) 5.64 (1 H, dt, *J* 15.0 and 7.0, CHCH₂), 5.46 (1 H, ddt, *J* 15.0, 7.0 and 1.0, CHCHOH), 4.06 (1 H, q, *J* 7.0, CHOH), 2.01 (2 H, q, *J* 7.0, CH=CHCH₂), 1.56-1.32 (7 H, m, remaining CH₂ and OH), 0.94 (3 H, t, *J* 7.0, CH₃) and 0.90 (3 H, t, *J* 7.0, CH₃).

(2E)-1-Propyl-hex-2-enyl carbamate 263



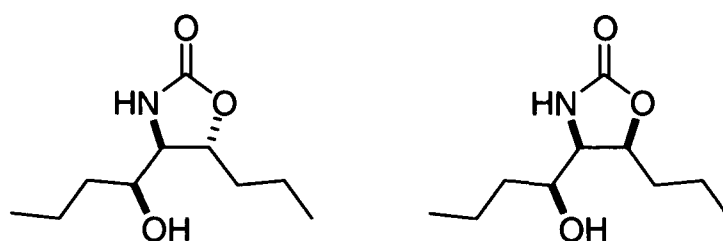
(5E)-Nonen-4-ol **262** (770 mg, 5.4 mmol) was subjected to the general carbamate formation procedure, affording the carbamate **263** as a yellow solid (960 mg, 95%).

R_f (EtOAc) 0.69; m.p. 29-32 °C; **IR** ν_{max} (CHCl₃) 3453, 3344 (NH₂), 1706 (C=O) and 1601 (NH₂); **¹H NMR** δ_H(400 MHz; CDCl₃) 5.71 (1 H, dt, *J* 15.0 and 7.0, CHPr), 5.39

(1 H, ddt, J 15.0, 8.0 and 2.0, $\text{CH}=\text{CHPr}$), 5.08 (1 H, q, J 7.0, CHOCO), 4.65 (2 H, br s, NH_2), 2.04-1.99 (2 H, m, allylic CH_2), 1.66-1.54 (2 H, m, CHOCH_2), 1.43-1.31 (4 H, m, $2 \times \text{MeCH}_2$) and 0.95-0.87 (6 H, m, $2 \times \text{Me}$); $^{13}\text{C NMR}$ $\delta_{\text{C}}(\text{CDCl}_3)$ 156.7 ($\text{C}=\text{O}$), 133.8 ($\text{C}_\text{A}=\text{C}_\text{B}$), 128.7 ($\text{C}_\text{A}=\text{C}_\text{B}$), 75.6 (CHOR), 36.8 (CH_2CHOR), 34.3, 22.1, 18.4 ($3 \times \text{CH}_2$), 13.9 and 13.6 ($2 \times \text{CH}_3$); **MS** m/z (CI) 186 (MH^+), 142 ($\text{MH}^+ - \text{CONH}_2$), 125 (100%, $\text{MH}^+ - \text{OCONH}_2$) and 95; **HRMS(CI)** Found MH^+ , 186.1496. $\text{C}_{10}\text{H}_{20}\text{NO}_2$ requires M 186.1494.

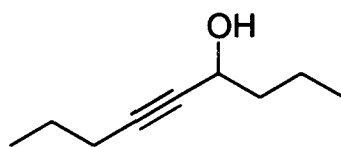
(1'SR, 4RS, 5RS)-4-(1'-Hydroxybutyl)-5-propyloxazolidin-2-one 264

(1'SR, 4RS, 5SR)-4-(1'-Hydroxybutyl)-5-propyloxazolidin-2-one 265



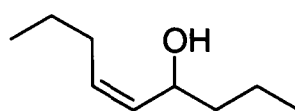
(2*E*)-1-Propyl-hexenyl carbamate **263** (200 mg, 1.1 mmol) was subjected to the general tethered aminohydroxylation procedure, using $(\text{DHQ})_2\text{PHAL}$ as the ligand. Purification of the crude compound by column chromatography (EtOAc) afforded the oxazolidinones **264** and **265** as a white solid (120 mg, 6:1, 57%).

R_f (EtOAc) 0.44; m.p. 87-90 °C; **IR** ν_{max} (CHCl_3) 3305 (br, OH and NH), 2960, 2874 (CH), 1747 and 1731 ($\text{C}=\text{O}$); $^1\text{H NMR}$ δ_{H} (400 MHz; CDCl_3); 6.48 (0.86 H, br s, *major* NH), 6.42 (0.14 H, br s, *minor* NH), 4.63 (0.14 H, ddd, J 10.5, 7.0 and 3.0, *minor* CHOCO), 4.39 (0.86 H, dt, J 8.5 and 5.0, *major* CHOCO), 3.71 (0.14 H, br m, *minor* CHOH), 3.61 (0.14 H, dd, J 7.5 and 3.0, *minor* CHNH), 3.46 (0.86 H, br m, *major* CHOH), 3.34 (0.86 H, t, J 4.0, *major* CHNH), 3.07 (0.86 H, br d, J 7.5, *major* OH), 2.93 (0.14 H, br d, J 7.5, *minor* OH), 1.79-1.30 (8 H, m, $2 \times \text{CH}_2\text{CH}_2$) and 1.00-0.93 (6 H, m, $2 \times \text{Me}$); $^{13}\text{C NMR}$ $\delta_{\text{C}}(\text{CDCl}_3)$ 161.2 (*minor* $\text{C}=\text{O}$), 160.4 (*major* $\text{C}=\text{O}$), 80.2 (*minor* CHOR), 79.4 (*major* CHOR), 72.1 (*major* CHOH), 68.9 (*minor* CHOH), 62.7 (*major* CHNH), 59.7 (*minor* CHNH), 37.2, 36.3, 35.2, 31.0, 19.6, 18.9, 18.8, 17.9 (methylene CH_2), 13.9, 13.8 (2 peaks) and 13.7 ($2 \times \text{CH}_3$); **MS** m/z (CI) 219 (MNH_4^+) and 202 (100%, MH^+); **HRMS (CI)** Found MNH_4^+ , 219.1712. $\text{C}_{10}\text{H}_{23}\text{N}_2\text{O}_3$ requires M 219.1709.

Non-5-yn-4-ol 266¹⁸⁹

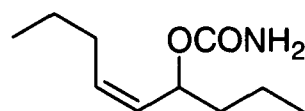
Diisopropylamine (1.60 g, 2.3 mL, 16 mmol) was dissolved in THF (40 mL) and cooled to -78°C . $n\text{-BuLi}$ in hexanes (1.6 M, 9.3 mL, 15 mmol) was added by syringe and the solution stirred for 5 minutes. The solution was allowed to warm to room temperature for 5 minutes before being cooled down again to -78°C . 1-Pentyne (1.0 g, 1.5 mL, 15 mmol) was injected and the solution stirred for 30 minutes. Butanal (1.3 g, 1.6 mL, 18 mmol) was then added by syringe and the solution stirred while allowing to warm to room temperature. When the reaction had gone to completion as indicated by TLC (10:90 EtOAc – light petrol), it was quenched by the addition of water and then diluted with Et_2O . The mixture was washed with 2 M HCl and brine. The ethereal extracts were collected, dried (MgSO_4), filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (10:90, EtOAc – petrol) to afford the alkyne **266** as an oil (2.2 g, 96%).

^1H NMR δ_{H} (400 MHz; CDCl_3) 4.37 (1 H, m, CHOH), 2.19 (2 H, td, J 7.0 and 2.0, $\text{CH}_2\text{C}\equiv\text{C}$), 1.73 (1 H, br s, OH), 1.70-1.61 (2 H, m), 1.58-1.45 (4 H, m) (methylene CH_2), 0.98 (3 H, t, J 7.0, CH_3) and 0.95 (3 H, J 7.0, CH_3).

(5Z)-Non-5-en-4-ol 267⁹³

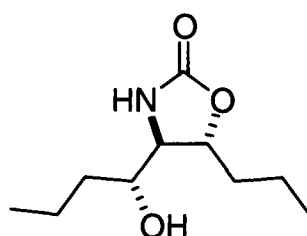
Non-5-yn-4-ol **266** (950 mg, 6.8 mmol) was dissolved in MeOH (10 mL). Lindlar catalyst (160 mg) was added and the suspension stirred under an atmosphere of hydrogen until TLC indicated no starting material was present. The mixture was filtered through celite, eluting with MeOH. The filtrate was concentrated *in vacuo* to afford the alcohol **267** as an oil (540 mg, 56%).

^1H NMR δ_{H} (400 MHz; CDCl_3) 5.49 (1 H, dtd, J 10.5, 8.0 and 1.0, $\text{CH}=\text{CHPr}$), 5.38 (1 H, ddt, J 10.5, 9.0 and 1.5, CHCHOH), 4.45 (1 H, dd, J 15.0 and 7.0, CHOH), 2.15-2.00 (2 H, m, C^7H_2), 1.66 (1 H, br s, OH), 1.59 (1 H, m, $\text{C}^3\text{H}_4\text{H}_\text{B}$), 1.45-1.30 (5 H, m, remaining CH_2) and 0.95-0.90 (6 H, m, $2 \times \text{CH}_3$).

(2Z)-1-Propyl-hexenyl carbamate 268

(5Z)-Nonen-4-ol **267** (540 mg, 3.8 mmol) was subjected to the general carbamate formation procedure, affording the *carbamate* **268** as an oil (710 mg, 100%).

R_f (EtOAc) 0.69; **IR** $\nu_{\max}$ (film) 3465, 3350 (NH₂), 2961, 2934, 2874 (CH), 1713 (C=O) and 1600 (NH₂); **¹H NMR** δ_H (400 MHz; CDCl₃) 5.55 (1 H, dt, J 10.5 and 7.5, CH=CHPr), 5.45 (1 H, dt, J 8.5 and 7.5, CHOR), 5.31 (1 H, m, CHCHOH), 4.62 (2 H, br s, NH₂), 2.20-2.07 (2 H, m, allylic CH₂), 1.73-1.62 (2 H, m, CHOHCH₂), 1.54-1.29 (4 H, m, remaining CH₂), 0.93 (3 H, t, J 7.5, CH₃) and 0.92 (3 H, t, J 7.5, CH₃); **¹³C NMR** δ_C (CDCl₃) 157.0 (C=O), 133.7 (C_A=C_B), 128.5 (C_A=C_B), 70.9 (CHOR), 37.1 (CH₂CHOR), 29.8, 22.6, 18.3 (3 $\times$ CH₂), 13.6 and 13.5 (2 $\times$ CH₃); **MS** m/z (CI) 203 (MNH₄⁺), 142 (MH⁺ – CONH₂), 124 (100%, MH⁺ – OCONH₂) and 95; **HRMS(CI)** Found MNH₄⁺, 203.1750. C₁₀H₂₃N₂O₂ requires M 203.1760.

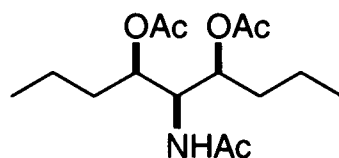
(1'*RS*, 4*RS*, 5*RS*)-4-(1'-Hydroxybutyl)-5-propyloxazolidin-2-one 269

(2Z)-1-Propyl-hexenyl carbamate **268** (200 mg, 1.1 mmol) was subjected to the general tethered aminohydroxylation procedure, using EtN^{*i*}Pr₂ as the ligand. Purification of the crude compound by column chromatography (EtOAc) afforded the *oxazolidinone* **269** as an oil (150 mg, 67%).

R_f (EtOAc) 0.44; **IR** $\nu_{\max}$ (film) 3294 (br, OH and NH), 2961, 2935, 2874 (CH), 1744 (C=O); **¹H NMR** δ_H (400 MHz; CDCl₃) 6.93 (1 H, br s, NH), 4.52 (1 H, dt, J 8.0 and 4.5, CHOR), 4.07 (1 H, br s, OH), 3.62 (1 H, m, CHOH), 3.36 (1 H, dd, J 4.0 and 3.2, CHNH), 1.66 (1 H, m), 1.58-1.20 (7 H, m) (4 $\times$ CH₂), 0.92 (3 H, t, J 7.0, CH₃) and 0.89 (3 H, t, J 7.0, CH₃); **¹³C NMR** δ_C (CDCl₃) 160.6 (C=O), 77.6 (CHOR), 71.0 (CHOH), 62.3 (CHNH), 37.9, 33.9, 19.0, 17.9 (methylene CH₂), 13.9 and 13.7 (2 $\times$ CH₃); **MS** m/z

(CI) 219 (MNH_4^+) and 202 (100%, MH^+) and 184; **HRMS (CI)** Found MH^+ , 202.1442. $\text{C}_{10}\text{H}_{20}\text{NO}_3$ requires M 202.1443.

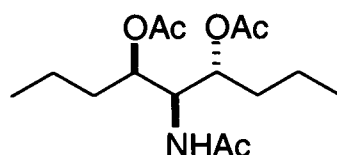
(4*RS*, 5*rs*, 6*SR*)-5-Acetylamino-4,6-diacetoxynonane 270



Oxazolidinones **264** and **265** (94 mg, 0.47 mmol) were subjected to the general oxazolidinone cleavage - peracetylation procedure. Purification of the crude compound by column chromatography (50% EtOAc – petrol) afforded the major *triacetate* **270** as a yellow oil (40 mg, 28%).

R_f (EtOAc) 0.42; **IR** ν_{max} (film) 3300 (br, NH), 2961, 2869 (CH), 1740 and 1661 (C=O); **^1H NMR** δ_{H} (400 MHz; CDCl_3); 5.65 (1 H, br d, J 10.0, NH), 4.96 (2 H, td, J 6.5 and 5.0, $2 \times \text{CHOAc}$), 4.21 (1 H, dt, J 10.0 and 5.0, CHNH), 2.06 (6 H, s, OAc), 2.01 (3 H, s, NHAc), 1.56-1.51 (4 H, m, C^3H_2 and C^7H_2), 1.36-1.22 (4 H, m, C^2H_2 and C^8H_2) and 0.88 (6 H, t, J 7.0, $2 \times \text{Me}$); **^{13}C NMR** δ_{C} (CDCl_3) 170.8 ($2 \times \text{OAc C=O}$), 170.0 (NHAc C=O), 72.8 ($2 \times \text{CHOAc}$), 53.9 (CHNHAc), 33.6 ($2 \times \text{CH}_2\text{CHOAc}$), 23.1 (NHCOCH₃), 20.9 ($2 \times \text{OCOCH}_3$), 18.4 ($2 \times \text{CH}_2\text{CH}_3$) and 13.7 ($2 \times \text{CH}_2\text{CH}_3$); **MS** m/z (CI) 302 (100%, MH^+) and 242 ($\text{M}^+ - \text{OAc}$); **HRMS (CI)** Found MH^+ , 302.1962. $\text{C}_{15}\text{H}_{28}\text{NO}_5$ requires M 302.1967.

(4*RS*, 6*SR*)-5-Acetylamino-4,6-diacetoxynonane 271

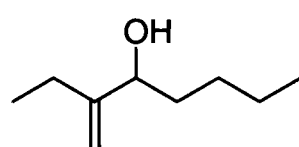


Oxazolidinone **269** (140 mg, 0.71 mmol) was subjected to the general oxazolidinone cleavage - peracetylation procedure. Purification of the crude compound by column chromatography (40% EtOAc – petrol) afforded the *triacetate* **271** as a white crystalline solid (140 mg, 66%).

R_f (EtOAc) 0.53; m.p. 96-98 °C; **IR** ν_{max} (CHCl_3) 3299 (NH), 2962, 2875 (CH), 1739, 1651 (C=O) and 1556; **^1H NMR** δ_{H} (400 MHz; CDCl_3) 5.77 (1 H, d, J 10.0, NH), 5.07 (1 H, ddd, J 7.5, 6.5 and 2.0, CHOAc), 4.75 (1 H, ddd, J 8.0, 5.0 and 4.0, CHOAc), 4.22

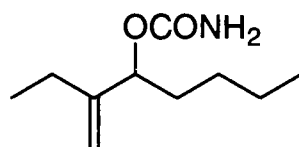
(1 H, ddd, J 11.0, 8.5 and 2.0, CHNHAc), 2.02 (3 H, s), 1.99 (3 H, s), 1.98 (3 H, s) ($3 \times$ COCH₃), 1.53-1.15 (8 H, m, $4 \times$ CH₂), 0.84 (3 H, t, J 7.0, CH₃) and 0.83 (3 H, t, J 7.0, CH₃); **¹³C NMR** δ_c (CDCl₃) 170.5, 170.0 (2 peaks) ($3 \times$ C=O), 71.7, 71.1 ($2 \times$ CHOAc), 52.6 (CHNHAc), 33.6, 33.5 ($2 \times$ CH₂CHOAc), 23.2 (NHCOCH₃), 20.9 ($2 \times$ OCOCH₃), 18.5, 18.3 ($2 \times$ CH₂CH₃) 13.9 and 13.8 ($2 \times$ CH₂CH₃); **MS** m/z (CI) 302 (MH⁺), 242 (100%, M⁺ – OAc) and 126; **HRMS (CI)** Found MH⁺, 302.1958. C₁₅H₂₈NO₅ requires M 302.1967.

3-Methylene-octan-4-ol 273



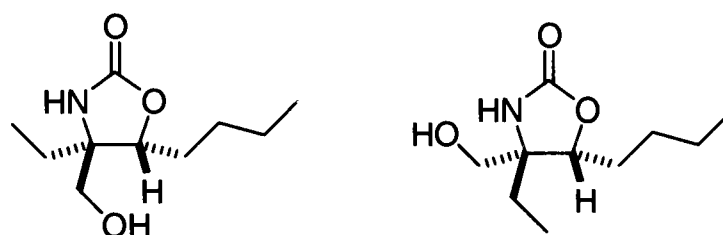
ⁿBuLi (1.5 M, 4.3 mL, 6.6 mmol) was added dropwise to a stirred solution of ethyl acrolein (500 mg, 0.58 mL, 6.0 mmol) in THF (20 mL) at –78 °C under argon. The solution was allowed to stir at –78 °C for 30 minutes before being allowed to warm to room temperature. The reaction was quenched by the addition of water (5 mL) and diluted with Et₂O. The mixture was washed with aqueous HCl (2 M) and brine. The organic layer was collected, dried (MgSO₄), filtered and concentrated *in vacuo*. The crude alcohol was purified by column chromatography (1:9, EtOAc – petrol) to afford the *alcohol* **273** as a colourless oil (360 mg, 42%).

R_f (1:4, EtOAc – petrol) 0.45; **IR** $\nu_{\max}$ (film) 3360 (OH), 2962, 2935 and 2874 (CH); **¹H NMR** δ_H (400 MHz; CDCl₃) 5.01 (1 H, dt, J 2.5 and 1.0, C=CH_AH_B), 4.85 (1 H, dt, J 3.0 and 1.5, C=CH_AH_B), 4.09 (1 H, t, J 6.5, CHOH), 2.13 (1 H, dqdd, J 15.0, 8.5, 1.0 and 1.0, allylic CH_AH_B), 2.01 (1 H, dqdd, J 15.0, 8.0, 1.5 and 1.0, allylic CH_AH_B), 1.61-1.50 (2 H, m, C⁵H₂), 1.47 (1 H, br s, OH), 1.40-1.25 (4 H, m, $2 \times$ CH₂), 1.08 (3 H, t, J 8.0, C¹H₃) and 0.91 (3 H, t, J 7.0, C⁸H₃); **¹³C NMR** δ_c (CDCl₃) 153.7 (CH₂=C), 108.3 (CH₂=C), 75.7 (CHOH), 35.2 (allylic CH₂), 27.9, 23.8, 22.6 ($3 \times$ CH₂), 14.0 and 12.2 ($2 \times$ CH₃); **MS** m/z (CI) 160 (MNH₄⁺), 142 (M⁺) and 125 (100%, M⁺ – OH); **HRMS (CI)** Found MNH₄⁺, 160.1694. C₉H₂₂NO requires M 160.1701.

1-(1'-Methylene-propyl)-pentyl carbamate 274

3-Methylene-octan-4-ol **273** (340 mg, 2.4 mmol) was subjected to the general carbamate formation procedure, affording the *carbamate* **274** as a low-melting white solid (400 mg, 90%).

R_f (EtOAc) 0.28; **IR** $\nu_{\max}$ (CHCl₃) 3437, 3337 (NH₂), 2958, 2936, 2874 (CH), 1689 (C=O) and 1611 (NH₂); **¹H NMR** δ_H (400 MHz; CDCl₃) 5.07 (1 H, t, J 7.0, CHOR), 5.01 (1 H, dt, J 2.5 and 1.0, C=CH_AH_B), 4.88 (1 H, dt, J 3.0 and 1.0, C=CH_AH_B), 4.74 (2 H, br s, NH₂), 2.05 (2 H, qdd, J 7.5, 1.0 and 1.0, allylic CH₂), 1.66-1.60 (2 H, m, C²H₂), 1.35-1.28 (4 H, m, remaining CH₂), 1.07 (3 H, t, J 7.5, C^{3'}H₃) and 0.90 (3 H, t, J 7.0, C⁵H₃); **¹³C NMR** δ_C (CDCl₃) 156.5 (C=O), 149.5 (C_A=C_B), 109.6 (C_A=C_B), 77.8 (CHOR), 33.0 (C²H₂), 27.5 (C³H₂), 24.4 (allylic CH₂), 22.5 (C⁴H₂), 13.9 (C⁵H₃) and 12.0 (CH₃); **MS** m/z (CI) 203 (MNH₄⁺), 186 (MH⁺), 142 (MH⁺ – CONH₂), 125 (100%, MH⁺ – OCONH₂) and 95; **HRMS(CI)** Found MNH₄⁺, 203.1768. C₁₀H₂₃N₂O₂ requires M 203.1760.

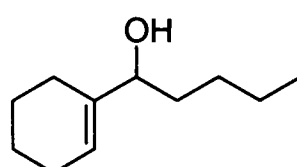
(4*RS*, 5*RS*)-5-Butyl-4-ethyl-4-hydroxymethyl-oxazolidinone 275**(4*SR*, 5*RS*)-5-Butyl-4-ethyl-4-hydroxymethyl-oxazolidinone 276**

1-(1'-Methylene-propyl)-pentyl carbamate **274** (200 mg, 1.1 mmol) was subjected to the general tethered aminohydroxylation procedure, using EtN^{*i*}Pr₂ as the ligand. Purification of the crude compound by column chromatography (EtOAc) afforded the *oxazolidinones* **275** and **275** as a white solid (150 mg, 8:1, 68%).

R_f (EtOAc) 0.28; **IR** $\nu_{\max}$ (CHCl₃) 3288 (br, OH and NH), 2957, 2874 (CH) and 1732 (C=O); **¹H NMR** δ_H (400 MHz; CDCl₃, major isomer); 6.93 (1 H, br s, NH), 4.49 (1 H, dd, J 6.0 and 3.0, OH), 4.20 (1 H, dd, J 8.0 and 7.0, CHOR), 3.62 (1 H, dd, J 12.0 and 5.0, CH_AH_BOH), 3.35 (1 H, dd, J 12.0 and 7.5, CH_AH_BOH), 1.68-1.43 (5 H, m), 1.37-

1.31 (3 H, m) ($4 \times \text{CH}_2$), 0.91 (3 H, t, J 7.5, CH_3) and 0.87 (3 H, t, J 7.0, CH_3); ^{13}C **NMR** δ_{C} (CDCl_3 , major isomer) 160.2 ($\text{C}=\text{O}$), 82.4 (CHOR), 64.5, 64.1 (CHNH and CH_2OH), 28.9, 28.4, 24.1, 22.5 ($4 \times \text{CH}_2$), 13.9 and 8.1 ($2 \times \text{CH}_3$); **MS** m/z (CI) 219 (MNH_4^+) and 202 (100%, MH^+); **HRMS (CI)** Found MNH_4^+ , 219.1715. $\text{C}_{10}\text{H}_{23}\text{N}_2\text{O}_3$ requires M 219.1709.

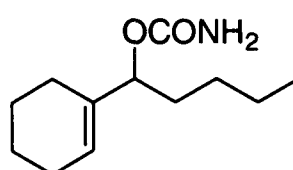
1-Cyclohex-1-enyl-pentan-1-ol **278**



$n\text{-BuLi}$ (1.6 M, 3.1 mL, 5.0 mmol) was added dropwise to a stirred solution of 1-cyclohexene-1-carboxyaldehyde (500 mg, 4.5 mmol) in THF (20 mL) at -78°C under argon. The solution was allowed to stir at -78°C for 30 minutes before being allowed to warm to room temperature. The reaction was quenched by the addition of water (5 mL) and diluted with Et_2O . The mixture was washed with aqueous HCl (2 M) and brine. The organic layer was collected, dried (MgSO_4), filtered and concentrated *in vacuo* to afford the *alcohol 278* without purification as an oil (730 mg, 95%)

R_f (1:1, EtOAc – petrol) 0.65; **IR** ν_{max} (film) 3340 (br, OH), 2930 and 2858 (CH); ^1H **NMR** δ_{H} (400 MHz; CDCl_3) 5.65 (1 H, br m, $\text{CH}=\text{CR}_2$), 3.95 (1 H, t, J 7.0, CHOH), 2.09-2.03 (3 H, m), 1.95-1.87 (1 H, m), 1.70-1.50 (6 H, m), 1.41-1.19 (4 H, m) ($7 \times \text{CH}_2$) and 0.91 (3 H, t, J 7.0, CH_3); ^{13}C **NMR** δ_{C} (CDCl_3) 140.0 ($\text{CH}=\text{CR}_2$), 123.0 ($\text{CH}=\text{CR}_2$), 76.8 (CHOH), 34.5, 28.0, 25.0, 23.3, 22.7 (3 peaks) ($7 \times \text{CH}_2$) and 14.0 (CH_3); **MS** m/z (CI) 186 (MNH_4^+) and 169 (100%, MH^+); **HRMS (CI)** Found MH^+ , 169.1593. $\text{C}_{11}\text{H}_{21}\text{O}$ requires M 169.1592.

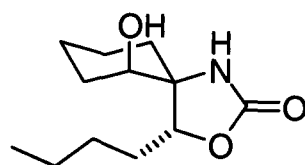
1-Cyclohexen-1-yl-pentyl carbamate **279**



1-Cyclohex-1-enyl-pentan-1-ol **278** (680 mg, 4.1 mmol) was subjected to the general carbamate formation procedure, affording the *carbamate 279* as a white solid (800 mg, 94%).

R_f (1:1, EtOAc – petrol) 0.68; m.p. 81-84 °C; **IR** $\nu_{\max}$ (CHCl₃) 3429, 3330, 3262, 3200 (NH₂), 2929, 2858 (CH), 1688 (C=O) and 1612 (NH₂); **¹H NMR** δ_H (400 MHz; CDCl₃) 5.69 (1 H, td, J 3.5 and 1.0, CH=CR₂), 4.97 (1 H, dd, J 7.5 and 6.5, CHOR), 4.73 (2 H, br s, NH₂), 2.04-2.02 (2 H, m), 1.96-1.94 (2 H, m) (2 × allylic CH₂), 1.65-1.52 (6 H, m), 1.35-1.22 (4 H, m) (remaining CH₂) and 0.89 (3 H, t, J 7.0, CH₃); **¹³C NMR** δ_C (CDCl₃) 156.7 (C=O), 136.1 (CH=CR₂), 124.6 (CH=CR₂), 79.1 (CHOR), 32.3, 27.6, 24.9, 23.9, 22.5, 22.4 (2 peaks) (7 × CH₂) and 13.9 (CH₃); **MS** m/z (FI) 211 (100%, M⁺); **HRMS (FI)** Found M⁺, 211.1578. C₁₀H₂₁NO₂ requires M 211.1572.

(4*RS*, 5*SR*, 6*SR*)-4-Butyl-6-hydroxy-3-oxa-1-aza-spiro[4.5]decan-2-one 280

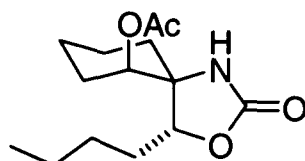


1-Cyclohexen-1-yl-pentyl carbamate **279** (200 mg, 0.95 mmol) was subjected to the general tethered aminohydroxylation procedure, using EtN^{*i*}Pr₂ as the ligand.

Purification of the crude compound by column chromatography (EtOAc) afforded the *oxazolidinone* **280** an oil (130 mg, 62%).

R_f (1:1 EtOAc – petrol) 0.17; **IR** $\nu_{\max}$ (CHCl₃) 3407, 3272 (br, OH and NH), 2938, 2863 (CH), 1732 (C=O); **¹H NMR** δ_H (400 MHz; CDCl₃) 7.55 (1 H, br s, NH), 4.67 (1 H, dd, J 7.0 and 2.5, CHOR), 3.52 (1 H, br s, OH), 3.24 (1 H, br m, CHOH), 1.90 (1 H, m), 1.81 (1 H, m), 1.72 (1 H, m), 1.64-1.18 (11 H, m) (7 × CH₂) and 0.88 (3H, t, J 7.5, CH₃); **¹³C NMR** δ_C (CDCl₃) 160.4 (C=O), 81.9 (CHOR), 71.9 (CHOH), 64.3 (CHNH), 31.4, 30.7, 29.2, 28.3, 23.8, 22.5, 21.2 (methylene CH₂) and 13.9 (CH₃); **MS** m/z (CI) 245 (MNH₄⁺) and 228 (100%, MH⁺); **HRMS (CI)** Found MNH₄⁺, 245.1861. C₁₂H₂₅N₂O₃ requires M 245.1865.

(4*RS*, 5*SR*, 6*SR*)-4-Butyl-2-oxo-3-oxa-1-aza-spiro[4.5]-dec-6-yl acetate 281



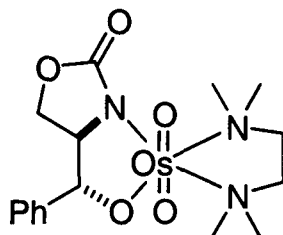
Oxazolidinone **280** (42 mg, 0.19 mmol) was dissolved in pyridine (2 mL) and acetic anhydride (1 mL). The mixture was stirred for 2 h, and then quenched by the addition

of aqueous CuSO₄ solution (5 mL). The mixture was extracted with ethyl acetate (2 × 20 mL), dried (MgSO₄) and concentrated under reduced pressure. Purification of the crude compound by column chromatography (40% EtOAc – petrol) afforded the oxazolidinone **281** as a white solid (27 mg, 54%).

m.p. 100-101 °C; **IR** ν_{max} (CHCl₃) 3243 (NH), 2955, 2872 (CH), 1739 (C=O); **¹H NMR** δ_{H} (400 MHz; CDCl₃) 7.67 (1 H, br s, NH), 4.68 (1 H, dd, *J* 11.0 and 4.5, CHOR), 4.24 (1 H, dd, *J* 11.0 and 2.5, CHOAc), 2.09 (3 H, s, Ac), 1.93-1.85 (2 H, m), 1.81-1.77 (1 H, m), 1.67-1.26 (11 H, m) (7 × CH₂) and 0.90 (3 H, t, *J* 8.0, Me); **¹³C NMR** δ_{C} (CDCl₃) 170.7 (acetate C=O), 159.6 (oxazolidinone C=O), 82.0 (CHOAc), 74.2 (CHOR), 62.6 (CNH), 31.0, 29.4, 28.1, 28.0, 23.2, 22.4 (6 × CH₂), 21.2 (acetate Me), 21.1 (CH₂) and 13.8 (Me); **MS** *m/z* (CI) 287 (MNH₄⁺) and 270 (100%, MH⁺); **HRMS (CI)** Found MH⁺, 270.1711. C₁₄H₂₄NO₄ requires *M* 270.1705.

5.6 – Experimental details for chapter 2.6

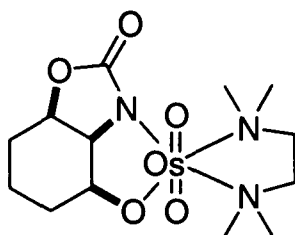
Osmate Ester 298



trans-Cinnamyl carbamate **176** (100 mg, 0.56 mmol) was subjected to the general azaglycolate osmate ester formation procedure. Purification of the crude compound by column chromatography (99:1, CH₂Cl₂ : MeOH) afforded the *osmate ester* **298** as an orange crystalline solid (110 mg, 36%).

R_f (99:1, CH₂Cl₂ : MeOH) 0.06; m.p. 210 °C (dec.); **IR** $\nu_{\max}$ (CHCl₃) 2993, 2927 (CH) and 1710 (C=O); **¹H NMR** δ_H (400 MHz; CDCl₃) 7.42-7.29 (5 H, m, ArH), 4.96 (1 H, d, J 9.0, PhCH), 4.47 (1 H, t, J 8.5, CH_AH_BOCO), 4.29 (1 H, t, J 8.5, CH_AH_BOCO), 4.17 (1 H, dt, J 9.0 and 8.5, CHN), 3.42-3.35 (2 H, m, TMEDA CH_AH_BCH_AH_B'), 3.31 (3 H, s, Me), 3.07 (3 H, s, Me), 3.03 (3 H, s, Me), 2.99-2.95 (2 H, m, TMEDA CH_AH_BCH_AH_B') and 2.87 (3 H, s, Me); **¹³C NMR** δ_C (CDCl₃) 164.0 (C=O), 140.8 (4° aryl C), 128.4, 128.0, 126.9 (aryl C), 94.3 (PhCH), 74.7 (CHNH), 66.3 (CHOCO), 64.8, 63.6 (TMEDA CH₂CH₂), 54.0, 53.1, 50.0 and 48.9 (2 × NMe₂); **MS** m/z (ESI) 532 (100%, MH⁺); **HRMS (ES)** Found MH⁺, 532.1488. C₁₆H₂₅N₃O₅¹⁹²Os requires M 532.1488.

Osmate Ester 299

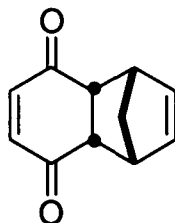


Cyclolix-2-enyl carbamate **211** (110 mg, 0.81 mmol) was subjected to the general azaglycolate osmate ester formation procedure. Purification of the crude compound by column chromatography (9:1, CH₂Cl₂:MeOH) afforded the *osmate ester* **299** as an orange crystalline solid (190 mg, 47%).

R_f (9:1, CH_2Cl_2 :MeOH) 0.33; m.p. 176 °C (dec.); **IR** ν_{max} (CHCl_3) 2935, 2864 (CH) and 1711 (C=O); **^1H NMR** δ_{H} (400 MHz; CDCl_3) 4.92 (1 H, dt, J 9.0 and 7.5, CHOOs), 4.28 (1 H, dd, J 7.0 and 7.0, CHNR), 4.04 (1 H, dt, J 11.0 and 6.0, CHOCO), 3.32-3.24 (2 H, m, TMEDA $\text{CH}_A\text{H}_B\text{CH}_A\text{H}_B$), 3.22 (3 H, s, Me), 3.02 (3 H, s, Me), 2.94 (3 H, s, Me), 2.90-2.83 (2 H, m, TMEDA $\text{CH}_A\text{H}_B\text{CH}_A\text{H}_B$), 2.79 (3 H, s, Me), 2.08 (1 H, m), 1.75-1.67 (2 H, m), 1.49-1.34 (2 H, m), 1.20 (1 H, m) (ring CH_2); **^{13}C NMR** δ_{C} (CDCl_3) 164.3 (C=O), 83.0 (CHOCO), 75.4 (CHNR), 70.3 (CHOOs), 64.7, 63.3 (TMEDA CH_2CH_2), 53.2, 52.2, 49.6, 49.5 ($2 \times \text{NMe}_2$), 29.4, 27.1 and 18.6 ($\text{CH}_2\text{CH}_2\text{CH}_2$); **MS** m/z (ESI) 1009 (M_2NH_4^+), 987, 863, 518 (MNa^+), 496 (100%, MH^+) and 340; **HRMS (ES)** Found MH^+ , 496.1484. $\text{C}_{13}\text{H}_{26}\text{N}_3\text{O}_5$ ^{192}Os requires M 496.1487.

5.7 – Experimental details for chapter 4.2

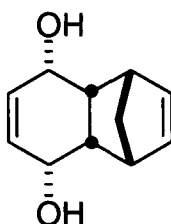
1,4,4a,8a-Tetrahydro-1,4-methano-naphthalene-5,8-dione **363**¹⁴⁷



Benzoquinone **360** (20 g, 0.19 mol) was dissolved in MeOH (500 mL) and freshly cracked cyclopentadiene (12 g, 0.19 mol) in MeOH (100 mL) was added in one portion. The red mixture was stirred at room temperature for 2 h, then cooled to -78°C and filtered. The product was collected and the filtrate concentrated by half, cooled to -78°C and filtered again to give a second crop of the adduct **363** as red crystals (22 g, 68 %).

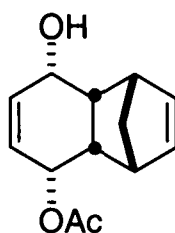
^1H NMR δ_{H} (400 MHz; CDCl_3) 6.54 (2 H, s, enone CH), 6.03 (2 H, t, J 3.5, norbornene CH=CH), 3.53-3.49 (2 H, m, bridgehead CH), 3.19 (2 H, dd, J 5.0 and 3.0, ring junction CH), 1.51 (1 H, dt, J 17.6 and 3.5, $\text{CH}_\text{A}\text{H}_\text{B}$) and 1.40 (1 H, dt, J 17.6 and 3.0, $\text{CH}_\text{A}\text{H}_\text{B}$).

1,4,4a,5,8,8a-Hexahydro-1,4-methano-naphthalene-5,8-diol **364**^{150, 190}



Dione **363** (13 g, 75 mmol) was subjected to the general Luche reduction procedure, extracting with ether, affording the alcohol **364** without purification as beige solid (12 g, 87%).

^1H NMR δ_{H} (400 MHz; d^6 -DMSO) 5.68 (2 H, t, norbornene CH=CH), 5.14 (2 H, s, CH=CH), 4.75 (2 H, d, J 8.0, OH), 4.26-4.21 (2 H, m, CHOH), 2.94-2.93 (2 H, m), 2.69-2.66 (2 H, m) (ring junction and bridgehead CH) and 1.23-1.10 (2 H, m, CH_2).

8-Hydroxy-1,4,4a,5,8,8a-hexahydro-1,4-methano-naphthalenyl-5-acetate 365¹⁹¹*Racemic Material:*

Diol **364** (14 g, 76 mmol) and CeCl_3 (2.8 g, 10 mol %) were dissolved in THF (250 mL). Acetic anhydride (71 mL, 0.76 mol) was added and the reaction mixture allowed to stir for 72 h. The mixture was diluted with Et_2O (250 mL) and washed with saturated aqueous NaHCO_3 (2×75 mL) and brine (75 mL). The organic layers were collected, dried (MgSO_4) and concentrated. Chloroform was added to the mixture and the insoluble starting material was reclaimed by filtration. The filtrate was concentrated again and the product **365** isolated by column chromatography (15-25% EtOAc – petrol) as a white solid (5.7 g, 34%).

*(-)-enantiomer:*¹⁹²

Lipoprotein lipase (Fluka 62336, 30 mg) was added to a solution of diacetate **366** (4.5 g, 25 mmol) in 0.1M, pH 7 phosphate buffer (400 mL) and THF (50 mL). The mixture was stirred at room temperature for 9 days. The mixture was then extracted with EtOAc (6×100 mL) and the organic extracts concentrated. The residue was purified by column chromatography (30% EtOAc – petrol) to afford the monoacetate **(-)-365** as a white solid (3.2 g, 57%).

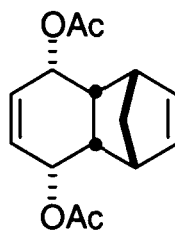
*(+)-enantiomer:*¹⁹³

Diol **364** (2.5 g, 14 mmol) was dissolved in THF (70 mL). Vinyl acetate (10 mL) was added, followed by lipoprotein lipase (Fluka 62336, 250 mg). The mixture was stirred for 4 days, by which time TLC indicated no starting material was present. The mixture was filtered to remove the enzyme, concentrated and purified by column chromatography (20-50% EtOAc – petrol) to afford the monoacetate **(+)-365** as a white solid (2.3 g, 75%).

$^1\text{H NMR}$ δ_{H} (400 MHz; CDCl_3) 5.88 (1 H, dd, J 5.5 and 3.0), 5.81 (1 H, dd, J 5.5 and 3.0) ($\text{C}^2\text{H}=\text{C}^3\text{H}$), 5.46 (1 H, dddd, J 10.5, 3.0, 2.0 and 1.0, C^6H), 5.37 (1 H, dq, J 8.5 and 3.0, CHOAc), 5.29 (1 H, dddd, J 11.0, 3.0, 2.0 and 1.0, C^7H), 4.47 (1 H, dq, J 8.5

and 3.0, CHOH), 3.07-2.99 (2 H, m), 2.88-2.83 (2 H, m) (bridgehead and ring junction CH), 2.12 (3 H, s, Me), 1.74 (1 H, br s, OH), 1.36 (1 H, dt, J 8.5 and 2.0, $\text{CH}_\text{A}\text{H}_\text{B}$) and 1.30 (1 H, dm, $\text{CH}_\text{A}\text{H}_\text{B}$).

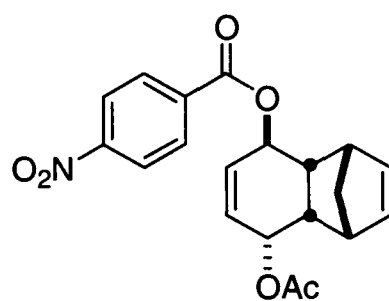
8-Acetoxy-1,4,4a,5,8,8a-hexahydro-1,4-methano-naphthalenyl-5-acetate 364a¹⁹²



Diol **364** (500 mg, 2.8 mmol) and DMAP (5 mg) were dissolved in pyridine (5 mL). Acetic anhydride (1 mL) was added and the reaction mixture stirred for 90 minutes. The mixture was concentrated and filtered through a pad of silica, eluting with 50% EtOAc – petrol. Concentration of the filtrate gave the diacetate **366** as a white solid (700 mg, 95%).

¹H NMR δ_H (400 MHz; CDCl_3) 5.82-5.81 (2 H, m, $\text{C}^2\text{H}=\text{C}^3\text{H}$), 5.38-5.34 (4 H, m, $\text{C}^6\text{H}=\text{C}^7\text{H}$ and CHOAc), 3.04-3.02 (2 H, m, ring junction CH), 2.82-2.81 (2 H, m, bridgehead CH), 2.12 (6 H, s, COMe), 1.30 (1 H, dt, J 8.5 and 1.5, $\text{CH}_\text{A}\text{H}_\text{B}$) and 1.26 (1 H, dt, J 8.5 and 1.5, $\text{CH}_\text{A}\text{H}_\text{B}$).

8-Acetoxy-1,4,4a,5,8,8a-hexahydro-1,4-methano-naphthalenyl-5-(4-nitro)-benzoate 366

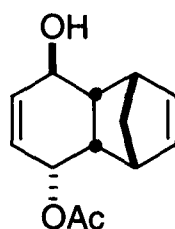


Alcohol **365** (3.3 g, 15 mmol), 4-nitrobenzoic acid (3.0 g, 18 mmol) and PPh_3 (6.0 g, 23 mmol) were dissolved in dry THF (100 mL) under an atmosphere of argon. Di-tert-butyl azodicarboxylate (5.2 g, 23 mmol) was added in one portion and the resulting yellow solution stirred for 40 minutes, by which time TLC analysis indicated all starting material had been consumed. The reaction mixture was concentrated and the residue purified by column chromatography (1:9 EtOAc – petrol) to afford the *benzoate* **366** as a yellow solid (4.6 g, 82%).

Note: Attempted precipitation of triphenylphosphine oxide from the reaction mixture with hexane also precipitated some product. Product of higher purity was obtained on larger scales by recrystallisation of the columned material from MeOH.

R_f (1:9 EtOAc - isohexane) 0.16; m.p. 88-89 °C; $[\alpha]_D^{20}$ (c = 1.20, MeCN); **IR** $\nu_{\max}$ (CHCl₃) 1723 (C=O), 1528 (N=O), 1270 and 1242; **¹H NMR** δ_H (400 MHz; CDCl₃) 8.31-8.19 (4 H, AA'BB', aryl CH), 6.11 (1 H, dd, J 5.5 and 3.0, C²H=C³H), 5.95 (1 H, dd, J 5.5 and 3.0, C²H=C³H), 5.90 (1 H, ddd, J 10.5, 4.5 and 1.5, C⁶H=C⁷H), 5.84 (1 H, dd, J 10.5 and 3.0, C⁶H=C⁷H), 5.62 (1 H, ddd, J 8.5, 3.5 and 2.0, CHOBz), 5.33 (1 H, t, J 4.5, CHOAC), 3.10-3.05 (2 H, m, C¹H and C^{4a}H), 2.87 (1 H, br s, C⁴H), 2.81 (1 H, dt, J 10.0 and 4.0, C^{8a}H), 2.13 (3 H, s, Me), 1.44 (1 H, dt, J 8.5 and 2.0, CH_AH_B), 1.38 (1 H, d br m, CH_AH_B); **¹³C NMR** δ_C (CDCl₃) 170.9 (benzoate C=O), 164.6 (acetate C=O), 151.0 (CNO₂), 137.3, 136.2 (4° aryl CCO), 134.2, 132.7, 131.1, 129.3, 123.9, 71.9, 68.6, 49.8 (CH₂), 47.2, 46.2, 43.9, 41.7 and 21.6 (Me); **MS** m/z (CI) 387 (MH⁺), 220 (M – COAr), 203 (M – OCOAr) and 143 (100%, M – OCOAr – OAc), ; **HRMS (CI)** Found: MNH₄⁺, 387.1562. C₂₀H₂₃N₂O₆⁺ requires M , 387.1556.

8-Hydroxy-1,4,4a,5,8,8a-hexahydro-1,4-methano-naphthalenyl-5-acetate 367

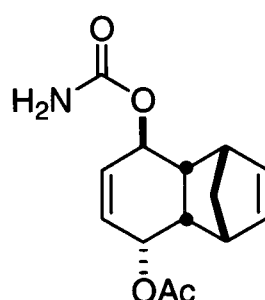


Diester **366** (950 mg, 2.6 mmol) was dissolved in THF (5 mL) and MeOH (45 mL) was added. Magnesium methoxide solution (10% in MeOH, 2.7 mL, 2.6 mmol) was added and the mixture stirred for 3 h. The mixture was concentrated and column chromatography (25% EtOAc – isohexane) afforded the *acetate* **367** as an oil (430 mg, 77%).

R_f (1:1 EtOAc - isohexane) 0.28; **IR** $\nu_{\max}$ (film) 3456 (OH) and 1730 (C=O); **¹H NMR** δ_H (400 MHz; CDCl₃) 6.13 (1 H, dd, J 5.5 and 3.0, C²H), 5.91 (1 H, ddd, J 10.0, 4.0 and 1.0, C⁷H), 5.80 (1 H, dd, J 5.5 and 3.0, C³H), 5.71 (1 H, ddd, J 10.0, 4.0 and 1.0, C⁶H), 5.51 (1 H, ddd, J 8.0, 4.5 and 1.0, CHOAc), 3.97 (1 H, ddd, J 5.0, 4.0 and 1.0, CHOH), 3.03 (1 H, br m, C⁴H), 2.87 (1 H, ddd, J 10.5, 8.0 and 3.0, C^{4a}H), 2.80 (1 H, br m, C¹H), 2.57 (1 H, ddd, J 10.0, 5.5 and 4.0, C^{8a}H), 2.07 (3 H, s, Me), 1.70 (1

H, br s, OH), 1.44 (1 H, dt, J 8.5 and 2.0, $\text{CH}_\text{A}\text{H}_\text{B}$) and 1.38 (1 H, br d, J 8.0, $\text{CH}_\text{A}\text{H}_\text{B}$); **^{13}C NMR** δ_C (CDCl_3) 171.0 (C=O), 137.5, 136.1, 134.0, 128.7, 68.3, 67.9, 50.3 (CH_2), 48.4, 46.3, 45.8, 42.4 and 21.8 (Me); **MS** m/z (CI) 238 (MNH_4^+), 220 (M^+), 203 ($\text{M}^+ - \text{OH}$), 161 ($\text{M}^+ - \text{OAc}$) and 143 (100%, $\text{M}^+ - \text{OAc} - \text{H}_2\text{O}$); **HRMS (CI)** Found: MNH_4^+ , 238.1450. $\text{C}_{13}\text{H}_{20}\text{NO}_3^+$ requires M , 238.1443.

8-Carbamoyloxy-1,4,4a,5,8,8a-hexahydro-1,4-methano-naphthalenyl-5-acetate **373**

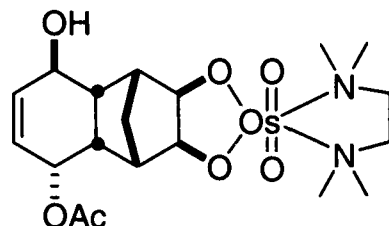


Alcohol **367** (340 mg, 1.5 mmol) was subjected to the general carbamate formation procedure, affording the crude carbamate. Column chromatography (30% EtOAc – isohehexane) gave the *carbamate* **373** as an oil (320 mg, 79%).

R_f (1:1 EtOAc - isohehexane) 0.10; **IR** ν_{max} (film) 3491, 3329 (NH_2), 2965 (CH) and 1716 (C=O); **^1H NMR** δ_H (400 MHz; CDCl_3) 6.05 (1 H, dd, J 5.5 and 3.0, C^3H), 5.88 (1 H, dd, J 5.5 and 3.0, C^2H), 5.81 (1 H, ddd, J 10.5, 4.5 and 2.0, C^7H), 5.73 (1 H, dd, J 11.0 and 3.0, C^6H), 5.52 (1 H, ddd, J 8.0, 3.0 and 1.5, CHOAc), 4.93 (1 H, t, J 4.5, CHOCONH_2), 4.80 (2 H, br s, NH_2), 3.01 (1 H, br s, C^1H), 2.94 (1 H, ddd, J 10.0, 8.5 and 3.0, C^{4a}H), 2.80 (1 H, br s, C^4H), 2.63 (1 H, dt, J 10.0 and 4.0, C^{8a}H), 2.09 (3 H, s, Me), 1.39 (1 H, dt, J , 8.5 and 2.0, $\text{CH}_\text{A}\text{H}_\text{B}$) and 1.32 (1 H, d br m, $\text{CH}_\text{A}\text{H}_\text{B}$); **^{13}C NMR** δ_C (CDCl_3) 170.6 (acetate C=O), 156.5 (carbamate C=O), 136.6 (C^2), 134.0 (C^3), 130.9 (C^6), 130.2 (C^7), 70.2 (CHOCONH_2), 68.3 (CHOAc), 49.4 (CH_2), 46.6 (C^1), 45.7 (C^4), 43.7 (C^{8a}), 41.3 (C^{4a}) and 21.2 (Me); **MS** m/z (FI) 263 (100%, M^+); **HRMS (CI)** Found: M^+ , 263.1145. $\text{C}_{14}\text{H}_{17}\text{NO}_4^+$ requires M , 238.1158.

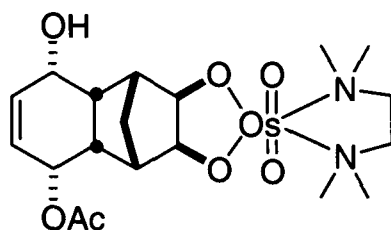
5.8 – Experimental details for chapter 4.3

Osmate ester 377



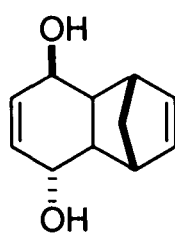
Alcohol **367** (60 mg, 0.34 mmol) was dissolved in CH_2Cl_2 (15 mL) under argon. The mixture was cooled to -78°C and tetramethylethylenediamine (51 μL , 0.34 mmol) was added. The mixture was stirred for 5 minutes before the addition of OsO_4 (86 mg, 0.34 mmol). The reaction mixture was allowed to warm to room temperature, turning brown in the process. After 2 h at room temperature, the mixture was concentrated and the product purified by column chromatography (5% MeOH – CH_2Cl_2) to afford the *osmate ester 377* as a green solid (64 mg, 32%).

R_f (1:19 MeOH - CH_2Cl_2) 0.12; m.p. 190°C (dec.); **IR** ν_{max} (CHCl_3) 3367 (OH), 2927 (CH) and 1724 ($\text{C}=\text{O}$); **$^1\text{H NMR}$** δ_{H} (400 MHz; CDCl_3) 6.03 (1 H, dddd, J 11.5, 6.5, 3.0 and 1.0, $\text{C}=\text{C}^7\text{HCHOH}$), 5.88 (1 H, dm, $\text{C}=\text{C}^6\text{HCHOAc}$), 5.72 (1 H, ddd, J 9.0, 3.0 and 1.5, CHOAc), 4.56 (1 H, dd, J 6.0 and 1.0, CHOOs), 4.39 (1 H, d, J 6.0, CHOH), 4.29 (1 H, dd, J 5.5 and 1.5, CHOOs), 3.09-3.00 (4 H, m, $\text{Me}_2\text{NCH}_2\text{CH}_2\text{NMe}_2$), 2.84 (9 H, br s, $3 \times \text{NMe}$), 2.79 (3 H, s, NMe), 2.75 (1 H, m, C^{4a}H), 2.63 (1 H, d br m, C^1H), 2.48 (1 H, d br m, C^4H), 2.38 (1 H, dt, J 10.5 and 2.0, $\text{CH}_\text{A}\text{H}_\text{B}$), 2.32 (1 H, dd, J 11.0 and 5.0, C^{8a}H), 2.16 (3 H, s, acetate Me), 1.86 (1 H, br s, OH) and 1.22 (1 H, d br m, $\text{CH}_\text{A}\text{H}_\text{B}$); **$^{13}\text{C NMR}$** δ_{C} (CDCl_3) 172.5 ($\text{C}=\text{O}$), 133.1, 128.7 ($\text{CH}=\text{CH}$), 93.5, 93.3 (C^2 and C^3), 69.1 (CHOAc), 64.5 (CHOH), 64.1, 64.0 ($\text{Me}_2\text{NCH}_2\text{CH}_2\text{NMe}_2$), 51.8, 51.6, 51.5, 51.1 ($4 \times \text{NMe}$), 50.4 (C^1), 48.7 (C^4), 43.6 (C^{8a}), 39.6 (C^{4a}), 36.1 (CH_2) and 21.3 (COMe); **MS** m/z (ESI) 1180 (M_2^+) and 592 (100%, M^+); **HRMS (ES)** Found: MH^+ , 593.1905. $\text{C}_{19}\text{H}_{33}\text{N}_2\text{O}_7^{192}\text{Os}^+$ requires M , 593.1903.

Osmate ester 378

Alcohol **365** (45 mg, 0.20 mmol) was dissolved in CH_2Cl_2 (15 mL) under argon. The mixture was cooled to -78°C and tetramethylethylenediamine (31 μL , 0.20 mmol) was added. The mixture was stirred for 5 minutes before the addition of OsO_4 (52 mg, 0.20 mmol). The reaction mixture was allowed to warm to room temperature, turning brown in the process. After 2 h at room temperature, the mixture was concentrated and the product purified by column chromatography (10% MeOH – CH_2Cl_2) to afford the *osmate ester 378* as a green solid (100 mg, 87%).

R_f (1:19 MeOH - CH_2Cl_2) 0.13; m.p. 210°C (dec.); **IR** ν_{max} (CHCl_3) 3378 (OH), 2926 (CH) and 1731 ($\text{C}=\text{O}$); **$^1\text{H NMR}$** δ_{H} (400 MHz; CDCl_3) 5.75 (1 H, dm, J 10.0, $\text{C}^7=\text{C}^6\text{HCHOAc}$), 5.54 (1 H, dm, J 10.5, $\text{C}^6=\text{C}^7\text{HCHOH}$), 5.37 (1 H, dq, J 8.0 and 3.0, CHOAc), 4.65-4.61 (2 H, m, $2 \times \text{CHOOs}$), 4.43 (1 H, m, CHOH), 3.07-3.00 (4 H, m, $\text{Me}_2\text{NCH}_2\text{CH}_2\text{NMe}_2$), 2.84 (9 H, br s, $3 \times \text{NMe}$), 2.79 (3 H, s, NMe), 2.67 (1 H, m, C^1H), 2.60 (1 H, m, C^{4a}H), 2.51-2.45 (3 H, m, C^4H , C^{8a}H and $\text{CH}_\text{A}\text{H}_\text{B}$), 2.25 (1 H, br s, OH), 2.15 (3 H, s, acetate Me) and 1.21 (1 H, d br m, $\text{CH}_\text{A}\text{H}_\text{B}$); **$^{13}\text{C NMR}$** δ_{C} (CDCl_3) 171.0 ($\text{C}=\text{O}$), 132.5 (C^6), 126.6 (C^7), 93.9, 93.4 (C^2 and C^3), 69.5 (CHOAc), 66.4 (CHOH), 64.1, 64.0 ($\text{Me}_2\text{NCH}_2\text{CH}_2\text{NMe}_2$), 51.8, 51.5, 51.4, 51.1 ($2 \times \text{NMe}_2$), 48.1, 47.2 (C^1), 41.2, 38.3 (C^{4a}), 36.7 (CH_2) and 21.3 (COMe); **MS** m/z (ESI) 1180 (M_2^+) and 593 (100%, MH^+); **HRMS (ES)** Found: MH^+ , 593.1902. $\text{C}_{19}\text{H}_{33}\text{N}_2\text{O}_7^{192}\text{Os}^+$ requires M , 593.1903.

1,4,4a,5,8,8a-Hexahydro-1,4-methano-naphthalene-5,8-diol 368¹⁹⁴

Diester **366** (7.0 g, 19 mmol) was suspended in MeOH (150 mL) and a solution of K_2CO_3 (26 g) in water (100 mL) was added. The mixture was allowed to stir for 48 h and then concentrated. The residue was resuspended in EtOAc (200 mL) and washed

with brine (3×10 mL). The organic layer was concentrated, resuspended in water (200 mL) and extracted with CH_2Cl_2 (3×100 mL). The organic layer was again concentrated to give the *diol* **368** as a white solid (2.8 g, 82%).

R_f (1:1 EtOAc – petrol) 0.1 ; m.p. 114 – 166 °C; $[\alpha]_D$ 132 ($c = 1.18$, MeCN); **IR** ν_{max} (CHCl_3) 3278 (OH), 2659 and 2922 (CH); **$^1\text{H NMR}$** δ_{H} (400 MHz; CDCl_3); 6.40 (1 H, dd, J 5.0 and 3.0), 5.96 (1 H, dd, J 5.0 and 3.0) ($\text{C}^2\text{H}=\text{C}^3\text{H}$), 5.88-5.87 (2 H, m, $\text{C}^6\text{H}=\text{C}^7\text{H}$), 4.45 (1 H, dd, J 7.0 and 3.0, CHOH), 3.87 (1 H, d, J 7.0, CHOH), 3.07 (1 H, br s), 2.93 (1 H, br s) (C^1 and C^4), 2.66 (1 H, ddd, J 11.0, 7.0 and 3.5), 2.56 (1 H, ddd, J 10.5, 7.0 and 3.0) (C^{4a} and C^{8a}), 1.68 (1 H, br s, OH), 1.52 (1 H, dt, J 8.0 and 2.0, $\text{CH}_\text{A}\text{H}_\text{B}$), 1.42 (1 H, d br m, J 8.0, $\text{CH}_\text{A}\text{H}_\text{B}$) and 1.10 (1 H, br s, OH); **$^{13}\text{C NMR}$** δ_{C} (CDCl_3) 137.8, 135.5, 133.7, 131.5 ($\text{C}^2=\text{C}^3$ and $\text{C}^6=\text{C}^7$), 68.2, 65.1 ($2 \times \text{CHOH}$), 50.3 (CH_2), 49.9 (bridgehead C), 45.3, 45.0 (C^{4a} and C^{8a}) and 44.8 (bridgehead C); **MS** m/z (CI) 178 (MH^+), 161 (100%, $\text{M}^+ - \text{OH}$) and 143 ($\text{MH}^+ - 2 \text{OH}$); **HRMS (CI)** Found: $\text{M}^+ - \text{OH}$, 161.0965. $\text{C}_{11}\text{H}_{13}\text{O}^+$ requires M , 161.0966.

Bromo ether **383**¹⁹⁵

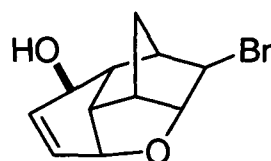


Diol **364** (100 mg, 0.56 mmol) was dissolved in CH_2Cl_2 (5 mL) and *N*-bromosuccinimide (100 mg, 0.56 mmol) was added in one portion. The mixture was stirred for 16 h and then concentrated. The residue was purified by column chromatography (25% EtOAc – petrol) to afford the *bromoether* **383** as a brown solid (55 mg, 38%).

R_f (1:3 EtOAc – petrol) 0.18; m.p. 128 – 129 °C (lit. 127 °C¹⁹⁵); **IR** ν_{max} (CHCl_3) 3396 (OH), 2970 and 2896 (CH); **$^1\text{H NMR}$** δ_{H} (400 MHz; CDCl_3) 5.95 (1 H, ddd, J 10.0, 5.0 and 2.5, $\text{C}^6\text{H}=\text{C}^7\text{H}$), 5.82 (1 H, dd, J 10.0 and 2.5, $\text{C}^6\text{H}=\text{C}^7\text{H}$), 4.61-4.59 (2 H, m, C^3H and C^8H), 4.36 (1 H, ddd, J 6.5, 5.0 and 1.0, C^5H), 4.16 (1 H, d, J 2.0, C^2HBr), 2.94 (1 H, tq, J 5.0 and 1.5, C^4H), 2.71 (1 H, br s, C^1H), 2.62 (1 H, dt, J 10.0 and 6.0, C^{4a}H), 2.47 (1 H, td, J 9.0 and 3.0, C^{8a}H), 2.18 (1 H, d, J 10.5, $\text{CH}_\text{A}\text{H}_\text{B}$), 1.73 (1 H, br s, OH) and 1.57 (1 H, dq, J 11.0 and 2.0, $\text{CH}_\text{A}\text{H}_\text{B}$); **$^{13}\text{C NMR}$** δ_{C} (CDCl_3) 131.7, 128.7, 90.7,

72.2, 65.4, 54.2, 50.9, 45.6, 41.9, 35.9 and 34.5; **MS** m/z (CI) 274 (MNH_4^+), 258 (MH^+) and 177 (100%, $\text{M}^+ - \text{Br}$); **HRMS (CI)** Found: MNH_4^+ , 274.0439. $\text{C}_{11}\text{H}_{17}\text{NO}_2\text{Br}^+$ requires M , 274.0443.

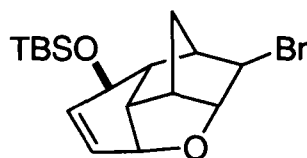
Bromo ether 384



Diol **368** (74 mg, 0.42 mmol) was dissolved in CH_2Cl_2 (10 mL) and *N*-bromosuccinimide (74 mg, 0.42 mmol) was added in one portion. The mixture was stirred for 16 h and then concentrated. The residue was purified by column chromatography (25% EtOAc – petrol) to afford the *bromoether* **384** as an oil (79 mg, 73%).

R_f (1:1 EtOAc – petrol) 0.30; $[\alpha]_D$ 119 ($c = 1.14$, CHCl_3); **IR** ν_{max} (CHCl_3) 3393 (OH), 2968 and 2888 (CH); **$^1\text{H NMR}$** δ_{H} (400 MHz; CDCl_3) 6.04 (1 H, ddd, J 10.0, 5.5 and 1.5, $\text{C}^6\text{H}=\text{C}^7\text{H}$), 5.95 (1 H, ddd, J 10.0, 3.0 and 1.0, $\text{C}^6\text{H}=\text{C}^7\text{H}$), 4.51 (1 H, d, J 5.0, C^3HOR), 4.36 (1 H, t, J 5.0, C^5H), 4.10 (1 H, m, C^8H), 3.61 (1 H, d, J 2.5, C^2HBr), 2.88 (1 H, tq, J 5.0 and 1.5, C^4H), 2.55–2.50 (2 H, m, C^1H and OH), 2.40 (1 H, dt, J 10.5 and 5.0, C^{4a}H), 2.31 (1 H, ddd, J 11.0, 3.5 and 1.5, C^{8a}H), 2.08 (1 H, dt, J 11.0 and 1.5, $\text{CH}_\text{A}\text{H}_\text{B}$) and 1.65 (1 H, dm, $\text{CH}_\text{A}\text{H}_\text{B}$); **$^{13}\text{C NMR}$** δ_{C} (CDCl_3) 132.4, 128.1, 89.4 (C^3OR), 71.9 (C^5OR), 64.2 (C^8OH), 55.0 (C^2Br), 49.1 (C^4), 48.0 (C^1), 45.7 (C^{8a}), 34.2 (C^{4a}) and 34.1 (CH_2); **MS** m/z (CI) 258, 256 (M^+), 194, 177 (100%, $\text{M}^+ - \text{Br}$) and 161 ($\text{MH}^+ - \text{Br} - \text{OH}$); **HRMS (CI)** Found: M^+ , 256.0107. $\text{C}_{11}\text{H}_{13}\text{O}_2\text{Br}^+$ requires M , 256.0099.

Silyl ether 385

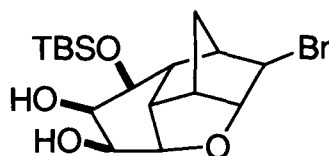


Bromoether **384** (4.1 g, 16 mmol), imidazole (2.6 g, 38 mmol) and DMAP (catalytic) were dissolved in CH_2Cl_2 (100 mL) and TBSCl (2.9 g, 19 mmol) was added in one portion. The reaction mixture was stirred for 3 h, by which time no starting material remained by TLC. Water (50 mL) was added and the mixture extracted with CH_2Cl_2 .

The organic extracts were dried (MgSO_4), filtered and concentrated to give the *silyl ether* **385** as a colourless oil (5.6 g, 95%).

R_f (1:9 EtOAc – petrol) 0.58; m.p. 55 - 58 °C; **IR** ν_{max} (film) 2954, 2926, 2889 and 2854 (CH); **$^1\text{H NMR}$** δ_{H} (400 MHz; CDCl_3) 6.01 (1 H, ddd, J 10.0, 6.0 and 2.5, $\text{C}^6\text{H}=\text{C}^7\text{H}$), 5.87 (1 H, dd, J 10.0 and 3.5, $\text{C}^6\text{H}=\text{C}^7\text{H}$), 4.53 (1 H, d, J 5.0, C^3HOR), 4.37 (1 H, t, J 5.5, C^5HOR), 4.09 (1 H, dt, J 3.5 and 2.0, C^8HOSi), 3.64 (1 H, d, J 2.0, C^2HBr), 2.88 (1 H, tq, J 5.0 and 1.5, C^4H), 2.52 (1 H, m, C^1H), 2.42 (1 H, dt, J 10.5 and 5.0, C^{4a}H), 2.30 (1 H, ddd, J 11.0, 4.0 and 2.0, C^{8a}H), 2.11 (1 H, d, J 11.0, $\text{CH}_\text{A}\text{H}_\text{B}$), 1.67 (1 H, dd, J 11.0 and 2.0, $\text{CH}_\text{A}\text{H}_\text{B}$), 0.91 (9 H, s, ^tBu) and 0.12 (6 H, s, SiMe_2); **$^{13}\text{C NMR}$** δ_{C} (CDCl_3) 133.6 (C^7H), 127.0 (C^6H), 89.3 (C^3HOR), 72.1 (C^5HOR), 65.1 (C^8HOSi), 55.3 (C^2HBr), 48.9 (C^4H), 47.9 (C^1H), 46.6 (C^1H), 34.6 (C^{8a}H) (C^{4a}H), 34.2 (CH_2), 25.8 (CMe_3), 18.3 (CMe_3) and -4.5 (SiMe_2); **MS** m/z (CI) 373, 371 (MH^+), 315, 313 ($\text{M}^+ - ^t\text{Bu}$), 258, 256 (100%, $\text{M}^+ - \text{OTBS}$) 241 and 239; **HRMS (CI)** Found: M^+ , 370.0949. $\text{C}_{17}\text{H}_{27}\text{O}_2\text{BrSi}^+$ requires M , 370.0964.

Diol **386**

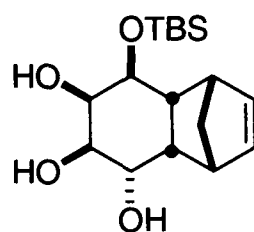


Silyl ether **385** (5.6 g, 15 mmol) and trimethylamine *N*-oxide (5.1 g, 46 mmol) were dissolved in CH_2Cl_2 (300 mL). This solution was treated with OsO_4 (10 mg) and stirred for 2 h, by which time all starting material had been consumed. The mixture was concentrated onto silica and purified by column chromatography (30% EtOAc – petrol) to afford the *diol* **386** as a viscous, colourless oil (4.6 g, 79%).

R_f (1:1 EtOAc – petrol) 0.43; **IR** ν_{max} (film) 3422 (br, OH), 2953, 2892 and 2854 (CH); **$^1\text{H NMR}$** δ_{H} (400 MHz; CDCl_3) 4.54 (1 H, dd, J 5.0 and 1.0, C^3HOR), 4.23 (1 H, dd, J 4.0 and 3.5, C^5HOR), 4.09 (1 H, t, J 2.5, C^8HOSi), 3.93 (1 H, dt, J 10.0 and 3.0, C^7HOH), 3.86 (1 H, d, J 2.5, C^2HBr), 3.83 (1 H, dt, J 9.0 and 3.0, C^6HOH), 3.41 (1 H, d, J 10.0, C^7OH), 2.93 (1 H, m, C^4H), 2.60-2.55 (2 H, m, C^{4a}H and C^6OH), 2.45 (1 H, br m, C^1H), 2.39 (1 H, ddd, J 6.5, 3.5 and 3.0, C^{8a}H), 2.21 (1 H, dm, $\text{CH}_\text{A}\text{H}_\text{B}$), 1.68 (1 H, dm, $\text{CH}_\text{A}\text{H}_\text{B}$), 0.91 (9 H, s, ^tBu), 0.15 (3 H, s) and 0.13 (3 H, s) (SiMe_2); **$^{13}\text{C NMR}$**

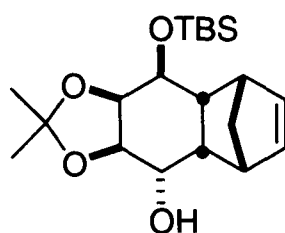
$\delta_{\text{C}}(\text{CDCl}_3)$ 88.3 (C^3OR), 82.3 (C^5OR), 72.5 (C^8OSi), 71.3 (C^7OH), 67.2 (C^6OH), 55.2 (C^2HBr), 48.1 (C^4H), 47.2 (C^{8a}H), 45.3 (C^1H), 36.3 (CH_2), 33.9 (C^{4a}H), 25.7 (CMe_3), 17.8 (CMe_3), -4.8 and -5.0 (SiMe_2); **MS** m/z (CI) 407, 405 (100%, MH^+); **HRMS (CI)** Found: MH^+ , 405.1090. $\text{C}_{17}\text{H}_{30}\text{O}_4\text{BrSi}^+$ requires M , 405.1097.

8-(tert-Butyl-dimethyl-silanyloxy)-1,4,4a,5,6,7,8,8a-octahydro-1,4-methanonaphthalene-5,6,7-triol 387



Diol **386** (42 mg, 0.10 mmol) was dissolved in MeOH (5 mL). Freshly activated zinc powder (54 mg, 0.83 mmol) and AcOH (5 drops) were added and the stirred mixture heated at reflux for 3 h. The mixture was allowed to cool, and concentrated onto silica. The *triol* **387** was isolated by column chromatography (50-80% EtOAc – petrol) as a white solid (16 mg, 49%).

R_f (EtOAc) 0.34; m.p. 121-123 °C; **IR** ν_{max} (CHCl_3) 3405 (br, OH), 2955, 2990, 2887 and 2857 (CH); **$^1\text{H NMR}$** δ_{H} (400 MHz; CDCl_3) 6.31 (1 H, dd, J 5.0 and 3.0), 6.14 (1 H, dd, J 5.0 and 3.5) ($\text{C}^2\text{H}=\text{C}^3\text{H}$), 4.21 (1 H, t, J 10.0, C^8HOSi), 3.81 (1 H, t, J 3.0, C^6HOH), 3.39 (1 H, dd, J 7.0 and 3.5, C^5HOH), 3.12 (1 H, br d, J 8.5, C^7HOH), 3.07 (1 H, br s), 3.00 (1 H, br s) (C^1H and C^4H), 2.94 (1 H, td, J 10.5 and 3.0, C^{8a}H), 2.81 (1 H, br s, C^7OH), 2.64 (1 H, br s, C^6OH), 2.43 (1 H, br s, C^5OH), 2.40 (1 H, ddd, J 9.5, 6.5 and 3.5, C^{4a}H), 1.46 (1 H, dt, J 8.0 and 2.0, $\text{CH}_\text{A}\text{H}_\text{B}$), 1.31 (1 H, d br m, $\text{CH}_\text{A}\text{H}_\text{B}$), 0.92 (9 H, s, tBu), 0.14 (3 H, s) and 0.09 (3 H, s) (SiMe_2); **$^{13}\text{C NMR}$** δ_{C} (CDCl_3) 138.1, 135.9 ($\text{C}^2=\text{C}^3$), 74.1 (C^6OH), 73.4 (2 peaks) (C^5OH and C^7OH), 70.6 (C^8OSi), 50.0 (CH_2), 46.7 (C^{4a}H), 45.6 (2 peaks) (C^1H and C^4H), 45.1 (C^{8a}H), 25.7 (CMe_3), 17.9 (CMe_3) and -4.5 (SiMe_2); **MS** m/z (CI) 327 (MH^+), 310 ($\text{M}^+ - \text{OH}$), 293 (100%, $\text{MH}^+ - 2 \text{OH}$), 235, 194, 177 and 159; **HRMS (CI)** Found: MH^+ , 327.1990. $\text{C}_{17}\text{H}_{31}\text{O}_4\text{Si}^+$ requires M , 327.1992.

Acetonide 389*A: Acetalisation*

Triol **387** (110 mg, 0.33 mmol) was dissolved in acetone (14 mL) and dimethoxypropane (2 mL). Tosic acid (5 mg) was added and the mixture stirred at room temperature for 90 minutes. The mixture was concentrated to a small amount of residual solvent and filtered through a pad of silica to afford the *acetonide 389* as a white solid (90 mg, 75%).

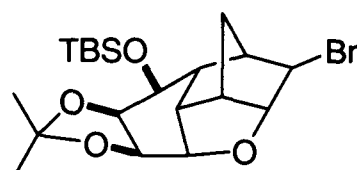
B: Birch reduction

Ammonia (100 mL) was distilled onto Na and FeCl₃ under argon at –78 °C, then again onto Na (310 mg, 13 mmol) under argon at –78 °C, generating a deep blue colour indicating the presence of solvated electrons. This solution was stirred for 20 minutes before the addition of a solution of acetonide **390** (1.2 g, 2.7 mmol) in dry THF (10 mL). The solution was stirred for a further 15 minutes at –78 °C, then the excess electrons quenched by the dropwise addition of isoprene. Once the blue colour had disappeared, the reduced product was protonated by the addition of saturated aqueous ammonium chloride (5 mL). The reaction mixture was opened to air and allowed to warm to room temperature, boiling off the ammonia. The residual water – THF mixture was extracted with ether, dried (MgSO₄), filtered and concentrated to afford the *acetonide 389* as a white solid (960 mg, 98%).

R_f (20% EtOAc – petrol) 0.70; m.p. 140–143 °C; **IR** $\nu_{\max}$ (CHCl₃) 3459 (OH), 2953, 2913 and 2845 (CH); **¹H NMR** δ_H (400 MHz; CDCl₃) 6.37 (1 H, dd, J 5.5 and 3.0), 6.21 (1 H, dd, J 5.5 and 3.0) (C²H=C³H), 4.22 (1 H, dd, J 7.5 and 3.0, C⁷H), 4.18 (1 H, dd, J 7.5 and 3.0, C⁶H), 4.10 (1 H, m, CHOH), 3.61 (1 H, dtd, J 9.0, 7.0 and 2.5, CHOSi), 2.99 (1 H, br m), 2.93 (1 H, br m) (C¹H and C⁴H), 2.65–2.59 (2 H, m, C^{4a}H and C^{8a}H), 1.74 (1 H, m, OH), 1.52 (1 H, dt, J 8.0 and 2.0, CH_AH_B), 1.47 (3 H, s, Me), 1.39 (1 H, d br m, CH_AH_B), 1.30 (3 H, s, Me), 0.92 (9 H, s, ^{*t*}Bu) and 0.08 (2 peaks, 2 × 3 H, s, SiMe₂); **¹³C NMR** δ_C (CDCl₃) 136.5, 136.2 (C²=C³), 108.2 (CMe₂), 78.1 (C⁷), 76.4 (C⁶), 70.9 (C⁸OSi), 69.7 (C⁵OH), 52.0 (CH₂), 45.8, 44.3 (C^{4a} and C^{8a}), 41.7, 40.6 (C⁴

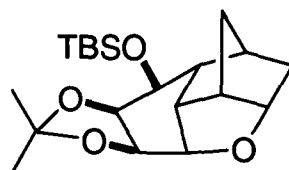
and C¹), 26.1 (CMe_AMe_B), 25.9 (CMe₃), 23.4 (CMe_AMe_B), 18.2 (CMe₃), -4.1 and -4.5 (SiMe₂); **MS** *m/z* (CI) 367 (MH⁺), 251 (M⁺ - TBS), 235 (100%, MH⁺ - OTBS) and 177; **HRMS (CI)** Found: MH⁺, 367.2289 C₂₀H₃₅O₄Si⁺ requires *M*, 367.2305.

Acetonide 390



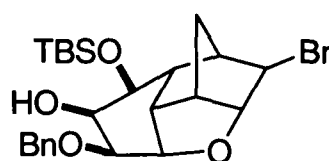
Diol **386** (1.4 g, 3.3 mmol) was dissolved in acetone (70 mL) and dimethoxypropane (14 mL). Tosic acid (25 mg) was added and the mixture stirred at room temperature for 50 minutes. The mixture was concentrated onto silica and purified by column chromatography (50-100% EtOAc – petrol) to afford the *acetonide* **390** as a white solid (1.4 g, 94%).

R_f (10% EtOAc – petrol) 0.72; m.p. 88-90 °C; **IR** *v*_{max} (film) 2979, 2859, 2951, 2889 and 2857 (CH); **¹H NMR** δ _H(400 MHz; CDCl₃) 4.40 (1 H, dd, *J* 5.0 and 1.0, C³HOR), 4.29 (1 H, dd, *J* 6.0 and 2.0, C⁶HOR), 4.19 (1 H, d, *J* 6.0, C⁷HOR), 4.03-4.00 (2 H, m, C²HBr and C⁵HOR), 3.63 (1 H, d, *J* 3.0, C⁸HOSi), 2.81 (1 H, m, C⁴H), 2.56 (1 H, dt, *J* 11.0 and 3.5, C^{8a}H), 2.51 (1 H, m, C¹H), 2.29 (1 H, ddd, *J* 11.0, 8.5 and 4.5, C^{4a}H), 2.17 (1 H, dm, CH_AH_B), 1.68 (1 H, dm, CH_AH_B), 1.42 (3 H, s, Me), 1.30 (3 H, s, Me), 0.90 (9 H, s, ^{*t*}Bu) and 0.10 (6 H, s, SiMe₂); **¹³C NMR** δ _C(CDCl₃) 109.1 (CMe₂), 87.5 (C³OR), 79.4 (C⁸OSi), 77.2 (C⁶OR), 75.0 (C⁷OR), 66.5 (C⁵OR), 55.9 (C²Br), 47.4 (C⁴H), 43.8 (C¹H), 41.8 (C^{8a}H), 39.2 (C^{4a}H), 35.2 (CH₂), 27.5 (CMe_AMe_B), 25.8 (CMe₃), 24.9 (CMe_AMe_B), 18.1 (CMe₃), -4.3 and -4.4 (SiMe₂); **MS** *m/z* (CI) 447, 445 (MH⁺), 389, 387 (M⁺ - ^{*t*}Bu), 331, 329 (100%, M⁺ - TBS) 315 and 313 (M⁺ - OTBS); **HRMS (CI)** Found: MNH₄⁺, 462.1685. C₂₀H₃₇O₄NBrSi⁺ requires *M*, 462.1675.

Acetonide 392

Acetonide **389** (30 mg, 82 μmol) was mixed with graphite (170 mg). The mixture was irradiated in a microwave for 1 minute at 150 W, reaching a maximum temperature of 262 °C and a maximum pressure of 3 psi. The cooled mixture was extracted with chloroform and filtered to remove the graphite. Column chromatography (25% EtOAc – petrol) afforded the *acetonide 392* as a yellow solid (11 mg, 37%).

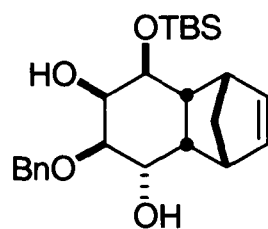
m.p. 65-66 °C; **IR** ν_{max} (CHCl_3) 2956 and 2857 (CH); **$^1\text{H NMR}$** δ_{H} (400 MHz; CDCl_3) 4.33 (1 H, dd, J 6.0 and 2.0, C^6HOR), 4.28 (1 H, t, J 6.0, C^3HOR), 4.22 (1 H, d, J 5.5, C^7HOR), 4.05 (1 H, dd, J 8.0 and 2.0, C^5HOR), 3.64 (1 H, d, J 3.0, C^8HOSi), 2.77 (1 H, m, C^4H), 2.55 (1 H, dt, J 11.0 and 3.5, C^{8a}H), 2.29 (1 H, br s, C^1H), 2.17 (1 H, dddd, J 11.0, 8.5, 4.0 and 2.0, C^{4a}H), 1.66 (1 H, dd, J 13.5 and 3.0, $\text{CH}_\text{A}\text{H}_\text{B}$), 1.59 (1 H, d br m, $\text{CH}_\text{A}\text{H}_\text{B}$), 1.46 (3 H, s, $\text{CMe}_\text{A}\text{Me}_\text{B}$), 1.38-1.32 (2 H, m, C^2H_2), 1.34 (3 H, s, $\text{CMe}_\text{A}\text{Me}_\text{B}$), 0.92 (9 H, s, ^tBu), 0.11 and 0.10 (SiMe_2); **$^{13}\text{C NMR}$** δ_{C} (CDCl_3) 108.7 (CMe_2), 79.6, 78.4, 77.5, 75.5, 68.1, 48.2, 41.6, 40.5, 36.9 (2 peaks, $2 \times \text{CH}_2$), 35.8, 27.5, 25.9 (CMe_3), 24.9, 18.1 (CMe_3), -4.2 and -4.3 (SiMe_2); **MS** m/z (CI) 367 (MH^+), 309 ($\text{M}^+ - ^t\text{Bu}$), 251 (100%, $\text{M}^+ - \text{TBS}$) and 235 ($\text{M}^+ - \text{OTBS}$); **HRMS (CI)** Found: MH^+ , 367.2292. $\text{C}_{20}\text{H}_{35}\text{O}_4\text{Si}^+$ requires M , 367.2305.

Benzyl ether 393

Diol **386** (190 mg, 0.47 mmol) was dissolved in toluene (10 mL) under argon. Freshly prepared Ag_2O (1.6 g, 7.0 mmol) and benzyl bromide (0.56 mL, 4.7 mmol) were added and the mixture stirred overnight. The mixture was concentrated onto silica and purified by column chromatography (20% EtOAc – petrol) to afford the *ether 393* as an oil (190 mg, 80%).

IR $\nu_{\max}$ (film) 3483 (OH), 2954, 2889 and 2857 (CH); **$^1\text{H NMR}$** δ_{H} (400 MHz; CDCl_3) 7.39-7.30 (5 H, m, ArH), 4.71 (1 H, d, J 11.5, $\text{PhCH}_\text{A}\text{H}_\text{B}$), 4.61 (1 H, d, J 11.5, $\text{PhCH}_\text{A}\text{H}_\text{B}$), 4.42 (1 H, dd, J 5.5 and 0.5, C^3HOR), 4.01 (2 H, app. d, C^5HOR and C^6HOBn), 3.86 (1 H, d, J 1.5, C^2HBr), 3.69 (1 H, dd, J 7.5 and 1.5, C^8HOSi), 3.53 (1 H, d, J 4.0, C^7HOH), 2.84 (1 H, m, C^4H), 2.78 (1 H, dt, J 11.0 and 4.0, C^{4a}H), 2.49 (1 H, m, C^1H), 2.46 (1 H, br s, OH), 2.33 (1 H, ddd, J 11.0, 7.0 and 4.0, C^{8a}H), 2.18 (1 H, dt, J 11.0 and 1.5, $\text{CH}_\text{A}\text{H}_\text{B}$), 1.71 (1 H, d, J 11.0, $\text{CH}_\text{A}\text{H}_\text{B}$), 0.91 (9 H, s, ^tBu), 0.10 (3 H, s) and 0.09 (3 H, s) (SiMe_2); **$^{13}\text{C NMR}$** δ_{C} (CDCl_3) 137.5 (4° aryl C), 128.5, 128.4, 127.9, 127.8 (aryl C), 87.6 (C^3OR), 80.5 (C^5OR), 79.1 (C^7OH), 71.8 (C^6OBn), 71.4 (PhCH_2), 68.7 (C^8OSi), 56.0 (C^2Br), 48.0 (C^4H), 44.3 (C^1H), 44.2 (C^{8a}H), 39.4 (C^{4a}H), 35.6 (CH_2), 25.8 (CMe_3), 18.0 (CMe_3), -4.5 and -4.6 (SiMe_2); **MS** m/z (ES) 518 (MNa^+), 516 (100%), 515, 497 (MH^+); **HRMS (ES)** Found: MH^+ , 495.1555. $\text{C}_{24}\text{H}_{36}\text{O}_4\text{BrSi}^+$ requires M , 495.1566.

6-Benzyloxy-8-(tert-butyl-dimethyl-silanyloxy)-1,4,4a,5,6,7,8,8a-octahydro-1,4-methano-naphthalene-5,7-diol 394

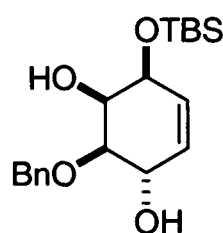


Alcohol **393** (240 mg, 0.48 mmol) was dissolved in MeOH (20 mL). Freshly activated zinc powder (250 mg, 3.8 mmol) and AcOH (5 drops) were added and the stirred mixture heated at reflux for 4 h. The mixture was allowed to cool, and concentrated onto silica. The *diol* **394** was isolated by column chromatography (40% EtOAc – petrol) as an oil (130 mg, 63%).

R_f (50% EtOAc – petrol) 0.65; **IR** $\nu_{\max}$ (CHCl_3) 3450 (br, OH), 2954, 2929 and 2857 (CH); **$^1\text{H NMR}$** δ_{H} (400 MHz; CDCl_3) 7.38-7.27 (5 H, m, ArH), 6.23 (1 H, dd, J 5.5 and 3.0, $\text{C}^2\text{H}=\text{C}^3\text{H}$), 6.09 (1 H, dd, J 5.5 and 3.0, $\text{C}^2\text{H}=\text{C}^3\text{H}$), 4.69 (1 H, d, J 11.5, $\text{PhCH}_\text{A}\text{H}_\text{B}$), 4.50 (1 H, d, J 11.5, $\text{PhCH}_\text{A}\text{H}_\text{B}$), 4.36 (1 H, t, J 10.0, C^8HOSi), 3.87 (1 H, dd, J 3.0 and 1.5, C^6HOBn), 3.28 (1 H, dd, J 7.0 and 3.0, C^5HOH), 3.09 (1 H, br s, C^1H), 3.00-2.94 (2 H, m, C^{8a}H and C^4H), 2.86 (1 H, dd, J 10.0 and 1.0, C^7HOH), 2.40 (1 H, ddd, J 11.0, 7.0 and 4.0, C^{4a}H), 2.36 (1 H, br s, OH), 2.09 (1 H, br s, OH), 1.43 (1 H, dt, J 8.5 and 2.0, $\text{CH}_\text{A}\text{H}_\text{B}$), 1.29 (1 H, d br m, $\text{CH}_\text{A}\text{H}_\text{B}$), 0.92 (9 H, s, ^tBu), 0.13 (3 H,

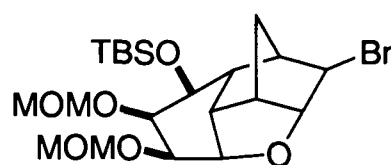
s) and 0.07 (3 H, s) (SiMe₂); **¹³C NMR** δ_{C} (CDCl₃) 138.6 (C²H=C³H), 138.2 (4° aryl C), 135.5 (C²H=C³H), 128.5, 127.9, 127.8 (aryl C), 81.3 (C⁷OH), 74.0 (C⁵OH), 71.7 (PhCH₂), 71.1 (C⁶OBn), 68.3 (C⁸OSi), 49.7 (CH₂), 47.0 (C^{4a}H), 45.6 (C¹H), 45.5, 44.9 (C^{8a}H and C⁴H), 25.7 (CMe₃), 17.9 (CMe₃) and -4.5 (2 peaks, SiMe₂); **MS** m/z (ES) 439 (100%, MNa⁺), 434 (MNH₄⁺) and 417 (MH⁺); **HRMS (ES)** Found: MH⁺, 417.2456. C₂₄H₃₇O₄Si⁺ requires M , 417.2461.

2-Benzyloxy-6-(tert-butyl-dimethyl-silanyloxy)-cyclohex-4-ene-1,3-diol **395**



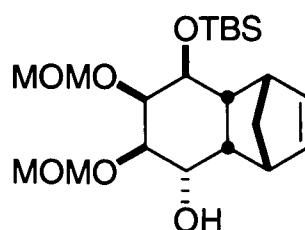
Diol **394** (92 mg, 0.22 mmol) was dissolved in diphenyl ether (15 mL) and transferred to a two-necked flask fitted with a quickfit thermometer and air condenser. The mixture was heated with stirring in an isomantle to 255 °C for 1 h, and then allowed to cool. The solution was loaded directly onto a silica column and the diphenyl ether flushed off with light petrol. The product was then flushed off with 1:1 EtOAc – petrol. Concentration of these fractions gave the *diol* **395** as a white solid (59 mg, 76%).

R_f (20% EtOAc – petrol) 0.30; m.p. 66-67 °C; **IR** ν_{max} (CHCl₃) 3429 (br, OH), 2954, 2929, 2886 and 2857 (CH); **¹H NMR** δ_{H} (400 MHz; CDCl₃) 7.42-7.29 (5 H, m, ArH), 5.72 (1 H, dt, J 10.5 and 2.0, C⁴H=C⁵H), 5.42 (1 H, dq, J 10.5 and 2.0, C⁴H=C⁵H), 4.83 (1 H, d, J 11.5, PhCH_AH_B), 4.64 (1 H, d, J 12.0, PhCH_AH_B), 4.62 (1 H, m, C⁶HOSi), 4.31 (1 H, dq, J 5.0 and 2.5, C³HOH), 4.19 (1 H, dt, J 3.5 and 2.0, C²HOR), 3.38 (1 H, dd, J 8.0 and 2.0, C¹HOH), 2.68 (1 H, br s, OH), 2.36 (1 H, br s, OH), 0.92 (9 H, s, ^tBu) and 0.13 (2 peaks, 2 × 3H, 2 × s, SiMe₂); **¹³C NMR** δ_{C} (CDCl₃) 138.1 (4° aryl C), 129.5, 128.5, 128.0 (2 peaks), 127.9 (aryl C and C⁴H=C⁵H), 82.4 (C¹OH), 71.5 (PhCH₂), 69.7 (C³OH), 69.4 (C²OR), 68.0 (C⁶OSi), 25.7 (CMe₃), 18.1 (CMe₃), -4.6 and -4.8 (SiMe₂); **MS** m/z (CI) 351 (100%, MH⁺) and 201; **HRMS (CI)** Found: MH⁺, 351.1982. C₁₉H₃₁O₄Si⁺ requires M , 351.1992.

Bis-methoxymethyl ether 396

Diol **386** (390 mg, 0.95 mmol) was dissolved in CH_2Cl_2 (15 mL) under argon. EtN^iPr_2 (2.0 mL, 11 mmol) and methoxymethyl chloride (720 μL , 9.5 mmol) were added, and the mixture heated at 40 °C overnight. The reaction was quenched by the addition of saturated aqueous ammonium chloride, and the mixture allowed to stir for 1 h open to air. The solution was washed with saturated aqueous ammonium chloride and water, and the organic layer collected and dried (MgSO_4). After concentration, the crude product was purified by column chromatography (10-15% EtOAc – petrol) to afford the ether **396** as a colourless oil (360 mg, 78%).

IR ν_{max} (film) 2954, 2929, 2890 and 2857 (CH); **$^1\text{H NMR}$** δ_{H} (400 MHz; CDCl_3) 4.91 (1 H, d, J 6.0), 4.73 (3 H, m) ($2 \times \text{CH}_2\text{O}_2$), 4.41 (1 H, br d, J 4.5, C^3HOR), 4.01 (1 H, d, J 3.5, C^7HOR), 3.96 (1 H, d, J 4.0, C^5HOR), 3.86 (1 H, d, J 2.0, C^2HBr), 3.76 (1 H, d, J 4.0, C^6HOR), 3.65 (1 H, d, J 8.5, C^8HOSi), 3.41 (3 H, s), 3.40 (3 H, s) ($2 \times \text{OMe}$), 2.83-2.76 (2 H, m, C^4H and C^{4a}H), 2.49 (1 H, br m, C^1H), 2.33 (1 H, ddd, J 11.0, 8.0 and 4.0, C^{8a}H), 2.19 (1 H, dm, $\text{CH}_\text{A}\text{H}_\text{B}$), 1.72 (1 H, d, J 11.0, $\text{CH}_\text{A}\text{H}_\text{B}$), 0.92 (9 H, s, ^tBu), 0.11 (3 H, s) and 0.10 (3 H, s) (SiMe_2); **$^{13}\text{C NMR}$** δ_{C} (CDCl_3) 96.9, 94.5 ($2 \times \text{CO}_2$), 87.8 (C^3OR), 82.5 (C^5OR), 76.8 (2 peaks, C^6OR and C^7OR), 68.9 (C^8OSi), 56.0 (C^2Br), 55.6, 55.5 ($2 \times \text{OMe}$), 47.9 (C^4H), 45.0 (C^{8a}H), 44.0 (C^1H), 40.2 (C^{4a}H), 35.7 (CH_2), 25.7 (CMe_3), 18.0 (CMe_3), -4.5 and -4.8 (SiMe_2); **MS** m/z (CI) 495, 493 (MH^+), 463, 461 ($\text{M}^+ - \text{OMe}$), 419, 417, 415, 331 (100%), 329, 287 and 285; **HRMS (CI)** Found: MH^+ , 495.1601. $\text{C}_{21}\text{H}_{37}\text{O}_4$ $^{81}\text{BrSi}^+$ requires M , 495.1601.

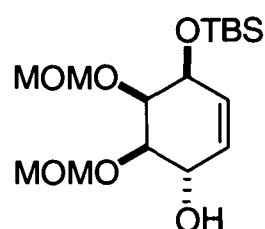
8-(tert-Butyl-dimethyl-silanyloxy)-6,7-bis-methoxymethoxy-1,4,4a,5,6,7,8,8a-octahydro-1,4-methano-naphthalen-5-ol 397

Ether **396** (1.3 g, 2.6 mmol) was dissolved in MeOH (50 mL). Freshly activated zinc powder (1.4 g, 21 mmol) and AcOH (5 drops) were added and the stirred mixture

heated at reflux for 2 h. The mixture was allowed to cool, and concentrated onto silica. The *alcohol 397* was isolated by column chromatography (20% EtOAc – petrol) as an oil (1.0 g, 92%).

R_f (20% EtOAc – petrol) 0.21; **IR** $\nu_{\max}$ (CHCl₃) 3484 (br, OH), 2956, 2931, 2892 and 2857 (CH); **¹H NMR** δ_H (400 MHz; CDCl₃) 6.28 (1 H, dd, J 5.5 and 3.0, C²H=C³H), 6.10 (1 H, dd, J 5.5 and 3.0, C²H=C³H), 4.83 (1 H, d, J 6.5), 4.74 (1 H, d, J 6.5), 4.72 (1 H, d, J 7.5), 4.67 (1 H, d, J 7.0) (2 × CH₂O₂), 4.21 (1 H, t, J 9.5, C⁸HOSi), 3.84 (1 H, t, J 1.0, C⁶HOR), 3.42 (3 H, app. s), 3.39 (3 H, app.s) (2 × OMe), 3.25 (1 H, dd, J 7.5 and 2.5, C⁵HOH), 3.08 (1 H, br s, C⁴H), 3.00 (1 H, td, J 10.5 and 3.0, C^{8a}H), 2.97 (1 H, br s, C¹H), 2.88 (1 H, d, J 9.0, C⁷HOR), 2.70 (1 H, br s, OH), 2.47 (1 H, ddd, J 11.0, 8.0 and 4.0, C^{4a}H), 1.44 (1 H, d br m, CH_AH_B), 1.30 (1 H, d, J 8.5, CH_AH_B), 0.92 (9 H, s, ^tBu), 0.12 (3 H, s) and 0.08 (3 H, s) (SiMe₂); **¹³C NMR** δ_C (CDCl₃) 138.3 (C²H=C³H), 135.4 (C²H=C³H), 96.7, 96.3 (2 × CO₂), 82.5 (C⁷OR), 78.1 (C⁶OR), 74.5 (C⁵OH), 69.7 (C⁸OSi), 55.6, 55.2 (2 × Me), 49.4 (CH₂), 48.2 (C^{4a}H), 45.8 (C⁴H), 44.9 (C¹H), 44.5 (C^{8a}H), 25.8 (CMe₃), 17.9 (CMe₃), −4.1 and −4.7 (SiMe₂); **MS** m/z (ES) 437 (100%, MNa⁺), 432 (MNH₄⁺) 415 (MH⁺) and 320; **HRMS (ES)** Found: MH⁺, 415.2515. C₂₁H₃₉O₆Si⁺ requires M , 415.2516.

4-(tert-Butyl-dimethyl-silanyloxy)-5,6-bis-methoxymethoxy-cyclohex-2-enol **398**

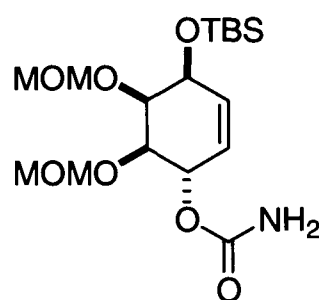


Alcohol **397** (620 mg, 1.5 mmol) was dissolved in diphenyl ether (15 mL) and transferred to a two-necked flask fitted with a quickfit thermometer and air condenser. The mixture was heated with stirring in an isomantle to 255 °C for 1 h, and then allowed to cool. The solution was loaded directly onto a silica column and the diphenyl ether flushed off with light petrol. The product was then flushed off with 1:1 EtOAc – petrol. Concentration of these fractions gave the *alcohol 398* as an oil (480 mg, 92%).

R_f (50% EtOAc – petrol) 0.45; **IR** $\nu_{\max}$ (CHCl₃) 3449 (br, OH), 2955, 2930, 2894 and 2857 (CH); **¹H NMR** δ_H (400 MHz; CDCl₃) 5.73 (1 H, dt, J 10.5 and 2.5, C²H=C³H),

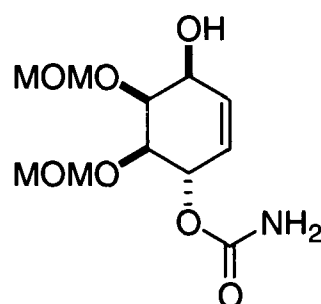
5.53 (1 H, dq, J 10.5 and 1.5, $C^2H=C^3H$), 4.85 (1 H, d, J 7.0), 4.82 (1 H, d, J 7.0), 4.78 (1 H, d, J 7.0), 4.76 (1 H, d, J 7.0) ($2 \times CH_2O_2$), 4.48 (1 H, m, C^4HOSi), 4.42 (1 H, m, C^1HOH), 4.14 (1 H, m, C^6HOR), 3.49-3.41 (8 H, m, $2 \times OMe$, OH and C^5HOR), 0.90 (9 H, s, tBu), 0.11 (3 H, s) and 0.10 (3 H, s) ($SiMe_2$); **^{13}C NMR** $\delta_C(CDCl_3)$ 129.8 ($C^2H=C^3H$), 128.6 ($C^2H=C^3H$), 97.1, 96.4 ($2 \times CO_2$), 82.6 (C^5OR), 77.0 (C^6OR), 70.2 (C^1OH), 69.1 (C^4OSi), 55.7, 55.4 ($2 \times OMe$), 25.8 (CMe_3), 18.2 (CMe_3), -4.8 ($SiMe_2$); **MS** m/z (CI) 349 (MH^+), 317 ($M^+ - OMe$), 287 (100%, $M^+ - OMOM$), 273, 255, 237 and 225; **HRMS (CI)** Found: MH^+ , 349.2034. $C_{16}H_{33}O_6Si^+$ requires M , 349.2046.

4-(*tert*-butyldimethylsilanyloxy)-5,6-bis-methoxymethoxy-cyclohex-2-enyl carbamate 401



Alcohol **398** (480 mg, 1.4 mmol) was subjected to the general carbamate formation procedure, affording the *carbamate 401* as a white solid (500 mg, 93%).

R_f (40% EtOAc – petrol) 0.37; m.p. 74-75 °C; **IR** ν_{max} (film) 3358 (br, NH_2), 2956, 2928, 2892, 2854 (CH) and 1725 (C=O); **1H NMR** δ_H (400 MHz; $CDCl_3$) 5.66 (1 H, dm), 5.56 (1 H, dm) ($C^2H=C^3H$), 5.53 (1 H, m, C^1HOR), 4.93 (2 H, br s, NH_2), 4.86 (1 H, d, J 7.0), 4.78 (1 H, d, J 7.0), 4.76 (1 H, d, J 7.0), 4.65 (1 H, d, J 7.0) ($2 \times CH_2O_2$), 4.41 (1 H, m, C^4HOSi), 4.15 (1 H, m, C^5HOR), 3.78 (1 H, dd, J 8.5 and 1.5, C^6HOR), 3.42 (3 H, d, J 1.0, OMe), 3.41 (3 H, d, J 1.0, OMe), 0.90 (9 H, s, tBu), 0.11 (3 H, s) and 0.10 (3 H, s) ($SiMe_2$); **^{13}C NMR** $\delta_C(CDCl_3)$ 156.5 (C=O), 131.2, 126.0 ($C^2H=C^3H$), 97.0, 94.9 ($2 \times CH_2O_2$), 76.1, 75.9 (C^5OR and C^6OR), 73.0 (C^1OR), 70.0 (C^4OSi), 55.5, 55.4 ($2 \times OMe$), 25.8 (CMe_3), 18.2 (CMe_3) and -4.8 ($SiMe_2$); **MS** m/z (ES) 414 (100%, MNa^+); **HRMS (ES)** Found: MNa^+ , 414.1934. $C_{17}H_{33}NO_7NaSi^+$ requires M , 414.1924.

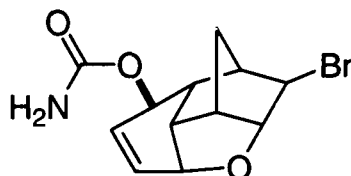
4-hydroxy-5,6-bis-methoxymethoxy-cyclohex-2-enyl carbamate 404

Silyl ether **401** (150 mg, 0.38 mmol) was dissolved in THF (2 mL) under argon. A solution of TBAF in THF (1 M, 0.77 mL, 0.77 mmol) was added and the solution stirred for 24 h. The mixture was concentrated onto silica and the product purified by column chromatography (EtOAc) to afford the *alcohol* **404** as a white solid (86 mg, 82%).

R_f (EtOAc) 0.32; m.p. 109-111 °C; **IR** $\nu_{\max}$ (film) 3332 and 3358 (br, OH and NH₂), 2951, 2898, 2826 (CH) and 1714 (C=O); **¹H NMR** δ_H (400 MHz; CDCl₃) 5.81 (1 H, d br m, J 9.5, C²H=C³H), 5.71 (1 H, dt, J 10.0 and 2.5, C²H=C³H), 5.47 (1 H, 7.0 and 2.0, C¹HOCO), 4.87 (1 H, d, J 7.0, CH_AH_BO₂), 4.80 (3 H, m, NH₂ and CH_AH_BO₂), 4.75 (1 H, d, J 7.0), 4.71 (1 H, d, J 7.0) (CH₂O₂), 4.28 (1 H, dtd, J 10.5, 4.5 and 2.5, C⁴HOH), 4.15 (1 H, m, C⁵HOR), 3.89 (1 H, dd, J 7.0 and 2.0, C⁶HOR), 3.43 (3 H, s, OMe), 3.41 (3 H, s, OMe) and 3.31 (1 H, d, J 11.0, OH); **¹³C NMR** δ_C (CDCl₃) 156.1 (C=O), 131.9, 125.4 (C²H=C³H), 97.1, 95.9 (2 × CH₂O₂), 76.7 (2 peaks, C⁵OR and C⁶OR), 71.9 (C¹OCO), 67.3 (C⁴OH), 55.9 and 55.6 (2 × OMe); **MS** m/z (CI) 295 (MNH₄⁺), 246 (M⁺ – OMe), 234 (M⁺ – CONH₂), 219 (M⁺ – OCONH₂), 214, 202, 185 (100%) and 172; **HRMS (CI)** Found: MNH₄⁺, 295.1504. C₁₁H₂₃N₂O₇⁺ requires M , 295.1505.

5.9 – Experimental details for chapter 4.4

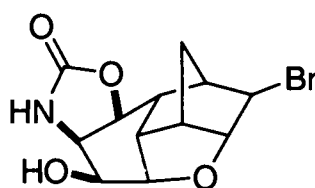
Carbamate 408



Alcohol **384** (390 mg, 1.5 mmol) was subjected to the general carbamate formation procedure, affording the *carbamate 408* as a white solid (360 mg, 80%).

m.p. 124-126 °C; $[\alpha]_D$ 106 ($c = 1.05$, CHCl_3); **IR** ν_{max} (CHCl_3) 3459, 3344 (br, NH_2), 2972 (CH) and 1716 ($\text{C}=\text{O}$); **$^1\text{H NMR}$** δ_{H} (400 MHz; CDCl_3) 6.16 (1 H, ddd, J 10.0, 6.0 and 2.0, $\text{C}^6\text{H}=\text{C}^7\text{H}$), 5.90 (1 H, dd, J 10.0 and 3.5, $\text{C}^6\text{H}=\text{C}^7\text{H}$), 5.07 (1 H, dt, J 3.0 and 1.5, C^8HOCO), 4.92 (2 H, br s, NH_2), 4.53 (1 H, d, J 4.5, C^3HOR), 4.40 (1 H, t, J 6.0, C^5HOR), 3.64 (1 H, d, J 2.5, C^2HBr), 2.89 (1 H, td, J 5.0 and 1.0, C^4H), 2.69 (1 H, d, J 1.0, C^1H), 2.39 (1 H, dt, J 10.5 and 5.0, C^{4a}H), 2.30 (1 H, dd, J 11.0 and 3.5, C^{8a}H), 2.09 (1 H, d, J 11.0, $\text{CH}_\text{A}\text{H}_\text{B}$) and 1.64 (1 H, ddd, J 11.0, 1.5 and 1.0, $\text{CH}_\text{A}\text{H}_\text{B}$); **$^{13}\text{C NMR}$** δ_{C} (CDCl_3); 156.3 ($\text{C}=\text{O}$), 130.0 ($\text{C}^6\text{H}=\text{C}^7\text{H}$), 128.5 ($\text{C}^6\text{H}=\text{C}^7\text{H}$), 89.4 (C^3OR), 71.8 (C^5OR), 67.3 (C^8OR), 54.7 (C^2Br), 49.2 (C^4H), 47.9 (C^1H), 43.2 (C^{8a}H), 34.1 (C^{4a}H) and 34.0 (CH_2); **MS** m/z (CI) 319, 317 (MNH_4^+), 302, 301 (MH^+), 258, 256 (100%, $\text{M}^+ - \text{CONH}_2$), 241 and 239 ($\text{M}^+ - \text{OCONH}_2$); **HRMS (CI)** Found: MH^+ , 300.0236. $\text{C}_{12}\text{H}_{15}\text{NO}_3\text{Br}^+$ requires M , 300.0235.

Oxazolidinone 409

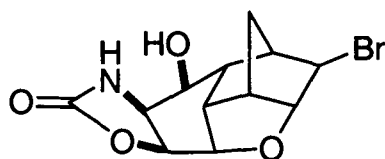


Carbamate **408** (360 mg, 1.2 mmol) was subjected to the general tethered aminohydroxylation procedure, using sodium citrate as the ligand. Purification of the crude compound by column chromatography (50% EtOAc – petrol) afforded the *oxazolidinone 409* as a white crystalline solid (200 mg, 56%).

R_f (EtOAc) 0.14; m.p. 220 °C (dec.); $[\alpha]_D$ 85 ($c = 1.47$, pyridine); **IR** ν_{max} (CHCl_3) 3357 (br, OH and NH), 2972, 2886 (CH) and 1742 ($\text{C}=\text{O}$); **$^1\text{H NMR}$** δ_{H} (400 MHz; d^5 -

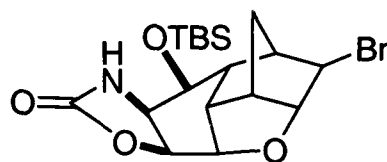
pyridine) 7.55 (1 H, d, J 4.0, NH), 4.80 (1 H, br m, C⁵HOR), 4.65 (1 H, br d, J 3.5, C³HOR), 4.50 (1 H, br m, C⁸HOR), 4.38 (1 H, br m, C⁷HNH), 4.06 (1 H, m, C⁶HOH), 4.02 (1 H, s, C²HBr), 2.83 (1 H, m, C¹H), 2.76-2.73 (2 H, m, C⁴H and C^{8a}H), 2.44 (1 H, s, C^{4a}H), 1.98 (1 H, d, J 11.0, CH_AH_B) and 1.52 (1 H, d, J 10.5, CH_AH_B); **¹³C NMR** δ_c (d^5 -pyridine) 161.3 (C=O), 89.4 (C³OR), 80.5 (C⁸OR), 76.5 (C⁵OR), 66.3 (C⁷NH), 57.0 (C²Br), 52.7 (C⁶OH), 48.4 (C^{8a}H), 48.1 (C^{4a}H), 39.0 (C¹H), 35.2 (C⁴H) and 34.4 (CH₂); **MS** m/z (ES) 315, 313 (100%, M – H⁺); **HRMS (ES)** Found: MH⁺, 316.0191. C₁₂H₁₅NO₄⁷⁹Br⁺ requires M , 316.0184.

Oxazolidinone 410



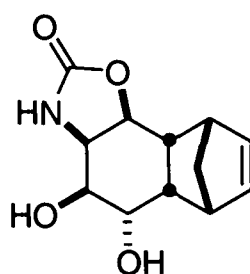
A run of the tethered aminohydroxylation protocol above at a higher ambient temperature (approx. 35 °C) led to the formation of oxazolidinone **409** (800 mg, 35%) and recovered starting material **408** (510 mg, 23%). In addition a third spot, oxazolidinone **410** was isolated as a white solid (380 mg, 16%).

R_f (EtOAc) 0.18; m.p. 195-196 °C (dec.); **IR** $\nu_{\max}$ (CHCl₃) 3435 (br, OH and NH), 2968 (CH) and 1739 (C=O); **¹H NMR** δ_H (400 MHz; d^5 -pyridine) 4.89 (1 H, dd, J 8.0 and 1.0, C⁶HOR), 4.47 (2 H, m, C⁷HNH and C³HOR), 4.41 (1 H, s, C²HBr), 4.35 (1 H, dd, J 7.5 and 2.5, C⁵HOR), 3.84 (1 H, m, C⁸HOH), 2.73 (1 H, br m), 2.65 (1 H, br m) (C¹H and C⁴H), 2.55-2.44 (2 H, m, C^{4a}H and C^{8a}H), 2.07 (1 H, dm, J 11.0, CH_AH_B) and 1.52 (1 H, d, J 11.0, CH_AH_B); **¹³C NMR** δ_c (d^5 -pyridine) 159.9 (C=O), 88.0 (C³OR), 77.8 (C⁸OH), 74.9 (C⁶OR), 64.7 (C⁵OR), 57.2 (C⁷NH), 57.1 (C²Br), 47.9, 44.7 (C¹H and C⁴H), 42.4, 39.1 (C^{4a}H and C^{8a}H) and 35.3 (CH₂); **MS** m/z (ES) 315, 313 (100%, M – H⁺); **HRMS (ES)** Found: (M – H⁺)⁺, 314.0027. C₁₂H₁₃NO₄Br⁺ requires M , 314.0028.

Silyl ether 411

Oxazolidinone **410** (160 mg, 0.50 mmol) was dissolved in dry DMF (0.50 mL). Imidazole (68 mg, 0.99 mmol) and TBSCl (90 mg, 0.80 mmol) were added, and the mixture stirred for 16 h. The solution was diluted with brine (25 mL) and extracted with EtOAc (2 × 25 mL). The combined organic extracts were concentrated onto silica and purified by column chromatography (30% EtOAc – petrol) to afford the silyl ether **411** as a white solid (110 mg, 53%).

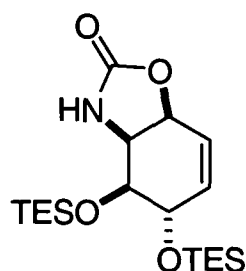
R_f (1:1 EtOAc – petrol) 0.68; m.p. 123–125 °C; **IR** $\nu_{\max}$ (CHCl₃) 3293 (NH), 2957, 2929, 2890 and 2857 (CH) and 1767 (C=O); **¹H NMR** δ_H (400 MHz; CDCl₃) 5.44 (1 H, br s, NH), 4.76 (1 H, d, J 8.5, C⁶HOR), 4.47 (1 H, d, J 5.0, C³HOR), 4.11 (1 H, m, C⁷HNH), 4.06 (1 H, s, C²HBr), 4.01 (1 H, dd, J 8.0 and 3.0, C⁵HOR), 3.81 (1 H, t, J 1.0, C⁸HOSi), 2.91 (1 H, br m, C⁴H), 2.63 (1 H, dt, J 11.0 and 3.0, C^{8a}H), 2.52 (1 H, dd, J 3.0 and 1.0, C¹H), 2.24–2.19 (2 H, m, C^{4a}H and CH_AH_B), 1.72 (1 H, d, J 11.0, CH_AH_B), 0.89 (9 H, s, ^tBu), 0.10 (3 H, s) and 0.09 (3 H, s) (SiMe₂); **¹³C NMR** δ_C (CDCl₃) 158.0 (C=O), 87.5 (C³OR), 76.3 (C⁸OSi), 74.5 (C⁶OR), 66.1 (C⁵OR), 55.8 (C⁷NH), 54.9 (C²Br), 47.5 (C⁴H), 43.9 (C¹H), 41.8 (C^{4a}H), 38.6 (C^{8a}H), 34.9 (CH₂), 25.6 (CMe₃), 17.8 (CMe₃), –4.5 and –4.6 (SiMe₂); **MS** m/z (ES) 429, 427 (100%, M – H⁺); **HRMS (ES)** Found: (M–H⁺)⁺, 430.1055. C₁₈H₂₉NO₄BrSi⁺ requires M , 430.1049.

Oxazolidinone diol 414

Oxazolidinone **409** (330 mg, 1.0 mmol) was dissolved in MeOH (15 mL). Freshly activated zinc powder (540 g, 8.3 mmol) and AcOH (5 drops) were added and the stirred mixture heated at reflux for 2.5 h. The mixture was allowed to cool, and concentrated onto silica. The *diol* **414** was isolated by column chromatography (EtOAc) as a gummy solid (240 mg, 97%).

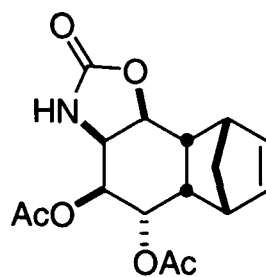
$[\alpha]_D$ 21.4 ($c = 0.55$, pyridine); **IR** $\nu_{\max}$ (CHCl_3) 3370 (br, OH and NH) and 1730 ($\text{C}=\text{O}$); **$^1\text{H NMR}$** δ_{H} (400 MHz; d^5 -pyridine); 8.74 (1 H, s, NH), 6.49 (1 H, d, J 2.0, $\text{C}^2\text{H}=\text{C}^3\text{H}$), 6.04 (1 H, d, J 2.5, $\text{C}^2\text{H}=\text{C}^3\text{H}$), 5.08 (2 H, br s, $2 \times \text{OH}$), 4.71 (1 H, dd, J 8.0 and 3.0, C^8HOR), 4.61 (1 H, d, J 6.5, C^5HOH), 4.27-4.26 (2 H, m, C^6HOH and C^7HNH), 3.16 (1 H, s, C^1H), 3.05 (1 H, s, C^{4a}H), 2.92 (2 H, app. s, C^4H and C^{8a}H), 1.35 (1 H, d, J 7.5, $\text{CH}_\text{A}\text{H}_\text{B}$) and 1.24 (1 H, d, J 7.5, $\text{CH}_\text{A}\text{H}_\text{B}$); **$^{13}\text{C NMR}$** δ_{C} (d^5 -pyridine); 160.4 ($\text{C}=\text{O}$), 140.3 ($\text{C}^2\text{H}=\text{C}^3\text{H}$), 133.0 ($\text{C}^2\text{H}=\text{C}^3\text{H}$), 78.6 (C^8OR), 69.8 (C^6OH), 69.4 (C^5OH), 55.1 (C^7NH), 51.2 (CH_2), 47.1, 46.2 (C^1H), 45.8 (C^{4a}H) and 44.2; **MS** m/z (ES) 236 (100%, $\text{M}-\text{H}^+$); **HRMS (ES)** Found: MH^+ , 238.1074. $\text{C}_{12}\text{H}_{16}\text{NO}_4^+$ requires M , 238.1079.

4,5-Bis-triethylsilanyloxy-3a,4,5,7a-tetrahydro-3H-benzooxazolidinone **416**



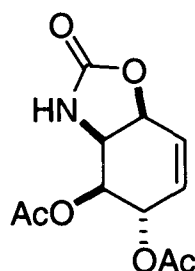
Bis-silyl ether **415** (72 mg, 0.15 mmol) was dissolved in diphenyl ether (15 mL) and transferred to a two-necked flask fitted with a quickfit thermometer and air condenser. The mixture was heated with stirring in an isomantle to 255 °C for 1 h, and then allowed to cool. The solution was loaded directly onto a silica column and the diphenyl ether flushed off with light petrol. The product was then flushed off with 1:1 EtOAc – petrol. Concentration of these fractions gave the *bis-silyl ether* **416** as an oil (54 mg, 87%).

IR $\nu_{\max}$ (CHCl_3) 3255 (NH), 2955, 2911, 2877 (CH) and 1761 ($\text{C}=\text{O}$); **$^1\text{H NMR}$** δ_{H} (400 MHz; CDCl_3) 5.87 (1 H, ddd, J 10.5, 6.5 and 0.5, $\text{C}^6\text{H}=\text{C}^7\text{H}$), 5.71 (1 H, ddd, J 10.0, 3.5 and 2.5, $\text{C}^6\text{H}=\text{C}^7\text{H}$), 5.27 (1 H, br s, NH), 5.02 (1 H, ddt, J 8.0, 4.0 and 1.0, C^{7a}HOR), 4.31 (1 H, dq, J 7.0 and 1.5, C^5HOSi), 4.22 (1 H, dd, J 7.5 and 3.5, C^{3a}HNH), 3.68 (1 H, dd, J 7.0 and 3.5, C^4HOSi), 0.97 (6 H, t, J 8.0, SiCH_2), 0.96 (6 H, t, J 8.0, SiCH_2) and 0.63 (18 H, q, J 8.0, $6 \times \text{Me}$); **$^{13}\text{C NMR}$** δ_{C} (CDCl_3) 158.7 ($\text{C}=\text{O}$), 135.8 ($\text{C}^6\text{H}=\text{C}^7\text{H}$), 122.6 ($\text{C}^6\text{H}=\text{C}^7\text{H}$), 73.2 (2 peaks, C^{7a}OR and C^4OSi), 68.3 (C^5OSi), 55.4 (C^{3a}NH), 6.8 ($2 \times \text{Me}$) and 4.9 (2 peaks, $2 \times \text{SiCH}_2$); **MS** m/z (CI) 417 (MNH_4^+) and 400 (100%, MH^+); **HRMS (CI)** Found: MH^+ , 400.2324. $\text{C}_{19}\text{H}_{38}\text{NO}_4\text{Si}_2^+$ requires M , 400.2339.

Bis-acetyloxazolidinone 417

Diol **414** (300 mg, 1.3 mmol) and DMAP (5 mg) were dissolved in pyridine (5 mL). Acetic anhydride (5 mL) was added and the reaction mixture stirred for 1 h. The mixture was diluted with saturated aqueous copper sulfate solution and extracted with EtOAc. The combined organic extracts were concentrated and filtered through a pad of silica, eluting with 50% EtOAc – petrol. Concentration of the filtrate gave the *diacetate* **417** as a white solid (240 mg, 59%).

m.p. 125 °C (dec.); **IR** ν_{max} (film) 3271 (br, NH), 2973, 2874 (CH) and 1747 (C=O); **¹H NMR** δ_{H} (400 MHz; CDCl₃) 6.30 (1 H, dd, J 6.0 and 3.0, C²H=C³H), 6.19-6.17 (2 H, m, C²H=C³H and NH), 5.34 (1 H, dd, J 9.0 and 7.0, C⁸HOR), 5.06 (1 H, dd, J 9.0 and 6.0, C⁶HOAc), 4.55 (1 H, dd, J 9.0 and 4.0, C⁵HOAc), 4.00 (1 H, dd, J 9.0 and 5.5, C⁷HNH), 3.06 (1 H, br m, C⁴H), 2.98 (1 H, ddd, J 10.0, 7.0 and 3.0, C^{8a}H), 2.91 (1 H, br m, C¹H), 2.76 (1 H, dt, J 10.5 and 4.0, C^{4a}H), 2.09 (3 H, s, Ac), 2.05 (3 H, s, Ac), 1.50 (1 H, dt, J 9.0 and 2.0, CH_AH_B) and 1.37 (1 H, d br m, CH_AH_B); **¹³C NMR** δ_{C} (CDCl₃) 170.6, 169.9 (2 × MeC=O), 158.8 (NHC=O), 138.6 (C²H=C³H), 134.1 (C²H=C³H), 77.6 (C⁵OAc), 69.1 (C⁸OR), 68.1 (C⁶OAc), 52.3 (C⁷NH), 51.0 (CH₂), 46.4 (C⁴H), 45.5 (C¹H), 42.6 (C^{4a}H), 41.9 (C^{8a}H), 21.0 and 20.7 (2 × Ac); **MS** m/z (ES) 320 (M – H⁺) and 278 (100%, M – Ac); **HRMS (ES)** Found: MH⁺, 322.1286. C₁₆H₂₀NO₆⁺ requires M , 322.1291.

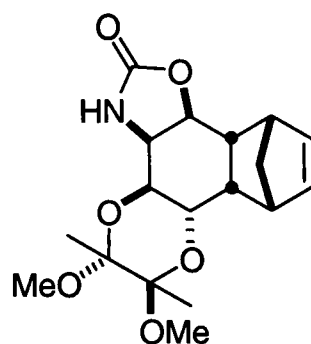
5-Acetoxy-2-oxo-2,3,3a,4,5,7a-hexahydro-benzooxazol-4-yl acetate 418

Bisacetate **417** (69 mg, 0.26 mmol) was dissolved in diphenyl ether (15 mL) and transferred to a two-necked flask fitted with a quickfit thermometer and air condenser. The mixture was heated with stirring in an isomantle to 255 °C for 1 h, then allowed to

cool. The solution was loaded directly onto a silica column and the diphenyl ether flushed off with light petrol. The product was then flushed off with 1:1 EtOAc – petrol. Concentration of these fractions gave the *bisacetate* **418** as an oil (51 mg, 69%).

R_f (EtOAc) 0.62; m.p. 146-148 °C; **IR** $\nu_{\max}$ (CHCl₃) 3291 (NH), 2942 (CH) and 1746 (C=O); **¹H NMR** δ_H (400 MHz; CDCl₃) 6.10 (1 H, br s, NH), 5.96 (1 H, ddd, J 10.5, 2.0 and 1.0, C⁶H=C⁷H), 5.91 (1 H, ddd, J 11.0, 3.5 and 1.0, C⁶H=C⁷H), 5.62 (1 H, dq, J 8.0 and 1.5, C⁵HOAc), 5.16 (1 H, dd, J 8.5 and 4.0, C⁴HOAc), 5.12 (1 H, ddd, J 8.0, 3.5 and 1.0, C^{7a}HOR), 4.43 (1 H, dd, J 8.0 and 4.0, CHNH), 2.11 (3 H, s, Ac) and 2.07 (3 H, s, Ac); **¹³C NMR** δ_C (CDCl₃) 170.1, 170.0 (2 × Ac C=O), 158.8 (NHC=O), 130.2 (C⁶H=C⁷H), 125.2 (C⁶H=C⁷H), 72.3 (C^{7a}OR), 70.1 (C⁴OAc), 67.0 (C⁵OAc), 52.6 (CHNH), 20.8 and 20.7 (2 × Ac); **MS** m/z (CI) 273 (MNH₄⁺), 256 (100%, MH⁺), 136 (M – 2 × OAc) and 94; **HRMS (CI)** Found: MH⁺, 256.0828. C₁₁H₁₄NO₆⁺ requires M , 256.0821.

Bis-acetal **419**



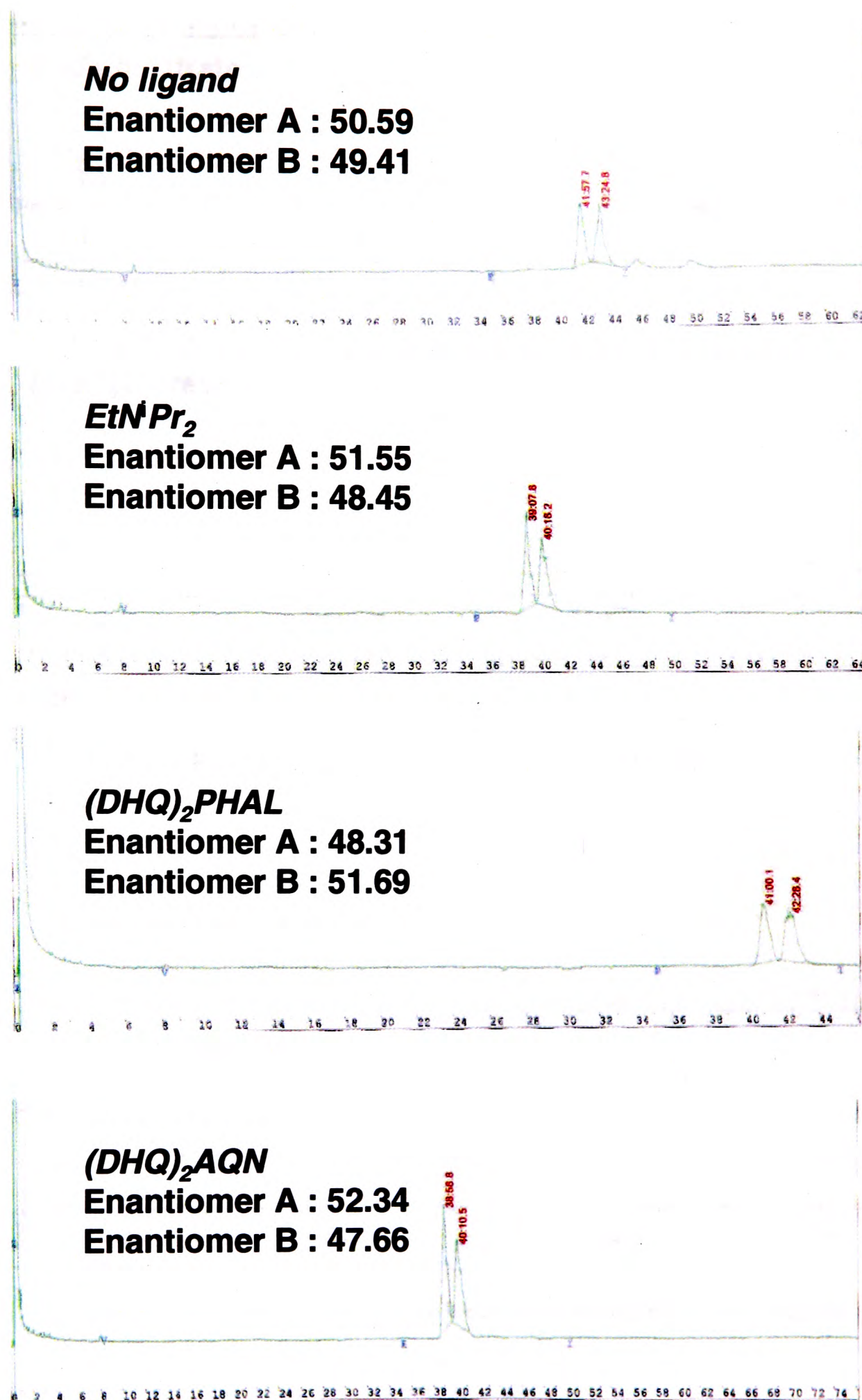
Diol **414** (140 mg, 0.58 mmol) was suspended in 2,2,3,3-tetramethoxybutane (120 mg, 0.70 mmol), triethylorthoformate (260 μ L, 2.3 mmol) and methanol (5 mL). Camphor sulfonic acid (7 mg) was added and the mixture was heated at reflux for 3 h. Once cooled, NaHCO₃ was added, and the mixture concentrated onto silica. The mixture was purified by column chromatography (30% EtOAc – petrol) to afford the *bis-acetal* **419** as a white solid (110 mg, 52%).

m.p. 218-220 °C; **IR** $\nu_{\max}$ (film) 3271 (br, NH), 2947 (CH) and 1759 (C=O); **¹H NMR** δ_H (400 MHz; CDCl₃) 6.36 (1 H, dd, J 5.5 and 3.0, C²H=C³H), 6.06 (1 H, dd, J 5.5 and 3.0, C²H=C³H), 5.29 (1 H, br s, NH), 4.63 (1 H, d, J 7.0, C⁸HOR), 4.07 (1 H, m, C⁶HOR), 3.81-3.75 (2 H, m, C⁷HNH and C⁵HOR), 3.19 (3 H, s, OMe), 3.17 (3 H, s, OMe), 3.14 (1 H, br m, C⁴H), 2.99 (1 H, br s, C¹H), 2.83 (1 H, dd, J 10.0 and 4.0,

$C^{8a}H$), 2.75 (1 H, ddd, J 10.5, 7.0 and 3.0, $C^{4a}H$), 1.45 (1 H, dt, J 8.5 and 1.5, CH_AH_B), 1.34 (1 H, d br m, CH_AH_B), 1.25 (3 H, s, Me) and 1.21 (3 H, s, Me); **^{13}C NMR** $\delta_c(CDCl_3)$ 158.1 (C=O), 140.2 ($C^2H=C^3H$), 132.9 ($C^2H=C^3H$), 99.8, 99.1 ($2 \times CO_2R_2$), 77.5 (C^8OR), 64.6 (C^6OR), 64.3 (C^5OR), 52.6 (C^7NH), 51.4 (CH_2), 47.7 (2 peaks, $2 \times OMe$), 47.3 (C^4H), 45.6 (C^1H), 44.4 ($C^{8a}H$), 42.8 ($C^{4a}H$), 17.7 and 17.4 ($2 \times Me$); **MS** m/z (ES) 396 ($M + HCOO^-$), 382, 349 ($M - H^+$), 274 and 254 (100%); **HRMS (ES)** Found: ($M + HCOO^-$), 396.1660. $C_{19}H_{26}NO_8^-$ requires M , 396.1658.

Appendix I

GC/HPLC traces

Figure 34 Chiral GC traces for the TA of *trans*-cinnamyl carbamate

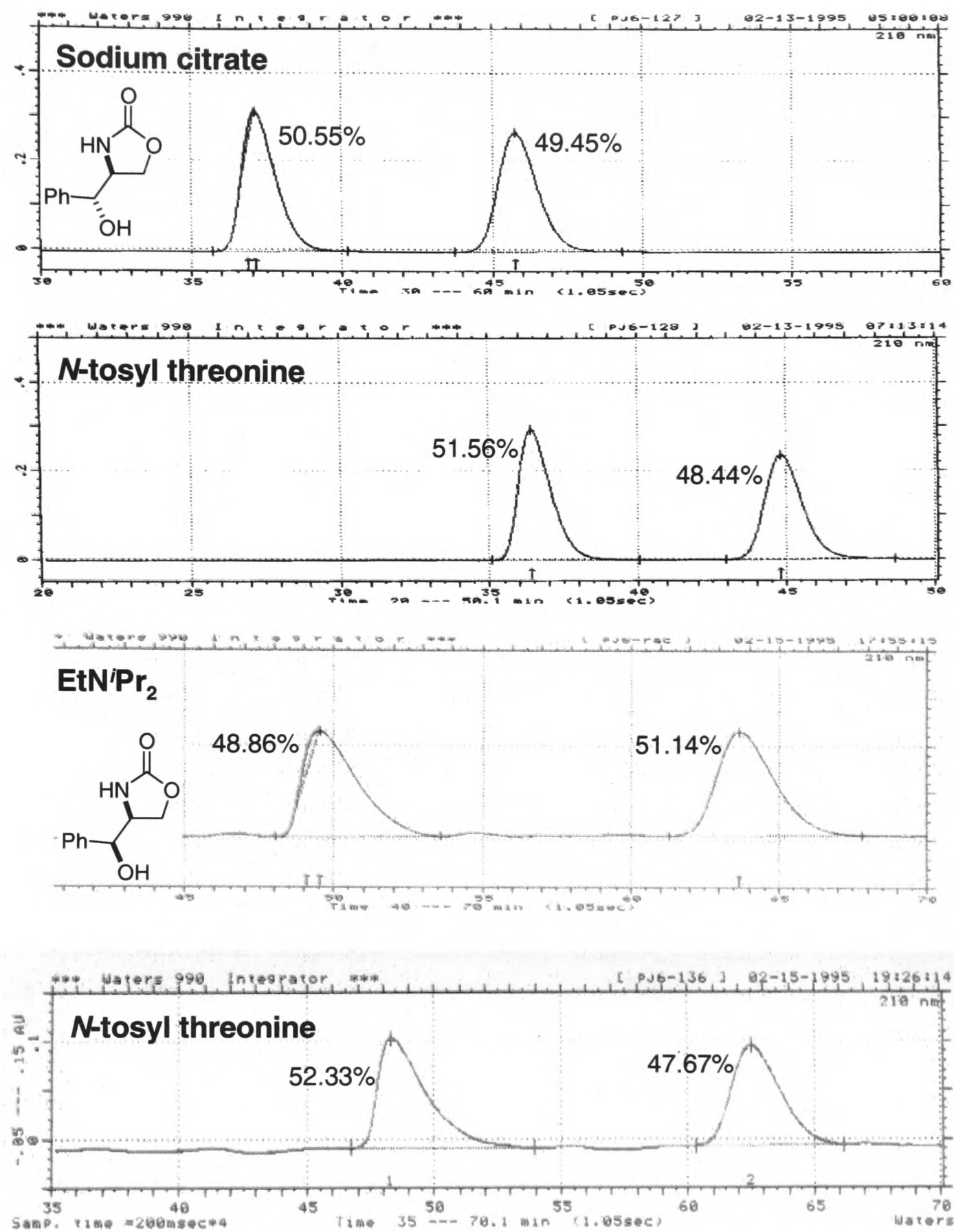


Figure 35 Chiral HPLC traces of products from TA using second-cycle ligands

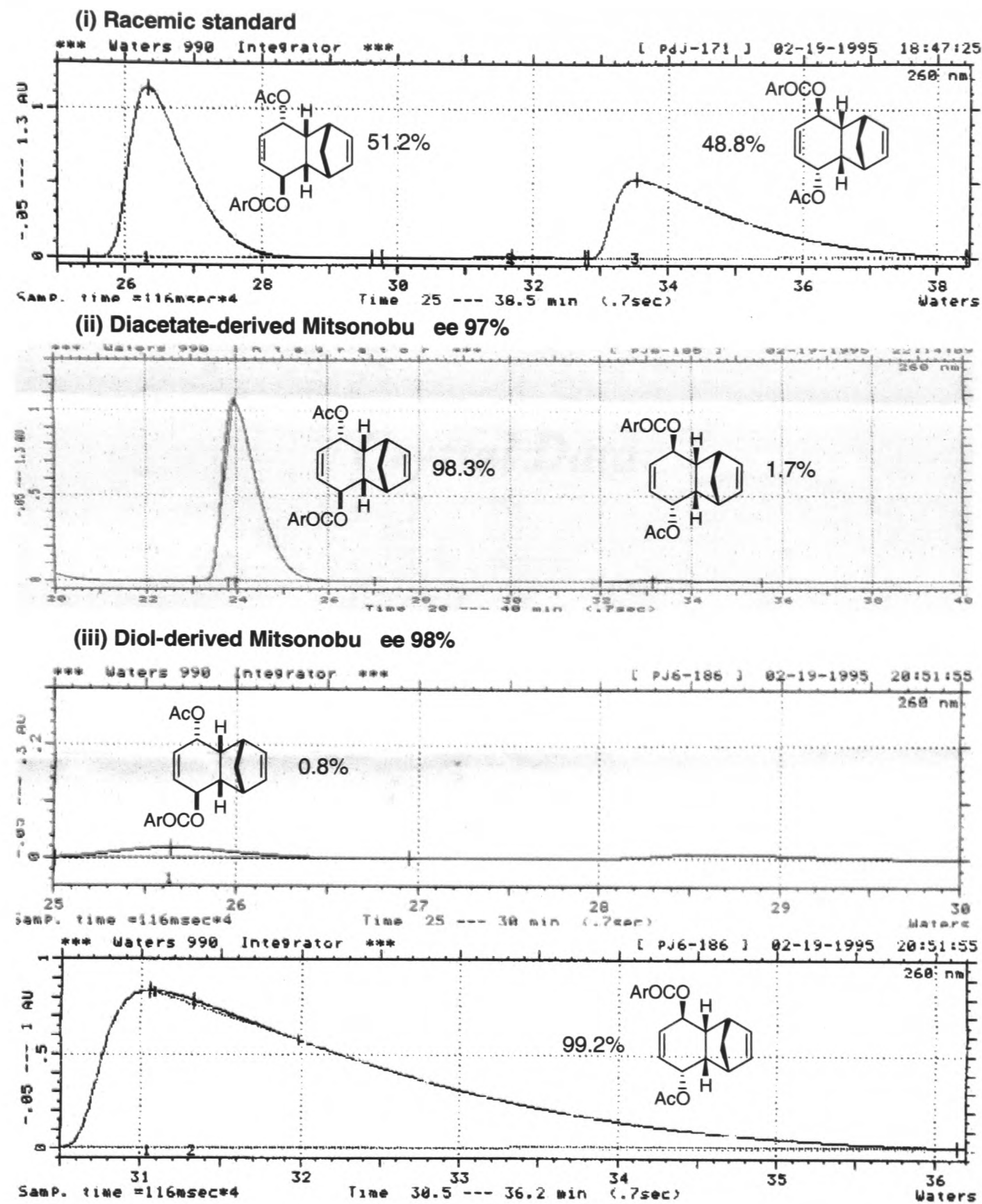


Figure 36 Chiral HPLC traces of Mitsunobu product 366

Appendix II

Crystal Data

PRINTCIF

1

19 Jun 2001

Acta Cryst. (1999): C55, 000-000

ENTER SECTION TITLE

FIRST AUTHORS NAME

FIRST AUTHORS ADDRESS. E-mail: enter email address

Abstract

ENTER ABSTRACT

Comment

ENTER TEXT

Experimental

ENTER EXPERIMENTAL SECTION

Crystal data $\text{C}_{10}\text{H}_{11}\text{NO}_3$ $M_r = 193.20$

Monoclinic

 $P2_1/n$ $a = 7.551(4) \text{ \AA}$ $b = 23.367(3) \text{ \AA}$ $c = 5.612(5) \text{ \AA}$ $\beta = 111.25(6)^\circ$ $V = 922.7(9) \text{ \AA}^3$ $Z = 4$ $D_x = 1.391 \text{ Mg m}^{-3}$ D_m not measuredMo $K\alpha$ radiation $\lambda = 0.71069 \text{ \AA}$

Cell parameters from 21 reflections

 $\theta = 7.2\text{--}9.2^\circ$ $\mu = 0.104 \text{ mm}^{-1}$ $T = 293(2) \text{ K}$

Plate

Colourless

 $0.45 \times 0.38 \times 0.08 \text{ mm}$

PRINTCIF

2

Data collection

Rigaku RAXIS diffractometer	$R_{\text{int}} = 0.047$
103 x 3 degree phi scans	$\theta_{\text{max}} = 25.06^\circ$
Absorption correction: none	$h = -8 \rightarrow 8$
11748 measured reflections	$k = -27 \rightarrow 0$
1520 independent reflections	$l = 0 \rightarrow 6$
1303 reflections with	every 0 reflections
$>2\sigma(I)$	intensity decay: none

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0533P)^2 + 0.2561P]$
$R(F) = 0.0390$	where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.1121$	$(\Delta/\sigma)_{\text{max}} = 0.001$
$S = 1.048$	$\Delta\rho_{\text{max}} = 0.293 \text{ e } \text{\AA}^{-3}$
1520 reflections	$\Delta\rho_{\text{min}} = -0.160 \text{ e } \text{\AA}^{-3}$
136 parameters	Extinction correction: <i>SHELXL</i>
H atoms treated by a mixture of independent	Extinction coefficient: 0.086(15)
and constrained refinement	Scattering factors from <i>International Tables</i>
	for <i>Crystallography</i> (Vol. C)

The data were collected using the RAXIS in 103 x 3 degree phi oscillations of 10 minutes per exposure. The structure was solved by direct methods, H atoms bonded to C were included in calculated positions, and those bonded to N and O were found by difference Fourier methods and refined isotropically. The non-H atoms were refined anisotropically.

Data collection: MSC RAXIS11 Control. Cell refinement: DENZO (Otwinowski, Z. 1988). Data reduction: DENZO (Otwinowski, Z. 1988). Program(s) used to solve structure: *SHELXS86* (Sheldrick, 1985). Program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997). Software used to prepare material for publication: *teXsan* (MSC, 1995).

ENTER ACKNOWLEDGEMENTS

Supplementary data for this paper are available from the IUCr electronic archives (Reference: PRINTCIF). Services for accessing these data are described at the back of the journal.

References

ENTER OTHER REFERENCES

Molecular Structure Corporation. (1995). *teXsan*. Single Crystal Structure Analysis Software. Version 1.7. MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA.
 Altomare, A., Casciarano, M., Giacovazzo, C., Guagliardi, A. (1993). *J. Appl. Cryst.* **26**, 343.

ENTER FIGURE CAPTIONS

ENTER TABLE LEGENDS

Supplementary data

The tables of data shown below are not normally printed in *Acta Cryst. Section C* but the data will be available electronically *via* the online contents pages at

<http://journals.iucr.org/c/journalhomepage.html>

Specific tables may be included in the printed manuscript at the discretion of the Co-editor. If you wish to include any of the following tables in your paper, please state which tables are required in the _publ_contact_letter field of the CIF. In the case of tables of atomic coordinates, please state whether you wish the coordinates of any H atoms to be included.

Table S1. Fractional atomic coordinates and equivalent isotropic displacement parameters ($\text{\AA}^2$)

$$U_{eq} = (1/3)\Sigma_i \Sigma_j U^{ij} a^i a^j a_i a_j.$$

	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{eq}
O1	0.37167 (15)	0.97717 (5)	0.1595 (2)	0.0479 (4)
O2	0.54269 (16)	0.90840 (5)	0.0638 (2)	0.0490 (4)
O3	1.01331 (19)	0.94230 (6)	0.8281 (2)	0.0549 (4)
H3O	1.127 (4)	0.9529 (10)	0.901 (5)	0.077 (8)
N1	0.6679 (2)	0.95085 (7)	0.4371 (3)	0.0470 (4)
H1N	0.663 (3)	0.9701 (9)	0.564 (4)	0.056 (6)
C1	0.5179 (2)	0.94878 (7)	0.2208 (3)	0.0394 (4)
C2	0.7338 (2)	0.88616 (8)	0.1772 (3)	0.0500 (5)
H2A	0.8169	0.9036	0.1004	0.060
H2B	0.7353	0.8460	0.1565	0.060
C3	0.7948 (2)	0.90233 (7)	0.4601 (3)	0.0445 (5)
H3	0.7627	0.8713	0.5548	0.053
C4	1.0016 (2)	0.91849 (7)	0.5897 (3)	0.0442 (4)
H4	1.0350	0.9478	0.4881	0.053
C5	1.1309 (2)	0.86694 (7)	0.6220 (3)	0.0393 (4)
C6	1.1439 (2)	0.82500 (8)	0.8021 (3)	0.0480 (5)
H6	1.0678	0.8273	0.9001	0.058
C7	1.2689 (3)	0.77970 (8)	0.8376 (4)	0.0561 (5)
H7	1.2770	0.7520	0.9600	0.067
C8	1.3816 (3)	0.77554 (8)	0.6928 (4)	0.0576 (5)
H8	1.4663	0.7454	0.7185	0.069
C9	1.3667 (3)	0.81608 (9)	0.5101 (4)	0.0570 (5)
H9	1.4468	0.8130	0.4096	0.068
C10	1.2424 (2)	0.86163 (8)	0.4746 (3)	0.0482 (5)
H10	1.2338	0.8889	0.3503	0.058

Table S2. Anisotropic displacement parameters ($\text{\AA}^2$)

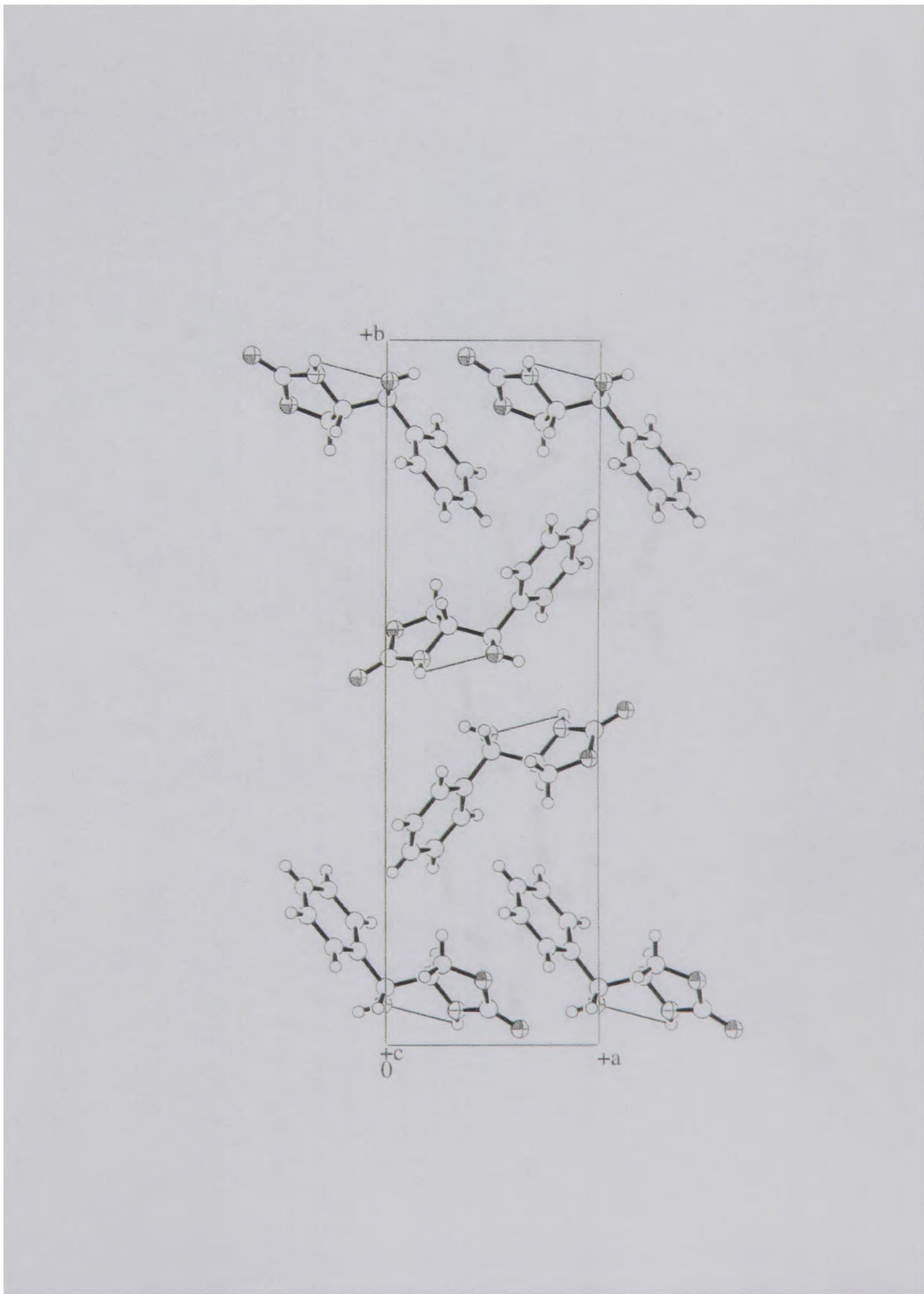
	<i>U</i> ₁₁	<i>U</i> ₂₂	<i>U</i> ₃₃	<i>U</i> ₁₂	<i>U</i> ₁₃	<i>U</i> ₂₃
O1	0.0344 (7)	0.0548 (8)	0.0464 (7)	0.0050 (5)	0.0048 (5)	−0.0024 (5)
O2	0.0419 (7)	0.0522 (7)	0.0418 (7)	0.0047 (5)	0.0020 (6)	−0.0100 (5)
O3	0.0377 (8)	0.0653 (9)	0.0522 (8)	0.0029 (6)	0.0051 (6)	−0.0221 (6)
N1	0.0351 (8)	0.0572 (9)	0.0394 (8)	0.0092 (6)	0.0022 (7)	−0.0110 (7)
C1	0.0338 (9)	0.0421 (9)	0.0380 (9)	−0.0013 (7)	0.0079 (7)	−0.0017 (6)
C2	0.0423 (10)	0.0530 (11)	0.0466 (10)	0.0086 (8)	0.0062 (8)	−0.0089 (8)
C3	0.0379 (9)	0.0445 (9)	0.0457 (10)	0.0033 (7)	0.0086 (8)	−0.0026 (7)
C4	0.0377 (9)	0.0445 (9)	0.0453 (10)	0.0021 (7)	0.0089 (8)	−0.0029 (7)
C5	0.0330 (9)	0.0414 (9)	0.0373 (9)	−0.0007 (6)	0.0053 (7)	−0.0028 (6)
C6	0.0471 (10)	0.0337 (11)	0.0452 (10)	0.0006 (8)	0.0170 (8)	0.0013 (7)
C7	0.0618 (12)	0.0443 (10)	0.0537 (11)	0.0049 (8)	0.0108 (10)	0.0075 (8)
C8	0.0456 (10)	0.0490 (11)	0.0671 (13)	0.0099 (8)	0.0070 (10)	−0.0072 (9)
C9	0.0425 (10)	0.0659 (12)	0.0651 (12)	0.0017 (9)	0.0226 (9)	−0.0097 (10)
C10	0.0437 (10)	0.0528 (11)	0.0470 (10)	−0.0019 (8)	0.0150 (8)	0.0026 (7)

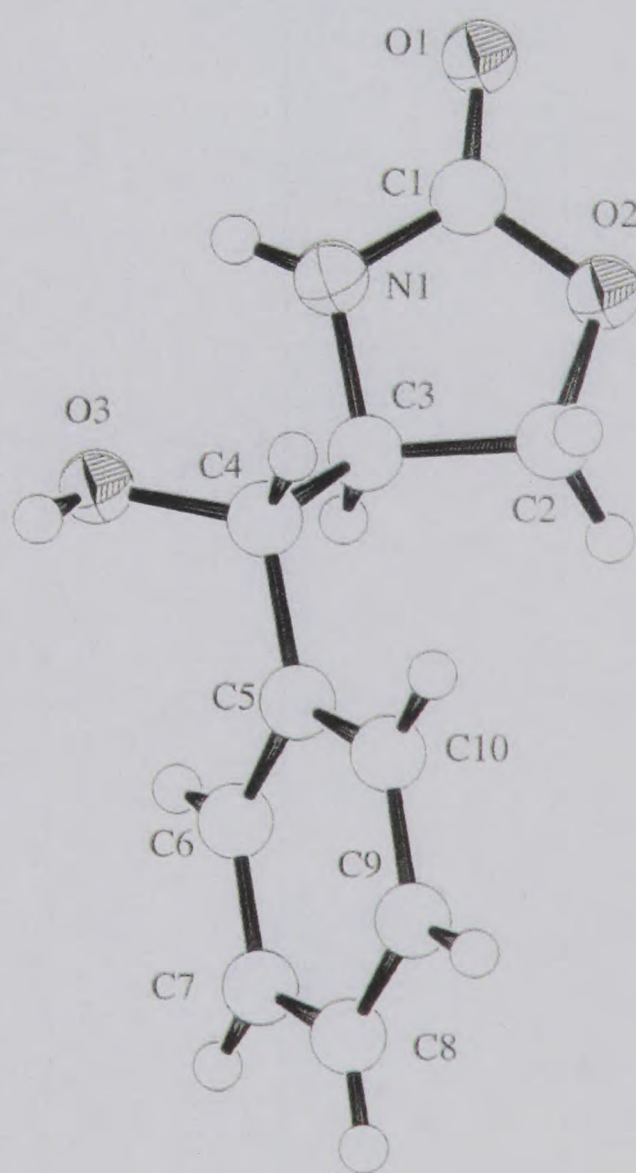
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Table S3. Geometric parameters ($\text{\AA}$, $^\circ$)

O1—C1	1.226 (2)	C4—C5	1.320 (2)
O2—C1	1.349 (2)	C4—H4	0.9800
O2—C2	1.446 (2)	C5—C10	1.383 (3)
O3—C4	1.422 (2)	C5—C6	1.385 (2)
O3—H3O	0.84 (3)	C6—C7	1.384 (3)
N1—C1	1.327 (3)	C6—H6	0.9300
N1—C3	1.460 (2)	C7—C8	1.373 (3)
N1—H1N	0.85 (2)	C7—H7	0.9300
C2—C3	1.531 (3)	C8—C9	1.371 (3)
C2—H2A	0.9700	C8—H8	0.9300
C2—H2B	0.9700	C9—C10	1.385 (3)
C3—C4	1.512 (2)	C9—H9	0.9300
C3—H3	0.9800	C10—H10	0.9300
C1—O2—C2	108.43 (13)	C3—C4—C5	111.49 (14)
C4—O3—H3O	106.0 (16)	O3—C4—H4	109.4
C1—N1—C3	111.58 (14)	C3—C4—H4	109.4
C1—N1—H1N	120.1 (14)	C5—C4—H4	109.4
C3—N1—H1N	124.1 (14)	C10—C5—C6	118.38 (16)
O1—C1—N1	128.34 (16)	C10—C5—C4	120.27 (15)
O1—C1—O2	121.26 (16)	O6—C5—C4	121.34 (15)
N1—C1—O2	110.39 (14)	C7—C6—C5	120.70 (17)
O2—C2—C3	104.19 (14)	C7—C6—H6	119.6
O2—C2—H2A	110.9	C5—C6—H6	119.6
C3—C2—H2A	110.9	C8—C7—C6	120.23 (18)
O2—C2—H2B	110.9	C8—C7—H7	119.9
C3—C2—H2B	110.9	C6—C7—H7	119.9
H2A—C2—H2B	108.9	C9—C8—C7	119.68 (18)
N1—C3—C4	112.27 (14)	C9—C8—H8	120.2
N1—C3—C2	99.12 (14)	C7—C8—H8	120.2
C4—C3—C2	115.52 (15)	C8—C9—C10	120.28 (18)
N1—C3—H3	109.8	C8—C9—H9	119.9
C4—C3—H3	109.8	C10—C9—H9	119.9
O2—C3—H3	109.8	C5—C10—C9	120.71 (17)
O3—C4—C3	104.58 (14)	C5—C10—H10	119.6
O3—C4—C5	112.32 (14)	C9—C10—H10	119.6
C3—N1—C1—O1	167.75 (16)	O3—C4—C5—C10	-134.77 (17)
C3—N1—C1—O2	-11.1 (2)	C3—C4—C5—C10	108.22 (18)
C2—O2—C1—O1	174.81 (15)	O3—C4—C5—C6	-43.7 (2)
C2—O2—C1—N1	-6.25 (19)	C3—C4—C5—C6	-73.3 (2)
C1—O2—C2—C3	19.70 (18)	C10—C5—C6—C7	1.6 (3)
C1—N1—C3—C4	144.40 (16)	C4—C5—C6—C7	-176.94 (16)
C1—N1—C3—C2	21.90 (19)	C5—C6—C7—C8	-0.5 (3)
O2—C2—C3—N1	-23.89 (17)	C6—C7—C8—C9	-0.9 (3)
O2—C2—C3—C4	-144.02 (15)	C7—C8—C9—C10	1.2 (3)
N1—C3—C4—O3	55.98 (18)	C6—C5—C10—C9	-1.3 (3)
C2—C3—C4—O3	168.64 (14)	C4—C5—C10—C9	177.22 (16)
N1—C3—C4—C5	177.60 (14)	C8—C9—C10—C5	-0.1 (3)
O2—C3—C4—C5	-89.74 (19)		





Hydrogen bonds with H...A < r(A) + 2.000 Angstroms and <DHA > 110 deg.					
D-H	d(D-H)	d(H...A)	<DHA	d(D...A)	A
O3-H3O	0.842	1.975	163.25	2.792	O1 [x+1, y, z+1]
N1-H1N	0.852	2.073	173.32	2.921	O1 [-x+1, -y+2, -z+1]

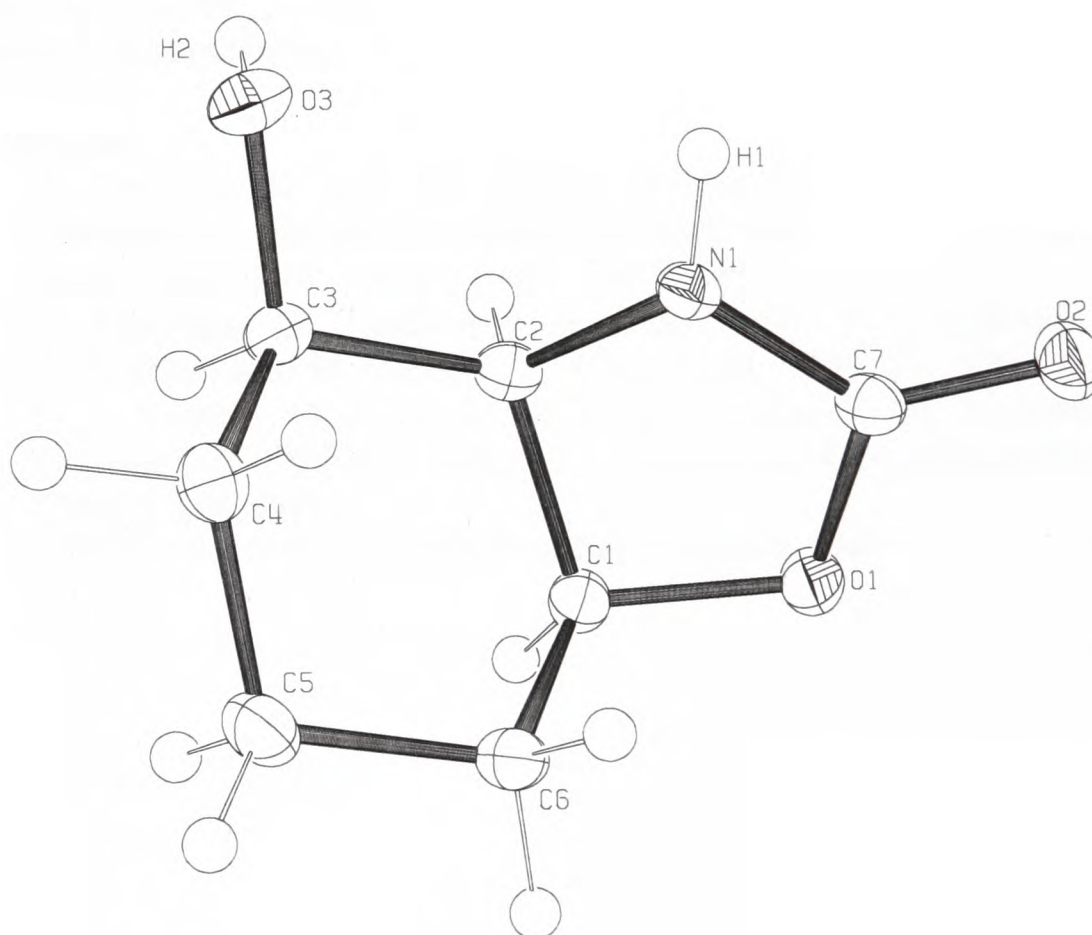
Inorganic Chemistry Crystallography Service

Single-crystal X-ray diffraction report for C₇H₁₁NO₃

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Crystals of **ARC172** were grown by evaporation from acetone. A single crystal having dimensions approximately 0.10 x 0.15 x 0.30 mm was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150K 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 package¹.

Examination of the systematic absences of the intensity data showed the space group to be *P* 2₁/c. The structure was solved using the direct-methods program SIR92², which located all non-hydrogen atoms. Subsequent full-matrix least-squares refinement was carried out using the CRYSTALS program suite³. Coordinates and anisotropic thermal parameters of all non-hydrogen atoms were refined. The N-H and O-H hydrogen atoms were located in a difference Fourier map and their coordinates and isotropic thermal parameters subsequently refined. C-H hydrogen atoms were positioned geometrically after each cycle of refinement. A 3-term Chebychev polynomial weighting scheme

was applied. Refinement converged satisfactorily to give $R = 0.0355$, $wR = 0.0423$.

Attached is a thermal ellipsoid plot (ORTEP-3⁴) at 40% 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.

Comment:

The N-H and O-H groups form hydrogen bonds to carbonyl O atoms of adjacent molecules. These link the molecules to form infinite sheets running parallel to the *bc* plane. The N···O and O···O distances are 2.843(1) and 2.958(2) Å respectively.

References:

- 1 Z. Otwinowski and W. Minor, *Processing of X-ray Diffraction Data Collected in Oscillation Mode, Methods Enzymol.*, 1997, **276**, Eds C. W. Carter and R. M. Sweet, Academic Press.
- 2 A. Altomare, G. Cascarano, G. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori and M. Camalli, *J. Appl. Cryst.* 1994, **27**, 435.
- 3 D. J. Watkin, C. K. Prout, J. R. Carruthers, P. W. Betteridge and R. I. Cooper, CRYSTALS issue 11, Chemical Crystallography Laboratory, Oxford, UK, 2001.
- 4 ORTEP-3 v. 1.0.2, C. K. Johnson and M. K. Burnett, 1998.

Table 1: Crystal data and refinement details

Crystal identification	ARC172
Chemical formula	C ₇ H ₁₁ NO ₃
Formula weight	157.17
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	<i>P</i> 2 ₁ / <i>c</i>
<i>a</i> (Å)	7.0929(2)
<i>b</i> (Å)	12.6011(4)
<i>c</i> (Å)	8.5910(3)
α (°)	90
β (°)	105.3757(14)
γ (°)	90
Cell volume (Å ³)	740.7
<i>Z</i>	4
Calculated density (Mg/m ³)	1.410
Absorption coefficient (mm ⁻¹)	0.110
<i>F</i> ₀₀₀	336.115
Crystal size (mm)	0.10 x 0.15 x 0.30
Description of crystal	Colourless block
Absorption correction	Semi-empirical from equivalent reflections
Transmission coefficients (min,max)	0.97, 0.99
θ range for data collection (°)	5.0 ≤ θ ≤ 27.5
Index ranges	-9 ≤ <i>h</i> ≤ 8, -16 ≤ <i>k</i> ≤ 16, -11 ≤ <i>l</i> ≤ 11
Reflections measured	5419
Unique reflections	1764
<i>R</i> _{int}	0.034
Observed reflections (<i>I</i> > 3 σ (<i>I</i>))	1291
Refinement method	Full-matrix least-squares on <i>F</i>
Parameters refined	108
Weighting scheme	Chebyshev 3-term polynomial
Goodness of fit	0.9057
<i>R</i>	0.0355
<i>wR</i>	0.0423
Residual electron density (min,max) (eÅ ⁻³)	-0.25, 0.28

Table 2: Atomic coordinates and equivalent isotropic thermal parameters (Å²) of non-hydrogen atoms

Atom	x	y	z	U _{equiv}
O(1)	0.84380(14)	0.56450(8)	0.82636(12)	0.0206
O(2)	0.97862(15)	0.60937(8)	0.62654(12)	0.0233
O(3)	0.75091(16)	0.22111(8)	0.62372(12)	0.0209
N(1)	0.85148(16)	0.44114(9)	0.64416(14)	0.0167
C(1)	0.7287(2)	0.47389(11)	0.85784(16)	0.0177
C(2)	0.81003(18)	0.38245(11)	0.77857(15)	0.0161
C(3)	0.6756(2)	0.2871(1)	0.72845(16)	0.0169
C(4)	0.4659(2)	0.31801(11)	0.64593(17)	0.0202
C(5)	0.3917(2)	0.39450(12)	0.75463(18)	0.0232
C(6)	0.5130(2)	0.49663(11)	0.78064(18)	0.0205
C(7)	0.89802(18)	0.54197(11)	0.68939(16)	0.0174

Table 3: Atomic coordinates and isotropic thermal parameters (Å²) of hydrogen atoms

Atom	x	y	z	U _{iso}
H(1)	0.901(3)	0.4135(15)	0.573(2)	0.024(4)
H(2)	0.852(4)	0.187(2)	0.689(3)	0.054(7)
H(11)	0.7379	0.4583	0.9738	0.0218
H(21)	0.9238	0.3449	0.8517	0.0192
H(31)	0.6726	0.2481	0.8291	0.0204
H(41)	0.4604	0.3534	0.5406	0.0239
H(42)	0.3820	0.2530	0.6262	0.0239
H(51)	0.4025	0.3599	0.8614	0.0284
H(52)	0.2518	0.4123	0.7026	0.0284
H(61)	0.4629	0.5450	0.8529	0.0257
H(62)	0.4992	0.5319	0.6739	0.0257

Table 4: Anisotropic thermal parameters (Å²)

Atom	U ₁₁	U ₂₂	U ₃₃	U ₂₃	U ₁₃	U ₁₂
O(1)	0.0255(5)	0.0186(5)	0.0203(5)	-0.0048(4)	0.0106(4)	-0.0050(4)
O(2)	0.0238(5)	0.0231(5)	0.0255(5)	-0.0032(4)	0.0108(4)	-0.0079(4)
O(3)	0.0270(5)	0.0180(5)	0.0177(5)	-0.0019(4)	0.0058(4)	0.0049(4)
N(1)	0.0172(5)	0.0177(6)	0.0175(6)	-0.0030(4)	0.0086(4)	-0.0016(4)
C(1)	0.0210(6)	0.0166(6)	0.0170(6)	-0.0011(5)	0.0076(5)	-0.0016(5)
C(2)	0.0149(6)	0.0184(6)	0.0147(6)	0.0008(5)	0.0033(5)	0.0025(5)
C(3)	0.0204(6)	0.0150(6)	0.0156(6)	0.0001(5)	0.0055(5)	0.0021(5)
C(4)	0.0175(6)	0.0216(7)	0.0206(7)	-0.0003(6)	0.0036(5)	-0.0026(5)
C(5)	0.0165(6)	0.0262(7)	0.0283(7)	0.0021(6)	0.0085(5)	0.0005(5)
C(6)	0.0206(6)	0.0192(7)	0.0246(7)	0.0018(5)	0.0108(6)	0.0036(5)
C(7)	0.0143(6)	0.0207(7)	0.0172(6)	-0.0035(5)	0.0042(5)	-0.0014(5)

Table 5: Bond lengths (Å)

O(1) - C(1)	1.4700(16)
O(1) - C(7)	1.3614(17)
O(2) - C(7)	1.2261(17)
O(3) - C(3)	1.4286(16)
O(3) - H(2)	0.89(3)
N(1) - C(2)	1.4652(17)
N(1) - C(7)	1.3439(18)
N(1) - H(1)	0.86(2)
C(1) - C(2)	1.5274(19)
C(1) - C(6)	1.524(2)
C(2) - C(3)	1.5232(19)
C(3) - C(4)	1.5195(18)
C(4) - C(5)	1.529(2)
C(5) - C(6)	1.531(2)

Note – geometrically-positioned H atoms have been excluded

Table 6: Bond angles (°)

C(1) - O(1) - C(7)	107.2(1)
C(3) - O(3) - H(2)	104.6(16)
C(2) - N(1) - C(7)	109.55(11)
C(2) - N(1) - H(1)	124.4(13)
C(7) - N(1) - H(1)	118.3(13)
O(1) - C(1) - C(2)	102.1(1)
O(1) - C(1) - C(6)	108.44(11)
C(2) - C(1) - C(6)	113.71(11)
N(1) - C(2) - C(1)	98.6(1)
N(1) - C(2) - C(3)	114.63(11)
C(1) - C(2) - C(3)	116.04(11)
O(3) - C(3) - C(2)	109.07(11)
O(3) - C(3) - C(4)	109.79(11)
C(2) - C(3) - C(4)	113.06(11)
C(3) - C(4) - C(5)	109.23(11)
C(4) - C(5) - C(6)	110.37(11)
C(1) - C(6) - C(5)	111.45(11)
O(1) - C(7) - O(2)	120.51(12)
O(1) - C(7) - N(1)	110.06(12)
O(2) - C(7) - N(1)	129.42(13)

Note – geometrically-positioned H atoms have been excluded

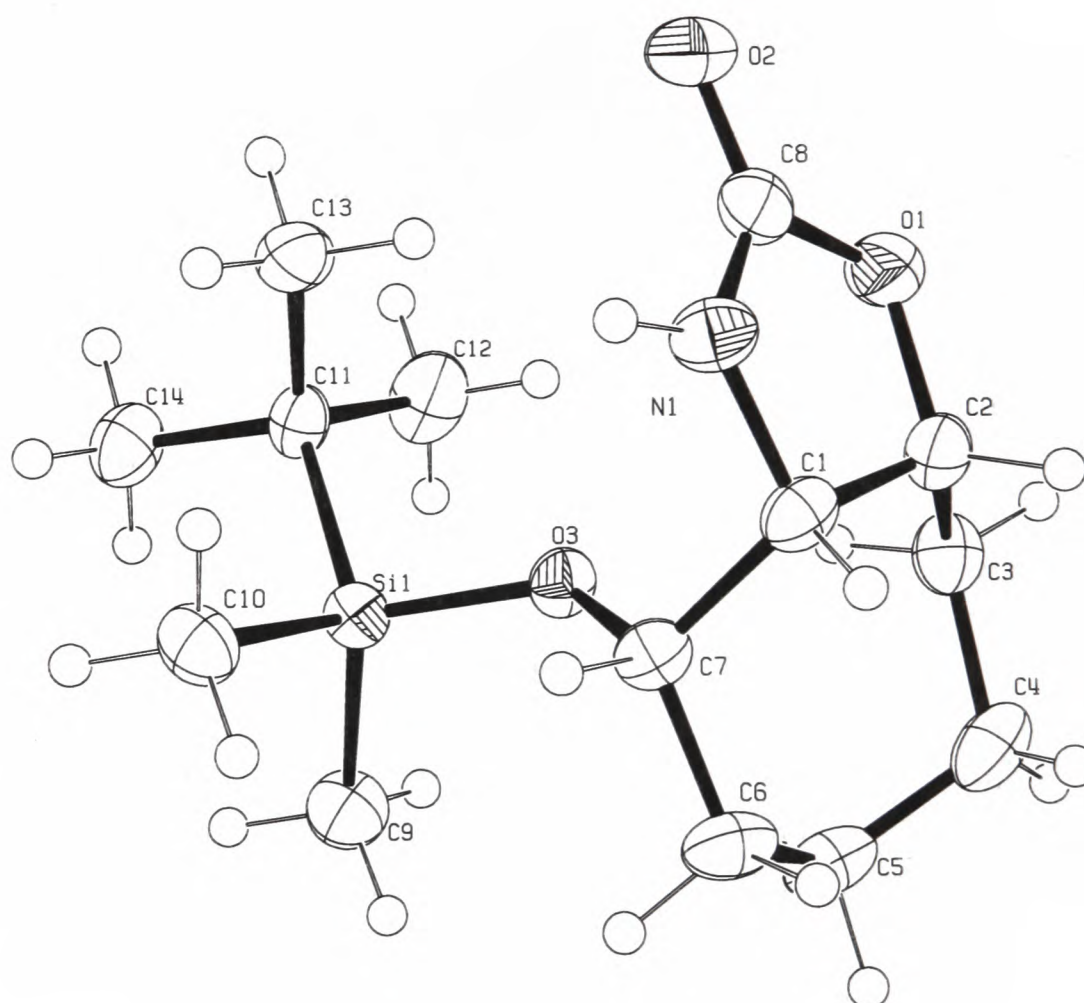
Inorganic Chemistry Crystallography Service

Single-crystal X-ray diffraction report for C₁₄H₂₇NO₃Si (ARC343)

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Crystals of **ARC343** were grown by evaporation from chloroform. A single crystal having dimensions approximately 0.08 x 0.30 x 0.32 mm was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150K 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 package¹.

Examination of the systematic absences of the intensity data showed the space group to be *P b c a*. The structure was solved using the direct-methods program SIR92², which located all non-hydrogen atoms. Subsequent full-matrix least-squares refinement was carried out using the CRYSTALS program suite³. Coordinates and anisotropic thermal parameters of all non-hydrogen atoms were refined. The NH hydrogen atom was located in a difference Fourier map and its coordinates and isotropic thermal parameter subsequently refined. Other

hydrogen atoms were positioned geometrically after each cycle of refinement. A 3-term Chebychev polynomial weighting scheme was applied. Refinement converged satisfactorily to give $R = 0.0367$, $wR = 0.0390$.

Attached is a thermal ellipsoid plot (ORTEP-3⁴) at 40% 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.

Comment:

The molecules are linked by hydrogen bonds between the NH group and the carbonyl O of a neighbouring molecule ($N(1) \cdots O(2)'$ 2.941(3) Å) to form centrosymmetric dimers.

References:

- 1 Z. Otwinowski and W. Minor, *Processing of X-ray Diffraction Data Collected in Oscillation Mode, Methods Enzymol.*, 1997, **276**, Eds C. W. Carter and R. M. Sweet, Academic Press.
- 2 A. Altomare, G. Cascarano, G. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori and M. Camalli, *J. Appl. Cryst.* 1994, **27**, 435.
- 3 D. J. Watkin, C. K. Prout, J. R. Carruthers, P. W. Betteridge and R. I. Cooper, CRYSTALS issue 11, Chemical Crystallography Laboratory, Oxford, UK, 2001.
- 4 ORTEP-3 v. 1.0.2, C. K. Johnson and M. K. Burnett, 1998.

Table 1: Crystal data and refinement details

Crystal identification	ARC343
Chemical formula	C ₁₄ H ₂₇ NO ₃ Si
Formula weight	285.46
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Orthorhombic
Space group	<i>P b c a</i>
<i>a</i> (Å)	11.2506(3)
<i>b</i> (Å)	11.8138(3)
<i>c</i> (Å)	24.1751(7)
α (°)	90
β (°)	90
γ (°)	90
Cell volume (Å ³)	3213.2
Z	8
Calculated density (Mg/m ³)	1.180
Absorption coefficient (mm ⁻¹)	0.151
<i>F</i> ₀₀₀	1248.847
Crystal size (mm)	0.08 x 0.30 x 0.32
Description of crystal	Colourless plate
Absorption correction	Semi-empirical from equivalent reflections
Transmission coefficients (min,max)	0.95, 0.99
θ range for data collection (°)	$5.0 \leq \theta \leq 27.5$
Index ranges	$0 \leq h \leq 14, 0 \leq k \leq 15, 0 \leq l \leq 31$
Reflections measured	29476
Unique reflections	4097
<i>R</i> _{int}	0.091
Observed reflections (<i>I</i> > 3σ(<i>I</i>))	1856
Refinement method	Full-matrix least-squares on <i>F</i>
Parameters refined	176
Weighting scheme	Chebychev 3-term polynomial
Goodness of fit	1.0813
<i>R</i>	0.0367
<i>wR</i>	0.0390
Residual electron density (min,max) (eÅ ⁻³)	-0.21, 0.20

Table 2: Atomic coordinates and equivalent isotropic thermal parameters (Å²) of non-hydrogen atoms

Atom	x	y	z	U _{equiv}
N(1)	0.58426(19)	0.37225(18)	0.51866(8)	0.0344
C(1)	0.6428(2)	0.28855(19)	0.55302(9)	0.0306
C(2)	0.5897(2)	0.1789(2)	0.5290(1)	0.0337
C(3)	0.5449(2)	0.0889(2)	0.5682(1)	0.0365
C(4)	0.6388(2)	0.0475(2)	0.60893(11)	0.0423
C(5)	0.6464(2)	0.1178(2)	0.66128(11)	0.0415
C(6)	0.6947(2)	0.2371(2)	0.6531(1)	0.0389
C(7)	0.62471(19)	0.3144(2)	0.61438(9)	0.0280
C(8)	0.4925(2)	0.3304(2)	0.49040(9)	0.0341
O(1)	0.48976(16)	0.21634(14)	0.49492(7)	0.0392
O(2)	0.41841(16)	0.38168(15)	0.46296(7)	0.0412
O(3)	0.50015(13)	0.31390(13)	0.62639(6)	0.0270
Si(1)	0.43170(5)	0.39396(5)	0.67247(2)	0.0262
C(9)	0.4301(2)	0.3210(2)	0.7408(1)	0.0398
C(10)	0.5077(2)	0.5334(2)	0.6793(1)	0.0366
C(11)	0.2763(2)	0.41227(18)	0.64509(9)	0.0291
C(12)	0.2196(2)	0.2969(2)	0.63339(13)	0.0486
C(13)	0.2817(2)	0.4797(2)	0.5909(1)	0.0390
C(14)	0.2002(2)	0.4763(2)	0.68712(11)	0.0415

Table 3: Atomic coordinates and isotropic thermal parameters (Å²) of hydrogen atoms

Atom	x	y	z	U _{iso}
H(1)	0.591(3)	0.444(2)	0.5236(11)	0.048(8)
H(11)	0.7316	0.2850	0.5521	0.0367
H(21)	0.6567	0.1396	0.5098	0.0405
H(31)	0.4768	0.1209	0.5897	0.0438
H(32)	0.5168	0.0229	0.5459	0.0438
H(41)	0.6194	-0.0322	0.6195	0.0507
H(42)	0.7179	0.0496	0.5901	0.0507
H(51)	0.6996	0.0775	0.6879	0.0498
H(52)	0.5648	0.1239	0.6773	0.0498
H(61)	0.6975	0.2744	0.6902	0.0467
H(62)	0.7771	0.2302	0.6380	0.0467
H(71)	0.6580	0.3915	0.6216	0.0336
H(91)	0.3886	0.3697	0.7686	0.0478
H(92)	0.5136	0.3069	0.7532	0.0478
H(93)	0.3873	0.2472	0.7373	0.0478
H(101)	0.4651	0.5806	0.7074	0.0440
H(102)	0.5917	0.5213	0.6915	0.0440
H(103)	0.5071	0.5731	0.6428	0.0440
H(121)	0.1372	0.3081	0.6189	0.0583
H(122)	0.2164	0.2518	0.6684	0.0583
H(123)	0.2682	0.2555	0.6053	0.0583
H(131)	0.1995	0.4899	0.5760	0.0468
H(132)	0.3181	0.5555	0.5981	0.0468
H(133)	0.3311	0.4377	0.5633	0.0468
H(141)	0.1179	0.4856	0.6722	0.0498
H(142)	0.1971	0.4327	0.7225	0.0498
H(143)	0.2358	0.5525	0.6941	0.0498

Table 4: Anisotropic thermal parameters (Å²)

Atom	U ₁₁	U ₂₂	U ₃₃	U ₂₃	U ₁₃	U ₁₂
N(1)	0.0354(11)	0.0325(12)	0.035(1)	0.0081(9)	-0.0019(9)	-0.002(1)
C(1)	0.0250(11)	0.0324(12)	0.0342(12)	0.0067(11)	0.004(1)	0.003(1)
C(2)	0.0335(13)	0.0337(12)	0.0340(12)	-0.0013(11)	0.003(1)	0.0079(11)
C(3)	0.0391(14)	0.0310(13)	0.0393(13)	-0.0022(11)	0.004(1)	-0.0003(11)
C(4)	0.0397(14)	0.0335(13)	0.0536(16)	0.0131(12)	0.0081(13)	0.0098(12)
C(5)	0.0306(12)	0.0485(15)	0.0453(14)	0.0170(13)	-0.0023(11)	0.0070(12)
C(6)	0.0264(12)	0.0523(16)	0.0381(13)	0.0096(12)	-0.0058(11)	0.0021(12)
C(7)	0.0185(11)	0.0310(12)	0.0344(12)	0.002(1)	-0.001(1)	-0.004(1)
C(8)	0.0401(14)	0.0361(13)	0.0261(12)	0.0024(11)	0.0052(11)	0.0029(12)
O(1)	0.047(1)	0.0338(9)	0.0373(9)	-0.0030(8)	-0.0096(8)	0.0025(8)
O(2)	0.046(1)	0.045(1)	0.0332(8)	0.0068(8)	-0.0082(8)	0.0039(9)
O(3)	0.0188(8)	0.0296(8)	0.0326(8)	-0.0024(7)	0.0007(6)	-0.0005(7)
Si(1)	0.0259(3)	0.0260(3)	0.0268(3)	0.0002(3)	0.0006(3)	-0.0018(3)
C(9)	0.0431(14)	0.0421(13)	0.0342(12)	0.0060(11)	0.0051(12)	-0.0009(13)
C(10)	0.0388(14)	0.0350(12)	0.0360(12)	-0.0040(11)	-0.0027(12)	-0.0061(11)
C(11)	0.0244(11)	0.0255(12)	0.0375(12)	-0.003(1)	0.0020(9)	0.001(1)
C(12)	0.0305(15)	0.0397(15)	0.0756(19)	-0.0084(15)	-0.0071(13)	-0.0040(12)
C(13)	0.0343(13)	0.0476(15)	0.0350(12)	-0.0003(12)	-0.0029(11)	0.0110(12)
C(14)	0.0359(13)	0.0420(14)	0.0465(15)	0.0001(12)	0.0085(12)	0.0079(12)

Table 5: Bond lengths (Å)

N(1) - C(1)	1.450(3)
N(1) - C(8)	1.333(3)
N(1) - H(1)	0.86(3)
C(1) - C(2)	1.540(3)
C(1) - C(7)	1.528(3)
C(2) - C(3)	1.510(3)
C(2) - O(1)	1.463(3)
C(3) - C(4)	1.524(4)
C(4) - C(5)	1.516(4)
C(5) - C(6)	1.523(4)
C(6) - C(7)	1.527(3)
C(7) - O(3)	1.431(3)
C(8) - O(1)	1.353(3)
C(8) - O(2)	1.225(3)
O(3) - Si(1)	1.6518(16)
Si(1) - C(9)	1.864(2)
Si(1) - C(10)	1.863(2)
Si(1) - C(11)	1.882(2)
C(11) - C(12)	1.531(3)
C(11) - C(13)	1.535(3)
C(11) - C(14)	1.529(3)

Note – geometrically-positioned H atoms have been excluded

Table 6: Bond angles (°)

C(1) - N(1) - C(8)	113.1(2)
C(1) - N(1) - H(1)	123.6(19)
C(8) - N(1) - H(1)	120.3(20)
N(1) - C(1) - C(2)	100.45(18)
N(1) - C(1) - C(7)	111.04(18)
C(2) - C(1) - C(7)	118.79(19)
C(1) - C(2) - C(3)	119.06(19)
C(1) - C(2) - O(1)	104.87(18)
C(3) - C(2) - O(1)	108.07(19)
C(2) - C(3) - C(4)	113.6(2)
C(3) - C(4) - C(5)	113.7(2)
C(4) - C(5) - C(6)	114.8(2)
C(5) - C(6) - C(7)	116.7(2)
C(1) - C(7) - C(6)	114.0(2)
C(1) - C(7) - O(3)	109.08(17)
C(6) - C(7) - O(3)	112.19(18)
N(1) - C(8) - O(1)	110.2(2)
N(1) - C(8) - O(2)	128.4(2)
O(1) - C(8) - O(2)	121.4(2)
C(2) - O(1) - C(8)	109.24(18)
C(7) - O(3) - Si(1)	126.22(14)
O(3) - Si(1) - C(9)	109.7(1)
O(3) - Si(1) - C(10)	110.6(1)
C(9) - Si(1) - C(10)	109.52(11)
O(3) - Si(1) - C(11)	105.18(9)
C(9) - Si(1) - C(11)	110.86(11)
C(10) - Si(1) - C(11)	110.86(11)
Si(1) - C(11) - C(12)	110.46(15)
Si(1) - C(11) - C(13)	108.84(15)
C(12) - C(11) - C(13)	108.7(2)
Si(1) - C(11) - C(14)	110.08(16)
C(12) - C(11) - C(14)	109.3(2)
C(13) - C(11) - C(14)	109.44(19)

Note – geometrically-positioned atoms have been excluded

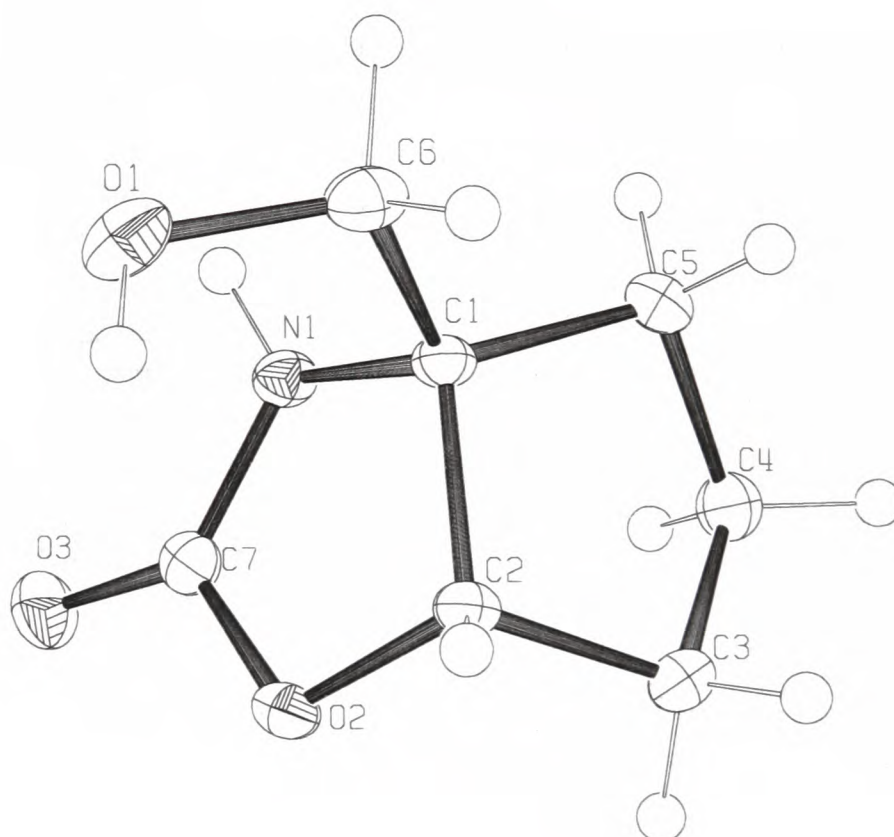
Inorganic Chemistry Crystallography Service

Single-crystal X-ray diffraction report for C₇H₁₁NO₃

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Crystals of **arc262** were grown by boundary diffusion between chloroform and acetone. A single crystal having dimensions approximately 0.20 x 0.24 x 0.40 mm was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150K 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 package¹.

Examination of the systematic absences of the intensity data showed the space group to be *P* 2₁/c. The structure was solved using the direct-methods program SIR92², which located all non-hydrogen atoms. Subsequent full-matrix least-squares refinement was carried out using the CRYSTALS program suite³. Coordinates and anisotropic thermal parameters of all non-hydrogen atoms were refined. The OH and NH hydrogen atoms were located in a difference Fourier map and their coordinates and isotropic thermal parameters were subsequently refined. Other hydrogen atoms were positioned geometrically after each cycle of refinement. A 5-term Chebychev polynomial weighting scheme was applied. Refinement converged satisfactorily to give *R* = 0.0326, *wR* = 0.0377.

Attached is a thermal ellipsoid plot (ORTEP-3⁴) at 40% 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.

Comment:

The O-H group forms a hydrogen bond to the carbonyl O atom of a neighbouring molecule (O(1)···O(3)' 2.7878(11) Å), while the N-H group forms a hydrogen bond to the hydroxyl O of a second neighbour (N(1)···O(1)" 2.8536(12) Å). These link the molecules to form infinite bilayers parallel to the crystallographic *bc* plane.

References:

- 1 Z. Otwinowski and W. Minor, *Processing of X-ray Diffraction Data Collected in Oscillation Mode, Methods Enzymol.*, 1997, **276**, Eds C. W. Carter and R. M. Sweet, Academic Press.
- 2 A. Altomare, G. Cascarano, G. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori and M. Camalli, *J. Appl. Cryst.* 1994, **27**, 435.
- 3 D. J. Watkin, C. K. Prout, J. R. Carruthers, P. W. Betteridge and R. I. Cooper, CRYSTALS issue 11, Chemical Crystallography Laboratory, Oxford, UK, 2001.
- 4 ORTEP-3 v. 1.0.2, C. K. Johnson and M. K. Burnett, 1998.

Table 1: Crystal data and refinement details

Crystal identification	ARC262
Chemical formula	C ₇ H ₁₁ NO ₃
Formula weight	157.17
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	<i>P</i> 2 ₁ / <i>c</i>
<i>a</i> (Å)	8.1765(2)
<i>b</i> (Å)	7.0870(2)
<i>c</i> (Å)	12.7097(4)
α (°)	90
β (°)	96.3440(14)
γ (°)	90
Cell volume (Å ³)	732.0
<i>Z</i>	4
Calculated density (Mg/m ³)	1.426
Absorption coefficient (mm ⁻¹)	0.112
<i>F</i> ₀₀₀	336.115
Crystal size (mm)	0.20 x 0.24 x 0.40
Description of crystal	Colourless block
Absorption correction	Semi-empirical from equivalent reflections
Transmission coefficients (min,max)	0.96, 0.98
θ range for data collection (°)	5.0 ≤ θ ≤ 27.5
Index ranges	-10 ≤ <i>h</i> ≤ 10, 0 ≤ <i>k</i> ≤ 9, 0 ≤ <i>l</i> ≤ 16
Reflections measured	7884
Unique reflections	1797
<i>R</i> _{int}	0.034
Observed reflections (<i>I</i> > 3 σ (<i>I</i>))	1345
Refinement method	Full-matrix least-squares on <i>F</i>
Parameters refined	108
Weighting scheme	Chebychev 5-term polynomial
Goodness of fit	1.0478
<i>R</i>	0.0326
<i>wR</i>	0.0377
Residual electron density (min,max) (eÅ ⁻³)	-0.19, 0.36

Table 2: Atomic coordinates and equivalent isotropic thermal parameters (Å²) of non-hydrogen atoms

Atom	x	y	z	U _{equiv}
C(1)	0.29282(12)	0.30954(14)	0.59812(7)	0.0153
C(2)	0.27870(12)	0.29741(14)	0.71893(8)	0.0156
C(3)	0.11014(13)	0.21121(16)	0.73029(8)	0.0198
C(4)	0.01213(13)	0.23213(16)	0.62105(8)	0.0220
C(5)	0.14362(14)	0.20011(16)	0.54605(8)	0.0220
C(6)	0.45596(14)	0.24002(15)	0.56476(8)	0.0205
O(1)	0.59076(9)	0.35798(12)	0.60324(6)	0.0231
N(1)	0.27393(11)	0.51247(12)	0.58133(7)	0.0163
C(7)	0.28942(11)	0.60972(15)	0.67214(8)	0.0168
O(2)	0.28875(9)	0.4918(1)	0.75607(6)	0.0194
O(3)	0.3017(1)	0.78054(11)	0.68536(7)	0.0243

Table 3: Atomic coordinates and isotropic thermal parameters (Å²) of hydrogen atoms

Atom	x	y	z	U _{iso}
H(1)	0.624(2)	0.327(2)	0.6676(14)	0.038(4)
H(2)	0.2985(19)	0.566(2)	0.5232(12)	0.032(4)
H(21)	0.3653	0.2193	0.7601	0.0188
H(31)	0.0548	0.2807	0.7850	0.0240
H(32)	0.1215	0.0751	0.7505	0.0240
H(41)	-0.0371	0.3610	0.6115	0.0264
H(42)	-0.0770	0.1352	0.6100	0.0264
H(51)	0.1697	0.0628	0.5406	0.0263
H(52)	0.1069	0.2511	0.4739	0.0263
H(61)	0.4772	0.1096	0.5931	0.0250
H(62)	0.4476	0.2372	0.4857	0.0250

Table 4: Anisotropic thermal parameters (Å²)

Atom	U ₁₁	U ₂₂	U ₃₃	U ₂₃	U ₁₃	U ₁₂
C(1)	0.0192(5)	0.0155(5)	0.0113(4)	0.0002(3)	0.0029(3)	0.0003(4)
C(2)	0.0183(5)	0.0164(5)	0.0121(4)	-0.0004(4)	0.0020(3)	0.0010(4)
C(3)	0.0212(5)	0.0219(5)	0.0169(5)	0.0012(4)	0.0051(4)	-0.0032(4)
C(4)	0.0186(5)	0.0265(6)	0.0207(5)	-0.0020(4)	0.0011(4)	-0.0051(4)
C(5)	0.0268(5)	0.0240(5)	0.0151(5)	-0.0050(4)	0.0016(4)	-0.0058(4)
C(6)	0.0236(5)	0.0205(5)	0.0185(5)	0.0002(4)	0.0073(4)	0.0041(4)
O(1)	0.0189(4)	0.0297(4)	0.0213(4)	0.0089(3)	0.0046(3)	0.0018(3)
N(1)	0.0195(4)	0.0160(4)	0.0135(4)	0.0017(3)	0.0021(3)	0.0011(3)
C(7)	0.0130(4)	0.0189(5)	0.0186(5)	-0.0009(4)	0.0017(3)	0.0007(4)
O(2)	0.0259(4)	0.0190(4)	0.0136(3)	-0.0033(3)	0.0030(3)	-0.0025(3)
O(3)	0.0276(4)	0.0160(4)	0.0293(4)	-0.0036(3)	0.0026(3)	-0.0017(3)

Table 5: Bond lengths (Å)

C(1) - C(2)	1.5548(13)
C(1) - C(5)	1.5327(14)
C(1) - C(6)	1.5254(14)
C(1) - N(1)	1.4596(13)
C(2) - C(3)	1.5289(14)
C(2) - O(2)	1.4558(12)
C(3) - C(4)	1.5317(14)
C(4) - C(5)	1.5305(15)
C(6) - O(1)	1.4261(14)
O(1) - H(1)	0.863(18)
N(1) - C(7)	1.3383(13)
N(1) - H(2)	0.873(16)
C(7) - O(2)	1.3553(13)
C(7) - O(3)	1.2248(13)

Note – geometrically-positioned H atoms have been excluded

Table 6: Bond angles (°)

C(2) - C(1) - C(5)	104.83(8)
C(2) - C(1) - C(6)	114.79(8)
C(5) - C(1) - C(6)	113.28(9)
C(2) - C(1) - N(1)	100.41(8)
C(5) - C(1) - N(1)	111.66(8)
C(6) - C(1) - N(1)	111.05(8)
C(1) - C(2) - C(3)	106.34(8)
C(1) - C(2) - O(2)	105.07(7)
C(3) - C(2) - O(2)	111.52(8)
C(2) - C(3) - C(4)	105.22(8)
C(3) - C(4) - C(5)	102.53(8)
C(1) - C(5) - C(4)	103.68(8)
C(1) - C(6) - O(1)	112.44(8)
C(6) - O(1) - H(1)	109.1(11)
C(1) - N(1) - C(7)	112.51(8)
C(1) - N(1) - H(2)	121.3(11)
C(7) - N(1) - H(2)	119.9(10)
N(1) - C(7) - O(2)	110.68(9)
N(1) - C(7) - O(3)	128.7(1)
O(2) - C(7) - O(3)	120.58(9)
C(2) - O(2) - C(7)	109.47(7)

Note – H atoms have been excluded

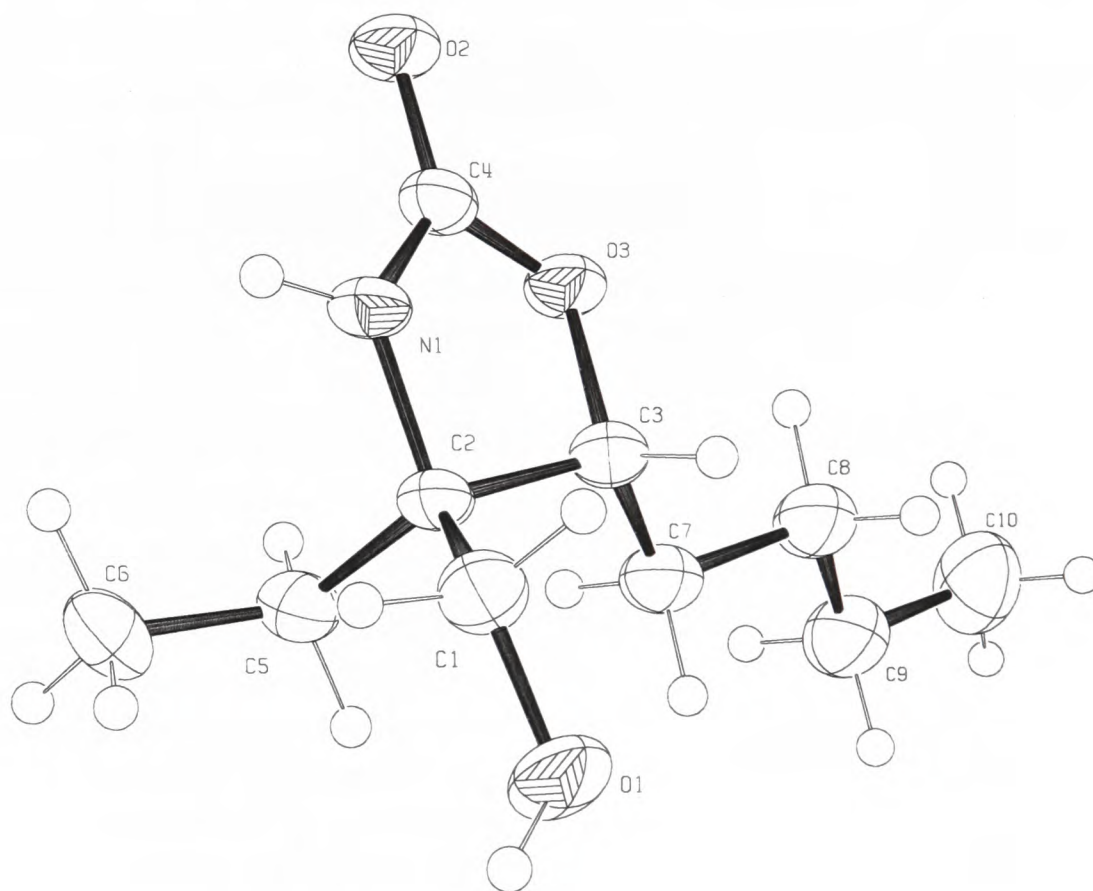
Inorganic Chemistry Crystallography Service

Single-crystal X-ray diffraction report for C₁₀H₁₉NO₃ (ARC408)

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Crystals of **ARC408** were grown by evaporation from acetone. A single crystal having dimensions approximately 0.24 x 0.36 x 0.36 mm was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150K 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 package¹.

Examination of the systematic absences of the intensity data showed the space group to be *P* 2₁/*a*. The structure was solved using the direct-methods program SIR92², which located all non-hydrogen atoms. Subsequent full-matrix least-squares refinement was carried out using the CRYSTALS program suite³. Coordinates and anisotropic thermal parameters of all non-hydrogen atoms were refined. The NH and OH hydrogen atoms were located in a difference Fourier map and their coordinates and isotropic thermal parameters subsequently refined. Other hydrogen atoms were positioned geometrically after each cycle of refinement. A 3-term Chebychev polynomial weighting scheme was applied. Refinement converged satisfactorily to give *R* = 0.0493, *wR* = 0.0607.

Attached is a thermal ellipsoid plot (ORTEP-3⁴) at 40% 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.

Comment:

The NH and OH groups both form hydrogen bonds to the carbonyl O atoms of neighbouring molecules:

Donor	H atom	Acceptor	Symmetry operator of acceptor	Donor...acceptor distance (Å)
O(1)	H(1)	O(2)	$x + 1, y, z$	2.7839(17)
N(1)	H(2)	O(2)	$-x, -y + 1, -z$	2.8823(18)

These hydrogen bonds link the molecules to form infinite chains running parallel to the crystallographic *a* axis.

References:

- 1 Z. Otwinowski and W. Minor, *Processing of X-ray Diffraction Data Collected in Oscillation Mode, Methods Enzymol.*, 1997, **276**, Eds C. W. Carter and R. M. Sweet, Academic Press.
- 2 A. Altomare, G. Cascarano, G. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori and M. Camalli, *J. Appl. Cryst.* 1994, **27**, 435.
- 3 D. J. Watkin, C. K. Prout, J. R. Carruthers, P. W. Betteridge and R. I. Cooper, *CRYSTALS* issue 11, Chemical Crystallography Laboratory, Oxford, UK, 2001.
- 4 ORTEP-3 v. 1.0.2, C. K. Johnson and M. K. Burnett, 1998.

Table 1: Crystal data and refinement details

Crystal identification	ARC408
Chemical formula	C ₁₀ H ₁₉ NO ₃
Formula weight	201.27
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	<i>P</i> 2 ₁ / <i>a</i>
<i>a</i> (Å)	7.7565(2)
<i>b</i> (Å)	10.4833(3)
<i>c</i> (Å)	14.0722(4)
α (°)	90
β (°)	96.1882(3)
γ (°)	90
Cell volume (Å ³)	1137.6
<i>Z</i>	4
Calculated density (Mg/m ³)	1.175
Absorption coefficient (mm ⁻¹)	0.086
<i>F</i> ₀₀₀	440.127
Crystal size (mm)	0.24 x 0.36 x 0.36
Description of crystal	Colourless block
Absorption correction	Semi-empirical from equivalent reflections
Transmission coefficients (min,max)	0.97, 0.98
θ range for data collection (°)	5.0 ≤ θ ≤ 27.5
Index ranges	-10 ≤ <i>h</i> ≤ 10, 0 ≤ <i>k</i> ≤ 13, 0 ≤ <i>l</i> ≤ 18
Reflections measured	13272
Unique reflections	2713
<i>R</i> _{int}	0.037
Observed reflections (<i>I</i> > 3 σ (<i>I</i>))	1768
Refinement method	Full-matrix least-squares on <i>F</i>
Parameters refined	135
Weighting scheme	Chebyshev 4-term polynomial
Goodness of fit	0.9987
<i>R</i>	0.0493
<i>wR</i>	0.0607
Residual electron density (min,max) (eÅ ⁻³)	-0.19, 0.30

Table 2: Atomic coordinates and equivalent isotropic thermal parameters (Å²) of non-hydrogen atoms

Atom	x	y	z	U _{equiv}
O(1)	0.60641(16)	0.41064(15)	0.21421(11)	0.0565
C(1)	0.46739(19)	0.40558(16)	0.14029(13)	0.0425
C(2)	0.31292(16)	0.47650(14)	0.17264(11)	0.0322
C(3)	0.23576(18)	0.40257(15)	0.25351(12)	0.0384
N(1)	0.16502(14)	0.46468(12)	0.0987(1)	0.0338
C(4)	0.01711(18)	0.44519(14)	0.13687(11)	0.0343
O(2)	-0.13144(13)	0.44805(12)	0.09666(8)	0.0421
O(3)	0.04746(12)	0.41970(11)	0.23074(8)	0.0392
C(5)	0.3518(2)	0.61675(15)	0.19561(12)	0.0394
C(6)	0.4054(2)	0.69437(17)	0.11195(14)	0.0508
C(7)	0.2862(2)	0.44335(18)	0.35461(12)	0.0453
C(8)	0.1998(2)	0.36552(19)	0.42825(13)	0.0499
C(9)	0.2485(3)	0.4153(2)	0.52874(15)	0.0606
C(10)	0.1594(3)	0.3469(2)	0.60402(17)	0.0697

Table 3: Atomic coordinates and isotropic thermal parameters (Å²) of hydrogen atoms

Atom	x	y	z	U _{iso}
H(1)	0.710(4)	0.422(3)	0.183(2)	0.098(9)
H(2)	0.164(3)	0.497(2)	0.0399(18)	0.056(6)
H(11)	0.5032	0.4467	0.0814	0.0510
H(12)	0.4350	0.3146	0.1263	0.0510
H(31)	0.2815	0.3134	0.2536	0.0457
H(51)	0.4482	0.6207	0.2488	0.0468
H(52)	0.2452	0.6564	0.2169	0.0468
H(61)	0.4284	0.7845	0.1328	0.0610
H(62)	0.5129	0.6569	0.0901	0.0610
H(63)	0.3099	0.6926	0.0582	0.0610
H(71)	0.2529	0.5349	0.3610	0.0538
H(72)	0.4147	0.4344	0.3688	0.0538
H(81)	0.0711	0.3706	0.4129	0.0595
H(82)	0.2377	0.2746	0.4250	0.0595
H(91)	0.2169	0.5077	0.5301	0.0720
H(92)	0.3766	0.4057	0.5446	0.0720
H(101)	0.1975	0.3846	0.6681	0.0841
H(102)	0.0310	0.3564	0.5897	0.0841
H(103)	0.1907	0.2544	0.6042	0.0841

Table 4: Anisotropic thermal parameters (Å²)

Atom	U ₁₁	U ₂₂	U ₃₃	U ₂₃	U ₁₃	U ₁₂
O(1)	0.0230(5)	0.0807(9)	0.0652(8)	0.0226(7)	0.0019(5)	0.0068(5)
C(1)	0.0264(7)	0.0412(8)	0.060(1)	0.0056(7)	0.0048(7)	0.0055(6)
C(2)	0.0205(6)	0.0325(7)	0.0425(8)	0.0023(6)	-0.0024(5)	-0.0020(5)
C(3)	0.0223(7)	0.0422(8)	0.0497(9)	0.0073(7)	-0.0010(6)	-0.0019(5)
N(1)	0.0205(6)	0.0384(6)	0.0416(7)	0.0002(5)	-0.0012(5)	-0.0041(4)
C(4)	0.0235(7)	0.0342(7)	0.0448(8)	0.0006(6)	0.0013(5)	-0.0024(5)
O(2)	0.0211(5)	0.0553(7)	0.0488(7)	0.0033(5)	-0.0018(4)	-0.0054(4)
O(3)	0.0215(5)	0.0516(6)	0.0439(6)	0.0071(5)	0.0003(4)	-0.0045(4)
C(5)	0.0356(8)	0.0370(8)	0.0443(8)	-0.0025(6)	-0.0016(6)	-0.0060(6)
C(6)	0.054(1)	0.0375(8)	0.0605(11)	0.0025(8)	0.0059(8)	-0.0160(7)
C(7)	0.0324(8)	0.056(1)	0.0461(9)	0.0084(7)	-0.0013(6)	-0.0078(7)
C(8)	0.0363(8)	0.0618(11)	0.051(1)	0.0142(8)	0.0002(7)	-0.0063(7)
C(9)	0.0540(11)	0.0740(13)	0.0521(11)	0.017(1)	-0.0027(9)	-0.0092(9)
C(10)	0.0751(15)	0.0788(16)	0.0564(12)	0.0196(11)	0.0130(11)	0.0041(11)

Table 5: Bond lengths (Å)

O(1) - C(1)	1.416(2)
O(1) - H(1)	0.96(3)
C(1) - C(2)	1.521(2)
C(2) - C(3)	1.549(2)
C(2) - N(1)	1.4687(18)
C(2) - C(5)	1.528(2)
C(3) - O(3)	1.4721(16)
C(3) - C(7)	1.497(2)
N(1) - C(4)	1.3341(19)
N(1) - H(2)	0.90(2)
C(4) - O(2)	1.2280(17)
C(4) - O(3)	1.3434(19)
C(5) - C(6)	1.525(2)
C(7) - C(8)	1.529(2)
C(8) - C(9)	1.516(3)
C(9) - C(10)	1.507(3)

Note – geometrically-positioned H atoms have been excluded

Table 6: Bond angles (°)

C(1) - O(1) - H(1)	106.3(19)
O(1) - C(1) - C(2)	108.89(15)
C(1) - C(2) - C(3)	110.76(12)
C(1) - C(2) - N(1)	109.09(13)
C(3) - C(2) - N(1)	98.3(1)
C(1) - C(2) - C(5)	112.93(12)
C(3) - C(2) - C(5)	114.14(13)
N(1) - C(2) - C(5)	110.63(11)
C(2) - C(3) - O(3)	103.41(11)
C(2) - C(3) - C(7)	118.25(13)
O(3) - C(3) - C(7)	108.87(13)
C(2) - N(1) - C(4)	111.56(13)
C(2) - N(1) - H(2)	123.3(14)
C(4) - N(1) - H(2)	120.8(15)
N(1) - C(4) - O(2)	128.00(15)
N(1) - C(4) - O(3)	111.06(12)
O(2) - C(4) - O(3)	120.94(13)
C(3) - O(3) - C(4)	107.63(11)
C(2) - C(5) - C(6)	114.45(14)
C(3) - C(7) - C(8)	113.78(14)
C(7) - C(8) - C(9)	111.40(15)
C(8) - C(9) - C(10)	113.88(18)

Note – geometrically-positioned H atoms have been excluded

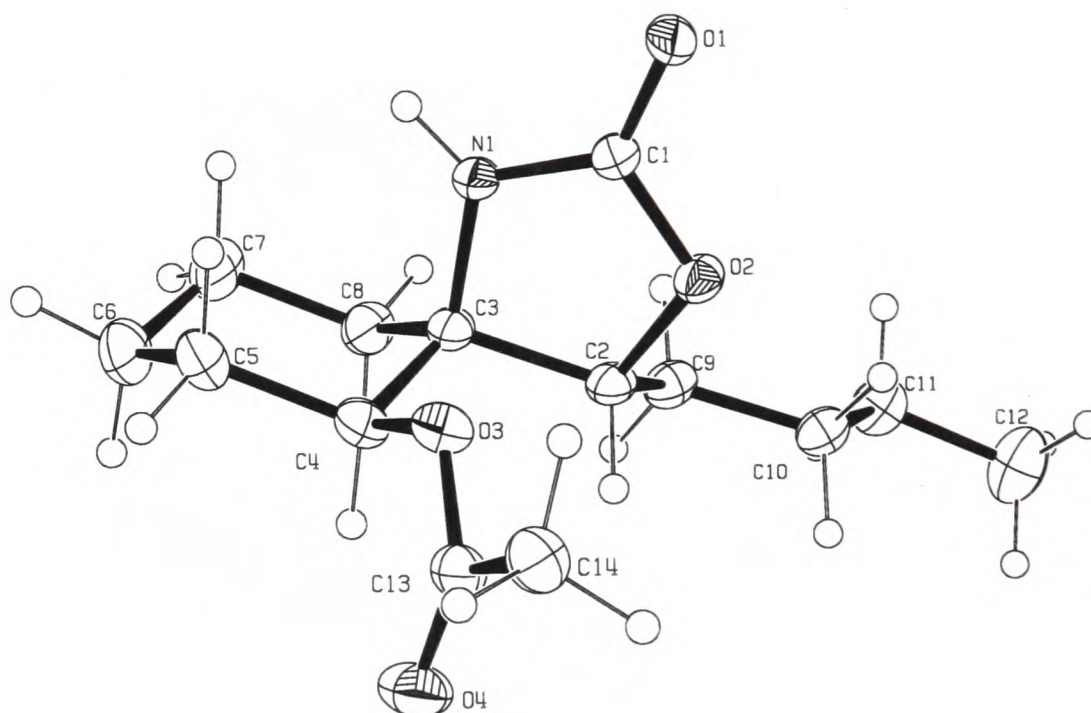
Inorganic Chemistry Crystallography Service

Single-crystal X-ray diffraction report for C₁₄H₂₃NO₄ (ARC643)

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View of one of the two crystallographically-distinct molecules. The second is similar although it differs slightly in the conformation of the 5-membered ring.

Crystals of **ARC643** were grown by evaporation from chloroform. A single crystal having dimensions approximately 0.12 x 0.38 x 0.42 mm was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150K 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 package¹.

The structure was solved in the space group *P* 1 using the direct-methods program SIR92², which located all non-hydrogen atoms. Subsequent full-matrix least-squares refinement was carried out using the CRYSTALS program suite³. Coordinates and anisotropic thermal parameters of all non-hydrogen atoms were refined. The refined thermal parameters of the atoms of one of the acetyl groups were highly anisotropic, indicative of disorder. This was modelled as disorder over two orientations related by a small rotation and displacement. The coordinates, isotropic thermal parameters and site occupancies of the non-hydrogen atoms were refined, with the overall occupancy constrained to unity. Geometric restraints were applied to the disordered fragments: the O-C bond lengths were restrained to 1.35(20) Å, the C=O bond lengths to 1.20(2) Å, the C-C bond lengths to 1.51(2) Å, O=C-O and

O=C-C angles to $124(2)^\circ$ and O-C-C angles to $112(2)^\circ$. The NH hydrogen atoms were located in a difference Fourier map and their coordinates and isotropic thermal parameters subsequently refined. Other hydrogen atoms were positioned geometrically after each cycle of refinement. A 3-term Chebychev polynomial weighting scheme was applied. Refinement converged satisfactorily to give $R = 0.0464$, $wR = 0.0525$.

Attached is a thermal ellipsoid plot (ORTEP-3⁴) at 40% 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 geometrically-positioned H atoms.

Comment:

The asymmetric unit of the crystal contains two distinct molecules which differ slightly in the conformation of their 5-membered rings

Each molecule is linked by hydrogen bonds to a neighbour related by a crystallographic centre of inversion to form a dimer. In both cases, the hydrogen bond is formed by the carbonyl O of the carbamate group (N(1)···O(1)' 2.850(2) Å, symmetry operator $-x, -y, -z$, N(2)···O(5)" 2.882(2) Å, symmetry operator $1-x, 1-y, 1-z$)

References:

- 1 Z. Otwinowski and W. Minor, *Processing of X-ray Diffraction Data Collected in Oscillation Mode, Methods Enzymol.*, 1997, **276**, Eds C. W. Carter and R. M. Sweet, Academic Press.
- 2 A. Altomare, G. Cascarano, G. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori and M. Camalli, *J. Appl. Cryst.* 1994, **27**, 435.
- 3 D. J. Watkin, C. K. Prout, J. R. Carruthers, P. W. Betteridge and R. I. Cooper, *CRYSTALS* issue 11, Chemical Crystallography Laboratory, Oxford, UK, 2001.
- 4 ORTEP-3 v. 1.0.2, C. K. Johnson and M. K. Burnett, 1998.

Table 1: Crystal data and refinement details

Crystal identification	ARC643
Chemical formula	C ₁₄ H ₂₃ NO ₄
Formula weight	269.34
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Triclinic
Space group	<i>P</i> 1
<i>a</i> (Å)	9.9259(2)
<i>b</i> (Å)	12.6602(3)
<i>c</i> (Å)	13.2162(3)
α (°)	104.4006(9)
β (°)	98.0982(10)
γ (°)	111.0639(9)
Cell volume (Å ³)	1451.60(6)
<i>Z</i>	4
Calculated density (Mg/m ³)	1.232
Absorption coefficient (mm ⁻¹)	0.090
<i>F</i> ₀₀₀	584
Crystal size (mm)	0.12 x 0.38 x 0.42
Description of crystal	Colourless plate
Absorption correction	Semi-empirical from equivalent reflections
Transmission coefficients (min,max)	0.96, 0.99
θ range for data collection (°)	5.0 ≤ θ ≤ 27.5
Index ranges	-12 ≤ <i>h</i> ≤ 12, -16 ≤ <i>k</i> ≤ 15, 0 ≤ <i>l</i> ≤ 17
Reflections measured	19533
Unique reflections	6530
<i>R</i> _{int}	0.036
Observed reflections (<i>I</i> > 3σ(<i>I</i>))	4096
Refinement method	Full-matrix least-squares on <i>F</i>
Parameters refined	349
Weighting scheme	Chebyshev 3-term polynomial
Goodness of fit	1.0787
<i>R</i>	0.0464
<i>wR</i>	0.0525
Residual electron density (min,max) (eÅ ⁻³)	-0.36, 0.47

Table 2: Atomic coordinates and equivalent isotropic thermal parameters (Å²) of non-hydrogen atoms

Atom	x	y	z	U _{equiv}
N(1)	0.04152(19)	0.15242(14)	0.06998(14)	0.0272
C(1)	0.1160(2)	0.12269(17)	0.14300(16)	0.0255
O(1)	0.12098(17)	0.02601(12)	0.13448(11)	0.0317
O(2)	0.18734(16)	0.21656(12)	0.23468(11)	0.0291
C(2)	0.1469(2)	0.31470(16)	0.22666(16)	0.0267
C(3)	0.0734(2)	0.27928(17)	0.10373(16)	0.0276
C(4)	0.1835(3)	0.34702(18)	0.04754(18)	0.0335
C(5)	0.1212(3)	0.3045(2)	-0.0741(2)	0.0439
C(6)	-0.0236(3)	0.3198(2)	-0.1023(2)	0.0518
C(7)	-0.1360(3)	0.2585(2)	-0.0455(2)	0.0448
C(8)	-0.0697(3)	0.29952(19)	0.07716(18)	0.0365
C(9)	0.0515(2)	0.32897(18)	0.30441(17)	0.0305
C(10)	0.1332(2)	0.35877(19)	0.42151(17)	0.0301
C(11)	0.0295(2)	0.3509(2)	0.49624(19)	0.0376
C(12)	0.1088(3)	0.3945(3)	0.6149(2)	0.0530
O(3)	0.31890(17)	0.32869(12)	0.07075(12)	0.0333
C(13)	0.4507(3)	0.42572(19)	0.10038(17)	0.0325
O(4)	0.4602(2)	0.52581(14)	0.11462(14)	0.0447
C(14)	0.5787(3)	0.3902(2)	0.10971(19)	0.0387
N(2)	0.47945(17)	0.34179(14)	0.47193(13)	0.0215
C(15)	0.5064(2)	0.36975(16)	0.38311(15)	0.0219
O(5)	0.50808(15)	0.45755(11)	0.35965(11)	0.0264
O(6)	0.53485(15)	0.28416(11)	0.31672(11)	0.0252
C(16)	0.4990(2)	0.18263(16)	0.35748(15)	0.0230
C(17)	0.5130(2)	0.23952(16)	0.47863(15)	0.0210
C(18)	0.6697(2)	0.28244(17)	0.55231(16)	0.0243
C(19)	0.6789(2)	0.34000(17)	0.67092(16)	0.0278
C(20)	0.5666(2)	0.25240(18)	0.71041(16)	0.0300
C(21)	0.4097(2)	0.21142(18)	0.63988(16)	0.0285
C(22)	0.4009(2)	0.15486(17)	0.52226(16)	0.0238
C(23)	0.5980(2)	0.11899(18)	0.32894(16)	0.0276
C(24)	0.5728(2)	0.06544(19)	0.20754(16)	0.0307
C(25)	0.6684(3)	-0.00264(19)	0.17829(18)	0.0338
C(26)	0.6486(3)	-0.0519(2)	0.0579(2)	0.0457
O(7)	0.24983(15)	0.11907(12)	0.46010(11)	0.0277
C(27)*	0.1712(5)	0.0017(4)	0.4005(4)	0.0284(13)‡
O(8)*	0.2242(3)	-0.0702(2)	0.3864(3)	0.0426(11)‡
C(28)*	0.0145(6)	-0.0298(5)	0.3522(4)	0.0352(16)‡
C(77)†	0.1587(8)	0.0071(6)	0.4218(7)	0.030(2)‡
O(58)†	0.1934(5)	-0.0710(4)	0.4394(5)	0.0472(17)‡
C(78)†	0.0093(8)	-0.0076(7)	0.3572(6)	0.025(2)‡

*disordered atom, site occupancy 0.604(8)

†disordered atom, site occupancy 0.396(8)

‡directly-refined value of U_{iso} (Å²)

Table 3: Atomic coordinates and isotropic thermal parameters ($\text{\AA}^2$) of hydrogen atoms

Atom	x	y	z	U_{iso}
H(1)	-0.011(3)	0.099(2)	0.004(2)	0.047(7)
H(21)	0.2301	0.3961	0.2487	0.0310
H(41)	0.2032	0.4336	0.0755	0.0409
H(51)	0.1961	0.3523	-0.1066	0.0539
H(52)	0.1009	0.2180	-0.1041	0.0539
H(61)	-0.0012	0.4071	-0.0794	0.0640
H(62)	-0.0673	0.2840	-0.1822	0.0640
H(71)	-0.2247	0.2779	-0.0592	0.0532
H(72)	-0.1680	0.1700	-0.0755	0.0532
H(81)	-0.0453	0.3867	0.1082	0.0434
H(82)	-0.1451	0.2532	0.1102	0.0434
H(91)	0.0213	0.3950	0.2987	0.0348
H(92)	-0.0396	0.2525	0.2838	0.0348
H(101)	0.2131	0.4420	0.4466	0.0344
H(102)	0.1798	0.3012	0.4250	0.0344
H(111)	-0.0268	0.4004	0.4851	0.0452
H(112)	-0.0423	0.2654	0.4765	0.0452
H(121)	0.0338	0.3866	0.6589	0.0636
H(122)	0.1803	0.4803	0.6364	0.0636
H(123)	0.1648	0.3453	0.6277	0.0636
H(141)	0.5401	0.3017	0.0938	0.0468
H(142)	0.6366	0.4137	0.0569	0.0468
H(143)	0.6450	0.4316	0.1847	0.0468
H(2)	0.483(3)	0.400(2)	0.530(2)	0.035(6)
H(161)	0.3968	0.1167	0.3250	0.0281
H(181)	0.6959	0.2122	0.5458	0.0299
H(182)	0.7429	0.3426	0.5281	0.0299
H(191)	0.7818	0.3642	0.7155	0.0323
H(192)	0.6570	0.4124	0.6785	0.0323
H(201)	0.5711	0.2924	0.7870	0.0370
H(202)	0.5908	0.1815	0.7060	0.0370
H(211)	0.3368	0.1514	0.6644	0.0368
H(212)	0.3842	0.2821	0.6472	0.0368
H(221)	0.4269	0.0845	0.5157	0.0295
H(231)	0.7045	0.1776	0.3602	0.0345
H(232)	0.5772	0.0531	0.3613	0.0345
H(241)	0.5971	0.1318	0.1757	0.0380
H(242)	0.4654	0.0091	0.1760	0.0380
H(251)	0.7757	0.0529	0.2125	0.0434
H(252)	0.6411	-0.0709	0.2077	0.0434
H(261)	0.7142	-0.0954	0.0443	0.0575
H(262)	0.6766	0.0155	0.0273	0.0575
H(263)	0.5420	-0.1083	0.0225	0.0575
H(281)	-0.0072	0.0427	0.3739	0.0422
H(282)	-0.0504	-0.0931	0.3780	0.0422
H(283)	-0.0061	-0.0604	0.2718	0.0422
H(781)	0.0141	0.0726	0.3568	0.0304
H(782)	-0.0716	-0.0446	0.3910	0.0304
H(783)	-0.0126	-0.0603	0.2813	0.0304

Table 4: Anisotropic thermal parameters (Å²)

Atom	U ₁₁	U ₂₂	U ₃₃	U ₂₃	U ₁₃	U ₁₂
N(1)	0.0327(9)	0.0194(8)	0.0258(9)	0.0050(7)	0.0005(7)	0.0107(7)
C(1)	0.029(1)	0.0227(9)	0.0231(9)	0.0051(8)	0.0048(8)	0.0103(8)
O(1)	0.0459(9)	0.0241(7)	0.0266(7)	0.0066(6)	0.0048(6)	0.0189(6)
O(2)	0.0335(8)	0.0245(7)	0.0263(7)	0.0018(6)	-0.0000(6)	0.0157(6)
C(2)	0.029(1)	0.0195(9)	0.029(1)	0.0036(8)	0.0028(8)	0.0114(8)
C(3)	0.0327(11)	0.0199(9)	0.027(1)	0.0047(8)	0.0010(8)	0.0122(8)
C(4)	0.0440(12)	0.024(1)	0.0346(12)	0.0110(9)	0.008(1)	0.0155(9)
C(5)	0.0620(16)	0.0365(12)	0.0363(13)	0.019(1)	0.0094(11)	0.0201(11)
C(6)	0.0740(19)	0.0447(14)	0.0413(14)	0.0185(12)	-0.0009(13)	0.0322(14)
C(7)	0.0504(15)	0.0439(13)	0.0386(13)	0.0080(11)	-0.0068(11)	0.0282(12)
C(8)	0.0392(12)	0.0322(11)	0.0371(12)	0.0071(9)	-0.001(1)	0.020(1)
C(9)	0.025(1)	0.029(1)	0.0334(11)	0.0041(9)	0.0031(8)	0.0118(8)
C(10)	0.023(1)	0.031(1)	0.0314(11)	0.0052(8)	0.0060(8)	0.0101(8)
C(11)	0.0280(11)	0.0458(13)	0.0392(13)	0.011(1)	0.0106(9)	0.017(1)
C(12)	0.0410(14)	0.083(2)	0.0352(13)	0.0158(13)	0.0153(11)	0.0256(14)
O(3)	0.0359(8)	0.0245(7)	0.0392(9)	0.0109(6)	0.0101(7)	0.0114(6)
C(13)	0.0430(12)	0.0282(11)	0.024(1)	0.0092(8)	0.0137(9)	0.0101(9)
O(4)	0.054(1)	0.0263(8)	0.049(1)	0.0103(7)	0.0183(8)	0.0113(7)
C(14)	0.0408(13)	0.0393(12)	0.0368(12)	0.016(1)	0.013(1)	0.014(1)
N(2)	0.0251(8)	0.0209(8)	0.0223(8)	0.0082(7)	0.0063(7)	0.0129(6)
C(15)	0.0193(9)	0.0231(9)	0.0228(9)	0.0069(7)	0.0037(7)	0.0091(7)
O(5)	0.0323(7)	0.0226(7)	0.0279(7)	0.0116(6)	0.0081(6)	0.0128(6)
O(6)	0.0342(7)	0.0227(6)	0.0249(7)	0.0102(5)	0.0110(6)	0.0158(6)
C(16)	0.027(1)	0.0201(9)	0.0235(9)	0.0082(7)	0.0067(8)	0.0101(7)
C(17)	0.0227(9)	0.0204(9)	0.0237(9)	0.0086(7)	0.0062(7)	0.0120(7)
C(18)	0.0218(9)	0.0245(9)	0.028(1)	0.0085(8)	0.0055(8)	0.0117(8)
C(19)	0.027(1)	0.027(1)	0.027(1)	0.0067(8)	0.0007(8)	0.0118(8)
C(20)	0.0361(11)	0.032(1)	0.024(1)	0.0110(8)	0.0058(9)	0.0161(9)
C(21)	0.0310(11)	0.0342(11)	0.027(1)	0.0154(9)	0.0116(9)	0.0155(9)
C(22)	0.0204(9)	0.0244(9)	0.029(1)	0.0117(8)	0.0043(8)	0.0103(7)
C(23)	0.0332(11)	0.028(1)	0.025(1)	0.0074(8)	0.0073(8)	0.0172(8)
C(24)	0.0383(11)	0.0322(11)	0.025(1)	0.0073(8)	0.0084(9)	0.0190(9)
C(25)	0.0441(13)	0.0332(11)	0.0313(11)	0.0101(9)	0.013(1)	0.023(1)
C(26)	0.0593(16)	0.0466(14)	0.0378(13)	0.0072(11)	0.0188(12)	0.0310(12)
O(7)	0.0213(7)	0.0257(7)	0.0342(8)	0.0099(6)	0.0031(6)	0.0090(6)

Table 5: Bond lengths (Å)

N(1) - C(1)	1.341(3)	N(2) - C(15)	1.342(2)
N(1) - C(3)	1.455(2)	N(2) - C(17)	1.468(2)
N(1) - H(1)	0.90(3)	N(2) - H(2)	0.91(3)
C(1) - O(1)	1.221(2)	C(15) - O(5)	1.221(2)
C(1) - O(2)	1.349(2)	C(15) - O(6)	1.357(2)
O(2) - C(2)	1.459(2)	O(6) - C(16)	1.462(2)
C(2) - C(3)	1.563(3)	C(16) - C(17)	1.547(3)
C(2) - C(9)	1.513(3)	C(16) - C(23)	1.510(3)
C(3) - C(4)	1.534(3)	C(17) - C(18)	1.537(3)
C(3) - C(8)	1.540(3)	C(17) - C(22)	1.533(3)
C(4) - C(5)	1.518(3)	C(18) - C(19)	1.530(3)
C(4) - O(3)	1.449(3)	C(19) - C(20)	1.519(3)
C(5) - C(6)	1.525(4)	C(20) - C(21)	1.527(3)
C(6) - C(7)	1.522(4)	C(21) - C(22)	1.516(3)
C(7) - C(8)	1.538(3)	C(22) - O(7)	1.452(2)
C(9) - C(10)	1.527(3)	C(23) - C(24)	1.523(3)
C(10) - C(11)	1.519(3)	C(24) - C(25)	1.523(3)
C(11) - C(12)	1.514(3)	C(25) - C(26)	1.513(3)
O(3) - C(13)	1.355(3)	O(7) - C(27)	1.359(5)
C(13) - O(4)	1.200(3)	C(27) - O(8)	1.195(5)
C(13) - C(14)	1.491(3)	C(27) - C(28)	1.460(6)
		O(7) - C(77)	1.295(7)
		C(77) - O(58)	1.220(7)
		C(77) - C(78)	1.527(9)

Note – geometrically-positioned H atoms have been excluded

Table 6: Bond angles (°)

C(1) - N(1) - C(3)	112.83(16)	C(15) - N(2) - C(17)	111.59(15)
C(1) - N(1) - H(1)	120.4(17)	C(15) - N(2) - H(2)	118.0(15)
C(3) - N(1) - H(1)	126.1(17)	C(17) - N(2) - H(2)	124.9(15)
N(1) - C(1) - O(1)	128.03(18)	N(2) - C(15) - O(5)	128.43(17)
N(1) - C(1) - O(2)	110.43(16)	N(2) - C(15) - O(6)	110.27(15)
O(1) - C(1) - O(2)	121.52(18)	O(5) - C(15) - O(6)	121.30(17)
C(1) - O(2) - C(2)	109.44(15)	C(15) - O(6) - C(16)	107.92(14)
O(2) - C(2) - C(3)	104.14(14)	O(6) - C(16) - C(17)	103.52(14)
O(2) - C(2) - C(9)	107.82(16)	O(6) - C(16) - C(23)	109.22(15)
C(3) - C(2) - C(9)	117.41(17)	C(17) - C(16) - C(23)	117.73(16)
N(1) - C(3) - C(2)	99.79(15)	N(2) - C(17) - C(16)	98.68(14)
N(1) - C(3) - C(4)	111.80(17)	N(2) - C(17) - C(18)	110.65(15)
C(2) - C(3) - C(4)	111.10(17)	C(16) - C(17) - C(18)	114.27(15)
N(1) - C(3) - C(8)	111.29(17)	N(2) - C(17) - C(22)	112.86(15)
C(2) - C(3) - C(8)	115.44(17)	C(16) - C(17) - C(22)	112.32(15)
C(4) - C(3) - C(8)	107.41(17)	C(18) - C(17) - C(22)	107.96(15)
C(3) - C(4) - C(5)	112.30(19)	C(17) - C(18) - C(19)	112.38(15)
C(3) - C(4) - O(3)	108.48(16)	C(18) - C(19) - C(20)	110.48(16)
C(5) - C(4) - O(3)	108.86(18)	C(19) - C(20) - C(21)	109.49(16)
C(4) - C(5) - C(6)	110.7(2)	C(20) - C(21) - C(22)	110.78(16)
C(5) - C(6) - C(7)	111.05(19)	C(17) - C(22) - C(21)	112.76(16)
C(6) - C(7) - C(8)	111.9(2)	C(17) - C(22) - O(7)	109.99(15)
C(3) - C(8) - C(7)	111.49(18)	C(21) - C(22) - O(7)	107.80(15)
C(2) - C(9) - C(10)	112.66(16)	C(16) - C(23) - C(24)	112.96(16)
C(9) - C(10) - C(11)	112.34(17)	C(23) - C(24) - C(25)	113.20(17)
C(10) - C(11) - C(12)	114.01(19)	C(24) - C(25) - C(26)	113.52(19)
C(4) - O(3) - C(13)	117.54(16)	C(22) - O(7) - C(27)	117.6(2)
O(3) - C(13) - O(4)	123.4(2)	O(7) - C(27) - O(8)	123.8(4)
O(3) - C(13) - C(14)	110.93(18)	O(7) - C(27) - C(28)	114.1(4)
O(4) - C(13) - C(14)	125.6(2)	O(8) - C(27) - C(28)	122.1(4)
		C(22) - O(7) - C(77)	120.2(3)
		O(7) - C(77) - O(58)	122.1(6)
		O(7) - C(77) - C(78)	110.2(5)
		O(58) - C(77) - C(78)	127.8(6)

Note – geometrically-positioned H atoms have been excluded

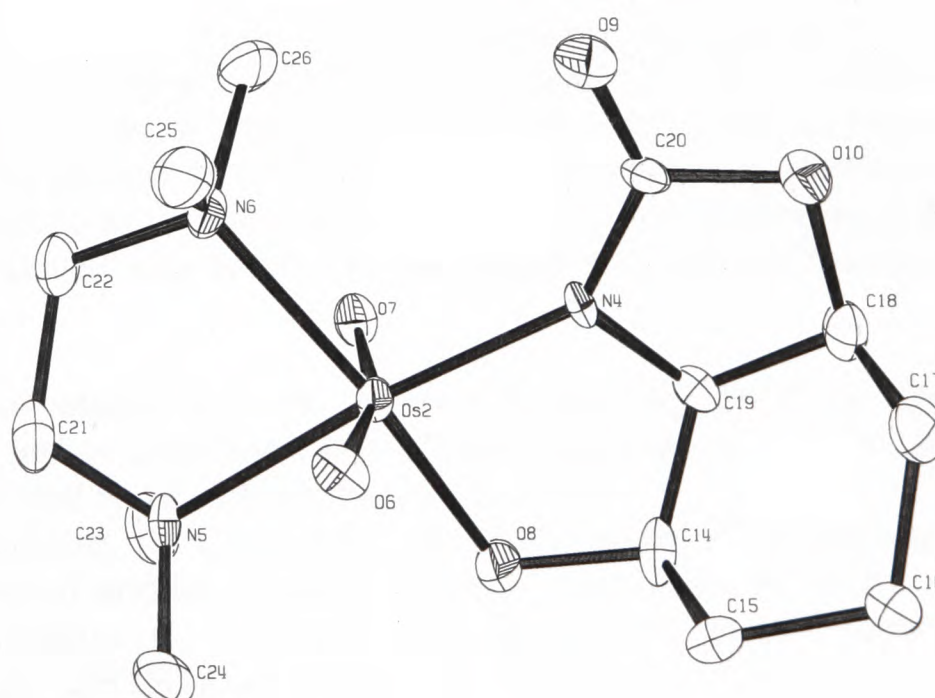
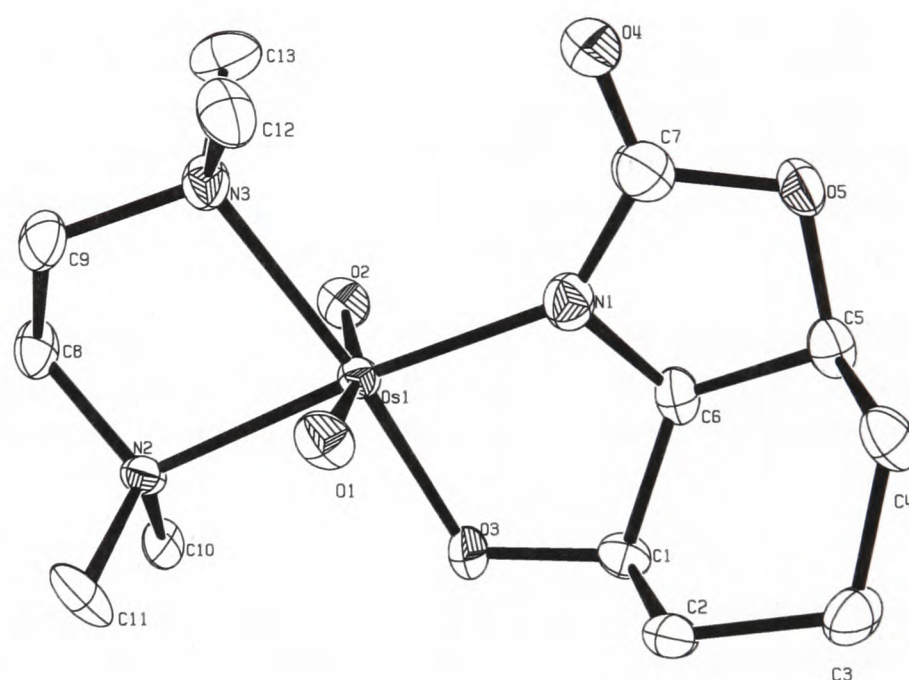
Inorganic Chemistry Crystallography Service

Single-crystal X-ray diffraction report for $C_{13}H_{25}N_3O_5Os \cdot 0.5H_2O$
(ARC339)

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Views of the two molecules of Os complex, each viewed along a similar axis with respect to the OsN_3O_3 unit. H atoms and solvent have been omitted.

Crystals of **ARC339** were grown by evaporation from chloroform. A single crystal having dimensions approximately 0.06 x 0.06 x 0.10 mm was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150K 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 package¹.

Examination of the systematic absences of the intensity data showed the space group to be $P 2_1/c$. The structure was solved using the direct-methods program SIR92², which located all non-hydrogen atoms. Subsequent full-matrix least-squares refinement was carried out using the CRYSTALS program suite³. Coordinates and anisotropic thermal parameters of all non-hydrogen atoms were refined. The hydrogen atoms of the solvent were located in a difference Fourier map and their coordinates subsequently refined. Other hydrogen atoms were positioned geometrically after each cycle of refinement. A 3-term Chebychev polynomial weighting scheme was applied. Refinement converged satisfactorily to give $R = 0.0318$, $wR = 0.0360$.

Attached is a thermal ellipsoid plot (ORTEP-3⁴) at 40% 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:

The asymmetric unit contains two crystallographically-distinct Os complexes and a single molecule of water. The two complexes are structurally similar, but differ in the conformation of the TMEDA ligand. This difference is essentially the result of a reflection of the entire ligand in the NOsN plane.

The water molecule forms hydrogen bonds to O atoms of two neighbouring complexes (O(11)···O(7)' 2.906(10), O(11)···O(9) 2.889(12) Å). These link molecules of one type of complex (Os(2) *etc.*) to form infinite helical chains running parallel to the *b* axis, adjacent members of which are related by a crystallographic screw axis. The molecules of the second type of complex are stacked in a similar way but do not participate in hydrogen bonding.

References:

- 1 Z. Otwinowski and W. Minor, *Processing of X-ray Diffraction Data Collected in Oscillation Mode, Methods Enzymol.*, 1997, **276**, Eds C. W. Carter and R. M. Sweet, Academic Press.
- 2 A. Altomare, G. Cascarano, G. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori and M. Camalli, *J. Appl. Cryst.* 1994, **27**, 435.
- 3 D. J. Watkin, C. K. Prout, J. R. Carruthers, P. W. Betteridge and R. I. Cooper, CRYSTALS issue 11, Chemical Crystallography Laboratory, Oxford, UK, 2001.
- 4 ORTEP-3 v. 1.0.2, C. K. Johnson and M. K. Burnett, 1998.

Table 1: Crystal data and refinement details

Crystal identification	ARC339
Chemical formula	C ₂₆ H ₅₂ N ₆ O ₁₁ Os ₂
Formula weight	1005.13
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	<i>P</i> 2 ₁ / <i>c</i>
<i>a</i> (Å)	14.3533(3)
<i>b</i> (Å)	10.2682(2)
<i>c</i> (Å)	22.1176(5)
α (°)	90
β (°)	97.8921(9)
γ (°)	90
Cell volume (Å ³)	3228.9
Z	4
Calculated density (Mg/m ³)	2.068
Absorption coefficient (mm ⁻¹)	7.929
F ₀₀₀	1946.457
Crystal size (mm)	0.06 x 0.06 x 0.10
Description of crystal	Red-brown block
Absorption correction	Semi-empirical from equivalent reflections
Transmission coefficients (min,max)	0.45, 0.62
θ range for data collection (°)	5.0 ≤ θ ≤ 27.5
Index ranges	-18 ≤ <i>h</i> ≤ 18, 0 ≤ <i>k</i> ≤ 13, 0 ≤ <i>l</i> ≤ 28
Reflections measured	24579
Unique reflections	7724
R _{int}	0.067
Observed reflections (<i>I</i> > 3 σ (<i>I</i>))	4109
Refinement method	Full-matrix least-squares on <i>F</i>
Parameters refined	412
Weighting scheme	Chebyshev 3-term polynomial
Goodness of fit	1.0521
R	0.0318
wR	0.0360
Residual electron density (min,max) (eÅ ⁻³)	-1.73, 2.46

Table 2: Atomic coordinates and equivalent isotropic thermal parameters (Å²) of non-hydrogen atoms

Atom	x	y	z	U _{equiv}
Os(1)	0.45274(2)	0.31164(4)	0.369564(13)	0.0158
O(1)	0.5150(4)	0.3267(6)	0.4421(3)	0.0244
O(2)	0.4137(4)	0.3256(7)	0.2917(3)	0.0246
O(3)	0.3272(4)	0.3068(6)	0.3956(3)	0.0262
C(1)	0.2962(5)	0.1827(9)	0.4134(4)	0.0239
C(2)	0.3263(7)	0.1583(8)	0.4814(4)	0.0286
C(3)	0.3043(7)	0.0157(9)	0.4968(4)	0.0293
C(4)	0.3656(6)	-0.0753(9)	0.4643(4)	0.0274
C(5)	0.3482(6)	-0.0600(9)	0.3954(4)	0.0234
C(6)	0.3373(6)	0.0811(9)	0.3741(4)	0.0229
N(1)	0.4361(6)	0.1195(8)	0.3714(4)	0.0252
C(7)	0.4852(7)	0.0103(11)	0.3617(5)	0.0308
O(4)	0.5637(5)	-0.0004(6)	0.3479(3)	0.0303
O(5)	0.4333(5)	-0.0989(6)	0.3700(3)	0.0279
N(2)	0.4531(5)	0.5266(8)	0.3652(3)	0.0172
C(8)	0.5276(6)	0.5619(9)	0.3264(4)	0.0232
C(9)	0.6154(6)	0.4838(9)	0.3458(5)	0.0269
N(3)	0.5954(5)	0.3401(7)	0.3415(3)	0.0214
C(10)	0.3607(6)	0.5747(8)	0.3357(5)	0.0261
C(11)	0.4715(7)	0.5894(9)	0.4263(4)	0.0301
C(12)	0.6719(6)	0.2719(9)	0.3810(5)	0.0284
C(13)	0.5995(6)	0.2963(11)	0.2775(4)	0.0302
Os(2)	0.024082(19)	0.18790(4)	0.636290(13)	0.0156
O(6)	0.0694(4)	0.1766(6)	0.5679(3)	0.0219
O(7)	0.0055(4)	0.1718(6)	0.7118(3)	0.0238
O(8)	-0.1104(4)	0.1788(6)	0.6027(3)	0.0258
C(14)	-0.1519(6)	0.3033(9)	0.5839(4)	0.0246
C(15)	-0.1485(6)	0.3293(9)	0.5172(4)	0.0249
C(16)	-0.1834(7)	0.4680(9)	0.5004(4)	0.0288
C(17)	-0.1174(6)	0.5661(9)	0.5362(4)	0.0285
C(18)	-0.1075(6)	0.5477(9)	0.6046(5)	0.0265
C(19)	-0.1054(6)	0.4064(8)	0.6250(4)	0.0216
N(4)	-0.0028(5)	0.3799(7)	0.6331(3)	0.0176
C(20)	0.0445(6)	0.4931(9)	0.6410(4)	0.0192
O(9)	0.1278(4)	0.5127(6)	0.6540(3)	0.0318
O(10)	-0.0175(5)	0.5973(6)	0.6321(3)	0.0290
N(5)	0.0380(5)	-0.0266(8)	0.6368(3)	0.0208
C(21)	0.1404(6)	-0.054(1)	0.6478(5)	0.0308
C(22)	0.1917(6)	0.0358(9)	0.6959(5)	0.0303
N(6)	0.1742(4)	0.1748(7)	0.6788(3)	0.0195
C(23)	-0.0130(7)	-0.089(1)	0.6843(5)	0.0351
C(24)	-0.0019(7)	-0.0814(9)	0.5781(4)	0.0291
C(25)	0.2415(6)	0.2147(9)	0.6372(5)	0.0299
C(26)	0.1949(7)	0.2529(11)	0.7357(5)	0.0340
O(11)	0.1873(6)	0.6659(12)	0.7619(5)	0.0685

Table 3: Atomic coordinates and isotropic thermal parameters ($\text{\AA}^2$) of hydrogen atoms

Atom	x	y	z	U_{iso}
H(11)	0.2260	0.1779	0.4070	0.0293
H(21)	0.3954	0.1744	0.4917	0.0360
H(22)	0.2912	0.2185	0.5058	0.0360
H(31)	0.3181	0.0020	0.5419	0.0361
H(32)	0.2364	-0.0031	0.4828	0.0361
H(41)	0.4332	-0.0557	0.4788	0.0322
H(42)	0.3516	-0.1673	0.4748	0.0322
H(51)	0.2900	-0.1121	0.3824	0.0277
H(61)	0.2904	0.0812	0.3362	0.0272
H(81)	0.5424	0.6568	0.3313	0.0277
H(82)	0.5040	0.5428	0.2827	0.0277
H(91)	0.6404	0.5062	0.3890	0.0322
H(92)	0.6635	0.5061	0.3188	0.0322
H(101)	0.3112	0.5513	0.3614	0.0323
H(102)	0.3632	0.6715	0.3312	0.0323
H(103)	0.3454	0.5339	0.2945	0.0323
H(111)	0.4209	0.5643	0.4510	0.0354
H(112)	0.5338	0.5600	0.4477	0.0354
H(113)	0.4720	0.6862	0.4214	0.0354
H(121)	0.6603	0.1758	0.3789	0.0330
H(122)	0.6735	0.3022	0.4241	0.0330
H(123)	0.7335	0.2915	0.3667	0.0330
H(131)	0.5863	0.2008	0.2741	0.0362
H(132)	0.6635	0.3142	0.2664	0.0362
H(133)	0.5514	0.3447	0.2490	0.0362
H(141)	-0.2204	0.3029	0.5879	0.0300
H(151)	-0.0822	0.3199	0.5085	0.0290
H(152)	-0.1895	0.2650	0.4921	0.0290
H(161)	-0.2484	0.4793	0.5109	0.0335
H(162)	-0.1839	0.4825	0.4556	0.0335
H(171)	-0.1422	0.6557	0.5263	0.0341
H(172)	-0.0537	0.5572	0.5231	0.0341
H(181)	-0.1635	0.5931	0.6170	0.0316
H(191)	-0.1417	0.4002	0.6604	0.0257
H(211)	0.1500	-0.1463	0.6620	0.0372
H(212)	0.1671	-0.0422	0.6088	0.0372
H(221)	0.1688	0.0189	0.7359	0.0353
H(222)	0.2607	0.0179	0.6998	0.0353
H(231)	-0.0816	-0.0681	0.6754	0.0429
H(232)	0.0127	-0.0543	0.7255	0.0429
H(233)	-0.0039	-0.1853	0.6836	0.0429
H(241)	-0.0710	-0.0628	0.5706	0.0345
H(242)	0.0085	-0.1777	0.5785	0.0345
H(243)	0.0293	-0.0411	0.5449	0.0345
H(251)	0.2304	0.3080	0.6254	0.0358
H(252)	0.3072	0.2040	0.6583	0.0358
H(253)	0.2322	0.1590	0.5998	0.0358
H(261)	0.1839	0.3472	0.7260	0.0391
H(262)	0.1527	0.2244	0.7656	0.0391
H(263)	0.2620	0.2395	0.7537	0.0391
H(1)	0.161(9)	0.628(13)	0.727(6)	0.05
H(2)	0.148(9)	0.671(13)	0.781(6)	0.05

Table 4: Anisotropic thermal parameters (Å²)

Atom	U ₁₁	U ₂₂	U ₃₃	U ₂₃	U ₁₃	U ₁₂
Os(1)	0.01831(16)	0.01321(17)	0.01640(17)	0.00115(16)	0.00381(12)	0.00195(15)
O(1)	0.034(3)	0.023(3)	0.016(3)	-0.001(3)	0.001(2)	0.001(3)
O(2)	0.023(3)	0.024(3)	0.026(3)	-0.002(3)	0.001(2)	0.001(3)
O(3)	0.030(3)	0.014(3)	0.037(3)	0.002(3)	0.013(3)	-0.002(3)
C(1)	0.017(4)	0.018(4)	0.038(5)	0.003(4)	0.009(3)	0.010(3)
C(2)	0.041(5)	0.019(5)	0.030(5)	0.001(4)	0.020(4)	0.006(4)
C(3)	0.032(5)	0.029(5)	0.030(5)	0.012(4)	0.013(4)	0.007(4)
C(4)	0.036(5)	0.018(4)	0.026(5)	0.002(4)	-0.001(4)	0.005(4)
C(5)	0.030(4)	0.018(4)	0.022(4)	-0.000(4)	-0.001(3)	-0.003(4)
C(6)	0.029(4)	0.017(4)	0.022(4)	0.002(4)	0.001(4)	-0.003(3)
N(1)	0.032(4)	0.022(4)	0.022(4)	0.002(3)	0.005(3)	-0.002(3)
C(7)	0.035(6)	0.028(6)	0.030(5)	-0.002(4)	0.005(4)	0.002(4)
O(4)	0.033(4)	0.025(3)	0.035(4)	0.001(3)	0.010(3)	0.003(3)
O(5)	0.041(4)	0.015(3)	0.029(3)	-0.003(3)	0.010(3)	-0.003(3)
N(2)	0.023(4)	0.014(4)	0.015(4)	-0.000(3)	0.006(3)	0.002(3)
C(8)	0.024(4)	0.016(4)	0.029(5)	0.008(4)	0.002(4)	-0.001(3)
C(9)	0.015(4)	0.023(5)	0.043(6)	0.000(4)	0.003(4)	-0.004(3)
N(3)	0.017(3)	0.019(4)	0.028(4)	0.001(3)	0.001(3)	-0.001(3)
C(10)	0.026(4)	0.008(4)	0.047(6)	0.008(4)	0.014(4)	0.007(3)
C(11)	0.053(6)	0.013(4)	0.022(5)	-0.004(4)	-0.001(4)	0.006(4)
C(12)	0.022(4)	0.021(5)	0.039(5)	0.001(4)	-0.005(4)	0.003(3)
C(13)	0.023(4)	0.050(6)	0.018(4)	-0.013(4)	0.002(3)	-0.003(4)
Os(2)	0.01499(15)	0.01235(17)	0.01899(17)	0.00092(15)	0.00083(12)	0.00194(14)
O(6)	0.027(3)	0.018(3)	0.021(3)	-0.002(3)	0.006(2)	-0.002(2)
O(7)	0.022(3)	0.021(3)	0.029(3)	-0.004(3)	0.004(2)	0.006(2)
O(8)	0.023(3)	0.018(3)	0.035(3)	-0.000(3)	-0.002(2)	0.001(3)
C(14)	0.025(4)	0.019(4)	0.031(4)	0.010(4)	0.008(3)	0.009(4)
C(15)	0.024(4)	0.026(5)	0.022(4)	-0.002(4)	-0.005(3)	-0.001(4)
C(16)	0.036(5)	0.019(5)	0.029(5)	-0.003(4)	-0.005(4)	-0.001(4)
C(17)	0.032(5)	0.020(4)	0.034(5)	0.008(4)	0.004(4)	-0.003(4)
C(18)	0.021(4)	0.020(4)	0.038(5)	-0.001(4)	0.002(4)	0.007(3)
C(19)	0.026(4)	0.015(4)	0.023(4)	-0.006(3)	0.002(3)	0.002(3)
N(4)	0.020(3)	0.007(3)	0.025(4)	-0.001(3)	-0.000(3)	0.003(3)
C(20)	0.024(4)	0.012(4)	0.020(4)	-0.002(3)	-0.004(3)	-0.005(3)
O(9)	0.026(3)	0.023(3)	0.044(4)	-0.002(3)	-0.001(3)	-0.006(3)
O(10)	0.036(4)	0.017(3)	0.031(4)	0.001(3)	-0.004(3)	-0.001(3)
N(5)	0.023(4)	0.013(4)	0.026(4)	0.004(3)	0.000(3)	0.008(3)
C(21)	0.027(5)	0.024(5)	0.042(6)	0.003(4)	0.007(4)	0.012(4)
C(22)	0.029(5)	0.017(5)	0.042(6)	0.008(4)	-0.004(4)	0.006(3)
N(6)	0.018(3)	0.020(4)	0.019(3)	-0.000(3)	-0.002(3)	0.007(3)
C(23)	0.045(6)	0.024(5)	0.038(6)	0.008(4)	0.012(5)	0.005(4)
C(24)	0.041(5)	0.016(5)	0.029(5)	0.000(4)	0.001(4)	-0.004(4)
C(25)	0.020(4)	0.033(6)	0.037(5)	-0.007(4)	0.004(4)	0.002(4)
C(26)	0.030(5)	0.041(6)	0.027(5)	-0.012(5)	-0.011(4)	0.008(4)
O(11)	0.031(4)	0.106(9)	0.073(6)	-0.040(6)	0.025(4)	-0.022(5)

Table 5: Bond lengths (Å)

Os(1) - O(1)	1.732(6)	Os(2) - O(6)	1.730(5)
Os(1) - O(2)	1.742(6)	Os(2) - O(7)	1.735(6)
Os(1) - O(3)	1.966(5)	Os(2) - O(8)	1.973(6)
Os(1) - N(1)	1.988(9)	Os(2) - N(4)	2.009(7)
Os(1) - N(2)	2.210(8)	Os(2) - N(5)	2.211(8)
Os(1) - N(3)	2.240(7)	Os(2) - N(6)	2.234(6)
O(3) - C(1)	1.423(11)	O(8) - C(14)	1.45(1)
C(1) - C(2)	1.528(13)	C(14) - C(15)	1.506(12)
C(1) - C(6)	1.528(12)	C(14) - C(19)	1.493(13)
C(2) - C(3)	1.545(13)	C(15) - C(16)	1.538(13)
C(3) - C(4)	1.530(12)	C(16) - C(17)	1.528(13)
C(4) - C(5)	1.516(12)	C(17) - C(18)	1.511(13)
C(5) - C(6)	1.525(12)	C(18) - C(19)	1.519(12)
C(5) - O(5)	1.470(11)	C(18) - O(10)	1.443(11)
C(6) - N(1)	1.481(11)	C(19) - N(4)	1.484(11)
N(1) - C(7)	1.357(13)	N(4) - C(20)	1.345(11)
C(7) - O(4)	1.212(11)	C(20) - O(9)	1.21(1)
C(7) - O(5)	1.372(12)	C(20) - O(10)	1.389(11)
N(2) - C(8)	1.50(1)	N(5) - C(21)	1.484(11)
N(2) - C(10)	1.480(11)	N(5) - C(23)	1.502(12)
N(2) - C(11)	1.490(11)	N(5) - C(24)	1.458(12)
C(8) - C(9)	1.505(12)	C(21) - C(22)	1.520(14)
C(9) - N(3)	1.504(11)	C(22) - N(6)	1.490(11)
N(3) - C(12)	1.483(11)	N(6) - C(25)	1.479(11)
N(3) - C(13)	1.494(11)	N(6) - C(26)	1.487(11)
O(11) - H(1)	0.90(13)	O(11) - H(2)	0.75(13)

Note – Geometrically-positioned H atoms have been excluded

Table 6: Bond angles (°)

O(1) - Os(1) - O(2)	164.3(3)	O(6) - Os(2) - O(7)	163.9(3)
O(1) - Os(1) - O(3)	96.2(3)	O(6) - Os(2) - O(8)	97.7(3)
O(2) - Os(1) - O(3)	96.2(3)	O(7) - Os(2) - O(8)	94.9(3)
O(1) - Os(1) - N(1)	96.7(3)	O(6) - Os(2) - N(4)	97.4(3)
O(2) - Os(1) - N(1)	94.5(3)	O(7) - Os(2) - N(4)	94.2(3)
O(3) - Os(1) - N(1)	81.5(3)	O(8) - Os(2) - N(4)	82.0(3)
O(1) - Os(1) - N(2)	87.0(3)	O(6) - Os(2) - N(5)	83.9(3)
O(2) - Os(1) - N(2)	82.9(3)	O(7) - Os(2) - N(5)	85.7(3)
O(3) - Os(1) - N(2)	92.6(3)	O(8) - Os(2) - N(5)	92.2(3)
N(1) - Os(1) - N(2)	173.3(3)	N(4) - Os(2) - N(5)	174.1(3)
O(1) - Os(1) - N(3)	82.5(3)	O(6) - Os(2) - N(6)	84.7(3)
O(2) - Os(1) - N(3)	84.1(3)	O(7) - Os(2) - N(6)	81.7(2)
O(3) - Os(1) - N(3)	173.9(3)	O(8) - Os(2) - N(6)	173.2(3)
N(1) - Os(1) - N(3)	104.6(3)	N(4) - Os(2) - N(6)	104.1(3)
N(2) - Os(1) - N(3)	81.3(3)	N(5) - Os(2) - N(6)	81.8(3)
Os(1) - O(3) - C(1)	115.9(5)	Os(2) - O(8) - C(14)	114.2(5)
O(3) - C(1) - C(2)	111.3(7)	O(8) - C(14) - C(15)	111.8(7)
O(3) - C(1) - C(6)	107.1(6)	O(8) - C(14) - C(19)	108.6(7)
C(2) - C(1) - C(6)	111.7(7)	C(15) - C(14) - C(19)	113.5(8)
C(1) - C(2) - C(3)	109.5(8)	C(14) - C(15) - C(16)	110.4(8)
C(2) - C(3) - C(4)	109.1(7)	C(15) - C(16) - C(17)	109.1(7)
C(3) - C(4) - C(5)	112.5(7)	C(16) - C(17) - C(18)	113.8(8)
C(4) - C(5) - C(6)	113.9(7)	C(17) - C(18) - C(19)	114.4(8)
C(4) - C(5) - O(5)	109.0(7)	C(17) - C(18) - O(10)	109.5(7)
C(6) - C(5) - O(5)	101.2(7)	C(19) - C(18) - O(10)	103.4(7)
C(1) - C(6) - C(5)	120.2(7)	C(14) - C(19) - C(18)	120.4(8)
C(1) - C(6) - N(1)	106.7(7)	C(14) - C(19) - N(4)	107.3(7)
C(5) - C(6) - N(1)	102.0(7)	C(18) - C(19) - N(4)	100.9(7)
Os(1) - N(1) - C(6)	112.5(6)	Os(2) - N(4) - C(19)	111.5(5)
Os(1) - N(1) - C(7)	138.6(7)	Os(2) - N(4) - C(20)	138.8(6)
C(6) - N(1) - C(7)	107.9(8)	C(19) - N(4) - C(20)	109.4(7)
N(1) - C(7) - O(4)	129.4(10)	N(4) - C(20) - O(9)	129.8(9)
N(1) - C(7) - O(5)	110.6(8)	N(4) - C(20) - O(10)	110.2(7)
O(4) - C(7) - O(5)	120.0(9)	O(9) - C(20) - O(10)	120.0(8)
C(5) - O(5) - C(7)	108.9(7)	C(18) - O(10) - C(20)	107.9(7)
Os(1) - N(2) - C(8)	105.8(5)	Os(2) - N(5) - C(21)	106.1(6)
Os(1) - N(2) - C(10)	110.2(5)	Os(2) - N(5) - C(23)	112.0(6)
C(8) - N(2) - C(10)	109.4(7)	C(21) - N(5) - C(23)	111.7(7)
Os(1) - N(2) - C(11)	113.2(5)	Os(2) - N(5) - C(24)	110.8(5)
C(8) - N(2) - C(11)	111.2(7)	C(21) - N(5) - C(24)	109.4(7)
C(10) - N(2) - C(11)	107.0(7)	C(23) - N(5) - C(24)	106.8(8)
N(2) - C(8) - C(9)	110.0(7)	N(5) - C(21) - C(22)	111.9(7)
C(8) - C(9) - N(3)	111.1(7)	C(21) - C(22) - N(6)	110.9(7)
Os(1) - N(3) - C(9)	106.5(5)	Os(2) - N(6) - C(22)	106.5(5)
Os(1) - N(3) - C(12)	113.9(5)	Os(2) - N(6) - C(25)	113.3(5)
C(9) - N(3) - C(12)	107.9(7)	C(22) - N(6) - C(25)	108.8(7)
Os(1) - N(3) - C(13)	112.3(5)	Os(2) - N(6) - C(26)	113.1(5)
C(9) - N(3) - C(13)	108.9(7)	C(22) - N(6) - C(26)	107.1(7)
C(12) - N(3) - C(13)	107.2(7)	C(25) - N(6) - C(26)	107.8(7)
H(1) - O(11) - H(2)	105.(12)		

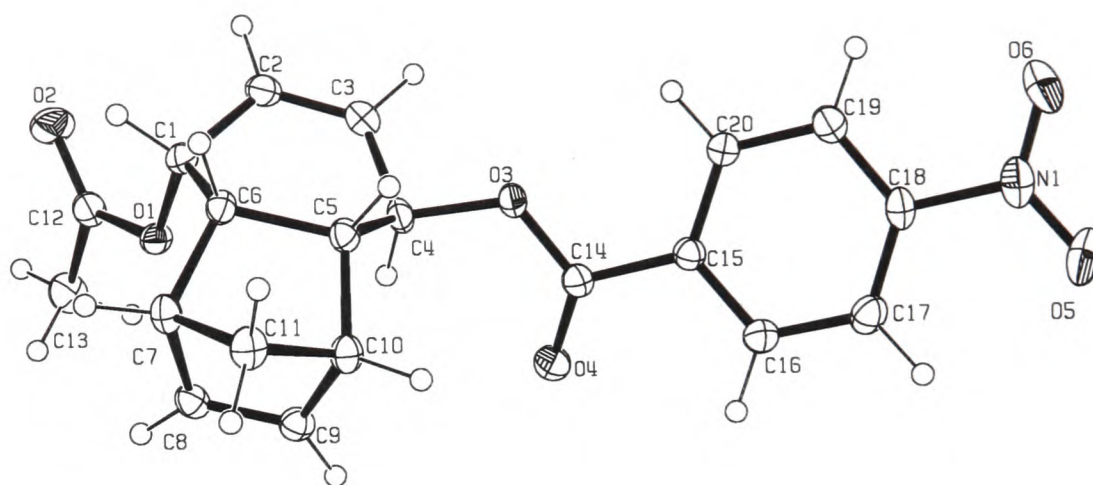
Note – Geometrically-positioned H atoms have been excluded

Inorganic Chemistry Crystallography Service

Single-crystal X-ray diffraction report for C₂₀H₁₉NO₆ (ARC587)

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Crystals of **ARC587** were grown by cooling of a saturated methanolic solution. A large single crystal was cut to give a fragment having dimensions approximately 0.30 x 0.34 x 0.34 mm. This was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150K 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 package¹.

The structure was solved in the space group $P\bar{1}$ using the direct-methods program SIR92², which located all non-hydrogen atoms. Subsequent full-matrix least-squares refinement was carried out using the CRYSTALS program suite³. Coordinates and anisotropic thermal parameters of all non-hydrogen atoms were refined. Hydrogen atoms were positioned geometrically after each cycle of refinement. A 3-term Chebychev polynomial weighting scheme was applied. Refinement converged satisfactorily to give $R = 0.0429$, $wR = 0.0533$.

Attached is a thermal ellipsoid plot (ORTEP-3⁴) at 40% 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 and W. Minor, *Processing of X-ray Diffraction Data Collected in Oscillation Mode, Methods Enzymol.*, 1997, **276**, Eds C. W. Carter and R. M. Sweet, Academic Press.
- 2 A. Altomare, G. Cascarano, G. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori and M. Camalli, *J. Appl. Cryst.* 1994, **27**, 435.
- 3 D. J. Watkin, C. K. Prout, J. R. Carruthers, P. W. Betteridge and R. I. Cooper, CRYSTALS issue 11, Chemical Crystallography Laboratory, Oxford, UK, 2001.
- 4 ORTEP-3 v. 1.0.2, C. K. Johnson and M. K. Burnett, 1998.

Table 1: Crystal data and refinement details

Crystal identification	ARC587
Chemical formula	C ₂₀ H ₁₉ NO ₆
Formula weight	369.37
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Triclinic
Space group	<i>P</i> 1
<i>a</i> (Å)	8.4018(2)
<i>b</i> (Å)	9.7448(3)
<i>c</i> (Å)	11.3421(3)
α (°)	99.0488(15)
β (°)	110.6383(16)
γ (°)	90.6076(10)
Cell volume (Å ³)	856.0
<i>Z</i>	2
Calculated density (Mg/m ³)	1.433
Absorption coefficient (mm ⁻¹)	0.107
<i>F</i> ₀₀₀	388
Crystal size (mm)	0.30 x 0.34 x 0.34
Description of crystal	Pale-yellow fragment
Absorption correction	Semi-empirical from equivalent reflections
Transmission coefficients (min,max)	0.96, 0.97
θ range for data collection (°)	5.0 ≤ θ ≤ 27.5
Index ranges	-10 ≤ <i>h</i> ≤ 10, -12 ≤ <i>k</i> ≤ 12, 0 ≤ <i>l</i> ≤ 14
Reflections measured	11061
Unique reflections	3875
<i>R</i> _{int}	0.044
Observed reflections (<i>I</i> > 3 σ (<i>I</i>))	2558
Refinement method	Full-matrix least-squares on <i>F</i>
Parameters refined	244
Weighting scheme	Chebyshev 3-term polynomial
Goodness of fit	1.0537
<i>R</i>	0.0429
<i>wR</i>	0.0533
Residual electron density (min,max) (eÅ ⁻³)	-0.34, 0.30

Table 2: Atomic coordinates and equivalent isotropic thermal parameters (Å²) of non-hydrogen atoms

Atom	x	y	z	U _{equiv}
C(1)	0.0179(2)	-0.10205(18)	0.25436(16)	0.0236
C(2)	0.0413(2)	-0.15288(19)	0.12936(16)	0.0268
C(3)	0.1634(2)	-0.09235(19)	0.10178(17)	0.0272
C(4)	0.2784(2)	0.02809(18)	0.19077(16)	0.0233
C(5)	0.1805(2)	0.12970(18)	0.25080(16)	0.0228
C(6)	0.0444(2)	0.05650(17)	0.29010(16)	0.0219
C(7)	0.0912(2)	0.12502(17)	0.43318(17)	0.0243
C(8)	0.2662(2)	0.08366(17)	0.50996(16)	0.0248
C(9)	0.3808(2)	0.14693(18)	0.47577(17)	0.0248
C(10)	0.2850(2)	0.23271(18)	0.37598(17)	0.0251
C(11)	0.1397(2)	0.27548(18)	0.42439(18)	0.0276
O(1)	0.13873(15)	-0.16895(12)	0.35340(11)	0.0233
C(12)	0.0882(2)	-0.29937(18)	0.35786(16)	0.0265
C(13)	0.2171(3)	-0.3572(2)	0.46379(19)	0.0341
O(2)	-0.0445(2)	-0.35947(15)	0.28584(14)	0.0408
O(3)	0.34423(16)	0.10129(14)	0.11205(11)	0.0270
C(14)	0.5062(2)	0.15404(19)	0.16077(16)	0.0245
O(4)	0.60846(17)	0.13765(16)	0.26251(13)	0.0361
C(15)	0.5460(2)	0.23780(18)	0.07320(16)	0.0227
C(16)	0.6861(2)	0.33490(19)	0.12414(17)	0.0273
C(17)	0.7270(2)	0.41483(19)	0.04626(18)	0.0297
C(18)	0.6243(2)	0.39513(18)	-0.08122(17)	0.0264
C(19)	0.4841(2)	0.2993(2)	-0.13534(17)	0.0299
C(20)	0.4458(2)	0.22047(19)	-0.05605(17)	0.0267
N(1)	0.6637(2)	0.48102(18)	-0.16501(17)	0.0362
O(5)	0.7994(2)	0.5519(2)	-0.12242(18)	0.0582
O(6)	0.5585(2)	0.47772(19)	-0.27265(16)	0.0530

Table 3: Atomic coordinates and isotropic thermal parameters (Å²) of hydrogen atoms

Atom	x	y	z	U _{iso}
H(11)	-0.1016	-0.1275	0.2462	0.0279
H(21)	-0.0349	-0.2319	0.0673	0.0309
H(31)	0.1790	-0.1283	0.0192	0.0332
H(41)	0.3701	-0.0065	0.2611	0.0299
H(51)	0.1318	0.1821	0.1785	0.0281
H(61)	-0.0755	0.0724	0.2381	0.0271
H(71)	0.0020	0.1050	0.4689	0.0311
H(81)	0.2912	0.0203	0.5746	0.0298
H(91)	0.5069	0.1391	0.5098	0.0292
H(101)	0.3596	0.3049	0.3628	0.0311
H(111)	0.1802	0.3392	0.5090	0.0346
H(112)	0.0459	0.3176	0.3616	0.0346
H(131)	0.1762	-0.4536	0.4647	0.0416
H(132)	0.2328	-0.2966	0.5474	0.0416
H(133)	0.3282	-0.3599	0.4500	0.0416
H(161)	0.7575	0.3471	0.2172	0.0321
H(171)	0.8277	0.4844	0.0815	0.0358
H(191)	0.4131	0.2875	-0.2284	0.0367
H(201)	0.3454	0.1506	-0.0920	0.0320

Table 4: Anisotropic thermal parameters ($\text{\AA}^2$)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C(1)	0.0197(8)	0.0272(9)	0.0230(8)	0.0069(7)	0.0056(6)	-0.0000(6)
C(2)	0.0289(9)	0.0267(9)	0.0216(8)	0.0034(7)	0.0056(7)	-0.0001(7)
C(3)	0.0311(9)	0.0288(9)	0.0231(8)	0.0059(7)	0.0105(7)	0.0041(7)
C(4)	0.0237(8)	0.0293(9)	0.0217(8)	0.0105(7)	0.0113(7)	0.0028(7)
C(5)	0.0235(8)	0.0232(8)	0.0236(8)	0.0092(6)	0.0088(6)	0.0016(6)
C(6)	0.0188(8)	0.0242(8)	0.0247(8)	0.0085(6)	0.0086(6)	0.0026(6)
C(7)	0.0298(9)	0.0207(8)	0.0271(9)	0.0054(6)	0.0155(7)	0.0018(7)
C(8)	0.0328(9)	0.0202(8)	0.0214(8)	0.0040(6)	0.0095(7)	0.0002(7)
C(9)	0.0261(9)	0.0225(8)	0.0245(8)	0.0036(6)	0.0076(7)	0.0006(6)
C(10)	0.0286(9)	0.0207(8)	0.0284(9)	0.0076(6)	0.0120(7)	0.0006(6)
C(11)	0.034(1)	0.0179(8)	0.034(1)	0.0058(7)	0.0161(8)	0.0040(7)
O(1)	0.0244(6)	0.0200(6)	0.0239(6)	0.0064(4)	0.0059(5)	-0.0021(5)
C(12)	0.035(1)	0.0197(8)	0.0256(9)	0.0007(6)	0.0133(8)	-0.0033(7)
C(13)	0.0458(12)	0.0223(9)	0.036(1)	0.0089(7)	0.0150(9)	0.0021(8)
O(2)	0.0462(9)	0.0299(7)	0.0367(8)	0.0007(6)	0.0059(7)	-0.0153(6)
O(3)	0.0228(6)	0.0381(7)	0.0231(6)	0.0120(5)	0.0092(5)	-0.0010(5)
C(14)	0.0237(8)	0.0288(9)	0.0222(8)	0.0044(6)	0.0096(7)	0.0012(7)
O(4)	0.0298(7)	0.0477(8)	0.0282(7)	0.0166(6)	0.0032(6)	-0.0030(6)
C(15)	0.0220(8)	0.0248(8)	0.0220(8)	0.0041(6)	0.0087(7)	0.0024(6)
C(16)	0.0271(9)	0.0289(9)	0.0243(8)	0.0013(7)	0.0087(7)	-0.0024(7)
C(17)	0.032(1)	0.0248(9)	0.033(1)	-0.0012(7)	0.0148(8)	-0.0041(7)
C(18)	0.033(1)	0.0233(8)	0.0307(9)	0.0071(7)	0.0202(8)	0.0032(7)
C(19)	0.0296(9)	0.036(1)	0.0259(9)	0.0096(7)	0.0106(7)	0.0015(8)
C(20)	0.0238(9)	0.0325(9)	0.0238(8)	0.0070(7)	0.0075(7)	-0.0024(7)
N(1)	0.046(1)	0.0310(9)	0.043(1)	0.0101(7)	0.0288(9)	0.0024(7)
O(5)	0.0625(12)	0.0547(11)	0.0660(12)	0.0184(9)	0.031(1)	-0.0199(9)
O(6)	0.0681(11)	0.0599(11)	0.0393(9)	0.0248(8)	0.0225(8)	-0.0015(9)

Table 5: Bond lengths (Å)

C(1) - C(2)	1.507(2)	O(1) - C(12)	1.350(2)
C(1) - C(6)	1.527(2)	C(12) - C(13)	1.497(3)
C(1) - O(1)	1.469(2)	C(12) - O(2)	1.203(2)
C(2) - C(3)	1.331(3)	O(3) - C(14)	1.337(2)
C(3) - C(4)	1.498(3)	C(14) - O(4)	1.207(2)
C(4) - C(5)	1.523(2)	C(14) - C(15)	1.499(2)
C(4) - O(3)	1.4670(19)	C(15) - C(16)	1.393(2)
C(5) - C(6)	1.568(2)	C(15) - C(20)	1.391(2)
C(5) - C(10)	1.565(2)	C(16) - C(17)	1.389(3)
C(6) - C(7)	1.561(2)	C(17) - C(18)	1.379(3)
C(7) - C(8)	1.518(3)	C(18) - C(19)	1.387(3)
C(7) - C(11)	1.545(2)	C(18) - N(1)	1.476(2)
C(8) - C(9)	1.336(3)	C(19) - C(20)	1.385(2)
C(9) - C(10)	1.516(2)	N(1) - O(5)	1.225(2)
C(10) - C(11)	1.542(3)	N(1) - O(6)	1.224(2)

Note – H atoms have been excluded

Table 6: Bond angles (°)

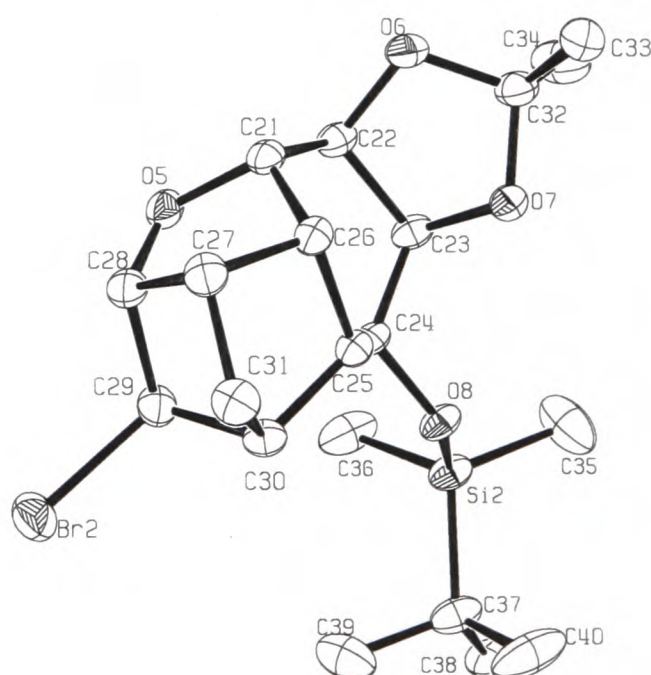
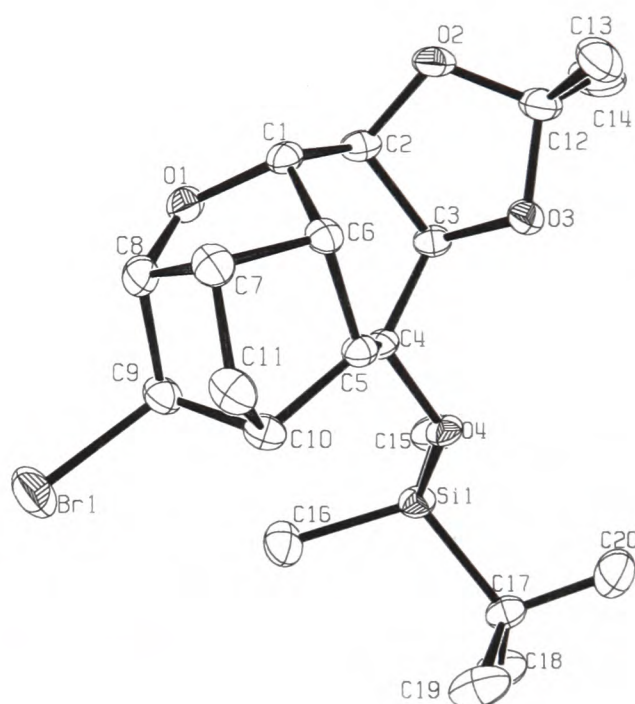
C(2) - C(1) - C(6)	111.38(14)	C(7) - C(11) - C(10)	93.99(13)
C(2) - C(1) - O(1)	108.22(14)	C(1) - O(1) - C(12)	115.23(13)
C(6) - C(1) - O(1)	111.04(13)	O(1) - C(12) - C(13)	111.32(15)
C(1) - C(2) - C(3)	119.86(16)	O(1) - C(12) - O(2)	123.55(17)
C(2) - C(3) - C(4)	121.93(16)	C(13) - C(12) - O(2)	125.12(17)
C(3) - C(4) - C(5)	111.41(14)	C(4) - O(3) - C(14)	118.76(13)
C(3) - C(4) - O(3)	106.24(14)	O(3) - C(14) - O(4)	124.82(16)
C(5) - C(4) - O(3)	107.85(13)	O(3) - C(14) - C(15)	111.44(14)
C(4) - C(5) - C(6)	113.55(14)	O(4) - C(14) - C(15)	123.73(16)
C(4) - C(5) - C(10)	117.76(14)	C(14) - C(15) - C(16)	118.49(15)
C(6) - C(5) - C(10)	102.85(13)	C(14) - C(15) - C(20)	121.33(16)
C(1) - C(6) - C(5)	117.08(14)	C(16) - C(15) - C(20)	120.18(16)
C(1) - C(6) - C(7)	118.79(14)	C(15) - C(16) - C(17)	120.27(16)
C(5) - C(6) - C(7)	102.65(13)	C(16) - C(17) - C(18)	117.88(17)
C(6) - C(7) - C(8)	108.79(13)	C(17) - C(18) - C(19)	123.47(17)
C(6) - C(7) - C(11)	99.19(13)	C(17) - C(18) - N(1)	118.68(17)
C(8) - C(7) - C(11)	99.34(14)	C(19) - C(18) - N(1)	117.85(17)
C(7) - C(8) - C(9)	107.83(14)	C(18) - C(19) - C(20)	117.71(17)
C(8) - C(9) - C(10)	107.56(15)	C(15) - C(20) - C(19)	120.50(17)
C(5) - C(10) - C(9)	107.89(14)	C(18) - N(1) - O(5)	118.01(18)
C(5) - C(10) - C(11)	99.45(14)	C(18) - N(1) - O(6)	118.09(17)
C(9) - C(10) - C(11)	99.73(14)	O(5) - N(1) - O(6)	123.90(18)

Note – H atoms have been excluded

Inorganic Chemistry Crystallography Service

Single-crystal X-ray diffraction report for C₂₀H₃₃BrO₄Si (ARC563)

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Views of the two crystallographically-distinct molecules

Crystals of **ARC563** were grown by evaporation from chloroform. A large single crystal was cut to give a fragment having dimensions approximately 0.20 x 0.24 x 0.24 mm. This was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150K 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 package¹.

The structure was solved in the space group $P\bar{1}$ using the direct-methods program SIR92², which located all non-hydrogen atoms. Subsequent full-matrix least-squares refinement was carried out using the CRYSTALS program suite³. Coordinates and anisotropic thermal parameters of all non-hydrogen atoms were refined. Hydrogen atoms were positioned geometrically after each cycle of refinement. A 3-term Chebychev polynomial weighting scheme was applied. Refinement converged satisfactorily to give $R = 0.0460$, $wR = 0.0579$.

Attached is a thermal ellipsoid plot (ORTEP-3⁴) at 40% 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:

The asymmetric unit contains two crystallographically-distinct molecules. The polycyclic cores of the molecules have very similar geometries and are approximately related by a non-crystallographic translation, but the TBDMS groups have different orientations.

The largest peak of residual electron density lies *ca.* 0.4 Å from one of the Si atoms (Si(2)), suggesting that this *t*-butyldimethylsilyl group may be disordered. However, attempts to model this led to no improvement in the agreement with the X-ray data and so disorder has been ignored.

References:

- 1 Z. Otwinowski and W. Minor, *Processing of X-ray Diffraction Data Collected in Oscillation Mode, Methods Enzymol.*, 1997, **276**, Eds C. W. Carter and R. M. Sweet, Academic Press.
- 2 A. Altomare, G. Cascarano, G. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori and M. Camalli, *J. Appl. Cryst.* 1994, **27**, 435.
- 3 D. J. Watkin, C. K. Prout, J. R. Carruthers, P. W. Betteridge and R. I. Cooper, CRYSTALS issue 11, Chemical Crystallography Laboratory, Oxford, UK, 2001.
- 4 ORTEP-3 v. 1.0.2, C. K. Johnson and M. K. Burnett, 1998.

Table 1: Crystal data and refinement details

Crystal identification	ARC563
Chemical formula	C ₂₀ H ₃₃ BrO ₄ Si
Formula weight	445.47
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Triclinic
Space group	<i>P</i> 1
<i>a</i> (Å)	12.0979(2)
<i>b</i> (Å)	12.2814(2)
<i>c</i> (Å)	16.6145(3)
α (°)	110.8231(8)
β (°)	102.1852(9)
γ (°)	94.4682(8)
Cell volume (Å ³)	2223.5
<i>Z</i>	4
Calculated density (Mg/m ³)	1.331
Absorption coefficient (mm ⁻¹)	1.923
<i>F</i> ₀₀₀	935.020
Crystal size (mm)	0.20 x 0.24 x 0.24
Description of crystal	Colourless fragment
Absorption correction	Semi-empirical from equivalent reflections
Transmission coefficients (min,max)	0.63, 0.68
θ range for data collection (°)	5.0 ≤ θ ≤ 27.5
Index ranges	-15 ≤ <i>h</i> ≤ 15, -15 ≤ <i>k</i> ≤ 14, 0 ≤ <i>l</i> ≤ 21
Reflections measured	32169
Unique reflections	10095
<i>R</i> _{int}	0.036
Observed reflections (<i>I</i> > 3 σ (<i>I</i>))	6993
Refinement method	Full-matrix least-squares on <i>F</i>
Parameters refined	469
Weighting scheme	Chebyshev 3-term polynomial
Goodness of fit	1.0305
<i>R</i>	0.0460
<i>wR</i>	0.0579
Residual electron density (min,max) (eÅ ⁻³)	-0.81, 1.79

Table 2: Atomic coordinates and equivalent isotropic thermal parameters (Å²) of non-hydrogen atoms

Atom	x	y	z	U _{equiv}
C(1)	0.3400(2)	0.4774(2)	-0.13780(18)	0.0262
C(2)	0.3344(2)	0.5450(2)	-0.04291(17)	0.0279
C(3)	0.2785(2)	0.4683(2)	-0.00131(17)	0.0256
C(4)	0.2972(2)	0.3413(2)	-0.03953(16)	0.0226
C(5)	0.2423(2)	0.2837(2)	-0.13952(17)	0.0232
C(6)	0.2482(2)	0.3691(2)	-0.19021(16)	0.0248
C(7)	0.2979(3)	0.2991(3)	-0.26740(18)	0.0319
C(8)	0.4236(3)	0.3189(3)	-0.21283(19)	0.0329
C(9)	0.4229(2)	0.2198(2)	-0.17632(19)	0.0310
C(10)	0.2950(2)	0.1775(2)	-0.19212(18)	0.0292
C(11)	0.2497(3)	0.1707(3)	-0.28809(19)	0.0358
O(1)	0.44587(16)	0.43085(17)	-0.13903(14)	0.0312
O(2)	0.25835(19)	0.62778(17)	-0.04537(14)	0.0355
O(3)	0.16069(16)	0.47824(17)	-0.02474(13)	0.0297
C(12)	0.1578(3)	0.5962(2)	-0.0201(2)	0.0348
C(13)	0.0527(3)	0.5957(3)	-0.0879(2)	0.0468
C(14)	0.1632(4)	0.6808(3)	0.0731(2)	0.0562
O(4)	0.25262(16)	0.27209(16)	0.00299(12)	0.0274
Si(1)	0.33253(7)	0.22805(7)	0.07600(5)	0.0279
C(15)	0.3966(3)	0.3539(3)	0.1835(2)	0.0460
C(16)	0.4515(3)	0.1601(3)	0.0323(2)	0.0440
C(17)	0.2304(3)	0.1160(2)	0.08899(18)	0.0313
C(18)	0.2862(3)	0.0818(3)	0.1662(2)	0.0482
C(19)	0.1931(4)	0.0056(3)	0.0039(2)	0.0560
C(20)	0.1244(4)	0.1695(4)	0.1084(3)	0.0612
Br(1)	0.49636(3)	0.09101(3)	-0.24206(3)	0.0514
C(21)	0.8326(2)	0.4623(2)	0.36167(18)	0.0283
C(22)	0.8359(2)	0.5359(2)	0.45817(18)	0.0300
C(23)	0.7814(2)	0.4664(2)	0.50503(17)	0.0288
C(24)	0.7894(2)	0.3368(2)	0.46819(16)	0.0250
C(25)	0.7298(2)	0.2770(2)	0.36870(16)	0.0243
C(26)	0.7370(2)	0.3574(2)	0.31436(17)	0.0264
C(27)	0.7794(2)	0.2791(3)	0.23585(18)	0.0321
C(28)	0.9065(3)	0.2943(3)	0.2869(2)	0.0334
C(29)	0.9039(2)	0.2009(3)	0.32890(19)	0.0321
C(30)	0.7759(2)	0.1653(2)	0.31710(17)	0.0287
C(31)	0.7268(3)	0.1537(3)	0.22049(18)	0.0341
O(5)	0.93545(16)	0.41042(18)	0.35735(14)	0.0333
O(6)	0.76575(19)	0.62445(18)	0.45872(14)	0.0359
O(7)	0.66541(17)	0.48482(17)	0.48761(13)	0.0316
C(32)	0.6693(3)	0.6034(3)	0.4926(2)	0.0362
C(33)	0.5616(3)	0.6115(3)	0.4322(3)	0.0468
C(34)	0.6898(4)	0.6901(3)	0.5879(2)	0.0586
O(8)	0.74133(16)	0.27286(17)	0.51250(12)	0.0301
Si(2)	0.79716(7)	0.26396(7)	0.60878(5)	0.0333
C(35)	0.7238(5)	0.3549(5)	0.6912(3)	0.0740
C(36)	0.9519(3)	0.3235(4)	0.6492(3)	0.0590
C(37)	0.7682(3)	0.1053(3)	0.5929(2)	0.0413
C(38)	0.7920(3)	0.0924(3)	0.6828(2)	0.0431
C(39)	0.8499(4)	0.0371(3)	0.5393(3)	0.0607
C(40)	0.6466(4)	0.0478(4)	0.5394(3)	0.0764
Br(2)	0.97043(3)	0.06433(3)	0.26593(2)	0.0466

Table 3: Atomic coordinates and isotropic thermal parameters ($\text{\AA}^2$) of hydrogen atoms

Atom	x	y	z	U_{iso}
H(11)	0.3307	0.5376	-0.1654	0.0343
H(21)	0.4154	0.5793	-0.0076	0.0335
H(31)	0.3114	0.4942	0.0644	0.0318
H(41)	0.3821	0.3440	-0.0284	0.0291
H(51)	0.1622	0.2574	-0.1389	0.0284
H(61)	0.1719	0.3935	-0.2045	0.0311
H(71)	0.2848	0.3187	-0.3218	0.0408
H(81)	0.4818	0.3182	-0.2477	0.0435
H(91)	0.4664	0.2470	-0.1124	0.0394
H(101)	0.2791	0.1062	-0.1780	0.0345
H(111)	0.2832	0.1130	-0.3320	0.0416
H(112)	0.1641	0.1527	-0.3091	0.0416
H(131)	-0.0177	0.5738	-0.0707	0.0632
H(132)	0.0539	0.6762	-0.0900	0.0632
H(133)	0.0521	0.5369	-0.1479	0.0632
H(141)	0.0932	0.6589	0.0908	0.0724
H(142)	0.1666	0.7632	0.0746	0.0724
H(143)	0.2331	0.6763	0.1155	0.0724
H(151)	0.4442	0.3249	0.2262	0.0533
H(152)	0.4460	0.4144	0.1735	0.0533
H(153)	0.3341	0.3900	0.2088	0.0533
H(161)	0.4987	0.1341	0.0771	0.0594
H(162)	0.5008	0.2195	0.0211	0.0594
H(163)	0.4185	0.0903	-0.0246	0.0594
H(181)	0.2305	0.0221	0.1720	0.0626
H(182)	0.3560	0.0472	0.1543	0.0626
H(183)	0.3085	0.1536	0.2227	0.0626
H(191)	0.1389	-0.0530	0.0120	0.0635
H(192)	0.2620	-0.0297	-0.0098	0.0635
H(193)	0.1541	0.0270	-0.0464	0.0635
H(201)	0.0694	0.1105	0.1154	0.0856
H(202)	0.1478	0.2419	0.1645	0.0856
H(203)	0.0867	0.1912	0.0579	0.0856
H(211)	0.8225	0.5204	0.3322	0.0369
H(221)	0.9189	0.5660	0.4893	0.0370
H(231)	0.8207	0.4934	0.5698	0.0348
H(241)	0.8736	0.3347	0.4783	0.0320
H(251)	0.6495	0.2569	0.3719	0.0299
H(261)	0.6625	0.3857	0.3015	0.0330
H(271)	0.7643	0.2951	0.1799	0.0413
H(281)	0.9621	0.2856	0.2491	0.0445
H(291)	0.9497	0.2313	0.3924	0.0421
H(301)	0.7585	0.0967	0.3341	0.0354
H(311)	0.7559	0.0914	0.1763	0.0409
H(312)	0.6411	0.1395	0.2024	0.0409
H(331)	0.4943	0.5970	0.4553	0.0634
H(332)	0.5674	0.6921	0.4300	0.0634
H(333)	0.5512	0.5508	0.3709	0.0634
H(341)	0.6230	0.6757	0.6116	0.0717
H(342)	0.7611	0.6791	0.6253	0.0717
H(343)	0.6988	0.7726	0.5898	0.0717

H(351)	0.7559	0.3513	0.7506	0.0981
H(352)	0.7365	0.4388	0.6962	0.0981
H(353)	0.6397	0.3233	0.6708	0.0981
H(361)	0.9829	0.3166	0.7077	0.0698
H(362)	0.9644	0.4084	0.6569	0.0698
H(363)	0.9925	0.2776	0.6049	0.0698
H(381)	0.7761	0.0069	0.6730	0.0571
H(382)	0.8741	0.1252	0.7156	0.0571
H(383)	0.7413	0.1365	0.7186	0.0571
H(391)	0.8350	-0.0482	0.5304	0.0721
H(392)	0.9314	0.0715	0.5732	0.0721
H(393)	0.8355	0.0442	0.4800	0.0721
H(401)	0.6345	-0.0369	0.5324	0.0874
H(402)	0.5915	0.0899	0.5713	0.0874
H(403)	0.6334	0.0525	0.4794	0.0874

Table 4: Anisotropic thermal parameters (Å²)

Atom	U ₁₁	U ₂₂	U ₃₃	U ₂₃	U ₁₃	U ₁₂
C(1)	0.0236(11)	0.0294(12)	0.0327(13)	0.0203(11)	0.006(1)	0.005(1)
C(2)	0.0297(13)	0.0253(12)	0.0288(13)	0.015(1)	0.001(1)	0.001(1)
C(3)	0.0299(13)	0.0261(12)	0.0235(11)	0.014(1)	0.004(1)	0.005(1)
C(4)	0.0236(11)	0.0252(11)	0.0239(11)	0.016(1)	0.0054(9)	0.0043(9)
C(5)	0.0227(11)	0.0229(11)	0.0253(11)	0.0121(9)	0.0041(9)	0.0033(9)
C(6)	0.0265(12)	0.0284(12)	0.0227(11)	0.014(1)	0.004(1)	0.009(1)
C(7)	0.0391(15)	0.0386(14)	0.0242(12)	0.0174(11)	0.0090(11)	0.0136(12)
C(8)	0.0355(14)	0.0390(15)	0.0343(14)	0.0202(12)	0.0163(12)	0.0121(12)
C(9)	0.0337(14)	0.0317(13)	0.0332(14)	0.0161(11)	0.0103(11)	0.0136(11)
C(10)	0.0318(13)	0.0257(12)	0.0288(13)	0.011(1)	0.0035(11)	0.007(1)
C(11)	0.0430(16)	0.0353(14)	0.0256(13)	0.0082(11)	0.0059(12)	0.0113(12)
O(1)	0.0240(9)	0.035(1)	0.0416(11)	0.0228(9)	0.0088(8)	0.0063(8)
O(2)	0.0477(12)	0.0268(9)	0.0426(11)	0.0215(9)	0.017(1)	0.0133(9)
O(3)	0.032(1)	0.0303(9)	0.034(1)	0.0173(8)	0.0129(8)	0.0122(8)
C(12)	0.0488(17)	0.0289(13)	0.0370(15)	0.0190(12)	0.0173(13)	0.0156(12)
C(13)	0.0496(19)	0.0524(19)	0.056(2)	0.0329(17)	0.0208(16)	0.0288(16)
C(14)	0.099(3)	0.0382(17)	0.0441(18)	0.0185(15)	0.034(2)	0.0268(19)
O(4)	0.0302(9)	0.0302(9)	0.0318(9)	0.0224(8)	0.0092(8)	0.0061(7)
Si(1)	0.0307(4)	0.0293(4)	0.0285(3)	0.0177(3)	0.0055(3)	0.0056(3)
C(15)	0.059(2)	0.0379(16)	0.0366(16)	0.0168(13)	0.0018(15)	-0.0032(15)
C(16)	0.0406(16)	0.058(2)	0.0503(18)	0.0339(16)	0.0171(14)	0.0227(15)
C(17)	0.0380(14)	0.0308(13)	0.0304(13)	0.0186(11)	0.0083(11)	0.0033(11)
C(18)	0.065(2)	0.0482(18)	0.0436(18)	0.0350(16)	0.0092(16)	0.0057(16)
C(19)	0.076(3)	0.0395(18)	0.0431(18)	0.0146(15)	0.0058(18)	-0.0120(17)
C(20)	0.054(2)	0.071(3)	0.089(3)	0.052(2)	0.039(2)	0.0194(19)
Br(1)	0.0525(2)	0.0515(2)	0.0622(2)	0.02419(17)	0.02675(17)	0.03120(16)
C(21)	0.0272(12)	0.0324(13)	0.0328(13)	0.0212(11)	0.0070(11)	0.006(1)
C(22)	0.0281(13)	0.0319(13)	0.0324(13)	0.0188(11)	0.0028(11)	0.0007(11)
C(23)	0.0342(14)	0.0301(12)	0.0228(12)	0.014(1)	0.003(1)	0.000(1)
C(24)	0.0260(12)	0.0312(12)	0.0229(11)	0.018(1)	0.004(1)	0.002(1)
C(25)	0.0240(12)	0.0291(12)	0.0215(11)	0.013(1)	0.0033(9)	0.003(1)
C(26)	0.0237(12)	0.0344(13)	0.0245(12)	0.0169(11)	0.003(1)	0.005(1)
C(27)	0.0355(14)	0.0405(15)	0.0271(13)	0.0198(12)	0.0080(11)	0.0113(12)
C(28)	0.0339(14)	0.0386(15)	0.0386(15)	0.0246(13)	0.0127(12)	0.0120(12)
C(29)	0.0319(14)	0.0396(15)	0.0338(14)	0.0217(12)	0.0106(11)	0.0138(12)
C(30)	0.0333(14)	0.0299(13)	0.0252(12)	0.0154(11)	0.0037(11)	0.0055(11)
C(31)	0.0413(15)	0.0382(15)	0.0228(12)	0.0132(11)	0.0049(11)	0.0084(12)
O(5)	0.0240(9)	0.0403(11)	0.0456(11)	0.0262(9)	0.0111(8)	0.0078(8)
O(6)	0.0437(12)	0.030(1)	0.0411(11)	0.0204(9)	0.0141(9)	0.0076(9)
O(7)	0.036(1)	0.032(1)	0.034(1)	0.0174(8)	0.0143(8)	0.0081(8)
C(32)	0.0502(17)	0.0304(14)	0.0362(15)	0.0176(12)	0.0182(13)	0.0096(12)
C(33)	0.0478(18)	0.0490(18)	0.062(2)	0.0337(17)	0.0248(16)	0.0197(15)
C(34)	0.098(3)	0.0395(18)	0.0418(19)	0.0134(15)	0.026(2)	0.0185(19)
O(8)	0.0309(9)	0.036(1)	0.0282(9)	0.0211(8)	0.0038(8)	-0.0005(8)
Si(2)	0.0361(4)	0.0362(4)	0.0292(4)	0.0203(3)	0.0003(3)	-0.0003(3)
C(35)	0.108(4)	0.090(3)	0.047(2)	0.035(2)	0.036(2)	0.061(3)
C(36)	0.048(2)	0.062(2)	0.064(2)	0.041(2)	-0.0127(18)	-0.0123(17)
C(37)	0.0472(18)	0.0384(16)	0.0370(15)	0.0229(13)	-0.0022(13)	-0.0064(13)
C(38)	0.0525(19)	0.0454(17)	0.0450(17)	0.0332(15)	0.0118(15)	0.0096(14)
C(39)	0.090(3)	0.0442(19)	0.0461(19)	0.0138(16)	0.015(2)	0.023(2)
C(40)	0.060(2)	0.073(3)	0.085(3)	0.053(3)	-0.028(2)	-0.033(2)
Br(2)	0.0518(2)	0.0503(2)	0.0550(2)	0.02978(16)	0.02532(16)	0.02828(15)

Table 5: Bond lengths (Å)

C(1) - C(2)	1.517(4)	C(21) - C(22)	1.525(4)
C(1) - C(6)	1.516(4)	C(21) - C(26)	1.510(4)
C(1) - O(1)	1.444(3)	C(21) - O(5)	1.444(3)
C(2) - C(3)	1.544(3)	C(22) - C(23)	1.539(4)
C(2) - O(2)	1.429(3)	C(22) - O(6)	1.429(3)
C(3) - C(4)	1.516(4)	C(23) - C(24)	1.509(4)
C(3) - O(3)	1.423(3)	C(23) - O(7)	1.424(3)
C(4) - C(5)	1.525(3)	C(24) - C(25)	1.531(3)
C(4) - O(4)	1.424(3)	C(24) - O(8)	1.420(3)
C(5) - C(6)	1.568(3)	C(25) - C(26)	1.565(3)
C(5) - C(10)	1.557(4)	C(25) - C(30)	1.554(4)
C(6) - C(7)	1.539(4)	C(26) - C(27)	1.535(4)
C(7) - C(8)	1.548(4)	C(27) - C(28)	1.552(4)
C(7) - C(11)	1.527(4)	C(27) - C(31)	1.529(4)
C(8) - C(9)	1.541(4)	C(28) - C(29)	1.542(4)
C(8) - O(1)	1.439(4)	C(28) - O(5)	1.446(4)
C(9) - C(10)	1.529(4)	C(29) - C(30)	1.528(4)
C(9) - Br(1)	1.971(3)	C(29) - Br(2)	1.968(3)
C(10) - C(11)	1.542(4)	C(30) - C(31)	1.540(3)
O(2) - C(12)	1.436(4)	O(6) - C(32)	1.442(4)
O(3) - C(12)	1.427(3)	O(7) - C(32)	1.426(3)
C(12) - C(13)	1.509(5)	C(32) - C(33)	1.501(5)
C(12) - C(14)	1.512(4)	C(32) - C(34)	1.516(5)
O(4) - Si(1)	1.6589(18)	O(8) - Si(2)	1.6453(19)
Si(1) - C(15)	1.856(3)	Si(2) - C(35)	1.868(4)
Si(1) - C(16)	1.869(3)	Si(2) - C(36)	1.844(4)
Si(1) - C(17)	1.878(3)	Si(2) - C(37)	1.865(3)
C(17) - C(18)	1.529(4)	C(37) - C(38)	1.528(4)
C(17) - C(19)	1.521(5)	C(37) - C(39)	1.562(6)
C(17) - C(20)	1.528(5)	C(37) - C(40)	1.515(5)

Note – H atoms have been excluded

Table 6: Bond angles (°)

C(2) - C(1) - C(6)	115.1(2)	C(22) - C(21) - C(26)	115.7(2)
C(2) - C(1) - O(1)	110.8(2)	C(22) - C(21) - O(5)	110.2(2)
C(6) - C(1) - O(1)	103.6(2)	C(26) - C(21) - O(5)	103.7(2)
C(1) - C(2) - C(3)	114.0(2)	C(21) - C(22) - C(23)	114.0(2)
C(1) - C(2) - O(2)	107.6(2)	C(21) - C(22) - O(6)	108.3(2)
C(3) - C(2) - O(2)	103.5(2)	C(23) - C(22) - O(6)	103.7(2)
C(2) - C(3) - C(4)	111.6(2)	C(22) - C(23) - C(24)	112.7(2)
C(2) - C(3) - O(3)	102.42(19)	C(22) - C(23) - O(7)	102.2(2)
C(4) - C(3) - O(3)	111.8(2)	C(24) - C(23) - O(7)	111.4(2)
C(3) - C(4) - C(5)	111.55(19)	C(23) - C(24) - C(25)	112.2(2)
C(3) - C(4) - O(4)	111.7(2)	C(23) - C(24) - O(8)	112.9(2)
C(5) - C(4) - O(4)	108.9(2)	C(25) - C(24) - O(8)	107.6(2)
C(4) - C(5) - C(6)	114.2(2)	C(24) - C(25) - C(26)	114.8(2)
C(4) - C(5) - C(10)	115.7(2)	C(24) - C(25) - C(30)	115.1(2)
C(6) - C(5) - C(10)	103.5(2)	C(26) - C(25) - C(30)	103.9(2)
C(1) - C(6) - C(5)	112.30(19)	C(21) - C(26) - C(25)	112.6(2)
C(1) - C(6) - C(7)	102.8(2)	C(21) - C(26) - C(27)	103.4(2)
C(5) - C(6) - C(7)	102.6(2)	C(25) - C(26) - C(27)	102.3(2)
C(6) - C(7) - C(8)	97.7(2)	C(26) - C(27) - C(28)	97.7(2)
C(6) - C(7) - C(11)	103.3(2)	C(26) - C(27) - C(31)	103.6(2)
C(8) - C(7) - C(11)	105.3(2)	C(28) - C(27) - C(31)	104.9(2)
C(7) - C(8) - C(9)	102.9(2)	C(27) - C(28) - C(29)	103.2(2)
C(7) - C(8) - O(1)	108.1(2)	C(27) - C(28) - O(5)	107.4(2)
C(9) - C(8) - O(1)	108.5(2)	C(29) - C(28) - O(5)	108.7(2)
C(8) - C(9) - C(10)	103.1(2)	C(28) - C(29) - C(30)	103.0(2)
C(8) - C(9) - Br(1)	111.04(19)	C(28) - C(29) - Br(2)	111.26(19)
C(10) - C(9) - Br(1)	110.96(19)	C(30) - C(29) - Br(2)	110.9(2)
C(5) - C(10) - C(9)	108.2(2)	C(25) - C(30) - C(29)	107.9(2)
C(5) - C(10) - C(11)	100.8(2)	C(25) - C(30) - C(31)	100.5(2)
C(9) - C(10) - C(11)	100.4(2)	C(29) - C(30) - C(31)	101.0(2)
C(7) - C(11) - C(10)	95.2(2)	C(27) - C(31) - C(30)	95.2(2)
C(1) - O(1) - C(8)	108.6(2)	C(21) - O(5) - C(28)	108.9(2)
C(2) - O(2) - C(12)	109.63(19)	C(22) - O(6) - C(32)	109.3(2)
C(3) - O(3) - C(12)	106.5(2)	C(23) - O(7) - C(32)	106.2(2)
O(2) - C(12) - O(3)	105.1(2)	O(6) - C(32) - O(7)	104.7(2)
O(2) - C(12) - C(13)	109.0(2)	O(6) - C(32) - C(33)	109.1(2)
O(3) - C(12) - C(13)	108.6(3)	O(7) - C(32) - C(33)	109.0(3)
O(2) - C(12) - C(14)	109.4(3)	O(6) - C(32) - C(34)	109.3(3)
O(3) - C(12) - C(14)	111.8(2)	O(7) - C(32) - C(34)	111.4(2)
C(13) - C(12) - C(14)	112.7(3)	C(33) - C(32) - C(34)	113.0(3)
C(4) - O(4) - Si(1)	124.34(16)	C(24) - O(8) - Si(2)	129.09(16)
O(4) - Si(1) - C(15)	111.15(13)	O(8) - Si(2) - C(35)	107.50(15)
O(4) - Si(1) - C(16)	110.51(12)	O(8) - Si(2) - C(36)	111.66(14)
C(15) - Si(1) - C(16)	108.29(17)	C(35) - Si(2) - C(36)	108.2(2)
O(4) - Si(1) - C(17)	104.32(11)	O(8) - Si(2) - C(37)	107.20(12)
C(15) - Si(1) - C(17)	111.56(14)	C(35) - Si(2) - C(37)	110.6(2)
C(16) - Si(1) - C(17)	111.01(15)	C(36) - Si(2) - C(37)	111.57(17)
Si(1) - C(17) - C(18)	110.7(2)	Si(2) - C(37) - C(38)	110.5(2)
Si(1) - C(17) - C(19)	110.5(2)	Si(2) - C(37) - C(39)	108.9(2)
C(18) - C(17) - C(19)	109.1(3)	C(38) - C(37) - C(39)	108.2(3)
Si(1) - C(17) - C(20)	108.8(2)	Si(2) - C(37) - C(40)	111.9(3)
C(18) - C(17) - C(20)	108.9(3)	C(38) - C(37) - C(40)	110.1(3)
C(19) - C(17) - C(20)	108.8(3)	C(39) - C(37) - C(40)	107.1(4)

Note – H atoms have been excluded

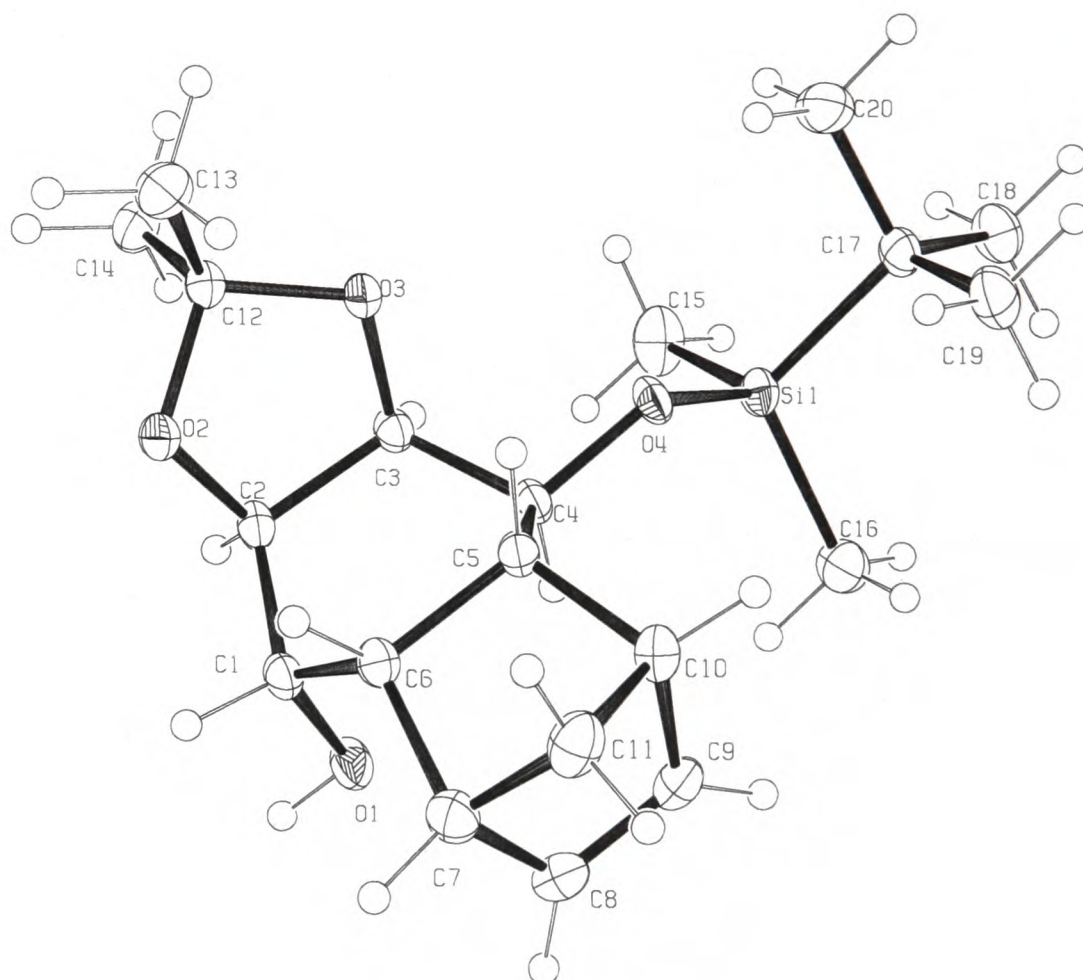
Inorganic Chemistry Crystallography Service

Single-crystal X-ray diffraction report for C₂₀H₃₄O₄Si (ARC562)

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Crystals of **ARC562** were grown by evaporation from acetone. An aggregate of crystals was cut to give a monocrystalline fragment having dimensions approximately 0.20 x 0.35 x 0.35 mm. This was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150K 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 package¹.

Examination of the systematic absences of the intensity data showed the space group to be *P* 2₁/*c*. The structure was solved using the direct-methods program SIR92², which located all non-hydrogen atoms. Subsequent full-matrix least-squares refinement was carried out using the CRYSTALS program suite³. Coordinates and anisotropic thermal parameters of all non-hydrogen atoms were refined. The hydroxyl hydrogen atom was located in a difference Fourier map and its coordinates and isotropic thermal parameter subsequently refined. Other hydrogen atoms were positioned geometrically after each cycle of

refinement. A 3-term Chebychev polynomial weighting scheme was applied. Refinement converged satisfactorily to give $R = 0.0354$, $wR = 0.0408$.

Attached is a thermal ellipsoid plot (ORTEP-3⁴) at 40% 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 geometrically-positioned H atoms.

Comment:

The OH group forms a hydrogen bond to one of the ketal O atoms of a neighbouring molecule related by the crystallographic screw axis ($O(1) \cdots O(2)'$ 2.7886(15) Å, symmetry operator $1-x, -1/2+y, 1/2-z$). The hydrogen bonds link the molecules to form an infinite chain running parallel to the crystallographic *b* axis.

References:

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- 2 A. Altomare, G. Cascarano, G. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori and M. Camalli, *J. Appl. Cryst.* 1994, **27**, 435.
- 3 D. J. Watkin, C. K. Prout, J. R. Carruthers, P. W. Betteridge and R. I. Cooper, *CRYSTALS* issue 11, Chemical Crystallography Laboratory, Oxford, UK, 2001.
- 4 ORTEP-3 v. 1.0.2, C. K. Johnson and M. K. Burnett, 1998.

Table 1: Crystal data and refinement details

Crystal identification	ARC562
Chemical formula	C ₂₀ H ₃₄ O ₄ Si
Formula weight	366.57
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	<i>P</i> 2 ₁ / <i>c</i>
<i>a</i> (Å)	15.2862(3)
<i>b</i> (Å)	6.4084(2)
<i>c</i> (Å)	21.9335(5)
α (°)	90
β (°)	108.0084(8)
γ (°)	90
Cell volume (Å ³)	2043.3
<i>Z</i>	4
Calculated density (Mg/m ³)	1.192
Absorption coefficient (mm ⁻¹)	0.135
<i>F</i> ₀₀₀	800.486
Crystal size (mm)	0.20 x 0.35 x 0.35
Description of crystal	Colourless fragment
Absorption correction	Semi-empirical from equivalent reflections
Transmission coefficients (min,max)	0.95, 0.97
θ range for data collection (°)	5.0 ≤ θ ≤ 27.5
Index ranges	-19 ≤ <i>h</i> ≤ 18, 0 ≤ <i>k</i> ≤ 8, 0 ≤ <i>l</i> ≤ 28
Reflections measured	22379
Unique reflections	5053
<i>R</i> _{int}	0.045
Observed reflections (<i>I</i> > 3 σ (<i>I</i>))	3076
Refinement method	Full-matrix least-squares on <i>F</i>
Parameters refined	230
Weighting scheme	Chebyshev 3-term polynomial
Goodness of fit	1.0456
<i>R</i>	0.0354
<i>wR</i>	0.0408
Residual electron density (min,max) (eÅ ⁻³)	-0.25, 0.26

Table 2: Atomic coordinates and equivalent isotropic thermal parameters (Å²) of non-hydrogen atoms

Atom	x	y	z	U _{equiv}
C(1)	0.4060(1)	0.3313(3)	0.24165(7)	0.0238
C(2)	0.4534(1)	0.2972(2)	0.31310(7)	0.0221
C(3)	0.3882(1)	0.2988(2)	0.35534(7)	0.0212
C(4)	0.2877(1)	0.3398(2)	0.31644(7)	0.0207
C(5)	0.2794(1)	0.5324(2)	0.27478(7)	0.0212
C(6)	0.3421(1)	0.5197(3)	0.23050(7)	0.0239
C(7)	0.27140(12)	0.5486(3)	0.16211(8)	0.0317
C(8)	0.20565(12)	0.3651(3)	0.14776(8)	0.0340
C(9)	0.15230(11)	0.3816(3)	0.18530(8)	0.0295
C(10)	0.18185(11)	0.5750(3)	0.22602(8)	0.0271
C(11)	0.20918(12)	0.7161(3)	0.17794(9)	0.0340
O(1)	0.35924(8)	0.14187(19)	0.21669(6)	0.0308
O(2)	0.51485(7)	0.46767(18)	0.33748(5)	0.0259
O(3)	0.42241(7)	0.46599(18)	0.39981(5)	0.0257
C(12)	0.5151(1)	0.5044(3)	0.40212(7)	0.0248
C(13)	0.53709(12)	0.7314(3)	0.41767(9)	0.0351
C(14)	0.58172(11)	0.3561(3)	0.44758(8)	0.0323
O(4)	0.23337(7)	0.36725(16)	0.35850(5)	0.0233
Si(1)	0.17397(3)	0.18166(7)	0.38018(2)	0.0228
C(15)	0.25280(13)	-0.0204(3)	0.4289(1)	0.0424
C(16)	0.09246(13)	0.0567(3)	0.30817(9)	0.0370
C(17)	0.1102(1)	0.3214(3)	0.42910(7)	0.0255
C(18)	0.05388(12)	0.1658(3)	0.45489(9)	0.0381
C(19)	0.04569(12)	0.4843(3)	0.38740(9)	0.0371
C(20)	0.17979(13)	0.4317(3)	0.48556(9)	0.0374

Table 5: Bond lengths (Å)

C(1) - C(2)	1.525(2)	C(9) - C(10)	1.513(2)
C(1) - C(6)	1.524(2)	C(10) - C(11)	1.542(2)
C(1) - O(1)	1.4289(19)	O(1) - H(1)	0.88(2)
C(2) - C(3)	1.5565(19)	O(2) - C(12)	1.4358(18)
C(2) - O(2)	1.4322(18)	O(3) - C(12)	1.4242(18)
C(3) - C(4)	1.532(2)	C(12) - C(13)	1.508(2)
C(3) - O(3)	1.4341(18)	C(12) - C(14)	1.519(2)
C(4) - C(5)	1.517(2)	O(4) - Si(1)	1.6529(11)
C(4) - O(4)	1.4305(16)	Si(1) - C(15)	1.864(2)
C(5) - C(6)	1.564(2)	Si(1) - C(16)	1.8633(19)
C(5) - C(10)	1.567(2)	Si(1) - C(17)	1.8839(16)
C(6) - C(7)	1.565(2)	C(17) - C(18)	1.536(2)
C(7) - C(8)	1.515(3)	C(17) - C(19)	1.530(2)
C(7) - C(11)	1.543(3)	C(17) - C(20)	1.533(2)
C(8) - C(9)	1.330(2)		

Note – geometrically-positioned H atoms have been excluded

Table 3: Atomic coordinates and isotropic thermal parameters (Å²) of hydrogen atoms

Atom	x	y	z	U _{iso}
H(1)	0.3955(16)	0.074(4)	0.1989(11)	0.050(6)
H(11)	0.4515	0.3640	0.2186	0.0301
H(21)	0.4831	0.1569	0.3157	0.0276
H(31)	0.3881	0.1603	0.3763	0.0264
H(41)	0.2649	0.2162	0.2881	0.0264
H(51)	0.2966	0.6446	0.3080	0.0258
H(61)	0.3911	0.6292	0.2396	0.0294
H(71)	0.3010	0.5725	0.1279	0.0386
H(81)	0.2029	0.2520	0.1158	0.0391
H(91)	0.1018	0.2838	0.1864	0.0338
H(101)	0.1356	0.6235	0.2467	0.0328
H(111)	0.2434	0.8442	0.1981	0.0396
H(112)	0.1559	0.7567	0.1402	0.0396
H(131)	0.5376	0.7600	0.4626	0.0423
H(132)	0.5989	0.7644	0.4134	0.0423
H(133)	0.4893	0.8203	0.3873	0.0423
H(141)	0.5815	0.3828	0.4924	0.0378
H(142)	0.6451	0.3790	0.4448	0.0378
H(143)	0.5624	0.2088	0.4354	0.0378
H(151)	0.2159	-0.1314	0.4416	0.0516
H(152)	0.2954	0.0456	0.4683	0.0516
H(153)	0.2895	-0.0839	0.4030	0.0516
H(161)	0.0571	-0.0551	0.3220	0.0459
H(162)	0.0489	0.1641	0.2827	0.0459
H(163)	0.1277	-0.0060	0.2812	0.0459
H(181)	0.0205	0.2422	0.4807	0.0488
H(182)	0.0961	0.0602	0.4826	0.0488
H(183)	0.0084	0.0936	0.4182	0.0488
H(191)	0.0119	0.5583	0.4135	0.0459
H(192)	0.0824	0.5875	0.3713	0.0459
H(193)	0.0005	0.4136	0.3502	0.0459
H(201)	0.1463	0.5062	0.5117	0.0454
H(202)	0.2224	0.3262	0.5129	0.0454
H(203)	0.2160	0.5347	0.4689	0.0454

Table 4: Anisotropic thermal parameters (Å²)

Atom	U ₁₁	U ₂₂	U ₃₃	U ₂₃	U ₁₃	U ₁₂
C(1)	0.0214(7)	0.0270(8)	0.0268(7)	-0.0050(6)	0.0129(6)	-0.0060(6)
C(2)	0.0184(7)	0.0210(7)	0.0295(8)	-0.0015(6)	0.0113(6)	-0.0014(6)
C(3)	0.0207(7)	0.0210(7)	0.0242(7)	-0.0014(6)	0.0103(6)	-0.0023(6)
C(4)	0.0187(7)	0.0225(8)	0.0247(7)	-0.0042(6)	0.0125(6)	-0.0026(6)
C(5)	0.0183(7)	0.0228(7)	0.0233(7)	-0.0022(6)	0.0079(6)	-0.0006(6)
C(6)	0.0216(7)	0.0275(8)	0.0245(7)	0.0004(6)	0.0098(6)	-0.0047(6)
C(7)	0.0298(8)	0.042(1)	0.0250(8)	0.0062(7)	0.0105(7)	0.0004(7)
C(8)	0.0306(8)	0.0425(11)	0.0247(8)	-0.0038(7)	0.0026(7)	-0.0004(7)
C(9)	0.0225(7)	0.0331(9)	0.0288(8)	-0.0008(7)	0.0019(6)	-0.0035(7)
C(10)	0.0215(7)	0.0283(9)	0.0320(8)	0.0016(7)	0.0092(6)	0.0017(7)
C(11)	0.0280(8)	0.034(1)	0.0370(9)	0.0090(8)	0.0054(7)	-0.0003(7)
O(1)	0.0262(6)	0.0318(7)	0.0396(7)	-0.0152(5)	0.0176(5)	-0.0063(5)
O(2)	0.0220(5)	0.0324(6)	0.0258(5)	-0.0037(5)	0.0111(4)	-0.0086(5)
O(3)	0.0186(5)	0.0340(6)	0.0266(5)	-0.0078(5)	0.0103(4)	-0.0054(5)
C(12)	0.0195(7)	0.0320(9)	0.0245(7)	-0.0013(7)	0.0091(6)	-0.0048(6)
C(13)	0.0345(9)	0.033(1)	0.0378(9)	-0.0071(8)	0.0119(8)	-0.0099(7)
C(14)	0.0225(7)	0.0426(11)	0.0293(8)	0.0004(7)	0.0043(6)	-0.0014(7)
O(4)	0.0221(5)	0.0250(6)	0.0282(5)	-0.0025(4)	0.0158(4)	-0.0025(4)
Si(1)	0.01949(19)	0.0226(2)	0.0284(2)	0.00099(18)	0.01051(16)	-0.00255(17)
C(15)	0.0351(9)	0.035(1)	0.0583(12)	0.0126(9)	0.0169(9)	0.0045(8)
C(16)	0.0352(9)	0.039(1)	0.041(1)	-0.0097(8)	0.0172(8)	-0.0136(8)
C(17)	0.0223(7)	0.0306(8)	0.0264(7)	0.0026(7)	0.0117(6)	-0.0028(7)
C(18)	0.0348(9)	0.0469(11)	0.0402(9)	0.0031(9)	0.0226(8)	-0.0091(8)
C(19)	0.0321(9)	0.042(1)	0.041(1)	0.0042(8)	0.0164(8)	0.0101(8)
C(20)	0.039(1)	0.0442(11)	0.0300(9)	-0.0042(8)	0.0127(8)	-0.0080(8)

Table 6: Bond angles (°)

C(2) - C(1) - C(6)	110.84(12)	C(9) - C(10) - C(11)	99.87(13)
C(2) - C(1) - O(1)	107.13(13)	C(7) - C(11) - C(10)	93.56(13)
C(6) - C(1) - O(1)	113.05(12)	C(1) - O(1) - H(1)	106.1(15)
C(1) - C(2) - C(3)	114.96(12)	C(2) - O(2) - C(12)	107.18(11)
C(1) - C(2) - O(2)	108.83(12)	C(3) - O(3) - C(12)	107.61(11)
C(3) - C(2) - O(2)	103.82(11)	O(2) - C(12) - O(3)	103.73(11)
C(2) - C(3) - C(4)	112.71(12)	O(2) - C(12) - C(13)	108.30(13)
C(2) - C(3) - O(3)	104.15(11)	O(3) - C(12) - C(13)	108.92(13)
C(4) - C(3) - O(3)	110.04(12)	O(2) - C(12) - C(14)	110.03(13)
C(3) - C(4) - C(5)	110.98(12)	O(3) - C(12) - C(14)	111.88(13)
C(3) - C(4) - O(4)	110.14(12)	C(13) - C(12) - C(14)	113.47(14)
C(5) - C(4) - O(4)	109.30(12)	C(4) - O(4) - Si(1)	125.25(9)
C(4) - C(5) - C(6)	112.20(12)	O(4) - Si(1) - C(15)	110.46(7)
C(4) - C(5) - C(10)	115.98(12)	O(4) - Si(1) - C(16)	110.38(7)
C(6) - C(5) - C(10)	102.82(12)	C(15) - Si(1) - C(16)	109.38(9)
C(1) - C(6) - C(5)	115.29(12)	O(4) - Si(1) - C(17)	104.39(7)
C(1) - C(6) - C(7)	117.77(13)	C(15) - Si(1) - C(17)	111.11(8)
C(5) - C(6) - C(7)	102.39(12)	C(16) - Si(1) - C(17)	111.05(8)
C(6) - C(7) - C(8)	108.91(13)	Si(1) - C(17) - C(18)	110.41(12)
C(6) - C(7) - C(11)	99.07(13)	Si(1) - C(17) - C(19)	109.6(1)
C(8) - C(7) - C(11)	99.85(14)	C(18) - C(17) - C(19)	109.37(14)
C(7) - C(8) - C(9)	107.70(15)	Si(1) - C(17) - C(20)	109.13(11)
C(8) - C(9) - C(10)	107.59(15)	C(18) - C(17) - C(20)	109.26(13)
C(5) - C(10) - C(9)	107.93(13)	C(19) - C(17) - C(20)	109.04(15)
C(5) - C(10) - C(11)	99.63(12)		

Note – geometrically-positioned H atoms have been excluded

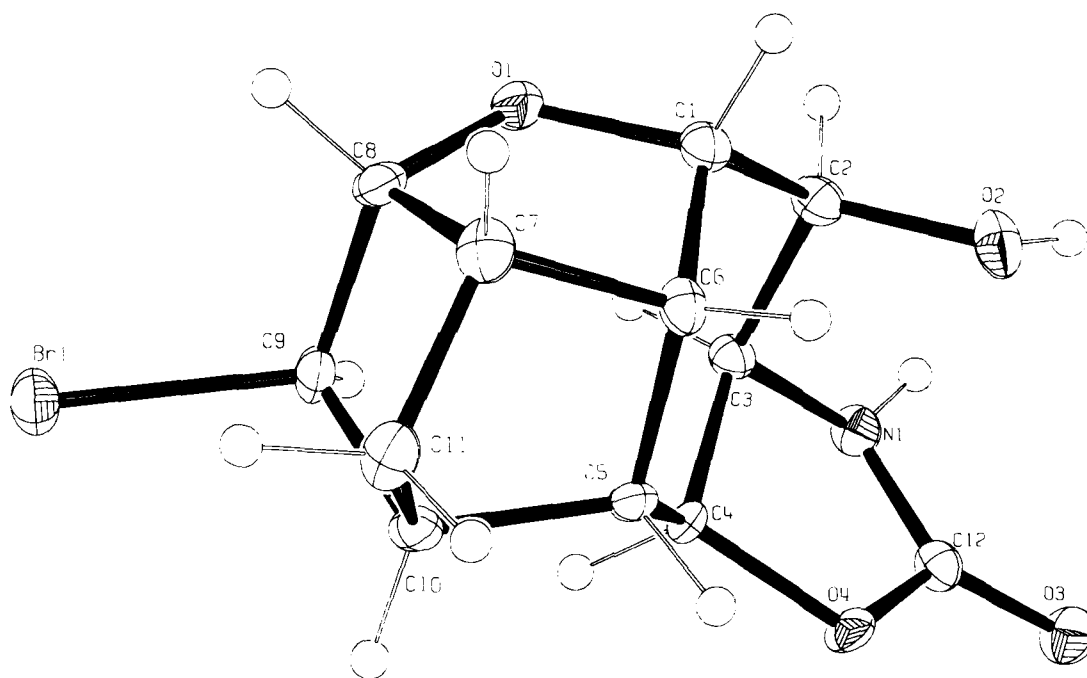
Inorganic Chemistry Crystallography Service

Single-crystal X-ray diffraction report for $C_{12}H_{14}BrNO_4$ (ARC644)

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Crystals of **ARC644** were grown by evaporation from pyridine. A polycrystalline aggregate was cut to give a fragment having dimensions approximately 0.08 x 0.18 x 0.22 mm. This was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150K in a stream of cold N_2 using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoK_{α} radiation, $\lambda = 0.71073 \text{ \AA}$). Intensity data were processed using the DENZO-SMN package¹.

Examination of the systematic absences of the intensity data showed the space group to be either $P 2_1$ or $P 2_1/m$. The structure was solved in the space group $P 2_1$ using the direct-methods program SIR92², which located all non-hydrogen atoms. Examination of the resulting model showed no additional symmetry to be present, confirming the choice of space group. Subsequent full-matrix least-squares refinement was carried out using the CRYSTALS program suite³. Coordinates and anisotropic thermal parameters of all non-hydrogen atoms were refined. The NH and OH hydrogen atoms were located in a difference Fourier map and their coordinates and isotropic thermal parameters subsequently refined. Other hydrogen atoms were positioned geometrically after each cycle of refinement. A 4-term Chebychev polynomial weighting scheme was applied. Refinement converged satisfactorily to give $R = 0.0270$, $wR = 0.0286$.

Attached is a thermal ellipsoid plot (ORTEP-3⁴) at 40% 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 geometrically-positioned H atoms.

Comment:

The NH and OH groups both form a hydrogen bond to the carbonyl O atom of a neighbouring molecule (O(2)···O(3)' 2.829(3) Å, N(1)···O(3)' 2.938(4) Å, symmetry operator 2-x, 1/2+y, 1-z). The hydrogen bonds link the molecules to form infinite chains running parallel to the crystallographic *b* axis.

Refinement of the Flack enantiopole parameter gave a value of 0.43(1), showing the crystal to be a racemic twin⁵.

References:

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- 2 A. Altomare, G. Cascarano, G. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori and M. Camalli, *J. Appl. Cryst.* 1994, **27**, 435.
- 3 D. J. Watkin, C. K. Prout, J. R. Carruthers, P. W. Betteridge and R. I. Cooper, CRYSTALS issue 11, Chemical Crystallography Laboratory, Oxford, UK, 2001.
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Table 1: Crystal data and refinement details

Crystal identification	ARC644
Chemical formula	C ₁₂ H ₁₄ BrNO ₄
Formula weight	316.15
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	<i>P</i> 2 ₁
<i>a</i> (Å)	9.3771(3)
<i>b</i> (Å)	6.5309(3)
<i>c</i> (Å)	9.9485(5)
α (°)	90
β (°)	111.9669(17)
γ (°)	90
Cell volume (Å ³)	565.02(4)
<i>Z</i>	2
Calculated density (Mg/m ³)	1.858
Absorption coefficient (mm ⁻¹)	3.645
<i>F</i> ₀₀₀	319.362
Crystal size (mm)	0.08 x 0.18 x 0.22
Description of crystal	Colourless fragment
Absorption correction	Semi-empirical from equivalent reflections
Transmission coefficients (min,max)	0.45, 0.75
θ range for data collection (°)	5.0 ≤ θ ≤ 27.5
Index ranges	-12 ≤ <i>h</i> ≤ 11, -8 ≤ <i>k</i> ≤ 7, 0 ≤ <i>l</i> ≤ 12
Reflections measured	4779
Unique reflections	2257
<i>R</i> _{int}	0.034
Observed reflections (<i>I</i> > 3 σ (<i>I</i>))	2046
Refinement method	Full-matrix least-squares on <i>F</i>
Parameters refined	172
Weighting scheme	Chebychev 4-term polynomial
Goodness of fit	1.0741
<i>R</i>	0.0270
<i>wR</i>	0.0286
Residual electron density (min,max) (eÅ ⁻³)	-0.72, 0.51

Table 2: Atomic coordinates and equivalent isotropic thermal parameters (Å²) of non-hydrogen atoms

Atom	x	y	z	U _{equiv}
C(1)	0.5063(4)	0.7621(5)	0.2960(4)	0.0203
C(2)	0.6714(4)	0.7059(6)	0.3262(4)	0.0202
C(3)	0.6814(4)	0.5166(5)	0.2380(3)	0.0168
C(4)	0.5837(3)	0.3340(5)	0.2513(3)	0.0167
C(5)	0.4371(4)	0.3780(5)	0.2791(4)	0.0161
C(6)	0.4160(3)	0.5951(5)	0.3332(4)	0.0178
C(7)	0.2488(4)	0.6472(6)	0.2357(4)	0.0213
C(8)	0.2768(3)	0.7053(5)	0.0970(3)	0.0197
C(9)	0.2806(3)	0.4924(5)	0.0279(3)	0.0181
C(10)	0.2852(3)	0.3417(5)	0.1463(3)	0.0183
C(11)	0.1684(3)	0.4393(9)	0.2025(3)	0.0222
O(1)	0.4263(2)	0.7981(4)	0.1415(2)	0.0220
O(2)	0.7393(3)	0.6672(4)	0.4781(3)	0.0245
N(1)	0.8340(3)	0.4255(6)	0.2986(3)	0.0200
C(12)	0.8359(3)	0.2761(5)	0.3938(3)	0.0192
O(3)	0.9472(3)	0.1944(4)	0.4849(3)	0.0269
O(4)	0.6911(3)	0.2174(4)	0.3729(3)	0.0201
Br(1)	0.09121(3)	0.45017(13)	-0.14437(3)	0.0248

Table 3: Atomic coordinates and isotropic thermal parameters (Å²) of hydrogen atoms

Atom	x	y	z	U _{iso}
H(1)	0.835(5)	0.675(7)	0.507(5)	0.030(11)
H(2)	0.917(6)	0.491(9)	0.321(5)	0.049(15)
H(11)	0.5116	0.8852	0.3575	0.0232
H(21)	0.7265	0.8182	0.2972	0.0246
H(31)	0.6487	0.5712	0.1370	0.0200
H(41)	0.5413	0.2634	0.1552	0.0180
H(51)	0.4547	0.2765	0.3589	0.0186
H(61)	0.4467	0.5909	0.4408	0.0208
H(71)	0.1921	0.7484	0.2727	0.0259
H(81)	0.1996	0.8014	0.0302	0.0223
H(91)	0.3691	0.4772	-0.0043	0.0203
H(101)	0.2705	0.1966	0.1118	0.0214
H(111)	0.1650	0.3694	0.2906	0.0268
H(112)	0.0622	0.4469	0.1268	0.0268

Table 5: Bond lengths (Å)

C(1) - C(2)	1.508(5)	C(7) - C(8)	1.546(5)
C(1) - C(6)	1.509(5)	C(7) - C(11)	1.528(7)
C(1) - O(1)	1.455(4)	C(8) - C(9)	1.558(5)
C(2) - C(3)	1.539(5)	C(8) - O(1)	1.436(4)
C(2) - O(2)	1.425(4)	C(9) - C(10)	1.523(4)
C(3) - C(4)	1.540(4)	C(9) - Br(1)	1.972(3)
C(3) - N(1)	1.456(4)	C(10) - C(11)	1.541(5)
C(4) - C(5)	1.527(5)	O(2) - H(1)	0.84(4)
C(4) - O(4)	1.465(4)	N(1) - C(12)	1.356(5)
C(5) - C(6)	1.555(5)	N(1) - H(2)	0.84(5)
C(5) - C(10)	1.556(4)	C(12) - O(3)	1.219(4)
C(6) - C(7)	1.542(4)	C(12) - O(4)	1.350(4)

Table 4: Anisotropic thermal parameters (Å²)

Atom	U ₁₁	U ₂₂	U ₃₃	U ₂₃	U ₁₃	U ₁₂
C(1)	0.0197(15)	0.0173(17)	0.0211(15)	-0.0043(13)	0.0043(12)	0.0026(13)
C(2)	0.0215(17)	0.0183(19)	0.0216(18)	-0.0040(15)	0.0091(14)	-0.0004(14)
C(3)	0.0163(14)	0.0152(15)	0.0185(14)	-0.0023(11)	0.0062(11)	0.0010(11)
C(4)	0.0163(14)	0.0136(17)	0.0152(14)	0.0034(12)	0.0003(11)	0.0031(12)
C(5)	0.0164(14)	0.0115(15)	0.0187(14)	0.0037(11)	0.0047(11)	-0.0009(11)
C(6)	0.0139(14)	0.0214(18)	0.0167(15)	-0.0025(13)	0.0039(12)	0.0012(13)
C(7)	0.0163(14)	0.0257(19)	0.0227(16)	-0.0015(13)	0.0081(12)	0.0047(13)
C(8)	0.0166(15)	0.0137(17)	0.0255(16)	0.0051(13)	0.0042(12)	0.0021(12)
C(9)	0.0130(12)	0.023(3)	0.0150(12)	0.0031(12)	0.001(1)	0.0001(12)
C(10)	0.0139(14)	0.0142(17)	0.0253(16)	0.0033(13)	0.0057(12)	-0.0010(12)
C(11)	0.0150(11)	0.0296(18)	0.0224(12)	0.006(2)	0.0076(9)	-0.001(2)
O(1)	0.0203(11)	0.0168(12)	0.0243(11)	0.004(1)	0.0031(9)	-0.002(1)
O(2)	0.0178(12)	0.0324(16)	0.0195(12)	-0.006(1)	0.0026(9)	0.001(1)
N(1)	0.0146(11)	0.022(2)	0.0234(11)	-0.0003(14)	0.0072(9)	0.0013(13)
C(12)	0.0153(14)	0.0206(18)	0.0208(15)	-0.0026(13)	0.0058(12)	0.0004(13)
O(3)	0.017(1)	0.0268(14)	0.0323(13)	0.0035(11)	0.004(1)	0.0052(11)
O(4)	0.0124(11)	0.0159(13)	0.0267(15)	0.0076(12)	0.001(1)	0.003(1)
Br(1)	0.01953(12)	0.02973(17)	0.01993(13)	-0.0008(2)	0.00136(9)	-0.0016(2)

Table 6: Bond angles (°)

C(2) - C(1) - C(6)	113.8(3)	C(8) - C(7) - C(11)	105.0(3)
C(2) - C(1) - O(1)	109.6(3)	C(7) - C(8) - C(9)	102.4(3)
C(6) - C(1) - O(1)	105.1(2)	C(7) - C(8) - O(1)	107.5(2)
C(1) - C(2) - C(3)	111.0(3)	C(9) - C(8) - O(1)	109.4(2)
C(1) - C(2) - O(2)	105.8(3)	C(8) - C(9) - C(10)	103.6(2)
C(3) - C(2) - O(2)	111.3(3)	C(8) - C(9) - Br(1)	110.28(19)
C(2) - C(3) - C(4)	114.1(3)	C(10) - C(9) - Br(1)	109.7(2)
C(2) - C(3) - N(1)	110.6(3)	C(5) - C(10) - C(9)	108.1(2)
C(4) - C(3) - N(1)	99.9(3)	C(5) - C(10) - C(11)	100.2(2)
C(3) - C(4) - C(5)	118.3(3)	C(9) - C(10) - C(11)	101.2(3)
C(3) - C(4) - O(4)	103.1(2)	C(7) - C(11) - C(10)	95.0(2)
C(5) - C(4) - O(4)	109.6(3)	C(1) - O(1) - C(8)	108.4(2)
C(4) - C(5) - C(6)	118.3(3)	C(2) - O(2) - H(1)	111.(3)
C(4) - C(5) - C(10)	114.7(3)	C(3) - N(1) - C(12)	109.7(2)
C(6) - C(5) - C(10)	103.8(2)	C(3) - N(1) - H(2)	124.(4)
C(1) - C(6) - C(5)	114.7(2)	C(12) - N(1) - H(2)	114.(4)
C(1) - C(6) - C(7)	102.6(3)	N(1) - C(12) - O(3)	128.2(3)
C(5) - C(6) - C(7)	102.4(3)	N(1) - C(12) - O(4)	110.3(3)
C(6) - C(7) - C(8)	98.2(2)	O(3) - C(12) - O(4)	121.5(3)
C(6) - C(7) - C(11)	104.1(3)	C(4) - O(4) - C(12)	108.7(3)

Note – geometrically-positioned H atoms have been excluded

Appendix III

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