Total syntheses of the nakinadine alkaloids

A thesis submitted in partial fulfilment of the requirement
for the degree of Doctor of Philosophy

by

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The work described in this thesis was carried out in the Chemistry Research Laboratory, University of Oxford from October 2009 until October 2013, under the supervision of Professor Stephen G. Davies. All of the work is my own unless otherwise stated and has not been submitted previously for any other degree at this or any other university.

Rushabh Surendra Shah

October 2013

For my dadi, nani and grandfathers

Abstract

Rushabh Surendra Shah D.Phil. Thesis

St. Anne's College Trinity Term 2013

This thesis is concerned with the development of methodology for the asymmetric syntheses of the nakinadine family of marine alkaloids and through these synthetic endeavours, seeks to confirm the structure and assign the relative and absolute configurations of these alkaloids for the first time.

Chapter 1 provides an overview on the importance of the α-aryl carbonyl motif and outlines general methods for its synthesis, with particular focus on the previously reported syntheses of biologically active α-aryl-β-amino acid derivatives.

Chapter 2 introduces the nakinadine family of marine alkaloids and describes the development of a diastereoselective protocol for the synthesis of α-phenyl-β^2-amino acids and culminates in the first total syntheses of nakinadines B and C.

Chapter 3 details investigations into the α-arylation of β^3-amino ester enolates using either benzyne as an electrophile or a Pd-catalysed protocol for the formation of α-phenyl-$\beta^{2,3}$-amino compounds, and hence, assesses its use as a potential route for the syntheses of α-phenyl-$\beta^{2,3}$-amino acids such as nakinadines A and D−F .

Chapter 4 delineates an optimised imino-aldol approach for the diastereodivergent syntheses of α-phenyl-$\beta^{2,3}$-amino esters, which after elaboration, allowed the first total asymmetric synthesis of both diastereosiomers of the reported structures of nakinadines A and D−F.

Chapter 5 is dedicated to the comparison of spectroscopic data of synthetic samples of all the nakinadine alkaloids, and their C(2)-epimers, with those reported for the natural samples which confirms the original structural assignments and establishes both the relative and absolute configurations within each natural product.

Chapter 6 contains full experimental procedures and characterisation data for all compounds synthesised in Chapters 2, 3 and 4.

I am indebted to my supervisor, Prof. Steve Davies, for accepting me into the research group, providing funding and for his continued input to the project throughout my time here in Oxford.

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I've been lucky to have some amazing housemates during my time here but in particular: Smita, Tom, Chaz, Cat and Becky, you've always been there for me. All the 'chats' we've had, although the details will be forgotten, the memories will linger on... To the countless friends I've made here (you know who you are) in particular Chaz, Smati, Spicy, Jess, Becky and Laura... one more lads?!! To my fellow cricketers: sorry I won't be around for the future but it was great fun! Thanks to all who made my PhD enjoyable and providing a much needed escape from the lab! Thanks again to Laura, Matt and Kylie for letting me stay during my last few weeks in Oxford. To all my London buddies: you've been with me since the beginning and it's been quite a journey (the cotajje and barnicle memories were special), so thanks for staying with me till the end. To my bobs: Dipen, Jiten, Manish, Rajiv, Rishi and Savan... the WhatsApp photos were a nice distraction, keep jammin' boys!!!

Jen, you've been through the highs and lows of PhD life with me. You've always been there and without your love and continued belief in me all this would not have been possible. I hope the rest of our lives will be less stressful!

To my family both here and in India, without your love, support and unwavering belief, I would not be the man I am today. Thank you all for being there for me. દાદી, બધા તમારા સપોર્ટ માટે તમે ખૂબ ખૂબ આભાર. Dad, thank you for always being there for me, I hope I have made you proud! Lastly, a very special mention has to go to my mum, without whom I really don't know how I would have survived my whole university life (8 years is a long time to survive if you don't really know how to cook!) Food aside, your daily encouragement and constant support will stay with me forever. Love you mum!!!

Abbreviations

≈	Approximately
(±)	Racemic
$[\alpha]_D$	Specific rotation
(*R*)	Rectus
(*E*)	Entgegen
(*S*)	Sinister
(*Z*)	Zusammen
δ_C	^{13}C NMR chemical shift
δ_H	^{1}H NMR chemical shift
μ	Experimental absorption coefficient
μL	Microlitres
μmol	Micromoles
μwave	Microwave irradiation
ν_{max}	IR absorption maximum
^{13}C NMR	Carbon NMR
^{1}H NMR	Proton NMR
AB	AB system
Ac	Acetyl
app	Apparent
aq	Aqueous
Ar	Aromatic
atm	Atmosphere(s)
ATR	Attentuated total reflectance
BHT	3,5-Di-*tert*-butyl-4-hydroxytoluene
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
br	Broad
Bu	Butyl
Bz	Benzoyl
C	Celsius
c	Concentration
CAN	Ceric ammonium nitrate
Cbz	Carboxybenzyl

cm	Centimetres
cm^{-1}	Wavenumber
COSY	Correlation spectroscopy
d	Doublet
dba	Dibenzylideneacetone
1,2-DCE	Dichloroethane
DEAD	Diethyl azodicarboxylate
deg	Degrees
DHP	3,4-Dihydro-2*H*-pyran
DIAD	Diisopropyl azodicarboxylate
DIBAL−H	Diisobutylaluminium hydride
DIPEA	*N*,*N*-Diisopropylethylamine
DME	Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMPU	*N*,*N*′-Dimethylpropyleneurea
DMSO	Dimethylsulfoxide
dr	Diastereoisomeric ratio
CSA	Camphorsulfonic acid
ε	Extinction coefficient
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	Enantiomeric excess
ent	Enantiomer
ESI^+	Postive electrospray ionisation
Et	Ethyl
equiv	Equivalents
EWG	Electron withdrawing group
g	Grams
h	Hours
HMBC	Heteronuclear multiple bond correlation
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
HMQC	Heteronuclear multiple quantum correlation
HOBt	Hydroxybenzotriazole
HSQC	Heteronuclear single-quantum correlation

i	Ipso
^{i}Bu	Isobutyl
IC_{50}	Half maximal inhibitory concentration
IBX	2-Iodoxybenzoic acid
^{i}Pr	Isopropyl
J	Coupling constant
K	Kelvin
KHMDS	Potassium bis(trimethylsilyl)amide
L	Litres
LCT	Liquid chromatography time of flight
LDA	Lithium di(isopropyl)amide
LiHMDS	Lithium bis(trimethylsilyl)amide
lit.	Literature
M	Molar
m	Meta
m	Metres
m	Milli
m	Multiplet
M	Cell formula weight
m/z	Mass to charge ratio
µ	Micro
Me	Methyl
Mes	Mesityl
MeOD	Deuterated methanol
MHz	Megahertz
min	Minute(s)
mol	Moles
mp	Melting point
Ms	Methanesulfonyl
MS	Mass Spectrometry
NaHMDS	Sodium bis(trimethylsilyl)amide
Nap	Naphthyl
Ns	2-Nitrobenzenesulfonyl
Nu	Nucleophile

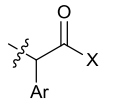
o	Ortho
p	Para
PGME	Phenylglycine methyl ester
Ph	Phenyl
Piv	Pivaloyl
PMP	*p*-Methoxyphenyl
ppm	Parts per million
PPTS	Pyridinium *p*-toluenesulfonate
q	Quartet
quant	Quantitative
quin	Quintet
R	Unspecified organic group
ref	Reference
R_f	Retention factor
rt	Room temperature
s	Singlet
satd	Saturated
S_N2	Substitution, nucleophilic, bimolecular
S_NAr	Substitution, nucleophilic, aromatic
t	Triplet
T	Temperature
TBAI	Tetrabutylammonium iodide
^{t}Bu	*tert*-Butyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMS	Trimethylsilyl
ToF	Time of flight
Ts	*p*-Toluenesulfonyl
UV	Ultraviolet
v	Volume
V	Unit cell volume
Z	Cell formula units

Contents

Chapter 1: Introduction

1.1 α-Aryl carbonyl compounds

The α-aryl carbonyl motif **1** is one which is prevalent in natural products.[1] Furthermore, many drug and potential therapeutic agents also contain this motif and hence, methods for their synthesis are highly sought after and are of interest to chemists and biologists alike (Figure 1).[2]

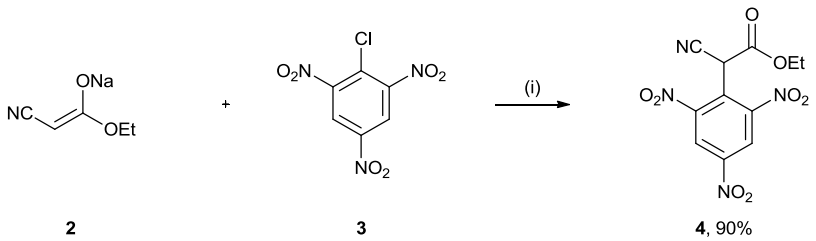


1, X = R, NR_2, OR

Figure 1. Generic structure of α-aryl carbonyl compounds.

1.2 Enolate arylation using electrophilic "Ar^+"

The most common method for the synthesis of α-alkyl carbonyl compounds is via nucleophic substitution (e.g., S_N2) of preformed carbonyl enolates with the requisite alkyl halides. Unfortunately, enolate arylation via nucleophilic aromatic substitution (S_NAr) of unsubstituted arenes cannot be performed simply by the addition of unactivated aryl halides. This is because the C−X bond lies in the same plane as the rest of the molecule as opposed to the analogous electrophilic carbon atom in alkyl halides which is tetrahedral.[3] However, the S_NAr of arenes consisting of one or more electron withdrawing groups with stabilised enolates has been known for over a century.[4] For example, Fairbourne and Fawson[5] showed that the sodium enolate of ethyl 2-cyanoacetate **2** can be successfully α-arylated with picryl chloride **3** to give the corresponding ester **4** in 90% yield (Scheme 1).



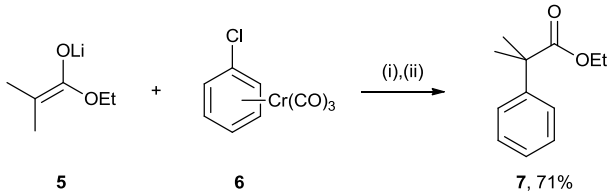
2 **3** **4**, 90%

Scheme 1. *Reagents and Conditions*: (i) EtOH, reflux, 4−5 h.

1.2.1 Synthesis of α-aryl carbonyl compounds via chromiumtricarbonyl complexes

For the synthesis of α-aryl carbonyl compounds with unsubstituted arenes, chemists have to resort to nucleophilic aromatic substitution using 'activated arenes' with preformed enolate or silyl enol

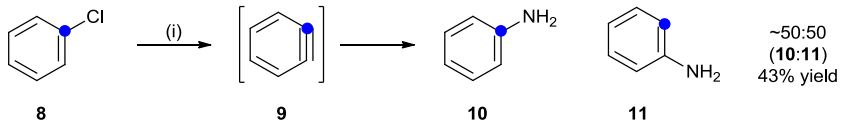
ether equivalents. Fischer and Öfele[6] were the first to report the use of (arene)chromiumtricarbonyl complexes in such reactions. Semmelhack and Hall[7] built upon this, by reacting lithium enolate **5** with π-(chlorobenzene)chromiumtricarbonyl complex **6** and after oxidative decomplexation of the $Cr(CO)_3$ unit with iodine, ester **7** was isolated in 71% yield (Scheme 2).



Scheme 2. *Reagents and Conditions*: (i) THF, −78 °C to 25 °C, 20 h; (ii) I_2.

1.2.2 Via aryne intermediates

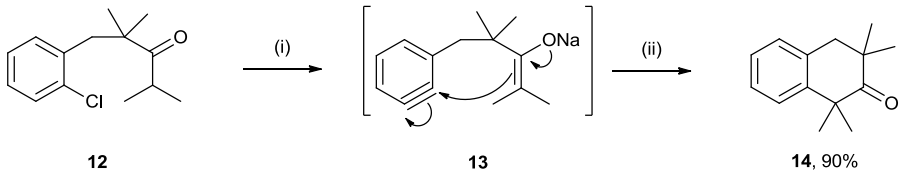
Roberts was the first to propose the "*at least transitory existence of electronically neutral benzyne intermediate*" when looking to explain the observed substitution reactions of halobenzenes.[8] In this study, treatment of ^{14}C-labelled chlorobenzene **8** with potassium amide in liquid ammonia at −33 °C gave the corresponding aniline compounds **10** and **11** in almost an equimolar ratio and were isolated in 43% combined yield, thus postulating the substitution reaction occurred via a benzyne intermediate **9** (Scheme 3).



Scheme 3. *Reagents and Conditions*: (i) KNH_2, NH_3, −33 °C. [● = ^{14}C isotope labelled carbon atom].

Benzyne **9** and any substituted derivative (i.e., an aryne) are highly reactive intermediates used in a range of polar and pericyclic reactions.[9] Arynes are generated *in situ* and provide a very electrophilic aromatic species due to the very weak C≡C triple bond. This reactivity has been exploited to enable the synthesis of a plethora of natural products via the nucleophilic addition of a wide range of nucleophiles.[10] This range encompasses enolate additions to aryne intermediates, which has received much interest over the years.[9] Loubinoux and Caubere demonstrated that haloarenes, in the presence of strong bases, react readily with a range of aliphatic and aromatic ketone enolates to give the corresponding α-alkylated and α-arylated bi-cyclic systems.[11] For example, ketone derivative **12** was treated with $NaNH_2$ in DME to give **14** in 90% yield; this

reaction was proposed to go via aryne intermediate **13**, formed by deprotonation α- to the ketone and deprotonation on the arene ring (Scheme 4).



12 **13** **14**, 90%

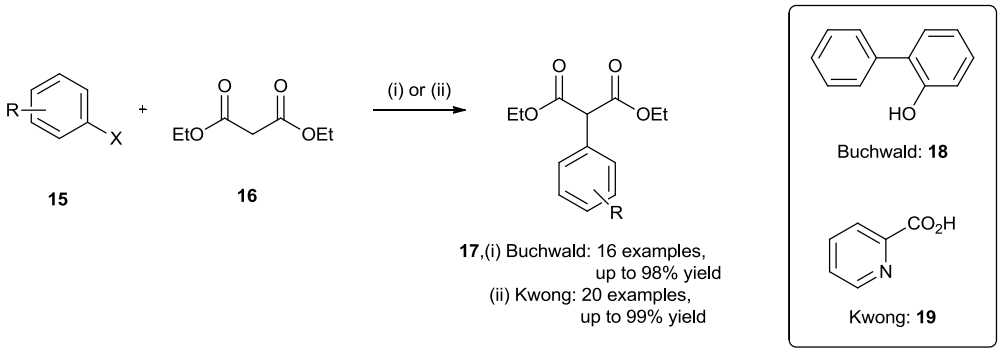
Scheme 4. *Reagents and Conditions*: (i) $NaNH_2$, DME, 40−45 °C, 12 h; (ii) HCl.

1.2.3 Transition Metal-catalysed α-arylation

Modern methods to achieve α-arylation rely upon transition-metal catalysed α-arylation of enolates which involves a nucleophilic enolate component cross-coupled with an electrophilic organometallic aryl halide species, thus generating a new C−C bond. Cross-coupling reactions have become a mainstay of synthetic organic chemistry owing to the versatility of the reagents utilised and functional group tolerability.[12] Enolates, like other nucleophiles, do not react with simple, unactivated haloarenes but in the presence of a transition-metal, substitution of the halide functionality can occur.

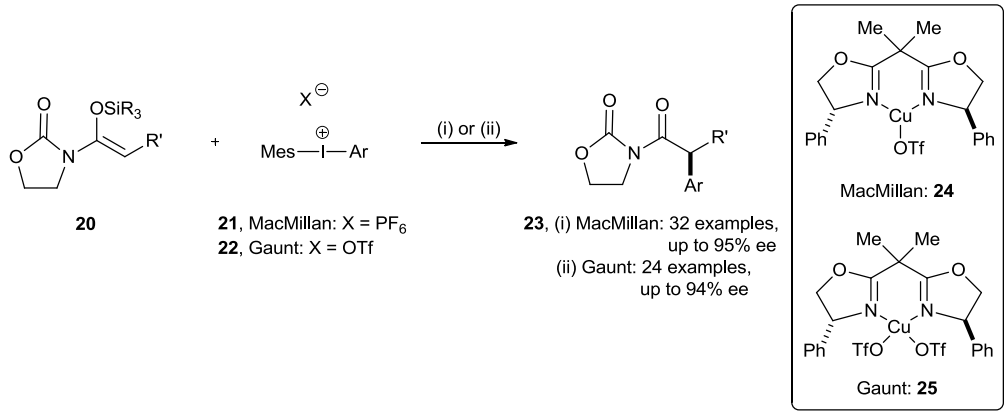
1.2.3.1 Copper-catalysed α-arylation

The reaction of carbanions derived from malonate esters with substituted arenes mediated by copper metal or copper salts was discovered by Hurtley in 1929,[13] and is a carbon analogue of the Ullman ether synthesis.[14] Over the past couple of decades, much work has focused on the use of this copper-catalysed process to achieve α-arylation of malonates.[15] However, early examples suffered from the use of very high reaction temperatures (>100 °C),[16] poor reproducibility and the use of stoichiometric amounts of copper complexes.[15] To negate this, Buchwald and Hennessy[17] developed a catalytic procedure using only 5 mol% of CuI alongside 10 mol% of monodentate ligand **18** at a reduced temperature of 70 °C to afford the corresponding α-aryl malonates **17** in good yield. Kwong *et al.*[18] optimised this reaction further by using 2-picolinic acid **19** as the ligand to enable transformations at rt, leading to the formation of **17** in up to 99% yield (Scheme 5).



Scheme 5. *Reagents and Conditions*: (i) CuI (5 mol%), **18** (10 mol%), $CsCO_3$, THF, 70 °C, 24−31 h; (ii) CuI (5 mol%), **19** (10 mol%), $CsCO_3$, 1,4-dioxane, rt, 2−28 h.

Recently, the use of chiral copper catalysts in conjunction with aryliodonium salts **21** and **22** has enabled the enantioselective synthesis of α-aryl oxazolidinone derivatives **23**. The use of chiral, bidentate Box ligands in α-arylation processes was pioneered by MacMillan[19] and Gaunt[20] leading to the formation of stable Cu(I) and Cu(II) chiral catalysts **24** and **25**. Preliminary studies required the use of preformed silylketene intermediates **20** derived from *N*-acyl oxazolidinones, which readily underwent facile conversion to the corresponding α-aryl oxazolidinone derivatives **23** in high yields and up to 95% ee (Scheme 6).

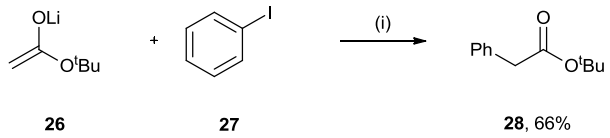


Scheme 6. *Reagents and Conditions*: (i) **24** (10 mol%), PhMe/CH_2Cl_2, 23 °C, 3 h; (ii) **25** (5 mol%), CH_2Cl_2, rt, 2 h.

1.2.3.2 Nickel-catalysed α-arylation

Another metal frequently used to enable α-arylation of enolates with aryl halides is nickel. Semmelhack *et al.* were the first to delineate the use of nickel catalysts for the conversion of the lithium enolate derived from acetophenone to phenylbenzyl ketone via the use of $Ni(PPh_3)_4$.[21] Although a sub-stoichiometric amount of the Ni-catalyst (14 mol%) was used, the reaction suffered from poor turnover and the overall conversion was only 50% from iodobenzene **27**. A few years later Millard and Rathke[22] reported the efficient conversion of enolate **26** derived from *tert*-butyl

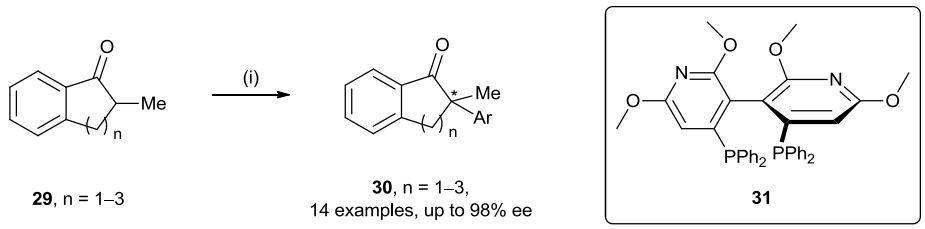
acetate to its α-phenyl ester derivative **28** in 66% isolated yield, although the use of stoichiometric amounts of $NiBr_2$ were needed to ensure good yields (Scheme 7).



26 **27** **28**, 66%

Scheme 7. *Reagents and Conditions*: (i) $NiBr_2$, BuLi, THF, −78 °C to rt, 30 min.

More recently, work has focused on the development of a highly enantioselective method for α-arylation of enolates. Kwong *et al.* reported the first examples, based on enolates derived from cyclic ketones **29**, via the use of the chiral, atropisomeric phosphine ligand **31**.[23] Quaternary stereocenters within **30** were formed in very high enantioselectivity (up to 98% ee) with a variety of aryl groups, and also included a rare example using chlorobenzene to achieve arylation (Scheme 8).



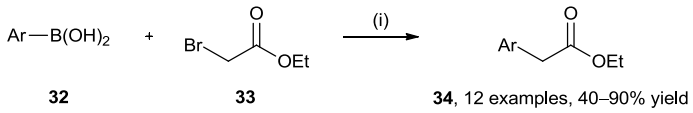
29, n = 1–3 **30**, n = 1–3, 14 examples, up to 98% ee **31**

Scheme 8. *Reagents and Conditions*: (i) ArX, $NiBr_2$, BuLi, THF, −78 °C to rt, 30 min.

1.2.3.3 Palladium-catalysed α-arylation

1.2.3.3.1 Suzuki-cross coupling

By far the most studied transition-metal catalysed cross-coupling processes involve the use of palladium. The Suzuki cross-coupling reaction[24] of sp^2-hybridised organoboron reagents with functionalised sp^3-hybridised halides or triflates is one which has received a great deal of attention for many decades and as such has become a key tool to synthesise complex molecules.[25] Gooßen reported an interesting application of this methodology whereby coupling of α-bromoacetic acid ethyl ester **33** could be achieved with arylboronic acids **32** to give α-aryl esters **34** in 40−90% yield (Scheme 9).[26]



Scheme 9. *Reagents and conditions*: (i) $Pd(OAc)_2$ (3 mol%), $(1\text{-Nap})_3P$ (9 mol%), K_3PO_4, THF, 20 °C, 16 h.

1.2.3.3.2 Palladium-catalysed α-arylation of enolates

In contrast, Miura,[27] Buchwald[28] and Hartwig[29] separately reported a complementary palladium-catalysed approach to achieve α-arylation of ketone enolates. The initial focus in this field concentrated in the development of Pd-precatalysts and ligands to increase the yield of α-arylation of simple ketones. The scope of the arylation was increased to incorporate enolates derived from esters, aldehydes and amides, amongst others.[12] The generally accepted mechanism for the process is consistent with the classical mechanism of palladium-catalysed cross-coupling processes. Initial oxidative addition of the aryl halide with the palladium(0) species is followed by transmetallation with the requisite enolate equivalent. Finally, reductive elimination furnishes the desired α-aryl carbonyl compound and regenerates the active palladium(0) species ready for the next catalytic cycle (Figure 2).

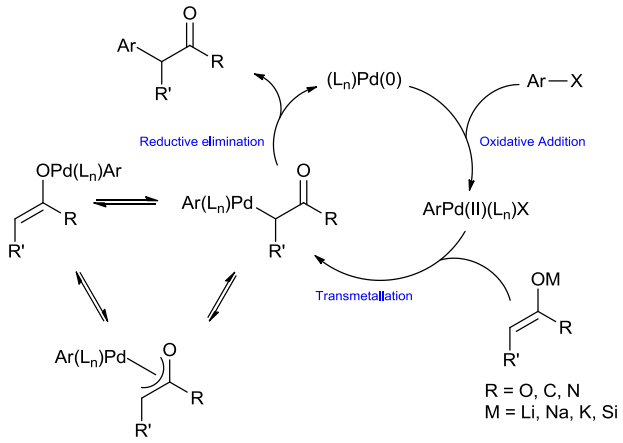


Figure 2. Mechanism of Pd-catalysed α-arylation. [L = Ligand].

More recently, the focus has shifted to the development of asymmetric variants, with several catalytic systems capable of α-arylation for the construction of quaternary stereocenters. High yields and selectivities have been achieved using both nickel and palladium precatalysts for the α-arylation of enolates derived from ketones, lactones and esters.[12]

1.3 α-Aryl-β-amino acids

A very important class of carbonyl compounds are β-amino acids, which have widespread biological and medicinal applications.[30] Seebach was the first to introduce the β-amino acid nomenclature (i.e., **35**−**38**) which is commonly used to denote the position of the side-chain (Figure 3).[31]

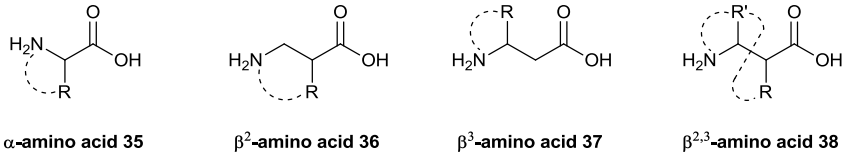


Figure 3. General nomenclature used for amino acids, also extends to cyclic derivatives.

α-Alkyl-β^2-amino acids have attracted a great amount of attention, owing to their prevalence in nature and use in medicinal therapy.[32] Work has highlighted both the preparation of individual, enantiopure monomer units as well as studies into the various structural properties of the derived β-peptides.[30] Although significant efforts have been made to enable the synthesis of a range of α-alkyl-β^2-amino acids, there are relatively few examples for the synthesis of α-aryl-β^2-amino acids, with research mainly focusing on the synthesis of 2-phenyl-3-aminopropanoic acid **39** due to its biological importance, as highlighted by the fact that a 2-phenyl-3-aminopropanoic acid (*R*)-**39** residue is present in the side-chain of the semisynthetic penicillin betacin **41**.[33] The ethyl ester derivative (*R*)-**40** is also known to exhibit significant neurological activity. As a consequence, analogues of **39** have become synthetic targets for many groups (Figure 4).[34]

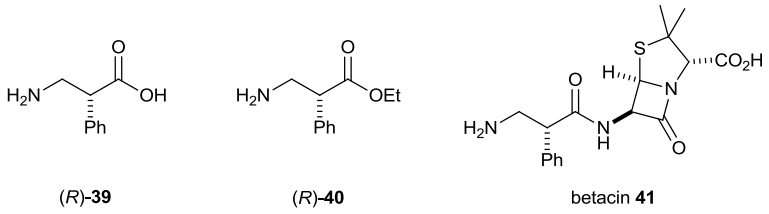
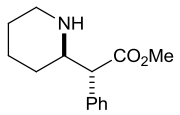


Figure 4. Structures of 2-phenyl-3-aminopropanoic acid (*R*)-**39**, its ethyl ester adduct (*R*)-**40** and betacin **41**.

The synthesis of α-aryl-β^{2,3}-amino acids on the other hand is somewhat limited to the synthesis of cyclic variants,[35] with an endocyclic nitrogen atom and the vast majority of the research is focused around the synthesis of various diastereoisomers of the psychostimulant drug methylphenidate **42** (marketed as Ritalin®). Ritalin® is a racemic mixture of (*R*,*R*)-**42** and (*S*,*S*)-**42** and is used to counter ADHD (attention deficit hyperactivity disorder) (Figure 5).

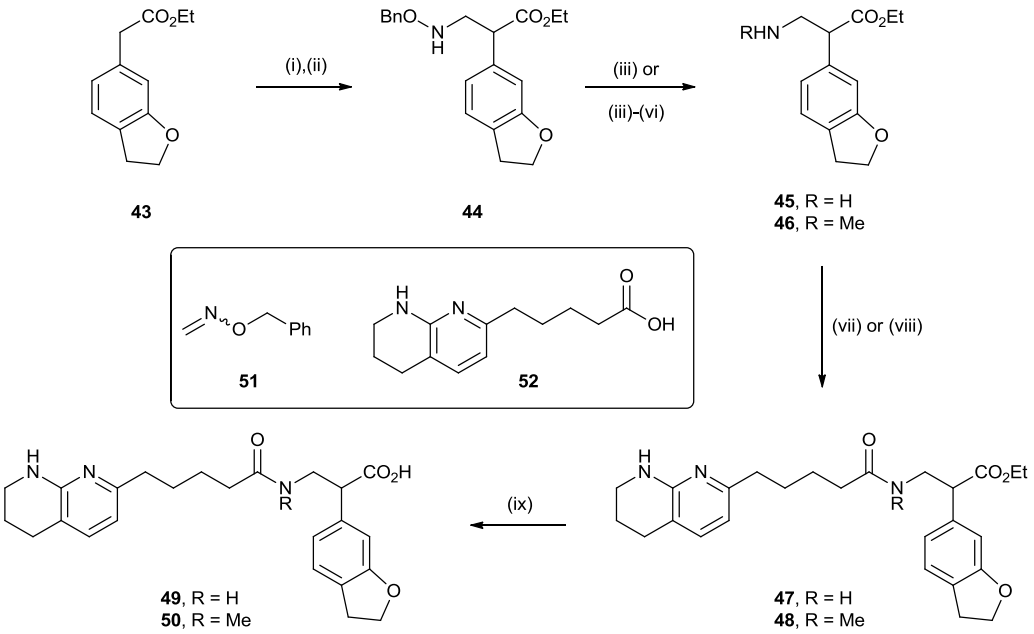


(*R*,*R*)-**42**

Figure 5. Structure of the (*R*,*R*)-diastereoisomer of methylphenidate (*R*,*R*)-**42**.

1.3.1 Synthesis of racemic α-aryl-β-amido acids derivatives

α-Aryl-β-amido acids such as **49** and **50** are derivatives of β^2-amino acids. Brashear *et al.* identified that the racemic α-aryl-β-amido compounds **49** and **50** were potent $\alpha_v\beta_3$ receptor antagonists and could be used to prevent and treat osteoporosis.[36] A common synthetic strategy was devised which relied upon a Mannich-type addition of the silyl enol ether of aryl acetate **43** to *O*-benzyloxime **51** (derived from formaldehyde). Subsequent hydrogenolysis of **44** gave primary β^2-amino ester **45**. Conversion of **45** to its *N*-methyl analogue **46** was facilitated by the "Ns-strategy" pioneered by Fukuyama.[37] Coupling of **45** and **46** with the requisite acid **52** under standard amide coupling conditions gave the corresponding α-aryl-β-amido esters **47** and **48**, which were hydrolysed to the desired α-aryl-β-amido acids **49** and **50** (Scheme 10). This methodology was applied to the synthesis of a small range of α-aryl-β-amido acids which all showed good levels of biological activity. Although the synthetic route was outlined, no yields for any of the chemical steps were disclosed by the authors.



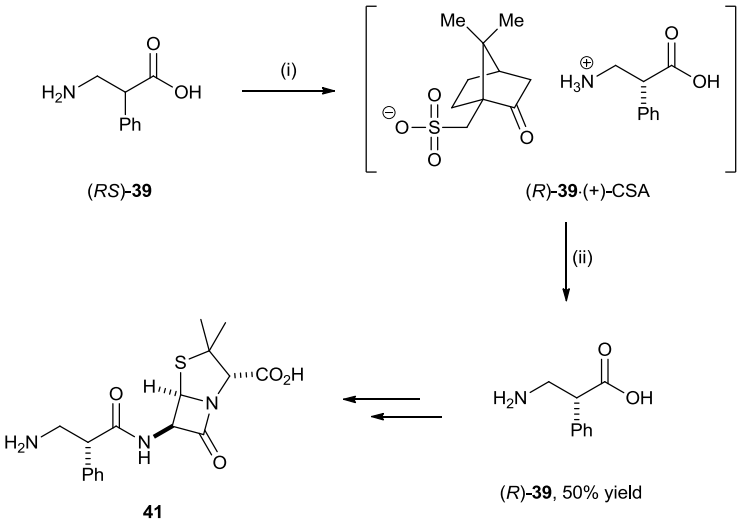
Scheme 10. *Reagents and* Conditions: (i) LDA, TMSCl, THF; (ii) **51**, TMSOTf, CH_2Cl_2; (iii) H_2, $Pd(OH)_2$, EtOH; (iv) 2-NsCl, $NaHCO_3$ (aq), CH_2Cl_2; (v) DIAD/DEAD, PPh_3, THF/MeOH; (vi) mercaptoacetic acid, Et_3N, CH_2Cl_2; (vii) **52**, EDC, HOBt, Et_3N, DMF; (viii) **52**, *N*,*N*,*N*′,*N*′-bis(tetramethylene)-chloroformamidinium hexafluorophosphate, CH_2Cl_2, DIPEA; (ix) NaOH (1.0 M aq), MeOH/THF.

1.3.2 Synthesis of racemic 2-phenyl-3-aminopropanoic acid 39

Posner was the first to establish the synthesis of racemic 2-phenyl-3-aminopropanoic acid (*RS*)-**39** over a century ago, via the addition of hydroxylamine to atropic acid.[38] Since then, there have been several reported syntheses of (*RS*)-**39**, although more recent efforts have focused on synthesising enantiopure **39**.

1.3.3 Synthesis of 2-phenyl-3-aminopropanoic acid 39 via resolution

The first reported isolation of enantiopure **39** was carried out by Testa *et al.*[33] Treatment of racemic (*RS*)-**39** with (+)-CSA and re-crystallisation of the two resultant diastereoisomers gave (*R*)-**39**·(+)-CSA, which was then washed with NaOH (10% aq) to furnish the desired enantiopure (*R*)-**39** in 50% yield. The absolute configuration within (*R*)-**39** was confirmed by Wyatt *et al.*[39] (*vide infra*). Subsequently, (*R*)-**39** was then converted to the penicillin analogue betacin **41** (Scheme 11).



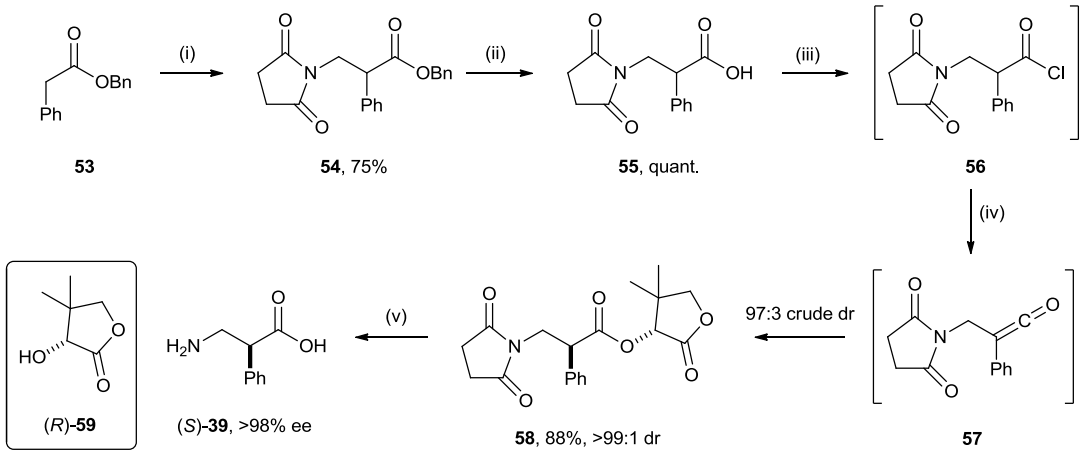
Scheme 11. *Reagents and* Conditions: (i) (+)-CSA, EtOH, 0 °C, 4 h; (ii) NaOH (10% aq).

1.3.4 Diastereoselective syntheses of α-aryl-β-amino acids

1.3.4.1 Via prochiral ketene

Calmes and Escale developed a synthetic route to (*S*)-**39** relying upon the diastereoselective addition of enantiopure lactone (*R*)-**59** to prochiral ketene **57**.[40] Coupling of the lithium enolate derived from benzyl phenylacetate **53** with *N*-bromomethylphthalimide gave the *N*-protected β^2-amino ester **54** in 75% yield. Hydrogenolysis of the *O*-benzyl group within **54** then conversion of the acid **55** to the corresponding acid chloride **56** [formed *in situ* by treatment with $(COCl)_2$] and

subsequent treatment with Et_3N gave the key ketene intermediate **57**. Diastereoselective addition of (*R*)-**59** gave the major diastereoisomer **58** in 88% yield and 97:3 dr which was enriched to >99:1 dr via recrystallisation. Hydrolysis of **58** under acidic conditions furnished 2-phenyl-3-aminopropanoic acid (*S*)-**39** without any accompanying racemisation (Scheme 12).

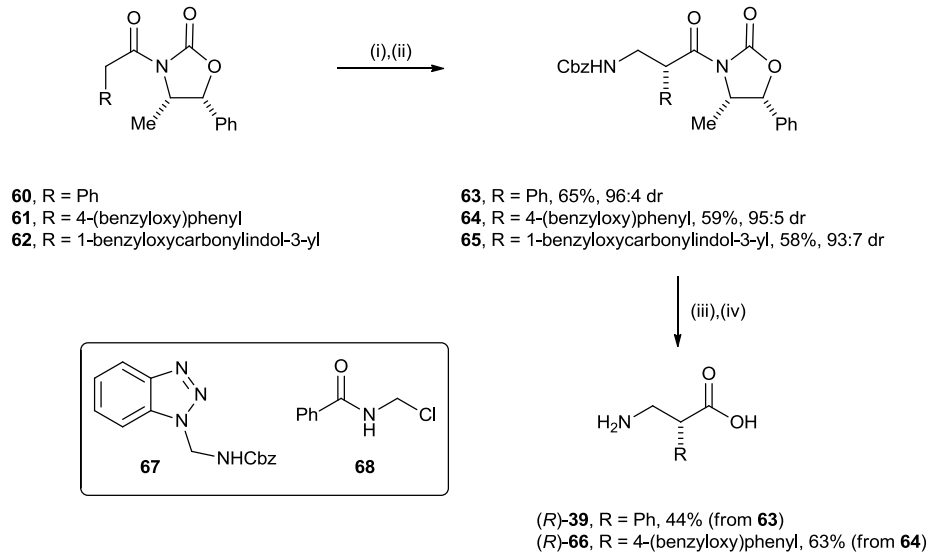


Scheme 12. *Reagents and* Conditions: (i) LDA, *N*-bromomethylphthalimide, THF, DMPU, −78 °C to rt, 16 h; (ii) H_2, $Pd(OH)_2$/C, EtOAc, −20 °C to rt, 5−6 h; (iii) $(COCl)_2$, 30 °C, 12 h; (iv) Et_3N, THF, 0 °C to rt, 1 h then (*R*)-**59**, THF, rt, 3 h; (v) AcOH/HCl (6.0 M aq) (1:10 v/v), reflux, 4−5 h.

1.3.4.2 Via *N*-acyl oxazolidinone derivatives

1.3.4.2.1 Synthesis of α-aryl-β^2-amino acids via enolate addition

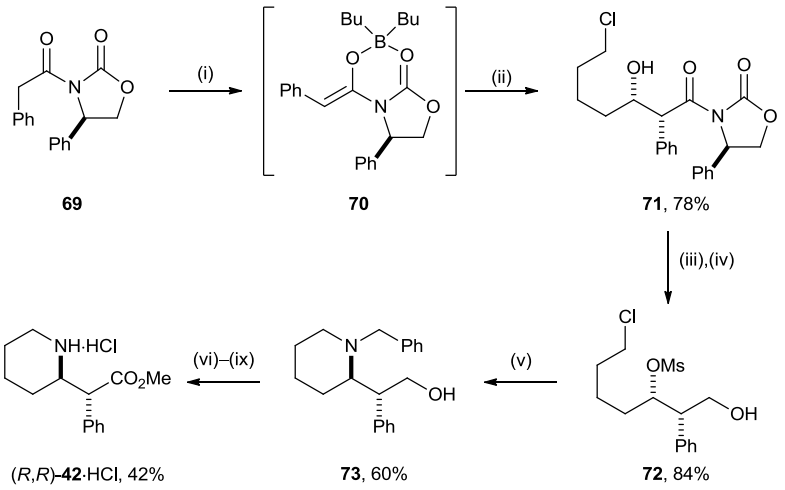
The asymmetric Mannich reaction of enolates derived from *N*-acyl oxazolidinones with imine equivalents provides a diastereoselective route to α-aryl-β^2-amino acids. Exploratory investigations carried out by Evans *et al.*[41] highlighted the use of *N*-(chloromethyl)-benzamide **68** as a useful amidomethylating agent. Subsequently, Wyatt *et al.* disclosed an analogous procedure ustilising a more stable benzotriazole derivative **67** as an amidomethylating agent for the synthesis of α-aryl-β^2-amino acids (*R*)-**39** and (*R*)-**66**.[39,42] The key step involves the Mannich reaction of the enolate derived from α-aryl substituted oxazolidinones **60**−**62** with electrophile **67** to give the aminoalkylation products **63**−**65** in moderate yields and high diastereoselectivity (up to 96:4 dr). Subsequent cleavage of the chiral auxiliary within **63** and **64** led to the formation of the corresponding *N*-Cbz protected α-aryl-β^2-amino acids, which after catalytic hydrogenolysis gave the free amino acids (*R*)-**39** and (*R*)-**66** in 44 and 63% yield, respectively (from **63** and **64**). The absolute (*R*)-configuration of **39** was unambiguously established via single X-ray diffraction analysis of the (+)-CSA salt (*R*)-**39**·(+)-CSA (Scheme 13).



Scheme 13. *Reagents and* Conditions: (i) LDA or LiHMDS, THF, −78 °C, 20 min; (ii) **67**, −78 °C, 2 h then rt; (iii) LiOH, H_2O_2 (30% aq), H_2O, 0 °C; (iv) H_2, Pd/C, AcOH.

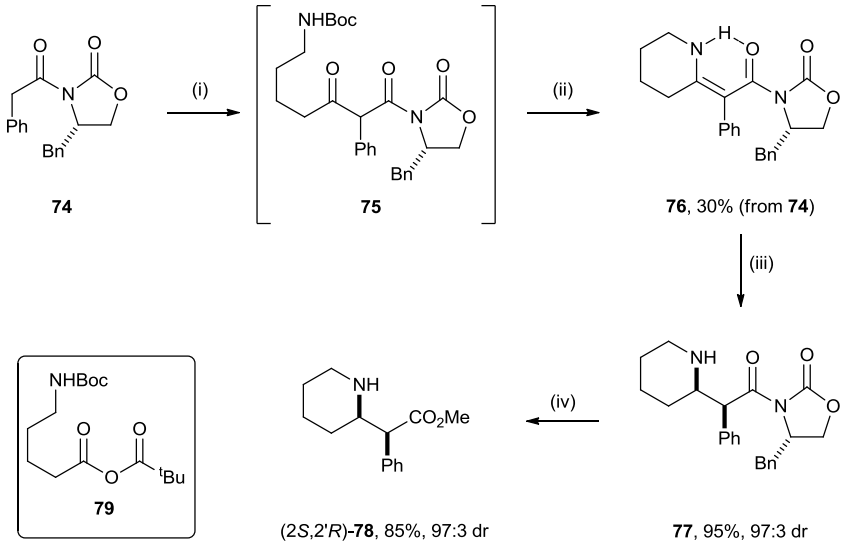
1.3.4.3.2 Synthesis of α-aryl-β^{2,3}-amino acids via enolate addition

Prashad *et al.*[43] demonstrated an approach based on the Evans oxazolidinone can also be used to perform diastereoselective reactions which can then be elaborated to reveal a β^{2,3}-amino acid derivative, specifically the (*R*,*R*)-diastereoisomer of methylphenidate (*R*,*R*)-**42**. Enolate formation of **69** in the presence of a Lewis acid results in the generation of a chelated (*Z*)-enolate **70** which can then be reacted with the requisite electrophile to provide the aldol adduct **71** in 78% yield. Subsequent mesylation of the secondary alcohol within **71**, followed by reduction of the oxazolidinone ring led to the smooth formation of primary alcohol **72** in 84% yield. Treatment of **72** with excess benzylamine results in inital intermolecular nucleophilic substitution of the mesylate, followed by intramolecular attack of the resultant secondary amine on the primary chloride furnishing cyclic β^{2,3}-amino alcohol **73** in 60% yield. Finally, a protocol involving hydrogenolytic cleavage of the *N*-benzyl group, *N*-Boc protection, oxidation of the primary alcohol moiety and acid-catalysed esterfication resulted in *N*-Boc deprotection and gave the HCl salt of (*R*,*R*)-methylphenidate (*R*,*R*)-**42**·HCl in 42% yield (Scheme 14).



Scheme 14. *Reagents and Conditions:* (i) Bu_2BOTf, DIPEA, CH_2Cl_2, –20 °C; (ii) $Cl(CH_2)_4CHO$, –20 °C to rt, 3 h then H_2O_2 (30% aq), MeOH; (iii) MsCl, Et_3N; (iv) $NaBH_4$, THF, H_2O, 0 °C to rt; (v) $PhCH_2NH_2$, 85°C, 3 h; (vi) H_2, Pd/C, EtOH; (vii) Boc_2O, THF; (viii) $NaIO_4$, $RuCl_3{\cdot}H_2O$, MeCN, H_2O, CCl_4; (ix) MeOH, HCl, 50 °C, 12 h.

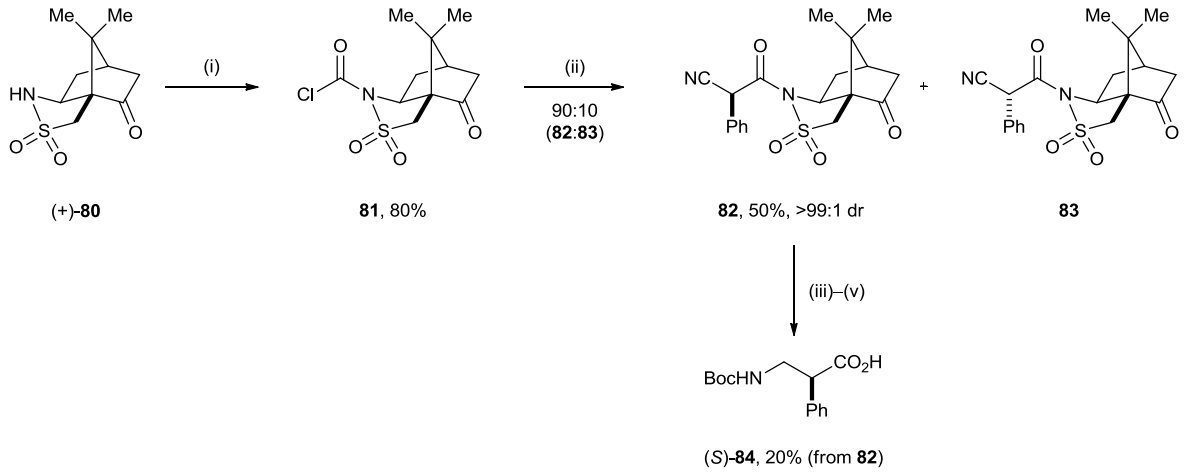
Prashad *et al.*[44] also reported a strategy to access (2*S*,2′*R*)-**78**, the C(2)-epimer of methylphenidate **42**, using a similar α-phenylacetyl Evans oxazolidinone **74**. Coupling of the lithium enolate of **74** with mixed anhydride **79**, followed by *N*-Boc deprotection and subsequent attack of the primary amine and tautomerisation gave enamine **76** in 30% isolated yield from **74**. Hydrogenation of **76** gave **77** in 95% yield and 97:3 dr. Treatment of **77** with MeOH in the presence of LnI_3 led to the formation of methyl ester (2*S*,2′*R*)-**78** in 85% yield and 97:3 dr (Scheme 15).



Scheme 15. *Reagents and Conditions*: (i) LiHMDS, THF, 0 °C, 1 h then **79**, Et_3N, PhMe, rt, 4 h; (ii) TFA, CH_2Cl_2, 0 °C to rt, 4 h then $NaHCO_3$ (aq); (iii) H_2, Pd/C, EtOAc, rt, 24 h; (iv) MeOH, LaI_3, THF, rt, 16 h.

1.3.4.3 Via chiral sultam

A diastereoselective synthesis of protected 2-phenyl-3-aminopropanoic acid (*S*)-**84** was also disclosed by Lavielle *et al.*[45] and was achieved via the use of Oppolzer's sultam chiral auxiliary (+)-**80**. Initial conversion of (+)-**80** to chiral carbonyl chloride **81** was followed by reaction with the sodium anion of phenylacetonitrile as the key diastereoselective step. The crude reaction mixture contained a 90:10 mixture of diastereoisomers **82** and **83**. The major diastereoisomer **82** was isolated in 50% yield and >99:1 dr. Reduction of **82** to give the intermediate amino alcohol, *N*-Boc protection and oxidation gave the protected β^2-amino acid (*S*)-**84** in 20% yield (from **82**). Although the enantiomeric excess of (*S*)-**84** was not determined, significant epimerisation was not indicated by the authors as established by comparison of specific rotation data with literature values (Scheme 16).

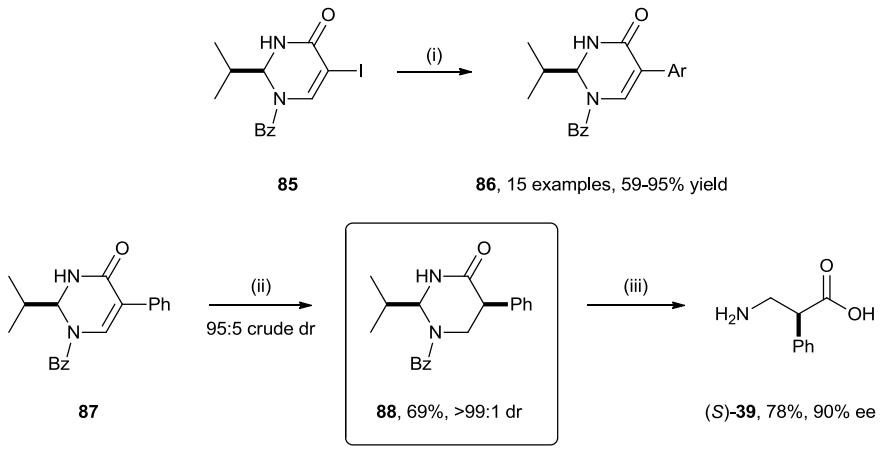


Scheme 16. *Reagents and Conditions*: (i) Et_3N, $(CCl_3O)_2CO$, CH_2Cl_2, 4 °C to rt, 16 h; (ii) NaH, phenylacetonitrile, DMSO, THF, −10 °C, 2 h; (iii) $LiAlH_4$, $AlCl_3$, THF, 2-methyltetrahydrofuran, 0 °C to rt, 4 h; (iv) Boc_2O, 1,4-dioxane, 0 °C to rt, 16 h; (v) pyridinium dichromate, DMF, rt, 14 h.

1.3.4.4 Palladium catalysed Suzuki-Miyaura reaction

Juaristi *et al*. showed that the Suzuki-cross coupling of organotrifluoroborate salts with diastereoisomerically pure pyrimidinones followed by hydrogenation of the endocyclic double bond provided α-aryl-β^2-amino acids in good yields and high enantiomeric excess. The Suzuki-cross coupling of a wide range of aryltrifluoroborate salts with pyrimidinone **85** were shown to proceed in good to excellent yield, with high functional group tolerance. Raney-Ni catalysed hydrogenation of α-phenyl adduct **87** gave a 95:5 mixture of *cis* and *trans* diastereoisomers, which were separable by column chromatography to give the major *cis* diastereoisomer **88** in 69% yield as a single

diastereoisomer (>99:1 dr). Partial epimerisation was noticed upon acid-catalysed hydrolysis of **88** giving (*S*)-**39** in 78% yield and 90% ee (Scheme 17).

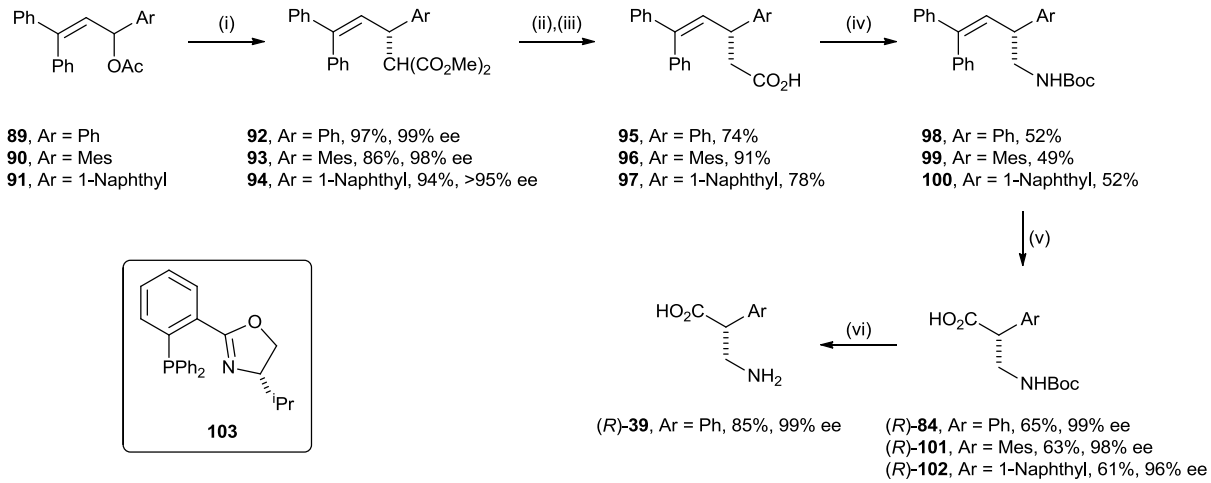


Scheme 17. *Reagents and Conditions*: (i) $Pd(OAc)_2$ (9 mol%), $ArBF_3K$, K_2CO_3, 1,4-dioxane/H_2O (3:1 v/v), 110 °C, 30−90 min; (ii) H_2, Raney-Ni, MeOH, 80 °C, 24 h; (iii) HCl (4.0 M aq), μwave, 98 °C, 6 h.

1.3.5 Enantioselective syntheses of α-aryl-β-amino acids via transtion-metal catalysis

1.3.5.1 Via Palladium catalysed asymmetric allylic substitution

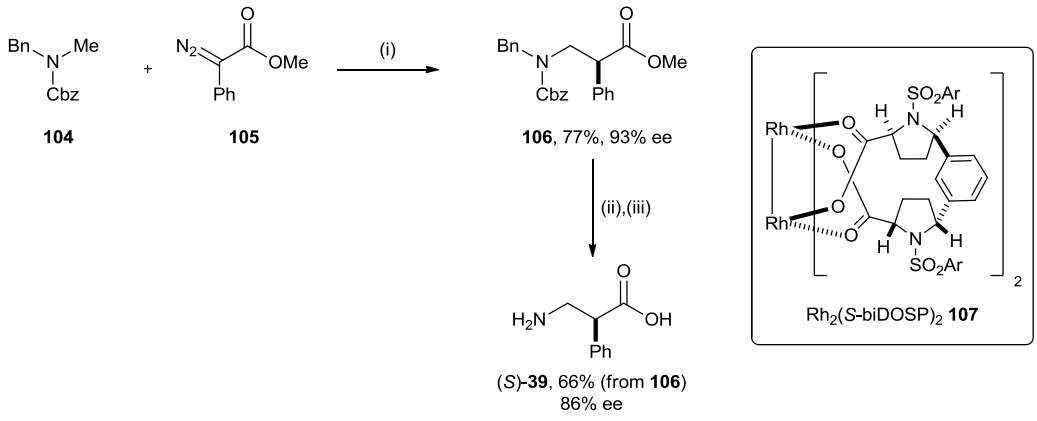
Enantioselective Pd-catalysed substitution of allylic acetates and subsequent elaboration can also lead to the formation of α-aryl-β^2-amino acids in good yields and extremely high enantioselectivity. Williams *et al.*[46] used [PdCl(allyl)$_2$] as a pre-catalyst and chiral ligand **103**, to displace the acetate group within **89**−**91** with sodiodimethylmalonate to give the corresponding substitution products **92**−**94** in high yields (86−97%) and with very high stereocontrol (>95% ee). Decarboxylation of these adducts, followed by hydrolysis gave the corresponding carboxylic acids **95**−**97** in good yields. Curtius-type reaction to give the corresponding *N*-Boc protected amides **98**−**100** proceeded in moderate yields. Oxidative cleavage then led to the formation of the protected β^2-amino acids (*R*)-**84**, (*R*)-**101** and (*R*)-**102** without any loss in stereochemical integrity. Deprotection of (*R*)-**84** under acidic conditions gave (*R*)-**39** in 85% yield and 99% ee (Scheme 18).



Scheme 18. *Reagents and* Conditions: (i) $NaCH(CO_2Me)_2$, $[PdCl(allyl)]_2$ (2.5 mol%), **103** (10 mol%), THF, 30 °C, 24−36 h; (ii) DMSO, NaCl, H_2O, 180 °C, 7 h; (iii) NaOH, H_2O, MeOH, reflux, 2 h; (iv) $(PhO)_2P(O)NEt_3$, ^tBuOH, reflux, 16 h; (v) $RuCl_3{\cdot}(H_2O)_n$, $NaIO_4$, MeCN, CCl_4, H_2O, 40 °C, 2 h; (vi) HCl (4.0 M aq), 1,4-dioxane, 4 h then DOWEX.

1.3.5.2 Via Rhodium catalysed C−H insertion

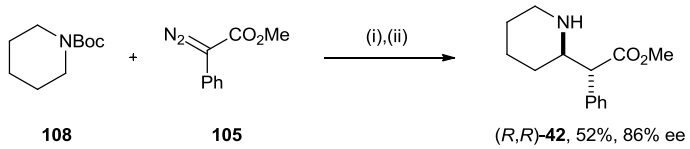
Davies *et al.* utilised rhodim catalysis to undergo C−H insertion of aryldiazoacetate **105** to *N*-protected methylamine **104** and thus enabled a concise synthesis of enantioenriched (*S*)-**39**.[47] It was shown that C−H insertion of **104** could be facilitated by *in situ* carbene formation (via the addition of phenyl diazomethyl ester **105** to chiral rhodium catalyst Rh_2(*S*-biDOSP)$_2$ **107** to give *N*-Cbz protected β^2-amino ester **106** in 77% yield and 93% ee. Subsequent ester hydrolysis under basic conditions and *N*-Cbz deprotection by transfer hydrogenation furnished (*S*)-**39** in 66% yield (from **106**) with only partial loss in stereochemical integrity (86% ee) (Scheme 19).



Scheme 19. *Reagents and* Conditions: (i) **107**, 2,2-dimethylbutane, 23 °C; (ii) $LiOH{\cdot}H_2O$, THF; (iii) HCO_2NH_4, Pd/C, MeOH. {Ar = *p*-$[CH_3(CH_2)_{10\text{-}12}]C_6H_4$}.

The use of metal carbenoid intermediates can also be exploited to enable the synthesis of cyclic α-aryl-$\beta^{2,3}$-amino esters,[35] and this approach provided an elegant, two-step synthesis of the

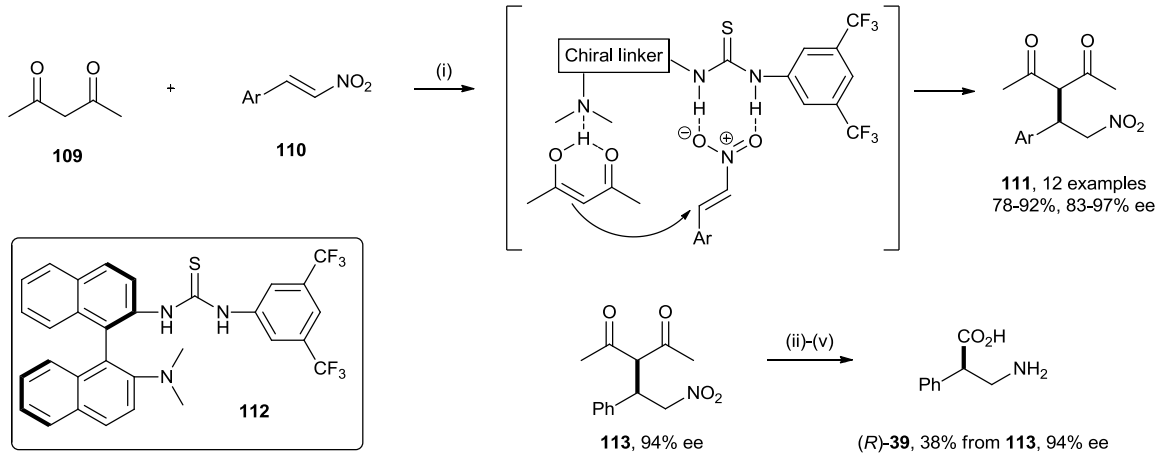
biologically active enantiomer of methylphenidate (*R*,*R*)-**42**.[35] C–H insertion of *N*-Boc pyrrolidine **108** was facilitated by *in situ* carbene formation [via the addition of phenyl diazomethyl ester **105** to chiral rhodium catalyst Rh_2(*S*-biDOSP)$_2$ **107**]. Subsequent *N*-Boc deprotection under acidic conditions furnished the desired (*R*,*R*)-**42** in 52% yield and 86% ee (Scheme 20).



Scheme 20. *Reagents and* Conditions: (i) **107**, 25 °C; (ii) TFA.

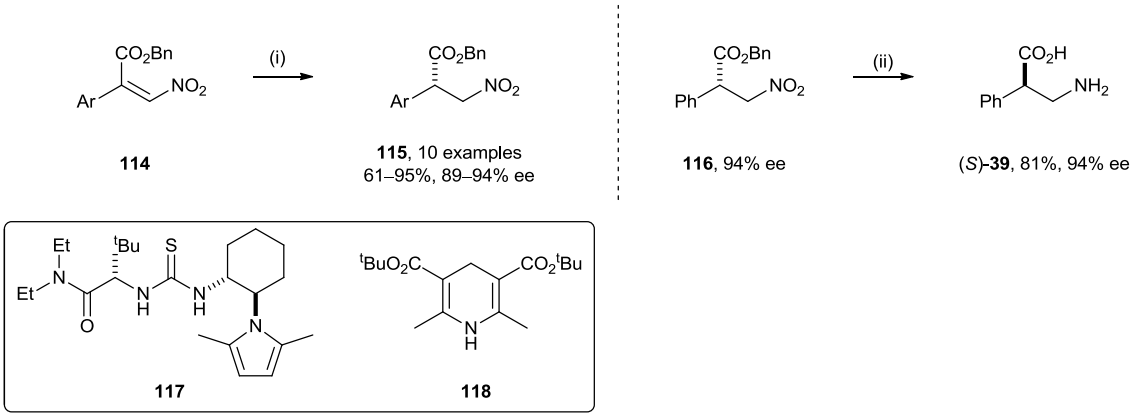
1.3.6 Enantioselective synthesis of α-aryl-β-amino acids via organocatalysis

More recent methods for the preparation of enantiopure α-aryl-β^2-amino acids are concerned with the use of more environmentally friendly, metal-free organocatalysts. Although organo-catalytic Mannich-type reactions for the synthesis of α-alkyl-β^2-amino acids have been reported,[48] these methods have not been applied to the synthesis of α-aryl variants. For the preparation of α-aryl-β^2-amino acids via organocatalysis, Wang *et al.* developed a novel bifunctional thiourea catalyst **112** which enabled the highly selective asymmetric Michael addition of 2,4-pentandione **109** to a range of *trans*-β-nitrostyrene derivatives **110** to give **111** in excellent yields and selectivities.[49] Reactions were carried out using mild conditions and with only 1 mol% of the chiral catalyst **112**. The phenyl adduct **113** was readily converted to the corresponding β^2-amino acid (*R*)-**39** via a four-step procedure to give (*R*)-**39** in 38% yield (from **113**) and without any loss in ee (Scheme 21).



Scheme 21. *Reagents and* Conditions: (i) **112** (1 mol%), Et_2O, rt, 24−60 h; (ii) oxone, TBAI, K_2CO_3, acetone, CH_2Cl_2, H_2O, 0 °C, 30 min; (iii) DIBAL−H, PhMe, −78 °C, 2 h; (iv) $KMnO_4$, $NaIO_4$, Na_2CO_3, 1,4-dioxane, H_2O, 23 °C, 24 h; (v) H_2 (50 psi), Pd/C, MeOH, 16 h.

Alternatively, List *et al.* highlighted a more expeditious route to enantioenriched α-aryl- and α-heteroaryl-β-amino acids by the use of asymmetric transfer hydrogenation of α-substituted-β-nitroacrylates.[50] A variety of β-nitroacrylates **114** were treated with Hantzch ester **118** in the presence of 10 mol% of chiral thiourea catalyst **117** leading to the formation of the saturated esters **115** in high enantioselectivity (up to 95% ee). Hydrogenolysis of the phenyl substituted derivative **116** gave the corresponding β^2-amino acid (*S*)-**39** in 81% yield and in 94% ee (Scheme 22).



Scheme 22. *Reagents and* Conditions: (i) **117** (10 mol%), **118**, PhMe, 0 °C, 24−48 h; (ii) H_2, Pd/C, MeOH, 6 h.

1.4 Project Aims

This project describes the development of methodologies aimed at the synthesis of enantiopure α-phenyl-β^2-amino acids **119** and α-phenyl-$\beta^{2,3}$-amino acids **120**. The key diastereoselective steps investigated were: (i) addition of an achiral lithium amide to a chiral α-phenyl-α,β-unsaturated carbonyl derivative followed by diastereoselective protonation; (ii) conjugate addition of a chiral lithium amide to an achiral α,β-unsaturated ester followed by trapping of the intermediary enolate with an electrophilic phenyl source; (iii) Mannich-type addition of an achiral α-phenyl carbonyl enolate to a chiral protected imine. It was envisaged that application of these strategies could culminate in first total asymmetric syntheses of the six members of the nakinadine family of alkaloids: α-phenyl-β^2-amino acids (nakinadines B and C) **119** and α-phenyl-$\beta^{2,3}$-amino acids (nakinadines A and D−F) **120** (Figure 6).

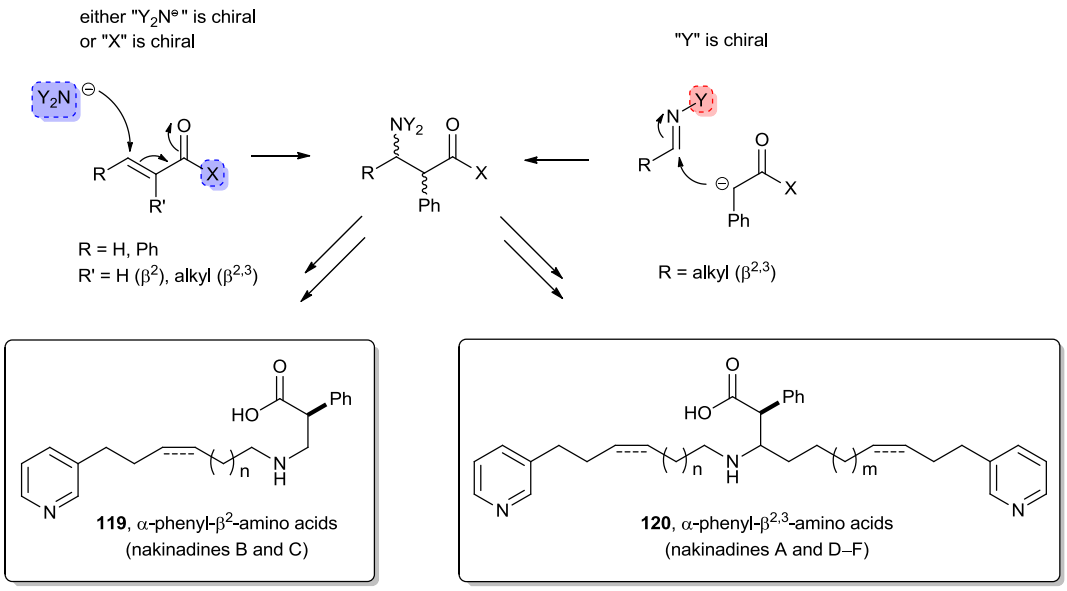


Figure 6. The proposed route to the nakinadine alkaloids.

1.5 References and notes

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Chapter 2: Asymmetric syntheses of nakinadines B and C

This chapter details the total asymmetric syntheses of the reported structures of the β^2-amino acid alkaloids nakinadines B **126** and C **127** using the conjugate addition of lithium dibenzylamide to *N*-α-phenylacryloyl SuperQuat derivative (*R*)-**121** as the key step (Figure 7).

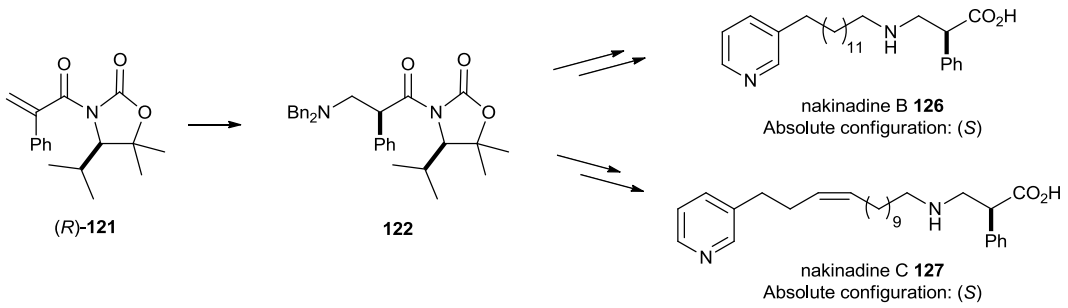


Figure 7. Outline of the key synthetic step towards the syntheses of nakinadines B **126** and C **127**.

2.1 Natural products isolated from the *Amphimedon* sp. marine sponge

Marine life provides scientists with an environment where a wide range of unique, diverse and structurally complex molecules can be discovered which have the potential to act as potent biological agents.[1] Recent work has highlighted marine sponges from several genera as key organisms which provide a rich variety of natural products (mainly alkaloids) with high biological activity.[2] Numerous natural products have been isolated from one such genera of marine sponge, *Amphimedon*, and these alkaloids have been found to portray varying degrees of cytolytic, cytotoxic and antimicrobial activities against murine, human and bacterial cell lines. Compounds isolated from *Amphimedon* often contain an amino functionality or a derivative thereof with an aliphatic *N*-substituent terminating with a pyridin-3-yl moiety. For example, amphimedoside A **123** was the first glycosylated 3-alkylpyridine alkaloid to be discovered and displayed moderate cytotoxicity against P388 murine leukaemia cells (IC_{50} 11 μg/mL) *in vitro*.[3] Similarly, pyrinodemin B **124**, a bis-alkylpyridine substituted isoxazolidine, is a potent inhibitor of L1210 murine leukaemia cells (IC_{50} 0.07 μg/mL)[4] (Figure 8).

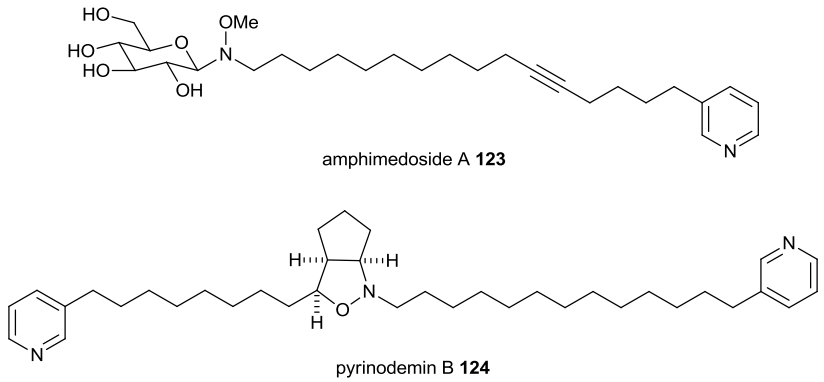


Figure 8. Natural products isolated from *Amphimedon* sp.

This trend is further complemented by the nakinadine family of alkaloids, which consist of six distinct members, each comprising an α-phenyl-β-amino acid residue as the core with long chain β- and/or *N*-alkyl substituents capped by pyridin-3-yl moieties. Nakinadine A **125** was the first reported member of this cytotoxic alkaloid family, and was isolated by Kobayashi *et al*. in 2007 from *Amphimedon* sp. found off the Okinawan coast.[5] Five further members of the nakinadine family (B−F **126**−**130**) were isolated from the same species a year later.[6] The overall structure of all these naturally occuring alkaloids was elucidated predominantly through a combination of standard ^{1}H and ^{13}C NMR spectroscopic techniques in combination with ESI MS/MS fragmentation analysis. Nakinadines B **126** and C **127** contain an *N*-substituted α-phenyl-β-aminopropanoic acid (β^{2}-amino acid) residue, whereas the other four members, nakinadines A **125** and D−F **128**−**130**, are $\beta^{2,3}$-amino acids containing an *N*-substituted α-phenyl-β-amino-ω-(pyridin-3-yl)alkanoic acid residue (Figure 9). The absolute (*S*)-configurations within nakinadines B **126** and C **126** were assigned by ^{1}H NMR spectroscopic studies according to the method reported by Nagai and Kusumi,[7] which relies on derivatisation of the amino acid moiety with the enantiomers of phenylglycine methyl ester (PGME). This is similar to the method developed by Mosher *et al.*,[8] which has become ubiquitous amongst synthetic chemists. Both nakinadines B **126** and C **127** exhibited limited cytotoxicity against L1210 murine leukemia (IC_{50} 3.0 and 5.0 mg/mL, respectively) and KB human epidermoid carcinoma cells (IC_{50} 7.0 and >10 mg/mL, respectively) *in vitro*.[6] At the outset of these studies no syntheses (asymmetric or otherwise) of any members of the nakinadine family had been reported.[9,10]

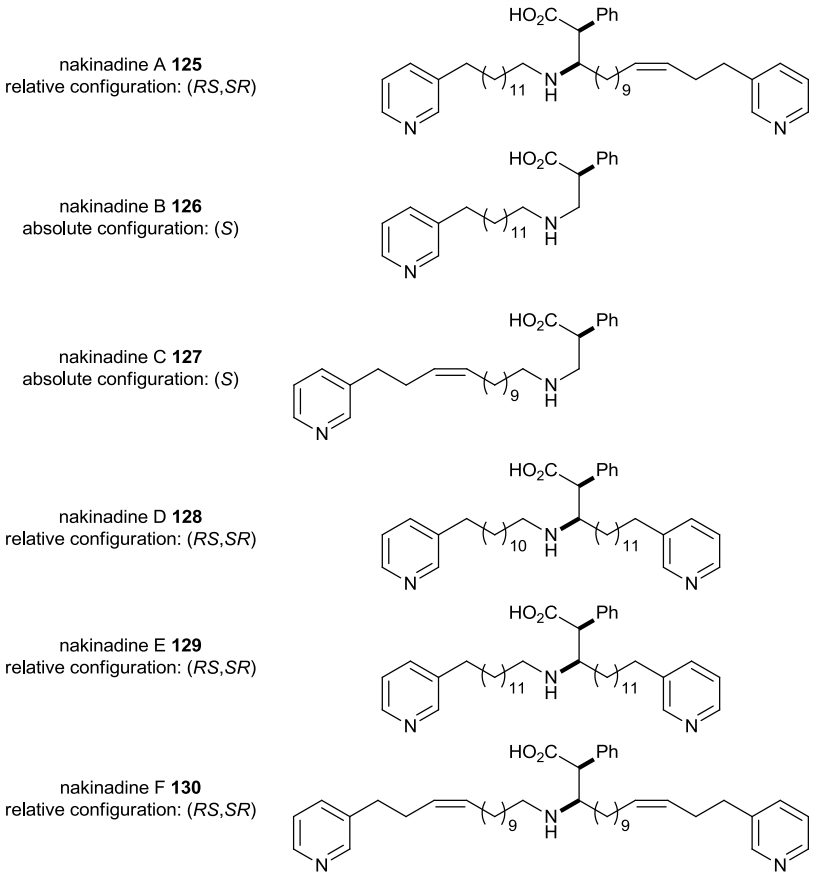


Figure 9. The reported structures of nakinadines A−F **125**−**130**.

2.2 Chapter Aim

This project set out to develop efficient routes for the syntheses of nakinadines A−F **125**−**130**. As the simplest members of the family, and indeed the only members of the family for which an absolute configuration had been proposed, nakinadines B **126** and C **127** were targeted first. It was hoped that through the development of these asymmetric syntheses, the structural and stereochemical assignments made by Kobayashi *et al.*[6] could be verified.

2.3 Retrosynthetic analyses of nakinadines B 126 and C 127

As nakinadines B **126** and C **127** share a common β^2-amino acid residue (i.e., 2-phenyl-3-aminopropanoic acid), initial disconnection of the C−N bond revealed the *N*-(ω-pyridin-3-yl)alkyl chain as an electrophilic component (for example, as aldehyde **131** or an activated form of alcohol **132**) and the β^2-amino adduct **133** as a nucleophilic component. It was envisaged that **133** could be synthesised from the conjugate addition of lithium dibenzylamide to an *N*-α-phenylacryloyl SuperQuat derivative **121** and subsequent hydrogenolysis using a previously reported strategy.[11,12] Once the key (*S*)-α-phenyl bearing stereogenic center had been set, a variety of coupling methods such as reductive *N*-alkylation or a Mitusnobu-type "Ns-strategy" could be implemented to test their efficacy (without prompting racemisation/epimerisation of the sensitive α-stereo-genic center) in the functionalisation the amino group, before deprotection to unmask the acid functionality (Figure 10).

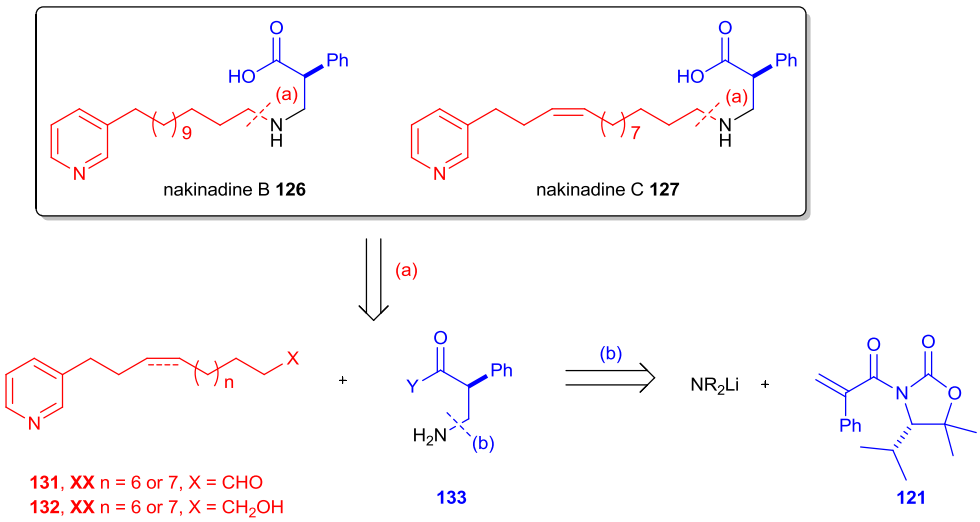
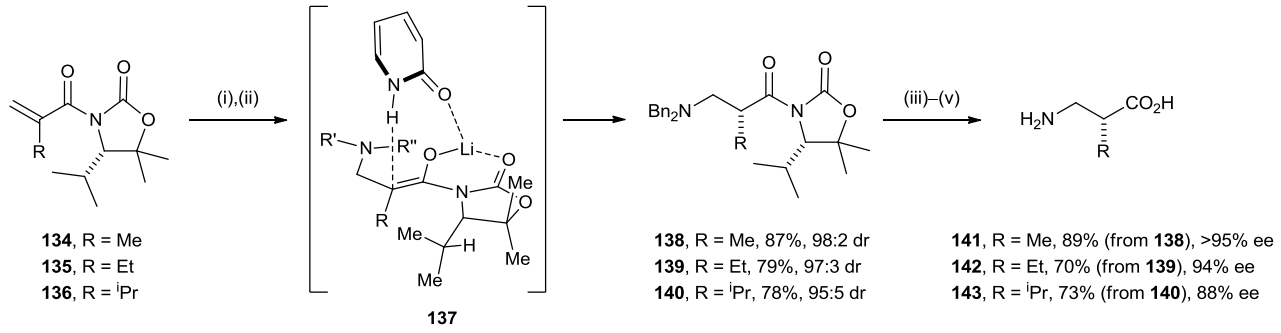


Figure 10. Retrosynthetic analysis of nakinadines B **126** and C **127**.

2.4 Previous studies

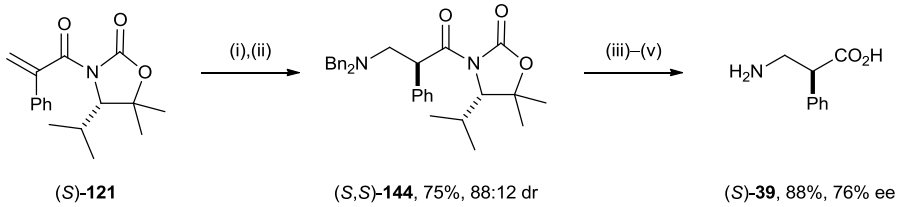
In 2004, Davies *et al.* reported that the conjugate addition of lithium dibenzylamide to a range of *N*-α-alkylacryloyl SuperQuat derivatives **134**−**136** followed by diastereoselective protonation of the resulting enolates with 2-pyridone gave the corresponding (4*S*,2'*R*)-β^2-amino adducts **138**−**140** in >95:5 dr. It was suggested that the key diastereoselective protonation step goes via a chelated transition state **137** with proton delivery occurring from the least hindered face.[11,12,13] The adducts **138**−**140** were efficiently converted to the corresponding enantioenriched 2-alkyl-3-aminopropionic

acids **141**−**143** by treatment with lithium hydroperoxide and subsequent hydrogenolysis of the protected β^2-adducts, without any accompanying racemisation or epimerisation (Scheme 23).



Scheme 23. *Reagents and Conditions:* (i) $LiNBn_2$, THF, −78 °C, 4 h; (ii) 2-pyridone, −78 °C to rt, 12 h; (iii) LiOH, H_2O_2 (30% aq), THF, H_2O, rt, 24 h; (iv) H_2 (1 atm), Pd/C, MeOH/H_2O/AcOH (40:4:1 v/v), rt, 24 h; (v) HCl (2.0 M aq).

The conjugate addition of lithium dibenzylamide to *N*-α-phenylacryloyl SuperQuat derivative (*S*)-**121** was also performed, and in contrast to the α-alkyl cases, was reported to give the major diastereoisomer (*S*,*S*)-**144** in 88:12 dr, which was isolated in 75% yield and in 88:12 dr. The stereochemistry of **144** was assigned by comparison of the specific rotation values with the literature value reported by Garbarino *et al.*[14] Global deprotection led to the isolation of 2-phenyl-3-aminopropanoic acid (*S*)-**39** in 88% yield and 76% ee {$[\alpha]_D^{25}$ +86.3 (*c* 1.0 in H_2O)}, thus highlighting the lack of accompanying racemisation and/or epimerisation during these chemical steps (Scheme 24).[15]

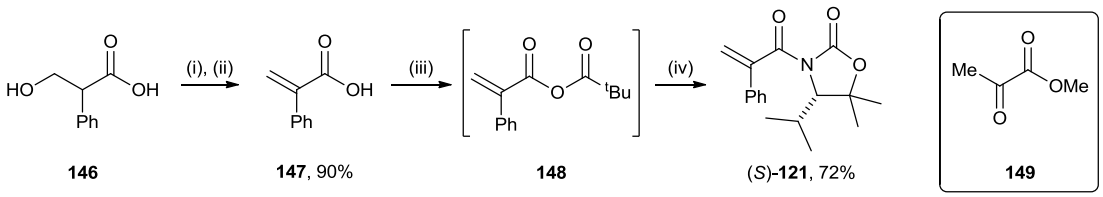


Scheme 24. *Reagents and Conditions:* (i) $LiNBn_2$, THF, −78 °C, 4 h; (ii) 2-pyridone, −78 °C to rt, 12 h; (iii) LiOH, H_2O_2 (30% aq), THF, H_2O, rt, 24 h; (iv) H_2 (1 atm), Pd/C, MeOH/H_2O/AcOH (40:4:1 v/v), rt, 24 h; (v) HCl (2.0 M aq).

2.5 Synthesis of the β-amino fragment of nakinadines B 126 and C 127

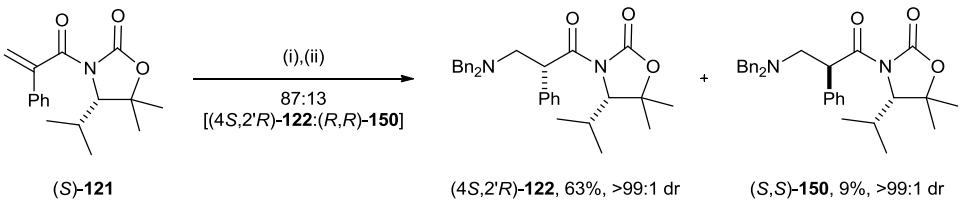
With large quantities of L-valine derived SuperQuat (*S*)-**145** in hand (prepared on a multi-gram scale using a previously reported procedure by Davies *et al.*),[16] an improved procedure for the synthesis of *N*-α-phenylacryloyl SuperQuat derivative (*S*)-**121** was developed. Previously, a synthesis of (*S*)-**121** had been reported by Davies *et al.*[12] proceeding via atropic acid **147** as a key intermediate, which was synthesised in 68% from methyl pyruvate **149**.[12] However, dehydration of

commercially available and inexpensive tropic acid **146** gave atropic acid **147** in 90% yield.[17] Treatment of **147** with pivaloyl chloride yielded the intermediate mixed anhydride **148**, and subsequent coupling with the lithium anion of SuperQuat (*S*)-**145** [prepared via the addition of BuLi to a solution (*S*)-**145** in THF at −78 °C] provided (*S*)-**121** in 72% isolated yield (from **147**)[18] (Scheme 25).



Scheme 25. *Reagents and conditions*: (i) KOH, H_2O, reflux, 1 h; (ii) HCl (12.0 M aq); (iii) pivaloyl chloride, Et_3N, THF, 0 °C, 1 h; (iv) (*S*)-**145**, BuLi, THF, –78 °C to rt, 2 h.

Conjugate addition of lithium dibenzylamide to *N*-acryloyl SuperQuat (*S*)-**121** followed by *in situ* addition of 2-pyridone resulted in the formation of two diastereoisomers in 87:13 dr. Complete separation of the diastereoisomers via exhaustive column chromatography led to the isolation of the major diastereoisomer **122** in 63% yield and >99:1 dr, and the minor diastereoisomer **150** in 9% yield and >99:1 dr (Scheme 26). The relative configuration within the major diastereoisomer **122** was established unambiguously via single crystal X-ray diffraction analysis of the HBF_4 salt **122**·HBF_4.[19] As the absolute (*S*)-configuration of the SuperQuat auxiliary (derived from L-valine) was known, the absolute (4*S*,2'*R*)-configuration of the major diastereoisomer **122** could be unambiguously assigned (Figure 11). Thus, the minor diastereoisomer **150** was unambiguously assigned the absolute (*S*,*S*)-configuration.



Scheme 26. *Reagents and Conditions*: (i) $LiNBn_2$, THF, −78 °C, 4 h; (ii) 2-pyridone, −78 °C to rt, 12 h.

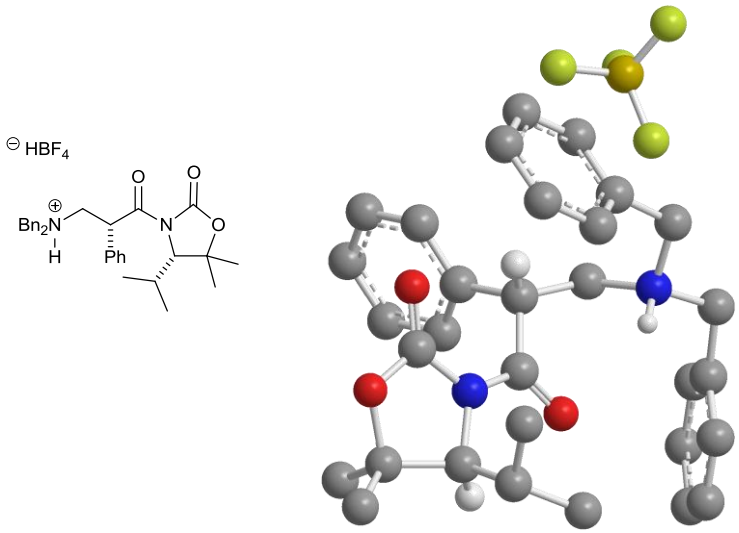
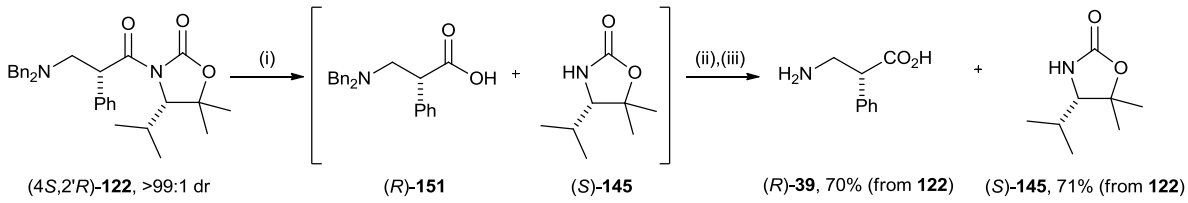


Figure 11. X-ray crystal structure of (4*S*,2′*R*)-**122**·HBF_4 (selected H atoms are omitted for clarity).

This stereochemical outcome is entirely consistent with the transition state model proposed by Davies *et al.* for the analogous α-alkyl series, but is in contradiction to that previously reported for this reaction, suggesting that the initial configurational assignment is in error. Therefore, following the strategy previously reported by Davies *et al.* for hydrolysis without epimerisation and racemisation,[20] (4*S*,2'*R*)-**122** was treated with LiOH in the presence of aq H_2O_2 in THF to yield a mixture of *N*,*N*-dibenzyl β-amino acid (*R*)-**151** and SuperQuat (*S*)-**145**. The crude reaction mixture was then subjected to a hydrogenolysis reaction using Pd/C in acidic media; formation of the HCl salt of **39** followed by purification by ion-exchange chromatography on DOWEX 50WX8 (100-200 mesh) yielded SuperQuat (*S*)-**145** in 71% yield (from **122**) {$[\alpha]_D^{20}$ +20.3 (*c* 1.0 in $CHCl_3$); lit.[16] $[\alpha]_D^{23}$ +21.3 (*c* 0.8 in $CHCl_3$)} and an authentic sample of (*R*)-2-phenyl-3-aminopropanoic acid (*R*)-**39** in 70% yield (from **122**) {$[\alpha]_D^{20}$ +84.7 (*c* 1.0 in H_2O)} (Scheme 27).



Scheme 27. *Reagents and Conditions*: (i) LiOH, H_2O_2 (30% aq), THF, 0 °C to rt, 24 h; (ii) H_2 (1 atm), Pd/C, MeOH/H_2O/AcOH (40:4:1 v/v), rt, 24 h; (iii) HCl (2.0 M aq).

The specific rotation value of this sample of (*R*)-**39** {$[\alpha]_D^{20}$ +84.7 (*c* 1.0 in H_2O)} is in accordance with the value previously reported by Davies *et al.* for (*S*)-**39** {lit.[11,12] $[\alpha]_D^{25}$ +93.0 (*c* 1.0 in H_2O)} prepared by this route, and thus established that both samples are (*R*)-configured. A full review of the specific rotation values reported for the enantiomers of **39** revealed some discrepancies (Table 1). Importantly, when Wyatt *et al.* reported the first asymmetric synthesis of (*R*)-**39** in 1995,[21] they included an X-ray crystal structure of (*R*)-**39**·(+)-CSA, and (*R*)-**39** was determined to have a specific rotation value of {$[\alpha]_D$ +94.0 (*c* 0.2 in H_2O)}.[14] Wyatt also commented on the incorrect assignment of **39** by Garbarino and Nunez.

Assigned absolute configuration	**Specific Rotation ($[\alpha]_D^T$ in H_2O)**	**Reference**
(*S*)	**T = 21, +95.0 (*c* 0.2)**	**14**
(*S*)	T = N/A, −92.0 (*c* 0.2)	22
(*S*)	T = 25, −87.6 (*c* 0.13)	23
(*S*)	T = 20, −81.0 (*c* 0.2)	24
(*S*)	T = 25, −81.7 (*c* 0.2)	25
(*R*)	T = 25, +85.0 (*c* 0.2)	26
(*R*)	T = N/A, +94.0 (*c* 0.2)	21
(*R*)	**T = 20, −95.0 (*c* 0.18)**	**27**
(*R*)	T = 30, +94.0 (*c* 0.2)	28
(*R*)	T = 25, +88.2 (*c* 0.5)	29
(*R*)	**T = 20, +84.7 (*c* 1.0)**	**This work: Synthetic (*R*)-39**
(*R*)*	**T = 25, +93.0 (*c* 1.0)**	**11,12**

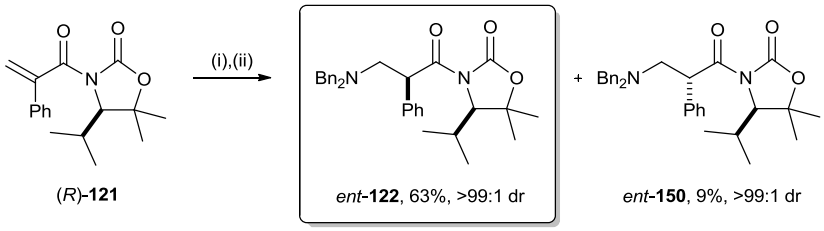
Table 1. Reported specific rotation values for 2-phenyl-3-aminopropanoic acid **39**. *Absolute configuration reassigned here.

Consequently, it is clear from this result that elaboration of **122** would give the (*R*)-enantiomer of both nakinadines B **126** and C **127**. As Kobayashi *et al.*[6] assigned the absolute (*S*)-configuration to the natural products, any synthesis of the "natural" enantiomers using this method should start from D-valine derived SuperQuat (*R*)-**145**.

2.6 Synthesis of key intermediates (*S*)-154 and 157

2.6.1 Synthesis of (*S*)-154

SuperQuat (*R*)-**145** was synthesised using the literature procedure described by Davies *et al.*,[16] in 44% yield over four steps from D-valine. Conversion of (*R*)-**145** to the *N*-acryloyl SuperQuat (*R*)-**121** was carried out in 72% overall yield via the mixed anhydride **148**. Conjugate addition of lithium dibenzylamide to (*R*)-**121** followed by diastereoselective protonation with 2-pyridone yielded an 87:13 mixture of diastereoisomers (4*R*,2′*S*)-**122** and (*R*,*R*)-**150** (Scheme 28). The expected absolute (4*R*,2′*S*)-configuration within the major diastereoisomer *ent*-**122** was confirmed following single crystal X-ray diffraction analysis of the HBF_4 salt *ent*-**122**·HBF_4 (Figure 12).[30,31]



Scheme 28. *Reagents and Conditions*: (i) $LiNBn_2$, THF, −78 °C, 4 h; (ii) 2-pyridone, –78 °C to rt, 16 h.

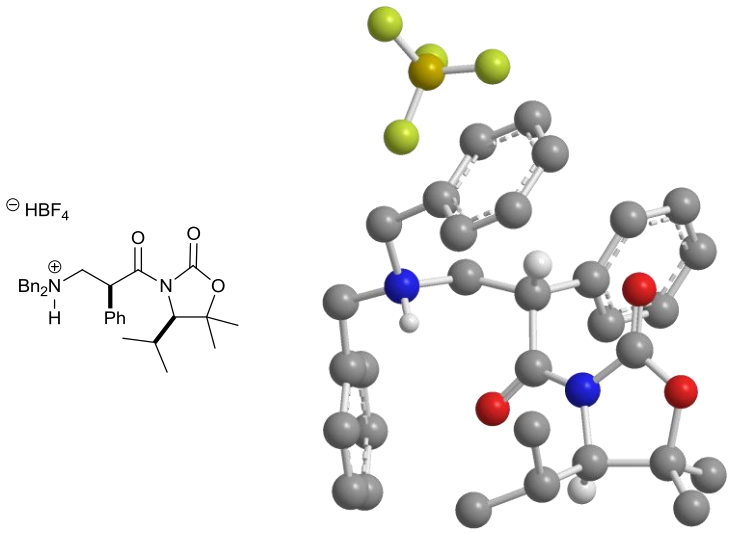
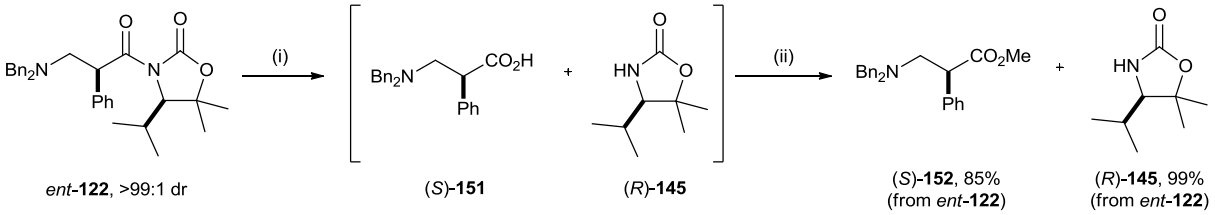


Figure 12. X-ray crystal structure of *ent*-**122**·HBF_4 (selected H atoms are omitted for clarity).

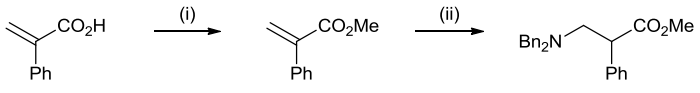
With a protocol for the preparation of the key α-stereocenter in place, a strategy involving hydrolysis, *N*-deprotection and *N*-alkylation could be employed to convert (4*R*,2′*S*)-**122** to the reported structure of nakinadine B **126**. As there is significant precedent concerning the reductive *N*-alkylation of amino esters,[32] preparation of the corresponding primary β^2-amino methyl ester (*S*)-**154** was explored, so that its subsequent *N*-alkylation could be investigated in detail. However, pilot

studies by Davies and Simal[33] showed extensive racemisation of (*S*)-**152** was observed when using a one-step esterification protocol via treatment of *ent*-**122** with lithium methoxide. Therefore, initial cleavage of *ent*-**122** using LiOH and aq H_2O_2 in THF gave an ~50:50 mixture of *N*,*N*-dibenzyl β^2-amino acid (*S*)-**151** and SuperQuat (*R*)-**145**, and subsequent addition of $SOCl_2$ to this crude mixture in MeOH provided *N*,*N*-dibenzyl-β^2-amino ester (*S*)-**152** in 85% yield (from *ent*-**122**). SuperQuat (*R*)-**145** {$[\alpha]_D^{20}$ −20.7 (*c* 1.0 in $CHCl_3$); lit.[34] $[\alpha]_D^{23}$ −24.2 (*c* 1.0 in $CHCl_3$)} was also isolated in 99% yield (from *ent*-**122**) (Scheme 29).



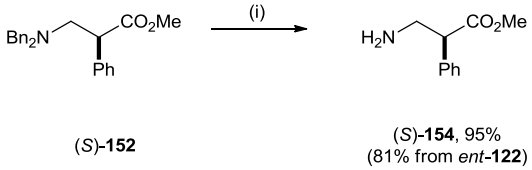
Scheme 29. *Reagents and Conditions*: (i) LiOH, H_2O_2 (30% aq), THF, 0 °C to rt, 24 h; (ii) $SOCl_2$, MeOH, 0 °C to rt, 16 h.

To determine the enantiomeric excess of (*S*)-**152**, an authentic racemic sample of **152** was synthesised. Addition of $SOCl_2$ to a solution of atropic acid **147** in MeOH gave methyl atropate **153** in 95% yield. Thermal addition of dibenzylamine to **153** furnished tertiary β^2-amino ester (*RS*)-**152** in 43% yield (Scheme 30). Subsequently, the enantiomeric excess of (*S*)-**152** was determined to be >99% ee by chiral HPLC following comparison with the authentic racemic sample of **152**,[35] thereby confirming that no epimerisation and/or racemisation had accompanied either of the chemical steps.



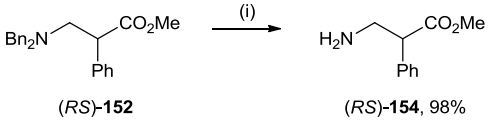
Scheme 30. *Reagents and Conditions*: (i) $SOCl_2$, MeOH, 0 °C to rt, 16 h; (ii) Bn_2NH, MeOH, µwave, 60 °C, 2 h.

Finally, hydrogenolytic removal of the *N*-benzyl groups within (*S*)-**152** gave the desired primary β^2-amino ester (*S*)-**154**[36] in 95% yield hence giving an improved 81% overall yield (from *ent*-**122**) (Scheme 31).



Scheme 31. *Reagents and Conditions*: (i) H_2 (1 atm), Pd/C, MeOH/AcOH/H_2O (40:4:1 v/v), rt, 16 h.

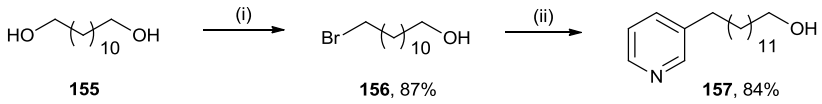
To determine the enantiomeric excess of (*S*)-**154**, again an authentic racemic sample **154** was synthesised. Hydrogenolysis of the *N*-benzyl groups within (*RS*)-**154** yielded primary β^2-amino ester (*RS*)-**154** in 98% yield (Scheme 32). Conversion of both (*S*)-**154** and (*RS*)-**54** to the corresponding Mosher's amide [reaction with (*R*)-Mosher's acid chloride][37] and analysis by ^{1}H and ^{19}F NMR spectroscopy enabled the enantiomeric excess of (*S*)-**154** to be determined as >99% ee.



Scheme 32. *Reagents and Conditions*: (i) H_2 (1 atm), Pd/C, MeOH/H_2O/AcOH (40:4:1 v/v), rt, 16 h.

2.6.2 Synthesis of 157

With both enantiopure and racemic **154** in hand, attention next turned to the synthesis of 13-(pyridin-3′-yl)tridecan-1-ol **157**, which was required for elaboration of **154** to nakinadine B **126**. Alcohol **157** was prepared via the method described by Baldwin *et al.*[38] Selective mono-bromination of commercially available 1,12-dodecanediol **155** resulted in the isolation of bromo-alcohol **156** in 87% yield. Subsequent coupling with the lithium anion of 3-picoline (prepared via treatment of 3-picoline with LDA in THF at −78 °C) gave the desired alcohol **157** in 84% yield (Scheme 33).

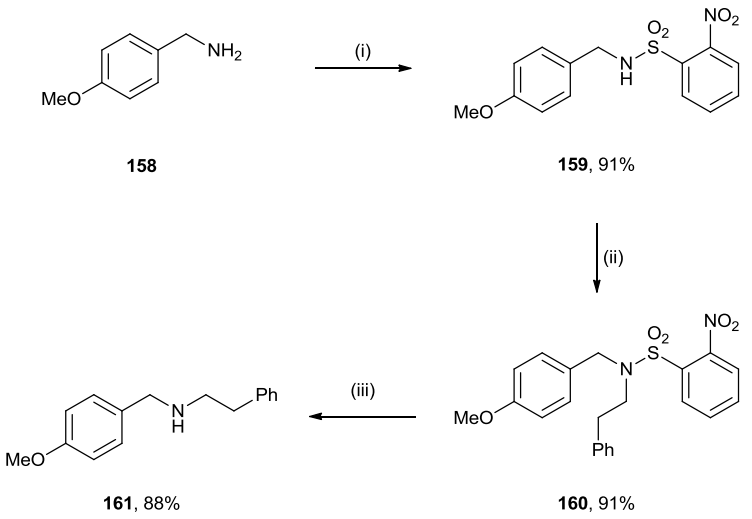


Scheme 33. *Reagents and Conditions*: (i) 48% aq HBr/cyclohexane (1:1 v/v), reflux, 6 h; (ii) LDA, 3-picoline, THF, −78 °C to rt, 16 h.

2.7 Investigation into *N*-alkylation of β²-amino ester 154

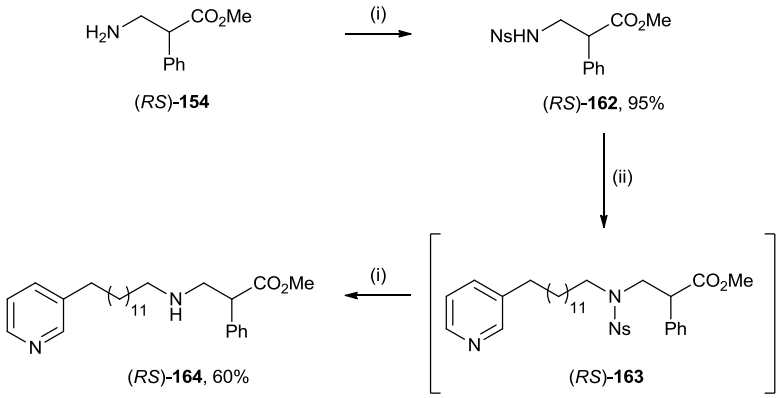
2.7.1 Via "Ns-strategy"

Recently, Fukuyama *et al.* reported a useful "Ns-strategy" for the conversion of primary amines into the corresponding secondary amines, facilitated by the initial conversion to *o*-nitro substituted benzenesulfonamides.[39] For example, it was shown that clean mono-alkylation of *p*-methoxybenzyl amine **158** could be achieved by conversion of **158** to sulfonamide **159** upon treatment with 2-NsCl and Et_3N, followed by coupling of **159** with 2-phenylethanol via a Mitsunobu reaction,[40] producing tertiary sulfonamide **160** in 91% yield, and final treatment of **160** with phenylthiolate leading to secondary amine **161** in 88% yield (Scheme 34).



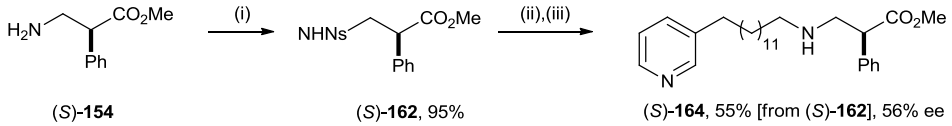
Scheme 34. *Reagents and Conditions*: (i) 2-NsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 20 min; (ii) 2-phenylethanol, PPh_3, DEAD, CH_2Cl_2; (iii) PhSH, K_2CO_3, DMF.

Therefore, initial work focused on application of the Fukuyama-Mitsunobu "Ns-strategy" to racemic β²-amino ester **154** and reaction with alcohol **157**. Conversion of **154** to *N*-nosyl β-amino ester **162** was effected by treatment with 2-NsCl and Et_3N in 95% yield. Mitsunobu reaction of sulfonamide **162** with alcohol **157** in the presence of PPh_3 and DEAD gave crude intermediate **163** which was deprotected with phenylthiolate to furnish the desired *N*-alkylated secondary β²-amino ester **164** in 60% yield (from **162**) (Scheme 35).



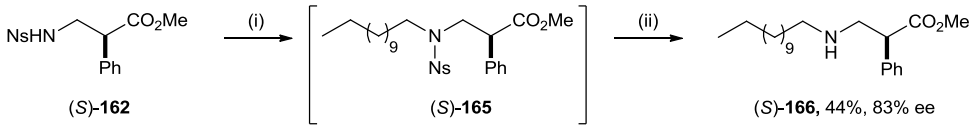
Scheme 35. *Reagents and Conditions*: (i) NsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 30 min; (ii) **157**, PPh_3, DEAD, CH_2Cl_2, 0 °C to rt, 2 h; (iii) PhSH, KOH, MeCN, 40 °C, 40 min.

With a working *N*-alkylation procedure developed, the same series of reactions were applied to (*S*)-**154**, whereby *N*-nosyl sulfonamide (*S*)-**162** was generated in 95% yield, and Mitsunobu reaction of (*S*)-**162** with **157** followed by deprotection of the *N*-nosyl group yielded (*S*)-**164** in 55% yield (from **162** (Scheme 36). The enantiomeric purity of (*S*)-**164** was determined to be 56% ee by ^{1}H and ^{19}F NMR spectroscopic analysis of the corresponding Mosher's amide (formed via reaction with (*R*)-Mosher's chloride, and comparison with the diastereoisomeric mixture of Mosher's amides resulting from the reaction of (*RS*)-**164** and (*R*)-Mosher's chloride.[41]



Scheme 36. *Reagents and Conditions*: (i) NsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 30 min; (ii) **157**, PPh_3, DEAD, CH_2Cl_2, 0 °C to rt, 2 h; (iii) PhSH, KOH, MeCN, 40 °C, 40 min.

To examine whether the pyridine group played a role in promoting racemisation, reaction with dodecan-1-ol was conducted. Thus, (*S*)-**166**, the *N*-dodecyl chain analogue of (*S*)-**164**, was synthesised in 44% [from (*S*)-**162**] (Scheme 37). The enantiomeric purity of (*S*)-**166** was determined to be 83% ee by comparison of ^{1}H NMR chemical shift resonances observed after mixing equimolar quantities of (*S*)-**166** with (*R*)-*O*-acetyl mandelic acid to those observed when (*RS*)-**166**[42] was mixed with (*R*)-*O*-acetyl mandelic acid. Hence, some racemisation is still observed, albeit to a lesser extent.

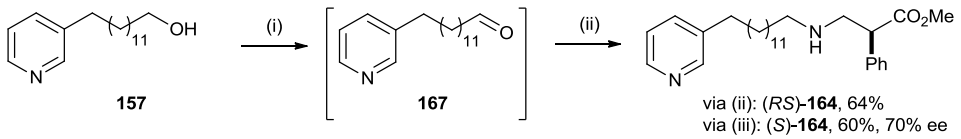


Scheme 37. *Reagents and Conditions*: (i) Dodecan-1-ol, PPh_3, DEAD, CH_2Cl_2, 0 °C to rt, 2 h; (ii) PhSH, KOH, MeCN, 40 °C, 40 min.

Therefore, due to the accompanying racemisation observed at the sensitive α-stereogenic center, both in the presence and absence of the pyridine group, the "Ns-strategy" was not explored further and an alternative method was sought.

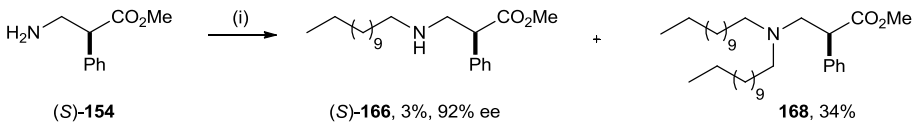
2.7.2 Via reductive *N*-alkylation

Coupling of aliphatic aldehydes with amines via reductive amination is another common method of converting primary amines into secondary or tertiary amines.[43] Again, this method for *N*-alkylation was first investigated on (*RS*)-**154**. Thus, IBX-mediated oxidation of alcohol **157** yielded aldehyde **167** and reaction of this aldehyde **167** (1 equiv) with (*RS*)-**154** (1 equiv) in the presence of AcOH and using $NaBH(OAc)_3$ as the hydride source gave (*RS*)-**164** as the only product, with no evidence of the formation of the corresponding tertiary amine in the crude reaction mixture and purification gave **164** in 64% yield. The analogous reaction was carried out with enantiopure (*S*)-**154**, yielding (*S*)-**164** in 60% yield and 70% ee (Scheme 38).[44]



Scheme 38. *Reagents and Conditions*: (i) IBX, EtOAc, 80 °C, 3 h; (ii) (*RS*)-**154**, $NaBH(OAc)_3$, AcOH, 1,2-DCE, rt, 16 h; (iii) (*S*)-**154**, $NaBH(OAc)_3$, AcOH, 1,2-DCE, rt, 16 h.

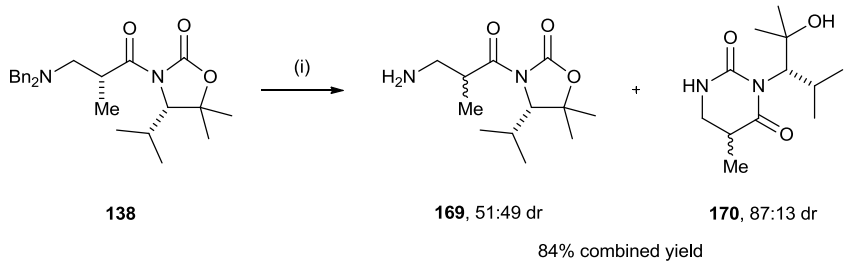
Again, a test to determine whether the pyridine group promoted racemisation was carried out, using dodecanal (1 equiv) as the aliphatic aldehyde. Surprisingly, although no starting material was observed in the crude reaction mixture, a mixture of secondary and tertiary amino esters (*S*)-**166** and **168** were observed in the ratio 5:95, respectively. Column chromatography led to the isolation of *N*,*N*-didodecyl-β^2-amino ester **168** in 34% yield and secondary β^2-amino ester (*S*)-**166** in 3% yield and 92% ee[45] (Scheme 39). As racemisation is still observed without the presence of a pyridine group, the reductive *N*-alkylation of β^2-amino ester (*S*)-**154** does not constitute an efficient process for the synthesis of enantiopure nakinadine B **126**.



Scheme 39. *Reagents and Conditions*: (i) dodecanal, $NaBH(OAc)_3$, AcOH, 1,2-DCE, rt, 1 h.

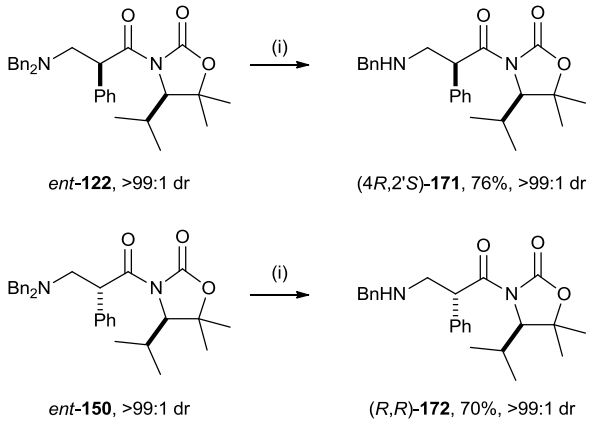
2.8 *N*-Alkylation prior to SuperQuat cleavage

As loss of stereochemical integrity in previously attempted strategies resulted in racemisation, elaboration before the cleavage of the oxazolidinone moiety was explored next. Here, loss of stereochemical integrity would involve epimerisation at the α-stereocenter, resulting in the formation of diastereoisomers, which would be easily detectable via ^{1}H NMR spectroscopic analysis. This revised route requires the sequential removal of both *N*-benzyl groups, introduction of the *N*-alkyl aliphatic chain, and cleavage of the SuperQuat auxiliary. Wright and Davies showed that hydrogenolytic bis-*N*-debenzylation of a related *N*(3)-β-(*N*,*N*-dibenzylamino)acyl SuperQuat **138** gave a mixture of primary amino adduct **169** as a 51:49 mixture of (2′)-epimers and *N*-acyl urea **170** (87:13 dr), formed presumably via intramolecular nucleophilic ring-opening of the oxazolidinone ring, in 84% combined yield (Scheme 40).[46]



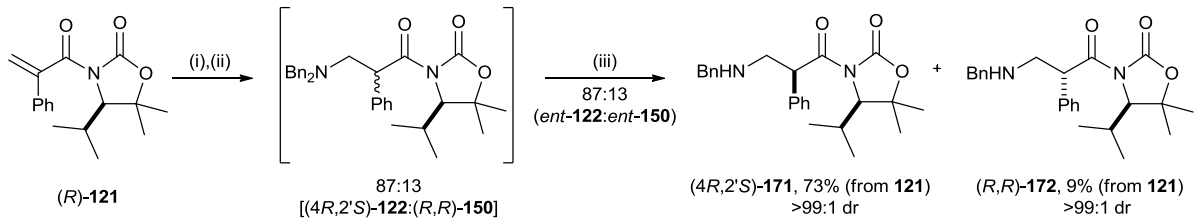
Scheme 40. *Reagents and Conditions*: (i) H_2 (5 atm), Pd/C, MeOH, rt, 15 h.

Thus, a stepwise chemoselective mono-*N*-debenzylation, mono-*N*-alkylation, *N*-debenzylation and final hydrolysis strategy was devised. Davies *et al.* have shown that selective mono-*N*-debenzylation of an *N*,*N*-dibenzylamino group can be successfully achieved using cerium ammonium nitrate (CAN).[47] Treatment of *ent*-**122** with CAN furnished mono-*N*-benzyl secondary amine (4*R*,2'*S*)-**171**, with no evidence of concomitant intramolecular ring-opening and urea formation. Purification via flash column chromatography gave **171** in 76% yield and >99:1 dr. The (*R*,*R*)-diastereoisomer *ent*-**150** was also mono-*N*-debenzylated in a similar fashion and gave an authentic sample of the epimer (*R*,*R*)-**172** in 70% yield and >99:1 dr, confirming that no epimerisation had occurred in this process (Scheme 41).



Scheme 41. *Reagents and Conditions*: (i) CAN, MeCN/H_2O (5:1 v/v), rt, 16 h.

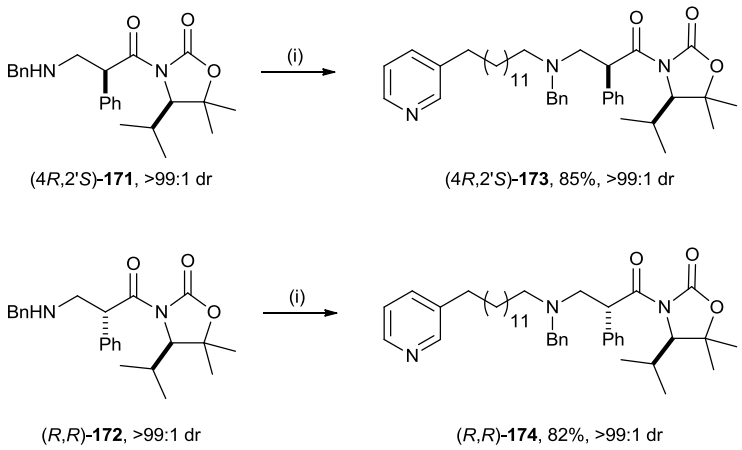
It was noticed that the secondary amine diastereoisomers (4*R*,2'*S*)-**171** and (*R*,*R*)-**172** displayed significant differences in R_f during chromatographic purification, and therefore it was predicted that they would be more amenable to separation via column chromatography than their tertiary amino counterparts *ent*-**122** and *ent*-**150**. Thus, an improved procedure was envisaged which would telescope the conjugate addition/mono-*N*-debenzylation steps. Conjugate addition of lithium dibenzylamide to (*R*)-**121** followed by diastereoselective protonation of the resultant enolate with 2-pyridone gave an 87:13 mixture of *ent*-**122** and *ent*-**150**, and treatment of the crude reaction mixture with CAN yielded an 87:13 mixture of **171** and **172**. Separation of the diastereoisomers via flash column chromatography yielded the major diastereoisomer **171** in 73% yield (from **121)**, and the minor diastereoisomer **150** in 9% yield (from **121**) as single diastereoisomers (>99:1 dr) in each case (Scheme 42). With (4*R*,2'*S*)-**171** in hand, further elaboration through *N*-alkylation, *N*-debenzylation, and subsequent cleavage of the SuperQuat auxiliary was attempted to complete the synthesis of (*S*)-nakinadine B **126**.



Scheme 42. *Reagents and Conditions:* (i) $LiNBn_2$, THF, −78 °C, 4 h; (ii) 2-pyridone, −78 °C to rt, 12 h; (iii) CAN, MeCN/H_2O (5:1 v/v), rt, 16 h.

As reductive *N*-alkylation of β-amino ester (*S*)-**154** proceeded in good yield (albeit with racemisation), a similar approach was adopted with *N*-benzyl secondary amine (4*R*,2'*S*)-**171**. The union of amine **171** with aldehyde **167** was achieved in the presence of $NaBH(OAc)_3$ which gave

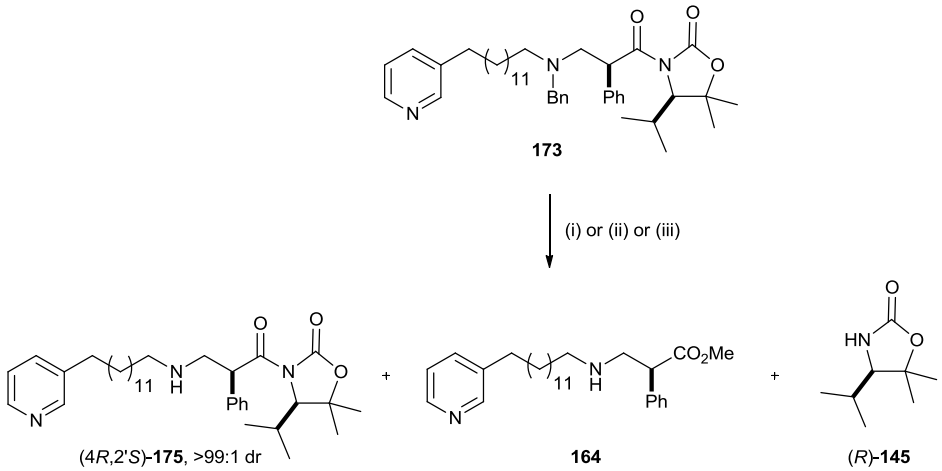
tertiary amine (4*R*,2'*S*)-**173** in 85% yield and >99:1 dr. To ensure that no epimerisation had occurred, the (*R*,*R*)-diasteroisomer (*R*,*R*)-**172** was also reductively *N*-alkylated with aldehyde **167** to give an authentic sample of (*R*,*R*)-**174** in 82% yield and >99:1 dr. Comparison of the ^{1}H NMR spectra for **173** and **174** confirmed that the stereochemical integrity at the α-position remained intact in both cases (Scheme 43).



Scheme 43. *Reagents and Conditions*: (i) **167**, $NaBH(OAc)_3$, AcOH, 1,2-DCE, rt, 16 h.

2.9 Synthesis of nakinadine B 126

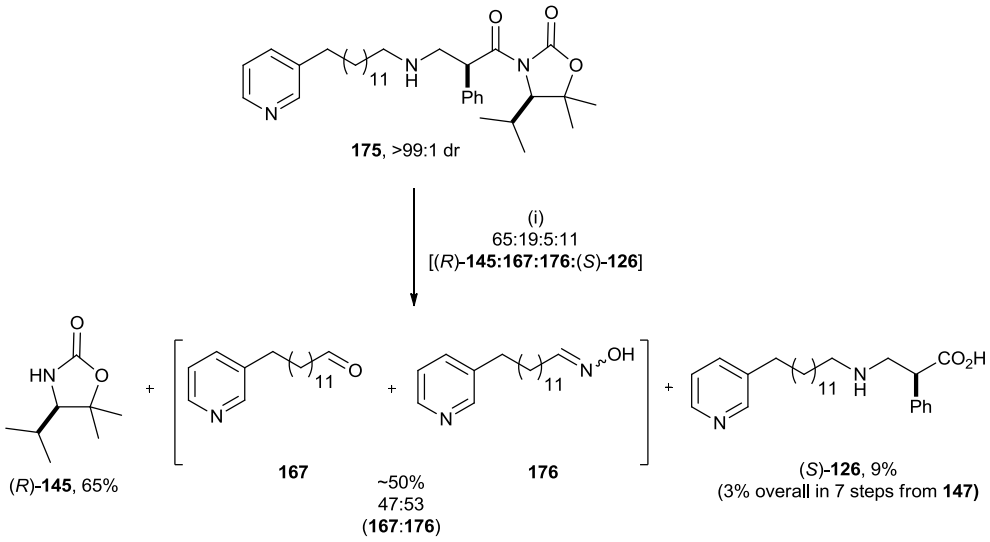
Continuing on, *N*-debenzylation of **173** to give the *N*-[13-(pyridin-3-yl)-tridecyl]-substituted secondary amine **175** was attempted. Initial Pd-catalysed hydrogenolysis using H_2 (1 atm), $Pd(OH)_2$/C and MeOH as solvent gave a mixture of SuperQuat (*R*)-**145**, methyl ester **164** and the desired secondary amine **175** in the ratio 49:45:6, respectively. Purification gave SuperQuat (*R*)-**145** which was isolated in 31% yield, β^2-amino ester **164** which was isolated in 25% yield (undetermined enantiopurity), and secondary amine **175** which was isolated in 5% yield and >99:1 dr. Changing the reaction solvent to EtOAc eliminated side-product formation and gave **175** in 63% isolated yield and >99:1 dr. Alternatively, oxidative deprotection of **173** with CAN gave **175** in 71% yield and >99:1 dr (Scheme 44).



Method	Yield of 175 (%)	Yield of 164 (%)	Yield of (*R*)-145 (%)
(i)	5	25	31
(ii)	63	0	0
(iii)	71	0	0

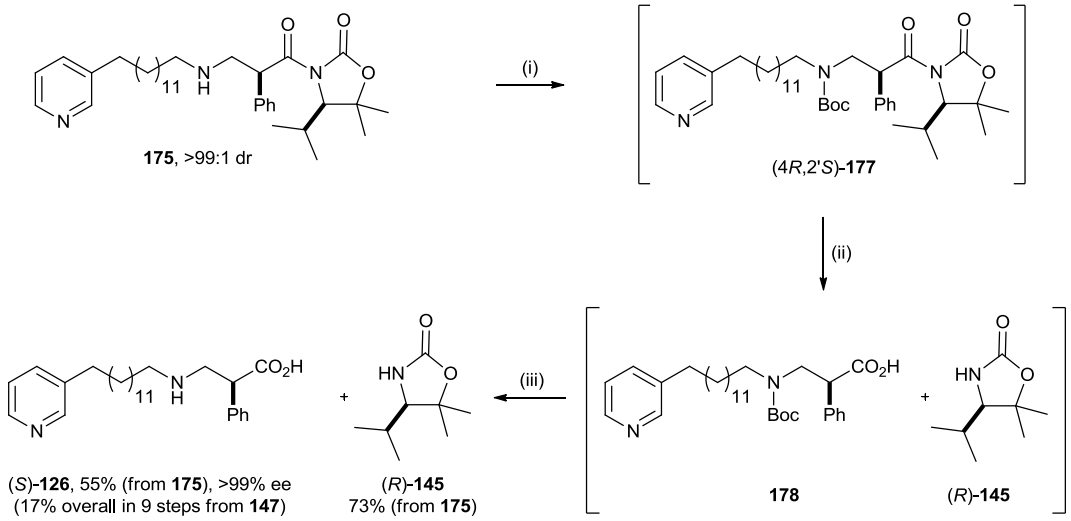
Scheme 44. *Reagents and Conditions:* (i) H_2 (1 atm), $Pd(OH)_2/C$, MeOH, rt, 16 h; (ii) H_2 (1 atm), $Pd(OH)_2/C$, EtOAc, rt, 16 h; (iii) CAN, $MeCN/H_2O$ (5:1 v/v), rt, 16 h.

With **175** in hand, cleavage of the SuperQuat auxiliary was attempted: treatment of **175** with LiOH and H_2O_2 (30% aq) gave a 65:19:5:11 mixture of SuperQuat (*R*)-**145**, 13-(pyridin-3′-yl)tridecanal **167**, the corresponding oxime **176**, and the desired β^2-amino acid (*S*)-**126**, respectively. Purification of the crude reaction mixture via flash column chromatography gave SuperQuat (*R*)-**145** in 65% yield {$[\alpha]_D^{20}$ −23.8 (*c* 1.0 in $CHCl_3$); lit.[34] $[\alpha]_D^{23}$ −24.2 (*c* 1.0 in $CHCl_3$)}, a mixture of aldehyde **167** and oxime **176** [as a mixture of (*E*)- and (*Z*)-diastereoisomers] in approximately 50% combined yield, and an impure sample of (*S*)-**126** (the reported structure of nakinadine B). Further purification of the sample of (*S*)-**126** by DOWEX 50WX8 ion-exchange chromatography (100-200 mesh) gave (*S*)-**126** {$[\alpha]_D^{20}$ –6.2 (*c* 1.0 in $CHCl_3$)} in 9% yield and in >99% ee.[48] Using this procedure, (*S*)-**126** was prepared in 3% overall yield in 7 steps from commercially available atropic acid **147** (Scheme 45). With a method already developed to determine the enantiomeric excess of (*S*)-**164**, the methyl ester of nakinadine B, conversion of (*S*)-**126** to its methyl ester (*S*)-**164** was achieved via treatment with $SOCl_2$ in MeOH, and coupling of this sample with (*R*)-Mosher's chloride showed the enantiomeric excess of (*S*)-**126** to be >99% upon comparison with an authentic racemic sample. Thus neither the hydrolysis reaction nor the esterification are therefore accompanied by competing racemisation.



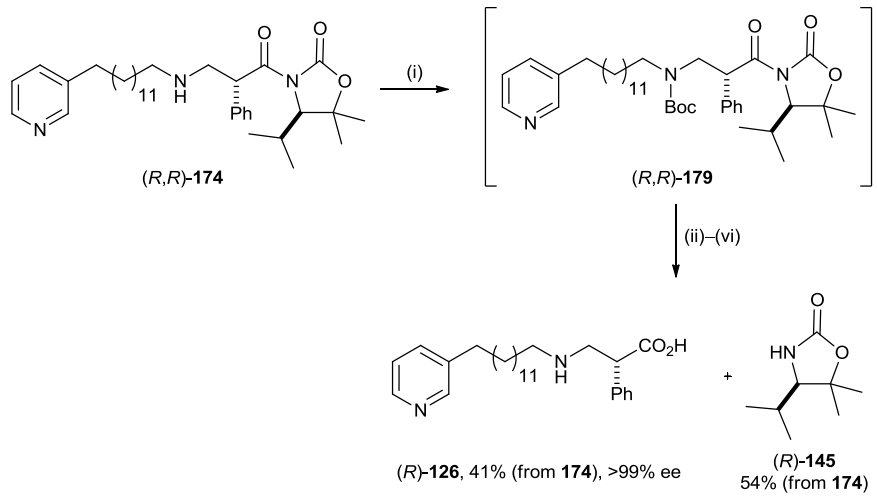
Scheme 45. *Reagents and Conditions*: (i) LiOH, H_2O_2 (30% aq), THF, H_2O, 0 °C to rt, 16 h.

The isolated yield of (*S*)-**126** was unacceptably low and the formation of aldehyde **167** and oxime **176** suggested that a competing *N*-oxidation process was also occurring. Interestingly, hydrolytic cleavage of tertiary amine **122** under identical conditions did not show this competing *N*-oxidative process and therefore, to overcome this, an alternative protocol incorporating *N*-protection was developed. *N*-Boc protection of **175** upon treatment with Boc_2O and $NaHCO_3$ in EtOH gave **177**, which was then subjected to a hydrolysis reaction with LiOH and aq H_2O_2. Fortunately, aldehyde **167** and oxime **176** were absent in the crude reaction mixture, which constituted an ~50:50 mixture of SuperQuat (*R*)-**145** and a species assigned as *N*-Boc nakinadine B **178**. Finally, *N*-Boc deprotection using HCl (2.0 M in Et_2O) gave an ~50:50 mixture of SuperQuat (*R*)-**145** and (*S*)-**126**·HCl, which was purified by ion-exchange chromatography on DOWEX 50WX8 (100-200 mesh) to give SuperQuat (*R*)-**145** {$[\alpha]_D^{20}$ −21.0 (*c* 1.0 in $CHCl_3$); lit.[49] $[\alpha]_D^{23}$ −24.2 (*c* 1.0 in $CHCl_3$)} in 73% yield and a synthetic sample of (*S*)-nakinadine B (*S*)-**126** {$[\alpha]_D^{20}$ −6.3 (*c* 1.0 in $CHCl_3$)} in 55% overall yield (from **175**) and >99% ee[48] (Scheme 46).[9]



Scheme 46. *Reagents and Conditions*: (i) Boc_2O, $NaHCO_3$, EtOH, rt, 16 h; (ii) LiOH, H_2O_2 (30% aq), THF, 0 °C to rt, 16 h; (iii) HCl (2.0 M in Et_2O), rt, 30 min.

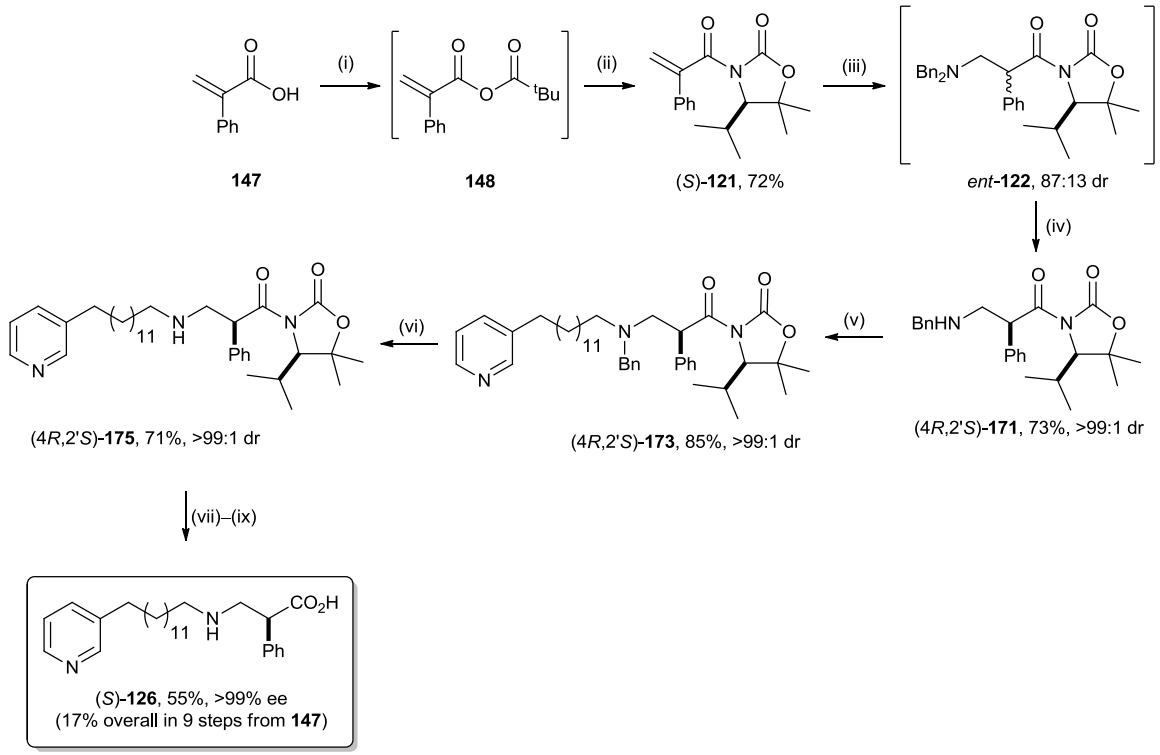
Similarly, an authentic sample of the (*R*)-enantiomer of nakinadine B (*R*)-**126** was also synthesised in this manner from (*R*,*R*)-**174**, giving SuperQuat (*R*)-**145** {$[\alpha]_D^{20}$ −22.3 (*c* 1.0 in $CHCl_3$); lit.[34] $[\alpha]_D^{23}$ −24.2 (*c* 1.0 in $CHCl_3$)} in 54% yield (from **174**) and nakinadine B (*R*)-**126** {$[\alpha]_D^{20}$ +6.5 (*c* 1.0 in $CHCl_3$)} in 41% yield (from **174**) and >99% ee[50] (Scheme 47).



Scheme 47. *Reagents and Conditions*: (i) CAN, MeCN/H_2O (5:1 v/v), rt, 16 h; (ii) Boc_2O, $NaHCO_3$, EtOH, rt, 16 h; (iii) LiOH, H_2O_2 (30% aq), THF, 0 °C to rt, 16 h; (iv) HCl (2.0 M in Et_2O), rt, 30 min.

2.10 Summary of nakinadine B 126 synthesis

The first asymmetric synthesis of the reported structure of (*S*)-(−)-nakinadine B (*S*)-**126** has been achieved from tropic acid **147** in 9 steps, 17% overall yield and in >99% ee (Scheme 48). An authentic sample of the (*R*)-enantiomer of nakinadine B (*R*)-**126** has also been synthesised via an analogous route. A full comparison of the spectroscopic and physical data of nakinadine B will be discussed in Chapter 5.

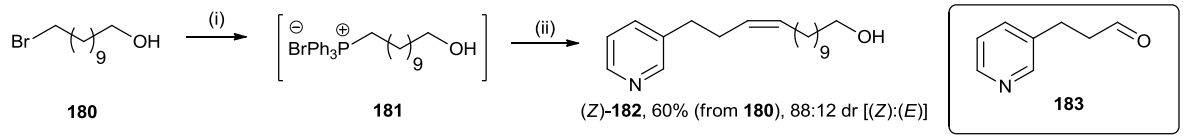


Scheme 48. *Reagents and Conditions*: (i) pivaloyl chloride, Et_3N, THF, 0 °C, 1 h; (ii) (*S*)-**145**, BuLi, THF, −78 °C to rt, 2 h; (iii) $LiNBn_2$, THF, −78 °C, 4 h then 2-pyridone, −78 °C to rt, 12 h; (iv) CAN, MeCN/H_2O (5:1 v/v), rt, 16 h; (v) **167**, $NaBH(OAc)_3$, AcOH, 1,2-DCE, rt, 16 h; (vi) CAN, MeCN/H_2O (5:1 v/v), rt, 16 h; (vii) Boc_2O, $NaHCO_3$, EtOH, rt, 16 h; (viii) LiOH, H_2O_2 (30% aq), THF, 0 °C to rt, 16 h; (ix) HCl (2.0 M in Et_2O), rt, 30 min.

2.11 Nakinadine C 127

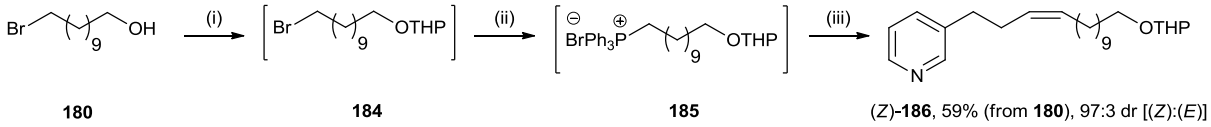
2.11.1 Synthesis of alcohol (*Z*)-182

With a secure route developed through to enantiopure (*S*)-nakinadine B (*S*)-**126**, the synthesis of (*S*)-nakinadine C (*S*)-**127** was next undertaken. It was envisaged that a directly analogous strategy could be utilised due to the structural similarities of these two species. Thus, the synthesis of unsaturated alcohol (*Z*)-**182** was initially attempted via a protecting group free Wittig olefination. A solution of 11-bromoundecan-1-ol **180** and PPh_3 in the MeCN was stirred at reflux to give phosphonium bromide salt **181** which was then treated with KHMDS in THF, followed by the addition of a solution of aldehyde **183** in THF [prepared from a Swern Oxidation[51] of commercially available 3-(pyridin-3′-yl)propanol] to give (*Z*)-**182** in 60% combined isolated yield (from **180**) as an 88:12 mixture of (*Z*):(*E*) isomers which were found to be inseparable by flash column chromatography (Scheme 49).



Scheme 49. *Reagents and Conditions*: (i) PPh_3, MeCN, reflux, 48 h; (ii) KHMDS, THF, **183**, −78 °C to rt, 2 h.

Previously, Baldwin *et al.* reported the formation of (*Z*)-**186** {98:2 dr [(*Z*):(*E*) ratio]} via the Wittig olefination of the ylide derived from *O*-THP protected phosphonium bromide salt **185**.[52] Hence, protection of 11-bromoundecan-1-ol **180** as its *O*-THP ether **184** was achieved upon treatment with 2,3-dihyropyran in the presence of PPTS. Heating a solution of PPh_3 and **184** in MeCN at reflux yielded phosphonium bromide salt **185**. Subsequent addition of KHMDS to **185** in THF, facilitated Wittig olefination with 3-(pyridin-3′-yl)propanal **183** to give (*Z*)-**186** as a 97:3 mixture of (*Z*):(*E*) isomers in 59% isolated yield (from **180**) (Scheme 50).



Scheme 50. *Reagents and Conditions*: (i) DHP, PPTS, CH_2Cl_2, rt, 16 h; (ii) PPh_3, MeCN, reflux, 48 h; (iii) KHMDS, THF, **183**, −78 °C to rt, 2 h.

The (*Z*):(*E*) ratio of both of these samples was determined by ^{1}H NMR spectroscopic analysis via integration of signals relating to the corresponding allylic CH_2 protons (δ_H 1.90 and δ_H 2.16 ppm) in C_6D_6 on a 700 MHz spectrometer.[53] Also, ^{1}H NMR spectroscopic analysis of homonuclear proton decoupling of both the neighbouring allylic CH_2 protons [C(10)H_2 and C(13)H_2] revealed a ^3J coupling constant of 10.3 Hz between C(11)*H* and C(12)*H*, which is consistent with the formation of a (*Z*)-alkene (Figure 13).

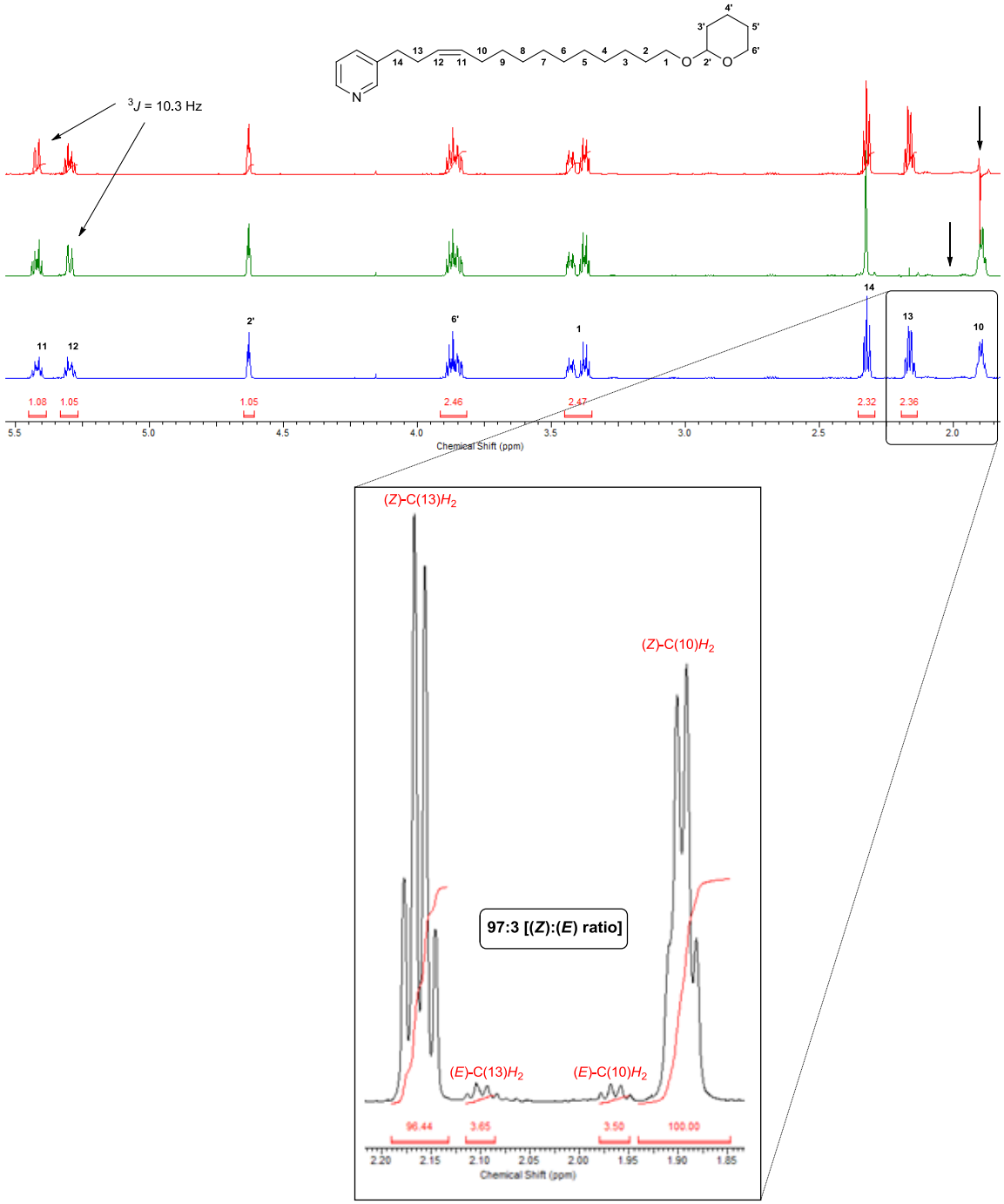
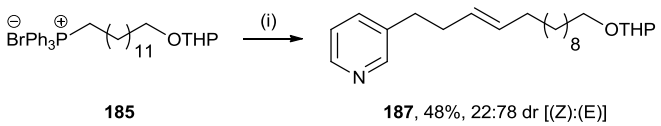


Figure 13. Homonuclear proton decoupling of (*Z*)-**186.**

In an effort to provide a sample enriched in (*E*)-**187**, a Kim modification of the Wittig reaction of **185** was attempted with aldehyde **183**, leading to the formation of **187** as a 22:78 mixture of (*Z*):(*E*) isomers in 48% combined isolated yield. Comparison of the ^{1}H NMR spectra of (*Z*)-**186** and **187** confirmed the identity of the two products formed in the Wittig reaction (Scheme 51).



185 **187**, 48%, 22:78 dr [(*Z*):(E)]

Scheme 51. *Reagents and Conditions*: (i) KHMDS, THF, **183**, −78 °C to rt, 2 h then MeOH, rt, 16 h.

Unfortunately, due to overlapping resonances, an accurate ^{3}J value could not be determined via a similar homonuclear proton decoupling analysis of **187** (Figure 14).[54]

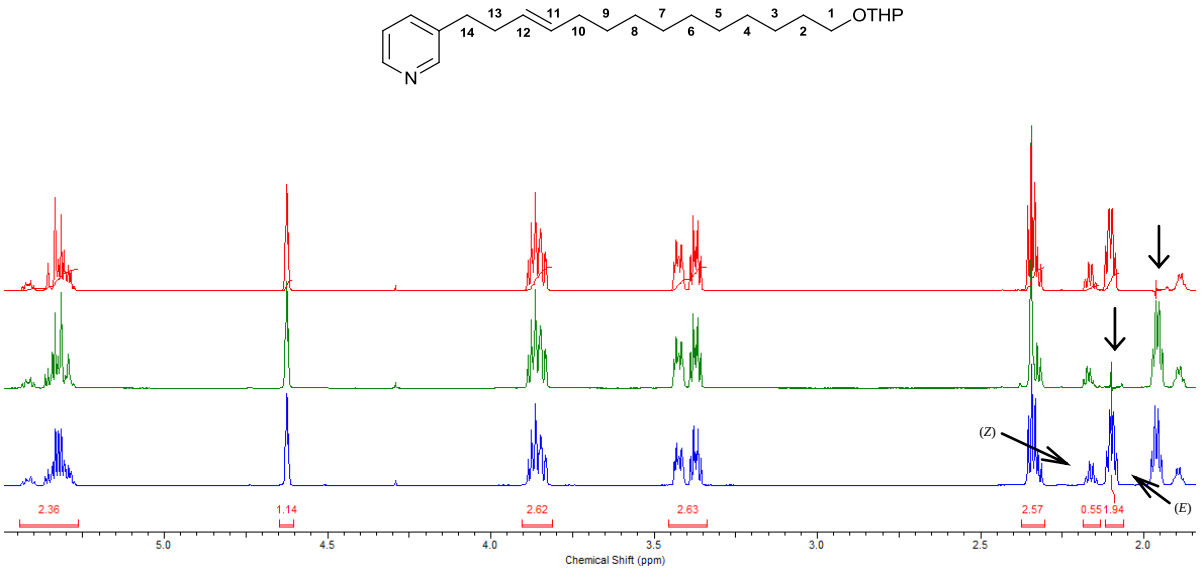
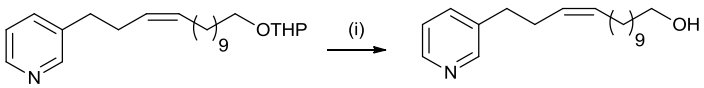


Figure 14. Homonuclear proton decoupling of **187.**

Deprotection of the *O*-THP group from within (*Z*)-**186** {97:3 [(*Z*):(*E*) ratio]} furnished alcohol (*Z*)-**182** in 89% yield and 97:3 dr [(*Z*):(*E*)][55] (Scheme 52).



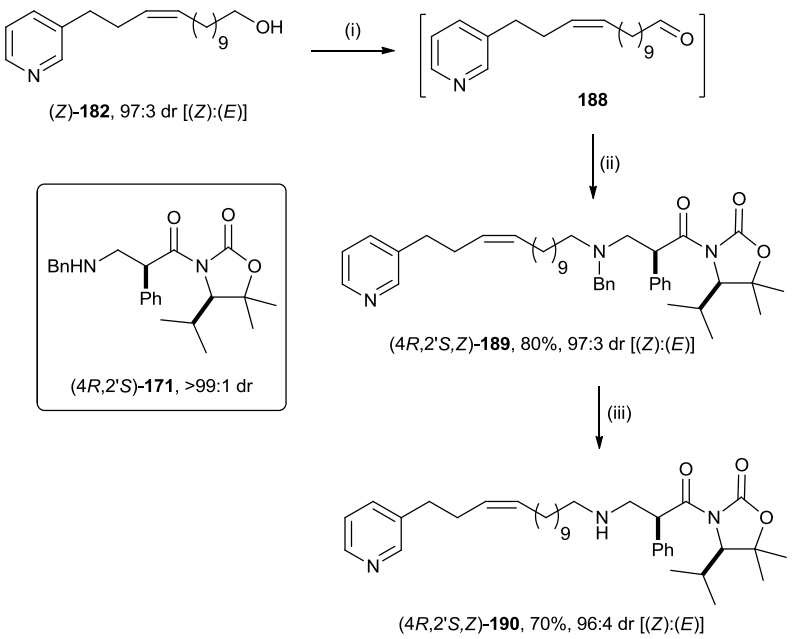
(*Z*)-**186**, 97:3 dr [(*Z*):(*E*)] (*Z*)-**182**, 89%, 97:3 dr [(*Z*):(*E*)]

Scheme 52. *Reagents and Conditions*: (i) HCl (3.0 M aq), MeOH, rt, 16 h.

2.11.2 Synthesis of nakinadine C 127

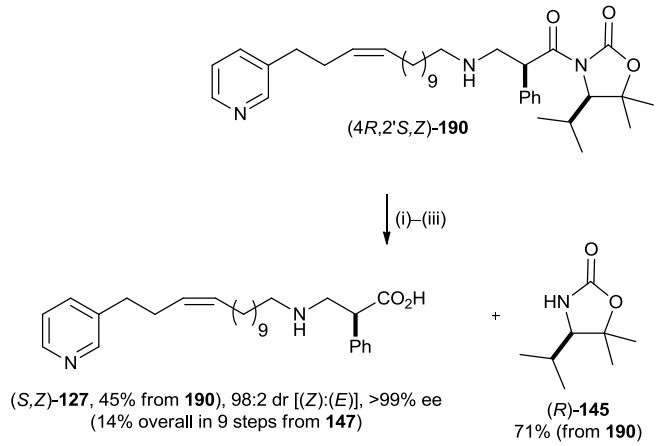
With a robust route to the key pyridin-3-yl alcohol (*Z*)-**182** in hand, IBX-mediated oxidation of alcohol (*Z*)-**182** led to the desired aldehyde **188** which was used immediately (without purification) to effect reductive *N*-alkylation of secondary amine (4*R*,2'*S*)-**171** in the presence of $NaBH(OAc)_3$ to give tertiary amine (4*R*,2'*S*,*Z*)-**189** in 80% yield and 97:3 dr [(*Z*):(*E*)].[56] Oxidative *N*-debenzylation

of (4*R*,2'*S*,*Z*)-**189** with CAN furnished secondary amine (4*R*,2'*S*,*Z*)-**190** in 70% yield and in 96:4 dr [(*Z*):(*E*)][57] (Scheme 53).



Scheme 53. *Reagents and Conditions:* (i) IBX, EtOAc, 80 °C, 3 h; (ii) (4*R*,2'*S*)-**171**, $NaBH(OAc)_3$, AcOH, 1,2-DCE, rt, 16 h; (iii) CAN, $MeCN/H_2O$ (5:1 v/v), rt, 16 h.

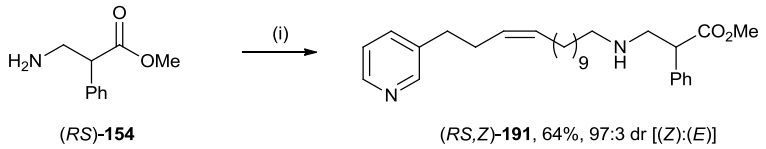
Finally, *N*-Boc protection, hydrolytic cleavage of the SuperQuat auxiliary and *N*-Boc-deprotection gave SuperQuat (*R*)-**145** in 71% yield (from **190**), alongside (*S*,*Z*)-**127**, the reported structure of (*S*,*Z*)-nakinadine C {$[\alpha]_D^{20}$ −5.9 (*c* 1.0 in $CHCl_3$)} in 45% yield (from **190**) (Scheme 54).[10]



Scheme 54. *Reagents and Conditions*: (i) Boc_2O, $NaHCO_3$, EtOH, rt, 16 h; (ii) LiOH, H_2O_2 (30% aq), THF, H_2O, 0 °C to rt, 16 h; (iii) HCl (2.0 M in Et_2O), rt, 30 min.

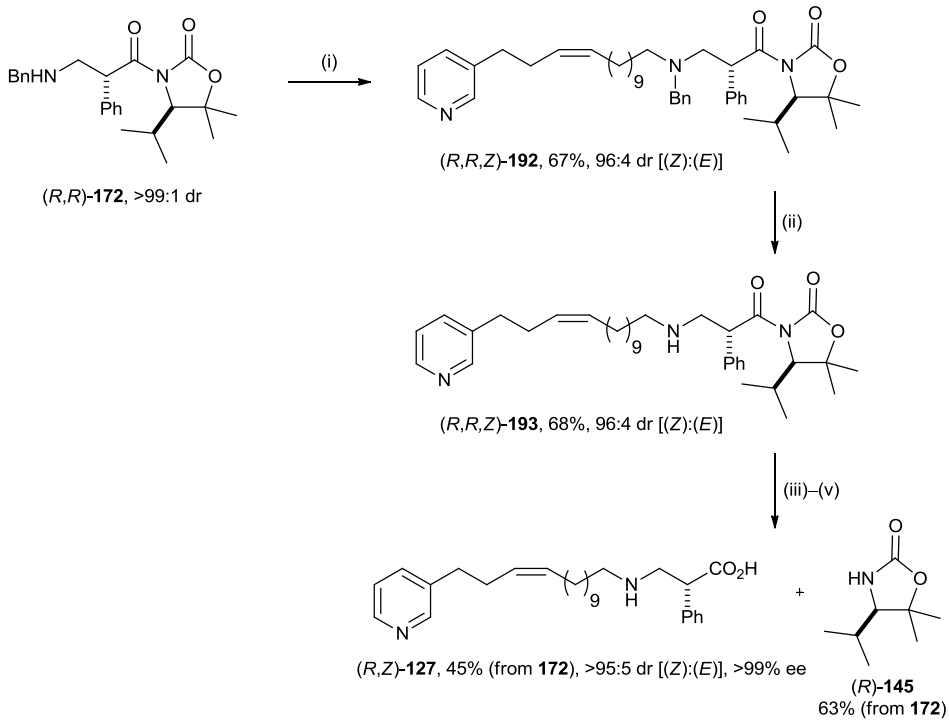
The (*Z*):(*E*) ratio of (*S*,*Z*)-**127** was determined by conversion of (*S*,*Z*)-**127** to the corresponding methyl ester (*S*,*Z*)-**191** upon treatment with $SOCl_2$ in MeOH and integration of the resonances corresponding to the allylic CH_2 protons in the 700 MHz ^{1}H NMR spectrum. Treatment of methyl

ester (*S*,*Z*)-**191** with (*R*)-Mosher's chloride gave the corresponding Mosher's amide. An authentic racemic sample of methyl ester (*RS*,*Z*)-**191** was synthesised in 64% yield by reductive *N*-alkylation of primary β^2-amino ester (*RS*)-**154** with aldehyde **188** (Scheme 55). Subsequent conversion of (*RS*,*Z*)-**191** to the corresponding Mosher's amide [formed from the reaction of (*RS*,*Z*)-**191** and (*R*)-Mosher's chloride] and comparison of the ^{1}H NMR spectroscopic data with that of the Mosher's amide formed from the reaction of (*S*,*Z*)-**191** with (*R*)-Mosher's chloride led to the determination of the enantiomeric excess.



Scheme 55. *Reagents and Conditions*: (i) **188**, $NaBH(OAc)_3$, AcOH, 1,2-DCE, rt, 16 h.

Similarly, the (*R*,*R*)-diastereoisomer **172** was subjected to an analogous set of reactions which: (i) confirmed no epimerisation/racemisation had occurred at the α-stereo-genic center during all the transformations; and (ii) enabled an authentic sample of the (*R*)-enantiomer of the reported structure of nakinadine C (*R*,*Z*)-**127** {$[\alpha]_D^{20}$ +5.8 (*c* 1.0 in $CHCl_3$)} to be synthesised in>95:5 dr and >99% ee[58] (Scheme 56).



Scheme 56. *Reagents and Conditions*: (i) **188**, $NaBH(OAc)_3$, AcOH, 1,2-DCE, rt, 16 h; (ii) CAN, $MeCN/H_2O$ (5:1 v/v), rt, 16 h; (iii) Boc_2O, $NaHCO_3$, EtOH, rt, 16 h; (iv) LiOH, H_2O_2 (30% aq), THF, H_2O, rt, 16 h; (v) HCl (2.0 M in Et_2O), rt, 30 min.

2.12 Conclusion

In conclusion, the asymmetric synthesis of enantiopure (−)-(*S*)-nakinadine B (*S*)-**126** has been carried out in 17% overall yield in 9 chemical steps from commercially available atropic acid **147**. Using the optimised strategy, enantiopure (−)-(*S*)-nakinadine C (*S*)-**127** {98:2 dr [(*Z*):(*E*)]} has also been synthesised in 14% overall yield in 9 chemical steps from atropic acid **147** (Figure 15). Full data comparison with those for samples of nakinadines B **126** and C **127** isolated from the natural source of both these compounds will be carried out in Chapter 5. Chapters 3 and 4 of this thesis will focus on the syntheses of the remaining members of the nakinadine family, each comprising 2 stereogenic centers.

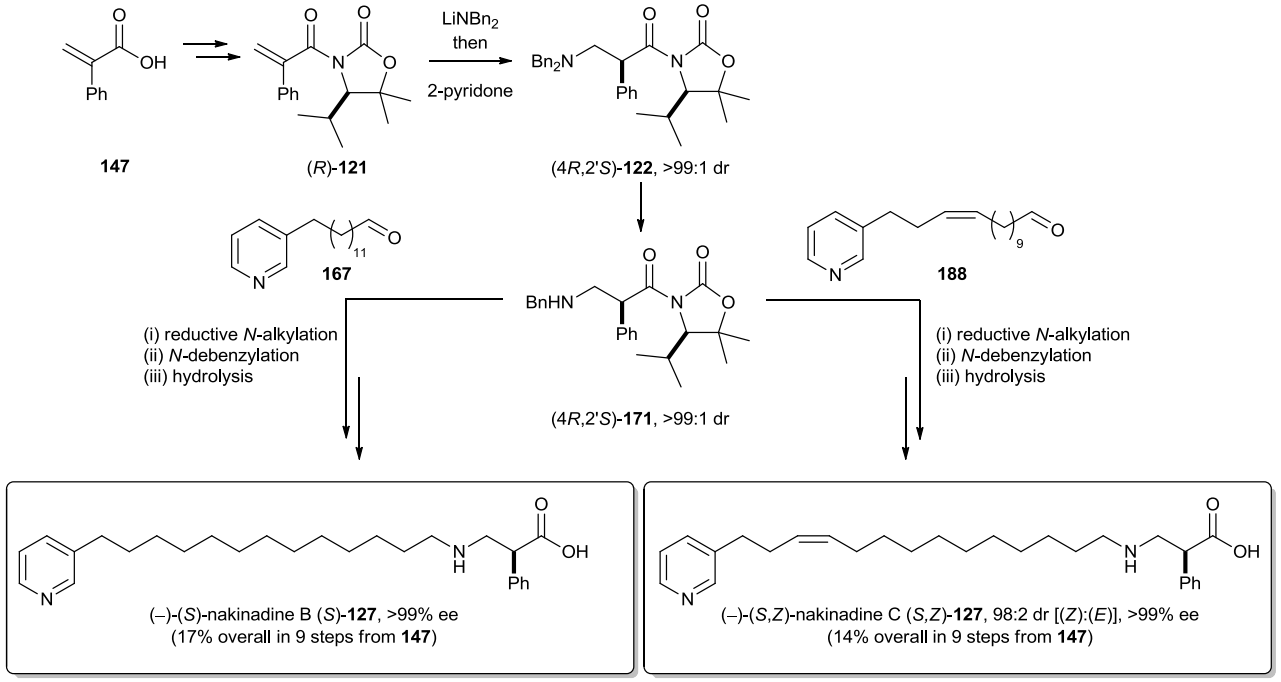


Figure 15. The optimised synthetic route to (−)-(*S*)-nakinadine B (*S*)-**126** and (−)-(*S*,*Z*)-nakinadine C (*S*,*Z*)-**127**.

2.13 References and notes

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[50] The enantiomeric purity of (*R*)-**126** was determined by conversion to the corresponding methyl ester (*R*)-**164** upon treatment with $SOCl_2$ in MeOH, and subsequent ^{1}H NMR spectroscopic analysis of the corresponding Mosher's amides, see: Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
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[54] ^{1}H NMR spectroscopic analysis of (*E*)-**187** was carried out by Dr. Barbara Odell.
[55] The (*Z*):(*E*) ratio of **182** was calculated by integration of the signals corresponding to the allylic protons in the ^{1}H NMR spectrum in C_6D_6 on a 700 MHz instrument.
[56] The (*Z*):(*E*) ratio of **189** was calculated by integration of the signals corresponding to the allylic protons in the ^{1}H NMR spectrum in C_6D_6 on a 700 MHz instrument.
[57] The (*Z*):(*E*) ratio of **190** was calculated by integration of the signals corresponding to the allylic protons in the ^{1}H NMR spectrum in C_6D_6 on a 700 MHz instrument.
[58] The enantiomeric excess of (*R*,*Z*)-**127** was determined by ^{1}H NMR spectroscopic analysis of the corresponding Mosher's amide formed from reaction of methyl ester [synthesised by treatment of (*R*,*Z*)-**127** with $SOCl_2$ in MeOH] and comparison with an authentic racemic sample.

Chapter 3: α-Arylation of β³-amino enolates

This chapter describes the studies towards the development of methodology to enable the α-arylation of β-amino enolates **195** derived from β³-amino esters **194** to give the corresponding α-phenyl-β²,³-amino esters **196**, and its potential application to the synthesis of nakinadines A **125** and D−F **128**−**130** (Figure 16).

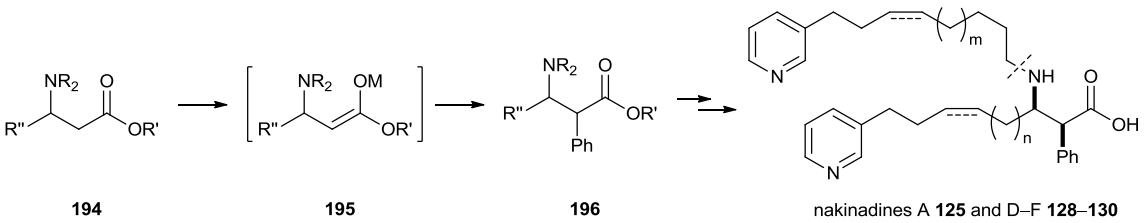
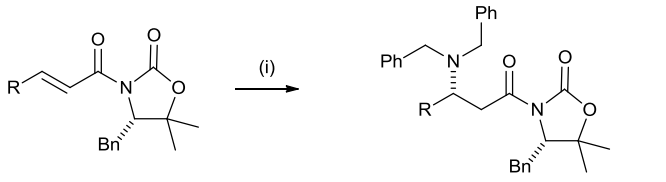


Figure 16. α-Arylation of β³-amino ester enolates **195** as a potential route to the nakinadines A **125** and D−F **128**−**130**.

3.1 Diastereoselective conjugate addition of lithium amides to α,β-unsaturated carbonyl compounds

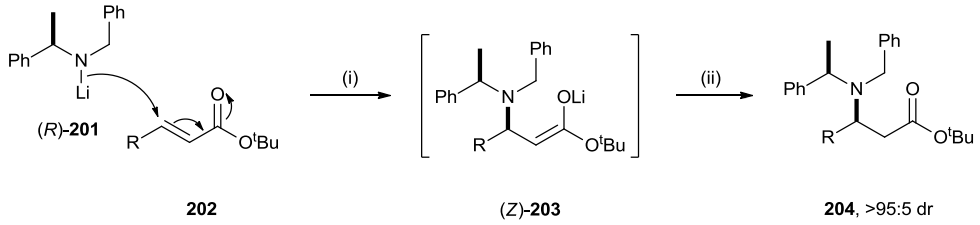
The use of *N*-acyl SuperQuat derivatives to access β³-amino scaffolds has previously been investigated: Davies *et al.*[1] observed that the conjugate addition of lithium dibenzylamide to β-substituted cinnamyl derivatives **197** and **198** proceeded to give **199** and **200** with incomplete conversion (76 and 67% conversion, respectively) and with very little stereocontrol at the β-position (58:42 and 61:39 dr, respectively). These results established that β-substituted *N*-acyl SuperQuat derivatives are poor substrates for the synthesis of β³-amino derivatives (Scheme 57).



Scheme 57. *Reagents and Conditions*: (i) lithium dibenzylamide, THF, –78 °C.

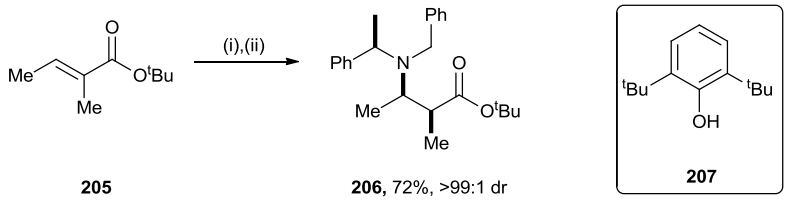
As an alternative approach to β³-amino acids, and their derivatives, extensive studies by Davies *et al.*[2] have demonstrated that the diastereoselective conjugate addition of the antipodes of enantiopure lithium amide **201** to a wide range of achiral α,β-unsaturated esters, such as **202**, followed by protonation of the intermediate lithium (*Z*)-β-amino enolate **203**[3] is

an effective way of synthesising β³-amino esters **204** in high diastereoisomeric purity (>95:5 dr) (Scheme 58).[4]



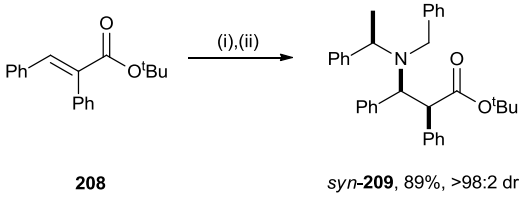
Scheme 58. *Reagents and Conditions*: (i) THF, −78 °C, 2 h; (ii) NH_4Cl (satd aq).

The synthesis of *syn*-α-alkyl-β²,³-amino derivatives was achieved via the conjugate addition of (*R*)-**201** to α-alkyl-α,β-unsaturated esters, such as **205**, and protonation of the resultant enolate.[5] For example, conjugate addition of (*R*)-**201** to *tert*-butyl tiglate **205** in PhMe followed by dilution of the reaction mixture with THF and selective protonation with the hindered phenol **207** gave *syn*-**206** in 72% yield as a single diastereoisomer (Scheme 59).



Scheme 59. *Reagents and Conditions:* (i) (*R*)-**201**, PhMe, −78 °C, 1 h then −30 °C, 2 h; (ii) **207**, THF, −78 °C to rt, 30 min.

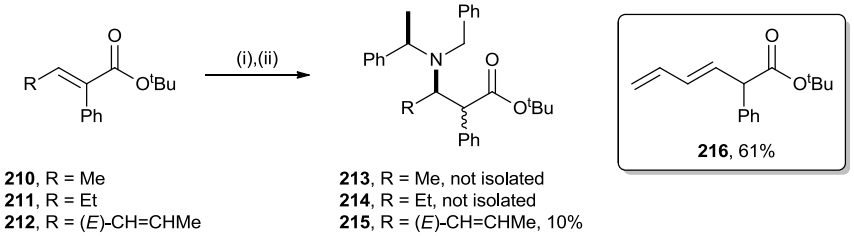
Davies *et al.* attempted to apply this approach to allow the synthesis of *syn*-α-phenyl-β²,³-amino esters.[6] Exploratory investigations focused on *tert*-butyl α-phenylcinnamate **208**, which, upon treatment with (*R*)-**201**, underwent conversion to *syn*-α-phenyl-β²,³-amino ester **209** in 89% yield and >98:2 dr (Scheme 60).



Scheme 60. *Reagents and Conditions:* (i) (*R*)-**201**, THF, −78 °C, 2 h; (ii) NH_4Cl (satd aq).

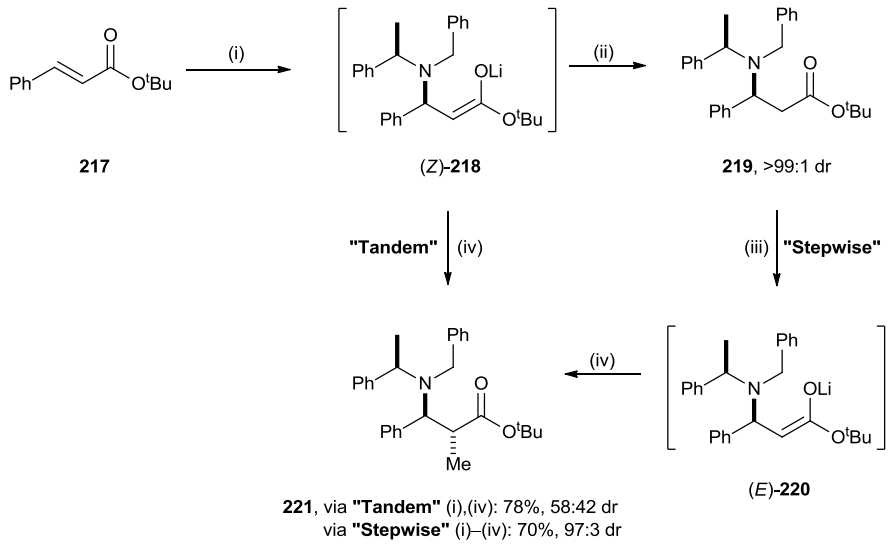
However, when the β-substituent was altered to incorporate an aliphatic side chain (e.g., **210**−**212**), the subsequent conjugate addition reaction of (*R*)-**201** to **210** and **211** gave only complex mixtures of products and conjugate addition of (*R*)-**201** to **212** was achieved in only

10% yield. In this case, the dominant reaction pathway was identified as being competing ε-deprotonation, resulting in formation of the unconjugated ester **216** as the major product, after work-up, which was isolated in 61% yield (Scheme 61).



Scheme 61. *Reagents and Conditions*: (i) (*R*)-**201**, THF, −78 °C, 2 h; (ii) NH_4Cl (satd aq).

A "tandem" one-pot approach for the synthesis of α-alkyl-β^{2,3}-amino ester derivatives has also been developed, proceeding via conjugate addition of lithium amide (*R*)-**201** to α,β-unsaturated ester **217** and treatment of the intermediate lithium (*Z*)-β-amino enolate **218** with MeI, which gave the corresponding *anti*-α-methyl-β^{2,3}-amino derivative **221** in 78% yield and 58:42 dr. Alternatively, a "stepwise" approach, upon treatment of β^3-amino ester **219** with LDA, followed by addition of MeI to the corresponding lithium (*E*)-β-amino enolate **220** gave **221** in 70% yield and 97:3 dr (Scheme 62).[7]



Scheme 62. *Reagents and Conditions*: (i) (*R*)-**201**, THF, −78 °C, 2 h; (ii) NH_4Cl (satd aq); (iii) LDA, THF, −78 °C, 1 h; (iv) MeI, THF, −78 °C to rt, 15 h.

3.2 Chapter Aims

As this strategy does not permit the synthesis of β-alkyl-α-phenyl-β^{2,3}-amino esters **222**, the focus of this chapter is to assess the efficacy of "tandem" and "stepwise" β^3-amino ester enolate arylation protocols as a common strategy for the synthesis of α-phenyl-β^{2,3}-amino acid derivatives. The reactions of β^3-amino ester enolates with two different electrophilic sources of "Ph$^+$" are scrutinised: (i) reaction with benzyne **9**, and (ii) by treatment with bromobenzene in the presence of a Pd-catalyst. As nakinadines A **125** and D−F **128**−**130** share a similar α-phenyl-β^{2,3}-amino acid core, it was envisaged that application of this methodology may allow successful syntheses of the remaining members of the nakinadine alkaloid family (Figure 17).

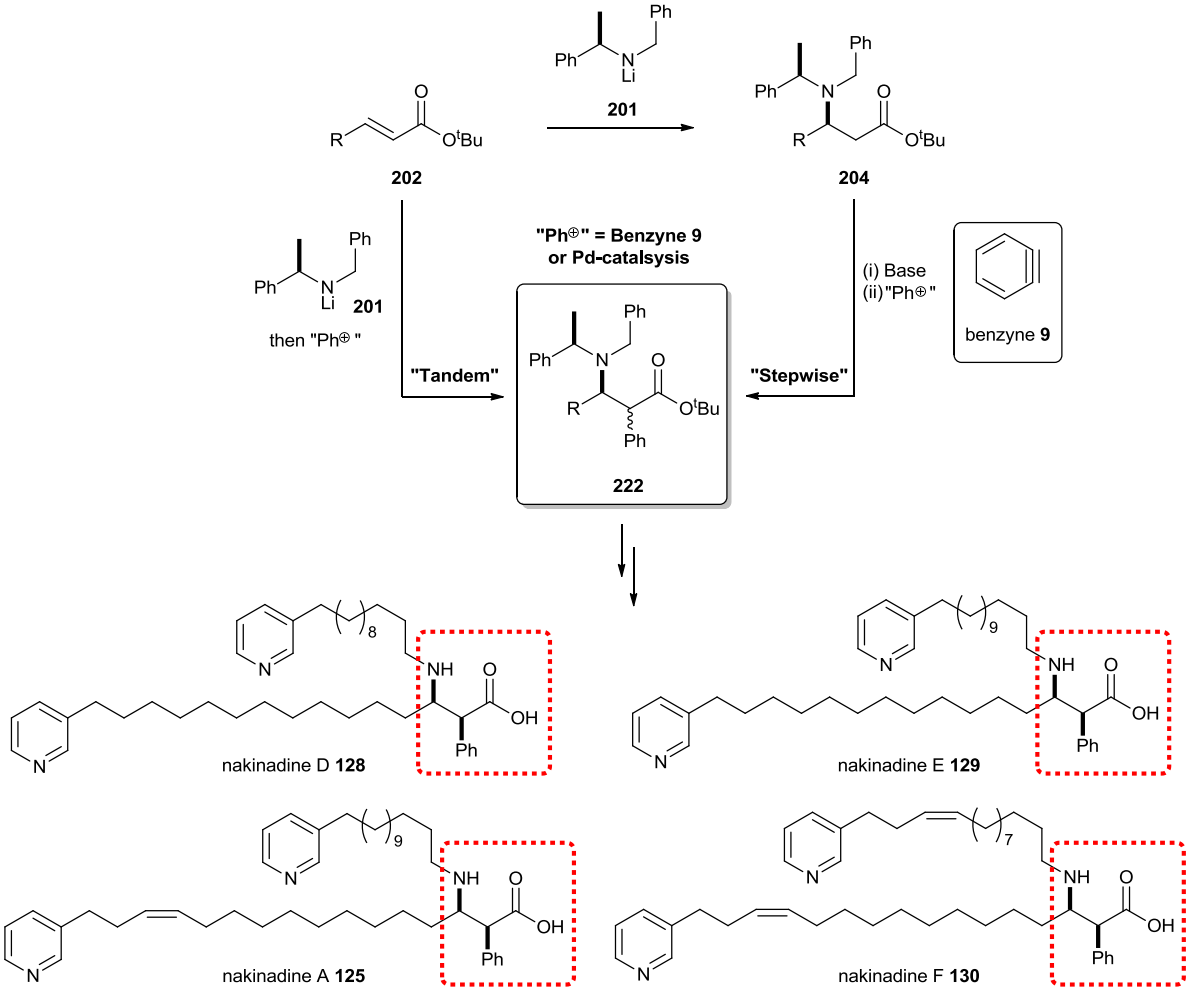


Figure 17. α-Arylation strategy for the synthesis of nakinadines A **125** and D−F **128**−**130**.

3.3 Addition of enolate nucleophiles to benzyne intermediates

3.3.1 General methods for benzyne generation

Synthetic chemists have exploited the extreme reactivity of benzyne and aryne intermediates to complete a wide range of complex natural product syntheses, and their usefulness is fast becoming recognised in the growing number of publications in this field.[8] The sheer variety of natural product targets synthesised using aryne chemistry has led to the development of various methods for the *in situ* generation of these unstable intermediates under mild conditions (rt or lower). The vast majority of methods for benzyne generation rely upon elimination from 1,2-difunctionalized benzene precursors (e.g., **223**−**226**)[9] and although mono-substituted benzenes **223** have been used, these require the use of very strong bases (Figure 18).

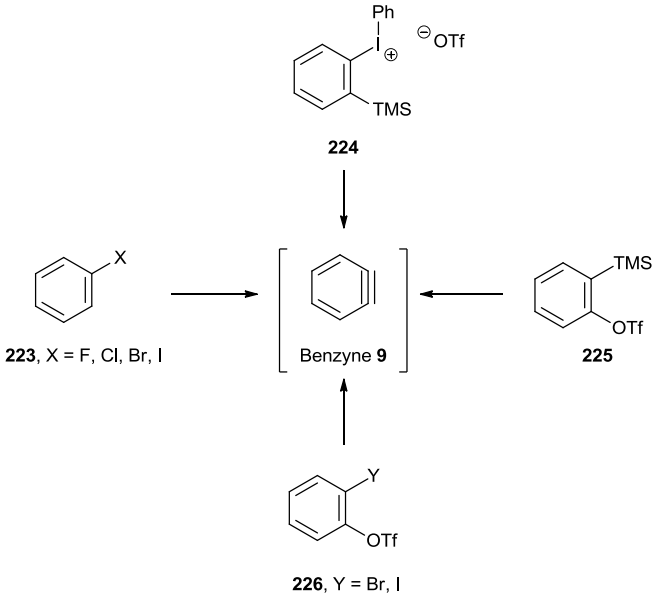
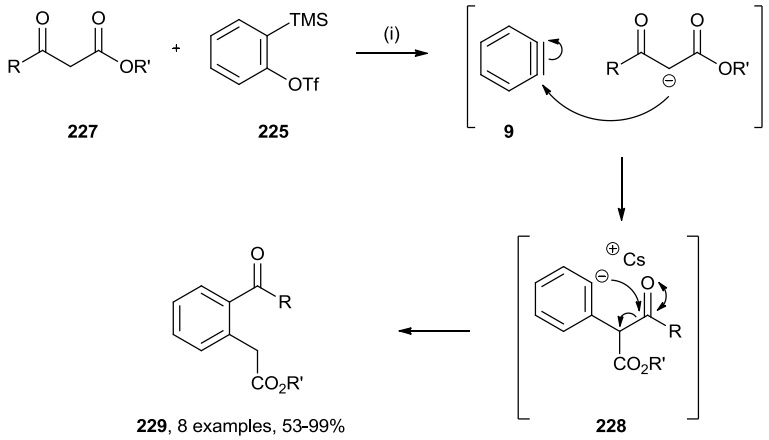


Figure 18. Safe and controlled methods of benzyne **9** generation.

3.3.2 Reactions of enolates with benzyne 9

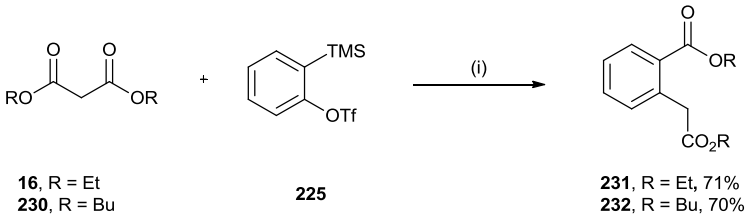
The addition of a carbon nucleophile to benzyne **9** provides a general way of synthesising C−Ar bonds. Kobayashi *et al.*[10] were the first to generate benzyne **9** under almost neutral conditions using the silyl phenyl triflate precursor **225**. Stoltz *et al.*[11] utilised these mild conditions (albeit at elevated temperatures) to react β-ketoesters **227** with **225** in the presence of CsF, which catalyses enolate formation as well as promoting formation of benzyne **9**, to furnish a range of *ortho*-substituted-α-aryl compounds **227** in moderate to excellent yields.

This observation is consistent with the attack of the initially formed *ortho*-carbanion within **228** on the ketone carbonyl, resulting in the loss of a stable enolate species, which upon protonation leads to the formation of **229**. Overall, this transformation constitutes the formal insertion of benzyne **9** into a $C_\alpha-C_\beta$ bond within **227** (Scheme 63).



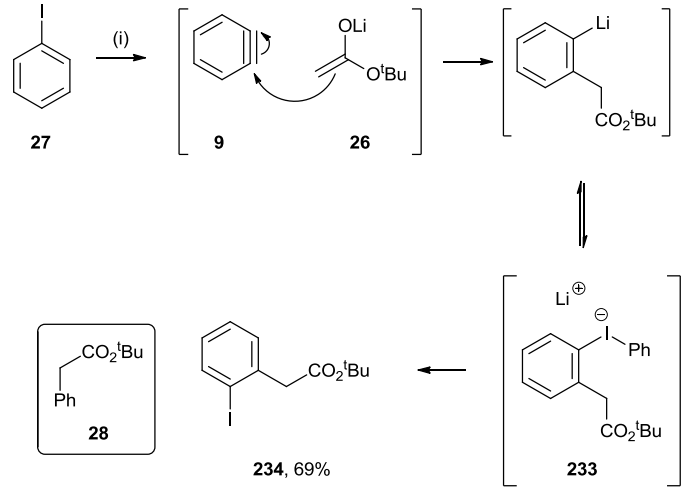
Scheme 63. *Reagents and conditions*: (i) CsF, MeCN, 80 °C, 40−60 min.

Kunai *et al.*[12] built upon this protocol to incorporate symmetric malonate esters **16** and **230**, and by using **225**, KF and 18-crown-6 insertion reactions could be carried out at rt in THF to give the corresponding adducts **231** and **232** in good yield (Scheme 64).



Scheme 64. *Reagents and conditions*: (i) KF, 18-crown-6, THF, rt, 3−5 h.

Alternatively, Durst *et al.*[13] reported that reaction of **26** (the lithium enolate of *tert*-butyl acetate) with benzyne **9** (generated *in situ* via treatment of iodobenzene **27** with LiTMP) gave *tert*-butyl 2-(*o*-iodophenyl)acetate **234** in 69% yield as the major product, alongside minor quantities of *tert*-butyl 2-(phenyl)acetate **28**. The reaction was proposed to go via an ate complex **233** to give the unexpected arylated compound **234**, with HRMS analysis confirming the incorporation of iodine in the product (Scheme 65).

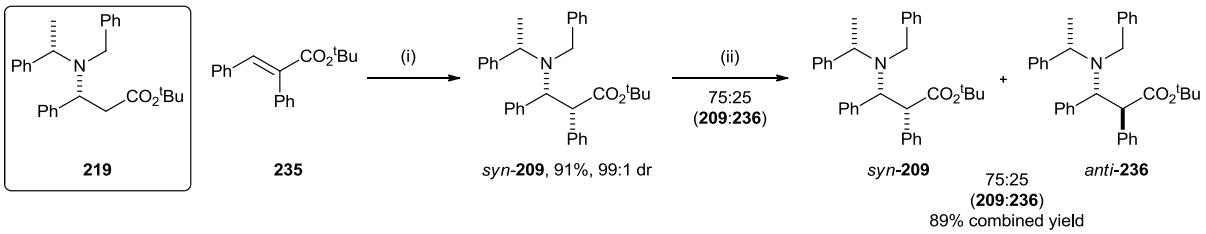


Scheme 65. *Reagents and conditions*: (i) LiTMP, THF, −40 °C.

3.4 Addition of β³-amino enolates to benzyne 9

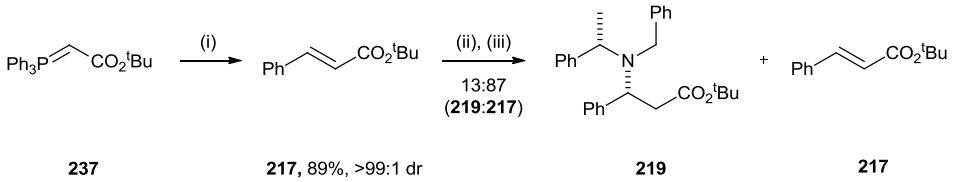
3.4.1 Via a "tandem" process

As it has been previously shown that enolates are amenable to nucleophilic addition to benzyne **9**, the initial focus of this study was to test the ability of β³-amino enolates to undergo addition to benzyne **9**. It was envisaged that using *tert*-butyl esters would deter direct attack of the intermediate *o*-anion at the ester carbonyl, hence reducing the propensity of formation of β-lactones. As Davies *et al.* have previously reported the synthesis of *syn*-**209**,[6] the *in situ* α-arylation of *tert*-butyl cinnamate derived adduct **219** was selected as the model system. Firstly, authentic samples of both of the possible diastereoisomers resulting from the proposed arylation reaction were synthesised. Conjugate addition of (*S*)-**201** to **235** resulted in the formation of *syn*-**209** in 99:1 dr, which was isolated in 91% yield and 99:1 dr after purification by flash column chromatography. Treatment of *syn*-**209** with KHMDS and ^{t}BuOH gave a 75:25 mixture of *syn*-**209** and *anti*-**236**. Purification of the crude reaction mixture via flash column chromatography gave a 75:25 mixture of *syn*-**209** and *anti*-**236**, respectively, in 89% combined yield (Scheme 66).



Scheme 66. *Reagents and Conditions*: (i) (*S*)-**201**, THF, −78 °C, 2 h; (ii) KHMDS, ^{t}BuOH, THF, rt, 16 h.

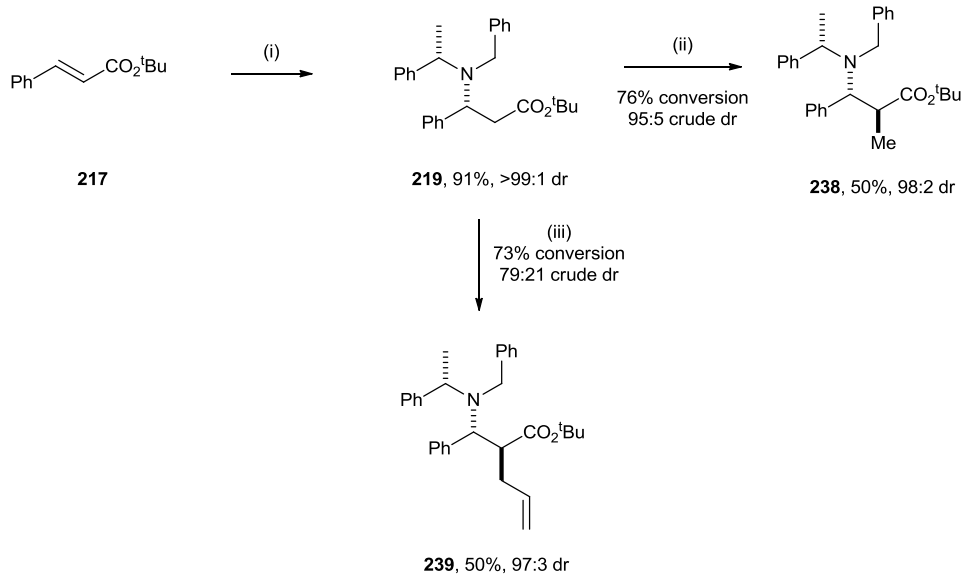
With authentic samples of both **209** and **236** in hand, preliminary studies into a "tandem" (i.e., one-pot) arylation procedure were conducted. Wittig olefination of stabilised phosphonium ylid **237** with benzaldehyde gave *tert*-butyl cinnamate **217** in 89% yield and >99:1 dr [(*E*):(*Z*)] ratio. Subsequent conjugate addition of lithium amide (*S*)-**201** to α,β-unsaturated ester **217** in THF at −78 °C was followed by the addition of KF, 18-crown-6 and benzyne precursor **225**, and the reaction mixture was warmed to rt over 16 h. ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed a 13:87 mixture of conjugate addition adduct **219** and *tert*-butyl cinnamate **217**, with no desired arylated products *syn*-**209** or *anti*-**236** being observed. A similar scenario was observed when CsF was used as the nucleophilic fluoride source (Scheme 67).



Scheme 67. *Reagents and Conditions*: (i) benzaldehyde, CH_2Cl_2, rt, 16 h; (ii) (*S*)-**201**, THF, −78 °C, 2 h then KF, 18-crown-6, **225**, −78 °C to rt, 16 h; (iii) citric acid (10% aq).

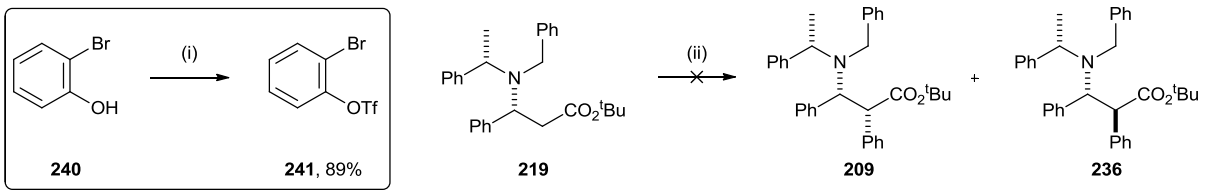
3.4.2 Via a "stepwise" approach

As the "tandem" procedure did not yield any arylated product, a two-step approach, involving initial conjugate addition to give **219** followed by re-generation of the enolate and attempted arylation of this enolate was next explored. With large quantities of **219** in hand (synthesised in 91% and >99:1 dr from **217**), it was first established that both the lithium and potassium enolates of **219** react with activated carbon electrophiles to give α-substituted adducts **238** and **239** in moderate yields and high diastereoselectivity, as previously reported (Scheme 68).[7]



Scheme 68. *Reagents and Conditions*: (i) (*S*)-**201**, THF, −78 °C, 2 h; (ii) LDA, −78 °C, 30 min, then MeI, −78 °C to rt, 16 h; (iii) KHMDS, −78 °C, 30 min, then allyl bromide, −78 °C to rt, 16 h.

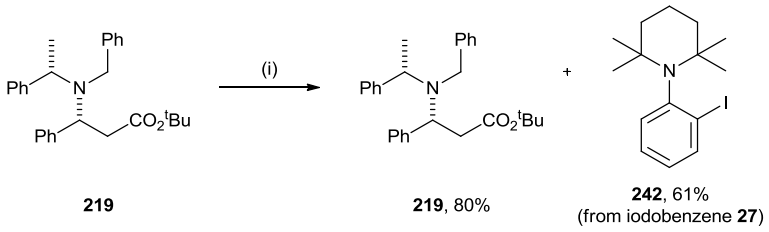
A preliminary investigation looking into the *in situ* enolate α-arylation of **219** was first carried out using a variety of methods for benzyne generation. Following the method outlined by Suzuki *et al.* for generation of benzyne **9** at −78 °C from *ortho*-bromotriflate **241**,[14] 2-bromophenol **240** was first converted to the corresponding bromotriflate **241** by treatment with Tf_2O and pyridine to give **241** in 89% yield. Formation of the potassium enolate of **219** by treatment with KHMDS at −78 °C was followed the addition of benzyne precursor **241** and BuLi. After 1 h at −78 °C, only the starting material **219** was present in the crude reaction mixture, with 100% consumption of the benzyne precursor **241** (Scheme 69).



Scheme 69. *Reagents and Conditions*: (i) Tf_2O, pyridine, CH_2Cl_2, 0 °C to rt, 16 h; (ii) KHMDS, THF, −78 °C, 1 h then **241**, BuLi, THF, −78 °C, 1 h.

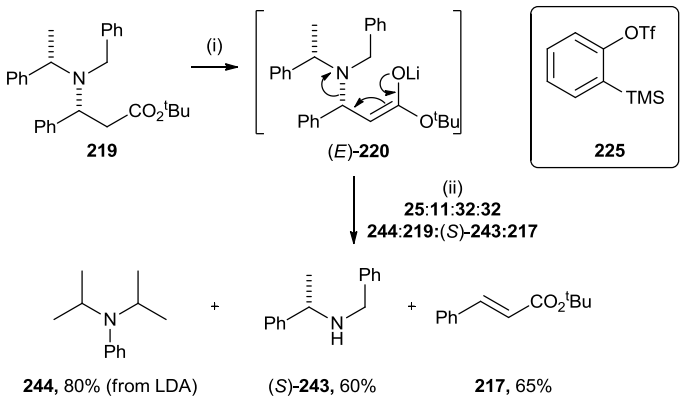
Durst *et al.* have generated benzyne **9** at −40 °C by using a combination of LiTMP and iodobenzene **27**.[13] It was envisaged that LiTMP could be used to form both the lithium enolate of **219** and generate benzyne **9** from iodobenzene **27**, and so **219** was treated with LiTMP and iodobenzene **27** in THF at −40 °C which gave a mixture of starting material **219** and *N*-arylated piperidine **242**, suggesting the intermediacy of benzyne **9**, along with some minor unidentifiable compounds, although these did not correspond to the α-arylated species

209 or **236**. After purification **242** was isolated in 61% yield from iodobenzene alongside **219** which was recovered in 80% yield (Scheme 70).



Scheme 70. *Reagents and Conditions*: (i) LiTMP, THF, −40 °C, 1 h then iodobenzene **27**, −40 °C, 4 h.

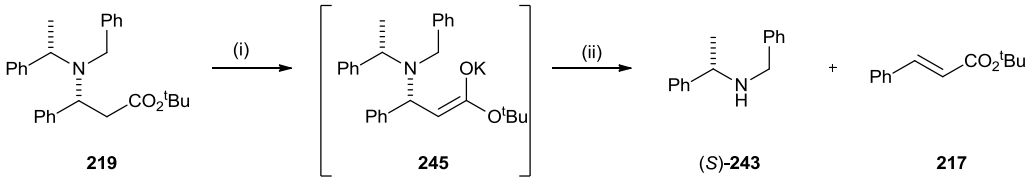
Use of trimethylsilyl triflate **225** as benzyne precursor in conjunction with a fluoride source was probed next. Treatment of **219** with LDA in THF at −78 °C gave lithium (*E*)-β-aminoenolate **220**,[7] which was followed by the addition of KF, 18-crown-6 and benzyne precursor **225**. After warming the reaction mixture to rt over 12 h, the crude material consisted of a 25:11:32:32 mixture of **244**, **219**, (*S*)-**243** and **217**, respectively. No α-arylated products (**209** or **236**) were observed and the major compound **244** was isolated in 80% yield (from LDA), presumably formed from the reaction of LDA or diisopropylamine with the intermediate benzyne **9**.[15] Noticeably, only 20% of the starting material **219** was recovered, but (*S*)-**243** and **217** were isolated in 60 and 65% yield, respectively, suggesting a competing enolate decomposition pathway was occurring. Changing the base from LDA to KHMDS resulted in complete decomposition of **219**, leading to the formation of a 50:50 mixture of (*S*)-**243** and **217** (Scheme 71).



Scheme 71. *Reagents and Conditions*: (i) LDA, THF, −78 °C, 30 min; (ii) **225**, KF, 18-crown-6, THF, −78 °C to rt, 12 h.

3.4.3 Investigation into the stability of enolate 245

As these results suggested that both the lithium and potassium β-amino enolates of **220** and **245** were unstable at elevated temperature, a study to determine the temperature at which enolate fragmentation begins to occur was performed. Treatment of **219** with KHMDS in THF at −78 °C was followed by subsequent warming to the stated temperature, for the stated time, before the addition of satd aq NH_4Cl. ^1H NMR spectroscopic analysis of the crude reaction mixtures showed (at temperatures less than −20 °C), no degradation of the lithium β-amino enolate **245** as starting material **219** was returned exclusively. Above −20 °C, however, appreciable amounts of retro-Michael products (*S*)-**243** and **217** were detected, and almost complete decomposition occurred at 20 °C after only 2 h (Scheme 72).



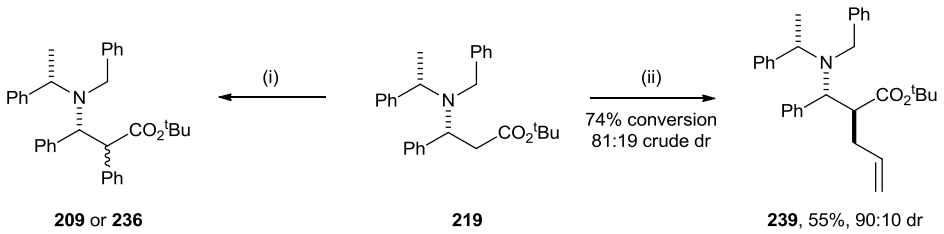
End Temperature (*T* °C)	Time (*t* h)	Crude product distribution 219:(*S*)-243:217
−78	2	100:0:0
−60	2	100:0:0
−40	2	100:0:0
−20	2	100:0:0
0	2	66:17:17
20	2	1:57:42
20	12	0:55:45

Scheme 72. *Reagents and conditions*: (i) KHMDS, THF, −78 °C, 1 h; (ii) −78 °C to *T* °C, *t* h.

3.4.4 Attempted α-arylation at −20 °C

As potassium β-amino enolate **245** is stable up to −20 °C, all subsequent reactions were carried out with this in mind. Reaction of the potassium enolate of **245** (formed from the reaction of **219** with KHMDS in THF at −78 °C) with KF, 18-crown-6 and benzyne precursor **225**, and warming of the resultant suspension to −20 °C over 12 h, unfortunately still only resulted in the return of starting material **219**, with full consumption of benzyne precursor **225** being noted. Enolate decomposition products (*S*)-**243** and **217** were not detected in the crude reaction mixture, as expected. To ensure that potassium β-amino enolate **245** was still present, an analogous reaction was performed where allyl bromide was added to the crude reaction mixture after 12 h at −20 °C, which furnished the α-allylated product **239** in 74% conversion

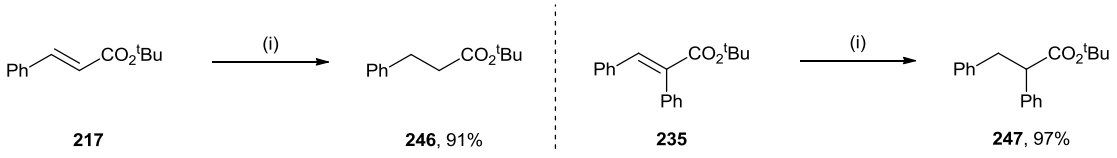
as an 81:19 mixture of diastereoisomers. Purification via flash column chromatography led to the isolation of **239** in 55% yield and 90:10 dr. The stereochemistry within **239** was assigned by analogy to previous examples in the literature.[7] This result confirmed the presence of the enolate at the end of the initial arylation reaction and established that the enolate **245** is unreactive towards benzyne **9** under these conditions (Scheme 73).



Scheme 73. *Reagents and Conditions*: (i) KHMDS, THF, −78 °C, 30 min then **225**, KF, 18-crown-6, THF, −78 °C to −20 °C, 12 h; (ii) KHMDS, THF, −78 °C, 30 min then **225**, KF, 18-crown-6, THF, −78 °C to −20 °C, 12 h then allyl bromide, −20 °C to rt, 12 h.

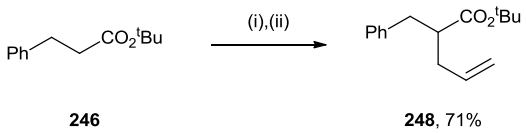
3.5 Attempted arylation of ester enolates

As the benzyne-mediated arylation protocol was shown to be incompatible with β-amino ester enolates, the arylation of simple ester enolates was briefly investigated. It was envisaged that the enolate of ester **246** would be more stable at higher temperature. Hydrogenation of the C=C double bond within *tert*-butyl cinnamate **217** gave saturated *tert*-butyl ester **246** in 91% yield, and this served as a substrate to test the efficacy of α-arylation. Hydrogenation of **235** gave an authentic sample of the α-phenyl product **247** in 97% yield (Scheme 74).



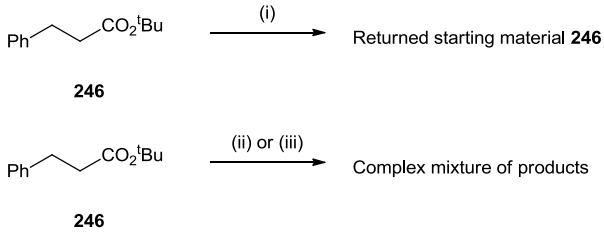
Scheme 74. *Reagents and conditions*: (i) H_2 (1 atm), $Pd(OH)_2/C$, EtOAc, rt, 16 h.

Similar to the β³-amino enolates, this simple ester enolate was also shown to be reactive towards carbon electrophiles. Formation of the potassium enolate of **246** via treatment with KHMDS in THF at −78 °C and reaction with allyl bromide gave α-allyl ester **248** in 71% yield (Scheme 75).



Scheme 75. *Reagents and conditions*: (i) KHMDS, THF, −78 °C, 30 min; (ii) allyl bromide, −78 °C to rt, 16 h.

With this in mind, ester **246** was subjected to arylation conditions using the procedure developed by Kunai *et al.* (treatment of benzyne precursor **225** in the presence of KF and 18-crown-6)[12] which unfortunately only resulted in the return of starting material **246**. Alternatively, when using BuLi and bromotriflate **241** as the benzyne precursor, a complex mixture of products was produced. ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed no peaks corresponding to the desired product **247**. When LiTMP and iodobenzene **27** were used, another complex mixture of products was obtained (Scheme 76).



Scheme 76. *Reagents and conditions*: (i) KHMDS, THF, −78 °C, 30 min then KF, 18-crown-6, **225**, −78 °C to rt, 16 h; (ii) KHMDS, −78 °C, 30 min, then BuLi, **241**, −78 °C 1 h; (iii) LiTMP, THF, −40 °C, 1 h then iodobenzene **27**, −40 °C, 4 h.

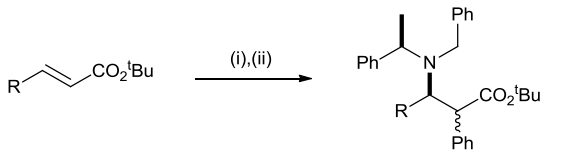
Therefore, since α-arylation of β³-amino ester and simple *tert*-butyl ester enolates using benzyne **9** was proving unfeasible, an alternative method was sought. The Pd-catalysed conversion of preformed ester enolates or silyl enol ethers with haloarenes provides a direct method for the construction of the α-aryl carbonyl motif, as highlighted in Chapter 1. Therefore it was envisaged that application of this methodology with use of preformed β³-amino enolates could pave the way for the general synthesis of α-phenyl-β²,³-amino acids, including nakinadines A **125** and D−F **128**−**130**.

3.6 Pd-catalysed α-arylation

3.6.1 Via a "tandem" procedure

Initial attempts at achieving this transformation focused on a one-pot procedure whereby lithium amide conjugate addition of an enantiopure lithium amide to an α,β-unsaturated ester could be followed by the addition of bromobenzene and the catalytic system used by Hartwig *et al.*[16] Since authentic samples of both the *syn*- and *anti*-diastereoisomers **209** and **236** were already synthesised, *tert*-butyl cinnamate **217** was again used as a model system. Unfortunately, attempted conjugate addition of (*R*)-**201** to *tert*-butyl cinnamate **217** in THF at −78 °C followed by the addition of $Pd(dba)_2$ (5 mol%), $P(^tBu)_3{\cdot}HBF_4$ (5 mol%) and

bromobenzene (1.1 equiv) and warming to rt returned only the conjugate addition adduct **219**, with no arylated compounds **209** or **236** detected by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. However, when *tert*-butyl crotonate **249** was subjected to an analogous set of conditions, a mixture of products including the desired α-arylated product **250** was observed. The crude diastereoisomeric ratio of **250** could not be determined due to overlapping resonances in the ^{1}H NMR spectrum. Purification via flash column chromatography gave **250** in 22% yield and 70:30 dr; the relative configuration of the major diastereoisomer was not assigned in this case (Scheme 77).



217, R = Ph
249, R = Me

209, R = Ph, 0%
250, R = Me, 22%, 70:30 dr

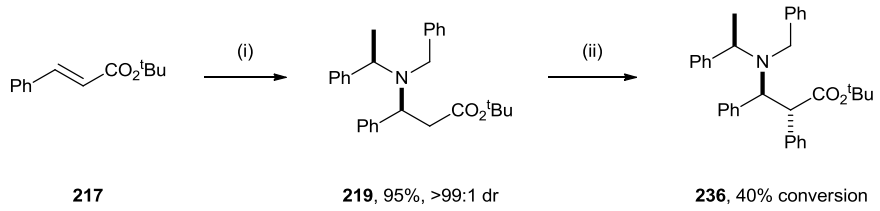
Scheme 77. *Reagents and Conditions*: (i) (*R*)-**201**, THF, −78 °C, 2 h; (ii) $Pd(dba)_2$, $P(^tBu)_3{\cdot}HBF_4$, bromobenzene, −78 °C to rt, 12 h.

As this "tandem" procedure led to the formation of several compounds, and the desired products were isolated in low yields, focus switched to a "stepwise" approach, relying upon α-arylation of enolates re-generated after the conjugate addition step.

3.6.2 Via a "Stepwise" procedure

3.6.2.1 α-Arylation of cinnamate and crotonate derived esters

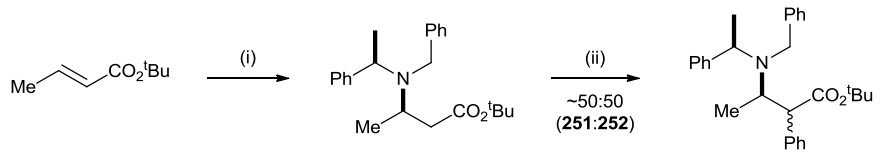
The α-arylation of the corresponding *tert*-butyl β-phenyl-β³-amino ester **219** was initially investigated, with **219** formed in 95% yield as a single diastereoisomer (>99:1 dr) from the conjugate addition of (*R*)-**201** to *tert*-butyl cinnamate **217**. Re-generation of the enolate followed by subsequent application of the Pd-catalysed arylation conditions developed by Hartwig[16] gave only 40% conversion to the desired α-phenyl product *anti*-**236**. Comparison of the ^{1}H NMR spectra of the crude reaction mixtures with that for the authentic sample of *anti*-**236** confirmed that the *anti*-diastereoisomer was formed, with *syn*-**209** not detected (Scheme 78).



217 **219**, 95%, >99:1 dr **236**, 40% conversion

Scheme 78. *Reagents and Conditions*: (i) (*R*)-**201**, THF, −78 °C, 2 h then NH_4Cl (satd aq); (ii) $Pd(dba)_2$, $P(^tBu)_3{\cdot}HBF_4$, LiHMDS, bromobenzene, PhMe, −20 °C to rt, 12 h.

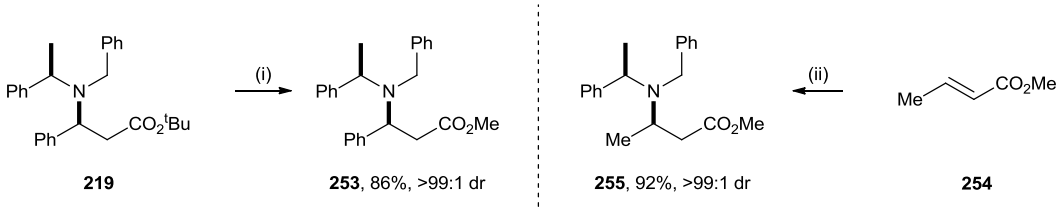
Analogously, conjugate addition of (*R*)-**201** to *tert*-butyl crotonate **249** gave **251** in 95% yield and >99:1 dr. Attempted α-arylation of this ester **251** led to a mixture of products containing a ~50:50 mixture of starting material **251** and the desired α-phenyl derivative **252**. The crude diastereoisomeric ratio of **252** could not be determined due to overlapping resonances in the ^{1}H NMR spectrum. Purification via flash column chromatography gave **252** in 34% yield and 87:13 dr. The relative configuration within **252** was not determined, although upon comparison of the ^{1}H NMR spectrum of **252** with that obtained for **250** (the product obtained from the "tandem" arylation reaction of *tert*-butyl crotonate **249**), it was shown that the major diastereoisomer **252** was the C(2)-epimer of **250** (Scheme 79).



249 **251**, 95%, >99:1 dr **252**, 34%, 87:13 dr

Scheme 79. *Reagents and Conditions*: (i) (*R*)-**201**, THF, −78 °C, 2 h then NH_4Cl (satd aq); (ii) $Pd(dba)_2$, $P(^tBu)_3{\cdot}HBF_4$, LiHMDS, bromobenzene, PhMe, −20 °C to rt, 12 h.

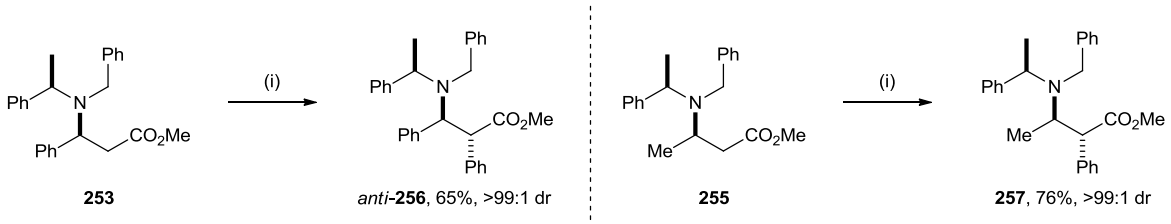
As the α-arylation of *tert*-butyl esters **219** and **251** proceeded with incomplete conversion, it was envisaged that changing to the corresponding methyl esters **253** and **255** would decrease the steric hindrance around the enolate and thus improve the reactivity. Transesterification of *tert*-butyl ester adduct **219** via treatment with $SOCl_2$ in MeOH gave **253** in 86% yield and >99:1 dr. Conjugate addition of (*R*)-**201** to methyl crotonate **254** gave the corresponding crotonate methyl ester adduct **255** in 92% yield and >99:1 dr (Scheme 80).



219 **253**, 86%, >99:1 dr **255**, 92%, >99:1 dr **254**

Scheme 80. *Reagents and Conditions*: (i) $SOCl_2$, MeOH, 50 °C, 12 h; (ii) (*R*)-**201**, THF, −78 °C, 2 h then NH_4Cl (satd aq).

Treatment of methyl ester **253** with LiHMDS (1.2 equiv), $Pd(dba)_2$ (5 mol%), $P(^tBu)_3$ (10 mol%) and bromobenzene (1.5 equiv) in PhMe at −20 °C, followed by warming to rt gave 100% conversion of **253** to the known *anti*-α-phenyl-β[2,3]-amino ester **256**,[6] which was isolated in 65% yield and >99:1 dr. Similarly, **255** was reacted under the same conditions to furnish α-phenyl adduct **257** in 76% yield as a single diastereoisomer (Scheme 81). The relative configuration within **257** was unambiguously assigned by single crystal X-ray diffraction analysis of the corresponding HBF_4 salt.[17] Since the absolute (*R*)-configuration of the α-methylbenzyl group was known, **257** was assigned the absolute (*R*,*R*,*R*)-configuration (Figure 19).



253 *anti*-**256**, 65%, >99:1 dr **255** **257**, 76%, >99:1 dr

Scheme 81. *Reagents and Conditions*: (i) $Pd(dba)_2$, $P(^tBu)_3 \cdot HBF_4$, LiHMDS, bromobenzene, PhMe, −20 °C to rt, 12 h.

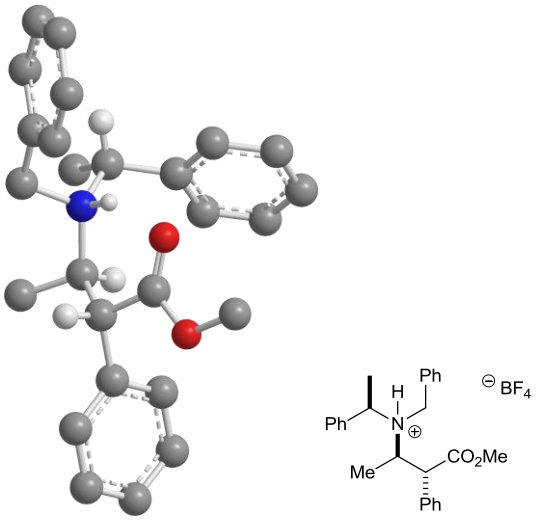


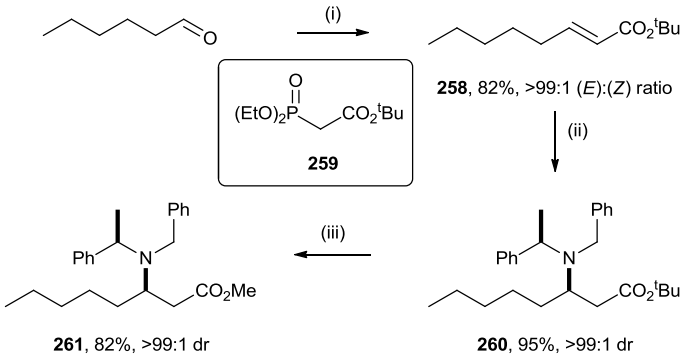
Figure 19. X-ray structure of (*R*,*R*,*R*)-**257**·HBF_4 (selected H atoms are omitted for clarity).

3.6.2.2 Extending the scope of the α-Arylation protocol

3.6.2.2.1 Syntheses of β³-amino esters 261, 264 and 267

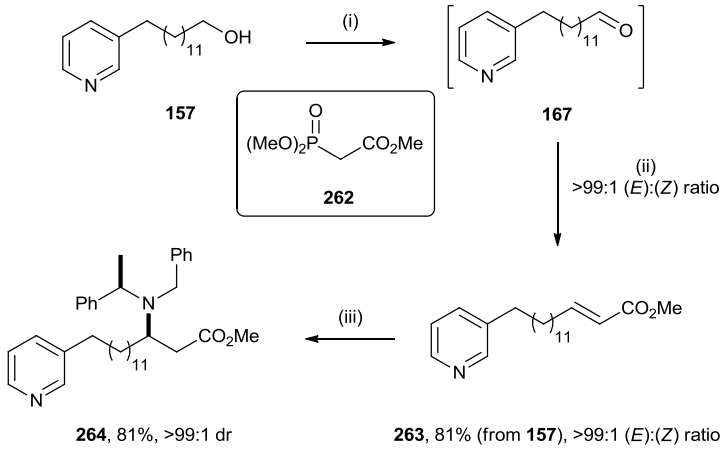
With an efficient protocol for the α-arylation of cinnamate- and crotonate-derived methyl esters **253** and **255** in hand, a small range of β-alkyl-β[3]-amino methyl esters were synthesised to explore the scope of the methodology, and to see if it was applicable to the synthesis of the

nakinadine alkaloids. Formation of hexanal derived acceptor **258** was carried out via a Horner-Wadsworth-Emmonds reaction[18] using hexanal, MeMgBr and phosphonate **259**, which gave **258** in 82% yield and >99:1 dr [(*E*):(*Z*)]. Conjugate addition of (*R*)-**201** to **258** led to the formation of β³-amino ester **260** in 95% yield and as a single diastereoisomer (>99:1 dr). Transesterification of **260** with $SOCl_2$ in MeOH led to the isolation of methyl ester **261** in 82% yield and >99:1 dr (Scheme 82).



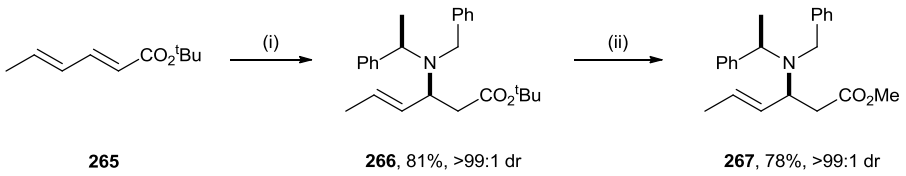
Scheme 82. *Reagents and Conditions*: (i) MeMgBr, **259**, THF, reflux, 12 h; (ii) (*R*)-**201**, THF, −78 °C, 2 h then satd aq NH_4Cl; (iii) $SOCl_2$, MeOH, 50 °C, 12 h.

IBX-mediated oxidation of primary alcohol **157** gave aldehyde **167** which was then reacted immediately in a Horner-Wadsworth-Emmonds reaction with MeMgBr and phosphonate **262**[18] to furnish α,β-unsaturated ester **263** in >99:1 dr [(*E*):(*Z*)]. Purification of the crude reaction mixture via flash column chromatography gave **263** in 81% yield (from **157**) as a single diastereoisomer (>99:1 dr). Conjugate addition of (*R*)-**201** to **263** in THF at −78 °C furnished β³-amino ester **264** in 81% yield and >99:1 dr (Scheme 83).



Scheme 83. *Reagents and Conditions*: (i) IBX, EtOAc, 80 °C, 3 h; (ii) MeMgBr, **262**, THF, reflux, 12 h; (iii) (*R*)-**201**, THF, −78 °C, 2 h then NH_4Cl (satd aq).

Finally, sorbyl derivative **266** was synthesised in 81% yield and >99:1 dr from *tert*-butyl sorbate **265** via addition of (*R*)-**201**. Transesterification to the methyl ester **267** was facilitated by addition of $SOCl_2$ to a solution of **266** in MeOH, which gave **267** in 78% yield and >99:1 dr (Scheme 84).

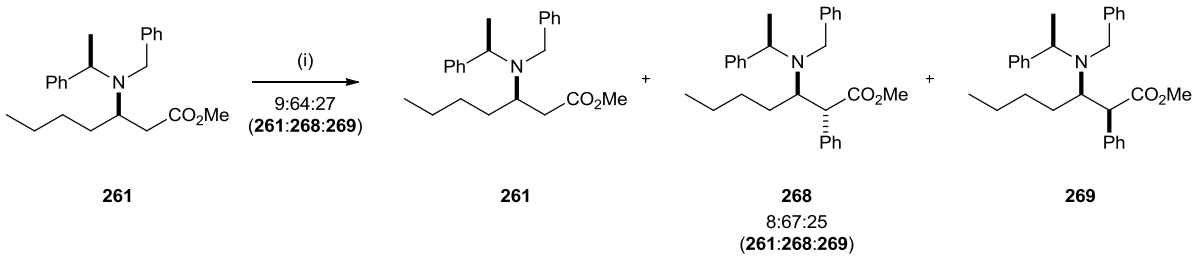


265 **266**, 81%, >99:1 dr **267**, 78%, >99:1 dr

Scheme 84. *Reagents and Conditions*: (i) (*R*)-**201**, THF, −78 °C, 2 h then NH_4Cl (satd aq); (ii) $SOCl_2$, MeOH, 50 °C, 12 h.

3.6.2.2.2 Attempted α-arylation of β³-amino esters 261, 264 and 267

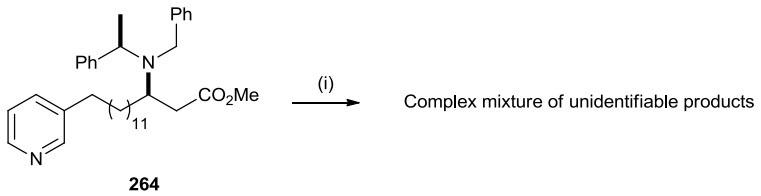
With methyl esters **261**, **264** and **267** in hand, α-arylation was attempted. When methyl ester **261** was subjected to the α-arylation reaction, several compounds were observed, including a 9:64:27 mixture of **261**, and two species assigned as the α-phenyl-diastereoisomers **268** and **269**. Attempted purification of the crude reaction mixture led to the isolation of a mixture of these species in an 8:67:25 ratio. The relative configuration of the major diastereoisomer **268** was assigned by analogy to that of **257** (Scheme 85).



261 **261** **268** 8:67:25 (**261**:**268**:**269**) **269**

Scheme 85. *Reagents and Conditions*: (i) $Pd(dba)_2$, $P(^tBu)_3 \cdot HBF_4$, LiHMDS, bromobenzene, PhMe, −20 °C to rt, 12 h.

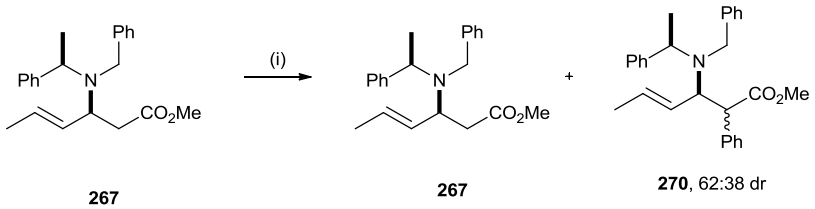
Unfortunately, reaction of **264** under the Pd-catalysed arylation conditions led to the formation of a complex mixture of unidentifiable products (Scheme 86). As it is known that pyridine containing compounds can poison Pd catalysts,[19] this may have a deleterious effect on the active catalyst and be responsible for the lack of observed arylation in this case.



264

Scheme 86. *Reagents and Conditions*: (i) $Pd(dba)_2$, $P(^tBu)_3{\cdot}HBF_4$, LiHMDS, bromobenzene, PhMe, −20 °C to rt, 12 h.

Although this result suggests that the pyridin-3-yl side-chain containing ester enolate is not amenable to direct arylation via this procedure, an alternative method could be used to α-arylate an ester with a latent handle which would enable further functionalisation to install the pyridin-3-yl group later on during the synthetic pathway. As such, the α-arylation of **267** was next investigated. Although methyl ester **267** showed some conversion to an α-phenyl adduct **270** (the crude diastereoisomeric ratio of **270** could not be determined due to overlapping resonances in the ^{1}H NMR spectrum), several other unidentifiable products were also detected. Attempted purification of the crude reaction mixture led to the isolation of an impure mixture of starting material **267** alongside α-phenyl ester **270** obtained in 62:38 dr (Scheme 87).



267 **267** **270**, 62:38 dr

Scheme 87. *Reagents and Conditions*: (i) $Pd(dba)_2$, $P(^tBu)_3{\cdot}HBF_4$, LiHMDS, bromobenzene, PhMe, −20 °C to rt, 12 h.

3.7 Conclusion

Ultimately, after numerous attempts the α-arylation of both lithium and potassium enolates derived from esters and β³-amino esters with benzyne intermediates was unsuccessful. An alternative procedure utilising bromobenzene in conjunction with Pd-catalysis was also assessed but was met with limited success. Although, this α-arylation protocol was not general to all the β³-amino esters tested, it was successful for cinnamate and crotonate methyl ester systems. Unfortunately, neither of these processes is compatible for the synthesis of the remaining members of the nakinadine family. Chapter 4 will investigate the asymmetric Mannich-type addition of achiral α-phenyl ester enolates to chiral sulfinyl imines as a route to synthesise nakinadines A **125** and D−F **128**−**130**.

3.8 References and Notes

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[16] Liu, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 5182.
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[19] For an example where pyridine has been used to poison a Pd-catalyst, see: Sajiki, H.; Hirota, K. *Chem. Pharm. Bull.* **2003**, *51*, 320.

Chapter 4: Asymmetric syntheses of nakinadines A and D−F

This chapter describes an imino-aldol approach (reaction of an achiral α-phenyl ester enolate **272** with a chiral *N*-sulfinyl imine **271** as the key diastereoselective step) towards the syntheses of nakinadines A **125** and D–F **128**–**130** (Figure 20). A diastereodivergent route to both the *syn*- and *anti*-diastereoisomers of nakinadines A **125** and D−F **128**−**130** was developed with a view to assigning both the relative and (hitherto unassigned) absolute configurations within the natural samples of these alkaloids.

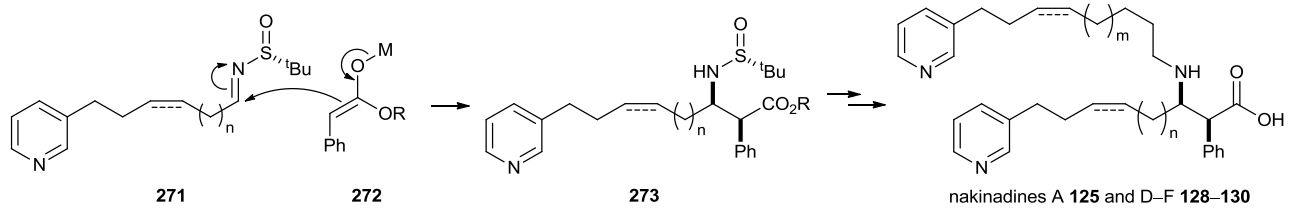
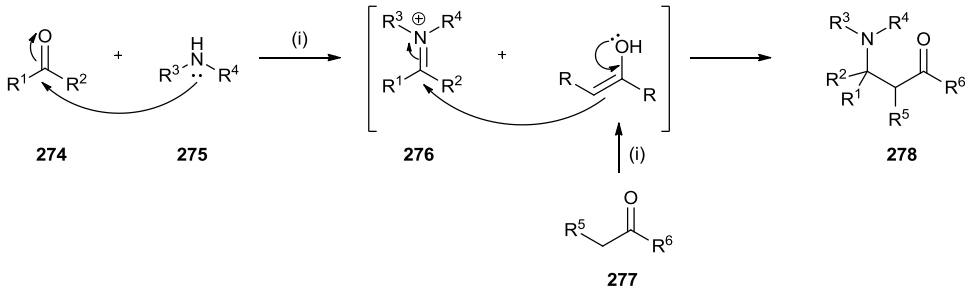


Figure 20. The imino-aldol reaction as the key step towards the asymmetric syntheses of nakinadines A **125** and D−F **128**−**130**.

4.1 The Mannich reaction

The Mannich reaction is an imino-aldol reaction consisting of the addition of an enolisable carbonyl species **277** with an iminium derivative **276** (formed via the condensation of a primary or secondary amine **275** with a carbonyl compound **274**) in the presence of a catalytic amount of either acid or base, resulting in the formation of β-amino carbonyl compounds (i.e., Mannich bases) **278**.[1] Several groups independently reported such transformations;[2] however, Mannich[1] was the first to recognise the generality of this reaction manifold (Scheme 88).



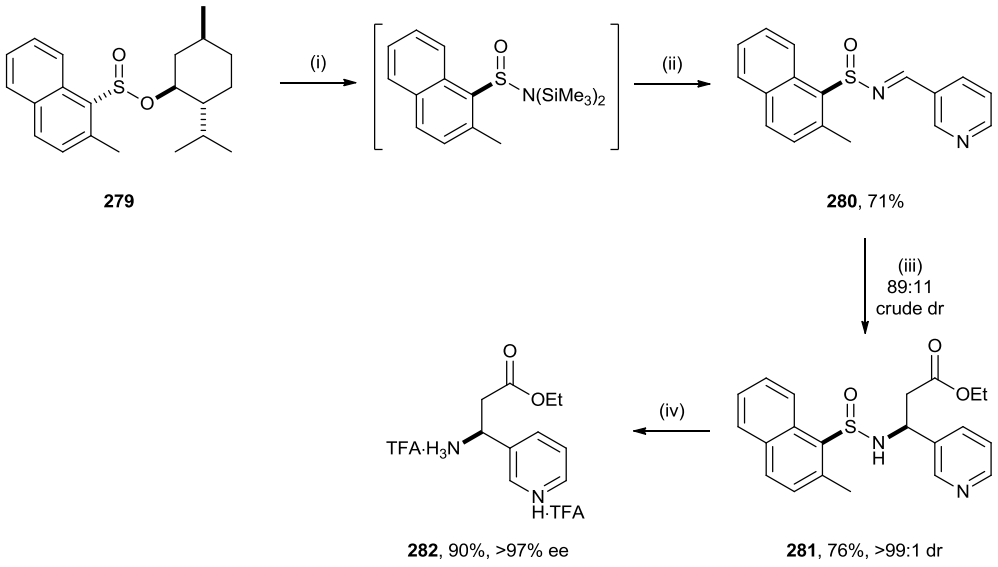
Scheme 88. *Reagents and Conditions*: (i) cat. acid.

The Mannich reaction has become a main-stay in synthetic organic chemistry as it is a key C−C bond forming reaction, and allows the synthesis of motifs found in many pharmaceutical drugs.[3] However, the Mannich reaction suffers from many drawbacks, including the formation of multiple products resulting from poly-substitution at the α-position, thus giving diminished yields of the

desired mono-substituted products, and the use of harsh conditions.[3] Therefore, significant efforts have been made to counteract these disadvantages.[3]

4.2 *N*-Sulfinyl imines in imino-aldol reactions

One method to circumvent the inherent problems with the use of unstable imine or iminium ions (generated *in situ*) in the Mannich reaction for the formation of β^3-amino esters and $\beta^{2,3}$-amino esters is to use *N*-sulfinyl imines, such as **280**, which tend to be air-stable and can be easily prepared via condensation of a sulfinamide with the requisite aldehyde or ketone under mild conditions. Compared to the corresponding *N*-alkyl imines, these compounds are much less prone to tautomerisation, and due to the electron withdrawing nature of the sulfinyl group they are also more electrophilic, and hence more reactive towards nucleophiles, such as enolates.[4] As an added benefit, the chirality associated with the presence of the sulfur atom also enables diastereoselective Mannich-type reactions to give diastereoisomerically pure products. Using this approach, Franklin *et al*. developed an asymmetric imino-aldol reaction between the lithium enolate of EtOAc with *N*-sulfinyl imine **280** (derived from chiral naphthalenesulfinate **279**) giving the major diastereoisomer **281** in 89:11 crude dr, which was isolated in 76% yield and >99:1 dr.[5] Subsequent treatment of **281** with TFA revealed the corresponding β^3-amino ester as its bis-TFA salt **282** in 90% yield and >97% ee (Scheme 89).

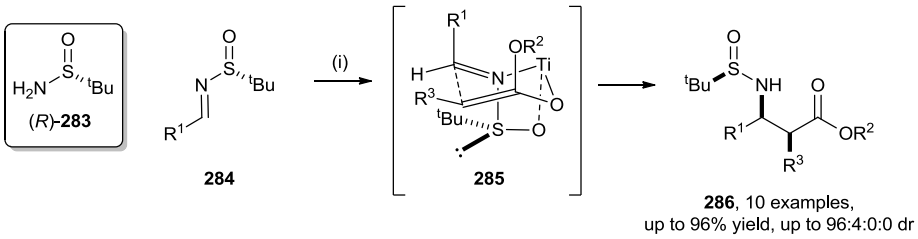


279 **280**, 71%

282, 90%, >97% ee **281**, 76%, >99:1 dr

Scheme 89. *Reagents and Conditions*: (i) LiHMDS, THF, −78 °C, 5 h; (ii) 3-pyridinecarboxaldehyde, CsF, THF, 0 °C to rt, 16 h; (iii) EtOAc, LiHMDS, THF, −78 °C, 6 h; (iv) TFA, EtOH, rt, 2 h.

Alternatively, Ellman *et al.* used *tert*-butylsulfinamide (*R*)-**283**[4] to enable the synthesis of a small range of β^3-amino acid derivatives. Extension of this methodology allowed the synthesis of α-alkyl-$\beta^{2,3}$-amino acid derivatives **286**.[4] Reaction of the titanium enolate of the requisite ester [formed by initial formation of the lithium enolate by treatment of $R^3CH_2CO_2R^2$ with LDA, followed by transmetallation to the titanium enolate by the addition of $ClTi(O^iPr)_3$] with various *N*-*tert*-butylsulfinyl imines **284** gave the desired $\beta^{2,3}$-sulfinamido esters **286** with high diastereoselectivity (up to 96:4:0:0 dr) and good yield (up to 96%). It was proposed that this highly *syn*-selective reaction proceeded via a chelated transition state **285** and upon work-up furnished the desired compounds (Scheme 90).[6]



Scheme 90. *Reagents and Conditions*: (i) $R^3CH_2CO_2R^2$, LDA, $ClTi(O^iPr)_3$, THF, −78 °C, 3 h.

4.3 Chapter Aim

It was envisaged that reaction of chiral *N*-*tert*-butylsulfinyl imine **288** (derived from aldehyde **167**, used for the synthesis of nakinadine B **126**) with a suitable α-phenyl ester enolate **272** would enable the formation of *syn*-α-phenyl-$\beta^{2,3}$-amino acid derivative **290**. Epimerisation of the α-stereocenter or the use of alternative imino-aldol conditions would provide access to the corresponding *anti*-α-phenyl-$\beta^{2,3}$-amino acid derivative **291**. Subsequent elaboration of both these diastereoisomers **290** and **291**, based upon initial *N*-deprotection then reductive *N*-alkylation [using aldehyde **287** (for nakinadine D **128**) or aldehyde **167** (for nakinadine E **129**)], and finally ester hydrolysis, would provide a route to both the diastereoisomers of nakinadines D (**128** and **294**) and E (**129** and **295**) in enantiopure form. An analogous set of reactions could be used for the synthesis of both the diastereoisomers of nakinadines A (**125** and **297**) and F (**130** and **296**) starting with *N*-sulfinyl imine **289** (derived from aldehyde **188**, used for the synthesis of nakinadine C **127**) (Figure 21).

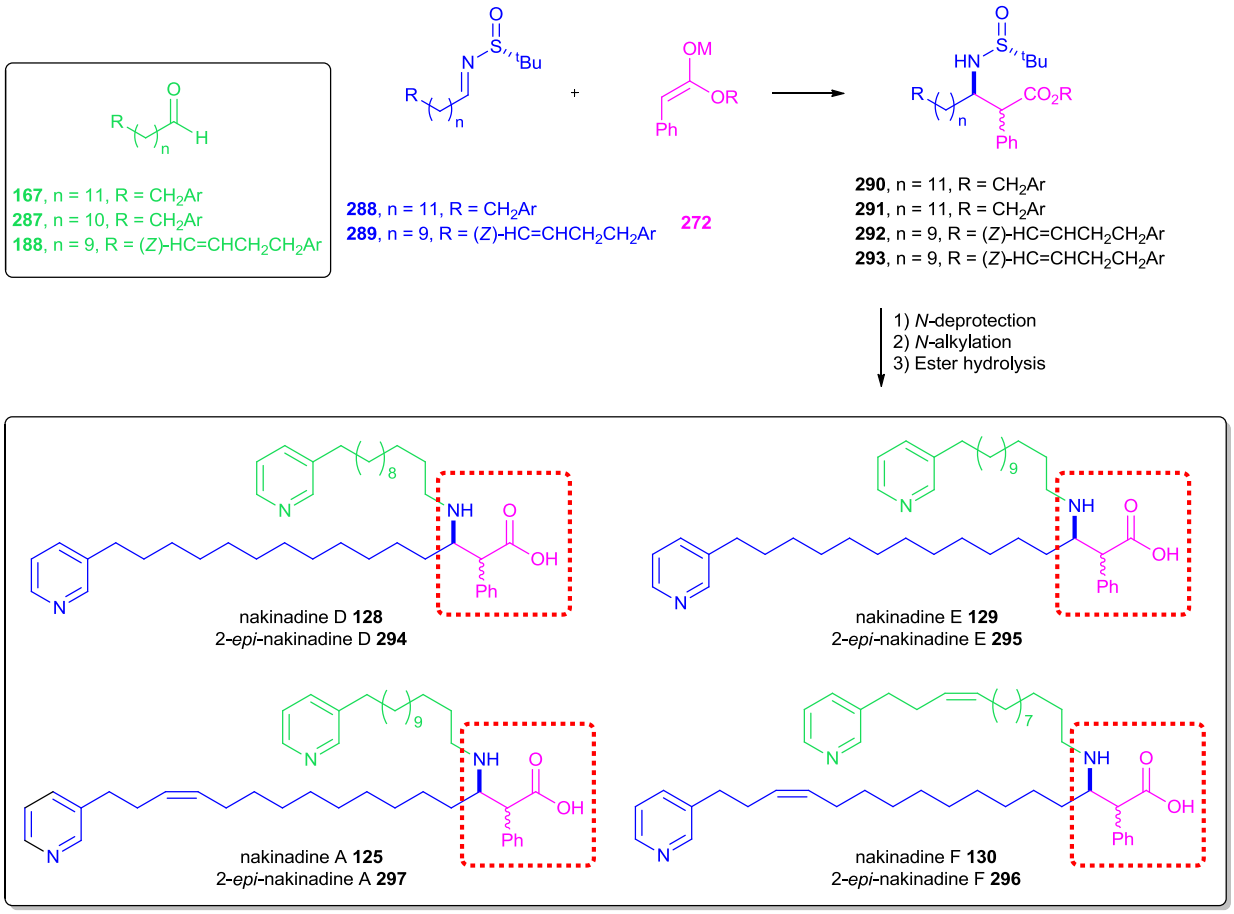
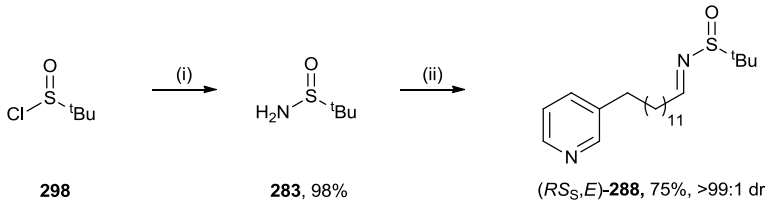


Figure 21. Proposed synthetic route for both diastereoisomers of the remaining members of the nakinadine family. [Ar = pyridin-3-yl].

4.4 Investigation into the imino-aldol reaction of 288

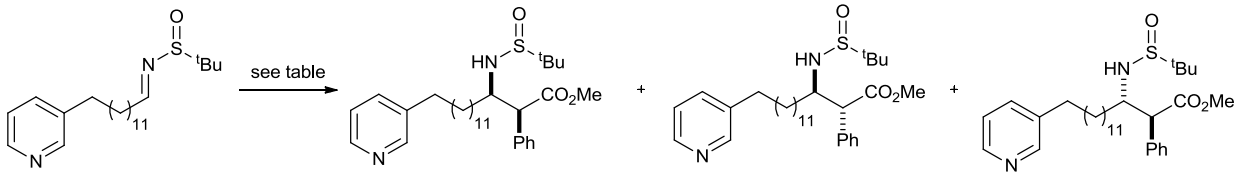
4.4.1 Initial studies using racemic 288

Racemic *N*-*tert*-butylsulfinyl imine **288** was first synthesised via a two step procedure. (RS_S)-*tert*-Butylsulfinyl chloride **298** was initially treated with ammonium hydroxide (35% aq) to give racemic *tert*-butylsulfinamide **283** in 98% yield.[7] Subsequent condensation of **283** with aldehyde **167** (prepared via oxidation of alcohol **157** with IBX) in the presence of $MgSO_4$ and a catalytic amount of PPTS gave (RS_S,*E*)-**288** in 75% yield as a single diasteroisomer (>99:1 dr), which was assigned as the (*E*)-isomer by analogy to previous reports in the literature (Scheme 91).[8]



Scheme 91. *Reagents and Conditions*: (i) NH_4OH (35% aq), CH_2Cl_2, 0 °C, 30 min; (ii) **167**, $MgSO_4$, PPTS, CH_2Cl_2, rt, 16 h.

Following the procedure outlined by Ellman *et al.*,[9] reaction of **288** with the titanium enolate of methyl phenylacetate was initially investigated. Thus, commercially available methyl phenylacetate (1.2 equiv) was treated with LDA (1.3 equiv) at −78 °C then transmetallated to the titanium enolate via the addition of $Ti(O^iPr)_3Cl$ (2.6 equiv), followed by the addition of (RS_S,*E*)-**288** (1.0 equiv). ^{1}H NMR spectroscopic analysis of the crude reaction mixture (in C_6D_6) showed incomplete consumption of **288** (≈37% conversion) after 3 h at −78 °C, resulting in the formation of two species, which were assigned as diastereoisomers **290** and **291**, in the ratio 77:23, respectively. Alongside this, reaction of the lithium enolate derived from methyl phenylacetate was also performed. This reaction resulted in the complete consumption of **288** and furnished a 56:38:6 ratio of three compounds, which were assigned as diastereoisomers **290**, **291** and **299**. Purification via flash column chromatography gave a 93:3:4 mixture of **290**, **291** and **299**, respectively, in 30% combined yield; further elution gave a 97:3 mixture of **291** and **290**, respectively, in 20% combined yield. The relative configurations within **290**, **291** and **299** were later unambiguously assigned by the synthesis of authentic samples of all the four possible diastereoisomers (*vide infra*). It was envisaged that addition of a chelating agent would enhance the diastereoselectivity of the reaction and so the imino-aldol reaction was repeated in the presence of LiCl (5.0 equiv).[10] ^{1}H NMR spectroscopic analysis of the crude reaction mixture revealed a 76:22:2 mixture of **290**, **291** and **299**, respectively, thus increasing the amount of **290** formed (Scheme 92).

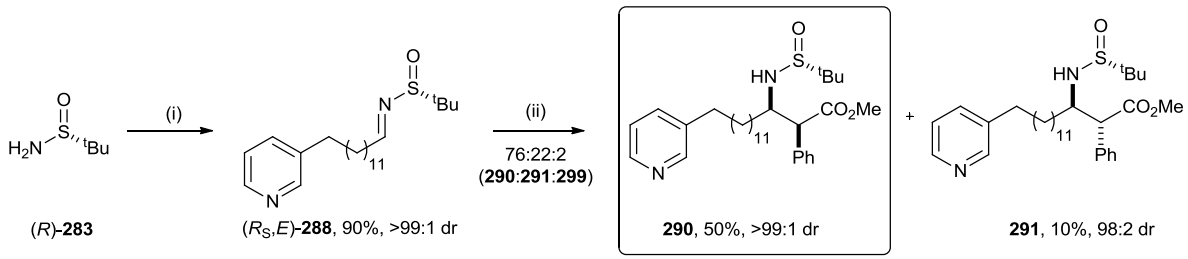


Method	Conversion of 288 (%)	Crude dr (290:291:299)	Yield (%) and purified dr of 290 (290:291:299)	Yield (%) and purified dr of 291 (290:291:299)
(i)	≈37	77:23:0	–	–
(ii)	100	56:38:6	30 (93:3:4)	20 (3:97:0)
(iii)	100	76:22:2	–	–

Scheme 92. *Reagents and Conditions*: (i) methyl phenylacetate, LDA, $Ti(O^iPr)_3Cl$, THF, −78 °C, 3 h; (ii) methyl phenylacetate, LDA, THF, −78 °C, 3 h; (iii) methyl phenylacetate, LiCl, LDA, THF, −78 °C, 3 h.

With a route to racemic **290** developed, enantiopure (R_S,*E*)-**288** was next subjected to this imino-aldol reaction. The requisite enantiopure *N*-*tert*-butylsulfinyl imine **288** was synthesised in 90% yield via a condensation of *tert*-butylsulfinamide (*R*)-**283**[11] with aldehyde **167**. Subsequent reaction with the lithium enolate of methyl phenylacetate in the presence of LiCl gave a 76:22:2 mixture of

290, **291** and **299**, respectively, with complete consumption of **288**. Hence, the reaction of the lithium enolate of methyl phenylacetate with both racemic and enantiopure **288** proceeded with identical diastereoselectivity. Purification of the crude reaction mixture via recrystallisation led to the isolation of **290** in 50% yield and >99:1 dr. Exhaustive chromatographic separation of the mixed fractions led to the isolation of **291** in 10% yield and 98:2 dr (Scheme 93). The relative configuration within **290** was established unambiguously via single crystal X-ray diffraction analysis.[12] As the absolute (R_S)-configuration of the *tert*-butylsulfinamide moiety was known, the absolute (2*S*,3*R*,R_S)-configuration within **290** was unambiguously assigned (Figure 22).



Scheme 93. *Reagents and Conditions*: (i) **167**, $MgSO_4$, PPTS, CH_2Cl_2, rt, 16 h; (ii) methyl phenylacetate, LiCl, LDA, THF, −78 °C, 3 h.

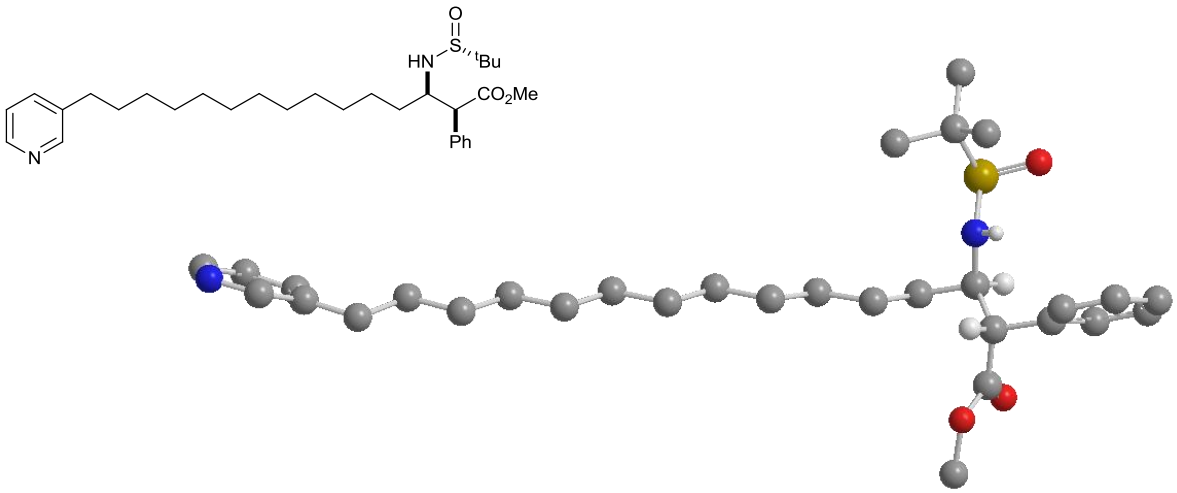
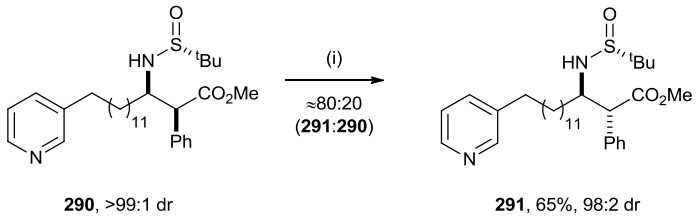


Figure 22. X-ray crystal structure of **290** (selected H atoms are omitted for clarity).

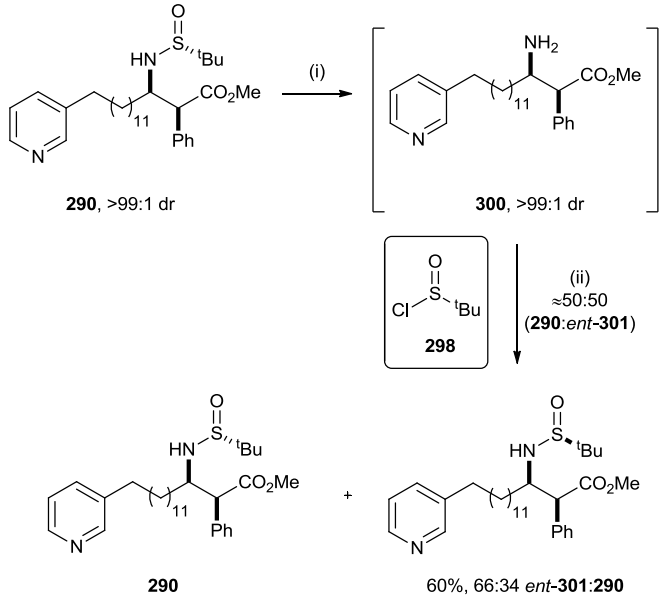
4.4.2 Synthesis of authentic samples of all four possible diastereoisomeric products

In order to unambiguously assign the identities of all four possible diastereoisomers of the imino-aldol reaction, epimerisation of the C(2)-stereocenter within **290** was investigated. Treatment of **290** with Na in MeOH at 0 °C for 8 h gave an ≈80:20 mixture of **291** and **290**, respectively. Purification of this mixture via exhaustive flash column chromatography led to the isolation of **291** in 65% yield and 98:2 dr, thus establishing that **291** and **290** are epimeric at C(2) and so the absolute (*R*,*R*,*R*)-configuration within **291** was also assigned (Scheme 94).



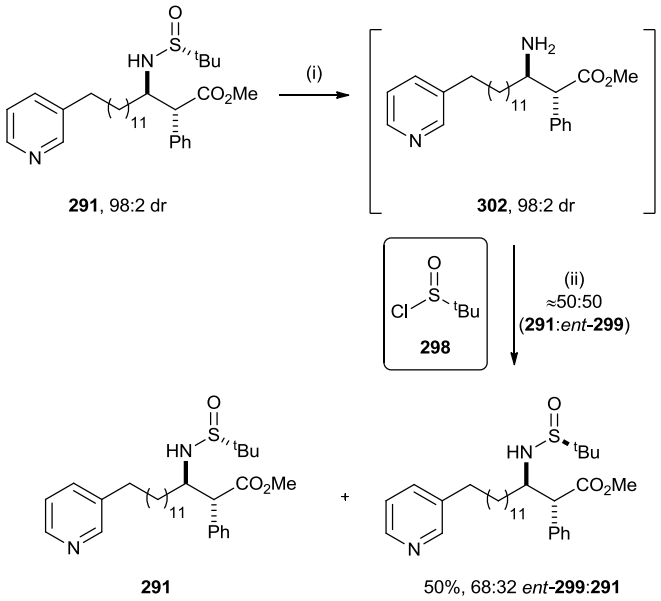
Scheme 94. *Reagents and Conditions*: (i) Na, MeOH, 0 °C, 8 h.

Removal of the *N*-*tert*-butylsulfinamide auxiliary within **290** (>99:1 dr) by treatment with HCl (1.25 M in MeOH) resulted in the formation of primary $\beta^{2,3}$-amino ester **300**, and subsequent treatment of **300** with racemic *tert*-butylsulfinyl chloride **298** (1.0 equiv) led to the formation of an ≈50:50 mixture of **290** and *ent*-**301**. Purification gave a 66:34 mixture of *ent*-**301** and **290** in 60% yield. Thus the absolute (2*S*,3*R*,S_S)-configuration within *ent*-**301** could be assigned, confirming that **301** was not formed during the imino-aldol reaction (Scheme 95).



Scheme 95. *Reagents and Conditions*: (i) HCl (1.25 M in MeOH), rt, 2 h; (ii) *tert*-butylsulfinyl chloride **298**, Et_3N, CH_2Cl_2, rt, 2 h.

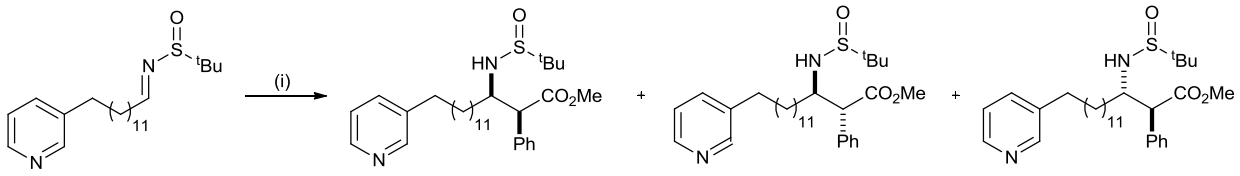
Similarly, **291** (98:2 dr) was treated with HCl (1.25 M in MeOH) to furnish the corresponding $\beta^{2,3}$-amino ester **302**. Comparison of ^{1}H NMR spectra of **300** and **302** in C_6D_6 confirmed the hydrolysis step proceeded, in each case, without any accompanying epimerisation. Reaction of **302** with racemic *tert*-butylsulfinyl chloride **298** (1.0 equiv) gave an ≈50:50 mixture of **291** and *ent*-**299**. Purification gave a 68:32 mixture of *ent*-**299** and **291** in 50% combined yield, thus establishing the absolute (*S*,*S*,*S*)-configuration within *ent*-**299** was established (Scheme 96).



Scheme 96. *Reagents and Conditions*: (i) HCl (1.25 M in MeOH), rt, 2 h; (ii) *tert*-butylsulfinyl chloride **298**, Et_3N, CH_2Cl_2, rt, 2 h.

4.4.3 Optimisation of the imino-aldol reaction

With authentic samples of all four possible diastereoisomeric products of the imino-aldol reaction (**290**, **291**, **299** and **301**) in hand, optimisation of the imino-aldol reaction was examined in order to increase the diastereoselectivity. Initially, this involved investigation into the effect of the metal counter-ion and the presence of chelating agents. Therefore, the requisite base was added to methyl phenylacetate and the stated additive, as applicable, in THF at −78 °C and after 30 min (R_S,*E*)-**288** was added and the reaction mixture was stirred for 3−6 h. The crude product distribution was then assessed by ^{1}H NMR spectroscopic analysis in C_6D_6, as stated. The use of silazide bases (LiHMDS, NaHMDS or KHMDS) in place of LDA resulted in the favourable formation of the *anti*-diastereoisomer **291**. The addition of LiCl (with LiHMDS or KHMDS) as a chelating agent altered the selectivity and greatly enhanced the formation of **290**. The presence of crown ethers (12-crown-4 for LiHMDS or 18-crown-6 for KHMDS) led to a decrease in the overall stereocontrol within the reaction. As an increase in the diastereoselectivity was observed using a chelating additive, the imino-aldol reaction was performed with MeMgBr as the base in conjunction with $MgBr_2$,[13] and after 6 h at −78 °C, complete conversion of **288** was achieved which gave an 86:14 mixture of **290** and **291**, respectively (Scheme 97).



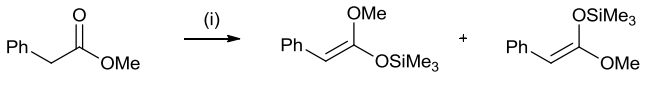
(*RS*$_S$,*E*)-**288**, >99:1 dr **290** **291** **299**

(*RS*$_S$,*E*)-288 (equiv)	Base (equiv)	Additive (equiv)	Time (*t* h)	Temperature (°C)	Conversion of 288 (%)	Crude dr (290, 291:299:301)
1.2	LDA (1.3)	None	3	−78	100	56:38:6:0
1.2	LDA (1.3)	LiCl (5.0)	3	−78	100	76:22:2:0
1.2	LiHMDS (1.3)	None	3	−78	100	32:62:6:0
1.2	NaHMDS (1.3)	None	3	−78	100	31:65:3:1
1.2	KHMDS (1.3)	None	3	−78	100	23:69:7:0
1.2	LiHMDS (1.3)	LiCl (5.0)	3	−78	100	82:15:2:1
1.2	KHMDS (1.3)	LiCl (5.0)	3	−78	100	74:25:1:0
1.2	LiHMDS (1.3)	12-crown-4 (1.5)	3	−78	100	65:29:5:1
1.2	KHMDS (1.3)	18-crown-6 (1.5)	3	−78	100	20:50:25:5
1.3	MeMgBr (1.2)	None	3	−78	42	84:16:0:0
1.3	MeMgBr (1.2)	$MgBr_2$ (5.0)	3	−78	73	86:14:0:0
1.3	MeMgBr (1.2)	$MgBr_2$ (5.0)	6	−78	100	86:14:0:0

Scheme 97. *Reagents and Conditions*: (i) base, additive, THF, −78 °C, 30 min then **288**, −78 °C, *t* h.

In order to provide insight into the origin of these results, the geometry of the intermediate enolates was determined. Treatment of methyl phenylacetate with the same range of bases as previously used (and in the presence of an additive, as necessary) was followed by trapping of the intermediate enolate(s) with TMSCl, giving the known silyl enol ethers (*E*)-**303** and (*Z*)-**304**.[14] ^{1}H NMR spectroscopic analysis of the crude silyl enol ethers in neutralised, anhydrous $CDCl_3$ allowed determination of the enolate geometries.[14] The use of lithium bases LDA and LiHMDS resulted in the formation of predominantly the (*E*)-isomer **303** (80:20 and 85:15 dr, respectively), however interestingly the subsequent imino-aldol reactions show opposing diastereoselectivity. Furthermore, when using KHMDS as the base, the (*Z*)-enolate is formed almost exclusively (97:3 dr) but gives a similar distribution of products as compared to LiHMDS. This suggests that the reaction is not only controlled by the enolate geometry but by the nature of the metal counter-ion in the subsequent

imino-aldol reaction itself. Unfortunately, conversion of the analogous magnesium enolate to **303** and **304** could not be achieved and resulted in the return of starting material only. When silyl enol ether **303** was generated in the presence of LiCl and LiHMDS, the (*E*)-selectivity of the enolate increased a small amount (90:10 dr) but resulted in a marked difference in the selectivity of the corresponding imino-aldol reaction. Interestingly, when LiCl is present during the enolate formation with KHMDS, a 74:26 mixture of (*E*)-**303** and (*Z*)-**304** is formed and the subsequent imino-aldol reaction with **288** produced a 74:25:1 mixture of products **290**, **291** and **299**, respectively (Scheme 98).

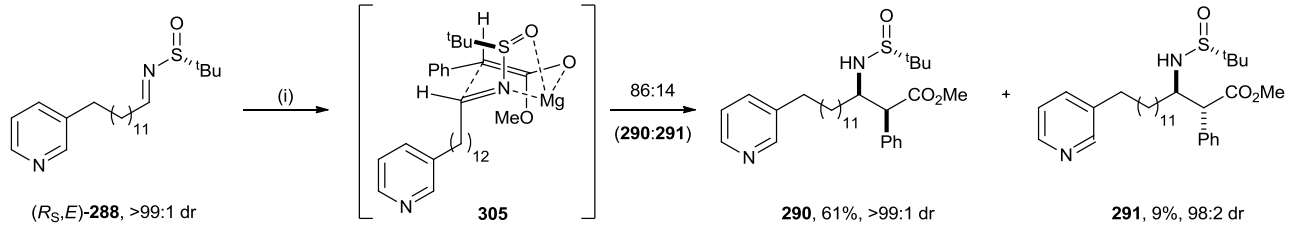


(*E*)-**303** (*Z*)-**304**

Base	Additive	(*E*)-303:(*Z*)-304	Crude dr upon reaction with 288 (290:291:299:301)
LDA	None	80:20	56:38:6:0
LiHMDS	None	85:15	32:62:6:0
LiHMDS	LiCl	90:10	82:15:2:1
KHMDS	None	3:97	23:69:7:0
KHMDS	LiCl	74:26	74:25:1:0
MeMgBr	MgBr	–	86:14:0:0

Scheme 98. *Reagents and Conditions*: (i) base, additive, THF, −78 °C, 30 min then TMSCl, −78 °C to rt, 1 h.

Following the optimised conditions identified above, reaction of (R_S,*E*)-**288** (>99:1 dr) with methyl phenylacetate, MeMgBr and $MgBr_2$ gave an 86:14 mixture of **290** and **291**, respectively. Purification via recrystallisation gave **290** in 61% yield and >99:1 dr. Further purification of the mixed fractions via exhaustive flash column chromatography led to the isolation of **291** in 9% yield and 98:2 dr. The formation of the *syn*-diastereoisomer **290** is entirely consistent with reaction of the intermediate (*E*)-enolate via a chelated transition state **305** (Scheme 99).

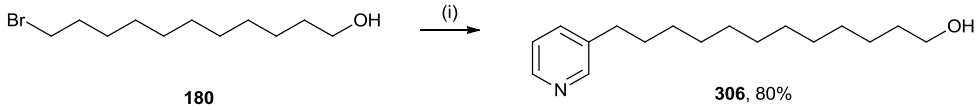


(R_S,*E*)-**288**, >99:1 dr **305** **290**, 61%, >99:1 dr **291**, 9%, 98:2 dr

Scheme 99. *Reagents and Conditions*: (i) methyl phenylacetate, MeMgBr, $MgBr_2$, THF, −78 °C, 6 h.

4.5 Elaboration of 290 to nakinadines D 128 and E 129

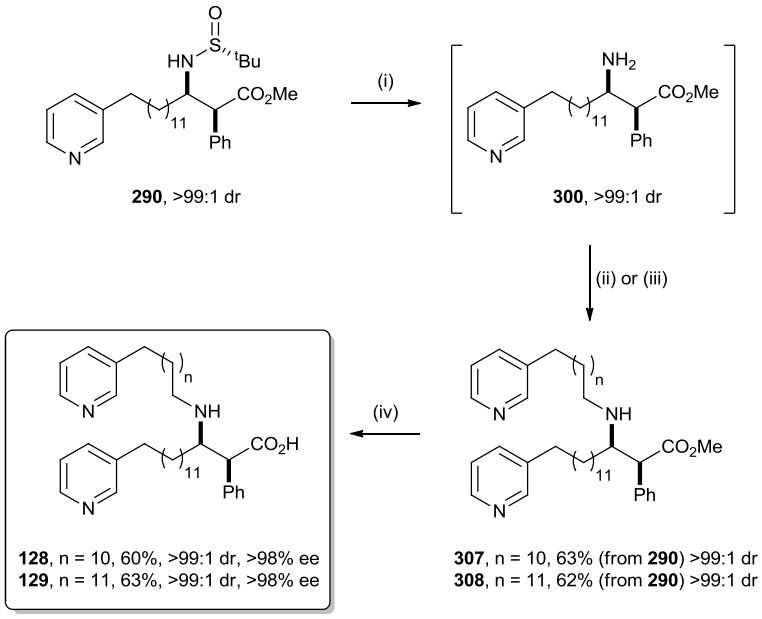
Next, alcohol **306**, which was required to install the *N*-alkyl side-chain within nakinadine D, was synthesised via an analogous strategy to that used for **157**. Coupling of 11-bromoundecan-1-ol **180** with the lithium anion of 3-picoline (prepared via treatment of 3-picoline with LDA in THF at −78 °C) gave **306** in 80% yield (Scheme 100).



180 **306**, 80%

Scheme 100. *Reagents and Conditions*: (i) LDA, 3-picoline, THF, −78 °C to rt, 16 h.

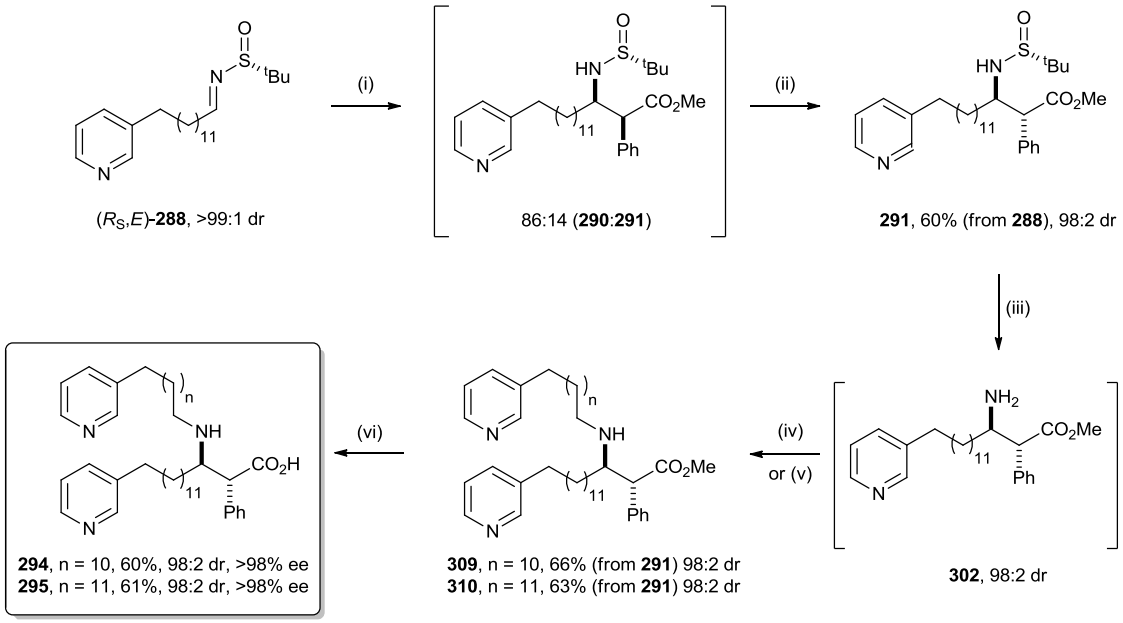
With **290** and alcohols **306** and **157** in hand, a strategy employing *N*-deprotection, reductive *N*-alkylation and finally ester hydrolysis was envisaged to complete the syntheses of nakinadines D **128** and E **129**. As previously established, the facile removal of the *N*-sulfinyl group within **290** can be achieved by the addition of HCl (1.25 M in MeOH) to give the corresponding primary $\beta^{2,3}$-amino ester **300** in >99:1 dr. Subsequent reaction of **300** with the requisite aldehyde **287** or **167** in the presence of AcOH and $NaBH(OAc)_3$ gave the corresponding secondary $\beta^{2,3}$-amino ester **307** or **308** in 62 and 63% yield, respectively, (from **290**) and >99:1 dr in each case. Heating a solution of **307** in HCl (3.0 M aq) to 100 °C for 8 h resulted in the complete hydrolysis of the methyl ester within **307**. Purification of the crude reaction mixture via Amberlite CG-400 ion-exchange chromatography (100-200 mesh, OH^- form) gave an impure sample of **128**. Further purification via flash column chromatography gave nakinadine D **128** {$[\alpha]_D^{20}$ −15.0 (*c* 0.5 in $CHCl_3$)} in 60% yield, >99:1 dr and >98% ee. The enantiomeric excess of **128** is assumed to be >98% ee based on the enantiopurity of the *tert*-butylsulfinamide (*R*)-**283** used. Following a similar experimental and purification procedure gave nakinadine E **129** {$[\alpha]_D^{20}$ −15.2 (*c* 0.5 in $CHCl_3$)} in 63% yield, >99:1 dr and >98% ee.[15] Therefore, nakinadines D **128** and E **129** were synthesised in 15 and 16% overall yield, respectively, over 8 steps from dodecanediol **155** (Scheme 101).



Scheme 101. *Reagents and Conditions*: (i) HCl (1.25 M in MeOH), rt, 2 h; (ii) **287**, $NaBH(OAc)_3$, AcOH, 1,2-DCE, rt, 16 h; (iii) **167**, $NaBH(OAc)_3$, AcOH, 1,2-DCE, rt, 16 h; (iv) HCl (3.0 M aq), 100 °C, 8 h.

4.6 Elaboration of 291 to 2-*epi*-nakinadines D 294 and E 295

The 2-*epi*-diastereoisomer of nakinadines D **294** and E **295** were synthesised from **291** using an analogous approach. A two-step procedure was utilised for the synthesis of **291**, whereby initial reaction of methyl phenylacetate with (*R*)-**288** using MeMgBr and $MgBr_2$ gave an 86:14 mixture of **290** and **291**. The crude reaction mixture was then diluted with MeOH and Na metal was added which gave an ≈80:20 mixture of **291** and **290**, respectively. Purification via exhaustive flash column chromatography gave **291** in 60% yield (from **288**) and 98:2 dr. Deprotection of the *N*-sulfinyl group within **291** via the addition of HCl (1.25 M in MeOH) gave primary $\beta^{2,3}$-amino ester **302** (98:2 dr) which was subsequently reacted with the requisite aldehyde **287** or **167** to furnish **309** or **310** in 66 and 63% yield, respectively, (from **291**) and 98:2 dr in each case. Comparison of the ^{1}H NMR spectra of the 2-*epi*-diastereoisomers **309** and **310** with the corresponding **307** and **308** confirmed no epimerisation had occurred during either of the steps. Complete hydrolysis of the methyl ester within **309** was achieved via the addition of HCl (3.0 M aq) and following purification, gave 2-*epi*-nakinadine D **294** {$[\alpha]_D^{20}$ +8.0 (*c* 1.0 in $CHCl_3$)} in 60% yield, 98:2 dr and >98% ee.[15] Similarly, treatment of **310** with HCl (3.0 M aq) gave 2-*epi*-nakinadine E **295** {$[\alpha]_D^{20}$ +8.4 (*c* 1.0 in $CHCl_3$)} in 61% yield, 98:2 dr and >98% ee.[15] Therefore, 2-*epi*-nakinadines D **294** and E **295** were synthesised in 16 and 15% overall yield, respectively, over 9 steps from dodecanediol **155** (Scheme 102).



Scheme 102. *Reagents and Conditions*: (i) methyl phenylacetate, MeMgBr, $MgBr_2$, THF, −78 °C, 6 h; (ii) Na, MeOH, 0 °C, 8 h; (iii) HCl (1.25 M in MeOH), rt, 2 h; (iv) **287**, $NaBH(OAc)_3$, AcOH, 1,2-DCE, rt, 16 h; (v) **167**, $NaBH(OAc)_3$, AcOH, 1,2-DCE, rt, 16 h; (vi) HCl (3.0 M aq), 100 °C, 8 h.

4.7 Synthesis of nakinadines A (125 and 297) and F (130 and 296)

As the reported structures of nakinadines A **125** and F **130** are very similar to those reported for nakinadines D **128** and E **129**, a complementary strategy involving the reaction of the magnesium enolate of methyl phenylacetate with chiral, unsaturated *N*-sulfinyl imine **289** was envisaged as the key step. In addition to the unsaturation within the ω-(pyridin-3-yl)alkanoic acid residue, nakinadine F **130** also contains an unsaturated *N*-ω-(pyridin-3-yl)alkyl chain. These features introduce the added possibility of geometric isomers for these alkaloids although they were not targeted in this case (Figure 23).

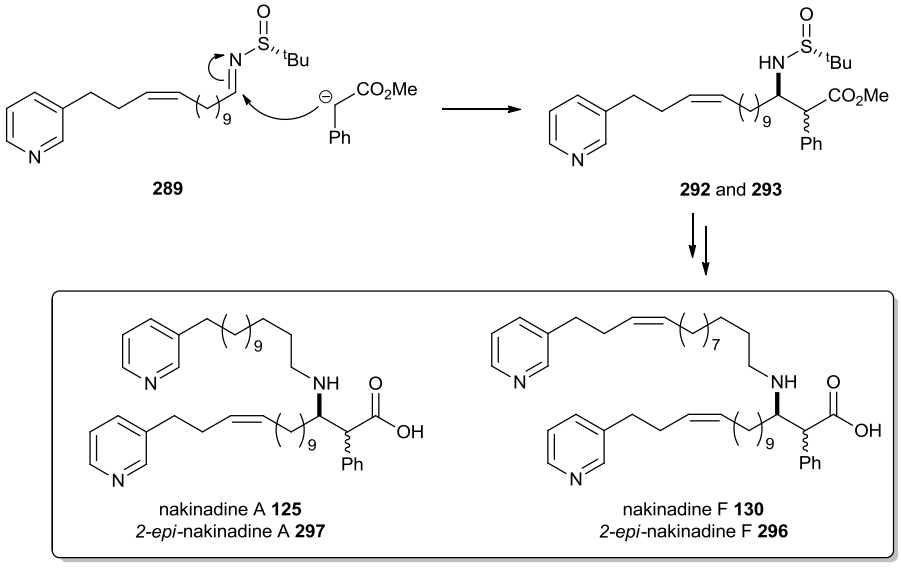
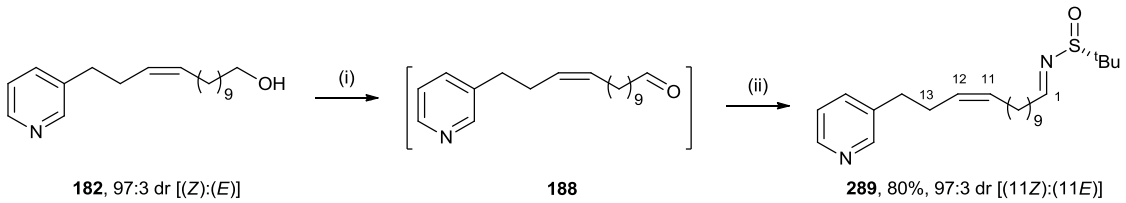


Figure 23. Synthetic route to nakinadines A (**125** and **297**) and F (**130** and **296)**.

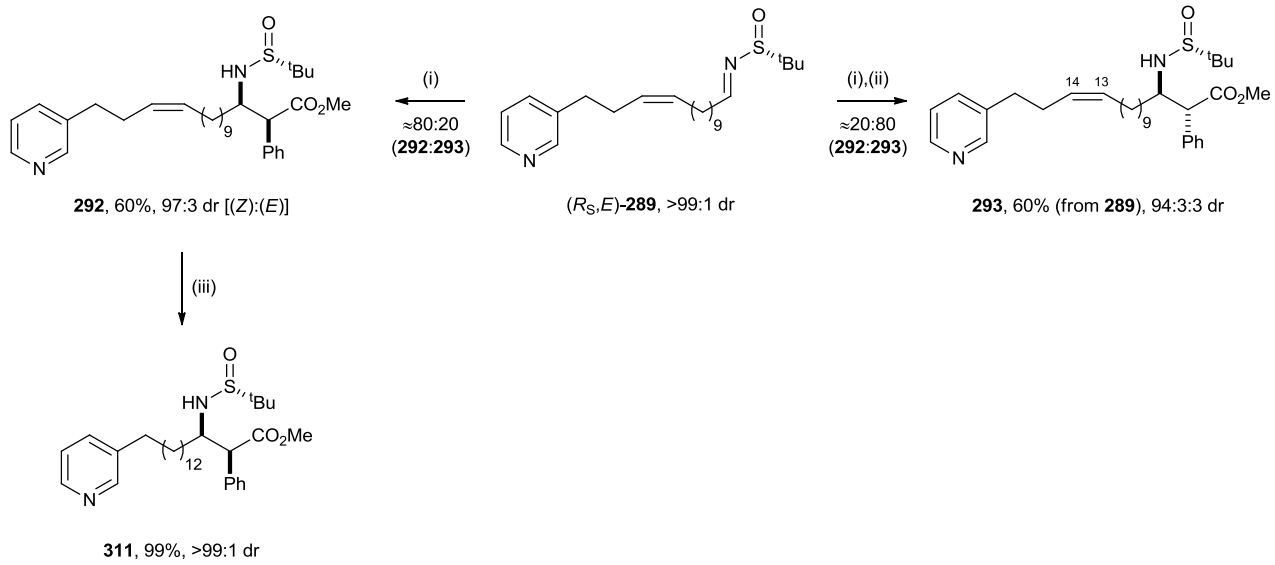
Oxidation of unsaturated alcohol **182** [97:3 dr (*Z*):(*E*)] gave aldehyde **188**, which was subsequently reacted with *N*-*tert*-butylsulfinamide (*R*)-**283** to give *N*-sulfinyl imine **289** in 80% yield and 97:3 dr [(11*Z*):(11*E*)]. The (*Z*):(*E*) ratio was determined by ^{1}H NMR spectroscopic analysis via integration of the resonances corresponding to the allylic protons [C(10)H_2 and C(13)H_2] in C_6D_6 on a 700 MHz spectrometer. Therefore, the imine fragment was formed with complete (*E*)-selectivity in this reaction, which is consistent with previously reported examples[8] (Scheme 103).



182, 97:3 dr [(*Z*):(*E*)] **188** **289**, 80%, 97:3 dr [(11*Z*):(11*E*)]

Scheme 103. *Reagents and Conditions*: (i) IBX, EtOAc, 80 °C, 3 h; (ii) (*R*)-**283**, $MgSO_4$, PPTS, CH_2Cl_2, rt, 16 h.

Addition of MeMgBr to a solution of methyl phenylacetate and $MgBr_2$ in THF followed by addition of **289** furnished an ≈80:20 mixture of **292** and **293**, respectively. Purification via exhaustive flash column chromatography gave **292** in 60% yield and 97:3 dr [(*Z*):(*E*)] and a sample of **293**, which was isolated in 10% yield and 94:3:3 dr [a mixture of the (2*S*,3*R*,13*Z*), (2*S*,3*R*,13*E*) and (2*R*,3*R*,13*Z*) diastereoisomers, respectively]. Reaction of **288** with methyl phenylacetate, MeMgBr and $MgBr_2$, followed by treatment of the crude reaction mixture with Na in MeOH at 0 °C gave an ≈20:80 mixture of **292** and **293**, respectively. Purification led to the isolation of a 94:3:3 mixture of (2*S*,3*R*,13*Z*), (2*S*,3*R*,13*E*) and (2*R*,3*R*,13*Z*) diastereoisomers, respectively, in 60% combined yield (from **289**). Hydrogenation of the double bond within **292**, gave saturated ester **311** in 99% yield and >99:1 dr, thus establishing that the 97:3 diastereoisomeric ratio within **292** related to the (*Z*):(*E*) ratio of the olefin (Scheme 104). The relative configuration within **311** was established unambiguously via single crystal X-ray diffraction analysis.[16] As the absolute (R_S)-configuration of the *N*-*tert*-butylsulfinamide auxiliary was known, the absolute (2*S*,3*R*,R_S)-configuration within **311** was thus unambiguously assigned, and hence, the absolute (2*S*,3*R*,R_S,*Z*)- and (*R*,*R*,*R*,*Z*)-configurations within **292** and **293** (the C(2)-epimer of **292**) were also assigned (Figure 24).



Scheme 104. *Reagents and Conditions*: (i) methyl phenylacetate, MeMgBr, $MgBr_2$, THF, −78 °C, 6 h; (ii) Na, MeOH, 0 °C, 8 h; (iii) H_2, $Pd(OH)_2$/C, MeOH, rt, 24 h.

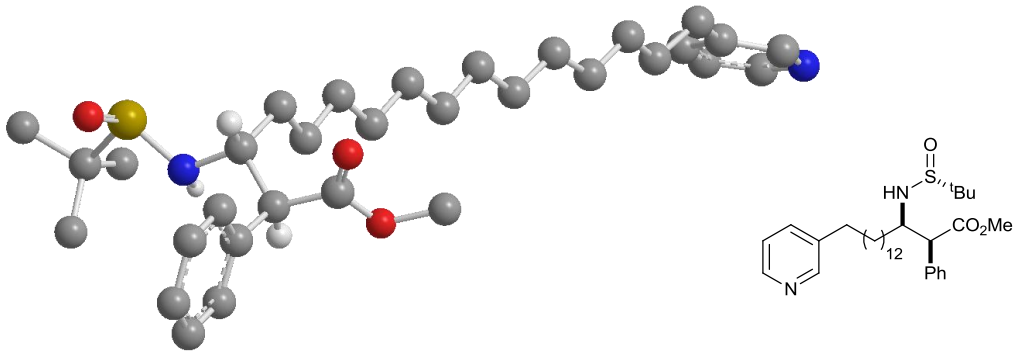
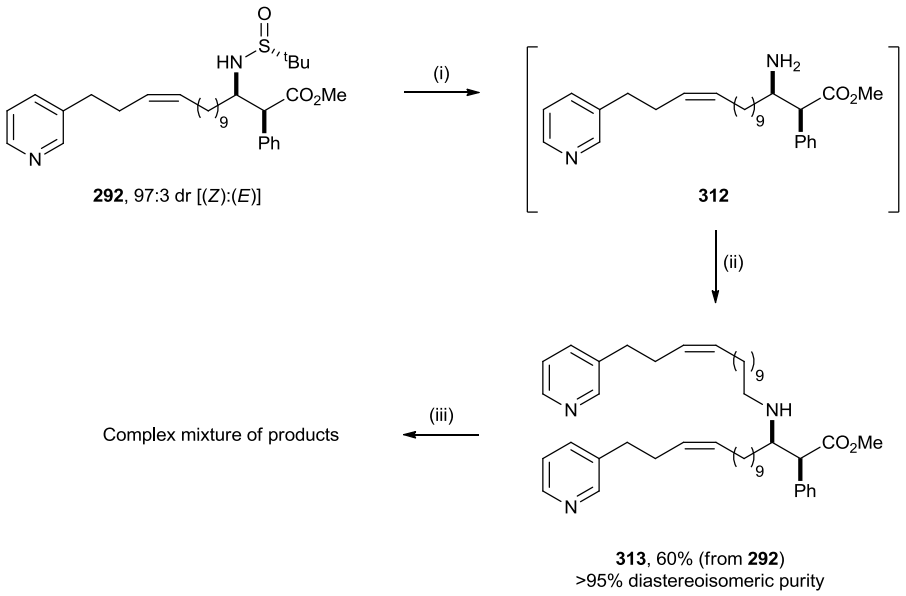


Figure 24. X-ray crystal structure of **311** (selected H atoms are omitted for clarity).

4.7.1 Elaboration of 292 to nakinadine F 130

Removal of the *N*-sulfinyl group within **292** via treatment with HCl (1.25 M in MeOH) gave **312** which was subsequently reacted with aldehyde **188** to give secondary $\beta^{2,3}$-amino ester **313** in 60% yield and >95% diastereoisomeric purity.[17] Unfortunately, attempted saponification of **313** using HCl (3.0 M aq) at 100 °C resulted in the formation of a complex mixture of products. Integration of peaks corresponding to the C=C double bond in the ^{1}H NMR spectrum of the crude reaction mixture showed that they had significantly decreased in intensity as compared to the remainder of the signals, suggesting that the C=C bonds may have undergone side-reactions. ESI mass spectrometric analysis of the crude reaction mixture showed peaks corresponding to the desired amino acid product **130**, alongside peaks consistent with the presence of hydration products of one

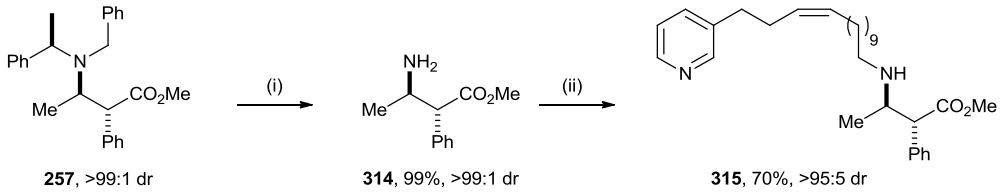
{[M+18]$^+$} or both {[M+36]$^+$} the C=C double bonds. The crude reaction mixture could not be further purified (Scheme 105).



Scheme 105. *Reagents and Conditions*: (i) HCl (1.25 M in MeOH), rt, 2 h; (ii) **188**, $NaBH(OAc)_3$, AcOH, 1,2-DCE, rt, 16 h; (iii) HCl (3.0 M aq), 100 °C, 8 h.

4.7.1.1 Model system for saponification

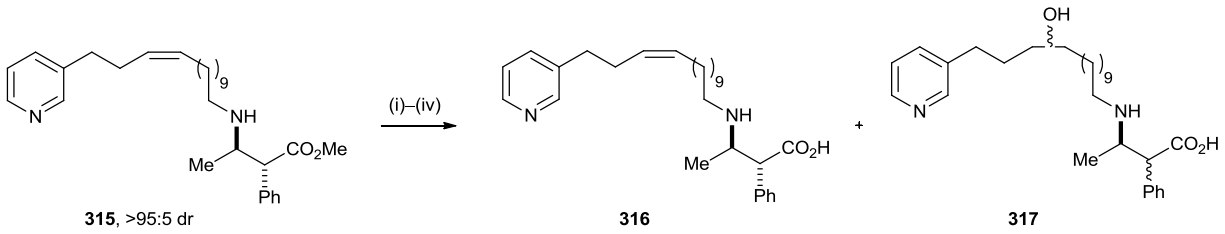
To determine the fate of the C=C double bond during the final hydrolysis step a model system was devised based upon a related *N*-[14-(pyridin-3-yl)tetradec-11-en-1-yl]-$\beta^{2,3}$-amino ester **315**. Hydrogenolysis of the *N*-benzyl and *N*-(α-methylbenzyl) groups within **257** (>99:1 dr) gave α-phenyl-$\beta^{2,3}$-amino ester **314** in 99% yield and >99:1 dr. Subsequent reductive *N*-alkylation with aldehyde **188** gave secondary $\beta^{2,3}$-amino ester **315** in 70% yield and >95:5 dr (Scheme 106).



Scheme 106. *Reagents and Conditions*: (i) H_2 (5 atm), $Pd(OH)_2$/C, MeOH, rt, 24 h; (ii) **188**, $NaBH(OAc)_3$, AcOH, 1,2-DCE, rt, 16 h.

Heating a solution of **315** in HCl (3.0 M aq) at 100 °C for 8 h resulted in the formation of several compounds. Initial purification via Serdolit® CG-400 I ion-exchange chromatography (100-200 mesh, OH^- form) followed by further purification via flash column chromatography gave **316** in 11% yield and >95:5 dr. Further elution gave a sample of a species which was tentatively assigned as **317** (of unknown regio and stereochemistry), in 30% yield, resulting from the possible addition

of H_2O with the C=C double bond. There are several literature procedures which have been used for the hydrolysis of methyl esters without accompanying epimerisation and these were tested with **315**. Use of Me_3SnOH[18] resulted in only return of starting material. Although using $KOSiMe_3$[19] did not result in the formation of any of side-product **317**, extensive epimerisation was observed, with **316** being isolated in 45% yield as an ≈55:45 mixture of C(2)-epimers in this case. Finally, using HCl (3.0 M aq) at a reduced temperature (70 °C) facilitated complete consumption of **315** after 80 h, without any of the hydrated compound **317** being observed by ESI mass spectrometric analysis, and with the signal intensity of the peaks corresponding to the olefinic protons matching those of the rest of the compound in the ^{1}H NMR spectrum of the crude reaction mixture. Purification of the crude reaction mixture gave **316** in 55% yield, without any detectable epimerisation (>95:5 dr) (Scheme 107).



315, >95:5 dr **316** **317**

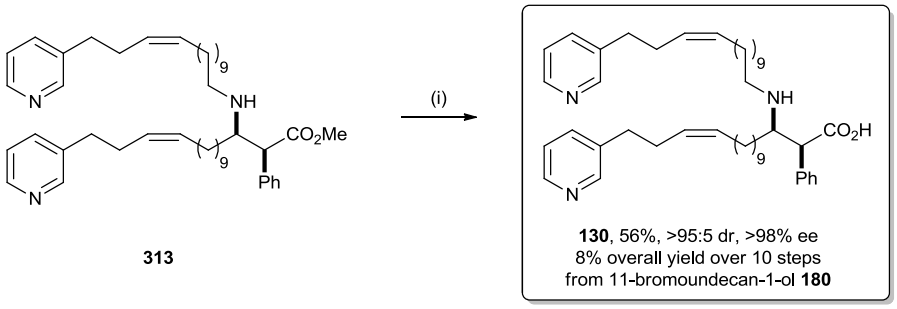
Method	Yield of 316 (%)	Yield of 317 (%)
(i)	11 (>95:5 dr)	30
(ii)	0	0
(iii)	45 (≈55:45 dr)	0
(iv)	55 (>95:5 dr)	0

Scheme 107. *Reagents and Conditions*: (i) HCl (3.0 M aq), 100 °C, 8 h; (ii) Me_3SnOH, 1,2-DCE, 80 °C, 48 h; (iii) $KOSiMe_3$, Et_2O, rt, 24 h; (iv) HCl (3.0 M aq), 70 °C, 80 h.

4.7.1.2 Synthesis of nakinadine F 130 using optimised conditions

With an improved procedure in hand, hydrolysis of **313** was attempted. Treatment of **313** with HCl (3.0 M aq) at 70 °C and purification of the crude reaction mixture via Serdolit® CG-400 I ion-exchange chromatography (100-200 mesh, OH^- form) followed by further purification via flash column chromatography gave **130** {$[\alpha]_D^{20}$ −15.1 (*c* 1.0 in $CHCl_3$)} in 56% yield, >95:5 dr and >98% ee.[15] The diastereoisomeric purity of **130** could not be determined more accurately due to overlapping signals in the ^{1}H NMR spectrum, although comparison of the spectra for **130** with those for 2-*epi*-nakinadine F **296** (subsequently prepared, *vide infra*) showed no epimerisation at the

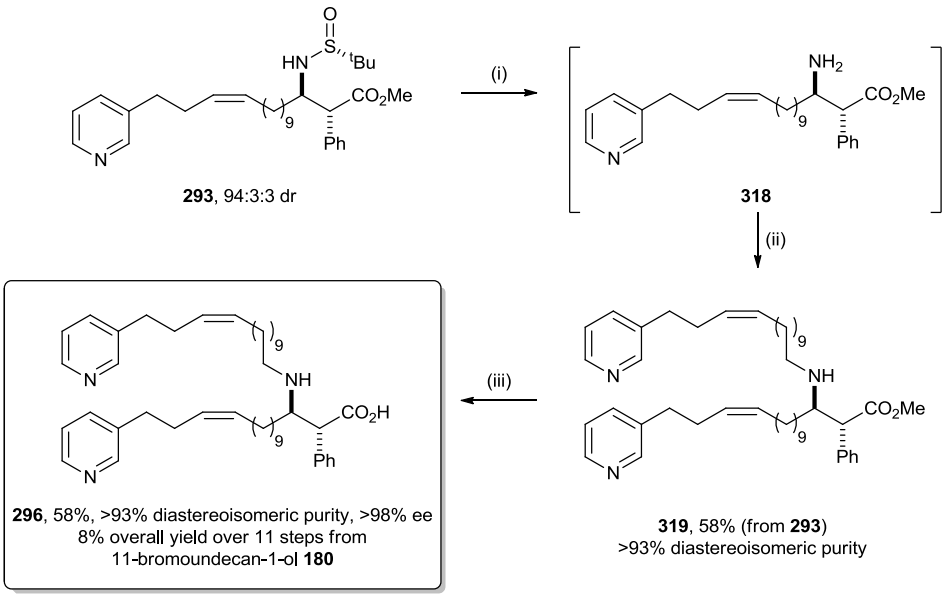
α-stereocenter had occurred. Therefore, nakinadine F **130** was synthesised in 8% overall yield over 10 steps from 11-bromoundecan-1-ol **180** (Scheme 108).



Scheme 108. *Reagents and Conditions*: (i) HCl (3.0 M aq), 70 °C, 80 h.

4.7.2 Elaboration of 293 to 2-*epi*-nakinadine F 296

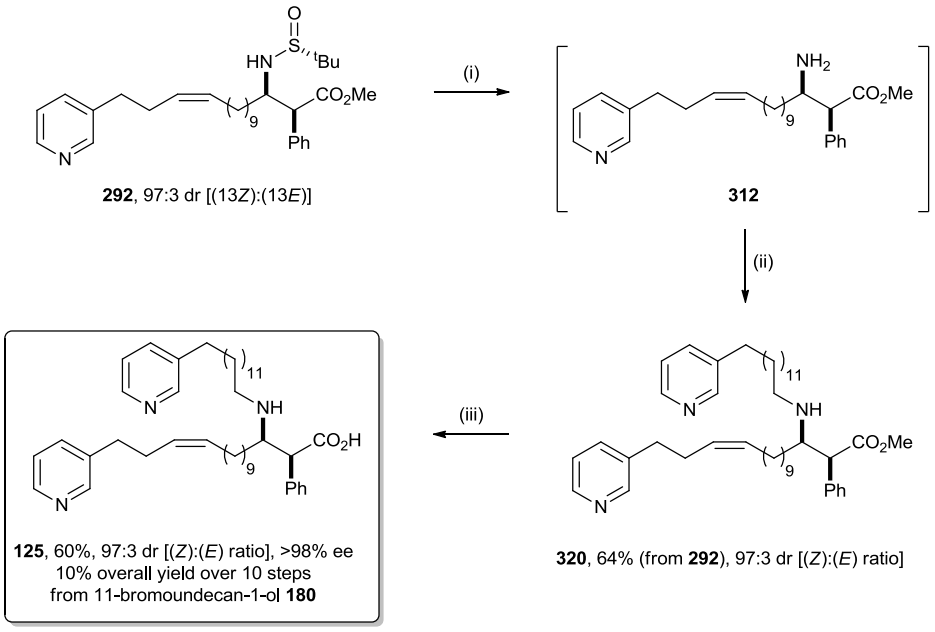
With an optimised route to nakinadine F **130** secured, the synthesis of 2-*epi*-nakinadine F **296** was undertaken. Deprotection of the *N*-sulfinyl group within **293** via reaction with HCl (1.25 M in MeOH) gave **318** which was subsequently reacted with aldehyde **188** to give **319** in 58% yield (from **293**) and >93% diastereoisomeric purity.[20] Hydrolysis of the methyl ester moiety within **319** via treatment with HCl (3.0 M aq) and purification of the crude reaction mixture via Serdolit® CG-400 I ion-exchange chromatography (100-200 mesh, OH^- form) followed by further purification via flash column chromatography gave **296** {$[\alpha]_D^{20}$ +8.1 (*c* 1.0 in $CHCl_3$)} in 58% yield, >93% diastereoisomeric purity and >98% ee.[15] Therefore, 2-*epi*-nakinadine F **296** was synthesised in 8% overall yield over 11 steps from 11-bromoundecan-1-ol **180** (Scheme 109).



Scheme 109. *Reagents and Conditions*: (i) HCl (1.25 M in MeOH), rt, 2 h; (iv) **188**, $NaBH(OAc)_3$, AcOH, 1,2-DCE, rt, 16 h; (iii) HCl (3.0 M aq), 70 °C, 80 h.

4.7.3 Elaboration of 292 to nakinadine A 125

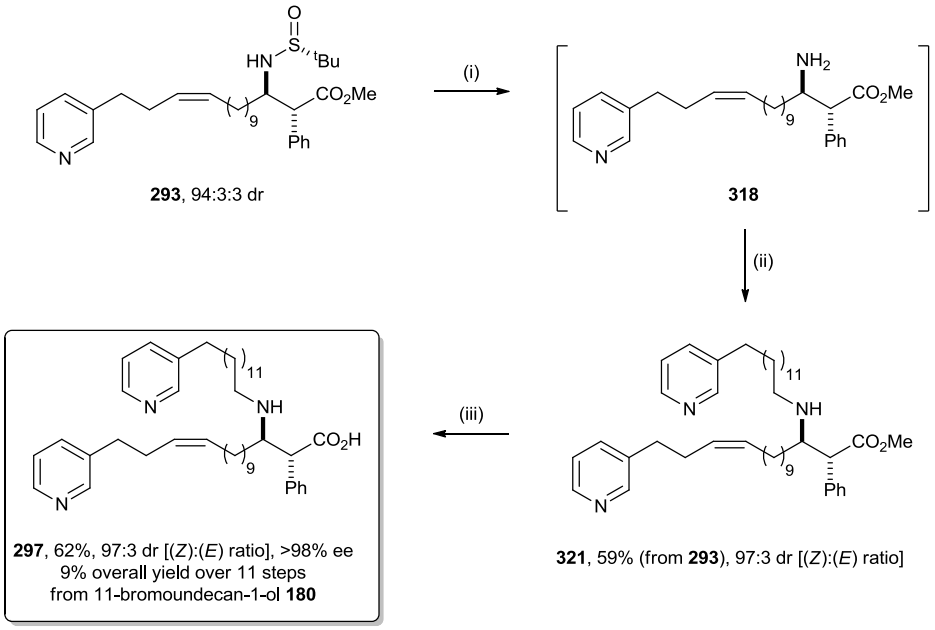
The synthesis of nakinadine A **125** was next targeted. Thus, reaction of **292** [97:3 dr (*Z*):(*E*)] with HCl (1.25 M in MeOH) gave **312** which was then reacted with aldehyde **167** to give **320** in 64% yield and 97:3 dr [(*Z*):(*E*) ratio]. The (*Z*):(*E*) ratio was determined by ^{1}H NMR spectroscopic analysis and integration of the resonances corresponding to the allylic protons [C(12)H_2 and C(15)H_2] in C_6D_6 on a 700 MHz spectrometer. Finally, hydrolysis of **320**upon treatment with HCl (3.0 M aq) at 70 °C followed by sequential purification via Serdolit CG-400 I ion exchange chromatography (100-200 mesh, OH^- form) and silica gel chromatography gave **125** in 60% yield, 97:3 dr [(*Z*):(*E*) ratio] and >98% ee.[15] Therefore, nakinadine A **125** was synthesised in 10% overall yield over 10 steps from 11-bromoundecan-1-ol **180** (Scheme 110).



Scheme 110. *Reagents and Conditions*: (i) HCl (1.25 M in MeOH), rt, 2 h; (ii) **167**, $NaBH(OAc)_3$, AcOH, 1,2-DCE, rt, 16 h; (iii) HCl (3.0 M aq), 70 °C, 80 h.

4.7.4 Elaboration of 293 to 2-*epi*-nakinadine A 297

Lastly, the synthesis of 2-*epi*-nakinadine A **297** was targeted. Reaction of **293** (94:3:3 dr) with HCl (1.25 M in MeOH) gave **318** which was then reacted with aldehyde **167** to give **321**, which after purification was isolated in 59% yield and 97:3 dr [(*Z*):(*E*) ratio]. Final hydrolysis of **321** upon treatment with HCl (3.0 M aq) at 70 °C followed by sequential purification via Serdolit CG-400 I ion exchange chromatography (100-200 mesh, OH^- form) and silica gel chromatography gave **297** in 62% yield, 97:3 dr [(*Z*):(*E*) ratio] and >98% ee.[15] Therefore, 2-*epi*-nakinadine A **297** was synthesised in 9% overall yield over 11 steps from 11-bromoundecan-1-ol **180** (Scheme 111).



Scheme 111. *Reagents and Conditions*: (i) HCl (1.25 M in MeOH), rt, 2 h; (ii) **167**, $NaBH(OAc)_3$, AcOH, 1,2-DCE, rt, 16 h; (iii) HCl (3.0 M aq), 70 °C, 80 h.

4.8 Conclusion

Both the *syn*- and *anti*-diastereoisomers of the reported structures of nakinadines A (**125** and **297**) and D−F (**128**−**130** and **294**−**296**) have been synthesised in 8−16% overall yield in 11 steps or fewer in all cases, from commercially available dodecanediol **155** or 11-bromoundecan-1-ol **180**. With all synthetic samples in hand, a comparison of the spectroscopic data with those reported for the natural products was undertaken, the results of which are outlined in the next chapter.

4.9 References and notes

[1] For a review on the Mannich reaction, see: Thompson, B. B. *J. Pharm. Sci.* **1968**, *57*, 715.
[2] (a) van Marle, C. M.; Tollens, B. *Ber.* **1903**, *36*, 1351. (b) Petrenko-Kritschenko, P.; Zoneff, N. *Ber.* **1906**, *39*, 1358. (c) Mannich, C.; Krosche, W. *Arch. Pharm.* **1912**, *250*, 647.
[3] Arend, M.; Westermann, B.; Risch, N. *Angew. Chem. Int. Ed.* **1998**, *37*, 1044.
[4] For a review on the synthesis and application of *tert*-butyl sulfinamide, see: Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600.
[5] Davis, F. A.; Szewczyk, J. M.; Reddy, R. E. *J. Org. Chem.* **1996**, *61*, 2222.
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[10] Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfield, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.
[11] The enantiopurity of (*R*)-**283** was >98% ee (purchased from Acros).
[12] X-ray crystal structure determination of **290** was carried out by Dr. Jim Thomson and Dr. Ai Fletcher.
[13] Claridge, T. D. W.; Davies, S. G.; Lee, J. A.; Nicholson, R. L.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Toms, S. M. *Org. Lett.* **2008**, *10*, 5437.
[14] Harker, W. R. R.; Carbery, D. R.; Carswell, E. L. *Org. Lett.* **2010**, *12*, 3712.
[15] The ee is assumed to be >98% based on the enantiopurity of the *tert*-butylsulfinamide (*R*)-**283** used.
[16] X-ray crystal structure determination of **311** was carried out by Dr. Amber Thompson and Dr. Ai Fletcher .
[17] The diastereoisomeric purity refers to the ratio of (2*S*,3*R*,13*Z*,11′*Z*) to all other possible diastereoisomers.
[18] Nicolaou, K. C.; Estrada, A. A.; Zak, M.; Lee, S. H.; Safina, B. S. *Angew. Chem. Int. Ed.* **2005**, *44*, 1378.

[19] (a) Laganis, E. D.; Chenard, B. L. *Tetrahedron Lett*. **1984**, *25*, 5831. (b) Polyak, F.; Lubell, W. D. *J. Org. Chem.* **2001**, *66*, 1171. (c) Motorina, I. A.; Huel, C.; Quiniou, E.; Mispelter, J.; Adjadj, E.; Grierson, D. S. *J. Am. Chem. Soc.* **2001**, *123*, 8.

[20] The diastereoisomeric purity refers to the ratio of (2*S*,3*R*,13*Z*,11′*Z*) to all other possible diastereoisomers.

Chapter 5: Stereochemical assignment of the nakinadine alkaloids

With synthetic samples of all the nakinadine alkaloids in hand, a comparison of the spectroscopic data with those reported for the natural samples was undertaken to confirm the structural assignments and establish the relative and absolute configurations within each natural product.

5.1 Structural assignment of nakinadines B and C

5.1.1 Nakinadine B

Kobayashi *et al.* elucidated the gross structures of nakinadine B **126** through a combination of IR and NMR spectroscopic analyses alongside MS/MS fragmentation analysis.[1] Through a similar analysis, the structural assignment of (*S*)-**126** was also determined. The ESI MS/MS fragmentation patterns of the synthetic sample of (*S*)-**126** with those reported for the natural product were almost identical, apart from the fragment at *m/z* 275 observed for the natural sample ($C_{18}H_{31}N_2^+$; i.e., $ArC_{13}H_{26}NH^+$ [Ar = 3-pyridyl]) being replaced by *m/z* 277 for (*S*)-**126** ($C_{18}H_{33}N_2^+$; i.e., $ArC_{13}H_{26}NH_3^+$ [Ar = 3-pyridyl]) (Figure 25).

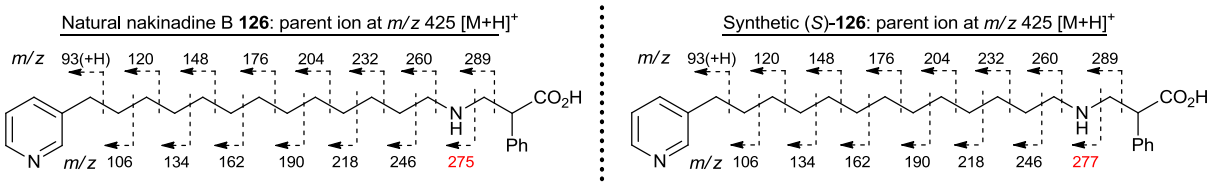


Figure 25. Comparison of ESI MS/MS fragmentation data for natural and synthetic nakinadine B **126**.

In the IR spectrum of nakinadine B **126**, Kobayashi *et al*. reported the presence of absorption bands at 3400–2600 cm^{-1} and 1733 cm^{-1} which were attributed to "the presence of carboxylic acid functionality".[1] However, these bands are inconsistent with an amino acid in its zwitterionic form.[2] Furthermore, absorptions around 1730 cm^{-1} were absent in the IR spectrum of synthetic (*S*)-**126**, and instead the presence of strong absorptions at 1653 and 1560 cm^{-1} were observed. These absorptions are consistent with numerous previously reported examples of zwitterionic β-amino acids by Davies *et al*.[3] An IR absorption at 1731 cm^{-1} was noted for the corresponding HCl salt of of (*S*)-**126**. Comparison of the ^1H NMR spectroscopic data of (*S*)-**126** (9 mM in $CDCl_3$) with those reported for the natural product **126** (unknown concentration in $CDCl_3$)[1] showed good agreement; the only difference was noticed for the resonance corresponding to C(18)H_2 of (*S*)-**126** which appeared as part of a multiplet centred on δ_H 1.65 ppm, and did not overlap with the resonances

associated with the other protons of the long aliphatic chain [C(9)H_2−C(17)H_2] at δ_H 1.20 ppm, as reported for the natural product (Figure 26).

	Proton #	Natural nakinadine B 126 600 MHz, δ_H (ppm)	Synthetic (*S*)-126 400 MHz, δ_H (ppm)
pyridin-3-yl moiety	2-H, 6-H	8.43 (2H, m)	8.44 (2H, m)
	4-H	7.48 (1H, m)	7.49 (1H, app dt)
	5-H	7.18 (1H, m)	7.20 (1H, m)
alkyl chain	7-H_2	2.59 (2H, m)	2.60 (2H, m)
	8-H_2	1.60 (2H, m)	1.65 (4H, m)
	9−17-H_2	1.20 (20H, m)	1.27 (18H, m)
	18-H_2	1.20 (20H, m)	1.65 (4H, m)
	19-H_2	2.89 (3H, br s)	2.95 (3H, m)
β-amino acid moiety	21-H_A	2.89 (3H, br s)	2.95 (3H, m)
	21-H_B	3.47 (1H, br s)	3.41 (1H, m)
	22-H	4.10 (1H, br s)	4.04 (1H, dd)
phenyl ring	25-H, 29-H	7.33 (2H, m)	7.38 (2H, m)
	26-H, 28-H	7.26 (2H, m)	7.31 (2H, m)
	27-H	7.20 (1H, m)	7.24 (1H, m)

Figure 26. ^{1}H NMR data comparison of (*S*)-**126** (9 mM in $CDCl_3$) with natural nakinadine B **126** (unknown concentration in $CDCl_3$). The numbering convention adopted by Kobayashi *et al*. has also been adopted here.

Interestingly, the ^{1}H NMR spectrum of (*S*)-**126** displayed a concentration dependence: when the spectrum was recorded at 9 mM the peaks associated with C(19)H_2 and C(21)H_A appeared as a 3H multiplet (centered on δ_H 2.95 ppm) but with increasing concentration became resolved into three distinct multiplets. The remainder of the spectrum remained essentially unchanged (Figure 27).

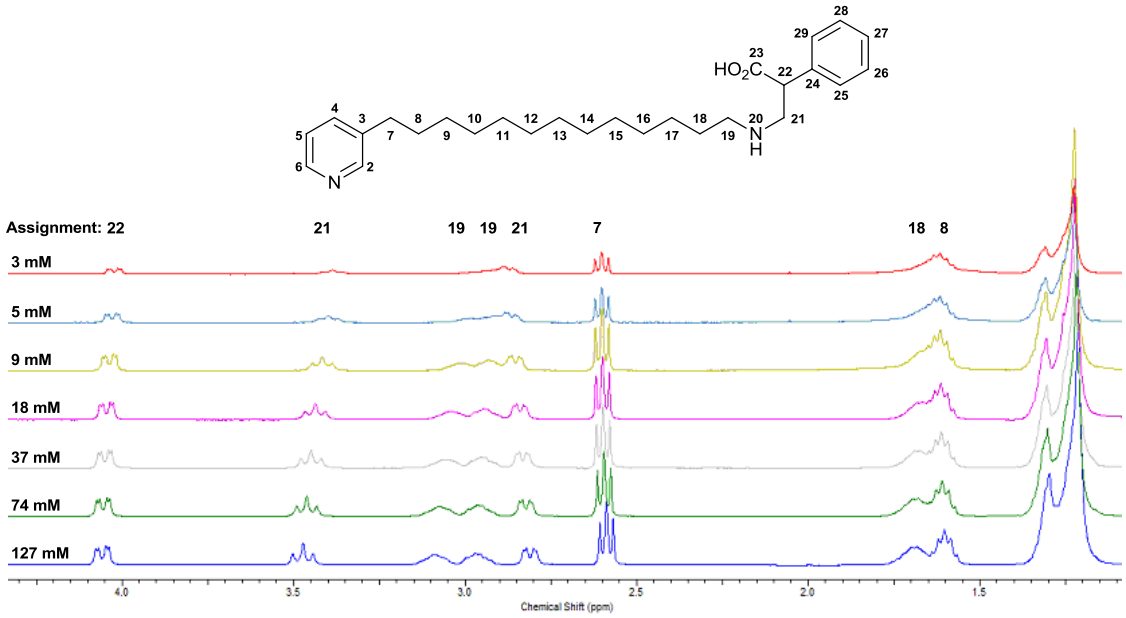
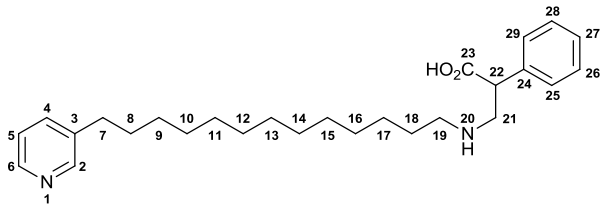


Figure 27. ^{1}H NMR concentration screen for synthetic (*S*)-**126** (400 MHz, $CDCl_3$).

Examination of the ^{13}C NMR spectroscopic data of (*S*)-**126** (127 mM in $CDCl_3$) showed good correlation against the reported chemical shift values for natural **126** (unknown concentration in $CDCl_3$) with most values falling within $|\Delta\delta| = 0.5$ ppm.[3] A few more significant differences were noticed for carbon atoms *C*(8), *C*(18), *C*(22) and *C*(24), which were all observed at chemical shift values with $|\Delta\delta| > 1.0$ ppm.[3] Although the origin of these slight differences is unclear, the structure of natural nakinadine B **126** and (*S*)-**126** appear to be the same (Figure 28).



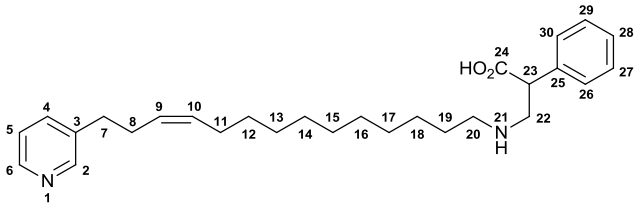
	Carbon #	Natural nakinadine B 126 150 MHz, δ_C (ppm)	Synthetic (*S*)-126 175 MHz, δ_C (ppm)
pyridin-3-yl moiety	2 (CH)	149.8	149.9
	3 (C)	138.4	137.9
	4 (CH)	135.8	135.7
	5 (CH)	123.2	123.1
	6 (CH)	147.1	147.1
alkyl chain	7 (CH_2)	33.0	33.0
	8 (CH_2)	29-30	31.1
	9−17 (CH_2)	26.8, 29−30	26.9, 29−30
	18 (CH_2)	29-30	25.2
	19 (CH_2)	47.9	47.6
β-amino acid moiety	21 (CH_2)	51.1	51.0
	22 (CH)	50.8	52.2
	23 (C)	176.6	176.2
phenyl ring	24 (C)	135.9	139.0
	25, 29 (CH)	128.7	128.1
	26, 28 (CH)	128.2	128.8
	27 (CH)	127.3	127.1

Figure 28. ^{13}C NMR data comparison of (*S*)-**126** (127 mM in $CDCl_3$) with natural nakinadine B **126** (unknown concentration in $CDCl_3$).

5.1.2 Nakinadine C

A similar analysis was performed for (*S*,*Z*)-**127** and comparison with the spectral data for natural nakinadine C **127** confirmed the structure originally proposed by Kobayashi *et al.*[1] However, similar discrepancies were noted between the IR spectra and the ESI MS/MS fragmentation analyses. Comparison of the ^1H NMR spectroscopic data of (*S*,*Z*)-**127** (127 mM in $CDCl_3$) with those reported for natural nakinadine C **127** (unknown concentration in $CDCl_3$) gave good agreement, whilst similar comparison of the ^{13}C NMR data showed generally good agreement, with most values having $|\Delta\delta| \leq 0.3$ ppm,[3] larger differences were observed for *C*(19) [$|\Delta\delta|$ ~4 ppm], *C*(23) [$|\Delta\delta|$ 0.7 ppm] and *C*(25) [$|\Delta\delta|$ 3.2 ppm] (Figure 29). Interestingly, for both

nakinadines B **126** and C **127**, the difference in resonances correspond to $NCH_2\mathit{C}H_2$ [C(18), nakinadine B; C(19), nakinadine C], $NCH_2\mathit{C}HPh$ [C(22), nakinadine B; C(23), nakinadine C], and *i-Ph* [C(24), nakinadine B; C(25), nakinadine C]. Although the origin of these differences is unclear, the structural assignments of both **126** and **127** are secure.



	Proton #	Natural nakinadine C 127 600 MHz, δ_H (ppm)	Synthetic (*S*,*Z*)-127 500 MHz, δ_H (ppm)
pyridin-3-yl moiety	2-H, 6-H	8.44 (2H, m)	8.41-8.46 (2H, m)
	4-H	7.49 (1H, m)	7.50 (1H, app dt)
	5-H	7.18 (1H, m)	7.19 (1H, dd)
alkyl chain	7-H_2	2.65 (2H, t)	2.66 (2H, t)
	8-H_2	2.35 (2H, dt)	2.36 (2H, app q)
	9-H	5.37 (2H, m)	5.33-5.45 (2H, m)
	10-H	5.37 (2H, m)	5.33-5.45 (2H, m)
	11-H_2	1.92 (2H, dt)	1.93 (2H, app q)
	12-18-H_2	1.2 (14H, m)	1.15-1.36 (14H, m)
	19-H_2	1.61 (2H, br s)	1.58-1.74 (2H, m)
	20-H_2	2.84 (3H, br s)	2.89-3.08 (2H, m)
β-amino acid moiety	22-H_A	2.84 (3H, br s)	2.85 (1H, dd)
	22-H_B	3.49 (1H, br s)	3.42 (1H, app t)
	23-H	4.11 (1H, br s)	4.04 (1H, dd)
phenyl ring	26-H, 30-H	7.33 (2H, m)	7.38 (2H, app d)
	27-H, 29-H	7.25 (2H, m)	7.30 (2H, app t)
	28-H	7.20 (1H, m)	7.23 (1H, app t)

	Carbon #	Natural nakinadine C 127 150 MHz, δ_C (ppm)	Synthetic (*S*,*Z*)-127 125 MHz, δ_C (ppm)
pyridin-3-yl moiety	2 (CH)	149.9	150.1
	3 (C)	137.3	137.2
	4 (CH)	135.8	135.9
	5 (CH)	123.2	123.2
	6 (CH)	147.2	147.3
alkyl chain	7 (CH_2)	33.0	33.0
	8 (CH_2)	28.7	28.7
	9 (CH)	127.7	127.7
	10 (CH)	131.4	131.4
	11 (CH_2)	26.7	27.2
	12−18 (CH_2)	27.2, 29−30	26.9, 29−30
	19 (CH_2)	29-30	25.4
	20 (CH_2)	47.9	47.6
β-amino acid moiety	22 (CH_2)	50.8	51.1
	23 (CH)	51.1	51.8
	24 (C)	176.7	176.4
phenyl ring	25 (C)	135.8	139.0
	26, 30 (CH)	128.2	128.2
	27, 29 (CH)	128.7	128.8
	28 (CH)	127.3	127.2

Figure 29. ^{1}H and ^{13}C NMR data comparison of (*S*,*Z*)-**127** ($CDCl_3$) with natural nakinadine C **127** ($CDCl_3$).

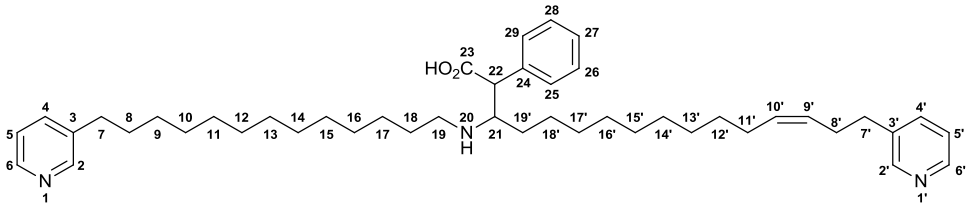
5.2 Assignment of relative configurations within nakinadines A and D−F

The gross structures of the synthetic samples of nakinadine A **125** and 2-*epi*-nakinadine A **297** were confirmed via a combination of IR[4] and NMR spectroscopic (^{1}H, ^{13}C, COSY, HSQC and HMBC) and ESI mass spectrometric analyses. Comparison of the ^{1}H and ^{13}C NMR data reported for natural nakinadine A **125** by Kobayashi *et al.*[5] with those of synthetic samples **125** and 2-*epi*-**297** showed that the NMR spectra were generally very similar. However, focusing on the peaks corresponding to the protons and carbons in the key region around the β-amino acid moiety [C(21) and C(22)], the chemical shifts in both the ^{1}H and ^{13}C NMR spectra of **125** matched more closely with the natural product than those of the corresponding 2-*epi*-diastereoisomer **297**. Therefore, this supports the relative *syn*-configuration originally proposed by Kobayashi *et al.*[5] (Figure 30 and 31). Similar observations were made regarding nakinadines D−F **128**−**130**, again supporting the relative configurations assigned by Kobayashi *et al*. (Figure 32−37).

5.3 Assignment of absolute configurations within the nakinadines alkaloids

Kobayashi *et al*. communicated only the specific rotation value for nakinadine A **125** {$[\alpha]_D^{23}$ −3.0 (*c* 1.0 in $CHCl_3$)}, with no values reported for nakinadines B−F **126**−**130**.[1,6] The specific rotation value for synthetic **125** was determined to be $[\alpha]_D^{23}$ −15.7 (*c* 1.0 in $CHCl_3$). Although the magnitudes of these specific rotation values do not match closely, their identical signs suggest that natural nakinadine A **125** is the (2*S*,3*R*,*Z*)-diastereoisomer **125**. The absolute (2*S*)-configurations within nakinadines B **126** and C **127** were also assigned by Kobayashi *et al.*[2] and so the absolute (2*S*)-configuration within nakinadine A **125** is also in accordance with this. Based on this, it seems likely that the nakinadine family of alkaloids are homochiral at C(2). Taking into consideration the relative (*RS*,*SR*)-configurations assigned to nakinadines D−F **128**−**130** by Kobayashi *et al.*,[1] it is proposed that these family members also share the absolute (2*S*,3*R*)-configuration.

5.4 ^{1}H and ^{13}C NMR data comparison for nakinadine A



	Proton #	Natural nakinadine A 125 600 MHz, δ_H (ppm)	Synthetic 125 500 MHz, δ_H (ppm)	|ΔΔ| ppm	Synthetic 297 500 MHz, δ_H (ppm)	|ΔΔ| ppm
pyridin-3-yl moiety	2-H, 2′-H, 6-H, 6′-H	8.44 (4H, m)	8.42 (4H, br s)	0.02	8.44 (4H, br s)	0
	4-H, 4′-H	7.49 (2H, m)	7.50 (2H, m)	0.01	7.49 (2H, m)	0
	5-H, 5′-H	7.19 (2H, m)	7.25 (part of 5H, m)	~0.06	7.20 (part of 3H, m)	~0.01
alkyl chain	7-H_2	2.56 (2H, t)	2.66 (part of 3H, m)	0.05	2.62 (part of 5H, m)	~0.06
	7′-H_2	2.62 (part of 3H, m)	2.66 (part of 3H, m)	~0.08	2.62 (part of 5H, m)	0
	8-18-H_2, 12′-19′-H_2	1.00-1.57 (38H, m)	1.10-1.68 (38H, m)	–	1.03-1.80 (38H, m)	–
	8′-H_2	2.33 (2H, m)	2.35 (2H, q)	0.02	2.35 (2H, q)	0.02
	9′-H	5.33 (part of 2H, m)	5.39 (part of 2H, m)	0.06	5.37 (part of 2H, m)	0.04
	10′-H	5.33 (part of 2H, m)	5.39 (part of 2H, m)	0.06	5.37 (part of 2H, m)	0.04
	11′-H_2	1.89 (2H, m)	1.92 (2H, q)	0.03	1.91 (2H, q)	0.02
	19-H_A	2.62 (part of 3H, m)	2.66 (part of 3H, m)	~0.08	2.62 (part of 5H, m)	0
	19-H_B	2.75 (1H, m)	2.83 (1H, m)	0.08	2.89 (1H, m)	0.14
β-amino acid moiety	21-H	3.19 (1H, br s)	3.11 (1H, m)	0.08	3.35 (1H, m)	0.24
	22-H	3.75 (1H, br s)	3.88 (1H, m)	0.13	3.69 (1H, d)	0.06
phenyl ring	25-H, 29-H	7.32 (2H, m)	7.36 (2H, m)	0.04	7.30 (part of 4H, m)	~0.02
	26-H, 28-H	7.20 (2H, m)	7.25 (part of 5H, m)	~0.05	7.30 (part of 4H, m)	~0.1
	27-H	7.15 (1H, m)	7.25 (part of 5H, m)	~0.1	7.20 (part of 3H, m)	~0.05

	Carbon #	Natural nakinadine A 125 150 MHz, δ_C (ppm)	Synthetic 125 125 MHz, δ_C (ppm)	|ΔΔ| ppm	Synthetic 297 125 MHz, δ_C (ppm)	|ΔΔ| ppm
pyridin-3-yl moiety	2, 2′ (CH)	149.6	149.7, 149.8	0.1, 0.2	149.9, 150.0	0.3, 0.4
	3, 3′ (C)	136.9	137.3, 138.0	0.4, 1.1	137.2, 137.9	0.3, 1.0
	4, 4′ (CH)	135.5	135.9, 136.2	0.4, 0.7	135.7, 135.9	0.2, 0.4
	5, 5′ (CH)	122.9	123.3	0.4	123.2	0.3
	6, 6′ (CH)	146.8	147.0	0.2	147.1, 147.2	0.3, 0.4
alkyl chain	7, 7′ (CH_2)	32.7	33.0, 33.1	0.3, 0.4	32.98, 33.00	0.3
	8 (CH_2)	30.8	31.1	0.3	31.1	0.3
	9-18 (CH_2), 8′ (CH_2), 11′–19′ (CH_2)	26.6, 26.9-30.0	26.2, 26.9-29.7	–	24.9, 26.7-29.6	–
	9′ (H)	127.4	127.7	0.3	127.6	0.2
	10′ (H)	131.1	131.4	0.3	131.4	0.3
	19 (CH_2)	44.9	45.9	1.0	44.6	0.3
β-amino acid moiety	21 (CH_2)	59.5	60.0	0.5	60.7	1.2
	22 (CH)	51.9	51.8	0.1	54.3	2.4
	23 (C)	176.0	175.0	1.0	176.7	0.7
phenyl ring	24 (C)	135.8	135.1	0.7	139.1	3.3
	25, 29 (CH)	129.4	128.7 or 129.6	0.7 or 0.2	128.5 or 128.7	0.9 or 0.7
	26, 28 (CH)	128.2	128.7 or 129.6	0.5 or 1.4	128.5 or 128.7	0.3 or 0.5
	27 (CH)	127.0	127.6	0.6	127.0	0

Figure 30. Comparison of ^{13}C NMR data for natural nakinadine A **125** ($CDCl_3$), synthetic **125** ($CDCl_3$) and **297** ($CDCl_3$).

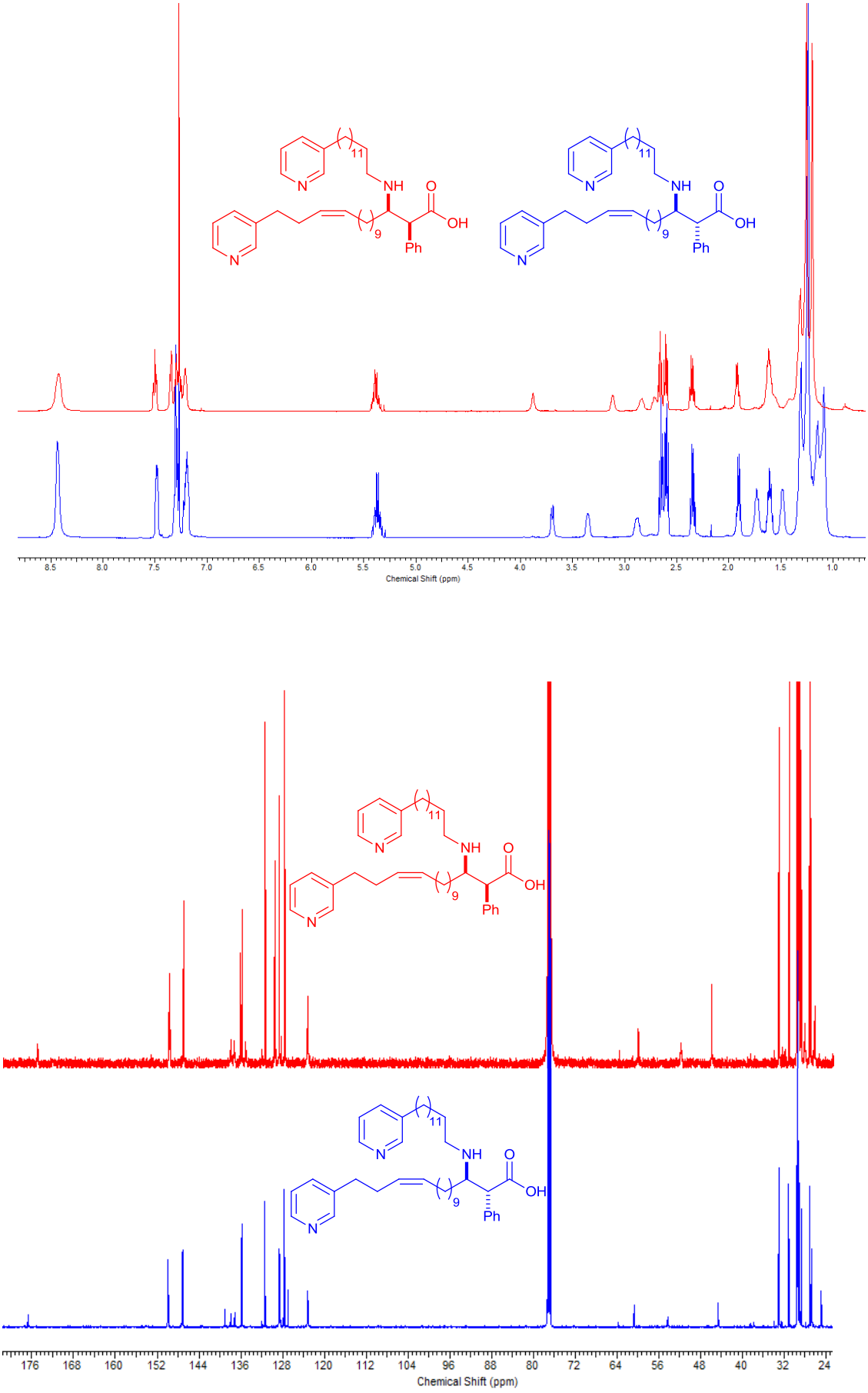
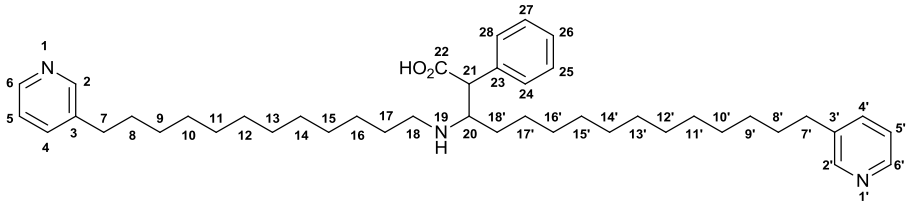


Figure 31. ^{1}H (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) spectra for **125** and **297**.

5.5 ^{1}H and ^{13}C NMR data comparison for nakinadine D



	Proton #	Natural nakinadine D 128 600 MHz, δ_H (ppm)	Synthetic 128 500 MHz, δ_H (ppm)	|ΔΔ| ppm	Synthetic 294 500 MHz, δ_H (ppm)	|ΔΔ| ppm
pyridin-3-yl moiety	2-H, 2′-H, 6-H, 6′-H	8.44 (4H, m)	8.42 (4H, m)	0.02	8.44 (4H, m)	0
	4-H, 4′-H	7.49 (2H, m)	7.48 (2H, app d)	0.01	7.48 (2H, app d)	0.01
	5-H, 5'-H	7.20 (2H, m)	7.22 (5H, m)	~0.02	7.20 (3H, m)	0
alkyl chain	7-H_2, 7′-H_2	2.60 (4H, m)	2.60 (4H, t)	0	2.59 (5H, m)	0.01
	8-17-H_2, 8′-18′-H_2	1.1-1.7 (42H, m)	1.03-1.70 (42H, m)	–	1.00-1.81 (42H, m)	–
	18-H_A	2.72 (1H, m)	2.71 (1H, m)	0.01	2.59 (5H, m)	~0.13
	18-H_B	2.82 (1H, m)	2.83 (1H, m)	0.01	2.88 (1H, m)	0.06
β-amino acid moiety	20-H	2.98 (1H, br. s)	3.14 (1H, m)	0.16	3.34 (1H, m)	0.36
	21-H	3.84 (1H, br. s)	3.82 (1H, br d)	0.02	3.70 (1H, m)	0.14
phenyl ring	24-H, 28-H	7.32 (4H, m)	7.34 (2H, app d)	0.02	7.30 (4H, m)	0.02
	25-H, 27-H	7.32 (4H, m)	7.22 (5H, m)	~0.12	7.30 (4H, m)	0.02
	26-H	7.19 (1H, m)	7.22 (5H, m)	~0.03	7.20 (3H, m)	~0.01

	Carbon #	Natural nakinadine D 128 150 MHz, δ_C (ppm)	Synthetic 128 125 MHz, δ_C (ppm)	|ΔΔ| ppm	Synthetic 294 125 MHz, δ_C (ppm)	|ΔΔ| ppm
pyridin-3-yl moiety	2, 2' (CH)	149.6	149.8	0.2	149.9	0.3
	3, 3' (C)	136.9	138.0	1.1	137.9	1.0
	4, 4' (CH)	135.5	135.8	0.3	135.7	0.2
	5, 5' (CH)	122.9	123.3	0.4	123.2	0.3
	6, 6' (CH)	146.8	147.0	0.2	147.1	0.3
alkyl chain	7, 7' (CH_2)	32.7	33.0	0.3	33.0	0.3
	8-17, 8'−18' (CH_2)	26.6, 26.9, 28-31	26.9, 28-31	–	24.9, 26.8, 28-31	–
	18 (CH_2)	44.9	45.7	0.8	44.6	0.3
β-amino acid moiety	20 (CH_2)	59.5	59.9	0.4	60.8	1.3
	21 (CH)	51.9	51.7	0.2	54.3	2.4
	22 (C)	176.0	175.1	0.9	176.7	0.7
phenyl ring	23 (C)	135.8	135.3	0.5	139.1	3.3
	24, 28 (CH)	129.4	129.6	0.2	128.7	0.7
	25, 27 (CH)	128.2	128.7	0.5	128.5	0.3
	26 (CH)	127.0	127.5	0.5	127.0	0

Figure 32. Comparison of ^{13}C NMR data for natural nakinadine D **128** ($CDCl_3$), synthetic **128** ($CDCl_3$) and **294** ($CDCl_3$).

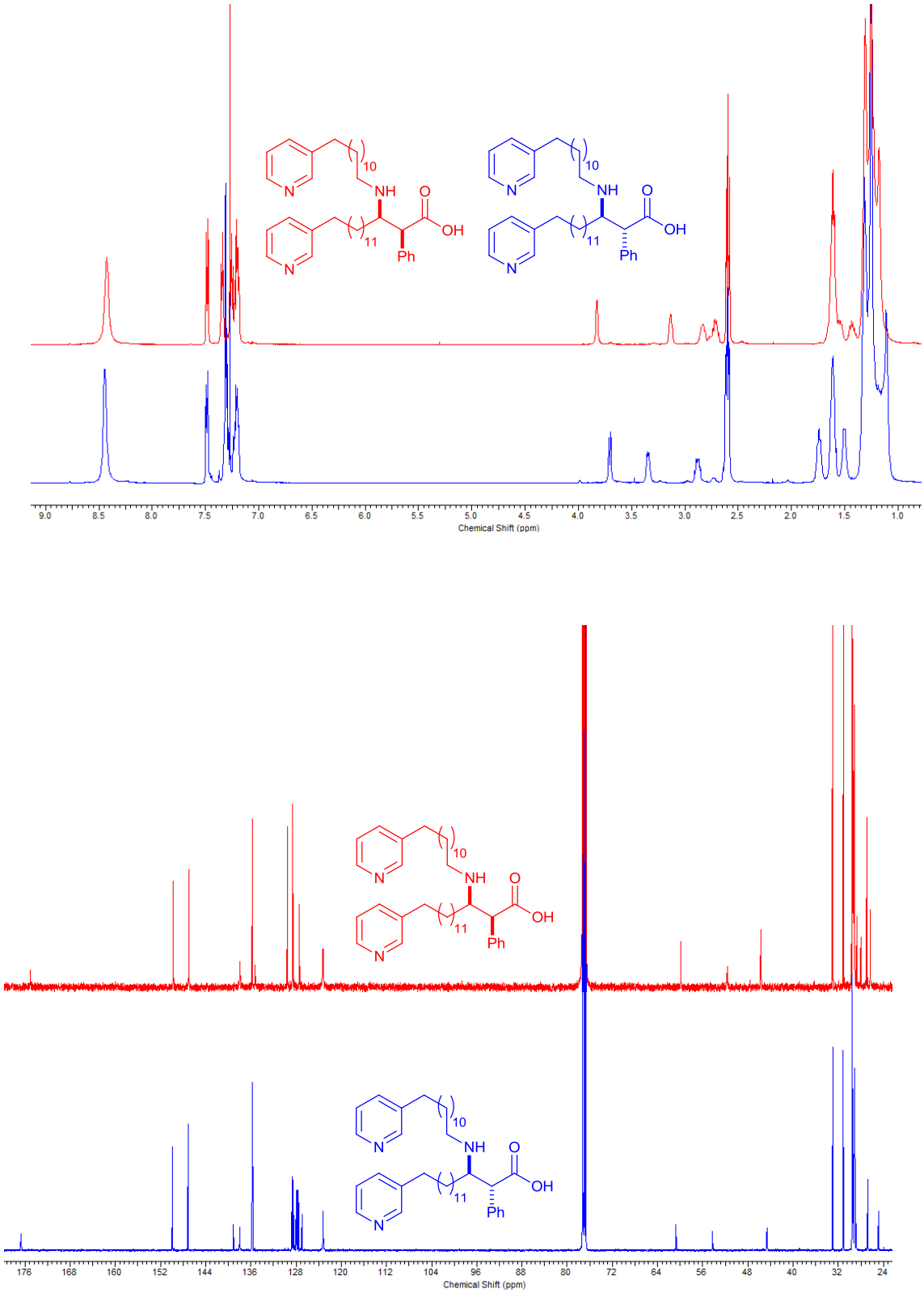
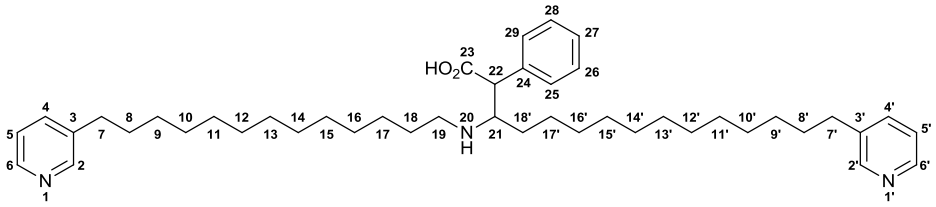


Figure 33. ^{1}H (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) spectra for **128** and **294**.

5.6 ^{1}H and ^{13}C NMR data comparison for nakinadine E



	Proton #	Natural nakinadine E 129 600 MHz, δ_H (ppm)	Synthetic 129 500 MHz, δ_H (ppm)	|ΔΔ| ppm	Synthetic 295 500 MHz, δ_H (ppm)	|ΔΔ| ppm
pyridin-3-yl moiety	2-H, 2'-H, 6-H, 6'-H	8.41 (4H, m)	8.43 (4H, m)	0.02	8.45 (4H, m)	0.04
	4-H, 4'-H	7.50 (2H, m)	7.49 (2H, app d)	0.01	7.49 (2H, app d)	0.01
	5-H, 5'-H	7.21 (2H, m)	7.22 (5H, m)	~0.01	7.22 (3H, m)	~0.01
alkyl chain	7-H_2, 7'-H_2	2.61 (4H, m)	2.60 (4H, t)	0.01	2.59 (5H, m)	0.02
	8-18-H_2, 8'-18'-H_2	1.0-1.8 (44H, m)	1.07-1.69 (44H, m)	–	1.02-1.80 (44H, m)	–
	19-H_A	2.72 (1H, m)	2.70 (1H, m)	0.02	2.59 (5H, m)	~0.13
	19-H_B	2.85 (1H, m)	2.84 (1H, m)	0.01	2.87 (1H, m)	0.02
β-amino acid moiety	21-H	3.05 (1H, br. s)	3.14 (1H, m)	0.09	3.34 (1H, m)	0.29
	22-H	3.87 (1H, br. s)	3.84 (1H, br d)	0.03	3.70 (1H, m)	0.17
phenyl ring	25-H, 29-H	7.33 (4H, m)	7.35 (2H, app d)	0.02	7.30 (4H, m)	0.03
	26-H, 28-H	7.33 (4H, m)	7.22 (5H, m)	~0.11	7.30 (4H, m)	0.03
	27-H	7.20 (1H, m)	7.22 (5H, m)	~0.02	7.22 (3H, m)	~0.02

	Carbon #	Natural nakinadine E 129 150 MHz, δ_C (ppm)	Synthetic 129 125 MHz, δ_C (ppm)	|ΔΔ| ppm	Synthetic 295 125 MHz, δ_C (ppm)	|ΔΔ| ppm
pyridin-3-yl moiety	2, 2' (CH)	149.6	149.9	0.3	149.9	0.3
	3, 3' (C)	136.9	138.0	1.1	138.0	1.1
	4, 4' (CH)	135.5	135.8	0.3	135.7	0.2
	5, 5' (CH)	122.9	123.3	0.4	123.3	0.4
	6, 6' (CH)	146.8	147.1	0.3	147.1	0.3
alkyl chain	7, 7' (CH_2)	32.7	33.0	0.3	33.0	0.3
	8-18, 8'-18' (CH_2)	26.6, 26.9, 28-30, 30.8	26.3, 26.9, 27.5, 28-30, 31.1	–	25.0, 26.7, 26.8, 28-30, 31.1	–
	19 (CH_2)	44.9	45.5	0.6	44.6	0.3
β-amino acid moiety	21 (CH_2)	59.5	59.9	0.4	60.8	1.3
	22 (CH)	51.9	51.9	0	54.3	2.4
	23 (C)	176.0	175.6	0.4	176.7	0.7
phenyl ring	24 (C)	135.8	135.6	0.2	139.0	3.2
	25, 29 (CH)	129.4	129.6	0.2	128.7	0.7
	26, 28 (CH)	128.2	128.6	0.4	128.5	0.3
	27 (CH)	127.0	127.4	0.4	127.0	0

Figure 34. Comparison of ^{13}C NMR data for natural nakinadine E **129** ($CDCl_3$), synthetic **129** ($CDCl_3$) and **295** ($CDCl_3$).

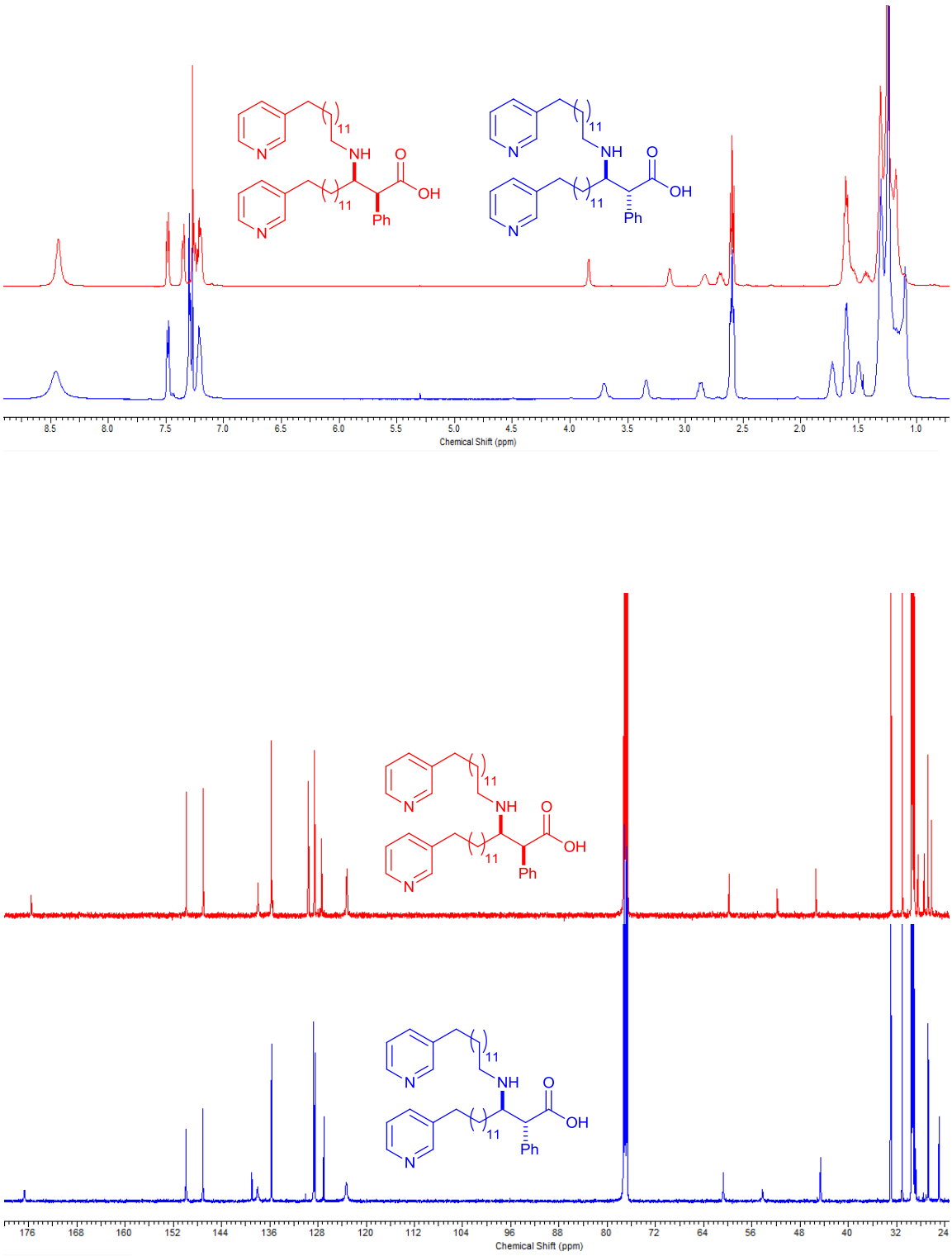
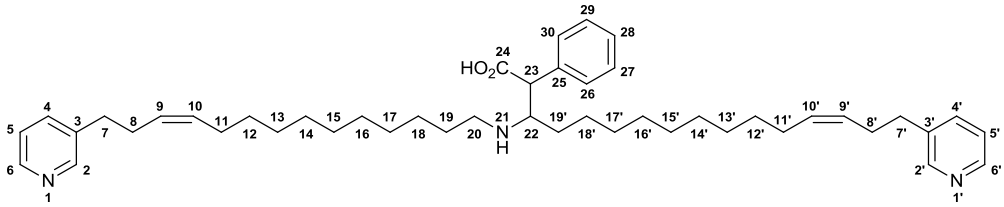


Figure 35. ^{1}H (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) spectra for **129** and **295**.

5.7 ^{1}H and ^{13}C NMR data comparison for nakinadine F



	Proton #	Natural Nakinadine F 130 600 MHz, δ_H (ppm)	Synthetic 130 500 MHz, δ_H (ppm)	|ΔΔ| ppm	Synthetic 296 500 MHz, δ_H (ppm)	|ΔΔ| ppm
pyridin-3-yl moiety	2-H, 2'-H, 6-H, 6'-H	8.40 (4H, m)	8.42 (4H, br s)	0.02	8.44 (4H, br s)	0.04
	4-H, 4'-H	7.49 (2H, m)	7.50 (2H, app d)	0.01	7.51 (2H, m)	0.02
	5-H, 5'-H	7.20 (2H, m)	7.24 (part of 5H, m)	~0.04	7.21 (part of 3H, m)	~0.01
alkyl chain	7-H_2, 7'-H_2	2.60 (2H, m), 2.65 (2H, m)	2.69 (part of 5H, m)	–	2.64 (part of 5H, m)	–
	8-H_2, 8'-H_2	2.35 (4H, m)	2.35 (4H, m)	0	2.36 (4H, m)	0.01
	9-H, 9'-H	5.38 (part of 4H, m)	5.39 (part of 4H, m)	0.01	5.39 (part of 4H, m)	0.01
	10-H, 10'-H	5.38 (part of 4H, m)	5.39 (part of 4H, m)	0.01	5.39 (part of 4H, m)	0.01
	11-H_2, 11'-H_2	1.0-1.7 (part of 36H, m)	1.93 (4H, m)	~0.20	1.92 (4H, m)	~0.20
	12-19-H_2, 12'-19'-H_2	1.0-1.7 (part of 36H, m)	1.12-1.71 (32H, m)	–	1.03-1.81 (32H, m)	–
	20-H_A	2.70 (1H, m)	2.69 (part of 5H, m)	~0.01	2.64 (part of 5H, m)	~0.06
	20-H_B	2.80 (1H, m)	2.82 (1H, m)	0.02	2.89 (1H, m)	0.09
β-amino acid moiety	22-H	3.01 (1H, br s)	3.11 (1H, m)	0.10	3.36 (1H, m)	0.35
	23-H	3.84 (1H, br s)	3.85 (1H, m)	0.01	3.72 (1H, d)	0.08
phenyl ring	26-H, 30-H	7.31 (part of 4H, m)	7.34 (2H, m)	~0.03	7.31 (part of 4H, m)	0
	27-H, 29-H	7.31 (part of 4H, m)	7.24 (part of 5H, m)	~0.07	7.31 (part of 4H, m)	0
	28-H	7.18 (1H, m)	7.24 (part of 5H, m)	~0.06	7.21 (part of 3H, m)	~0.03

	Carbon #	Natural nakinadine F 130 150 MHz, δ_C (ppm)	Synthetic 130 125 MHz, δ_C (ppm)	|ΔΔ| ppm	Synthetic 296 125 MHz, δ_C (ppm)	|ΔΔ| ppm
pyridin-3-yl moiety	2, 2′ (CH)	149.6	149.8, 149.9	0.2, 0.3	150.0	0.4
	3, 3′ (C)	136.9	137.3	0.4	137.2	0.3
	4, 4′ (CH)	135.5	135.97, 136.04	~0.5	135.9	0.4
	5, 5′ (CH)	122.9	123.2	0.3	123.2	0.3
	6, 6′ (CH)	146.8	147.1, 147.2	0.3, 0.4	147.3	0.5
alkyl chain	7, 7′ (CH_2)	32.7	33.0	0.3	33.0	0.3
	8, 11−19 (CH_2), 8′, 11′−19′ (CH_2)	26.6, 26.9, 28−30	26.3, 27−30	–	24.7, 26.8, 27−30	–
	9, 9′ (H)	127.4	127.7	0.3	127.7	0.3
	10, 10′ (H)	131.1	131.4	0.3	131.4	0.3
	20 (CH_2)	44.9	45.8	0.9	44.8	0.1
β-amino acid moiety	21 (CH_2)	59.5	60.0	0.5	60.7	1.2
	23 (CH)	51.9	51.9	0	54.4	2.5
	24 (C)	176.0	175.3	0.7	176.7	0.7
phenyl ring	25 (C)	135.8	135.5	0.3	138.9	3.1
	26, 30 (CH)	129.4	129.6	0.2	128.8	0.6
	27, 29 (CH)	128.2	128.6	0.4	128.5	0.3
	28 (CH)	127.0	127.4	0.4	127.1	0.1

Figure 36. Comparison of ^{13}C NMR data for natural nakinadine F **130** ($CDCl_3$), synthetic **130** ($CDCl_3$) and **296** ($CDCl_3$).

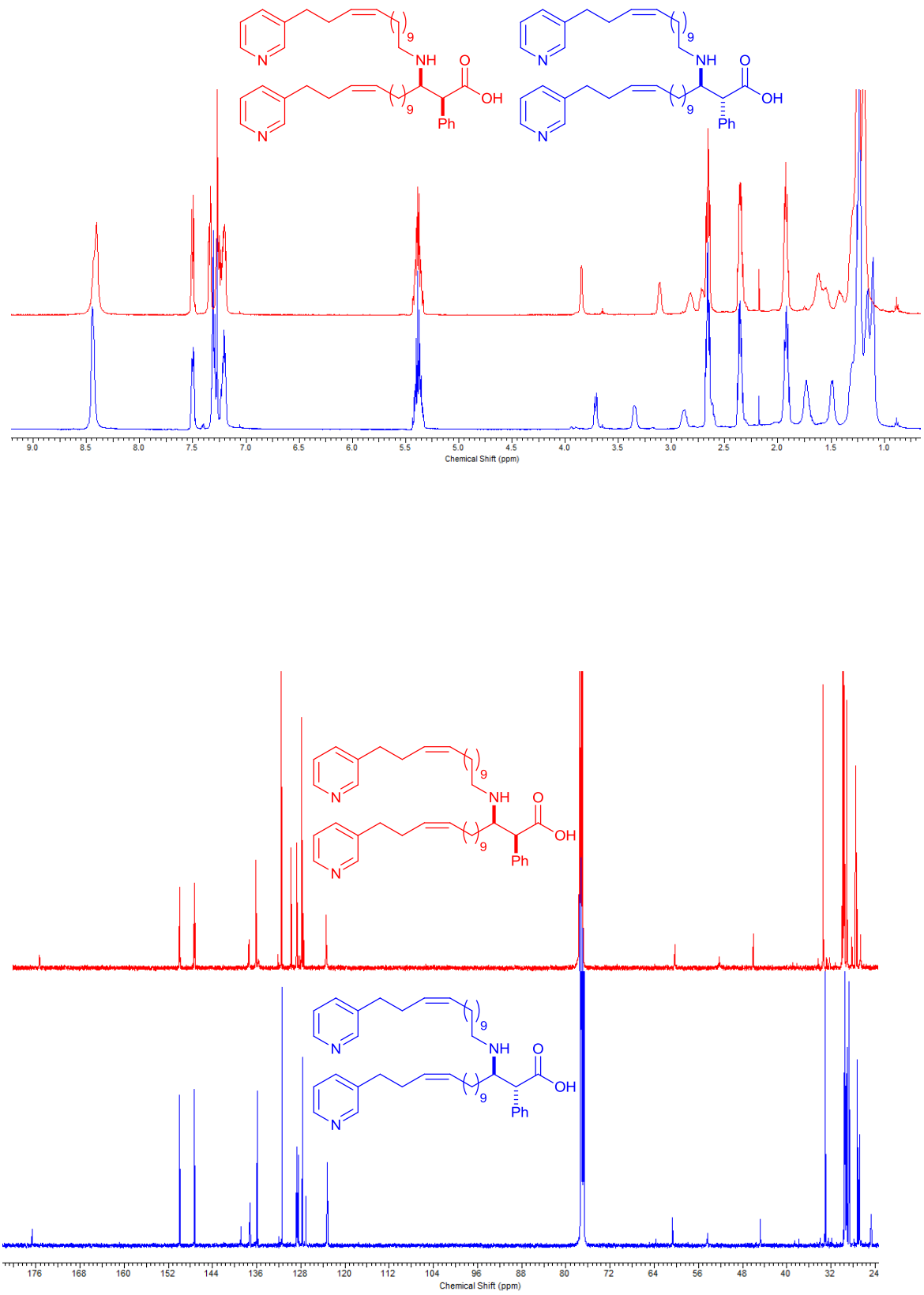


Figure 37. ^{1}H (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) spectra for **130** and **296**.

5.8 Conclusion

In conclusion, asymmetric syntheses of nakinadines A−F **125**−**130** have been developed. These syntheses employ the conjugate addition of lithium dibenzylamide to a chiral *N*-acyl SuperQuat derivative **121** followed by diastereoselective protonation as the key step to the syntheses of nakinadines B **126** and C **127** (β^2-amino acids) and an imino-aldol reaction between a chiral *N*-sulfinyl imine **271** to an α-phenyl ester enolate to enable the syntheses of nakinadines A **125** and D−F **128**−**130** ($\beta^{2,3}$-amino acids). Comparison of spectroscopic data for the synthetic samples with those reported for the natural products confirmed the structural assignments made by Kobayashi *et al*., and established the absolute configuration within nakinadine A **125**, hence allowing the absolute configurations within nakinadines D−F **128**−**130** to be proposed (Figure 38).

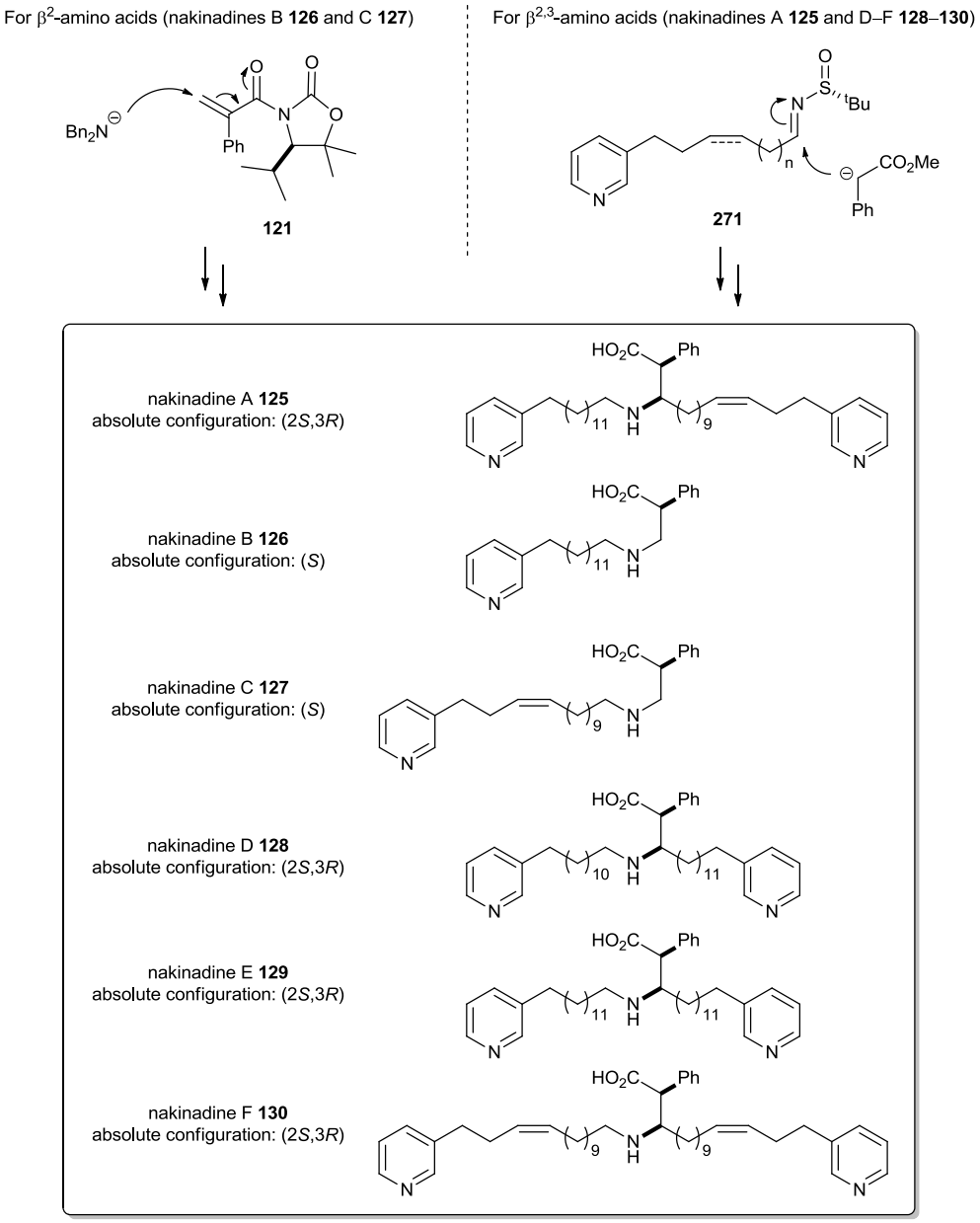


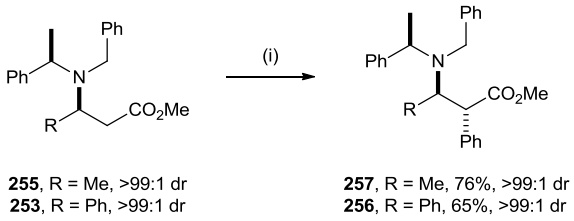
Figure 38. Syntheses of the nakinadine alkaloids.

5.9 References and notes

[1] Nishi, T.; Kubota, T.; Fromont, J.; Sasaki, T.; Kobayashi, J. *Tetrahedron* **2008**, *64*, 3127.
[2] Williams, D. H.; Flemming, I. Spectroscopic Methods in Organic Chemistry, 5th Edn, 1995.
[3] $|\Delta\delta|$ refers to the absolute value of $(\delta_{natural}) - (\delta_{synthetic})$.
[4] The IR spectrum for both the diastereoisomers of nakinadines A and D−F showed peaks at ~1595 and ~1575 cm^{-1} which are characteristic of a zwitterionic $\beta^{2,3}$-amino acid. The corresponding peaks for zwitterionic β^{2}-amino acids (nakinadines B and C) were observed at ~1655 and ~1560 cm^{-1}.
[5] Kubota, T.; Nishi, T.; Fukushi, E.; Kawabata, J.; Fromont, J.; Kobayashi, J. *Tetrahedron Lett.* **2007**, *48*, 4983.
[6] Accurate specific rotation values for nakinadines B−F **126**−**130** were requested from the authors but unfortunately they were unable to provide exact values instead indicating "*large variances in values caused by the relatively small amount of sample isolated*".

Future Work

The syntheses of the nakinadine alkaloids have been successfully achieved using either a conjugate addition or imino-aldol approach and the methodologies developed are flexible and should be readily applicable to the synthesis of a range of structural analogues. As part of these studies, Pd-catalysed α-arylation of β^3-amino enolates was explored and demonstrated some promising results (Scheme 112).



Scheme 112. *Reagents and Conditions*: (i) $Pd(dba)_2$, $P(^tBu)_3 \cdot HBF_4$, LiHMDS, bromobenzene, PhMe, −20 °C to rt, 12 h.

There has been much work carried out on the α-arylation of simple carbonyl enolate compounds and this has led to the identification of a plethora of catalytic systems. Thus, future work will be concerned with the development of a general Pd-catalysed α-arylation methodology to enable access to a wider range of α-aryl-$\beta^{2,3}$-amino acid derivatives. This will commence with an investigation into screening a variety of catalytic systems and could culminate in the synthesis of more diverse α-aryl-$\beta^{2,3}$-amino carbonyl targets, such as Ritalin® **42**. Hence, successful application of these conditions to **322** would provide **323** and further elaboration of **323** via ring-closing metathesis and subsequent hydrogenation could pave the path to **42** (Figure 39).

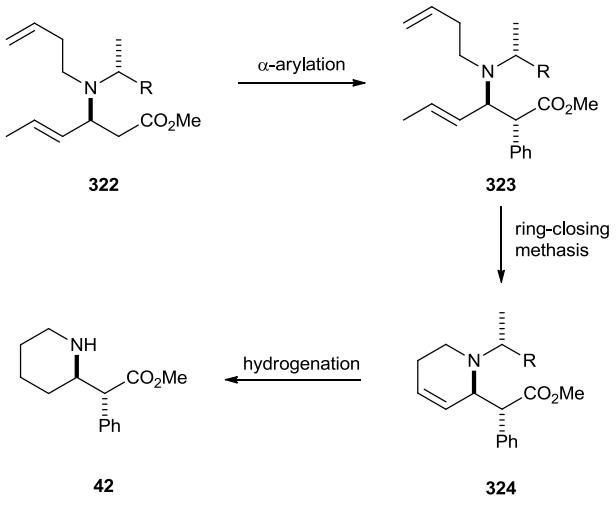


Figure 39. Development of a robust α-arylation protocol to enable the synthesis of Ritalin®.

Chapter 6: Experimental

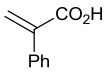
6.1 General Experimental

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame-dried and cooled under a flow of nitrogen prior to use. Reactions were cooled to 0 °C by means of an ice-water slush bath and to −78 °C by a dry ice-acetone bath. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[1] The term "petrol" refers to petroleum spirit in the boiling range 30-40 °C. Water was purified by an Elix® UV-10 system. 2-Pyridone, LiCl and $MgBr_2$ were dried under high vacuum at 190 °C prior to use. BuLi was supplied as a solution in hexanes and was titrated against 2,2-diphenylacetic acid prior to use. LiHMDS, KHMDS, MeMgBr were supplied as a solution in the stated solvents. All other solvents and reagents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over $MgSO_4$ or Na_2SO_4 and the dessicant removed *via* filtration prior to concentration *in vacuo*. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), 1% aq $KMnO_4$, or Dragendorff's reagent. Flash column chromatography was performed on Kieselgel 60 silica on a glass column, or on a Biotage SP4 flash column chromatography platform. Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter or 341 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer or a diamond ATR module (ATR) as a thin film on NaCl plates (film). Selected characteristic peaks are reported in cm^{-1}. UV spectra were recorded on a Perkin Elmer UV/Vis Lambda 2 Spectrometer. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated. The field was locked by external referencing to the relevant deuteron resonance. Chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. Low-resolution mass spectra were recorded on either a a Micromass LCT Premier or Agilent Quadrupole 6120 LC/MS spectrometer. Accurate mass measurements were run on either a Bruker MicroTOF internally calibrated with polyalanine, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m × 0.25 mm) using amyl acetate as a lock mass, by the mass spectrometry department of the Chemistry Research

Laboratory, University of Oxford, UK. Chiral HPLC was carried out on an Agilent Technologies 1200 series machine in the stated solvent system using either a Chiralpak® AD-H column.

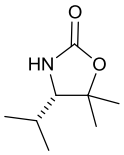
6.2 Experimental for chapter 2

Atropic acid 147[2]



Tropic acid **146** (10.0 g, 60.2 mmol) was added to a stirred solution of KOH (13.0 g) in H_2O (30 mL) and the resultant solution was refluxed for 1 h before being cooled to 0 °C and HCl (12.0 M aq, 40 mL) was added. The resultant mixture was filtered, washed with cold H_2O (20 ml) and dried to constant weight to yield **147** as a white solid (7.9 g, 90%);[2] mp 98−99 °C; {lit.[2] 101−103 °C}; δ_H (400 MHz, $CDCl_3$) 6.02 (1H, d, *J* 1.0, C(3)H_A), 6.54 (1H, d, *J* 1.0, C(3)H_B), 7.34-7.48 (5H, m, *Ph*).

(*S*)-5,5-Dimethyl-4-isopropyloxazolidin-2-one (SuperQuat) (*S*)-145[3]



Step 1. $SOCl_2$ (93 mL, 1.28 mol) was added dropwise to a stirred solution of (*S*)-valine (100 g, 0.85 mol) in MeOH (1.5 L) at 0 °C and the reaction mixture was left to warm to rt over 24 h before being concentrated *in vacuo* to give (*S*)-valine methyl ester hydrochloride as a white solid (143 g, quant.).

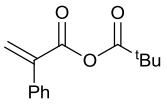
Step 2. $NaHCO_3$ (215 g, 2.56 mol) and Boc_2O (195 g, 0.9 mol) were added sequentially to a stirred solution of hydrochloride salt (143 g, 0.85 mol) in EtOH (500 mL) at 0 °C and the reaction mixture was left to warm to rt over 48 h before being concentrated *in vacuo*. The residue was partitioned between EtOAc (500 mL) and H_2O (500 mL) and the organic layer was washed with satd aq $NaHCO_3$ (2 × 100 mL), brine (2 × 100 mL), dried and concentrated *in vacuo* to give (*S*)-*N*-*tert*-butoxycarbonyl valine methyl ester as a yellow oil (187 g, 95%); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, d, *J* 6.8, CH*Me*$_A$), 0.96 (3H, d, *J* 6.8, CH*Me*$_B$), 1.45 (9H, s, C*Me*$_3$), 2.08-2.18 (1H, m, C*H*Me$_A$Me$_B$), 3.74 (3H, s, O*Me*), 4.23 (1H, dd, *J* 9.2, 4.8, NC*H*), 5.02 (1H, br. d, *J* 9.2, N*H*).

Step 3. MeI (1.0 g, 16 mmol) was added dropwise to a stirred suspension of Mg turnings (79.0 g, 3.24 mol) in Et_2O (1.6 L) with gentle heating to initiate formation of the Grignard reagent. Once an exothermic reaction had commenced, a solution of MeI (201 mL, 3.22 mol) in Et_2O (0.8 L) was

added dropwise as to maintain the reaction at gentle reflux. Upon completion of the addition, the reaction mixture was left to stir at rt for 1 h before cooling to 0 °C and a solution of (*S*)-*N*-*tert*-butoxycarbonyl valine methyl ester (187 g, 0.81 mol) in Et_2O (0.8 L) was added dropwise over 15 min and the reaction mixture was left to warm to rt over 48 h. The reaction mixture was cooled to 0 °C and satd aq NH_4Cl (100 mL) was added dropwise, followed HCl (2.0 M aq, 500 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 1 L). The combined organic extracts were washed with brine (500 mL), dried and concentrated *in vacuo* to give (*S*)-*tert*-butyl (2-hydroxy-2,4-dimethylpentan-3-yl)carbamate as a yellow solid (149 g, 79%); δ_H (400 MHz, $CDCl_3$) 0.91 (3H, d, *J* 6.8, C(4)*Me*), 0.95 (3H, d, *J* 6.8, C(5)H_3), 1.24 (3H, s, C(2)*Me*), 1.27 (3H, s, C(1)H_3), 1.45 (9H, s, CMe_3), 1.84-1.87 (1H, m, C(4)*H*), 2.21 (1H, br s, O*H*), 3.77 (1H, d, *J* 2.0, C(3)*H*), 4.51 (1H, br s, N*H*).

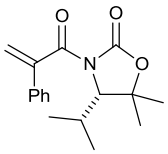
Step 4. KO^{t}Bu (80.2 g, 0.70 mol) was added in one portion to a stirred solution of (*S*)-*tert*-butyl (2-hydroxy-2,4-dimethylpentan-3-yl)carbamate (149 g, 0.64 mol) in THF (1.5 L) at 0 °C and the resultant mixture was left to stir for 30 min before the addition of satd aq NH_4Cl (200 mL). The subsequent mixture was diluted with EtOAc (400 mL) and the phases were separated. The aqueous layer was extracted with EtOAc (2 × 200 mL) and the combined organic extracts were washed with brine (100 mL), dried and concentrated *in vacuo*. Purification via recrystallization (EtOAc/hexane) gave (*S*)-**145** as white needles (72.2 g, 72%); mp 88−91 °C (EtOAc/hexane); {lit.[3] 88−89 °C (Et_2O/hexane)}; $[\alpha]_D^{25}$ +15.2 (*c* 1.0 in $CHCl_3$); {lit.[3] $[\alpha]_D^{23}$ +21.3 (*c* 0.8 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 0.93 (3H, d, *J* 6.6, CH*Me*$_A$Me$_B$), 1.00 (3H, d, *J* 6.6, CHMe$_2$), 1.39 (3H, s, C(5)*Me*$_A$), 1.49 (3H, s, C(5)*Me*$_B$), 2.20-2.27 (1H, m, C*H*Me$_A$Me$_B$), 3.19 (1H, d, *J* 8.5, C(4)*H*), 5.95 (1H, br s, N*H*).

2-Phenylacrylic pivalic anhydride 148



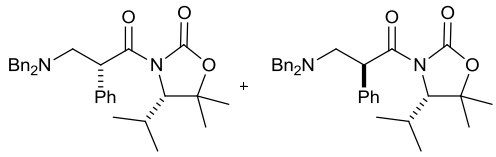
Et_3N (1.88 mL, 13.5 mmol) and pivaloyl chloride (1.67 mL, 13.5 mmol) were added sequentially to a stirred solution of atropic acid **147** (2.00 g, 13.5 mmol) in THF (35 mL) at 0 °C. The resultant suspension was stirred at 0 °C for 1 h and then filtered. The filter cake was washed with THF (20 mL) and the filtrate was concentrated *in vacuo*. 30–40 °C Petrol (20 mL) was added to the residue, the resultant suspension was filtered, and the filtrate was concentrated *in vacuo* to give **148** as a yellow oil (2.78 g, 89%); δ_H (400 MHz, $CDCl_3$) 1.26 (9H, s, CMe_3), 6.09 (1H, d, *J* 1.0, C(3)H_A), 6.46 (1H, d, *J* 1.0, C(3)H_B), 7.36-7.46 (5H, m, *Ar*).

(*S*)-*N*(3)-(2′-Phenylacryloyl)-4-isopropyl-5,5-dimethyloxazolidin-2-one (*S*)-121[4]



BuLi (2.50 M in hexanes, 5.28 mL, 13.2 mmol) was added dropwise via syringe to a stirred solution of (*S*)-**145** (1.89 g, 12.0 mmol) in THF (30 mL) at −78 °C. After stirring for 10 min, a solution of **148** (2.78 g, 12.0 mmol) in THF (10 mL) −78 °C was added dropwise via cannula. After a further 30 min, the cooling bath was removed and reaction mixture was left to warm to rt over 2 h, before the sequential addition of satd aq NH_4Cl (5 mL) and H_2O (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 80:20) gave (*S*)-**121** as a white solid (2.75 g, 72% from atropic acid **147**, 81% from SuperQuat (*S*)-**145**);[4] mp 72−73 °C; {lit.[4] mp 73−74 °C}; $[\alpha]_D^{25}$ +70.0 (*c* 1.0, $CHCl_3$); {lit.[4] $[\alpha]_D^{25}$ +70.8 (*c* 0.6 $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.00 (3H, d, *J* 6.8, CH*Me*$_A$Me$_B$), 1.15 (3H, d, *J* 6.8, CHMe$_A$*Me*$_B$), 1.39 (3H, s, C(5)*Me*$_A$), 1.52 (3H, s, C(5)*Me*$_B$), 2.20-2.27 (1H, m, C*H*Me$_2$), 4.25 (1H, d, *J* 3.1, C(4)*H*), 5.47 (1H, s, C(3′)*H*$_A$), 5.77 (1H, s, C(3′)*H*$_B$), 7.27-7.53 (5H, m, *Ph*).

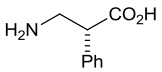
(4*S*,2′*R*)- and (*S*,*S*)-*N*(3)-(2′-Phenyl-3′-*N*,*N*-dibenzylamino)propanoyl)-4-isopropyl-5,5-dimethyloxazolidin-2-one 122 and 150



BuLi (1.60 M in hexanes, 1.69 mL, 2.70 mmol) was added dropwise via syringe to a stirred solution of dibenzylamine (548 mg, 2.78 mmol) in THF (10 mL) at −78 °C. After stirring for 30 min, a solution of (*S*)-**121** (500 mg, 1.74 mmol) in THF (10 mL) at −78 °C was added dropwise via cannula and the resultant mixture was left to stir for a further 4 h at −78 °C, before the addition of 2-pyridone (500 mg, 5.22 mmol) and the reaction mixture was left to warm to rt over 16 h. Et_2O (30 mL) was added and the resultant solution was washed sequentially with 10% aq citric acid (10 mL), satd aq $NaHCO_3$ (10 mL) and brine (10 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to give an 87:13 mixture of **122** and **150**. Purification via flash column chromatography (gradient elution, 1% → 10% Et_2O in 30–40 °C petrol) gave **122** as a colourless oil (531 mg, 63%, >99:1 dr); $[\alpha]_D^{25}$ +5.3 (*c* 1.0 in $CHCl_3$); ν_{max} 1768 (C=O, exocyclic), 1697 (C=O, endocyclic); δ_H (400 MHz, $CDCl_3$) 0.96 (3H, s, C(5)*Me*$_A$), 1.08 (3H, d, *J* 6.9, CH*Me*$_A$), 1.16 (3H, d, *J* 6.9, CH*Me*$_B$), 1.46 (3H, s,

C(5)*Me*$_B$), 2.14–2.26 (1H, m, C*H*Me$_2$), 2.87 (1H, dd, *J* 12.9, 6.1, C(3′)*H*$_A$), 3.43 (1H, dd, *J* 12.9, 8.3, C(3′)*H*$_B$), 3.72 (4H, app s, N(C*H*$_2$Ph)$_2$), 4.06 (1H, d, *J* 3.0, C(4)*H*), 5.59 (1H, dd, *J* 8.3, 6.1, C(2′)*H*), 7.22–7.36 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.1 (CH*Me*$_B$), 21.2 (C(5)*Me*$_A$), 21.5 (CH*Me*$_A$), 28.1 (C(5)*Me*$_B$), 29.4 (*C*HMe$_2$), 46.9 (C(2′)), 57.0 (*C*(3′)), 58.2 (N(*C*H$_2$Ph)$_2$), 67.0 (*C*(4)), 82.7 (*C*(5)), 126.7, 127.3 (*p-Ph*), 128.0, 128.4, 128.6, 128.9 (*o,m-Ph*), 137.3, 138.9, 139.0, (*i-Ph*), 153.4 (*C*(2)), 173.2 (*C*(1′)); *m/z* (ESI$^+$) 485 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{37}N_2O_3^+$ ([M+H]$^+$) requires 485.2799; found 485.2785. Further elution gave **150** as a colourless oil ((76 mg, 9%, >99:1 dr); $[\alpha]_D^{25}$ −7.3 (*c* 2.0 in $CHCl_3$); ν_{max} 1768 (C=O, exocyclic), 1697 (C=O, endocyclic); δ_H (400 MHz, $CDCl_3$) 0.59 (3H, d, *J* 6.9, CH*Me*$_A$), 0.79 (3H, d, *J* 6.9, CH*Me*$_B$), 1.48 (3H, s, C(5)*Me*$_A$), 1.49 (3H, s, C(5)*Me*$_B$), 1.93–2.06 (1H, m, C*H*Me$_2$), 2.90 (1H, dd, *J* 13.1, 6.1, C(3′)*H*$_A$), 3.41 (1H, dd, *J* 13.1, 8.6, C(3′)*H*$_B$), 3.66 (4H, AB system, J_{AB} 13.6, N(C*H*$_2$Ph)$_2$), 4.26 (1H, d, *J* 3.0, C(4)*H*), 5.52 (1H, dd, *J* 8.6, 6.1, C(2′)*H*), 7.20–7.41 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.3 (CH*Me*$_B$), 21.2 (C(5)*Me*$_A$), 21.3 (CH*Me*$_A$), 28.7 (C(5)*Me*$_B$), 29.7 (*C*HMe$_2$), 47.2 (C(2′)), 56.9 (*C*(3′)), 58.1 (N(*C*H$_2$Ph)$_2$), 65.8 (*C*(4)), 82.3 (*C*(5)), 126.8, 127.2 (*p-Ph*), 128.1, 128.3, 128.9 (*o,m-Ph*), 137.4, 139.0 (*i-Ph*), 153.1 (*C*(2)), 173.6 (*C*(1′)); *m/z* (ESI$^+$) 485 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{37}N_2O_3^+$ ([M+H]$^+$) requires 485.2799; found 485.2785.

(*R*)-2-Phenyl-3-aminopropanoic acid (*R*)-39[4]

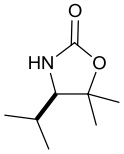


Step 1. H_2O_2 (30% aq, 8.3 mL) and LiOH (290 mg, 6.93 mmol) were sequentially added to a stirred solution of **122** (560 mg, 1.16 mmol) in THF (10 mL) at 0 °C and the reaction mixture was left to warm to rt over 16 h before the addition of satd aq Na_2SO_3 (50 mL). The resultant mixture was diluted with EtOAc (30 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 30 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to furnish a 50:50 mixture of β-amino acid (*R*)-**151** and SuperQuat (*S*)-**145** (550 mg).

Step 2. Pd (10% wt on C, 200 mg) was added to a stirred degassed solution of a 50:50 mixture of β-amino acid (*R*)-**151** and SuperQuat (*S*)-**145** (550 mg) in MeOH (4 mL), H_2O (0.4 mL) and AcOH (0.1 mL). The suspension was stirred under H_2 (1 atm) for 24 h before being filtered though Celite®. The Celite® pad was washed with MeOH (~20 mL) and the filtrate was concentrated *in vacuo*. The residue was co-evaporated with HCl (2.0 M in Et_2O, 3 × 5 mL). Purification via ion exchange chromatography on Dowex 50WX8 (100-200 mesh, eluent H_2O) gave SuperQuat (*S*)-**145** as white needles (129 mg, 71% from **122**); mp 87−88 °C; {lit.[5] mp 87 °C}; $[\alpha]_D^{20}$ +20.3 (*c* 1.0 in $CHCl_3$);

{lit.[5] $[\alpha]_D^{23}$ +21.3 (*c* 0.8 in $CHCl_3$)}. Further elution (eluent 1.0 M aq NH_4OH) gave (*R*)-**39** as a white solid (134 mg, 70% from **122**); mp 220−222 ˚C; {lit.[4] mp 224−225 ˚C}; $[\alpha]_D^{20}$ +84.7 (*c* 1.0 in H_2O); {lit.[6] for enantiomer $[\alpha]_D$ +94.0 (*c* 0.2 in H_2O)}; δ_H (400 MHz, D_2O) 3.28 (1H, dd, *J* 13.1, 7.6, C(3)H_A), 3.49 (1H, dd, *J* 13.1, 7.6, C(3)H_B), 3.93 (1H, app t, *J* 7.6, C(2)*H*), 7.25-7.40 (5H, m, *Ph*).

(*R*)-5,5-Dimethyl-4-isopropyloxazolidin-2-one (*R*)-145[5]



Step 1. $SOCl_2$ (13.2 mL, 320 mmol) was added dropwise to a stirred solution of (*R*)-valine (25.0 g, 213 mmol) in MeOH (400 mL) at 0 °C and the reaction mixture was left to warm to rt over 24 h before being concentrated *in vacuo* to give (*R*)-valine methyl ester hydrochloride as a white solid (35.7 g, quant.).

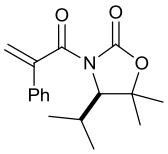
Step 2. $NaHCO_3$ (53.8 g, 640 mmol) and Boc_2O (48.9 g, 224 mmol) were added sequentially to a stirred solution of hydrochloride salt (35.7 g, 213 mmol) in EtOH (125 mL) at 0 °C and the reaction mixture was left to warm to rt over 48 h before being concentrated *in vacuo*. The residue was partitioned between EtOAc (200 mL) and H_2O (200 mL) and the organic layer was washed with satd aq $NaHCO_3$ (2 × 100 mL), brine (2 × 100 mL), dried and concentrated *in vacuo* to give (*R*)-*N*-*tert*-butoxycarbonyl valine methyl ester as a yellow oil (34.6 g, 70%).

Step 3. MeMgBr (2.40 M in Et_2O, 249.0 mL, 598 mmol) was added dropwise to a stirred solution of (*R*)-*N*-*tert*-butoxycarbonyl valine methyl ester (34.6 g, 150 mmol) in THF (500 mL) at 0 °C and the reaction mixture was stirred for 48 h at rt before being cooled to 0 °C and satd aq NH_4Cl (150 mL) added dropwise, followed by HCl (2.0 M aq, 150 mL). The phases were separated and the aqueous layer was extracted with Et_2O (2 × 250 mL). The combined organic extracts were washed with brine (150 mL), dried and concentrated *in vacuo* to give (*R*)-*tert*-butyl 2-hydroxy-2,4-dimethylpentan-3-ylcarbamate as a yellow oil (29.6 g, 86%).

Step 4. KO^tBu (14.0 g, 124.6 mmol) was added in one portion to a stirred solution of (*R*)-*tert*-butyl 2-hydroxy-2,4-dimethylpentan-3-ylcarbamate (26.2 g, 113.3 mmol) in THF (800 mL) at 0 °C and the resultant mixture was left to stir for 30 min before the addition of satd aq NH_4Cl (200 mL). The subsequent mixture was diluted with EtOAc (200 mL) and the phases were separated. The aqueous layer was extracted with EtOAc (2 × 100 mL) and the combined organic extracts were

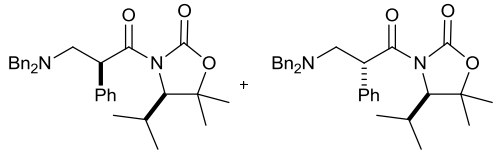
washed with brine (2 × 100 mL), dried and concentrated *in vacuo*. Purification by recrystallization (EtOAc/hexane) gave SuperQuat (*R*)-**145** as white needles (13.0 g, 73%);[5] mp 87−88 °C (EtOAc/hexane); {lit.[5] 87 °C (EtOAc/hexane)}; $[\alpha]_D^{25}$ −25.2 (*c* 1.0 in $CHCl_3$); {lit.[5] $[\alpha]_D^{25}$ −24.2 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 0.94 (3H, d, *J* 6.7, CH*Me*$_A$Me$_B$), 0.99 (3H, d, *J* 6.5, $CHMe_2$), 1.40 (3H, s, C(5)*Me*$_A$), 1.50 (3H, s, C(5)*Me*$_B$), 1.79-1.92 (1H, m, C*H*Me$_A$Me$_B$), 3.19 (1H, dd, *J* 8.7, 0.9, C(4)*H*), 5.15 (1H, br s, N*H*).

(*R*)-*N*(3)-(2′-Phenylacryloyl)-4-isopropyl-5,5-dimethyloxazolidin-2-one (*R*)-121[4]



BuLi (2.50 M in hexanes, 5.28 mL, 13.2 mmol) was added dropwise via syringe to a stirred solution of (*R*)-**145** (1.89 g, 12.0 mmol) in THF (30 mL) at −78 °C. After stirring for 10 min, a solution of **148** (2.78 g, 12.0 mmol) in THF (10 mL) −78 °C was added dropwise via cannula. After a further 30 min, the cooling bath was taken away and the reaction mixture was left to warm to rt over 2 h before the sequential addition of satd aq NH_4Cl (5 mL) and H_2O (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 80:20) gave (*R*)-**121** as a white solid (2.79 g, 72% from atropic acid **147**, 81% from **145**);[4] mp 70−72 °C; {lit.[4] for enantiomer 73−74 °C}; $[\alpha]_D^{25}$ −68.0 (*c* 1.0 in $CHCl_3$); {lit.[4] for enantiomer $[\alpha]_D^{25}$ +70.8 (*c* 0.6 in $CHCl_3$)}.

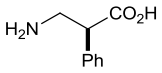
(4*R*,2′*S*)-and (*R*,*R*)-*N*(3)-(2′-Phenyl-3′-*N*,*N*-dibenzylamino)propanoyl-4-isopropyl-5,5-dimethyloxazolidin-2-one *ent*-122 and *ent*-150



BuLi (2.30 M in hexanes, 37.3 mL, 85.9 mmol) was added dropwise via syringe to a stirred solution of dibenzylamine (17.4 mL, 90.4 mmol) in THF (250 mL) at −78 °C. After stirring for 30 min, a solution of (*R*)-**121** (13.0 g, 45.2 mmol) in THF (200 mL) at −78 °C was added dropwise via cannula and the resultant mixture was left to stir for a further 4 h at −78 °C before the addition of 2-pyridone (13.0 g) and the reaction mixture was left to warm to rt over 16 h. Et_2O (300 mL) was

added and the resultant solution was sequentially washed with 10% aq citric acid solution (100 mL), satd aq $NaHCO_3$ (100 mL) and brine (100 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to give an 87:13 mixture of *ent*-**122** and *ent*-**150**. Purification via column chromatography (gradient elution 1% → 10% Et_2O in 30-40 °C petrol) gave *ent*-**122** as a colourless viscous oil (13.8 g, 63%, >99:1 dr);[i] $[\alpha]_D^{25}$ −5.1 (*c* 1.0 in $CHCl_3$). Further elution gave *ent*-**150** as a colourless viscous oil (1.99 g, 9%, >99:1 dr); $[\alpha]_D^{25}$ +7.4 (*c* 2.0 in $CHCl_3$).

(*S*)-2-Phenyl-3-aminopropanoic acid (*S*)-39[4]

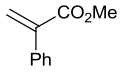


Step 1. H_2O_2 (30% aq, 8.1 mL) and LiOH (276 mg, 6.57 mmol) were sequentially added to a stirred solution of *ent*-**122** (530 mg, 1.10 mmol) in THF (10 mL) at 0 °C and the reaction mixture was left to warm to rt over 16 h before the addition of satd aq Na_2SO_3 (50 mL). The resultant mixture was diluted with EtOAc (30 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 30 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to furnish a 50:50 mixture of β-amino acid (*S*)-**151** and SuperQuat (*R*)-**145** (530 mg).

Step 2. Pd (10% wt on C, 200 mg) was added to a stirred degassed solution of a 50:50 mixture of β-amino acid (*S*)-**151** and SuperQuat (*R*)-**145** (530 mg) in MeOH (4 mL), H_2O (0.4 mL) and AcOH (0.1 mL). The suspension was stirred under H_2 (1 atm) for 24 h before being filtered though Celite®. The Celite® pad was washed with MeOH (20 mL) and the filtrate was concentrated *in vacuo*. The residue was co-evaporated with HCl (2.0 M in Et_2O, 3 × 5 mL). Purification via ion exchange chromatography on Dowex 50WX8 (100-200 mesh, eluent H_2O) gave SuperQuat (*R*)-**145** as white needles (120 mg, 70% from *ent*-**122**); mp 87−88 °C; {lit.[5] 87 °C; $[\alpha]_D^{20}$ −22.1 (*c* 1.0 in $CHCl_3$); {lit.[5] $[\alpha]_D^{23}$ −24.2 (*c* 1.0 in $CHCl_3$)}. Further elution (1.0 M aq NH_4OH eluent) gave (*S*)-**39** as a white solid (124 mg, 65% from *ent*-**122**); mp 220−222 °C {lit.[4] 224−225 °C}; $[\alpha]_D^{20}$ −92.0 (*c* 1.0 in H_2O); {lit.[6] $[\alpha]_D$ +94.0 (*c* 0.2 in H_2O).

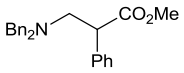
[i] Data as per page 109.

Methyl atropate 153[7]



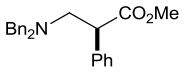
Thionyl chloride (0.74 mL, 10.1 mmol) was added dropwise via syringe to a solution of atropic acid **147** (1.00 g, 6.80 mmol) in MeOH (20 mL) at 0 °C and the reaction mixture was left to warm to rt over 24 h before being concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (20 mL) and satd aq $NaHCO_3$ (20 mL) and the organic layer was washed with satd aq $NaHCO_3$ (3 × 20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give **153** as a colourless oil (1.05 g, 95%);[7] δ_H (400 MHz, $CDCl_3$) 3.82 (3H, s, O*Me*), 5.89 (1H, d, *J* 0.9, C(3)H_A), 6.36 (1H, d, *J* 0.9, C(3)H_B), 7.33-7.43 (5H, m, *Ph*).

Methyl (*RS*)-2-phenyl-3-(*N*,*N*-dibenzylamino)-propanoate (*RS*)-152



Dibenzylamine (0.23 mL, 2.18 mmol) was added dropwise to a stirred solution of **153** (353 mg, 2.18 mmol) in MeOH (3 mL) and the resultant solution was heated to 60 °C for 2 h in a microwave before being concentrated *in vacuo*. Purification by column chromatography (gradient elution 5% → 10% EtOAc in 30-40 °C petrol) gave (*RS*)-**152** as a colourless oil (337 mg, 43%); ν_{max} (film) 1734 (C=O); δ_H (400 MHz, $CDCl_3$) 2.80 (1H, dd, *J* 13.0, 6.3, C(3)H_A), 3.25 (1H, dd, *J* 13.0, 9.3, C(3)H_B), 3.58 (2H, d, *J* 13.6, N(CH_ACH_BPh)$_2$), 3.65 (3H, s, O*Me*), 3.66 (2H, d, *J* 13.6, N(CH$_A$CH_BPh)$_2$), 3.86 (1H, dd, *J* 9.3, 6.3, C(2)*H*), 7.17-7.33 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 50.8 (*C*(2)), 51.9 (O*Me*), 57.5 (*C*(3)), 58.5 (N(*C*H$_2$Ph)$_2$), 126.9, 127.3 (*p-Ph*), 128.1, 128.2, 128.5, 128.9 (*o*,*m-Ph*), 137.3, 139.1 (*i-Ph*), 173.5 (*C*(1)); *m/z* (ESI$^+$) 360 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{26}NO_2^+$ ([M+H]$^+$) requires 360.1958; found 360.1958.

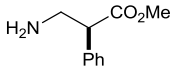
Methyl-(*S*)-2-phenyl-3-(*N*,*N*-dibenzylamino)-propanoate (*S*)-152



Step 1. H_2O_2 (30% aq, 8.5 mL) and LiOH (290 mg, 6.93 mmol) were sequentially added to a stirred solution of **122** (560 mg, 1.16 mmol) in THF (10 mL) at 0 °C and the reaction mixture was left to warm to rt over 16 h before the addition of satd aq Na_2SO_3 (50 mL). The resultant mixture was diluted with EtOAc (30 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 30 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to furnish a 50:50 mixture of β-amino acid (*S*)-**151** and SuperQuat (*R*)-**145** (550 mg).

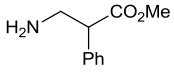
Step 2. $SOCl_2$ (0.13 mL, 1.73 mmol) was added dropwise via syringe to this mixture (550 mg) in MeOH (5 mL) at 0 °C and the reaction mixture was left to warm to rt over 16 h before being concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (50 mL) and satd aq $NaHCO_3$ (50 mL) and the layers were separated. The organic layer was extracted with satd aq $NaHCO_3$ (3 × 30 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution 5% → 10% EtOAc in 30-40 °C petrol) gave (*S*)-**152** as a colourless viscous oil (353 mg, 85% >99% ee); $[\alpha]_D^{25}$ +11.0 (*c* 1.0 in $CHCl_3$). Further elution (gradient elution 10% → 20% EtOAc in 30-40 °C petrol) gave (*R*)-**145** as a white solid (180 mg, 99%); mp 88−89 °C; {lit.[5] 87 °C}; $[\alpha]_D^{20}$ −20.7 (*c* 1.0 in $CHCl_3$); {lit.[5] $[\alpha]_D^{23}$ −24.2 (*c* 1.0 in $CHCl_3$). The enantiomeric excess of **152** was determined by Chiral HPLC, giving resolution of both enantiomers: AD-H Daicel chiral column, flow rate 1 mL/min (*iso*-propanol/hexane 2:98), (*R*)-enantiomer t_R = 6.5 min and (*S*)-enantiomer t_R = 7.6 min.

Methyl (*S*)-2-phenyl-3-aminopropanoate (*S*)-154



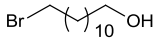
Pd (10% wt on C, 177 mg) was added to a stirred degassed solution of (*S*)-**152** (353 mg, 0.98 mmol) in MeOH (7.0 mL), H_2O (0.7 mL) and AcOH (0.2 mL). The suspension was stirred under H_2 (1 atm) for 24 h before being filtered though Celite®. The Celite® pad was washed with MeOH (20 mL) and the filtrate was concentrated *in vacuo* to give (*S*)-**154** as a colourless oil (167 mg, 95%, 99% ee); $[\alpha]_D^{20}$ −59.4 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1728 (C=O); δ_H (400 MHz, $CDCl_3$) 3.03 (1H, dd, *J* 13.0, 6.2, C(3)H_A), 3.31 (1H, dd, *J* 13.0, 8.2, C(2)H_B), 3.66 (1H, dd, *J* 8.2, 6.2, C(2)*H*), 3.69 (3H, s, O*Me*), 7.26-7.36 (5H, m, *Ph*); δ_c (100MHz, $CDCl_3$) 45.5 (C(3)), 51.9 (O*Me*), 55.3 (C(2)), 127.5, 128.0, 128.8 (*o,m,p-Ph*), 137.0 (*i-Ph*), 173.5 (C(1)); *m/z* (ESI^+) 180 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{10}H_{14}NO_2^+$ ($[M+H]^+$) requires 180.1019, found 180.1022.

Methyl (*RS*)-2-phenyl-3-aminopropanoate (*RS*)-154



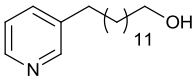
Pd (10% wt on C, 0.50 g) was added to a stirred degassed solution of (*RS*)-**152** (1.00 g, 3.71 mmol) in MeOH (5 mL). The suspension was stirred under H_2 (1 atm) for 24 h before being filtered though Celite®. The Celite® pad was washed with MeOH (20 mL) and the filtrate was concentrated *in vacuo* to give **154** as a colourless oil (0.65 g, 98%).

12-Bromododecan-1-ol 156[8]



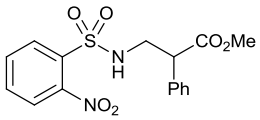
HBr (48% aq, 30 mL) was added to a stirred solution of 1,12-dodecandiol **155** (2.00 g, 9.90 mmol) in cyclohexane (30 mL) and the resultant mixture was stirred at reflux for 6 h, then allowed to cool to rt before the layers were separated. The aqueous layer was extracted with hexane (3 × 30 mL) and the combined organic extracts were washed with satd aq $NaHCO_3$ (4 × 30 mL), brine (30 mL) then dried ($MgSO_4$) and concentrated *in vacuo*. Purification via column chromatography (gradient elution, 5% → 30% EtOAc in 30-40 °C petrol) gave **156** as a colourless oil (2.28 g, 87%);[8] δ_H (400 MHz, $CDCl_3$) 1.21-1.47 (16H, m, C(3)H_2–C(10)H_2), 1.53-1.62 (2H, m, C(2)H_2), 1.86 (2H, quintet, *J* 7.1, C(11)H_2), 3.42 (2H, t, *J* 6.8, C(12)H_2), 3.62-3.68 (2H, m, C(1)H_2).

13-(Pyridin-3′-yl)tridecan-1-ol 157[9]



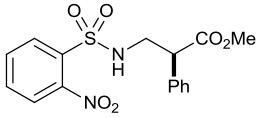
BuLi (2.50 M in hexanes, 0.33 mL, 2.35 mmol) was added dropwise via syringe to a stirred solution of diisopropylamine (0.33 mL, 2.35 mmol) in THF (5 mL) at −78 °C. After 30 min 3-picoline (0.23 mL, 2.35 mmol) was added via syringe and the reaction mixture was stirred for a further 30 min before the addition of a solution of **156** (250 mg, 0.94 mmol) in THF (3 mL). After 10 min, the cooling bath was taken away and the reaction mixture was allowed to warm to rt over 16 h before the sequential addition of satd aq NH_4Cl (10 mL) and H_2O (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 20% → 70% EtOAc in 30-40 °C petrol) gave **157** as an off-white solid (219 mg, 84%);[9] mp 48–49 °C; {lit.[9] 47–49 °C}; δ_H (400 MHz, $CDCl_3$) 1.21-1.40 (18H, m, C(3)H_2–C(11)H_2), 1.53-1.70 (4H, m, C(2)H_2, C(12)H_2), 2.61 (2H, t, *J* 7.7, C(13)H_2), 3.65 (2H, t, *J* 6.7, C(1)H_2), 7.18-7.24 (1H, m, C(5′)*H*), 7.47-7.52 (1H, m, C(4′)*H*), 8.41-8.46 (2H, m, C(2′)*H*, C(6′)*H*).

Methyl (*RS*)- 2-phenyl-3-(2′-nitrobenzenesulfonamido)propanoate (*RS*)-162



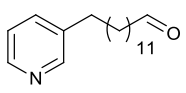
NEt_3 (0.31 mL, 2.23 mmol) and nitrobenzenesulfonyl chloride (494 mg, 2.23 mmol) were added sequentially to a stirred solution of (*RS*)-**154** (400 mg, 2.23 mmol) in CH_2Cl_2 (8 mL) at rt and the reaction mixture was stirred at rt for 30 min before the addition of HCl (1.0 M aq, 6 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 4:1) gave (*RS*)-**162** as a yellow oil (769 mg, 95%); ν_{max} (film) 1729 (C=O), 1539, 1346 (NO_2); δ_H (400MHz, $CDCl_3$) 3.40-3.50 (1H, m, C(3)H_A), 3.60-3.67 (1H, m, C(3)H_B), 3.68 (3H, s, O*Me*), 3.89 (1H, (1H, dd, *J* 8.9, 6.0, C(2)*H*), 7.15-7.20 (2H, m, *Ph*), 7.25-7.36 (3H, m, *Ph*), 7.70-7.77 (2H, m, C(4′)*H*), C(5′)*H*), 7.84-7.90 (1H, m, C(3′)*H*), 8.06-8.13 (1H, m, C(6′)*H*); δ_c (100MHz, $CDCl_3$) 46.1 (*C*(3)), 51.5 (O*Me*), 52.4 (*C*(2)), 125.4 (*C*(3′)), 127.8 (*o*,*m-Ph*), 128.1(*p-Ph*), 129.0 (*o*,*m-Ph*), 130.8 (*C*(6′)), 132.9, 133.6, 133.6 (*C*(1′), (*C*(4′), (*C*(5′)), 135.2 (*C*(*i-Ph*), 147.8 (*C*(2′)), 172.5 (*C*(1)); *m/z* (ESI^+) 387 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{16}H_{16}N_2NaO_6S^+$ ($[M+Na]^+$) requires 387.0621, found 387.0612.

Methyl-(*S*)- 2-phenyl-3-(2′-nitrobenzenesulfonamido)propanoate (*S*)-162



Et_3N (0.16 mL, 1.12 mmol) and 2-Nitrobenzenesulfonyl chloride (298 mg, 1.12 mmol) were added sequentially to a stirred solution of (*S*)-**154** (200 mg, 1.12 mmol) in CH_2Cl_2 (5 mL) at rt and the reaction mixture was stirred at rt for 30 min before the addition of HCl (1.0 M aq, 5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 4:1) gave (*S*)-**162** as a yellow oil (386 mg, 95%); $[\alpha]_D^{20}$ −66.5 (*c* 1.0 in $CHCl_3$).

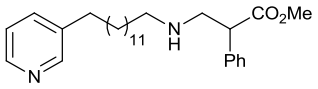
13-(Pyridin-3′-yl)tridecanal 167



IBX (2.07 g, 7.39 mmol) was added to a stirred solution of **157** (0.68 g, 2.46 mmol) in EtOAc (15 mL) at rt and the reaction mixture was stirred at 80 °C for 3 h before being cooled to rt and filtered

though Celite®. The Celite® pad was washed with EtOAc (30 mL) and the filtrate was concentrated *in vacuo* to give **167** as a yellow oil (0.67 g, 99%); δ_H (400 MHz, $CDCl_3$) 1.22-1.37 (16H, m, C(4)H_2−C(11)H_2), 1.56-1.68 (4H, m, C(3)H_2, C(12)H_2), 2.43 (2H, td, *J* 7.4, *J* 1.9 C(2)H_2), 2.61 (2H, t, *J* 7.7, C(13)H_2), 7.19-7.24 (1H, m, C(5′)*H*), 7.48-7.53 (1H, m, C(4′)*H*), 8.41-8.47 (2H, m, C(2′)*H*, C(6′)*H*), 9.77 (1H, t, *J* 1.9, C(1)*H*).

Methyl (*RS*)-2-phenyl-3-(13′-(pyridin-3′′-yl)tridecylamino)propanoate (*RS*)-164



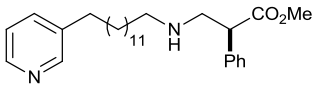
Method A. Step 1. DEAD (56 μL, 0.36 mmol) was added dropwise via syringe to a stirred solution of PPh_3 (94 mg, 0.36 mmol) and (*RS*)-**162** (131 mg, 0.36 mmol) in CH_2Cl_2 (3 mL) at 0 °C. After 1 h, a solution of **157** (99 mg, 0.36 mmol) in CH_2Cl_2 (2 mL) was added and the reaction mixture was left to warm to rt over 2 h and concentrated *in vacuo* to give the crude reaction mixture (350 mg).

Step 2. KOH (11.0 M aq, 62 μL, 0.68 mmol) was added to a stirred solution of PhSH (69 μL, 0.68 mmol) in MeCN (2 mL) at 0 °C. After 5 min, a solution of the crude reaction mixture from the previous step (350 mg) in MeCN (4 mL) was added, and the resultant mixture was left to stir at 40 °C for 40 min before being allowed to cool to rt and partitioned between H_2O (20 mL) and CH_2Cl_2 (20 mL). The aqueous layer was washed with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc/Et_3N, 50:49:1) gave (*RS*)-**164** as a pale yellow viscous oil (72 mg, 60% from (*RS*)-**162**); ν_{max} (film) 1735 (C=O); δ_H (400 MHz, $CDCl_3$) 1.20-1.37 (18H, m, C(3′)H_2−C(11′)H_2), 1.40-1.48 (2H, m, C(2′)H_2), 1.56-1.66 (2H, m, C(12′)H_2), 2.60 (4H, app t, *J* 7.6, C(1′)H_2, C(13′)H_2), 2.90 (1H, dd, *J* 12.0, 6.7, C(3)H_A), 3.28 (1H, dd, *J* 12.0, 8.5, C(3)H_B), 3.68 (3H, s, O*Me*), 3.84 (1H, dd, *J* 8.5, 6.7, C(2)*H*), 7.20 (1H, dd, *J* 7.7, 4.9, C(5′′)*H*), 7.25-7.37 (5H, m, *Ph*), 7.49 (1H, d, *J* 7.8, C(4′′)*H*), 8.41-8.46 (2H, m, C(2′′)*H*, C(6′′)*H*); δ_C (100 MHz, $CDCl_3$) 27.2, 29.1, 29.4, 29.5, 29.6, 29.9, 31.1 (*C*(2′)−*C*(12′)), 33.0 (*C*(13′)), 49.7 (*C*(2)), 51.9 (*C*(1′)), 52.0 (O*Me*), 52.6 (*C*(3)), 123.2 (*C*(5′′)), 127.5 (*p-Ph*), 128.0, 128.8 (*o,m-Ph*), 135.8 (*i-Ph*), 137.3 (*C*(4′′)), 138.0 (*C*(3′′)), 147.1 (*C*(6′′)), 149.9 (*C*(2′′)), 173.7 (*C*(1)); *m/z* (ESI^+) 439 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{28}H_{43}N_2O_2^+$ ($[M+H]^+$) requires 439.3319; found 439.3313.

Method B. A solution of (*RS*)-**154** (123 mg, 0.69 mmol) in 1,2-DCE (3 mL) was added to a stirred solution of **167** (190 mg, 0.69 mmol) in 1,2-DCE (3 mL) at rt. After 5 min, AcOH (1 drop) and

$NaBH(OAc)_3$ (292 mg, 1.38 mmol) were added and the resultant mixture was stirred at rt for 16 h before the addition of satd aq $NaHCO_3$ (10 mL). The layers were separated and the aqueous layer was extraced with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc/Et_3N, 50:49:1) gave (*S*)-**164** as a pale yellow viscous oil (193 mg, 64%).

Methyl (*S*)-2-phenyl-3-[*N*-13′-(pyridin-3′′-yl)tridec-1′-ylamino]propanoate (*S*)-164

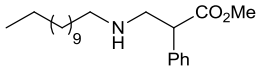


Method A. *Step 1*. DEAD (65 μL, 0.41 mmol) was added dropwise via syringe to a stirred solution of PPh_3 (108 mg, 0.41 mmol) and (*S*)-**162** (150 mg, 0.41 mmol) in CH_2Cl_2 (3 mL) at 0 °C. After 1 h, a solution of **167** (114 mg, 0.41 mmol) in CH_2Cl_2 (2 mL) was added and the reaction mixture was left to warm to rt over 2 h and concentrated *in vacuo* to give the crude reaction mixture (400 mg).

Step 2. KOH (11.0 M aq, 95 μL, 1.03 mmol) was added to a stirred solution of PhSH (106 μL, 1.03 mmol) in MeCN (4 mL) at 0 °C. After 5 min, a solution of the crude reaction mixture from the previous step (400 mg) in MeCN (4 mL) was added, and the resultant mixture was left to stir at 40 °C for 40 min before being allowed to cool to rt and partitioned between H_20 (20 mL) and CH_2Cl_2 (20 mL). The aqueous layer was washed with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc/Et_3N, 50:49:1) gave (*S*)-**164** as a pale yellow viscous oil (103 mg, 55% from (*S*)-**162**, 56% ee);[10] $[\alpha]_D^{25}$ −3.0 (*c* 0.5 in $CHCl_3$).

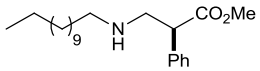
Method B. A solution of (*S*)-**154** (123 mg, 0.69 mmol) in 1,2-DCE (3 mL) was added to a stirred solution of **167** (190 mg, 0.69 mmol) in 1,2-DCE (3 mL) at rt. After 5 min, AcOH (1 drop) and $NaBH(OAc)_3$ (292 mg, 1.38 mmol) were added and the resultant mixture was stirred at rt for 16 h before the addition of satd aq $NaHCO_3$ (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc/Et_3N, 50:49:1) gave (*S*)-**164** as a pale yellow viscous oil (180 mg, 60%, 70% ee);[10] $[\alpha]_D^{25}$ −4.0 (*c* 0.5 in $CHCl_3$).

Methyl (*RS*)-2-phenyl-3-(*N*-dodec-1′-ylamino)propanoate (*RS*)-166



Dodecylamine (370 mg, 2.00 mmol) was added dropwise to a stirred solution of **153** (324 mg, 2.0 mmol) in MeOH (2 mL) and the resultant mixture was heated to 100 °C for 1 h in a Microwave before being concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 2:1) gave (*RS*)-**166** as a white solid (547 mg, 79%); mp 25−26 °C; ν_{max} (film) 1734 (C=O); δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.8, C(12′)H_3), 1.20-1.36 (18H, m, C(3′)H_2−C(11′)H_2), 1.38-1.49 (2H, m, C(2′)H_2), 2.54-2.66 (2H, m, C(1′)H_2), 2.90 (1H, dd, *J* 12.0, 6.6, C(3)H_A), 3.28 (1H, dd, *J* 12.0, 8.6, C(3)H_B), 3.66 (3H, s, O*Me*), 3.83 (1H, dd, *J* 8.6, 6.6, C(2)*H*), 7.23-7.36 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.0 (*C*(12′)), 22.6, 27.1, 29.3, 29.41, 29.49, 29.51, 29.53, 29.57, 29.9 (*C*(2′)-*C*(11′)), 49.6 (*C*(1′)), 51.86 (O*Me*), 51.88 (*C*(2)), 52.6 (*C*(3)), 127.4, 127.9, 128.7 (*o*,*m*,*p*-*Ph*), 137.3 (*i*-*Ph*), 173.5 (C(1)); *m/z* (ESI^+) 348 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{22}H_{28}NO_2^+$ ($[M+H]^+$) requires 348.2897; found 348.2897.

Methyl (*S*)-2-phenyl-3-(*N*-dodec-1′-ylamino)propanoate (*S*)-166



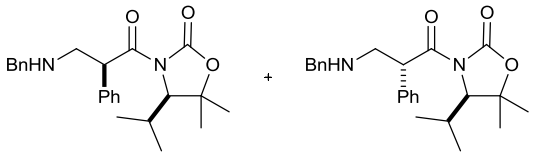
Method A. Step 1. DEAD (0.11 mL, 0.68 mmol) was added dropwise via syringe to a stirred solution of PPh_3 (178 mg, 0.68 mmol) and (*S*)-**162** (126 mg, 0.68 mmol) in CH_2Cl_2 (3 mL) at 0 °C. After 1 h, dodecanol (190 mg, 0.52 mmol) was added dropwise and the reaction mixture was left to warm to rt over 2 h and concentrated *in vacuo* to give the crude reaction mixture (350 mg).

Step 2. KOH (11.0 M aq, 0.12 mL, 1.30 mmol) was added to a stirred solution of PhSH (0.13 mL, 1.30 mmol) in MeCN (3 mL) at 0 °C. After 5 min, a solution of the crude reaction mixture from the previous step (350 mg) in MeCN (3 mL) was added, and the resultant mixture was left to stir at 40 °C for 40 min before being allowed to cool to rt and partitioned between H_2O (10 mL) and CH_2Cl_2 (20 mL). The aqueous layer was washed with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 2:1) gave (*S*)-**166** as a pale yellow solid (80 mg, 44% from (*S*)-**162**, 83% ee);[11] mp 26−27 °C; $[\alpha]_D^{20}$ −25.6 (*c* 0.5 in $CHCl_3$).

Method B. Dodecanal (0.12 mL, 0.56 mmol) was added to a stirred solution of (*S*)-**154** (100 mg, 0.56 mmol) in 1,2-DCE (5 mL) at rt. After 5 min, AcOH (0.05 mL) and $NaBH(OAc)_3$ (292 mg, 1.38 mmol) were added and the resultant mixture was stirred at rt for 1 h, before the addition of satd aq $NaHCO_3$ (10 mL). The layers were separated and the aqueous layer was extracted with

CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 2:1) gave **168** as a pale yellow oil (98 mg, 34%); $[\alpha]_D^{20}$ −5.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1741 (C=O); δ_H (400 MHz, $CDCl_3$) 0.89 (6H, t, *J* 6.9, C(12′)H_3, C(12″)H_3), 1.16-1.45 (40H, m, C(2′)H_2−C(11′)H_2, C(2″)H_2−C(11″)H_2), 2.32-2.52 (4H, m, C(1′)H_2, C(1″)H_2), 2.60 (1H, dd, *J* 13.0, 5.1, C(3)H_A), 3.22 (1H, dd, *J* 13.0, 10.1, C(3)H_B), 3.67 (3H, s, O*Me*), 3.79 (1H, dd, *J* 10.1, 5.1, C(2)*H*), 7.22-7.38 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(12′), *C*(12″)), 22.7, 27.1, 27.4, 29.4, 29.64, 29.67, 29.71, 29.73, 31.9 (*C*(2′)-*C*(11′), *C*(2″)-*C*(11″)), 51.0 (O*Me*), 51.8 (*C*(2)), 54.4 (*C*(1′), *C*(1″)), 58.5 (*C*(3)), 127.2 (*p-Ph*), 128.0, 128.5 (*o,m-Ph*), 137.8 (*i-Ph*), 173.9 (*C*(1)); *m/z* (ESI^+) 516 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{34}H_{62}NO_2^+$ ($[M+H]^+$) requires 516.4775; found 516.4761. Further elution (eluent 30-40 °C petrol/Et_2O, 2:1) gave (*S*)-**166** as a pale yellow solid (8 mg, 3%, 92% ee);[11] mp 26−27 °C; $[\alpha]_D^{20}$ −29.6 (*c* 0.5 in $CHCl_3$).

(4*R*,2′*S*)-and (*R*,*R*)-*N*(3)-(2′-Phenyl-3′-*N*-benzylamino)propanoyl-4-isopropyl-5,5-dimethyloxazolidin-2-one (4*R*,2′*S*)-171 and (*R*,*R*)-172



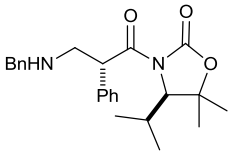
Method A. Step 1. BuLi (2.20 M in hexanes, 3.30 mL, 7.28 mmol) was added dropwise to a stirred solution of dibenzylamine (1.47 mL, 7.67 mmol) in THF (60 mL) at −78 °C under nitrogen. After stirring for 30 min, a solution of (*R*)-**121** (1.10 g, 3.83 mmol) in THF (50 mL) at −78 °C was added dropwise via cannula. The reaction mixture was stirred for 4 h at −78 °C, before the addition of 2-pyridone (1.09 g, 11.5 mmol). The resultant mixture was allowed to warm to rt over 16 h. Et_2O (50 mL) was added and the resultant solution was washed sequentially with 10% aq citric acid (30 mL), satd aq $NaHCO_3$ (30 mL) and brine (30 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to give an 87:13 mixture of *ent*-**122** and *ent*-**150** (1.85 g).

Step 2. CAN (4.41 g, 8.05 mmol) was added to a solution of the 87:13 mixture of *ent*-**122** and *ent*-**150** (1.85 g, 3.83 mmol) in MeCN (50 mL) and H_2O (10 mL) at rt. The reaction mixture was stirred at rt for 16 h, before the addition of satd aq $NaHCO_3$ (40 mL). The resultant mixture was stirred vigorously for 20 min. The organic layer was decanted off and brine (40 mL) was added to the aqueous layer. The resultant solution was extracted with EtOAc (3 × 40 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give an 87:13 mixture of **171** and **172**. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O/Et_3N, 74:25:1) gave

171 as a colourless oil (1.10 g, 73% from **121**, >99:1 dr); $[\alpha]_D^{20}$ −89.8 (*c* 1.0 in $CHCl_3$); ν_{max} 1772 (C=O, exocyclic), 1697 (C=O, endocyclic); δ_H (400 MHz, $CDCl_3$) 1.00 (3H, d, *J* 6.9, CH*Me*$_A$), 1.03 (3H, s, C(5)*Me*$_A$), 1.10 (3H, d, *J* 6.9, CH*Me*$_B$), 1.45 (3H, s, C(5)*Me*$_B$), 1.57 (1H, br s, N*H*), 2.09–2.21 (1H, m, C*H*Me$_2$), 2.97 (1H, dd, *J* 11.9, 6.0, C(3′)*H*$_A$), 3.40 (1H, dd, *J* 11.9, 9.1, C(3′)*H*$_B$), 3.85 (2H, app s, NC*H*$_2$Ph), 4.08 (1H, d, *J* 3.3, C(4)*H*), 5.38 (1H, dd, *J* 9.1, 6.0, C(2′)*H*), 7.20–7.38 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.1 (CH*Me*$_B$), 21.3 (C(5)*Me*$_A$), 21.6 (CH*Me*$_A$), 28.3 (C(5)*Me*$_B$), 29.5 (*C*HMe$_2$), 49.2 (*C*(2′)), 52.7 (*C*(3′)), 53.4 (N*C*H$_2$Ph), 67.0 (*C*(4)), 82.7 (*C*(5)), 126.8, 127.5 (*p-Ph*), 128.0, 128.3, 128.6, 128.6 (*o*,*m-Ph*), 136.9, 140.2 (*i-Ph*), 153.2 (*C*(2)), 173.7 (*C*(1′)); *m/z* (ESI^+) 395 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{24}H_{31}N_2O_3^+$ ($[M+H]^+$) requires 395.2329; found 395.2324. Further elution gave **172** as a pale yellow oil (0.14 g, 9% from **121**, >99:1 dr); $[\alpha]_D^{20}$ +20.2 (*c* 1.0 in $CHCl_3$); ν_{max} 1771 (C=O, exocyclic), 1698 (C=O, endocyclic); δ_H (400 MHz, $CDCl_3$) 0.63 (3H, d, *J* 6.9, CH*Me*$_A$), 0.83 (3H, d, *J* 6.9, CH*Me*$_B$), 1.42 (3H, s, C(5)*Me*$_A$), 1.46 (3H, s, C(5)*Me*$_B$), 1.76 (1H, br s, N*H*), 1.98–2.09 (1H, m, C*H*Me$_2$), 2.96 (1H, dd, *J* 11.9, 5.8 C(3′)*H*$_A$), 3.39 (1H, dd, *J* 11.9, 9.4, C(3′)*H*$_B$), 3.81 (2H, app s, NC*H*$_2$Ph), 4.24 (1H, d, *J* 2.8, C(4)*H*), 5.38 (1H, dd, *J* 9.4, 5.8, C(2′)*H*), 7.20–7.35 (8H, m, *Ph*), 7.43–7.48 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.3 (CH*Me*$_A$), 21.3 (C(5)*Me*$_B$), 21.3 (CH*Me*$_B$), 28.8 (C(5)*Me*$_A$), 29.7 (*C*HMe$_2$), 49.2 (*C*(2′)), 52.2 (C(3′)), 53.6 (N*C*H$_2$Ph), 66.0 (*C*(4)), 82.6 (*C*(5)), 126.9, 127.5 (*p-Ph*), 128.0, 128.3, 128.5, 128.8, (*o*,*m-Ph*), 137.0, 140.0 (*i-Ph*), 153.2 (*C*(2)), 173.9 (*C*(1′)); *m/z* (ESI^+) 395 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{24}H_{31}N_2O_3^+$ ($[M+H]^+$) requires 395.2329; found 395.2317.

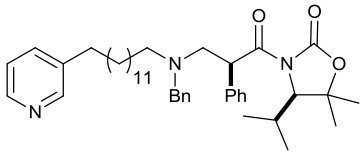
Method B. CAN (1.90 g, 3.47 mmol) was added to a solution of *ent*-**122** (0.80 g, 1.65 mmol) in MeCN (25 mL) and H_2O (5 mL) at rt. The reaction mixture was stirred at rt for 16 h, before the addition of satd aq $NaHCO_3$ (20 mL). The resultant mixture was stirred vigorously for 20 min. The organic layer was decanted off and brine (20 mL) was added to the aqueous layer. The resultant solution was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O/Et_3N, 74:25:1) gave **171** as a colourless oil (0.49 g, 76%, >99:1 dr).

(*R*,*R*)-*N*(3)-(2′-Phenyl-3′-*N*-benzylamino)propanoyl-4-isopropyl-5,5-dimethyloxazolidin-2-one 172



CAN (285 mg, 0.52 mmol) was added to a solution of *ent*-**150** (120 mg, 0.25 mmol) in MeCN (3.0 mL) and H_2O (0.6 mL) at rt and the resultant mixture was stirred at rt for 16 h before the addition of satd aq $NaHCO_3$ (10 mL). The reaction mixture was stirred vigorously for 20 min, the organic layer was then decanted off and brine (10 mL) was added to the aqueous layer. The resultant solution was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O/Et_3N, 74:25:1) gave **172** as a colourless oil (68 mg, 70%, >99:1 dr); $[\alpha]_D^{20}$ +20.1 (*c* 1.0 in $CHCl_3$).

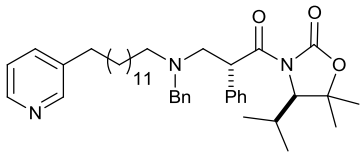
(4*R*,2′*S*)-*N*(3)-{2′-Phenyl-3′-[*N*-benzyl-*N*-13′′-(pyridin-3′′′-yl)tridecylamino]propanoyl}-4-isopropyl-5,5-dimethyloxazolidin-2-one 173



A solution of **171** (0.64 g, 1.62 mmol) in 1,2-DCE (10 mL) was added to a stirred solution of **167** (0.67 g, 2.44 mmol) in 1,2-DCE (10 mL) at rt. After 5 min, AcOH (0.1 mL) and $NaBH(OAc)_3$ (0.69 g, 3.23 mmol) were added and the resultant mixture was stirred at rt for 16 h before the addition of satd aq $NaHCO_3$ (30 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O/Et_3N, 59:40:1) gave **173** as a yellow oil (0.90 g, 85%, >99:1 dr); $[\alpha]_D^{20}$ –26.2 (*c* 1.0 in $CHCl_3$); ν_{max} 1774 (C=O, exocyclic), 1700 (C=O, endocyclic); δ_H (400 MHz, $CDCl_3$) 0.96 (3H, s, C(5)*Me*$_A$), 1.02 (3H, d, *J* 6.9, CH*Me*$_A$), 1.11 (3H, d, *J* 6.9, CH*Me*$_B$), 1.14-1.38 (18H, m, C(3′′)H_2–C(11′′)H_2), 1.39-1.51 (5H, m, C(12′′)H_2, C(5)*Me*$_B$), 1.62 (2H, quintet, *J* 7.3, C(2′′)H_2), 2.09-2.21 (1H, m, C*H*Me$_2$), 2.36-2.45 (1H, m, C(1′′)H_A), 2.47-2.56 (1H, m, C(1′′)H_B), 2.60 (2H, t, *J* 7.8, C(13′′)H_2), 2.67 (1H, dd, *J* 12.8, 4.8, C(3′)H_A), 3.46 (1H, dd, *J* 12.8, 9.7, C(3′)H_B), 3.59 (1H, d, *J* 13.7, NCH_AH$_B$Ph), 3.77 (1H, d, *J* 13.7, NCH$_A$$H_B$Ph), 4.06 (1H, d, *J* 3.0, C(4)*H*), 5.52 (1H, dd, *J* 9.7, 4.8, C(2′)*H*), 7.16-7.34 (11H, m, C(5′′′)*H*, *Ph*), 7.45-7.50 (1H, m, C(4′′′)*H*), 8.40-8.48 (2H, m, C(2′′′)*H*), C(6′′′)*H*); δ_C (100 MHz, $CDCl_3$) 17.0 (CH*Me*$_A$), 21.2 (C(5)*Me*$_B$), 21.4 (CH*Me*$_B$), 26.7 (C(5)*Me*$_A$), 27.2 (*C*HMe$_2$), 29.1, 29.3, 29.5 (C(3′′)-C(12′′)), 31.1 (C(2′′)), 32.9 (C(13′′)), 47.0 (*C*(2′)), 53.8 (C(1′′)), 58.0 (*C*(3′)), 58.7

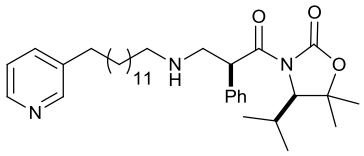
(N*C*H$_2$Ph), 66.9 (*C*(4)), 82.5 (*C*(5)), 123.1 (*C*(5‴)), 126.6, 127.2 (*p-Ph*), 127.8, 128.4, 128.9 (*o,m-Ph*), 135.6 (*C*(4‴)), 137.4, 137.9, 139.4 (*i-Ph*, *C*(3‴)), 147.1 (*C*(6‴)), 149.9 (*C*(2‴)), 153.4 (*C*(2)), 173.5 (*C*(1′)); *m/z* (ESI$^+$) 654 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{42}H_{60}N_3O_3^+$ ([M+H]$^+$) requires 654.4629; found 654.4625.

(*R*,*R*)-*N*(3)-{2′-Phenyl-3′-[*N*-benzyl-*N*-13′′-(pyridin-3‴-yl)tridecylamino]propanoyl}-4-isopropyl-5,5-dimethyloxazolidin-2-one 174



A solution of **172** (640 mg, 1.62 mmol) in 1,2-DCE (10 mL) was added to a stirred solution of **167** (670 mg, 2.44 mmol) in 1,2-DCE (10 mL) at rt. After 5 min, AcOH (0.1 mL) and NaBH(OAc)$_3$ (685 mg, 3.23 mmol) were added and the resultant mixture was stirred at rt for 16 h before the addition of satd aq NaHCO$_3$ (30 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O/Et_3N, 59:40:1) gave **174** as a yellow oil (870 mg, 82%, >99:1 dr); $[\alpha]_D^{20}$ +2.9 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1773 (C=O, exocyclic), 1700 (C=O, endocyclic); δ_H (400 MHz, $CDCl_3$) 0.60 (3H, d, *J* 6.9, CH*Me*$_A$), 0.79 (3H, d, *J* 6.9, CH*Me*$_B$), 1.09-1.51 (20H, m, C(3′′)*H*$_2$−C(12′′)*H*$_2$), 1.44 (3H, s, C(5)*Me*$_A$), 1.47 (3H, s, C(5)*Me*$_B$), 1.62 (2H, quintet, *J* 7.3, C(2′′)*H*$_2$), 1.94-2.04 (1H, m, C*H*Me$_2$), 2.32-2.41 (1H, m, C(1′′)*H*$_A$), 2.41-2.52 (1H, m, C(1′′)*H*$_B$), 2.60 (2H, t, *J* 7.9, C(13′′)*H*$_2$), 2.68 (1H, dd, *J* 12.7, 4.6, C(3′)*H*$_A$), 3.48 (1H, dd, *J* 12.7, 10.5, C(3′)*H*$_B$), 3.56 (1H, d, *J* 13.7, NC*H*$_A$H$_B$Ph), 3.73 (1H, d, *J* 13.7, NCH$_A$*H*$_B$Ph), 4.24 (1H, d, *J* 3.2, C(4)*H*), 5.53 (1H, dd, *J* 10.5, 4.6, C(2′)*H*), 7.17-7.33 (9H, m, C(5‴)*H*, *Ph*), 7.41-7.53 (3H, m, C(4‴)*H*, *Ph*), 8.40-8.50 (2H, m, C(2‴)*H*), C(6‴)*H*); δ_C (100 MHz, $CDCl_3$) 16.3 (CH*Me*$_A$), 21.2 (C(5)*Me*$_A$), 21.4 (CH*Me*$_B$), 26.7 (C(5)*Me*$_B$), 27.2 (*C*HMe$_2$), 29.1, 29.3, 29.5 (*C*(3′′)−*C*(12′′)), 31.1 (*C*(2′′)), 32.9 (*C*(13′′)), 47.0 (*C*(2′′)), 53.8 (*C*(1′′)), 58.0 (*C*(3′)), 58.7 (N*C*H$_2$Ph), 66.9 (*C*(4)), 82.5 (*C*(5)), 123.1 (*C*(5‴)), 126.6, 127.2 (*p-Ph*), 127.8, 128.4 128.4, 128.9 (*o,m-Ph*), 135.6 (*C*(4‴)), 137.4, 137.9, 139.4 (*i-Ph*, *C*(3‴)), 147.1 (*C*(6‴)), 149.9 (*C*(2‴)), 153.1 (*C*(2)), 173.8 (*C*(1′)); *m/z* (ESI$^+$) 654 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{42}H_{60}N_3O_3^+$ ([M+H]$^+$) requires 654.4629; found 654.4645.

(4*R*,2′*S*)-*N*(3)-{2′-Phenyl-3′-[*N*-13′′-(pyridin-3′′′-yl)tridecylamino]propanoyl}-4-isopropyl-5,5-dimethyloxazolidin-2-one 175



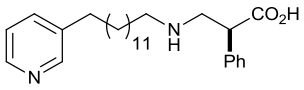
Method A. CAN (705 mg, 1.29 mmol) was added to a solution of **173** (400 mg, 0.61 mmol) in MeCN (10 mL) and H_2O (2 mL) at rt and the resultant mixture was stirred for 16 h before the addition of satd aq $NaHCO_3$ (10 mL). The reaction mixture was stirred vigorously for 20 min and the organic layer was decanted off and brine (10 mL) was added to the aqueous layer. The resultant solution was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification via flash column chromatography (eluent $CHCl_3$/NH_4OH, 99:1) gave **175** as a colourless oil (245 mg, 71%, >99:1 dr); $[\alpha]_D^{20}$ −57.3 (*c* 1.0 in $CHCl_3$); ν_{max} 1774 (C=O, exocyclic), 1700 (C=O, endocyclic); δ_H (500 MHz, $CDCl_3$) 0.99 (3H, d, *J* 6.9, CH*Me*$_A$), 1.01 (3H, s, C(5)*Me*$_A$), 1.08 (3H, d, *J* 6.9, CH*Me*$_B$), 1.17-1.36 (18H, m, C(3′′)*H*$_2$−C(11′′)*H*$_2$), 1.38-1.48 (5H, m, C(12′′)*H*$_2$, C(5)*Me*$_B$), 1.61 (2H, quintet, *J* 7.4, C(2′′)*H*$_2$), 2.09-2.19 (1H, m, C*H*Me$_2$), 2.55-2.71 (4H, m, C(1′′)*H*$_2$), C(13′′)*H*$_2$), 2.93 (1H, dd, *J* 12.1, 6.0, C(3′)*H*$_A$), 3.36 (1H, dd, *J* 12.1, 9.1, C(3′)*H*$_B$), 4.07 (1H, d, *J* 3.2, C(4)*H*), 5.33 (1H, dd, *J* 9.1, 6.0, C(2′)*H*), 7.16-7.37 (6H, m, C(5′′′)*H*, *Ph*), 7.46-7.50 (1H, m, C(4′′′)*H*), 8.41-8.46 (2H, m, C(2′′′)*H*), C(6′′′)*H*); δ_C (125 MHz, $CDCl_3$) 17.0 (CH*Me*$_A$), 21.2 (C(5)*Me*$_B$), 21.6 (CH*Me*$_B$), 28.3 (C(5)*Me*$_A$), 29.4 (*C*HMe$_2$), 29.1, 29.5, 29.6, 30.1 (C(3′′)−C(12′′)), 31.1 (C(2′′)), 33.0 (C(13′′)), 49.1 (*C*(2′)), 49.4 (C(1′′)), 53.3 (C(3′)), 66.9 (*C*(4)), 82.6 (*C*(5)), 123.2 (*C*(5′′′)), 127.5 (*p-Ph*), 128.6 (*o,m-Ph*), 135.7 (*C*(4′′′)), 137.0, 138.0 (*C*(3′′′), *i-Ph*), 147.1 (*C*(6′′′)), 150.0 (*C*(2′′′)), 153.1 (*C*(2)), 173.8 (*C*(1′)); *m/z* (ESI^+) 564 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{35}H_{54}N_3O_3^+$ ($[M+H]^+$) requires 564.4160; found 564.4154.

Method B. $Pd(OH)_2$/C (30% w/w of substrate, 20 mg) was added to a stirred degassed solution of **173** (65 mg, 0.10 mmol) in EtOAc (2 mL). The resultant suspension was stirred under H_2 (1 atm) for 16 h before being filtered though Celite®. The Celite® pad was washed with EtOAc (10 mL) and the filtrate was concentrated *in vacuo*. Purification via flash column chromatography (eluent $CHCl_3$/NH_4OH, 99:1) gave **175** as a colourless oil (35 mg, 63%, >99:1 dr); $[\alpha]_D^{20}$ −57.1 (*c* 1.0 in $CHCl_3$).

Method C. $Pd(OH)_2$/C (30% w/w of substrate, 20 mg) was added to a stirred degassed solution of **173** (100 mg, 0.10 mmol) in MeOH (2 mL). The resultant suspension was stirred under H_2 (1 atm) for 16 h before being filtered though Celite®. The Celite® pad was washed with EtOAc (10 mL) and

the filtrate was concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 90:10) gave (*R*)-**145** as a white solid (7.5 mg, 31%); mp 87−88 °C; {lit.[5] mp 87 °C}; $[\alpha]_D^{20}$ −21.2 (*c* 0.25 in $CHCl_3$); {lit.[5] $[\alpha]_D^{23}$ −24.2 (*c* 1.0 in $CHCl_3$)}. Further elution (eluent 30-40 °C petrol/EtOAc, 50:50) gave **164** (17 mg, 25%). Further Further elution (eluent 30-40 °C petrol/EtOAc, 80:20) gave **175** (4.3 mg, 5%); $[\alpha]_D^{20}$ −60.0 (*c* 0.1 in $CHCl_3$).

(*S*)-2-Phenyl-3-[*N*-13′-(pyridin-3″-yl)tridecylamino]propanoic acid (*S*)-126



Method A. Step 1. $NaHCO_3$ (53 mg, 0.64 mmol) and Boc_2O (0.11 mL, 0.48 mmol) were added sequentially to a stirred solution of **175** (180 mg, 0.32 mmol) in EtOH (5 mL) at 0 °C, and the reaction mixture was left to warm to rt over 16 h, before being concentrated *in vacuo*. The residue was dissolved in EtOAc (15 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (2 × 15 mL) and brine (2 × 15 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give **177** (180 mg).

Step 2. H_2O_2 (30% aq, 0.81 mL) and LiOH (69 mg, 1.63 mmol) were added sequentially to **177** (180 mg) in THF (2.5 mL) at 0 °C and the reaction mixture was left to warm to rt over 16 h before the addition of satd aq Na_2SO_3 (10 mL). EtOAc (10 mL) was added and the phases were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was dissolved in HCl (2.0 M in Et_2O, 3 mL) and left to stir for 30 min at rt before being concentrated *in vacuo* to give a 50:50 mixture of (*R*)-**145** and **126**·HCl. Purification via ion exchange chromatography on Dowex 50WX8 (100-200 mesh, eluent H_2O) gave (*R*)-**145** as white needles (37 mg, 73% from **175**); mp 86−88 °C; {lit.[5] 87 °C}; $[\alpha]_D^{20}$ −21.0 (*c* 1.0 in $CHCl_3$); {lit.[5] $[\alpha]_D^{23}$ −24.2 (*c* 1.0 in $CHCl_3$)}. Further elution (eluent 35% aq NH_4OH), followed by filtration of the precipitate formed after 24 h gave (*S*)-**126** as a white solid (74 mg, 55% from **175**, >99% ee);[12] mp 121−122 °C; $[\alpha]_D^{20}$ −6.3 (*c* 1.0 in $CHCl_3$); ν_{max} 3030, 2921, 2851, 1653, 1560; λ_{max} (MeOH) 258 (3900), 263 (4400), 269 (3200); δ_H (400 MHz, 9 mM, $CDCl_3$) 1.16-1.38 (18H, m, C(3′)H_2−C(11′)H_2), 1.56-1.74 (4H, m, C(2′)H_2, C(12′)H_2), 2.56-2.64 (2H, m, C(13′)H_2), 2.81-3.09 (3H, m, C(3)H_A, C(1′)H_2), 3.35-3.47 (1H, m, C(3)H_B), 4.04 (1H, dd, *J* 12.0, 3.9 C(2)*H*), 7.18-7.21 (1H, m, C(5″)*H*), 7.21-7.26 (1H, m, *p-Ph*), 7.28-7.33 (2H, m, *m-Ph*), 7.36-7.40 (2H, m, *o-Ph*), 7.49 (1H, app dt, *J* 7.8, 2.2, C(4″)*H*), 8.41-8.47 (2H, m, C(2″)*H*, C(6″)*H*); δ_H (700 MHz, 127 mM, $CDCl_3$) 1.10-1.44 (18H, m, C(3′)H_2−C(11′)H_2), 1.59-1.65 (2H, m, C(12′)H_2), 1.65-1.77 (2H, m, C(2′)H_2), 2.60 (2H, t, *J* 7.8, C(13′)H_2), 2.80-2.86 (1H, m, C(3)H_A), 2.94-3.01

(1H, m, C(1′)H_A), 3.04-3.14 (1H, m, C(1′)H_B), 3.44-3.52 (1H, m, C(3)H_B), 4.07 (1H, dd, *J* 11.9, 3.4 C(2)*H*), 7.20 (1H, app dd, *J* 7.8, 4.9, C(5″)*H*), 7.21-7.24 (1H, m, *p-Ph*), 7.27-7.31 (2H, m, *m-Ph*), 7.40 (2H, app d, *J* 7.3, *o-Ph*), 7.47-7.50 (1H, m, C(4″)*H*), 8.40-8.47 (2H, m, C(2″)*H*), C(6″)*H*), 10.1 (1H, br s, N*H*); δ_C (175 MHz, 127 mM, $CDCl_3$) 25.2 (*C*(12′)), 26.9, 29.07, 29.09, 29.34, 29.36, 29.46, 29.47, 29.50, 29.53, (*C*(3′)-*C*(11′)), 31.1 (*C*(2′)), 33.0 (*C*(13′)), 47.6 (*C*(1′)), 51.0 (*C*(3)), 52.2 (*C*(2)), 123.1 (*C*(5″)), 127.1 (*p-Ph*), 128.1 (*m-Ph*), 128.8 (*o-Ph*), 135.7 (*C*(4″)), 137.9 (*C*(3″)), 139.0 (*i-Ph*), 147.1 (*C*(6″)), 149.9 (*C*(2″)), 176.2 (*C*(1)); *m/z* (ESI^+) 425 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{27}H_{41}N_2O_2^+$ ($[M+H]^+$) requires 425.3163; found 425.3165.

Method B. H_2O_2 (30% aq, 1.80 mL) and LiOH (152 mg, 3.62 mmol) were sequentially added to **175** (335 mg, 0.60 mmol) in THF (5.4 mL) at 0 °C and the reaction mixture was left to warm to rt over 16 h, before the addition of satd aq Na_2SO_3 (25 mL). EtOAc (25 mL) was added and the phases were separated. The aqueous layer was extracted with $CHCl_3$ (3 × 25 mL) and the combined organic extracts were concentrated *in vacuo* to give a 65:19:5:11 mixture of (*R*)-**145**, **167**, **176** and **126**, respectively.[13] Purification via flash column chromatography (eluent $CHCl_3$/MeOH, 9:1) gave (*R*)-**145** as a white solid (61 mg, 65%); $[\alpha]_D^{20}$ –23.8 (*c* 1.0 in $CHCl_3$). Further elution (eluent $CHCl_3$/MeOH, 9:1) gave a 47:53 mixture of **167** and **176** as a colourless oil (87 mg). Data for **176**:[14] δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.46-1.55 (2H, m, C(3)H_2), 2.32-2.40 (2H, m, C(2)H_2), 2.63 (2H, t, *J* 7.7, C(13)H_2), 6.73 (0.46H, t, *J* 7.5, C(1)*H*), 7.41 (0.54H, t, *J* 6.5, C(1)*H*), 9.62 (1H, s, O*H*). Further elution (eluent $CHCl_3$/MeOH, 9:1) gave an impure sample of (*S*)-**126**. Further purification via ion exchange chromatography on Dowex 50WX8 (100-200 mesh, eluent 35% aq NH_4OH), followed by filtration of the precipitate formed after 24 h gave (*S*)-**126** as a white solid (23 mg, 9% from **175**, >99% ee).[12]

(*R*)-2-Phenyl-3-[*N*-13′-(pyridin-3″-yl)tridecylamino]propanoic acid (*R*)-126

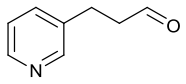
Step 1. CAN (534 mg, 0.97 mmol) was added to a stirred solution of **174** (303 mg, 0.46 mmol) in MeCN (10 mL) and H_2O (2 mL) at rt and the resultant mixture was stirred for 16 h before the addition of satd aq $NaHCO_3$ (10 mL). The reaction mixture was stirred vigorously for 20 min, the organic layer was then decanted off and brine (10 mL) was added. The resultant solution was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification via flash column chromatography (eluent $CHCl_3$/NH_4OH, 99:1)

gave **179** as a colourless viscous oil (250 mg); δ_H (400 MHz, $CDCl_3$) 0.61 (3H, d, *J* 6.9, CH*Me*$_A$), 0.83 (3H, d, *J* 6.9, CH*Me*$_B$), 1.16-1.37 (20H, m, C(3″)*H*$_2$−C(12″)*H*$_2$), 1.43 (3H, s, C(5)*Me*$_A$), 1.45 (3H, s, C(5)*Me*$_B$), 1.61 (2H, quintet, *J* 7.3, C(2″)*H*$_2$), 1.94-2.07 (1H, m, C*H*Me$_2$), 2.55-2.67 (4H, m, C(1″)*H*$_2$, C(13″)*H*$_2$), 2.94 (1H, dd, *J* 11.9, 5.5, C(3′)*H*$_A$), 3.39 (1H, dd, *J* 11.9, 9.6, C(3′)*H*$_B$), 4.23 (1H, d, *J* 2.9, C(4)*H*), 5.34 (1H, dd, *J* 9.6, 5.5, C(2′)*H*), 7.17-7.33 (4H, m, C(5‴)*H*, *Ph*), 7.40-7.55 (3H, m, C(4‴)*H*, *Ph*), 8.38-8.49 (2H, m, C(2‴)*H*), C(6‴)*H*).

Step 2. $NaHCO_3$ (53 mg, 0.64 mmol) and Boc_2O (0.11 mL, 0.48 mmol) were added sequentially to a stirred solution of **179** (180 mg, 0.32 mmol) in EtOH (5 mL) at 0 °C, and the resultant mixture was left to warm to rt over 16 h before being concentrated *in vacuo*. The residue was diluted with EtOAc (15 mL), washed with satd aq $NaHCO_3$ (2 × 15 mL) and brine (2 × 15 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give *N*-Boc-**179** as a yellow oil (210 mg).

Step 3. H_2O_2 (30% aq, 0.96 mL) and LiOH (81 mg, 1.92 mmol) were sequentially added to the residue from the previous step (210 mg) in THF (2.9 mL) at 0 °C and the resultant mixture was left to warm to rt over 16 h before the addition of satd aq Na_2SO_3 (10 mL). EtOAc (10 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was dissolved in HCl (2.0 M in Et_2O, 3 mL) and left to stir for 30 min at rt before being concentrated *in vacuo*. Purification via ion exchange chromatography on Dowex 50WX8 (100-200 mesh, eluent H_2O) gave (*R*)-**145** as white needles (39 mg, 54% from **174**); mp 87−88 °C; {lit.[5] 87 °C}; $[\alpha]_D^{20}$ −22.3 (*c* 1.0 in $CHCl_3$); {lit.[5] $[\alpha]_D^{23}$ −24.2 (*c* 1.0 in $CHCl_3$)}. Further elution (eluent 35% aq NH_4OH), followed by filtration of the precipitate formed after 24 h gave (*R*)-**126** as a white solid (81 mg, 41% from **174**, >99% ee);[12] mp 124−125 °C; $[\alpha]_D^{20}$ +6.5 (*c* 1.0 in $CHCl_3$).

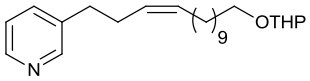
3-(Pyridin-3′-yl)propanal 183



DMSO (16.5 mL, 232 mmol) was added dropwise via syringe to a stirred solution of $(ClCO)_2$ (9.98 mL, 116 mmol) in CH_2Cl_2 (300 mL) at −78 °C. After 10 min a solution of 3-(pyridin-3′-yl)propanol (9.98 mL, 77.3 mmol) in CH_2Cl_2 (100 mL) was added dropwise via cannula and the resultant solution was stirred for 30 min. A solution of Et_3N (53.9 mL, 387 mmol) in CH_2Cl_2 (100 mL) was added via cannula and the resultant mixture was left to stir for 30 min before the cooling bath was removed and the reaction was left to warm to rt over 1 h before the addition of H_2O (100 mL). The

organic layer was washed with H_2O (3 × 100 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give **183** as a brown oil (10.3 g); δ_H (400 MHz, $CDCl_3$) 2.84 (2H, td, *J* 7.3, 1.0, C(2)H_2), 2.98 (2H, t, *J* 7.3, C(3)H_2), 7.23-7.29 (1H, m, C(5′)*H*), 7.54-7.58 (1H, m, C(4′)*H*), 8.47-8.51 (2H, m, C(2′)*H*, C(6′)*H*), 9.84 (1H, t, *J* 1.0, C(1)*H*).

(*Z*)-1-Tetrahydropyran-2′-yl-14-(pyridin-3′′-yl)tetradec-11-ene (*Z*)-186[15]



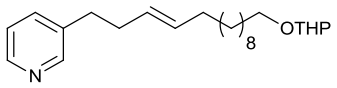
Step 1. DHP (8.20 mL, 96.7 mmol) and PPTS (162 mg, 0.64 mmol) were added sequentially to a stirred solution of 11-bromodecan-1-ol **180** (16.12 g, 64.5 mmol) in CH_2Cl_2 (150 mL) at rt and the resultant mixture was left to stir at rt for 16 h before the addition of Na_2CO_3 (2.0 M aq, 50 mL). The organic layer was washed with Na_2CO_3 (2.0 M aq, 50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give **184** as a yellow oil (21.62 g); δ_H (400 MHz, $CDCl_3$) 1.25-1.65 (20H, m, C(2)H_2–C(9)H_2, C(3′)H_2, C(5′)H_2), 1.69-1.77 (1H, m, C(4′)H_A), 1.80-1.92 (3H, m, C(4′)H_B, C(10)H_2), 3.36-3.46 (3H, m, C(1)H_A, C(11)H_2), 3.47-3.56 (1H, m, C(6′)H_A), 3.74 (1H, dt, *J* 9.6, 7.0, C(1)H_B), 3.85-3.93 (1H, m, C(6′)H_B), 4.58 (1H, dd, *J* 4.3, 2.6, C(2′)*H*).

Step 2. PPh_3 (16.91 g, 64.5 mmol) was added to a stirred solution of **184** (21.62 g) in MeCN (200 mL) and the resultant mixture was heated at reflux for 48 h before being concentrated *in vacuo* to give **185** as an orange viscous oil (38.5 g); δ_H (400 MHz, $CDCl_3$) 1.16-1.92 (24H, m, C(2)H_2–C(10)H_2, C(3′)H_2–C(5′)H_2), 3.34-3.44 (1H, m, C(1)H_A), 3.47-3.55 (1H, m, C(6′)H_A), 3.71 (1H, dt, *J* 9.6, 6.9, C(1)H_B), 3.84-3.93 (3H, m, C(11)H_2, C(6′)H_B), 4.55-4.58 (1H, m, C(2′)*H*), 7.45-7.97 (15H, m, *Ph*).

Step 3. KHMDS (0.7 M in PhMe, 92.1 mL, 64.5 mmol) was added dropwise to a solution of **185** (38.5 g) in THF (350 mL) at −78 °C and the reaction mixture was left to warm to rt over 1 h before being cooled to −78 °C and a solution of **183** (10.3 g) in THF (50 mL) was added via cannula. After 5 min the cooling bath was removed and the reaction mixture was left to warm to rt over 2 h before the addition of H_2O (50 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL) and the combined organic extracts were then dried (Na_2SO_4) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc/NEt_3, 94:5:1) gave **186** as a yellow viscous oil (14.07 g, 59% from **180**, 97:3 (*Z*):(*E*) ratio);[15] δ_H (400 MHz, C_6D_6) 1.19-1.47 (18H, m, C(2)H_2–C(9)H_2, C(4′)H_2), 1.58-1.70 (4H, m, C(3′)H_2, C(5′)H_2), 1.85-1.93 (2H, m, C(10)H_2), 2.16 (2H, app q, *J* 7.6, C(13)H_2), 2.32 (2H, t, *J* 7.6, C(14)H_2), 3.34-3.46 (2H, m,

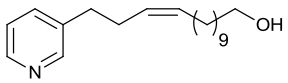
C(1)H_2), 3.81-3.92 (2H, m, C(6′)H_2), 4.63 (1H, t, *J* 3.3, C(2′)*H*) 5.25-5.34 (1H, m, C(12)*H*), 5.38-5.47 (1H, m, C(11)*H*), 6.74 (1H, dd, *J* 7.7, 4.7, C(5″)*H*), 7.01 (1H, app d, *J* 7.7, C(4″)*H*), 8.46-8.50 (1H, m, C(6″)*H*), 8.54 (1H, d, *J* 1.8, C(2″)*H*).

1-(Pyridin-3′-yl)-14-(tetrahydropyran-2″-yloxy)tetradec-3-ene 187[15]



KHMDS (0.5 M in PhMe, 4.38 mL, 2.09 mmol) was added dropwise to a stirred solution of **185** (2.61 g, 2.09 mmol) in THF (50 mL) at −78 °C and the reaction mixture was left to stir for 1 h before a solution of **183** (282 mg, 2.09 mmol) in THF (20 mL) was added via cannula. After 5 min the cooling bath was removed and the reaction mixture was left to warm to rt over 30 min before the addition of MeOH (50 mL) and the resultant mixture was stirred at rt over 16 h before the addition of H_2O (40 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 40 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc/NEt_3, 94:5:1) gave **187** as a yellow viscous oil (374 mg, 48%, 22:78 (*Z*):(*E*) ratio);[15] Data for (*E*)-isomer: δ_H (400 MHz, C_6D_6) 1.30-1.48 (18H, m, C(6)H_2–C(13)H_2, C(4″)H_2), 1.59-1.70 (4H, m, C(5″)H_2, C(3″)H_2), 1.92-2.00 (2H, m, C(5)H_2), 2.06-2.13 (2H, m, C(2)H_2), 2.31-2.34 (2H, m, C(1)H_2), 3.34-3.46 (2H, m, C(14)H_2), 3.81-3.91 (2H, m, C(2″)H_2), 4.63 (1H, t, *J* 3.4, C(1″)H_2) 5.25-5.36 (2H, m, C(3)*H*, C(4)*H*), 6.74 (1H, dd, *J* 7.8, 4.8, C(5′)*H*), 6.99 (1H, d, *J* 7.6, C(4′)*H*), 8.48 (1H, d, *J* 4.3, C(6′)*H*), 8.54 (1H, br s, C(2′)*H*).

(*Z*)-14-(Pyridin-3′-yl)tetradec-11-en-1-ol 182[15]



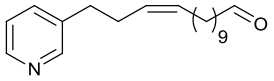
Method A. HCl (3.0 M aq, 25.1 mL) was added dropwise to a stirred solution of (*Z*)-**186** (14.07 g, 37.7 mmol, 97:3 (*Z*):(*E*) ratio) in MeOH (200 mL) at rt and the resultant mixture was left to stir at rt for 16 h before being concentrated *in vacuo*. The residue was partitioned between KOH (2.0 M aq, 50 mL) and EtOAc (50 mL0 and the phases separated. The aqueous layer was extracted with EtOAc (3 × 100 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc/Et_3N, 75:24:1) gave **182** as a yellow oil (9.70 g, 89%, 97:3 (*Z*):(*E*) ratio);[15] δ_H (400 MHz, C_6D_6) 1.11-1.47 (16H, m, C(2)H_2–C(9)H_2), 1.84-1.94 (2H, m, C(10)H_2), 2.15 (2H, app q, *J* 7.6, C(13)H_2),

2.31 (2H, t, *J* 7.6, C(14)H_2), 3.44 (2H, t, *J* 6.3, C(1)H_2), 5.25-5.34 (1H, m, C(12)*H*), 5.37-5.47 (1H, m, C(11)*H*), 6.72 (1H, app dd, *J* 7.8, 4.8, C(5′)*H*), 6.98 (1H, app dt, *J* 7.8, 1.8, C(4′)*H*), 8.45 (1H, app dd, *J* 4.8, 1.8, C(6′)*H*), 8.52 (1H, app d, *J* 1.8, C(2′)*H*).

Method B. *Step 1*. PPh_3 (2.61 g, 9.95 mmol) was added to a stirred solution of **180** (2.50 g, 9.95 mmol) in MeCN (20 mL) and the resultant mixture was heated at reflux for 48 h before being concentrated *in vacuo* to give **181** as an orange viscous oil (5.10 g).

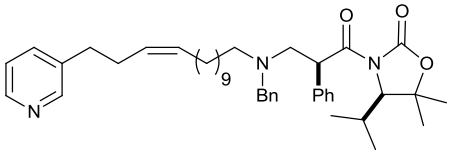
Step 2. KHMDS (0.7 M in PhMe, 14.2 mL, 9.95 mmol) was added dropwise to a solution of **181** (5.10 g) in THF (50 mL) at −78 °C and the reaction mixture was left to warm to rt over 1 h before being cooled to −78 °C and a solution of **183** (1.12 g, 8.29 mmol) in THF (20 mL) was added via cannula. After 5 min the cooling bath was removed and the reaction mixture was left to warm to rt over 2 h before the addition of H_2O (50 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL) and the combined organic extracts were then dried (Na_2SO_4) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc/NEt_3, 94:5:1) gave **182** as a yellow viscous oil (1.44 g, 60% from **180**, 88:12 (*Z*):(*E*) ratio).[15]

(*Z*)-14-(Pyridin-3′-yl)tetradec-11-enal 188



IBX (872 mg, 3.11 mmol) was added to a stirred solution of **182** (300 mg, 1.04 mmol) in EtOAc (4 mL) at rt and the resultant mixture was left to stir at 80 °C for 3 h before being cooled to rt and filtered though Celite® (eluent EtOAc, ~10 mL), and concentrated *in vacuo* to give **188** as a yellow oil (295 mg); δ_H (400 MHz, $CDCl_3$) 1.04-1.40 (12H, m, C(4)H_2−C(9)H_2), 1.52-1.72 (2H, m, C(3)H_2), 1.81-1.98 (2H, m, C(10)H_2), 2.27-2.47 (4H, m, C(13)H_2, C(2)H_2), 2.64 (2H, t, *J* 7.6, C(14)H_2), 5.27-5.47 (2H, m, C(11)*H*, C(12)*H*), 7.21-7.26 (1H, m, C(5′)*H*), 7.51-7.56 (1H, m, C(4′)*H*), 8.43-8.48 (2H, m, C(2′)*H*, C(6′)*H*), 9.76-9.79 (1H, m, C(1)*H*).

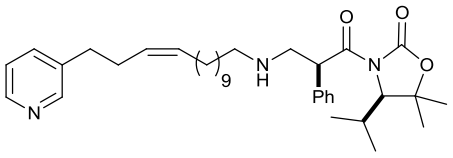
(4*R*,2′*S*,*Z*)-*N*(3)-(2′-Phenyl-3′-{*N*-benzyl-*N*-[14″-(pyridin-3‴-yl)tetradec-11″-en-1″-yl]amino}propanoyl)-4-isopropyl-5,5-dimethyloxazolidin-2-one 189



A solution of **171** (898 mg, 2.28 mmol) in 1,2-DCE (20 mL) was added to a stirred solution of **188** (984 mg, 3.43 mmol) in 1,2-DCE (20 mL) at rt. After 5 min, AcOH (0.2 mL) and $NaBH(OAc)_3$ (963 mg, 4.56 mmol) were added and the resultant mixture was stirred at rt for 16 h before the

addition of satd aq $NaHCO_3$ (40 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O/Et_3N, 59:40:1) gave **189** as a colourless oil (1.21 g, 80%, 97:3 (*Z*):(*E*) ratio); $[\alpha]_D^{20}$ −32.6 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1774 (C=O, exocyclic), 1701 (C=O, endocyclic); δ_H (400 MHz, C_6D_6) 0.67 (3H, s, C(5)*Me*$_A$), 0.97 (3H, s, C(5)*Me*$_B$), 1.07 (3H, d, *J* 6.9, CH*Me*$_A$), 1.22 (3H, d, *J* 6.9, CH*Me*$_B$), 1.30-1.44 (14H, m, C(3″)*H*$_2$−C(9″)*H*$_2$), 1.60-1.74 (2H, m, C(2″)*H*$_2$), 1.84-1.95 (1H, m, C*H*Me$_2$), 1.98-2.07 (2H, m, C(10″)*H*$_2$), 2.28 (2H, app q, *J* 7.3, C(13″)*H*$_2$), 2.45 (2H, t, *J* 7.7, C(14″)*H*$_2$), 2.55-2.64 (1H, m, C(1″)*H*$_A$), 2.69-2.80 (1H, m, C(1″)*H*$_B$), 2.86 (1H, dd, *J* 12.6, 4.6, C(3′)*H*$_A$), 3.70 (1H, d, *J* 13.6, NC*H*$_A$H$_B$Ph), 3.86 (1H, dd, *J* 12.6, 10.1, C(3′)*H*$_B$), 3.96 (1H, d, *J* 13.6, NCH$_A$*H*$_B$Ph), 4.03 (1H, d, *J* 2.8, C(4)*H*), 5.37-5.46 (1H, m, C(12″)*H*), 5.50-5.59 (1H, m, C(11″)*H*), 6.06 (1H, dd, *J* 10.1, 4.6, C(2′)*H*), 6.88 (1H, app dd, *J* 7.6, 4.8, C(5‴)*H*), 7.12-7.19 (2H, m, C(4‴)*H*, *Ph*), 7.21-7.30 (3H, m, *Ph*), 7.35 (2H, app t, *J* 7.3, *Ph*), 7.51 (2H, app d, *J* 7.2, *Ph*), 7.68 (2H, app d, *J* 7.2, *Ph*), 8.58 (1H, app dd, *J* 4.8, 1.4, C(6‴)*H*), 8.64 (1H, app d, *J* 1.8, C(2‴)*H*); δ_C (100 MHz, C_6D_6) 17.5 (CH*Me*$_A$), 21.1 (C(5)*Me*$_B$), 22.2 (CH*Me*$_B$), 27.8, 28.0, 28.2 (*C*(2″), *C*(10″), part of *C*(3″)-*C*(9″)), 28.3 (C(5)*Me*$_A$), 29.4 (*C*(13″)), 30.0 (part of *C*(3″)-*C*(9″)), 30.2 (*C*HMe$_2$), 30.4, 30.5 (part of *C*(3″)-*C*(9″)), 33.5 *C*(14″)), 48.0 (*C*(2′)), 54.8 (*C*(1″)), 59.3 (*C*(3′)), 59.9 (N*C*H$_2$Ph), 67.2 (*C*(4)), 82.3 (*C*(5)), 123.5 (*C*(5‴)), 127.5, 128.0 (*p-Ph*), 128.5, 128.8, 129.3, 129.5, 129.8 (*C*(12″), *o,m-Ph*), 131.8 (*C*(11″)), 135.8 (*C*(4‴)), 137.4, 138.8, 140.5 (*C*(3‴), *i-Ph*), 148.3 (*C*(6‴)), 151.1 (*C*(2‴)), 154.1 (*C*(2)), 174.1 (*C*(1′)); *m/z* (ESI$^+$) 666 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{43}H_{60}N_3O_3^+$ ([M+H]$^+$) requires 666.4629; found 666.4632.

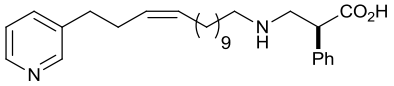
(4*R*,2′*S*,*Z*)-*N*(3)-(2′-Phenyl-3′-{*N*-[14″-(pyridin-3‴-yl)tetradec-11″-en-1″-yl]amino}propanoyl)-4-isopropyl-5,5-dimethyloxazolidin-2-one 190



CAN (299 mg, 0.55 mmol) was added to a stirred solution of **189** (173 mg, 0.26 mmol, 97:3 (*Z*):(*E*) ratio) in MeCN (5 mL) and H_2O (1 mL) at rt and the resultant mixture was stirred at rt for 16 h before the addition of satd aq $NaHCO_3$ (5 mL). The resultant mixture was stirred vigorously for 20 min, the organic layer was then decanted off and brine (5 mL) was added. The resultant solution was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification via flash column chromatography (eluent $CHCl_3$/NH_4OH, 99:1)

gave **190** as a colourless viscous oil (105 mg, 70%, 96:4 (*Z*):(*E*) ratio); $[\alpha]_D^{20}$ −55.2 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1773 (C=O, exocyclic), 1697 (C=O, endocyclic); δ_H (400 MHz, C_6D_6) 0.65 (3H, s, C(5)*Me*$_A$), 0.90 (3H, s, C(5)*Me*$_B$), 0.96 (3H, d, *J* 6.8, CH*Me*$_A$), 1.11 (3H, d, *J* 6.8, CH*Me*$_B$), 1.26-1.37 (14H, m, C(3″)*H*$_2$−C(9″)*H*$_2$), 1.39-1.50 (2H, m, C(2″)*H*$_2$), 1.73-1.84 (1H, m, C*H*Me$_2$), 1.90-2.00 (2H, m, C(10″)*H*$_2$), 2.22 (2H, app q, *J* 7.5, C(13″)*H*$_2$), 2.39 (2H, t, *J* 7.5, C(14″)*H*$_2$), 2.54-2.70 (2H, m, C(1″)*H*$_2$), 2.98 (1H, dd, *J* 11.6, 5.1, C(3′)*H*$_A$), 3.86 (1H, app t, *J* 10.8, C(3′)*H*$_B$), 3.99 (1H, d, *J* 2.8, C(4)*H*), 5.31-5.40 (1H, m, C(12″)*H*), 5.43-5.52 (1H, m, C(11″)*H*), 5.78 (1H, dd, *J* 10.1, 5.1, C(2′)*H*), 6.81 (1H, app dd, *J* 7.6, 4.8, C(5‴)*H*), 7.05-7.13 (2H, m, C(4‴)*H*, *Ph*), 7.16-7.24 (2H, m, *Ph*), 7.66 (2H, app d, *J* 7.3, *Ph*), 8.49-8.56 (1H, m, C(6‴)*H*), 8.58-8.62 (1H, m, C(2‴)*H*); δ_C (100 MHz, C_6D_6) 17.4 (CH*Me*$_A$), 21.1 (C(5)*Me*$_B$), 22.3 (CH*Me*$_B$), 27.9, 28.1 (*C*(10″), part of *C*(2″)-*C*(9″)), 28.3 (C(5)*Me*$_A$), 29.4, 30.0 (*C*(13″), part of *C*(2″)−*C*(9″)), 30.3 (*C*HMe$_2$), 30.3, 30.4, 30.5, 31.0 (part of *C*(2″)-*C*(9″)), 33.5 *C*(14″)), 50.2 (*C*(2′)), 50.5 (*C*(1″)), 54.8 (*C*(3′)), 67.0 (*C*(4)), 82.2 (*C*(5)), 123.5 (*C*(5‴)), 128.0, 128.3, 128.5, 129.3, 129.5 (*C*(12″), *o*,*m*,*p*-*Ph*), 131.7 (*C*(11″)), 135.8 (*C*(4‴)), 137.4, 138.6, (*C*(3‴), *i*-*Ph*), 148.3 (*C*(6‴)), 151.1 (*C*(2‴)), 153.9 (*C*(2)), 174.4 (*C*(1′)); *m/z* (ESI$^+$) 576 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{36}H_{54}N_3O_3^+$ ([M+H]$^+$) requires 576.4160; found 576.4160.

(*S*)-2-Phenyl-3-{*N*-[14′-(pyridin-3″-yl)tetradec-11′-enyl]amino}propanoic acid (*S*)-127

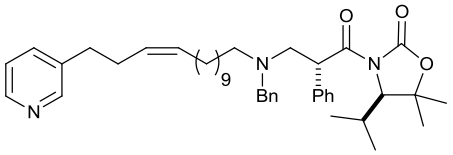


Step 1. $NaHCO_3$ (33 mg, 0.39 mmol) and Boc_2O (67 μL, 0.29 mmol) were added sequentially to a stirred solution of **190** (112 mg, 0.19 mmol, 96:4 (*Z*):(*E*) ratio) in EtOH (2 mL) at 0 °C, and the reaction was left to warm to rt over 16 h before being concentrated *in vacuo*. The residue was dissolved in EtOAc (5 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (2 × 5 mL) and brine (2 × 5 mL), then dried (Na_2SO_4) and concentrated *in vacuo* to give a yellow oil (100 mg).

Step 2. H_2O_2 (30% aq, 0.45 mL) and LiOH (37 mg, 0.89 mmol) were added sequentially to a stirred solution of the residue from the previous step (100 mg) in THF (1.5 mL) at 0 °C and the reaction mixture was left to warm to rt over 16 h before the addition of satd aq Na_2SO_3 (5 mL). EtOAc (10 mL) was then added and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was dissolved in HCl (2.0 M in Et_2O, 2 mL) and left to stir at rt for 30 min before being concentrated *in vacuo* to give a 50:50 mixture of (*R*)-**145** and (*S*)-127·HCl. Purification via ion exchange chromatography on

Dowex 50WX8 (100-200 mesh, eluent H_2O) gave (*R*)-**145** as white needles (37 mg, 73% from **190**); mp 87−88 °C; {lit.[5] 87−88 °C}; $[\alpha]_D^{20}$ −23.6 (*c* 1.0 in $CHCl_3$); {lit.[5] $[\alpha]_D^{23}$ −24.2 (*c* 1.0 in $CHCl_3$)}. Further elution (eluent 35% aq NH_4OH), followed by filtration of the precipitate formed after 24 h gave (*S*)-**127** as a white solid (38 mg, 45% from **190**, 98:2 (*Z*):(*E*) ratio, >99% ee);[16] mp 124−125 °C; $[\alpha]_D^{20}$ −5.9 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3030, 2923, 2852, 1653 (υ_{as} CO_2^-), 1564 (β_{as} NH_2^+); λ_{max} (MeOH) 258 (3540), 263 (4049), 269 (2926); δ_H (500 MHz, $CDCl_3$) 1.15-1.36 (14H, m, C(3′)H_2−C(9′)H_2), 1.58-1.74 (2H, m, C(2′)H_2), 1.93 (2H, app q, *J* 6.8, C(10′)H_2), 2.36 (2H, app q, *J* 7.4, C(13′)H_2), 2.66 (2H, t, *J* 7.4, C(14′)H_2), 2.85 (1H, dd, *J* 11.3, 3.4, C(3)H_A), 2.89-3.08 (2H, m, C(1′)H_2), 3.42 (1H, app t, *J* 11.3, C(3)H_B), 4.04 (1H, dd, *J* 11.8, 3.4, C(2)*H*), 5.33-5.45 (2H, m, C(11′)*H*, C(12′)*H*), 7.19 (1H, dd, *J* 7.7, 4.9, C(5″)*H*), 7.23 (1H, app t, *J* 7.4, *p-Ph*), 7.30 (2H, app t, *J* 7.4, *m-Ph*), 7.38 (2H, app d, *J* 7.4, *o-Ph*), 7.50 (1H, app dt, *J* 7.7, 2.0, C(4″)*H*), 8.41-8.46 (2H, m, C(2″)*H*), C(6″)*H*); δ_C (125 MHz, $CDCl_3$) 25.4 (*C*(2′)), 26.9 (part of (*C*(3′)−*C*(9′)), 27.2 (*C*(10′)), 28.7 (*C*(13′)), 29.12, 29.25, 29.41, 29.48, 29.53 (part of *C*(3′)−*C*(9′)), 33.0 (*C*(14′)), 47.6 (*C*(1′)), 51.1 (*C*(3)), 51.8 (*C*(2)), 123.2 (*C*(5″)), 127.2 (*p-Ph*), 127.7 (*C*(12′)), 128.2 (*o-Ph*), 128.8 (*m-Ph*), 131.4 (*C*(11′)), 135.9 (*C*(4″)), 137.2 (*C*(3″)), 139.0 (*i-Ph*), 147.3 (*C*(6″)), 150.0 (*C*(2″)), 176.4 (*C*(1)); *m/z* (ESI^+) 437 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{28}H_{41}N_2O_2^+$ ($[M+H]^+$) requires 437.3163; found 437.3154. Data for (*E*)-isomer: δ_C (125 MHz, $CDCl_3$) [selected peaks] 32.5 (*C*(10′)), 33.1 (*C*(14′)), 34.0 (*C*(13′)), 128.4, 132.0 (*C*(11′), *C*(12′)).

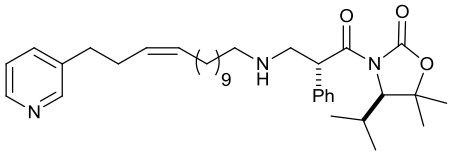
(*R*,*R*,*Z*)-*N*(3)-(2′-Phenyl-3′-{*N*-benzyl-*N*-[14″-(pyridin-3‴-yl)tetradec-11″-en-1″-yl]amino}propanoyl)-4-isopropyl-5,5-dimethyloxazolidin-2-one 192



A solution of **172** (170 mg, 0.43 mmol) in 1,2-DCE (3 mL) was added to a stirred solution of **188** (184 mg, 0.64 mmol) in 1,2-DCE (3 mL) at rt. After 5 min, AcOH (0.1 mL) and $NaBH(OAc)_3$ (182 mg, 0.86 mmol) were added and the resultant mixture was stirred at rt for 16 h before the addition of satd aq $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O/Et_3N, 59:40:1) gave **192** as a colourless oil (190 mg, 67%, 96:4 (*Z*):(*E*) ratio); $[\alpha]_D^{20}$ +6.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1772 (C=O, exocyclic), 1700 (C=O, endocyclic); δ_H (400 MHz, C_6D_6) 0.48 (3H, d, *J* 6.7, CHMe_A), 0.71 (3H, d, *J* 6.7, CHMe_B), 0.92 (3H, s, C(5)Me_A), 1.14 (3H, s, C(5)Me_B), 1.17-1.29 (14H, m, C(3″)H_2−C(9″)H_2),

1.46-1.61 (3H, m, C(2″)H_2, CHMe$_2$), 1.85-1.94 (2H, m, C(10″)H_2), 2.28 (2H, app q, *J* 7.6, C(13″)H_2), 2.33 (2H, t, *J* 7.6, C(14″)H_2), 2.36-2.44 (1H, m, C(1″)H_A), 2.53-2.62 (1H, m, C(1″)H_B), 2.69 (1H, dd, *J* 12.8, 4.1, C(3′)H_A), 3.51 (1H, d, *J* 13.6, NCH_AH$_B$Ph), 3.70-3.82 (2H, m, C(3′)H_B, NCH$_A$$H_B$Ph), 4.15 (1H, d, *J* 2.8, C(4)*H*), 5.25-5.34 (1H, m, C(12″)*H*), 5.37-5.46 (1H, m, C(11″)*H*), 5.96 (1H, dd, *J* 10.6, 4.1, C(2′)*H*), 6.76 (1H, app dd, *J* 7.3, 4.8, C(5‴)*H*), 7.00-7.09 (2H, m, C(4‴)*H*), *Ph*), 7.10-7.19 (3H, m, *Ph*), 7.22 (2H, app t, *J* 7.6, *Ph*), 7.35 (2H, app d, *J* 7.3, *Ph*), 7.68 (2H, app d, *J* 7.3, *Ph*), 8.43-8.56 (2H, m, C(2‴)*H*, C(6‴)*H*); δ_C (100 MHz, C_6D_6) 16.8 (CHMe_A), 21.3 (C(5)Me_A), 21.9 (CHMe_B), 27.7, 27.9, 28.1 (*C*(2″), *C*(10″), part of *C*(3″)−*C*(9″)), 28.8 (C(5)Me_B), 29.4 (*C*(13″)), 30.0, 30.35, 30.41, 30.47 (part of *C*(3″)-*C*(9″), *C*HMe$_2$), 33.5 (*C*(14″)), 48.1 (*C*(2′)), 54.7 (*C*(1″)), 58.9 (*C*(3′)), 60.0 (N*C*H$_2$Ph), 66.1 (*C*(4)), 82.2 (*C*(5)), 123.5 (*C*(5‴)), 127.5, 128.0 (*p-Ph*), 128.5, 128.8, 129.2, 129.7, 129.8 (*C*(12″), *o*,*m-Ph*), 131.8 (*C*(11″)), 135.8 (*C*(4‴)), 137.4, 138.8, 140.5 (*C*(3‴), *i-Ph*), 148.2 (*C*(6‴)), 151.0 (*C*(2‴)), 153.9 (*C*(2)), 174.4 (*C*(1′)); *m/z* (ESI$^+$) 666 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{43}H_{60}N_3O_3^+$ ([M+H]$^+$) requires 666.4629; found 666.4629.

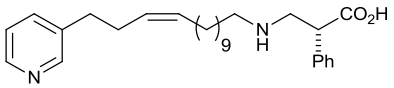
(*R*,*R*)-*N*(3)-{2′-Phenyl-3′-[*N*-14″-(pyridin-3‴-yl)tetradec-11″-en-1″-ylamino]propanoyl}-4-isopropyl-5,5-dimethyloxazolidin-2-one 193



CAN (294 mg, 0.54 mmol) was added to a stirred solution of **192** (170 mg, 0.26 mmol, 96:4 (*Z*):(*E*) ratio) in MeCN (5 mL) and H_2O (1 mL) at rt and the resultant mixture was stirred at rt for 16 h before the addition of satd aq $NaHCO_3$ (10 mL). The resultant mixture was stirred vigorously for 20 min, the organic layer was decanted off and brine (10 mL) was added. The resultant solution was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification via flash column chromatography (eluent $CHCl_3$/NH_4OH, 99:1) gave **193** as a colourless viscous oil (100 mg, 68%, 96:4 (*Z*):(*E*) ratio); $[\alpha]_D^{20}$ +11.6 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1774 (C=O, exocyclic), 1698 (C=O, endocyclic); δ_H (500 MHz, C_6D_6) 0.53 (3H, d, *J* 6.9, CHMe_A), 0.75 (3H, d, *J* 6.9, CHMe_B), 0.88 (3H, s, C(5)Me_A), 1.07 (3H, s, C(5)Me_B), 1.20-1.41 (16H, m, C(2″)H_2−C(9″)H_2), 1.51-1.60 (1H, m, CHMe$_2$), 1.86-1.95 (2H, m, C(10″)H_2), 2.17 (2H, app q, *J* 7.7, C(13″)H_2), 2.30-2.36 (2H, m, C(14″)H_2), 2.45-2.58 (2H, m, C(1″)H_2), 2.86 (1H, dd, *J* 11.1, 4.8, C(3′)H_A), 3.53-3.61 (1H, m, C(3′)H_B), 4.11 (1H, d, *J* 3.2, C(4)*H*), 5.26-5.35 (1H, m, C(12″)*H*), 5.39-5.46 (1H, m, C(11″)*H*), 5.74 (1H, dd, *J* 11.1, 4.8, C(2′)*H*), 6.75 (1H, app

dd, *J* 7.7, 4.8, C(5‴)*H*), 6.99-7.03 (1H, m, C(4‴)*H*), 7.05-7.10 (1H, m, *Ph*), 7.17-7.21 (2H, m, *Ph*), 7.71-7.77 (2H, m, *Ph*), 8.48 (1H, app dd, *J* 4.8, 1.6, C(6‴)*H*), 8.54 (1H, app d, *J* 1.9, C(2‴)*H*); δ_C (125 MHz, C_6D_6) 16.9 (CH*Me*$_A$), 21.2 (C(5)*Me*$_A$), 22.0 (CH*Me*$_B$), 27.9, 28.0 (*C*(10″), part of *C*(2″)-*C*(9″)), 28.7 (C(5)*Me*$_B$), 29.4 (*C*(13″)), 30.0, 30.3, 30.4, 31.0 (part of *C*(2″)−*C*(9″), *C*HMe$_2$), 33.5 (*C*(14″)), 50.1 (*C*(2′)), 50.6 (*C*(1″)), 54.4 (*C*(3′)), 66.2 (*C*(4)), 82.3 (*C*(5)), 123.5 (*C*(5‴)), 128.0, 128.3, 128.5, 128.7, 129.2, 129.7 (*C*(12″), *Ph*), 131.7 (*C*(11″)), 135.7 (*C*(4‴)), 137.4, 138.8 (C(3‴), *i-Ph*), 148.3 (*C*(6‴)), 151.1 (*C*(2‴)), 154.1 (*C*(2)), 174.8 (*C*(1′)); *m/z* (ESI$^+$) 576 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{36}H_{54}N_3O_3^+$ ([M+H]$^+$) requires 576.4160; found 576.4155.

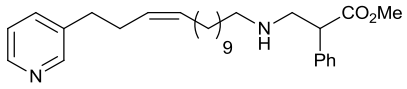
(*R*)-2-Phenyl-3-{*N*-[14′-(pyridin-3″-yl)tetradec-11′-enyl]amino}propanoic acid (*R*)-127



Step 1. $NaHCO_3$ (22 mg, 0.26 mmol) and Boc_2O (46 μL, 0.20 mmol) were added sequentially to a solution of **193** (76 mg, 0.13 mmol, 96:4 (*Z*):(*E*) ratio) in EtOH (2 mL) at 0 °C, and the reaction was left to warm to rt over 16 h before being concentrated *in vacuo*. The residue was dissolved in EtOAc (5 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (2 × 5 mL) and brine (2 × 5 mL), then dried (Na_2SO_4) and concentrated *in vacuo* to give a yellow oil (80 mg).

Step 2. H_2O_2 (30% aq, 0.36 mL) and LiOH (30 mg, 0.71 mmol) were added sequentially to a stirred solution of the residue from the previous step (80 mg) in THF (1.5 mL) at 0 °C and the reaction mixture was left to warm to rt over 16 h before the addition of satd aq Na_2SO_3 (10 mL). EtOAc (10 mL) was then added and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was dissolved in HCl (2 M in Et_2O, 2 mL) and left to stir at rt for 30 min before being concentrated *in vacuo*. Purification via ion exchange chromatography on Dowex 50WX8 (100-200 mesh, eluent H_2O) gave (*R*)-**145** as white needles (13 mg, 63% from **193**); mp 87−88 °C; {lit.[5] 87 °C}; $[\alpha]_D^{20}$ −24.1 (*c* 1.0 in $CHCl_3$); {lit.[5] $[\alpha]_D^{23}$ −24.2 (*c* 1.0 in $CHCl_3$)}. Further elution (eluent 35% aq NH_4OH), followed by filtration of the precipitate formed after 24 h gave (*R*)-**127** as a white solid (25 mg, 48% from **193**, 95:5 (*Z*):(*E*) ratio, >99% ee);[16] mp 125−126 °C; $[\alpha]_D^{20}$ +5.8 (*c* 1.0 in $CHCl_3$).

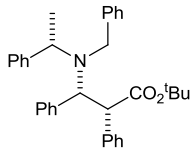
Methyl (*RS*)-2-phenyl-3-(14′-(pyridin-3′′-yl)tetradec-11′-enylamino)propanoate 191



A solution of (*RS*)-**154** (123 mg, 0.69 mmol) in 1,2-DCE (3 mL) was added to a stirred solution of **188** (190 mg, 0.69 mmol) in 1,2-DCE (3 mL) at rt. After 5 min, AcOH (0.1 mL) and $NaBH(OAc)_3$ (292 mg, 1.38 mmol) were added and the resultant mixture was stirred at rt for 16 h before the addition of satd aq $NaHCO_3$ (10 mL). The phases were separated and the aqueous layer was extraced with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc/Et_3N, 50:49:1) gave **191** as a pale yellow viscous oil (193 mg, 64%); ν_{max} (film) 1733 (C=O); δ_H (400 MHz, $CDCl_3$) 1.15-1.36 (14H, m, C(3′)H_2−C(9′)H_2), 1.38-1.51 (2H, m, C(2′)H_2), 1.86-1.99 (2H, m, C(10′)H_2), 2.29-2.41 (2H, m, C(13′)H_2), 2.58-2.71 (4H, m, C(1′)H_2, C(14′)H_2), 2.91 (1H, dd, *J* 12.0, 6.7, C(3)H_A), 3.28 (1H, dd, *J* 12.0, 8.5, C(3)H_B), 3.67 (3H, s, O*Me*), 3.84 (1H, dd, *J* 8.5, 6.7, C(2)*H*), 5.31-5.46 (2H, m, C(11′)*H*, C(12′)*H*), 7.20 (1H, dd, *J* 7.7, 4.9, C(5′′)*H*), 7.25-7.37 (5H, m, *Ph*), 7.45-7.53 (1H, m, C(4′′)*H*), 8.40-8.47 (2H, m, C(2′′)*H*, C(6′′)*H*); δ_C (100 MHz, $CDCl_3$) 27.2, 28.7, 29.2, 29.4, 29.5, 29.8 ((*C*(2′)−*C*(10′), *C*(13′)), 33.0 (*C*(14′)), 49.6 (*C*(1′)), 51.8 (*C*(2)), 52.0 (O*Me*), 52.6 (*C*(3)), 123.1 (*C*(5′′)), 127.5 (*p-Ph*), 127.6 (*C*(12′)), 128.0, 128.8 (*o*,*m-Ph*), 131.4 (*C*(11′)), 135.9 (*C*(4′′)), 137.16, 137.23 (*i-Ph*, *C*(3′′)), 147.3 (*C*(6′′)), 150.0 (*C*(2′′)), 173.6 (*C*(1)); *m/z* (ESI^+) 451 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{29}H_{43}N_2O_2^+$ ($[M+H]^+$) requires 451.3319; found 451.3304.

6.3 Experimental for chapter 3

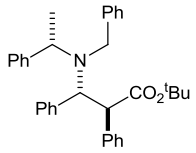
***tert*-Butyl (2*R*,3*R*,α*S*)-2,3-diphenyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]propanoate 209**



BuLi (2.30 M in hexanes, 0.24 mL, 0.55 mmol) was added dropwise via syringe to a stirred solution of (*S*)-**243** (120 mg, 0.57 mmol) in THF (2 mL) at −78 °C. After stirring for 30 min, a solution of **235** (100 mg, 0.36 mmol) in THF (2 mL) at −78 °C was added dropwise via cannula and the resultant mixture was left to stir for 2 h at −78 °C, before the addition of satd aq NH_4Cl (2 mL) and the reaction mixture was left to warm to rt over 15 min. Et_2O (20 mL) was added and the resultant solution was washed sequentially with 10% aq citric acid (10 mL), satd aq $NaHCO_3$ (10 mL) and brine (10 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Purification via flash column

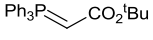
chromatography (eluent 30-40 °C petrol/Et_2O, 50:1) yielded **209** as a colourless oil (159 mg, 91%, 99:1 dr); $[\alpha]_D^{20}$ –21.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1727 (C=O); δ_H (400MHz, $CDCl_3$) 0.89 (3H, d, *J* 6.8, C(α)*Me*), 0.99 (9H, s, C*Me*$_3$), 3.70 (1H, d, *J* 13.6, NC*H*$_A$), 3.97-4.07 (2H, m, NC*H*$_B$, C(α)*H*), 4.28 (1H, d, *J* 11.8, C(2)*H*), 4.46 (1H, d, *J* 11.8, C(3)*H*), 6.87-6.93 (2H, m, *Ph*), 7.03-7.09 (2H, m, *Ph*), 7.13-7.50 (16H, m, *Ph*); δ_C (100MHz, $CDCl_3$) 13.6 (C(α)*Me*), 27.3 (C*Me*$_3$), 50.3 (N*C*H$_2$), 54.9 (*C*(α)), 56.7 (*C*(2)), 62.5 (*C*(3)), 80.4 (*C*Me$_3$), 126.5, 126.7, 127.1, 127.2 (*p-Ph*), 127.7, 128.0, 128.4, 129.1, 129.3, 129.5 (*o,m-Ph*), 137.1, 139.7, 140.4, 143.5 (*i-Ph*), 171.3 (*C*(1)); *m/z* (ESI^+) 492 ($M+H^+$, 100%); HRMS (ESI^+) $C_{34}H_{37}NNaO_2^+$ ($M+H^+$) requires 514.2717; found 514.2718.

tert-Butyl (2*S*,3*R*,α*S*)-2,3-diphenyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]propanoate 236



KHMDS (0.50 M in PhMe, 0.50 mL, 0.25 mmol) was added dropwise via syringe to a stirred solution of ^tBuOH (24 μL, 0.25 mmol) in THF (2 mL) at rt. After stirring for 15 min, a solution of **209** (123 mg, 0.25 mmol) in THF (2 mL) was added dropwise via cannula and the resultant mixture was left to stir for 16 h at rt before being concentrated *in vacuo*. The residue was partitioned between satd aq NH_4Cl (5 mL) and Et_2O (10 mL) and the phases separated. The aqueous layer was extracted with Et_2O (10 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 50:1) yielded **236** as a colourless oil (110 mg, 89%, 25:75 dr); δ_H (400MHz, $CDCl_3$) [selected peaks] 0.98 (3H, d, *J* 6.8, C(α)*Me*), 1.26 (9H, s, C*Me*$_3$), 3.45 (1H, d, *J* 14.2, NC*H*$_A$), 4.69 (1H, d, *J* 12.0, C(3)*H*), 6.79-7.34 (20H, m, *Ph*); δ_C (100MHz, $CDCl_3$) [selected peaks] 16.7 (C(α)*Me*), 27.9 (C*Me*$_3$), 51.0 (N*C*H$_2$), 56.3 (*C*(α)), 57.7 (*C*(2)), 63.9 (*C*(3)), 80.5 (*C*Me$_3$), 126.5, 126.6, 126.7 (*p-Ph*), 127.6, 127.75, 127.80, 127.82, 128.25, 129.0, 129.1, 129.7 (*o,m-Ph*), 137.4, 140.6, 144.6 (*i-Ph*), 172.1 (*C*(1)).

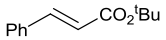
tert-Butyl-2-(triphenylphosphoranylidene)acetate 237[17]



tert-Butyl bromoacetate (50.0 mL, 0.34 mol) was added to a stirred solution of PPh_3 (89.4 g, 0.34 mol) in EtOAc (500 mL) and the reaction mixture was left to stir for 16 h at rt and the resultant precipitate was filtered. The precipitate was washed with Et_2O (250 mL) before being added portionwise to a stirred solution of NaOH (2.0 M aq, 500 mL) at 0 °C. After 15 min, CH_2Cl_2 (250

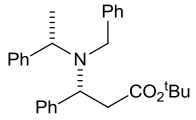
mL) was added and the phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 250 mL) and concentrated *in vacuo* to approximately 100 mL. Upon standing at rt for 30 min, the reaction flask was scratched and crystallized from solution to give **237** as a white solid (100.0 g, 78%);[17] mp 155−156 °C; {lit.[17] 154−155 °C}; δ_H (400 MHz, $CDCl_3$) 1.23 (9H, br s, C*Me*$_3$), 2.69 (1H, br s, PC*H*), 7.41-7.72 (15H, m, *Ph*).

tert-Butyl cinnamate 217[18]



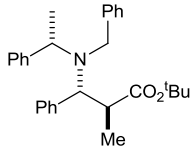
tert-Butyl-2-(triphenylphosphoranylidene)acetate **237** (2.00 g, 5.30 mmol) was added portionwise to a stirred solution of benzaldehyde (0.54 mL, 5.30 mmol) in CH_2Cl_2 (50 mL) and the resultant mixture was stirred for 16 h at rt before being concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 12:1) gave **217** as a colourless oil (964 mg, 89%, >99:1 dr);[18] δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s, C*Me*$_3$), 6.38 (1H, d, *J* 16.1, C(2)*H*), 7.36-7.40 (3H, m, *Ph*), 7.52 (2H, dd, *J* 6.5, 3.2, *Ph*), 7.60 (1H, d, *J* 16.1, C(3)*H*).

tert-Butyl (3*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 219[19]



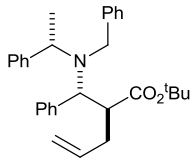
BuLi (2.36 M in hexanes, 15.8 mL, 37.2 mmol) was added dropwise via syringe to a stirred solution of (*S*)-**243** (8.11 g, 38.4 mmol) in THF (120 mL) at −78 °C. After stirring for 30 min, a solution of **217** (4.90 g, 24.0 mmol) in THF (120 mL) at −78 °C was added dropwise via cannula and the resultant mixture was left to stir for a further 2 h at −78 °C, before the addition of satd aq NH_4Cl (50 mL) and the reaction mixture was left to warm to rt over 15 min. Et_2O (100 mL) was added and the resultant solution was washed sequentially with 10% aq citric acid (50 mL), satd aq $NaHCO_3$ (50 mL) and brine (50 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 98:2) gave **219** as a colourless oil (9.08 g, 91%, >99:1 dr); $[\alpha]_D^{25}$ −4.3 (*c* 1.0 in $CHCl_3$); {lit.[19] $[\alpha]_D^{24}$ −4.2 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.22 (9H, s, C*Me*$_3$), 1.26 (3H, d, *J* 6.8, C(α)*Me*), 2.45-2.58 (2H, m, NC*H*$_2$), 3.63-3.73 (2H, m, NC*H*$_2$Ph), 3.96-4.03 (1H, m, C(α)*H*), 4.37-4.43 (1H, m, NC*H*), 7.15-7.49 (15H, m, *Ph*).

tert-Butyl (2*S*,3*R*,α*S*)- 2-methyl 3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 238[20]



BuLi (2.34 M in hexanes, 0.29 mL, 0.68 mmol) was added dropwise to a solution of DIPA (95 μL, 0.68 mmol) in THF (3 mL) at −78 °C and the reaction mixture was left to stir at −78 °C for 1 h and a solution of **219** (260 mg, 0.62 mmol) in THF (3 mL) was added dropwise and the subsequent solution stirred at −78 °C for 30 min. MeI (0.12 mL, 1.86 mmol) was added dropwise and the reaction mixture left to warm to rt over 16 h before the addition of satd aq NH_4Cl (5 mL). The aqueous layer was extracted with Et_2O (2 x 20 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 50:1) gave **238** as a colourless oil (134 mg, 50%, 98:2 dr);[20] $[\alpha]_D^{20}$ +35.5 (*c* 1.0 in $CHCl_3$); {lit.[20] for enantiomer $[\alpha]_D^{25}$ −36.8 (*c* 0.6 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 0.76 (3H, d, *J* 6.8, C(2)*Me*), 1.06 (3H, d, *J* 6.8, C(α)*Me*), 1.52 (9H, s, C*Me*$_3$), 3.13 (1H, dq, *J* 11.1, 6.8, C(2)*H*), 3.60 (1H, d, *J* 14.2, NCH_APh), 4.02 (1H, d, *J* 14.2, NCH_BPh), 4.11 (1H, d, *J* 11.1, C(3)*H*), 4.18 (1H, q, *J* 6.8, C(α)*H*), 7.17-7.41 (15H, m, *Ph*).

Methyl (2*S*,3*S*,α*R*)-2-allyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropionate 239

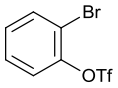


Method A. KHMDS (0.5 M in PhMe, 0.94 mL, 0.47 mmol) was added dropwise to a stirred solution of **219** (129 mg, 0.31 mmol) in THF (3 mL) at −78 °C and the reaction mixture was stirred for 1 h after which allyl bromide (54 μL, 0.62 mmol) was added dropwise and the subsequent solution left to warm to rt over 16 h before the addition of satd aq NH_4Cl (2 mL). The aqueous layer was extracted with Et_2O (2 x 20 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 50:1) gave **239** as a colourless oil (71 mg, 50%, 97:3 dr); $[\alpha]_D^{20}$ +23.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 1.01 (3H, d, *J* 6.9, C(α)*Me*), 1.49 (9H, s, C*Me*$_3$), 1.75-1.83 (1H, m, C(1′)H_A), 1.85-1.96 (1H, m, C(1′)H_B), 3.15 (1H, td, *J* 11.0, 3.6, C(2′)*H*), 3.61 (1H, d, *J* 14.2, NCH_APh), 4.07-4.14 (2H, m, C(3)*H*, NCH_BPh), 4.20 (1H, q, *J* 6.9, C(α)*H*), 4.81-4.89 (2H, m, C(3′)H_2), 5.49-5.61 (1H, m, C(2′)*H*), 7.18-7.42 (15H, m, *Ph*); δ_C (100 MHz,

$CDCl_3$) 15.4 (C(α)*Me*), 28.2 (C*Me*$_3$), 35.5 (*C*(1′)), 49.3 (*C*(2)), 50.9 (N*C*H$_2$Ph), 56.7 (*C*(3)), 64.3 (*C*(α)), 80.6 (*C*Me$_3$), 116.4 (*C*(3′)), 126.5, 126.6 (*p-Ph*), 127.3, 127.9, 128.2, 129.0, 129.3 (*o,m-Ph*), 135.2 (*C*(2′)), 138.6, 140.4, 144.3 (*i-Ph*), 173.5 (*C*(1)); *m/z* (ESI$^+$) 456 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{38}NO_2^+$ ([M+H]$^+$) requires 456.2897; found 456.2883.

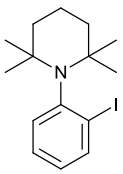
Method B. KHMDS (0.5 M in PhMe, 0.58 mL, 0.29 mmol) was added dropwise via syringe to a stirred solution of **219** (80 mg, 0.19 mmol) in THF (2 mL) at −78 °C. After stirring for 1 h 18-Crown-6 (203 mg, 0.77 mmol), **225** (93 μL, 0.39 mmol) and KF (45 mg, 0.77 mmol) were sequentially added and the reaction mixture allowed to warm to −20 °C over 12 h before the addition of allyl bromide (50 μL, 0.58 mmol) and the resultant suspension was allowed to warm to rt over 12 before the addition of satd aq NH_4Cl (2 mL). The aqueous layer was extracted with Et_2O (2 x 20 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 50:1) gave **239** as a colourless oil (48 mg, 55%, 90:10 dr); $[\alpha]_D^{20}$ +23.5 (*c* 1.0 in $CHCl_3$).

2-Bromophenyl trifluoromethanesulfonate 241[21]



Pyridine (1.40 mL, 17.34 mmol) and Tf_2O (2.33 mL, 13.87 mmol) were sequentially added to a stirred solution of 2-bromophenol **240** (2.00 g, 11.56 mmol) in CH_2Cl_2 (50 mL) at 0 °C and the resultant mixture was left to warm to rt over 16 h before the addition of HCl (1.0 M aq, 20 mL). The phases were separated and the organic layer was washed with brine (25 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 petrol) gave **241** as a colourless oil (3.14g, 89%);[21] δ_H (400 MHz, $CDCl_3$) 7.25-7.31 (1H, m, *Ar*), 7.35–7.45 (2H, m, *Ar*), 7.71 (1H, dd, *J* 8.1, 1.5, *Ar*).

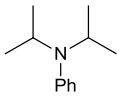
1-(2′-iodophenyl)-2,2,6,6-tetramethylpiperidine 242[22]



BuLi (2.30 M in hexanes, 0.84 mL, 1.94 mmol) was added dropwise via syringe to a stirred solution of 2,2,6,6-tetramethylpiperidine (0.33 mL, 1.94 mmol) in THF (4 mL) at −40 °C. After stirring for 30 min, a solution of **219** (162 mg, 0.39 mmol) in THF (2 mL) was added. After a further 1 h, **27** (87 μL, 078 mmol) was added dropwise via syringe and the resultant solution was

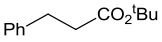
left to stir for 4 h before the addition of satd aq NH_4Cl (2 mL). The phases were separated and the aqueous layer was extracted with Et_2O (2 x 10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 50:1) gave **242** as a colourless oil (163 mg, 61% from **27**);[22] δ_H (300 MHz, $CDCl_3$) 0.92 (6H, s, C(2)Me_2) 1.28 (6H, s, C(6)Me_2), 1.52-1.99 (6H, m, C(3)H_2−C(5)H_2), 6.85-6.95 (1H, m, *Ar*), 7.26-7.35 (1H, m, *Ar*), 7.40-7.47 (1H, m, *Ar*), 7.90-7.98 (1H, m, *Ar*). Further elution gave **219** as a colourless oil (130 mg, 80%).

_N,N_-Diisopropylaniline 244[23]



BuLi (2.44 M in hexanes, 0.16 mL, 0.39 mmol) was added dropwise to a solution of diisopropylamine (55 μL, 0.39 mmol) in THF (2 mL) at −78 °C and the reaction mixture was left to stir at −78 °C for 1 h and a solution of **219** (80 mg, 0.19 mmol) in THF (2 mL) was added dropwise and the subsequent solution stirred at −78 °C for 30 min. 18-Crown-6 (203 mg, 0.77 mmol), **225** (93 μL, 0.39 mmol) and KF (45 mg, 0.77 mmol) were sequentially added and the reaction mixture was stirred at −78 °C for 30 min then left to warm to rt over 12 h before the addition of satd aq NH_4Cl (2 mL). The phases were separated and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic extracts were washed with brine (2 x 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Acetone, 100:1) gave **244** as a colourless oil (55 mg, 80% from diisopropylamine);[23] δ_H (400 MHz, $CDCl_3$) 1.22 (12H, d, *J* 6.7, (CHMe_2)$_2$), 3.72-3.84 (2H, m, (CHMe$_2$)$_2$), 6.75-6.82 (1H, m, *p-Ph*), 6.87-6.95 (2H, m, *o-Ph*), 7.16-7.25 (2H, m, *m-Ph*). Further elution gave **219** as a colourless oil (28 mg, 35%); $[\alpha]_D^{25}$ −4.2 (*c* 1.0 in $CHCl_3$); {lit.[19] $[\alpha]_D^{25}$ −4.2 (*c* 1.0 in $CHCl_3$)}. Further elution gave **217** as a colourless oil (26 mg, 65%). Further elution gave (*S*)-**243** as a pale yellow oil (41 mg, 60%); $[\alpha]_D^{20}$ −52.8 (*c* 1.0 in $CHCl_3$); {lit.[24] $[\alpha]_D^{23}$ −53.1 (*c* 1.0 in $CHCl_3$)}.

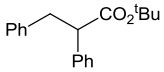
***tert*-Butyl 3-phenylpropanoate 246**[25]



$Pd(OH)_2$ (20% wt on C, 0.20 g) was added to a degassed solution of **217** (1.00 g, 4.90 mmol) in EtOAc (5 mL). The suspension was stirred under H_2 (1 atm) for 24 h before being filtered though Celite®. The Celite® pad was washed with EtOAc (10 mL) and the filtrate was concentrated *in vacuo* to give **246** as a colourless oil (0.92 g, 91%);[25] δ_H (400 MHz, $CDCl_3$) 1.43 (9H, s, CMe_3),

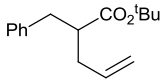
2.55 (2H, t, *J* 7.9, C(2)H_2), 2.92 (2H, t, *J* 7.9, C(3)H_2), 7.18-7.23 (3H, m, *Ph*), 7.26-7.32 (2H, m, *Ph*).

tert-Butyl (*RS*)-2,3-diphenylpropanoate 247



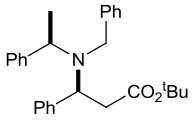
$Pd(OH)_2$ (20% wt on C, 36 mg) was added to a degassed solution of **235** (180 mg, 0.64 mmol) in EtOAc (5 mL). The suspension was stirred under H_2 (1 atm) for 24 h before being filtered though Celite®. The Celite® pad was washed with EtOAc (10 mL) and the filtrate was concentrated *in vacuo* to give **247** as a white solid (175 mg, 97%); mp 39−40 °C; ν_{max} (film) 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 1.39 (9H, s, C*Me*$_3$), 3.07 (1H, dd, *J* 13.8, 6.4, C(3)H_A), 3.45 (1H, dd, *J* 13.8, 9.2, C(3)H_B), 3.85 (1H, dd, *J* 9.2, 6.4, C(2)*H*), 7.20-7.44 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.8 (C*Me*$_3$), 39.9 (*C*(3)), 54.4 (*C*(2)), 80.6 (*C*Me$_3$), 126.2, 127.0 (*p-Ph*), 127.7, 128.1, 128.4, 128.9 (*o,m-Ph*), 139.19, 139.22 (*i-Ph*), 172.4 (*C*(1)); *m/z* (ESI^+) 305 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{19}H_{22}NaO_2^+$ ($[M+H]^+$) requires 305.1512; found 305.1505.

tert-Butyl (*RS*)-2-allyl-3-phenylpropanoate 248



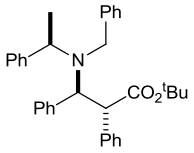
KHMDS (0.5 M in PhMe, 0.87 mL, 0.44 mmol) was added dropwise to a solution of **246** (60 mg, 0.29 mmol) in THF (mL) at −78 °C. After 30 min allyl bromide (76 μL, 0.87 mmol) was added dropwise via syringe and the subsequent solution left to warm to rt over 16 h before the addition of satd aq NH_4Cl (2 mL). The aqueous layer was extracted with Et_2O (10 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 100:1) gave **248** as a colourless oil (51 mg, 71%); ν_{max} (film) 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 1.34 (9H, s, C*Me*$_3$), 2.19-2.29 (1H, m, C(1′)H_A), 2.31-2.41 (1H, m, C(1′)H_B), 2.60-2.69 (1H, m, C(2)*H*), 2.71-2.79 (1H, m, C(3)H_A), 2.85-2.94 (1H, m, C(3)H_B), 5.01-5.12 (2H, m, C(3′)H_2), 5.72-5.85 (1H, m, C(2′)*H*), 7.16-7.23 (3H, m, *Ph*), 7.24-7.31 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 28.0 (C*Me*$_3$), 36.4 (*C*(1′)), 38.0 (*C*(3)), 47.8 (*C*(2)), 80.3 (*C*Me$_3$), 116.8 (*C*(3′)), 126.2 (*p-Ph*), 128.2, 129.0, (*o,m-Ph*), 135.4 (*C*(2′)), 139.4 (*i-Ph*), 174.2 (*C*(1)); *m/z* (ESI^+) 269 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{16}H_{22}NaO_2^+$ ($[M+H]^+$) requires 269.1512; found 269.1505.

***tert*-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate *ent*-219**[26]



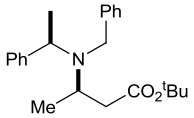
BuLi (2.50 M in hexanes, 0.30 mL, 0.76 mmol) was added dropwise via syringe to a stirred solution of (*R*)-**243** (166 mg, 0.78 mmol) in THF (2.5 mL) at −78 °C. After stirring for 30 min, a solution of **217** (100 mg, 0.49 mmol) in THF (2.5 mL) at −78 °C was added dropwise via cannula and the resultant mixture was left to stir for a further 2 h at −78 °C before the addition of satd aq NH_4Cl (2 mL) and the reaction mixture was left to warm to rt over 15 min. Et_2O (10 mL) was added and the resultant solution was washed sequentially with 10% aq citric acid (5 mL), satd aq $NaHCO_3$ (5 mL) and brine (5 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 9:1) gave *ent*-**219** as a colourless oil (193 mg, 95%, >99:1 dr);[26] $[\alpha]_D^{25}$ +4.4 (*c* 1.0 in $CHCl_3$); {lit.[26] $[\alpha]_D^{25}$ +3.9 (*c* 0.7 in $CHCl_3$)}.

***tert*-Butyl (2*R*,3*S*,α*R*)-2,3-diphenyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]propanoate *ent*-236**



$Pd(dba)_2$ (8.2 mg, 0.014 mmol) and $P(^tBu)_3{\cdot}HBF_4$ (8.2 mg, 0.028 mmol) were diluted with PhMe (1 mL) and the resultant mixture was stirred at rt for 10 min before being cooled to −20 °C and LiHMDS (1.0 M in PhMe, 0.34 mL, 0.34 mmol) and a solution of *ent*-**219** (116 mg, 0.28 mmol) in PhMe (2 mL) were sequentially added. After 15 min, bromobenzene (45 μL, 0.42 mmol) was added dropwise and the reaction mixture was left to warm to rt over 12 h. The reaction mixture was filtered through a short silica pad (~5 g, eluent Et_2O) and the filtrate was concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 100:1) gave *ent*-**236** as a yellow oil (120 mg, 40% conversion, >99:1 dr).[ii]

***tert*-Butyl (3*R*,αR)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]butanoate 251**[27]

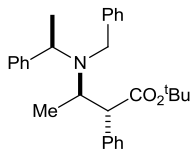


BuLi (2.50 M in hexanes, 8.72 mL, 21.8 mmol) was added dropwise via syringe to a stirred solution of (*R*)-**243** (4.75 g, 22.5 mmol) in THF (70 mL) at −78 °C. After stirring for 30 min, a solution of

[ii] Data as per page 138.

249 (2.00 g, 14.1 mmol) in THF (70 mL) at −78 °C was added dropwise via cannula and the resultant mixture was left to stir for a further 2 h at −78 °C before the addition of satd aq NH_4Cl (40 mL) and the reaction mixture was left to warm to rt over 15 min. Et_2O (150 mL) was added and the resultant solution was washed sequentially with 10% aq citric acid (100 mL), satd aq $NaHCO_3$ (100 mL) and brine (100 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 9:1) gave **251** as a colourless oil (4.74 g, 95%, >99:1 dr);[27] $[\alpha]_D^{20}$ −5.1 (*c* 1.0 in $CHCl_3$); {lit.[27] $[\alpha]_D^{25}$ −5.2 (*c* 1.1 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.12 (3H, d, *J* 6.8, C(4)H_3), 1.33 (3H, d, *J* 6.8, C(α)*Me*), 1.39 (9H, s, CMe_3), 2.02 (1H, dd, *J* 14.3, 9.2, C(2)H_A), 2.38 (1H, dd, *J* 14.3, 4.6, C(2)H_B), 3.38-3.48 (1H, m, C(3)*H*), 3.61 (1H, d, *J* 15.0, NCH_APh), 3.76 (1H, d, *J* 15.0, NCH_BPh), 3.89 (1H, q, *J* 6.8, C(α)*H*), 7.19-7.43 (10H, m, *Ph*).

***tert*-Butyl (2*R*,3*R*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-2-phenylbutanoate 252**

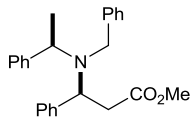


Method A. BuLi (2.50 M in hexanes, 0.44 mL, 1.10 mmol) was added dropwise via syringe to a stirred solution of (*R*)-**243** (238 mg, 1.13 mmol) in THF (3.5 mL) at −78 °C. After stirring for 30 min, a solution of **249** (100 mg, 0.70 mmol) in THF (3.5 mL) at −78 °C was added dropwise via cannula and the resultant mixture was left to stir for a further 2 h at −78 °C. $Pd(dba)_2$ (20.2 mg, 0.035 mmol), $P(^tBu)_3{\cdot}HBF_4$ (10.2 mg, 0.035 mmol) and PhBr (81 μL, 0.77 mmol) were added and the reaction mixture was left to warm to rt over 16 h. Et_2O (25 mL) was added and the resultant solution was washed sequentially with 10% aq citric acid (10 mL), satd aq $NaHCO_3$ (10 mL) and brine (10 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 100:1) gave **252** as a colourless oil (67 mg, 22%, 30:70 dr); Data for major diastereosiomer: δ_H (400 MHz, $CDCl_3$) 1.31 (3H, d, *J* 6.3, C(4)H_3), 1.33-1.38 (12H, m, CMe_3, C(α)*Me*), 3.58 (1H, d, *J* 10.3, C(2)*H*), 3.60-3.67 (1H, m, C(3)*H*), 3.68-3.78 (2H, m, NCH_2Ph), 3.82-3.89 (1H, m, C(α)*H*), 6.86-7.30 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.2 (C(α)*Me*), 15.8 (*C*(4)H_3), 27.8 (CMe_3), 49.5 (NCH_2Ph), 53.9 (*C*(3)H), 56.1 (*C*(α)H), 59.0 (*C*(2)H), 126.3, 126.5, 126.6 (*p-Ph*), 127.7, 128.81, 128.82, 128.9, 128.9, 129.0 (*o,m-Ph*), 137.8, 140.6, 143.9 (*i-Ph*), 172.7 (*C*(1)).

Method B. $Pd(dba)_2$ (8.2 mg, 0.014 mmol) and $P(^tBu)_3{\cdot}HBF_4$ (8.2 mg, 0.028 mmol) were diluted with PhMe (1 mL) and the resultant mixture was stirred at rt for 10 min before being cooled to −20

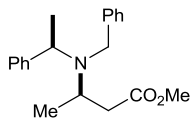
°C and LiHMDS (1.0 M in PhMe, 0.34 mL, 0.34 mmol) and a solution of **251** (100 mg, 0.28 mmol) in PhMe (2 mL) were sequentially added. After 15 min, bromobenzene (45 μL, 0.42 mmol) was added dropwise and the reaction mixture was left to warm to rt over 12 h. The reaction mixture was filtered through a short silica pad (~5 g, eluent Et_2O) and the filtrate was concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 100:1) gave **252** as a colourless oil (41 mg, 34%, 87:13 dr); Data for major diastereosiomer: ν_{max} (film) 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 0.64 (3H, d, *J* 6.8, C(4)H_3), 1.39-1.47 (12H, m, CMe_3, C(α)*Me*), 3.33 (1H, d, *J* 11.0, C(2)*H*), 3.69-3.78 (2H, m, NCH_2Ph), 3.85 (1H, dq, *J* 11.0, 6.8, C(3)*H*), 4.15 (1H, q, *J* 7.1, C(α)*H*), 7.18-7.43 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.6 (*C*(4)H_3), 19.1 (C(α)*Me*), 28.0 (CMe_3), 49.2 (N*C*H_2Ph), 57.9 (*C*(3)H), 59.3 (*C*(2)H), 61.3 (*C*(α)H), 126.5, 126.6, 127.0 (*p-Ph*), 127.8, 128.1, 128.3, 128.5, 128.9 (*o,m-Ph*), 137.8, 141.9, 144.0 (*i-Ph*), 172.6 (*C*(1)); *m/z* (ESI^+) 430 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{29}H_{36}NO_2^+$ ($[M+H]^+$) requires 430.2741; found 430.2735.

Methyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 253[26]



$SOCl_2$ (0.26 mL, 3.61 mmol) was added dropwise to a stirred solution of *ent*-**219** (1.00 g, 2.41 mmol) in MeOH (10 mL) at 0 °C and the reaction mixture was left to warm to rt over 16 h before being concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (30 mL) and satd aq $NaHCO_3$ (30 mL) and the phases were separated. The organic layer was washed with satd aq $NaHCO_3$ (3 × 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 5:1) gave **253** as a colourless oil (0.78 g, 86%, >99:1 dr);[26] $[\alpha]_D^{20}$ −4.4 (*c* 1.0 in CH_2Cl_2); {lit.[26] $[\alpha]_D^{20}$ −4.2 (*c* 1.1 in CH_2Cl_2)}; δ_H (400 MHz, $CDCl_3$) 1.23 (3H, d, *J* 6.8, C(α)*Me*), 2.58 (1H, dd, *J* 15.0, 9.2, C(2)H_A), 2.70 (1H, dd, *J* 15.0, 5.8, C(2)H_B), 3.48 (3H, s, O*Me*), 3.65-3.79 (2H, m, NCH_2Ph), 4.02 (1H, q, *J* 6.8, C(α)*H*), 4.45 (1H, dd, *J* 9.2, 5.8, C(3)*H*), 7.16-7.48 (15H, m, *Ph*).

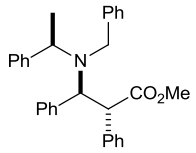
Methyl (3*R*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]butanoate 255[26]



BuLi (2.50 M in hexanes, 12.4 mL, 31.0 mmol) was added dropwise via syringe to a stirred solution of (*R*)-**243** (6.75 g, 32.0 mmol) in THF (100 mL) at −78 °C. After stirring for 30 min, a

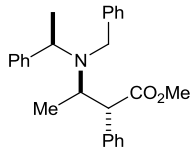
solution of **254** (2.01 mL, 20.0 mmol) in THF (100 mL) at −78 °C was added dropwise via cannula and the resultant mixture was left to stir for a further 2 h at −78 °C, before the addition of satd aq NH_4Cl (30 mL) and the reaction mixture was left to warm to rt over 15 min. Et_2O (150 mL) was added and the resultant solution was washed sequentially with 10% aq citric acid (100 mL), satd aq $NaHCO_3$ (100 mL) and brine (100 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 9:1) gave **255** as a colourless oil (5.73 g, 92%, >99:1 dr);[26] $[\alpha]_D^{20}$ −3.8 (*c* 1.0 in $CHCl_3$); {lit.[26] $[\alpha]_D^{20}$ −3.4 (*c* 1.2 in CH_2Cl_2)}; δ_H (400 MHz, $CDCl_3$) 1.15 (3H, d, *J* 6.5, C(4)H_3), 1.36 (3H, d, *J* 7.0, C(α)*Me*), 2.13 (1H, dd, J 14.3, 7.9, C(2)H_A), 2.38 (1H, dd, *J* 14.3, 6.3, C(2)H_B), 3.40-3.50 (1H, m, C(3)*H*), 3.51 (3H, s, O*Me*), 3.67-3.77 (2H, m, NCH_2Ph), 3.90 (1H, q, *J* 7.0, C(α)*H*), 7.19-7.36 (8H, m, *Ph*), 7.39-7.45 (2H, m, *Ph*).

Methyl (2*R*,3*S*,α*R*)-2-phenyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-phenylpropanoate 256



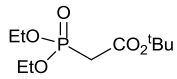
$Pd(dba)_2$ (6.2 mg, 0.011 mmol) and $P(^tBu)_3{\cdot}HBF_4$ (6.2 mg, 0.021 mmol) were diluted with PhMe (0.7 mL) and the resultant mixture was stirred at rt for 10 min before being cooled to −20 °C and LiHMDS (1.0 M in PhMe, 0.26 mL, 0.26 mmol) and a solution of **253** (80 mg, 0.21 mmol) in PhMe (1.4 mL) were sequentially added. After 15 min, bromobenzene (34 μL, 0.32 mmol) was added dropwise and the reaction mixture was left to warm to rt over 12 h. The reaction mixture was filtered through a short silica pad (~5 g, eluent Et_2O) and the filtrate was concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 50:1) gave **256** as a colourless oil (63 mg, 65%, >99:1 dr); $[\alpha]_D^{20}$ −47.8 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1733 (C=O); δ_H (500 MHz, $CDCl_3$) 1.01 (3H, d, *J* 6.8, C(α)*Me*), 3.55 (3H, s, O*Me*), 3.69 (1H, d, *J* 13.9, NCH_APh), 4.18 (1H, d, *J* 13.9, NCH_BPh), 4.31 (1H, q, *J* 6.8, C(α)*H*), 4.43 (1H, d, *J* 12.0, C(2)*H*), 4.69 (1H, d, *J* 12.0, C(3)*H*), 6.97-7.45 (20H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 14.8 (C(α)*Me*), 50.8 (NCH_2Ph), 51.7 (O*Me*), 55.4 (*C*(2)H), 56.0 (*C*(α)H), 64.0 (*C*(3)H), 126.5, 126.8, 127.0 (*p-Ph*), 127.81, 127.82, 128.0, 128.1, 128.2, 129.0, 129.1, 129.4 (*o,m-Ph*), 136.3, 137.7, 139.9, 144.2 (*i-Ph*), 172.9 (*C*(1)); *m/z* (ESI^+) 450 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{31}H_{31}NNaO_2^+$ ($[M+Na]^+$) requires 472.2247; found 472.2251.

Methyl (2*R*,3*R*,*αR*)-2-phenyl 3-[*N*-benzyl-*N*-(*α*-methylbenzyl)amino]butanoate 257



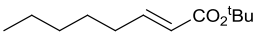
$Pd(dba)_2$ (9.2 mg, 0.016 mmol) and $P(^tBu)_3 \cdot HBF_4$ (9.3 mg, 0.032 mmol) were diluted with PhMe (1 mL) and the resultant mixture was stirred at rt for 10 min before being cooled to −20 °C and LiHMDS (1.0 M in PhMe, 0.39 mL, 0.39 mmol) and a solution of **255** (100 mg, 0.32 mmol) in PhMe (2 mL) were sequentially added. After 15 min, bromobenzene (51 μL, 0.48 mmol) was added dropwise and the reaction mixture was left to warm to rt over 12 h. The reaction mixture was filtered through a short silica pad (~5 g, eluent Et_2O) and the filtrate was concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 50:1) gave **257** as a colourless oil (95 mg, 76%, >99:1 dr); $[\alpha]_D^{25}$ −11.2 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1733 (C=O); δ_H (400 MHz, $CDCl_3$) 0.82 (3H, d, *J* 6.8, C(4)H_3), 1.46 (3H, d, *J* 6.9, C(α)*Me*), 3.48 (3H, s, O*Me*), 3.59 (1H, d, *J* 10.9, C(2)*H*), 3.73 (1H, d, *J* 14.1, NCH_APh), 3.82 (1H, dq, *J* 10.9, 6.8, C(3)*H*), 3.90 (1H, d, *J* 14.1, NCH_BPh) 4.12 (1H, q, *J* 6.9, C(α)*H*), 7.21-7.46 (15H, m, *Ph*); δ_C (100MHz, $CDCl_3$) 14.3 (*C*(4)H_3), 16.6 (C(α)*Me*), 49.6 (N*C*H_2Ph), 51.5 (O*Me*), 56.4 (*C*(3)H), 58.3 (*C*(α)H), 58.5 (*C*(2)H), 126.6, 126.7, 127.3 (*p-Ph*), 127.8, 128.0, 128.1, 128.4, 128.7, 129.0 (*o,m-Ph*), 137.3, 140.9, 144.0 (*i-Ph*), 173.3 (*C*(1)); *m/z* (ESI^+) 388 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{26}H_{30}NO_2^+$ ($[M+H]^+$) requires 388.2271; found 388.2280.

***tert*-Butyl-2-(diethoxyphosphoryl)acetate 259**[28]



Triethylphosphite (11.6 mL, 67.7 mmol) was added to *tert*-butyl 2-bromoacetate (10.0 mL) and the mixture was stirred at 50 °C for 24 h before being concentrated *in vacuo* to give **259** as a colourless oil (17.0 g, quant);[28] δ_H (400 MHz, $CDCl_3$) 1.36 (6H, t, *J* 7.1, OCH_2CH_3), 1.48 (9H, s, CMe_3), 2.89 (2H, d, *J* 21.3, PCH_2), 4.11-4.23 (4H, m, OCH_2CH_3).

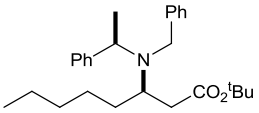
***tert*-Butyl (*E*)-oct-2-enoate 258**[29]



MeMgBr (3.0 M in Et_2O, 1.30 mL, 3.90 mmol) was added dropwise to a stirred solution of **259** (984 mg, 3.90 mmol) in THF (20 mL) at rt and the reaction mixture stirred at rt for 15 min. A solution of hexanal (0.47 mL, 3.90 mmol) in THF (20 ml) was added dropwise and the reaction mixture stirred at reflux for 16 h before the addition of satd aq NH_4Cl (20 mL). The aqueous layer

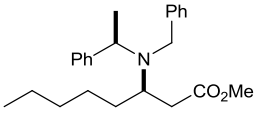
was extracted with EtOAc (2 × 50 mL) and the combined organic extracts were washed with brine (30 mL), dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution 5% → 20% Et_2O in 30-40 °C petrol) gave **258** as a colourless oil (634 mg, 82%, >99:1 dr);[29] δ_H (400 MHz, $CDCl_3$) 0.84-0.94 (3H, m, C(8)H_3), 1.25-1.37 (4H, m, C(6)H_2,C(7)H_2), 1.40-1.51 (11H, m, CMe_3, C(5)H_2), 2.12-2.21 (2H, m, C(4)H_2), 5.74 (1H, dt, *J* 15.6, 1.5, C(2)*H*), 6.87 (1H, dt, *J* 15.6, 7.1, C(3)*H*).

tert-Butyl (3*R*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]octanoate 260[26]



BuLi (2.50 M in hexanes, 0.62 mL, 1.56 mmol) was added dropwise via syringe to a stirred solution of (*R*)-**243** (341 mg, 1.61 mmol) in THF (5 mL) at −78 °C. After stirring for 30 min, a solution of **258** (200 mg, 1.01 mmol) in THF (5 mL) at −78 °C was added dropwise via cannula and the resultant mixture was left to stir for a further 2 h at −78 °C before the addition of satd aq NH_4Cl (5 mL) and the reaction mixture was left to warm to rt over 1 h. Et_2O (20 mL) was added and the resultant solution was washed sequentially with 10% aq citric acid (10 mL), satd aq $NaHCO_3$ (10 mL) and brine (10 mL), then dried ($MgSO_4$) and concentrated in vacuo. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 5:1) yielded **260** as a colourless oil (393 mg, 95%, >99:1 dr); $[\alpha]_D^{20}$ +7.1 (*c* 1.0 in $CHCl_3$); {lit.[26] $[\alpha]_D^{20}$ +7.6 (*c* 1.4 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.3, C(8)H_3), 1.12-1.37 (11H, m, C(4)H_2−C(7)H_2, C(α)Me), 1.40 (9H, s, CMe_3), 1.82-2.00 (2H, m, C(2)H_2), 3.24-3.36 (1H, m, C(3)*H*), 3.48 (1H, d, *J* 15.0, NC$H_A$$H_B$Ph), 3.73-3.89 (2H, m, NC$H_A$$H_B$Ph, C(α)*H*), 7.21-7.39 (8H, m, *Ph*), 7.43 (2H, app d, *J* 7.2, *Ph*).

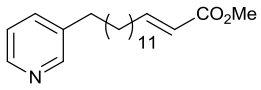
Methyl (3*R*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]octanoate 261[30]



$SOCl_2$ (0.13 mL, 1.83 mmol) was added dropwise to a stirred solution of **260** (500 mg, 1.22 mmol) in MeOH (5 mL) at 0 °C and the reaction mixture was left to warm to rt over 16 h before being concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (20 mL) and satd aq $NaHCO_3$ (20 mL) and the layers were separated. The organic layer was washed with satd aq $NaHCO_3$ (3 × 20 mL), dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 5:1) gave **261** as a colourless oil (433 mg, 85%,

>99:1 dr);[30] $[\alpha]_D^{20}$ +9.1 (*c* 1.0 in $CHCl_3$); {lit.[30] for enantiomer $[\alpha]_D^{20}$ −9.9 (*c* 1.2 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 0.93 (3H, t, *J* 7.2, C(8)H_3), 1.19-1.41 (11H, m, C(5)H_2−C(7)H_2, C(α)Me), 1.50-1.64 (2H, m, C(4)H_2), 2.01-2.14 (2H, m, C(2)H_2), 3.29-3.39 (1H, m, C(3)*H*), 3.57 (3H, s, O*Me*), 3.60 (1H, d, *J* 15.0, NC$H_A$$H_B$Ph), 3.77-3.92 (2H, m, NC$H_A$$H_B$Ph, C(α)*H*), 7.22-7.41 (8H, m, *Ph*), 7.44-7.49 (2H, m, *Ph*).

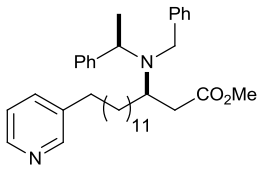
Methyl (*E*)-15-(pyridin-3′-yl)pentadec-2-enoate 263



Step 1. IBX (7.71 g, 27.5 mmol) was added to a stirred solution of **157** (2.54 g, 9.18 mmol) in EtOAc (50 mL) at rt and the reaction mixture was stirred at 80 °C for 3 h before being cooled to rt and filtered though Celite®. The Celite® pad was washed with EtOAc (30 mL) and the filtrate was concentrated *in vacuo* to give **167** as a yellow oil (2.50 g, 99%).

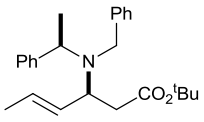
Step 2. MeMgBr (3.0 M in Et_2O, 2.75 mL, 8.26 mmol) was added dropwise to a stirred solution of **262** (1.73 g, 8.26 mmol) in THF (50 mL) at rt and the reaction mixture stirred at rt for 15 min. A solution of **167** (2.50 g) in THF (30 ml) was added dropwise and the reaction mixture stirred at reflux for 16 h before the addition of satd aq NH_4Cl (20 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL) and the combined organic extracts were washed with brine (30 mL), dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution 5% → 20% Et_2O in 30-40 °C petrol) gave **263** as a colourless oil (2.44 g, 81% from **157**, >99:1 dr); ν_{max} (film) 1724 (C=O), 1657 (C=C); δ_H (400 MHz, $CDCl_3$) 1.19-1.50 (18H, m, C(5)H_2−C(13)H_2), 1.56-1.67 (2H, m, C(14)H_2), 2.15-2.23 (2H, m, C(4)H_2), 2.57-2.63 (2H, m, C(15)H_2), 3.73 (O*Me*), 5.82 (1H, dt, *J* 15.7, 1.5, C(2)*H*), 6.98 (1H, dt, *J* 15.7, 7.0, C(3)*H*), 7.20 (1H, app dd, *J* 7.8, 4.8, C(5′)*H*), 7.45-7.52 (1H, m, C(4′)*H*), 8.40-8.47 (2H, m, C(2′)*H*, C(6′)*H*); δ_C (100 MHz, $CDCl_3$) 28.0, 29.10, 29.13, 29.36, 29.38, 29.48, 29.50, 29.57, 29.61 (*C*(5)−*C*(13)), 31.1 (*C*(14)), 32.2 (*C*(4)), 33.0 (*C*(15)), 51.4 (O*Me*), 120.8 (*C*(2)), 123.2 (*C*(5′)), 135.7 (*C*(4′)), 137.9 (*C*(3′)), 147.2 (*C*(6′)), 149.8 (*C*(3)), 150.0 (*C*(2′)), 167.2 (*C*(1)); *m/z* (ESI^+) 332 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{21}H_{34}NO_2^+$ ($[M+H]^+$) requires 332.2571; found 332.2584.

Methyl (3*R*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-15-(pyridin-3′-yl)pentadecanoate 264



BuLi (2.50 M in hexanes, 1.12 mL, 2.81 mmol) was added dropwise via syringe to a stirred solution of (*R*)-**243** (608 mg, 2.88 mmol) in THF (9 mL) at −78 °C. After stirring for 30 min, a solution of **263** (600 mg, 1.81 mmol) in THF (9 mL) at −78 °C was added dropwise via cannula and the resultant mixture was left to stir for 2 h at −78 °C, before the addition of satd aq NH_4Cl (5 mL) and the reaction mixture was left to warm to rt over 1 h. Et_2O (30 mL) was added and the resultant solution was washed sequentially with 10% aq citric acid (20 mL), satd aq $NaHCO_3$ (20 mL) and brine (20 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc/Et_3N, 90:10:1) yielded **264** as a colourless oil (801 mg, 81%, >99:1 dr); $[\alpha]_D^{20}$ +4.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1736 (C=O); δ_H (400 MHz, $CDCl_3$) 1.17-1.40 (21H, m, C(5)H_2−C(13)H_2, C(α)*Me*), 1.48-1.69 (4H, m, C(4)H_2, C(14)H_2), 2.00-2.13 (C(2)H_2), 2.57-2.65 (2H, m, C(15)H_2), 3.27-3.37 (1H, m, C(3)*H*), 3.52-3.61 (4H, m, NC$H_A$$H_B$Ph, O*Me*), 3.80 (1H, d, *J* 14.9, NCH$_A$$H_B$Ph), 3.86 (1H, q, *J* 6.8, C(α)*H*), 7.17-7.28 (3H, m, C(5′)*H*, *Ph*), 7.29-7.38 (6H, m, *Ph*), 7.44 (2H, app d, *J* 7.3, *Ph*), 7.49 (1H, app dt, *J* 7.8, 1.8, C(4′)*H*), 8.42-8.48 (2H, m, C(2′)*H*), C(6′)*H*); δ_C (100 MHz, $CDCl_3$) 19.2 (C(α)*Me*), 27.0, 29.1, 29.3, 29.46, 29.54, 31.1, 32.9, 33.4 (*C*(4)-*C*(15)), 36.6 (*C*(2)), 49.8 (N*C*H$_2$Ph), 51.2 (O*Me*), 54.0 (*C*(3)), 57.6 (*C*(α)), 123.1 (*C*(5′)), 126.5, 126.7 (*p-Ph*), 127.8, 127.9, 128.1, 128.2 (*o*,*m-Ph*), 135.6 (*C*(4′)), 137.8, 141.6, 143.1 (*i-Ph*, *C*(3′)), 147.1 (*C*(6′)), 149.9 (*C*(2′)), 173.2 (*C*(1)); *m/z* (ESI^+) 543 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{36}H_{51}N_2O_2^+$ ($[M+H]^+$) requires 543.3945; found 543.3941.

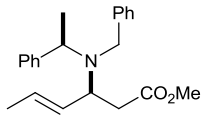
***tert*-Butyl (3*S*,α*R*,*E*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 266**[31]



BuLi (2.50 M in hexanes, 1.61 mL, 4.01 mmol) was added dropwise via syringe to a stirred solution of (*R*)-**243** (876 mg, 4.14 mmol) in THF (13 mL) at −78 °C. After stirring for 30 min a solution of **265** (435 mg, 2.59 mmol) in THF (13 mL) at −78 °C was added dropwise via cannula and the reaction mixture was left to stir for 2 h before the addition of satd aq NH_4Cl (5 mL) and the reaction mixture was left to warm to rt over 1 h. Et_2O (30 mL) was added and the resultant solution was washed sequentially with 10% aq citric acid (20 mL), satd aq $NaHCO_3$ (20 mL) and brine (20 mL),

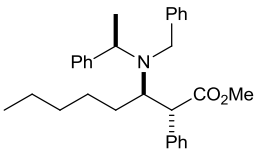
then dried ($MgSO_4$) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 20:1) gave **266** as a pale yellow oil (796 mg, 81%, >99:1 dr);[31] $[\alpha]_D^{20}$ −19.2 (*c* 1.0 in $CHCl_3$); {lit.[31] $[\alpha]_D^{24}$ −23.3 (*c* 2.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.35 (9H, s, C*Me*$_3$), 1.37 (3H, d, *J* 7.1, C(α)*Me*), 1.69 (3H, d, *J* 4.4, C(6)*H*$_3$), 2.22 (1H, dd, *J* 14.2, 9.7, C(2)*H*$_A$), 2.35 (1H, dd, *J* 14.2, 5.8, C(2)*H*$_B$), 3.66 (2H, app s, NC*H*$_2$Ph), 3.75 (1H, m, C(3)*H*), 4.00 (1H, q, *J* 7.1, C(α)*H*), 5.46-5.59 (2H, m, C(4)*H*, C(5)*H*), 7.16-7.40 (10H, m, *Ph*).

Methyl (3S,*αR*,*E*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 267[32]



$SOCl_2$ (0.09 mL, 1.18 mmol) was added dropwise to a stirred solution of **266** (300 mg, 0.79 mmol) in MeOH (5 mL) at 0 °C and the reaction mixture was left to warm to rt over 16 h before being concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (20 mL) and satd aq $NaHCO_3$ (20 mL) and the layers were separated. The organic layer was washed with satd aq $NaHCO_3$ (3 × 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 5:1) gave **267** as a colourless oil (412 mg, 78%, >99:1 dr);[32] $[\alpha]_D^{20}$ −25.1 (*c* 1.0 in $CHCl_3$); {lit.[32] $[\alpha]_D^{20}$ −25.4 (*c* 3.38 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.40 (3H, d, *J* 6.8, C(α)*Me*), 1.72 (3H, d, *J* 5.5, C(6)*H*$_3$), 2.32 (1H, dd, *J* 14.3, 7.5, C(2)*H*$_A$), 2.50 (1H, dd, *J* 14.3, 7.5, C(2)*H*$_B$), 3.52 (3H, s, O*Me*), 3.64-3.83 (3H, m, C(3)*H*, NC*H*$_2$Ph), 4.02 (1H, q, *J* 6.8, C(α)*H*), 5.49-5.65 (2H, m, C(4)*H*, C(5)*H*), 7.19-7.41 (10H, m, *Ph*).

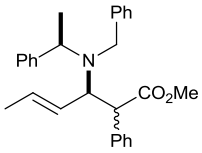
Methyl (2*R*,3*R*,*αR*)-2-phenyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]octanoate 268



$Pd(dba)_2$ (7.8 mg, 0.014 mmol) and $P(^tBu)_3{\cdot}HBF_4$ (7.9 mg, 0.027 mmol) were diluted with PhMe (1 mL) and the resultant mixture was stirred at rt for 10 min before being cooled to −20 °C and LiHMDS (1.0 M in PhMe, 0.33 mL, 0.33 mmol) and a solution of **261** (100 mg, 0.27 mmol) in PhMe (2 mL) were sequentially added. After 15 min, bromobenzene (43 μL, 0.41 mmol) was added dropwise and the reaction mixture was left to warm to rt over 12 h. The reaction mixture was filtered through a short silica pad (~5 g, eluent Et_2O) and the filtrate was concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 50:1) gave an 8:67:25 mixture of **261**, **268** and **269** as a yellow oil (72 mg); Data for major diastereoisomer **268**:

δ_H (300 MHz, $CDCl_3$) [selected peaks] 0.75 (3H, t, *J* 7.1, C(8)H_3), 0.83-1.37 (8H, m, C(4)H_2−C(7)H_2), 1.45 (3H, d, *J* 7.0, C(α)*Me*), 3.60 (3H, s, O*Me*), 4.14 (1H, q, *J* 7.0, C(α)*H*), 7.21-7.44 (10H, m, *Ph*); δ_C (75 MHz, $CDCl_3$) [selected peaks] 13.9 (*C*(8)), 18.9 (C(α)*Me*), 22.2, 27.7, 30.5, 32.1 (*C*(4)−*C*(7)), 50.2 (N*C*H_2Ph), 60.2 (*C*(α)), 137.2, 141.8, 144.7 (*i-Ph*), 173.8 (*C*(1)).

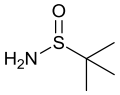
Methyl (3*S*,α*R*,*E*)-2-phenyl 3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 270



$Pd(dba)_2$ (8.5 mg, 0.015 mmol) and $P(^tBu)_3{\cdot}HBF_4$ (7.9 mg, 0.030 mmol) were diluted with PhMe (1 mL) and the resultant mixture was stirred at rt for 10 min before being cooled to −20 °C and LiHMDS (1.0 M in PhMe, 0.36 mL, 0.36 mmol) and a solution of **267** (100 mg, 0.297 mmol) in PhMe (2 mL) were sequentially added. After 15 min, bromobenzene (47μL, 0.44 mmol) was added dropwise and the reaction mixture was left to warm to rt over 12 h. The reaction mixture was filtered through a short silica pad (~5 g, eluent Et_2O) and the filtrate was concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 50:1) gave an impure mixture of **267** and **270** as a yellow oil (82 mg); Data for major diastereoisomer: δ_H (300 MHz, $CDCl_3$) [selected peaks] 1.35-1.43 (6H, m, C(6)H_3, C(α)*Me*), 3.40 (3H, s, O*Me*), 4.14 (1H, q, *J* 6.8, C(α)*H*), 5.02-5.24 (2H, m, C(4)*H*, C(5)*H*), 7.03-7.40 (15H, m, *Ph*).

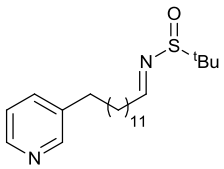
6.4 Experimental for chapter 4

(*RS*)-2-Methylpropane-2-sulfinamide (*RS*)-283[34]



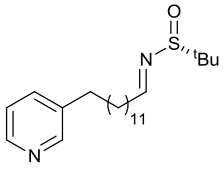
A solution of *tert*-butylsulfinyl chloride **298** (5.00 g, 35.6 mmol) in CH_2Cl_2 (130 mL) was added dropwise to NH_4OH (35% aq, 130 mL) at 0 °C and the reaction mixture was left to stir for 30 min before the addition of NaCl until the solution was saturated. H_2O (250 mL) was added and the phases separated. The aqueous layer was washed with CH_2Cl_2 (2 × 100 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give (*RS*)-**283** as a white solid (4.22 g, 98%);[33] mp 99−101 °C; {lit.[34] 98−102 °C}; δ_H (400 MHz, $CDCl_3$) 1.24 (9H, s, CMe_3), 3.68 (2H, br s, NH_2).

(*E*,*RS*$_S$)-*N*-[(13-(Pyridin-3′-yl)triadec-1-ylidene]-*tert*-butylsulfinamide 288



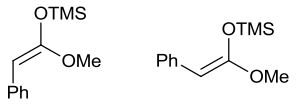
A solution of **167** (0.99 g, 3.61 mmol) in CH_2Cl_2 (4 mL) was added dropwise via syringe to a stirred mixture of PPTS (43 mg, 0.17 mmol), $MgSO_4$ (2.06 g, 17.2 mmol) and (*RS*)-**283** (417 mg, 3.44 mmol) in CH_2Cl_2 (4 mL) and the resultant mixture was stirred at rt for 16 h before being filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent petrol/EtOAc, 60:40) gave **288** as a pale yellow oil (845 mg, 75%, >99:1 dr); ν_{max} (film) 1084, 1622; δ_H (400 MHz, $CDCl_3$) 1.17 (9H, s, C*Me*$_3$), 1.20-1.37 (16H, m, C(4)*H*$_2$−C(11)*H*$_2$), 1.54-1.64 (4H, m, C(3)*H*$_2$, C(12)*H*$_2$), 2.48 (2H, td, *J* 7.3, 4.8, C(2)*H*$_2$), 2.57 (2H, t, *J* 7.7, C(13)*H*$_2$), 7.17 (1H, dd, C(5′)*H*), 7.43-7.49 (1H, m, C(4′)*H*), 8.04 (1H, t, *J* 4.8, C(1)*H*), 8.37-8.45 (2H, m, C(2′)*H*), C(6′)*H*); δ_C (100 MHz, $CDCl_3$) 22.2 (C*Me*$_3$), 25.4 (*C*(3)), 29.0, 29.1, 29.2, 29.3, 29.4, 29.5 (*C*(4)-*C*(11)), 31.0 (*C*(12)), 32.9 (*C*(13)), 36.0 (*C*(2)), 56.4 (*C*Me$_3$), 123.1 (*C*(5′)), 135.7 (*C*(4′)), 137.9 (*C*(3′)), 147.0 (*C*(6′)), 149.8 (*C*(2′)), 169.7 (N=*C*H); *m/z* (ESI$^+$) 379 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{39}N_2OS^+$ ([M+H]$^+$) requires 379.2778; found 379.2769.

(*E*,*R*$_S$)-*N*-[(13-(Pyridin-3′-yl)triadec-1-ylidene]-*tert*-butylsulfinamide (*R*)-288



A solution of **167** (1.97 g, 7.15 mmol) in CH_2Cl_2 (10 mL) was added dropwise via syringe to a stirred mixture of PPTS (90 mg, 0.36 mmol), $MgSO_4$ (4.30 g, 35.7 mmol) and (*R*)-**283** (866 mg, 7.15 mmol) in CH_2Cl_2 (10 mL) and the resultant mixture was stirred at rt for 16 h before being filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent, petrol/EtOAc, 60:40) gave **288** as a pale yellow oil (2.43 g, 90%, >99:1 *E*:*Z*); $[\alpha]_D^{20}$ −158.0 (*c* 1.0 in $CHCl_3$).

(*E*)- and (*Z*)-1-Methoxy-2-phenylethenoltrimethylsilane 303 and 304[35]



Method A. LiHMDS (1.0 M in THF, 0.36 mL, 0.36 mmol) was added dropwise to a stirred solution of methyl phenylacetate (47 μL, 0.33 mmol) in THF (1 mL) at −78 °C. After 30 min, TMSCl (63 μL, 0.50 mmol) was added dropwise and the resultant mixture was allowed to warm to rt over 1 h before being concentrated *in vacuo* to give an 85:15 mixture of (*E*)-**303**:(*Z*)-**304**. Data for (*E*)-**303**:[35] δ_H (400 MHz, $CDCl_3$) 0.37 (9H, s, OSi*Me*$_3$), 3.74 (3H, s, O*Me*), 4.72 (1H, s, C*H*), 7.03-7.10 (1H, m, *p*-Ph), 7.25-7.30 (2H, m, *m*-Ph), 7.43-7.47 (2H, m, *o*-Ph). Data for (*Z*)-**304**: δ_H (400 MHz, $CDCl_3$) 0.33 (9H, s, Si*Me*$_3$), 3.70 (3H, s, O*Me*), 4.63 (1H, s, C*H*), 7.02-7.09 (1H, m, Ph), 7.17-7.40 (2H, m, Ph), 7.45-7.50 (2H, m, Ph).

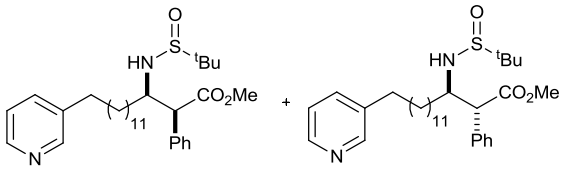
Method B. BuLi (2.50 M in hexanes, 0.15 mL, 0.37 mmol) was added dropwise to a stirred solution of DIPA (51 μL, 0.37 mmol) in THF (0.5 mL) −78 °C. After 30 min, a solution of methyl phenylacetate (47 μL, 0.33 mmol) in THF (0.5 mL) at −78 °C was added. After 30 min, TMSCl (63 μL, 0.50 mmol) was added dropwise and the resultant mixture was allowed to warm to rt over 1 h before being concentrated *in vacuo* to give an 80:20 mixture of (*E*)-**303**:(*Z*)-**304**.

Method C. KHMDS (0.5 M in PhMe, 0.72 mL, 0.36 mmol) was added dropwise to a stirred solution of methyl phenylacetate (47 μL, 0.33 mmol) in THF (1 mL) at −78 °C. After 30 min, TMSCl (63 μL, 0.50 mmol) was added dropwise and the resultant mixture was allowed to warm to rt over 1 h before being concentrated *in vacuo* to give an 3:97 mixture of (*E*)-**303**:(*Z*)-**304**.

Method D. LiHMDS (1.0 M in THF, 0.36 mL, 0.36 mmol) was added dropwise to a stirred suspension of methyl phenylacetate (47 μL, 0.33 mmol) and LiCl (72 mg, 1.66 mmol) in THF (1 mL) at −78 °C. After 30 min, TMSCl (63 μL, 0.50 mmol) was added dropwise and the resultant mixture was allowed to warm to rt over 1 h before being concentrated *in vacuo* to give an 90:10 mixture of (*E*)-**303**:(*Z*)-**304**.

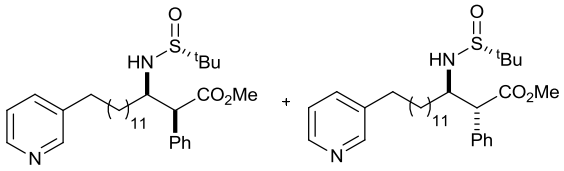
Method E. KHMDS (0.5 M in PhMe, 0.72 mL, 0.36 mmol) was added dropwise to a stirred suspension of methyl phenylacetate (47 μL, 0.33 mmol) and LiCl (72 mg, 1.66 mmol) in THF (1 mL) at −78 °C. After 30 min, TMSCl (63 μL, 0.50 mmol) was added dropwise and the resultant mixture was allowed to warm to rt over 1 h before being concentrated *in vacuo* to give an 74:26 mixture of (*E*)-**303**:(*Z*)-**304**.

Methyl (2*S*,3*R*,*RS*$_S$)- and (2*R*,3*R*,*RS*$_S$)-2-phenyl-3-(*N*-*tert*-butylsulfinamido)-15-(pyridin-3′-yl)pentadecanoate 290 and 291



Optimisation of the imino-aldol reaction. The requisite base (1.2−1.3 equiv) was added dropwise to a stirred mixture of methyl phenylacetate (1.2−1.3 equiv) and the requisite additive (1.5−5.0 equiv) in THF (0.2 M) at −78 °C. After 30 min, a solution of **288** (1.0 equiv) in THF (0.2 M) was added and the resultant mixture was stirred at −78 °C for 3−6 h before the addition of satd aq NH_4Cl (2 mL). After warming to rt over 15 min, the reaction mixture was diluted with EtOAc (5 mL) and the phases were separated. The aqueous layer was extracted with EtOAc (5 mL) and the combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give the crude reaction mixture which was analysed by ^{1}H NMR spectroscopy in C_6D_6.

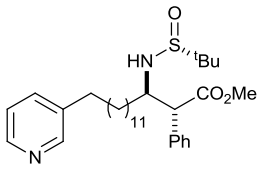
Methyl (2*S*,3*R*,*R*$_S$)- and (*R*,*R*,*R*)-2-phenyl-3-(*N*-*tert*-butylsulfinamido)-15-(pyridin-3′-yl)pentadecanoate 290 and 291



MeMgBr (2.86 M in Et_2O, 0.56 mL, 1.59 mmol) was added dropwise to a stirred suspension of methyl phenylacetate (0.24 mL, 1.72 mmol) and $MgBr_2$ (1.21 g, 6.61 mmol) in THF (10 mL) at −78 °C. After 1 h, a solution of **288** (0.50 g, 1.32 mmol) in THF (5 mL) was added via syringe and the resultant mixture stirred at −78 °C for 6 h before the addition of satd aq NH_4Cl (5 mL). After warming to rt over 15 min, the reaction mixture was diluted with EtOAc (20 mL) and the phases were separated. The aqueous layer was extracted with EtOAc (20 mL) and the combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give an 86:14 mixture of **290** and **291**. Purification via recrystallization (Et_2O/petrol) gave (2*S*,3*R*,*R*$_S$)-**290** as a white solid (425 mg, 61%, >99:1 dr); mp 65−67°C; $[\alpha]_D^{20}$ −51.2 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1068, 1456, 1734 (C=O); δ_H (500 MHz, C_6D_6) 0.99 (9H, s, C*Me*$_3$), 1.12-1.42 (19H, m, C(6)*H*$_2$−C(14)*H*$_2$, C(5)*H*$_A$), 1.50-1.70 (2H, m, C(4)*H*$_A$, C(5)*H*$_B$), 1.82-1.93 (1H, m, C(4)*H*$_B$), 2.27 (2H, t, *J* 7.7, C(15)*H*$_2$), 3.30 (3H, s, O*Me*), 3.93 (1H, d, *J* 6.9, N*H*), 3.97-4.04 (1H, m, C(3)*H*), 4.27 (1H, d, *J* 6.0, C(2)*H*), 6.76 (1H, app dd, *J* 7.9, 4.7, C(5′)*H*), 6.99-7.05 (2H, m, C(4′)*H*), *p*-*Ph*), 7.07-7.13 (2H, m, *m*-*Ph*), 7.29-7.33 (2H, m, *o*-*Ph*), 8.47-8.53 (1H, m, C(6′)*H*), 8.54-8.62 (1H, m, C(2′)*H*); δ_C (125 MHz, C_6D_6) 22.9 (C*Me*$_3$), 26.6 (*C*(5)), 29.8, 30.1, 30.2, 30.3, 30.4 (*C*(6)-*C*(13)),

31.8 (*C*(14)), 32.8 (*C*(4)), 33.5 (*C*(15)), 52.0 (O*Me*), 55.8 (*C*Me$_3$), 57.2 (*C*(2)), 58.7 (*C*(3)), 123.6 (*C*(5')), 128.7 (*p-Ph*), 129.2 (*m-Ph*), 130.4 (*o-Ph*), 135.5 (*C*(4')), 136.6 (*i-Ph*), 138.1 (*C*(3')), 148.2 (*C*(6')), 151.0 (*C*(2')), 173.2 (*C*(1)); *m/z* (ESI$^+$) 529 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{49}N_2O_3S^+$ ([M+H]$^+$) requires 529.3458; found 529.3454. Further purification via flash column chromatography gave (*R*,*R*,*R*)-**291** as a colourless oil (63 mg, 9%, 98:2 dr); $[\alpha]_D^{20}$ +14.8 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1069, 1456, 1736 (C=O); δ_H (400 MHz, C_6D_6) 1.03 (9H, s, C*Me*$_3$), 1.10-1.43 (20H, m, C(5)*H*$_2$−C(14)*H*$_2$), 1.44-1.58 (1H, m, C(4)*H*$_A$), 1.60-1.74 (1H, m, C(4)*H*$_B$), 2.26 (2H, t, *J* 7.6, C(15)*H*$_2$), 3.33 (3H, s, O*Me*), 3.48 (1H, d, *J* 8.6, N*H*), 4.04-4.14 (1H, m, C(3)*H*), 4.26 (1H, d, *J* 7.8, C(2)*H*), 6.75 (1H, app dd, *J* 7.7, 4.7, C(5′)*H*), 6.99-7.07 (2H, m, C(4′)*H*), *p-Ph*), 7.10-7.16 (2H, m, *m-Ph*), 7.44-7.52 (2H, m, *o-Ph*), 8.48-8.53 (1H, m, C(6′)*H*), 8.55-8.59 (1H, m, C(2′)*H*); δ_C (125 MHz, C_6D_6) 23.0 (C*Me*$_3$), 26.3 (*C*(5)), 29.8, 29.9, 30.1, 30.3, 30.4 (*C*(6)-*C*(13)), 31.7 (*C*(14)), 33.3 (*C*(4)), 33.5 (*C*(15)), 52.1 (O*Me*), 56.1 (*C*Me$_3$), 58.0 (*C*(2)), 59.3 (*C*(3)), 123.6 (*C*(5')), 128.2 (*p-Ph*), 129.2 (*m-Ph*), 130.4 (*o-Ph*), 135.6 (*C*(4')), 136.4 (*i-Ph*), 138.1 (*C*(3')), 148.2 (*C*(6')), 151.0 (*C*(2')), 173.1 (*C*(1)); *m/z* (ESI$^+$) 529 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{49}N_2O_3S^+$ ([M+H]$^+$) requires 529.3458; found 529.3455.

Methyl (*R*,*R*,*R*)-2-phenyl-3-(*N-tert*-butylsulfinamido)-15-(pyridin-3′-yl)pentadecanoate 291



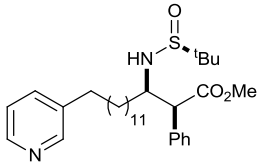
Method A. Na (13 mg, 0.57 mmol) was added to a solution of **290** (60 mg, 0.11mmol) in MeOH (0.5 mL) at 0 °C and the reaction mixture was stirred for 8 h before the addition of satd aq NH_4Cl (1 mL). The reaction mixture was diluted with EtOAc (10 mL) and the phases were separated. The aqueous layer was extracted with EtOAc (5 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give a 20:80 mixture of **290** and **291**. Purification via flash column chromatography gave (*R*,*R*,*R*)-**291** as a colourless oil (39 mg, 65%, 98:2 dr); $[\alpha]_D^{20}$ +14.2 (*c* 1.0 in $CHCl_3$).

Method B. *Step 1*. MeMgBr (2.86 M in Et_2O, 0.39 mL, 1.11 mmol) was added dropwise via syringe to a stirred suspension of methyl phenylacetate (0.17 mL, 1.20 mmol) and $MgBr_2$ (850 mg, 4.62 mmol) in THF (5 mL) at −78 °C. After 1 h, a solution of **288** (348 mg, 0.92 mmol) in THF (5 mL) at −78 °C was added, and the resultant suspension was stirred at −78 °C for 6 h before the addition of satd aq NH_4Cl (5 mL). The resultant mixture was allowed to warm to rt over 15 min, then diluted

with EtOAc (20 mL) and the phases were separated. The aqueous layer was extracted with EtOAc (20 mL) and the combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give an 86:14 mixture of **290** and **291** as a yellow oil (490 mg).

Step 2. Na (106 mg, 4.62 mmol) was added to a stirred solution of the residue from the previous step (490 mg) in MeOH (5 mL) at 0 °C, and the resultant mixture was stirred for 8 h at 0 °C before the dropwise addition of satd aq NH_4Cl (5 mL). The resultant mixture was allowed to warm to rt over 15 min, then diluted with CH_2Cl_2 (20 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give a 20:80 mixture of **290** and **291**. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 40:60) gave **290** as a white solid (44 mg, 9% from **288**, >99:1 dr); $[\alpha]_D^{20}$ −51.0 (*c* 1.0 in $CHCl_3$). Further elution gave **291** as a colourless oil (291 mg, 60% from **288**, 98:2 dr); $[\alpha]_D^{20}$ +15.0 (*c* 1.0 in $CHCl_3$).

Methyl (2*S*,3*R*,*S*$_S$)-2-phenyl-3-(*N*-*tert*-butylsulfinamido)-15-(pyridin-3′-yl)pentadecanoate *ent*-301

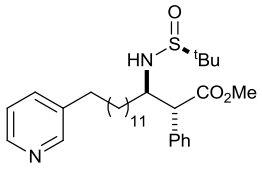


Step 1. **290** (69 mg, 0.13 mmol) was diluted with HCl (1.25 M in MeOH, 2 mL) and the resultant solution was left to stir for 2 h at rt before being concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and satd aq $NaHCO_3$ (5 mL) and the layers were separated. The organic layer was washed with satd aq $NaHCO_3$ (2 × 5 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give **300** as a white solid which was used without further purification (55 mg).

Step 2. Et_3N (20 μL, 0.14 mmol) and *tert*-butyl sulfinyl chloride **298** (16 μL, 0.13 mmol) were sequentially added to a solution of **300** (55 mg, 0.13 mmol) in CH_2Cl_2 (2 mL) at 0 °C and the reaction mixture was warmed to rt over 2 h before being concentrated *in vacuo*. The residue was partitioned between satd aq $NaHCO_3$ (5 mL) and CH_2Cl_2 (5 mL), the phases were separated and the organic layer was washed with satd aq $NaHCO_3$ (5 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give an ≈50:50 mixture of *ent*-**301** and **290**. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 40:60) gave *ent*-**301** as a white solid (41 mg, 60%, 64:36 dr); Data for *ent*-**301**: δ_H (400 MHz, C_6D_6) [selected peaks] 0.84 (9H, s, C*Me*$_3$), 2.27 (2H, t, *J* 7.6, C(15)*H*$_2$), 3.08 (1H, d, *J* 7.1, N*H*), 3.25 (3H, s, O*Me*), 3.85 (1H, d, *J* 9.1, C(2)*H*), 4.02-4.12 (1H, m, C(3)*H*), 6.76 (1H, app dd, *J* 7.7, 4.7, C(5′)*H*), 6.99-7.06 (2H, m, C(4′)*H*), *p*-*Ph*), 7.08-7.15 (2H, m, *m*-*Ph*),

7.41-7.48 (2H, m, *o-Ph*), 8.45-8.52 (1H, m, C(6′)*H*), 8.54-8.60 (1H, m, C(2′)*H*); δ_C (100 MHz, C_6D_6) [selected peaks] 22.8 (C*Me*$_3$), 26.5 (*C*(5)), 31.8 (*C*(14)), 33.5 (*C*(15)), 34.8 (*C*(4)), 51.8 (O*Me*), 55.8 (*C*Me$_3$), 58.6 (*C*(2)), 60.4 (*C*(3)), 123.6 (*C*(5')), 128.3 (*p-Ph*), 129.1 (*m-Ph*), 130.4 (*o-Ph*), 135.6 (*C*(4')), 137.3 (*i-Ph*), 138.2 (*C*(3')), 148.1 (*C*(6')), 151.0 (*C*(2')), 173.1 (*C*(1)).

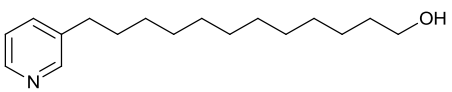
Methyl (2*R*,3*R*,*S*$_S$)-2-phenyl-3-(*N*-*tert*-butylsulfinamido)-15-(pyridin-3′-yl)pentadecanoate *ent*-299



Step 1. **291** (64 mg, 0.12 mmol) was diluted with HCl (1.25 M in MeOH, 2 mL) and the resultant solution was left to stir for 2 h at rt before being concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (20 mL) and satd aq $NaHCO_3$ (10 mL) and the layers were separated. The organic layer was washed with satd aq $NaHCO_3$ (2 × 10 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give **302** as a white solid which was used without further purification (51 mg).

Et_3N (18 μL, 0.13 mmol) and *tert*-butyl sulfinyl chloride **298** (15 μL, 0.12 mmol) were sequentially added to a solution of **302** (51 mg) in CH_2Cl_2 (2 mL) at 0 °C and the reaction mixture was warmed to rt over 2 h before being concentrated *in vacuo*. The residue was partitioned between satd aq $NaHCO_3$ (5 mL) and CH_2Cl_2 (5 mL), the phases were separated and the organic layer was washed with satd aq $NaHCO_3$ (5 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give an ≈50:50 mixture of *ent*-**299** and **291**. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 40:60) gave *ent*-**299** as a white solid (32 mg, 50%, 68:32 dr); Data for *ent*-**299**: δ_H (500 MHz, C_6D_6) [selected peaks] 1.07 (9H, s, C*Me*$_3$), 2.26 (2H, t, *J* 7.6, C(15)*H*$_2$), 3.30 (3H, s, O*Me*), 3.89-4.00 (3H, m, N*H*, C(2)*H*, C(3)*H*), 6.76 (1H, app dd, *J* 7.7, 4.7, C(5′)*H*), 7.26 (2H, app d, *J* 7.3, *o-Ph*), 8.50 (1H, app d, *J* 4.4, C(6′)*H*), 8.55-8.60 (1H, m, C(2′)*H*); δ_C (125 MHz, C_6D_6) [selected peaks] 23.0 (C*Me*$_3$), 25.9 (*C*(5)), 52.0 (O*Me*), 55.9 (*C*Me$_3$), 59.0 (*C*(2)), 60.3 (*C*(3)), 135.6 (*C*(4')), 137.9 (*i-Ph*), 138.1 (*C*(3')), 148.2 (*C*(6')), 151.0 (*C*(2')), 173.8 (*C*(1)).

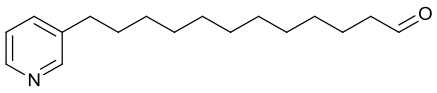
12-(Pyridin-3'-yl)dodecan-1-ol 306[8]



BuLi (2.40 M in hexanes, 8.32 mL, 20.0 mmol) was added dropwise via syringe to a stirred solution of diisopropylamine (2.80 mL, 20.0 mmol) in THF (60 mL) at 0 °C. After 1 h, the solution was

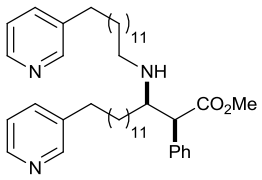
cooled to -78 °C and a solution of 3-picoline (1.94 mL, 20.0 mmol) in THF (10 mL) was added. After a further 30 min, a solution of **180** (2.00 g, 7.99 mmol) in THF (10 mL) was added. After 10 min, the cooling bath was taken away and the reaction mixture allowed to warm to rt over 16 h before the addition of satd aq NH_4Cl (20 mL) and H_2O (30 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 × 30 mL) and the combined organic extracts dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution 20% → 70% EtOAc in 30-40 °C petrol) gave **306** as an off-white solid (1.69 g, 80%);[8] mp 46−47 °C; {lit. 48-50 °C}; δ_H (400 MHz, $CDCl_3$) 1.22-1.41 (16H, m, C(3)H_2−C(10)H_2), 1.52-1.67 (4H, m, C(2)H_2, C(11)H_2), 2.61 (2H, t, *J* 7.7, C(12)H_2), 3.64 (2H, t, *J* 6.7, C(1)H_2), 7.21 (1H, dd, *J* 7.8, 4.8, C(5′)*H*), 7.47-7.54 (1H, m, C(4′)*H*), 8.40-8.48 (2H, m, C(2′)*H*, C(6′)*H*).

12-(Pyridin-3'-yl)dodecanal 287



IBX (303 mg, 1.08 mmol) was added to a solution of **306** (100 mg, 0.36 mmol) in EtOAc (2 mL) at rt and the reaction mixture was stirred at 80 °C for 3 h, before being cooled to rt and filtered though Celite® (eluent EtOAc, ~10 mL) and the filtrate was concentrated *in vacuo* to give **287** as a yellow oil (93 mg, 98%); ν_{max} (film) 1723 (C=O); δ_H (400 MHz, $CDCl_3$) 1.11–1.35 (14H, m, C(4)H_2–C(10)H_2), 1.48–1.64 (4H, m, C(3)H_2, C(11)H_2), 2.36 (2H, td, *J* 7.4, 1.9, C(2)H_2), 2.54 (2H, t, *J* 7.7, C(12)H_2), 7.16 (1H, dd, *J* 7.7, 4.9, C(5′)*H*), 7.43–7.48 (1H, m, C(4′)*H*), 8.35–8.42 (2H, m, C(2′)*H*, C(6′)*H*), 9.70 (1H, t, *J* 1.9, C(1)*H*).

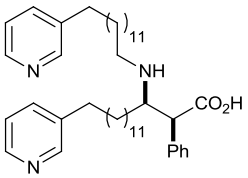
Methyl (2*S*,3*R*)-2-phenyl-3-{*N*-[13′′-(pyridin-3′′′-yl)tridecyl]amino}-15-(pyridin-3′-yl)pentadecanoate 308



Step 1. **290** (53 mg, 0.10 mmol) was diluted with HCl (1.25 M in MeOH, 2 mL) and the resultant solution was left to stir for 2 h at rt before being concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and satd aq $NaHCO_3$ (5 mL) and the layers were separated. The organic layer was washed with satd aq $NaHCO_3$ (2 × 5 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give **300** as a white solid which was used without further purification (40 mg).

Step 2. A solution of **167** (26 mg, 0.095 mmol) in 1,2-DCE (1 mL) was added to a stirred solution of **300** (40 mg, 0.095 mmol) in 1,2-DCE (1 mL) at rt. After 5 min, AcOH (1 drop) and $NaBH(OAc)_3$ (40 mg, 0.190 mmol) were added and the resultant mixture was stirred at rt for 16 h, before the addition of satd aq $NaHCO_3$ (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O/Et_3N, 40:59:1) gave **308** as a pale yellow oil (40 mg, 62%); $[\alpha]_D^{20}$ −14.5 (*c* 1.0, $CHCl_3$); ν_{max} (film) 1735 (C=O); δ_H (400 MHz, C_6D_6) 1.10-1.76 (44H, m, C(4)H_2−C(14)H_2, C(2")H_2−C(12")H_2), 2.27 (4H, t, *J* 7.6, C(15)H_2, C(13")H_2), 2.35-2.45 (1H, m, C(1")H_A), 2.47-2.56 (1H, m, C(1")H_B), 3.30 (3H, s, O*Me*), 3.44-3.52 (1H, m, C(3)*H*), 3.85 (1H, d, *J* 9.3, C(2)*H*), 6.76 (2H, app dd, *J* 7.7, 4.8, C(5′)*H*, C(5‴)*H*), 7.00-7.10 (3H, m, C(4′)*H*, C(4‴)*H*, *p-Ph*), 7.12-7.17 (2H, m, *m-Ph*), 7.47-7.53 (2H, m, *o-Ph*), 8.47-8.52 (2H, m, C(6′)*H*, C(6‴)*H*), 8.54-8.60 (2H, m, C(2′)*H*, C(2‴)*H*); δ_C (100 MHz, C_6D_6) 26.2, 27.9, 29.8, 30.2, 30.3, 30.4, 30.5, 30.7, 31.2, 31.8, 33.0 (*C*(4)-*C*(14), *C*(2")-*C*(12")), 33.5 (*C*(15), *C*(13"), 46.8 (*C*(1")), 51.7 (O*Me*), 57.1 (*C*(2)), 60.9 (*C*(3)), 123.5 (*C*(5'), *C*(5‴)), 128.0, 129.2, 129.8 (*o,m,p-Ph*), 135.5 (*C*(4'), (*C*(4‴)), 138.07, 138.09, 138.13 (*C*(3'), (*C*(3‴), (*i-Ph*)), 148.2 (*C*(6'), (*C*(6‴)), 151.0 (*C*(2'), (*C*(2‴)), 173.8 (*C*(1)); *m/z* (ESI^+) 685 ($[M+H]^+$, 5%), 343 ($[M+2H]^{2+}$, 65%), 229 ($[M+3H]^{3+}$, 100%); HRMS (ESI^+) $C_{45}H_{70}N_3O_2^+$ ($[M+H]^+$) requires 684.5463; found 684.5468.

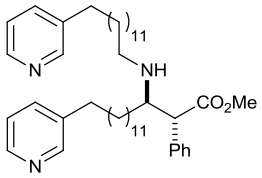
(2*S*,3*R*)-2-Phenyl-15-(pyridin-3'-yl)-3-((13''-(pyridin-3'''-yl)tridec-13''-yl)amino)pentadecanoic acid 129



308 (40 mg, 0.06 mmol) was diluted with HCl (3.0 M aq, 2 mL) and the resultant solution was stirred at 100 °C for 8 h before being concentrated *in vacuo*. Purification via ion exchange chromatography on Serdolit CG-400 I [100-200 mesh, OH^- form, eluent AcOH (2.0 M aq)] gave an impure sample of **129**. Further purification via flash column chromatography **129** as a colourless oil (25 mg, 63%, >99:1 dr); $[\alpha]_D^{20}$ −15.2 (*c* 1.0 in $CHCl_3$); ν_{max} 2921, 2851, 1651, 1574; δ_H (500 MHz, $CDCl_3$) 1.07-1.69 (44H, m, C(4)H_2−C(14)H_2, C(2")H_2−C(12")H_2), 2.60 (4H, t, *J* 7.7, C(15)H_2, C(13")H_2), 2.66-2.74 (1H, m, C(1")H_A), 2.78-2.89 (1H, m, C(1")H_B), 3.10-3.18 (1H, m, C(3)*H*), 3.84 (1H, br d, *J* 2.8, C(2)*H*), 7.16-7.28 (5H, m, C(5′)*H*, C(5‴)*H*, *m,p-Ph*), 7.35 (2H, app d, *J* 7.3, *o-Ph*), 7.49 (2H, app d, *J* 7.9, C(4′)*H*, C(4‴)*H*), 8.31-8.54 (4H, m, C(6′)*H*, C(6‴)*H*, C(2′)*H*, C(2‴)*H*);

δ_C (125 MHz, $CDCl_3$) 26.3, 26.8, 26.9, 27.5, 28.5, 29.09, 29.12, 29.23, 29.28, 29.36, 29.39, 29.48, 29.53, 29.6, 30.3, 31.1 (*C*(4)-*C*(14), *C*(2")-*C*(12")), 33.0 (*C*(15), *C*(13"), 45.5 (*C*(1")), 51.9 (*C*(2)), 59.9 (*C*(3)), 123.3 (*C*(5'), *C*(5''')), 127.4 (*p-Ph*), 128.6 (*m-Ph*), 129.6 (*o-Ph*), 135.6 (*i-Ph*), 135.8 (*C*(4'), *C*(4''')), 138.0 (*C*(3'), *C*(3''')), 147.1 (*C*(6'), *C*(6''')), 149.9 (*C*(2'), *C*(2''')), 175.6 (*C*(1)); *m/z* (ESI^+) 671 ($[M+H]^+$, 5%), 336 ($[M+2H]^{2+}$, 65%), 224 ($[M+3H]^{3+}$, 100%); HRMS (ESI^+) $C_{44}H_{68}N_3O_2^+$ ($[M+H]^+$) requires 670.5306; found 670.5282.

(*R*,*R*)-Methyl-2-phenyl-15-(pyridin-3'-yl)-3-((13''-(pyridin-3'''-yl)tridecyl)amino)pentadecanoate 310

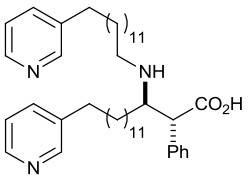


Step 1. **291** (157 mg, 0.30 mmol) was diluted with HCl (1.25 M in MeOH, 5 mL) and the resultant solution was left to stir for 2 h at rt before being concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (20 mL) and satd aq $NaHCO_3$ (10 mL) and the layers were separated. The organic layer was washed with satd aq $NaHCO_3$ (2 × 10 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give **302** as a white solid which was used without further purification (120 mg).

Step 2. A solution of **167** (82 mg, 0.28 mmol) in 1,2-DCE (3 mL) was added to a stirred solution of **302** (120 mg, 0.28 mmol) in 1,2-DCE (3 mL) at rt. After 5 min, AcOH (1 drop) and $NaBH(OAc)_3$ (118 mg, 0.56 mmol) were added and the resultant mixture was stirred at rt for 16 h, before the addition of satd aq $NaHCO_3$ (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O/Et_3N, 40:59:1) gave **310** as a pale yellow oil (128 mg, 63%, 98:2 dr); $[\alpha]_D^{20}$ +22.0 (*c* 1.0, $CHCl_3$); ν_{max} (film) 1736 (C=O); δ_H (400 MHz, C_6D_6) 1.08-1.55 (44H, m, C(4)H_2−C(14)H_2, C(2")H_2−C(12")H_2), 2.26 (4H, t, *J* 7.6, C(15)H_2, C(13")H_2), 2.65-2.83 (2H, m, C(1")H_2), 3.37 (3H, s, O*Me*), 3.44-3.52 (1H, m, C(3)*H*), 3.76 (1H, d, *J* 9.8, C(2)*H*), 6.76 (2H, app dd, *J* 7.7, 4.8, C(5′)*H*, C(5‴)*H*), 6.99-7.09 (3H, m, C(4′)*H*, C(4‴)*H*, *p-Ph*), 7.12-7.19 (2H, m, *m-Ph*), 7.44-7.50 (2H, m, *o-Ph*), 8.47-8.53 (2H, m, C(6′)*H*, C(6‴)*H*), 8.54-8.60 (2H, m, C(2′)*H*, C(2‴)*H*); δ_C (100 MHz, C_6D_6) 25.5, 28.2, 29.8, 30.2, 30.3, 30.4, 30.5, 30.6, 31.5, 31.7, 31.8 (*C*(4)-*C*(14), *C*(2")-*C*(12")), 33.5 (*C*(15), *C*(13"), 47.3 (*C*(1")), 51.7 (O*Me*), 58.2 (*C*(2)), 61.0 (*C*(3)), 123.5 (*C*(5'), *C*(5''')), 128.0 (*p-Ph*), 129.2, 129.5 (*o*,*m-Ph*), 135.5 (*C*(4'), (*C*(4''')), 138.1, 138.4 (*C*(3'), (*C*(3'''), (*i-Ph*)), 148.2 (*C*(6'),

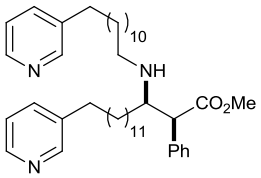
(*C*(6''')), 151.1 (*C*(2'), (*C*(2''')), 174.2 (*C*(1)); *m/z* (ESI$^+$) 685 ([M+H]$^+$, 5%), 343 ([M+2H]$^{2+}$, 65%), 229 ([M+3H]$^{3+}$, 100%); HRMS (ESI$^+$) $C_{45}H_{70}N_3O_2^+$ ([M+H]$^+$) requires 684.5463; found 684.5459.

(2*R*,3*R*)-2-Phenyl-15-(pyridin-3'-yl)-3-((13''-(pyridin-3'''-yl)tridec-13''-yl)amino)pentadecanoic acid 295



310 (80 mg, 0.12 mmol) was diluted with HCl (3.0 M aq, 4 mL) and the resultant solution was stirred at 100 °C for 8 h before being concentrated *in vacuo*. Purification via ion exchange chromatography on Amberlite CG 400 [100-200 mesh, OH^- form, eluent AcOH (2.0 M aq)] followed by flash column chromatography (eluent $CHCl_3$/MeOH, 95:5) gave **295** as a colourless oil (48 mg, 61%, 98:2 dr); $[\alpha]_D^{20}$ +8.4 (*c* 1.0 in $CHCl_3$); ν_{max} 2919, 2849, 1652, 1573; δ_H (500 MHz, $CDCl_3$) 1.02-1.80 (44H, m, C(4)H_2–C(14)H_2, C(2'')H_2–C(12'')H_2), 2.54-2.64 (5H, m, C(15)H_2, C(13'')H_2, C(1'')H_A), 2.81-2.93 (1H, m, C(1'')H_B), 3.28-3.40 (1H, m, C(3)*H*), 3.64-3.76 (1H, m, C(2)*H*), 7.11-7.25 (3H, m, C(5')*H*, C(5''')*H*, *p-Ph*), 7.35 (4H, m, *o*,*m-Ph*), 7.49 (2H, app d, *J* 7.2, C(4')*H*, C(4''')*H*), 8.25-8.69 (4H, m, C(6′)*H*, C(6‴)*H*, C(2′)*H*, C(2‴)*H*); δ_C (125 MHz, $CDCl_3$) 27.1, 27.6, 28.3, 28.8, 29.11, 29.14, 29.20, 29.28, 29.34, 29.39, 29.40, 29.48, 29.52, 29.55, 29.59, 29.62, 31.0, 31.1 (*C*(4)-*C*(14), *C*(2'')-*C*(12'')), 33.0 (*C*(15), *C*(13''), 44.7 (*C*(1'')), 54.3 (*C*(2)), 60.8 (*C*(3)), 123.3 (*C*(5'), *C*(5''')), 127.0 (*p-Ph*), 128.5 (*m-Ph*), 128.7 (*o-Ph*), 135.7 (*C*(4'), *C*(4''')), 138.0 (*C*(3'), *C*(3'''), 139.0 (*i-Ph*), 147.1 (*C*(6'), *C*(6''')), 149.9 (*C*(2'), *C*(2''')), 176.7 (*C*(1)); *m/z* (ESI$^+$) 671 ([M+H]$^+$, 5%), 336 ([M+2H]$^{2+}$, 65%), 224 ([M+3H]$^{3+}$, 100%); HRMS (ESI$^+$) $C_{44}H_{68}N_3O_2^+$ ([M+Na]$^+$) requires 692.5125; found 692.5121.

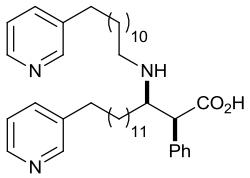
(2*S*,3*R*)-Methyl-2-phenyl-15-(pyridin-3'-yl)-3-[(13''-(pyridin-3'''-yl)tridecyl]aminopentadecanoate 307



Step 1. **290** (40 mg, 0.076 mmol) was diluted with HCl (1.25 M in MeOH, 1.5 mL) and the resultant solution was left to stir for 2 h at rt before being concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and satd aq $NaHCO_3$ (5 mL) and the layers were separated. The organic layer was washed with satd aq $NaHCO_3$ (2 × 5 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give **300** as a white solid which was used without further purification (31 mg).

Step 2. A solution of **287** (21 mg, 0.079 mmol) in 1,2-DCE (1 mL) was added to a stirred solution of **300** (31 mg) in 1,2-DCE (1 mL) at rt. After 5 min, AcOH (1 drop) and $NaBH(OAc)_3$ (32 mg, 0.152 mmol) were added and the resultant mixture was stirred at rt for 16 h, before the addition of satd aq $NaHCO_3$ (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification via flash column chromatography (eluent $CHCl_3$/MeOH, 99:1) gave **307** as a pale yellow oil (32 mg, 63% from **290**); $[\alpha]_D^{20}$ −16.6 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1735 (C=O); δ_H (500 MHz, C_6D_6) 1.11-1.47 (38H, m, part of C(4)H_2−C(14)H_2, C(2″)H_2−C(11″)H_2), 1.57-1.76 (4H, part of C(4)H_2−C(14)H_2, C(2″)H_2−C(11″)H_2), 2.24-2.30 (4H, m, C(15)H_2, C(12″)H_2), 2.37-2.45 (1H, m, C(1″)H_A), 2.48-2.56 (1H, m, C(1″)H_B), 3.30 (3H, s, O*Me*), 3.45-3.51 (1H, m, C(3)*H*), 3.85 (1H, d, *J* 9.5, C(2)*H*), 6.76 (2H, app dd, *J* 7.9, 4.4, C(5′)*H*, C(5‴)*H*), 6.98-7.09 (3H, m, C(4′)*H*, C(4‴)*H*, *p-Ph*), 7.12-7.17 (2H, m, *m-Ph*), 7.48-7.53 (2H, m, *o-Ph*), 8.50 (2H, br d, *J* 4.4, C(6′)*H*, C(6‴)*H*), 8.54-8.61 (2H, br s, C(2′)*H*, C(2‴)*H*); δ_C (125 MHz, C_6D_6) 26.2, 27.9, 29.8, 30.2, 30.3, 30.4, 30.5, 30.7, 31.2, 31.8, 33.0 (*C*(4)−*C*(14), *C*(2″)−*C*(11″)), 33.5 (*C*(15), *C*(12″), 46.8 (*C*(1″)), 51.7 (O*Me*), 57.1 (*C*(2)), 60.9 (*C*(3)), 123.5 (*C*(5′), *C*(5‴)), 128.0 (*p-Ph*), 129.2, 129.8 (*o,m-Ph*), 135.5 (*C*(4′), (*C*(4‴)), 138.07, 138.09, 138.14 (*C*(3′), (*C*(3‴), (*i-Ph*)), 148.2 (*C*(6′), (*C*(6‴)), 151.0 (*C*(2′), (*C*(2‴)), 173.8 (*C*(1)); *m/z* (ESI^+) 670 ($[M+H]^+$, 5%), 336 ($[M+2H]^{2+}$, 100%), 224 ($[M+3H]^{3+}$, 90%); HRMS (ESI^+) $C_{44}H_{68}N_3O_2^+$ ($[M+H]^+$) requires 670.5306; found 670.5302.

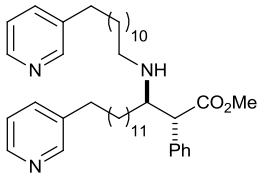
(2*S*,3*R*)-2-Phenyl-15-(pyridin-3′-yl)-3-((12″-(pyridin-3‴-yl)dodec-12″-yl)amino)pentadecanoic acid 128



307 (22 mg, 0.033 mmol) was diluted with HCl (3.0 M aq, 1 mL) and the resultant solution was stirred at 100 °C for 8 h before being concentrated *in vacuo*. Purification via ion exchange chromatography on Serdolit CG-400 I [100-200 mesh, OH^- form, eluent AcOH (2.0 M aq)] followed by flash column chromatography (eluent $CHCl_3$/MeOH, 97:3) gave **128** as a colourless oil (13 mg, 60%, >99:1 dr); $[\alpha]_D^{20}$ −15.0 (*c* 1.0 in $CHCl_3$); ν_{max} 2924, 2853, 1575; δ_H (500 MHz, $CDCl_3$) 1.07-1.73 (42H, m, C(4)H_2−C(14)H_2, C(2″)H_2−C(11″)H_2), 2.60 (4H, t, *J* 7.7, C(15)H_2, C(12″)H_2), 2.67-2.75 (1H, m, C(1″)H_A), 2.77-2.89 (1H, m, C(1″)H_B), 3.10-3.17 (1H, m, C(3)*H*), 3.82 (1H, br d, *J* 2.8, C(2)*H*), 7.16-7.29 (5H, m, C(5′)*H*, C(5‴)*H*, *m,p-Ph*), 7.34 (2H, app d, *J* 7.3, *o-Ph*), 7.48 (2H, app d, *J* 7.9, C(4′)*H*, C(4‴)*H*), 8.34-8.54 (4H, m, C(6′)*H*, C(6‴)*H*, C(2′)*H*, C(2‴)*H*);

δ_C (125 MHz, $CDCl_3$) 26.9, 28.0, 28.7, 29.05, 29.07, 29.11, 29.21, 29.25, 29.29, 29.34, 29.43, 29.45, 29.46, 29.49, 29.51, 29.67, 30.9, 31.1 (*C*(4)−*C*(14), *C*(2″)−*C*(11″)), 33.0 (*C*(15), *C*(12″)), 45.7 (*C*(1″)), 51.7 (*C*(2)), 59.9 (*C*(3)), 123.3 (*C*(5′), *C*(5‴)), 127.5 (*p-Ph*), 128.7 (*m-Ph*), 129.6 (*o-Ph*), 135.3 (*i-Ph*), 135.8 (*C*(4′), *C*(4‴), 138.0 (*C*(3′), *C*(3‴), 147.0 (*C*(6′), *C*(6‴)), 149.8 (*C*(2′), *C*(2‴)), 175.1 (*C*(1)); *m/z* (ESI^+) 656 ($[M+H]^+$, 5%), 329 ($[M+2H]^{2+}$, 75%), 220 ($[M+3H]^{3+}$, 100%); HRMS (ESI^+) $C_{43}H_{66}N_3O_2^+$ ($[M+H]^+$) requires 656.5150; found 656.5123.

(2*R*,3*R*)-Methyl-2-phenyl-15-(pyridin-3′-yl)-3-[(13″-(pyridin-3‴-yl)tridecyl]aminopentadecanoate (2*R*,3*R*)-309

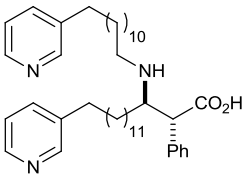


Step 1. **291** (180 mg, 0.34 mmol) was diluted with HCl (1.25 M in MeOH, 4 mL) and the resultant solution was left to stir for 2 h at rt before being concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (20 mL) and satd aq $NaHCO_3$ (10 mL) and the layers were separated. The organic layer was washed with satd aq $NaHCO_3$ (2 × 10 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give **302** as a white solid which was used without further purification (144 mg).

Step 2. A solution of **287** (89 mg, 0.34 mmol) in 1,2-DCE (4 mL) was added to a stirred solution of **302** (144 mg) in 1,2-DCE (4 mL) at rt. After 5 min, AcOH (1 drop) and $NaBH(OAc)_3$ (144 mg, 0.68 mmol) were added and the resultant mixture was stirred at rt for 16 h, before the addition of satd aq $NaHCO_3$ (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification via flash column chromatography (eluent $CHCl_3$/MeOH, 99:1) gave **309** as a pale yellow oil (150 mg, 66% from **291**); $[\alpha]_D^{20}$ +10.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1735 (C=O); δ_H (500 MHz, C_6D_6) 0.97-1.56 (42H, m, C(4)H_2−C(14)H_2, C(2″)H_2−C(11″)H_2), 2.22-2.31 (4H, m, C(15)H_2, C(12″)H_2), 2.66-2.81 (2H, m, C(1″)H_2), 3.37 (3H, s, O*Me*), 3.44-3.51 (1H, m, C(3)*H*), 3.75 (1H, d, *J* 9.8, C(2)*H*), 6.76 (2H, app dd, *J* 7.9, 4.7, C(5′)*H*, C(5‴)*H*), 6.98-7.08 (3H, m, C(4′)*H*, C(4‴)*H*, *p-Ph*), 7.11-7.17 (2H, m, *m-Ph*), 7.44-7.49 (2H, m, *o-Ph*), 8.46-8.52 (2H, m, C(6′)*H*, C(6‴)*H*), 8.70 (2H, br s, C(2′)*H*, C(2‴)*H*); δ_C (125 MHz, C_6D_6) 25.5, 28.2, 29.8, 30.2, 30.3, 30.4, 30.5, 30.6, 31.5, 31.7, 31.8 (*C*(4)−*C*(14), *C*(2″)-*C*(11″)), 33.5 (*C*(15), *C*(12″), 47.3 (*C*(1″)), 51.7 (O*Me*), 58.2 (*C*(2)), 61.0 (*C*(3)), 123.5 (*C*(5′), *C*(5‴)), 128.0 (*p-Ph*), 129.2, 129.5 (*o,m-Ph*), 135.5 (*C*(4′), (*C*(4‴)), 138.07, 138.09, 138.37 (*C*(3′), (*C*(3‴), (*i-Ph*)), 148.2 (*C*(6′), (*C*(6‴)), 151.0 (*C*(2′),

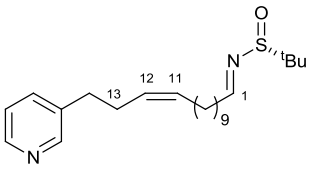
(*C*(2‴)), 174.3 (*C*(1)); *m/z* (ESI$^+$) 670 ([M+H]$^+$, 5%), 336 ([M+2H]$^{2+}$, 100%), 224 ([M+3H]$^{3+}$, 90%); HRMS (ESI$^+$) $C_{44}H_{68}N_3O_2^+$ ([M+H]$^+$) requires 670.5306; found 670.5300.

(2*R*,3*R*)-2-Phenyl-15-(pyridin-3′-yl)-3-((12″-(pyridin-3‴-yl)dodec-12″-yl)amino)pentadecanoic acid 294



309 (100 mg, 0.15 mmol) was diluted with HCl (3.0 M aq, 5 mL) and the resultant solution was stirred at 100 °C for 8 h before being concentrated *in vacuo*. Purification via ion exchange chromatography on Serdolit CG-400 I [100-200 mesh, OH^- form, eluent AcOH (2.0 M aq)] followed by flash column chromatography (eluent $CHCl_3$/MeOH, 97:3) gave **294** as a colourless oil (59 mg, 60%, 98:2 dr); $[\alpha]_D^{20}$ +8.0 (*c* 1.0 in $CHCl_3$); ν_{max} 2922, 2852, 1596, 1574; δ_H (500 MHz, $CDCl_3$) 1.03-1.41 (34H, m, C(5)H_2–C(13)H_2, C(3″)H_2–C(10″)H_2), 1.46-1.54 (2H, m, C(5)H_2), 1.57-1.67 (4H, m, C(14)H_2, C(11″)H_2), 1.69-1.80 (2H, m, C(2″)H_2), 2.55-2.67 (5H, m, C(15)H_2, C(1″)H_A), C(12″)H_2), 2.81-2.94 (1H, m, C(1″)H_B), 3.31-3.39 (1H, m, C(3)*H*), 3.67-3.75 (1H, m, C(2)*H*), 7.16-7.25 (3H, m, C(5′)*H*, C(5‴)*H*, *p-Ph*), 7.27-7.35 (4H, m, *o*,*m-Ph*), 7.46-7.52 (2H, m, C(4′)*H*, C(4‴)*H*), 8.45 (4H, br s, C(2′)*H*, C(2‴)*H*, C(6′)*H*, C(6‴)*H*); δ_C (125 MHz, $CDCl_3$) 24.9, 26.75, 26.81, 28.8, 29.10, 29.13, 29.35, 29.38, 29.39, 29.48, 29.51, 29.56 (*C*(4)–*C*(13), *C*(2″)–*C*(10″)), 31.1 (*C*(14), *C*(11″)), 33.0 (*C*(15), *C*(12″)), 44.6 (*C*(1″)), 54.3 (*C*(2)), 60.8 (*C*(3)), 123.2 (*C*(5′), *C*(5‴)), 127.0 (*p-Ph*), 128.5 (*m-Ph*), 128.7 (*o-Ph*), 135.7 (*C*(4′), *C*(4‴)), 137.9 (*C*(3′), *C*(3‴)), 139.1 (*i*-Ph), 147.1 (*C*(6′), *C*(6‴)), 149.9 (*C*(2′), *C*(2‴)), 176.7 (*C*(1)); *m/z* (ESI$^+$) 656 ([M+H]$^+$, 5%), 329 ([M+2H]$^{2+}$, 75%), 220 ([M+3H]$^{3+}$, 100%); HRMS (ESI$^+$) $C_{43}H_{65}N_3NaO_2^+$ ([M+Na]$^+$) requires 678.4969; found 678.4942.

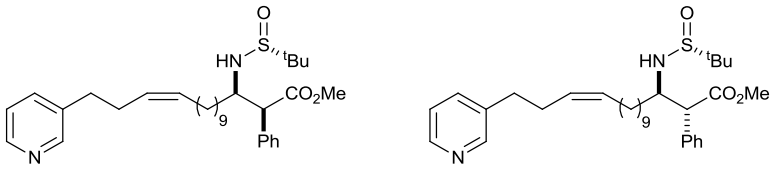
(*E*,*R*$_S$)-*N*-[(11*Z*)-(14-(Pyridin-3′-yl)tetradec-11-en-1-ylidene]-*tesrt*-butylsulfinamide 289



Step 1. IBX (2.33 g, 8.30 mmol) was added to a stirred solution of **182** (800 mg, 2.77 mmol) in EtOAc (8 mL) at rt and the resultant suspension was heated at 80 °C for 3 h before being allowed to cool to rt and filtered through Celite® (eluent EtOAc, ~10 mL). The filtrate was concentrated *in vacuo* to give **188** as a yellow oil (794 mg).

Step 2. (*R*)-**283** (328 mg, 2.71 mmol, >98% ee), PPTS (35 mg, 0.14 mmol) and $MgSO_4$ (1.75 g, 13.6 mmol) were sequentially added to a stirred solution of **188** (794 mg) in CH_2Cl_2 (10 mL) and the resultant suspension was stirred at rt for 16 h before being filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 60:40) gave **289** as a colourless oil (864 mg, 80%, 97:3 (11*Z*):(11*E*) ratio);[36] $[\alpha]_D^{20}$ −144.4 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1622, 1085; δ_H (400 MHz, C_6D_6) 1.15-1.51 (23H, m, C*Me*$_3$, C(3)*H*$_2$−C(9)*H*$_2$), 1.95-2.04 (2H, m, C(10)*H*$_2$), 2.18-2.32 (4H, m, C(2)*H*$_2$, C(13)*H*$_2$), 2.45 (2H, t, *J* 7.5, C(14)*H*$_2$), 5.35-5.45 (1H, m, C(12)*H*), 5.46-5.56 (1H, m, C(11)*H*), 6.88 (1H, dd, *J* 7.7, 4.8, C(5′)*H*), 7.11-7.18 (1H, m, C(4′)*H*), 8.24 (1H, t, *J* 4.6, C(1)*H*), 8.53-8.65 (2H, m, C(2′)*H*, C(6′)*H*); δ_C (100 MHz, C_6D_6) 22.7 (C*Me*$_3$), 26.0, 27.9, 29.4, 29.8, 29.9, 30.0, 30.1, 30.2, 30.3 (*C*(3)−*C*(10), *C*(13)), 33.5 (*C*(14)), 36.5 (*C*(2)), 56.4 (*C*Me$_3$), 123.5 (*C*(5′)), 128.7 (*C*(12)), 131.7 (*C*(11)), 135.8 (*C*(4′)), 137.4 (*C*(3′)), 148.2 (*C*(6′)), 151.0 (*C*(2′)), 169.8 (*C*(1)); *m/z* (ESI^+) 391 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{23}H_{39}N_2OS^+$ ($[M+H]^+$) requires 391.2778; found 391.2765.

Methyl (2*S*,3*R*,13*Z*,*R*$_S$)- and (2*R*,3*R*,13*Z*,*R*$_S$)-2-phenyl-3-(*N*-*tert*-butylsulfinamido)-16-(pyridin-3′-yl)hexadec-13-enoate 292 and 293



Method A. MeMgBr (2.86 M in Et_2O, 0.54 mL, 1.54 mmol) was added dropwise via syringe to a stirred suspension of methyl phenylacetate (0.23 mL, 1.67 mmol) and $MgBr_2$ (1.18 g, 6.41 mmol) in THF (6 mL) at −78 °C. After 1 h, a solution of **289** (0.50 g, 1.28 mmol) in THF (6 mL) at −78 °C was added, and the resultant suspension was stirred at −78 °C for 6 h before the addition of satd aq NH_4Cl (5 mL). The resultant mixture was allowed to warm to rt over 15 min, then diluted with EtOAc (20 mL) and the phases were separated. The aqueous layer was extracted with EtOAc (20 mL) and the combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give an ≈80:20 mixture of **292** and **293**. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 40:60) gave **292** as a colourless oil (415 mg, 60%, 97:3 (*Z*):(*E*) ratio); $[\alpha]_D^{20}$ −52.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1736 (C=O), 1455, 1071; δ_H (400 MHz, C_6D_6) 0.99 (9H, s, C*Me*$_3$), 1.18-1.41 (13H, m, C(6)*H*$_2$−C(11)*H*$_2$, C(5)*H*$_A$), 1.51-1.68 (2H, m, C(4)*H*$_A$, C(5)*H*$_B$), 1.82-1.93 (3H, m, C(4)*H*$_B$, C(12)*H*$_2$), 2.16 (2H, q, *J* 7.5, C(15)*H*$_2$), 2.33 (2H, t, *J* 7.6, C(16)*H*$_2$), 3.31 (3H, s, O*Me*), 3.94 (1H, d, *J* 7.3, N*H*), 3.97-4.03 (1H, m, C(3)*H*), 4.27 (1H, d, *J* 6.0, C(2)*H*), 5.26-5.34 (1H, m, C(14)*H*), 5.38-5.46 (1H, m, C(13)*H*), 6.72-6.79 (1H, m, C(5′)*H*),

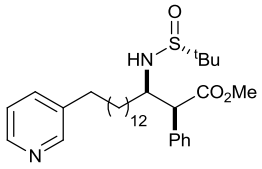
6.99-7.05 (2H, m, C(4′)*H*, *Ph*), 7.08-7.13 (2H, m, *Ph*), 7.29-7.34 (2H, m, *Ph*), 8.45-8.63 (2H, m, C(2′)*H*), C(6′)*H*); δ_C (125 MHz, C_6D_6) 22.9 (C*Me*$_3$), 26.6, 27.9, 29.4, 30.0, 30.1, 30.26, 30.29 (*C*(5)−*C*(12), *C*(15)), 32.9 (*C*(4)), 33.5 (*C*(16)), 52.0 (O*Me*), 55.7 (*C*Me$_3$), 57.2 (*C*(2)), 58.7 (*C*(3)), 123.5 (*C*(5′)), 127.9 (*p*-Ph), 128.9 (*C*(14)), 129.2 (*Ph*), 130.4 (*Ph*), 131.7 (*C*(13)), 135.7 (*C*(4′)), 136.6 (*i-Ph*), 137.4 (*C*(3′)), 148.3 (*C*(6′)), 151.1 (*C*(2′)), 173.2 (*C*(1)); *m/z* (ESI$^+$) 541 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{32}H_{49}N_2O_3S^+$ ([M+H]$^+$) requires 541.3458; found 541.3468. Further elution (eluent 30-40 °C petrol/EtOAc, 40:60) gave **293** as a colourless oil (69 mg, 10%, 94:3:3 dr);[37] $[\alpha]_D^{20}$ +15.8 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1736 (C=O), 1455, 1070; δ_H (400 MHz, C_6D_6) 1.03 (9H, s, C*Me*$_3$), 1.12-1.37 (19H, m, C(5)*H*$_2$−C(10)*H*$_2$, C(4)*H*$_A$, C(11)*H*$_A$), 1.45-1.57 (1H, m, C(11)*H*$_B$), 1.62-1.75 (1H, m, C(4)*H*$_B$),1.84-1.93 (2H, m, C(12)*H*$_2$), 2.16 (2H, q, *J* 7.4, C(15)*H*$_2$), 2.32 (2H, t, *J* 7.6, C(16)*H*$_2$), 3.34 (3H, s, O*Me*), 3.55 (1H, d, *J* 8.3, N*H*), 4.04-4.14 (1H, m, C(3)*H*), 4.26 (1H, d, *J* 7.8, C(2)*H*), 5.25-5.35 (1H, m, C(14)*H*), 5.37-5.46 (1H, m, C(13)*H*), 6.72-6.79 (1H, m, C(5′)*H*), 6.98-7.07 (2H, m, C(4′)*H*, *Ph*), 7.11-7.15 (2H, m, *Ph*), 7.46-7.50 (2H, m, *Ph*), 8.47-8.58 (2H, m, C(2′)*H*, C(6′)*H*); δ_C (100 MHz, C_6D_6) 23.0 (C*Me*$_3$), 26.3, 27.9, 29.4, 29.9, 30.19, 30.24 (*C*(5)−*C*(12), *C*(15)), 33.0 (*C*(4)), 33.5 (*C*(16)), 52.1 (O*Me*), 56.1 (*C*Me$_3$), 58.1 (*C*(2)), 59.4 (*C*(3)), 123.5 (*C*(5′)), 128.2 (*p*-Ph), 128.9 (*C*(14)), 129.2 (*Ph*), 130.4 (*Ph*), 131.7 (*C*(13)), 135.8 (*C*(4′)), 136.4 (*i-Ph*), 137.4 (*C*(3′)), 148.3 (*C*(6′)), 151.0 (*C*(2′)), 173.1 (*C*(1)); *m/z* (ESI$^+$) 541 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{32}H_{49}N_2O_3S^+$ ([M+H]$^+$) requires 541.3458; found 541.3437.

Method B. *Step 1*. MeMgBr (2.86 M in Et_2O, 0.39 mL, 1.11 mmol) was added dropwise via syringe to a stirred suspension of methyl phenylacetate (0.17 mL, 1.20 mmol) and $MgBr_2$ (850 mg, 4.62 mmol) in THF (5 mL) at −78 °C. After 1 h, a solution of **289** (360 mg, 0.92 mmol) in THF (5 mL) at −78 °C was added, and the resultant suspension was stirred at −78 °C for 6 h before the addition of satd aq NH_4Cl (5 mL). The resultant mixture was allowed to warm to rt over 15 min, then diluted with EtOAc (20 mL) and the phases were separated. The aqueous layer was extracted with EtOAc (20 mL) and the combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give an ≈80:20 mixture of **292** and **293** (510 mg).

Step 2. Na (106 mg, 4.62 mmol) was added to a stirred solution of the residue from the previous step (510 mg) in MeOH (5 mL) at 0 °C, and the resultant mixture was stirred for 8 h at 0 °C before the dropwise addition of satd aq NH_4Cl (5 mL). The resultant mixture was allowed to warm to rt over 15 min, then diluted with CH_2Cl_2 (20 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give an ≈20:80 mixture of **292** and **293**. Purification via flash column

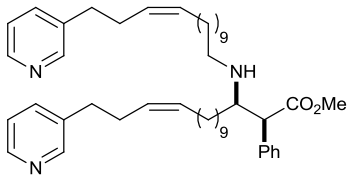
chromatography (eluent 30-40 °C petrol/EtOAc, 40:60) gave **292** as a colourless oil (45 mg, 9%, 97:3 (*Z*):(*E*) ratio);[36] $[\alpha]_D^{20}$ −51.0 (*c* 1.0 in $CHCl_3$). Further elution gave **293** as a colourless oil (299 mg, 60% from **289**, 94:3:3 dr); $[\alpha]_D^{20}$ +15.4 (*c* 1.0 in $CHCl_3$).

Methyl (2*S*,3*R*,R_S)-2-phenyl-3-(*N*-*tert*-butylsulfinamido)-16-(pyridin-3′-yl)hexadecanoate 311



$Pd(OH)_2$ (20% wt on C, 30 mg) was added to a degassed solution of **292** (100 mg, 0.19 mmol, 97:3 dr [(*Z*):(*E*)]) in MeOH (3 mL). The suspension was stirred under H_2 (1 atm) for 24 h before being filtered though Celite® (eulent MeOH, 10 mL) and the filtrate was concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 40:60) gave **311** as a white solid (100 mg, 99%, >99:1 dr); mp 68−69°C; $[\alpha]_D^{20}$ −50.2 (*c* 1.0, $CHCl_3$); ν_{max} (film) 1735 (C=O), 1456, 1070; δ_H (400 MHz, C_6D_6) 0.99 (9H, s, C*Me*$_3$), 1.12-1.44 (21H, m, C(6)*H*$_2$−C(15)*H*$_2$, C(5)*H*$_A$), 1.48-1.69 (2H, m, C(4)*H*$_A$, C(5)*H*$_B$), 1.81-1.93 (1H, m, C(4)*H*$_B$), 2.26 (2H, t, *J* 7.7, C(16)*H*$_2$), 3.30 (3H, s, O*Me*), 3.91-4.04 (2H, m, N*H*, C(3)*H*), 4.27 (1H, d, *J* 6.1, C(2)*H*), 6.74-6.82 (1H, m, C(5′)*H*), 7.00-7.05 (2H, m, C(4′)*H*, *Ph*), 7.07-7.13 (2H, m, *Ph*), 7.28-7.33 (2H, m, *Ph*), 8.47-8.62 (2H, m, C(2′)*H*, C(6′)*H*); δ_C (100 MHz, C_6D_6) 22.9 (C*Me*$_3$), 26.6, 29.8, 30.1, 30.2, 30.3, 30.39, 30.44, 30.46 (*C*(5)−*C*(14)), 31.8 (*C*(15)), 32.8 (*C*(4)), 33.5 (*C*(16)), 52.1 (O*Me*), 55.8 (*C*Me$_3$), 57.2 (*C*(2)), 58.7 (*C*(3)), 123.5 (*C*(5′)), 128.7 (*p-Ph*), 129.2 (*m-Ph*), 130.4 (*Ph*), 135.6 (*C*(4′)), 136.6 (*i-Ph*), 138.1 (*C*(3′)), 148.2 (*C*(6′)), 151.0 (*C*(2′)), 173.2 (*C*(1)); *m/z* (ESI^+) 543 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{32}H_{50}N_2NaO_3S^+$ ($[M+Na]^+$) requires 565.3434; found 565.3416.

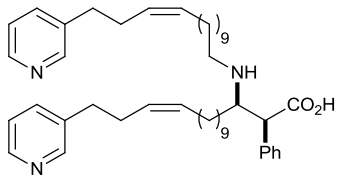
Methyl (2*S*,3*R*,13*Z*,11′′*Z*)-2-phenyl-3-{*N*-[14′′-(pyridin-3′′′-yl)tetradec-11′′-enyl]amino}-16-(pyridin-3′-yl)hexadec-13-enoate 313



Step 1. **292** (297 mg, 0.55 mmol) was dissolved in HCl (1.25 M in MeOH, 4 mL) and the resultant solution was left to stir for 2 h at rt before being concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and satd aq $NaHCO_3$ (10 mL) and the layers were separated. The organic layer was washed with satd aq $NaHCO_3$ (2 × 5 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a white solid (239 mg).

Step 2. A solution of **188** (159 mg, 0.55 mmol) in 1,2-DCE (4 mL) was added to a stirred solution of the residue from the previous step (239 mg) in 1,2-DCE (4 mL) at rt. After 5 min, AcOH (1 drop) and $NaBH(OAc)_3$ (235 mg, 1.11 mmol) were added and the resultant mixture was stirred at rt for 16 h before the addition of satd aq $NaHCO_3$ (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification via flash column chromatography (eluent $CHCl_3$/MeOH, 99:1) gave **313** as a pale yellow oil (233 mg, 60% from **292**, >95% diastereoisomeric purity); $[\alpha]_D^{20}$ −17.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1734 (C=O); δ_H (500 MHz, C_6D_6) 1.10-1.75 (32H, m, C(4)H_2–C(11)H_2, C(2″)H_2–C(9″)H_2), 1.85-1.95 (4H, m, C(12)H_2, C(10″)H_2), 2.14-2.21 (4H, m, C(15)H_2, C(13″)H_2), 2.29-2.44 (5H, m, C(16)H_2, C(14″)H_2, C(1″)H_A), 2.47-2.56 (1H, m, C(1″)H_B), 3.30 (3H, s, O*Me*), 3.45-3.52 (1H, m, C(3)*H*), 3.85 (1H, d, *J* 9.1, C(2)*H*), 5.26-5.35 (2H, m, C(14)*H*, C(12″)H_2), 5.38-5.46 (2H, m, C(13)*H*, C(11″)H_2), 6.71-6.79 (2H, m, C(5′)*H*, C(5‴)*H*), 6.98-7.10 (3H, m, C(4′)*H*, C(4‴)*H*, *p-Ph*), 7.12-7.19 (2H, m, *m-Ph*), 7.48-7.53 (2H, m, *o-Ph*), 8.45-8.59 (4H, m, C(2′)*H*, C(2‴)*H*, C(6′)*H*, C(6‴)*H*); δ_C (125 MHz, C_6D_6) 26.2, 27.9, 29.4, 30.0, 30.26, 30.32, 30.34, 30.38, 30.42, 30.48, 30.7, 31.2 (*C*(5)–*C*(12), *C*(15), *C*(2″)–*C*(10″), *C*(13″)), 33.0 (*C*(4)), 33.5 (*C*(16), *C*(14″)), 46.8 (*C*(1″)), 51.7 (O*Me*), 57.1 (*C*(2)), 60.9 (*C*(3)), 123.5 (*C*(5′), *C*(5‴)), 128.0 (*p*-Ph), 128.9 (*C*(14), *C*(12″)), 129.2, 129.8 (*o*,*m-Ph*), 131.71, 131.73 (*C*(13), *C*(11″)), 135.7 (*C*(4′), *C*(4‴)), 137.4, 138.1 (*i-Ph*, *C*(3′), *C*(3‴)), 148.3 (*C*(6′), *C*(6‴)), 151.1 (*C*(2′), *C*(2‴)), 173.8 (*C*(1)); *m/z* (ESI^+) 709 ($[M+H]^+$, 5%), 355 ($[M+2H]^{2+}$, 50%), 237 ($[M+3H]^{3+}$, 100%); HRMS (ESI^+) $C_{47}H_{70}N_3O_2^+$ ($[M+H]^+$) requires 708.5463; found 708.5468.

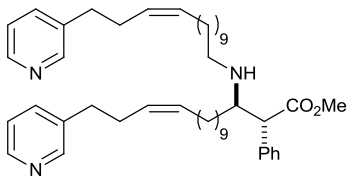
(2*S*,3*R*,13*Z*,11″*Z*)-2-Phenyl-3-{*N*-[14″-(pyridin-3‴-yl)tetradec-11″-enyl]amino}-16-(pyridin-3′-yl)hexadec-13-enoic acid 130



313 (60 mg, 0.085 mmol) was dissolved in HCl (3.0 M aq, 2 mL) and the resultant solution was stirred at 70 °C for 80 h before being concentrated *in vacuo*. Purification via ion exchange chromatography on Serdolit CG-400 I [100-200 mesh, OH^- form, eluent AcOH (2.0 M, aq)] followed by flash column chromatography (eluent $CHCl_3$/MeOH, 97:3) gave **130** as a colourless oil (33 mg, 56%, >95:5 dr); $[\alpha]_D^{20}$ −15.1 (*c* 1.0 in $CHCl_3$); ν_{max} 2924, 2853, 1594, 1575; δ_H (500 MHz, $CDCl_3$) 1.12-1.71 (32H, C(4)H_2–C(11)H_2, C(2″)H_2–C(9″)H_2), 1.85-2.00 (4H, m, C(12)H_2,

C(10″)H_2), 2.29-2.41 (4H, m, C(15)H_2, C(13″)H_2), 2.60-2.77 (5H, m, C(16)H_2, C(1″)H_A, C(14″)H_2), 2.78-2.86 (1H, m, C(1″)H_B), 3.05-3.16 (1H, m, C(3)*H*), 3.85 (1H, m, C(2)*H*), 5.33-5.44 (4H, m, C(13)*H*, C(14)*H*, C(11″)H_2, C(12″)H_2), 7.19-7.29 (3H, m, C(5′)*H*, C(5‴)*H*, *m*,*p*-*Ph*), 7.31-7.37 (2H, m, *o*-*Ph*), 7.50 (2H, app d, *J* 7.6, C(4′)*H*, C(4‴)*H*), 8.42 (4H, br s, C(6′)*H*, C(6‴)*H*, C(2′)*H*, C(2‴)*H*); δ_C (125 MHz, $CDCl_3$) 26.3, 26.9, 27.14, 27.17, 27.9, 28.8, 29.12, 29.20, 29.22, 29.28, 29.37, 29.38, 29.45, 29.48, 29.49, 29.7 (*C*(4)−*C*(12), *C*(15), *C*(2″)−*C*(10″), *C*(13″)), 33.0 (*C*(16), *C*(14″)), 45.8 (*C*(1″)), 51.9 (*C*(2)), 60.0 (*C*(3)), 123.2 (*C*(5′), *C*(5‴)), 127.4 (*p*-*Ph*), 127.7 (*C*(14), *C*(12″)), 128.6, 129.6 (*o*,*m*-*Ph*), 131.4 (*C*(13), *C*(11″)), 135.5 (*i*-*Ph*), 135.97, 136.04 (*C*(4′), *C*(4‴)), 137.3 (*C*(3′), *C*(3‴)), 147.1, 147.2 (*C*(6′), *C*(6‴)), 149.8, 149.9 (*C*(2′), *C*(2‴)), 175.3 (*C*(1)); *m/z* (ESI^+) 695 ($[M+H]^+$, 5%), 348 ($[M+2H]^{2+}$, 40%), 232 ($[M+3H]^{3+}$, 100%); HRMS (ESI^+) $C_{46}H_{68}N_3O_2^+$ ($[M+H]^+$) requires 694.5306; found 694.5299.

Methyl (2*R*,3*R*,13*Z*,11″*Z*)-2-phenyl-3-{*N*-[14″-(pyridin-3‴-yl)tetradec-11″-enyl]amino}-16-(pyridin-3′-yl)hexadec-13-enoate 319

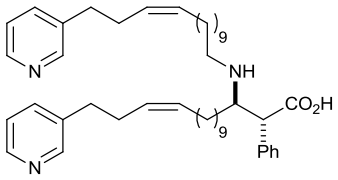


Step 1. **293** (170 mg, 0.32 mmol) was dissolved in HCl (1.25 M in MeOH, 4 mL) and the resultant solution was left to stir for 2 h at rt before being concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and satd aq $NaHCO_3$ (10 mL) and the layers were separated. The organic layer was washed with satd aq $NaHCO_3$ (2 × 5 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a white solid (137 mg).

Step 2. A solution of **188** (90 mg, 0.32 mmol) in 1,2-DCE (4 mL) was added to a stirred solution of the residue from the previous step (137 mg) in 1,2-DCE (4 mL) at rt. After 5 min, AcOH (1 drop) and $NaBH(OAc)_3$ (133 mg, 0.63 mmol) were added and the resultant mixture was stirred at rt for 16 h before the addition of satd aq $NaHCO_3$ (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification via flash column chromatography (eluent $CHCl_3$/MeOH, 99:1) gave **319** as a pale yellow oil (129 mg, 58% from **293**, >93% diastereoisomeric purity); $[\alpha]_D^{20}$ −17.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1735 (C=O); δ_H (500 MHz, C_6D_6) 1.04-1.58 (32H, m, C(4)H_2−C(11)H_2, C(2″)H_2−C(9″)H_2), 1.85-1.96 (4H, m, C(12)H_2, C(10″)H_2), 2.13-2.21 (4H, m, C(15)H_2, C(13″)H_2), 2.29-2.37 (4H, m, C(16)H_2, C(14″)H_2) 2.66-2.82 (2H, m, C(1″)H_2), 3.37 (3H, s, O*Me*), 3.44-3.52 (1H, m, C(3)*H*), 3.76 (1H, d, *J* 10.1, C(2)*H*), 5.26-5.34 (2H, m, C(14)*H*,

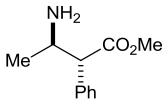
C(12″)H_2), 5.38-5.46 (2H, m, C(13)*H*, C(11″)H_2), 6.72-6.78 (2H, m, C(5′)*H*, C(5‴)*H*), 6.98-7.09 (3H, m, C(4′)*H*, C(4‴)*H*, *p-Ph*), 7.13-7.19 (2H, m, *m-Ph*), 7.45-7.49 (2H, m, *o-Ph*), 8.44-8.62 (4H, m, C(2′)*H*, C(2‴)*H*, C(6′)*H*, C(6‴)*H*); δ_C (125 MHz, C_6D_6) 25.5, 27.91, 27.93, 28.1, 29.4, 29.98, 30.03, 30.27, 30.30, 30.33, 30.36, 30.43, 30.45, 30.53, 30.7, 31.5, 31.7 (*C*(4)−*C*(12), *C*(15), *C*(2″)−*C*(10″), *C*(13″)), 33.5 (*C*(16), *C*(14″)), 47.3 (*C*(1″)), 51.7 (O*Me*), 58.2 (*C*(2)), 61.0 (*C*(3)), 123.5 (*C*(5′), *C*(5‴)), 128.0 (*p*-Ph), 128.9 (*C*(14), *C*(12″)), 129.2, 129.5 (*o*,*m-Ph*), 131.70, 131.72 (*C*(13), *C*(11″)), 135.7 (*C*(4′), *C*(4‴)), 137.4, 138.4 (*i-Ph*, *C*(3′), *C*(3‴)), 148.3 (*C*(6′), *C*(6‴)), 151.1 (*C*(2′), *C*(2‴)), 174.3 (*C*(1)); *m/z* (ESI^+) 709 ($[M+H]^+$, 5%), 355 ($[M+2H]^{2+}$, 50%), 237 ($[M+3H]^{3+}$, 100%); HRMS (ESI^+) $C_{47}H_{70}N_3O_2^+$ ($[M+H]^+$) requires 708.5463; found 708.5445.

(2*R*,3*R*,13*Z*)-2-Phenyl-3-{*N*-[13″-(pyridin-3‴-yl)tridecyl]amino}-16-(pyridin-3′-yl)hexadec-13-enoic acid 296



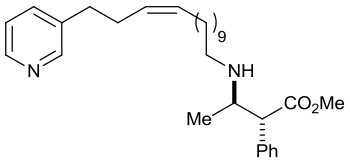
319 (60 mg, 0.085 mmol) was dissolved in HCl (3.0 M aq, 2 mL) and the resultant solution was stirred at 70 °C for 80 h before being concentrated *in vacuo*. Purification via ion exchange chromatography on Serdolit CG-400 I (100-200 mesh, OH^- form, eluent AcOH (2.0 M aq)] followed by flash column chromatography (eluent $CHCl_3$/MeOH, 97:3) gave **296** as a colourless oil (34 mg, 58%, >93% diastereoisomeric purity); $[\alpha]_D^{20}$ +8.1 (*c* 1.0 in $CHCl_3$); ν_{max} 2924, 2853, 1599, 1576; δ_H (500 MHz, $CDCl_3$) 1.03-1.81 (32H, C(4)H_2−C(11)H_2, C(2″)H_2−C(9″)H_2), 1.86-1.98 (4H, m, C(12)H_2, C(10″)H_2), 2.31-2.40 (4H, m, C(15)H_2, C(13″)H_2), 2.57-2.71 (5H, m, C(16)H_2, C(1″)H_A, C(14″)H_2), 2.88-2.94 (1H, m, C(1″)H_B), 3.30-3.41 (1H, m, C(3)*H*), 3.72 (1H, d, *J* 8.8, C(2)*H*), 5.32-5.46 (4H, m, C(13)*H*, C(14)*H*, C(11″)H_2, C(12″)H_2), 7.16-7.25 (3H, m, C(5′)*H*, C(5‴)*H*, *p-Ph*), 7.26-7.35 (4H, m, *o*,*m-Ph*), 7.47-7.54 (2H, m, C(4′)*H*, C(4‴)*H*), 8.44 (4H, br s, C(6′)*H*, C(6‴)*H*, C(2′)*H*, C(2‴)*H*); δ_C (125 MHz, $CDCl_3$) 24.7, 26.8, 27.18, 27.20, 28.7, 29.10, 29.19, 29.26, 29.36, 29.40, 29.43, 29.47, 29.48, 29.50, 29.54, 29.7 (*C*(4)−*C*(12), *C*(15), *C*(2″)−*C*(10″), *C*(13″)), 33.0 (*C*(16), *C*(14″)), 44.8 (*C*(1″)), 54.4 (*C*(2)), 60.7 (*C*(3)), 123.2 (*C*(5′), *C*(5‴)), 127.1 (*p-Ph*), 127.7 (*C*(14), *C*(12″)), 128.5, 128.8 (*o*,*m-Ph*), 131.4 (*C*(13), *C*(11″)), 135.9 (*C*(4′), *C*(4‴)), 137.2 (*C*(3′), *C*(3‴)), 138.9 (*i-Ph*), 147.3 (*C*(6′), *C*(6‴)), 150.0 (*C*(2′), *C*(2‴)), 176.7 (*C*(1)); *m/z* (ESI^+) 695 ($[M+H]^+$, 5%), 348 ($[M+2H]^{2+}$, 40%), 232 ($[M+3H]^{3+}$, 100%); HRMS (ESI^+) $C_{46}H_{68}N_3O_2^+$ ($[M+H]^+$) requires 694.5306; found 694.5290.

(*R*,*R*)-Methyl-2-phenyl-3-aminobutanoate 314



$Pd(OH)_2$/C (10% wt on C, 225 mg) was added to a stirred degassed solution of **257** (450 mg, 1.16 mmol) in MeOH (5 mL) and resultant suspension was stirred under H_2 (5 atm) for 24 h before being filtered though Celite® (eluent MeOH, 20 mL) and the filtrate was concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 20:80) gave **314** as a white solid (222 mg, 99%); mp 26−28 °C; $[\alpha]_D^{20}$ +68.2 (*c* 2.0 in $CHCl_3$); ν_{max} (film) 1730 (C=O); δ_H (500 MHz, $CDCl_3$) 0.87 (3H, d, *J* 6.5, C(4)H_3), 3.37 (1H, d, *J* 9.5, C(2)*H*), 3.50-3.57 (1H, m, C(3)*H*), 3.68 (3H, s, O*Me*), 7.25-7.40 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 21.1 (*C*(4)), 50.1 (*C*(3)), 52.0 (O*Me*), 61.2 (*C*(2)), 127.5 (*p-Ph*), 128.3, 128.7 (*o*,*m-Ph*), 137.1 (*i-Ph*), 173.9 (*C*(1)); *m/z* (ESI^+) 194 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{11}H_{16}NO_2^+$ ($[M+H]^+$) requires 194.1176; found 194.1174.

Methyl (2*R*,3*R*)-2-phenyl-3-{N-[14-(pyridin-3′′-yl)tetradec-11′-enyl]amino}butanoate 315

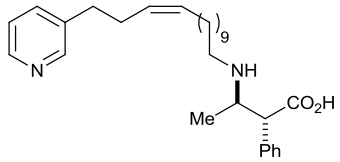


Step 1. IBX (675 mg, 2.41 mmol) was added to a stirred solution of **182** (232 mg, 0.80 mmol) in EtOAc (4 mL) at rt and the resultant suspension was heated at 80 °C for 3 h before being allowed to cool to rt and filtered through Celite® (eluent EtOAc, ~10 mL). The filtrate was concentrated *in vacuo* to give a yellow oil (229 mg).

Step 2. A solution of **314** (155 mg, 0.80 mmol) in 1,2-DCE (2 mL) was added to a stirred solution of the residue from the previous step (229 mg) in 1,2-DCE (2 mL) at rt. After 5 min, AcOH (1 drop) and $NaBH(OAc)_3$ (339 mg, 0.36 mmol) were added and the resultant mixture was stirred at rt for 16 h before the addition of satd aq $NaHCO_3$ (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 40:60) gave **315** as a pale yellow oil (260 mg, 70%); $[\alpha]_D^{25}$ +10.3 (*c* 1.0, $CHCl_3$); ν_{max} (film) 1735 (C=O); δ_H (500 MHz, $CDCl_3$) 0.87 (3H, d, *J* 6.5, C(4)H_3), 1.21-1.36 (14H, m, C(3′)H_2−C(9′)H_2), 1.42-1.50 (2H, m, C(3′)H_2), 1.91-1.97 (2H, m, C(10′)H_2), 2.33-2.40 (2H, m, C(13′)H_2), 2.56 (1H, dt, *J* 11.0, 7.3, C(1′)H_A), 2.67 (2H, t, *J* 7.6, C(14′)H_2), 2.72 (1H, dt, *J* 11.0, 7.3, C(1′)H_B), 3.33 (1H, dq, *J* 9.8, 6.5, C(3)*H*), 3.47 (1H, d, *J* 9.8, C(2)*H*), 3.66 (3H, s, O*Me*), 5.33-5.45

(2H, m, C(11′)H_2, C(12′)H_2), 6.76 (2H, app dd, *J* 7.7, 4.8, C(5′)*H*, C(5‴)*H*), 7.25-7.34 (5H, m, *Ph*), 7.51 (1H, app dt, *J* 7.6, 1.8, C(4″)*H*), 8.42-8.48 (2H, m, C(2′)*H*, C(6′)*H*); δ_C (125 MHz, $CDCl_3$) 17.7 (*C*(4)), 27.2, 27.3, 28.7, 29.3, 29.5, 29.6, 30.4 (*C*(2′)-*C*(10′), *C*(13′)), 33.1 (*C*(14′)), 46.9 (*C*(1′)), 51.9 (O*Me*), 55.8 (*C*(3)), 59.1 (*C*(2)), 123.2 (*C*(5″)), 127.4 (*p-Ph*), 127.7 (*C*(12′)), 128.56, 128.62 (*o,m-Ph*), 131.5 (*C*(11′)), 135.9 (*C*(4″)), 137.0 (*C*(3″)), 137.2 (*i-Ph*), 147.3 (*C*(6″)), 150.0 (*C*(2″)), 174.0 (*C*(1)); *m/z* (ESI^+) 465 ($[M+H]^+$, 25%), 233 ($[M+2H]^{2+}$, 100%); HRMS (ESI^+) $C_{30}H_{45}N_2O_2^+$ ($[M+H]^+$) requires 465.3476; found 465.3487.

(2*R*,3*R*)-2-Phenyl-3-{*N*-[14-(pyridin-3″-yl)tetradec-11′-enyl]amino}butanoic acid 316

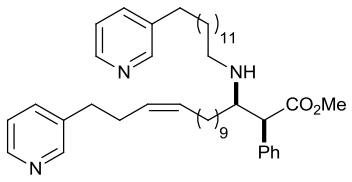


Method A. **315** (50 mg, 0.11 mmol) was diluted with HCl (3.0 M aq, 2 mL) and the resultant solution was stirred at 100 °C for 8 h before being concentrated *in vacuo*. Purification via ion exchange chromatography on Serdolit CG-400 I [100-200 mesh, OH^- form, eluent AcOH (2.0 M aq)] followed by flash column chromatography (eluent $CHCl_3$/MeOH, 97:3) gave **316** as a colourless oil (5.4 mg, 11%, >95:5 dr); $[\alpha]_D^{20}$ −10.5 (*c* 0.2 in $CHCl_3$); ν_{max} 2925, 2852, 1606, 1579; δ_H (500 MHz, $CDCl_3$) 1.07 (3H, d, *J* 6.5, C(4)H_3), 1.17-1.45 (14H, m, C(3′)H_2–C(9′)H_2), 1.71-2.00 (2H, m, C(10′)H_2), 2.33-2.40 (2H, m, C(13′)H_2), 2.62-2.78 (3H, m, C(1′)H_A, C(14′)H_2), 3.04 (1H, br s, C(1′)H_B), 3.40 (1H, br s, C(3)*H*), 3.65 (1H, br s, C(2)*H*), 5.33-5.45 (2H, m, C(11′)H_2, C(12′)H_2), 7.16-7.38 (6H, m, *Ph*, C(5″)*H*), 7.49-7.57 (1H, m, C(4″)*H*), 8.46 (2H, br s, C(2″)*H*, C(6″)*H*); δ_C (125 MHz, $CDCl_3$) 14.3 (*C*(4)), 26.7, 26.8, 27.2, 28.8, 29.1, 29.2, 29.46, 29.53 (*C*(2′)-*C*(10′), *C*(13′)), 33.1 (*C*(14′)), 44.6 (*C*(1′)), 56.7 (*C*(3)), 57.3 (*C*(2)), 123.2 (*C*(5″)), 127.2 (*p-Ph*), 127.7 (*C*(12′)), 128.6, 128.8 (*o,m-Ph*), 131.5 (*C*(11′)), 136.0 (*C*(4″)), 138.7 (*C*(3″), *i-Ph*), 147.2 (*C*(6″)), 149.9 (*C*(2″));[38] *m/z* (ESI^+) 451 ($[M+H]^+$, 25%), 226 ($[M+2H]^{2+}$, 100%); HRMS (ESI^+) $C_{29}H_{43}N_2O_2^+$ ($[M+H]^+$) requires 451.3319; found 451.3301. Further elution gave **317** as a colourless oil (15.2 mg, 30%); ν_{max} 2925, 2852, 1606, 1579; δ_H (500 MHz, MeOD) 1.08 (3H, d, *J* 6.3, C(4)H_3), 1.25-1.86 (20H, m, C(3′)H_2–C(9′)H_2, C(13′)H_2, CH_2CHOH), 2.61-2.75 (2H, m, C(14′)H_2), 2.84-2.94 (1H, m, C(1′)H_A), 3.00-3.10 (1H, m, C(1′)H_B), 3.41-3.65 (3H, m, C(2)*H*, C(3)*H*, CH_2CHOH), 7.24-7.43 (6H, m, *Ph*, C(5″)*H*), 7.68-7.75 (1H, m, C(4″)*H*), 8.39 (2H, br s, C(2″)*H*, C(6″)*H*); *m/z* (ESI^+) 469 ($[M+H]^+$, 25%), 235 ($[M+2H]^{2+}$, 100%); HRMS (ESI^+) $C_{29}H_{44}N_2NaO_2^+$ ($[M+H]^+$) requires 491.3244; found 491.3255.

Method B. KOTMS (21 mg, 0.161 mmol) was added to a solution of **315** (30 mg, 0.065 mmol) in Et_2O (2 mL) and the resultant solution was stirred at rt for 24 h before being concentrated *in vacuo* and the resultant residue was co-evaporated with HCl (2 M in Et_2O, 2 × 3 mL). Purification via ion exchange chromatography on Serdolit CG-400 I [100-200 mesh, OH^- form, eluent AcOH (2.0 M aq)] followed by flash column chromatography (eluent $CHCl_3$/MeOH, 97:3) gave **316** as a colourless oil (13.1 mg, 45%, ≈55:45 dr).

Method C. **315** (30 mg, 0.065 mmol) was diluted with HCl (3.0 M aq, 1 mL) and the resultant solution was stirred at 70 °C for 80 h before being concentrated *in vacuo*. Purification via ion exchange chromatography on Serdolit CG-400 I [100-200 mesh, OH^- form, eluent AcOH (2.0 M aq)] followed by flash column chromatography (eluent $CHCl_3$/MeOH, 97:3) gave **317** as a colourless oil (16 mg, 55%, >95:5 dr).

Methyl (2*S*,3*R*,*Z*)-2-phenyl-3-{*N*-[13′′-(pyridin-3′′′-yl)tridecyl]amino}-16-(pyridin-3′-yl)hexadec-13-enoate 320

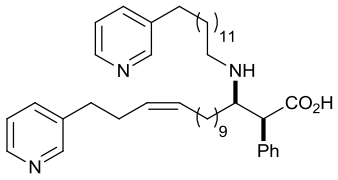


Step 1. **292** (102 mg, 0.19 mmol) was dissolved in HCl (1.25 M in MeOH, 4 mL) and the resultant solution was left to stir for 2 h at rt before being concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and satd aq $NaHCO_3$ (10 mL) and the layers were separated. The organic layer was washed with satd aq $NaHCO_3$ (2 × 5 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a white solid (80 mg).

Step 2. A solution of **167** (52 mg, 0.19 mmol) in 1,2-DCE (2 mL) was added to a stirred solution of the residue from the previous step (80 mg) in 1,2-DCE (2 mL) at rt. After 5 min, AcOH (1 drop) and $NaBH(OAc)_3$ (80 mg, 0.36 mmol) were added and the resultant mixture was stirred at rt for 16 h before the addition of satd aq $NaHCO_3$ (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification via flash column chromatography (eluent $CHCl_3$/MeOH, 99:1) gave **320** as a pale yellow oil (84 mg, 64%, 97:3 (*Z*):(*E*) ratio); $[\alpha]_D^{20}$ −15.4 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1735 (C=O); δ_H (500 MHz, C_6D_6) 1.12-1.46 (34H, m, C(6)H_2–C(11)H_2, C(2′′)H_2–C(12′′)H_2), 1.56-1.75 (4H, m, C(4)H_2, C(5)H_2), 1.87-1.93 (2H, m, C(12)H_2), 2.13-2.20 (2H, m, C(15)H_2), 2.24-2.35 (4H, m, C(16)H_2, C(13′′)H_2), 2.37-2.44 (1H, m, C(1′′)H_A), 2.48-2.55 (1H, m, C(1′′)H_B), 3.30

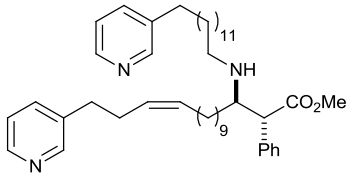
(3H, s, O*Me*), 3.45-3.51 (1H, m, C(3)*H*), 3.85 (1H, d, *J* 9.1, C(2)*H*), 5.26-5.34 (1H, m, C(14)*H*), 5.38-5.46 (1H, m, C(13)*H*), 6.72-6.79 (2H, m, C(5′)*H*, C(5‴)*H*), 6.98-7.09 (3H, m, C(4′)*H*, C(4‴)*H*, *p-Ph*), 7.12-7.19 (2H, m, *m-Ph*), 7.48-7.53 (2H, m, *o-Ph*), 8.45-8.62 (4H, m, C(2′)*H*, C(2‴)*H*, C(6′)*H*, C(6‴)*H*); δ_C (125 MHz, C_6D_6) 26.2, 27.9, 29.4, 29.8, 30.0, 30.2, 30.29, 30.32, 30.35, 30.42, 30.46, 30.48, 30.7, 31.2, 31.8 (*C*(5)−*C*(12), *C*(15), *C*(2″)−*C*(12″)), 33.0 (*C*(4)), 33.5 (*C*(16), *C*(13″)), 46.8 (*C*(1″)), 51.7 (O*Me*), 57.1 (*C*(2)), 60.9 (*C*(3)), 123.5 (*C*(5′), *C*(5‴)), 128.2 (*p*-Ph), 128.9 (*C*(14)), 129.2 (*Ph*), 129.8 (*Ph*), 131.7 (*C*(13)), 135.5, 135.7 (*C*(4′), *C*(4‴)), 137.4, 138.08, 138.14 (*i-Ph*, *C*(3′), *C*(3‴)), 148.2, 148.3 (*C*(6′), *C*(6‴)), 151.0, 151.1 (*C*(2′), *C*(2‴)), 173.8 (*C*(1)); *m/z* (ESI^+) 697 ($[M+H]^+$, 5%), 349 ($[M+2H]^{2+}$, 50%), 233 ($[M+3H]^{3+}$, 100%); HRMS (ESI^+) $C_{46}H_{70}N_3O_2^+$ ($[M+H]^+$) requires 696.5463; found 696.5455.

(2*S*,3*R*,13*Z*)-2-Phenyl-3-{*N*-[13″-(pyridin-3‴-yl)tridecyl]amino}-16-(pyridin-3′-yl)hexadec-13-enoic acid 125



320 (46 mg, 0.066 mmol) was dissolved in HCl (3.0 M aq, 2 mL) and the resultant solution was stirred at 70 °C for 80 h before being concentrated *in vacuo*. Purification via ion exchange chromatography on Serdolit CG-400 I (100-200 mesh, OH^- form, eluent AcOH (2.0 M aq)] followed by flash column chromatography (eluent $CHCl_3$/MeOH, 97:3) gave **125** as a colourless oil (27 mg, 60%, 97:3 (*Z*):(*E*) ratio); $[\alpha]_D^{20}$ −15.7 (*c* 1.0 in $CHCl_3$); ν_{max} 2924, 2853, 1594, 1576; δ_H (500 MHz, $CDCl_3$) 1.12-1.68 (38H, C(4)H_2−C(11)H_2, C(2″)H_2−C(12″)H_2), 1.92 (2H, q, *J* 6.7, C(12)H_2), 2.35 (2H, q, *J* 7.2, C(15)H_2), 2.57-2.75 (5H, m, C(16)H_2), C(1″)H_A), C(13″)H_2), 2.78-2.88 (1H, m, C(1″)H_B), 3.06-3.16 (1H, m, C(3)*H*), 3.82-3.94 (1H, m, C(2)*H*), 5.32-5.46 (2H, m, C(13)*H*, C(14)*H*), 7.18-7.32 (5H, m, C(5′)*H*, C(5‴)*H*, *Ph*), 7.33-7.39 (2H, m, *Ph*), 7.47-7.53 (2H, m, C(4′)*H*, C(4‴)*H*), 8.30-8.54 (4H, app br s, C(6′)*H*, C(6‴)*H*, C(2′)*H*, C(2‴)*H*); δ_C (125 MHz, $CDCl_3$) 26.2, 26.9, 27.1, 28.1, 28.8, 28.9, 29.1, 29.19, 29.23, 29.35, 29.37, 29.44, 29.50, 29.56, 29.7 (*C*(4)−*C*(12), *C*(15), *C*(2″)−*C*(11″)), 31.1 (*C*(12″)), 33.0, 33.1 (*C*(16), *C*(13″)), 45.9 (*C*(1″)), 51.8 (*C*(2)), 60.0 (*C*(3)), 123.3 (*p-Ph*), 127.6 (*C*(5′), *C*(5‴)), 127.7 (*C*(14)), 128.7, 129.6 (*o,m-Ph*), 131.4 (*C*(13)), 135.1 (*i-Ph*), 135.9, 136.2 (*C*(4′), *C*(4‴)), 137.3, 138.0 (*C*(3′), *C*(3‴)), 147.0 (*C*(6′), *C*(6‴)), 149.7, 149.8 (*C*(2′), *C*(2‴)), 175.0 (*C*(1)); *m/z* (ESI^+) 682 ($[M+H]^+$, 5%), 342 ($[M+2H]^{2+}$, 40%), 228 ($[M+3H]^{3+}$, 100%); HRMS (ESI^+) $C_{45}H_{68}N_3O_2^+$ ($[M+H]^+$) requires 682.5306; found 682.5280.

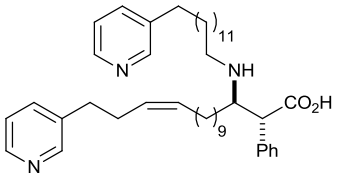
(2*R*,3*R*,13*Z*)-Methyl-2-phenyl-16-(pyridin-3′-yl)-3-((13″-(pyridin-3‴-yl)tridecyl)amino)hexadec-13-enoate (2*R*,3*R*,13*Z*)-321



Step 1. **293** (114 mg, 0.21 mmol) was dissolved in HCl (1.25 M in MeOH, 5 mL) and the resultant solution was left to stir for 2 h at rt before being concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and satd aq $NaHCO_3$ (10 mL) and the layers were separated. The organic layer was washed with satd aq $NaHCO_3$ (2 × 5 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a colourless oil (90 mg).

Step 2. A solution of **167** (58 mg, 0.21 mmol) in 1,2-DCE (2 mL) was added to a stirred solution of the residue from the previous step (90 mg) in 1,2-DCE (2 mL) at rt. After 5 min, AcOH (1 drop) and $NaBH(OAc)_3$ (89 mg, 0.42 mmol) were added and the resultant mixture was stirred at rt for 16 h before the addition of satd aq $NaHCO_3$ (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification via flash column chromatography (eluent $CHCl_3$/MeOH, 99:1) gave **321** as a pale yellow oil (87 mg, 59%, 97:3 (*Z*):(*E*) ratio); $[\alpha]_D^{20}$ +20.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1735 (C=O); δ_H (500 MHz, C_6D_6) 1.12-1.56 (38H, m, C(4)H_2−C(11)H_2, C(2″)H_2−C(12″)H_2), 1.85-1.93 (2H, m, C(12)H_2), 2.13-2.20 (2H, m, C(15)H_2), 2.24-2.36 (4H, m, C(16)H_2, C(13″)H_2), 2.66-2.82 (2H, m, C(1″)H_2), 3.37 (3H, s, O*Me*), 3.43-3.53 (1H, m, C(3)*H*), 3.73-3.82 (1H, m, C(2)*H*), 5.26-5.34 (1H, m, C(14)*H*), 5.37-5.46 (1H, m, C(13)*H*), 6.71-6.80 (2H, m, C(5′)*H*, C(5‴)*H*), 6.97-7.09 (3H, m, C(4′)*H*, C(4‴)*H*, *Ph*), 7.12-7.19 (2H, m, *Ph*), 7.45-7.49 (2H, m, *Ph*), 8.41-8.67 (4H, m, C(2′)*H*, C(2‴)*H*, C(6′)*H*, C(6‴)*H*); δ_C (125 MHz, C_6D_6) 25.5, 27.9, 28.2, 29.4, 29.8, 30.0, 30.2, 30.28, 30.30, 30.33, 30.42, 30.46, 30.51, 30.53, 30.57, 31.4, 31.8 (*C*(4)−*C*(12), *C*(15), *C*(2″)−*C*(12″)), 33.5 (*C*(16), *C*(13″)), 47.3 (*C*(1″)), 51.7 (O*Me*), 58.1 (*C*(2)), 61.0 (*C*(3)), 123.5 (*C*(5′), *C*(5‴)), 128.2 (*p*-Ph), 128.8 (*C*(14)), 129.2 (*Ph*), 129.5 (*Ph*), 131.7 (*C*(13)), 135.5, 135.7 (*C*(4′), *C*(4‴)), 137.4, 138.1, 138.3 (*i-Ph*, *C*(3′), *C*(3‴)), 148.2, 148.3 (*C*(6′), *C*(6‴)), 151.0, 151.1 (*C*(2′), *C*(2‴)), 174.2 (*C*(1)); *m/z* (ESI^+) 697 ($[M+H]^+$, 5%), 349 ($[M+2H]^{2+}$, 50%), 233 ($[M+3H]^{3+}$, 100%); HRMS (ESI^+) $C_{46}H_{70}N_3O_2^+$ ($[M+H]^+$) requires 696.5463; found 696.5449.

(2*R*,3*R*,13*Z*)-2-Phenyl-3-{*N*-[13′′-(pyridin-3′′′-yl)tridecyl]amino}-16-(pyridin-3′-yl)hexadec-13-enoic acid 297



321 (53 mg, 0.076 mmol) was dissolved in HCl (3.0 M aq, 3 mL) and the resultant solution was stirred at 70 °C for 80 h before being concentrated *in vacuo*. Purification via ion exchange chromatography on Serdolit CG-400 I [100-200 mesh, OH^- form, eluent AcOH (2.0 M aq)] followed by flash column chromatography (eluent $CHCl_3$/MeOH, 97:3) gave **297** as a colourless oil (32 mg, 62%, 97:3 (*Z*):(*E*) ratio); $[\alpha]_D^{20}$ +7.9 (*c* 1.0 in $CHCl_3$); ν_{max} 2923, 2852, 1596, 1575; δ_H (500 MHz, $CDCl_3$) 1.03-1.80 (38H, C(4)H_2−C(11)H_2, C(2′′)H_2−C(12′′)H_2), 1.91 (2H, app q, *J* 6.6, C(12)H_2), 2.35 (2H, app q, *J* 6.9, C(15)H_2), 2.55-2.69 (5H, m, C(16)H_2), C(1′′)H_A), C(13′′)H_2), 2.82-2.95 (1H, m, C(1′′)H_B), 3.30-3.40 (1H, m, C(3)*H*), 3.69 (1H, d, *J* 8.8, C(2)*H*), 5.31-5.43 (2H, m, C(13)*H*, C(14)*H*), 7.16-7.24 (3H, m, C(5′)*H*, C(5′′′)*H*, *Ph*), 7.28-7.32 (4H, m, *Ph*), 7.45-7.52 (2H, m, C(4′)*H*, C(4′′′)*H*), 8.30-8.58 (4H, br s, C(6′)*H*, C(6′′′)*H*, C(2′)*H*, C(2′′′)*H*); δ_C (125 MHz, $CDCl_3$) 24.9, 26.7, 26.8, 27.2, 28.7, 28.8, 29.09, 29.10, 29.13, 29.19, 29.33, 29.39, 29.42, 29.48, 29.49, 29.54, 29.58, 29.61 (*C*(4)−*C*(12), *C*(15), *C*(2′′)−*C*(11′′)), 31.1 (*C*(12′′)), 32.98, 33.00 (*C*(16), *C*(13′′)), 44.6 (*C*(1′′)), 54.3 (*C*(2)), 60.7 (*C*(3)), 123.2 (*p-Ph*), 127.0 (*C*(5′), *C*(5′′′)), 127.6 (*C*(14)), 128.5, 128.7 (*o,m-Ph*), 131.4 (*C*(13)), 135.7, 135.9 (*C*(4′), *C*(4′′′)), 137.2, 137.9 (*C*(3′), *C*(3′′′)), 139.1 (*i-Ph*), 147.1, 147.2 (*C*(6′), *C*(6′′′)), 149.9, 150.0 (*C*(2′), *C*(2′′′)), 176.7 (*C*(1)); *m/z* (ESI^+) 682 ($[M+H]^+$, 5%), 342 ($[M+2H]^{2+}$, 40%), 228 ($[M+3H]^{3+}$, 100%); HRMS (ESI^+) $C_{45}H_{68}N_3O_2^+$ ($[M+H]^+$) requires 682.5306; found 682.5284.

6.5 References and notes:

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[11] The enantiomeric excess of (*S*)-**166** was determined by ^1H NMR spectroscopic analysis of the chemical shift resonances observed after mixing equimolar quantities of (*S*)-**166** with (*R*)-*O*-acetyl mandelic acid to those observed when (*RS*)-**166** was mixed with (*R*)-*O*-acetyl mandelic acid.

[12] The enantiomeric purity of **126** was determined by conversion to the corresponding methyl ester (*S*)-**164** upon treatment with $SOCl_2$ in MeOH, and subsequent ^{1}H NMR spectroscopic analysis of the corresponding Mosher's amides, see: Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

[13] The amount of the other oxime diastereoisomer could not be determined accurately due to peak overlap in the ^{1}H NMR spectrum of the crude reaction mixture.

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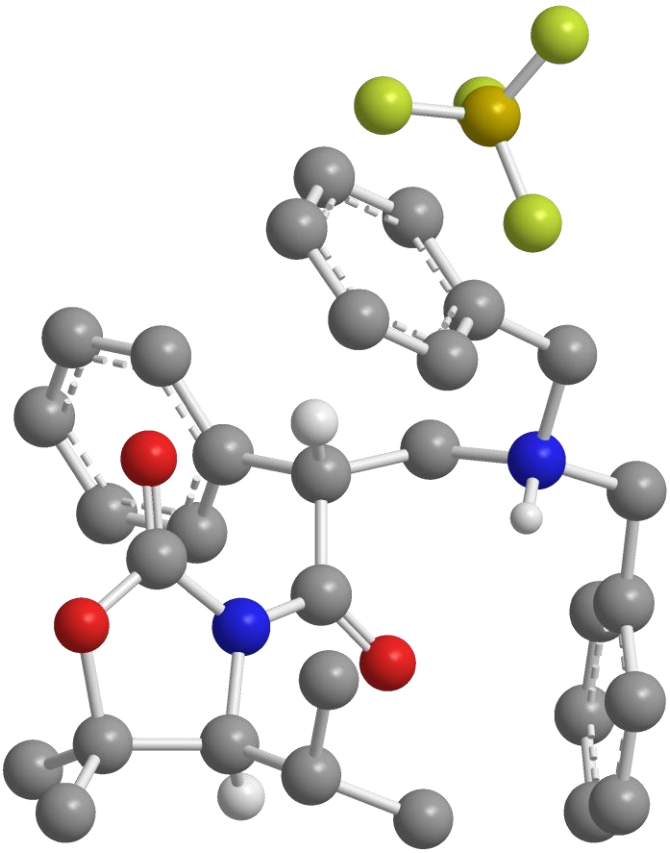
[36] The (*Z*):(*E*) ratio was determined by ^{1}H NMR spectroscopy integration of signals corresponding to the allylic CH_2 protons on a 700 MHz instrument.

[37] The 94:3:3 dr refers to a mixture of [(2*S*,3*R*,13*Z*,R_S):(2*R*,3*R*,13*Z*,R_S):(2*S*,3*R*,13*E*,R_S)] as determined by ^{1}H NMR spectroscopy integration of signals corresponding to the allylic CH_2 protons [for (13*E*):(13*Z*) isomers] and integration of signals corresponding to a phenyl C*H* proton [for (2*S*) and (2*R*) isomers] on a 700 MHz instrument.

[38] The resonance associated with the C(1) carbon was not observed.

Appendix A: X-Ray crystal structure data for 122·HBF_4

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 122·HBF_4

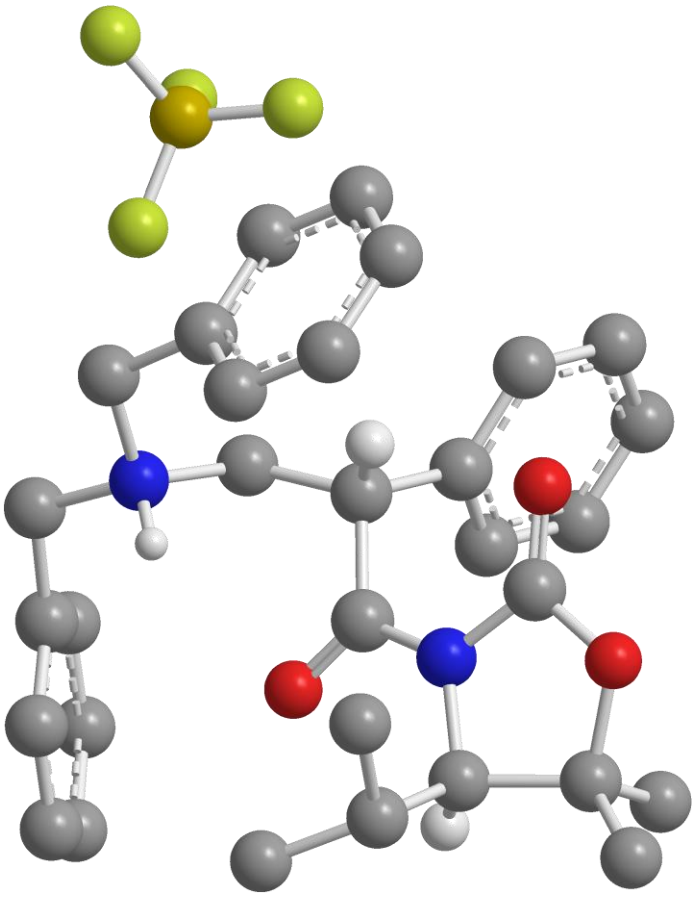
Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **122**·HBF_4 [$C_{31}H_{37}BF_4N_2O_3$]: M = 572.45, monoclinic, space group $P\ 2_1$, a = 11.9601(3) Å, b = 11.3444(3) Å, c = 12.6727(4) Å, β = 117.3068(14)°, V = 1527.82(8) Å^3, Z = 2, μ = 0.0095 mm^{-1}, colourless plate, crystal dimensions = 0.07 × 0.08 × 0.21 mm^3. A total of 3657 unique reflections were measured for $5 < \theta < 27$ and 3657 reflections were used in the refinement. The final parameters were wR_2 = 0.078 and R_1 = 0.054 [I>–3.0σ(I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

[1] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

Appendix A: X-Ray crystal structure data for *ent*-122·HBF_4

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for *ent*-122·HBF_4

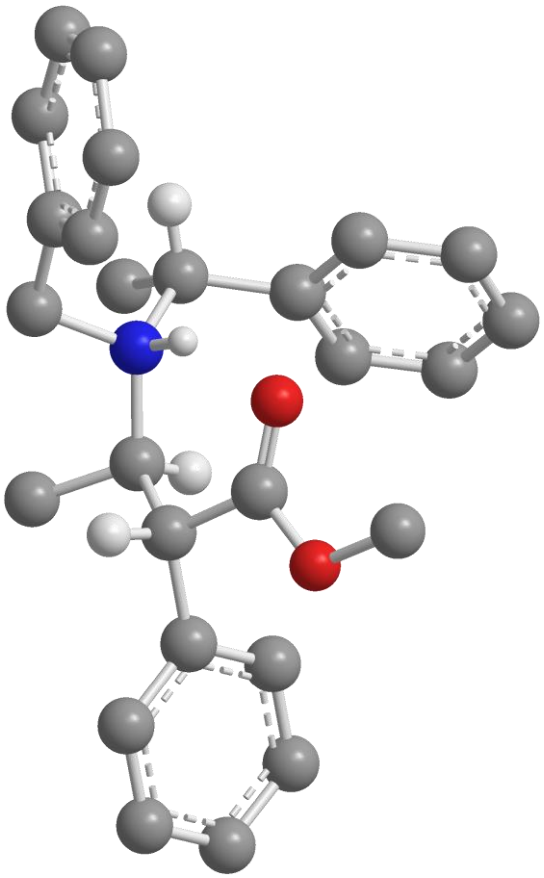
Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[2]

X-ray crystal structure data for *ent*-**122**·HBF_4 [$C_{31}H_{37}BF_4N_2O_3$]: M = 572.45, monoclinic, space group $P\ 2_1$, a = 11.9648(3) Å, b = 11.3421(4) Å, c = 12.6719(4) Å, β = 117.4185(13)°, V = 1526.48(8) $Å^3$, Z = 2, μ = 0.096 mm^{-1}, colourless plate, crystal dimensions = 0.06 × 0.22 × 0.24 mm^3. A total of 3634 unique reflections were measured for $5 < \theta < 27$ and 3634 reflections were used in the refinement. The final parameters were wR_2 = 0.114 and R_1 = 0.060 [I>–3.0σ(I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

[2] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

Appendix A: X-Ray crystal structure data for 257

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 257

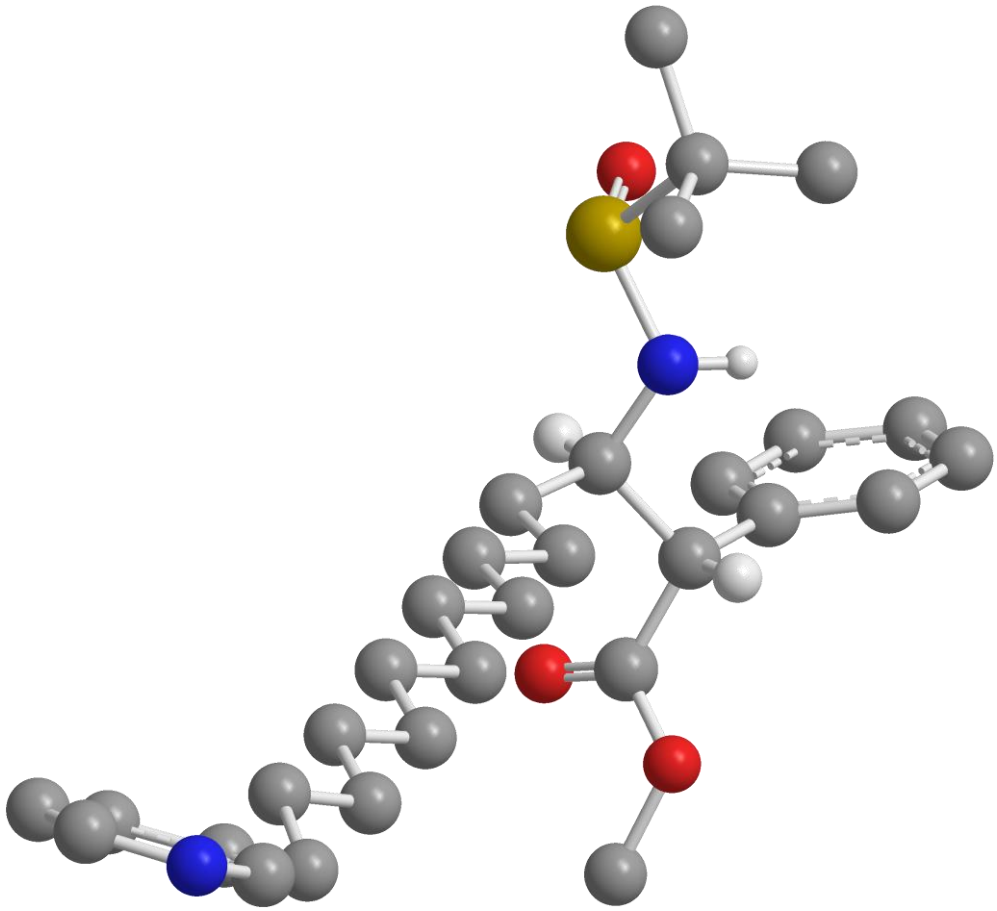
Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[3]

X-ray crystal structure data for **257** [$C_{26}H_{30}BF_4NO_2$]: M = 475.33, orthorhombic, space group $P\,2_1\,2_1\,2_1$, a = 8.7595(9) Å, b = 15.9072(18) Å, c = 17.448(3) Å, V = 2431.3(5) Å^3, Z = 4, μ = 0.101 mm^{-1}, colourless block, crystal dimensions = 0.08 × 0.11 × 0.19 mm^3. A total of 1884 unique reflections were measured for 5 < θ < 23 and 1884 reflections were used in the refinement. The final parameters were wR_2 = 0.130 and R_1 = 0.096 [I>–3.0σ(I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

[3] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

Appendix A: X-Ray crystal structure data for 290

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 290

Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[4]

X-ray crystal structure data for **290** [$C_{31}H_{48}N_2O_3S$]: M = 528.80, monoclinic, space group $C\,2$, a = 20.1712(6) Å, b = 5.58190(10) Å, c = 28.3409(9) Å, β = 107.750(4)°, V = 3039.10(16) Å^3, Z = 4, μ = 1.191 mm^{-1}, colourless prism, crystal dimensions = 0.15 × 0.15 × 0.26 mm^3. A total of 5872 unique reflections were measured for 3 < θ < 76 and 5849 reflections were used in the refinement. The final parameters were wR_2 = 0.095 and R_1 = 0.041 [I>–3.0σ(I)], with Flack enantiopole = –0.011(14).[5] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

[4] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.
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