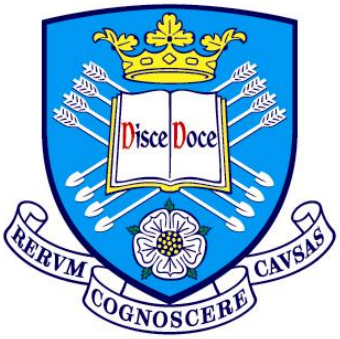
Asymmetric Approaches to Manzamine A and Substituted Nitriles

A dissertation submitted for the degree of Doctor of Philosophy in Chemistry



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June 2013

Dedication

To my parents, my husband and my little daughters Manar and Maram.

Declaration

This dissertation records the work carried out in the Department of Chemistry, University of Sheffield, between July 2009 and July 2013 and is original except where acknowledged by reference. No part of this work is being, nor has been, submitted for a degree, diploma or any other qualification at any other university.

Acknowledgements

First of all, I thank the almighty Allah for the power He has provided me with to complete this work.

I would like to express my gratitude to Professor Iain Coldham for his supervision, encouragement and invaluable advice throughout this work. Thank you for always being available for me, to answer my questions.

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My greatest thanks are to two people: the first man and teacher in my life, my father.

اتقدم بكل الشكر والتقدير الي استاذي الاول وقدوتي الحسنة الي من دعمني ماديا ومعنويا من بداية دراستي وكان له الفضل في كل ما انا فيه الان ابي العزيز. اطال الله في عمره.

The most Compassionate woman in my life my mother.

اتقدم بكل شكري وتقديري لامي الحبيبة, دعمك ودعاءك الدائم كان وسيكون زادي طوال حياتي. اتمنى من الله ان يحفظك لي دائما.

I would also like, of course, to thank the most important people in my life, in fact they are all my life: my husband Zaid (thank you very much for the person you are: kind hearted, gentle, caring and understanding) and my two little angels Manar and Maram for being supportive all the way through.

Abbreviations

Ar	Aryl
Boc	*tert*-Butoxycarbonyl
BSA	bis(trimethylsilyl) acetamide
CAN	ceric ammonium nitrate
Cat.	Catalyst
Cbz	Carboxybenzyl
CSA	Camphorsulfonic acid
dba	dibenzylideneacetone
d	Day
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DDQ	Dichlorodicyanoquinone
DEAD	Diethylazodicarboxylate
de	Diastereomeric excess
DIBAL-H	Diisobutylaluminium hydride
DMAP	4-*N*,*N*-Dimethylaminopyridine
DMF	Dimethyl formamide
DMP	Dess-Martin Periodinane
DMSO	Dimethyl sulfoxide
dppb	1,3-bis-(diphenylphosphino)butane
dr	Diastereomeric ratio
eq.	Equivalent
er	Enantiomeric ratio
GC	Gas chromatography
HMDS	Hexamethyldisilazane
HMPA	Hexamethyl phosphoramide
HPLC	High performance liquid chromatography
hr	Hour
IBX	2-Iodoxybenzoic acid
IC_{50}	50% maximal inhibitory concentration
Im	imidazole
IR	infra red
LDA	Lithium diisopropylamide

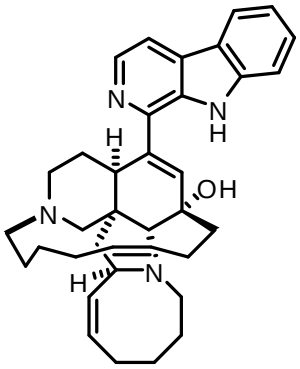
m-CPBA	*m*-Chloroperbenzoic acid
min.	Minutes
Ms	Methanesulfonyl
MS	molecular sieves
MW	Microwave
NBS	*N*-Bromosuccinimide
NCS	*N*-chlorosuccinimide
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine *N*-oxide
PMB	*para*-methoxbenzyl
PMP	*para*-methoxyphenyl
p-NBSA	*para*-Nitrobenzenesulfonic acid
PPL	Porcine pancreas lipase
PPTS	Pyridinium *p*-toluenesulfonate
^{i}Pr	Isopropyl
Py	Pyridine
R_f	Retention factor
rt.	Room temperature
TBAF	Tetra-*n*-butylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
TBHP	*tert*-Butyl hydroperoxide
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidyl
TMS	Trimethylsilyl
TPAP	Tetrapropylammonium perruthenate
Triton B	Benzyltrimethylammonium hydroxide
Ts	Toluenesulfonyl

Table of contents

Abstract

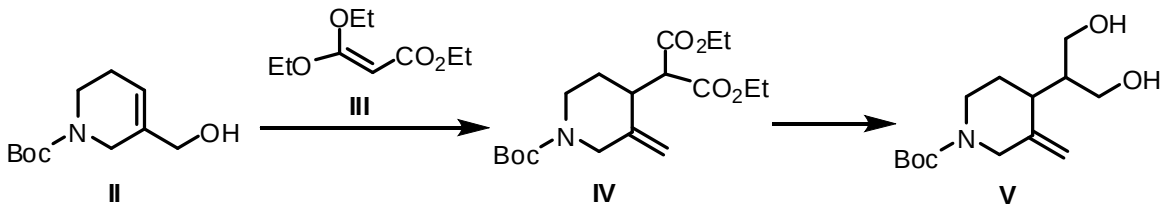
This thesis describes research in two areas–the first relating to early steps in a synthesis of the core ring system of the natural product manzamine A, and the second relating to nitrile anion chemistry.

The alkaloid manzamine A **I** was first isolated from the marine sponge *Haliclona sp*. It has attracted international attention because of its interesting structure and extraordinary biological activity.



I

Several approaches were examined towards the asymmetric synthesis of manzamine A. Firstly, a Claisen rearrangement strategy was carried out by reacting alcohol **II** with diethoxyacrylate **III** to give diester **IV**. Reduction of the diester **IV** using $LiAlH_4$ gave the diol **V**. To distinguish between the two alcohol groups, enzymatic resolution was utilised, although unfortunately, separation of the mixture of the diastereoisomers was not possible.

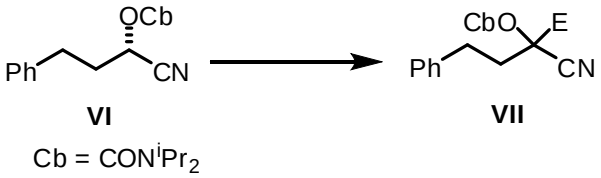


II **III** **IV** **V**

The enantioselective hydroxymethylation of an aldehyde in the presence of a chiral catalyst was also investigated, but due to the low yields in this sequence, an alternative approach was explored. An asymmetric Ficini-Claisen rearrangement using chiral ynamides gave mediocre yields and poor selectivities.

Nitriles are important building blocks in several natural products and pharmaceuticals. A deprotonation / electrophile quenching method for an enantioenriched nitrile with

stereocentre α to the nitrile group has been developed. Deprotonation was carried out using a magnesium base with the substrate **VI**, followed by subsequent electrophilic quench to give a range of products **VII**.



VI **VII**

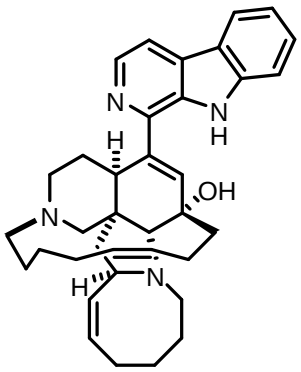
Cb = CON^iPr_2

Firstly, organomagnesium species were prepared then quenched with acetone and furnished the substituted nitrile **VII** in reasonable yield ~50% with good levels of enantioselectivity (up to 90:10 er). The optimised conditions were applied to different electrophiles, and good er values and reasonable yields were obtained (45-60%, 90:10-92:8 er). The reaction using the electrophile *in situ* was demonstrated with a variety of electrophiles to exhibit good yields and selectivity (40-72%, 60:40-91:9 er). In the case of methyl cyanoformate and benzyl cyanoformate as electrophiles, good enantiomer ratios were achieved in moderate yield (40%, 91:9 er, 52%, 91:9 er respectively).

1 Manzamine Chemistry

1.1 Overview of Manzamine A

The Manzamines are an interesting family of *β*-carboline-containing alkaloids with a unique 5-,6-,6-,8-,13-membered heterocyclic ring system, first isolated from marine sponges in the late 1980`s. The first example of this family was isolated from the marine sponge *Haliclona sp.* collected near Manzamo Island by Higa and co-workers in 1986.[1] Its structure, including its absolute configuration, was established by X-ray diffraction as manzamine A **1** (Figure 1-1).[2]



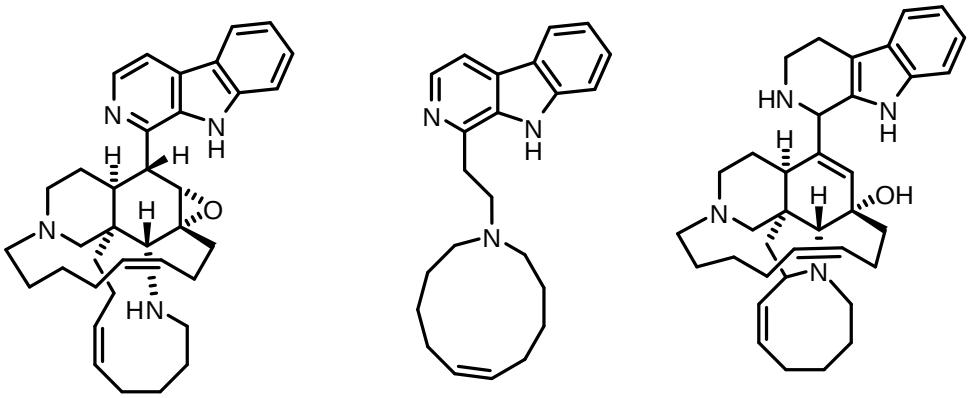
1

Figure 1-1

In recent years, the manzamines have attracted international attention as a result of their interesting structures and extraordinary biological activity. To date, there are 80 manzamines that have been isolated from 16 species of marine sponge distributed from the Red Sea to Indonesia.[2]

1.2 Manzamine Family Members

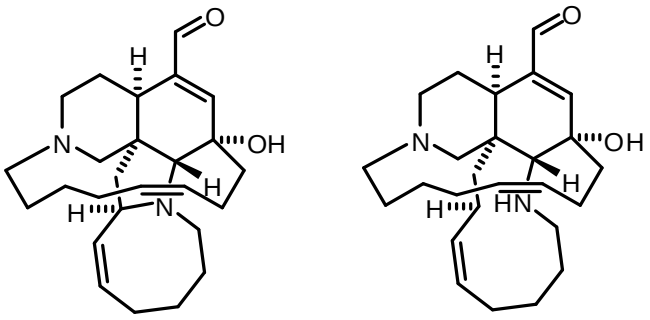
Manzamine A was first isolated as the main constituent from the marine sponge *Haliclona sp*.[2] along with the minor constituent manzamines B **2**, C **3** and D **4** (Figure 1-2).



2 **3** **4**

Figure 1-2

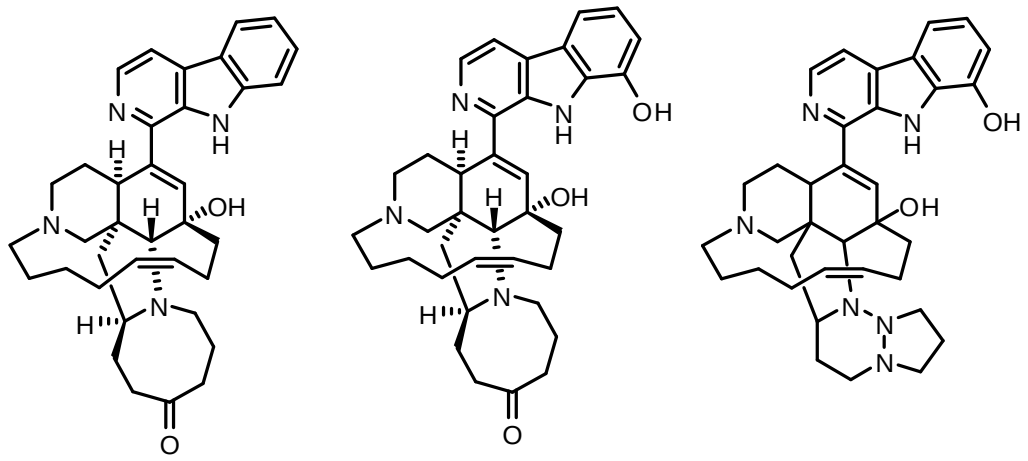
Interestingly, similar compounds ircinal A **5** and ircinal B **6** (Figure 1-3) which both lack the *β*-carboline moiety were isolated from the Okinawan sponge *Ircinia sp.*[3] These compounds could potentially be intermediates in the biosynthesis of manzamines A and B.



5 **6**

Figure 1-3

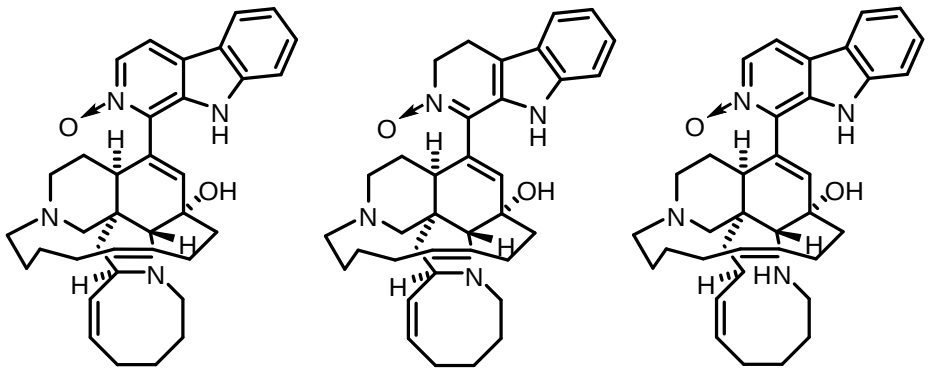
Other members of the manzamine family, manzamines E **7** and F **8** were isolated from an Okinawan *Xestospongia sp*.[4] Both compounds **7** and **8** possess a ketone functional group in the eight-membered ring segment of the molecule. Notably, manzamine F **8** was separated earlier from a sponge *Pellina sp*. and named as keramamine B with a misassigned 1, 2, 3-triazacyclohexane moiety.[5] Later, the structure of keramamine B **9** was revised as manzamine F **8** (Figure 1-4).[6]



7 **8** **9**

Figure 1-4

Manzamine alkaloids have been isolated from different sponges since the discovery of manzamine A. Edrada has isolated manzamine A *N*-oxide **10**, 3,4-dihydromanzamine A *N*-oxide **11** and manzamine J N-oxide **12** from the Philippine marine sponge *Xestospongia asmorica* (Figure 1-5).[7]



10 **11** **12**

Figure 1-5

In addition to the *N*-oxide manzamines, a series of hydroxyl substituted manzamines were isolated. The marine sponges *Haliclona sp*., *Xestospongia.sp*.,[4] *Acanthostrongylophora.sp*.,[4,8] *Pachypellina sp*.[9] and *Pellina.sp*.[5] have all yielded manzamine alkaloids with either 6- or 8-mono hydroxyl substituents around the *β*-carboline ring. The 6-hydroxy substituted compounds are manzamine Y **13**, 6-hydroxymanzamine E **14** and manzamine X **15**. The 8-hydroxy substituted compounds

are 8-hydroxymanzamine J **16**, manzamine K **17** and manzamine F **8** (keramamine B) (Figure 1-6).

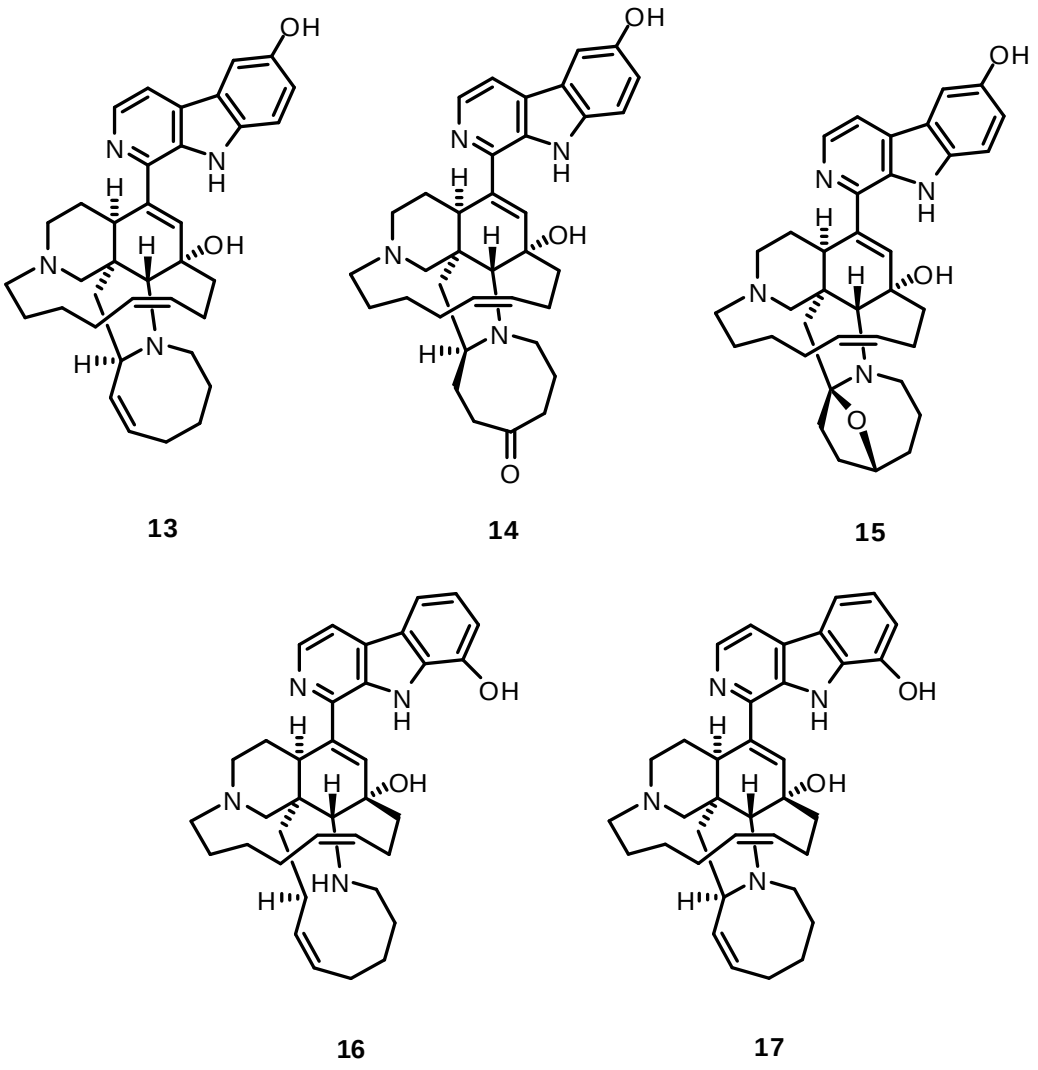


Figure 1-6

1.3 Biological Activity

Manzamine alkaloids have shown different bioactivities such as antimicrobial, antiparasitic, cytotoxic, antineuroinflammatory and pesticidal.[2] Manzamine A and 8-hydroxymanzamine A exhibit improved potency against malarial parasites both *in vitro* and *in vivo* compared to chloroquine and artemisinin, current medicinal treatments for malaria. In addition, manzamine A displays inhibitory activity in *vitro* on the growth of P388 leukaemia cells in mice (IC_{50} = 0.07 µg/mL),[1] besides antibacterial activity against *Staphylococcus aureus* bacterium for which the minimum inhibitory concentration is 6.3 µg/mL.[5] Manzamine A and other manzamine alkaloids have also shown significant

activity as anti-inflammatory agents, and activity against infectious diseases such as tuberculosis and toxoplasmosis.[10,11]Manzamine A has been found to have insecticidal activity against *S.littoralis* larvae.[12]

1.4 Biogenetic Pathways

In 1992 Baldwin and Whitehead suggested a simple biosynthetic pathway for manzamine A.[13] A macrocyclic bisdihydropyridine **21** results from the condensation of a C10 dialdehyde, acrolein and ammonia. The bisdihydropyridine **21** could then be converted *via* a Diels-Alder [4+2] cycloaddition reaction to give the initial pentacyclic intermediate **20**, which is an intermediate in the synthesis of manzamine B **2**. With some modifications this pathway could provide access to other members of the manzamine family (Figure 1-7).

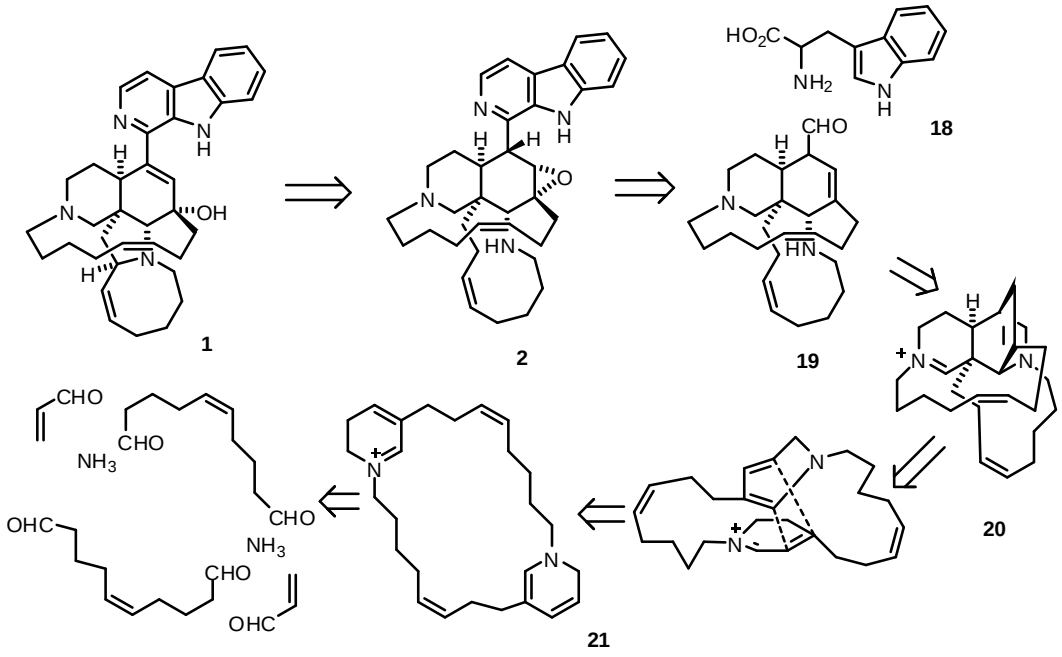
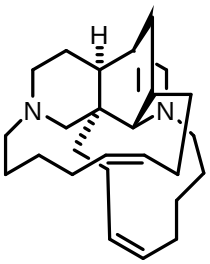


Figure 1-7

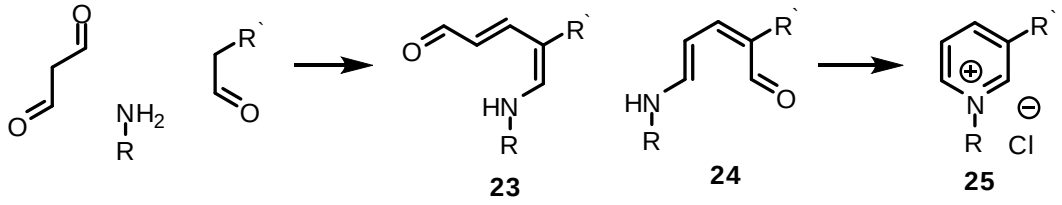
The theoretical proposal was supported by the isolation of ircinal A **5** and ircinal B **6** which are similar to Baldwin`s intermediate.[3] In addition, keramiphidin B **22** (Figure 1-8) was extracted from an Amphimedon sponge and also appears similar to pentacyclic intermediate **20**.[14] Keramiphidin B was synthesised by Baldwin and co-workers in a very low yield using a biomimetic approach related to that shown in Figure 1-7.[15]



22

Figure 1-8

Some years later, the Marazano group provided a modification to Baldwin`s proposal. Condensation of malonaldehyde with an aldehyde and a primary amine produces aminopentadienal derivatives **23** and **24**, with a derivative **23** more likely to cyclise in acidic media to generate alkylpyridinium salt **25** (Scheme 1-1).[16]



23 **24** **25**

Scheme 1-1

Moreover, dihydropyridinium **26** and aminopentadienal **27** species would react in different ways to produce cycloadducts **28** and **29** respectively. In fact these polycyclic structures would be advanced intermediates in the syntheses of manzamine A **1** and halicyclamine A **30** (Figure 1-9).

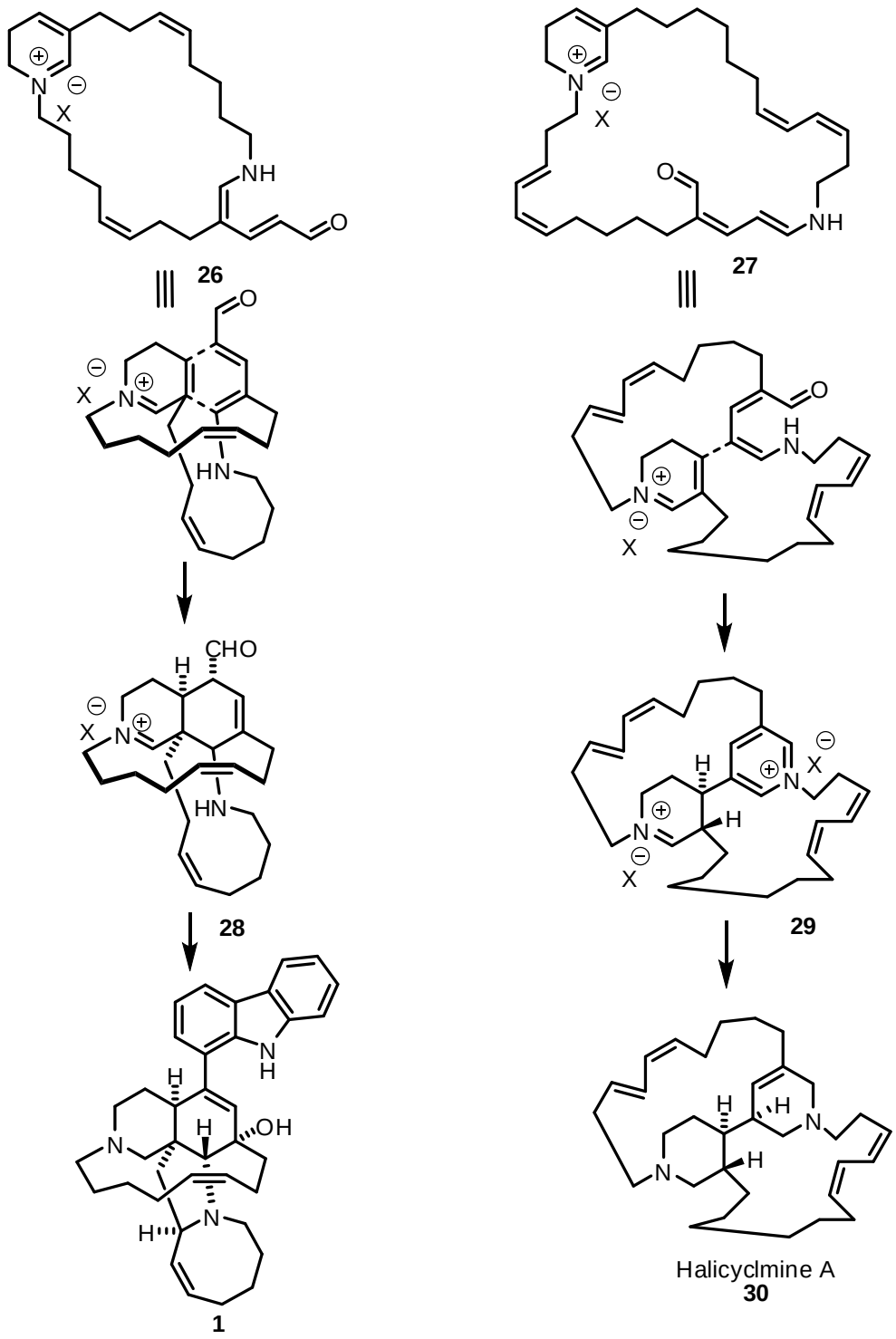


Figure 1-9

Marazano and co-workers reported the synthesis of an intermediate amino alcohol which could be used as an intermediate in the total synthesis of manzamine A (Figure 1-10).[17,18,19]

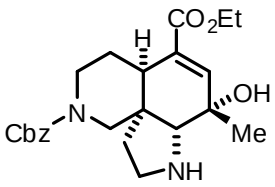


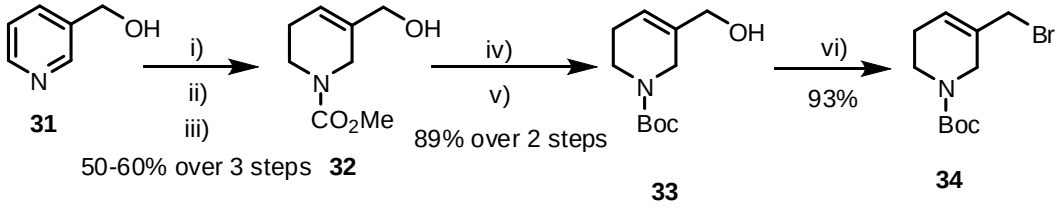
Figure 1-10

1.5 Total Syntheses of Manzamine A 1

The unusual ring system of manzamine A **1** has attracted great interest as one of the most challenging natural product targets for total synthesis. There have been four total syntheses of manzamine A, by Winkler and co-workers in 1998,[20] by Martin and co-workers in 1999,[21] by Fukuyama and co-workers in 2010,[22] and by Dixon and co-workers in 2012.[23]

1.5.1 Winkler`s Synthesis

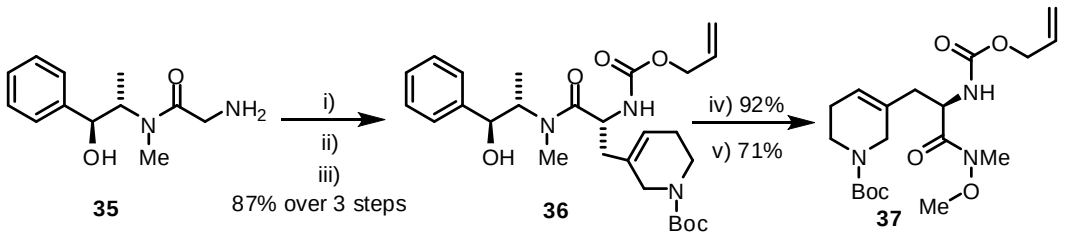
The *N*-protection of pyridine-3-methanol (**31**) followed by reduction resulted in the tetrahydropiperidine **32** after treatment with methyl chloroformate. Deprotection and then reprotection of the nitrogen produced the allylic alcohol **33** which was then transformed to bromide **34** (Scheme 1-2).



Reagents and conditions: i) BnBr; ii) $NaBH_4$; iii) MeOCOCl; iv) KOH, MeOH:H_2O; v) Boc_2O; vi) PPh_3, Br_2, ImH.

Scheme 1-2

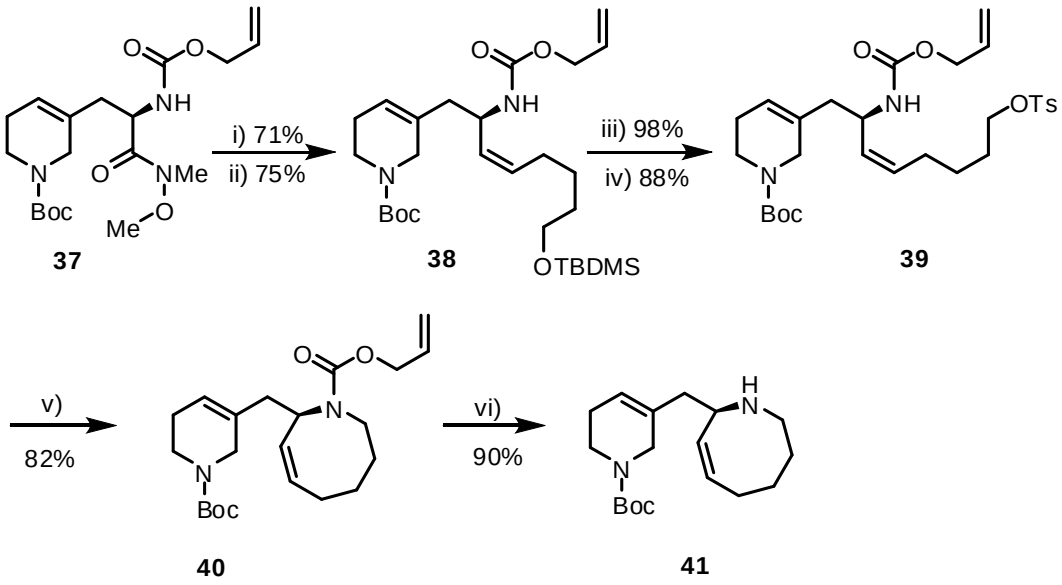
Deprotonation of glycinamide **35** with LDA followed by addition of the bromide **34** and gave *N*-protection compound **36**. A further couple of steps formed the Weinreb amide **37** (Scheme 1-3).



Reagents and conditions: i) LDA, LiCl; ii) **34**; iii) Alloc-Cl; iv) NaOH; v) EtOCOCl, NMM, HN(Me)OMe.HCl.

Scheme 1-3

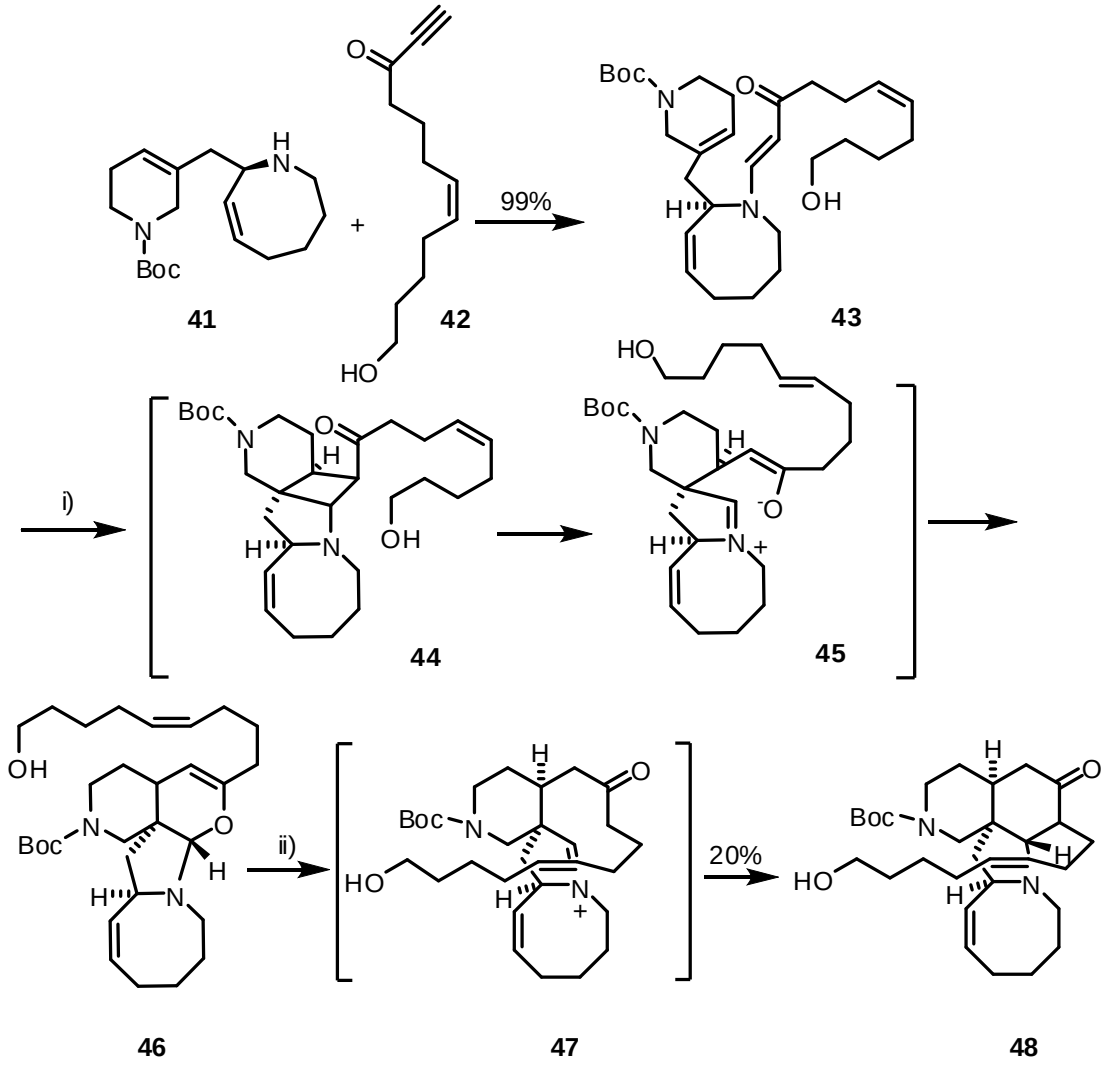
Reduction, Wittig reaction, deprotection of the silyl ether and conversion to the tosylate gave compound **39**. Deprotonation promoted cyclisation and finally treatment with tetrakis (triphenylphosphine) palladium provided the secondary amine **41** (Scheme 1-4).



Reagents and conditions: i) $LiAlH_4$; ii) KHMDS, $Ph_3P(CH_2)_5OTBDMSBr$; iii) PPTS, MeOH; iv) TsCl, Et_3N, DMAP; v) NaH; vi) $Pd(PPh_3)_4$, dimedone.

Scheme 1-4

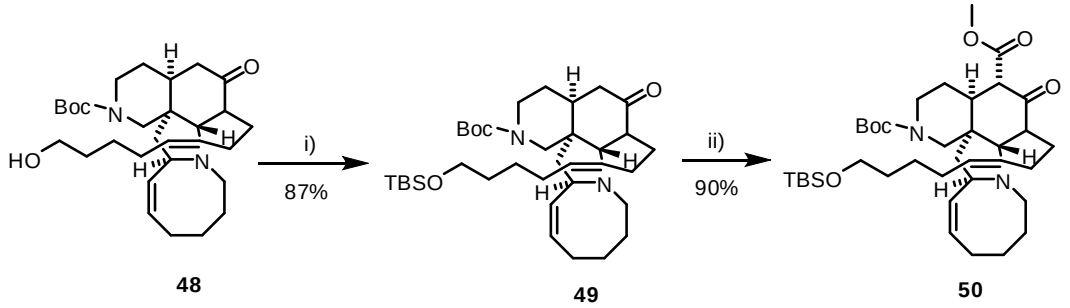
Vinylogous amide **43** was produced in an excellent yield from treatment of the secondary amine **41** with alkynyl ketone **42**. [2+2] Cycloaddition of vinylogous amide **43** gave intermediate tetracycle **44** which ring-opens *in situ* by a retro-Mannich fragmentation to give tricyclic amine **45**. Cyclisation of the enolate onto the iminium ion gave aminal **46**. Tetracyclic ABCE compound **48** was obtained by exposure of aminal **46** to pyridinium acetate *via* iminium intermediate **47**. The tetracycle **48** was formed as a single stereoisomer in 20% yield from vinylogous amide **43 (**Scheme 1-5).



Reagents and conditions: i) *hv*, ii) py, AcOH.

Scheme 1-5

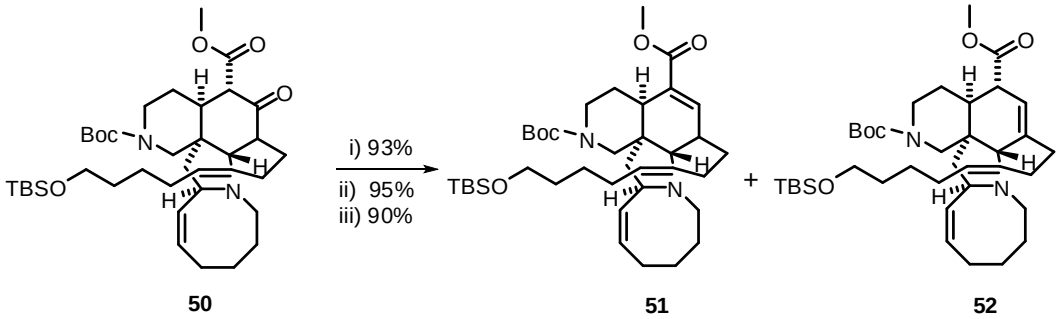
Introduction of the *β*-carboline moiety started with the protection of the alcohol **48** by TBSCl to give **49**, followed by the trapping of the enolate with Mander`s reagent (MeOCOCN) to afford *β*-ketoester **50 (**Scheme 1-6).



Reagents and conditions: i) TBSCl, ImH; ii) LiHMDS, MeOCOCN.

Scheme 1-6

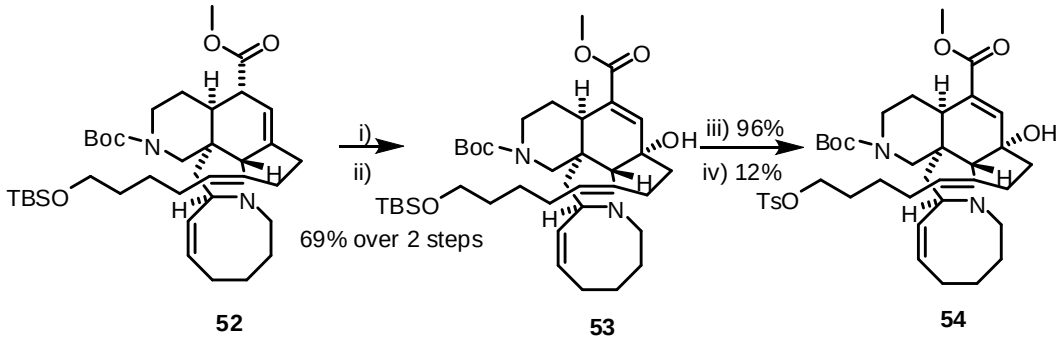
The ketoester **50** was then reduced using $NaBH_4$ to give an alcohol, which was converted to the mesylate, followed by elimination with DBU to give a mixture of *α-β* and *β-γ* unsaturated products **51** and **52** in a 2:1 ratio respectively (Scheme 1-7).



Reagents and conditions: i) $NaBH_4$; ii) MsCl, Et_3N; iii) DBU, benzene.

Scheme 1-7

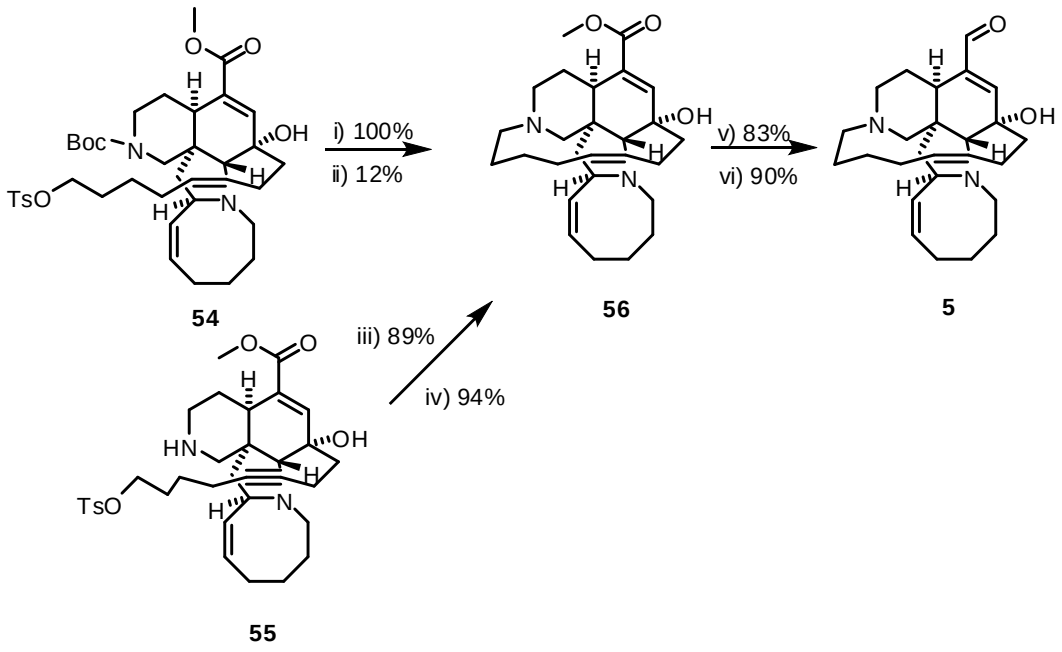
Epoxidation of the unconjugated ester **52** followed by treatment with basic conditions produced allylic alcohol **53**. Deprotection of the silyl group followed by conversion of the alcohol to the tosylate was performed to give compound **54** in 12% yield (Scheme 1-8).



Reagents and conditions: i) *m*-CPBA; ii) NaOMe; iii) TBAF; iv) TsCl, Et_3N.

Scheme 1-8

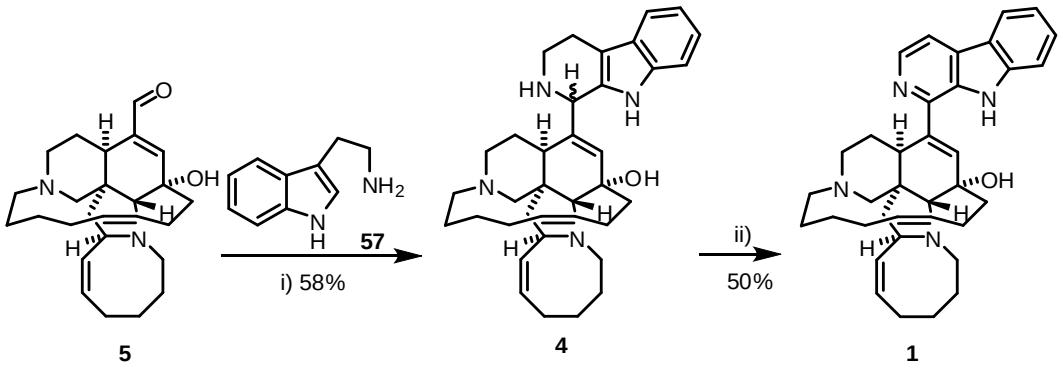
After removal of the *N*-Boc protecting group, macrocyclisation was achieved under high dilution conditions in the presence of Hünig`s base, however product **56** was produced in a disappointing 12% yield. The unsaturated ester **56** was therefore prepared by a different route from alkyne **55**. The reduction of ester **56** followed by Dess-Martin oxidation obtained ircinal A **5** (Scheme 1-9).



Reagents and conditions: i) TFA; ii) $^{i}Pr_2NEt$; iii) $^{i}Pr_2NEt$; iv) H_2, Lindlar catalyst; v) DIBAL-H; vi) DMP.

Scheme 1-9

Ircinal A **5** was converted into manzamine A **1** following a procedure reported by Kobayashi[3] *via* a Pictet-Spengler cyclisation of **5** with tryptamine **57** in the presence of trifluoroacetic acid to produce the tetrahydro-*β*-carboline moiety, manzamine D **4**, which upon treatment with DDQ provided manzamine A **1** (Scheme 1-10).

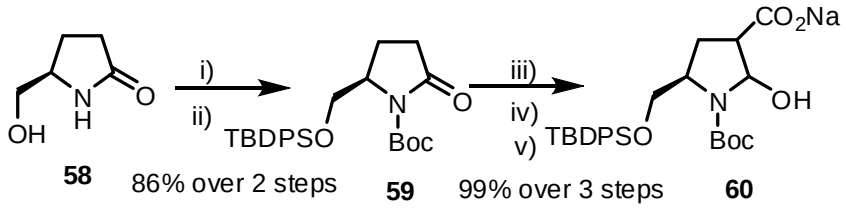


Reagents and conditions: i) TFA; ii) DDQ.

Scheme 1-10

1.5.2 Martin`s Synthesis

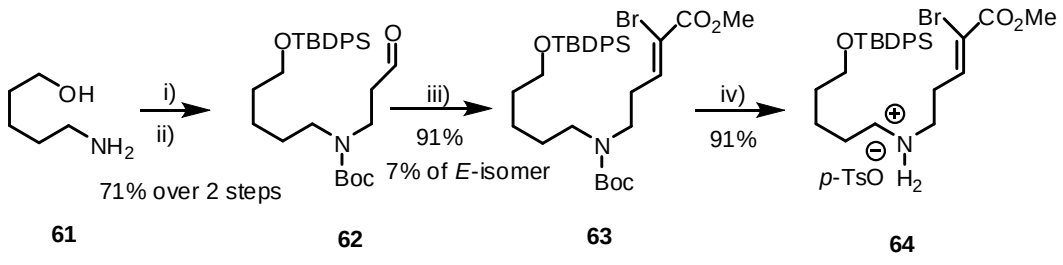
Martin`s synthesis is the second total synthesis of manzamine A and was first published in 1999, followed by a paper detailing further optimisation in 2002.[21,24] The synthesis consists of a domino Stille/Diels-Alder reaction to create the tricyclic ring system, followed by two sequential ring closing metatheses to form the D and E ring system.[24,25] The alcohol and amide functionalities in the starting material pyroglutaminol (**58**) were protected using TBDPS and Boc groups respectively to give compound **59**, followed by a carboxylation to give sodium salt **60** in a quantitative yield (Scheme 1-11).



Reagents and conditions: i) TBDPSCl, ImH, DMF; ii) Boc_2O, DMAP, Et_3N; iii) LiHMDS, THF, CO_2, –78 °C; iv) $NaBH_4$, EtOH, 0 °C; v) Na_2CO_3.

Scheme 1-11

The other coupling fragment **64** was obtained from the *N*-Boc protection of commercially available 5-aminopentanol (**61**) followed by *O*-protection as the silyl ether. Reaction with acrolein under acidic conditions provided aldehyde **62**. Wittig olefination was performed to afford the alkene **63** followed by the removal of the Boc protecting group to give the tosylate amine salt **64** in excellent yield (Scheme 1-12) .

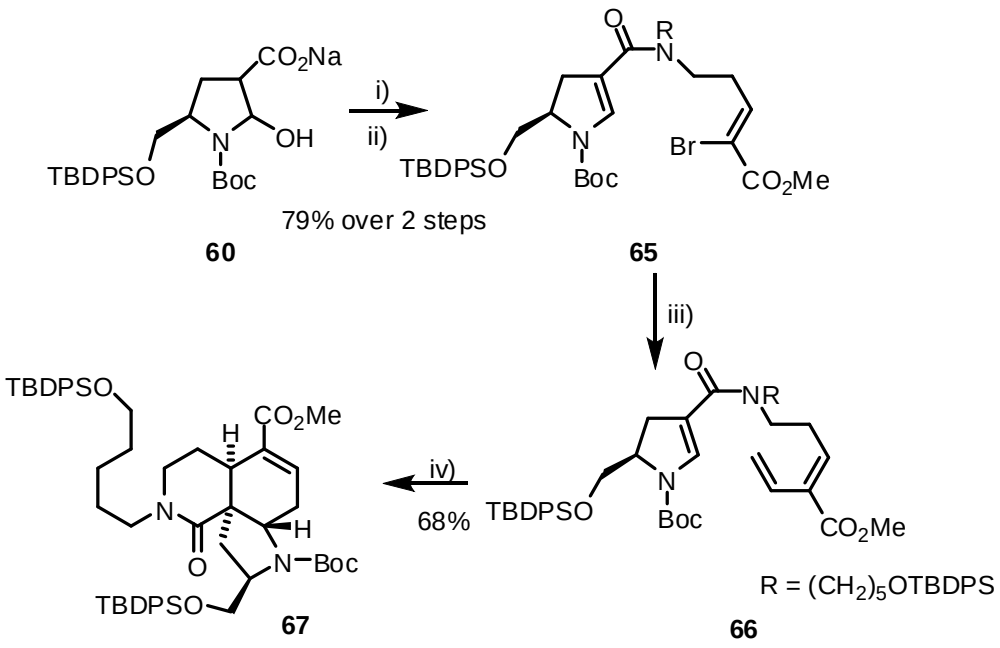


Reagents and conditions: i) Boc_2O then TBDPSCl; ii) acrolein, CSA; iii) $Ph_3P{=}C(Br)CO_2Me$, CH_2Cl_2; iv) TMSOTf, 2,6-lutidine then *p*-TsOH.

Scheme 1-12

The carboxylate **60** was transformed to the acid chloride and then reacted with amino salt **64** to give the amide **65**. Stille cross coupling afforded triene **66**, which underwent

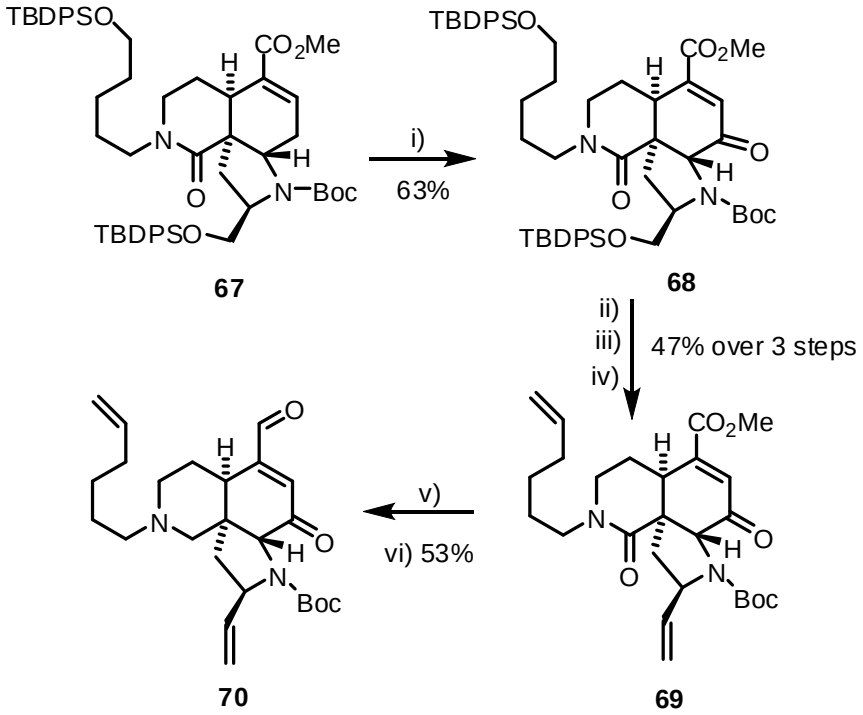
an intramolecular [4+2] cycloaddition upon heating in toluene to provide tricyclic product **67** in 68% yield (Scheme 1-13).



Reagents and conditions: i) $(COCl)_2$; ii) (**64**), Et_3N; iii) vinyltributylstannane, $Pd(PPh_3)_4$; iv) PhMe, reflux.

Scheme 1-13

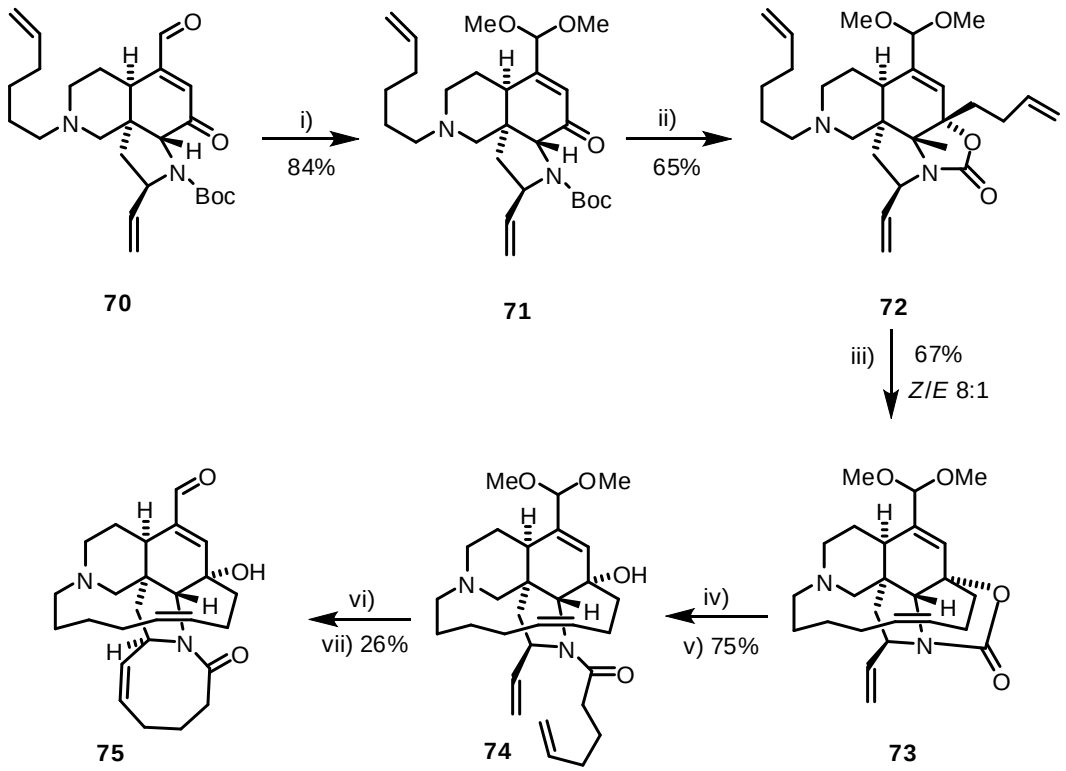
Oxidation of unsaturated ester **67** gave the enone **68**, which then underwent deprotection of both alcohol groups. Swern oxidation, double Wittig olefination, DIBAL reduction and DMP oxidation afforded dialkene **70** (Scheme 1-14).



Reagents and conditions: i) CrO_3, 3,5-dimethylpyrazole, CH_2Cl_2, −18 °C; ii) HCl, MeOH; iii) $(COCl)_2$, DMSO, Et_3N; iv) $Ph_3P{=}CH_2$, −78 °C→ rt.; v) DIBAL-H. vi) DMP.

Scheme 1-14

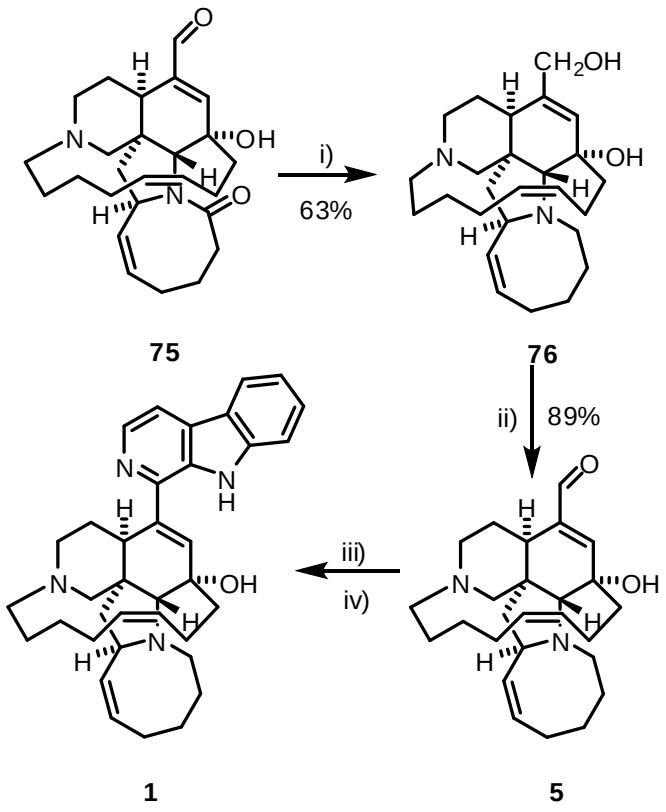
After the aldehyde **70** was protected as an acetal **71**, butenyllithium was added to the ketone to provide the tertiary alcohol which directly closed on the *N*-Boc group to give oxazolidinone **72**. The 13-membered ring was achieved with 67% of the Z-isomer from treatment of oxazolidinone **72** with Grubbs` 1st generation catalyst. Basic conditions opened the oxazolidinone followed by acylation to produce amide **74** then ring closing metathesis gave product **75** (Scheme 1-15).



Reagents and conditions: i) $HC(OMe)_3$, MeOH, HCl; ii) $H_2C{=}CHCH_2CH_2Li$, –78 °C→ −20°C, then H_2O; iii) Grubbs I; iv) KOH, MeOH, heat; v) $H_2C{=}CHCH_2CH_2CH_2COCl$, Et_3N, CH_2Cl_2; vi) Grubbs I; vii)1M HCl.

Scheme 1-15

Reduction of lactam **75** by DIBAL-H afforded ircinol A **76** which, under oxidation by Dess-Martin periodinane, was converted to ircinal A **5**. Martin followed the same procedure as Winkler to insert the *β*-carboline moiety *via* a Pictet-Spengler cyclisation (Scheme 1-16).



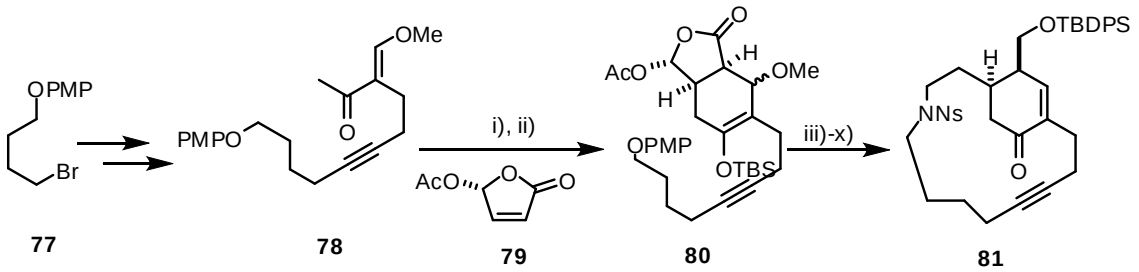
Reagents and conditions: i) DIBAL-H; ii) DMP; iii) tryptamine, TFA; iv) DDQ, Et_3N.

Scheme 1-16

1.5.3 Fukuyama Synthesis

Fukuyama has reported an efficient route for the synthesis of manzamine A **1**.[22] The key steps of this synthesis are: a stereoselective Diels-Alder reaction, 15 membered ring formation *via* an intramolecular Mitsunobu reaction, [3,3] sigmatropic rearrangement and finally ring closing metathesis.

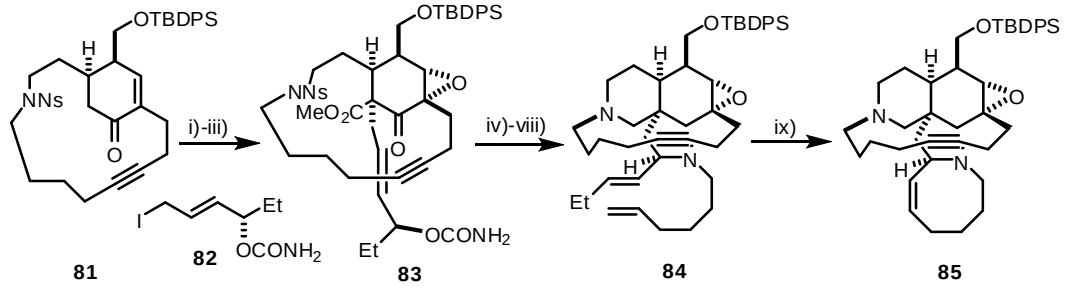
Protected bromide **77** was transformed to the vinylogous ketone **78** before being reacted with enantioenriched butenolide **79** in a Diels-Alder reaction to afford the acetyloxylactone **80** in a 97% yield. After a couple of steps, formation of 15 membered ring amine system **81** was performed in an excellent yield *via* intramolecular Mitsunobu reaction (Scheme 1-17).



Reagents and conditions: i) TBSOTf, Et_3N, Et_2O; ii) Lactone **79**, NaOAc, toluene, reflux, 97% (two steps, *endo*/*exo* 2:1); iii) Et_3N, MeOH; $MeOCH_2PPh_3Cl$, KHMDS, THF; MeI, $^{i}Pr_2NEt$, DMF, 89% (*E*/*Z*) 1:1 for *endo*, 1:4 for *exo*); iv) $LiAlH_4$, Et_2O, 99%; v) TBDPSCl, ImH, CH_2Cl_2, 99%; vi) *p*-$TsOH \cdot H_2O$, acetone, 97%; vii) $NaBH(OAc)_3$, AcOH, benzene, 88%; viii) NsNHBoc, DEAD, PPh_3, benzene, 97%; ix) TFA, CAN, CH_3CN / H_2O, 81%; x) DEAD, PPh_3, toluene, 85%.

Scheme 1-17

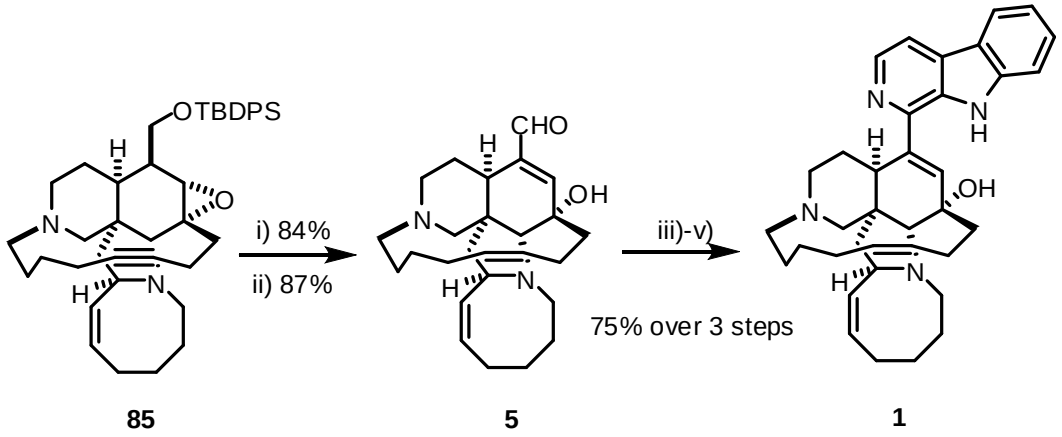
The cyclic amine **81** was alkylated with MeO_2CCN, then reacted with allyl iodide **82**, then transformed into adduct **83** which underwent a [3,3] sigmatropic rearrangement to give, after several further steps, the adduct **84**. Subsequent transformations led to formation of diamine **84**. The crucial step, the ring closing metathesis, was performed using Hoveyda-Grubbs catalyst in CH_2Cl_2 at room temperature to furnish the pentacyclic product **85** in 41% yield (Scheme 1-18).



Reagents and conditions: i) LHMDS, THF; MeOCOCN; ii) **82**, K_3PO_4, DMF, 69% over 2 steps; iii) TBHP, triton B,CH_3CN/benzene, 62%; iv) TFAA, Et_3N, CH_2Cl_2, AcOH, $Mg(ClO_4)_2$, benzene; v) $NaBH(OCOCF_3)_3$, THF, TFA, 5-hexenoylchloride, Et_3N, 80% over 2 steps; vi) $LiAlH_4$, $AlCl_3$, Et_2O, 93%; vii) IBX, *t*BuOH; viii) PhSH, Cs_2CO_3, CH_3CN, $NaBH(OCOCF_3)_3$, THF, 89% over 2 steps; ix) Hoveyda-Grubbs catalyst (1.0 eq.), PMPOH,CH_2Cl_2, 41%.

Scheme 1-18

The adduct **85** was transformed to ircinal A **5** before finally being converted to manzamine A **1** in 75% yield for the last three steps (Scheme 1-19).

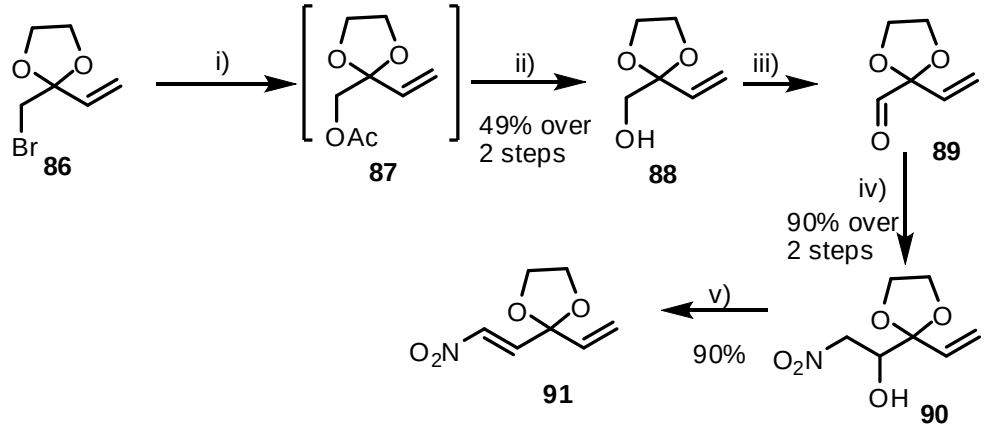


Reagents and conditions: i) TBAF, THF, 50 °C, H_2, Lindlar's catalyst, quinoline, MeOH, rt.; ii) DMP, CH_2Cl_2, rt.; iii) tryptamine, TFA, CH_2Cl_2, rt.; iv) TFA,CH_2Cl_2, rt.; v) DDQ, CH_2Cl_2/benzene, rt.

Scheme 1-19

1.5.4 Dixon's Total Synthesis

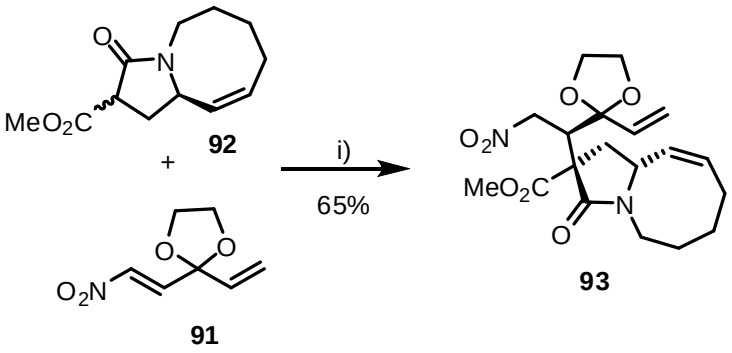
Recently, Dixon and co-workers have developed a novel short total synthesis of manzamine A **1** using Michael addition, nitro Mannich/lactamisation, Nef reaction, RCM and finally cross coupling as key steps.[23] Firstly, nitro olefin **91** was prepared in 5 steps using standard reactions from commercially available starting material (**86**) (Scheme 1-20).[23]



Reagents and conditions: i) KOAc, Aliquat 336; ii) K_2CO_3, MeOH; iii) $COCl_2$, DMSO, Et_3N, CH_2Cl_2; iv) CH_3NO_2, EtOH; v) MsCl, Et_3N, CH_2Cl_2.

Scheme 1-20

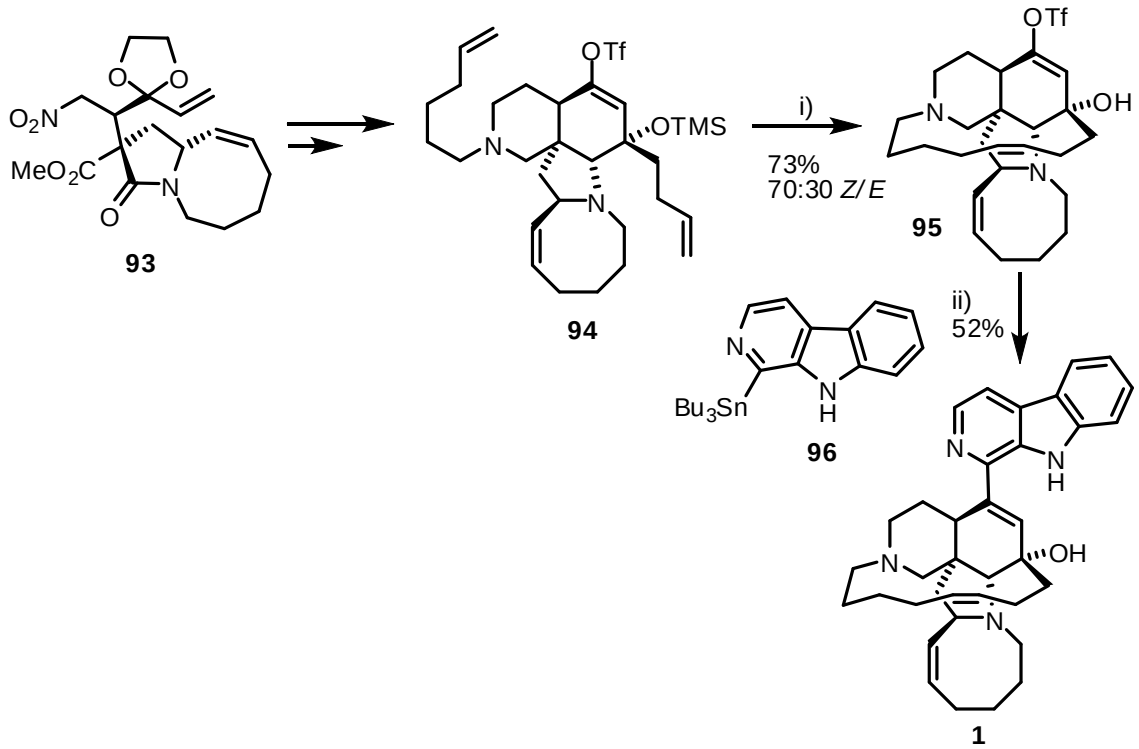
The bicyclic intermediate **92** was prepared in 6 steps and in 24% overall yield[26] before reacting with nitro olefin **91** in diastereoselective Michael addition to give the desired diastereoisomer **93** in 65% yield. The stereochemistry of **93** was determined by X-ray diffraction (Scheme 1-21).



Reagents and conditions: i) KHMDS, 18-crown-6.

Scheme 1-21

The intermediate **93** was transformed into the key intermediate triflate **94** which undergoes Grubbs I catalysed olefin metathesis to produce the pentacycle **95** in 73% yield as a 70:30 *Z:E* mixture of diastereoisomers. Finally, cross-coupling of the intermediate **95** with tributylstannylated β-carboline **96** catalysed by palladium (0) afforded manzamine A **1** in 52% yield (Scheme 1-22).



Reagents and conditions: i) Grubbs I (20 mol%), CH_2Cl_2; ii) $Pd(PPh_3)_4$, (12 mol%), **96**, DMF.

Scheme 1-22

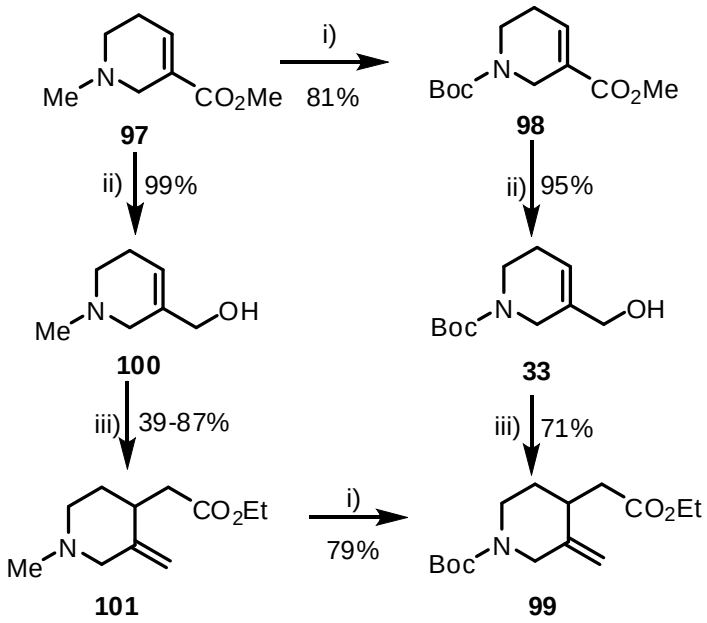
1.5.5 Different Syntheses toward Manzamine A Ring System

Manzamine A **1** has been the subject of many synthetic efforts. In fact, there have been several syntheses of different analogues of manzamine A. The ABC core has been achieved by many interested research groups such as those of Marazano,[17] Langlois,[27] Markó,[28] Leonard[29] and Brands.[30] Also there have been numerous investigations towards the manzamine A core ring systems, for instance in Pandit`s route, the ABCDE subunit was synthesised *via* an intermolecular Diels-Alder reaction,[31,32,33] followed by olefin metathesis to afford the D and E ring systems.

The cyclised ABCE tetracyclic ring system has been achieved by Nakagawa, who used an intermolecular Diels-Alder reaction as the key step.[34,35] Yamamura has reported the synthesis of the ABCD core of manzamine A.[36,37] Furthermore, Hart[38] has succeeded in producing the ABCE cycloadduct using Mitsunobu conditions. In addition, the tricyclic ABC core was targeted by Overman,[39] where the ABC core synthesis was performed *via* a Mannich cyclisation as the key step.

1.6 Previous Work in the Group

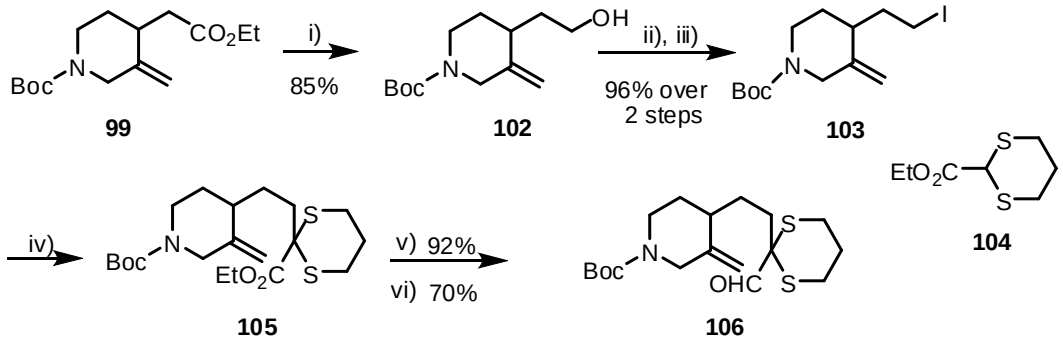
The synthesis of the ABC ring system of manzamine A has been investigated in the Coldham group, in an efficient short route. The key step is a stereoselective [3+2] azomethine ylide cycloaddition, which inserts rings B and C simultaneously with the formation of three new stereocentres.[40] The commercially available arecoline (**97**) was converted to compound **98**, then reduced by $LiAlH_4$ to give alcohol **33**. Allylic alcohol **33** was reacted with triethyl orthoacetate under Johnson-Claisen rearrangement conditions to give the ester **99** with the *exo*-methylene needed for the key cycloaddition step. Another approach to the cycloadduct piperidine **99** was by reducing the arecoline **97** followed by a Johnson-Claisen rearrangement, then conversion of the resulting *N*-methyl derivative **101** to the *N*-Boc protected piperidine **99** (Scheme 1-23).



Reagents and conditions: i) MeCH(Cl)OCOCl, PhMe, heat, then MeOH, heat, then Boc_2O, CH_2Cl_2, Et_3N; ii) $LiAlH_4$, THF, 0 °C; iii) $MeC(OEt)_3$, xylene, 2,4-dinitrophenol, heat.

Scheme 1-23

Treatment of ester **99** with $LiAlH_4$ gave alcohol **102** which was converted to the iodide **103**. The iodide was reacted with dithiane **104** to give the ester **105**. Reduction of the ester **105** to the alcohol followed by Swern oxidation afforded the aldehyde **106** which was required for the cycloaddition step (Scheme 1-24).

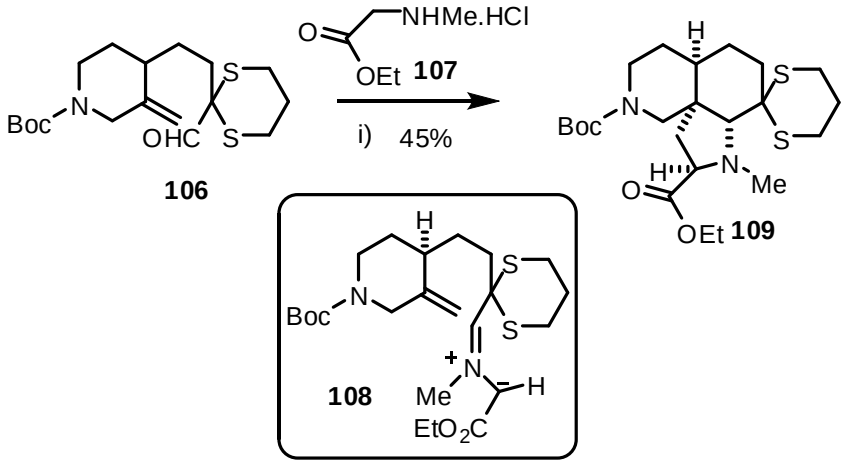


Reagents and conditions: i) $LiAlH_4$, THF, 0 °C; ii) CBr_4, Ph_3P, CH_2Cl_2; iii) NaI, acetone; iv) *n*BuLi, THF, HMPA, **104** followed by addition of **103**, −78 °C→rt.; v) $LiAlH_4$, THF, 0 °C; vi) $(COCl)_2$ (2.2 eq.), DMSO, CH_2Cl_2, − 60 °C, then Et_3N.

Scheme 1-24

To set up the ABC core of manzamine A, secondary amine (**107**) was condensed with aldehyde **106** to give azomethine ylide **108** and then a [3+2] cycloaddition reaction inserted rings B and C in a single step to produce the ABC ring system of manzamine A

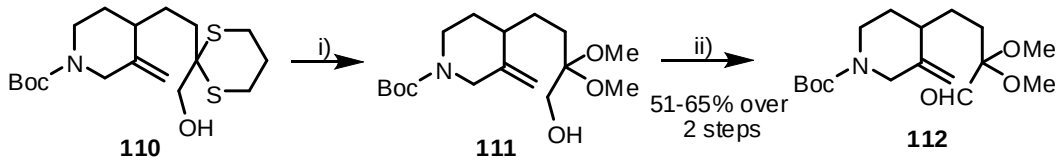
(Scheme 1-25). The structure and stereochemistry of cycloadduct **109** as a single diastereomer was confirmed by single crystal X-ray diffraction, which showed the *cis*-fused AB and BC rings.



Reagents and conditions: i) $^{i}Pr_2NEt$, PhMe, heat, 24 h.

Scheme 1-25

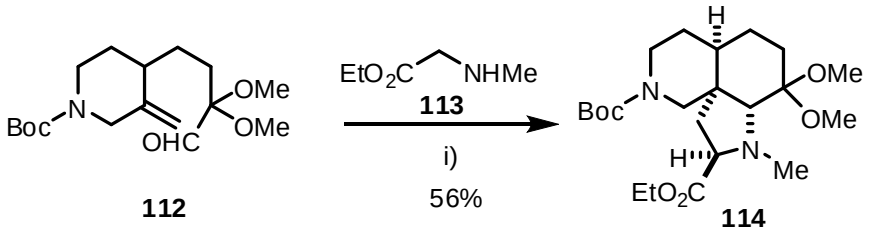
Unfortunately, attempts to remove the *N*-methyl group from compound **109** or cycloaddition reaction using other amino-esters were unsuccessful. The reaction of alcohol **110** with *N*-chlorosuccinimide and $AgNO_3$ in MeOH gave the acetal **111** which was oxidised to the alternative aldehyde **112** (Scheme 1-26).[41]



Reagents and conditions: i) NCS, $AgNO_3$, collidine, THF, MeOH, 0 °C; ii) 2.2 eq. of $(COCl)_2$, DMSO, CH_2Cl_2, − 60 °C then Et_3N.

Scheme 1-26

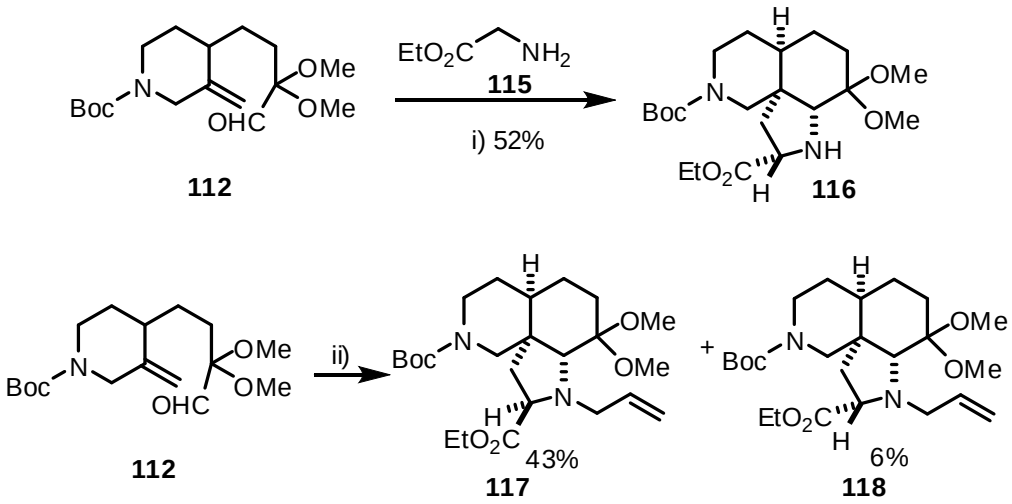
Condensation of aldehyde **112** with *N*-methylglycine ethyl ester (**113**) produced tricyclic amine **114** as the major diastereomer. The cycloadduct has *cis* geometry between the AB and BC rings with an *exo* location of the ethyl ester group (Scheme 1-27).[41]



Reagents and conditions: i) PhMe, reflux.

Scheme 1-27

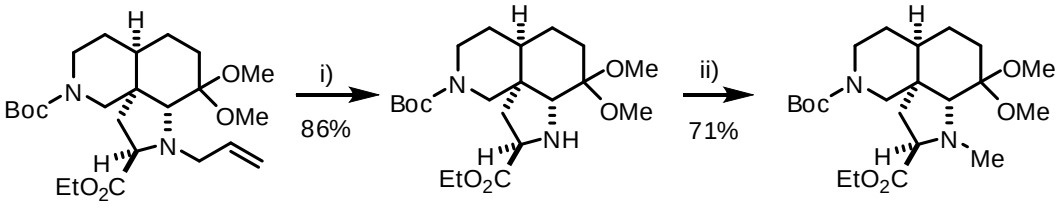
In contrast, the condensation of the aldehyde **112** with glycine ethyl ester **115** under heating in a sealed tube afforded cycloadduct **116** with an *endo* ester group. However, when aldehyde **112** was condensed with *N*-allylglycine ethyl ester it produced a separable mixture of the two isomers **117** and **118**, with the desired stereoisomer **117** as the major product. Confirmation of the relative stereochemistry of the cycloadduct **117** was obtained by comparison (by NMR spectroscopy) with **109** which an X-ray crystal structure had been obtained (Scheme 1-28).



Reagents and conditions: i) PhMe, 130 °C; ii) $EtO_2CCH_2NHCH_2CH{=}CH_2$, PhMe, reflux.

Scheme 1-28

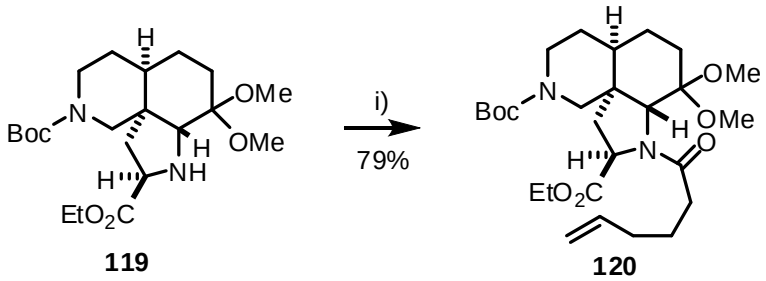
De-allylation of compound **117** with palladium (0) gave the tricyclic product **119**, which was a different diastereomer from cycloadduct **116**. The reaction between compound **119** and methyl iodide provided the cycloadduct **114** (Scheme 1-29). This demonstrated that the major stereoisomer in the key cycloaddition reaction with *N*-allylglycine ethyl ester was compound **117**.



Reagents and conditions: i) $Pd(dba)_2$, dppb, thiosalicyclic acid, THF, rt.; ii) MeI, DMF, K_2CO_3.

Scheme 1-29

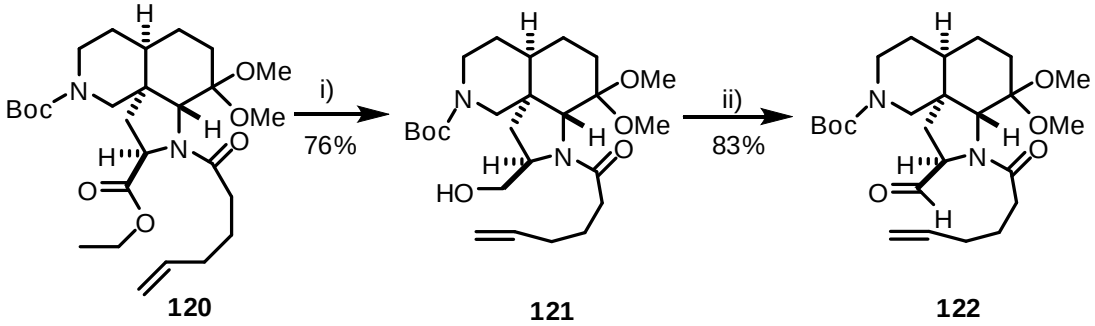
In fact, the *N*-unsubstituted pyrrolidine compound **119** opens the way towards the generation of the ABCE ring system of manzamine A. Indeed this was investigated by the Coldham group[42] in an efficient pathway with the correct relative stereochemistry. *N*-Acylation of the tricyclic compound **119** was accomplished under phase-transfer conditions to give the amide **120** in good yield (Scheme 1-30).



Reagents and conditions: i) $ClCO(CH_2)_3CH{=}CH_2$, NaOH, CH_2Cl_2, rt.

Scheme 1-30

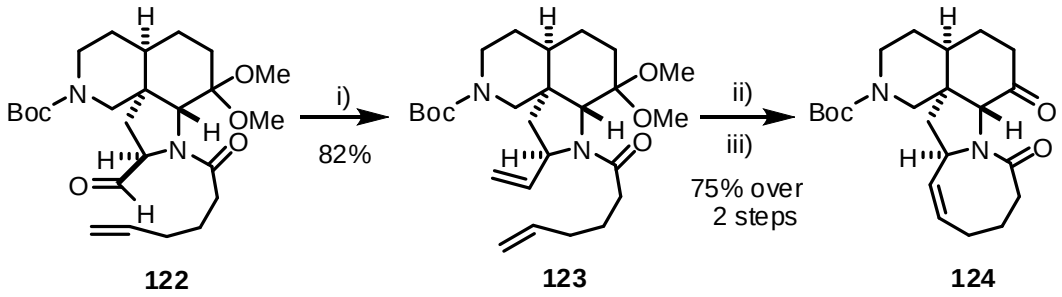
The ester **120** was reduced by $Ca(BH_4)_2$ to produce the alcohol **121**, followed by an oxidation using TPAP to give the aldehyde **122** (Scheme 1-31).



Reagents and conditions: i) $NaBH_4$, $CaCl_2$, EtOH, rt.; ii) TPAP, NMO, CH_2Cl_2, rt.

Scheme 1-31

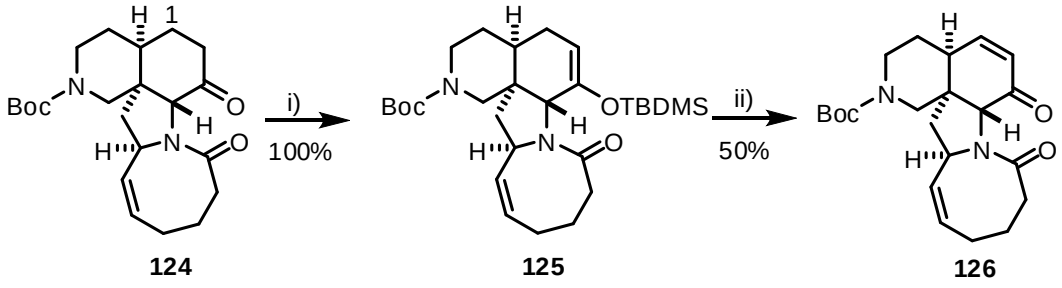
Then the olefination of the aldehyde **122** afforded the alkene **123**, which was reacted with Grubbs` second generation catalyst to achieve a tetracyclic compound. Deprotection of the acetal group under acid conditions gave the ketone **124** in good yield over the two steps of ring closing metathesis and deprotection (Scheme 1-32).



Reagents and conditions: i) $MePPh_3Br$, KHMDS, THF, −78 °C →rt.; ii) Grubbs II (15 mol%), benzene, 60 °C; iii) PPTS, acetone, H_2O, rt.

Scheme 1-32

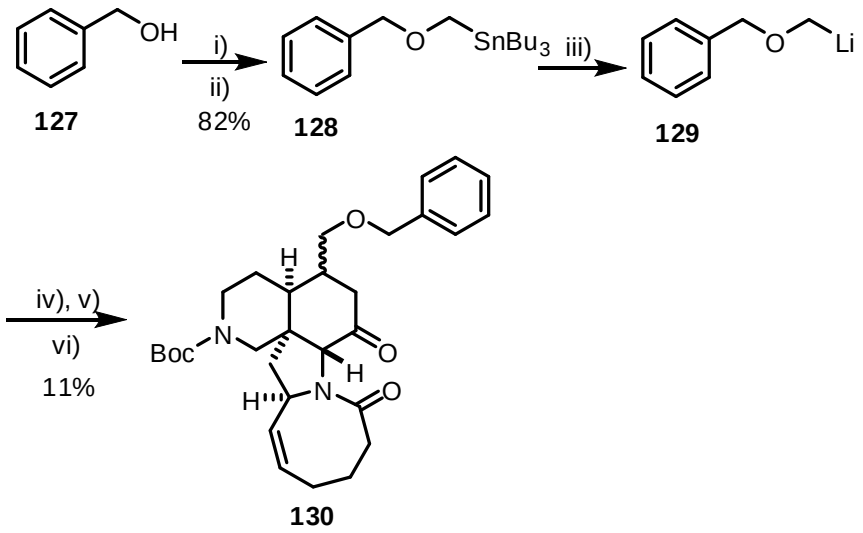
Another target was to introduce a one-carbon unit at the C-1 location to allow the introduction of an aldehyde group which was needed for the *β*-carboline moiety in the synthesis of ircinal A **5** and manzamine A **1**. A 1,4-conjugate addition could be a good method to introduce this one carbon unit. Therefore, the compound **124** was treated with KHMDS and TBDMSCl to obtain compound **125** which was reacted with palladium acetate to give the desired enone **126** (Scheme 1-33).[42]



Reagents and conditions: i) KHMDS, −78 °C, THF, TBDMSCl; ii) $Pd(OAc)_2$ (3 eq.), DMSO, 80 °C.

Scheme 1-33

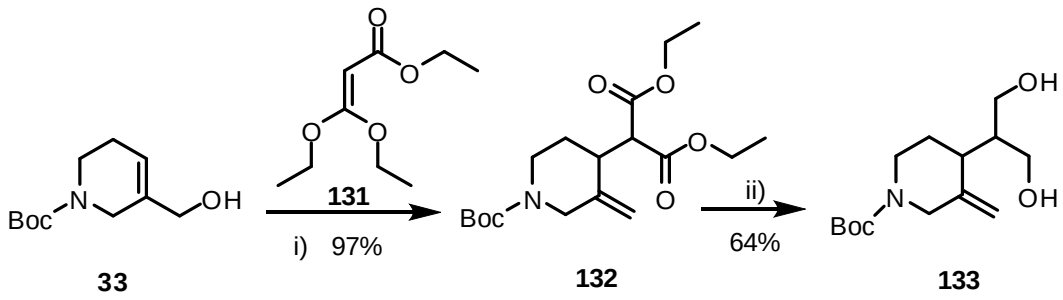
To perform the conjugate addition, organolithium compound **129** was prepared then reacted with enone **126** to give the desired product **130** as a single diastereoisomer but in poor yield (Scheme 1-34).[43]



Reagents and conditions: i) NaH, THF; ii) Bu_3SnCH_2I (10 eq.), DMF; iii) *n*BuLi, THF, −78 °C, 10 min; iv) Cu(I)Br. Me_2S (5 eq.), $^{i}Pr_2S$, ^{i}PrMgCl, THF, −78 °C, 15 min; v) TMSCl; vi) enone (**126)** (1 eq.), THF, −78 °C, 1 h, then − 40 °C, 1 h, then 0 °C, 10 min.

Scheme 1-34

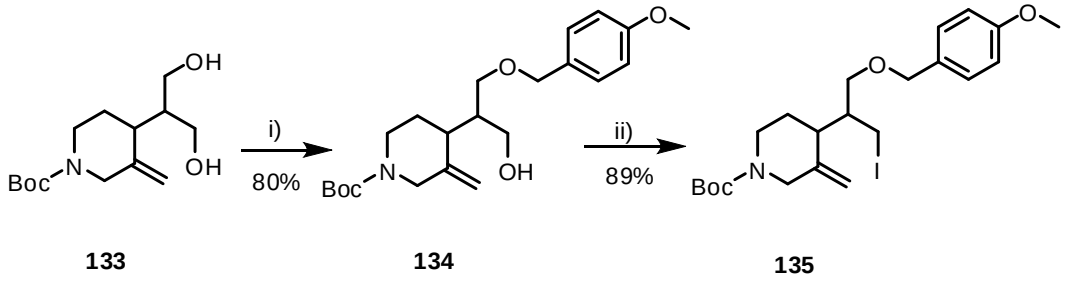
As a result of the low yield in this route, it was decided to synthesise the aldehyde required for the key cycloaddition reaction with an extra one carbon unit, which would avoid the conjugate addition problems. Allylic alcohol **33** was treated with diethoxy acrylate (**131**) in xylene using a Dean-Stark apparatus for 18 h to produce diester **132** in 66% yield. Optimisation improved the yield to 97%, by using toluene as a solvent without the use of Dean-Stark apparatus and decreasing the reaction time to 90 min. The diester **132** was reduced to the diol **133** using $LiAlH_4$ in 64% yield (Scheme 1-35).



Reagents and conditions: i) Acrylate (**131**) (2 eq.), 2,4-dinitrophenol (0.1 eq.), PhMe, 90 min, heat; ii) $LiAlH_4$ (1.0 M solution in THF, 2 eq.), THF, 0 °C, 1 h.

Scheme 1-35

The diol **133** was reacted with 4-methoxybenzyl chloride to obtain alcohol **134** as an inseparable mixture (1:1) of diastereoisomers. Conversion of the alcohol **134** to the iodide **135** was achieved in good yield (Scheme 1-36).

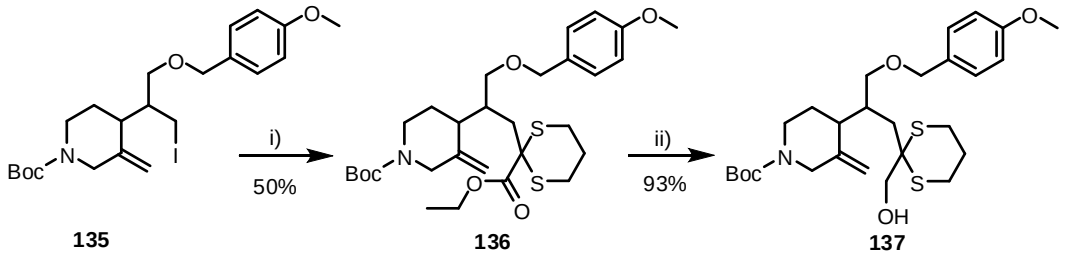


133 **134** **135**

Reagents and conditions: i) NaH (1 eq.), diol (**133**) (1 eq.) THF, 0 °C, 50 min then 4-methoxybenzyl chloride (1.1 eq.), TBAI (1 eq.), THF, 0 °C→rt., 3 d; ii) PPh_3 (1.1 eq.), imidazole (1.1 eq.), I_2 (1.1 eq), CH_2Cl_2, rt., 5 min then alcohol (**134**) (1 eq.), CH_2Cl_2, 5 min.

Scheme 1-36

Treatment of the iodide **135** with the anion of ethyl 1,3-dithiane-2-carboxylate afforded the ester **136** in 50% yield. The dithiane ester **136** was treated with $LiAlH_4$ to provide the alcohol **137** in excellent yield (Scheme 1-37).

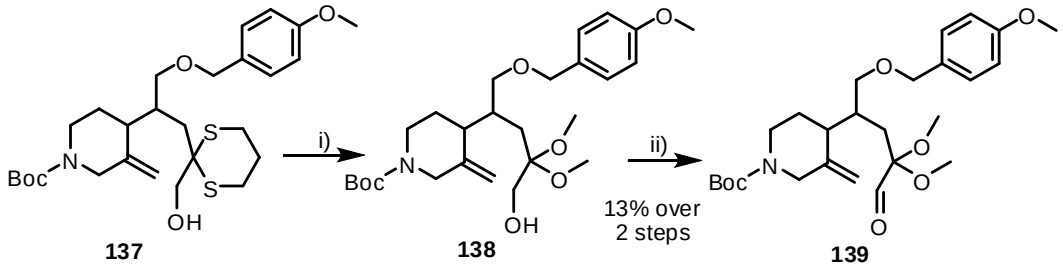


135 **136** **137**

Reagents and conditions: i) *n*BuLi (1.3 eq.), HMPA (4.5 eq.), ethyl 1,3-dithiane-2-carboxylate (1.3 eq.), THF, −78 ° C, 1.5 h, then iodide (1 eq.), THF, −78 °C→rt., 3 d; ii) $LiAlH_4$ (1.1 eq.), THF, 0 °C, 40 min.

Scheme 1-37

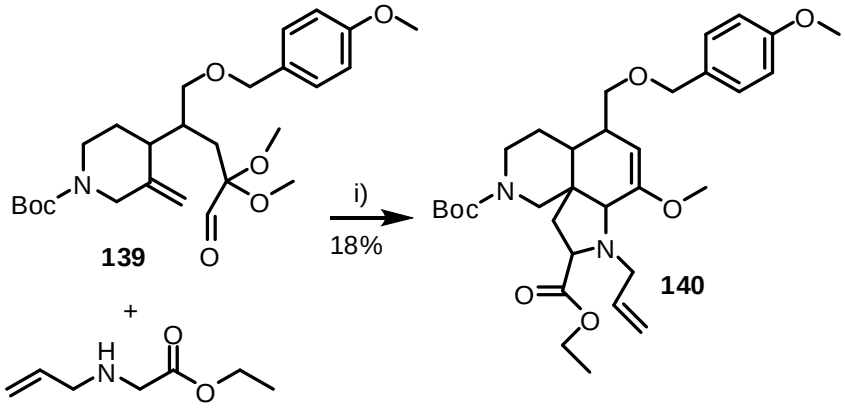
Transacetalation of compound **137** gave the dimethyl acetal **138**, which was followed by oxidation to obtain aldehyde **139** in poor yield over two steps (Scheme 1-38).



Reagents and conditions: i) $AgNO_3$ (4.5 eq.), 2, 4, 6-collidine (8 eq.), NCS (4 eq.), MeOH :THF (1:1), 0 °C, 1 h; ii) TPAP (5 mol%), NMO (1.5 eq.), CH_2Cl_2, 4 Å MS, 2 h.

Scheme 1-38

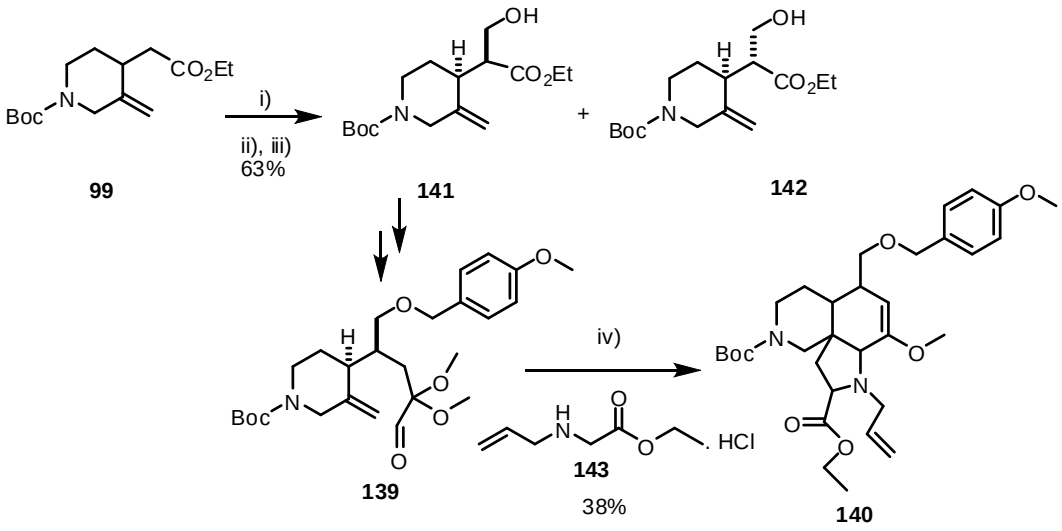
The ABC tricyclic core of manzamine A was achieved by treating aldehyde **139** (as a mixture of diastereomers) with *N*-allylglycine ethyl ester to furnish the cycloadduct **140** in 18% yield (Scheme 1-39).



Reagents and conditions: i) *N*-allyl glycine ethyl ester (4 eq.), aldehyde **139** (1eq.), PhMe, reflux, 2 d.

Scheme 1-39

This result suggests that only one diastereomer of **139** undergoes cycloaddition. It was found that, when the ester **99** was treated with base, followed by alkylation using paraformaldehyde as the electrophile, the alcohols **141** and **142** were formed as a separable (1:1) mixture of diastereoisomers (Scheme 1-40). The isomer **141** (determined by an X-ray crystal structure of a derivative of the isomer **142**) has been converted to compound **140** in 38% yield (stereochemistry undetermined) from compound **139** (Scheme 1-40).[44-45]



Reagents and conditions: i) *n*BuLi (1.2 eq.), $^{i}Pr_2NH$ (1.3 eq.), THF, 0 °C, 30 min; ii) −78 °C, 3.5 h; iii) CH_2O (3 eq.), −78 °C→rt.; **143** (2 eq.), $^{i}Pr_2NEt$ (2 eq.), toluene, reflux, 2 d.

Scheme 1-40

1.7 Aims

The main aim of this project was to investigate a stereoselective approach to the alcohol **144** using a modified strategy to achieve an asymmetric synthesis of manzamine A (Figure 1-11). The plan is to apply the same initial strategy used in the Coldham group for the preparation of diol **133** (Scheme 1-35).[44,46-47] To distinguish between the two alcohol groups, enzymatic resolution could potentially be used.

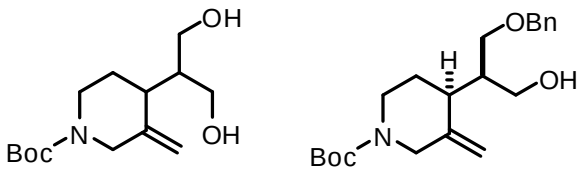
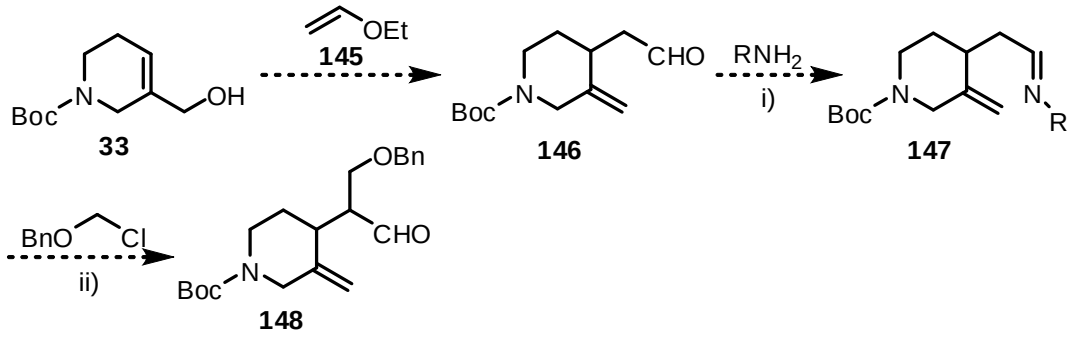


Figure 1-11

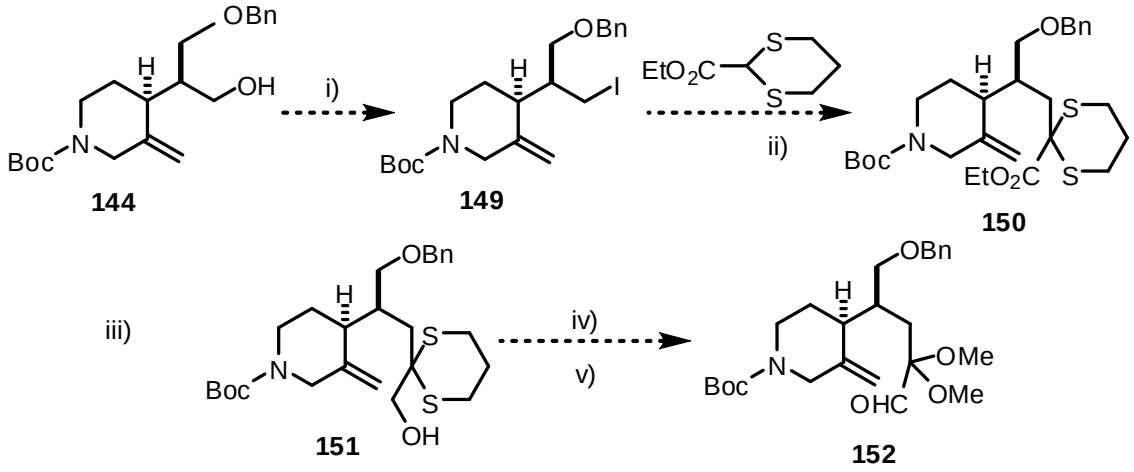
Alcohol **33** with ethyl vinyl ether (**145**) is known to give aldehyde **146**.[41] This rearrangement could be investigated using a chiral catalyst. Imine formation, alkylation and hydrolysis would then give aldehyde **148** (Scheme 1-41).



Reagents and conditions: i) RNH_2= $^tBuNH_2$ or SAMP/RAMP; ii) LDA, $BnOCH_2Cl$ then H_3O^+.

Scheme 1-41

Alcohol **144** could be converted to iodide **149**, which could then be transformed to aldehyde **152** which is required for the azomethine ylide cycloaddition step based on previous work in the group (Scheme 1-42).



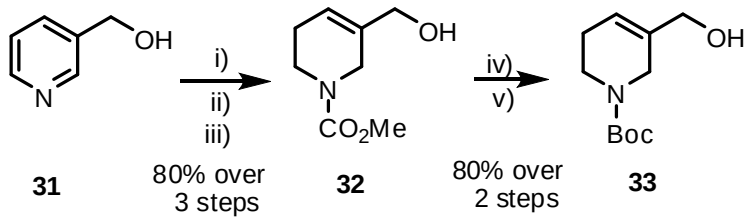
Reagents and conditions: i) I_2, PPh_3; ii) *n*BuLi; iii) $LiAlH_4$; iv) NCS, $AgNO_3$, MeOH; v) Swern oxidation.

Scheme 1-42

2 Results and Discussion

2.1 Claisen Rearrangement Strategy

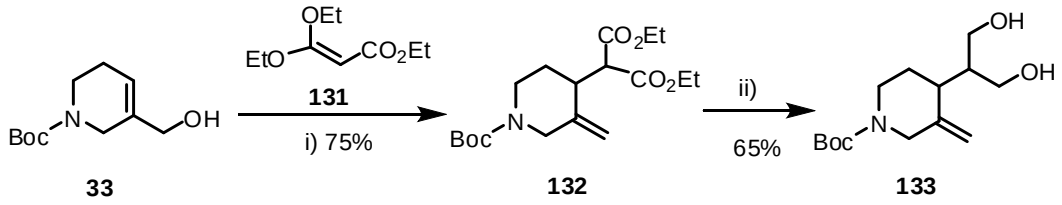
The first step was carried out using the same strategy as published by Winkler,[20] and as utilised by Dobson and Pathak in the Coldham group[48] for the preparation of the allylic alcohol **33** from commercially available 3-hydroxymethylpyridine (**31**) (Scheme 2-1).



Reagents and conditions: i) BnBr; ii) $NaBH_4$; iii) MeOCOCl; iv) KOH, MeOH:H_2O; v) Boc_2O.

Scheme 2-1

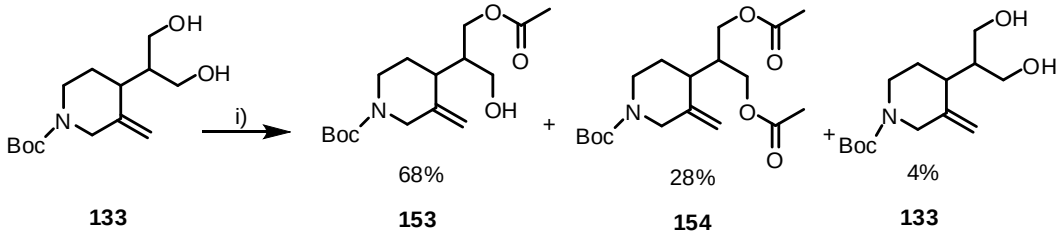
Claisen rearrangement[49] of alcohol **33** using diethoxyacrylate **131** at 110 °C furnished diester **132** in good yield (75%). Subsequent reduction of the diester **132** using $LiAlH_4$ gave the diol **133** in good yield (65%) (Scheme 2-2).



Reagents and conditions: i) 2,4-dinitrophenol, PhMe, 110 °C; ii) $LiAlH_4$, THF, 0 °C, 1 h.

Scheme 2-2

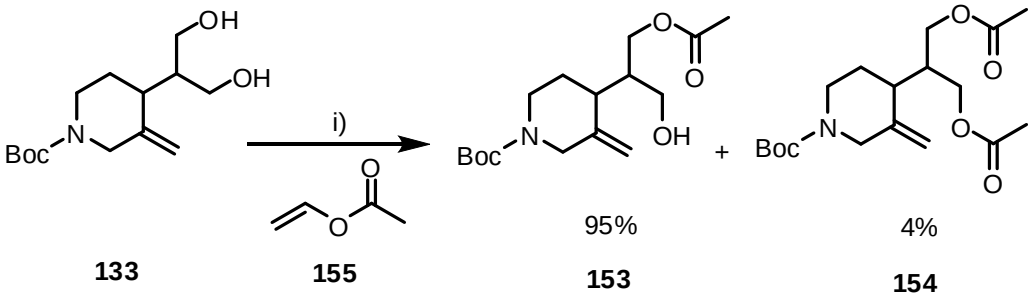
To distinguish between the two alcohol groups,[50] acetylation of the diol **133** using acetic anhydride in CH_2Cl_2 afforded the monoacetate **153** (68%). In addition, the diacetate **154** (28%) and a small amount of unprotected diol **133** (4%) were obtained (Scheme 2-3).



Reagents and conditions: i) Ac_2O, Py, DMAP, CH_2Cl_2, rt., 24 h.

Scheme 2-3

Biocatalysis was considered to achieve high levels of diastereo- and enantioselectivity. Lipase enzymes have proved to be one of the most effective classes of biological catalysts.[51] Treatment of the diol **133** with vinyl acetate and lipase PPL led to the formation of the monoacetate **153** in 95% yield along with a trace amount of diacetate **154** (Scheme 2-4).

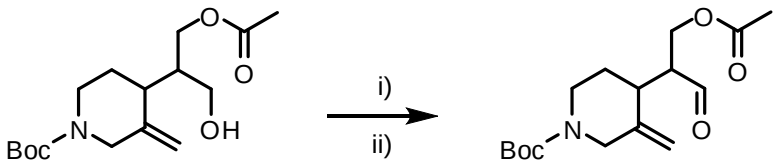


Reagents and conditions: i) PPL, rt., 24 h.

Scheme 2-4

Unfortunately, separation of the mixture of the diastereoisomers by chiral stationary phase (CSP) GC analysis was not possible.

Another attempt to resolve the diastereoisomers was by oxidising the alcohol **153** using Swern oxidation to afford the aldehyde **156** in a poor yield 29% (Scheme 2-5). However, CSP-GC analysis of the mixture of the diastereoisomers gave a single peak.



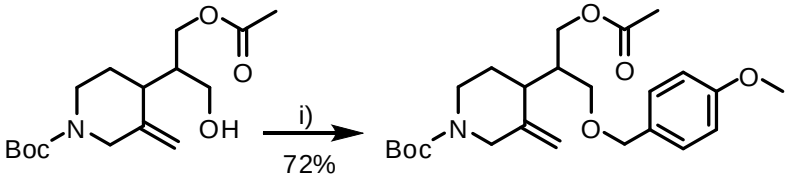
153
racemic mixture of diastereoisomers

156

Reagents and conditions: i) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C; ii) Et_3N, –78 °C→rt., 1.5 h.

Scheme 2-5

Protection of the alcohol **153** using a *para*-methoxybenzyl group could offer a good solution for the separation of the mixture of diastereoisomers by HPLC. The desired protected alcohol **157** was prepared in good yield (72%) by treating the alcohol **153** with 4-methoxybenzyl alcohol in diethyl ether (Scheme 2-6). All attempts (using a range of HPLC columns or GC) to achieve a good separation of the diastereomers of acetate **157** were unsuccessful.



153 **157**

Reagents and conditions: i) NaH , Et_2O, rt., then 4-methoxybenzyl chloride, 0 °C, Cl_3CCN, CH_2Cl_2, then **153**, CSA, 18h.

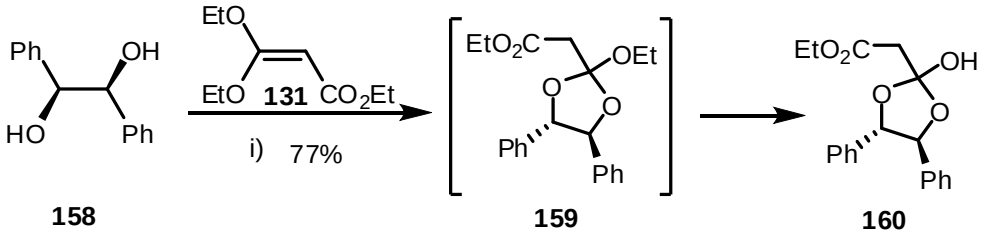
Scheme 2-6

Although it may be possible to separate the diastereoisomers by another method, it was decided to investigate alternative chemistry.

Cyclic ortho ester route

An attempt to solve the problem of separating the diastereomers was by the use of enantioenriched diol (**158**) and acrylate (**131**) to prepare cyclic ortho ester **159**. This may then be used in a Claisen rearrangement with allylic alcohol **33** and could afford separable diastereoisomers.[52] Commercially available (*R*,*R*)-(+)-hydrobenzoin (**158**) was reacted with ethyl 3,3-diethoxyacrylate (**131**) *via* a Michael addition reaction in CH_2Cl_2 at 30 ^oC to afford hydroxy acetal **160** in 77% yield. Changing the reaction conditions by using different temperatures (20 ^oC, 35 ^oC, 40 ^oC) and different solvents

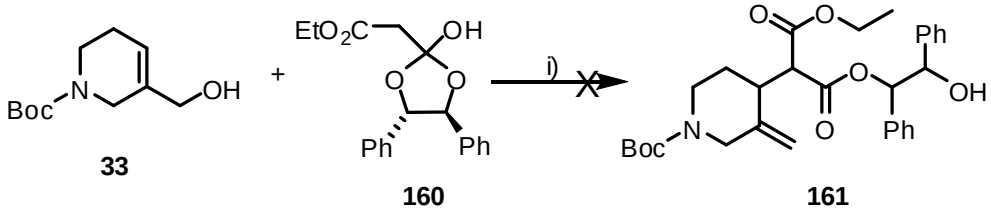
such as toluene and CH_2Cl_2 gave the same product. However, the source of the water was unclear (Scheme 2-7).



Reagents and conditions: i) CSA (0.5 eq.), CH_2Cl_2, 40 °C, 24 h.

Scheme 2-7

The ethoxy acetal **159** is an unstable compound and is rapidly transformed to alcohol **160** which was observed by analysis of the ^{1}H NMR spectroscopic data of the crude reaction material, as only one set of ethyl proton peaks for the ester were observed. IR spectroscopy also indicated the presence of an OH peak at 3430 cm^{-1}. Although the desired ethoxyacetal **159** was not formed, the alcohol **160** was utilised as a substrate in the Claisen rearrangement with allylic alcohol **33** and 2,4-dinitrophenol in toluene. However, the reaction failed to give the desired product. Consumption of the starting material **160** was not observed after 2 d by TLC and the crude ^{1}H NMR spectrum was not clear.



Reagents and conditions: i) 2,4-dinitrophenol, PhMe, 110 °C, 2 d.

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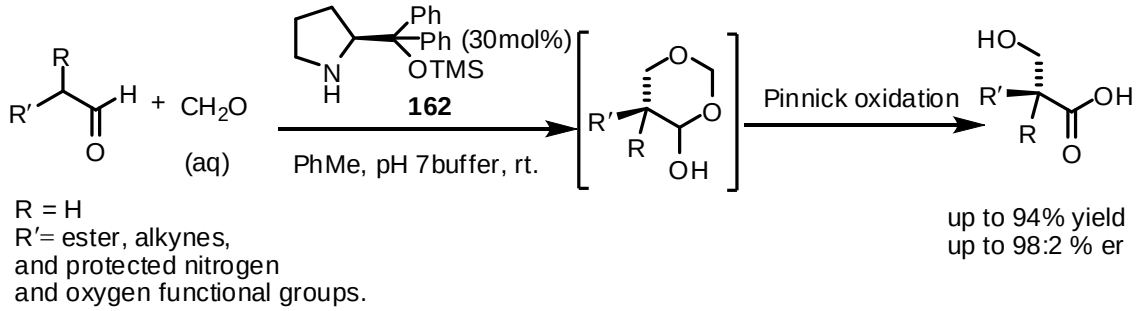
Scheme 2-8

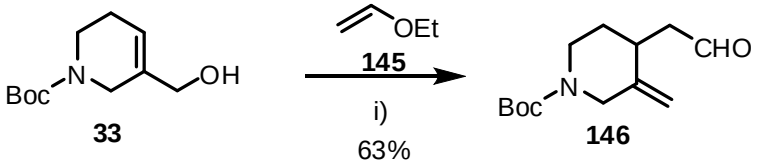
Carboxylic acid route

In the literature it was reported that the enantioselective hydroxymethylation of aldehydes using *α,α*-diphenyl prolinol trimethylsilyl ether **162** as an organocatalyst affords carboxylic acids in very good yields and excellent enantioselectivities (Scheme 2-9).[53]



Scheme 2-9

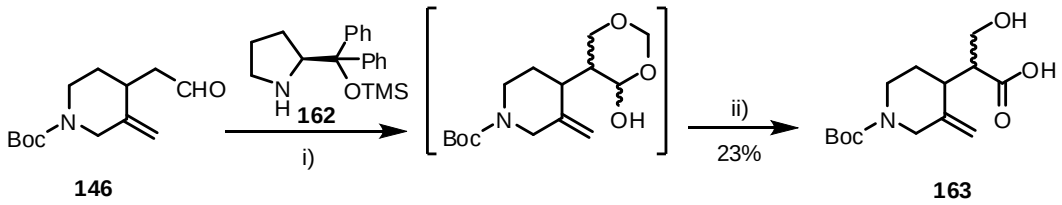
This route may be used to give the required substrate with the desired stereochemistry. Firstly, alcohol **33** was heated with freshly distilled ethyl vinyl ether (**145**) and $Hg(OAc)_2$ in a sealed tube at 135 ^oC for 5 d to afford the desired aldehyde **146** in 63% yield (Scheme 2-10).[41]



Reagents and conditions: i) $Hg(OAc)_2$ (0.1 eq.), xylene, 135 ^oC , 5 d.

Scheme 2-10

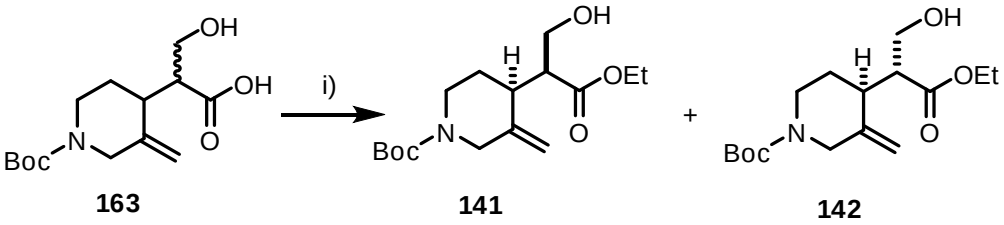
Next, the aldehyde **146** was added to a solution of the catalyst **162** (0.3 eq.) and aqueous formaldehyde solution (37% aq.) in toluene and stirred together at room temperature for 15 h. The isolated organic layer was dissolved in *t*-butanol and 2-methyl-2-butene and this was added to a solution of $NaClO_2$ and $NaH_2PO_4.H_2O$ in H_2O at room temperature for 24 h. This produced the desired acid **163** in a poor yield (Scheme 2-11). IR spectroscopy clearly showed a broad absorption at 3222 cm^{-1}.



Reagents and conditions: i) **162** (0.3 eq.), pH 7 buffer, CH_2O, PhMe, rt., 15 h; ii) *t*BuOH, 2-methyl-2-butene, $NaH_2PO_4.H_2O$, $NaClO_2$, 24 h.

Scheme 2-11

Carboxylic acid **163** was converted to ester[54] **141, 142** to allow the diastereomeric ratio to be measured. The carboxylic acid **163** was dissolved in DMF then treated with K_2CO_3 and EtI at 0 ^oC. The reaction mixture was stirred overnight to give the esters **141** and **142** as a separable mixture of diastereoisomers (1:1) in a good yield (Scheme 2-12). However, attempts to resolve the mixture of diastereoisomers of the racemic compound into four separable peaks using CSP-GC were unsuccessful. Therefore we were unable to determine the enantiomeric ratio of either diastereomer of the esters **141** or **142** (and hence the acid **163**). Due to the low yields in this sequence, we decided to explore an alternative approach.



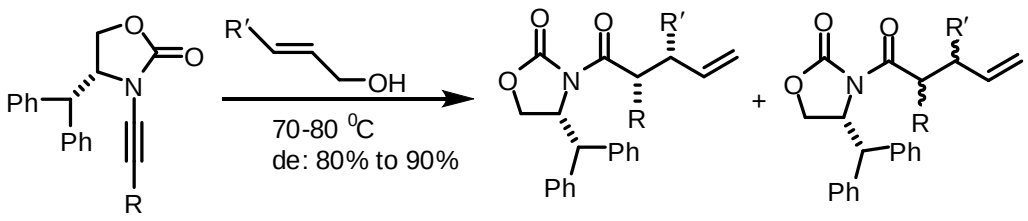
163 **141** **142**

Reagents and conditions: i) EtI, K_2CO_3, DMF, 0 ^oC, 24 h, 51% one diastereoisomer, 49% other diastereoisomer.

Scheme 2-12

Ficini-Claisen rearrangement

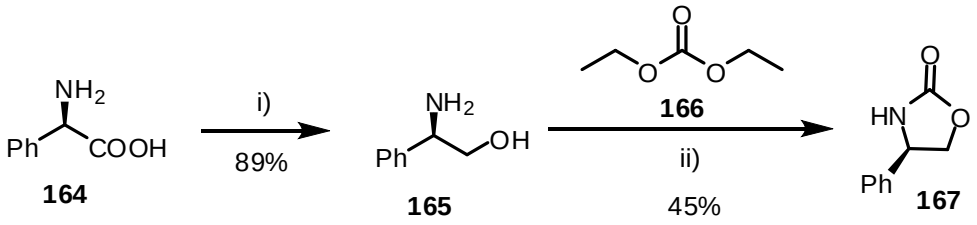
An alternative approach which was examined was an asymmetric Ficini-Claisen rearrangement using chiral ynamides. Ficini-Claisen rearrangements can be efficiently promoted by *p*-nitrobenzene sulfonic acid leading to high levels of diastereoselectivity using different allylic alcohols and chiral ynamides (Scheme 2-13).[55]



Scheme 2-13

To synthesise the ynamide, commercially available phenyl glycine (**164**) was reduced to phenyl glycinol **165** using $NaBH_4$ in the presence of iodine to furnish desired product **165** in an excellent yield (89%).[56,57,58] Next, reaction of diethyl carbonate (**166**) with

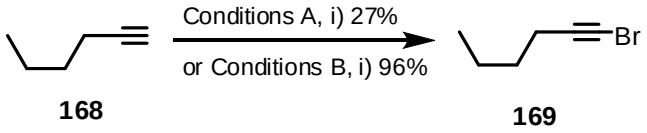
phenyl glycinol **165** at 125 °C produced the oxazolidin-2-one **167** in moderate yield (45%) (Scheme 2-14).[59]



Reagents and conditions: i) $NaBH_4$, I_2, THF, reflux, 24 h; ii) K_2CO_3, 125 °C, 3 h.

Scheme 2-14

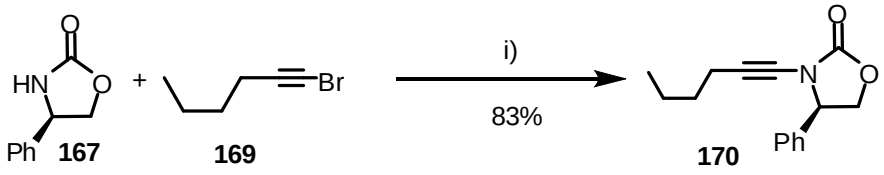
The synthesis of the second fragment[60] to make the ynamide was carried out *via* the bromination of 1-hexyne **168** using NBS to give the bromoalkyne **169** but in poor yield (27%). The poor yield and purification difficulties led to the use of bromine as the brominating agent.[61] After deprotonation of the alkyne **168** with *n*BuLi, bromine was added dropwise to give desired bromoalkyne **169** in excellent yield (96%) (Scheme 2-15).



Reagents and conditions: A. i) NBS, $AgNO_3$, acetone, 90 min; or B. i) *n*BuLi, Br_2, THF, –78 °C.

Scheme 2-15

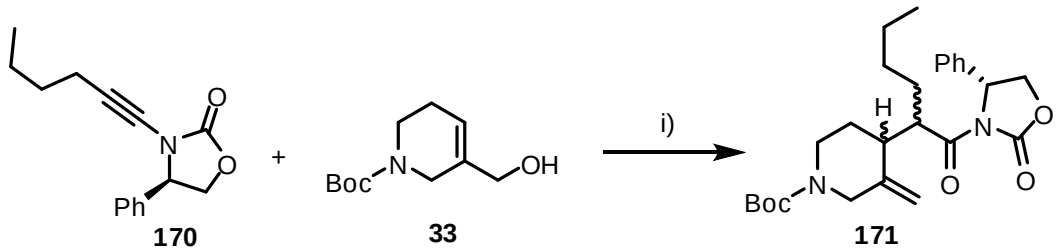
The reaction[62] of oxazolidinone **167** with bromoalkyne **169** was carried out in toluene and catalysed by phenanthroline-$CuSO_4$ (0.2 eq.–0.1 eq.). Complete consumption of starting material was observed after 2 days by TLC. After a work up, column chromatography purification afforded the ynamide **170** in good yield (Scheme 2-16).



Reagents and conditions: i) $CuSO_4.5H_2O$ (0.2 eq.), 1,10-phenanthroline (0.1 eq.), K_2CO_3, PhMe, 75 °C , 2 d.

Scheme 2-16

Next, the ynamide **170**, camphorsulfonic acid and allylic alcohol **33** were heated in toluene in a sealed tube at 160 °C for 2 d. Conversion of all of the starting material was not observed by TLC (Scheme 2-17 and Table 2.1, entry 1). However, the ^{1}H NMR spectrum showed the alkene peaks at 4.52 and 4.39 ppm and a single peak at 1.43 ppm which corresponds to the Boc group (Scheme 2-17). However, it was not possible to separate the product from the starting materials.



Reagents and conditions: i) CSA, PhMe, 160 °C.

Scheme 2-17

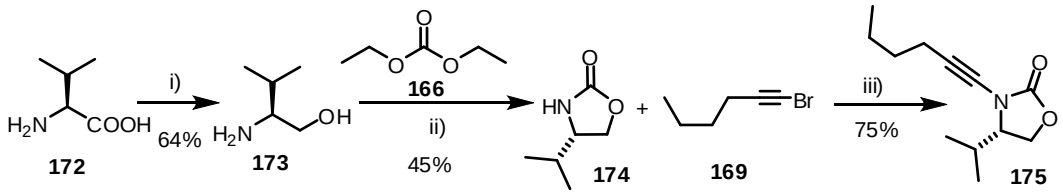
The same reaction was also carried out in a microwave reactor (160 °C, 3 bar, 8 h) which gave similar results. Optimisation of the reaction using different solvents such as chlorobenzene and a different acid (K_{10}) were unsuccessful (Table 2.1, entries 2-4).

Table 2-1[a]

Entry	Solvent	Catalyst	Yield of **171**[b]
1	PhMe	CSA (0.1 eq.)	40% with SM
2	PhMe	K_{10} (0.01 g)	Boc deprotection
3	PhMe	K_{10} (0.005g)	Boc deprotection
4	Chlorobenzene	CSA (0.1 eq.)	40% with SM

[a] The reactions were carried out in a microwave (160 °C, 3 bar, 8h). [b] Yield based on isolated yields after column chromatography.

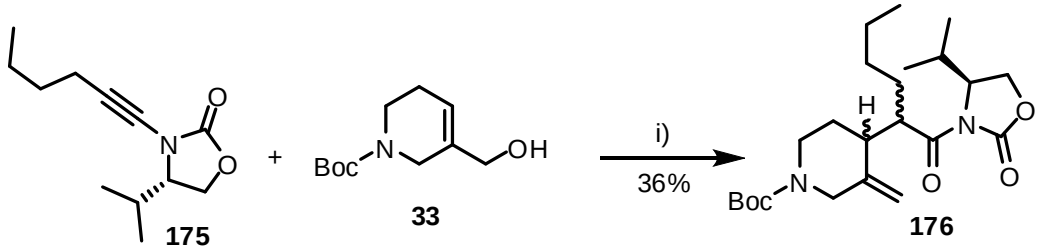
It was suggested that switching to a different oxazolidinone may solve the problem. The oxazolidinone **174** was also made using a similar protocol to the one used earlier (Scheme 2-18).



Reagents and conditions: i) $NaBH_4$, I_2, THF, reflux, 24 h; ii) K_2CO_3, 125 ^oC, 3 h; iii) $CuSO_4.5H_2O$ (0.2 eq.), 1,10-phenanthroline (0.1 eq.), K_2CO_3, PhMe, 75 °C , 2 d.

Scheme 2-18

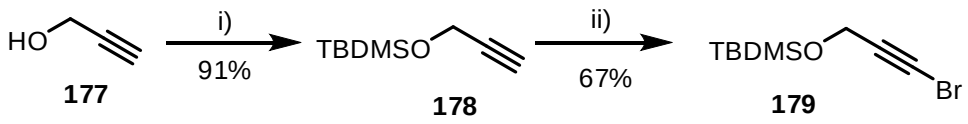
The Claisen rearrangement of ynamide **175** with allylic alcohol **33** was performed under similar conditions to before and gave the desired product **176** in poor yield (Scheme 2-19). Analysis of the ^1H NMR spectrum of the crude reaction material showed the alkene peaks at 4.85 and 4.75 ppm. Two diastereoisomers (3:1) were formed (out of a possible four in total), as judged by ^1H NMR spectroscopy, which were inseparable by column chromatography.



Reagents and conditions: i) CSA (0.1 eq.), PhMe, 160 °C, 2 d.

Scheme 2-19

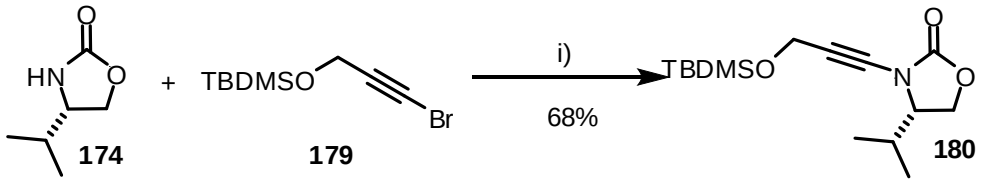
This rearrangement method was therefore showing some promise but also some issues. We decided to investigate the actual ynamide needed for our synthesis (rather than the model with a butyl group). The propargylic alcohol **177** was protected with a TBDMS group before bromination with bromine to afford the desired bromoalkyne **179** in 67% yield (Scheme 2-20).



Reagents and conditions: i)TBDMSOTf, Et_3N, CH_2Cl_2, –78 °C, 1 h; ii) *n*BuLi, Br_2 , THF, –78 °C, 45 min.

Scheme 2-20

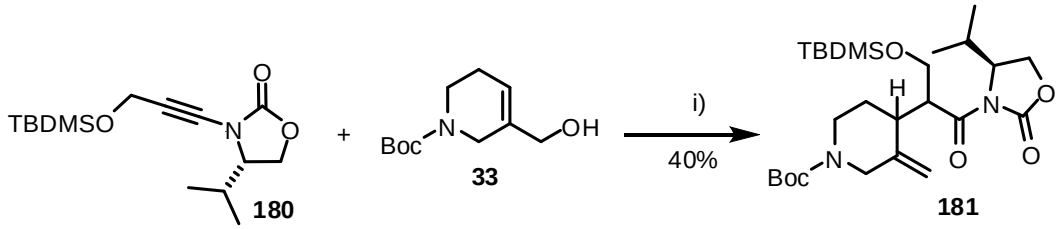
The same procedure as ynamide **175** was applied to prepare the ynamide **180** in 68% yield (Scheme 2-21).



Reagents and conditions: i) $CuSO_4.5H_2O$ (0.2 eq.), 1,10-phenanthroline (0.1 eq.), K_2CO_3, PhMe, 75 °C, 2 d.

Scheme 2-21

Ynamide **180** was used in a Claisen rearrangement to produce the product **181**. Several conditions were investigated using camphorsulfonic acid or *p*-nitrobenzenesulfonic acid catalysts, but the best yield achieved was 40% when using 0.5 eq. of CSA (Scheme 2-22 and Table 2.2, entry 4).



Reagents and conditions: i) CSA (0.5 eq.), PhMe, 160 °C, 2d.

Scheme 2-22

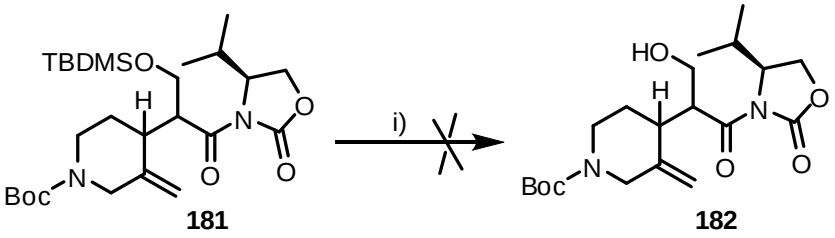
The product was an inseparable mixture of two diastereoisomers that was indicated by two spots on the TLC. The diastereomeric ratio was determined to be 3:1 from the ^{1}H NMR spectrum. The same reaction was carried out in a microwave reactor (160 °C, 6 bar, 4 h) and gave the product **181** in a 40% yield, but in 4 h instead of 2 d.

Table 2-2[a]

Entry	Catalyst	Yield of **181**[b]	dr[c]
1	CSA (0.1)	32% + SM	–
2	CSA (0.2 eq.)	37%	3:1
3	CSA (0.3 eq.)	39%	3:1
4	CSA (0.5 eq.)	40%	3:1
5	CSA (0.6 eq.)	Boc deprotection	–
6	*p*-NBSA (0.1 eq.)	36% + SM	–
7	*p*-NBSA (0.2 eq.)	39%	3:1
8	*p*-NBSA (0.3 eq.)	Boc deprotection	–

[a] The reactions were carried out in a microwave (160 °C, 6 bar, 4h). [b] Yield based on isolated yields after column chromatography. [c] Diastereomeric ratio determined by ^{1}H NMR.

It was hoped that removal of the TBDMS group from compound **181** would provide a compound that would allow the isomers to be separated. The deprotection reaction was performed using the standard protocol (TBAF, THF, rt., 6 h), but resulted in a complex ^{1}H NMR spectrum and no starting material was observed (Scheme 2-23).



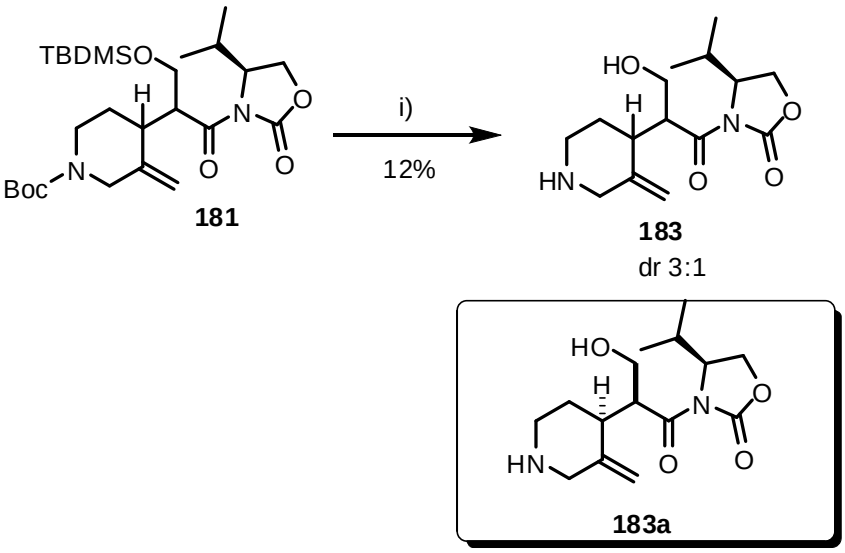
181 **182**

Reagents and conditions: i) TBAF, THF, rt., 6 h.

Scheme 2-23

Then, trifluoroacetic acid (TFA) was used instead of TBAF to remove the *N*-Boc protecting group.[63] TFA was added to a solution of the compound **181** in CH_2Cl_2 at room temperature. Analysis of the ^{1}H NMR spectrum of the crude reaction material showed the appearance of a hydroxy group signal at 3.93 ppm, and the Boc group signal disappeared. After flash column chromatography the deprotected product **183** was obtained in a poor yield (12%). From GC analysis, the ratio of the diastereoisomers was

found to be 3:1 (Scheme 2-24). The identity of the two isomers of **183** is unclear. However, from comparison with related reactions,[55] it is anticipated that the major diastereomer is compound **183a**.



Reagents and conditions:i) TFA, CH_2Cl_2, rt., 2 h.

Scheme 2-24

2.2 Conclusion

In conclusion, different methods were examined to obtain the substrate needed to perform the asymmetric synthesis of manzamine A. A Claisen rearrangement strategy gave the diol **133**, and to distinguish between the two alcohol groups, enzymatic resolution was utilised, although unfortunately, separation of the mixture of the diastereoisomers was not possible. The enantioselective hydroxymethylation of an aldehyde in the presence of a chiral catalyst was also investigated, but due to the low yields in this sequence, an alternative approach was explored. An asymmetric Ficini-Claisen rearrangement using chiral ynamides gave mediocre yields and poor selectivities. However, the difficulties in separating the isomers combined with mediocre yields and poor selectivities has led to no further work being conducted at present in this area.

3 Nitrile Chemistry

3.1 Nitriles in Nature and Pharmaceuticals

Nitriles are important building blocks in several natural products and include an interesting and diverse set of secondary metabolites. The structures vary from simple, long-chain alkylnitriles to more complex motifs such as the calyculins, with new, more complex structures being continually discovered. The number of nitrile containing natural products has risen from 33, in a 1981 review,[64-66] to more than 120 (excluding cyanogenic glycosides).[65-67] Nitrile-containing natural products are known to be derived from amino acids in plants,[68] arthropods,[69] bacteria and fungi (Figure 3-1).[67]

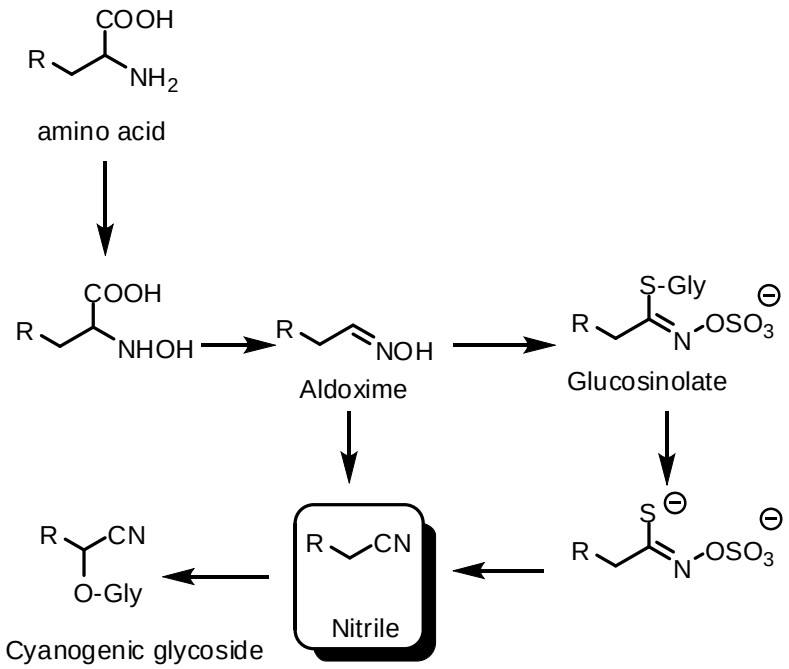
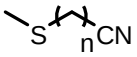


Figure 3-1

The increasing number of nitrile-containing natural products led to the need for a general classification of these compounds which depends on the hybridisation of the nitrile-bearing carbon. They were divided into three general classes; alkanenitriles, α,β-unsaturated nitriles, and aromatic nitriles.

The smallest alkanenitriles are volatile sulfur-containing nitriles that largely occur in *Cruciferae*. The long-chain nitrile 5-methylthiopentanenitrile **184** was isolated during

the hydrolysis of broccoli[70] while the longer chain nitriles **185** and **186** were synthesised and shown to be constituents of the scent of watercress (Figure 3-2).[71]



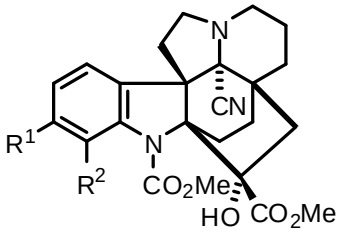
184 n=4

185 n=7

186 n=8

Figure 3-2

A number of α-amino nitriles have been isolated from a variety of sources. The origin of the nitrile group in α-amino nitriles has not been determined, but probably arises by the addition of cellular cyanide to imines.[67] For example**,** lahadinines A **187** and B **188** were obtained from a leaf extract of *Kopsia pauciflora* Hook (Figure 3-3).[72]



187 $R^1 = R^2 = -O-CH_2-O-$

188 $R^1 = R^2 = OMe$

Figure 3-3

β-Amino nitriles are less common than α-amino nitriles with the most common nitriles **189**, **190** and **191**, **192** isolated from *Lathyrus* species (Figure 3-4).[73]

189 R=H

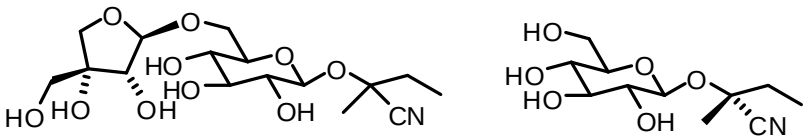
190 R=glutamyl

191 R=H

192 R=glutamyl

Figure 3-4

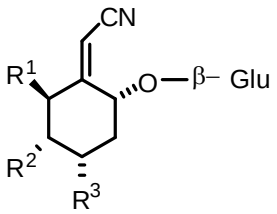
Cyanogenic glycosides are the most common natural nitriles. These nitriles have been isolated extensively from plants (over 1000 species representing more than 100 families),[74] fungi, bacteria and a number of animals,[75] particularly those that feed on cyanogenic plants.[68] For example, a recent investigation of the root cortex of cassava (*Manihot esculenta*) led to the isolation of the glycoside **193**,[76] which is an apiosyl derivative of lotaustralin **194** (Figure 3-5).



193 **194**

Figure 3-5

α,β-Unsaturated nitriles have various structures and different biological profiles. The largest subgroup of α,β-unsaturated nitriles are the nitrilosides that contain a cyanomethylenecyclohexane unit with variable hydroxylations around the ring. Ehretiosides A **195**, A2 **196**, and A3 **197** were isolated from *Ehretia philippinensis* and are good examples which are used in folk medicine in the Philippines (Figure 3-6).[77]



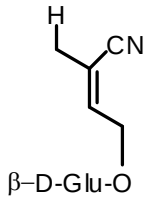
195 R^1=OH, R^2=$(CH_3)_2C=CHCO_2$, R^3=OH

196 R^1=OH, R^2=OH, R^3=$(CH_3)_2C=CHCO_2$

197 R^1=$(CH_3)_2C=CHCO_2$, R^2=OH, R^3=OH

Figure 3-6

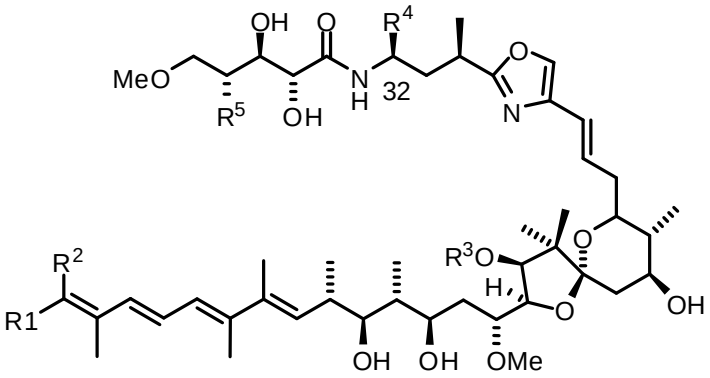
Another subclass of α,β-unsaturated nitriles is methylbutenenitriles. The simplest of the 2-methylbut-2-enenitriles is multifidin **198**, isolated from the latex of *Jatropha multitida*.[78] Multifidin was later isolated from the root of *Rhodiola quadrifida*, a traditional Chinese medicine used as a treatment for burns (Figure 3-7).[79]



198

Figure 3-7

The most biologically powerful unsaturated nitriles are the calyculins[80-82] from the marine sponges *Discodermia calyx* [83] and *Lamellomorpha strongylata*.[84] They are inhibitors of protein phosphatase 1 and 2A[85] and exhibit antitumour activities. Calyculin A **199** (Figure 3-8) has antitumour activity against Ehrlich and P388 leukaemia in mice and has been the focus of several synthetic endeavors.[86-89]



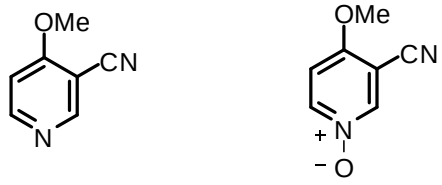
Calyculine A **199**

R^1=H, R^2=CN, R^3=PO_3H_2, R^4=H, R^5=NMe_2.

Figure 3-8

The calyculins have the same basic carbon skeleton with variations in the *E*/*Z*-geometry of the unsaturated nitrile, the C6–C7 olefin, and the presence or absence of methyl substitution at C-32.

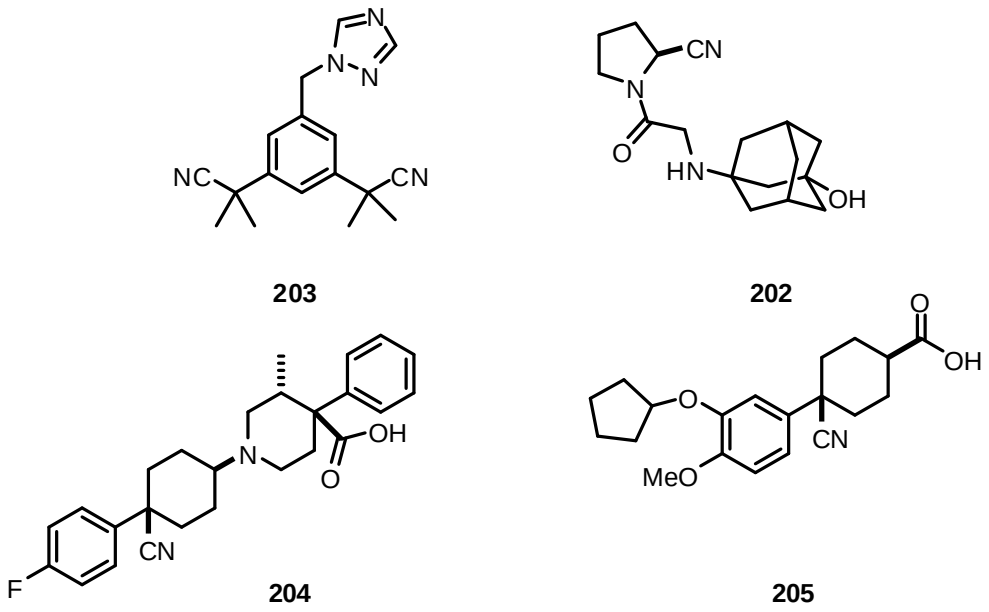
Another class of nitriles are the aromatic nitriles where the nitrile group is connected directly to the aromatic ring; they are relatively less abundant than the other categories. The most common aromatic nitriles are 3-cyano-4-methoxy pyridine **200** from *Hernandia nymphaefolia*,[90] malloapeltine **201** from *Mallotus apelta* (Figure 3-9). [91]



200 **201**

Figure 3-9

Nitriles play pivotal roles in many pharmaceuticals used for the treatment of a range of conditions.[68,92] For example, vildagliptin[93-94] **202** is used as an antidiabetic drug, anastrazole[95-96] **203** is a blockbuster drug used for treating oestrogen-dependent breast cancer, and the H_1-receptor antagonist levocabastine **204** is used for allergic conjunctivitis.[97] In addition, cilomilast **205** was reported as a phosphor diesterase inhibitor and an anti-inflammatory and anti-asthmatic agent[98] (Figure 3-10).



203 **202**

204 **205**

Figure 3-10

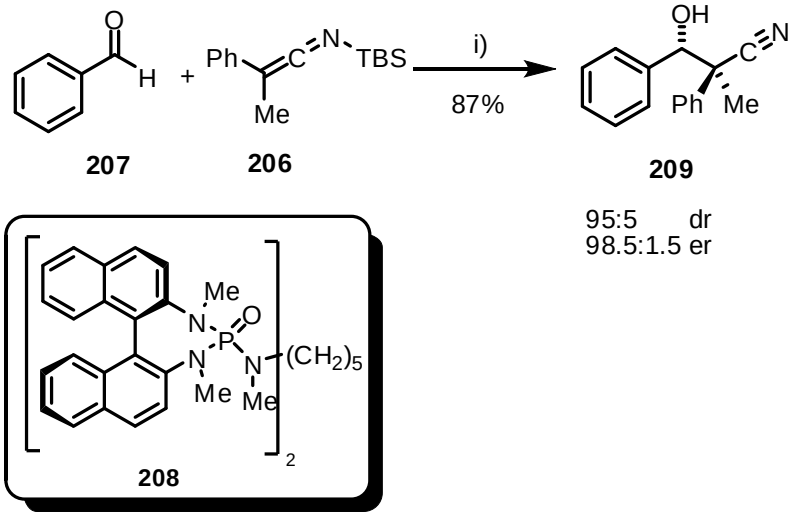
3.2 Nitrile Chemistry:Towards Asymmetric α-Alkylation

Nitriles are very important building blocks and have wide applications in organic synthesis due to their ability to be transformed into many functional groups such as amides, carboxylic acids, ketones, amines and aldehydes *via* relatively simple and well known chemical reactions.[99] In addition, nitriles undergo easy deprotonation of the α-

protons using various bases which can be followed by quenching with different electrophiles.[100] Due to the rich chemistry of the nitrile group, several reactions have been reported to synthesise racemic nitriles.[101-106] On the other hand, synthesis of nitriles in high levels of enantiomeric purity is still a challenging topic in organic chemistry.

3.2.1 Asymmetric Synthesis of α-Substituted Nitriles

The stereoselective synthesis of quaternary carbon centres is a challenging topic in asymmetric synthesis. Quaternary stereogenic centres can be generated through Lewis base catalysed aldol reactions of silyl ketene imines with aromatic aldehydes.[107] Silyl ketene imine **206** was added to benzaldehyde (**207**) using a $SiCl_4$/bisphosphoramide catalyst system **208**, to produce nitrile **209** in good yield with high levels of both diastereo- and enantioselectivity (Scheme 3-1).

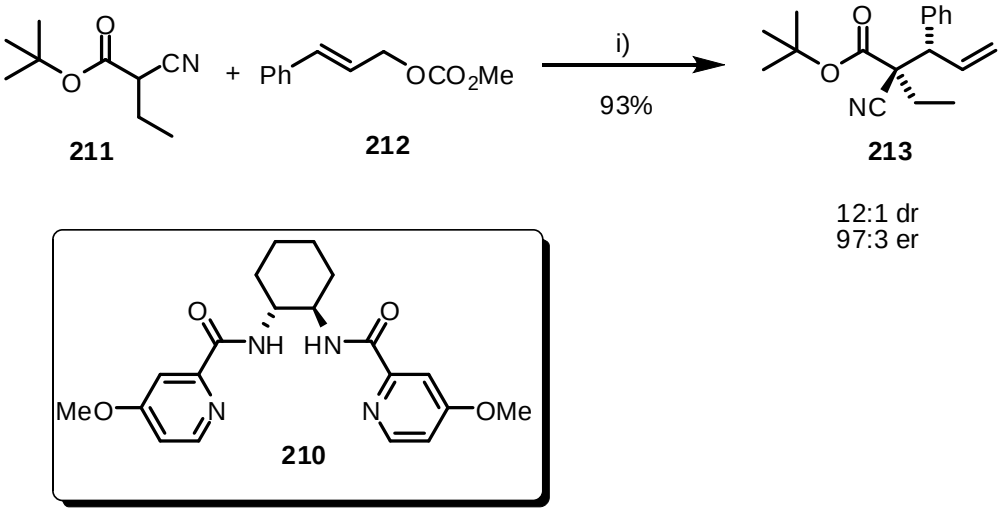


Reagents and conditions: i) $SiCl_4$, **208** (5 mol%), CH_2Cl_2, –78 ºC, 2 h.

Scheme 3-1

Different aryl substituted silyl ketene imines and a wide range of aromatic aldehydes were examined and β-hydroxy nitrile products were isolated in high yields and excellent selectivities.

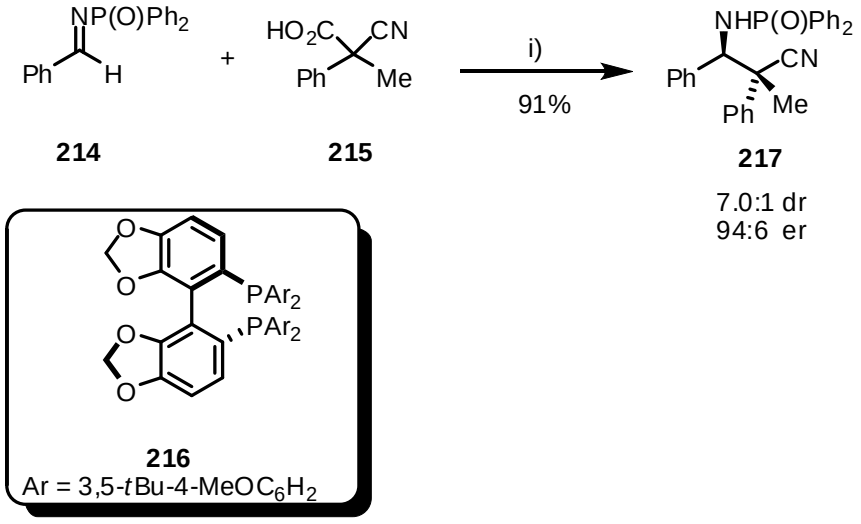
Ligand **210** was used in a molybdenum-catalysed asymmetric allylic alkylation of cyanoester nucleophiles such as **211** and led to the synthesis of functionalised quaternary stereocentres in compound **213** which provides access to amino acids and interesting chiral building blocks (Scheme 3-2).[108]



Reagents and conditions: i) **210 (**15 mol %), $Mo(CO)_6$ (10 mol%), NaH (10 mol%), BSA (2 eq.), THF, 60 ºC. 17 h.

Scheme 3-2

A Cu-catalysed decarboxylative asymmetric Mannich-type reaction was utilised to generate α-quaternary and β-trisubstituted chiral nitrile compounds.[109] The reaction of imine **214** with racemic carboxylic acid **215** was carried out under mild conditions using 10 mol% CuOAc-(*R*)-DTBM-SEGPHOS **216** (the best ligand in terms of diastereo- and enantioselectivity) to give nitrile **217** in 91% yield with high selectivity (Scheme 3-3).



Reagents and conditions: i) **216** (5 mol %), THF, 0 ºC. 12 h.

Scheme 3-3

The reaction exhibits broad substrate scope in both imines and cyanocarboxylic acids. The products were isolated in high yields and high diastereo- and enantioselectivity.[109]

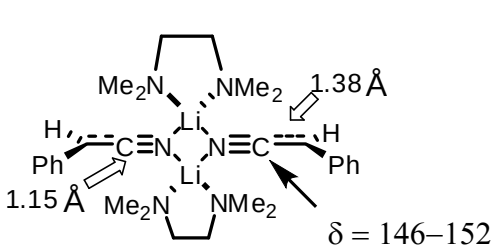
3.2.2 Metallated Nitriles

The former strategy relied on using chiral ligands to obtain high levels of stereo- and enantioselectivity. The asymmetric alkylation of metallated nitriles represents a continuing challenge and there are only a few examples of this chemistry in the literature. Metallated nitriles are powerful nucleophiles and have been used for carbon-carbon bond formation due to the small steric demand of the CN unit. Inductive stabilisation of the anion by the cyano group localises significant charge density on carbon creating a small and electron-rich nucleophile.[110] Metallated nitriles are chemical chameleons whose exact structural identity depends on the nature of the metal, the solvent, the temperature and the structure of the nitrile. In the case of highly electropositive metals such as Li a planar intermediate (e.g. **218**) will be formed because lithium co-ordinates to the nitrogen. While less electropositive metals (Mg, B, Cu, Zn, Pd) co-ordinate to the nucleophilic carbon to form *C*-metallated species **219** (Figure 3-11).[110-111]

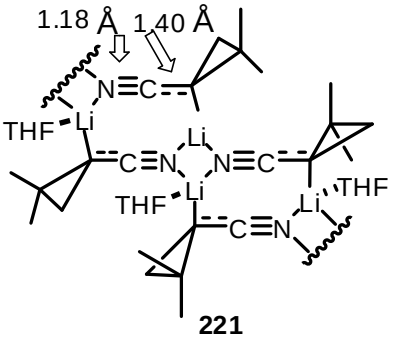
219 **218**

Figure 3-11

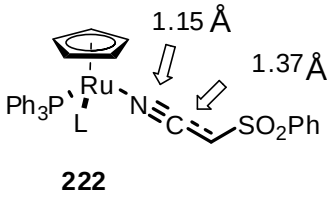
The inductive effect of the CN group was obvious from the X-ray crystal structures of metallated nitriles (Figure 3-12), which showed short C–CN bonds (1.36–1.45 Å, structure **220**) because of electrostatic contraction between the carbanion and the electron deficient nitrile group. The length of CN bond (1.15–1.20 Å, structure **222**) in metallated nitriles is only slightly extended compared with the neutral nitriles (1.14 Å).
In addition, the geometries of the metallated carbons which range from planar in *N*-metallated nitriles **220**[112] to pyramidal in *C*-metallated nitriles **221**[113] and **223** can be seen.[114] Lithiated nitriles showed exclusive tendency to *N*-lithiatiation, but *N*- and *C*-co-ordinated complexes exhibit a fast equilibration between **224** and **225** structures in Et_2O at –100 °C.[115]



220

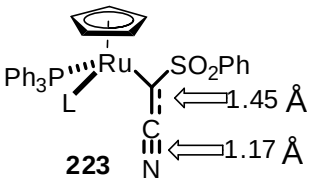


221



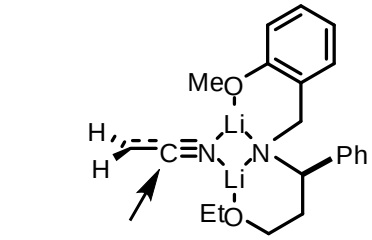
222

L= Ph_3P, L= *t*BuNC

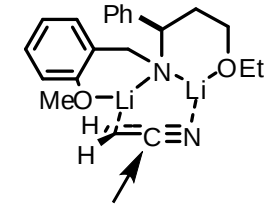


223

L= Ph_3P, L= *t*BuNC



224



225

Figure 3-12

NMR spectroscopic analysis of metallated nitriles showed similar structures in solution to the solid state structures. The ^{6}Li-^{15}N NMR coupling constants confirmed the presence of *N*-lithiated dimer structure **220** in ether-toluene mixtures.[116-117] However, only in the case of cyclopropanecarbonitriles **221**[116] or in the presence of a strong ligand were lithiated nitriles coaxed into co-ordinating with the nucleophilic carbon.[115,118]

^{13}C NMR spectroscopy showed different chemical shifts for the metallated nitriles **222** and **223** giving an idea about the preference for *N*- or *C*- co-ordination depending on the phosphine ligand (Figure 3-13).[111,119] The chemical shift ranges for *N*-lithiated nitrile **220** are between δ = 146-152 depending on the solvent.[120-121] Different chemical shifts were observed for *N*-lithiated nitrile **224** δ = 155.3 and *C*-lithiated nitrile **225** δ = 148.5.[115] In contrast to lithium, magnesiated nitriles exhibit a distinctive preference for co-ordination to carbon and this was confirmed by the ^{13}C NMR shift **226** (Figure 3-12).

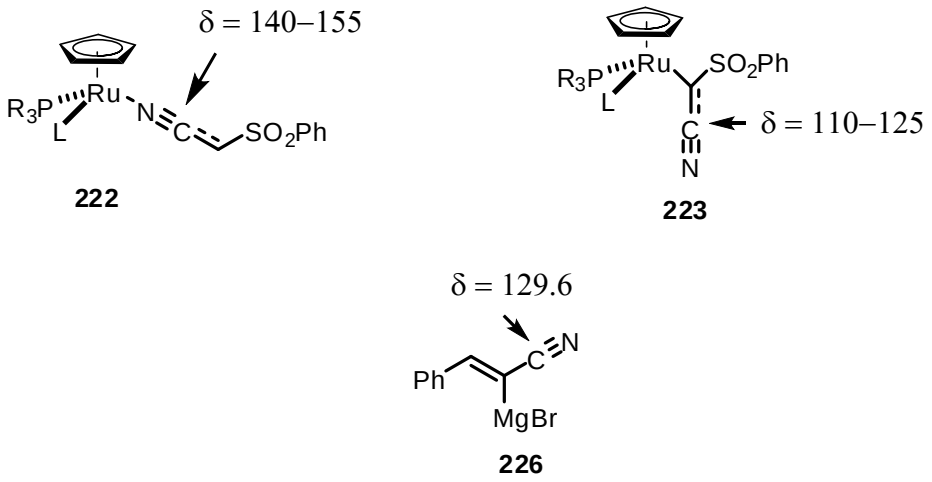


Figure 3-13

Comparing the ^{13}C NMR chemical shifts of magnesiated nitrile **227** with *N*-lithiated nitrile **228**[120] indicated that they have similar structures (Figure 3-14). The preference for *C*- or *N*-metallation is therefore influenced by the carbon scaffold.[111]

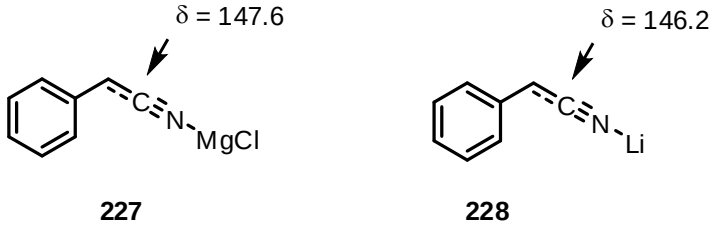
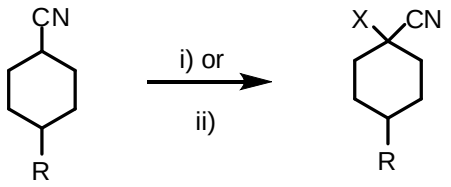


Figure 3-14

Deprotonation of α-nitrile is a common method to generate metallated nitriles, as will be discussed in section 3.2.2.3. Halogen or sulfoxide-metal exchange protocols were also used to make metallated nitriles and will be discussed in the next section.

3.2.2.1 Halogen-Metal Exchange

An efficient route to generate a metallated nitrile without the need for amide bases is through halogen-metal exchange. Fleming and co-workers used a halogen-metal strategy. The halonitriles were prepared by treating nitrile **229**, **230** with PBr_3/Br_2 or PCl_5/pyridine to provide the desired halonitriles **231-233** in good yields (Scheme 3-4).[100]



R = H **229**

R = *t*Bu **230**

X = Br, R = H **231** 90%

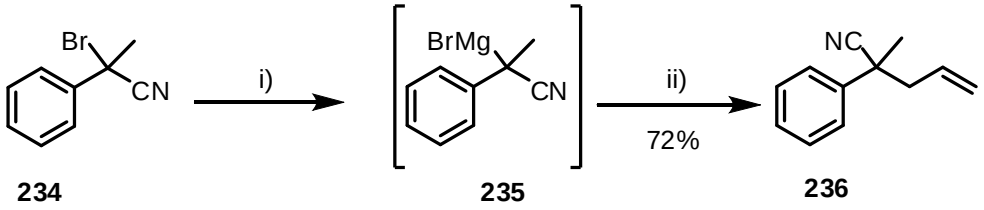
X = Br, R = *t*-Bu **232** 73%

X = Cl, R = H **233** 81%

Reagents and conditions: i) PBr_3, Br_2, or ii) PCl_5/py.

Scheme 3-4

With a range of α-halonitriles in hand, halogen-metal exchange was found to be extremely fast. The reaction of nitrile **234** with ^{i}PrMgBr in THF at –78 °C caused the colour of the solution to change immediately to yellow. This produced metallated nitrile **235** which was trapped with allyl bromide to give the corresponding quaternary nitrile **236** in a good yield (Scheme 3-5).[100]

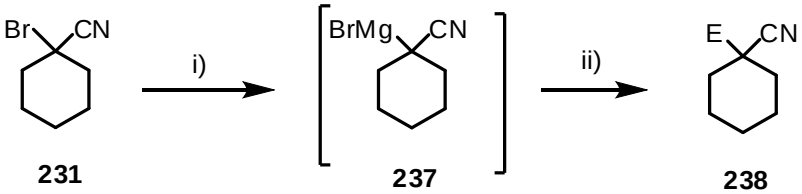


234 **235** **236**

Reagents and conditions: i) ^{i}PrMgBr, THF, –78 °C; ii) allyl bromide.

Scheme 3-5

Nitrile **231** was also used for halogen-metal exchange followed by trapping with a range of electrophiles (acyl cyanide, acid chloride, ketones and aldehydes) to afford different alkylated nitriles in moderate to good yields (Scheme 3-6).



231 **237** **238**

Reagents and conditions: i) ^{i}PrMgBr, THF, –78 °C; ii) E^{+}.

Scheme 3-6

Noticeably, the yield of the electrophilic alkylation reactions performed *in situ* (the solution of ^{i}PrMgBr in THF was added to a solution of the nitrile and electrophile at –78

°C) was much higher than normal addition. However, this chemistry has not yet been tested with enantiomerically pure bromonitrile **234**.

The mechanism of halogen-metal exchange with a cyclic nitrile was studied extensively.[100,110,122] It was proposed that the cyclic metallated nitriles can be exist in three different structures (*N*–metallated nitrile **243** or two diastereomeric *C*-metallated nitriles **241**, **242**) and these rapidly equilibrate (Figure 3-15). Addition of ^{i}PrMgCl to the solution of methyl cyanoformate and a diastereomeric mixture of nitrile **239** in THF at –78 °C gave ester nitrile **244** (dr >12:1) with retention of configuration (Figure 3-15).

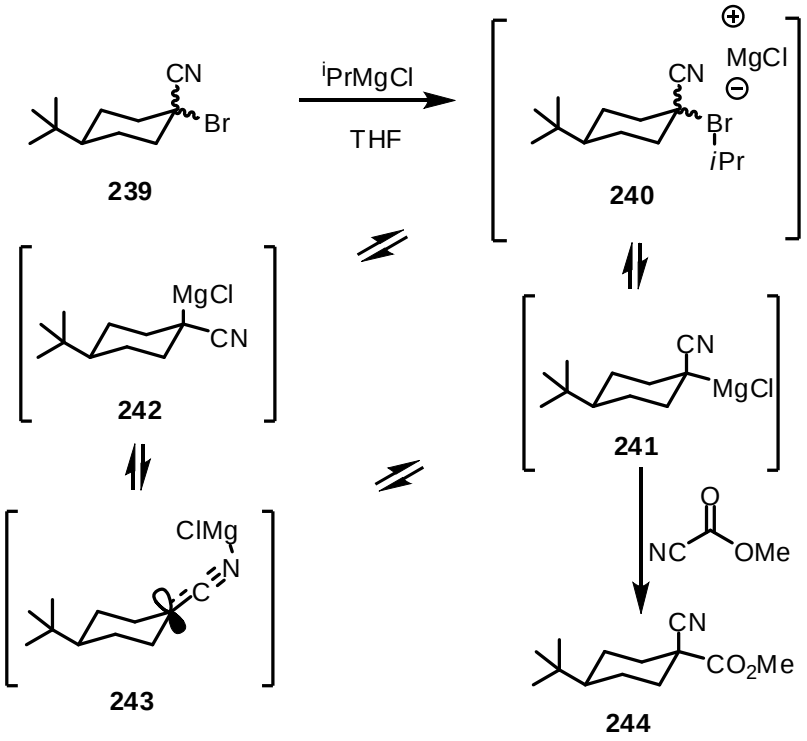
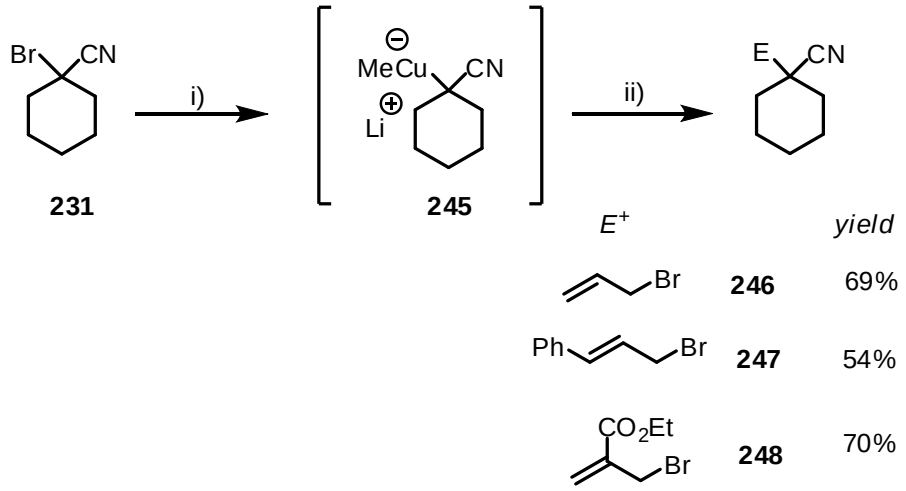


Figure 3-15

The result indicated that the ester nitrile is generated through a retentive alkylation of *C*-metalated nitrile **241** which is favoured because this places the small nitrile group in the axial position and the larger solvated metal in the equatorial orientation. *C*-Metallated nitrile **241** could be obtained directly from bromate **240** and diastereomer **241** could potentially be mixed with another diastereomer **242**, or the bromate **240** could rearrange to *N*-metallated nitrile **243** through **242**. Conversion of **242** to **241** is assumed to happen through intermediate **243** by migration of the metal from carbon to nitrogen and then back again onto the opposite face. The proposed equilibration steps must be facile because *in situ* metal-halogen exchange and alkylation with either single diastereomer of bromonitrile **239** gave the same acylated nitrile **244**.

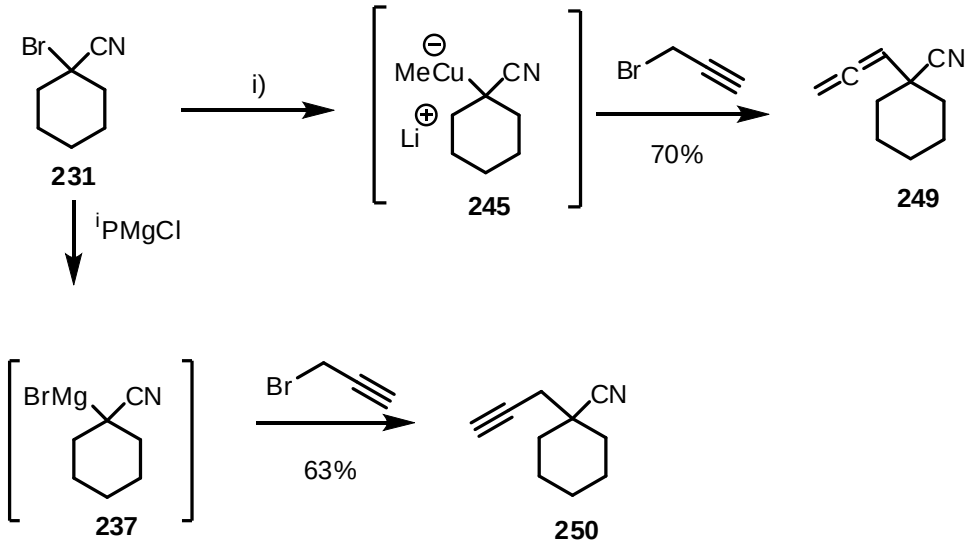
Alkylation of copper-metallated nitriles can exhibit excellent yields.[122-123] Copper-halogen exchange with bromonitrile **231** was achieved in 1.5 h by using Me_2CuLi at 0 °C followed by trapping with different allylic electrophiles to generate a range of alkylated nitriles **246-248** in good yields (Scheme 3-7).



Reagents and conditions: i) Me_2CuLi, THF, 0 °C, 1.5 h; ii) E^+.

Scheme 3-7

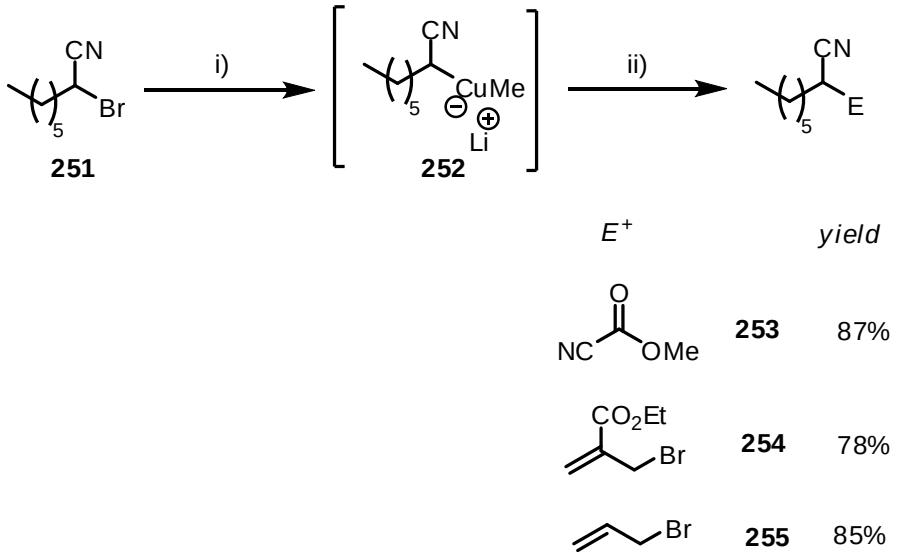
Alkylated nitrile **249** was obtained from reacting nitrile **231** with Me_2CuLi followed by trapping with propargyl bromide with complete S_N2' alkylation. On the other hand, the same reaction carried out with ^iPrMgCl gave the alkylated nitrile **250** through S_N2 alkylation (Scheme 3-8).



Reagents and conditions: i) Me_2CuLi, THF, 0 °C, 1.5 h.

Scheme 3-8

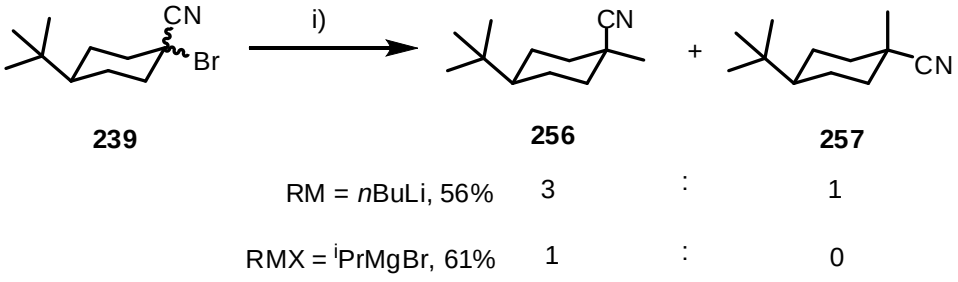
Copper-halogen exchange was examined with α-halonitrile **251**. This gave high yields of alkylated nitriles **253**-**255** after trapping with allylic and carbonyl electrophiles (Scheme 3-9).[122]



Reagents and conditions: i) Me_2CuLi, THF, 0 °C, 1.5 h; ii) E^+.

Scheme 3-9

Halogen-lithium exchange is extremely rapid with an alkyllithium and allows selective exchange with a range of electrophiles providing alkylated products in high yields.[122] The lithiated nitriles showed moderate selectivity compared to magnesiated nitriles. For example, halogen-lithium exchange using *n*BuLi with nitrile **239** at –78 °C in the presence of methyl iodide gave two diastereoisomers **256**, **257** in a 3:1 ratio. On the other hand, only the equatorially methylated nitrile **256** was obtained when the same reaction was carried out with ^{i}PrMgBr, even at higher temperature (Scheme 3-10).[123]



Reagents and conditions: i) RMX, MeI, –78 °C.

Scheme 3-10

In Knochel`s group,[124] bromine-magnesium exchange was observed in the reaction of dibromide **258** with ^{i}PrMgCl in a mixture of Et_2O and CH_2Cl_2 (1:4) at –50 °C for 5 min, forming the *cis*-magnesium carbenoid **259** with a diastereomeric ratio of 99:1. This can be stereoselectively trapped with several electrophiles (I_2, $MeSSO_2Me$, $PhSSO_2Ph$ and allyl bromide [in the presence of CuCN•2LiCl]) to provide the desired cyclopropane nitriles **260**-**263** in good yields (72-86%) with stereochemically defined quaternary centres with a high level of selectivity (dr = 91:9 to 99:1) (Scheme 3-11).

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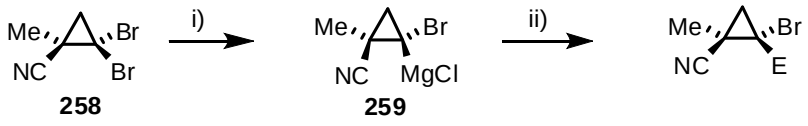


258 **259**

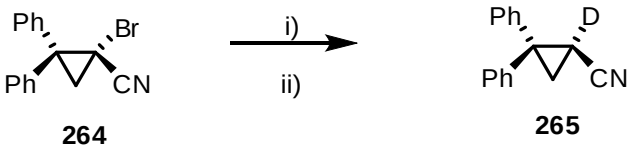
cis:trans ≥ 99:1

E^+		*yield*	*cis:trans*
I_2	**260**	77%	99:1
$MeSSO_2Me$	**261**	72%	93:7
$PhSSO_2Ph$	**262**	86%	95:5
allyl bromide	**263**	78%	99:1

Reagents and conditions: i) ^{i}PrMgCl, Et_2O:CH_2Cl_2, 1:4, –50 °C, 5 min; ii) E^+, –50 °C → 25 °C.

Scheme 3-11

After developing the strategy of halogen-metal exchange, Carlier and Zhang [125] carried out bromine-magnesium exchange on nitrile **264** using 2.2 equivalents of ^{i}PrMgCl at –100 °C for 1 min. The reaction resulted in an excellent conversion (90%) and high level of stereoselectivty (showing that the racemisation is slow at –100 °C) (Scheme 3-12). A series of experiments was carried out at different temperatures and reaction times. This illustrated that longer reaction times and high temperatures led to lower enantiomeric excesses.



264 **265**

90% (90:10 er)

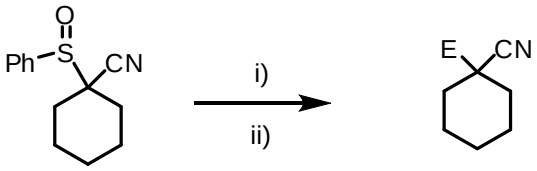
Reagents and conditions: i) ^{i}PrMgCl (2.2 eq.), Et_2O, –100 °C; ii) D_2O.

Scheme 3-12

3.2.2.2 Sulfoxide-Metal Exchange

Another efficient route to generate metallated nitriles is sulfoxide-metal exchange when the sulfoxide is located alpha to the nitrile.[124,126-127]

Recently, Fleming and co-workers applied sulfinyl-metal exchange to install a quaternary centre which is found in numerous nitrile-containing pharmaceuticals.[128-129] Sulfinylnitrile **266** was treated with ^{i}PrMgCl at –78 °C and led to rapid exchange affording the magnesiated nitrile, which was successfully trapped with a range of the electrophiles (ketone, ester, acid chloride) to give a variety of quaternary nitriles in excellent yields (Scheme 3-13).



266

E^+		*yield*
cyclohexanone	**267**	92%
CH_3OCOCN	**268**	91%
*t*BuCHO	**269**	90%

Reagents and conditions: i) ^{i}PrMgCl, THF, –78 °C; ii) E^+.

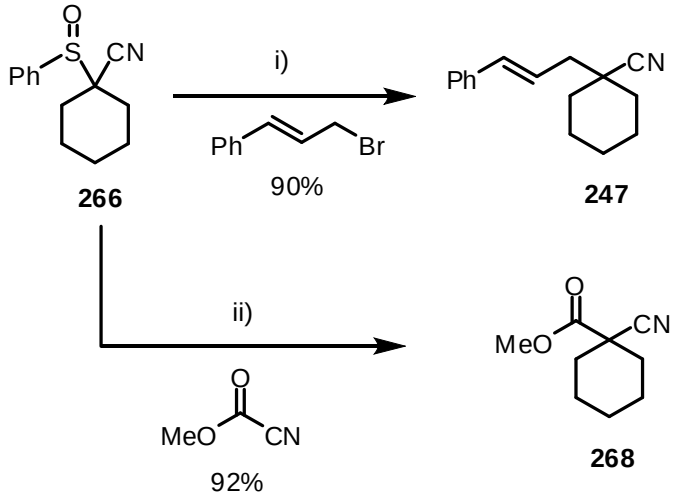
Scheme 3-13

In addition, the same conditions were applied to different cyclic, bicyclic and acyclic sulfinylnitriles with a range of electrophiles such as alkyl halides, benzylidene malononitrile, diphenyldisulfide and isopropyl iodide. All the reactions successfully gave the desired products in high yields without competitive addition or deprotonation.

Several *in situ* exchange-alkylations were carried out (^{i}PrMgCl was added to a cooled THF solution of the sulfinyl nitrile containing the electrophile), and alkylated nitriles were produced in excellent yields without any observable reaction between the ^{i}PrMgCl and the electrophiles. The same strategy was demonstrated with sulfinylnitrile **266** using other organometallics to efficiently generate the desired alkylated nitriles in high yields (Scheme 3-14).

It should be noted that these sulfinyl-metal exchange reactions were carried out using achiral or racemic nitriles, so the intermediate metallated nitriles were either achiral or

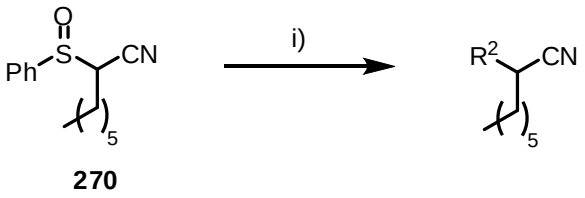
racemic and the possibility to transfer chirality to the organometallic and hence the product was not studied.



Reagents and conditions: i) BuLi, THF, –78 °C; ii) $Et_2ZnBuLi$, THF, 0 °C.

Scheme 3-14

The sequential exchange-alkylation protocol was extended to tertiary sulfinyl nitrile **270** and successfully provided the desired alkylated nitrile.[129] A series of sulfinyl-magnesium exchange reactions with tertiary sulfinylnitriles (alkyl, cyclopropyl and benzylic substituents) and ^{i}PrMgCl (2 equivelents) was performed and followed by trapping with different electrophiles (alkyl cyanoformate, pivaloyl chloride, or benzoyl chloride) to give tertiary nitriles **253**, **271**, **272** in good yields (70-90%) (Scheme 3-15).



R^2-X		*yield*
CH_3OCOCN	**253**	70%
*t*BuCHO	**271**	72%
BnBr	**272**	81%

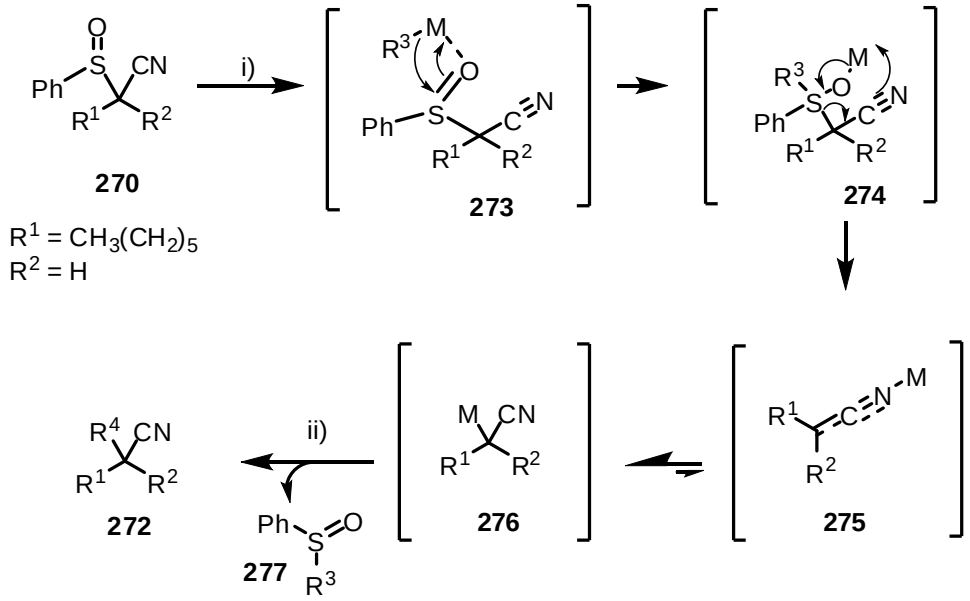
Reagents and conditions: i) ^{i}PrMgCl (2 eq.), THF, –78 °C.

Scheme 3-15

The mechanistic study indicated that the exchange is expected to occur through the sulfurane **274**. A complex can be formed between magnesium and the sulfoxide oxygen

and then attack on sulfur could occur. The metal could transfer from oxygen to nitrogen with minimal charge build up.

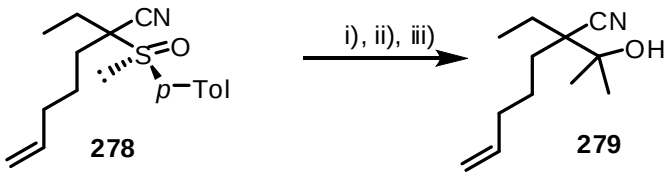
For exchange with butyllithium, the *N*-lithiated species **275** is directly generated from the intermediate **274**. On the other hand, the exchange with ^{i}PrMgCl will likely lead to a rapid equilibration between the *N*-magnesiated nitrile **275** (M=MgCl) and the *C*-magnesiated nitrile **276** (M=MgCl). A near quantitative amount of ^{i}PrSOPh was isolated in all the exchange procedures employing ^{i}PrMgCl whereas BuSOPh **277** was isolated from the corresponding reaction with BuLi.



Reagents and conditions: i) R^3M, –78 °C; ii) R^4X = BnBr.

Scheme 3-16

This mechanism suggests that chirality transfer is unlikely as enantiopurity would be lost during formation of *N*-metallated nitrile **275**. This possibility was investigated by Hélène Guerrand in the Coldham group.[130] Treatment of the sulfoxide **278** (single diastereomer of unknown relative configuration and single enantiomer) with ^{i}PrMgCl followed by the addition of acetone as the electrophile gave racemic product **279** (Scheme 3-17).

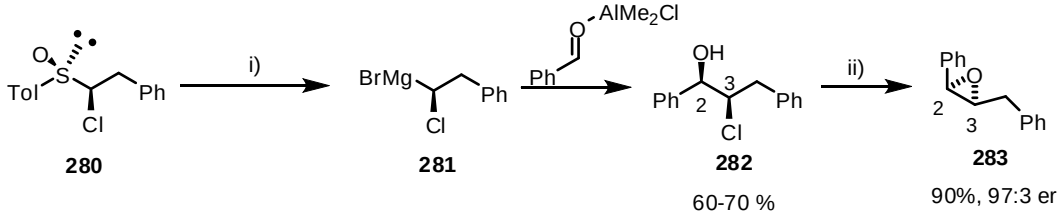


Reagents and conditions: i) ^{i}PrMgCl, Et_2O, –107 ^{o}C, 5 s; ii) acetone, 30 min, –107 ^{o}C; iii) NH_4Cl (aq).

Scheme 3-17

In Hoffmann`s group,[131] sulfoxide-metal exchange was applied to generate a chiral α-chloro Grignard reagent which was reported to be a configurationally stable species.[132-133, 134] This was then used in stereoselective synthesis.

Reaction of sulfoxide **280** with ethylmagnesium bromide in THF at –78 °C gave Grignard reagent **281** which was trapped with activated benzaldehyde to give chlorohydrin **282** in 60–70% yield with 90:10 (syn/anti) ratio, the crude of the mixture of diastereisomers **282** were converted to the epoxides **283**, which were obtained in 88:12 ratio (major diastereomer of **283** is shown) (Scheme 3-18). The enantiomeric ratio of the major diastereomer of epoxides **283** was determined to be 97:3 er by ^{1}H NMR spectroscopic analyses in the presence of chiral reagent. The comparison with the absolute configuration of known material indicated that the major enantiomer of **283** has the configuration (2*R*,3*S*). Therefore the chlorohydrin **282** should have the indicated configuration (2*R*,3*R*). That proved the sulfoxide-metal exchange was successfully employed to generate a chiral Grignard reagent. The reaction occurred with retention of configuration at the chlorine-bearing carbon center.



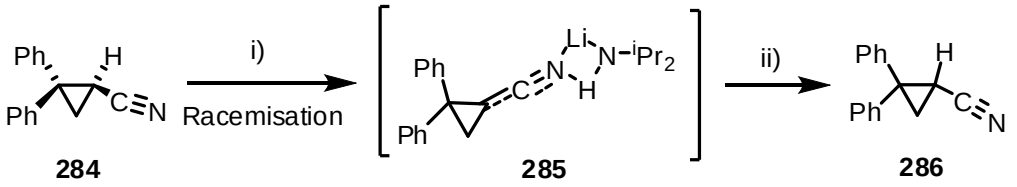
Reagents and conditions: i) EtMgBr, THF, –78 °C; ii) KOH, EtOH.

Scheme 3-18

3.2.2.3 Deprotonation-Electrophile Quench Sequence

Metallated nitriles are typically synthesised by deprotonating the parent nitriles with metal amides.[135-136]Co-ordination of the metal to the carbon has the potential to make

the tetrahedral nucleophilic carbon a stereogenic center. Carlier[117,137] reported that deprotonation of cyclopropanecarbonitrile **284** using LDA followed by protonation (using H_2O) produced the racemic product **286** through intermediate *N*-metallated nitrile **285** (Scheme 3-19).[122]

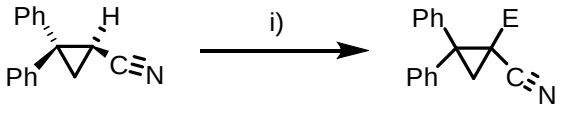


284 **285** **286**

Reagents and conditions: i) LDA, Et_2O; ii) –78 °C, 10 s, H_2O.

Scheme 3-19

Carlier and Zhang carried out several deprotonation attempts on nitrile **284** using different bases (LDA, LiHMDS, KHMDS) in different solvents (THF, Et_2O, Me_2O, toluene) followed by trapping with different electrophiles (MeI, BnI, D_2O). Only racemic products were obtained even under *in situ* quench conditions, which showed that the anions are not configurationally stable (Scheme 3-20).[125]

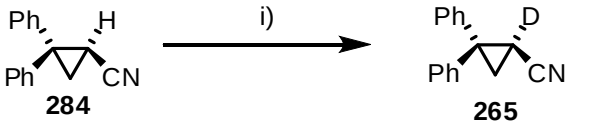


284 **287**

Reagents and conditions: i) base, solvent, ii) –135 °C, EX.

Scheme 3-20

The first evidence for enantioselective metallation and substitution of a nitrile was reported by Walborsky and Motes.[138] They deprotonated cyclopropanecarbonitrile **284** using NaOMe in CD_3OD.[138] The deuterated compound **265** was generated with 99% enantiomeric excess with retention of configuration. The anion must have microscopic configurational stability and is trapped *in situ* by the solvent as soon as it forms.



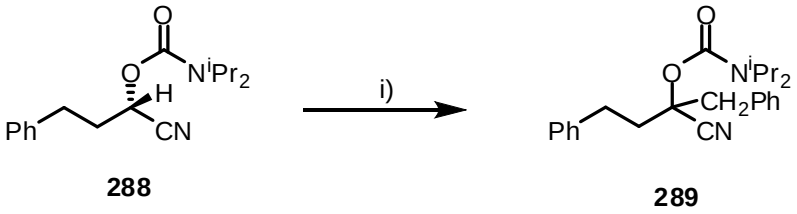
284 **265**

97% (> 99:1 er)

Reagents and conditions: i) NaOMe (1 M), CD_3OD, 50 °C, 3 d.

Scheme 3-21

Nevertheless, magnesiated nitriles showed macroscopic configurational stability,[125] bromine-magenesium exchange took place followed by quenching with D_2O after 1 min, giving the product **265** in good enantiomeric ratio (90:10) (Scheme 3-12). As mentioned above, synthesis of an enantioenriched nitrile anion is a difficult and challenging task due to rapid racemisation by formation of a sp^2-hybridised keteniminate.[135] Takeda and co-workers examined the generation of an α-chiral nitrile carbanion by deprotonation of enantioenriched *O*-carbamoyl cyanohydrin **288** and trapping *in situ* with benzyl bromide (Scheme 3-22).[139] This resulted in a 35% yield of product **289** with a poor selectivity (53:47 er). Although longer reaction times did not improve the enantiomeric ratio, changing the solvent to toluene slightly improved the enantiomeric excess (56:44 er) (Scheme 3-22). This reaction suggests that a lithiated nitrile can be trapped intermolecularly without complete racemisation.



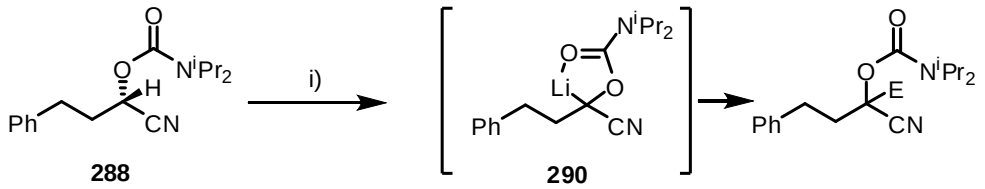
288 **289**

40%, 56:44 er

Reagents and conditions: i) BnBr (5 eq.), LDA (1.1 eq.), toluene, –80 °C.

Scheme 3-22

We decided to explore the metallation of nitrile **288** with a magnesium base (see section 3.4). During our study, Takeda and co-workers reported further work (employing *in situ* method by addition of LDA to a mixture of the nitrile and the electrophile) using *N*,*N*-dialkylcarbamoyloxy groups.[118] The carbonyl oxygen is thought to act as a fixing agent for lithium onto the carbon atom in chiral carbanions.[118,139] The low enantiomeric ratio of the benzylated product **289** was explained by the low reactivity of benzyl bromide which is not reactive enough to trap the carbanion before racemisation. More reactive electrophiles such as ethyl chloroformate, ethyl cyanoformate, and ethyl cyanoforamate were utilised and improved the enantiomeric ratio to 74:26 (Scheme 3-23).



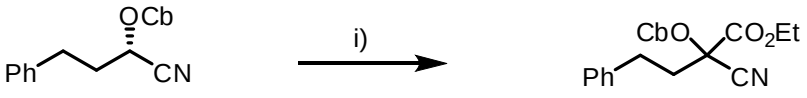
288 **290**

E^+		*yield*	*er*
BnBr	**289**	45%	52:48
EtOCOCl	**291**	85%	52:48
EtOCOCN	**291**	39%	74:26

Reagents and conditions: i) E^+ (5 eq.), LDA (1.1 eq.), Et_2O, –80 °C.

Scheme 3-23

After extensive study and optimisation of conditions (electrophile equivalents, the solvent, the base) the best results were obtained using nitrile **288** with 3 equivalents of LDA and ethyl cyanoformate in Et_2O at –98 °C (Scheme 3-24). The absolute configuration of the product **291** was not determined**.**



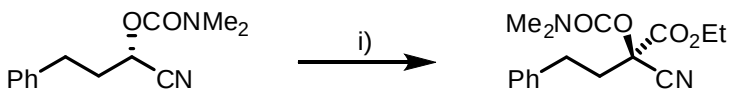
288 **291**

Cb = $C(O)N^iPr_2$ 92%, 74:26 er

Reagents and conditions: i) EtOCOCN (3 eq.), LDA (3 eq.), Et_2O, –98 °C.

Scheme 3-24

The effect of the alkyl group in the carbamate was also examined by utilising different groups ($NiPr_2$, NMe_2, NEt_2, $N(CH_2)_4$, $N(CH_2)_5$). The less sterically hindered dimethylcarbamoyl derivative **292** showed the highest enantioselectivity (90:10 er) with an excellent yield 92% using the very low temperature –114 °C as long as the electrophile (EtOCOCN) was present *in situ* (Scheme 3-25).



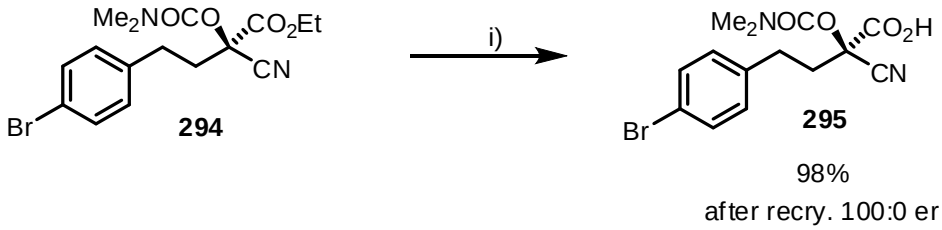
292 **293**

92% 90:10 er

Reagents and conditions: i) EtOCOCN (3 eq.), LDA (3 eq.), THF-Et_2O (2:1), –114 °C.

Scheme 3-25

With optimised conditions in hand, different electrophiles were used. The best result was achieved with EtOCOCN (92% yield, 90:10 er) while almost racemic products were obtained in case of benzyl bromide and ethyl chloroformate. However, excellent yields and good enantioselectivity were achieved with PhCOCl (90%, 84:16 er) and $CH_3CH_2CH_2COCl$ (84%, 81:19 er). The absolute configuration of the major enantiomer of product **293** was determined using X-ray crystallography of the *p*-bromophenyl derivative, demonstrating that the substitution reaction occurs with inversion of configuration (Scheme 3-26).



Reagents and conditions: i) NaOMe, $MeOH/H_2O$.

Scheme 3-26

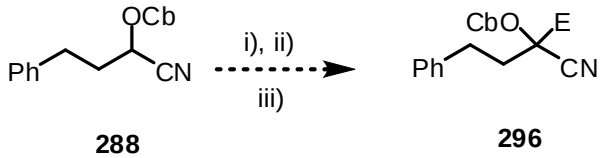
3.3 The Project Aim

Our group is interested in the synthesis of alkaloids using nitrile anion chemistry.[140-144] As mentioned, the nitrile group is important as it is found in natural products, pharmaceuticals and is useful in organic synthesis. Nitrile anions can be alkylated efficiently to give alkylated products in excellent yields, even when forming quaternary centres. However, these products are formed as mixtures of enantiomers.

The aim of this project is to control the stereoselectivity of the deprotonation–alkylation sequence to synthesise enantiomerically enriched α-substituted nitriles. The plan was to examine the deprotonation of acyclic enantioenriched nitrile **288** (first reported by Takeda),[139] with magnesium bases followed by quenching with electrophiles to give enantiomerically enriched products. Magnesium bases were chosen due to the strong tendency for magnesium to co-ordinate to the carbon to generate *C*-metallated species.[100,110,123-124] This could possibly lead to formation of enantiomerically enriched nitriles.

Firstly, racemic nitrile $\mathbf{288}_{rac}$ and the corresponding enantioenriched nitrile will be synthesised using the literature synthesis.[139,145]

The resulting racemic nitrile **288**$_{rac}$ will be deprotonated using different bases (LDA, ^{i}PrMgCl, TMPMgCl) followed by trapping with an electrophile. Optimised reaction conditions will then be developed for enantiomerically enriched nitrile **288** (Scheme 3-27).



288 **296**

Cb = $CON^{i}Pr_2$

Reagents and conditions: i) Base, Et_2O, –78 ^{o}C; ii) electrophile, E^{+}; iii) NH_4Cl (aq).

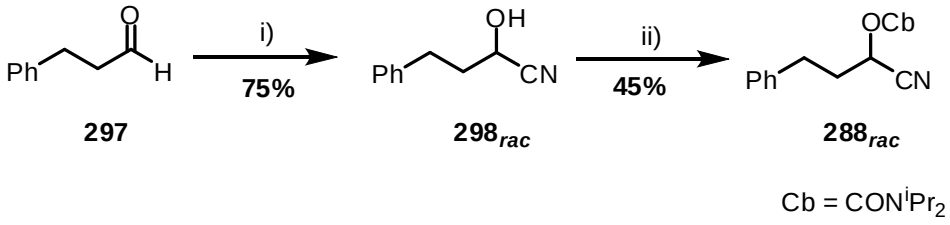
Scheme 3-27

Different electrophiles will be examined to achieve the best possible yield and stereoselectivity. The configurational stability of the chiral metallated nitrile intermediate will be investigated by determination of the enantiomeric ratio using chiral HPLC. In addition we will endeavor to determine the absolute configuration of any major enantiomer.

3.4 Results and Discussion

3.4.1 Synthesis of Racemic and Enantiomerically Enriched Starting Material

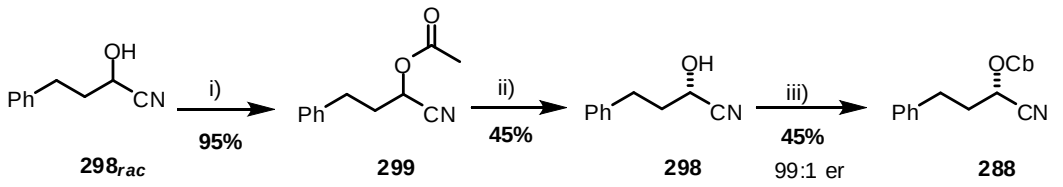
In order to prepare the nitrile starting material, aldehyde (**297**) was treated with NaCN and $NaHCO_3$ at 0 °C to afford cyanohydrin $\mathbf{298}_{rac}$ in good yield after 24 h.[145] The cyanohydrin $\mathbf{298}_{rac}$ was then reacted with triphosgene, triethylamine and diisopropylamine to prepare the carbamate $\mathbf{288}_{rac}$. A carbamate group has proved to be a good group for acting as a fixing agent, possibly due to its ability to co-ordinate to the metal on the carbon.[118,139] The reaction afforded the desired racemic nitrile $\mathbf{288}_{rac}$ in moderate yield (66%) when a small scale reaction was carried out. However, only a 45% yield was obtained in a large scale reaction (Scheme 3-23).[139]



Reagents and conditions: i) $NaHSO_3$, NaCN, 0 °C → rt., 4 h; ii) $Cl_3COCOOCCl_3$, Et_2O, Et_3N, $^iPr_2NH$, rt., 3 h.

Scheme 3-28

Synthesis of the enantioenriched nitrile **288** was started by acylation of alcohol $\mathbf{298}_{rac}$ using standard conditions (Py, Ac_2O, CH_2Cl_2, rt)[146] to give the desired product **299** in nearly quantitative yield. Kinetic resolution utilising Amano lipase PS[139,147] and purification using flash column chromatography eluting with petrol−ether 8:2 furnished the desired alcohol **298** in 45% yield. From the literature the (*S*)-cyanohydrin was obtained as the major enantiomer by comparsion with (*R*)- cyanohydrin.[148] It was then protected using triphosgene using the formerly used procedure for making carbamate $\mathbf{288}_{rac}$. The carbamate **288** was produced in 45% yield in excellent enantiomeric ratio 99:1 (Scheme 3-29). The er was determined by a chiral stationary phase HPLC.



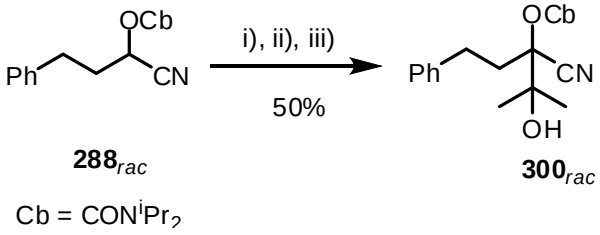
Reagents and conditions : i) Ac_2O, Py, CH_2Cl_2, rt., 24 h; ii) Amano Lipase PS, THF-H_2O, 50 °C, 2 h; iii) $Cl_3COCOOCCl_3$, Et_2O, Et_3N, $^iPr_2NH$, rt., 3 h.

Scheme 3-29

3.4.2 Metallation-Acetone Racemic and Enantiomerically Enriched Quench of Carbamate 288*rac*

From previous studies,[110-111,122-124,138,149-150] it was suggested that magnesium prefers to co-ordinate to the carbon to generate a *C*-metallated species which would form a chiral *C*-metallated nitrile. Grignard reagents were examined to compare with LDA as the base. ^{i}PrMgCl was used to make a metallated nitrile followed by electrophilic quench.

Firstly, the study started with the racemic nitrile **288***rac*. Commercially available ^{i}PrMgCl (1.2 equivalents) was added to a solution of nitrile **288***rac* in THF at –78 ºC, after 10 min dry acetone was added then the mixture was stirred for 30 min. The mixture was left to warm to room temperature before quenching with aqueous ammonium chloride giving the alcohol **300** in 50% yield (Scheme 3-30). The enantiomers were resolved using chiral stationary phase HPLC (cellulose-1).

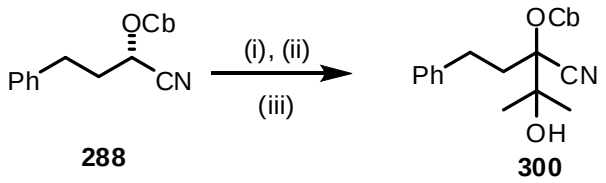


Reagents and conditions: i) ^{i}PrMgCl, THF, –78 ^{o}C; ii) 10 min, acetone; iii) NH_4Cl (aq).

Scheme 3-30

With racemic alcohol **300***rac* in hand, a similar procedure could be used starting from the enantiomerically enriched starting material. The Grignard reagent ^{i}PrMgCl was added to the solution of enantiomerically enriched nitrile **288** in Et_2O at low temperature

(–107 °C), then quenched with acetone using different amounts of both the base and electrophile (Table 3-1, Scheme 3-31).



288 **300**

Cb = CON^iPr_2

Reagents and conditions: i) ^{i}PrMgCl, Et_2O, –107 °C; ii) after time, acetone; iii) NH_4Cl (aq).

Scheme 3-31

Starting with the use of 1.2 equivalents of the base and normal addition (the base was added to the solution of starting material in the solvent) of Grignard reagent to the nitrile **288** followed by addition of 1.1 equivalents of the electrophile after 10 min. After stirring for 30 min the reaction mixture was quenched with aqueous NH_4Cl. The desired product was obtained in poor yield but with promising er of 82:18 (entry 1).

Table 3-1[a]

Entry	Base eq.	Acetone eq.	Time	Add.	Yield of **300**[b]	er[c]
1	1.2	1.1	10 min	Normal	44%	82:18
2	1.2	1.1	10 min	Inverse	30%	87:13
3	1.2	1.1	1 min	Inverse	15%	85:15
4	1.2	1.1	5 sec	Inverse	10%	84:16

[a] For conditions, see Scheme 3-31. [b]Yield based on isolated yields after column chromatography. [c] Enantiomer ratio determined by CSP-HPLC.

Focussing on improving the enantiomeric ratio, reversing the Grignard reagent addition mode (solution of starting material in the solvent (25°C) was added to the cooled (–107 °C) solution of base in the solvent) using same base equivalents and reaction time, a poor yield was again obtained (30% yield) but with a slight improvement of er 87:13 (entry 2). Next, the electrophile was added after 1 min or after 5 sec (less time would give less chance to racemise before trapping with acetone). In each case lower yields with almost the same enantiomeric ratio were observed (entries 3,4). The low yields are possibly because the time for deprotonation is insufficient, but it was

expected that this would give higher er due to less time for racemisation. These results indicated that the magnesiated nitrile is configurationally stable for at least for 10 min at low temperature. On the other hand, it is not clear why 99:1 er cannot be achieved as the enantiomeric ratio of the starting material is 99:1.

Next, improving the chemical yield was the main aim. The amount of the base and the electrophile were raised to 2 equivalents and 3 equivalents respectively under the above procedure. Similar results were obtained for both the chemical yield and enantiomeric ratio (Table 3-2).

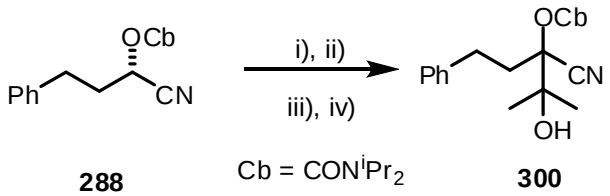
Table 3-2[a]

Entry	Base eq.	Acetone eq.	Time	Yield of **300**[b]	er[c]
1	2	3	10 min	30%	85:15
2	4	5	10 min	45%	91:9
3	4	5	1 min	35%	85:15
4	4	5	5 s	30%	87:13

[a] For conditions, see Scheme 3-31. [b]Yield based on isolated yields after column chromatography. [c] Enantiomer ratio determined by CSP-HPLC.

Increasing base equivalents to four and electrophile equivalents to five improved both the yield and er (45% yield, 91:9 er, entry 2). Decreasing the addition time of the electrophile to 1 min or to 5 sec led to a marginal decrease of ers to 85:15, 87:13 and the yields to 30% and 35% respectively (entries 3, 4).

It should be noted that the use of four equivalents of ^{i}PrMgCl and five equivalents of acetone gave the best yield and selectivity (Table 3-2, entry 2). Thus with this amount of the base and electrophile, different solvents and different addition modes could be tested (Scheme 3-32, Table 3-3).



288 **300**

Reagents and conditions: i) ^{i}PrMgCl, solvent, temp. °C; ii) nitrile **288**; iii) after time, acetone; iv) after 30 min NH_4Cl (aq).

Scheme 3-32

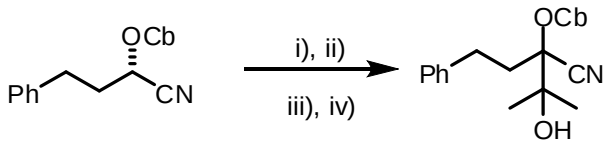
In the case of an *in situ* quench (a solution of enantiomerically enriched nitrile **288** and acetone was added to a solution of ^{i}PrMgCl in Et_2O at –107 ^{o}C) the product **300** was obtained in low yield and similar er (Table 3-3, entry 1). Changing the solvent to THF:Et_2O (1:1) decreased the yield to 24% compared to 45% with Et_2O (Table 3-2, entry 2), and slightly decreased the er to 89:11 instead 91:9 with Et_2O (Table 3-3, entry 2). Also, ^{t}BuOMe was tested as a solvent but resulted in poor selectivity (71:29 er) and moderate yield 50% (entry 3). It was clear that Et_2O is the best solvent for both chemical yield and enantioselectivity. To examine the configurational stability of magnesiated nitrile species, addition of acetone after 30 min gave 80% yield and 60:40 er. As expected, the er drops if the organomagnesium species is left for longer times prior to electrophilic quench (entry 4). Increasing the reaction temperature to –78°C resulted in racemic product (entry 5).

Table 3-3[a]

Entry	Temp. °C	Solvent	Add. time of E^+	Yield of **300**[b]	er[c]
1	–107	Et_2O	*In situ*	24%	87:13
2	–107	THF:Et_2O	10 min	24%	89:11
3	–107	^{t}BuOMe	10 min	50%	71:29
4	–107	Et_2O	30 min	80%	60:40
5	–78	Et_2O	10 min	75%	50:50

[a] For conditions, see Scheme 3-32. [b]Yield based on isolated yields after column chromatography. [c] Enantiomer ratio determined by CSP-HPLC.

These findings revealed that the best yield achieved using ^{i}PrMgCl in good enantiomeric enrichment is 45%, so it might not be the best base for deprotonation even though it showed a good enantioselectivity. Diethyl ether is the best solvent and an organomagnesium intermediate showed configurational stability at –107 °C. The poor yield led us to investigate and explore more reaction conditions, especially the base used (Table 3-4, Scheme 3-33).



288 Cb = CON^iPr_2 **300**

Reagents and conditions: i) Base, Et_2O, –107 ^oC; ii) nitrile **288**; iii) after time, acetone; iv) after 30 min NH_4Cl (aq).

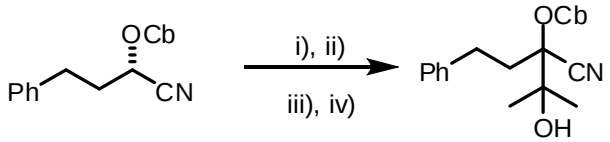
Scheme 3-33

Table 3-4[a]

Entry	Base eq.	acetone eq.	Time	Yield of **300**[b]	er[c]
1	$^nBu_2Mg$ 4 eq.	5	10 min	45%	80:20
2	TMPMgCl.LiCl 5 eq.	6	10 min	73%	70:30
3	TMPMgCl 4 eq.	5	10 min	81%	61:39
4	TMPMgCl 4 eq.	5	2 min	55%	85:15

[a] For conditions, see Scheme 3-33. [b]Yield based on isolated yields after column chromatography. [c] Enantiomer ratio determined by CSP-HPLC.

Using $^nBu_2Mg$ as a new base resulted in similar yield (45%) but the enantiomeric ratio was diminished from 91:9 to 80:20 (entry 1). An encouraging yield of 73% was achieved by switching to five equivalents of TMPMgCl.LiCl but with a decrease in er to 70:30 (entry 2). The low er probably resulted from the presence of LiCl as the Li cation could co-ordinate to the nitrogen atom to give higher probability of racemisation through an achiral ketenimine structure. Using the same base without LiCl gave higher yield but the er suffered another decrease (81%, 61:39 er, entry 3). Adding the electrophile after 2 minutes gave moderate yield and reasonable selectivity (55% yield, 85:15 er, entry 4). From these results it was clear that decreasing the reaction time improved the selectivity but lowered the yield dramatically. In addition, a good selectivity was achieved by using ^{i}PrMgCl and a good yield was obtained with using TMPMgCl. It was therefore decided to test a combination of ^{i}PrMgCl and TMPH or TMPMgCl (Scheme 3-34, Table 3-5). Starting with ^{i}PrMgCl and catalytic TMPH gave reasonable results (40% yield, 86:14 er, entry 1). Switching to ^{i}PrMgCl-TMPMgCl system gave similar results (entry 2), but increasing TMPMgCl equivalents 5 fold improved the yield significantly to 75% with a slight decrease of er to 82:18 (entry 3). Immediate addition of the electrophile provided good er (90:10) with similar yield of 40% (entry 4).



288 Cb = CON^iPr_2 **300**

Reagents and conditions: i) Base + additive, Et_2O, –107 °C; ii) nitrile **288**; iii) after time, acetone; iv) after 30 min NH_4Cl (aq).

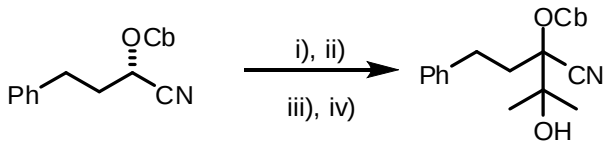
Scheme 3-34

Table 3-5[a]

Entry	Base + Additive	Time	Yield of **300**[b]	er[c]
1	^{i}PrMgCl 4 eq. + TMPH 0.2 eq.	10 min	40%	86:14
2	^{i}PrMgCl 4 eq. + TMPMgCl 0.2 eq.	10 min	45%	83:17
3	^{i}PrMgCl 4 eq. + TMPMgCl 1 eq.	10 min	75%	82:18
4	^{i}PrMgCl 4 eq. + TMPMgCl 0.2 eq.	5 s	40%	90:10

[a] For conditions, see Scheme 3-34. [b]Yield based on isolated yields after column chromatography. [c] Enantiomer ratio determined by CSP-HPLC.

From these results it did not appear that the mixed base system was giving improved yield coupled with high er. Therefore, optimising only TMPMgCl, which showed reasonable results (55%, 85:15 er), was considered. The addition of the starting material in Et_2O (0.5 mL) at room temperature to a cooled (–107 °C) solution of the base in Et_2O may affect the enantiomeric ratio due to the warming of the reaction mixture. The decision was made to add the solution of starting material (inverse addition) dropwise to the cooled (–107 °C) reaction mixture (Scheme 3-35, Table 3-6).



288 Cb = CON^iPr_2 **300**

Reagents and conditions: i) TMPMgCl (4 eq.), Et_2O, –107 °C; ii) nitrile **288** (100 mg); iii) after time, acetone (5 eq.); iv) after 30 min NH_4Cl (aq.

Scheme 3-35

Table 3-6[a]

Entry	Add. time	Time	Yield of **300**[b]	er[c]
1	5 min-hand add.	2 min	50%	85:15
2	4 min-syringe pump[d]	2 min	48%	81:19
3	4 min-syringe pump[e]	2 min	48%	88:12
4	4 min-syringe pump[f]	2 min	50%	85:15
5	4 min-syringe pump[g]	2 min	50%	87:13
6	1 min-syringe pump[h]	5 sec	50%	85:15

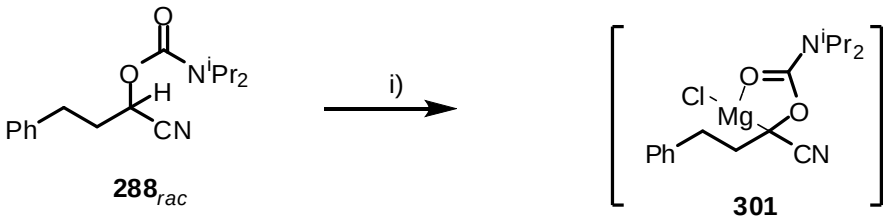
[a] For conditions, see Scheme 3-35. [b] Yield based on isolated yields after column chromatography. [c] Enantiomer ratio determined by CSP-HPLC. [d] 0.14 M (0.5 mL + SM, 2 mL + TMPMgCl), [e] 0.14 M (2 mL + SM, 0.5 mL + TMPMgCl), [f] 0.12 M (2.5 mL + SM, 0.5 mL + TMPMgCl), [g] 0.1 M (2.5 mL + SM, 1 mL + TMPMgCl), [h] 0.14 M (0.5 mL+ SM, 2 mL + TMPMgCl).

The first attempt involved a solution of enantiomerically enriched nitrile **288** in Et_2O (0.5 mL), added by hand dropwise over 5 min to a cooled solution of TMPMgCl in Et_2O (2 mL). After 2 min, addition of acetone gave the product **300** (entry 1) with similar results to the one pot addition (55%, 85:15 er, Table 3-4, entry 4). The reaction was carried out under the same conditions except the addition of nitrile **288** in Et_2O (0.5 mL) solution was by syringe pump. This gave a similar yield but a slight decrease in the er was observed (entry 2). Dilution of the starting material solution using 2.0 mL of Et_2O resulted in slight improvement in the enantiomeric ratio to 88:12 with the same yield of 48% (entry 3). Having these promising results, further reactions were carried out with more diluted starting material solution (2.5 mL Et_2O) but resulted in the same results (50%, 85:15 er, entry 4). Using a solution of 1.0 mL Et_2O and TMPMgCl provided a similar result (entry 5). Interestingly, even with decreasing the starting material addition time (by syringe pump) to 1 min and acetone addition to 5 sec, a 50% yield was achieved (entry 6).

It was clear that enantiomeric ratios greater than 90:10 are not readily achievable using TMPMgCl, but it is a good base as around 50% yield was achieved. Low yields may be attributed to the steric bulkiness of the starting material **288**. Further investigations would be studied later, by examining different electrophiles with this starting material or by using less sterically hindered starting materials with acetone. It is worth

mentioning that no significant difference was observed between applying dropwise or simultaneous addition.

Infra-red spectroscopy is a well known technology in the field to determine the amount of base required, as well as the time required to complete the deprotonation. The starting material **288** is a suitable substrate for IR spectroscopy *via* measuring the change in carbonyl group stretch between the starting material and intermediate. The reaction with the IR probe was carried out with 2.5 mmol of substrate in 7.0 mL of the solvent. Racemic nitrile **288*rac*** ($\nu_{C=O}$ 1712 cm^{-1}) was stirred in Et_2O at –75 °C followed by addition of 1.0 equivalent of TMPMgCl. A decrease in absorbance at 1712 cm^{-1} in the starting material and an increase in absorbance at 1632 cm^{-1} for the magnesiated intermediate **301** (Scheme 3-36) was observed. The deprotonation was very fast and complete formation of the magnesiated intermediate **301** was observed within 2 min of addition of TMPMgCl (Figure 3-16).



288*rac*

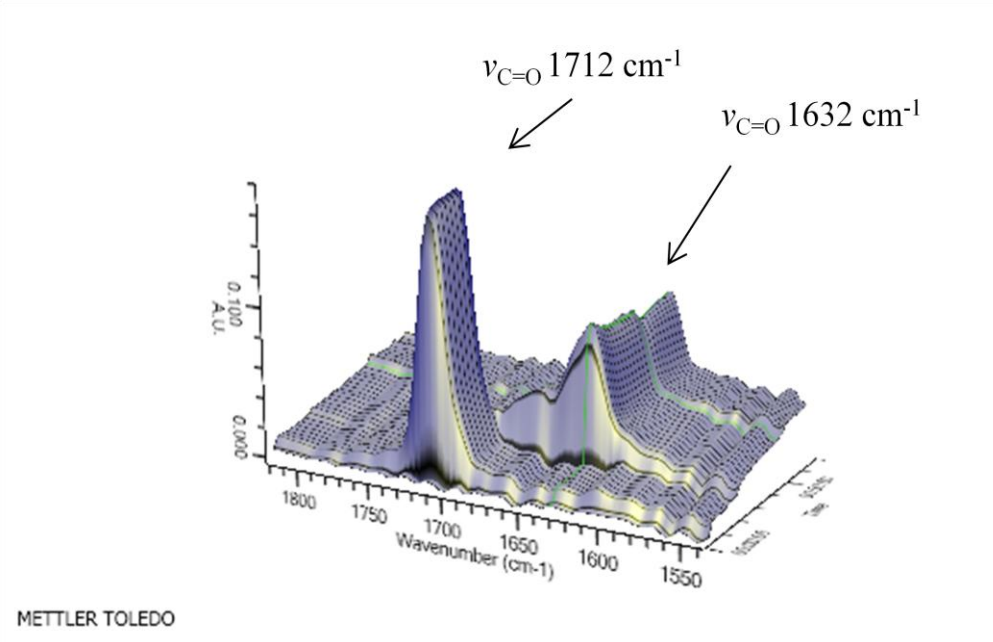
301

$\nu_{C=O}$ 1712cm^{-1}

$\nu_{C=O}$ 1632 cm^{-1}

Reagents and conditions: i) TMPMgCl (1 eq.), Et_2O, –75 °C.

Scheme 3-36



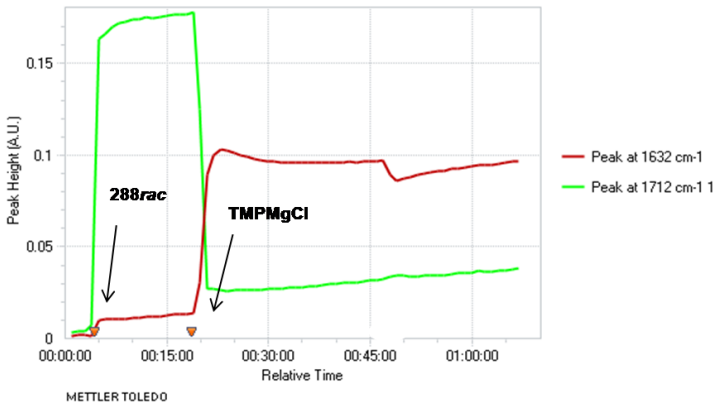
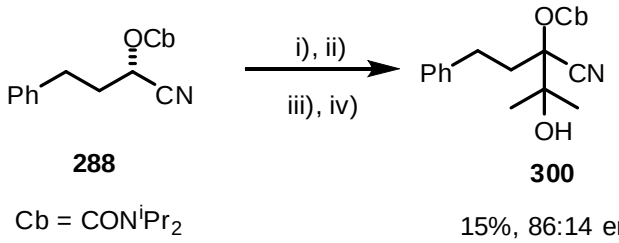


Figure 3-16

After this result, the reaction was carried out with only 1 equivalent of TMPMgCl to determine the yield and er. A solution of enantiomerically enriched nitrile **288** (100 mg) in Et_2O (2 mL) was added dropwise using the syringe pump over 4 min to a cooled (–107 ^oC) solution of TMPMgCl in 0.5 mL Et_2O. After 2 min acetone was added and the product **300** was isolated in 15% yield with 86:14 er (Scheme 3-37).



288 **300**

Cb = CON^iPr_2 15%, 86:14 er

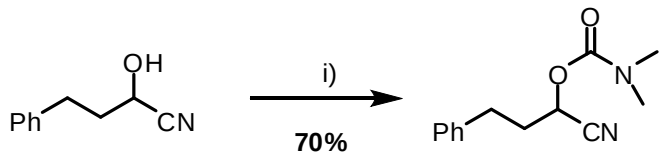
Reagents and conditions: i) TMPMgCl (1 eq.), Et_2O, –107 ^oC; ii) nitrile **288** (100 mg); iii) after 2 min, acetone (1 eq.); iii) after 30 min NH_4Cl (aq).

Scheme 3-37

The reaction was repeated with 1.2 equivalents of TMPMgCl and 3 equivalents of acetone using the same conditions except the addition time was 1 min (syringe pump) and acetone was added after 5 sec. Under these conditions only 10% yield was obtained (recovered starting materials 89%) with 85:15 er. These disappointing were results as react IR showed that the deprotonation was very fast and complete formation of the magnesiated intermediate was observed within 2 min after addition of one equivalent of TMPMgCl at –78 ^oC (Figure 3-16).

As mentioned earlier, acetone quench with a less sterically hindered substrate could increase the rate of quench and therefore improve the er. Dimethylcarbamoyl derivative **292** was prepared using the previous method for preparing starting material **288**. The

desired product was obtained in 70% yield and HPLC conditions to resolve the enantiomers were developed (Scheme 3-38).

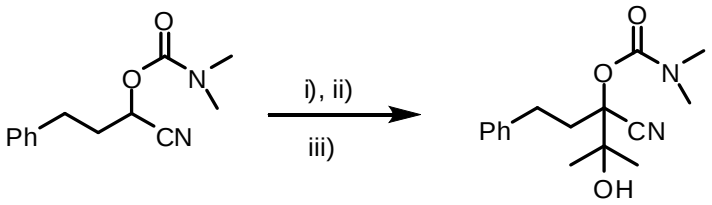


298$_{rac}$ **292**$_{rac}$

Reagents and conditions: i) $Cl_3COCOOCCl_3$, Et_2O, 0 °C, Et_3N, $HNMe_2$, 0 °C→ rt., 3 h.

Scheme 3-38

The reaction with acetone was carried out at –78 °C using ^{i}PrMgCl as base which was added to the racemic nitrile **292**$_{rac}$. After 10 min, dry acetone was added, then the reaction mixture was stirred at –78 °C for 30 min before allowing to warm to room temperature. The reaction was then quenched with aqueous NH_4Cl (Scheme 3-39).



292$_{rac}$ **302**$_{rac}$

Reagents and conditions: i) ^{i}PrMgCl, THF, –78 °C; ii) acetone; iii) after 30 min NH_4Cl (aq).

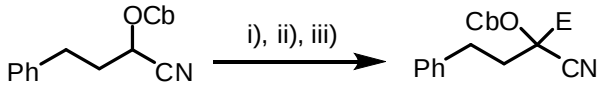
Scheme 3-39

Unfortunately, only a trace of the product **302** was isolated. The work was continued with the previous starting material **288**, while Dr Graeme Barker, another member in the group, carried out a study with dimethyl carbamoyl derivative **292**. At this point, ~50% yield and an enantiomeric ratio 85:15 of product **300** (using inverse addition with four equivalents of TMPMgCl and five equivalents of acetone) was accepted as the best results achieved for the acetone quench. With these optimised conditions different electrophiles would be investigated.

3.4.3 Scope of Metallation-Electrophile Quench of Racemic and Enantiomerically Enriched Carbamate 288

To study a range of electrophilic quenches, different electrophiles such as chloroformates, cyanoformate, aldehydes, ketones and acid chlorides needed to be tested. The reactions were carried out under typical conditions, in which the base was added to a cooled (–78 °C) solution of racemic starting material in Et_2O, and after 10

min the electrophile was added. After 30 min the reaction mixture was allowed to warm to the room temperature before aqueous NH_4Cl was added. Next, chiral stationary phase HPLC conditions were explored for all the electrophiles used to obtain methods for determining the enantiomeric ratios after trapping enantiomerically enriched nitrile **288** (Table 3-7, Scheme 3-40).



288$_{rac}$ Cb = CON^iPr_2 **303-311**

Reagents and conditions: i) base, Et_2O, –78 ^oC; ii) 10 min, E^+; iii) 30 min then NH_4Cl (aq).

Scheme 3-40

The first examined electrophile was methyl iodide. The nitrile **288**$_{rac}$ was reacted with ^{i}PrMgCl (4 equivalents) or TMPMgCl (4 equivalents) as a base, followed by addition of methyl iodide. However only unreacted starting material was recovered (Table 3-7, entries 1 and 2). Changing the base to LDA (1.2 equivalents) produced the desired product **303** in moderate yield (60% yield, entry 3). An excellent yield was obtained when using CH_3OCOCl as the electrophile with ^{i}PrMgCl as the base (entry 4). Benzaldehyde was also utilised as the electrophile, giving 77% yield (entry 5). With cyclopentanone as the electrophile, only 54% yield was obtained using TMPMgCl as the base (entry 6). A moderate yield resulted when benzoyl chloride was used as the electrophile (entry 7).

Table 3-7[a]

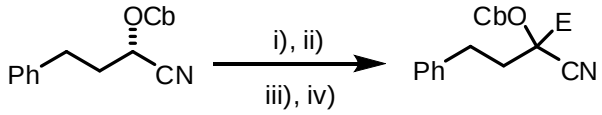
Entry	E^+	Base	Yield[b]	Product
1	CH_3I (5 eq.)	^{i}PrMgCl (4 eq.)	Only SM	**288**$_{rac}$
2	CH_3I (5 eq.)	TMPMgCl (4 eq.)	Only SM	**288**$_{rac}$
3	CH_3I (1.1 eq.)	LDA (1.2 eq.)	60%	**303**
4	CH_3OCOCl (5 eq.)	^{i}PrMgCl (4 eq.)	95%	**304**
5	PhCHO (5 eq.)	^{i}PrMgCl (4 eq.)	77%	**305** dr 1:1[c]
6	cyclopentanone (5 eq.)	TMPMgCl (4 eq.)	54%	**306**
7	PhCOCl (6 eq.)	LDA (5.5 eq.)	72%	**307**
8	C_2H_5OCOCN (6 eq.)	LDA (5.5 eq.)	82%	**291**
9	$PhCH_2OCOCN$ (5 eq.)	TMPMgCl (4 eq.)	50%	**308**
10	HCHO (5 eq.)	^{i}PrMgCl (4 eq.)	Only SM	**288**$_{rac}$
11	HCHO (5 eq.)	TMPMgCl (4 eq.)	Only SM	**288**$_{rac}$
12	^{t}BuCHO (5 eq.)	^{i}PrMgCl (4 eq.)	17%	**309** dr 1:0[c]
13	CH_3CHO (6 eq.)	LDA (5.5 eq.)	86%	**310** dr 1:1[c]
14	PhOCOCl (6 eq.)	LDA (5.5 eq.)	93%[d]	**311**

[a] For conditions, see Scheme 3-40. [b]Yield based on isolated yields after column chromatography. [c] Diastereomeric ratio determined by ^{1}H NMR. [d]Yield of the product **311** and the electrophile.

Ethyl cyanoformate and benzyl cyanoformate were used for racemic quench and reasonable yields of **291** and **308** were obtained (entries 8 and 9). With all the electrophiles which have been tried so far, reasonable yields of **303**-**308** as well as suitable conditions for the HPLC were achieved.

With cracked formaldehyde as the electrophile no product was isolated with either ^{i}PrMgCl or TMPMgCl (entries 10 and 11). The reaction was carried out under the same conditions with pivaldehyde and only 17% yield was obtained (entry 12). The reaction with acetaldehyde gave a better yield of 86% (entry 13). However, a method for resolving the enantiomers of products **309** and **310** by chiral stationary phase HPLC or

GC was not determined after using a range of HPLC columns (cellulose-1, cellulose-2, AD, OD and OJ). With phenyl chloroformate, purification problems prevented the determination of the reaction yield as the product **311** and the electrophile have similar R_f values (entry 14). Having different racemic nitrile products in hand, synthesis of the enantiomerically enriched nitrile products and enantiomeric ratio determination was carried out (Scheme 3-41).



288 Cb = CON^iPr_2 **303-304**

Reagents and conditions: i) Base, Et_2O, –107 °C; ii) **288**; iii) E^+; iv) after 30 min NH_4Cl (aq).

Scheme 3-41

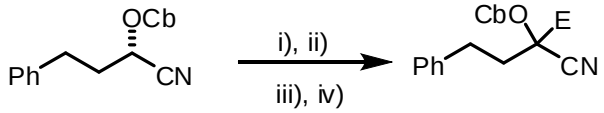
After the promising results with acetone (44% and 82:18 er, Table 3-1) were obtained, methyl iodide was examined as electrophile employing LDA as base (no product was obtained using ^{i}PrMgCl Table 3-8, entry 1). The reaction was carried out at –107 °C, and the enantiomerically enriched nitrile **288** was added to LDA, followed by the methyl iodide after 10 min. After 30 min the reaction was quenched with aqueous NH_4Cl at –107 °C, to give the desired product **303** in moderate yield but with complete racemisation (entry 2). This is probably due to lithium co-ordinating to the nitrogen atom and allowing the intermediate to racemise very quickly before trapping with the electrophile. Methyl chloroformate was also tested with LDA as the base to give the desired product **304** in excellent yield but in racemic form (90% yield, entry 3). Switching the base to ^{i}PrMgCl and using inverse addition protocol with the electrophile was added after 10 min, a moderate yield of the product **304** was obtained with slight improvement in the selectivity (60% yield, 60:40 er, entry 4).

Table 3-8[a]

Entry	E^+	Base	Yield[b]	er[c]	Product
1	CH_3I (5eq.)	^iPrMgCl (4 eq.)	0%	-	-
2	CH_3I (1.1 eq.)	LDA (1.2 eq.)	60%	50:50	**303**
3	CH_3OCOCl (6 eq.)	LDA (5.5 eq.)	90%	50:50	**304**
4	CH_3OCOCl (5 eq.)	^iPrMgCl (4 eq.)	60%	60:40	**304**

[a] For conditions, see Scheme 3-41. [b] Yield based on isolated yields after column chromatography. [c] Enantiomer ratio determined by CSP-HPLC.

Beside our developed optimised conditions with acetone, there is another method developed by Dr Graeme Barker (with dimethylcarbamoyl derivative **292)**. In this method, a solution of 3 equivalents of the enantiomerically enriched nitrile in 0.5 mL mixture of Et_2O:THF (1:1) was added dropwise over 4 min (using a syringe pump) to a cooled (–107 °C) solution of 3 equivalents TMPMgCl and 2.5 mL mixture of Et_2O:THF (1:1), followed by addition of the electrophile after 10 s (Table 3-9, Scheme 3-42).



288 Cb = CON^iPr_2 **304-308**

Reagents and conditions: i) TMPMgCl, Et_2O:THF, –107 °C; ii) nitrile **288**; iii) E^+; iv) after 30 min NH_4Cl (aq).

Scheme 3-42

A method to determine the er of the product **304** had been found by using CSP-HPLC, so the idea was to examine methyl cyanoformate which is a reactive electrophile. The reaction was carried out under the above conditions giving the desired product **304** with a decrease in the chemical yield to 38% but with improvement in enantiomeric ratio to 81:19 er (compared with 60:40 er for methyl chloroformate) (Table 3-9, entry 1).

Table 3-9[a]

Entry	E^+	Add time of E^+	Yield[b]	er[c]	Product
1	CH_3OCOCN	10 s	38%	81:19	**304**
2	CH_3COCH_3	10 s	48%	86:14	**300**
3	CH_3OCOCN	*in situ*	40%	91:9	**304**
4	CH_3COCH_3	*in situ*	13%	73:27	**300**
5	$PhCH_2OCOCN$	*in situ*	52%	91:9	**308**
6	C_2H_5OCOCN	*in situ*	72%	81:19	**291**
7	PhCOCl	*in situ*	40%	63:37	**307**
8	cyclopentanone	2 min	50%	92:8	**306**
9	PhCHO	2 min	60%	dr 1:1, 92:8, 84:16	**305**

[a] For conditions, see Scheme 3-42. [b] Yield based on isolated yields after column chromatography. [c] Enantiomer ratio determined by CSP-HPLC.

When acetone was tested with these conditions, similar results were obtained to the results reported in Table 3-6, entry 6 (entry 2). Next, Dr Graeme Barker found (with dimethylcarbamoyl **292** substrate) more exciting results with the *in situ* trapping. The solution of enantiomerically enriched nitrile **288** in a mixture of Et_2O:THF (1:1) was mixed with the electrophile (3 equivalents), then the mixture was added dropwise over 4 min (using a syringe pump) to a cooled (– 107 ^oC) solution of TMPMgCl (3 equivalents) in a mixture of Et_2O:THF (1:1). After the reaction mixture was stirred at –107 ^oC for 30 min, the reaction was quenched using aqueous NH_4Cl at – 107 ^oC. Methyl cyanoformate was the first electrophile attempted with this procedure and a significant improvement was obtained in the enantiomeric ratio (91:9) but with only 40% yield (entry 3). Under the *in situ* trapping protocol, acetone was examined as the electrophile but a poor chemical yield (13%) was obtained with poor enantioselectivity 73:27 (entry 4) which indicated that acetone is not a good electrophile for *in situ* quench.

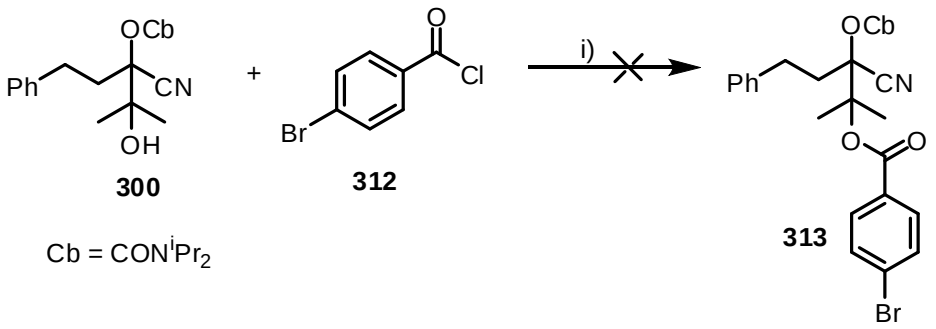
More experiments were carried out under the *in situ* protocol with different electrophiles. Utilising benzyl cyanoformate resulted in a moderate yield with a good enantiomeric ratio 91:9 (entry 5). In the case of ethyl cyanoformate the chemical yield improved to 72% but the enantiomeric ratio decreased to 81:19 (entry 6). With benzoyl chloride, low chemical yield and poor er were obtained (40%, 63:37, entry 7). Benzaldehyde and cyclopentanone were examined under the optimised conditions. A

solution of enantiomerically enriched nitrile **288** in Et_2O (2.0 mL) was added (using a syringe pump) over 4 min to a cooled (–107 °C) solution of TMPMgCl in Et_2O (1.0 mL), after 2 min the electrophile was added. In the case of cyclopentanone, reasonable yield and good enantioselectivity were obtained (50%, 92:8 er, entry 8). Benzaldehyde offered moderate yield of 60% and good enantiomeric ratios 92:8 and 84:16 er with 1:1 diastereomeric ratio (entry 9).

3.4.4 Absolute Configuration Determination

The absolute configuration of the major enantiomer **300** was investigated, in order to know if the substitution reaction occurs with inversion or retention of configuration. A heavy atom is required to be installed in the nitrile product **300** for absolute configuration determination by X-ray crystallographic analysis.

The alcohol **300** was treated with 4-bromobenzoyl chloride (**312**) in CH_2Cl_2, but only starting material was recovered (Scheme 3-43).

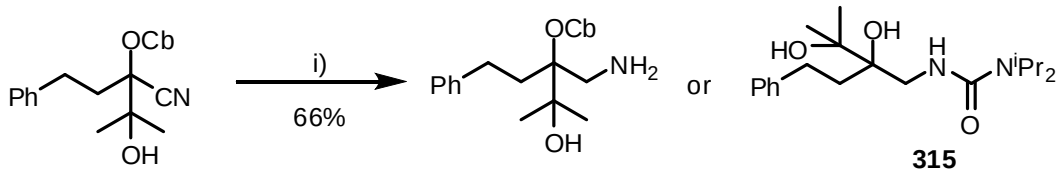


Reagents and conditions: i) DMAP, Et_3N, CH_2Cl_2, rt. → 0 °C → rt.

Scheme 3-43

Repeating the reaction at room temperature using pyridine instead of DMAP, again returned only starting material. The poor results may be attributed to steric reasons as the alcohol **300** is a tertiary alcohol and hindered.

Another attempt was performed by reduction of the CN group to a primary amine, which would be able to react with 4-bromobenzoyl chloride. Lithium aluminum hydride was added to a cooled (0 °C) solution of alcohol **300** in THF, and the reaction was monitored by TLC until there was complete consumption of the starting material. The product **314** (it could be an amide **315**)[139] was obtained in 66% yield after purification by column chromatography (petrol:EtOAc 1:1), (Scheme 3-44).



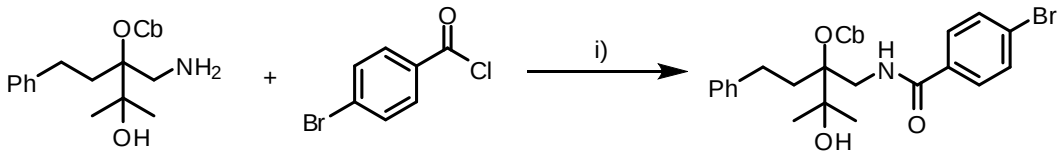
300 **314** **315**

Cb = CON^iPr_2

Reagents and conditions: i) $LiAlH_4$, THF, rt.

Scheme 3-44

The amine **314** was then reacted with 4-bromobenzoyl chloride in CH_2Cl_2 and pyridine at room temperature. After stirring the reaction mixture for 24 h, the mixture was purified by column chromatography. Unfortunately it was not possible to isolate clean product **316** which was oil, even though presence of the product was apparent from Mass and NMR spectra (Scheme 3-45).



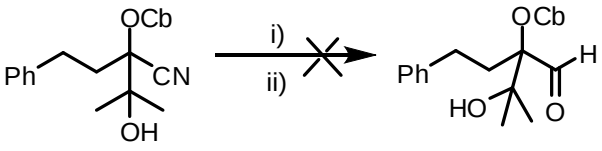
313 **312** **316**

Cb = CON^iPr_2

Reagents and conditions: i) Py, CH_2Cl_2, rt.

Scheme 3-45

Another protocol considered was the reaction of nitrile **300** with DIBAL-H which would give aldehyde **317**, which would react with a hydrazine including a heavy atom. DIBAL-H (1.5 equivalents) was added to a solution of alcohol **300** in CH_2Cl_2 at –78 °C. However only starting material was observed by TLC, even when the reaction was warmed to room temperature or when 2 equivalents of DIBAL-H were used (Scheme 3-46).



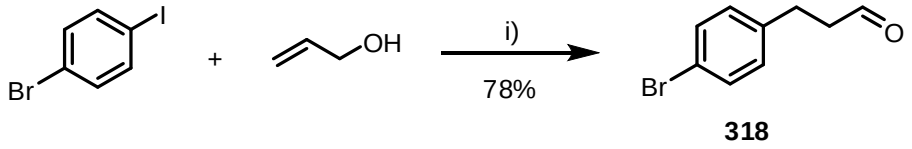
300 **317**

Cb = CON^iPr_2

Reagents and conditions: i) DIBAL-H, CH_2Cl_2, –78 °C; ii) HCl (aq).

Scheme 3-46

After all these disappointing results, another strategy was utilised, namely preparing a substrate with a bromine atom present. Firstly, the aldehyde was synthesised by reacting 4-bromoiodobenzene and allyl alcohol in the presence of $NaHCO_3$, Bu_4NCl and $Pd(OAc)_2$ in anhydrous DMF at 40 ^oC for 20 h. Purification of the crude reaction mixture gave 78% yield of the desired product **318** (Scheme 3-47).[151]

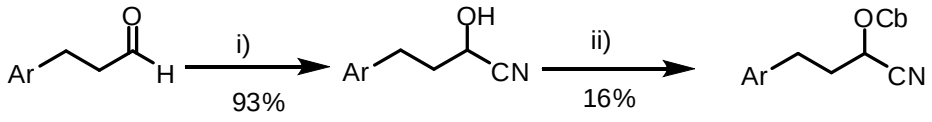


318

Reagents and conditions: i) $NaHCO_3$, Bu_4NCl, $Pd(OAc)_2$, DMF, 40 ^oC.

Scheme 3-47

With aldehyde **318** in hand, the racemic nitrile starting material was prepared using the method used earlier for nitrile **288** (Scheme 3-28). The aldehyde **318** was reacted with $NaHSO_3$ and NaCN for 24 h giving cyanohydrin **319** in excellent yield (93%). Then cyanohydrin **319**$_{rac}$ was treated with triphosgene and diisopropylamine to give the desired racemic nitrile **320**$_{rac}$ in a poor yield (16%) (Scheme 3-48).



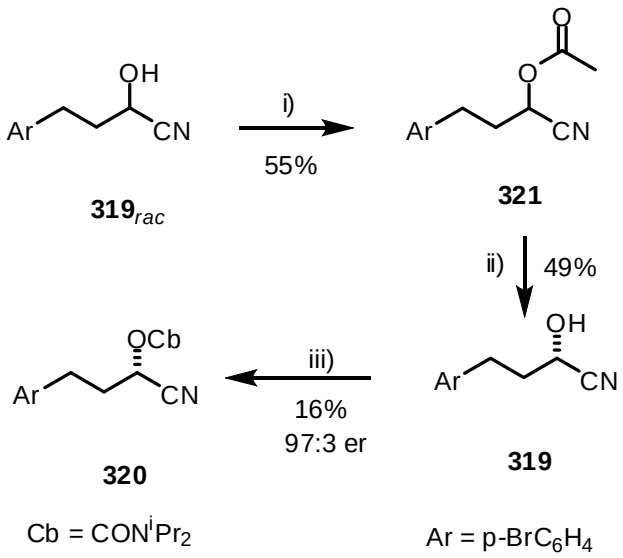
318 **319** **320**

Ar = p-BrC_6H_4 Cb = CON^iPr_2

Reagents and conditions: i) $NaHSO_3$, NaCN, 0 °C → rt., 4h; ii) $Cl_3COCOOCl_3$, Et_2O, Et_3N, $^iPr_2NH$, rt., 3 h.

Scheme 3-48

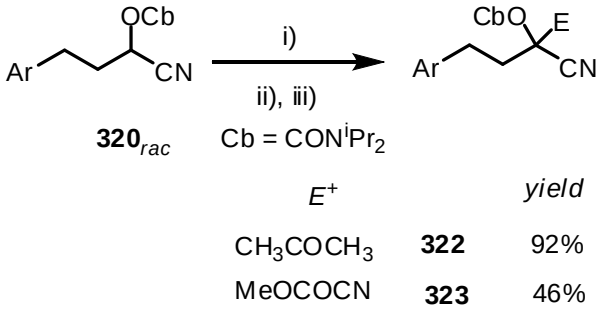
Enantiomerically enriched starting material **320** was successfully synthesised. Reaction of cyanohydrin **319**$_{rac}$ with acetic anhydride for 24 h provided acetate **321** in moderate yield, then the lipase reaction gave 49% yield of the desired cyanohydrin **319**. This was converted to carbamate **320** in poor yield, but with an excellent er of 97:3 as determined by CSP-HPLC. The absolute configuration of the nitrile **320** is assumed to be as shown (*S* enantiomer) based on comparsion of *S*-cyanohydrin **319** with known *R*-cyanohydrin **319**[148] (Scheme 3-49).



Reagents and conditions: i) Ac_2O, Py, CH_2Cl_2, rt.; ii) Amano Lipase PS, THF-H_2O, 50 °C, 2h; iii) $Cl_3COCOOCl_3$, Et_2O, Et_3N, $^iPr_2NH$, rt., 3h.

Scheme 3-49

The typical procedure for quenching with racemic nitrile **288** was applied. TMPMgCl was added to a solution of nitrile **320** in Et_2O at –78 °C, followed by addition of electrophile after 10 min. The reaction mixture was stirred at the same temperature for 30 min before warming to room temperature and quenching with aqueous NH_4Cl. The use of acetone as the electrophile provided the desired product **322** in excellent yield (92%), while only 46% of the product **323** was obtained when methyl cyanoformate was used (Scheme 3-50).

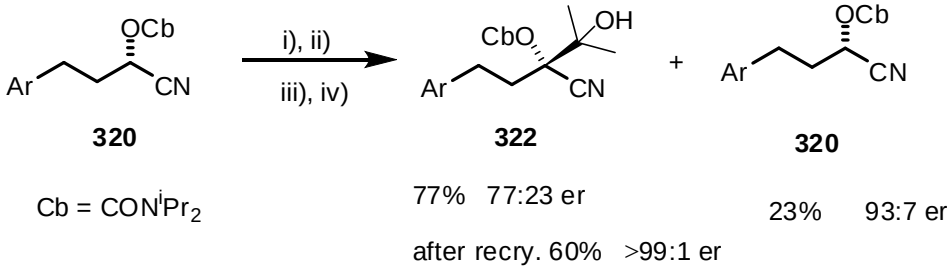


Reagents and conditions: i) TMPMgCl, Et_2O, –78 °C; ii) 10 min, E^+; iii) after 30 min NH_4Cl (aq).

Scheme 3-50

After HPLC conditions were determined, the reaction was carried out by reacting enantiomerically enriched starting material **320** firstly with acetone. A solution of nitrile **320** in Et_2O was added dropwise (using a syringe pump) over 4 min to a solution of

TMPMgCl at –107 °C. After 2 min acetone was added, then the reaction mixture was stirred at –107 °C for 30 min before quenching with aqueous NH_4Cl. The desired alcohol **322** was obtained in 77% yield and 77:23 er which was improved to > 99:1 after recrystallisation. The rest of the material was recovered nitrile **320** in 23% yield and 93:7 er (Scheme 3-51).



Reagents and conditions: i) TMPMgCl, Et_2O, –107 °C; ii) nitrile **320**; iii) acetone; iv) after 30 min NH_4Cl (aq).

Scheme 3-51

With the required compound **322** in hand, the absolute configuration for the major enantiomer of compound **322** was determined by X-ray crystallographic analysis, indicating that the reaction occurs with retention of configuration (Figure 3-17).

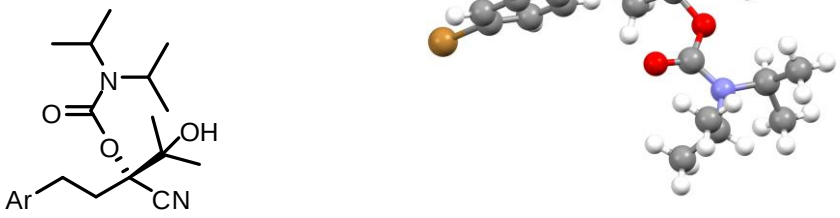
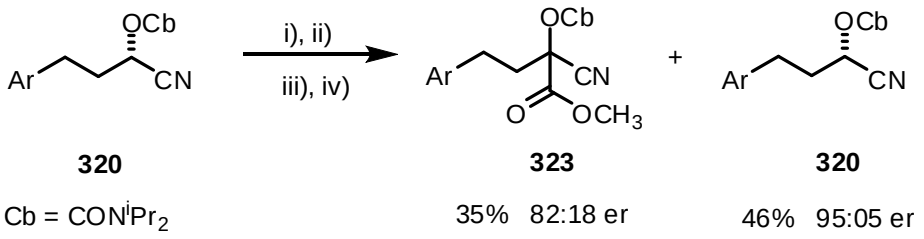


Figure 3-17

This result was not as expected, because it was reported that similar reactions occur with inversion of configuration.[118] The product **323** resulting from methyl cyanoformate quench was also investigated. The reaction was carried out at –107 °C using the *in situ* strategy. A solution of enantiomerically enriched nitrile **320** with methyl cyanoformate in THF:Et_2O (1:1) was added dropwise (by syringe pump) over 4 min to a cooled (–107 °C) solution of TMPMgCl in THF:Et_2O (1:1). After stirring for 30 min the reaction was quenched at –107 °C. The reaction mixture was purified by column chromatography (petrol–EtOAc 9:1) and provided the required product **323** in 35% yield and 82:18 er with 46% yield of recovered starting material **320** (Scheme 3-52).



320 **323** **320**

Cb = CON^iPr_2 35% 82:18 er 46% 95:05 er

Reagents and conditions: i) TMPMgCl, Et_2O:THF, –107 °C; ii) nitrile **320**; iii) methyl cyanoformate; iv) after 30 min NH_4Cl (aq).

Scheme 3-52

Unfortunately, all attempts to recrystallise the nitrile **323** were not successful. We were therefore not able to verify the absolute configuration of the product from electrophilic quench with methyl cyanoformate. Based on the literature,[118] we would expect that reaction would occur with inversion of configuration. However we have found that acetone quenches with retention of configuration, so it is possible that the bulkier CON^iPr_2 group hinders approach of the electrophile and thereby favours retention of configuration.

3.5 Conclusion

A deprotonation / electrophile quenching method for an enantioenriched nitrile with a stereocentre α to the nitrile group has been developed. The deprotonation was carried out using a magnesium base. Firstly, organomagnesium species were formed, then subsequent quench with acetone furnished the substituted nitrile **300** in moderate yield (45%) and good enantioselectivity (90:10 er) using ^{i}PrMgCl, while using TMPMgCl as a base provided 50% yield and 85:15 er. The optimised conditions with TMPMgCl were applied to cyclopentanone as the electrophile and gave a good yield and enantiomer ratio (50%, 92:8 er), with benzaldehyde as the electrophile a reasonable chemical yield (60%) and selectivity (dr 1:1, 92:8, 84:16 er) were obtained. A strategy for alkylation of the enantioenriched nitrile using a magnesium base and the electrophile *in situ* was demonstrated with a variety of electrophiles exhibiting good yields. Unfortunately, only with methyl cyanoformate and benzyl cyanoformate were good enantiomer ratios of the products achieved in moderate yields (40%, 91:9 er, 52%, 91:9 er respectively).

The absolute configuration of the major enantiomer of the alcohol **300** from electrophilic quench with acetone was determined by X-ray crystallographic analysis, indicating that the reaction occurs with retention of configuration. However, in the case

of methyl cyanoformate as the electrophile the absolute configuration of the product was not determined. Selected results from section 3.4 have been reported.[152]

3.6 Future work

Determination of the absolute configuration of the product from electrophilic quench with benzyl cyanoformate and methyl cyanoformate would be an important addition to this project and would provide evidence for whether the reaction occurs *via* retention or inversion.

Alkylation of the copper metallated nitrile would be of interest. If the copper species could be generated by addition of CuI, CuBr or CuCN.2LiCl to the reaction mixture of magnesiated nitrile followed by subsequent electrophilic quench, then electrophiles such as MeI, which did not trap with the magnesiated nitrile, may be successful.

4 Experimental

4.1 General

All reagents were obtained from commercial suppliers and were used without further purification unless otherwise stated. Solvents were obtained from Grubbs dry solvent system (model: SPS-200-6). LiCl was flame-dried under vacuum before using, $^{i}PrMgCl$[153] was titrated before using. Thin Layer Chromatography was performed on Machery-Nagel-Alugram Sil G/UV 254 silica plates and visualised by UV irradiation at 254 nm or by staining with an alkaline $KMnO_4$ dip. Flash column chromatography was performed using DAVISIL silica gel (40-63 micron mesh).

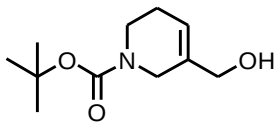
^{1}H NMR spectra were recorded on either a Bruker AC250 (250 MHz), Bruker AC400 (400 MHz) or a Bruker AC500 (500 MHz) instrument. Chemical shifts are reported in ppm with respect to the residual solvent peaks with multiplicities given as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Coupling constants (*J* values) are quoted to the nearest 0.5 Hz with values in Hertz (Hz) and are corrected. ^{13}C NMR spectra were recorded on the same instruments as for the ^{1}H NMR experiments at either 63 MHz, 100 MHz or 125 MHz. ^{1}H-^{1}H and ^{1}H-^{13}C correlation spectra were run in order to confirm the assignment of peaks.

Low resolution and high resolution mass spectra were recorded on a Micro mass Autospec for Electron Impact (EI) and on a Walters LCT instrument for Electrospray (ES). Infra-Red (IR) spectra were recorded on a Perkin Elmer Spectrum RX Fourier Transform–IR System. Only selected peaks are reported and absorption maxima are given in cm^{-1}. Specific rotations were calculated from optical rotation recorded on an AA-10 automatic polarimeter. X-ray data was measured on a Bruker Smart CCD area detector with Oxford Cryosystems low temperature system. Melting points were recorded on a Gallenkamp hot stage and were uncorrected. Gas chromatographs were recorded on a Perkin Elmer Arnel Autosystem XL GC using an Astec CHIRALDEX B-DM fused silica capillary column (30 m × 0.25 mm × 0.12 μm film thickness). HPLCs were recorded using a Gilson machine. React IR experiments were recorded using a Mettler-Toledo ReactIR 4000 instrument.

Formation of TMPMgCl [154]

TMPH (3mL, 18 mmol) was added to ^{i}PrMgCl (9 mL, 18 mmol, 2 M in THF or Et_2O) under N_2 at room temperature and left to stir overnight in the dark. THF or Et_2O (10 mL) was added. The mixture was titrated against iodine to determine the concentration.[153]

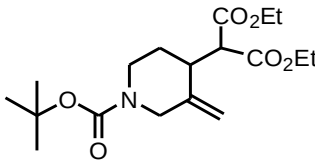
5-Hydroxymethyl-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester 33[48]



Benzyl bromide (5.80 mL, 48.1 mmol) was added dropwise to a solution of pyridine-3-methanol (5.0 g, 45.8 mmol) in CH_2Cl_2 (17 mL). The mixture was allowed to stir for 18 h at room temperature and then evaporated to give the crude salt as an oil which was used without purification in the next step. $NaBH_4$ (3.40 g, 91.7 mmol) was added portionwise over 15 min to a solution of the salt in methanol (50 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred overnight. The methanol was removed under reduced pressure and the residue was treated with 1N NaOH (42 mL). The resulting mixture was extracted with diethyl ether (3 × 15 mL) and the organic layers were combined, dried ($MgSO_4$) and evaporated to give the *N*-benzyl-tetrahydropyridine as an oil (8.40 g, 90%) which was used in the next step without purification. $NaHCO_3$ (1.95 g, 23.0 mmol) was added to a solution of amine (8.40 g, 41.3 mmol) in toluene (65 mL). Methyl chloroformate (4.20 mL, 54.2 mmol) was added dropwise over 15 min to the stirred mixture at room temperature, and the mixture was heated at 110 °C for 16 h. The reaction mixture was allowed to cool to room temperature and the toluene was removed under reduced pressure. The resulting residue was dissolved in EtOAc (3 × 15 mL) and was washed with water (10 mL), 0.5 *M* HCl (10 mL) and brine (10 mL) then dried ($MgSO_4$) and evaporated to afford the crude methylcarbamate **32** (4.37 g, 56%) as an oil, which was used without purification in the next step. A solution of KOH (6.25 g, 111. 6 mmol) in water (25 mL) was added to a solution of the above crude methylcarbamate **32** in methanol (25 mL) and the resulting mixture was stirred at reflux for 18 h. The mixture was cooled to 0 °C and then treated with $NaHCO_3$ (9.35 g, 111.0 mmol) and di-tert-butyl-dicarbonate (4.85 g, 22.3 mmol).

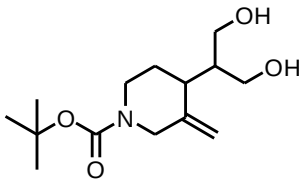
The reaction mixture was stirred at 0 °C for 1 h and then for 4 h at room temperature. The methanol was evaporated and the remaining aqueous solution was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with 0.5 M HCl (2 × 10 mL), water (10 mL), saturated $NaHCO_3$ then dried ($MgSO_4$). The solvent was evaporated and the crude material was purified by column chromatography on silica gel, eluting with petrol–EtOAc (50:50), to provide the alcohol **33** (6.0 g, 62%) as an oil; R_f 0.58 [petrol–EtOAc (50:50)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.80 (1H, s, CH), 4.01 (2H, s, CH_2), 3.89 (2H, s, CH_2), 3.47 (2H, t, *J* 5.5, CH_2), 2.12 (2H, br. s, CH_2), 1.94 (1H, s, OH), 1.45 (9H, s, 3 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.0 (CO), 132.4 (C), 128.8 (CH), 79.7 (C), 68.1 (CH_2), 44.4 (CH_2), 41.5 (CH_2), 30.3 (CH_2), 28.5 (CH_3); HRMS (ES) found: MNa^+, 236.1252. $C_{11}H_{19}NO_3Na^+$ requires MNa^+, 236.1263; LRMS *m*/*z* (ES) 236 (100%, MNa^+). Data in accordance with the literature.[48]

2-(1-*tert*-Butoxycarbonyl-3-methylene-piperidin-4-yl)-malonic acid diethyl ester 132[49]



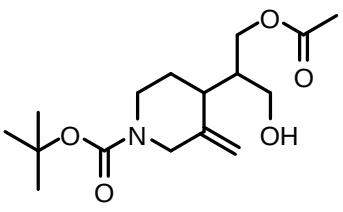
A mixture of the allylic alcohol **33** (0.30 g, 1.4 mmol), 2,4-dinitrophenol (0.03 g, 14.0 mmol) and 3,3-diethoxyacrylic acid ethyl ester (0.50 mL, 2.8 mmol) in toluene (8 mL) were heated under reflux for 90 min. The solvent was evaporated and the residue was purified by column chromatography, eluting with petrol–EtOAc (9:1) to give the diester **132** (0.30 g, 75%) as an oil; R_f 0.33 [petrol–EtOAc 9:1]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.96 (1H, s, C=C*H*H), 4.78 (1H, s, C=CH*H*), 4.15–4.11 (2H, m, CH_2), 4.12–4.08 (2H, m, CH_2), 3.99 (1H, d, *J* 14, CH), 3.84 (1H, d, *J* 14, CH), 3.70 (1H, d, *J* 11, CH), 3.59–3.57 (1H, m, CH), 3.40–3.33 (1H, m, CH), 3.10-3.04 (1H, m, CH), 1.79–1.75 (1H, m, CH), 1.58–1.54 (1H, m, CH), 1.46 (9H, s, 3 × CH_3), 1.27 (3H, t, *J* 7, CH_3), 1.18 (3H, t, *J* 7, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.0 (C=O), 154.6 (C=O), 142.8 (C), 111.3 (CH_2), 79.7 (C), 61.6 (CH_2), 61.5 (CH_2), 53.7 (CH), 48.8 (CH_2), 41.9 (CH_2), 40.9 (CH), 29.5 (CH_2), 28.4 (CH_3), 14.1 (CH_3), 14.0 (CH_3); HRMS (ES) found: MH^+, 356.2090. $C_{18}H_{30}NO_6$ requires MH^+, 356.2073; LRMS *m*/*z* (ES) 300 (100%), 356 (MH^+). Data in accordance with the literature.[49]

4-(2-Hydroxy-1-hydroxymethyl-ethyl)-3-methylene-piperidine-1-carboxylic acid *tert*-butyl ester 133[155]

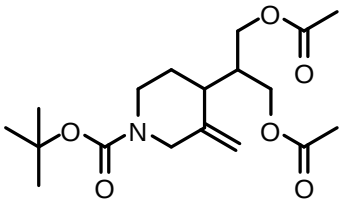


A solution of diester **132** (1.64 g, 4.6 mmol) in THF (15 mL) was added dropwise at 0 °C to $LiAlH_4$ suspension in THF. After 1 h water (3 mL), NaOH (3 mL, 4 M) and water (8 mL) were added and the mixture was filtered through Celite. The solvent was evaporated and the crude material was purified by column chromatography, eluting with EtOAc, to afford the diol **133** (0.85 g, 65%) as an oil; R_f 0.44 [EtOAc]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.87 (1H, br.s, C=C*H*H), 4.86 (1H, s, C=CH*H*), 3.99–3.95 (2H, m, CH_2), 3.84–3.73 (4H, m, 2 × CH_2), 3.53–3.46 (2H, m, CH_2), 2.65 (2H, br.s, 2 × OH), 2.46−2.41 (1H, m, CH), 2.06–1.99 (1H, m, CH), 1.79−1.71 (1H, m, CH), 1.67−1.60 (1H, m, CH), 1.46, (9H, s, 3 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 154.9 (C=O), 143.9 (C), 111.5 (CH_2), 79.7 (C), 65.3 (CH_2), 63.9 (CH_2), 41.0 (CH_2), 40.1 (CH), 38.5 (CH), 28.5 (CH_2), 28.4 (CH_3); HRMS (ES) found: MNa^+, 294.1680. $C_{14}H_{25}NO_4Na$ requires MNa^+, 294.1681; LRMS *m*/*z* (ES) 294 (100%, MNa^+). Data in accordance with the literature.[155]

4-(2-Acetoxy-1-hydroxymethyl-ethyl)-3-methylene-piperidine-1-carboxylic acid *tert*-butyl ester 153 and 4-(2-Acetoxy-1-acetoxymethyl-ethyl)-3-methylene-piperidine-1-carboxylic acid *tert*-butyl ester 154



153



154

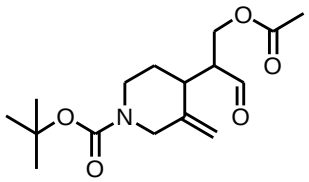
A mixture of diol **133** (0.20 g, 0.73 mmol), Ac_2O (0.10 mL, 0.75 mmol), DMAP and pyridine (0.05 mL, 0.74 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 24 h. Water (5 mL) was added and the solution was extracted with CH_2Cl_2 (3 × 5 mL).

The combined organic layers were washed with brine (5.0 mL), dried ($MgSO_4$) evaporated and the residue was purified by column chromatography, eluting with EtOAc, to afford the acetate **153** (0.15 g, 68%) as a mixture of diastereomers as (1:1) as an oil; R_f 0.64 [EtOAc]; ν_{max}/cm^{-1} 3445, 2950, 1735, 1665, 1160; ^1H NMR (400 MHz, $CDCl_3$) δ = 4.99 (1H, br.s, C=C*H*H), 4.85 (0.5H, s, C=CH*H*), 4.83 (0.5H, s, C=CH*H*), 4.38 (0.5H, d, *J* 3.5, CH), 4.35 (0.5H, d, *J* 3.5, CH), 4.21 (0.5H, d, *J* 4.5, CH), 4.18 (0.5H, d, *J* 4.5, CH), 4.12 (0.5H, d, *J* 6.5, CH), 4.09 (0.5H, d, *J* 6.5, CH), 3.96 (0.5H, d, *J* 10, CH), 3.93 (0.5H, d, *J* 10, CH), 3.80−3.75 (1H, m, CH), 3.74−3.72 (1H, m, CH), 3.66−3.58 (0.5H, m, CH), 3.54−3.46 (0.5H, m, CH), 3.43−3.31 (1H, m, CH), 2.38−2.33 (1H, m, CH), 2.09−2.08 (2H, m, CH&OH), 2.06 (3H, s, CH_3), 1.74−1.70 (1H, m, CH), 1.66−1.56 (1H, m, CH), 1.42 (9H, s, 3 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.6 (C=O), 171.5 (C=O), 154.7 (C=O), 154.6 (C=O), 143.8 (C), 143.5 (C), 111.9 (CH_2), 111.6 (CH_2), 79.7 (C), 79.6 (C), 63.6 (CH_2), 62.3 (CH_2), 61.5 (CH_2), 59.8 (CH_2), 40.8 (CH_2), 39.2 (CH), 39.0 (CH), 38.9 (CH), 38.7 (CH), 28.4 (CH_3), 28.3 (CH_2), 28.2 (CH_2), 20.9 (CH_3); HRMS (ES) found: MH^+, 314.1974. $C_{16}H_{28}NO_5$ requires MH^+, 314.1967; LRMS *m*/*z* (ES) 214 (100%, MH^+).

Di acetate **154** (0.07 g, 28%) as an oil; R_f 0.82 [EtOAc]; ν_{max}/cm^{-1} 2915, 1740, 1690, 1225, 1165; ^1H NMR (400 MHz, $CDCl_3$) δ = 5.02 (1H, br.s, C=C*H*H), 4.86 (1H, s, C=CH*H*), 4.27 (1H, dd, *J* 8, 4.5, CH), 4.17 (1H, dd, *J* 8, 4.5, CH), 4.08 (1H, dd, *J* 8, 5, CH), 3.99 (1H, dd, *J* 8, 5, CH), 3.90 (1H, d, *J* 14, CH), 3.82 (1H, d, *J* 14, CH), 3.52−3.38 (2H, m, CH_2), 2.40−2.30 (2H, m, 2 × CH), 2.08 (3H, s, CH_3), 2.06 (3H, s, CH_3), 1.79−1.74 (1H, m, CH), 1.66−1.46 (1H, m, CH), 1.46 (9H, s, 3 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.9 (C=O), 154.6 (C=O), 143.1 (C), 112.0 (CH_2), 79.7 (C), 63.1 (CH_2), 61.9 (CH_2), 39.5 (CH), 35.9 (CH), 29.6 (CH_2), 28.1 (CH_3), 28.1 (CH_2), 20.8 (CH_3); HRMS (ES) found: MH^+, 356.2083. $C_{18}H_{30}NO_6$ requires MH^+, 356.2073; LRMS *m*/*z* (ES) 256 (100%, MH^+), 240 (40).

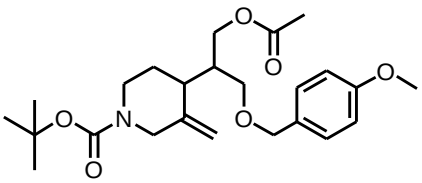
The diol **133** (0.48 g, 1.8 mmol) and lipase PPL (0.72 g) and vinyl acetate (17 mL) were stirred together at room temperature for 24 h. The lipase was removed by filtration, the solution was evaporated then purified by column chromatography eluting with EtOAc, to give the acetate **153** (0.55 g, 95%) and acetate **154** (0.02 g, 4%) as oils; data as above.

4-(2-Acetoxy-1-formyl-ethyl)-3-methylene-piperidine-1-carboxylic acid *tert*-butyl ester 156



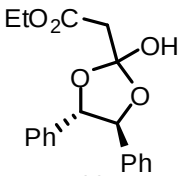
To oxalyl chloride (0.15 mL, 1.3 mmol) in CH_2Cl_2 (5 mL), at −78 °C was added DMSO (0.20 g, 2.5 mmol) in CH_2Cl_2 (1 mL) dropwise. After 15 min, alcohol **153** (0.33 g, 1.05 mmol) in CH_2Cl_2 (2 mL) was added dropwise, followed by triethylamine (0.75 mL, 5.3 mmol) after 15 min. The mixture was allowed to stir at −78 °C for 15 min and then warmed to room temperature. The mixture was diluted with CH_2Cl_2 (5 mL) and water (5 mL). The resulting mixture was extracted with CH_2Cl_2 (5 mL), the combined organic layers were washed with HCl 1*M* (2 × 5 mL) and brine (5 mL), dried ($MgSO_4$), then evaporated and purified by column chromatography, eluting with petrol–EtOAc (6:4), to give the aldehyde **156** as an inseparable mixture of diastereomers (1:0) (0.09 g, 29%) as a gum; R_f 0.63 [petrol–EtOAc 7:3]; ν_{max}/cm^{-1} 2975, 1690, 1420, 1365; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.68 (1H, s, CHO), 5.02 (1H, br.s, C=C*H*H), 4.78 (1H, s, C=CH*H*), 4.39−4.32 (2H, m, CH_2), 4.15−4.07 (1H, m, CH), 3.81−3.66 (2H, m, CH_2), 3.24−3.18 (1H, m, CH), 2.94−2.89 (1H, m, CH), 2.77−2.71 (1H, m, CH), 2.04 (3H, s, CH_3), 1.75−1.68 (2H, m, CH_2), 1.43 (9H, s, 3 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 193.6 (C=O), 170.2 (C=O), 154.5 (C=O), 150.3 (C=C), 110.2 (CH_2), 79.6 (C), 65.5 (CH_2), 61.0 (CH_2), 44.0 (CH_2), 39.2 (CH), 36.5 (CH), 30.8 (CH_2), 28.4 (CH_3); HRMS (ES) found: MH^+, 312.1808. $C_{16}H_{26}NO_5$ requires MH^+, 312.1811; LRMS *m*/*z* (ES) 312 (MH^+).

4-[2-Acetoxy-1-(4-methoxy-benzyloxymethyl)-ethyl]-3-methylene-piperidine-1-carboxylic acid *tert*-butyl ester 157

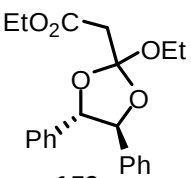


P-Methoxybenzyl chloride (0.35 g, 2.6 mmol) was added dropwise at room temperature to a mixture of the NaH (0.03 g, 1.3 mmol) in Et_2O (2 mL). After 30 min the mixture was cooled to 0 °C and Cl_3CCN (0.26 mL, 2.55 mmol) was added. The mixture was allowed to stir for 4 h at room temperature; the resulting solution was evaporated and the residue was dissolved in petrol (4 mL) and MeOH (2 drops), filtered through Celite and evaporated to give the crude trichloroacetimidate as oil. CH_2Cl_2 (15 mL), alcohol **133** (0.40 g, 1.3 mmol) and CSA (0.03 g, 0.13 mmol) were added to the oil and the mixture was allowed to stir at room temperature. After 18 h with saturated aq. $NaHCO_3$ (2 mL) was added and the mixture was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with water (5 mL), dried ($MgSO_4$) then evaporated Purification by column chromatography, eluting with petrol–EtOAc (9:1), gave the ester **157** as an inseparable mixture of diastereomers (1:1) (0.40 g, 72%) as an oil; R_f 0.22 [petrol–EtOAc 9:1]; ν_{max}/cm^{-1} 3290, 1720, 1675, 1165; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.33−7.23 (2H, m, ArH), 6.92−6.88 (2H, m, ArH), 4.98 (1H, br.s, C=C*H*H), 4.83 (0.5H, s, C=H*H*), 4.82 (0.5H, s, C=H*H*), 4.45 (1H, d, *J* 10, CH), 4.41 (1H, d, *J* 10, CH), 4.31 (0.5H, d, *J* 4, CH), 4.30 (0.5H, d, *J* 5, CH), 4.28 (0.5H, d, *J* 4, CH), 4.27 (0.5H, d, *J* 5, CH), 4.13−4.04 (1H, m, CH), 4.00−3.91 (1H, m, CH), 3.80 (3H, s, OCH_3), 3.50−3.38 (4H, m, 2 × CH_2), 2.46−2.35 (1H, m, CH), 2.30−2.22 (1H, m, CH), 2.02 (3H, s, CH_3), 1.75−1.69 (1H, m, CH), 1.63−1.56 (1H, m, CH), 1.46 (9H, s, 3 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.7 (C=O), 172.7 (C=O), 159.1 (C=O), 158.1 (C=O), 154.6 (C), 153.6 (C), 130.0 (C), 129.2 (ArH), 128.7 (ArH), 128.66 (ArH), 113.9 (ArH), 113.7 (ArH), 111.7 (CH_2), 111.6 (CH_2), 79.7 (C), 72.8 (CH_2), 72.6 (CH_2), 68.5 (CH_2), 67.1 (CH_2), 63.8 (CH_2), 55.3 (CH_3), 40.8 (CH_2), 39.5 (CH), 37.2 (CH), 28.9 (CH_2), 28.4 (CH_3), 28.2 (CH_2), 20.9 (CH_3); HRMS (ES) found: MH^+, 434.2554. $C_{24}H_{36}NO_6$ requires MH^+, 434.2543; LRMS *m*/*z* (ES) 437 (100%).

(2-Ethoxy-4,5-diphenyl-[1,3]dioxolan-2-yl)-acetic acid ethyl ester 159[52] **and (2-Hydroxy-4,5-diphenyl-[1,3]dioxolan-2-yl)-acetic acid ethyl ester 160**



160

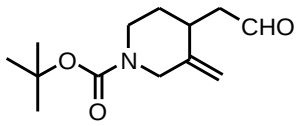


159

The diol **158** (0.50 g, 2.3 mmol), acrylate (0.60 mL, 3.5 mmol) and CSA (0.27 g, 1.2 mmol) were heated in CH_2Cl_2 (10 mL) at 40 °C for 24 h. The solvent was then evaporated and the residue was purified by column chromatography, eluting with petrol–EtOAc (9:1), to give the ester **159** which is transformed to alcohol **160** (0.69 g, 77%) as an oil; R_f 0.26 [petrol–EtOAc 7:3]; ν_{max}/cm^{-1} 3430, 3120, 1730, 1265; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.26−7.20 (5H, m, ArH), 7.17−7.09 (5H, m, ArH), 5.91 (1H, d, *J* 8, CH), 4.95 (1H, d, *J* 8, CH), 4.27 (2H, q, *J* 7, CH_2), 3.54 (1H, d, *J* 16, CH), 3.46 (1H, d, *J* 16, CH), 1.31 (3H, t, *J* 7, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.4 (C=O), 138.4 (C), 136.1 (C), 128.2 (ArH), 128.1 (ArH), 127.5 (ArH), 127.3 (ArH), 127.0 (ArH), 127.0 (ArH), 106.0 (C) 77.3 (CH), 62.1 (CH_2), 41.7 (CH_2), 14.1 (CH_3); HRMS (ES) found: MH^+, 329.1396. $C_{19}H_{21}O_5$ requires MH^+, 329.1389; LRMS *m*/*z* (ES) 329 (MH^+), 311 (100%).

The ester **159**; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36−7.30 (10H, m, ArH), 5.05 (1H, d, *J* 9, CH), 5.01 (1H, d, *J* 9, CH), 4.28−4.25 (1H, m, CH), 4.24−4.19 (1H, m, CH), 4.00−3.93 (1H, m, CH), 3.92–3.85 (1H, m, CH), 3.21 (1H, d, *J* 14, CH), 3.16 (1H, d, *J* 14, CH), 1.35 (3H, t, *J* 7, CH_3), 1.30 (3H, t, *J* 7, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.4 (C=O), 136.3 (C), 136.0 (C), 119.6 (C), 128.5 (ArH), 128.1(ArH), 127.5 (ArH), 127.3 (ArH), 126.9 (ArH), 126.8 (ArH), 86.8 (CH), 85.7 (CH), 60.8 (CH_2), 58.3 (CH_2), 42.3 (CH_2), 15.4 (CH_3), 14.3 (CH_3).

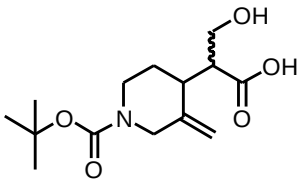
3-Methylene-4-(2-oxo-ethyl)-piperidine-1-carboxylic acid *tert*-butyl ester 146[41]



A mixture of alcohol **33** (0.56 g, 2.6 mmol), $Hg(OAc)_2$ (0.09 g, 0.26 mmol), freshly distilled ethyl vinyl ether **145** (3.52 mL, 36.7 mmol) and xylene (3 mL) were heated in a sealed tube at 135 °C for 5 d. After cooling to room temperature, the solvent was evaporated and the residue was purified by column chromatography, eluting with petrol–EtOAc (8:2), to give the aldehyde **146** (0.39 g, 63%) as an oil that crystallizes at low temperature: mp: 53−55 °C, [lit.[41] 53−55 °C]; R_f 0.28 [petrol–EtOAc 8:2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.77 (1H, s, CHO), 4.92 (1H, br.s, C=C*H*H), 4.65 (1H, s, C=CH*H*), 4.28 (1H, d, *J* 12, CH), 3.91 (1H, d, *J* 12, CH), 3.52−3.43 (1H, m, CH),

3.11−3.00 (1H, m, CH), 2.79−2.67 (2H, m, CH_2), 2.50-2.39 (1H, m, CH), 1.84−1.74 (1H, m, CH), 1.42 (9H, s, 3 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 201.2 (CH), 154.6 (C=O), 109.3 (CH_2), 79.7 (C), 50.7 (CH_2), 46.05 (CH_2), 43.1 (CH_2), 35.5 (CH), 32.6 (CH_2), 28.4 (3 × CH_3); HRMS (ES) found: MH^+, 240.1603. $C_{13}H_{22}NO_3$ requires MH^+, 240.1600; LRMS *m*/*z* (ES) 240 (MH^+) 184 (100%). Data in accordance with the literature.[41]

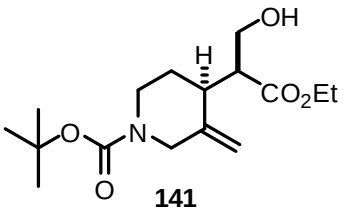
4-(1-Carboxy-2-hydroxy-ethyl)-3-methylene-piperidine-1-carboxylic acid *tert* butyl ester 163



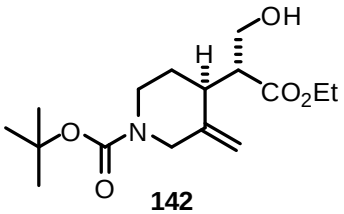
To a stirred solution of α,α-diphenylprolinol trimethylsilyl ether **162** (0.13 mL, 0.42 mmol) in toluene (4 mL) was added solid pH 7 buffer (dibasic sodium phosphate and monobasic potassium phosphate) (0.07 g) followed by formaldehyde solution (37% aq., 0.40 mL, 4.2 mmol) at room temperature for 15 h. The aldehyde **146** (0.33 g, 1.4 mmol) was added in one portion to the stirred solution and the resulting mixture was stirred for 15 h. The two layers were separated and the toluene was evaporated. The residue was dissolved in t-butanol (7 mL) before addition of 2-methyl-2-butene (2 mL, 13.8 mmol), $NaClO_2$, (80%, 0.5 g, 5.5 mmol), and aqueous $NaH_2PO_4.H_2O$ (0.76 g, 5.5 mmol) then the mixture was stirred overnight at room temperature. The solvent was evaporated and the residue was dissolved in EtOAc (15 mL), diluted with 10% HCl (4 mL), saturated NaCl (4 mL), extracted with EtOAc (3 × 15 mL). The combined organic layers were dried (Na_2SO_4), the solvent was evaporated then the residue was purified by column chromatography, eluting with CH_2Cl_2–MeOH (8:2), to give the acid **163** as a mixture of diastereisomers (1:1); as a solid (0.39 g, 23%); mp: 85−88 °C; ν_{max}/cm^{-1} 2930, 1685, 1420, 1365, 1160; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.00 (0.5H, s, C=C*H*H), 4.97 (0.5H, s, C=C*H*H), 4.92 (0.5H, s, C=CH*H*), 4.86 (0.5H, s, C=CH*H*), 4.07 (1H, d, *J* 14, CH), 3.93−3.85 (1H, m, CH), 3.70−3.62 (2H, m, CH_2), 3.38−3.27 (2H, m, CH_2), 2.97−2.92 (1H, m, CH), 2.79−2.67 (1H, m, CH), 1.88−1.75 (1H, m, CH), 1.66 −1.60 (1H, m, CH), 1.45 (9H, s, 3 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.0 (C=O), 154.9 (C=O), 154.8 (C=O), 125.9 (C), 125.7 (C), 80.2 (C), 80.1 (C), 62.5 (CH_2), 60.9 (CH_2), 48.4

(CH), 47.4 (CH), 42.5 (CH_2), 42.2 (CH_2), 39.8 (CH), 39.7 (CH), 29.7 (CH_2), 28.4 (CH_3), 28.3 (CH_2); HRMS (ES) found: MH^-, 284.1502 $C_{14}H_{22}NO_5$ requires MH^-, 284.1498; LRMS *m*/*z* (ES) 284 (MH^-).

4-(1-Ethoxycarbonyl-2-hydroxy-ethyl)-3-methylene-piperidine-1-carboxylic acid *tert*-butyl ester 141 and 142[155]



141



142

K_2CO_3 (0.03 g, 0.2 mmol) and EtI (0.29 g, 0.19 mmol) were added to a solution of the acid **153** (0.25 g, 0.09) in DMF (1 mL) at 0°C then stirred together overnight at room temperature. The reaction was quenched with water (5 mL) and extracted with Et_2O (3 × 5 mL). The organic layer was washed with water (5 mL), brine (5 mL), dried ($MgSO_4$), then the solvent was evaporated and the residue was purified by column chromatography, eluting with petrol–EtOAc (6:4), to give a separable mixture of diastereomeric esters (1:1) (51% top spot, 49% bottom spot, 100%) as oils;

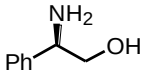
142

R_f 0.26 [petrol–EtOAc 6:4]; ν_{max}/cm^{-1} 3455, 2940, 2875, 1730, 1690, 1675; ^1H NMR (400 MHz, $CDCl_3$) δ = 4.96 (1H, s, C=C*H*H), 4.79 (1H, s, C=CH*H*), 4.14−4.13 (2H, m, CH_2), 3.96 (1H, d, *J* 14, CH), 3.84−3.81 (3H, m, CH), 3.67 (1H, d, *J* 14, CH), 3.38−3.19 (1H, m, CH), 2.92−2.80 (1H, m, CH), 2.77−2.72 (1H, m, CH), 2.34 (1H, br.s, OH), 1.80−1.73 (1H, m, CH), 1.58−1.48 (1H, m, CH), 1.43 (9H, s, 3 × CH_3), 1.23 (3H, t, *J* 7, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.5 (C=O), 154.6 (C=O), 143.1 (C), 111.1 (CH_2), 79.7 (C), 62.5 (CH_2), 60.9 (CH_2), 49.0 (CH_2), 47.2 (CH), 41.4 (CH_2), 39.9 (CH), 29.8 (CH_2), 28.43 (CH_3), 14.3 (CH_3); HRMS (ES) found: MH^+, 314.1971. $C_{16}H_{28}NO_5$ requires MH^+, 314.1967; LRMS *m*/*z* (ES) 314 (MH^+), 258 (100%). Data in accordance with the literature.[155]

141

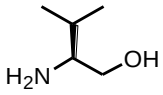
R_f 0.32 [petrol–EtOAc 6:4]; ν_{max}/cm^{-1} 3425, 2980, 2935, 1730, 1695, 1425; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.02 (1H, br.s, C=C*H*H), 4.91 (1H, s, C=CH*H*), 4.25−4.17 (2H, m, CH_2), 4.12–4.03 (1H, m, CH), 3.80–3.75 (2H, m, CH), 3.68 (1H, d, *J* 14, CH), 3.63−3.55 (1H, m, CH), 3.39–3.32 (1H, m, CH), 2.92−2.88 (1H, m, CH), 2.73−2.68 (1H, m, CH), 2.09 (1H, br.s, OH), 1.77−1.67 (1H, m, CH), 1.63−1.49 (1H, m, CH), 1.45 (9H, s, 3 × CH_3), 1.29 (3H, t, *J* 7, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.2 (C=O), 154.6 (C=O), 142.2 (C), 113.1 (CH_2), 79.7 (C), 62.5 (CH_2), 60.9 (CH_2), 48.8 (CH_2), 47.2 (CH), 40.5 (CH_2), 39.9 (CH), 28.4 (CH_3), 28.3 (CH_2), 14.3 (CH_3); HRMS (ES) found: MH^+, 314.1977. $C_{16}H_{28}NO_5$ requires MH^+, 314.1967; LRMS *m*/*z* (ES) 258 (100%), 214 (MH^+). Data in accordance with the literature.[155]

(*R*)-Phenylglycinol 165[56]



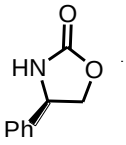
A solution of I_2 (1.47 g, 5.8 mmol) in THF (4 mL) was added dropwise to a solution of amino acid **164** (0.50 g, 3.3 mmol) and $NaBH_4$ (0.32 g, 8.6 mmol) in dry THF (4 mL) then the reaction mixture was heated to reflux for 20 h and then cooled to room temperature. The methanol (2 mL) was added cautiously until the mixture became clear, the solvent was evaporated and to the remaining residue was added 20% KOH aqueous solution (3 mL) then stirred under reflux for 3 h. After cooling to room temperature, the reaction mixture was extracted with DCM (3 × 5 mL) then the combined organic layers were dried ($MgSO_4$), evaporated to afford the crude amino alcohol **165** (0.40 g, 89%) as a gum which was used without further purification; $[\alpha]^{23}_D$ −28 (c 0.75, 1 M HCl) [lit.[56] $[\alpha]^{20}_D$ −32 (c 0.75, 1 M HCl)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41−7.26 (5H, m, ArH), 4.07 (1H, dd, *J* 8.5 and 4.5, CH), 3.76 (1H, dd, *J* 10.5, 4.5, CH), 3.57 (1H, dd, *J* 10.5, 8.5 CH), 2.5 (3H, br.s, OH & NH_2); ^{13}C NMR (63 MHz, $CDCl_3$) δ = 142.5 (C), 128.6 (CH), 127.5 (CH), 126.5 (CH), 67.9 (CH_2), 57.4 (CH); HRMS (ES) found: MH^+, 138.0913. $C_8H_{12}NO$ requires MH^+, 138.0919; LRMS *m*/*z* (ES) 138 (100%, MH^+), 121 (20). Data in accordance with the literature.[56]

(*S*)-2-Amino-3-methylbutan-1-ol[56]



Using the same method as the glycionl **165**, a solution of I_2 (3.80 g, 14.9 mmol) in THF (10 mL) was added dropwise to solution of amino acid **172** (1.00 g, 8.54 mmol) and $NaBH_4$ (0.81 g, 21.3 mmol) in dry THF (10 mL) giving the valinol **173** (0.56 g, 64%) as a gum which was used without further purification; $[\alpha]^{23}_D$ +14 (c 10, EtOH) [lit.[56] $[\alpha]^{20}_D$ +17 (c 10, EtOH)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.47 (3H, br.s, OH & NH_2), 3.70 (1H, dd, *J* 8.5, 2.5, CH), 3.45 (1H, dd, *J* 8.5, 2.5, CH), 2.78 (1H, br s, CH), 1.76-1.69 (1H, m, CH), 0.92 (3H, d, *J* 6.5, CH_3), 0.88 (3H, d, *J* 6.5, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 62.8 (CH_2), 58.6 (CH), 30.1 (CH), 19.1 (CH_3), 18.8 (CH_3); HRMS (ES) found: MH^+, 104.1080 $C_5H_{14}NO$ requires MH^+, 104.1075; LRMS *m*/*z* (ES) 104 (MH^+), 72 (100%, MH^+). Data in accordance with the literature.[56]

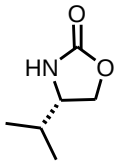
(*R*)-4-Phenyloxazolidin-2-one167[59]



A dried 10 mL three-necked RBF with a magnetic stirring bar was fitted with a thermometer adapter, a Vigreux column connected to distillation condenser, and a glass stopper. An argon inlet line was connected at the vacuum outlet of the condenser apparatus. After the system had been evacuated and inert gas flushed, a (*R*)-phenyl glycionl **165** (1.03 g, 7.5 mmol) and K_2CO_3 (0.11 g, 0.75 mmol) were dissolved in diethyl carbonate (2 mL, 15.0 mmol). The mixture was heated in oil bath at 125°C and the distillation receiver flask was cooled in an ice bath. After the ethanol distillation was completed the reaction mixture was allowed to cool at room temperature then extracted with CH_2Cl_2 (3 × 5mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$) and evaporated to give a solid. This was dissolved in minimum amount of hot ethyl acetate and allowed to cool. After crystals formed, filtered off and washed with cold ether to give compound **167** (0.55 g, 45%) as a solid; R_f 0.46 [DCM−MeOH 95:05]; mp: 41−43 °C; $[\alpha]^{21}_D$ −48 (c 1.00, $CHCl_3$) [lit.[59] $[\alpha]^{21}_D$ −46 (c 1.00, $CHCl_3$)] ; ν_{max}/cm^{-1} 2930, 2870, 1770, 1455, 1320, 1120; ^{1}H NMR (250

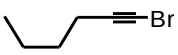
MHz, $CDCl_3$) δ = 7.43−7.32 (5H, m, ArH), 5.28 (1H, br s, NH), 4.94 (1H, dd, *J* 8.5, 7, CH), 4.73 (1H, t, *J* 8.5, CH), 4.20 (1H, dd, *J* 8.5, 7, CH); ^{13}C NMR (63 MHz, $CDCl_3$) δ = 160.2 (C=O), 139.4 (C), 129.2 (ArH), 128.89 (ArH), 126.1 (ArH), 72.5 (CH_2), 56.4 (CH); HRMS (ES) found: MH^+, 164.0708. $C_9H_{10}NO_2$ requires MH^+, 164.0712; LRMS *m*/*z* (ES) 164 (100%, MH^+). Data in accordance with the literature.[59]

(*S*)-4-Isopropyloxazolidin-2-one174[59]



Using the same method as the oxazolidinone **167**, L- valinol (1.22 g, 11.8 mmol), K_2CO_3 (0.16 g, 1.2 mmol) and diethyl carbonate (3.0 mL, 24.4 mmol) gave the oxazolidinone **174** (0.34 g, 47%) as a solid; R_f 0.52 [DCM–MeOH 95:05]; mp: 51−53 °C; $[\alpha]^{21}_D$ −26 (c 1.00, $CHCl_3$) [lit.[59] $[\alpha]^{21}_D$ −28 (c 1.00, $CHCl_3$)] ; ν_{max}/cm^{-1} 3240, 3100, 1735, 1705, 1490, 1235, 1025; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.80 (1H, br s, NH), 4.48 (1H, dd, *J* 7, 3, CH), 4.14 (1H, dd, *J* 7, 3, CH), 3.66−3.61 (1H, m, CH), 1.83−1.72 (1H, m, CH), 0.99 (3H, d, *J* 6.5, CH_3), 0.93 (3H, d, *J* 6.5, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.0 (C=O), 68.6 (CH_2), 58.3 (CH), 32.6 (CH), 18.0 (CH_3), 17.6 (CH_3); HRMS (ES) found: MH^+, 130.0863. $C_6H_{12}NO_2$ requires MH^+, 130.0868; LRMS *m*/*z* (ES) 130 (100%, MH^+). Data in accordance with the literature.[59]

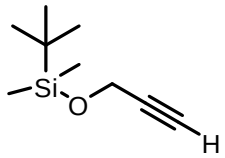
1-Bromo-hex-1-yne 169[60]



n-BuLi (5.80 mL, 14.6 mmol) was added dropwise to a solution of alkyne **168** (1.40 mL, 12.2 mmol) in THF (25 mL) at −78 °C. The resulting solution was stirred for 30 min then Br_2 (0.90 mL, 17.1 mmol) was added dropwise until the red colour persists. This light red solution was stirred at −78 °C for an additional 15 min. Saturated $Na_2S_2O_3$ solution (5 mL) was added and the mixture was extracted with ether (3 × 5 mL). The combined organic layers were dried ($NaSO_4$), evaporated and purified by column chromatography, eluting with petrol, to give alkynyl bromide **169** (1.89 g, 96%) as an

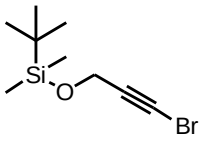
oil; R_f 0.69 [petrol]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.16 (2H, t, *J* 7, CH_2), 1.49−1.40 (2H, m, CH_2), 1.38−1.31 (2H, m, CH_2), 0.88 (3H, t, *J* 7, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 80.3 (C), 37.3 (C), 30.3 (CH_2), 21.8 (CH_2), 19.3 (CH_2), 13.4 (CH_3); HRMS (EI) found: MI^+, 159.9888. $C_6H_9{}^{79}Br$ requires MI^+, 159.9887; LRMS *m*/*z* (EI) 161 (5), 133 (5), 119 (30), 81 (100%). Data in accordance with the literature.[60]

tert-Butyl-dimethyl-prop-2-ynyloxy-silane 178



^{t}Butyldimethylsilyl trifluoromethylsulfonate (0.93 mL, 4.3 mmol) was added dropwise to a solution of alcohol **177** (0.20 mL, 3.6 mmol) and Et_3N (0.66 mL, 4.7 mmol) in CH_2Cl_2 (10 mL) at −75 °C. After 1 h, water (5 mL) was added then and the reaction mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers was dried ($MgSO_4$), evaporated and purified by column chromatography, eluting with CH_2Cl_2, to give the product **178** (0.55g, 91%) as an oil; R_f 0.78 [DCM]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.30 (2H, d, *J* 2.5, CH_2), 2.38 (1H, t, *J* 2.5, CH), 0.90 (9H, s, 3 × CH_3), 0.12 (6H, s, 2 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 82.4 (C), 72.8 (CH), 53.4 (CH_2), 25.8 (CH_3), 18.3 (C), -5.2 (CH_3); HRMS (EI) found: M^+, 170.1123. $C_9H_{18}OSi$ requires M^+, 170.1127; LRMS m/z (EI) 170 (EI^+), 113 (100%).

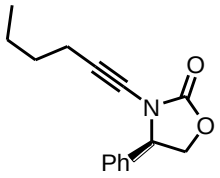
(3-Bromo-prop-2-ynyloxy)-_tert_-butyl-dimethyl-silane 179[60]



Using the same method as the alkynyl bromide **169**, *n*-butyllithium (5.90 mL, 14.1 mmol, 2.5 M in hexanes), the alkyne **178** (2.0 g, 12.0 mmol) in THF (35 mL) and Br_2 (0.85 mL, 16.5 mmol) gave, after purification by column chromatography, eluting with petroleum ether, the bromide **179** (1.94 g, 67%) as an oil; R_f 0.27 [petrol]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.29 (2H, s, CH_2), 0.86 (9H, s, 3 × CH_3), 0.08 (6H, s, CH_3); ^{13}C

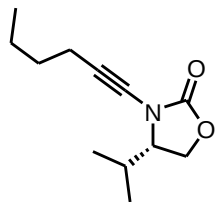
NMR (100 MHz, $CDCl_3$) δ = 78.6 (C), 52.5 (CH_2), 44.6 (C), 25.8 (CH_3), 18.2 (C), -5.2 (CH_3). Data in accordance with the literature.[60]

(*R*)-3-(Hex-1-ynyl)-4-phenyloxazolidin-2-one 170[156, 157]



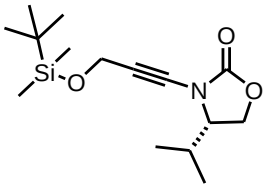
To a solution of oxazolidinone **167** (0.20 g, 1.2 mmol), K_2CO_3 (0.34 g, 2.5 mmol), $CuSO_4.H_2O$ (0.03 g, 0.13 mmol) and 1,10-phenanthroline (0.05 g, 0.25 mmol) was added a solution of bromo alkyne **169** (0.22 g, 1.4 mmol) in toluene (2 mL). The reaction mixture was heated at 75 °C for 48 h. the mixture was cooled to room temperature, diluted with EtOAc (4 mL) and filtered through Celite. The solvent was evaporated and the crude material was purified by column chromatography, eluting with petrol–EtOAc (4:6), to give the desired ynamide **170** (0.25 g, 83%), as a solid; R_f 0.46 [petrol–EtOAc 8:2]; mp: 43−45 °C; [lit.[158] 49 °C]; $[\alpha]^{21}_D$ −172 (c 1.00, $CHCl_3$); [lit.[158] $[\alpha]^{20}_D$ −162 (c 1.40, $CHCl_3$)]; ν_{max}/cm^{-1} 2930, 2865, 1775, 1410, 1360, 1120; ^{1}H NMR (250 MHz, $CDCl_3$) δ = 7.46−7.38 (3H, m, ArH), 7.35−7.32 (2H, m, ArH), 5.00 (1H, dd, *J* 7.5, 1.5, CH), 4.70 (1H, t, *J* 7.5, CH), 4.22 (1H, dd, *J* 7.5, 1.5, CH), 2.16 (2H, t, *J* 7, CH_2), 1.36−1.25 (2H, m, CH_2), 1.21−1.12 (2H, m, CH_2), 0.7 (3H, t, *J* 7, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.3 (C=O), 136.4 (C), 129.3 (ArH), 129.2 (ArH), 126.9 (ArH), 72.9 (C), 70.6 (CH_2), 69.0 (C), 62.1 (CH), 30.6 (CH_2), 21.5 (CH_2), 17.9 (CH_2), 13.5 (CH_3); HRMS (ES) found: MH^+, 244.1336. $C_{15}H_{18}NO_2$ requires MH^+, 244.1338; LRMS *m*/*z* (ES) 244 (100%, MH^+). Data in accordance with the literature.[156, 157]

(*S*)-3-(Hex-1-ynyl)-4-isopropyloxazolidin-2-one 175



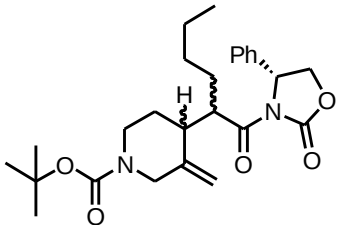
Using the same method as the ynamide **170**, to a mixture of oxazolidinone **174** (0.15 g, 1.2 mmol), K_2CO_3 (0.32 g, 2.4 mmol), $CuSO_4.H_2O$ (0.02 g, 0.11), 1,10-phenanthroline (0.04 g, 0.23 mmol) and a bromoalkyne **169** (0.21 g, 1.3 mmol) gave the ynamide **175** (0.18 g, 75%) as a solid; R_f [petrol–EtOAc 8:2]; mp: 35−40 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.35 (1H, dd, *J* 8.5, 7, CH), 4.14-4.09 (1H, m, CH), 3.92-3.87 (1H, m, CH), 2.31 (2H, t, *J* 7, CH_2), 2.25−2.14 (1H, m, CH), 1.55-1.47 (2H, m, CH_2), 1.46-1.35 (2H, m, CH_2), 0.97 (3H, d, *J* 3.5, CH_3), 0.96 (3H, d, *J* 3.5, CH_3), 0.90 (3H, t, *J* 7, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.7 (C=O), 75.2 (C), 69.8 (C), 69.3 (CH_2), 61.8 (CH), 30.9 (CH_2), 29.0 (CH), 21.9 (CH_2), 18.1 (CH_2), 17.2 (CH_3), 13.6 (CH_3); HRMS (ES) found: MH^+, 210.1484. $C_{12}H_{20}NO_2$ requires MH^+, 210.1494; LRMS *m*/*z* (ES) 210 (100%, MH^+).

(*S*)-3-(3-(*tert*-Butyldimethylsilyloxy)prop-1-ynyl)-4-isopropyloxazolidin-2-one 180



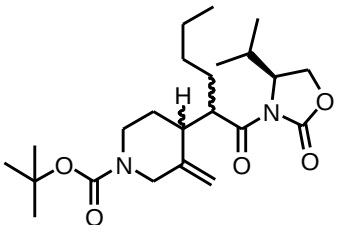
Using the same method as the ynamide **175**, to a mixture of oxazolidinone **174** (0.50 g, 3.9 mmol), K_2CO_3 (1.07 g, 7.7 mmol), $CuSO_4.H_2O$ (0.09 g, 0.38), 1,10-phenanthroline (0.13 g, 0.80 mmol) and a bromoalkyne (1.06 g, 4.3 mmol) in toluene (8 mL) gave the ynamide **180** (0.77 g, 68%) as a solid; R_f 0.54 [petrol–EtOAc 8:2]; mp: 48−50 °C; $[\alpha]^{21}_D$ +40 (c 1.00, $CHCl_3$); ν_{max}/cm^{-1} 2930, 2855, 1760, 1740, 1425, 1250, 1205; ^{1}H NMR (250 MHz, $CDCl_3$) δ = 4.47 (2H, s, CH_2), 4.36 (1H, t, *J* 9, CH), 4.16−4.09 (1H, m, CH), 3.97−3.92 (1H, m, CH), 2.29−2.17 (1H, m, CH) 0.97 (3H, d, *J* 7, CH_3), 0.95 (3H, d, *J* 7, CH_3), 0.90 (9H, s, 3 × CH_3), 0.12 (6H, s, 2 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.2 (C=O), 74.1 (C), 65.0 (C), 64.5 (CH_2), 61.6 (CH), 51.8 (CH_2), 28.9 (CH), 25.8 (CH_3), 18.3 (C), 17.2 (CH_3), –5.0 (CH_3), –5.1 (CH_3); HRMS (ES) found: MH^+, 298.1839. $C_{15}H_{28}NO_3Si$ requires MH^+, 298.1838; LRMS *m*/*z* (ES) 315 (100%), 298 (MH^+).

3-Methylene-4-[1-(2-oxo-4-phenyl-oxazolidine-3-carbonyl)-pentyl]-piperidine-1-carboxylic acid *tert*-butyl ester 171



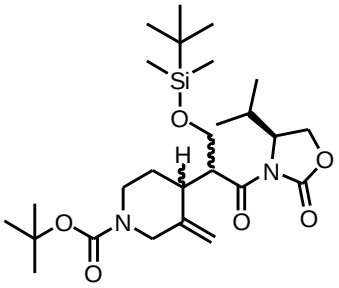
Ynamide 158 (0.05 g, 0.20 mmol), CSA (0.005 g, 0.02 mmol) and allylic alcohol **33** (0.09 g, 0.42 mmol) were heated in toluene (4 mL) in a sealed tube for 48 h. The reaction mixture was cooled to room temperature, filtered through Celite then the solvent was evaporated. The residue was purified by column chromatography, eluting with petrol–EtOAc (7.5:2.5), to give an inseparable mixture of diastereomers (3_{Major}:1_{minor}) **171** (0.04 g, 32%), as an oil; R_f 0.58 [petrol–EtOAc 7.5:2.5]; ν_{max}/cm^{-1} 2925, 2860, 1775, 1690, 1380, 1320, 1190, 1165; ^{1}H NMR (250 MHz, $CDCl_3$) δ = 7.38−7.24 (5H, m, ArH), 5.43 (1H, dd, *J* 5, 3.5, CH), 5.01–4.97 (1H, m, CH), 4.72–4.70 (0.25H, m, CH_m), 4.68−4.65 (0.75H, m, CH_M), 4.52 (1H, s, C=*H*H), 4.39 (0.25H, s, C=HH_m), 4.38 (0.75H, s, C=CHH_M), 4.38−4.24 (2H, m, CH_2), 3.93 (1H, d, *J* 14, CH), 3.77 (1H, d, *J* 14, CH), 3.25−3.16 (1H, m, CH), 2.51−2.43 (1H, m, CH), 1.70−1.45 (1H, m, CH), 1.67−1.45 (3H, m, CH), 1.42 (9H, s, 3 × CH_3), 1.27−1.22 (4H, m, 2 × CH_2), 0.86 (3H, t, *J* 6, CH_3); ^{13}C NMR (65 MHz, $CDCl_3$) δ = 175.1 (C=O), 166.5 (C=O), 152.5 (C=O), 139.1 (C), 129.2 (ArH), 128.9 (ArH), 128.7 (ArH), 126.4 (ArH), 125.9 (ArH), 105.5 (CH_2), 103.5 (CH_2), 79.5 (C), 69.9 (CH_2), 69.5 (CH_2), 65.8 (CH_2), 57.7 (CH), 57.5 (CH), 43.1 (CH), 43.0 (CH), 35.5 (CH_2), 35.4 (CH_2) 31.2 (CH_2), 31.1 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 28.4 (CH_3), 28.4 (CH_2), 27.3 (CH_2), 23.8 (CH_2), 22.9 (CH_2), 21.0 (CH), 14.2 (CH_3), 13.9 (CH_3); HRMS (ES) found: MH^+, 457.2705 $C_{26}H_{37}N_2O_5$ requires MH^+, 457.2702; LRMS *m*/*z* (ES), 457 (MH^+), 401 (100%).

4-[1-(4-Isopropyl-2-oxo-oxazolidine-3-carbonyl)-pentyl]-3-methylene-piperidine-1-carboxylic acid *tert*-butyl ester 176



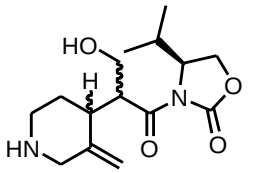
Using the same method as the compound **171**, ynamide **175** (0.10 g, 0.47 mmol), CSA (0.01 g, 0.05 mmol) and allylic alcohol **33** (0.2 g, 1.0 mmol) were heated in toluene (6 mL) in a sealed tube for 48 h. The reaction mixture was cooled to room temperature, filtered through Celite then the solvent was evaporated. The residue was purified by column chromatography, eluting with petrol–EtOAc (7.5:2.5), to give an inseparable mixture of diastereomers **176** (3_{Major}:1_{minor}) (0.08 g, 36%), as an oil; R_f 0.80 [petrol–EtOAc 7.5:2.5]; ν_{max}/cm^{-1} 2960, 2870, 1775, 1690, 1385, 1365, 1110, 1165; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.85 (1H, br.s, C=C*H*H$_m$), 4.75 (1H, s, C=CH*H*$_M$), 4.46−4.42 (1H, m, CH), 4.41−4.38 (1H, m, CH), 4.36−4.29 (1H, m, CH), 4.19−4.15 (2H, m, CH_2), 3.96 (1H, d, *J* 14, CH), 3.90−3.85 (1H, m, CH), 3.50−3.37 (2H, m, CH_2), 2.99−2.91 (0.75H, m, CH), 2.86−2.78 (0.25H, m, CH), 2.67−2.62 (1H, m, CH), 2.40−2.30 (1H, m, CH), 1.66−1.55 (2H, m, CH_2), 1.41 (9H, s, 3 × CH_3), 1.33−1.11 (4H, m, 2 × CH_2), 0.91 (2.25H, d, *J* 7, CH_3), 0.90 (0.75H, d, *J* 7, CH_3),0.89 (2.75H, d, *J* 7, CH_3), 0.88 (0.75H, d, *J* 7, CH_3), 0.83 (3H, m, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.7 (C=O), 173.4 (C=O), 154.8 (C=O), 154.7 (C=O), 154.1 (C=O), 153.9 (C=O), 143.2 (C), 105.3 (CH_2), 103.5 (CH_2), 79.5 (C), 63.3 (CH_2), 62.8 (CH_2), 58.6 (CH), 58.4 (CH), 43.4 (CH), 42.4 (CH), 35.5 (CH_2), 31.3 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 28.4 (CH_3), 28.4 (CH), 28.3 (CH), 27.9 (CH_2), 24.1 (CH_2), 22.9 (CH_2), 22.4 (CH_2), 18.0 (CH_3), 17.9 (CH_3), 14.5 (CH_3), 13.9 (CH_3) ; HRMS (ES) found: MH^+, 423.2832. $C_{23}H_{38}N_2O_5$ requires MH^+, 423.2832; LRMS m/z (ES) 423 (MH^+), 367 (100%).

4-[1-(*tert*-Butyl-dimethyl-silanyloxymethyl)-2-(4-isopropyl-2-oxo-oxazolidin-3-yl)-2-oxo-ethyl]-3-methylene-piperidine-1-carboxylic acid *tert*-butyl ester 181



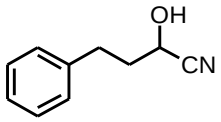
Ynamide **180** (0.20 g, 0.81 mmol), CSA (0.09 g, 0.41 mmol) and allylic alcohol **33** (0.20 g, 0.81 mmol) were heated in toluene (8 mL) in a sealed tube for 48 h. The reaction mixture was cooled to room temperature, filtered through Celite and the solvent was evaporated. The residue was purified by column chromatography, eluting with petrol–EtOAc (2.5:7.5), to give an inseparable mixture of diastereomers **181** (3_{Major}:1_{minor}) (0.17 g, 40%), as an oil; R_f 0.86 [petrol–EtOAc 7.5:2.5]; ν_{max}/cm^{-1} 2930, 1775, 1690, 1465, 1385, 1365, 1200; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.86 (1H, br s, C=C*H*H$_m$), 4.78 (1H, s, C=CH*H*$_M$), 4.70 (1H, dt, *J* 10, 5, CH$_m$), 4.45−4.41 (2H, m, CH$_{2M}$), 4.21−4.15 (2H, m, CH$_{2m}$), 3.87−3.74 (2H, m, CH$_2$), 3.63−3.44 (2H, m, CH$_2$), 3.25−3.18 (0.75H, m, CH), 3.14–3.07 (0.25H, m, CH), 2.82−2.73 (1H, m, CH), 2.31−2.22 (1H, m, CH), 1.75−1.70 (1H, m, CH), 1.59−1.50 (1H, m, CH), 1.43 (9H, s, 3 × CH$_3$), 0.91 (3H, d, *J* 7, CH$_3$), 0.83 (9H, s, 3 × CH$_3$), 0.80 (3H, d, *J* 7, CH$_3$), 0.014 (3H, s, CH$_3$) 0.005 (3H, s, CH$_3$);^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.6 (C=O), 174.5 (C=O), 154.6 (C=O), 154.5 (C=O), 153.9 (C=O), 153.8 (C=O), 142.4 (C), 111.4 (CH$_2$), 111.5 (CH$_2$), 79.5 (C), 63.6 (CH$_2$), 62.8 (CH$_2$), 60.3 (CH$_2$), 58.7 (CH), 58.6 (CH$_2$), 58.3 (CH), 44.5 (CH), 41.2 (CH), 38.6 (CH$_2$), 28.6 (CH), 28.4 (CH$_3$), 28.7 (CH$_2$), 25.8 (CH), 25.7 (CH$_3$), 21.0 (CH), 18.0 (CH), 18.0 (C), 14.7 (CH$_3$), 14.6 (CH$_3$), −5.6 (CH$_3$), −5.5 (CH$_3$); HRMS (ES) found: MH$^+$, 511.3178. $C_{26}H_{47}N_2O_6Si$ requires MH$^+$, 511.3203; LRMS *m*/*z* (ES) 511 (MH$^+$), 455 (100%).

3-[3-Hydroxy-2-(3-methylene-piperidin-4-yl)-propionyl]-4-isopropyl-oxazolidin-2-one 183



CF_3CO_2H (0.10 g, 1.3 mmol) was added to *N*-Boc protected compound **170** (0.14 g, 0.27 mmol) in CH_2Cl_2 (2 mL) at room temperature. After 12 h, aq. NaOH solution 10 % (2 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried ($MgSO_4$) and evaporated to give an inseparable mixture of diastereomers **183** (3:1) (0.01 g, 12%); as an oil; R_f 0.19 [petrol–EtOAc 6:4]; ν_{max}/cm^{-1} 3245, 2960, 2950, 1740, 1465, 1390, 1240; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.80 (2H, br s, CH_2), 4.46–4.44 (1H, m, CH), 4.44–4.42 (1H, m, CH), 4.31−4.27 (2H, m, CH), 4.25−4.21 (1H, m, CH), 4.12−4.08 (2H, m, CH_2), 3.93 (1H, br.s, NH), 3.63−3.57 (2H, m, CH_2), 3.25−3.10 (1H, m, CH), 2.52−2.44 (1H, m, CH), 2.44−2.30 (1H, m, CH), 1.79−1.67 (2H, m, CH_2), 1.62 (1H, br.s, OH), 0.95 (3H, d, *J* 7, CH_3), 0.90 (3H, d, *J* 7, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.5 (C=O), 172.5 (C=O), 154.5 (C=O), 154.3 (C=O), 145.1 (C), 144.0 (C), 103.1 (CH_2), 103.0 (CH_2), 68.5 (CH_2), 63.6 (CH_2), 58.7 (CH), 58.4 (CH), 58.2 (CH), 58.1 (CH), 58.0 (CH_2), 38.3 (CH_2), 32.6 (CH), 30.0 (CH_2), 28.4 (CH), 27.5 (CH), 18.0 (CH_3), 17.6 (CH_3); HRMS (ES) found: MH^+, 297.1066. $C_{15}H_{25}N_2O_4$ requires MH^+, 297.1073; LRMS *m*/*z* (ES) 297 (20%).

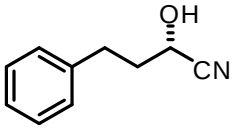
2-Hydroxy-4-phenylbutanenitrile 298$_{rac}$ [159]



3-Phenylpropionaldehyde (**297**) (10.0 g, 74.5 mmol) was added dropwise to a stirred solution of 37% aqueous $NaHSO_3$ (16.0 mL, 74.5 mmol) at 0°C. A solution of NaCN (3.7 g, 74.5 mmol) in H_2O (15mL) was added dropwise. The reaction mixture was stirred at room temperature for 18 h, and then was extracted with Et_2O (3 × 25 mL). The combined organic layers were dried ($MgSO_4$) and evaporated, the residue was purified by column chromatography, eluting with petrol–Et_2O (8:2), to give the alcohol **298**$_{rac}$

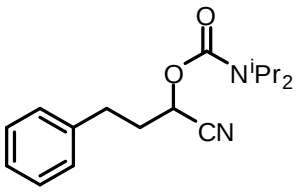
(9.0 g, 75%) as an oil; R_f 0.39 [petrol–EtOAc 8:2]; ν_{max}(film)/cm^{-1} 3400, 2975, 1375; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.90−6.86 (2H, m, Ar*H*), 6.81−6.76 (3H, m, Ar*H*), 3.96 (1H, t, *J* 7, CH), 3.47 (1H, br.s, OH), 2.42−2.38 (2H, m, CH_2), 1.72−1.66 (2H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 139.6 (Ar), 128.7 (ArH), 128.5 (ArH), 126.6 (ArH), 120.0 (*C*N), 60.3 (CH), 36.5 (CH_2), 30.6 (CH_2); HRMS (EI) Found: MH^+, 162.0922. $C_{10}H_{12}NO$ requires MH^+, 162.0919; LRMS *m/z* (EI) 162 (100%, MH^+). Data in accordance with the literature.[159]

(*2S*)-2-Hydroxy-4-phenylbutanenitrile 298[139]



To a solution of ester **299** (4.88 g, 24.0 mmol) in 10% THF−H_2O (30 mL) was added amano lipase PS (0.50 g). After stirring for 2 h at 50 °C, EtOAc (30 mL) and brine (30 mL) were added. The mixture was filtered through Celite and extracted with EtOAc (3 × 25 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography, eluting with petrol–Et_2O, (8:2) to give the alcohol **298** (1.57 g, 41%) as an oil; $[\alpha]^{21}_D$ +10 (c 1.00, $CHCl_3$); other data as above. Data in accordance with the literature.[139]

1-Cyano-3-phenylpropyl N,N-*bis*(propan-2-yl)carbamate 288$_{rac}$[139]

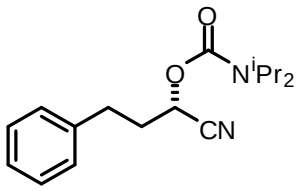


To a solution of triphosgene (0.36 g, 2.5 mmol) in Et_2O (18 mL) was added triethylamine (0.9 mL, 6.5 mmol) at room temperature. After stirring for 30 min, alcohol **298**$_{rac}$ (1.0 g, 6.5 mmol) in Et_2O (9 mL) was added. After stirring for 30 min, diisopropylamine (0.9 mL, 6.5 mmol) and triethylamine (0.9 mL, 6.5 mmol) were added. After 2 h, the mixture was filtered through Celite and concentrated. The residue was purified by column chromatography, eluting with petrol–Et_2O (8:2), to give the nitrlie **288**$_{rac}$ (0.59 g, 66%) as a yellow oil; R_f 0.78 [petrol–EtOAc 8:2]; ν_{max}/cm^{-1} 2975,

2930, 2800, 1705, 1435; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.37–7.33 (2H, m, Ar*H*), 7.27–7.20 (3H, m, Ar*H*), 5.40 (1H, t, *J* 7, CH), 4.06 (1H, br.s, NC*H*Me_2), 3.77 (1H, br.s, NC*H*Me_2), 2.90–2.84 (2H, m, CH_2), 2.31–2.22 (2H, m, CH_2) 1.25 (12H, d, *J* 7, 2 × NC*Me*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ =153.3 (C=O), 139.4 (Ar), 128.7 (ArH), 128.3 (ArH), 126.6 (ArH), 117.5 (*C*N), 61.2 (CH), 47.4 (N*C*HMe_2), 46.0 (N*C*HMe_2), 34.4 (CH_2), 31.0 (CH_2), 21.7 (NCH*Me*$_2$), 20.7 (NCH*Me*$_2$); HRMS (ES) found: MH^+, 289.1928. $C_{17}H_{25}N_2O_2$ requires MH^+, 289.1916; LRMS *m*/*z* (ES) 289 (100%, MH^+). Data in accordance with the literature.[139]

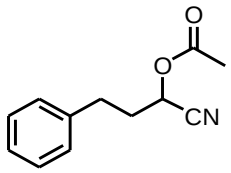
Resolution between the enantiomers of compound **288**$_{rac}$ was achieved using a Beckman system fitted with a Lux × 3u cellulose–1 column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1mL·min^{-1}; ambient temperature, detection by UV absorbance at 254 nm. Injection volume 20 μL of the sample prepared in a 2 g·L^{-1} solution of the eluent. Under these conditions, the faster running component and slower running component were eluted at 15.7 min and 32.1 min respectively with an analysis time of 60.0 min.

(*1S*)-1-Cyano-3-phenylpropyl N,N-*bis*(propan-2-yl)carbamate 288[139]



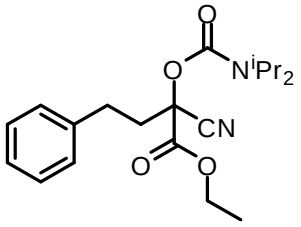
To a solution of triphosgene (0.66 g, 2.5 mmol) in Et_2O (18 mL) was added triethylamine (0.9 mL, 6.5 mmol) at room temperature. After stirring for 30 min, alcohol **298** (1.0 g, 6.5 mmol), in Et_2O (9 mL) was added. After stirring for 30 min, diisopropylamine (0.9 mL, 6.5 mmol) and triethylamine (0.9 mL, 6.5 mmol) were added. After 2 h, the mixture was filtered through Celite and concentrated. The residue was purified by column chromatography, eluting with petrol–Et_2O (8:2), to give the nitrile **288** (0.59 g, 66%) as a yellow oil; $[\alpha]^{20}_{D}$ –18.3 (c 1.20, $CHCl_3$) [lit.[139] $[\alpha]^{20}_{D}$ –20.4 (c 1.20, $CHCl_3$)]; other data as above. The enantiomeric ratio was determined to be 99:1 by CSP-HPLC (major enantiomer eluted at 32.1 min). Data in accordance with the literature.[139]

1-Cyano-3-phenylpropyl acetate 299 [50]



A mixture of alcohol **298**$_{rac}$ (10 g, 62 mmol), Ac_2O (7.6 g, 74.5 mmol), and pyridine (6 mL, 74.5 mmol) in dichloromethane (420 mL) were stirred at room temperature. After 24 h, water was added before extracting with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with brine (25 mL) then dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography, eluting with petrol–Et_2O (8:2), to give the acetate **299** (11.5 g, 91%) as an oil; R_f 0.65 [petrol–EtOAc 8:2]; ν_{max}/cm^{-1} 2995, 2960, 2250, 1735, 1380; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36–7.32 (2H, m, Ar*H*), 7.28–7.20 (3H, m, Ar*H*), 5.28 (1H, t, *J* 7, CH), 2.88–2.84 (2H, m, CH_2), 2.29–2.23 (2H, m, CH_2), 2.15 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.0 (C=O), 139.0 (Ar), 128.8 (ArH), 128.3 (ArH), 126.7 (ArH), 116.7 (*C*N), 60.5 (CH), 33.7 (CH_2), 30.7 (CH_2), 20.3 (CH_3); HRMS (ES) found: MH^+, 204.1026. $C_{12}H_{14}NO_2$ requires MH^+, 204.1025; LRMS *m*/*z* (ES) 204 (100%, MH^+).

Ethyl 2-[160]**-2-cyano-4-phenylbutanoate 291**$_{rac}$



Method 1 (starting with racemic starting material):

n-Butyllithium (0.4 mL, 0.95 mmol, 2.5 M solution in hexanes) was added to diisopropylamine (0.15 mL, 1.02 mmol) in Et_2O (2.5 mL) at –78°C and stirred for 10 min. Nitrile **288**$_{rac}$ (0.05 g, 0.17 mmol) in Et_2O (0.5 mL) was added. After 10 min, ethyl cyanoformate (0.1 mL, 1.02 mmol) was added and the mixture was stirred at –78 °C for 30 min. The reaction mixture was allowed to warm to room temperature. Saturated aqueous ammonium chloride solution (2 mL) was added and the mixture was extracted

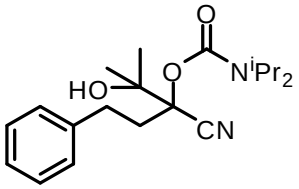
with Et_2O (3 × 2 mL). The organic layers were dried ($MgSO_4$) and evaporated. Purification by column chromatography, eluting with petrol–EtOAc (9:1), gave the ester **291**$_{rac}$ (0.05 g, 82%) as an oil; R_f 0.42 [petrol–EtOAc (8:2)]; ν_{max} (film)/cm^{-1} 2970, 2940, 1760, 1715, 1435; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36–7.32 (2H, m, Ar*H*), 7.28–7.23 (3H, m, Ar*H*), 4.39–4.26 (2H, m, CH_2), 4.09–4.00 (1H, m, NC*H*Me$_2$), 3.80–3.73 (1H, m, NC*H*Me$_2$), 3.03–2.90 (2H, m, CH_2), 2.48–2.36 (2H, m, CH_2), 1.35 (3H, t, *J* 7, CH_3), 1.32–1.25 (12H, m, NCH*Me$_2$*); ^{13}C NMR (100 MHz, $CDCl_3$) δ =165.6 (C=O), 152.7 (C=O), 139.2 (Ar), 128.7 (ArH), 128.3 (ArH), 126.6 (ArH), 116.0 (*C*N), 73.5 (C), 62.9 (CH_2), 47.4 (N*C*HMe$_2$), 46.1 (N*C*HMe$_2$), 38.6 (CH_2), 30.4 (CH_2), 21.6 (NCH*Me$_2$*), 21.3 (NCH*Me$_2$*), 20.3 (NCH*Me$_2$*), 20.2 NCH*Me$_2$*), 13.9 (CH_3); HRMS (ES) found: MH$^+$, 361.2132. $C_{20}H_{29}N_2O_4$ requires MH$^+$, 361.2127; LRMS *m*/*z* (ES) 361 (100%, MH$^+$).

Resolution between the enantiomers of compound **291**$_{rac}$ was achieved using a Beckman system fitted with a CHIRALPAK AD column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1mL·min^{-1}; ambient temperature, detection by UV absorbance at 254 nm. Injection volume 20 μL of the sample prepared in a 2 g·L^{-1} solution of the eluent. Under these conditions, the faster running component and slower running component were eluted at 8.12 min and 9.08 min respectively with an analysis time of 120.00 min.

Method 3 (starting with an enantiomerically enriched starting material, inverse addition):

A solution of nitrile **288** (0.10 g, 0.35 mmol) and dry ethyl cyanoformate (0.10 mL, 0.10 mmol) in dry Et_2O: THF (1:1) (0.5 mL) was added dropwise over 4 min using syringe pump to a solution of TMPMgCl (3.3 mL, 1.04 mmol, 0.4 M solution in Et_2O:THF) in dry Et_2O:THF (1:1) (2.5 mL) at –107 °C. The mixture was stirred at –107 °C for 30 min. Saturated aqueous ammonium chloride solution (2 mL) was added at –107 °C. The reaction mixture was allowed to warm to room temperature then extracted with Et_2O (3 × 2 mL). The organic layers were dried ($MgSO_4$) and evaporated. Purification by column chromatography, eluting with petrol–EtOAc (9:1), gave the ester **291** (0.09 g, 72%) as an oil; $[\alpha]^{23}_D$ +27.0 (c 1.00, $CHCl_3$); other data as above. The enantiomeric ratio was determined to be 80:20 by CSP-HPLC (major enantiomer eluted at 9.08 min).

1-Cyano-2-hydroxy-2-methyl-1-(2-phenylethyl) propyl N,N-*bis*(propan-2-yl) carbamate 300$_{rac}$

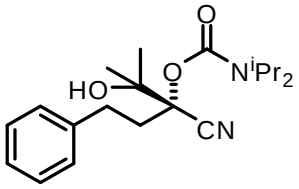


Method 1 (starting with racemic starting material):

Isopropyl magnesium chloride (0.45 mL, 0.85 mmol, 2 M solution in diethyl ether) was added to racemic nitrile **288**$_{rac}$ (0.20 g, 0.7 mmol) in dry Et_2O (3 mL) at –78 °C. After 10 min, dry acetone (0.06 mL, 0.75 mmol) was added and the mixture was stirred at −78 °C for 30 min. The reaction mixture was allowed to warm to room temperature and saturated aqueous ammonium chloride solution (2 mL) was added. The mixture was extracted with Et_2O (3 × 2 mL), then the organic layers were dried ($MgSO_4$) and evaporated. Purification by column chromatography, eluting with petrol–EtOAc (9:1), gave the alcohol **300**$_{rac}$ (0.15 g, 62%) as plates; R_f 0.40 [petrol–EtOAc 8:2]; m.p. 86−88 °C; ν_{max} (film)/cm^{-1} 3490, 2970, 2255, 1700, 1430, 1330; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35–7.31 (2H, m, Ar*H*), 7.26–7.22 (3H, m, Ar*H*), 5.03 (1H, s, OH), 4.05–3.88 (2H, m, NC*H*Me$_2$), 2.99 (1H, td, *J* 13, 4.5, CH), 2.82 (1H, td, *J* 13, 4.5, CH), 2.74–2.66 (1H, m, CH), 2.29–2.19 (1H, m, CH), 1.43 (3H, s, CH_3), 1.42 (3H, s, CH_3), 1.30 (12H, d, *J* 7, 2 × CH*Me$_2$*); ^{13}C NMR (100 MHz, $CDCl_3$) δ =153.4 (C=O), 140.2 (Ar), 128.6 (ArH), 128.3 (ArH), 126.4 (ArH), 117.8 (*C*N), 85.7 (C), 74.8 (C), 47.0 (N*C*HMe$_2$), 46.9 (N*C*HMe$_2$), 35.1 (CH_2), 31.4 (CH_2), 26.3 (CH_3), 26.1 (CH_3), 21.4 (NCH*Me$_2$*), 21.2 (NCH*Me$_2$*), 20.3 (NCH*Me$_2$*); HRMS (ES) found: MH$^+$, 347.2318. $C_{20}H_{31}N_2O_3$ requires MH$^+$, 347.2335; LRMS *m*/*z* (ES) 347 (100%, MH$^+$).

Resolution between the enantiomers of compound **300**$_{rac}$ was achieved using a Beckman system fitted with a Lux × 3u cellulose–1 column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1mL·min^{-1}; ambient temperature, detection by UV absorbance at 254 nm. Injection volume 20 μL of the sample prepared in a 2 g·L^{-1} solution of the eluent. Under these conditions, the faster running component and slower running component were eluted at 14.5 min and 17.0 min respectively with an analysis time of 30 min.

(1*R*)-1-Cyano-2-hydroxy-2-methyl-1-(2-phenylethyl) propyl N,N-*bis*(propan-2-yl) carbamate 300



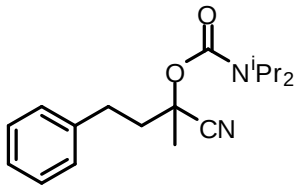
Method 2 (starting with enantiomerically enriched starting material, normal addition):

Isopropyl magnesium chloride (0.45 mL, 0.85 mmol, 2 M solution in diethyl ether) was added to the nitrile **288** (0.20 g, 0.69 mmol) in dry Et_2O (3 mL) at –78 °C. After 10 min, dry acetone (0.06 mL, 0.76 mmol) was added and the mixture was stirred at –78 °C for 30 min. Saturated aqueous ammonium chloride solution (2 mL) was added and the mixture was extracted with Et_2O (3 × 2 mL). The organic layers were dried ($MgSO_4$) and evaporated. Purification by column chromatography, eluting with petrol–EtOAc (9:1), gave the alcohol **300** (0.14 g, 60%) as a plates; $[\alpha]^{23}_D$ –8.0 (*c* 1.00, $CHCl_3$); other data as above. The enantiomeric ratio was determined to be 80:20 by CSP-HPLC (major enantiomer eluted at 14.5 min).

Method 3 (starting with enantiomerically enriched starting material, inverse addition):

A solution of nitrile **288** (0.10 g, 0.35 mmol) in dry Et_2O (2 mL) was added dropwise over 4 min using a syringe pump to a solution of TMPMgCl (3.5 mL, 1.4 mmol, 0.4 M solution in diethyl ether) in dry Et_2O (1 mL) at –107 °C. After 2 min, dry acetone (0.12 mL, 1.75 mmol) was added and the mixture was stirred at –107 °C for 30 min. Saturated aqueous ammonium chloride solution (2 mL) was added at –107 °C. The reaction mixture was allowed to warm to room temperature then extracted with Et_2O (3 × 2 mL). The organic layers were dried ($MgSO_4$) and evaporated. Purification by column chromatography, eluting with petrol–EtOAc (9:1), gave the alcohol **300** (0.12 g, 50%); $[\alpha]^{23}_D$ –8.0 (*c* 1.00, $CHCl_3$); other data as above. The enantiomeric ratio was determined to be 87:13 by CSP-HPLC (major enantiomer eluted at 14.5 min).

1-Cyano-1-methyl-3-phenylpropyl N,N-*bis*(propan-2-yl)carbamate 303$_{rac}$



Method 1 (starting with a racemic starting material):

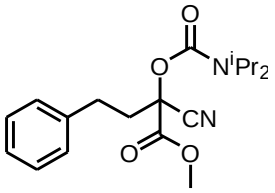
To diisopropylamine (0.06 mL, 0.45 mmol) in THF (2.5 mL) at –78 °C was added *n*-butyllithium (0.15 mL, 0.40 mmol, 2.5 M solution in hexanes). After 10 min, nitrile **288**$_{rac}$ (0.10 g, 0.35 mmol) in THF (0.5 mL) was added. After 10 min, iodomethane (0.03 mL, 0.40 mmol) was added and the mixture was stirred at –78 °C for 30 min, before being allowed to warm to room temperature. Saturated aqueous ammonium chloride solution (2 mL) was added and the mixture was extracted with Et_2O (3 × 2 mL). The organic layers were dried ($MgSO_4$) and evaporated. Purification by column chromatography, eluting with petrol–EtOAc (9:1), gave the nitrile **303** (0.06 g, 60%) as plates; R_f 0.71 [petrol–EtOAc (8:2)]; m.p. 65−67 °C; ν_{max}(film)/cm^{-1} 2980, 2870, 1705, 1435; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35–7.31 (2H, m, Ar*H*), 7.26–7.23 (3H, m, Ar*H*), 4.13 (1H, br.s, NC*H*Me$_2$), 3.71 (1H, br.s, NC*H*Me$_2$), 2.98–2.83 (2H, m, CH_2), 2.42–2.34 (1H, m, CH), 2.29–2.22 (1H, m, CH), 1.84 (3H, s, CH_3), 1.26 (6H, d, *J* 7, CH*Me$_2$*), 1.25 (6H, d, *J* 7, CH*Me$_2$*); ^{13}C NMR (100 MHz, $CDCl_3$) δ =152.8 (C=O), 140.1 (Ar), 128.6 (ArH), 128.3 (ArH), 126.4 (ArH), 119.5 (*C*N), 71.5 (C), 46.9 (N*C*HMe$_2$), 45.5 (N*C*HMe$_2$), 42.0 (CH_2), 30.5 (CH_2), 25.3 (CH_3), 21.6 (NCH*Me$_2$*), 20.4 (NCH*Me$_2$*); HRMS (ES) found: MH$^+$, 303.2066. $C_{18}H_{27}N_2O_2$ requires MH$^+$, 303.2073; LRMS *m*/*z* (ES) 303 (100%, MH$^+$).

Resolution between the enantiomers of compound **303**$_{rac}$ was achieved using a Beckman system fitted with a CHIRALCEL OD column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (90:10 v/v) as the mobile phase at a flow rate of 1mL·min^{-1}; ambient temperature, detection by UV absorbance at 254 nm. Injection volume 20 μL of the sample prepared in a 2 g·L^{-1} solution of the eluent. Under these conditions, the faster running component and slower running component were eluted at 8.1 min and 8.9 min respectively with an analysis time of 60.0 min.

Method 2 (starting with enantiomerically enriched starting material, normal addition):

n-Butyllithium (0.15 mL, 0.4 mmol, 2.5 M solution in hexanes) was added to diisopropylamine (0.06 mL, 0.45 mmol) in THF (2.5 mL) at –78 °C and stirred for 10 min. Enantiomerically enriched nitrile **288** (0.10 g, 0.35 mmol) in THF (0.5 mL) was added. After 10 min, iodomethane (0.03 mL, 0.35 mmol) was added and the mixture was stirred at –78 °C for 30 min. Saturated aqueous ammonium chloride solution (2 mL) was added and the mixture was extracted with Et_2O (3 × 2 mL). The organic layers were dried ($MgSO_4$) and evaporated. Purification by column chromatography, eluting with petrol–EtOAc (9:1), gave the nitrile **303** (0.06 g, 60%). Spectroscopic data as above. The enantiomeric ratio was determined to be 50:50 by CSP-HPLC (method as above).

Methyl2-{[*bis*(propan-2-yl)carbamoyl]*oxy*}-2-cyano-4-phenylbutanoate 304$_{rac}$



Method 1 (starting with racemic starting material):

n-Butyllithium (0.79 mL, 1.9 mmol, 2.5 M solution in hexanes) was added to diisopropylamine (0.30 mL, 2.08 mmol) in THF (2.5 mL) at –78 °C and stirred for 10 min. Nitrile **288**$_{rac}$ (0.10 g, 0.35 mmol) in THF (0.5 mL) was added. After 10 min, methyl chloroformate (0.15 mL, 2.07 mmol) was added and the mixture was stirred at –78 °C for 30 min. The reaction mixture was allowed to warm to room temperature, saturated aqueous ammonium chloride solution (2 mL) was added and the mixture was extracted with Et_2O (3 × 2 mL). The organic layers were dried ($MgSO_4$) and evaporated. Purification by column chromatography, eluting with petrol–EtOAc (9:1), gave the ester **304**$_{rac}$ (0.10 g, 80%) as needles; R_f 0.37 [petrol–EtOAc (8:2)]; m.p. 70−73 °C; ν_{max} (film)/cm^{-1} 2970, 2940, 1760, 1710, 1435; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36–7.32 (2H, m, Ar*H*), 7.27–7.22 (3H, m, Ar*H*), 4.08–3.99 (1H, m, NC*H*Me$_2$), 3.87 (3H, s, CH_3), 3.81–3.72 (1H, m, NC*H*Me$_2$), 3.03–2.89 (2H, m, CH_2), 2.44–2.36 (2H, m, CH_2), 1.31–1.25 (12H, m, 2 × CH*Me$_2$*); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.5 (C=O),

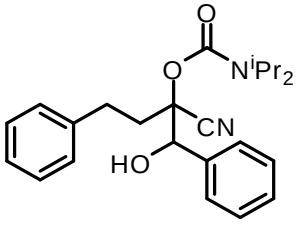
154.0 (C=O), 139.1 (Ar), 128.7 (ArH), 128.3 (ArH), 126.6 (ArH), 115.9 (*C*N), 73.3 (C), 53.8 (CH_3), 47.4 (N*C*HMe$_2$), 46.2 (N*C*HMe$_2$), 38.6 (CH_2), 30.3 (CH_2), 21.3 (NCH*Me$_2$*), 20.3 (NCH*Me$_2$*); HRMS (ES) found: MH^+, 347.1955. $C_{19}H_{27}N_2O_4$ requires MH^+, 347.1971; LRMS *m*/*z* (ES) 347 (100%, MH^+).

Resolution between the enantiomers of compound **304**$_{rac}$ was achieved using a Beckman system fitted with a Lux × 3u cellulose–1 column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1mL·min^{-1}; ambient temperature, detection by UV absorbance at 254 nm. Injection volume 20 μL of the sample prepared in a 2 g·L^{-1} solution of the eluent. Under these conditions, the faster running component and slower running component were eluted at 16.9 min and 20.9 min respectively with an analysis time of 60.0 min.

Method 3 (starting with enantiomerically enriched starting material, inverse addition):

A solution of nitrile **288** (0.05 g, 0.17 mmol) and dry methyl chloroformate (0.05 mL, 0.52 mmol) in dry Et_2O: THF (1:1) (0.5 mL) was added dropwise over 4 min using a syringe pump to a solution of TMPMgCl (1.5 mL, 0.52 mmol, 0.4 M solution in Et_2O: THF) in dry Et_2O: THF (1:1) (2.5 mL) at –107 °C. The mixture was stirred at –107 °C for 30 min. Saturated aqueous ammonium chloride solution (2 mL) was added at –107 °C. The reaction mixture was allowed to warm to room temperature then extracted with Et_2O (3 × 2 mL). The organic layers were dried ($MgSO_4$) and evaporated. Purification by column chromatography, eluting with petrol–EtOAc (9:1), gave the ester **304** (0.025 g, 40%) as needles; $[\alpha]^{23}_D$ +3.0 (*c* 1.00, $CHCl_3$); other data as above. The enantiomeric ratio was determined to be 91:9 by CSP-HPLC (major enantiomer eluted at 16.6 min).

1-Cyano-1-[hydroxyl (phenyl) methyl]-3-phenylpropyl N,N-*bis*(propan-2-yl) carbamate 305$_{rac}$



Method 1 (starting with racemic starting material):

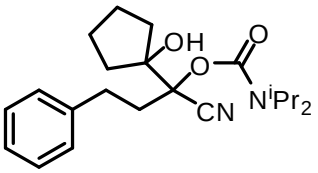
Isopropyl magnesium chloride (1.20 mol, 1.4 mmol, 1.15 M solution in diethyl ether) was added to nitrile **288**$_{rac}$ (0.1 g, 0.35 mmol) in Et_2O (3 mL) at –78 °C. After 10 min, dry benzaldehyde (0.20 mL, 1.75 mmol) was added and the mixture was stirred at –78 °C for 30 min. The reaction mixture was allowed to warm to room temperature and saturated aqueous ammonium chloride solution (2 mL) was added. The mixture was extracted with Et_2O (3 × 2 mL), Then the organic layers were dried ($MgSO_4$) and evaporated. Purification by column chromatography, eluting with petrol–EtOAc (9:1), gave an inseparable mixture of diastereomers **305** (1:1) (0.10 g, 77%) as plates; R_f 0.30 [petrol–EtOAc 8:2]; m.p. 150−154 °C; ν_{max} (film)/cm^{-1} 3445, 2965, 2940, 2255, 1685, 1455; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.47–7.17 (10H, m, Ar*H*), 5.50 (0.5H, d, *J* 5, CH or OH), 5.24 (0.5H, d, *J* 6.5, CH or OH), 4.83 (0.5H, d, *J* 6.5, CH or OH), 4.38 (0.5H, d, *J* 5, CH or OH), 4.02–3.92 (1H, m, NC*H*Me$_2$), 3.75–3.63 (1H, m, NC*H*Me$_2$), 3.02–2.77 (2H, m, CH_2), 2.59–2.23 (2H, m, CH_2), 1.32–1.27 (6H, m, NCH*Me$_2$*), 1.13–0.97 (6H, m, NCH*Me$_2$*); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.7 (C=O), 153.6 (C=O), 140.1 (Ar), 140.0 (Ar), 137.5 (ArH), 137.2 (ArH), 128.69 (ArH), 128.66 (ArH), 128.39 (ArH), 128.35 (ArH), 128.30 (ArH), 127.4 (ArH), 126.5 (ArH), 126.4 (ArH), 126.38 (ArH), 126.3 (ArH), 117.9 (*C*N), 117.1 (*C*N), 80.7 (C), 76.5 (CH), 75.5 (CH), 46.9 (N*C*HMe$_2$), 46.5 (N*C*HMe$_2$), 37.2 (CH_2), 35.2 (CH_2), 30.8 (CH_2), 30.7 (CH_2), 21.1 (NCH*Me$_2$*), 21.0 (NCH*Me$_2$*), 20.8 (NCH*Me$_2$*), 20.3 (NCH*Me$_2$*); HRMS (ES) found: MH$^+$, 395.2334. $C_{24}H_{31}N_2O_3$ requires MH$^+$, 395.2335; LRMS *m*/*z* (ES) 395 (100%, MH$^+$).

Resolution between diastereomers **305**$_{rac}$ was achieved using a Beckman system fitted with a Lux × 3u cellulose–1 column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1mL·min^{-1}; ambient temperature, detection by UV absorbance at 254 nm. Injection volume 20 μL of the sample prepared in a 2 g·L^{-1} solution of the eluent. Under these conditions, the faster running component and slower running component were eluted at 30.3 min, 38.2 min, 51.4 min and 60.0 min respectively with an analysis time of 90.00 min.

Method 3 (starting with enantiomerically enriched starting material, inverse addition):

A solution of nitrile **288** (0.10 g, 0.35 mmol) in dry Et_2O (2 mL) was added dropwise over 4 min using a syringe pump to a solution of TMPMgCl (3.80 mL, 1.4 mmol, 0.4 M solution in diethyl ether) in dry Et_2O (1 mL) at –107 °C. After 2 min, dry benzaldehyde (0.2 mL, 1.75 mmol) was added and the mixture was stirred at –107 °C for 30 min. Saturated aqueous ammonium chloride solution (2 mL) was added at –107 °C. The reaction mixture was allowed to warm to room temperature then extracted with Et_2O (3 × 2 mL). The organic layers were dried ($MgSO_4$) and evaporated. Purification by column chromatography, eluting with petrol–EtOAc (9.5:0.5), gave the alcohol **305** (0.075 g, 60%) as a (1:1) mixture of diastereomers as plates; $[\alpha]^{23}_D$ +6.0 (*c* 1.00, $CHCl_3$); other data as above. The enantiomeric ratios were determined to be 92:8 and 84:16 by CSP-HPLC (major enantiomers eluted at 30.3 min and 38.2 min).

1-Cyano-1-(1-hydroxycyclopentyl)-3-phenylpropylN,N-*bis*(propan-2-yl) carbamate 306$_{rac}$



Method 1 (starting with racemic starting material):

TMPMgCl (3.80 mL, 1.4 mmol, 0.4 M solution in diethyl ether) was added to the nitrile **288**$_{rac}$ (0.10 g, 0.35 mmol) in Et_2O (3 mL) at –78 °C. After 10 min, dry cyclopentanone (0.15 mL, 1.75 mmol) was added. After 30 min, the reaction mixture was allowed to warm to room temperature then saturated aqueous ammonium chloride solution (2 mL) was added and the mixture was extracted with Et_2O (3 × 2 mL). The organic layers were dried ($MgSO_4$) and evaporated. Purification by column chromatography, eluting with Petrol–EtOAc (9:1), gave the alcohol **306** (0.07 g, 54%) as needles; R_f 0.77 [petrol–EtOAc 8:2]; m.p. 135−137 °C; ν_{max} (film)/cm^{-1} 3465, 2970, 2940, 1700; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34–7.30 (2H, m, Ar*H*), 7.25–7.22 (3H, m, Ar*H*), 4.47 (1H, s, OH), 4.09–3.97 (1H, m, NC*H*Me$_2$), 3.91–3.79 (1H, m, NC*H*Me$_2$), 3.02–2.95 (1H, m, CH), 2.88–2.79 (2H, m, CH_2), 2.31–2.23 (1H, m, CH), 2.12–1.99 (2H, m, CH_2), 1.97–1.87

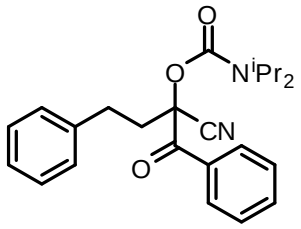
(2H, m, CH_2), 1.79–1.71 (4H, m, 2 × CH_2), 1.28 (12H, d, *J* 7, 2 × CH*Me*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ =153.3 (C=O), 140.3 (Ar), 128.6 (ArH), 128.3 (ArH), 126.3 (ArH), 118.3 (*C*N), 85.8 (C), 85.7 (C), 47.1 (N*C*HMe$_2$), 46.5 (N*C*HMe$_2$), 38.0 (CH_2), 37.9 (CH_2), 35.3 (CH_2), 31.3 (CH_2), 24.7 (CH_2), 24.0 (CH_2), 21.4 (NCH*Me*$_2$), 20.3 (NCH*Me*$_2$); HRMS (ES) found: MH^+, 373.2475. $C_{22}H_{33}N_2O_3$ requires MH^+, 373.2491; LRMS *m*/*z* (ES) 373 (100%, MH^+).

Resolution between the enantiomers of compound **306**$_{rac}$ was achieved using a Beckman system fitted with a Lux × 3u cellulose–1 column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1mL·min^{-1}; ambient temperature, detection by UV absorbance at 254 nm. Injection volume 20 μL of the sample prepared in a 2 g·L^{-1} solution of the eluent. Under these conditions, the faster running component and slower running component were eluted at 14.4 min and 20.3 min respectively with an analysis time of 40.00 min.

Method 3 (starting with enantiomerically enriched starting material, inverse addition):

A solution of nitrile **288** (0.10 g, 0.35 mmol) in dry Et_2O (2 mL) was added dropwise over 4 min using a syringe pump to a solution of TMP magnesium chloride (3.80 mL, 1.4 mmol, 0.4 M solution in diethyl ether) in dry Et_2O (1 mL) at –107 °C. After 2 min, dry cyclopentanone (0.16 mL, 1.75 mmol) was added and the mixture was stirred at –107 °C for 30 min. Saturated aqueous ammonium chloride solution (2 mL) was added at –107 °C. The reaction mixture was allowed to warm to room temperature then extracted with Et_2O (3 × 2 mL). The organic layers were dried ($MgSO_4$) and evaporated. Purification by column chromatography, eluting with petrol–EtOAc (9:1), gave the alcohol **306** (0.065 g, 50%) as needles; $[\alpha]^{23}_D$ –2.0 (*c* 1.00, $CHCl_3$); other data as above. The enantiomeric ratio was determined to be 92:8 by CSP-HPLC (major enantiomer eluted at 14.4 min).

1-Benzoyl-1-cyano-3-phenylpropyl N,N-*bis*(propan-2-yl)carbamate 307$_{rac}$



Method 1 (starting with racemic starting material):

To diisopropylamine (0.29 mL, 2.08 mmol) in Et_2O (2.5 mL) at –78 °C was added *n*-butyllithium (0.79 mL, 1.9 mmol, 2.5 M solution in hexanes). After 10 min, nitrile **288**$_{rac}$ (0.1 g, 0.35 mmol) in Et_2O (0.5 mL) were added. After 10 min, dry benzoyl chloride (0.25 mL, 2.04 mmol) was added and the mixture was stirred at –78 °C for 30 min, before being allowed to warm to room temperature, saturated aqueous ammonium chloride solution (2 mL) was added and the mixture was extracted with Et_2O (3 × 2 mL). The organic layers were dried ($MgSO_4$) and evaporated. Purification by column chromatography, eluting with petrol–EtOAc (9:1), gave the nitrile **307**$_{rac}$ (0.10 g, 72%) as plates; R_f 0.65 [petrol–EtOAc (8:2)]; m.p. 127−130 °C; ν_{max}(film)/cm^{-1} 2970, 2940, 1735, 1705, 1690, 1430; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.03 (2H, d, *J* 7.5, Ar*H*), 7.58 (1H, t, *J* 7.5, Ar*H*), 7.46 (2H, t, *J* 7.5, Ar*H*), 7.36–7.31 (2H, m, Ar*H*), 7.26–7.24 (3H, m, Ar*H*), 3.92–3.85 (1H, m, CH), 3.75–3.69 (1H, m, CH), 3.14–3.01 (2H, m, CH_2), 2.71–2.64 (1H, m, CH), 2.59–2.51 (1H, m, CH), 1.31–1.15 (12H, m, 2 × NCH*Me*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ =190.4 (C=O), 151.9 (C=O), 139.4 (Ar), 133.3 (ArH), 128.8 (ArH), 128.7 (ArH), 128.5 (ArH), 128.3 (ArH), 128.2 (ArH), 126.6 (ArH), 116.8 (*C*N), 79.6 (C), 46.8 (N*C*HMe$_2$), 46.7 (N*C*HMe$_2$), 38.5 (CH_2), 30.8 (CH_2), 21.4 (NCH*Me*$_2$), 21.3 (NCH*Me*$_2$), 20.3 (NCH*Me*$_2$), 19.7 (NCH*Me*$_2$); HRMS (ES) found: MH$^+$, 393.2161. $C_{24}H_{29}N_2O_3$ requires MH$^+$, 393.2178; LRMS *m*/*z* (ES) 393 (100%, MH$^+$).

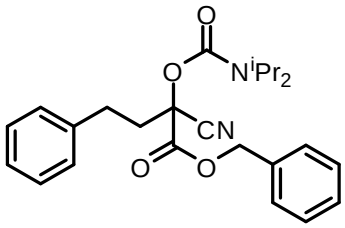
Resolution between the enantiomers of compound **307**$_{rac}$ was achieved using a Beckman system fitted with a Lux × 3u cellulose–1 column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1mL·min^{-1}; ambient temperature, detection by UV absorbance at 254 nm. Injection volume 20 μL of the sample prepared in a 2 g·L^{-1} solution of the eluent. Under these conditions, the faster running component and slower running

component were eluted at 15.0 min and 18.7 min respectively with an analysis time of 70.00 min.

Method 3 (starting with an enantiomerically enriched starting material, inverse addition):

A solution of nitrile **288** (0.10 g, 0.35 mmol) and dry benzoyl chloride (0.12 mL, 1.04 mmol) in dry Et_2O:THF (1:1) (0.5 mL) was added dropwise over 4 min using a syringe pump to a solution of TMPMgCl (3.05 mL, 1.04 mmol, 0.4 M solution in Et_2O:THF, 1:1) in dry Et_2O:THF (1:1) (2.5 mL) at –107 °C. The mixture was stirred at –107 °C for 30 min. Saturated aqueous ammonium chloride solution (2 mL) was added at –107 °C. The reaction mixture was allowed to warm to room temperature then extracted with Et_2O (3 × 2 mL). The organic layers were dried ($MgSO_4$) and evaporated. Purification by column chromatography, eluting with petrol–EtOAc (9:1), gave the product **307** (0.04 g, 40%) as plates; $[\alpha]^{23}_{D}$ +2 (c 1.00, $CHCl_3$); other data as above. The enantiomeric ratio was determined to be 63:37 by CSP-HPLC (method as above, major enantiomer eluted at 14.9 min).

Benzyl 2-{[*bis*(propan-2-yl)carbamoyl]*oxy*}-2-cyano-4-phenylbutanoate 308$_{rac}$



Method 1 (starting with racemic starting material):

TMPMgCl (3.5 mL, 3.80 mmol, 0.4 M solution in diethyl ether) was added to nitrile **288**$_{rac}$ (0.1 g, 0.35 mmol) in Et_2O (3 mL) at –78 °C. After 10 min, dry benzyl cyanoformate (0.25 mL, 1.70 mmol) was added and the mixture was stirred at –78 °C for 30 min. Saturated aqueous ammonium chloride solution (2 mL) was added and the mixture was extracted with Et_2O (3 × 2 mL). The organic layers were dried ($MgSO_4$) and evaporated. Purification by column chromatography, eluting with petrol–EtOAc (9.5:0.5), gave the ester **308**$_{rac}$ (0.07 g, 50%) as an oil; R_f 0.51 [petrol–EtOAc 8:2]; ν_{max} (flim)/cm^{-1} 2970, 2940, 2255, 1760, 1720, 1440; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41–7.13 (10H, m, Ar*H*), 5.37 (1H, d, *J* 12, CH), 5.21 (1H, d, *J* 12, CH), 4.09–3.99

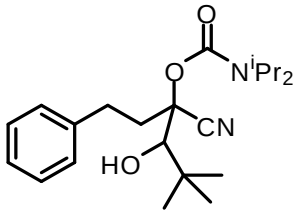
(1H, m, NC*H*Me_2), 3.77–3.71 (1H, m, NC*H*Me_2), 2.95–2.79 (2H, m, CH_2), 2.46–2.33 (2H, m, CH_2), 1.27–1.22 (12H, m, NCH*Me_2*); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.5 (C=O), 152.7 (C=O), 139.1 (Ar), 134.4 (ArH), 128.75 (ArH), 128.71 (ArH), 128.6 (ArH), 128.5 (ArH), 128.3 (ArH), 126.6 (ArH), 115.9 (*C*N), 73.5 (C), 68.7 (CH_2), 47.4 (N*C*HMe_2), 46.1 (N*C*HMe_2), 38.6 (CH_2), 30.3 (CH_2), 21.5 (NCH*Me_2*), 21.3 (NCH*Me_2*), 20.2 (NCH*Me_2*); HRMS (ES) found: MH^+, 423.2279. $C_{25}H_{31}N_2O_4$ requires MH^+, 423.2284; LRMS *m*/*z* (ES) 423 (100%, MH^+).

Resolution between the enantiomers of compound **308**$_{rac}$ was achieved using a Beckman system fitted with a Lux × 3u cellulose–1 column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1mL·min^{-1}; ambient temperature, detection by UV absorbance at 254 nm. Injection volume 20 μL of the sample prepared in a 2 g·L^{-1} solution of the eluent. Under these conditions, the faster running component and slower running component were eluted at 21.4 min and 26.9 min respectively with an analysis time of 120.00 min.

Method 3 (starting with enantiomerically enriched starting material, inverse addition):

A solution of nitrile **288** (0.05 g, 0.17 mmol) and dry benzyl cyanoformate (0.08 mL, 0.52 mmol) in dry Et_2O: THF (1:1) (0.5 mL) was added dropwise over 4 min using a syringe pump to a solution of TMPMgCl (1.3 mL, 0.52 mmol, 0.4 M solution in Et_2O: THF) in dry Et_2O: THF (1:1) (2.5 mL) at –107 °C. The mixture was stirred at –107 °C for 30 min. Saturated aqueous ammonium chloride solution (2 mL) was added at –107 °C. The reaction mixture was allowed to warm to room temperature then extracted with Et_2O (3 × 2 mL). The organic layers were dried ($MgSO_4$) and evaporated. Purification by column chromatography, eluting with petrol–EtOAc (9.5:0.5), gave the ester **308** (0.04 g, 52%) as an oil; $[\alpha]^{23}_D$ +12 (c 1.00, $CHCl_3$); other data as above. The enantiomeric ratio was determined to be 91:9 by CSP-HPLC (major enantiomer eluted at 21.4 min).

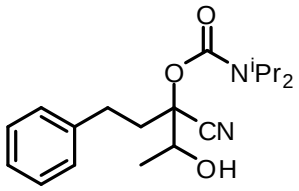
1-Cyano-2-hydroxy-3,3-dimethyl-1-(2-phenylethyl)butylN,N-*bis*(propan-2-yl) carbamate 309$_{rac}$



Method 1 (starting with racemic starting material):

Isopropyl magnesium chloride (1.5 mL, 1.4 mmol, 0.95 M solution in diethyl ether) was added to the racemic nitrile **288**$_{rac}$ (0.10 g, 0.35 mmol) in dry Et_2O (3 mL) at –78 °C. After 10 min, dry pivaldehyde (0.20 mL, 1.75 mmol) was added and the mixture was stirred at –78 °C for 30 min. The reaction mixture was allowed to warm to room temperature and saturated aqueous ammonium chloride solution (2 mL) was added. The mixture was extracted with Et_2O (3 × 2 mL), then the organic layers were dried ($MgSO_4$) and evaporated. Purification by column chromatography, eluting with petrol–EtOAc (9:1), gave one diastereomer of alcohol **309**$_{rac}$ (1:0) (0.03 g, 17%) as plates; R_f 0.54 [petrol–EtOAc 8:2]; m.p. 133−137 °C; ν_{max} (film)/cm^{-1} 2975, 2930, 1705, 1675; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35–7.31 (2H, m, Ar*H*), 7.26–7.22 (3H, m, Ar*H*), 4.07–4.00 (1H, m, OH or CH), 3.86–3.76 (3H, m, 2 × NC*H*Me$_2$, CH or OH), 2.88–2.71 (3H, m, 3 × CH), 2.48–2.40 (1H, m, CH), 1.32 (6H, d, *J* 7, CH*Me$_2$*) 1.26 (6H, d, *J* 7, CH*Me$_2$*) 1.12 (9H, s, 3 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ =167.7 (C=O), 140.2 (Ar), 130.8 (ArH), 128.8 (ArH), 128.3 (ArH), 126.4 (ArH), 118.0 (*C*N), 79.3 (CH), 81.2 (C), 47.1 (N*C*HMe$_2$), 47.0 (N*C*HMe$_2$), 36.5 (C), 39.4 (CH_2), 28.9 (CH_2), 25.2 (CH_3), 21.7 (NCH*Me$_2$*), 20.4 (NCH*Me$_2$*); HRMS (ES) found: MH$^+$, 375.2649. $C_{22}H_{35}N_2O_3$ requires MH$^+$, 375.2648; LRMS *m*/*z* (ES) 375 (100%, MH$^+$).

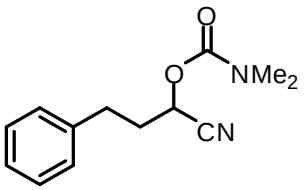
1-Cyano-2-hydroxy-1-(2-phenylethyl)propyl N,N-*bis*(propan-2-yl)carbamate 310$_{rac}$



Method 1 (starting with racemic starting material):

n-Butyllithium (0.95 mL, 1.90 mmol, 2.5 M solution in hexanes) was added to diisopropylamine (0.30 mL, 2.07 mmol) in Et_2O (2.5 mL) at –78 °C and stirred for 10 min. Nitrile **288**$_{rac}$ (0.10 g, 0.35 mmol) in Et_2O (0.5 mL) was added. After 10 min, a dry acetaldehyde (0.12 mL, 2.07 mmol) was added and the mixture was stirred at –78 °C for 30 min. The reaction mixture was allowed to warm to room temperature. Saturated aqueous ammonium chloride solution (2 mL) was added and the mixture was extracted with Et_2O (3 × 2 mL). The organic layers were dried ($MgSO_4$) and evaporated. Purification by column chromatography, eluting with petrol–EtOAc (8:2), gave an inseparable mixture of diastereomers **310**$_{rac}$ (1:1) (0.10 g, 86%) as an oil; R_f 0.37 [petrol–EtOAc (8:2)]; ν_{max} (film)/cm^{-1} 3490, 2975, 2880, 2250, 1735, 1375; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35–7.31 (2H, m, Ar*H*), 7.26–7.22 (3H, m, Ar*H*), 4.37–4.30 (0.5H, m, CH), 4.25–4.18 (0.5H, m, CH), 4.08–3.95 (1.5H, m, NC*H*Me$_2$, OH), 3.87–3.83 (1.5H, m, NC*H*Me$_2$, OH), 2.91–2.77 (2H, m, CH_2), 2.49–2.41 (1.5H, m, CH), 2.31–2.23 (0.5H, m, CH), 1.39 (1.5H, d, *J* 6, CH_3), 1.34 (1.5H, d, *J* 6, CH_3), 1.28 (12H, s, 2 × NCH*Me$_2$*); ^{13}C NMR (100 MHz, $CDCl_3$) δ =153.2 (C=O), 153.0 (C=O), 140.1 (Ar), 140.0 (Ar), 128.7 (ArH), 128.6 (ArH), 128.4 (ArH), 128.3 (ArH), 126.5 (ArH), 126.4 (ArH), 117.9 (*C*N), 117.2 (*C*N), 81.4 (C), 80.8 (C), 70.4 (CH), 70.2 (CH), 47.6 (N*C*HMe$_2$), 46.5 (N*C*HMe$_2$), 37.0 (CH_2), 35.3 (CH_2), 30.7 (CH_2), 30.6 (CH_2), 21.4 (NCH*Me$_2$*), 20.3 (NCH*Me$_2$*), 18.1 (CH_3), 18.0 (CH_3); HRMS (ES) found: MH$^+$, 333.2165. $C_{19}H_{29}N_2O_3$ requires MH$^+$, 333.2178; LRMS *m*/*z* (ES) 333 (100%, MH$^+$).

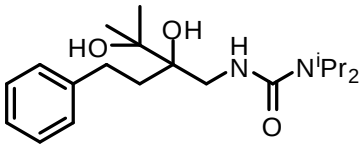
1-Cyano-3-phenylpropyl N,N-dimethylcarbamate 292$_{rac}$



To a solution (0 °C) of triphosgene (0.37 g, 1.25 mmol) in Et_2O (12 mL) was added triethylamine (0.55 mL, 3.75 mmol). After stirring at 0 °C for 20 min, a solution of alcohol **298**$_{rac}$ (0.50 g, 3.10 mmol) in Et_2O (4.0 mL) was added. After stirring at 0 °C for 30 min, dimethylamine (1.86 mL, 3.72 mmol) was added followed by stirring at 0 °C for 25 min before triethylamine (0.52 mL, 3.72 mmol) was added. After stirring at 0 °C for 45 min then 25 ºC for 30 min, the mixture was filtered through Celite and concentrated, the residue was purified by column chromatography, eluting with petrol–

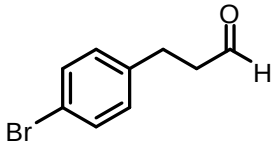
Et_2O (8:2), to give the nitrile **292**$_{rac}$ (0.50 g, 70%) as plates; R_f 0.46 [petrol–Et_2O (8:2)]; m.p. 53-55 °C; ν_{max} (film)/cm^{-1} 2975, 2950, 2255, 1365; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35–7.31 (2H, m, Ar*H*), 7.26–7.20 (3H, m, Ar*H*), 5.33 (1H, t, *J* 7, CH), 2.96 (3H, s, CH_3), 2.90 (3H, s, CH_3), 2.88–2.84 (2H, m, CH_2), 2.30–2.24 (2H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.4 (C=O), 139.2 (ArH), 128.7 (ArH), 128.3 (ArH), 126.6 (ArH), 117.3 (*C*N), 61.9 (CH), 36.7 (CH_3), 35.8 (CH_3), 33.9 (CH_2), 31.1 (CH_2); HRMS (ES) found: MH$^+$, 233.1281. $C_{13}H_{17}N_2O_2$ requires MH$^+$, 233.1290; LRMS *m*/*z* (ES) 233 (100%, MH$^+$).

1-[2,3-Dihydroxy-3-methyl-2-(2-phenylethyl)butyl]-3,3-bis(propan-2-yl)urea 315



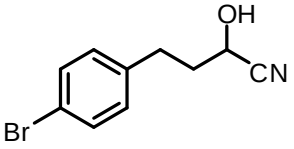
To a cooled (0 °C) solution of alcohol **300** (0.08 g, 0.23 mmol) in THF (3.0 mL) was added lithium aluminum hydride (0.02 g, 0.72 mmol). After stirring for 10 min, the cooling bath was removed. The mixture was stirred for 4 h at room temperature, then 1M NaOH solution (1.0 mL) was added. The mixture was filtered through Celite with 9:1 CH_2Cl_2:MeOH (10 mL). The mixture was extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were dried ($MgSO_4$) and evaporated. Purification by column chromatography, eluting with petrol–EtOAc (1:1), gave the alcohol **315** (0.06 g, 66%) as plates; R_f 0.59 [petrol–EtOAc 1:1]; m.p. 199−201 °C; ν_{max} (film)/cm^{-1} 3445, 1755, 1055; ^{1}H NMR (400 MHz, DMSO) δ = 7.26–7.22 (2H, m, Ar*H*), 7.15–7.13 (3H, m, Ar*H*), 6.08 (1H, s, NH), 4.78 (2H, s, 2 × OH), 3.85–3.78 (2H, m, 2 × NC*H*Me$_2$), 3.44–3.39 (1H, m, CH), 3.21–3.16 (1H, m, CH), 2.66–2.53 (2H, m, CH_2), 1.88–1.80 (1H, m, CH), 1.67–1.60 (1H, m, CH), 1.18 (6H, d, *J* 7, NCH*Me$_2$*), 1.17 (6H, d, *J* 7, NCH*Me$_2$*), 1.16 (3H, s, CH_3), 1.13 (3H, s, CH_3); ^{13}C NMR (100 MHz, DMSO) δ = 157.3 (C=O), 144.2 (Ar), 131.7 (ArH), 128.6 (ArH), 125.73 (ArH), 75.9 (C), 75.3 (C), 44.8 (2 × CH), 44.6 (CH_2), 36.4 (CH_2), 30.3 (CH_2), 25.7 (2 × CH_3), 21.9 (2 × NCH*Me$_2$*); HRMS (ES) found: MH$^+$, 351.2652. $C_{20}H_{35}N_2O_3$ requires MH$^+$, 351.2648; LRMS *m*/*z* (ES) 351 (100%, MH$^+$).

3-(4-Bromophenyl)propanal 318[160]



A mixture of 4-bromoiodobenzene (10.0 g, 35.5 mmol), 2-propen-1-ol (3.05g, 53.0 mmol), sodium hydrogencarbonate (7.50 g, 88.5 mmol), tetra-*n*-butylammonium chloride (9.80 g, 35.5 mmol) and palladium acetate (0.16 g, 0.70 mmol) in anhydrous DMF (35 mL) were heated at 40 °C for 24 h. The solution was allowed to cool to room temperature, diluted with Et_2O (80 mL) then filtered through Celite. After evaporation of the solvents the residue was purified by column chromatography, eluting with petrol–EtOAc (9:1), to give the aldehyde **318** (5.88 g, 78%) as an oil; R_f 0.41 [petrol–EtOAc (8:2)]; ν_{max} (film)/cm^{-1} 2830, 2735, 1725, 1490; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.78 (1H, s, CHO), 7.39 (2H, d, *J* 8, Ar*H*), 7.06 (2H, d, *J* 8, Ar*H*), 2.89 (2H, t, *J* 7, CH_2), 2.75 (2H, t, *J* 7, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 201.0 (C=O), 139.4 (Ar), 131.6 (ArH), 130.1 (ArH), 120.0 (Ar), 44.9 (CH_2), 27.4 (CH_2); HRMS (EI) Found: M^+, 211.9844. $C_9H_9O^{79}Br$ requires M^+, 211.9837; LRMS *m/z* (EI) 214 (94%), 212 (100%, MH^+), 211 (13), 156 (68). Data in accordance with the literature.[160]

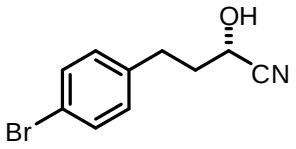
4-(4-Bromophenyl)-2-hydroxybutanenitrile 319$_{rac}$



The aldehyde **318** (5.80 g, 27.5 mmol) was added dropwise to a stirred solution of 37% aqueous $NaHSO_3$ (20 mL, 27.5 mmol) at 0 °C. A solution of NaCN (1.35 g, 27.5 mmol) in H_2O (20 mL) was added dropwise. The reaction mixture was stirred at room temperature for 18 h, after that was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated, the residue was purified by column chromatography, eluting with petrol–Et_2O (8:2), to give the alcohol **319**$_{rac}$ (9.0 g, 75%) as an oil; R_f 0.17 [petrol–EtOAc 8:2]; ν_{max}(film)/cm^{-1} 3350, 2935, 2920, 2255, 1665, 1490; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45 (2H, d, *J* 8.5, Ar*H*), 7.10 (2H, d, *J* 8.5, Ar*H*), 4.44 (1H, dd, *J* 12, 6, CH), 2.87–2.80 (3H, m, CH_2, OH), 2.21–2.10 (2H, m,

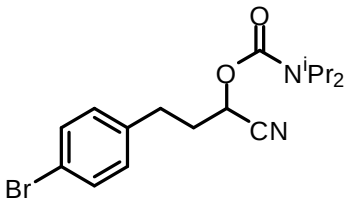
CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 138.5 (Ar), 131.8 (ArH), 130.2 (ArH), 120.4 (Ar), 119.6 (*C*N), 60.2 (CH), 36.3 (CH_2), 30.0 (CH_2); HRMS (EI) found: HRMS (EI) found: M^+, 238.9955. $C_{10}H_{10}NO^{79}Br$ requires M^+, 238.9946; LRMS m/z (EI) 241 (76%), 239 (79), 238 (14), 77 (100).

(2*S*)-4-(4-bromophenyl)-2-hydroxybutanenitrile 319



To a solution of ester **318**$_{rac}$ (3.98 g, 14.0 mmol), in 10% THF−H_2O (20 mL) was added amano lipase PS (0.30 g). After 2 h at 50 °C, EtOAc (20 mL) and brine (20 mL) were added. The mixture was filtered through Celite, extracted with EtOAc (3 × 15 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography, eluting with petrol–Et_2O (8:2), to give the alcohol **319** (1.65 g, 49%). Data as above.

3-(4-Bromophenyl)-1-cyanopropyl N,N-*bis*(propan-2-yl) carbamate 320$_{rac}$



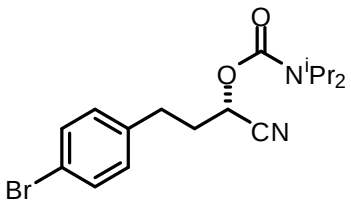
Method 1 (starting with racemic starting material):

To a solution of triphosgene (1.30 g, 4.5 mmol) in Et_2O (45 mL) was added triethylamine (1.75 mL, 12.5 mmol) at room temperature. After stirring for 30 min, alcohol **319**$_{rac}$ (2.0 g, 12.5 mmol), in Et_2O (25 mL) was added. After 30 min, diisopropylamine (1.75 mL, 12.5 mmol) and triethylamine (1.75 mL, 12.5 mmol) were added. After 2 h, the mixture was filtered through Celite and concentrated. The residue was purified by column chromatography, eluting with petrol–Et_2O (8:2), to give the nitrile **320**$_{rac}$ (0.70 g, 15%) as plates; m.p. 50−52 °C; R_f 0.43 [petrol–Et_2O 8:2]; ν_{max}(film)/cm^{-1} 2980, 2940, 2250, 2180, 1715, 1445; ^1H NMR (400 MHz, $CDCl_3$) δ =

7.45 (2H, d, *J* 8.5, Ar*H*), 7.09 (2H, d, *J* 8.5, Ar*H*), 5.41 (1H, t, *J* 6.5, CH), 4.04 (1H, br.s, NC*H*Me$_2$), 3.75 (1H, br.s, NC*H*Me$_2$), 2.87–2.79 (2H, m, CH$_2$), 2.26–2.19 (2H, m, CH$_2$), 1.25 (6H, d, *J* 7, NCH*Me$_2$*), 1.24 (6H, d, *J* 7, NCH*Me$_2$*); ^{13}C NMR (100 MHz, CDCl$_3$) δ =152.9 (C=O), 138.3 (Ar), 131.8 (ArH), 130.0 (ArH), 120.4 (Ar), 117.4 (*C*N), 61.0 (CH), 47.2 (CH), 45.8 (CH), 34.2 (CH$_2$), 30.4 (CH$_2$), 21.4 (NCH*Me$_2$*), 20.7 (NCH*Me$_2$*), 20.3 (NCH*Me$_2$*); HRMS (ES) found: MH$^+$, 367.1031. $C_{17}H_{24}N_2O_2$ ^{79}Br requires MH$^+$, 367.1021; LRMS *m*/*z* (ES) 369 (100%, MH$^+$), 367 (100%, MH$^+$).

Resolution between the enantiomers of compound **320**$_{rac}$ was achieved using a Beckman system fitted with a Lux × 3u cellulose–1 column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1mL·min^{-1}; ambient temperature, detection by UV absorbance at 254 nm. Injection volume 20 μL of the sample prepared in a 2 g·L^{-1} solution of the eluent. Under these conditions, the faster running component and slower running component were eluted at 15.9 min and 19.4 min respectively with an analysis time of 60.0 min.

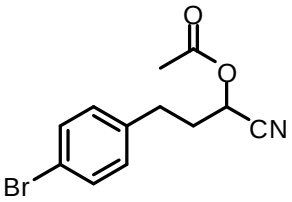
(*1S*)-3-(4-Bromophenyl)-1-cyanopropyl N,N-*bis*(propan-2-yl)carbamate 320



Method 2 (starting with enantiomerically enriched starting material):

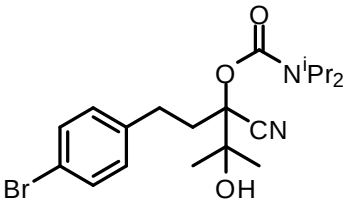
To a solution of triphosgene (1.15 g, 4.0 mmol) in Et$_2$O (30 mL) was added triethylamine (1.70 mL, 12.0 mmol) at room temperature. After stirring for 30 min, alcohol **319** (1.60 g, 10.0 mmol), in Et$_2$O (20 mL) was added. After stirring for 30 min, diisopropylamine (1.75 mL, 12.5 mmol) and triethylamine (1.75 mL, 12.0 mmol) were added. After 2 h, the mixture was filtered through Celite and concentrated. The residue was purified by column chromatography, eluting with petrol−Et$_2$O (8:2), to give the nitrile **320** (0.40 g, 10%); $[\alpha]^{21}_D$ –15 (*c* 1.00, CHCl$_3$); other Data as above. The enantiomeric ratio was determined to be 97:3 by CSP- HPLC (major enantiomer eluted at 19.4 min).

3-(4-Bromophenyl)-1-cyanopropyl acetate 321



A mixture of alcohol **319**$_{rac}$ (4.0 g, 25.5 mmol), Ac_2O (3.12 g, 30.5 mmol), pyridine (2.5 mL, 74.5 mmol) in dichloromethane (172 mL) were stirred at room temperature. After 24 h, water was added before extracting with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with brine (25 mL) then dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography, eluting with petrol–Et_2O (8:2), to give the ester **321** (3.98 g, 55%) as an oil; R_f 0.37 [petrol–Et_2O 8:2]; ν_{max} (film)/cm^{-1} 2940, 2930, 1760, 2250, 1490, 1225; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45 (2H, d, *J* 8.5, ArH), 7.08 (2H, d, *J* 8.5, ArH), 5.28 (1H, t, *J* 6.5, CH), 2.84–2.76 (2H, m, CH_2), 2.25–2.18 (2H, m, CH_2), 2.14 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.0 (C=O), 138.0 (Ar), 131.8 (ArH), 130.0 (ArH), 120.5 (Ar), 116.5 (*C*N), 60.3 (CH), 33.5 (CH_2), 30.1 (CH_2), 20.3 (CH_3); HRMS (EI) Found: M^+, 281.0064. $C_{12}H_{12}NO_2{}^{79}Br$ requires M^+, 281.0051; LRMS *m/z* (EI) 281 (14%), 171 (46), 115 (73).

1-[2-(4-Bromophenyl)ethyl]-1-cyano-2-hydroxy-2-methylpropyl N,N-*bis*(propan-2-yl) carbamate 322$_{rac}$



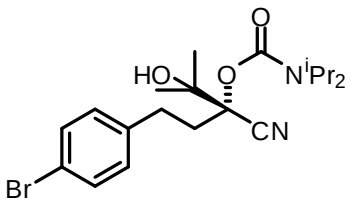
Method 1 (starting with racemic starting material):

TMPMgCl (2.80 mL, 1.05 mmol, 0.4 M solution in diethyl ether) was added to the nitrile **320**$_{rac}$ (0.10 g, 0.27 mmol) in Et_2O (3 mL) at –78 °C. After 10 min, dry acetone (0.10 mL, 1.35 mmol) was added. After 30 min, the reaction mixture was allowed to warm to room temperature, saturated aqueous ammonium chloride solution (2 mL) was added and the mixture was extracted with Et_2O (3 × 2 mL). The organic layers were dried ($MgSO_4$) and evaporated. Purification by column chromatography, eluting with

petrol–EtOAc (9:1), gave the alcohol **322**$_{rac}$ (0.10 g, 92%) as a plates; R_f 0.45 [petrol–EtOAc 9:1]; m.p. 143−145 °C; ν_{max} (film)/cm^{-1} 3005, 2980, 1705, 1280; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.44 (2H, d, *J* 8.5, Ar*H*), 7.10 (2H, d, *J* 8.5, Ar*H*), 4.85 (1H, s, OH), 4.01–3.85 (2H, m, 2 × C*H*Me$_2$), 2.98–2.90 (1H, m, CH), 2.82–2.64 (2H, m, CH_2), 2.24–2.16 (1H, m, CH), 1.42 (6H, s, 2 × CH_3), 1.31–1.25 (12H, m, NCH*Me$_2$*); ^{13}C NMR (100 MHz, $CDCl_3$) δ =153.3 (C=O), 139.2 (Ar), 131.7 (ArH), 130.1 (ArH), 120.2 (Ar), 117.8 (*C*N), 85.4 (C), 74.8 (C), 47.0 (CH), 46.9 (CH), 34.7 (CH_2), 30.9 (CH_2), 26.2 (CH_3), 21.4 (NCH*Me$_2$*), 21.2 (NCH*Me$_2$*), 20.3 (NCH*Me$_2$*); HRMS (ES) found: MH$^+$, 425.1432. $C_{20}H_{30}N_2O_3{}^{79}Br$ requires MH$^+$, 425.1440; LRMS *m*/*z* (ES) 427 (100%, MH$^+$), 425 (100%, MH$^+$).

Resolution between the enantiomers of compound **322**$_{rac}$ was achieved using a Beckman system fitted with a Lux × 3u cellulose–1 column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1mL·min^{-1}; ambient temperature, detection by UV absorbance at 254 nm. Injection volume 20 μL of the sample prepared in a 2 g·L^{-1} solution of the eluent. Under these conditions, the faster running component and slower running component were eluted at 13.2 min and 17.1 min respectively with an analysis time of 60.0 min.

(1*R*)-1-[2-(4-Bromophenyl)ethyl]-1-cyano-2-hydroxy-2methylpropyl N,N-*bis*(propan-2-yl) carbamate 322

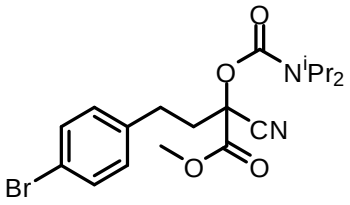


Method 3 (starting with enantiomerically enriched starting material, inverse addition):

A solution of nitrile **320** (0.10 g, 0.27 mmol) in dry Et_2O (2 mL) was added over 4 min using a syringe pump to TMP magnesium chloride (3.60 mL, 1.09 mmol, 0.3 M solution in diethyl ether) in dry Et_2O (1 mL). After 2 min, dry acetone (0.10 mL, 1.36 mmol) was added and the mixture was stirred at –107 °C for 30 min. Saturated aqueous ammonium chloride solution (2 mL) was added at –107 °C. The reaction mixture was

allowed to warm to room temperature then extracted with Et_2O (3 × 2 mL). The organic layers were dried ($MgSO_4$) and evaporated. Purification by column chromatography, eluting with petrol–EtOAc (9:1), gave the nitrile **322** (0.09 g, 77%) as plates; $[\alpha]^{23}_D$ –3.0 (*c* 1.00, $CHCl_3$); other data as above. The enantiomeric ratio was determined to be 77:23 (after recrystallization 99:1) by CSP- HPLC (major enantiomer eluted at 17.1 min). The absolute configuration of nitrile **322** was determined by X-ray crystallographic analysis (see Appendix).

Methyl 2-{[*bis*(propan-2-yl)carbamoyl]*oxy*}-4-(4-bromophenyl)-2-cyanobutanoate 323$_{rac}$



Method 1 (starting with racemic starting material):

TMPMgCl (2.70 mL, 1.09 mmol, 0.4 M solution in diethyl ether) was added to the nitrile **320**$_{rac}$ (0.10 g, 0.27 mmol) in Et_2O (3 mL) at –78 °C. After 10 min, dry methyl cyanoformate (0.10 mL, 1.35 mmol) was added and the mixture was stirred at –78 °C for 30 min. The reaction mixture was allowed to warm to room temperature and saturated aqueous ammonium chloride solution (2 mL) was added and extracted with Et_2O (3 × 2 mL). The organic layers were dried ($MgSO_4$) and evaporated. Purification by column chromatography, eluting with petrol–EtOAc (9:1), gave the ester **323**$_{rac}$ (0.05 g, 46%) as plates; R_f 0.57 [petrol–EtOAc 9:1]; m.p. 97−100 °C; ν_{max} (film)/cm^{-1} 2975, 2935, 2250, 1765, 1710, 1440; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45 (2H, d, *J* 8.5, Ar*H*), 7.11 (2H, d, *J* 8.5, Ar*H*), 4.04–3.94 (1H, m, NC*H*Me$_2$), 3.87 (3H, s, CH_3), 3.79–3.67 (1H, m, NC*H*Me$_2$), 2.99–2.84 (2H, m, CH_2), 2.45–2.33 (2H, m, CH_2), 1.29–1.24 (12H, m, NCH*Me*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.1 (C=O), 152.5 (C=O), 138.1 (Ar), 131.8 (ArH), 130.1 (ArH), 120.5 (Ar), 115.8 (*C*N), 73.2 (C), 53.9 (CH_3), 47.3 (CH), 46.2 (CH), 38.2 (CH_2), 29.8 (CH_2), 21.5 (NCH*Me*$_2$), 21.2 (NCH*Me*$_2$), 20.3 (NCH*Me*$_2$), 20.2 (NCH*Me*$_2$); HRMS (ES) found: MH$^+$, 425.1062. $C_{19}H_{26}N_2O_4{}^{79}Br$ requires MH$^+$, 425.1076; LRMS *m*/*z* (ES) 425 (100%, MH$^+$), 427 (90%, MH$^+$).

Resolution between the enantiomers of compound **323**$_{rac}$ was achieved using a Beckman system fitted with a Lux × 3u cellulose–1 column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1mL·min^{-1}; ambient temperature, detection by UV absorbance at 254 nm. Injection volume 20 μL of the sample prepared in a 2 g·L^{-1} solution of the eluent. Under these conditions, the faster running component and slower running component were eluted at 17.4 min and 23.1 min respectively with an analysis time of 120.0 min.

Method 3 (starting with enantiomerically enriched starting material, inverse addition):

A solution of nitrile **320** (0.05 g, 0.14 mmol) and dry methyl cyanoformate (0.03 mL, 0.40 mmol) in dry Et_2O: THF (1:1) (0.5 mL) was added at –107 °C over 4 min using a syringe pump to TMPMgCl (1.02 mL, 0.40 mmol, 0.4 M solution in Et_2O: THF, 1:1) in dry Et_2O: THF (1:1) (2.5 mL). The mixture was stirred at –107 °C for 30 min. Saturated aqueous ammonium chloride solution (2 mL) was added at –107 °C. The reaction mixture was allowed to warm to room temperature then extracted with Et_2O (3 × 2 mL). The organic layers were dried (MgSO4) and evaporated. Purification by column chromatography, eluting with petrol–EtOAc (9:1), gave the ester **323** (0.02 g, 35%) as plates; $[\alpha]^{23}_{D}$ +3 (c 1.00, $CHCl_3$); other data as above. The enantiomeric ratio was determined to be 82:18 by CSP-HPLC (major enantiomer eluted at 17.4 min).

5 References

(1) Sakai, R.; Higa, T. *J. Am. Chem. Soc.* **1986**, *108*, 6404.
(2) Peng, J. N.; Kudrimoti, S.; Prasanna, S.; Odde, S.; Doerksen, R. J.; Pennaka, H. K.; Choo, Y. M.; Rao, K. V.; Tekwani, B. L.; Madgula, V.; Khan, S. I.; Wang, B.; Mayer, A. M. S.; Jacob, M. R.; Tu, L. C.; Gertsch, J.; Hamann, M. T. *J. Med. Chem.* **2010**, *53*, 61.
(3) Kondo, K.; Shigemori, H.; Kikuchi, Y.; Ishibashi, M.; Sasaki, T.; Kobayashi, J. *J. Org. Chem.* **1992**, *57*, 2480.
(4) Kobayashi, M.; Chen, Y. J.; Aoki, S.; In, Y.; Ishida, T.; Kitagawa, I. *Tetrahedron* **1995**, *51*, 3727.
(5) Nakamura, H.; Deng, S. Z.; Kobayashi, J.; Ohizumi, Y.; Tomotake, Y.; Matsuzaki, T.; Hirata, Y. *Tetrahedron Lett.* **1987**, *28*, 621.
(6) Ichiba, T.; Sakai, R.; Kohmoto, S.; Saucy, G.; Higa, T. *Tetrahedron Lett.* **1988**, *29*, 3083.
(7) Edrada, R. A.; Proksch, P.; Wray, V.; Witte, L.; Muller, W. E. G.; VanSoest, R. W. M. *J. Nat. Prod.* **1996**, *59*, 1056.
(8) Rao, K. V.; Kasanah, N.; Wahyuono, S. U.; Tekwani, B. L.; Schinazi, R. F.; Hamann, M. T. *J. Nat. Prod.* **2004**, *67*, 1314.
(9) Ichiba, T.; Corgiat, J. M.; Scheuer, P. J.; Kellyborges, M. *J. Nat. Prod.* **1994**, *57*, 168.
(10) El Sayed, K. A.; Kelly, M.; Kara, U. A. K.; Ang, K. K. H.; Katsuyama, I.; Dunbar, D. C.; Khan, A. A.; Hamann, M. T. *J. Am. Chem. Soc.* **2001**, *123*, 1804.
(11) Higa, T.; Tanaka, J.; Ohtani, II; Musman, M.; Roy, M. C.; Kuroda, I. *Pure Appl. Chem.* **2001**, *73*, 589.
(12) Peng, J. N.; Shen, X. Y.; El Sayed, K. A.; Dunbar, D. C.; Perry, T. L.; Wilkins, S. P.; Hamann, M. T. *J. Agri. Food Chem.* **2003**, *51*, 2246.
(13) Baldwin, J. E.; Whitehead, R. C. *Tetrahedron Lett.* **1992**, *33*, 2059.
(14) Kobayashi, J.; Tsuda, M.; Kawasaki, N.; Matsumoto, K.; Adachi, T. *Tetrahedron Lett.* **1994**, *35*, 4383.
(15) Baldwin, J. E.; Claridge, T. D. W.; Culshaw, A. J.; Heupel, F. A.; Lee, V.; Spring, D. R.; Whitehead, R. C.; Boughtflower, R. J.; Mutton, I. M.; Upton, R. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 2661.
(16) Jakubowicz, K.; Ben Abdeljelil, K.; Herdemann, M.; Martin, M. T.; Gateau-Olesker, A.; Al Mourabit, A.; Marazano, C.; Das, B. C. *J. Org. Chem.* **1999**, *64*, 7381.
(17) Herdemann, M.; Al-Mourabit, A.; Martin, M. T.; Marazano, C. *J. Org. Chem.* **2002**, *67*, 1890.
(18) Michelliza, S.; Al-Mourabit, A.; Gateau-Olesker, A.; Marazano, C. *J. Org. Chem.* **2002**, *67*, 6474.
(19) Giral, A. L.; Mahuteau-Betzer, F.; Gateau-Olesker, A.; Marazano, C. *Eur. J. Org. Chem.* **2003**, 1859.
(20) Winkler, J. D.; Axten, J. M. *J. Am. Chem. Soc.* **1998**, *120*, 6425.
(21) Martin, S. F.; Humphrey, J. M.; Ali, A.; Hillier, M. C. *J. Am. Chem. Soc.* **1999**, *121*, 866.
(22) Toma, T.; Kita, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **2010**, *132*, 10233.
(23) Jakubec, P.; Hawkins, A.; Felzmann, W.; Dixon, D. J. *Journal of the American Chemical Society* **2012**, *134*, 17482.

(24) Humphrey, J. M.; Liao, Y. S.; Ali, A.; Rein, T.; Wong, Y. L.; Chen, H. J.; Courtney, A. K.; Martin, S. F. *J. Am. Chem. Soc.* **2002**, *124*, 8584.
(25) Martin, S. F.; Rein, T.; Liao, Y. S. *Tetrahedron Lett.* **1991**, *32*, 6481.
(26) Jakubec, P.; Cockfield, D. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 16632.
(27) Magnier, E.; Langlois, Y.; Merienne, C. *Tetrahedron Lett.* **1995**, *36*, 9475.
(28) Markó, I. E.; Southern, J. M.; Adams, H. *Tetrahedron Lett.* **1992**, *33*, 4657.
(29) Leonard, J.; Fearnley, S. P.; Finlay, M. R.; Knight, J. A.; Wong, G. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2359.
(30) Brands, K. M. J.; DiMichele, L. M. *Tetrahedron Lett.* **1998**, *39*, 1677.
(31) Brands, K. M. J.; Meekel, A. A. P.; Pandit, U. K. *Tetrahedron* **1991**, *47*, 2005.
(32) Pandit, U. K. *J. Heterocyclic Chem.* **1994**, *31*, 615.
(33) Pandit, U. K.; Overkleeft, H. S.; Borer, B. C.; Bieraugel, H. *Eur. J. Org. Chem.* **1999**, 959.
(34) Torisawa, Y.; Hosaka, T.; Tanabe, K.; Suzuki, N.; Motohashi, Y.; Hino, T.; Nakagawa, M. *Tetrahedron* **1996**, *52*, 10597.
(35) Uchida, H.; Nishida, A.; Nakagawa, M. *Tetrahedron Lett.* **1999**, *40*, 113.
(36) Li, S. M.; Ohba, S.; Kosemura, S.; Yamamura, S. *Tetrahedron Lett.* **1996**, *37*, 7365.
(37) Li, S. M.; Yamamura, S.; Hosomi, H.; Ohba, S. *Tetrahedron Lett.* **1998**, *39*, 2601.
(38) Campbell, J. A.; Hart, D. J. *Tetrahedron Lett.* **1992**, *33*, 6247.
(39) Kamenecka, T. M.; Overman, L. E. *Tetrahedron Lett.* **1994**, *35*, 4279.
(40) Coldham, I.; Coles, S. J.; Crapnell, K. M.; Fernandez, J. C.; Haxell, T. F. N.; Hursthouse, M. B.; Moseley, J. D.; Treacy, A. B. *Chem. Commun.* **1999**, 1757.
(41) Coldham, I.; Crapnell, K. M.; Fernandez, J. C.; Moseley, J. D.; Rabot, R. *J. Org. Chem.* **2002**, *67*, 6181.
(42) Coldham, I.; Pih, S. M.; Rabot, R. *Synlett* **2005**, 1743.
(43) S.Pih In *unpublished results.*
(44) Ageel, K. Ph.D.thesis, University of Sheffield, 2013.
(45) Pathak, R. In *unpublished results*.
(46) Dobson, B. C. Ph.D thesis, University of Sheffield, 2007.
(47) Pil, S. In *unpublished results*.
(48) Winkler, J. D.; Axten, J.; Hammach, A. H.; Kwak, Y. S.; Lengweiler, U.; Lucero, M. J.; Houk, K. N. *Tetrahedron* **1998**, *54*, 7045.
(49) Raucher, S.; Jones, D. S. *Synth. Commun.* **1985**, *15*, 1025.
(50) Zhang, H. X.; Reddy, M. S.; Phoenix, S.; Deslongchamps, P. *Angew. Chem. Int. Ed.* **2008**, *47*, 1272.
(51) Guanti, G.; Banfi, L.; Brusco, S.; Narisano, E. *Tetrahedron: Asymmetry* **1994**, *5*, 537.
(52) Methot, J. L.; Morency, L.; Ramsden, P. D.; Wong, J.; Leger, S. *Tetrahedron Lett.* **2002**, *43*, 1147.
(53) Boeckman, R. K., Jr.; Miller, J. R. *Org. Lett.* **2009**, *11*, 4544.
(54) Muto, S.; Bando, M.; Mori, K. *Eur. J. Org. Chem.* **2004**, 1946.
(55) Mulder, J. A.; Hsung, R. P.; Frederick, M. O.; Tracey, M. R.; Zificsak, C. A. *Org. Lett.* **2002**, *4*, 1383.
(56) Luo, S. P.; Xu, D. Q.; Yue, H. D.; Wang, L. P.; Yang, W. L.; Xu, Z. Y. *Tetrahedron: Asymmetry* **2006**, *17*, 2028.
(57) McKennon, M. J.; Meyers, A. I.; Drauz, K.; Schwarm, M. *J. Org. Chem.* **1993**, *58*, 3568.
(58) Itoh, T.; Takagi, Y.; Nishiyama, S. *J. Org. Chem.* **1991**, *56*, 1521.
(59) MacNevin, C. J.; Moore, R. L.; Liotta, D. C. *J. Org. Chem.* **2008**, *73*, 1264.

(60) Niggemann, M.; Jelonek, A.; Biber, N.; Wuchrer, M.; Plietker, B. *J. Org. Chem.* **2008**, *73*, 7028.
(61) Zhang, Y. S.; Hsung, R. P.; Tracey, M. R.; Kurtz, K. C. M.; Vera, E. L. *Org. Lett.* **2004**, *6*, 1151.
(62) Zhang, X. J.; Zhang, Y. S.; Huang, J.; Hsung, R. P.; Kurtz, K. C. M.; Oppenheimer, J.; Petersen, M. E.; Sagamanova, I. K.; Shen, L. C.; Tracey, M. R. *J. Org. Chem.* **2006**, *71*, 4170.
(63) Wanner, M. J.; Koomen, G. J. *J. Org. Chem.* **1996**, *61*, 5581.
(64) Huebel, W. *Dtsch. Apoth.-Ztg.* **1981**, *121*, 863.
(65) Scheuer, P. J. *Acc. Chem. Res.* **1992**, *25*, 433.
(66) F. Fleming, F. *Nat. Prod. Rep.* **1999**, *16*, 597.
(67) Legras, J. I.; Chuzel, G.; Arnaud, A.; Galzy, P. *World J. Microbiol. Biotechnol.* **1990**, *6*, 83.
(68) Fleming, F. F. *Nat. Prod. Rep.* **1999**, *16*, 597.
(69) Duffy, S. S. *Cyanide in Biology*; Acadimic Press, London, 1981.
(70) Chiang, W. C. K.; Pusateri, D. J.; Leitz, R. E. A. *J. Agri. Food Chem.* **1998**, *46*, 1018.
(71) MacLeod, A. J.; MacLeod, G. *Phytochemistry* **1977**, *16*, 907.
(72) Kam, T.-S.; Yoganathan, K. *Phytochemistry* **1997**, *46*, 785.
(73) Sarma, S. P., Padmanaban, G. *Toxic Constituents of Plant Foodstuffs* Academic Press, New York, London, 1969.
(74) Berlin, V. S. G. H. *Encyclopedia of Plant Physiology*, 1980.
(75) Eyjolfsson, R. *Fortschr. Chem. Org. Naturst.* **1970**, *28*, 74.
(76) Prawat, H.; Mahidol, C.; Ruchirawat, S.; Prawat, U.; Tuntiwachwuttikul, P.; Tooptakong, U.; Taylor, W. C.; Pakawatchai, C.; Skelton, B. W.; White, A. H. *Phytochemistry* **1995**, *40*, 1167.
(77) Simpol, L. R.; Otsuka, H.; Ohtani, K.; Kasai, R.; Yamasaki, K. *Phytochemistry* **1994**, *36*, 91.
(78) van, d. B. A. J. J.; Horsten, S. F. A. J.; Kettenes-van, d. B. J. J.; Kroes, B. H.; Labadie, R. P. *Phytochemistry* **1995**, *40*, 597.
(79) Yoshikawa, M.; Shimada, H.; Shimoda, H.; Murakami, N.; Yamahara, J.; Matsuda, H. *Chem. Pharm. Bull.* **1996**, *44*, 2086.
(80) Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K.; Fujita, S.; Furuya, T. *J. Am. Chem. Soc.* **1986**, *108*, 2780.
(81) Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K.; Koseki, K. *J. Org. Chem.* **1988**, *53*, 3930.
(82) Okada, A.; Watanabe, K.; Umeda, K.; Miyakado, M. *Agric. Biol. Chem.* **1991**, *55*, 2765.
(83) Matsunaga, S.; Fujiki, H.; Sakata, D.; Fusetani, N. *Tetrahedron* **1991**, *47*, 2999.
(84) Dumdei, E. J.; Blunt, J. W.; Munro, M. H. G.; Pannell, L. K. *J. Org. Chem.* **1997**, *62*, 2636.
(85) Ishihara, H.; Martin, B. L.; Brautigan, D. L.; Karaki, H.; Ozaki, H.; Kato, Y.; Fusetani, N.; Watabe, S.; Hashimoto, K.; et, a. *Biochem. Biophys. Res. Commun.* **1989**, *159*, 871.
(86) Smith, A. B., III; Friestad, G. K.; Duan, J. J. W.; Barbosa, J.; Hull, K. G.; Iwashima, M.; Qiu, Y.; Spoors, P. G.; Bertounesque, E.; Salvatore, B. A. *J. Org. Chem.* **1998**, *63*, 7596.
(87) Pihko, P. M.; Koskinen, A. M. P. *J. Org. Chem.* **1998**, *63*, 92.
(88) Tánimoto, N.; Gerritz, S. W.; Sawabe, A.; Noda, T.; Filla, S. A.; Masamune, S. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 673.
(89) Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434.

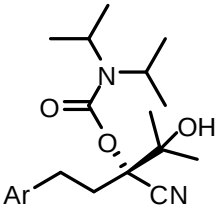
(90) Yakushijin, K.; Sugiyama, S.; Mori, Y.; Murata, H.; Furukawa, H. *Phytochemistry* **1980**, *19*, 161.
(91) Cheng, X.-F.; Meng, Z.-M.; Chen, Z.-L. *Phytochemistry* **1998**, *49*, 2193.
(92) Fleming, F. F.; Yao, L.; Ravikumar, P. C.; Funk, L.; Shook, B. C. *J. Med. Chem.* **2010**, *53*, 7902.
(93) He, H.; Tran, P.; Yin, H.; Smith, H.; Batard, Y.; Wang, L.; Einolf, H.; Gu, H.; Mangold, J. B.; Fischer, V.; Howard, D. *Drug Metab. Dispos.* **2009**, *37*, 536.
(94) Hughes, T. E.; Mone, M. D.; Russell, M. E.; Weldon, S. C.; Villhauer, E. B. *Biochemistry* **1999**, *38*, 11597.
(95) Milani, M.; Jha, G.; Potter, D. A. *Clin. Med. Ther.* **2009**, *1*, 141.
(96) Jackson, T.; Woo, L. W. L.; Trusselle, M. N.; Chander, S. K.; Purohit, A.; Reed, M. J.; Potter, B. V. L. *Org. Biomol. Chem.* **2007**, *5*, 2940.
(97) Noble, S.; McTavish, D. *Drugs* **1995**, *50*, 1032.
(98) Rennard, S.; Knobil, K.; Rabe, K. F.; Morris, A.; Schachter, N.; Locantore, N.; Canonica, W. G.; Zhu, Y.; Barnhart, F. *Drugs* **2008**, *68*, 3.
(99) March, J. *Advanced Organic Chemistry*; John Wiley & Sons: New York, 1985.
(100) Fleming, F. F.; Zhang, Z.; Knochel, P. *Org. Lett.* **2004**, *6*, 501.
(101) Harrison, C. R.; Hodge, P.; Rogers, W. J. *Synthesis* **1977**, 41.
(102) Correia, J. *Synthesis* **1994**, 1127.
(103) Sosnovsky, G.; Krogh, J. A.; Umhoefer, S. G. *Synthesis* **1979**, 722.
(104) Le, B. J. F.; Cuvigny, T.; Larcheveque, M.; Normant, H. *Synthesis* **1976**, 238.
(105) Corey, E. J.; Enders, D. *Chem. Ber.* **1978**, *111*, 1337.
(106) Oldenziel, O. H.; Van Leusen, D.; Van Leusen, A. M. *J. Org. Chem.* **1977**, *42*, 3114.
(107) Denmark, S. E.; Wilson, T. W.; Burk, M. T.; Heemstra, J. R., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 14864.
(108) Trost, B. M.; Miller, J. R.; Hoffman, C. M., Jr. *J. Am. Chem. Soc.* **2011**, *133*, 8165.
(109) Yin, L.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 9610.
(110) Fleming, F. F.; Gudipati, S. *Eur. J. Org. Chem.* **2008**, 5365.
(111) Purzycki, M.; Liu, W.; Hilmersson, G.; Fleming, F. F. *Chem. Commun.* **2013**, *49*, 4700.
(112) Zarges, W.; Marsch, M.; Harms, K.; Boche, G. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1392.
(113) Boche, G.; Harms, K.; Marsch, M. *J. Am. Chem. Soc.* **1988**, *110*, 6925.
(114) Naota, T.; Tannna, A.; Murahashi, S.-I. *J. Am. Chem. Soc.* **2000**, *122*, 2960.
(115) Sott, R.; Granander, J.; Hilmersson, G. *J. Am. Chem. Soc.* **2004**, *126*, 6798.
(116) Boche, G.; Harms, K.; Marsch, M. *J. Am. Chem. Soc.* **1988**, *110*, 6925.
(117) Carlier, P. R.; Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 11602.
(118) Sasaki, M.; Takegawa, T.; Ikemoto, H.; Kawahata, M.; Yamaguchi, K.; Takeda, K. *Chem. Commun.* **2012**, *48*, 2897.
(119) Naota, T.; Tannna, A.; Murahashi, S.-I. *Chem. Commun.* **2001**, 63.
(120) Crowley, P. J.; Leach, M. R.; Meth-Cohn, O.; Wakefield, B. J. *Tetrahedron Lett.* **1986**, *27*, 2909.
(121) Firl, J.; Runge, W.; Hartmann, W.; Utikal, H. P. *Chem. Lett.* **1975**, 51.
(122) Fleming, F. F.; Zhang, Z.; Wang, L.; Knochel, P. *J. Org. Chem.* **2005**, *70*, 2200.
(123) Fleming, F. F.; Gudipati, S.; Zhang, Z.; Liu, W.; Steward, O. W. *J. Org. Chem.* **2005**, *70*, 3845.
(124) Kopp, F.; Sklute, G.; Polborn, K.; Marek, I.; Knochel, P. *Org. Lett.* **2005**, *7*, 3789.
(125) Carlier, P. R.; Zhang, Y. *Org. Lett.* **2007**, *9*, 1319.
(126) Melzig, L.; Rauhut, C. B.; Knochel, P. *Synthesis* **2009**, 1041.

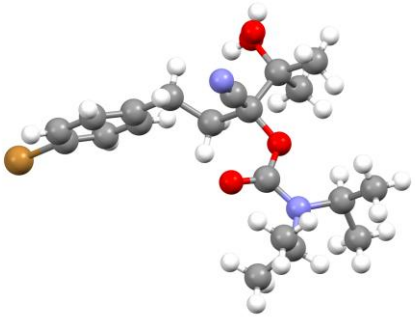
(127) Melzig, L.; Rauhut, C. B.; Knochel, P. *Chem. Commun.* **2009**, 3536.
(128) Nath, D.; Fleming, F. F. *Angew. Chem. Int. Ed.* **2011**, *50*, 11790.
(129) Nath, D.; Fleming, F. F. *Chem. Eur. J.* **2013**, *19*, 2023.
(130) Guerrand, H. D. Ph.D.thesis, University of Sheffield, 2012.
(131) Hoffmann, R. W.; Nell, P. G. *Angew. Chem. Int. Ed.* **1999**, *38*, 338.
(132) Hoffmann, R. W.; Kusche, A. *Chem. Ber.* **1994**, *127*, 1311.
(133) Hoffmann, R. W.; Julius, M.; Chemla, F.; Ruhland, T.; Frenzen, G. *Tetrahedron* **1994**, *50*, 6049.
(134) Klute, W.; Krüger, M.; Hoffmann, R. W. *Chem. Ber.* **1996**, *129*, 633.
(135) Fleming, F. F.; Shook, B. C. *Tetrahedron* **2002**, *58*, 1.
(136) Arseniyadis, S.; Kyler, K. S.; Watt, D. S. *Org. React. (N. Y.)* **1984**, *31*, 1.
(137) Carlier, P. R.; Lo, C. W. S. *J. Am. Chem. Soc.* **2000**, *122*, 12819.
(138) Walborsky, H. M.; Motes, J. M. *J. Am. Chem. Soc.* **1970**, *92*, 2445.
(139) Sasaki, M.; Kawanishi, E.; Shirakawa, Y.; Kawahata, M.; Masu, H.; Yamaguchi, K.; Takeda, K. *Eur. J. Org. Chem.* **2008**, 3061.
(140) Coldham, I.; Burrell, A. J. M.; White, L. E.; Adams, H.; Oram, N. *Angew. Chem. Int. Ed.* **2007**, *46*, 6159.
(141) Burrell, A. J. M.; Coldham, I.; Watson, L.; Oram, N.; Pilgram, C. D.; Martin, N. G. *J. Org. Chem.* **2008**, *74*, 2290.
(142) Burrell, A. J. M.; Coldham, I.; Oram, N. *Org. Lett.* **2009**, *11*, 1515.
(143) Burrell, A. J. M.; Watson, L.; Martin, N. G.; Oram, N.; Coldham, I. *Org. Biomol. Chem.* **2010**, *8*, 4530.
(144) Coldham, I.; Burrell, A. J. M.; Guerrand, H. D. S.; Watson, L.; Martin, N. G.; Oram, N. *Beilstein J. Org. Chem.* **2012**, *8*, 107.
(145) Deleuze-Masquéfa, C.; Gerebtzoff, G.; Subra, G.; Fabreguettes, J.-R.; Ovens, A.; Carraz, M.; Strub, M.-P.; Bompart, J.; George, P.; Bonnet, P.-A. *Bioorg. Med. Chem.* **2004**, *12*, 1129.
(146) Reddy, M. S.; Zhang, H.; Phoenix, S.; Deslongchamps, P. *Chem. Asian J.* **2009**, *4*, 725.
(147) Yokoshima, S.; Ueda, T.; Kobayashi, S.; Sato, A.; Kuboyama, T.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 2137.
(148) Effenberger, F. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1555.
(149) Mycka, R. J.; Eckenhoff, W. T.; Steward, O. W.; Barefoot, N. Z.; Fleming, F. F. *Tetrahedron* **2013**, *69*, 366.
(150) Fleming, F. F.; Liu, W. *Eur. J. Org. Chem.* **2009**, *2009*, 699.
(151) Gibson, S. E.; Jones, J. O.; McCague, R.; Tozer, M.; Whitcombe, N. J. *Synlett* **1999**, 954.
(152) Barker, G.; Alshawish, M. R.; Skilbeck, M. C.; Coldham, I. *Angew.Chem. Int.Ed.* **2013**, n/a.
(153) Krasovskiy, A.; Knochel, P. *Synthesis* **2006**, 890.
(154) Krasovskiy, A.; Krasovskaya, V.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 2958.
(155) Dobson, B. C., University of Shessield, 2007.
(156) Frederick, M. O.; Hsung, R. P.; Lambeth, R. H.; Mulder, J. A.; Tracey, M. R. *Organic Letters* **2003**, *5*, 2663.
(157) Kurtz, K. C. M.; Frederick, M. O.; Lambeth, R. H.; Mulder, J. A.; Tracey, M. R.; Hsung, R. P. *Tetrahedron* **2006**, *62*, 3928.
(158) Frederick, M. O.; Hsung, R. P.; Lambeth, R. H.; Mulder, J. A.; Tracey, M. R. *Org. Lett.* **2003**, *5*, 2663.
(159) Deleuze-Masquéfa, C.; Gerebtzoff, G.; Subra, G.; Fabreguettes, J.-R.; Ovens, A.; Carraz, M.; Strub, M.-P.; Bompart, J.; George, P.; Bonnet, P.-A. *Bioorg. Med. Chem* **2004**, *12*, 1129.

(160) Erkkilä, A.; Pihko, P. M. *J. Org. Chem.* **2006**, *71*, 2538.

6 Appendix

X-ray crystal structure determination data of **322**





CCDC	935316	
Identification code	oic232_0m	
Empirical formula	C20 H29 Br N2 O3	
Formula weight	425.36	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 6.4769(2)Å	a= 90°.
	b = 12.6253(3)Å	b= 90°.
	c = 24.9911(6) Å	g = 90°.
Volume	2043.59(9) $Å^3$	
Z	4	
Density (calculated)	1.383 Mg/m^3	
Absorption coefficient	2.033 mm^{-1}	
F(000)	888	
Crystal size	0.32 x 0.21 x 0.19 mm^3	
Theta range for data collection	1.63 to 29.30°.	

Index ranges	-8<=h<=8, -17<=k<=14, -32<=l<=31
Reflections collected	15089
Independent reflections	5172 [R(int) = 0.0285]
Completeness to theta = 25.00°	99.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.6987 and 0.5624
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5172 / 144 / 253
Goodness-of-fit on F2	1.166
Final R indices [I>2sigma(I)]	R1 = 0.0474, wR2 = 0.1125
R indices (all data)	R1 = 0.0638, wR2 = 0.1257
Absolute structure parameter	0.008(13)
Largest diff. peak and hole	1.401 and -0.707 e.$Å^{-3}$