The University Of Sheffield.

Synthetic Approaches to 2-Substituted 4-Hydroxypiperidines

A Dissertation Submitted for the Degree of Doctor of Philosophy

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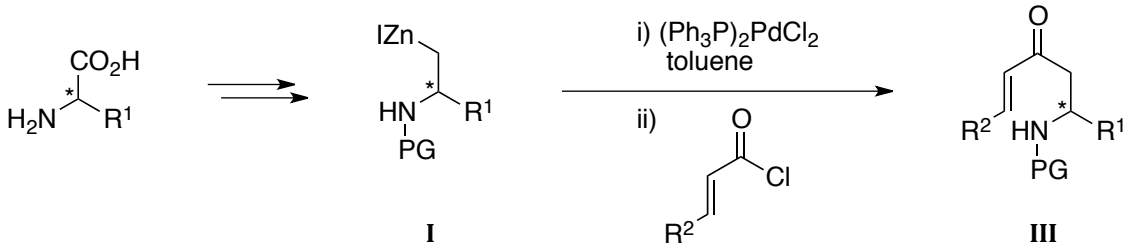
Declaration

This dissertation records the work carried out in the Department of Chemistry, University of Sheffield and AstraZeneca, Alderley Park, Macclesfield between September 2010 and September 2014, and is original except where acknowledged by reference. No portion of this work is being, nor has been, submitted for a degree, diploma or any other qualification at any other university.

Abstract

This thesis describes synthetic efforts towards the synthesis of enantiomerically pure, 2-substituted 4-hydroxypiperidines using Negishi cross coupling reactions. A selection of α-amino acids were converted into protected β-amino organozinc reagents **I**, which were reacted with α,β-unsaturated acid chlorides **II** under palladium catalysis to give a range of amino enones **III**, in moderate to good yields (Scheme A).

Scheme A. The synthesis and subsequent cross coupling reaction of α-amino derived organozinc reagents **I**.



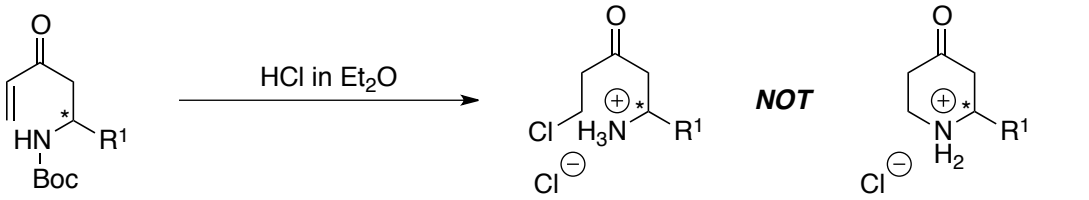
I
R^1 = Me, ^{i}Pr, CO_2Me, $CO_2{}^t$Bu
PG = Boc, TFA, Cbz

II
R^2 = H, Ph

III
41–66%
7 examples

Attempts to apply a literature cyclisation method using hydrogen chloride in diethyl ether to Boc protected amino enones **III** led to the discovery that the products of these reactions are actually β-chloroketones **IV**, rather than the previously reported 4-oxopiperidinium salts **V** (Scheme B).

Scheme B. Treatment of amino enones **III** with hydrogen chloride in diethyl ether, leading to β-chloroketones **IV** rather than the previously reported 4-oxopiperidinium salts **V**.



III
R^1 = CO_2Me, $CO_2{}^t$Bu, ^{i}Pr

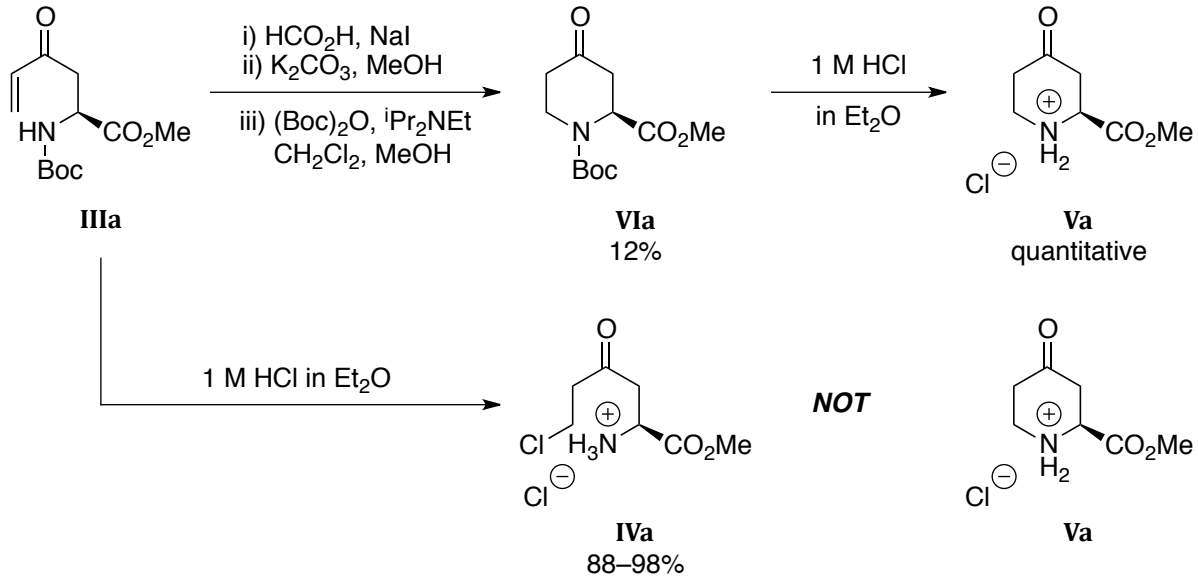
IV
R^1 = CO_2Me, CO_2H, ^{i}Pr
87–98%

V
R^1 = CO_2Me, CO_2H, ^{i}Pr

After extensive experimentation, the cyclisation of amino enone **IIIa** was achieved through deprotection of the amine, followed by a base mediated ring closing reaction (Scheme C). Re-

protection of the amine allowed the product **VIa** to be isolated, albeit in a low yield. Although the desired reduction of 4-oxopiperidines **VI** could not be investigated due to difficulties in repeating the cyclisation reaction, the deprotection of compound **VIa** was achieved, producing a sample of methyl 4-oxo-L-pipecolate **Va**. This compound was compared to the product of the treatment of compound **IIIa** with hydrogen chloride, corroborating the earlier claim that the product of this latter reaction was in fact β-chloroketone **IVa**, rather than the cyclic structure **Va** that was initially expected based on the claims in the literature.

Scheme C. Successful cyclisation of amino enone **IIIa** and subsequent deprotection leading to methyl 4-oxo-L-pipecolate **Va**, allowing its comparison with compound **IVa**.



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Finally, but by no means least, I would like to thank God. Difficult though this PhD has been, I thank him for his unfaltering faithfulness and love, and for getting me through to the other side. I hope that he has used these last four years to grow my faith in him and my love for him, and trust that he will continue to do the same in the future, no matter what it holds in store.

Contents

Abbreviations

(aq)	aqueous
)))	sonication
Ac	acetyl
app.	apparent
aq.	aqueous
Ar	aryl
ATR	attenuated total reflectance
ax	axial
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br.	broad
Cbz	benzyloxycarbonyl
cf.	compare
conc.	concentrated
Cy	cyclohexyl
d	doublet
d.r.	diastereomeric ratio
DABCO	1,4-diazobicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
dd	doublet of doublets
ddd	doublet of doublet of doublets
decomp.	decomposition
DMA	*N*,*N*-dimethylacetamide
DMAP	dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMI	1,3-dimethyl-2-imidazolidinone
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
dt	doublet of triplets
E	electrophile

e.g.	for example
E1cB	unimolecular elimination via the conjugate base
ee	enantiomeric excess
eq	equatorial
eq.	equivalents
ES	electrospray
Et	ethyl
FGI	functional group interconversion
Fmoc	9-fluorenylmethyloxycarbonyl
HIV	human immunodeficiency virus
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
i.e.	that is
^{i}Bu	*iso*-butyl
^{i}Pr	*iso*-propyl
IR	infrared
L	ligand
LA	Lewis acid
lit.	literature
LUMO	lowest unoccupied molecular orbital
m	multiplet
m.p.	melting point
M.S.	molecular sieves
m/z	mass to charge ratio
Me	methyl
M_r	molecular weight
MS	mass spectrometry
^{n}Bu	*n*-butyl
NMR	nuclear magnetic resonance
^{n}Pr	*n*-propyl
Nu	nucleophile
o-tol	*ortho*-tolyl
o/n	overnight
P	product

p-tol	*para*-tolyl
PG	protecting group
Ph	phenyl
phen	phenanthroline
Phth	phthaloyl
ppm	parts per million
q	quartet
R	generic group
r.t.	room temperature
R_f	retention factor
s	singlet
sat.	saturated
^{s}Bu	*sec*-butyl
SM	starting material
S_N2	bimolecular nucleophilic substitution
SPhos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
t	triplet
^{t}Bu	*tert*-butyl
Tf	trifyl (trifluoromethanesulfonyl)
TFA	trifluoroacetyl
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
Tr	trityl (triphenylmethyl)
Ts	tosyl (*para*-toluenesulfonyl)
UV	ultraviolet
X	halogen (unless otherwise stated)
Zn*	activated zinc

1. Introduction

1.1 Background

1.1.1 Natural Occurrence of 4-Hydroxypiperidines

The piperidine ring system is a very common structure in Nature.[1] Much effort has been spent in synthesising substituted piperidines, especially in a stereoselective manner.[2] One group of compounds within the piperidine family are the 4-hydroxypiperidines. Although less commonly encountered in Nature, there are a number of natural products that contain this structure (Figure 1). The synthesis of naturally occurring *cis*-4-hydroxy-L-pipecolic acid **L-1** has been an area of particular interest,[3] one of the reasons being that it forms part of the HIV-protease inhibitor Palinavir (Figure 2).[4]

Figure 1. Examples of substituted 4-hydroxypiperidine natural products.

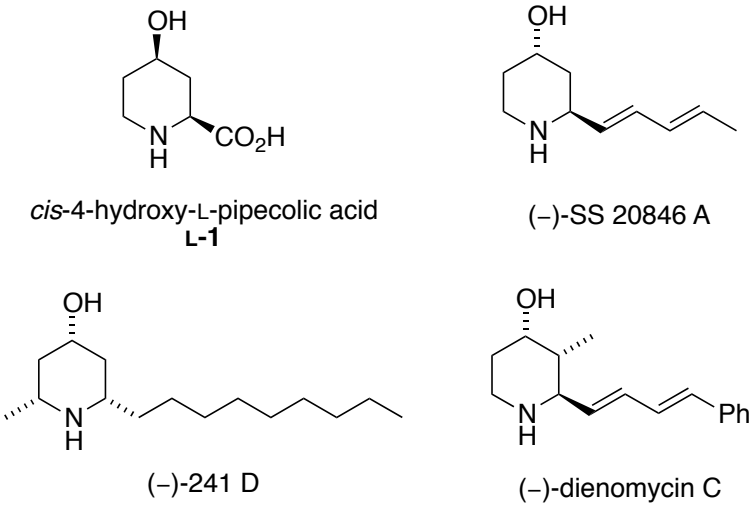
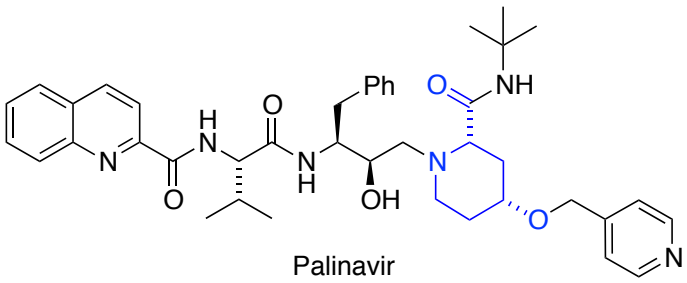


Figure 2. HIV-protease inhibitor Palinavir, containing a *cis*-4-hydroxy-L-pipecolic acid subunit.

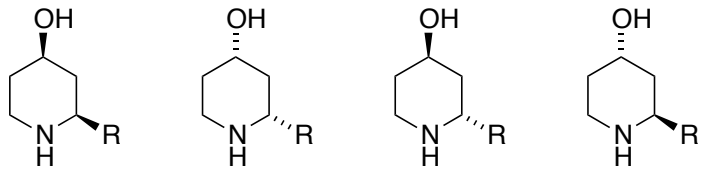


1.1.2 Pharmaceutical Relevance of 4-Hydroxypiperidines

4-Hydroxypiperidines are small, polar, chiral molecules containing two heteroatoms, which make them attractive as pharmaceutical building blocks. Their small size means that they can be attached to a lead compound in order to try and optimise its properties without increasing the overall molecular weight too dramatically. This is an important consideration that is highlighted in Lipinski's Rule of Five, which states that ideal oral drug candidates should have a molecular weight of less than 500 Daltons.[5] The two heteroatoms allow two different sites of attachment, and their polarity could be used to increase the water solubility of a potential drug, which is often a challenge for the medicinal chemist.

When 4-hydroxypiperidines are substituted, they often become chiral. As a result, there can be a large number of different stereoisomers for any given substituted 4-hydroxypiperidine. For example, for a 2-substituted 4-hydroxypiperidine there are four possible isomers: two diastereoisomers (*cis* and *trans*), both of which have two enantiomers (Figure 3).

Figure 3. The four possible stereoisomers for every 2-substituted 4-hydroxypiperidine.

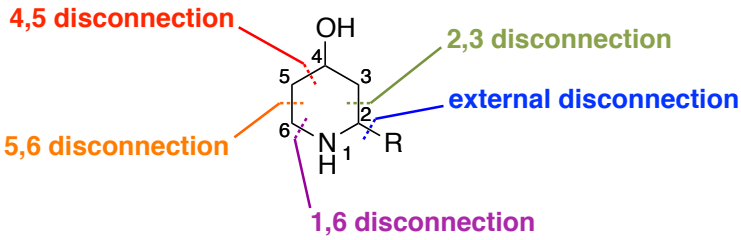


This stereochemical diversity allows for different areas of chemical space around the piperidine ring to be occupied by the substituents. This is important when optimising a lead compound, as certain spatial configurations may fit better with the desired biological target. This point is supported by findings from Lovering and co-workers, who stated that lead compounds are more likely to progress through clinical trials to become drugs if they are more saturated, due to their ability to be more three-dimensional in shape, and so explore more chemical space than their flatter, unsaturated analogues.[6] Lovering and co-workers also reported that increased saturation correlates with a lower melting point and a greater aqueous solubility, both important factors for the success of a drug candidate. These additional benefits of increased saturation in drug molecules enhance the potential usefulness of substituted 4-hydroxypiperidines as pharmaceutical building blocks.

1.2 Previous Syntheses of 4-Hydroxypiperidines

There are a number of syntheses of 4-hydroxypiperidines in the literature, some of which give the products as a racemate, and others that give the products in an enantiomerically enriched form. This review will only discuss the latter, as these are of much greater use in the synthesis of natural products or molecules of pharmaceutical interest. The syntheses reviewed have been divided into different categories, based on the key disconnections used by the authors (Figure 4). The disconnections shown are numbered according to which atoms of the piperidine ring are joined in the ring-forming step. In some cases the 6-membered ring is present in the starting material, and a substituent has been added to this ring; these have been designated an external disconnection.

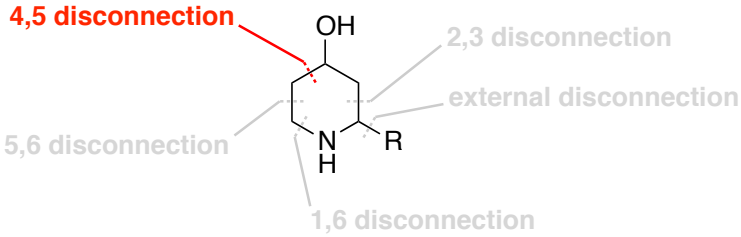
Figure 4. Different key disconnections used in the previous syntheses of various substituted 4-hydroxypiperidines.



1.2.1 Previous Syntheses using a 4,5 Disconnection

Of the many syntheses of substituted 4-hydroxypiperidines found in the literature, there are a few which involve a cyclisation step that connects together carbon atoms 4 and 5 (Figure 5). One such example has been reported by Snaith and co-workers, who have synthesised a number of 2,5-disubstituted 4-hydroxypiperidines using carbonyl ene and Prins cyclisation reactions.[7-9]

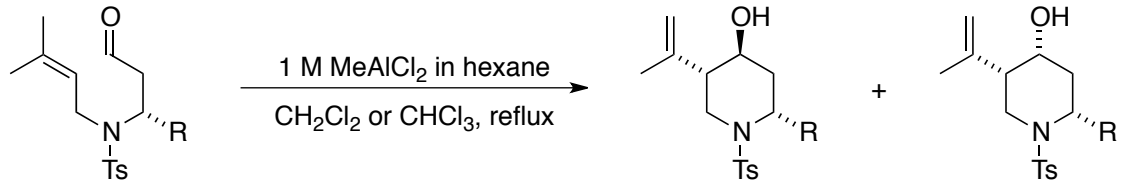
Figure 5. A 4,5 disconnection used to construct substituted 4-hydroxypiperidines.



1.2.1.1 Snaith and co-workers

The cyclisation precursors **2** were synthesised in good yields over 4 steps from a range of enantiomerically pure β-amino alcohols. Compounds **2** were then subjected to carbonyl ene cyclisation conditions with one equivalent of $MeAlCl_2$ acting as a Lewis acid (Scheme 1).[7-8] In every case the *trans* diastereoisomer **3** was produced as the major product, along with a small amount of the *cis* diastereoisomer **4**.

Scheme 1. Lewis acid mediated carbonyl ene cyclisation of compounds **2**.



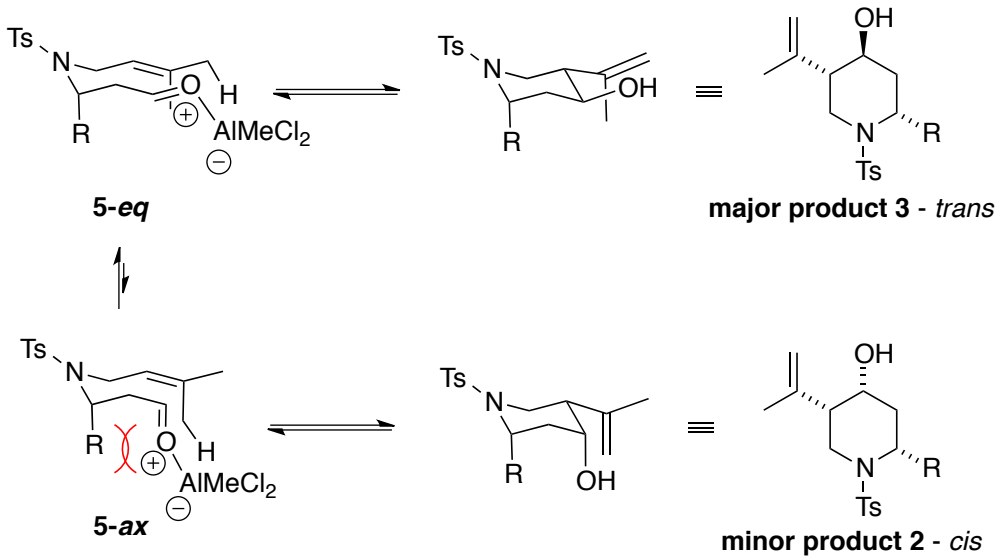
2 **3** **4**

R = Me, ^{i}Pr, ^{t}Bu, Ph, Bn

64–88% of **3**
3:**4** ≥95:5

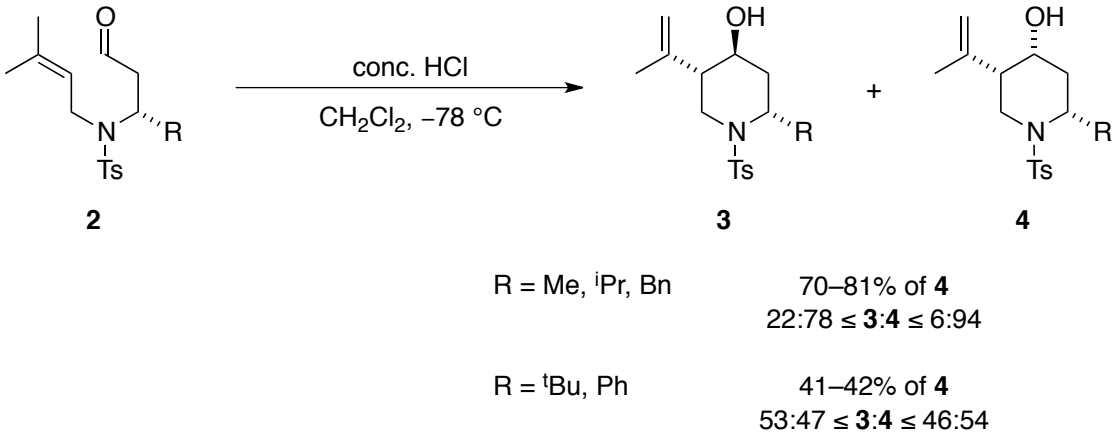
The diastereoselectivity of these reactions arises from a combination of factors. Under the equilibrating reaction conditions, the thermodynamic product **3** is favoured. This product contains both the alkene and alcohol groups in the more stable equatorial orientation (Figure 6). At the same time the R group prefers to adopt an axial orientation so as to avoid the pseudo 1,3-allylic strain with the tosyl group.[8,10] Equilibration to the thermodynamic product **3** occurs even at room temperature, as the conversion of conformer **5-*ax*** to conformer **5-*eq*** also lessens the strain present in the transition state, which results from the 1,3-diaxial interaction between the aldehyde coordinated to the Lewis acid and the R group in conformer **5-*ax***. This factor also favours the production of compound **3** as the major product.

Figure 6. Rationale for the diastereoselectivity of the Lewis acid mediated cyclisation of compounds **2**.



When the same precursor molecules were cyclised in the presence of a Brønsted acid, in this case hydrochloric acid, the opposite diastereoselectivity was generally observed, with the major product containing the isopropenyl group and the alcohol *cis* to each other (Scheme 2).[7-8]

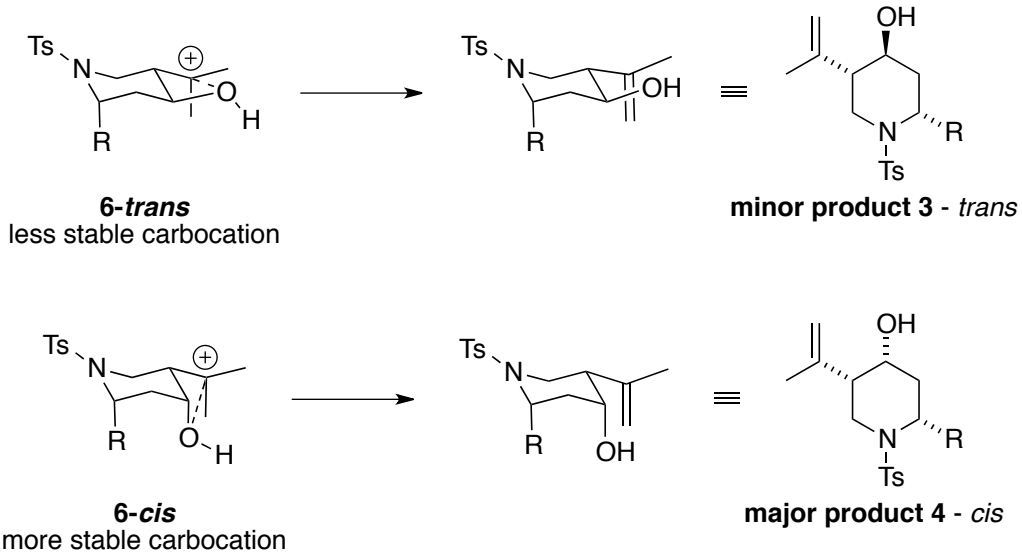
Scheme 2. Brønsted acid mediated Prins cyclisation of compounds **2**.



The observed diastereoselectivity in favour of the *cis* product is explained by invoking a concerted, asynchronous Prins cyclisation mechanism.[9] If the mechanism were fully stepwise, addition of the alkene onto the aldehyde would give cationic intermediate **6** (Figure 7). The positive charge could be stabilised by one of the lone pairs on the oxygen atom, which can either by *cis* or *trans* to the isopropyl group. Although at first sight the oxygen-cation interactions for these two transition states

appear similar, Snaith and co-workers have shown through calculations at the B3LYP/6-31G(d) level of theory that when R = H the **6-*cis*** carbocation is more stable than the **6-*trans*** carbocation by 0.82 kcal. Although they readily admit that this difference is too small to completely account for the diastereoselectivity of this cyclisation, they do suggest that these calculations go some way to explaining the observed *cis* selectivity.

Figure 7. Rationale for the diastereoselectivity of the Brønsted acid mediated cyclisation of compounds **2**, based on carbocation stabilities.

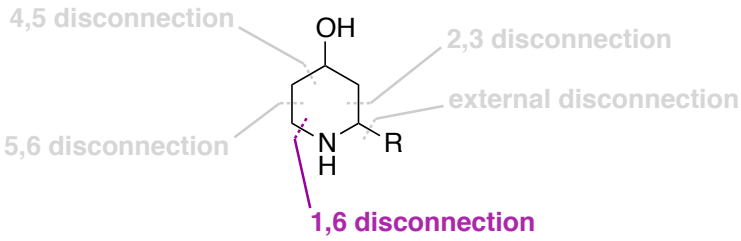


This explanation is also consistent with the observed reduction in diastereoselectivity as the R group increases in size.[7-8] More bulky R groups experience a greater degree of 1,3-diaxial strain with the alcohol group in carbocation **6-*cis***. Significant amounts of the *trans* product **3** were formed for both the *tert*-leucinol and phenylglycinol derived products, which contain the bulky *tert*-butyl and the relatively bulky phenyl groups respectively. In all of these cases the R group is placed in an axial orientation so as to avoid pseudo 1,3-allylic strain with the tosyl group, as previously explained.

1.2.2 Previous Syntheses using a 1,6 Disconnection

A much more common disconnection that has been made in order to construct substituted 4-hydroxypiperidines is between the nitrogen atom and carbon number 6 (Figure 8). The majority of the methods reviewed here chose to first form a 4-oxopiperidine before subsequently reducing the ketone to give the desired 4-hydroxypiperidine.

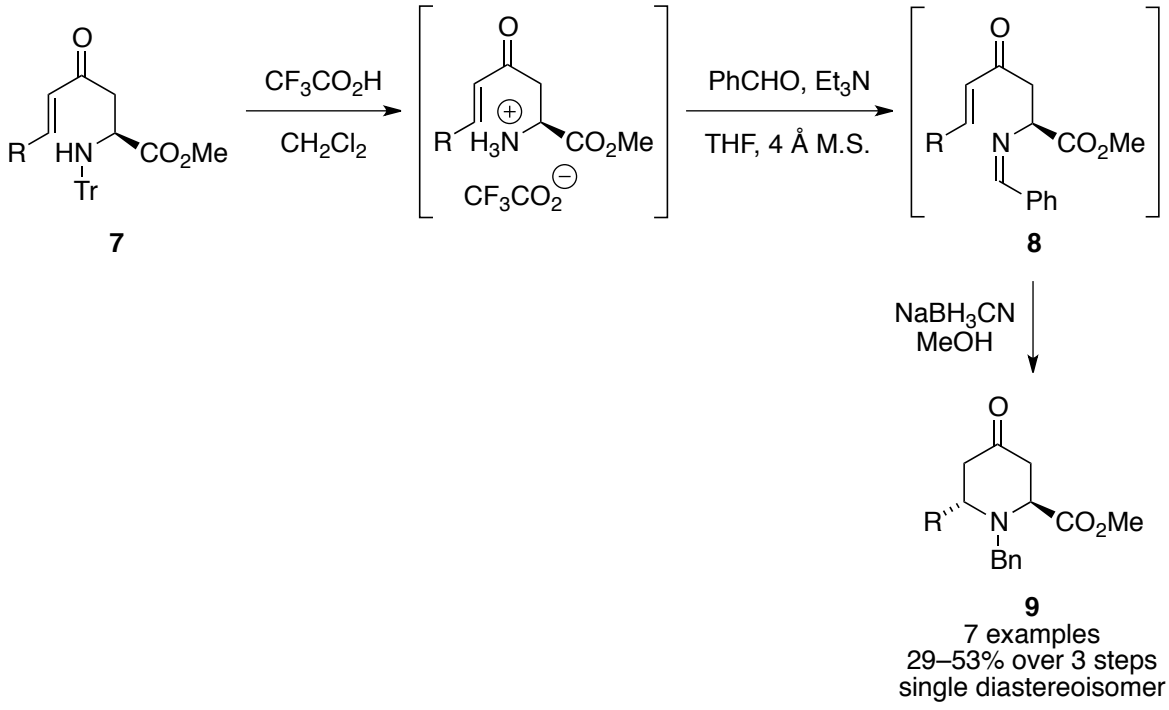
Figure 8. A 1,6 disconnection used to construct substituted 4-hydroxypiperidines.



1.2.2.1 Sutherland and co-workers

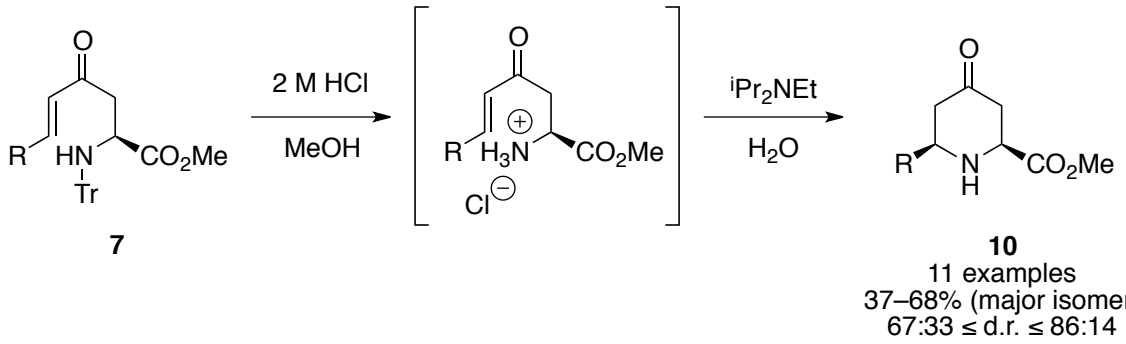
Sutherland and co-workers have reported the synthesis of a range of substituted enones **7** from L-aspartic acid using a Horner-Wadsworth-Emmons reaction.[11-12] Treatment of these enones **7** with trifluoroacetic acid removed the trityl protecting group to give the free amines as their trifluoroacetate salts (Scheme 3), which were then reacted with benzaldehyde to yield benzyl imines **8**.[11] Reaction with sodium cyanoborohydride allowed both reduction of the imine group and conjugate addition of the resulting amine to yield the *trans* 6-substituted 4-oxopipecolic acids **9** as single diastereoisomers.

Scheme 3. Synthesis of *trans* 6-substituted pipecolic acid derivatives **9**.



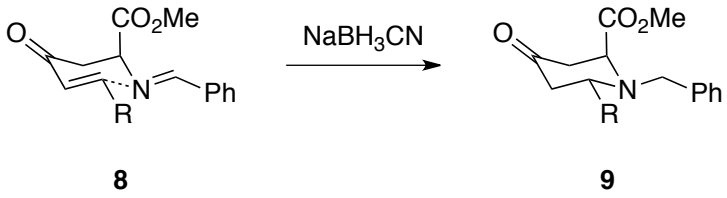
Similarly, treatment of enones **7** with hydrochloric acid yielded the free amines as their hydrochloride salts, which were then cyclised using Hünig's base to give the *cis* diastereoisomers **10** as the major products (Scheme 4).[12]

Scheme 4. Synthesis of *cis* 6-substituted pipecolic acid derivatives **10**.



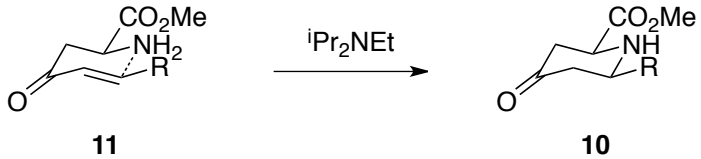
The authors justified the selectivity of these cyclisations based on the chair-like conformations adopted by the molecules. During the cyclisation of compounds **8**, both the benzyl imine and R group are placed in pseudo-equatorial positions, whilst the ester group is positioned pseudo-axial to avoid 1,3-allylic strain with the imine (Figure 9). This leads, after reduction of the imine and subsequent cyclisation, to the *trans* diastereoisomer **9** preferentially.

Figure 9. Rationale for the diastereoselectivity of the reduction/cyclisation of compounds **8**.



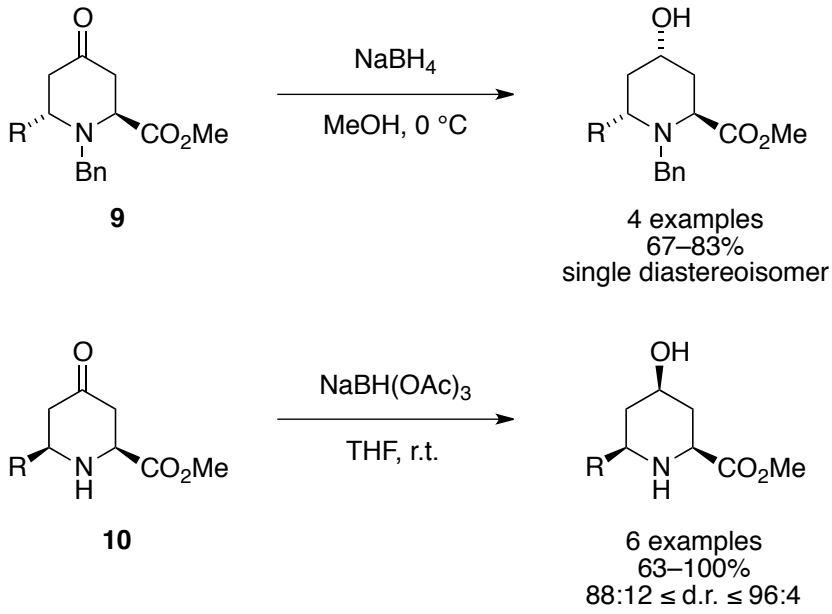
A chair-like conformation is also proposed for the base mediated cyclisation of free amines **11**. Both the ester and R group are placed in pseudo-equatorial positions (Figure 10), which leads primarily to the *cis* diastereoisomer **10**.

Figure 10. Rationale for the diastereoselectivities observed in the cyclisation of compounds **11**.



Both the *cis* and *trans* 6-substituted 4-oxopipecolic acids were reduced diastereoselectively to give the equatorial alcohols, using sodium borohydride or sodium triacetoxyborohydride respectively (Scheme 5).[11-12]

Scheme 5. Diastereoselective reduction of *cis* and *trans* 6-substituted 4-oxopipecolic acids **9** and **10**.

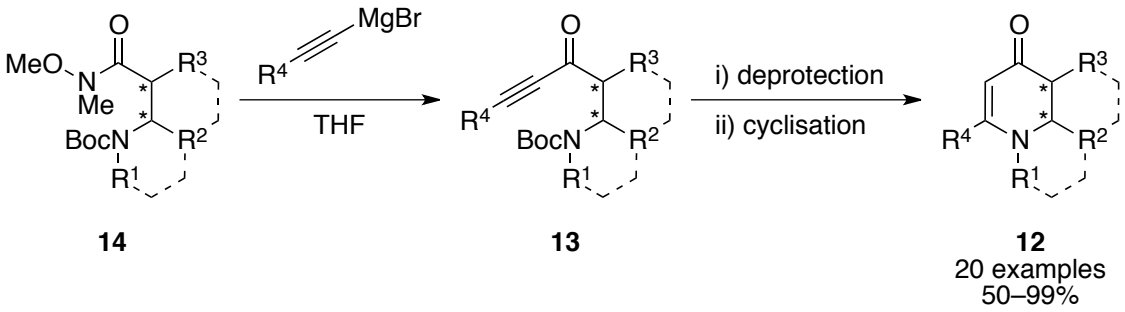


1.2.2.2 Georg and co-workers

Another research group to use the 1,6 disconnection is that of Georg and co-workers, who have developed a synthesis of substituted 2,3-dihydro-4-pyridones **12** from amino ynones **13**.[13] Although the authors did not convert these products into 4-hydroxpiperidines, this could easily be envisioned by reduction of both the alkene and ketone functional groups in compounds **12**.

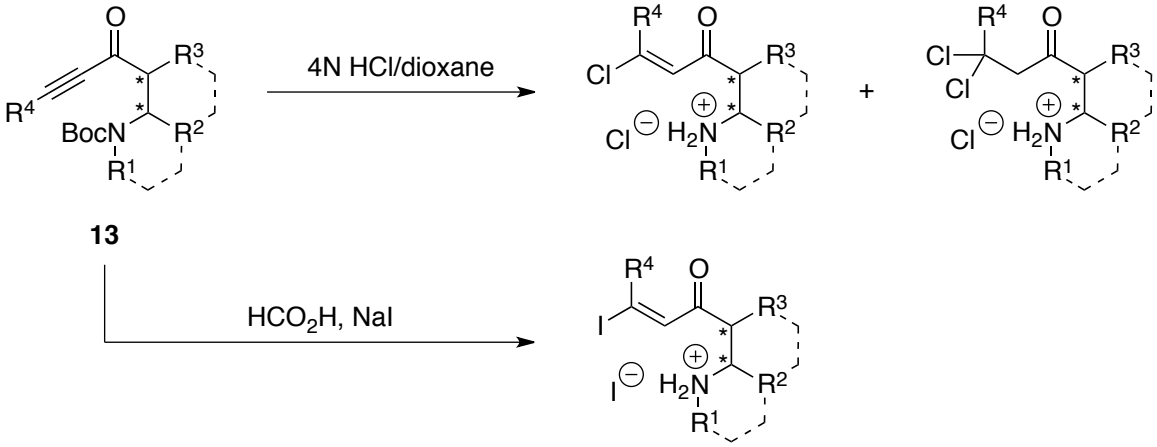
The required ynones **13** were synthesised by the addition of an alkynyl Grignard reagent to Weinreb amides **14** (Scheme 6), which themselves were derived from α- or β-amino acids. The general strategy involves an acidic deprotection of the *tert*-butoxycarbonyl group followed by a base mediated cyclisation step.

Scheme 6. General synthesis of substituted 2,3-dihydro-4-pyridones **12** from amino acid derived Weinreb amides **14**.



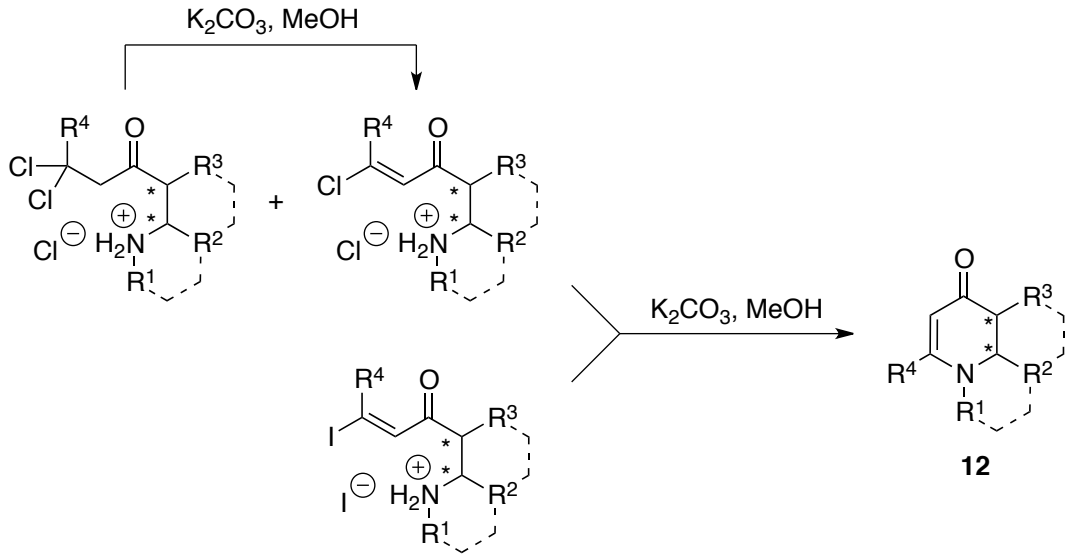
Two complementary nitrogen deprotection methods were disclosed, either using hydrogen chloride in dioxane or formic acid combined with sodium iodide. The presence of a halide ion was required as these were found to add to the ynone to form various β-haloketones (Scheme 7). When the deprotection was carried out without the halide anion, the desired cyclisation proved either to be low yielding or unsuccessful.

Scheme 7. Acidic deprotection of amino ynones **13** to yield various β-haloketones.



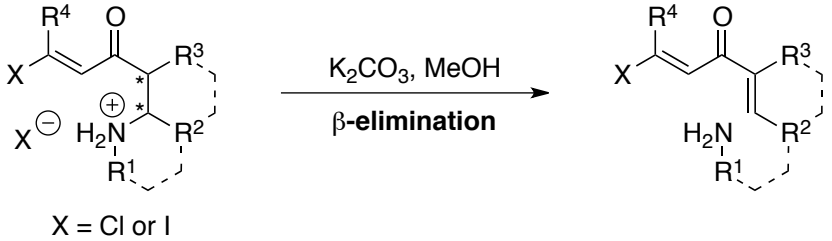
Once formed, the β-haloketones were cyclised using potassium carbonate in methanol (Scheme 8). If hydrogen chloride had been used previously and the β-dichloroketone was present, this was first converted to the β-chloroenone. Regardless of which β-haloenone was present, these underwent a *6-endo-trig* cyclisation followed by loss of HX to yield the target substituted 2,3-dihydro-4-pyridone **12**.

Scheme 8. Base-promoted cyclisation of β-haloenones to give 2,3-dihydro-4-pyridones **12**.



One problem encountered in this synthesis was epimerization of both the α- and β-stereocentres, which occurred in a number of cases. Some of the issues resulting from acid mediated α-epimerisation could be overcome by changing the deprotection method from the strongly acidic hydrogen chloride to the weaker formic acid. However, for the slower cyclisation reactions of internal ynones, base induced β-amino elimination proved a significant problem (Scheme 9). When R^1 was not tethered to some other part of the molecule, β-amino elimination resulted in the irreversible loss of R^1NH_2 from the starting material, giving a lower yield of 2,3-dihydro-4-pyridone.

Scheme 9. Base induced β-amino elimination of intermediate β-haloenones.

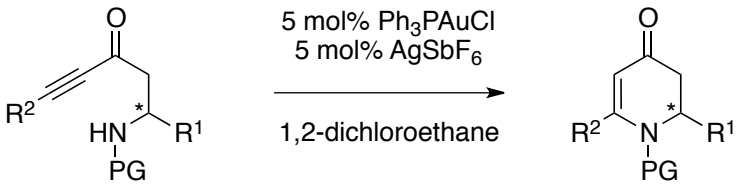


In conclusion, depending on the exact nature of the substitution of the starting material, Georg and co-workers have provided methodology that gives the desired substituted 2,3-dihydro-4-pyridones **12** in yields ranging from 50 to 99%. The products were isolated with diastereomeric ratios or enantiomeric ratios ranging between 58:42 and >99:1, based on the initial stereochemistry of the starting materials.

1.2.2.3 Gouault and co-workers

In 2011, Gouault and co-workers reported a gold(I)-catalysed cyclisation of a range of α-amino acid derived ynones **15** to give 2,6-disubstituted 2,3-dihydro-4-pyridones **16** in good yields (Scheme 10).[14]

Scheme 10. Gold(I)-catalysed cyclisation of amino ynones **15** to give 2,3-dihydro-4-pyridones **16**.



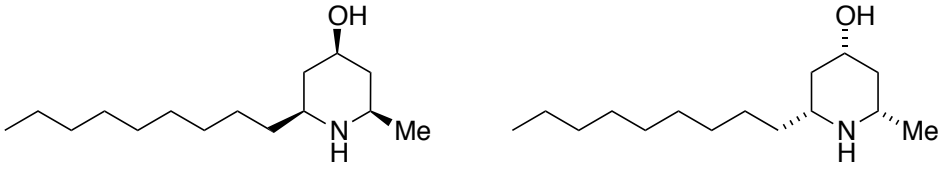
15

16
9 examples
70–93%

R^1 = H, Me, ^{i}Bu, Bn, CH_2OBn, ^{s}Bu
R^2 = Ph, ^{n}Pr, $^nC_9H_{19}$
PG = Boc, Cbz

This methodology was used to synthesise both enantiomers of the natural product 241D (Figure 11) by removal of the protecting group and stereoselective hydrogenation of both the alkene and ketone functional groups.[15]

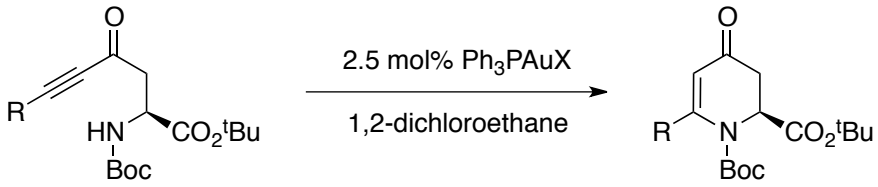
Figure 11. Both enantiomers of natural product 241D synthesised by Gouault and co-workers.



(+)-241D (–)-241D

Gouault and co-workers have recently published an extension of this methodology involving the synthesis of 6-substituted 4-hydroxypipecolates.[16] As before the key step was a gold(I)-catalysed cyclisation, in this case performed on L-aspartic acid derived ynones **17** (Scheme 11). For internal alkynes **17a** and **17b**, very good yields of the desired 2,3-dihydro-4-pyridones were achieved using $Ph_3PAuNTf_2$ as the catalyst. However, the cyclisation of terminal alkyne **17c** proved much more challenging, with the best yield of 33% being achieved when $Ph_3PAuOTf$ was used as the catalyst.

Scheme 11. Gold(I)-catalysed cyclisation of amino ynones **17** to give 2,3-dihydro-4-pyridones **18**.

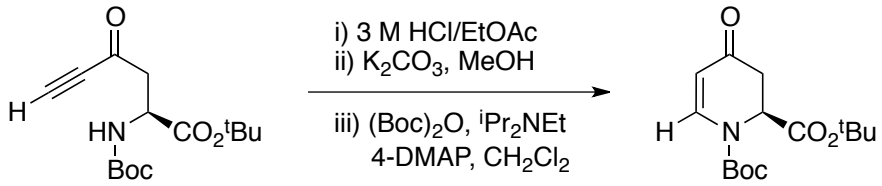


R = ^{n}Pr, **17a**
R = Ph, **17b**
R = H, **17c**

R = ^{n}Pr, X = NTf_2, **18a**, 97%
R = Ph, X = NTf_2, **18b**, 95%
R = H, X = OTf, **18c**, 33%

Due to the low yield obtained in the gold-catalysed cyclisation of the terminal alkyne **17c**, the authors instead applied the conditions reported by Georg and co-workers.[13] These conditions proved effective, and after Boc protection the desired 2,3-dihydro-4-pyridone **18c** was isolated in a 75% yield (Scheme 12).

Scheme 12. Application of Georg and co-workers' conditions to enable the cyclisation of alkyne **17c**.

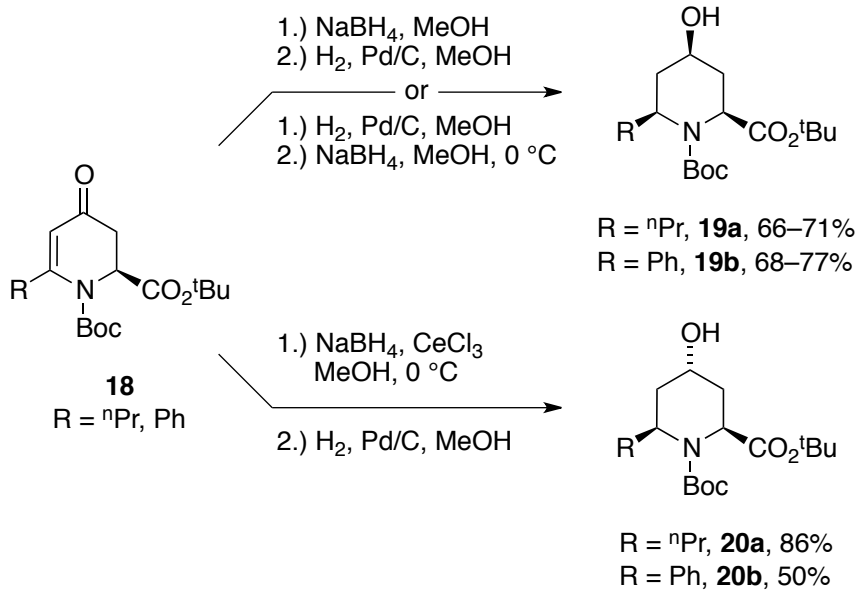


17c

18c
75%

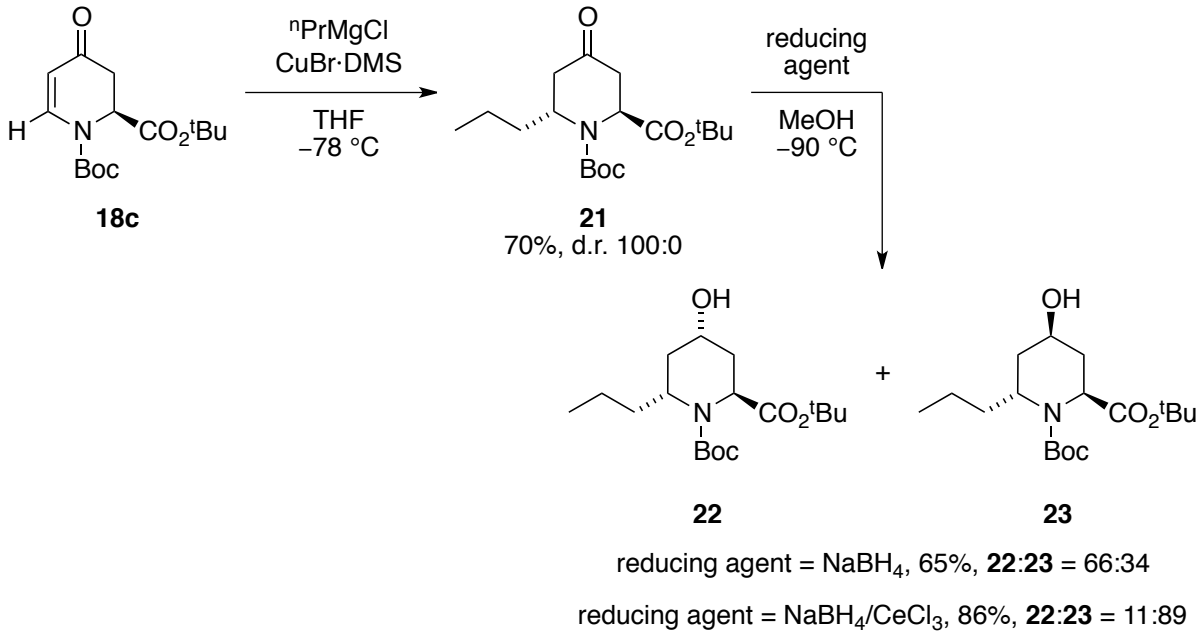
With the desired 2,3-dihydro-4-pyridones in hand, Gouault and co-workers then went on to investigate the chemoselective and diastereoselective reductions of these compounds in order to access 6-substituted 4-hydroxypipecolates. Through careful choice of conditions for the reductions, they were able to synthesise both epimers of the resulting *cis* 2,6-disubstituted 4-hydroxypiperidines **19** and **20** in good yields (Scheme 13). All of these reductions proceeded to give the products with diastereomeric ratios of 90:10 or greater, with the exception of the synthesis of compound **20b**, which was produced along with its C-6 epimer in a 60:40 ratio.

Scheme 13. Synthesis of two sets of epimeric 6-substituted 4-hydroxypipecolates by reduction of the corresponding 2,3-dihydro-4-pyridones **18**.



In order to access *trans* 2,6-disubstituted 4-hydroxypiperidines, the authors next investigated the reactivity of unsubstituted compound **18c** (Scheme 14). Copper-catalysed conjugate addition of ^{n}PrMgCl yielded the *trans* 6-disubstituted 4-oxopipecolate **21** as a single diastereoisomer. Following this, reduction of the ketone with $NaBH_4$ at −90 °C favoured production of epimer **22**, whereas the use of $NaBH_4$ in combination with $CeCl_3$ gave an excess of the other diastereoisomer **23**.

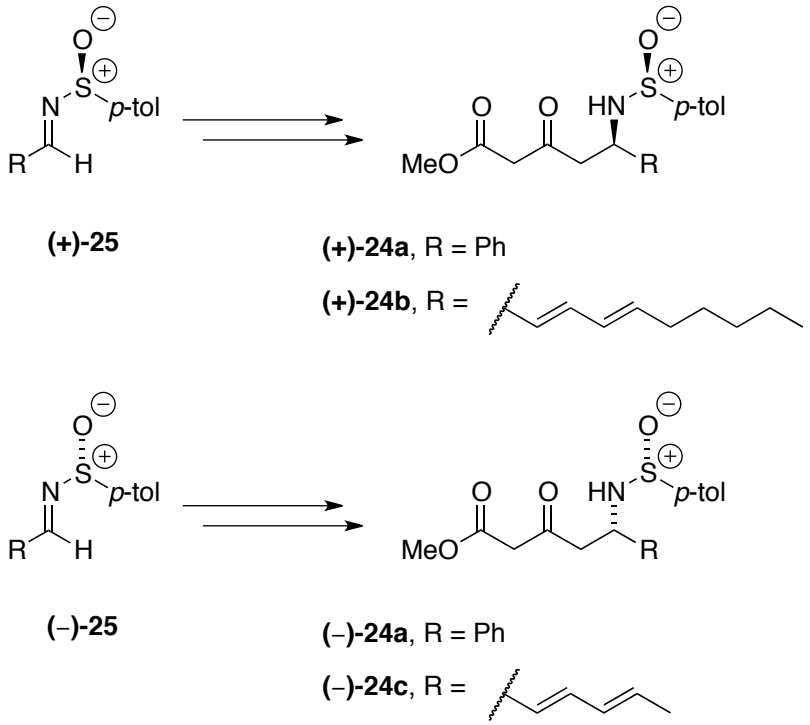
Scheme 14. Synthesis of *trans*-6-substituted 4-hydroxypipecolates **22** and **23**.



1.2.2.4 Davis and co-workers

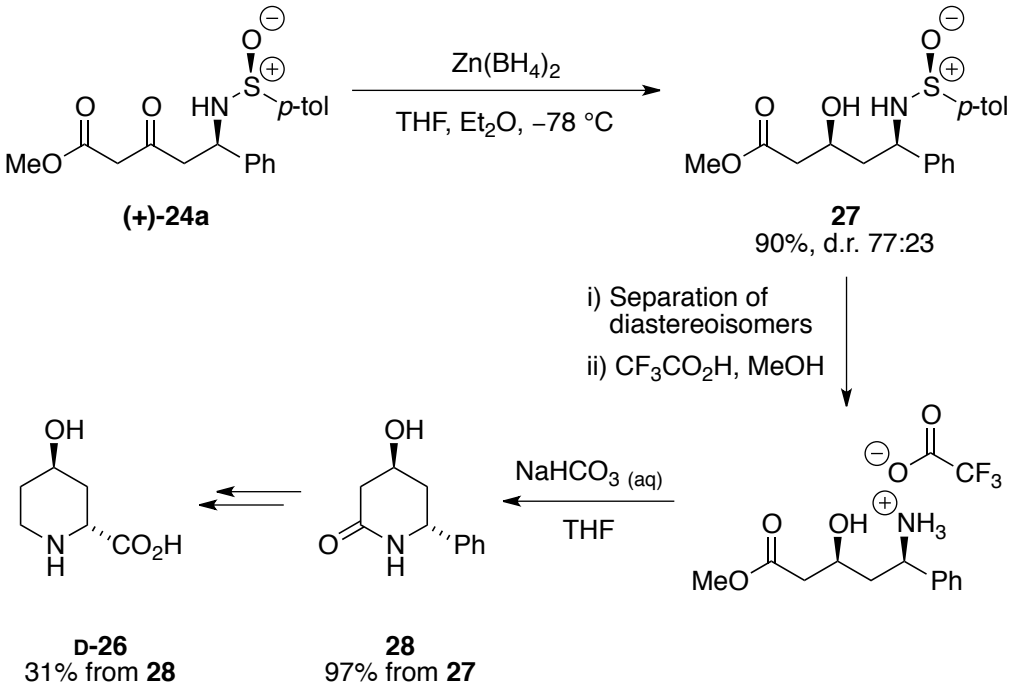
Davis and co-workers have also used a 1,6 disconnection to synthesise a number of 4-hydroxypiperidine containing natural products from *N*-sulfinyl δ-amino β-keto esters **24** (Scheme 15).[17-19] The important chiral amine functionality present in these molecules was installed by a diastereoselective addition of an enolate to the required *N*-sulfinyl imines **25**, directed by the chiral sulfinyl group (Scheme 15).[17-21] The diastereomeric ratio of the products from this addition was greater than 98:2 in all cases.

Scheme 15. Some *N*-sulfinyl δ-amino β-keto esters **24** synthesised by Davis and co-workers.



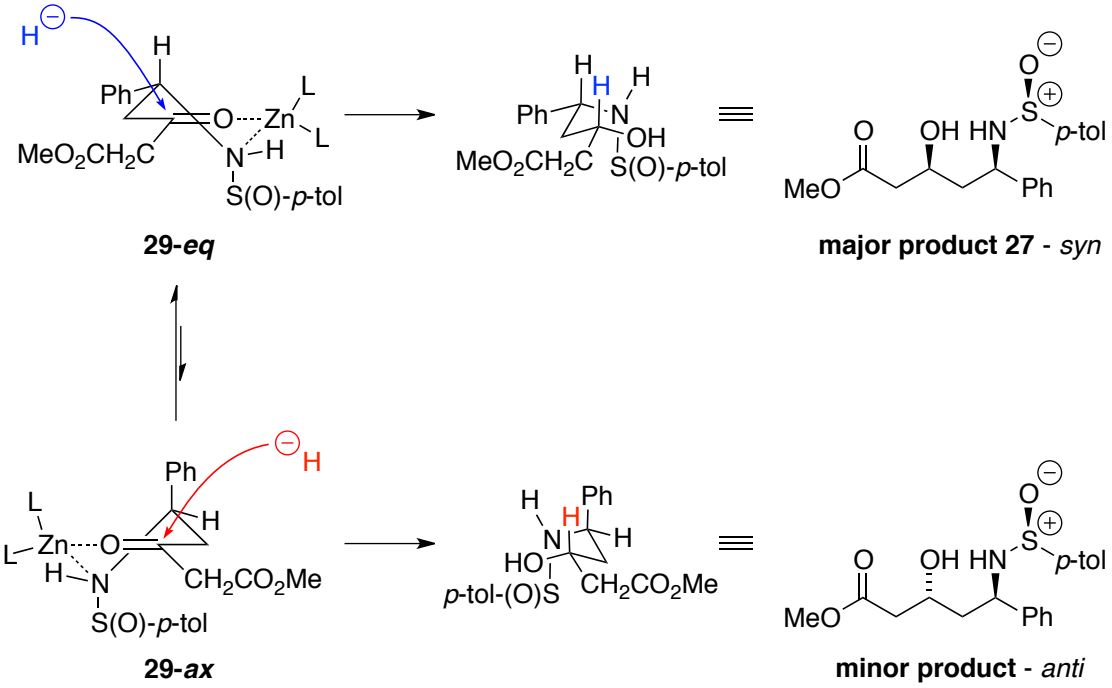
Compound **(+)-24a** was used to synthesise *trans*-4-hydroxy-D-pipecolic acid **D-26** (Scheme 18).[17] $Zn(BH_4)_2$ was used to reduce compound **(+)-24a** to give *syn* alcohol **27** in a 77:23 mixture with its diastereoisomer, the *anti* alcohol. After separation of these compounds by column chromatography, removal of the sulfinyl group from *syn* alcohol **27** and base mediated cyclisation gave *trans*-6-phenyl-4-hydroxypiperidin-2-one **28**. Subsequent reduction of the amide using $LiAlH_4$, followed by oxidative conversion of the phenyl ring into a carboxylic acid, yielded *trans*-4-hydroxy-D-pipecolic acid **D-26**.

Scheme 16. Synthesis of *trans*-4-hydroxy-D-pipecolic acid **D-26** from compound **(+)-24a**.



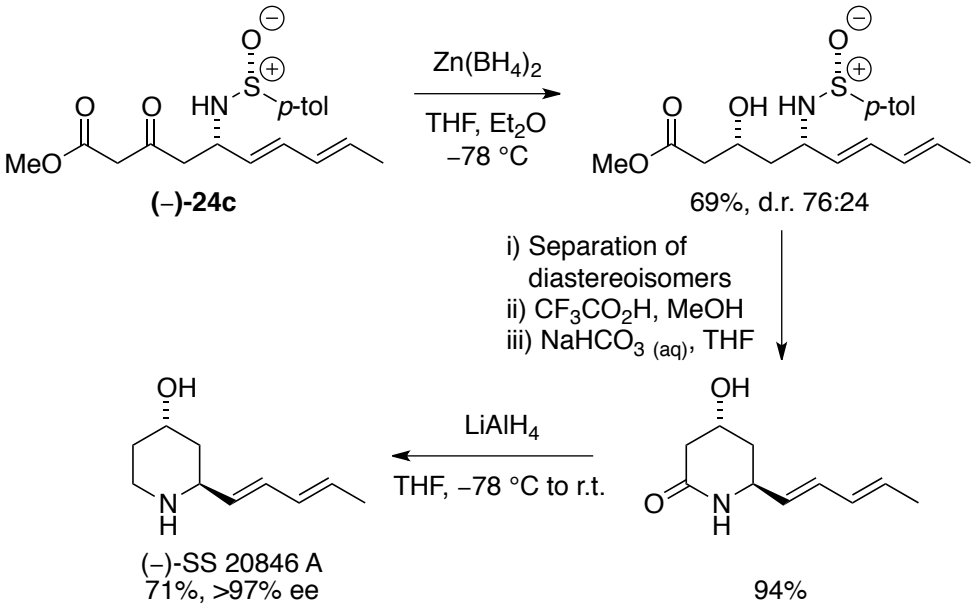
The reduction of *N*-sulfinyl δ-amino β-keto ester **(+)-24a** is stereoselective because of the influence of the existing amino stereocentre. The zinc coordinates to both the amine and the carbonyl groups, giving two possible half-chair conformations (Figure 12). Hydride delivery in these half-chair conformations comes from the top face, so as to proceed via the more stable chair-like transition state, compared to the twist boat transition state that would occur if the hydride were delivered from the bottom face. External hydride delivery occurs preferentially to conformer **29-*eq***, as in conformer **29-*ax*** the incoming hydride experiences a steric clash with the pseudo-axial phenyl group. This preferential hydride delivery leads to the *syn* alcohol **27** as the major product.

Figure 12. Rationale for the observed diastereoselective reduction of compound **(+)-24a**.



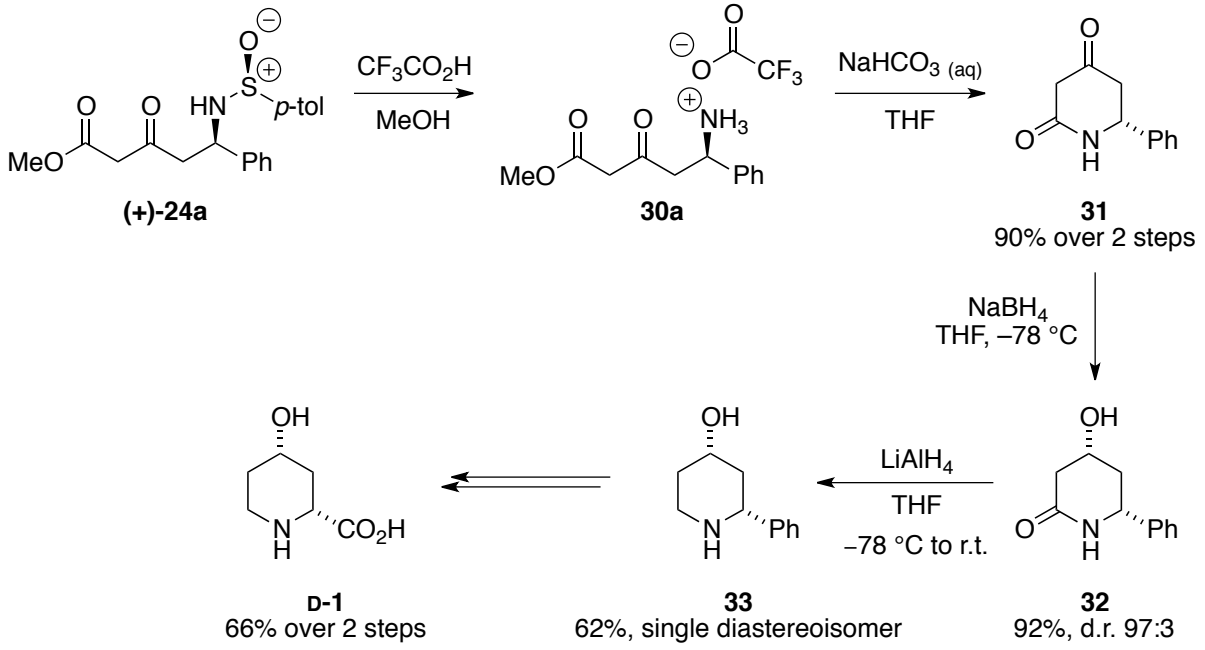
The alkaloid (−)-SS 20846 A was also synthesised by Davis and co-workers using this methodology (Scheme 17).[18] This synthesis involved the diastereoselective reduction of the related *N*-sulfinyl δ-amino β-keto ester **(−)-24c** using $Zn(BH_4)_2$.

Scheme 17. Synthesis of (−)-SS 20846 A from compound **(−)-24c**.



Davis and co-workers have also synthesised *cis*-4-hydroxy-D-pipecolic acid **D-1** from *N*-sulfinyl δ-amino β-keto ester **(+)-24a** by reversing the order of the ketone reduction and cyclisation steps in the synthetic strategy (Scheme 18).[17] After removal of the sulfinyl group, ammonium salt **30a** was cyclised using $NaHCO_3$, resulting in 6-phenylpiperidin-2,4-one **31**. The ketone was then reduced stereoselectively using $NaBH_4$ to give *cis*-6-phenyl-4-hydroxypiperidin-2-one **32**, with a diastereomeric ratio of 97:3. The amide was reduced using $LiAlH_4$, with diastereomerically pure product **33** being isolated after column chromatography. This compound was converted into *cis*-4-hydroxy-D-pipecolic acid **D-1** in the same manner as previously described for compound **28** (see Scheme 16, p16).

Scheme 18. Synthesis of *cis*-4-hydroxy-D-pipecolic acid **D-1** from compound **(+)-24a**.

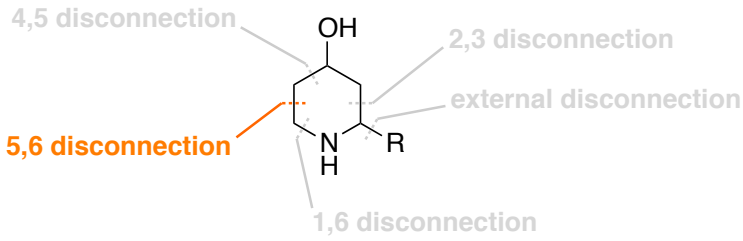


By applying the previously described chemistry to the other enantiomer of the starting material, *N*-sulfinyl δ-amino β-keto ester **(–)-24a**, Davis and co-workers were also able to synthesise *cis*- and *trans*-4-hydroxy-L-pipecolic acid **L-1** and **L-26**.[17]

1.2.3 Previous Syntheses using a 5,6 Disconnection

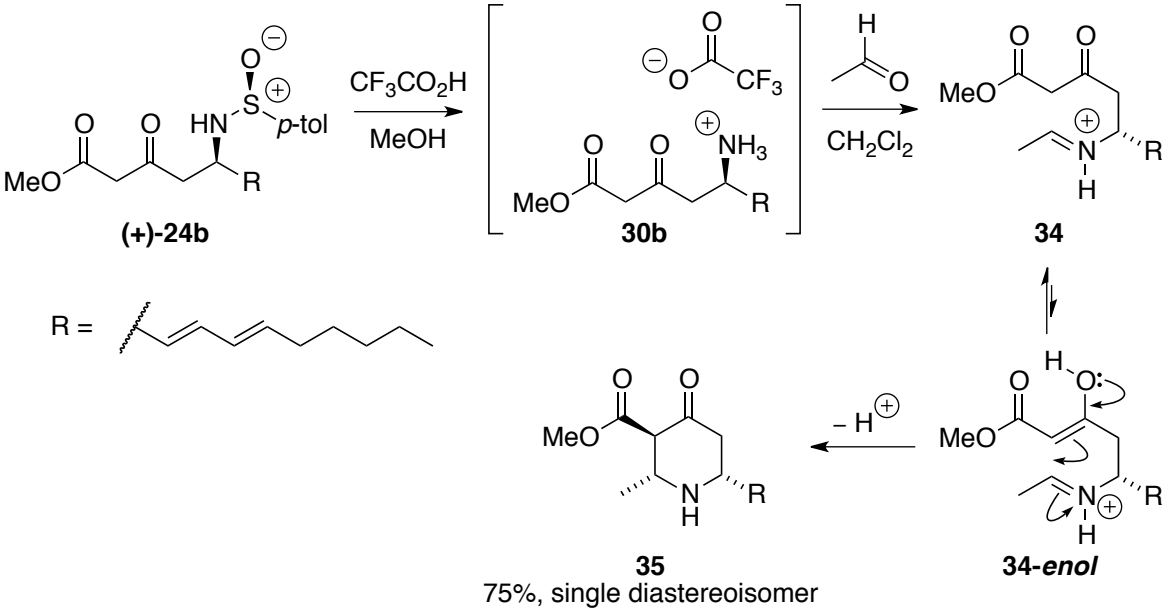
Davis and co-workers have also adapted their strategy outlined above to produce 2,6-disubstituted piperidines,[19] this time making use of a 5,6 disconnection (Figure 13).

Figure 13. A 5,6 disconnection used to construct substituted 4-hydroxypiperidines.



Since 5-10% of *N*-sulfinyl δ-amino β-keto ester **(+)-24b** exists in its enol form, the authors proposed that it would be possible to perform an intramolecular Mannich reaction between this enol and the iminium ion **34**, formed by the condensation of acetaldehyde with compound **30b** (Scheme 19). This did indeed occur, and the cyclised product **35** was isolated in good yield as a single diastereoisomer.

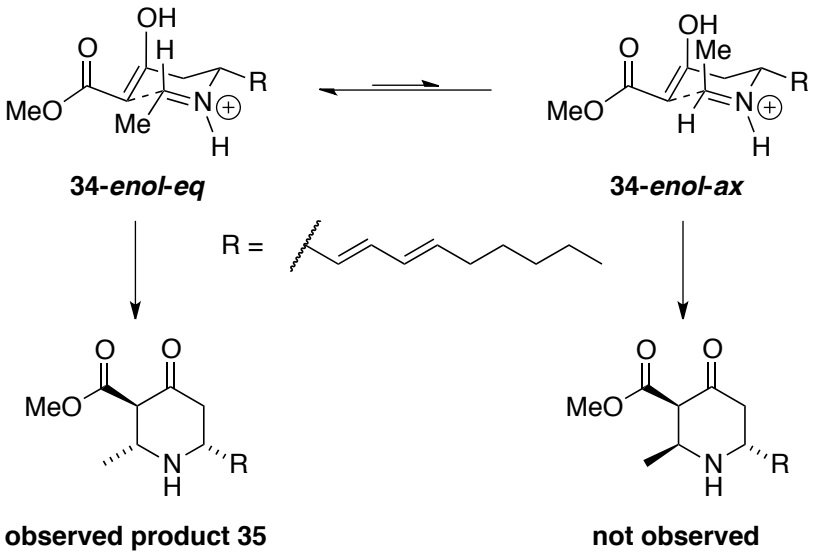
Scheme 19. Mannich reaction used to form 2,5,6-trisubstituted 4-hydroxypiperidine **35** from compound **(+)-24b**.



The stereoselectivity of this Mannich reaction arises from the relative stability of the two possible transition states that place both the large R group and the carbomethoxy group in pseudo-equatorial positions (Figure 14). These differ in the orientation of the methyl substituent of the iminium ion: the more stable transition state **34-*enol-eq*** also places the methyl group in a pseudo-equatorial position, whereas the less stable transition state **34-*enol-ax*** places the methyl group in a pseudo-

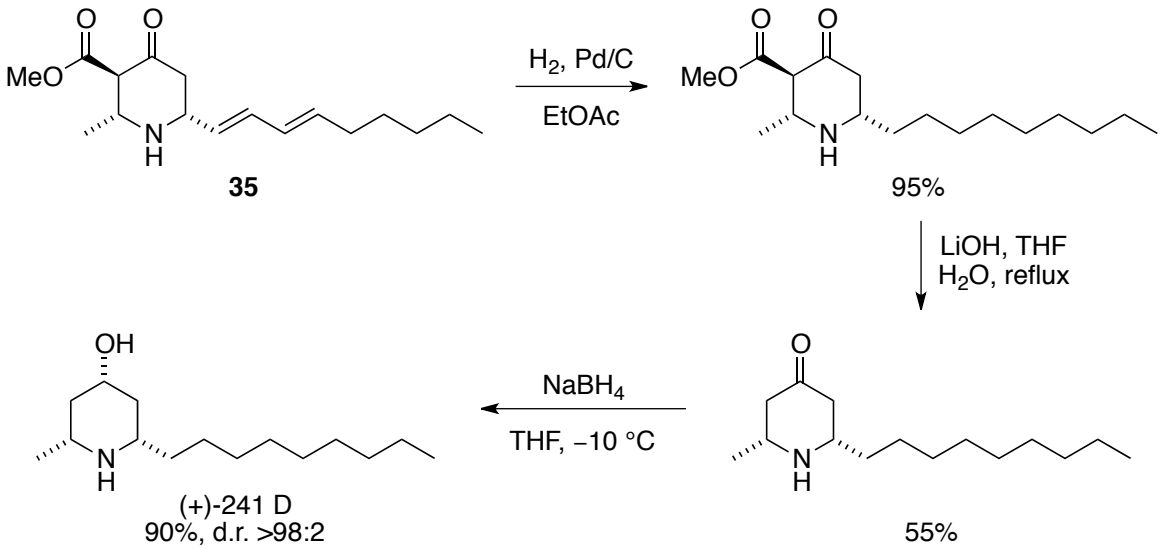
axial position. Reaction through the more stable transition state **34-*enol-eq*** leads to the observed product **35**.

Figure 14. Rationale for the diastereoselectivity of the Mannich reaction.



Subsequent hydrogenation, decarboxylation and reduction of compound **35** gave alkaloid (+)-241 D (Scheme 20).

Scheme 20. Conversion of compound **35** into alkaloid (+)-241 D.



1.2.4 Previous Syntheses using a 2,3 Disconnection

1.2.4.1 Troin, Canet and co-workers

A similar intramolecular Mannich type reaction has been used by Troin, Canet and co-workers to synthesise a wide variety of 4-hydroxypiperidines via the corresponding 4-oxopiperidines (Scheme 21).[22-28] Due to the position of the substituents, this is classed as a 2,3 disconnection (Figure 15).

Scheme 21. General synthesis of 4-hydroxypiperidines by Troin, Canet and co-workers.

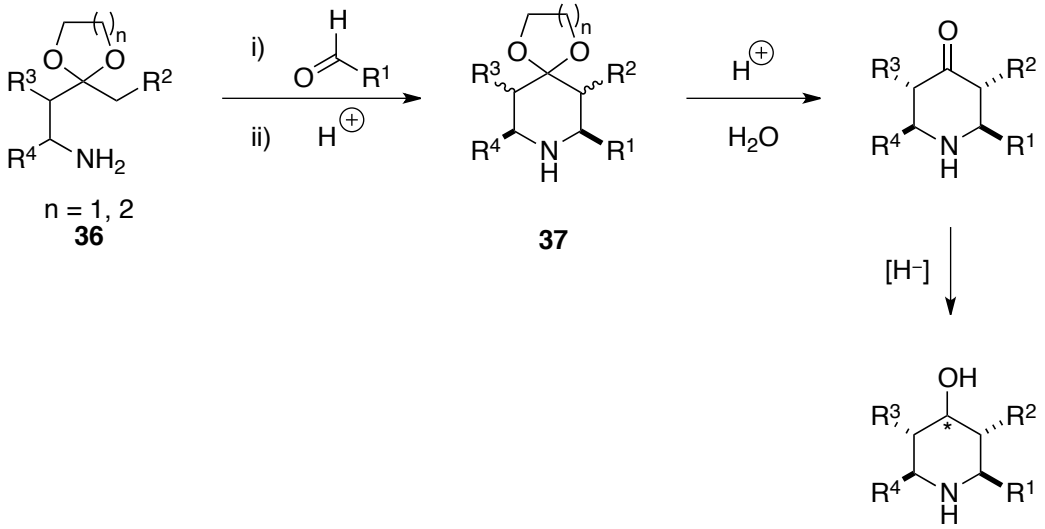
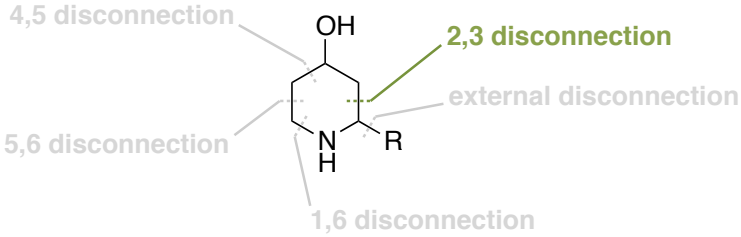
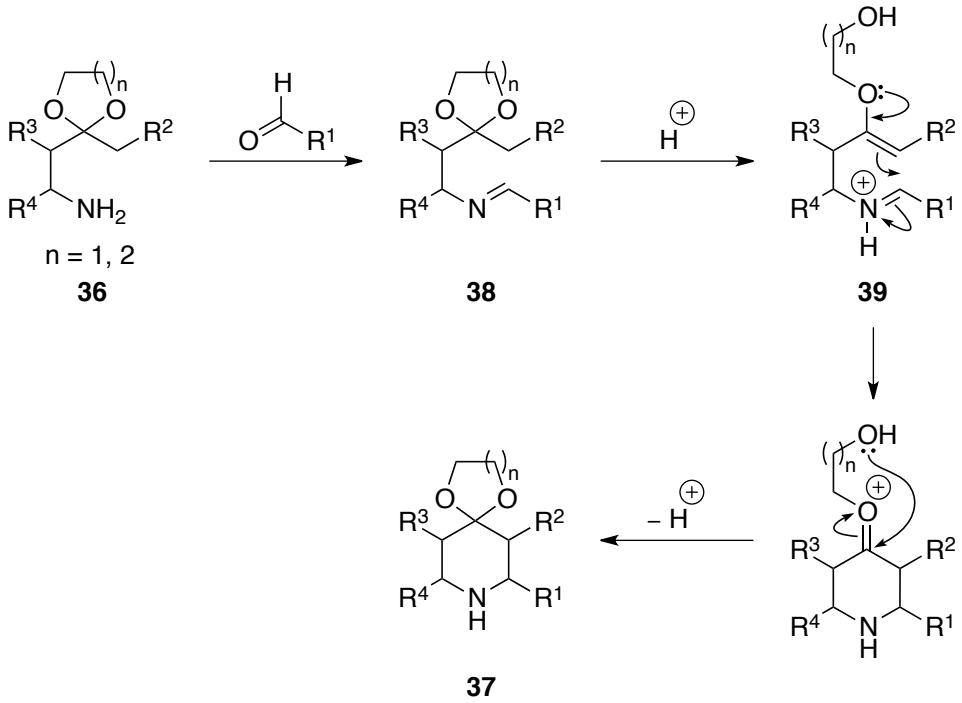


Figure 15. A 2,3 disconnection used to construct substituted 4-hydroxypiperidines.



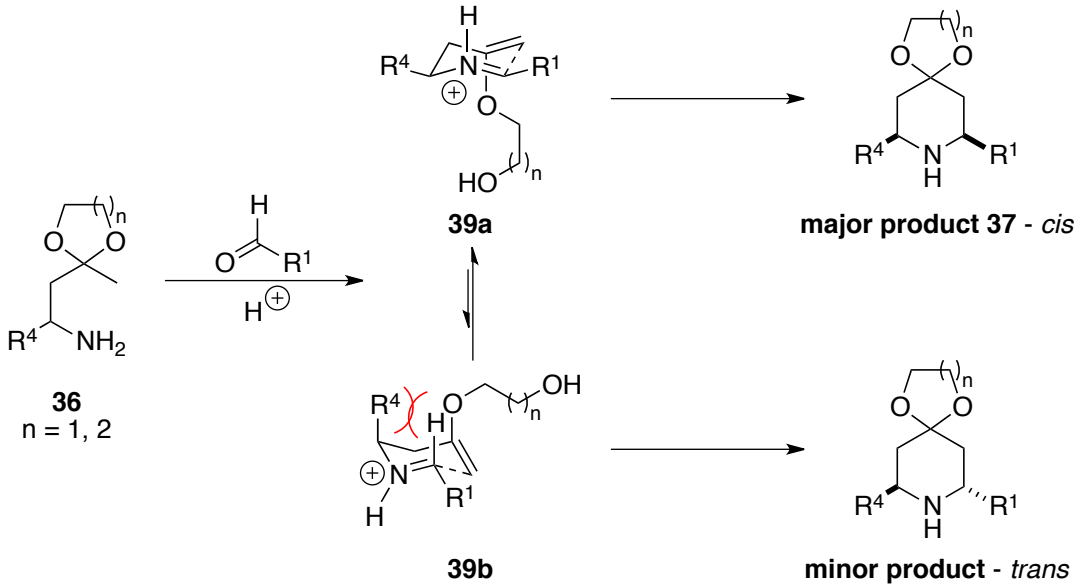
In this reaction an acetal protected 4-oxo amine **36** reacts with an aldehyde to form imine **38** (Figure 16).[22-25] Under the acidic reaction conditions the imine is protonated and the acetal group is converted to enol ether **39**, which then cyclises onto the iminium ion. Finally, reformation of the acetal group yields the final product **37**.

Figure 16. Mechanism of the Mannich type reaction between compounds **36** and an aldehyde.



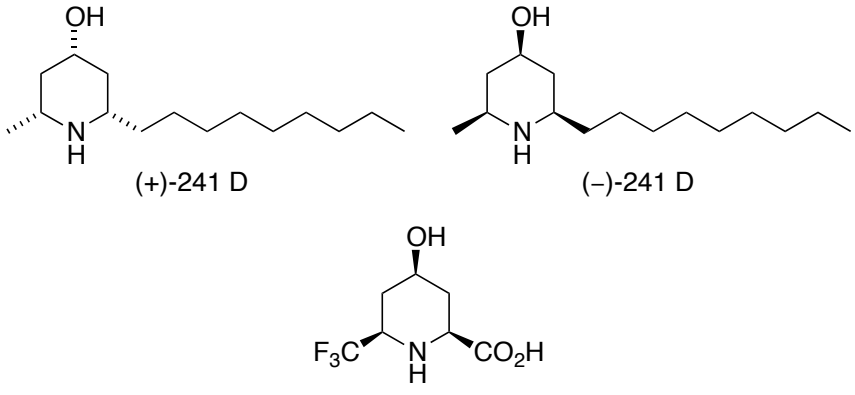
If there is a substituent in the α-position of the starting amine **36** (i.e. $R^4 \neq H$), then the stereochemistry of the R^1 group at the 2-position of the piperidine is induced during the cyclisation. There are two possible transition states that place the R^1 group in the more stable pseudo-equatorial position: **39a** and **39b** (Figure 17). Conformer **39b** is disfavoured due to the 1,3-diaxial strain between the R^4 group and the hydrogen from the aldehyde.[22] For this reason conformer **39a**, where the R^4 group is in a pseudo-equatorial position, is favoured, which leads to the *cis*-2,6-disubstituted piperidine. The stereochemistry of the remaining two stereocentres (R^2 and R^3) is set during the acidic acetal deprotection step, where equilibration occurs to give the more thermodynamically stable isomer of the final product (see Scheme 21, p21).

Figure 17. Rationale for the stereochemistry induced at the 2-position of the piperidine during the Mannich-type reaction (substituents R^2 and R^3 omitted for clarity).



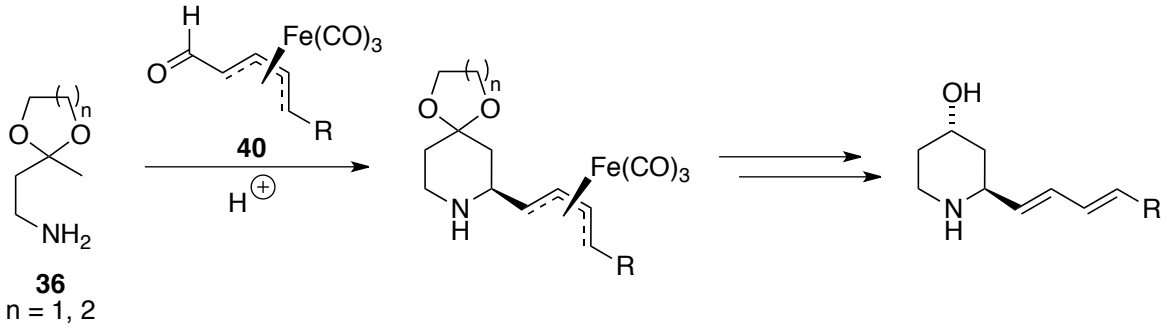
Since this cyclisation process is diastereoselective, beginning with an enantiomerically pure amine leads to an enantiomerically enriched product. Troin and co-workers have synthesised both enantiomers of the natural alkaloid 241 D using this methodology,[24] as well as *cis*,*cis*-4-hydroxy-6-trifluoromethyl -L-pipecolic acid (Figure 18).[25]

Figure 18. Some alkaloids prepared by Troin and co-workers.



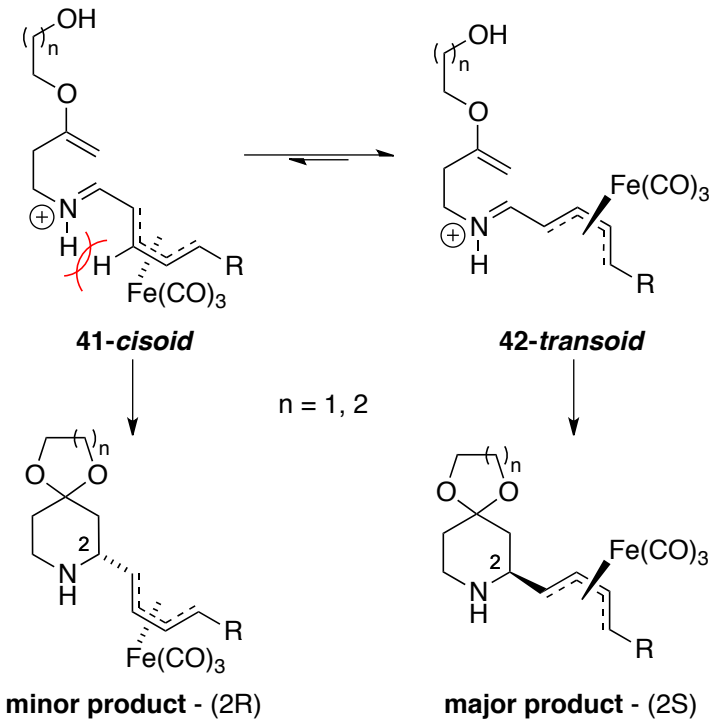
In a related method, Troin, Canet and co-workers used chiral, non-racemic iron tricarbonyl diene complexes **40** to construct 2-substituted 4-hydroxypiperidines (Scheme 22).[26-28]

Scheme 22. Use of chiral, non-racemic iron tricarbonyl diene complexes **40** in the synthesis of 2-substituted 4-hydroxypiperidines.



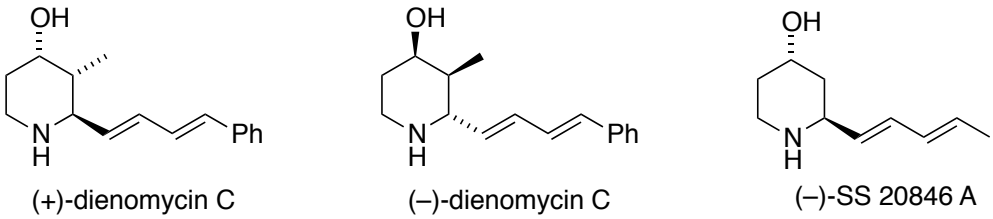
The iron tricarbonyl group acts as a directing group for the cyclisation,[26-27] since it blocks one face of the imine formed during the reaction. There are two possible conformations in which this imine can exist, which differ in the orientation of the imine with respect to the diene (Figure 19). The *transoid* conformation is more stable than the *cisoid* conformation, since in conformer **41-*cisoid*** there is a steric clash between the iminium hydrogen and one of the hydrogen atoms on the diene. For this reason the major product is the (2*S*)-isomer.

Figure 19. Origin of the diastereoselectivity in the cyclisation of amine **36** and aldehyde **40**.



This methodology has been used to prepare the natural products (+)- and (−)-dienomycin and (−)-SS 20846 A (Figure 20).[27-28]

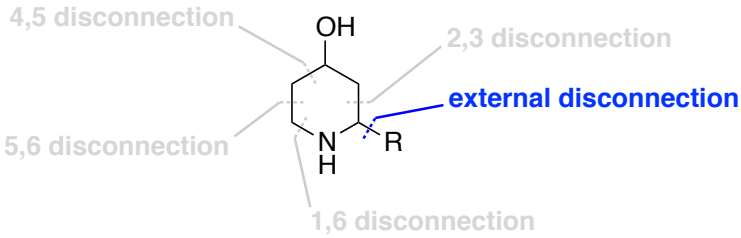
Figure 20. Natural products prepared by Troin, Canet and co-workers using chiral iron tricarbonyl diene complexes.



1.2.5 Previous Syntheses using an External Disconnection

All of the previous syntheses reviewed so far have constructed the piperidine ring during the synthesis. However, there have been a number of syntheses of substituted 4-hydroxpiperdines where the 6-membered ring is already present in the starting material, and the substituents are added during the synthesis. For the purposes of this review this methodology has been classified as an external disconnection (Figure 21).

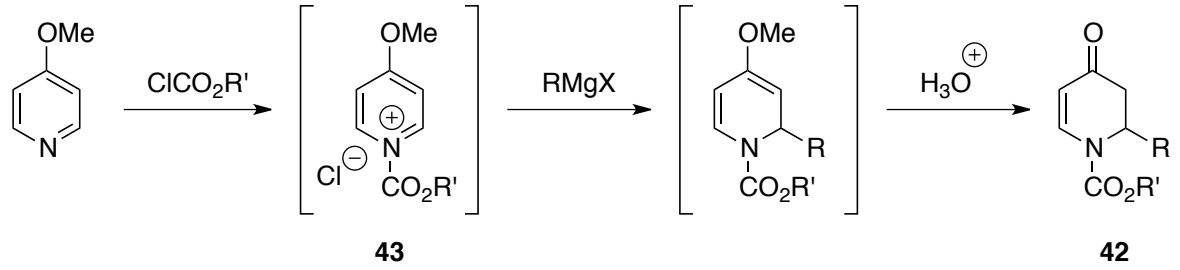
Figure 21. An external disconnection used to construct substituted 4-hydroxypiperidines.



1.2.5.1 Comins and co-workers

All of the syntheses of 4-hydroxypiperidines reviewed that employ the external disconnection are based on Comins and co-workers' methodology. In 1986, Comins and co-workers were first to report the synthesis of 2-substituted 2,3-dihydro-4-pyridones **42** by the addition of Grignard reagents to *N*-acylpyridinium salts **43** derived from 4-methoxypyridine (Scheme 23).[29]

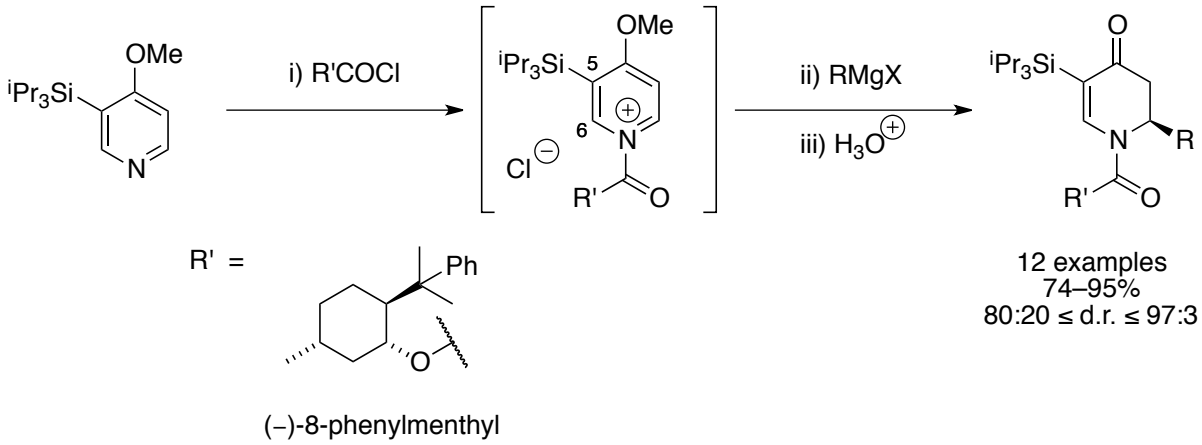
Scheme 23. General scheme for formation of 2-substituted 2,3-dihydro-4-pyridones **42** from 4-methoxypyridine.



43 **42**

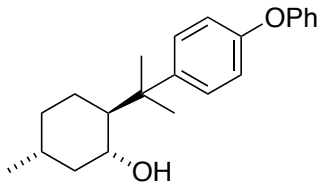
Comins and co-workers also published a stereoselective variant of this reaction.[30-31] They found that the (−)-8-phenylmenthylcarbonyl auxiliary gave good to excellent diastereoselectivities,[30-32] when there was a bulky triisopropylsilyl group installed at carbon 5 to block attack of the nucleophile at carbon 6 (Scheme 24). Both the auxiliary and the blocking group could be subsequently removed to give the free 2,3-dihydro-4-pyridone.

Scheme 24. Diastereoselective synthesis of 2,3-dihydro-4-pyridones, using a triisopropylsilyl blocking group and a (−)-8-phenylmenthylcarbonyl auxiliary.

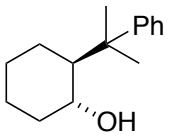


Comins and co-workers also reported that the related auxiliary containing (−)-8-(4-phenoxyphenyl)menthol (Figure 22) gave excellent diastereoselectivities in this reaction (d.r. ≥ 89:11).[30,33] Changing the chiral group to *trans*-2-(α-cumyl)cyclohexanol, which can be synthesised as either enantiomer, gave access to both enantiomers of the desired products, with similarly high levels of diastereoselectivity (d.r. > 92:8).[30,34-38]

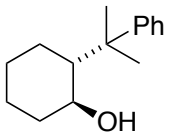
Figure 22. Other chiral auxiliaries used by Comins and co-workers.



(–)-8-(4-phenoxyphenyl) menthol



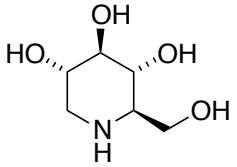
(–)-*trans*-2-(α-cumyl) cyclohexanol



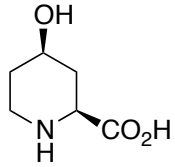
(+)-*trans*-2-(α-cumyl) cyclohexanol

Comins and co-workers have synthesised a number of 4-hydroxypiperidine containing natural products through reduction of both the alkene and ketone functional groups in the 2,3-dihydro-4-pyridones (Figure 23).[32-38] During this process they extended the range of nucleophiles that could be added to the *N*-acylpyridinium ion to include lithium acetylides,[36] zinc enolates[37] and alkyl organocuprates.[38]

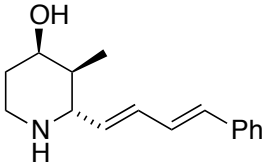
Figure 23. 4-Hydroxypiperidine containing natural products synthesised by Comins and co-workers.



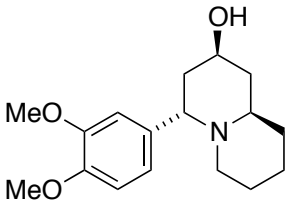
(+)-1-deoxynojirimycin



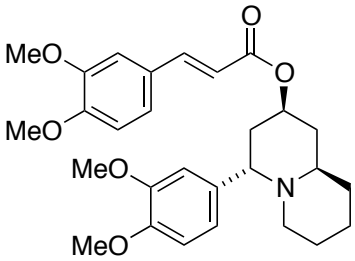
cis-4-hydroxy-L-pipecolic acid



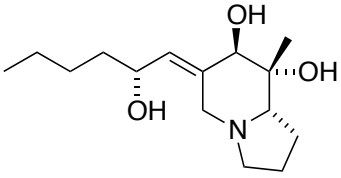
(+)-dienomycin C



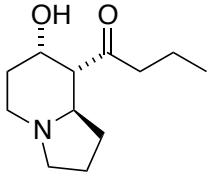
(–)-lasubine I



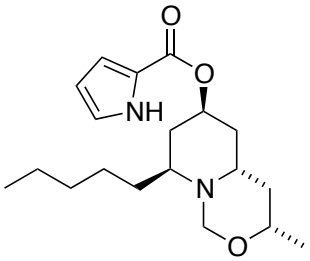
(+)-subcosine I



(+)-allopumiliotoxin



(+)-elaeokanine C

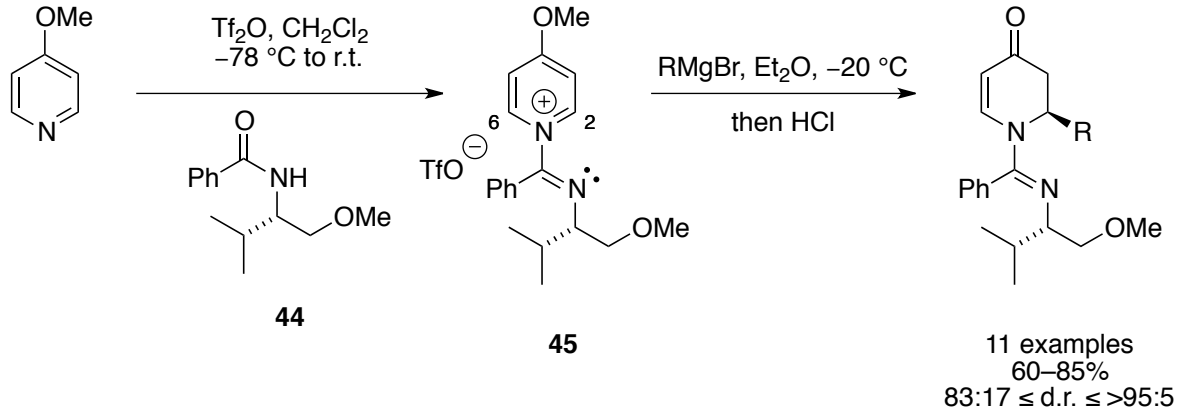


(+)-hyperaspine

1.2.5.2 Charette and co-workers

Comins and co-workers' work has been expanded by various authors, giving complementary methods to make chiral 2-substitued 2,3-dihydro-4-pyridones. Charette and co-worker reported the use of L-valine derived chiral auxiliary **44** that enabled the diastereoselective addition of Grignard reagents to pyridinium salt **45**, without the use of a blocking group on the pyridine (Scheme 25).[39] Instead the phenyl group in the auxiliary acts as a blocking group preventing attack of the nucleophile at carbon 6, whilst the lone pair of the imidate nitrogen can coordinate to the organometallic reagent aiding attack at carbon 2.[40] A range of alkyl, alkenyl, alkynyl and aryl Grignard reagents were used in this reaction.

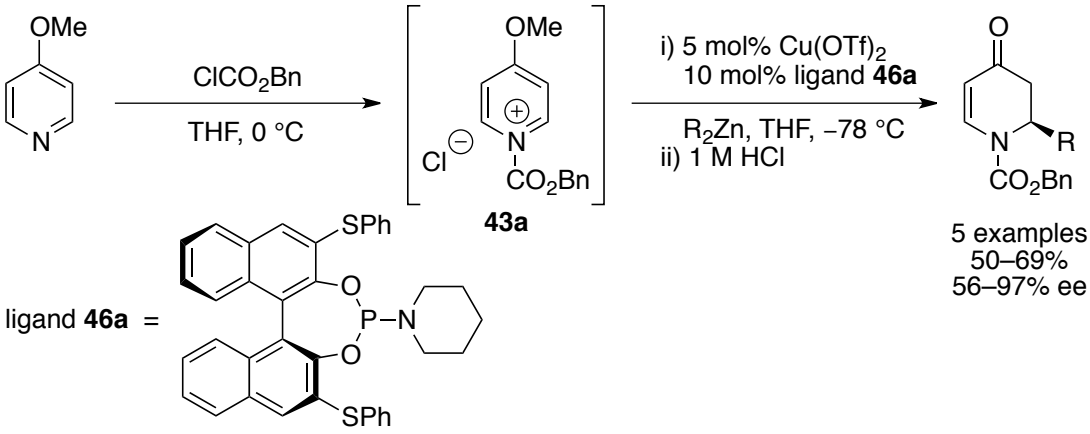
Scheme 25. Use of chiral auxiliary **44** in the diastereoselective addition of Grignard reagents to pyridinium salt **45**.



1.2.5.3 Minnaard, Feringa and co-workers

In 2009, Minnaard, Feringa and co-workers published the first catalytic, enantioselective synthesis of 2,3-dihydro-4-pyridones using this methodology, making use of the copper-catalysed addition of diorganozinc reagents to achiral *N*-acylpyridinium salt **43a** (Scheme 26).[41] The authors found that chiral phosphoramidite ligand **46a** generally allowed the products to be formed in good yield and good enantiomeric excess.

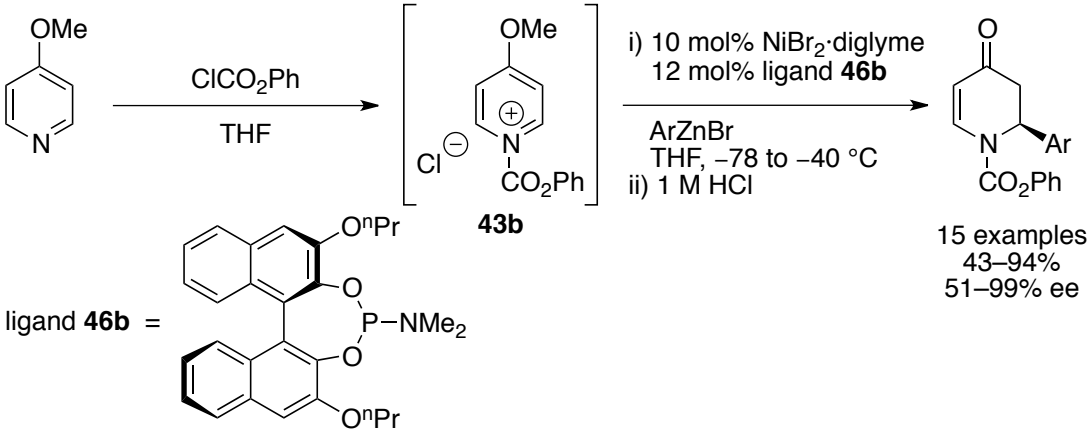
Scheme 26. Enantioselective, copper-catalysed addition of diorganozinc reagents to *N*-acylpyridinium salt **43a**.



1.2.5.4 Doyle and co-workers

Recently, Doyle and co-workers have developed a related nickel-catalysed enantioselective addition of aryl organozinc reagents to *N*-acylpyridinium salt **43b** (Scheme 27).[42] After optimisation, they found that ligand **46b** gave the products with good enantiomeric excesses. The best excesses were seen for aryl zinc reagents with electron-withdrawing substituents, while electron neutral aryl zinc reagents gave modest enantiomeric excesses. Electron rich aryl zinc reagents generally gave poor enantiomeric excesses due to the competing background reaction between the organozinc reagent and the pyridinium ion, without the involvement of the chiral catalyst. This was also found to be the case for alkyl zinc reagents, which is why the reaction was limited to the use of aryl zinc reagents.

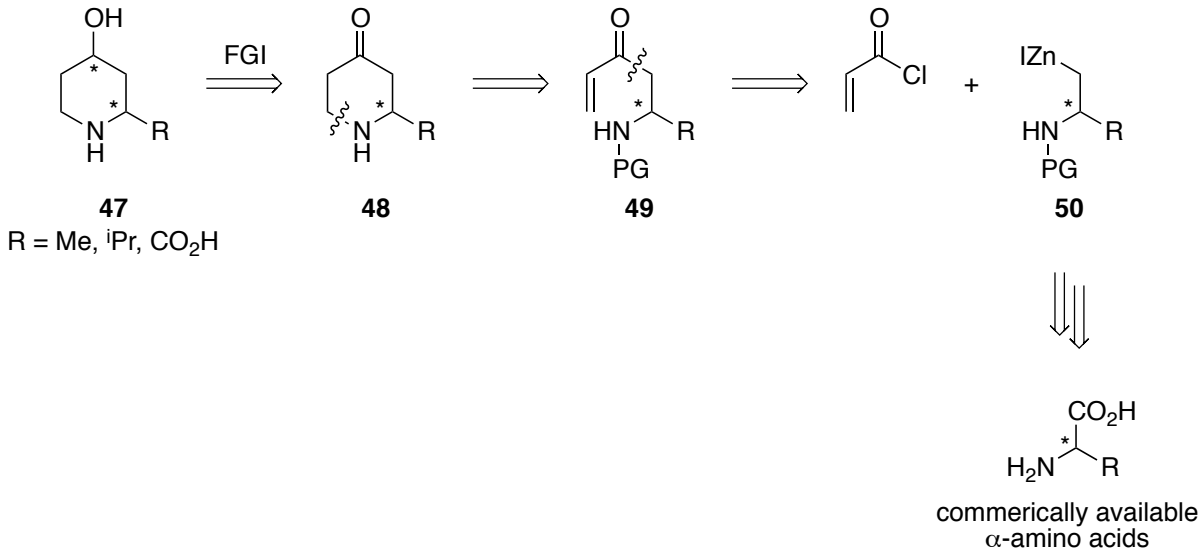
Scheme 27. Enantioselective, nickel-catalysed addition of aryl organozinc reagents to *N*-acylpyridinium salt **43b**.



1.3 Retrosynthetic Analysis of Target Molecules

The target molecules for this project are 2-substituted 4-hydroxypiperidines **47** (Scheme 28). These are of interest as small, chiral pharmaceutical building blocks, as well as being present in a number of natural products (see Chapter 1.1, p1). Retrosynthetic analysis of these compounds shows that they could be synthesised via the reduction of 2-substituted 4-oxopiperidines **48**. These in turn could be made by cyclising intermediates **49**, which could result from the palladium-catalysed Negishi cross coupling reaction of acryloyl chloride with a variety of α-amino acid derived organozinc reagents **50**.

Scheme 28. Retrosynthetic analysis of 2-substituted 4-hydroxypiperidines **47**.



47 **48** **49** **50**

R = Me, ^{i}Pr, CO_2H

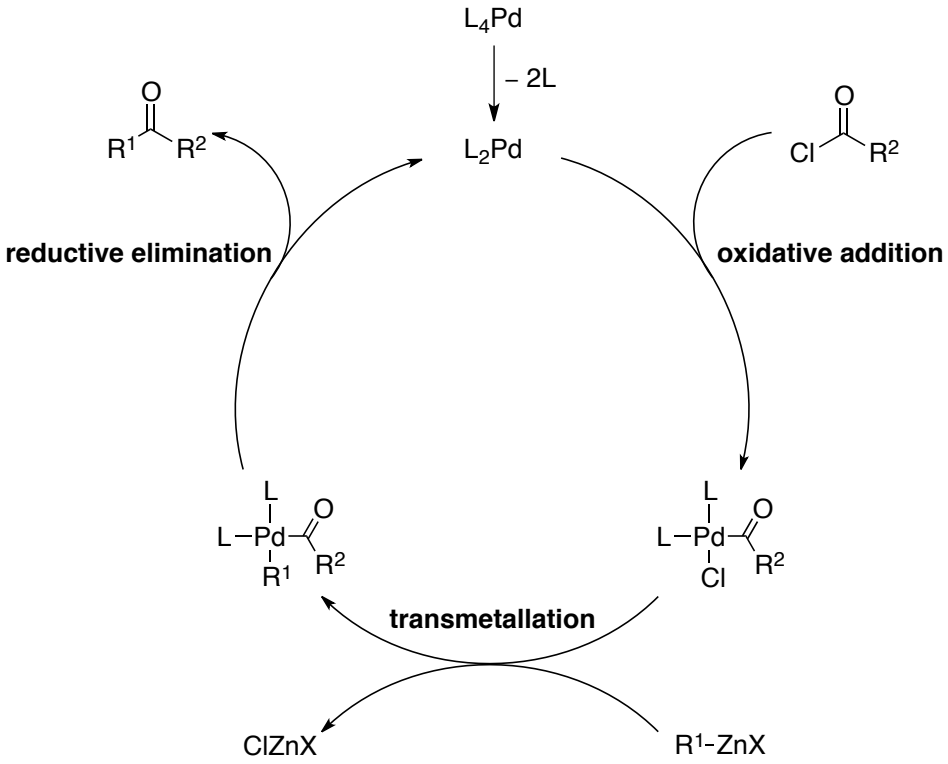
1.4 Organozinc Reagents

1.4.1 Reaction of Organozinc Reagents with Acid Chlorides

The key step in the retrosynthetic analyses of 2-substituted 4-hydroxypiperidines **47** is the palladium-catalysed Negishi cross coupling reaction of an organozinc reagent with a suitable acid chloride (see Scheme 28, p30).

There are three key steps in the (simplified) catalytic cycle for the Negishi cross coupling reaction of an organozinc reagent with an acid chloride (Figure 24).[43] The first step is the oxidative addition of the active catalyst, a fourteen electron *bis*-ligated palladium(0) species, to the acid chloride. This is followed by transmetallation of the R^1 group from the zinc to the palladium. Finally, reductive elimination occurs to yield the cross coupled product, reforming the active catalyst.

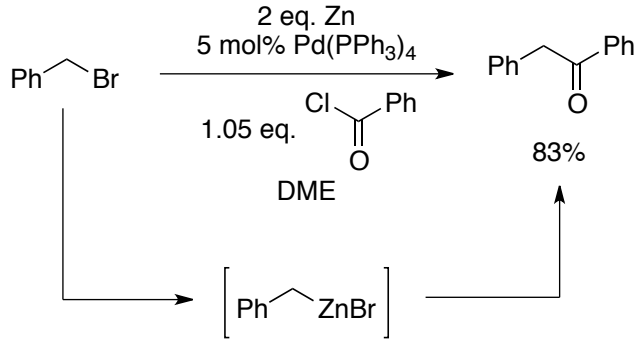
Figure 24. Simplified catalytic cycle for the Negishi cross coupling reaction of an organozinc reagent with an acid chloride.



The first example of a reaction between an organozinc reagent and an acid chloride was reported by Freund in 1861.[44-45] He reacted diethylzinc and dimethylzinc with simple acid chlorides and observed the formation of the corresponding ketones.

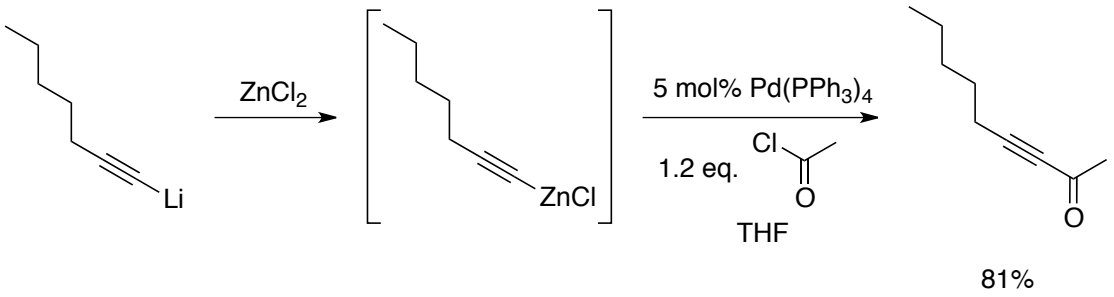
In 1981, Fujisawa and co-workers discovered that benzyl bromide could be reductively coupled with acid chlorides in the presence of two equivalents of zinc and a sub-stoichiometric amount of a palladium phosphine catalyst.[46] They suggested that the benzyl organozinc reagent was being formed *in situ* before reacting with the acid chloride, with the palladium species acting as a catalyst for the reaction (Scheme 29).

Scheme 29. Reductive coupling of benzyl bromide and benzoyl chloride in the presence of zinc and $Pd(PPh_3)_4$.

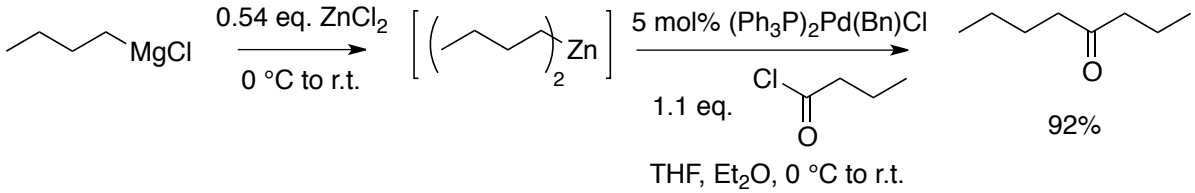


This discovery of palladium phosphine complexes as good catalysts for the acylation of organozinc reagents was supplemented by work published independently by Negishi and co-workers in 1983,[47] and Grey in 1984.[48] An example of a reaction reported by each of the authors is shown below (Scheme 30 and Scheme 31).

Scheme 30. An example from the work of Negishi and co-workers showing the use of a palladium catalyst for the acylation of an alkynyl organozinc reagent.

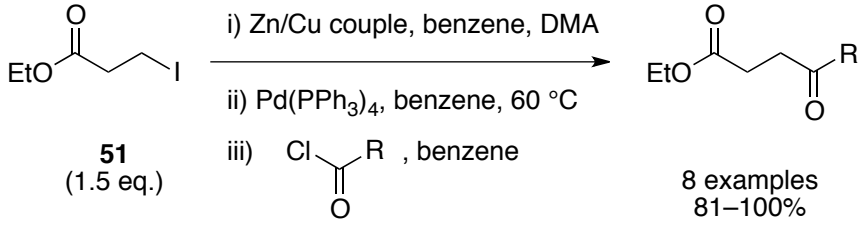


Scheme 31. An example from the work of Grey showing the use of a palladium catalyst for the acylation of an alkyl organozinc reagent.



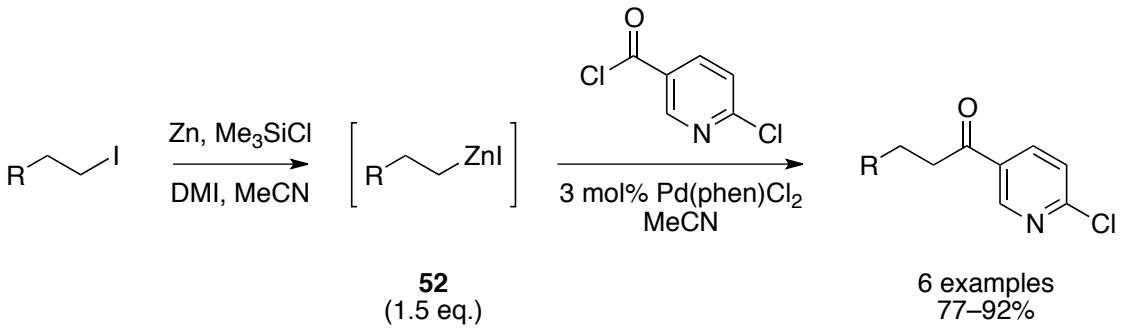
The Negishi cross coupling reaction of organozinc reagents with acid chlorides has been used by a number of researchers to construct ketones.[43] An example of this is seen in the reaction of the zinc homoenolate derived from iodide **51** with a number of acid chlorides, reported by Yoshida and co-workers (Scheme 32).[49]

Scheme 32. The Negishi cross coupling reaction of zinc homoenolate derived from iodide **51** with a variety of acid chlorides.



A more recent example was published by Iwai, Ohno and co-workers, who used the Negishi cross coupling reaction to synthesise pyridyl ketones (Scheme 33).[50]

Scheme 33. Synthesis of pyridyl ketones using the Negishi cross coupling reaction of various organozinc reagents **52**.

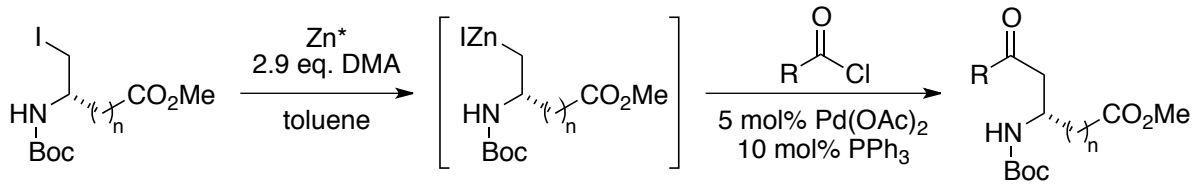


1.4.2 Amino Acid Derived Organozinc Reagents

1.4.2.1 Negishi Cross Coupling Reactions with Acid Chlorides

Jackson and co-workers have also used the reactivity of organozinc reagents towards acid chlorides to construct ketones. Specifically, they have synthesised a variety of oxygenated α-, β- and γ-amino acids using amino acid derived organozinc reagents.[51-54] For example, L-aspartic acid and L-glutamic acid derived organozinc reagents **53a** and **54** were cross coupled with various acid chlorides to yield 5-oxo-3-amino acids **55** and 6-oxo-4-amino acids **56** (Scheme 34) in moderate yields (Table 1).[51] The presence of DMA was necessary to stabilise the organozinc reagent. Although DMF is the usual solvent of choice for these reactions, it was not a suitable solvent in this case, as it is known to react with acid chlorides.

Scheme 34. Synthesis of 5-oxo-3-amino acids and 6-oxo-4-amino acids via the Negishi cross coupling reactions of L-aspartic acid and L-glutamic acid derived organozinc reagents **53a** and **54** with various acid chlorides.



n = 1, **53a**
n = 2, **54**

n = 1, **55**
n = 2, **56**

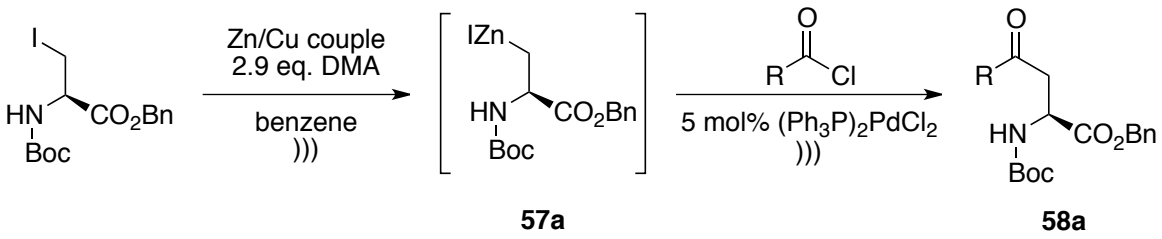
Zn* = zinc activated by treatment with Me_3SiCl

Table 1. Yields for the Negishi cross coupling reaction of L-aspartic acid and L-glutamic acid derived organozinc reagents **53a** and **54** with various acid chlorides.

Entry	R	Yield of compound **55** (%)	Yield of compound **56** (%)
1	Ph	59	51
2	CH_2=CH	46	48
3	$AcOCH_2$	49	52
4	$CH_3(CH_2)_4$	20	–
5	2-Furyl	51	45

Similarly, L-serine derived organozinc reagent **57a** was cross coupled with a number of acid chlorides to give 4-oxo-2-amino acids **58a** (Scheme 35) in moderate to good yields (Table 2).[52-53]

Scheme 35. Synthesis of 4-oxo-2-amino acids via the Negishi cross coupling reaction of L-serine derived organozinc reagent **57a** with various acid chlorides.



57a **58a**

Table 2. Yields for the Negishi cross coupling reaction of L-serine derived organozinc reagent **57a** with various acid chlorides.

Entry	R	Yield of compound **58a** (%)
1	Ph	70
2	2-Furyl	90
3	Me	80
4	Et	83
5	$^{i}PrCH_2$	76
6	$^{t}BuCH_2$	84
7	Bn	41
8	*trans*-PhCH=CH	72
9	4-MeO-C_6H_4	43
10	4-AcO-C_6H_4	63
11	$ClCH_2$	39[a]
12	$AcOCH_2$	64
13	$PhthNCH_2$	53
14	CH_2=CH	58[b]

[a] Reaction stirred without sonication.

[b] 1.5 eq. HMPA used in place of DMA.[55]

The differently protected L-serine derived organozinc reagent **57b** was also cross coupled with various acid chlorides under similar conditions (Scheme 36 and Table 3).[54]

Scheme 36. Synthesis of 4-oxo-2-amino acids **58b** via the Negishi cross coupling reaction of L-serine derived organozinc reagent **57b** with various acid chlorides.

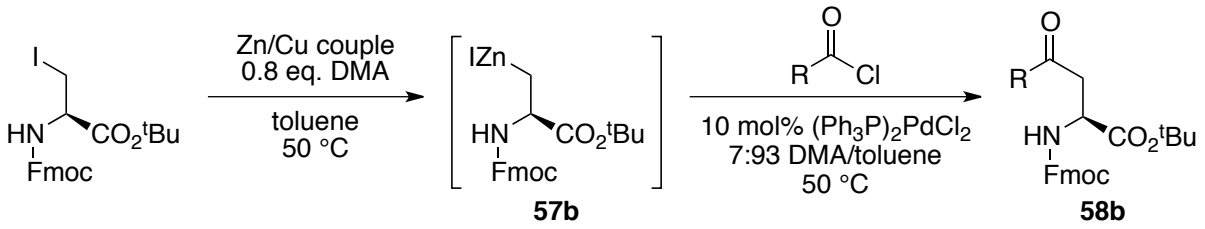
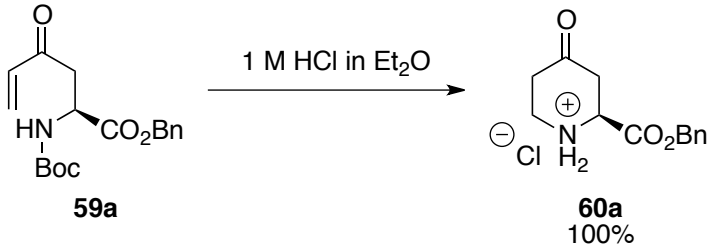


Table 3. Yields for the Negishi cross coupling reaction of L-serine derived organozinc reagent **57b** with various acid chlorides.

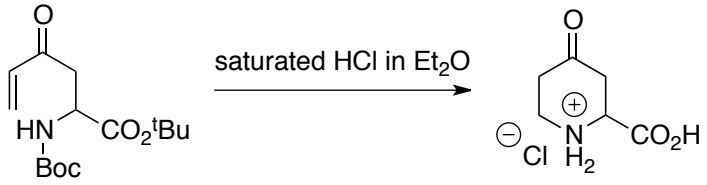
Entry	R	Yield of compound **58b** (%)
1	$AcOCH_2$	47
2	Et	47
3	(*S*)-*N*-Trifluoroacetylpyrrolidin-2-yl	46
4	$PhthNCH_2$	43
5	CH_2=CH	42

Of particular interest are the cross coupling reactions of L-serine derived organozinc reagents **57** with acryloyl chloride (Table 2, entry 14 and Table 3, entry 5), as these provide access to amino enones. Subsequent treatment of amino enone **59a** with 1 M hydrogen chloride in Et_2O was reported by Jackson and co-workers to give benzyl 4-oxopipecolate **60a** in a quantitative yield (Scheme 37).[52] This work was based on a very similar acidic cyclisation of the racemic amino acid **(±)-59b** carried out by Obrecht and co-workers, which was reported to give 4-oxo-pipecolic acid hydrochloride **(±)-60b** in similarly high yields (Scheme 38).[56-57] These reactions give a precedent for the proposed cyclisation of intermediates **49** to give 4-oxopiperidines **48**, shown earlier in the retrosynthetic analysis of 2-substituted 4-hydroxypiperidines **47** (see Scheme 28, p30).

Scheme 37. Previously reported acid mediated Boc deprotection and subsequent cyclisation of compound **59a** to give benzyl 4-oxopipecolate **60a**.



Scheme 38. Previously reported acid mediated Boc deprotection and subsequent cyclisation of compound **(±)-59b** to give 4-oxopipecolate **(±)-60b**.



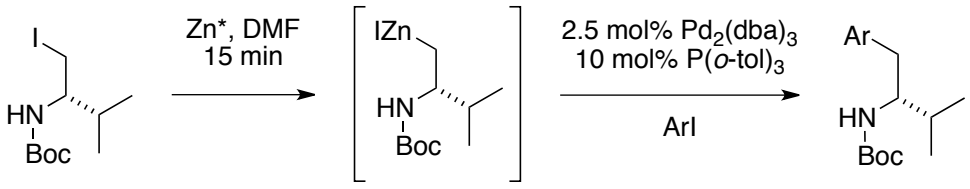
(±)-59b **(±)-60b**
99–100%

1.4.2.2 Negishi Cross Coupling Reactions with Aromatic Iodides

Other amino acid derived organozinc reagents have been synthesised in the literature, although their Negishi cross coupling reaction with acid chlorides has not been investigated. Instead, they have generally been used in the Negishi cross coupling reaction with aromatic halides to yield β-arylethylamine derivatives. This thesis is going to concentrate on the use of organozinc reagents derived from L-valine and L-alanine, as these are of particular interest to this project.

Jackson and co-workers have reported the palladium-catalysed Negishi cross coupling reaction of L-valine derived organozinc reagent **62a** in the synthesis of a range of β-phenylethylamine derivatives **63a** (Scheme 39) in moderate to good yields (Table 4).[58]

Scheme 39. The Negishi cross coupling reaction of L-valine derived organozinc reagent **62a** with various aromatic iodides.



61a **62a** **63a**

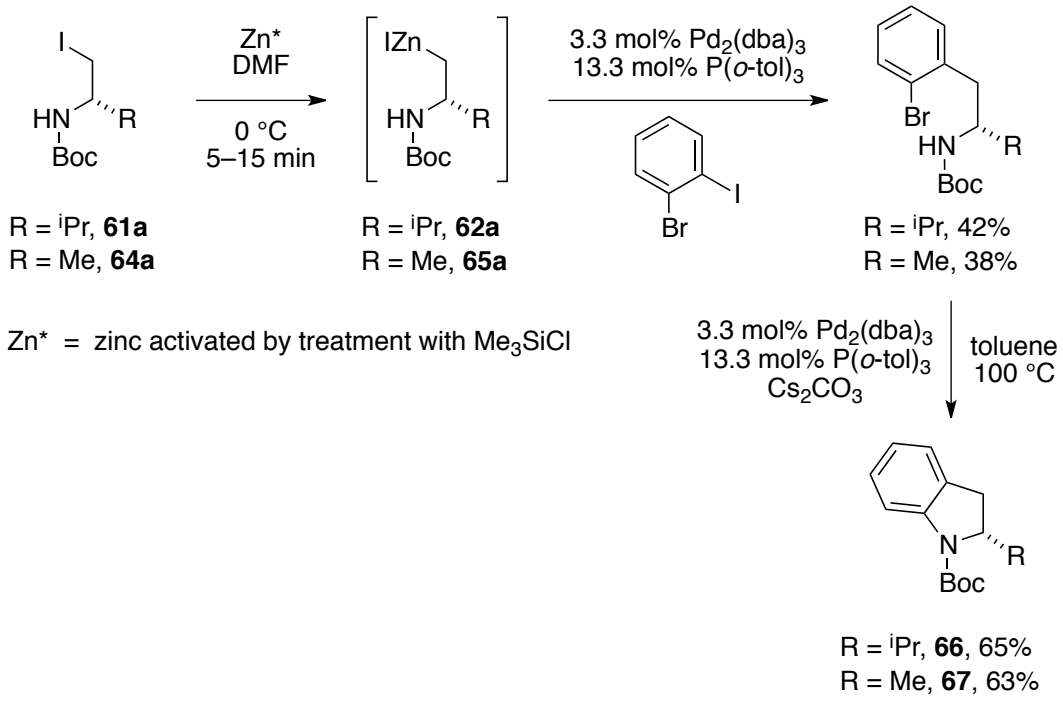
Zn* = zinc activated by sequential treatment with 1,2-dibromoethane and Me_3SiCl

Table 4. Yields for the Negishi cross coupling reaction of L-valine derived organozinc reagent **62a** with various aromatic iodides.

Entry	Ar	Yield of compound **63a** (%)
1	Ph	71
2	1-Naphthyl	63
3	4-NO_2-C_6H_4	79
4	4-MeO-C_6H_4	53

In a similar manner, Jackson and co-workers have used reported the Negishi cross coupling reactions of both organozinc reagent **62a** and L-alanine derived organozinc reagent **65a** with 2-bromoiodobenzene in the synthesis of enantiomerically pure 2-substituted *N*-Boc indolines **66** and **67** (Scheme 40).[59] In these reactions the zinc insertion step was conducted at 0 °C, due to the instability of organozinc reagents **62a** and **65a** (see Chapter 1.4.2.3, p40).

Scheme 40. Synthesis of 2-substituted *N*-Boc indolines **66** and **67** using the Negishi cross coupling reaction of organozinc reagents **62a** and **65a** with 2-bromoiodobenzene.



More recently, the synthesis of various β-phenylethylamine derivatives **63** has been revisited.[60] The synthesis of compounds **63a** had already been achieved by the reaction of *N*-Boc protected organozinc reagent **62a** with various aromatic iodides (see Scheme 39, p37 and Table 4 above).[58]

The corresponding *N*-TFA protected organozinc reagent **62b** was prepared by Jackson and co-workers and reacted with a variety of aromatic iodides to yield β-phenylethylamine derivatives **63b** (Scheme 41).[60] Moderate to good yields were obtained when using 5 mol% of the palladium catalyst (Table 5, Method A). In some cases it was found that a tenfold decrease in catalyst loading to 0.5 mol% still gave acceptable yields of product (Table 5, Method B).

Scheme 41. Synthesis of β-phenylethylamine derivatives **63b** using L-valine derived organozinc reagent **62b**.

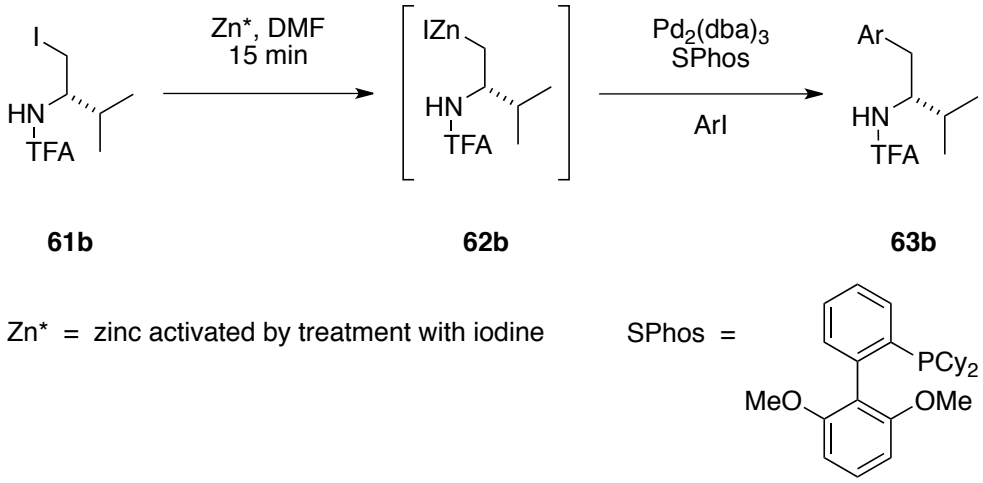


Table 5. Yields for the palladium-catalysed cross coupling reaction organozinc reagent **62b** with various aromatic iodides.

Entry	Ar	Yield of compound **63b** (%)	
		Method A[a]	Method B[b]
1	Ph	63	58
2	4-Me-C_6H_4	70	42
3	4-CO_2Me-C_6H_4	51	–
4	4-F-C_6H_4	61	60
5	4-MeO-C_6H_4	57	37
6	3-MeO-C_6H_4	74	–
7	2-MeO-C_6H_4	42	–

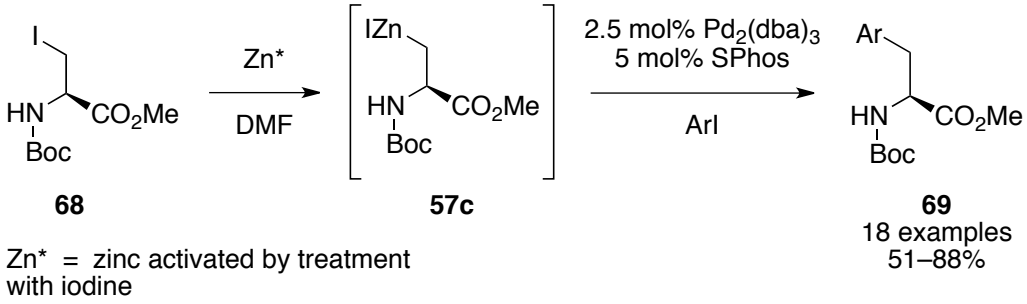
[a] 2.5 mol% $Pd_2(dba)_3$, 5 mol% SPhos

[b] 0.25 mol% $Pd_2(dba)_3$, 0.5 mol% SPhos

The major difference in reaction conditions used for these reactions was the improved catalyst system involving Buchwald's biaryl ligand SPhos,[61] which has recently been shown to be an excellent

ligand for the palladium-catalysed Negishi cross coupling reaction of aromatic halides with L-serine derived organozinc reagent **57c** (Scheme 42).[62] The TFA protecting group was chosen as a result of studies on the stability of various β-amino organozinc reagents (see Chapter 1.4.2.3, below). However, it was also noted that the iodide **61b** was more stable than its *N*-Boc protected analogue **61a**,[60] and that the yield for the iodination of *N*-TFA-L-valinol was higher than that of *N*-Boc-L-valinol (70% cf. 56%).[58,60]

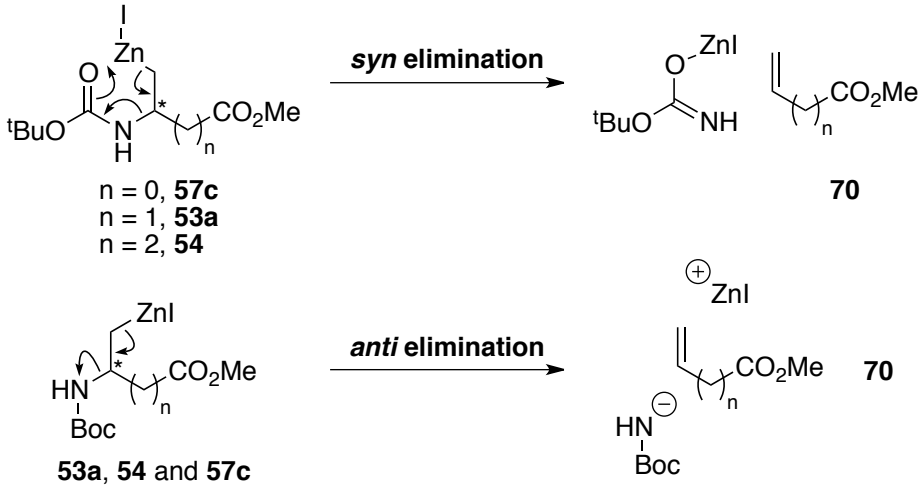
Scheme 42. Synthesis of phenylalanine derivatives **69** using a $Pd_2(dba)_3$/SPhos catalyst system.[62]



1.4.2.3 Stability of Organozinc Reagents

The stability of amino acid derived organozinc reagents **53a**, **54** and **57c** has been studied by Jackson and co-workers.[51,63-66] The main decomposition route for these compounds is β-elimination, which leads to the corresponding alkenes **70** (Scheme 43). Jackson and co-workers have proposed that this a *syn* elimination process, as opposed to the more commonly encountered *anti* elimination.

Scheme 43. Possible *syn* and *anti* β-eliminations of organozinc reagents **53a**, **54** and **57c** leading to alkenes **70**.



When ^{13}C NMR spectra were collected for organozinc reagents **53a**, **54** and **57c** in THF-d_8, a significant downfield shift was seen in the carbonyl peak of the carbamate group, when compared to the same peak in the starting iodides (Table 6).[63-64] This was taken as evidence of the coordination of the carbonyl oxygen to the electron deficient zinc atom, which sets up the molecule for a *syn* elimination. This downfield shift did not occur when the same zinc reagents were analysed in DMF-d_7, suggesting that DMF can disrupt this interaction by coordinating to the zinc atom itself. In fact, as more equivalents of DMF were added to organozinc reagent **57c** in THF-d_8, the downfield shift was seen to decrease (Table 7).[51]

Table 6. Change in the ^{13}C NMR chemical shift of the carbamate carbonyl group of organozinc reagents **53a**, **54** and **57c**, upon zinc insertion in THF-d_8 and DMF-d_7.

Entry	Organozinc Reagent	Δδ carbamate / ppm[a]	
		THF-d_8	DMF-d_7
1	**57c**	+2.711	−0.868
2	**53a**	+3.747	−0.535
3	**54**	+3.923	−0.687

[a] The reference was taken as the chemical shift of the carbamate carbonyl in the starting iodides.

Table 7. Change in the ^{13}C NMR chemical shift of the carbamate carbonyl group of organozinc reagent **57c** in THF-d_8, upon titration with DMF.

Entry	Eq. of DMF	Δδ carbamate / ppm[a]
1	0	+2.711
2	0.5	+2.180
3	1	+1.785
4	2	+1.045
5	4	+0.526

[a] The reference was taken as the chemical shift of the carbamate carbonyl in the starting iodide **68**.

These proposals are supported by kinetic data, which showed that organozinc reagent **53a** decomposed with a rate constant of 0.26×10^{-4} s^{-1} in DMF at 298 K, approximately four times slower than in THF, when the rate constant was 1.02×10^{-4} s^{-1}.[51] These decompositions were found to be first order. Further evidence for a *syn* elimination came from analysis of the kinetic activation parameters of organozinc reagent **53a**. The entropy of activation $\Delta S^{\ddagger}$ was found to be negative in

both THF and DMF. In the transition state of an *anti* elimination, three molecules would be forming from one single molecule of organozinc reagent, anticipating a positive value of $\Delta S^{\ddagger}$ (see Scheme 43, p40). However, in order for a *syn* elimination to occur, the molecule first has to organise itself into the required cyclic transition state. The observed negative $\Delta S^{\ddagger}$ values are therefore better explained by a *syn* elimination process, with its highly ordered transition state.

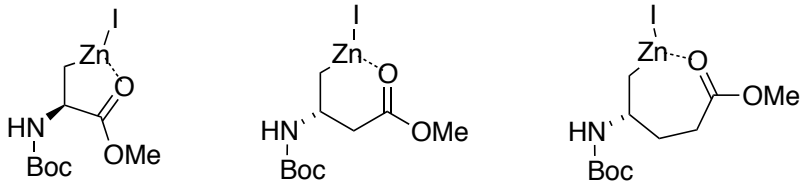
Jackson and co-workers also observed that the carbonyl of the ester in organozinc reagents **53a**, **54** and **57c** was able to coordinate to the zinc atom, in both THF and DMF, as judged by a downfield shift in the ^{13}C NMR spectra (Table 8).[63-64] The ester coordination depended on the proximity of the ester to the zinc atom, as different ring sizes were formed in each case. Serine derived zinc reagent **57c** showed the largest downfield shift, and forms a five membered ring upon coordination of the ester to the zinc atom (Figure 25). Aspartic acid derived zinc reagent **53a** had a lower downfield shift in the NMR spectrum, and forms a six membered ring. Finally the seven membered ring that forms in the case of glutamic derived zinc reagent **54** correlates to the very small downfield shift observed. This ester coordination has been proposed to compete with carbamate coordination, and has been used to explain the observed order of stability for these three compounds, with organozinc reagent **57c** being the most stable to β-elimination, and organozinc reagent **54** being the least stable.

Table 8. Change in the ^{13}C NMR chemical shift of the ester carbonyl group of organozinc reagents **53a**, **54** and **57c**, upon zinc insertion in THF-d_8 and DMF-d_7.

Entry	Organozinc Reagent	Δδ ester / ppm[a]	
		THF-d_8	DMF-d_7
1	**57c**	+5.347	+5.786
2	**53a**	+1.464	+0.872
3	**54**	+0.675	+0.115

[a] The reference was taken as the chemical shift of the ester carbonyl in the starting iodides.

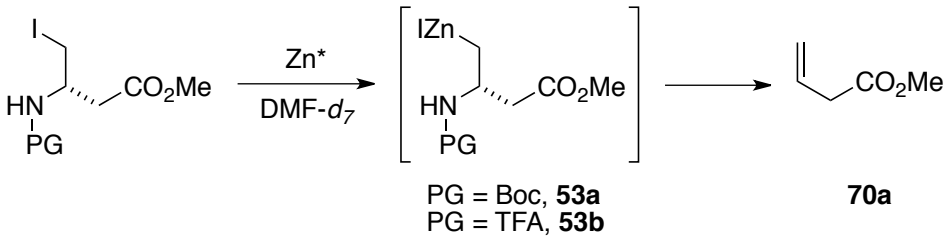
Figure 25. Different ring sizes formed upon coordination of the ester carbonyl to the zinc atom in organozinc reagents **53a**, **54** and **57c**.



57c **53a** **54**

Given that the interaction between the carbonyl of the Boc group and the zinc atom seemed to be key in the β-elimination process, Jackson and co-workers investigated the effect of choosing a protecting group with a less coordinating carbonyl group, namely the trifluoroacetyl group. *N*-TFA protected organozinc reagent **53b** was synthesised, and its decomposition was studied and compared to that of its *N*-Boc protected analogue **53a** (Scheme 44).[65-66]

Scheme 44. Major product of the decomposition of organozinc reagents **53a** and **53b** in DMF-d_7.



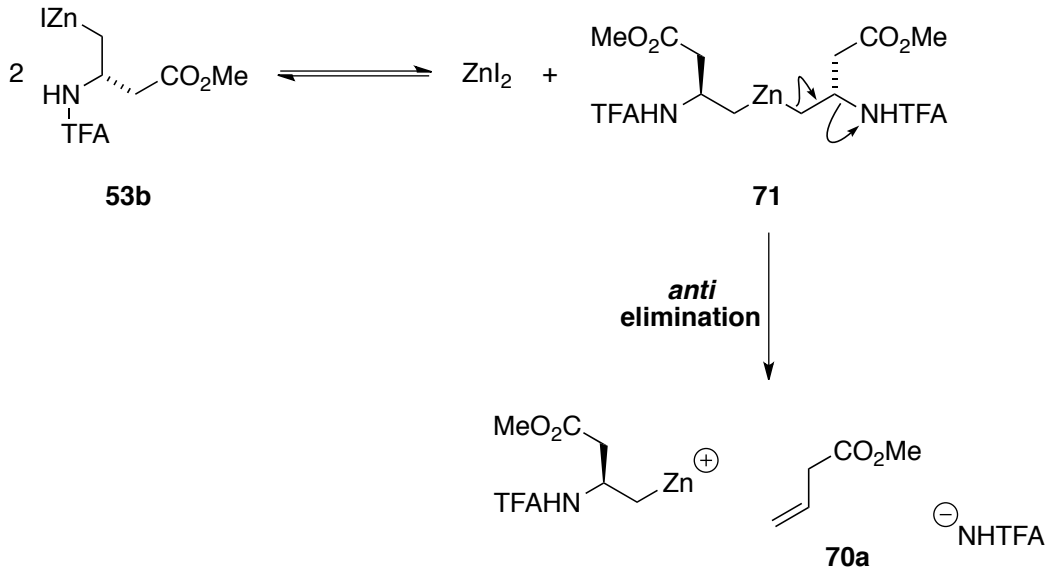
PG = Boc, **53a**
PG = TFA, **53b**

70a

Zn* = zinc activated by treatment with Me_3SiCl

The major product of each decomposition pathway was methyl but-3-enoate **70a**. The rate constant for the first-order elimination of organozinc reagent **53a** was found to be 9.0×10^{-6} s^{-1}.[66] This is smaller than the previously determined value (see p41), a difference taken to be due to a change in the zinc activation procedure. ^{1}H NMR analysis of compound **53b** showed that it decomposed by a second-order β-elimination process, with a rate constant of $2.8 \pm 0.5 \times 10^{-6}$ M^{-1} s^{-1}, more than three times slower than the elimination of compound **53a**. Jackson and co-workers suggested that the electron-withdrawing trifluoromethyl group reduces the coordination of the carbonyl of the protecting group to the zinc atom, which in turn suppresses the *syn* elimination that is observed for the corresponding *N*-Boc protected organozinc reagent **53a**. Instead, they proposed that a Schlenk pre-equilibrium forms between two molecules of organozinc iodide **53b** and one molecule of diorganozinc reagent **71**, which then undergoes an *anti* elimination (Scheme 45). Although in theory organozinc reagent **53b** itself can undergo an *anti* elimination, it was suggested that this would be disfavoured, because the electron density in the carbon-zinc bond would be reduced by the electron-withdrawing iodide attached to the zinc. However, *anti* elimination of diorganozinc reagent **71** would be favoured, as there is no longer an electron-withdrawing group attached to the zinc atom. This mechanism accounts for the observed second order nature of the elimination, as the concentration of diorganozinc reagent **71** formed in the Schlenk pre-equilibrium depends on the square of the concentration of organozinc iodide **53b**.

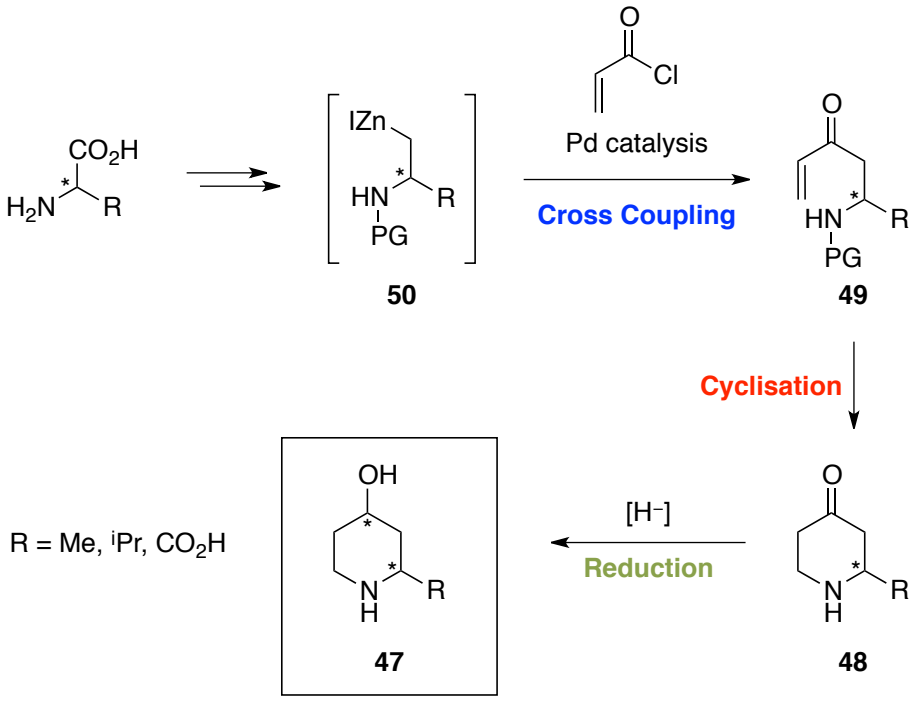
Scheme 45. Proposed mechanism for the second-order elimination of organozinc reagent **53b**.



1.5 Project Aims

This project aims to develop a synthetic route to various small, enantiomerically pure 2-substituted 4-hydroxypiperdines **47** (Scheme 46). The key step will be the palladium-catalysed Negishi cross coupling reaction of an amino acid derived organozinc reagent **50** with a suitable acid chloride. The stereochemistry in the final products will be controlled through the choice of chiral starting materials and a final diastereoselective reduction.

Scheme 46. Proposed synthesis of 2-substituted 4-hydroxypiperidines **47**.

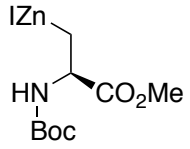


2. Results and Discussion

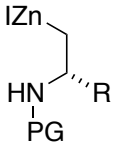
2.1 Synthesis of Amino Acid Derived Iodides

The key intermediates required for the proposed synthesis of various 2-substituted 4-hydroxypiperidines (see Scheme 46, p45) are the amino acid derived organozinc reagents **57c**, **62a**, **62b**, **65a** and **65b** (Figure 26). In order to access these compounds, the corresponding iodides **61a**, **61b**, **64a**, **64b** and **68** needed to be synthesised from the appropriate α-amino acids.

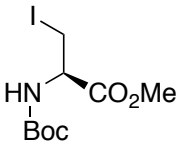
Figure 26. Key amino acid derived organozinc intermediates **57c**, **62a**, **62b**, **65a** and **65b** and the corresponding iodides **61a**, **61b**, **64a**, **64b** and **68**.



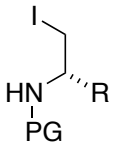
57c



PG = Boc, R = ^{i}Pr, **62a**
PG = TFA, R = ^{i}Pr, **62b**
PG = Boc, R = Me, **65a**
PG = TFA, R = Me, **65b**



68



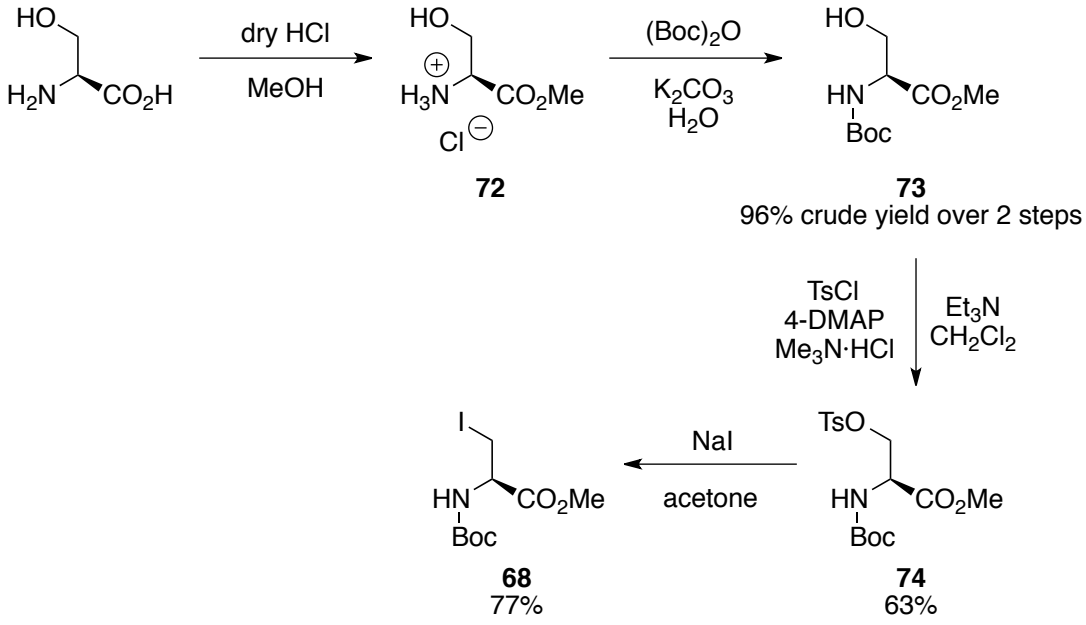
PG = Boc, R = ^{i}Pr, **61a**
PG = TFA, R = ^{i}Pr, **61b**
PG = Boc, R = Me, **64a**
PG = TFA, R = Me, **64b**

All five iodide compounds had been previously synthesised,[58,60,67-69] and so these syntheses were repeated starting from the commercially available amino acids or amino alcohols.

2.1.1 L-Serine Derived Iodide

L-Serine was converted to its methyl ester hydrochloride salt **72** by treatment with methanolic hydrogen chloride, as reported by Dondoni and Perrone (Scheme 47).[70] Boc protection of compound **72** using $(Boc)_2O$ in water with K_2CO_3 as the base[71] gave *N*-Boc-L-serine methyl ester **73** in a 96% crude yield over two steps. Tosylation of alcohol **73**, followed by iodination of the resulting tosylate **74** were carried out using the method reported by Jackson and co-workers,[69] giving iodide **68** in a 47% overall yield from L-serine.

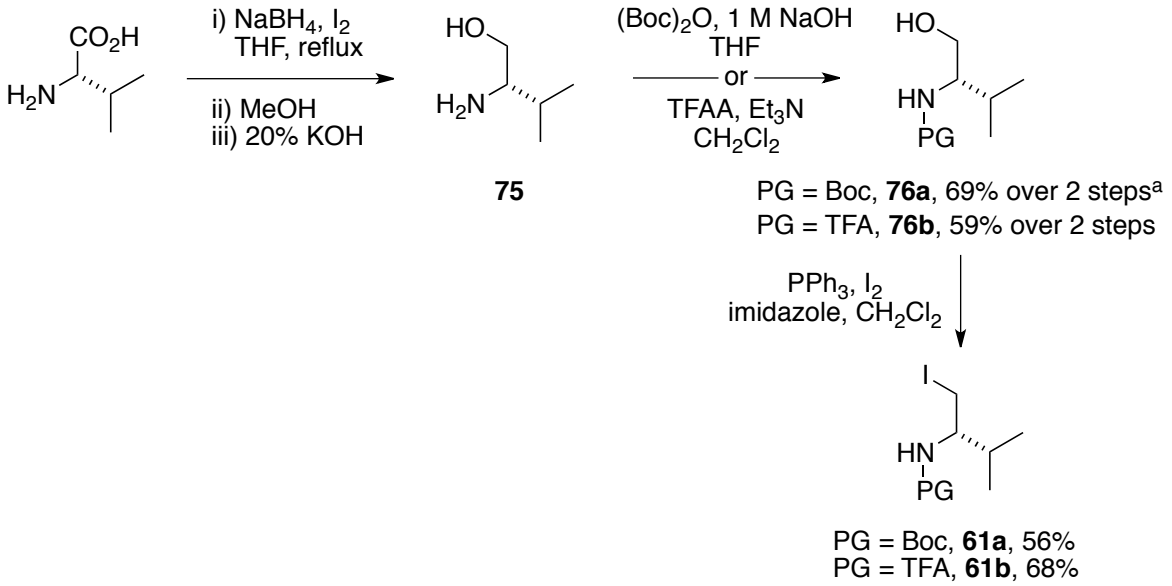
Scheme 47. Preparation of iodide **68** from L-serine.



2.1.2 L-Valine Derived Iodides

In order to access iodide **61a**, L-valine was first reduced with $NaBH_4/I_2$ to give L-valinol **75** (Scheme 48), using Meyers and co-workers' procedure.[72] The crude amino alcohol was Boc protected following the procedure described by Jackson and co-workers,[58] to yield *N*-Boc-L-valinol **76a** in 69% yield over the two steps. Finally, iodination of the alcohol using PPh_3/I_2/imidazole gave iodide **61a** in a 56% yield. Alternatively, crude L-valinol was TFA protected using trifluoroacetic anhydride, according to the procedure recently reported by Jackson and co-workers.[60] This gave *N*-TFA-L-valinol **76b** in a 59% yield over two steps (TFA protection of commercially available L-valinol gave compound **76b** in an 80% yield). Iodination of alcohol **76b** using I_2/PPh_3/imidazole[60] gave iodide **61b** in a 68% yield.

Scheme 48. Synthesis of iodides **61a** and **61b** from L-valine.



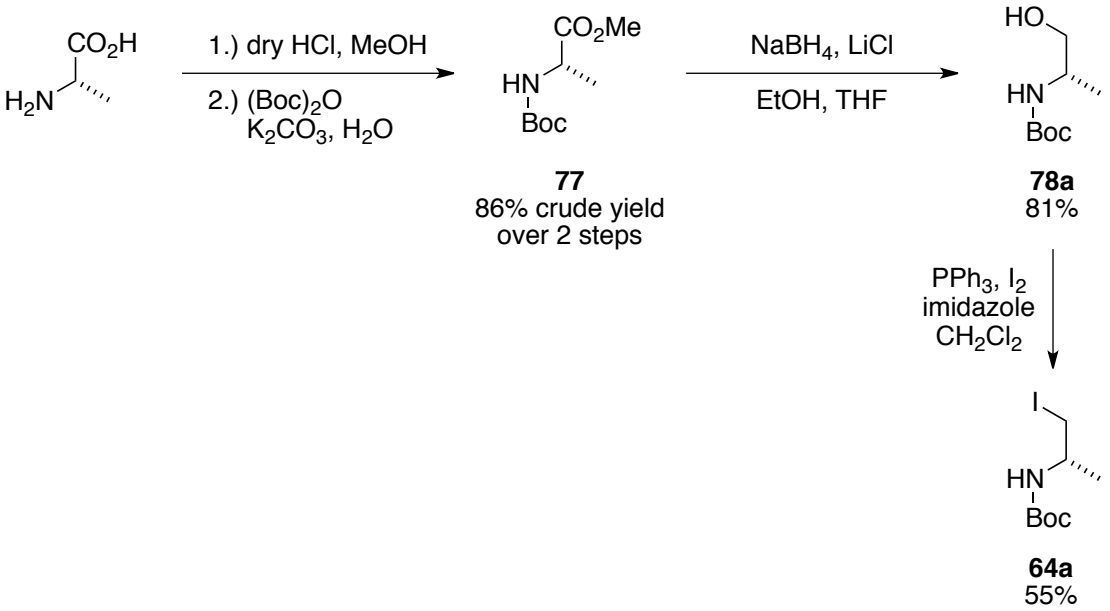
[a] Yield calculated from ^{1}H NMR spectrum due to the presence of $(Boc)_2O$.

2.1.3 L-Alanine Derived Iodides

The L-alanine derived *N*-Boc protected iodide **64a** proved to be more challenging to synthesise than its L-valine derived counterpart **61a**, due to low yields for the reduction of L-alanine. Although the literature reports that $NaBH_4/I_2$ can be used to reduce this amino acid, with yields varying from 60 to ≥88%,[73-77] this reaction proved difficult to repeat. The yield of the reduction was somewhat improved by changing the reducing agent to $LiAlH_4$, following the procedure set out by Hegedus and Hsiao,[78] but was still lower than the yields reported in the literature. One possible reason that the yields achieved for the reduction of L-alanine were lower than those reported is the high water solubility of the product L-alaninol, which may make its isolation during an aqueous workup difficult.

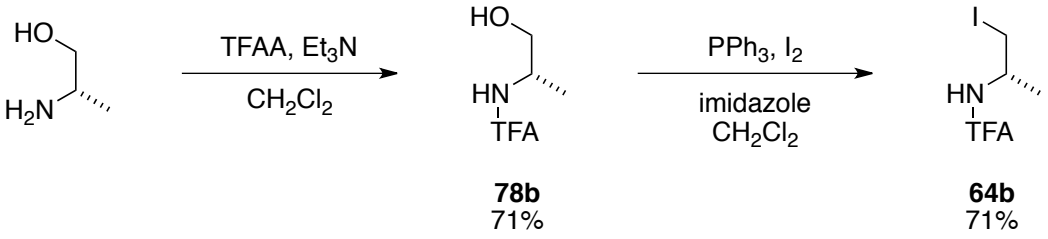
As a result of the low yields achieved for the reduction of L-alanine, it was decided to adapt the synthetic strategy. Accordingly, the carboxylic acid group in L-alanine was protected as a methyl ester, followed by Boc protection of the amine group to give *N*-Boc-L-alanine methyl ester **77** in an 86% crude yield (Scheme 49). The ester in compound **77** was then reduced using $LiBH_4$, which was formed *in situ* from $NaBH_4$ and LiCl, as reported by Shioiri and co-workers.[79] The reduction proceeded to give *N*-Boc-L-alaninol **78a** in a yield of 81%. The iodination of alcohol **78a** was then carried out using I_2/PPh_3/imidazole, as previously reported by Jackson and co-workers.[67] The product **64a** was isolated in a 55% yield.

Scheme 49. Synthesis of iodide **64a** from L-alanine via the reduction of *N*-Boc-L-alanine methyl ester **77**.



In order to synthesise TFA protected iodide **64b** it was decided to purchase the amino alcohol directly, as the protecting group would not be compatible with a $LiBH_4$ reduction. Therefore L-alaninol was TFA protected using a modified version of Kihlberg and co-workers' procedure,[68] which yielded the protected alcohol **78b** in a 71% yield (Scheme 50). This compound was iodinated using I_2/PPh_3/imidazole to produce iodide **64b** in a 71% yield.

Scheme 50. Synthesis of iodide **64b** from L-alaninol.



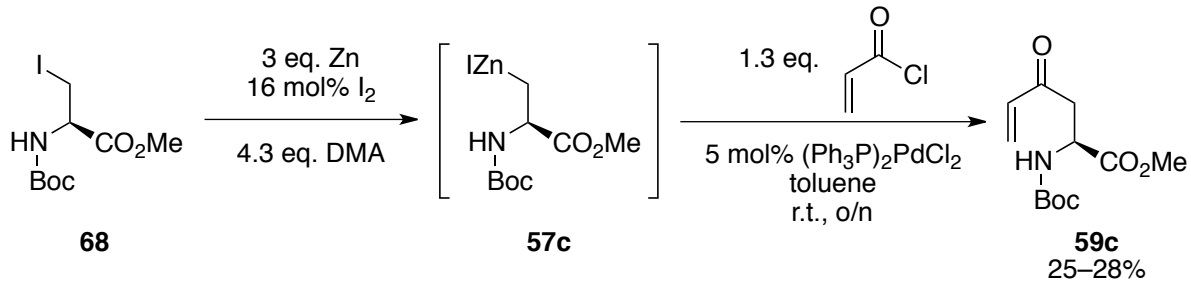
2.2 Formation of Organozinc Reagents and Cross Coupling Reactions

With iodides **61a**, **61b**, **64a**, **64b** and **68** in hand, attention was turned to the key palladium-catalysed Negishi cross coupling reaction of the corresponding organozinc reagents **57c**, **62a**, **62b**, **65a** and **65b** with acryloyl chloride.

2.2.1 Reaction Optimisation

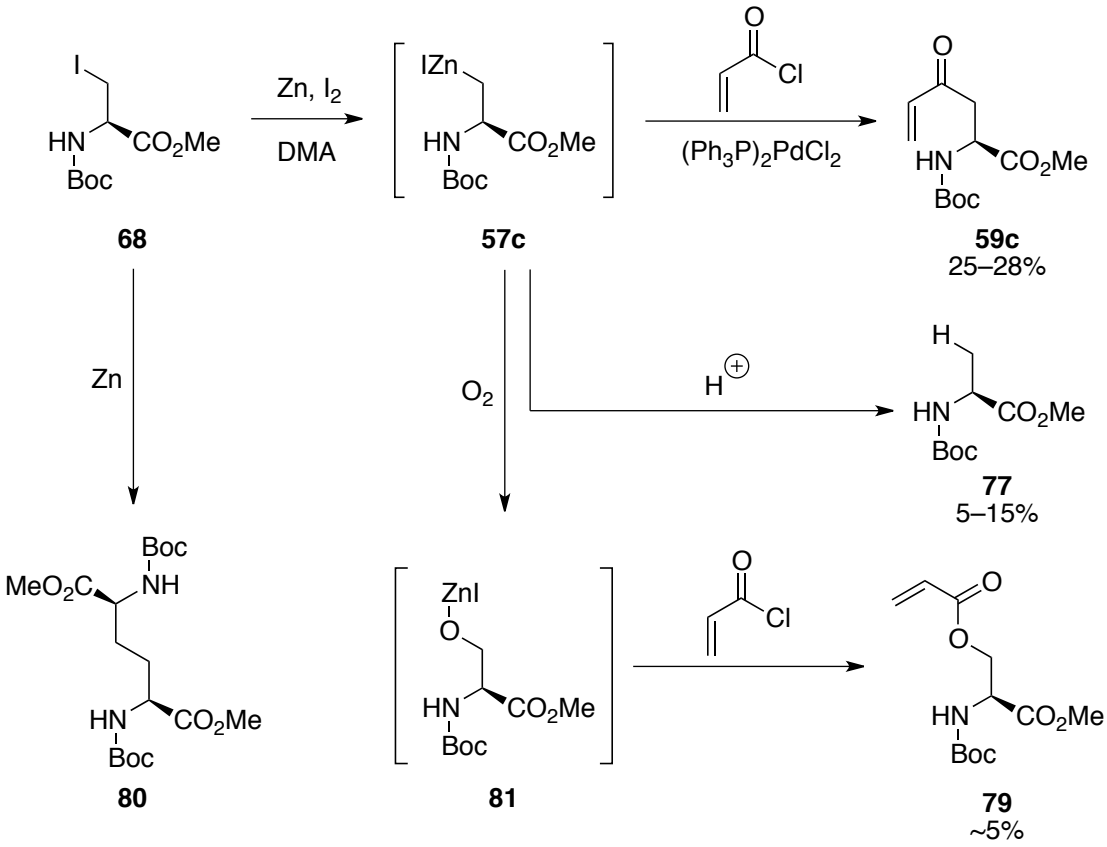
Optimisation was initially carried out on the reaction between L-serine derived organozinc reagent **57c** and acryloyl chloride (Scheme 51). Although previous cross coupling reactions with acid chlorides carried out in the Jackson group used a zinc/copper couple or zinc activated with trimethylsilyl chloride to form the organozinc reagent,[51-54] it was initially decided to use zinc activated with iodine. This method of zinc activation was developed by Huo,[80] and recently Jackson and co-workers have shown it to be successful in forming α-amino acid derived organozinc reagents.[60,62] DMA was the polar aprotic solvent chosen to stabilise the organozinc reagent, in combination with toluene as a co-solvent, as previously used within the Jackson group.[51,54] Just over four equivalents of DMA were used, because ^{1}H NMR studies of organozinc reagent **57c** in DMF/THF suggested that four equivalents was the minimum amount of a polar aprotic solvent needed to stabilise the organozinc reagent.[51] $(Ph_3P)_2PdCl_2$ was chosen as the catalyst for this reaction, as it has previously been shown to be an effective catalyst for the Negishi cross coupling reaction of α-amino acid derived organozinc reagents with acid chlorides.[53-54]

Scheme 51. Initial conditions for the reaction of organozinc reagent **57c** with acryloyl chloride.



Initial attempts to perform this reaction gave the product **59c** in a 25-28% yield (Scheme 51). As well as the desired product, a number of by-products were also observed, which have been identified as compounds **77**, **79** and **80** (Scheme 52).

Scheme 52. By-products formed in the reaction of organozinc reagent **57c** with acryloyl chloride, and probable routes to their formation.



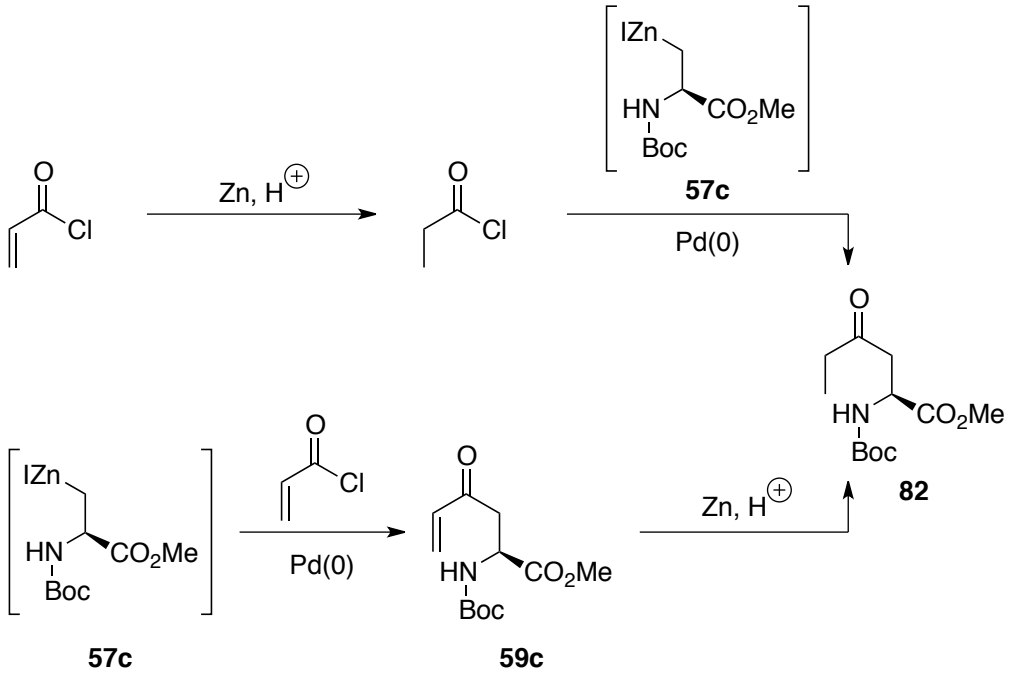
Protonation of organozinc reagents is a well-known side reaction, and it was unsurprising to see the protonated product **77** as a by-product. However, the observation of the ester **79** was more unusual. The most likely explanation for the formation of this compound is that small amounts of oxygen present in the reaction were able to oxidise the organozinc reagent to form the zinc alkoxide **81**, which then reacted with acryloyl chloride to form ester **79**. The presence of this compound shows that the initial conditions for the cross coupling reaction were not optimum as a result of oxygen in the reaction, which may have entered the system either while the solid reagents were being added to the reaction, or as an impurity in the nitrogen supply.

Another minor by-product seen by ^{1}H NMR was compound **80**. This compound is a dimer of the starting iodide **68**, and has been previously observed within the Jackson group during the Negishi reaction of organozinc reagent **57c** with aromatic halides.[81] It is not yet conclusively known how this product forms, although one possibility is that the zinc mediates a Wurtz-type coupling between two molecules of the alkyl iodide **68**. Examples of this type of reaction are known in the literature.[82-84]

As seen from the combined yield of product, protonated product and oxidised product (Scheme 52), the initial mass balance for this reaction was low, at less than 50%. Even considering that some of iodide **68** has undergone dimerisation to form compound **80**, a significant amount of the organozinc reagent remained unaccounted for. Although later reaction optimisation improved the mass balance, the disappearance of the organozinc reagent remained a problem when trying to understand what was occurring in the reaction mixture.

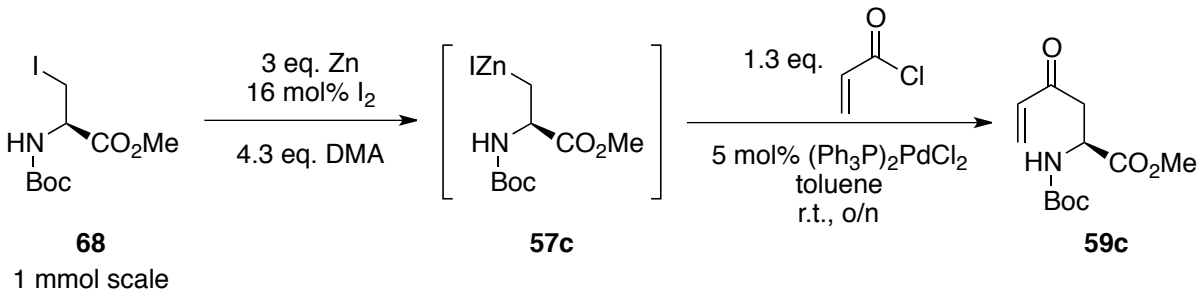
One further by-product that was identified from this reaction was compound **82** (Scheme 53). This compound must have arisen from the reduction of an alkene: either in the acid chloride prior to it reacting with the organozinc reagent, or in the product **59c** after a successful cross coupling reaction had occurred. This reduction may have been mediated by zinc and a small amount of acid, which would have formed if any of the acid chloride were hydrolysed by water present in the reaction mixture or during the aqueous workup. The formation of by-product **82** was minimised by removing the organozinc reagent from the excess zinc dust after the zinc insertion had occurred, and performing the cross coupling reaction in a second flask.

Scheme 53. Possible routes to by-product **82**.



Next, a number of the reaction conditions were changed in an attempt to increase the yield of product **59c** (Scheme 54 and Table 9). However, most of these variations failed to improve the yield of the desired product.

Scheme 54. Initial conditions for the reaction of organozinc reagent **59c** with acryloyl chloride.



68
1 mmol scale

57c

59c

Table 9. Variables changed in an attempt to increase the yield of cross coupled product **59c**.

Entry	Variable	Yield of compound 59c (%)
1	Zn activated with $BrCH_2CH_2Br/Me_3SiCl$ in DMA/toluene.	27
2	3 eq. acid chloride were used.	25
3	The reaction was run at 50 °C after the zinc insertion.	25
4	1.8 eq. of LiCl were added after the zinc insertion.	29
5	**Initial reaction conditions performed on a 3 mmol scale.**	**38**

Firstly, the zinc was activated with 1,2-dibromoethane and trimethylsilyl chloride instead of using iodine. However, this change in the zinc activation procedure failed to improve the yield of the product (Table 9, entry 1). The iodine activation method was used thereafter, as it was quicker and easier to perform.

It was thought that a possible side reaction could be the polymerisation of the acid chloride, since acryloyl residues are common monomers used in the production of polymers. In order to test this theory, the amount of acid chloride was increased from 1.3 to 3 equivalents (entry 2). However, this also failed to increase the yield of the product.

The previously reported reaction between the differently protected organozinc reagent **57b** and acryloyl chloride was conducted at 50 °C, rather than at room temperature (see Scheme 36 and Table 3, entry 5, p36).[52] However, increasing the temperature for the reaction of organozinc reagent **57c** with acryloyl chloride to 50 °C had no effect on the yield of the product (Table 9, entry 3).

One further attempt to optimise the yield involved the addition of 1.8 equivalents of LiCl to the reaction (entry 4). Organ and co-workers have shown that LiCl and other Lewis acid additives vastly

improve the yield of the Negishi cross coupling reaction between ^{n}BuZnBr and 3-bromo-1-phenylpropane.[85] They proposed that the role of the anion from the Lewis acid was to form higher order zincates, which were more reactive towards transmetallation than the corresponding organozinc halide.[85-86] Recent work within the Jackson group work has shown that these additives can be used to improve the yield of the Negishi cross coupling reaction between organozinc reagent **57c** and unreactive electrophiles, including some cycloalkenyl triflates[87] and 2-iodothiophene.[88] Even though acryloyl chloride is a very reactive electrophile, the addition of LiCl was investigated on one occasion. However, no significant improvement in yield was observed.

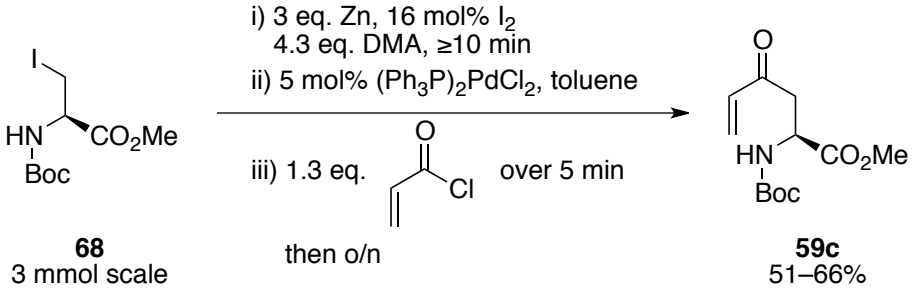
Pleasingly, increasing the scale of the reaction from 1 mmol to 3 mmol showed approximately a 10% improvement in the yield, resulting in 38% of the desired product **59c** (entry 5). One possible reason for this increase in yield is the aforementioned sensitivity of the organozinc reagent to water and oxygen impurities (see Scheme 52 and Scheme 53, p51). On a larger scale, the relative amount of any water or oxygen impurities compared to the amount of organozinc reagent present will be less, and therefore the amount of undesired by-products arising from these impurities will be reduced.

It was also discovered that the length of time allowed for the zinc insertion was important, and needed to be minimised. Careful monitoring of the zinc insertion to completion by TLC (≥10 min), followed by immediate addition of the remaining reagents to the same flask (i.e. no longer transferring the organozinc reagent away from the excess zinc) resulted in yields of the product ranging from 36 to 49%.

Finally, it was noted that the addition of the acid chloride caused an exotherm to occur. It was thought that an increase in temperature might cause degradation of the sensitive organozinc reagent, and so precautions were taken: the reaction flask was placed in a water bath before the acid chloride was added, and the acid chloride was added slowly over a period of 5 minutes.

All of these adaptations taken together make up the optimised conditions for the reaction of organozinc reagent **57c** with acryloyl chloride, which have reproducibly given yields of the desired product **59c** between 51 and 66% on a 3 mmol scale (Scheme 55). Scaling up the reaction to a 10 mmol scale gave yields of up to 53% of the product, although the consistency of the reaction yield dropped when the reaction was carried out on this larger scale (28–53% yield).

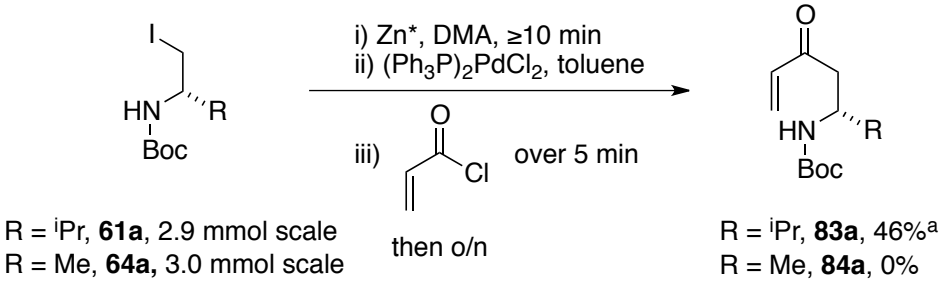
Scheme 55. Optimised conditions for the formation of compound **59c**.



2.2.2 *N*-Boc Protected Organozinc Reagents

With a set of optimised conditions in hand, attention was turned to the other Boc protected amino acid derived organozinc reagents of interest. The L-valine and L-alanine derived organozinc reagents **62a** and **65a** were reacted with acryloyl chloride under the optimised reaction conditions, namely performing the reaction on a 3 mmol scale, carefully monitoring the zinc insertion to completion by TLC and adding the acid chloride slowly with the reaction flask placed in a water bath (Scheme 56). It should be noted that the yields quoted for the cross coupling reactions reported from this point forward are the best yields achieved in each case; however, the efficiency of these reactions proved to be somewhat erratic, and a large variability in the yield of the desired products was generally observed.

Scheme 56. Application of the optimised cross coupling conditions to the reaction of acryloyl chloride with the L-valine and L-alanine derived organozinc reagents **62a** and **65a**, formed from iodides **61a** and **64a**.

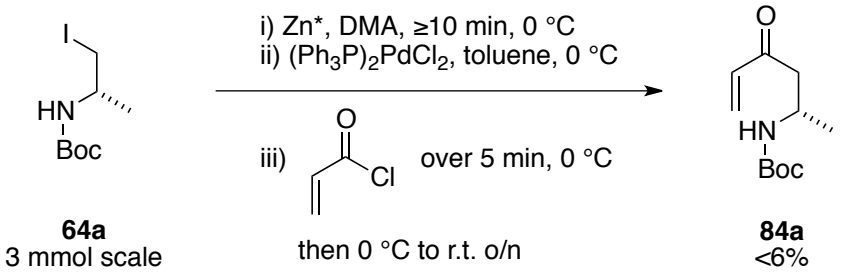


[a] Yield calculated from ^{1}H NMR spectrum due to presence of compound **85a** (see Figure 27, p57).

Pleasingly, for L-valine derived organozinc reagent **62a** the product **83a** was formed, albeit in a modest 46% yield. However, in the case of L-alanine derived organozinc reagent **65a**, no product

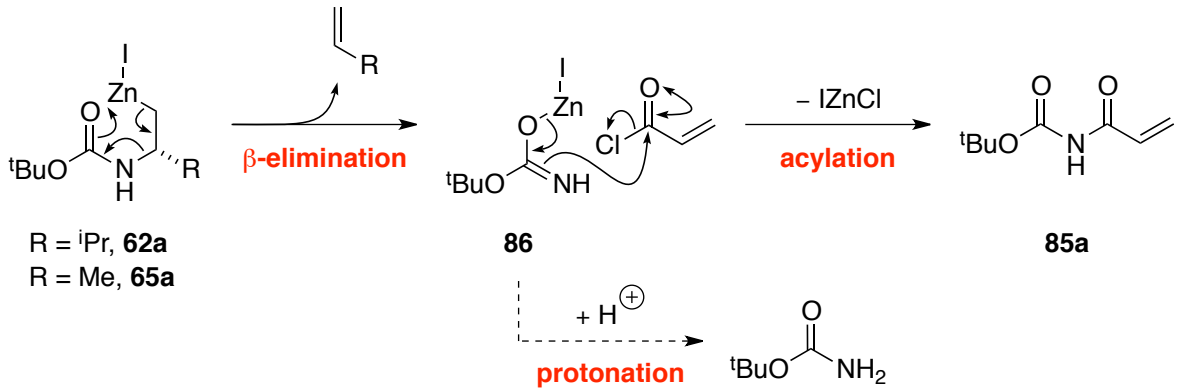
84a was observed. When organozinc reagent **65a** was previously synthesised, the zinc insertion was performed at 0 °C due to the instability of the organozinc reagent (see Scheme 40, p38).[59] For this reason, the reaction was repeated, with the formation of the organozinc reagent and the addition of the acid chloride being carried out at 0 °C, before the reaction was allowed to warm up to room temperature overnight (Scheme 57). ^{1}H NMR analysis of the crude reaction mixture showed that it consisted of an approximately 4:1 mixture of the iodide **64a** and the desired product **84a**, suggesting that the zinc insertion reaction had not gone to completion. ^{1}H NMR, ^{13}C NMR and MS analysis of the fractions collected after column chromatography confirmed the presence of the desired product, albeit in a very low yield (<6%).

Scheme 57. Adaptation of the optimised cross coupling conditions to the reaction of acryloyl chloride with organozinc reagent **65a**, formed from iodide **64a**.



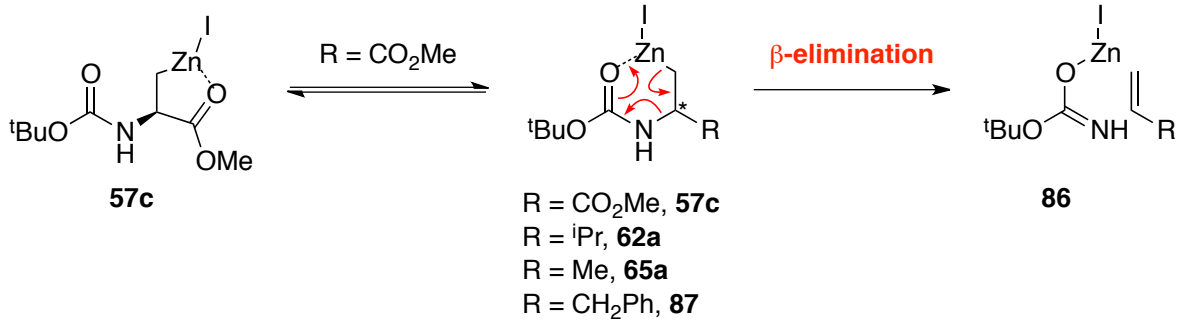
In both of the cross coupling reactions of *N*-Boc amino organozinc reagents **62a** and **65a**, an unexpected by-product **85a** was observed by ^{1}H NMR spectroscopy (Figure 27). A plausible mechanism for the formation of this by-product involves *syn* β-elimination of the organozinc reagents, initiated by an interaction between the carbonyl of the carbamate and the electron deficient zinc atom. This is known to be a major decomposition pathway for this class of molecules (see Chapter 1.4.2.3, p40). Once formed, zinc enolate **86** could then react with acryloyl chloride to produce the observed compound **85a**. It may be that not all of compound **86** reacts with the acid chloride, and some of it is protonated upon workup to give *tert*-butyl carbamate. The possible formation of this compound, coupled with the loss of the volatile alkene by-product produced during β-elimination, goes some way to explaining the poor mass balance observed for the Negishi cross coupling reactions of *N*-Boc amino organozinc reagents **62a** and **65a**.

Figure 27. Plausible route to by-product **85a** via β-elimination of organozinc reagents **62a** and **65a**, and possibility of the production of *tert*-butyl carbamate as another by-product.



The fact that by-product **85a** was formed for L-valine and L-alanine derived organozinc reagents **62a** and **65a**, but was not observed during the cross coupling reaction of L-serine derived organozinc reagent **57c**, highlights the comparative stability of organozinc reagent **57c** to β-elimination. This is thought to be due to a stabilising interaction between the ester carbonyl and the electron deficient zinc atom (Figure 28, see also Table 8, p42), which can compete with the key carbamate-zinc interaction. This ester-zinc interaction is not present in compounds **62a** and **65a**, and therefore β-elimination is expected to occur more quickly. Although the decomposition of organozinc reagents **62a** and **65a** has not been studied kinetically, the rate of β-elimination for the analogous L-phenylalanine derived zinc reagent **87** (Figure 28, R = CH_2Ph) has previously been determined.[89] Compound **87** was found to undergo elimination almost five times faster than L-serine derived organozinc reagent **57c** ($k = 9.7 \times 10^{-6}$ s^{-1} cf. $k = 2.0 \times 10^{-6}$ s^{-1}), a difference that is consistent with the proposed stabilisation of compound **57c** as the result of an ester-zinc interaction.

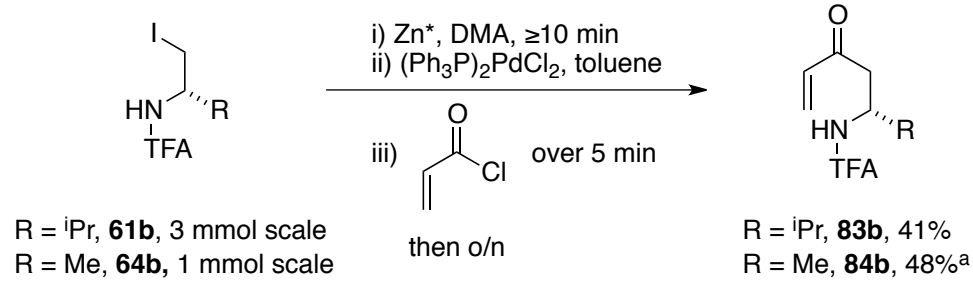
Figure 28. Stabilising ester-zinc interaction in organozinc reagent **57c**, which can compete with the carbamate-zinc interaction that leads to β-elimination.



2.2.3 *N*-TFA Protected Organozinc Reagents

In order to try and avoid the problem of β-elimination, attention was next turned to the nitrogen protecting group. The trifluoroacetyl protecting group has previously been employed by Jackson and co-workers, who used it to slow down the elimination of β-amido organozinc reagents (see Chapter 1.4.2.3, p40).[66] Therefore, the reactions of *N*-TFA protected organozinc reagents **62b** and **65b** with acryloyl chloride were attempted (Scheme 58). L-Valine derived organozinc reagent **62b** gave the product **83b** in a similar yield to its Boc protected analogue (41% cf. 46%, see Scheme 56, p55). However, in contrast to its Boc protected analogue **65a** (see Scheme 57, p56), L-alanine derived organozinc reagent **65b** reacted with acryloyl chloride to give the product **84b** in a much more respectable yield of 48%.

Scheme 58. Application of the optimised cross coupling conditions to the reaction of acryloyl chloride with the L-valine and L-alanine derived organozinc reagents **62b** and **65b**, formed from iodides **61b** and **64b**.



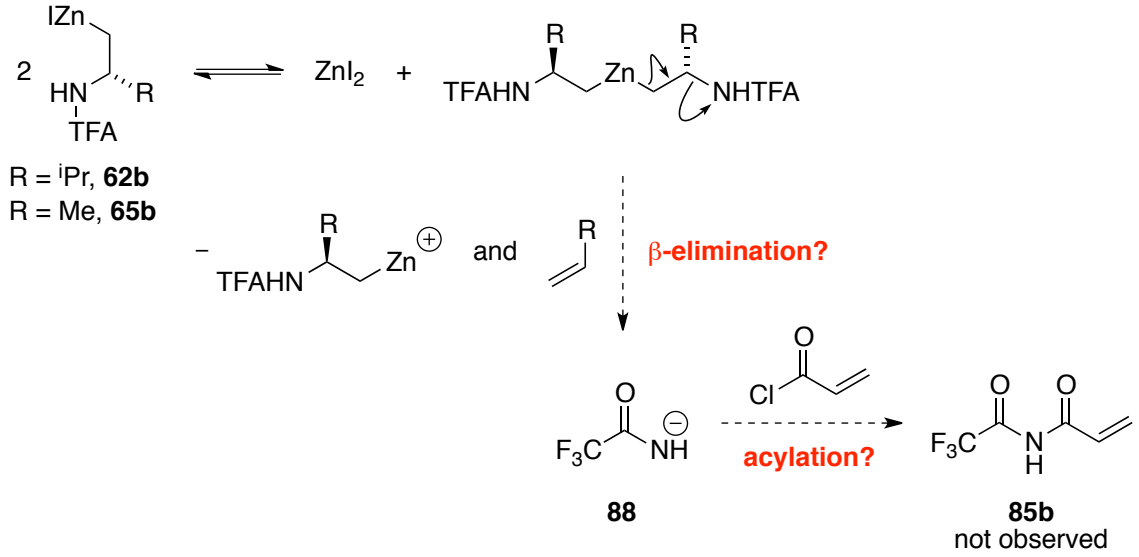
R = ^{i}Pr, **61b**, 3 mmol scale
R = Me, **64b,** 1 mmol scale

R = ^{i}Pr, **83b**, 41%
R = Me, **84b**, 48%[a]

[a] Best yield achieved at 3 mmol scale was 16%.

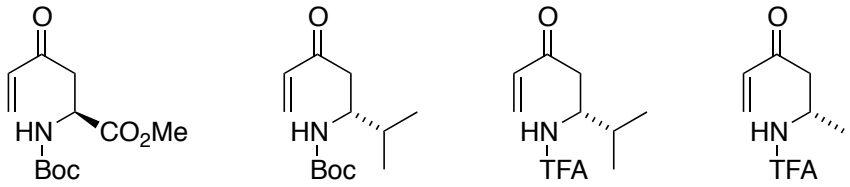
In these reactions, the analogous elimination by-product **85b** was not observed (Figure 29). However, this does not rule out the possibility of β-elimination. Assuming that organozinc reagents **62b** and **65b** underwent an *anti* elimination as proposed by Jackson and co-workers[66] (see Scheme 45, p44), the product would be the trifluoroacetamide anion **88**. This species may not be nucleophilic enough to react with acryloyl chloride, because of the electron-withdrawing nature of the CF_3 group. Therefore, the absence of by-product **85b** does not prove that elimination is not occurring. However, the fact that TFA protected organozinc reagent **65b** succeeded in forming the desired cross coupled product **84b**, where its Boc protected analogue **65a** struggled, suggests that the TFA protecting group has indeed helped to stabilise these sensitive organozinc reagents.

Figure 29. Speculations as to the nucleophilicity of anion **88**, which would form if organozinc reagents **62b** and **65b** underwent an *anti* β-elimination.



In summary, the Negishi cross coupling reaction of various amino acid derived organozinc reagents with acryloyl chloride proved successful in providing access to four key amino enone intermediates **59c**, **83a**, **83b** and **84b** (Figure 30), enabling the cyclisation of these intermediates to be investigated.

Figure 30. Four key amino enone intermediates **59c**, **83a**, **83b** and **84b** synthesised using the Negishi cross coupling reaction of various amino acid derived organozinc reagents with acryloyl chloride.



59c **83a** **83b** **84b**

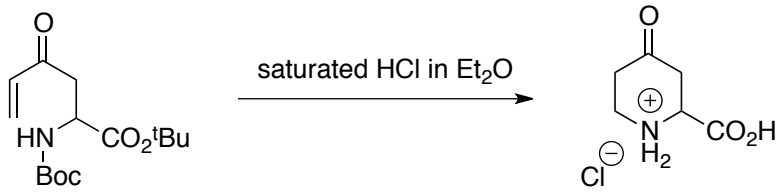
2.3 Attempted Hydrogen Chloride Mediated Cyclisations

The next step in the proposed synthetic route towards 2-substituted 4-hydroxypiperidines **47** was the cyclisation of the cross coupled intermediates **49** to form 4-oxopiperidines **48** (see Scheme 46, p45). For the Boc protected compounds **59c** and **83a**, an acid mediated cyclisation was envisaged based on very similar cyclisations previously reported in the literature.[52,56-57]

2.3.1 Literature Cyclisations

The first authors to report such a cyclisation were Obrecht and co-workers (Scheme 59).[56-57] They claimed that by treating racemic protected 4-oxoamino acid **(±)-59b** with saturated hydrogen chloride in diethyl ether they were able to affect a global deprotection and carry out a cyclisation reaction to yield compound **(±)-60b**.

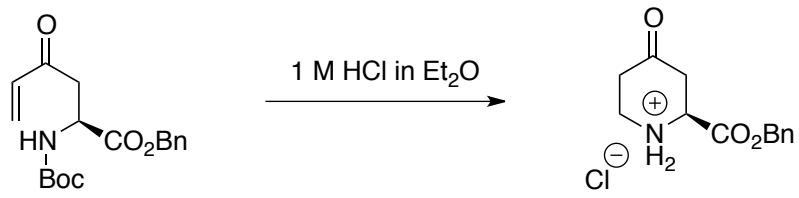
Scheme 59. The synthesis of 4-oxopipecolic acid hydrochloride **(±)-60b** as reported by Obrecht and co-workers.



(±)-59b **(±)-60b**
99–100%

Based on this work, Jackson and co-workers synthesised the closely related substrate **59a** and subjected it to similar conditions in order to synthesise benzyl 4-oxopipecolate hydrochloride **60a** (Scheme 60).[52]

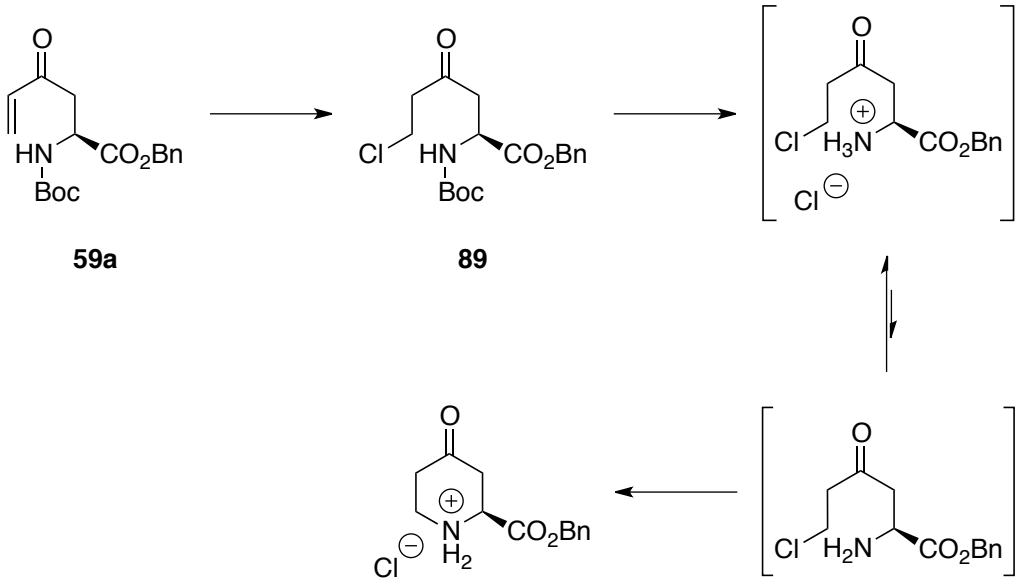
Scheme 60. The apparent cyclisation of compound **59a** to give compound **60a** reported by Jackson and co-workers.



59a **60a** 100%

The proposed mechanism for this reaction is based on the observation made by Jackson and co-workers that the Boc deprotection for compound **59a** is slow, and that the hydrogen chloride first reacts with the double bond to form an intermediate β-chloroketone **89** (Scheme 61). This compound then was proposed to react further to give cyclised product **60a**, presumably through removal of the nitrogen protecting group, followed by an S_N2 reaction between the small percentage of free amine present in solution (in equilibrium with its ammonium salt) and the alkyl chloride.

Scheme 61. The proposed mechanism for the reported hydrogen chloride mediated cyclisation of Boc protected amine **59a**, proceeding via the intermediate β-chloroketone **89**.



59a **89** **60a**

2.3.2 Cyclisation Attempts and Further Reactions

Given the literature precedent, the obvious first step was to treat compounds **59c** and **83a** with HCl in Et_2O. These reactions did indeed appear to yield the target compounds **60c** and **90** as their hydrochloride salts (Scheme 62), and the ^{1}H NMR data for compound **60c** were very similar to the data reported by Obrecht for compound **(±)-60b** (Table 10). However, the yields for these reactions were each greater than 100% despite the products appearing clean by ^{1}H NMR spectroscopy, raising doubts about the structure of the products.

Scheme 62. Presumed cyclisation of compounds **59c** and **83a**.

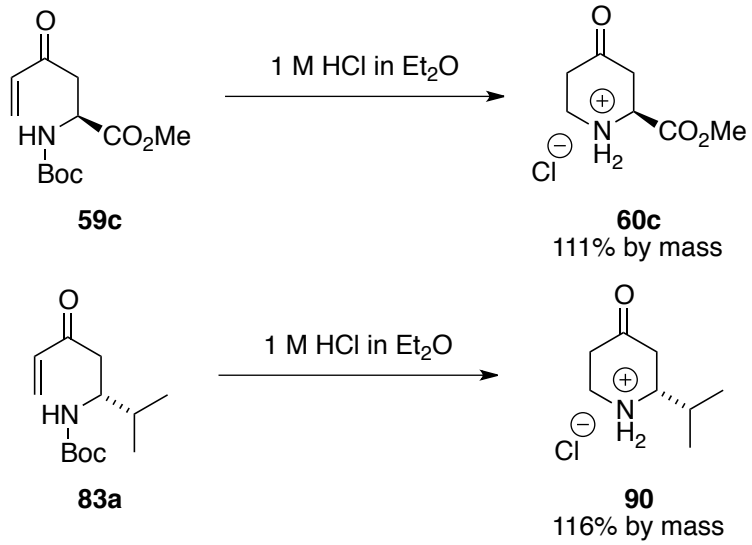
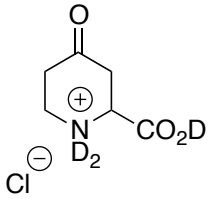


Table 10. Comparison of the ^{1}H NMR data for compound **60c** with Obrecht's data for compound **(±)-60b**.

^{1}H NMR Data for Compound 60c (CD_3OD)	**Obrecht's ^{1}H NMR Data for Compound (±)-60b (CD_3OD)[56-57]**
3.06 (2H, t, *J* = 6.4)	3.05 (2H, dt, *J* = 6, 2)
3.21–3.30 (2H, m)	3.20 (1H, dd, *J* = 7, 20)
–	3.29 (1H, dd, *J* = 4, 20)
3.80 (2H, t, *J* = 6.4)	3.79 (2H, t, *J* = 6)
3.84 (3H, s)	–
4.38 (1H, dd, *J* = 4.4, 6.1)	4.30 (1H, dd, *J* = 4, 7)

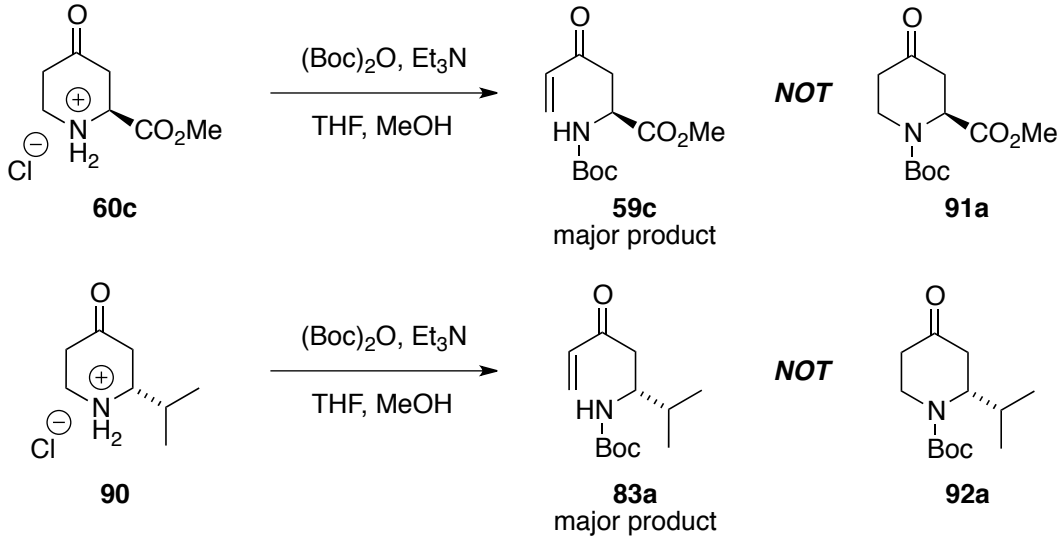


(±)-60b

Analysis of compound **60c** by mass spectrometry showed the presence of a mass ion at 158.0812, consistent with the desired formula $C_7H_{12}NO_3^+$. However, there were also a pair of mass ions in a 3:1 ratio at 194.0577 and 196.0546 that corresponded to the molecular formula $C_7H_{13}ClNO_3^+$, suggesting that the product may contain one extra hydrogen atom and one extra chlorine atom.

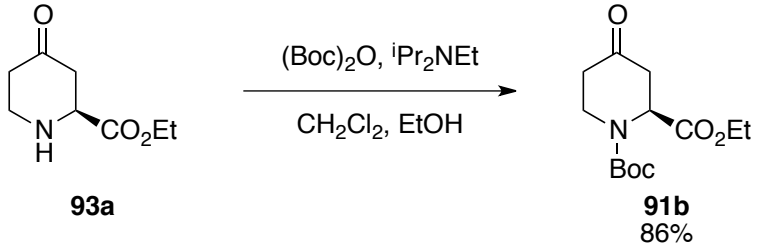
Further suspicions were aroused when the Boc protection of compounds **60c** and **90** was attempted. After treatment with $(Boc)_2O$ and Et_3N, ^1H NMR analysis of the crude mixtures showed that the major products were actually compounds **59c** and **83a**, rather than the desired *N*-Boc 4-oxopiperidines **91a** and **92a** (Scheme 63).

Scheme 63. Presumed structures of compounds **60c** and **90**, which were Boc protected to give enones **59c** and **83a** rather than the expected piperidines **91a** and **92a**.



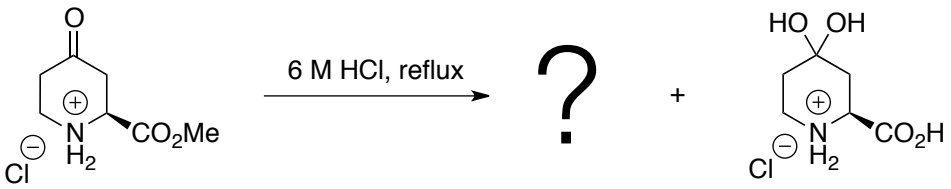
Although an E1cB elimination of the 4-oxopiperidines could in theory lead to the observed products **59c** and **83a**, this seems unlikely as the successful Boc protection of ethyl 4-oxopipecolate **93a** has previously been reported under very similar conditions (Scheme 64).[90]

Scheme 64. Boc protection of ethyl 4-oxopipecolate **93a** reported by Machetti and co-workers.



Another unexpected result was obtained upon attempting the acidic ester hydrolysis of compound **60c** (Scheme 65). Two products were observed by ^{1}H NMR spectroscopy in a 4:1 ratio. The minor product was identified as hydrated 4-oxopipecolic acid hydrochloride **94a·H$_2$O** by comparison with the literature ^{1}H NMR data for this compound, which is known to predominate over the non-hydrated ketone **94a** in D_2O.[91-92] However, the identity of the major product remained unknown.

Scheme 65. Presumed structure of compound **60c** and the products of its acidic ester hydrolysis.



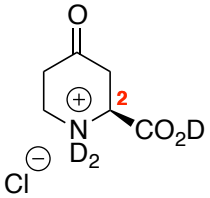
60c **94a·H$_2$O**

~ 4:1

Although the ^{13}C NMR data for this unknown compound are similar to the literature data for the non-hydrated ketone **94a** (Table 11),[91-92] they do not match exactly. This is seen most clearly for the signal in the unknown compound at 48.4 ppm, which corresponds to carbon 2 in compound **94a** (highlighted in red), which has a chemical shift of 57.4 ppm. Given this discrepancy, and the fact that ketone **94a** should only be present in very small amounts due to the hydration equilibrium lying heavily towards the hydrate **94a·H$_2$O**, it seems likely that the major product of the acidic ester hydrolysis is in fact another compound.

Table 11. Comparison of the ^{13}C NMR data for the unknown compound and the literature ^{13}C NMR data given for the ketone **94a**.

^{13}C NMR Data for Unknown Compound (D_2O)	**Literature ^{13}C NMR Data for Compound 94a (D_2O)[91-92]**
38.0	37.9
41.6	41.2
44.1	42.8
48.4	**57.4**
171.1	171.1
207.8	206.7

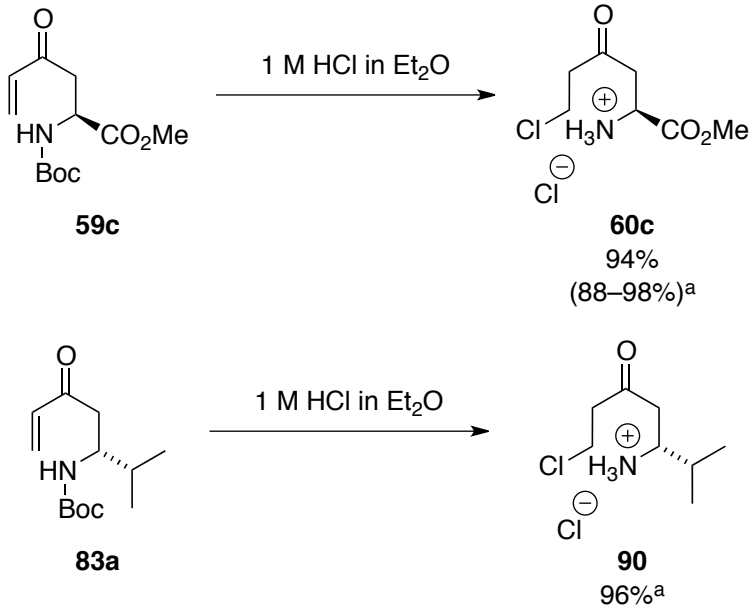


94a

2.3.3 Proposed Structural Revisions

All of these unexpected results brought the structure of compounds **60c** and **90** into question. It was decided to propose a revision of the structures of these compounds to the β-chloroketones shown below (Scheme 66), as these structures seem to better fit the data.

Scheme 66. Proposals for the revised structures of compounds **60c** and **90** in order to explain the unexpected results.



[a] See below for clarification about the yield of these reactions upon repetition.

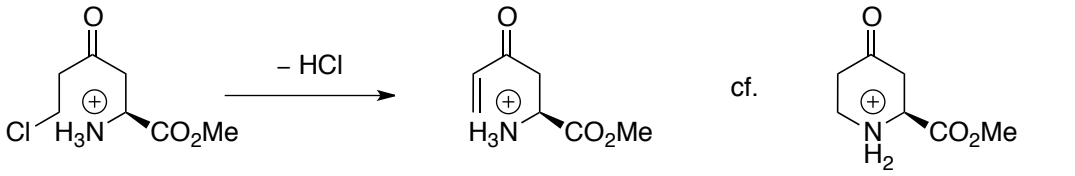
Firstly, this proposed structural revision solves the problem of the greater than 100% yields seen in the acidic deprotection of compounds **59c** and **83a** (see Scheme 62, p62). Taking into account the extra mass gained through addition of HCl to the enones, the resulting yields are much more reasonable at 94% and 96%.

It should be noted that for both reactions there were a few cases upon repetition when the yield was calculated to be >100%, even after adjusting the molecular weight of the product in line with the proposed structural revision. Although this appears problematic, there are a few points that help to explain how the mass of the product may have been inflated: firstly, if they were any remaining starting material (or intermediate *N*-Boc β-chloroketone) present, this would increase the mass of the sample while perhaps not being visible in the NMR spectrum when D_2O was used to prepare the sample, as these compounds would be sparingly soluble in this solvent; secondly, as noted in

Obrecht's *Organic Syntheses* paper for a very similar compound,[57] the samples were found to be hygroscopic while they still contained hydrogen chloride, and so extra mass may arise from the absorption of water from the atmosphere; finally, if the sample still contained Et_2O the mass would be increased, but all of the diethyl ether may not be visible in the NMR spectrum, as again it is not very soluble in D_2O. As a result of the extensive evidence that the products of this type of reaction are β-chloroketones (see below), the few examples where the yield proved to be greater than 100% were put down to unknown factors such as those previously mentioned, and the yield of the reactions of compounds **60c** and **90** with ethereal hydrogen chloride were quoted as 88–98% and 96%, based on the examples of these reactions which gave product with yields of less than 100%.

The newly proposed structures explain the mass spectrometry data for compound **60c**. The β-chloroketone structure corresponds to the mass ion 194.0577 (with its corresponding ^{37}Cl isotope 196.0546), and loss of HCl from this compound during analysis would lead to the formation of enone **95a**, which corresponds to the other mass ion 158.0812 (Scheme 67). It should be noted that compound **95a** has the same molecular formula as the desired cyclic product, explaining why there initially seemed to be mass spectrometry evidence that the cyclisation had occurred.

Scheme 67. Proposed loss of HCl from compound **60c** during mass spectrometry.



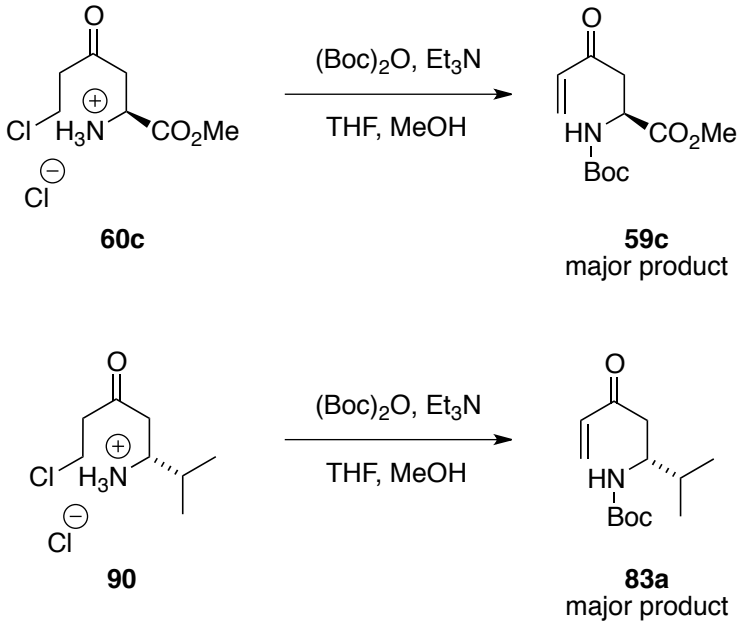
60c
observed m/z = 194.0577
calculated m/z = 194.0584

95a
observed m/z = 158.0818
calculated m/z = 158.0817

calculated m/z = 158.0817

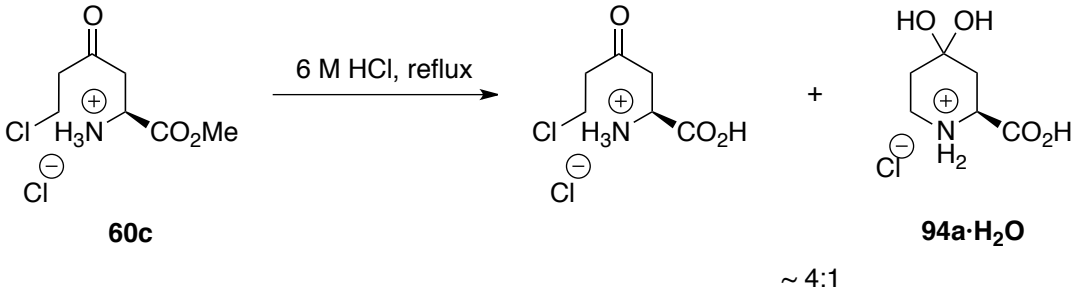
The results of the Boc protections (see Scheme 63, p63) are also consistent with these structures, as loss of HCl from the β-chloroketones under the basic reaction conditions seems very plausible, and would lead to the enones **59c** and **83a** as the major products (Scheme 68).

Scheme 68. Proposed loss of HCl during Boc protection of compounds **60c** and **90** leading to enones **59c** and **83a**.



Finally, the results of the acidic ester hydrolysis of compound **60c** are also explained by revising its structure. Under the harsh reaction conditions it seems reasonable that a small amount of the starting material could undergo an S_N2 cyclisation reaction as well as the desired ester hydrolysis, leading to cyclised compound **94a·H₂O** (Scheme 69). In line with these proposals, the previously unknown structure of the major product can be assigned as the uncyclised β-chloroketone shown below.

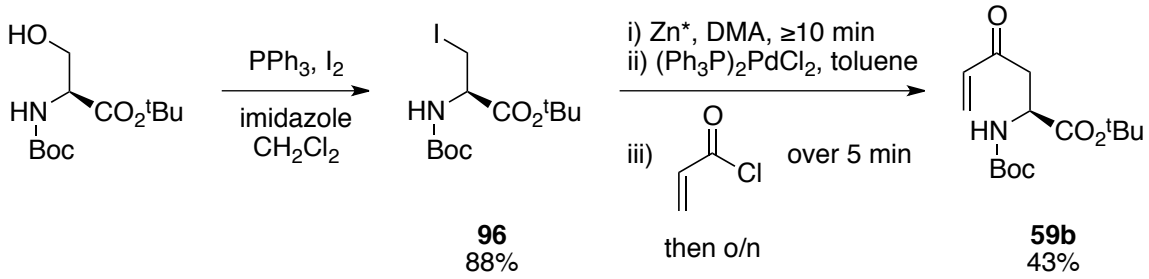
Scheme 69. Products of the acidic ester hydrolysis of compound **60c**.



2.3.4 Repetition of Literature Cyclisation

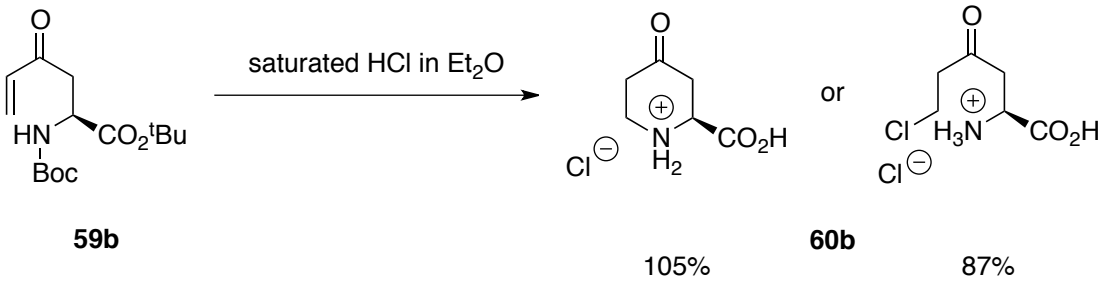
Given the evidence outlined above that the products of the acidic deprotection reactions appear to be uncyclised β-chloroketones rather than cyclised 4-oxopiperidines, the results of the cyclisation reported previously by Jackson and co-workers (Scheme 60)[52] and ultimately the original cyclisation reported by Obrecht and co-workers (Scheme 59)[56-57] were also brought into question. It was decided to attempt to repeat the original cyclisation reported by Obrecht. To this end, enantiomerically pure starting material **59b** was synthesised in two steps from commercially available *N*-Boc-L-serine *tert*-butyl ester (Scheme 70).

Scheme 70. Synthesis of compound **59b**.



Once synthesised, compound **59b** was subjected to the exact cyclisation conditions described by Obrecht and co-workers, namely treatment with saturated hydrogen chloride in diethyl ether (Scheme 71).[57] As previously observed, the yield of the reaction provided some useful information: from the mass of product isolated, if the cyclised structure were correct then the yield would be 105%, whereas if the uncyclised structure is assumed the yield would be 87%. At this point the product was subjected to extensive analysis to try and determine whether it was indeed 4-oxopipecolic acid hydrochloride as reported, or whether it was actually the β-chloroketone instead.

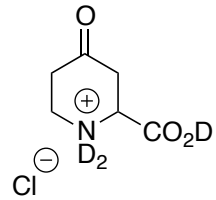
Scheme 71. Treatment of compound **59b** with saturated HCl in Et_2O, and the two possible structures of the product **60b**.



The characterisation data collected for the product of this reaction were first compared to the data provided by Obrecht and co-workers. The published data were limited to a ^{1}H NMR spectrum in methanol-d_4, an IR spectrum collected as a Nujol mull and a melting point range. Given that enantiomerically pure amino acid **59b** had been used, whereas Obrecht synthesised a racemic compound, there was no guarantee that the melting points would match. However, the values proved to be similar, with the product decomposing slowly above temperatures of ~145 °C, whereas Obrecht and co-workers reported a decomposition at 139–142 °C.[57] The IR spectrum also broadly matched Obrecht's data, after discounting the reported signals arising from the use of Nujol.[57]

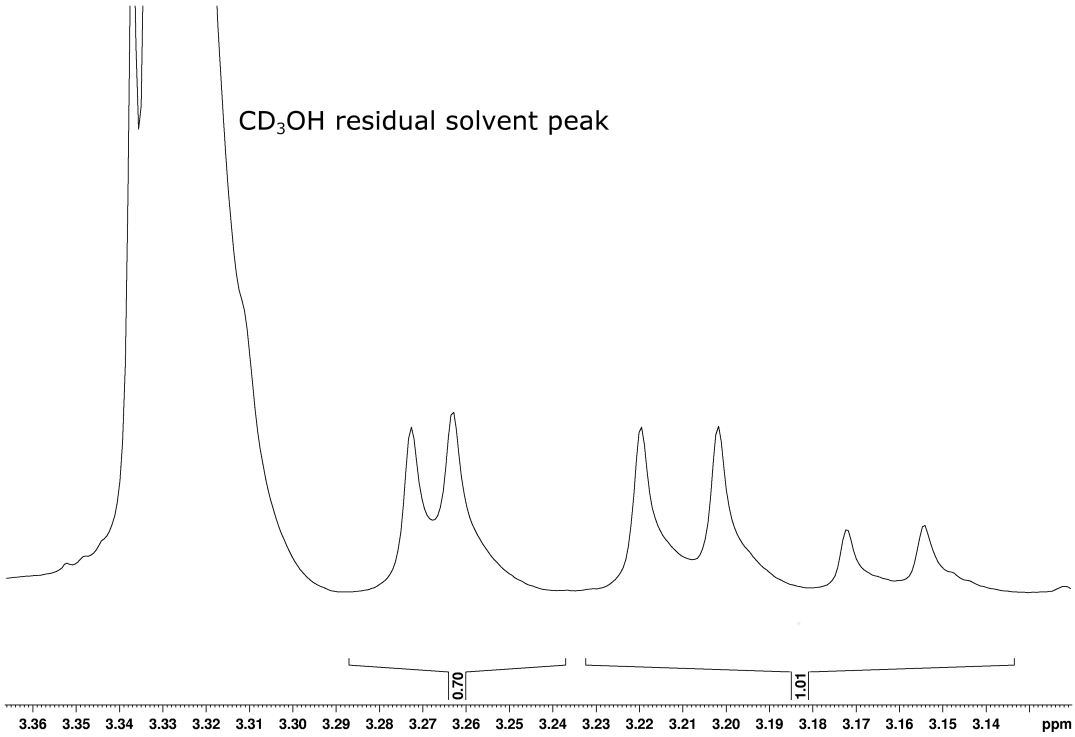
The most important characterisation data reported were the ^{1}H NMR data. Comparison of the data given by Obrecht[56-57] with those collected for the compound of interest showed a good match (Table 12), giving confidence that the same product had indeed been made. The signal corresponding to the doublet of doublets reported at 3.29 ppm was partially overlapping with the CD_3OH residual solvent signal (Figure 31), but the chemical shift and remaining coupling constant of this signal were inferred by analysis of the coupling constants of the other double doublet in the ABX spin system at 3.19 ppm.

Table 12. Comparison of Obrecht's ^{1}H NMR data for compound **(±)-60b** and the ^{1}H NMR data collected for compound **60b**.

^{1}H NMR Data for Compound 60b (CD_3OD)	**Obrecht's ^{1}H NMR Data for Compound (±)-60b (CD_3OD)[56-57]**	
3.06 (2H, td, *J* = 6.4, 1.9)	3.05 (2H, dt, *J* = 6, 2)	
3.19 (1H, dd, *J* = 7.1, 19.0)	3.20 (1H, dd, *J* = 7, 20)	
3.29 (1H, dd, *J* = 3.8, 19.0)[a]	3.29 (1H, dd, *J* = 4, 20)	
3.81 (2H, t, *J* = 6.4)	3.79 (2H, t, *J* = 6)	
4.31 (1H, dd, *J* = 3.8, 7.1)	4.30 (1H, dd, *J* = 4, 7)	**(±)-60b**

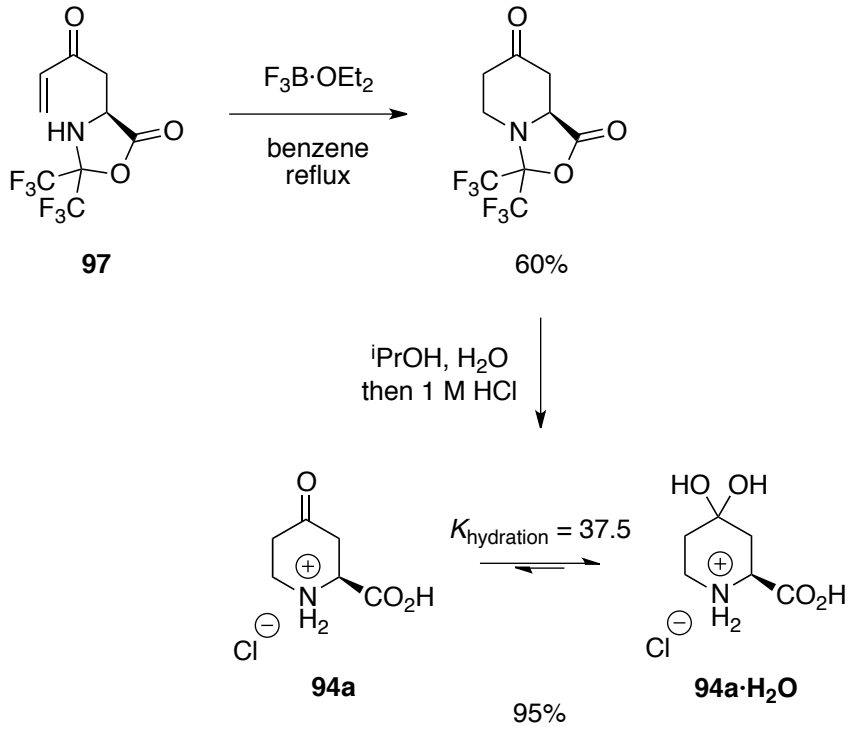
[a] Chemical shift and larger *J* value inferred due to overlap of signal with solvent peak (see above).

Figure 31. Overlap of double doublet of the ABX spin system with the residual solvent peak in ^{1}H NMR spectrum of compound **60b**.



Given that the ^{1}H NMR data for the product were almost identical to those reported by Obrecht and co-workers, attention was next turned to the other characterisation data provided for cyclic compound **94a** in the literature. This compound was synthesised independently by Burger and co-workers in 1996, using a related conjugate addition reaction on the protected amino acid **97** (Scheme 72).[91-92] The authors reported ^{13}C NMR data for the hydrate **94a·H$_2$O**, which predominates in D_2O (97.4% by ^{1}H NMR spectroscopy). They also stated that the ^{1}H NMR data for compound **94a·H$_2$O** were essentially the same as those reported for the racemic hydrobromide salt of 4-oxopipecolic acid **98·H$_2$O**, as reported by Herdeis and Engel.[93]

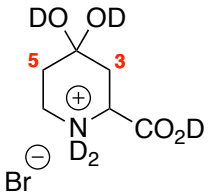
Scheme 72. Synthesis of 4-oxo-L-pipecolic acid **94a** by Burger and co-workers.



Comparison of the ^{1}H NMR data for compound **60b** and Herdeis's data for compound **98·D$_2$O** showed significant differences (Table 13), with the clearest difference being in the most shielded signals (highlighted in red).

Table 13. Comparison of Herdeis's ^{1}H NMR data for compound **98·D$_2$O** and the ^{1}H NMR data collected for compound **60b**.

^{1}H NMR Data for Compound 60b (HCl salt, D$_2$O)	**Herdeis's ^{1}H NMR Data for Compound 98·D$_2$O (HBr salt, D$_2$O)[93]**
2.97 (2H, t, *J* = 6.1)	**1.86–2.14 (3H, m)**
3.21 (1H, br. s)	–
3.23 (1H, br. s)	**2.41 (1H, ddd, *J* = 2.2, 4.0, 14.3)**
3.65 (2H, t, *J* = 6.1)	3.23 (1H, ddd, *J* = 4.3, 11.3, 13.0)
–	3.51 (1H, td, *J* = 13.0, 4.3)
4.22 (1H, t, *J* = 5.1)	4.16 (1H, dd, *J* = 4.0, 11.5)



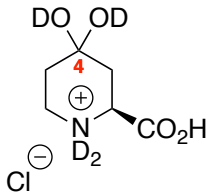
98·D$_2$O

Herdeis reported three protons giving a signal at 1.86–2.14 ppm and another single proton at 2.41 ppm. These signals correspond to the four protons on carbons 3 and 5, and the chemical shifts are

indicative of protons α to a hydrated ketone. The corresponding signals in the compound of interest are much less shielded, at 2.97, 3.21 and 3.23 ppm respectively. These chemical shifts are indicative of protons α to a non-hydrated ketone.

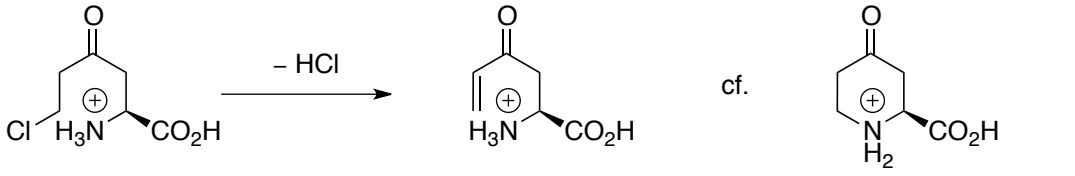
Comparison of the ^{13}C NMR data collected for compound **60b** with the data reported by Burger and co-workers showed further differences, the clearest being the signal corresponding to carbon 4 (highlighted in red). Burger and co-workers reported that this signal has a chemical shift of 92.4 ppm, consistent with the shift of a hydrated ketone. The corresponding signal in compound **60b** is very different with a chemical shift of 207.8 ppm, again indicative of a non-hydrated ketone.

Table 14. Comparison of Burger's data ^{13}C NMR data for compound **94a·D$_2$O** and the ^{13}C NMR data collected for compound **60b**.

^{13}C NMR Data for Compound 60b (D_2O)	**Burger's ^{13}C NMR Data for Compound 94a·D_2O (D_2O)[91-92]**	
38.0	35.2	
41.6	38.7	
44.1	42.5	
48.6 and 48.9	56.5	
–	**92.4**	
171.2	172.6	**94a·D_2O**
207.8	–	

Analysis of the compound of interest by mass spectrometry again showed possible mass ions for both potential products, with a signal at 144.0663 and pair of signals in a 3:1 ratio at 180.0429 and 182.0409. However, as previously described for compound **60c** (Scheme 67), if compound **60b** is a β-chloroketone, it could easily lose HCl during the analysis to produce compound **95b**, which has the same exact mass as the cyclic product reported (Scheme 73).

Scheme 73. Possible structures corresponding to the mass ions observed for compound **60b**.



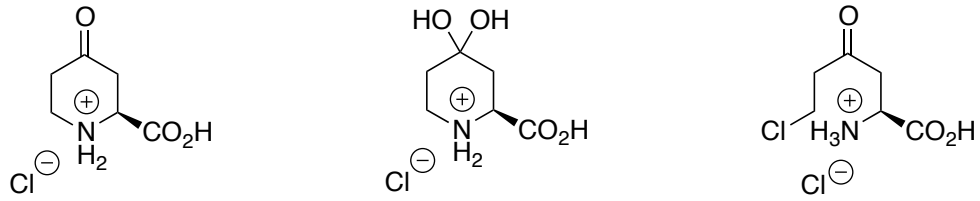
60b (?)
observed m/z = 180.0429
calculated m/z = 180.0427

95b
observed m/z = 144.0663
calculated m/z = 144.0661

60b (?)
calculated m/z = 144.0661

Although it proved very difficult to establish the structure of the product of the literature cyclisation conclusively using mass spectrometry, it was thought that elemental analysis might be a more useful tool, as this technique should be able to distinguish between the possible cyclised and uncyclised structures, on the basis of their differing numbers of chlorine atoms (Scheme 74).

Scheme 74. Possible structures and molecular formulae of compound **60b**.



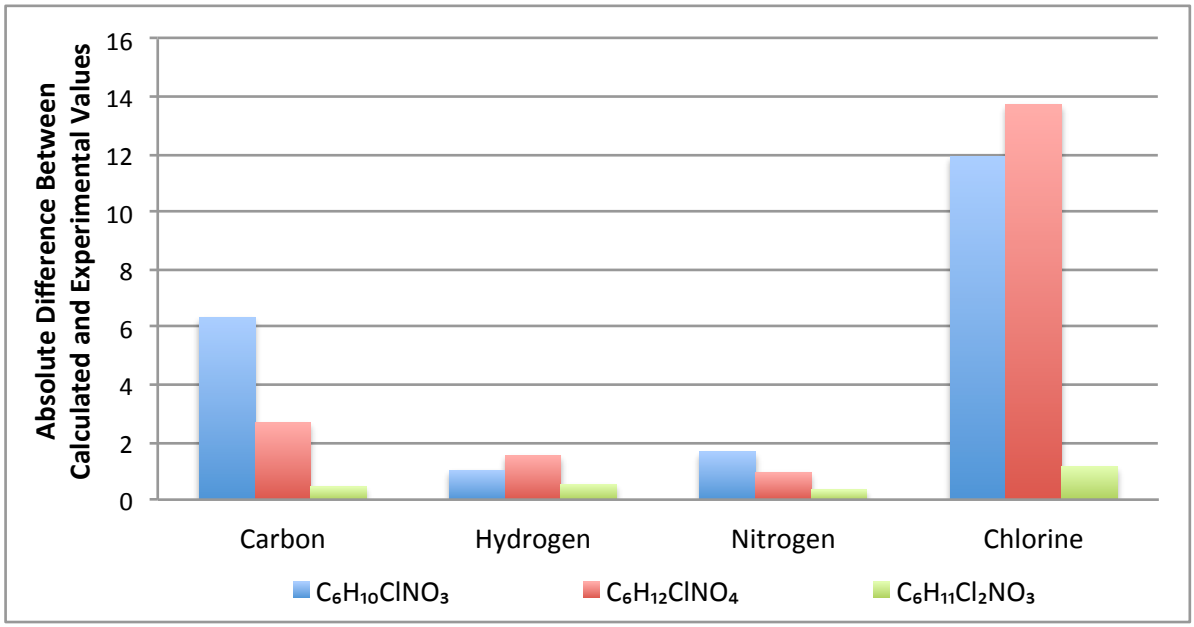
$C_6H_{10}ClNO_3$ $C_6H_{12}ClNO_4$ $C_6H_{11}Cl_2NO_3$

Table 15. Comparison of the calculated and experimental elemental compositions for compound **60b**.

Formula	Carbon (%)	Hydrogen (%)	Nitrogen (%)	Chlorine (%)
$C_6H_{10}ClNO_3$	40.12	5.61	7.80	19.74
$C_6H_{12}ClNO_4$	36.47	6.12	7.09	17.94
$C_6H_{11}Cl_2NO_3$	33.35	5.13	6.48	32.82
Experimental Values	33.80	4.59	6.14	31.67

Although the absolute percentage difference between the experimental values for the elemental composition and the calculated values are relatively large in all cases, it is very clear that the β-chloroketone structure fits the experimental data the closest, with the starkest difference seen in the percentage of chlorine (Table 15 and Graph 1). It is interesting to note that elemental analysis provided the most conclusive evidence as to the identity of compound **60b**, despite the fact that over 180 years have passed since Liebig developed the capability to easily perform the technique in the laboratory.[94] This shows the continuing value of elemental analysis to the organic chemist, alongside the more modern characterisation techniques.

Graph 1. The absolute difference between the calculated elemental compositions for the possible structures of compound **60b** and the experimentally determined elemental composition.

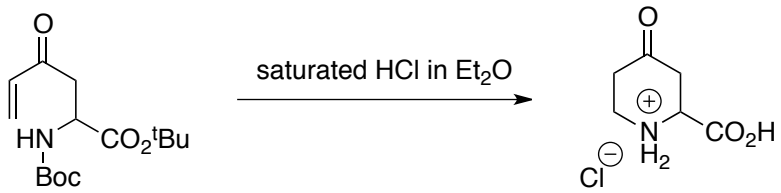


2.3.5 Analysis of Yields for Literature Cyclisations

It has already been observed that the yields for the reaction of amino enones with hydrogen chloride in diethyl ether were found to be greater than 100% when a cyclic structure of the product was assumed (see Scheme 62, p62 and Scheme 71, p68). However, when Obrecht and co-workers reported the reaction of amino enone **(±)-59b** with hydrogen chloride in diethyl ether, they reported yields of 100% and 99% for their cyclic product.[56-57] It was decided to re-examine these two papers, paying careful attention to the yields that were reported and the calculations that were used to work out these yields.

The earlier of the two papers of interest was published in *Synthetic Communications* in 1988.[56] In it, Obrecht and co-worker reported the reaction of amino enone **(±)-59b** with ethereal hydrogen chloride on a 1 mmol scale, giving the product in a yield of 100% (Scheme 75).

Scheme 75. Reaction of amino enone **(±)-59b** with ethereal hydrogen chloride, as reported by Obrecht and co-worker in *Synthetic Communications*.[56]



(±)-59b
amount reported = 1 mmol
mass used = 298 mg
M_r = 299.36 gmol^{-1}

(±)-60b
yield reported = 100%
mass produced = 170 mg
M_r = 179.60 gmol^{-1}

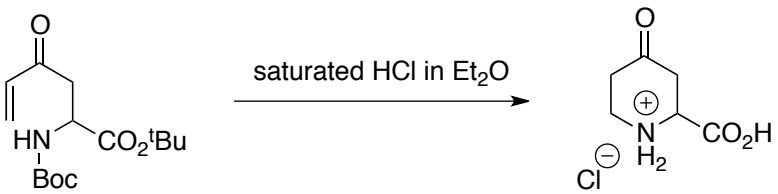
By calculating the yield using the masses of starting material (SM) and product (P) recorded in the paper, a slightly lower yield of 95% is obtained (Equation 1). It is unclear why there is a small discrepancy between the yield reported in the paper and the yield calculated from the recorded data; however, this difference is unimportant for the current discussion, as both values are ≤100% and therefore are feasible yields for the synthesis of the claimed cyclic product **(±)-60b**.

Equation 1:

$$yield = \frac{mass_P / M_{r_P}}{mass_{SM} / M_{r_{SM}}} = \frac{170/179.60}{298/299.36} \times 100 = \frac{0.94654788}{0.99545697} \times 100 = 95\%$$

The second paper of interest by Obrecht was published in *Organic Syntheses* in 1993.[57] The reaction of amino enone **(±)-59b** with hydrogen chloride was reported to be performed on a 30.8 mmol scale, and the yield was quoted to be 99% (Scheme 76).

Scheme 76. Reaction of amino enone **(±)-59b** with ethereal hydrogen chloride, as reported by Obrecht and co-workers in *Organic Syntheses*.[57]



(±)-59b
amount reported = 30.8 mmol
mass used = 8.73 g
M_r = 299.36 gmol^{-1}

(±)-60b
yield reported = 99%
mass produced = 5.48 g
M_r = 179.60 gmol^{-1}

The reported yield is based on the claim that the reaction was carried out upon 30.8 mmol of the starting material (which is the limiting reagent); using this value in the yield calculation gives the yield to be 99%, the same value as the paper (Equation 2).

Equation 2:

$$yield = \frac{mass_P / M_{r_P}}{moles_{SM}} = \frac{5.48/179.60}{0.0308} \times 100 = \frac{0.03051225}{0.0308} \times 100 = 99\%$$

However, when the number of moles of the starting material is calculated using the mass of the compound and its molecular weight, the smaller value of 29.2 mmol is obtained (Equation 3). This has the consequence that when this new (corrected) value for the molar amount of starting material is introduced into the yield calculation, the corrected yield is found to be 105% (Equation 4).

Equation 3:

$$moles_{SM} = \frac{mass_{SM}}{M_{r_{SM}}} = \frac{8.73}{299.36} = 0.02916221\ mol \approx 29.2\ mmol$$

Equation 4:

$$yield = \frac{mass_P / M_{r_P}}{mass_{SM} / M_{r_{SM}}} = \frac{5.48/179.60}{8.73/299.36} \times 100 = \frac{0.03051225}{0.02916221} \times 100 = 105\%$$

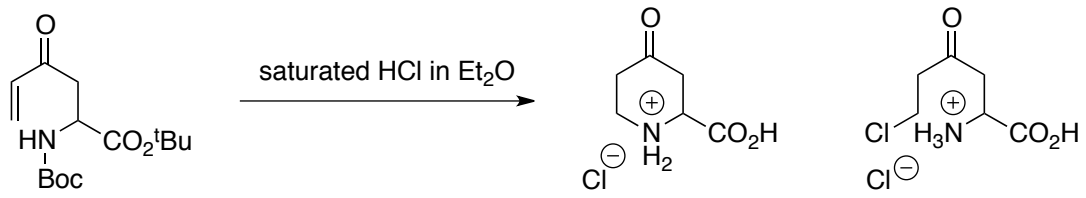
If the yield is calculated for this reaction assuming the product is actually the uncyclised β-chloroketone (M_r = 216.06 $gmol^{-1}$), a yield of 87% is now obtained (Equation 5).

Equation 5:

$$yield = \frac{mass_P / M_{r_P}}{mass_{SM} / M_{r_{SM}}} = \frac{5.48/216.06}{8.73/299.36} \times 100 = \frac{0.02536333}{0.02916221} \times 100 = 87\%$$

Therefore, if the product of the reaction reported by Obrecht and co-workers in *Organic Syntheses* is the cyclic 4-oxopiperidine then the yield is 105%, whereas if the product is the acyclic β-chloroketone then the yield is 87% (Scheme 77). This anomaly in the yield of the product as reported by Obrecht and co-workers appears to have gone unnoticed due to an error in calculating the molar amount of starting material used in the reaction. It is noteworthy that the corrected yields now match the yields achieved when the current author repeated this reaction (see Scheme 71, p68).

Scheme 77. Possible structures and yields of compound **(±)-60b**, based on the data reported by Obrecht and co-workers in *Organic Syntheses*.[57]

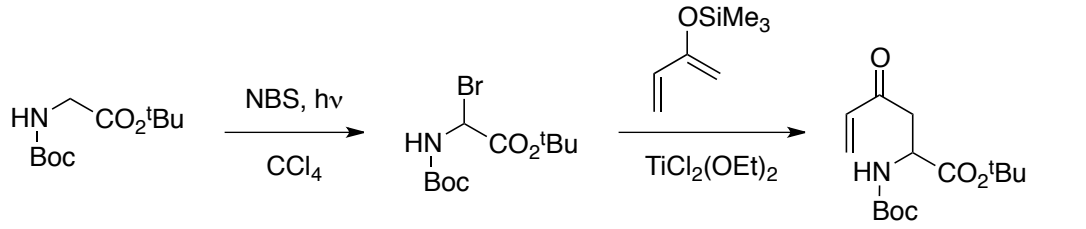


(±)-59b
mass used = 8.73 g
M_r = 299.36 gmol^{-1}
actual amount = 29.2 mmol

(±)-60b
mass produced = 5.48 g
M_r = 179.60 gmol^{-1} M_r = 216.06 gmol^{-1}
105% 87%

Of course, it is possible that of the two pieces of inconsistent information provided by Obrecht for the starting material **(±)-59b** (mass = 8.73 g, molar amount = 30.8 mmol) the mistake has actually been made in recording the mass, and 30.8 mmol of compound **(±)-59b** were used in the reaction. However, this seems unlikely when the preceding reaction is considered, in which amino enone **(±)-59b** was synthesised from protected glycine **99**, with the reported yields ranging from 33 to 36% (Scheme 78).[57]

Scheme 78. Synthesis of amino enone **(±)-59b** from protected glycine **99**.[57]



99
amount reported = 86.5 mmol
mass used = 20.0 g
M_r = 231.29 gmol^{-1}

(±)-59b
yield reported = 33–36%
mass produced = 8.44–8.73 g
M_r = 299.36 gmol^{-1}

If these yields are calculated using the masses given in the paper, the lower limit of 33% is found to be correct (Equation 6), but the upper limit of 36% is wrong; the correct yield for 8.73 g of compound **(±)-59b** is actually 34%, as this mass of compound corresponds to 29.2 mmol (Equation 7). A yield of 36% would have resulted if 30.8 mmol of compound **(±)-59b** had been produced (Equation 8). It is this same incorrect molar amount that is quoted for the reaction of compound **(±)-59b** with hydrogen chloride, and so it seems that the mistake that was made in calculating the

number of moles of compound **(±)-59b** produced from protected glycine **99** was then responsible for the mistake made in calculating the yield of the product of the reaction of compound **(±)-59b** with hydrogen chloride.

Equation 6:

$$yield = \frac{mass_P / M_{r_P}}{mass_{SM} / M_{r_{SM}}} = \frac{8.44/299.36}{20.0/231.29} \times 100 = \frac{0.02819348}{0.08647153} \times 100 = 33\%$$

Equation 7:

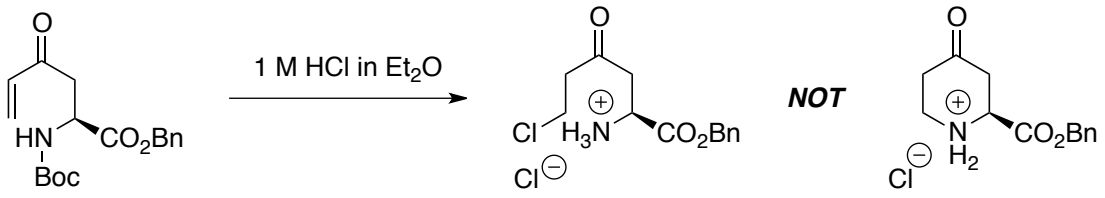
$$yield = \frac{mass_P / M_{r_P}}{mass_{SM} / M_{r_{SM}}} = \frac{8.73/299.36}{20.0/231.29} \times 100 = \frac{0.02916221}{0.08647153} \times 100 = 34\%$$

Equation 8:

$$yield = \frac{moles_P}{mass_{SM} / M_{r_{SM}}} = \frac{0.0308}{20.0/231.29} \times 100 = \frac{0.0308}{0.08647153} \times 100 = 36\%$$

Unfortunately, Jackson and co-workers' previous paper reporting a very similar cyclisation[52] (based heavily on the precedent set by Obrecht and co-workers) was published in *Tetrahedron Letters* and contained no experimental data. A careful search of the relevant laboratory notebooks also failed to yield enough useful information to enable an analysis of the yield for this reaction, which was quoted to be 100% in the paper. However, it is now believed that the product of this reaction **60a** is actually the β-chloroketone rather than the 4-oxopipecolate (Scheme 79), in line with the evidence outlined above for related reactions.

Scheme 79. The reaction of amino enone **59a** with ethereal hydrogen chloride, which is now believed to have given the β-chloroketone product, rather than the 4-oxopipecolate previously reported by Jackson and co-workers.



59a **60a**

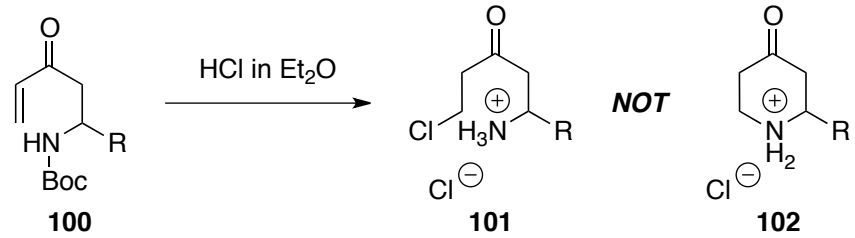
To summarise, an analysis of the yield of the supposedly cyclised product **(±)-60b** reported by Obrecht and co-workers in their *Organic Syntheses* paper (or more accurately, the yield reported by

the checkers) shows that a mistake was made in the mole calculations, and in fact the yield of the product as stated in the paper would have been 105%. This unreasonable value for the reaction yield provides further evidence that the product of this reaction is not the claimed 4-oxopiperidine. However, if the product were actually the β-chloroketone (as proposed by the current author) then the yield of the reaction would become much more reasonable at 87%.

2.3.6 Conclusions

All of the evidence outlined above points towards the conclusion that the treatment of 4-oxoamino acids **100** with hydrogen chloride in diethyl ether leads to the formation of β-chloroketones **101** rather than the previously reported 4-oxopiperidines **102** (Scheme 80).

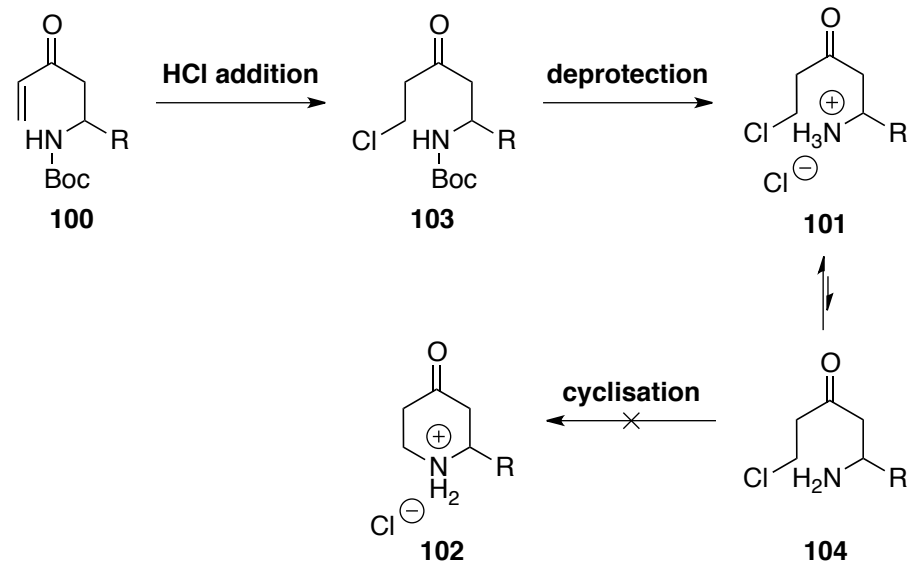
Scheme 80. Product of the treatment of 4-oxoamino acids **100** with HCl in Et_2O.



100 **101** **102**

This conclusion is supported by analysis of the reaction mechanism. The first step in the reaction is the previously observed addition of hydrogen chloride to enone **100** to give intermediate **103** (Scheme 81). This is presumably followed by deprotection of the Boc group to form ammonium salt **101**. It was previously believed that the small percentage of free amine **104** present in solution then underwent an intramolecular S_N2 cyclisation to form the desired piperidinium salt **102** (see Scheme 61, p61). However, under the strongly acidic reaction conditions the concentration of free amine will be very small, as the equilibrium will lie heavily towards the protonated amine. As such, it seems entirely reasonable that the reaction stops at this point, yielding the β-chloroketone **101** as the final product.

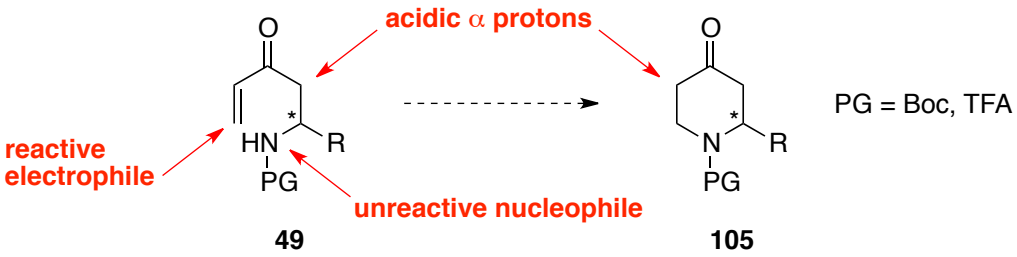
Scheme 81. Proposed mechanism for the treatment of 4-oxoamines **100** with hydrogen chloride in diethyl ether.



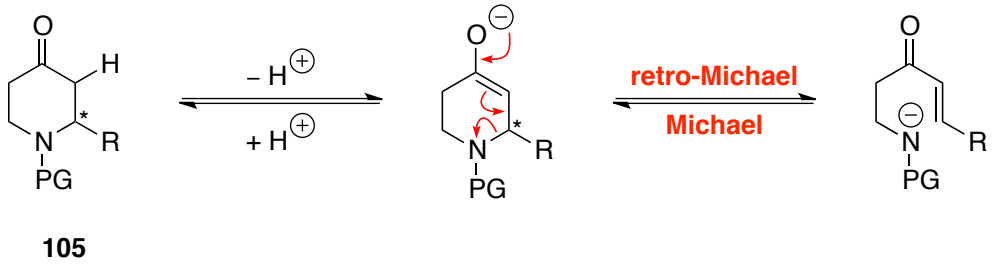
2.4 Alternative Cyclisation Strategies

Given that the hydrogen chloride mediated reactions were failing to yield cyclised products, an alternative cyclisation strategy was sought. There were a number of potential challenges to be overcome in achieving the desired cyclisation (Scheme 82): the high electrophilicity of the terminal enone; the low nucleophilicity of the protected amine; and the potentially high acidity of the protons α to the ketone in both the starting material and the product, which could facilitate unwanted retro-Michael reactions (Scheme 83).

Scheme 82. Potential challenges to overcome in the cyclisation of protected amino enones **49**.

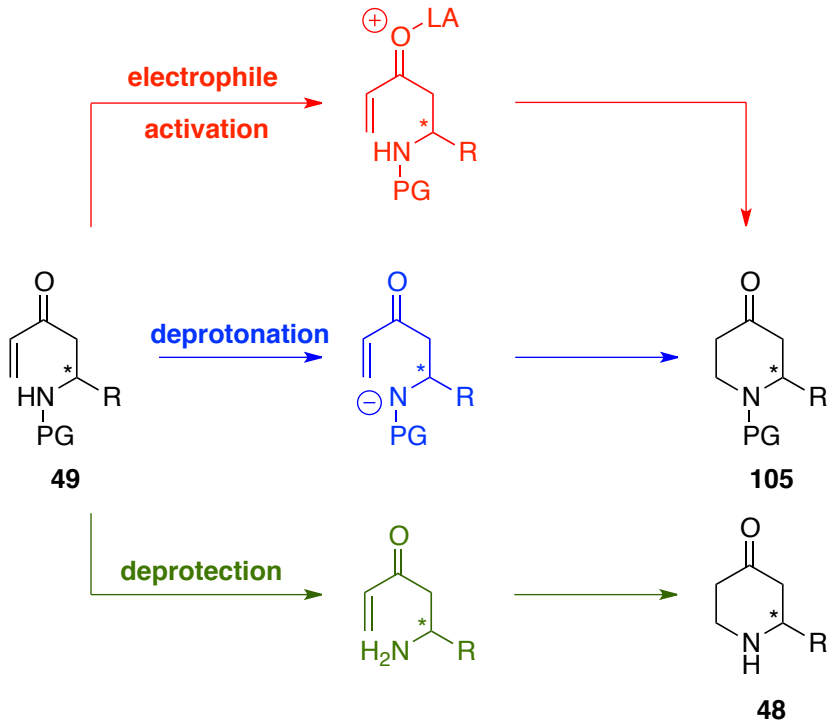


Scheme 83. An example of a deprotonation-induced retro-Michael reaction for compounds **105**.



Three distinct cyclisation strategies were envisaged, which aimed to overcome the potential reactivity issues of amino enones **49**: activation of the enone with a Lewis (or Brønsted) acid in order to increase its electrophilicity even further; deprotonation of the protected amine to make it more nucleophilic; and deprotection of the amine, again aiming to increase its nucleophilicity (Figure 32).

Figure 32. The three alternative cyclisation strategies envisaged.

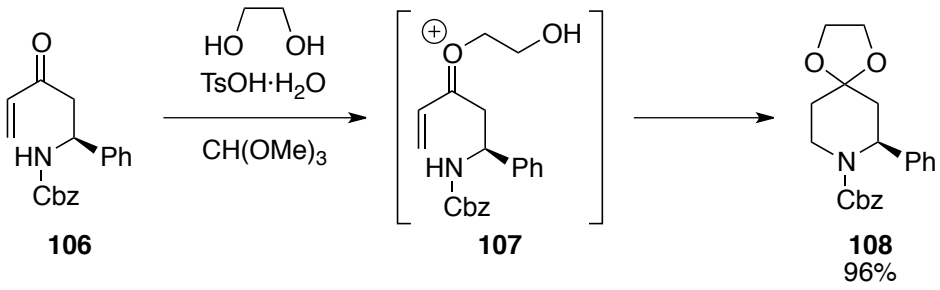


2.4.1 Electrophile Activation Strategy

2.4.1.1 Trimethyl Orthoformate/Tosic Acid Activation

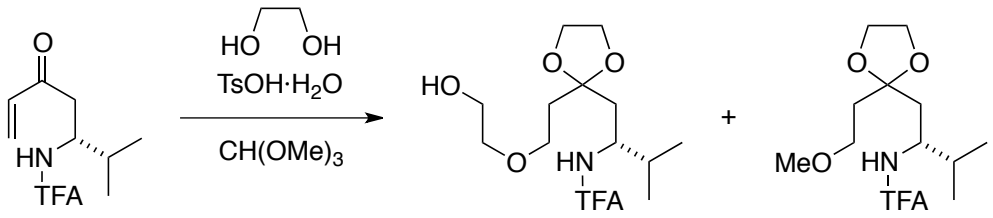
The inspiration for activating the already reactive enone in order to allow addition of the relatively non-nucleophilic protected amine came from a paper published by Troin and co-workers.[95] They reported the cyclisation of Cbz protected amino enone **106** in excellent yield, using trimethyl orthoformate and tosic acid to activate the enone, presumably via intermediate **107** (Scheme 84). The product was isolated as the ethylene glycol acetal **108**.

Scheme 84. Enone activation using ethylene glycol, trimethyl orthoformate and tosic acid.



When trying to apply these conditions, TFA protected amino enone **83b** was chosen as the substrate, as it was thought that tosic acid might be able remove a Boc protecting group, causing complications. An initial attempt at cyclising TFA protected compound **83b** under these conditions gave rise to compounds **109** and **110**, instead of the desired cyclised product (Scheme 85).

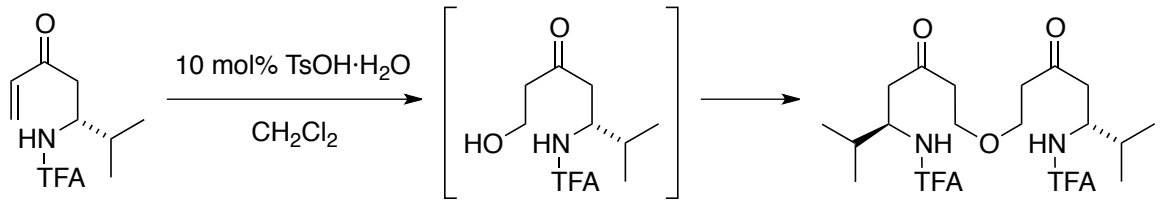
Scheme 85. Attempted cyclisation of compound **83b**.



83b **109** 32% **110** 23%

Upon reflection this is perhaps unsurprising, as a trifluoroacetamide will be much less nucleophilic than a benzyl carbamate due to the highly electron-withdrawing nature of the CF_3 group. As such, both the ethylene glycol in the reaction and the methanol formed during the reaction have added to the enone in preference to the protected amine, leading to the observed products. In order to try and avoid this problem, compound **83b** was reacted with tosic acid in dichloromethane without trimethyl orthoformate or ethylene glycol, to try and remove competing nucleophiles from the reaction (Scheme 86). However, no cyclisation occurred, with compound **111** being isolated instead. This appears to have resulted from addition of water to enone **83b**, followed by addition of the resulting alcohol **112** to another molecule of starting material. Although the tosic acid used was monohydrated, only 10 mol% of this compound was used, implying that there must have been another source of water in the reaction to allow 60% of the product to have formed. Given that dry dichloromethane was used as the solvent, it may be that the product **111** was actually formed during the aqueous reaction workup.

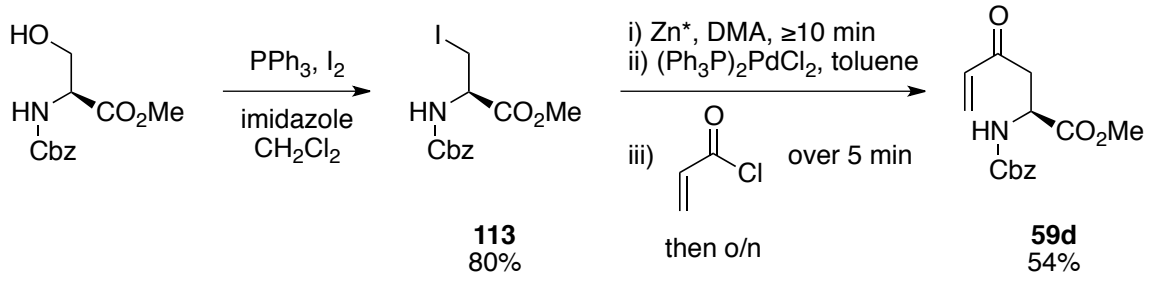
Scheme 86. Attempted "nucleophile free" cyclisation of compound **83b**.



83b **112** **111** 60%

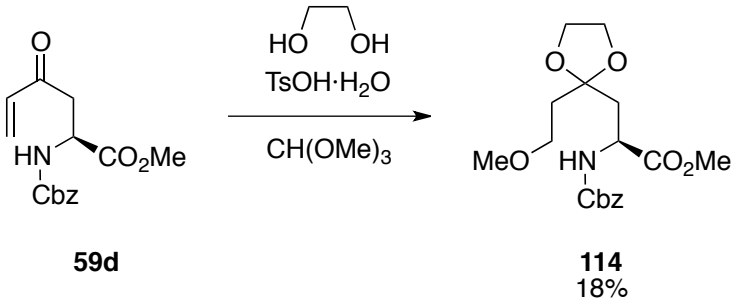
Given the intrinsic low nucleophilicity of the TFA protected amines and the susceptibility of the Boc protected amines to deprotection under acidic conditions, it was decided to synthesise Cbz protected amino enone **59d** in order to have a substrate more similar to the literature precedent. The required enone was synthesised from commercially available *N*-Cbz-L-serine methyl ester, using the already established methodology involving iodination of the alcohol followed by organozinc reagent formation and palladium-catalysed Negishi cross coupling with acryloyl chloride (Scheme 87). This cross coupling reaction proceeded in 54% yield, comparable to the yields achieved for Boc protected organozinc reagent **57c** (see Scheme 55, p55), suggesting that the Cbz group is another viable choice of nitrogen protecting group for these cross coupling reactions.

Scheme 87. Synthesis of Cbz protected amino enone **59d** from *N*-Cbz-L-serine methyl ester.



With Cbz protected amino enone **59d** in hand, the trimethyl orthoformate mediated cyclisation was attempted. However, despite the similarity of compound **59d** to compound **106**, which was cyclised using this methodology (see Scheme 84, p82),[95] the only product isolated from this reaction was methanol adduct **114** (Scheme 88).

Scheme 88. Attempted cyclisation of compound **59d** using Troin and co-workers' conditions.



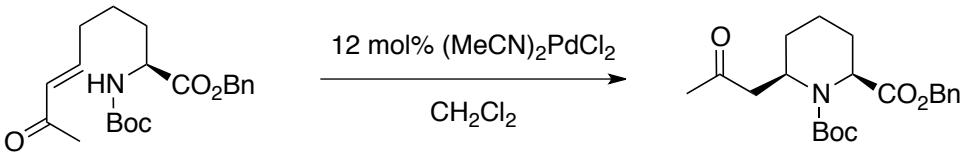
One possible explanation for the formation of compound **114** rather than the desired piperidine is that the methyl ester present in compound **59d** is more electron-withdrawing than the phenyl group in compound **106**. This may reduce the nucleophilicity of the benzyl carbamate slightly, so

that addition of the methanol produced during the reaction is more favourable than an intramolecular aza-Michael reaction.

2.4.1.2 Palladium(II) Activation

One further attempt to encourage cyclisation involved the use of a palladium(II) catalyst to try and activate the enone. This approach drew inspiration from the cyclisation of the related amino enone **115** (Scheme 89), an unpublished result from the Jackson lab,[96] based on the work reported by Young and co-workers.[97]

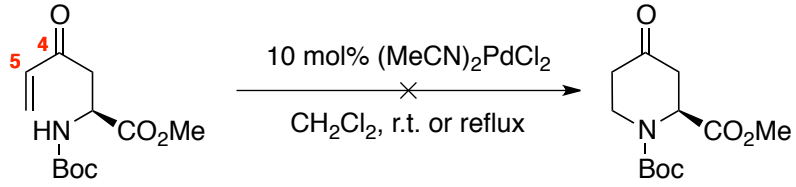
Scheme 89. Palladium(II)-catalysed *6-exo-trig* cyclisation of compound **115**.[96]



115 62%
d.r. 69:31

However, despite the apparent similarities between compound **115** and compound **59c**, reacting the latter with 10 mol% $(MeCN)_2PdCl_2$ in CH_2Cl_2 at room temperature or reflux for extended periods of time resulted in no reaction, returning only unreacted starting material (Scheme 90). This difference in the ease of performing these very similar *6-endo-trig* and *6-exo-trig* cyclisations is interesting given that both are favoured by Baldwin's rules.[98] It may be the result of the reduced flexibility of compound **59c**, due to the presence of two sp^2 atoms (carbons 4 and 5, highlighted in red) between the nitrogen and carbon atoms that need to interact in order for the cyclisation to occur.

Scheme 90. Unsuccessful attempt to cyclise compound **59c** using Pd(II) catalysis.



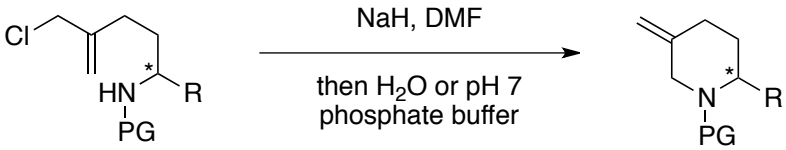
59c **91a**

2.4.2 Deprotonation Strategy

2.4.2.1 Deprotonation Using Sodium Hydride

Given the lack of success achieving cyclisation by activating the electrophile, another method was sought. A deprotonation of the protected amine was envisaged, based on unpublished work from the Jackson group involving the deprotonation and subsequent cyclisation of a number of amino allylic chlorides **116** to yield 5-methylenepiperidines **117** (Scheme 91).[99]

Scheme 91. Base mediated cyclisation of amino alkenes **116**.

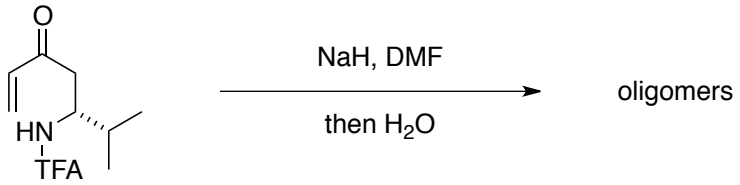


116
PG = Boc, TFA
R = CO_2Me, ^iPr, Bn,
CH_2CO_2Me, $CH_2CH_2CO_2Me$

117
55–85%

Although the previous work showed that sodium hydride was basic enough to deprotonate both Boc and TFA protected amines, TFA protected amino enone **83b** was chosen as the substrate, since the trifluoroacetamide proton should be significantly more acidic than the corresponding *tert*-butyl carbamate proton. Accordingly, compound **83b** was treated with sodium hydride in DMF, before the reaction was quenched with water (Scheme 92).

Scheme 92. Attempted base-promoted cyclisation of compound **83b**.

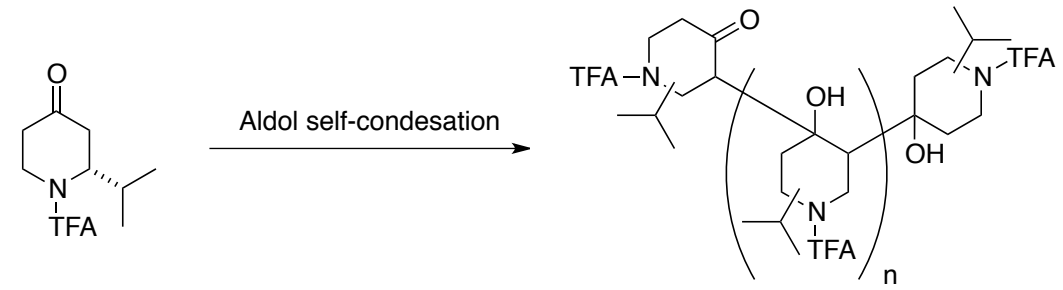


83b

It was difficult to determine whether cyclisation had occurred due to the broad nature of the peaks in the ^1H NMR spectrum, although the lack of alkene protons looked promising. Analysis of the product by mass spectrometry revealed a number of peaks corresponding to the mass of three to six

molecules of product (and/or starting material), suggesting an oligomerisation process. One plausible possibility is that the base remaining in the reaction mixture after the cyclisation promotes an aldol self-condensation of 4-oxopiperidine **92b**, leading to oligomeric material **118** (Scheme 93).

Scheme 93. Possible aldol oligomerisation of compound **92b**.



92b

$C_{10}H_{14}NO_2F_3$

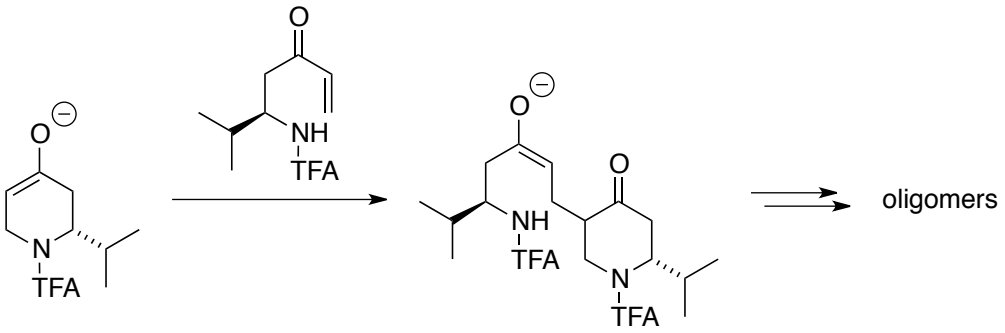
118, n = 1–4

$(C_{10}H_{14}NO_2F_3)_{n+2}\cdot Na^+$

n = 1, observed m/z = 734.3
n = 2, observed m/z = 971.4
n = 3, observed m/z = 1208.5
n = 4, observed m/z = 1445.6

Alternatively, the initial enolate **119** formed after conjugate addition could add to another molecule of starting material (Scheme 94). This would form another enolate **120**, allowing the oligomerisation process to continue.

Scheme 94. Possible oligomerisation process involving sequential conjugate addition reactions.



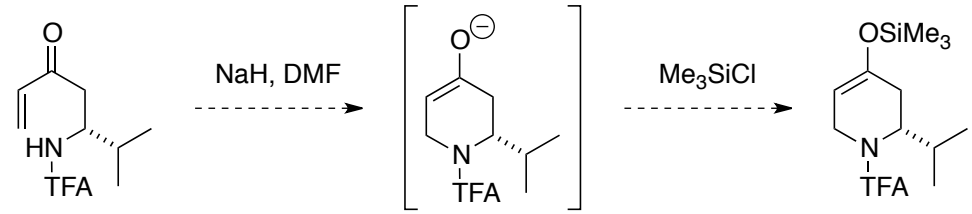
119 **120**

In the previous group work, one of the products **117a** (PG = Boc, R = CO_2Me, see Scheme 91, p86) was no longer enantiomerically pure after a standard aqueous workup.[99] This is because the sodium hydroxide formed when quenching the leftover sodium hydride was able to epimerise the product's

relatively acidic stereocentre. This racemisation process was avoided by using a pH 7 phosphate buffer solution in the workup. In order to test whether the oligomerisation process observed for compound **83b** was caused by sodium hydroxide formed during the workup, the reaction was repeated using a pH 7 phosphate buffer workup. Although analysis of the crude reaction mixture by mass spectrometry showed no mass ions consistent with oligomeric products, the ^{1}H NMR spectrum proved to be complicated, and showed little evidence that the desired cyclic product was present either.

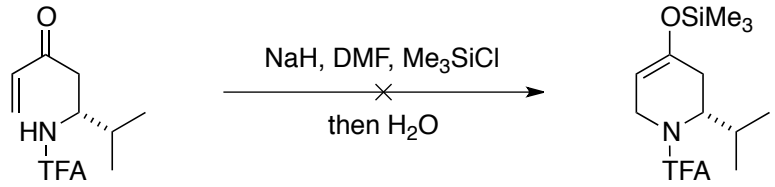
Another potential solution to the problem of oligomerisation would be to trap the enolate initially formed after the conjugate addition as its silyl enol ether (Scheme 95). However, when this reaction was attempted with all the reagents added at the same time, only the starting material was observed after the reaction (Scheme 96).

Scheme 95. Proposed trapping of enolate **119** to prevent oligomerisation.



83b **119** **121**

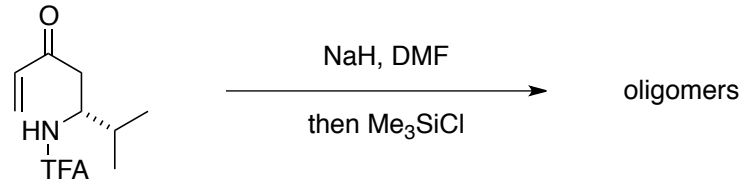
Scheme 96. Attempted trapping of enolate formed after cyclisation of compound **83b**.



83b **121**

Attempting to perform the cyclisation and then to subsequently quench the reaction with trimethylsilyl chloride also failed to yield the desired silyl enol ether, instead again forming oligomeric material (Scheme 97).

Scheme 97. Attempted cyclisation of compound **83b**, followed by trapping of the intermediate enolate.

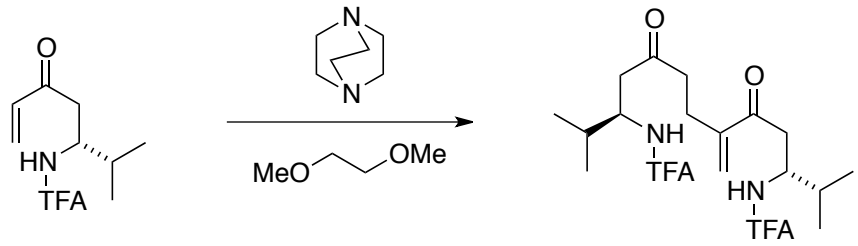


83b

2.4.2.2 Deprotonation Using Milder Bases

It was thought that the problems detailed above were due to the strongly basic nature of sodium hydride, and so a milder base was looked for. Attempts at cyclising compound **83b** using DBU in toluene proved unsuccessful, with no identifiable products being isolated, suggesting decomposition of the starting material. Encouraged by a report of DABCO being used to deprotonate a trifluoroacetamide to allow it to undergo an aza-Michael reaction,[100-101] this was chosen as the next base to attempt the cyclisation. However, when this reaction was attempted no cyclised product was observed. Instead, the unusual dimeric product **122** was formed in a fairly low yield of 27% (Scheme 98).

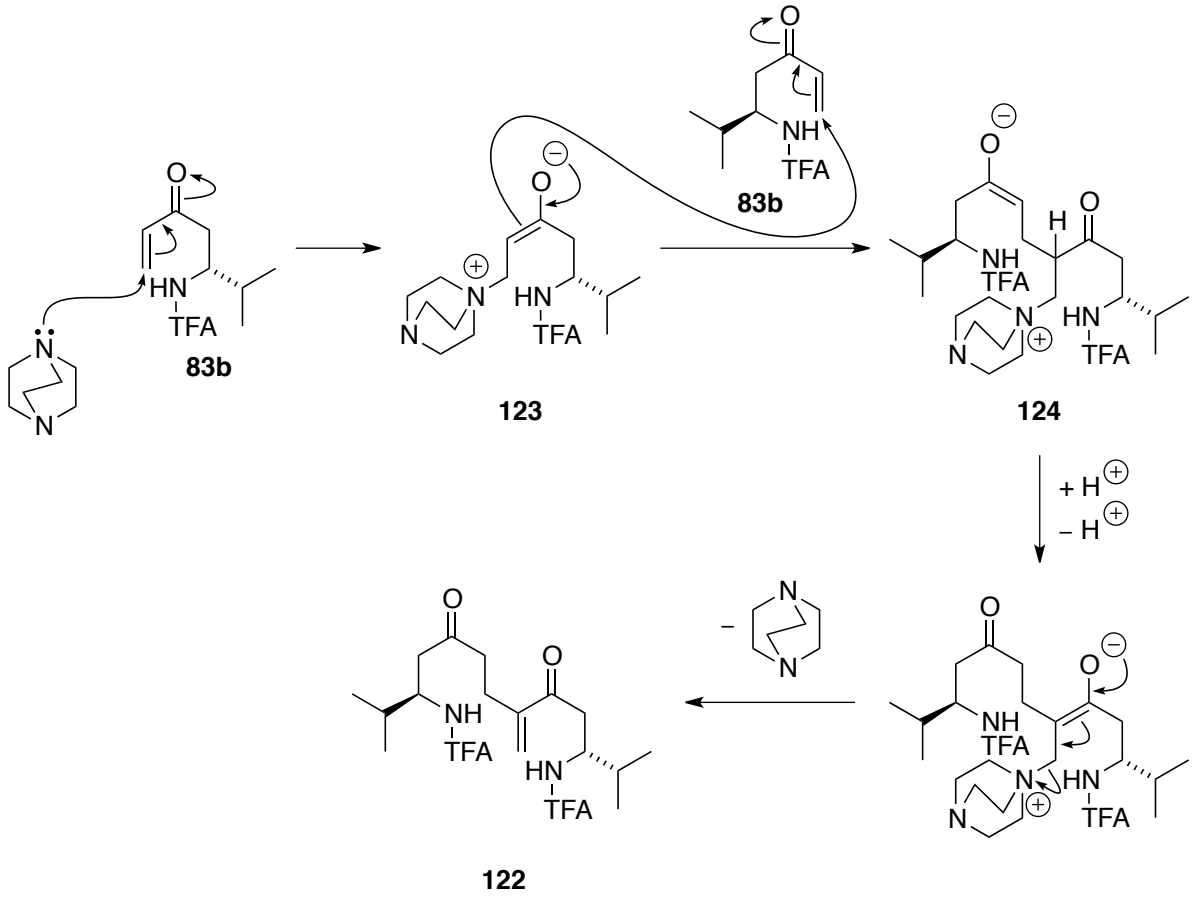
Scheme 98. Formation of compound **122** during the attempted base mediated cyclisation of compound **83b**.



83b **122**
27%

It is thought that this product was the result of a Baylis-Hillman type mechanism, where DABCO added to the enone to form zwitterion **123** (Scheme 99). The enolate then reacted with another molecule of starting material to form intermediate **124**, which, upon tautomerisation and elimination of DABCO, gave rise to the observed product **122**.

Scheme 99. Proposed Baylis-Hillman type mechanism for the formation of compound **122**.



This proposal seems reasonable, as DABCO is well known to catalyse Baylis-Hillman reactions. In fact, this type of dimerisation of enones is known in the literature, and is called the Rauhut-Currier reaction (or the vinylogous Baylis-Hillman reaction).[102] Although this reaction is usually mediated by trialkylphosphines, DABCO has also been shown be a suitable catalyst, for example in the dimerisation of methyl vinyl ketone.[103]

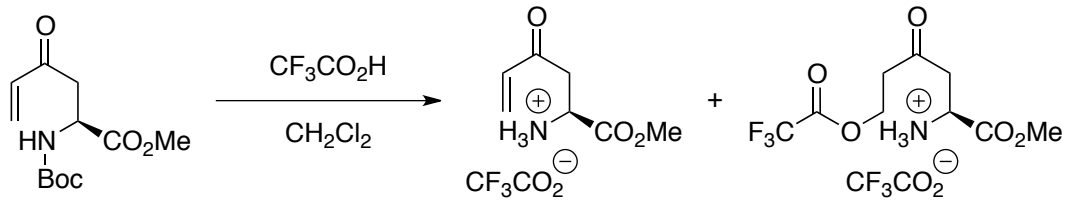
2.4.3 Deprotection Strategy

2.4.3.1 Trifluoroacetic Acid Mediated Boc Deprotection

The third strategy adopted to try and cyclise amino enones **49** involved removal of the protecting group to yield the more nucleophilic free amine. In fact, this was the original synthetic plan, before the discovery that hydrogen chloride was able to add to the enone (see chapter 2.3, p60).

Trifluoroacetic acid proved able to remove the Boc group from compound **59c** to produce ammonium salt **125**, although if the reaction was left for too long the trifluoroacetic acid was also found to add to the enone to form trifluoroacetate **126** (Scheme 100). This highlights the highly electrophilic nature of the terminal enone in compound **59c** as trifluoroacetate is a very poor nucleophile, highlighted by the fact that the pK_a of trifluoroacetic acid is 3.45 in DMSO.[104] This unwanted side reaction could be avoided by stopping the reaction as soon as the deprotection was judged to be complete by TLC.

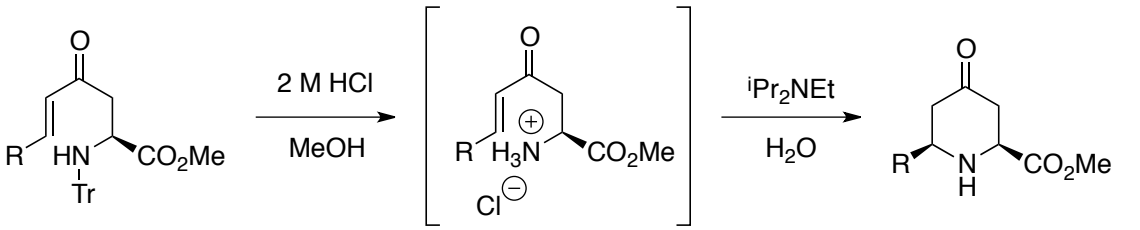
Scheme 100. Deprotection of amine **59c** using trifluoroacetic acid, and subsequent undesired conjugate addition of trifluoroacetate yielding compound **126**.



59c **125** **126**

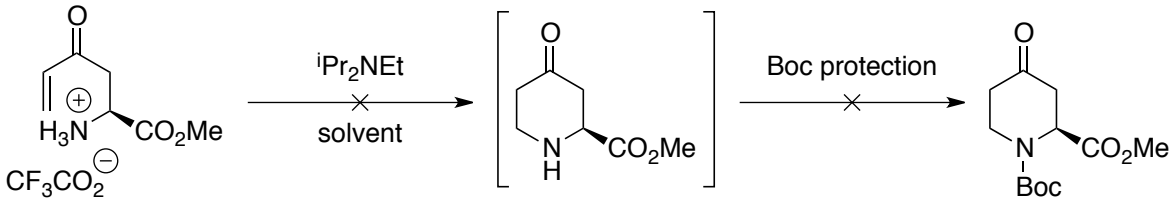
With compound **125** in hand, the next step was to treat it with a base to neutralise the ammonium salt and hopefully carry out the desired *6-endo-trig* cyclisation. This seemed to be a reasonable prospect, given the work of Sutherland and co-workers who cyclised substituted enones **7** using Hünig's base (Scheme 101).[12] However, all attempts to carry out this cyclisation under similar conditions, either under anhydrous conditions or in the presence of water, failed to yield any identifiable products (Scheme 102). In each case the reaction mixture was treated with $(Boc)_2O$ to aid in the isolation of potentially water soluble products.

Scheme 101. Base-promoted cyclisation of substituted enones by Sutherland and co-workers.



7 **127** **10**
11 examples
37–68% (major isomer)
67:33 ≤ d.r. ≤ 86:14

Scheme 102. Attempted base mediated cyclisation and Boc protection of ammonium salt **125**.

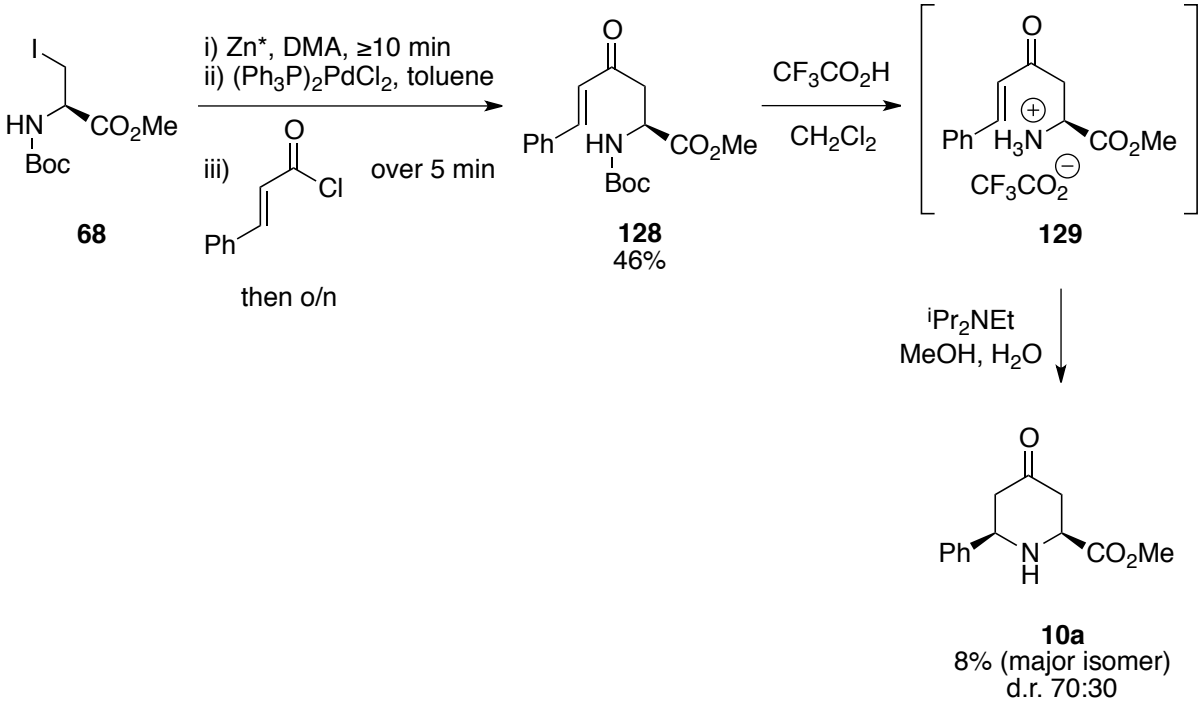


125 **91a**

solvent = THF, CH_2Cl_2, CH_2Cl_2/MeOH, CH_2Cl_2/MeOH/H_2O, MeOH/H_2O

It was decided to try and synthesise a phenyl-substituted enone, as this would be more closely related to the compounds that were cyclised by Sutherland and co-workers. Accordingly, the cross coupling reaction between the organozinc reagent **57c** derived from iodoalanine **68** and cinnamoyl chloride was performed, yielding phenyl-substituted enone **128** in a 46% yield (Scheme 103). This compound was then deprotected using trifluoroacetic acid to give ammonium salt **129**, which is almost identical to one of the intermediates **127** formed by Sutherland (R = Ph, see Scheme 101, p91). Finally, repetition of Sutherland's cyclisation conditions gave the desired *trans*-6-phenyl-4-oxo-L-pipecolate **10a**. The diastereomeric ratio of the two isomers of product was determined to be 70:30, which is similar to the reported ratio of 75:25. However, the yield for the overall reaction was much lower than the yield reported by Sutherland and co-workers (8% cf. 56%). Despite the low (unoptimised) yield for this reaction, this result does suggest that the cyclisation of substituted enones such as **128** using this methodology is easier than the cyclisation of the corresponding terminal enone **59c**.

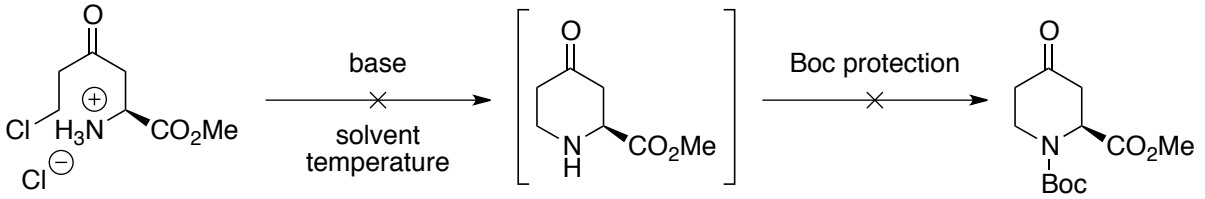
Scheme 103. Synthesis and subsequent cyclisation of phenyl-substituted enone **128**.



2.4.3.2 β-Chloroketones as Starting Materials

It was thought that the β-chloroketone **60c**, the product of the HCl/Et_2O mediated deprotection of amino enone **59c** (see Scheme 66, p65), might also be a suitable substrate for a base mediated cyclisation. However, all attempts to cyclise this compound under basic conditions failed to yield any identifiable products, after Boc protection (Scheme 104, Table 16). Variation of the base and the solvent (entries 1–4) had no effect on the outcome of the reaction. It was thought that the cyclisation might be promoted under thermal conditions, if hydrogen chloride were extruded from the starting material to give the more nucleophilic free amine. To this effect, compound **60c** was heated in toluene at reflux with and without Et_3N (entries 5–6), but again no product was observed after Boc protection. Finally, the starting material was placed under high vacuum using a Kügelrohr distillation apparatus, and heated to try and force the extrusion of hydrogen chloride. Heating to 240 °C (entry 7) caused complete pyrolysis of compound **60c**, and although this could be minimised by lowering the temperature to 150 °C (entry 8), the desired cyclised product was still not observed.

Scheme 104. Attempted base mediated cyclisation and Boc protection of ammonium salt **60c**.



60c **93b** **91a**

Table 16. Various unsuccessful combinations of bases, solvents and temperatures in the attempted cyclisation of ammonium salt **60c**.

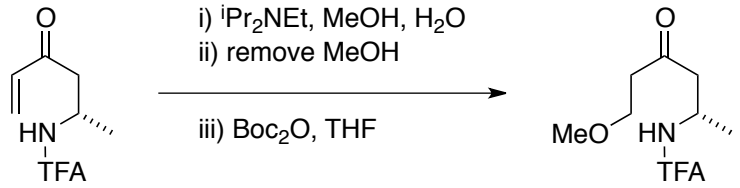
Entry	Base	Solvent	Temperature
1	K_2CO_3	MeOH	r.t.
2	$^{i}Pr_2NEt$	THF	r.t.
3	$^{i}Pr_2NEt$	MeOH/H_2O	r.t.
4	Et_3N	MeOH-d_4	r.t.
5	Et_3N	toluene	110 °C
6	–	toluene	110 °C
7[a]	–	–	240 °C
8[a]	–	–	150 °C

[a] Reaction performed in a Kügelrohr distillation apparatus under high vacuum.

2.4.3.3 Attempted Base Mediated TFA Deprotection

As well as removal of the Boc protecting group from amino enone **59c**, the deprotection of a TFA protected amino enone was also briefly investigated, a process which highlighted potential problems with this protecting group within the current synthetic strategy. TFA groups are removed under basic conditions, and so compound **84b** was treated with Hünig's base in a mixture of methanol and water in order to try and remove the protecting group and encourage cyclisation (Scheme 105). However, after Boc protection, compound **130** was isolated instead of the desired 4-oxopiperidine. Compound **130** arose from the addition of methanol to the enone, whilst the TFA protecting group remained intact. The formation of this by-product suggests that base promoted removal of the TFA group in compounds such as **84b** may be very difficult, due to the competing reaction of any other nucleophilic species with the highly electrophilic enone. As such, it was decided to focus on the Boc protected amines for the deprotection/cyclisation studies.

Scheme 105. Attempted deprotection/cyclisation of TFA protected amine **84b**, leading instead to methanol adduct **130**.

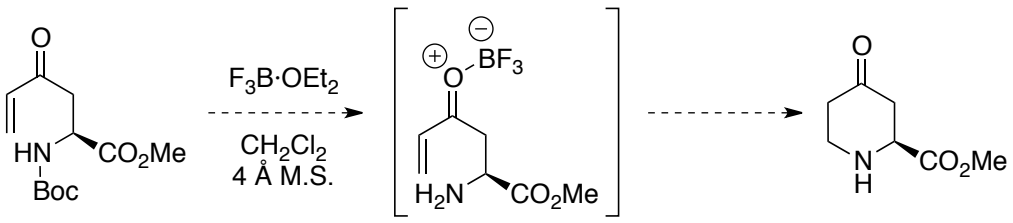


84b **130** 41%

2.4.3.4 Boron Trifluoride Mediated Boc Deprotection

It was noted that boron trifluoride diethyl etherate had previously been employed as a Lewis acid to encourage the cyclisation of amino enones,[91-92,95] and is also a reagent used to deprotect Boc protected amines. Compound **59c** was therefore treated with $F_3B{\cdot}OEt_2$ in an attempt to simultaneously deprotect the amine and activate the electrophile towards cyclisation (Scheme 106). However, after re-protection of the amine, none of the desired 4-oxopiperidine was observed.

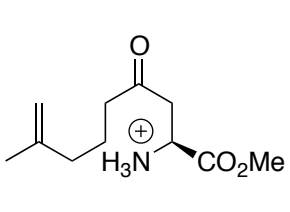
Scheme 106. Proposed simultaneous deprotection/electrophile activation of compound **59c** using $F_3B{\cdot}OEt_2$.



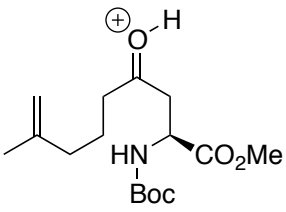
59c **131** **93b**

Analysis of the reaction mixture by mass spectrometry after the attempted cyclisation, and again after re-protection of the amine, showed mass ions with the exact masses 214.1433 and 314.1962. These are 57 mass units above the masses of the desired unprotected and protected products, and match the molecular formulae of $C_{11}H_{20}NO_3^+$ and $C_{16}H_{28}NO_3^+$. The observed mass ions may correspond to structures **132** and **133** (Figure 33).

Figure 33. Proposed structures for the mass ions observed in the reaction of compound **59c** with $F_3B{\cdot}OEt_2$.



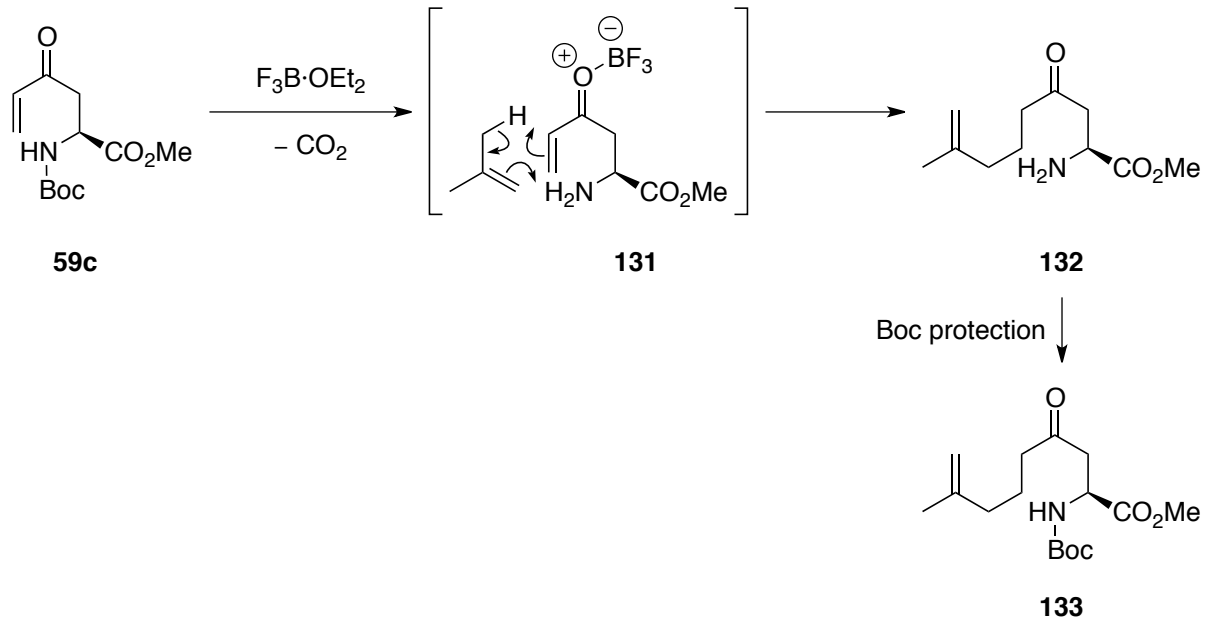
132
observed m/z = 214.1433
calculated m/z = 214.1443



133
observed m/z = 314.1962
calculated m/z = 314.1967

Although these compounds were not isolated from the reaction mixture, a plausible mechanism for their formation involves an Alder-ene reaction between the proposed intermediate **131** and isobutene, liberated during the deprotection the starting material **59c** (Scheme 107). This mechanism seems reasonable, as coordination of the electron-withdrawing BF_3 group to the carbonyl in intermediate **131** will lower the LUMO energy of the alkene, facilitating the proposed pericyclic reaction. It is possible that the free amine in compound **131** also coordinates to BF_3, which would make it less nucleophilic and so less able to undergo the desired *6-endo-trig* cyclisation.

Scheme 107. Proposed BF_3 mediated Alder-ene reaction between isobutene and intermediate **131**.

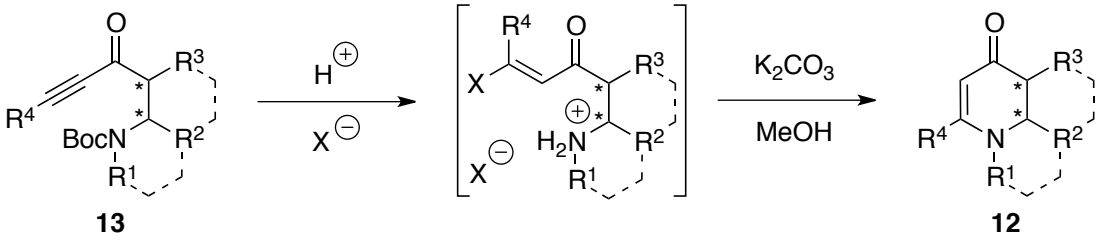


59c **131** **132** **133**

2.4.3.5 Formic Acid/Sodium Iodide Mediated Boc Deprotection

Given the lack of success in cyclising Boc protected amino enone **59c**, inspiration was sought from further afield in the literature. A study by Georg and co-workers on the deprotection/cyclisation of amino ynones **13** highlighted an interesting dependence on halide ions, based on their observation that ynones **13** were converted to β-haloenones before the cyclisation occurred (Scheme 108, also see Chapter 1.2.2.2, p9).[13] These results are analogous to the formation of β-chloroketones upon treatment of amino enones **59c** and **83a** with HCl/Et_2O (see Scheme 66, p65).

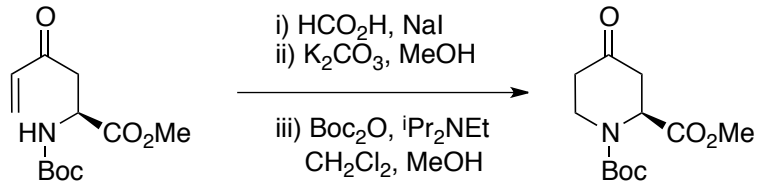
Scheme 108. Formation of β-haloenones during the cyclisation of amino ynones **13**.[13]



13 **12**

Georg and co-workers reported three distinct deprotection methods: 4 M HCl in dioxane; iodotrimethylsilane; and a combination of formic acid and sodium iodide. The latter of these proved to be the best set of conditions for minimising stereochemical erosion of the starting materials when terminal alkynes were employed. It was decided to apply these conditions to amino enone **59c**, which was therefore treated with formic acid and sodium iodide, followed by potassium carbonate in methanol and then Boc_2O (Scheme 109). Very pleasingly, this cyclisation was successful and yielded the desired Boc protected 4-oxopiperidine **91a**, albeit in a modest yield of 12%.

Scheme 109. Successful cyclisation of compound **59c** by applying Georg and co-workers' conditions.



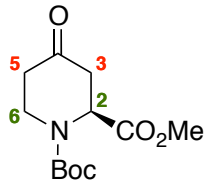
59c **91a** 12%

The cyclic product **91a** was identified by comparison of its ^1H and ^{13}C NMR spectra with those of the closely related ethyl *N*-Boc-4-oxo-L-pipecolate **91b**, which has previously been synthesised by Machetti and co-workers.[90,105] Both sets of spectra were very similar (Table 17 and Table 18, key

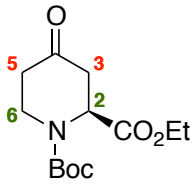
signals highlighted in red and green), with the only slight variation being between the chemical shifts of the carbamate carbonyls (highlighted in blue). However, the close correlation between the NMR spectra, and the presence of the correct mass ion when the sample was analysed by mass spectrometry (observed mass of Na adduct: 280.1152, calculated mass of Na adduct: 280.1161), gave confidence that compound **91a** was indeed the desired 4-oxopiperidine.

Table 17. Comparison of the ^{1}H NMR data for compounds **91a** and **91b**.

Compound **91a**'s ^{1}H NMR Data ($CDCl_3$)	Compound **91b**'s ^{1}H NMR Data ($CDCl_3$)[90,105]
–	1.26 (3H, t, *J* = 7.4)
1.45 (9H, br. s)	1.48 (9H, s)
2.41–2.60 (2H, m)	**2.54 (2H, m)**
2.69–2.88 (2H, m)	**2.80 (2H, m)**
3.54–3.70 (1H, m)	**3.64 (1H, m)**
3.73 (3H, s)	–
4.00–4.10 (1H, m)	**4.02 (1H, dt, *J* = 14.0, 5.8)**
–	4.16 (2H, q, *J* = 7.4)
4.87 and 5.15 (1H, 2 × br. s)	**4.80 and 5.05 (1H, m, two conformers)**



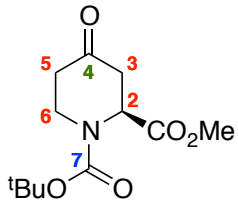
91a



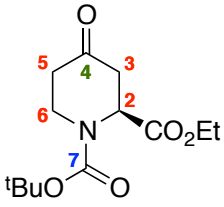
91b

Table 18. Comparison of the ^{13}C NMR data for compounds **91a** and **91b**.

Compound **91a**'s ^{13}C NMR Data ($CDCl_3$)	Compound **91b**'s ^{13}C NMR Data ($CDCl_3$)[90,105]
–	14.1
28.2	28.2
39.3 and 40.5	**39.33 and 40.46**
39.8	**39.7**
41.0 and 41.2	**41.1**
52.6	–
53.9 and 54.7	**54.1 and 54.8**
–	61.7
81.2	81.1
154.3 and 154.8	**146.7**
171.5 and 171.7	171.1
205.8	**205.9**



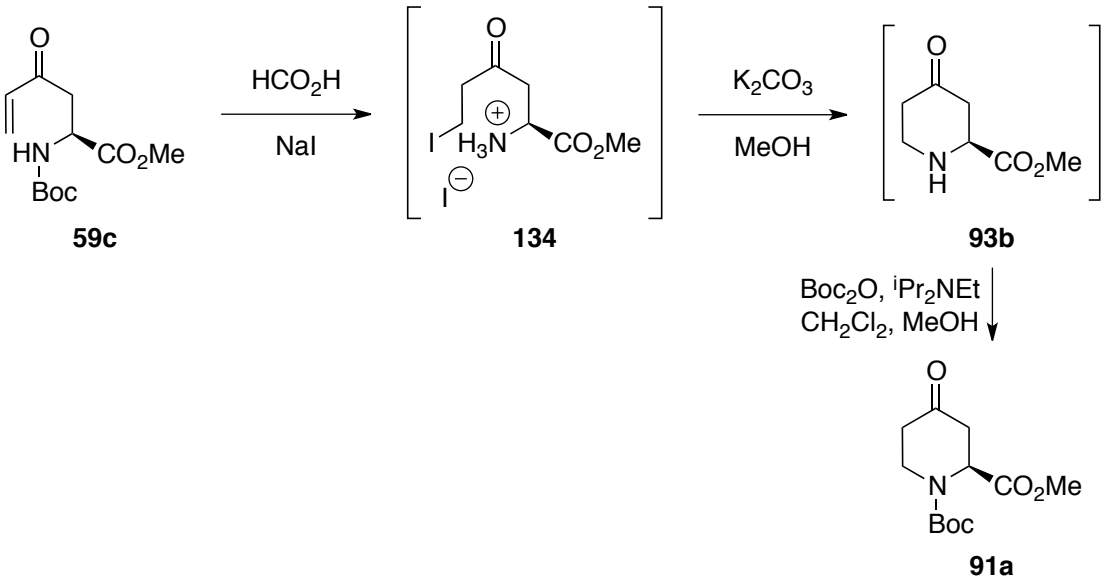
91a



91b

The mechanism of this reaction is presumably related to the observations made previously as to the highly electrophilic nature of terminal enones such as **59c**, and the findings of Georg and co-workers in the activation of amino ynones using halide sources. It is proposed that the formic acid removes the Boc protecting group, whilst the iodide adds to the enone to form β-iodoketone **134** (Scheme 110). This compound is then neutralised by the potassium carbonate before undergoing a *6-exo-tet* cyclisation (or conceivably a *6-endo-trig* cyclisation, if HI is first eliminated from compound **134**) to yield 4-oxopiperidine **93b**, which is finally Boc protected to give the observed product **91a**.

Scheme 110. Proposed mechanism for cyclisation of compound **59c**.

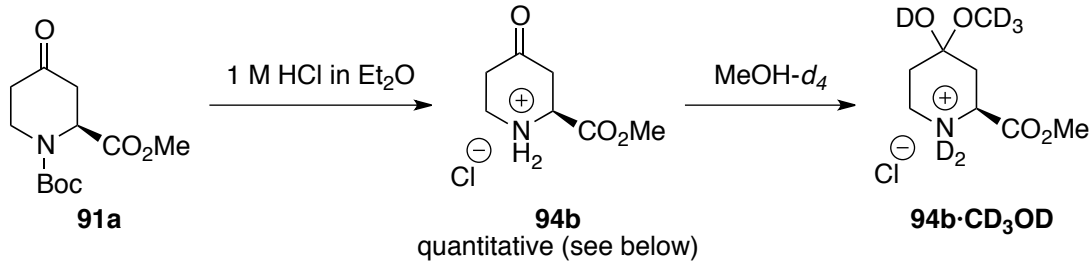


Comparison of the ^{1}H NMR data for compound **91a** with some of the impure ^{1}H NMR spectra recorded after the previously attempted base-promoted cyclisations of compounds **59c** and **60c** (see Scheme 102, p92 and Scheme 104, p94) showed that the desired product had indeed been present in these reaction mixtures, albeit in very small amounts. However, compound **91a** had never been unambiguously identified as a product of these previous cyclisations. This may in part be due to the fact that compound **91a** was not observable by mass spectrometry when it was passed through a liquid chromatography column before entering the spectrometer; it was only detected when it was directly infused into the spectrometer, after being stabilised with Na^{+} ions.

2.5 Deprotection of Cyclised Product

Unfortunately, the cyclisation of amino enone **59c** proved to be unreliable, either giving a lower yield of product or no product at all upon repetition. Likewise, a single attempt to cyclise the related L-valine derived amino enone **83a** under the same conditions failed to yield the desired product. The resulting lack of materials, coupled with time constraints, meant that the planned reduction of these *N*-Boc 4-oxopiperidines could not be attempted. However, compound **91a** was treated with 1 M HCl in Et_2O in order to access 4-oxopiperidine **94b** (Scheme 111). The characterisation data for this compound were compared with those of compound **60c**, to further test the proposal that compound **60c** is an acyclic β-chloroketone, and not a cyclic 4-oxopiperidine (see Chapter 2.3, p60).

Scheme 111. Deprotection of *N*-Boc 4-oxopiperidine **91a**, and subsequent hemi-acetal formation.



91a | **94b** quantitative (see below) | **94b·CD_3OD**

The deprotection of 4-oxopiperidine **91a** took considerably longer than that of compound **59c** (11 days cf. 3 days), and the product appeared to be a hemi-acetal when dissolved in MeOH-d_4. This is not unexpected, as similar compounds in the literature have been reported to form hemi-acetals and hydrates.[91-93,106-107] The reaction yield based on the mass of the product was calculated to be 104%, which, given the previous discrepancies in the yields of similar reactions (see Chapter 2.3, p60) might raise questions about the structure of the product. However, this deprotection was performed on a very small scale (0.15 mmol), meaning that small changes in mass result in large changes in the yield; the product weighed 30.2 mg, only 1.2 mg more than the theoretical maximum mass. This additional mass may be due to a very small amount of an impurity visible in the ^{1}H NMR spectrum, or it may be that this difference is within the error margin of the balance. As a result of these factors, together with characterisation data that suggests that the structure of the product is correct (see below), the yield of compound **94b** has been stated to be quantitative.

The fact that 4-oxopipecolate **94b** forms a hemi-acetal in MeOH-d_4 highlights the differences between this compound and compound **60c** (Table 19 and Figure 34). The clearest differences are seen in the chemical shifts of the protons attached to carbons 3 and 5 (highlighted in red), although there are considerable differences between almost all of the signals.

Table 19. Comparison of the ^{1}H NMR data for compounds **94b·CD$_3$OD** and **60c** in MeOH-*d*$_4$.

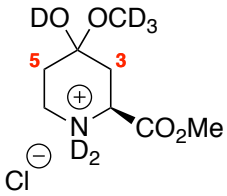
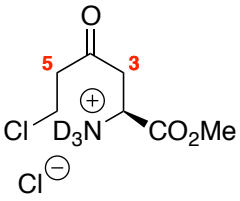
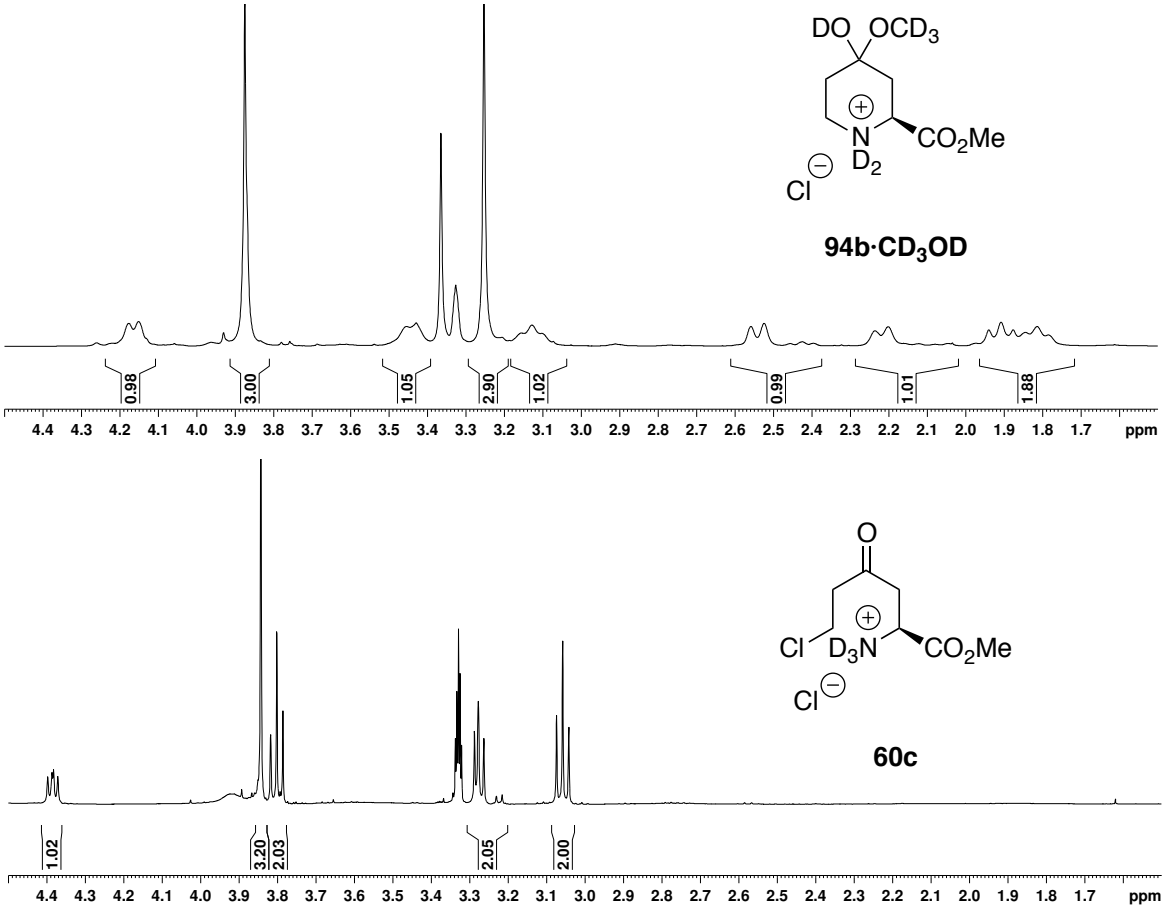
Compound **94b**'s ^{1}H NMR Data (CD_3OD)		Compound **60c**'s ^{1}H NMR Data (CD_3OD)	
	1.71–2.00 (2H, m)	**3.06 (2H, t, *J* = 6.4)**	
	**2.02–2.29 (1H, m)**	**3.21–3.30 (2H, m)**	
	2.37–2.61 (1H, m)	–	
	3.04–3.18 (1H, m)	3.80 (2H, t, *J* = 6.4)	
	3.39–3.53 (1H, m)	–	
94b·CD$_3$OD	3.88 (3H, s)	3.84 (3H, s)	**60c**
	4.16 (1H, d, *J* = 10.0)	4.38 (1H, dd, *J* = 4.4, 6.1)	

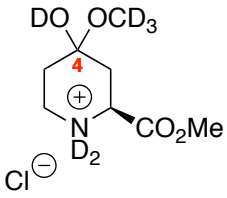
Figure 34. Comparison of the ^{1}H NMR spectra for compounds **94b·CD$_3$OD** and **60c** in MeOH-*d*$_4$.



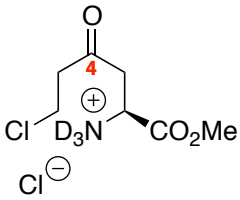
The differences between the two compounds can also be seen in the ^{13}C NMR data (Table 20 and Figure 35). The chemical shift of 96.2 ppm for carbon 4 (highlighted in red) in compound **94b·CD$_3$OD** is indicative of a hemi-acetal, whereas the corresponding carbon in compound **60c** appears at 204.1 ppm, where a free ketone would be expected.

Table 20. Comparison of the ^{13}C NMR data for compounds **94b·CD$_3$OD** and **60c** in MeOH-*d*$_4$.

Compound 94b's ^{13}C NMR Data (CD$_3$OD)[a,b]		**Compound 60c's ^{13}C NMR Data (CD$_3$OD)**
	28.6	37.3
	32.4	41.4
	40.8	44.2
	52.6	48.1
	54.5	52.5
	96.2	–
	168.3	168.7
	–	**204.1**



94b·CD$_3$OD

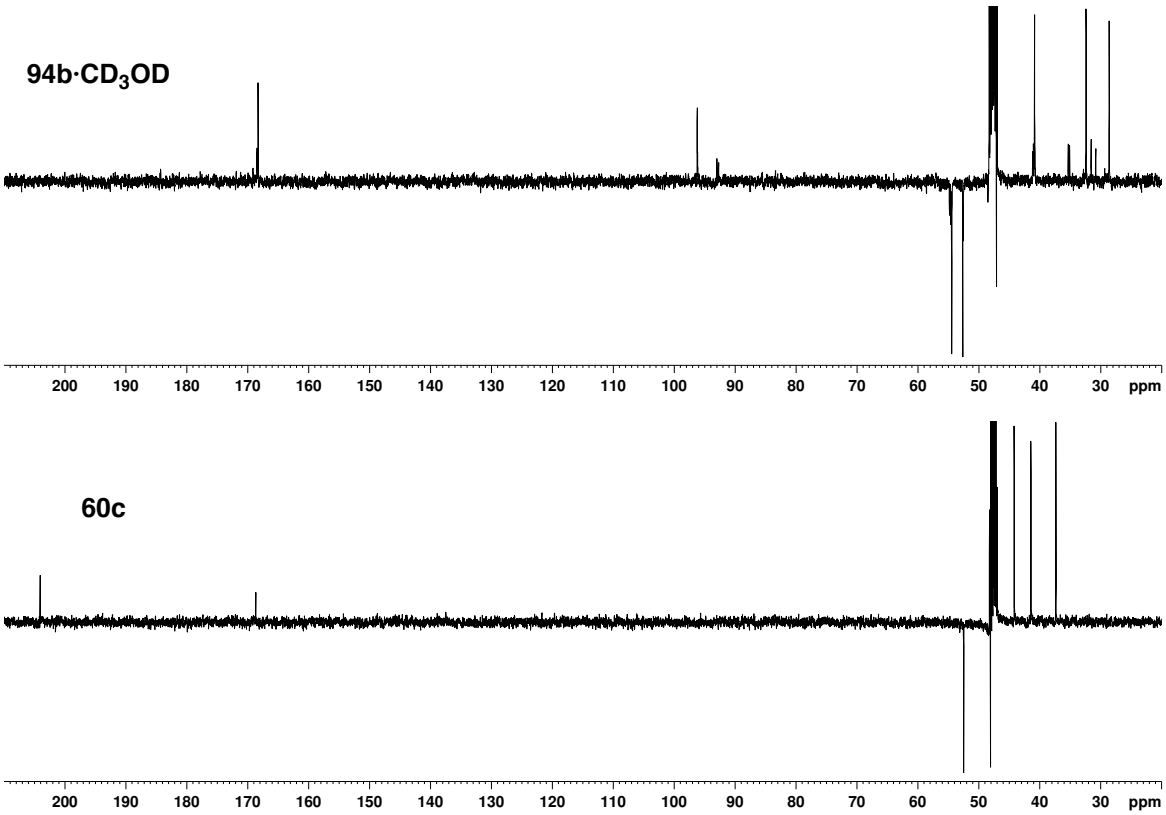


60c

[a] Only the data for the major product are shown (the extra signals in the ^{13}C NMR spectrum may be due to the presence of the second possible diastereoisomer of the product).

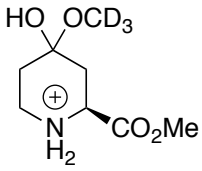
[b] The septet expected for the CD$_3$ signal of the hemi-acetal was not visible, presumably because it is hidden by the large septet at 47.7 ppm arising from the use of CD$_3$OD as the NMR solvent.

Figure 35. Comparison of the ^{13}C NMR spectra for compounds **94b·CD$_3$OD** and **60c** in MeOH-*d*$_4$.



When compound **94b·CD$_3$OD** was analysed by mass spectrometry the mass ion 193.1265 was observed, which corresponds to the molecular formula $C_8H_{13}D_3NO_4^+$ and is consistent with structure **94b·CD$_3$OH** (Figure 36). Although the sample submitted for mass spectrometry was fully deuterated as it was dissolved in MeOH-*d*$_4$, the solvent system used during mass spectrometry was 0.1% formic acid dissolved in a gradient of acetonitrile/water. This means that any labile deuterium atoms would exchange with hydrogen atoms in the mildly acidic medium, explaining the existence of the observed product **94b·CD$_3$OH**; whilst the deuterium atoms attached to the oxygen and nitrogen atoms have been replaced by hydrogen atoms, the CD_3 group of the hemi-acetal has remained in the structure as these deuterium atoms were not labile in the solvent system.

Figure 36. Mass ion found upon accurate mass analysis of compound **94b·CD$_3$OD**.



94b·CD$_3$OH
observed m/z = 193.1265
calculated m/z = 193.1268

In order to try and simplify the ^{1}H and ^{13}C NMR spectra of compound **94b**, conversion of hemi-acetal **94b·CD$_3$OD** into hydrate **94b·D$_2$O** was attempted, as there is only one possible diastereoisomer for this product. Repeated removal of the solvent from compound **94b·CD$_3$OD** and re-dissolution in D_2O resulted in the successful formation of the desired compound **94b·D$_2$O**. When the sample was submitted for NMR analysis, the labile protons attached to nitrogen and oxygen appeared to have exchanged for deuterium atoms, as expected. Interestingly, it appeared that some of the protons α to the ketone in **94b·D$_2$O** had also exchanged with deuterium atoms, as judged by the reduction in the integration of these signals in the ^{1}H NMR spectrum, and a reduction in intensity of the corresponding carbon peaks in the ^{13}C NMR spectrum. A similar hydrogen-deuterium exchange process has previously been reported to occur in 1,3-disubstituted 4-oxopiperidines.[106]

The α-deuteration of compound **94b** can be explained by considering the intermediate ketone **94b-*d*$_2$**, which would form during equilibration between the hemi-acetal **94b-*d*$_2$·CD$_3$OD** and the hydrate **94b-*d*$_2$·D$_2$O** (Scheme 112). The α-protons in compound **94-*d*$_2$** will be relatively acidic because they are adjacent to a ketone. Furthermore, they will be particularly acidic in this compound because of the inductive effect of protonated nitrogen. (This inductive effect is also responsible for the

increased electrophilicity of the ketone, explaining the ease of hydrate/hemi-acetal formation.) As a result of the increased acidity of these α-protons, it is not surprising that they are able to undergo deuterium exchange under the equilibrating conditions. This can happen in theory up to four times to produce compound **94b-*d*$_6$·D$_2$O**. When a sample of compound **94b-*d*$_n$·D$_2$O** dissolved in D_2O was submitted for analysis by mass spectrometry, mass ions for poly-deuterated products with up to six deuterium atoms were observed, as well as the non-deuterated mass ion 176.0916 (Figure 37).

Scheme 112. Proposed mechanism for the α-deuteration of 4-oxopiperidine **94b-*d*$_2$**.

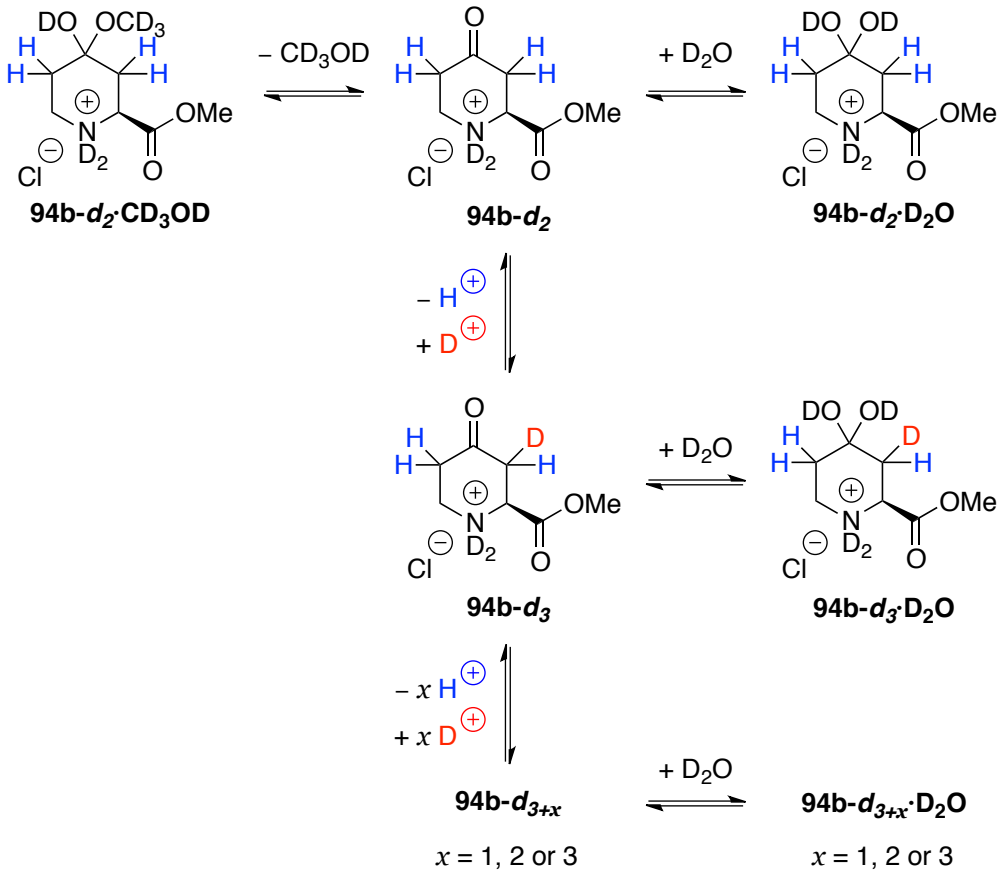
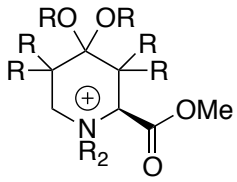


Figure 37. Observed mass ions that correspond to poly-deuterated isotopologues of hydrate **94b·H$_2$O**.



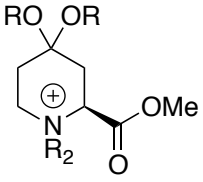
94b·R$_2$O
R = H or D

$C_7H_{14-n}D_nNO_4^+$

n = 0, observed m/z = 176.0916
calculated m/z = 176.0923
n = 1, observed m/z = 177.0940
n = 2, observed m/z = 178.1016
n = 3, observed m/z = 179.1091
n = 4, observed m/z = 180.1158
n = 5, observed m/z = 181.1204
n = 6, observed m/z = 182.1281

In order to be able to report complete NMR data for compound **94b·D₂O**, and to be able to compare its NMR data with those of compound **60c**, poly-deuterated compound **94b-*dₙ*·D₂O** was repeatedly dissolved in H_2O and concentrated under vacuum to replace the deuterium atoms α to the ketone with hydrogen atoms. After this, ^{1}H and ^{13}C NMR data were collected in D_2O, and as expected the α-protons were once again visible, confirming the presence of the desired compound **94b·D₂O**. Accurate mass analysis of the product showed the desired mass ion 176.0917, as well mass ions showing the inclusion of up to three deuterium atoms, consistent with deuterium exchange of some of the labile hydrogen atoms attached to the nitrogen or oxygen atoms (Figure 38).

Figure 38. Mass ions found upon accurate mass analysis of compound **94b·D₂O** after repeated equilibration in H_2O.



94b·R₂O
R = H or D

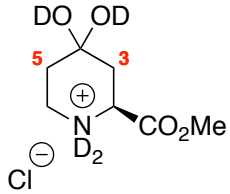
$C_7H_{14-n}D_nNO_4^+$

n = 0, observed m/z = 176.0917
calculated m/z = 176.0923
n = 1, observed m/z = 177.0970
n = 2, observed m/z = 178.1043
n = 3, observed m/z = 179.1123

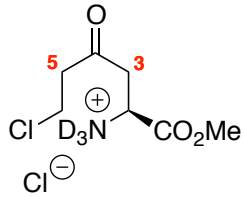
Comparison of the ^{1}H and ^{13}C NMR data for compound **94b·D₂O** and compound **60c** in D_2O showed differences consistent with those already described for compound **94b·CD₃OD** (Table 21, Figure 39, Table 22, and Figure 40, key signals highlighted in red, cf. Table 19, p 101 and Table 20, p102).

Table 21. Comparison of the ^{1}H NMR data for compounds **94b·D₂O** and **60c** in D_2O.

Compound 94b's ^{1}H NMR Data (D_2O)	**Compound 60c's ^{1}H NMR Data (D_2O)**
1.82–1.90 (1H, m)	**3.00 (2H, td, *J* = 6.0, 3.1)**
1.90–1.99 (1H, m)	–
2.02 (1H, dd, *J* = 11.0, 14.3)	**3.27–3.32 (2H, m)**
2.31 (1H, ddd, *J* = 2.3, 3.9, 14.3)	–
3.13–3.21 (1H, m)	3.68 (2H, t, *J* = 6.0)
3.43 (1H, dt, *J* = 13.1, 4.6)	–
3.75 (3H, s)	3.71 (3H, s)
4.20 (1H, dd, *J* = 3.9, 11.0)	4.35 (1H, t, *J* = 5.1)



94b·D₂O



60c

Figure 39. Comparison of the ^{1}H NMR spectra for compounds **94b·D$_2$O** and **60c** in D$_2$O.

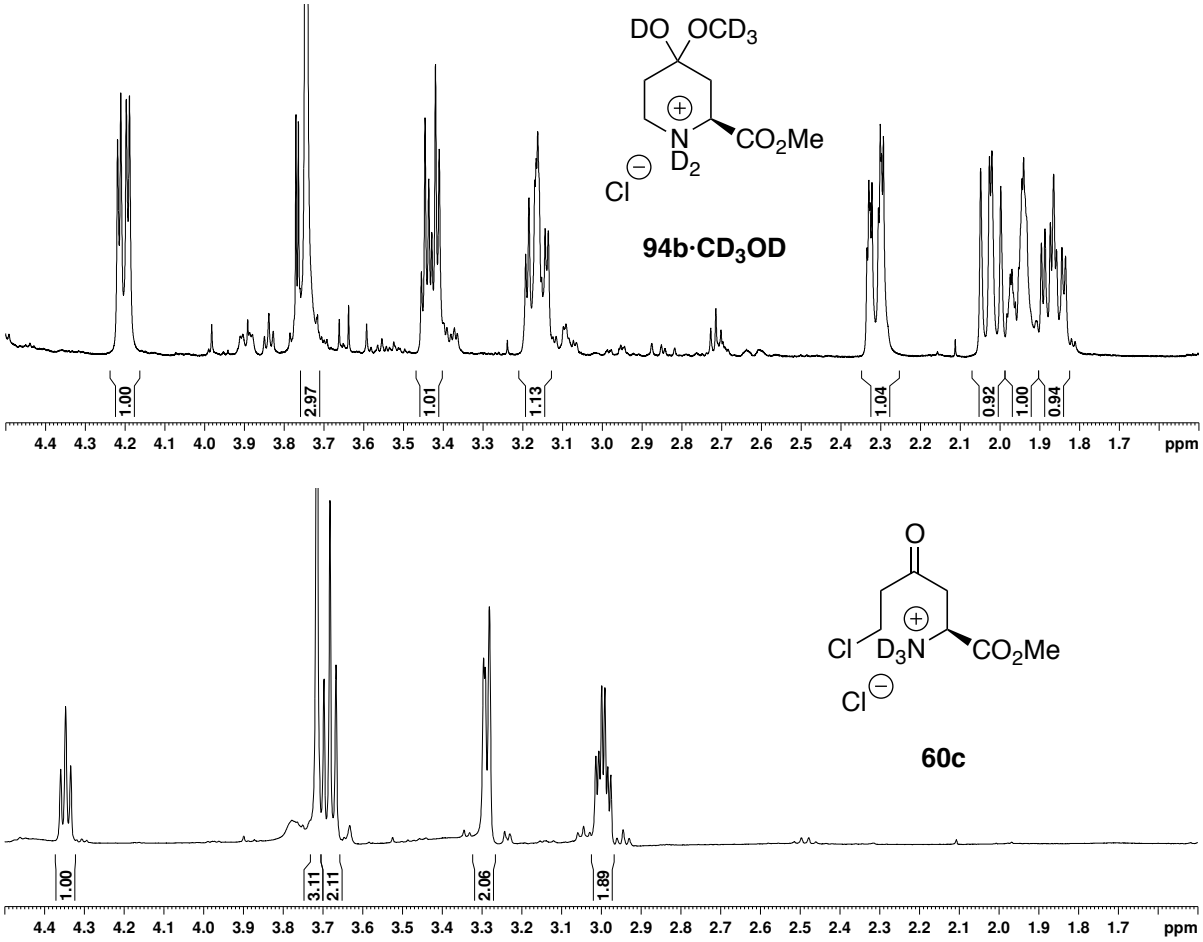
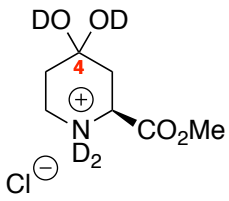
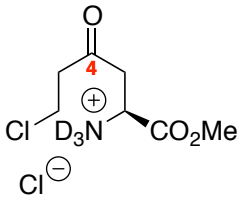


Table 22. Comparison of the ^{13}C NMR data for compounds **94b·D$_2$O** and **60c** in D$_2$O.

Compound **94b**'s ^{13}C NMR Data (D$_2$O)	Compound **60c**'s ^{13}C NMR Data (D$_2$O)
33.5	38.0
36.8	41.5
40.9	44.0
53.7	48.3
54.6	53.8
90.4	–
169.3	169.8
–	**207.7**

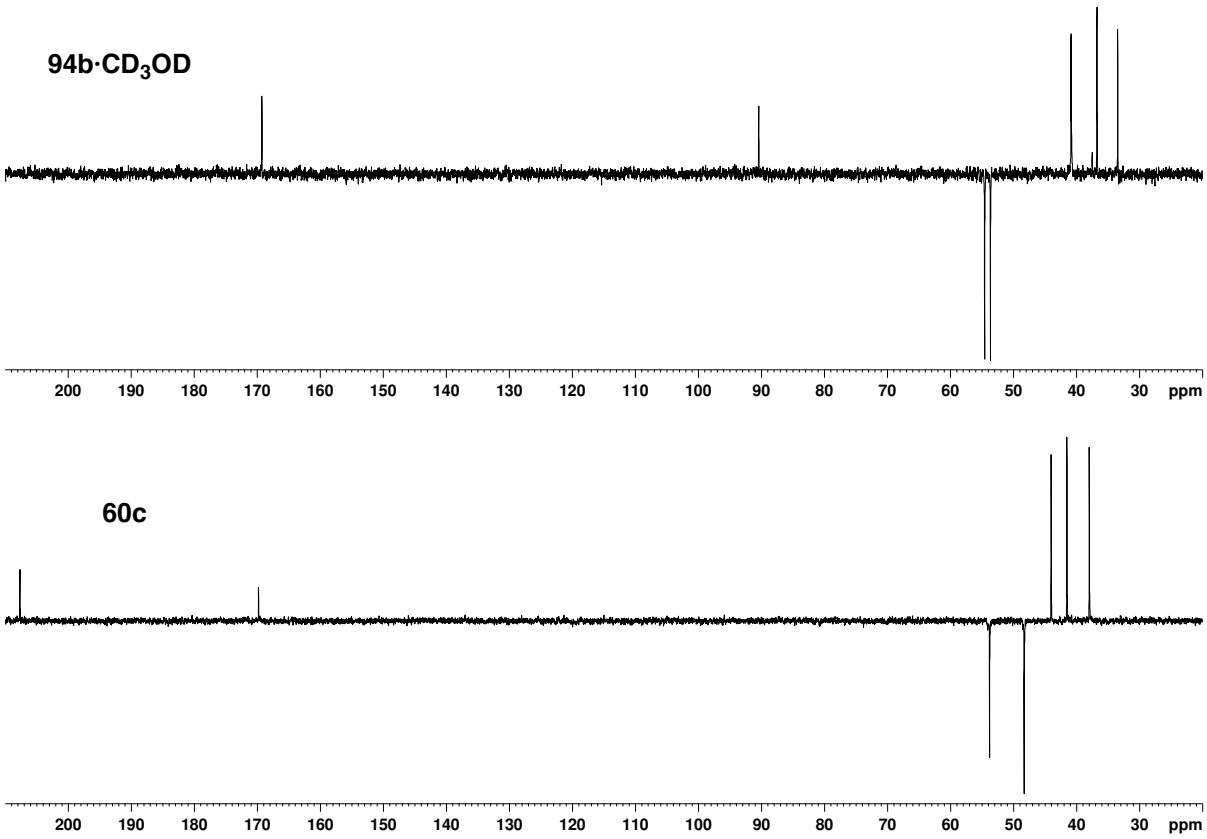


94b·D$_2$O



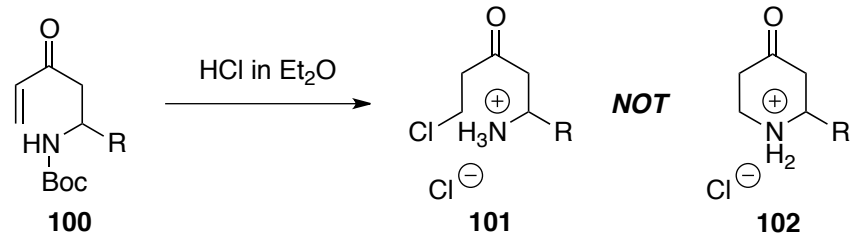
60c

Figure 40. Comparison of the ^{13}C NMR spectra for compounds **94b·D₂O** and **60c** in D_2O.



The fact that a genuine sample of 4-oxopipecolate **94b** has different characterisation data to compound **60c** (the product of the HCl/Et_2O mediated deprotection of compound **59c**) provides further evidence to support the earlier claim that treatment of *N*-Boc amino enones **100** with HCl in Et_2O yields β-chloroketones **101**, rather than the previously reported 4-oxopiperidines **102** (Scheme 113, also see Chapter 2.3, p60).

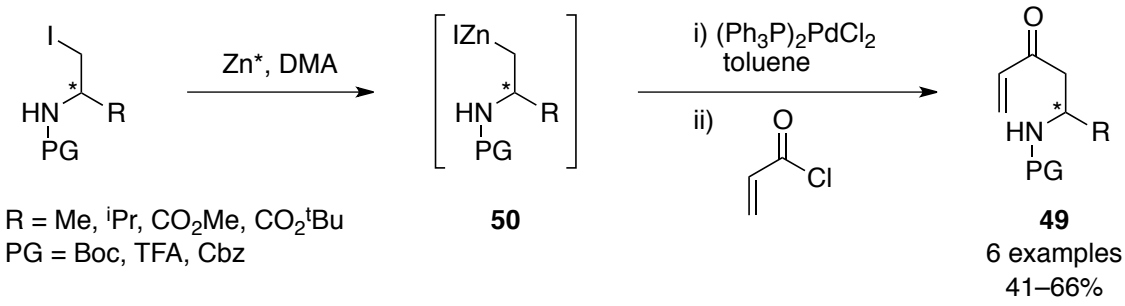
Scheme 113. The products of the treatment of Boc protected amino enones **100** with HCl in Et_2O are β-chloroketones **101**, rather than the previously claimed 4-oxopiperidines **102**.



3. Conclusions

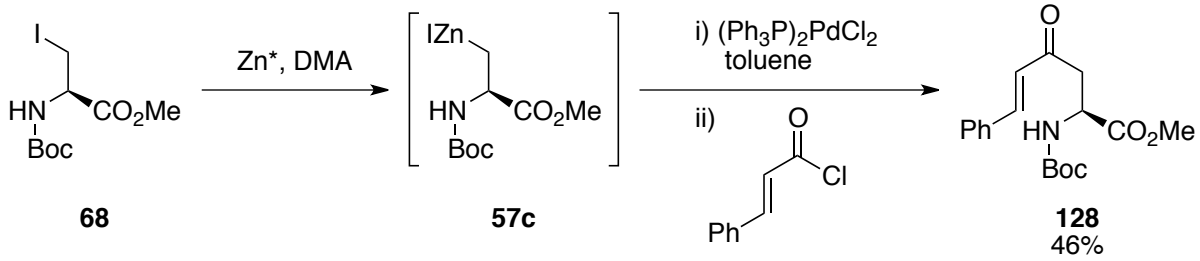
Various α-amino acid derived organozinc reagents **50** have been reacted with acryloyl chloride under palladium catalysis to give the desired amino enones **49**, generally in moderate yields (Scheme 114). This reaction was exemplified with organozinc reagents containing three different protecting groups, namely the *tert*-butoxycarbonyl, trifluoroacetyl and benzyloxycarbonyl groups. Of all the organozinc reagents studied, only the Boc protected L-alanine derived reagent (i.e. PG = Boc, R = Me) failed to undergo the Negishi cross coupling reaction efficiently, as a result of its particular instability, presumably towards β-elimination.

Scheme 114. Negishi cross coupling reaction between the α-amino acid derived organozinc reagents **50** and acryloyl chloride, leading to amino enones **49**.



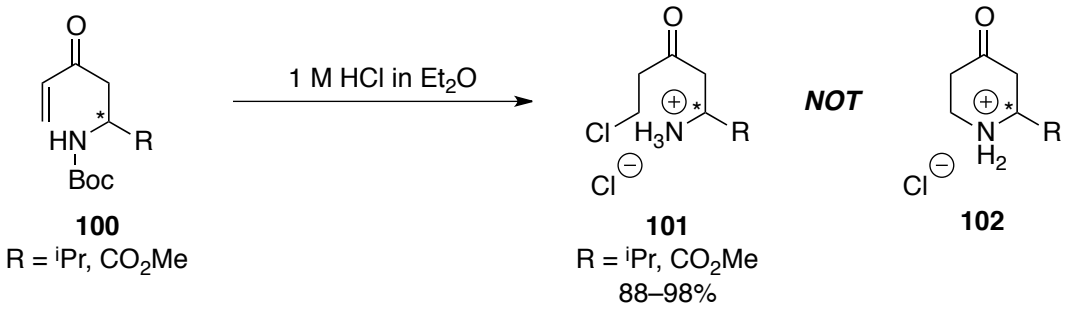
L-Serine derived organozinc reagent **57c** was also reacted with cinnamoyl chloride, showing that 6-substituted amino enones can also be accessed using this methodology (Scheme 115).

Scheme 115. Synthesis of phenyl-substituted amino enone **128** from the L-serine derived organozinc reagent **57c**.



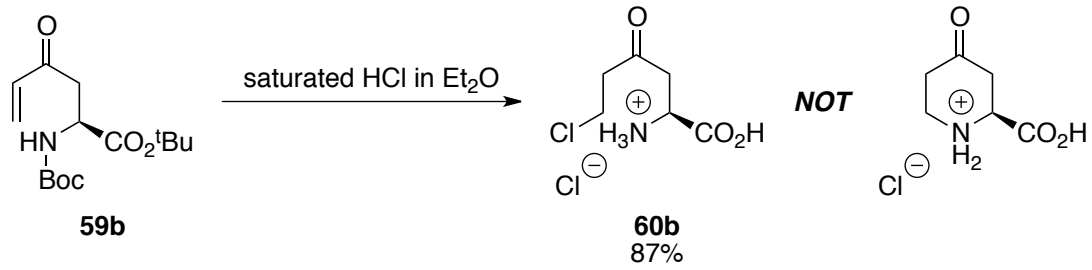
Attempts to cyclise the Boc protected amino enones **100**, by applying conditions reported for the synthesis of 4-oxopipecolates,[52,56-57] led to the uncyclised β-chloroketones **101** rather than the expected 4-oxopiperidinium salts **102** (Scheme 116).

Scheme 116. Treatment of amino enones **100** with hydrogen chloride in diethyl ether, leading to β-chloroketones **101** rather than 4-oxopiperidinium salts **102**.



The original hydrogen chloride mediated cyclisation reported in the literature was repeated (Scheme 117),[56-57] and the product was shown to be β-chloroketone **60b** rather than the previously claimed 4-oxopipecolic acid hydrochloride, through extensive analysis of its characterisation data. It is of interest to note that the original procedure was published in *Organic Syntheses*,[57] and therefore had been independently checked in the laboratory of one of the members of the journal's Board of Editors before publication. While this aspect of *Organic Syntheses*' approach to publishing undoubtedly gives the reader increased confidence in the reliability of the synthetic procedure, this example highlights the fact that a reproducible procedure is not free from the possibility of error; while Obrecht's procedure consistently gives the same product (it has been successfully repeated by the checkers at *Organic Syntheses*, and by the current author), the mistake made in identifying the structure of the final product was not rectified through the checking procedure, and perhaps could not have been.

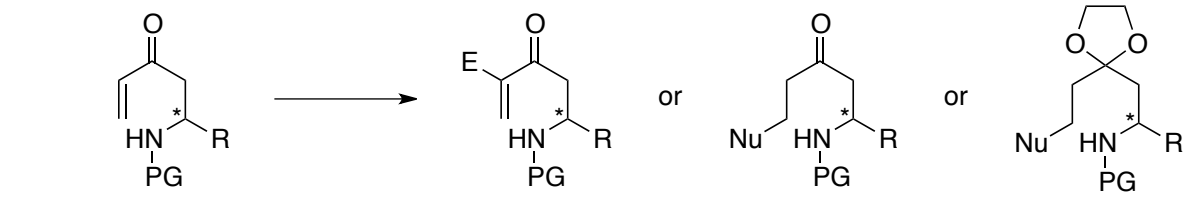
Scheme 117. Repetition of Obrecht's reported cyclisation reaction, which gave β-chloroketone **60b** rather than the previously reported 4-oxopipecolic acid hydrochloride.



Given the lack of success in cyclising the Boc protected amino enones **100** using hydrogen chloride in diethyl ether, alternative cyclisation methods were sought. However, most of the reactions attempted failed to yield cyclic products. In some cases these failed cyclisation reactions gave rise to

a range of identifiable by-products **135**, **136** and **137** (Scheme 118). Some of the difficulties involved in carrying out this cyclisation included: the high reactivity of the terminal enone towards nucleophiles; the low reactivity of the protected amine as a nucleophile; the acidity of the protons α to the ketone, leading in some cases to oligomerisation; and the high water solubility of any products containing a free amine as the result of a deprotection reaction.

Scheme 118. Various classes of by-product formed from the unsuccessful attempts to cyclise amino enones **100**.



100
R = Me, ^{i}Pr, CO_2Me, $CO_2{}^{t}Bu$
PG = Boc, TFA, Cbz

135
1 example

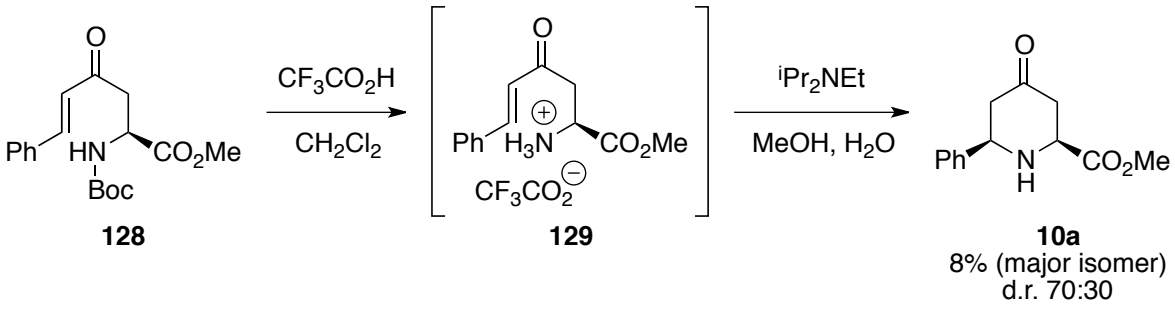
136
3 examples

137
3 examples

E = electrophile, Nu = nucleophile

In contrast to the terminal enones **100**, phenyl substituted amino enone **128** was cyclised relatively easily (Scheme 119). The Boc group was removed using trifluoroacetic acid, which generated the trifluoroacetate salt **129**. This intermediate was cyclised by applying the conditions reported by Sutherland and co-workers for the cyclisation of essentially the same intermediate (generated in a different manner), namely treatment with Hünig's base in a mixture of methanol and water.[12] Without reaction optimisation, the product **10a** was obtained in a much lower yield than Sutherland and co-workers reported (8% cf. 56%), although the diastereomeric ratio of the products was similar to the reported value. Surprisingly, this methodology proved to be unsuitable for the cyclisation of the corresponding terminal enone **59c**, highlighting a difference in the ease of cyclising substituted and terminal amino enones of this type.

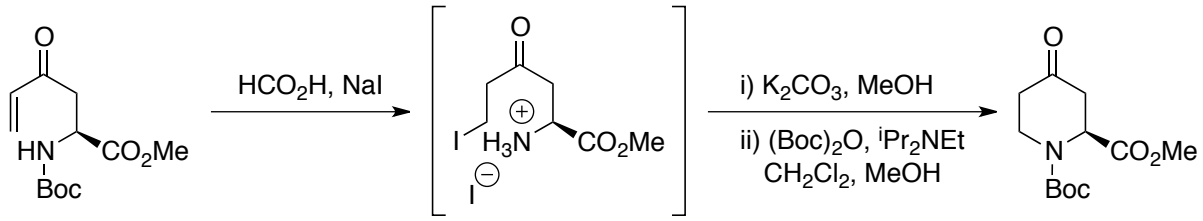
Scheme 119. Cyclisation of phenyl substituted amino enone **128** by deprotection of the Boc group, followed by application of the basic conditions reported by Sutherland and co-workers.



128 **129** **10a**
8% (major isomer)
d.r. 70:30

Pleasingly, after extensive experimentation and careful searching of the literature, a successful cyclisation methodology for the terminal enone **59c** was developed, inspired by the work of Georg and co-workers.[13] It is proposed that removal of the Boc group in the presence of sodium iodide formed the intermediate β-iodoketone **134** (Scheme 120), which was cyclised using potassium carbonate dissolved in methanol. Finally, the resulting amine was re-protected in order to aid in its isolation. This gave the desired Boc protected 4-oxopiperidine **91a**, albeit in a rather low yield of 12%.

Scheme 120. Successful cyclisation of amino enone **59c** leading to Boc protected 4-oxopiperidine **91a**.

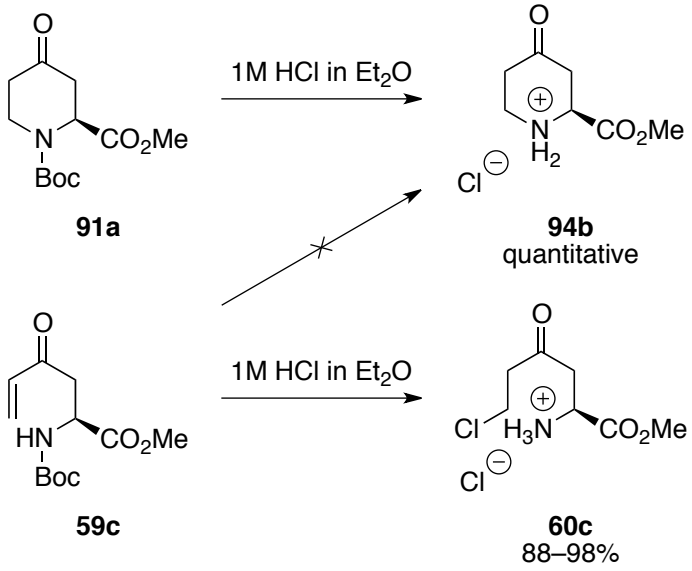


59c **134** **91a**
12%

Unfortunately, this cyclisation reaction proved difficult to repeat, and one attempt to cyclise the corresponding L-valine derived amino enone **83a** using these conditions was also unsuccessful. As a result, the planned reduction of the 4-oxopiperidines **105** to form the target 4-hydroxypiperidines **47** could not be attempted due to a lack of the required compounds. Instead, the Boc protecting group in compound **91a** was removed to give the free amine as its hydrochloride salt **94b** (Scheme 121). The ^{1}H and ^{13}C NMR characterisation data for compound **94b** were compared with the corresponding data for compound **60c**, the product of the treatment of amino enone **59c** with ethereal hydrogen chloride, and the two products were clearly seen to be different compounds. This

provided further evidence that the product of the latter reaction was not the 4-oxopiperidine, as had previously been reported for very similar compounds.[52,56-57]

Scheme 121. Deprotection of compound **91a**, and comparison of the product **94b** with the product of the treatment of amino enone **59c** with hydrogen chloride in diethyl ether.

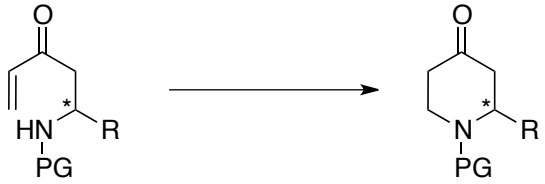


In conclusion, while the palladium-catalysed Negishi cross coupling reaction of a range of amino acid derived organozinc reagents **50** with acryloyl chloride was successful in generating 2-substituted amino enones **49**, the project's ultimate aim of devising a general route to chiral, 2-substituted 4-hydroxypiperidines **47** using this chemistry has proved largely unsuccessful. This is in part due to the fact that the proposed synthetic route was based on a false premise, namely that treating Boc protected amino enones **100** with hydrogen chloride in diethyl ether leads to the corresponding 4-oxopiperidinium salts **102**, and also because this cyclisation proved particularly difficult to achieve, despite its apparent simplicity. While these facts have resulted in a fair amount of disappointment and frustration during the course of this PhD, there is some comfort for the author in the fact that the real outcome of the hydrogen chloride mediated reactions has been determined, thus contributing some new knowledge to the chemical community. The experience has also proved to be a valuable exercise in scientific writing, as preparing this thesis required a clear, logical argument to be written justifying the fact that it is claiming to correct the outcome of a reaction published in *Organic Syntheses*. It is hoped that this result will be published in the near future, once the best manner in which to do this has been established, given the potential sensitivity of the situation.

4. Future Work

The most obvious area for future work would be the development of a reliable method for the cyclisation of amino enones **49** to give protected 4-oxopiperidines **105** (Scheme 122). Although this cyclisation has been performed for compound **59c** (R = CO_2Me, PG = Boc), the reaction proved to be difficult to repeat, and as such does not yet represent an efficient general methodology for carrying out this transformation.

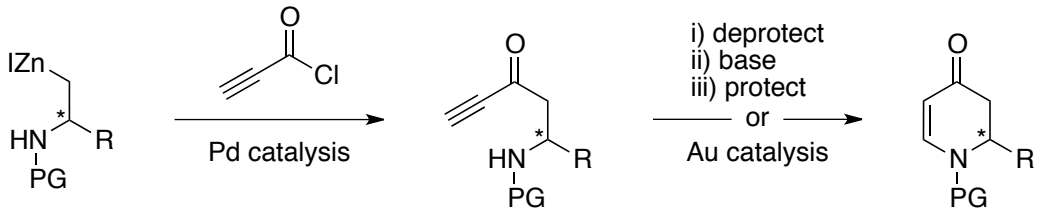
Scheme 122. Desired cyclisation of amino enones **49** to give 4-oxopiperidines **105**.



49 **105**

One possible solution to this problem would be to adapt the synthetic strategy, and to react organozinc reagents **50** with propiolyl chloride, which in principle would lead to amino ynones **138** (Scheme 123). These should prove to be suitable cyclisation precursors, as there have been published examples of the cyclisation of this type of molecule, using either basic conditions[13,16] or gold catalysis.[14-16] The use of a Negishi cross coupling reaction to access amino ynones **138** would provide a complementary method to the existing routes, which commonly involve the addition of an alkynyl organometallic reagent to a Weinreb amide formed from the required β-amino acid, often itself produced by homologation of the corresponding α-amino acid.[13-16]

Scheme 123. Possible synthesis of 2,3-dihydro-4-pyridones **139** via amino ynones **138**.

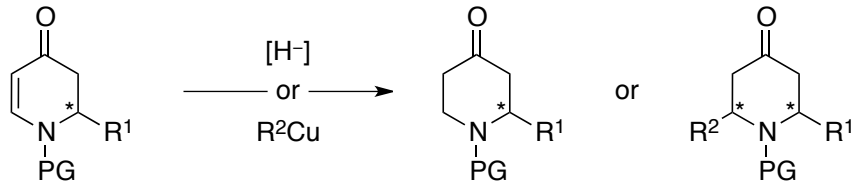


50 **138** **139**

The products of the above cyclisation reaction would be 2,3-dihydro-4-pyridones **139**, which contain an unwanted alkene (Scheme 124). This double bond could be removed using a variety of reducing

conditions, as reported by Gouault[14-16] and Comins,[33-35] amongst others. Alternatively, a substituent at the 6-position could be introduced through the conjugate addition of an organocopper reagent, again as previously showcased by Gouault[16] and Comins.[32,37]

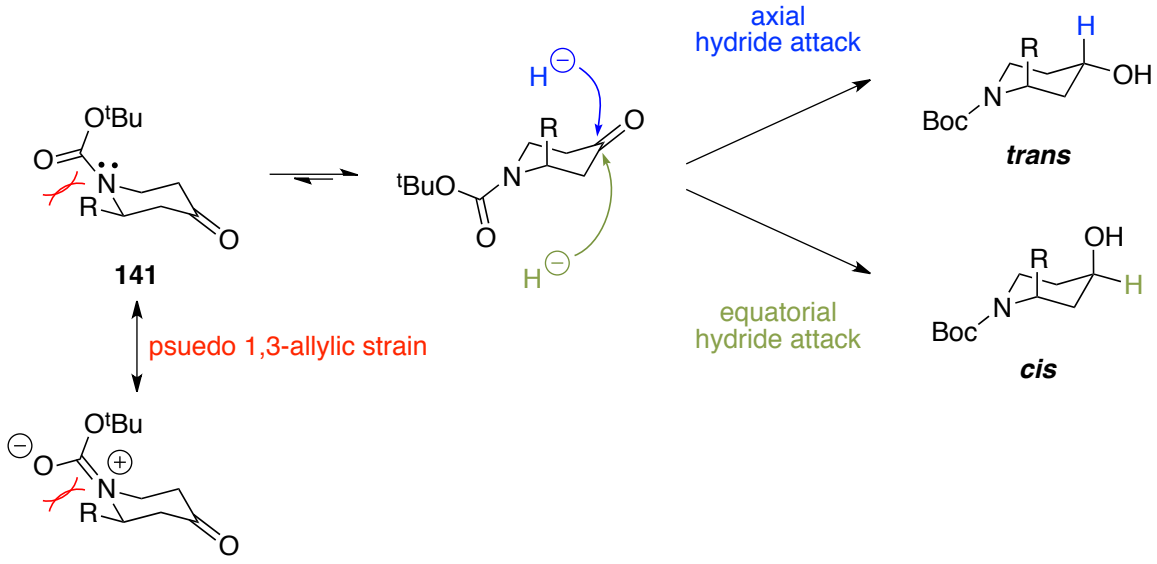
Scheme 124. Proposed synthesis of substituted 4-oxopiperidines **105** and **140** from 2,3-dihydro-4-pyridones **139**.



139 **105** **140**

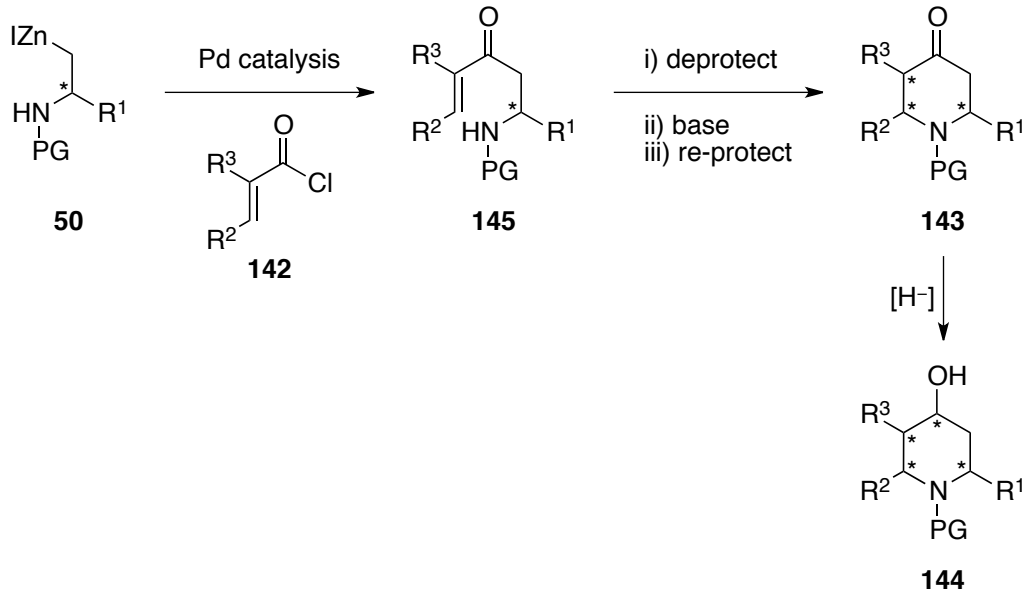
Once a reliable method to produce the substituted 4-oxopiperidines **105** (or **140**) had been developed, the next step would be to investigate the reduction of the ketone, enabling access to both diastereoisomers of the target 2-substituted 4-hydroxypiperidines. There is a good precedent in the literature for controlling the diastereoselectivity of the reduction of an *N*-protected 2-substituted 4-oxopiperidine, especially when the nitrogen is conjugated with the protecting group.[27,35,105,108-113] This relies on the fact that the substituent in the 2-position will adopt an axial orientation so as to avoid pseudo 1,3-allylic strain with the protecting group, caused by the delocalisation of the nitrogen lone pair (Figure 41).[10] Once the chair has adopted this orientation, reduction can occur from either face of the ketone, either along an axial or an equatorial trajectory. A number of different theories have been put forward that attempt to explain the stereoselectivities observed for the reduction of substituted cyclohexanones.[114-115] This is a complicated matter, as the outcome of these reductions is influenced by both the steric environment of the ketone and the choice of reducing agent.[114] Future work for this project would involve investigating the stereoselectivity of the reduction of a range of *N*-Boc 2-substituted 4-oxopiperidines **141**, with the aim of favouring the production of either diastereoisomer of the product by varying the reducing agent and reaction conditions.

Figure 41. Expected conformation of *N*-Boc 2-substituted 4-oxopiperidines **141**, which should allow for diastereocontrol during their reduction.



Other future work could involve investigating ways of synthesising more heavily substituted 4-hydroxypiperidines using a Negishi cross coupling methodology, such as those including a substituent in the 5-position. One possibility would be to react organozinc reagents **50** with substituted α,β-unsaturated acid chlorides **142**, which after cyclisation would produce 2,5,6-trisubstituted 4-oxopiperidines **143**, with the introduction of two new stereocentres (Scheme 125).

Scheme 125. Proposed synthesis of 2,5,6-trisubstituted 4-hydroxypiperidines **144** using a Negishi cross coupling methodology.



Obviously, the success of this synthetic strategy relies on the development of a successful cyclisation method for the substituted amino enones **145**. However, the cyclisation reaction conditions reported by Sutherland and co-workers[12] using Hünig's base should be suitable, given the similarity in structure between the compounds they were able to cyclise and compounds **145**. Finally, reduction of the ketone in compounds **143** would lead to the desired 4-hydroxypiperidines **144**. Again, a high level of diastereocontrol could be expected for the final reduction step, depending on the exact stereochemical distribution of the substitutents in 4-oxopiperidines **143**.

5. Experimental

5.1 General

All reactions were performed with stirring using a magnetic stirrer bar, and those that required dry solvents were performed in flame dried glassware under an atmosphere of nitrogen, unless otherwise stated. All solvents used were of HPLC quality and were purchased from Fisher Scientific, VWR International or Sigma Aldrich. Dry DMA was distilled from calcium hydride and stored under N_2 over 4Å molecular sieves. All other dry solvents were obtained from the in-house Grubbs dry solvent system (model: SPS-200-6). Tosyl chloride was recrystallised from chloroform/petroleum ether prior to use.[69] Acryloyl chloride and cinnamoyl chloride were freshly distilled before use. Saturated hydrogen chloride in diethyl ether was prepared by bubbling dry hydrogen chloride gas through dry diethyl ether. Dry hydrogen chloride gas was generated by slowly adding concentrated sulfuric acid to sodium chloride, and was dried by bubbling through concentrated sulfuric acid. All other reagents and solvents were used as received from suppliers without further purification, unless otherwise stated. Petroleum ether refers to the fraction that boils between 40 and 60 °C.

The volume of organic and aqueous solvents used during reaction work-ups was proportional to the scale of the reaction. Where the quantities are not given in the experimental then the following general rules can be applied: for larger scale reactions (>10 mmol) the portions of solvent used in the workup are likely to be similar in volume to the total volume of the reaction mixture; for smaller scale reactions (<10 mmol) the portions of solvent used in the workup may well be larger in volume than the total volume of the reaction mixture, but never by more than a factor of seven.

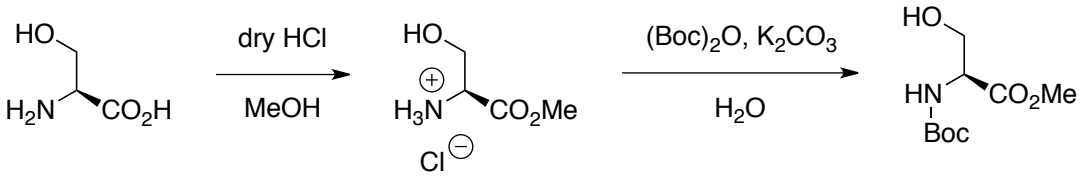
Flash column chromatography was performed by hand under pressure on silica gel 60 purchased from Davisil Fluorochem, or on a Teledyne Isco CombiFlash Companion or RF automated chromatography machine (when heptane is reported as a solvent)**.** All columns were monitored by TLC using pre coated silica plates, which were visualised with UV irradiation at 254 nm, basic $KMnO_4$ and/or methanolic ninhydrin.

Melting points were measured on a Linkam HFS91 heating stage, with a TC92 controller, and are uncorrected. Infrared spectra were measured on a Perkin Elmer Paragon 1000, Spectrum RX I, Spectrum Two, Spectrum 65 or Spectrum 100 FT-IR spectrometer. Only selected peaks were reported, and the absorption maxima are given to the nearest cm^{-1}. ^{1}H and ^{13}C NMR spectra were

recorded on a Bruker Avance III HD 500, Avance DRX 500, Avance III HD 400, Avance I 400, Avance DPX 400 or Avance I 250 spectrometer at room temperature. Chemical shifts are assigned relative to the residual solvent peaks and are quoted in parts per million to the nearest 0.01 ppm for ^{1}H spectra and the nearest 0.1 ppm for ^{13}C spectra. The multiplicities are defined as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. = broad, app. = apparent. Coupling constants are quoted in Hertz to the nearest 0.1 Hz, and have been rationalised. High resolution mass spectra were recorded on a MicroMass LCT Premier XE or a Thermo Scientific LTQ-FT spectrometer operating in electrospray mode. Optical rotations were measured on an Optical Activity Ltd. AA-10 Series Automatic polarimeter at 589 nm. Specific rotations are given to the nearest 0.1 degrees, and the concentrations are given to the nearest 0.1 units of 10 mg/mL.

5.2 Synthesis of Amino Acid Derived Iodides

Methyl (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-3-hydroxypropanoate (73)



72 **73**

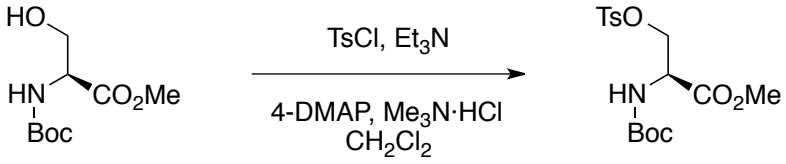
Acetyl chloride (46 mL, 647 mmol, 2.8 eq.) was added dropwise to MeOH (300 mL) at 0 °C over 15 min under N_2 in a flame-dried flask. To this was added L-serine (24.004 g, 228 mmol, 1.0 eq.), and the solution was heated to reflux for 2 h. The solution was then cooled to room temperature, and the solvent was removed under reduced pressure to yield L-serine methyl ester hydrochloride **72** as a white solid (47.453 g), which was used without further purification: m.p. 150–165 °C (decomp.) (lit. ~165 °C)[116]; δ_H (250 MHz, D_2O) 3.73 (3H, s, CH_3), 3.86 (1H, dd, *J* = 3.5, 12.6, CH*H*OH), 3.98 (1H, dd, *J* = 4.1, 12.6, C*H*HOH), 4.15 (1H, t, *J* = 3.8, CH); δ_C (101 MHz, D_2O) 53.9 (CH or CH_3), 54.8 (CH or CH_3), 59.4 (CH_2), 169.0 (CO); $[\alpha]_D^{23}$ +5.0, *c* 2.0, MeOH (lit. +5.0 ± 0.5, *c* 2.0, MeOH).[116]

The crude L-serine methyl ester hydrochloride **72** (47.449 g) was dissolved in H_2O (115 mL). K_2CO_3 (31.573 g, 228 mmol, 1.0 eq.) was added to the solution and allowed to dissolve over a few minutes. $(Boc)_2O$ (49.769 g, 228 mmol, 1.0 eq.) was added to the solution, and the reaction was stirred at room temperature overnight. The reaction mixture was extracted with Et_2O (3 × 115 mL). the combined organic extracts were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure (rotary evaporator, then high vacuum for 2 d) to yield methyl (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-3-hydroxypropanoate **73** as a colourless oil (47.885 g, 96% crude yield from L-serine), which was used without further purification: δ_H (400 MHz, $CDCl_3$) 1.47 (9H, s, $C(CH_3)_3$), 2.51 (1H, t, *J* = 6.1, OH), 3.80 (3H, s, CO_2CH_3), 3.88–4.02 (2H, m, CH_2), 4.19–4.49 (1H, m, C*H*NH), 5.50 (1H, br. d, *J* = 5.3, NH); δ_C (101 MHz, $CDCl_3$) 28.2 ($C(CH_3)_3$), 52.5 (NHCH or CO_2CH_3), 55.7 (NHCH or CO_2CH_3), 63.0 (CH_2), 80.1 ($C(CH_3)_3$), 155.8 (CO carbamate), 171.5 (CO ester); $[\alpha]_D^{20}$ −16.3, *c* 4.1, MeOH (lit. −19.1, *c* 4.07, MeOH).[70]

This product contained 2% $(Boc)_2O$ and 11% ^{t}BuOH by ^{1}H NMR analysis.

These characterisation data are in accordance with the literature values.[70]

Methyl (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-3-[(4-methylbenzenesulfonyl)oxy]propanoate (74)

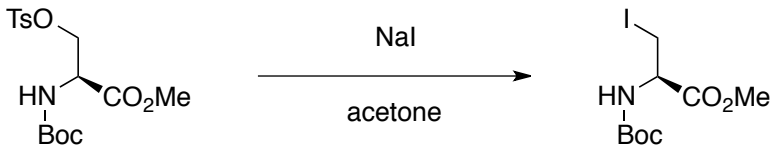


73 **74**

Crude methyl (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-3-hydroxypropanoate **73** (26.236 g, 120 mmol, 1.0 eq.) was dissolved in dry CH_2Cl_2 (200 mL). 4-DMAP (0.703 g, 5.75 mmol**,** 4.8 mol%), $Me_3N{\cdot}HCl$ (1.113 g, 11.6 mmol, 9.7 mol%) and TsCl (22.664 g, 119 mmol, 1.0 eq.) were added to the solution at 0 °C. Et_3N (17 mL, 122 mmol, 1.0 eq.) dissolved in dry CH_2Cl_2 (50 mL) was added to the suspension dropwise at 0 °C over 45 min. The resulting white suspension was stirred for a further 2 h at 0 °C, before it was poured onto a mixture of ice (100 mL), water (100 mL) and 2 M HCl (50 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were washed with brine (2 × 120 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to yield the crude product as a mixture of a white solid and a colourless oil (42.335 g). The mixture was dissolved in hot Et_2O (140 mL) and filtered to remove the insoluble white/cream solid. The filtrate was allowed to cool to room temperature before being further cooled to 0 °C. Petroleum ether (250 mL) was added in 5 portions over 2 h until crystallisation began, and the crude product was left at –20 °C over the weekend. Filtration of the crystals formed yielded methyl (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-3-[(4-methylbenzenesulfonyl)oxy]propanoate **74** as a white powder (28.090 g, 63%): m.p. 72–76 °C (lit. 74–76 °C)[69]; δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s, $C(CH_3)_3$), 2.48 (3H, s, $C_6H_4CH_3$), 3.72 (3H, s, CO_2CH_3), 4.31 (1H, dd, *J* = 2.9, 10.1, C*H*$HOSO_2$), 4.42 (1H, dd, *J* = 3.0. 10.1, CH*H*OSO_2), 4.50–4.56 (1H, m, C*H*NH), 5.32 (1H, d, *J* = 7.6, NH), 7.38 (2H, app. d, *J* = 8.2, Ar H), 7.79 (2H, app. d, *J* = 8.2, Ar H); δ_C (101 MHz, $CDCl_3$) 21.7 ($C_6H_4CH_3$), 28.2 ($C(CH_3)_3$), 52.9 (CH or CO_2CH_3), 53.0 (CH or CO_2CH_3), 69.5 (CH_2), 80.5 ($C(CH_3)_3$), 128.0 (Ar CH), 129.9 (Ar CH), 132.4 (Ar quat. C), 145.2 (Ar quat. C), 154.9 (CO carbamate), 169.0 (CO ester); $[\alpha]_D^{23}$ +3.5, *c* 2.0, MeOH (lit. +3.0, *c* 2.0, MeOH).[69]

These characterisation data are in accordance with the literature values.[69]

Methyl (2*R*)-2-{[(*tert*-butoxy)carbonyl]amino}-3-iodopropanoate (68)

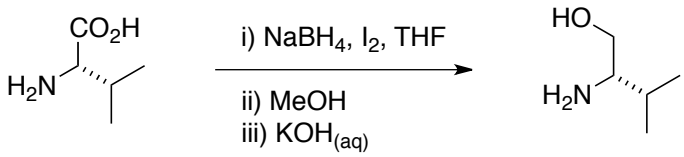


74 **68**

Methyl (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-3-[(4-methylbenzenesulfonyl)oxy]propanoate **74** (28.090 g, 75.2 mmol, 1.0 eq.) was dissolved in acetone (160 mL). NaI (13.530 g, 90.3 mmol, 1.2 eq.) was added in one portion, and the flask was covered in aluminium foil. After stirring for 3 d, further NaI (3.383 g, 22.6 mmol, 0.3 eq.) was added in one portion and the reaction was stirred for 1 d. The brown slurry was filtered, and the brown solid isolated was washed with acetone until the solid was colourless. The flask containing the filtrate was covered with aluminium foil to exclude light and the solvent was removed under reduced pressure to yield a brown oil. This oil was partitioned between Et_2O (150 mL) and 1 M $Na_2S_2O_3$ (60 mL). The organic layer was washed with 1 M $Na_2S_2O_3$ (40 mL) and brine (50 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to yield the crude product as a white solid (21.225 g). The solid was dissolved in hot petroleum ether (30 mL) before being cooled to 0 °C. This began the crystallisation, which was allowed to complete at −20 °C overnight. After filtration, a pale yellow solid was isolated. This solid was washed with cold petroleum ether and air dried to give, after grinding, methyl (2*R*)-2-{[(*tert*-butoxy)carbonyl]amino}-3-iodopropanoate **68** as a pale yellow powder (19.101 g, 77%): m.p. 42–49 °C (lit. 45–47 °C)[69]; δ_H (400 MHz, $CDCl_3$) 1.48 (9H, s, C(CH_3)$_3$), 3.54–3.65 (2H, m, CH_2I), 3.83 (3H, s, CO_2CH_3), 4.50–4.58 (1H, m, C*H*NH), 5.37 (1H, d, *J* = 6.8, NH); δ_C (101 MHz, $CDCl_3$) 7.8 (CH_2), 28.3 (C(CH_3)$_3$), 53.0 (CH or CH_3), 53.7 (CH or CH_3), 80.5 (*C*(CH_3)$_3$), 154.8 (CO carbamate), 170.0 (CO ester); $[\alpha]_D^{20}$ −3.7, *c* 3.0, MeOH (lit. −3.7, *c* 3.0, MeOH).[69]

These characterisation data are in accordance with the literature values.[69]

(2*S*)-2-Amino-3-methylbutan-1-ol (75)

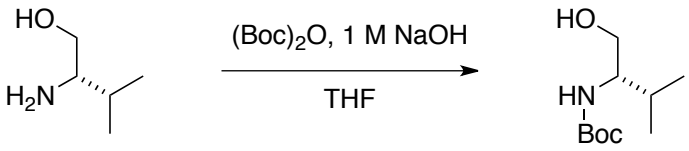


75

$NaBH_4$ (6.969 g, 184.2 mmol, 2.9 eq.) and L-valine (7.540 g, 64.4 mmol, 1.0 eq.) were added to dry THF (200 mL), and the resulting white suspension was cooled to 0 °C. I_2 (19.299 g, 76.0 mmol, 1.2 eq.) dissolved in dry THF (50 mL) was added dropwise to the suspension over 1.25 h, and gas evolution was observed. A stopper was removed during the addition to allow release of this gas. Once all the I_2 had been added, the solution was heated at reflux overnight. After cooling to room temperature, MeOH (60 mL) was added slowly until all of the white solid had dissolved, leaving a colourless solution. Gas evolution was observed while the MeOH was added. The solvent was removed under reduced pressure to yield a white slurry, which was dissolved in 20% aq. KOH (150 mL). This solution was stirred at room temperature for 4.25 h, before being extracted with CH_2Cl_2 (3 × 150 mL). Extra water and brine were added to aid this difficult separation. The combined organic extracts were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to yield the crude (2*S*)-2-amino-3-methylbutan-1-ol **75** as a colourless oil (~6.3 g, 95% crude yield), which was used without further purification: δ_H (400 MHz, $CDCl_3$) 0.86 (3H, d, *J* = 6.8, CH_3), 0.87 (3H, d, *J* = 6.8, CH_3), 1.46–1.64 (1H, m, C*H*(CH_3)$_2$), 2.54 (1H, ddd, *J* = 3.7, 6.4, 8.5, NHC*H*), 3.07 (app. 3.5H, br. s, NH_2 and OH), 3.28 (1H, dd, *J* = 8.5, 10.7, C*H*H), 3.59 (1H, dd, *J* = 3.7, 10.7, CH*H*).

These characterisation data are in accordance with the literature values.[117]

***tert*-Butyl *N*-[(2*S*)-1-hydroxy-3-methylbutan-2-yl]carbamate (76a)**



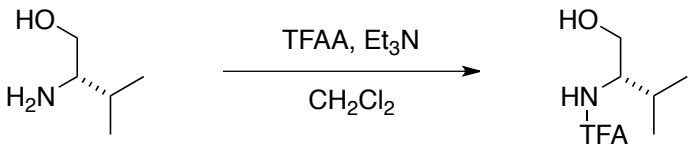
75 **76a**

Crude (2*S*)-2-amino-3-methylbutan-1-ol **75** (~6.1 g) was dissolved in THF (140 mL). 1 M NaOH (65 mL, 65.0 mmol, 1.1 eq.) was added, followed by $(Boc)_2O$ (12.919 g, 59.1 mmol, 1.0 eq. assuming 100% conversion of L-valine to (2*S*)-2-amino-3-methylbutan-1-ol). The reaction mixture was stirred at room temperature overnight before the THF was removed under reduced pressure. The remaining aqueous solution was acidified to pH 5 with 2 M HCl and extracted with EtOAc (3 × 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to yield crude *tert*-butyl *N*-[(2*S*)-1-hydroxy-3-methylbutan-2-yl]carbamate **76a** as a colourless oil (10.785 g, 82% crude yield over two steps), which was used without further purification: δ_H (400 MHz, $CDCl_3$) 0.95 (3H, d, *J* = 6.9, $CH(CH_3)(CH_3)$), 0.97 (3H, d, *J* = 6.9, $CH(CH_3)(CH_3)$), 1.46 (9H, s, $C(CH_3)_3$), 1.75–1.93 (1H, m, $CH(CH_3)_2$), 2.52 (1H, br. s, OH), 3.30–3.54 (1H, m, NHC*H*), 3.62 (1H, dd, *J* = 6.6, 10.8, C*H*H), 3.67–3.76 (1H, m, CH*H*), 4.70 (1H, d, *J* = 6.7, NH); δ_C (101 MHz, $CDCl_3$) 18.4 (CH_3), 19.4 (CH_3), 28.3 ($C(CH_3)_3$ or $CH(CH_3)_2$), 29.1 ($C(CH_3)_3$ or $CH(CH_3)_2$), 57.8 (NHCH), 63.2 (CH_2), 79.1 ($C(CH_3)_3$), 156.7 (CO); $[\alpha]_D^{23}$ −14.2, *c* 1.1, MeOH (lit. −16.7, *c* 1.0, MeOH).[79]

This sample was found to contain 13% of $(Boc)_2O$ by ^1H NMR analysis.

These characterisation data are in accordance with the literature values.[79,118]

2,2,2-Trifluoro-*N*-[(2*S*)-1-hydroxy-3-methylbutan-2-yl]acetamide (76b)



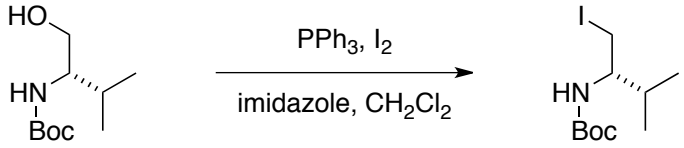
75 **76b**

Commercially available L-valinol **75** (4.645 g, 45.0 mmol, 1.0 eq.) dissolved in CH_2Cl_2 (20 mL) and Et_3N (22 mL, 158 mmol, 3.5 eq.) were added to CH_2Cl_2 (300 mL), and the colourless solution was cooled to 0 °C. TFAA (7.5 mL, 53.7 mmol, 1.2 eq.) was added over 40 min, producing a white gas. The reaction mixture was warmed at room temperature overnight before being concentrated under reduced pressure. EtOAc (100 mL) was added, and the solution was washed sequentially with sat. aq. $NaHCO_3$ (120 mL), 1 M HCl (120 mL) and brine (120 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to yield 2,2,2-trifluoro-*N*-[(2*S*)-1-hydroxy-3-methylbutan-2-yl]acetamide **76b** as an off-white solid (7.166 g, 80%), which was used without further purification: m.p. 91–97 °C (lit. 85–86 °C)[119]; δ_H (400 MHz, $CDCl_3$) 0.99 (3H, d, *J* = 6.8, $CH(CH_3)(CH_3)$), 1.03 (3H, d, *J* = 6.8, $CH(CH_3)(CH_3)$), 1.87 (app. 1.8H, br. s, OH), 1.93–2.05 (1H, m, $CH(CH_3)_2$), 3.74–3.87 (3H, m, CH_2 and NHC*H*), 6.57 (1H, s, NH); δ_C (101 MHz, $CDCl_3$) 18.7 (CH_3), 19.3 (CH_3), 28.9 ($CH(CH_3)_2$), 57.5 (NHCH), 62.1 (CH_2), 116.0 (q, *J* = 287.7, CF_3), 157.8 (q, *J* = 36.8, CO); $[\alpha]_D^{23}$ −9.5, *c* 13.5, MeOH (lit. +7.01, *c* 13.5, MeOH, opposite enantiomer).[119]

Repeating this procedure using crude (2*S*)-2-amino-3-methylbutan-1-ol **75** produced from the reduction of L-valine gave the product **76b** in a 59% yield over two steps.

These characterisation data are in accordance with the literature values.[119-120]

***tert*-Butyl *N*-[(2*S*)-1-iodo-3-methylbutan-2-yl]carbamate (61a)**



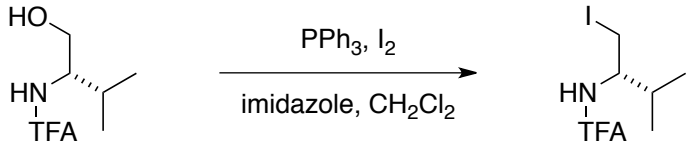
76a **61a**

PPh_3 (6.585 g, 25.1 mmol, 1.6 eq.) and imidazole (1.699 g, 25.0 mmol, 1.5 eq.) were dissolved in dry CH_2Cl_2 (325 mL) to give a colourless solution. I_2 (7.072 g, 27.9 mmol, 1.7 eq.) was added portionwise, producing a brown solution. After ~30 min, commercially available *N*-Boc-L-valinol **76a** (3.292 g, 16.2 mmol, 1.0 eq.) in dry CH_2Cl_2 (75 mL) was added to the reaction mixture. The flask was covered in aluminium foil and stirred at room temperature for 5 h. The solvent was removed under reduced pressure to yield a brown slurry, which was dissolved in the minimum volume of CH_2Cl_2 and filtered through a silica plug, eluting with Et_2O. The solvent was removed under reduced pressure to yield the crude product as a brown oil. This oil was purified by column chromatography, using a gradient of 0:100 EtOAc/heptane to 10:90 EtOAc/heptane as the solvent system. *tert*-Butyl *N*-[(2*S*)-1-iodo-3-methylbutan-2-yl]carbamate **61a** was isolated as a pale yellow solid (2.848 g, 56%), which was stored under N_2 in the dark at −20 °C: m.p. 73–74 °C (lit. 49–51 °C)[58]; R_f 0.6 (20:80 EtOAc/petroleum ether); δ_H (400 MHz, $CDCl_3$) 0.94 (3H, d, *J* = 6.7, CH(C*H*$_3$)(CH$_3$)), 0.99 (3H, d, *J* = 6.7, CH(CH$_3$)(C*H*$_3$)), 1.47 (9H, s, C(CH$_3$)$_3$), 1.72–1.86 (1H, m, C*H*(CH$_3$)$_2$), 3.09–3.17 (1H, m, NHC*H*), 3.35 (1H, dd, *J* = 4.5, 10.3, C*H*H), 3.44 (1H, dd, *J* = 4.2, 10.3, CH*H*), 4.59 (1H, d, *J* = 8.6, NH); δ_C (101 MHz, $CDCl_3$) 13.3 (CH_2), 18.2 (CH(*C*H$_3$)(CH$_3$)), 19.3 (CH(CH$_3$)(*C*H$_3$)), 28.4 (C(*C*H$_3$)$_3$), 32.3 (*C*H(CH$_3$)$_2$), 55.5 (NHCH), 79.5 (*C*(CH$_3$)$_3$), 155.4 (CO); $[\alpha]_D^{23}$ −15.5, *c* 1.8, $CHCl_3$ (lit. −18.1, *c* 1.75, $CHCl_3$).[58]

Repeating this procedure using *tert*-butyl *N*-[(2*S*)-1-hydroxy-3-methylbutan-2-yl]carbamate **76a** produced from the reduction and subsequent Boc protection of L-valine gave the product **61a** as a yellow solid in a 39% yield.

These characterisation data are in accordance with the literature values.[58]

2,2,2-Trifluoro-*N*-[(2*S*)-1-iodo-3-methylbutan-2-yl]acetamide (61b)

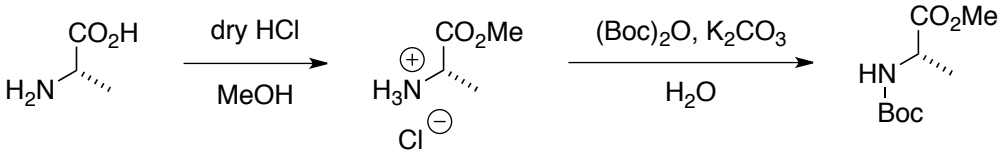


76b **61b**

PPh_3 (8.975 g, 34.2 mmol, 1.05 eq.), imidazole (2.333 g, 34.3 mmol, 1.05 eq.) and I_2 (8.726 g, 34.4 mmol, 1.05 eq.) were dissolved in dry CH_2Cl_2 (110 mL) at 0 °C, producing an orange suspension. 2,2,2-Trifluoro-*N*-[(2*S*)-1-hydroxy-3-methylbutan-2-yl]acetamide **76b** (6.504 g, 32.7 mmol, 1.0 eq.) was added portionwise to the reaction mixture over 30 min at 0 °C. The flask was covered in aluminium foil and stirred at room temperature overnight. The reaction mixture was filtered, and solvent was removed under reduced pressure to yield a light brown slurry. This slurry was dissolved in EtOAc (290 mL), filtered again, and the white solid was washed with a small portion of EtOAc. The solution was washed with sat. aq. $Na_2S_2O_3$ (330 mL) and brine (330 mL), and was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the crude product as a yellow oil. This oil was purified by column chromatography, using a gradient of 0:100 EtOAc/heptane to 20:80 EtOAc/heptane as the solvent system. 2,2,2-Trifluoro-*N*-[(2*S*)-1-iodo-3-methylbutan-2-yl]acetamide **61b** was isolated as a white solid (6.908 g, 68%), which was stored under N_2 in the dark at −20 °C: m.p. 101–109 °C (lit. 114–116 °C)[60]; R_f 0.3 (10:90 EtOAc/petroleum ether); δ_H (250 MHz, $CDCl_3$) 0.99 (3H, d, *J* = 6.6, CH(C*H*$_3$)(CH$_3$)), 1.01 (3H, d, *J* = 6.6, CH(CH$_3$)(C*H*$_3$)), 1.79–1.98 (1H, m, C*H*(CH$_3$)$_2$), 3.22–3.56 (3H, m, NHC*H* and CH_2), 6.24 (1H, br. s, NH); δ_C (101 MHz, $CDCl_3$) 9.9 (CH_2), 18.3 (CH_3), 19.0 (CH_3), 32.3 (*C*H(CH$_3$)$_2$), 55.1 (NHCH), 115.8 (q, *J* = 288.1, CF_3), 156.9 (q, *J* = 37.2, CO); $[\alpha]_D^{23}$ −43.0, *c* 1.0, $CHCl_3$ (lit. −42.0, *c* 1.0, $CHCl_3$).[60]

These characterisation data are in accordance with the literature values.[60]

Methyl (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}propanoate (77)



77

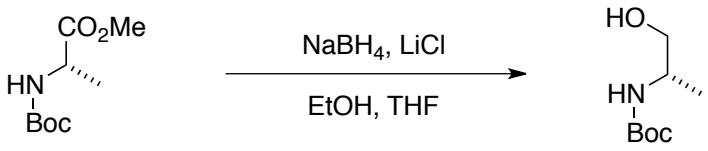
Acetyl chloride (23 mL, 323 mmol, 2.8 eq.) was added dropwise to MeOH (150 mL) at 0 °C over 10 min. After 5 min, L-alanine (10.155 g, 114 mmol, 1.0 eq.) was added, and the solution was heated at reflux overnight. The solution was cooled to room temperature, and the solvent was removed under reduced pressure to yield the crude (2*S*)-1-methoxy-1-oxopropan-2-aminium chloride (17.483 g), which was used without further purification: δ_H (400 MHz, D_2O) 1.43 (3H, d, *J* = 7.3, CHCH_3), 3.71 (3H, s, CO_2CH_3), 4.08 (1H, q, *J* = 7.3, CH).

The crude (2*S*)-1-methoxy-1-oxopropan-2-aminium chloride (17.483 g) was dissolved in H_2O (57 mL). K_2CO_3 (15.756 g, 114 mmol, 1.0 eq.) was added to the solution which was stirred for 5 min. $(Boc)_2O$ (24.870 g, 114 mmol, 1.0 eq.) was added to the solution, and the reaction was stirred at room temperature for 3 d. The reaction mixture was extracted with Et_2O (3 × 60 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a mixture of methyl (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}propanoate and $(Boc)_2O$. Petroleum ether (30 mL) was added, and the solvent removed under reduced pressure to yield methyl (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}propanoate **77** as a white solid (19.902 g, 86% crude yield from L-alanine), which was used without further purification: m.p. 28–33 °C (lit. 31–33 °C)[121]; δ_H (400 MHz, $CDCl_3$) 1.39 (3H, d, *J* = 7.2, CHCH_3), 1.45 (9H, s, $C(CH_3)_3$), 3.76 (3H, s, CO_2CH_3), 4.08–4.41 (1H, m, CH), 5.07 (1H, br. s, NH); δ_C (101 MHz, $CDCl_3$) 18.6 (CH*C*H_3), 28.3 ($C(CH_3)_3$), 49.1 (CH or CO_2CH_3), 52.3 (CH or CO_2CH_3), 79.8 ($C(CH_3)_3$), 155.1 (CO carbamate), 173.8 (CO ester); $[\alpha]_D^{20}$ −2.0, *c* 1.0, $CHCl_3$ (lit. −3.4, *c* 1.0, $CHCl_3$).[122]

This product was found to contain 14% $(Boc)_2O$ and 4% ^{t}BuOH by ^{1}H NMR analysis.

These characterisation data are in accordance with the literature values.[121-122]

***tert*-Butyl *N*-[(2*S*)-1-hydroxypropan-2-yl]carbamate (78a)**



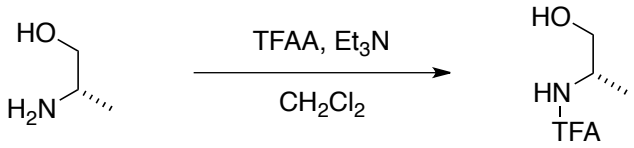
77 **78a**

Crude methyl (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}propanoate **77** (19.795 g, 97.4 mmol, 1.0 eq.) was dissolved in THF (140 mL). To the reaction mixture was added LiCl (8.260 g, 195 mmol, 2.0 eq.), which had previously been dried by heating with a blow torch under high vacuum. $NaBH_4$ (7.369g, 195 mmol, 2.0 eq.) was added portionwise before EtOH (280 mL) was added. After stirring for 15 min an exotherm was noted, so an ice bath was used to cool the reaction for 10 min before being stirred at room temperature overnight. A white foamy mixture was produced, to which was slowly added 10% citric acid (100 mL) with cooling from an ice bath. After stirring at 0 °C for ~2 h, most of the solid had dissolved, leaving a white gum. The liquid was decanted from this white gum, and the solvent was removed under reduced pressure yielding a white solid. H_2O (280 mL) was added, and the solution was extracted with CH_2Cl_2 (3 × 240 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to yield *tert*-butyl *N*-[(2*S*)-1-hydroxypropan-2-yl]carbamate **78a** as a white solid (13.924 g). The white gum previously isolated was re-dissolved in 10% citric acid (100 mL), and the solvent was removed under reduced pressure to yield a white solid. This solid was dissolved in H_2O (100 mL), and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to yield more product as a mixture of a white solid and a colourless oil (0.081 g). The two crops of product were combined and the solvent removed under reduced pressure again to yield *tert*-butyl *N*-[(2*S*)-1-hydroxypropan-2-yl]carbamate **78a** as a white solid (13.828 g, 81%), which was used without purification: m.p. 57–61 °C (lit. 59–61 °C)[122]; δ_H (400 MHz, $CDCl_3$) 1.14 (3H, d, *J* = 6.8, CHC*H*$_3$), 1.44 (9H, s, C(C*H*$_3$)$_3$), 3.19 (1H, br. s, OH), 3.44–3.54 (1H, m, C*H*H), 3.56–3.65 (1H, m, CH*H*), 3.67–3.85 (1H, m, CH), 4.84 (1H, d, *J* = 5.8, NH); δ_C (101 MHz, $CDCl_3$) 17.3 (CH*C*H$_3$), 28.4 (C(*C*H$_3$)$_3$), 48.4 (NHCH), 66.8 (CH_2), 79.5 (*C*(CH$_3$)$_3$), 156.3 (CO); $[\alpha]_D^{23}$ −14.9, *c* 1.0, $CHCl_3$ (lit. −9.3, *c* 1.0, $CHCl_3$).[122]

This product was found to contain 5% methyl (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}propanoate **77** by ^{1}H NMR analysis.

These characterisation data are in accordance with the literature values.[122]

2,2,2-Trifluoro-*N*-[(2*S*)-1-hydroxypropan-2-yl]acetamide (78b)

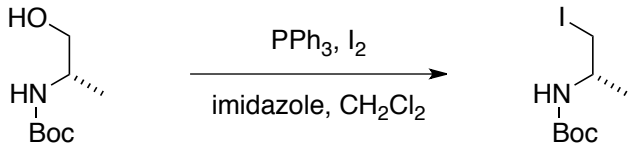


78b

Commercially available L-alaninol (3.5 mL, 45.0 mmol, 1.0 eq.) and Et_3N (22 mL, 158 mmol, 3.5 eq.) were dissolved in CH_2Cl_2 (300 mL), and the solution was cooled to 0 °C. TFAA (7.5 mL, 53.7 mmol, 1.2 eq.) was added portionwise over 45 min. The reaction mixture was warmed to room temperature and stirred overnight, before the solution was concentrated under reduced pressure to give a yellow liquid. EtOAc (100 mL) was added, and the solution was washed with sat. aq. $NaHCO_3$ (120 mL). The aqueous layer was re-extracted with EtOAc (100 mL), and the combined organic extracts were washed with 0.1 M HCl (240 mL) and brine (240 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to yield 2,2,2-trifluoro-*N*-[(2*S*)-1-hydroxypropan-2-yl]acetamide **78b** as a white solid (5.239 g, 68%), which was used without further purification: m.p. 68–72 °C (lit. 80 °C)[119]; δ_H (400 MHz, $CDCl_3$) 1.29 (3H, d, *J* = 6.8, CH_3), 2.10 (app. 2H, br. s, OH), 3.65 (1H, dd, *J* = 4.8, 11.1, C*H*H), 3.78 (1H, dd, *J* = 3.7, 11.1, CH*H*), 4.10–4.21 (1H, m, CH), 6.72 (1H, br. s, NH); δ_C (101 MHz, $CDCl_3$) 16.5 (CH_3), 47.8 (CH), 65.1 (CH_2), 115.8 (q, *J* = 287.8, CF_3), 156.9 (q, *J* = 37.1, CO); $[\alpha]_D^{23}$ −12.9, *c* 1.0, $CHCl_3$ (lit. −16.3, *c* 1.0, $CHCl_3$).[68]

These characterisation data are in accordance with the literature values.[68,119]

***tert*-Butyl *N*-[(2*S*)-1-iodopropan-2-yl]carbamate (64a)**



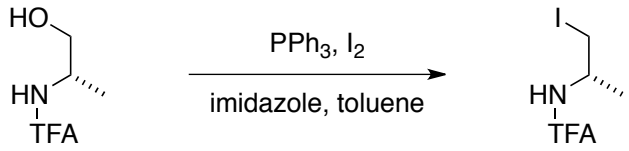
78a **64a**

PPh_3 (11.76 g, 44.8 mmol, 1.0 eq.) and imidazole (3.06 g, 45.0 mmol, 1.0 eq.) were dissolved in dry CH_2Cl_2 (200 mL). I_2 (12.60 g, 49.6 mmol, 1.1 eq.) was added portionwise, producing a dark brown solution. After 5 min, commercially available *N*-Boc-L-alaninol **78a** (7.91 g, 45.1 mmol, 1.0 eq.) in dry CH_2Cl_2 (40 mL) was added to the reaction mixture. The flask was covered in aluminium foil and stirred at room temperature for 5 h. The solvent was removed under reduced pressure to yield a brown slurry, which was dissolved in the minimum volume of CH_2Cl_2 and filtered through a silica plug, eluting with Et_2O. The resulting brown solution was concentrated under reduced pressure to give the crude product as a brown oil. The crude product was purified by column chromatography, using a gradient of 0:100 EtOAc/heptane to 20:80 EtOAc/heptane as the solvent system. *tert*-Butyl *N*-[(2*S*)-1-iodopropan-2-yl]carbamate **64a** was isolated as a yellow solid (7.087 g, 55%), which was stored under N_2 in the dark at −20 °C: m.p. 60–62 °C (lit. 60–62 °C)[67]; R_f 0.3 (10:90 EtOAc/petroleum ether); δ_H (400 MHz, $CDCl_3$) 1.22 (3H, d, *J* = 6.5, CHC*H*$_3$), 1.47 (9H, s, C(CH_3)$_3$), 3.31 (1H, dd, *J* = 3.5, 9.8, C*H*H), 3.36–3.48 (1H, m, CH*H* or CH), 3.48–3.61 (1H, m, CH*H* or CH), 4.62 (1H, br. s, NH); δ_C (101 MHz, $CDCl_3$) 15.9 (CH_2), 21.2 (CH*C*H$_3$), 28.4 (C(*C*H$_3$)$_3$), 45.9 (CH), 79.7 (*C*(CH$_3$)$_3$), 154.8 (CO carbamate); $[\alpha]_D^{23}$ −21.0, *c* 1.0, $CHCl_3$ (lit. −15.3, *c* 1.0, $CHCl_3$).[67]

Repeating this procedure using *tert*-butyl *N*-[(2*S*)-1-hydroxypropan-2-yl]carbamate **78a** produced from the reduction of methyl (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}propanoate **77** gave the product **64a** as a yellow solid in an unoptimised 28% yield.

These characterisation data are in accordance with the literature values.[67]

2,2,2-Trifluoro-*N*-[(2*S*)-1-iodopropan-2-yl]acetamide (64b)

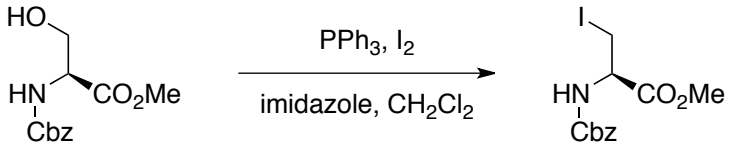


78b **64b**

PPh_3 (6.890 g, 26.3 mmol, 1.05 eq.), imidazole (1.779 g, 26.1 mmol, 1.05 eq.) and I_2 (6.667 g, 26.3 mmol, 1.05 eq.) were dissolved in dry CH_2Cl_2 (75 mL) at 0 °C. 2,2,2-Trifluoro-*N*-[(2*S*)-1-hydroxypropan-2-yl]acetamide **78b** (4.273 g, 25.0 mmol, 1.0 eq.) was added portionwise at 0 °C over 30 min. The flask was covered in aluminium foil, warmed to room temperature and stirred overnight. The reaction mixture was filtered, and solvent was removed under reduced pressure to yield a brown oil. This oil was dissolved in EtOAc (250 mL) and filtered again. The resulting brown solution was washed with sat. aq. $Na_2S_2O_3$ (250 mL) and brine (250 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to yield the crude product as a yellow oil, which solidified upon standing. The crude product was purified by column chromatography, using a gradient of 0:100 EtOAc/heptane to 20:80 EtOAc/heptane as the solvent system. 2,2,2-Trifluoro-*N*-[(2*S*)-1-iodopropan-2-yl]acetamide **64b** was isolated as a white solid (4.757 g, 68%), which was stored under N_2 in the dark at −20 °C: m.p. 88–90 °C (sublimation begins at lower temperatures); R_f 0.6 (30:70 EtOAc/petroleum ether); δ_H (400 MHz, $CDCl_3$) 1.35 (3H, d, *J* = 6.6, CH_3), 3.33 (1H, dd, *J* = 4.0, 10.5, C*H*H), 3.50 (1H, dd, *J* = 4.6, 10.5, CH*H*), 3.86–3.97 (1H, m, CH), 6.31 (1H, br. s, NH); δ_C (101 MHz, $CDCl_3$) 12.4 (CH_2), 20.7 (CH_3), 45.6 (CH), 115.6 (q, *J* = 287.8, CF_3), 156.5 (q, *J* = 37.4, CO); $[\alpha]_D^{23}$ −46.2, *c* 1.0, $CHCl_3$ (lit. −47.2, *c* 1.0, $CHCl_3$).[68]

These characterisation data are in accordance with the literature values.[68]

Methyl (2*R*)-2-{[(benzyloxy)carbonyl]amino}-3-iodopropanoate (113)

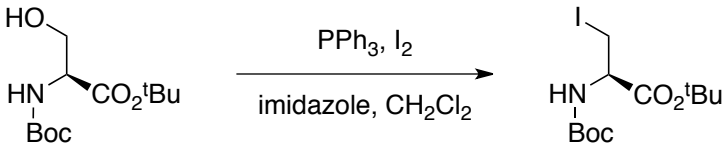


113

PPh_3 (5.243 g, 20.0 mmol, 1.0 eq.), imidazole (1.364 g, 20.0 mmol, 1.0 eq.) and ground I_2 (5.591 g, 22.0 mmol, 1.1 eq.) were dissolved in dry CH_2Cl_2 (100 mL). After 5 min, *N*-Cbz-L-serine methyl ester (5.068 g, 20.0 mmol, 1.0 eq.) was added to the reaction mixture. The flask was covered in aluminium foil and stirred at room temperature for 4.5 h. The solvent was removed under reduced pressure, the resulting residue was dissolved in the minimum volume of CH_2Cl_2 and filtered through a silica plug, eluting with Et_2O. The solution was concentrated under reduced pressure to give the crude product as a brown oil. The crude product was purified by column chromatography, using 10:90 EtOAc/petroleum ether as the solvent system. The pinky orange solid isolated was dissolved in CH_2Cl_2 and washed sequentially with sat. aq. $Na_2S_2O_3$ and H_2O. The organic layer was dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to yield methyl (2*R*)-2-{[(benzyloxy)carbonyl]amino}-3-iodopropanoate **113** as a white solid (5.784 g, 80%), which was stored under N_2 in the dark at −20 °C: m.p. 69–70 °C (lit. 69–71 °C)[123]; R_f 0.2 (10:90 EtOAc/petroleum ether); δ_H (400 MHz, $CDCl_3$) 3.60 (1H, dd, *J* = 4.0, 10.4, IC*H*H), 3.64 (1H, dd, *J* = 3.7, 10.4, ICH*H*), 3.83 (3H, s, CH_3), 4.58–4.65 (1H, m, CH), 5.14 (1H, d, *J* = 12.2, PhC*H*H), 5.18 (1H, d, *J* = 12.2, PhCH*H*), 5.66 (1H, d, *J* = 7.2, NH), 7.33–7.43 (5H, m, Ar H); δ_C (101 MHz, $CDCl_3$) 7.4 (CH_2I), 53.2 (CH or CH_3), 54.4 (CH or CH_3), 67.3 (Ph*C*H_2), 128.1 (Ar CH), 128.3 (Ar CH), 128.6 (Ar CH), 136.0 (Ar quat. C), 155.5 (CO carbamate), 169.7 (CO ester); $[\alpha]_D^{23}$ +40.0, *c* 1.0, $CHCl_3$ (lit. −6.1, *c* 1.0, $CHCl_3$).[123]

With the exception of the specific rotation, these characterisation data are in accordance with the literature values.[123]

***tert*-Butyl (2*R*)-2-{[(*tert*-butoxy)carbonyl]amino}-3-iodopropanoate (96)**



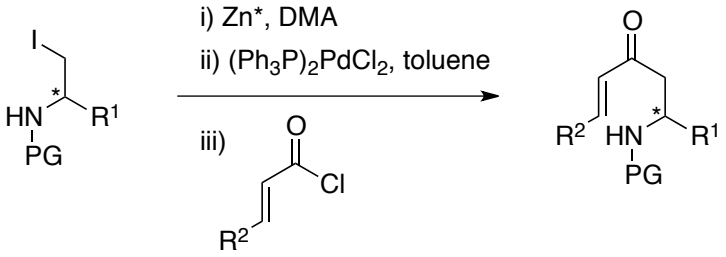
96

PPh_3 (0.792 g, 3.0 mmol, 1.0 eq.), imidazole (0.203 g, 3.0 mmol, 1.0 eq.) and I_2 (0.790 g, 3.1 mmol, 1.0 eq.) were dissolved in dry CH_2Cl_2 (50 mL), producing an orange solution. After 5 min, *N*-Boc-L-serine *tert*-butyl ester (0.784 g, 3.0 mmol, 1.0 eq.) was added to the reaction mixture. The flask was covered in aluminium foil and stirred at room temperature for 1 h. The solvent was removed under reduced pressure, and the resulting oil was dissolved in the minimum volume of CH_2Cl_2 and filtered through a silica plug, eluting with Et_2O. The solution was concentrated under reduced pressure to give the crude product as a brown oil. The crude product was purified by column chromatography, using 3:97 EtOAc/petroleum ether as the solvent system. *tert*-Butyl (2*R*)-2-{[(*tert*-butoxy)carbonyl]amino}-3-iodopropanoate **96** was isolated as a cream solid (0.982 g, 88%), which was stored under N_2 in the dark at −20 °C: m.p. 77–78 °C (lit. 67–71 °C)[124]; R_f 0.7 (30:70 EtOAc/petroleum ether); δ_H (250 MHz, $CDCl_3$) 1.47 (9H, s, $C(CH_3)_3$), 1.52 (9H, s, $C(CH_3)_3$), 3.52–3.62 (2H, m, CH_2), 4.33–4.40 (1H, m, CH), 5.37 (1H, d, *J* = 6.8, NH); δ_C (101 MHz, $CDCl_3$) 8.9 (CH_2), 28.0 ($C(CH_3)_3$), 28.3 ($C(CH_3)_3$), 53.7 (CH), 80.2 ($C(CH_3)_3$), 83.3 ($C(CH_3)_3$), 154.9 (CO carbamate), 168.5 (CO ester); $[\alpha]_D^{23}$ +20.2, *c* 1.0, CH_2Cl_2 (lit. +19.7, *c* 1.0, CH_2Cl_2).[124]

These characterisation data are in accordance with the literature values.[124]

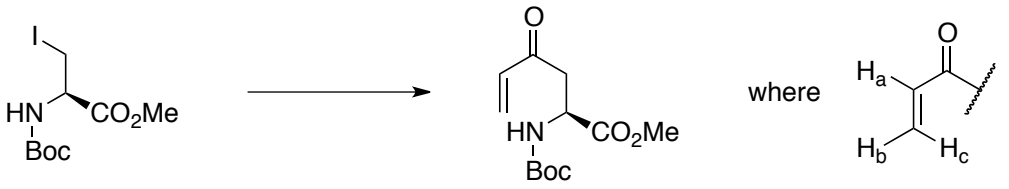
5.3 Formation of Organozinc Reagents and Cross Coupling Reactions

General Method for the Formation of the Organozinc Reagents and the Cross Coupling Reactions



A flame-dried round-bottomed side arm flask was charged with zinc (3.0 eq.) and briefly flame-dried again under vacuum, before dry DMA (0.4 mL/mmol iodide, 4.3 eq.) was added under nitrogen with stirring. Iodine (8 mol%) was added, and the solution became brown before returning to colourless again. The amino acid derived iodide (1.0 eq.) was added to the flask, followed by more iodine (8 mol%), resulting in the same colour changes. The zinc insertion was monitored by TLC, and when complete (≥10min) the reaction was placed into a water bath, and dry toluene (2 mL/mmol iodide) was added to the reaction mixture, followed by $(Ph_3P)_2PdCl_2$ (5 mol%). Finally, the freshly distilled acid chloride (1.3 eq.) was added via syringe over 5 min. The reaction was left stirring overnight in the water bath. The reaction mixture was either purified directly using column chromatography, or worked up before column chromatography, as described in the individual experiments.

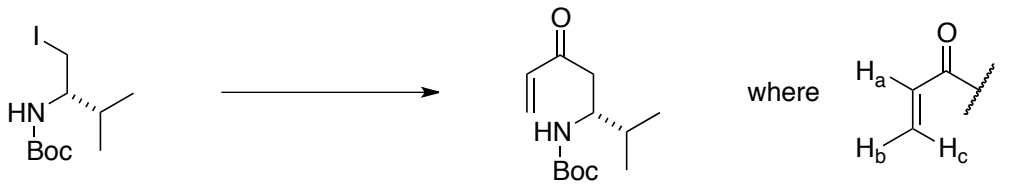
Methyl (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-4-oxohex-5-enoate (59c)



68 **59c**

The general procedure was followed, using 3.0 mmol (0.987 g) of methyl (2*R*)-2-{[(*tert*-butoxy)carbonyl]amino}-3-iodopropanoate **68**. The crude product was placed directly onto a silica gel column and purified using a gradient of 10:90 EtOAc/petroleum ether to 20:80 EtOAc/petroleum ether as the solvent system. Methyl (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-4-oxohex-5-enoate **59c** was isolated as a white solid when very pure, or more commonly as a brown solid (0.395–0.510 g, 51–66%): m.p. 49–53 °C; R_f 0.5 (50:50 EtOAc/petroleum ether); ν_{max}(ATR)/cm^{-1} 3386, 2966, 1747, 1737, 1692, 1678, 1617, 1502; δ_H (400 MHz, $CDCl_3$) 1.43 (9H, s, $C(CH_3)_3$), 3.16 (1H, dd, *J* = 4.1 and 18.0, COC*H*H), 3.34 (1H, dd, *J* = 4.2 and 18.0, COCH*H*), 3.73 (3H, s, CH_3), 4.44–4.65 (1H, m, C*H*NH), 5.53 (1H, d, *J* = 8.3, NH), 5.92 (1H, dd, *J* = 1.2 and 10.0, H_b), 6.25 (1H, dd, *J* = 1.2 and 17.7, H_c), 6.33 (1H, dd, *J* = 10.0 and 17.7, H_a); δ_C (101 MHz, $CDCl_3$) 28.3 ($C(CH_3)_3$), 41.4 (CH_2), 49.4 (CO_2CH_3 or CHNH), 52.6 (CO_2CH_3 or CHNH), 80.0 ($C(CH_3)_3$), 129.7 ($CH=CH_2$), 136.0 ($CH=CH_2$), 155.5 (CO ester), 171.9 (CO carbamate), 198.3 (CO enone); $[\alpha]_D^{22}$ +32.0, *c* 1.0, $CHCl_3$; *m/z* (ES+) found: 258.1341, $C_{12}H_{19}NO_5$ requires MH^+ 258.1341.

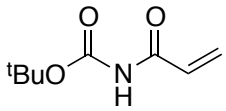
***tert*-Butyl *N*-[(3*R*)-2-methyl-5-oxohept-6-en-3-yl]carbamate (83a)**



61a **83a**

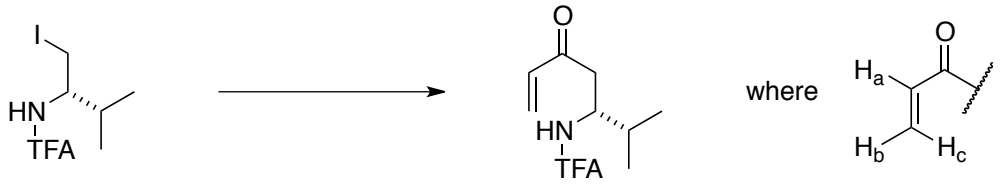
The general procedure was followed, using 2.9 mmol (0.895 g) of *tert*-butyl *N*-[(2*S*)-1-iodo-3-methylbutan-2-yl]carbamate **61a**. The crude product was placed directly onto a silica gel column and purified using 10:90 EtOAc/petroleum ether as the solvent system, yielding a white solid (0.340 g). ^{1}H NMR analysis showed that 93% of this solid was *tert*-butyl *N*-[(3*R*)-2-methyl-5-oxohept-6-en-3-yl]carbamate **83a** (0.318g, 46%): m.p. 52–55 °C; R_f 0.4 (30:70 EtOAc/petroleum ether); ν_{max}(ATR)/cm^{-1} 3370, 2962, 2930, 2877, 1682, 1616, 1516, 1443, 1404, 1391, 1365, 1333, 1308, 1246, 1168; δ_H (400 MHz, $CDCl_3$) 0.91 (3H, d, *J* = 6.9, CH(CH_3)(CH_3)), 0.93 (3H, d, *J* = 6.9, CH(CH_3)(CH_3)), 1.43 (9H, br. s, C(CH_3)$_3$), 1.84–1.97 (1H, m, C*H*(CH_3)$_2$), 2.77 (1H, dd, *J* = 5.2, 15.9, COC*H*H), 2.84 (1H, dd, *J* = 6.4, 15.9, COCH*H*), 3.73–3.87 (1H, m, NHC*H*), 4.91 (1H, br. d, *J* = 8.7, NH), 5.87 (1H, app. d, *J* = 10.4, H_b), 6.25 (1H, app. d, *J* = 17.6, H_c), 6.38 (1H, dd, *J* = 10.4, 17.6, H_a); δ_C (101 MHz, $CDCl_3$) 18.5 (C(*C*H$_3$)(CH$_3$)), 19.5 (C(CH$_3$)(*C*H$_3$)), 28.4 (C(*C*H$_3$)$_3$), 31.5 (*C*H(CH$_3$)$_2$), 41.8 (CO*C*H$_2$), 53.1 (NHCH), 79.1 (*C*(CH$_3$)$_3$), 128.6 (CH=*C*H$_2$), 136.5 (*C*H=CH$_2$), 155.6 (CO carbamate), 199.7 (CO enone); $[\alpha]_D^{25}$ −25.0, *c* 1.0, $CHCl_3$; *m/z* (ES+) found: 242.1768, $C_{13}H_{23}NO_3$ requires MH^+ 242.1756.

The remaining 7% of the white solid isolated was found to be *tert*-butyl *N*-(prop-2-enoyl)carbamate **85a** (0.023g, 5%).



85a

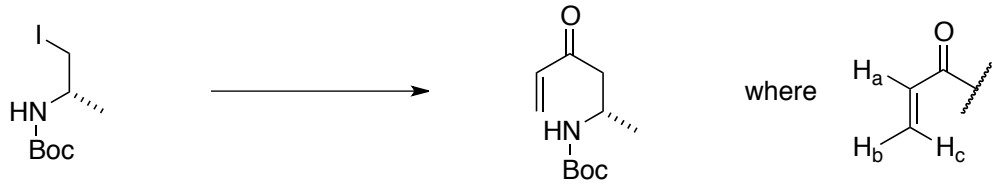
2,2,2-Trifluoro-*N*-[(3*R*)-2-methyl-5-oxohept-6-en-3-yl]acetamide (83b)



61b **83b**

The general procedure was followed, using 3.0 mmol (0.925 g) of 2,2,2-trifluoro-*N*-[(2*S*)-1-iodo-3-methylbutan-2-yl]acetamide **61b**. The reaction mixture was diluted with EtOAc (50 mL), and washed sequentially with 1 M HCl (50 mL) and brine (3 × 30 mL). The aqueous layer was re-extracted with EtOAc (3 × 50 mL), and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield the crude product as a brown oil. The crude product was purified by column chromatography using a gradient of 10:90 EtOAc/petroleum ether to 20:80 EtOAc/petroleum ether as the solvent system. 2,2,2-Trifluoro-*N*-[(3*R*)-2-methyl-5-oxohept-6-en-3-yl]acetamide **83b** (0.290 g, 41%) was isolated as a white solid: m.p. 83–84 °C; R_f 0.5 (40:60 EtOAc/petroleum ether); ν_{max}(ATR)/cm^{-1} 3287, 2976, 2914, 1702, 1613, 1562, 1474, 1402, 1373, 1306, 1257, 1153; δ_H (400 MHz, $CDCl_3$) 0.94 (3H, d, *J* = 6.8, CH_3), 0.97 (3H, d, *J* = 6.8, CH_3), 1.97–2.11 (1H, m, C*H*(CH_3)$_2$), 2.79 (1H, dd, *J* = 4.7, 17.7, COC*H*H), 3.12 (1H, dd, *J* = 4.9, 17.7, COCH*H*), 3.99–4.08 (1H, m, NHC*H*), 5.96 (1H, dd, *J* = 1.2, 10.1, H_b), 6.29 (1H, dd, *J* = 1.2, 17.6, H_c), 6.38 (1H, dd, *J* = 10.1, 17.7, H_a), 7.26 (1H, br. s, NH, coincides with $CHCl_3$ residual solvent peak); δ_C (101 MHz, $CDCl_3$) 19.0 (CH_3), 19.5 (CH_3), 30.8 (*C*H(CH_3)$_2$), 39.6 (CH_2), 52.7 (NHCH), 115.9 (q, *J* = 288.0, CF_3), 129.7 (CH=*C*H_2), 136.3 (*C*H=CH_2), 156.8 (q, *J* = 36.7, CO amide), 199.4 (CO enone); $[\alpha]_D^{23}$ −57.0, *c* 1.0, $CHCl_3$; *m/z* (ES+) found: 238.1047, $C_{10}H_{14}NO_2F_3$ requires MH^+ 238.1055.

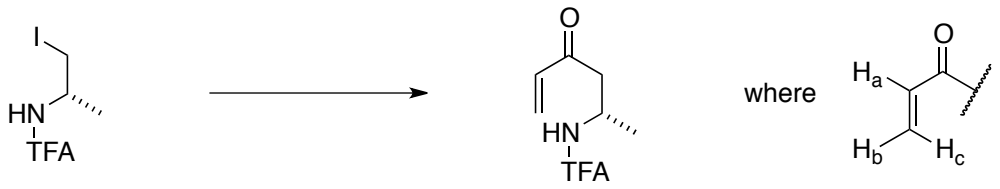
***tert*-Butyl *N*-[(2*S*)-4-oxohex-5-en-2-yl]carbamate (84a)**



64a **84a**

The general procedure was followed, using 3.0 mmol (0.775 g) of *tert*-butyl *N*-[(2*S*)-1-iodopropan-2-yl]carbamate **64a**, except that an ice bath was used in place of a water bath. The reaction was put in the ice bath before the iodide was added, and once all the reagents had been added the reaction was left to warm up to room temperature in the ice bath overnight. The reaction mixture was then diluted with EtOAc (50 mL), and washed sequentially with 1 M HCl (50 mL) and brine (3 × 30 mL). The aqueous layer was re-extracted with EtOAc (4 × 50 mL), and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield the crude product as a mixture of a brown oil and a brown solid. The crude product was purified by column chromatography using a gradient of 10:90 EtOAc/petroleum ether to 20:80 EtOAc/petroleum ether as the solvent system. *tert*-Butyl *N*-[(2*S*)-4-oxohex-5-en-2-yl]carbamate **84a** (<0.041 g, <6%) was observed by ^{1}H NMR, ^{13}C NMR and MS analysis of the fractions collected: R_f 0.2 (20:80 EtOAc/petroleum ether); δ_H (400 MHz, $CDCl_3$) 1.21 (3H, d, *J* = 6.8, CHC*H*$_3$), 1.43 (9H, br. s, C(C*H*$_3$)$_3$), 2.69 (1H, dd, *J* = 6.6 and 16.0, COC*H*H), 2.93 (1H, dd, *J* = 4.5 and 16.0, COCH*H*), 3.97–4.13 (1H, m, C*H*H), 4.94 (1H, br. s, NH), 5.88 (1H, dd, *J* = 1.4 and 10.1, H_b), 6.26 (1H, dd, *J* = 1.4 and 17.7, H_c), 6.35 (1H, dd, *J* = 10.1 and 17.7, H_a); δ_C (101 MHz, $CDCl_3$) 20.5 (CH*C*H$_3$), 28.4 (C(*C*H$_3$)$_3$), 33.8 (CH_2), 43.6 (CH), 79.3 (*C*(CH$_3$)$_3$), 128.8 (*C*H=CH$_2$), 136.8 (CH=*C*H$_2$), 155.1 (CO carbamate), 199.4 (CO enone); *m/z* (ES+) found: 214.1438, $C_{11}H_{19}NO_3$ requires MH^+ 214.1443.

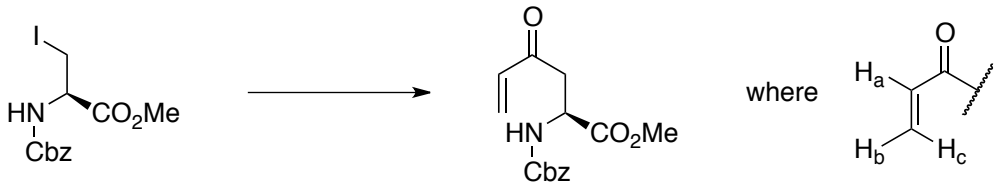
2,2,2-Trifluoro-*N*-[(2*S*)-4-oxohex-5-en-2-yl]acetamide (84b)



64b **84b**

The general procedure was followed, using 1.0 mmol (0.282 g) of 2,2,2-trifluoro-*N*-[(2*S*)-1-iodo-3-methylbutan-2-yl]acetamide **64b**. The reaction mixture was diluted with EtOAc (50 mL), and washed sequentially with 1 M HCl (50 mL) and brine (3 × 30 mL). The aqueous layer was re-extracted with EtOAc (3 × 50 mL), and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield the crude product as a brown oil. The crude product was purified by column chromatography using 25:75 EtOAc/petroleum ether as the solvent system. 2,2,2-Trifluoro-*N*-[(2*S*)-4-oxohex-5-en-2-yl]acetamide **84b** (0.100 g, 49%) was isolated as a brown solid: R_f 0.2 (20:80 EtOAc/petroleum ether); δ_H (250 MHz, $CDCl_3$) 1.33 (3H, d, *J* = 6.8, CH_3), 2.83 (1H, dd, *J* = 5.7, 17.4, C*H*H), 3.03 (1H, dd, *J* = 4.3, 17.4, CH*H*), 4.36–4.47 (1H, m, CH), 5.96 (1H, dd, *J* = 1.3, 10.0, H_b), 6.28 (1H, dd, *J* = 1.3, 17.7, H_c), 6.37 (1H, dd, *J* = 10.0, 17.7, H_a), 7.36 (1H, br. s, NH); δ_C (101 MHz, $CDCl_3$) 19.4 (CH_3), 42.8 (CH_2), 43.0 (CH), 115.8 (app. d, *J* = 287.9, CF_3), 129.9 (CH=*C*H_2), 136.5 (*C*H=CH_2), 156.5 (app. d, *J* = 36.7, CO amide), 199.3 (CO enone); *m/z* (ES+) found: 210.0733, $C_8H_{10}NO_2F_3$ requires MH^+ 210.0742. Unfortunately the product could not be further characterised due to extensive decomposition after long-term storage, along with difficulties encountered in obtaining a clean sample when re-synthesising or re-purifying the compound.

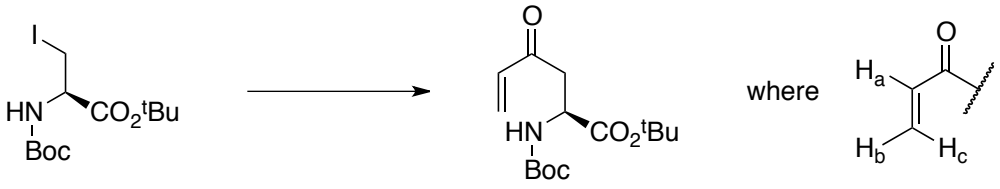
Methyl (2*S*)-2-{[(benzyloxy)carbonyl]amino}-4-oxohex-5-enoate (59d)



113 **59d**

The general procedure was followed, using 3.0 mmol (1.092 g) of methyl (2*R*)-2-{[(benzyloxy) carbonyl]amino}-3-iodopropanoate **113**. The reaction mixture was diluted with EtOAc (50 mL), and washed with brine (3 × 30 mL). The aqueous layer was re-extracted with EtOAc (3 × 50 mL), and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield the crude product as a brown oil. The crude product was purified by column chromatography using 10:90 EtOAc/petroleum ether as the solvent system. Methyl (2*S*)-2-{[(benzyloxy)carbonyl]amino}-4-oxohex-5-enoate **59d** (0.472 g, 54%) was isolated as a brown oil: R_f 0.5 (50:50 EtOAc/petroleum ether); ν_{max}(ATR)/cm^{-1} 3365, 3034, 2953, 1706, 1616, 1508, 1454, 1437, 1400, 1337, 1211; δ_H (400 MHz, $CDCl_3$) 3.19 (1H, dd, *J* = 4.2, 18.2, COC*H*H), 3.41 (1H, dd, *J* = 4.2, 18.2, COCH*H*), 3.76 (3H, s, CH_3), 4.63–4.71 (1H, m, CH), 5.13 (2H, s, $PhCH_2$), 5.82 (1H, d, *J* = 8.6, NH), 5.95 (1H, dd, *J* = 1.2, 10.0, H_b), 6.27 (1H, dd, *J* = 1.2, 17.6, H_c), 6.35 (1H, dd, *J* = 10.0, 17.6, H_a), 7.31–7.43 (5H, m, Ar H); δ_C (62.8 MHz, $CDCl_3$) 41.3 (CO*C*H_2), 49.9 (CH or CH_3), 52.7 (CH or CH_3), 67.1 ($PhCH_2$), 128.0 (Ar CH), 128.2 (Ar CH), 128.5 (Ar CH), 129.6 (*C*H=CH_2), 136.0 (CH=*C*H_2), 136.2 (Ar quat. C), 156.0 (CO carbamate), 171.4 (CO ester), 198.0 (CO enone); $[\alpha]_D^{24}$ −9.2, *c* 0.4, DMSO; *m/z* (ES+) found: 292.1194, $C_{15}H_{17}NO_5$ requires MH^+ 292.1185.

***tert*-Butyl (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-4-oxohex-5-enoate (59b)**

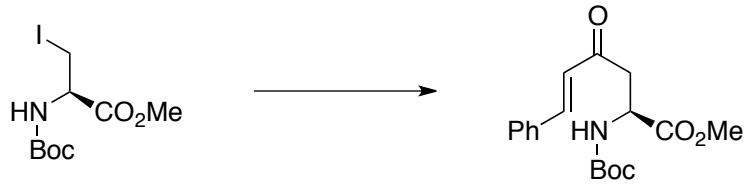


96 **59b**

The general procedure was followed, using 2.7 mmol (1.007 g) of *tert*-butyl (2*R*)-2-{[(*tert*-butoxy)carbonyl]amino}-3-iodopropanoate **96**. The reaction mixture was diluted with EtOAc (50 mL), and washed with brine (3 × 30 mL). The aqueous layer was re-extracted with EtOAc (3 × 50 mL), and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield the crude product as a brown oil. The crude product was purified by column chromatography using 5:95 EtOAc/toluene as the solvent system. *tert*-Butyl (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-4-oxohex-5-enoate **59b** (0.346 g, 43%) was isolated as a white solid: m.p. 69–74 °C; R_f 0.3 (20:80 EtOAc/petroleum ether); ν_{max}(ATR)/cm^{-1} 3450, 2979, 2931, 1720, 1692, 1676, 1616, 1491, 1454, 1399, 1366, 1334, 1286, 1248, 1221, 1152; δ_H (400 MHz, $CDCl_3$) 1.45 (18H, s, 2 × $C(CH_3)_3$), 3.10 (1H, dd, *J* = 4.3, 17.8, COC*H*H), 3.31 (1H, dd, *J* = 4.3, 17.8, COCH*H*), 4.33–4.55 (1H, m, NHC*H*), 5.51 (1H, d, *J* = 8.3, NH), 5.94 (1H, dd, *J* = 1.3, 10.1, H_b), 6.27 (1H, dd, *J* = 1.3, 17.7, H_c), 6.36 (1H, dd, *J* = 10.1, 17.7, H_a); δ_C (101 MHz, $CDCl_3$) 27.9 ($C(CH_3)_3$), 28.3 ($C(CH_3)_3$), 41.5 (CH_2), 50.1 (NHCH), 79.7 ($C(CH_3)_3$), 82.1 ($C(CH_3)_3$), 129.3 ($CH=CH_2$), 136.3 ($CH=CH_2$), 155.6 (CO carbamate), 170.3 (CO ester), 198.4 (CO enone); $[\alpha]_D^{23}$ +21.0, *c* 1.0, $CHCl_3$; *m/z* (ES+) found: 300.1804, $C_{15}H_{25}NO_5$ requires MH^+ 300.1811.

These characterisation data are in accordance with the literature values for the racemic compound **(±)-59b**.[56-57]

Methyl (2*S*,5*E*)-2-{[(*tert*-butoxy)carbonyl]amino}-4-oxo-6-phenylhex-5-enoate (128)



68 **128**

The general procedure was followed, using 3.0 mmol (0.989 g) of methyl (2*R*)-2-{[(*tert*-butoxy)carbonyl]amino}-3-iodopropanoate **68**. The reaction mixture was diluted with EtOAc (50 mL), and washed with brine (3 × 30 mL). The aqueous layer was re-extracted with EtOAc (3 × 50 mL), and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield the crude product as a brown oily solid. The crude product was purified by column chromatography using 20:80 EtOAc/petroleum ether as the solvent system. Methyl (2*S*,5*E*)-2-{[(*tert*-butoxy)carbonyl]amino}-4-oxo-6-phenylhex-5-enoate **128** (0.461 g, 46%) was isolated as a brown oily solid: R_f 0.5 (30:70 EtOAc/petroleum ether); ν_{max}(ATR)/cm^{-1} 3437, 2978, 1744, 1706, 1662, 1609, 1577, 1495, 1450, 1437, 1392, 1366, 1339, 1288, 1248, 1207, 1162; δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s, $C(CH_3)_3$), 3.24 (1H, dd, *J* = 4.2, 17.9, C*H*H), 3.45 (1H, dd, *J* = 4.4, 17.9, CH*H*), 3.74 (3H, s, CH_3), 4.58–4.67 (1H, m, NHC*H*), 5.63 (1H, d, *J* = 8.7, NH), 6.71 (1H, d, *J* = 16.3, COC*H*=CH), 7.32–7.42 (3H, m, Ar H), 7.50–7.60 (3H, m, COCH=C*H* and Ar H); δ_C (101 MHz, $CDCl_3$) 28.3 ($C(CH_3)_3$), 42.4 (CH_2), 49.6 (CH or CO_2CH_3), 52.6 (CH or CO_2CH_3), 80.0 ($C(CH_3)_3$), 125.6 (CO*C*H=CH or Ar CH), 128.4 (CO*C*H=CH or Ar CH), 129.0 (CO*C*H=CH or Ar CH), 130.8 (CO*C*H=CH or Ar CH), 134.1 (Ar quat. C), 143.9 (COCH=*C*H), 155.6 (CO carbamate), 172.0 (CO ester), 197.6 (CO enone); $[\alpha]_D^{23}$ +38.8, *c* 1.0, $CHCl_3$ (lit. +56.9, c 1.0, $CHCl_3$)[125]; *m/z* (ES+) found: 334.1639, $C_{18}H_{23}NO_5$ requires MH^+ 334.1654.

These characterisation data are in accordance with the literature values.[125]

5.4 Attempted Hydrogen Chloride Mediated Cyclisations

(2*S*)-6-Chloro-1-methoxy-1,4-dioxohexan-2-aminium chloride (60c)

59c **60c**

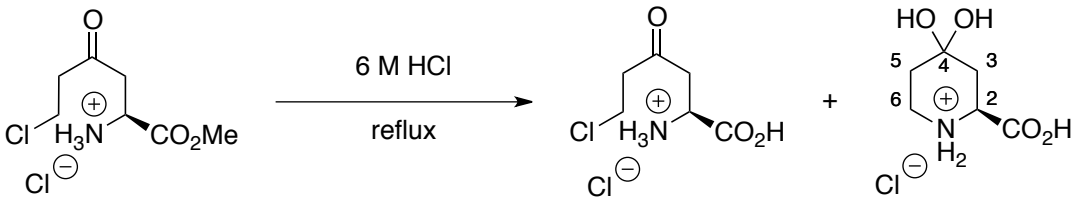
Methyl (2*S*)-2-(*tert*-butoxycarbonylamino)-4-oxohex-5-enoate **59c** (0.320 g, 1.2 mmol, 1.0 eq.) was dissolved in 1 M hydrogen chloride in diethyl ether (12.5 mL, 12.5 mmol, 10 eq.) and stirred at room temperature for 3 d. Removal of the solvent under reduced pressure yielded (2*S*)-6-chloro-1-methoxy-1,4-dioxohexan-2-aminium chloride **60c** as a pale orange solid (0.270 g, 94%): m.p. 138 °C (decomp.); R_f 0.5 (10:90 MeOH/CH_2Cl_2); ν_{max}(ATR)/cm^{-1} 2920, 2849, 2636, 1745, 1711, 1596, 1570, 1495, 1442, 1428, 1402, 1380, 1321, 1296, 1252, 1234, 1194, 1162; δ_H (400 MHz, D_2O) 3.00 (2H, td, *J* = 6.0, 3.1, CH_2), 3.27–3.32 (2H, m, CH_2), 3.68 (2H, t, *J* = 6.0, CH_2), 3.71 (3H, s, CH_3), 4.35 (1H, t, *J* = 5.1, CH); δ_H (400 MHz, CD_3OD) 3.06 (2H, t, *J* = 6.4, CH_2), 3.21–3.30 (2H, m, CH_2), 3.80 (2H, t, *J* = 6.4, CH_2), 3.84 (3H, s, CH_3), 4.38 (1H, dd, *J* = 4.4, 6.1, CH); δ_C (101 MHz, D_2O) 38.0 (CH_2), 41.5 (CH_2), 44.0 (CH_2), 48.3 (CH or CH_3), 53.8 (CH or CH_3), 169.8 (CO ester), 207.7 (CO ketone); δ_C (101 MHz, CD_3OD) 37.3 (CH_2), 41.4 (CH_2), 44.2 (CH_2), 48.1 (CH_3), 52.5 (CH), 168.7 (CO ester), 204.1 (CO ketone); $[\alpha]_D^{23}$ +20.0, *c* 1.0, H_2O; *m/z* (ES+) found: 194.0577, $C_7H_{13}NO_3{}^{35}Cl_2$ requires $(M-Cl)^+$ 194.0584.

(3*R*)-7-Chloro-2-methyl-5-oxoheptan-3-aminium chloride (90)

83a **90**

tert-Butyl *N*-[(3*R*)-2-methyl-5-oxohept-6-en-3-yl]carbamate **83a** (0.097 g, 0.4 mmol, 1.0 eq.) was dissolved in 1 M hydrogen chloride in diethyl ether (4.0 mL, 4.0 mmol, 10 eq.) and stirred at room temperature for 3 d. Removal of the solvent under reduced pressure yielded (3*R*)-7-chloro-2-methyl-5-oxoheptan-3-aminium chloride **90** as a brown oil (0.082 g, 96%), after drying under high vacuum: R_f 0.0 (EtOAc); ν_{max}(ATR)/cm^{-1} 2962, 2902, 1711, 1610, 1510, 1471, 1395; δ_H (400 MHz, D_2O) 0.86 (3H, d, *J* = 6.8, CH_3), 0.87 (3H, d, *J* = 6.8, CH_3), 1.81–1.95 (1H, m, *C*H(CH_3)$_2$), 2.78 (1H, dd, *J* = 9.3, 19.3, H_3NCHC*H*H), 2.95–3.04 (app. 2.6H, m, H_3NCHCH*H* and ClCH_2CH_2), 3.39–3.52 (1H, m, H_3NC*H*), 3.69 (app. 1.7H, t, *J* = 6.1, ClCH_2); δ_C (101 MHz, $CDCl_3$) 16.7 (CH_3), 17.3 (CH_3), 29.8 (CH), 38.1 (CH_2), 41.1 (CH_2), 44.5 (CH_2), 52.3 (CH), 209.5 (CO); $[\alpha]_D^{20}$ +38.5, *c* 3.6, MeOH; *m/z* (ES+) found: 178.0997, $C_8H_{17}NO^{35}Cl_2$ requires $(M-Cl)^+$ 178.0999.

(1*S*)-1-Carboxy-5-chloro-3-oxopentan-1-aminium chloride (60b) and (2*S*)-2-carboxy-4,4-dihydroxypiperidin-1-ium chloride (94a·H_2O)



60c **60b** **94a·H_2O**

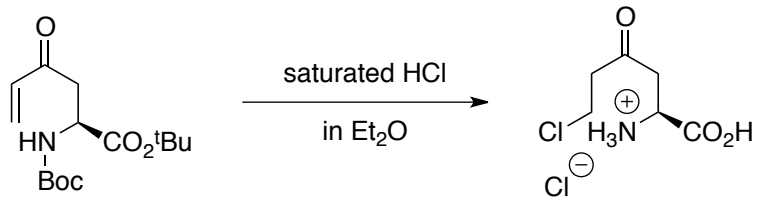
(2*S*)-6-Chloro-1-methoxy-1,4-dioxohexan-2-aminium chloride **60c** (0.097 g, 0.42 mmol, 1.0 eq.) was dissolved in 6 M hydrochloric acid (2.5 mL, 15.0 mmol, 35.5 eq.) and heated at reflux for 3 h. After cooling to room temperature, the reaction was diluted with MeOH, and the solvent was removed under reduced pressure to yield the mixture of products as a brown gum (0.075 g). ^{1}H NMR analysis showed that the product consisted of an approximate 80:20 mix of (1*S*)-1-carboxy-5-chloro-3-oxopentan-1-aminium chloride **60b** and (2*S*)-2-carboxy-4,4-dihydroxypiperidin-1-ium chloride **94a·H_2O**.

(1*S*)-1-Carboxy-5-chloro-3-oxopentan-1-aminium chloride **60b**: δ_H (400 MHz, D_2O) 2.99 (2H, t, *J* = 6.1, $ClCH_2CH_2$), 3.21–3.25 (2H, m, H_3NCHCH_2), 3.67 (2H, t, *J* = 6.1, $ClCH_2$), 4.23 (1H, t, *J* = 5.3, CH); δ_C (101 MHz, D_2O) 38.0 (CH_2), 41.6 (CH_2), 44.1 (CH_2), 48.4 (CH), 171.1 (CO acid), 207.8 (CO ketone).

(2*S*)-2-Carboxy-4,4-dihydroxypiperidin-1-ium chloride **94a·H_2O**: δ_H (400 MHz, D_2O) 1.79–1.97 (3H, m, H^{3a}, H^{5a}, H^{5e}), 2.30 (1H, ddd, *J* = 2.5, 3.8, 14.3, H^{3e}), 3.11 (1H, td, *J* = 12.5, 3.9, H^{6a}), 3.36–3.42 (1H, m, H^{6e}), 4.03 (1H, dd, *J* = 3.8, 11.7, H^{2a}); δ_C (101 MHz, D_2O) 33.5 (C^5), 37.0 (C^3), 40.9 (C^6), 54.8 (C^2), 90.7 (C^4), 171.1 (CO); *m/z* (ES+) found: 162.0764, $C_6H_{12}NO_4Cl$ requires $(M-Cl)^+$ 162.0766.

These characterisation data are in accordance with the literature values.[91-93]

(1*S*)-1-Carboxy-5-chloro-3-oxopentan-1-aminium chloride (60b)



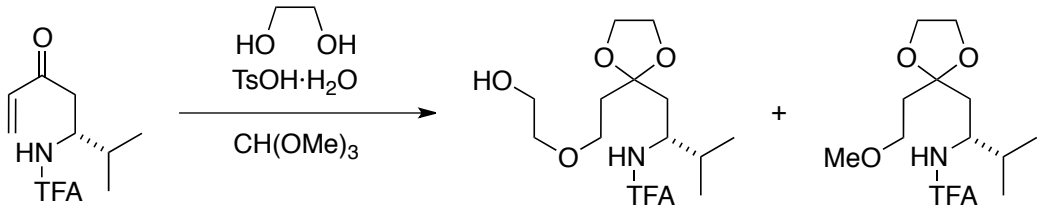
59b **60b**

tert-Butyl (2*S*)-2-{[(*tert*-butoxy)carbonyl]amino}-4-oxohex-5-enoate **59b** (0.059 g, 0.20 mmol, 1.0 eq.) was dissolved in saturated hydrogen chloride in Et_2O (1.8 mL) and the reaction was left without stirring at room temperature overnight. The solvent was removed with a pipette and the yellow solid was sequentially washed with dry Et_2O (4 × 5 mL), which was removed by pipette after each successive washing. The resulting solid was dried under high vacuum, yielding (1*S*)-1-carboxy-5-chloro-3-oxopentan-1-aminium chloride **60b** as a pale cream solid (0.037 g, 87%): m.p. >135 °C (decomp.); R_f 0.0 (10:90 MeOH/EtOAc); ν_{max}(ATR)/cm^{-1} 2871, 2635, 2560, 2159, 2024, 1977, 1743, 1709, 1586, 1501, 1482, 1423, 1390, 1349, 1242, 1220, 1205, 1152, 1141; δ_H (400 MHz, CD_3OD) 3.06 (2H, td, *J* = 6.4, 1.9, $ClCH_2CH_2$), 3.19 (1H, dd, *J* = 7.1, 19.0, $H_3NCHCHH$), 3.29 (1H, dd, *J* = 3.8, 19.0, $H_3NCHCHH$, inferred due to partial overlap with CD_3OH signal), 3.81 (2H, t, *J* = 6.4, $ClCH_2$), 4.31 (1H, dd, *J* = 3.8, 7.1, H_3NCH); δ_H (400 MHz, D_2O) 2.97 (2H, t, *J* = 6.1, $ClCH_2CH_2$), 3.18–3.25 (2H, m, H_3NCHCH_2), 3.65 (2H, t, *J* = 6.1, $ClCH_2$), 4.22 (1H, t, *J* = 5.2, CH); δ_C (101 MHz, CD_3OD) 37.3 (CH_2), 41.5 (CH_2), 44.3 (CH_2), 48.1 (CH), 169.5 (CO acid), 204.2 (CO ketone); δ_C (101 MHz, D_2O) 38.0 (CH_2), 41.6 (CH_2), 44.1 (CH_2), 48.6 and 48.9 (CH), 171.2 (CO acid), 207.8 (CO ketone); $[\alpha]_D^{25}$ +20.2, *c* 1.0, MeOH; *m/z* (ES+) found: 180.0429, $C_6H_{11}{}^{35}Cl_2NO_3$ requires $(M-Cl)^+$ 180.0427; found C 33.80%, H 4.59%, N 6.14%, Cl 31.67%, $C_6H_{11}Cl_2NO_3$ requires C 33.35%, H 5.13%, N 6.48%, Cl 32.82%.

These characterisation data are in accordance with the literature values.[56-57] (See Chapter 2.3, p60 for the reason why there are structural differences between this compound and the compound reported in the literature.)

5.5 Alternative Cyclisation Strategies

2,2,2-Trifluoro-*N*-[(2*R*)-1-{2-[2-(2-hydroxyethoxy)ethyl]-1,3-dioxolan-2-yl}-3-methylbutan-2-yl]acetamide (109) and 2,2,2-trifluoro-*N*-[(2*R*)-1-[2-(2-methoxyethyl)-1,3-dioxolan-2-yl]-3-methylbutan-2-yl]acetamide (110)



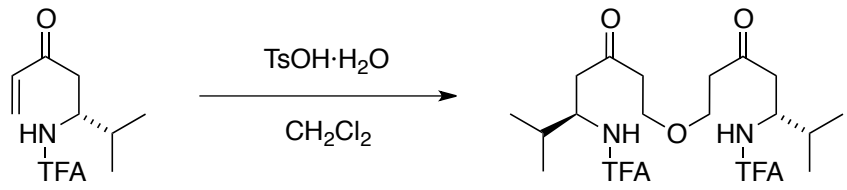
83b **109** **110**

A non-flame-dried round bottomed flask under N_2 was charged with 2,2,2-trifluoro-*N*-[(3*R*)-2-methyl-5-oxohept-6-en-3-yl]acetamide **83b** (0.089 g, 0.38 mmol, 1.0 eq.) and $TsOH{\cdot}H_2O$ (0.005 g, 0.02 mmol, 6 mol%) before being evacuated and purged with nitrogen five times. Ethylene glycol (0.11 mL, 1.97 mmol, 5.3 eq.) and $CH(OMe)_3$ (0.21 mL, 1.92 mmol, 5.1 eq.) were added, and the reaction was stirred at room temperature overnight. The reaction mixture was diluted with CH_2Cl_2 (5 mL), and washed with sat. aq. $NaHCO_3$ (5 mL) and brine (5 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated to give the crude product as a pale brown oil. The crude product was purified chromatographically on three successive columns, using a gradient of 0:100 to 100:0 EtOAc/heptane as the first solvent system, followed by a gradient of 0:100 to 50:50 EtOAc/heptane as the second solvent system and a gradient of 0:100 to 30:70 EtOAc/heptane as the third solvent system.

2,2,2-Trifluoro-*N*-[(2*R*)-1-{2-[2-(2-hydroxyethoxy)ethyl]-1,3-dioxolan-2-yl}-3-methylbutan-2-yl]acetamide **109** was isolated as a brown oil (0.042 g, 32%): R_f 0.5 (50:50 EtOAc/petroleum ether); ν_{max}(thin film)/cm^{-1} 3306, 2964, 2930, 2881, 1703, 1206, 1188, 1156; δ_H (400 MHz, $CDCl_3$) 0.91 (6H, t, *J* = 7.1, 2 × CH_3), 1.81–2.23 (app. 7H, m, C*H*$(CH_3)_2$, CH_2CCH_2 and OH), 3.51–3.64 (4H, m, CH_2OCH_2), 3.72–3.78 (2H, m, HOC*H*$_2$), 3.89–4.00 (4H, m, OCH_2CH_2O), 4.03–4.13 (1H, m, NHC*H*), 6.97 (1H, d, *J* = 7.1, NH); δ_C (101 MHz, $CDCl_3$) 17.8 (CH_3), 18.0 (CH_3), 31.9 (*C*H$(CH_3)_2$), 36.8 (2 × CH_2), 51.5 (NHCH), 61.7 (CH_2), 64.5 (CH_2), 64.9 (CH_2), 66.9 (CH_2), 72.0 (CH_2), 109.9 (quat. C), 116.0 (q, *J* = 288.2, CF_3), 156.8 (q, *J* = 36.4, CO amide); $[\alpha]_D^{23}$ 0.0, *c* 1.2, $CHCl_3$; *m/z* (ES+) found: 366.15042, $C_{14}H_{24}NO_5F_3$ requires MNa^+ 366.14988.

2,2,2-Trifluoro-*N*-[(2*R*)-1-[2-(2-methoxyethyl)-1,3-dioxolan-2-yl]-3-methylbutan-2-yl]acetamide **110** was isolated as a pale brown oil (0.027 g, 23%): R_f 0.1 (50:50 EtOAc/petroleum ether); ν_{max}(thin film)/cm^{-1} 3308, 2965, 2928, 2897, 2879, 1704, 1557, 1466, 1391, 1373, 1205, 1184, 1159, 1118; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, d, *J* = 6.9, CH(C*H*$_3$)(CH$_3$)), 0.92 (3H, d, *J* = 6.9, CH(CH$_3$)(C*H*$_3$)), 1.79–1.96 (4H, m, CH_2CCH_2), 1.98–2.10 (1H, m, C*H*(CH$_3$)$_2$), 3.35 (3H, s, OCH_3), 3.45–3.55 (2H, m, CH_3OCH_2), 3.89–3.99 (4H, m, OCH_2CH_2O), 4.00–4.08 (1H, m, NHC*H*), 7.17 (1H, d, *J* = 5.4, NH); δ_C (101 MHz, $CDCl_3$) 17.4 (CH(*C*H$_3$)(CH$_3$)), 18.1 (CH(CH$_3$)(*C*H$_3$)), 31.6 (*C*H(CH$_3$)$_2$), 36.1 (CH_2CCH_2), 36.9 (CH_2CCH_2), 51.6 (NHCH), 58.6 (OCH_3), 64.4 (OCH_2CH_2O), 64.8 (OCH_2CH_2O), 68.6 (CH_3OCH_2), 109.9 (quat. C), 116.1 (q, *J* = 288.4, CF_3), 156.8 (q, *J* = 36.3, CO amide); $[\alpha]_D^{23}$ −11.4, *c* 1.1, $CHCl_3$; *m/z* (ES+) found: 314.15781, $C_{13}H_{22}NO_4F_3$ requires MH^+ 314.15837.

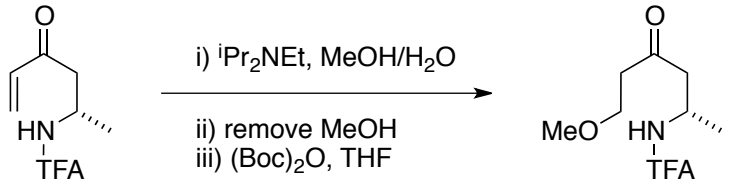
2,2,2-Trifluoro-*N*-[(3*R*)-2-methyl-7-{[(5*R*)-6-methyl-3-oxo-5-(trifluoroacetamido)heptyl]oxy}-5-oxoheptan-3-yl]acetamide (111)



83b **111**

2,2,2-Trifluoro-*N*-[(3*R*)-2-methyl-5-oxohept-6-en-3-yl]acetamide **83b** (0.095 g, 0.40 mmol, 1.0 eq.) was dissolved in dry CH_2Cl_2 (0.8 mL) under N_2 in a non-flame-dried flask, and $TsOH·H_2O$ (0.008 g, 0.04 mmol, 10 mol%) was added. The resulting solution was stirred at room temperature for 3 d, before being diluted with CH_2Cl_2 (5 mL) and washed with sat. aq. $NaHCO_3$ (5 mL) and brine (5 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated to give the crude product as a brown solid. The crude product was purified by column chromatography using a gradient of 0:100 to 100:0 EtOAc/heptane as the solvent system. 2,2,2-Trifluoro-*N*-[(3*R*)-2-methyl-7-{[(5*R*)-6-methyl-3-oxo-5-(trifluoroacetamido)heptyl]oxy}-5-oxoheptan-3-yl]acetamide **111** was isolated as a white solid (0.060 g, 61%): m.p. 145–150 °C; R_f 0.3 (50:50 EtOAc/petroleum ether); ν_{max}(thin film)/cm^{-1} 3292, 2968, 1703, 1558, 1383, 1208, 1183, 1167; δ_H (400 MHz, $CDCl_3$) 0.94 (6H, d, *J* = 6.7, CH_3), 0.95 (6H, d, *J* = 6.7, CH_3), 1.92–2.06 (2H, m, C*H*$(CH_3)_2$), 2.64 (4H, t, *J* = 5.9, OCH_2CH_2), 2.69 (2H, dd, *J* = 4.6, 17.7, NHCHC*H*H), 2.88 (2H, dd, *J* = 5.9, 17.7, NHCHCH*H*), 3.67 (4H, t, *J* = 5.9, OCH_2), 3.96–4.06 (2H, m, NHC*H*), 7.14 (2H, d, *J* = 8.6, NH); δ_C (101 MHz, $CDCl_3$) 18.9 (CH_3), 19.4 (CH_3), 30.9 (*C*H$(CH_3)_2$), 43.1 ($COCH_2$), 43.6 ($COCH_2$), 52.4 (NHCH), 65.9 (OCH_2), 115.9 (q, *J* = 288.1, CF_3), 156.8 (q, *J* = 36.7, CO amide), 208.3 (CO ketone); $[\alpha]_D^{23}$ −54.2, *c* 1.0, $CHCl_3$; *m/z* (ES+) found: 493.21286, $C_{20}H_{30}N_2O_5F_6$ requires MH^+ 493.21317.

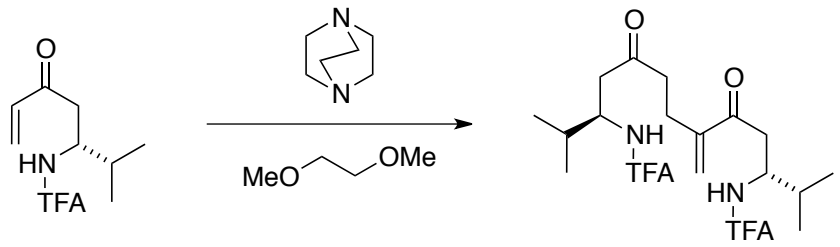
2,2,2-Trifluoro-*N*-[(2*S*)-6-methoxy-4-oxohexan-2-yl]acetamide (130)



84b **130**

2,2,2-Trifluoro-*N*-[(2*S*)-4-oxohex-5-en-2-yl]acetamide **84b** (0.070 g, 0.34 mmol, 1.0 eq.) was dissolved in 2:1 MeOH/H_2O (15 mL). $^{i}Pr_2NEt$ (3.5 mL, 20.2 mmol, 60.2 eq.) was added, and the solution was stirred at room temperature overnight. The MeOH was removed under reduced pressure, before a solution of $(Boc)_2O$ (0.096 g, 0.44 mmol, 1.3 eq.) in THF (10 mL) was added, and the reaction was stirred at room temperature for a further 24 h. The THF was removed under reduced pressure, and the aqueous solution was diluted with H_2O (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product as a yellow oil. The crude product was purified by column chromatography using a gradient of 0:100 to 40:60 EtOAc/heptane as the solvent system. 2,2,2-Trifluoro-*N*-[(2*S*)-6-methoxy-4-oxohexan-2-yl]acetamide **130** was isolated as a white oily solid (0.033 g, 41%), which fully solidified upon standing: m.p. 57–58 °C; R_f 0.3 (50:50 EtOAc/petroleum ether); ν_{max}(thin film)/cm^{-1} 3424, 2985, 2935, 1704, 1650, 1644, 1639, 1561, 1459, 1376, 1208, 1188, 1158; δ_H (400 MHz, $CDCl_3$) 1.31 (3H, d, *J* = 6.8, CHC*H*$_3$), 2.67 (2H, app. t, *J* = 6.0, OCH_2CH_2), 2.73 (1H, dd, *J* = 5.4, 17.6, NHCHC*H*H), 2.85 (1H, dd, *J* = 4.5, 17.6, NHCHCH*H*), 3.34 (3H, s, OCH_3), 3.60–3.71 (2H, m, OCH_2), 4.29–4.42 (1H, m, NHC*H*), 7.31 (1H, br. s, NH); δ_C (101 MHz, $CDCl_3$) 19.4 (CH*C*H$_3$), 42.9 (CH), 43.6 ($COCH_2$), 46.8 ($COCH_2$), 58.9 (OCH_3), 67.5 (OCH_2), 115.8 (q, *J* = 287.8, CF_3), 156.4 (q, *J* = 36.8, CO amide), 208.6 (CO ketone); $[\alpha]_D^{23}$ −48.0, *c* 1.3, $CHCl_3$; *m/z* (ES+) found: 242.09987, $C_9H_{14}NO_3F_3$ requires MH^+ 242.09985.

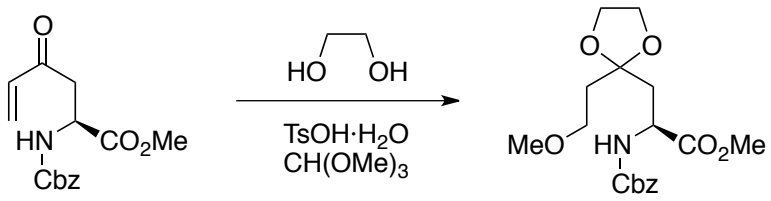
***N*-[(3*R*,11*R*)-2,12-Dimethyl-6-methylidene-5,9-dioxo-11-(trifluoroacetamido)tridecan-3-yl]-2,2,2-trifluoroacetamide (122)**



83b **122**

2,2,2-Trifluoro-*N*-[(3*R*)-2-methyl-5-oxohept-6-en-3-yl]acetamide **83b** (0.095 g, 0.40 mmol, 1.0 eq.) and DABCO (0.047 g, 0.42 mmol, 1.0 eq.) were dissolved in DME (5 mL) in a flame-dried flask, and the reaction was stirred at room temperature for 3 d. The reaction mixture was poured onto 5% AcOH (5 mL) at 0 °C, before being extracted with EtOAc (10 mL) and washed with H_2O (10 mL). The organic layer was dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to yield the crude product as a light brown oil. The crude product was purified by column chromatography using a gradient of 10:90 to 50:50 EtOAc/petroleum ether as the solvent system. *N*-[(3*R*,11*R*)-2,12-Dimethyl-6-methylidene-5,9-dioxo-11-(trifluoroacetamido)tridecan-3-yl]-2,2,2-trifluoroacetamide **122** was isolated as a white solid (0.026 g, 27%): m.p. 135–137 °C; R_f 0.5 (50:50 EtOAc/petroleum ether); ν_{max}(thin film)/cm^{-1} 3297, 3105, 2965, 2924, 2877, 2854, 1701, 1677, 1638, 1559, 1474, 1427, 1416, 1390, 1372, 1327, 1303, 1279, 1261, 1204, 1180; δ_H (400 MHz, $CDCl_3$) 0.90–1.00 (12H, m, 4 × CH_3), 1.91–2.03 (2H, m, 2 × C*H*$(CH_3)_2$), 2.47–2.68 (5H, m, CH_2=CC*H*$_2$C*H*$_2$ and NHCHC*H*H), 2.83 (1H, dd, *J* = 5.8, 17.5, NHCHCH*H*), 2.90 (1H, dd, *J* = 4.4, 16.9, NHCHC*H*H), 3.12 (1H, dd, *J* = 6.3, 16.9, NHCHCH*H*), 3.92–4.10 (2H, m, 2 × NHC*H*), 5.92 (1H, s, C=C*H*H), 6.07 (1H, s, C=CH*H*), 7.10 (2H, app. t, *J* = 8.9, 2 × NH); δ_C (101 MHz, $CDCl_3$) 18.9 (CH_3), 18.9 (CH_3), 19.5 (CH_3), 19.5 (CH_3), 25.1 (CH_2=C*C*H$_2$), 30.9 (*C*H$(CH_3)_2$), 31.0 (*C*H$(CH_3)_2$), 38.0 (CO*C*H$_2$), 41.8 (CO*C*H$_2$), 42.8 (CO*C*H$_2$), 52.6 (NHCH), 53.1 (NHCH), 115.9 (app. d, *J* = 288.5, 2 × CF_3), 126.9 (*C*H$_2$=C), 147.0 (CH_2=*C*), 156.8 (app. d, *J* = 37.0, CO amide), 156.9 (app. d, *J* = 36.8, CO amide), 200.1 (CO enone), 208.7 (CO ketone); $[\alpha]_D^{23}$ −54.0, *c* 0.5, $CHCl_3$; *m/z* (ES+) found: 475.2033, $C_{20}H_{28}N_2O_4F_6$ requires MH^+ 475.2032.

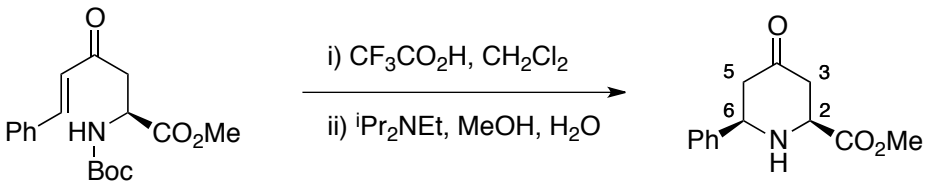
Methyl (2*S*)-2-{[(benzyloxy)carbonyl]amino}-3-[2-(2-methoxyethyl)-1,3-dioxolan-2-yl]propanoate (114)



59d **114**

Methyl (2*S*)-2-{[(benzyloxy)carbonyl]amino}-4-oxohex-5-enoate **59d** (0.232 g, 0.79 mmol, 1.0 eq.) and TsOH·H_2O (0.010 g, 0.05 mmol, 7 mol%) were dissolved in ethylene glycol (0.22 mL, 3.94 mmol, 5.0 eq.) and $CH(OMe)_3$ (0.43 mL, 3.93 mmol, 4.9 eq.). The reaction was stirred at room temperature for 5 h, before being diluted with CH_2Cl_2 (5 mL) and stirred at room temperature overnight. The solution was further diluted with CH_2Cl_2 (5 mL) and washed with sat. aq. $NaHCO_3$ (10 mL). The aqueous layer was re-extracted with CH_2Cl_2 (10 mL) and EtOAc (10 mL) due to formation of a gel. The combined organic extracts were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to give the crude product, which was purified by column chromatography using 50:50 EtOAc/petroleum ether as the solvent system. Methyl (2*S*)-2-{[(benzyloxy)carbonyl]amino}-3-[2-(2-methoxyethyl)-1,3-dioxolan-2-yl]propanoate **114** was isolated as a colourless oil (0.051 g, 18%): R_f 0.3 (50:50 EtOAc/petroleum ether); ν_{max}(ATR)/cm^{-1} 3422, 2952, 2893, 1718, 1501, 1454, 1437, 1347, 1205, 1175, 1111, 1047; δ_H (400 MHz, $CDCl_3$) 1.89 (2H, t, *J* = 6.5, $CH_3OCH_2CH_2$), 2.24 (1H, dd, *J* = 6.8, 15.1, NHCHC*H*H), 2.30 (1H, dd, *J* = 4.6, 15.1 NHCHCH*H*), 3.33 (3H, s, CH_2OCH_3), 3.45 (2H, t, *J* = 6.5, CH_3OCH_2), 3.74 (3H, s, CO_2CH_3), 3.86–4.05 (4H, m, OCH_2CH_2O), 4.40–4.50 (1H, m, NHC*H*), 5.10 (1H, d, *J* = 12.3, PhC*H*H), 5.16 (1H, d, *J* = 12.3, PhCH*H*), 6.05 (1H, d, *J* = 7.4, NH), 7.29–7.45 (5H, m, Ar H); δ_C (101 MHz, $CDCl_3$) 37.2 (CH_2CCH_2), 37.8 (CH_2CCH_2), 50.7 (CO_2CH_3 or CH), 52.2 (CO_2CH_3 or CH), 58.7 (CH_2OCH_3), 64.4 (OCH_2CH_2O), 64.8 (OCH_2CH_2O), 66.8 (CH_2Ph), 68.2 (CH_3OCH_2), 109.9 (quat. C), 128.1 (Ar CH), 128.1 (Ar CH), 128.5 (Ar CH), 136.5 (Ar quat. C), 156.0 (CO carbamate), 172.7 (CO ester); $[\alpha]_D^{23}$ +5.1, *c* 1.6, $CHCl_3$; *m/z* (ES+) found: 368.1708, $C_{18}H_{25}NO_7$ requires MH^+ 368.1709.

Methyl (2*S*,6*R*)-4-oxo-6-phenylpiperidine-2-carboxylate (10a)

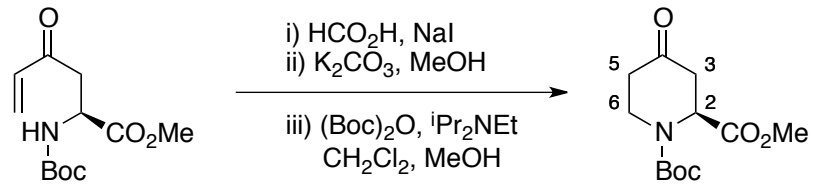


128 **10a**

Methyl (2S,5E)-2-{[(*tert*-butoxy)carbonyl]amino}-4-oxo-6-phenylhex-5-enoate **128** (0.190 g, 0.57 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (6 mL) and CF_3CO_2H (0.42 mL, 5.5 mmol, 9.6 eq.) was added. The reaction was stirred at room temperature for 1.5 h before being concentrated by blowing N_2 over the reaction for ~1 h. The residue was placed under vacuum for 15 min, before being dissolved in 2:1 MeOH/H_2O (30 mL). $^{i}Pr_2NEt$ (0.5 mL, 2.87 mmol, 5.0 eq.) was added and the reaction was stirred at room temperature overnight. The reaction was partitioned between EtOAc (40 mL) and brine (40 mL), and the aqueous layer was extracted with EtOAc (40 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product as a mixture of a white solid and a light brown oil. The crude product was purified by column chromatography using a gradient of 1:10:90 to 1:30:70 Et_3N/EtOAc/petroleum ether as the solvent system. Methyl (2*S*,6*R*)-4-oxo-6-phenylpiperidine-2-carboxylate **10a** was isolated as a pale yellow solid (0.011 g, 8%): m.p. 112–116 °C; R_f 0.2 (10 mL of 30:70 EtOAc/petroleum ether + 3 drops Et_3N); δ_H (400 MHz, $CDCl_3$) 2.51–2.68 (4H, m, H^{3a}, H^{3e}, H^{5a} and NH), 2.78–2.86 (1H, m, H^{5e}), 3.76–3.84 (4H, m, CH_3 and H^6), 3.94–4.00 (1H, m, H^2), 7.32–7.46 (5H, m, Ar H); δ_C (101 MHz, $CDCl_3$) 43.9 (CH_2), 50.1 (CH_2), 52.5 (CH_3), 57.9 (CH), 60.2 (CH), 126.6 (Ar CH), 128.2 (Ar CH), 128.9 (Ar CH), 141.7 (Ar quat. C), 171.4 (CO ester), 206.5 (CO ketone); $[\alpha]_D^{23}$ +53.5, *c* 0.4, $CHCl_3$ (lit. +43.9, *c* 0.9, $CHCl_3$).[12]

These characterisation data are in accordance with the literature values.[12]

1-*tert*-Butyl 2-methyl (2*S*)-4-oxopiperidine-1,2-dicarboxylate (91a)

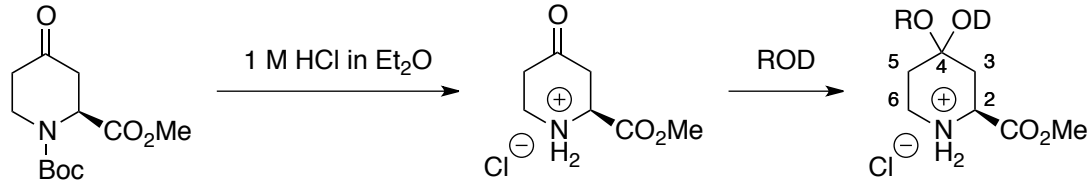


59c **91a**

Methyl (2*S*)-2-(*tert*-butoxycarbonylamino)-4-oxohex-5-enoate **59c** (0.129 g, 0.50 mmol, 1.0 eq.) was dissolved in formic acid (5 mL, 132.5 mmol, 264.5 eq.) under argon in a flame-dried flask. The reaction was stirred for 6.25 h at room temperature, before the solvent was removed by blowing air over the reaction overnight. The resulting material was dissolved in methanol (50 mL) and potassium carbonate (0.358 g, 2.59 mmol, 5.2 equiv.) was added. The reaction was stirred at room temperature for 6 h, before the solvent was removed and the remaining material was re-dissolved in 4:1 CH_2Cl_2/MeOH (25 mL). $(Boc)_2O$ (0.171 g, 0.79 mmol, 1.6 eq.) and $^{i}Pr_2NEt$ (0.17 mL, 0.98 mmol, 2.0 eq.) were added, and the reaction was stirred at room temperature for 5 d. The solvent was removed the crude reaction mixture was dissolved in 2:1 Et_2O/CH_2Cl_2 (30 mL) and was washed with 1 M HCl (30 mL). Brine was added to aid the difficult separation. The aqueous layer was re-extracted with 2:1 Et_2O/CH_2Cl_2 (30 mL), and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield the crude product as a brown liquid. The crude product was purified by column chromatography using a gradient of 0:100 to 30:70 EtOAc/petroleum ether as the solvent system. 1-*tert*-Butyl 2-methyl (2*S*)-4-oxopiperidine-1,2-dicarboxylate **91a** was isolated as a white solid (0.016 g, 12%): R_f 0.2 (30:70 EtOAc/petroleum ether); ν_{max}(ATR)/cm^{-1} 2976, 1734, 1695, 1393, 1366, 1318, 1249, 1202, 1159; δ_H (500 MHz, $CDCl_3$) 1.45 (9H, br. s, $C(CH_3)_3$), 2.41–2.60 (2H, m, H^{5a} and H^{5e}), 2.69–2.88 (2H, m, H^{3a} and H^{3e}), 3.54–3.70 (1H, m, H^{6a}), 3.73 (3H, s, CO_2CH_3), 4.00–4.10 (1H, m, H^{6e}), 4.87 and 5.15 (1H, 2 × br. s, H^2); δ_C (126 MHz, $CDCl_3$) 28.2 ($C(CH_3)_3$), 39.3 and 40.5 (C^3, C^5 or C^6), 39.7 (C^3, C^5 or C^6), 41.0 and 41.2 (C^3, C^5 or C^6), 52.6 (CO_2CH_3 or C^2), 53.9 and 54.7 (CO_2CH_3 or C^2), 81.2 ($C(CH_3)_3$), 154.3 and 154.8 (CO carbamate), 171.5 and 171.7 (CO ester), 205.8 (CO ketone); $[\alpha]_D^{24}$ −16.0, *c* 1.5, $CHCl_3$; *m/z* (ES+) found: 280.1152, $C_{12}H_{19}NO_5$ requires MNa^+ 280.1161.

5.6 Deprotection of Cyclised Product

(2*S*)-2-(Methoxycarbonyl)-4-oxopiperidin-1-ium chloride (94b)



1-*tert*-Butyl 2-methyl (2*S*)-4-oxopiperidine-1,2-dicarboxylate **91a** (0.039 g, 0.15 mmol, 1.0 eq.) was dissolved in 1 M hydrogen chloride in diethyl ether (1.5 mL, 1.5 mmol, 10.0 eq.) and stirred at room temperature for 17 d. The solvent was removed under reduced pressure to yield (2*S*)-2-(methoxycarbonyl)-4-oxopiperidin-1-ium chloride **94b** as a colourless solid (0.031 g, quantitative). Upon dissolution in MeOH-d_4 the product was converted into its hemi-acetal **94b·CD₃OD**, which was isolated as a colourless oil after removal of the solvent. After repeated removal of the solvent and re-dissolution of the compound in D_2O it was converted into its hydrate **94b·D₂O**, which was isolated as a brown oil after removal of the solvent.

(2*S*)-4-($^2H_3$)Methoxy-2-(methoxycarbonyl)-4-[(^{2}H)oxy]piperidin-1-ium chloride **94b·CD₃OD**: δ_H (400 MHz, CD_3OD) 1.71–2.00 (2H, m, H^{5a} and H^{5e}), 2.02–2.29 (1H, m, H^{3a}), 2.37–2.61 (1H, m, H^{3e}), 3.04–3.18 (1H, m, H^{6a}), 3.39–3.53 (1H, m, H^{6e}), 3.88 (3H, s, CH_3), 4.16 (1H, d, *J* = 10.0, H_2); δ_C (101 MHz, CD_3OD) 28.6 (C^5), 32.4 (C^3), 40.8 (C^6), 52.6 (C^2 or CH_3), 54.5 (C^2 or CH_3), 96.2 (C^4), 168.3 (CO ester); *m/z* (ES+) found: 193.1265, $C_8H_{13}D_3NO_4Cl$ (**94b·CD₃OH**) requires $(M-Cl)^+$ 193.1268.

(2*S*)-2-(Methoxycarbonyl)-4,4-bis[(^{2}H)oxy]piperidin-1-ium chloride **94b·D₂O**: ν_{max}(ATR)/cm^{-1} 3320, 2958, 2737, 2484, 1737, 1627, 1437, 1360, 1275, 1219, 1155, 1097; δ_H (500 MHz, D_2O) 1.82–1.90 (1H, m, H^{5a}), 1.90–1.99 (1H, m, H^{5e}), 2.02 (1H, dd, *J* = 11.0, 14.3, H^{3a}), 2.31 (1H, ddd, *J* = 2.3, 3.9, 14.3, H^{3e}), 3.13–3.21 (1H, m, H^{6a}), 3.43 (1H, dt, *J* = 13.1, 4.6, H^{6e}), 3.75 (3H, s, CH_3), 4.20 (1H, dd, *J* = 3.9, 11.0, H^2); δ_C (101 MHz, D_2O) 33.5 (C^5), 36.8 (C^3), 40.9 (C^6), 53.7 (C^2 or CH_3), 54.6 (C^2 or CH_3), 90.4 (C^4), 169.3 (CO ester); $[\alpha]_D^{24}$ +5.9, *c* 0.5, H_2O; *m/z* (ES+) found: 176.0917, $C_7H_{14}NO_4Cl$ (**94b·H₂O**) requires $(M-Cl)^+$ 176.0923.

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