A Unified Approach to (–)-FR901483 and (+)-TAN1251B

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Thesis submitted to the University of Nottingham for the degree of Doctor of Philosophy

August 2010

Abstract

This thesis describes studies, which have been realised towards the total syntheses of two natural products (–)-FR901483 (**1**) and (+)-TAN1251B (**3**), which are thought to be biosynthetically related.

The introduction summarises the isolation and biological activities of both natural products. It then focuses on previous methods used to overcome the key challenges in their syntheses: formation of their related tricyclic cores and the quaternary stereocentre next to nitrogen. Our initial retrosynthetic analysis is presented, which proposes the formation of both targets from a common intermediate. 1,5-CH insertion of an alkylidene carbene would allow formation of this common intermediate, containing the challenging quaternary stereocentre adjacent to nitrogen, in a stereoselective fashion. A brief review of work employing this methodology, which has been described within the Hayes group towards these natural products follows.

The results and discussion begins with the synthesis of the common intermediate. From here, work towards the formation of the tricyclic core of (–)-FR901483 (**1**) is presented. The initially proposed route of closing the final ring of the tricyclic core *via* a regioselective intramolecular aldol cyclisation was found to be unsuccessful. A revised route involving an intramolecular peptide coupling as the key ring closing step gives our first tricyclic derivative of (–)-FR901483 (**1**). Formation of a related tricycle is subsequently achieved *via* a palladium-catalysed alkenylation reaction. The unsuccessful attempts at elaboration of this structure are then discussed. Finally, the progress made in a revised route towards the formation of a key intermediate in Fukuyama's synthesis of (–)-FR901483 (**1**) is depicted. The progress made towards the target, and possible work for the future is then reviewed.

In the final part of the results and discussion, efforts made towards the synthesis of (+)-TAN1251B (**3**) are presented. The successful installation of the key hydroxyl group alpha to the ketone in a stereoselective manner *via* treatment of a silyl enol ether derived from the common intermediate with DMDO is reported. From here, formation of the tricyclic core is achieved using an intramolecular peptide coupling. Further elaboration allows installation of the side-chain and results in the carbon skeleton required for the total synthesis of (+)-TAN1251B (**3**). A summary of this work and the future steps required to complete the synthesis are then presented.

The thesis concludes with an experimental section, which gives detailed procedures and full characterisation data for the novel compounds discussed in the results and discussion part.

Acknowledgements

I would like to thank my supervisor, Dr Chris Hayes for giving me the opportunity to work on this interesting project, and for his help and guidance during the past three years.

I am grateful to all the Hayes group members, past and present that I have had the opportunity to work with: Ben, Hetti, Will, Hélo, Abdul, Susie, Yves, Dave, Rima, Maliha, Lilia, Duncan, Laura, Jamie, Naomi, Laura and Hannah. A special thanks to Will and Hélo for all their help and support when I first started in Nottingham and to Laura for being a good project student. I want to thank Dr William Esmieu, Rima Al Harthy and Dr Hannah Bartrum for thoroughly proofreading this manuscript. I would also like to say thank you to all the other chemists in the department, especially to the Lygo and Moody groups for all their help during my PhD.

In addition I would like to thank all the analytical and technical staff for their help: Dane Toplis for fixing everything, Eric, Chris and Jim from stores, William and Sandy for the crystal structures, Graham and Mick for mass spec and Kev for all the help with NMRs and for being a good friend too. Thanks also to Sue for running the tea room and to Meryl Richardson.

I would like to thank the University of Nottingham for funding my PhD.

I am really grateful to my parents for their support during all these years and finally to my girlfriend, Hannah, for all the love she shows me every day.

Contents

Abbreviations

Å	Ångström(s)
Ac	acetyl
AIBN	azobisisobutyronitrile
aq.	aqueous
Ar	aryl
AMP	5’-adenylic acid (adenosine-5'-monophosphate)
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	tert-butyloxycarbonyl
Bu	butyl
cat.	catalytic
Cbz	benzyloxycarbonyl
CD	circular dichroism
18-crown-6	1,4,7,10,13,16-hexaoxacyclooctadecane
CSA	camphor sulfonic acid
d	day(s)
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane

DMF	dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
DPPA	diphenylphosphoryl azide
dppf	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
ED	effective dose
ee	enantiomeric excess
ESI	electrospray ionisation
Et	ethyl
g	gram
h	hour(s)
HMPA	hexamethylphosphoramide
HPLC	high-performance liquid chromatography
Hz	Hertz
^{i}Pr	*iso*-propyl
I.R.	infrared
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
lit.	literature
M	molar
m	*meta*
m-CPBA	*meta*-chloroperbenzoic acid

Me	methyl
min	minute(s)
mL	millilitre(s)
mol	moles
Ms	methanesulfonyl (mesyl)
MS	molecular sieves
MW	microwave
^{n}Bu	*normal* butyl
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
NaHMDS	sodium bis(trimethylsilyl)amide
Ns	4-nitrobenzenesulfonyl
o-	*ortho*-
p-	*para*-
PCC	pyridinium chlorochromate
PG	protecting group
Ph	phenyl
PMB	*p*-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *p*-toluene sulfonate
psi	pounds per square inch
PTSA	*p*-toluene sulfonic acid
quant.	quantitative
rac	racemic
SM	starting material

rt	room temperature
TBAB	tetrabutylammonium bromide
TBAI	tetrabutylammonium iodide
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
^{t}Bu	*tert*-butyl
TES	triethylsilyl
Tf	trifluoromethanesulfonate (triflate)
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TMS	trimethylsilyl
Tris	triisopropylbenzenesulfonyl
Troc	2,2,2-trichloroethoxycarbonyl
Ts	*p*-toluenesulfonyl (tosyl)
UV	ultra-violet

Chapter 1: Introduction

1.0 Introduction

This thesis describes studies towards the total syntheses of two biosynthetically related alkaloid natural products: (–)-FR901483 and (+)-TAN1251B. We developed a common approach for the construction of both molecules.

1.1 Isolation and biological activity

(–)-FR901483 (**1)** (figure 1) was isolated from the fermentation broth of the fungal strain *Cladobotryum* sp. No. 11231, in 1996 by scientists at the Fujisawa Pharmaceutical Company from litter collected at Iwaki, Japan.[1]

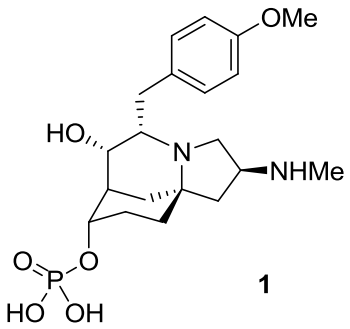

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Figure 1. Structure of (–)-FR901483 (**1**)

At its core, the molecule contains an azatricyclic ring system, consisting of a 2-azabicyclo[3.3.1]nonane and a spiro-fused pyrrolidine ring, which was previously unprecedented in Nature. The structure and relative stereochemistry of **1** was elucidated from a combination of chemical and spectroscopic evidence, and confirmed by X-ray crystallography.[1] The absolute stereochemistry was later established by Snider and Lin when

they reported the first total synthesis of **1**.[2]

(–)-FR901483 (**1**) exhibits potent immunosuppressive activity *in vitro* and was found to significantly prolong graft survival time in the rat skin allograft model.[1] Experimental results indicated that (–)-FR901483 (**1**) has a non-specific immunosuppressive profile and led to the conclusion that it might be an anti-metabolite. Its activity is thought to be a result of interference with *de novo* purine nucleotide biosynthesis *via* inhibition of key enzymes involved in the pathway. In particular, it is likely that the enzyme which catalyses the formation of adenylosuccinate (adenylosuccinate synthetase) and/or the enzyme which catalyses the formation of AMP (adenylosuccinase) are inhibited. The mode of action of (–)-FR901483 (**1**) differs from that of known immunosuppressants including Cyclosporine A and Tacrolimus (FK-506) and this could be therapeutically significant given the toxic drug-associated side-effects of both drugs.[1]

The TAN1251 alkaloids were isolated in 1994 from a culture of *Penicillium thomii* RA-89 by scientists at Takeda Chemical Industries Ltd. in Japan.[3] These compounds possess a novel tricyclic ring system, consisting of a 1,4-diazabicyclo[3.2.1]octane ring and a spiro-fused cyclohexanone ring. The relative stereochemistry of (+)-TAN1251B (**3**, Figure 2) was determined by X-ray crystallography, and CD analysis of a derivative of **3** allowed determination of its absolute stereochemistry.[4] Since (–)-TAN1251A (**2**) is converted into **3** by *Penicillium thomii* RA-89, the absolute stereochemistry of both compounds was assumed to be the same.[4] The absolute and relative stereochemistry of (+)-TAN1251D (**5**) and the relative stereochemistry of (+)-TAN1251C (**4**) were established later by Snider and Lin after completion of their total syntheses.[4]

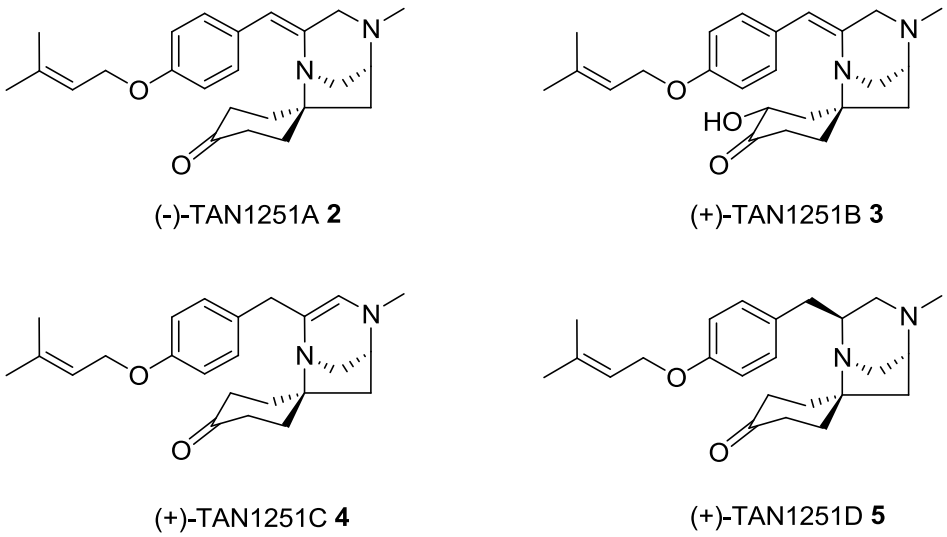


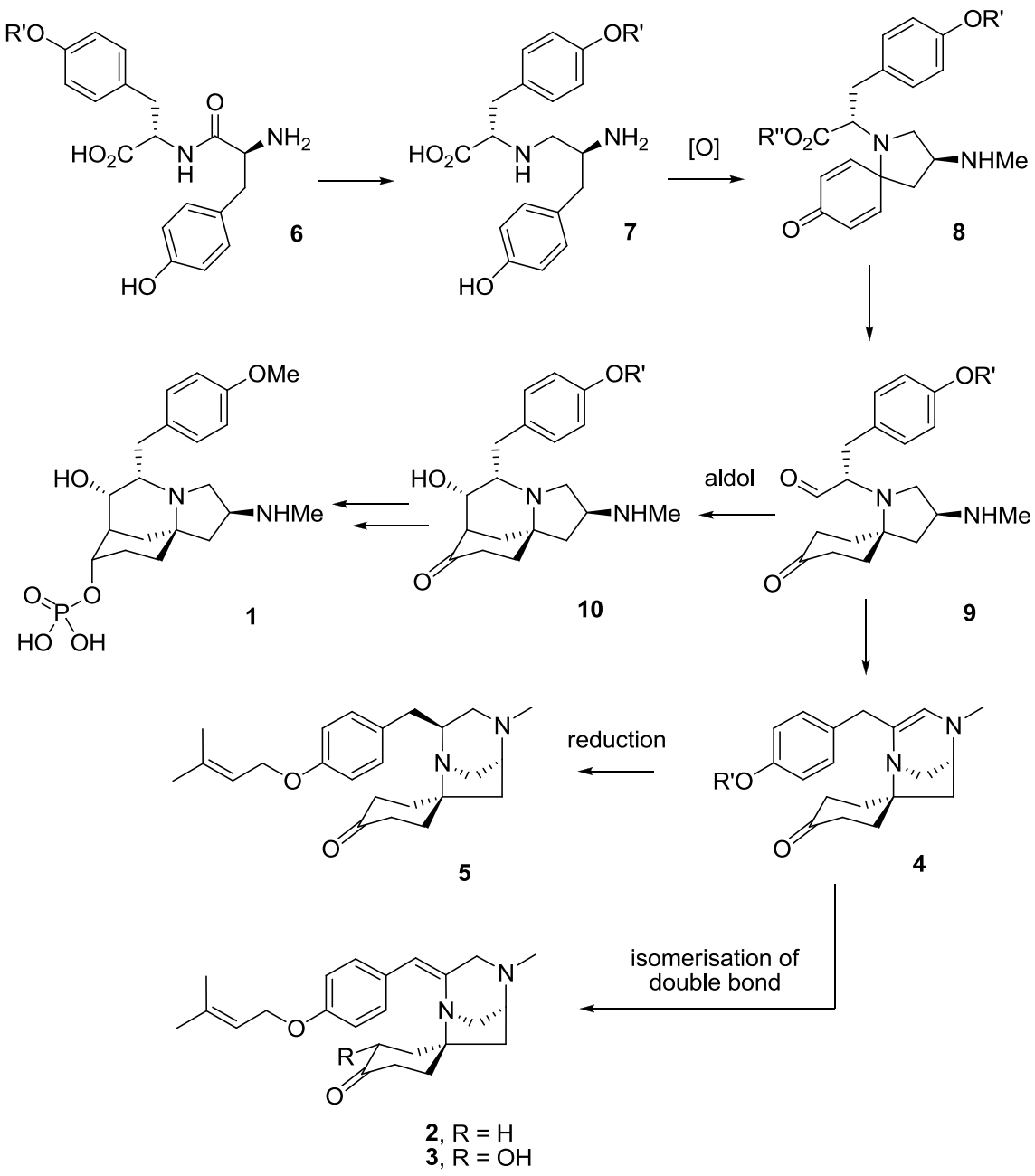
Figure 2. Structures of TAN1251 alkaloids

To date, only **2** and **3** have shown interesting biological activity and are of value as mydriatic or antispasmodic/antiulcer agents. They are both muscarinic antagonists, which exhibit cholinergic activity and cause acetylcholine-induced contraction of Guinea pig ileum with ED_{50} values of 8.0 nM and 10 nM respectively. The affinity of TAN1251B (**3**) for the muscarinic acetylcholine receptor is stronger than that of atropine.[5]

1.2 Proposed biosynthesis

It is known that the natural product (–)-FR901483 (**1**) and the TAN1251 family (**2**-**5**) are biosynthetically related and are derived from the same dipeptide **6** consisting of two molecules of *L*-tyrosine (scheme 1).[1] Under oxidative conditions **6** would form the spirolactam **8**, which can subsequently be converted into the key keto-aldehyde intermediate **9** by simple chemical transformations. From here, an intramolecular aldol reaction of **9** would afford the tricyclic skeleton of (–)-FR901483 (**1**), or alternatively intramolecular enamine

formation from **9** would provide an advanced intermediate in the synthesis of the TAN1251 alkaloids.



Scheme 1. Proposed biosynthesis of (–)-FR901483 (**1**) and TAN1251 (**2**-**5**) family

1.3 Previous syntheses

This part of the introduction will focus first on previous total syntheses of (–)-FR901483 (**1**) and studies conducted towards the formation of the tricyclic core. The focus will then turn towards the different syntheses of the members of the TAN1251 alkaloids family. The introduction concludes with what has been achieved previously in this area within the Hayes group.

1.3.1 Previous syntheses of (–)-FR901483 (1)

There have been six enantioselective total syntheses of (–)-FR901483 (**1**) reported so far, as well as two racemic syntheses, and a number of model studies towards the tricyclic core of **1**. Each of these will be briefly described in the order stated, highlighting only the key steps in the synthesis or study: the selective formation of the quaternary stereocentre and the formation of the tricyclic core of the molecule.

1.3.1.1 Snider's synthesis[6,2]

Snider and Lin reported the most comprehensive work towards the total syntheses of (–)-FR901483 (**1**) and all the TAN1251 alkaloids (**2-5**). Initially, in 1998, they reported the synthesis of racemic desmethylamino FR901483 (**11**, Figure 3).[6]

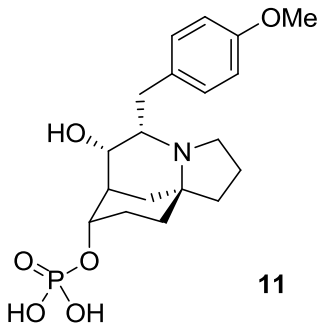
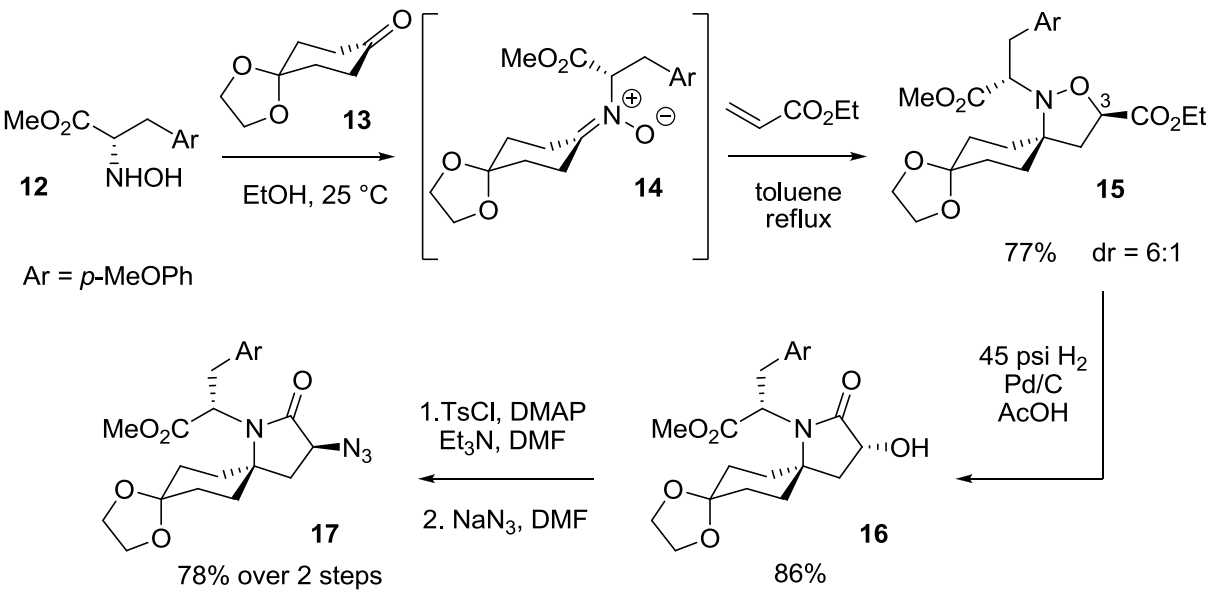


Figure 3. Desmethylamino FR901483

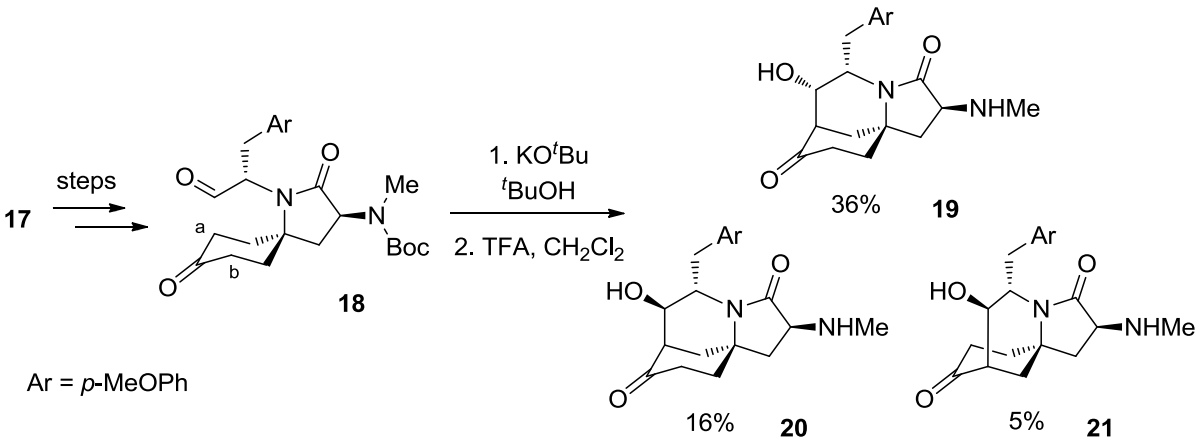
One year later they published the first total synthesis of enantiopure (–)-FR901483 (**1**),[2] using the method developed in their first publication.[6] To create the quaternary centre adjacent to nitrogen, they utilised a 1,3-dipolar cycloaddition of nitrone **14** with ethyl acrylate (scheme 2). The nitrone was obtained by reaction between optically active hydroxylamine **12** and cyclohexanone **13**.



Scheme 2. Snider's 1,3-dipolar cycloadition

The 1,3-dipolar cycloaddition afforded the desired product **15** (major) and its diastereoisomer

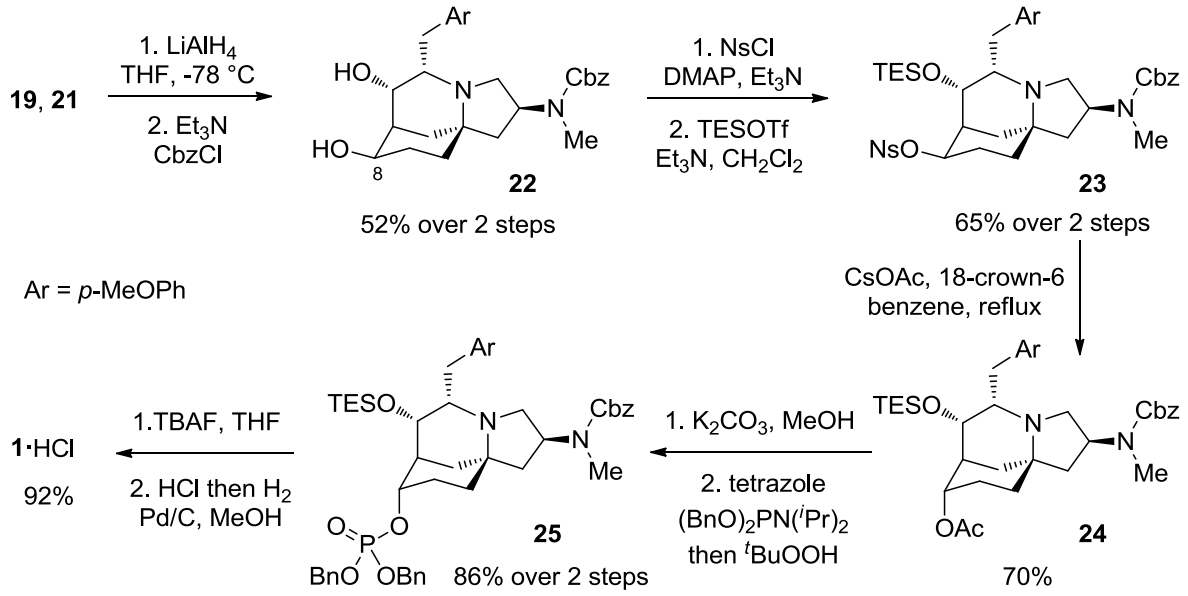
(minor), which was epimeric at the C(3) position. The diastereoisomers proved inseparable at this stage and therefore subsequent steps were conducted on the 6:1 mixture. Hydrogenolysis of **15** in acidic media afforded the desired spiro-fused pyrrolidine ring **16** in good yield (scheme 2). Inversion of the stereochemistry at C(3) was achieved *via* tosylation of alcohol **16** and subsequent displacement with sodium azide to give **17**, at which point the two diastereoisomers could be separated. Further simple chemical transformations allowed access to the key aldehyde **18** (scheme 3). Although this approach allowed rapid access to the aldol precursor **18**, there were problems when attempting to close the last ring of the tricycle. As there is little to discriminate the diastereotopic methylenes (a and b) adjacent to the ketone, poor regio- and stereocontrol were observed during the intramolecular aldol reaction. As a result, a mixture of three products was obtained. The major product, formed in modest yield was the required tricycle **19**, which proved inseparable from its diastereoisomer **21**. Again, the material was taken through the synthesis as a mixture until separation was possible.



Scheme 3. Snider's tricycle formation *via* aldol reaction

The amide and ketone functionalities were reduced with $LiAlH_4$, and the resultant amine protected with a Cbz group to afford diol **22** (scheme 4), which, at this point could be

separated from its diastereoisomer. Inversion of the stereochemistry at C(8) was completed in three steps: nosylation of the equatorial alcohol, protection of the axial alcohol as the triethylsilyl ether and displacement of the nosylate with cesium acetate to afford **24**. The acetate group was then hydrolysed to allow introduction of a dibenzyl phosphite ester, which was subsequently oxidised to the dibenzyl phosphate ester **25**. A three step sequence allowed removal of all the protecting groups to afford the monohydrochloride salt of (–)-FR901483 (**1**) in 22 overall steps and a yield of 2%.

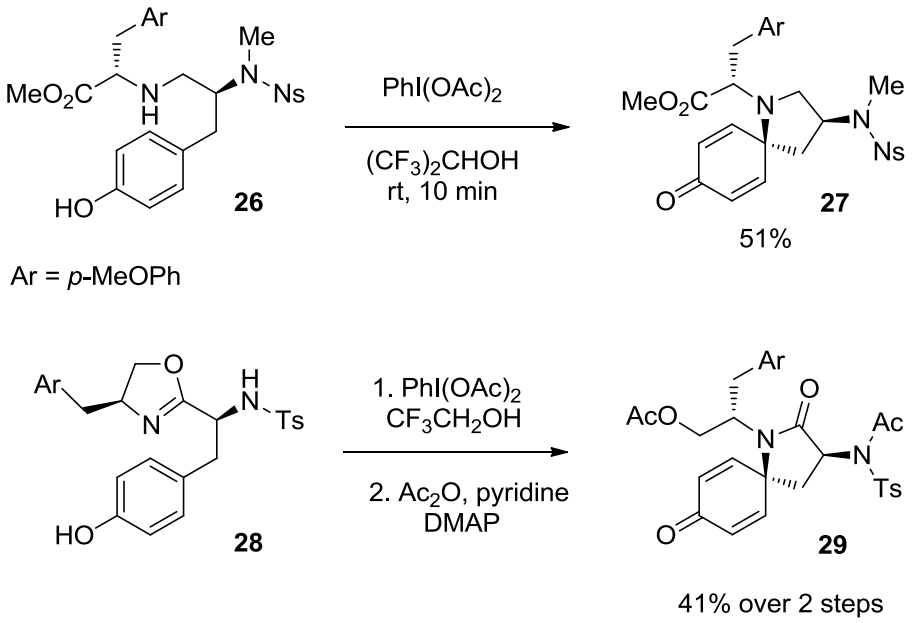


Scheme 4. Completion of Snider's synthesis of (–)-FR901483 (**1**)

1.3.1.2 Sorensen's[7] and Ciufolini's syntheses[8-10]

In 2001, two groups published very similar approaches to the total synthesis of (–)-FR901483 (**1**), which were inspired by the biosynthetic pathway depicted previously (scheme 1). Indeed, the formation of the key 5,6-spirocycle was realised using an oxidative spiroannulation.

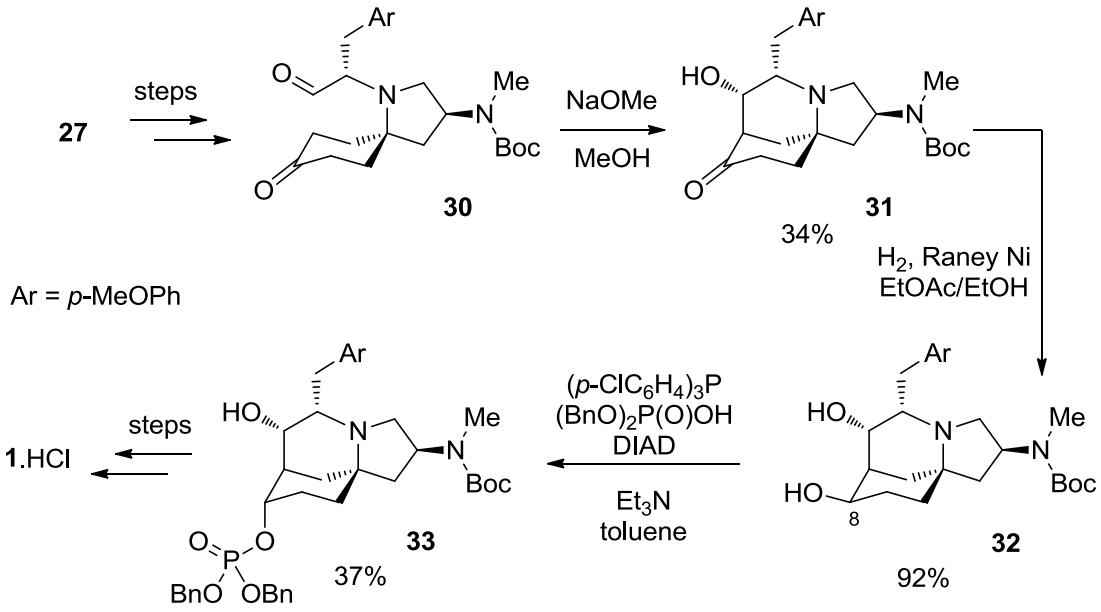
Sorensen's method was to expose the aminophenol **26** to iodobenzene diacetate in 1,1,1,3,3,3-hexafluoro-2-propanol to afford the dienone **27** in a reasonable 51% yield (based on 70% of starting material consumed).[7] Ciufolini's method used a variant of this chemistry, which involved the use of oxazoline as a nucleophile instead of the free secondary amine.[9-10] The oxazoline **28** was thus treated with the same oxidant, which was then followed by an acetylation step leading to the isolation of 41% of the dienone **29**.



Scheme 5. Sorensen's and Ciufolini's constructions of the quaternary stereocentre

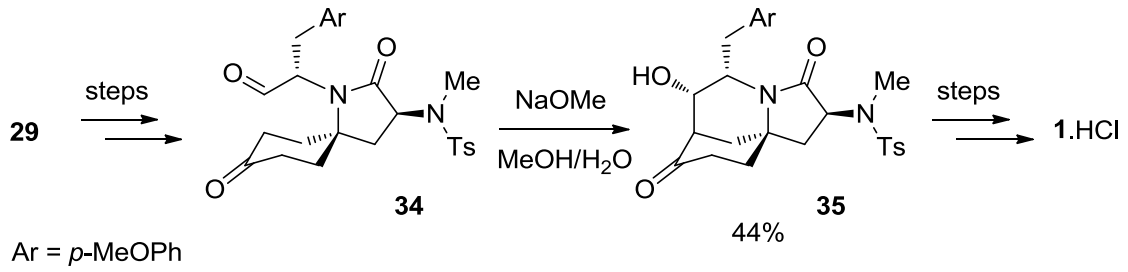
Sorensen's intermediate **27** was elaborated further to the aldol precursor **30** (analogous to Snider's intermediate **18**) by protecting group manipulations, complete reduction of the dienone and methyl ester, and subsequent re-oxidation to the keto aldehyde **30**. From this point, the tricyclic core was established using an aldol cyclisation, in an analogous manner to that previously described by Snider.[2] Thus, treatment of **30** with sodium methoxide in methanol yielded the desired tricycle **31** in 34% yield (scheme 6). However, again this reaction suffered from a lack of regiocontrol (also observed by Snider[2]) and 40% of other

isomeric aldol products were isolated in addition to the desired compound. Sorensen's synthesis of (–)-FR901483 (**1**) was continued by reduction of the ketone to give the alcohol **32**, which was then involved in a Mitsunobu reaction with dibenzyl hydrogen phosphate. This procedure shortened the synthesis compared to Snider's route as it allowed inversion of the stereochemistry at C(8) and installation of the phosphate ester in a single step, though in poor yield. Protecting group removal completed the synthesis.



Scheme 6. Sorensen's end-game

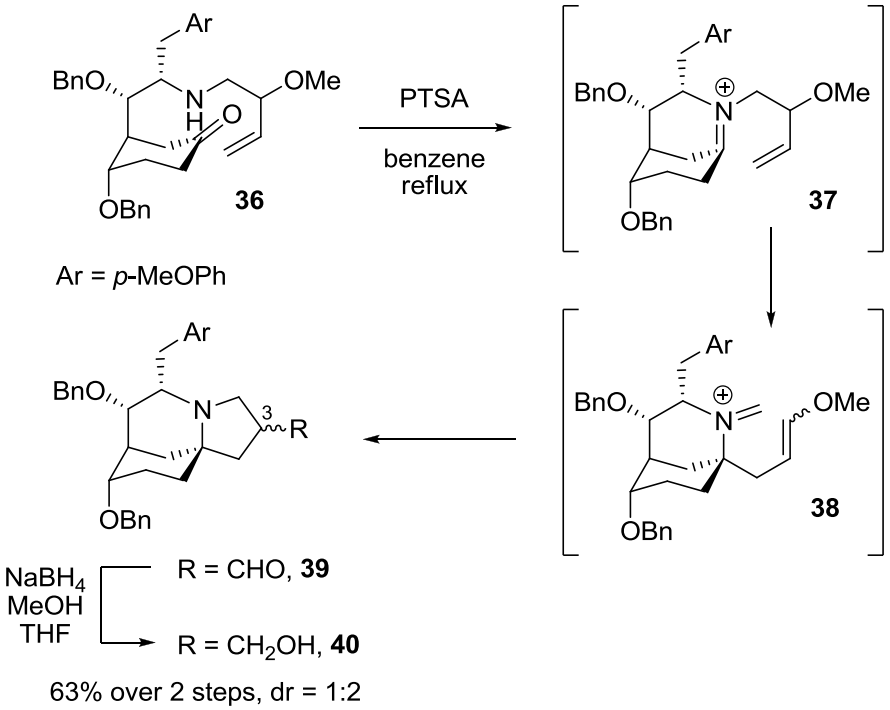
From intermediate **29**, Ciufolini completed the synthesis of (–)-FR901483 (**1**)[9-10] using a very similar approach to that employed by Sorensen.[7] Again, although the oxidative spiroannulation step proved to be an efficient way of constructing two of the three rings of the tricyclic core, the key aldol cyclisation lacked regioselectivity and afforded the desired tricycle **35** in only 44% yield (scheme 7). In addition, from the same intermediate **29**, Ciufolini also reported the synthesis of (+)-TAN1251C (**4**, section **1.3.3.3**).[10]



Scheme 7. Ciufolini's end game

1.3.1.3 Brummond's synthesis[11-12]

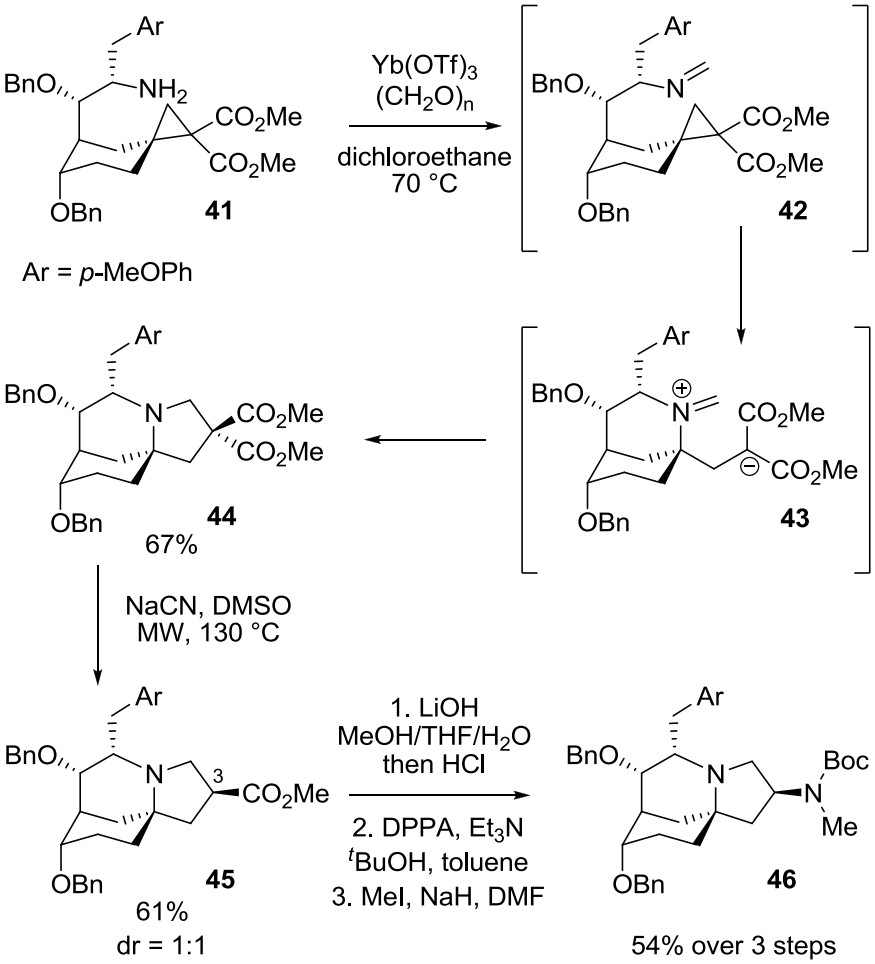
Brummond described a racemic approach to the core structure of FR901483 in 2001,[11] and then four years later a formal synthesis of enantiopure (–)-FR901483 using the same methodology.[12] The strategy was to perform a tandem cationic aza-Cope/Mannich cyclisation as the key step for construction of both the tricycle and the quaternary stereocentre next to nitrogen. Amino-ketone **36** was treated with PTSA in refluxing benzene to afford the desired unstable aldehyde **39**, which was then reduced to the alcohol and isolated (scheme 8). Unfortunately, they obtained the desired product (minor) along with its diastereoisomer epimeric at the C(3) position (major) in a 1:2 ratio. However, treatment of the crude aldehyde **39** from the cyclisation with *L*-phenylalanine enabled epimerisation at the C(3) position and resulted in isolation of the diastereoisomers in a 2:1 ratio, this time in favour of the desired product. After reduction to the alcohol **40**, the diastereoisomers were separated and the relevant isomer was converted, in a few simple transformations, into compound **33** (an advanced intermediate in Sorensen's synthesis of (–)-FR901483 (**1**)[7]).



Scheme 8. Brummond's tricycle construction

1.3.1.4 Kerr's synthesis[13]

More recently in 2009, Kerr reported a total synthesis of (–)-FR901483 (**1**) where an intramolecular imine/cyclopropane annulation was employed to provide the key pyrrolidine ring and put in place the stereocentre next to the nitrogen.[13] Addition of amine **41** to a dilute solution of paraformaldehyde in the presence of ytterbium (III) triflate afforded 67% of the desired tricycle **44** (scheme 9).

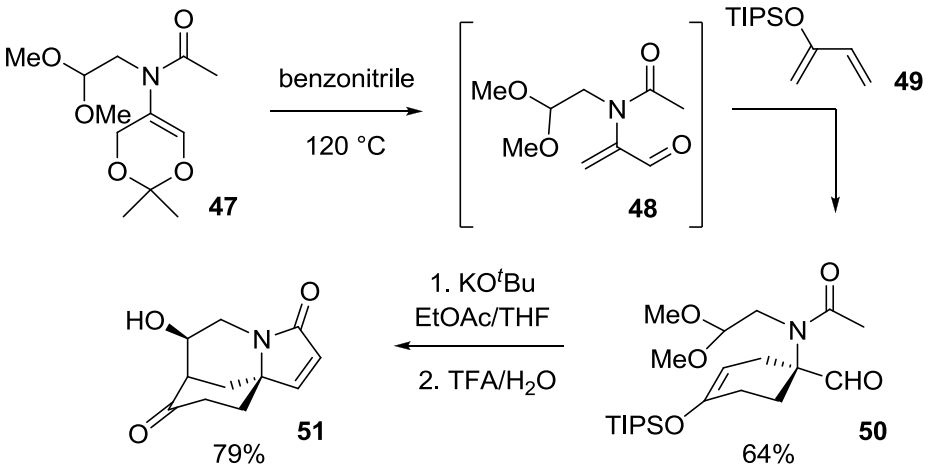


Scheme 9. Kerr's tricycle formation

This was followed by a Krapcho dealkoxycarbonylation,[14] which unfortunately afforded a 1:1 mixture of the desired product **45** and its epimer at the C(3) position. However, these isomers were separable and it was possible, to some extent, to recycle the undesired diastereoisomer by exposure to KHMDS, which resulted in epimerisation to a 1:1 mixture of diastereoisomers. Hydrolysis of the remaining ester of **45**, followed by a Curtius rearrangement[15] furnished the *N*-Boc protected amine, which was methylated to afford the compound **46** (a known intermediate in Brummond's synthesis[12]). From here, the synthesis was completed using methodology previously reported by Sorensen.[7]

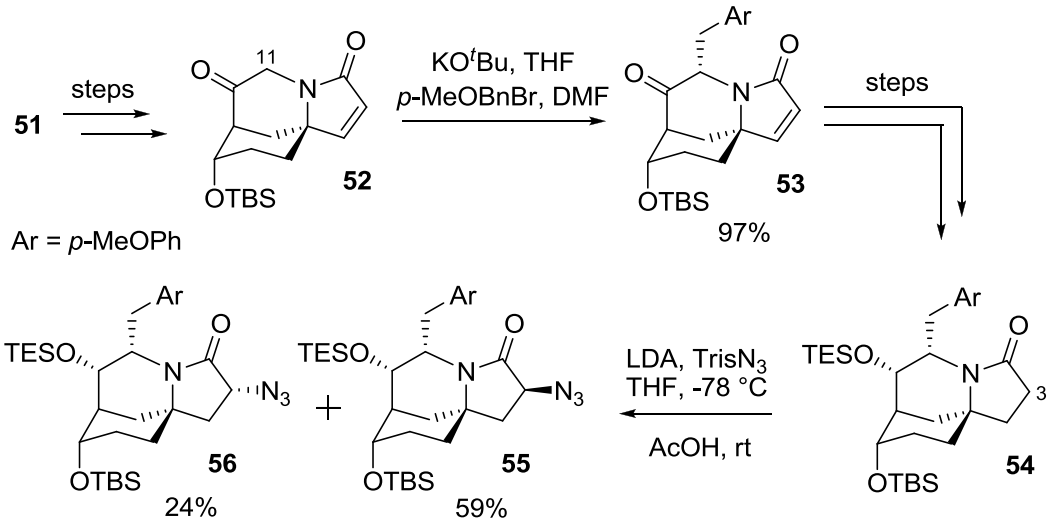
1.3.1.5 Funk's synthesis[16]

Funk used another method to construct the quaternary stereocentre in his racemic synthesis of FR901483 in 2001.[16] The 1,3-dioxin **47** was heated in benzonitrile to generate the amidoacrolein **48**, which was trapped *in situ* with the silyloxydiene **49** to afford aldehyde **50**. Two consecutive aldol reactions generated the tricycle **51**, core of FR901483 (**1**), in good yield (scheme 10).



Scheme 10. Funk's tricycle construction

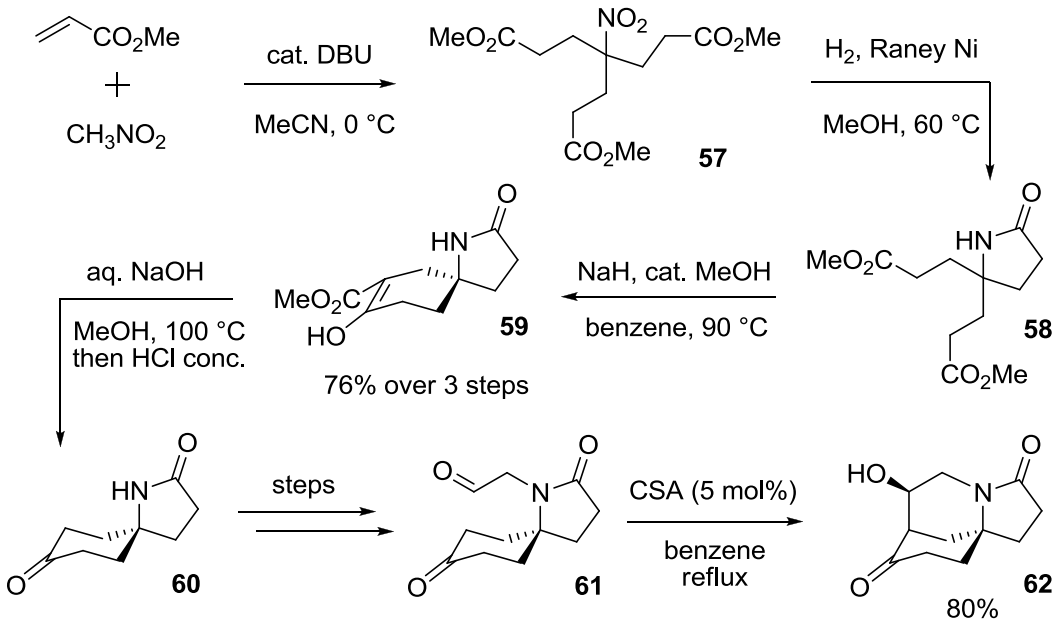
One interesting feature of this synthesis is the installation of the *p*-methoxybenzyl group (PMB) at the C(11) position, which had to be done at a late stage (scheme 11). Stereoselective *p*-methoxybenzylation of the enolate of **52** led to formation of **53**. The introduction of the amine functionality at C(3) was accomplished by azidification of the enolate derivative of lactam **54**, which led to the desired product **55** in 59% yield. In addition, a significant amount of the undesired diastereoisomer **56** was also isolated. The synthesis was completed in a few simple transformations including reduction of the azide and lactam functionalities, manipulation of protecting groups and introduction of the phosphate ester.



Scheme 11. Funk's end game

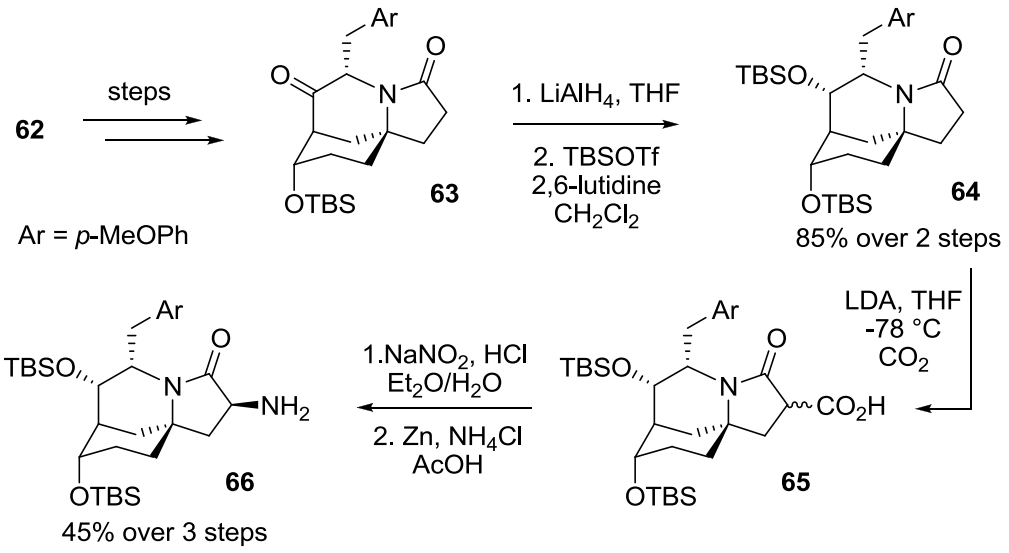
1.3.1.6 Fukuyama's syntheses[17-19]

In 2004, Fukuyama described the synthesis of racemic FR901483 (**1**)[17-18] where he rapidly constructed the spirolactam. Michael addition of nitromethane to methyl acrylate provided the triester **57**, which upon reduction of the nitro group and ester-amide exchange furnished lactam **58** (scheme 12). Dieckman condensation of **58** afforded spirolactam **59**, which after basic hydrolysis of the methyl ester and subsequent neutralisation with acid decarboxylated to provide spirolactam **60**. A four-step sequence involving protection of the ketone, allylation of the amide, cleavage of the protecting group and oxidative cleavage of the double bond afforded keto-aldehyde **61**. This was then used in an intramolecular aldol reaction comparable to the one used originally in Snider's synthesis,[2] to prepare **62**, the tricyclic core of FR901483.



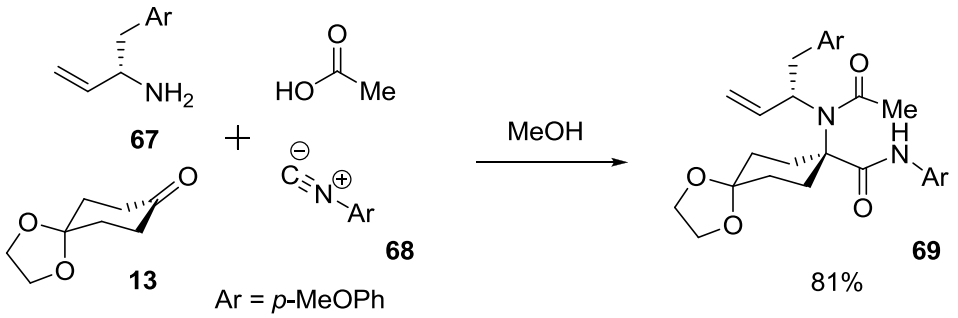
Scheme 12. Fukuyama's racemic synthesis of FR901483

From **62**, the method used by Fukuyama to install the PMB group was similar to that previously employed by Funk,[16] and in a few steps the intermediate **63** was reached. Selective reduction of the ketone and protection of the resultant alcohol gave **64** (scheme 13). Addition of solid CO_2 to the enolate of **64** afforded carboxylic acid **65**. Nitrosation followed by decarboxylation was achieved *via* treatment with sodium nitrite under acidic conditions. Amine **66** was isolated as a single isomer after reduction of the oxime with zinc in acetic acid. The racemic synthesis was completed in a few steps including methylation of the nitrogen, reduction of the lactam and introduction of the phosphate ester.



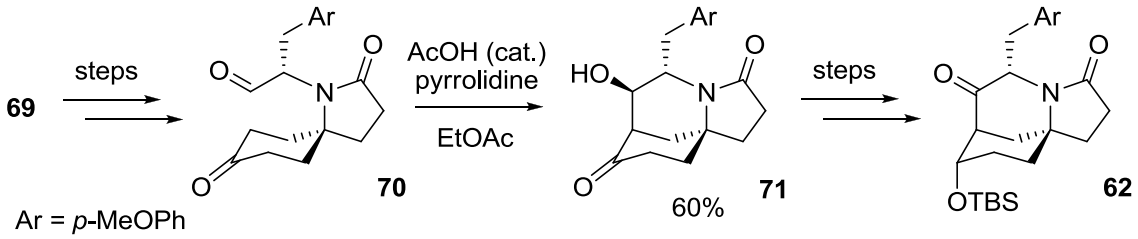
Scheme 13. Fukuyama's end game

Recently in 2010, Fukuyama published a stereocontrolled synthesis[19] of an optically active compound **63**, a key intermediate in his racemic synthesis.[17-18] This time, he utilised an Ugi reaction,[20] similar to one previously employed by Sorensen for his second-generation synthesis of the tricyclic core of FR901483 (section **1.3.2.7**).[21] Reaction between chiral amine **67** (prepared in seven steps from commercially available *N*-Boc tyrosine methyl ester), protected cyclohexanone **13**, *p*-methoxyphenyl isocyanide **68** and acetic acid afforded in one step and in good yield compound **69**, in which all of the carbon atoms needed for the synthesis of the tricycle were assembled (scheme 14).



Scheme 14. Fukuyama's Ugi reaction

Conversion of **69** into the key aldol precursor **70** was achieved in a few steps including an intramolecular Dieckmann condensation in which the spiro-lactam ring was constructed. An intramolecular aldol reaction of **70**, analogous to the approach previously reported by Snider (section **1.3.1.1**),[2] was used to close the tricyclic core of (–)-FR901483. Thus, treatment of **70** with acetic acid, and a catalytic amount of pyrrolidine afforded the tricycle **71** as a single diastereoisomer (scheme 15). The rest of the synthesis consisted of simple chemical transformations to obtain **62**, an intermediate in the racemic synthesis.



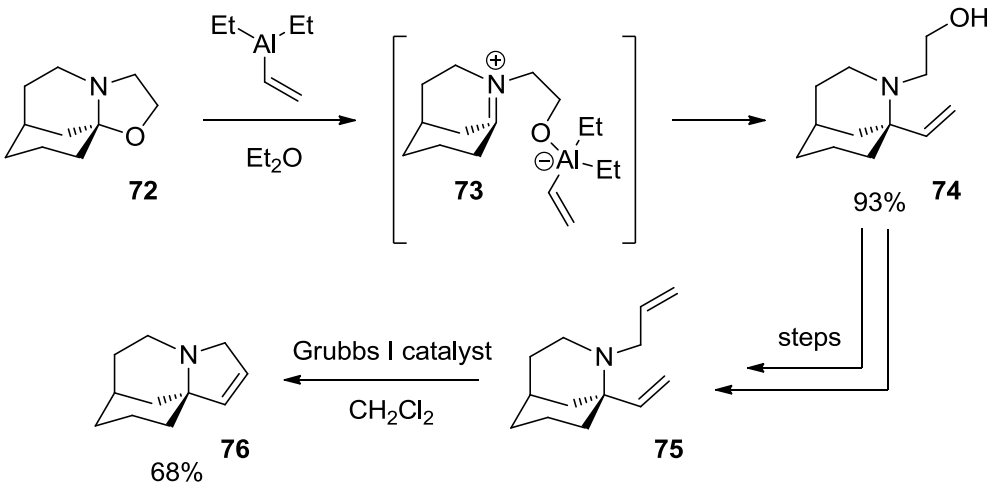
Scheme 15. Fukuyama's 2nd generation tricyclic closure

1.3.2 Model studies towards (–)-FR901483 (1)

In addition to the total syntheses described previously, (–)-FR901483 (**1**) has been the subject of numerous model studies. It has attracted substantial synthetic interest, in particular because the formation of the quaternary stereocentre next to the nitrogen, and the formation of the tricyclic core represent two significant challenges. As discussed previously, this part of the introduction will focus on how these challenges were met.

1.3.2.1 Kibayashi's approach[22-23]

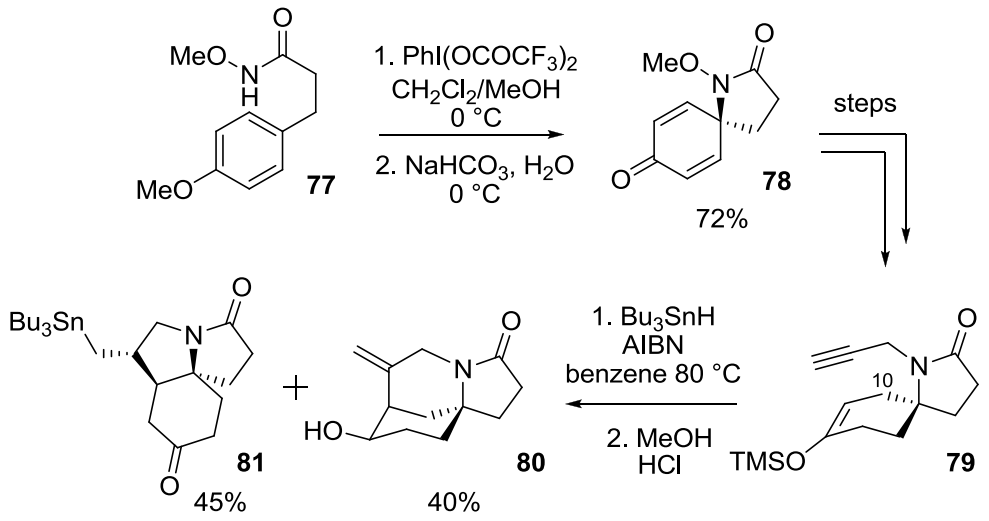
An interesting method for the formation of the quaternary centre adjacent to nitrogen in the synthesis of the tricyclic structure of (–)-FR901483 was used by Kibayashi.[22-23] This approach was based on vinylation at the bridgehead position of 2-azabicyclo[3.3.1]nonane *via* an anti-Bredt iminium ion. Thus, the racemic tricyclic oxazilidine **72** was treated with $Et_2AlCH{=}CH_2$ to form the bridgehead iminum ion **73**, which susbsequently underwent nucleophilic attack by the vinyl group to give the desired bicycle **74** in excellent yield. The last ring of the tricycle was closed a few steps later by metathesis to give the tricycle core **76** (scheme 16).



Scheme 16. Kibayashi's approach

1.3.2.2 Wardrop's approach[24]

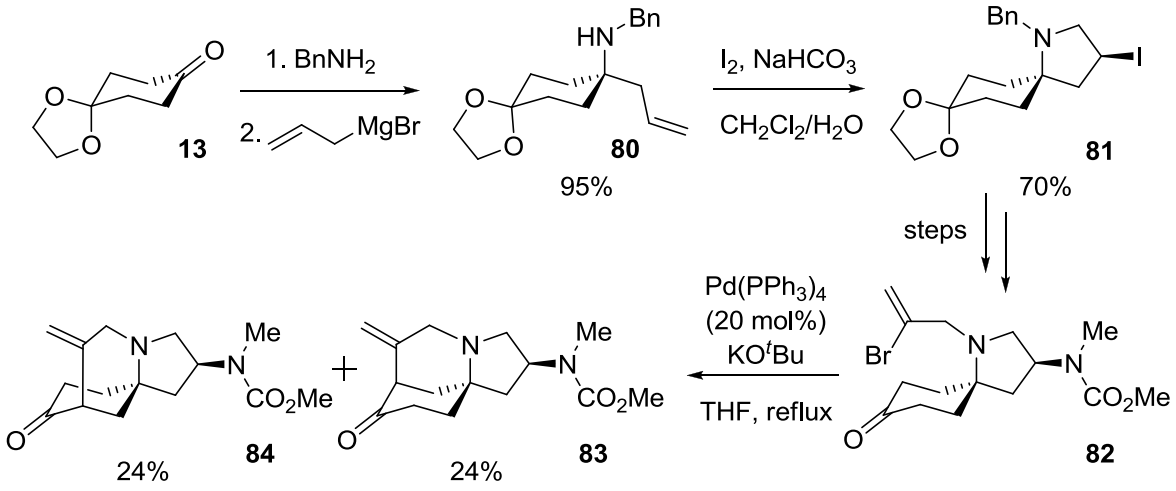
In 2001 Wardrop reported a formal synthesis of racemic desmethylamino FR901483 **11**,[24] which employed the cyclisation of an *N*-alkoxy-*N*-acylnitrenium ion to form the key 5,6-spirocycle intermediate. Thus, oxidative spiroannulation of phenol derivative **77** was achieved using bis(trifluoroacetoxy)iodobenzene to afford the 5,6-spirocycle **78** in good yield. A series of simple chemical transformations converted the spirocycle into the trimethylsilyl enol ether **79**, precursor for a radical cyclisation. Treatment of **79** with Bu_3SnH and AIBN, followed by protodestannylation with methanolic HCl gave the desired cyclisation product **80** in 40% yield (scheme 17). Unfortunately, the major compound isolated from the reaction was the undesired tricycle **81**. This presumably forms as a result of a 1,5-transfer of the allylic hydrogen atom at C(10) to form an allylic radical, which subsequently undergoes diastereoselective cyclisation with the pendant vinyl stannane.



Scheme 17. Wardrop's approach

1.3.2.3 Bonjoch's approach[24-28]

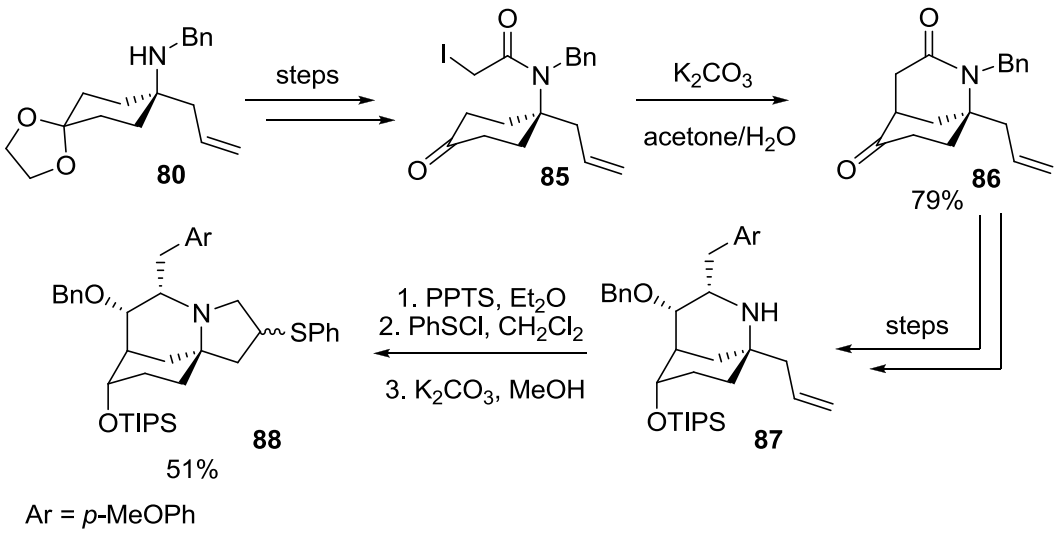
Bonjoch used a different method to complete a synthesis of the tricyclic core of FR901483,[28] in which formation of the quaternary centre adjacent to the nitrogen was achieved using an intermediate imine species. Cyclohexanone **13** was easily converted into the corresponding imine, which was then treated with allylmagnesium bromide to give homoallylic amine **80** in excellent yield (scheme 18). Treatment of **80** with iodine under basic conditions resulted in formation of the iodoaminocyclisation product **81**. Closing the ring to yield the tricyclic structure was achieved *via* an intramolecular Pd-catalysed coupling of vinyl bromide with the enolate made *in situ* from ketone **82**. Unfortunately, this step proceeded without regiocontrol, and they obtained the desired tricycle **83** in poor yield along with its regioisomer **84** in a 1:1 ratio.



Scheme 18. Bonjoch's approach

1.3.2.4 Weinreb's approach[29]

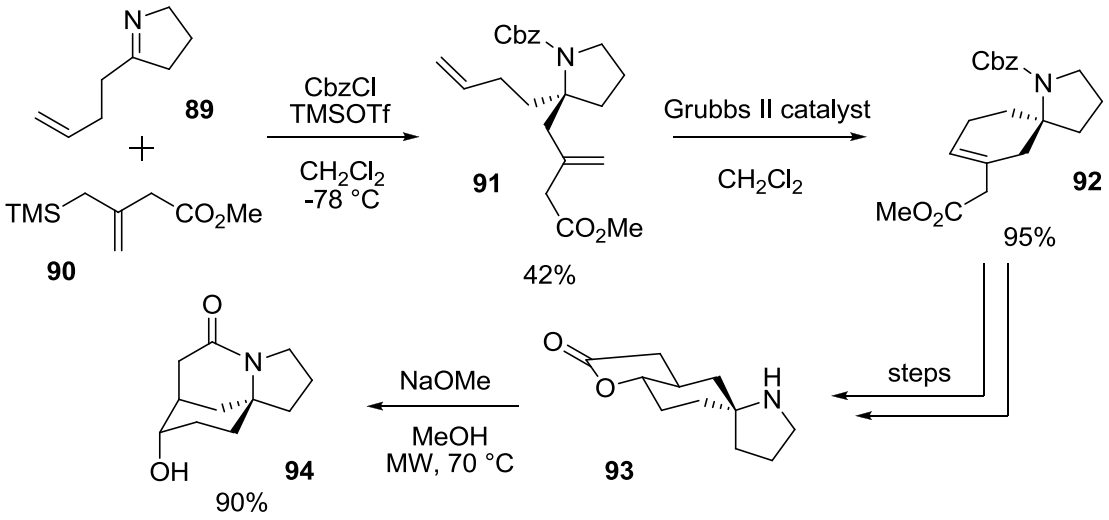
Weinreb employed the imine chemistry previously used by Bonjoch[25] to form the quaternary centre next to nitrogen (and the same intermediate **80**).[29] However, from this key intermediate a different approach for the synthesis of the tricyclic core was employed. Homoallylic amine **80** was converted into iodo-ketone **85**, which cyclised under basic conditions to afford the desired bicyclo[3.3.1]nonanone **86** in good yield (scheme 19). The tricyclic structure **88** of FR901483 (**1**) was obtained in reasonable yield by a *5-endo-trig* cyclisation of homoallylic amine **87**, which occurred upon treatment with phenylsulfenyl chloride in the presence of a mild acid, pyridinium *p*-toluenesulfonate (PPTS).



Scheme 19. Weinreb's approach

1.3.2.5 Martin's approach[30]

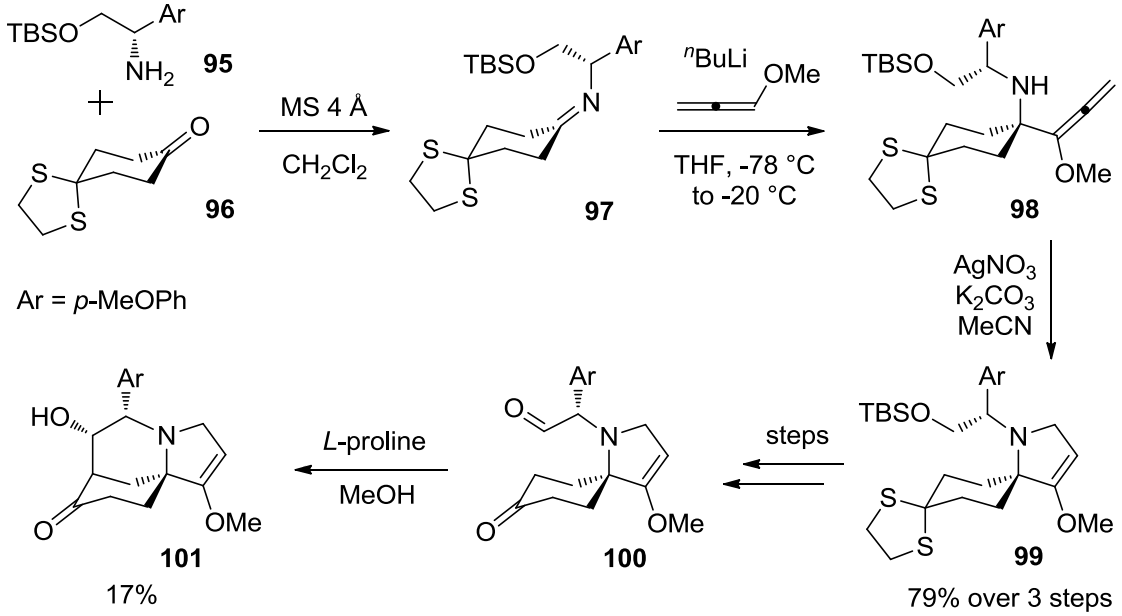
In this approach to the tricyclic core of (–)-FR901483 (**1**), Martin used the nucleophilic addition of a silane to an iminium ion for the formation of the quaternary centre next to nitrogen.[30] The iminium ion was generated *in situ* from the addition of CbzCl to the imine **89** and after addition of the allyl silane **90** in the presence of trimethylsilyl triflate, the desired product **91** was isolated in moderate yield (scheme 20). Subsequent ring closing metathesis of diene **91**, using Grubbs' second generation catalyst,[31] afforded the 5,6-spirocycle **92** in excellent yield. This was quickly converted into the lactone **93**, which underwent lactone-lactam rearrangement under microwave irradiation in a methanolic NaOMe solution to give tricycle **94**.



Scheme 20. Martin's approach

1.3.2.6 Reissig's approach[32]

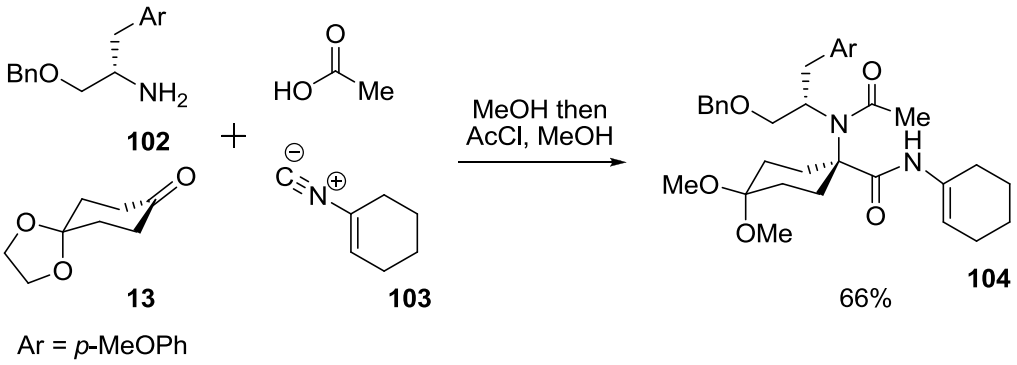
Reissig employed an approach to the tricyclic core of (–)-FR901483 (**1**),[32] which used the reaction of lithiated methoxyallene with a protected enantiopure ketimine as the key step. Firstly condensation of the *L*-tyrosine derivative **95** with the cyclohexanone derivative **96** afforded imine **97**, which upon addition of lithiated methoxyallene was converted to the allenylamine **98** (scheme 21). Subsequent treatment with $AgNO_3$ and K_2CO_3 afforded the key 5,6-spirocycle **99** in good yield over the three steps. The third ring of the tricycle was closed *via* an intramolecular aldol cyclisation, in an analogous manner to that previously described by Snider.[2] However, even after extensive optimisation, they were only able to isolate the desired tricycle **101** in 17% yield using *L*-proline in methanol. Under these conditions they also isolated three other tricyclic structures (diastereo- and regioisomers of the desired product) in a combined yield of 42%.



Scheme 21. Reissig's approach

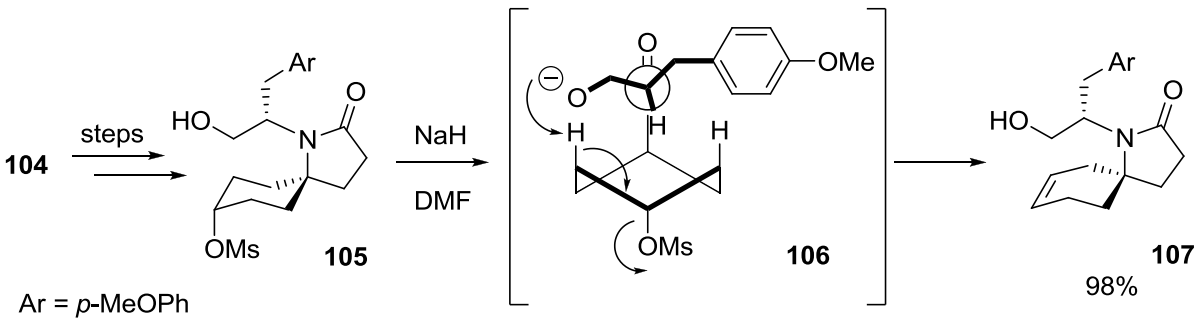
1.3.2.7 Sorensen's second-generation approach[21]

After his total synthesis (section **1.3.1.2**),[7] Sorensen recently published a synthesis of the tricyclic core structure of (–)-FR901483 using an Ugi four-component coupling reaction.[20-21] Thus, mixing chiral amine **102**, protected cyclohexanone **13**, cyclohexenyl isocyanide **103** and acetic acid afforded, in one step and in good yield, compound **104**. This reaction allowed the formation of the key carbon-nitrogen bond in addition to putting in place all of the carbon atoms needed for formation of the tricyclic core (scheme 22).



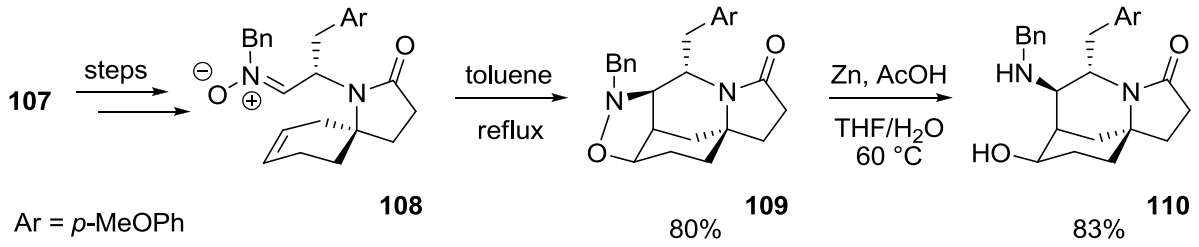
Scheme 22. Sorensen's Ugi four component coupling reaction

The pyrrolidine ring was closed using an intramolecular Dieckmann cyclisation, and after simple transformations the key intermediate **105** was reached. From here, an internal base-mediated elimination of the mesylate provided the desired alkene **107** in excellent yield and with excellent regioselectivity (scheme 23). The regioselectivity was rationalised by the hypothesis that the bulky nitrogen side-chain would restrict rotation of the C-N bond and favour a conformation in which the hydroxide (the internal base) would be close to only one of the axial C-H bonds with an antiperiplanar relationship to the mesylate.



Scheme 23. Regioselective elimination of mesylate

A high-yielding two step sequence, which involved an intramolecular nitrone/alkene dipolar cycloaddition of **108** to isoxazolidine **109** followed by reduction of the N-O bond with zinc, completed the synthesis of the tricyclic core of (–)-FR901483 (**1**) (scheme 24).



Scheme 24. Sorensen's formation of the tricyclic core

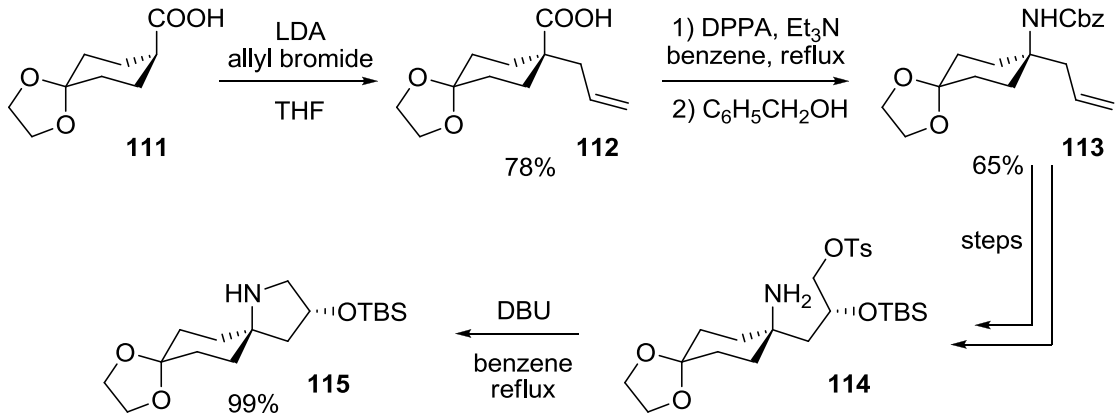
1.3.3 Synthetic approaches to the TAN1251 family of alkaloids

In this next part of the introduction, the focus will turn to the previous methods employed for the synthesis of different members of the TAN1251 family. To date, there has been only one reported synthesis of (+)-TAN1251B (**3**), which was achieved from transformations of (–)-TAN1251A (**2**). In contrast (–)-TAN1251A (**2**) has been synthesised the most (five times

including one racemic synthesis) and (+)-TAN1251C (**4**) and (+)-TAN1251D (**5**) have each been made twice. The syntheses will be described briefly, highlighting only the key steps, and in particular formation of the quaternary centre next to nitrogen and the formation of the tricyclic core of the molecule.

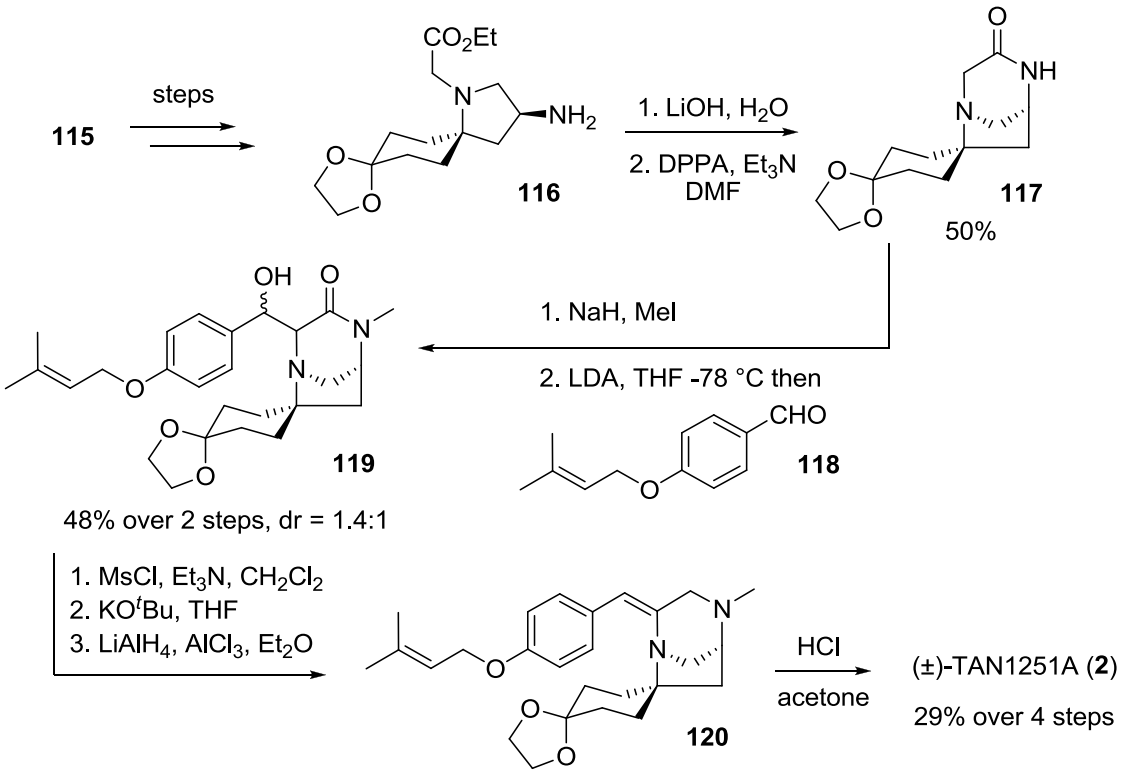
1.3.3.1 Kawahara's approach[4,33-34]

In 1998, Kawahara reported the first racemic synthesis of TAN1251A (**2**).[4,33] The strategy involved formation of the key spirocycle **115**, which was further elaborated to enable the final ring of the tricyclic core to be closed *via* an intramolecular peptide coupling. The key spirocycle **115** was synthesised in a few steps from carboxylic acid **111** (scheme 25). Alkylation of **111**, followed by Curtius rearrangement using DPPA and benzyl alcohol gave the protected amine **113**. Simple chemical transformations provided the free amine **114**, which was subsequently cyclised by treatment with DBU in refluxing benzene to afford spirocycle **115**.



Scheme 25. Kawahara's racemic synthesis

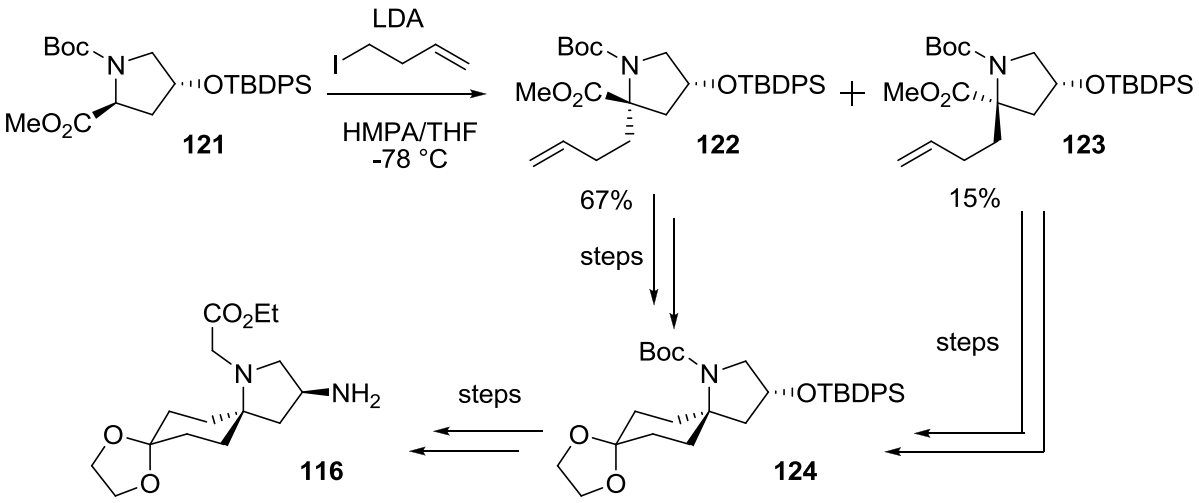
Conversion to amino-ester **116** was realised in a couple of steps involving *N*-alkylation, reaction under Mitsunobu conditions and hydrogenation of the resulting azide (scheme 26). Hydrolysis of the ester functionality in **116** afforded the free amino-acid, which was subsequently cyclised using DPPA and triethylamine to give tricycle **117**. Methylation of the amine, followed by aldol reaction with aldehyde **118** afforded a mixture of diastereoisomers **119**. From here the synthesis was completed by dehydration of the hydroxyl functionality, reduction of the amide and cleavage of the ketal protecting group.



Scheme 26. Kawahara's end-game

A few years later, in 2002 Kawahara published the synthesis of the optically active compound **116**,[34] a key intermediate in his racemic synthesis.[4,33] This time, Kawahara used alkylation of a *trans*-4-hydroxy-*L*-proline derivative **121** with 4-iodo-1-butene to construct the quaternary centre (scheme 27). This reaction led to the formation of a mixture of

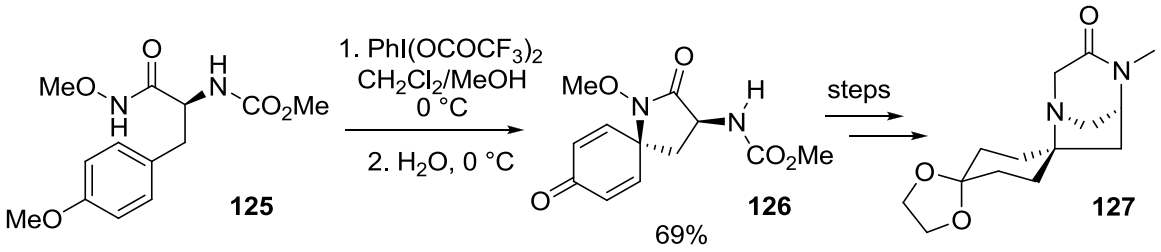
diastereoisomers **122** and **123** in a ratio of 4.5:1. These were both separately converted into the same intermediate **124**, which was transformed in a couple of steps into amino-ester **116**, key intermediate in their racemic synthesis.



Scheme 27. Kawahara's enantiopure synthesis

1.3.3.2 Wardrop's approach[35]

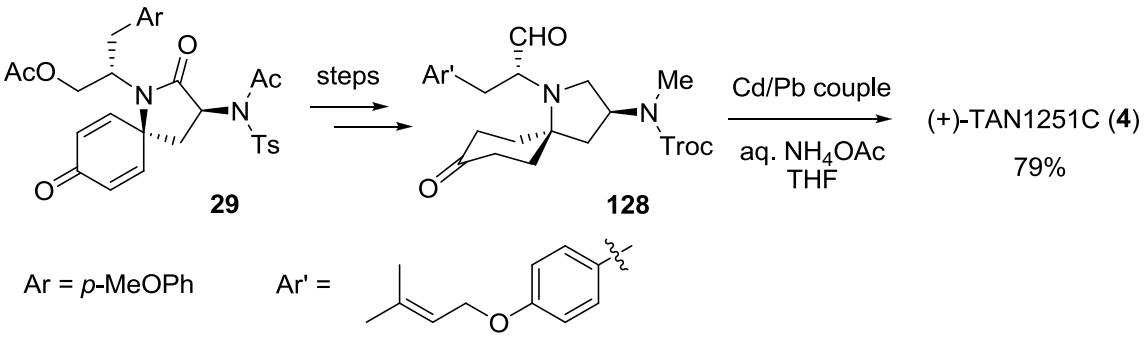
In a formal synthesis of (–)-TAN1251A (**2**),[35] Wardrop's group used a very similar approach to the one they employed for (–)-FR901483 (**1**) (section **1.3.2.2**).[24] In the early stages of this synthesis, a compound derived from *L*-tyrosine **125** was treated with bis(trifluoroacetoxy)iodobenzene to form the desired oxidative spiroannulation product **126** in reasonable yield (scheme 28). Simple chemical transformations, including a DPPA-mediated cyclisation, led to **127**, an advanced intermediate in Kawahara's racemic synthesis,[4-33] in good overall yield. The group did actually finish the first synthesis of enantiopure (–)-TAN1251A (**2**), from **127** by employing Kawahara's route.[4-33]



Scheme 28. Wardrop's approach

1.3.3.3 Ciufolini's approach[10]

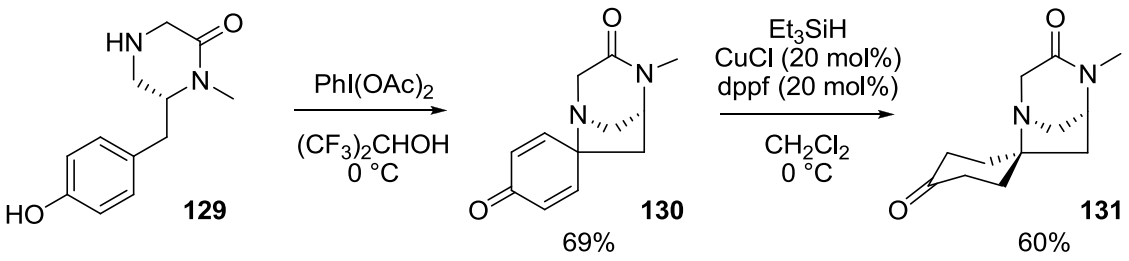
As mentioned previously (section **1.3.1.2**), Ciufolini completed the total synthesis of (+)-TAN1251C (**4**) in addition to the total synthesis of (–)-FR901483 (**1**) from the same common intermediate **27**.[10] The key step used to form this 5,6-spirocyclic intermediate **29** was an oxidative spiroannulation. Subsequently, a series of simple manipulations allowed access to the aldehyde **128** (scheme 29). This was treated with a cadmium/lead couple, which resulted in Troc deprotection and subsequent cyclisation to afford enantiopure (+)-TAN1251C (**4**) in good yield.



Scheme 29. Ciufolini's end game

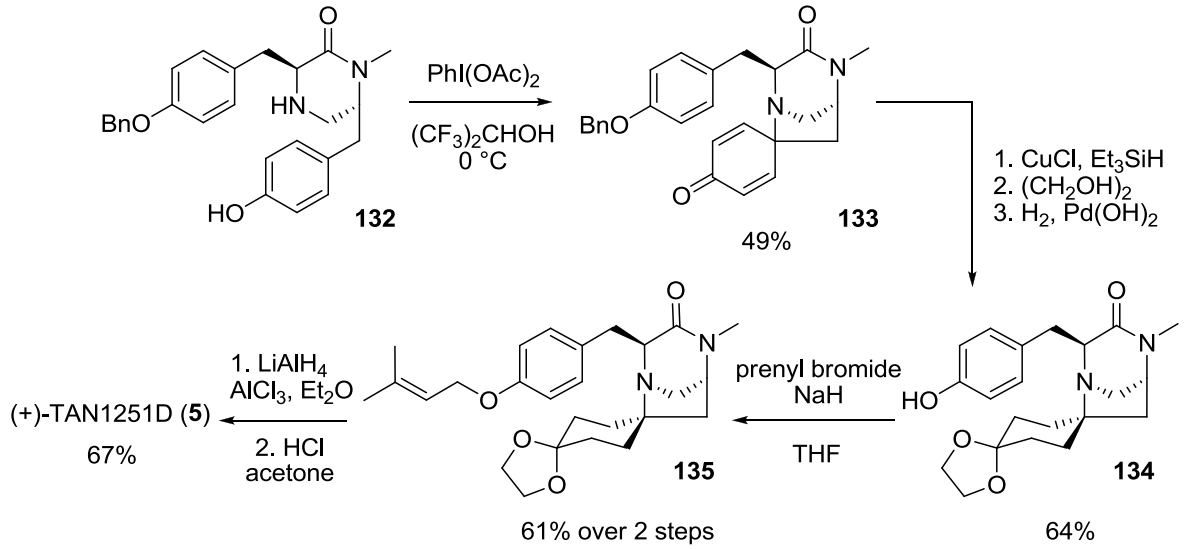
1.3.3.4 Honda's approach[36-37]

Honda used a similar oxidative spiroannulation to that used by Ciufolini[9] (and Sorensen) at a late stage of the synthesis in order to form the last ring of the tricyclic core of (–)-TAN1251A (**2**).[36] Treatment of amino-phenol **129** with iodobenzene diacetate afforded the desired tricycle **130** in good yield (scheme 30). Reduction of the dienone **130** to the ketone **131** was achieved using a mixture of triethylsilane in the presence of a catalytic amount of CuCl and dppf, as other reduction methods proved to be inefficient for the required transformation. Ketone **131** was protected as its ketal form to give the advanced intermediate **127** in Wardrop's synthesis of (–)-TAN1251A (**2**).[35]



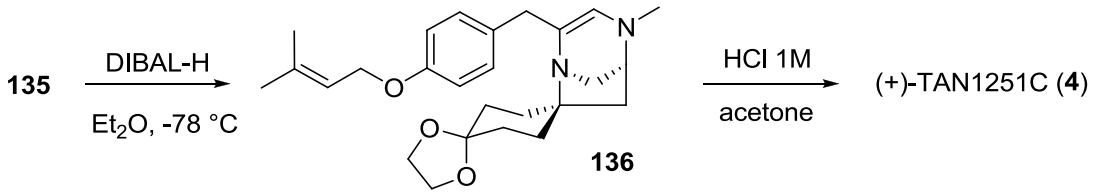
Scheme 30. Honda's approach to (–)-TAN1251A (**2**)

Honda used a similar approach for the synthesis of (+)-TAN1251D (**5**),[37] where the more advanced amino-phenol substrate **132** was treated with iodobenzene diacetate to afford the tricyclic structure **133** with most of the side chain already in place (scheme 31). Reduction of the dienone using CuH, protection of the ketone and removal of the benzyl group by hydrogenation afforded phenol **134**. Prenylation afforded **135**, which was subsequently reduced to the amine and finally converted to (+)-TAN1251D (**5**) after hydrolysis of the ketal group.



Scheme 31. Honda's synthesis of (+)-TAN1251D (**5**)

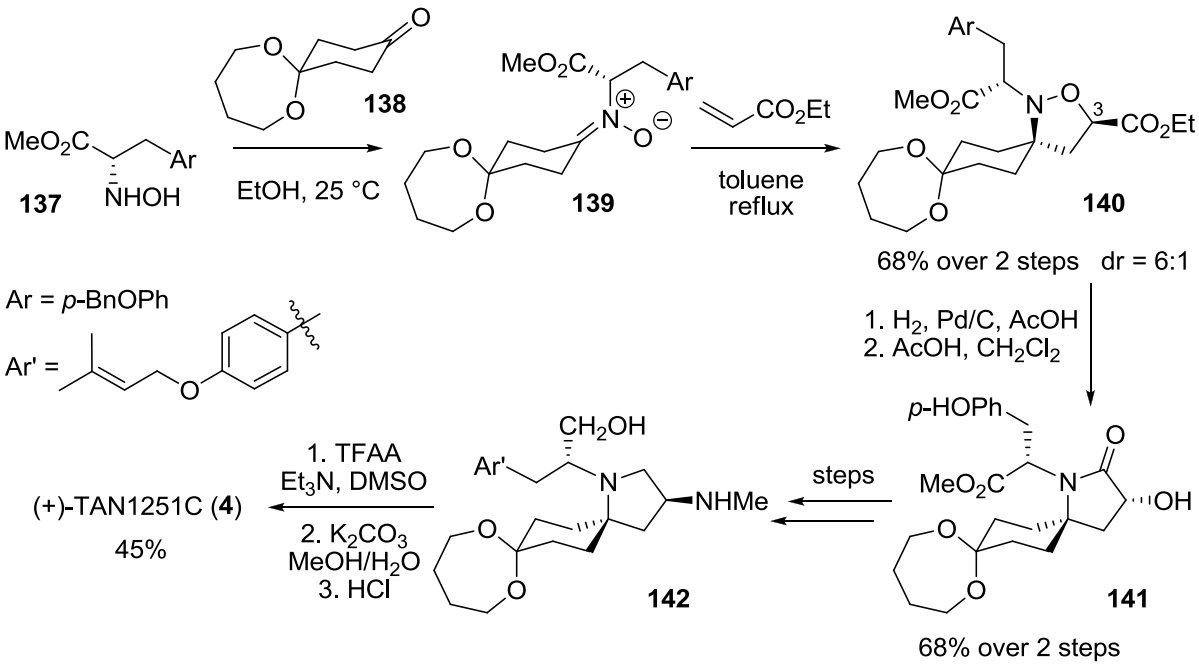
In addition, in two steps from the advanced intermediate **135** in the synthesis of (+)-TAN1251D (**5**), Honda was also able to synthesise (+)-TAN1251C (**4**).[37] DIBAL-H reduction of the amide functionality in **135** gave the desired enamine **136** in good yield (scheme 32). Unmasking of the ketone in **136** gave (+)-TAN1251C (**4**).



Scheme 32. Honda's synthesis of (+)-TAN1251C (**4**)

1.3.3.5 Snider's approach[5]

The most important work towards the synthesis of the TAN1251 alkaloids has been conducted by Snider.[5] To date, he is the only one to have synthesised all the members of the family. For the synthesis of (+)-TAN1251C (**4**), from which (–)-TAN1251A (**2**) and (+)-TAN1251D (**5**) were synthesised, a 1,3-dipolar cycloaddition of nitrone **139** with ethyl acrylate was used to construct the quaternary centre (scheme 33). This is a similar method to the one used in his work towards (–)-FR901483 (**1**) (section **1.3.1.1**),[2] except that the nitrone is protected slightly differently in order to avoid incompatibility with some of the reaction conditions employed.



Scheme 33. Snider's synthesis of (+)-TAN1251C

The cycloaddition yielded a mixture of the desired product **140** in addition to its diastereoisomer, epimeric at the C(3) position in a 6:1 ratio. Cleavage of the N-O bond in **140**

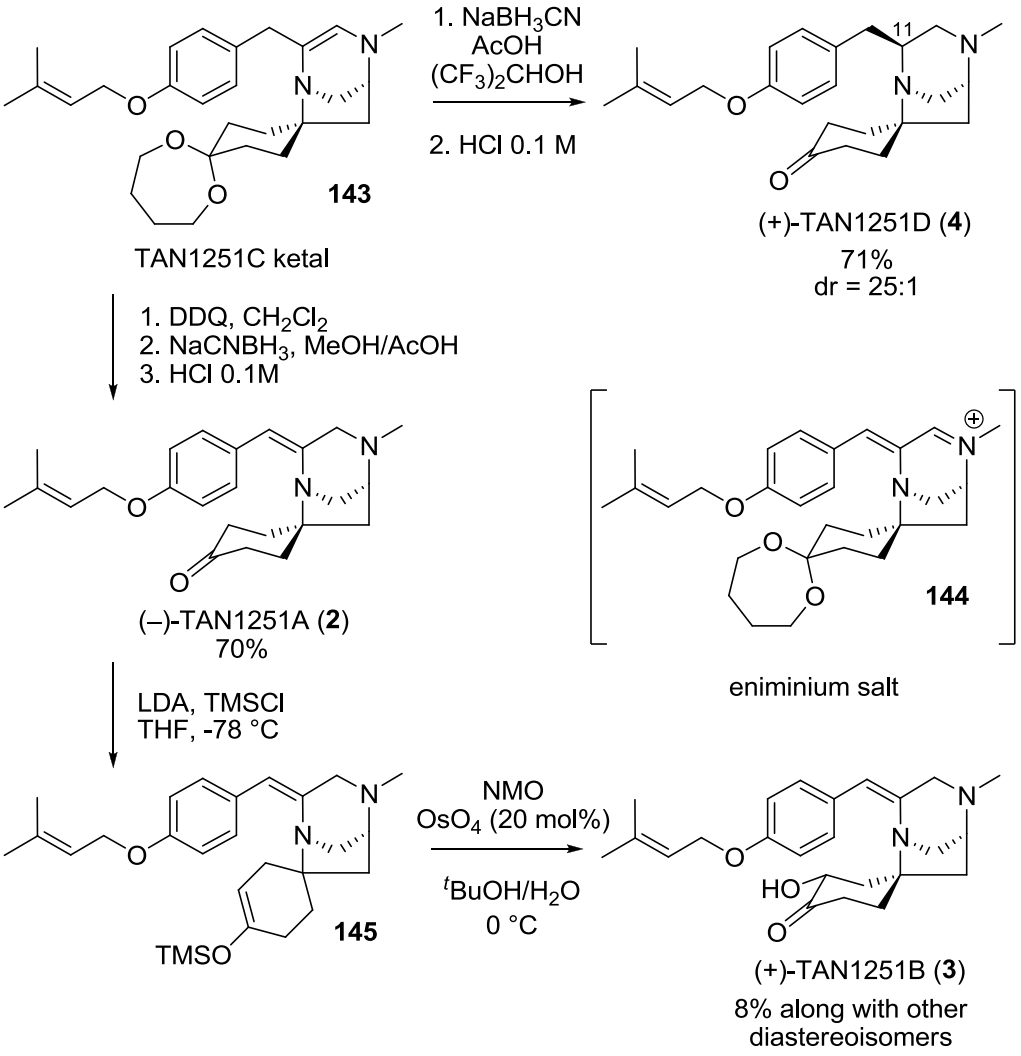
and concurrent removal of the benzyl group was followed by the acid-catalysed formation of spiro-lactam **141**. A few steps enabled conversion of **141** into amino alcohol **142**, which was treated with trifluoroacetic anhydride and triethylamine in DMSO to form an aldehyde intermediate. Hydrolysis of the trifluoroacetamide group and subsequent cyclisation formed the ketal of (+)-TAN1251C (**4**), which after acidic hydrolysis afforded **4**.

(+)-TAN1251D (**5**) was obtained by reduction of **143** (the ketal of (+)-TAN1251C (**4**)) followed by acidic hydrolysis of the ketal (scheme 34). Depending on the solvent employed for the reduction with sodium cyanoborohydride, varying amounts of the undesired diastereomer (epimer at the C(11) position) were isolated. However, using the polar 1,1,1,3,3,3-hexafluoro-2-propanol as a solvent allowed isolation of a separable mixture of the desired product along with its diastereoisomer in a 25:1 ratio.

(–)-TAN1251A (**2**) was also obtained from **143** after DDQ oxidation to afford the eniminium salt **144**, which was subsequently reduced to afford the ketal of (–)-TAN1251A (**2**) (scheme 34). Acidic hydrolysis subsequently gave (–)-TAN1251A (**2**) in good yield.

(+)-TAN1251B (**3**) is possibly the most challenging of the four members of the family to synthesise, since the presence of the hydroxyl group alpha to the ketone turns the quaternary centre next to the nitrogen into a stereocentre. Treatment of (–)-TAN1251A (**2**) with LDA formed a mixture of enolates, which were quenched by trimethylsilyl chloride to give a mixture of silyl enol ethers **145** (scheme 34). After oxidation of the crude mixture of **145** with osmium tetroxide, Snider was able to obtain a complicated mixture of products containing (+)-TAN1251B (**3**) in a small amount, which after much effort he was able to isolate using HPLC Chiralpack AD column. The other products isolated resulted from a lack of

regiocontrol in the formation of the silyl enol ether, and a lack of stereocontrol in the subsequent oxidation step.



Scheme 34. Snider's synthesis of all members of TAN1251 family

1.3.4 Summary of the syntheses of (–)-FR901483 (1) and (+)-TAN1251B (3)

In most of the previous syntheses reviewed above there has not been a satisfactory solution to the stereoselective formation of (–)-FR901483 (**1**) or (+)-TAN1251B (**3**). In particular, the

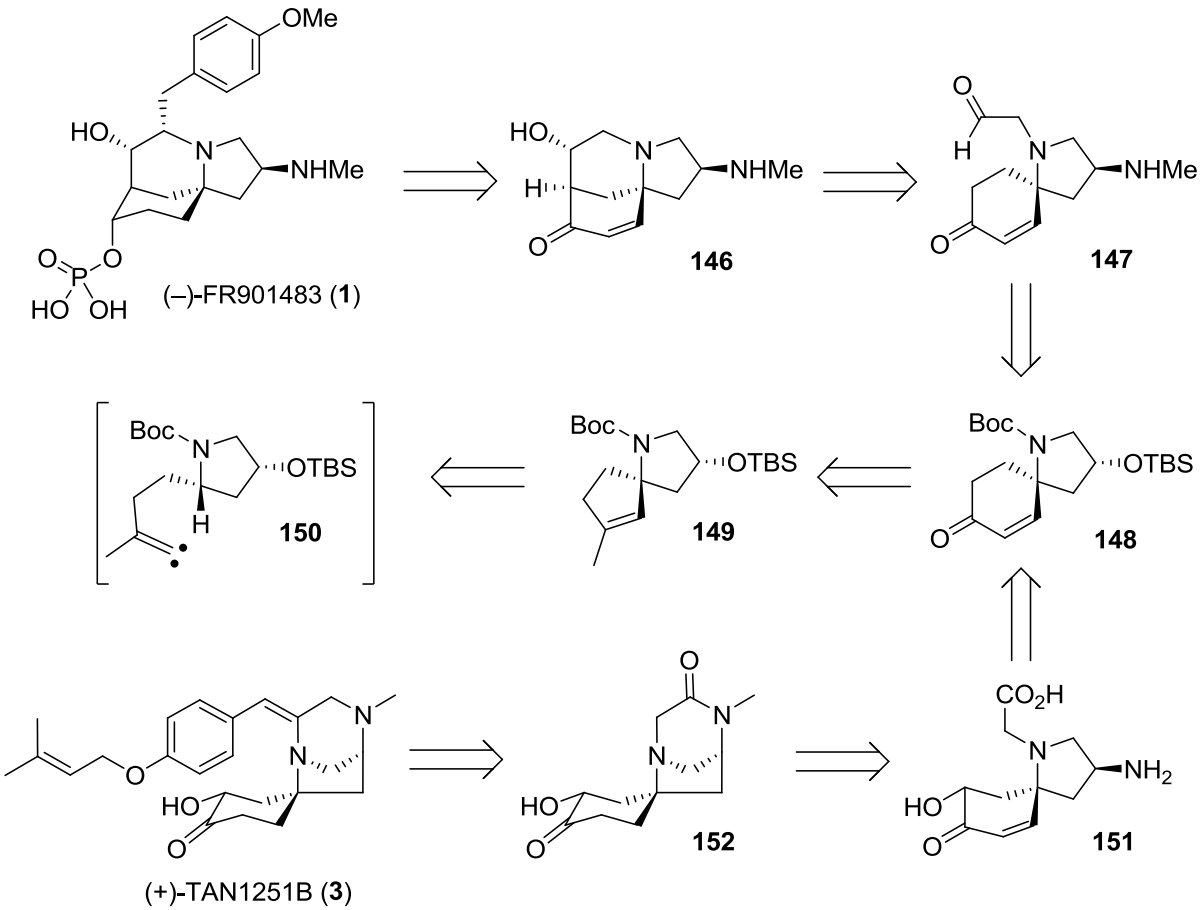
issue of installing the quaternary stereocentre adjacent to the nitrogen has not always been addressed. When considering the previous syntheses of (–)-FR901483 (**1**), although a substantial amount of work has been performed, in many cases the quaternary centre next to the nitrogen was converted into a stereocentre at a late stage in the synthesis by closing the third ring of the tricycle *via* an intramolecular aldol condensation. This aldol condensation was often not selective, giving the desired product in low yield in addition to other regio- and stereoisomers. Other syntheses, which employed different methodologies for their cyclisation steps also suffered from a lack of diastereoselectivity.

To date, the only total synthesis of enantiopure (+)-TAN1251B (**3**) is the one reported by Snider.[5] However, this does not represent a satisfactory solution for its formation since it was synthesised in very low yield from (–)-TAN1251A (**2**). In addition, the current synthesis does not address the issue of installing the quaternary stereocentre adjacent to the nitrogen in a selective fashion.

1.4 Retrosynthetic analysis

As discussed in the description of the previous syntheses of (–)-FR901483 (**1**) and its tricyclic core, the main challenges for the synthesis of **1** are the stereoselective construction of the quaternary centre next to the nitrogen and the formation of the tricyclic structure in both a regio- and stereoselective manner. For the synthesis of (+)-TAN1251B (**3**), the main challenge is again the formation of the quaternary stereocentre next to the nitrogen in addition to the regio- and stereoselective formation of the hydroxyl group alpha to the ketone. The biosynthetic relationship between (–)-FR901483 (**1**) and the TAN1251 family (**2**-**5**) led us to

make the hypothesis that both compounds could be achieved from the same synthetic intermediate. Our retrosynthetic analysis for (–)-FR901483 (**1**) brought us to the tricyclic intermediate **146** with the idea that the phosphate ester moiety and the *p*-methoxybenzyl group could be added at a late stage of the synthesis (scheme 35). Tricycle **146** could be accessed from a regioselective aldol reaction of keto-aldehyde **147**. To avoid the regioselectivity problems encountered in the previous syntheses, we decided to block one side of the 6-membered ring with a double bond in order to ensure the aldol reaction occurred in the desired position. Keto-aldehyde **147** would be easily accessible from the 5,6-spirocyclic enone **148**.



Scheme 35. Retrosynthetic analysis of (–)-FR901483 (**1**) and (+)-TAN1251B (**3**)

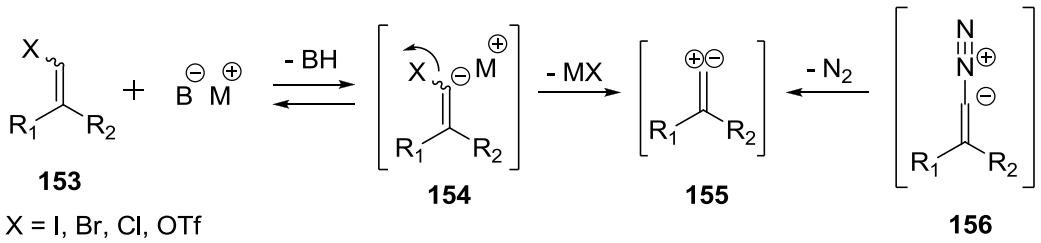
This key intermediate **148** can also be used to install in a regioselective fashion the hydroxyl group alpha to the ketone, which is needed for the synthesis of (+)-TAN1251B (**3**). The side-chain could be added at a late stage from tricycle **152**, which would be the product of the intramolecular peptide coupling of amino-acid **151**. For the synthesis of our common and key intermediate **148**, we now face a new and exciting challenge, which is the construction of a quaternary stereocentre next to nitrogen. We envisaged that the 5,6-spirocyclic enone **148** could be accessed from the 5,5-spirocyclic alkene **149**, which would be the result of a 1,5-CH alkylidene carbene insertion. This methodology has been applied already within the Hayes group[38-43] and should provide an elegant way of installing the stereocentre next to nitrogen since it proceeds with complete retention of stereochemistry.

1.5 Alkylidene Carbenes[44-46]

Alkylidene carbenes are versatile reagents in organic synthesis, which undergo a variety of distinct C-C bond forming reactions. Their regioselectivity in intramolecular cyclisation reactions is excellent and they react predominantly by 1,5 C-H insertion, irrespective of the substitution pattern of the molecule. In addition, they reliably react with retention of stereochemistry at the insertion site.

There are quite a few methods, which have been developed for alkylidene carbene generation but two of the most commonly used will be briefly discussed. The first method involves the base mediated α-elimination of vinyl halides[47,48] or enol triflates[49,50] **153** (scheme 36). A strong amide base (e.g. KHMDS) is the preferred choice for this transformation since it enables the reaction temperature to be kept low, and thus minimises unwanted side-reactions of the carbene.[51,52] The second method employs the thermal decomposition of diazoalkenes

156 and since it does not involve the use of a strong base, a wider range of functionality can be tolerated. One approach to forming the desired diazoalkenes **156** involves treating the corresponding ketone with lithiated trimethylsilyldiazomethane at low temperature.[53,54] Warming up of the reaction results in evolution of nitrogen and formation of the alkylidene carbene **155**.



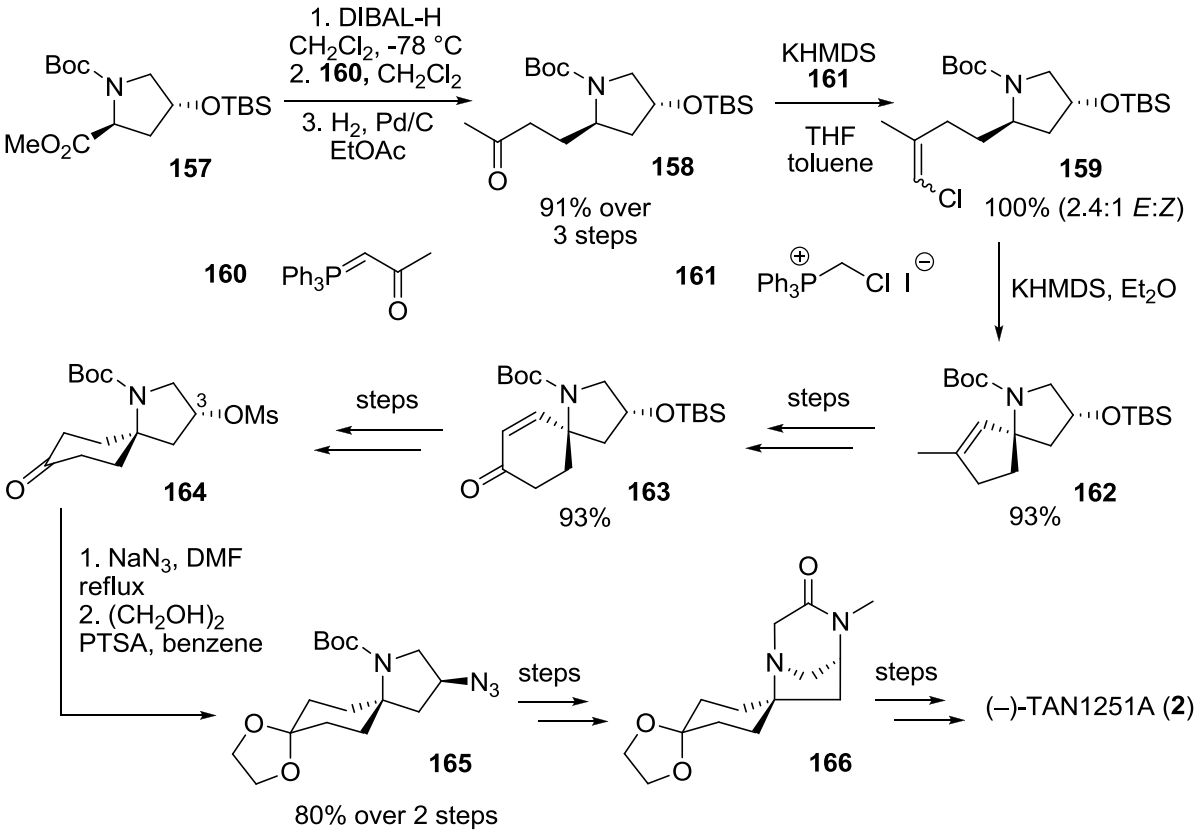
Scheme 36. Methods for generation of alkylidene carbenes[55]

1.3.5 Previous work within the Hayes group

1.3.5.1 Synthesis of (–)-TAN1251A (2)[56,57] and work towards (+)-TAN1251B (3)[57-59]

In 2004, an enantioselective synthesis of (–)-TAN1251A (**2**) was completed by James Auty, working within the Hayes group.[56,57] The *trans*-4-hydroxy-*L*-proline derivative **157** was converted into ketone **158** in good yield by a three step sequence consisting of a DIBAL-H reduction, Wittig reaction and hydrogenation (scheme 37). A second Wittig reaction allowed formation of a vinylchloride as a mixture of *Z* and *E* isomers, which were treated with KHMDS to afford the insertion product **162**. The 5,5-spirocycle **162** was converted into the 5,6-spirocycle **163** in a few steps involving oxidative cleavage of the double bond, an

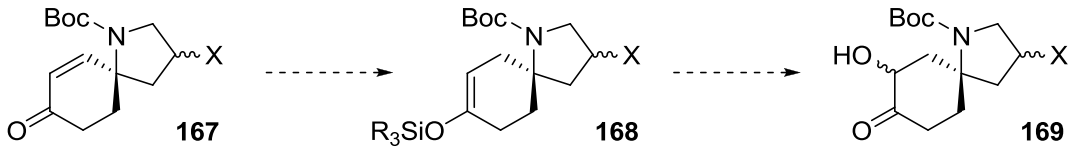
intramolecular aldol reaction and then dehydration of the aldol product. Exchange of protecting groups on the hydroxyl group and hydrogenation of the double bond furnished saturated ketone **164**. Installation of the azide group with inversion of stereochemistry at C(3), followed by protection of the ketone as a ketal led to the formation of azide **165**, intermediate in Kawahara's second-generation synthesis.[34] From here the synthesis of (–)-TAN1251A (**2**) was completed using the method of Wardrop[35] and Kawahara.[34]



Scheme 37. Hayes's synthesis of (–)-TAN1251A

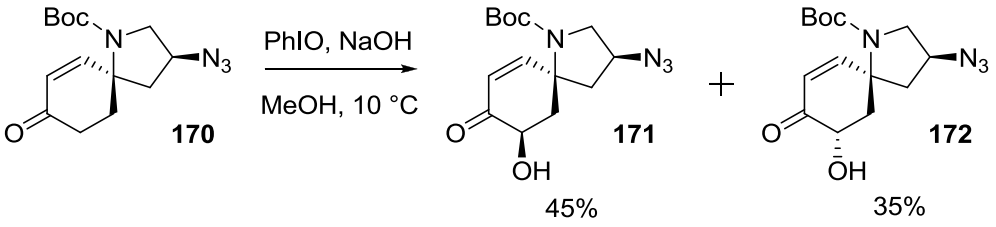
Auty then attempted to use his key intermediate **163** for a total synthesis of (+)-TAN1251B (**3**) as the quaternary stereocentre required for its synthesis was already in place.[57] It was envisaged that the double bond of the enone could be used as a tool for insertion of the hydroxyl group. This could be envisaged *via* conjugate reduction of enone **167** followed by

trapping of the resultant enolate as a silyl enol ether to give **168** (scheme 38). Oxidation of silyl enol ether **168** would then give the desired α-hydroxy ketone **169**. Unfortunately, despite literature precedent for this kind of transformation,[60-63] it was never possible to form the silyl enol ether **168** or isolate the desired α-hydroxy ketone **169**.



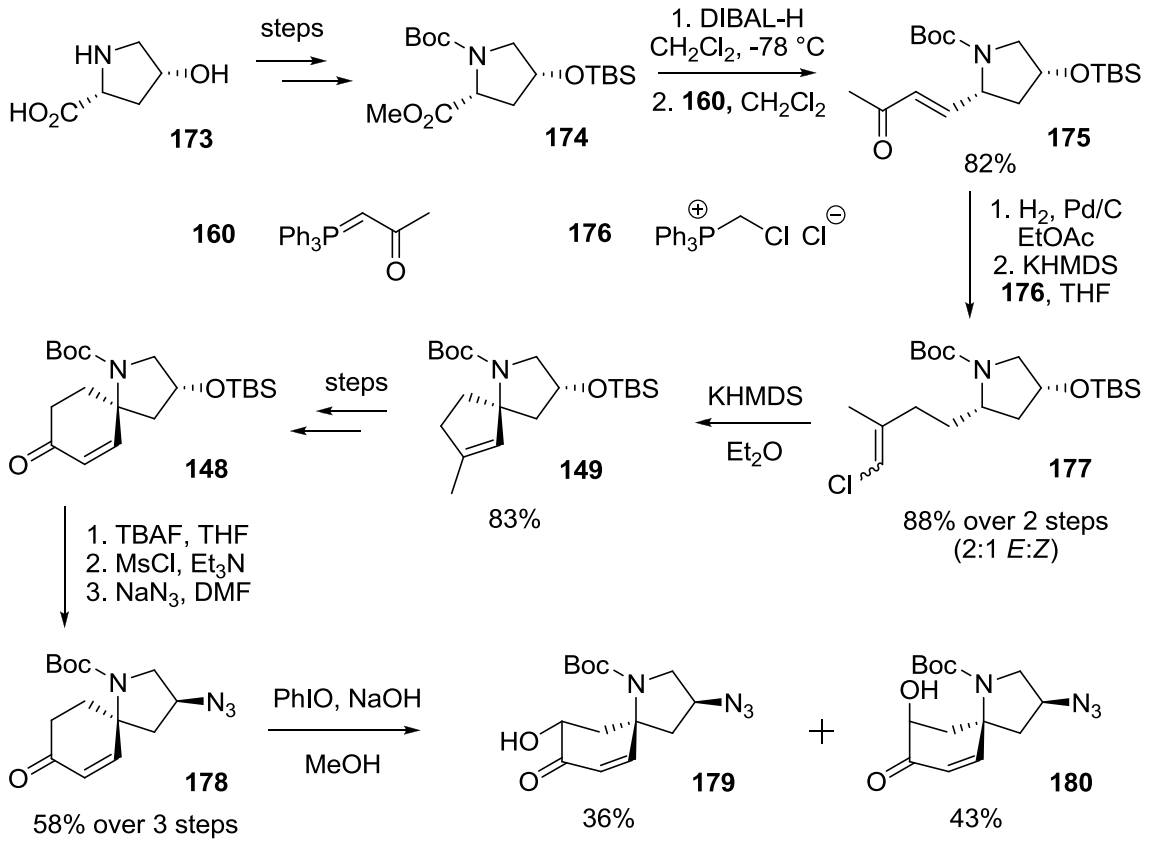
Scheme 38. Possible formation of α-hydroxy ketone

A final, alternative approach was attempted by Auty using the ketone **170**.[57] This time, it was thought that use of the double bond as a blocking group would allow α-hydroxylation to occur selectively on the opposite side of the carbonyl to the double bond. Indeed, oxidation using iodosobenzene with NaOH in methanol afforded a separable mixture of isomers **171** and **172** in a 1.3:1 ratio (scheme 39). Although the product had the wrong regiochemistry for completing the total synthesis of (+)-TAN1251B (**3**), this problem could be solved if the oxidation conditions were applied to the epimer of **170** (at the quaternary centre).



Scheme 39. Successful attempt of α-hydroxylation

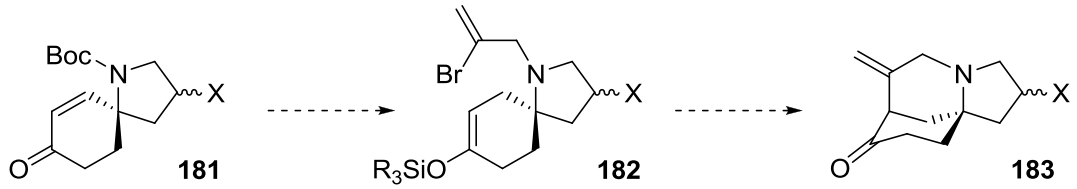
Following the progress made by Auty, Asnuzilawati Asari continued the work towards (+)-TAN1251B (**3**).[58,59] Using the chemistry developed previously, but starting from *cis*-4-hydroxy-*D*-proline **173**, the 5,6-spirocycle **148**, diastereoisomer of **163** (scheme 37), was obtained (scheme 40). This was subsequently converted into its azido version **178** in just three steps before being treated with the oxidation conditions previously employed by Auty.[57] The desired product with the hydroxyl group in the equatorial position **179** was obtained along with its epimer **180**. Unfortunately the major compound was the undesired axial hydroxy ketone **180**, and attempted epimerisation of this compound to the desired stereoisomer was unsuccessful.



Scheme 40. Synthesis of **179**, precursor to (+)-TAN1251B (**3**)

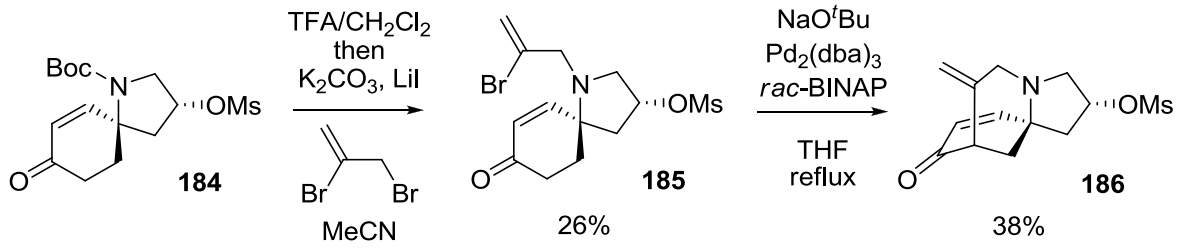
1.3.5.2 Work towards (–)-FR901483 (1)[57,58,64]

Auty also initiated work towards a total synthesis of (–)-FR901483 (**1**).[57] The original plan involved as a key step, the selective formation of the same silyl enol ether **182** as that required for the synthesis of (+)-TAN1251B (**3**, scheme 41). As all previous attempts to form this enol ether had been unsuccessful, it was no longer possible to use the double bond as a means for controlling the regioselectivity of the cyclisation step in the manner originally proposed.



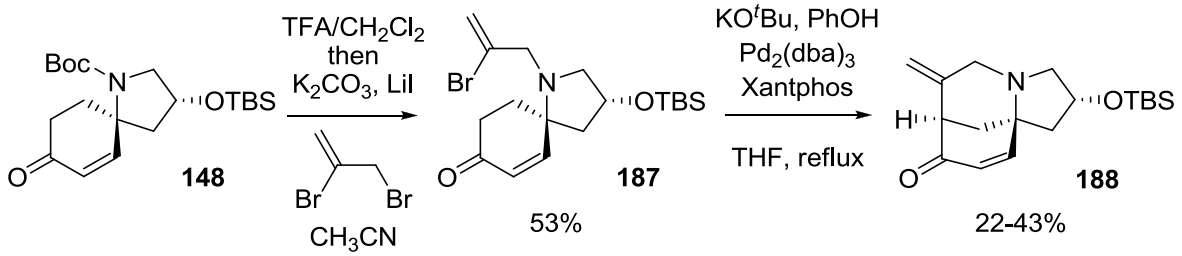
Scheme 41. Original plan for the synthesis of the tricycle of (–)-FR901483 (**1**)

However, considering the way this problem was solved during work towards the synthesis of (+)-TAN1251B (**3**), it was hypothesised that the double bond could act as a blocking group to enable a regioselective cyclisation to occur on the opposite side of the ring to the double bond. Indeed, Auty was able to obtain the tricycle structure **186** using methodology developed by Bonjoch,[28] which involved a palladium-catalysed cyclisation of vinylbromide **185**.[57] The cyclisation precursor **185** was made in two steps from enone **184** (scheme 42). Although the yield was fairly low over these steps, some starting material was also recovered and it was encouraging to see that the cyclisation could work. Again, although the product had the wrong regiochemistry for completing the total synthesis of (–)-FR901483 (**1**), use of the epimer of **181** (at the quaternary centre) should overcome this problem.



Scheme 42. Tricycle formation

Asari continued Auty's work, and synthesised the correct diastereoisomer of the key 5,6-spirocycle **148** for (+)-TAN1251B (**3**).[58,64] Conversion to the vinyl bromide **187** proceeded in reasonable yield using the conditions previously employed by Auty (scheme 43).[57] After extensive optimisation of the palladium-catalysed alkenylation reaction, the desired tricycle **188** was formed in moderate yield as a single regio- and stereoisomer.



Scheme 43. Tricycle formation

1.6 Aims of the research

As mentioned previously, the aim of this research is to develop a common strategy for a novel and efficient approach towards the biosynthetically related alkaloids (–)-FR901483 (**1**) and (+)-TAN1251B (**3**). As shown in our retrosynthetic analysis (scheme 35, p. 38) we

envisaged that the 5,6-spirocycle **148** could be an intermediate in the syntheses of both of these targets. Firstly therefore, we aimed to focus on a scalable and efficient synthesis of this key compound **148**. We then proposed to work towards the syntheses of both (–)-FR901483 (**1**) and (+)-TAN1251B (**3**) from this common intermediate.

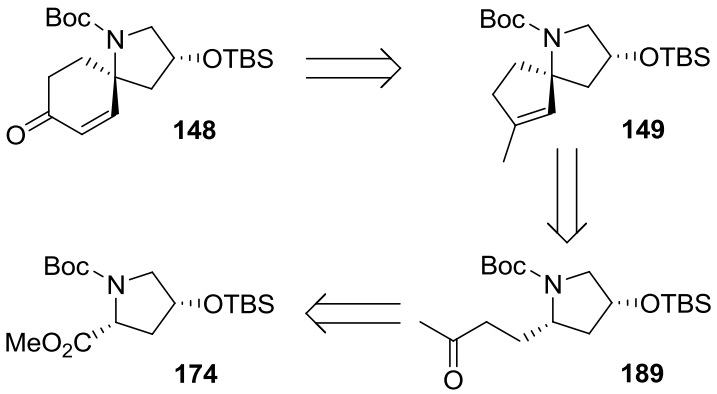
Chapter 2: Results and discussion

2.0 Results and discussion

Firstly, the synthesis of our key intermediate **148** *via* a 1,5-CH insertion will be described and discussed. Then the focus will turn to the progress made towards the total synthesis of (–)-FR901483 (**1**), before moving to discuss the progress made towards the total synthesis of (+)-TAN1251B (**3**). We will conclude this section by describing work to be considered in the future in order to complete both syntheses.

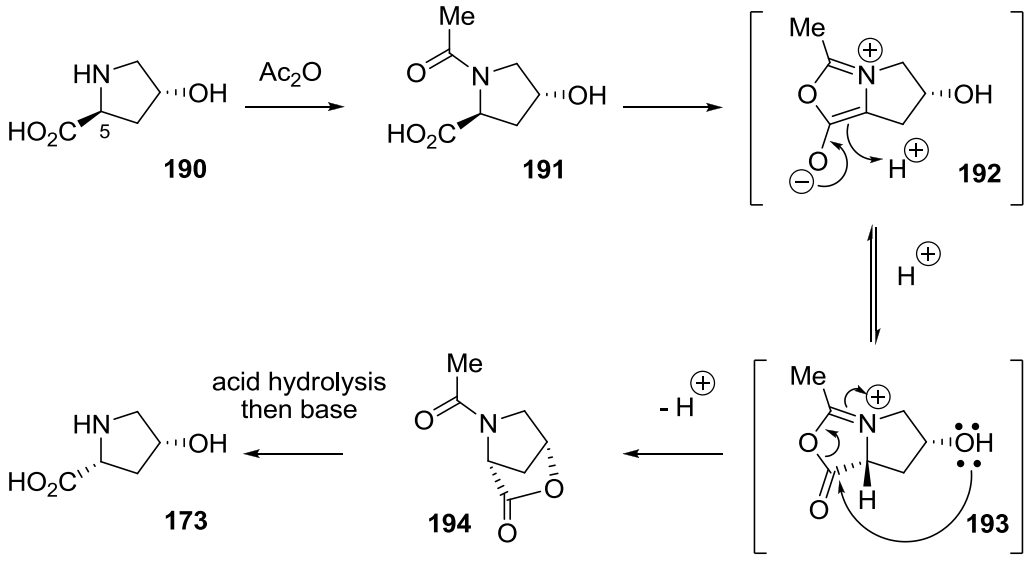
2.1 Formation of the key intermediate

In order to develop an efficient approach to the total synthesis of (–)-FR901483 (**1**) and (+)-TAN1251B (**3**), we first required an efficient synthesis of the 5,6-spirocyclic enone **148**, our key intermediate. Our retrosynthetic analysis has shown that **148** could be accessed from the 5,5-spirocycle alkene **149** (scheme 44), *via* a 1,5-CH insertion of a suitable carbene cyclisation precursor **189,** followed by a ring expansion. Ketone **189** can be accessed from a suitably protected *cis*-4-hydroxy-*D*-proline derivative **174**, *via* simple chemical transformations.



Scheme 44. Retrosynthesis of our key intermediate **148**

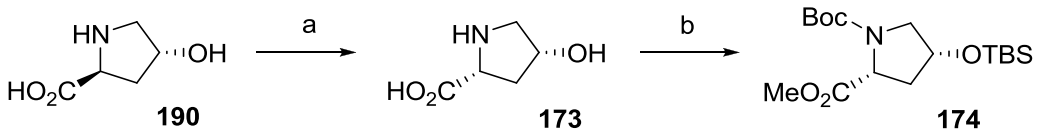
Since *cis*-4-hydroxy-*D*-proline **173** is quite expensive (£300 for 10 g)[65] and a large amount of it was required for our synthesis, we looked for a way to convert the inexpensive *trans*-4-hydroxy-*L*-proline **190**[65] into our desired chiral pool starting material. Lowe reported a method to achieve this,[66] which initially involved the treatment of *trans*-4-hydroxy-*L*-proline **190** with acetic anhydride to give the *N*-acylated compound **191** (scheme 45). The presence of this *N*-acyl group allowed formation of the corresponding bicyclic mesoionic intermediate **192**. Selective protonation is controlled by the existing stereocentre and occurs from the less hindered side (opposite to the hydroxyl group) to form **193**. From here, intramolecular attack of the hydroxyl goup onto the carbonyl leads to lactone **194**. This lactone **194** is therefore obtained with inversion of configuration at C(5). Subsequent acidic hydrolysis affords the hydrochloride salt of *cis*-4-hydroxy-*D*-proline, and basification or use of an ion-exchange resin allows isolation of **173**.[67]



Scheme 45. Proposed mechanism for the epimerisation of **190**[67]

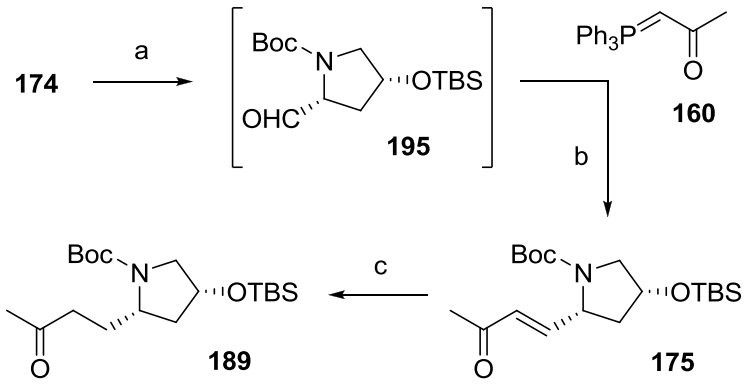
This method allowed isolation of the desired *cis*-4-hydroxy-*D*-proline **173** in good yield

(scheme 46) and the method also proved to be easily scalable (it has been performed on a 70 g scale using normal laboratory glassware). **173** was then suitably protected using a sequence of straight forward chemical transformations: the carboxylic acid was protected as the methyl ester; the amine as a carbamate (Boc group), and the free hydroxyl group as a TBS ether. The use of the orthogonal protecting TBS and Boc groups was deliberate at this stage to enable selective manipulations at a later stage in the synthesis. In addition, many subsequent steps in the synthesis required the protecting groups to be resistant to basic conditions. The protected derivative of *cis*-4-hydroxy-*D*-proline **174** was obtained in 70 % yield over the 3 steps, and no purification by column chromatography was necessary.



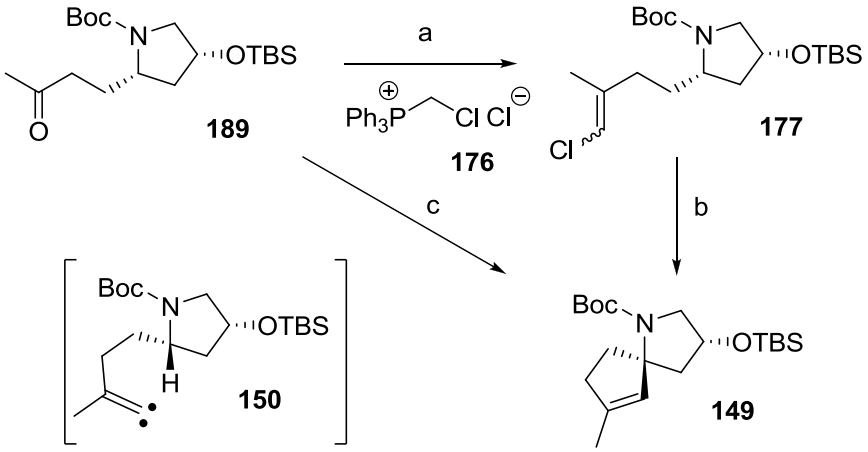
Scheme 46. *Reagents and conditions*: (a) i. Ac_2O:AcOH (1:4), reflux, 5.5 h; ii. 2 M HCl, reflux, 3 h; iii. precipitation in Et_3N:H_2O:EtOH (4:5:30) then recrystallisation, overall yield : 39%; (b) i. AcCl, MeOH, reflux 7 h; ii. Boc_2O, Et_3N, CH_2Cl_2, 0 ˚C - r.t., 20 h, 70% over 2 steps; iii. TBSCl, imidazole, DMF, 30 min, 60 ˚C, quant.

The ester **174** was then reduced using DIBAL-H to the unstable aldehyde **195**, which was used without purification in a subsequent Wittig reaction with 1-triphenylphosphoranylidene-2-propanone **160** to afford the *α,β*-unsaturated ketone **175** in good yield (scheme 47). The enone functionality was then reduced to give the ketone **189** using catalytic hydrogenation.



Scheme 47. *Reagents and conditions:* (a) DIBAL-H, CH_2Cl_2, -78 ˚C, 3.5 h then MeOH, 1 h; (b) **160**, CH_2Cl_2, 5 d, 80% over 2 steps; (c) H_2, Pd/C, EtOAc, 2 d, quant.

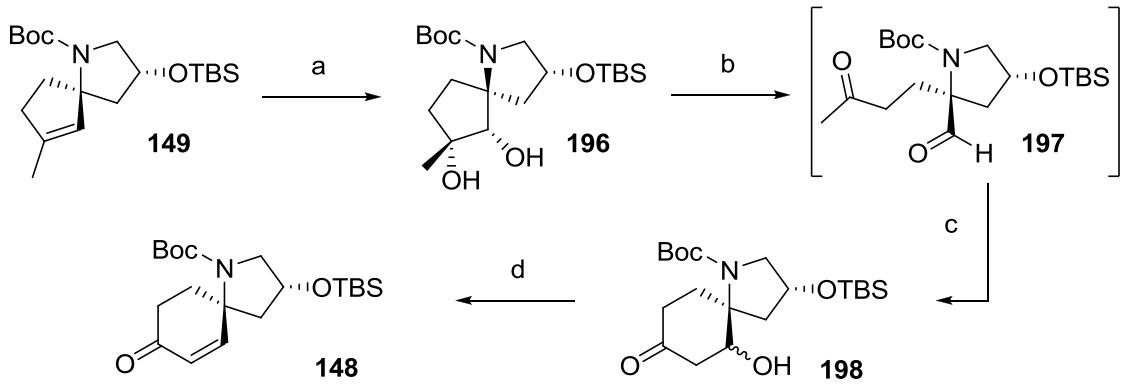
From this point we considered two possible routes in order to achieve the alkylidene carbene insertion. The first route involved the formation of the vinyl chloride **177**, which could be made *via* a Wittig-like reaction using KO^{t}Bu (solid or made *in situ*) and ylide **176** (scheme 48). Treatment of the resultant mixture of *E* and *Z* isomers (ratio 2:1) with KHMDS afforded the desired insertion product **149** in excellent yield and as a single diastereoisomer. The second route employed another well-known method for the formation of an alkylidene carbene and treatment of the ketone **189** with lithiated trimethylsilyldiazomethane afforded the desired insertion product **149**, again in excellent yield.



Scheme 48. *Reagents and conditions:* (a) KO^{t}Bu, **176**, THF, 1 h, 88%, E:Z (2:1); (b) KHMDS, Et_2O, 3 h, 91%; (c) $TMSCHN_2$, ^{n}BuLi then **189**, THF, 85%.

Although the alkylidene carbene insertion proceeded with complete retention of configuration, it is important to note that epimerisation of **149** readily occurs at the newly formed quaternary stereocentre when the product is exposed to acid. Indeed, the trace acid contained in deuterated chloroform is enough to result in the observation of both diastereoisomers by ^{1}H NMR. This problem can be avoided if the ^{1}H NMR is recorded using d_6-DMSO or when the $CDCl_3$ is neutralised with K_2CO_3 prior to use. Racemisation studies on a similar substrate have been conducted by previous members of the Hayes group.[55,58,68]

The ring expansion to convert the 5,5-spirocycle **149** into the 5,6-spirocyclic enone **148** was achieved in a straightforward sequence involving oxidative cleavage, intramolecular aldol reaction and dehydration of the resultant alcohol (scheme 49). Firstly, dihydroxylation of alkene **149** afforded the 1,2-diol **196**, and subsequent periodate cleavage furnished keto-aldehyde **197**. A base-catalysed aldol reaction of **197** resulted in formation of alcohol **198**, which was dehydrated *via* elimination of the corresponding mesylate under basic conditions.



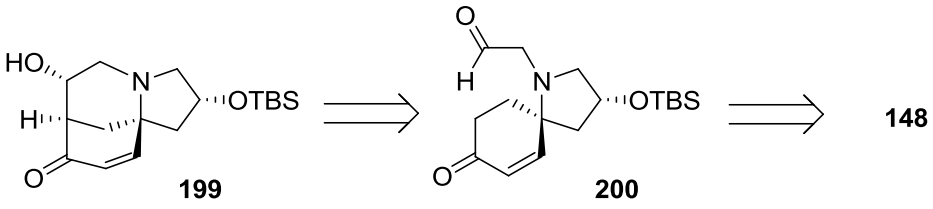
Scheme 49. *Reagents and conditions:* (a) $K_2OsO_4.2H_2O$ (1 mol%), NMO.H_2O, acetone:H_2O (10:1), 4 d, 86%; (b) $NaIO_4$, THF:H_2O (2:1), 1 h; (c) KOH, EtOH, 0 ˚C, 2 h, 84% over 2 steps; (d) MsCl, Et_3N, CH_2Cl_2, 0 ˚C to r.t., 2 d, 92%.

The synthesis of our key intermediate **148** was thus completed in an overall yield of 12.3% in

12 steps from *trans*-4-hydroxy-*L*-proline **190** (or in 32% over 11 steps starting from commercially available *cis*-4-hydroxy-*D*-proline **173**). The whole synthetic sequence has been regularly performed on a multigram scale without difficulty.

2.2 Progress towards the total synthesis of (–)-FR901483 (1)

With a successful route to our 5,6-spirocyclic enone intermediate **148**, the first challenge in the synthesis of (–)-FR901483 (**1**) was to investigate the key aldol cyclisation step for closing the last ring of the tricyclic core. It was important to verify whether the use of a double bond as a blocking group would enable the cyclisation on keto-aldehyde **200** to occur in a regioselective manner (scheme 50).

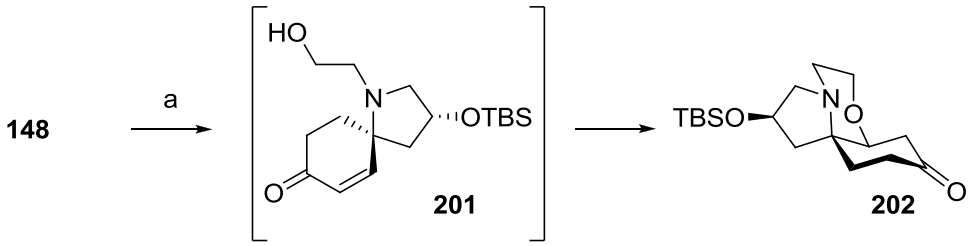


Scheme 50. Reminder of retrosynthetic analysis

2.2.1 Aldol approach

We envisaged that we could obtain the desired precursor for the aldol reaction **200** by oxidation of the corresponding alcohol **201**. It was thought that we could obtain the alcohol **201** directly from the key 5,6-spirocyclic intermediate **148**. However, removal of the Boc

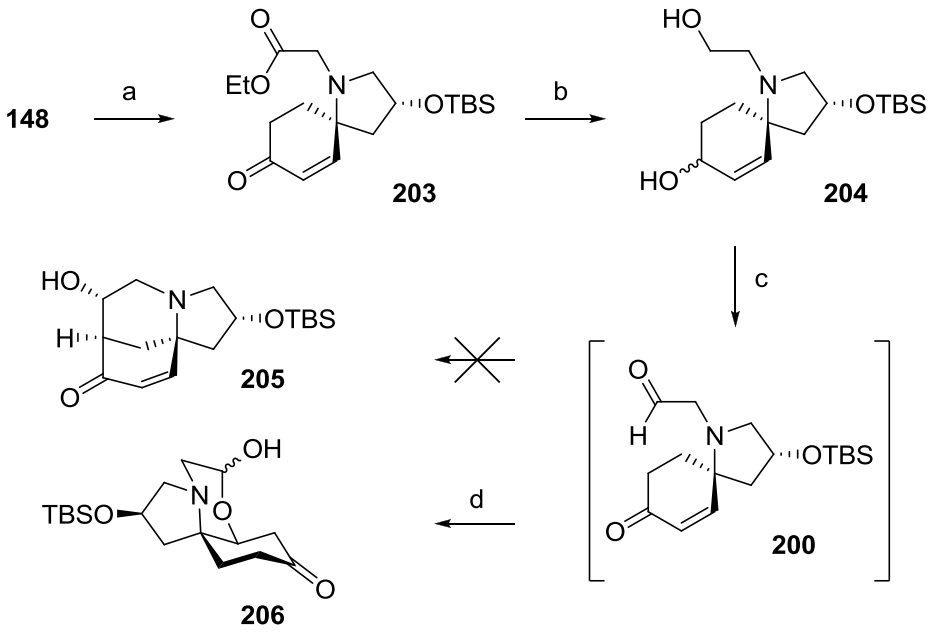
group of **148** with TFA and treatment of the resultant free amine with oxirane (condensed gas), led to formation of an unexpected tricyclic structure **202** in excellent yield (scheme 51). This product is probably the result of an intramolecular Michael addition of the alcohol to the enone functionality in **201**. This suggests that we did indeed manage to form our desired keto-alcohol **201**, but that it is inherently too reactive to be isolated. It was therefore not possible to oxidise it for subsequent use in the aldol reaction and a new approach was needed.



Scheme 51. *Reagents and conditions:* (a) i. TFA, CH_2Cl_2, 1 h; ii. oxirane, CH_2Cl_2:MeOH (1:1), -30 ˚C, 3 h, then r.t., 1 d, 87%.

Alkylation of the free amine in **148** with ethylbromoacetate afforded the keto-ester **203** in good yield (scheme 52). Lithium aluminium hydride reduction of the ester and ketone functionalities in the molecule afforded the corresponding diol **204**. We then attempted to convert this into the desired keto-aldehyde **200** *via* double Swern oxidation. The ^{1}H NMR spectrum of the crude reaction mixture did indicate that the desired keto-aldehyde **200** was indeed the sole product of the reaction. Unfortunately, all attempts to purify it were unsuccessful, presumably due to it being highly unstable. Use of the crude reaction mixture directly for the next cyclisation step was therefore considered. The two sets of conditions, which had been used previously in the total synthesis of (–)-FR901483 (**1**) by Snider[2] were both applied to our substrate, but the desired tricycle **205** was never isolated (scheme 52). Instead a complex mixture was obtained, within which the main product was the tricyclic hemiacetal structure **206**. Isolation of this undesired product may result from the fact that

under the reaction conditions the hydrate of aldehyde **200** is formed. This could then undergo intramolecular Michael addition to the enone functionality to give the hemiacetal **206**.



Scheme 52. *Reagents and conditions:* (a) i. TFA, CH_2Cl_2 1h; ii. $BrCH_2CO_2Et$, NaI, K_2CO_3, MeCN, r.t., 18 h, 87% over 2 steps; (c) i. $LiAlH_4$, THF, 0 ˚C, 30 min then r.t., 20 h, 93 %; ii. $(COCl)_2$, DMSO, CH_2Cl_2, -78 ˚C, 1 h then Et_3N, -78 ˚C - r.t.; (d) NaOMe, MeOH, 0 ˚C, 2 h or KO^{t}Bu, toluene.

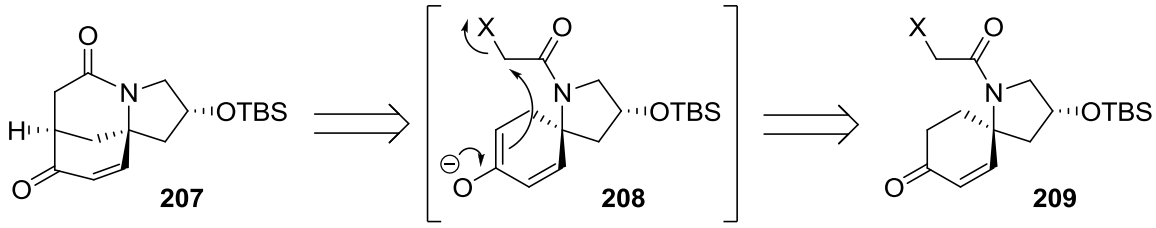
At this point it seemed that use of the double bond as a blocking group for the aldol cyclisation was not viable due to its innate reactivity. This was disappointing, but we decided to investigate the use of different methodology for closing the third ring of the tricyclic core of (–)-FR901483 (**1**).

2.2.2 Enolate chemistry: first-generation approach

After reviewing the literature on previous works towards (–)-FR901483 (**1**), it was thought that Weinreb's model study,[29] might be applicable to our synthesis (see **85** to **86**, scheme 19,

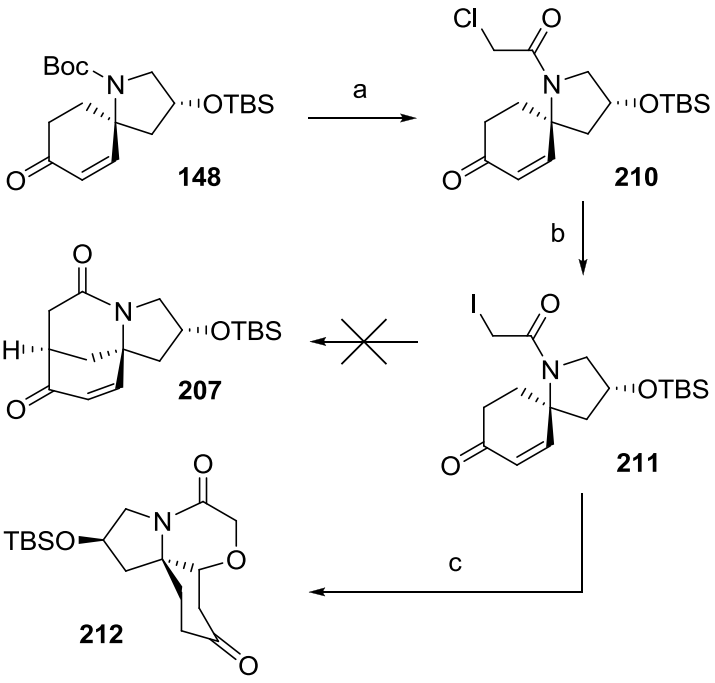
p. 23). The study showed good precedent for the formation of the 2-azabicyclo-[3.3.1]-nonane ring **86** by intramolecular coupling of an *α*-iodo-amide and a ketone (*via* its enolate) in the presence of base.

Based on this methodology reported by Weinreb,[29] the new retrosynthetic analysis is shown (scheme 53). The key tricyclic core **207** of our target would therefore be obtained from an intramolecular cyclisation involving the alkylation of enolate **208** derived from ketone **209**. With the double bond still blocking one side of the ring, the enolate should be formed on the opposite side, thus allowing us to control the regioselectivity of the reaction.



Scheme 53. Revised retrosynthetic analysis

Starting with key intermediate **148**, Boc deprotection followed by alkylation of the free amine with chloroacetylchloride afforded the corresponding *α*-chloro-amide **210** in good yield (scheme 54). Halide exchange was achieved *via* a Finkelstein reaction and proceeded quantitatively to provide iodo-ketone **211**.



Scheme 54. *Reagents and conditions:* (a) TFA, CH_2Cl_2 then $ClCH_2COCl$, Et_3N, CH_2Cl_2, 0 ˚C, 1h then r.t., 3 h, 77% over 2 steps; (b) NaI, acetone, 4 h, 97%; (c) K_2CO_3, acetone:H_2O (3:1), 10 d, 68% (91% based on SM recovered).

Treatment with K_2CO_3, according to the procedure used by Weinreb[29] however, failed to give the desired tricycle **207**, affording instead the unexpected tricycle **212**. Formation of this product could be explained by displacement of the iodide with water, followed by an intramolecular Michael addition to the enone in a similar fashion to that observed whilst trying to close the ring *via* an aldol cyclisation of alcohol **201** (scheme 51, p. 54). The tricycle **212** was crystalline, enabling us to obtain an X-ray crystal structure, which confirmed our interpretation of the spectroscopic data (figure 4).

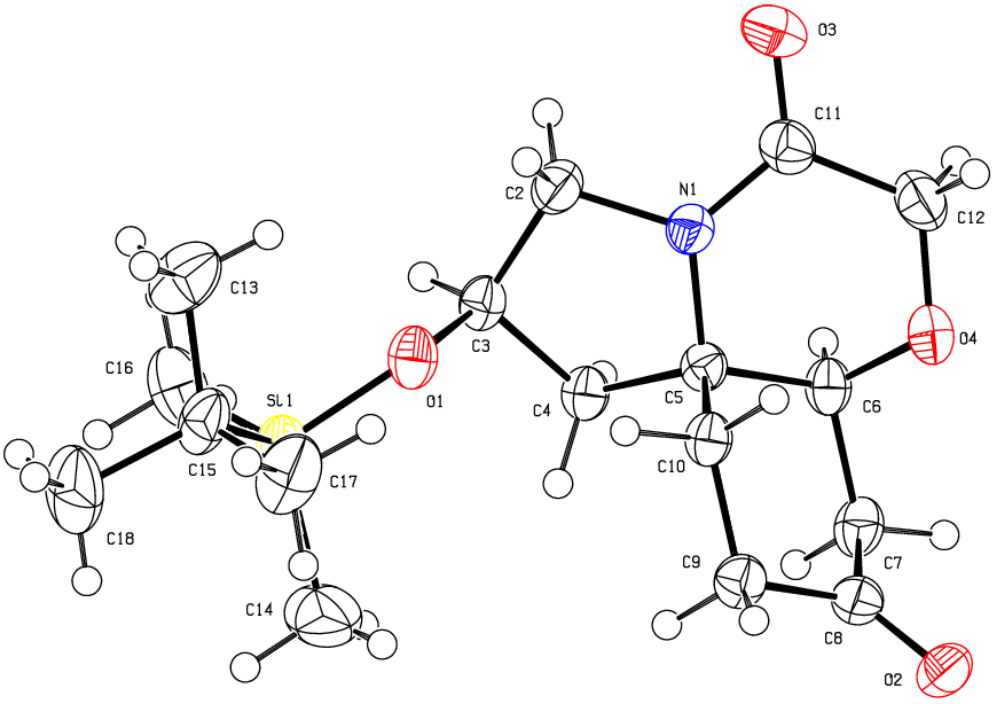


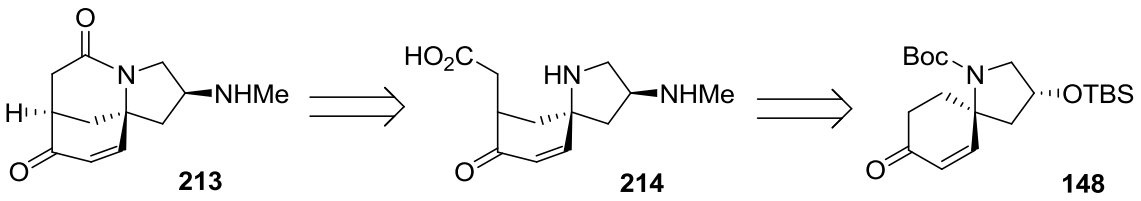
Figure 4. X-ray crystal structure of tricycle **212**

Attempts to perform the cyclisation step were continued and a variety of bases were screened (avoiding water to prevent halide displacement) for the reaction. The conditions were applied to both the keto-iodide **210** and the chloride **211**, but most of them led to recovery of the starting material (*N*,*N*-diisopropylethylamine, LDA, KHMDS) or halide displacement with the base (triethylamine). Even at higher temperatures, no conversion to the desired product was observed.

These results appeared to confirm that the double bond, which was hoped would block one side of the 6-membered ring to enable a regioselective cyclisation, was unfortunately too reactive under the conditions used and was actually blocking formation of the correct tricycle.

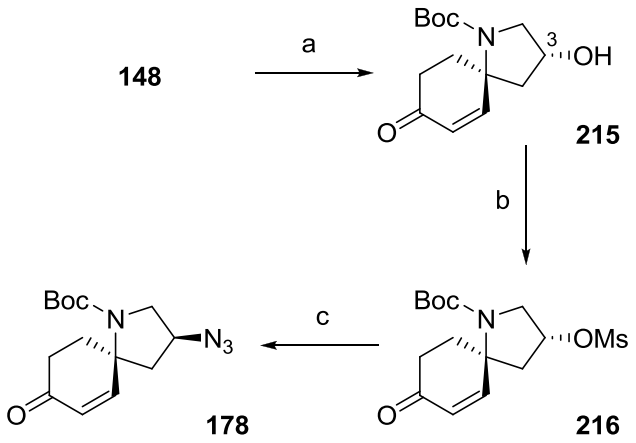
2.2.3 Enolate chemistry: second-generation approach

The proposal of closing the last ring of the tricyclic core of (–)-FR901483 (**1**) using enolate chemistry in this manner was reconsidered. It was now thought that a new disconnection was needed, in which this time the enolate chemistry could be used to install a carboxylic acid side-chain on key intermediate **148** (scheme 55). This, after installation of the amino group, would lead to the amino acid **214**, which could undergo an intramolecular peptide coupling to close the final ring and form tricycle **213**. The new retrosynthetic analysis is shown (scheme 55).



Scheme 55. Revised retrosynthetic analysis

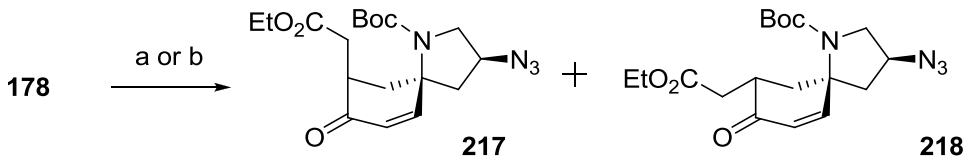
We decided to work on a more advanced intermediate, with the amino group of the natural product installed (protected as an azide) in order to reduce the number of transformations required later in the synthesis. A short 3-step sequence allowed us to invert the stereocentre at C(3) and install the azido group. Deprotection of the TBS group of **148** using TBAF solution afforded alcohol **215** (scheme 56). Mesylation of the alcohol followed by reaction with sodium azide afforded the azido compound **178** with inversion of configuration at this centre in good yield from our key intermediate **148**.



Scheme 56. *Reagents and conditions:* (a) TBAF, THF, 0 ˚C, 1h then r.t. 2 d, 92%; (b) MsCl, Et_3N, CH_2Cl_2, r.t., 16 h, 98%; (c) NaN_3, DMF, 80 ˚C, 2 d, 91%.

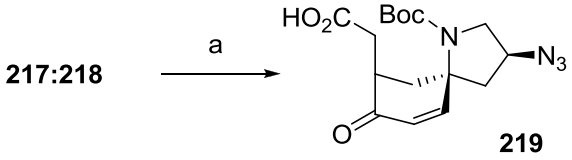
With successful formation of the more advanced enone **178**, installation of the side-chain was investigated. Thus enone **178** was treated with LDA to form the corresponding enolate, which upon reaction with ethylbromoacetate resulted in the isolation of a mixture of diastereoisomers in 21% yield in addition to the recovery of a substantial amount of starting material (41%) (scheme 57). We were pleased to observe that the desired axial ester **217** was the major product, formed in a 2.5:1 ratio to the equatorial isomer **218**. Although we were able to recover starting material (that could be recycled) from this reaction after purification, the yield of desired product was still low, and needed improvement. It is known that using an additive such as HMPA or DMPU in alkylation reactions of this type can improve yields,[69] and due to its reduced toxicity[70] the use of DMPU was investigated for our system. Pleasingly, the yield increased from 21% to 60% (in addition to the isolation of 20% of starting material that could again be recycled). Unfortunately the stereoselectivity of the reaction was reduced with isolation of the axial isomer **217** and the equatorial isomer **218** in a ratio of only 1:1.3 respectively. This was disappointing as we required the axial isomer in order for the key cyclisation step to proceed. In addition the mixture of diastereoisomers proved to be difficult to separate, and therefore the next step was performed on the mixture,

in anticipation of being able to separate them at a later stage.

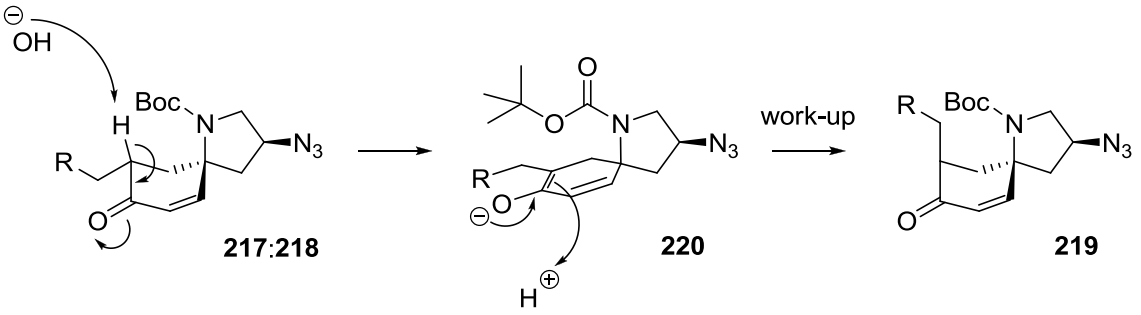


Scheme 57. *Reagents and conditions:* (a) LDA, THF, 1 h then $BrCH_2CO_2Et$, 4 h, **217** 15%, **218** 6%, **178** 41%; (b) LDA, THF, 1 h then $BrCH_2CO_2Et$ and DMPU, 4 h, **217** 26%, **218** 34%, **178** 20%.

Hydrolysis of the mixture of esters **217**:**218** was performed as a biphasic reaction using aqueous NaOH solution (2 M) and THF, and surprisingly we observed formation of the acid **219** as a single diastereomer (Scheme 58). We suspected that it would be the desired axial product as there appeared to be a plausible mechanism to explain this result (scheme 59). Using NaOH as a base could lead to the presence of the enolate **220** in the reaction mixture. Upon work-up, re-protonation of the enolate from the bottom face could be preferred, due to the bulky Boc group sterically shielding the top face. If this bias towards reprotonation from the bottom face was substantial then this would explain the exclusive presence of the axial isomer **219**.

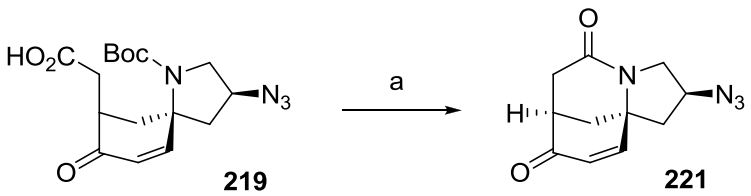


Scheme 58. *Reagents and conditions:* (a) NaOH (2M):THF (1:1), 2 d, 90%.



Scheme 59. Proposed mechanism of epimerisation

The key cyclisation step (which would only be possible with the axial isomer) was attempted. Boc deprotection of **219** followed by an intramolecular peptide coupling of the resultant free amine with the carboxylic acid, using DPPA and triethylamine in DMF afforded the desired tricyclic structure **221** in excellent yield (scheme 60). This provided further evidence that the carboxyl group was in the axial position.



Scheme 60. *Reagents and conditions:* (a) i. TFA, CH_2Cl_2, 1 h.; ii. DPPA, Et_3N, DMF, 2 h, 99% over 2 steps.

We were pleased to subsequently be able to confirm the structure of the tricycle **221** by X-ray crystallography (figure 5).

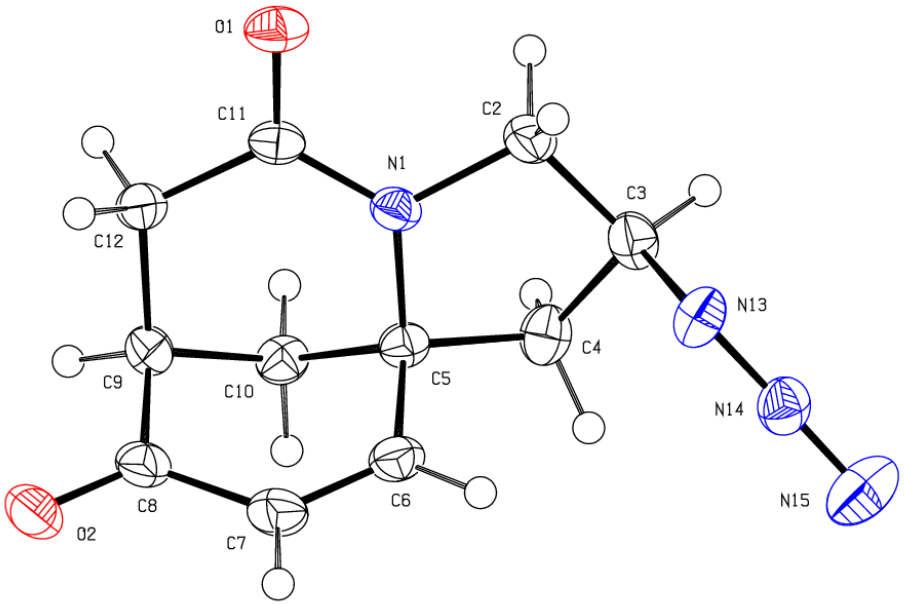
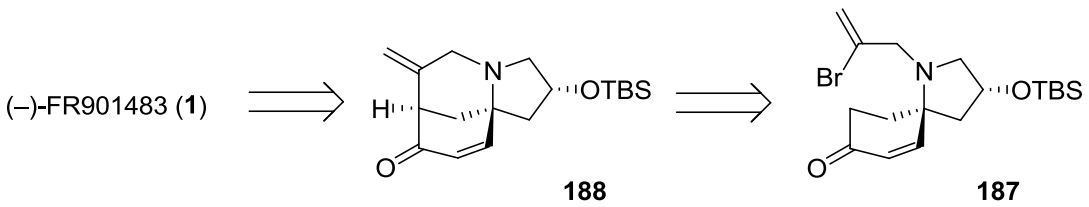


Figure 5. X-ray crystal structure of tricycle **221**

This study was really important as it showed that it was indeed possible to form the novel tricyclic structure **221** of (–)-FR901483 (**1**) using this methodology. However, it was not immediately obvious that it would be possible to install the *p*-methoxybenzyl (PMB) in a stereoselective manner at C(11). In addition, there were concerns about introducing the hydroxyl group at the C(12) position. We therefore decided to continue the work towards (–)-FR901483 (**1**) using an approach that had been developed previously within the Hayes group[58,64] and which perhaps had more chance of enabling us to complete the total synthesis. Some promising studies using this methodology had already been conducted when this decision was made.

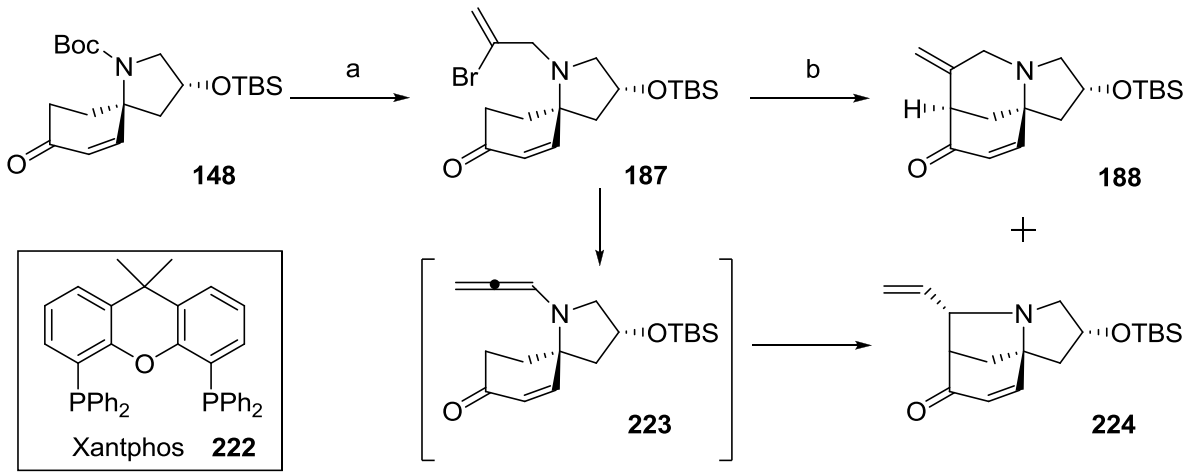
2.2.4 Palladium-catalysed cyclisation approach

The strategy previously employed within the Hayes group involved the use of a palladium-catalysed cyclisation to close the final ring of the tricycle.[58,64] Thus our new retrosynthesis involves disconnection of (–)-FR901483 (**1**) to the advanced tricycle **188**, product of the cyclisation of vinyl bromide **187** (Scheme 61). This cyclisation offers a significant advantage over the previous methodology (section **2.2.3**), as it should be relatively straightforward to form the ketone at the C(12) postion. This would subsequently enable installation of the PMB group at the C(11) position using enolate chemistry previously described by Funk[16] and in addition it should be trivial to convert the ketone into the required hydroxyl group.



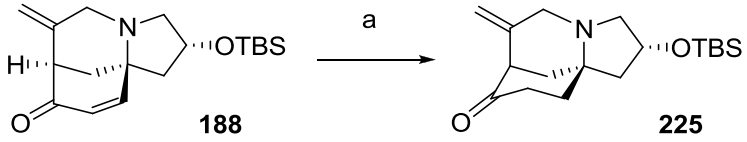
Scheme 61. Revised retrosynthetic analysis

Boc cleavage and *N*-alkylation of the resultant amine with 2,3-dibromopropene converted the key-intermediate **148** into the vinyl bromide **187**, precursor to the cyclisation step in good yield (scheme 62). Treatment with $Pd_2(dba)_3$ in the presence of Xanpthos (**222**) and KOPh (made *in situ* from phenol and KO^{t}Bu) afforded the desired tricycle **188** in reasonable yield, along with a significant amount of an unusual tricycle **224**. The formation of the latter can be explained by the palladium-catalysed cyclisation of an allene such as **223**, which had been previously observed by Asari during optimisation of this process.[64]



Scheme 62. *Reagents and conditions:* (a) TFA, CH_2Cl_2 then 2,3-dibromopropene, K_2CO_3, NaI, MeCN, 74%; (b) 10 mol% $Pd_2(dba)_3$, 20 mol% **222**, KO^{t}Bu/PhOH, THF, 4 h (**188**, 30-52% and **224**, 19-30% depending on the scale).

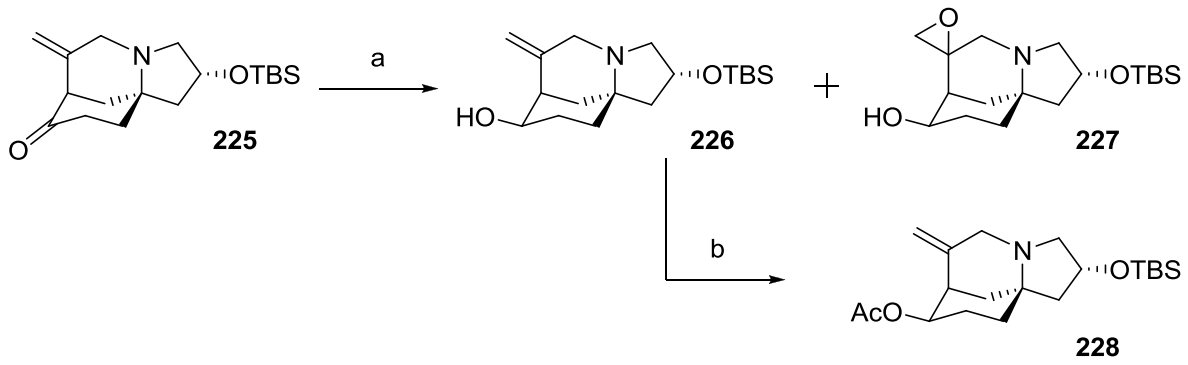
Having succeeded in forming a reasonable amount of the tricyclic core **188**, the next challenge was to move towards completing a total synthesis of (–)-FR901483 (**1**). The double bond of the enone had served its purpose as a blocking group (preventing cyclisation onto the undesired side of the ring) and was not needed anymore. It was successfully removed *via* a dissolving metal (Birch) reduction to give the desired keto-alkene **225** in good yield (scheme 63).[71]



Scheme 63. *Reagents and conditions:* (a) Li, NH_3, THF, 1h, 60%

The next key challenge in the synthesis was installation of the PMB group at the C(11) position. As discussed previously, the exocyclic double bond of **225** needs to be converted into the corresponding ketone in order for this to be plausible. Firstly, it was necessary to

protect the ketone at C(8) and to achieve this we decided to reduce it to the corresponding alcohol and then install a protecting group. This strategy would both remove the possibility of any selectivity issues during the introduction of the PMB group and form a more advanced intermediate in the synthesis of (–)-FR901483 (**1**). Reduction of the ketone of **225** with sodium borohydride afforded the alcohol **226** as a single diastereoisomer in good yield (scheme 64). This product was the result of axial attack by the reductant, although interestingly the use of L-selectride gave the same single diastereoisomer in comparable yield. Although the diastereoisomer **226** formed was opposite in configuration to that required, previous work on (–)-FR901483 (**1**) has shown that it is possible to invert this centre and install the phosphate ester in one step (section **1.3.1.2**).[7]

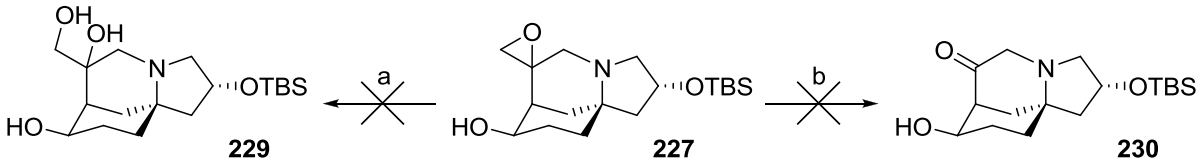


Scheme 64. *Reagents and conditions:* (a) $NaBH_4$, MeOH, 0 ˚C then r.t., 2 h, 86%; (b) Ac_2O:pyridine (1:1), 12 h, 78%.

The alcohol **226** was found to be quite unstable at room temperature and during the purification process an unexpected compound, tentatively assigned as the epoxy compound **227** was isolated on a number of occasions. In addition, protection of the alcohol **226** was not as straightforward as expected. Attempted benzyl or benzoyl protection led to complete recovery of starting material, whilst attempted TBS protection allowed isolation of only a

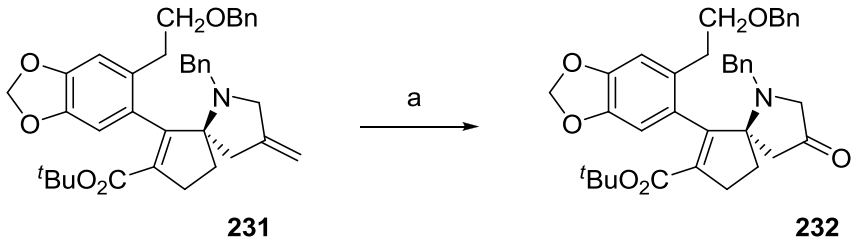
small amount of the desired product. Fortunately acetate protection proved to be reasonably efficient and afforded **228** in 56% over two steps from ketone **225**.

The formation of this epoxy compound **227** remains unexplained. Epoxidation of a double bond in air is known, but requires the presence of a metal (e.g. Co, Mo, Ag)[72-74] so it is difficult to understand how this could occur under the reaction conditions applied. We did, however try to render this material useful for our synthesis by investigating its conversion into the desired ketone **230** directly[75] or to the intermediate diol **229** (scheme 65).[76] Unfortunately, attempted opening of the epoxide **227** proved to be impossible, even under forcing conditions, which prevented it being useful to the synthesis. Its formation was for us only proof of the high reactivity of the double bond.



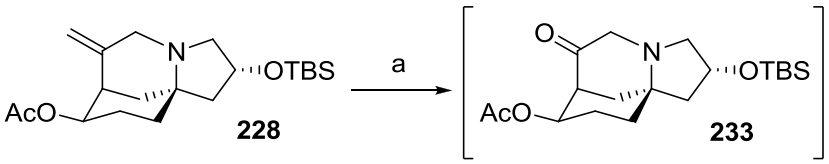
Scheme 65. *Reagents and conditions:* (a) 5% $HClO_4$ (aq.), THF[76] or NaOH (1M), acetone or H_2SO_4 (2M), MeCN; (b) $NaIO_4$, H_5IO_6, THF/H_2O (10/1), r.t.[75]

With the suitably protected alkene **228** in hand, the next step was to convert it into the corresponding ketone. This type of transformation could be achieved *via* ozonolysis, but might not be compatible with the presence of a tertiary amine, which could oxidise under the reaction conditions to form a *N*-oxide. A procedure reported by Mariano in a formal synthesis of Cephalotaxine employed a similar transformation to the one we required, where the tertiary amine was protected as an ammonium salt (scheme 66).[77]



Scheme 66. *Reagents and conditions:* (a) $HClO_4$, O_3, CH_2Cl_2:MeOH then DMS, 63%.[77]

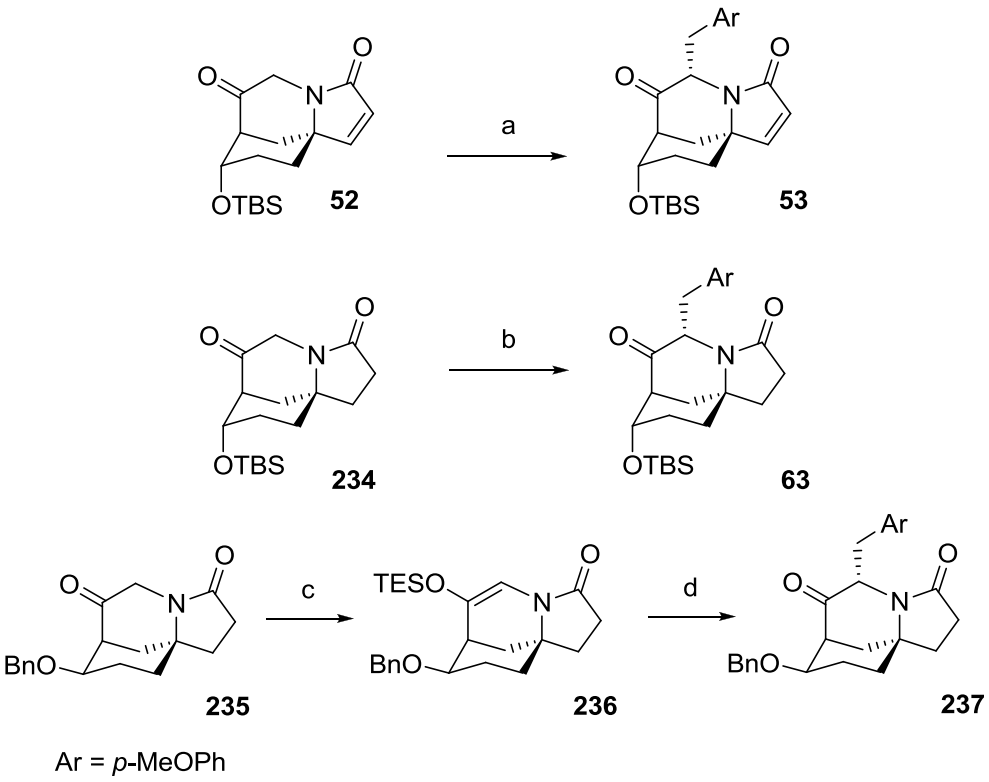
This method was applied to our substrate **228** and pleasingly we did indeed obtain our desired ketone **233** (scheme 67). The yield had to be estimated by analysis of the ^{1}H NMR spectrum of the crude reaction mixture as the ketone appeared to be highly unstable and purification by silica gel chromatography was not possible. In addition the ketone **233** could not be stored and was used immediately in the next step of the synthesis.



Scheme 67. *Reagents and conditions:* (a) $HClO_4$, O_3, CH_2Cl_2:MeOH (1:2) then DMS, 90% (based on analysis of ^{1}H NMR spectrum of crude reaction mixture).

The key alkylation of ketone **233** to install the PMB group could now be investigated. Although in previous work towards (–)-FR901483 (**1**), most research groups had installed the PMB group early on in the synthesis, there are a few examples where it was installed at a late stage. In Funk's route to (–)-FR901483 (**1**),[16] ketone **52** was treated with KO^{t}Bu and the resultant enolate reacted with *p*-methoxybenzylbromide to afford the PMB alkylated compound **53** (a, scheme 68). Fukuyama applied a very similar approach to his advanced substrate **234**, which only differed by the use of KHMDS as a base for the initial

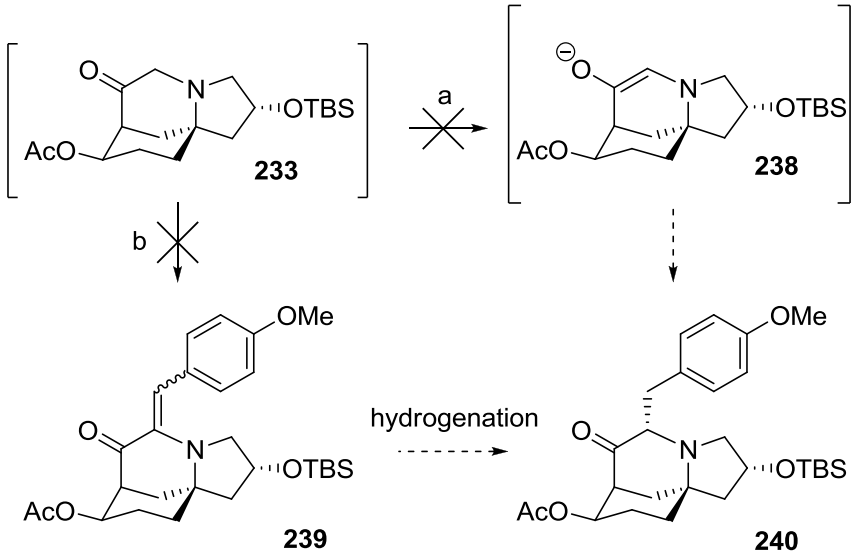
deprotonation (b, scheme 68).[17,18] Wardrop employed a stepwise procedure to achieve the same transformation, where the enolate of **235** was trapped as silyl enol ether **236**, which was then alkylated with *p*-methoxybenzylbromide in the presence of $ZnCl_2$ (c and d, scheme 68).[24] Based on this amount of literature precedent we were confident that the installation of the PMB group in our substrate would be possible.



Scheme 68. *Reagents and conditions:* (a) KO^{t}Bu, THF then *p*-MeOBnBr, DMF, 97%;[16] (b) KHMDS, TMEDA then *p*-MeOBnBr, THF, -78 ˚C to r.t., 64%;[17,18] (c) KHMDS, TESCl, THF, -50 ˚C, 15 min; (d) *p*-MeOBnBr, $ZnCl_2 \cdot Et_2O$, Et_2O, -78 ˚C to -25˚C, 16 h, 68% over 2 steps.[24]

Therefore the crude ketone **233** was firstly treated with KO^{t}Bu (in an attempt to form enolate **238**) and then *p*-methoxybenzylbromide was added (Scheme 69). Unfortunately a mixture of degradation products was isolated from this reaction and formation of the desired product **240** was not observed. The process was repeated using KHMDS as the base, but again only degradation of the starting material was observed. Attempts to form enolate **238** and

subsequently trap it as a silyl enol ether were also unsuccessful. A final effort to install the PMB group involved attempting an aldol condensation of **233** with *p*-methoxybenzaldehyde, but unfortunately once again only degradation of the ketone **233** was observed.

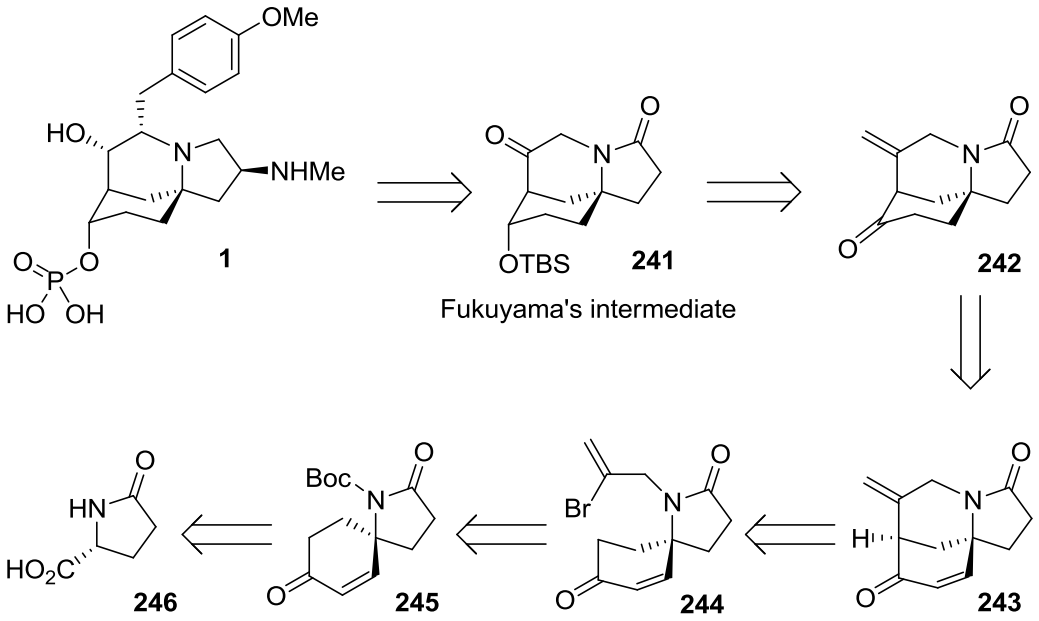


Scheme 69. *Reagents and conditions:* (a) KHMDS or KO^{t}Bu, TMEDA, THF then *p*-MeOBnBr or KHMDS, then TESCl, then *p*-MeOBnBr, $ZnCl_2$; (b) *p*-methoxybenzaldehyde, KOH, MeOH.

Given the similarity of our substrate with previous precedence in the literature, it was disappointing not to be able to obtain the desired product **240**. It may simply be that the innate instability of the starting ketone **233** caused it to decompose under the reaction conditions. The major difference between this compound and the substrates reported to undergo this transformation is that it contains a tertiary amine instead of an amide moiety.[16-18,24] This difference could contribute to explaining the problem with stability that we encountered with ketone **233** and led us to reconsider our retrosynthesis.

2.2.5 Amide series approach

At this point in the project, we reviewed previous work on (–)-FR901483 (**1**) and reflected on what we had learnt whilst working on our different routes. This led us to realise that it might be possible to rapidly reach one of the intermediates in Fukuyama's synthesis[17-18] of (–)-FR901483 (**1**) using chemistry that was developed within the Hayes group. The new retrosynthetic analysis is shown below (scheme 70).

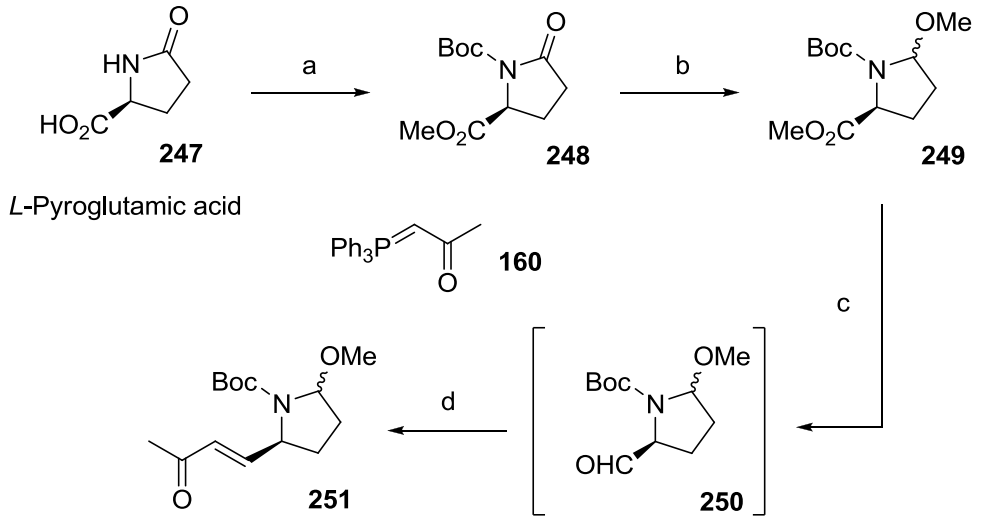


Scheme 70. Revised retrosynthetic analysis

Fukuyama's intermediate **241** could be accessed from the terminal alkene **242** *via* similar transformations to those previously utilised in the tertiary amine series (section **2.1**). This alkene **242** could result from a dissolving metal reduction of enone **243**. The key step in this route would involve a regioselective palladium-catalysed alkenylation of the 5,6-spirocyclic enone **244** to afford **243**, the tricyclic core of our target molecule. The Hayes group has previously developed a method to synthesise 5,6-spirocycles (comparable to **245**), which

contain a quaternary stereocentre next to nitrogen, *via* an alkylidene carbene 1,5-CH insertion. Thus *D*-pyroglutamic acid **246** would be an ideal chiral pool starting material; however the much cheaper *L*-pyroglutamic acid **247** was used for preliminary model studies.

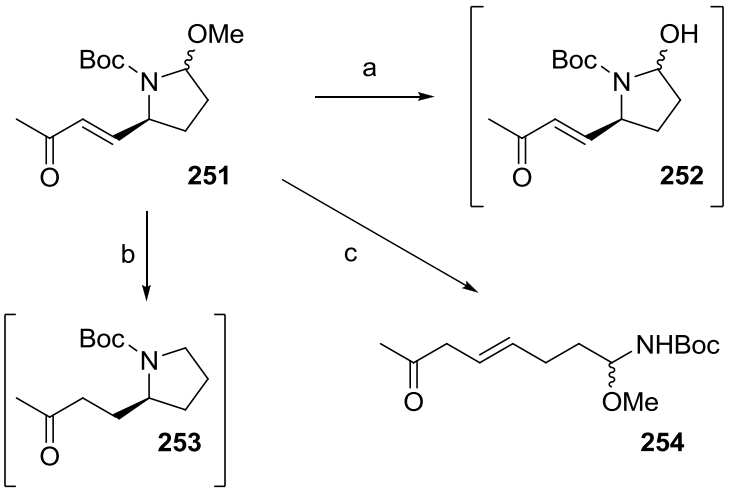
The preliminary protection steps were carried out smoothly following a literature procedure reported by Aggarwal[78] to afford ester **249** (scheme 71). The sequence involved esterification of **247** and protection of the amide as a methyl aminal (after Boc protection of the amide and reduction of the carbonyl group). Protection of the amide was necessary in order to avoid any potential problems with this functionality in some of the steps of the synthesis, which would require strong base. One minor change to Aggarwal's procedure was made,[78] which involved the use of L-selectride in place of lithium triethylborohydride (super hydride) for the reduction. The reaction proceeded in comparable yield to that reported.[78]



Scheme 71. *Reagents and conditions:* (a) i. $SOCl_2$, MeOH, 2 h; ii. Boc_2O, DMAP, MeCN, 3 h, 50% over 2 steps; (b) i. L-selectride, THF, -78 °C, 2 h; ii. PTSA, MeOH, 20 h, 66% over 2 steps; (c) DIBAL-H, CH_2Cl_2, -78 ˚C, 3 h then MeOH, 1 h; (d) **160**, CH_2Cl_2, 4 d, 76% over 2 steps.

Reduction of ester **249** to the corresponding aldehyde **250** was achieved smoothly using

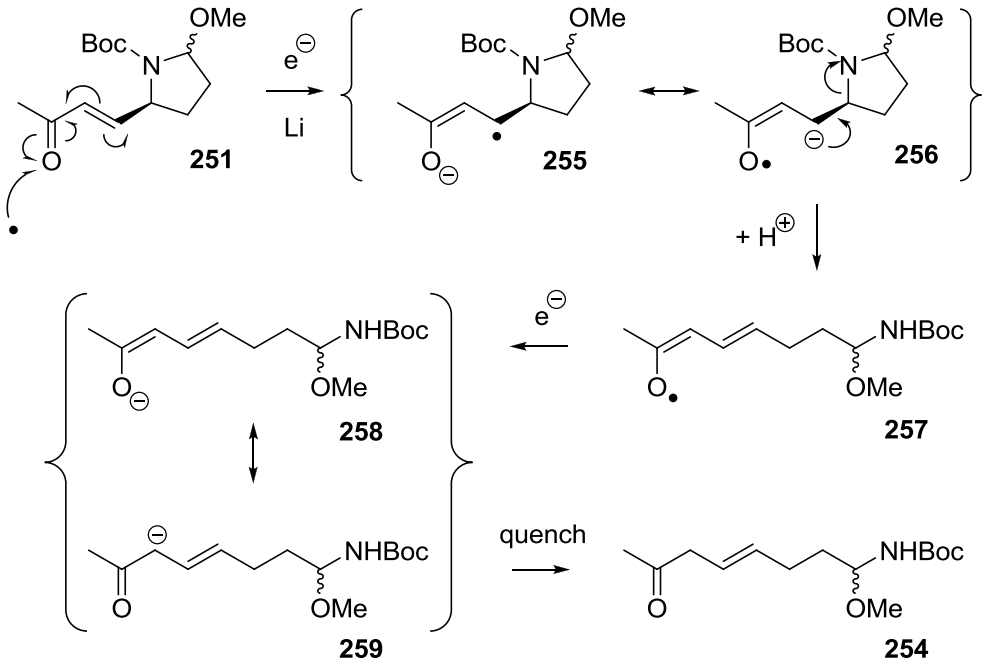
DIBAL-H, and was followed by a subsequent Wittig reaction with 1-triphenylphosphoranylidene-2-propanone **160**, which gave the enone **251** in good yield. The yield of the Wittig reaction was greatly improved (and the reaction time shortened) when it was performed at high concentration. The 1,4-reduction of the enone **251** appeared to be more complicated than was first envisaged. Under normal hydrogenation conditions using palladium over carbon as a catalyst, the ^{1}H NMR spectrum of the crude reaction mixture indicated that both reduction of the double bond and hydrolysis of the aminal had occurred to give **252** (scheme 72). We thought that the slight acidity of this catalyst could offer an explanation for this result and therefore we tried employing palladium hydroxide instead. Unfortunately in this case, the aminal moiety was reduced completely to afford the corresponding amine **253**, as confirmed by interpretation of the ^{1}H NMR spectrum of the crude reaction mixture.



Scheme 72. *Reagents and conditions:* (a) H_2, Pd/C, EtOAc, 12 h; (a) H_2, $Pd(OH)_2$, EtOAc, 12 h; (b) Li, NH_3, THF, -78 °C, 68%.

A dissolving metal (Birch) reduction was also attempted, but this resulted in the isolation of an acyclic product **254**, derived from opening of the pyrrolidine ring. There is a plausible

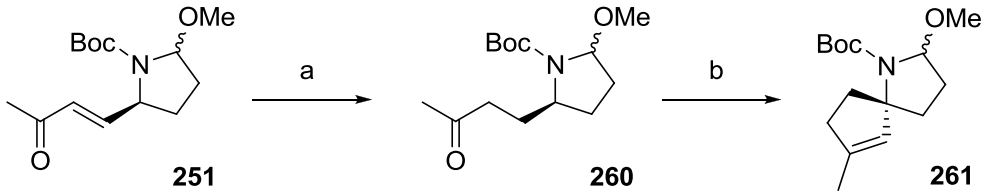
mechanism, which could explain the formation of this novel compound **254** (scheme 73). Electron addition to enone **251** would form the radical anion **255**, from which the pyrrolidine ring can be opened to afford the diene **257** after protonation of the amine. Addition of another electron would form the enolate species **258** and subsequent quenching of the anion *via* protonation would lead to the formation of the β,γ-unsaturated ketone **254**.



Scheme 73. Proposed mechanism for opening of the pyrrolidine ring *via* Birch reduction

After further attempts (use of DIBAL-H, L-selectride, Raney Nickel) where mostly starting material was recovered, we employed the use of sodium dithionite (sodium hydrosulfite: $Na_2S_2O_4$) in water and dioxane.[79] Pleasingly we were actually able to isolate the desired product **260** although the yield was poor (scheme 74). This provided some optimism that the transformation was possible on our substrate and eventually conditions were found, which provided the reduced product **260** in quantitative yield. This involved hydrogenation of enone **251** using a palladium over carbon catalyst again, but critically a few drops of pyridine were

added to the reaction mixture. Presumably the use of slightly basic conditions for the hydrogenation was important for the stability of the aminal protecting group.

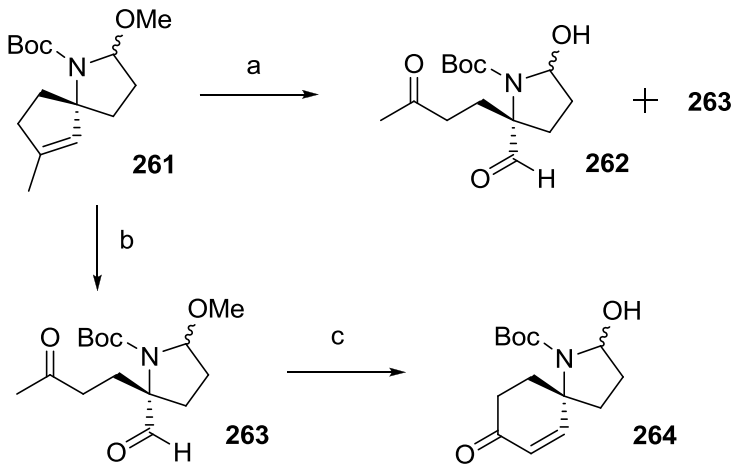


Scheme 74. *Reagents and conditions:* (a) H_2, Pd/C, pyridine, EtOAc, quantitative or $Na_2S_2O_4$, H_2O, dioxane, 26%; (b) $TMSCHN_2$, ^nBuLi, THF, -60 °C to r.t., 79%.

The next step was the alkylidene carbene insertion to form 5,5 spirocycle **261**, which was achieved using lithiated trimethylsilyldiazomethane in good yield (scheme 74). The use of KHMDS for the 1,5-CH insertion was not investigated as it required an additional step.

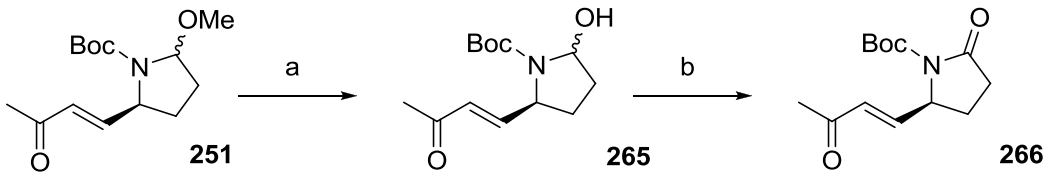
The ring expansion of spirocycle **261** was conducted using a similar oxidative cleavage/aldol reaction/dehydration sequence to that described previously for the amine series (section **2.1**). The dihydroxylation proceeded without complication using potassium osmate and *N*-methylmorpholine-*N*-oxide. Cleavage of the resulting diol was less straightforward and use of sodium periodate gave a mixture of products (scheme 75). The major product was indeed a keto aldehyde (**262**), but demethylation of the aminal protecting group had occurred and the desired keto-aldehyde **263** was isolated only in low yield. In order to avoid this unwanted side reaction, we attempted the diol cleavage using lead tetraacetate in dry CH_2Cl_2 and pleasingly this afforded the desired product **263** in good yield from the 5,5-spirocycle **261**. Aldol reaction of the keto-aldehyde **263** using potassium hydroxide, followed by mesylation of the resultant alcohol and subsequent elimination gave the desired 5,6-spirocyclic enone **264**. Pleasingly, and perhaps not that surprisingly after the observations of its high acid

lability, the aminal was hydrolysed during simple purification on silica gel.



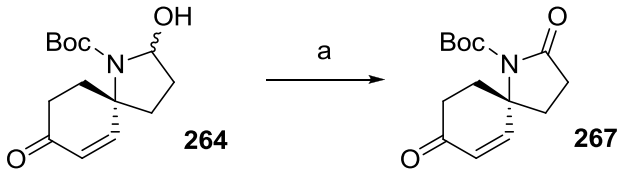
Scheme 75. *Reagents and conditions:* (a) i. $K_2OsO_4.2H_2O$, NMO.H_2O, acetone:H_2O (10:1), 4 d, 93%; ii. $NaIO_4$, THF:H_2O (2:1), 1 h, **262**, 69% and **263**, 16%; (b) i. $K_2OsO_4.2H_2O$, NMO.H_2O, acetone:H_2O (10:1), 4 d, 93%; ii. $Pb(OAc)_4$, CH_2Cl_2, 10 min, 90% (based on analysis of ^{1}H NMR spectrum of crude reaction mixture); (c) i. KOH, EtOH, 0 ˚C, 1.5 h; ii. MsCl, Et_3N, CH_2Cl_2, 0 ˚C - r.t., 3 d, 18% over 3 steps.

The challenge now was to re-oxidise the aminal **264** into the corresponding amide. For this purpose, a model study was undertaken on a less advanced intermediate **251**, which was similar in term of key functionalities (i.e. presence of the enone moiety). Firstly the aminal **251** was hydrolysed with a simple acidic wash (HCl 2M) to give **265** (scheme 76). From here use of the Collins oxidation[80] (preparation of the CrO_3·(pyridine)$_2$ complex *in situ*) according to the procedure of Katsuo[81] afforded only a small amount of the desired amide **266**. However pleasingly the use of pyridinium chlorochromate (PCC)[82] in dry CH_2Cl_2 as reported by Burke[83] was more efficient and the desired amido-enone **266** was obtained in 60% yield.



Scheme 76. *Reagents and conditions:* (a) HCl wash, 84%; (b) CrO_3, pyridine, Ac_2O, CH_2Cl_2, 4 Å molecular sieves, 26% (50% based on recovered SM) or PCC, CH_2Cl_2, 4 Å molecular sieves, 20 h, 59%.

We therefore applied these conditions (PCC in dry CH_2Cl_2) to the advanced substrate **264**, and pleasingly obtained the key 5,6-spirocyclic intermediate **267** in good yield (scheme 77). This intermediate was a colourless solid and it was possible to confirm the structure by X-ray crystallography (figure 6).



Scheme 77. *Reagents and conditions:* (a) PCC, CH_2Cl_2, 4 Å molecular sieves, 20 h, 62%.

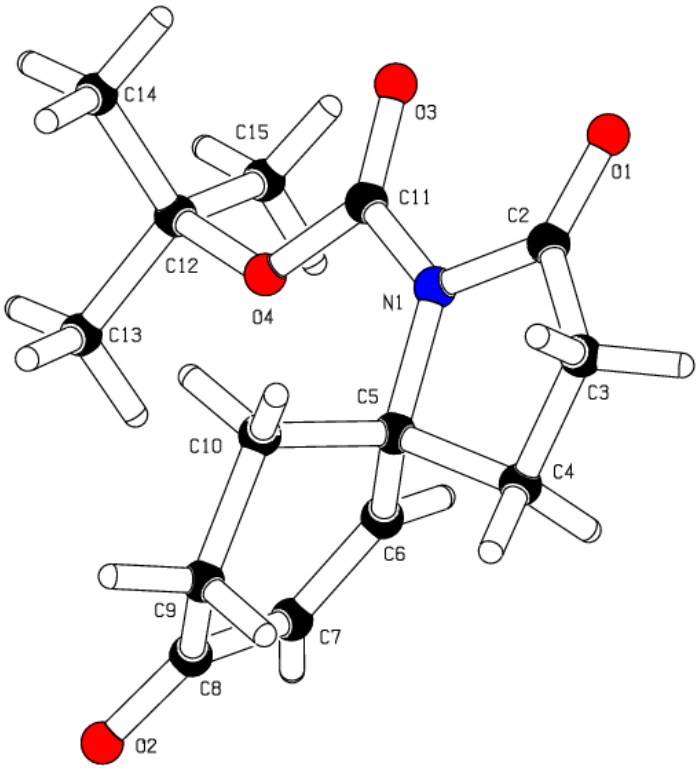
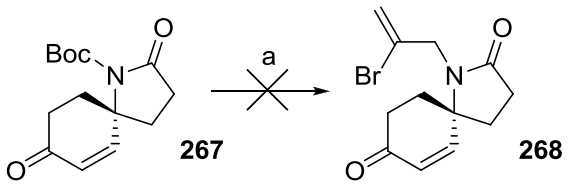


Figure 6. X-ray crystal structure of key intermediate **267**

We had now reached the key intermediate **267** in our synthesis in an overall yield of 2% over 11 steps. The next challenge was to investigate a palladium-catalysed alkenylation reaction for closing the last ring of the tricyclic structure and to subsequently complete a formal synthesis of (–)-FR901483 (**1**) by reaching Fukuyama's intermediate **241**.[17-18]

The first step towards achieving this goal was to alkylate the Boc-deprotected 5,6-spirocycle **267** in order to form the vinylbromide **268**, precursor to the cyclisation step. Therefore after removal of the Boc group in acidic conditions, the resulting TFA salt was treated with sodium hydride and 2,3-dibromopropene.[84] Unfortunately, only a complex mixture of products was observed, with no indication of formation of the desired compound **268** (scheme 78). A

variety of different bases were employed, for the alkylation step (including KO^{t}Bu and NaOH) but unfortunately no more than a trace of the desired product **268** was ever obtained.

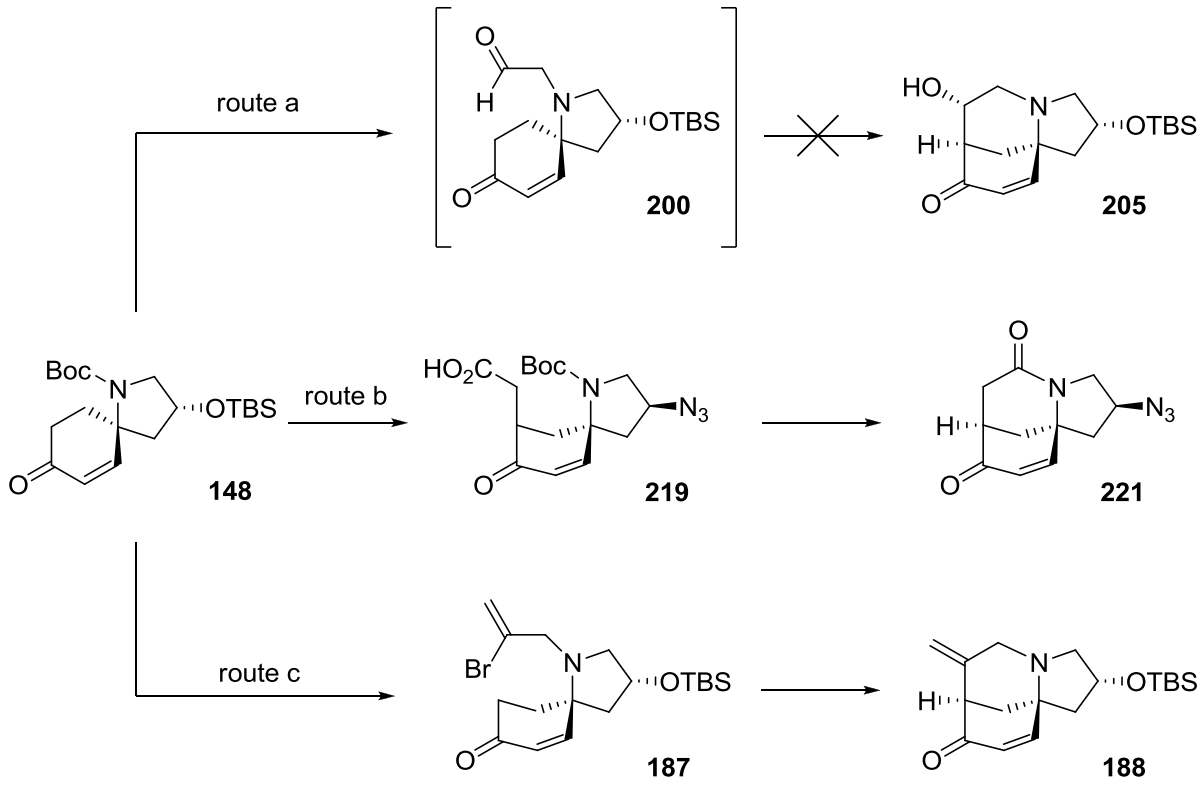


Scheme 78. *Reagents and conditions:* (a) i. TFA, CH_2Cl_2; ii. 2,3-dibromopropene, NaH, DMF or 2,3-dibromopropene, TBAB, NaOH (2M), EtOAc or 2,3-dibromopropene, KO^{t}Bu, THF.

It was really disappointing to have reached this key-intermediate **267** and not be able to alkylate to afford the desired vinyl bromide. This was particularly frustrating as we could not attempt the key palladium-catalysed alkenylation.

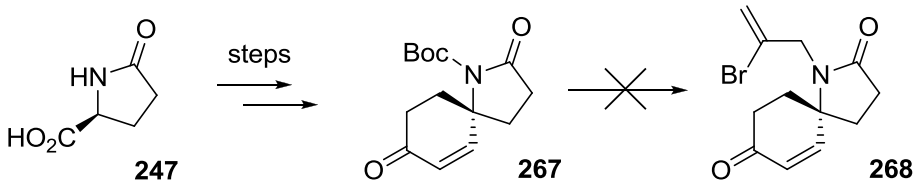
2.2.6 Summary of progress made towards (–)-FR901483 (1)

From *cis*-4-hydroxy-*L*-proline, the key 5,6-spirocyclic intermediate **148** was synthesised, using a 1,5-CH insertion of an alkylidene carbene as the key step, in good yield and on a multigram scale. Our initial hypothesis was that the presence of the enone functionality in **148** would enable a regioselective aldol reaction to be employed to close the final ring of the tricyclic core **205** of (–)-FR901483 (**1**).Unfortunately the apparent innate reactivity of the double bond, which we had hoped would act as a blocking group, prevented this from being possible (route a, scheme 79).



Scheme 79. Summary of progress towards (–)-FR901483 (**1**)

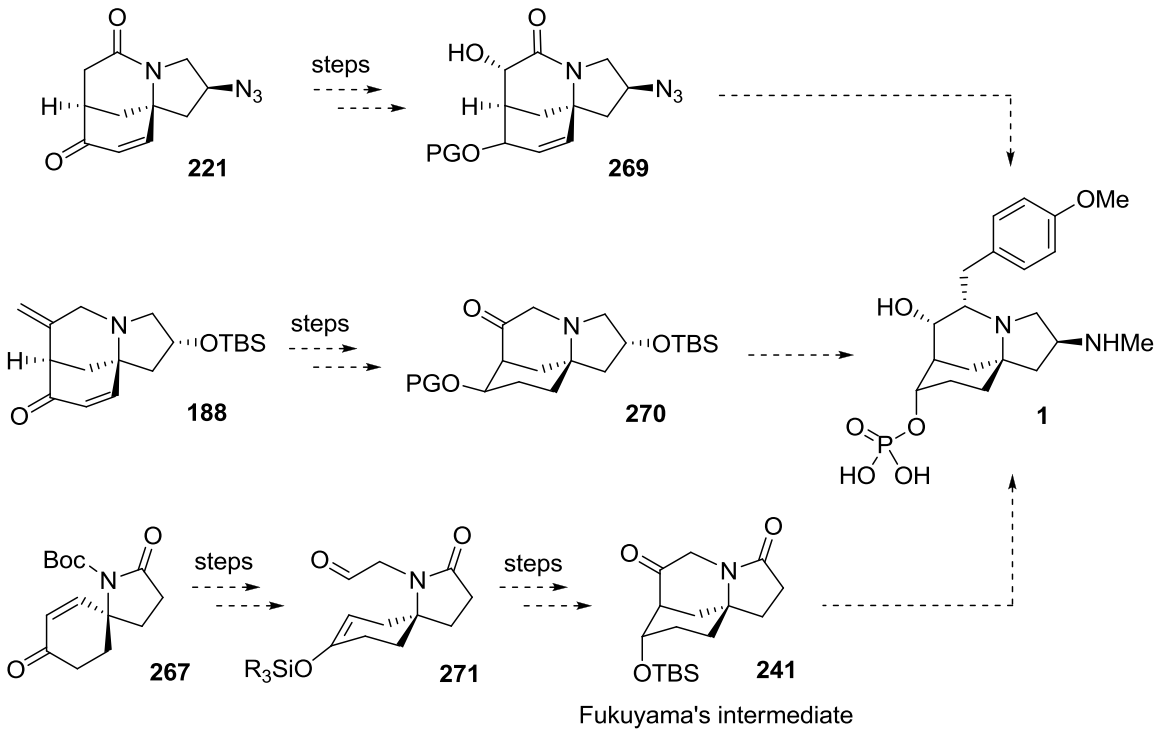
Revision of our retrosynthesis led to the proposal that the final ring could be formed *via* an intramolecular peptide coupling of amino acid **219** derived from the key intermediate **148** (route b, scheme 79). Pleasingly, this route did indeed lead to formation of the tricyclic core **221** of (–)-FR901483 (**1**) in excellent yield and with excellent stereoselectivity. Having shown that it was possible to form the tricyclic core, in order to move forward towards a total synthesis, a new route was envisaged. This involved a key palladium-catalysed cyclisation of vinyl bromide **187**, derived from alkylation of the key intermediate **148** (route c, scheme 79). Indeed this methodology was successful and the tricyclic core **188** of (–)-FR901483 (**1**) was again constructed. Unfortunately, problems with the stability of compounds later in this synthesis, and failure to install the key PMB side-chain led us to regretfully abandon this route. In the final approach, it was thought that use of a palladium-catalysed alkenylation reaction of *N*-alkylated **268** would allow rapid access to a key intermediate in Fukuyama's synthesis of (–)-FR901483 (**1**) (scheme 80).[17,18] Unfortunately, the formation of the precursor **268** to this key step was not possible and therefore disappointingly we were not able to investigate this route any further.



Scheme 80. Summary of amide series approach towards (–)-FR901483 (**1**)

2.2.7 Future work towards completing the synthesis of (–)-FR901483 (1)

From the work presented thus far we can envisage moving forwards towards completing a total synthesis of (–)-FR901483 (**1**) in several different ways. From the tricycle **221**, formation of the hydroxy intermediate **269** could be realised *via* α-hydroxylation (scheme 81). From this point, installation of the side-chain should be possible, and (–)-FR901483 (**1**) should subsequently be attained after a few straight forward transformations. Alternatively, if the problems with stability of the ketone derived from **188** could be overcome, perhaps by modifying its structure slightly, it should be simpler to introduce the PMB group. Subsequent introduction of the amine functionality and inversion of stereochemistry at the hydroxyl group in order to finish the synthesis, are well described in the literature.[2,7]



Scheme 81. Possible future work

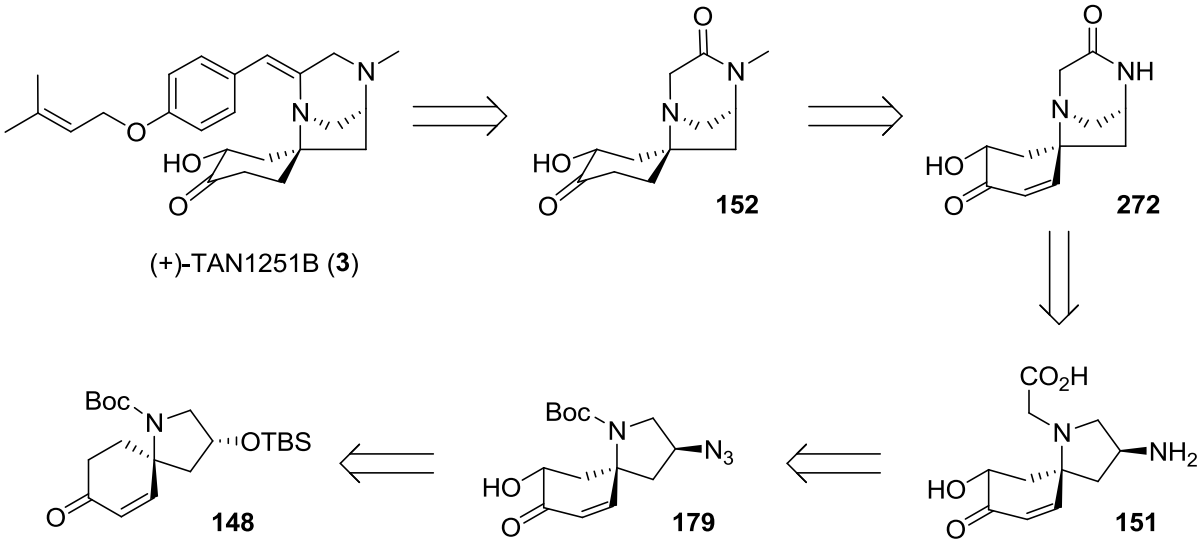
For a formal synthesis of (–)-FR901483 (**1**), Fukuyama's key intermediate **241** could be reached.[17-18] Although attempts at achieving this within this thesis were unsuccessful, we can envisage another route to this intermediate **241**. Starting with the amide intermediate **267**, transformation of the enone to the silyl enol ether **271** could be followed by an aldol cyclisation. This would form the tricyclic core of (–)-FR901483 (**1**), and only a few subsequent steps would be required to reach Fukuyama's intermediate **241**.[17-18]

2.3 Progress towards the total synthesis of (+)-TAN1251B (3)

The next part of this thesis will present the progress made from our key 5,6-spirocyclic enone intermediate **148** towards the total synthesis of (+)-TAN1251B (**3**). Installation of the hydroxyl group adjacent to the ketone is the main challenge of this synthesis.

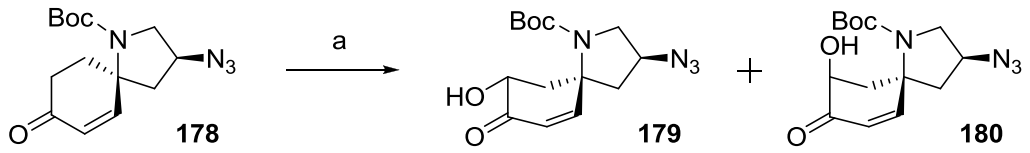
2.3.1 Enantioselective *α*-hydroxylation to the ketone

As described previously, (+)-TAN1251B (**3**) could be accessed from the advanced tricycle **152** (scheme 82), where the side chain would be installed using a similar method to that used by Auty in his synthesis of (–)-TAN1251A.[56] This tricycle would result from simple chemical transformations of tricycle **272**, which could be accessed by cyclisation of amino acid **151**. This amino acid **151** can be formed from the *N*-Boc protected azido compound **179**. This then makes our main synthetic challenge the *α*-hydroxylation of the key intermediate ketone **148**.



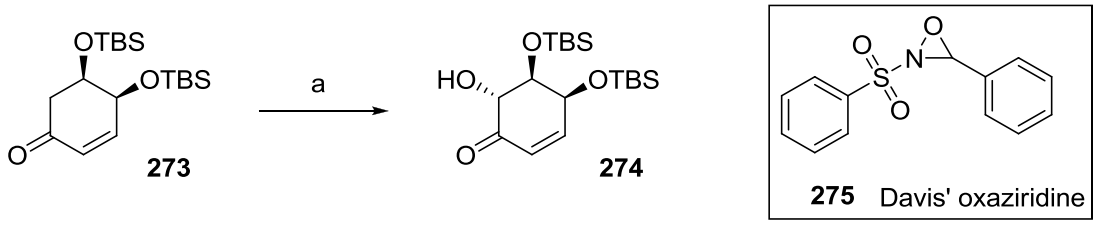
Scheme 82. Retrosynthetic analysis of (+)-TAN1251B (**3**)

From the common intermediate **148**, inversion of stereochemistry at C(3) with installation of the azido group to afford enone **178** was realised as described previously in the work towards (–)-FR901483 (**1**) (scheme 56, p. 60). Although numerous methods exist for the preparation of simple α–hydroxy ketones,[85] methods for the preparation of α–hydroxy enones, particularly in a stereoselective manner are less common. However, the presence of the double bond in our intermediate should offer an advantage in this transformation by blocking one site where the hydroxylation could take place. Previous work in this area by Asari[58,59] during her studies towards (+)-TAN1251B (**3**) used a method inspired by Moriarty's work.[86-88] Treatment of the substrate **178** with iodosobenzene disappointingly afforded a mixture of diastereoisomers **179** and **180** in a 79% combined yield and a 1:1.2 ratio respectively (scheme 83). In addition Asari found that the two diastereoisomers were difficult to separate by column chromatography and hence it was almost impossible to isolate a sufficient amount of the correct stereoisomer in order to proceed with the synthesis.



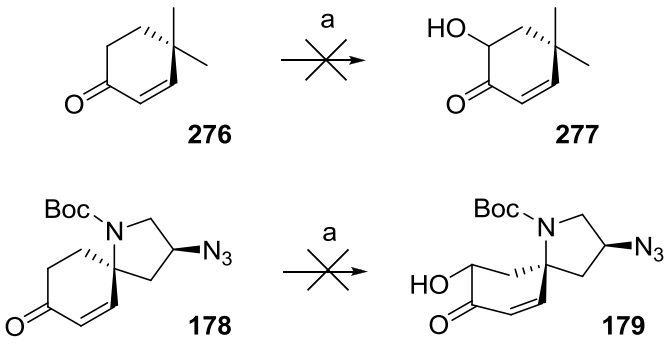
Scheme 83. *Reagents and conditions:* (a) PhIO, NaOH, MeOH 0 °C, 3 h, **179**, 36% and **180**, 43%.

This method was not satisfactory and as a key step in the synthesis, we were keen to improve on Asari's initial result. O'Brien[89] reported that treatment of the enolate derived from a cyclic enone **273** with Davis' oxaziridine **275**[90] led to the formation of a single diastereoisomer of the hydroxy ketone **274** in excellent yield (scheme 84). It was postulated that the high degree of stereoselectivity arose from attack of the enolate onto the oxaziridine occurring *trans* to the bulky TBS groups.



Scheme 84. *Reagents and conditions:* (a) NaHMDS, THF, -78 °C, 30 min then **275**, 91%.[89]

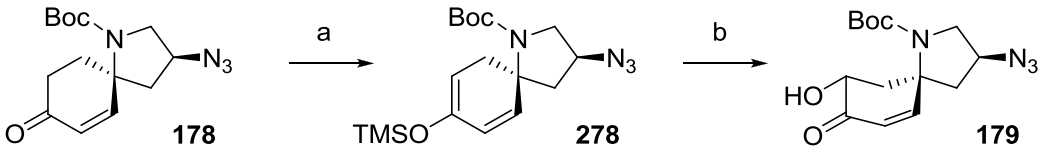
We thought that we could apply this methodology to our system and made the hypothesis that the bulky Boc group could influence the stereochemical outcome of the reaction in an analogous manner to the TBS groups in O'Brien's system.[89] Initially we used a model cyclic enone **276** and were disappointed to find that in our hands this method did not result in the isolation of any of the desired *α*-hydroxy enone **277** (scheme 85). We used a variety of bases to form the enolate (KHMDS, LiHMDS, LDA) but only ever recovered the starting material **276**. We did attempt the reaction on our real substrate **178**, but unsurprisingly it failed to provide any of the desired product **179**.



Scheme 85. *Reagents and conditions:* (a) base, THF, -78 °C, 30 min then **275**.

An alternative method for the formation of *α*-hydroxy enones involves the trapping of the enolate as a silyl enol ether, followed by treatment with an oxidant such as *m*-CPBA, OsO_4 or

DMDO.[91-93] One possible limitation of this transformation is that it can often occur with little stereoselectivity. However, we decided to employ these conditions[93] to our key substrate **178**. Thus, the enone **178** was treated with LDA to form the corresponding enolate, which was then trapped using trimethylsilylchloride to give the desired silyl enol ether **278** in good yield after purification on silica gel (scheme 86). Treatment of this intermediate **278** with DMDO led to the formation of a single compound in excellent yield.



Scheme 86. *Reagents and conditions:* (a) TMSCl, LDA, THF, -78 °C, 4 h, **278**, 72%, **178**, 24%; (b) DMDO, acetone, -78 °C, 20 min, 97%.

The product **179** was crystalline and we were able to confirm that it was the desired pseudo-equatorial alcohol by X-ray crystallography (figure 7). We postulated that the high degree of diastereoselectivity could be explained by the bulky Boc group sterically blocking the top face of the molecule. This would force the attack of DMDO to occur from the bottom face, resulting in formation of the pseudo equatorial product. This was a really pleasing result and represented a significant improvement to the method used previously by Asari.[58,59]

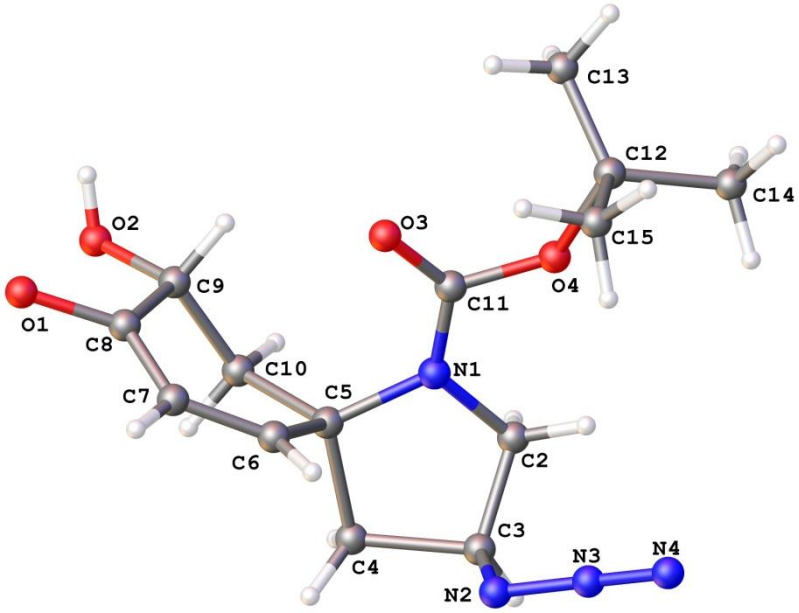
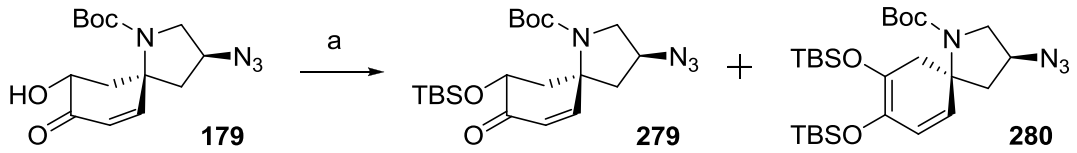


Figure 7. X-ray crystal structure of key intermediate **179**

2.3.2 Formation of the tricyclic core of (+)-TAN1251B (3)

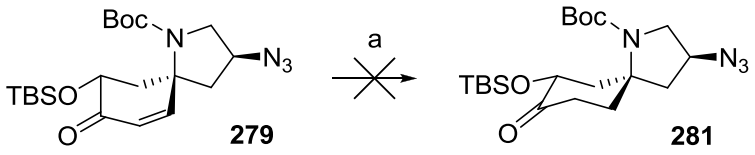
With the desired hydroxy ketone **179** in hand, the next challenge was to close the final ring to obtain the tricyclic core structure of (+)-TAN1251B (**3**). Initially the alcohol was protected with a TBS group, chosen to be compatible with the conditions proposed for the rest of the synthesis. Treatment of the hydroxy ketone **179** with TBSCl and imidazole afforded the desired product **279** in a moderate 60% yield (scheme 87). However the use of TBS triflate and 2,6-lutidine afforded the TBS protected alcohol in 87% yield. Unfortunately when the reaction was scaled up to 500 mg (initially a 50 mg scale was employed), we observed formation of the undesired doubly TBS-protected compound **280**. This compound is presumably a result of attack of the TBS triflate by the lone pair of the carbonyl and

subsequent removal of the acidic proton alpha to it. This side-product **280** was formed in a 25% yield, and the isolated yield of our desired product **279** was reduced to 53%.



Scheme 87. *Reagents and conditions:* (a) TBSCl, imidazole, DMF, 60% or TBSOTf, 2,6-lutidine, CH_2Cl_2, 2 h, -78 °C, **279**, 87%-53%, **280**, 0-25% depending on scale.

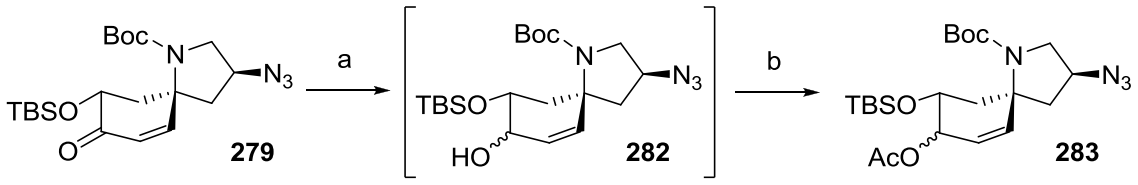
However, we still managed to isolate enough material to pursue our synthesis of the cyclisation precursor. It was therefore decided to move on with the synthesis and re-optimise this step at a later point. The next transformation required reduction of the double bond, which had served its purpose in the regioselective hydroxylation, whilst keeping the azido (masked amine) group intact. Unfortunately, it proved almost impossible to reduce the double bond without reducing the azido group. One example reported in the literature,[94] where this chemoselectivity had been possible, employed Wilkinson's catalyst in a homogeneous catalysed hydrogenation. We therefore applied this method to our substrate **279**, but this unfortunately resulted in complete recovery of starting material (scheme 88). Even at higher pressures of hydrogen no conversion was observed.



Scheme 88. *Reagents and conditions:* (a) $RhCl(Ph_3P)_3$, benzene, H_2 (10 bars), 1 d.

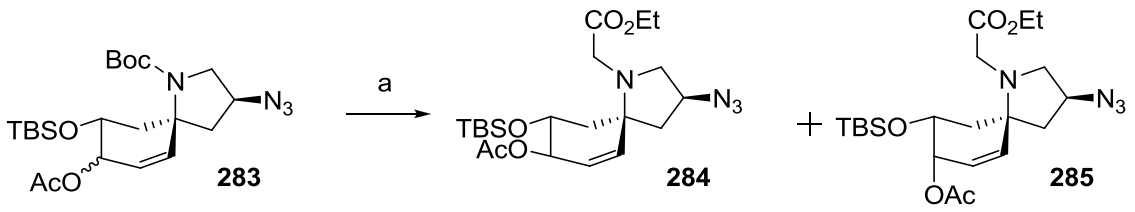
Based on the difficulties in achieving this chemoselective reduction, it was decided to

investigate reducing the double bond in addition to the azide later in the synthesis, when it was necessary to unmask the amine. Therefore, the next step was now to protect the enone functionality of **279** in preparation for the key cyclisation step. Attempts to convert the enone **279** into its acetal were unsuccessful, so instead it was envisaged that ketone **279** could be reduced to the corresponding alcohol and protected. Treatment of ketone **279** with L-selectride afforded the desired product **282** as a mixture of diastereoisomers in a 1:5 ratio (scheme 89). The major diastereoisomer was thought to be the pseudo-equatorial isomer, but since the alcohols would be re-oxidised to the ketone at a later point in the synthesis, the stereochemistry at this centre was not critical. Treatment of the crude alcohols **282** with acetic anhydride in pyridine gave the protected diols **283** in excellent yield and in the same diastereoisomeric ratio.



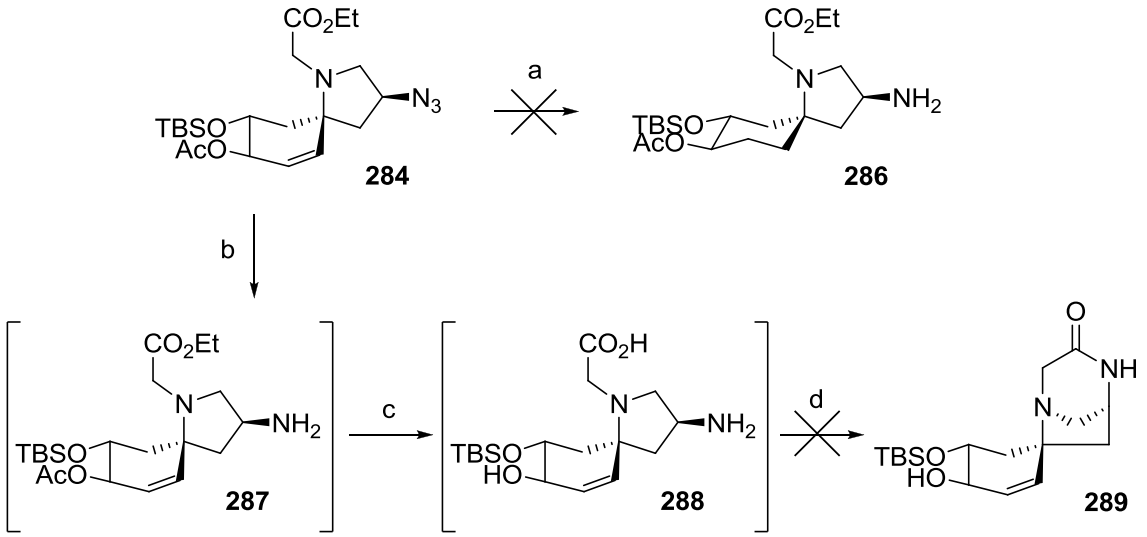
Scheme 89. *Reagents and conditions:* (a) L-selectride, THF, -78 °C, 2 h; (b) Ac_2O, pyridine, 14 h (86% over 2 steps).

Only a few steps remained before the key cyclisation step could be attempted. Boc deprotection of amine **283** was readily achieved using TFA, and the free amine was subsequently alkylated with ethylbromoacetate in the presence of K_2CO_3 and NaI (scheme 90). At this point separation of the major pseudo-equatorial diastereoisomer **284** and the minor pseudo-axial diastereoisomer **285** was possible.



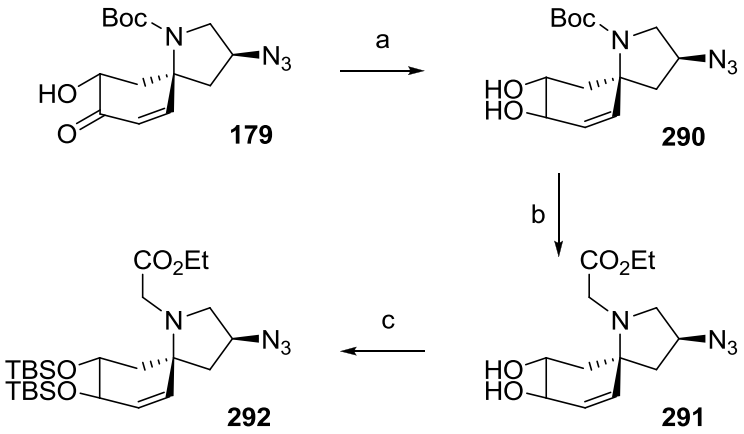
Scheme 90. *Reagents and conditions:* (a) i. TFA/CH_2Cl_2, 1 h; ii. $BrCH_2CO_2Et$, NaI, K_2CO_3, MeCN, 3 days, **284**, 74%, **285**, 15%.

To simplify spectroscopic analysis of the subsequent key steps, initially the synthesis was continued with only the major pseudo-equatorial isomer **284**. At a later point, with a robust route in hand, both diastereoisomers could be utilised. The last steps before the key cyclisation required conversion of the azido group to the free amine (and the ethyl ester to the carboxylic acid). It was thought that hydrogenation of the double bond could be achieved at the same time as reduction of the azide. Unfortunately we were not able to isolate any of the desired product **286** after hydrogenation of **284** using either palladium over carbon or palladium hydroxide. Although it was disappointing not to be able to combine the two steps, we decided to look specifically at reducing the azide. Pleasingly, the Staudinger reaction proceeded cleanly for our substrate **284** and the free amine **287** was clearly the only compound in the ^{1}H NMR spectrum of the crude product (scheme 91). Subsequent treatment of the amine **287** with $LiOH.H_2O$ resulted in the formation of a highly polar product, which could not be purified. However, the mass of the product was consistent with hydrolysis of the ester functionality, and perhaps not surprisingly cleavage of the acetate protecting group to give the free amino acid **288**. This crude product was treated directly with DPPA and triethylamine to try and affect the cyclisation, but unfortunately the desired product **289** was not isolated. It was thought that this result could be due to the free hydroxyl group interfering with the reaction and therefore we reflected on our initial choice of protecting the alcohol moiety with an acetate group.



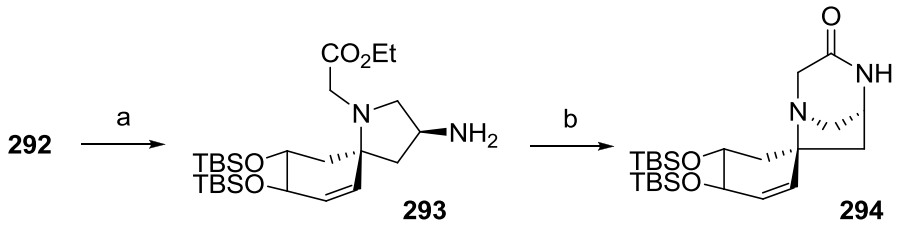
Scheme 91. *Reagents and conditions:* (a) H_2, Pd/C or $Pd(OH)_2$, EtOAc; (b) Ph_3P, H_2O, THF, reflux, 4 h; (c) $LiOH.H_2O$, THF, 2 h; (d) DPPA, Et_3N, DMF.

It was decided to try to protect both alcohol functionalities as a silyl ether, which would also serve to reduce the number of steps in the synthesis. Literature precedence suggests it is possible to selectively deprotect an allylic TBS-protected alcohol in the presence of another TBS-protected alcohol.[95-97] This strategy would enable us to make use of the double bond again in our synthesis. Starting from the keto-alcohol **179**, reduction of the ketone using L-selectride pleasingly afforded the desired diol **290** in good yield and as a single diastereoisomer (scheme 92). Prior to protection of the diol as the TBS ethers, installation of the *N*-ethyl acetate group in place of the *N*-Boc group was achieved. Use of the conditions employed previously gave our desired *N*-alkylated product **291** in 85% yield. The diol **291** was then protected as planned with the two TBS groups, using TBS triflate and 2,6-lutidine to give the desired product **292** in 91% yield.



Scheme 92. *Reagents and conditions:* (a) L-selectride, THF, -78 °C, 2 h, 80% (b) i. TFA/CH_2Cl_2, 1 h; ii. $BrCH_2CO_2Et$, NaI, K_2CO_3, MeCN, 3 d, 85%; (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 2 h, -78 °C, 91%.

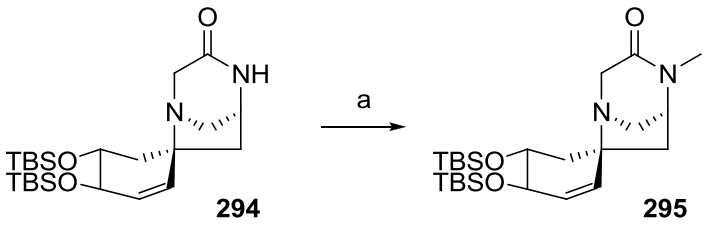
At this point it was just necessary to convert the azide into the free amine and hydrolyse the ester before the cyclisation could be attempted. Treatment of the azide **291** with PPh_3 in H_2O/THF afforded the free amine **293** in excellent yield (scheme 93). Hydrolysis of the ester of **293** was achieved using K_2CO_3 in methanol and subsequent amide coupling with DPPA and triethylamine afforded the desired tricycle **294** in 40% yield over two steps from amine **293**. This was a pleasing result as we had successfully synthesised an advanced intermediate in the synthesis of (+)-TAN1251B (**3**) containing the key tricyclic core.



Scheme 93. *Reagents and conditions:* (a) Ph_3P, H_2O, THF, 85 °C, 4 h, 93%; (b) i. K_2CO_3, MeOH; ii. DPPA, Et_3N, DMF, r.t., 2 h, 40% over 2 steps.

2.3.3 Installation of the side-chain of (+)-TAN1251B (3)

Our next step involved alkylating at the amide nitrogen, which was readily achieved using NaH and MeI to afford the advanced tricycle **295** in 90% yield (scheme 94). Pleasingly the tricycle was crystalline and its structure and stereochemistry were unambiguously confirmed by X-ray crystallography (figure 8).



Scheme 94. *Reagents and conditions:* (a) NaH, MeI, THF, 0 °C, 2 h, 90%.

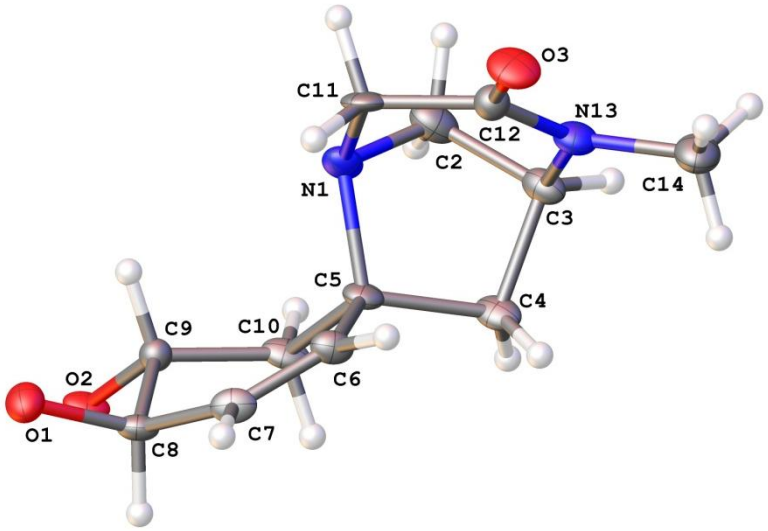
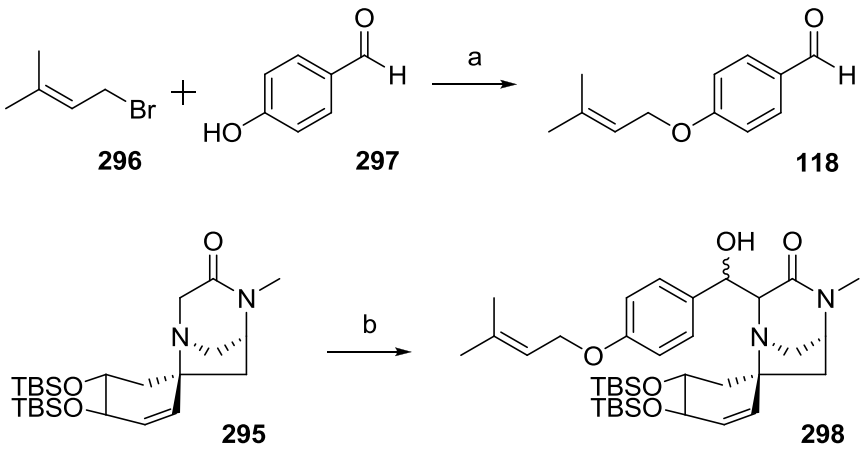


Figure 8. X-ray crystal structure of key intermediate **295**

(The TBS groups on oxygen atoms (O1 and O2) have been omitted for clarity)

The installation of the key side-chain could now be attempted. The necessary aldehyde **118** was easily synthesised from prenyl bromide **296** and 4-hydroxybenzaldehyde **297** in good yield (scheme 95). Treatment of the tricycle **295** with LDA resulted in formation of the corresponding enolate, which was then reacted with the aldehyde **118** to afford the desired product **298** as a mixture of diasteroisomers in good yield. Separation of the two diastereoisomers was possible, although the stereochemical outcome of this reaction was not important. Both of the stereocentres, introduced in this step, would be removed *via* dehydration later in the synthesis. Installation of this side-chain means that all the carbon atoms needed to complete the synthesis of (+)-TAN1251B (**3**) are now in place.

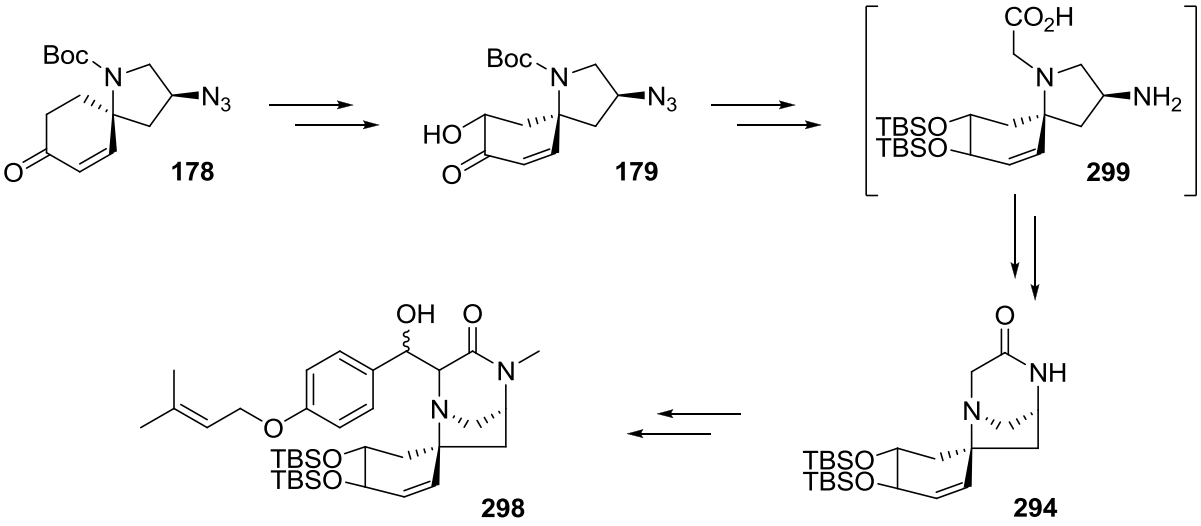


Scheme 95. *Reagents and conditions:* (a) K_2CO_3, acetone, reflux, 2 h, 80%; (b) LDA, THF, -78 °C, 30 min then **118**, 2 h, 73% (combined yield).

2.3.4 Summary of progress made towards (+)-TAN1251B (3)

From the common intermediate **178**, the key step in the synthesis of (+)-TAN1251B **(3**) was installation of the hydroxyl group alpha to the ketone (scheme 96). Pleasingly, this

transformation occurred in a completely regio- and stereoselective manner and with excellent yield.



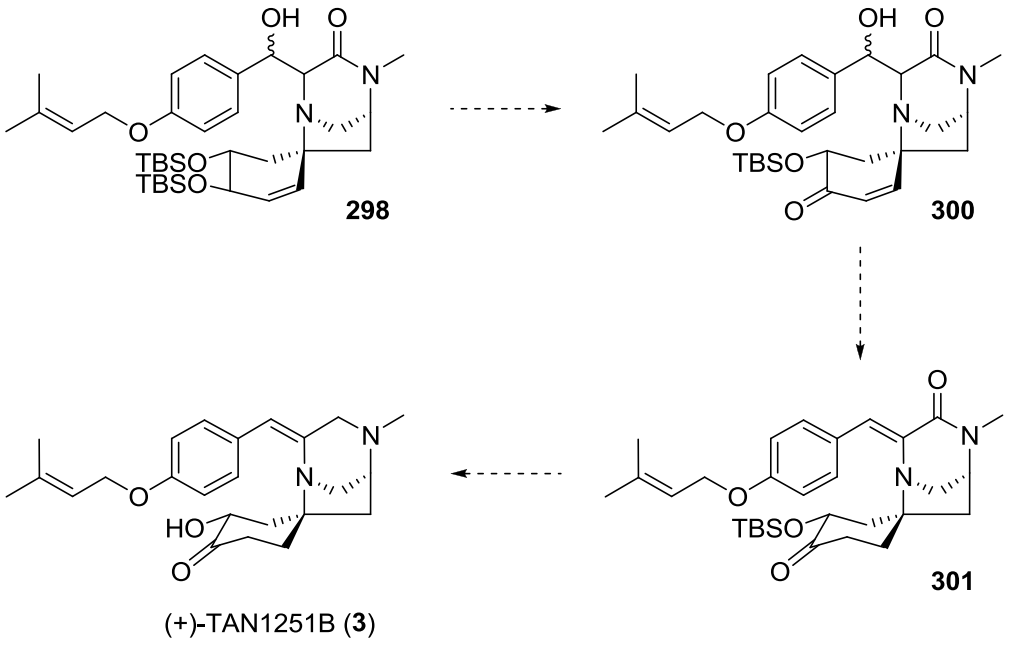
Scheme 96. Progress towards (+)-TAN1251B (**3**)

The tricyclic core was subsequently formed *via* an intramolecular peptide coupling of the amino acid **299**, which was derived in a few simple transformations from the *α*-hydroxy ketone **179**. Subsequent methylation of the nitrogen of the amide, and introduction of the side-chain were achieved in good yield to afford the advanced intermediate **298**. At this point, the carbon skeleton required for completion of the total synthesis of (+)-TAN1251B (**3**) is in place.

2.2.7 Future work towards completing the synthesis of (+)-TAN1251B (3)

As shown in the summary of work achieved so far, the intermediate **298** is only steps away from a total enantioselective synthesis of (+)-TAN1251B. From this point, we can envisage

selective deprotection of the allylic TBS-protected alcohol and subsequent oxidation to the give the enone **300** (scheme 97).[95-97] 1,4-Reduction of the enone followed by dehydration would afford the ketone **301**. From here, the synthesis of (+)-TAN1251B (**3**) could be completed by reduction of the amide moiety and removal of the TBS protecting group.



Scheme 97. Completing the synthesis of (+)-TAN1251B (**3**)

Chapter 3: Experimental

3.1 General Experimental

Starting materials were obtained from commercial suppliers and used without further purification unless otherwise stated. THF was distilled from potassium/benzophenone. CH_2Cl_2 was distilled from CaH_2. MeOH was distilled from Mg/I_2. Et_3N was distilled from CaH_2. Thin-layer chromatography (TLC) was carried out on Merck silica gel 60 F_{254} aluminium plates. They were visualised by exposure to UV light (254 nm) followed by staining with basic potassium permanganate and/or vanillin as appropriate. Flash column chromatography was carried out using Merck silica gel 60, 35-70 μm as the stationary phase with solvents of analytical purity. All petrol used was petroleum ether (boiling point: 40-60 °C) and all water was previously de-ionised.

NMR spectra were obtained as dilute solutions in the appropriate solvent at 25 °C unless otherwise stated. ^1H NMR and ^{13}C spectra were recorded using a Bruker DPX 360 MHz, AV 400 MHz, AVIII 400 MHz or Jeol EX 270 MHz spectrometer. All chemical shifts were recorded on the δ-scale using residual solvent as an internal standard ($CDCl_3$: δ_H 7.26, δ_C 77.16; d_6-DMSO: δ_H 2.50, δ_C 39.52, D_2O: δ_H 4.79). All coupling constants are reported in Hertz (Hz) and are rationalised. Multiplicities are labelled s (singlet), d (doublet), t (triplet), q (quartet), p (pentet) or some combination thereof. Where necessary the prefixes *br* (broad) or *app* (apparent) were used. Assignments were made based on chemical shift and where appropriate, with the benefit of DEPT sequences and correlation techniques (COSY, HMQC, HMBC). Infrared spectra were recorded using a Perkin-Elmer 1600 FT spectrophotometer, as dilute solutions in $CHCl_3$ unless otherwise stated. Mass spectra were recorded using a Bruker MicrOTOF 61 spectrometer using electrospray ionisation (ESI^+) technique. Optical rotations were measured on a JASCO DIP-370 or a ADP440 polarimeters at a wavelength of 589 nm

with a path length of 50 or 100 mm. Concentrations were given as g/100 ml. Microanalytical data were obtained using an Exeter Analytical CE-440 elemental analyser. Melting points (mp) were measured using a Stuart SMP3.

3.1 General Procedures

Preparation of DMDO

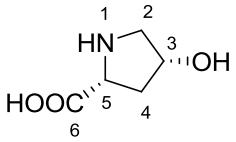
Following a modified procedure of Esmieu,[55] a single neck, 3L round bottom flask was equipped with an air condenser and connected to a two neck 250 mL receiving flask cooled to -78 °C. The air condenser was wrapped in a polyethylene bag containing solid CO_2 and maintained in place with cable ties. The 3L flask was charged with $NaHCO_3$ (29.0 g, 345 mmol), H_2O (127 mL) and acetone (reagent grade, 96 mL) and cooled to 0 °C with vigorous stirring. A suba-seal was placed on top of the air condenser. Oxone (60.0 g) was added in one portion and all joints were sealed with sealing tape. Suction (20 mmHg) was applied through a water aspirator connected to the receiving flask. The ice bath was removed and the yellow DMDO solution was distilled under reduced pressure into the receiving flask over 30 minutes. The vacuum was carefully controlled by venting the apparatus through a needle placed in the suba-seal to prevent over-spilling. The solution was poured onto anhydrous K_2CO_3 pre-cooled at 0 °C, then filtered in a pre-cooled (-78 °C) 100 mL flask. The flask was flushed with argon, stoppered with a glass stopper and stored in a freezer at -25 °C until required. Before utilisation, the concentration of the solution was determined by iodometric titration: A 0.02 M aqueous solution of sodium thiosulfate (496 mg $Na_2S_2O_3.5H_2O$ in 100 mL of water) was prepared and placed in a graduated burette. A 100 mL conical flask was

charged with NaI (2.00 g), water (70 mL), glacial acetic acid (1 mL), and the solution of DMDO (2 mL) was added to give a yellow solution. The solution was then titrated with the aqueous solution of $Na_2S_2O_3$ until complete disappearance of the yellow colour. The concentration was then calculated using the following equation: Concentration = [(molarity of titrant) × (mL of titrant)]/[(mL of DMDO solution) × 2] and was found to be in the range 0.05 to 0.07 M.

Preparation of LDA

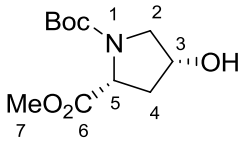
To a solution of diisopropylamine (5.32 mL, 37.8 mmol, freshly distilled over NaH) and dry THF (35 mL), cooled (0 °C) under argon, was added dropwise ^{n}BuLi (23.5 mL, 35.2 mmol, 1.50 M in hexanes). The resultant light yellow solution was stirred for 30 min at 0 °C before being used.

Cis-4-hydroxy-*D*-proline (173)[66]



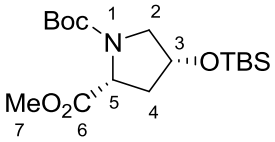
A solution of glacial acetic acid (872 mL) and acetic anhydride (256 mL, 2.67 mol) was heated to 50 °C. *Trans*-4-hydroxy-*L*-proline **190** (70.0 g, 534 mmol) was added in one portion, and the mixture was heated under reflux for 5.5 h. The solvent was removed under reduced pressure to give a thick oil, which was dissolved in HCl (2 M, 1020 mL) and stirred under reflux for 3 h. The solution was treated with charcoal while hot, then filtered through celite®. The filtrate was concentrated under reduced pressure to afford a yellow oil. Trituration with Et_2O gave a white precipitate which was collected by suction filtration. The white solid was recrystallised from ethanol to afford the hydrochloride salt of *cis*-4-hydroxy-*D*-proline (62.0 g, 69%). 20.0 g of this salt was dissolved in the minimum volume of water (50 mL), and triethylamine (40 mL) and ethanol (300 mL) were added sequentially. A white solid precipitated formed, which was collected by suction filtration, followed by recrystallisation from water/ethanol to afford the pure *cis*-4-hydroxy-*D*-proline **173** (27.0 g, 39% total yield for the epimerisation) as a white solid; mp: 252-254˚C (decomp.) [lit.,[66] mp: 250-254˚C (decomp.)]; $[\alpha]_D^{27}$ 59.6 (c 2.0, H_2O) [lit.,[66] $[\alpha]_D^{25}$ 60.3 (c 2.0, H_2O)]; δ_H (400 MHz, D_2O) 4.50-4.47 (1H, m, C^3H), 4.12 (1H, dd, *J* 10.4 and 2.4, C^5H), 3.37 (1H, *app* dt, *J* 12.6 and 2.4, $C^2H_AH_B$), 3.28 (1H, ddd, *J* 12.6, 4.0 and 2.4, $C^2H_AH_B$), 2.40 (1H, ddd, *J* 14.6, 10.4 and 4.8, $C^4H_AH_B$), 2.15 (1H, *app* dp, *J* 14.6 and 2.4, $C^4H_AH_B$); δ_C (100 MHz, D_2O) 174.5 (C=O), 69.1 (CH), 59.7 (CH), 52.9 (CH_2), 37.1 (CH_2); *m/z* EI^+ found 132.0661 (M+H, $C_5H_{10}NO_3$ requires 132.0662).

N-Boc-*cis*-4-hydroxy-*D*-proline methyl ester (302)[58]



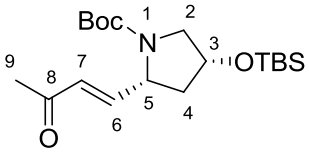
Acetyl chloride (21.3 mL, 288 mmol) was slowly added to dry methanol (197 mL) under argon at 0 °C. *Cis*-4-hydroxy-*D*-proline **173** (27.0 g, 206 mmol) was added and the mixture was heated under reflux for 7 h. The mixture was cooled to rt, and trituration with Et_2O gave a precipitate, which was collected by suction filtration and dried under high vacuum to give white needles (31.9 g, 85%). This hydrochloride salt (31.9 g, 176 mmol) was then suspended in dry CH_2Cl_2 (300 mL) under argon at 0 °C. Di-*tert*-butyl dicarbonate (42.2 g, 193 mmol) dissolved in dry CH_2Cl_2 (100 mL) and then triethylamine (61.2 mL, 439 mmol) were slowly added. The mixture was stirred for 3 days during which time the ice bath expired. The reaction mixture was hydrolysed with HCl (1M, 400 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic layers were washed with saturated $NaHCO_3$ solution (200 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The resulting oil was kept in the fridge for 3 days until crystallisation was complete. The solid was triturated with hexane, and the Boc-protected amine **302** (35.1 g, 70%) was collected by suction filtration as a white solid. $[\alpha]_D^{27}$ 11.0 (c 0.8, $CHCl_3$) [lit.,[58] $[\alpha]_D^{23}$ 2.2 (c 0.2, $CHCl_3$)]; δ_H (270 MHz, d_6-DMSO, 70 °C) 4.79 (1H, d, *J* 3.6, O*H*); 4.23-4.18 (2H, m, C^5H and C^3H), 3.64 (3H, s, C^7H_3), 3.52 (1H, dd, *J* 10.8 and 5.7, $C^2H_AH_B$), 3.16-3.10 (1H, m, $C^2H_AH_B$), 2.41-2.30 (1H, m, $C^4H_AH_B$), 1.84 (1H, *app* dt, *J* 12.8 and 4.9, $C^4H_AH_B$), 1.37 (9H, s, $CO_2C(CH_3)_3$). Spectroscopic data matched that previously reported.[58]

N-Boc-*cis*-4-(*tert*-butyl-dimethyl-silyloxy)-*D*-proline methyl ester (174)[58]



Imidazole (9.73 g, 143 mmol) and *tert*-butyl-dimethylsilyl chloride (23.7 g, 157 mmol) were added to a stirred solution of the alcohol **302** (35.1 g, 143 mmol) in dry DMF (65 mL) under argon at 0 °C. The mixture was then stirred at 60 °C for 1 h before being cooled to rt and water (300 mL) added. The mixture was then diluted with Et_2O (200 mL), the layers were separated, and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were sequentially washed with HCl (1 M, 300 mL) and saturated $NaHCO_3$ solution (200 mL) before being dried over $MgSO_4$, and concentrated *in vacuo*.to afford **174** (51.0 g, 100%) as a colourless oil pure by ^{1}H NMR. $[\alpha]_D^{27}$ 37.1 (c 1.0, $CHCl_3$) [lit.,[58] $[\alpha]_D^{23}$ 36.8 (c 1.0, $CHCl_3$)]; δ_H (270 MHz, d_6-DMSO, 70 °C) 4.43-4.37 (1H, m, C^3H), 4.27 (1H, dd, *J* 8.9 and 3.8, C^5H), 3.63 (3H, s, C^7H_3), 3.56 (1H, dd, *J* 10.6 and 5.3, $C^2H_AH_B$), 3.12 (1H, dd, *J* 10.6 and 3.3, $C^2H_AH_B$), 2.45-2.34 (1H, m, $C^4H_AH_B$), 1.91 (1H, *app* dt, *J* 12.9 and 3.8, $C^4H_AH_B$), 1.38 (9H, s, $CO_2C(CH_3)_3$), 0.85 (9H, s, Si-$C(CH_3)_3$), 0.05 (6H, s, 2 × Si-CH_3). Spectroscopic data matched that previously reported.[58]

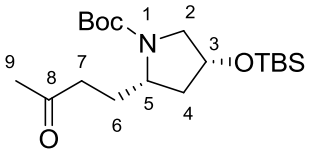
N-Boc-(2*R*,4*R*)-2-((*E*)-3-oxo-but-1-enyl)-4-(*tert*-butyl-dimethyl-silyloxy)-pyrrolidine (175)[58]



DIBAL-H (96.4 mL, 1.50 M in toluene, 145 mmol) was added dropwise *via* syringe pump over 3 h to a cold (-78 °C) stirred solution of ester **174** (26.0 g, 72.3 mmol) in dry CH_2Cl_2

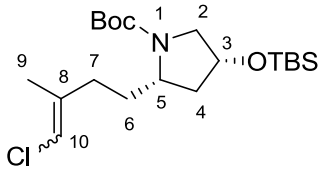
(350 mL) under argon. The mixture was stirred for another 2 h before the dropwise addition of dry methanol (90 mL). The solution was allowed to warm to rt and then potassium sodium tartrate solution (2 M, 350 mL) was added and the mixture stirred vigorously for 30 min. The organic layer was separated and the aqueous layer further extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give the crude aldehyde **195** (23.8 g) as a clear, colourless oil. The procedure was then repeated on the same scale to give a second batch of the crude aldehyde (combined mass 47.6 g). 1-Triphenylphosphoroanylidene-2-propanone **160** (60.4 g, 189 mmol) was added to a stirred solution of the crude aldehyde (47.6 g, 145 mmol) in CH_2Cl_2 (75 mL). The reaction mixture was stirred for 5 days before concentration of the solution *in vacuo*. Trituration with petrol gave a white precipitate of triphenylphosphine oxide, which was removed by filtration. The filtrate was concentrated *in vacuo* and the crude product was purified by column chromatography (8:2 petrol/Et_2O then 1:1 petrol/Et_2O) to give the aldehyde (3.40 g, 7%) which could be recycled, followed by the enone product **175** (41.6 g, 77%) as a yellow oil. $[\alpha]_D^{22}$ -12.4 (c 0.8, $CHCl_3$) [lit.,[58] $[\alpha]_D^{27}$ -10.4 (c 0.50, $CHCl_3$)]; δ_H (270 MHz, d_6-DMSO, 70 °C) 6.81 (1H, dd, *J* 16.1 and 6.9, C^6*H*), 5.96 (1H, dd, *J* 16.1 and 1.0, C^7*H*), 4.45-4.35 (2H, m, C^3*H* and C^5*H*), 3.55 (1H, dd, *J* 11.5 and 4.8, C^2H_AH$_B$), 3.20 (1H, *app* dt, *J* 11.5 and 1.5, C^{2}H$_A$$H_B$), 2.33 (1H, ddd, *J* 13.3, 8.9, 4.8, C^4H_AH$_B$), 2.16 (3H, s, C^9H_3), 1.74 (1H, *app* dq, *J* 13.3 and 1.5, C^{4}H$_A$$H_B$), 1.39 (9H, s, $CO_2C(CH_3)_3$), 0.86 (9H, s, Si-C(CH_3)$_3$), 0.06 (6H, s, 2 × Si-CH_3). Spectroscopic data matched that previously reported.[58]

N-Boc-(2*R*,4*R*)-2-(3-oxo-butyl)-4-(*tert*-butyl-dimethyl-silyloxy)-pyrrolidine (189)[58]



Palladium (1.50 g, 10% on carbon) was added in one portion to a stirred solution of the enone **175** (20.3 g, 55.0 mmol) in EtOAc (110 mL). The reaction vessel was purged with hydrogen by three evacuate/fill cycles and the mixture was stirred under a hydrogen atmosphere (balloon) for 24 h. The catalyst was removed by removed by filtration through Celite®, and the filtrate was concentrated *in vacuo* to afford the crude ketone **189** (20.4 g, 99%) as a yellow oil. For analytical purposes, some of the crude product was purified by column chromatography (4:1 petrol/Et_2O) to afford the pure ketone **189** as a yellow oil. $[\alpha]_D^{27}$ 20.6 (c 0.5, $CHCl_3$) [lit.,[58] $[\alpha]_D^{26}$ 8.9 (c 0.5, $CHCl_3$)]; δ_H (270 MHz, d_6-DMSO, 70 °C) 4.38-4.29 (1H, m, C^3H), 3.75-3.65 (1H, m, C^5H), 3.57 (1H, dd, *J* 11.5 and 5.6, $C^2H_AH_B$), 3.03 (1H dd, *J* 11.5 and 3.3, $C^2H_AH_B$), 2.45-2.35 (2H, m, C^7H), 2.18-2.10 (1H, m, $C^4H_AH_B$), 2.07 (3H, s, C^9H_3), 2.05-1.97 (1H, m, $C^6H_AH_B$), 1.83-1.71 (1H, m, $C^6H_AH_B$), 1.57 (1H, *app* dt, *J* 13.1 and 3.5, $C^4H_AH_B$), 1.41 (9H, s, $CO_2C(CH_3)_3$), 0.88 (9H, s, Si-$C(CH_3)_3$), 0.07 (6H, s, 2 × Si-CH_3). Spectroscopic data matched that previously reported.[58]

N-Boc-(2*S*,4*R*)-2-(4-chloro-3-methyl-but-3-enyl)-4-(*tert*-butyl-dimethyl-silyloxy)-pyrrolidine (177)[58]

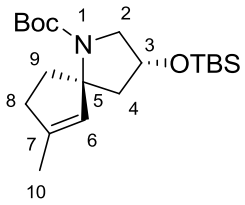


EITHER: KH (suspension in mineral oil) was added to a flame-dried flask under argon. The solid was washed with dry pentane (3 × 10 mL) by addition, and removal of the liquid *via* syringe. The resultant white solid (3.10 g, 77.3 mmol) was dried under high vacuum for 1 min. The flask was slowly filled with argon before dry THF (90 mL) was added. The flask was cooled to 0 °C and ^{t}BuOH (5.73 g, 77.3 mmol) was added, followed by the portionwise addition of (chloromethyl)triphenylphosphonium chloride **176** (27.7 g, 79.9 mmol). Subsequently, more THF (40 mL) was added prior to the slow addition of ketone **189** (9.09 g, 24.5 mmol) in THF (20 mL). The mixture was then stirred for 2 h at 0 °C, and 1 h at rt before being diluted with Et_2O (50 mL) and saturated NH_4Cl solution (50 mL). The aqueous layer was extracted with Et_2O (3 × 50 mL) and then the combined organic extracts washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (7:1 petrol/Et_2O) to afford vinyl chloride **177** (9.21 g, 93%) as a light yellow oil (mixture of (*E*)-and (*Z*)-isomers in 2:1 ratio).

OR: KO^{t}Bu (80.2 mg, 714 μmol) was suspended in dry THF (2 mL) under argon and the mixture was cooled down at 0 °C. Then (chloromethyl)triphenylphosphonium chloride **176** (256 mg, 738 μmol) was added and the resultant yellow solution stirred for 10 min, before the slow addition of ketone **189** (88.5 mg, 23.8 μmol) in THF (2 mL). The mixture was stirred for 1 h at 0 °C, and two days at rt before being diluted with Et_2O (10 mL) and saturated NH_4Cl solution (10 mL). The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic fractions washed with brine (20 mL), dried over $MgSO_4$, and concentrated

in vacuo. The crude product was purified by column chromatography (11:1 petrol/Et_2O) to afford the vinyl chloride **177** (85.5 mg, 88%) as a light yellow oil. $[\alpha]_D^{23}$ 14.1 (c 0.6, $CHCl_3$) [lit.,[58] $[\alpha]_D^{27}$ 13.5 (c 0.8, $CHCl_3$)]; Data was collected for a mixture of (*E*)-and (*Z*)-isomers in a 2:1 ratio: δ_H (400 MHz, d_6-DMSO): Data for the (*E*)-isomer : 6.03 (1H, s, $C^{10}H$), 4.36 (1H, s, C^3H), 3.62 (1H, s, C^5H), 3.5 (1H, dd, *J* 11.2 and 5.2, $C^2H_AH_B$), 3.02 (1H, m, $C^2H_AH_B$), 2.22-2.01 (3H, m, C^7H_2 and $C^4H_AH_B$), 1.98-1.86 (1H, m, $C^4H_AH_B$), 1.73 (3H, s, C^9H_3), 1.72-1.59 (2H, m, C^6H_2), 1.39 (9H, s, $CO_2C(CH_3)_3$), 0.86 (9H, s, Si-$C(CH_3)_3$), 0.05 (6H, s, 2 × Si-CH_3); Data for the (*Z*)-isomer, where different from the (*E*)-isomer : 5.99 (1H, s, $C^{10}H$); *m/z* ESI^+ found 426.2202 (M+Na, $C_{20}H_{38}NO_3SiClNa$ requires 426.2207); ν_{max}/cm^{-1} ($CHCl_3$): 2930, 2857, 1682 (C=O), 1397, 1115, 1080, 1039, 1003. Spectroscopic data matched that previously reported.[58]

N-Boc-(3*R*,5*S*)-3-(*tert*-butyl-dimethyl-silyloxy)-7-methyl-1-azaspiro[4.4]non-6-ene (149)[58]

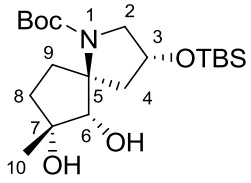


EITHER: KHMDS (90.0 mL, 45.0 mmol, 0.50 M in toluene) was added to a stirred solution of the vinyl chloride **177** (9.10 g, 22.5 mmol) in dry Et_2O (70 mL) under argon. The reaction mixture was stirred for 3 h before removal of the solvent *in vacuo* to give the crude product. Purification by column chromatography (9:1 petrol/Et_2O) afforded the 5,5-spirocycle **149** (7.55 g, 91%) as a yellow oil.

OR: ^{n}BuLi (17.4 ml, 2.50 M in hexane, 43.3 mmol) was added dropwise over 1 h *via* syringe pump to a stirred, cooled (-78 °C) solution of trimethylsilyldiazomethane (25.0 mL, 50.0

mmol, 2.00 M in hexane) in dry THF (150 mL) under argon. The mixture was stirred for 1 h at -78 °C before a solution of the ketone **189** (12.4 g, 33.3 mmol) in dry THF (150 mL) was added slowly over 30 min *via* cannula. The mixture was stirred for another 1 h at -78 °C before being warmed slowly to 0 °C (over 40 min). The reaction was then quenched with saturated NH_4Cl solution (150 mL). The two layers were separated and the aqueous layer was further extracted with Et_2O (3 × 120 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (95:5 petrol/Et_2O) to afford the 5,5-spirocycle **149** (10.6 g, 86%) as a yellow oil. $[\alpha]_D^{24}$ 74.4 (c 0.7, $CHCl_3$) [lit.,[58] $[\alpha]_D^{28}$ 69.2 (c 1.3, $CHCl_3$)]. δ_H (400 MHz, d_6-DMSO, 70 °C) 5.08 (1H, d, *J* 1.4, C^6*H*), 4.32-4.27 (1H, m, C^3*H*), 3.47 (1H, dd, *J* 11.6 and 4.7, C^2*H*$_A$H$_B$), 3.25 (1H, *app* dt, *J* 11.6 and 1.9, C^{2}H$_A$*H*$_B$), 2.33-2.10 (4H, m, C*H*$_2$ and C*H*$_2$), 1.96 (1H, dd, *J* 13.0 and 4.5, C*H*$_2$), 1.83 (1H, ddd, *J* 13.0, 2.8 and 1.8, C*H*$_2$), 1.68 (3H, s, C^{10}*H*$_3$), 1.73 (3H, s, C^9*H*$_3$), 1.35 (9H, s, $CO_2C(CH_3)_3$), 0.88 (9H, s, Si-C(C*H*$_3$)$_3$), 0.07 (6H, s, 2 × Si-C*H*$_3$); *m/z* ESI$^+$ found 390.2418 (M+Na, $C_{20}H_{37}NO_3SiNa$ requires 390.2440); ν_{max}/cm^{-1} ($CHCl_3$): 2929, 2856, 1672 (C=O), 1391, 1366, 1129, 1075. Spectroscopic data matched that previously reported.[58]

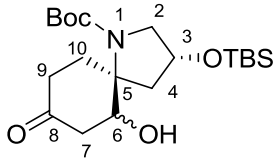
N-Boc-(3*R*,5*S*,6*S*,7*R*)-3-(*tert*-butyl-dimethyl-silyloxy)-6,7-dihydroxy-7-methyl-1-azaspiro[4.4]nonane (196)[58]



N-Methyl-morpholine-*N*-oxide monohydrate (11.6 g, 86.2 mmol) followed by potassium osmate dihydrate (106 mg, 287 μmol) was added to a stirred solution of spirocycle **149** (10.6

g, 28.7 mmol) in acetone (170 mL) and water (17 mL). The mixture was stirred for 4 days at rt before the addition of sodium thiosulfate (500 mg). The mixture was then allowed to stir for another 15 h. Water (150 mL) was added and the aqueous layer extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude was purified by column chromatography (6:4 petrol/EtOAc) to afford the diol product **196** (9.87g, 86%) as a white foam. $[\alpha]_D^{27}$ -32.7 (c 0.5, $CHCl_3$) [lit.,[58] $[\alpha]_D^{24}$ -25.3 (c 0.2, $CHCl_3$)]. δ_H (400 MHz, d_6-DMSO, 70 °C): 4.53 (1H, br s, OH), 4.33 (1H, *app* p, *J* 5.1, C^3H), 4.14 (1H, br s, OH), 3.60 (1H, s, C^6H), 3.39 (1H, dd, *J* 11.1 and 5.4, $C^2H_AH_B$), 3.15 (1H, dd *J* 11.1 and 4.1, $C^2H_AH_B$), 2.65-2.55 (1H, m, $C^4H_AH_B$), 2.23-2.07 (1H, m, $C^4H_AH_B$), 1.94-1.70 (2H, m, $C^{8/9}H_2$), 1.62-1.49 (2H, m, $C^{8/9}H_2$), 1.41 (9H, s, $CO_2C(CH_3)_3$), 1.15 (3H, s, $C^{10}H_3$), 0.87 (9H, s, Si-$C(CH_3)_3$), 0.05 (6H, s, 2 × Si-CH_3); *m/z* ESI^+ found 424.2484 (M+Na, $C_{20}H_{39}NO_5SiNa$ requires 424.2490); ν_{max}/cm^{-1} ($CHCl_3$): 3550, 2929, 1679 (C=O), 1454, 1392, 1088. Spectroscopic data matched that previously reported.[58]

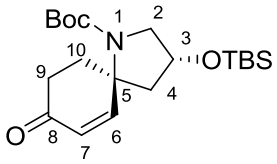
N-Boc-(3*R*,5*S*)-3-(*tert*-butyl-dimethyl-silyloxy)-6-hydroxy-8-oxo-1-azaspiro[4.5]decane (198)[58]



Sodium periodate (10.4 g, 48.7 mmol) was added to a stirred solution of the diol **196** (9.79 g, 24.3 mmol) in THF (94 mL) and water (47 mL). The mixture was stirred for 1 h before the addition of water (200 mL). The aqueous layer was extracted with Et_2O (3 × 100 mL) and the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude keto-aldehyde **197** which was used without further purification. Potassium hydroxide (682

mg, 12.1 mmol) was added to a stirred, cooled (0 °C) solution of the crude keto-aldehyde (9.71g, 24.3 mmol) in dry ethanol (100 mL). The mixture was stirred for 2 h at rt before saturated NH_4Cl solution (180 mL) was added and the aqueous layer extracted with Et_2O (3 × 150 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude was purified by column chromatography (7:3 petrol/EtOAc) to afford the keto-alcohol **198** (8.20 g, 84% over 2 steps) as a white foam. $[\alpha]_D^{27}$ -23.2 (c 0.4, $CHCl_3$) [lit.,[58] $[\alpha]_D^{24}$ -4.6 (c 0.4, $CHCl_3$)]; Data was collected for a mixture of diastereoisomers in a 2:1 ratio: δ_H (400 MHz, d_6-DMSO): Data for the major isomer: 5.15 (1H, d, *J* 4.8, OH), 4.54-4.46 (1H, m, $C^{3/6}H$), 4.44-4.38 (1H, m, $C^{3/6}H$), 3.48-3.40 (1H, m, $C^2H_AH_B$), 3.37-3.28 (1H, m, $C^2H_AH_B$), 2.56-2.20 (5H, m, C^7H_2, C^9H_2 and $C^{4/10}H_2$), 2.15-2.07 (1H, m, $C^{4/10}H_2$), 2.01-1.87 (2H, m, $C^{4/10}H_2$), 1.38 (9H, s, $CO_2C(CH_3)_3$), 0.86 (9H, s, Si-$C(CH_3)_3$), 0.07 (6H, s, 2 × Si-CH_3); Data for the minor isomer, where different from the major isomer: 5.22 (1H, d, *J* 4.8, OH), 4.36-4.27 (1H, m, $C^{3/6}H$); *m/z* ESI^+ found 422.2321 (M+Na, $C_{20}H_{37}NO_5SiNa$ requires 422.2339); ν_{max}/cm^{-1} ($CHCl_3$): 3610, 2954, 2930, 2857, 1716, 1681 (C=O), 1391, 1367, 1140, 1078, 1041. Spectroscopic data matched that previously reported.[58]

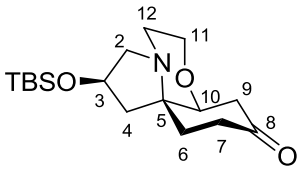
N-Boc-(3*R*,5*S*)-3-(*tert*-butyl-dimethyl-silyloxy)-8-oxo-1-azaspiro[4.5]dec-6-ene (148)[58]



Methanesulfonyl chloride (2.38 mL, 30.8 mmol) and triethylamine (7.92 mL. 61.6 mmol) were sequentially added to a stirred solution of the alcohol **198** (8.20 g, 20.5 mmol) in dry CH_2Cl_2 (150 mL) at 0 °C under argon. The mixture was stirred for 2 days during which time

the ice bath expired. Saturated NH_4Cl solution (150 mL) was added and the aqueous layer extracted with CH_2Cl_2 (3 × 120 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude was purified by column chromatography (3:1 petrol/EtOAc) to afford the 5,6-spirocycle **148** (7.25 g, 92%) as a yellow oil. $[\alpha]_D^{23}$ 62.3 (c 1.3, $CHCl_3$) [lit.,[58] $[\alpha]_D^{25}$ 63.3 (c 1.7, $CHCl_3$)]. δ_H (400 MHz, d_6-DMSO, 70 °C): 6.80 (1H, d, *J* 10.2, C^6*H*), 5.76 (1H, d, *J* 10.2, C^7*H*), 4.46-4.40 (1H, m, C^3*H*), 3.66 (1H, dd, *J* 11.7 and 4.7, C^2*H*$_A$H$_B$), 3.32 (1H, *app* d, *J* 11.7, C^{2}H$_A$*H*$_B$), 2.69-2.21 (5H, m, C^4*H*$_2$, C^9*H*$_2$ and C^{10}*H*$_A$H$_B$), 2.05-1.95 (1H, m, C^{10}H$_A$*H*$_B$), 1.38 (9H, s, $CO_2C(CH_3)_3$), 0.88 (9H, s, Si-C(C*H*$_3$)$_3$), 0.09 (6H, s, 2 × Si-C*H*$_3$); *m/z* ESI$^+$ found 404.2209 (M+Na, $C_{20}H_{35}NO_4SiNa$ requires 404.2228); ν_{max}/cm^{-1} ($CHCl_3$): 2930, 2884, 2857, 1792, 1681 (C=O), 1460, 1382, 1368, 1138, 1113, 1075, 1042. Spectroscopic data matched that previously reported.[58]

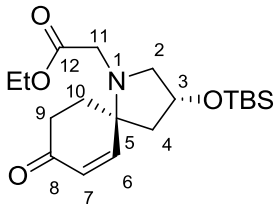
(2*R*,6a*S*,10a*S*)-2-(*tert*-butyl-dimethyl-silyloxy)-octahydro-6-oxa-3a-aza-cyclopenta[*d*]naphthalene-8-one (202)



Trifluoroacetic acid (1.29 mL, 16.8 mmol) was added to a stirred solution of the Boc-protected amine **148** (214 mg, 561 μmol) in dry CH_2Cl_2 (5 mL) under argon. The mixture was stirred for 1 h at rt before being diluted with CH_2Cl_2 (5 mL) and water (5 mL). The mixture was cooled to 0 °C and NaOH (2 M) was added (until the aqueous phase was pH 10). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo* to a volume of about 5 mL. The solution was cooled to -30 °C under argon and the flask equipped with a cold finger. Oxirane gas (in

excess) was condensed in the flask and the mixture stirred for 3 h at -30 °C, then for 1 day at room temperature. The mixture was concentrated *in vacuo* and the crude product purified by column chromatography (95:5 CH_2Cl_2/MeOH) to afford the pure tricycle **202** (160 mg, 87% over 2 steps) as a yellow oil. $[\alpha]_D^{25}$ -31.6 (c 0.36, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 4.48 (1H, *app* tdd, *J* 7.0, 4.0 and 2.8, C^3H); 3.83 (1H, app dd, *J* 11.6 and 3.6, $C^{11}H_AH_B$); 3.60 (1H, td, *J* 11.6 and 3.2, $C^{11}H_AH_B$), 3.52 (1H, m, $C^{10}H$); 3.37 (1H, dd, *J* 9.6 and 7.0, $C^2H_AH_B$), 2.98 (1H, td, *J* 11.6 and 3.6, $C^{12}H_AH_B$), 2.63 (1H, dd, *J* 9.6 and 4.0, $C^2H_AH_B$), 2.55-2.49 (2H, m, $C^9H_AH_B$ and $C^{12}H_AH_B$), 2.45-2.35 (4H, m, $C^6H_AH_B$, C^7H_2 and $C^9H_AH_B$), 1.97-1.84 (3H, m, C^4H_2, $C^6H_AH_B$), 0.88 (9H, s, Si-C(CH_3)$_3$), 0.06 (3H, s, Si-CH_3), 0.05 (3H, s, Si-CH_3); δ_C (100 MHz, $CDCl_3$) 209.2 (C=O), 81.2 (CH), 69.5 (CH), 66.1 (CH_2), 60.0 (CH_2), 59.5 (C), 45.2 (CH_2), 43.8 (CH_2), 43.2 (CH_2), 38.0 (CH_2), 25.9 (3 × CH_3), 21.2 (CH_2), 18.1 (C), -4.7 (2 × CH_3); *m/z* ESI^+ found 326.2141 (M+H, $C_{17}H_{32}NO_3Si$ requires 326.2146); ν_{max}/cm^{-1} ($CHCl_3$): 2930, 2857, 1720, 1119, 1084, 1044.

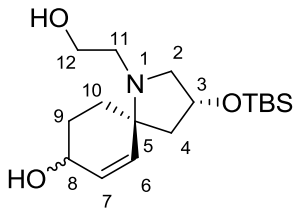
N-Ethyl-acetate-(3*R*,5*S*)-3-(*tert*-butyl-dimethyl-silyloxy)-8-oxo-1-azaspiro[4.5]dec-6-ene (203)



Trifluoroacetic acid (3.44 mL, 44.7 mmol) was added to a stirred solution of the Boc-protected amine **148** (568 mg, 1.49 mmol) in dry CH_2Cl_2 (15 mL) under argon. The mixture was stirred for 1 h at rt before being diluted with CH_2Cl_2 (5 mL) and water (5 mL). The mixture was cooled to 0 °C and NaOH (2 M) was added (until the aqueous phase was pH 10). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers

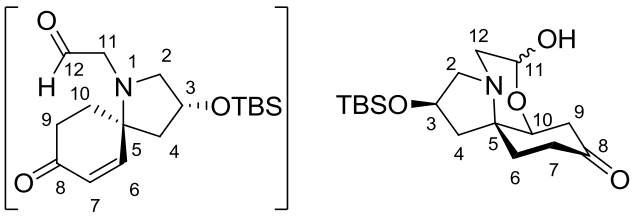
were dried over $MgSO_4$ and concentrated *in vacuo*. To a solution of the free amine in dry acetonitrile (15 mL), potassium carbonate (823 mg, 5.96 mmol), sodium iodide (446 mg, 2.98 mmol) and ethylbromoacetate (330 μL, 2.98 mmol) were added sequentially). The mixture was stirred for 20 h at rt before water (20 mL) was added and the aqueous layer extracted with EtOAc (3 × 20 mL). The combined organic layers were washed sequentially with saturated $Na_2S_2O_3$ solution (20 mL) and brine (15 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (4:1 petrol/EtOAc) to afford the ethyl ester **203** (477 mg, 87% over 2 steps) as a yellow oil. $[\alpha]_D^{25}$ 1.2 (c 0.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 6.69 (1H, dd, *J* 10.4 and 2.0, C^6H), 5.96 (1H, dd, *J* 10.4 and 0.8, C^7H), 4.51-4.45 (1H, m, C^3H), 4.15 (2H, q, *J* 7.2, $CO_2CH_2CH_3$), 3.62 (1H, dd, *J* 10.0 and 6.8, $C^2H_AH_B$), 3.37 (1H, d, *J* 16.4, $C^{11}H_AH_B$), 3.24 (1H, d, *J* 16.4, $C^{11}H_AH_B$), 2.66 (1H, dd, *J* 10.0 and 4.0, $C^2H_AH_B$), 2.56-2.39 (2H, m, C^9H_2), 2.32-2.26 (1H, m, $C^{10}H_AH_B$), 2.08-1.96 (3H, m, C^4H_2 and $C^{10}H_AH_B$), 1.26 (3H, t, *J* 7.2, $CO_2CH_2CH_3$), 0.86 (9H, s, Si-C(CH_3)$_3$), 0.04 (3H, s, Si-CH_3), 0.03 (3H, s, Si-CH_3); δ_C (100 MHz, $CDCl_3$) 199.3 (C=O), 171.3 (C=O), 156.6 (CH), 130.6 (CH), 70.2 (CH), 63.9 (C), 61.0 (CH_2), 60.9 (CH_2), 50.9 (CH_2), 44.4 (CH_2), 35.5 (CH_2), 27.4 (CH_2), 25.9 (3 × CH_3), 18.0 (C), 14.3 (CH_3), -4.7 (2 × CH_3); *m/z* ESI^+ found 368.2255 (M+H, $C_{19}H_{34}NO_4Si$ requires 368.2252) and 390.2063 (M+Na, $C_{19}H_{33}NO_4SiNa$ requires 390.2071); ν_{max}/cm^{-1} ($CHCl_3$): 2954, 2930, 2857, 1743, 1679, 1381, 1106, 1061. Found C, 61.9; H, 9.1; N, 3.7. $C_{19}H_{33}NO_4Si$ requires C, 62.1; H, 9.1; N, 3.8%.

(3*R*,5*S*)-3-(tert-butyl-dimethyl-silyloxy)-1-(2-hydroxy-ethyl)-1-azaspiro[4.5]dec-6-en-8-ol (204)



Lithium aluminium hydride (3.93 mL, 1.00 M in THF, 3.93 mmol) was added dropwise to a cooled (0 °C), stirred solution of ethyl ester **203** (962 mg, 2.62 mmol) in dry THF (35 mL). The mixture was stirred for 24 h, during which time the ice bath expired. The mixture was then cooled to 0 °C, and saturated Na_2SO_4 solution (25 mL) was slowly added. The aqueous layer was extracted with EtOAc (3 × 25 mL) and the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (8:1 $CHCl_3$/MeOH) to afford the diol **204** (799 mg, 93%) as a colourless oil. $[\alpha]_D^{26}$ -0.7 (c 0.4, $CHCl_3$); Data was collected for a mixture of diastereoisomers in a 5:1 ratio: δ_H (400 MHz, $CDCl_3$): Data for the major isomer: 5.76 (1H, dd, *J* 10.0 and 1.2, C^7H), 5.38 (1H, d, *J* 10.0, C^6H), 4.41-4.34 (1H, m, C^3H), 4.25-4.18 (1H, m, C^8H), 3.58-3.48 (2H, m, $C^{12}H_2$), 3.24 (1H, *app* t, *J* 8.4, $C^2H_AH_B$), 2.67-2.55 (3H, m, $C^2H_AH_B$ and $C^{11}H_2$), 2.16-2.09 (1H, m, $C^9H_AH_B$), 2.02-1.89 (2H, m, $C^4H_AH_B$ and $C^{10}H_AH_B$), 1.86-1.75 (1H, m, $C^4H_AH_B$), 1.67-1.58 (1H, m, $C^{10}H_AH_B$), 1.54-1.43 (1H, m, $C^9H_AH_B$), 0.87 (9H, s, Si-C(CH_3)$_3$), 0.04 (3H, s, Si-CH_3), 0.03 (3H, s, Si-CH_3); Data for the minor isomer, where different from the major isomer: 5.89 (1H, dd, *J* 10.0 and 4.4, C^7H), 5.53 (1H, d, *J* 10.0, C^6H), 4.14-4.09 (1H, m, C^8H), 3.30 (1H, *app* t, *J* 8.0, $C^2H_AH_B$), 2.77-2.68 (1H, m, $C^2H_AH_B$); δ_C (100 MHz, $CDCl_3$) 134.6 (CH), 133.9 (CH), 70.0 (CH), 67.4 (CH), 63.9 (C), 59.5 (CH_2), 58.8 (CH_2), 50.1 (CH_2), 48.1 (CH_2), 31.4 (CH_2), 27.6 (CH_2), 25.9 (3 × CH_3), 18.1 (C), -4.7 (2 × CH_3); *m/z* ESI^+ found 328.2298 (M+H, $C_{17}H_{34}NO_3Si$ requires 328.2302); ν_{max}/cm^{-1} ($CHCl_3$): 3604, 3434, 2930, 2885, 2857, 1462, 1392, 1362, 1108, 1078, 1053, 906.

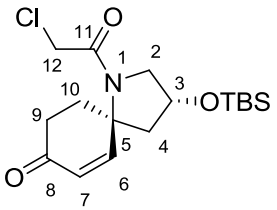
(2*R*,6a*S*,10a*S*)-2-(*tert*-butyl-dimethyl-silyloxy)-6-hydroxy-octahydro-6-oxa-3a-aza-cyclopenta[*d*]naphthalene-8-one (206)



Freshly distilled dimethylsulfoxide (177 μL, 2.49 mmol) was added dropwise to a cooled (-60 °C), stirred solution of oxalyl chloride (172 mg, 1.36 mmol) in dry CH_2Cl_2 (2.5 mL). The mixture was stirred for 1 h at this temperature before the slow addition of diol **204** (102 mg, 311 μmol) dissolved in dry CH_2Cl_2 (1.5 mL). The mixture was stirred for 90 min at -60 °C before the slow addition of triethylamine (434 μL, 3.11 mmol). The mixture was then stirred for another 60 min at -60 °C before being allowed to warm up to rt. Saturated NH_4Cl solution (5 mL) was added and the aqueous layer extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude aldehyde **200** as a colourless oil. δ_H (500 MHz, $CDCl_3$) 9.63 (1H, dd, *J* 2.2 and 1.0 $C^{12}H$), 6.62 (1H, dd, *J* 10.5 and 2.0, $C^{6}H$), 5.98 (1H, dd, *J* 10.5 and 1.0, $C^{7}H$), 4.51-4.46 (1H, m, $C^{3}H$), 3.47 (1H, dd, *J* 9.8 and 7.0, $C^{2}H_AH_B$), 3.36 (1H, dd, *J* 17.5 and 1.0, $C^{11}H_AH_B$), 3.24 (1H, dd, *J* 17.5 and 2.2, $C^{11}H_AH_B$), 2.65 (1H, dd, *J* 9.8 and 3.5, $C^{2}H_AH_B$), 2.53 (1H, dddd, *J* 17.0, 4.5, 3.5 and 1.0, $C^{9}H_AH_B$), 2.46 (1H, ddd, *J* 17.0, 13.5 and 5.0 $C^{9}H_AH_B$), 2.32-2.27 (1H, m, $C^{10}H_AH_B$), 2.05-2.02 (2H, m, $C^{4}H_AH_B$, $C^{10}H_AH_B$), 1.98 (1H, dd, *J* 13.0 and 5.0, $C^{4}H_AH_B$), 0.86 (9H, s, Si-C(CH_3)$_3$), 0.04 (3H, s, Si-CH_3), 0.03 (3H, s, Si-CH_3); *m/z* ESI^+ found 346.1812 (M+Na, $C_{17}H_{29}NO_3SiNa$ requires 346.1809); ν_{max}/cm^{-1} ($CHCl_3$): 2952, 2929, 2857, 1730 (C=O), 1681 (C=O), 1383, 1107, 1074. The aldehyde **200** was used in its crude form for further reactions as, after attempted purification, a complex mixture of products were formed, including the side product **206**. In addition, this side-

product **206** was also formed during attempted reactions involving the aldehyde **200**. Data was collected for a mixture of diastereoisomers in a 2:1 ratio: δ_H (400 MHz, $CDCl_3$): Data for the major isomer: 5.12 (1H, *br s*, $C^{11}H$), 4.55-4.46 (1H, m, C^3H), 4.17 (1H, *app* s, $C^{10}H$), 3.41 (1H, dd, *J* 9.2 and 7.2, $C^2H_AH_B$), 3.01 (1H, dd, *J* 12.4 and 2.4, $C^{12}H_AH_B$), 2.77-2.60 (2H, m, $C^2H_AH_B$ and $C^{12}H_AH_B$), 2.56-2.33 (5H, m, C^6H_2, C^7H_2 and $C^9H_AH_B$), 1.98-1.85 (3H, m, C^4H_2 and $C^9H_AH_B$), 0.87 (9H, s, Si-C(CH_3)$_3$), 0.06 (3H, s, Si-CH_3), 0.04 (3H, s, Si-CH_3); Data for the minor isomer, where different from the major isomer: 4.87 (1H, dd, *J* 8.8 and 2.6, $C^{11}H$), 3.70 (1H, *br* s, $C^{10}H$), 3.32 (1H, dd, *J* 9.2 and 7.2, $C^2H_AH_B$), 2.86 (1H, dd, *J* 12.4 and 2.6, $C^{12}H_AH_B$); δ_C (100 MHz, $CDCl_3$): Data for the major isomer: 209.5 (C=O), 90.5 (CH), 73.8 (CH), 69.4 (CH), 60.7 (CH_2), 58.6 (C), 48.2 (CH_2), 44.5 (CH_2), 43.0 (CH_2), 37.9 (CH_2), 25.9 (3 × CH_3), 20.3 (CH_2), 18.1 (C), -4.7 (2 × CH_3); Data for the minor isomer, where different from the major isomer: 93.5 (CH), 79.2 (CH), 69.9 (CH), 59.9 (CH_2), 59.3 (C), 49.8 (CH_2), 44.7 (CH_2), 42.4 (CH_2), 21.3 (CH_2); *m/z* ESI^+ found 342.2078 (M+H, $C_{17}H_{32}NO_4Si$ requires 342.2095); ν_{max}/cm^{-1} ($CHCl_3$): 3595, 2930, 2856, 1718 (C=O), 1118, 1090, 1054, 950, 908.

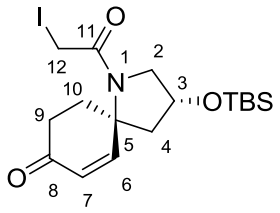
N-Acetyl-chloride-(3*R*,5*S*)-3-(*tert*-butyl-dimethyl-silyloxy)-8-oxo-1-azaspiro[4.5]dec-6-ene (210)



Trifluoroacetic acid (1.71 mL, 22.1 mmol) was added to a stirred solution of the Boc-protected amine **148** (282 mg, 738 μmol) in dry CH_2Cl_2 (5 mL) under argon. The mixture was stirred for 1 h at rt before being diluted with CH_2Cl_2 (5 mL) and water (5 mL). The mixture was cooled to 0 °C and NaOH (2 M) was added (until the aqueous phase was pH 10).

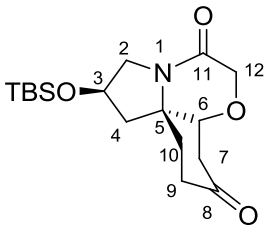
The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo* to a volume of about 10 mL. Then the mixture was cooled to 0 °C under argon before the addition of triethylamine (118 μl, 849 μmol). A solution of chloroacetylchloride (115 mg, 1.02 mmol) in CH_2Cl_2 (2 mL) was added dropwise and the resultant mixture stirred for 1 h at 0 ˚C and then 3 h at rt. The mixture was again cooled to 0 ˚C and water (20 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (1:1 petrol/EtOAc) to afford the keto-chloride **210** (204 mg, 77% over 2 steps) as a yellow oil which crystallised under high vacuum. $[\alpha]_D^{25}$ 58.3 (c 0.7, $CHCl_3$); mp : 62-63 °C; δ_H (270 MHz, d_6-DMSO, 70 °C) 6.81 (1H, d, *J* 10.3, C^6H), 5.75 (1H, d, *J* 10.3, C^7H), 4.53 (1H, m, C^3H), 4.27 (1H, d, *J* 13.2, $C^{12}H_AH_B$), 4.17 (1H, d, *J* 13.2, $C^{12}H_AH_B$), 3.89 (1H, dd, *J* 11.0 and 4.7, $C^2H_AH_B$), 3.54 (1H, *app* d, *J* 11.0, $C^2H_AH_B$), 2.78 (1H, td, *J* 13.2 and 5.1, $C^9H_AH_B$), 2.58-2.29 (3H, m, $C^9H_AH_B$ and $C^{10}H_2$), 2.24 (1H, *app* d, *J* 13.6, $C^4H_AH_B$), 1.98 (1H, dd, *J* 13.6 and 4.7, $C^4H_AH_B$), 0.89 (9H, s, Si-C(CH_3)$_3$), 0.11 (6H, s, Si-(CH_3)$_2$); δ_C (100 MHz, $CDCl_3$) 198.1 (C=O), 164.8 (C=O), 155.6 (CH), 127.2 (CH), 70.5 (CH), 64.6 (C), 57.0 (CH_2), 43.0, (CH_2), 42.0 (CH_2) 35.2 (CH_2), 29.4 (CH_2), 25.7 (3 × CH_3), 18.0 (C), -4.7 (CH_3), -4.8 (CH_3); *m/z* ESI^+ found 380.1404 (M+Na, $C_{17}H_{28}NO_3SiClNa$ requires 380.1419); ν_{max}/cm^{-1} ($CHCl_3$): 2954, 2931, 2858, 1678, 1660, 1383, 1115, 1080, 1039, 1004. Found C, 56.9; H, 7.9; N, 3.3. $C_{17}H_{28}NO_3SiCl$ requires C, 57.0; H, 7.9; N, 3.9%.

N-Acetyl-iodide-(3*R*,5*S*)-3-(*tert*-butyl-dimethyl-silyloxy)-8-oxo-1-azaspiro[4.5]dec-6-ene (211)



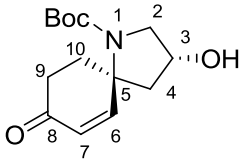
Sodium iodide (80.4 mg, 536 μmol) was added to a stirred solution of the keto-chloride **210** (64 mg, 179 μmol) in acetone (2 mL). The mixture was stirred for 4 h before removal of the solvent *in vacuo*. The residue was dissolved in water (10 mL) and EtOAc (10 mL). The two layers were separated and the aqueous layer was further extracted with EtOAc (2 × 10 mL). The combined organic layers were washed sequentially with saturated $Na_2S_2O_3$ solution (10 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (8:2 petrol/EtOAc) to give the pure iodo-ketone **211** (77.8 mg, 97%) as an orange solid. $[\alpha]_D^{27}$ 55.0 (c 0.2, $CHCl_3$); mp : 71-73 °C; δ_H (400 MHz, $CDCl_3$) 6.73 (1H, d, *J* 10.2, C^6H), 5.92 (1H, d, *J* 10.2, C^7H), 4.52 (1H, *app* s, C^3H), 3.82 (1H, dd, *J* 10.8 and 4.4, $C^2H_AH_B$), 3.65 (1H, d, *J* 9.6, $C^{12}H_AH_B$), 3.60 (1H, d, *J* 9.6, $C^{12}H_AH_B$), 3.53 (1H, *app* d, *J* 10.8, $C^2H_AH_B$), 2.99-2.90 (1H, m, $C^9H_AH_B$), 2.60-2.51 (1H, m, $C^{10}H_AH_B$), 2.50-2.36 (2H, m, $C^9H_AH_B$ and C^{10} H_AH_B), 2.26 (1H, *app* d, *J* 13.8, $C^4H_AH_B$), 1.92 (1H, dd, *J*, 13.8 and 4.4, C^4 H_AH_B), 0.90 (9H, s, Si-C(CH_3)$_3$), 0.11 (6H, s, Si-(CH_3)$_2$); δ_C (100 MHz, $CDCl_3$) 198.2 (C=O), 166.5 (C=O), 155.6 (CH), 127.1 (CH), 70.5 (CH), 64.4 (C), 57.9 (CH_2), 42.1 (CH_2), 35.1 (CH_2), 29.1 (CH_2), 25.8 (3 × CH_3), 18.0 (C), -0.6 (CH_2), -4.7 (CH_3), -4.8 (CH_3); *m/z* ESI^+ found 450.0939 (M+H, $C_{17}H_{29}NO_3SiI$ requires 450.0956) and 472.0764 (M+Na, $C_{17}H_{28}NO_3SiINa$ requires 472.0775); ν_{max}/cm^{-1} ($CHCl_3$): 2931, 2858, 1678, 1650, 1399, 1383, 1115, 1080, 1031, 1003. Found C, 45.5; H, 6.2; N, 2.9. $C_{17}H_{28}NO_3SiI$ requires C, 45.4; H, 6.3; N, 3.1%.

(2*R*,6a*S*,10a*S*)-2-(*tert*-butyl-dimethyl-silyloxy)-hexahydro-6-oxa-3a-aza-cyclopenta[*d*]naphthalene-4,8-dione (212)



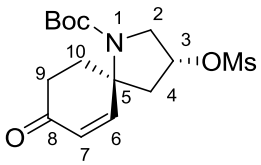
A solution of potassium carbonate (45.5 mg, 329 μmol) in water (0.5 mL) was added to a stirred solution of the iodo-ketone **211** (77.8 mg, 173 μmol) in acetone (1.5 mL). The mixture was stirred for 10 days before removal of the solvent *in vacuo*. The residue was dissolved in water (10 mL) and EtOAc (10 mL). The two layers were separated and the aqueous layer was further extracted with EtOAc (2 × 10 mL). The combined organic layers were washed sequentially with water (10 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (3:2 CH_2Cl_2/Et_2O) to afford the pure amide **212** (40.0 mg, 68%) as colourless columns, which were analysed by X-ray crystallography (see **Appendix**). $[\alpha]_D^{23}$ 60.0 (c 0.3, $CHCl_3$); mp : 149-151 °C; δ_H (400 MHz, $CDCl_3$) 4.56 (1H, *app* t, *J* 6.0, C^3H), 4.32 (1H, d, *J* 16.8, $C^{12}H_AH_B$), 4.12 (1H, d, *J* 16.8, $C^{12}H_AH_B$), 4.12 (1H, dd, *J* 14.0 and 6.0, $C^2H_AH_B$), 3.66 (1H, dd, *J*, 4.0 and 2.8, C^6H), 3.42 (1H, *app* d, *J* 14.0, $C^2H_AH_B$), 2.70-2.60 (2H, m, $C^7H_AH_B$, $C^9H_AH_B$), 2.55 (1H, dd, *J* 15.6 and 4.0, $C^7H_AH_B$), 2.44-2.22 (4H, m, $C^4H_AH_B$, $C^9H_AH_B$ and $C^{10}H_2$), 1.89-1.81 (1H, *app* ddd, *J* 13.2, 6.0 and 1.2, $C^4H_AH_B$), 0.88 (9H, s, Si-C(CH_3)$_3$), 0.09 (6H, s, Si-(CH_3)$_2$); δ_C (100 MHz, $CDCl_3$) 206.5 (C=O), 165.6 (C=O), 79.9 (CH), 69.3 (CH), 67.2 (CH_2), 62.4 (C), 54.9 (CH_2), 44.2 (CH_2), 41.8 (CH_2), 37.5 (CH_2), 30.4 (CH_2), 25.7 (3 × CH_3), 17.9 (C), -4.8 (CH_3), -4.9 (CH_3); *m/z* ESI^+ found 340.1924 (M+H, $C_{17}H_{30}NO_4Si$ requires 340.1939) and 362.1754 (M+Na, $C_{17}H_{29}NO_4SiNa$ requires 362.1758); ν_{max}/cm^{-1} ($CHCl_3$): 2954, 2930, 2858, 1726, 1649, 1454, 1133, 1102, 1087.

N-Boc-(3*R*,5*S*)-3-hydroxy-8-oxo-1-azaspiro[4.5]dec-6-ene (215)[58]



TBAF (29.4 mL, 1.00 M in THF, 29.4 mmol) was added to a cooled (0 °C), stirred solution of enone **148** (5.61 g, 14.7 mmol) in dry THF (60 mL). The mixture was stirred for 2 days at rt before removal of the solvent *in vacuo*. The crude product was purified directly by column chromatography (1:1 petrol/EtOAc then EtOAc 100%) to afford the deprotected alcohol **215** (3.63 g, 92%) as a white solid. $[\alpha]_D^{27}$ 96.5 (c 0.4, $CHCl_3$) [lit.,[58] $[\alpha]_D^{29}$ 64.9 (c 0.1, $CHCl_3$)]. δ_H (400 MHz, d_6-DMSO): 6.80 (1H, dd, *J* 10.4 and 2.0, C^6H), 5.75 (1H, d, *J* 10.4, C^7H), 5.09 (1H, d, *J* 2.4, OH), 4.29-4.23 (1H, m, C^3H), 3.54 (1H, *app* td, *J* 10.8 and 4.8, $C^2H_AH_B$), 3.36-3.30 (1H, m, $C^2H_AH_B$), 2.70-2.20 (5H, m, C^4H_2, C^9H_2 and $C^{10}H_AH_B$), 1.93-1.82 (1H, m, $C^{10}H_AH_B$), 1.39 and 1.33 (9H, s, $CO_2C(CH_3)_3$); *m/z* ESI^+ found 290.1371 (M+Na, $C_{14}H_{21}NO_4Na$ requires 290.1363); ν_{max}/cm^{-1} ($CHCl_3$): 3612, 2978, 1682 (C=O), 1382, 1368, 1137, 1110. Spectroscopic data matched that previously reported.[58]

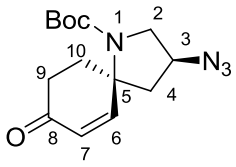
N-Boc-(3*R*,5*S*)-3-(methanesulfonyloxy)-8-oxo-1-azaspiro[4.5]dec-6-ene (216)[58]



Methanesulfonyl chloride (1.57 mL, 20.3 mmol) and triethylamine (5.66 mL. 40.6 mmol) were added to a stirred solution of the alcohol **215** (3.62 g, 13.5 mmol) in dry CH_2Cl_2 (130 mL) at rt under argon. The mixture was stirred overnight at rt before removal of the solvent *in*

vacuo. The crude product was purified directly by column chromatography (2:8 petrol/EtOAc) to afford the mesylated alcohol **216** (4.56 g, 98%) as a white solid. $[\alpha]_D^{24}$ 64.2 (c 0.5, $CHCl_3$) [lit.,[58] $[\alpha]_D^{29}$ 25.0 (c 0.1, $CHCl_3$)]. δ_H (400 MHz, d_6-DMSO) 6.84 (1H, dd, *J* 10.4 and 2.4, C^6H), 5.81 (1H, d, *J* 10.4, C^6H), 5.27 (1H, *app* t, *J* 4.8, C^3H), 3.85-3.76 (1H, m, $C^2H_AH_B$), 3.68-3.62 (1H, m, $C^2H_AH_B$), 3.27 (3H, s, SO_2CH_3), 2.70-2.55 (3H, m, C^9H_2 and $C^4H_AH_B$), 2.40-2.32 (1H, m, $C^4H_AH_B$), 2.27-2.07 (2H, m, $C^{10}H_2$), 1.40 and 1.34 (9H, s, $CO_2C(CH_3)_3$); *m/z* ESI^+ found 368.1133 (M+Na, $C_{15}H_{23}NO_6SNa$ requires 368.1138); ν_{max}/cm^{-1} ($CHCl_3$): 2978, 1682 (C=O), 1381, 1368, 1347, 1139, 962, 900. Spectroscopic data matched that previously reported.[58]

N-Boc-(3*R*,5*S*)-3-azido-8-oxo-1-azaspiro[4.5]dec-6-ene (178)[58]

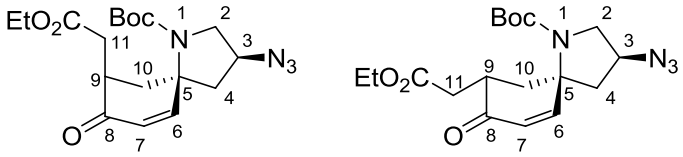


Sodium azide (2.14 g, 32.9 mmol) was added to a stirred solution of the mesylated alcohol **216** (4.55 g, 13.2 mmol) in dry DMF (90 mL) under argon. The mixture was stirred at 80 °C for 2 days. Water (150 mL) was added and the aqueous layer extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with water (150 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (7:3 petrol/EtOAc) to afford the azido compound **178** (3.50 g, 91%) as a colourless oil. $[\alpha]_D^{22}$ 30.4 (c 0.7, $CHCl_3$) [lit.,[58] $[\alpha]_D^{31}$ 28.2 (c 1.4, $CHCl_3$)]. δ_H (400 MHz, d_6-DMSO) 6.91 (1H, d, *J* 10.0, C^6H), 5.77 (1H, d, *J* 10.0, C^7H), 4.39 (1H, *app* p, *J* 6.0, C^3H), 3.70-3.60 (1H, m, $C^2H_AH_B$), 3.34 (1H, dd, *J* 11.6 and 6.0 $C^2H_AH_B$), 2.71-2.52 (3H, m, C^9H_2 and $C^4H_AH_B$), 2.38-2.30 (1H, m, $C^4H_AH_B$), 2.06-1.83 (2H, m, $C^{10}H_2$), 1.39 and 1.33 (9H, s, $CO_2C(CH_3)_3$); *m/z*

ESI^+ found 315.1425 (M+Na, $C_{14}H_{20}N_4O_3Na$ requires 315.1428); ν_{max}/cm^{-1} ($CHCl_3$): 2938, 2105, 1682 (C=O), 1380, 1368, 1154, 1136. Spectroscopic data matched that previously reported.[58]

N-Boc-(3*R*,5*S*,9*R*)-3-azido-8-oxo-9-(ethyl-acetate)-1-azaspiro[4.5]dec-6-ene (217)

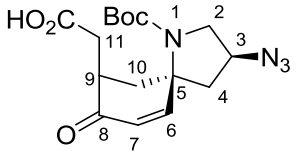
N-Boc-(3*R*,5*S*,9*S*)-3-azido-8-oxo-9-(ethyl-acetate)-1-azaspiro[4.5]dec-6-ene (218)



Freshly prepared LDA (1.98 mL, 0.611 M in THF, 1.21 mmol) was slowly added to a cooled (-78 °C), stirred solution of the enone **178** (272 mg, 930 μmol) in dry THF (9 mL). The mixture was stirred for 1 h at -78 °C before the addition of ethylbromoacetate (515 μL, 4.65 mmol) dissolved in dry DMPU (1.12 mL, 9.30 mmol). The mixture was then stirred for another 3 h at -78 °C before being allowed to warm slowly to rt overnight. Saturated $NaHCO_3$ solution (10 mL) was added and the aqueous layer extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (8:2 petrol/EtOAc then 6:4 petrol/EtOAc) to afford the ethyl ester **217:218** (203 mg, 57%) as a yellow oil, in addition to the recovery of some starting material **178** (72.5 mg, 27%). $[\alpha]_D^{27}$ 93.9 (c 0.8, $CHCl_3$); Data was collected for a mixture of diastereoisomers in a 1:1.4 ratio: δ_H (270 MHz, d_6-DMSO, 90 °C): Data for the major isomer **218**: 6.73 (1H, dd, *J* 10.0 and 1.4, C^6H), 5.95 (1H, d, *J* 10.0, C^7H), 4.40-4.28 (1H, m, C^3H), 4.14-4.00 (2H, m, $CO_2CH_2CH_3$), 3.66 (1H, dd, *J* 5.9 and 2.6 $C^2H_AH_B$), 3.56-

3.38 (1H, m, $C^2H_AH_B$), 2.98-2.86 (1H, m, C^9H), 2.72-2.54 (2H, m, $C^{11}H_2$), 2.47-2.36 (1H, m, $C^{10}H_AH_B$), 2.35-2.23 (1H, m, $C^4H_AH_B$), 2.19-2.06 (1H, m, $C^4H_AH_B$), 2.03-1.90 (1H, m, $C^{10}H_AH_B$), 1.38 (9H, s, $CO_2C(CH_3)_3$), 1.20 (3H, t, *J* 7.0, $CO_2CH_2CH_3$); Data for the minor isomer **217**, where different from the major isomer: 6.88 (1H, dd, *J* 10.0 and 2.2, C^6H), 5.80 (1H, d, *J* 10.0, C^7H), 3.71 (1H, dd, *J* 5.9 and 2.9, $C^2H_AH_B$), 1.21 (3H, t, *J* 7.0, $CO_2CH_2CH_3$); δ_C (68 MHz, d_6-DMSO, 90 °C): Data for the major isomer **218**: 198.1 (C=O), 170.9 (C=O), 155.6 (CH), 149.9 (C=O), 127.4 (CH), 79.4 (C), 61.4 (C), 59.3 (CH_2), 56.9 (CH), 51.6 (CH_2), 46.9 (CH_2), 40.6 (CH), 39.7 (CH_2), 34.2 (CH_2), 27.5 (3 × CH_3), 13.5 (CH_3); Data for the minor isomer **217**, where different from the major isomer: 196.9 (C=O), 170.7 (C=O), 152.5 (CH), 152.0 (C=O), 125.2 (CH), 79.3 (C), 56.8 (CH), 50.9 (CH_2), 47.4 (CH_2), 38.7 (CH_2), 33.6 (CH_2); *m/z* ESI^+ found 401.1797 (M+Na, $C_{18}H_{26}N_4O_5Na$ requires 401.1795); ν_{max}/cm^{-1} ($CHCl_3$): 2980, 2934, 2105 (N_3), 1727, 1682, 1368, 1154, 1137, 1097.

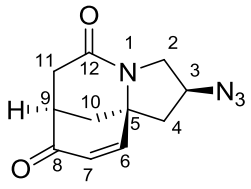
N-Boc-(3*R*,5*S*,9*R*)-3-azido-8-oxo-9-(acetic-acid)-1-azaspiro[4.5]dec-6-ene (219)



NaOH (2 M, 4 mL) was added to a stirred solution of ethyl ester **217:218** (110 mg, 290 μmol) in THF (1.5 mL) and the resultant mixture stirred vigorously for 2 days at rt. The mixture was then diluted with Et_2O (10 mL) and cooled to 0 °C before the slow addition of concentrated HCl with vigorous agitation (until the pH of the solution was slightly acidic). The aqueous layer was then extracted with Et_2O (3 × 20 mL) and the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column

chromatography (95:4:1 CH_2Cl_2/MeOH/AcOH) to afford the acid **219** (91.1 mg, 90%) as a white solid. $[\alpha]_D^{25}$ 75.3 (c 0.8, $CHCl_3$); mp: 62-64 °C; δ_H (270 MHz, d_6-DMSO, 90 °C) 6.87 (1H, dd, *J* 10.2 and 2.3, C^6H), 5.80 (1H, d, *J* 10.2, C^7H), 4.35 (1H, *app* pent, *J* 5.9, C^3H), 3.68 (1H, dd, *J* 11.3 and 5.9 $C^2H_AH_B$), 3.43 (1H, ddd, *J* 11.3, 5.9 and 1.0, $C^2H_AH_B$), 2.93-2.80 (1H, m, $C^{11}H_AH_B$), 2.73-2.54 (3H, m, $C^4H_AH_B$, $C^9H_AH_B$ and $C^{10}H_AH_B$), 2.31 (1H, dd, *J* 16.5 and 5.9, $C^{11}H_AH_B$), 2.10 (1H, dd, *J* 13.3 and 5.9, $C^4H_AH_B$), 1.99 (1H, ddd, *J* 12.1, 4.4 and 2.3, $C^{10}H_AH_B$), 1.38 (9H, s, $CO_2C(CH_3)_3$); δ_C (68 MHz, d_6-DMSO, 90 °C) 197.1 (C=O), 172.0 (C=O), 155.5 (CH), 152.0 (C=O), 125.3 (CH), 79.2 (C), 61.4 (C), 56.8 (CH), 50.9 (CH_2), 41.4 (CH_2), 40.5 (CH), 38.1 (CH_2), 33.6 (CH_2), 27.6 (3 × CH_3); *m/z* ESI^+ found 373.1479 (M+Na, $C_{16}H_{22}N_4O_5Na$ requires 373.1482); ν_{max}/cm^{-1} ($CHCl_3$): 3176, 2977, 2931, 2105 (N_3), 1710, 1682, 1392, 1368, 1138.

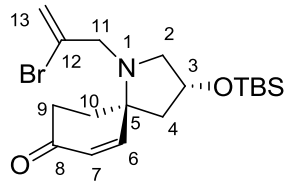
Tricycle (221)



Trifluoroacetic acid (406 μL, 5.23 mmol) was added to a stirred solution of acid **219** (61.6 mg, 176 μmol) in CH_2Cl_2 at rt under argon. The mixture was stirred for 90 min before the solvent was removed *in vacuo*. Triethylamine (73.5 μL, 528 μmol) and DPPA (56.9 μL, 264 μmol) were added to a cooled (0 °C), stirred solution of the crude free amine in dry DMF (5 mL). The mixture was then stirred at rt overnight before removal of the solvent *in vacuo*. The crude product was purified by column chromatography (9:1 CH_2Cl_2/MeOH) to afford the tricycle **221** (40.0 mg, 99%) as colourless rods, which were analysed by X-ray crystallography (see **Appendix**). $[\alpha]_D^{25}$ 396.3 (c 0.6, $CHCl_3$); mp : 108-110 °C; δ_H (400 MHz,

$CDCl_3$) 7.34 (1H, d, *J* 9.6 C^6H), 5.94 (1H, d, *J* 9.6, C^7H), 4.47-4.40 (1H, m, C^3H), 3.99 (1H, dd, *J* 13.6 and 6.8, $C^2H_AH_B$), 3.61 (1H, d, *J* 13.6, $C^2H_AH_B$), 3.03-2.96 (1H, m, C^9H), 2.77 (1H, dd, *J* 19.0 and 8.4, $C^{11}H_AH_B$), 2.61 (1H, d, *J* 12.4, $C^{10}H_AH_B$), 2.46 (1H, d, *J* 19.0, $C^{11}H_AH_B$), 2.35 (1H, d, *J* 14.0, $C^4H_AH_B$), 2.12 (1H, dd, *J* 14.0 and 6.4, $C^4H_AH_B$), 1.84 (1H, d, 12.6, $C^{10}H_AH_B$); δ_C (100 MHz, $CDCl_3$) 199.9 (C=O), 167.1 (C=O), 152.4 (CH), 127.5 (CH), 58.7 (C), 58.1 (CH), 51.4 (CH_2), 43.5 (CH_2), 41.4 (CH), 37.6 (CH_2), 33.7 (CH_2); *m/z* ESI^+ found 255.0846 (M+Na, $C_{11}H_{12}N_4O_2Na$ requires 255.0852); ν_{max}/cm^{-1} ($CHCl_3$): 2117 (N_3), 1683 (C=O), 1640 (C=O). Found C, 56.9; H, 5.4; N, 24.1. $C_{11}H_{12}N_4O_2$ requires C, 56.9; H, 5.2; N, 22.1% (loss of azido group possible at high temperature).

(3*R*,5*S*)-1-(2-bromo-allyl)-3-(*tert*-butyl-dimethyl-silyloxy)-1-azaspiro[4.5]dec-6-en-8-one (187)[58]

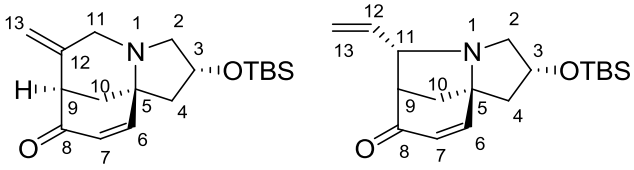


Trifluoroacetic acid (12.3 mL, 160 mmol) was added to a stirred solution of the Boc-protected amine **148** (2.04 g, 5.34 mmol) in dry CH_2Cl_2 (50 mL) under argon. The mixture was stirred for 1 h at rt before being diluted with CH_2Cl_2 (10 mL) and water (10 mL). The mixture was then cooled to 0 °C and NaOH (2 M) was added (until the aqueous layer was pH 10). The aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL) and the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo* to dryness. Potassium carbonate (3.69 g, 26.7 mmol), sodium iodide (397 mg, 2.67 mmol) and 2,3-dibromopropene (1.30 mL, 13.3 mmol) were added to a stirred solution of the crude free amine in dry acetonitrile (50 mL). The mixture was stirred for 2 days at rt, before another addition of 2,3-dibromopropene (521

μL, 5.34 mmol) and sodium iodide (159 mg, 1.07 mmol). The mixture was stirred for another 2 days. Water (40 mL) was added and the aqueous layer extracted with EtOAc (3 × 40 mL). The combined organic layers were washed sequentially with saturated $Na_2S_2O_3$ solution (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (10:1 petrol/EtOAc) to afford the vinyl bromide **187** (1.58 g, 74% over 2 steps) as a yellow oil. $[\alpha]_D^{26}$ 23.9 (c 0.5, $CHCl_3$) [lit.,[58] $[\alpha]_D^{25}$ 25.5 (c 0.8, $CHCl_3$)]. δ_H (400 MHz, $CDCl_3$) 6.69 (1H, dd, *J* 8.4 and 1.6, C^6H), 5.97 (1H, d, *J* 8.4, C^7H), 5.90 (1H, d, *J* 0.8, $C^{13}H_AH_B$), 5.52 (1H, *app* s, $C^{13}H_AH_B$), 4.46-4.41 (1H, m, C^3H), 3.38-3.33 (1H, m, $C^2H_AH_B$) 3.35 (1H, d, *J* 12.4, $C^{11}H_AH_B$), 3.27 (1H, d, *J* 12.4, $C^{11}H_AH_B$), 2.61 (1H, dd, *J* 8.0 and 2.8, $C^2H_AH_B$), 2.55-2.50 (1H, m, $C^9H_AH_B$), 2.49-2.41 (1H, m, $C^9H_AH_B$), 2.32-2.27 (1H, m, $C^4H_AH_B$), 2.05-1.98 (3H, m, $C^4H_AH_B$ and $C^{10}H_2$), 0.87 (9H, s, Si-C(CH_3)$_3$), 0.05 (3H, s, Si-CH_3), 0.04 (3H, s, Si-CH_3); *m/z* ESI^+ found 400.1300 (M+H, $C_{18}H_{31}NO_2{}^{79}BrSi$ requires 400.1302); ν_{max}/cm^{-1} ($CHCl_3$): 2954, 2930, 2857, 1678 (C=O), 1382, 1106, 1062, 900. Spectroscopic data matched that previously reported.[58]

(1*S*,3*R*)-3-(*tert*-butyl–dimethyl-silyloxy)-7-methylene-5-aza-tricyclo[6.3.1.0]-dodec-10-en-9-one (188)[58]

Tricyclic structure (224)



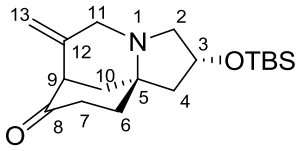
$Pd_2(dba)_3$ (365 mg, 353 μmol), Xantphos (408 mg, 706 μmol), potassium-*tert*-butoxide (991 mg, 8.83 mmol), and phenol (997 mg, 10.6 mmol) were added to a dry flask, which was then flushed with argon. Dry THF (25 mL) was added and the mixture stirred at reflux for 10 min.

A solution of vinyl bromide **187** (1.41 g, 3.53 mmol) in dry THF (20 mL) was then added slowly and the mixture stirred for 4 h at reflux. The mixture was allowed to cool to rt and was poured into NaOH (1 M, 150 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 60 mL) and the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was dry-loaded onto silica and purified by column chromatography (4:1 petrol/EtOAc then 1:1 petrol/EtOAc) to afford the desired tricycle **188** (589 mg, 52%) as a yellow oil and the undesired tricycle (221 mg, 19%) **224** as a yellow oil. Data for tricycle **188**: $[\alpha]_D^{24}$ 16.0 (c 0.7, $CHCl_3$) [lit.,[58] $[\alpha]_D^{24}$ 41.1 (c 0.2, $CHCl_3$)]. δ_H (400 MHz, $CDCl_3$) 6.49 (1H, dd, *J* 10.0 and 2.2, C^6*H*), 6.18 (1H, dd, *J* 10.0 and 0.8, C^7*H*), 5.01 (1H, br s, C^{13}*H*$_A$H$_B$), 4.90 (1H, br s, C^{13}H$_A$*H*$_B$), 4.61-4.54 (1H, m, C^3*H*), 3.37 (1H, d, *J* 14.4, C^{11}*H*$_A$H$_B$), 3.24-3.18 (2H, m C^{11}*H*$_A$H$_B$ and C^9*H*), 2.90 (2H, d, *J* 5.2, C^2*H*$_2$), 2.28 (1H, dd, *J* 12.8 and 7.6, C^4*H*$_A$H$_B$), 2.26 (1H, dd, *J* 12.4 and 3.2, C^{10}*H*$_A$H$_B$), 2.11 (1H, *J* 12.4, 3.2 and 2.2 C^{10}H$_A$*H*$_B$), 1.76 (1H, dd, *J* 12.8 and 4.8, C^{4}H$_A$*H*$_B$), 0.89 (9H, s, Si-C(C*H*$_3$)$_3$), 0.06 (6H, s, 2 × Si-C*H*$_3$); *m/z* ESI$^+$ found 320.2027 (M+H, $C_{18}H_{30}NO_2Si$ requires 320.2027); ν_{max}/cm^{-1} ($CHCl_3$): 2930, 2857, 1680 (C=O), 1124, 1105, 1087, 1056, 902. Spectroscopic data matched that previously reported.[58]

Data for tricycle **224**: $[\alpha]_D^{24}$ 4.78 (c 1.002, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.13 (1H, dd, *J* 9.6 and 1.6, C^6*H*), 5.83-5.92 (2H, m, C^7*H* and C^{12}*H*), 5.28 (1H, ddd, *J* 16.8, 1.6 and 0.8, C^{13}*H*$_A$H$_B$), 5.22 (1H, dd, *J* 10.0 and 1.6, C^{13}H$_A$*H*$_B$), 4.50 (1H, *app* pent, *J* 5.3, C^3*H*), 3.58 (1H, d, *J* 9.6, C^{11}*H*), 3.01 (1H, dd, *J* 10.4 and 5.3, C^2*H*$_A$H$_B$), 2.96 (1H, *app* d, *J* 4.4, C^9*H*), 2.89 (1H, dd, *J* 10.4 and 5.3, C^{2}H$_A$*H*$_B$), 2.26 (1H, ddd, *J* 11.2, 4.4 and 1.6, C^{10}*H*$_A$H$_B$), 2.20-2.14 (2H, m, C^4*H*$_A$H$_B$ and C^{10}H$_A$*H*$_B$), 2.00 (1H, dd, *J* 13.2 and 5.3, C^{4}H$_A$*H*$_B$), 0.89 (9H, s, Si-C(C*H*$_3$)$_3$), 0.07 (3H, s, Si-C*H*$_3$), 0.06 (3H, s, Si-C*H*$_3$); δ_C (100 MHz, $CDCl_3$) : 201.8 (C=O), 160.5 (CH), 137.1 (CH), 127.7 (CH), 118.9 (CH_2), 74.6 (CH), 70.2 (C), 63.5 (CH), 60.4 (CH), 55.5 (CH), 43.2 (CH_2), 42.1 (CH_2), 25.9 (3 × CH_3), 18.2 (C) -4.8 (2 × CH_3); *m/z* ESI$^+$

found 320.2042 (M+H, $C_{18}H_{30}NO_2Si$ requires 320.2040); ν_{max}/cm^{-1} ($CHCl_3$) : 2954, 2929, 2885, 2857, 1674 (C=O), 1375, 1115, 1061, 1043, 901.

(1*S*,3*R*)-3-(*tert*-butyl–dimethyl-silyloxy)-7-methylene-5-aza-tricyclo[6.3.1.0]-dodecan-9-one (225)[58]

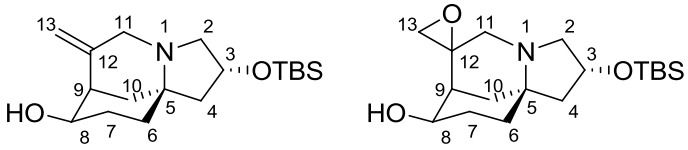


A 2-neck flask equipped with a cold finger condenser was flame-dried, flushed with Argon for 20 minutes and then flushed with dry ammonia. The flask was cooled to -78 °C and dry ice/acetone was added to the cold trap of the condenser. After ammonia (~ 100 mL) was condensed in the flask, a small piece of lithium solid (washed with petrol) was added and the solution turned deep blue in a few seconds. After 10 minutes of stirring, a solution of enone **188** (750 mg, 2.35 mmol) in dry THF (25 mL) was added slowly. The mixture was stirred for 2 h at -78 °C, and the excess of lithium was quenched with anhydrous NH_4Cl until the solution became transparent again. Then Et_2O (30 mL) was added and the mixture left stirring overnight in order to allow the ammonia to evaporate. Water (50 ml) was added and the two layers were separated before the aqueous layer was further extracted with Et_2O (3 × 40 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (1:1 petrol/EtOAc) to afford the pure ketone **225** (543 mg, 72%) as a yellow oil. $[\alpha]_D^{24}$ 70.3 (c 0.7, $CHCl_3$) [lit.,[58] $[\alpha]_D^{24}$ 45.0 (c 0.1, $CHCl_3$)]. δ_H (400 MHz, $CDCl_3$) 4.99 (1H, *app* s, $C^{13}H_AH_B$), 4.93 (1H, *app* s, $C^{13}H_AH_B$), 4.42 (1H, *app* pent, *J* 5.6, C^3H), 3.60 (1H, d, *J* 14.0, $C^{11}H_AH_B$), 3.54 (1H, d, *J* 14.0, $C^{11}H_AH_B$), 3.28 (1H, dd, *J* 10.2 and 5.6, $C^2H_AH_B$), 3.26-3.28 (1H, m, C^9H), 2.89 (1H,

ddd, *J* 12.4, 7.6 and 3.2, $C^{7}H_{A}H_{B}$), 2.71 (1H, ddd, *J* 10.2, 5.6 and 0.8, $C^{2}H_{A}H_{B}$), 2.41 (1H, *app* dt, *J* 13.6 and 3.2, $C^{10}H_{A}H_{B}$), 2.20 (1H, *app* ddt, *J* 12.4, 6.0 and 2.0, $C^{7}H_{A}H_{B}$), 1.94-1.86 (2H, m, $C^{4}H_{A}H_{B}$ and $C^{6}H_{A}H_{B}$), 1.86-1.79 (1H, m, $C^{10}H_{A}H_{B}$), 1.76-1.67 (2H, m, $C^{4}H_{A}H_{B}$ and $C^{6}H_{A}H_{B}$), 0.88 (9H, s, Si-C(CH_3)$_3$), 0.06 (6H, s, 2 × Si-CH_3); *m/z* ESI^+ found 322.2199 (M+H, $C_{18}H_{32}NO_2Si$ requires 322.2197); ν_{max}/cm^{-1} ($CHCl_3$): 2929, 2857, 1708 (C=O), 1124, 1106, 1089, 1048, 905, 864. Spectroscopic data matched that previously reported.[58]

(1*S*,3*R*)-3-(*tert*-butyl–dimethyl-silyloxy)-7-methylene-5-aza-tricyclo[6.3.1.0]-dodecan-9-ol (226)

(1*S*,3*R*)-3-(*tert*-butyl–dimethyl-silyloxy)-7-epoxy-5-aza-tricyclo[6.3.1.0]-dodecan-9-ol (227)

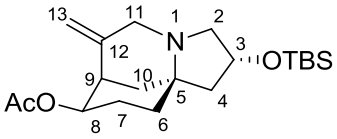


Sodium borohydride (33.1 mg, 875 μmol) was added to a stirred and cooled (0 °C) solution of ketone **225** (268 mg, 834 μmol) in dry methanol (12 mL) under argon. The mixture was stirred for 90 min at 0 °C before the careful addition of water (5 mL). The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (1:4 MeOH/$CHCl_3$) to afford the pure alcohol **226** (231 mg, 86%) as a yellow oil. In addition, varying amounts of the undesired side-product **227** were also obtained. Data for the alcohol **226**: $[\alpha]_D^{25}$ 11.4 (c 0.3, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 5.05 (1H, *app* s, $C^{13}H_{A}H_{B}$), 4.92 (1H, *app* s, $C^{13}H_{A}H_{B}$), 4.37 (1H, *app* pent, *J* 6.0, $C^{3}H$), 3.64 (1H, *app* dt, *J* 10.8 and 5.2, $C^{8}H$), 3.58 (1H, d, *J* 15.0, $C^{11}H_{A}H_{B}$), 3.46 (1H, d, *J* 15.0, $C^{11}H_{A}H_{B}$), 3.24 (1H, dd, *J* 9.6 and 6.0,

$C^2H_AH_B$), 2.75 (1H, br s, C^9H), 2.61 (1H, dd, *J* 9.6 and 6.0, $C^2H_AH_B$), 2.14 (1H, *app* dt, *J* 13.2 and 3.2, $C^{10}H_AH_B$), 1.85 (1H, dd, *J* 12.8 and 6.0, $C^4H_AH_B$), 1.80-1.73 (1H, m, $C^7H_AH_B$), 1.64-148 (4H, m, $C^4H_AH_B$, $C^7H_AH_B$, $C^{10}H_AH_B$ and $C^6H_AH_B$), 1.40-1.30 (1H, m, $C^6H_AH_B$), 0.87 (9H, s, Si-C(CH_3)$_3$), 0.04 (6H, s, 2 × Si-CH_3); δ_C (100 MHz, $CDCl_3$) 144.3 (C), 111.8 (CH_2), 71.4 (CH), 70.5 (CH), 63.2 (CH_2), 58.2 (C), 56.0 (CH_2), 48.4 (CH_2), 42.5 (CH), 37.6 (CH_2), 34.8 (CH_2), 29.7 (CH_2), 26.0 (3 × CH_3), 18.2 (C), -4.7 (2 × CH_3); *m/z* ESI^+ found 324.2367 (M+H, $C_{18}H_{34}NO_2Si$ requires 324.2353); ν_{max}/cm^{-1} ($CHCl_3$) : 3608, 2929, 2857, 1390, 1094, 1049, 906.

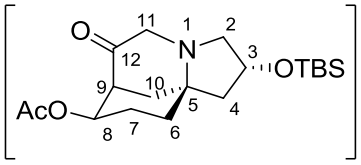
Data for the side product **227**: $[\alpha]_D^{27}$ 20.6 (c 0.3, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 4.36 (1H, *app* pent, *J* 5.0, C^3H), 3.50 (1H, br s, C^8H), 3.30 (1H, d, *J* 13.0, $C^{13}H_AH_B$), 3.21 (1H, dd, *J* 10.5 and 5.0, $C^2H_AH_B$), 275 (1H, d, *J* 4.5, $C^{11}H_AH_B$), 2.68 (1H, d, *J* 4.5, $C^{11}H_AH_B$) 2.52 (1H, ddd, *J* 10.5, 5.0 and 1.0, $C^2H_AH_B$), 2.49 (1H, d, *J* 13.0, $C^{13}H_AH_B$), 2.33 (1H, br s, C^9H), 2.12 (1H, *app* dt, *J* 13.5 and 3.5, $C^{10}H_AH_B$), 2.09-1.98 (1H, m, $C^7H_AH_B$), 1.91-1.85 (1H, m, $C^4H_AH_B$), 1.79 (1H, *app* dd, *J* 12.5 and 6.0, $C^7H_AH_B$), 1.64-1.58 (2H, m, $C^4H_AH_B$ and $C^6H_AH_B$), 1.45 (1H, dd, *J* 13.5 and 2.5, $C^{10}H_AH_B$), 1.32 (1H, *app* td, *J* 13.0 and 4.5, $C^6H_AH_B$), 0.86 (9H, s, Si-C(CH_3)$_3$), 0.04 (3H, s, Si-CH_3), 0.03 (3H, s, Si-CH_3); δ_C (100 MHz, $CDCl_3$) 74.2 (CH), 71.6 (CH), 63.3 (CH_2), 61.2 (C), 57.9 (C), 56.6 (CH_2), 53.8 (CH_2), 48.2 (CH_2), 39.1 (CH_2), 38.1 (CH), 35.1 (CH_2), 30.5 (CH_2), 26.0 (3 × CH_3), 18.2 (C), -4.7 (2 × CH_3); *m/z* ESI^+ found 340.2312 (M+H, $C_{18}H_{34}NO_3Si$ requires 340.2312); ν_{max}/cm^{-1} ($CHCl_3$) : 2930, 2857, 1648, 1462, 1362, 1050, 907.

(1*S*,3*R*)-3-(*tert*-butyl–dimethyl-silyloxy)-7-methylene-5-aza-tricyclo[6.3.1.0]-dodecan-9-ol acetate (228)



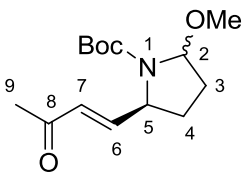
Pyridine (0.5 mL) was added to a stirred solution of the alcohol **226** (53.9 mg, 167 μmol) in Ac_2O (0.5 mL) under argon. The mixture was stirred for 15 h at rt before the solvents were removed *in vacuo*. The residue was dissolved in EtOAc (10 mL), and the organic layer washed sequentially with saturated $NaHCO_3$ solution (10 mL) and HCl (2 M). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography using (1:9 MeOH/$CHCl_3$) to afford the pure acetate-protected alcohol **228** (52.9 mg, 86%) as a yellow oil. $[\alpha]_D^{28}$ 26.1 (c 0.7, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 5.14 (1H, *app* s, $C^{13}H_AH_B$), 4.97 (1H, *app* s, $C^{13}H_AH_B$), 4.81 (1H, ddd, *J* 9.6, 5.2 and 4.4 C^8H), 4.45-4.40 (1H, m, C^3H), 3.86 (1H, d, *J* 14.4, $C^{11}H_AH_B$), 3.59 (1H, dd, *J* 11.2 and 5.2, $C^2H_AH_B$), 3.52 (1H, d, *J* 14.4, $C^{11}H_AH_B$), 2.93 (1H, br s, C^9H), 2.76 (1H, ddd, *J* 11.2, 4.0 and 1.0, $C^2H_AH_B$), 2.38 (1H, *app* dt, *J* 13.6 and 3.6, $C^{10}H_AH_B$), 2.02 (3H, s, CO_2CH_3), 2.02-1.98 (3H, m, $C^4H_AH_B$, C^6H_2 and $C^7H_AH_B$), 1.85-1.79 (1H, m, $C^7H_AH_B$), 1.70 (1H, ddd, *J* 13.2, 3.6 and 1.0, $C^4H_AH_B$), 1.60-1.58 (1H, m, $C^{10}H_AH_B$), 0.85 (9H, s, Si-C(CH_3)$_3$), 0.03 (6H, s, Si-(CH_3)$_2$); δ_C (100 MHz, $CDCl_3$) 170.6 (C=O), 139.2 (C), 116.0 (CH_2), 73.6 (CH), 70.3 (CH), 62.7 (CH_2), 61.2 (C), 54.9 (CH_2), 47.9 (CH_2), 38.4 (CH), 35.1 (CH_2), 34.2 (CH_2), 25.8 (3 × CH_3), 25.1 (CH_2), 21.4 (CH_3), 18.0 (C), -4.8 (2 × CH_3); *m/z* ESI^+ found 366.2465 (M+H, $C_{20}H_{36}NO_3Si$ requires 366.2459); ν_{max}/cm^{-1} ($CHCl_3$) : 2930, 2857, 1728 (C=O), 1368, 1099, 1046, 903.

(1*S*,3*R*)-3-(*tert*-butyl–dimethyl-silyloxy)-7-oxo-5-aza-tricyclo[6.3.1.0]-dodecan-9-ol acetate (233)



Following a modified procedure reported by Mariano,[77] 60% aq. perchloric acid (30 μL,) was added to a stirred solution of alkene **228** (33.0 mg, 90.3 μmol) in a mixture of CH_2Cl_2/MeOH (2.5 mL/7.5 mL) in a flask equipped with an inlet and outlet for gases. Firstly, O_2 was bubbled through the mixture to check the permeability of the system. Then O_3 was bubbled through the mixture for 20 s after which point TLC analysis showed complete consumption of starting material. The mixture was stirred for 30 min at -78 °C before the slow addition of dimethylsulfide (0.4 mL), followed, 5 min later by saturated $NaHCO_3$ solution (0.4 mL). The mixture was allowed to warm to rt, poured into cold water (10 mL) and extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give a colourless oil. Purification of the crude product **233** (29.5 mg, 90%) was unsuccessful as degradation occurred during column chromatography. The crude product was therefore used in the next step without further purification.

N-Boc-(*S*,*E*)-2-methoxy-5-(3-oxobut-1-enyl)-pyrrolidine (251)

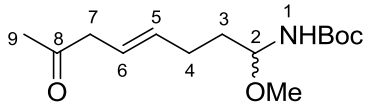


A solution of DIBAL-H (2.84 mL of a 1.00 M solution in hexane, 2.84 mmol) was added dropwise (*via* syringe pump) to a cooled (-78 °C), stirred solution of the methyl ester **249**

(369 mg, 1.42 mmol) in dry CH_2Cl_2 (15 mL) under argon. The mixture was stirred for 2 h at -78 °C before the dropwise addition of dry methanol (1 mL). The reaction was warmed to rt and potassium sodium tartrate solution (2 M, 15 mL) was added. The mixture was stirred for 1 h before the addition of water (15 mL) and CH_2Cl_2 (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic layers dried over $MgSO_4$. The solvent was removed *in vacuo* to afford the crude aldehyde **250** (371 mg) as a colourless oil. 1-Triphenylphoshoranylidene-2-propanone **160** (590 mg, 1.85 mmol) was added to a stirred solution of the crude aldehyde **250** in CH_2Cl_2 (5 mL) under argon. The mixture was stirred for 5 days at rt. The solvent was removed *in vacuo* and the resulting solid redissolved in the minimum amount of CH_2Cl_2. Addition of petrol resulted in the formation of a solid, which was then triturated. The solid was filtered and washed several times with petrol before the filtrate was collected and the solvent removed *in vacuo*. The crude product was purified by column chromatography (8:2 petrol/EtOAc) to afford enone **251** (244 mg, 64 %) as a yellow oil. $[\alpha]_D^{21}$ - 49.7 (c 0.7, $CHCl_3$); Data was collected for a mixture of diastereoisomers in a 1:1 ratio: δ_H (270 MHz, d_6-DMSO, 90 °C): Data for the first isomer: 6.69 (1H, dd, *J* 16.0 and 6.3, C^6H), 6.07 (1H, dd, *J* 16.0 and 1.0, C^7H), 5.16 (1H, dd, *J* 3.2 and 2.1, C^2H), 4.43-4.31 (1H, m, C^5H), 3.27 (3H, s, OCH_3), 2.31-2.12 (1H, m, $C^3H_AH_B$) 2.20 (3 H, s, C^9H_3), 1.88-1.65 (2H, m, $C^3H_AH_B$ and $C^4H_AH_B$), 1.48-1.34 (1H, m, $C^4H_AH_B$), 1.41-1.40 (9H, $CO_2C(CH_3)_3$; Data for the second isomer, where different from the first isomer: 6.68 (1H, dd, *J* 16.0 and 6.3, C^6H), 5.94 (1H, dd, *J* 16.0 and 1.0, C^7H), 5.06 (1H, *app* d, *J* 3.6, C^2H), 2.19 (3H, s, C^9H_3); δ_C (100 MHz, $CDCl_3$): Data was collected for a mixture of diastereoisomers and rotamers: 198.7/198.6/198.1 (C=O), 154.2/153.6 (C=O), 147.2/146.8 (CH), 130.4/129.6/129.4 (CH), 89.8/89.6/89.2 (CH), 80.8/80.7/80.6 (C), 58.0/57.4 (CH), 56.6/56.3/55.7 (CH_3), 30.0/29.3/29.1/28.1/27.5/27.4/27.1 (2 × CH_2 + CH_3), 28.4 (3 × CH_3). *m/z* ESI^+ found 292.1514 (M+Na, $C_{14}H_{23}NO_4Na$ requires 292.1519); ν_{max}/cm^{-1} ($CHCl_3$) : 2979, 2934, 1695,

1368, 1120, 1078, 976.

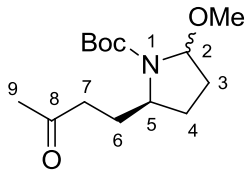
N-Boc-(*E*)-1-methoxy-7-oxo-oct-4-enyl (254)



A 2-neck flask equipped with a cold finger condenser was flame-dried, flushed with argon for 20 minutes and then flushed with dry ammonia. The flask was cooled to -78 °C and dry ice/acetone was added to the cold trap of the condenser. After ammonia (10-15 mL) was condensed in the flask, a small piece of lithium solid (washed with petrol) was added and the solution turned deep blue in a few seconds. After 10 minutes of stirring, a solution of enone **251** (60.0 mg, 223 μmol) in dry THF (8 mL) was added slowly. The mixture was stirred for 2 hours at -78 °C, and the excess of lithium was quenched with dry NH_4Cl until the solution became transparent again. Then Et_2O (20 mL) was added and the mixture left stirring overnight in order to allow the ammonia to evaporate. Water (30 ml) was added and the aqueous phase extracted with Et_2O (3 × 25 mL). The combined organic layers were dried over $MgSO_4$ and the mixture concentrated *in vacuo*. The crude product was purified by column chromatography (8:2 petrol/EtOAc) to afford the carbamate **254** (41.0 mg, 68%) as a colourless oil. $[\alpha]_D^{25}$ 7.5 (c 0.4, $CHCl_3$); data was collected for a mixture of diastereoisomers: δ_H (400 MHz, $CDCl_3$): 5.59-5.50 (2H, m, C^5H and C^6H), 4.87-4.74 (2H, m, C^2H and NH), 3.30 (3H, s, OCH_3), 3.20-3.10 (2H, m, C^7H_2), 2.14-2.09 (2H, m, C^4H_2), 2.12 (3H, s, C^9H_3), 1.75-1.65 (1H, m, $C^3H_AH_B$), 1.63-1.53 (1H, m, $C^3H_AH_B$), 1.43 (9H, s, $CO_2C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 207.5/206.9 (C=O), 155.5 (C=O), 133.7/132.2 (CH), 122.9/122.0 (CH), 82.4 (CH), 79.9 (C), 55.4 (CH_3), 47.6 (CH_2), 35.2 (CH_2), 29.5 (CH_2), 28.4 (3 × CH_3), 28.2 (CH_3). *m/z* ESI^+ found 292.1666 (M+Na, $C_{14}H_{25}NO_4Na$ requires 292.1676); ν_{max}/cm^{-1} ($CHCl_3$) :

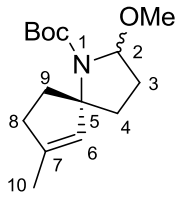
3436, 2933, 1714, 1494, 1368, 1158, 1049. Found C, 61.9; H, 9.3; N, 4.8. $C_{14}H_{25}NO_4$ requires C, 62.0; H, 9.3; N, 5.2%.

N-Boc-(*S*)-2-methoxy-5-(3-oxo-butyl)-pyrrolidine (260)



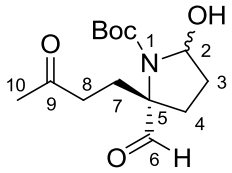
Pyridine (1.00 mL) was added to a stirred solution of enone **251** (1.38 g, 5.13 mmol) in EtOAc (40 mL) and the mixture degased with argon for 20 min. Then palladium (100 mg, 10% on C) was added and the mixture stirred for one day under an atmosphere of hydrogen (balloon). The catalyst was removed by filtration through a short pad of celite®, which was washed several times with EtOAc. The solvent was then removed *in vacuo* to afford pure ketone **260** (1.38 g, 99%) as a yellow oil. $[\alpha]_D^{30}$ - 43.9 (c 0.7, $CHCl_3$); Data was collected for a mixture of diastereoisomers and rotamers: δ_H (400 MHz, $CDCl_3$) 5.30-5.00 (1H, m, C^2H), 3.80 (1H, br s, C^5H), 3.31 (3H, s, OCH_3), 2.43 (2H, t, *J* 7.6, C^7H_2), 2.14 (3H, s, C^9H_3), 2.15-1.98 (2H, m, C^3H_2), 1.90-1.67 (4H, m, C^4H_2 and C^6H_2), 1.47 (9H, s, $CO_2C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) : 208.7 (C=O), 155.3 (C=O), 89.7 (CH), 80.2 (C), 57.4 (CH), 55.2 (CH_3), 41.2/40.4/39.7 (CH_2), 32.4/31.6/30.8/29.9/29.5 (3 × CH_2 + CH_3), 28.6 (3 × CH_3); *m/z* ESI^+ found 294.1662 (M+Na, $C_{14}H_{25}NO_4Na$ requires 294.1676); ν_{max}/cm^{-1} ($CHCl_3$) : 2934, 1690, 1391, 1367, 1119, 1078. Found C, 61.9; H, 9.4; N, 4.9. $C_{14}H_{25}NO_4$ requires C, 62.0; H, 9.3; N, 5.2%.

(*R*)-2-methoxy-7-methyl-1-azaspiro[4.4]non-6-ene (261)



^{n}BuLi (185 µl, 2.20 M in hexane, 407 µmol) was added to a cooled (-78 °C), stirred solution of trimethylsilyldiazomethane (235 µL, 2.00 M in Et_2O, 470 µmol) in dry THF (15 mL) under argon. The mixture was stirred for 45 minutes at -78 °C before a solution of ketone **260** (85.0 mg, 313 µmol) in dry THF (5 mL) was added slowly. The mixture was stirred for another 90 minutes at -78 °C before slowly being warmed to 0 °C. After 30 minutes of stirring at 0 °C, the reaction was quenched with saturated NH_4Cl solution (10 mL). The aqueous phase was extracted with Et_2O (3 × 15 mL), the combined organic layers dried over $MgSO_4$ and the mixture concentrated *in vacuo*. Purification of the crude product was attempted using column chromatography (95:5 petrol/EtOAc) to afford the spirocycle **261** (66.4 mg, 79%) as a yellow oil. However, it has never been possible to purify this product to a satisfactory standard, and due to its instability it was used immediately.

N-Boc-(*S*)-2-formyl-5-hydroxy-2-(3-oxo-butyl)-pyrrolidine (262)

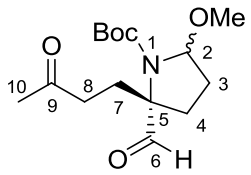


N-Methyl-morpholine-*N*-oxide monohydrate (58.7 mg, 435 µmol) followed by potassium osmate dihydrate (2.70 mg, 7.24 µmol) was added to a stirred solution of spirocycle **261** (38.7 mg, 145 µmol) in acetone (1.5 mL) and water (0.15 mL). The mixture was stirred for 4 days at rt before the addition of sodium thiosulfate (20 mg). The mixture was then allowed to

stir for another 2 h. Water (10 mL) was added and the aqueous layer extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude diol which was used without further purification. Sodium periodate (52.4 mg, 245 mmol) was added to a stirred solution of diol (36.9 mg, 123 μmol) in a mixture of THF/water (2:1, 1.2 mL). The mixture was stirred for 1 hour before water (5 mL) was added and the aqueous layer extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and the mixture concentrated *in vacuo*. The crude product was purified by column chromatography (5:4 petrol/EtOAc) to afford **262** (25.2 mg, 69%) as a colourless oil and **263** (5.90 mg, 16%) as a white foam. Data for the major product **262**: $[\alpha]_D^{24}$ 36.4 (c 0.9, $CHCl_3$); data was collected for a mixture of rotamers and diastereoisomers: δ_H (400 MHz, $CDCl_3$) : 9.47-9.28 (1H, m, $C^{10}H$), 5.72-5.41 (1H, m, $C^{2}H$), 4.00-3.20 (1H, m, $C^{7}H_AH_B$), 2.67-2.43 (2H, m, $C^{7}H_AH_B$ and $C^{3}H_AH_B$), 2.17-2.14 (3H, m, $C^{9}H_3$), 2.14-2.08 (1H, m, $C^{3}H_AH_B$) 2.05-1.65 (4H, m, $C^{4}H_2$ and $C^{6}H_2$), 1.49-1.41 (9H, m, $CO_2C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 208.7/207.7 (C=O), 199.1/198.8/198.7 (CHO), 154.0/153.3 (C=O), 84.0/83.6 (CH), 82.3/82.1/81.7 (C), 71.8/71.4 (C), 39.2/38.8/38.4/38.0 (CH_2), 31.8/31.2/30.8 (CH_2), 30.5/30.3/29.9 (CH_2), 28.5 (CH_3), 28.2 (3 × CH_3), 26.5/26.0/25.8 (CH_2); *m/z* ESI^+ found 308.1450 (M+Na, $C_{14}H_{23}NO_5Na$ requires 308.1450); ν_{max}/cm^{-1} ($CHCl_3$) : 3586, 2977, 2934, 2814, 1737, 1689, 1456, 1369, 1141, 1046, 980.

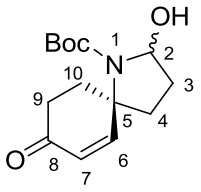
Data for the minor product **263**: see below.

N-Boc-(*S*)-2-formyl-5-methoxy-2-(3-oxo-butyl)-pyrrolidine (263)



$Pb(OAc)_4$ (335 mg, 755 μmol) was added to a stirred solution of diol (189 mg, 629 μmol, obtained as described previously) in dry CH_2Cl_2 (0.5 mL). The mixture was stirred for 10 min before water (12 mL) was added and the aqueous layer extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over $MgSO_4$ and the mixture concentrated *in vacuo*. The crude product was used in the next step without further purification. For analytical purposes, some of the crude product was purified by column chromatography (6:4 petrol/EtOAc) to afford the pure compound **263** as a white foaming solid. $[\alpha]_D^{24}$ 34.4 (c 0.6, $CHCl_3$); Data was collected for a mixture of rotamers and diasteroisomers: δ_H (400 MHz, $CDCl_3$) 9.53-9.31 (1H, m, $C^{10}H$), 5.42-4.96 (1H, m, C^2H), 3.43-3.33 (3H, m, OCH_3), 2.68-2.55 (1H, m, $C^7H_AH_B$), 2.53-2.40 (1H, m, $C^7H_AH_B$), 2.18-2.14 (3H, m, C^9H_3), 2.18-2.10 (2H, m, C^3H_2), 1.95-1.72 (4H, m, C^4H_2 and C^6H_2), 1.47-1.41 (9H, m, $CO_2C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 207.9 (C=O), 200.2/199.7 (CHO), 154.1 (C=O), 90.6 (CH), 81.9/81.4 (C), 71.6 (C), 56.2/55.8 (CH_3), 39.2/38.8/38.1/37.6 (CH_2), 31.8/31.2/30.8 (CH_2), 30.6/30.2/30.0 (CH_2), 28.4 (CH_3), 28.2 (3 × CH_3), 26.6/26.2/26.0 (CH_2); *m/z* ESI^+ found 322.1611 (M+Na, $C_{15}H_{25}NO_5Na$ requires 322.1625); ν_{max}/cm^{-1} ($CHCl_3$) : 2979, 2935, 1735, 1698, 1456, 1368, 1141, 1081.

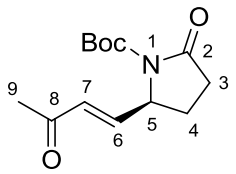
N-Boc-(*R*)-2-hydroxy-8-oxo-1-azaspiro[4.5]dec-6-ene-1 (264)



Potassium hydroxide (17.6 mg, 314 μmol) was added to a stirred, cooled (0 °C) solution of crude aldehyde **263** (188 mg, 628 μmol) in dry ethanol (8 mL). The mixture was stirred for 2 h at rt before the mixture was concentrated *in vacuo*. The residue was dissolved in saturated NH_4Cl solution (25 mL) and Et_2O (25 mL) and the aqueous layer extracted with Et_2O (2 × 25 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give the crude keto-alcohol. Methanesulfonyl chloride (742 μL, 9.59 mmol) and triethylamine (2.67 mL. 19.2 mmol) were sequentially added to a stirred solution of the crude keto alcohol (1.43 g, 4.79 mmol) in dry CH_2Cl_2 (70 mL) at 0 °C under argon. The mixture was stirred for 2 days during which time the ice bath expired. Saturated NH_4Cl solution (100 mL) was added and the aqueous layer extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Attempted purification of the crude product by column chromatography led to significant loss of material and therefore it was used directly in the next reaction. For analytical purposes, some of the crude product was purified by column chromatography (1:1 petrol/EtOAc) to afford the pure 5,6-spirocycle **264** as a yellow oil. $[\alpha]_D^{24}$ -115.3 (c 0.6, $CHCl_3$); Data was collected for a mixture of rotamers and diastereoisomers: δ_H (400 MHz, $CDCl_3$) 6.85-6.68 (1H, m, C^6*H*), 5.95-5.80 (1H, m, C^7*H*), 5.60-5.40 (1H, m, C^2*H*), 2.70-2.32 (3H, m, C^9*H*$_2$, C^{10}*H*$_A$H$_B$), 2.21-2.05 (2H, C^3*H*$_2$), 2.04-1.81 (3H, m, C^4*H*$_2$, C^{10}H$_A$*H*$_B$), 1.47-1.38 (9H, $CO_2C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 198.3/198.0 (C=O), 157.9/157.6/157.3 (CH), 154.1/152.5 (C=O), 127.7/126.8/126.4 (CH), 83.4/82.9/82.3 (CH), 81.7/81.4 (C), 63.1/62.7/62.3 (C), 35.7/35.4 (CH_2), 33.2/32.1 (CH_2), 31.0/30.9/30.7 (CH_2), 30.2/30.1/29.4 (CH_2), 28.6/28.4 (3 × CH_3); *m/z* ESI$^+$ found 290.1352 (M+Na,

$C_{14}H_{21}NO_4Na$ requires 290.1363); ν_{max}/cm^{-1} ($CHCl_3$) : 3582, 2978, 1730 (C=O), 1674 (C=O), 1368, 1137, 1042, 972, 900.

N-Boc-(*S*,*E*)-2-oxo-5-(3-oxo-but-1-enyl)-pyrrolidine (266)



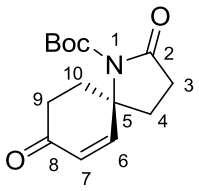
Enone **251** (52.3 mg, 194 μmol) was dissolved in CH_2Cl_2 (10 mL) in a separating funnel, and washed with HCl (2 M, 2 × 10 mL). The combined aqueous layers were then extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic layers dried over $MgSO_4$ before being concentrated *in vacuo* to afford enone **265** (41.8 mg, 84%) as a colourless oil.

EITHER: Crushed 4 Å molecular sieves (30 mg) were added to a stirred solution of **265** (19.9 mg, 78.0 μmol) in dry CH_2Cl_2 (1 mL) under argon. The mixture was stirred for 10 minutes before the addition of pyridinium chlorochromate (PCC) (33.6 mg, 156 μmol). The mixture was stirred for 20 h before celite® was added and the crude product dry loaded onto silica gel. The crude product was then purified by flash chromatography (2:8 petrol/EtOAc) to afford the amide **266** (11.6 mg, 59%) as a colourless solid.

OR: Pyridine (60 μL, 745 μmol) was dissolved in CH_2Cl_2 (0.6 mL) under argon and CrO_3 (40 mg, 400 μmol) was added. The mixture was stirred for 10 minutes and then a solution of **265** (24.7 mg, 91.8 μmol) in CH_2Cl_2 (1 mL) was added dropwise, followed by acetic anhydride (39 μL, 400 μmol). The reaction mixture was stirred for an additional 1 h before being purified by column chromatography (2:8 petrol/EtOAc) to afford the amide **266** (6.0 mg, 26%) as a colourless solid. $[\alpha]_D^{23}$ -131.7 (c 0.6, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 6.72 (1H, dd, *J* 16.0 and 6.4, C^6*H*), 6.15 (1H, d, *J* 16.0, C^7*H*), 4.78 (1H, *app* td, *J* 6.4 and 2.6, C^5*H*),

2.55 (1H, *app* dt, *J* 17.2 and 9.2, $C^3H_AH_B$), 2.48 (1H, ddd, *J* 17.2, 9.2 and 6.2, $C^3H_AH_B$), 2.37-2.27 (1H, m, $C^4H_AH_B$), 2.26 (3H, s, C^9H_3), 1.91-1.82 (1H, m, $C^4H_AH_B$), 1.48 (9H, s, $CO_2C(CH_3)$); δ_C (100 MHz, $CDCl_3$) 197.5 (C=O), 173.5 (N-C=O), 149.6 (C=O), 144.3 (CH), 130.0 (CH), 83.7 (C), 58.2 (CH), 31.1 (CH_2), 28.1 (3 × CH_3), 23.9 (CH_2); *m/z* ESI^+ found 276.1202 (M+Na, $C_{13}H_{19}NO_4Na$ requires 276.1206); ν_{max}/cm^{-1} ($CHCl_3$) : 2981, 2930, 1783 (C=O), 1747, 1716, 1679, 1632, 1370,1310, 1149, 977.

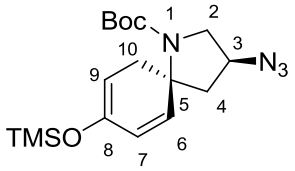
N-Boc-(*S*)-2,8-dioxo-1-azaspiro[4.5]dec-6-ene (267)



The crude derivative of enone **264** (1.35 g, 4.79 mmol) was dissolved in CH_2Cl_2 (50 mL) in a separating funnel, and washed with HCl (2 M, 2 × 60 mL). The combined aqueous layers were then extracted with CH_2Cl_2 (2 × 40 mL) and the combined organic layers dried over $MgSO_4$ before being concentrated *in vacuo* to afford enone **264** as a colourless oil. Crushed 4 Å molecular sieves (2.00 g) were added to a stirred solution of enone **264** (1.28 g, 4.79 mmol) in dry CH_2Cl_2 (50 mL) under argon. The mixture was stirred for 10 minutes before the addition of pyridinium chlorochromate (PCC) (2.06 g, 9.58 mmol). The mixture was stirred for 20 h before celite® was added and the crude product dry loaded onto silica gel. The crude product was purified by column chromatography (3:7 petrol/EtOAc) to afford the pure amide **267** (554 mg, 43% over 3 steps) as colourless blocks, which were analysed by X-ray crystallography (see **Appendix**). $[\alpha]_D^{24}$ -83.5 (c 0.4, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 6.80 (1H, d, *J* 10.0, C^6H), 5.94 (1H, d, *J* 10.0, C^7H), 2.77 (1H, *app* dt, *J* 13.2 and 6.0, $C^9H_AH_B$), 2.66-2.51 (4H, m, C^3H_2, and $C^{10}H_2$), 2.30 (1H, ddd, *J* 12.8, 8.4 and 2.0, $C^4H_AH_B$), 2.09 (1H, br d, *J*

13.2, $C^9H_AH_B$), 1.98-1.88 (1H, m, $C^4H_AH_B$), 1.49 (9H, s, $CO_2C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 196.9 (C=O), 173.3 (N-C=O), 154.3 (C=O), 149.5 (C=O), 127.0 (CH), 84.4 (C), 63.4 (CH), 34.8 (CH_2), 30.7 (CH_2), 30.3 (CH_2), 28.1 (3 × CH_3), 27.2 (CH_2); *m/z* ESI^+ found 288.1206 (M+Na, $C_{14}H_{19}NO_4Na$ requires 288.1206); ν_{max}/cm^{-1} ($CHCl_3$) : 2981, 2936, 1781 (C=O), 1747, 1714, 1682, 1371, 1340, 1304, 1151, 1140, 1080.

N-Boc-(3*S*,5*S*)-3-azido-8-(trimethyl-silyloxy)-1-azaspiro[4.5]deca-6,8-diene (278)

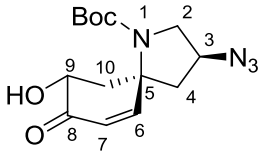


Freshly prepared LDA (8.25 mL, 0.528 M in THF, 4.36 mmol) was slowly added to a cooled (-78 °C), stirred solution of enone **178** (1.06 g, 3.63 mmol) and freshly distilled chlorotrimethylsilane (1.39 mL, 10.9 mmol) in dry THF (30 mL) under argon. The mixture was then stirred for 4 h at -78 °C. Saturated $NaHCO_3$ solution (25 mL) was added and the mixture was allowed to warm to rt. The organic layer was separated and the aqueous layer extracted with Et_2O (3 × 40 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (8:2 petrol/EtOAc then 6:4 petrol/EtOAc) to afford the TMS enol ether **278** (938 mg, 72%) as a yellow oil in addition to recovered starting material **178** (258 mg, 24%). $[\alpha]_D^{26}$ -90.6 (c 0.4, $CHCl_3$); δ_H (270 MHz, d_6-DMSO, 90 °C) 5.74 (1H, d, *J* 10.0, C^6H), 5.50 (1H, dd, *J* 10.0 and 2.3, C^7H), 4.86-4.81 (1H, m, C^9H), 4.28 (1H, *app* pent, *J* 6.0, C^3H), 3.61 (1H, dd, *J* 11.4 and 6.0, $C^2H_AH_B$), 3.32 (1H, dd, *J* 11.4 and 6.0, $C^2H_AH_B$), 3.09-2.96 (1H, m, $C^{10}H_AH_B$), 2.56 (1H, dd, *J* 13.1 and 6.0, $C^4H_AH_B$), 2.10 (1H, dd, *J* 16.8 and 6.2, $C^{10}H_AH_B$), 1.82 (1H, dd, *J*

13.1 and 6.0, $C^4H_AH_B$), 1.40 (s, 9H, $CO_2C(CH_3)_3$, 0.18 (s, 9H, Si-$(CH_3)_3$); δ_C (68 MHz, d_6-DMSO, 90 °C) 152.2 (C=O), 146.4 (C), 136.6 (CH), 122.4 (CH), 100.7 (CH), 78.6 (C), 61.4 (C), 55.8 (CH), 50.9 (CH_2), 43.0 (CH_2), 32.4 (CH_2), 27.7 (3 × CH_3), -0.4 (3 × CH_3); *m/z* ESI^+ found 387.1823 (M+Na, $C_{17}H_{28}N_4O_3SiNa$ requires 387.1820); ν_{max}/cm^{-1} ($CHCl_3$) : 2931, 2103 (N_3), 1682 (C=O), 1394, 1367, 1157, 893.

The TMS enol ether was used as soon as possible in the next step (no more than 2 days after preparation).

N-Boc-(3*S*,5*R*,9*R*)-3-azido-9-hydroxy-8-oxo-1-azaspiro[4.5]dec-6-ene (179)

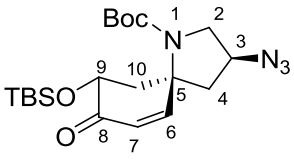


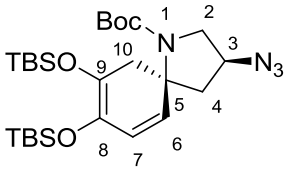
Freshly titrated DMDO (64.2 mL, 41.0 mM in acetone, 2.63 mmol) was slowly added to a cooled (-78 °C), stirred solution of the silyl enol ether **278** (914 mg, 2.51 mmol) in dry acetone (20 mL) under argon. The mixture was then stirred for 20 min at -78 °C. Water (10 mL) was added and the mixture allowed to warm to rt before the solvent was removed *in vacuo*. Water (30 mL) was added and the aqueous layer extracted with Et_2O (3 × 25 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (7:3 petrol/EtOAc) to afford the *α*-hydroxy ketone **179** (750 mg, 97%) as white needles, which were analysed by X-ray crystallography (see **Appendix**). $[\alpha]_D^{25}$ 129.2 (c 0.7, $CHCl_3$) [lit.,[58] $[\alpha]_D^{29}$ 166.7 (c 0.03, $CHCl_3$)]; mp: 64-65 °C; δ_H (270 MHz, d_6-DMSO, 90 °C) 6.81 (1H, dd, *J* 10.3 and 1.3, C^6H), 5.86 (1H, d, *J* 10.3, C^7H), 5.39 (1H, br s, OH), 4.34 (1H, *app* tt, *J* 5.8 and 5.0 C^3H), 4.19 (1H, *app* t *J* 4.6, C^9H), 3.67 (1H, dd *J* 11.4 and 5.8, $C^2H_AH_B$), 3.42 (1H, ddd, *J* 11.4, 5.0 and 0.8, $C^2H_AH_B$), 2.70 (1H,

dd, *J* 9.9 and 4.6, $C^{10}H_AH_B$), 2.65 (1H, dd, *J* 9.9 and 4.6, $C^{10}H_AH_B$), 2.11 (1H, dd, *J* 12.8 and 5.8, $C^4H_AH_B$) 2.04 (1H, ddd, *J* 12.8, 5.0 and 1.3, $C^4H_AH_B$), 1.37 (9H, s, $CO_2C(CH_3)_3$; δ_C (68 MHz, d_6-DMSO, 90 °C) 196.7 (C=O), 153.9 (C=O), 152.1 (CH), 125.0 (CH), 79.2 (C), 68.9 (CH), 60.0 (C), 56.9 (CH), 51.0 (CH_2), 45.3 (CH_2), 40.0 (CH_2), 27.6 (3 × CH_3); *m/z* ESI^+ found 331.1372 (M+Na, $C_{14}H_{20}N_4O_4Na$ requires 331.1377); ν_{max}/cm^{-1} ($CHCl_3$) : 3512, 2931, 2105 (N_3), 1688 (C=O), 1368, 1155, 1135, 1097. Found C, 54.7; H, 6.6; N, 17.8. $C_{14}H_{20}N_4O_4$ requires C, 54.5; H, 6.5; N, 18.2% (loss of azido group possible at high temperature). Spectroscopic data matched that previously reported.[58]

N-Boc-(3*S*,5*R*,9*R*)-3-azido-9-(*tert*-butyl-dimethyl-silyloxy)-8-oxo-1-azaspiro[4.5]dec-6-ene (279)

N-Boc-(3*S*,5*R*)-3-azido-8,9-bis(*tert*-butyl-dimethyl-silyloxy)-1-azaspiro[4.5]deca-6,8-diene (280)



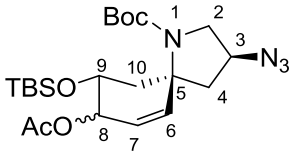


2,6-Lutidine (18.0 μL, 154 μmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (35.4 μL, 15.4 μmol) were added to a cooled (0 °C), stirred solution of alcohol **179** (23.8 mg, 77.2 μmol) in dry CH_2Cl_2 (2 mL) under argon. The mixture was stirred for 5 min at 0 °C and then 1 h at rt. Saturated $NaHCO_3$ solution (10 mL) was added, the organic layer separated and the aqueous layer extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (19:1 petrol/EtOAc) to afford the TBS-protected alcohol **279** (28.2 mg, 86%) as a colourless sticky oil. In addition, varying amounts of the undesired side-product

280 was also isolated. Data for alcohol **279**: $[\alpha]_D^{27}$ 78.0 (c 0.8, $CHCl_3$); δ_H (270 MHz, d_6-DMSO, 90 °C) 6.85 (1H, dd, *J* 10.3 and 1.5, C^6H), 5.87 (1H, dd, *J* 10.3 and 0.9, C^7H), 4.42-4.32 (2H, m, C^3H and C^9H), 3.68 (1H, dd *J* 11.5 and 5.9, $C^2H_AH_B$), 3.42 (1H, ddd, *J* 11.5, 4.8 and 1.1, $C^2H_AH_B$), 2.75-2.64 (2H, m, $C^{10}H_2$), 2.17-2.05 (2H, m, C^4H_2), 1.38 (9H, s, $CO_2C(CH_3)_3$, 0.89 (9H, Si-$C(CH_3)_3$, 0.11 (3H, Si-CH_3), 0.06 (3H, Si-CH_3); δ_C (68 MHz, d_6-DMSO, 90 °C) 195.0 (C=O), 154.1 (CH), 152.1 (C=O), 124.8 (CH), 79.3 (C), 70.8 (CH), 60.0 (C), 57.0 (CH), 50.9 (CH_2), 45.2 (CH_2), 40.5 (CH_2), 27.6 (3 × CH_3), 25.2 (3 × CH_3), 17.4 (C), -5.4 (CH_3), -5.6 (CH_3); *m/z* ESI^+ found 445.2242 (M+Na, $C_{20}H_{34}N_4O_4SiNa$ requires 445.2242); ν_{max}/cm^{-1} ($CHCl_3$) : 2929, 2855, 2104 (N_3), 1688 (C=O), 1380, 1368, 1100, 974, 903.

Data for the side-product **280**: $[\alpha]_D^{23}$ -63.7 (c 1.0, $CHCl_3$); mp: 80-82 ˚C; δ_H (270 MHz, d_6-DMSO, 90 °C) 5.54 (1H, d, *J* 9.9, C^7H), 5.40 (1H, d, *J* 9.9, C^6H), 4.31 (1H, *app* pent, *J* 5.8, C^3H), 3.61 (1H, dd, *J* 11.4 and 5.8, $C^2H_AH_B$), 3.36-3.24 (2H, m, $C^2H_AH_B$ and $C^{10}H_AH_B$), 2.56-2.42 (1H, m, $C^4H_AH_B$), 2.00 (1H, d, *J* 16.2, $C^{10}H_AH_B$), 1.91 (1H, dd, *J* 12.3 and 5.8, $C^4H_AH_B$), 1.40 (9H, s, $CO_2C(CH_3)_3$), 0.94 (18H, 2 × Si-$C(CH_3)_3$), 0.18 (6H, Si-$(CH_3)_2$), 0.11 (6H, Si-$(CH_3)_2$); δ_C (68 MHz, d_6-DMSO, 90 °C) 152.2 (C=O), 132.0 (C), 129.1 (C), 128.7 (CH), 122.7 (CH), 78.7 (C), 62.9 (C), 55.7 (CH), 51.0 (CH_2), 44.4 (CH_2), 27.7 (3 × CH_3), 27.5 (CH_2), 25.3 (3 × CH_3), 25.2 (3 × CH_3), 17.4 (C), 17.3 (C), -4.1 (CH_3), -4.4 (CH_3), -4.5 (CH_3), -4.6 (CH_3); *m/z* ESI^+ found 559.3102 (M+Na, $C_{26}H_{48}N_4O_4Si_2Na$ requires 559.3112); ν_{max}/cm^{-1} ($CHCl_3$) : 2930, 2857, 2104 (N_3), 1682 (C=O), 1383, 1367, 1150, 890.

N-Boc-(3*S*,5*R*,9*R*)-3-azido-9-(*tert*-butyl-dimethyl-silyloxy)-8-acetoxy-1-azaspiro[4.5]dec-6-ene (283)

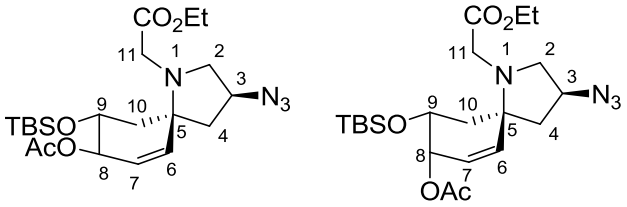


L-Selectride (1.03 mL, 1.00 M in THF, 1.03 mmol) was slowly added to a cooled (-78 °C), stirred solution of enone **279** (415 mg, 982 μmol) in dry THF (10 mL) under argon. The mixture was then stirred for 1 h at -78 °C. Saturated $NaHCO_3$ solution (20 mL) was added, the organic layer separated and the aqueous layer extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude alcohol **282** (387 mg, 93%) as a colourless sticky oil. Acetic anhydride (2.5 mL) was added to a stirred solution of crude alcohol **282** (370 mg, 872 μmol) in pyridine (2.5 mL) under argon. The mixture was then stirred overnight at rt under argon before being concentrated *in vacuo*. The residue was dissolved in EtOAc and the organic layer washed with saturated $NaHCO_3$ solution (15 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (8:2 petrol/EtOAc) to afford the acetate-protected alcohol **283** (378 mg, 93%) as a colourless oil. $[\alpha]_D^{27}$ 80.8 (c 0.8, $CHCl_3$); Data was collected for a mixture of diastereoisomers in a 4:1 ratio: δ_H (270 MHz, d_6-DMSO, 90 °C): Data for the major isomer: 5.66 (1H, *app* dt, *J* 10.8 and 1.9, C^7H), 5.55-5.43 (1H, m, C^6H), 5.28-5.22 (1H, m, C^8H), 4.44-4.36 (1H, m, C^9H), 4.34-4.22 (1H, m, C^3H), 3.62 (1H, dd, *J* 11.6 and 6.0, $C^2H_AH_B$), 3.32 (1H, ddd, *J* 11.6, 5.1 and 1.1, $C^2H_AH_B$), 2.57-2.48 (1H, m, $C^{10}H_AH_B$), 2.42 (1H, dd, *J* 14.0 and 2.8, $C^4H_AH_B$), 2.03 (3H, s, $COCH_3$), 2.03-1.94 (1H, m, $C^{10}H_AH_B$), 1.88 (1H, ddd, *J* 14.0, 5.9 and 1.1, $C^4H_AH_B$), 1.40 (9H, s, $CO_2C(CH_3)_3$), 0.90 (9H, Si-$C(CH_3)_3$), 0.09 (3H, Si-CH_3), 0.07 (3H, Si-CH_3); Data for the minor isomer, where different from the major isomer: 5.81 (1H, d, *J* 10.2, C^7H), 4.97-4.91

(1H, m, C^8H), 3.38 (1H, ddd, *J* 11.7, 4.4 and 1.1, $C^2H_AH_B$), 2.01 (3H, s, $COCH_3$), 1.75 (1H, dd, *J* 13.8 and 7.2, $C^4H_AH_B$); δ_C (68 MHz, d_6-DMSO, 90 °C): Data for the major isomer: 169.2 (C=O), 152.1 (C=O), 134.4 (CH), 123.4 (CH), 78.7 (C), 69.6 (CH), 67.5 (CH), 60.1 (C), 56.6 (CH), 50.7 (CH_2), 45.2 (CH_2), 38.5 (CH_2), 27.6 (3 × CH_3), 25.3 (3 × CH_3), 20.3 (CH_3), 17.3 (C), -5.1 (CH_3), -5.5 (CH_3); Data for the minor isomer, where different from the major isomer: 169.1 (C=O), 68.2 (CH), 56.5 (CH), 46.3 (CH_2), 27.7 (3 × CH_3), 25.2 (3 × CH_3), 20.2 (CH_3), -5.4 (CH_3); *m/z* ESI^+ found 489.2494 (M+Na, $C_{22}H_{38}N_4O_5SiNa$ requires 489.2504); ν_{max}/cm^{-1} ($CHCl_3$) : 2930, 2856, 2103 (N_3), 1682 (C=O), 1368, 1112, 964.

N-Ethyl-acetate-(3*S*,5*R*,8*R*,9*R*)-3-azido-9-(*tert*-butyl-dimethyl-silyloxy)-8-acetoxy-1-azaspiro[4.5]dec-6-ene (284)

N-Ethyl-acetate-(3*S*,5*R*,8*S*,9*R*)-3-azido-9-(*tert*-butyl-dimethyl-silyloxy)-8-acetoxy-1-azaspiro[4.5]dec-6-ene (285)



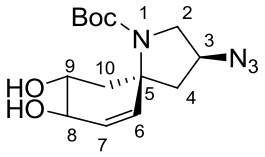
Trifluoroacetic acid (1.83 mL, 23.8 mmol) was added to a stirred solution of Boc-protected amine **283** (370 mg, 792 μmol) in dry CH_2Cl_2 (10 mL) under argon. The mixture was then stirred at rt, during which time the reaction was followed carefully by TLC. When TLC analysis indicated complete consumption of the starting material (40 min), the mixture was concentrated *in vacuo* to dryness. Potassium carbonate (328 mg, 2.38 mmol), sodium iodide (177 mg, 1.19 mmol) and ethylbromoacetate (132 μL, 1.19 mmol) were added to a stirred solution of the free amine in dry acetonitrile (8 mL). The mixture was stirred for 5 days at rt.

Water (15 mL) was added, the organic layer separated and the aqueous layer extracted with EtOAc (3 × 20 mL). The combined organic layers were washed sequentially with saturated $Na_2S_2O_3$ solution (15 mL) and brine (15 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (9:1 petrol/EtOAc) to afford the ethyl ester **284** (265 mg, 74% over 2 steps) as a yellow oil along with its diastereoisomer, **285** (52.2 mg, 15%). Data for the major isomer **284**: $[\alpha]_D^{24}$ 105.7 (c 0.7, $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 5.74 (1H, dd, *J* 10.4 and 2.3, C^6H), 5.61 (1H, ddd, *J* 10.4, 2.3 and 1.2, C^7H), 5.23 (1H, *app* dt, *J* 3.2 and 2.3, C^8H), 4.24-2.19 (1H, m, C^9H), 4.15 (1H, q, *J* 7.2, CO_2CH_2), 4.14-4.06 (1H, m, C^3H), 3.41 (1H, dd, *J* 10.0 and 7.2, $C^2H_AH_B$), 3.27 (1H, d, *J* 16.8, $C^{11}H_AH_B$), 3.18 (1H, d, *J* 16.8, $C^{11}H_AH_B$), 2.82 (1H, dd, *J* 10.0 and 4.8, $C^2H_AH_B$), 2.39 (1H, dd, *J* 14.0 and 8.4, $C^4H_AH_B$), 2.07 (3H, s, $COCH_3$), 2.01 (1H, dd *J* 14.0 and 4.8, $C^4H_AH_B$), 1.82-1.79 (2H, m, $C^{10}H_2$), 1.25 (3H, t, *J* 7.2, $CO_2CH_2CH_3$), 0.89 (9H, Si-C(CH_3)$_3$), 0.05 (3H, Si-CH_3), 0.04 (3H, Si-CH_3); δ_C (100 MHz, $CDCl_3$) 171.3 (C=O), 170.8 (C=O), 133.3 (CH), 126.7 (CH), 70.4 (CH), 67.8 (CH), 63.2 (C), 60.9 (CH_2), 58.6 (CH), 56.7 (CH_2), 50.8 (CH_2), 46.1 (CH_2), 37.6 (CH_2), 25.9 (3 × CH_3), 21.4 (CH_3), 18.3 (C), 14.3 (CH_3), -4.3 (CH_3), -4.9 (CH_3); *m/z* ESI^+ found 453.2540 (M+H, $C_{21}H_{37}N_4O_5Si$ requires 453.2528); ν_{max}/cm^{-1} ($CHCl_3$) : 2930, 2856, 2103 (N_3), 1732 (C=O), 1372, 1088, 978.

Data for the minor isomer **285**. $[\alpha]_D^{24}$ -22.6 (c 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 5.79 (1H, d, *J* 10.4, C^6H), 5.70 (1H, dd, *J* 10.4 and 3.2, C^7H), 4.97 (1H, *app* t, *J* 4.0, C^8H), 4.20-4.05 (3H, m, CO_2CH_2 and C^3H), 3.97-3.93 (1H, m, C^9H), 3.36 (1H, dd, *J* 10.0 and 7.2, $C^2H_AH_B$), 3.32 (1H, d, *J* 16.8, $C^{11}H_AH_B$), 3.25 (1H, d, *J* 16.8, $C^{11}H_AH_B$), 2.90 (1H, dd, *J* 10.0 and 4.4, $C^2H_AH_B$), 2.39 (1H, dd, *J* 13.6 and 8.0, $C^4H_AH_B$), 2.05 (3H, s, $COCH_3$), 1.96 (1H, dd *J* 13.6 and 4.8, $C^4H_AH_B$), 1.92 (1H, dd, *J* 14.0 and 3.2, $C^{10}H_AH_B$), 1.61 (1H, dd, *J* 14.0 and 7.2, $C^{10}H_AH_B$), 1.26 (3H, t, *J* 7.0, $CO_2CH_2CH_3$), 0.86 (9H, Si-C(CH_3)$_3$), 0.07 (3H, Si-CH_3), 0.06 (3H, Si-CH_3); δ_C (100 MHz, $CDCl_3$) 171.3 (C=O), 170.4 (C=O), 135.1 (CH), 125.9 (CH),

71.4 (CH), 68.4 (CH), 63.0 (C), 60.9 (CH_2), 58.5 (CH), 56.9 (CH_2), 51.1 (CH_2), 46.3 (CH_2), 36.7 (CH_2), 25.8 (3 × CH_3), 21.3 (CH_3), 18.1 (C), 14.3 (CH_3), -4.7 (CH_3), -4.8 (CH_3); *m/z* ESI^+ found 453.2541 (M+H, $C_{21}H_{37}N_4O_5Si$ requires 453.2528) and found 475.2357 (M+Na, $C_{21}H_{36}N_4O_5SiNa$ requires 475.2347); ν_{max}/cm^{-1} ($CHCl_3$) : 2930, 2856, 2104 (N_3), 1732 (C=O), 1371, 1116, 966.

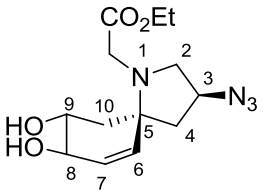
N-Boc-(3*S*,5*R*,8*R*,9*R*)-3-azido-8,9-dihydroxy-1-azaspiro[4.5]dec-6-ene (290)



L-Selectride (473 μL, 1.00 M in THF, 473 μmol) was slowly added to a cooled (-78 °C), stirred solution of enone **179** (58.3 mg, 189 μmol) in dry THF (1.5 mL) under argon. The mixture was then stirred for 2 h at -78 °C. Saturated $NaHCO_3$ solution (10 mL) was added, the organic layer separated and the aqueous layer extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (3:7 petrol/EtOAc) to afford the diol **290** (47.0 mg, 80%) as a colourless sticky oil. $[\alpha]_D^{24}$ 73.7 (c 0.7, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 6.00-5.93 (1H, m, C^7H), 5.68 (1H, d, *J* 10.0, C^6H), 4.21-4.15 (1H, m, C^9H), 4.08 (1H, *app* pent, *J* 6.4, C^3H), 3.91-3.74 (2H, m, C^8H and O*H*), 3.69 (1H, dd, *J* 11.6 and 6.4, $C^2H_AH_B$), 3.37-3.27 (1H, m, $C^2H_AH_B$), 2.65 (1H, *app* d, *J* 14.0, $C^{10}H_AH_B$), 2.40 (1H, dd, *J* 12.8 and 6.4, $C^4H_AH_B$), 2.17 (1H, br s, O*H*), 2.02-1.92 (1H, m, $C^4H_AH_B$), 1.75 (1H, dd, *J* 14.0 and 3.6, $C^{10}H_AH_B$), 1.42 (s, 9H, $CO_2C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 153.1 (C=O), 134.6 (CH), 127.1 (CH), 80.6 (C), 70.5 (CH), 67.4 (CH), 59.9 (C), 57.4 (CH), 51.6 (CH_2), 46.8 (CH_2), 36.2 (CH_2), 28.6 (3 × CH_3); *m/z* ESI^+ found 333.1526 (M+Na, $C_{14}H_{22}N_4O_4Na$ requires 333.1533);

ν_{max}/cm^{-1} ($CHCl_3$) : 3612 (OH), 3403 (OH), 2978, 2932, 2104 (N_3), 1681 (C=O), 1385, 1368, 1092.

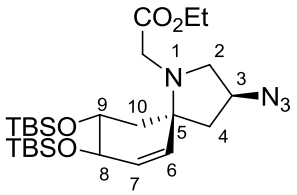
N-Ethyl-acetate-(3*S*,5*R*,8*R*,9*R*)-3-azido-8,9-dihydroxy-1-azaspiro[4.5]dec-6-ene (291)



Trifluoroacetic acid (2.41 mL, 31.2 mmol) was added to a stirred solution of Boc-protected amine **290** (323 mg, 1.04 mmol) in dry CH_2Cl_2 (20 mL) under argon. The mixture was then stirred for at rt, during which time the reaction was followed carefully by TLC. When TLC analysis indicated complete consumption of the starting material (1 h), the mixture was concentrated *in vacuo* to dryness. Potassium carbonate (432 mg, 3.12 mmol), sodium iodide (233 mg, 1.56 mmol) and ethylbromoacetate (174 μL, 1.56 mmol) were added to a stirred solution of the free amine in dry acetonitrile (10 mL). The mixture was stirred for 3 days at rt. Saturated $Na_2S_2O_3$ solution (20 mL) was added, the organic layer separated and the aqueous layer extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (EtOAc) to afford the ethyl ester **291** (266 mg, 86% over 2 steps) as a colourless oil. $[\alpha]_D^{23}$ 15.5 (c 0.7, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 5.77 (1H, dd, *J* 10.4 and 2.0, C^7H), 5.55 (1H, d, *J* 10.4, C^6H), 4.20-4.05 (3H, m, CO_2CH_2 and C^3H), 3.93 (1H, *app* dt, *J* 7.6 and 2.0, C^9H), 3.72-2.63 (1H, m, C^8H), 3.37 (2H, s, $C^{11}H_2$), 3.28 (1H, dd, *J* 10.4 and 7.2, $C^2H_AH_B$), 2.98 (1H, dd, *J* 10.4 and 4.4, $C^2H_AH_B$), 2.16-2.07 (2H, m, $C^4H_AH_B$ and $C^{10}H_AH_B$), 1.95 (1H, dd, *J* 13.4 and 5.6, $C^4H_AH_B$), 1.49 (1H, dd, *J* 13.4 and 11.6, $C^{10}H_AH_B$),

1.25 (3H, t, *J* 7.2, $CO_2CH_2CH_3$); δ_C (100 MHz, $CDCl_3$) 171.9 (C=O), 131.8 (CH), 131.7 (CH), 72.6 (CH), 70.8 (CH), 64.3 (C), 61.1 (CH_2), 58.4 (CH), 57.0 (CH_2), 51.8 (CH_2), 47.3 (CH_2), 38.1 (CH_2), 14.3 (CH_3); *m/z* ESI^+ found 319.1373 (M+Na, $C_{13}H_{20}N_4O_4Na$ requires 319.1373); ν_{max}/cm^{-1} ($CHCl_3$) : 3610, 2938, 2104 (N_3), 1741 (C=O), 1378, 1323, 1056.

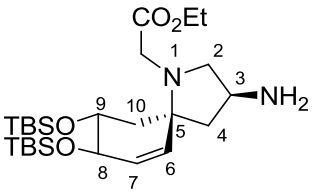
N-Ethyl-acetate-(3*S*,5*R*,8*R*,9*R*)-3-azido-8,9-bis(*tert*-butyl-dimethyl-silyloxy)-1-azaspiro[4.5]dec-6-ene (292)



2,6-Lutidine (313 μL, 2.68 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (616 μL, 2.68 mmol) were added to a cooled (-78 °C), stirred solution of diol **291** (265 mg, 895 μmol) in dry CH_2Cl_2 (10 mL) under argon. The mixture was then stirred for 2 h at -78 °C. Saturated $NaHCO_3$ solution (15 mL) was added, the organic layer separated and the aqueous layer extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (92:8 petrol/EtOAc) to afford the bis-TBS-protected alcohol **292** (439 mg, 93%) as a colourless oil. $[\alpha]_D^{24}$ -14.3 (c 0.8, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 5.73 (1H, dd, *J* 10.0 and 3.9, C^7H), 5.66 (1H, d, *J* 10.0, C^6H), 4.15 (2H, q, *J* 7.2, CO_2CH_2), 4.12-4.06 (1H, m, C^3H), 3.86-3.82 (1H, m, C^9H), 3.79 (1H, *app* t, *J* 3.9, C^8H), 3.38 (1H, dd, *J* 10.0 and 7.2, $C^2H_AH_B$), 3.33 (1H, d, *J* 16.8, $C^{11}H_AH_B$), 3.21 (1H, d, *J* 16.8, $C^{11}H_AH_B$), 2.85 (1H, dd, *J* 10.0 and 4.8, $C^2H_AH_B$), 2.33 (1H, dd, *J* 13.8 and 8.4, $C^4H_AH_B$), 2.00 (1H, dd, *J* 14.0 and 2.8, $C^{10}H_AH_B$), 1.94 (1H, dd, *J* 13.8 and 4.8, $C^4H_AH_B$), 1.52 (1H, dd, *J* 14.0 and 5.2, $C^{10}H_AH_B$), 1.25 (3H, t, *J* 7.2, $CO_2CH_2CH_3$), 0.88 (18H, s, 2 × Si-C(CH_3)$_3$), 0.07 (6H, s, (Si-CH_3)$_2$), 0.06

(6H, s, Si-CH_3)$_2$); δ_C (100 MHz, $CDCl_3$) 171.7 (C=O), 132.5 (CH), 129.5 (CH), 71.6 (CH), 68.5 (CH), 62.9 (C), 60.7 (CH_2), 58.7 (CH), 56.8 (CH_2), 50.9 (CH_2), 46.1 (CH_2), 34.9 (CH_2), 26.0 (3 × CH_3), 25.9 (3 × CH_3), 18.2 (C), 18.1 (C), 14.3 (CH_3), -4.3 (CH_3), -4.5 (2 × CH_3), -4.6 (CH_3); *m/z* ESI^+ found 525.3276 (M+H, $C_{25}H_{49}N_4O_4Si_2$ requires 525.3287) and 547.3097 (M+Na, $C_{25}H_{48}N_4O_4Si_2Na$ requires 547.3106); ν_{max}/cm^{-1} ($CHCl_3$) : 2950, 2930, 2886, 2857, 2103 (N_3), 1741 (C=O), 1361, 1108, 1070, 866, 838.

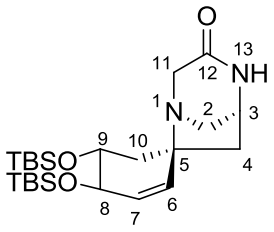
N-Ethyl-acetate-(3*S*,5*R*,8*R*,9*R*)-3-amino-8,9-bis(*tert*-butyl-dimethyl-silyloxy)-1-azaspiro[4.5]dec-6-ene (293)



Triphenylphosphine (321 mg, 1.22 mmol) and water (1 mL) were added to a stirred solution of azide **292** (428 mg, 816 μmol) in THF (10 mL). The mixture was heated to 80 °C and kept at reflux for 4 hours. The solvent was then removed *in vacuo*. The crude compound was purified by column chromatography (1:19 MeOH/CH_2Cl_2 then 2:3 MeOH/CH_2Cl_2) to afford the free amine **293** (380 mg, 93%) as a pale yellow oil. $[\alpha]_D^{23}$ -35.8 (c 0.7, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 5.70-5.65 (1H, m, C^7*H*), 5.60 (1H, d, *J* 10.4, C^6*H*), 4.14 (2H, q, *J* 7.0, CO_2CH_2), 3.82-3.76 (2H, m, C^8*H* and C^9*H*), 3.57 (1H, *app* p, *J* 7.0, C^3*H*), 3.30 (1H, d, *J* 16.8, C$^{11}H_AH_B$), 3.21 (1H, d, *J* 16.8, C^{11}H$_A$*H*$_B$), 3.13 (1H, dd, *J* 9.2 and 7.0, C$^2H_AH_B$), 2.70 (1H, dd, *J* 9.2 and 7.0, C^{2}H$_A$*H*$_B$), 2.31 (1H, dd, *J* 13.0 and 7.0, C$^4H_AH_B$), 1.99-1.93 (1H, m, C$^{10}H_AH_B$), 1.70 (2H, *br* s, NH_2), 1.55 (1H, dd, *J* 13.0 and 7.0, C^{4}H$_A$*H*$_B$), 1.52-1.45 (1H, m, C^{10}H$_A$*H*$_B$), 1.24 (3H, t, *J* 7.0, $CO_2CH_2CH_3$), 0.88 (9H, s, Si-C(CH_3)$_3$), 0.87 (9H, s, Si-C(CH_3)$_3$), 0.07-0.04 (12H, *app* m, 4 × Si-CH_3); δ_C (100 MHz, $CDCl_3$) 172.1 (C=O), 134.1

(CH), 129.6 (CH), 71.7 (CH), 69.4 (CH), 63.6 (C), 60.9 (CH_2), 60.6 (CH_2), 51.2 (CH_2), 50.7 (CH_2), 49.6 (CH), 34.7 (CH_2), 26.1 (3 × CH_3), 26.0 (3 × CH_3), 18.2 (C), 18.1 (C), 14.3 (CH_3), -4.3 (CH_3), -4.4 (2 × CH_3), -4.5 (CH_3); *m/z* ESI^+ found 499.3375 (M+H, $C_{25}H_{51}N_2O_4Si_2$ requires 499.3382); ν_{max}/cm^{-1} ($CHCl_3$) : 2954, 2929, 2894, 2857, 1739 (C=O), 1069, 867.

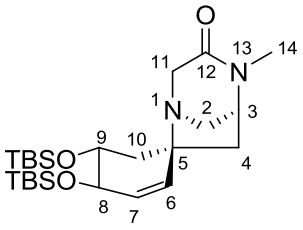
(1'*R*,4'*R*,5*S*,5'*R*)-4',5'-bis(*tert*-butyl-dimethyl-silyloxy)-1,4-diazaspiro[bicyclo[3.2.1]octane-7,1'-cyclohex[2]en]-3-one (294)



K_2CO_3 (21.0 mg, 152 μmol) was added to a stirred solution of amine **293** (380 mg, 763 μmol) in MeOH (10 mL). The mixture was stirred overnight at rt before the solvent was removed *in vacuo*. Triethylamine (319 μL, 2.29 mmol) followed by DPPA (247 μL, 1.14 mmol) were added to a stirred solution of the crude amino-acid in dry DMF (17 mL). The mixture was then stirred at rt for 3 h. Water (20 mL) was added, the organic layer separated and the aqueous layer extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with water (3 × 30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (EtOAc) to afford the tricycle **294** (137 mg, 40% over 2 steps) as a white solid. $[\alpha]_D^{27}$ -16.5 (c 0.6, $CHCl_3$); mp: 207-208 °C (decomp.); δ_H (400 MHz, $CDCl_3$) 6.35 (1H, *br* d, *J* 3.2, N*H*), 5.65 (1H, dd, *J* 10.0 and 1.8, C^7H), 5.50 (1H, *br* d, *J* 10.0, C^6H), 4.01 (1H, dt, *J* 7.6 and 1.8, C^8H), 3.91 (1H, ddd, *J* 10.8, 7.6 and 2.6, C^9H), 3.87-3.82 (1H, m, C^3H), 3.60 (1H, d, *J* 18.6, $C^{11}H_AH_B$), 3.51 (1H, d, *J* 18.6, $C^{11}H_AH_B$), 3.18 (1H, dd, *J* 12.0 and 2.4, $C^2H_AH_B$), 2.94 (1H, *app* d, *J* 12.0, $C^2H_AH_B$), 2.10 (1H, dd, *J* 13.2 and 2.6,

$C^{10}H_AH_B$), 1.83 (1H, *app* d, *J* 12.0, $C^4H_AH_B$), 1.70 (1H, dd, *J* 13.2 and 4.0, $C^{10}H_AH_B$), 1.42 (1H *app* t, *J* 12.0, $C^4H_AH_B$), 0.91 (9H, s, Si-C(CH_3)$_3$), 0.90 (9H, s, Si-C(CH_3)$_3$), 0.10 (3 × Si-CH_3), 0.09 (Si-CH_3); δ_C (100 MHz, $CDCl_3$) 170.8 (C=O), 134.3 (CH), 130.8 (CH), 74.3 (CH), 72.7 (CH), 65.7 (C), 56.6 (CH_2), 56.5 (CH_2), 54.5 (CH), 51.1 (CH_2), 45.2 (CH_2), 26.2 (6 × CH_3), 18.4 (C), 18.2 (C), -3.8 (CH_3), -3.9 (CH_3), -4.5 (2 × CH_3); *m/z* ESI^+ found 453.2955 (M+H, $C_{23}H_{45}N_2O_3Si_2$ requires 453.2963) and found 475.2776 (M+Na, $C_{23}H_{44}N_2O_3Si_2Na$ requires 475.2783); ν_{max}/cm^{-1} ($CHCl_3$) : 3408, 2955, 2929, 2894, 2857, 1664 (C=O), 1098, 1046, 1002, 871. Found C, 60.7; H, 9.8; N, 6.2. $C_{23}H_{44}N_2O_3Si_2$ requires C, 61.0; H, 9.8; N, 6.2%.

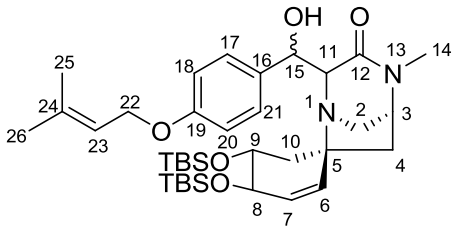
(1'*R*,4'*R*,5*S*,5'*R*)-4',5'-bis(*tert*-butyl-dimethyl-silyloxy)-4-methyl-1,4-diazaspiro[bicyclo[3.2.1]octane-7,1'-cyclohex[2]en]-3-one (295)



NaH (13.2 mg, 329 μmol, 60% in oil) was added to a stirred, cooled (0 °C) solution of tricycle **294** (135 mg, 299 μmol) in dry THF (4 mL) under argon. The mixture was stirred for 15 min at 0 °C before the addition of iodomethane (56.0 μL, 898 μmol). The mixture was stirred for a further 2 h at 0 °C before saturated $Na_2S_2O_3$ solution (10 mL) was added. The organic layer was separated and the aqueous layer extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (1.5:8.5 petrol/EtOAc) to afford the *N*-methyl tricycle **295** (112 mg, 80%) as white needles, which

were analysed by X-ray crystallography (see **Appendix**). $[\alpha]_D^{30}$ -14.0 (c 0.6, $CHCl_3$); mp: 125-126 °C; δ_H (400 MHz, $CDCl_3$) 5.62 (1H, dd, *J* 10.0 and 2.0, C^7H), 5.37 (1H, *app* dt, *J* 10.0 and 1.6, C^6H), 4.00 (1H, *app* dt, *J* 7.6 and 2.0, C^8H), 3.90 (1H, ddd, *J* 11.0, 7.6, and 3.0, C^9H), 3.67-3.63 (1H, m, C^3H), 3.53 (1H, d, *J* 18.4, $C^{11}H_AH_B$), 3.47 (1H, d, *J* 18.4, $C^{11}H_AH_B$), 3.23 (1H, dd, *J* 12.0 and 2.8, $C^2H_AH_B$), 2.95-2.90 (1H, m, $C^2H_AH_B$), 2.90 (3H, s, $C^{14}H_3$), 2.05 (1H, dd, *J* 13.4 and 2.4, $C^4H_AH_B$), 1.84 (1H, *app* dt, *J* 13.0 and 3.0, $C^{10}H_AH_B$), 1.65 (1H, dd, *J* 13.4 and 4.4, $C^4H_AH_B$), 1.42 (1H, dd, *J* 13.0 and 11.0, $C^{10}H_AH_B$); δ_C (100 MHz, $CDCl_3$) 168.5 (C=O), 134.2 (CH), 130.9 (CH), 74.3 (CH), 72.7 (CH), 65.7 (C), 61.2 (CH), 56.7 (CH_2), 56.6 (CH_2), 48.3 (CH_2), 45.2 (CH_2), 33.6 (CH_3), 26.2 (6 × CH_3), 18.4 (C), 18.2 (C), -3.8 (CH_3), -3.9 (CH_3), -4.5 (CH_3), -4.6 (CH_3); *m/z* ESI^+ found 467.3118 (M+H, $C_{24}H_{47}N_2O_3Si_2$ requires 467.3120) and found 489.2939 (M+Na, $C_{24}H_{46}N_2O_3Si_2Na$ requires 489.2939); ν_{max}/cm^{-1} ($CHCl_3$) : 2955, 2930, 2894, 2857, 1640 (C=O), 1399, 1096, 1043, 870. Found C, 61.8; H, 10.0; N, 6.0. $C_{24}H_{46}N_2O_3Si_2$ requires C, 61.7; H, 9.9; N, 6.0%.

(1'R,4'R,5S,5'R)-4',5'-bis(*tert*-butyl-dimethyl-silyloxy)-2-(hydroxy(4-(3-methylbut-2-enyloxy)phenyl)methyl)-4-methyl-1,4-diazaspiro[bicyclo[3.2.1]octane-7,1'-cyclohex[2]en]-3-one (298)



Freshly prepared LDA (391 μL, 710 mM in THF, 278 μmol) was slowly added to a cooled (-78 °C), stirred solution of enone **295** (108 mg, 232 μmol) in THF (3 mL) under argon. The mixture was stirred for 30 min before addition of aldehyde **118** (88.0 mg, 46.3 mmol) in dry

THF (0.5 mL). The mixture was then stirred for 4 h at -78 °C. Saturated $NaHCO_3$ solution (15 mL) was added and the mixture was allowed to warm to rt. The organic layer was separated and the aqueous layer extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (2:3 petrol/EtOAc then 3:2 petrol/EtOAc) to afford the aldol product **298** as a separable 3:1 mixture of diastereoisomers (110.3 mg, 73%) as a colourless oil. Data for the major isomer: $[\alpha]_D^{25}$ -0.8 (c 0.8, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.24 (2H, d, *J* 8.8, $C^{18}H$, $C^{20}H$), 6.86 (2H, d, *J* 8.8, $C^{17}H$, $C^{20}H$), 5.63 (1H, dd, *J* 10.0 and 1.8, $C^{7}H$), 5.48 (1H, *app* tt, *J* 6.8 and 1.2, $C^{23}H$), 5.33 (1H, *br* d, *J* 10.0, $C^{6}H$), 4.89 (1H, d, *J* 6.4, $C^{15}H$), 4.47 (2H, d, *J* 6.8, $C^{22}H_2$), 3.97 (1H, *app* dt, *J* 6.6 and 1.8, $C^{8}H$), 3.84 (1H, d, *J* 6.4, $C^{11}H$), 3.73 (1H, ddd, *J* 11.2, 6.6 and 2.8, $C^{9}H$), 3.60-3.57 (1H, m, $C^{3}H$), 3.27 (1H, dd, *J* 12.4 and 1.8, $C^{2}H_AH_B$), 2.89 (3H, s, $C^{14}H_3$), 2.59 (1H, d, *J* 12.4, $C^{2}H_AH_B$), 1.99 (1H, dd, *J* 13.6 and 2.4, $C^{4}H_AH_B$), 1.83 (1H, *app* dt, *J* 11.2 and 2.8, $C^{10}H_AH_B$), 1.78 (3H, s, $C^{25}H_3$), 1.72 (3H, s, $C^{26}H_3$), 1.65 (1H, dd, *J* 13.6 and 4.4, $C^{4}H_AH_B$), 1.44 (1H, *app* t, *J* 11.2, $C^{10}H_AH_B$), 0.92 (9H, s, Si-C(CH_3)$_3$), 0.88 (9H, s, Si-C(CH_3)$_3$), 0.09 (3H, s, Si-CH_3), 0.08 (3H, s, Si-CH_3), 0.05 (3H, s, Si-CH_3), 0.04 (3H, s, Si-CH_3); δ_C (100 MHz, $CDCl_3$) 168.7 (C=O), 158.4 (C), 138.0 (C), 135.1 (CH), 134.1 (C), 130.2 (CH), 128.2 (CH), 119.9 (CH), 114.4 (CH), 74.6 (CH), 74.2 (CH), 72.7 (CH), 66.9 (CH), 66.3 (C), 64.7 (CH_2), 61.3 (CH), 52.0 (CH_2), 47.6 (CH_2), 45.0 (CH_2), 33.7 (CH_3), 26.1 (6 × CH_3), 25.9 (CH_3), 18.3 (C), 18.2 (C), 18.1 (CH_3), -3.9 (2 × CH_3), -4.6 (CH_3), -4.8 (CH_3); *m/z* ESI^+ found 657.4114 (M+H, $C_{36}H_{61}N_2O_5Si_2$ requires 657.4114) and found 679.3931 (M+Na, $C_{36}H_{60}N_2O_5Si_2Na$ requires 679.3933); ν_{max}/cm^{-1} ($CHCl_3$) : 3369 (OH), 2954, 2930, 2894, 2857, 1645 (C=O), 1463, 1398, 1314, 1096, 1043, 1000, 871.

Data for the minor isomer: $[\alpha]_D^{25}$ -13.1 (c 0.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.21 (2H, d, *J* 8.4, $C^{18}H$, $C^{20}H$), 6.85 (2H, d, *J* 8.4, $C^{17}H$, $C^{20}H$), 5.63 (1H, d, *J* 9.8, $C^{7}H$), 5.51-5.44 (1H, m, $C^{23}H$), 5.36 (1H, d, *J* 9.8, $C^{6}H$), 5.26 (1H, *br* s, O*H*), 4.81 (1H, d, *J* 9.2, $C^{15}H$), 4.53-4.39 (2H,

m, $C^{22}H_2$), 3.88 (1H, d, *J* 7.2, $C^{8}H$), 3.78 (1H, d, *J* 9.2, $C^{11}H$), 3.66 (1H, *br* s, $C^{3}H$), 3.30-3.18 (2H, m, $C^{9}H$, $C^{2}H_AH_B$), 2.97 (3H, s, $C^{14}H_3$), 2.62 (1H, d, *J* 12.4, $C^{2}H_AH_B$), 2.01 (1H, d, *J* 13.2, $C^{4}H_AH_B$), 1.78 (3H, s, $C^{25}H_3$), 1.72 (3H, s, $C^{26}H_3$), 1.65-1.54 (2H, m, $C^{4}H_AH_B$, $C^{10}H_AH_B$), 1.33-1.29 (1H, m, $C^{10}H_AH_B$), 0.95 (9H, s, Si-C(CH_3)$_3$), 0.78 (9H, s, Si-C(CH_3)$_3$), 0.07 (3H, s, Si-CH_3), 0.06 (3H, s, Si-CH_3), -0.11 (3H, s, Si-CH_3), -0.30 (3H, s, Si-CH_3); δ_C (100 MHz, $CDCl_3$) 171.3 (C=O), 158.4 (C), 137.8 (C), 135.1 (CH), 133.5 (C), 130.2 (CH), 128.7 (CH), 120.0 (CH), 114.5 (CH), 75.6 (CH), 74.1 (CH), 72.0 (CH), 66.0 (CH), 64.5 (CH_2 and C), 61.6 (CH), 52.5 (CH_2), 47.5 (CH_2), 44.9 (CH_2), 33.9 (CH_3), 26.2 (CH_3), 26.1 (3 × CH_3), 25.9 (3 × CH_3), 18.3 (C), 18.1 (CH_3), 17.8 (C), -4.0 (CH_3), -4.2 (CH_3), -4.6 (CH_3), -5.2 (CH_3); *m/z* ESI^+ found 657.4101 (M+H, $C_{36}H_{61}N_2O_5Si_2$ requires 657.4114) and found 679.3922 (M+Na, $C_{36}H_{60}N_2O_5Si_2Na$ requires 679.3933); ν_{max}/cm^{-1} ($CHCl_3$) : 3388 (OH), 2955, 2930, 2856, 1622 (C=O), 1462, 1398, 1097, 1044, 1000, 873.

References

1. Sakamoto, K.; Tsujii, E.; Abe, F.; Nakanishi, T.; Yamashita, M.; Shigematsu, N.; Izumi, S.; Okuhara, M. *J. Antibiot.* **1996**, *49*, 37-44.
2. Snider, B. B.; Lin, H. *J. Am. Chem. Soc.* **1999**, *121*, 7778-7786.
3. Shirafuji, H.; Tubotani, S.; Ishimaru, T.; Harada, S. *PCT Int. Appl.* **1991**, WO91/13887-; *Chem. Abstr.* **1992**, *116*, 39780t.
4. Nagumo, S.; Nishida, A.; Yamazaki, C.; Murashige, K.; Kawahara, N. *Tetrahedron Lett.* **1998**, *39*, 4493-4496.
5. Snider, B. B.; Lin, H. *Org Lett.*, **2000**, *2*, 643-646 + supporting info.
6. Snider, B. B.; Lin, H.; Foxman, B. M. *J. Org. Chem.* **1998**, *63*, 6442-6443.
7. Sheffler, G.; Seike, H.; Sorensen, E. J. *Angew. Chem. Int. Ed.* **2000**, *39*, 4593-4596.
8. Braun, N. A.; Ciufolini, M. A.; Peters, K.; Peters, E.-M. *Tetrahedron Lett.* **1998**, *39*, 4667-4670.
9. Ousmer, M.; Braun, N. A.; Bavoux, C.; Perrin, M.; Ciufolini, M. A. *Org. Lett.* **2001**, *3*, 765-767.
10. Ousmer, M.; Braun, N. A.; Bavoux, C.; Perrin, M.; Ciufolini, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 7534-7538.
11. Brummond, K. M.; Lu, J. *Org. Lett.* **2001**, *3*, 1347-1349.
12. Brummond, K. M.; Hong, S. P. *J. Org. Chem.* **2005**, *70*, 907-916.
13. Carson, C. A.; Kerr, M. A. *Org. Lett.* **2009**, *11*, 777-779.
14. Krapcho, A. P.; Glynn, G. A.; Grenon, B. J. *Tetrahedron Lett.* **1967**, *8*, 215-217.
15. Shioiri, T.; Ninomiya, K.; Yamada, S.-I. *J. Am. Chem. Soc.* **1972**, *94*, 6203-6205.
16. Maeng, J.-H.; Funk, R. L. *Org. Lett.* **2001**, *3*, 1125-1128.
17. Kan, T.; Fujimoto, T.; Ieda, S.; Asoh, Y.; Kitaoka, H.; Fukuyama, T. *Org. Lett.* **2004**,

6, 2729-2731.

18. Ieda, S.; Asoh, Y.; Fujimoto, T.; Kitaoka, H.; Kan, T.; Fukuyama, T. *Heterocycles* **2009**, *79*, 721-738.
19. Ieda, S.; Kan, T.; Fukuyama, T. *Tetrahedron Lett.*, **2010**, *51*, 4027-4029.
20. Gokel, G.; Luedke, G.; Ugi, I. In *Isonitrile Chemistry*; Ugi, I., Ed.; Academic Press: New York, **1971**, 145.
21. Seike, H.; Sorensen, E. J. *Synlett* **2008**, 695-701.
22. Yamazaki, N.; Suzuki, H.; Kibayashi, C. *J. Org. Chem.* **1997**, *62*, 8280-8281.
23. Suzuki, H.; Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.*, **2001**, *42*, 3013-3015.
24. Wardrop, D. J.; Zhang, W. *Org. Lett.* **2001**, *3*, 2353-2356.
25. Quirante, J.; Escolano, C.; Massot, M.; Bonjoch, J. *Tetrahedron* **1997**, *53*, 1391-1402.
26. Bonjoch, J.; Diaba, F.; Puigbó, G.; Solé, D.; Segarra, V.; Santamaria, L.; Beleta, J.; Ryder, H.; Palacios, J.-M. *Bioorg. Med. Chem.* **1999**, *7*, 2891-2897.
27. Puigbó, G.; Diaba, F.; Bonjoch, J. *Tetrahedron* **2003**, *59*, 2657-2665.
28. Bonjoch, J.; Diaba, F.; Puigbó, G.; Peidró, E.; Solé, D. *Tetrahedron Lett.* **2003**, *44*, 8387-8390.
29. Kropf, J. E., Meigh, I. C., Bebbington, M. W. P.; Weinreb, S. M. *J. Org. Chem*, **2006**, *71*, 2046-2055.
30. Simila, S. T. M.; Martin, S. F. *J. Org. Chem.* **2007**, *72*, 5342-5349.
31. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs R. H. *Org. Lett.* **1999**, *1*, 953-956.
32. Kaden, S.; Reissig, H.-S. *Org. Lett.* **2006**, *8*, 4763-4766.
33. Nagumo, S.; Nishida, A.; Yamazaki, C.; Matoba, A.; Murashige, K.; Kawahara, N. *Tetrahedron* **2002**, *58*, 4917-4924.
34. Nagumo, S.; Matoba, A.; Ishii, Y.; Yamaguchi, S.; Akutsu, N.; Nishijima, H.; Nishida, A.; Kawahara, N. *Tetrahedron* **2002**, *58*, 9871-9877.

35. Wardrop, D. J.; Basak, A. *Org. Lett.* **2001**, *3*, 1053-1056.

36. Mizutani, H; Takayama, J.; Soeda, Y.; Honda, T. *Tetrahedron Lett.* **2002**, *43*, 2411-2414.

37. Mizutani, H; Takayama, J.; Honda, T. *Synlett* **2005**, 328-330.

38. Gabaitsekgosi, R.; Hayes, C. J. *Tetrahedron Lett.* **1999**, *40*, 7713-7716.

39. Bradley, D. M.; Mapitse, R.; Thomson, N. M.; Hayes, C. J. *J. Org. Chem.* **2002**, *67*, 7613-7617.

40. Mapitse, R.; Hayes, C. J. *Tetrahedron Lett.* **2002**, *43*, 3541-3542.

41. Worden, S. M.; Mapitse, R.; Hayes, C. J. *Tetrahedron Lett.* **2002**, *43*, 6011-6014.

42. Esmieu, W. R.; Worden, S. M.; Catterick, D.; Wilson, C.; Hayes, C. J. *Org. Lett.* **2008**, *10*, 3045-3048.

43. Hameed, A.; Blake, A. J.; Hayes, C. J. *J. Org. Chem.* **2008**, *73*, 8045-8048.

44. Stang, P. J. *Chem. Rev.* **1978**, *78*, 383-405.

45. Kirmse, W. *Angew. Chem. Int. Ed. Eng.* **1997**, *36*, 1164-1170.

46. Knorr, R. *Chem. Rev.* **2004**, *104*, 3795-3850.

47. Erickson, K. L.; Wolinsky, J. *J. Am. Chem. Soc.* **1965**, *87*, 1142-1143.

48. Walsh, R. A.; Bottini, A. T. *J. Org. Chem.* **1970**, *35*, 1086-1092.

49. Stang, P. J.; Mangum, M. G.; Fox, D. P.; Haak, P. *J. Am. Chem. Soc.* **1974**, *96*, 4562-4569.

50. Ohira, S.; Yamasaki, K.; Nozaki, H.; Yamato, M; Nakayama, M. *Tetrahedron Lett.* **1995**, *36*, 8843-8844.

51. Taber, D. F.; Sahli, A.; Yu, H.; Meagley, R. P. *J. Org. Chem.* **1995**, *60*, 6571-6573.

52. Taber, D. F.; Meagley, R. P. *J. Org. Chem.* **1996**, *61*, 5723-5728.

53. Colvin, E. W.; Hamill, B. J. *J. Chem. Soc., Chem. Comm.* **1973**, 151-152.

54. Colvin, E. W.; Hamill, B. J. *J. Chem. Soc., Perkin Trans. 1* **1977**, 869-874.

55. Esmieu, W. R. PhD dissertation, University of Nottingham, **2008**.

56. Auty, J. M. A.; Churcher, I.; Hayes, C. J. *Synlett*, **2004**, 1443-1445.

57. Auty, J. M. PhD dissertation, University of Nottingham, **2005**.

58. Asari, A. PhD dissertation, University of Nottingham, **2007**.

59. Asari, A.; Hayes, C. J. *Sains Malaysiana* **2009**, *38*, 869-872.

60. Churchill, M. R.; Bezman, S. A.; Osborn, J. A.; Wormald, J. *Inorganic chemistry* **1972**, *11*, 1818-1825.

61. Koreeda, M.; Koo, S. *Tetrahedron Lett.* **1990**, *31*, 831-834.

62. Zeng, G. Z.; Chan, T. H. *Organometallics* **1995**, *14*, 70-79.

63. Yun, J.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 1129-1131.

64. Asari, A.; Angelov, P.; Auty J. M.; Hayes, C. J. *Tetrahedron Lett.* **2007**, *48*, 2631-2634.

65. Price on the 17th July 2010, from Fisher Scientific UK Ltd. The price for *trans*-4-hydroxy-*L*-proline is £78 for 100 g.

66. Lowe, G.; Vilaivan, T. *J. Chem. Soc., Perkin Trans. 1*, **1997**, 539-546.

67. Dalla Croce, P.; La Rosa, C. *Tetrahedron : Asymmetry*, **2002**, *13*, 197-201.

68. Worden, S. M. PhD dissertation, University of Nottingham, **2004**.

69. Fataftah, Z. A.; Kopka, I. E.; Rathke, M. W. *J. Am. Chem. Soc.* **1980**, *102*, 3959-3960.

70. Muklopadhyay, T.; Seebach, D. *Helvetica Chimica Acta*, **2004**, *65*, 385-391.

71. Frontier, A. J.; Raghavan, S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2000**, *122*, 6151-6159.

72. Zhan, H.-J.; Xia, Q.-H.; Lu, X.-H, Zhang, Q. ; Yuan, H.-X.; Su, K.-X. ; Ma, X.-T. *Catalysis Comm.* **2007**, *8*, 1472-1478.

73. Rao, S. N.; Munshi, K. N.; Rao, N. N. *J. Mol. Catal. A: Chem.* **2000**, *156*, 205-211.

74. Lu, J.; Luo, M.; Lei, H.; Li, C. *Applied Catalysis* **2002**, *237*, 11-19.

75. Moreau, R. J. ; Sorensen, E. J. *Tetrahedron* **2007**, *63*, 6446-6453.

76. Aladro, F. J.;Guerra, F. M.; Moreno-Dorado, F. J.; Bustamante, J. M.; Jorge, Z. D.; Massanet, G. M. *Tetrahedron* **2001**, *57*, 2171-2178.

77. Lin, X.; Kavash, R. W.; Mariano, P. S. *J. Org. Chem.* **1996**, *61*, 7335-7347.

78. Aggarwal, V. K.; Astle, C. J.; Iding, H.; Wirz, B.; Rogers-Evans, M. *Tetrahedron Lett.* **2005**, *46*, 945-947.

79. Dhillon, R. S.; Singh, R. P.; Kaur, D. *Tetrahedron Lett.* **1995**, *36*, 1107-1108.

80. Collins, J. C.; Hess, W. W.; Frank, F. J. *Tetrahedron Lett.* **1968**, *9*, 3363-3366.

81. Katsuo, S.; Kazuhiro, M.; Hideaki, M.; Yukio, M. *Chem. Pharm. Bull.* **1996**, *44*, 1823-1830.

82. Corey, E. J.; Suggs, W. J. *Tetrahedron Lett.* **1975**, *16*, 2647-2650.

83. Lee, K.; Zhang, M.; Liu, H.; Yang, D.; Burke, T. R. *J. Med. Chem.* **2003**, *46*, 2621-2630.

84. Martini, E.; Ghelardini, C.; Dei, S.; Guandalini, L.; Manetti, D.; Melchiorre, M.; Norcini, M; Scapecchi, S.; Teodori, E.; Novella-Romanelli, M. *Bioorg. Med. Chem.* **2008**, *16*, 1431-1443.

85. For a review up to 1995 see: Davis, F. A.; Chen, B.-C. In *Houben-Weyl:stereoselective Synthesis*. For a recent review see: Plietker, B. *Tetrahedron Asymmetry* **2005**, *16*, 3453-3459.

86. Moriarty, R. M.; Duncan, M. P.; Prakash, O. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1781-1784.

87. Moriarty, R. M.; John, L. S.; Du, P. C. *J. Chem. Soc., Chem. Comm.* **1981**, *12*, 641-642.

88. Moriarty, R. M.; Hu, H.; Gupta, S. C. *Tetrahedron Lett.* **1981**, *22*, 1283-1286.

89. De Sousa, S. E.; O'Brien, P.; Pilgram, C. D. *Tetrahedron Lett.* **2001**, *42*, 8081-8063.

90. Davis, F. A.; Vishwakarma, L. C.; Billmers, J. M.; Finn, J. *J. Org. Chem.* **1984**, *49*, 3241-3243.

91. Wang, H.; Andemichael, Y. W.; Vogt, F. G. *J. Org. Chem.* **2009**, *74*, 478-481

92. Yoshimura, Y.; Inoue, J.; Yamazaki, N.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **2006**, *47*, 3489-3492.

93. Gallen, M. J.; Williams, C. M. *Org. Lett.* **2008**, *10*, 713-715.

94. Sakairi, N.; Hayashida, M.; Kuzuhara, H. *Tetrahedron Lett.* **1987**, *28*, 2871-2874.

95. Stevenson, N. G.; De Savi, C.; Harrity, J. P. A. *Synlett* **2006**, *14*, 2272-2274.

96. Paterson, I.; Findlay, A. D.; Florence, G. J. *Tetrahedron* **2007**, *63*, 5806-5819.

97. Motoyoshi, H.; Horigome, M.; Watanabe, H.; Kitahara, T. *Tetrahedron* **2006**, *62*, 1378-1389.

Appendix

X-ray crystallographic data for tricycle **212** (sppyra)

Table 1. Crystal data and structure refinement for sppyra at 150(2)K.

Empirical formula	$C_{17}H_{29}NO_4Si$	
Formula weight	339.50	
Crystal description	colourless column	
Crystal size	0.42 × 0.17 × 0.15 mm	
Crystal system	Orthorhombic	
Space group	P 2_1 2_1 2_1	
Unit cell dimensions	a = 7.1508(5) Å	α = 90 °
	b = 11.5559(8) Å	β = 90 °
	c = 22.7795(17) Å	γ = 90 °
Volume	1882.4(2) $Å^3$	
Reflections for cell refinement	6871	
Range in θ	2.51 ° to 27.18 °	
Z	4	
Density (calculated)	1.198 Mg/m^3	
Absorption coefficient	0.143 mm^{-1}	
F(000)	736	
Diffractometer type	Bruker SMART1000 CCD area detector	
Wavelength	0.71073 Å	
Scan type	ω	
Reflections collected	16329	
θ range for data collection	1.98 ° to 27.50 °	
Index ranges	$-9 \le h \le 9$, $-15 \le k \le 14$, $-28 \le l \le 29$	
Independent reflections	4289 [R_{int} = 0.0312]	
Observed reflections	3840 [$I > 2\sigma(I)$]	
Absorption correction	Semi-empirical from equivalents	
Max. and Min. transmission	0.98000 and 0.87176	
Decay correction	0%	
Structure solution by	direct and difmap methods	
Hydrogen atom location	geom	
Hydrogen atom treatment	constr	
Data / restraints / parameters	4289/0/208 (least-squares on F^2)	
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0354, wR2 = 0.0869	
Final R indices (all data)	R1 = 0.0416, wR2 = 0.0914	
Goodness-of-fit on F^2	1.024	
Absolute structure parameter	0.04(11)	
Final maximum δ/σ	0.001	

Weighting scheme

calc w =1/[$\sigma^2(F_o^2)$ + (0.0556P)^2 + 0.1395P] where P = (F_o^2 + 2F_c^2)/3

Largest diff. peak and hole 0.220 and -0.261 e.Å^{-3}

Table 2. Atomic coordinates (× 10^4) and equivalent isotropic displacement parameters (Å^2 × 10^3) for sppyra. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Si1	2175(1)	9553(1)	2114(1)	37(1)
N1	-2587(2)	8929(1)	627(1)	29(1)
O1	307(2)	9307(1)	1706(1)	35(1)
C2	-1787(2)	8212(1)	1093(1)	34(1)
O2	-1445(2)	13127(1)	-293(1)	40(1)
C3	222(2)	8666(1)	1173(1)	29(1)
O3	-5109(2)	7782(1)	467(1)	46(1)
O4	-3488(2)	10302(1)	-328(1)	34(1)
C4	569(2)	9425(1)	632(1)	28(1)
C5	-1351(2)	9900(1)	461(1)	26(1)
C6	-1555(2)	10095(1)	-201(1)	29(1)
C7	-498(2)	11160(1)	-408(1)	34(1)
C8	-1012(2)	12222(1)	-58(1)	32(1)
C9	-921(2)	12080(1)	598(1)	32(1)
C10	-1959(2)	10988(1)	801(1)	28(1)
C11	-4123(2)	8618(1)	332(1)	34(1)
C12	-4599(2)	9316(2)	-214(1)	40(1)
C13	3755(3)	8273(2)	2105(1)	54(1)
C14	3458(4)	10848(2)	1839(1)	71(1)
C15	1193(3)	9819(1)	2868(1)	41(1)
C16	-42(4)	8789(2)	3053(1)	55(1)
C17	-43(4)	10902(2)	2869(1)	58(1)
C18	2783(4)	9977(2)	3312(1)	65(1)

Table 3. Bond lengths [Å], angles and torsions [°] for sppyra.

Si1-O1	1.651(12)
Si1-C13	1.862(2)
Si1-C14	1.864(2)
Si1-C15	1.881(18)
N1-C11	1.337(2)
N1-C2	1.463(19)
N1-C5	1.477(18)
O1-C3	1.424(18)
C2-C3	1.540(2)
O2-C8	1.215(19)
C3-C4	1.533(2)

O3-C11	1.235(2)
O4-C12	1.413(2)
O4-C6	1.432(19)
C4-C5	1.529(2)
C5-C6	1.531(19)
C5-C10	1.539(19)
C6-C7	1.519(2)
C7-C8	1.509(2)
C8-C9	1.505(2)
C9-C10	1.535(2)
C11-C12	1.521(2)
C15-C17	1.532(3)
C15-C18	1.533(3)
C15-C16	1.541(3)

O1-Si1-C13	110.39(8)
O1-Si1-C14	110.34(9)
C13-Si1-C14	109.61(13)
O1-Si1-C15	103.88(8)
C13-Si1-C15	111.48(9)
C14-Si1-C15	111.04(10)
C11-N1-C2	122.25(13)
C11-N1-C5	124.47(12)
C2-N1-C5	112.51(12)
C3-O1-Si1	127.13(10)
N1-C2-C3	104.87(12)
O1-C3-C4	112.46(12)
O1-C3-C2	108.50(12)
C4-C3-C2	104.55(12)
C12-O4-C6	111.73(12)
C5-C4-C3	105.37(12)
N1-C5-C4	101.49(11)
N1-C5-C6	107.94(12)
C4-C5-C6	112.89(12)
N1-C5-C10	108.79(11)
C4-C5-C10	114.73(12)
C6-C5-C10	110.38(11)
O4-C6-C7	106.36(12)
O4-C6-C5	108.37(12)
C7-C6-C5	112.19(13)
C8-C7-C6	111.97(12)
O2-C8-C9	122.86(15)
O2-C8-C7	121.99(15)
C9-C8-C7	115.15(13)
C8-C9-C10	111.59(13)
C9-C10-C5	112.54(12)
O3-C11-N1	123.67(15)
O3-C11-C12	119.34(15)
N1-C11-C12	116.92(14)
O4-C12-C11	116.90(13)
C17-C15-C18	109.25(16)
C17-C15-C16	107.43(18)
C18-C15-C16	109.68(17)
C17-C15-Si1	110.53(12)

C18-C15-Si1	110.22(15)
C16-C15-Si1	109.68(11)
C13-Si1-O1-C3	-35.79(15)
C14-Si1-O1-C3	85.52(16)
C15-Si1-O1-C3	-155.40(12)
C11-N1-C2-C3	162.61(14)
C5-N1-C2-C3	-7.78(16)
Si1-O1-C3-C4	-89.39(14)
Si1-O1-C3-C2	155.45(11)
N1-C2-C3-O1	106.47(13)
N1-C2-C3-C4	-13.74(15)
O1-C3-C4-C5	-87.95(15)
C2-C3-C4-C5	29.57(15)
C11-N1-C5-C4	-144.38(14)
C2-N1-C5-C4	25.75(15)
C11-N1-C5-C6	-25.50(18)
C2-N1-C5-C6	144.63(12)
C11-N1-C5-C10	94.28(16)
C2-N1-C5-C10	-95.59(14)
C3-C4-C5-N1	-33.23(14)
C3-C4-C5-C6	-148.50(12)
C3-C4-C5-C10	83.87(14)
C12-O4-C6-C7	173.55(11)
C12-O4-C6-C5	-65.64(16)
N1-C5-C6-O4	56.74(15)
C4-C5-C6-O4	168.08(12)
C10-C5-C6-O4	-62.03(16)
N1-C5-C6-C7	173.86(12)
C4-C5-C6-C7	-74.79(16)
C10-C5-C6-C7	55.09(16)
O4-C6-C7-C8	65.46(16)
C5-C6-C7-C8	-52.86(17)
C6-C7-C8-O2	-130.32(15)
C6-C7-C8-C9	50.46(19)
O2-C8-C9-C10	131.44(16)
C7-C8-C9-C10	-49.35(18)
C8-C9-C10-C5	51.13(17)
N1-C5-C10-C9	-172.58(12)
C4-C5-C10-C9	74.57(15)
C6-C5-C10-C9	-54.33(17)
C2-N1-C11-O3	8.4(2)
C5-N1-C11-O3	177.65(14)
C2-N1-C11-C12	-168.70(14)
C5-N1-C11-C12	0.5(2)
C6-O4-C12-C11	39.70(19)
O3-C11-C12-O4	176.49(15)
N1-C11-C12-O4	-6.2(2)
O1-Si1-C15-C17	-63.24(15)
C13-Si1-C15-C17	177.89(14)
C14-Si1-C15-C17	55.35(19)
O1-Si1-C15-C18	175.89(13)
C13-Si1-C15-C18	57.02(16)
C14-Si1-C15-C18	-65.52(17)

O1-Si1-C15-C16	55.03(15)
C13-Si1-C15-C16	-63.84(17)
C14-Si1-C15-C16	173.62(15)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 \times 10^3$) for sppyra. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Si1	43(1)	43(1)	26(1)	2(1)	-4(1)	-3(1)
N1	31(1)	29(1)	26(1)	2(1)	-1(1)	-1(1)
O1	40(1)	41(1)	24(1)	-1(1)	-1(1)	6(1)
C2	36(1)	33(1)	33(1)	7(1)	0(1)	1(1)
O2	39(1)	35(1)	45(1)	13(1)	-1(1)	-2(1)
C3	34(1)	30(1)	25(1)	0(1)	-1(1)	4(1)
O3	45(1)	42(1)	51(1)	-3(1)	-6(1)	-14(1)
O4	33(1)	41(1)	28(1)	1(1)	-6(1)	3(1)
C4	30(1)	31(1)	23(1)	-1(1)	1(1)	4(1)
C5	28(1)	27(1)	22(1)	-1(1)	1(1)	0(1)
C6	32(1)	34(1)	21(1)	-2(1)	-1(1)	4(1)
C7	38(1)	42(1)	22(1)	4(1)	3(1)	2(1)
C8	26(1)	35(1)	36(1)	6(1)	0(1)	-4(1)
C9	37(1)	29(1)	31(1)	-2(1)	-1(1)	2(1)
C10	31(1)	31(1)	22(1)	-1(1)	1(1)	3(1)
C11	38(1)	34(1)	31(1)	-6(1)	0(1)	-2(1)
C12	36(1)	50(1)	35(1)	-2(1)	-9(1)	-5(1)
C13	40(1)	75(1)	46(1)	-10(1)	-5(1)	12(1)
C14	81(2)	83(2)	48(1)	9(1)	-3(1)	-39(1)
C15	64(1)	36(1)	24(1)	0(1)	-6(1)	6(1)
C16	84(2)	49(1)	31(1)	1(1)	13(1)	2(1)
C17	89(2)	43(1)	41(1)	-5(1)	-4(1)	17(1)
C18	87(2)	73(1)	34(1)	-11(1)	-20(1)	12(1)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$) for sppyra.

	x	y	z	U(eq)
H2A	-1779	7386	977	41
H2B	-2510	8295	1461	41
H3A	1130	8008	1183	35
H4A	1440	10064	727	33
H4B	1107	8961	308	33
H6A	-1110	9396	-420	35
H7A	862	11018	-372	40
H7B	-780	11298	-828	40

H9A	-1482	12766	788	39
H9B	404	12031	722	39
H10A	-3320	11104	747	33
H10B	-1723	10867	1224	33
H12A	-4513	8794	-558	49
H12B	-5917	9569	-182	49
H13A	4238	8155	1707	80
H13B	3059	7584	2229	80
H13C	4801	8404	2375	80
H14A	3955	10687	1446	106
H14B	4492	11028	2106	106
H14C	2602	11509	1820	106
H16A	-552	8931	3446	82
H16B	712	8081	3058	82
H16C	-1071	8700	2772	82
H17A	-538	11030	3265	87
H17B	-1083	10795	2594	87
H17C	701	11574	2749	87
H18A	2255	10119	3703	97
H18B	3558	10637	3196	97
H18C	3552	9275	3322	97

X-ray crystallographic data for tricycle **221** (chn3no)

Table 1. Crystal data and structure refinement for chn3no at 150(2)K.

Empirical formula	$C_{11}H_{12}N_4O_2$	
Formula weight	232.25	
Crystal description	colourless rod	
Crystal size	0.35 × 0.17 × 0.05 mm	
Crystal system	Orthorhombic	
Space group	P 2_1 2_1 2_1	
Unit cell dimensions	a = 9.4647(10) Å	α = 90 °
	b = 10.3435(11) Å	β = 90 °
	c = 11.1653(12) Å	γ = 90 °
Volume	1093.1(2) $Å^3$	
Reflections for cell refinement	3291	
Range in θ	2.69 ° to 27.48 °	
Z	4	
Density (calculated)	1.411 Mg/m^3	
Absorption coefficient	0.102 mm^{-1}	
F(000)	488	
Diffractometer type	Bruker SMART APEX CCD area detector	
Wavelength	0.71073 Å	
Scan type	ω	
Reflections collected	6949	
θ range for data collection	2.68 ° to 27.50 °	
Index ranges	$-12 \le h \le 12$, $-11 \le k \le 13$, $-14 \le l \le 10$	
Independent reflections	1459 [R_{int} = 0.0230]	
Observed reflections	1427 [$I > 2\sigma(I)$]	
Absorption correction	Semi-empirical from equivalents	
Max. and Min. transmission	0.995 and 0.873	
Decay correction	0%	
Structure solution by	direct and difmap methods	
Hydrogen atom location	geom	
Hydrogen atom treatment	constr	
Data / restraints / parameters	1459/0/154 (least-squares on F^2)	
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0422, wR2 = 0.1021	
Final R indices (all data)	R1 = 0.0433, wR2 = 0.1027	
Goodness-of-fit on F^2	1.167	
Final maximum δ/σ	0.000	

Weighting scheme

calc w = $1/[\sigma^2(F_o^2) + (0.0519P)^2 + 0.2896P]$ where $P = (F_o^2+2F_c^2)/3$

Largest diff. peak and hole 0.287 and -0.202 e.Å^{-3}

Table 2. Atomic coordinates (× 10^4) and equivalent isotropic displacement parameters (Å^2 × 10^3) for chn3no. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N1	8224(1)	8037(1)	1675(1)	23(1)
C2	8194(2)	7052(2)	733(1)	31(1)
C3	7232(2)	5999(2)	1217(2)	28(1)
C4	6326(2)	6682(2)	2163(2)	29(1)
C5	7284(2)	7727(1)	2702(1)	22(1)
C6	8202(2)	7242(2)	3729(1)	27(1)
C7	8747(2)	8036(2)	4533(2)	32(1)
C8	8517(2)	9448(2)	4484(1)	28(1)
O2	9053(1)	10173(1)	5212(1)	35(1)
C9	7610(2)	9943(2)	3461(1)	25(1)
C10	6507(2)	8942(2)	3096(1)	24(1)
C11	8853(2)	9190(2)	1498(1)	23(1)
O1	9613(1)	9393(1)	624(1)	32(1)
C12	8527(2)	10276(2)	2367(1)	25(1)
N13	8157(1)	4965(1)	1738(1)	30(1)
N14	7513(2)	4058(1)	2192(1)	30(1)
N15	7031(2)	3182(2)	2642(2)	47(1)

Table 3. Bond lengths [Å], angles and torsions [°] for chn3no.

N1-C11	1.347(2)
N1-C2	1.465(2)
N1-C5	1.4861(19)
C2-C3	1.519(2)
C3-N13	1.500(2)
C3-C4	1.532(2)
C4-C5	1.534(2)
C5-C10	1.521(2)
C5-C6	1.523(2)
C6-C7	1.322(2)
C7-C8	1.477(2)
C8-O2	1.217(2)
C8-C9	1.517(2)
C9-C10	1.526(2)
C9-C12	1.537(2)
C11-O1	1.2305(18)
C11-C12	1.516(2)

N13-N14	1.2283(19)
N14-N15	1.132(2)
C11-N1-C2	121.24(13)
C11-N1-C5	124.68(12)
C2-N1-C5	113.09(12)
N1-C2-C3	104.76(13)
N13-C3-C2	107.43(13)
N13-C3-C4	112.87(14)
C2-C3-C4	104.51(13)
C3-C4-C5	105.31(12)
N1-C5-C10	109.51(12)
N1-C5-C6	108.11(11)
C10-C5-C6	109.26(12)
N1-C5-C4	101.72(12)
C10-C5-C4	114.19(12)
C6-C5-C4	113.62(13)
C7-C6-C5	121.96(15)
C6-C7-C8	122.09(15)
O2-C8-C7	121.51(15)
O2-C8-C9	122.05(15)
C7-C8-C9	116.43(14)
C8-C9-C10	111.04(13)
C8-C9-C12	110.75(13)
C10-C9-C12	109.04(12)
C5-C10-C9	107.89(12)
O1-C11-N1	121.77(14)
O1-C11-C12	119.98(14)
N1-C11-C12	118.14(13)
C11-C12-C9	117.20(13)
N14-N13-C3	114.52(13)
N15-N14-N13	174.00(17)
C11-N1-C2-C3	-172.42(13)
C5-N1-C2-C3	-3.28(17)
N1-C2-C3-N13	-98.13(14)
N1-C2-C3-C4	22.00(16)
N13-C3-C4-C5	83.73(15)
C2-C3-C4-C5	-32.70(16)
C11-N1-C5-C10	30.93(19)
C2-N1-C5-C10	-137.77(13)
C11-N1-C5-C6	-88.02(16)
C2-N1-C5-C6	103.29(14)
C11-N1-C5-C4	152.09(14)
C2-N1-C5-C4	-16.60(15)
C3-C4-C5-N1	29.68(15)
C3-C4-C5-C10	147.52(13)
C3-C4-C5-C6	-86.25(16)
N1-C5-C6-C7	89.43(18)
C10-C5-C6-C7	-29.7(2)
C4-C5-C6-C7	-158.47(15)
C5-C6-C7-C8	-0.7(3)
C6-C7-C8-O2	-178.09(16)
C6-C7-C8-C9	0.4(2)

O2-C8-C9-C10	-150.97(15)
C7-C8-C9-C10	30.56(19)
O2-C8-C9-C12	87.73(18)
C7-C8-C9-C12	-90.74(17)
N1-C5-C10-C9	-59.71(15)
C6-C5-C10-C9	58.52(15)
C4-C5-C10-C9	-172.99(13)
C8-C9-C10-C5	-59.95(16)
C12-C9-C10-C5	62.34(16)
C2-N1-C11-O1	-11.6(2)
C5-N1-C11-O1	-179.45(13)
C2-N1-C11-C12	164.49(13)
C5-N1-C11-C12	-3.3(2)
O1-C11-C12-C9	-178.06(14)
N1-C11-C12-C9	5.8(2)
C8-C9-C12-C11	86.88(16)
C10-C9-C12-C11	-35.58(18)
C2-C3-N13-N14	178.30(14)
C4-C3-N13-N14	63.63(18)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 \times 10^3$) for chn3no. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N1	27(1)	24(1)	18(1)	0(1)	3(1)	4(1)
C2	47(1)	24(1)	22(1)	0(1)	1(1)	8(1)
C3	32(1)	25(1)	28(1)	-3(1)	-9(1)	5(1)
C4	26(1)	25(1)	36(1)	-1(1)	-2(1)	1(1)
C5	22(1)	24(1)	22(1)	2(1)	2(1)	1(1)
C6	33(1)	25(1)	23(1)	5(1)	3(1)	5(1)
C7	40(1)	35(1)	21(1)	4(1)	-5(1)	3(1)
C8	30(1)	33(1)	20(1)	-1(1)	6(1)	-3(1)
O2	41(1)	41(1)	24(1)	-8(1)	4(1)	-9(1)
C9	27(1)	24(1)	23(1)	-3(1)	3(1)	1(1)
C10	21(1)	26(1)	26(1)	2(1)	4(1)	1(1)
C11	21(1)	30(1)	19(1)	4(1)	-1(1)	3(1)
O1	32(1)	38(1)	24(1)	5(1)	8(1)	1(1)
C12	28(1)	26(1)	22(1)	2(1)	-1(1)	-3(1)
N13	29(1)	23(1)	39(1)	4(1)	-2(1)	-1(1)
N14	30(1)	25(1)	33(1)	0(1)	-1(1)	4(1)
N15	44(1)	36(1)	61(1)	16(1)	9(1)	3(1)

Table 5. Hydrogen coordinates (× 10^4) and isotropic displacement parameters (Å^2 × 10^3) for chn3no.

	x	y	z	U(eq)
H2A	9153	6710	580	37
H2B	7811	7414	-21	37
H3A	6625	5639	565	34
H4A	6017	6064	2787	35
H4B	5480	7075	1790	35
H6A	8388	6342	3794	32
H7A	9304	7688	5164	38
H9A	7111	10744	3731	30
H10A	5879	8745	3781	29
H10B	5922	9279	2430	29
H12A	8049	10975	1917	30
H12B	9435	10629	2662	30

X-ray crystallographic data for spirocycle **267** (spirco)

Table 1. Crystal data and structure refinement for spirco at 150(2)K.

Empirical formula	$C_{14}H_{19}NO_4$	
Formula weight	265.30	
Crystal description	colourless block	
Crystal size	0.42 × 0.41 × 0.25 mm	
Crystal system	Orthorhombic	
Space group	P 2_1 2_1 2_1	
Unit cell dimensions	a = 10.4932(6) Å	α = 90 °
	b = 10.7663(6) Å	β = 90 °
	c = 24.8152(14) Å	γ = 90 °
Volume	2803.4(3) $Å^3$	
Reflections for cell refinement	6179	
Range in θ	2.54 ° to 24.22 °	
Z	8	
Density (calculated)	1.257 Mg/m^3	
Absorption coefficient	0.092 mm^{-1}	
F(000)	1136	
Diffractometer type	Bruker SMART1000 CCD area detector	
Wavelength	0.71073 Å	
Scan type	ω	
Reflections collected	24794	
θ range for data collection	2.06 ° to 27.51 °	
Index ranges	$-13 \leq h \leq 13$, $-35 \leq k \leq 13$, $-32 \leq l \leq 31$	
Independent reflections	3627 [R_{int} = 0.0549]	
Observed reflections	2821 [$I > 2\sigma(I)$]	
Decay correction	0%	
Structure solution by	direct and difmap methods	
Hydrogen atom location	geom	
Hydrogen atom treatment	constr	
Data / restraints / parameters	3627/0/349 (least-squares on F^2)	
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0328, wR2 = 0.0674	
Final R indices (all data)	R1 = 0.0471, wR2 = 0.0715	
Goodness-of-fit on F^2	0.932	
Final maximum δ/σ	0.000	

Weighting scheme

calc $w = 1/[\sigma^2(F_o^2) + (0.0391P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$

Largest diff. peak and hole 0.147 and -0.152 e.Å^{-3}

Table 2. Atomic coordinates (× 10^4) and equivalent isotropic displacement parameters (Å^2 × 10^3) for spirco. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N1	3986(1)	8411(1)	8001(1)	29(1)
C2	3797(2)	8721(2)	7459(1)	33(1)
O1	3009(1)	9441(1)	7289(1)	42(1)
C3	4750(2)	7998(2)	7133(1)	38(1)
C4	5080(2)	6900(2)	7491(1)	34(1)
C5	4933(2)	7391(2)	8076(1)	26(1)
C6	4420(2)	6370(2)	8425(1)	29(1)
C7	5133(2)	5698(2)	8760(1)	31(1)
C8	6500(2)	5930(2)	8831(1)	32(1)
O2	7121(1)	5362(1)	9168(1)	45(1)
C9	7098(2)	6886(2)	8468(1)	31(1)
C10	6172(2)	7914(2)	8308(1)	29(1)
C11	3362(2)	9017(2)	8427(1)	34(1)
O3	2634(2)	9864(1)	8371(1)	48(1)
O4	3734(1)	8504(1)	8888(1)	35(1)
C12	3206(2)	8898(2)	9419(1)	34(1)
C13	3895(3)	8053(2)	9805(1)	55(1)
C14	3525(3)	10237(2)	9526(1)	58(1)
C15	1789(2)	8647(3)	9425(1)	61(1)
N1'	-541(1)	2450(1)	7979(1)	28(1)
C2'	-798(2)	2641(2)	7430(1)	32(1)
O1'	-1541(1)	2043(1)	7161(1)	39(1)
C3'	9(2)	3713(2)	7243(1)	38(1)
C4'	1034(2)	3832(2)	7674(1)	35(1)
C5'	385(2)	3377(2)	8198(1)	26(1)
C6'	1375(2)	2789(2)	8550(1)	31(1)
C7'	1910(2)	3376(2)	8964(1)	36(1)
C8'	1527(2)	4622(2)	9134(1)	35(1)
O2'	2020(2)	5123(1)	9523(1)	62(1)
C9'	546(2)	5277(2)	8803(1)	30(1)
C10'	-338(2)	4410(2)	8492(1)	28(1)
C11'	-1316(2)	1698(2)	8306(1)	31(1)
O3'	-2239(1)	1141(1)	8152(1)	41(1)
O4'	-849(1)	1722(1)	8806(1)	32(1)
C12'	-1568(2)	1192(2)	9272(1)	31(1)
C13'	-694(2)	1499(2)	9738(1)	40(1)
C14'	-2843(2)	1850(2)	9321(1)	44(1)
C15'	-1707(2)	-204(2)	9201(1)	38(1)

Table 3. Bond lengths [Å], angles and torsions [°] for spirco.

N1-C2	1.402(2)
N1-C11	1.404(2)
N1-C5	1.492(2)
C2-O1	1.210(2)
C2-C3	1.503(3)
C3-C4	1.518(3)
C4-C5	1.552(3)
C5-C6	1.501(2)
C5-C10	1.530(2)
C6-C7	1.332(3)
C7-C8	1.466(3)
C8-O2	1.224(2)
C8-C9	1.505(3)
C9-C10	1.525(2)
C11-O3	1.198(2)
C11-O4	1.329(2)
O4-C12	1.491(2)
C12-C14	1.503(3)
C12-C13	1.507(3)
C12-C15	1.511(3)
N1'-C2'	1.403(2)
N1'-C11'	1.405(2)
N1'-C5'	1.496(2)
C2'-O1'	1.211(2)
C2'-C3'	1.505(3)
C3'-C4'	1.523(3)
C4'-C5'	1.548(2)
C5'-C6'	1.498(2)
C5'-C10'	1.529(2)
C6'-C7'	1.330(3)
C7'-C8'	1.462(3)
C8'-O2'	1.221(2)
C8'-C9'	1.494(3)
C9'-C10'	1.526(3)
C11'-O3'	1.201(2)
C11'-O4'	1.335(2)
O4'-C12'	1.493(2)
C12'-C13'	1.513(3)
C12'-C14'	1.519(3)
C12'-C15'	1.520(3)

C2-N1-C5	112.83(15)
C11-N1-C5	124.05(14)
O1-C2-N1	125.75(19)
O1-C2-C3	126.85(18)
N1-C2-C3	107.41(16)
C2-C3-C4	103.90(16)
C3-C4-C5	105.01(15)
N1-C5-C6	111.80(14)
N1-C5-C10	110.00(14)
C6-C5-C10	110.90(15)

N1-C5-C4	101.60(14)
C6-C5-C4	109.08(15)
C10-C5-C4	113.15(16)
C7-C6-C5	123.86(17)
C6-C7-C8	122.13(18)
O2-C8-C7	121.13(19)
O2-C8-C9	121.95(18)
C7-C8-C9	116.93(17)
C8-C9-C10	112.75(15)
C9-C10-C5	111.90(15)
O3-C11-O4	127.21(19)
O3-C11-N1	124.31(18)
O4-C11-N1	108.47(15)
C11-O4-C12	122.17(14)
O4-C12-C14	110.26(17)
O4-C12-C13	102.24(15)
C14-C12-C13	111.07(19)
O4-C12-C15	108.95(17)
C14-C12-C15	112.9(2)
C13-C12-C15	110.9(2)
C2'-N1'-C11'	122.21(16)
C2'-N1'-C5'	112.41(15)
C11'-N1'-C5'	123.33(14)
O1'-C2'-N1'	125.51(18)
O1'-C2'-C3'	126.85(18)
N1'-C2'-C3'	107.64(17)
C2'-C3'-C4'	104.21(16)
C3'-C4'-C5'	104.65(15)
N1'-C5'-C6'	112.35(15)
N1'-C5'-C10'	109.71(14)
C6'-C5'-C10'	112.00(15)
N1'-C5'-C4'	100.98(14)
C6'-C5'-C4'	108.50(14)
C10'-C5'-C4'	112.83(15)
C7'-C6'-C5'	122.78(17)
C6'-C7'-C8'	122.87(18)
O2'-C8'-C7'	121.13(19)
O2'-C8'-C9'	121.14(18)
C7'-C8'-C9'	117.69(17)
C8'-C9'-C10'	114.06(15)
C9'-C10'-C5'	112.65(15)
O3'-C11'-O4'	126.91(18)
O3'-C11'-N1'	124.79(17)
O4'-C11'-N1'	108.30(15)
C11'-O4'-C12'	121.85(14)
O4'-C12'-C13'	101.71(14)
O4'-C12'-C14'	109.23(15)
C13'-C12'-C14'	111.73(17)
O4'-C12'-C15'	109.68(16)
C13'-C12'-C15'	111.27(17)
C14'-C12'-C15'	112.65(17)

C11-N1-C2-O1	-7.5(3)
C5-N1-C2-O1	173.61(17)

C11-N1-C2-C3	172.44(17)
C5-N1-C2-C3	-6.5(2)
O1-C2-C3-C4	-156.89(19)
N1-C2-C3-C4	23.2(2)
C2-C3-C4-C5	-30.6(2)
C2-N1-C5-C6	-128.73(16)
C11-N1-C5-C6	52.4(2)
C2-N1-C5-C10	107.59(17)
C11-N1-C5-C10	-71.3(2)
C2-N1-C5-C4	-12.53(19)
C11-N1-C5-C4	168.56(17)
C3-C4-C5-N1	26.2(2)
C3-C4-C5-C6	144.41(17)
C3-C4-C5-C10	-91.64(19)
N1-C5-C6-C7	-146.60(18)
C10-C5-C6-C7	-23.4(2)
C4-C5-C6-C7	101.8(2)
C5-C6-C7-C8	2.1(3)
C6-C7-C8-O2	174.82(18)
C6-C7-C8-C9	-5.7(3)
O2-C8-C9-C10	-149.67(17)
C7-C8-C9-C10	30.9(2)
C8-C9-C10-C5	-52.1(2)
N1-C5-C10-C9	171.57(14)
C6-C5-C10-C9	47.4(2)
C4-C5-C10-C9	-75.58(19)
C2-N1-C11-O3	-1.5(3)
C5-N1-C11-O3	177.33(17)
C2-N1-C11-O4	179.45(16)
C5-N1-C11-O4	-1.8(2)
O3-C11-O4-C12	3.6(3)
N1-C11-O4-C12	-177.36(16)
C11-O4-C12-C14	-62.6(2)
C11-O4-C12-C13	179.26(18)
C11-O4-C12-C15	61.8(2)
C11'-N1'-C2'-O1'	-13.5(3)
C5'-N1'-C2'-O1'	-177.66(17)
C11'-N1'-C2'-C3'	166.46(16)
C5'-N1'-C2'-C3'	2.27(19)
O1'-C2'-C3'-C4'	-162.39(19)
N1'-C2'-C3'-C4'	17.7(2)
C2'-C3'-C4'-C5'	-30.07(19)
C2'-N1'-C5'-C6'	-136.07(16)
C11'-N1'-C5'-C6'	59.9(2)
C2'-N1'-C5'-C10'	98.66(17)
C11'-N1'-C5'-C10'	-65.3(2)
C2'-N1'-C5'-C4'	-20.65(18)
C11'-N1'-C5'-C4'	175.37(16)
C3'-C4'-C5'-N1'	30.40(18)
C3'-C4'-C5'-C6'	148.65(16)
C3'-C4'-C5'-C10'	-86.63(19)
N1'-C5'-C6'-C7'	-149.01(17)
C10'-C5'-C6'-C7'	-25.0(2)
C5'-C6'-C7'-C8'	100.2(2)

C5'-C6'-C7'-C8'	3.7(3)
C6'-C7'-C8'-O2'	178.4(2)
C6'-C7'-C8'-C9'	-3.6(3)
O2'-C8'-C9'-C10'	-156.6(2)
C7'-C8'-C9'-C10'	25.4(2)
C8'-C9'-C10'-C5'	-46.4(2)
N1'-C5'-C10'-C9'	170.77(14)
C6'-C5'-C10'-C9'	45.3(2)
C4'-C5'-C10'-C9'	-77.49(19)
C2'-N1'-C11'-O3'	1.3(3)
C5'-N1'-C11'-O3'	163.75(18)
C2'-N1'-C11'-O4'	-178.48(16)
C5'-N1'-C11'-O4'	-16.0(2)
O3'-C11'-O4'-C12'	-10.1(3)
N1'-C11'-O4'-C12'	169.70(14)
C11'-O4'-C12'-C13'	-177.26(16)
C11'-O4'-C12'-C14'	-59.0(2)
C11'-O4'-C12'-C15'	64.9(2)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 \times 10^3$) for spirco. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N1	31(1)	23(1)	32(1)	3(1)	-3(1)	3(1)
C2	34(1)	28(1)	38(1)	9(1)	-7(1)	-7(1)
O1	38(1)	39(1)	50(1)	18(1)	-9(1)	-2(1)
C3	46(1)	39(1)	30(1)	3(1)	-4(1)	-1(1)
C4	44(1)	29(1)	30(1)	-1(1)	-5(1)	2(1)
C5	28(1)	23(1)	29(1)	1(1)	-2(1)	2(1)
C6	28(1)	25(1)	35(1)	0(1)	-1(1)	-1(1)
C7	36(1)	27(1)	32(1)	1(1)	2(1)	2(1)
C8	37(1)	29(1)	29(1)	-6(1)	-4(1)	9(1)
O2	49(1)	49(1)	37(1)	0(1)	-12(1)	16(1)
C9	26(1)	31(1)	35(1)	-9(1)	-3(1)	3(1)
C10	28(1)	25(1)	33(1)	-3(1)	1(1)	-1(1)
C11	33(1)	25(1)	43(1)	2(1)	-6(1)	1(1)
O3	54(1)	39(1)	51(1)	-2(1)	-8(1)	22(1)
O4	37(1)	36(1)	33(1)	2(1)	4(1)	12(1)
C12	35(1)	33(1)	34(1)	-6(1)	5(1)	4(1)
C13	72(2)	60(2)	33(1)	2(1)	9(1)	20(1)
C14	81(2)	39(1)	53(1)	-10(1)	0(1)	-11(1)
C15	41(1)	83(2)	60(2)	-17(1)	13(1)	-9(1)
N1'	29(1)	29(1)	25(1)	-3(1)	1(1)	-1(1)
C2'	33(1)	32(1)	29(1)	-5(1)	1(1)	8(1)
O1'	46(1)	39(1)	33(1)	-12(1)	-6(1)	5(1)
C3'	44(1)	43(1)	26(1)	0(1)	6(1)	2(1)
C4'	34(1)	38(1)	31(1)	2(1)	8(1)	-1(1)
C5'	25(1)	26(1)	27(1)	-1(1)	1(1)	-1(1)
C6'	28(1)	26(1)	39(1)	4(1)	3(1)	0(1)

C7'	32(1)	33(1)	43(1)	8(1)	-10(1)	2(1)
C8'	41(1)	30(1)	35(1)	4(1)	-7(1)	-6(1)
O2'	87(1)	42(1)	58(1)	-5(1)	-42(1)	-1(1)
C9'	36(1)	26(1)	30(1)	1(1)	-2(1)	1(1)
C10'	28(1)	27(1)	28(1)	-1(1)	-1(1)	2(1)
C11'	31(1)	29(1)	32(1)	-5(1)	1(1)	0(1)
O3'	39(1)	47(1)	38(1)	-4(1)	-3(1)	-13(1)
O4'	32(1)	37(1)	26(1)	2(1)	1(1)	-9(1)
C12'	34(1)	30(1)	30(1)	3(1)	6(1)	-5(1)
C13'	47(1)	41(1)	31(1)	-2(1)	2(1)	-9(1)
C14'	40(1)	47(1)	46(1)	5(1)	10(1)	3(1)
C15'	39(1)	33(1)	41(1)	2(1)	2(1)	-5(1)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$) for spirca.

	x	y	z	U(eq)
H3A	5516	8506	7056	46
H3B	4374	7717	6788	46
H4A	5963	6618	7424	41
H4B	4490	6199	7424	41
H6A	3534	6192	8407	35
H7A	4743	5048	8960	38
H9A	7416	6471	8139	37
H9B	7838	7261	8655	37
H10A	6582	8456	8036	34
H10B	5974	8428	8628	34
H13A	4814	8206	9782	83
H13B	3718	7186	9712	83
H13C	3602	8217	10173	83
H14A	4446	10361	9488	87
H14B	3263	10457	9892	87
H14C	3075	10765	9266	87
H15A	1635	7768	9347	92
H15B	1370	9160	9152	92
H15C	1444	8851	9782	92
H3'A	-502	4483	7218	45
H3'B	393	3536	6887	45
H4'A	1316	4705	7711	41
H4'B	1781	3309	7586	41
H6'A	1633	1961	8474	37
H7'A	2569	2968	9158	43
H9'A	983	5832	8544	36
H9'B	23	5805	9044	36
H10C	-826	4901	8225	33
H10D	-954	4031	8745	33
H13D	-639	2403	9780	59
H13E	157	1162	9667	59
H13F	-1033	1131	10070	59
H14D	-2711	2750	9305	66
H14E	-3241	1630	9666	66

H14F	-3400	1593	9025	66
H15D	-863	-578	9155	56
H15E	-2228	-375	8882	56
H15F	-2121	-557	9520	56

Full X-ray crystallographic data for *α*-hydroxy ketone **179** and tricycle **295** were not available at the time of submission.