Towards the Total Synthesis of Ficellomycin

Submitted by

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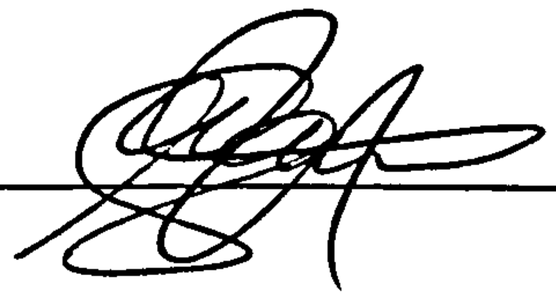
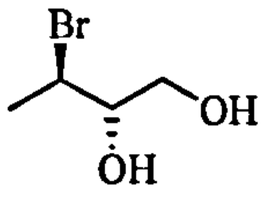
"I certify that all material in this thesis which is not my own work has been identified and that no material is included for which a degree has previously been conferred upon me,

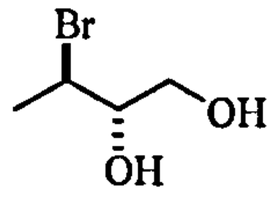
signed  "

The Convention of Stereochemical Descriptors

Throughout this thesis, the stereochemical descriptors shown in **I** and **II** have been used to represent the stereochemistry of single enantiomers and the stereochemistry of racemates respectively, as proposed by Maehr.



Single Enantiomer, **I**



Racemate, **II**

Reference: Maehr, H. *J. Chem. Educ.*, **1985**, *62*, 114-120.

Abstract

Chapter One provides a review of the literature relating to the isolation, structure elucidation and biological activity of ficellomycin, a natural product with antibiotic activity. This chapter also provides an overview of published synthetic routes towards ficellomycin and 1-azabicyclo[3.1.0]hexanes.

Chapter Two describes our synthetic efforts to the 1-azabicyclo[3.1.0]hexane core of ficellomycin. Initially, a model system developed in the group with a double cyclisation as key step was optimised. This involved the reduction of a 1,2-azido alcohol, using a solid-supported triphenylphosphine reagent, to an aziridine that undergoes conjugate addition onto a tethered dehydroamino acid *in situ*. Under these conditions, azido alcohol **94** led to the formation of the four stereoisomeric bicycles **45 a/b, 142 a/b,** in 45% overall yield in a 3:1:5:1 ratio.

A second approach towards the natural product is also described. This involved the development of a system wherein the C-5 amino substituent is incorporated. Two open chain γ-aldehydes **212** and **232,** were made in 8 and 10 steps respectively from **168** using a sequence that involved *anti*-1,4-addition of azide onto **168,** formation of Weinreb amides **211** and **231** and their chemoselective reduction as key steps. Reaction of these aldehydes with phosphonate **99** using DBN, produced alkenes **214** and **230** respectively, and exclusively, as the (*Z*)-isomers. Further stereocontrolled cyclisation to piperidines **220** and **235** possessing the required 3*S*, 5*S*, 6*R*-stereochemistry was achieved in good yields by hydrogenation using Lindlar's catalyst. We anticipate that these intermediates could be further advanced to the natural product.

Chapter Three draws conclusions from the work to date, and discusses future options with respect to the completion of the synthesis to the natural product.

Chapter Four contains detailed experimental procedures for the novel compounds described within this thesis.

Abbreviations

Ac	Acetyl
Alloc	Allyloxycarbonyl
ax	Axial
AZT	Azidothymidine
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
b.p.	Boiling point
Bu	Butyl
CAN	Ammonium cerium(IV) nitrate
cat.	Catalyst/catalytic
Cbz	Benzyloxycarbonyl
CDI	Carbonyl-*N*,*N*'-di-imidazole
COLOC	Long range ^{1}H-^{13}C correlation spectrum
CI	Chemical ionisation
COSY	Correlation spectroscopy
CSA	Camphor sulfonic acid
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DCC	*N*,*N*-dicyclohexylcarbodiimide
de.	Diastereomeric excess
DIBAL-H	Di-*iso*-butylaluminium hydride
DIPT	Di-*iso*-propyl tartrate
DMAP	4-Dimethylaminopyridine
DME	1,2-Dimethoxyethane

DMF	*N*, *N*-Dimethylformamide
DMP	2,2-dimethoxypropane
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
dr.	Diastereomeric ratio
E.	*Escherichia*
ee	enantiomeric excess
EDTA	Ethylenediaminetetraacetic acid
EI	Electron ionisation
ES	Electrospray
Et	Ethyl
eq.	Equivalent/equatorial
FAB	Fast atom bombardment
gem	Geminal
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
IC_{50}	Mean Inhibition Concentration
Imid	Imidazole
IR	Infra red
LCMS	Liquid Chromatography Mass Spectrometry
LD_{50}	Mean Lethal Dose
LDA	Lithium diisopropyl amide
LRMS	Low resolution mass spectrometry
m-CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl

MHz	Mega-Hertz
mmTr	monomethoxytrityl
m.p.	Melting point
Ms	methanesulfonyl
MS	Mass Spectrometry
MWt	Molecular weight
NBS	*N*-Bromosuccinimide
NMO	4-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
NVoc	Nitroveratryl
P.	Penicillium
PCC	Pyridinium chlorochromate
pH	potential of Hydronium ions
pK_a	-log K_a (acidity constant)
PMB	*para*-Methoxybenzyl
ppm	parts per million
PPTS	Pyridinium-*p*-toluenesulfonate
RT	Room Temperature
S_N2	Substitution Nucleophilic Bimolecular
S_Nib	Internal backside nucleophilic substitution
TBAF	Tetra-*n*-butylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
TBS	Tributylsilyl

TCA	Trichloroacetic acid
TEMPO	2,2,6,6-Tetramethylpiperidine *N*-oxide
TES	Triethylsilyl
Teoc	Triethylsilyloxycarbonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMEDA	*N,N,N,N*-Tetramethylethylene diamine
TMS	Trimethylsilyl
TMSE	Trimethylsilylethyl
TMSI	Trimethylsilyl iodide
TPAP	Tetra-*n*-propylammonium perruthenate
Ts	*para*-Toluenesulfonyl
*p*TSA	*para*-Toluenesulfonic acid
*p*TSCl	*para*-Toluenesulfonyl chloride
UV	Ultra violet
vic	Vicinal

Chapter One:

Introduction to Ficellomycin

1. Introduction to Ficellomycin

1.1. Background

The isolation of ficellomycin (U-47,929) was first described in 1976 by Argoudelis *et al.* at the Upjohn Company.[1] It was one of three natural products, displaying antibacterial activity, produced by and isolated from a culture broth of *Streptomyces ficellus* (UC®5438). In 1989, Kuo and co-workers proposed structure **1** for ficellomycin as represented in Figure 1, through a combination of NMR, MS, chemical degradation and derivatisation studies, which revealed the presence of a highly strained 1-azabicyclo[3.1.0]hexane ring system **2**.[2]

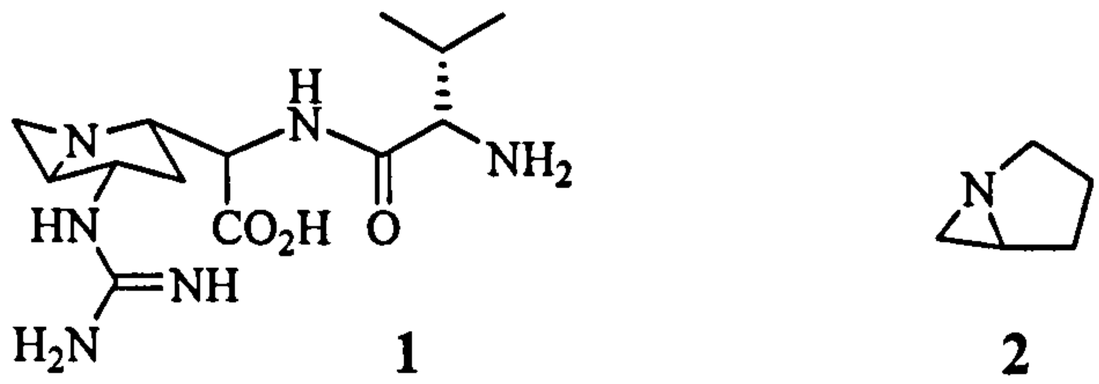


Figure 1

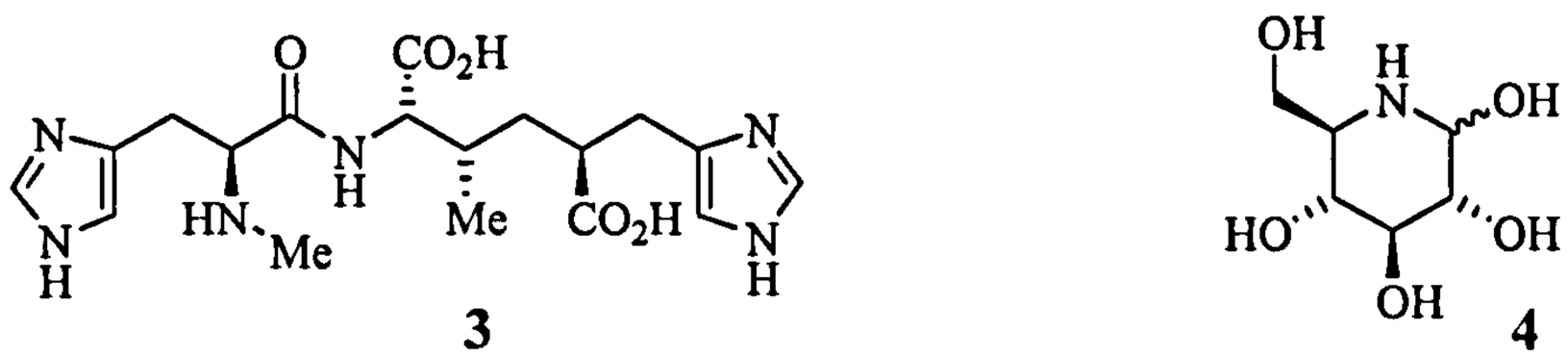
The unusual structural features and prominent biological activity have attracted the attention of the synthetic chemistry community. To date, there have been several efforts directed towards its synthesis by the groups of Armstrong,[3] Yudin,[4] and our own,[5] but no reported total synthesis.

In this Chapter, the isolation and biological properties of ficellomycin **1**, its structural elucidation and the stereochemical ambiguities that surround this natural product are described. General synthetic routes to the skeleton of this and related natural products are discussed. Synthetic efforts towards the total synthesis of ficellomycin **1** in our and other groups are also described.

Although the natural product is most likely a zwitterion at neutral or physiological pH, we represent it in the neutral form throughout this thesis, in the same way as it is represented in the literature.

1.2. Isolation

Ficellomycin **1** was produced by and isolated from the culture broth of *Streptomyces ficellus* (UC®5438) together with two other natural products displaying antibiotic activity; one of them, was designated feldamycin **3**, and the other, was later identified as nojirimycin **4**, which had been isolated and described in 1967 by Ishida and Kumagai (Figure 2).[6]



3 **4**

Figure 2

The production and isolation of the three antibiotics were guided using bioassays. For ficellomycin **1**, the process was followed by assaying against *Staphylococcus aureus* and *Penicillium oxalicum*, as well as by paper or thin layer chromatography developed with ninhydrin.

The isolation of ficellomycin has been achieved on a large (5,000 L) scale. For the isolation of the natural product, the broth was filtered through diatomaceous earth. Acid washed florisil chromatography separated feldamycin **3** from ficellomycin **1** (eluting system, water then 50% aqueous acetone), and Amberlite XAD-4 chromatography separated nojirimycin **4** from ficellomycin **1** (pH 10, eluting system water then 20% methanol/water).

From this, 20 g of ficellomycin preparation were dissolved in water (pH found 10.4) and purified by ion-exchange column chromatography with Dowex-1 (X-4) in the hydroxide form, eluting with water.

Fractions active to ninhydrin staining in TLC and bioautography on *S. aureus* were combined and freeze-dried to afford 8.3 g of pure ficellomycin, isolated as an amorphous colourless material $\{[\alpha]_D^{25} = +39\ (c\ 1, \text{water})\}$, soluble in water and lower alcohols and stable at pH 8-10.

1.3. Biological Properties

Ficellomycin **1**, at pH 8-10, displays high *in vitro* activity against *S. aureus* including strains resistant to penicillin, streptomycin, neomycin, macrolides and lincosaminide antibiotics. It is moderately effective in the treatment of experimental *S. aureus* infections in mice (subcutaneously, CD_{50} *ca* 7.6 mg/kg) and strains resistant to either streptomycin or erythromycin (subcutaneously, CD_{50} of 10 and 11 mg/kg, respectively). It is inactive against Gram negative bacteria, viruses and a variety of fungi, except *Penicilium oxalicum*. The acute LD_{50} values in mice are approximately of 800 mg/kg *via* intraperitoneal or intravenous administration.

For the other co-isolated metabolites, feldamycin **3** displays high activity against *Sarcina lutea*, slight activity against *S. aureus* and inactivity against *P. oxalicum*; it has also been tested as an inhibitor of depigmentation of *S. bikiniensis* and B16 melanoma cells.[7] Nojirimycin **4** is active against Gram positive and negative bacteria (including *S. aureus* and *Escherichia coli*) and inactive against *P. oxalicum*.

It seems likely that the aziridine is the structural feature responsible for the antibiotic activity of ficellomycin. A plausible mode of action could involve the inhibition of DNA synthesis, since the aziridine ring is often an effective alkylating agent, and is a key determinant in the antitumoral activity of structurally related natural products.[5]

Reusser established that both ficellomycin **1** and feldamycin **3** target the DNA replication process; they impair semiconservative DNA replication, but not DNA repair synthesis in bacteria.[8] Approximately 50% inhibition was observed in the presence of 0.5-1 mM of ficellomycin when assayed *in vitro* against whole bacterial E. coli cells. Greater potency (100-200 μg/mL concentration) was observed towards inhibition in DNA replication in toluenised cells at 100-200 μg/mL concentration.

Reusser has suggested that ficellomycin does not inhibit the initial steps of replication including the polymerases, but causes the accumulation of a DNA population with a mean size of 34 *S*, formed in the presence of the antibiotic, which must be deficient in some function and lack the ability of being integrated into larger DNA fragments, and consequently into the whole bacterial chromosome.[8]

Ficellomycin **1** and feldamycin **3** do not stabilise double-stranded DNA against heat denaturation, but increase the melting point of synthetic polydeoxynucleotide poly[d(A-T)] by 1-3 °C, which was put forward as evidence for them being weak DNA alkylators. No evidence of base pair intercalation was found by UV difference spectroscopy or circular dichroism.[8]

Although it has been widely speculated that the antimicrobial activity of ficellomycin is due to its aziridine functionality,[2] this has not been verified (*vide supra*). In fact, some or all of its biological activity may be associated with the free guanidine group in its structure. It has been suggested that its "*aziridine ring system may be stabilised by the neighbouring guanidino group*".[2] The potential important role of ficellomycin and/or its analogues incorporated as the active ingredients in antibiotic and antifungal pharmaceutical compositions has made them, amongst other guanidine-containing compounds, the subject of a recently published patent application.[9]

The outermost bacterial cell surface is usually negatively charged overall, rendering bacteria susceptible to cationic species, such as protonated guanidines.[9]

Due to their strongly basic character, guanidines are fully protonated at physiological pH and this may be the basis for the specificity of these compounds as they provide the molecule with cationic and hydrophobic domains which can orient themselves *via* hydrogen bonding and electrostatic van der Waals interactions with the bacterial cell wall.[10]

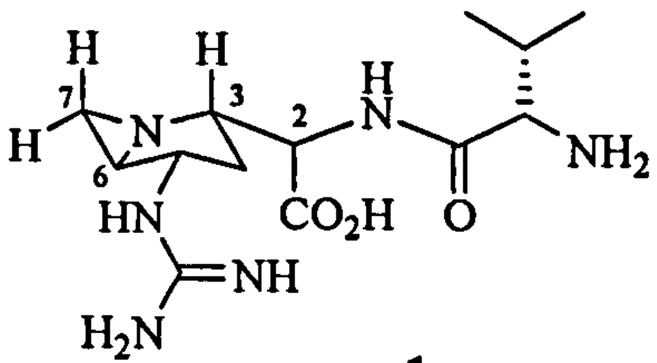
1.4. Structure Elucidation

In the original isolation paper, Argoudelis determined some structural and chemical features of ficellomycin through preliminary analytical and chemical studies.[1] The formation of a penta-trimethylsilyl derivative subjected to fast atom bombardment mass spectroscopy determined that ficellomycin has a molecular formula of $C_{13}H_{24}N_5O_3$ (MWt 312); NMR, mass spectrometry and acid and base hydrolysis provided evidence for the presence of an L-Valine residue, bound to the rest of the

molecule *via* a peptide bond. The presence of a free amino group was supported by the positive response of ficellomycin to ninhydrin.[1] The basic character and behaviour of ficellomycin, along with a positive Sakaguchi test revealed the presence of a primary guanidino group.

In 1989, Kuo determined the identity of the heterocyclic core of ficellomycin and its substitution pattern, through NMR studies.[2] Moreover, treatment with MeOH/HCl produced a methyl ester, which revealed the presence of a carboxylic acid, which was not identified in the original paper. This acid group completed the count for exchangeable protons observed in the ^{1}H NMR spectrum.

^{1}H-^{1}H COSY identified the L-valine and an additional 8 hydrogen spin system. The observation of a characteristic methylene group with characteristic small geminal coupling constants (2.1 Hz) and vicinal coupling constants (5.3 and 3.5 Hz) suggested the presence of an aziridine ring (Figure 3). Two additional methylene hydrogens with large geminal coupling constants (13.4 Hz) was indicative of a six-membered ring. The location of the guanidine and the dipeptide substituents at C-3 and C-5 was readily achieved, the bicyclic structure of the core being confirmed by use of a long range ^{1}H-^{13}C correlation (COLOC) spectrum. The complete structure proposed by Kuo was valyl-2-[4-guanidyl-1-azabicyclo[3.1.0]hexane-2-yl]glycine **1**.



1

Selected ^{1}H NMR homonuclear coupling constants (300 MHz, D_2O)

J_{gem} (7_{ax}-7_{eq})	=	2.1 Hz
J_{vic} (6-7_{eq})	=	5.5 Hz
J_{vic} (6-7_{ax})	=	3.5 Hz
J_{gem} (4_{ax}-4_{eq})	=	13.4 Hz

Figure 3

Although Kuo provided details of the homonuclear coupling constants, no further support was provided for the formulated stereochemical assignment. For example, no nOe difference studies were reported. These were subsequently performed by Armstrong, who revised the stereochemistry and assigned the 1-azabicyclo[3.1.0]hexane conformation to a boat **6** (Figure 4).[3] Crucially, nOe enhancements were seen between H-7, H-4 and H-2. These results indicate that the dipeptide substituent, the aziridine and the guanidine group are all on the same face of the molecule. Furthermore, H-3 and H-5 showed reciprocal nOe enhancements, demonstrating they are *syn* to one another. No nOe enhancements were observed between H-7_{ax} and H-5.

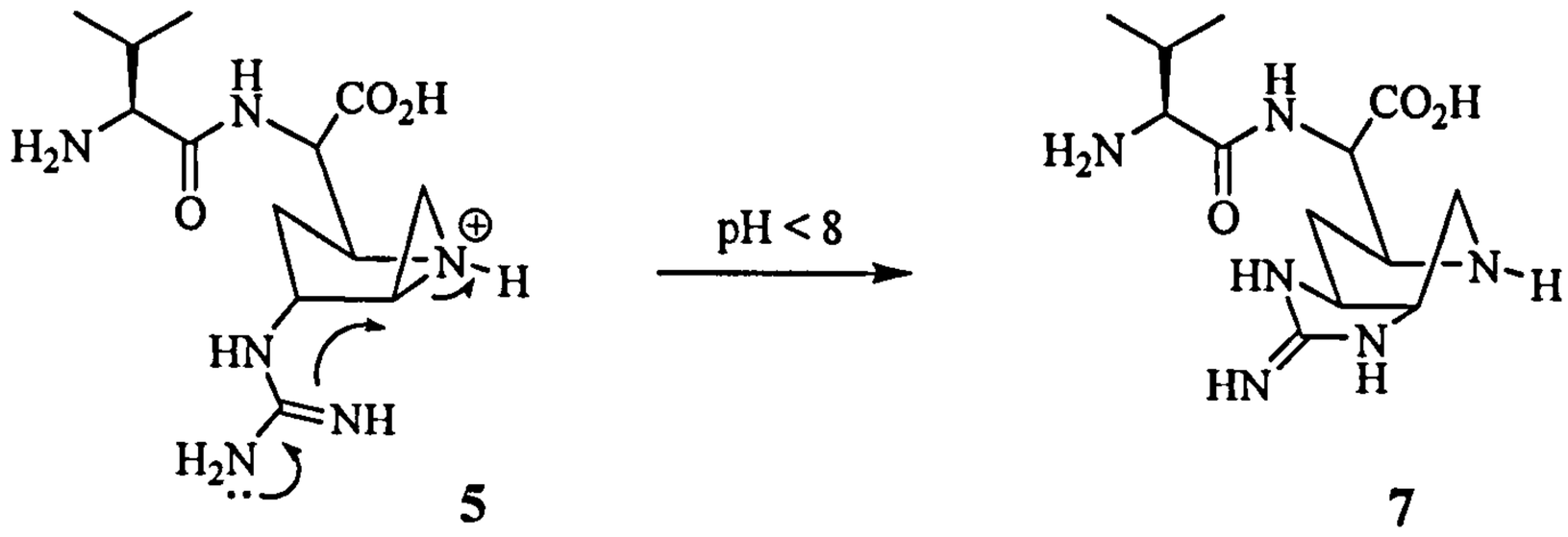
Figure 4

Additionally, Armstrong supported his findings using the work of Shustov *et al.*, who had studied the solution conformations of 1-azabicyclo- and diazabicyclo-[3.1.0]hexanes.[11] These studies had established that such systems prefer a boat conformation unless geminal substituents are introduced simultaneously at C-6 or C-3. This manifests itself in upfield chemical shifts of the C-3 and C-6 signals in the ^{13}C NMR spectrum due to steric compression. Indeed, these signals occur at 27.9 and 22.3 ppm in ficellomycin, whereas they might be expected at > 30 and > 40 ppm, respectively, in the corresponding chair form.

Hence, Armstrong proposed structure **5** as shown in Figure 4 with the absolute stereochemistry as displayed. However, he stated, it could also be its diastereomer **6** (Figure 3). The stereochemistry of the amino centre at C-2 is not known, Armstrong suggested that it is most likely the *S*-configuration as illustrated if it is assumed to derive biogenetically from the L-amino acid.

1.5. Chemical Stability of Ficellomycin

During the isolation of ficellomycin, it was determined that the natural product displayed its antibiotic activity in a narrow pH range (8-10) within which it is stable. At pH < 8, a new form of the natural product was produced, designated "inactive ficellomycin" by Argoudelis, which did not display biological activity. Further analysis determined that it has the same molecular formula, indicating an "intramolecular change".[1] Armstrong, subsequently proposed that "inactive ficellomycin" **7** arises from ficellomycin **5** by intramolecular nucleophilic opening of the aziridine ring by the guanidine (Scheme 1).



5 **7**

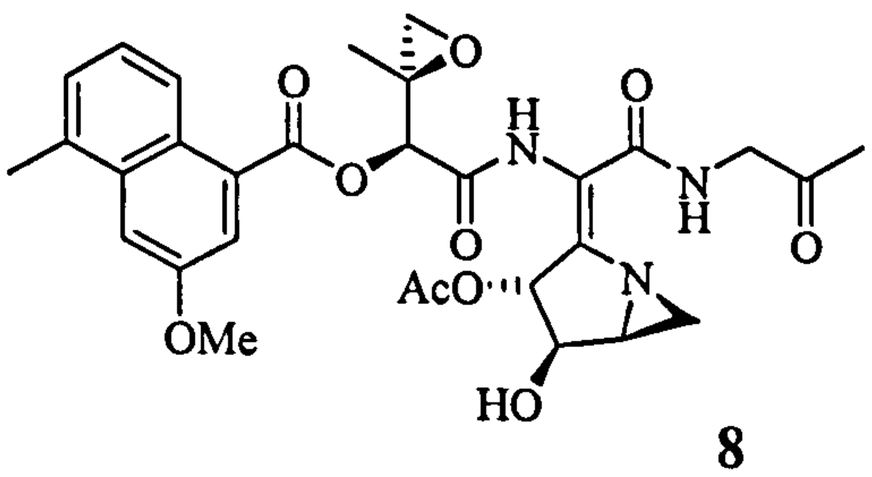
Scheme 1

1.6. Structurally Related Natural Products

1.6.1 Other Aziridine Containing Systems

The most closely related natural products to ficellomycin are those isolated from *Streptomyces griseofuscus*, namely azinomycins A (**8**) and B (**9**) (Azinomycin B, also known as carzinophilin, has also been isolated from *Streptomyces sahachiroi*), respectively (Figure 5).[12,13]

These compounds contain an unsaturated 1-azabicyclo[3.1.0]hexane-2-ylidene core. They are active against Gram positive and negative bacteria, and inactive against yeast and fungi. These natural products have anticancer properties, with azinomycin A **8** being more cytotoxic in *in vitro* tests against the L5178Y tumour cell line (IC_{50} = 0.07 μg/mL for **8**; 0.11 μg/mL for **9**)[12] and azinomycin B **9** being more potent *in vivo* against P388 leukemia, B-16 melanoma, and Ehrlich carcinoma.[14] Work performed by Shipman and co-workers on structurally related synthetic compounds have highlighted the role of the epoxide and the aziridine in the antitumoural activities of these natural products through inter-strand crosslinking of DNA.[15] This proceeds most likely *via* a two step process by alkylation of the adenosine (N-7) by the aziridine (C-10) followed by alkylation of the guanine (N-7) by the epoxide (C-21).[16] Like ficellomycin **5**, the azinomycins are stable at alkaline pH 6-9 but acid labile and biologically inactive when the pH is lowered to 5.[12,13]



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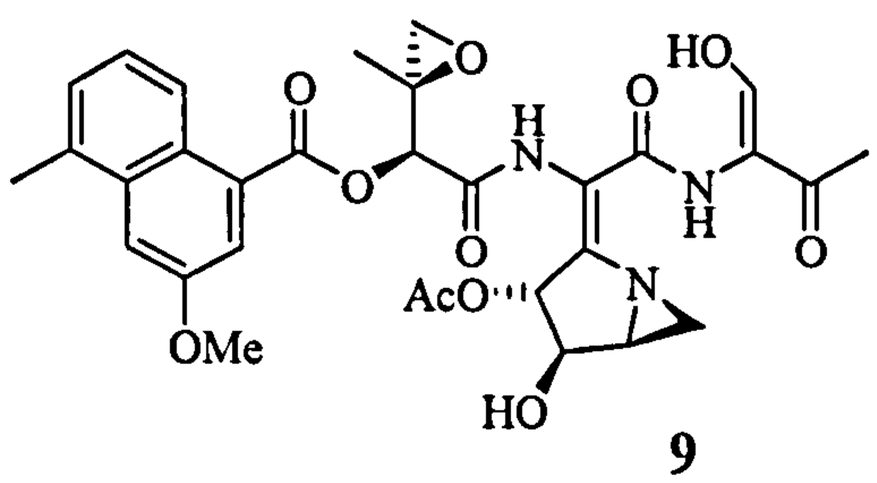

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Figure 5

Other natural products containing aziridine rings or precursors and to aziridinium cations, are also known to impair DNA replication. These include mitomycin C **10**,[17] Antibiotic 593A **11**,[18] Streptolutin **12**[19] and Nitrogen mustards e.g. **13**[20] (Figure 6).

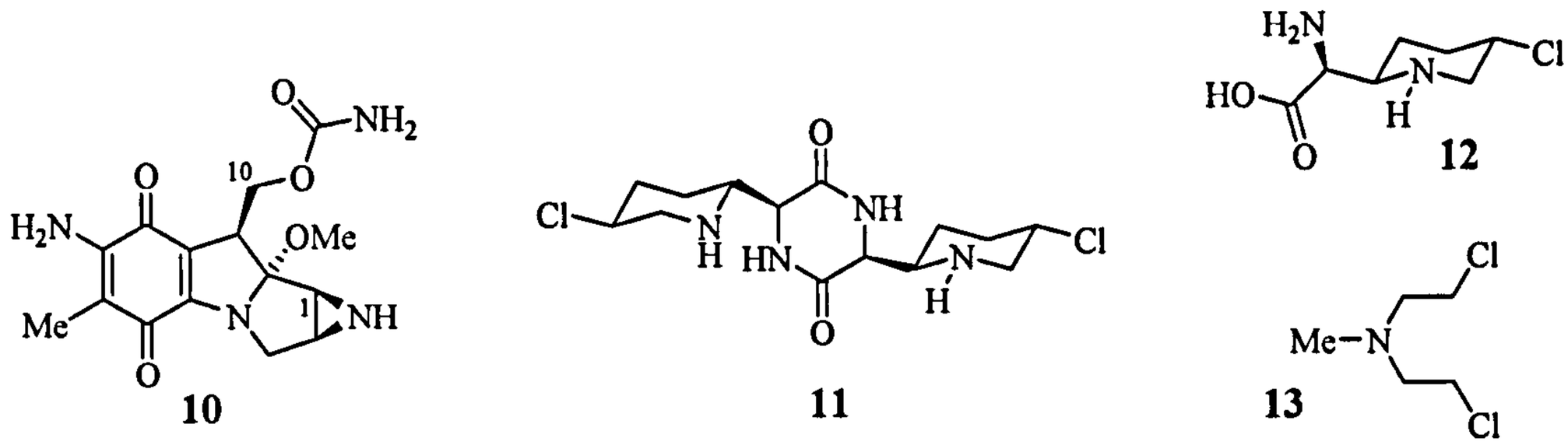


Figure 6

Mitomycin C **10**, after bioreduction, forms inter-strand cross-links between C-1 and C-10 with Guanine residues on the opposite DNA strands.[17]

Antibiotic 593 A **11** displays a high antibiotic and antineoplastic activity.[18] This natural product, isolated from *Streptomyces griseoluteus* as the hydrochloride salt, closely resembles the structure of the synthetic nitrogen mustards, such as *N*-methyl-bis-(2-chloroethyl)amine (mechlorethamine) (**13**)[21] and accordingly, a similar mode of action has been proposed.[19]

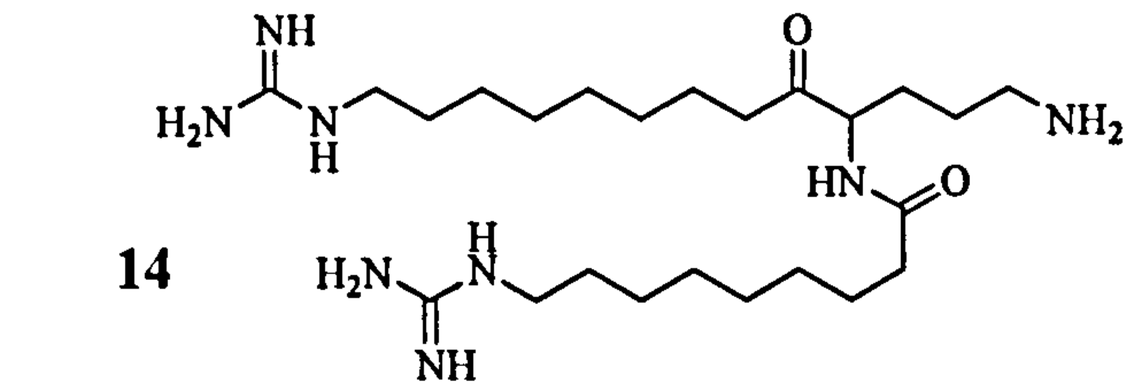
Based on the studies on the behaviour of 1-azabicyclo[3.1.0]hexane **2** in the presence of acids,[22] Armstrong suggested that antibiotic 593 A **11** may in fact be an 1-azabicyclo[3.1.0]hexane **2** in its natural form with the isolation of **11** being an artifact of the isolation procedure which involved treatment with hydrochloric acid. Even if **11** is the true form for the natural product, the 1-azabicyclo[3.1.0]hexane **2** may be the biologically relevant DNA-alkylating species in cells.[23]

1.6.2 Guanidine Containing Natural Products

Although not the main topic of this thesis, it is appropriate to briefly discuss the biological importance of the guanidine functional group in medicinally important natural and synthetic compounds.

There are many examples of natural products that contain a free guanidine group. Extensive reviews have been compiled by Berlinck and Hannon *et al.*[24]

Examples include Eulicin **14**,[25] isolated from a *Streptomyces* strain, which is a potent antibiotic against a broad spectrum of Gram-positive and negative bacteria and a dose dependent HIV infection inhibitor;[26] Segetalin H **15**,[27] isolated from a member of the Caryophyllaceae plant family which has an estrogen-like activity. GE20372 factor A **16**,[28] isolated from *Streptomyces* sp. ATCC 55925, is a new HIV-1 protease inhibitor; and Nazumamide A **17**,[29] obtained from the sponge *Theonella* sp. which interacts with human thrombin. The most potent inhibitor of the influenza virus, sialidase inhibitor (GG167) **18** is a guanidine containing compound (Figure **7**).[30] In addition, several mono- and bis-guanidine salts, have been recently disclosed as an effective water treatment to control protozoa and protozoan cysts that host *Legionella pneumophila*, a bacterium that causes Legionnaire's disease, and which may be responsible for its growth.[31]



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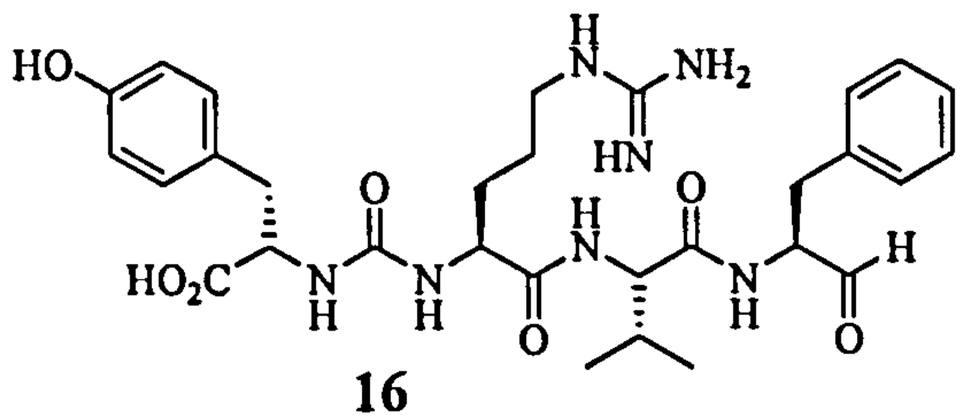

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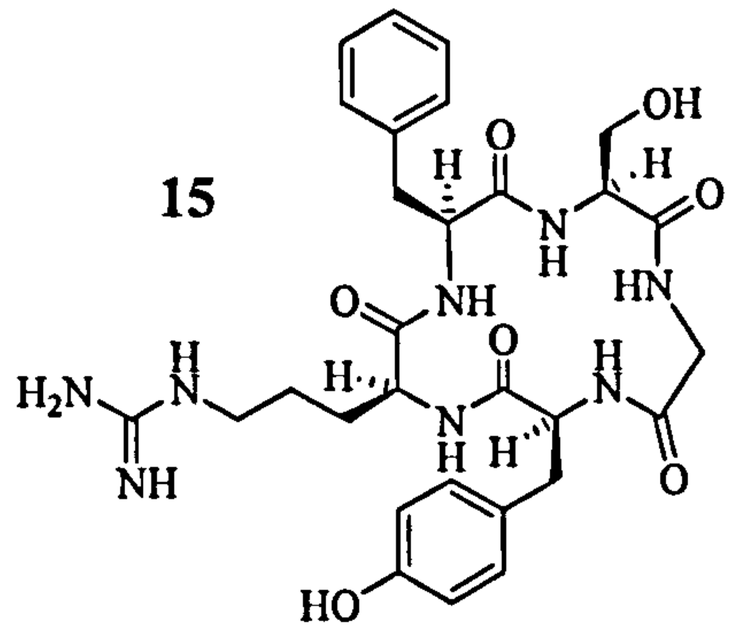

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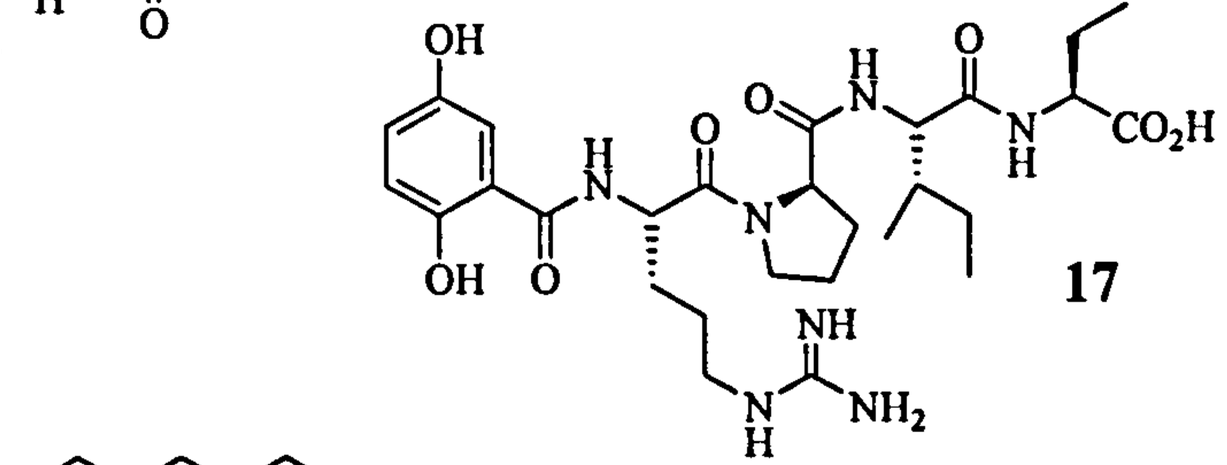

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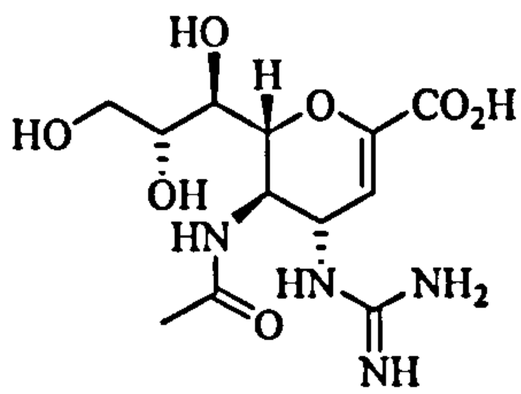

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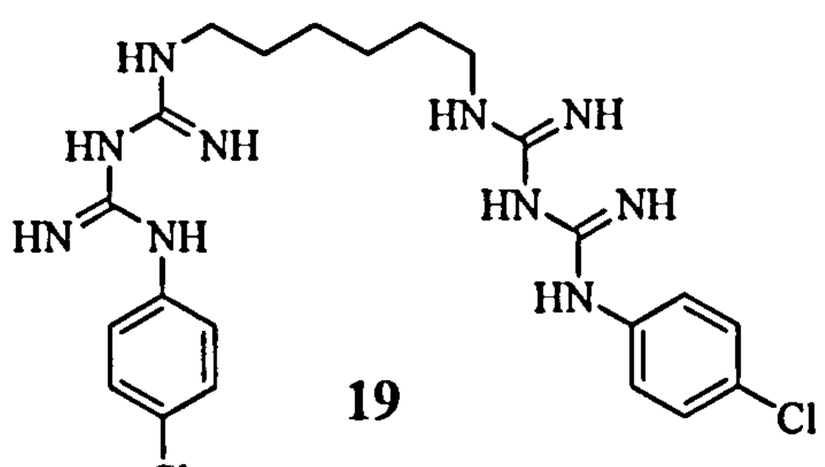


19

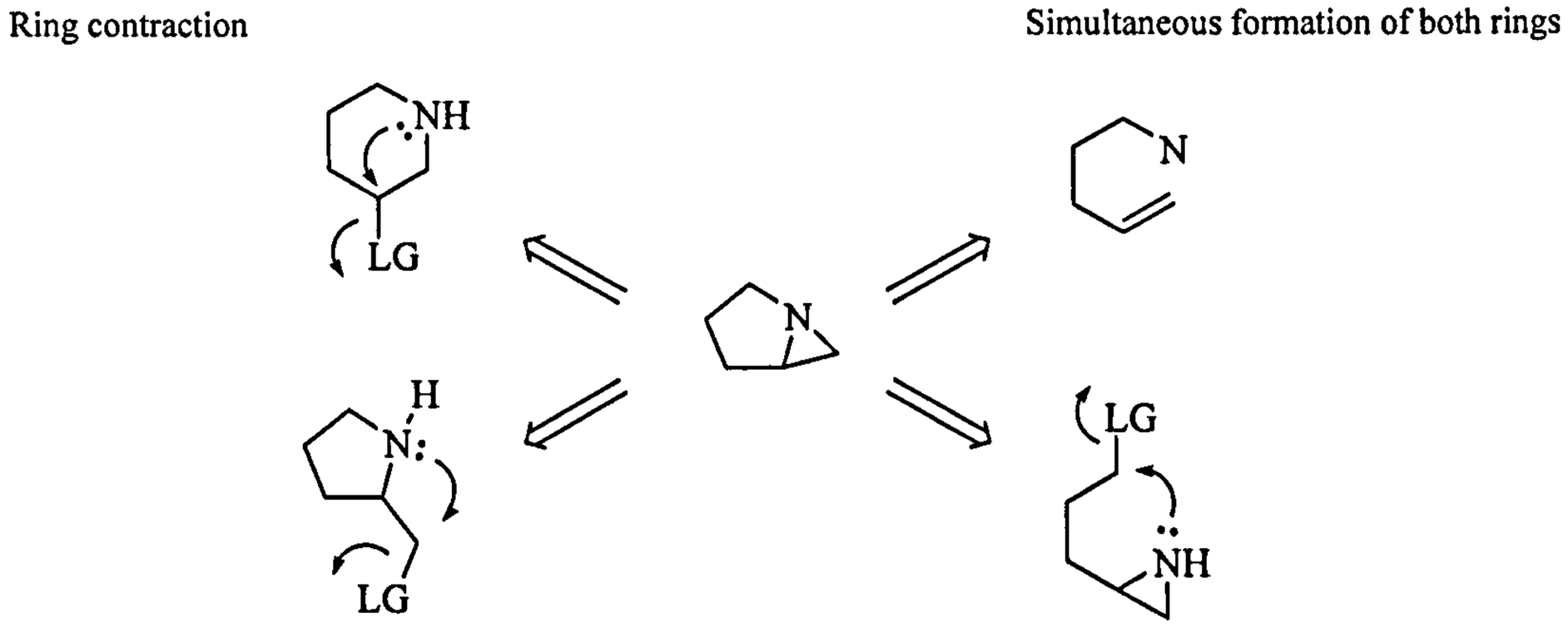
Figure 7

One of the most commonly used guanidine containing drugs is chlorhexidine **19**, an antiseptic with both bacteriostatic and bacteriocidal activity against gram positive and negative bacteria, viruses, bacterial spores and fungi.[32] It is frequently incorporated as the active ingredient in mouth wash.[33]

Other therapeutic applications of substituted guanidine containing compounds include antihypertensives, cardiotonics, H_2 antagonist/agonists and anti-tumour agents.[34]

1.7. Synthesis of 1-azabicyclo[3.1.0]hexanes

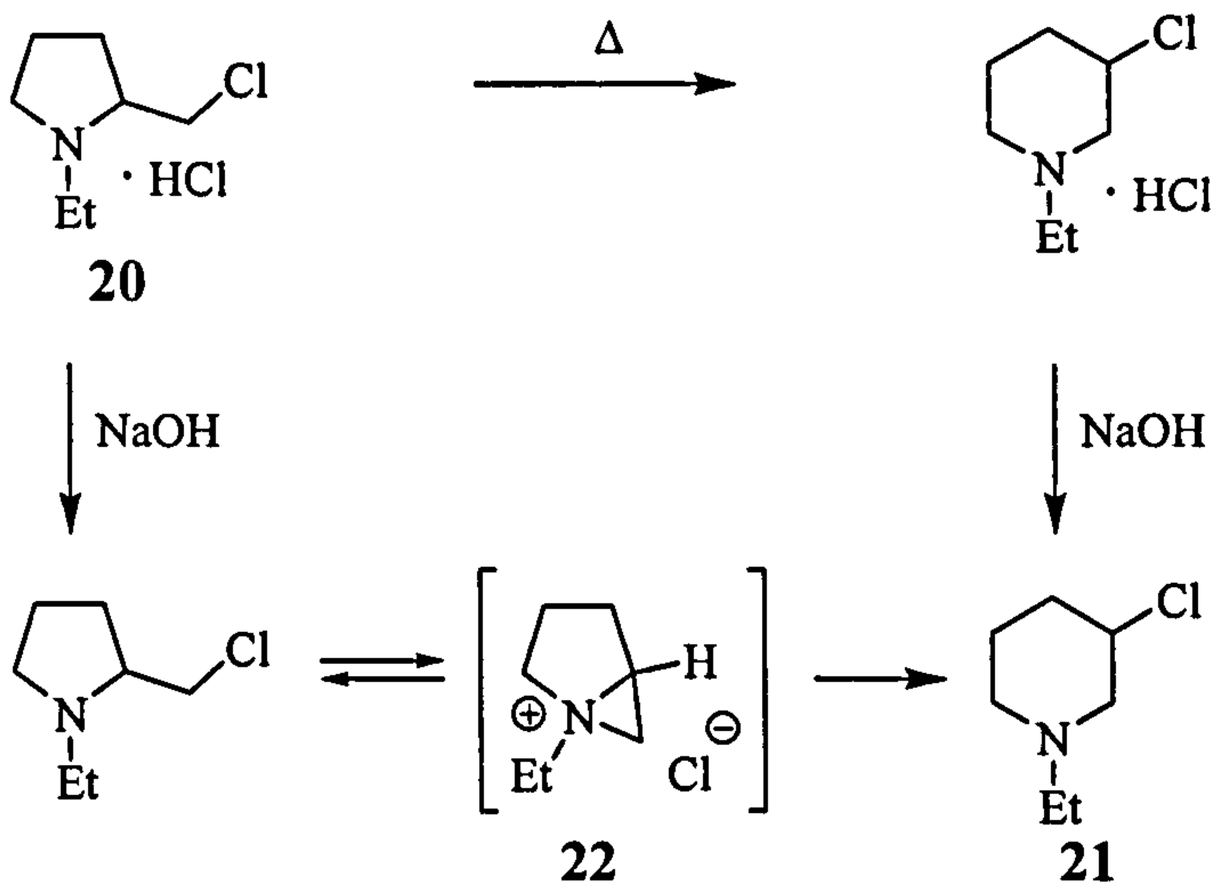
Although ficellomycin **5** and the azinomycins **8**, **9** are the only natural products containing 1-azabicyclo[3.1.0]hexane **2** ring systems, this heterocyclic system has been known for over fifty years and various synthetic routes have been devised for its assembly (Scheme 2). They will be briefly surveyed herein, according to the general strategies depicted in Scheme 2.



Scheme 2

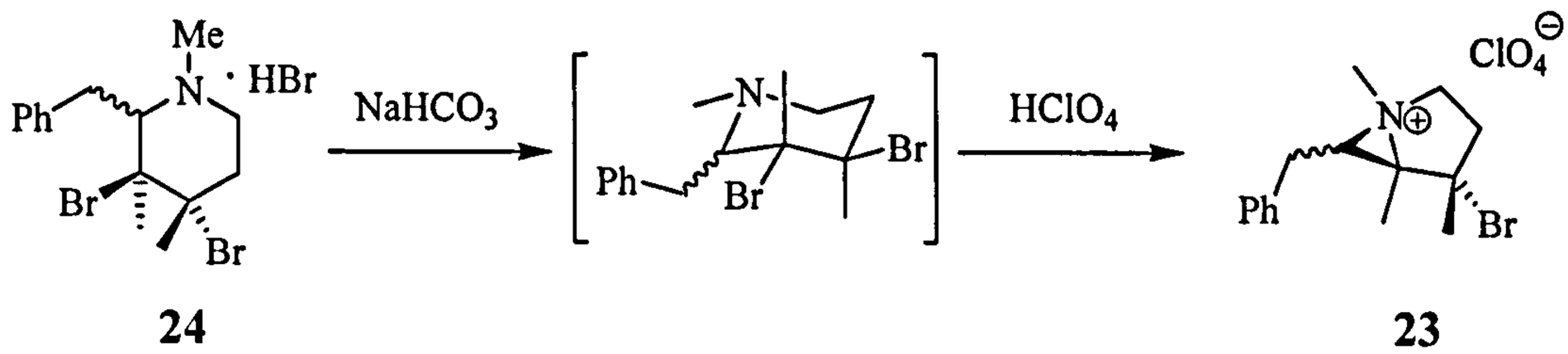
1.7.1. Formation by Ring Contraction

The 1-azabicyclo[3.1.0]hexane system was first reported, although not isolated, by Fuson in 1948.[35] It was proposed that the alkali-mediated rearrangement of 1-ethyl-2-chloromethylpyrrolidine hydrochloride **20** to 1-ethyl-3-chloropiperidine **21** proceeded *via* a bicyclic intermediate **22** (Scheme 3).



Scheme 3

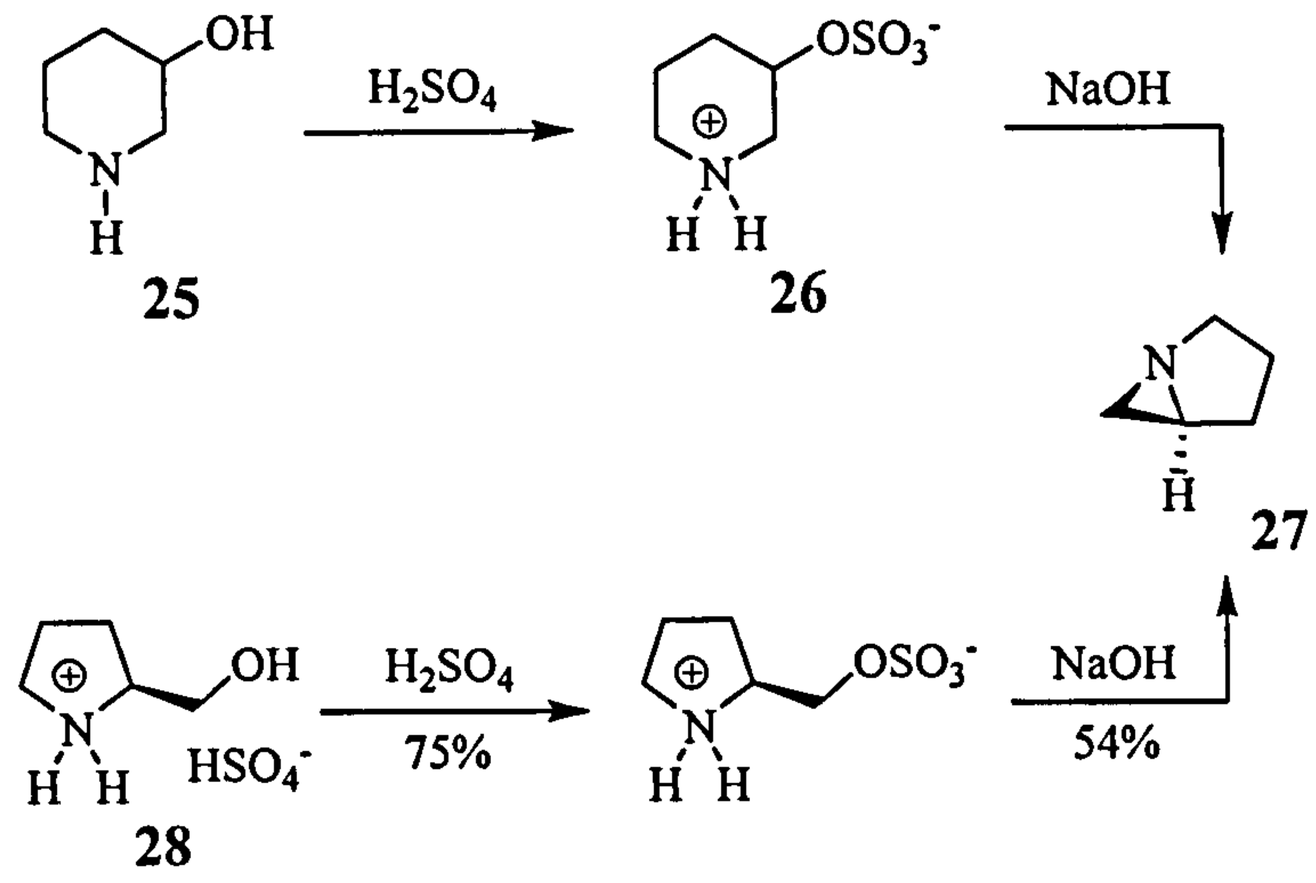
Related bicycles were subsequently isolated as crystalline perchlorate salts **23** in the synthesis of a *β*-benzomorphan after treating an epimeric mixture of tetrahydropyridine dibromide **24** with sodium bicarbonate. It was proposed that the ring contraction took place through backside displacement of the bromine at C-3 by the tertiary amine (Scheme 4).[36]



Scheme 4

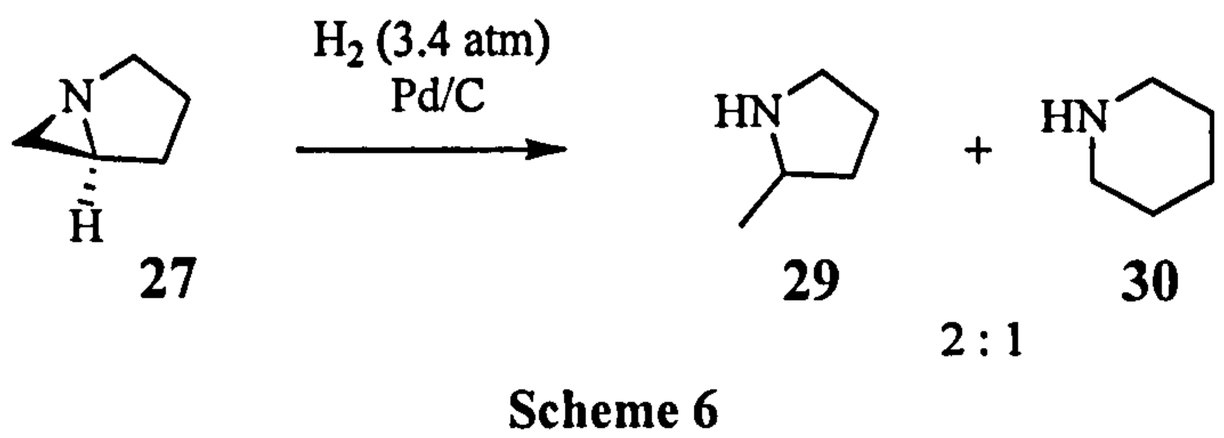
Gassman performed a similar ring contraction of a piperidine to the parent 1-azabicyclo[3.1.0]hexane **2**. This was achieved by conversion of 3-hydroxypiperidine **25**, to its sulfuric acid ester **26** by treatment with sulfuric acid.[37] Treatment of this ester with sodium hydroxide and subsequent steam distillation afforded (5*S*)-azabicyclo[3.1.0]hexane **27** in low yield. The alternative ring closure from a preformed pyrrolidine was therefore explored. Using the same methodology, L-

prolinol **28** was converted to 1-azabicyclo[3.1.0]hexane **27** in an improved 54% yield (Scheme 5).



Scheme 5

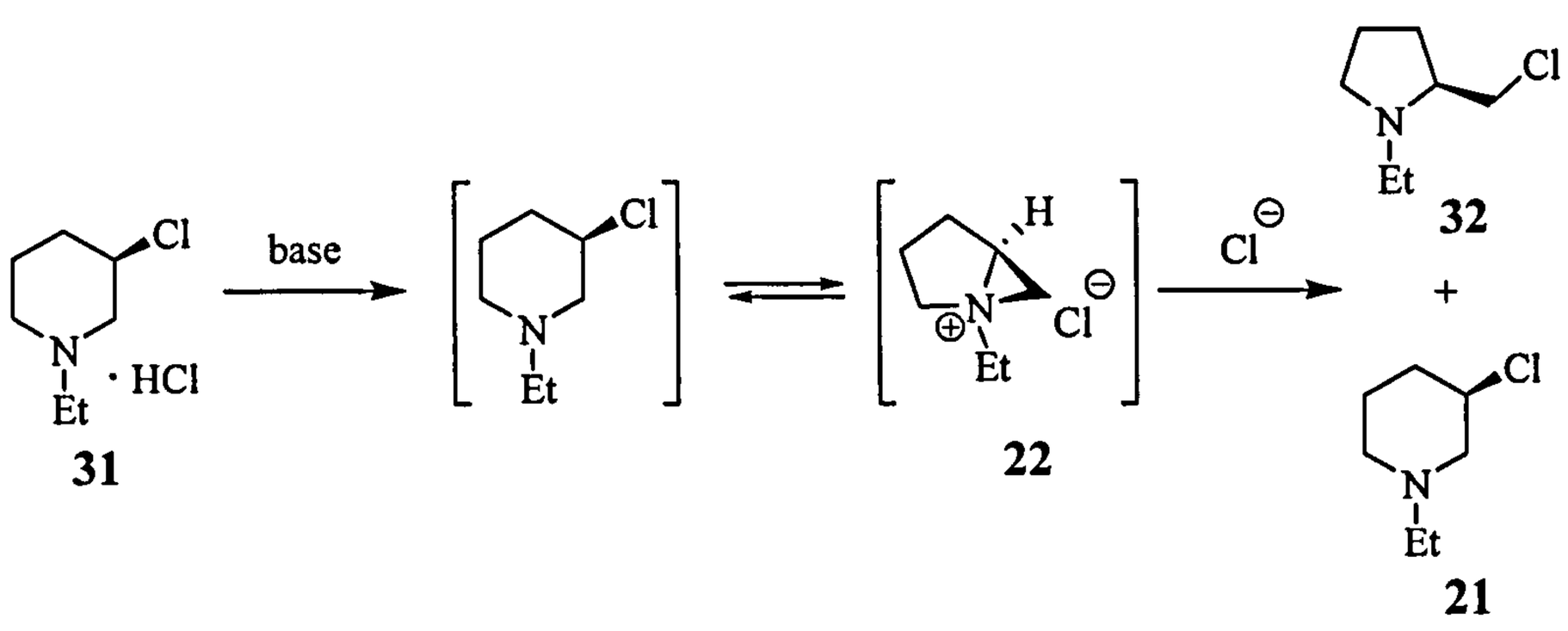
The reactivity of bicycle **27** was examined by these authors. It was observed that **27** was stable for several months stored at 5 °C over potassium hydroxide, while treatment with methyl iodide afforded a violent reaction which resulted in the formation of an opaque white solid. Reduction of **27** with H_2/Pd-C afforded two products formed in a 2:1 ratio, namely, 2-methylpyrrolidine (**29**) and piperidine (**30**) (Scheme 6).[37]



Scheme 6

In 1972, Hammer *et al.* reported mechanistic studies on the rearrangement reactions of 1-alkyl-3-chloro piperidines **31**.[38] These workers provided synthetic, kinetic and stereochemical evidence that suggested that their rearrangement proceeded *via* a two-step process involving neighbouring group participation in which the bicyclic

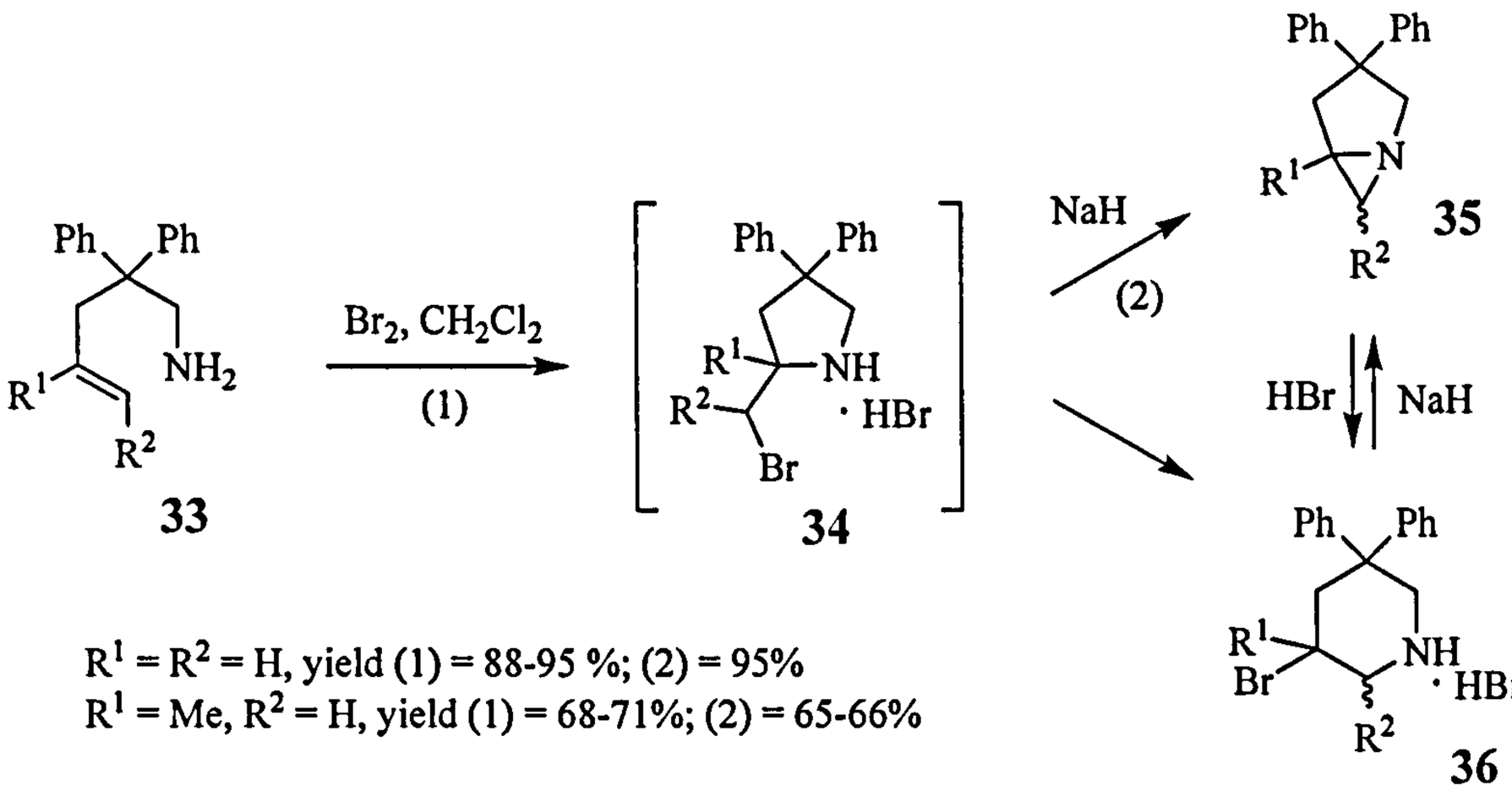
aziridinium ion intermediate **22** was formed. The first and rate-determining step involved displacement of chloride by nitrogen in what was designated as an "internal backside nucleophilic substitution" ($S_Ni b$) mechanism. The second step involved nucleophilic attack on the intermediate by chloride ion, *via* an S_N2 displacement to give the observed pyrrolidine **32** and piperidine **21** products (Scheme 7).[38]



Scheme 7

1.7.2. Formation from preformed pyrrolidine

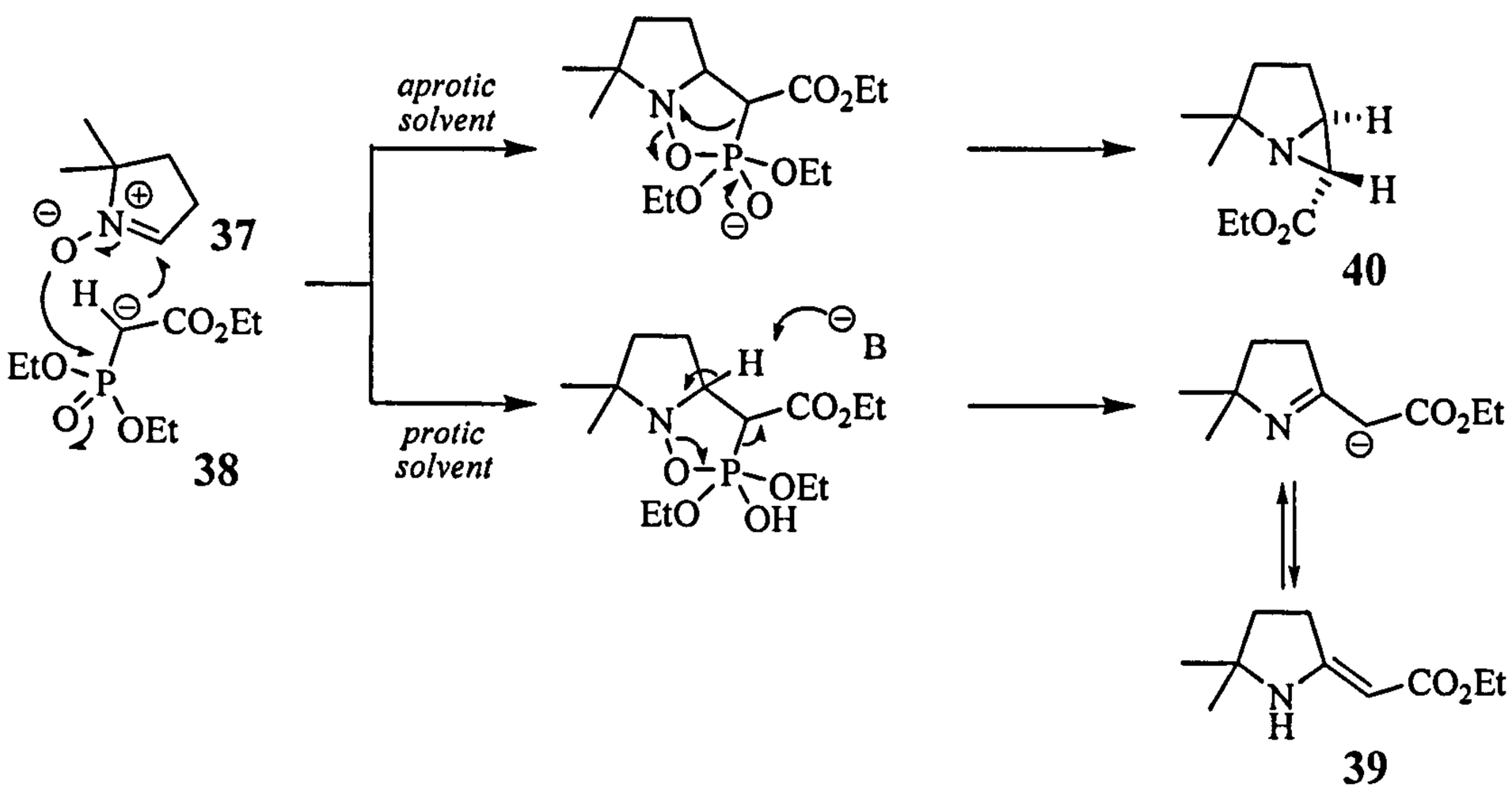
Intramolecular haloamination of pentenylamine derivatives was used by Horning *et al.* in 1974, to assemble 1-azabicyclo[3.1.0]hexanes.[39] A series of 2,2-diphenyl-4-pentenylamines **33** were reacted with bromine to afford pyrrolidinium salts **34** that upon treatment with sodium hydride in DMF resulted in the formation of 1-azabicyclo[3.1.0]hexane derivatives **35**. These products could be further converted to the corresponding piperidinium salts **36** on treatment with anhydrous hydrogen bromide. Regeneration of **35** from **36** could be accomplished by treatment with sodium hydride (Scheme 8).[39]



$R^1 = R^2 = H$, yield (1) = 88-95 %; (2) = 95%
R^1 = Me, $R^2 = H$, yield (1) = 68-71%; (2) = 65-66%

Scheme 8

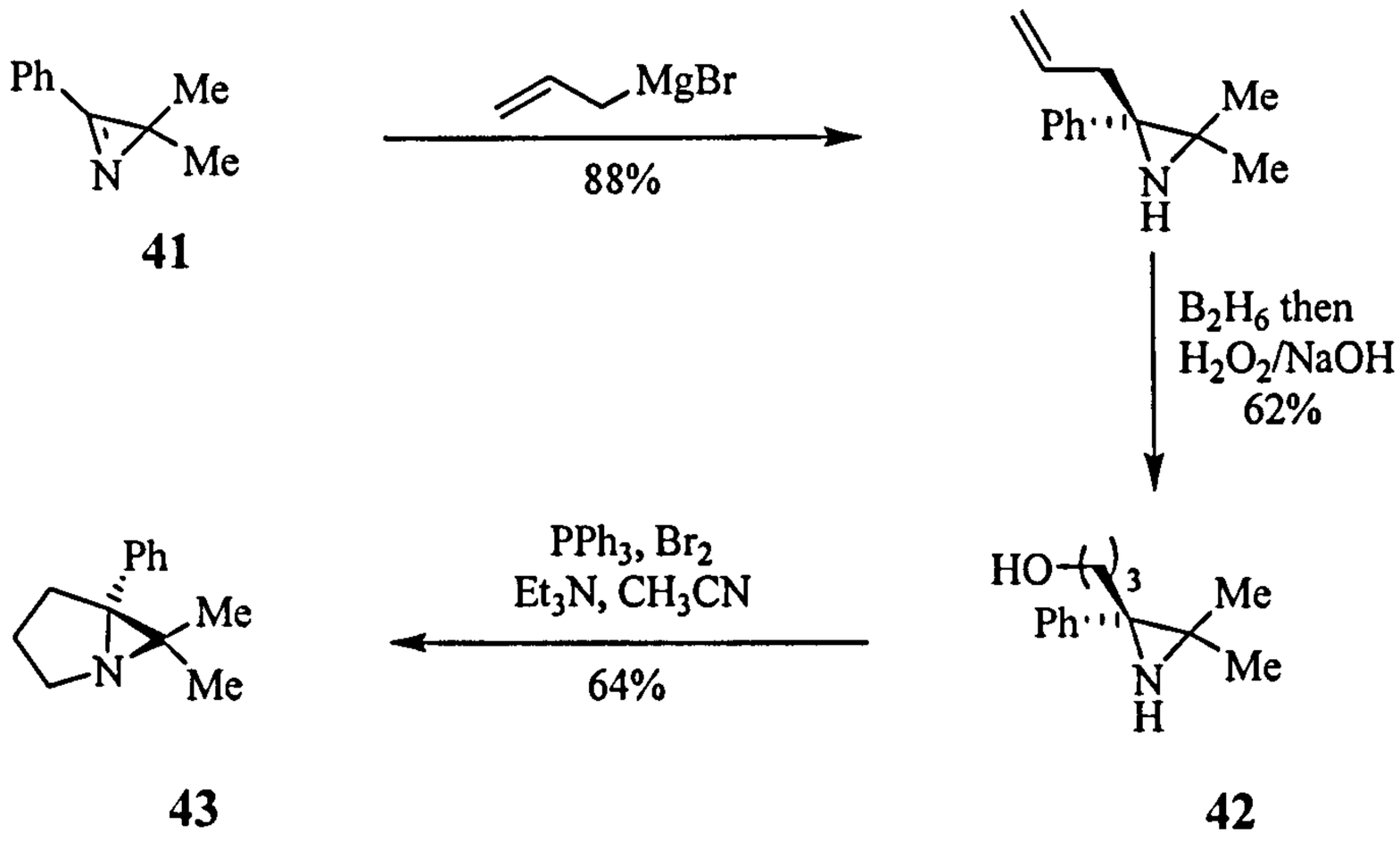
The formation of 1-azabicyclo[3.1.0]hexanes from aldonitrones and ylids has been reported by Breuer *et al.*[40] Reactions of pyrrolidone *N*-oxide **37** and diethyl cyanomethylphosphonate and dialkyl alkoxycarbonylphosphonates **38** using sodium hydride in 1,2-dimethoxyethane favoured aziridine formation (Scheme 9). Enamine **39** formed preferentially using metal alkoxides in protic solvents. Since aziridine **40** and enamine **39** do not interconvert under the reaction conditions, the authors suggested two different mechanistic pathways (Scheme 9)



Scheme 9

1.7.3. Formation from preformed aziridine

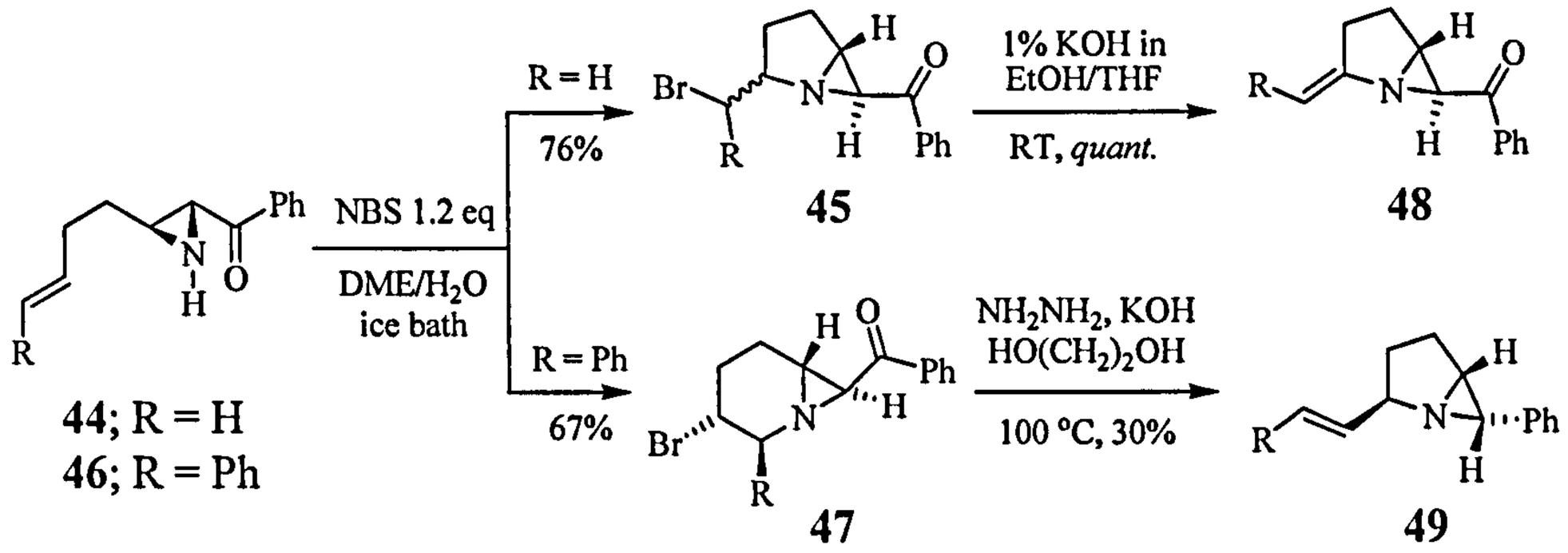
The synthesis of 1-azabicyclo[3.1.0]hexanes through cyclisation of preformed aziridines was first reported by Laurent and co-workers, who studied the hydroboration of ethylenic aziridines.[41] Addition of allyl magnesium bromide to **41**, followed by hydroboration furnished aziridino alcohol **42**. Upon addition of triphenylphosphine and bromine, the alcohol was transformed to the corresponding bromide which spontaneously cyclised to 1-azabicyclo[3.1.0]hexane **43** (Scheme 10).[42]



41 **42** **43**

Scheme 10

More recently, Yudin has examined an oxidative cycloamination reaction of olefins tethered to aziridines for the construction of substituted pyrrolidines and piperidines. Aziridine precursors are converted into 1-azabicyclo[3.1.0]hexanes and 1-azabicyclo[4.1.0]heptanes upon treatment with *N*-bromosuccinimide in DME/water.[43] Precursor **44** containing a terminal double bond preferentially formed **45** whereas aryl-substituted substrate **46** favoured **47** (Scheme 11). Bicycle **45** can be converted into exo-methylene bicyclic aziridines **48** through dehydrobromination in quantitative yields, and **47** can be converted into **49** under hydrazinolysis conditions.



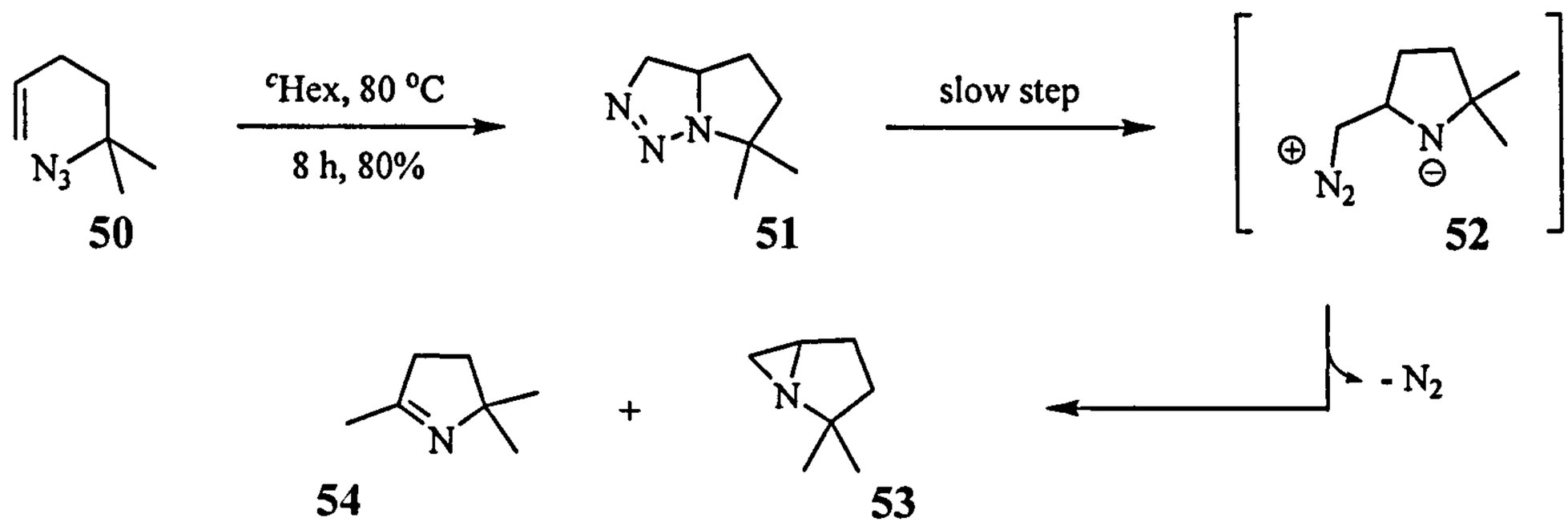
44; R = H
46; R = Ph

45 **47** **48** **49**

Scheme 11

1.7.4. Simultaneous Formation of Both Rings

The simultaneous formation of both rings of 1-azabicyclo[3.1.0]hexanes was first reported by Logothetis, in 1965, in a study of the thermal decomposition of olefinic azides in refluxing hydrocarbon solvents.[44] Using δ,ε-unsaturated azide **50**, intramolecular addition to the double bond takes place in a [3+2]-cycloaddition, to afford a stable triazoline **51**. Further opening to a diazonium intermediate **52**, and subsequent loss of molecular nitrogen gives a mixture of bicycle **53** and cyclic imine **54** (Scheme 12).

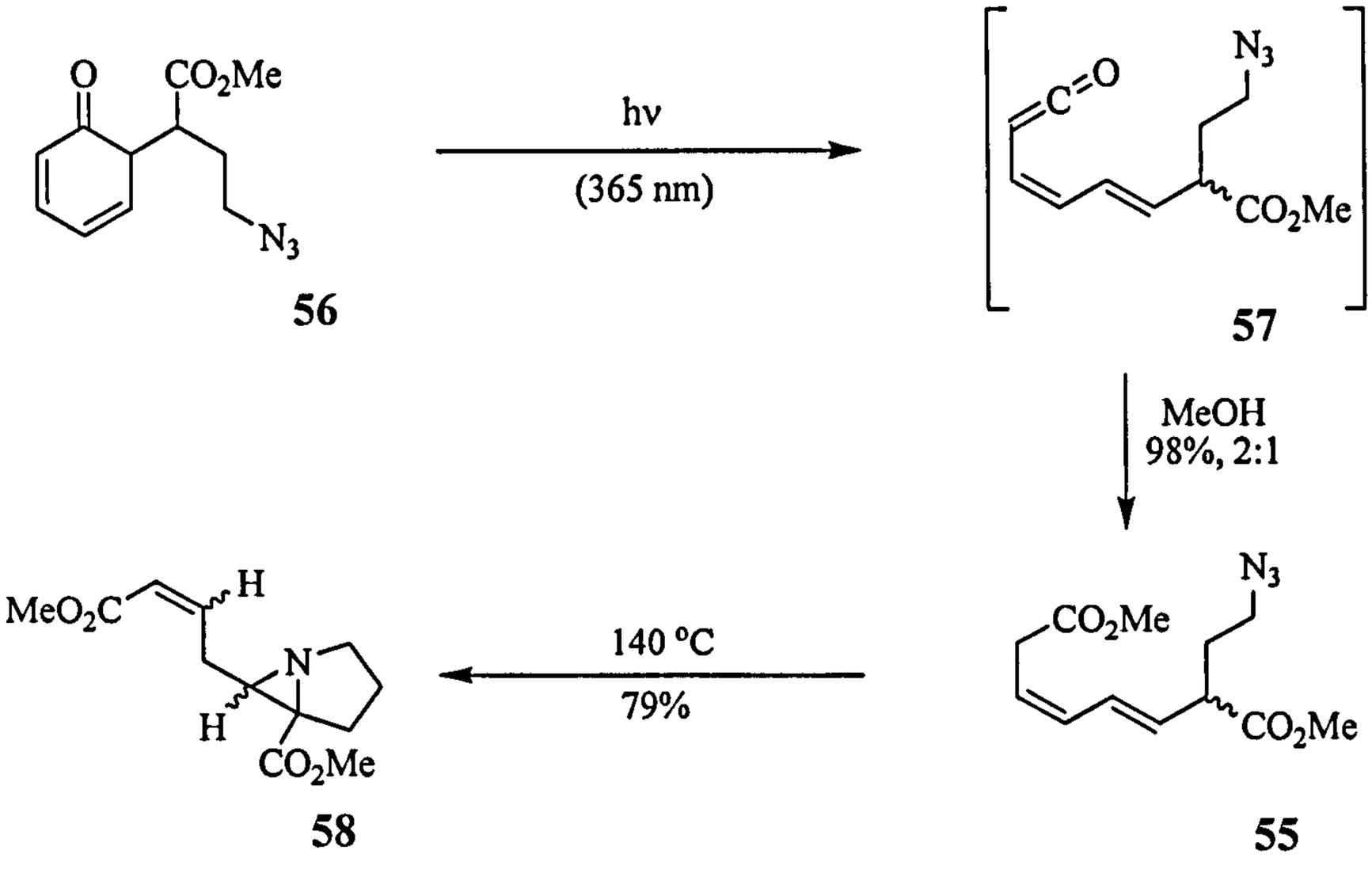


50 **51** **52** **54** **53**

2.2 : 1

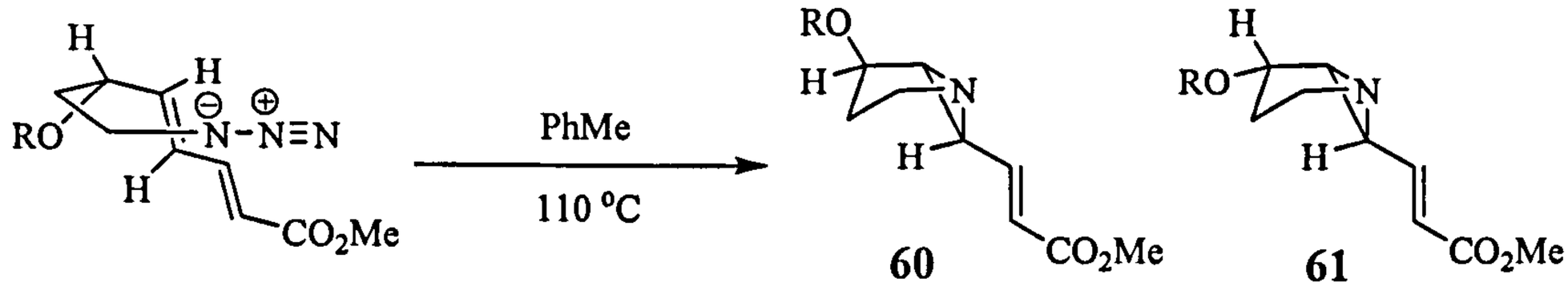
Scheme 12

In 1987, Schultz and co-workers reported related intramolecular azide-olefin cycloadditions.[45] Thermolysis of azido diene **55**, formed through photorearrangement of 2,4-cyclohexadienone **56** *via* ketene **57**, in refluxing xylenes yielded vinyl aziridine **58** as a mixture of diastereomers (Scheme 13).



Scheme 13

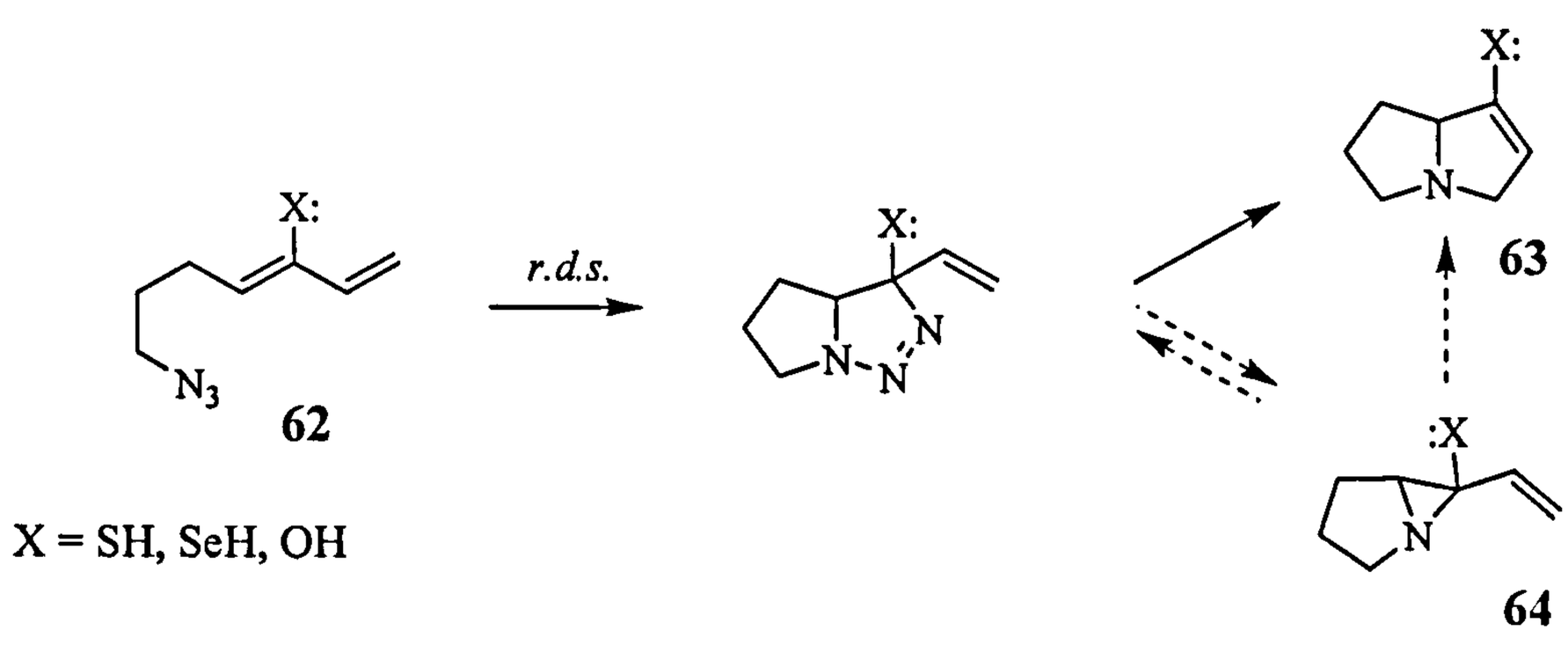
Hudlicky *et al.* determined that when stereocentres were present on the linking tether of the azido diene **59**, high levels of diastereocontrol can be achieved using bulky ether substituents in the formation of the vinyl 1-azabicyclo[3.1.0]hexane products **60** and **61** (Scheme 14).[46]



59a R = H — 64 : 36 (50%)
59b R = TDS — 100 : 00 (70%)

Scheme 14

A related strategy for the syntheses of pyrrolizidines and indolizidines was used by Pearson *et al.*, which involved intramolecular cycloaddition of azides onto electron-rich 1,3-dienes.[47] The presence of an electron-donating sulfur, selenium or oxygen containing substituent on diene **62** led to 5-*endo-trig* cyclisation to **63**, rather than formation of 1-azabicyclo[3.1.0]hexane species **64** (Scheme 15).



Scheme 15

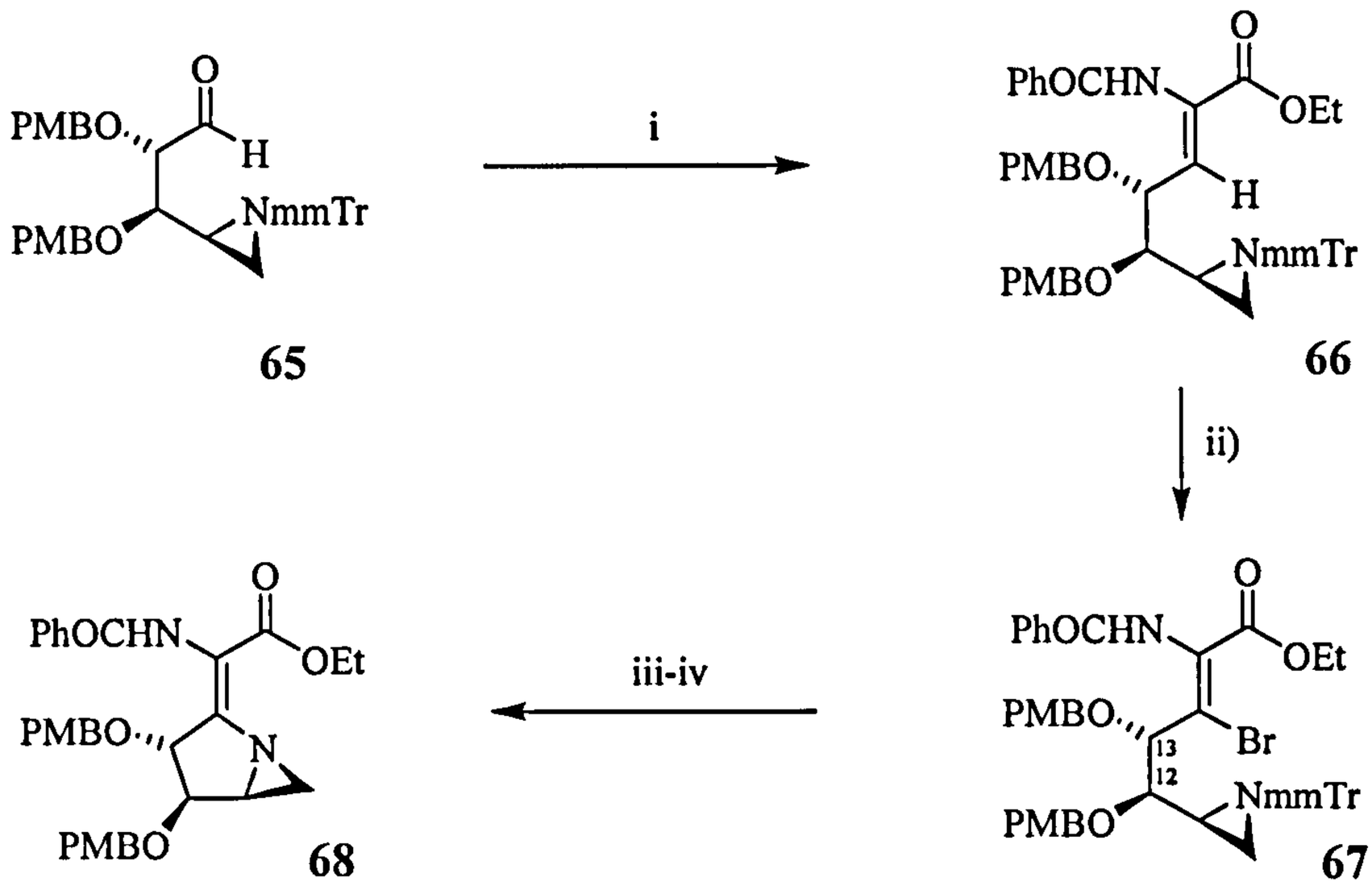
1.7.5. Formation of the 1-Azabicyclo-[3.1.0]hex-2-ylidine skeleton of the Azinomycins

Synthetic routes to these natural products are discussed in this section. In these compounds, the exocyclic double bond presents an additional synthetic challenge, hence the chemistry is discussed separately from the general strategies described above.

1.7.5.a. Formation from preformed aziridine

The heterocyclic core of azinomycin A **8** was achieved by Armstrong *et al.* in 1996 using a cyclisation that formed the pyrrolidine ring.[48] This convergent synthesis involved the reaction of protected aziridine-aldehyde **65** derived from D-arabinose, and a suitably substituted glycine phosphonate, to produce alkene **66** by means of a

Horner-Wadsworth-Emmons olefination. Further bromination of the double bond of **66** afforded **67,** which upon deprotection of the aziridine underwent addition-elimination to yield bicycle **68** in 91% yield (Scheme 16).

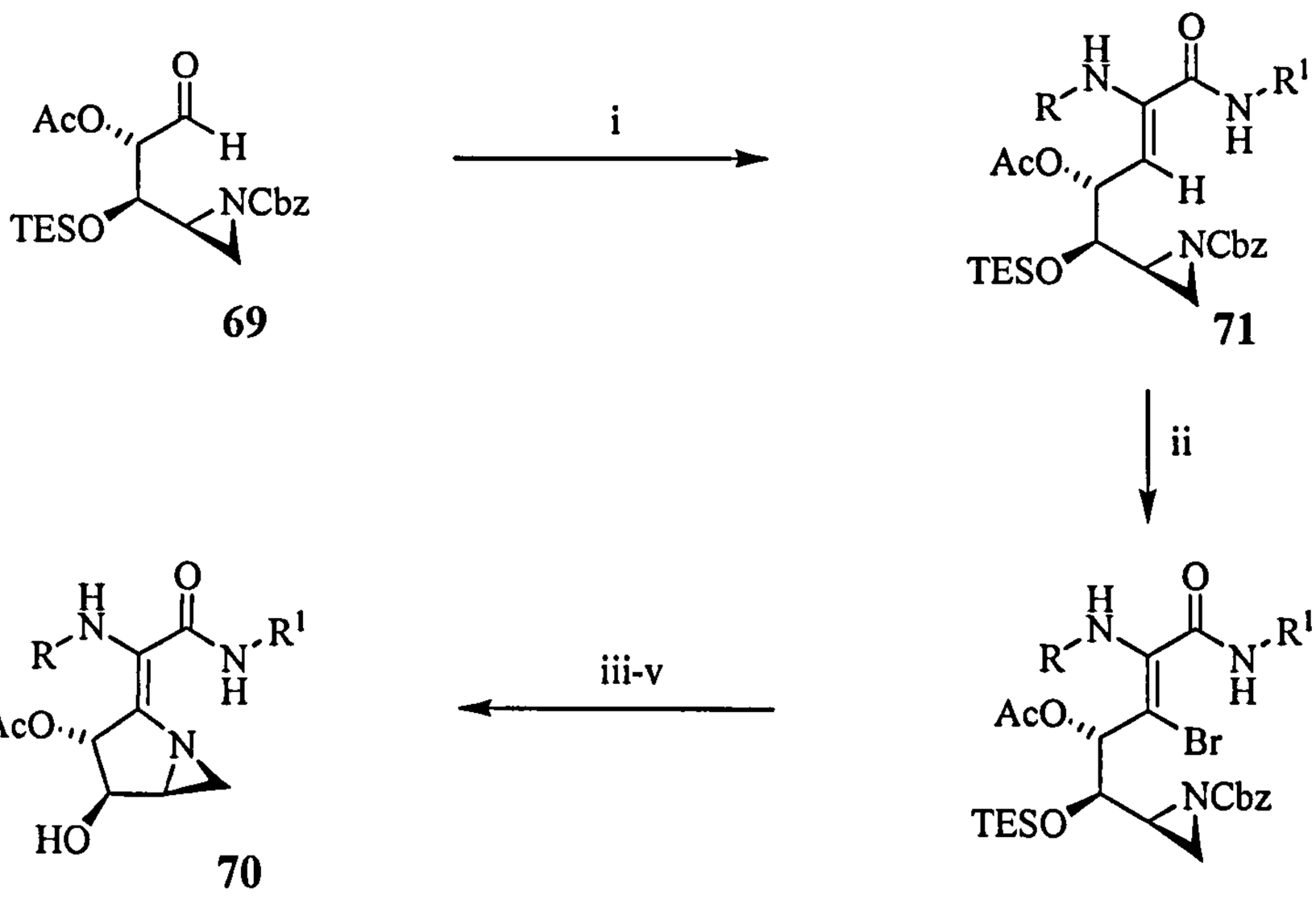


Scheme 16. *Reagents and conditions*: i) $PhCONHCH(PO(OEt)_2)CO_2Et$, LDA, THF -78 °C, 70% (3.7:1 *Z*:*E*); ii) NBS, $CHCl_3$, 76%; iii) CCl_3CO_2H, CD_3CN, RT; iv) Et_3N, 50 °C, 16 h, 91%.

The monomethoxytrityl protecting group (mmTr) in the aziridine proved essential. Different protecting groups for the C-12/C-13 alcohols (azinomycin numbering) were evaluated, although replacement of *p*-methoxybenzyl groups for triethylsilyl ethers was not fruitful.[49]

Subsequently, Coleman *et al.* achieved the first asymmetric total synthesis of Azinomycin A **8** using a similar synthetic approach but different protecting groups.[50] In this approach, they installed the required acetate at C-13 in aldehyde **69** prior to olefination and cyclisation. This greatly reduced the number of protecting group manipulations once bicycle **70** was assembled. The proximity of the C-13 acetate proved problematic during olefination, resulting in low 40% yield for the required *E*

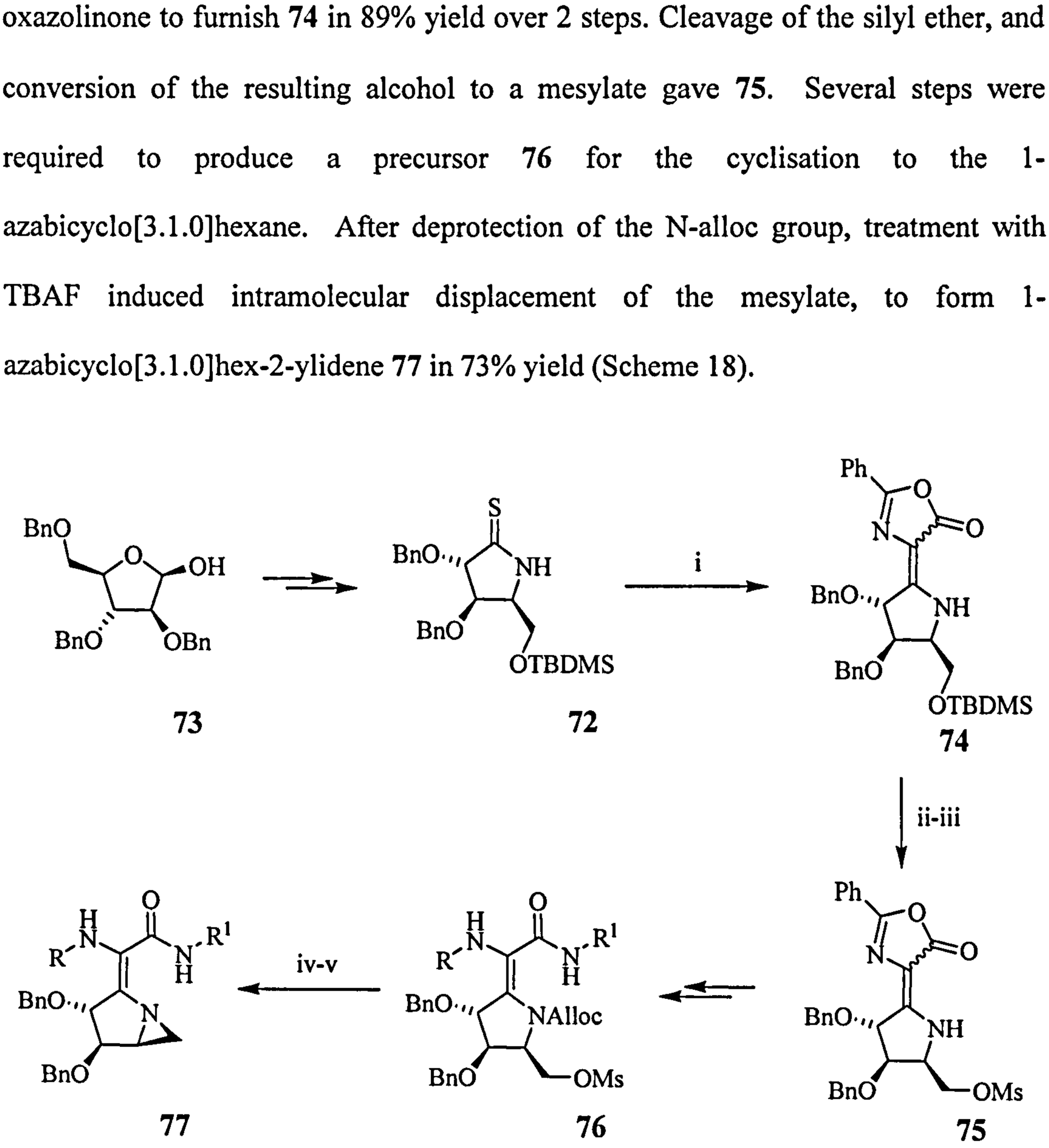
isomer **71** but this was offset by the simplicity of the route and reduction in the number of steps. The aziridine was protected as a benzyl carbamate, which could be deprotected by a palladium-catalyzed, silane-mediated process to afford the free aziridine. Further displacement of the bromide in the presence of Dowex anion exchange resin (CO_3^{2-} form) afforded the 1-azabicyclo[3.1.0]hex-2-ylidene core **70**. The stability of **70** to basic conditions was exploited to cleave the C-12 triethylsilyl ether as the last step of the synthesis (Scheme 17).



Scheme 17. *Reagents and conditions*: $RHC(PO(OMe)_2)CONHR^1$, KO^{t}Bu, CH_2Cl_2 or THF, 75%; ii) *excess* NBS, DABCO, CH_2Cl_2 then ^{t}BuOK, CH_2Cl_2, 40%; iii) $PdCl_2$, Et_3SiH, CH_2Cl_2, 50%; iv) Dowex (CO_3^{2-}), CH_2Cl_2, 64%; v) ^{n}Bu$_4$NF/HF, 95%.

1.7.5.b. Formation from a preformed pyrrolidine

Terashima *et al.* have adopted an approach whereby the bicycle is assembled from a preformed pyrrolidine ring in their route to fully protected azinomycin B **9**.[51] Thiolactam **72** is accessible from 2,3,5-*tri*-O-benzyl-*β*-D-arabinofuranose (**73**) in several steps. This thiolactam was then *S*-methylated and reacted with 2-Ph-Δ^2-5-oxazolinone to furnish **74** in 89% yield over 2 steps. Cleavage of the silyl ether, and conversion of the resulting alcohol to a mesylate gave **75**. Several steps were required to produce a precursor **76** for the cyclisation to the 1-azabicyclo[3.1.0]hexane. After deprotection of the N-alloc group, treatment with TBAF induced intramolecular displacement of the mesylate, to form 1-azabicyclo[3.1.0]hex-2-ylidene **77** in 73% yield (Scheme 18).



Scheme 18. *Reagents and conditions*: i) MeI, CH_2Cl_2 then 2-Ph-Δ^2-5-oxazolinone, toluene, 80 °C, 81% over two steps; ii) TBAF, THF then iii) MsCl, Et_3N, CH_2Cl_2, 89% over two steps; iv) $Pd(Ph_3P)_4$, dimedone, THF, 97%; v) TBAF, 4 Å MS, THF, 73%.

This type of cyclisation has proven rather versatile and has been adopted by other groups,[52] including our own.[15, 53]

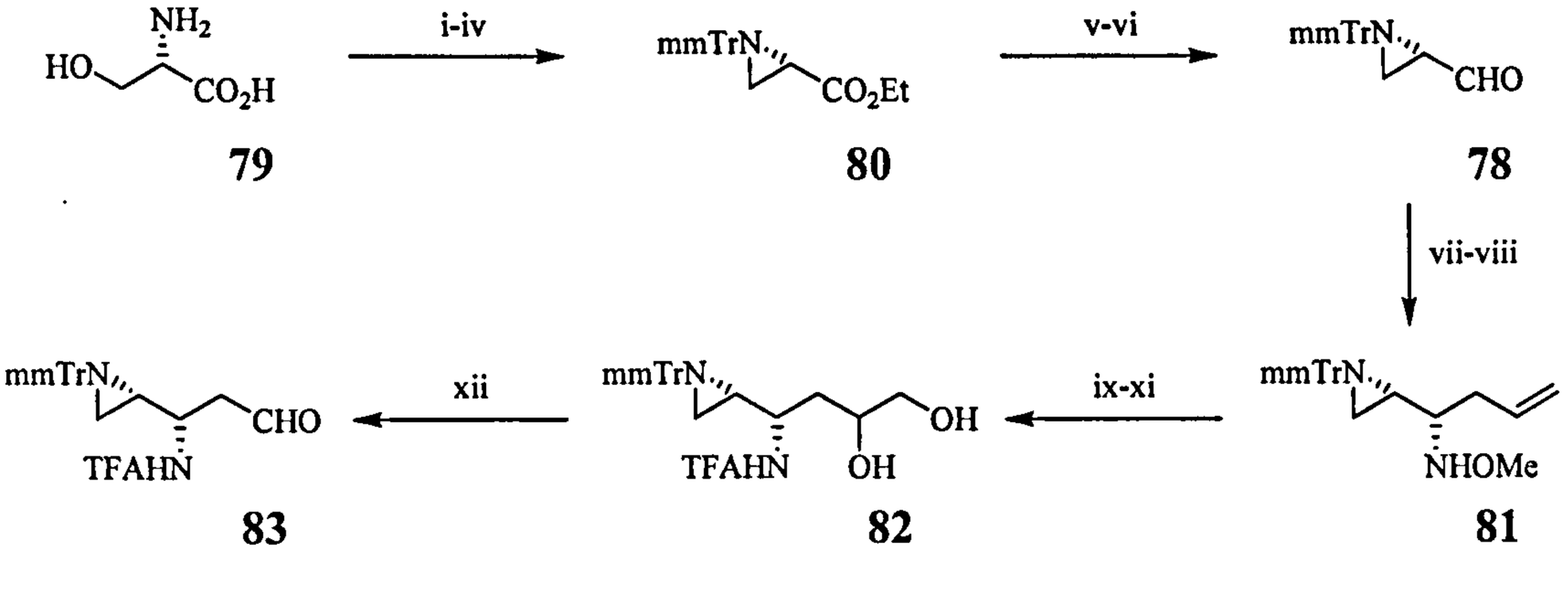
1.7.6. Formation of the 1-azabicyclo[3.1.0]hexane of ficellomycin

In this section, the synthetic efforts performed by our and other groups towards the natural product are detailed.

1.7.6.a. Formation from preformed aziridine

The first recorded approach to the total synthesis of ficellomycin **5** was performed by Dr Zuchun Zhao, in his PhD thesis, supervised by R. W. Armstrong, whose work on the azinomycins **8** has already been discussed (*vide supra*).[3] Unsurprisingly, their first synthetic approach was based on the nucleophilic addition of an aziridine onto a dehydroamino acid.

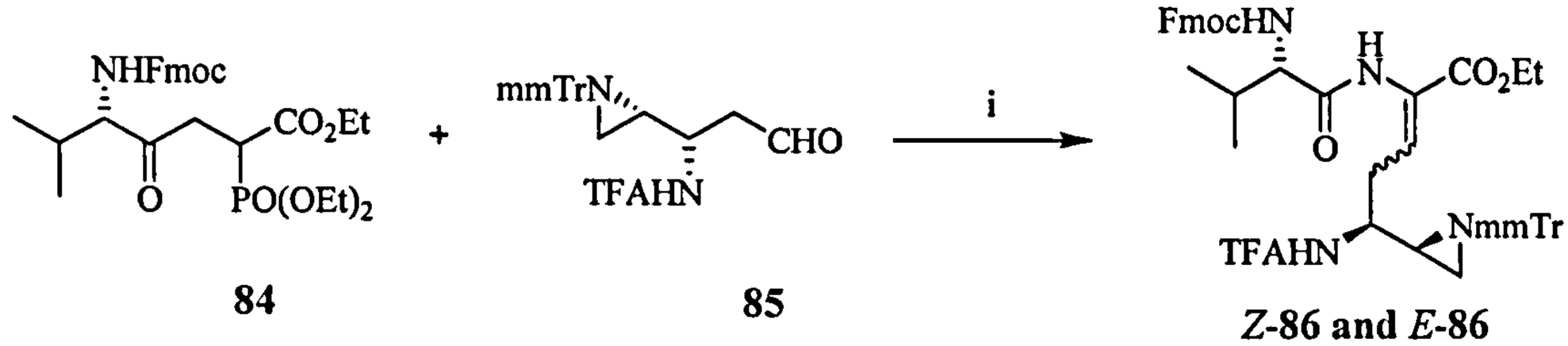
The requisite substrate was made from aziridine 2-carboxaldehyde **78**, made from L-serine ethyl ester **79** *via* ester **80**.[54] The monomethoxytrityl (mmTr) group was chosen to protect the aziridine nitrogen. Aldehyde **78** was converted to the corresponding oxime ether, then treated with allyl magnesium bromide to give amine **81** as a single diastereomer. Reduction of the N-O bond in **81** with lithium aluminium hydride and protection of the resulting amine as the trifluoroacetamide proceeded in 69% yield over the two steps. Direct ozonolysis of the terminal alkene proved problematic, however, treatment of the terminal olefin using OsO_4/NMO followed by cleavage of the resulting diol **82** with lead acetate afforded aldehyde **83** in 54% over the four steps.



79 **80** **78** **81** **82** **83**

Scheme 19. *Reagents and conditions*: i) $SOCl_2$, EtOH, 0 °C–RT, 2h; ii) mmTrCl, Et_3N, CH_2Cl_2, -78 °C; iii) TsCl, Et_3N; iv) Et_3N, THF, reflux, 12h; v) $LiAlH_4$, THF, -78 °C, 90%; vi) Swern oxidation, 95%; vii) $MeONH_3Cl$, Et_3N, CH_2Cl_2, 15 h, 94%; viii) allylMgBr, THF, - 78 °C, 10 min, 92%; ix) $LiAlH_4$, THF, - 78 °C, 14h, 86%; x) CF_3CO_2Et, Et_3N, THF, 13h, 90%; xi) OsO_4, NMO, $(CH_3)_2CO/H_2O$ (1:1, v/v), 74%; xii) $Pb(OAc)_4$, EtOAc, Et_3N, 0 °C, 10 min, 94%.

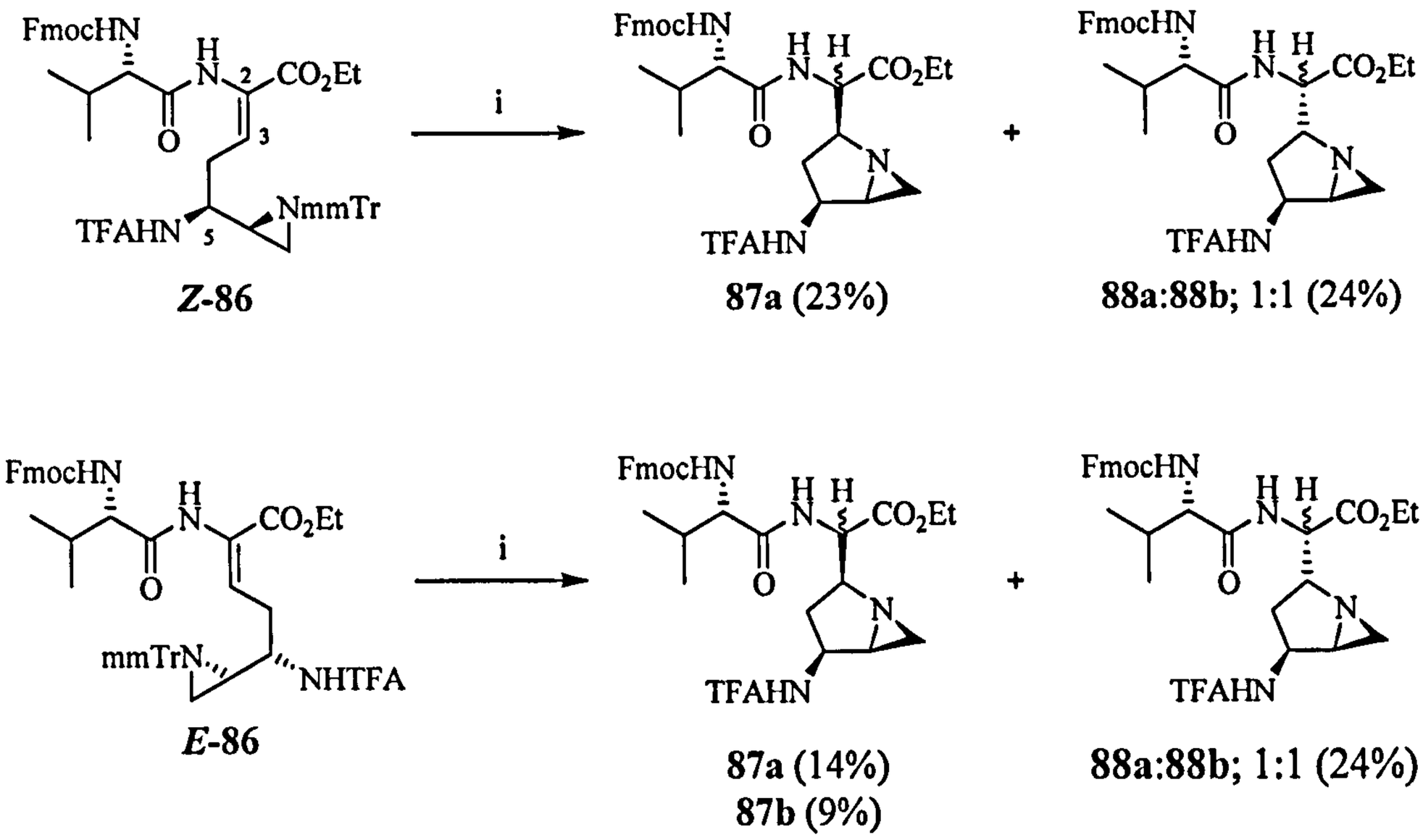
LDA-mediated olefination of **84** with **85** produced dehydroamino acid as a separable 8:1 mixture of *E*-**86** with *Z*-**86** in 86% combined yield (Scheme 20) with *E*-**86** being the major adduct. Careful cleavage of the amino protecting group from **86** was achieved using TCA, with the reaction being quenched by addition of Et_3N. Attempts to isolate the free aziridine on preparative TLC resulted in cyclisation to a mixture of 1-azabicyclo[3.1.0]hexanes along with uncyclised aziridine. It was proposed that the cyclisation was catalysed by the weak acid in a polar environment. Interestingly, the diastereomeric ratio of products was dependent on the acidity of the silica used; untreated silica afforded a 1:1 ratio, whereas pre-treated with Et_3N, afforded a 3:1 ratio.



84 **85** ***Z*-86 and *E*-86**

Scheme 20. *Reagents and conditions*: i) LDA, THF, -78 °C to -10 °C, 86% (*E*:*Z*; 8:1)

Cyclisation of *Z*-**86** and separation by preparative TLC yielded three of the expected four aziridine diastereomers (Scheme 21). Only one diastereomer **87a** or **87b**, with an all *syn*-stereochemical relationship was isolated in a 23% yield, its *syn*-configuration being determined by nOe difference studies. Both diastereomers with an *anti*-relationship between C-3 and C-5, **88a** and **88b**, epimeric at the α-position, were isolated as an inseparable 1:1 mixture in 24% yield.



Scheme 21. *Reagents and conditions*: i) TCA, CH_2Cl_2, then Et_3N, SiO_2.

When *E*-**86** was subjected to the cyclisation conditions, **87a** and **87b** differing in C-2 stereochemistry, were isolated in 14 and 9% yield, respectively, while **88a** and **88b** were obtained as an inseparable 1:1 mixture in 24% yield (Scheme 21). The authors predicted that introducing a bulkier group than TFA as the amino protecting group at C-5 might help favour the formation of the desired *syn*-diastereomers. While the stereochemistry at C-3 is dictated by the preferred conformation during the transition state for cyclisation, that of C-2 is determined by the approach of a proton either

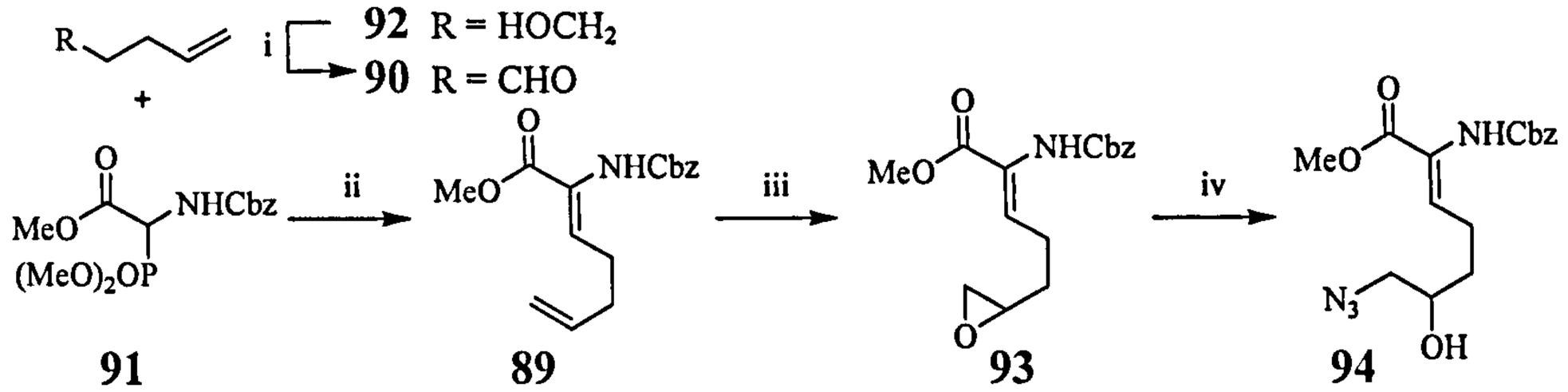
from an external source or alternatively, intramolecular *syn*-protonation from produced aziridinium ion resulting from conjugate addition.

Work in our group has focused on the synthesis of the 1-azabicyclo[3.1.0]hexane core of ficellomycin *via* a triphenylphosphine promoted double cyclisation of an azido alcohol.[55] In this route, the bicycle is assembled in one step from acyclic precursors by the cyclisation of an aziridine, generated *in situ*, onto a suitably substituted dehydroamino acid derivative, the aziridine being produced through the well-known Staudinger reaction of an azido alcohol with triphenylphosphine.[56] At the time the authors began their studies they were unaware of the work of Armstrong and Zhao.[3]

To test the viability of this approach, a model system was devised devoid of the C-5 amino substituent and the L-valine residue.[5] Diene **89** was assembled through olefination of 4-pentenal **90** with a commercially available phosphonate **91**. On a large scale, this phosphonate can be conveniently synthesised according to the procedures of Ben-Ishai and Schmidt (Scheme 22).[57, 58] The formation of diene **89** was accomplished using a two step procedure from 4-penten-1-ol **92** by oxidation with PCC and further reaction with phosphonate **91** and DBN. Only one geometrical isomer was isolated, which was determined by nOe analysis of **93** to be the expected *Z*-isomer **89**.[58]

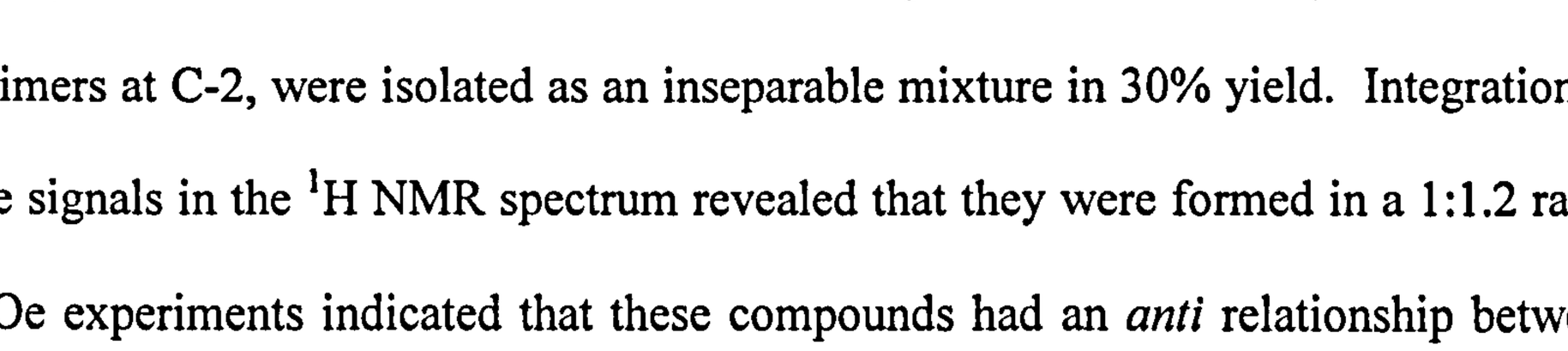
Stereo- and regioselective epoxidation of the terminal olefin of **89** with 3-chloroperoxybenzoic acid afforded exclusively terminal epoxide **93**.[59] Ring opening

of **93** with sodium azide and ammonium chloride in a regioselective manner provided the required 1,2-azido alcohol precursor **94**.



Scheme 22. *Reagents and conditions*: i) PCC, CH_2Cl_2; ii) DBN, CH_2Cl_2, 79% over two steps; iii) 3-chloroperoxybenzoic acid, CH_2Cl_2, 88%; iv) NaN_3, NH_4Cl, EtOH, 3 d, 65%.

The key cyclisation reaction was performed under several conditions, the best conditions involved heating **94** in the presence of triphenylphosphine (1.4 equivalents) in acetonitrile at 70 °C (Scheme 23). Repeated column chromatography was required to remove the triphenylphosphine oxide by-product, which eluted at nearly the same R_f as one of the aziridine components. In this way, **95a** and **95b**, epimers at C-2, were isolated as an inseparable mixture in 30% yield. Integration of the signals in the ^1H NMR spectrum revealed that they were formed in a 1:1.2 ratio. NOe experiments indicated that these compounds had an *anti* relationship between the aziridine ring and C-3, resembling the stereochemistry proposed by Kuo for ficellomycin, i.e. **1**.

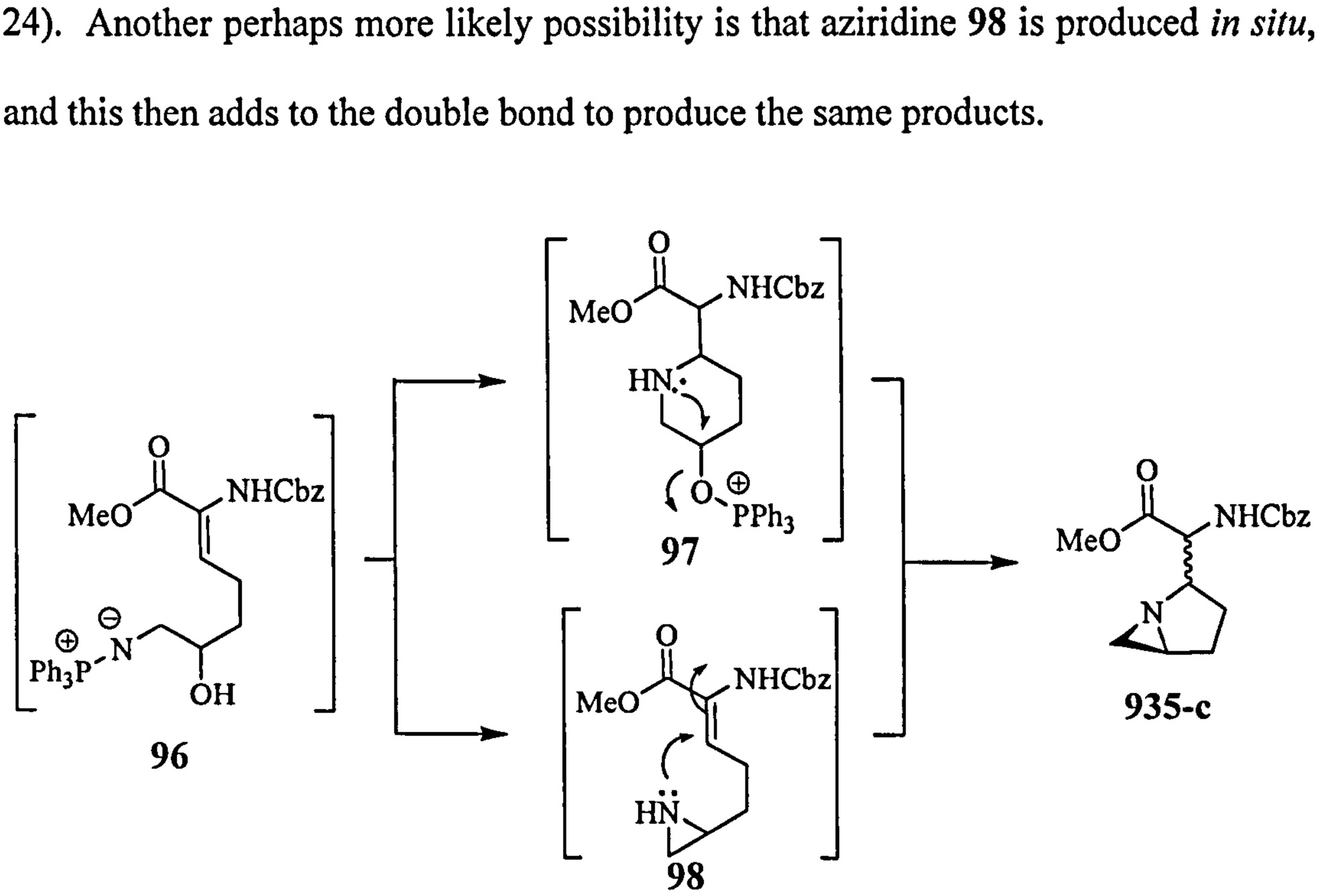


Scheme 23. *Reagents and conditions*: i) PPh_3, CH_3CN, 35%.

Further elution provided a more polar diastereomer **95c** isolated in just 5% yield. The ^1H NMR was rather broad, but nOe studies indicated a *syn* relationship between

the aziridine ring and the C-3 centre. This stereochemistry is consistent with Armstrong's structural proposal for ficellomycin, i.e. **5**. A further fraction was isolated from the column, displaying the right molecular mass (*m/z* = 305). It was postulated that this might be the epimer of **95c** at the C-2 position, although due to an inexplicable broadness of the ^{1}H NMR signals, this compound was not properly characterised.

Two possible mechanisms were proposed to account for the double cyclisation (Scheme 24). Imino phosphorane **96**, formed by nucleophilic attack of triphenylphosphine on the azide, might add onto the dehydroamino acid to form piperidine **97**. Subsequent migration of the triphenylphosphine group to oxygen, ring contraction and release of triphenylphosphine oxide would lead to **95a-95c** (Scheme 24). Another perhaps more likely possibility is that aziridine **98** is produced *in situ*, and this then adds to the double bond to produce the same products.

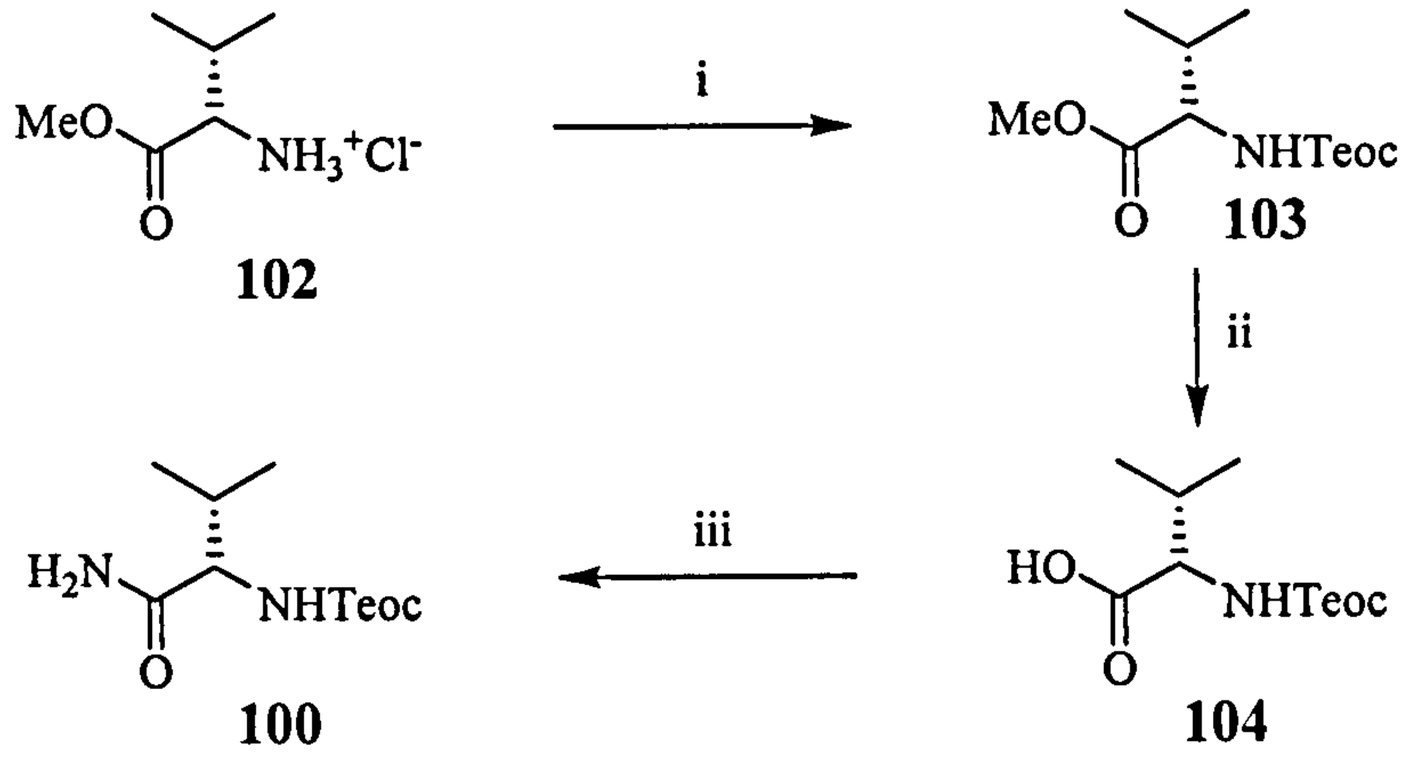


Scheme 24

Hence, a rapid method for the assembly of the 1-azabicyclo[3.1.0]hexanes was developed, with the modest combined yield (35%) for the cyclisation products being offset by the brevity and convenience of the approach. In addition, since the absolute stereochemistry at C-2 and C-3 of the natural product is unknown, access to all possible diastereomers was viewed as a possible advantage, at least in the first instance.

Efforts to extend this approach to "ficellomycin-like" structures was investigated, by introducing the second amino acid residue and the amino substituent at C-5.

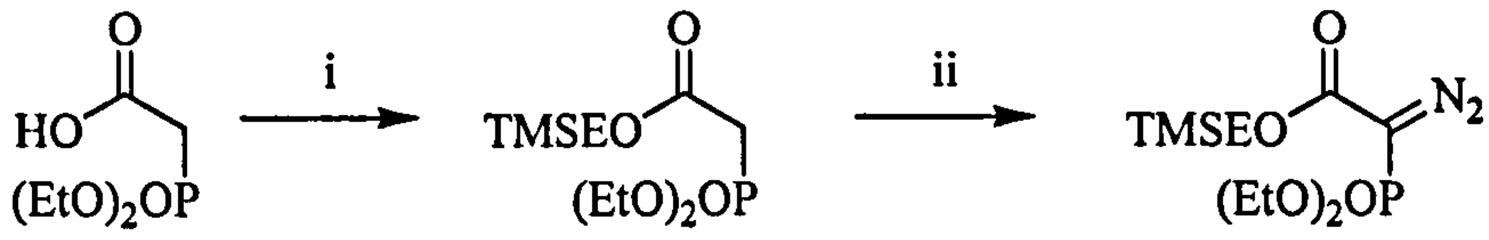
Phosphonate **99** was synthesised in a 5-step sequence in 26% overall yield using a $Rh_2(OAc)_4$ catalysed condensation[60] of amide **100** with diazo phosphonate **101**.[55] The two key building blocks for this coupling were assembled in the following way. Commercially available (*S*)-valine methyl ester **102** was *N*-protected with as a trimethylsilyloxycarbamate (Teoc) to give **103**.[61] Saponification of this ester with potassium hydroxide gave **104** which was transformed into amide **100** *via* the mixed anhydride (Scheme 25).[62]



102 **103** **104** **100**

Scheme 25. *Reagents and conditions*: i) Teoc-OSuc, 1,4-dioxane, H_2O, Et_3N, 89%; ii) 2M KOH, THF, 100%; iii) EtOCOCl, NH_3 aq., Et_3N, THF, 57%; Teoc = $-CO(CH_2)_2Si(CH_3)_3$.

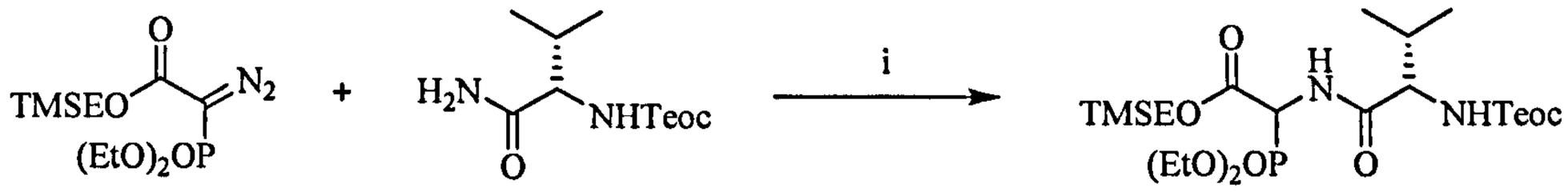
Diazo phosphonate **101** was made in two steps from commercially available starting materials. Protection of (diethoxyphosphono)acetic acid (**105**) as its trimethylsilylethyl ester gave **106**, which was treated with the diazo transfer agent 1-acetamido-4-benzenesulfonyl azide in the presence of cesium carbonate to give **101** in 83% yield over the two steps (Scheme 26).[63]



105 **106** **101**

Scheme 26. *Reagents and conditions*: i) DCC, DMAP cat., 2-trimethylsilylethanol, THF, 90%; ii) Cs_2CO_3, 1-acetamido-4-benzenesulfonyl azide, THF, 92%.

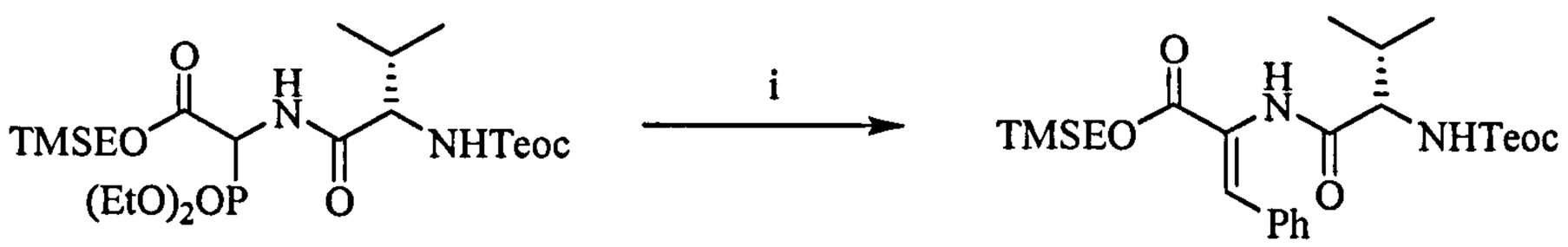
Coupling of **100** and **101** was performed by refluxing **100** and **101** together with rhodium(II) acetate in toluene for 48 hours.[62] Phosphonate **99** was isolated after column chromatography as a single diastereomer in 55% yield (Scheme 27).



101 **100** **99**

Scheme 27. *Reagents and conditions*: i) $Rh_2[OCOCH_3]_4$, $PhCH_3$, 110 °C, 48h, 55%.

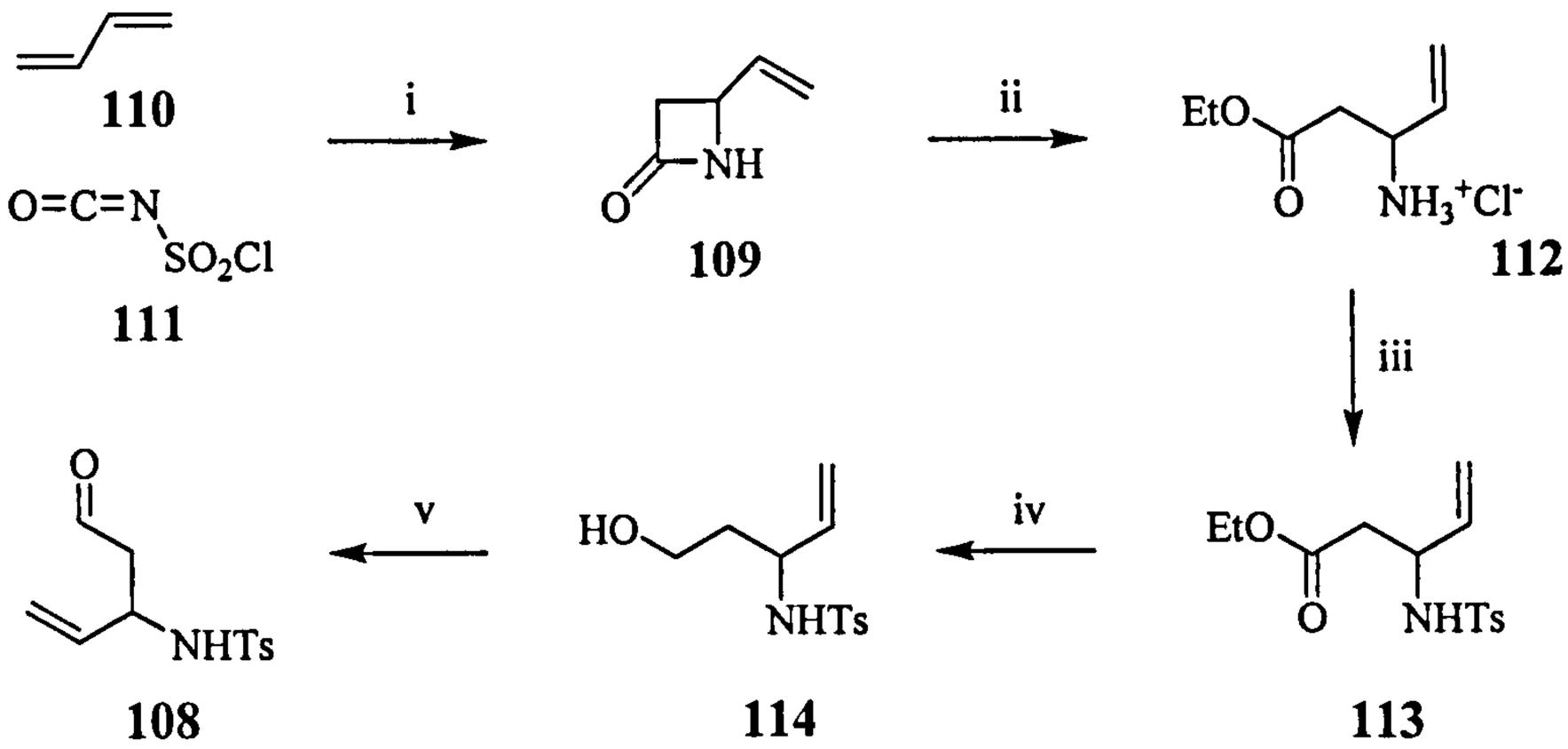
Olefination of **99** with benzaldehyde was undertaken using DBN (Scheme 28). The NMR spectrum in the presence of (*R*)-(-)-2,2,2-trifluoro-1-(9-anthryl)ethanol of the resulting *Z*-olefin **107** was compared against that obtained using (±)-**99**.[64] This established that no racemisation had occurred during the synthesis of (*S*)-**107** (ee >90%).



99 **107**

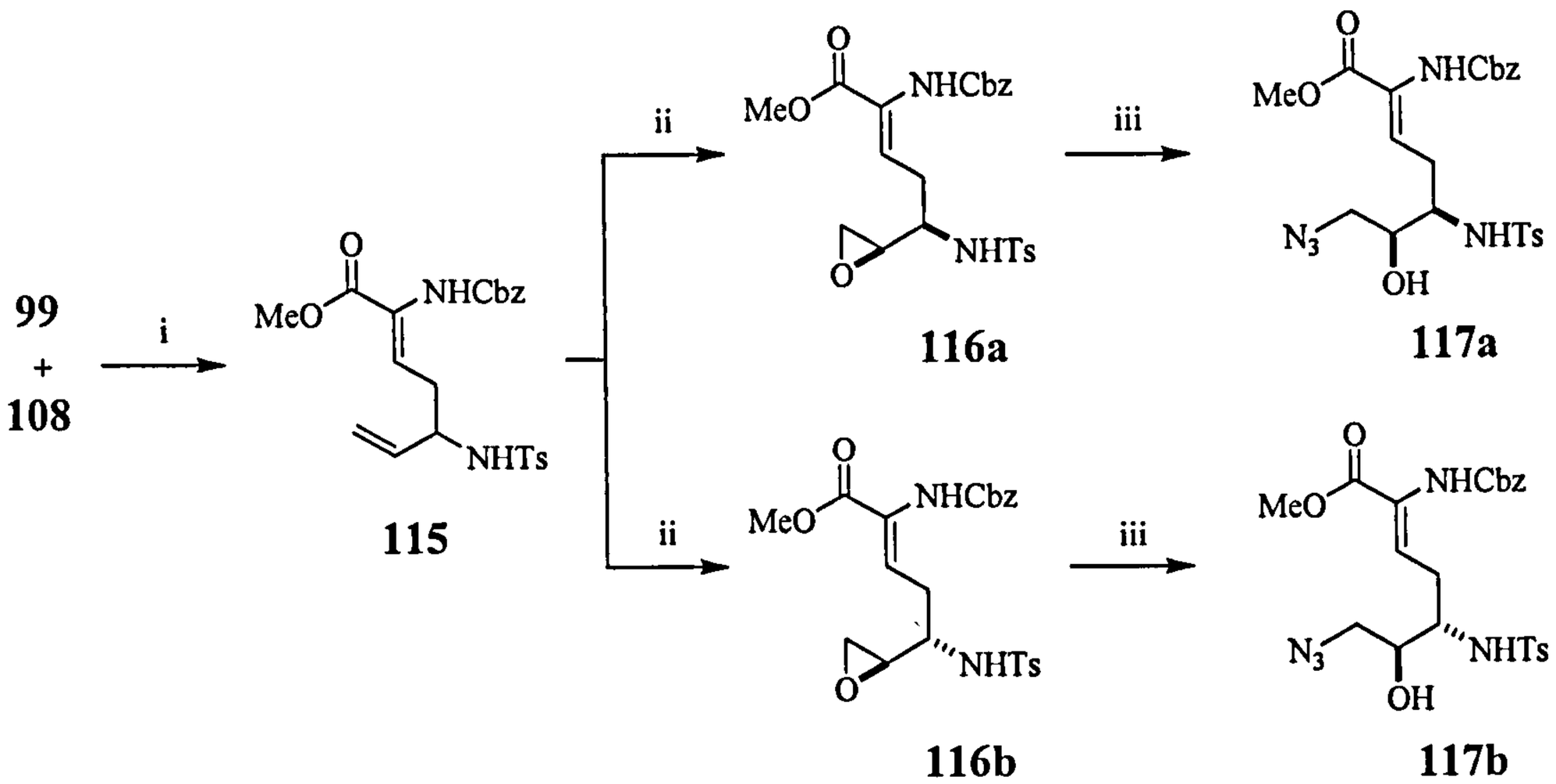
Scheme 28. *Reagents and conditions*: i) C_6H_5CHO, DBN, CH_2Cl_2, 5 °C-RT, 16 h, 88%.

To explore the impact of the C-5 amino substituent on the double cyclisation, aldehyde **108** was synthesised *via* 4-vinyl-azetidin-2-one (**109**), following a procedure described by Goebel *et al.*[65] The *β*-lactam **109** was made by cycloaddition between 1,3-butadiene (**110**) and chlorosulfonyl isocyanate (**111**). **109** was ring opened with acidic ethanol,[66] and the resulting amine **112** protected as its *p*-toluenesulfonamide to give **113.** Reduction of **113** to alcohol **114** with lithium aluminium hydride followed by Swern oxidation provided aldehyde **108** in a very modest 8% yield over the 5 steps.[67]



Scheme 29. *Reagents and conditions*: i) Et_2O, 70 h, 16%; ii) HCl (g), EtOH, 100%; iii) TsCl, Et_3N, 80%; iv) $LiAlH_4$, THF, 86%; v) oxalyl chloride, DMSO, CH_2Cl_2, Et_3N, 74%.

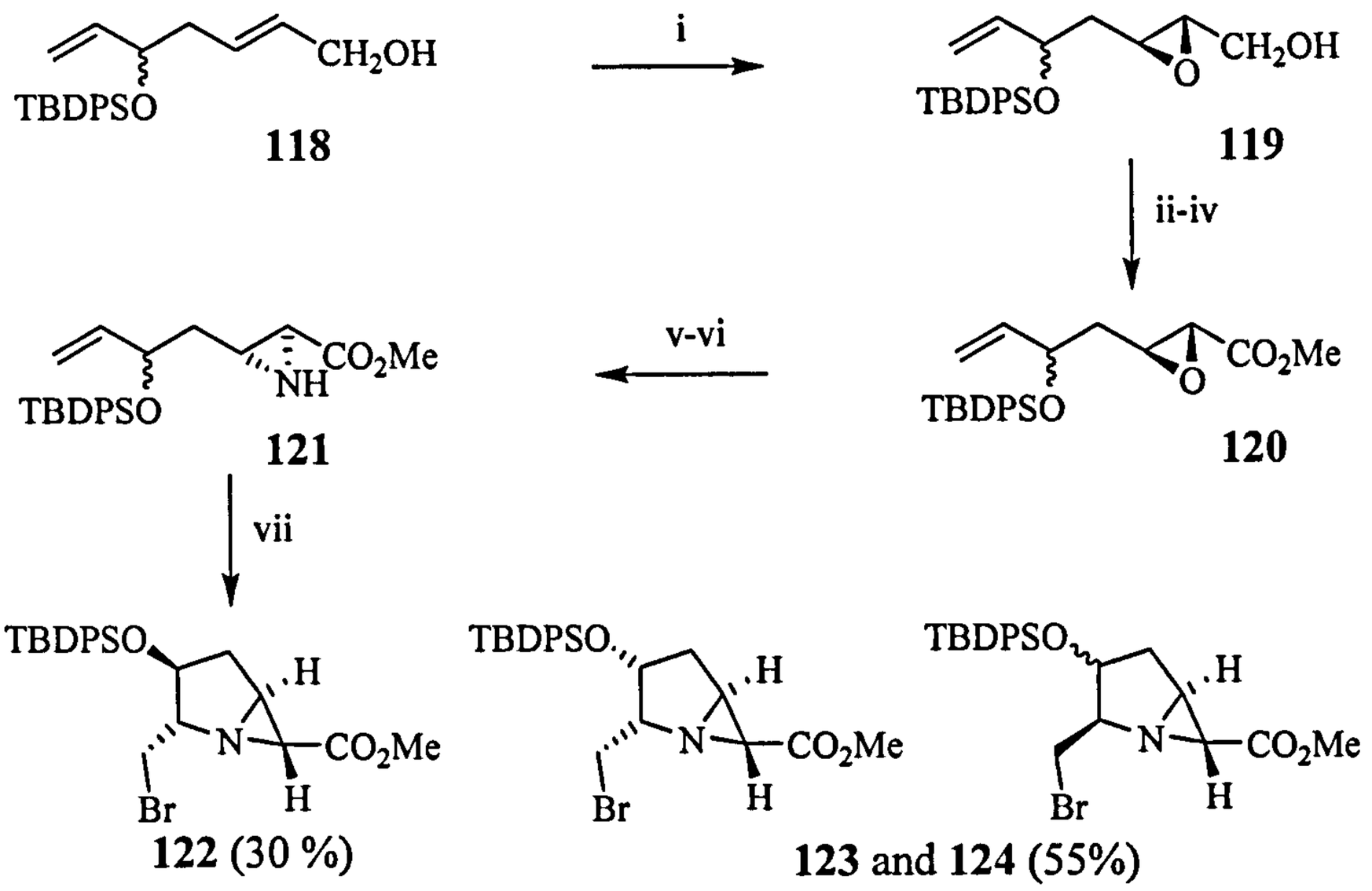
Aldehyde **108** was subjected to the same olefination conditions as those employed previously to give analogously, *Z*-alkene **115**. The epoxidation step was problematic, both in terms of conversion and selectivity, and finally, a procedure described by Yang *et al.* using methyl(trifluoromethyl)dioxirane was used.[68] A mixture 71:29 of **116a**:**116b** was obtained in 65% yield. The stereochemistry of the major diastereomer was assigned tentatively as that indicated. Regioselective ring opening of epoxide **116a** with sodium azide provided azido alcohol **117a** in 54% yield, while minor diasteromer **116b** led to just 27% of **117b**. Due to constraints in the availability of starting material, cyclisation of small amounts of these azido alcohols was performed using tributylphosphine to ease isolation and purification of the products. Two fractions were obtained, displaying the expected molecular ion (*m/z*= 474) for the double cyclisation product, but unfortunately the rest of the analytical data did not provide convincing evidence of product formation.



Scheme 30. *Reagents and conditions*: i) DBN, CH_2Cl_2, 0 °C-RT, 57%; ii) CF_3COCH_3, $NaHCO_3$, oxone®, CH_3CN, Na_2.EDTA aq., 0 °C, 65%, (**116a**:**116b**; 71:29); iii) NaN_3, NH_4Cl, MeOH, 50 °C, 6 h, (**117a**, 54%; **117b**, 27%).

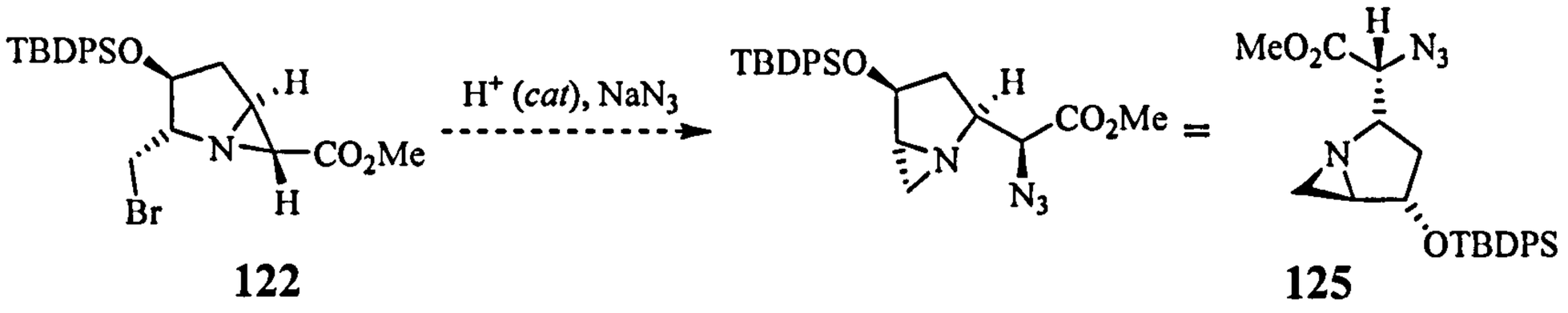
More recently, Chen *et al.* working under the supervision of Professor Andrei K. Yudin at the University of Toronto, reported a novel synthetic approach employing an oxidative cyclisation of olefin-containing aziridines.[4, 69] Two related synthetic routes have been devised.

Hydroxyl directed epoxidation of allylic alcohol **118** gave epoxide **119** in 86% yield (Scheme 31). Stepwise oxidation to the acid followed by esterification with azidotrimethylsilane afforded epoxy ester **120** in 70% over the three steps. The aziridine **121** was assembled by ring opening of the epoxide with azide followed by Staudinger reaction. Oxidative cycloamination with *N*-bromosuccinimide provided three bicycles in 85% combined yield. **122** was isolated as a single diastereomer in 30% yield, along with **123** and **124** (one of them, being epi-**122**), which were obtained as an inseparable mixture in 55% yield.



Scheme 31. *Reagents and conditions*: i) $VO(acac)_2$, TBHP, DCM, 86%; ii) Swern; iii) $NaClO_2$, NaH_2PO_4; iv) $TMSCHN_2$, DCM, 70% over three steps; v) NaN_3, NH_4Cl, vi) PPh_3, CH_3CN, 40% over two steps; vii) NBS, DCM, 85%.

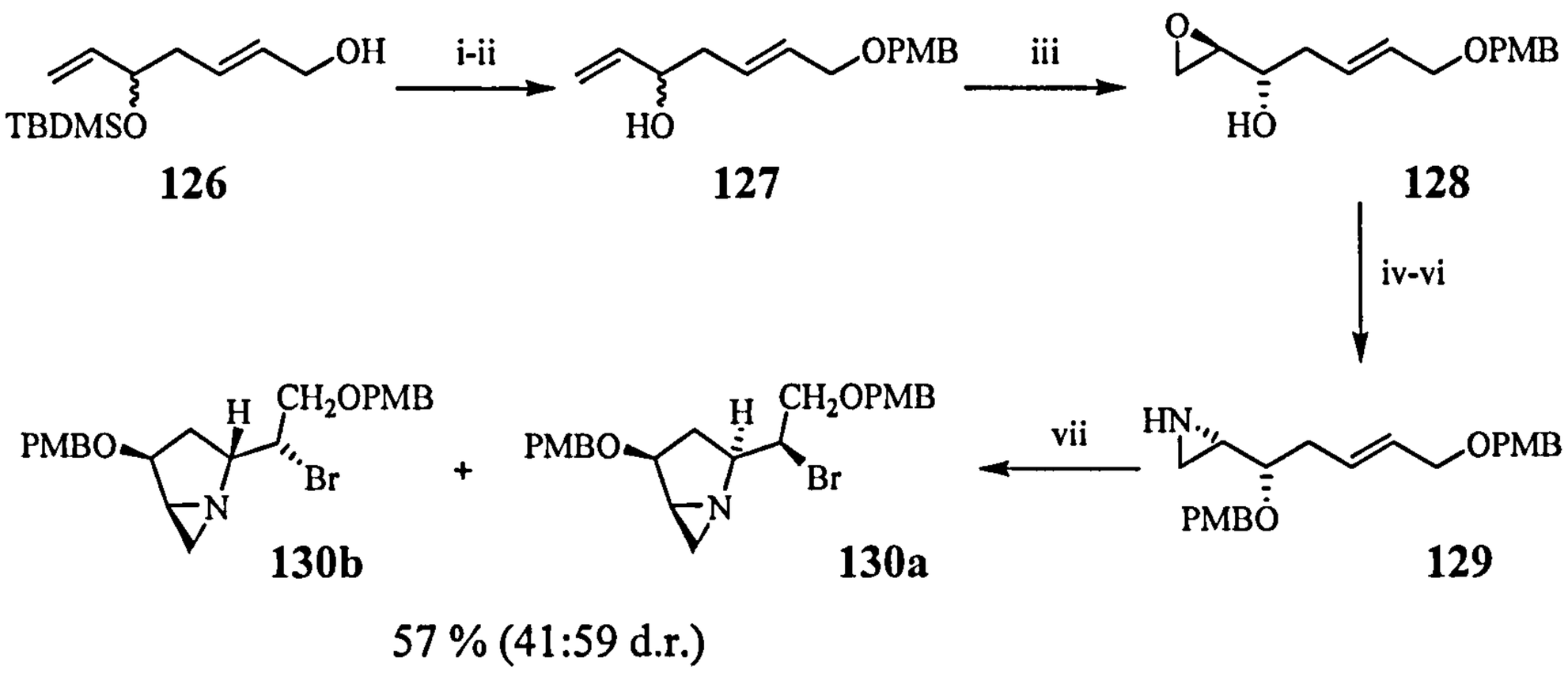
It was proposed that **122**, after acid-catalysed aziridine opening with sodium azide could provide a 1-azabicyclo[3.1.0]hexane **125** consistent with Kuo's proposal for the natural product **1**. However, it is unclear how the stereochemistry could be preserved at C-5 during the introduction of the guanidine group (Scheme 32).



Scheme 32

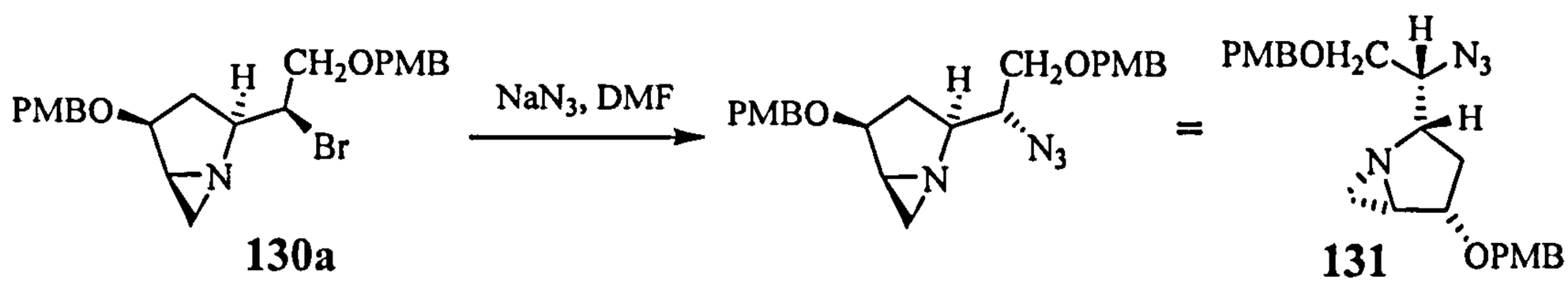
An improved route using a Sharpless asymmetric epoxidation of the terminal olefin has also been described.[70] In this approach, **126** was converted into secondary alcohol **127**, which underwent kinetic resolution under Sharpless asymmetric epoxidation to give **128** in 40% yield. Further manipulation gave **129** which was again subjected to the oxidative cyclisation protocol. Using *N*-bromosuccinimide,

two diastereomers **130a** and **130b** were isolated in 57% yield in a diastereomeric 41:59 ratio (Scheme 33).



Scheme 33. *Reagents and conditions*: i) PMBCl, Bu_4NI, NaH, THF, 92%; ii) TBAF, THF, 80%; iii) L-(+)-DIPT, $Ti(O^iPr)_4$, TBHP, DCM, -20 °C, 3 days, 45%; iv) PMBCl, Bu_4NI, NaH, THF, 86%; v) NaN_3, NH_4Cl, $MeOH/H_2O$, vi) PPh_3, CH_3CN, 50%; vii) NBS, DCM, 57%.

Bromide **130a** was treated with sodium azide to give azide **131**, which the authors intend to advance towards the natural product, bearing the same stereochemistry as that proposed by Armstrong.[3] Again, the introduction of the guanidine will require two inversions to preserve the stereochemistry at C-5 (Scheme 34).

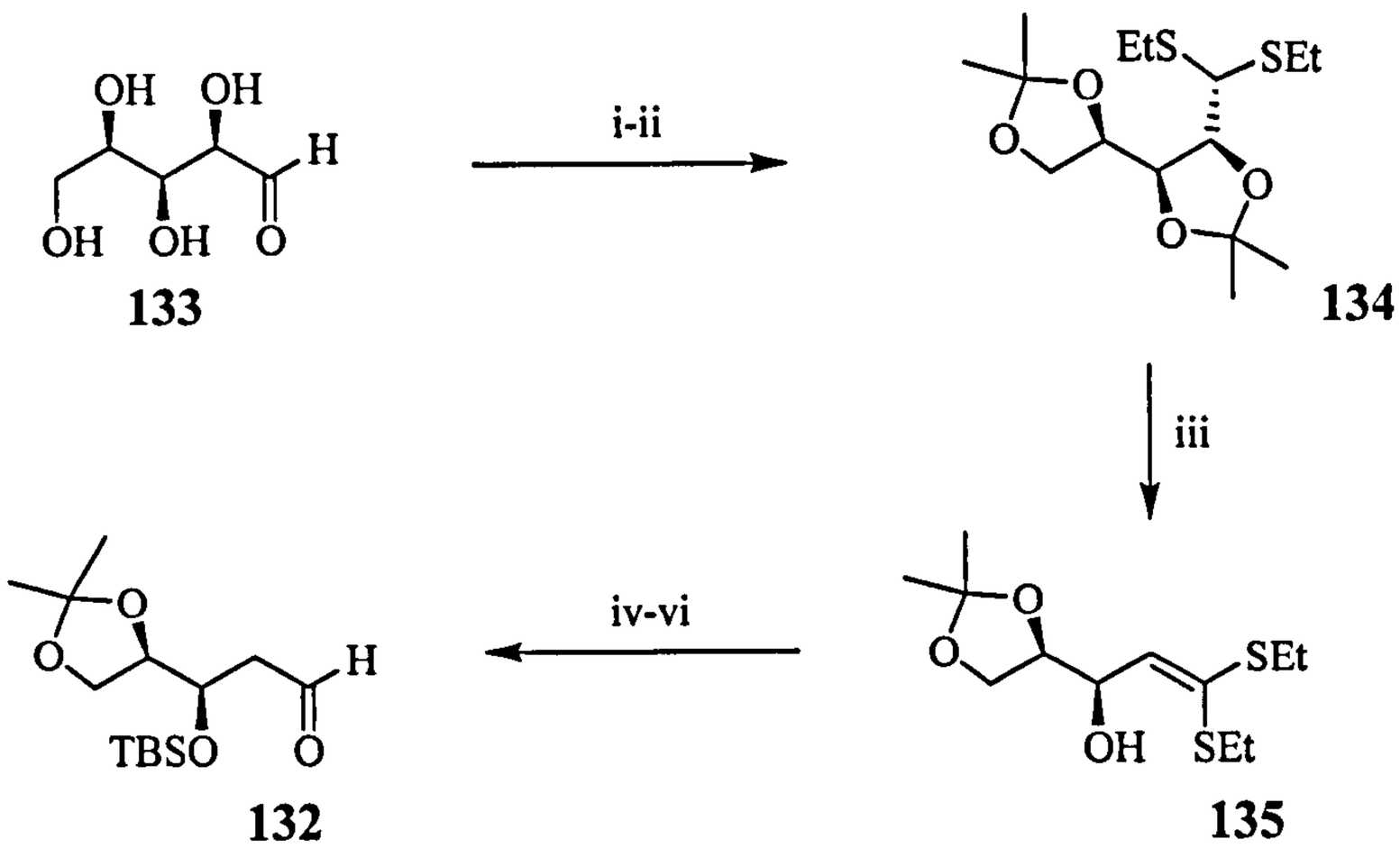


Scheme 34

1.7.6.b. Formation from a preformed pyrrolidine

An approach to ficellomycin from a preformed pyrrolidine has been devised by Armstrong and Zhao.[3] It was intended that this route would provide a cyclisation precursor where the stereochemistry of all chiral centres would be known. It was assembled from aldehyde **132**, itself derived from D-xylose (**133**) in six steps. These

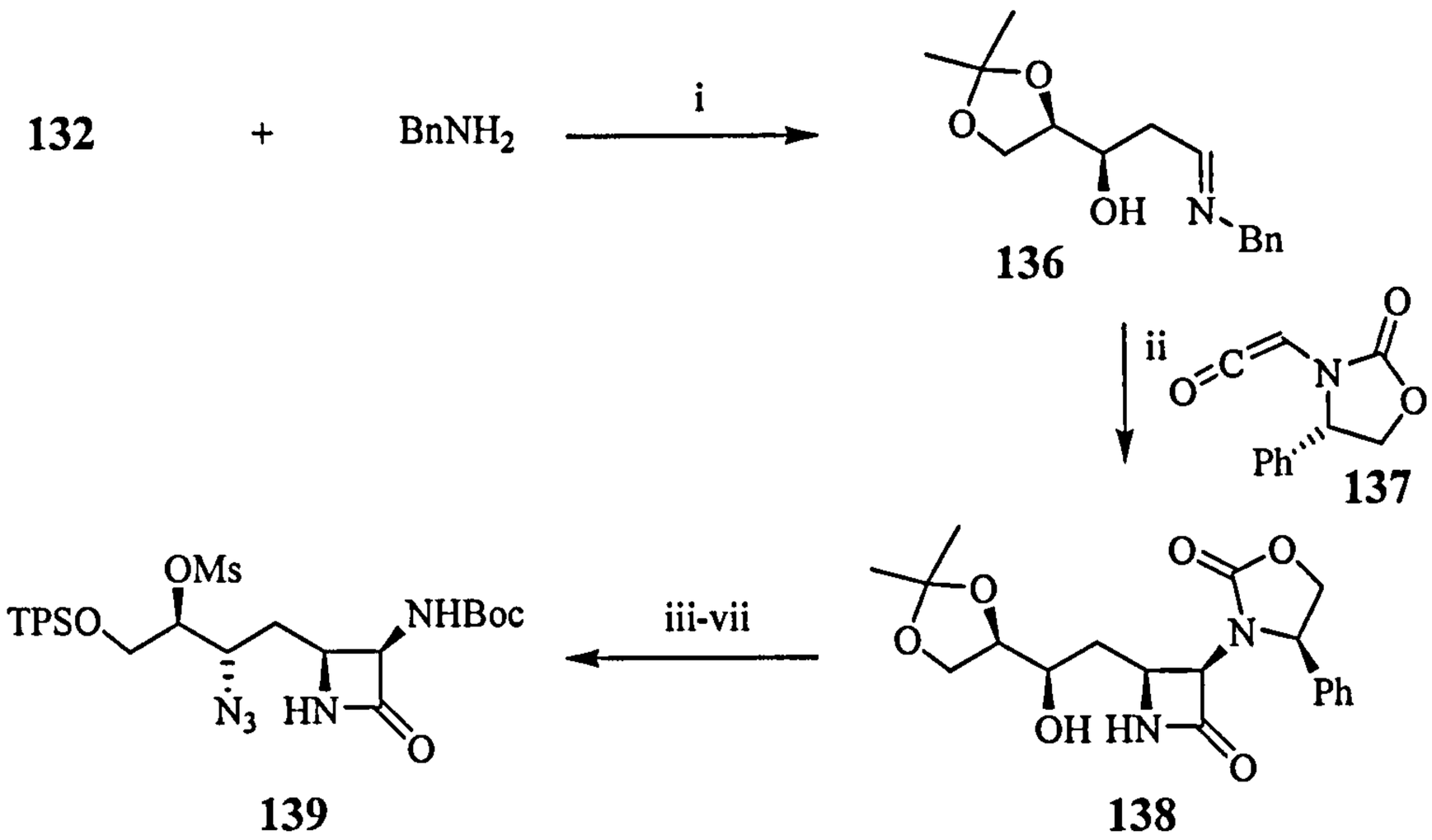
involved conversion of **133** to dithioacetal **134**, followed by abstraction of the C-1 hydrogen using ^{t}BuOK and elimination of acetone to furnish **135**.[71] Reduction with lithium aluminium hydride, protection of the free alcohol as a TBS silyl ether, followed by selective cleavage of the dithioacetal gave aldehyde **132** in 30% overall yield (Scheme 35).



133 **134** **135** **132**

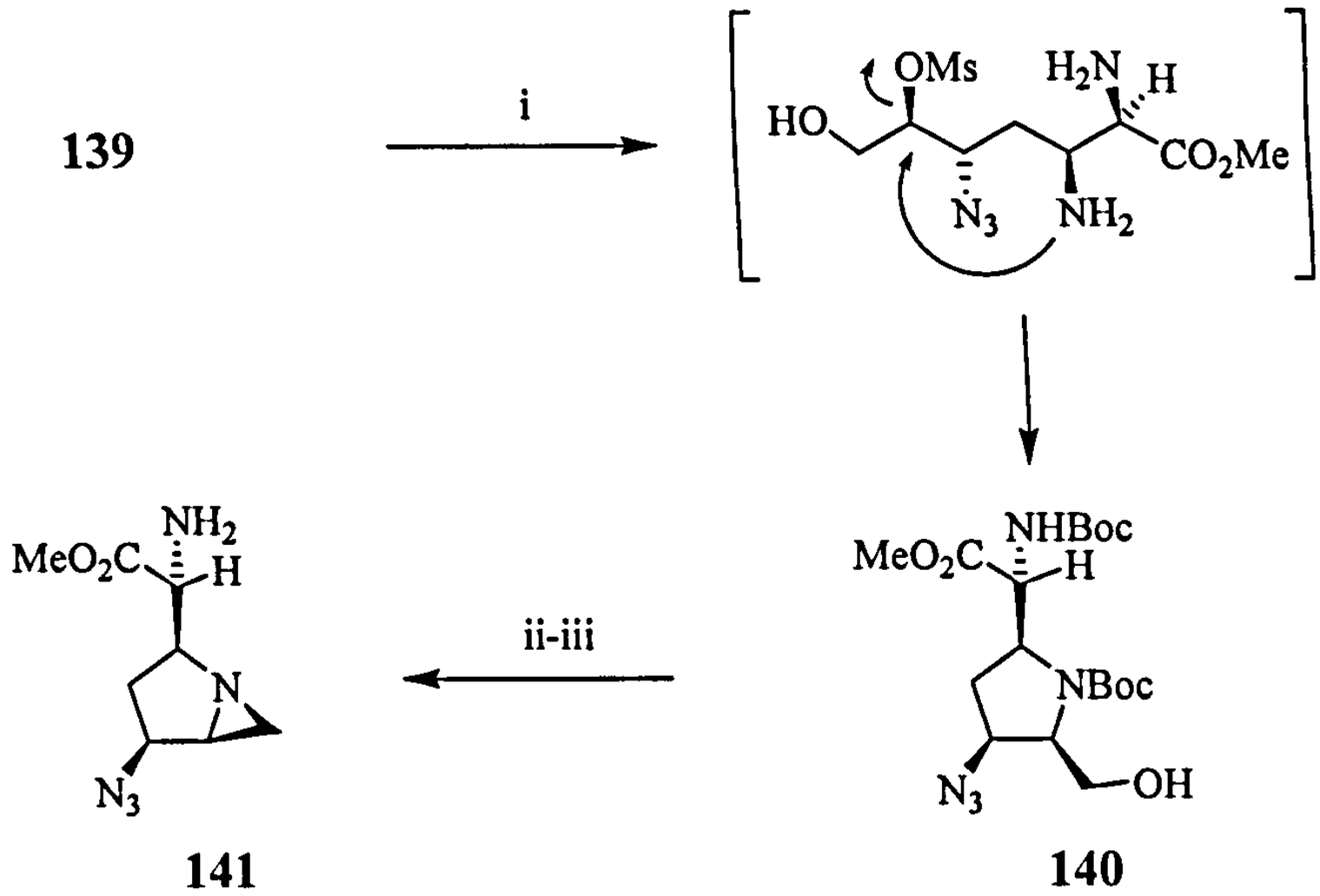
Scheme 35. *Reagents and conditions*: i) EtSH, HCl; ii) $(CH_3)_2CO$, H_3PO_4, 75% over 2 steps; iii) KO^{t}Bu, DMSO:THF, 1:3, 82%; iv) $LiAlH_4$, THF, 80%; v) TBSCl, Imid., DMF, 92%; vi) $HgO/HgCl_2$, $(CH_3)_2CO/H_2O$, 66%.

Treatment of **132** with benzylamine afforded imine **136** which was further reacted with homochiral ketene **137** *via* a [2+2] cycloaddition to produce a mixture of azetidinones. Purification by column chromatography provided the required *cis* isomer as the major product **138**.[72] Dissolving metal reduction cleaved the chiral auxiliary, which was re-protected as a *tert*-butyl carbamate. Additional simple functional group interconversions yielded **139** in 13% overall yield over seven steps from aldehyde **132** (Scheme 36).



Scheme 36. *Reagents and conditions*: i) Et_2O, Na_2SO_4, 0 °C, 2h, *quant.*; ii) Toluene, 60 °C, 3h, 41%; iii) Li, NH_3, THF:^{t}BuOH, 10:1, -78 °C, 10 min then Boc_2O, THF/H_2O, 81%; TBAF, THF, RT, 1h, 95%; iv) MsCl, Et_3N, CH_2Cl_2, RT, 30 min, 90%; v) NaN_3, DMF, 90-100 °C, 13 h, 76%; vi) *p*TSA, MeOH, RT, 15 h then PTSCl, Imid., DMF, RT, 2h, 70%; vii) MsCl, Et_3N, CH_2Cl_2, RT, 30 min, 90%.

Treatment of lactam **139** with hydrochloric acid in methanol induced simultaneous *tert*-butyl carbamate and silyl ether cleavage, and opening of the azetidinone ring. Addition of Et_3N induced closure to pyrrolidine in a regiocontrolled manner, which was isolated as **140** after further Boc protection. In this manner, all the stereochemistry around the pyrrolidine ring was set, along with that at C-2. Mesylation of the pendant alcohol followed by cleavage of the *tert*-butyl carbamate protecting group and base induced cyclisation gave 1-azabicyclo[3.1.0]hexane **141** *albeit* in a modest 31% yield (Scheme 37). No further advances from **141** to ficellomycin have been described.



Scheme 37. *Reagents and conditions*: i) HCl, MeOH, 0 °C, 35 min then Et_3N, Boc_2O, RT, 1h, 75%; ii) MsCl, Et_3N, CH_2Cl_2, RT, 2h, 95%; iii) HCl, MeOH, then Na_2CO_3, 0 °C, 30 min, 31%.

1.8. Conclusions

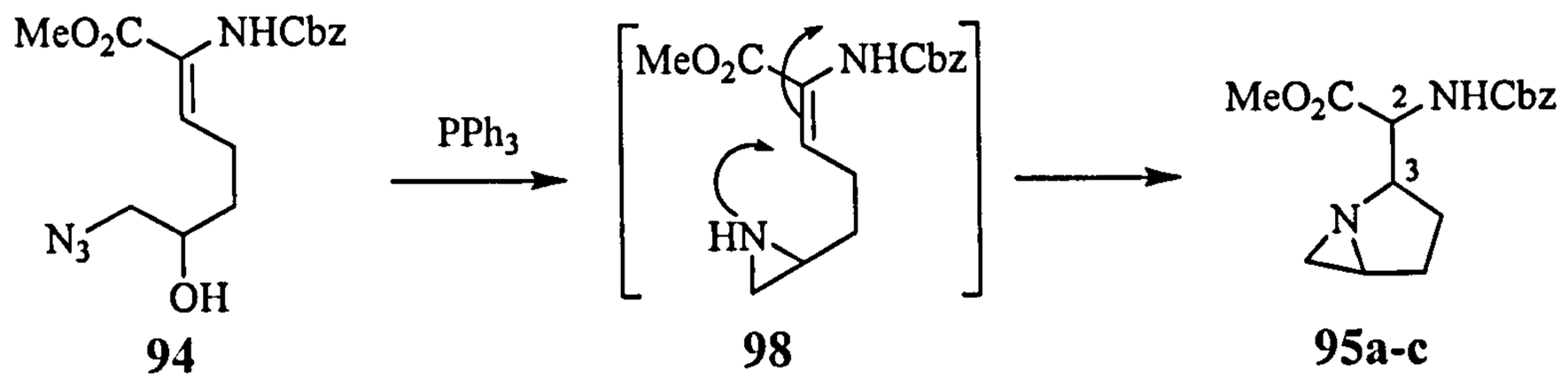
Ficellomycin is a structurally complex natural product with important antibiotic activity. Routes to 1-azabicyclo[3.1.0]hexanes are known involving a variety of disconnections, some key examples being highlighted herein. Several innovative methods have been applied to synthesis of "ficellomycin-like" structures although none have yet delivered the natural product. My thesis work has been concerned with further developing and extending work already undertaken by Dr David Paumier, with a view to achieving the first total synthesis of this intriguing natural product.

Chapter Two:

Results and Discussion

2.1. Assembly of the 1-azabicyclo-[3.1.0]hexane system

In seeking the most expedient route to ficellomycin, Dr David Paumier, another PhD student in the Shipman group, developed a route to a model compound namely **95a-c** whereby an NH aziridine **98** generated *in situ* from the corresponding 1,2-azido alcohol **94** by a Staudinger-type reaction, undergoes spontaneous closure onto a suitably activated double bond in a Michael-type reaction (Scheme 38).



94 **98** **95a-c**

Scheme 38

The route to the 1,2-azido alcohol precursor **94** undertaken by Dr David Paumier was discussed previously (Scheme 22).

The cyclisation was initially performed, by David Paumier, in the presence of triphenylphosphine (1.4 equivalents) in acetonitrile at 70 °C. Purification of the aziridines **95a-c** was hampered by the presence of excess triphenylphosphine and triphenylphosphine oxide, which eluted at nearly the same R_f as one of the products.

A total of three bicycles **95a-c** were isolated and characterised. Two of them, epimeric at C-2 (dr 1:1.2) were obtained as an inseparable mixture in 30% yield. On the basis of nOe difference studies, both of them were tentatively assigned as having an *anti* relationship between the aziridine ring and C-3.

Further elution provided a more polar diastereomer in 5% yield, displaying a *syn* relationship between the aziridine ring and the C-3 centre. A further fraction was obtained from the column, displaying the correct molecular mass (m/z = 305), but no characterisation data for this compound was obtained.

To overcome the problems encountered with isolation and purification of the bicycles generated in the Staudinger-type reaction, David Paumier tested tributylphosphine as an alternative. However, no improvement in yield was forthcoming.

At the start of my PhD studies, I was tasked with examining alternative methods for achieving this transformation, in an effort to improve this chemistry.

The resynthesis of azido alcohol **94** was readily achieved in accordance with the reported method (Scheme 22).

Several alternative phosphine sources and purification methods are known. For example, triphenylphosphine and triphenylphosphine oxide can be removed through addition of a metal salt to form a complex with the oxide. Alternatively, a high-loading chloromethylated polystyrene modified *in situ* with sodium iodide, can be used as a scavenger resin.[73] Aqueous work-up to remove water soluble phosphines is also an option. However, all these methods require further manipulation of the reaction mixture, which we viewed as undesirable because of the potential sensitivity of **95**.[74]

We attempted using a more polar 4-dimethylaminophenyl diphenylphosphine, but this resulted in a rise in impurities and failed to improve yields. Having considered the alternatives, we elected to examine the use of a polymer-supported variant of triphenylphosphine. The conventional use of synthetic polymers was introduced by Merrifield who, in the 1960s was the first to use them as reagents in synthetic organic chemistry.[75] The general advantage of solid-phase synthesis is the simplicity of work up which usually involves just a simple filtration.[76]

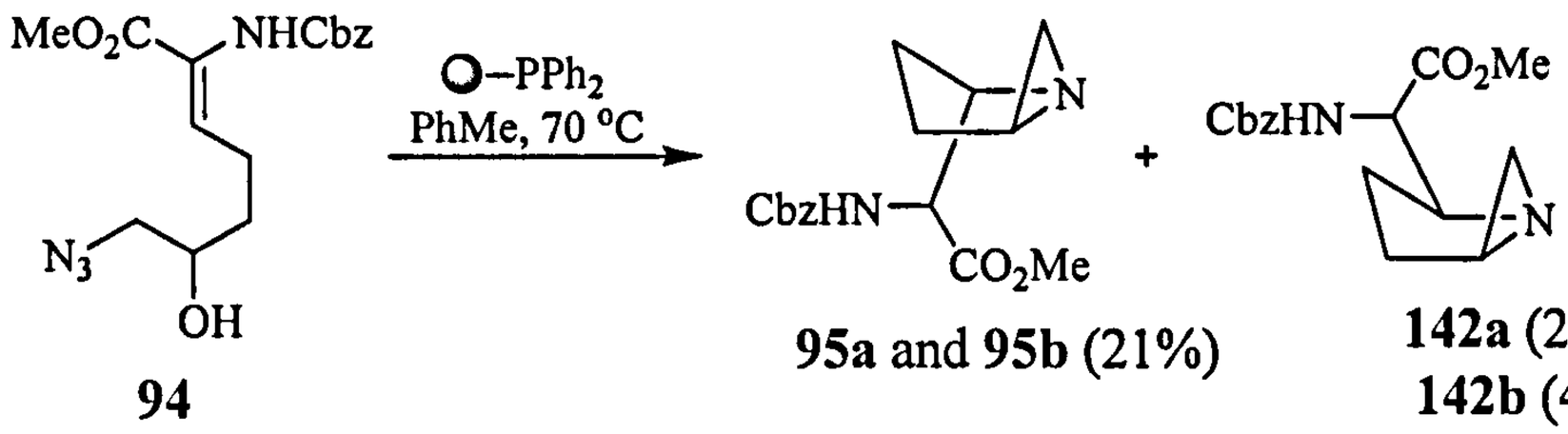
Some disadvantages with supported substrates and reagents are apparent, such as the steric bulk of the polymer.[77] The extent of swelling or solvation, porosity and mechanical stability of the polymer can also affect the diffusion of reagents into the reactive sites. Changes in reactivity in comparison to solution phase reactions are frequently encountered, but these may be overcome by suitable modification of the reaction conditions.

Poly-triphenylphosphine (poly-TPP) is commercially available (Fluka) and has been used as a precursor to form Wittig reagents in THF and benzene.[78] It has been used successfully in Mitsunobu[79] and Staudinger/Aza-Wittig[80] reactions, and several total syntheses have been reported with/on polymer supported reagents/resins.[81]

Encouraged by these reports, we decided to explore the use poly-TPP (*ca* 3 mmol/g, polystyrene cross-linked with 2% divinylbenzene, Fluka) in the cyclisation of azido alcohol **94**. As far as we are aware, polymer supported phosphines have not been previously used for aziridine formation from 1,2-azido alcohols.

In the original study, acetonitrile was used as the solvent. However, polyTPP is reported to swell poorly in this solvent.[82] Therefore, toluene was selected, as it had been used successfully by Dr David Paumier using TPP.

Swelling of poly-TPP (1.1. eq.) was performed by gentle stirring in toluene for 30 minutes before the start of the reaction. Subsequent addition of 1,2-azido alcohol **94** and heating for 16 hours at 70 °C provided **95a,b** and **142a,b** devoid of phosphine oxide contamination after filtration and washing with dichloromethane and evaporation (Scheme 39).



94

95a and **95b** (21%)

142a (20%)
142b (4%)

Scheme 39

Gratifyingly, analysis of the crude reaction mixture by ^{1}H NMR revealed full conversion of the starting material to products, indicating efficient reactivity of the supported phosphine. However, a relatively low mass recovery was witnessed (*ca* 70%), which did not improve after repeated washing of the resin with dichloromethane. We cannot account for this low mass recovery, but suggest that these relatively small substrates/products may become trapped within resin cavities.

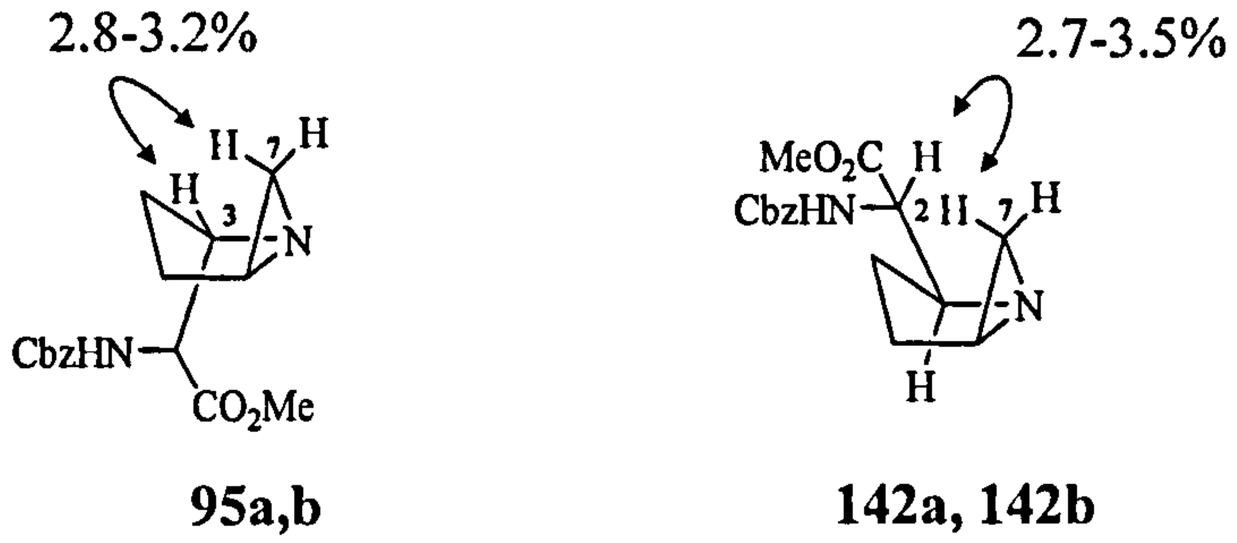
The distinctive pattern of the aziridine hydrogens was readily discerned in the ^{1}H NMR spectrum. Integration of these signals indicated the presence of all four possible diastereomers with modest diastereoselectivity (crude dr **95a**:**95b**:**142a**:**142b** = *ca* 3:1:5:1). These products proved quite stable and could be

purified by chromatography on silica gel pre-treated with triethylamine. The chromatography was performed on silica (Merck Kieselgel 60 GF254) using a moderately polar eluting solvent (20 → 100% ethyl acetate in petroleum ether, 1% triethylamine), which allowed separation of three different components (**95a/b, 142a** and **142b**).

The use of methanol as co-solvent resulted in low yields and poor product purity. Although not isolated, the most likely degradation product is that arising from ring opening of the aziridine by methanol, which may occur even in triethylamine pre-treated silica. No product was collected using neutral alumina as support, and the use of a less acidic type of silica (GF_{254}) yielded no separation of the different diastereomers and only modest yield of products (68%).

The *anti*-diastereomers **95a** and **95b**, epimeric at C-2, were isolated as an inseparable 3:1 mixture in 21% yield, this is in contrast to the 1:1.2 diastereomeric ratio observed when the reaction is performed in solution phase. The more polar *syn*-diastereomers **142a** and **142b**, also epimeric at C-2, were isolated as separate components in 20 and 4% yields, respectively.

Overall, the reaction shows a very modest preference for the production of the *syn*-diastereomers (*syn*:*anti*; 1.2:1). The stereochemical assignments of all the products was confirmed by nOe studies conducted in benzene. Both *anti*-diastereomers **95a** and **95b** showed strong reciprocal nOe enhancements (2.8-3.2%) between H-3 and H-7_{endo}. In contrast, *syn*-diastereomers **142a** and **142b** showed nOe enhancements (2.7-3.5%) between H-2 and H-7_{endo}. At this point in time, it has not been possible to determine the relative stereochemistry at C-2 in either *syn*- or *anti*-diastereomers.



95a,b **142a, 142b**

Figure 8

In collaboration with my CASE supervisor at AstraZeneca, the biological activity of **95a/b** and **142a** and **142b** was tested against a variety of common pathogens (See Appendix Three). However in the screens used, **95a/b** and **142a** and **142b** had no biological activity. This may indicate that other portions of the natural product (e.g. guanidine, valine residue, free CO_2H) are important for antibiotic activity. Alternatively, the high lipophilicity of these compounds may limit their bioavailability.

Whilst little stereoselectivity was observed in this model system, it does provide access to ficellomycin-like molecules in a very concise manner. In fact, the lack of stereocontrol may be viewed as an advantage since there is some doubt over the stereochemistry at C-3, and the stereochemistry at C-2 is not known (*vide supra*).

The use of poly-TPP represents a significant advance over the original method developed by Paumier. The overall yield is improved (45% *cf* 35%), isolation is greatly simplified and all the diastereomers were successfully isolated and characterised.

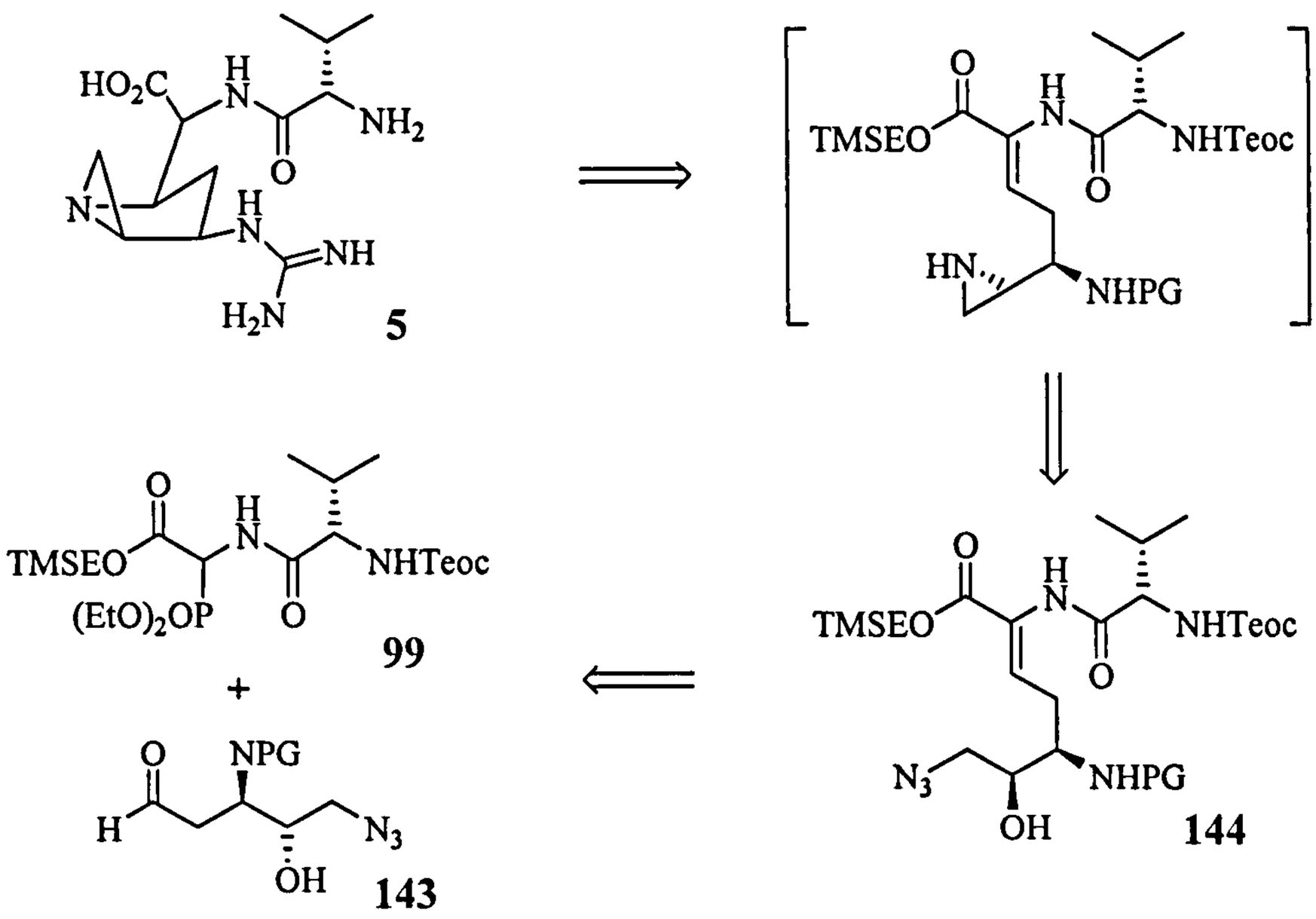
At this point in our own studies, we became aware of the work performed by Armstrong and Zhao and their revision to the stereochemistry of ficellomycin **5**.

To apply this chemistry to the synthesis of the natural product, the synthesis of an 1,2-azido alcohol precursor bearing the C-5 amino substituent was needed. Significant problems had been encountered by Dr David Paumier attempting to achieve this goal (*vide supra*).

In view of the poor stereoselectivity witnessed herein, and the difficulties encountered by David Paumier in building/cyclising substrates bearing C-5 amino substituents, we decided to abandon this strategy and explore a more stereoselective approach to ficellomycin.

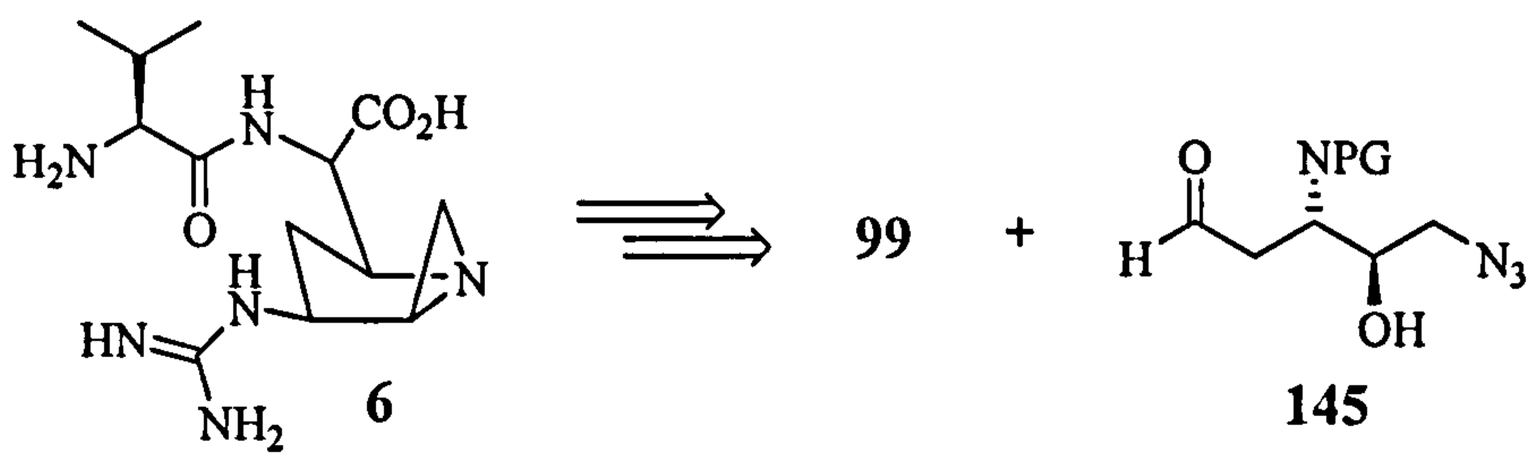
2.2. Towards a C-5 Amino Substituted System

Since it is highly likely that either **5** or its diastereomer **6** is the correct sterechemistry for ficellomycin, it seemed desirable to develop an enantioselective route to the lower half of the natural product that would enable access to **5** or **6**. Thus, aldehyde **143** would, after olefination with **99**, provide a cyclisation precursor **144** with the correct stereochemistry to access **5** (Scheme 40).



Scheme 40

Analogously, its enantiomer **145** would provide a suitable starting material to access **6**, using the same route. (Scheme 41).

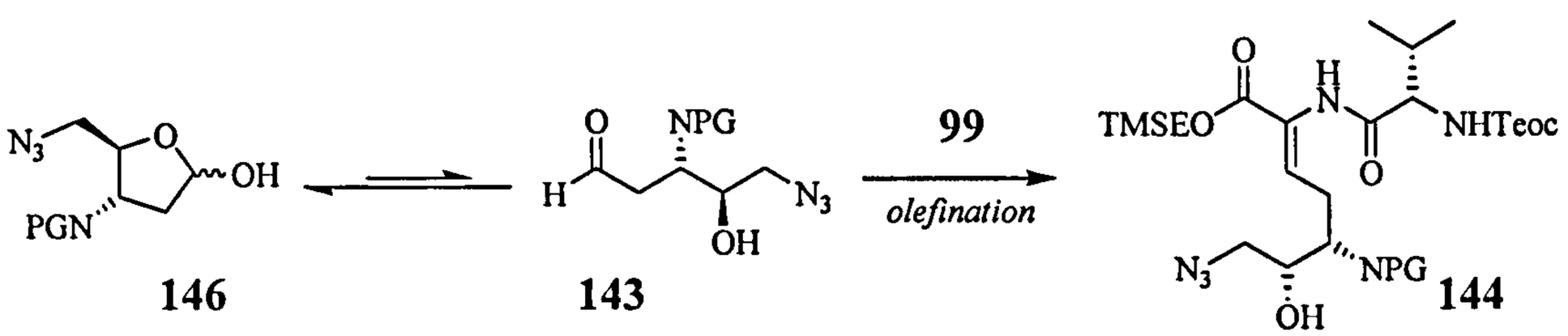


Scheme 41

In this chapter, we describe our synthetic efforts to develop an enantioselective synthesis of aldehydes **143** and **145** and its further manipulation to set the stereochemistry and structure needed to complete the natural product.

In our attempt to design the most expedient route to aldehydes **143** and **145**, we were drawn to the idea of exploiting the well-known equilibrium between lactols and γ-hydroxy-aldehydes.

Thus, olefination of phosphonate **99** with a suitably substituted lactol **146** would yield in one step 1,2-azido alcohol **144**, the precursor for the double cyclisation. Although the lactol **146** would be more thermodynamically stable than aldehyde **143**, the olefination of the aldehyde would drive the reaction to completion on the basis of Le Chatelier's principle (Scheme 42).

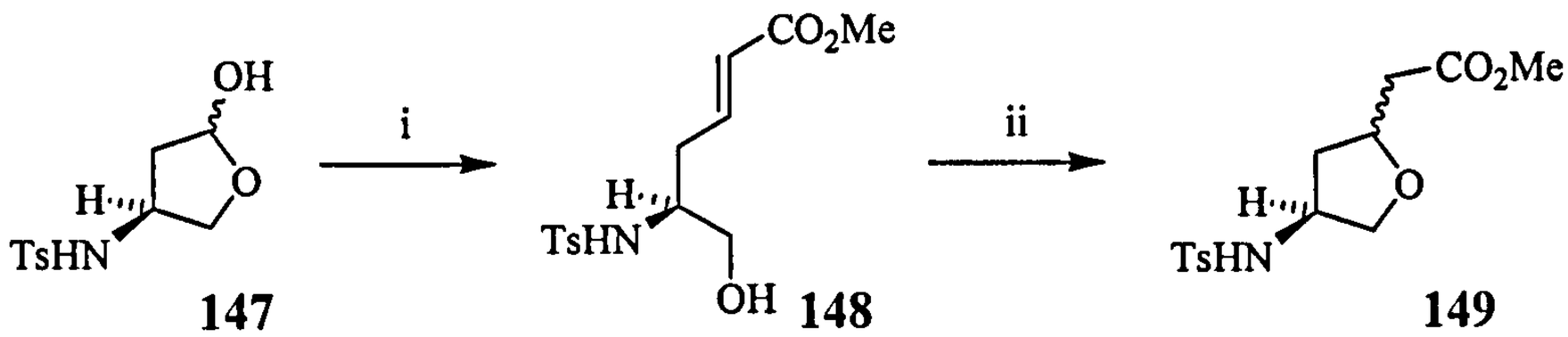


Scheme 42

The remaining question to be addressed in the synthesis design relates to when to introduce the C-5 guanidine moiety. Several strategies can be envisaged of which the most practical are: (i) introducing it early in the synthesis in a protected form, with mild deprotection late in the synthesis (i.e. after installation of the 1-azabicyclo-[3.1.0]hexane ring); (ii) introducing the guanidine late in the synthesis from the corresponding C-5 protected amine. We opted for the latter option, and decided to first establish a synthesis of **144** bearing a protected C-5 amino substituent.

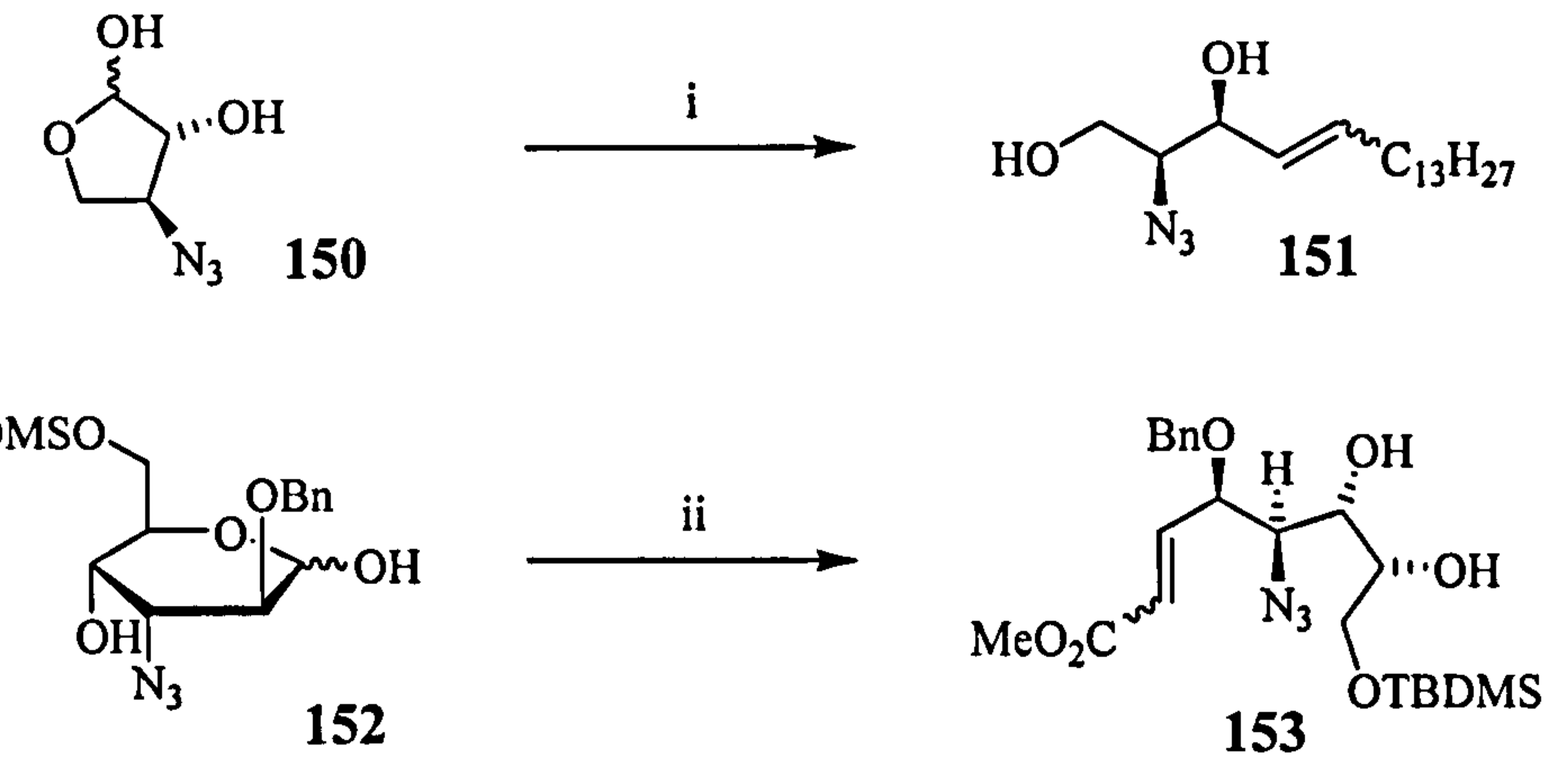
With respect to olefination of γ-lactols, a number of examples are known. Two are briefly highlighted herein. Rapoport showed that lactol **147** can be used in olefinations employing the Wittig or HWE reagents.[83] For example, under Masamune Roush conditions,[84] reaction with methyl diethylphosphonoacetate afforded unsaturated ester **148** in 71% yield. The modest yields observed were due to intramolecular Michael addition of the alcohol onto the olefin to form

tetrahydrofuran **149**. This was confirmed by treatment of **148** with sodium hydride, which resulted in clean formation of this tetrahydrofuran in 89% yield (Scheme 43).



Scheme 43. *Reagents and conditions*: i) $(EtO)_2P(O)CH_2CO_2CH_3$, LiCl, $^iPr_2NEt$, CH_3CN, 71%; ii) NaH, 89%.

Several examples of Wittig olefinations of ylides with lactols containing azide groups were uncovered (Scheme 44).[85] These encouraged us to think that the chemistry outlined in Scheme 42 would be viable.

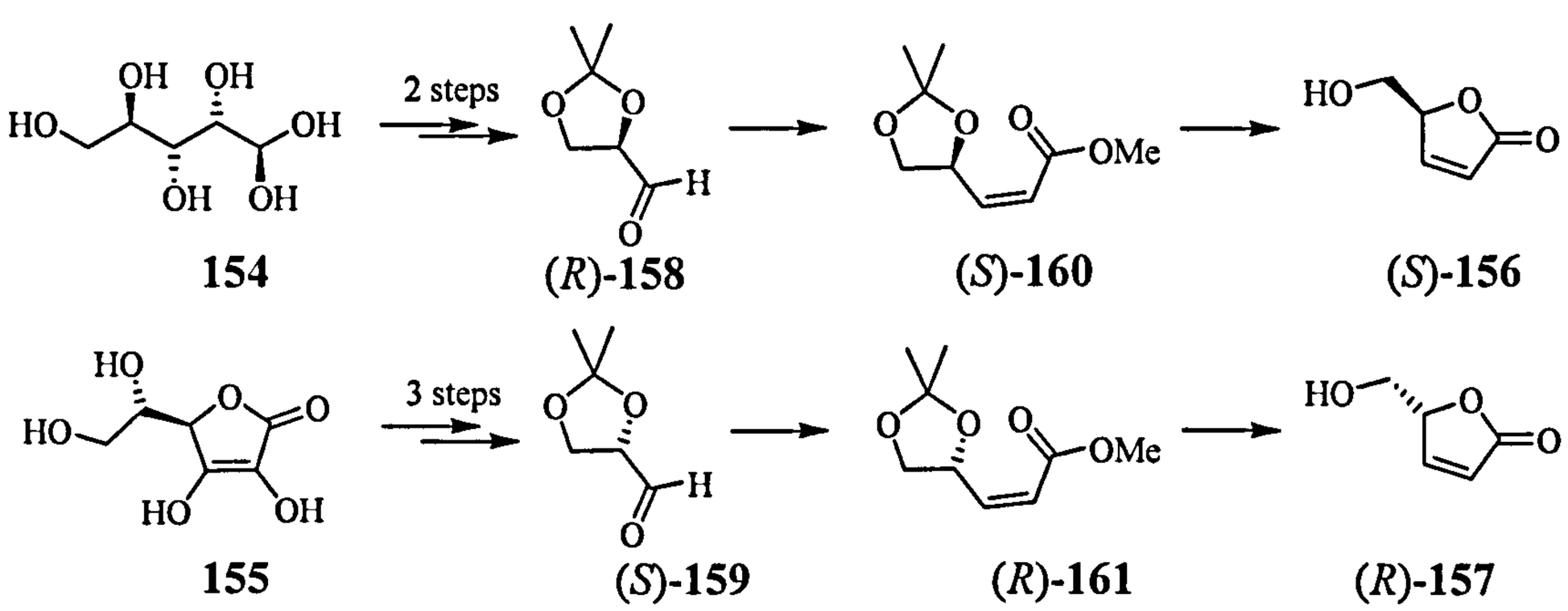


Scheme 44. *Reagents and conditions*: i) *n*-tetradecylphosphonium bromide (3.2 equiv.), *n*-BuLi (2.8 equiv.), THF, *cis*-**151** 24.4%; *trans*-**151** 6%; ii) $Ph_3P{=}CHCO_2Me$, PhH, 90 °C, 60% (1:1, *E*:*Z*).

This led us to design the route to the lactols using D-mannitol (**154**) and L-ascorbic (**155**) acid as starting materials. The route begins with the formation of lactones (*S*)-**156** and (*R*)-**157** *via* the D-(*R*)- and L-(*S*)-glyceraldehyde acetonide building blocks (*S*)-**158** and (*R*)-**159**, respectively.[86,87,88] These lactones are commercially available albeit at a prohibitive price (Aldrich, £27.20, 250 mg and Fluka, £65.60, 100 mg, for *S* and *R*, respectively). Since the absolute stereochemistry of the ring carbons in

ficellomycin is unresolved, it was important that access to either enantiomeric series could be realised in a predictable way.

Further manipulation of **156** into lactol substrates for olefination reactions is detailed in the following section.

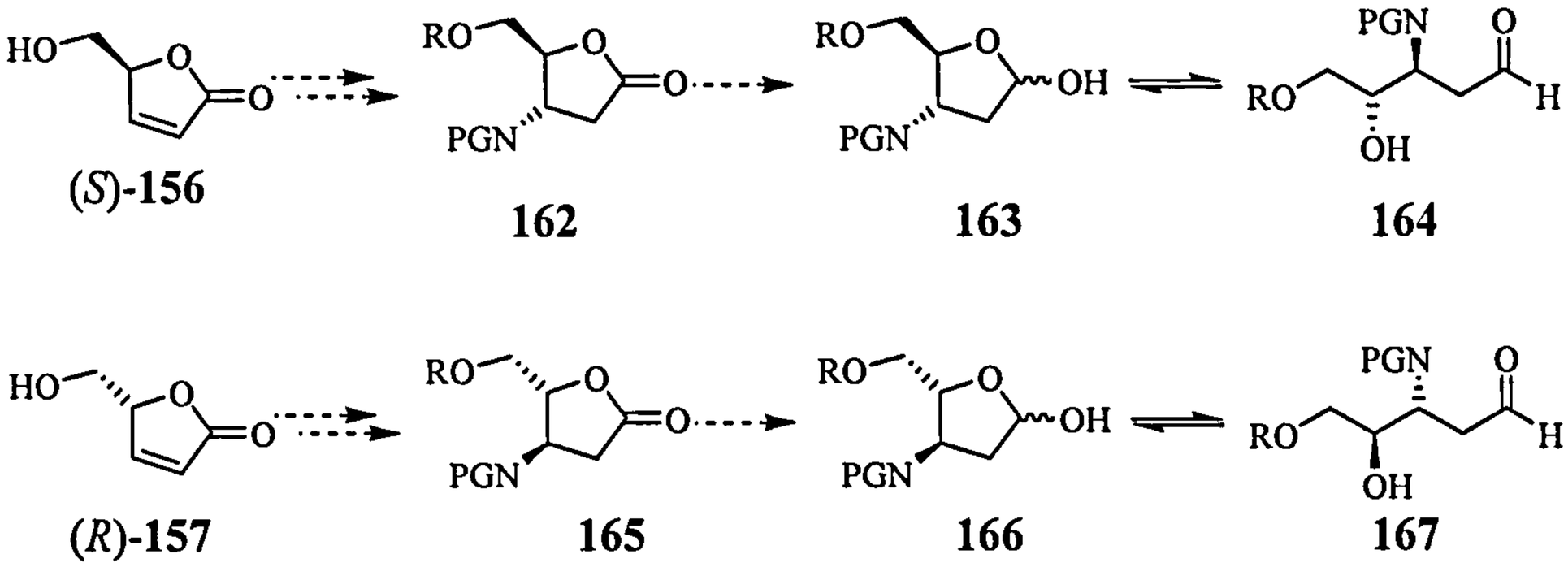


Scheme 45

The synthesis of enone (*S*)-**156** is reported to be straightforward. D-Glyceraldehyde acetonide (*R*)-**158** can be obtained from D-mannitol **(154)** in two synthetic steps namely, protection of the sugar and oxidative cleavage using sodium periodate (Scheme 45). The synthesis of the enantiomer (*R*)-**157** from L-ascorbic acid (**155**) is one step longer, since it requires the hydrogenation of L-ascorbic acid over palladium on carbon under high pressure followed by protection and oxidative cleavage to form L-glyceraldehyde acetonide (*S*)-**159**.[87] Other alternative synthetic routes to L-glyceraldehyde acetonide include using erythrulose as starting material and performing the oxidative cleavage using lead(IV) acetate[89] or sodium periodate.[90]

By use of a sterically hindered protecting group for the primary alcohol in (*S*)-156, we hoped to direct conjugate addition of an amine nucleophile to the *Si*-face to give

162 (Scheme 46). Subsequent reduction of the lactone to the lactol **163** would provide the anticipated dynamic equilibrium between the lactol and the desired aldehyde **164**. An identical approach could be adopted starting from (*R*)-**157**.



(*S*)-**156** **162** **163** **164**

(*R*)-**157** **165** **166** **167**

(where R and PG = protecting group)

Scheme 46

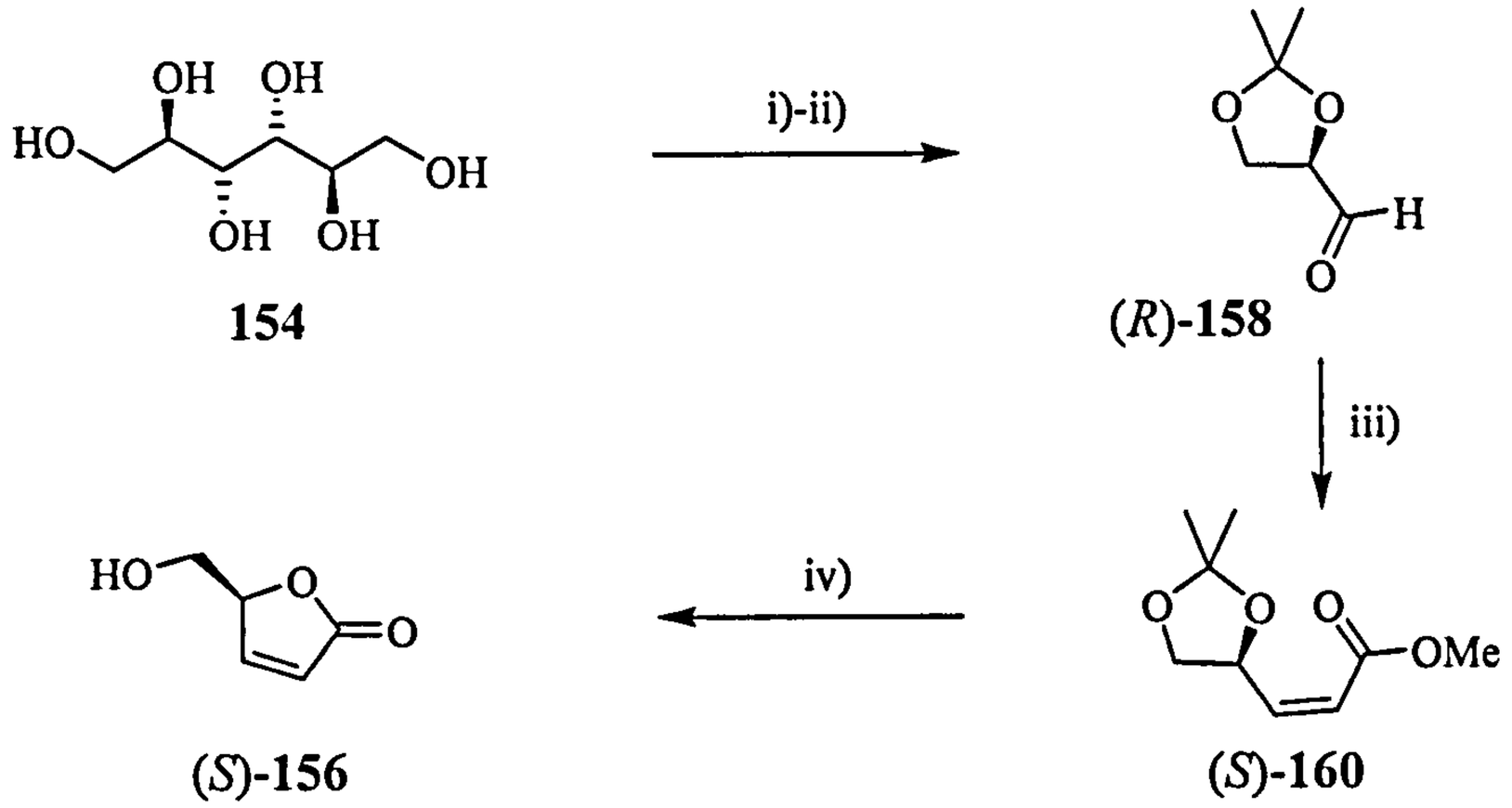
Since the absolute stereochemistry in the natural product is unknown, we decided to develop the synthesis from D-mannitol (**154**) as it is slightly shorter in the first instance (*vide infra*).

2.3. Stereocontrolled Synthesis of Aldehyde and Attempted Olefinations

The synthesis of enone (*S*)-**156** proved straightforward and it allowed us to obtain 73 g of D-glyceraldehyde acetonide (*R*)-**158** from 100 g of **154** in one day. However, (*R*)-**158** is highly unstable and prone to polymerisation. It is reported that the polymer can be cracked and subsequently used, but in our hands we found that cracking the polymer was not efficient with only about 60% of aldehyde being recovered.

Thus, D-glyceraldehyde acetonide (*R*)-**158** was freshly made and subjected to the olefination reaction immediately after distillation. In this way, aldehyde (*R*)-**158** was

prepared in a reproducible 70-73% yield. The olefination was uneventful giving (*S*)-**160** as an 8:1 mixture of isomers in favour of the required (*Z*)-form. Subsequent cyclisation to enone (*S*)-**156** was achieved using Dowex 50W-X8 according to the method developed by Sugisaki *et al.* (Scheme 47).[88]

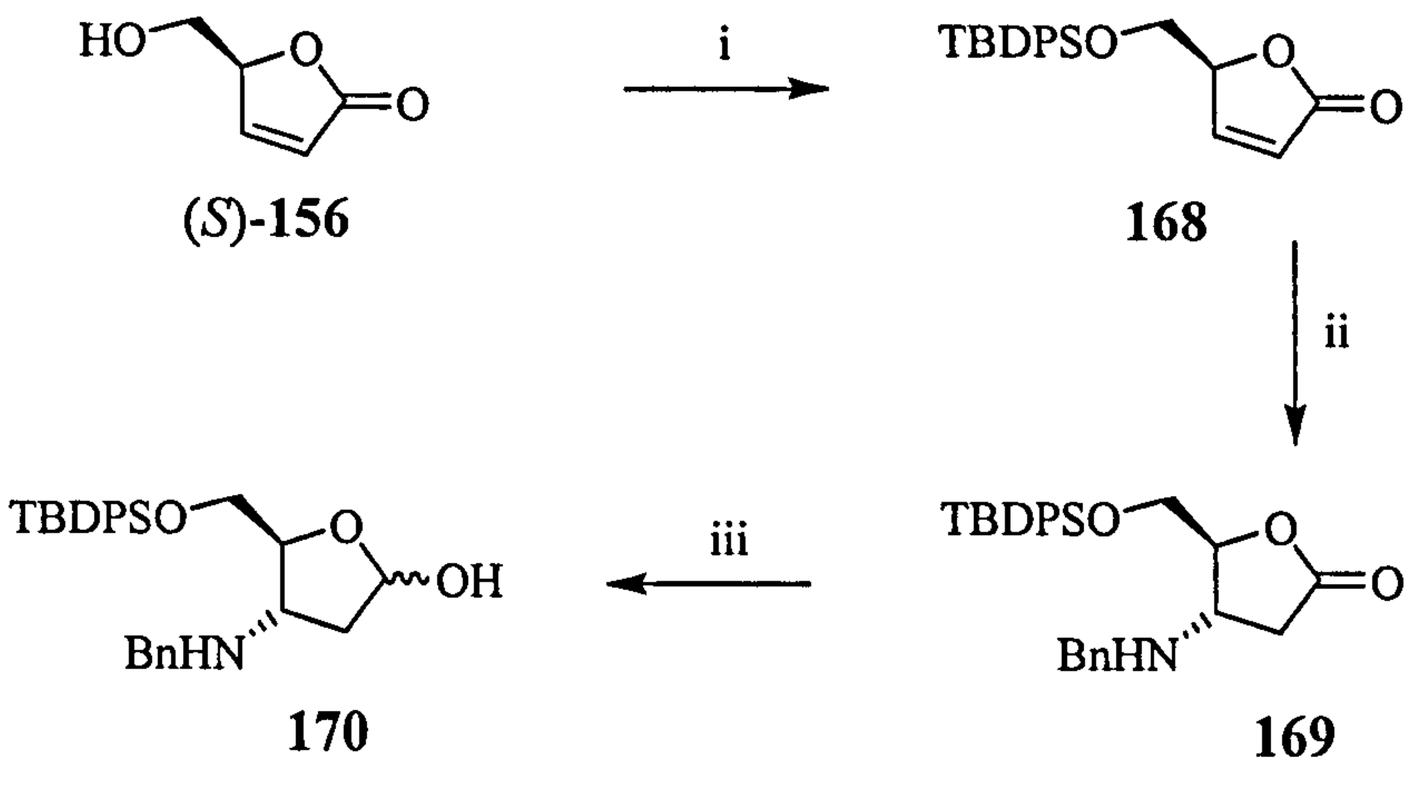


154 (*R*)-**158** (*S*)-**160** (*S*)-**156**

Scheme 47. *Reagents and conditions*: 2,2-DMP, 1,2-DME, $SnCl_2$, pyr., *quant.*; ii) $NaIO_4$, $NaHCO_3$, CH_2Cl_2, 0 °C → RT, 73%; iii) $(CH_3)_3P{=}CHCO_2CH_3$, MeOH, -10 °C, 86% (8:1, *Z*:*E*); iv) Dowex 50W-X8, EtOH, RT, 99%.

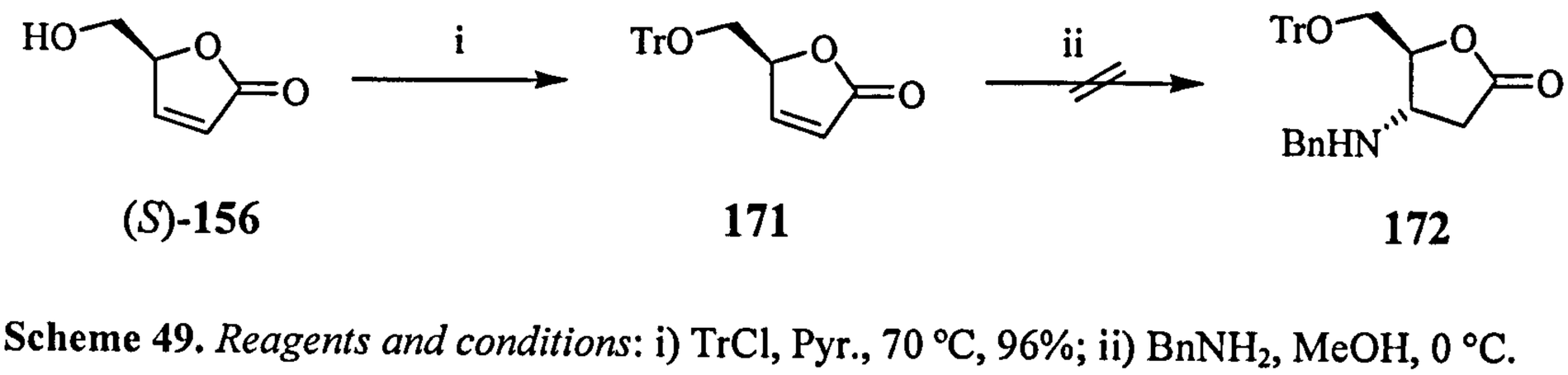
Perlmutter had shown that lactone (*S*)-**156**, after protection of the primary alcohol as a *tert*-butyldiphenylsilyl ether **168**, reacts with benzylamine in methanol, to give **169**.[91] They reported that lactone **169** was obtained in a disappointingly 43% yield over the 2 steps.

We re-examined this procedure on a small scale, but a similarly low 39% yield was obtained for **169** which was inconvenient at this early stage in the synthesis. Further reduction of this lactone to lactol **170** using DIBAL-H in THF at -78 °C proceeded in a modest 41% yield (Scheme 48).



Scheme 48. *Reagents and conditions*: i) $BnNH_2$, MeOH, 0 °C; (ii) $^tBuPh_2SiCl$, Imid., DMF, 48 h, 39% over two steps (*lit.* yield 43%); iii) DIBAL-H, THF, -78 C, 41%.

Next, we were drawn to the idea of using a trityl-protected lactone in this transformation. This might help block the top face of the enone and add crystallinity to the product, aiding product purification. The crystalline trityl-protected lactone **171** was prepared in 74% yield using a published method.[92] Addition of benzylamine to a solution of **171** in methanol at 0 °C did not show consumption of starting material even after three days (Scheme 49). Use of 4 equivalents of benzylamine and subjecting the mixture to reflux overnight led to a complicated mixture of products none of whom, as judged by TLC and ^{1}H-NMR, appeared to be **172**.

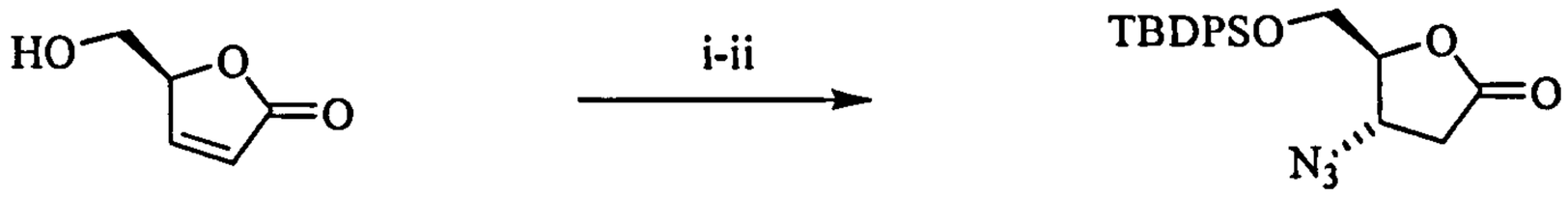


Scheme 49. *Reagents and conditions*: i) TrCl, Pyr., 70 °C, 96%; ii) $BnNH_2$, MeOH, 0 °C.

We postulate that there are two possibilities why this reaction failed. The first being that benzylamine is too large to add to the conjugated double bond adjacent to a highly sterically hindered centre; the second possibility may be that the enone is a poor Michael acceptor. This problem might be surmounted by activation of the

carbonyl through use of a protic or Lewis acid. Unfortunately, benzylamine would protonate or coordinate to the Lewis acid under these conditions. Hence, we sought alternative nitrogen nucleophiles for this transformation. The use of a protic acid seemed inappropriate if the trityl group were to be maintained as the alcohol protecting group. However, Chu, in the synthesis of anti-HIV nucleosides based on 3'-azido-3'-deoxythymidine (AZT),[93] had shown that TBDPS-protected lactone **168**, reacted with sodium azide (10 equiv.) and acetic acid (30 equiv.) in THF-water to give azido lactone **173** in 71% yield (Scheme 50). In this procedure, the acetic acid has a double function: since it has a pK_a of approximately 4.5 comparable to that of hydrazoic acid (pK_a 4.7), it generates hydrazoic acid *in situ*, in addition it activates the carbonyl group of the lactone *via* protonation. Although Chu reported that the reaction proceeded through an *anti*-1,4-addition, no further evidence was provided.

For safety reasons, we modified the procedure slightly, and sodium azide (30 equiv.) was added in small batches to avoid evolution of the hazardous hydrazoic acid in high concentrations. To this end, sodium azide was added portionwise over four days every twelve hours. The reaction was maintained under a slow flow of nitrogen which was purged through a potassium hydroxide scrubber. In this way, azido lactone **173** was obtained in 79% yield in crystalline form as a single diastereomer after column chromatography (Scheme 50). X-ray crystallography of a single crystal of **173** grown from diethyl ether confirmed that *anti*-1,4-addition had occurred (Figure 9).



(*S*)-**156** **173**

Scheme 50. *Reagents and conditions*: i) TBDPSCl, Imid., DMF, 96%; ii) NaN_3, CH_3CO_2H, THF:H_2O (1:1.3), 5d, 79% (lit. 71%).

Using trityl-protected lactone **171**, the corresponding azido lactone **174** was isolated in a reduced 52%, presumably due to the acid lability of the trityl group (Scheme 51).

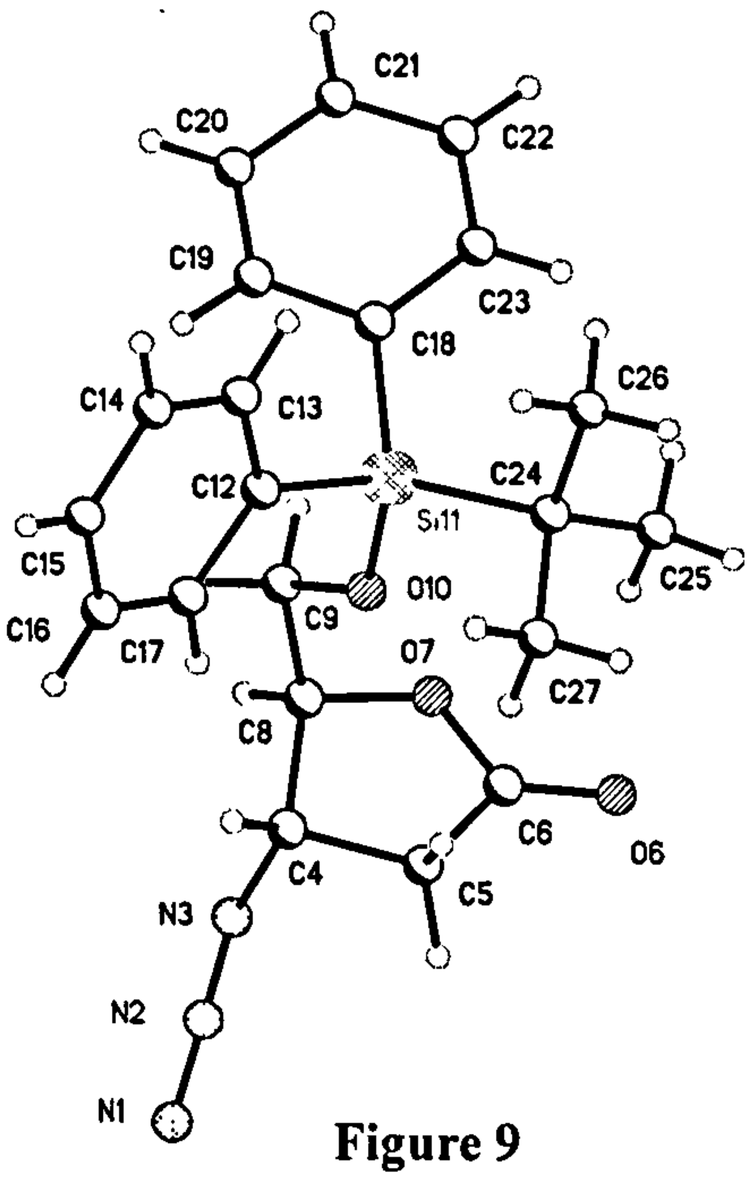
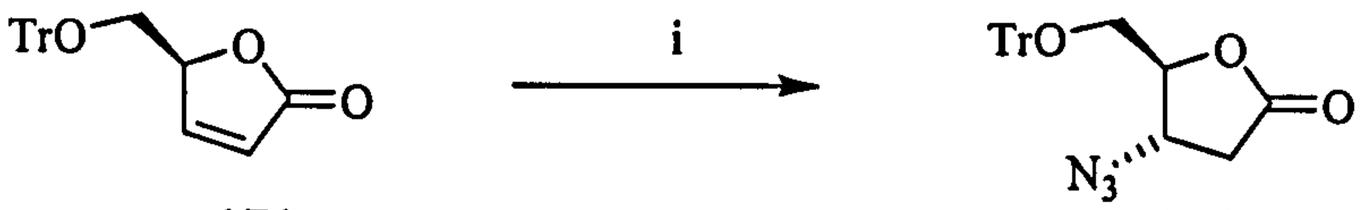


Figure 9

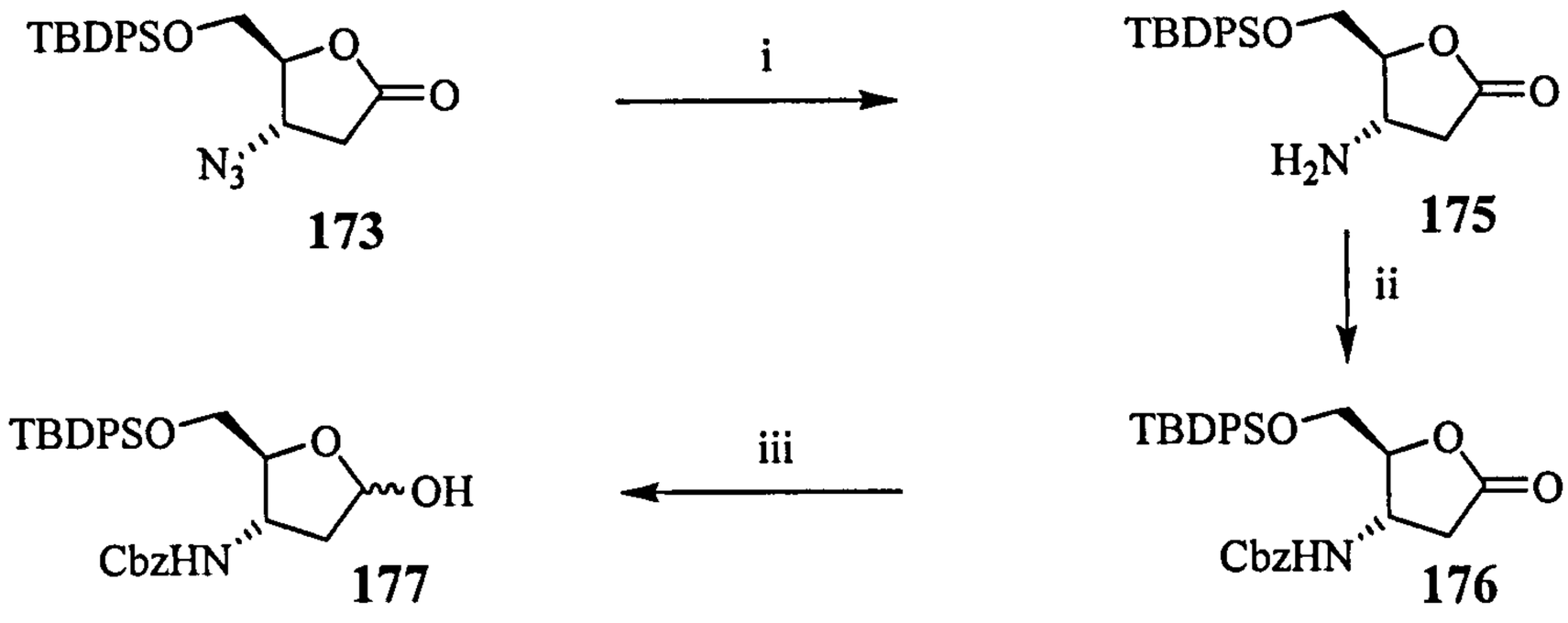
The azide in **173** was reduced to the amine **175** by hydrogenation and protected as the benzyloxycarbamate in 88% yield to give **176** over two steps. Reduction of lactone **176** to lactol **177** proceeded smoothly using DIBAL-H (1.5 equiv.) in THF at - 78 °C. This lactol was stable and could be purified by column chromatography, after which it was isolated in 89% yield as a 1.5:1 anomeric mixture. No peaks corresponding to the aldehyde tautomer were observed in the ^{1}H-NMR spectrum.



171 **174**

Scheme 51. *Reagents and conditions*: i) NaN_3, CH_3CO_2H, THF:H_2O (1:1.3), 5d, 52%

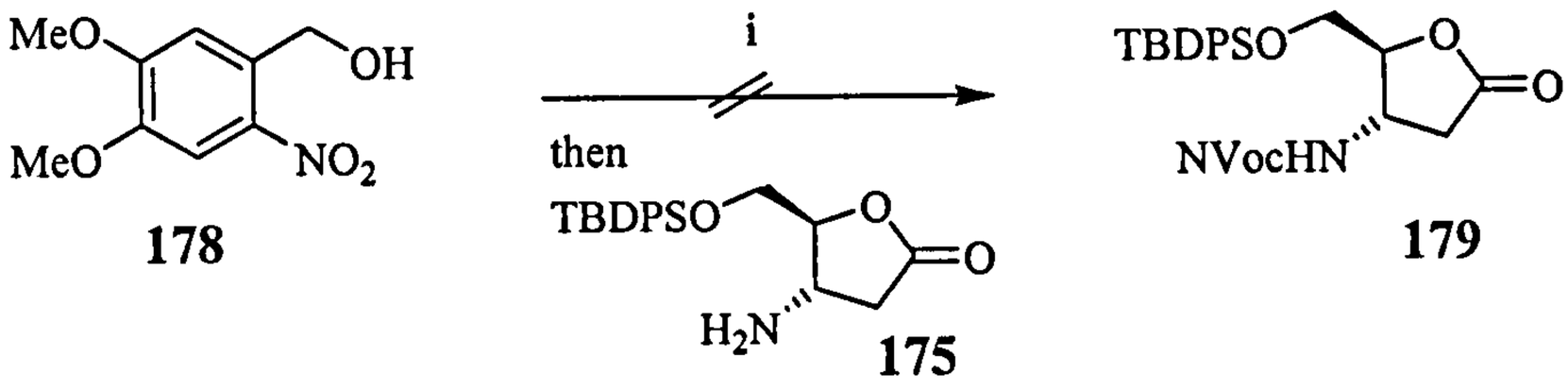
The Cbz protecting group was chosen as it resembles more closely the structure of photocleavable protecting groups which we intended to ultimately use in the total synthesis. Also, it was possible that the Cbz protecting group could itself be cleaved under UV irradiation.[94]



Scheme 52. *Reagents and conditions*: i) H_2, Pd-C, EtOAc, 90%; ii) CbzCl, Na_2CO_3, THF:H_2O (1:1), 98%; iii) DIBAL-H, THF, -78 °C, 89%.

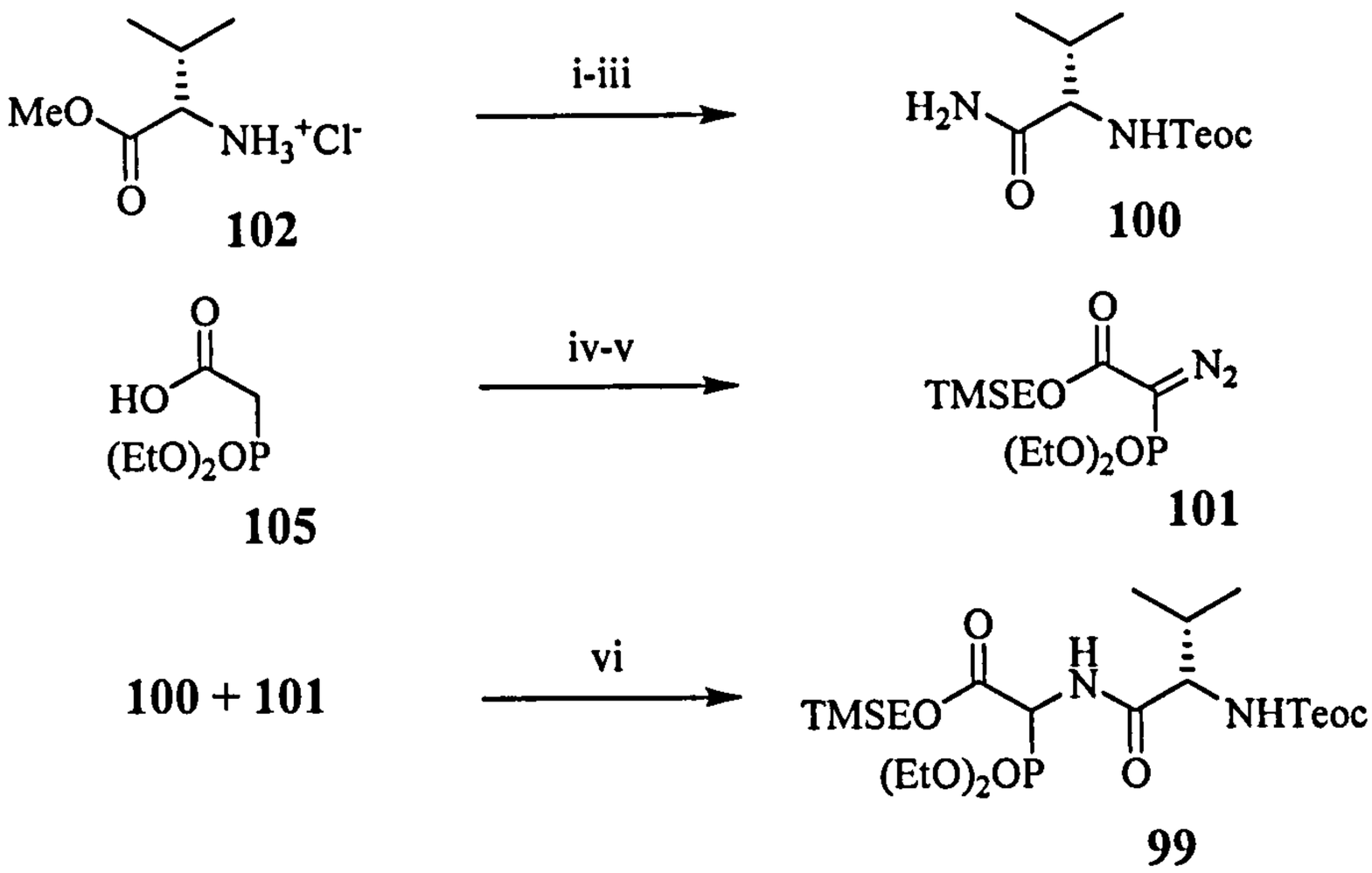
Use of a photocleavable protecting group at this amino centre was investigated briefly. It was assumed that if the guanidine was introduced late in the synthesis after assembly of the bicyclic core, it would be essential to further manipulate the system under neutral or slightly basic conditions. It was imagined that a photocleavable protecting group might be ideal, as it could be cleaved under very mild conditions.

Therefore, we attempted the introduction of 6-nitroveratryloxycarbonyl (NVoc) amino protecting group at the lactone stage **175** (Scheme 53).[95] Standard procedures involved treatment of 6-nitroveratryl alcohol (**178**) with phosgene gas but we opted to alternative means such as triphosgene[96] or 1,1'-carbonyl-di-imidazole.[97] However, these attempts met with failure and **179** was not formed in the reaction. This may be due to lower reactivity of these reagents compared to phosgene. Since using commercially available nitroveratryl chloroformate would be expensive at this stage and the increased sensitivity of intermediates would hinder the development of a route to the aldehyde, we decided to revisit this issue at a later time, if required.



Scheme 53. *Reagents and conditions*: i) $(Cl_3CO)_2CO$ or CDI, Et_3N, CH_2Cl_2; then **175**, Et_3N, DMAP, CH_2Cl_2.

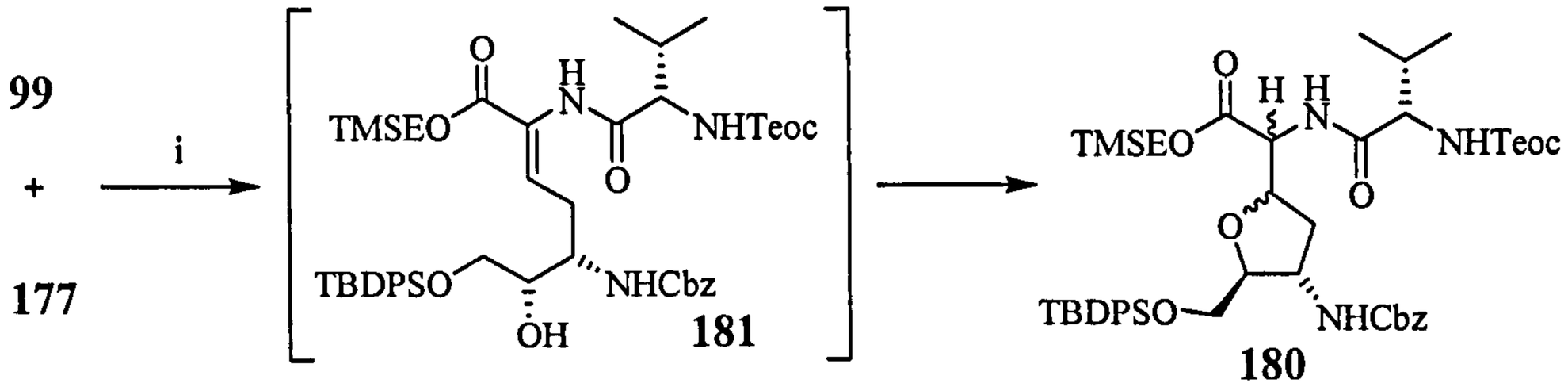
Lactol **177** was subjected to olefination with phosphonate **99**, prepared according to the method of Paumier and reproduced in similar yields (Scheme 54).[54]



Scheme 54. *Reagents and conditions*: i) Teoc-OSuc, 1,4-dioxane, H_2O, Et_3N; ii) 2M KOH, THF; iii) EtOCOCl, NH_3 aq., Et_3N, THF, 58% over the three steps;iv) DCC, DMAP cat., 2-trimethylsilylethanol, THF; v)Cs_2CO_3, 1-acetamido-4-benzensulfonyl azide, THF, 91% over two steps; vi) $Rh_2[OCO(CH_2)_6CH_3]_4$, $PhCH_3$, 110 °C, 48h, 79%.

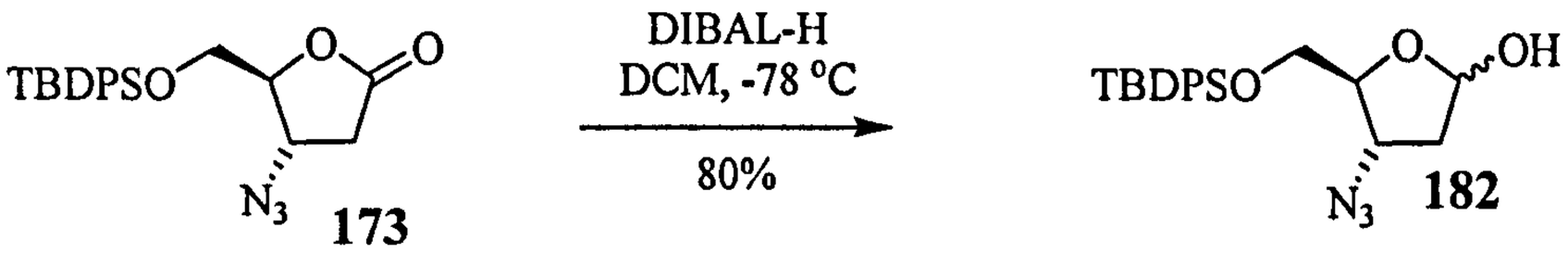
The olefinations were conducted under Masamune Roush conditions,[84] and also using DBN/DCM, for comparison. Similar results were obtained in both cases. Although a UV active spot was observed by TLC, perhaps indicative of enone formation, a series of other spots developed as the reaction progressed. The major product, tentatively assigned as **180**, was isolated in 52% yield. The ^{1}H-NMR spectrum was complex, perhaps indicating the formation of diastereomers. No olefinic signals were seen in the NMR spectrum, but it did possess the correct molecular weight for **181** (*m/z* = 693) (Scheme 55). When this product was

subjected to mesylation (MsCl, 1.3 eq.; Et_3N, 1.4 eq.) or to hydrogenation (H_2 1atm, 10% Pd/C, 10 wt%, EtOAc), no change occurred as indicated by NMR, reaffirming the absence of the free alcohol, or olefin. Similar cyclisation to tetrahydrofurans was reported by Rapoport (Scheme 43).[83]



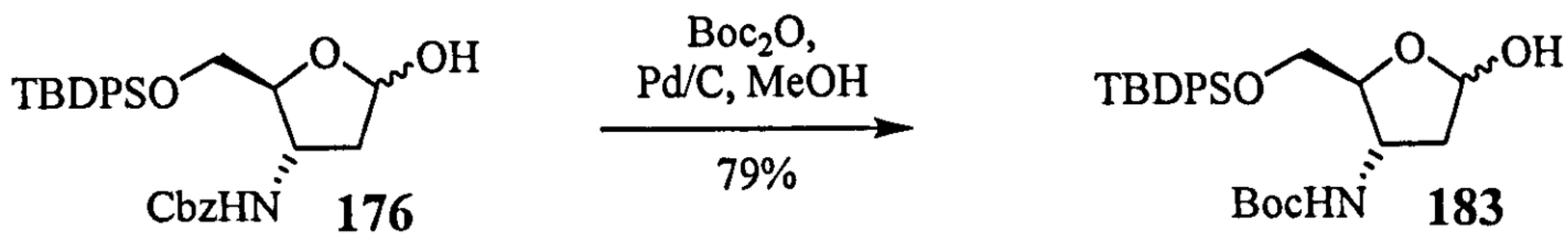
Scheme 55. *Reagents and conditions*: LiCl, Et_3N, CH_3CN, RT; or DBN, CH_2Cl_2, 10 °C-RT.

The fact that both, TBDPS and Cbz protecting groups were bulky led us to consider whether they might force the secondary alcohol to adopt a spatial orientation that would favour cyclisation to the tetrahydrofuran. Both substituents are locked in a favourable *anti* disposition upon cyclisation. To explore this idea further, three additional lactols were synthesised and evaluated in the Horner-Wadsworth-Emmons reaction. The compounds made were **182, 183** and **184** (Schemes 56 to 58). Azido lactol **182** being made by simple DIBAL-H reduction of lactone **173** (Scheme 56)



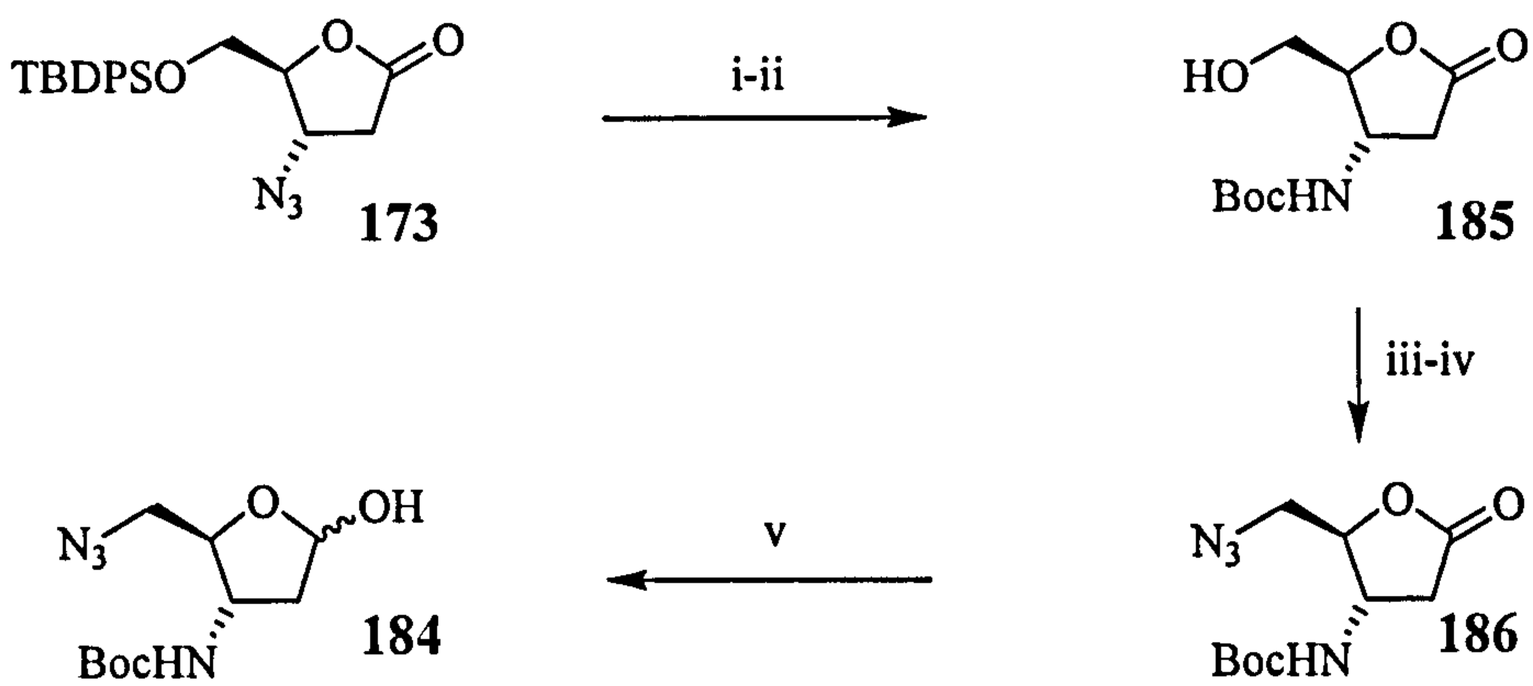
Scheme 56

Boc-protected lactol **183** was conveniently made by hydrogenolysis of **176** and *in situ* protection with Boc anhydride (Scheme 57).



Scheme 57

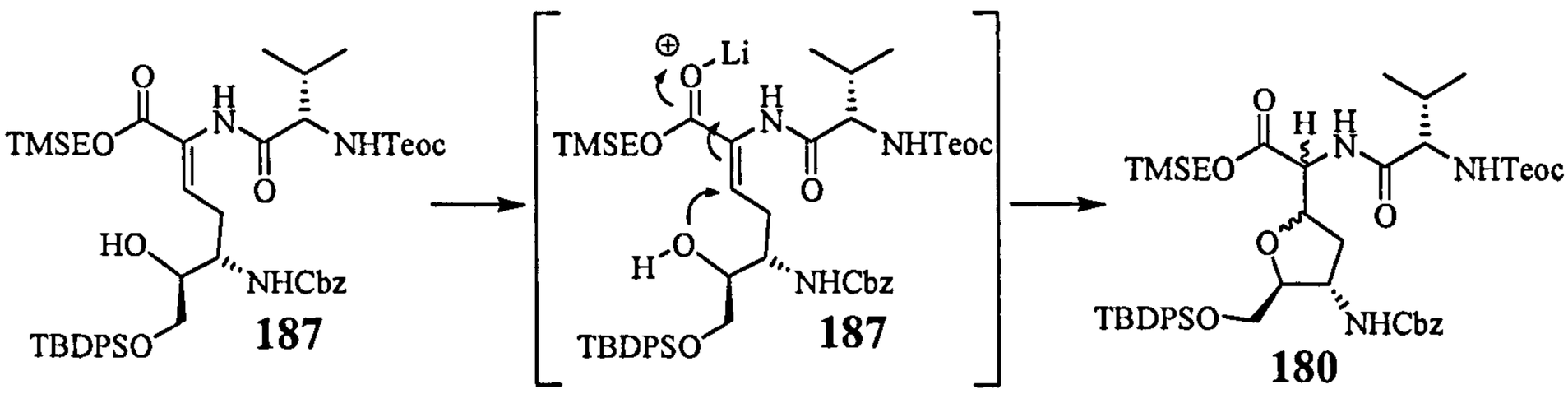
Azido lactol **184** was prepared uneventfully in five steps from **173** in 54% overall yield (Scheme 58). These involved reduction of azide **173** and Boc protection of the resulting free amine *in situ*, cleavage of the silyl ether to alcohol **185**, mesylation and displacement with azide. The resulting lactone **186** was then reduced to the corresponding lactol **184** using the same conditions as previously described.



Scheme 58. *Reagents and conditions*: i) Boc_2O, H_2, 10% Pd/C, EtOAc, 72%; ii) TBAF, THF, 0 °C, 91%; iii) MsCl, Et_3N, CH_2Cl_2, 0 °C → RT; iv) NaN_3, DMF, 70 °C, 84% over two steps; v) DIBAL-H, CH_2Cl_2, -78 °C, 98%.

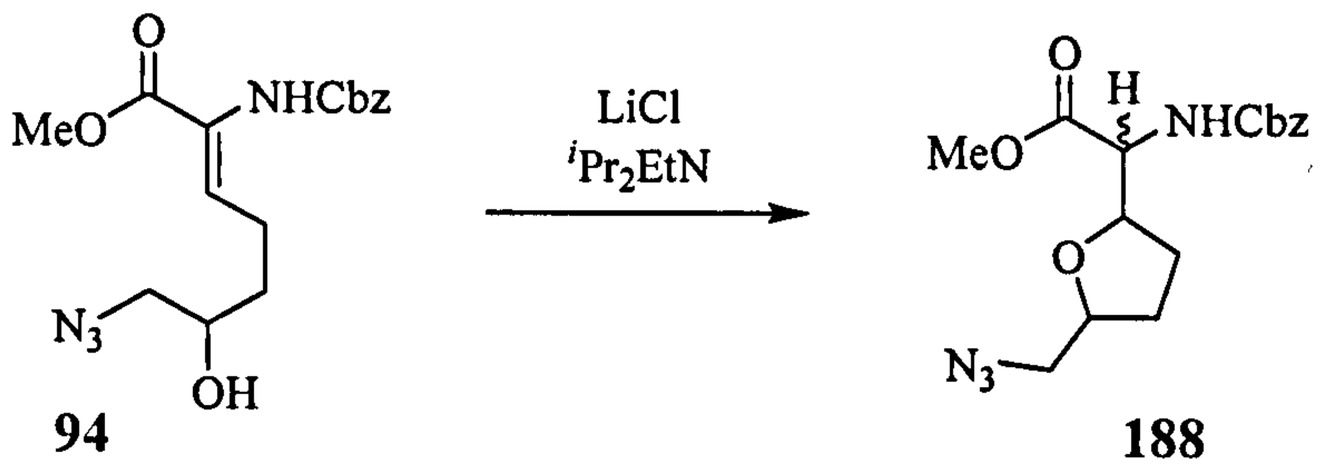
Unfortunately, Horner-Wadsworth-Emmons reactions with **182-184** were disappointing. Olefination of lactols **182-184** and phosphonate **99**, using DBN in dichloromethane or alternatively potassium carbonate in DMF led to complex mixtures. LC-MS analysis of olefination of **184** and **99** indicated the presence of components having the correct mass (*m/z* = 658) for the alkene or cyclised tetrahydrofuran, however, during the reaction, the concentration of UV-active species, which are presumed to be alkene, decreased while the concentration of four UV-inactive species, which could correspond to the four possible tetrahydrofuran diastereomers, appeared to increase with time.

The bases employed i.e. DBN and Hünig's base, are weak, and we were initially surprised that spontaneous cyclisation occurred. Of course, under Masamune Roush conditions, the lithium cation forms a tight complex with the β-ketophosphonate facilitating deprotonation of the phosphonate using a weak base. Such a mechanism might explain the observed propensity for THF formation, as the lithium cation might act as a simple Lewis acid, activating the acceptor for Michael addition (Scheme 59).



Scheme 59

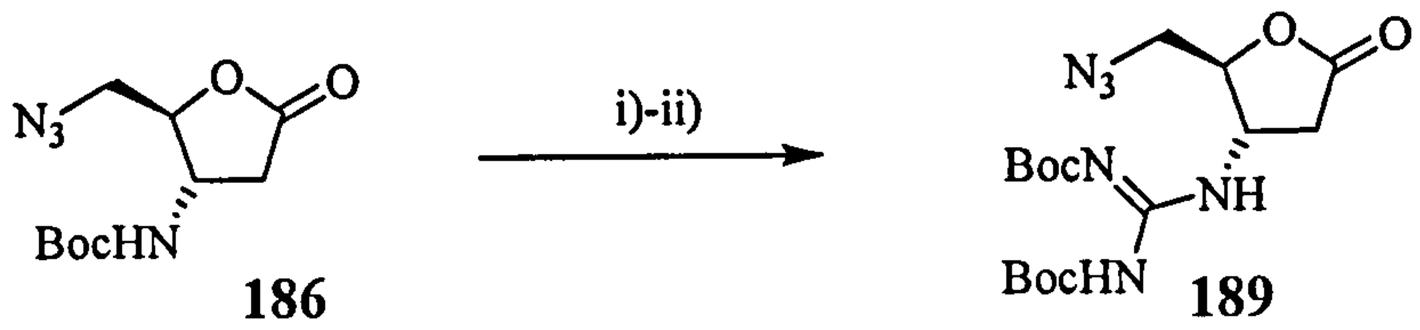
To test this idea, we subjected azido alcohol **94** to the olefination conditions. Again, a complicated mixture of products was observed (m/z = 348), which we attribute to the tetrahydrofuran **188** formation (Scheme 60). At this point, it seemed preferable to lengthen the route and arrive at the olefination step with an open chain aldehyde in which the C-4 hydroxyl group is protected.



Scheme 60

At this juncture, we tested the replacement of the C-5 amino substituent of **86** by a protected guanidine. This can be readily realised at the lactone stage using

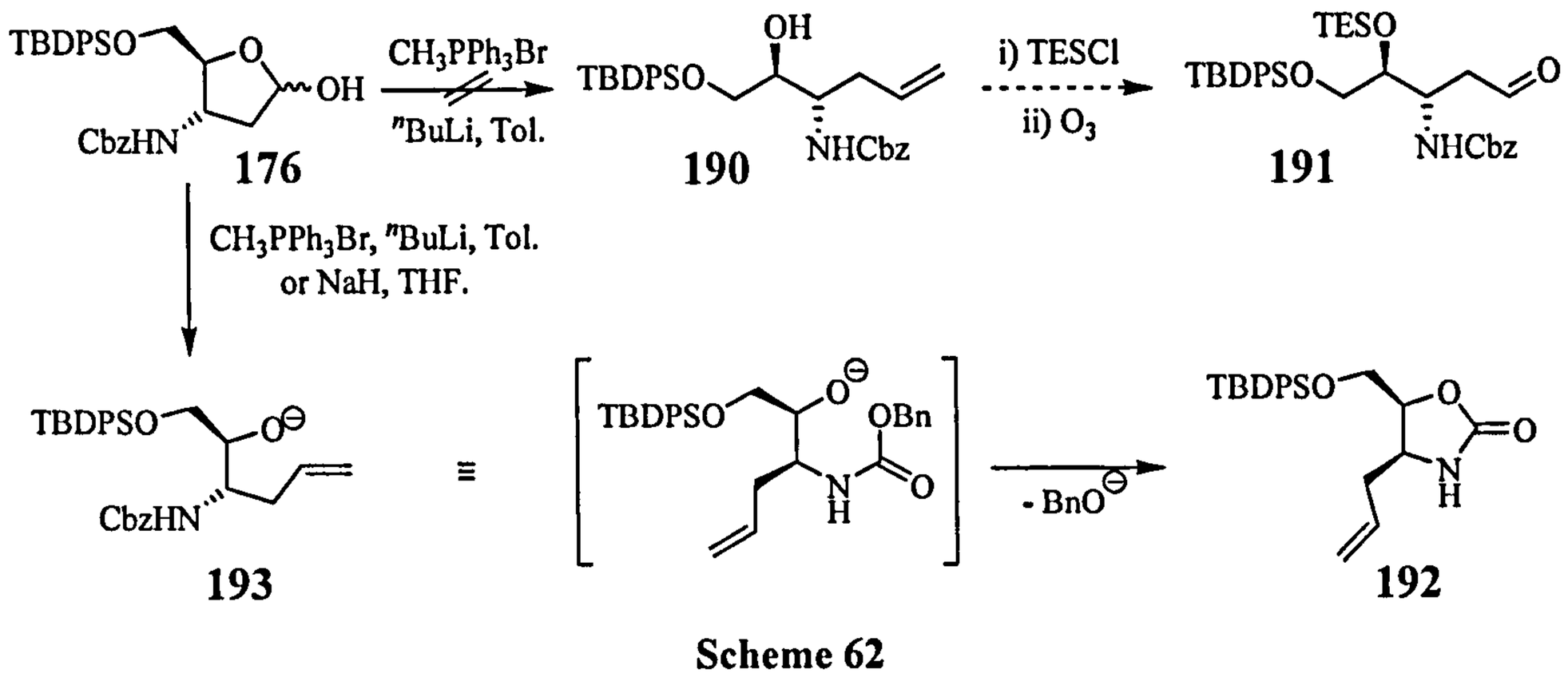
Goodman's reagent in good yield to the guanidine containing lactone **189** (Scheme 61).[8]



186 **189**

Scheme 61. *Reagents and conditions*: i) TFA, CH_2Cl_2, 0 °C; ii) Goodman's reagent, Et_3N, CH_2Cl_2, RT, 16 h, 91% over two steps.

Initially, we attempted to form terminal olefin **190** by reaction of lactol **176** with triphenylphosphonium bromide in the presence of *n*-butyllithium. We envisaged that **190** could be transformed into aldehyde **191** by subsequent protection and ozonolysis (Scheme 62) Unfortunately, the Wittig reaction did not afford the expected terminal olefin, but an oxazolidinone **192** *albeit* in low purity, as a result of the formed alkoxide ion **193** attacking the carbonyl centre of the carbamate. Using NaH in THF, it was possible to synthesise **192** in 45% isolated yield. Related cyclisations have been observed.[98]



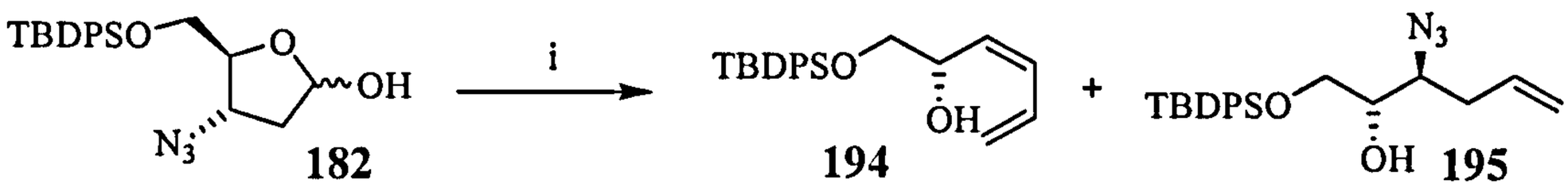
176 **190** **191**

193 **192**

Scheme 62

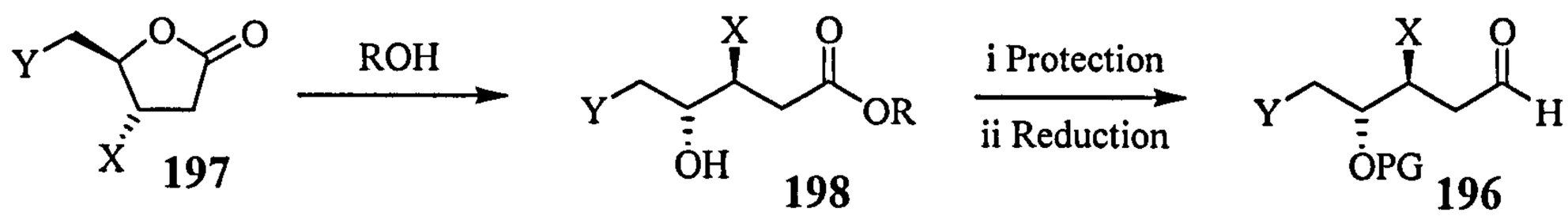
Whilst oxazolidinones can, after N-Boc protection, be ring opened using cesium carbonate,[99] the increased number of steps that would be required meant this approach was not investigated further.

To overcome oxazolidinone formation, we explored the use of azido lactol **182**. In this case, the aldehyde group could be observed by ^{1}H-NMR spectroscopy as a minor component (aldehyde:lactol; 1:26). Upon subjection of lactol **182** to Wittig olefination, (1,3*Z*)-diene **194** was isolated as the major product (30%) (Scheme 63). The stereochemistry was assigned on the basis of $J_{2,3}$ coupling constant ($J_{2,3}$ = 10.8 Hz). Clearly, the basicity of the reaction mixture had promoted elimination of the azide to form the diene. Alkene **195** was also recovered, however in a very low 1.4% yield. A third compound was also isolated in 18% yield, although its structure was not elucidated.



Scheme 63. *Reagents and conditions*: i) Ph_3PCH_3Br, ^{n}BuLi, toluene, 0 °C, **194** (30%), **195** (1.4%).

To overcome these problems, we decided to examine an alternative route to the open chain aldehyde **196** required for the Horner-Wadsworth-Emmons reaction. Ring opening of the lactone **197** to the *γ*-hydroxy ester **198**, and protection of the resultant hydroxyl group prior to reduction was expected to allow access to the required aldehyde **196** (Scheme 64).

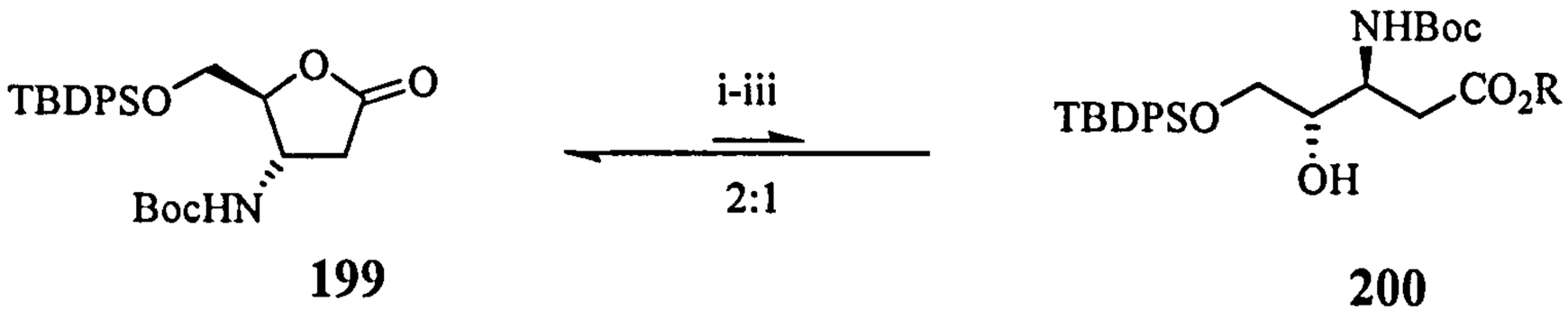


Scheme 64

Several examples of opening of lactones to *γ*-hydroxy esters are known. This can be achieved by hydrolysis to the *γ*-hydroxy acid and subsequent esterification with diazomethane derivatives[100] or alkylation with an alkyl halide.[101] Alternatively,

transesterification using an alcohol in combination with a Lewis acid[102] can be used which exploits the difference in reactivity between lactones and the corresponding open chain esters.

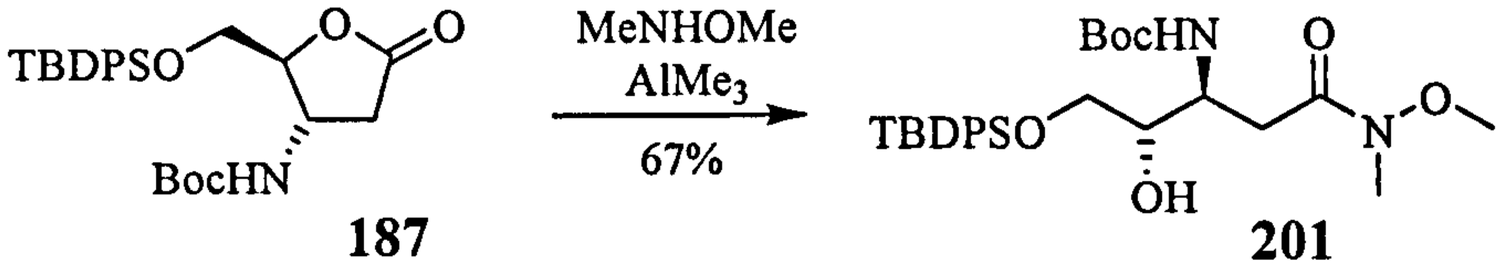
With this in mind, the transesterification of **199**, formed as an intermediate in the synthesis of **185** (Scheme 58), was attempted by stirring it in methanol in the presence of boron trifluoride etherate (-20 °C → RT). Analysis of the crude mixture by ^{1}H NMR revealed a 2:1 mixture of **199** and **200**, respectively (Scheme 65). Similar results were obtained when **199** was treated with acetyl chloride in methanol, or triethylamine in methanol. We were also unsuccessful in driving the reaction to completion using potassium hydroxide (reflux, 4 h) and methyl iodide (RT, 24 h) (Scheme 65).



199 **200**

Scheme 65. *Reagents and conditions*: a) MeOH, $BF_3 \cdot OEt_2$, -20 °C → RT, 3 h; b) AcCl, MeOH, overnight; c) MeOH, Et_3N, RT, overnight.

Next, we decided to explore the difference in reactivity of amides relative to esters. This is exploited in the efficient procedure developed by Weinreb for transforming esters into *N*-methoxy-*N*-methylamides.[103] Since amides are typically more stable than the corresponding esters, their formation should be essentially irreversible. γ-Lactones have been opened using *N*-methoxy-*N*-methyl amine in good yields, to the corresponding γ-hydroxy amides.[104] When lactone **199** was treated with trimethylaluminium and *N*-methoxy-*N*-methyl amine, amide **201** was produced in an encouraging 67% yield after column chromatography (Scheme 66).

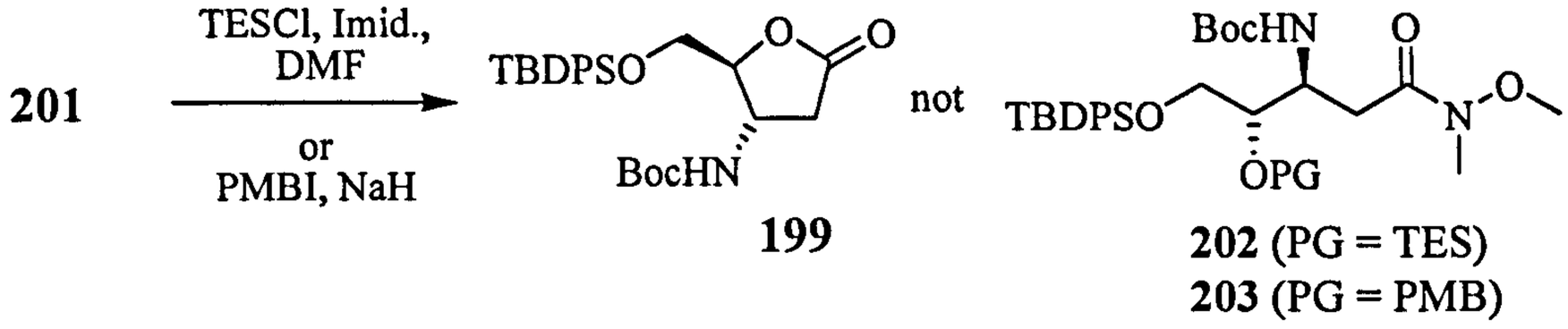


187 **201**

Scheme 66

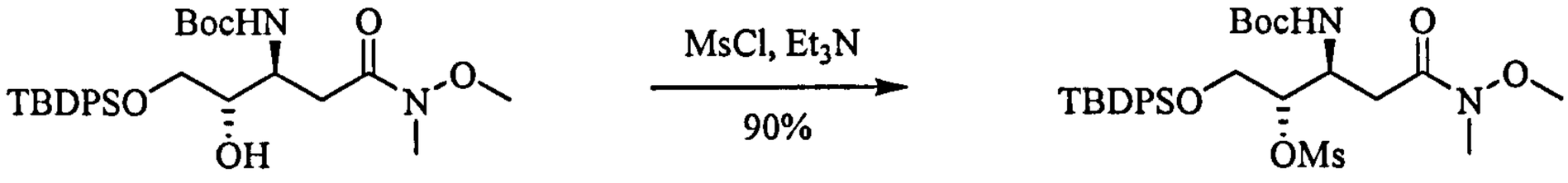
Next, protection of the resulting alcohol was examined. In considering suitable protecting groups, we needed to take into account their stability to DIBAL-H reduction and Horner-Wadsworth-Emmons olefination conditions, prior to deprotection and transformation to an azide. Triethylsilyl or *p*-methoxybenzyl ethers seemed appropriate choices since they can be cleaved under mildly acidic or oxidative conditions, respectively, and would be expected to be stable under the reaction conditions required for the reduction/Horner-Wadsworth-Emmons reaction.

Protection of the secondary alcohol of **201** was attempted using triethylsilyl chloride and imidazole in DMF,[105] and alternatively, by subjecting the alcohol to *p*-methoxybenzyl iodide, formed *in situ* by reacting *p*-methoxybenzyl bromide, sodium hydride and tetra-*n*-butyl ammonium iodide (Scheme 66).[106] In both cases, only the γ–lactone **199** was observed with none of the required ethers (**202** or **203**) being observed. In the case of the silyl protection, the silyl chloride presumably acts as a Lewis acid activating the carbonyl group and making it susceptible to nucleophilic attack by the alcohol. In the case of the etherification with PMBI, the deprotonated alcohol is sufficiently nucleophilic to add to the carbonyl group, yielding the unwanted lactone after ejection of NaNMe(OMe).



Scheme 67

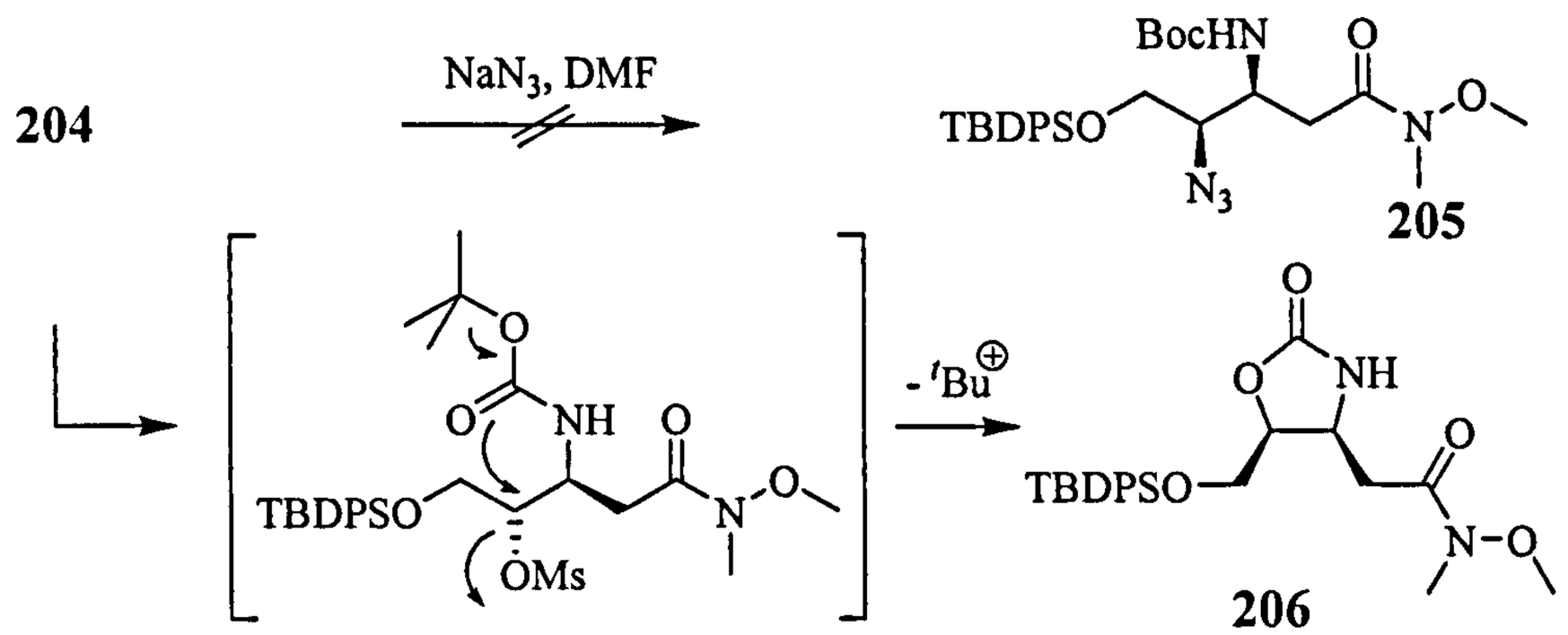
Clearly, milder conditions were required. Moreover, since protection of alcohol would add steps to the synthesis, we were drawn to the idea of converting it to the azide via the corresponding mesylate. Gratifyingly, mesylation of alcohol **201** proceeded uneventfully providing **204** in 90% yield (Scheme 68).



201 **204**

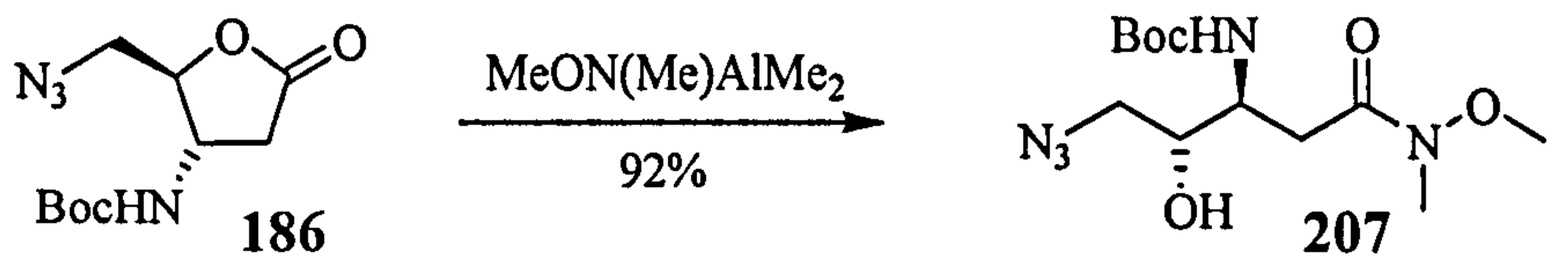
Scheme 68

Mesylate **204** was stirred in DMF with sodium azide at 50 °C overnight, however the reaction was very slow so the temperature was raised to 95 °C. After 4 hours at this elevated temperature, all the starting material was consumed. Unfortunately, the major product obtained after column chromatography had a molecular weight (m/*z* = 457) inconsistent with simple S_N2 displacement of the mesylate by azide to form **205**. In addition, no signals attributable to the *tert*-butyl carbamate group could be seen in the ^1H NMR spectrum, and no azide stretch was witnessed by IR spectroscopy. Based on these data, we propose that **204** undergoes an intramolecular reaction leading to oxazolidinone **206**. Indeed, when **204** was stirred in neat DMF at 95 °C, the same oxazolidinone was formed, confirming no involvement of sodium azide in the reaction (Scheme 69).



Scheme 69

As we had lactone **186** to hand, we subjected it to the same sequence of reactions. Thus treatment of lactone **186** with trimethyl aluminium and *N*-methoxy-*N*-methyl amine gave Weinreb amide **207** in an excellent 92% yield (Scheme 70). As an aside it is noteworthy that Weinreb amide **207** can be obtained in a good state of purity after filtration through a short pad of silica following workup. This is convenient and desirable, since on a large scale, purification by conventional silica gel chromatography gives rise to significant amounts of lactone **186**, decreasing the isolated yield.

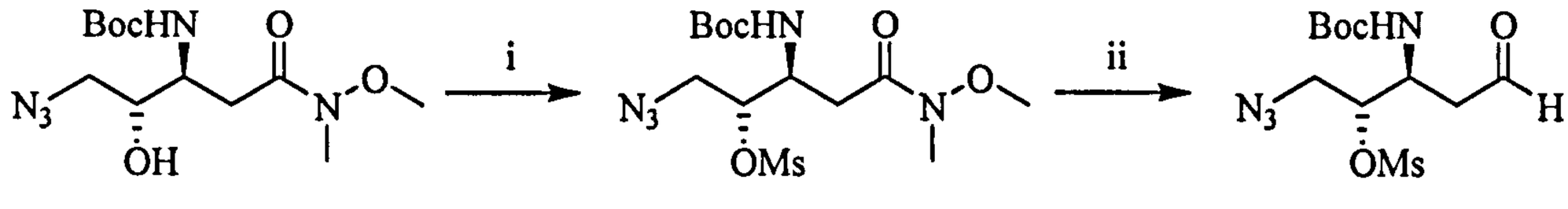


Scheme 70

At this point, we again were confronted with the problem of protecting the C-4 hydroxyl group. A series of protecting groups were tested, in the hope this system would be less prone to re-lactonisation. Under many conditions tested (PMBCl, NaH, TBAI, THF; PMBCl, NaH, DMF; PMBBr, NaH, DMF; TESCl, Imid., DMF; TESCl, Et_3N, DMAP, DCM; TESOTf, Pyr., MeCN/Et_2O) the lactone **186** was again produced as the sole product. Attempted tritylation (TrCl, Et_3N, DMAP, DCM) led

to complete recovery of starting materials whereas efforts to introduce a THP ether at C-4 (DMP, *p*-TSA) led to a complex mixture of products.

Since the search for a protecting group was not fruitful, mesylation was attempted. Gratifyingly, mesylation of alcohol **207** afforded **208** in 75% yield. Further reduction of **208** to the aldehyde **209** proceeded in a reproducible 55% yield (Scheme 71). This reduction was found to be very sluggish with starting material (*ca.* 40%) recovered. Whilst inconvenient, this could then be recycled, increasing the yield to 95% based on recovered starting material. It is remarkable that total chemoselectivity is observed during this reaction, the mesylate does not undergo reduction to the corresponding alkane.

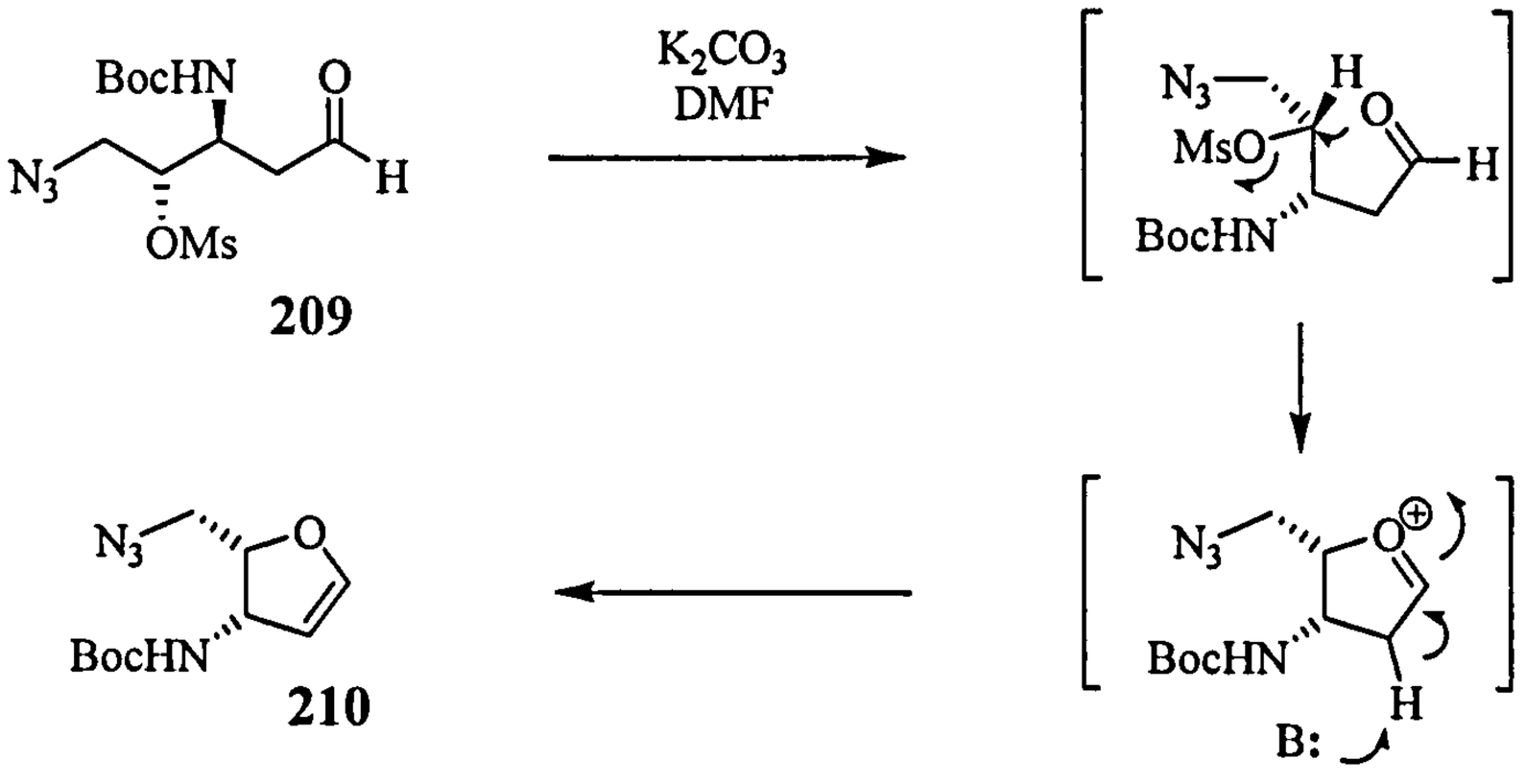


207 **208** **209**

Scheme 71. *Reagents and conditions*: i) MeNHOMe, $AlMe_3$, CH_2Cl_2, 0 °C→RT, 92%; ii) MsCl, Et_3N, DMAP, CH_2Cl_2, 75%; iii) DIBAL-H, THF, -78 °C, 55%.

With aldehyde **209** in hand, we could finally attempt the olefination reaction with phosphonate **99**. During the reaction of **209** with phosphonate **99** in DMF using K_2CO_3 as base, the aldehyde was consumed, as judged by thin layer chromatography. However, although 1:1 stoichiometry of phosphonate to aldehyde was used, it was clear that phosphonate **99** had not been completely consumed. Disappointingly, aldehyde **209** had undergone an intramolecular reaction to form dihydrofuran **210** in 26% yield (Scheme 72). The formation of this material was readily apparent from the distinctive alkene signals in the ^1H NMR spectra (δ = 6.42-6.40 and 4.92 ppm with J = 3.0 Hz) and ^{13}C (δ = 146.7; 100.5 ppm). Presumably it arises from displacement of the mesylate group by the carbonyl oxygen with inversion at C-4

followed by loss of a proton by the base to neutralise the charge. Treatment of aldehyde **209** in a suspension of potassium carbonate (1 eq.) in DMF in the absence of the phosphonate afforded the same product. Since the driving force for this elimination is the neutralisation of the oxonium cation, the use of weaker bases in this process was not expected to radically change the outcome.



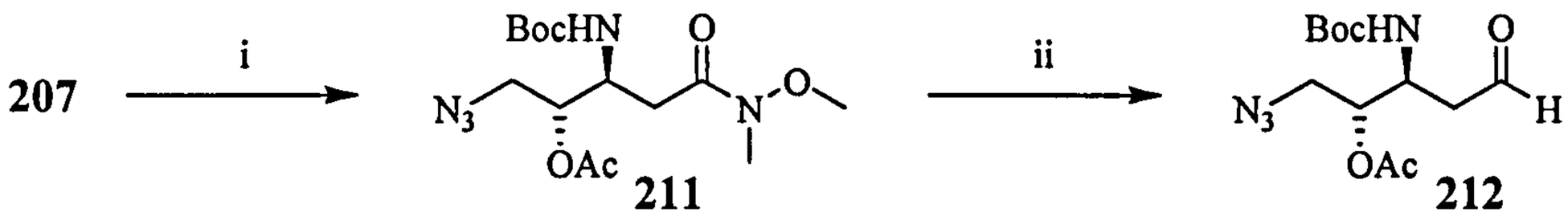
Scheme 72

Eventually, a satisfactory solution to these problems was forthcoming. In spite of all the difficulties encountered in the protection of amide **207** (*vide supra*), we finally established that an acetate group could be successfully introduced at C-4.

Weinreb amide **207** could be acylated to **211** in 94% yield under basic conditions using acetic anhydride and pyridine and a catalytic amount of 4-dimethylaminopyridine (Scheme 73). We cannot readily explain why this transformation, and indeed the mesylation to form **208**, are successful in light of all our earlier failures with seemingly similar reagents.

We were concerned that it would not prove possible to selectively reduce the Weinreb amide group of **207** in the presence of the acetate group. One can argue that the amide **207** will coordinate more strongly to DIBAL-H since it is more Lewis

basic, leading to the requisite chemoselectivity. Some experimental precedent in support of this hypothesis can be found in the literature.[107] We were greatly relieved that the reduction of **211** to aldehyde **212** proceeded in a very respectable 79% yield.



Scheme 73. *Reagents and conditions*: i) Ac_2O, Pyr., 4-DMAP, CH_2Cl_2, 0 °C → RT, 94%; ii) DIBAL-H, THF, - 78 °C, 79%.

In summary, we achieved the synthesis of a stable aldehyde **212** in 38% overall yield and 7 steps from azido lactone **173**. Although olefination reactions with earlier substrates (eg. **177, 182-184**) had not been successful, we were optimistic that similar problems could not be encountered with **212**. As we will see in the following section, this optimism was well founded.

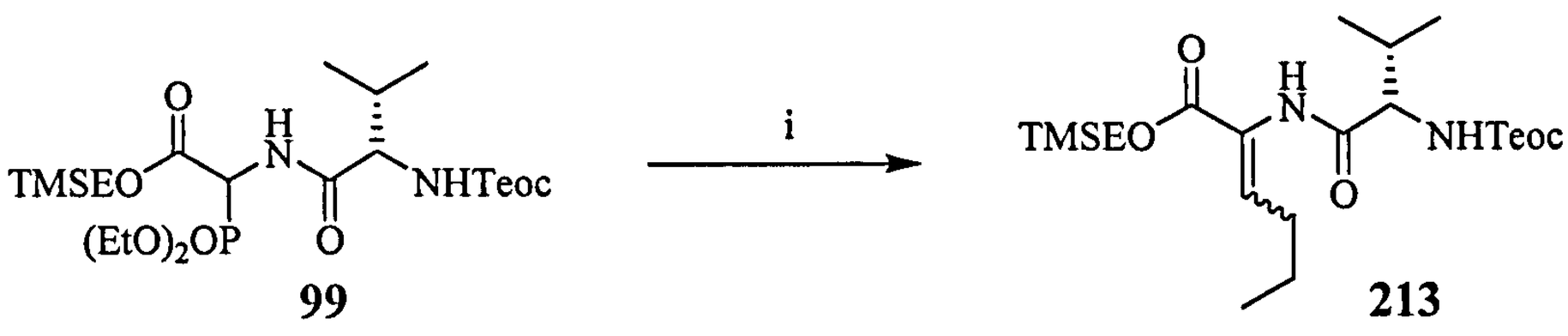
2.4. Olefination Reactions

Having developed a 7-step enantioselective route to a fully protected aldehyde **212** from lactone **173** (Section 2.3), we were now in a position to explore olefination conditions that would lead to the desired *Z*-alkene **144**.

2.4.1. Preliminary Studies

Before utilising aldehyde **212**, some preliminary experiments were conducted with phosphonate **99** with *n*-butyraldehyde (Scheme 74). Two sets of conditions were examined, namely DBN in dichloromethane and LiCl/^{i}Pr$_2$NEt in acetonitrile. When the reaction was performed under Masamune-Roush conditions both geometrical isomers were produced in a *ca.* 4:1 ratio as judged by ^{1}H NMR spectroscopy. After

column chromatography, (*Z*)- and (*E*)-**213** were isolated in 59 and 15% yields, respectively.



Scheme 74. *Reagents and conditions*: i) ^{n}PrCHO, LiCl, $^{i}Pr_2EtN$, CH_3CN, *Z*-**213** 59% and *E*-**213** 15%.

The geometries of the two olefins were established by nOe experiments. (*E*)-**213** shows a reciprocal enhancement (1.8-2.0%) between H-3 and the adjacent NH of the peptide chain. No such enhancement is observed in (*Z*)-**213,** but instead a reciprocal enhancement (2.8-3.6%) between H-4 and this NH is observed (Figure 10).

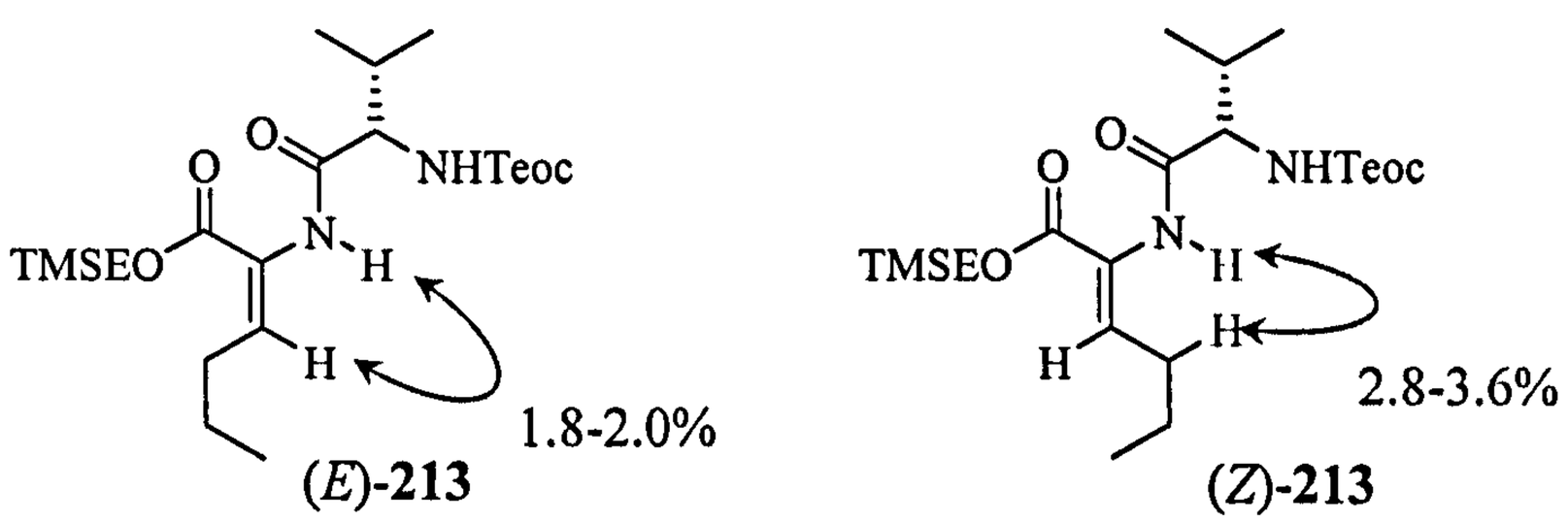
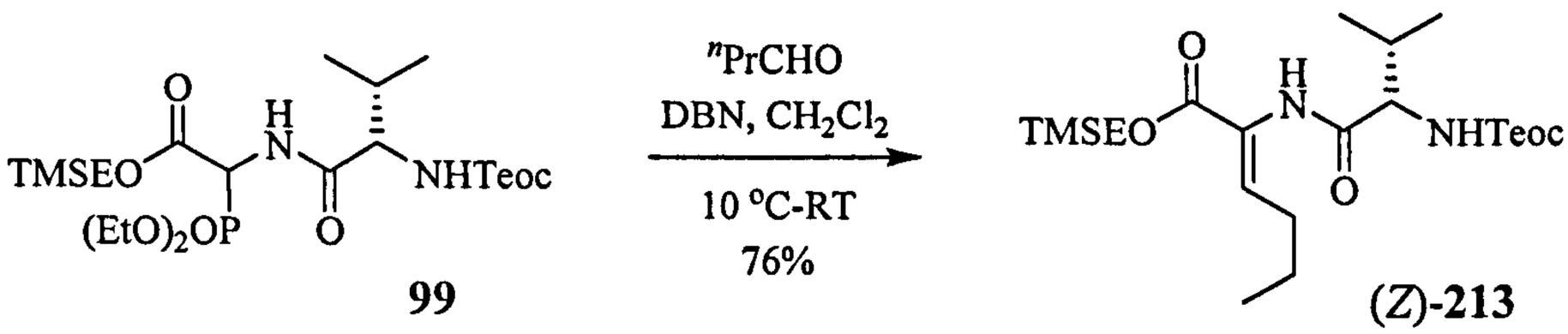


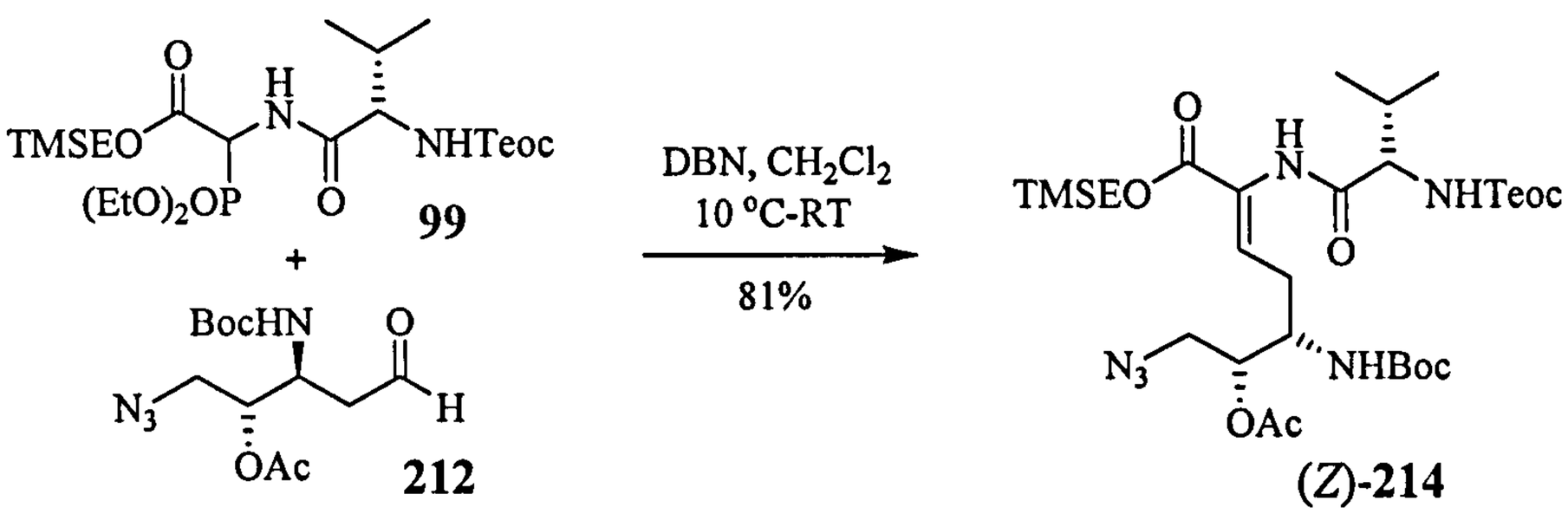
Figure 10

Using DBN in dichloromethane, only (*Z*)-**213,** was obtained in 76% yield after column chromatography (Scheme 75). The presence of the other geometrical isomer could not be detected in the crude reaction mixture.



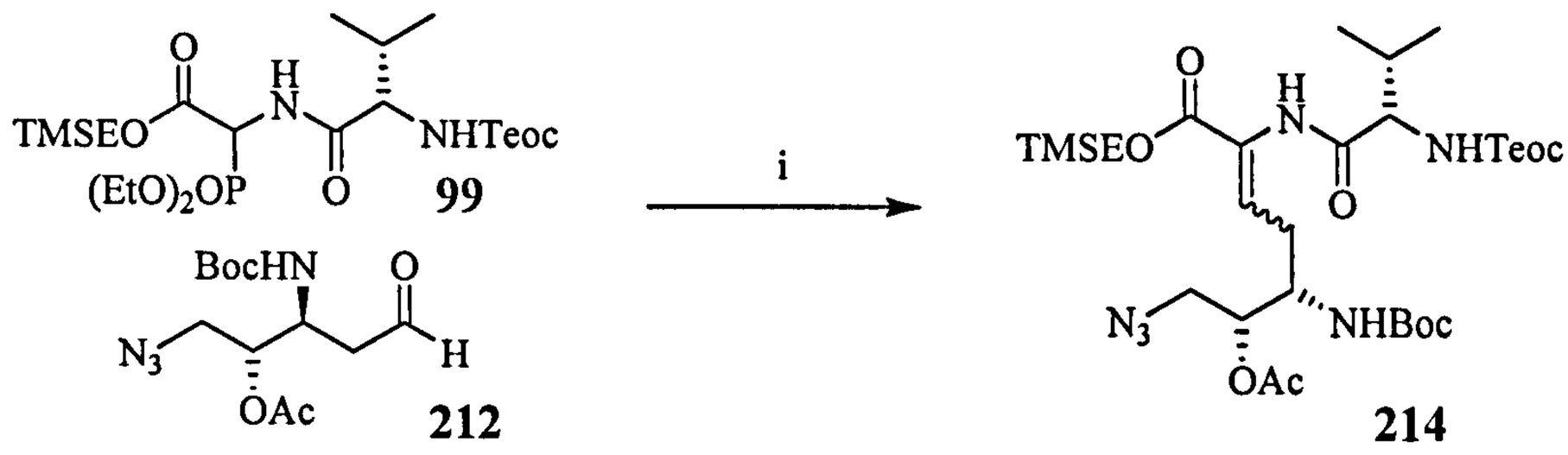
Scheme 75

We anticipated that using a fully protected aldehyde in the olefination, the problems seen using lactols **176** and **182-184** would no longer arise (Section 2.2). This hypothesis proved correct and when aldehyde **212** was reacted with phosphonate **99** using DBN in dichloromethane, only the *Z*-isomer was formed and after column chromatography, it was isolated in 81% yield (Scheme 76).



Scheme 76

To confirm the Z-selectivity of this reaction, this olefination was repeated using the less stereoselective Masamune-Roush conditions. Under these conditions, both geometrical isomers were obtained in 5:1 *Z*:*E* ratio and isolated in 51% and 11% yields, respectively, after column chromatography (Scheme 77).

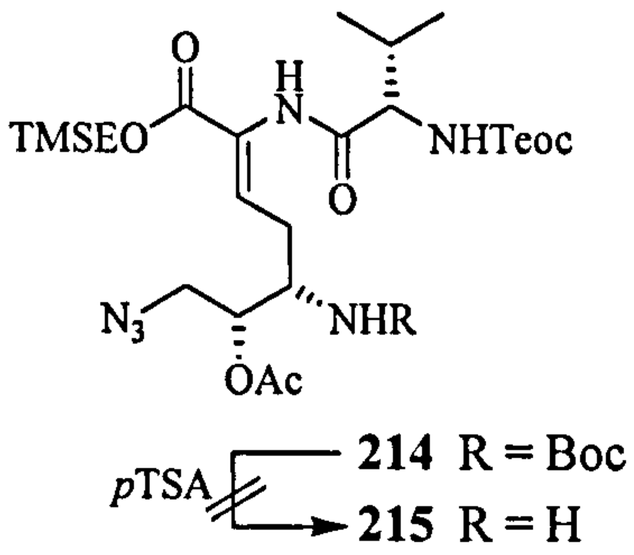


Scheme 77. *Reagents and conditions*: i) LiCl, $^{i}Pr_2EtN$, CH_3CN, *Z*-**214** 51% and *E*-**214** 11%.

With both isomers in hand, it was possible to confirm the stereochemistry of (*Z*)-**214** using nOe difference experiments. The alkene hydrogen at H-3 was well resolved as an apparent triplet at 6.5 ppm with $J = 7.8$ Hz for *E*-**214**, and at 6.6 ppm with $J = 7.0$ Hz for *Z*-**214**. Moreover, the carbamate NH was easily discerned as a singlet at 8.74

and 8.47 ppm, respectively. Strong reciprocal nOe enhancements (1.4-2.5%) between these two signals were witnessed for the *E*-isomer, but not for *Z*-**214.** Instead, a strong reciprocal enhancement (1.2-1.7%) between NH and the allylic methylene group (H-4) was observed.

(*Z*)-**214** was now just two steps away from the key cyclisation. The C-5 amino substituent had to be exchanged for the photo-cleavable protecting group and the cleavage of the acetate was also required. In the literature, the orthogonal cleavage of a *tert*-butyl carbamate in the presence of trimethylsilylethyl carbamate is reported.[108] We adopted essentially the same procedure using *para*-toluenesulfonic acid, but used dichloromethane as the solvent rather than ethanol. The reaction was run at room temperature, rather than at 60-65 °C to more carefully control the deprotection.



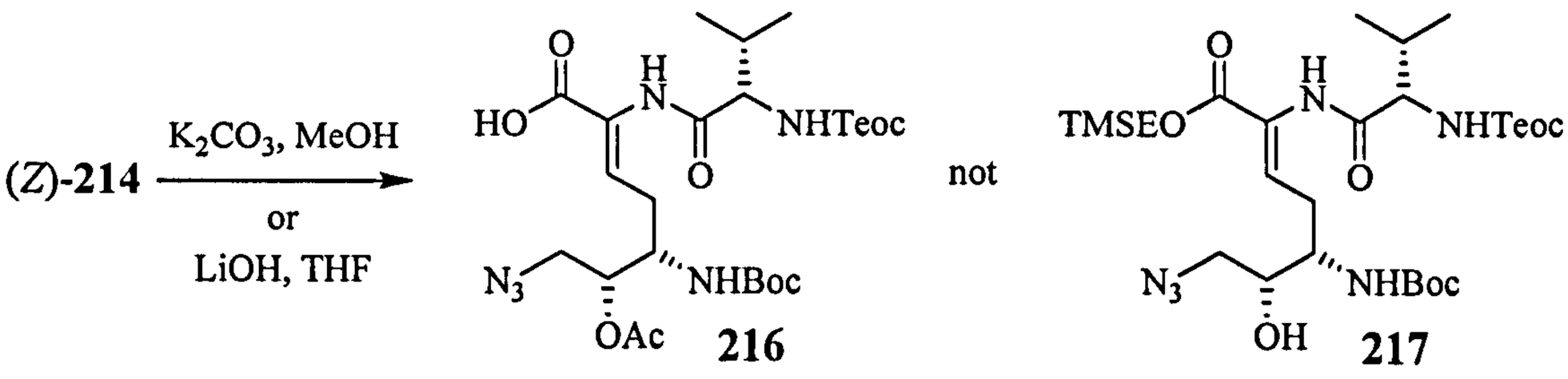
Scheme 78

After five hours, an aliquot was analysed by electrospray mass spectrometry. Alkene **214** (*m/z* = 701) was still present and no formation of the free amine **215** could be observed (Scheme 78). The reaction was left to stir overnight at which point ES-MS indicated that **214** had been consumed. The desired molecular ion at 601 [M+H$^+$] was observed, but analysis by ^{1}H NMR was not encouraging. In the case of **214**, we have three acid labile protecting groups, and competitive cleavage of the Boc and TMSE protecting groups is conceivable.

Unable to cleave the Boc group at this juncture, we elected to advance the synthesis to explore the cyclisation with the Boc group retained. If successful, we reasoned that this protecting group might be removed at a subsequent step. Alternatively, the use of a different phosphonate in the Horner-Wadsworth-Emmons reaction would

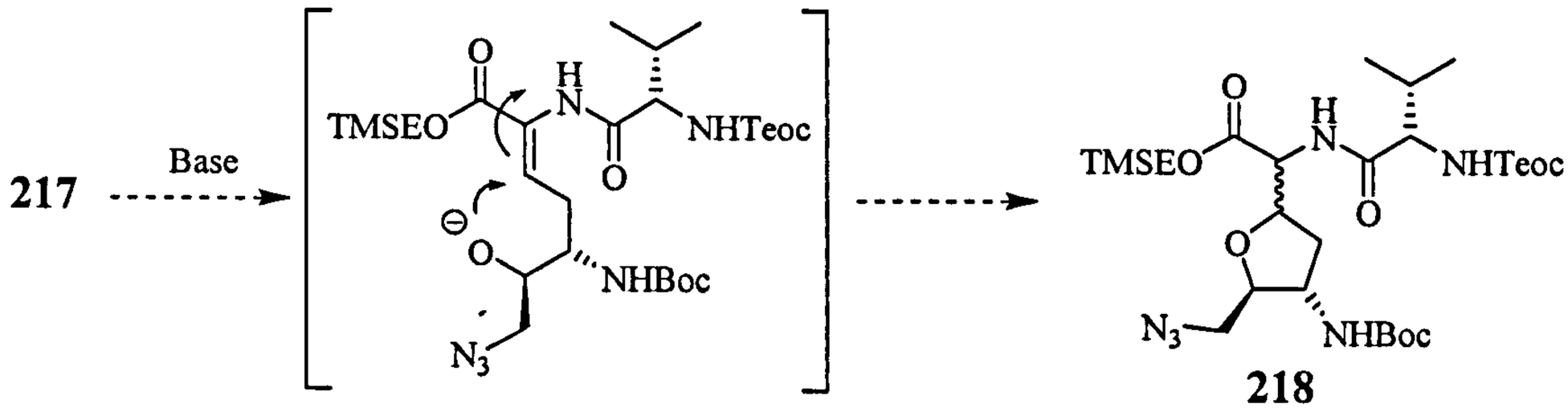
allow the introduction of alternative protecting groups in the "Northern" half of this substrate, potentially circumventing the need for a chemoselective deprotection.

Treatment of *Z*-**214** in methanol in the presence of potassium carbonate led to cleavage of the trimethylsilylethyl ester to the free acid **216** rather than the required acetate **217** as judged by ^{1}H NMR. The same result was observed when the saponification was performed with lithium hydroxide (1 *eq.*) in aqueous THF. No cleavage of the acetate group was observed (Scheme 79).



Scheme 79

With respect to achieving the double cyclisation, an azido alcohol is essential. Up until this point, the synthesis of this material has not been possible. Indeed, even if selective removal of the acetate could be achieved, closure to the corresponding tetrahydrofuran **206** seems likely based upon our earlier findings (Scheme 80).



Scheme 80

Due to these concerns, we decided to explore the formation of the bicycle in two steps, *via* ring contraction of the corresponding piperidine, formed by an initial ring closure, to form a piperidine.

2.4.2. Preliminary synthetic attempts towards a piperidine

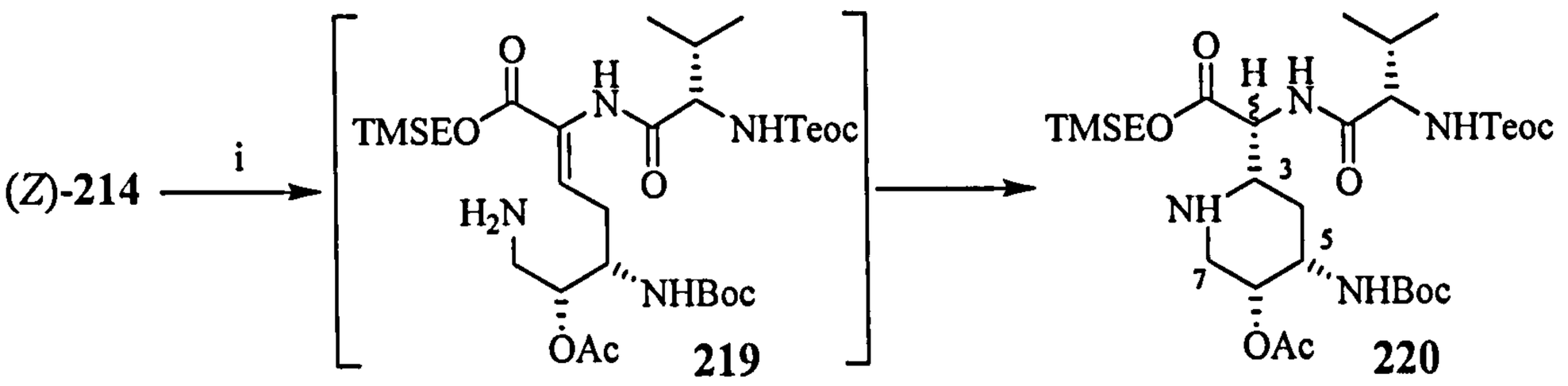
The plan was to chemoselectively reduce the azide group of **214** to the corresponding amine **219**, which we expected to undergo spontaneous ring closure to the piperidine **220** *via* a Michael addition. Moreover, we hoped that the substituents on the chain would guide the stereochemical outcome of this addition process (*vide infra*).

We decided to exploit the low reactivity of trisubstituted alkenes to hydrogenation at atmospheric pressure. Alternatively, reduction *via* the Staudinger reaction, is possible although purification problems associated with the triphenylphosphine oxide by-product formation might arise.[55] By using a protic solvent or a weak base, *in situ* cyclisation to the piperidine could be anticipated.

To achieve the required reduction, the hydrogenation of *Z*-**214** was undertaken using 10% Pd/C in ethanol, and alternatively in ethyl acetate. Gratifyingly, we observed the formation of the piperidine **220** with no additional base being necessary. Similar results were obtained in both solvents although slightly higher yields being achieved in EtOAc (69% *vs* 60%). Of the four possible diastereomers that could be produced from this reaction, only two could be detected by ^{1}H NMR. Piperidine **220** was obtained as an inseparable mixture of epimers, with the exact ratio being dependent on the choice of solvent (EtOAc 1:3; EtOH 1:1.5) (Scheme 81).

Assignment of the stereochemistry of piperidine **220** was very difficult, in part due to the broadness of some of the ^{1}H NMR signals. Bearing this in mind, we were expecting to see three clear reciprocal nOe enhancements upon irradiation of the axial hydrogens at C-3, C-5 and C-7 (ficellomycin numbering). However, the NMR spectrum for the epimeric mixture of piperidines was not clear and the peaks could only be tentatively assigned. We believe that apart from signal overlap, the ring could be flipping on the NMR time scale leading to broadness. At this juncture, we could not confirm that the piperidine **220** had the stereochemistry we anticipated.

Later studies revealed that in fact, the two diastereomers produced are indeed epimeric at C-2 and that the C-3 centre has been completely controlled in this cyclisation. A rationale for these observations will be detailed later (Section 2.3.3.).

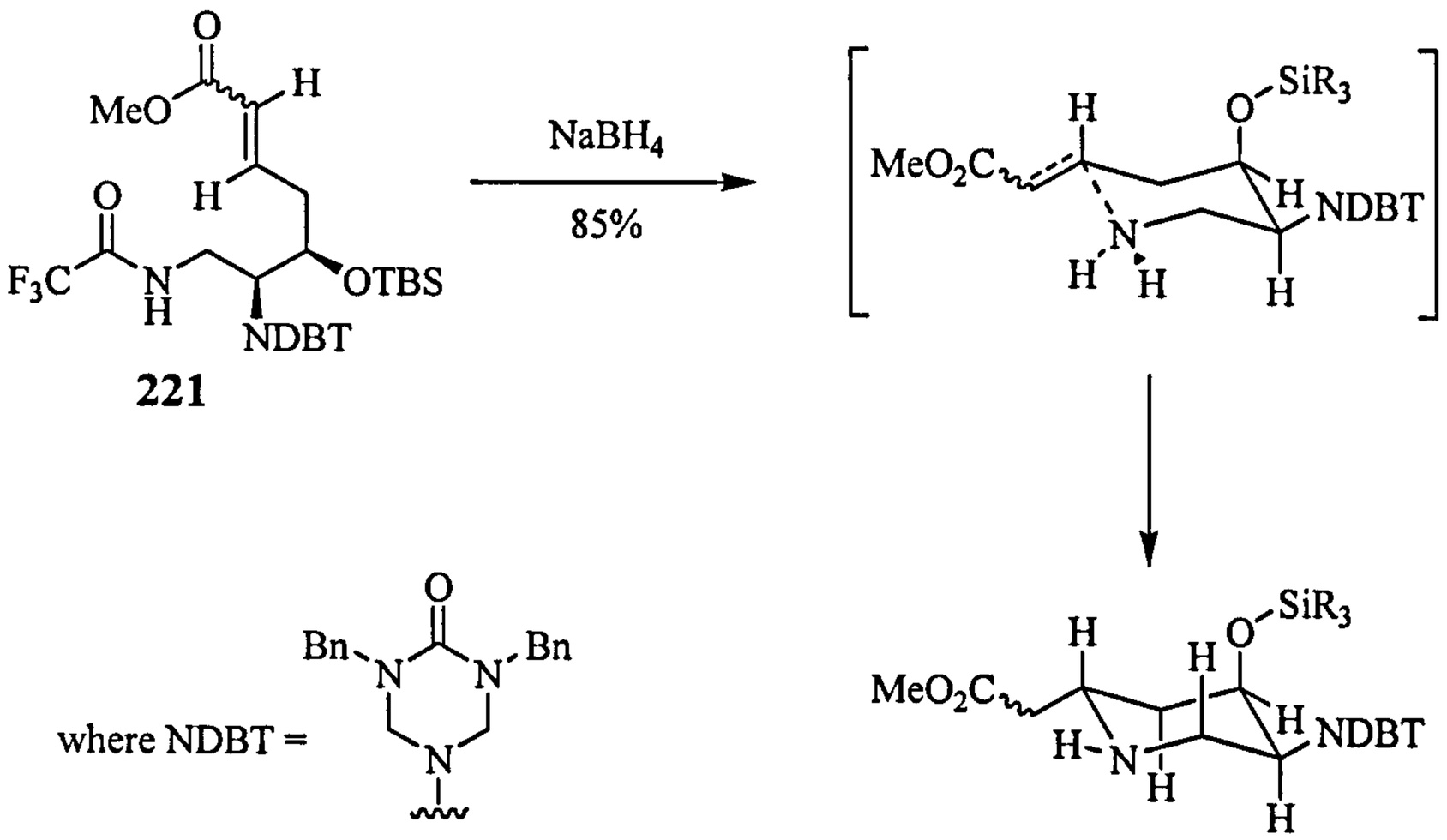


Scheme 81. *Reagents and conditions*: i) Pd/C (10%), EtOH, 60% (1:3); or Pd/C (10%), EtOAc, 69% (1:1.5).

2.4.3. Synthesis and piperidine formation using related substrates

Knapp has undertaken some closely analogous cyclisations as part of work directed towards the synthesis of (+)-tetrahydropseudodistomin.[109] These workers used a 'large' protecting group, namely a dibenzyltriazone (DBT) group to encourage this substituent to adopt a pseudo equatorial orientation in the cyclisation transition state.[110]

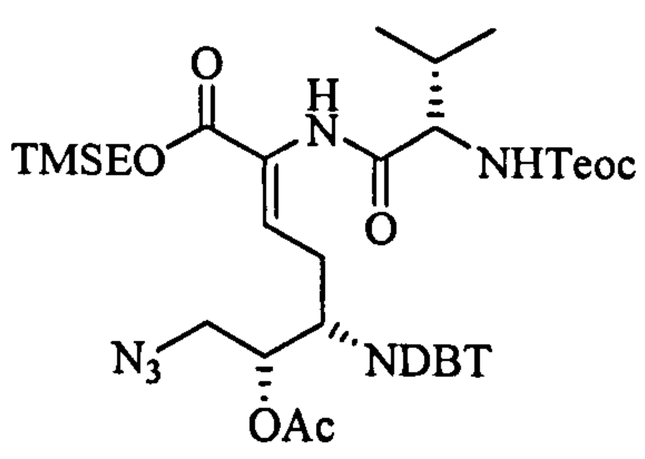
Using *trans* or a *cis* and *trans* mixture of **221**, cyclisation produced a single piperidine **222** in good yield (Scheme 82). The stereochemistry in the cyclisation reaction was rationalised in terms of the conformation of the transition state. If both the alkene and the silyl ether adopted a pseudo axial conformation in the transition state, there would exist an unfavoured 1,3-diaxial interaction between the alkene and the silyl ether group, whereas this would not occur in a transition state where the alkene assumed an equatorial conformation.



221 **222**

Scheme 82

We imagined that a DBT protected C-5 amino group might be a useful alternative for the Boc group used in our original cyclisation (**219** → **220**). To explore this idea, we set about the synthesis of olefin **223**. It was envisaged that the introduction of the DBT could be accomplished at the Weinreb amide stage. The cleavage of the Boc group from **211** using a solution of TFA in dichloromethane proceeded smoothly. However, the introduction of the DBT protecting

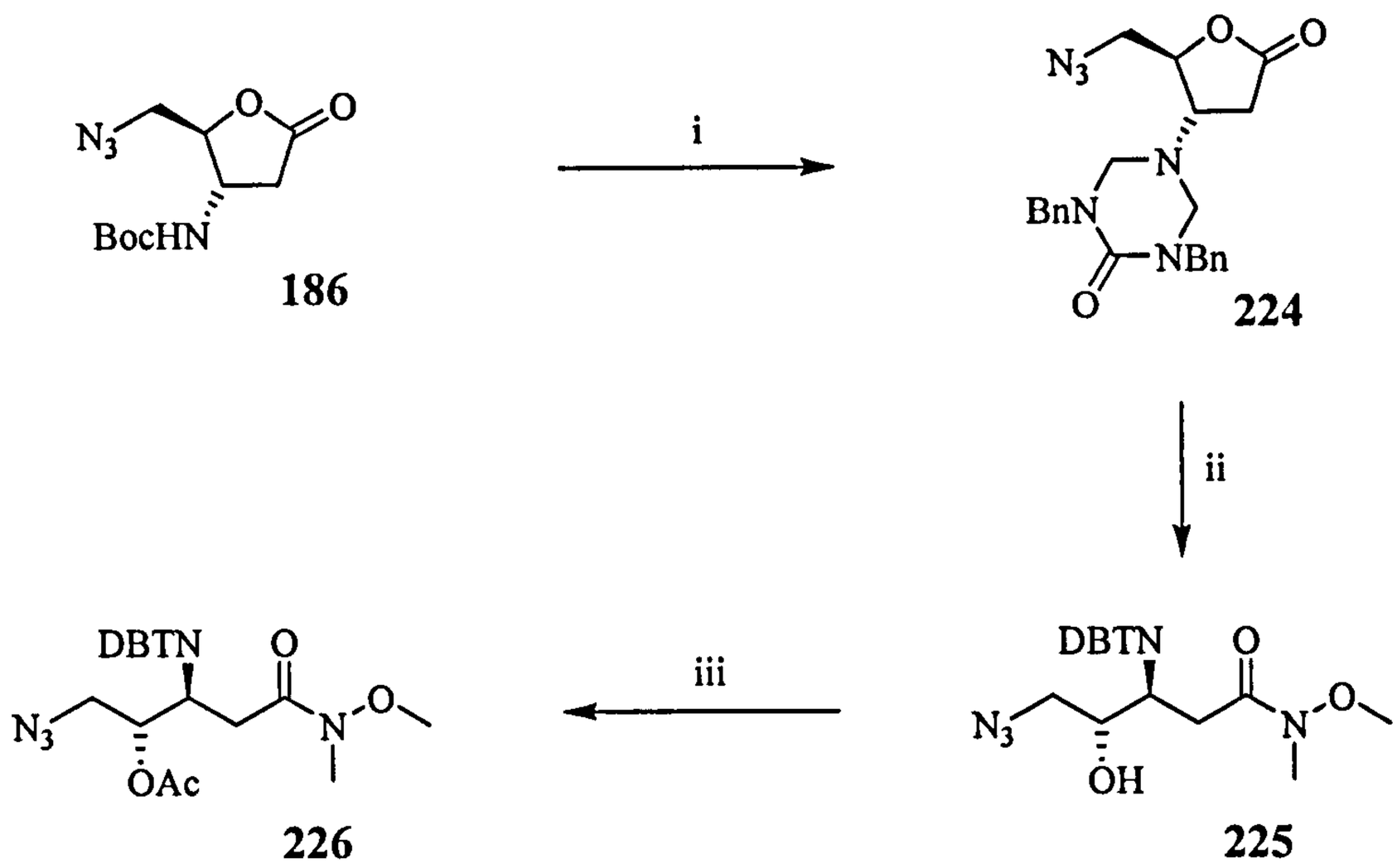


223
Figure 11

group onto the resulting free amine ($^{i}Pr_2EtN$, *aq*. HCHO then dibenzylurea, EtOAc, Δ) led to a complicated mixture of products.

Due to these complications, the introduction of the protecting group was attempted at an earlier point in the synthesis. Thus, lactone **186** was treated with TFA in dichloromethane to afford the deprotected lactone. Initial attempts to isolate the free amine by dissolving the TFA salt in water and extracting with ether resulted in low yields.

To circumvent these problems, the reaction was repeated and the solution concentrated to afford the TFA salt of this amine. Introduction of the DBT group was performed by treating this TFA salt with an excess of Hünig's base followed by addition of an aqueous solution of formaldehyde. This mixture was azeotroped with toluene, then treated with dibenzylurea in ethyl acetate at reflux to afford protected lactone **224** in a satisfactory 47% yield after column chromatography (Scheme 83). Further conversion to amide **225** *via* **224** was achieved in 86% yield in an identical way to that used earlier.



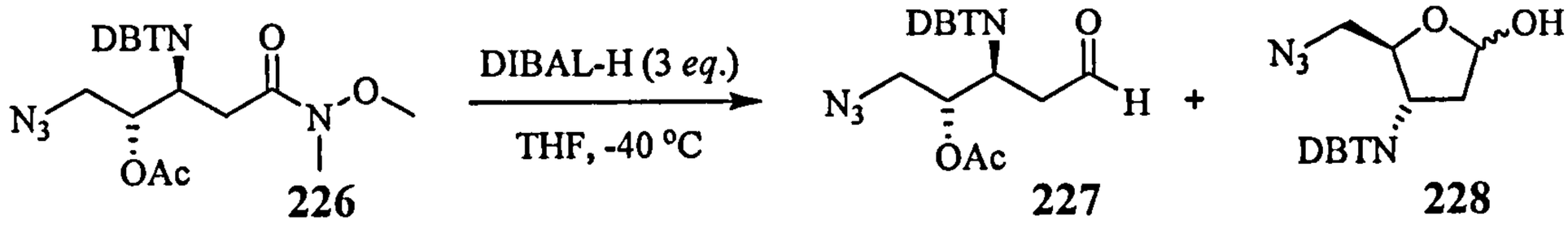
Scheme 83. *Reagents and conditions*: i) TFA, CH_2Cl_2, 0 °C then $^iPr_2EtN$, HCHO (*aq.*) then $(BnNH)_2CO$, EtOAc, 70 °C, 47%; ii) $AlMe_3$, MeONHMe, CH_2Cl_2, 0 °C → RT; iii) Ac_2O, Pyr., CH_2Cl_2, 86% over two steps.

The next stage of the synthesis was the reduction of the Weinreb amide; this proved problematic. Initially, amide **226** was treated with DIBAL-H (1.5 eq.) for 4 hours at -78 °C. After work up, 50% conversion to aldehyde was witnessed as estimated by ^1H NMR analysis. However, aldehyde **227** was only isolated in 28% yield after column chromatography.

We attempted to optimise this transformation by increasing the reaction temperature from -78 °C to -40 °C. In a separate experiment conducted at -40 °C we lengthened the reaction time from 4 to 16 hours. Neither of these attempts led to an increase in product formation. Concerned about the potentially instability of **227** during column chromatography, we decided to use triethylamine pretreated silica for product isolation. This led to the formation of a further by-product which was not identified.

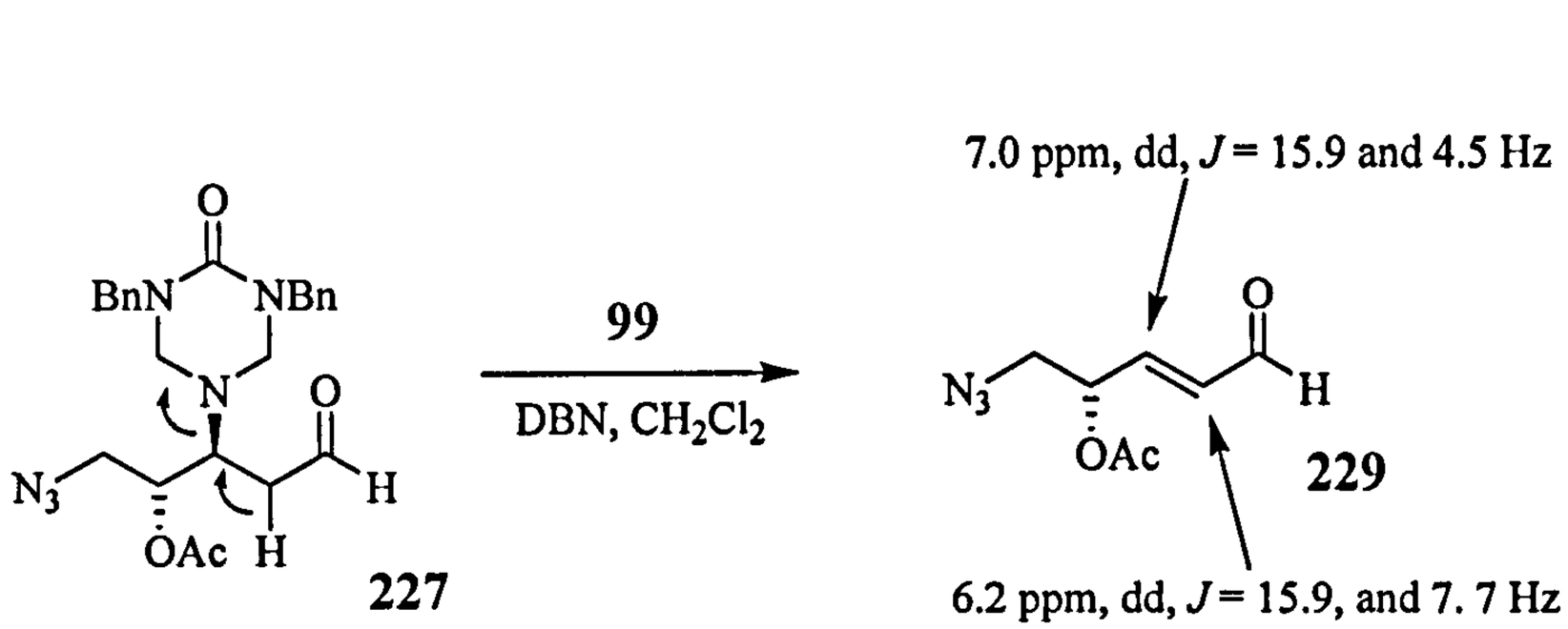
Over-reduction of the amide to the corresponding alcohol was also attempted. Using 3 equivalents of DIBAL-H resulted in a mixture of aldehyde **227** (28%) and lactol

228 (48%) were produced. The latter compound arising from cleavage of the acetate and subsequent addition to the aldehyde (Scheme 84).



Scheme 84

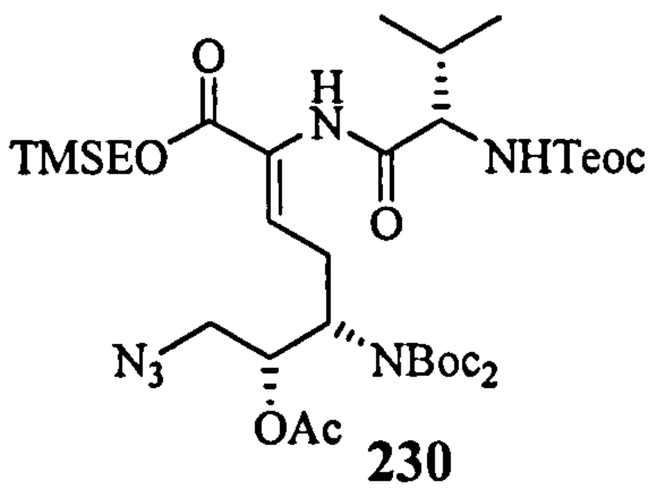
Undeterred, the crude mixture of Weinreb amide/aldehyde was subjected to the olefination conditions. A 3:1 mixture of aldehyde **227** and amide **228** produced by treatment with DIBAL-H (1.5 *eq.*, 4 hours) was subjected to Horner-Wadsworth-Emmons olefination with phosphonate **99** (Scheme 85). A complicated mixture of products was observed, among which, we isolated α,β-unsaturated aldehyde **229** (*m/z* = 389 $[M+Na]^+$) in 18% yield. Clearly, under the basic reaction conditions, elimination of the DBT group had occurred leading to the formation of **229**.



Scheme 85

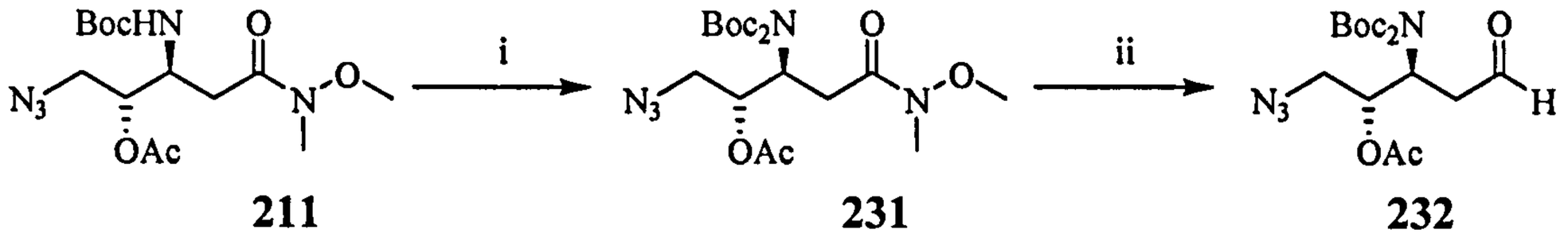
The low yields witnessed for the introduction of the DBT group into lactone **186**, coupled with problems associated with its smooth conversion to aldehyde **227** and complications seen in initial Horner-Wadsworth-Emmons reactions led us to abandon further efforts to use this protecting group.

Concurrent to these studies, we were also exploring the preparation and cyclisation reactions of another substrate bearing a larger C-5 substituent, namely alkene **230**. The introduction of a second *tert*-butyl carbamate group usually requires relatively forcing conditions, for example use of a stoichiometric amount of 4-dimethylaminopyridine and di-*tert*-butyldicarbonate.[111] Gratifyingly, when Weinreb amide **211** was subjected to these conditions, we obtained the di-Boc amine **231** in 93% yield. Reduction of this compound to the corresponding aldehyde **232** proceeded in a very high 93% yield after column chromatography (Scheme 86). This reduction is better than the corresponding conversion of **211** to **212** (Scheme 73), suggesting that removal of the carbamate NH is advantageous.



230

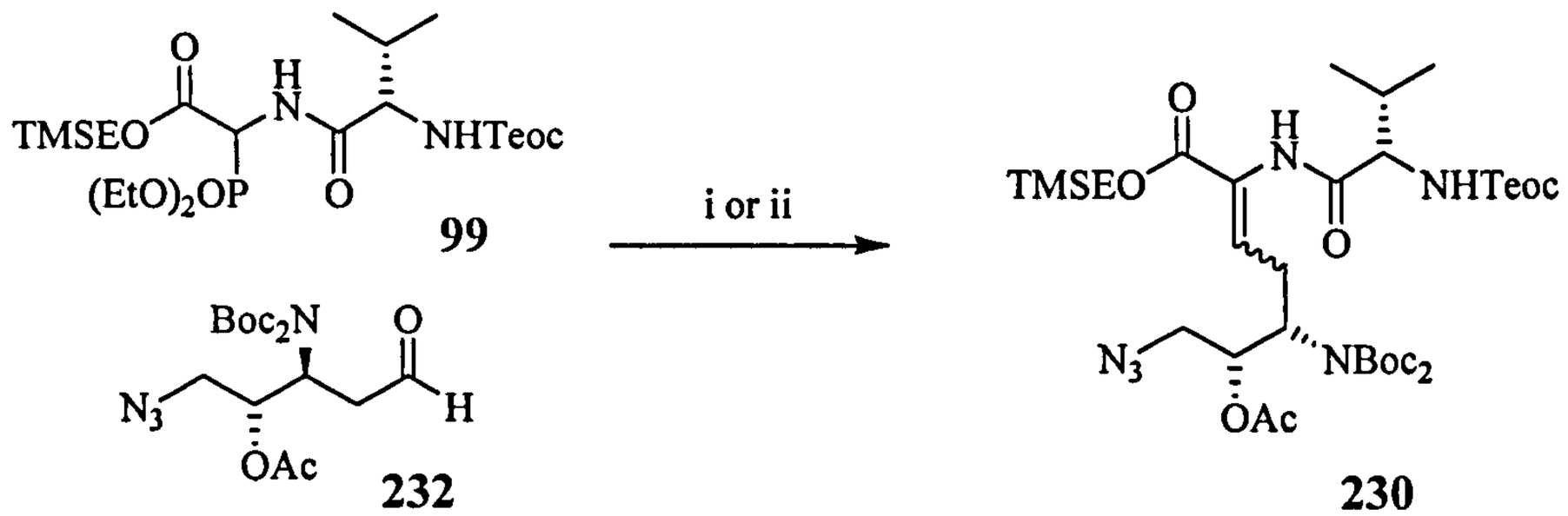
Figure 12



211 **231** **232**

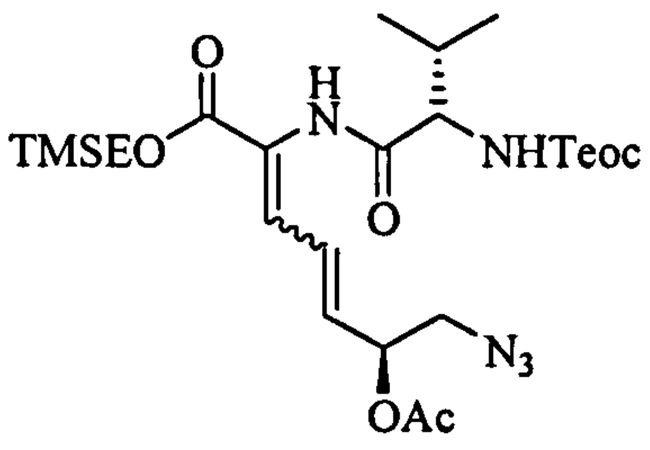
Scheme 86. *Reagents and conditions*: i) Boc_2O, DMAP, CH_3CN, 60 °C, 93%; ii) DIBAL-H, THF, - 78 °C, 93%.

This *N,N*-di-Boc protected aldehyde **232** was then subjected to both sets of olefination conditions (Scheme 87). The DBN mediated olefination conditions produced *Z*-**230** in 72% yield, whilst the Masamune-Roush conditions formed *Z*-**230** in 54% yield along with the unwanted *E*-olefin in 5% yield. The assignment of the stereochemistry was performed by analogy to **214**.



Scheme 87. *Reagents and conditions*: i) DBN, CH_2Cl_2, 10 °C, 72% (*Z*)-**230**; or ii) $^iPr_2EtN$, LiCl, CH_3CN, 10 °C, 54% (*Z*)-**230**, 5% (*E*)-**230**.

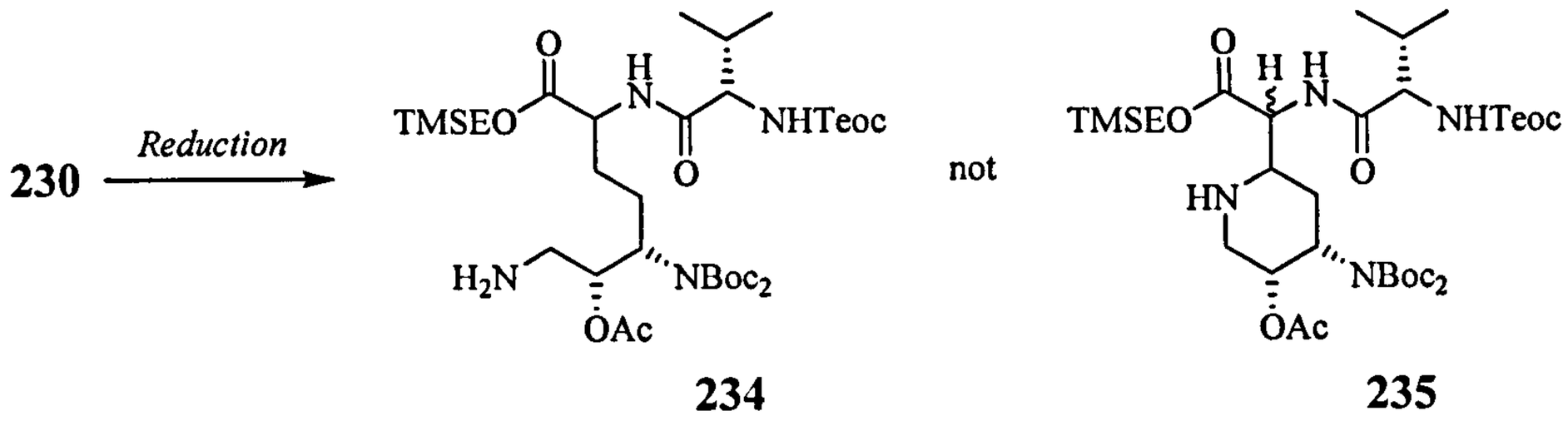
Interestingly, when the olefination reaction was conducted at room temperature, elimination of bis-*tert*-butyl imidate was observed (*ca.* 10%) giving **233** ($^3J_{3,4}$ = 11 Hz, $^3J_{4,5}$ = 15 Hz) This material could be derived from **230**, or from **232** followed by subsequent olefination with **99**. This problem was overcome by reducing the internal temperature of the olefination to 0 °C.



233

Figure 13

With quantities of **230** in hand, our attention turned to the reduction/cyclisation sequence. By analogy with the conversion of **214** → **220**, the hydrogenation was initially performed using 1 atmosphere of hydrogen with 10% Pd/C as catalyst in ethyl acetate (Scheme 88). No chemoselectivity was achieved, and the major product of the reaction was amino alkane **234**, obtained in 41% yield, resulting from the reduction of both the azide and the double bond; piperidine **235** was not isolated.

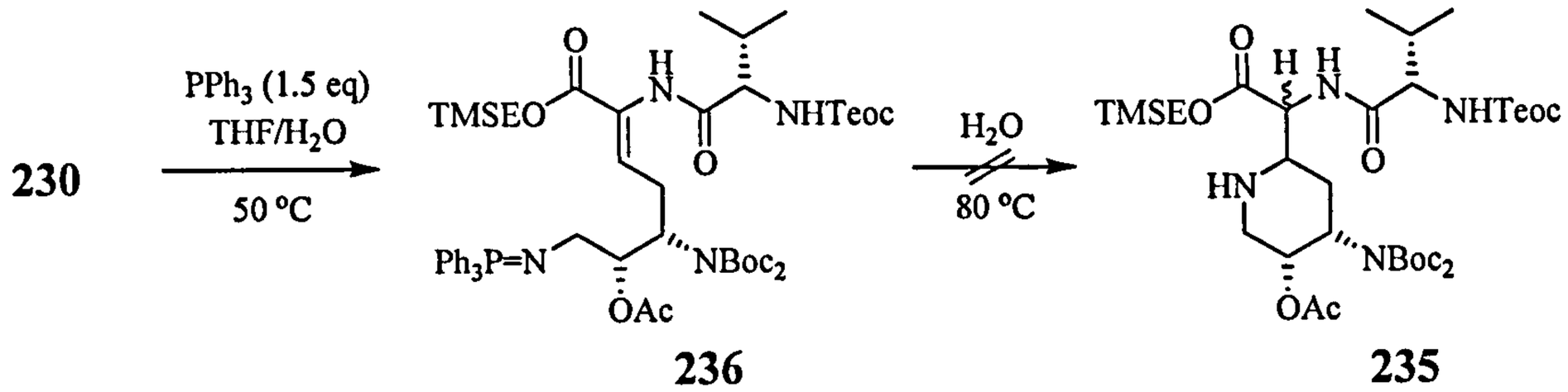


234 **235**

Scheme 88

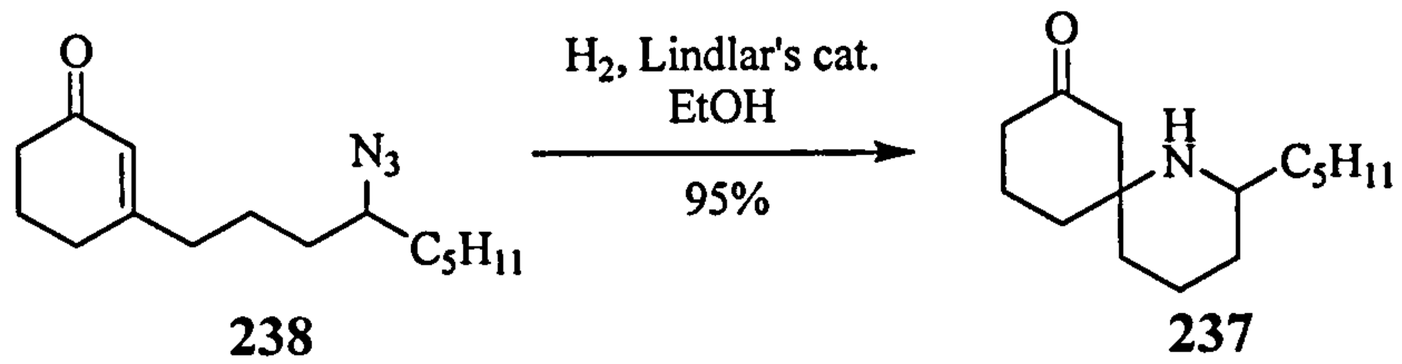
Using 3% Pd/C as catalyst, the reaction was very sluggish, and after 48 hours only a small amount (5%) of amino alkane **234** was observed in the crude reaction mixture as judged by ^{1}H NMR. When this reaction was repeated in a microwave CEM Discovery (100 W, T = 35 °C), the formation of amino alkane **234** was observed after just 10 minutes. To attempt to overcome these problems, we switched to using palladium hydroxide (10 wt%, H_2 1 atm., EtOAc) as catalyst although this was also unsuccessful.

Next, reduction of the azide was attempted using a Staudinger reaction. Stirring alkene **230** and triphenylphosphine in aqueous THF (1:50 v/v) at 50 °C overnight,[112] led to complete consumption of starting material. By ES-MS, a molecular ion of 556 was observed, and ^{1}H NMR analysis of the complex mixture indicated that the olefin remained. ^{31}P NMR suggested the presence of the iminophosphorane (26 ppm) rather than triphenylphosphine oxide (30 ppm). Presuming the reaction mixture to contain iminophosphorane **236**, we attempted to promote cyclisation by stirring the crude mixture in water at 80 °C for 3 hours. However, no change was observed (Scheme 89).



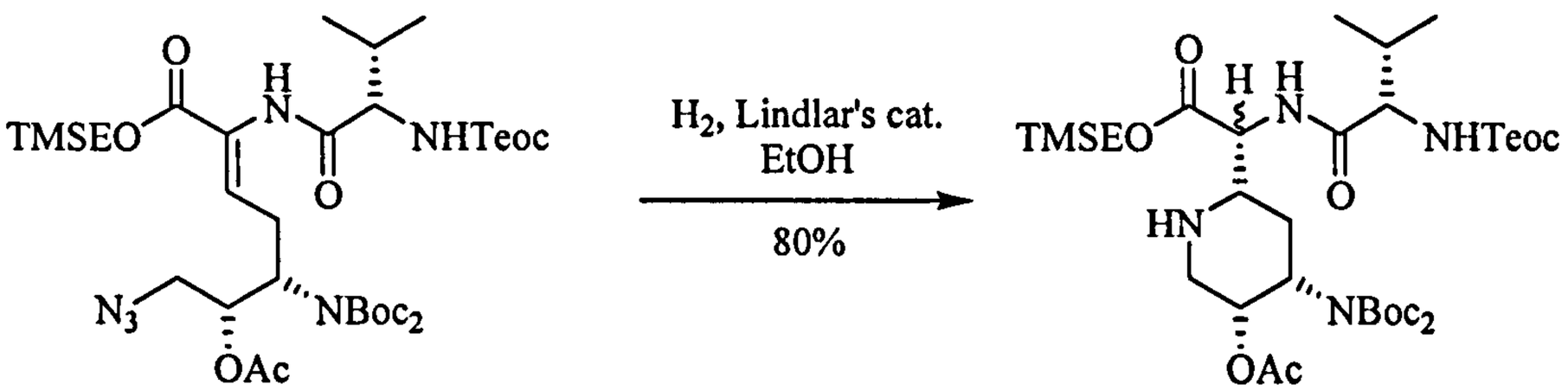
Scheme 89

Next, we tested the use of poisoned palladium catalysts. Corey[113] has reported the chemoselective reduction of azides using Lindlar's catalyst.[114] For example, **237** was obtained after reduction of **238** in 95% yield (Scheme 90).



Scheme 90

Gratifyingly, when we tested this procedure, piperidine **235** was isolated in 80% yield after column chromatography, as an inseparable 6:1 mixture of epimers at C-2.



Scheme 91

In the light of these positive results, we re-subjected alkene **214** to the reaction conditions and gratifyingly found that this method yielded piperidine **220** in 89% yield, as a mixture of 5:1 epimers at C-2 (*cf.* 60% and 1:1.5 epimeric mixture using 10% Pd/C) (Scheme 81). Thus, efficient cyclisation can be achieved using either

substrate. Moreover, only one Boc group is needed to exert complete control over the stereochemistry at C-3.

2.4.4. Stereochemical Assignments

The stereochemical elucidation of **235** was deduced by NMR, using a combination of nOe studies and analysis of geminal coupling constants (Figure 14). Clear reciprocal enhancements between H-5, and H-7_{ax} and H-3 were observed suggesting that these three hydrogens were axial. Furthermore, we could clearly observe large coupling constants consistent with the presence of di-axially disposed hydrogens. Thus, H-5 was observed as a double doublet of doublets with one large coupling ($^3J_{5,4ax}$ = 12.8 Hz) and two smaller couplings ($^3J_{5,4eq}$ = 2.4 and $^3J_{5,6}$ = 2.0 Hz) consistent with axial-equatorial couplings and one axial-axial coupling. For H-7_{ax}, one large geminal coupling constant value ($^2J_{7ax,7eq}$ = 14 Hz) was observed, along with a smaller ($^3J_{7ax,6}$ = 3Hz) assigned as an axial-equatorial coupling to H-6; H-6 was observed as a broad singlet, characteristic of small (equatorial-equatorial and axial-equatorial) coupling constants. Both minor and major diastereomers display the same characteristics in terms of nOe and coupling constants, confirming that they are epimeric at C-2, i.e. they have the same relative configuration at C-3. Whilst we have been able to confidently deduce the stereochemistry at C-3 using this analysis, the configuration at C-2 in the major isomer remains undetermined.

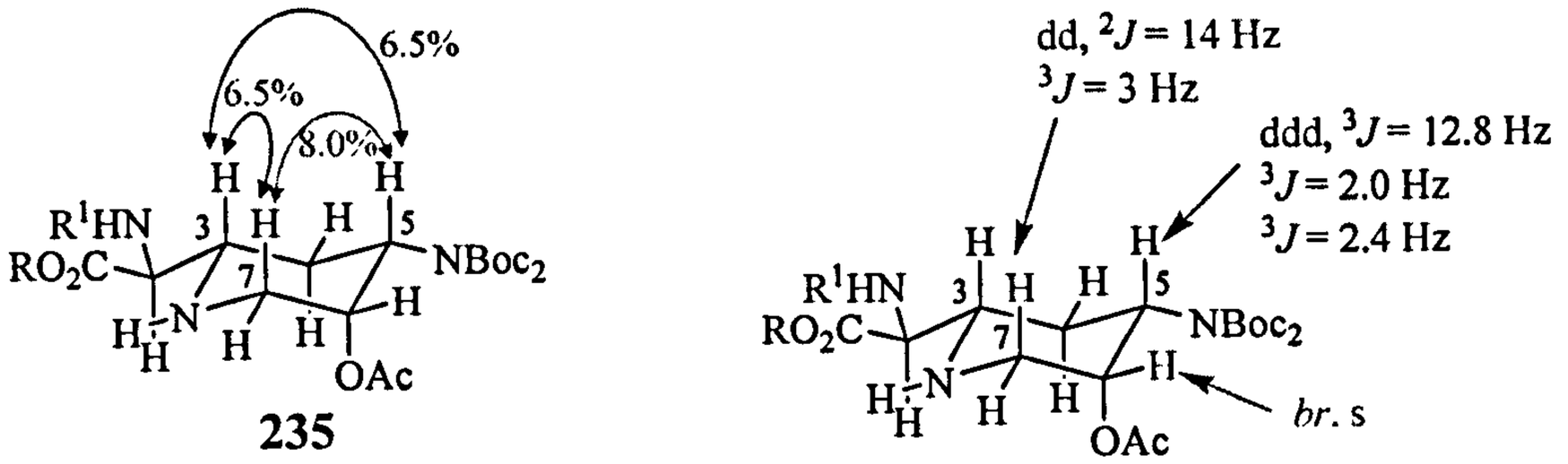


Figure 14

Analysis of the homonuclear coupling constants indicated that piperidine **220** also had the same conformation as that of **235**, showing clearly 1,3-diaxial couplings in the case of H-5 and H-7_{ax}. Thus, H-5 is observed as a double triplet ($^3J_{5,4}$ = 13 Hz; $^3J_{5,4eq} \approx {}^3J_{5,6}$ = 1.5-2 Hz). For H-7_{ax}, only the geminal coupling constant is large ($^2J_{7ax,7eq}$ = 14 Hz, $^2J_{7ax,6}$ = 2 Hz). H-6 is again observed as a broad singlet, characteristic of a series of small coupling constants (equatorial-equatorial and axial-equatorial). Furthermore, nOe difference studies indicated that H-3, H-5 and H-7_{ax} are all axial due to the existence of reciprocal nOe enhancements (Figure 15).

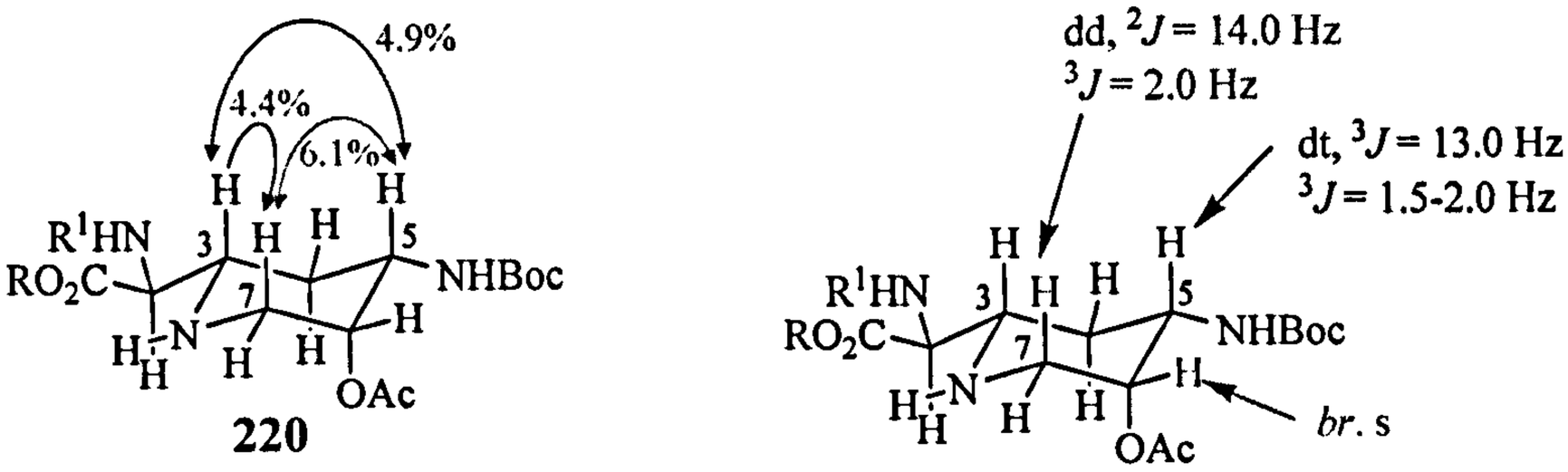


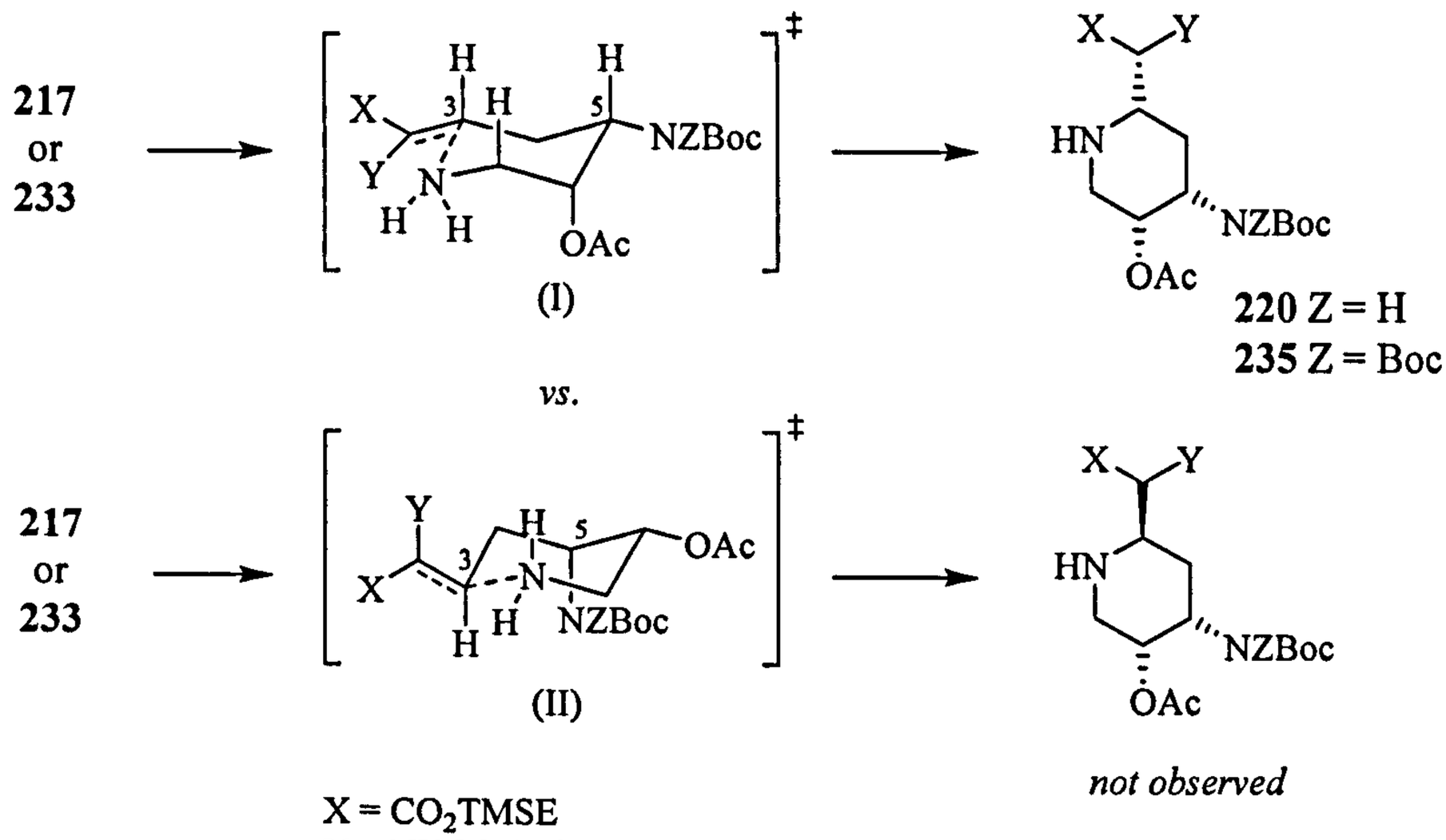
Figure 15

2.4.5. Stereochemical rationale of cyclisations to 220 and 235

It has been reported that the intramolecular 1,4-Michael type addition of primary amino olefins into piperidines is kinetically controlled, and the stereochemistry is independent of the olefin geometry.[115] Knouzi *et al.* explain this as a result of a chair transition state where the substituents are arranged to minimise steric interactions.

Knapp used similar transition states to rationalise the stereochemical course of the cyclisation of **222** to **221** (Scheme 82).

The conformational and stereochemical outcome of these intramolecular reaction can be rationalised. At least four possible transition states can be imagined for this cyclisation. Since the stereochemistry at C-5 and C-6 is set from that within aldehydes **212** and **232**, these centres must be *syn* in the product. The stereochemistry of the valine amino acid residue, is also fixed and of L-stereochemistry. Based upon the work of Knapp, we believe that the alkene of **217** and **233** adopts a pseudo equatorial conformation in the transition state. Assuming the reaction proceeds *via* a lower energy chair conformation, two competing transition states are accessible (Scheme 92). In (I) the NHBoc or $NBoc_2$ group adopts a pseudo equatorial orientation with the acetate axial, whereas in (II) their orientations are reversed.



Scheme 92

Our results using **220** and **235**, are consistent with transition state (I) being the preferred pathway.

The preference of a substituent in a cyclohexane ring to adopt an equatorial position over an axial one is reflected by its A value, with larger substituents possessing larger A values (e.g. A (^{t}Bu) > 4.5 kcal/mol).[116] Our results are supported by measurements of A-values. The A value for an acetate group is 0.6-0.79 kcal/mol. Whilst we have not been able to obtain a literature value for NHBoc, the A value for NH_2 is 1.2-1.7 kcal/mol.[117] We reason that NHBoc and $N(Boc)_2$ must have A values at least as large as this $\geq$ 1.7 kcal/mol, supporting the notion that the amino group is larger than acetate will prefer to be orientated equatorial in the transition state.

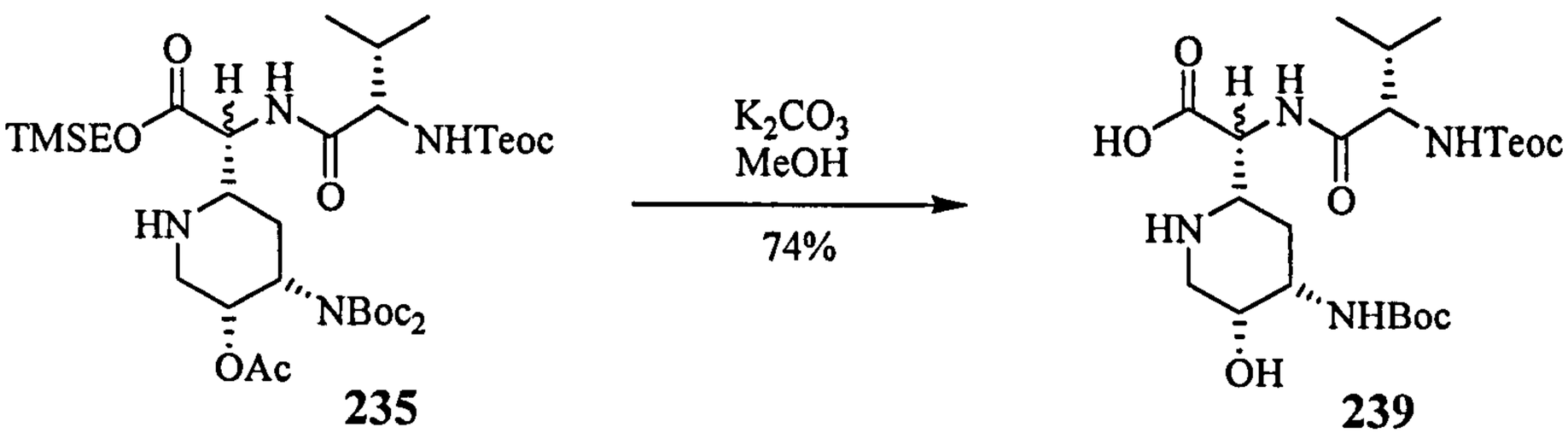
The fact that both epimers at C-2 are observed would indicate that the protonation step is not fully selective.

2.5. Further Work to Ficellomycin

To make further progress towards ficellomycin, we anticipated that cleavage of the acetate group and conversion to a leaving group would set the stage for a second cyclisation to the 1-azabicyclo-[3.1.0]hexane.

Acetate cleavage is often carried out using potassium carbonate in methanol. This produces the corresponding alcohol and methyl acetate, which is easily removed *in vacuo*. However, we faced another problem, the presence of two esters in **234** suggested that these conditions would, most probably, cause transesterification of the trimethylsilylethyl ester. To overcome this problem, we decided to use

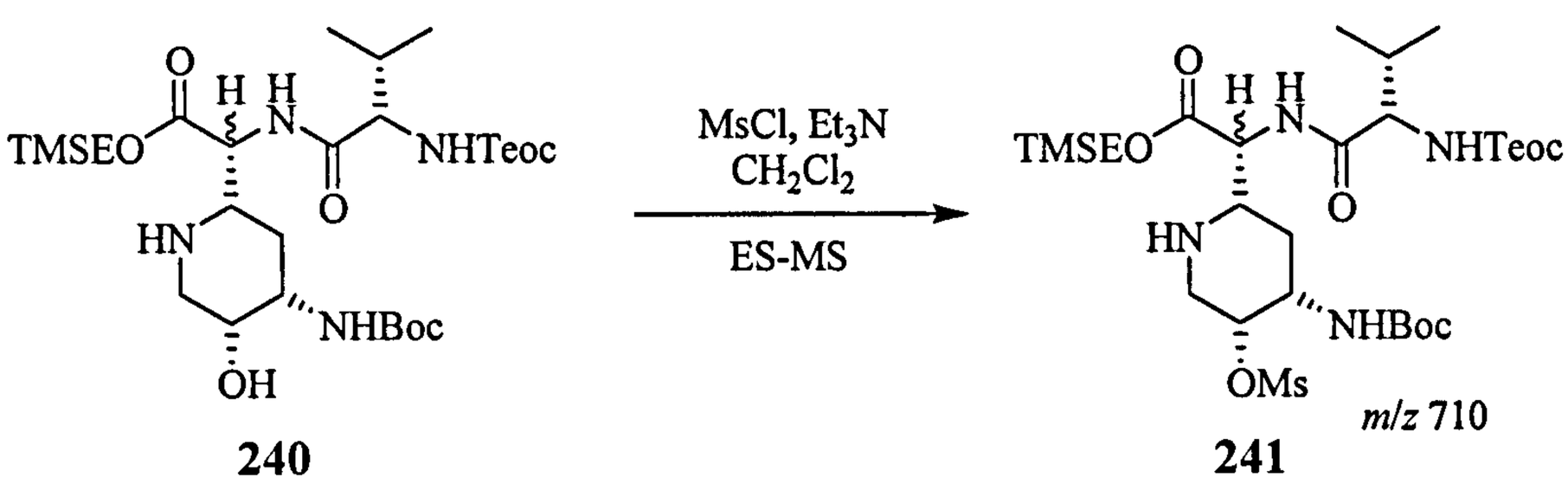
trimethylsilylethanol as the solvent, this alcohol, although greasy, is a liquid (bp = 71-73 °C). When we treated piperidine **234** with a suspension of potassium carbonate in this solvent, at room temperature or at 50 °C, no reaction was observed. However, heating the reaction at 70 °C overnight brought major changes as judged by ES-MS, with the molecular ion for acetate cleavage (*m/z* = 633) being observed. However, since the ^{1}H-NMR remained almost the same, we inferred that a small quantity of the hydrolysed acetate had been formed, which ionises more readily in the MS source. Adding water to the reaction mixture to increase the solubility of potassium carbonate in trimethylsilyl ethanol had no beneficial effect. Treatment of **235** with potassium carbonate in methanol for 1 hour followed by purification by column chromatography using 1% ammonia in the eluting solvent provided carboxylic acid **239** as a white solid in 74% yield. This occurred with concomitant cleavage of one Boc group. This result suggested that water was present in the methanol, as hydrolysis of the TMSE ester occurred and no transesterification was observed. Using freshly purchased dry methanol, some carboxylic acid could still be observed (10%). To obviate these problems, it seemed prudent to use wet methanol and subsequently re-esterify the resulting carboxylic acid.



Scheme 93

Similar results were observed when **220** was treated with potassium carbonate in methanol. We attempted the mesylation of the crude alcohol **240** obtained from this

reaction. An analysis of the crude reaction mixture revealed the presence of a mixture of free alcohol and mesylate by ES-MS (*m/z* = 710) but ^{1}H NMR failed to yield convincing evidence regarding this transformation, so we can only tentatively propose that the cyclisation precursor **241** was formed.

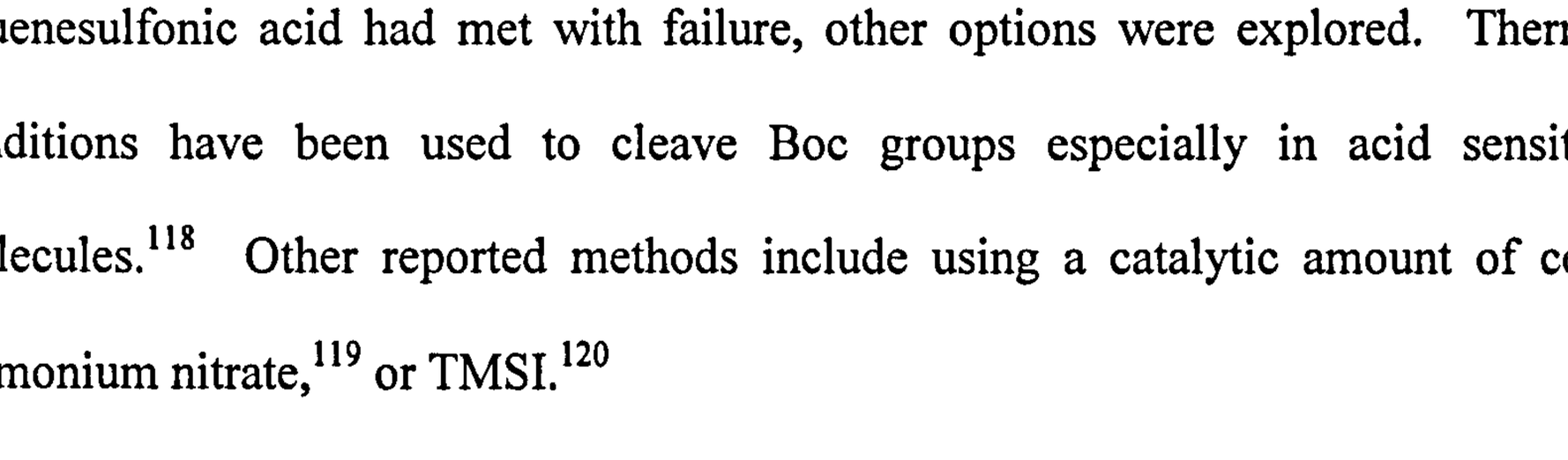


240 **241**

Scheme 94

Next, we decided to examine if we could find conditions under which the Boc and Teoc carbamates could be removed orthogonally. Since earlier attempts to cleave the Boc of **214** (Scheme 78) in the presence of the Teoc group using *para*-toluenesulfonic acid had met with failure, other options were explored. Thermal conditions have been used to cleave Boc groups especially in acid sensitive molecules.[118] Other reported methods include using a catalytic amount of ceric ammonium nitrate,[119] or TMSI.[120]

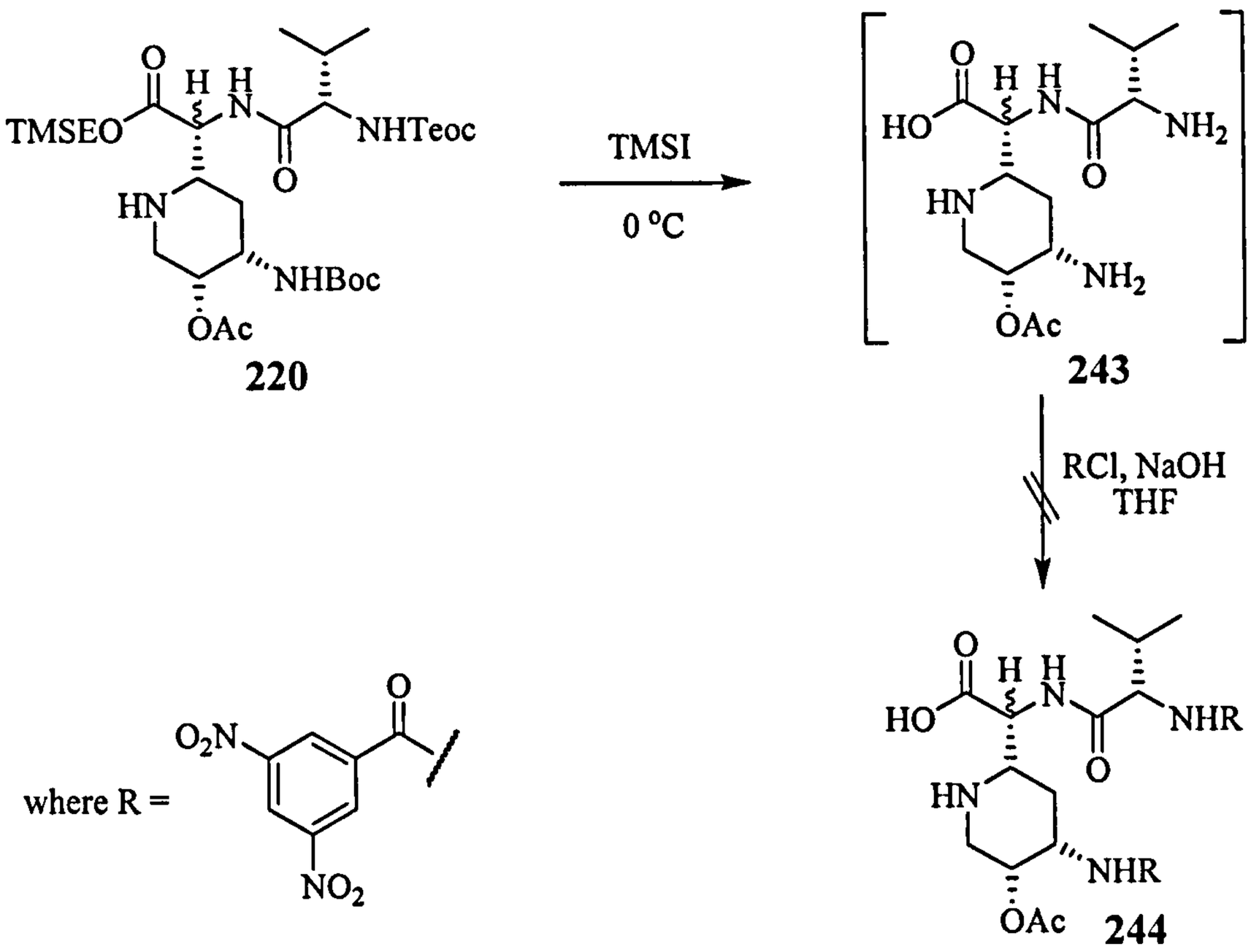
When we subjected piperidine **220** to the reported CAN-based conditions, no change was observed after three days at 80 °C (Scheme 95).



220 **242**

Scheme 95

Using trimethylsilyl iodide, deprotection of the amine and cleavage of the TMSE was observed after 1 hour at 0 °C, as judged by ES-MS. Attempts to isolate **242** after derivatisation with 3,5-dinitrobenzoyl chloride were unsuccessful. A complicated mixture developed and attempted purification resulted in the isolation of a crude solid with the correct mass for the formation of one amide (*m/z* = 525), which was not crystalline and judging by ^{1}H NMR, corresponded to a mixture of amide products.



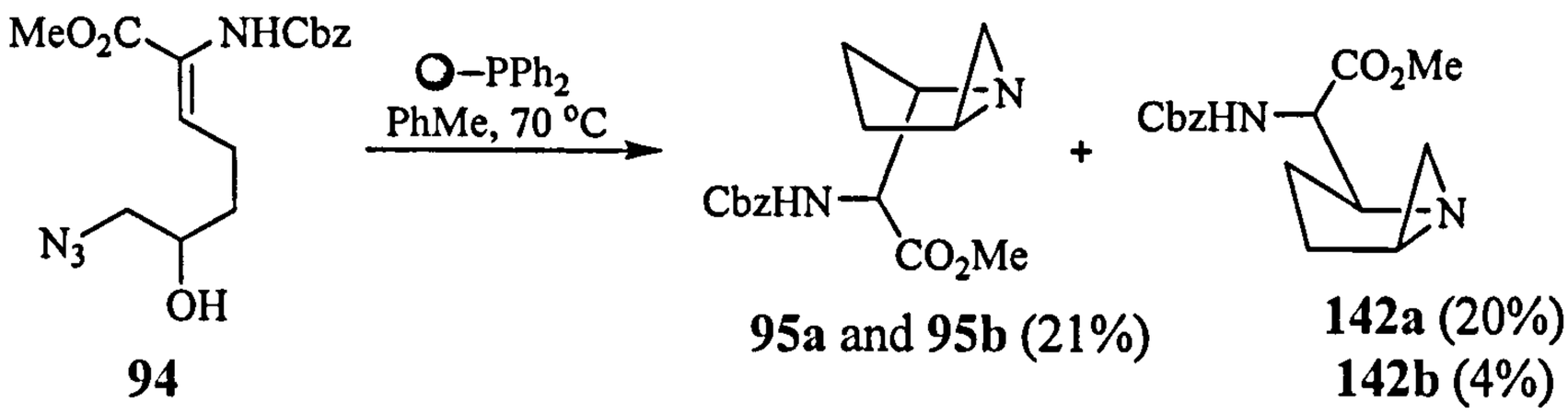
Scheme 96

At this juncture, time constraints prevented further development of the chemistry.

Chapter Three:

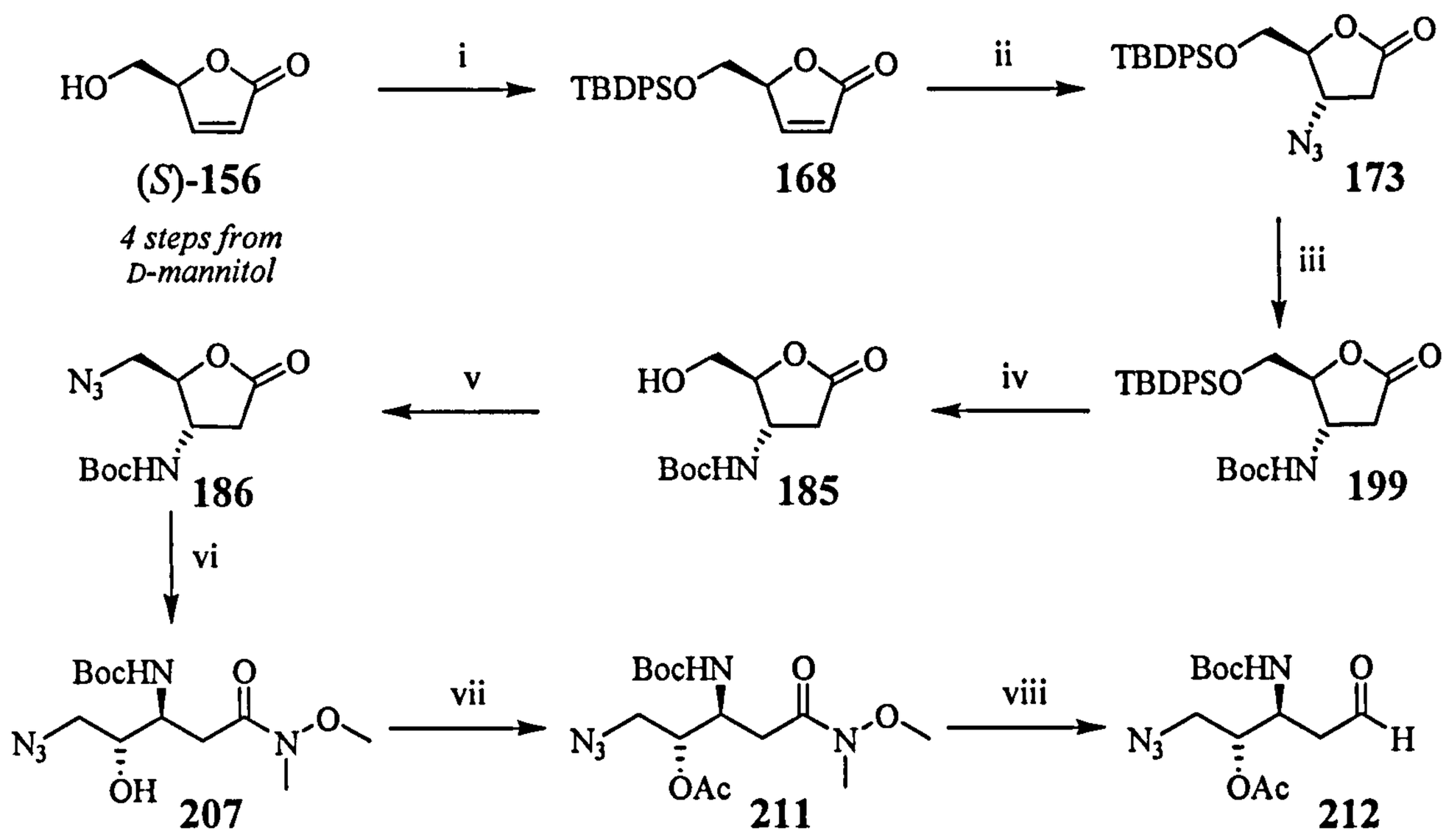
Conclusions and Perspectives

To summarise, we have optimised an existing procedure to form the 1-azabicyclo[3.1.0]hexane core of ficellomycin that had already been developed in the group. Treatment of azido alcohol **94** with poly-triphenylphosphine as the reagent, formed an NH aziridine *in situ* which underwent subsequent intramolecular conjugate addition onto a dehydroamino ester. This procedure gave access to all four possible diastereomers, epimeric at C-2 and C-3. In relation to the earlier solution phase method, it gave an increase in the overall yield, simplified isolation and purification. The *anti*-diastereomers **95a** and **95b** were isolated as a 3:1 mixture in 21% yield, and the *syn*-diastereomers **142a** and **142b** were isolated in 20 and 4% yield, respectively.



Scheme 97

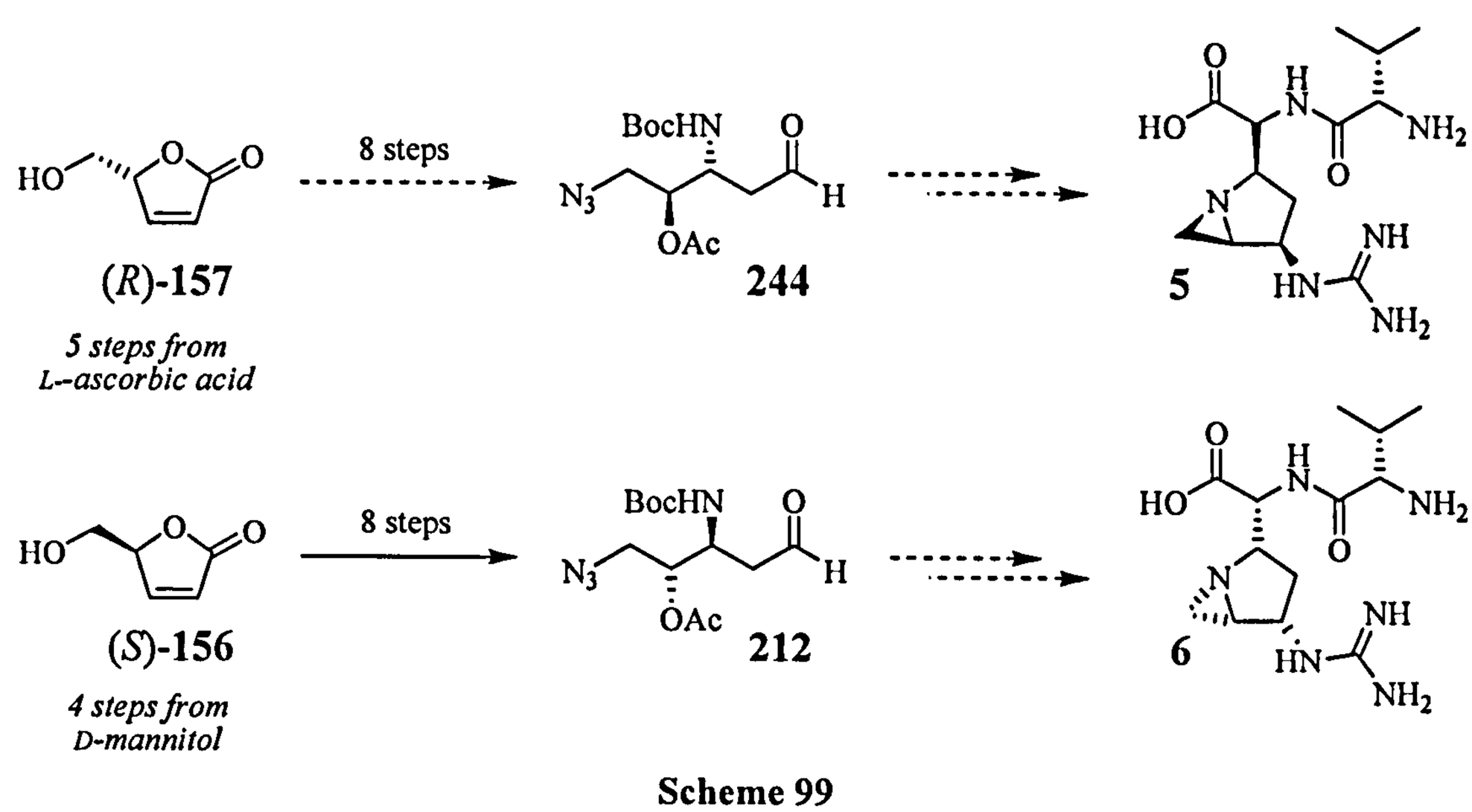
Moreover, we have established an enantioselective route to aldehyde **212**, suitable for application to the total synthesis, in 28% yield over eight steps from enone (*S*)-**156**, itself commercially available or accessible in 4 steps from D-mannitol. Key to the success of this sequence were stereocontrolled azide addition to **173**, controlled opening of lactone **186** using MeONHMe and chemoselective reduction of **211**.



(*S*)-156 — *4 steps from D-mannitol*; **168**; **173**; **199**; **185**; **186**; **207**; **211**; **212**

Scheme 98. *Reagents and conditions*: i) TBDPSCl, Imid., DMF, 96%; ii) NaN_3, CH_3CO_2H, THF:H_2O (1:1.3), 5 d, 79%; iii) H_2, 10 % Pd/C, EtOAc, 90%; iv) TBAF, THF, 0 °C, 91%; v) MsCl, Et_3N, CH_2Cl_2, 0 °C → RT; then NaN_3, DMF, 70 °C, 84% over two steps; vi) MeONHMe, $AlMe_3$, CH_2Cl_2, 0 °C → RT, 71%; vii) Ac_2O, Pyr., 4-DMAP, CH_2Cl_2, 94%; viii) DIBAL-H, THF, -78 °C, 79%.

It is expected that starting from the known enantiomeric lactone (*R*)-**157**, the antipode of aldehyde **212** could be obtained. Aldehyde **244** should lead to the stereochemistry proposed by Armstrong for ficellomycin, whereas aldehyde **212** should lead to its diastereomer.

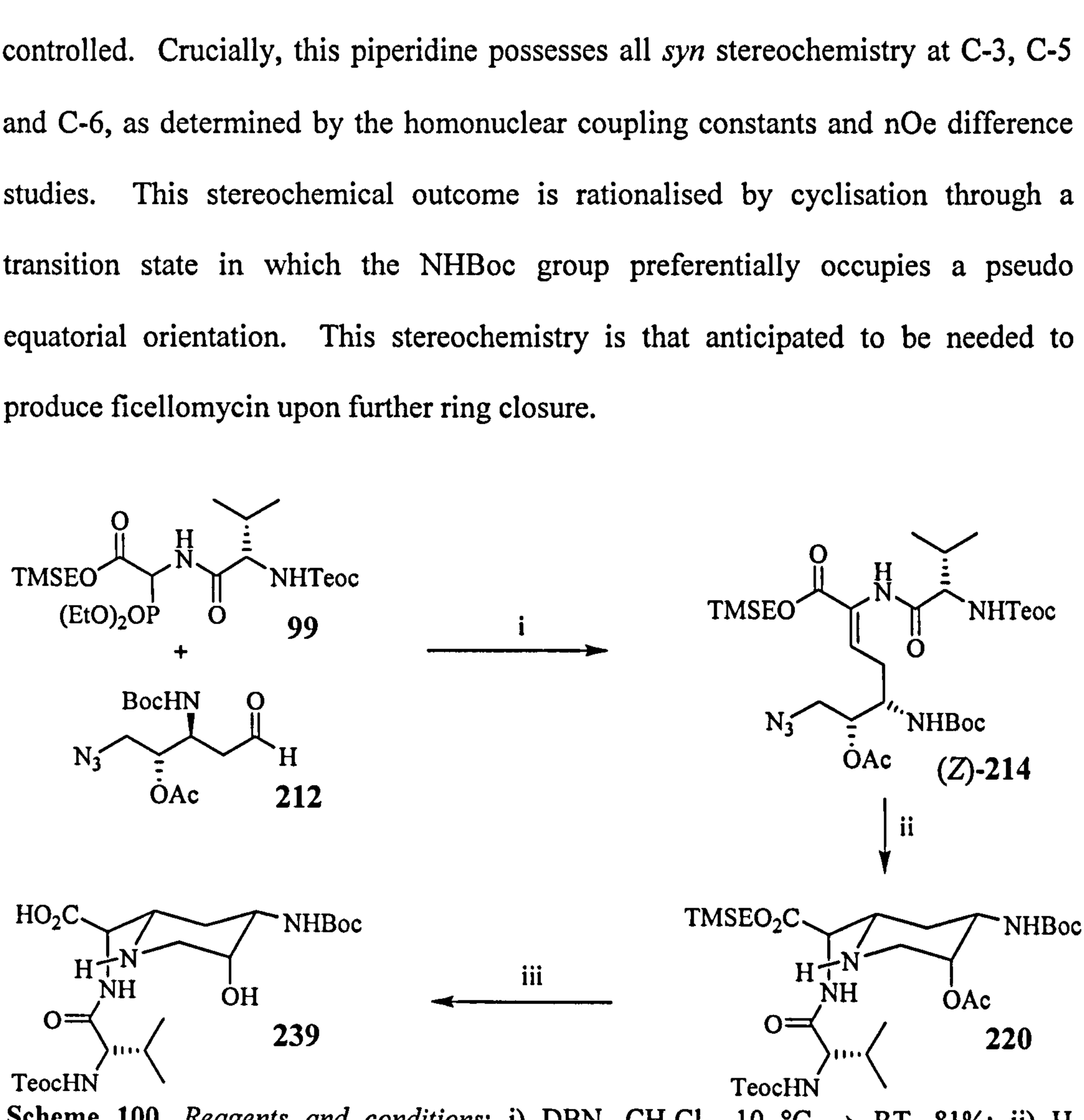


(*R*)-157 — *5 steps from L-ascorbic acid*; **244**; **5**

(*S*)-156 — *4 steps from D-mannitol*; **212**; **6**

Scheme 99

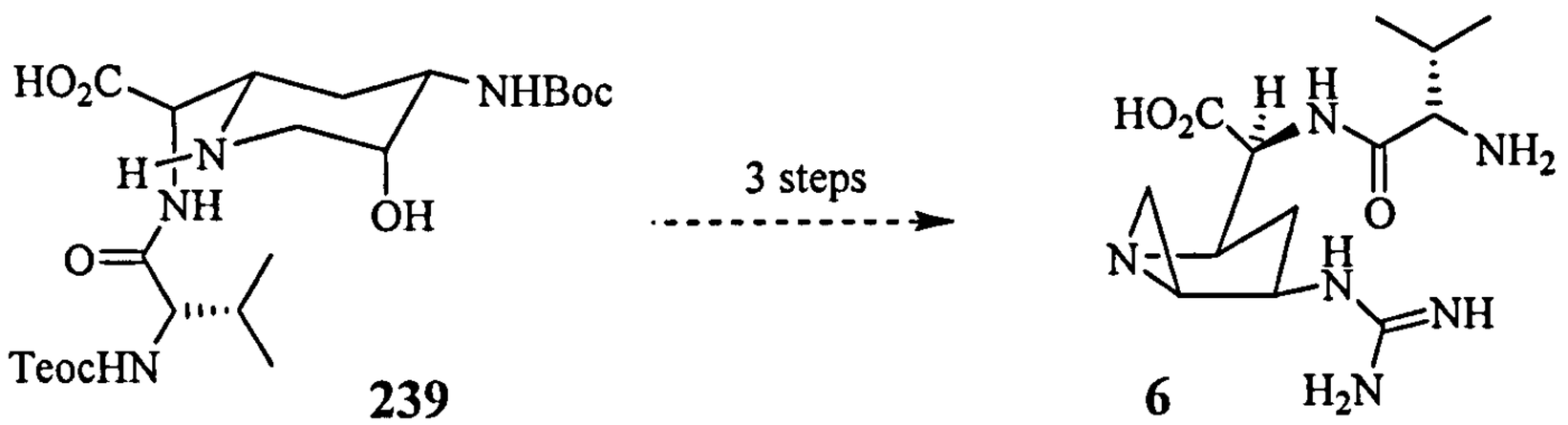
We have established that aldehyde **212** participates readily in olefination reactions with phosphonate **99**, prepared according to the protocol of David Paumier, to form preferentially the *Z*-olefin. Moderate selectivity was achieved with Masamune Roush conditions (*Z*:*E*; 5:1) which could be improved using DBN as base. Further cyclisation of (*Z*)-**214** by chemoselective reduction of the azide group using Lindlar's catalyst produced piperidine **220** in which the stereochemistry at C-3 is fully controlled. Crucially, this piperidine possesses all *syn* stereochemistry at C-3, C-5 and C-6, as determined by the homonuclear coupling constants and nOe difference studies. This stereochemical outcome is rationalised by cyclisation through a transition state in which the NHBoc group preferentially occupies a pseudo equatorial orientation. This stereochemistry is that anticipated to be needed to produce ficellomycin upon further ring closure.



Scheme 100. *Reagents and conditions*: i) DBN, CH_2Cl_2, 10 °C → RT, 81%; ii) H_2, $Pd/CaCO_3$, $Pb(OAc)_4$, EtOH, 89%; iii) K_2CO_3, MeOH, 74%.

Time constraints prevented us making much further progress towards the natural product. It was demonstrated that hydrolysis of the acetate occurred concurrent with the saponification of the trimethylsilyl ethyl ester. This precursor, is potentially two

steps away from the ring-contraction to form a 1-azabicyclo[3.1.0]hexane with the same stereochemistry as **6**. This would require re-introduction of the trimethylsilyl ethyl ester, mesylation of the alcohol and base-mediated ring closure. Examples of similar ring closures, albeit in simpler systems are known.[121] If TBAF were used in this last step, both protecting groups in the dipeptide segment would also be cleaved concomitantly.



Scheme 101

At this point in time it is unclear whether **239** possesses the required orthogonality in protecting groups to further the synthesis to the natural product. The protecting groups for the phosphonate unit were chosen with a double cyclisation strategy in mind. Future work might be best undertaken with alternative protecting groups on this part of the molecule.

The introduction of the guanidine group is currently an unsolved challenge. Whilst it is conceivable that this group could be introduced prior to piperidine formation, it is perhaps more prudent to introduce this polar substituent late in the synthesis.

Another unresolved problem is the separation of the C-2 epimers. This may be possible once some rigidity is conferred to the system, probably after the 1-azabicyclo[3.1.0]hexane is assembled, at which point rigorous assignment of their

relative stereochemistry could be undertaken. Work to resolve these challenges and complete the synthesis is ongoing in the group.

Chapter Four:

Experimental Section

4.1. General Experimental

Solvents and reagents were used as supplied or purified using standard procedures. [122] Dry solvents were obtained from Aldrich™ as anhydrous in Sure/Seal™ bottles. Petroleum ether refers to the fraction of petroleum ether having a boiling point between 40-60 °C. All reactions were carried out under an atmosphere of nitrogen unless otherwise stated. Commercially available compounds were generally used without purification. Analytical thin layer chromatography was carried out using aluminium backed plates coated with Merck Kieselgel 60 F_{254}. Plates were visualised under UV light and developed with potassium permanganate or cerium ammonium molybdate followed by heating. Column chromatography was carried out using Matrex silica 60 unless otherwise stated.

Infrared spectra were recorded in the range of 4000 - 600 cm^{-1} using a Perkin Elmer Spectrum One FT-IR spectrometer with internal calibration.

^{1}H and ^{13}C NMR spectra were recorded using the Bruker DPX 300, Bruker Advance DPX 400 or Bruker DRX 500 spectrometers at operating frequencies 300, 400 and 500 MHz respectively for ^{1}H NMR and 75, 100 and 125 MHz, respectively for the ^{13}C NMR using deuterated solvents as quoted. Chemical shifts are quoted in ppm relative to tetramethylsilane as reference with coupling constants being given to the nearest 0.5 Hz, assignments derived from COSY (^{1}H-^{1}H correlation), HMQC (^{1}H-^{13}C correlation) and PENDANT editing. The abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; sext, sextet; sept, septet; m, multiplet; *br*, broad and *app*, apparent are used.

Low resolution mass spectra were recorded on a Kratos Profile HV3 or an Esquire 2000 platform with electrospray ionisation. High resolution mass spectra were obtained using a Kratos analytical MS80 RFAO spectrometer and a Micromass Quattro II instrument (EPSRC Mass Spectrometry Service, Swansea). Compounds characterised by high-resolution mass spectrometry were chromatographically homogeneous.

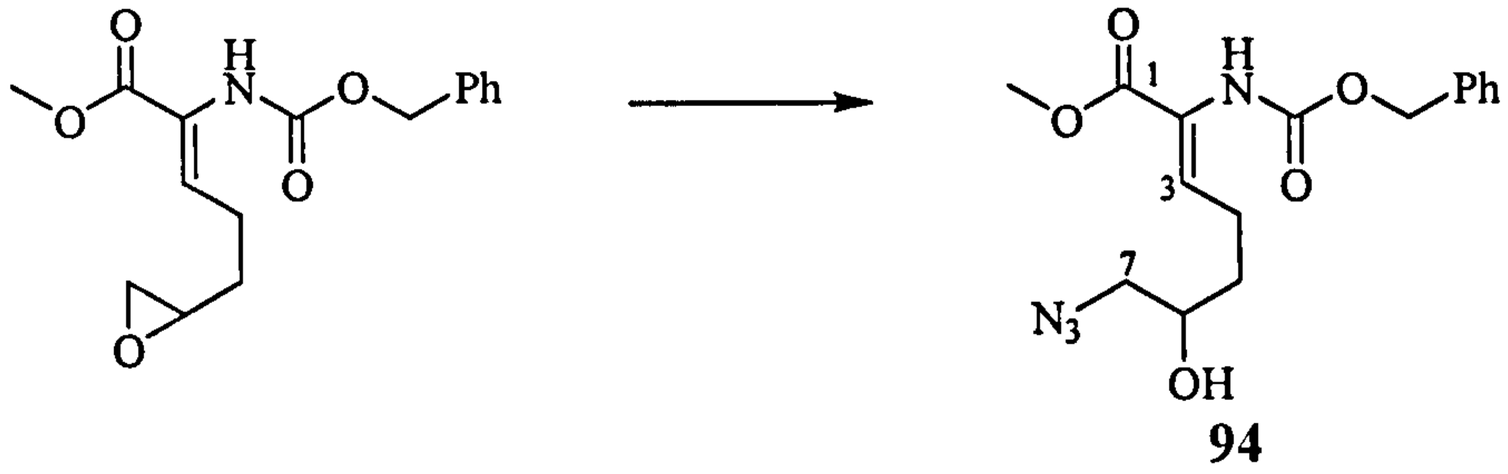
Elemental analysis was performed in a Carlo Erba 1160 apparatus (Warwick Analytical Service Ltd.)

Melting points were determined using the Gallenkamp MPD350 apparatus and are reported uncorrected.

Optical rotations were measured on an Optical Activity Ltd. AA-1000 polarimeter, values are quoted in $10^{-1}cm^2g^{-1}$.

4.2. Experimental

Methyl-(2*Z*)-7-azido-2-(benzyloxycarbonylamino)-6-hydroxy-hept-2-en-1-oate (94).[55]

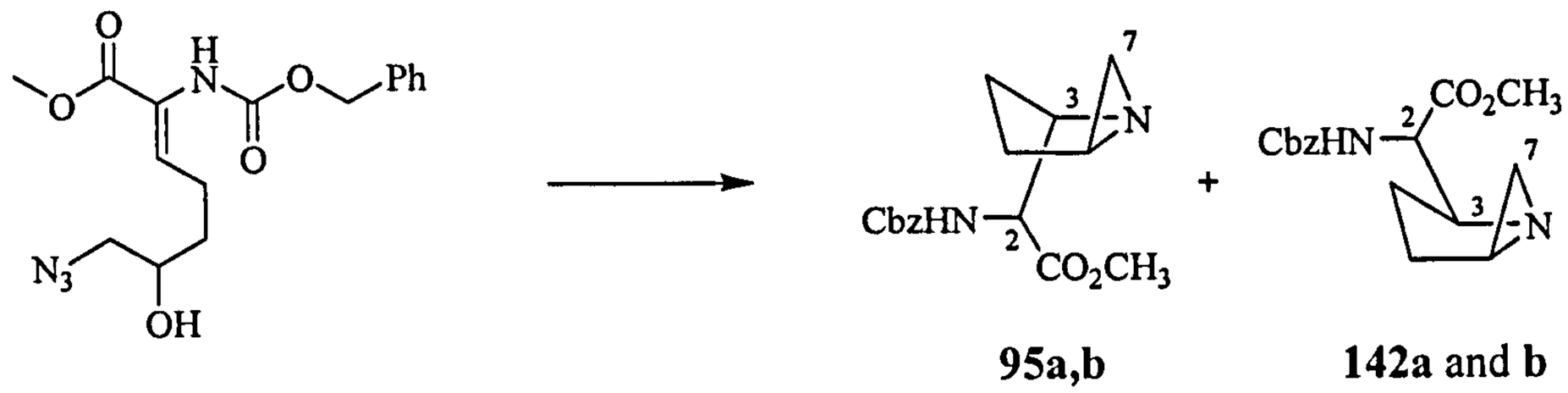


94

To a stirred solution of methyl (2*Z*)-2-(benzyloxycarbonylamino)-6-epoxyhept-2-en-1-oate (1.30 g, 4.30 mmol) in dry ethanol (43 mL) at room temperature were added sodium azide (1.11 g, 17.00 mmol) and ammonium chloride (682 mg, 12.80 mmol) and the resulting solution was stirred for 9 days. Ethanol was removed *in vacuo* and the residue dissolved in water and extracted with ethyl acetate (3 x 40 mL), the combined organic fractions were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Silica gel column chromatography (5→ 30% ethyl acetate in petroleum ether) provided **94** (765 mg, 52%) as a colourless oil; R_f 0.07 (ethyl acetate/petroleum ether, 30%); ν_{max} (neat)/cm^{-1} 3421, 3330, 2953, 2097, 1719, 1509; δ_H (400 MHz, C_6D_6) 7.18-7.02 (5H, m, ArH), 6.49 (1H, *app.* t, $J_{3\text{-}4}$ = 7.5 Hz, H-3), 6.40 (1H, *br.* s, NH), 4.97 (2H, s, CH_2), 3.41 (1H, d, $J_{OH\text{-}6}$ = 2.3 Hz, OH), 3.56 (1H, *app.* d, $J_{6\text{-}5}$ = 6.8 Hz, H-6), 3.32 (3H, s, CH_3), 2.68 (1H, dd, $J_{7\text{-}7'}$ = 12.7, $J_{7\text{-}6}$ = 6.5Hz, H-7), 2.62 (2H, dd, $J_{7\text{-}7'}$ = 12.7, $J_{7\text{-}6}$ = 3.9 Hz, H-7'), 2.17 (1H, *app.* sextet, $J_{4\text{-}4'}$ = 14.0, $J_{4\text{-}5}$ = 7.6, $J_{4\text{-}3}$ = 7.5 Hz, H-4), 2.03 (1H, *app.* sextet, $J_{4'\text{-}4}$ = 14.0, $J_{4\text{-}5}$ = 7.6, $J_{4'\text{-}3}$ = 7.5 Hz, H-4'), 1.30-1.23 (1H, m, H-5), 1.11-1.01 (1H, m, H-5'), δ_C (100 MHz, C_6D_6) 164.9 (CH_3OCO), 154.8 (NHCO), 137.0 (C-3), 136.6 (ArC) 128.7 (2 x ArCH), 128.5 (ArCH), 127.8 (2 x ArCH), 116.3 (C-2), 70.0 (C-

6), 67.6 (CH_2), 56.7 (C-7), 51.9 (CH_3O), 32.7 (C-5), 24.5 (C-4). Spectroscopic data were in accordance with the reported values of Paumier.[55]

Methyl 2-(1-azabicyclo[3.1.0]hex-2-yl)-2-(benzyloxycarbonylamino)acetate (95a and b[55]; 142a and b)



95a,b **142a and b**

Diphenylphosphino-polystyrene (732 mg, 2.19 mmol) was gently stirred in dry toluene (10 mL) for 30 min. To this **94** was added (696 mg, 1.99 mmol) in dry toluene (30 mL) and the resulting solution was stirred for 20 min at room temperature, then warmed to 70 °C and heated overnight. It was then allowed to cool down to room temperature, filtered through celite and rinsed with dichloromethane (3 x 30 mL). The filtrate was concentrated *in vacuo*. Silica gel column chromatography (20 → 100% ethyl acetate in petroleum ether; 1% triethylamine) yielded methyl-2-(1-azabicyclo[1.3.0]hexan-2-yl)-2-(benzyloxycarbonylamino)acetate derivatives (278 mg, 45%) as a mixture of four diastereomers as white foams:

142a (123 mg, 20%); R_f 0.05 (20% ethyl acetate in petroleum ether); ν_{max} (neat)/cm^{-1} 3319, 3172, 2947, 1712, 1708, 1527, 1435; δ_H (400 MHz, C_6D_6) 7.22-7.18 (2H, m, ArH), 7.11-7.01 (3H, m, ArH), 5.99 (1H, d, J = 9.0 Hz, NH), 5.09 (1H, d, J = 12.3 Hz,

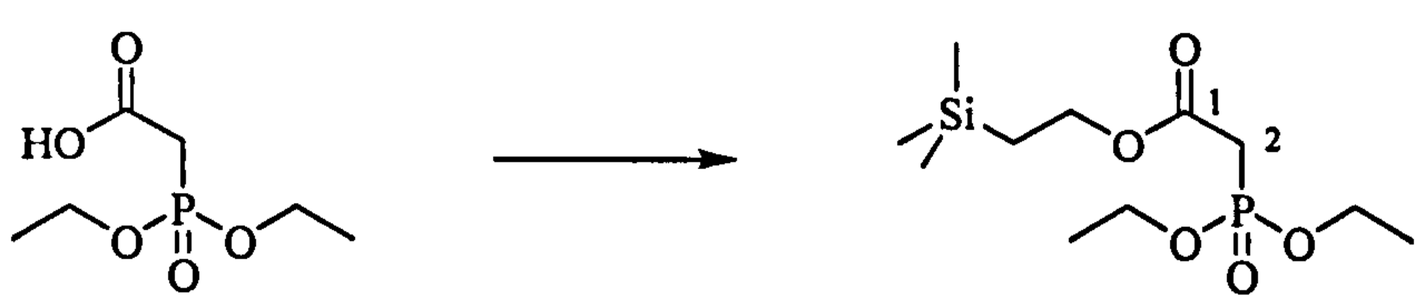
C*H*HPh), 5.01 (1H, d, J = 12.3 Hz, CH*H*Ph), 4.54 (1H, t, J = 8.4 Hz, H-2), 3.33 (3H, s, CH_3O), 3.21-3.14 (1H, m, H-3), 2.07-2.02 (1H, m, H-6), 1.59-1.52 (1H, m, H-5), 1.43-1.33 (1H, m, H-5'), 1.26 (1H, d, J = 4.8 Hz, H-7_{exo}), 1.20-1.05 (2H, m, H-4), 0.99 (1H, d, J = 2.0 Hz, H-7_{endo}); δ_C (100 MHz, C_6D_6) 172.2 (CH_3OCO), 156.2 (NHCOO), 137.2 (ArC), 128.4-128.3 (ArCH), 67.0 (CH_2Ph), 65.4 (C-3), 56.8 (C-2), 51.7 (CH_3O), 38.7 (C-6), 26.0 (C-5), 23.1 (C-7), 22.2 (C-4); MS (ES^+) *m/z* 327 [$M+Na^+$] (30), 305 [$M+H^+$] (100), 91 (100%); HRMS (ES^+) calculated for $C_{16}H_{21}N_2O_4$ 305.1496 [$M+H^+$]; found 3051492. Anal. calcd. for $C_{16}H_{20}NO_4$: C, 63.14; H, 6.62; N, 9.20 %. Found: C, 63.10; H, 6.65; N, 8.80%.

142b (26 mg, 4%), R_f 0.13 (ethyl acetate/petroleum ether, 20%); ν_{max} (neat)/cm^{-1} 3368, 3181, 2948, 1710, 1499; δ_H (400 MHz, C_6D_6) 7.22-7.16 (3H, m, ArH and NH), 7.11-6.99 (3H, m, ArH), 5.08 (1H, d, J = 12.0 Hz, C*H*HPh), 5.03 (1H, d, J = 12.0 Hz, CH*H*Ph), 4.33 (1H, dd, J = 8.8, 6.6 Hz, H-2), 3.38-3.29 (4H, m, CH_3O and H-3), 2.15-2.09 (1H, m, H-6), 1.51 (1H, dd, J =13.0, 8.0 Hz, H-5), 1.44-1.34 (1H, m, H-5'), 1.22 (1H, d, J = 5.0 Hz, H-7_{exo}), 1.18-1.09 (1H, m, H-4), 1.05-0.96 (1H, m, H-4'), 0.93 (1H, m, H-7_{endo}); δ_C (100 MHz, C_6D_6) 172.0 (CH_3OCO), 156.6 (NHCOO), 137.3 (ArC), 128.5-128.2 (ArCH), 70.0 (CH_2Ph), 63.7 (C-3), 57.7 (C-2), 51.8 (CH_3O), 38.8 (C-6), 26.2 (C-5), 22.8 (C-7), 22.5 (C-4); MS (ES^+) *m/z* 327 [$M+Na^+$] (30), 305 [$M+H^+$] (100), 91 (100%); HRMS (ES^+) calculated for $C_{16}H_{21}N_2O_4$ 305.1496 [$M+H^+$], found 305.1496.

95a and **b** (129 mg, 21%); R_f 0.18 (20% ethyl acetate in petroleum ether); ν_{max} (neat)/cm^{-1} 3334, 2951, 1731, 1498; δ_H (400 MHz, C_6D_6) 7.22-7.15 (2H, m, ArH), 7.11-

7.00 (3H, m, ArH), 5.87 (0.75H, d, J = 8.5 Hz, NH), 5.73 (0.25H, d, J = 8.0 Hz, NH), 5.14-4.98 (2H, m, CH_2Ph), 4.48 (0.25H, dd, J = 8.5, 3.8 Hz, H-2), 4.40-4.33 (0.75H, m, H-2), 3.41 (0.25H, dd, J = 8.5, 3.5 Hz, H-3), 3.33 (0.75H, s, CH_3O), 3.29 (2.25H, s, CH_3O), 2.95 (0.75H, t, J = 7.5 Hz, H-3), 2.02-1.98 (0.75H, m, H-6), 1.91-1.85 (0.25H, m, H-6), 1.61-1.43 (3H, m, 2 x H-5, H-4), 1.31 (0.75H, d, J = 5.2 Hz, H-7_{exo}), 1.29 (0.25H, d, J = 5.5 Hz, H-7_{exo}), 1.18-0.88 (1H, m, H-4), 0.56 (0.75H, d, J = 3.3 Hz, H-7_{endo}), 0.53 (0.25H, d, J = 3.5 Hz, H-7_{endo}); δ_C (100 MHz, C_6D_6) 172.0 (CH_3OCO), 171.4 (CH_3OCO), 157.0 (NHCOO), 156.2 (NHCOO), 137.2 (ArC), 128.5-128.4 (ArCH), 67.1 (CH_2Ph), 67.0 (CH_2Ph), 66.9 (C-3), 66.0 (C-3), 59.9 (C-2), 58.1 (C-2), 51.9 (CH_3O), 51.7 (CH_3O), 41.0 (C-6), 40.0 (C-6), 28.2 (C-7), 28.0 (C-7), 26.1 (C-5), 25.0 (C-5), 24.3 (C-4), 22.6 (C-4); LRMS (ES^+) *m/z* 327 [M+Na^+] (10), 305 [M+H^+] (25), 91 (100%); HRMS (ES^+) calculated for $C_{16}H_{21}N_2O_4$ 305.1496 [M+H^+], found 305.1493. Spectroscopic data were in accordance with the reported values of Paumier.[55]

2-(Trimethylsilyl)ethyl (diethoxyphosphoryl)acetate (106).[55]

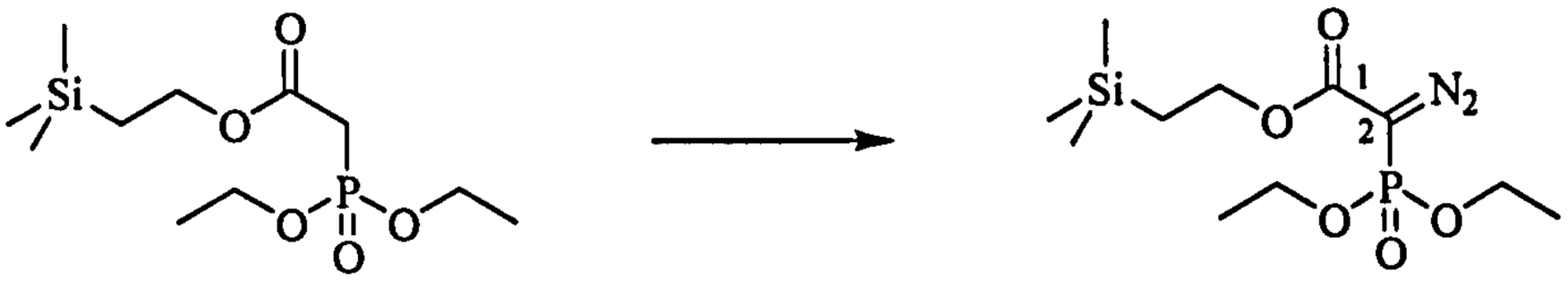


106

To a stirred solution of diethylphosphonoacetic acid (7.84 g, 39.90 mmol) in dry tetrahydrofuran (150 mL) was added 2-trimethylsilylethanol (8.00 mL, 55.90 mmol) followed by a solution of DCC (13.17 g, 63.90 mmol) and DMAP (635 mg, 5.19 mmol) in dry tetrahydrofuran (150 mL). The reaction mixture was stirred for 2 days at room

temperature, after which the precipitate was collected by filtration and washed with cold diethyl ether (50 mL). The filtrate was concentrated *in vacuo* and the resulting yellow oil purified by silica gel column chromatography (50 → 100% ethyl acetate in petroleum ether) to give **106** (11.75 g; 99%) as a colourless oil. R_f 0.54 (ethyl acetate, 100%); ν_{max} (neat)/cm^{-1} 2955, 1733, 1249, 1100, 834 ($Si(CH_3)_3$); δ_H (400 MHz, $CDCl_3$) 4.15-4.04 (6H, m, CO_2CH_2, 2 x CH_3CH_2O), 2.85 (2H, d, $J_{2\text{-}P}$ = 21.6 Hz, H-2), 1.25 (6H, t, $J_{Me\text{-}CH2}$ = 7.2 Hz, 2 x CH_3CH_2O), 0.93 (2H, t, $J_{SiCH\text{-}HCO}$ = 8.5 Hz, CH_2Si), 0.00 (9H, s, $Si(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 165.7 (d, $J_{C1\text{-}P}$ = 5.7 Hz, C-1), 63.1 ($SiCH_2CH_2$), 62.4 (d, $J_{C\text{-}P}$ = 6.5 Hz, 2 x OCH_2CH_3), 34.3 (d, $J_{C2\text{-}P}$ = 133.8 Hz, C-2), 17.1 ($SiCH_2$), 16.1 (d, $J_{C\text{-}P}$ = 6.5 Hz, 2x CH_3CH_2O), -1.8 ($Si(CH_3)_3$). ^{1}H NMR data were in accordance with the reported values of Paumier.[55]

2-(Trimethylsilyl)ethyl diazo(diethoxyphosphoryl)acetate (101).[55]

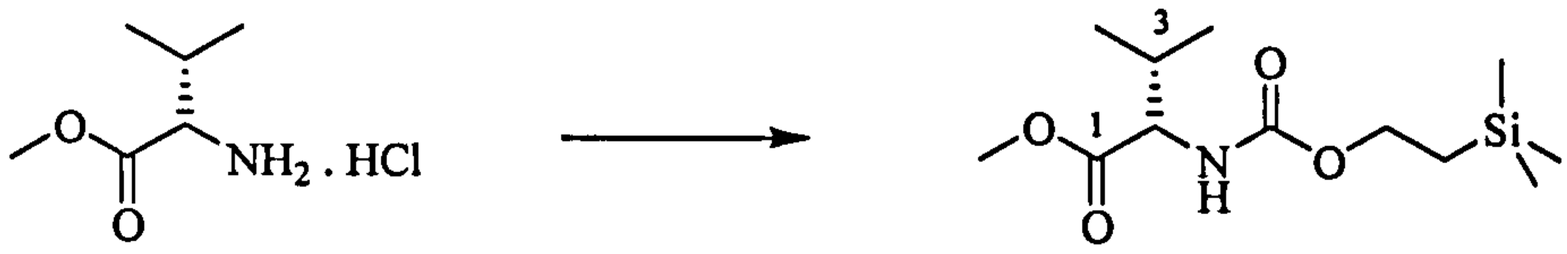


101

To a stirred mixture of **106** (1.18 g, 4.00 mmol) and cesium carbonate (1.30 g, 4.00 mmol) in dry tetrahydrofuran (7.50 mL) was added dropwise a solution of 4-acetamidobenzensulfonyl azide (950 mg, 4.00 mmol) in dry tetrahydrofuran (3.74 mL). The reaction mixture was stirred for 4 h at room temperature, filtered, concentrated *in vacuo*, and the resulting residue was partitioned between water (5 mL) and ethyl acetate (5 mL), the resulting solution was extracted with ethyl acetate (3 x 10 mL). The

combined organic fractions were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Silica gel column chromatography (20% ethyl acetate in petroleum ether) yielded **101** (1.18 g, 92%) as a pale yellow oil. R_f 0.05 (20% ethyl acetate in petroleum ether); ν_{max} (neat)/cm^{-1} 2955, 2122, 1703, 1445, 1274, 1112, 1017, 835; δ_H (400 MHz, $CDCl_3$) 4.23-4.19 (2H, m, $SiCH_2CH_2$), 4.13-4.05 (4H, m, 2 x CH_3CH_2O), 1.30-1.26 (6H, m, 2 x CH_3CH_2O), 0.98-0.93 (2H, m, ($SiCH_2$)), 0.00 (9H, s, $Si(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 175.5 (C-1), 163.3 (d, $J_{C\text{-}P}$ =11.4 Hz, C-2), 63.9 ($SiCH_2CH_2$), 63.4 (d, $J_{C\text{-}P}$ = 5.7 Hz, 2 x CH_3CH_2O), 17.4 ($SiCH_2$), 15.9 (d, $J_{C\text{-}P}$ = 6.9 Hz, 2 x CH_3CH_2O), -1.7 ($Si(CH_3)_3$). Spectroscopic data were in accordance with the reported values of Paumier.[55]

(2*S*)-3-Methyl-2-[2-(trimethylsilyl)ethoxycarbonylamino]butyrate (103).[55]

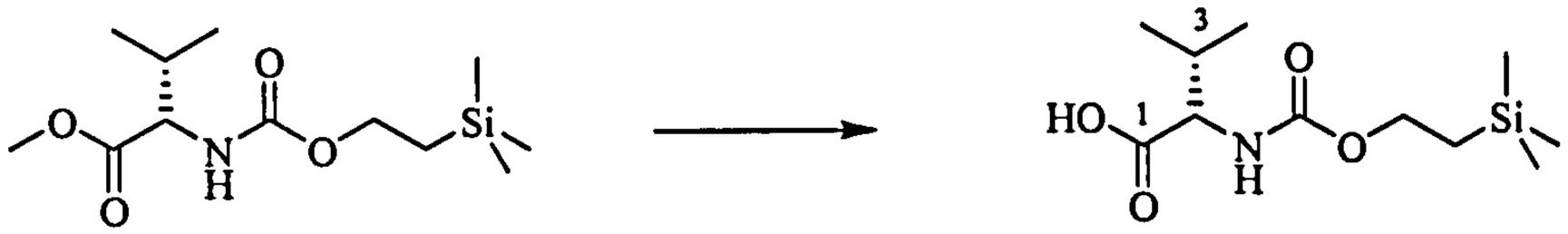


103

To a stirred solution of *L*-valine methyl ester hydrochloride (5.00 g, 29.80 mmol) in water (25 mL) was added a solution of triethylamine (5.95 mL, 42.70 mmol) in dioxane (25 mL) followed by 1-[2-(trimethylsilyl)ethoxycarbonyloxy]pyrrolidin-2, 5-dione (8.42 g, 32.50 mmol). The reaction mixture was stirred at room temperature overnight, then diluted with water (125 mL), acidified to pH ~2 with aqueous saturated potassium hydrogen sulfate solution (50 mL) and extracted with diethyl ether (3 x 200 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to

yield, without further purification, to yield **103** (7.17 g, 87%) as a colourless oil. ν_{max} (neat)/cm^{-1} 3346, 2955, 1717, 1347, 1090, 833; δ_H (400 MHz, $CDCl_3$) 5.17 (1H, d, $J_{NH\text{-}2}$ = 8.5 Hz, NH), 4.21 (1H, dd, $J_{2\text{-}NH}$ = 8.5, $J_{2,3}$ = 4.8 Hz, H-2), 4.09 (2H, dd, $J_{H'\text{-}H}$ = 9.5, $J_{H\text{-}2H}$ = 8.5 Hz, $SiCH_2CHH'$), 3.66 (3H, s, CH_3O), 2.10-2.05 (1H, m, H-3), 0.94-0.92 (2H, m, ($SiCH_2$), 0.89 (3H, d, $J_{Me\text{-}3}$ = 6.8 Hz, CH_3), 0.82 (3H, d, $J_{Me\text{-}3}$ = 6.8 Hz, CH_3), 0.00 (9H, s, $(CH_3)_3Si$); δ_C (100 MHz, $CDCl_3$) 172.6 (CO), 156.5 (CO), 63.2 ($SiCH_2CH_2$), 58.7 (C-2), 52.0 (CH_3O), 31.1 (C-3), 18.8 (CH_3), 17.6 (CH_2Si), 17.4 (CH_3), -1.7 $(SiCH_3)_3$). Spectroscopic data were in accordance with the reported values of Paumier.[55]

(2*S*)-3-Methyl-2-[2-(trimethylsilyl)ethoxycarbonylamino]butyric acid (104).[61]

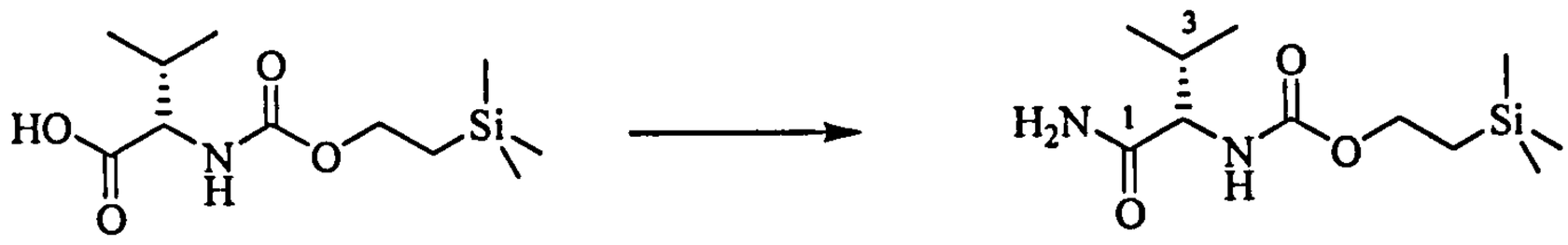


104

To a stirred solution of **103** (7.17 g, 26.0 mmol) in tetrahydrofuran (48 mL) was added sodium hydroxide solution (2M, 25.5 mL). The reaction mixture was stirred for 3 h at room temperature, diluted with ethyl acetate (50 mL) and acidified with aqueous hydrochloric acid (37 %, 4.50 mL). The aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford **104** (7.26 g, 100%) as a colourless oil. $[\alpha]_D^{27}$ -2.7 ($CHCl_3$, *c* 11.7), ref. $[\alpha]_D^{28}$ - 4.5 ($CHCl_3$, *c* 11.4)[60]; ν_{max} (neat)/cm^{-1} 2960, 1715, 1249, 834; δ_H (400 MHz, DMSO) 12.49 (1H, *br.* s, OH), 7.18 (1H, d, $J_{NH\text{-}2}$ = 8.5 Hz, NH),

4.09-4.01 (2H, m, CH_2CH$_2$Si), 3.83 (1H, dd, $J_{2\text{-NH}}$ = 8.5, $J_{2\text{-}3}$ = 6.5 Hz, H-2), 2.02 (1H, m, H-3), 0.95-0.91 (2H, m, CH$_2$Si), 0.87 (6H, t, $J_{\text{Me-}3}$ = 6.7 Hz, 2 x CH$_3$), 0.02 (9H, s, Si(CH$_3$)$_3$); δ_C (100 MHz, DMSO) 173.4 (CO), 156.5 (CO), 61.7 (*C*H$_2$CH$_2$Si), 59.4 (C-2), 29.5 (C-3), 19.2 (CH$_3$), 18.0 (CH$_3$), 17.4 (CH$_2$Si), -1.5 (Si(CH$_3$)$_3$). Spectroscopic data were in accordance with the reported values of Shute *et al.*[61]

(2*S*)-3-Methyl-2-[2-(trimethylsilyl)ethoxycarbonylamino]butyric amide (100).[55]

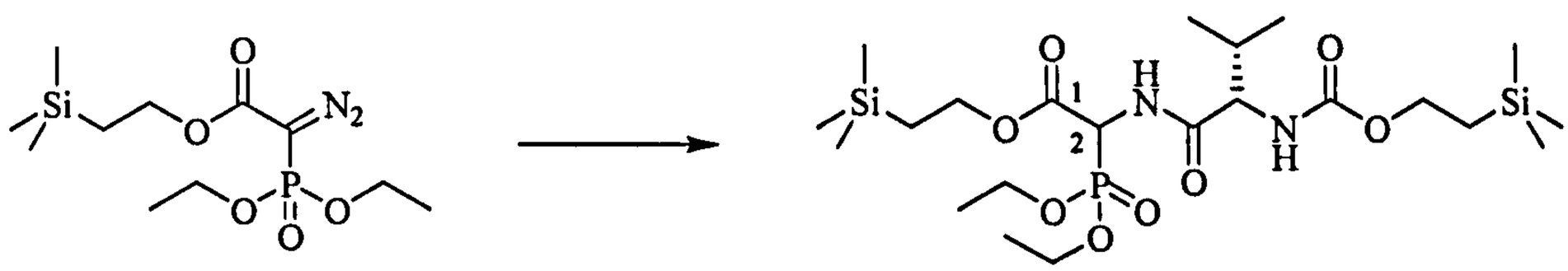


100

To a stirred solution of **104** (440 mg, 1.70 mmol) in tetrahydrofuran (4 mL) at 0 °C was added triethylamine (225 µL, 1.70 mmol) followed by fast addition of ethyl chloroformate (157 µL, 1.70 mmol). The resulting solution was stirred at 0 °C for 1h, followed by the addition of aqueous ammonia (28%, 512 µL) in tetrahydrofuran (185 µL). After stirring for 1 h at 0 °C, the mixture was diluted with ethyl acetate (10 mL) and water (5 mL). The aqueous layer was extracted with ethyl acetate (3 x 8 mL) and the combined organic layers were washed with a saturated aqueous solution of NaHCO$_3$ (15 mL), brine (15 mL), 1 M aqueous hydrochloric acid (15 mL) and water (15 mL). The organic layer was then dried over Na$_2$SO$_4$, filtered and concentrated *in vacuo* to provide a colourless gel, which crystallised on addition of petroleum ether to give **100** (298 mg, 67%) as a colourless solid; mp 148-149 °C (Ref. mp 147 °C)[55]; $[\alpha]_D^{24}$ - 7.0 (CHCl$_3$, *c* 8.3), ref. $[\alpha]_D^{28}$ - 7.1 (CHCl$_3$, *c* 0.08))[55]; ν_{max} (neat)/cm^{-1} 3335, 2955, 1655, 1244, 831;

δ_H (400 MHz, $CDCl_3$) 6.02 (1H, s, NH), 5.66 (1H, s, NH), 5.20 (1H, d, $J_{NH\text{-}2}$ = 8.5 Hz, NH), 4.17-4.12 (2H, m, CO_2CH_2), 4.00 (1H, *app.* t, $J_{3\text{-}2}$ = 6.6 Hz, H-3), 2.13 (1H, *app.* sextet, $J_{2\text{-}3}$ = 6.6 Hz, H-2), 0.98-0.92 (8H, m, 2 x CH_3, 2 x $CH_2Si(CH_3)_3$), 0.02 (9H, s, $Si(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 174.0 (CO), 156.9 (CO), 63.5 (CO_2CH_2), 59.8 (C-2), 30.7 (C-3), 19.2 (CH_3), 17.7 (CH_3), 17.6 (CH_2Si), -1.5 ($Si(CH_3)_3$); LRMS (FAB^+) *m/z*: 261 [MH^+], 136 (83%); HRMS (FAB^+): calcd. for $C_{11}H_{25}N_2O_3Si$ 261.163346, found 261.163441. Spectroscopic data were in accordance with the reported values of Paumier *et al.*[55]

(2*S*)-(Diethoxy-phosphoryl)-[3-methyl-2-(2-trimethylsilanyl-ethoxycarbonylamino)-butyrylamino]acetic acid 2-trimethylsilanyl ethyl ester (99).[55]



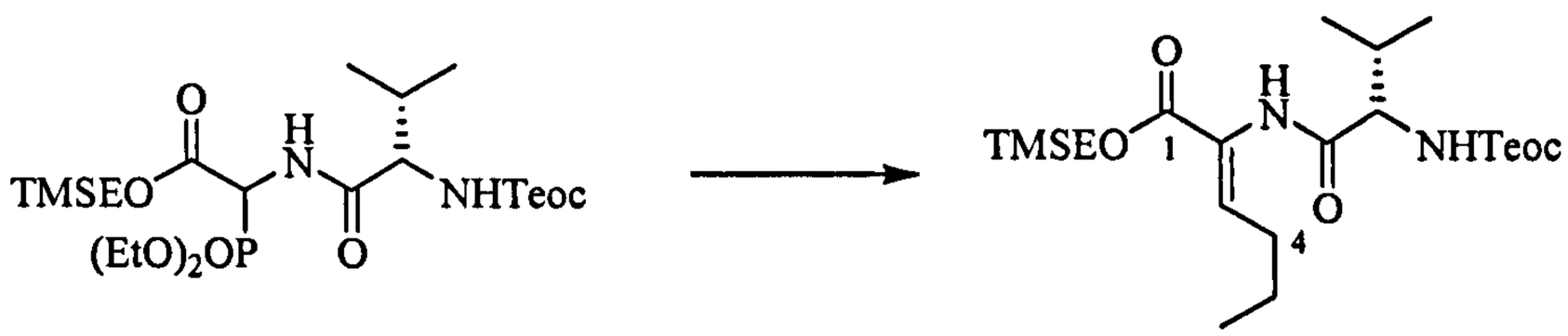
99

To a stirred solution of **100** (150 mg, 0.57 mmol) and **101** (260 mg, 0.81 mmol) in toluene (2 mL) was added rhodium(II) octanoate dimer (10 mg, 2 mol%). The resulting mixture was heated for 24 h at 80 °C and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether; 40%) to provide **99** (251 mg, 79%) as a colourless solid; mp 107-109 °C (Ref. mp 109 °C); R_f 0.4 (40% ethyl acetate in petroleum ether); $[\alpha]_D^{25}$ - 10.7 ($CHCl_3$, *c* 9.7), ref. $[\alpha]_D^{27}$ - 18.7 ($CHCl_3$, *c* 9.7)[54]; ν_{max} (neat)/cm^{-1} 3326, 2954, 1738, 1715, 1685, 1295, 1050, 833; δ_H

(400 MHz, $CDCl_3$) 7.33-7.22 (1H, dd, J = 35.7, J = 7.4 Hz, NH), 6.70-6.68 (1H, m, NH), 5.14 (0.5H, dd, $J_{2\text{-NH}}$ = 9.0 Hz, H-2), 5.08 (0.5H, dd, $J_{2\text{-NH}}$ = 9.0 Hz, H-2), 4.30-4.11 (9H, m, C*H*CH$(CH_3)_2$, 2 x CO_2CH_2, 2 x CH_3CH_2OP), 2.21-2.13 (1H, m, C*H*$(CH_3)_2$), 1.35-1.28 (6H, m, 2 x CH_3CH_2OP), 1.06-0.91 (10H, m, 2 x CH_2Si, 2 x CH_3), 0.02 (18H, s, $Si(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 171.0 (d, J = 10.8 Hz, C-1), 166.5 (CO), 156.6 (NH*C*O$(CH)_2(CH_3)_2$), 65.0 (CO_2CH_2), 64.9 (CO_2CH_2), 63.8 (d, $J_{C\text{-P}}$ = 6.5 Hz,CH_3CH_2O), 63.5 (d, $J_{C\text{-P}}$ = 6.9 Hz, CH_3CH_2O), 59.9 (*C*HCH$(CH_3)_2$), 50.7 (d, $J_{C\text{-P}}$ = 146.6 Hz, C-2), 31.2 (*C*H$(CH_3)_2$), 19.2 (CH_3), 19.1 (CH_3), 17.6 (CH_2Si), 17.4 (d, $J_{C\text{-P}}$ =CH_3CH_2O), 17.3 (CH_2Si), 16.3 (d, $J_{C\text{-P}}$ = 5.7, CH_3CH_2O), -1.5 ($Si(CH_3)_3$), -1.6 ($Si(CH_3)_3$); LRMS (FAB^+) *m/z* 555 [MH^+], 188 (37), 144 (35), 137 (20%); HRMS (FAB^+): calcd. for $C_{22}H_{48}N_2O_8PSi_2$ 555.2686 [MH^+]; found 555.2687. Anal. calcd. for $C_{22}H_{47}N_2O_8PSi_2$: C, 47.63; H, 8.54; N, 5.05%. Found: C, 47.64; H, 8.54; N, 4.85%.

Spectroscopic data were in accordance with the reported values of Paumier.[55]

(2*Z*)-2-(Trimethylsilyl)ethylacetyl-2-[(trimethylsilyl)ethoxycarbonylamino-(2*S*)-*iso*-propylcarbonylamino]hex-2-ene (213)

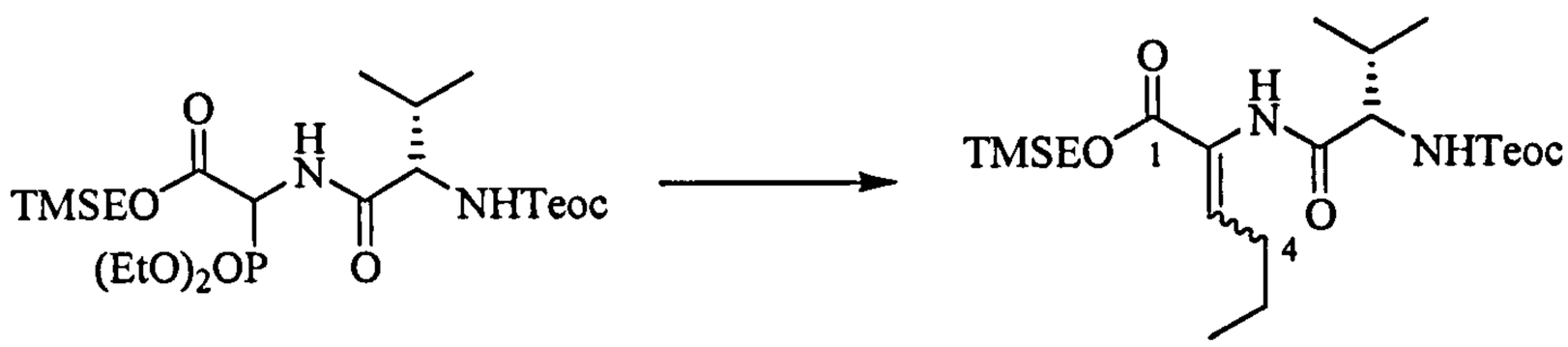


213

To a stirred solution of **99** (40 mg, 0.072 mmol) in dichloromethane (1 mL) at -10 °C, was added dropwise DBN (8.60 μL, 0.072 mmol), and the resulting mixture was stirred

for 10 minutes. *n*-Butanal (6.70 μL, 0.072 mmol) was added dropwise keeping the internal temperature below 10 °C. The reaction mixture was stirred at 10 °C for 1 h and allowed to warm to room temperature with further stirring overnight. The mixture was concentrated *in vacuo* to yield a colourless oil, which after purification by silica gel column chromatography (30% ethyl acetate in petroleum ether; 30%) yielded (*Z*)-**213** as a colourless oil (28 mg, 76%). R_f 0.64 (50% ethyl acetate in petroleum ether); ν_{max}(neat)/cm^{-1} 3294, 2956, 2898, 2875, 1719, 1669, 1514, 830; δ_H (300 MHz, Acetone-d_6) 8.44 (1H, s, =CN*H*-CO), 6.55 (1H, *app*. t, J = 7.4 Hz, H-3), 6.11 (1H, d, $J_{NH\text{-}CH}$ = 8.3 Hz, NH), 4.24-4.09 (5H, m, $(CH_3)_2CHCH$ + 2 x CO_2CH_2), 2.14 (3H, *app*. q, $J_{4\text{-}5}$ = 7.3 Hz, H-4 + $(CH_3)_2CHCH$), 1.46 (2H, *app*. sext. $J_{5\text{-}4}$ = 7.3 Hz, H-5), 1.06-0.88 (13H, m, H-6 + 2 x CH_3 + 2 x CH_2Si), 0.06 (9H, s, 3 x CH_3), 0.04 (9H, s, 3 x CH_3); δ_C (75 MHz, Acetone-d_6) 171.0 (CO), 170.0 (CO), 164.8 (CO), 137.6 (C-3), 127.5 (C-2), 63.3 (CO_2CH_2), 63.0 (CO_2CH_2), 60.8 ($COCHCH(CH_3)_2$), 31.6 ($CH(CH_3)_2$), 30.0 (C-4), 22.0 (C-5), 19.7 (C-6), 18.0 ($SiCH_2$), 18.0 (CH_3), 17.7 ($SiCH_2$), 14.0 (CH_3), -1.5 ($Si(CH_3)_3$), -1.6 ($Si(CH_3)_3$); LRMS (FAB^+) *m/z* 495 [$M+Na^+$], 473 [$M+H^+$], 417 (20), 188 (60), 144 (45 %); HRMS (FAB^+) calculated for $C_{22}H_{45}N_2O_5Si_2$, 473.2867 [$M+H^+$]; found 473.2860.

(2*S*)-[3-Methyl-2-(2-trimethylsilylethoxycarbonylamino)-butyrylamino]-3-propyl_ acrylic acid 2-trimethylsilyl ethyl ester (213)



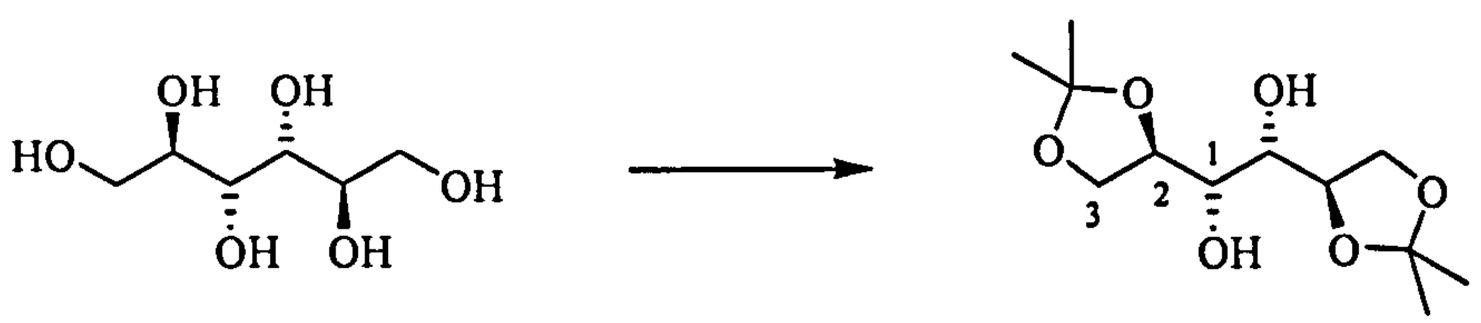
(*Z*)- and (*E*)-213

To a stirred suspension of lithium chloride (9 mg, 0.22 mmol) in dry acetonitrile (0.5 mL) was added **99** (40 mg, 0.072 mmol) followed by DIPEA (12.5 μL, 0.072 mmol). To the clear solution was added *n*-butyraldehyde (6.70 μL, 0.072 mmol) in acetonitrile (0.5 mL), then the reaction mixture was stirred overnight at room temperature. Water (1 mL) was added and the solution extracted with dichloromethane (3 x 1 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a colourless oil which was purified by silica gel column chromatography (30% ethyl acetate in petroleum ether) to yield **213** as a colourless oil:

(*Z*)-**213** (20 mg, 59%), data as previously described, and (*E*)-**213** (5 mg, 15%): R_f 0.58 (50% ethyl acetate in petroleum ether) δ_H (300 MHz, Acetone-d_6) 8.68 (0.2H, s, =CNHCO), 8.43 (0.8H, s, =CNHCO), 6.55 (0.8H, *app.* t, J = 7.5 Hz, H-3), 6.45 (0.2H, *app.* t, J = 7.7 Hz, H-3), 6.18 (0.2H, d, J = 7.4 Hz, NH), 6.10 (0.8H, d, J = 8.5 Hz, NH), 4.29-4.09 (6H, m, C*H*CH$(CH_3)_2$ + 2 x CO_2CH_2), 2.44 (0.4H, *app.* q, J = 7.5 Hz, H-4 + CHC*H*$(CH_3)_2$), 2.16 (1.6H, *app.* sept. J = 6.8 Hz, H-4 + CHC*H*$(CH_3)_2$), 1.46 (2H, *app.* sext, J = 7.4 Hz, H-5), 1.07-0.88 (13H, m, H-6 + 2 x CH_3 + 2 x CH_2Si), 0.06 (9H, s, $Si(CH_3)_3$), 0.04 (9H, s, $Si(CH_3)_3$); δ_C (75 MHz, Acetone-d_6) 170.9 (CO), 170.7 (CO),

164.8 (CO), 137.6 (C-3), 128.0 (C-2), 63.3 (CO_2CH_2), 62.9 (CO_2CH_2), 60.4 ($CHCH(CH_3)_2$), 31.6 ($CHCH(CH_3)_2$), 30.0 (C-4), 22.0 (C-5), 22.7 (C-5) 19.7(C-6), 19.5 (C-6), 18.2 ($SiCH_2$), 18.0 ($SiCH_2$), 17.7 ($SiCH_2$), 14.3 (CH_3), 14.0 (CH_3), 13.9 (CH_3), -1.5 ($Si(CH_3)_3$), -1.6 ($Si(CH_3)_3$).

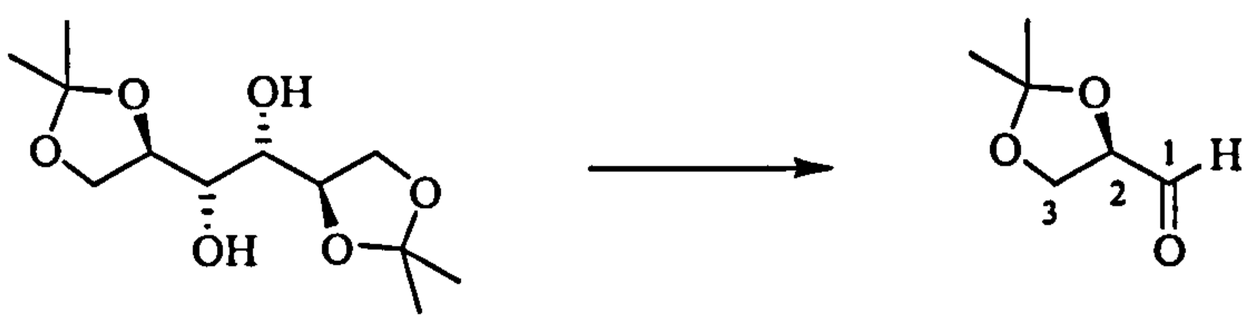
1,2-5,6-Diisopropylidene-D-mannitol.[86]



D-Mannitol (100.00 g, 549 mmol) and 2,2-dimethoxypropane (160 mL, 1.30 mol) were mechanically stirred in freshly distilled 1,2-dimethoxyethane (240 mL) at room temperature. Stannous chloride (100 mg, 0.66 mmol) was added and the reaction was warmed up to reflux for 90 min. The heat was removed and once the reaction had ceased to reflux, pyridine (240 μL) was added. The mixture was allowed to cool to room temperature and the solvent removed *in vacuo*. The resulting crude was redissolved in dichloromethane (600 mL) and mechanically stirred under reflux until most of the solids had dissolved. The heat was removed and once reflux had ceased, celite (20 g) was added. The mixture was cooled to room temperature, the slurry was filtered through celite, and the filtrate was washed with dichloromethane (2 x 100 mL). The organic washings were combined and concentrated, to provide 1,2-5,6-diisopropylidene-D-mannitol (144 g, 100%), which was used without further purification; mp 120-122 °C (Lit. mp 118-120 °C)[85]; $[\alpha]_D^{21}$ + 1.5 (CH_3OH, *c* 20), lit. $[\alpha]_D^{20}$ + 1.9 (CH_3OH, *c* 20)[85]; ν_{max}

(neat)/cm^{-1} 3394-3273, 2978, 1157; δ_H (400 MHz, $CDCl_3$) 4.18 (2H, dd, $J_{1\text{-}1'}$ = 12.3, $J_{1\text{-}2}$ = 6.2 Hz, H-1), 4.11 (2H, dd, $J_{3\text{-}3'}$ = 8.5, $J_{3\text{-}2}$ = 6.2 Hz, H-3), 3.96 (2H, dd, $J_{3'\text{-}3}$ = 8.5, $J_{3\text{-}2}$ = 6.2 Hz, H-3'), 3.74 (2H, d, $J_{2\text{-}3}$ = 6.2 Hz, H-2), 2.56 (2H, bs, OH), 1.41 (6H, s, CH_3), 1.35 (6H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 109.4 (2 x $(CH_3)_2C$), 76.3 (2 x C-1), 71.2 (2 x C-2), 66.7 (2 x C-3), 26.7 (2 x CH_3), 25.2 (2 x CH_3). Spectroscopic data were in accordance with the reported values of Schmid *et al.*[86]

2, 3-*O*-isopropylidene-D-glyceraldehyde ((*R*)-158).[86]

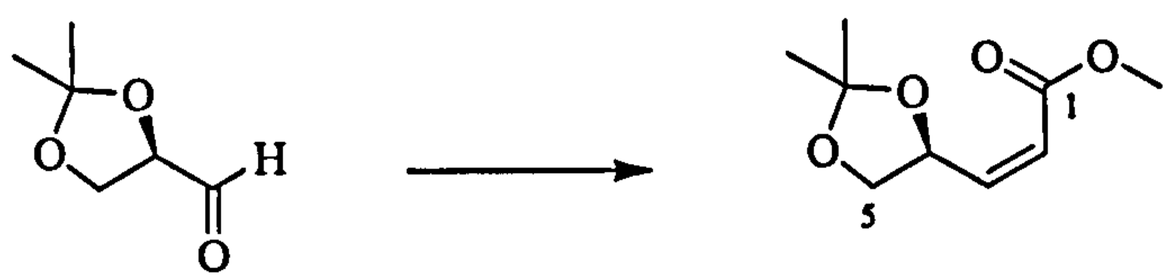


(*R*)-**158**

1,2-5,6-Diisopropylidene-D-mannitol (100.00 g, 381.00 mmol) was mechanically stirred in dichloromethane (1 L) at 0 °C with saturated $NaHCO_3$ solution (40 mL). Sodium *meta*periodate (163.1 g, 762.0 mmol) was added in portions, maintaining the internal temperature below 35 °C. Once addition was complete, the reaction was stirred for 20 min at 0 °C and for 2 h at room temperature. $MgSO_4$ (90.0 g) was added and after stirring for 20 min, the reaction was filtered. The residue was washed with dichloromethane (2 x 600 mL) and the solvent from the filtrate was removed by distillation. The remaining oil was distilled at 30 mmHg and the fraction collected between 67-73 °C provided (*R*)-**158** (72.23 g, 73%). $[\alpha]_D^{19}$ + 60 (C_6H_6, *c* 1.7), lit. $[\alpha]_D^{23}$ + 70-80 (C_6H_6, *c* 1.0-1.5)[85]; ν_{max} (neat)/cm^{-1} 2989, 2938, 1734, 1374, 1149; δ_H (400 MHz,

$CDCl_3$) 9.63 (1H, *app.* t, $J_{1\text{-}2}$ = 1.5 Hz, CHO), 4.30 (1H, ddd, $J_{2\text{-}3}$ = 7.6, $J_{2\text{-}3'}$ = 4.8, $J_{2\text{-}1}$ = 1.5 Hz, H-2), 4.09 (1H, *app.* t, $J_{3\text{-}2}$ = 7.6 Hz, H-3), 4.02 (1H, dd, $J_{3'\text{-}3}$ = 8.8, $J_{3'\text{-}2}$ = 4.8 Hz, H-3'), 1.40 (3H, s, CH_3), 1.33 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 201.6 (CHO), 111.1 ($(CH_3)_2C$), 79.7 (C-3), 65.4 (C-2), 26.1 (CH_3), 25.0 (CH_3). Spectroscopic data were in accordance with the reported values of Schmid *et al.*[86]

(*Z*)-Methyl 3-((*S*)-2, 2-dimethyl-1, 3-dioxolan-4-yl)acrylate (160).[88]



160

To a stirred solution of (*R*)-**158** (3.74 g, 28.70 mmol) in methanol (120 mL) at -10 °C was added methyl (trimethylphosphoranylidene)acetate (11.52 g, 34.40 mmol) then the mixture was stirred at -10 °C for 20 h. The reaction mixture was concentrated *in vacuo*, diethyl ether (20 mL) was added and the mixture filtered. The filtrate was concentrated *in vacuo* to give a colourless oil that after purification by silica gel column chromatography (10% diethyl ether in petroleum ether) afforded (*Z*)-**160** (4.05 g; 76%) as a colourless oil. R_f 0.08 (10% diethyl ether in petroleum ether); ν_{max} (neat)/cm^{-1} 2988-2878, 1723, 714; δ_H (400 MHz, $CDCl_3$) 6.33 (1H, dd, $J_{3\text{-}2}$ = 11.7, $J_{3\text{-}4}$ = 6.7 Hz, H-3), 5.82 (1H, dd, $J_{2\text{-}3}$ = 11.7, $J_{2\text{-}4}$ = 1.4 Hz, H-2), 5.46 (1H, qd, $J_{4\text{-}3}$ = 6.7, $J_{4\text{-}2}$ = 1.4 Hz, H-4), 4.34 (1H, *app.* t, $J_{5\text{-}5'}$ = 7.6 Hz, H-5), 3.68 (3H, s, CH_3O_2C), 3.58 (1H, *app.* t, $J_{5'\text{-}5}$ = 7.6 Hz, H-5'), 1.41 (3H, s, CH_3), 1.35 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 166.0 (CO), 149.5 (C-3), 120.2 (C-2), 109.7 ($C(CH_3)_2$), 73.5 (C-4), 69.3 (C-5), 51.4 (CH_3O_2C), 26.5

(CH_3), 25.3 (CH_3); further elution provided (*E*)-**160** (532 mg; 10%) was also isolated as a colourless oil. R_f 0.03 (10% diethyl ether in petroleum ether); δ_H (400 MHz, $CDCl_3$) 6.88 (1H, dd, $J_{2\text{-}3}$ = 15.7, $J_{2\text{-}4}$ = 5.7 Hz, H-2), 6.10 (1H, dd, $J_{3\text{-}2}$ = 15.7, $J_{3\text{-}4}$ = 1.5 Hz, H-3), 4.68-4.63 (1H, m, H-4), 4.17 (1H, dd, $J_{5\text{-}5'}$ = 8.3, $J_{5\text{-}4}$ = 6.6 Hz, H-5), 3.74 (3H, s, CH_3O_2C), 3.66 (1H, dd, $J_{5'\text{-}5}$ = 8.3, $J_{5'\text{-}4}$ = 7.0 Hz, H-5'), 1.43 (3H, s, CH_3), 1.39 (3H, s, CH_3). Spectroscopic data were in accordance with the reported values of Sugisaki *et al.*[88]

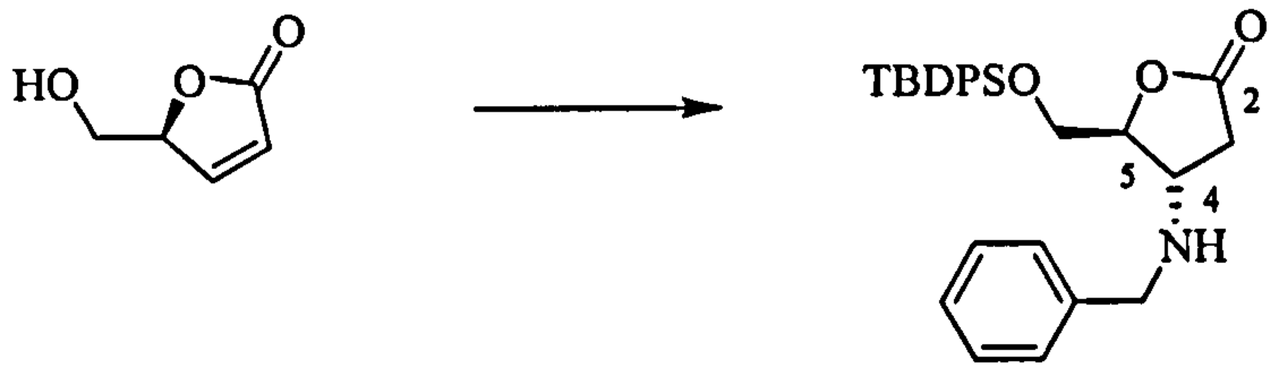
(5*S*)-(Hydroxymethyl)furan-2(5*H*)-one (156).[88]

156

To a stirred solution of (*Z*)-**160** (195 mg, 0.373 mmol) in ethanol (26 mL) was added DOWEX 50W-X8 (614 mg) and the suspension stirred for 8 h. The mixture was filtered and the solvent removed *in vacuo*. The crude product was dissolved in dichloromethane (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Silica gel colum chromatography (80% diethyl ether in petroleum ether; 80%) provided **156** (84 mg, 99%) as a colourless gel. R_f 0.41 (5% methanol in ethyl acetate); $[\alpha]_D^{28.1}$ - 132.7 (water, *c* 1.1), Lit. $[\alpha]_D^{25}$ - 143 (water, *c* 1.135); ν_{max} (neat)/cm^{-1} 3388, 2968-2942, 1714, 1596, 1385, 1333, 1110, 1048, 717-683; δ_H (400 MHz, $CDCl_3$) 7.48 (1H, dd, $J_{3\text{-}4}$ = 5.8, $J_{3\text{-}5}$ = 1.5 Hz, H-3), 6.16 (1H, dd, $J_{4\text{-}3}$ = 5.8, $J_{4\text{-}5}$ = 2.0 Hz, H-4), 5.14 (1H, ddd, $J_{5\text{-}6'}$ = 5.0, $J_{5\text{-}6}$

= 3.8, $J_{5\text{-}4}$ = 2.0 Hz, H-5), 3.95 (1H, dd, $J_{6\text{-}6'}$ = 12.3, $J_{6\text{-}5}$ = 3.8 Hz, H-6), 3.76 (1H, dd, $J_{6'\text{-}6}$ = 12.3, $J_{6'\text{-}5}$ = 5.0 Hz, H-6'), 2.95 (1H, s, OH); δ_C (100 MHz, $CDCl_3$) 173.4 (C-2), 153.8 (C-3), 122.9 (C-4), 84.2 (C-5), 62.2 (C-6); LRMS (EI^+) *m/z*: 115 [$M+H^+$], 97 (10), 84 (100), 83 (35%); HRMS (EI^+): calculated for $C_5H_7O_3$ 115.0395 [$M+H^+$], found 115.0398. Spectroscopic data were in accordance with the reported values of Sugisaki *et al.*[88]

(4*S*, 5*S*)-4-Benzylamino-4-[(*tert*-butyldiphenylsilyl)oxymethyl]dihydro-2(3*H*)-furan-one (169).[91]

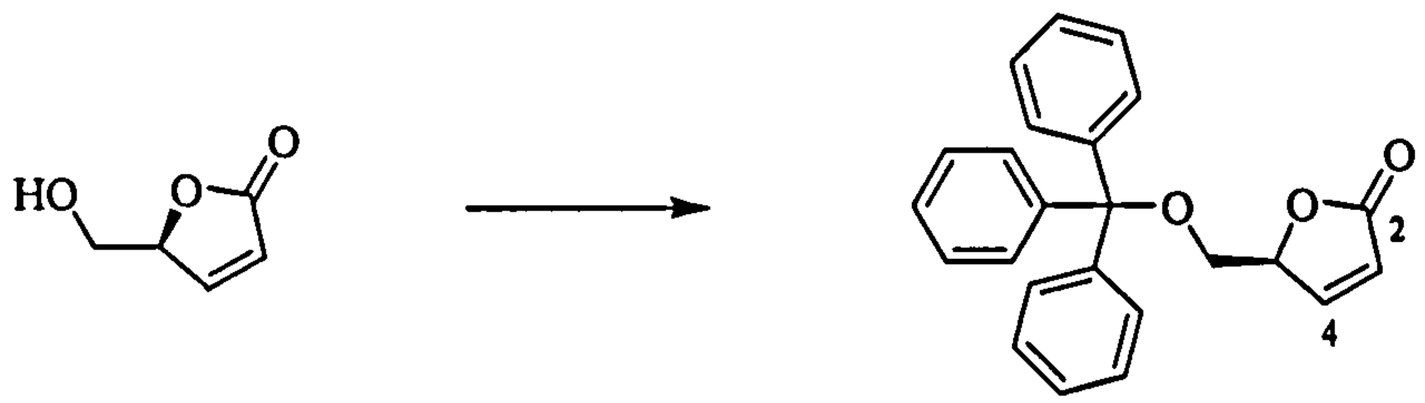


169

To a stirred solution of **156** (500 mg, 4.39 mmol) in dry methanol (3.4 mL) at 0 °C was added dropwise benzylamine (480 μL, 4.39 mmol) and the mixture stirred for 36 h at 0 °C. It was then concentrated *in vacuo* and the residue dissolved in *N*, *N*'-dimethylformamide (10 mL). To the resulting solution was added *tert*-butyldiphenylsilyl chloride (1.5 mL, 6.45 mmol) and imidazole (470 mg, 6.90 mmol). The reaction mixture was stirred for 48 h at room temperature, was then partitioned between water (30 mL) and diethyl ether (30 mL) and the aqueous phase extracted with diethyl ether (3 x 20 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Silica gel column chromatography (50% diethyl ether in petroleum ether)

provided **169** (0.789 g, 39%) as a yellow oil. R_f 0.1 (60% diethyl ether in light petroleum); $[\alpha]_D^{23}$ + 20.3 ($CHCl_3$, *c* 1.1), lit. $[\alpha]_D^{20}$ + 15.3 ($CHCl_3$, *c* 1.08)[90]; ν_{max}(neat)/cm^{-1} 3072, 2931, 2858, 1774, 1361, 1111; δ_H (400 MHz, $CDCl_3$) 7.69-7.64 (4H, m, ArH), 7.49-7.41 (6H, m, ArH), 7.36-7.29 (5H, m, ArH), 4.38 (1H, *app.* q, $J_{5\text{-}4}$ = 3.4 Hz, H-5), 3.90-3.86 (2H, dd, $J_{CH\text{-}Ar}$ = 11.3, $J_{CH\text{-}NH}$ = 3.8 Hz, $PhCH_2$), 3.80 (2H, d, $J_{CH\text{-}5}$ = 5.5 Hz, OCH_2), 3.67 (1H, *app.* q, $J_{4\text{-}3'}$ = 3.7 Hz, H-4), 2.98-2.91 (1H, dd, $J_{3\text{-}3'}$ = 17.8, $J_{3\text{-}4}$ = 7.8 Hz, H-3), 2.46-2.40 (1H, dd, $J_{3'\text{-}3}$ = 17.8, $J_{3'\text{-}4}$ = 4.0 Hz, H-3'), 1.07 (9H, s, $Si(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 175.8 (CO), 139.1 (ArC), 135.6 (2 x ArCH), 135.5 (2 x ArCH), 132.6 (ArC), 132.4 (ArC), 129.9 (2 x ArCH), 128.6 (2 x ArCH), 128.0 (2 x ArCH), 127.8 (3 x ArCH), 127.4 (2 x ArCH), 85.1 (C-5), 64.2 (CH_2), 55.7 (C-4), 51.6 (CH_2O), 36.5 (C-3), 26.7 ($SiC(CH_3)_3$), 19.1 ($SiC(CH_3)_3$). Spectroscopic data were in accordance with the reported values of Collis *et al.*[91]

(5*S*)-[(Triphenylmethoxy)methyl]-2(5*H*)-furanone (171).[92]

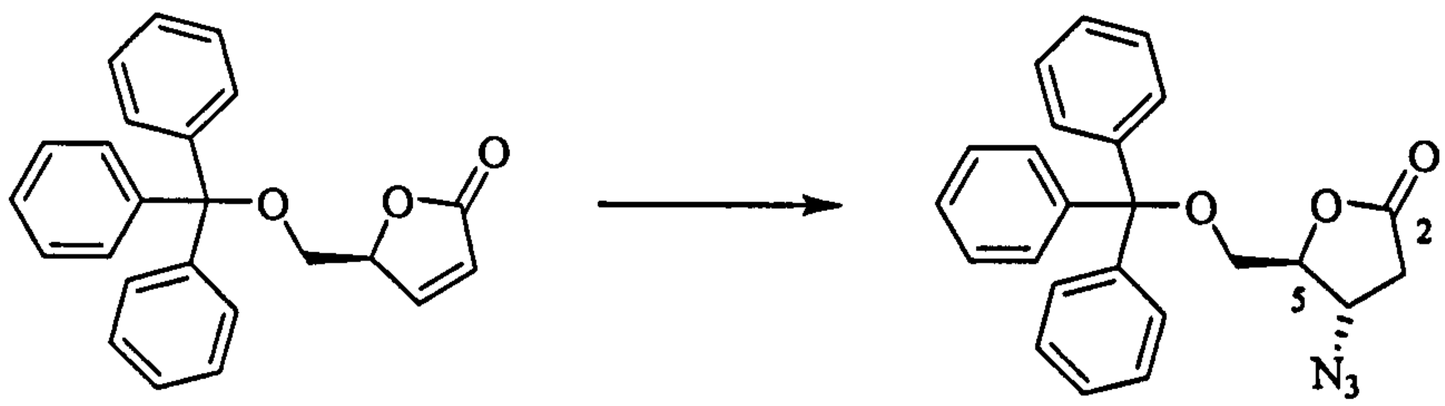


171

To a stirred solution of **156** (1.00 g, 8.77 mmol) in dry pyridine (50 mL) was added trityl chloride (2.90 g, 10.50 mmol) and the resulting solution heated at 70 °C for 16 h. On cooling to room temperature, it was poured onto ice-water (20 mL) and extracted with diethyl ether (3 x 15 mL). The combined organic layer was washed with 0.1 M HCl to

acidic pH, then washed with saturated aqueous $NaHCO_3$ solution (20 mL) and water (20 mL), it was then dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a colourless oil. Purification by silica gel column chromatography (50% ethyl acetate in petroleum ether) gave **171** (2.31 g, 74%) as a white crystalline solid. mp 152-155 °C (Lit. mp 152-154 °C)[91]; R_f 0.28 (100% ethyl acetate); $[\alpha]_D^{23}$ - 82.6 (*c* 3.51, $CHCl_3$), Lit. $[\alpha]_D^{20}$ - 95.1 (*c* 3.42, $CHCl_3$)[91]; ν_{max} (neat)/cm^{-1} 3092, 2927, 1751, 1607, 1489, 1450; δ_H (400 MHz, $CDCl_3$) 6.84-6.78 (6H, m, ArH + H-3), 6.64-6.62 (10H, m, ArH), 5.59 (1H, dd, J = 5.6, J = 2.1 Hz, H-4), 4.49 (1H, tt, J = 6.7, $J_{5\text{-}6}$ = 4.9, J = 1.7, H-5), 2.79 (2H, dd, $J_{6\text{-}5}$ = 4.9, J = 2.5 Hz, H-6); δ_C (100 MHz, $CDCl_3$) 172.8 (C-2), 154.2 (C-4), 143.3 (3 x ArC), 128.6 (6 x ArCH), 128.0 (6 x ArCH), 127.3 (3 x ArCH), 122.5 (C-3), 87.0 (CPh_3), 82.1 (C-5), 63.4 (C-6); LRMS (FAB^+) *m/z* 356 [$M+H^+$], 259 (5), 243 (100), 154 (56%); HRMS (FAB^+): calcd. for $C_{24}H_{21}O_3$ 356.141 [$M+H^+$], found 356.140. Spectroscopic data were in accordance with the reported values of García *et al.*[92]

(4*S*, 5*S*)-4-Azido-5-[(triphenylmethoxy)methyl]-2(5*H*)-furanone (174).

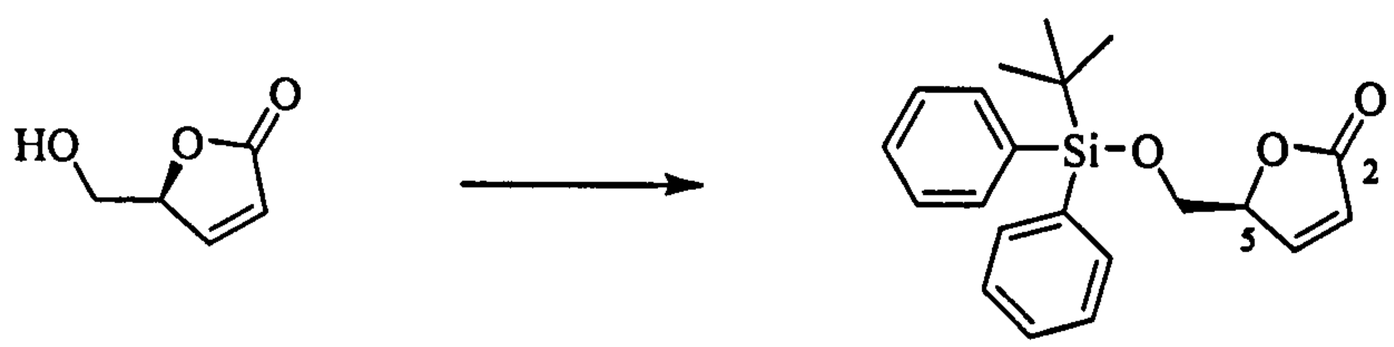


174

To a stirred solution of **171** (100 mg, 0.28 mmol) in water (100 μL), tetrahydrofuran (150 μL), and glacial acetic acid (17.4 M; 496 μL, 8.63 mmol), was added sodium azide

(CAUTION) (200 mg, 3.07 mmol) and the reaction mixture stirred at room temperature for three days. Water (1 mL) was then added, and the crude reaction mixture extracted with ethyl acetate (3 x 1 mL). The combined organic layers were washed with water (2 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give an oil, which was purified by silica gel column chromatography (40% ethyl acetate in petroleum ether) to give **174** (59 mg, 52%) as a colourless oil. R_f 0.45 (40% ethyl acetate in petroleum ether); ν_{max} (neat)/cm^{-1} 3059, 2929, 2101, 1781, 1597, 1490, 1448; δ_H (400 MHz, $CDCl_3$) 7.50-7.27 (15 H, m, ArH), 4.60-4.57 (1H, m, H-4), 4.55 (1H, *br.* q, $J_{5\text{-}6}$ = 3.2 Hz, H-5), 3.57-3.53 (1H, dd, $J_{6\text{-}6'}$ = 10.8, $J_{6\text{-}5}$ = 3.2 Hz, H-6), 3.35-3.32 (1H, dd, $J_{6'\text{-}6}$ = 10.8, $J_{6'\text{-}5}$ = 3.5 Hz, H-6'), 3.21-3.14 (1H, dd, $J_{3\text{-}3'}$ = 18.0, $J_{3\text{-}4}$ = 7.7 Hz, H-3), 2.64 (1H, dd, $J_{3'\text{-}3}$ = 18.0, $J_{3'\text{-}4}$ = 3.6 Hz, H-3'); δ_C (100 MHz, $CDCl_3$) 173.9 (C-2), 142.9 (3 x ArC), 128.4 (5 x ArCH), 128.1 (5 x ArCH), 127.4 (5 x ArCH), 87.5 (Ph_3CO), 83.3 (C-5), 63.1 (C-6), 58.8 (C-4), 35.1 (C-3); LRMS (ES^+) *m/z*: 423 [$MH+Na^+$], 243 (100), 165 (40%); HRMS (FAB^+): calculated for $C_{24}H_{21}N_3O_3Na$ 422.1475 [$M+Na^+$], found 422.1477.

(5*S*)-[(*tert*-Butyldiphenylsilyl)oxymethyl]-2(5*H*)-furanone (168).[93]

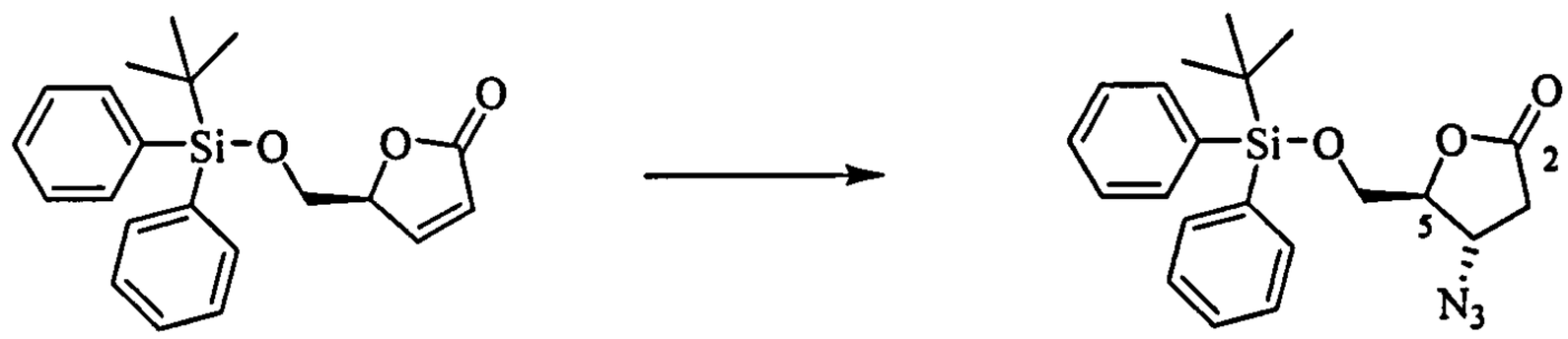


168

To a stirred solution of **156** (17.70 g, 155.00 mmol) and imidazole (20.70 g, 304.00 mmol) in *N*, *N*'-dimethylformamide (200 mL) at 0 °C, was added *tert*-butyldiphenylsilyl

chloride (32.37 mL, 185.00 mmol). The mixture was stirred at room temperature for 16 h then water (200 mL) was added, and the mixture was extracted with diethyl ether (3 x 200 mL). The combined organic layers were washed with water (200 mL) and brine (200 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a pale yellow oil, which was purified by silica gel column chromatography (10% ethyl acetate in petroleum ether) to give **168** (52.77 g, 96%) as a white solid. mp 80-81 °C (Lit. mp 79-80 °C)[92]; R_f 0.22 (20% ethyl acetate in petroleum ether); $[\alpha]_D^{18}$ - 80.7 (*c* 1.05, $CHCl_3$), Lit. $[\alpha]_D^{25}$ - 81.8 (*c* 1.05, $CHCl_3$)[92]; ν_{max} (neat)/cm^{-1} 3070, 2935-2858, 1749, 1604, 1330, 1099; δ_H (400 MHz, $CDCl_3$) 7.64-7.61 (4H, m, ArH), 7.46-7.37 (7H, m, ArH + H-3), 6.17 (1H, dd, *J* = 5.6 Hz, H-4), 5.06 (1H, *app*. hept, *J* = 1.8 Hz, H-5), 3.90 (1H, dd, *J* = 10.9, *J* = 4.3 Hz, SiOC*H*H), 3.86 (1H, dd, *J* = 10.9, *J* = 4.9 Hz, SiOCH*H*), 1.03 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 172.9 (CO), 153.9 (C-3), 135.6 (2 x ArCH), 132.7 (ArC), 132.5 (ArC), 130.0 (2 x ArCH), 129.9 (2 x ArCH), 127.9 (2 x ArCH), 127.8 (2 x ArCH), 122.7 (C-4), 83.2 (C-5), 63.3 (CH_2), 26.7 ($C(CH_3)_3$), 19.2 ($C(CH_3)_3$); LRMS (ES^+) *m/z*: 353 [$M+H^+$], 327 (100 %); HRMS (FAB^+): calcd. for $C_{21}H_{25}O_3Si$ 353.157 [$M+H^+$], found 353.156. Spectroscopic data were in accordance with the reported values of Jeong *et al.*[93]

4-(*S*)-Azido-5(*S*)-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-3,4-dihydro-(5*H*)-furan-2-one (173).[93]



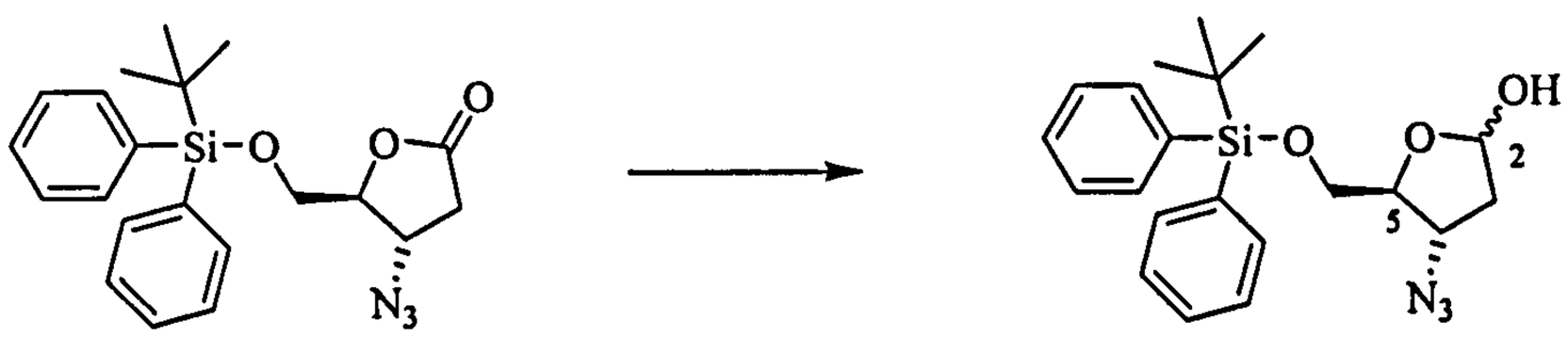
173

To a vigorously stirred suspension of **168** (10.00 g, 0.28 mmol) in glacial acetic acid (50 mL), water (20 mL) and tetrahydrofuran (15 mL), was added portionwise sodium azide (CAUTION) (20 g) over 4 days (8 portions), after which time the reaction mixture was stirred for an additional day. Water (20 mL) was added and the mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with water (30 mL), then the organic phase was transferred to a beaker and neutralised with a saturated solution of $NaHCO_3$. The combined organic layers were then washed with water (20 mL), then brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a colourless oil. Purification by silica gel column chromatography (5% ethyl acetate in petroleum ether) gave **173** (8.90 g, 79%) as a white crystalline solid: mp 74-77 °C (Lit. mp 72-74 °C)[92]; R_f 0.25 (10% ethyl acetate in petroleum ether); $[\alpha]_D^{19}$ + 19.8 ($CHCl_3$, *c* 1.53), lit. $[\alpha]_D^{25}$ + 19.0 ($CHCl_3$, *c* 1.53)[92]; ν_{max} (neat)/cm^{-1} 2932, 2860, 2112, 1787, 1260, 1111; δ_H (400 MHz, $CDCl_3$) 8.65-7.61 (4H, m, ArH), 7.49-7.37 (6H, m, ArH), 4.41-4.38 (2H, m, H-4 + H-5), 3.89 (1H, dd, J_{gem} = 11.7, $J_{CHH\text{-}5}$= 3.0 Hz, SiOC*H*H), 3.77 (1H, dd, J_{gem} = 11.7, $J_{CHH\text{-}5}$ = 2.3 Hz, SiOCH*H*), 3.04 (1H, dd, $J_{3\text{-}3'}$ = 18.0, $J_{3\text{-}4}$ = 7.6 Hz, H-3), 2.57 (1H, dd, $J_{3'\text{-}3}$ = 18.0, $J_{3'\text{-}4}$ = 3.0 Hz, H-3'), 1.05 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 173.8 (CO), 135.6 (2 x ArCH), 135.4 (2 x ArCH),

134.6 (ArCH), 132.4 (ArC), 131.8 (ArC), 130.2 (2 x ArCH), 128.0 (2 x ArCH), 127.5 (ArCH), 84.2 (C-5), 63.6 (CH_2), 58.6 (C-4), 35.2 (C-3), 26.7 ($C(CH_3)_3$), 19.1 ($C(CH_3)_3$); LRMS (CI^+) *m/z*: 413 [$M+NH_4^+$], 370 (70), 274 (60%); HRMS (ES^+): calcd. for $C_{21}H_{29}N_4O_3Si$ 413.2003 [$M+NH_4^+$], found 413.2002. Anal. calcd. for $C_{21}H_{25}N_3O_3Si$: C, 63.77; H, 6.37; N, 10.62%. Found: C, 63.75; H, 6.39; N, 10.48%.

^1H NMR data were in accordance with the reported values of Jeong *et al.*[93]

(4*S*, 5*S*)-4-Azido-5-*O*-(*tert*-butyldiphenylsilyl)-2, 3-dideoxy-α, β-D-*erythro*pento-furanose (182).[93]

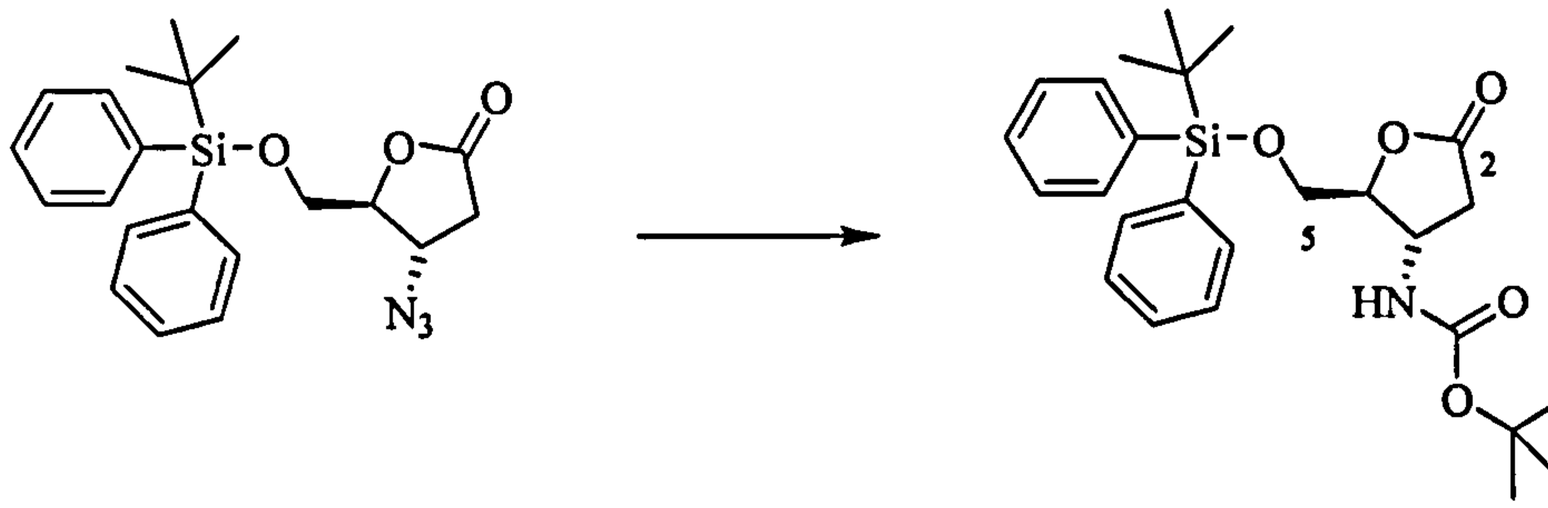


182

To a stirred solution of **173** (1.00 g, 2.53 mmol) in dichloromethane (60 mL) at -78 °C, was added dropwise a solution of DIBAL-H (1M in hexanes; 37.90 mL, 38.00 mmol). The mixture was stirred at -78 °C for 4 h and then quenched by addition of a solution of methanol in chloroform (1:5, v/v; 60 mL). The solution was warmed to room temperature, then aqueous sodium potassium tartrate (30 mL) was added. The resulting solution was further stirred for 1 h, then extracted with chloroform (3 x 60 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield a colourless oil which was purified by silica gel column chromatography (15% ethyl acetate in petroleum ether) to give **182** (804 mg, 80%) as a colourless oil; $[\alpha]_D^{21}$ +

17.9 (*c* 1.42, $CHCl_3$); lit. $[\alpha]_D^{25}$ + 11.5 (*c* 1.41, $CHCl_3$)[92]; R_f 0.40 (30% ethyl acetate in light petroleum); ν_{max} (neat)/cm^{-1} 3418, 3072-2858, 2101, 1260, 1111; δ_H (400 MHz, $CDCl_3$) 7.72-7.58 (4H, m, ArH), 7.48-7.40 (6H, m, ArH), 5.58-5.53 (1H, m, H-2), 4.30-4.24 (1H, m, H-4), 4.19 (0.5H, dt, J = 7.8, J = 2.8 Hz, H-5), 4.04 (0.5H, *app*.q, J = 4.3 Hz, H-5), 3.86-3.64 (2H, m, H-6), 3.41 (0.5H, d, $J_{OH\text{-}2}$ = 6.3 Hz, OH), 3.20 (0.5H, d, $J_{OH\text{-}2}$ = 6.3 Hz, OH), 2.38-2.29 (1H, m, H-3), 21.7-2.11 (0.5H, m, H-3'), 2.06 (0.5H, dd, $J_{3'\text{-}3}$ = 14.0, J = 1.7 Hz, H-3'), 1.12 (4.5H, s, 3 x CH_3), 1.09 (4.5H, s, 3x CH_3); δ_C (100 MHz, $CDCl_3$) 135.6 (ArCH), 135.5 (ArCH), 135.4 (ArCH), 132.9 (ArC), 132.8 (ArC), 132.5 (ArC), 130.0 (ArCH), 129.9 (ArCH), 129.8 (3 x ArCH), 127.9 (ArCH), 127.8 (ArCH), 127.7 (ArCH), 98.7 (C-2), 98.5 (C-2), 85.2 (C-5), 84.0 (C-5), 64.7 (C-6), 64.0 (C-6), 61.5 (C-4), 60.9 (C-4), 40.4 (C-3), 39.1 (C-3), 26.8 (3 x CH_3), 26.7 (3 x CH_3), 19.2 ($C(CH_3)_3$); LRMS (CI^+) *m/z* 397 [$M+H^+$], 372 (20), 89 (100%); HRMS (ES^+): calculated for $C_{21}H_{31}N_4O_3Si$ 415.2160 [$M+NH_4^+$], found 415.2162. Spectroscopic data were in accordance with the reported values of Jeong *et al.*[93]

(4*S*, 5*S*)-4-(*tert*-Butyloxycarbonylamino)-5-[(*tert*-(butyldiphenylsilyl)oxymethyl] dihydro-2-(5*H*)furanone (199).

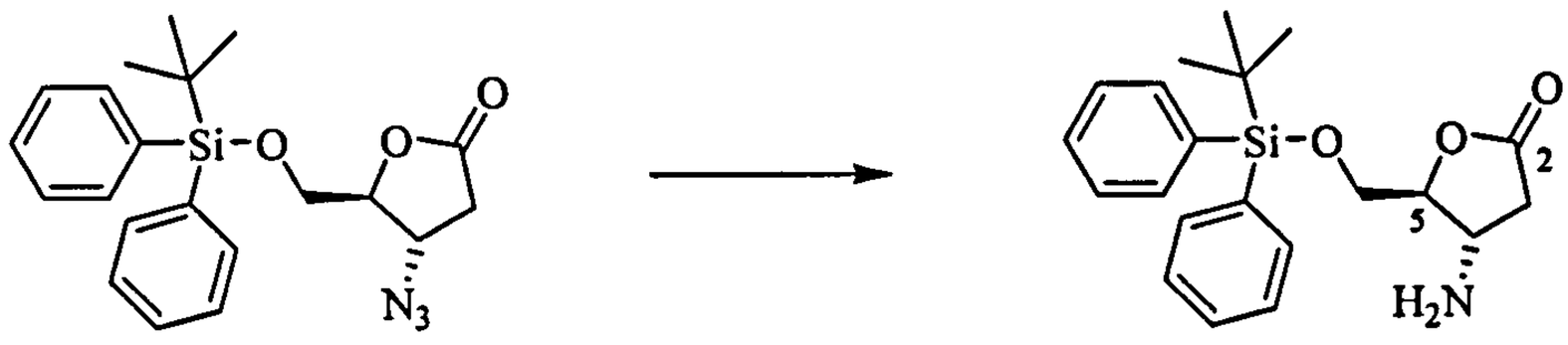


199

To a stirred suspension of palladium on carbon (10% w/w; 278 mg) in ethyl acetate (15 mL), was added a mixture of **173** (2.77 g, 7.00 mmol) and di-*tert*-butyl dicarbonate (1.83 g, 8.40 mmol) in ethyl acetate (13 mL). This suspension was stirred under an atmosphere of hydrogen for 16 h. After which time it was filtered through a celite pad, and the filtrate concentrated *in vacuo* to give a colourless oil. Purification by silica gel column chromatography (10% ethyl acetate in dichloromethane) gave **199** (2.38 g, 72%) as a white powder; mp 148-150 °C; $[\alpha]_D^{29.5}$ + 8.4 ($CHCl_3$, *c* 1.0); R_f 0.4 (20% ethyl acetate in dichloromethane); ν_{max} (neat)/cm^{-1} 3329, 2960, 2930, 2930, 2857, 1778, 1683, 1530; δ_H (400 MHz, Acetone-d_6) 7.76-7.71 (4H, m, ArH), 7.51-7.43 (6H, m, ArH), 6.63 (1H, s, NH), 4.50 (2H, *br*. s, H-4, H-5), 3.95 (1H, dd, $J_{6\text{-}6'}$ = 11.6, $J_{6\text{-}5}$ = 2.2 Hz, H-6), 3.90 (1H, dd, $J_{6\text{-}6'}$ = 11.6, $J_{6'\text{-}5}$ = 2.9 Hz, H-6'), 2.99 (1H, dd, $J_{3\text{-}3'}$ = 17.7, $J_{3\text{-}4}$ = 8.8 Hz, H-3), 2.58 (1H, dd, $J_{3'\text{-}3}$ = 17.7, $J_{3'\text{-}4}$ = 4.6 Hz, H-3'), 1.41 (9H, s, $OC(CH_3)_3$), 1.05 (9H, s, $SiC(CH_3)_3$); δ_C (100 MHz, Acetone-d_6) 175.2 (C-2), 156.1 (CO), 136.2 (3 x ArCH), 133.6 (ArC), 133.4 (ArC), 130.7 (ArCH), 128.7 (3 x ArCH), 128.6 (3 x ArCH), 86.3 (C-5), 79.4 ($C(CH_3)_3$), 64.9 (C-6), 49.5 (C-4), 35.7 (C-3), 28.4 (3 x CH_3), 26.9 (3 x CH_3), 19.6 ($SiC(CH_3)_3$); LRMS (FAB^+) *m/z* 492 [$M+Na^+$], 470 (100), 460 (60%); HRMS

(FAB$^+$): calculated for $C_{26}H_{36}NO_5Si$ 470.236 [M+H$^+$], found 470.235. Anal. calcd. for $C_{26}H_{35}NO_5Si$: C, 66.49; H, 7.51; N, 2.98%. Found: C, 66.44; H, 7.54; N, 2.96%.

(4*S*, 5*S*)-4-Amino-5-(*tert*-butyldiphenylsilyl)oxymethyldihydro-2-(5*H*)furanone (175).[91]

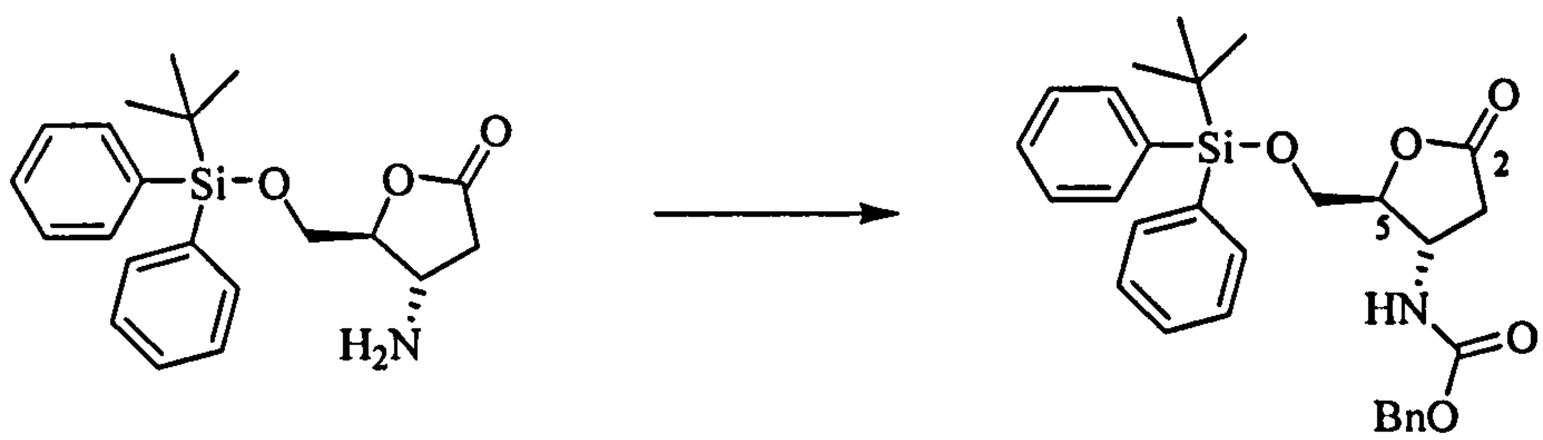


175

A suspension of **173** (3.40 g, 8.60 mmol) and palladium on carbon (340 mg; 10% w/w) in ethyl acetate (33 mL) was stirred under an atmosphere of hydrogen for 4 h. The suspension was filtered through a pad of celite and concentrated *in vacuo*, to give a yellow oil that was purified by silica gel column chromatography (0 → 10% methanol in ethyl acetate) to give **175** (3.05 g, 90%) as a colourless oil. R_f 0.18 (10% methanol in ethyl acetate, 10%); $[\alpha]_D^{18}$ + 10.7 ($CHCl_3$, *c* 0.72), Lit. $[\alpha]_D^{20}$ + 19.4 ($CHCl_3$, *c* 0.72)[90]; ν_{max} (neat)/cm^{-1} 3372, 2932-2858, 1770, 1589, 1259, 1175, 1111; δ_H (400 MHz, $CDCl_3$) 7.68-7.64 (4H, m, ArH), 7.48-7.39 (6H, m, ArH), 4.18 (1H, *app.* q, J = 3.5 Hz, H-5), 3.89-3.79 (3H, m, CH_2 + H-4), 2.97 (1H, dd, $J_{3\text{-}3'}$ = 17.6, J = 7.6 Hz, H-3), 2.30 (1H, dd, $J_{3'\text{-}3}$ = 17.6, J = 4.9 Hz, H-3'), 1.06 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 175.6 (C-2), 135.5 (2 x ArCH), 135.4 (2 x ArCH), 135.4 (2 x ArCH), 132.7 (ArC), 132.2 (ArC), 129.9 (2 x ArCH), 127.8 (2 x ArCH), 87.6 (C-5), 63.7 (CH_2), 50.1 (C-4), 38.9 (C-3), 26.7 ($C(CH_3)_3$), 19.1 ($C(CH_3)_3$); LRMS (CI$^+$) *m/z* 387 [M+NH$_4^+$] (90), 370 [M+H$^+$],

(50), 274 (20), 250 (20), 72 (60), 70 (100%); HRMS (ES^+) calculated for $C_{21}H_{28}NO_3Si$ 370.1833 [$M+H^+$]; found 370.1833. Spectroscopic data were in accordance with the reported values of Collis *et al.*[91]

(4*S*, 5*S*)-4-Benzyloxycarbonylamino-5-[(*tert*-butyldiphenylsilyl)oxymethyl]dihydro-2(5*H*)furanone (176).[91]

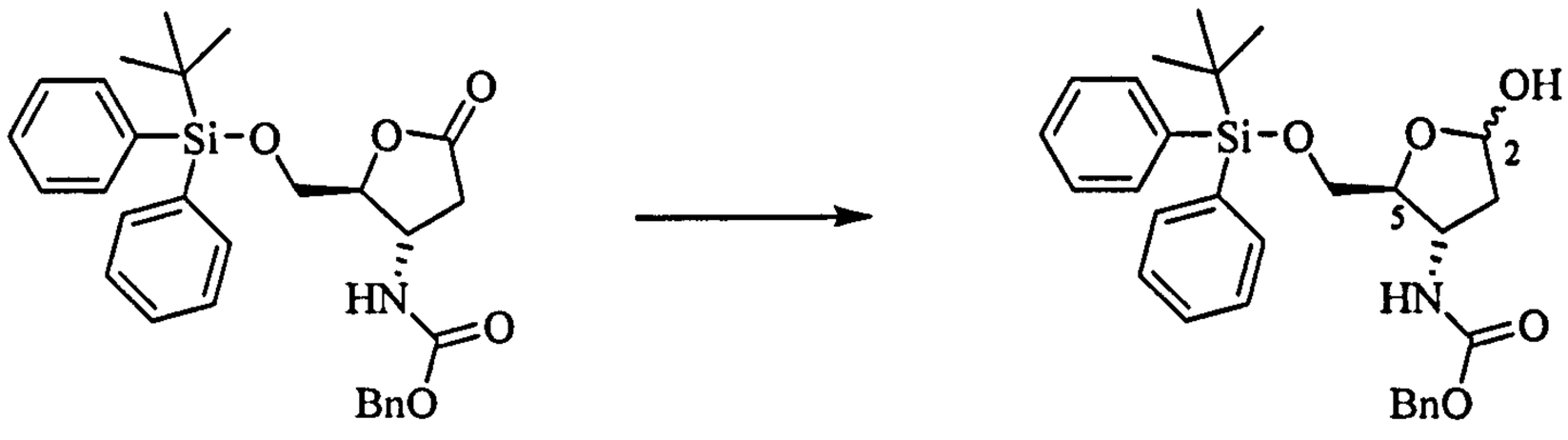


176

To a stirred solution of **175** (1.35 g, 3.65 mmol) in tetrahydrofuran/water (1:1, v/v; 30 mL) was added sodium carbonate (774 mg, 7.3 mmol) then the mixture was cooled to 0 °C. Benzyloxycarbonyl chloride (584 μL, 4.09 mmol) was added dropwise. After 1h, the mixture was allowed to warm to room temperature and stirring continued for a further 2.5 h. The mixture was diluted with diethyl ether (15 mL), washed with water (10 mL) and the aqueous phase back extracted with diethyl ether (3 x 15 mL). The combined organic fractions were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give an oil. Purification by silica gel column chromatography (10% ethyl acetate in petroleum ether) gave **176** (1.76g, 98%) as a white foam. R_f 0.31 (30% ethyl acetate in petroleum ether); $[\alpha]_D^{21}$ + 17.1 ($CHCl_3$, *c* 0.693); lit. $[\alpha]_D^{20}$ + 18.9 ($CHCl_3$, *c* 0.695)[90]; ν_{max} (neat)/cm^{-1} 3326, 3032-2859, 1777, 1699, 1488, 1528; δ_H (400 MHz, Acetone-d_6) 7.76-

7.71 (5H, m, ArH), 7.50-7.42 (5H, m, ArH), 7.38-7.29 (5H, m, ArH), 7.00 (1H, *br.* d, $J_{NH\text{-}4}$ = 4.0 Hz, NH), 5.09 (2H, s, CH_2Ph), 4.63-4.57 (1H, m, H-4), 4.54 (1H, *app.* q, J = 2.8 Hz, H-5), 3.97-3.91 (2H, *br.* m, H-6), 3.03 (1H, dd, $J_{3\text{-}3'}$ = 17.8, $J_{3\text{-}4}$ = 9.0 Hz, H-3), 2.61 (1H, dd, $J_{3'\text{-}3}$ = 17.8, $J_{3'\text{-}4}$ = 4.8 Hz, H-3'), 1.06 (9H, s, 3 x CH_3); δ_C (100 MHz, Acetone-d_6) 175.1 (CO), 156.7 (CO), 137.9 (ArC), 136.2 (3 x ArCH), 133.5 (ArC), 133.3 (ArC), 130.7 (3 x ArCH), 129.1 (3 x ArCH), 128.7 (6 x ArCH), 86.1 (C-5), 66.7 (OCH_2Ph), 64.9 (C-6), 49.9 (C-4), 35.7 (C-3), 26.9 (3 x CH_3), 19.6 ($C(CH_3)_3$); LRMS (FAB^+) *m/z* 504.0 [$M+H^+$] (44), 445.9 (100), 426.0 (25), 336.0 (26), 197.0 (30), 135.0 (77%); HRMS (FAB^+) calculated for $C_{29}H_{34}NO_5Si$, 504.220 [$M+H^+$]; found 504.219. Spectroscopic data were in accordance with the reported values of Collis *et al.*[91]

(4*S*, 5*S*)-4-Benzyloxycarbonylamino-5-*O*-[(*tert*-butyldimethylsilyl)oxymethyl]-2, 3-dideoxy-α, β-D-erythropentofuranose (177).

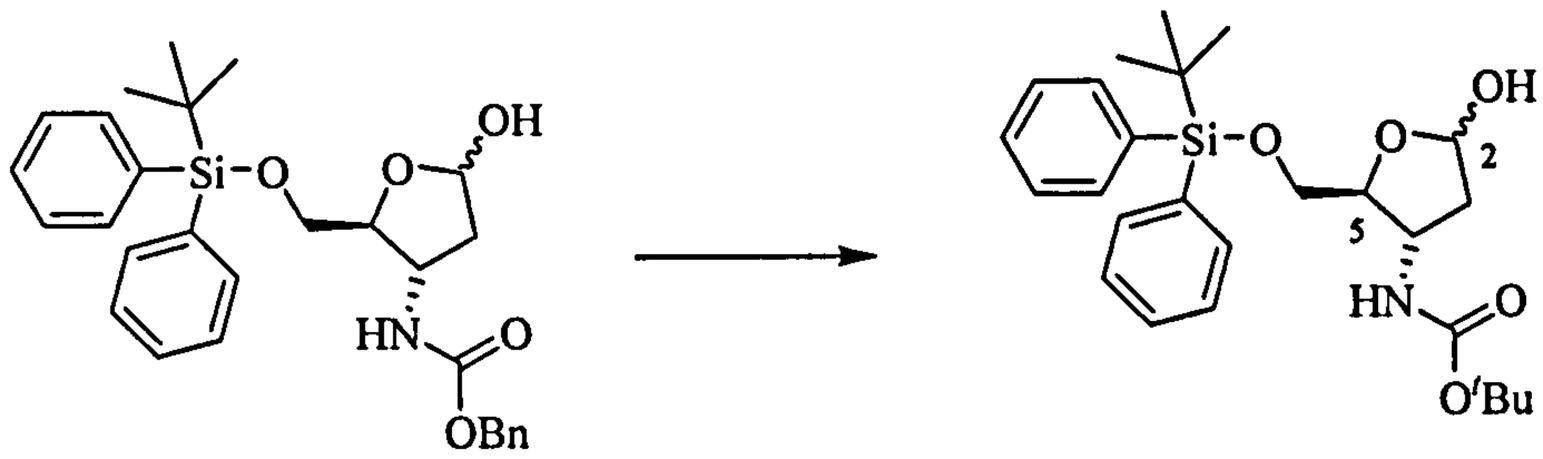


177

To a stirred solution of **176** (1.74 g, 3.54 mmol) in toluene (13 mL) at –78 °C was added di-*iso*-butyl aluminium hydride (1M in hexanes; 5.32 mL, 5.32 mmol) dropwise and the mixture stirred for 2 h at -78 °C. The reaction was quenched by the addition of methanol (13 mL) at -78 °C and allowed to warm to room temperature. A concentrated aqueous

solution of Rochelle's salt (10 mL) was added and the mixture stirred for a further 2 h, then this solution was extracted with ethyl acetate (3 x 10 mL). The combined organic phases washed with sodium hydrogen carbonate (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a colourless oil. Purification by silica gel column chromatography (10% ethyl acetate in dichloromethane) gave **177** (1.54 g, 89%) as a colourless oil. R_f 0.31 (30% ethyl acetate in light petroleum); $[\alpha]_D^{29}$ + 27.7 ($CHCl_3$, *c* 1.0); ν_{max} (neat)/cm^{-1} 3409, 3070, 2931, 2857, 1698, 1513, 1111; δ_H (400 MHz, Acetone-d_6) 7.76-7.74 (5H, m, ArH), 7.47-7.30 (10H, m, ArH), 6.55 (0.3H, d, *J* = 7.5 Hz, NH), 6.39 (0.7H, d, *J* = 8.3 Hz, NH), 5.58 (0.4H, *app*. t, *J* = 3.7 Hz, H-2), 5.50-5.46 (0.6H, m, H-2), 5.09 (3H, s, CH_2 + OH), 4.48 (0.3H, *app*. quin., *J* = 7.6 Hz, H-4), 4.35 (0.7H, *app*. sept., *J* = 3.8 Hz, H-4), 4.14 (0.7H, *app*. q, *J* = 4.1 Hz, H-5), 3.97 (0.3H, *app*. q, *J* = 5.0 Hz, H-5), 3.89-3.81 (0.6H, m, H-6), 3.79 (1.4H, d, *J* = 3.5 Hz, H-6), 2.41-2.36 (0.7H, m, H-3), 2.21-2.16 (0.3H, ddd, *J* = 12.5, *J* = 7.6, *J* = 1.7 Hz, H-3), 1.87-1.82 (1H, ddd, *J* = 13.3, *J* = 3.5, *J* = 1.5 Hz, H-3'), 1.05 (9H, s, $(CH_3)_3$); δ_C (100 MHz, Acetone-d_6) 156.6 (CO), 138.1 (ArC), 136.2 (3 x ArCH), 134.1 (2 x ArC), 130.4 (3 x ArCH), 129.1 (3 x ArCH), 128.5 (6 x ArCH), 98.9 (C-2), 98.5 (C-2), 85.0 (C-5), 84.6 (C-5), 66.9 (CH_2), 66.5 (C-6), 64.5 (CH_2), 52.6 (C-4), 41.1 (C-3), 40.8 (C-3), 27.0 (3 x CH_3), 19.6 (Si*C*$(CH_3)_3$); LRMS (FAB^+) *m/z* 528 [M+Na^+] (30), 488 (55), 448 (35), 269 (100%); HRMS (FAB^+) calculated for $C_{28}H_{35}NO_5NaSi$, 528.218 [M+Na^+]; found 528.219.

(4*S*, 5*S*)-4-(*tert*-Butyloxycarbonylamino)-5-*O*-[(*tert*-butyldiphenylsilyl)oxymethyl]-2, 3-dideoxy-α, β-D-erythropentofuranose (183).



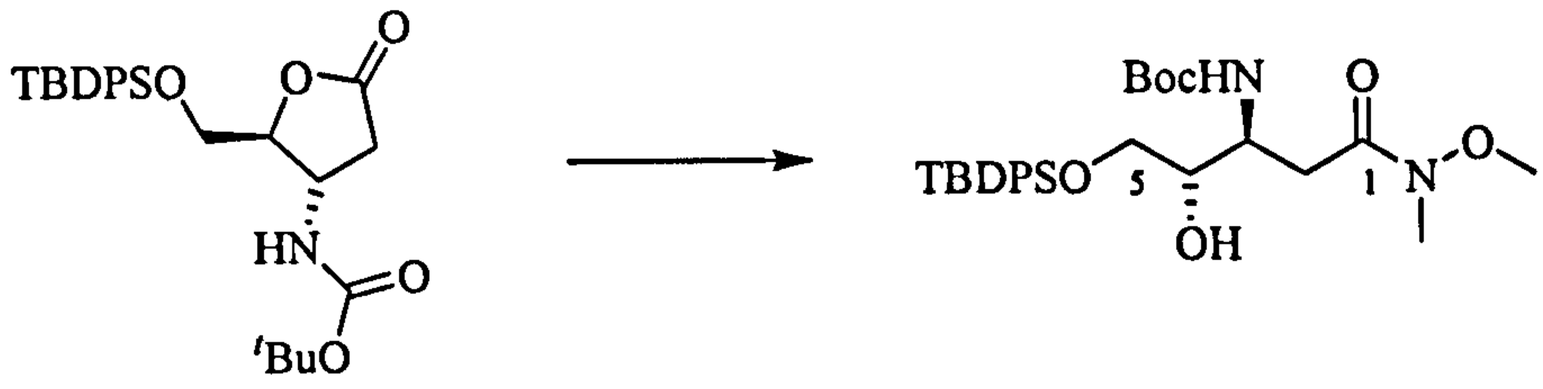
183

A suspension of **177** (300 mg, 0.60 mmol), di-*tert*-butyl dicarbonate (170 mg, 13.80 mmol) and 10% palladium on carbon (60 mg) in methanol (15 mL) was stirred at room temperature under an atmosphere of hydrogen for 3 h. The suspension was filtered through celite to remove the catalyst and concentrated *in vacuo* to give a colourless oil. Purification by silica gel column chromatography (10% ethyl acetate in dichloromethane) gave **183** (217 mg, 79%) as a colourless oil: $[\alpha]_D^{27}$ + 69.2 ($CHCl_3$, *c* 1.0); R_f 0.46 (10% ethyl acetate in dichloromethane); ν_{max} (neat)/cm^{-1} 3409, 3070, 2931, 2857, 1698, 1111; δ_H (400 MHz, Acetone-d_6) 7.76-7.74 (4H, m, ArH), 7.47-7.30 (6H, m, ArH), 6.55 (0.3H, d, *J* = 7.5 Hz, NH), 6.39 (0.7H, d, *J* = 8.3 Hz, NH), 5.58 (0.4H, *app*. t, *J* = 3.7 Hz, H-2), 5.50-5.46 (0.6H, m, H-2), 4.48 (0.3H, *app*. quin, *J* = 7.6 Hz, H-4), 4.35 (0.7H, *app*. sep., *J* = 3.8 Hz, H-4), 4.14 (1H, *app*.q, *J* = 4.1 Hz, H-5), 3.77 (2H, d, *J* = 4.0 Hz, H-6), 2.41-2.36 (1H, m, H-3), 2.21-2.16 (0.5H, ddd, *J* = 12.5, *J* = 7.6, *J* = 1.7 Hz, OH), 2.03-1.96 (0.5H, m, OH), 1.87-1.82 (1H, ddd, *J* = 13.3, *J* = 3.5, *J* = 1.5 Hz, H-3'), 1.42 (6H, s, 2 x CH_3), 1.40 (3H, s, CH_3), 1.06 (3H, s, CH_3), 1.05 (6H, s, 2 x CH_3); δ_C (100 MHz, Acetone-d_6) 146.8 (CO), 138.1 (ArC), 136.4 (3 x ArCH minor), 136.2 (3 x ArCH), 134.1 (ArC), 130.5 (2 x ArCH minor), 130.4 (2 x ArCH), 128.5 (4 x ArCH

minor), 128.4 (5 x ArCH), 98.9 (C-2 major), 98.5 (C-2 minor), 85.0 (C-5 major), 84.6 (C-5 minor), 78.9 ($C(CH_3)_3$), 66.9 (C-6 minor), 65.6 (C-6 major), 52.1 (C-4 major), 51.9 (C-4 minor), 41.1 (C-3 minor), 40.8 (C-3 major), 28.5 ($C(CH_3)_3$), 27.1 (3 x CH_3 minor), 27.0 (3 x CH_3), 19.7 ($SiC(CH_3)_3$); LRMS (FAB^+) *m/z*: 494 [$M+Na^+$], 472 (30), 460 (60), 454 (100%); HRMS (ES^+): calculated for $C_{26}H_{37}N_5O_5NaSi$ 494.233 [$M+Na^+$], found 494.235.

(3*S*, 4*R*)-3-(*tert*-Butyloxycarbonylamino)-4-hydroxy-5-[(*tert*-butyldiphenylsilyl)oxy]-

***N*, *O*-dimethylpentanamide (201).**

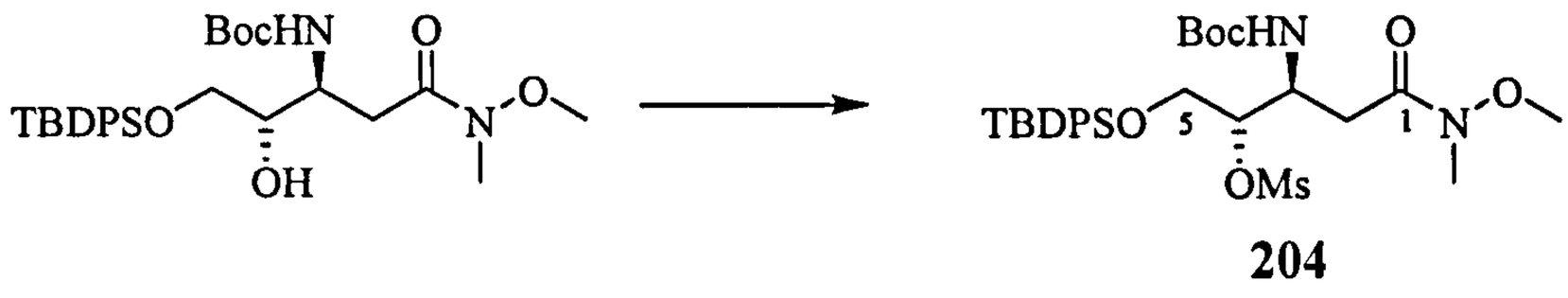


201

To a stirred suspension of *N*, *O*-dimethylhydroxylamine hydrochloride (1.38 g, 14.20 mmol) in dichloromethane (60 mL) was slowly added trimethylaluminium (2M in hexanes; 7.08 mL, 14.20 mmol) at 0 °C. The mixture was allowed to warm to room temperature, then stirred at this temperature for a further 30 minutes. A solution of **199** (1.33 g, 2.83 mmol) in dichloromethane (14 mL) was added and the mixture, stirred overnight at room temperature. Hydrochloric acid (0.5 M; 30 mL, 60 mmol) was added then the mixture diluted with dichloromethane (30 mL). The aqueous layer was re-

extracted with dichloromethane (3 x 40 mL), and the combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a colourless oil. Purification by silica gel column chromatography (40% ethyl acetate in *iso*-hexane) to yield **201** (1.00 g, 67%) as a colourless oil. R_f 0.38 (50% ethyl acetate in petroleum ether); $[\alpha]_D^{29.7}$ + 9.3 ($CHCl_3$, *c* 1.0); ν_{max} (neat)/cm^{-1} 3423, 2932, 2858, 1710, 1645, 1110; δ_H (300 MHz, Acetone-d_6) 7.77-7.74 (4H, m, ArH), 7.49-7.39 (6H, m, ArH), 6.02 (1H, d, $J_{NH\text{-}4}$ = 8.5 Hz, NH), 4.30 (1H, d, $J_{OH\text{-}5}$ = 5.6 Hz, OH), 4.16-4.17 (1H, m, H-4), 3.87 (1H, quin., J = 5.6 Hz, H-5), 3.81-3.76 (1H, dd, $J_{6\text{-}6'}$ = 10.6, $J_{6\text{-}5}$ = 4.2 Hz, H-6), 3.75-3.69 (1H, dd, $J_{6'\text{-}6}$ = 10.6, $J_{6'\text{-}5}$ = 4.2, H-6'), 3.70 (3H, s, OCH_3), 3.11 (3H, s, NCH_3), 2.91 (1H, dd, $J_{3\text{-}3'}$ = 16.2, $J_{3\text{-}4}$ = 6.2 Hz, H-3), 2.71 (1H, dd, $J_{3'\text{-}3}$ = 16.2, $J_{3'\text{-}4}$ = 4.7 Hz, H-3'), 1.35 (9H, s, $OC(CH_3)_3$), 1.06 (9H, s, $SiC(CH_3)_3$); δ_C (75 MHz, Acetone-d_6) 172.4 (CO), 155.9 (CO), 136.1 (4 x ArCH), 134.0 (2 x ArC), 130.3 (4 x ArCH), 128.4 (2 x ArCH), 78.6 ($C(CH_3)_3$), 74.0 (C-5), 66.6 (C-6), 61.3 (CH_3), 50.5 (C-4), 32.9 (C-3), 32.5 (CH_3), 28.4 (3 x CH_3), 27.0 (3 x CH_3), 19.6 ($C(CH_3)_3$); LRMS (FAB^+) *m/z* 531 [$M+H^+$] (50), 431 (100), 373 (20), 154 (35%); HRMS (FAB^+) calculated for $C_{28}H_{43}N_2O_6Si$, 531.2890 [$M+H^+$]; found 531.2906.

(3*S*, 4*R*)-3-*tert*-Butyloxycarbonylamino-4-methanesulfonyloxy-5-*tert*-butyldiphenylsilyl)oxy)-*N*, *O*-dimethylpentanamide (204).

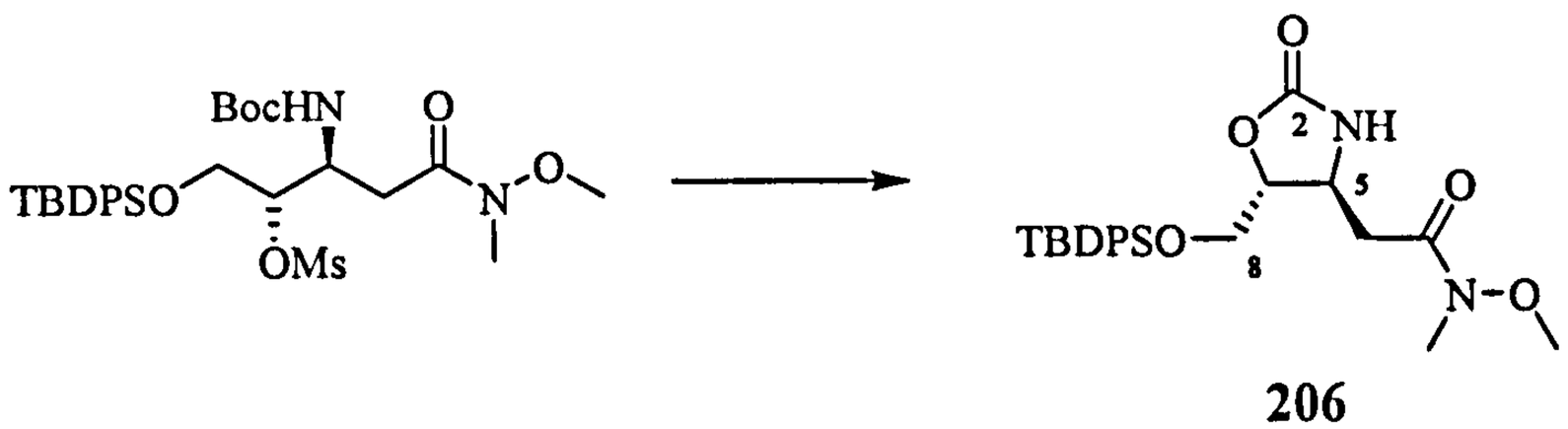


204

To a stirred solution of **201** (1.00 g, 1.89 mmol) in dry dichloromethane (20 mL) at 0 °C was added portionwise triethylamine (789 μL, 5.66 mmol) and methanesulfonyl chloride (379 μL, 4.90 mmol). The reaction mixture was stirred at 0 °C for 30 minutes, then warmed to room temperature and stirred for a further 16 h. The mixture was concentrated *in vacuo*, then the residue re-dissolved in ethyl acetate (20 mL) and washed with saturated aqueous ammonium chloride (10 mL). The aqueous phase was re-extracted with ethyl acetate (3 x 10 mL) then the combined organic phases washed with water (10 mL), brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (20 → 100% ethyl acetate in *iso*-hexane) gave **204** (1.04 g, 90%) as a white solid; mp 180 - 110 °C; R_f 0.25 (40% ethyl acetate in *iso*-hexane); $[\alpha]_D^{30.3}$ - 17.4 ($CHCl_3$, *c* 1.0); ν_{max} (neat)/cm^{-1} 2933-2858, 1754, 1653, 1472, 1427, 1315, 1111, 1040; δ_H (400 MHz, Acetone-d_6) 7.78-7.74 (4H, m, ArH), 7.51-7.43 (6H, m, ArH), 6.20 (1H, d, J = 8.0 Hz, NH), 5.01 (1H, *app.* q, J = 5.0 Hz, H-4), 4.48-4.41 (1H, m, H-3), 4.02-3.94 (2H, m, H-6), 3.69 (3H, s, OCH_3), 3.12 (3H, s, NCH_3), 3.92 (3H, s, SCH_3), 2.88 (1H, dd, $J_{2\text{-}3}$ = 6.8, $J_{2\text{-}2'}$ = 16.8 Hz, H-3), 2.75 (1H, dd, $J_{2'\text{-}3}$ = 4.4, $J_{2'\text{-}2}$ = 16.8 Hz, H-2'), 1.37 (9H, s, $OC(CH_3)_3$), 1.08 (9H, s,

$SiC(CH_3)_3$); δ_C (75 MHz, Acetone-d_6) 172.0 (CO), 155.7 (CO), 136.2 (ArCH), 136.1 (ArCH), 133.5 (ArC), 133.3 (ArC), 130.6 (4 x ArCH), 128.6 (4 x ArCH), 83.4 (C-4), 79.1 ($C(CH_3)_3$), 64.2 (C-5), 61.4 (CH_3), 48.4 (C-3), 38.5 (2 x CH_3), 32.7 (C-2), 28.4 (3 x CH_3), 27.0 (3 x CH_3), 19.6 ($SiC(CH_3)_3$); LRMS (ES^+) *m/z* 631 [$M+Na^+$] (100), 609 [$M+H^+$] (74), 509 (26%); HRMS (ES^+) calculated for $C_{28}H_{44}N_2O_8SSi$, 609.2660 [$M+H^+$]; found 609.2660.

(4*S*, 5*R*)-4-[(*tert*-butyldiphenylsilyl)oxymethyl]-5-(*N*, *O*-Dimethylaminoethyl)-1, 3-oxazolidin-2-one (206).

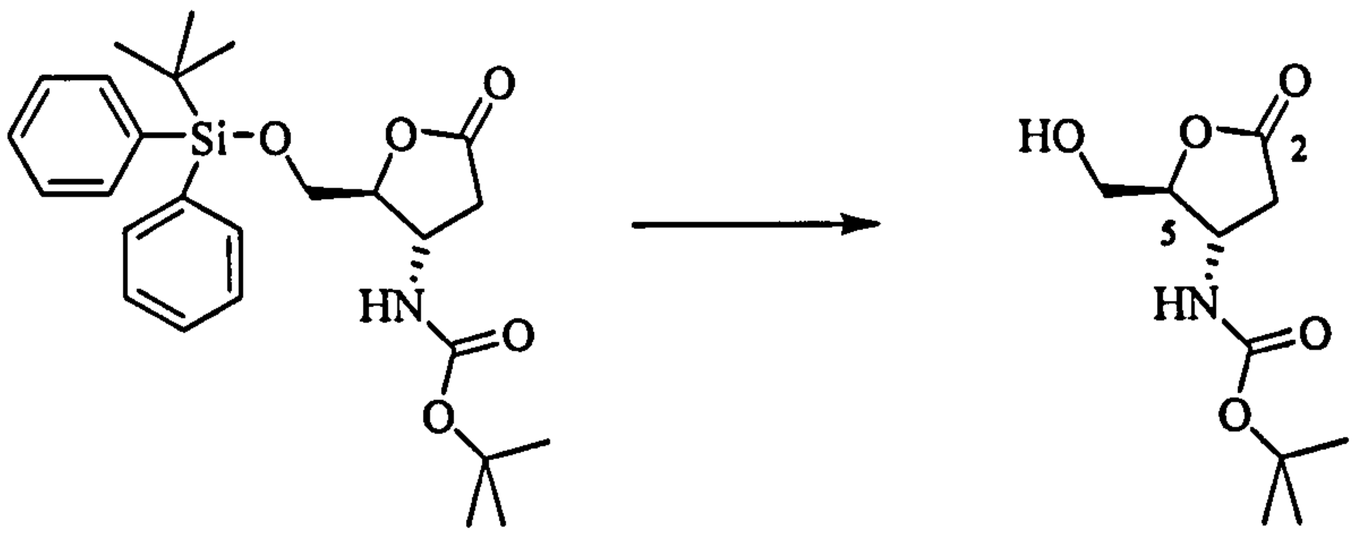


206

To a stirred solution of **204** (288 mg, 0.47 mmol) in *N*, *N'*-dimethylformamide (9 mL) was added sodium azide (307 mg, 4.7 mmol). The mixture was heated for 1 h at 95 °C. On cooling to room temperature, the mixture was diluted with diethyl ether (5 mL) and water (5 mL), then extracted with diethyl ether (3 x 5 mL). The combined organic fractions were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give an oil, which after silica gel column chromatography (40% ethyl acetate in dichloromethane) gave **206** (30 mg, 14%) as a colourless oil. R_f 0.40 (100% ethyl acetate); $[\alpha]_D^{22}$ + 2.1 ($CHCl_3$, *c* 1.0); ν_{max} (neat)/cm^{-1} 3294, 3072, 2932, 2857, 1754, 1655, 1427, 1111; δ_H (300 MHz, Acetone-d_6) 7.76-7.73 (4H, m, ArH), 7.50-7.40 (6H,

m, ArH), 6.55 (1H, s, NH), 4.40 (1H, dt, $J_{4\text{-}5}$ = 5.1, $J_{4\text{-}8}$ = 3.5 Hz, H-4), 4.25-4.18 (1H, m, H-5), 3.94 (2H, *app.* d, $J_{8\text{-}4}$ = 3.5 Hz, H-8), 3.73 (3H, s, OCH_3), 3.12 (3H, s, CH_3), 2.86 (2H, m, H-6), 1.05 (9H, s, $C(CH_3)$); δ_C (75 MHz, Acetone-d_6) 170.4 (CO), 158.4 (CO), 136.3 (2 x ArCH), 136.2 (2 x ArCH), 133.9 (ArC), 133.7 (ArC), 130.6 (2 x ArCH), 128.5 (2 x ArCH), 128.5 (2 x ArCH), 81.8 (C-4), 65.2 (C-8), 61.5 (OCH_3), 50.7 (C-5), 38.5 (C-6), 27.0 (3 x CH_3), 20.5 (NCH_3), 14.3 ($SiC(CH_3)_3$); LRMS (FAB^+) *m/z* 457 [$M+H^+$] (70), 399 (40), 307 (25), 154 (100%); HRMS (FAB^+) calculated for $C_{24}H_{33}N_2O_5Si$, 457.2157 [$M+H^+$]; found 457.2157.

(4*S*, 5*R*)-4-*tert*-Butyloxycarbonylamino-5-hydroxymethyl-2(5*H*)furan-2-one (185).

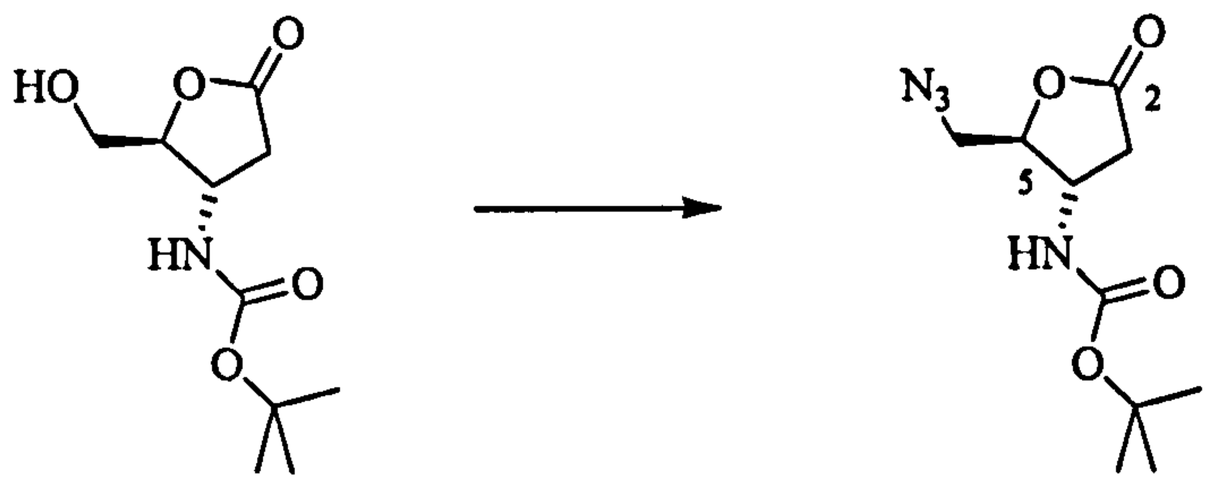


185

To a stirred solution of **199** (5.16 g, 10.90 mmol) in tetrahydrofuran (150 mL) at 0 °C, was added *n*-tetrabutylammonium fluoride (1M in THF; 16.50 mL, 16.50 mmol) dropwise and the resulting mixture stirred for 4 h at 0 °C. The mixture was concentrated *in vacuo*, re-dissolved in ethyl acetate (100 mL) then washed with saturated aqueous ammonium chloride solution (30 mL), water (30 mL) and finally brine (30 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a colourless oil, which after purification by silica gel column chromatography (40% ethyl

acetate in petroleum ether) gave **185** (2.30 g, 91%) as a white solid; mp 127-130 °C; $[\alpha]_D^{28.2}$ - 2.0 ($CHCl_3$, *c* 1.0); R_f 0.42 (100% ethyl acetate); ν_{max} (neat)/cm^{-1} 3410, 3354, 2980, 1764, 1682; δ_H (300 MHz, Acetone-d_6) 6.62 (1H, s, OH), 4.39 (1H, q, $J_{5\text{-}4}$ = 6.9, $J_{5\text{-}6}$ = 3.7 Hz, H-5), 4.34-4.25 (2H, m, H-4 + NH), 3.86-3.79 (1H, ddd, $J_{6\text{-}6'}$ = 5.8, $J_{6'\text{-}5}$ = 2.9, *J* = 2.9 Hz, H-6), 3.78-3.70 (1H, ddd, $J_{6'\text{-}6}$ = 5.8, $J_{6'\text{-}5}$ = 3.7, *J* = 3.6 Hz, H-6'), 2.91 (1H, dd, $J_{3\text{-}3'}$ = 17.9, *J* = 8.9 Hz, H-3), 2.49 (1H, dd, $J_{3'\text{-}3}$= 17.9, *J* = 4.9 Hz, H-3'), 1.41 (9H, s, 3 x CH_3); δ_C (75 MHz, Acetone-d_6) 175.1 (CO), 156.8 (CO), 86.5 (C-5), 79.1 ($C(CH_3)_3$), 62.4 (C-6), 49.1 (C-4), 35.1 (C-3), 28.0 (3 x CH_3); LRMS (ES^+) *m/z* 485 [2M+Na^+] (100), 254 [M+Na^+] (16); HRMS (ES^+) calculated for $C_{10}H_{21}N_2O_5$, 249.1445 [M+NH_4^+]; found 249.1449. Anal. calcd. for $C_{10}H_{17}NO_5$: C, 51.94; H, 7.41; N, 6.06 %. Found: C, 52.07; H, 7.40; N, 5.99%.

(4*S*, 5*R*)-4-[(*tert*-Butyloxycarbonylamino)-5-azidomethyl]-2(5*H*)furan-2-one (186).



186

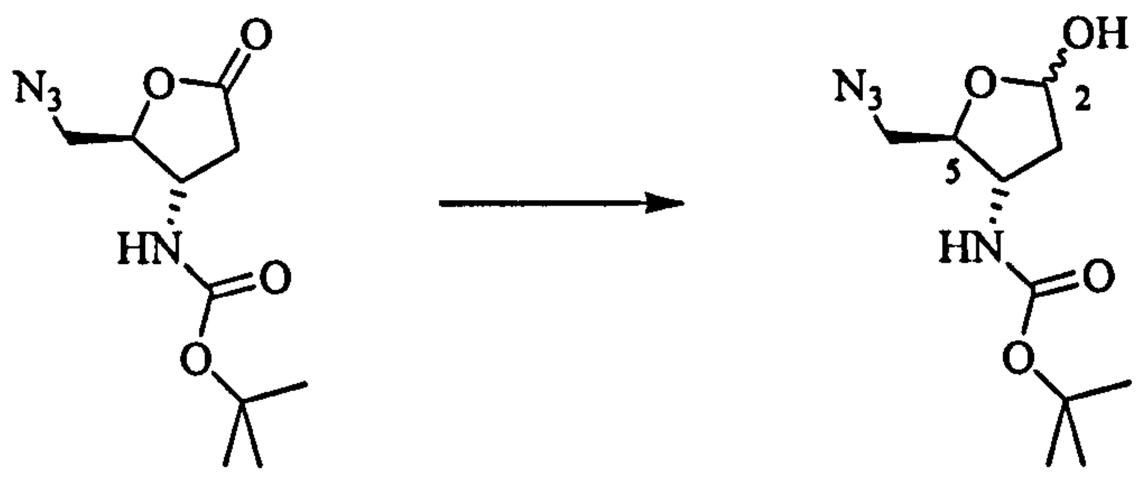
To a stirred solution of **185** (2.10 g, 9.08 mmol) in dichloromethane (40 mL) at 0 °C was added triethylamine (1.77 mL, 1.40 mmol) and methanesulfonyl chloride (914 μL, 1.30 mmol). The mixture was stirred for 16 h at room temperature. It was then concentrated *in vacuo*. The residue was re-dissolved in ethyl acetate (20 mL), washed with aqueous

saturated ammonium chloride solution (10 mL), water (10 mL) and finally brine (10 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude mesylate (3.10 g) as a yellow solid which was used without further purification; mp 117-118 °C; R_f 0.67 (100% ethyl acetate); ν_{max} (neat)/cm^{-1} 3335, 2981, 2942, 1766, 1680, 1529, 1358, 1180; δ_H (300 MHz, Acetone-d_6) 6.69 (1H, s, NH), 4.65-4.62 (1H, *br*. m, H-5), 4.57 (1H, dd, $J_{6\text{-}6'}$ = 11.5, $J_{6\text{-}5}$ = 2.5 Hz, H-6), 4.47 (1H, dd, $J_{6'\text{-}6}$ = 11.5, $J_{6'\text{-}5}$ = 5.0 Hz, H-6'), 4.35 (1H, *br*. quin, J = 7.0 Hz, H-4), 3.18 (3H, s, CH_3SO_2), 2.94 (1H, dd, $J_{3\text{-}3'}$ = 17.9, $J_{3\text{-}4}$ = 9.1 Hz, H-2), 2.65 (1H, dd, $J_{3'\text{-}3}$ = 17.9, $J_{3'\text{-}4}$ = 6.5 Hz, H-3'), 1.42 (9H, s, 3 x CH_3); δ_C (75 MHz, Acetone-d_6) 173.9 (CO), 155.8 (CO), 82.7 (C-5), 79.5 ($C(CH_3)_3$), 69.6 (C-6), 48.8 (C-4), 36.9 (CH_3SO_2), 34.2 (C-3), 28.0 (3 x CH_3); LRMS (ES^+) *m/z* 332 [$M+Na^+$] (100), 276 (19), 254 (35%).

To a stirred solution of this mesylate (3.10 g) in *N*, *N'*-dimethylformamide (24 mL) was added sodium azide (1.63 g, 25.00 mmol). The mixture was warmed to 70 °C and stirred for 2 h. On cooling to room temperature, water (25 mL) was added, and the mixture extracted with diethyl ether (3 x 10 ml). The combined organic fractions were washed with sodium bicarbonate (10 mL), brine (10 mL), then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (60% ethyl acetate in petroleum ether) gave **186** (1.95 g, 84% over two steps) as a white solid; mp 84-86 °C; $[\alpha]_D^{29}$ + 30.9 ($CHCl_3$, *c* 1.0); R_f 0.58 (60% ethyl acetate in petroleum ether); ν_{max} (neat)/cm^{-1} 3353, 2983, 2937, 2096, 1777, 1678; δ_H (300 MHz, Acetone-d_6) 6.63 (1H, s, NH), 4.52-4.48 (1H, m, H-5), 4.31-4.22 (1H, m, H-4), 3.77 (1H, dd, $J_{6\text{-}6'}$ = 13.6, J = 3.2 Hz, H-6), 3.68 (1H, dd, $J_{6'\text{-}6}$ = 13.6, J = 5.6 Hz, H-6'), 2.94 (1H, dd, $J_{3\text{-}3'}$ = 17.8,

J = 8.9 Hz, H-3), 2.61 (1H, dd, $J_{3'-3}$ = 17.8, J = 6.6 Hz, H-3'), 1.41 (9H, s, 3 x CH_3); δ_C (75 MHz, Acetone-d_6) 174.1 (CO), 155.9 (CO), 84.0 (C-5), 79.4 ($C(CH_3)_3$), 53.0 (C-6), 49.8 (C-4), 34.5 (C-3), 28.1 (3 x CH_3); LRMS (ES^+) *m/z* 535 [2M+Na^+] (22), 279 [M+Na^+] (100), 129 (25), 122 (42%); HRMS (ES^+) calculated for $C_{10}H_{20}N_5O_4$, 274.1510 [M+NH_4^+]; found 274.1510. Anal. calcd. for $C_{10}H_{16}N_4O_4$: C, 46.87; H, 6.29; N, 21.86%. Found: C, 46.89; H, 6.23; N, 21.47%.

(4*S*, 5*R*)-4-[(*tert*-Butyloxycarbonylamino)-4-azido]-2, 3-dideoxy-α, β-D-erythropento-furanose (184).

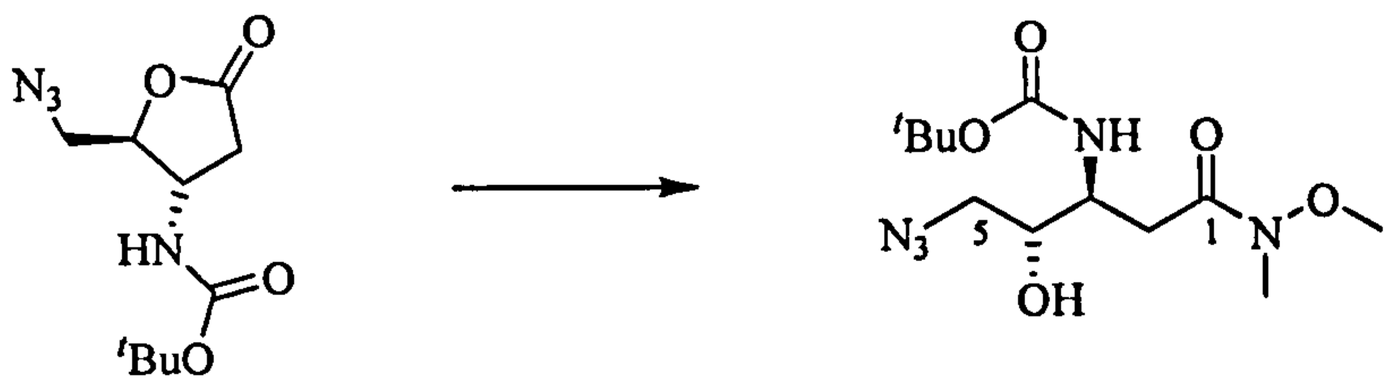


184

To a stirred solution of **186** (100 mg, 0.39 mmol) in dry dichloromethane (5 mL) at -78 °C was added a solution of di-*iso*-butylaluminium hydride (1M in hexanes; 590 µL, 0.59 mmol) dropwise. The reaction mixture was stirred at -78 °C for 3 h, then saturated aqueous potassium sodium tartrate (5 mL) was added, and the solution stirred for a further 2 h. The mixture was extracted with dichloromethane (3 x 5 mL), then the combined organic phases washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (80% ethyl acetate in petroleum ether) gave **184** (96 mg, 95%)as a white amorphous solid; mp = 74-

75 °C; $[\alpha]_D^{27}$ + 69.2 ($CHCl_3$, *c* 1.0); R_f 0.58 (80% ethyl acetate in petroleum ether); ν_{max} (neat)/cm^{-1} 3348, 2975, 2933, 2098, 1683; δ_H (400 MHz, CD_2Cl_2) 5.51 (0.78H, *br.* s, H-2), 5.46 (0.22H, *app.* t, *J* = 3.9 Hz, H-2), 5.39 (1H, d, *J* = 8.3 Hz, NH), 4.81 (0.25 Hz, s, OH), 4.43 (0.75H, s, OH), 4.23-4.15 (0.17H, m, H-5), 4.11 (0.83H, dt, *J* = 5.5, *J* = 3.7 Hz, H-5), 3.92-3.81 (0.7H, m, H-4), 3.80-3.78 (0.3H, m, H-4), 3.49-3.37 (1.2H, m, H-6), 3.23 (0.8H, dd, *J* = 12.8, *J* = 5.2 Hz, H-6), 2.28-2.16 (1H, m, H-3), 1.89-1.84 (0.1H, m, H-3'), 1.78 (0.9H, dd, *J* = 13.8, *J* = 2.1 Hz, H-3'), 1.35 (9H, 3 x CH_3); δ_C (100 MHz, CD_2Cl_2) 155.8 (CO), 99.1 (C-2 major), 98.6 (C-2 minor), 84.1 (C-5 minor), 83.9 (C-5 major), 80.1 ($C(CH_3)_3$), 53.6 (C-6 major), 53.5 (C-6 minor), 52.5 (C-4 major), 52.5 (C-4 minor), 40.4 (C-3 minor), 39.9 (C-3 major), 28.4 (3 x CH_3 major), 28.4 (3 x CH_3 minor); LRMS (CI^+) *m/z* 259 [$M+H^+$] (10), 241 (60), 202 (100), 159 (15%); HRMS (ES^+) calculated for $C_{10}H_{19}N_4O_4$, 259.140 [$M+H^+$]; found 259.139. Anal. calcd. for $C_{10}H_{18}N_5O_4$: C, 46.50; H, 7.02; N, 21.69%. Found: C, 46.72; H, 7.04; N, 21.14%.

(3*S*, 4*R*)-3-(*tert*-Butyloxycarbonylamino)-4-hydroxy-5-azido-*N*, *O*-dimethylpentan-amide (107).

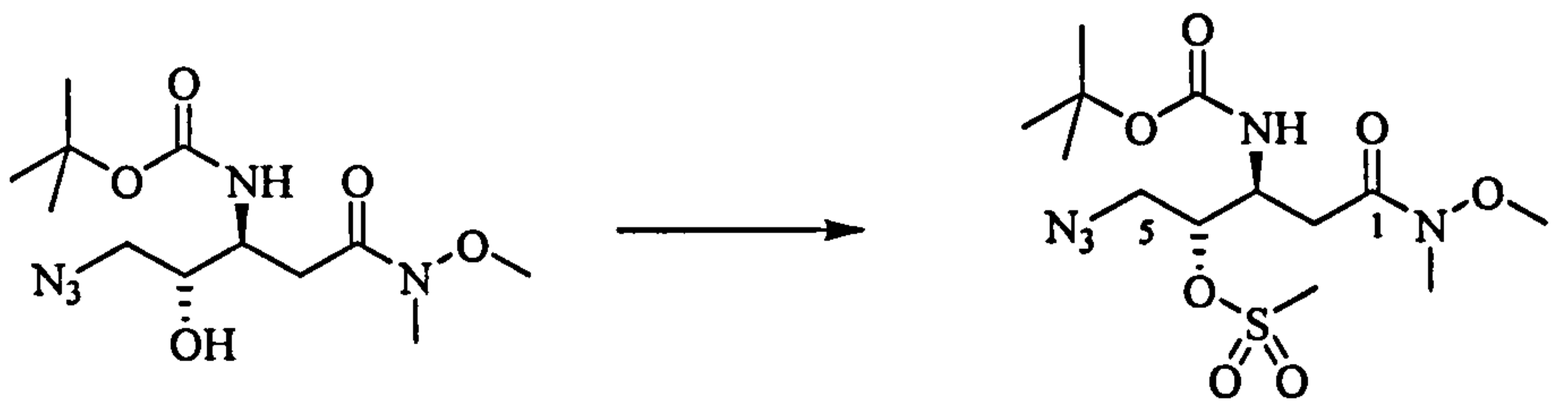


107

To a stirred solution of *N*, *O*-dimethylhydroxylamine hydrochloride (1.89 g, 19.50 mmol) in dry tetrahydrofuran (35 mL) at 0 °C was added dropwise trimethylaluminium (2M in hexanes; 9.80 mL, 19.50 mmol). The mixture was stirred for 30 min at room temperature and a solution of **186** (1.00 g, 3.90 mmol) in dichloromethane (35 mL) was then added. The mixture was stirred for 4 h, then quenched by the addition of a saturated aqueous solution of potassium sodium tartrate (70 mL) and stirred for 2 h. It was then extracted with dichloromethane (3 x 40 mL), washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a colourless oil that after purification by silica gel column chromatography (60% ethyl acetate in petroleum ether) afforded **207** as a white foam (1.14 g, 92%); $[\alpha]_D^{19}$ + 14.6 ($CHCl_3$, *c* 1.0); R_f 0.26 (60% ethyl acetate in petroleum ether); ν_{max} (neat)/cm^{-1} 3354, 2977, 2937, 2097, 1687, 1641; δ_H (400 MHz, Acetone-d_6) 6.05 (1H, d, J = 7.5 Hz, NH), 4.71 (1H, d, J = 6.0 Hz, OH), 3.98-3.85 (2H, m, H-4 + H-3), 3.73 (3H, s, CH_3), 3.36 (1H, dd, $J_{5\text{-}5'}$ = 12.9, J = 2.7 Hz, H-5), 3.30 (1H, dd, $J_{5'\text{-}5}$ = 12.9, J = 7.0 Hz, H-5'), 3.12 (3H, s, CH_3), 2.89 (1H, dd, $J_{2\text{-}2'}$ = 16.0, J = 5.8 Hz, H-2), 2.75 (1H, dd, $J_{2'\text{-}2}$ = 16.0, J = 4.3 Hz, H-2'), 1.39 (9H, s, 3 x CH_3); δ_C (100 MHz, Acetone-d_6) 169.8 (CO), 156.0 (CO), 78.9 ($C(CH_3)_3$), 73.2 (C-3), 61.3 (CH_3), 55.0 (C-5), 50.9 (C-6), 33.0 (C-2), 31.9 (CH_3), 28.3 (3 x CH_3); LRMS

(FAB$^+$) *m/z* 318 [M+H$^+$] (100), 262 (35), 218 (50), 201 (15), 154 (30), 136 (20%); HRMS (FAB$^+$) calculated for $C_{12}H_{24}N_5O_5$, 318.177 [M+H$^+$]; found 318.176.

(3*S*, 4*R*)-3-(*tert*-Butyloxycarbonylamino)-4-methanesulfonyloxy-5-azido-*N*, *O*-dimethylpentanamide (208).

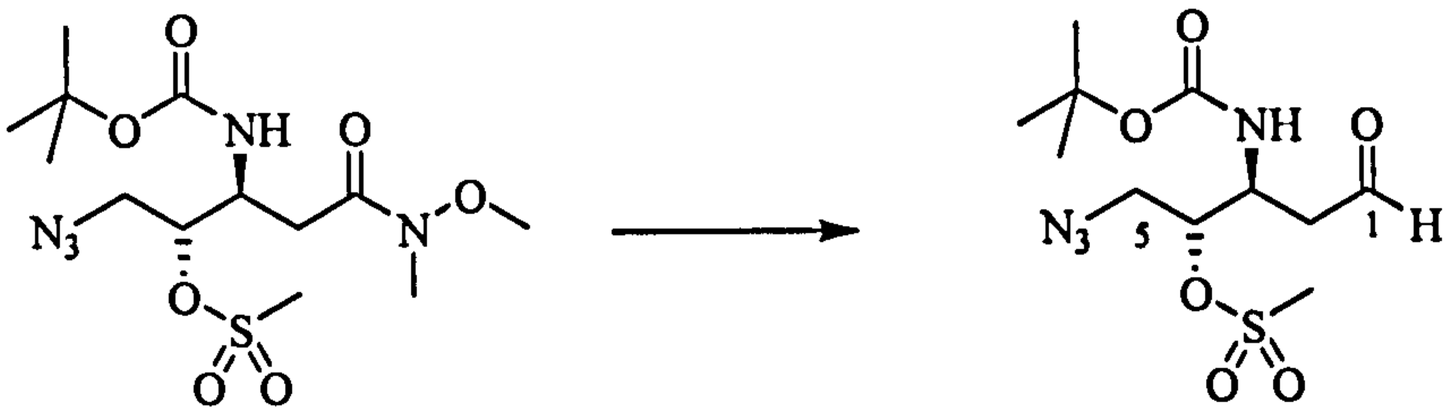


208

To a stirred solution of **207** (1.00 g, 3.15 mmol) in dry dichloromethane (20 mL) at 0 °C was added triethylamine (1.32 mL, 9.45 mmol) then methanesulfonyl chloride (634 µL, 8.19 mmol) dropwise. The mixture was allowed to warm to room temperature, then stirred for 4 h. The mixture was concentrated *in vacuo*, re-dissolved in ethyl acetate (20 mL), then washed with saturated aqueous ammonium chloride (5 mL), water (5 mL) and brine (5 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow oil. Purification by silica gel column chromatography (60% ethyl acetate in petroleum ether) gave **208** (939 mg, 75%) as a white foam; $[\alpha]_D^{24}$ - 23.7 ($CHCl_3$, *c* 1.0); R_f 0.45 (60% ethyl acetate in petroleum ether); ν_{max} (neat)/cm^{-1} 3338, 2978, 2938, 2105, 1705, 1650, 1497, 1391, 1344; δ_H (400 MHz, Acetone-d_6) 4.97 (1H, dt, $J_{4\text{-}5}$ = 10.0, $J_{4\text{-}3}$ = 6.3 Hz, H-4), 4.29 (1H, dd, $J_{3\text{-}2}$ = 11.5, $J_{3\text{-}4}$ = 6.3 Hz, H-3), 3.84 (1H, dd, $J_{5\text{-}5'}$ = 13.7, $J_{5\text{-}4}$ = 3.8 Hz, H-5), 3.73 (3H, s, CH_3), 3.64 (1H, dd, $J_{5'\text{-}5}$ = 13.7, $J_{5'\text{-}$

$_4$ = 6.3 Hz, H-5'), 3.23 (3H, s, CH_3), 3.12 (3H, s, CH_3), 2.88 (1H, dd, $J_{2\text{-}2'}$ = 16.7, $J_{2\text{-}3}$ = 6.8 Hz, H-2), 2.79 (1H, dd, $J_{2'\text{-}2}$ = 16.7, $J_{2'\text{-}3}$ = 4.5 Hz, H-2'), 1.40 (9H, s, 3 x CH_3); δ_C (100 MHz, Acetone-d_6) 171.7 (CO), 155.6 (CO), 81.0 (C-4), 79.1 ($C(CH_3)_3$), 61.3 (CH_3), 51.9 (C-5), 48.7 (C-3), 38.4 (CH_3), 32.4 (C-2), 31.9 (CH_3), 28.2 (3 x CH_3) ; LRMS (ES^+) *m/z* 813 [2M+Na^+] (6), 435 [M+K^+] (15), 418 [M+Na^+] (100), 396 [M+H] (13), 340 (31), 296 (15%); HRMS (ES^+) calculated for $C_{13}H_{26}N_5O_7S$, 396.1547 [M+H]; found 396.1547.

(3*S*, 4*R*)-3-(*tert*-Butyloxycarbonylamino)-4-methanesulfonyloxy-5-azido-pentanal (209).

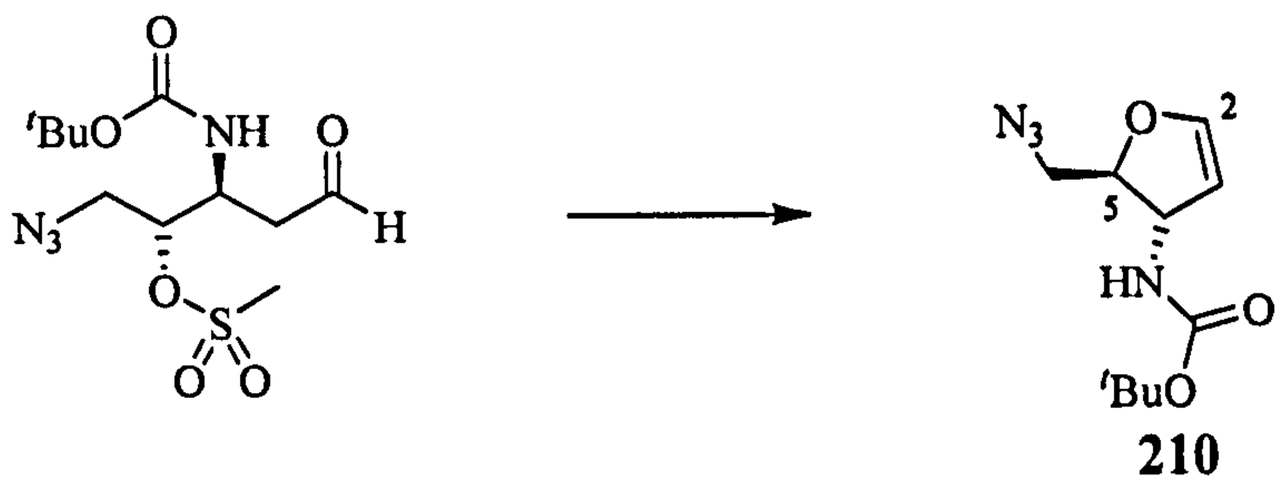


209

To a stirred solution of **208** (100 mg, 0.25 mmol) in dry tetrahydrofuran (5 mL) at -78 °C was added a solution of di-*iso*-butylaluminium hydride (1M in hexanes; 375 µL, 0.36 mmol) dropwise. The mixture was stirred at -78 °C for 4 h, then transferred *via canula* to a stirred mixture of ethyl acetate (5 mL) and saturated aqueous potassium sodium tartrate (5 mL) at 0 °C. After stirring overnight at room temperature, the mixture was extracted with ethyl acetate (3 x 5 mL). The combined organic layers washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by silica gel

column chromatography (30% ethyl acetate in petroleum ether) gave **209** (46 mg, 55%) as a colourless oil; $[\alpha]_D^{27}$ - 44.0 ($CHCl_3$, *c* 1.0); R_f 0.56 (60% ethyl acetate in petroleum ether); ν_{max} (neat)/cm^{-1} 3381, 2979, 2939, 2106, 1699, 1513, 1392, 1336; δ_H (400 MHz, Acetone-d_6) 9.71 (1H, d, $J_{1\text{-}2}$ = 2.1 Hz, CHO), 6.32 (1H, d, $J_{NH\text{-}3}$ = 8.3 Hz, NH), 4.90 (1H, *app.* dt, $J_{4\text{-}5'}$ = 6.0, J = 4.0 Hz, H-4), 4.44 (1H, dddd, $J_{3\text{-}2}$ = 9.4, $J_{3\text{-}NH}$ = 8.3, $J_{3\text{-}2'}$ = 4.2, $J_{3\text{-}4}$ = 4.1 Hz, H-3), 3.83 (1H, dd, $J_{5\text{-}5'}$ = 13.6, $J_{5\text{-}4}$ = 3.8 Hz, H-5), 3.66 (1H, dd, $J_{5\text{-}5'}$ = 13.6, $J_{5'\text{-}4}$ = 6.3 Hz, H-5'), 3.23 (3H, s, CH_3S), 2.88 (1H, ddd, $J_{2\text{-}2'}$ = 17.2, $J_{2\text{-}3}$ = 9.4, $J_{2\text{-}1}$ = 2.1 Hz, H-2), 2.74 (1H, *br.* dd, $J_{2'\text{-}2}$ = 17.2, $J_{2'\text{-}3}$ = 4.2 Hz, H-2'), 1.40 (9H, s, 3 x CH_3); δ_C (100 MHz, Acetone-d_6) 200.1 (CHO), 155.7 (CO), 80.4 (C-4), 79.4 ($C(CH_3)_3$), 51.8 (C-5), 47.4 (C-3), 44.1 (C-2), 38.5 (CH_3S), 28.2 (3 x CH_3); LRMS (ES^+) *m/z* 359 [M+Na^+] (100), 281 (20%); HRMS (ES^+) calculated for $C_{11}H_{20}N_4NaO_6S$, 359.0996 [M+Na^+]; found 359.0992.

(4*S*, 5*R*)-4-(*tert*-Butyloxycarbonylamino)-5-azidomethyl-2, 3-dihydrofuran (210).

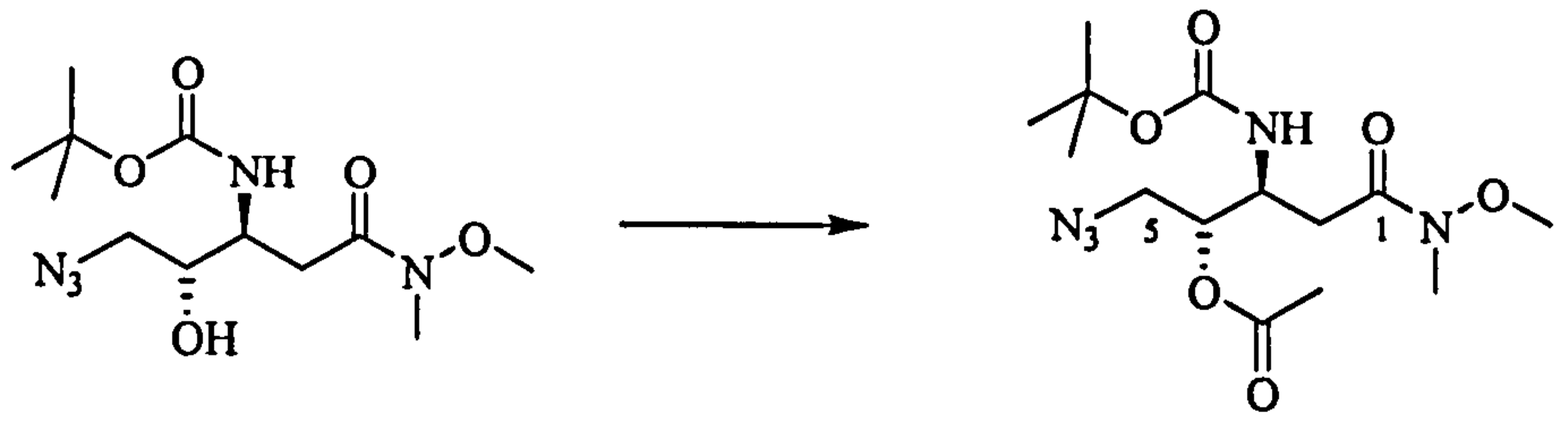


210

To a stirred solution of **209** (90 mg, 0.27 mmol) in dry *N*, *N*'-dimethylformamide (1 mL), was added potassium carbonate (37 mg, 0.27 mmol). After 6 h, water (1 mL) was added, and the mixture extracted with diethyl ether (3 x 1 mL). The combined organic

layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (30% ethyl acetate in petroleum ether) afforded **210** (18 mg, 28%) as a colourless oil. R_f 0.72 (60% ethyl acetate in petroleum ether); $[\alpha]_D^{29}$ - 11.2 ($CHCl_3$, *c* 1.0); ν_{max} (neat)/cm^{-1} 3346, 2978, 2932, 2932, 2098, 1702, 1615; δ_H (400 MHz, Acetone-d_6) 7.16 (1H, d, $J_{NH\text{-}4}$ = 8.8 Hz, NH), 6.41 (1H, dd, $J_{2\text{-}3}$ = 3.0, $J_{2\text{-}5}$ = 1.9 Hz, H-2), 5.70 (1H, dd, $J_{4\text{-}NH}$ = 8.8 Hz, $J_{4\text{-}5}$ = 4.6 Hz, H-4), 4.92 (1H, t, $J_{3\text{-}2}$ = 2.9 Hz, H-3), 3.48-3.44 (1H, dd, $J_{6\text{-}6'}$ = 12.3, $J_{6\text{-}5}$ = 5.8 Hz, H-6), 3.39 (1H, dd, $J_{6'\text{-}6}$ = 12.3, $J_{6'\text{-}5}$ = 7.1 Hz, H-6'), 3.07-3.01 (1H, m, H-5), 1.42 (9H, s, 3 x CH_3); δ_C (100 MHz, Acetone-d_6) 155.34 (CO), 146.7 (C-2), 100.5 (C-3), 87.5 (C-4), 79.5 ($C(CH_3)_3$), 54.0 (C-6), 48.4 (C-5), 28.2 (3 x CH_3); LRMS (ES^+) *m/z* 503 (100) [2M+Na^+], 263 (28%) [M+Na^+]; HRMS (ES^+) calculated for $C_{10}H_{20}N_5O_3$, 258.1561 [M+NH_4^+]; found 258.1560.

(3*S*, 4*R*)-3-(*tert*-Butyloxycarbonylamino)-4-acetyloxy-5-azido-*N*, *O*-dimethylpentan-amide (211).

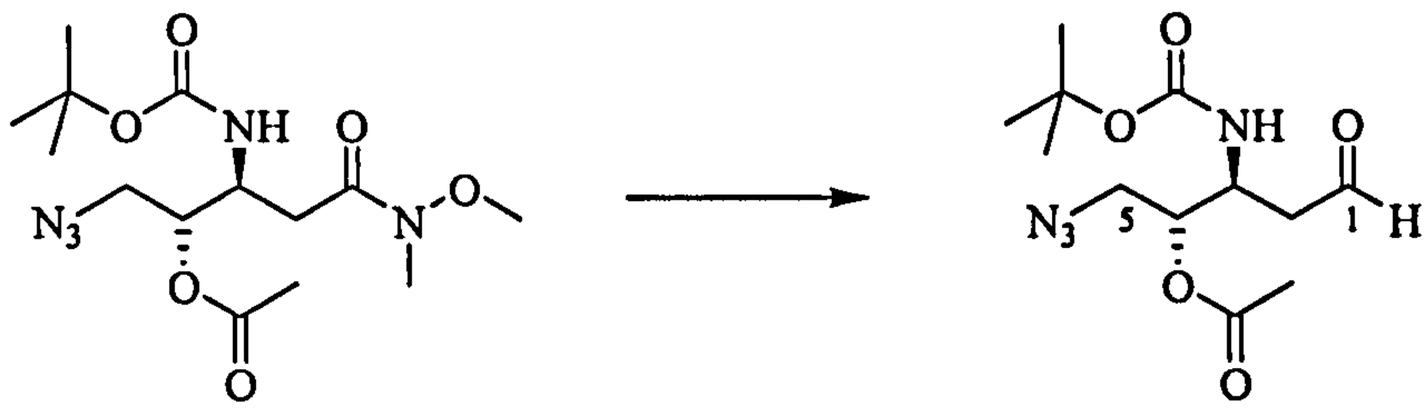


211

To a stirred solution of **207** (1.00 g, 3.15 mmol) in dry dichloromethane (20 mL) at 0 °C were added dry pyridine (2.55 mL, 31.50 mmol), 4-dimethylaminopyridine (231 mg, 1.89 mmol) and acetic anhydride (1.84 mL, 19.50 mmol). The mixture was stirred at

room for 4 h, then concentrated *in vacuo*. Purification by silica gel column chromatography (20% ethyl acetate in petroleum ether) gave **211** (1.06 g, 94%) as a white amorphous solid; mp 74-76 °C; $[\alpha]_D^{21}$ + 9.9 ($CHCl_3$, *c* 1.0); R_f 0.37 (40% ethyl acetate in petroleum ether); ν_{max} (neat)/cm^{-1} 3334, 2977, 2103, 1739, 1681, 1657, 1532; δ_H (400 MHz, Acetone-d_6) 5.81 (1H, d, J_{NH-3} = 9.0 Hz, NH), 5.11-5.06 (1H, m, H-4), 4.08 (1H, *app*. sept., J = 4.7 Hz, H-3), 3.58 (3H, s, CH_3), 3.46 (1H, dd, $J_{5-5'}$ = 13.3, J_{5-4} = 3.0 Hz, H-5), 3.34 (1H, dd, $J_{5'-5}$ = 13.3, $J_{5'-4}$ = 6.3 Hz, H-5'), 3.07 (3H, s, CH_3), 2.81 (1H, *br*. d, $J_{2-2'}$ = 16.6 Hz, H-2), 2.45 (1H, dd, $J_{2'-2}$ = 16.6, J = 4.3 Hz, H-2'), 2.00 (3H, s, CH_3CO_2), 1.33 (9H, s, 3 x CH_3); δ_C (100 MHz, Acetone-d_6) 171.8 (CO), 169.7 (CO), 155.1 (CO), 79.4 ($C(CH_3)_3$), 72.7 (C-4), 61.1 (CH_3), 51.3 (C-5), 47.6 (C-3), 31.8 (CH_3), 31.5 (C-2), 28.1 (3 x CH_3), 20.6 (CH_3CO_2); LRMS (ES^+) *m/z* 382 [M+Na^+] (100), 326 (12), 282 (40%); HRMS (ES^+) calculated for $C_{14}H_{26}N_5O_6$, 360.1878 [M+H^+]; found 360.1877. Anal. calcd. for $C_{14}H_{25}N_5O_6$: C, 46.79 ; H, 7.01; N, 19.49%. Found: C, 46.78; H, 7.01; N, 19.19%.

(3*S*, 4*R*)-3-(*tert*-Butyloxycarbonylamino)-4-acetyloxy-5-azido-pentanal (212).

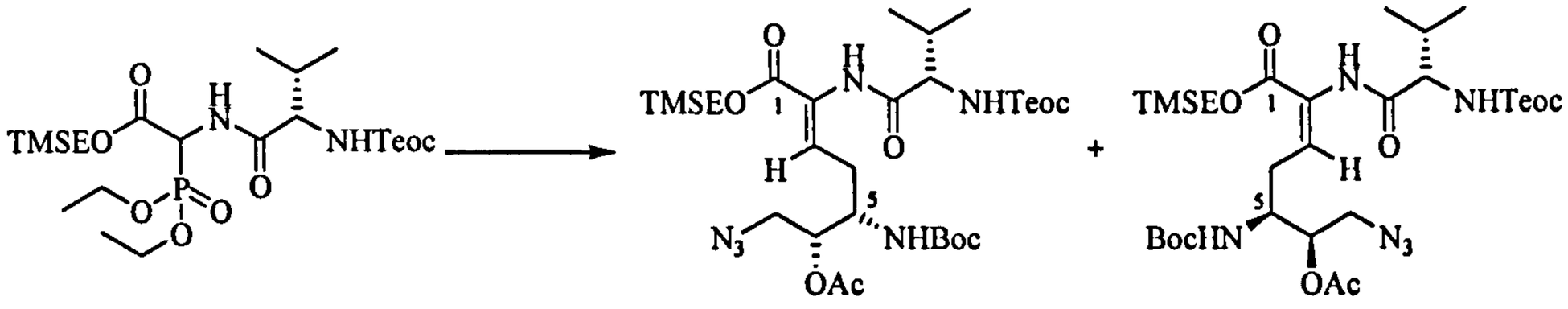


212

To a stirred solution of **211** (50 mg, 0.14 mmol) in dry tetrahydrofuran (1 mL) at -50 °C was added di-*iso*-butylaluminium hydride (1M in hexanes; 153 μL, 0.15 mmol) dropwise. The mixture was stirred at -50 °C for 4 h, then transferred *via canula* to a stirred solution of ethyl acetate (1 mL) and saturated aqueous of potassium sodium tartrate (2 mL) at 0 °C. After sitrring overnight at room temperature, the mixture was extracted with ethyl acetate (3 x 2 mL). The combined organic layers washed with brine (2 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (30% diethyl ether in petroleum ether) gave **212** (33 mg, 79%) as a colourless oil; $[\alpha]_D^{28}$ + 1.2 ($CHCl_3$, *c* 1.02); R_f 0.45 (40% diethyl ether in dichloromethane); ν_{max} (neat)/cm^{-1} 3353, 2979, 2099, 1712, 1517; δ_H (400 MHz, CD_2Cl_2) 9.71 (1H, *br*. t, $J_{1\text{-}2}$ = 1.3 Hz, H-1), 5.19 (1H, d, $J_{NH\text{-}3}$ = 8.8 Hz, NH), 5.07 (1H, *app*. sext., *J* = 3.0 Hz, H-4), 4.31 (1H, *app*. quin., *J* = 6.8 Hz, H-3), 3.55 (1H, dd, $J_{5\text{-}5'}$ = 13.4, $J_{5\text{-}4}$ = 3.8 Hz, H-5), 3.46 (1H, dd, $J_{5'\text{-}5}$ = 13.4, $J_{5'\text{-}4}$ = 5.8 Hz, H-5'), 2.68 (1H, d, $J_{2\text{-}2'}$ = 6.0, $J_{2\text{-}1}$ = 1.2 Hz, H-2), 2.67 (1H, d, $J_{2'\text{-}2}$ = 6.0, $J_{2'\text{-}1}$ = 1.3 Hz, H-2') , 2.10 (3H, s, CH_3), 1.43 (9H, s, 3 x CH_3); δ_C (100 MHz, CD_2Cl_2) 200.3 (C-1), 170.4 (CO), 155.4 (CO), 80.3 ($C(CH_3)_3$), 73.4 (C-4), 51.5 (C-5), 47.0 (C-3), 44.8 (C-2), 28.3 (3 x CH_3),

20.9 (CH_3); LRMS (ES^+) *m/z* 623 [2M+Na^+] (36), 323 [M+Na^+] (100), 217 (48%); HRMS (ES^+) calculated for $C_{12}H_{20}N_4O_5Na$, 323.1326 [M+Na^+]; found 323.1324.

(5*S*, 6*R*, 2*Z*)-[(2*S*)-3-Methyl-2-(2-trimethylsilylethoxycarbonylamino)butyrylamino] -5-(*tert*-butyloxycarbonylamino)-6-acetyloxy-7-azido-heptyl-2-ene-2-trimethyl-silyl ethyl ester (214).



(*Z*)-214 (*E*)-214

Method A:

To a stirred suspension of lithium chloride (13 mg, 0.31 mmol) in dry acetonitrile (1 mL) were added **99** (170 mg, 0.31 mmol) in acetonitrile (2 mL), then di-*iso*-propylethyl amine (53 μL, 0.31 mmol). After 10 min, **212** (92 mg, 0.31 mmol) in acetonitrile (1 mL) was added. The mixture was stirred for 16 h at room temperature, then concentrated *in vacuo*. The residue was re-dissolved in ether (4 mL), washed with water (1 mL) then brine (1 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (20% diethyl ether in dichloromethane) gave (*E*)-**214** (24 mg, 11%); $[\alpha]_D^{28}$ - 38.3 ($CHCl_3$, *c* 1.0); R_f 0.35 (20% diethyl ether in dichloromethane); ν_{max} (neat)/cm^{-1} 3307, 2957, 2100, 1713, 1683, 1515; δ_H (500 MHz, Acetone-d_6) 8.74 (1H, s, =CNHCO), 6.50 (1H, *app.* t, $J_{3\text{-}4}$ = 7.8 Hz, H-3), 6.17 (1H, *br.*

s, NHBoc), 6.13 (1H, d, J_{NH-8} = 9.4 Hz, NHTeoc), 5.10 (1H, *app.* sept., J_{6-7} = 3.4 Hz, H-6), 4.31-4.26 (2H, m, CO_2CH_2), 4.15-4.09 (2H, m, CO_2CH_2), 4.05 (1H, *app.* t, J_{8-9} = 7.1 Hz, NHC*H*CH$(CH_3)_2$), 3.93-3.89 (1H, m, H-5), 3.58 (1H, dd, $J_{7-7'}$ = 13.3, J_{7-6} = 3.4 Hz, H-7), 3.52 (1H, dd, $J_{7'-7}$ = 13.3, J = 7.5 Hz, H-7'), 2.68-2.60 (2H, m, H-4), 2.16 (1H, q, J_{9-10} = 6.7 Hz, NHCHC*H*$(CH_3)_2$), 2.07 (3H, s, CH_3CO), 1.39 (9H, s, 3 x CH_3), 0.99-0.96 (4H, dd, J = 8.5, J = 5.0 Hz, 2 x CH_2Si), 0.94 (6H, d, J_{10-9} = 6.7 Hz, 2 x CH_3), 0.07 (9H, s, $Si(CH_3)_3$), 0.04 (9H, s, $Si(CH_3)_3$); δ_C (125 MHz, Acetone-d_6) 170.9 (CO), 170.3 (CO), 164.5 (CO), 157.2 (CO), 156.3 (CO), 129.1 (C-2), 126.4 (C-3), 79.0 (*C*$(CH_3)_3$), 74.3 (C-6), 63.9 (CO_2CH_2), 63.0 (CO_2CH_2), 61.2 (C-9), 52.0 (C-5), 51.6 (C-7), 31.4 (C-8), 30.5 (C-4), 28.4 (3 x CH_3), 20.8 (*C*H_3CO), 19.5 (CH_3), 18.2 (CH_2Si), 18.0 (CH_3), 17.8 (CH_2Si) -1.6 ($Si(CH_3)_3$), -1.7 ($Si(CH_3)_3$); LRMS (ES^+) *m/z* 723 [M+Na^+] (46), 701 [M+H^+] (29), 601 (100%); HRMS (ES^+) calculated for $C_{30}H_{57}N_6O_9Si_2$, 701.3720 [M+H^+]; found 701.3721.

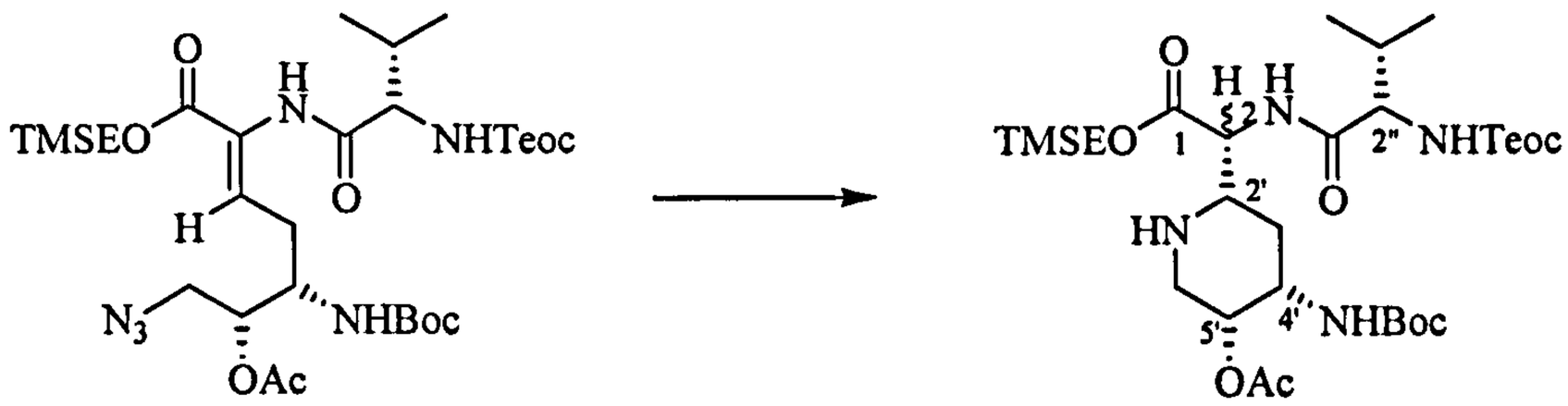
Further elution provided (*Z*)-**214a** (106 mg, 51%) as a colourless glassy solid; mp 74-75 °C; $[\alpha]_D^{28}$ + 3.9 ($CHCl_3$, *c* 1.0); R_f 0.32 (20% diethyl ether in dichloromethane); ν_{max} (neat)/cm^{-1} 3320, 2956, 2100, 1715, 1685, 1518; δ_H (400 MHz, Acetone-d_6) 8.47 (1H, s, =CNHCO), 6.59 (1H, *app.* t, J = 7.0 Hz, H-3), 6.45 (1H, d, J_{NH-5} = 8.5 Hz, NHBoc), 6.18 (1H, d, J = 7.5 Hz, NHTeoc), 5.13-5.09 (1H, m, H-6), 4.21 (4H, *app.* t, J = 8.4 Hz, 2 x CO_2CH_2), 4.16-4.06 (1H, m, NHC*H*$CH(CH_3)_2$), 3.97 (1H, *app.* sep, J = 5.0 Hz, H-5), 3.50-3.41 (2H, m, H-7), 2.50-2.33 (2H, m, H-4), 2.19 (1H, *app.* sext, J = 6.8 Hz, $(CH_3)_2$C*H*CHNH), 2.06 (3H, s, CH_3CO), 1.40 (9H, s, 3 x CH_3), 1.04-0.99 (10H, m, 2 x CH_2Si + NHCHC$H(CH_3)_2$), 0.05 (9H, *br.* s, $C(CH_3)_3$), 0.04 (9H, *br.* s, $C(CH_3)_3$); δ_C (100

MHz, Acetone-d_6) 171.1 (CO), 170.3 (CO), 164.6 (CO), 157.4 (CO), 156.4 (CO), 133.7 (C-3), 128.7 (C-2), 79.1 ($C(CH_3)_3$), 74.3 (C-6), 63.7 (CO_2CH_2), 63.1 (CO_2CH_2), 61.2 (NHCH), 51.7 (C-7), 51.2 (C-5), 31.5 ($(CH_3)_2CHCHNH$), 28.6 (C-4), 28.5 (3 x CH_3), 20.9 (CH_3CO), 19.7 ((CH_3CH_3)CHCHNH), 18.2 ((CH_3CH_3)CHCHNH), 17.8 (2 x CH_2Si), -1.5 ($Si(CH_3)_3$), -1.6 ($Si(CH_3)_3$); LRMS (ES^+) *m/z* 723 [$M+Na^+$] (18), 601 (100%); HRMS (ES^+) calculated for $C_{30}H_{56}N_6NaO_9Si_2$, 723.3540 [$M+Na^+$]; found 723.3539. Anal. calcd. for $C_{30}H_{56}N_6O_9Si_2$: C, 51.40; H, 8.05; N, 11.99%. Found: C, 51.61; H, 8.05; N, 11.39%.

Method B:

To a stirred solution of **99** (185 mg, 0.33 mmol) in dichloromethane (2 mL) at 10 °C was added DBN (40 μL, 0.33 mmol) dropwise. After 10 min, to this mixture was added **212** (100 mg, 0.33 mmol) in dichloromethane (1 mL) at 10 °C. After stirring overnight at room ptemperature, the solution was concentrated *in vacuo*. Purification by silica gel column chromatography (10% diethyl ether in dichloromethane) gave (*Z*)-**214** (181 mg, 81%) as a colourless glassy solid. Data as previously described.

(2*R*, 4*S*', 5*R*', 2*S*")- and (2*S*, 4*S*', 5*R*', 2*S*")-(5'-Acetoxy-4'-*tert*-butyloxycarbonylamino-piperidin-2'-yl)-[(2"-trimethylsilylethoxycarbonylamino) butyrylamino]-acetic acid trimethylsilylethyl ester (220).



220

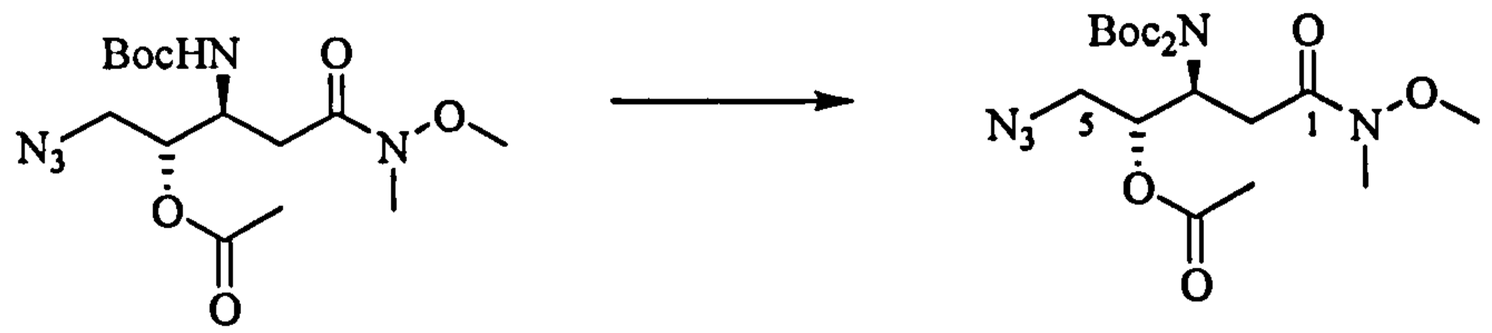
Method A: A suspension of (*Z*)-**214** (160 mg, 0.235 mmol) and palladium on carbon (16 mg; 10% w/w) in ethyl acetate (1 mL) was stirred under an atmosphere of hydrogen for 4 h. The mixture was filtered through celite to remove the catalyst, then concentrated *in vacuo*. Purification by column chromatography (20% diethyl ether in dichloromethane) gave **220** (106 mg, 69%) as a white glassy solid and as an inseparable 1:1.2 mixture of epimers at C-2 as judged by ^{1}H NMR spectroscopy; R_f 0.30 (20% diethyl ether in dichloromethane); ν_{max} (neat)/cm^{-1} 3319, 2955, 1712, 1510; δ_H (500 MHz, CD_2Cl_2) 6.82 (0.45H, *br.* s, C-NHCO), 6.77 (0.55H, d, $J_{NH\text{-}2}$= 7.3 Hz, C-NHCO), 5.22 (1H, *br.* s, NHVal), 4.86 (1H, *br.* s, H-5'), 4.73 (1H, *br.* s, NHBoc), 4.51 (0.39H, *br.* dd, $J_{2\text{-}NH}$ = 7.2, $J_{2\text{-}2'}$ = 5.4 Hz, H-2), 4.47 (0.61H, dd, $J_{2\text{-}NH}$ = 7.3, $J_{2\text{-}2'}$ = 3.5 Hz, H-2), 4.26 (2H, dd, J = 9.7, J = 6.6 Hz, CH_2CO_2), 4.20-4.15 (2H, m, CH_2CO_2), 4.07-3.99 (1H, m, H-2"), 3.82 (1H, *br.* s, H-4'), 3.25 (1H, dd, $J_{6'\text{-}6'a}$ = 15, $J_{6'\text{-}5'}$ = 2.2 Hz, H-6'), 3.17 (0.54H, *app.* d, J = 11.3 Hz, H-2'), 2.99 (0.46H, *app.* d, J = 13.5 Hz, H-2'), 2.77 (1H, *app.* t, J = 12.9 Hz, H-6'a), 2.16 (1H, *app.* sext., J = 6.6 Hz, H-3"), 2.11 (1.17H, s, CH_3CO), 2.10 (1.83H, s, CH_3CO), 1.79 (1H, *app.* td, J = 9.4, J = 2.0 Hz, H-3'), 1.44 (11H, *br.* s,

$C(CH_3)_3$ + H-4'a + NH_{pip}) 1.09-0.93 (10H, m, 2 x CH_2Si + 2 x CH_3), 0.09 (3.51H, s, $Si(CH_3)_3$), 0.08 (5.49H, s, $Si(CH_3)_3$), 0.07 (9H, s, $Si(CH_3)_3$); δ_C (125 MHz, CD_2Cl_2) 172.1 (CO), 171.9 (CO major), 171.6 (CO), 171.1 (CO major), 171.0 (CO), 170.7 (CO major), 170.5 (CO), 170.4 (CO major), 156.9 (CO), 155.0 (CO major), 79.7 ($C(CH_3)_3$), 70.1 (C-5'), 69.9 (C-5' major), 64.6 (CH_2CO_2 major), 64.5 (CH_2CO_2 major), 64.4 (CH_2CO_2), 63.7 (CH_2CO_2), 60.6 (C-2"), 60.4 (C-2' major), 57.3 (C-2'), 56.9 (C-2' major), 56.5 (C-2 major), 56.2 (C-2), 49.7 (C-4'), 49.6 (C-4' major), 48.6 (C-6'), 48.4 (C-6' major), 31.9 (C-3' major), 31.5 (C-3"), 31.0 (C-3'), 30.5 (C-3" major), 28.4 (3 x CH_3), 21.4 (CH_3CO major), 21.3 (CH_3CO), 19.5 (C-4" major), 19.3 (C-4"), 19.2 (C-4"), 18.0 (2 x CH_2Si major), 17.9 (C-10 major), 17.6 (2 x CH_2Si), -1.4 (2 x $Si(CH_3)_3$ major), -1.5 (2 x $Si(CH_3)_3$); LRMS (ES^+) *m/z* 697 [$M+Na^+$] (12), 675 [$M+H^+$] (100%); HRMS (ES^+) calculated for $C_{30}H_{59}N_4O_9Si_2$, 675.3815 [$M+H^+$]; found 675.3819.

Method B: A suspension of (*Z*)-**214** (100 mg, 0.143 mmol) and Lindlar's catalyst (20 mg; 20 % w/w) in ethanol (1 mL) was stirred under an atmosphere of hydrogen for 20 h. The mixture was filtered through celite to remove the catalyst, then concentrated *in vacuo*. Purification by column chromatography (20% diethyl ether in dichloromethane) gave **220** (86 mg, 89%) as a white glassy solid and as an inseparable 1:5 mixture of epimers at C-2 as judged by ^1H NMR spectroscopy; δ_H (500 MHz, CD_2Cl_2) 6.83 (0.16H, d, J = 7.8 Hz, CHN*H*CO), 6.76 (0.84H, d, $J_{NH\text{-}2}$ = 7.3 Hz, CHN*H*CO), 5.22 (1H, *br.* s, NHVal), 4.87 (1H, s, H-5'), 4.72 (1H, d, $J_{NH\text{-}4'}$ = 7.8 Hz, NHBoc), 4.52-4.48 (0.16H, *br.* m, H-2), 4.46 (0.84H, dd, $J_{2\text{-}NH}$ = 7.3, J = 3.5 Hz, H-2), 4.28-4.25 (2H, m, CO_2CH_2), 4.22-4.11 (2H, m, CO_2CH_2), 4.08-4.01 (1H, m, H-2"), 3.82 (1H, *br.* s, H-4'), 3.25 (1H,

dd, $J_{6'\text{-}6'a}$ = 14.2, J = 2.3 Hz, H-6'), 3.16 (0.87H, *app. br.* d, J = 11.6 Hz, H-2'), 2.98 (0.13H, *app. br.* d, J = 11.6 Hz, H-2'), 2.78 (1H, *br.* d, $J_{6'\text{-}6'a}$ = 14.2 Hz, H-6'a), 2.19-2.14 (1H, m, H-3"), 2.12 (0.48H, s, CH_3CO), 2.11 (2.52H, s, CH_3CO), 1.80 (1H, app. dt, $J_{3'\text{-}3'a}$ = 12.6, J = 3.2 Hz, H-3'), 1.44 (11H, *br.* s, NH_{pip} + H-3'a + 3 x CH_3), 1.09-0.94 (10H, m, 2 x $SiCH_2$ + 2 x CH_3), 0.087 (1.44H, s, $SiC(CH_3)_3$), 0.08 (7.56H, s, $SiC(CH_3)_3$), 0.07 (9H, s, $SiC(CH_3)_3$).

(3*S*, 4*R*)-3-(Di-*tert*-butyloxycarbonyl)amino-4-acetyloxy-5-azido-*N*, *O*-dimethyl-pentanamide (231).

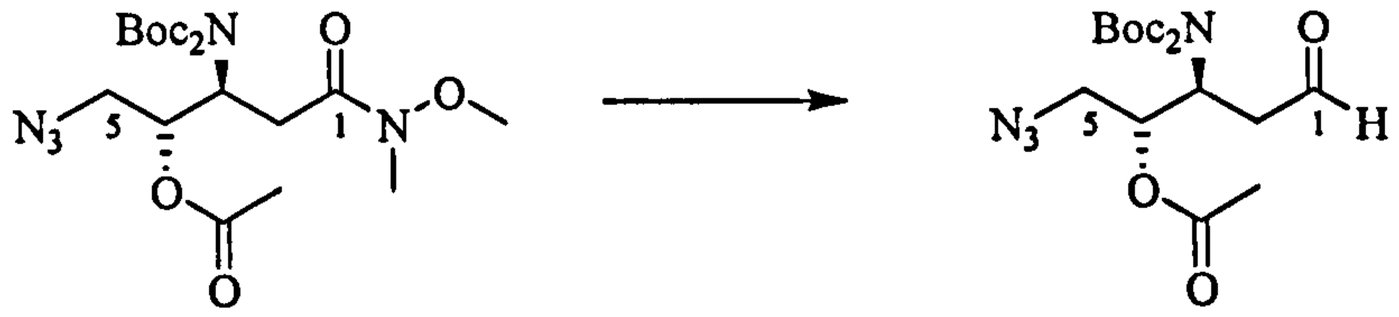


231

To a stirred solution of **211** (760 mg, 1.65 mmol) in dry acetonitrile (10 mL) were added di-*tert*-butyldicarbonate (1.80 g, 8.27 mmol) and 4-dimethylaminopyridine (404 mg, 3.31 mmol) in dry acetonitrile (5 mL). The mixture was heated at 60 °C overnight. On cooling, the orange solution was concentrated *in vacuo*. Purification by silica gel column chromatography (100% dichloromethane) afforded **231** (859 mg, 93%) as a yellow oil; $[\alpha]_D^{30}$ - 2.8 ($CHCl_3$, *c* 1.0); R_f 0.39 (20% ethyl acetate in dichloromethane); ν_{max} (neat)/cm^{-1} 2980, 2938, 2099, 1744, 1701, 1667, 1349, 1368, 1221; δ_H (400 MHz, CD_2Cl_2) 5.53-5.48 (1H, m, H-4), 4.80 (1H, td, $J_{3\text{-}2}$ = 8.9, $J_{3\text{-}4}$ = 4.8 Hz, H-3), 3.68 (3H, s, CH_3O), 3.54 (1H, dd, $J_{5\text{-}5'}$ = 13.4, $J_{5\text{-}4}$ = 3.0, H-5), 3.39 (1H, dd, $J_{5'\text{-}5}$ = 13.4, $J_{5'\text{-}4}$ = 6.0,

H-5'), 3.15 (3H, s, CH_3N), 3.02 (1H, dd, $J_{2\text{-}2'}$ = 15.8, $J_{2\text{-}3}$ = 8.9 Hz, H-2), 2.70 (1H, dd, $J_{2'\text{-}2}$ = 15.8, $J_{2'\text{-}3}$ = 4.5 Hz, H-2'), 2.10 (3H, s, CH_3CO), 1.52 (18H, s, 3 x CH_3); δ_C (100 MHz, CD_2Cl_2) 171.3 (CO), 170.0 (CO), 152.4 (2 x CO), 83.0 (2 x $C(CH_3)_3$), 72.6 (C-4), 61.1 (CH_3O), 53.6 (C-3), 51.5 (C-5), 33.9 (C-2), 32.2 (CH_3N), 27.9 (6 x CH_3), 20.9 (CH_3CO); LRMS (ES^+) *m/z* 482 [M+Na^+] (100), 360 (37), 304 (49%); HRMS (ES^+) calculated for $C_{19}H_{33}N_5NaO_8$, 482.2221 [M+Na^+]; found 482.2222. Anal. calcd. for $C_{19}H_{33}N_5O_8$: C, 49.66; H, 7.24; N, 15.24%. Found: C, 49.61; H, 7.25; N, 14.93%.

(3*S*, 4*R*)-3-Di-(*tert*-butyloxycarbonylamino)-4-acetyloxy-5-azido-pentanal (232).

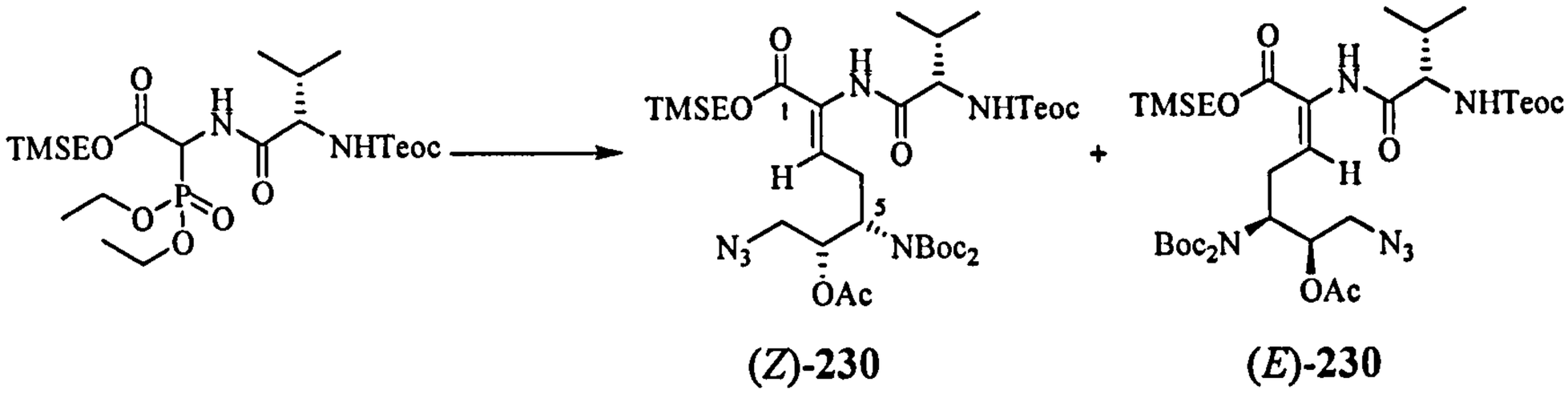


232

To a stirred solution of **231** (318 mg, 0.57 mmol) in dry tetrahydrofuran (3 mL) at -78 °C was added di-*iso*-butylaluminium hydride (1M in hexanes; 850 µL, 0.85 mmol) dropwise. The mixture was stirred at -78 °C for 8 h, then transferred *via* cannula to a mixture of ethyl acetate (3 mL) and saturated aqueous potassium sodium tartrate (5 mL) at 0 °C. After stirring overnight whith warming to room temperature, the mixture was extracted with ethyl acetate (3 x 3 mL). The combined organic layers washed with brine (1 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (10% ethyl acetate in dichloromethane) gave **232** (211 mg,

93%) as a colourless oil; $[\alpha]_D^{28}$ + 11.1 ($CHCl_3$, *c* 1.0); R_f 0.70 (20% ethyl acetate in dichloromethane); ν_{max} (neat)/cm^{-1} 2980, 2934, 2101, 1729, 1701, 1369, 1350, 1219; δ_H (400 MHz, CD_2Cl_2) 9.70 (1H, t, $J_{1\text{-}2}$ = 2.0 Hz, H-1), 5.49-5.45 (1H, ddd, J = 9.5, $J_{4\text{-}3}$ = 5.2, $J_{4\text{-}5}$ = 3.2 Hz, H-4), 4.86 (1H, *app.* td, $J_{3\text{-}2}$ = 8.5, $J_{3\text{-}2'}$ = 5.3, J = 5.2 Hz, H-3), 3.58 (1H, dd, $J_{5\text{-}5'}$ = 13.6, $J_{5\text{-}4}$ = 3.2 Hz, H-5), 3.38 (1H, dd, $J_{5'\text{-}5}$ = 13.6, $J_{5'\text{-}4}$ = 5.2 Hz, H-5'), 2.92 (1H, ddd, $J_{2\text{-}2'}$ = 16.9, $J_{2\text{-}3}$ = 8.5, $J_{2\text{-}1}$ = 2.1 Hz, H-2), 2.72 (1H, ddd, $J_{2'\text{-}2}$ = 16.9, $J_{2'\text{-}3}$ = 5.3, $J_{2'\text{-}1}$ = 1.9 Hz, H-2'), 2.07 (3H, s, CH_3), 1.51 (18H, s, 6 x CH_3); δ_C (100 MHz, CD_2Cl_2) 199.5 (C-1), 170.1 (CO), 153.0 (2 x CO), 83.8 (2 x $C(CH_3)_3$), 72.8 (C-4), 51.8 (C-3), 51.6 (C-5), 44.6 (C-2), 28.0 (6 x CH_3), 20.9 (CH_3); LRMS (ES^+) *m/z* 439 [$M+K^+$] (15), 423 [$M+Na^+$] (100), 217 (31%); HRMS (ES^+) calculated for $C_{17}H_{28}N_4NaO_7$, 423.1850 [$M+Na^+$]; found 423.1853. Anal. calcd. for $C_{17}H_{28}N_4O_7$: C, 50.99; H, 7.05; N, 13.99%. Found: C, 50.80; H, 7.09; N, 13.75%.

(5*S*, 6*R*, 2*Z*)-[(2*S*)-3-Methyl-2-(2-trimethylsilylethoxycarbonylamino)butyrylamino] -(5-di-(*tert*-butyloxycarbonyl)amino)-6-acetyloxy-7-azido-heptyl-2-ene-2-trimethyl-silylethyl ester (230).



(*Z*)-230 (*E*)-230

Method A. To a stirred solution of **99** (1.08 g, 1.96 mmol) in dichloromethane (10 mL) at 10 °C was added DBN (212 μL, 1.78 mmol) dropwise. After 30 min, **232** (712 mg, 1.78 mmol) in dichloromethane (10 mL) was added and the mixture was stirred overnight at room temperature. Concentration *in vacuo* followed by purification by silica gel column chromatography (10% ethyl acetate in dichloromethane) gave (*Z*)-**230** (1.02 g, 72%) as a colourless oil. $[\alpha]_D^{29}$ + 3.5 ($CHCl_3$, *c* 1.0); R_f 0.4 (20% ethyl acetate in dichloromethane); ν_{max}(neat)/cm^{-1} 3313, 2957, 2101, 1745, 1702; δ_H (500 MHz, $CDCl_3$) 7.52 (1H, s, =CNH), 6.49 (1H, *app*. t, $J_{3\text{-}4}$ = 7.3 Hz, H-3), 5.37 (1H, ddd, $J_{6\text{-}5}$ = 9.3, J = 4.7, J = 3.1, H-6), 5.20 (1H, *br*. d, $J_{NH\text{-}8}$ = 7.9 Hz, NHTeoc), 4.40 (1H, td, $J_{5\text{-}6}$ = 9.3, J = 5.7 Hz, H-5), 4.23-4.13 (5H, m, 2 x CO_2CH_2 + H-8), 3.56 (1H, dd, $J_{7\text{-}7'}$ = 13.6, $J_{7\text{-}6}$ = 2.8 Hz, H-7), 3.29 (1H, dd, $J_{7'\text{-}7}$ = 13.6, $J_{7'\text{-}6}$ = 4.7 Hz, H-7'), 2.64 (1H, *app*. sext., J = 7.9 Hz, H-4), 2.55-2.47 (1H, m, H-4'), 2.21 (1H, *app*. sept. J = 6.3 Hz, H-9), 2.07 (3H, s, CH_3CO), 1.48 (9H, s, $(CH_3)_3$), 1.47 (9H, s, $(CH_3)_3$), 1.00-0.93 (10H, m, 2 x CH_2Si + 2 x CH_3), 0.02 (18H, s, 2 x $Si(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) 170.0 (CO), 169.9 (CO), 169.8 (CO), 164.0 (CO), 156.6 (CO), 152.9 (CO), 131.9 (C-3), 127.9 (C-2), 83.4 ($C(CH_3)_3$),

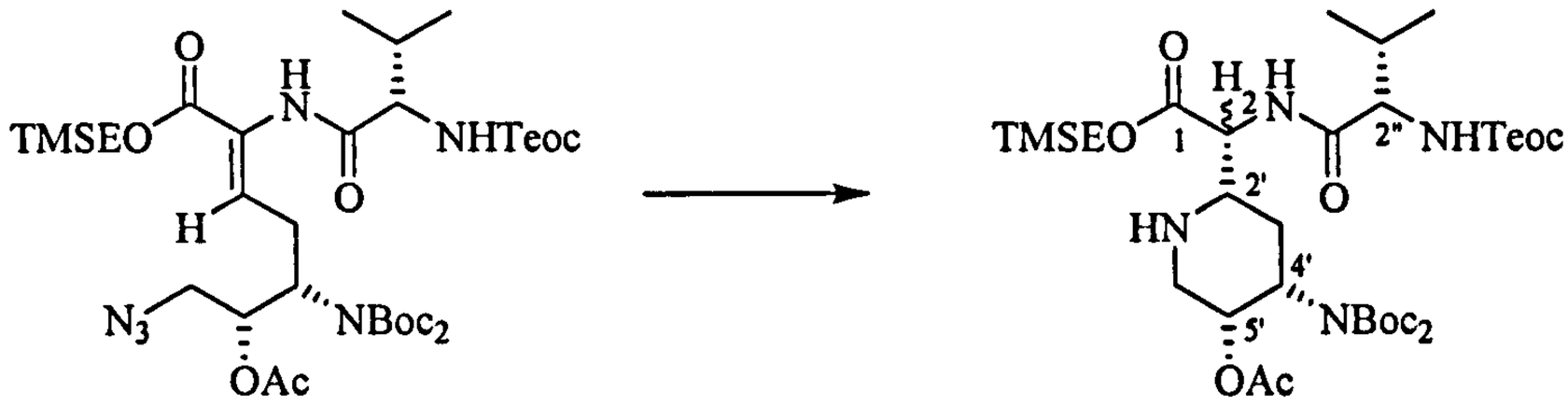
83.3 ($C(CH_3)_3$), 73.3 (C-6), 63.9 (CO_2CH_2), 63.5 (CO_2CH_2), 60.1 (C-8), 55.4 (C-5), 51.3 (C-7), 31.2 ($CH(CH_3)_2$), 29.5 (C-4), 27.9 (2 x $(CH_3)_3$), 20.9 (CH_3CO), 19.3 (CH_3), 17.6 (CH_2Si), 17.4 (CH_3), 17.3 (CH_2Si), -1.5 $(SiCH_3)_3$), -1.6 $(Si(CH_3)_3$); LRMS (ES^+) *m/z* 823 [M+Na^+] (80), 701 (36), 601 (100%); HRMS (ES^+) calculated for $C_{35}H_{64}N_6O_{11}Si_2Na$, 823.4064 [M+$Na^+$]; found 823.4161. Anal. calcd. for $C_{35}H_{64}N_6O_{11}Si_2$: C, 52.48; H, 8.05; N, 10.49%. Found: C, 52.40; H, 8.10; N, 10.18%.

Method B. To a stirred suspension of lithium chloride (5 mg, 0.12 mmol) in dry acetonitrile (0.5 mL) was added **99** (69 mg, 0.12 mmol) in acetonitrile (1 mL), then di-*iso*-propylethyl amine (22 μL, 0.12 mmol). After 10 min, **232** (50 mg, 0.12 mmol) in acetonitrile (0.5 mL) was added, then the mixture stirred for 16 h at room temperature. The mixture was concentrated *in vacuo*, re-dissolved in ether (2 mL), washed with water (1 mL) then brine (1 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (50% diethyl ether in petroleum ether) gave (*E*)-**230** (5.3 mg, 5%) as a colourless oil; R_f 0.29 (50% diethyl ether in petroleum ether); $[\alpha]_D^{26}$ + 10.6 ($CHCl_3$, *c* 1.0); ν_{max} (neat)/cm^{-1} 3266, 2979, 2934, 2101, 1797, 1761, 1520; δ_H (500 MHz, Acetone-d_6) 7.80 (1H, s, =CNHCO), 7.18 (1H, *app*.t, $J_{3\text{-}4}$ = 7.5 Hz, H-3), 5.52 (1H, ddd, J = 9.1 J = 7.8, J = 2.8 Hz, H-6), 5.13 (1H, d, J = 6.9 Hz, NHTeoc), 4.45 (1H, dt, J = 9.4, J = 5.5 Hz, H-5), 4.28 (2H, *app*. q, J = 9.1 Hz, CO_2CH_2), 4.16 (2H, *app.* t, J = 8.8 Hz, CO_2CH_2), 3.99 (1H, *br*. s, H-8), 3.57 (1H, dd, J = 13.4, J = 2.8 Hz, H-7), 3.33 (1H, dd, J = 13.4, J = 5.0 Hz, H-7'), 3.07 (1H, td, J = 16.3, J = 8.5 Hz, H-4), 3.00-2.94 (1H, m, H-4'), 2.18-2.14 (1H, m, H-9), 2.08 (3H, s, CH_3CO), 1.48 (18H, s, 2 x $(CH_3)_3$), 1.09 (2H, *app.* t, J = 8.9 Hz, CH_2Si),

0.99-0.95 (5H, m, CH_2Si + CH_3), 0.91 (3H, d, J = 6.9 Hz, CH_2Si), 0.01 (9H, s, $SiCH_3$), 0.03 (9H, s, $SiCH_3$); δ_C (125 MHz, Acetone-d_6) 170.0 (CO), 169.6 (CO), 163.8 (CO), 156.7 (CO), 152.7 (CO), 151.8 (CO), 127.1 (C-3), 126.1 (C-2), 83.0 (2 x $C(CH_3)_3$), 73.7 (C-6), 64.5 (CO_2CH_2), 60.9 (C-8), 60.4 (CO_2CH_2), 56.5 (C-5), 51.4 (C-7), 31.0 ($CH(CH_3)_2$), 28.7 (C-4), 27.9 (6 x CH_3), 21.0 (CH_3CO), 19.3 (CH_3), 17.7 (CH_2Si), 17.5 (CH_2Si), 14.2 (CH_3), -1.5 ($Si(CH_3)_3$), -1.6 ($Si(CH_3)_3$); LRMS (ES^+) *m/z* 823 [M+Na^+] (80), 701 (36), 601 (100%); HRMS (ES^+) calculated for $C_{35}H_{64}N_6O_{11}Si_2Na$, 823.4064 [M+$Na^+$]; found 823.4067.

Further elution gave (*Z*)-**230** (54 mg; 54%) as a colourless oil. Data as previously described.

(2*R*, 4*S*', 5*R*', 2*S*")- and (2*S*, 4*S*', 5*R*', 2*S*")-(5'-Acetoxy-4'-di-*tert*-butyloxycarbonylamino-piperidin-2'-yl)-[(2"-trimethylsilylethoxycarbonylamino) butyrylamino]-acetic acid trimethylsilylethyl ester (235).

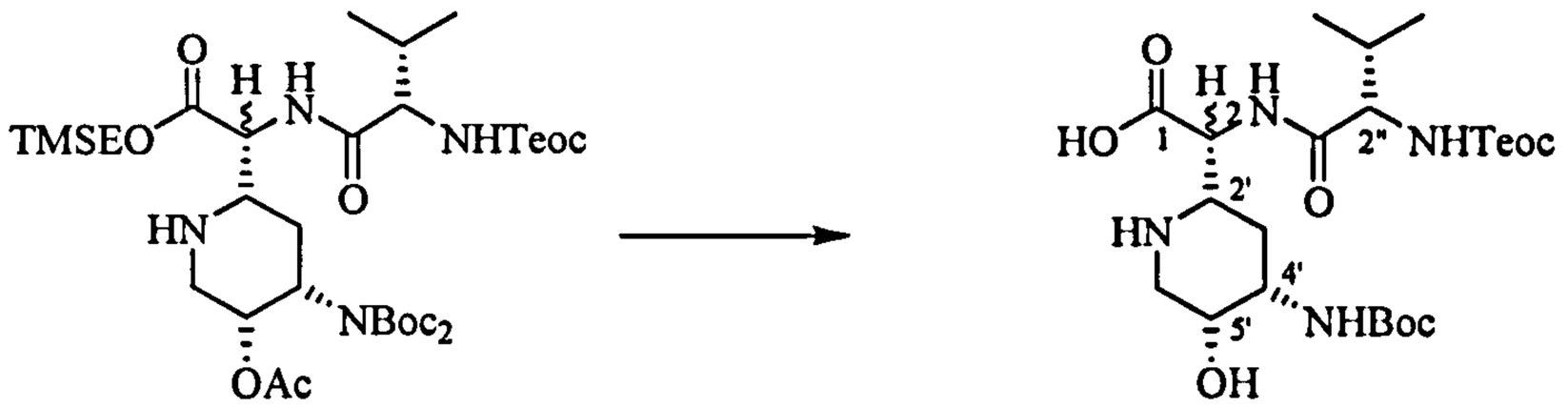


235

A suspension of **230** (500 mg, 0.625 mmol) and Lindlar's catalyst (100 mg; 20 % w/w) in ethanol (7 mL) was stirred under an atmosphere of hydrogen for 20 h. The mixture was filtered through celite to remove the catalyst, then concentrated *in vacuo*. Purification by column chromatography (50% diethyl ether in dichloromethane) gave **235** (387 mg, 80%) as a white glassy solid and as a 6:1 mixture of epimers at C-2, as judged by ^{1}H NMR spectroscopy, mp 74-75 °C; $[\alpha]_D^{35}$ -2.7 ($CHCl_3$, *c* 1.0); R_f 0.4 (diethyl ether/dichloromethane, 60%); ν_{max} (neat)/cm^{-1} 3321, 2956, 1745, 1707, 1526; δ_H (500 MHz, CD_3CN) 7.04 (0.15H, d, *J* = 7.0 Hz, CHN*H*CO), 6.97 (0.85H, d, *J* = 6.9 Hz, CHN*H*CO), 5.63 (1H, *br*. d, *J* = 8.5 Hz, NHTeoc), 5.02 (1H, *br*. s, H-5'), 4.44 (0.18H, dd, *J* = 7.8, *J* = 4.0 Hz, H-2), 4.40 (0.82H, dd, *J* = 7.5, *J* = 4.0 Hz, H-2), 4.26-4.11 (4H, m, 2 x CH_2CO_2), 4.08 (1H, dt, *J* = 13.2, *J* = 2.9 Hz, H-4'), 4.01 (1H, *br*. t, *J* = 7.0 Hz, H-2"), 3.09 (1H, dt, *J* = 11.6, *J* = 3.1 Hz, H-2'), 3.01 (1H, dd, $J_{7\text{-}7'}$ = 14.8, *J* = 2.5 Hz, H-6'), 2.76 (1H, *br*. d, $J_{7'\text{-}7}$ = 14.8 Hz, H-6'a), 2.11-2.04 (1H, m, H-3"), 2.02 (3H, *br*. s, CH_3CO), 1.66 (1H, dt, *J* = 12.2, *J* = 3.1 Hz, H-3'), 1.46 (3H, s, CH_3), 1.45 (17H, s, 5 x $C(CH_3)_3$ + H-3'a + NH_{pip}), 1.07-0.87 (10H, m, 2 x CH_2Si + 2 x CH_3), 0.05

(9H, *br.* s, $SiC(CH_3)_3$), 0.03 (9H, *br.* s, $SiC(CH_3)_3$); δ_C (125 MHz, CD_3CN) 172.6 (CO), 172.4 (CO), 172.4 (CO), 171.4 (CO), 171.3 (2 x CO), 171.0 (2 x CO), 157.5 (CO), 153.5 (CO), 153.5 (CO), 153.4 (CO), 83.1 (2 x $C(CH_3)_3$ minor), 83.0 (2 x $C(CH_3)_3$ major), 69.0 (C-5' major), 68.9 (C-5' minor), 64.4 (CH_2CO_2 major), 64.2 (2 x CH_2CO_2 minor), 63.6 (CH_2CO_2 major), 61.1 (C-4' major), 60.9 (C-4' minor), 58.3 (C-2" minor), 58.1 (C-2" major), 57.3 (C-2' major), 57.1 (C-2' minor), 56.8 (C-2 major), 56.7 (C-2 minor), 49.4 (C-6' minor), 49.3 (C-6' major), 31.7 (C-3" major), 31.6 (C-3" minor), 29.5 (C-3' major), 29.4 (C-3' minor), 28.0 (2 x $C(CH_3)_3$ major + minor), 21.6 (CH_3CO major + minor), 19.7 (CH_3 major), 19.6 (CH_3 minor), 19.5 (CH_3 minor), 18.2 ($SiCH_2$ major + minor), 18.0 (CH_3 major), 17.8 ($SiCH_2$ major + minor), -1.5 ($Si(CH_3)_3$ major + minor), -1.6 ($Si(CH_3)_3$ major + minor); LRMS (ES^+) *m/z* 797 [$M+Na^+$] (14), 775 [$M+H^+$](100), 391 (6), 167 (12%); HRMS (ES^+) calculated for $C_{35}H_{67}N_4O_{11}Si_2$, 775.4339 [$M+H^+$]; found 775.4339. Anal. calcd. for $C_{35}H_{66}N_4O_{11}Si_2$: C, 54.24; H, 8.58; N, 7.23%. Found: C, 54.06; H, 8.60; N, 6.97%.

(2*R*,4*S*',5*R*',2*S*")- and (2*S*,4*S*',5*R*',2*S*")-(5'-Hydroxy-4'-di-*tert*-butyloxycarbonyl amino-piperidin-2'-yl)-[(2"-trimethylsilylethoxycarbonylamino)butyrylamino] acetic acid (239).

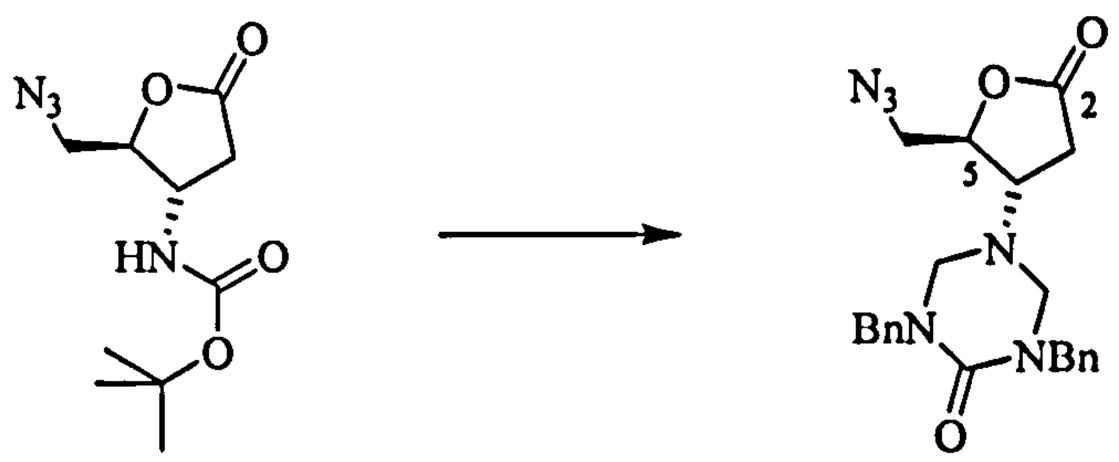


239

To a stirred solution of **235** (100 mg, 0.129 mmol) in methanol (5 mL) was added potassium carbonate (17.8 mg, 0.129 mmol). After 2 h, the mixture was concentrated *in vacuo* then purified by column chromatography (20% methanol in dichloromethane; 1% ammonia) to give **239** (69 mg, 74%) as a white powder; mp 195-196 °C; R_f 0.29 (20% methanol in dichloromethane); ν_{max} (neat)/cm^{-1} 3333, 2960, 1663, 1619, 1530; δ_H (400 MHz, MeOD-d_4) 4.49 (0.6H, *app.* d, J = 3.5 Hz, H-2), 4.42 (0.4H, d, J = 5.8 Hz, H-2), 4.29-4.22 (1.2H, m, CO_2CH_2), 4.19-4.11 (0.8H, m, CO_2CH_2), 4.06 (1H, d, $J_{2"\text{-}3"}$ = 6.5 Hz, H-2"), 4.02 (1H, *br.* s, H-5'), 3.77-3.67 (1H, m, H-4'), 3.59 (1H, *app.* d, J = 12.3 Hz, H-2'), 3.44-3.40 (1H, m, H-6'), 3.19 (1H, t, $J_{6'a\text{-}6'}$ = 12.3 Hz, H-6'a), 2.19 (1H, *app.* sext. $J_{3"\text{-}2"}$ = 6.5 Hz, H-3"), 1.99-1.56 (2H, m, H-3'), 1.47 (9H, s, 3 x CH_3), 1.08-0.97 (8H, m, CH_2Si + 2 x CH_3), 0.09 (9H, s, $Si(CH_3)_3$); δ_C (100 MHz, MeOD-d_4) 174.1 (CO), 173.9 (CO), 159.0 (CO), 157.3 (CO), 80.4 ($C(CH_3)_3$), 64.9 (C-5'), 64.8 (CO_2CH_2), 64.3 (CO_2CH_2), 62.1 (C-2"), 62.0 (C-2"), 59.3 (C-4'), 57.0 (C-2), 56.1 (C-2'), 55.6 (C-2), 49.9 (C-6'), 49.8 (C-6'), 31.7 (C-3"), 28.7 (3 x CH_3), 25.6 (C-3'), 19.9 (CH_3), 18.6 (CH_2Si), 18.3 (CH_3), -1.3 ($Si(CH_3)_3$), -1.4 ($Si(CH_3)_3$); LRMS (ES^+) *m/z* 555 [$M+Na^+$]

(47), 533 [M+H$^+$] (100), 391 (8%); HRMS (ES$^+$) calculated for $C_{23}H_{45}N_4O_8Si$, 533.3001 [M+H$^+$]; found 533.3002.

(4*S*,5*R*)-4-(1, 3-Dibenzylhexahydro-2-oxo-1, 3, 5-triazin-5-yl)-5-azido-2(5*H*)furanone (224).

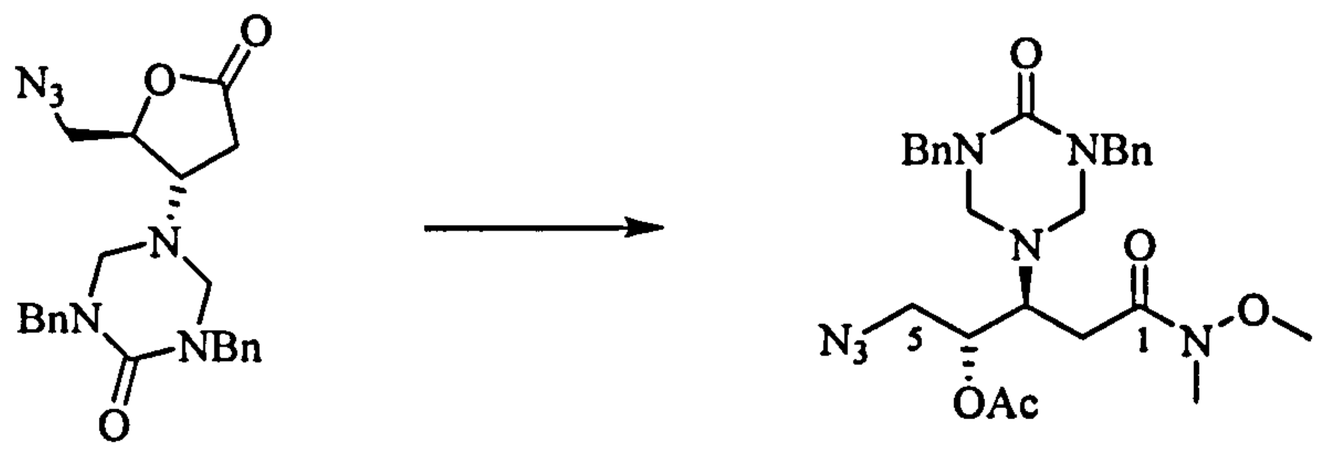


224

To a stirred solution of trifluoroacetic acid (7.5 mL) and dichloromethane (205 mL) at 0 °C was added **186** (3.00 g, 11.70 mmol) in dichloromethane (50 mL). The mixture was stirred at 0 °C for 6 h, then concentrated *in vacuo*, to give the free amine. This material was stirred with formaldehyde (30% in water; 8.8 mL, 117.0 mmol) and di-*iso*-propylethyl amine (2.04 mL, 11.70 mmol) for 10 min. The mixture was concentrated *in vacuo,* azeotroped with toluene (2 x 50 mL), then concentrated *in vacuo* to constant weight. This amine-formaldehyde adduct was dissolved in ethyl acetate (50 mL) and *N*, *N*'-dibenzylurea (2.81 g, 11.7 mmol) added. The mixture was heated at reflux for 1 h. On cooling to room temperature, the mixture was diluted with ethyl acetate (50 mL), washed with water (50 mL), and the organic phase dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (10% ethyl acetate in dichloromethane) gave **224** (2.24 g, 46% over three steps) as a colourless

amorphous solid; mp 128-129 °C; $[\alpha]_D^{25}$ + 25.8 ($CHCl_3$, *c* 1.02); R_f 0.26 (20% ethyl acetate in dichloromethane); ν_{max} (neat)/cm^{-1} 3030, 2919, 2101, 1783, 1634, 1354; δ_H (400 MHz, CD_2Cl_2) 7.44-7.34 (10H, m, ArH), 4.57 (2H, d, J = 15.0 Hz, 2 x CH), 4.46 (2H, d, J = 15.0 Hz, 2 x CH), 4.22-4.13 (5H, m, H-4 + 2 x CH_2), 3.36-3.31 (1H, ddd, J = 6.2, J = 4.8, J = 4.5 Hz, H-4), 3.14 (1H, dd, $J_{6\text{-}6'}$ = 13.6, $J_{6\text{-}5}$ = 3.0 Hz, H-6), 2.68 (1H, dd, $J_{6'\text{-}6}$ = 13.6, $J_{6'\text{-}5}$ = 4.8 Hz, H-6'), 2.16 (2H, ddd, J = 18.1, J = 8.0, J = 6.0 Hz, H-3); δ_C (100 MHz, CD_2Cl_2) 173.8 (CO), 155.7 (C-2), 138.5 (2 x ArC), 129.1 (4 x ArCH), 128.8 (4 x ArCH), 128.1 (2 x ArCH), 81.5 (C-5), 63.7 (2 x CH_2), 56.6 (C-4), 52.8 (C-6), 48.5 (2 x CH_2), 32.9 (C-3); LRMS (ES^+) *m/z* 460 [$M+K^+$] (8), 443 [$M+Na^+$] (38), 421 [$M+H^+$] (100), 391 (7%); HRMS (ES^+) calculated for $C_{22}H_{25}N_6O_3$, 421.1983 [$M+H^+$]; found 421.1983.

(3*S*, 4*R*)-3-(1, 3-Dibenzylhexahydro-2-oxo-1, 3, 5-triazin-5-yl)-4-acetyloxy-5-azido-*N*, *O*-dimethylpentanamide (226).



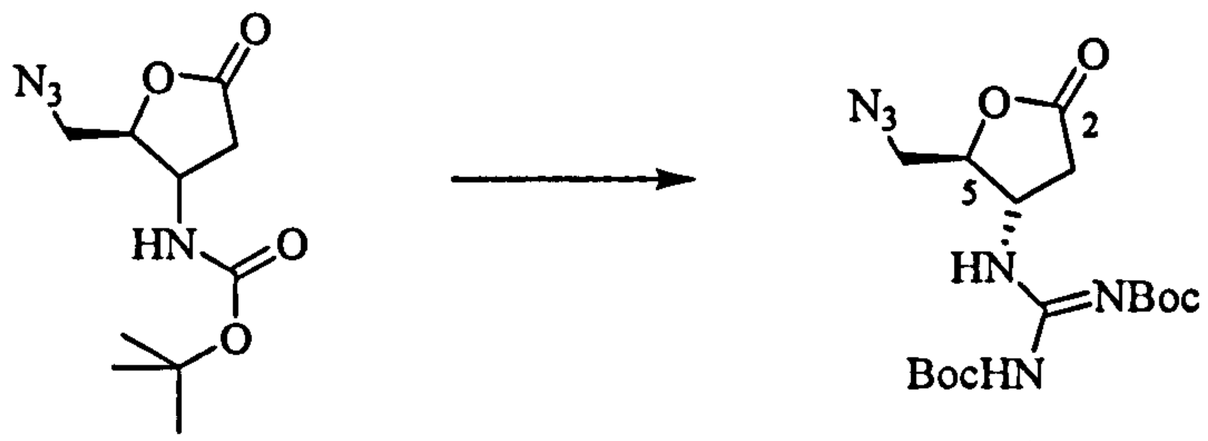
226

To a stirred solution of *N*, *O*-dimethylhydroxylamine hydrochloride (2.55 g, 26.10 mmol) in dichloromethane (60 mL) at 0 °C was added trimethylaluminium (2M in hexane; 13.08 mL, 26.10 mmol). After 30 min at room temperature, **224** (2.20 g, 5.25 mmol) in dichloromethane (60 mL) was added. The mixture was stirred for 4 h, then quenched by the addition of saturated aqueous potassium sodium tartrate (100 mL). After 2 h, the mixture was extracted with dichloromethane (3 x 40 mL), then the combined organic phase washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. This gave **225** (2.69 g) as a white foam that was used without further purification; R_f 0.2 (60% ethyl acetate in petroleum ether); ν_{max} (neat)/cm^{-1} 3357, 2919, 2098, 1622; δ_H (400 MHz, CD_2Cl_2) 7.39-7.20 (10H, m, ArH), 4.56 (2H, d, J = 15 Hz, 2 x CH), 4.47 (2H, d, J = 15 Hz, 2 x CH), 4.22 (4H, *br.* d, J = 2.8 Hz, 2 x CH_2), 3.73 (1H, d, $J_{OH\text{-}4}$ = 7.0 Hz, OH), 3.61 (4H, m, CH_3 + H-4), 3.28-3.22 (3H, m, H-5 + H-3), 3.16 (3H, s, CH_3), 2.74 (1H, dd, $J_{2\text{-}2'}$ = 16.7, $J_{2\text{-}3}$ = 3.0 Hz, H-2), 2.57 (1H, dd, $J_{2'\text{-}2}$ = 16.7, $J_{2'\text{-}3}$ = 6.5 Hz, H-2'); δ_C (100 MHz, CD_2Cl_2) 172.9 (CO), 156.1 (CO), 138.6 (2 x ArC), 128.8 (4 x ArCH), 128.3 (4 x ArCH), 127.5 (2 x ArCH), 72.0 (C-4), 64.6 (2 x CH_2), 61.5 (CH_3), 59.8 (C-3), 55.4 (C-5), 48.8 (2 x CH_2), 32.3 (CH_3), 30.9 (C-2); LRMS

(ES^+) *m/z* 504 [M+Na^+] (100), 421 (30), 242 (64%); HRMS (ES^+) calculated for $C_{24}H_{32}N_7O_4$, 482.2510 [M+H^+]; found 482.2508.

This free alcohol was dissolved in dichloromethane (45 mL) at 0 °C. To this solution were added dry pyridine (4.23 mL, 52.3 mmol), 4-dimethylaminopyridine (383 mg, 3.14 mmol) and acetic anhydride (3.06 mL, 32.4 mmol). After stirring at room temperature overnight, the mixture was concentrated *in vacuo*. Purification by silica gel column chromatography (10% ethyl acetate in dichloromethane) gave **226** (2.04 g, 74% over two steps) as a white foam; $[\alpha]_D^{29}$ - 13.3 ($CHCl_3$, *c* 1.2); R_f 0.13 (50% ethyl acetate in petroleum ether); ν_{max} (neat)/cm^{-1} 2938, 2098, 1743, 1639; δ_H (400 MHz, $CDCl_3$) 7.40-7.35 (7H, m, ArH), 7.34-7.29 (3H, m, ArH), 4.97 (1H, *app.* sept., J = 3.4 Hz, H-4), 4.63 (2H, d, J = 15.1 Hz, 2 x CH), 4.51 (2H, d, J = 15.1 Hz, 2 x CH), 4.23 (2H, d, J = 11.4 Hz, 2 x CH), 4.18 (2H, d, J = 11.4 Hz, 2 x CH), 3.84 (1H, *app.* dt, J = 8.8, J = 5.8 Hz, H-3), 3.64 (3H, s, CH_3), 3.44 (1H, dd, $J_{5\text{-}5'}$ = 13.2, $J_{5\text{-}4}$ = 3.4 Hz, H-5), 3.39 (1H, dd, $J_{5'\text{-}5}$ = 13.2, $J_{5'\text{-}4}$ = 5.4 Hz, H-5'), 3.22 (3H, s, CH_3), 2.77 (1H, dd, $J_{2\text{-}2'}$ = 17.6, $J_{2\text{-}3}$ = 6.0 Hz, H-2), 2.50 (1H, dd, $J_{2'\text{-}2}$ = 16.6, $J_{2'\text{-}3}$ = 4.0 Hz, H-2'), 2.07 (3H, s, CH_3); δ_C (100 MHz, CD_2Cl) 171.1 (CO), 170.1 (CO), 155.5 (CO), 137.6 (2 x ArC), 128.4 (4 x ArCH), 128.0 (4 x ArCH), 127.2 (2 x ArCH), 72.9 (C-4), 64.1 (2 x CH_2), 61.0 (CH_3), 58.4 (C-3), 51.8 (C-5), 48.6 (2 x CH_2), 32.0 (CH_3), 30.9 (C-2), 20.7 (CH_3); LRMS (ES^+) *m/z* 524 [M+H^+] (100 %); HRMS (ES^+) calculated for $C_{26}H_{34}N_7O_5$, 524.2616 [M+H^+]; found 524.2622.

(4*S*, 5*R*)-4-[(*N*, *N'*-bis-(*tert*-Butyloxycarbonylamino)guanidine-5-azidomethyl]-2(5*H*) furan-2-one (189).



189

To a stirred solution of trifluoroacetic acid (2.6 mL) and dichloromethane (7.4 mL) at 0 °C was added **186** (189 mg, 0.740 mmol) in dichloromethane (7.4 mL). After 6h, the mixture was warmed to room temperature and the residue was re-dissolved in dichloromethane (7 mL), triethylamine (205 μL, 1.48 mmol) was added dropwise, followed by *N*, *N'*-bis-(*tert*-butyloxycarbonylamino)guanidine triflate (289 mg, 0.74 mmol). The mixture was stirred overnight at room temperature, then concentrated *in vacuo*. Purification by silica column chromatography (20% diethyl ether in petroleum ether) gave **189** (268 mg, 91%) as a white solid; mp 97-99 °C; $[\alpha]_D^{24}$ + 11.9 ($CHCl_3$, *c* 1.0); ν_{max} (neat)/cm^{-1}; R_f 0.27 (20% diethyl ether in petroleum ether); ν_{max} (neat)/cm^{-1} 3314, 2982, 2936, 2105, 1788, 1726, 1610; δ_H (400 MHz, Acetone-d_6) 11.51 (1H, s, NHBoc), 8.55 (1H, d, $J_{NH\text{-}4}$ = 6.5 Hz, NHC=N), 4.80-4.73 (1H, m, H-4), 4.69 (1H, *app.* td, $J_{5\text{-}6'}$ = 5.2, $J_{5\text{-}6}$ = 3.0 Hz, H-5), 3.89-3.85 (1H, dd, $J_{6\text{-}6'}$ = 13.4, $J_{6\text{-}5}$ = 3.0 Hz, H-6), 3.82-3.77 (1H, dd, $J_{6'\text{-}6}$ = 13.4, $J_{6'\text{-}5}$ = 5.2 Hz, H-6'), 3.05-3.00 (1H, dd, $J_{3\text{-}3'}$ = 18.0, $J_{3\text{-}4}$ = 9.5, H-3), 2.86-2.79 (1H, dd, $J_{3'\text{-}3}$ = 18.0, $J_{3'\text{-}4}$ = 6.5 Hz, H-3'), 1.51 (9H, s, 3 x CH_3), 1.44 (9H, s, 3 x CH_3); δ_C (100 MHz, Acetone-d_6) 173.9 (CO), 163.7 (CO), 156.3 (CO), 153.0 (C=N), 122.0 ($C(CH_3)_3$), 118.8 ($C(CH_3)_3$, 83.8 (C-5), 53.3 (C-6), 49.5 (C-4), 34.7

(C-3), 28.1 (3 x CH_3), 27.8 (3 x CH_3); LRMS (ES^+) 819 [2M+Na^+] (7), 617 (24), 421 [M+Na^+] (38), 399 [M+H^+] (100%); HRMS (ES^+) calculated for $C_{16}H_{27}N_6O_4$, 399.1987 [M+H^+]; found 399.1983.

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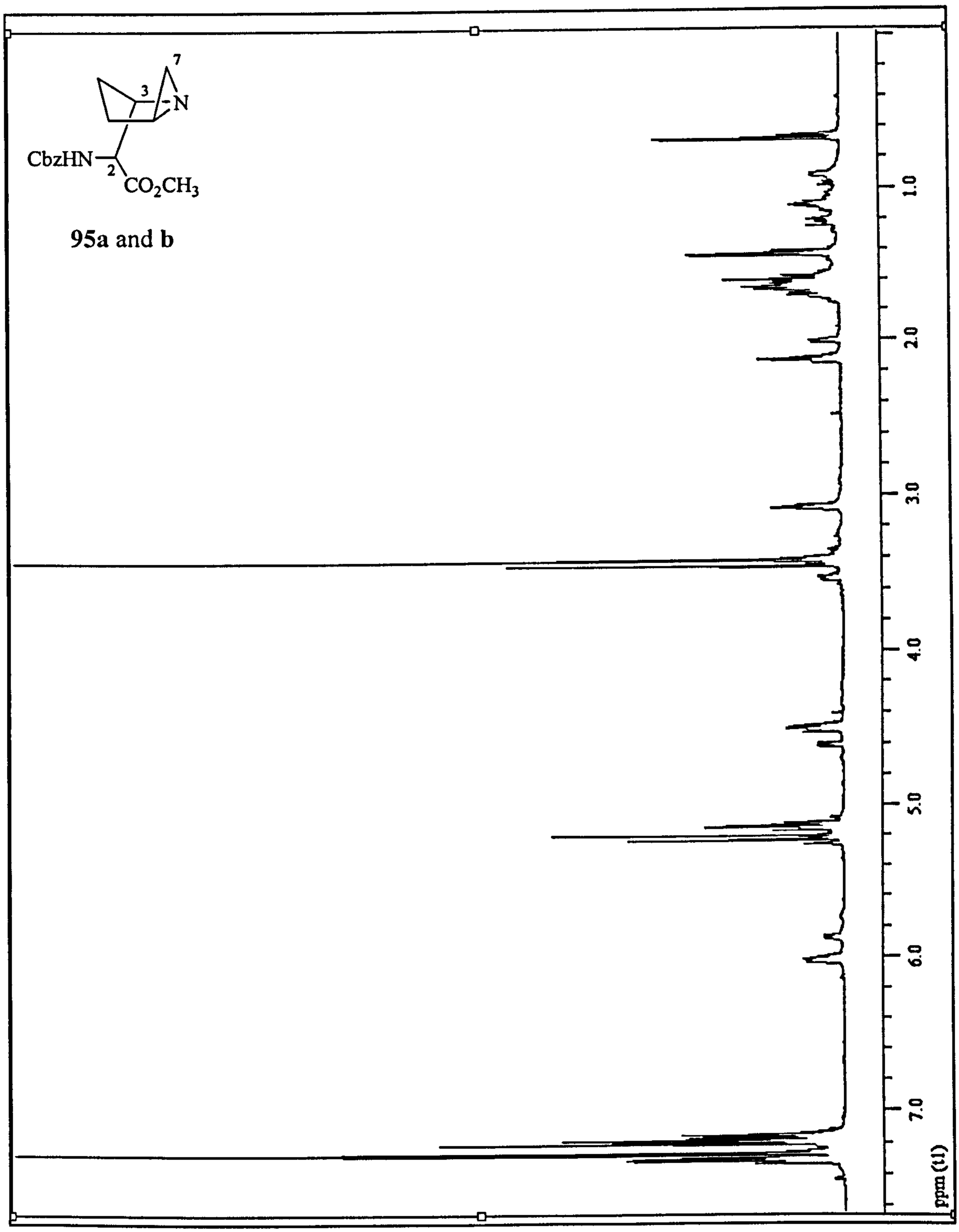
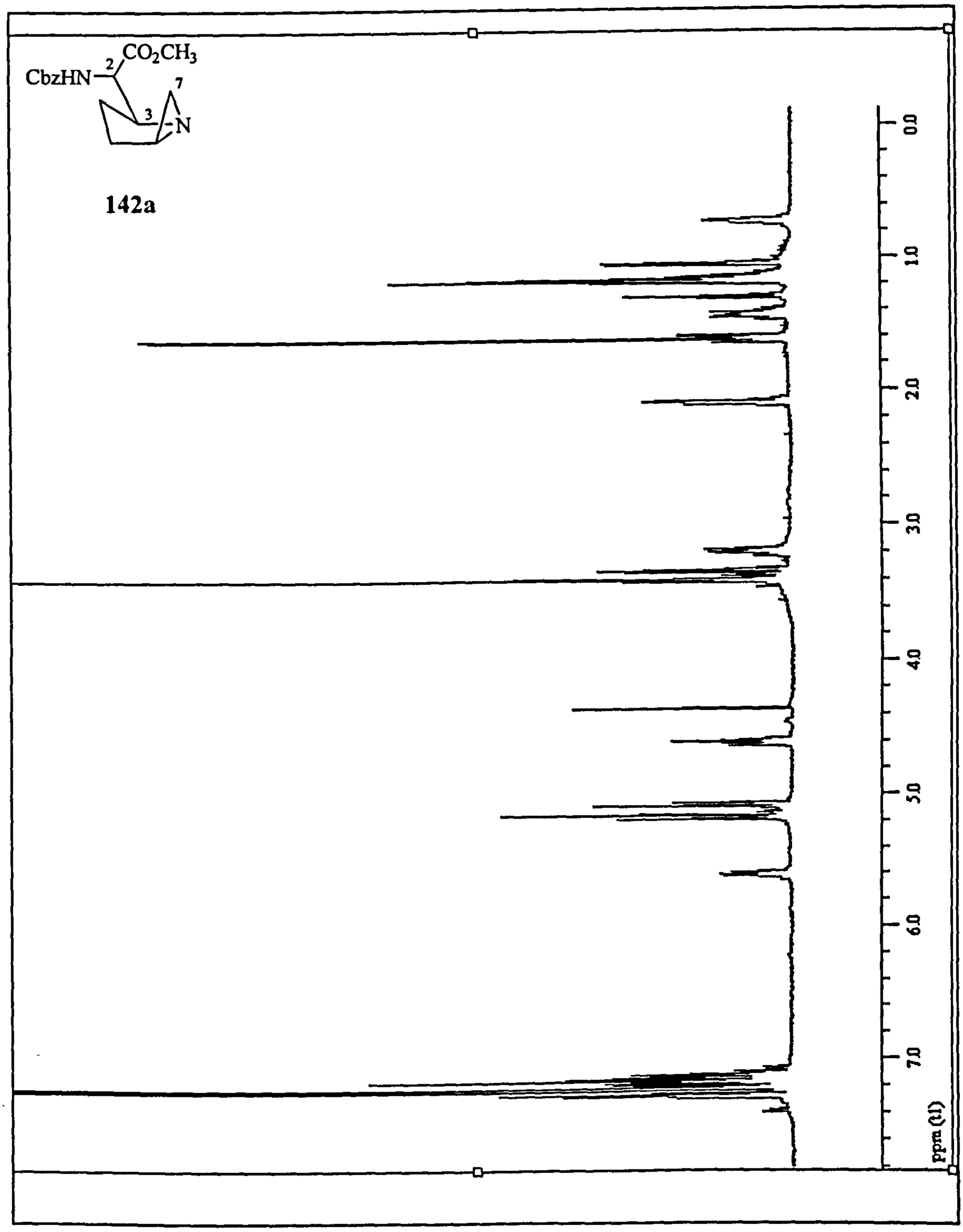
Appendix One

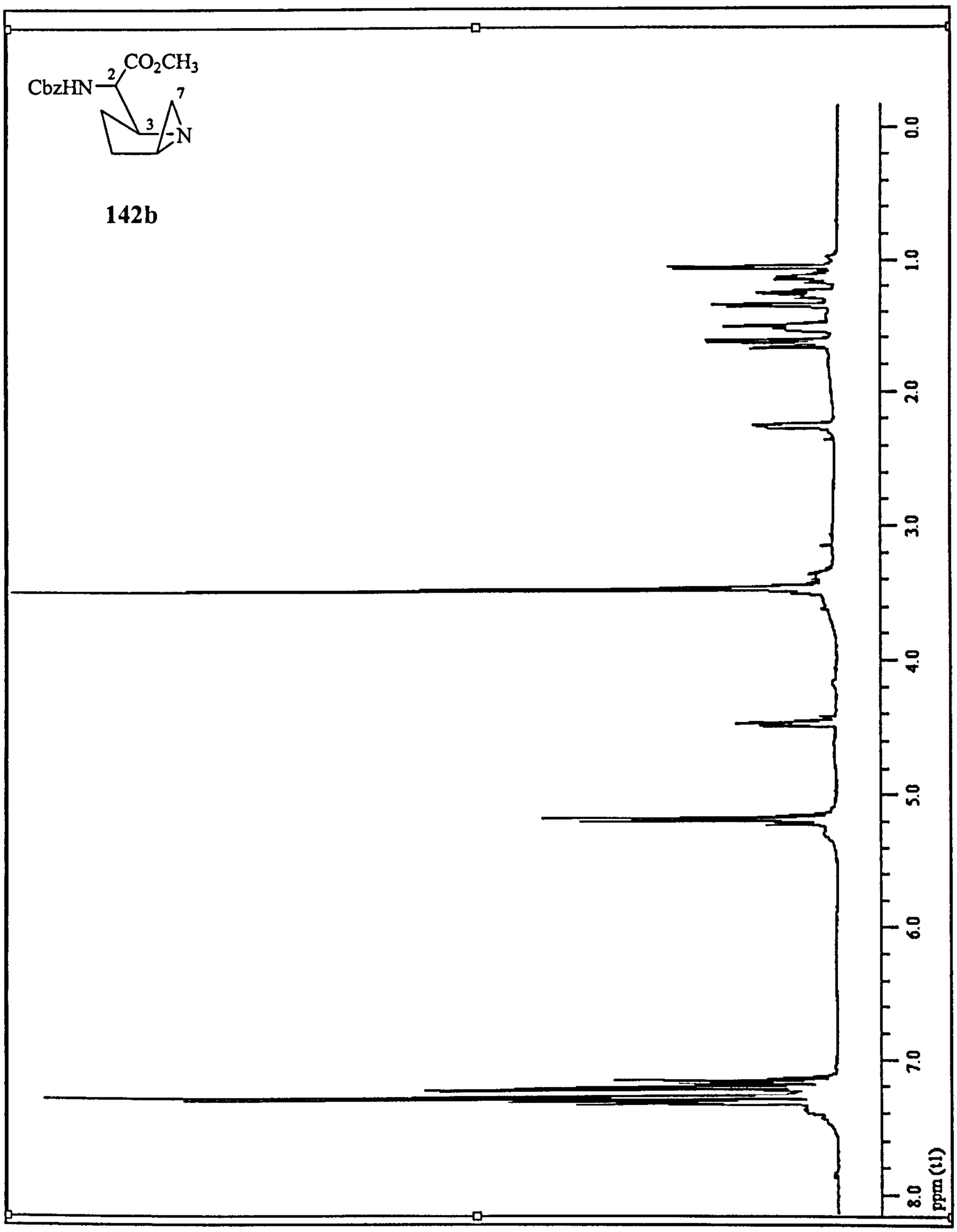
Selected NMR Spectra for 45a,b, 142a, 142b, 235 and 220



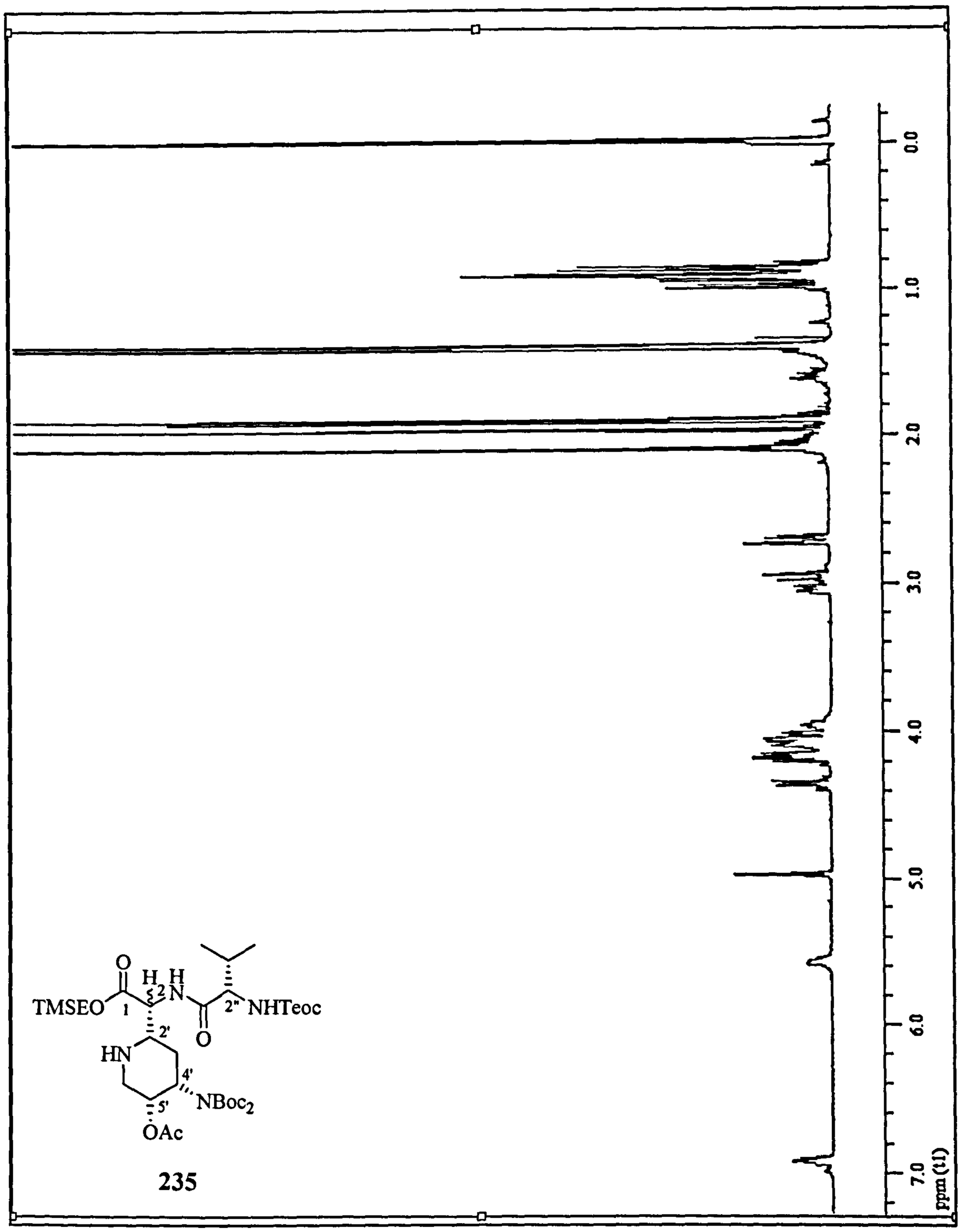
^{1}H NMR Data **95a,b**; 500 MHz, C_6D_6



^{1}H NMR Data **142a**; 500 MHz, C_6D_6

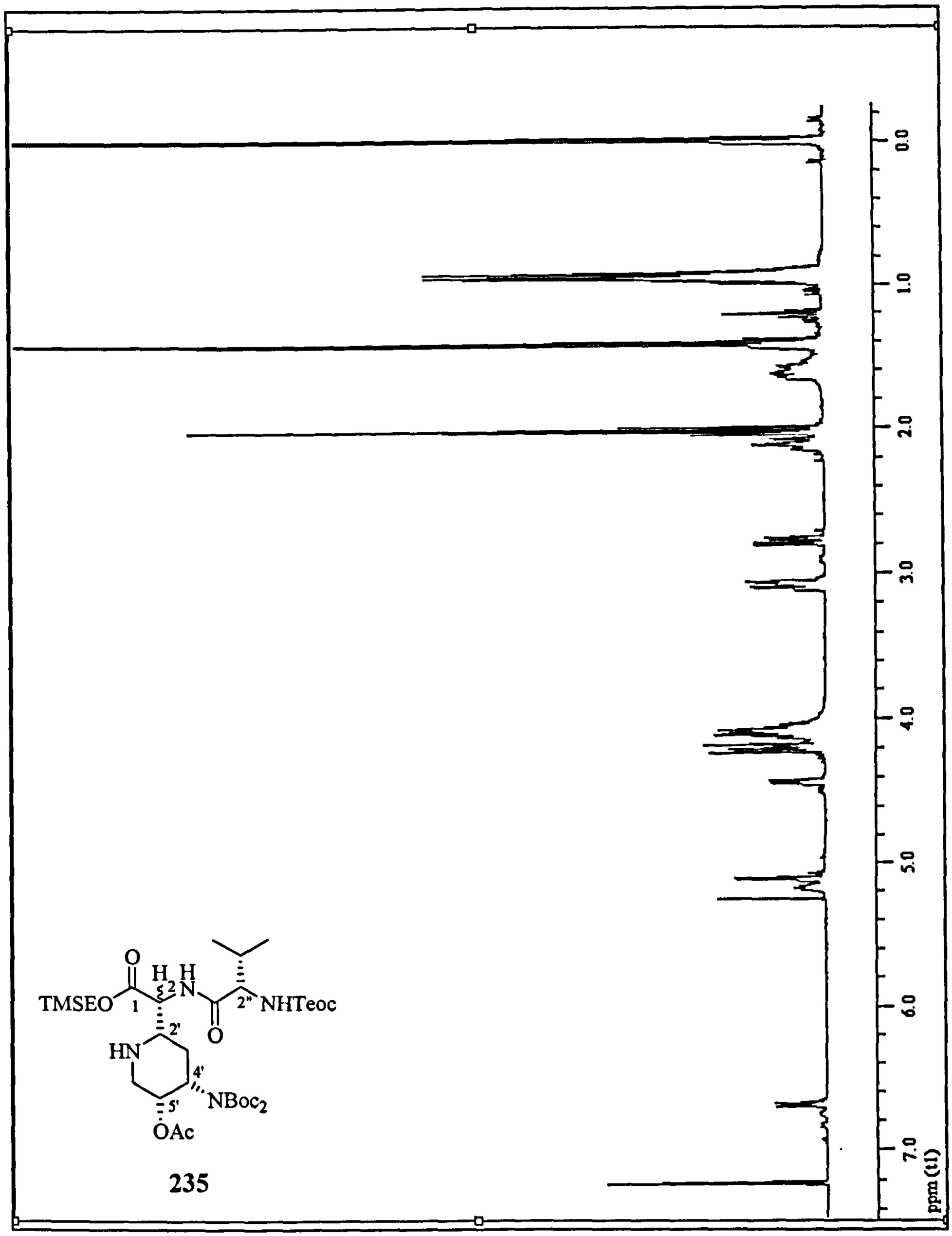


^{1}H NMR Data **142b**; 500 MHz, C_6D_6



235

^{1}H NMR Data **235**; 500 MHz, CD_3CN



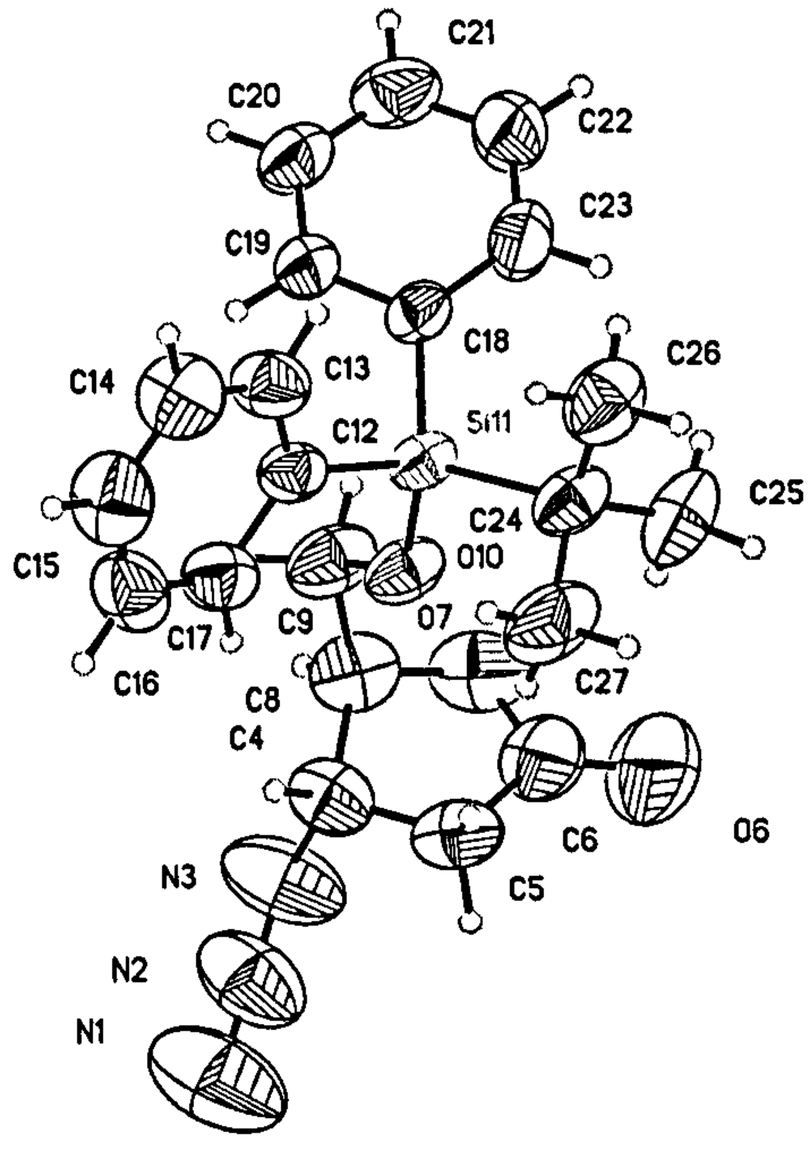
235

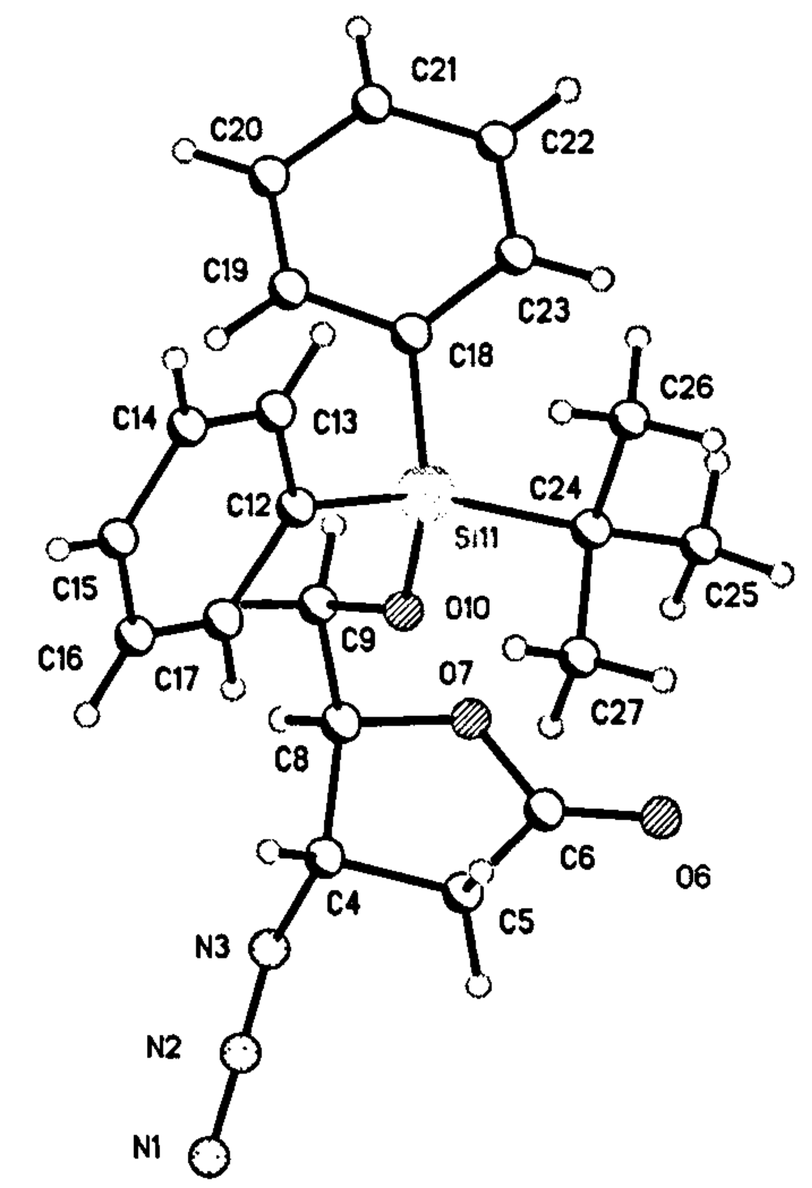
^{1}H NMR Data **220**; 500 MHz, $CHCl_3$

Appendix Two

X-Ray Crystallographic Data for

173





X-ray crystal structure of **173**

Table 1. Crystal data and structure refinement for **173.**

Identification code	**173**	
Empirical formula	C_{21} H_{25} N_3 O_3 Si	
Formula weight	395.53	
Temperature	293(2)K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 9.8190(3) Å	α = 90.00 (2)°.
	b = 10.2558(3) Å	β = 90.00 (2)°.
	c = 21.7107(7) Å	γ = 90.00 (2)°.
Volume, Z	2029.6 (3) $Å^3$, 2	
Density (calculated)	1.202 Mg/m^3	
Absorption coefficient	1.154 mm^{-1}	
F(000)	840	
Crystal size	0.20 x 0.10 x 0.02 mm^3	
Theta range for data collection	1.74 to 70.56°.	
Index ranges	-10/ 11, -12/ 12, -24/ 26.	
Reflections collected	14036	
Independent reflections	4020 [R_{int} = 0.0696]	
Completeness to theta = 23.26°	99.3 %	
Absorption correction	Semi-empirical from equivalents	

Max. and min. transmission	0.7966 to 0.9773.
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4020/ 12/ 257
Goodness-of-fit on F^2	1.042
Final R indices [I>2sigma(I)]	R1 = 0.0448, wR2 = 0.1121
Extinction coefficient	0.0039(4)
Absolute structure parameter	x = -0.05(3).
Largest diff. peak and hole	0.219 and -0.139 e.$Å^{-3}$
Detector	Siemens SMART (Siemens, 1994) three-circle system with CCD area detector

H-atoms were given isotropic displacement parameters equal to 1.2 (or 1.5 for methyl hydrogen atoms) times the equivalent isotropic displacement parameter of the atom to which the H-atom is attached.

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **173.** U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	X	Y	Z	U (eq)
N(1)	4416(5)	-2552(6)	11861(2)	174(2)
N(2)	3905(4)	-1796(5)	11559.2(17)	120(1)
N(3)	3298(4)	-985(4)	11299.7(16)	125(1)
C(4)	3615(3)	-792(3)	10639.8(13)	72(1)
C(5)	3034(3)	-1862(3)	10250.4(17)	79(1)
C(6)	1689(4)	-1360(4)	10048.2(19)	91(1)
O(6)	811(3)	-1952(3)	9791.9(18)	151(1)
O(7)	1571(2)	-103(3)	10184.7(12)	89(1)
C(8)	2803(4)	384(3)	10431.2(14)	74(1)
C(9)	3500(4)	1219(3)	9956.8(14)	79(1)
O(10)	3815(2)	439.0(16)	9439.7(8)	62(1)
Si(11)	4382.3(7)	998.4(6)	8773.5(3)	51(1)
C(12)	6268(3)	1188(2)	8834.6(12)	54(1)
C(13)	7022(3)	1830(3)	8392.6(14)	70(1)
C(14)	8430(4)	1879(4)	8407.6(18)	87(1)
C(15)	9117(3)	1265(4)	8870.9(19)	88(1
C(16)	8416(4)	625(3)	9317.8(17)	79(1)
C(17)	7006(3)	588(3)	9301.8(14)	67(1)
C(18)	3602(3)	2634(2)	8626.2(12)	52(1)
C(19)	4089(3)	3701(2)	8942.9(13)	61(1)
C(20)	3520(3)	4925(3)	8890.8(15)	73(1)
C(21)	2441(4)	5121(3)	8517.0(17)	81(1)
C(22)	1933(4)	4098(4)	8180.9(18)	92(1)
C(23)	2498(3)	2879(3)	8239.1(15)	77(1)
C(24)	3973(3)	-324(3)	8201.3(13)	66(1)
C(25)	2462(4)	-706(4)	8217.5(17)	93(1)
C(26)	4368(4)	123(3)	7547.5(13)	85(1)
C(27)	4814(4)	-1530(3)	8372.2(19)	96(1)

Table 3. Bond lengths [A] and angles [deg] for **173.**

N(1)-N(2)	1.132(5)	N(2)-N(3)	1.168(5)
N(3)-C(4)	1.479(4)	C(4)-C(5)	1.498(5)
C(4)-C(8)	1.514(4)	C(4)-H(4A)	0.9800
C(5)-C(6)	1.483(5)	C(5)-H(5A)	0.9700
C(5)-H(5B)	0.9700	C(6)-O(6)	1.193(4)
C(6)-O(7)	1.328(5)	O(7)-C(8)	1.414(4)
C(8)-C(9)	1.504(4)	C(8)-H(8A)	0.9800
C(9)-O(10)	1.413(3)	C(9)-H(9A)	0.9700
C(9)-H(9B)	0.9700	O(10)-Si(11)	1.6527(19)
Si(11)-C(12)	1.866(3)	Si(11)-C(18)	1.871(3)
Si(11)-C(24)	1.883(3)	C(12)-C(13)	1.380(4)
C(12)-C(17)	1.390(4)	C(13)-C(14)	1.384(5)
C(13)-H(13A)	0.9300	C(14)-C(15)	1.365(5)
C(14)-H(14A)	0.9300	C(15)-C(16)	1.359(5)
C(15)-H(15A)	0.9300	C(16)-C(17)	1.385(5)
C(16)-H(16A)	0.9300	C(17)-H(17A)	0.9300
C(18)-C(19)	1.379(4)	C(18)-C(23)	1.394(4)
C(19)-C(20)	1.379(4)	C(19)-H(19A)	0.9300
C(20)-C(21)	1.350(5)	C(20)-H(20A)	0.9300
C(21)-C(22)	1.372(5)	C(21)-H(21A)	0.9300
C(22)-C(23)	1.374(5)	C(22)-H(22A)	0.9300
C(23)-H(23A)	0.9300	C(24)-C(27)	1.533(4)
C(24)-C(25)	1.535(4)	C(24)-C(26)	1.541(4)
C(25)-H(25A)	0.9600	C(25)-H(25B)	0.9600
C(25)-H(25C)	0.9600	C(26)-H(26A)	0.9600
C(26)-H(26B)	0.9600	C(26)-H(26C)	0.9600
C(27)-H(27A)	0.9600	C(27)-H(27B)	0.9600
C(27)-H(27C)	0.9600	N(1)-N(2)-N(3)	173.1(5)
N(2)-N(3)-C(4)	117.1(4)	N(3)-C(4)-C(5)	111.6(3)
N(3)-C(4)-C(8)	106.6(3)	C(5)-C(4)-C(8)	102.4(3)
N(3)-C(4)-H(4A)	111.9	C(5)-C(4)-H(4A)	111.9
C(8)-C(4)-H(4A)	111.9	C(6)-C(5)-C(4)	104.6(3)
C(6)-C(5)-H(5A)	110.8	C(4)-C(5)-H(5A)	110.8
C(6)-C(5)-H(5B)	110.8	C(4)-C(5)-H(5B)	110.8
H(5A)-C(5)-H(5B)	108.9	O(6)-C(6)-O(7)	122.4(4)
O(6)-C(6)-C(5)	127.2(4)	O(7)-C(6)-C(5)	110.4(3)
C(6)-O(7)-C(8)	110.6(3)	O(7)-C(8)-C(9)	109.3(3)
O(7)-C(8)-C(4)	106.4(3)	C(9)-C(8)-C(4)	114.8(3)
O(7)-C(8)-H(8A)	108.7	C(9)-C(8)-H(8A)	108.7
C(4)-C(8)-H(8A)	108.7	O(10)-C(9)-C(8)	108.8(2)
O(10)-C(9)-H(9A)	109.9	C(8)-C(9)-H(9A)	109.9
O(10)-C(9)-H(9B)	109.9	C(8)-C(9)-H(9B)	109.9

H(9A)-C(9)-H(9B)	108.3	C(9)-O(10)-Si(11)	124.95(16)
O(10)-Si(11)-C(12)	107.95(11)	O(10)-Si(11)-C(18)	108.82(11)
C(12)-Si(11)-C(18)	108.97(11)	O(10)-Si(11)-C(24)	104.80(11)
C(12)-Si(11)-C(24)	109.50(12)	C(18)-Si(11)-C(24)	116.46(13)
C(13)-C(12)-C(17)	116.0(3)	C(13)-C(12)-Si(11)	122.2(2)
C(17)-C(12)-Si(11)	121.6(2)	C(12)-C(13)-C(14)	122.5(3)
C(12)-C(13)-H(13A)	118.8	C(14)-C(13)-H(13A)	118.8
C(15)-C(14)-C(13)	119.6(3)	C(15)-C(14)-H(14A)	120.2
C(13)-C(14)-H(14A)	120.2	C(16)-C(15)-C(14)	119.9(3)
C(16)-C(15)-H(15A)	120.0	C(14)-C(15)-H(15A)	120.0
C(15)-C(16)-C(17)	120.1(3)	C(15)-C(16)-H(16A)	119.9
C(17)-C(16)-H(16A)	119.9	C(16)-C(17)-C(12)	121.8(3)
C(16)-C(17)-H(17A)	119.1	C(12)-C(17)-H(17A)	119.1
C(19)-C(18)-C(23)	115.3(2)	C(19)-C(18)-Si(11)	119.0(2)
C(23)-C(18)-Si(11)	125.7(2)	C(18)-C(19)-C(20)	122.8(3)
C(18)-C(19)-H(19A)	118.6	C(20)-C(19)-H(19A)	118.6
C(21)-C(20)-C(19)	120.2(3)	C(21)-C(20)-H(20A)	119.9
C(19)-C(20)-H(20A)	119.9	C(20)-C(21)-C(22)	119.4(3)
C(20)-C(21)-H(21A)	120.3	C(22)-C(21)-H(21A)	120.0(3)
C(21)-C(22)-C(23)	120.0(3)	C(21)-C(22)-H(22A)	120.0
C(23)-C(22)-H(22A)	120.0	C(22)-C(23)-C(18)	122.3(3)
C(22)-C(23)-H(23A)	118.9	C(18)-C(23)-H(23A)	118.9
C(27)-C(24)-C(25)	108.0(3)	C(27)-C(24)-C(26)	109.1(3)
C(25)-C(24)-C(26)	109.9(3)	C(27)-C(24)-Si(11)	107.9(2)
C(25)-C(24)-Si(11)	112.0(2)	C(26)-C(24)-Si(11)	109.86(19)
C(24)-C(25)-H(25A)	109.5	C(24)-C(25)-H(25B)	109.5
H(25A)-C(25)-H(25B)	109.5	C(24)-C(25)-H(25C)	109.5
H(25A)-C(25)-H(25C)	109.5	H(25B)-C(25)-H(25C)	109.5
C(24)-C(26)-H(26A)	109.5	C(24)-C(26)-H(26B)	109.5
H(26A)-C(26)-H(26B)	109.5	C(24)-C(26)-H(26C)	109.5
H(26A)-C(26)-H(26C)	109.5	H(26B)-C(26)-H(26C)	109.5
C(24)-C(27)-H(27A)	109.5	C(24)-C(27)-H(27B)	109.5
H(27A)-C(27)-H(27B)	109.5	C(24)-C(27)-H(27C)	109.5
H(27A)-C(27)-H(27C)	109.5	H(27B)-C(27)-H(27C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for **173.**
The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
N(1)	155(3)	241(5)	126(3)	79(3)	17(3)	39(4)
N(2)	103(3)	182(4)	75(2)	47(3)	10(2)	6(3)
N(3)	137(3)	163(4)	74(2)	40(2)	28(2)	46(3)
C(4)	68(2)	92(2)	58(2)	12(2)	15(1)	7(2)
C(5)	72(2)	66(2)	100(3)	22(2)	12(2)	8(2)
C(6)	54(2)	102(3)	118(3)	26(2)	4(2)	-23(2)
O(6)	91(2)	149(3)	212(3)	24(3)	-28(2)	-49(2)
O(7)	58(2)	94(2)	116(2)	24(2)	25(1)	20(1)
C(8)	86(3)	70(2)	67(2)	-6(2)	27(2)	11(2)
C(9)	116(3)	53(2)	68(2)	-6(2)	24(2)	-1(2)
O(10)	84(1)	44(1)	58(1)	-4(1)	20(1)	-3(1)
Si(11)	61(1)	39(1)	54(1)	-2(1)	8(1)	-3(1)
C(12)	66(2)	42(1)	54(2)	-2(1)	2(1)	5(1)
C(13)	65(2)	74(2)	71(2)	16(2)	4(2)	1(2)
C(14)	66(2)	105(3)	91(2)	7(2)	18(2)	-3(2)
C(15)	54(2)	98(3)	111(3)	-13(2)	3(2)	14(2)
C(16)	76(2)	74(2)	86(2)	-6(2)	-17(2)	23(2)
C(17)	79(2)	57(2)	64(2)	3(2)	3(2)	8(2)
C(18)	48(2)	45(1)	61(2)	2(1)	4(1)	-6(1)
C(19)	65(2)	45(1)	72(2)	0(1)	-13(1)	0(1)
C(20)	84(2)	45(2)	91(2)	-4(2)	-5(2)	-3(2)
C(21)	78(2)	54(2)	112(3)	8(2)	5(2)	14(2)
C(22)	75(2)	73(2)	128(3)	1(2)	-39(2)	8(2)
C(23)	70(2)	59(2)	102(2)	-10(2)	-24(2)	-6(2)
C(24)	81(2)	48(2)	68(2)	-10(1)	15(2)	-8(2)
C(25)	97(3)	82(2)	99(2)	-29(2)	15(2)	-36(2)
C(26)	111(3)	78(2)	66(2)	-19(2)	15(2)	-18(2)
C(27)	139(4)	45(2)	104(3)	-19(2)	11(2)	4(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for **173.**

	x	y	z	U(eq)
H(4A)	4593	-677	10569	87
H(5A)	3616	-2037	9899	95
H(5B)	2930	-2657	10488	95
H(8A)	2593	923	10792	89
H(9A)	2906	1929	9835	94
H(9B)	4327	1588	10128	94
H(13A)	6567	2247	8072	84
H(14A)	8906	2327	8104	104
H(15A)	10064	1285	8881	106
H(16A)	8883	211	9635	95
H(17A)	6541	151	9612	80
H(19A)	4834	3591	9203	73
H(20A)	3881	5618	9114	88
H(21A)	2045	5942	8488	98
H(22A)	1206	4230	7913	111
H(23A)	2132	2194	8012	92
H(25A)	2318	-1456	7961	139
H(25B)	1921	7	8068	139
H(25C)	2202	-907	8633	139
H(26A)	4190	-568	7260	127
H(26B)	5318	340	7538	127
H(26C)	3840	876	7437	127
H(27A)	4595	-2232	8097	144
H(27B)	4609	-1785	8787	144
H(27C)	5767	-1329	8339	144

Appendix Three

Biological Data for 95a and 95b, 142a and 142b

Table 6. Biological Screening for compounds **95a** and **95b**, **142a** and **142b**.

	Linezolid	Thiamphenicol	142a	142b	95a and 95b
Gram-positive bacteria					
Enterococcus faecium ARC521	2	4	>64	>64	>64
Staphylococcus aureus ARC516 (MSS)	2	16	>64	>64	>64
Staphylococcus aureus ARC517 (MRS)	2	64	>64	>64	>64
Streptococcus pneumoniae ARC509 (PenS)	0.50	2	>64	>64	>64
Streptococcus pneumoniae ARC548	1	2	>64	>64	>64
Streptococcus pneumoniae AR556 (ARC548LinezR)	32	16	>64	>64	>64
Gram-negative bacteria					
Bacteroides fragilis ARC454	2	2	>64	>64	>64
Haemophilus influenzae ARC446	8	1	>64	>64	>64
Haemophilus influenzae ARC713	8	1	>64	>64	>64
Haemophilus influenzae ARC737	16	1	>64	>64	>64
Haemophilus influenzae ARC158 (efflux mutant)	4	>64	>64	>64	>64
Moraxella catarrhalis ARC445	2	0.25	>64	>64	>64
Escherichia coli ARC 523	>64	>64	>64	>64	>64
Escherichia coli ARC 524 (efflux mutant)	8	32	>64	>64	>64
Yeast					
Candida albicans ARC527	>64	>64	>64	>64	>64