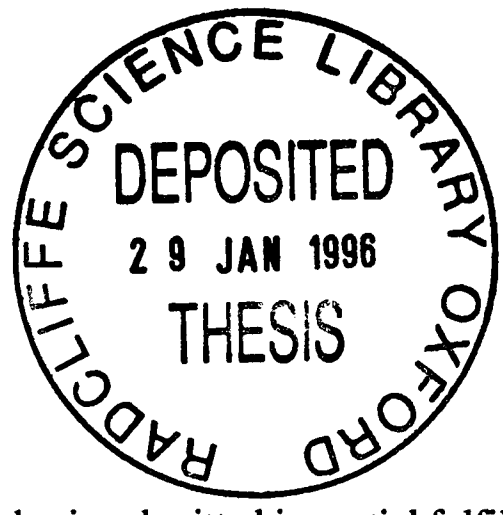
Syntheses of Polyfunctionalised Cyclopentanes

by

Andrew W.H. Hui
Linacre College, Oxford
1995



A thesis submitted in partial fulfilment

of the requirement for the degree of D. Phil.

To my parents
for their support over the years

Syntheses of Polyfunctionalised Cyclopentanes

Andrew W.H. Hui, Linacre College, Oxford

D.Phil., Trinity Term 1995

Abstract

This thesis describes the syntheses of some polyfunctionalised cyclopentanes *via* intramolecular aldol condensations of sugar δ-lactone precursors.

The known azido carbocycle (1*S*,2*R*,3*S*,4*R*,5*R*)-methyl [5-azido-1,2,3,4-tetrahydroxy-2,3-*O*-isopropylidene-cyclopentane] carboxylate was prepared from 2-deoxy-2-iodo-3,4:6,7-di-*O*-isopropylidene-**D**-*glycero*-**D**-*talo*-heptono-1,5-lactone in five steps. The key reaction was a base-induced intramolecular aldol cyclisation of a 5-iodo-formyl-2,6-lactone. Borohydride reduction of the methyl ester gave an azido triol. Deprotection followed by reduction of the azide functionality produced an amino pentol. The analogous tetrahydroxy β-amino acid was synthesised from the azido carbocycle in three steps. The inhibitory activity of the amino pentol against human liver glycosidases is reported.

Two azido bicyclic lactones, (1*R*,4*R*,5*R*,6*R*,7*R*)-4-azido-5,6,7-trihydroxy-5,6-*O*-isopropylidene-2-oxa-bicyclo[2.2.1]heptan-3-one and (1*S*,4*S*,5*R*,6*R*,7*R*)-4-azido-5,6,7-trihydroxy-5,6-*O*-isopropylidene-2-oxa-bicyclo[2.2.1]heptan-3-one, were prepared from 3,4:6,7-di-*O*-isopropylidene-**D**-*glycero*-**D**-*talo*-heptono-1,5-lactone in five steps. The (1*R*,4*R*,5*R*,6*R*,7*R*)-compound was further elaborated to give an amino pentol *via* a series of borohydride reduction / deprotection / catalytic hydrogenation. A novel carbocyclic spirohydantoin was synthesised by two alternative routes. The second route also provided access to an *N'*-phenyl spirohydantoin. The inhibitory activities of the amino pentol and the spirohydantoin against human liver glycosidases are reported.

The azido bicyclic lactone triol (1*R*,4*S*,5*R*,6*R*,7*R*)-4-azido-5,6,7-trihydroxy-2-oxa-bicyclo[2.2.1]heptan-3-one underwent reduction of the azide functionality with concomitant epimerisation to give the (5*S*)-epimeric amine. The structure of this material was confirmed by X-ray diffraction analysis of a crystalline derivative. Treatment of the azido triol with base under non-aqueous conditions resulted in a retro-aldol reaction to give the (5*S*)-epimeric azide, the relative configuration of which was determined by single crystal X-ray analysis. A third ketal protected azido bicyclic lactone was prepared *via* a base-induced retro-aldol epimerisation. Five tetrahydroxy-cyclopentane α-amino acids, including a pair of enantiomers, were synthesised from the azido bicyclic lactones. The structures of two of the α-amino acids were established by X-ray crystallographic analysis, whilst the enantiomeric compounds were identified using circular dichroism spectrometry.

The diketal protected (2*R*,3*R*,4*R*,5*R*)-tetrahydroxy-cyclopentane α-amino acid was incorporated into six oligopeptides. Peptide coupling at the *C*-terminus of the carbocyclic amino acid was carried out using two amino acid *tert*-butyl esters. Chain extension at the *N*-terminus was achieved by reaction with *N*-benzyloxycarbonyl protected amino acids in the presence of 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride as the carbodiimide reagent. Complete deprotection of a tetrapeptide is described.

ACKNOWLEDGEMENTS

Firstly I would like to thank my supervisor, Dr. George Fleet, for his support and understanding, and from whom I have learned much over the past four years. Many thanks are also due to my industrial supervisor, Dr. Dick Storer, for his joint supervision of the project and for an enjoyable three months at Greenford.

I am indebted to Dr. Rob Nash for his invaluable expertise on matters regarding ion exchange chromatography, and for making me feel welcome in Aberystwyth.

I would very much like to thank all the technical staff at the Dyson Perrins Laboratory, especially Elizabeth and Val. None of this work would have been possible without their enthusiasm and dedication far beyond the call of duty.

Many thanks to my diligent team of proof-readers, who are forever critical of style and grammar: Helen, Jeremy, John, Gordon, Angela, Tilmann and Rachel. Any mistakes remaining are due to me, not them.

The Perkin Lab (and Little P) has been a stimulating and fun place to work in, and I have enjoyed my time there immensely. Thanks to Annabel, for being supportive through good times and bad; and to Helen, for being a good companion. Thanks are also due to Eleri, for Welsh treats and trips, and for being there to talk to; thanks to Joe, for the supply of endless obscure foreign film videos; thanks to Fez, for lending a hand in desperate times; thanks to Ken, for proving that Orientals can hold their beers; thanks to Simon, for having an opinion on everything; thanks to Dave, for being more interested in darts than in chemistry; thanks to Neil, for all matters electrical and electronic; thanks to Ben S, for being a father figure; thanks to Tilmann and Thomas, for their Germanic attitude to chemistry; and to Yves for the use of his stapler. Thanks also to Jeremy, for introduction to the ENO and the ROH; and to Tig, Russell, Philippa, Ben D, John, Andy, Katy, Martin, Dan, Jaya, Dave, Alan, Jon, Des, Jong, Yong, Carlos and Yolanda, without whom the Perkin experience would not have been complete.

CONTENTS

List of Abbreviations i

Note concerning nomenclature iv

CHAPTER 1 Introduction 1

(i) Biological Activities 1

(ii) Potential Applications 4

(iii) Previous Synthetic Approaches 5

(a) Previous syntheses from non-carbohydrate starting materials 6

(b) Previous syntheses from carbohydrate starting materials 12

(c) A novel intramolecular aldol cyclisation from sugar lactones 17

References 25

CHAPTER 2 Syntheses of Polyfunctionalised Cyclopentanes 30

Sugar Lactones as Chirons 30

General Retrosynthetic Analysis 30

Previous Syntheses of α-Iodo and α-Azido Heptonolactones 32

Results and Discussion :- 34

2.1 Preparation of the α-iodo aldehyde (**1.47**) and subsequent syntheses of polyfunctionalised cyclopentanes 35

2.2 Preparation of the α-azido aldehyde (**1.51**) and subsequent syntheses of polyfunctionalised cyclopentanes 40

2.3 Syntheses of tetrahydroxy-cyclopentane α-amino acids 47

2.4 Incorporation of a tetrahydroxy-cyclopentane α-amino acid into peptides 69

References 79

CHAPTER 3	**Experimental Procedures**	82
	General Experimental Procedures	82
	Experimental Procedures :-	
	Results and Discussion Section 2.1	83
	Results and Discussion Section 2.2	94
	Results and Discussion Section 2.3	112
	Results and Discussion Section 2.4	131
	References	151
Appendix 1		i
Appendix 2		i
Appendix 3		i
Appendix 4		i

ABBREVIATIONS

The following abbreviations are used in this thesis:-

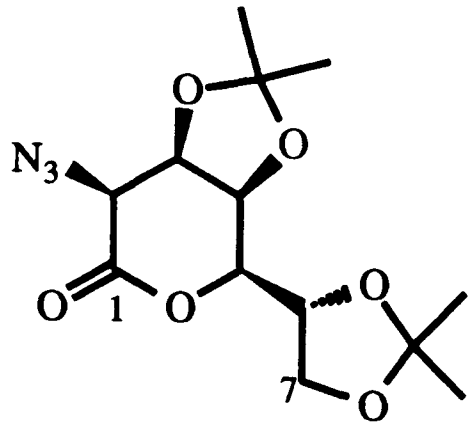
Ac	acetyl
AdoHcy	*S*-adenosylhomocysteine
AdoMet	*S*-adenosylmethionine
AMP	adenosine monophosphate
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br	broad
^{n}Bu	normal butyl
^{t}Bu	*tert*-butyl
CMAW	chloroform : methanol : acetic acid : water
18-crown-6	1,4,7,10,13,16-hexaoxacyclooctadecane
CSA	(±)-10-camphorsulphonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCCI	*N,N'*-dicyclohexylcarbodiimide
d	doublet
dd	double doublet
ddd	double double doublet
DIBAH	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DMAP	4-(*N,N*-dimethylamino)-pyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulphoxide
EDCI	1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride
equiv	equivalent
Et	ethyl

Fmoc	9-fluorenylmethoxycarbonyl
Gly	glycyl
h	hour
HOBT	1-hydroxybenzotriazole
IC_{50}	50% inhibition concentration
iPr	isopropyl
IR	infrared
Lit.	literature value
m	multiplet
*m*CPBA	3-chloroperoxybenzoic acid
Me	methyl
Men	menthyl
min	minute
m.p.	melting point
Ms	methylsulphonyl
NMM	4-methylmorpholine
NMO	4-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
PCC	pyridinium chlorochromate
Pfp	pentafluorophenyl
Ph	phenyl
Phe	phenylalanyl
Phth	phthalimide
PPTS	pyridinium *para*-toluenesulphonate
Py	pyridine
quant	quantitative
RT	room temperature
s	singlet
t	triplet

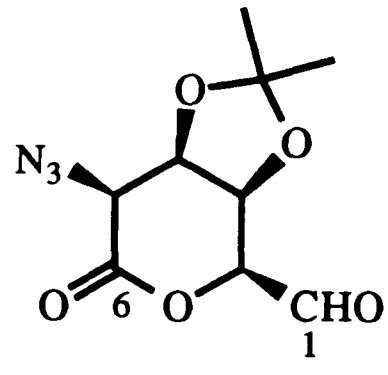
TBTU	*O*-(1H-benzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium tetrafluoroborate
TFA	trifluoroacetic acid
Tf	trifluoromethanesulphonyl
THF	tetrahydropyran
t.l.c.	thin layer chromatography
triflate	trifluoromethanesulphonate
*p*TSA	*para*-toluenesulphonic acid
Ts	*para*-toluenesulphonyl
Z	benzyloxycarbonyl

NOTE CONCERNING NOMENCLATURE

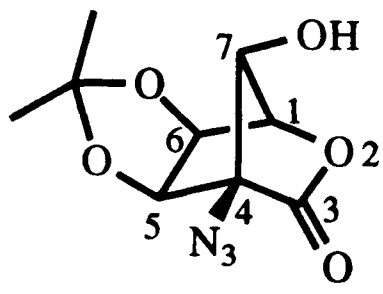
The compounds in this thesis are numbered according to the systems shown for the examples below.



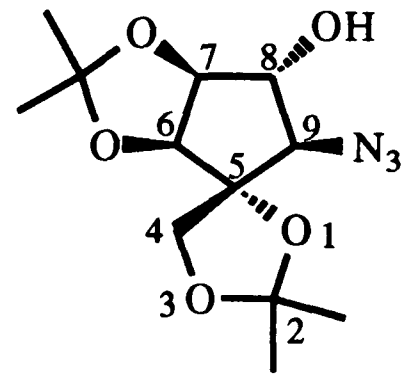
2-Azido-2-deoxy-3,4:6,7-di-*O*-isopropylidene-**D**-*glycero*-**D**-*talo*-heptono-1,5-lactone



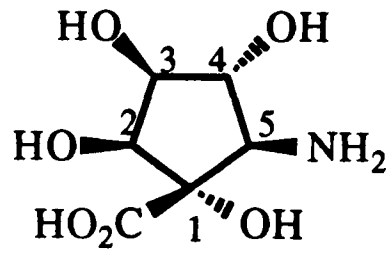
5-Azido-5-deoxy-3,4-*O*-isopropylidene-**D**-*altrurono*-2,6-lactone



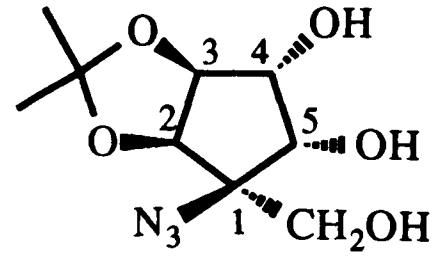
(1*R*,4*R*,5*R*,6*R*,7*R*)-4-Azido-5,6,7-trihydroxy-5,6-*O*-isopropylidene-2-oxa-bicyclo [2.2.1]heptan-3-one



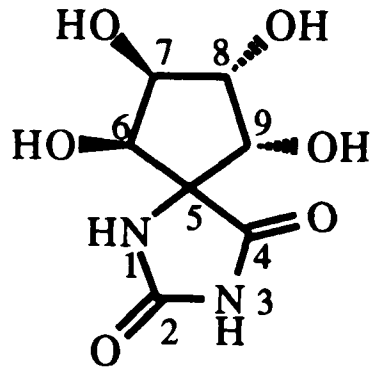
(5*R*,6*S*,7*S*,8*R*,9*R*)-9-Azido-6,7,8-trihydroxy-6,7-*O*-isopropylidene-2,2-dimethyl-1,3-dioxa-spiro[4.4]nonane



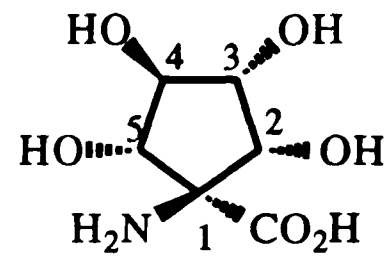
(1*S*,2*S*,3*S*,4*R*,5*R*)-5-Amino-1,2,3,4-tetrahydroxy-cyclopentane carboxylic acid



(1*R*,2*R*,3*S*,4*R*,5*R*)-1-Azido-2,3,4,5-tetrahydroxy-1-(hydroxymethyl)-2,3-*O*-isopropylidene-cyclopentane



(6*R*,7*R*,8*R*,9*R*)-1,3-Diaza-6,7,8,9-tetrahydroxy-spiro [4.4]nonan-2,4-dione



(1*S*,2*R*,3*R*,4*R*,5*S*)-1-Amino-2,3,4,5-tetrahydroxy-cyclopentane carboxylic acid

CHAPTER 1

Introduction

During recent years, a number of naturally occurring polyfunctionalised cyclopentanes have been isolated. Reported examples include aristeromycin (**1.1**), allosamidin (**1.2**), trehazolin / trehalostatin (**1.3**), and the mannostatins A (**1.4**) and B (**1.5**). These materials possess a wide range of interesting biological properties. Therefore there is considerable interest in the studies towards their total synthesis and biosynthesis, as well as in the development of novel synthetic cyclopentanes. A noteworthy example of the latter category is the Merrell Dow cyclopentylamine (**1.6**). These compounds will now be discussed in turn, with reference to:

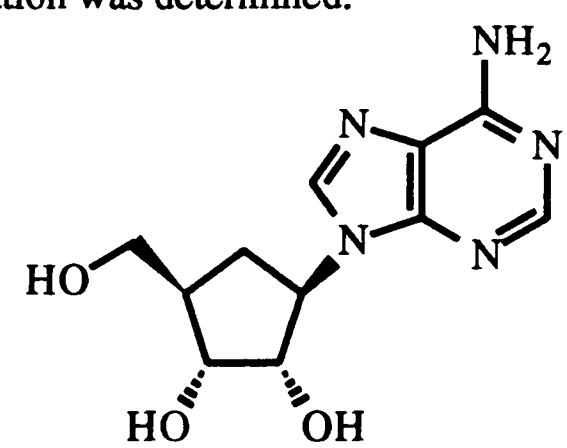
(i) Biological activities;

(ii) Potential applications;

(iii) Previous synthetic approaches.

(i) Biological Activities.

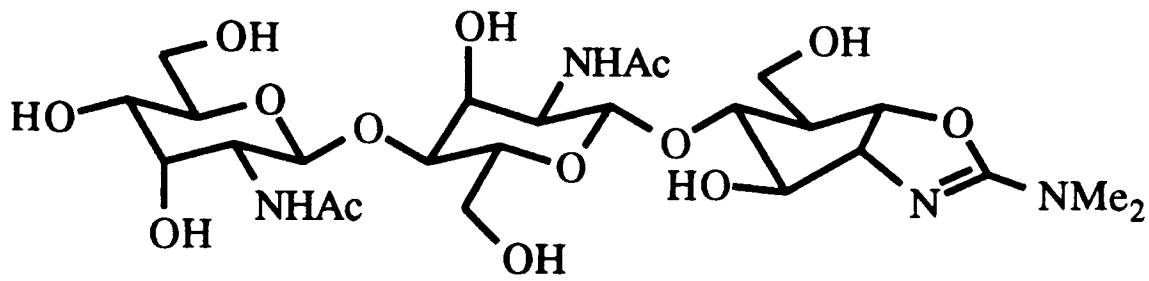
The carbocyclic analogue of adenosine was first synthesised in racemic form in 1966.[1] Shortly thereafter the (-) enantiomer, named aristeromycin (**1.1**), was isolated from the fermentation broth of *Streptomyces citricolor*, its structure was elucidated, and its absolute configuration was determined.[2]



Aristeromycin (**1.1**)

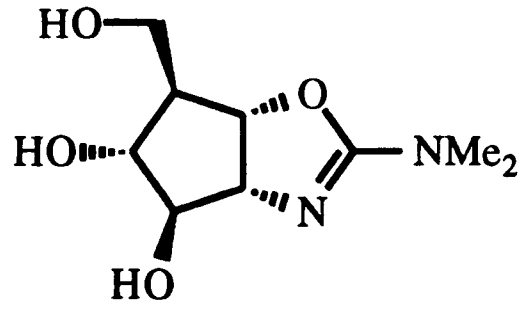
Aristeromycin (**1.1**) exhibits a variety of biological activities.[3,4] These include the inhibition of AMP synthesis in mammalian cells, the inhibition of cell division and elongation in rice plants, and the inhibition of the enzyme *S*-adenosylhomocysteine hydrolase.[5]

Chitin is the major structural component in both fungal cell walls and insect exoskeletons. Such importance has generated much interest in the search for chemical agents capable of interfering with its biosynthesis. This has resulted in the isolation of the chitotriose analogue allosamidin (**1.2**) from the mycelia of *Streptomyces* sp. 1713[6] and from the fermentation broth of sp. A82516.[7]



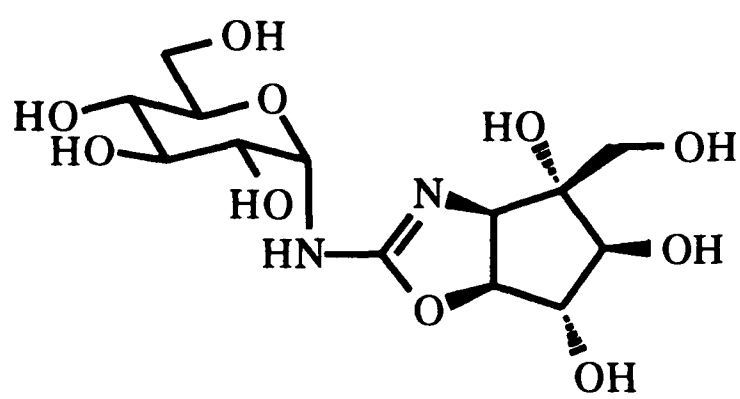
Allosamidin (**1.2**)

Allosamidin (**1.2**) was found to exhibit strong inhibition of chitinases of both insect and fungal origin, and prevented insect larval ecdysis *in vivo*.[6,8,9] The pseudotrisaccharide structure of this molecule is composed of two β-1,4-linked *N*-acetyl-**D**-allosamine residues connected to a novel cyclopentanoxazoline core, allosamizoline (**1.7**).[8,10]

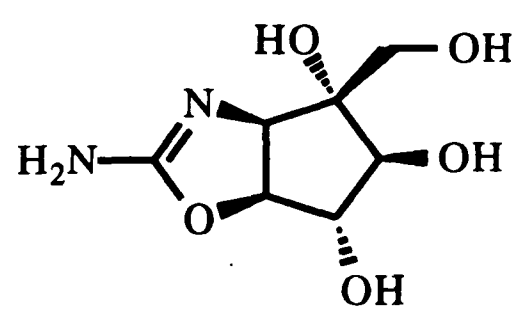


Allosamizoline (**1.7**)

Trehazolin / trehalostatin were isolated independently by two research groups from the culture broths of *Amycolatopsis* sp. SANK 60791[11] and *Micromonospora* sp. SANK 62390[12] respectively. Initially these were assigned different stereochemistry, but they have recently been shown to possess the same structure (**1.3**). The absolute configuration of trehazolin / trehalostatin was firmly established by total synthesis and chemical correlation with **L**-aspartic acid.[13,14] The structure consists of a glucosyl moiety attached to a polyhydroxylated aminocyclopentane aglycon residue, trehalamine (**1.8**).[15]



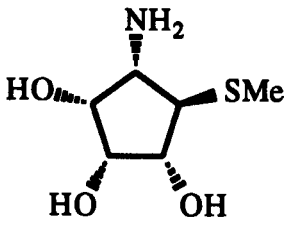
Trehazolin / trehalostatin (**1.3**)



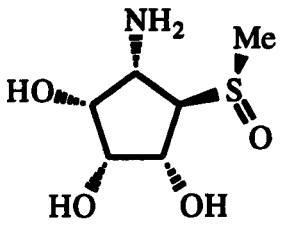
Trehalamine (**1.8**)

While trehazolin / trehalostatin (**1.3**) is a potent and specific inhibitor of blowfly, silkworm and porcine trehalases,[11,12] trehalamine (**1.8**) is a poor trehalase inhibitor with greater inhibitory activity against rat intestinal sucrase and sweet almond β-glucosidase.[15]

There is a growing realisation of the functional importance of glycoconjugates present on the surface of mammalian cells. This has led to the search for inhibitors that act at various steps in the biosynthetic pathway. In the course of screening for an inhibitor of α-mannosidase, mannostatins A (**1.4**) and B (**1.5**) were isolated from the culture broth of *Streptoverticillium verticillus* var. *quintum* ME3-AG3.[16]



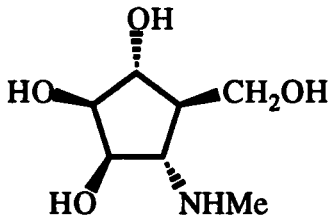
Mannostatin A (**1.4**)



Mannostatin B (**1.5**)

The structural assignments of these compounds were first established by NMR spectroscopy and mass spectrometry,[16] and their absolute configurations were later confirmed by X-ray crystallographic analysis of mannostatin B tetraacetate.[17] Among its broad spectrum of biological activities, mannostatin A (**1.4**) competitively inhibits jack bean, mung bean, and rat liver lysosomal α-mannosidases.[18] It is also a potent inhibitor of Golgi processing mannosidase II. To date, the mannostatins represent the only known carbocyclic, naturally occurring mannosidase inhibitors.

Another example of a carbocyclic mannosidase inhibitor is the Merrell Dow cyclopentylamine (**1.6**).[19] It was first synthesised as a result of molecular modelling studies and was subsequently found to be a potent inhibitor of jack bean α-mannosidase.



Merrell Dow cyclopentane (**1.6**)

(ii) Potential Applications.

Interest in nucleoside analogues[5,20] and mannosidase inhibitors[21] have been focused on their potential applications as antiviral agents.

The inhibition of virus multiplication by nucleoside analogues coincides with a rapid inhibition of *S*-adenosylhomocysteine (AdoHcy) hydrolase activity in the infected cells. This leads to an increase in the intracellular AdoHcy / *S*-adenosylmethionine (AdoMet) ratio. These findings indicate that the antiviral actions of these compounds may be related to an inhibition of AdoMet-dependent methylation reactions which are essential to the production of new virus particles (*e.g.* viral messager RNA).[22]

In virus infected cell cultures, mannosidase inhibitors are found to block the normal formation of complex oligosaccharides on the viral glycoproteins and to cause the accumulation of hybrid types of oligosaccharides.[18] Incomplete glycoprotein processing results in loss of cellular recognition of the target cells, with consequential reduction in virus infectivity and inhibition of viral replication.[21]

Inhibitors of chitinases are of potential importance in insect growth regulation[23] and as antifungal agents,[24] while trehalase inhibitors are lead compounds towards effective insecticides or insect antifeedants.[25]

(iii) Previous Synthetic Approaches.

Approaches to the synthesis of polyfunctionalised cycopentanes may be divided into three broad categories:

(a) Previous syntheses from non-carbohydrate starting materials;

(b) Previous syntheses from carbohydrate starting materials;

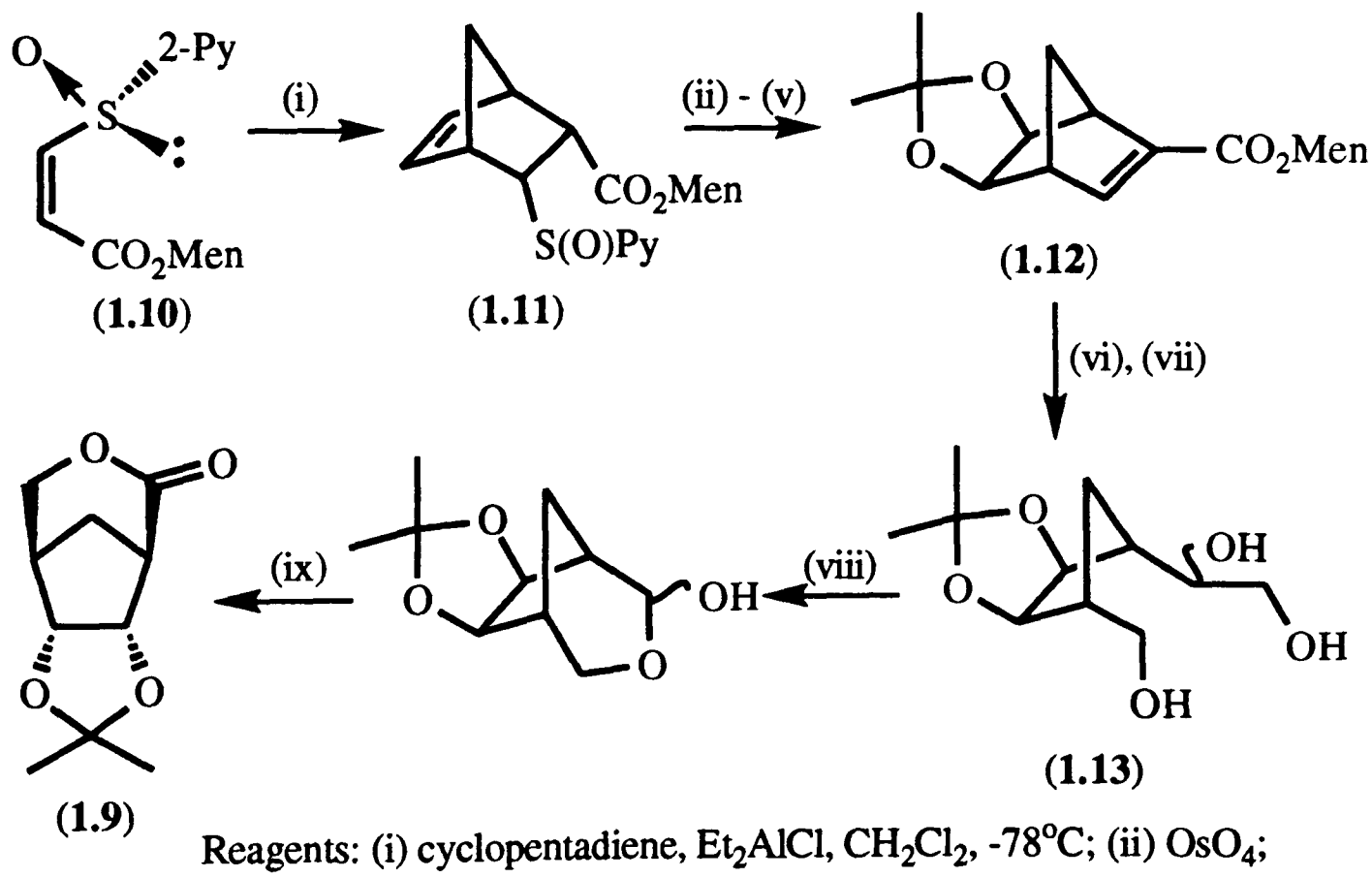
(c) A novel intramolecular aldol cyclisation from sugar lactones.

Each of these approaches will now be discussed in turn.

(a) Previous Syntheses From Non-Carbohydrate Starting Materials.

The density of chiral functionality in the polyfunctionalised cyclopentanes described hitherto represents a considerable challenge for the organic chemist. Syntheses from non-carbohydrate starting materials require the regio- and stereoselective introduction of up to five adjacent functional groups.

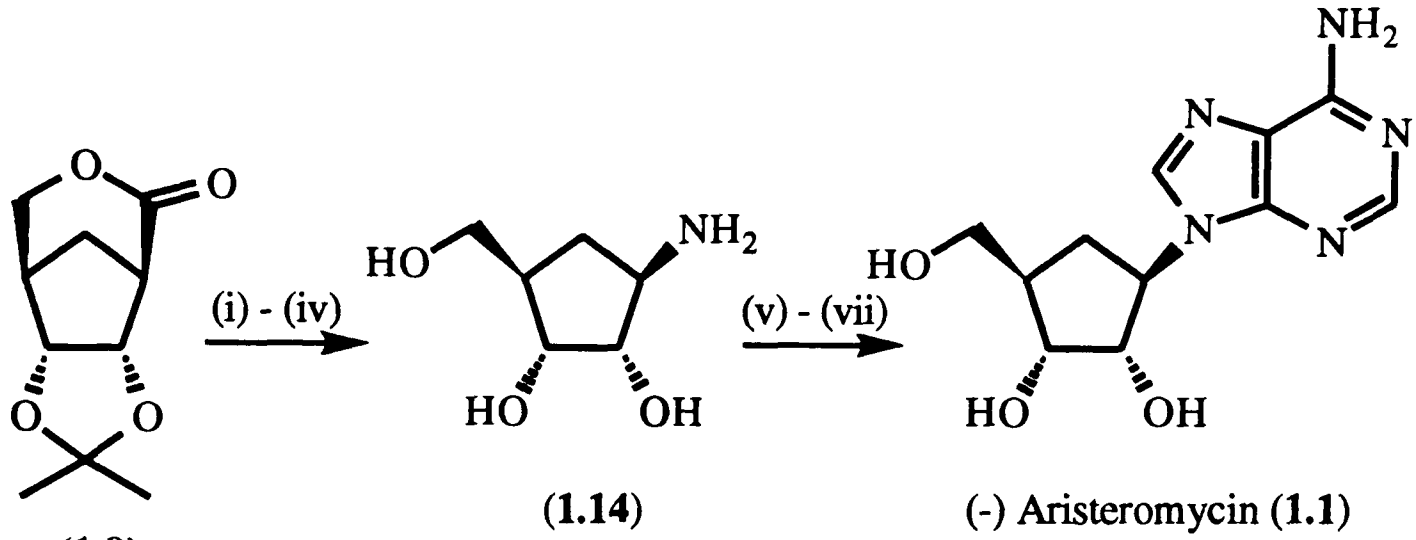
The first enantiospecific synthesis of aristeromycin (**1.1**) was provided by Ohno and co-workers *via* the homochiral bicyclic lactone (+) (**1.9**).[26] Koizumi and co-workers have since reported more efficient syntheses to the bicyclic lactone (+) (**1.9**), utilising asymmetric Diels-Alder reactions.[27] Thus reaction of (S_S)-menthyl-3-(2-pyridylsulphinyl)acrylate (**1.10**) with cyclopentadiene gave the *endo* cycloadduct (**1.11**) which was transformed into the unsaturated ester (**1.12**) in four stages. Ozonolysis of (**1.12**) followed by lithium aluminium hydride reduction afforded the triol (**1.13**). Periodate cleavage of the diol moiety and subsequent oxidation provided the Ohno lactone (+) (**1.9**) in 22% overall yield (**Scheme 1.1**).



Reagents: (i) cyclopentadiene, Et_2AlCl, CH_2Cl_2, -78°C; (ii) OsO_4; (iii) 2,2-dimethoxypropane, *p*TSA; (iv) *m*CPBA; (v) DBU; (vi) O_3 then Me_2S; (vii) $LiAlH_4$; (viii) $NaIO_4$; (ix) $CrO_3.2Py$, CH_2Cl_2.

Scheme 1.1

Further elaboration of the Ohno lactone (**1.9**) towards the synthesis of aristeromycin (**1.1**) is outlined in **Scheme 1.2**. This involved opening of the lactone with ammonia followed by acetylation, Hofmann degradation and deprotection to give the chiral amino triol (**1.14**). Stepwise construction of the adenine base onto the amine function was then effected in three stages[28] to afford (-) aristeromycin (**1.1**).

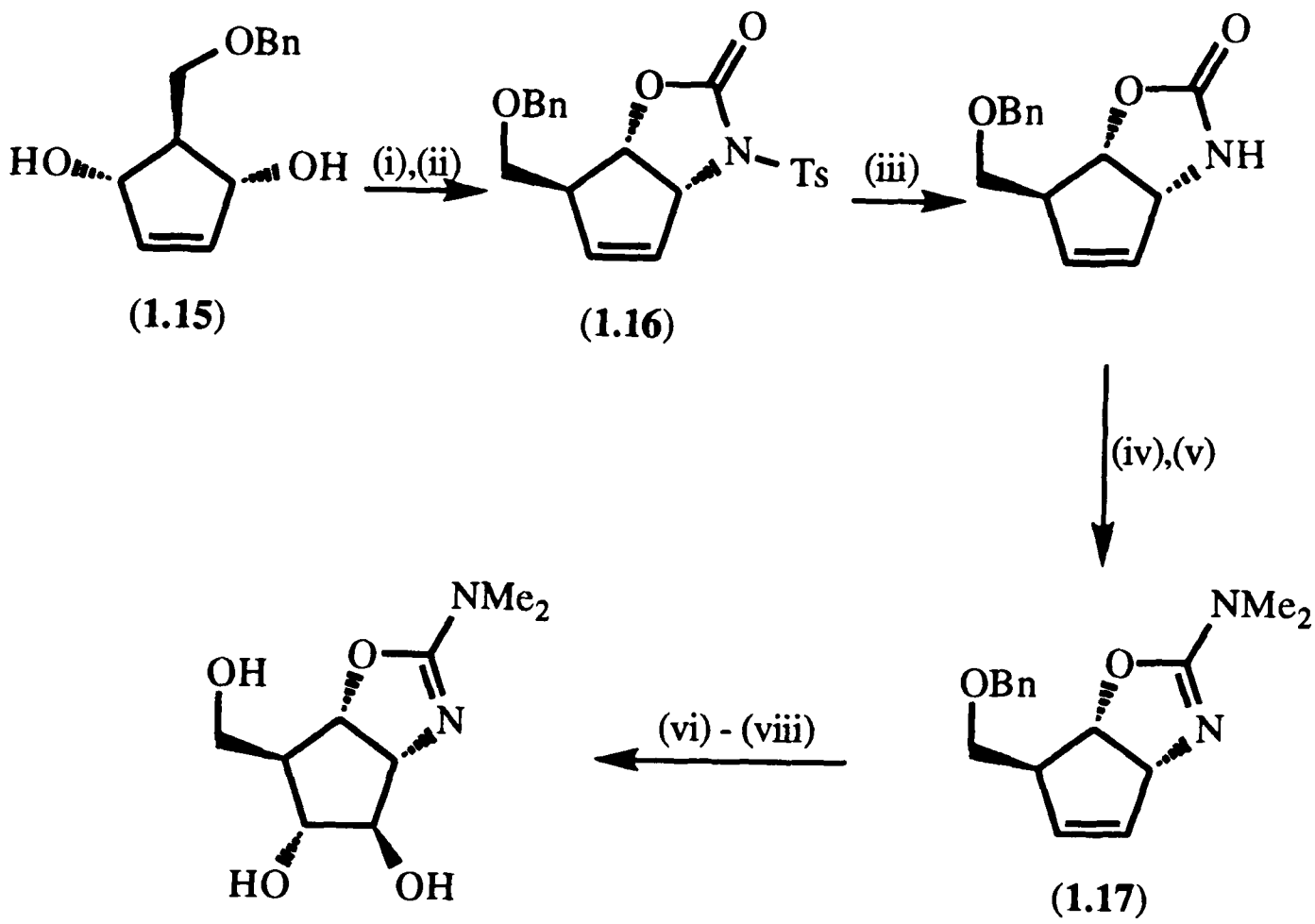


(**1.9**) (**1.14**) (-) Aristeromycin (**1.1**)

Reagents: (i) NH_3; (ii) Ac_2O, Py; (iii) $Pb(OAc)_4$, ^tBuOH;
(iv) aqueous HCl; (v) 5-amino-4,6-dichloropyrimidine;
(vi) triethylorthoformate; (vii) NH_3.

Scheme 1.2

Trost and co-workers have recently reported a synthesis of racemic allosamizoline (**1.7**) (**Scheme 1.3**).[29] The starting material was the known cyclopentene diol (**1.15**)[30], which in turn was derived from cyclopentadiene. The strategy utilised a palladium (0) catalyst in the formation of the oxazolidinone (**1.16**). A sequence of epoxidation / hydrolysis then provided allosamizoline (**1.7**), together with the isomeric *trans*-3,4-diol. The heterocyclic oxazoline (**1.17**) was also converted to the corresponding *cis*-3,4-diols *via cis*-dihydroxylation in the presence of osmium tetroxide.

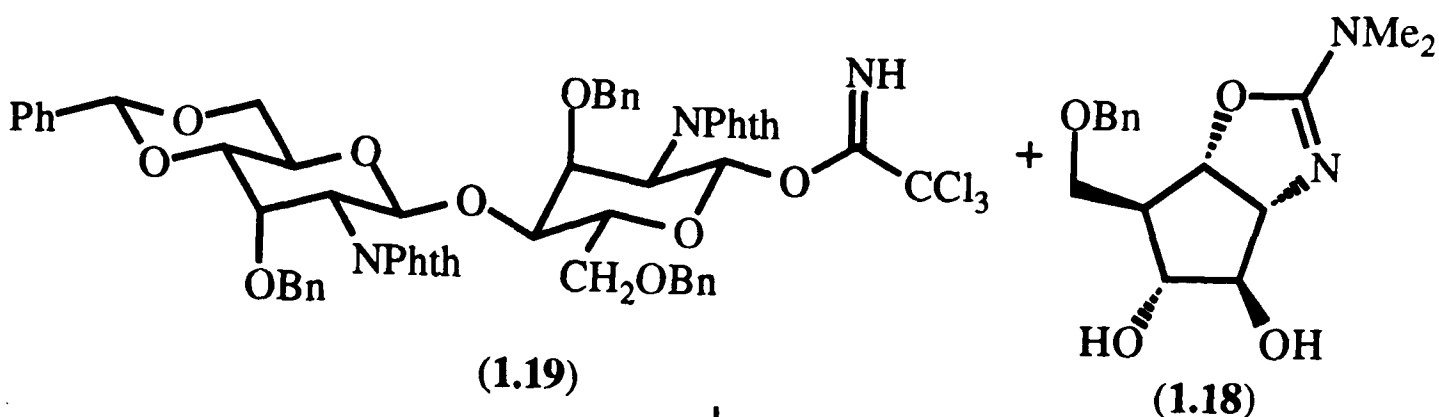


(±) Allosamizoline (**1.7**)

Reagents: (i) TsNCO (2 equiv); (ii) 1.5 mol% $Pd[(OiPr)_3P]_4$; (iii) Na, naphthalene, -78°C; (iv) CH_3OTf; (v) Me_2NH; (vi) 5.4 M CF_3CO_3H, TFA, 0°C - RT; (vii) 10% aqueous TFA, 40°C; (viii) H_2, Pd.

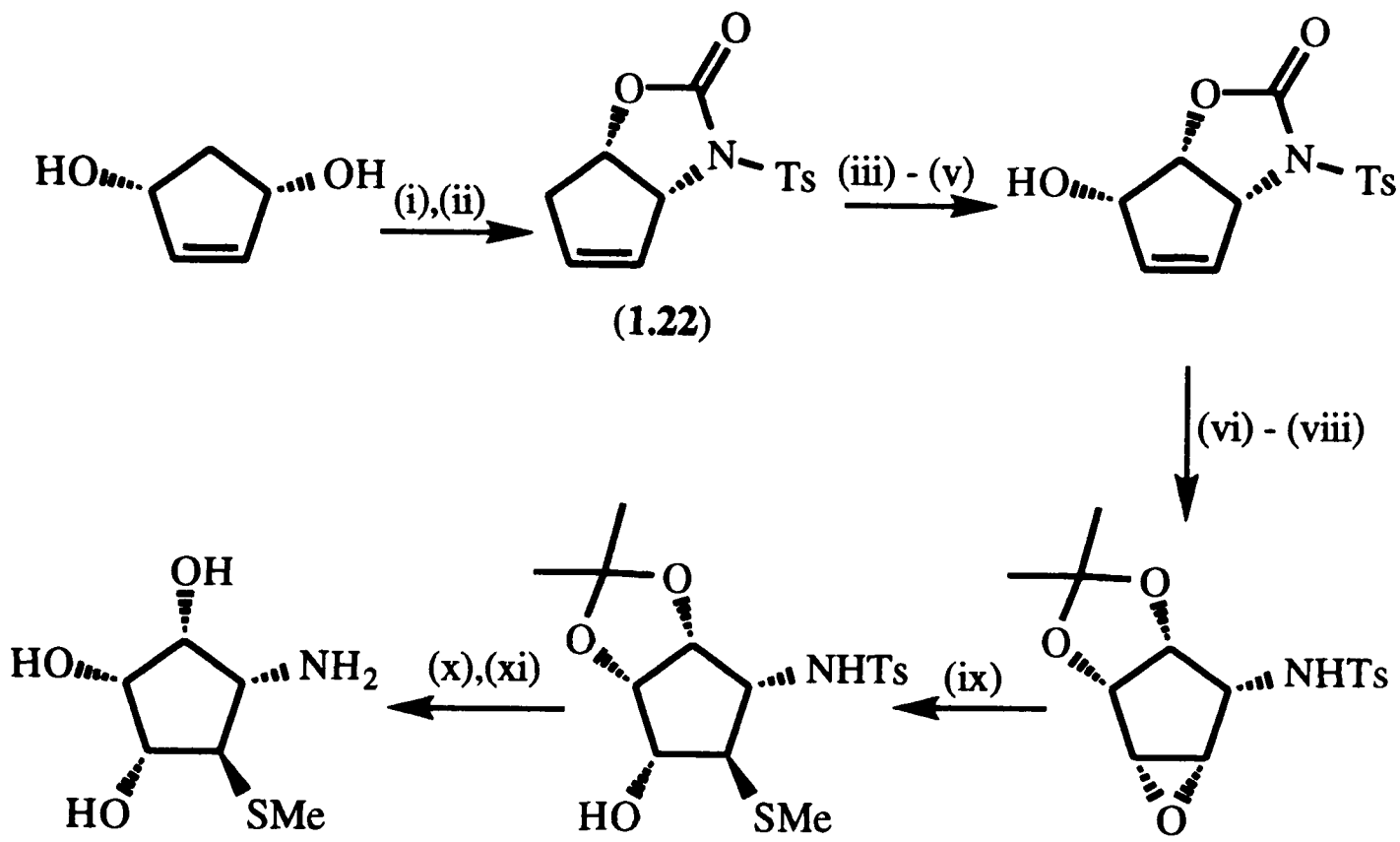
Scheme 1.3

6-*O*-Benzylallosamizoline (**1.18**), an intermediate in the above synthesis, was coupled to the synthetic disaccharide trichloroacetimidate (**1.19**) to give a mixture of the pseudotrisaccharides (**1.20**) and (**1.21**). Separation, deprotection and acetylation of the correct isomer (**1.21**) afforded allosamidin (**1.2**) (**Scheme 1.4**).[31]


Ph
O
O
O
O
OBn
NPhth
O
NH
CCl3
OBn
NPhth
CH2OBn
(1.19)
+
NMe2
OBn
O
N
HO
OH
(1.18)
Me3SiOTf,
CH2Cl2,
molecular sieves.
Ph
OBn
NPhth
HO
OBn
NPhth
OBn
BnO
NMe2
(1.20)
+
Ph
OBn
NPhth
OBn
NPhth
OBn
OBn
HO
NMe2
(1.21)
OH
HO
NHAc
OH
NHAc
OH
OH
HO
NMe2
Allosamidin (1.2)

Scheme 1.4

An analogous approach was adopted in the synthesis of mannostatin A (**1.4**), as shown in **Scheme 1.5**.[32] Thus cyclopent-2-ene-1,4-diol was converted to the oxazolidinone (**1.22**) *via* the palladium-catalysed ionisation / cyclisation reaction. Stereoselective introduction of the allylic hydroxyl group was then achieved *via* allylic oxidation and reduction. Epoxidation followed by treatment with lithium thiomethoxide and deprotection completed the eleven-step synthesis of mannostatin A (**1.4**).



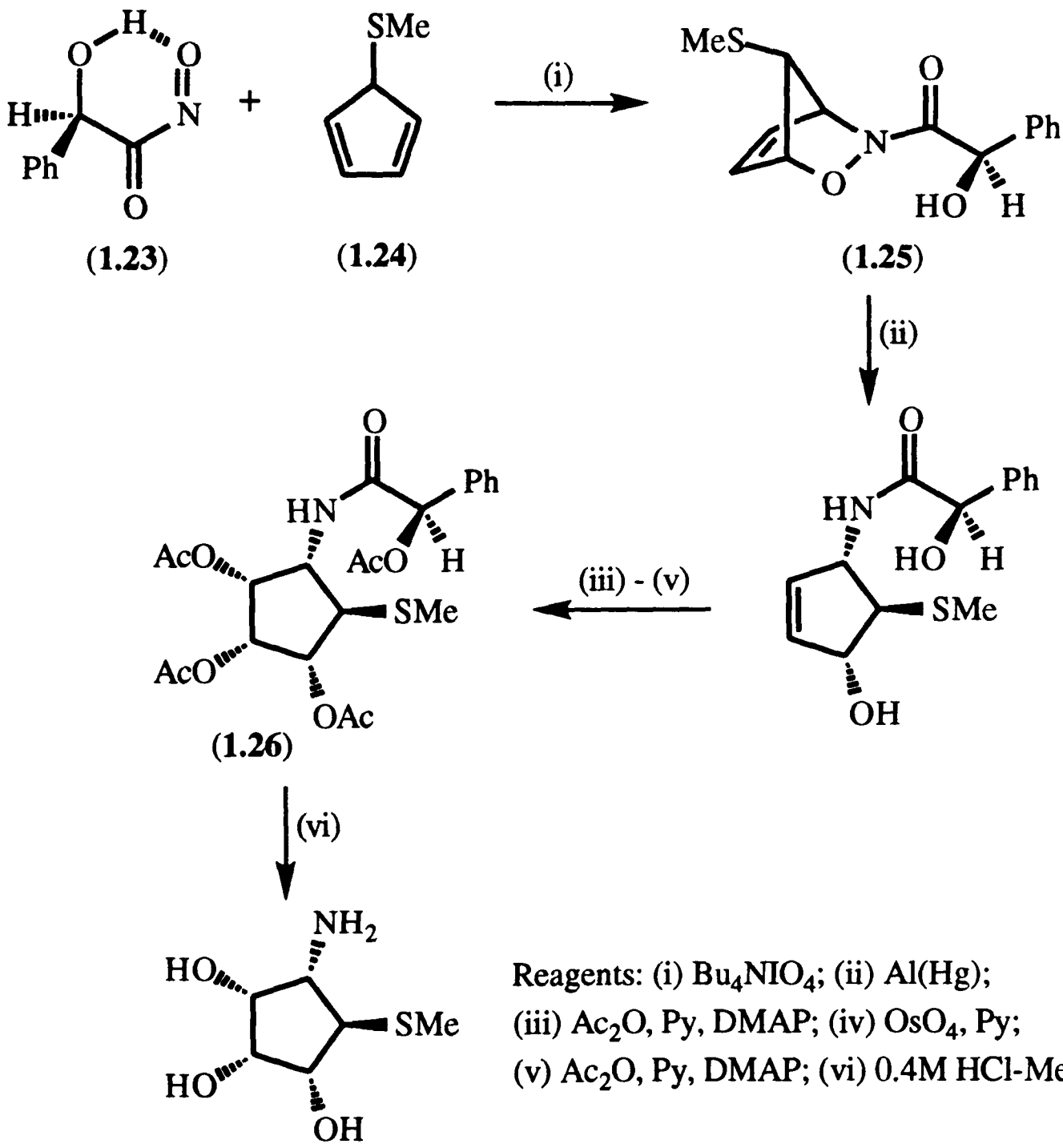
(±) Mannostatin A (**1.4**)

Reagents: (i) TsNCO (2 equiv); (ii) 1.8 mol% $Pd[(OiPr)_3P]_4$; (iii) SeO_2; (iv) Dess-Martin periodinane; (v) $NaBH_4$, $CeCl_3$; (vi) K_2CO_3, MeOH; (vii) 2,2-dimethoxypropane, CSA; (viii) CF_3CO_3H, Na_2HPO_4, CH_2Cl_2; (ix) MeSLi, THF; (x) Na, NH_3; (xi) 60% aqueous TFA.

Scheme 1.5

The development of chiral phosphine ligands has since resulted in enantioselective oxazolidinone formation[33] and has thereby completed the formal asymmetric syntheses of allosamizoline (**1.7**) and mannostatin A (**1.4**).

An alternative synthesis of mannostatin A (**1.4**) was reported by Ganem and co-workers (**Scheme 1.6**).[34] In this case, the application of asymmetric hetero Diels-Alder chemistry generated three of the five stereocentres with the correct heteroatoms attached. Thus asymmetric cycloaddition of the acylnitroso dienophile (**1.23**), derived from (*R*)-mandelic acid, with 1-(methylthio)-cyclopenta-2,4-diene (**1.24**) gave the key intermediate (**1.25**). Reductive cleavage of the N-O bond followed by stoichiometric osmylation and acetylation produced the tetraacetate (**1.26**). Deprotection gave optically active (+) mannostatin A (**1.4**).

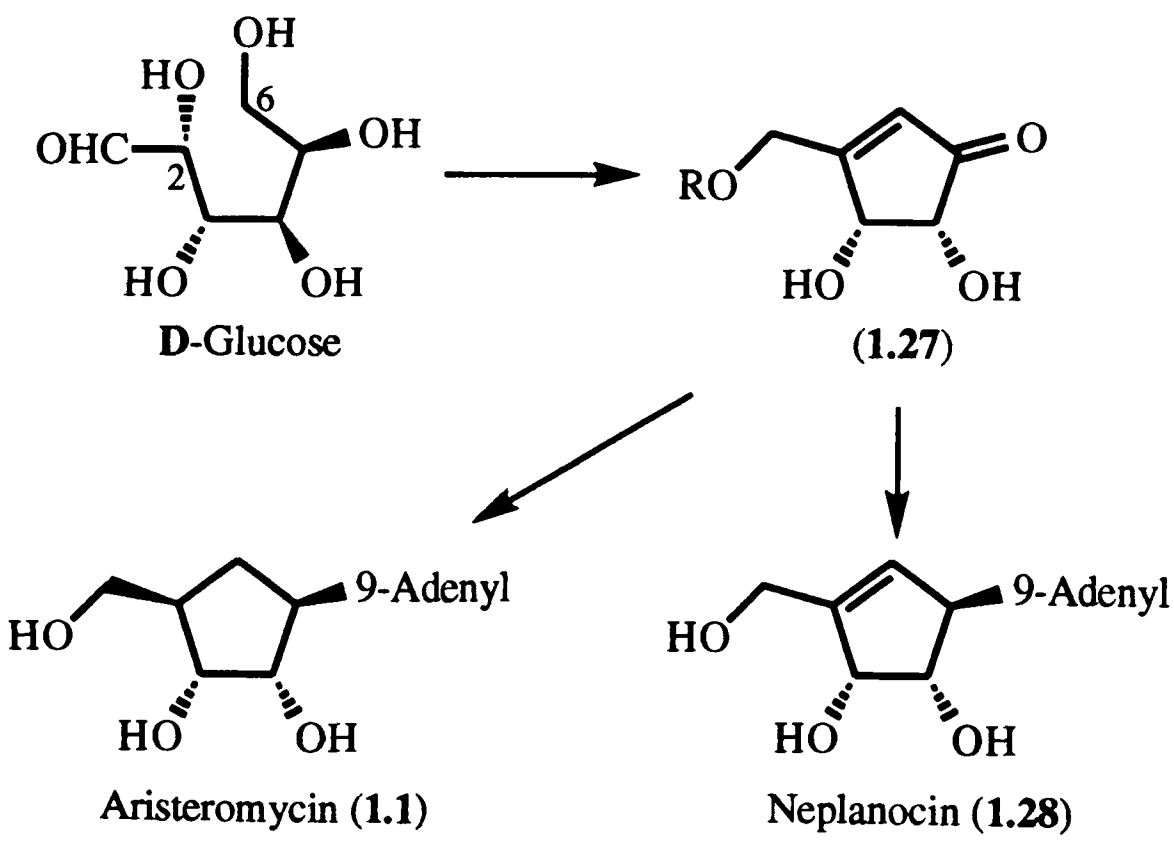


Scheme 1.6

(b) Previous Syntheses From Carbohydrate Starting Materials.

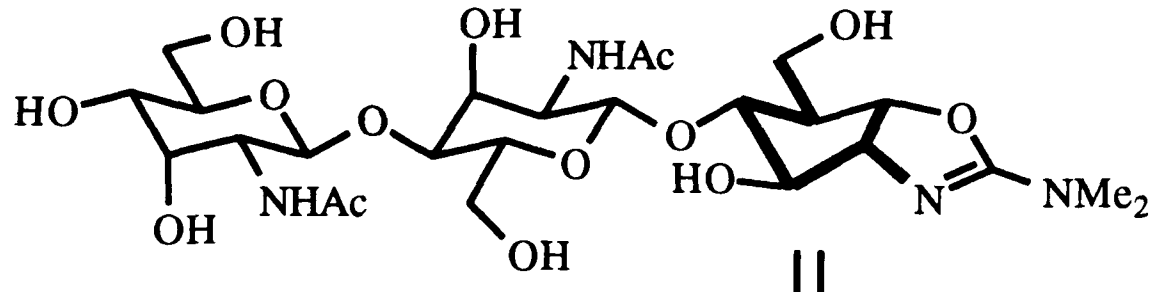
Monosaccharides represent a set of versatile precursors for the synthesis of polyfunctionalised cyclopentanes. The inherent density of chiral functionality in the starting materials should facilitate stereospecific synthesis of such demanding targets. While nature appears to utilise aldol-type reactions in the biosynthesis of highly functionalised cyclopentanes,[35] there are a variety of chemical procedures available to the synthetic chemist for cyclopentane formation from monosaccharide precursors. These include intramolecular radical cyclisations,[36] intramolecular aldol[37] and Wittig[38] cyclisations, cycloadditions[19,39] and transition metal-mediated cyclisations[40].

Biosynthetic studies on the incorporation of radiolabelled glucose into aristeromycin (**1.1**) suggest that the carbocyclic ring is created by C-C bond formation between C-2 and C-6 of **D**-glucose.[41] This is thought to occur *via* oxidation at C-4 or C-5 of a hexose, followed by an aldol-like cyclisation that is presumed to lead to a cyclopentenone derivative (**1.27**, R = H or phosphate) (**Scheme 1.7**). The intermediacy of the enone (**1.27**) is further supported by the concurrence of the unsaturated antibiotic neplanocin A (**1.28**)[42] with aristeromycin (**1.1**).[43]

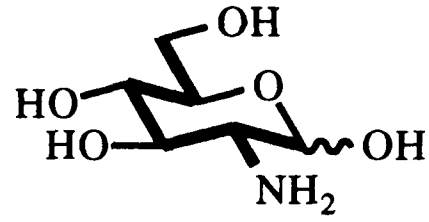


Scheme 1.7

The origin of the cyclopentanoid portion of allosamidin (**1.2**) has been elucidated by means of feeding experiments with labelled precursors.[44] It was concluded that the carbon skeleton and nitrogen atom of **D**-glucosamine (**1.29**) were incorporated fully into allosamizoline (**1.7**) (**Scheme 1.8**). The precise mechanism of cyclisation is yet to be reported, although it has been postulated that glucosamine might cyclise to form the alicyclic ring *via* an intermediate 4-keto or 6-formyl glucosamine, which would undergo an aldol condensation on C-5 with C-1.



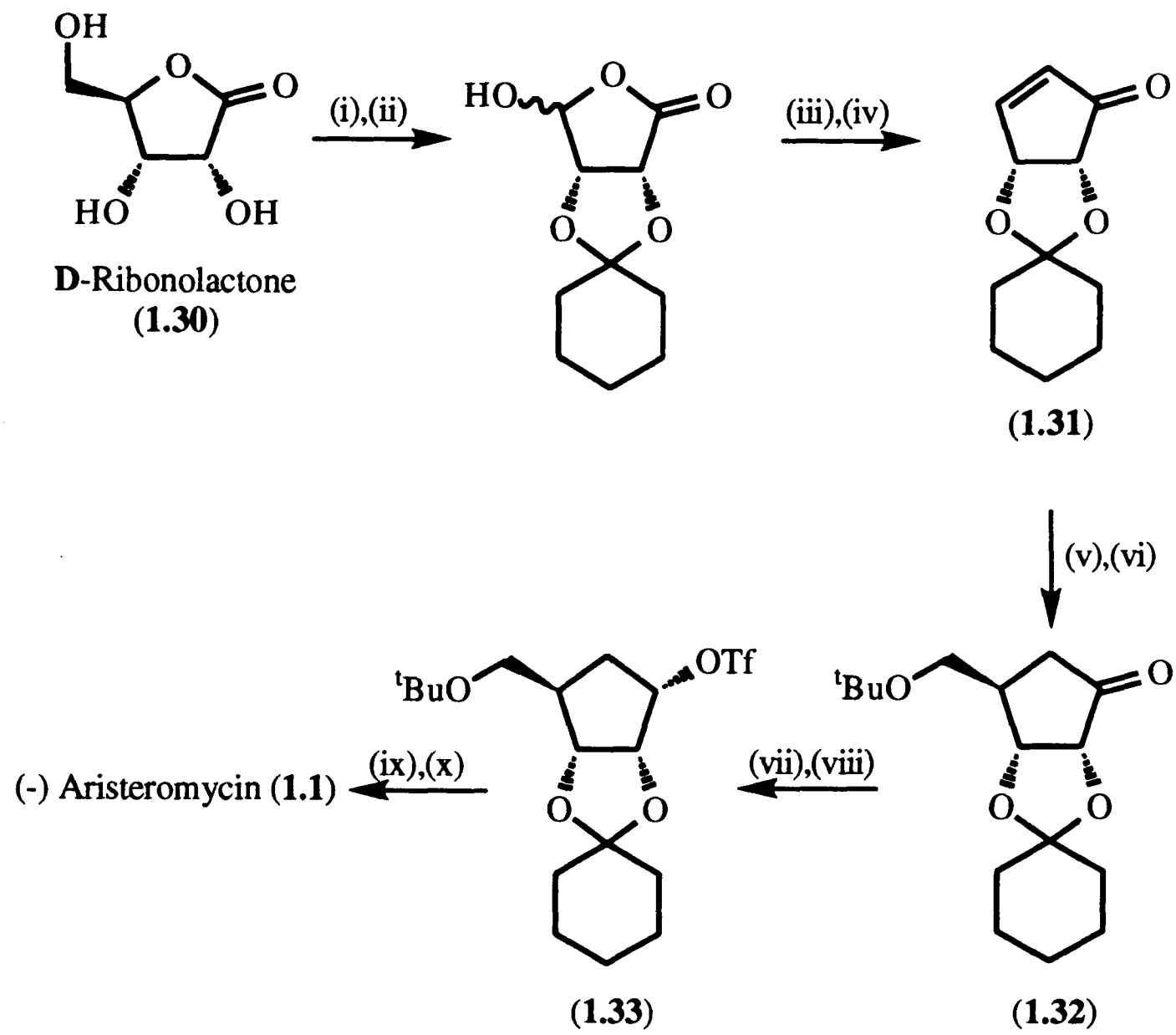
Allosamidin (**1.2**)



D-Glucosamine (**1.29**)

Scheme 1.8

Borchardt and co-workers have achieved the most efficient enantiospecific synthesis of aristeromycin (**1.1**) to date (**Scheme 1.9**).[45] **D**-Ribonolactone (**1.30**) was converted to the dihydroxy-cyclopentenone (**1.31**) in four steps in 65% overall yield.[38] Organocuprate conjugate addition followed by acidic work-up gave the cyclopentenone (**1.32**) as one diastereomer. Diastereoselective reduction of the carbonyl group followed by treatment with trifluoromethanesulphonyl anhydride afforded the triflate (**1.33**). Displacement with adenide anion and deprotection completed the nine-step 'convergent' synthesis of aristeromycin (**1.1**) (overall yield 18%).

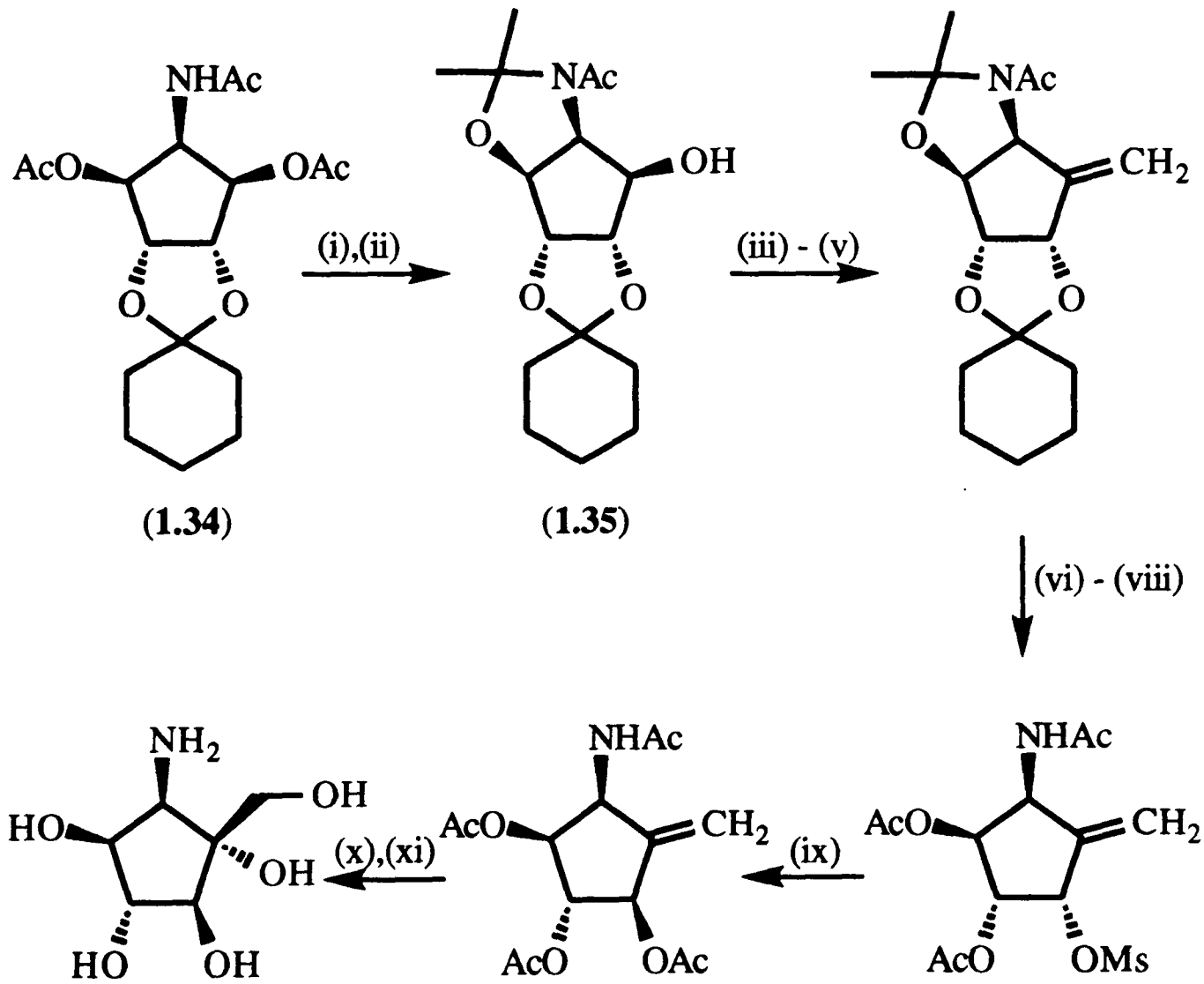


Reagents: (i) Cyclohexanone, $FeCl_3$; (ii) H_2O, NaOH, $NaIO_4$;
(iii) 2-propanol, PPTS; (iv) $MePO(OMe)_2$, ^nBuLi, THF;
(v) $(^tBuOCH_2)_2CuLi$; (vi) AcOH, MeOH; (vii) DIBAH; (viii) Tf_2O,
Py; (ix) adenine, NaH, 18-crown-6, DMF; (x) 66% aqueous TFA.

Scheme 1.9

The cyclopentenone (**1.31**) has also been used as a divergent intermediate in the synthesis of neplanocin A (**1.28**) and a number of structural analogues thereof.[38]

An enantiospecific synthesis of trehazolin (**1.3**), by Ogawa and co-workers,[14] utilised the protected aminohydroxycyclopentane (**1.34**)[46,47] as the starting material (**Scheme 1.10**). Isolation of the enantiomerically pure alcohol (-) (**1.35**) was achieved *via* resolution of the corresponding diastereomeric (*S*)-acetylmandelates, and its absolute configuration was established by chemical correlation with **L**-aspartic acid.

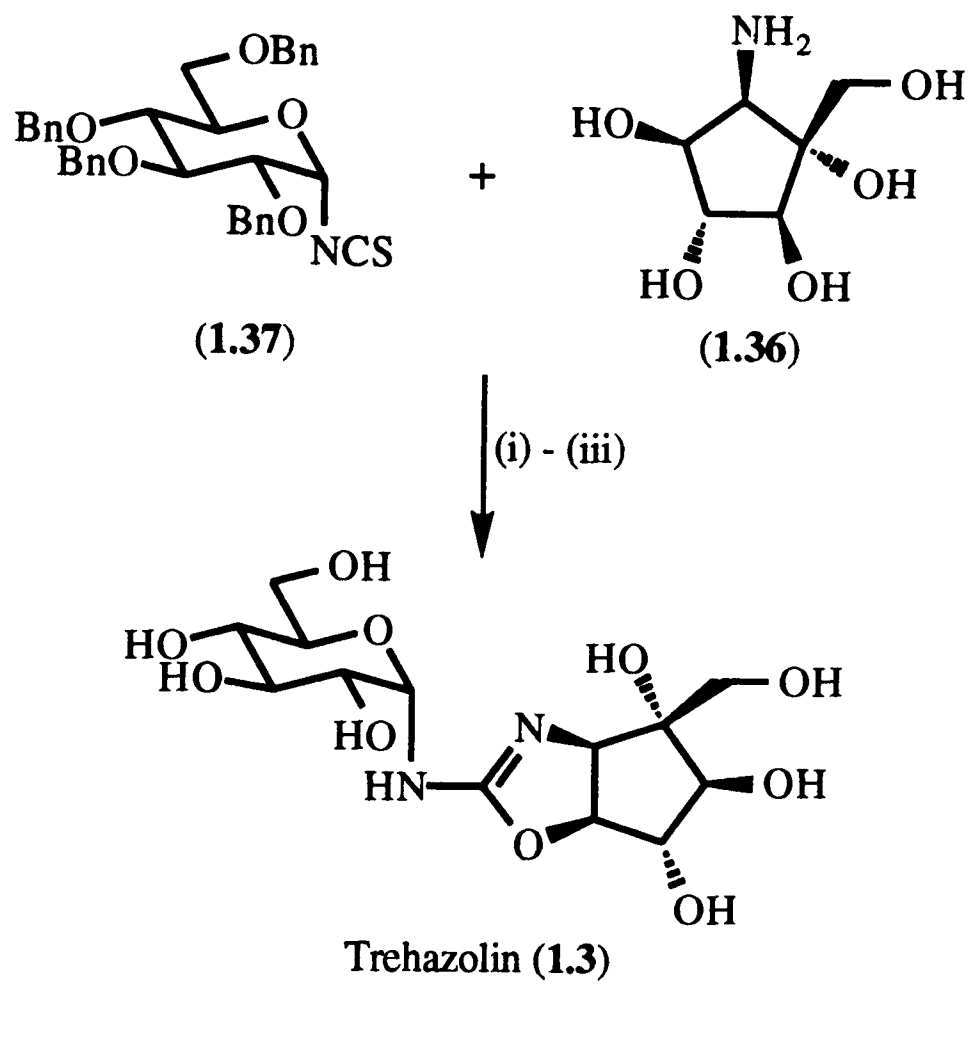


(1.34) **(1.35)** **(1.36)**

Reagents: (i) NaOMe, MeOH; (ii) 2,2-dimethoxypropane, TsOH, DMF; (iii) PCC, CH_2Cl_2; (iv) CH_2N_2, DMSO / Et_2O; (v) $P(OMe)_3$; (vi) 80% aqueous AcOH; (vii) MsCl, Py; (viii) Ac_2O, Py; (ix) NaOAc, DMF; (x) OsO_4, NMO, 80% aqueous acetone.

Scheme 1.10

Coupling of the amine (**1.36**) with the protected α-glucopyranosyl isothiocyanate (**1.37**) followed by isoureido ring formation and subsequent deprotection produced trehazolin (**1.3**) (**Scheme 1.11**).



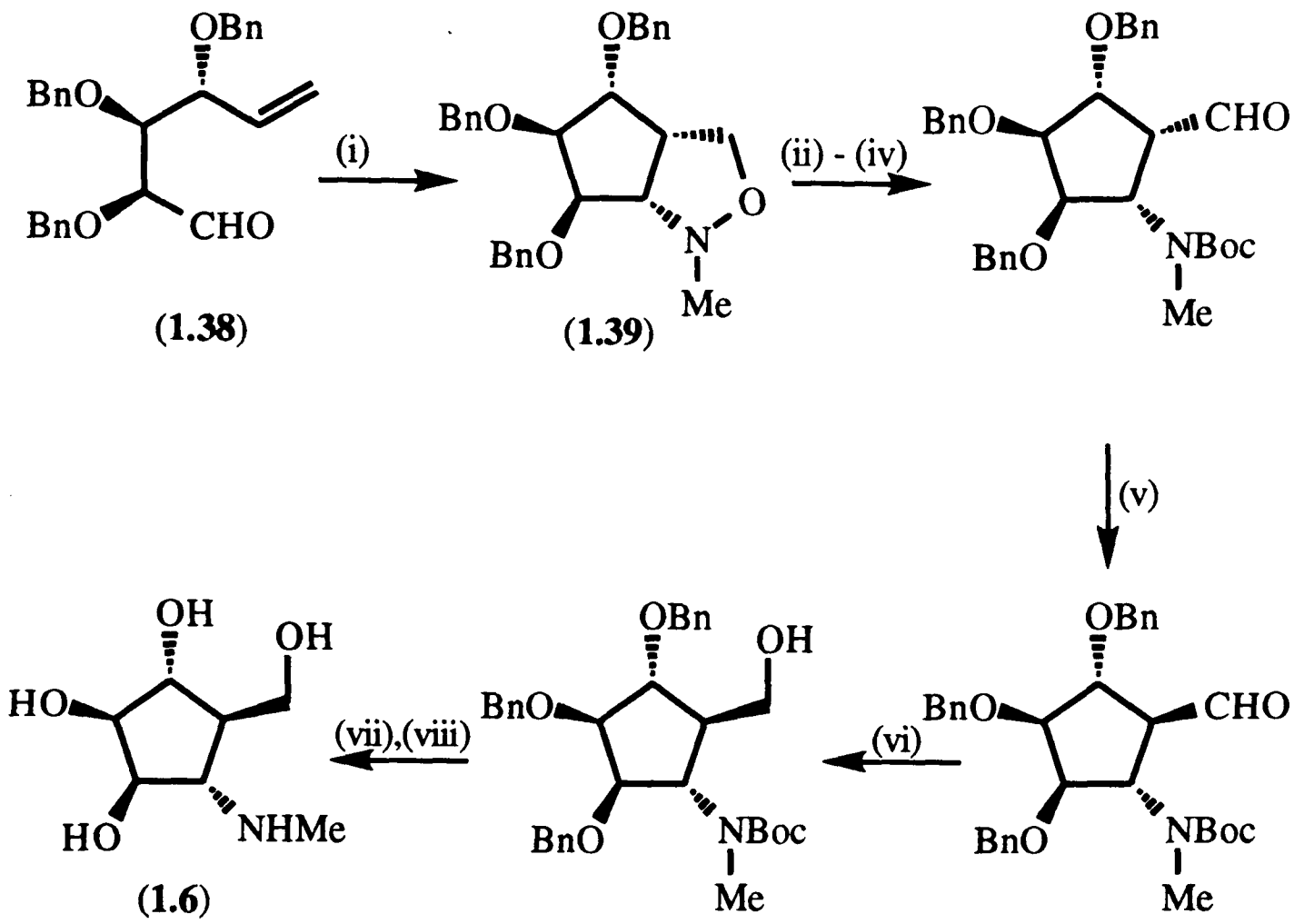
(**1.37**) + (**1.36**)

Trehazolin (**1.3**)

Reagents: (i) 75% aqueous DMF;
(ii) HgO, acetone-Et_2O; (iii) Na, NH_3.

Scheme 1.11

Farr and co-workers reported the first synthesis of the Merrell Dow cyclopentylamine (**1.6**) (**Scheme 1.12**).[19] The key cyclisation step involved the intramolecular cycloaddition of the *N*-methyl nitrone derived from the aldehyde (**1.38**) to give the known isoxazolidine (**1.39**).[39] Reductive cleavage of the N-O bond followed by a sequence of oxidation / epimerisation / reduction and deprotection yielded the cyclopentylamine (**1.6**).



Reagents: (i) MeNHOH, MeOH; (ii) Zn, AcOH; (iii) $(Boc)_2O$; (iv) Dess-Martin periodinane; (v) DBU; (vi) $NaBH_4$; (vii) H_2, Pd; (viii) HCl(g).

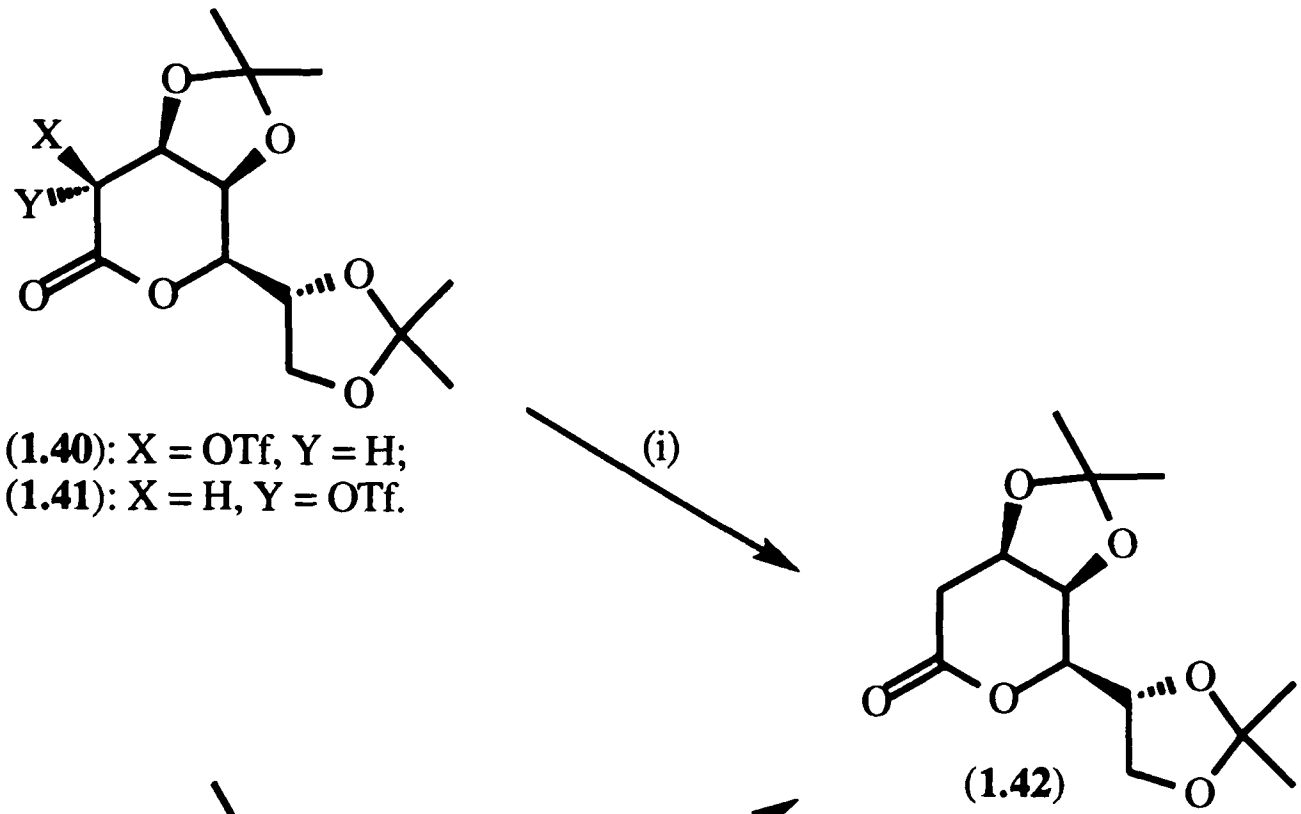
Scheme 1.12

(c) A Novel Intramolecular Aldol Cyclisation From Sugar Lactones.

Aldol condensations have been rarely used in the synthesis of cyclopentanes from monosaccharide precursors. The Ferrier cyclisation is a widely used aldol reaction for the construction of 3-hydroxy-cyclohexanones.[48] However, this reaction cannot be used for the synthesis of complex cyclopentanones,[49] the cyclisations being disfavoured by their (enol-*endo*)-5-*exo*-*trig* character.[50]

Investigations into the nucleophilic displacement of α-triflates of carbohydrate lactones have revealed that treatment of either of the epimeric α-triflates of the δ-lactone, (**1.40**) or (**1.41**), with lithium iodide trihydrate resulted in the formation of the corresponding reduced product (**1.42**). This compound was also isolated as the

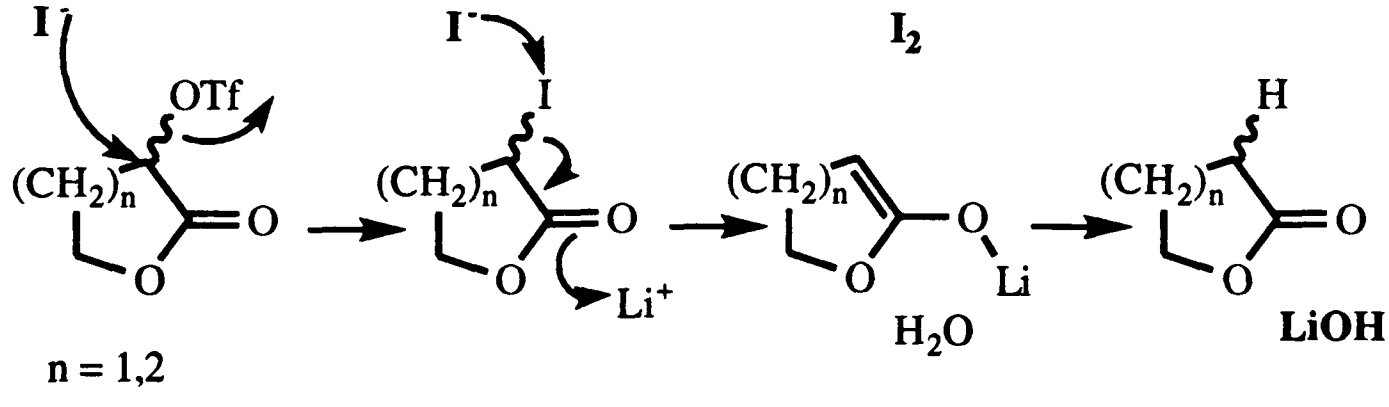
sole product when either of the α-iodides, (**1.43**) or (**1.44**), was exposed to the same reaction conditions (**Scheme 1.13**).[51]



Reagents: (i) $LiI.3H_2O$, THF.

Scheme 1.13

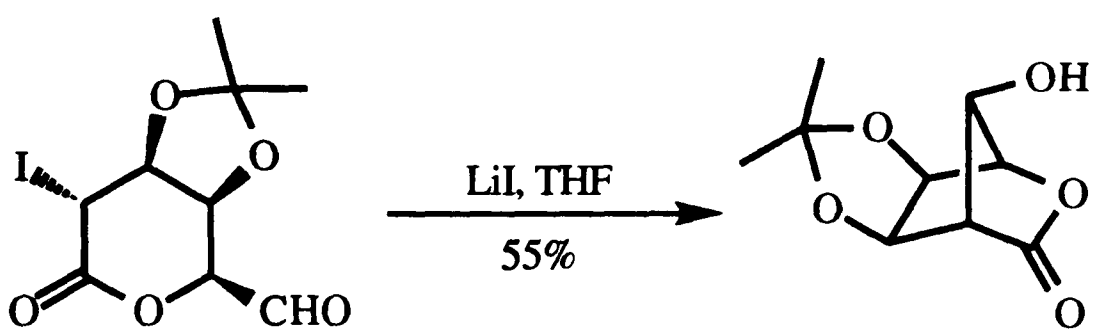
A plausible mechanism for these reactions has been proposed, and is shown in **Scheme 1.14**. It is thought to involve an initial S_N2 displacement of triflate by iodide, followed by release of iodine *via* further attack at the halogen. The resultant lithium enolate is then protonated to give the 2-deoxy lactone.



Scheme 1.14

This reaction, proving quite general, has been used in the preparation of a number of 2-deoxy carbohydrate lactones.[52]

Conversion of C-6 of a suitable δ-lactone to an electrophile, in this case an aldehyde, would facilitate the trapping of the intermediate enolate anion *via* an intramolecular aldol reaction. This would provide a possible strategy for the synthesis of polyhydroxylated cyclopentanes. As expected, treatment of the iodo aldehyde (**1.45**) with anhydrous lithium iodide afforded the bicyclic lactone (**1.46**) in 55% yield as the reductive aldol cyclisation product (**Scheme 1.15**).[53]

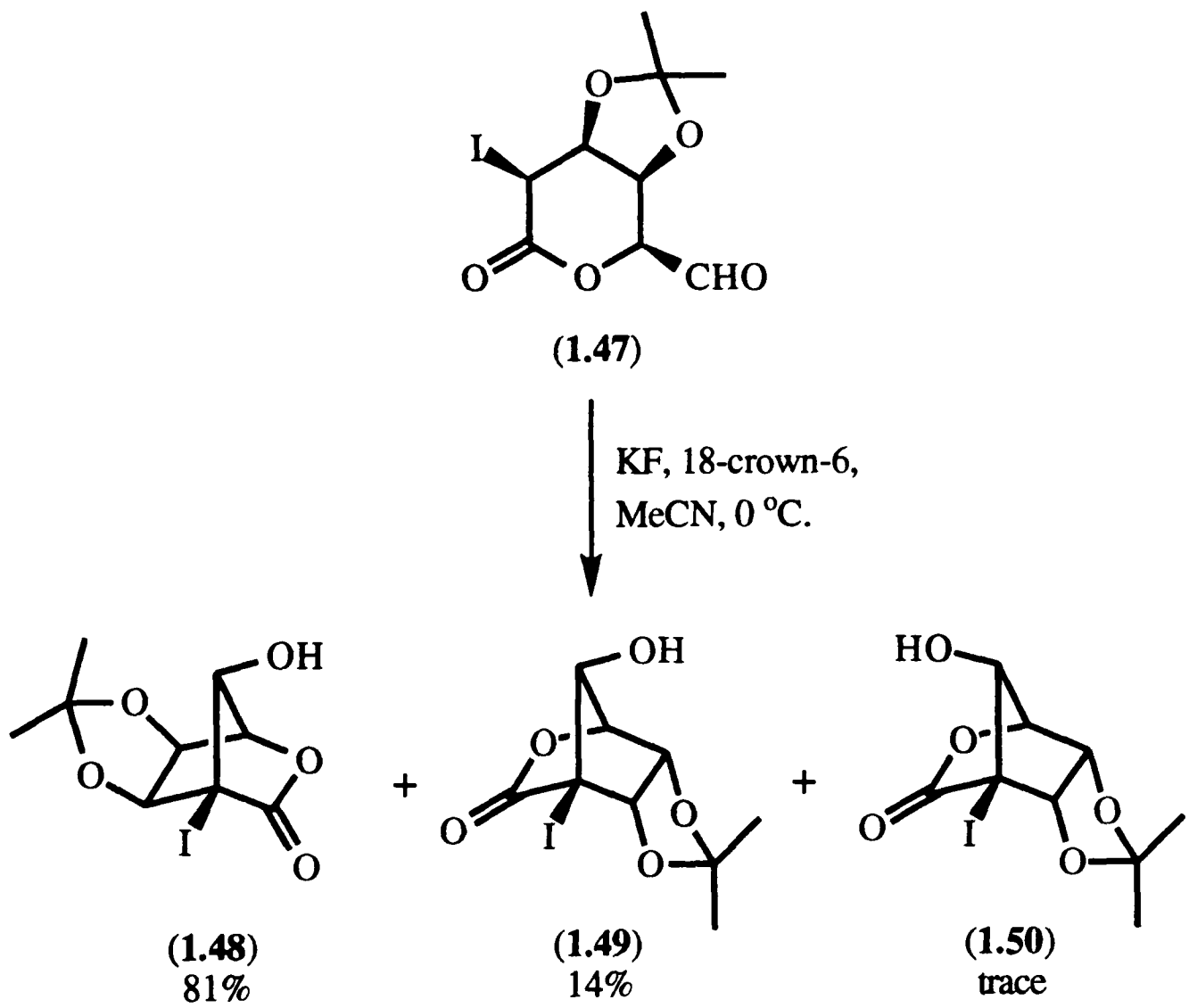


(1.45) **(1.46)**

Scheme 1.15

Further synthetic studies have indicated that the proton α to the carbonyl group in both α-iodo[52] and α-azido[54] δ-lactones could be removed reversibly. This would suggest that the intervening carbanion did not undergo significant fragmentation of the β-oxygen substituent. Removal of this proton by treatment with a suitable base and subsequent trapping of the resultant anion by an aldehyde function derived at C-6 of a lactone precursor would result in a 'straight' aldol condensation. It was envisaged that this approach would provide a simple synthetic route to heteroatom-substituted polyhydroxylated cyclopentanes.

Treatment of the iodo aldehyde (**1.47**) with potassium fluoride in acetonitrile gave a mixture of three products, (**1.48**), (**1.49**) and (**1.50**) (**Scheme 1.16**). All resulted from initial deprotonation α to the lactone carbonyl group followed by intramolecular cyclisation onto the aldehyde.[55] The structure of the major product (**1.48**) was established by single crystal X-ray analysis.[53] Reduction of the iodide with tributyl tin hydride afforded the bicyclic lactone (**1.46**), thus further confirming the structure of the latter compound as the reductive aldol cyclisation product.



(**1.47**)

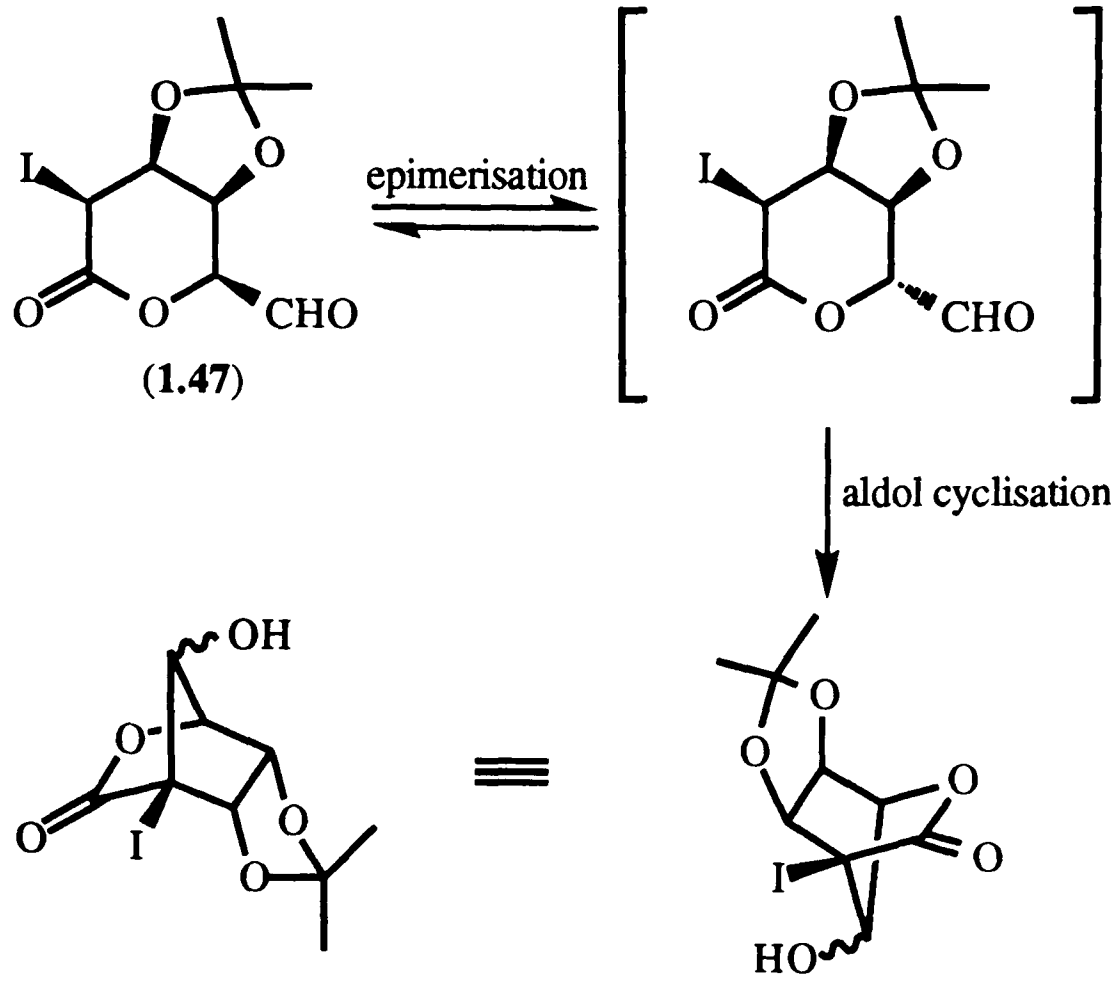
(**1.48**) 81%

(**1.49**) 14%

(**1.50**) trace

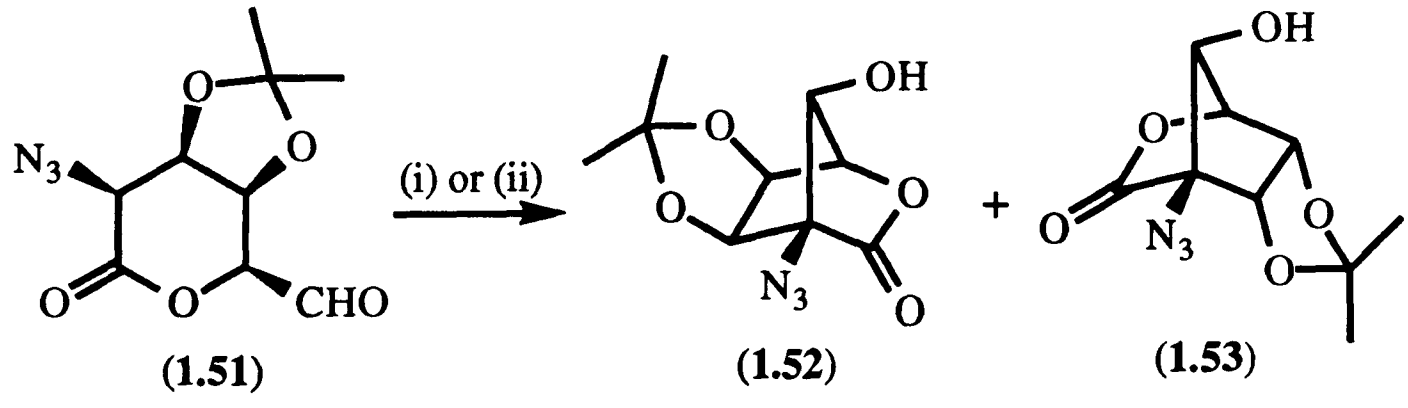
Scheme 1.16

The formation of the minor products is thought to proceed *via* the initial epimerisation α to the aldehyde and subsequent intramolecular aldol cyclisation (**Scheme 1.17**).



Scheme 1.17

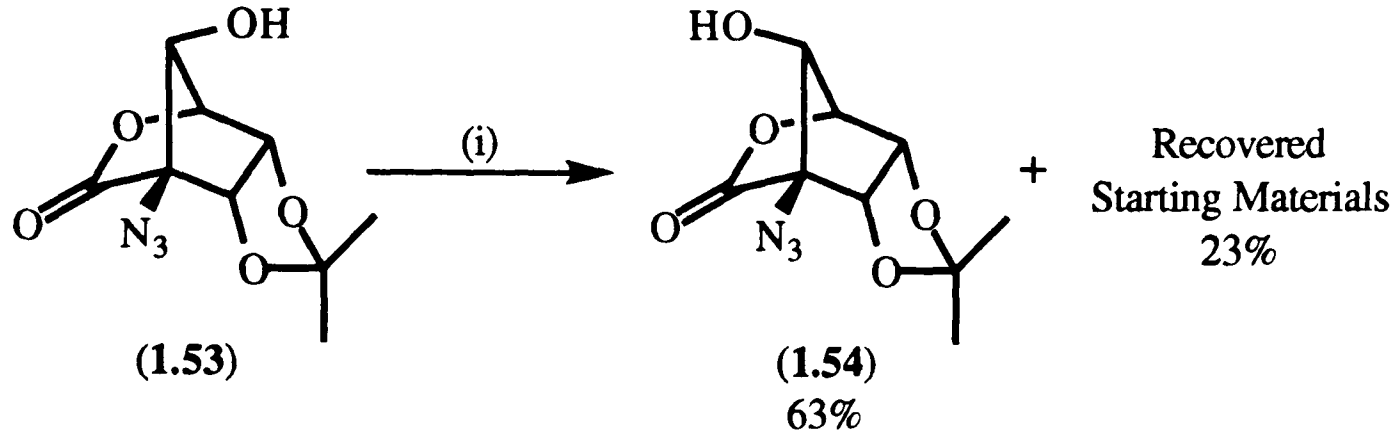
An analogous intramolecular aldol reaction was effected when the azido aldehyde (**1.51**) was treated with potassium fluoride (**Scheme 1.18**). In this case, two cyclisation products, (**1.52**) and (**1.53**), were isolated.[56] The major product (**1.52**) was formed by direct closure of the carbanion α to the lactone carbonyl onto the exocyclic aldehyde, while the minor product (**1.53**) arose from initial epimerisation α to the aldehyde. Furthermore, treatment of the azido aldehyde (**1.51**) with sodium azide in acetonitrile produced the same mixture of carbocyclic products, but in the opposite ratio (**Scheme 1.18**).[57]



Reagents: (i) KF, 18-crown-6, MeCN:- 55% 25%
(ii) NaN_3, 18-crown-6, MeCN:- 17% 53%

Scheme 1.18

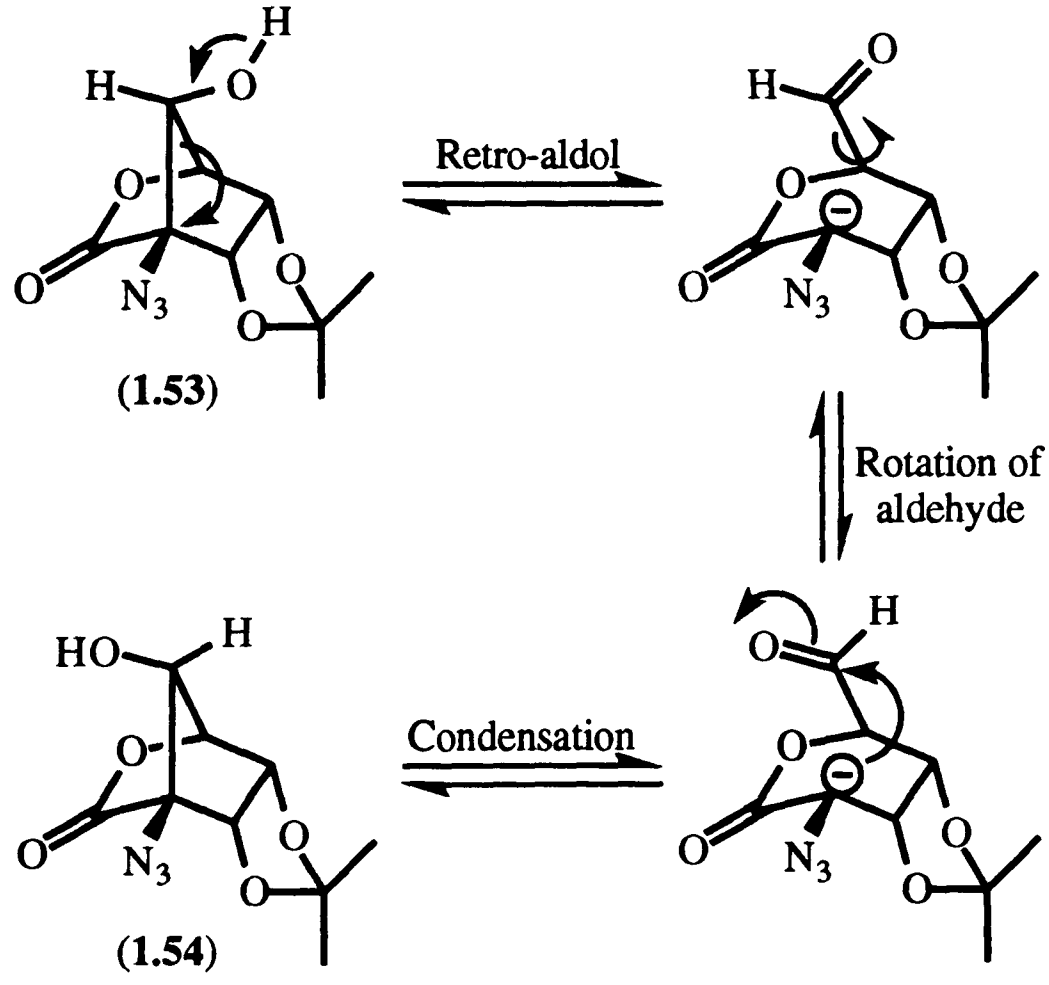
During the investigation into the ring opening reactions of the bicyclic lactones, it was found that treatment of the azido lactone (**1.53**) with liquid ammonia resulted in the epimerisation of the free hydroxyl group to give a third azido lactone (**1.54**) (**Scheme 1.19**).[56]



Reagents and conditions: liquid NH_3, -45 °C to RT over 30 min.

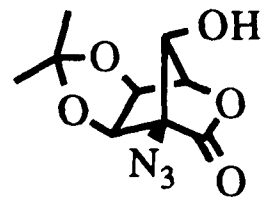
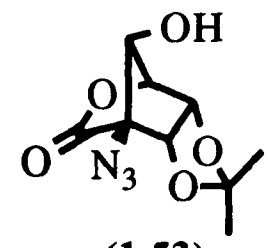
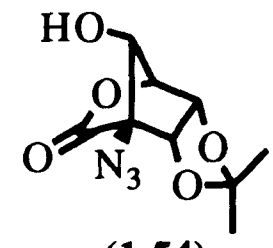
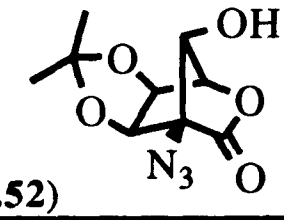
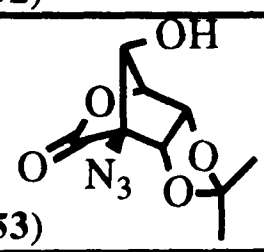
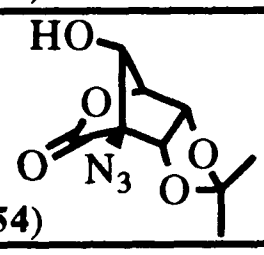
Scheme 1.19

It was postulated that epimerisation of the hydroxyl group occurred *via* a base-induced retro-aldol reaction (**Scheme 1.20**). Rotation of the bond α to the aldehyde carbonyl followed by recondensation of the enolate anion onto the opposite face of the aldehyde effected epimerisation and formation of the bicyclic lactone (**1.54**). The structure of this material was confirmed by X-ray crystallographic analysis.[58]



Scheme 1.20

The interconversion of the two bicyclic lactones, (**1.53**) and (**1.54**), prompted an investigation to examine whether any or all of the azido bicyclic lactones would undergo base-catalysed isomerisations.[58] Two sets of reaction conditions were employed, namely potassium fluoride and sodium azide in acetonitrile, and the results are outlined in **Table 1.1**. The left hand column denotes the pure starting material used, and the percentages refer to the percentage yields of each of the three carbocycles isolated after exposure to the reaction conditions described.

Starting materials \ **Products**	 **(1.52)**	 **(1.53)**	 **(1.54)**
 **(1.52)**	(a) no epimerisation	—	—
	(b) no epimerisation	—	—
 **(1.53)**	(a) 8%	17%	54%
	(b) 4%	42%	50%
 **(1.54)**	(a) 6%	19%	44%
	(b) —	22%	78%

Reaction conditions: (a) KF, 18-crown-6, MeCN, RT, 24 h;
(b) NaN_3, 18-crown-6, MeCN, RT, 48 h.

Table 1.1

As can be seen, the bicyclic lactone (**1.52**) did not undergo any retro-aldol isomerisation under either set of reaction conditions. Both of the other two carbocycles (**1.53**) and (**1.54**) were converted into mixtures of carbocycles by retro-

aldol reactions induced by either set of basic reaction conditions. On the basis of these observations, it has been suggested that the formation of the carbocycle (**1.53**) may be kinetically favoured, whilst the epimeric (**1.54**) is thermodynamically more stable.[56] The fact that the latter compound (**1.54**) has not been isolated from either of the cyclisation reactions described in **Scheme 1.18** may be because this material is chromatographically inseparable from the aldehyde (**1.51**). In both cyclisation reactions some starting aldehyde persisted, thus obscuring the observation and isolation of trace amounts of the carbocycle (**1.54**).

The efficacy of the cyclisation reactions has prompted extensive investigations into the applicability of such an intramolecular aldol approach to a number of different carbohydrate lactone systems.[59] This thesis details further investigations into the generality of the retro-aldol reaction and the syntheses of a variety of polyfunctionalised cyclopentanes from the heteroatom-substituted bicyclic lactones described above.

References.

1. Shealy, Y.F.; Clayton, J.D.; *J. Am. Chem. Soc.*, 1966, **88**, 3885.

2. (a) Kusaka, T.; Yamomoto, H.; Shibata, M.; Muroi, M.; Kishi, T.; Mizuno, K.; *J. Antibiot.*, 1967, **21**, 255; (b) Kishi, T.; Muroi, M.; Kusaka, T.; Nishikawa, M.; Kamiya, K.; Mizuno, K.; *Chem. Pharm. Bull.*, 1972, **20**, 940.

3. Suhadolnik, R.J.; *Nucleoside Antibiotics*; Wiley-Interscience: New York, 1970; p. 236.

4. Suhadolnik, R.J.; *Nucleosides as Biological Probes*; Wiley: New York, 1979; p. 147.

5. Guranowski, A.; Montgomery, J.A.; Cantoni, G.L.; Chiang, P.K.; *Biochemistry*, 1981, **20**, 110.

6. Sakuda, S.; Isogai, A.; Matsumoto, S.; Suzuki, A.; *J. Antibiot.*, 1987, **40**, 296.

7. Somers, P.J.B.; Yao, R.C.; Doolin, L.E.; McGowan, M.J.; Fukuda, D.S.; Mynderse, J.S.; *J. Antibiot.*, 1987, **40**, 1751.

8. Sakuda, S.; Isogai, A.; Matsumoto, S.; Suzuki, A.; Koseki, D.S.; *Tetrahedron Lett.*, 1986, **27**, 2475.

9. Koga, D.; Isogai, A.; Sakuda, S.; Matsumoto, S.; Suzuki, A.; Kimura, S.; Ide, A.; *Agric. Biol. Chem.*, 1987, **51**, 471.

10. (a) Sakuda, S.; Isogai, A.; Makita, T.; Matsumoto, S.; Koseki, K.; Kodama, H.; Suzuki, A.; *Agric. Biol. Chem.*, 1987, **51**, 3251; (b) Sakuda, S.; Isogai, A.; Matsumoto, S.; Suzuki, A.; Koseki, K.; Kodama, H.; Yamada, Y.; *Agric. Biol. Chem.*, 1988, **52**, 1615.

11. Nakayama, T.; Amachi, T.; Murao, S.; Sakai, T.; Shin, T.; Kenny, P.T.M.; Iwashita, T.; Zagorski, M.; Komura, H.; Nomoto, K.; *J. Chem. Soc. Chem. Commun.*, 1991, 919.

12. Ando, O.; Satake, H.; Itoi, K.; Sato, A.; Nakajima, M.; Takahashi, S.; Haruyama, H.; Ohkuma, Y.; Kinoshita, T.; Enokita, R.; *J. Antibiot.*, 1991, **41**, 1165.

13. Kobayashi, Y.; Miyazaki, H.; Shiozaki, M.; *J. Org. Chem.*, 1994, **59**, 813.

14. Uchida, C.; Yamagishi, T.; Ogawa, S.; *J. Chem. Soc., Perkin Trans. I*, 1994, 589.

15. Ando, O.; Nakajima, M.; Hamano, K.; Itoi, K.; Takahashi, S.; Takamatsu, Y.; Sato, A.; Enokita, R.; Okazaki, T.; Haruyama, H.; Kinoshita, T.; *J. Antibiot.*, 1993, **46**, 1116.

16. Aoyagi, T.; Yamamoto, T.; Kojiri, K.; Morishima, H.; Nagai, M.; Hamada, M.; Takeuchi, T.; Umezawa, H.; *J. Antibiot.*, 1989, **42**, 883, and references cited therein.

17. Morishima, H.; Kojiri, K.; Yamamoto, T.; Aoyagi, T.; Nakamura, H.; Iitaka, Y.; *J. Antibiot.*, 1989, **42**, 1008.

18. Tropea, J.E.; Kaushal, G.P.; Pastuszak, I.; Mitchell, M.; Aoyagi, T.; Molyneux, R.; Elbein, A.D.; *Biochemistry*, 1990, **29**, 10062.

19. Farr, R.A.; Peet, N.P.; Kang, M.S.; *Tetrahedron Lett.*, 1990, **31**, 7109.

20. (a) For a review of the biological properties of early racemic aristeromycin analogues: Marquez, V.E.; Lim, M-I.; *Med. Res. Rev.*, 1986, **6**, 1; (b) For a review of the syntheses of carbocyclic nucleoside analogues: Borthwick, A.D.; Biggadike, K.; *Tetrahedron*, 1992, **48**, 571.

21. Winkler, D.A.; Holan, G.; *J. Med. Chem.*, 1989, **32**, 2084, and references cited therein.

22. Borchardt, R.T.; Keller, B.T.; Patel-Thombre, U.; *J. Biol. Chem.*, 1984, **259**, 4353, and references cited therein.

23. Cabib, E.; Sburlati, A.; Bowers, B.; Silverman, S.J.; *J. Cell. Biol.*, 1989, **108**, 1665.

24. Sakuda, S.; Nishimoto, Y.; Ohi, M.; Watanabe, M.; Takayama, S.; Isogai, A.; Yamada, Y.; *Agric. Biol. Chem.*, 1990, **54**, 1333.

25. (a) Murao, S.; Miyata, S.; *Agric. Biol. Chem.*, 1980, **44**, 219; (b) Yamada, Y.; Asano, N.; Yamaguchi, T.; Matsui, K.; *J. Antibiot.*, 1987, **40**, 563.

26. Arita, M.; Adachi, K.; Ito, Y.; Sawai, H.; Ohno, M.; *J. Am. Chem. Soc.*, 1983, **105**, 4049.

27. (a) Arai, Y.; Hayashi, K.; Koizumi, T.; *Tetrahedron Lett.*, 1988, **29**, 6143; (b) Arai, Hayashi, Y.; Yamamoto, M.; Takayama, H.; Koizumi, T.; *J. Chem. Soc., Perkin Trans. I*, 1988, 3133.

28. Montgomery, J.A.; Temple, C.; *J. Am. Chem. Soc.*, 1957, **79**, 5238.

29. Trost, B.M.; Van Vranken, D.L.; *J. Am. Chem. Soc.*, (a) 1990, **112**, 1261; (b) 1993, **115**, 444.

30. Martin, J.C.; Madhavan, G.V.; *J. Org. Chem.*, 1986, **51**, 1287.

31. Maloisel, J.L.; Vasella, A.; Trost, B.M.; Van Vranken, D.L; (a) *J. Chem. Soc. Chem. Commun.*, 1991, 1099; (b) *Helv. Chim. Acta*, 1992, **75**, 1515.

32. Trost, B.M.; Van Vranken, D.L.; *J. Am. Chem. Soc.*, 1991, **113**, 6317.

33. Trost, B.M.; Van Vranken, D.L.; *Angew. Chem., Int. Ed. Engl.*, 1992, **31**, 228.

34. Ganem, B.; King, S.B.; *J. Am. Chem. Soc.*, 1994, **116**, 562.

35. Ferrier, R.J.; Middleton, S.; *Chem. Rev.*, 1993, **93**, 2779.

36. (a) Vite, G.D.; Alonso, R.; Fraser-Reid, B.; *J. Org. Chem.*, 1989, **54**, 2268; (b) Alonso, R.A.; Vite, G.D.; McDevitt, R.E.; Fraser-Reid, B.; *J. Org. Chem.*, 1992, **57**, 573.

37. Bélanger, P.; Prasit, P.; *Tetrahedron Lett.*, 1988, **29**, 5521.

38. Borcherding, D.R.; Scholtz, S.A.; Borchardt, R.T.; *J. Org. Chem.*, 1987, **52**, 5457.

39. Bernet, B.; Vasella, A.; *Helv. Chim. Acta*, 1979, **62**, (a) 1990; (b) 2400; (c) 2411.

40. Magnus, P.; Becker, D.P.; *J. Am. Chem. Soc.*, 1987, **109**, 7495.

41. Parry, R.J.; Bornemann, V.; Subramanian, R.; *J. Am. Chem. Soc.*, 1989, **111**, 5819.

42. Yaginuma, S.; Muto, N.; Tsujino, M.; Sudata, Y.; Hayashi, M.; Otani, M.; *J. Antibiot.*, 1981, **34**, 359.

43. (a) Roberts, S.M.; Thorpe, A.J.; Turner, N.J.; Blows, W.M.; Buss, A.D.; Dawson, M.J.; Noble, D.; Rudd, B.A.M.; Sidebottom, P.J.; Wall, W.F.; *Tetrahedron Lett.*, 1993, **34**, 4083; (b) Parry, R.J.; Jiang, Y.; *Tetrahedron Lett.*, 1994, **35**, 9665.

44. Zhou, Z-Y.; Sakuda, S.; Yamada, Y.; *J. Chem. Soc., Perkin Trans. I*, 1992, 1649.

45. Wolfe, M.S.; Anderson, B.L.; Borcherding, D.R.; Borchardt, R.T.; *J. Org. Chem.*, 1990, **55**, 4712.

46. (a) Angyal, S.J.; Gero, S.D.; *Aust. J. Chem.*, 1965, **18**, 1973; (b) Ashluwalia, R.; Angyal, S.J.; Luttrell, B.M.; *Aust. J. Chem.*, 1970, **23**, 1819.

47. Angyal, S.J.; Tate, M.E.; Gero, S.D.; *J. Chem. Soc.*, 1961, 4116.

48. Ferrier, R.J.; Prasit, P.; *Pure Appl. Chem.*, 1983, **55**, 565.

49. Ferrier, R.J.; Haines, S.R.; *J. Chem. Soc., Perkin Trans. I*, 1984, 1689.

50. Baldwin, J.E.; Lusch, M.J.; *Tetrahedron*, 1982, **38**, 2939.

51. Elliott, R.P. 'Sugars as Homochiral Starting Materials', D.Phil. Thesis, Oxford University, 1992, Chapter 2.

52. Elliott, R.P.; Fleet, G.W.J.; Gyoung, Y.S.; Ramsden, N.G.; Smith, C.; *Tetrahedron Lett.*, 1990, **31**, 3785.

53. Elliott, R.P.; Fleet, G.W.J.; Pearce, L.; Smith, C.; Watkin, D.J.; *Tetrahedron Lett.*, 1991, **43**, 6227.

54. Bruce, I.; Fleet, G.W.J.; Girdhar, A.; Haraldsson, M.; Peach, J.M.; Watkin, D.J.; *Tetrahedron*, 1990, **46**, 19.

55. Elliott, R.P.; Hui, A.; Fairbanks, A.J.; Nash, R.J.; Winchester, B.G.; Way, G.; Smith, C.; Lamont, R.B.; Storer, R.; Fleet, G.W.J.; *Tetrahedron Lett.*, 1993, **34**, 7949.

56. Fairbanks, A.J.; Elliott, R.P.; Smith, C.; Hui, A.; Way, G.; Storer, R.; Taylor, H.; Watkin, D.J.; Winchester, B.G.; Fleet, G.W.J.; *Tetrahedron Lett.*, 1993, **34**, 7953.

57. Elliott, R.P. 'Sugars as Homochiral Starting Materials', D.Phil. Thesis, Oxford University, 1992, Chapter 4.

58. Fairbanks, A.J. 'Sugar Lactones in Synthesis', D.Phil. Thesis, Oxford University, 1993, Chapter 4.

59. (a) Beacham, A.R.; Part II Thesis, Oxford University, 1991; (b) Hsia, K.Y.; Part II Thesis, Oxford University, 1991; Burrows, J.N.; Part II Thesis, Oxford University, 1993.

CHAPTER 2

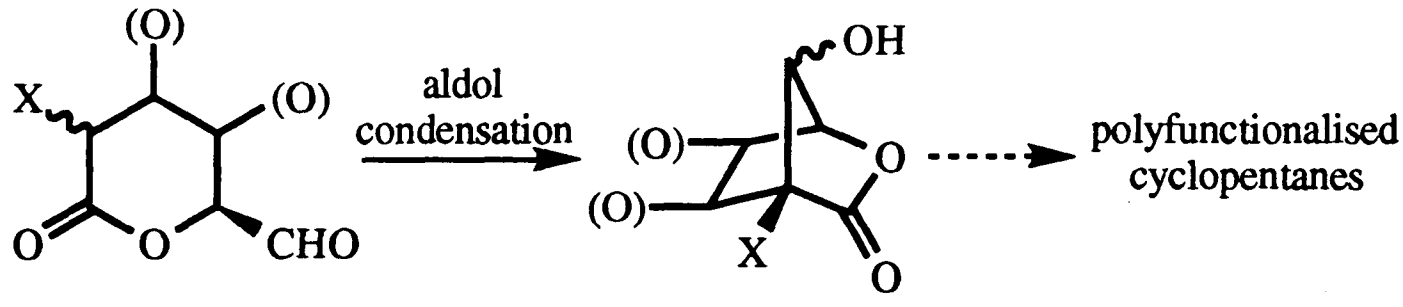
Syntheses of Polyfunctionalised Cyclopentanes

Sugar Lactones as Chirons.

One-carbon extensions of certain protected hexose sugars have been achieved *via* the Kiliani reaction[1] to give heptonolactones. These higher sugars are difficult to obtain by other means. In particular, 4-hydroxy-1,5-lactones, which are prone to isomerise to the thermodynamically more stable 1,4-lactones,[2] can be derived from the Kiliani ascension of C-3 protected hexose precursors. This approach has been used in the preparation of a number of heptono-1,5-lactones.[3] These materials contain seven adjacent functional groups and five contiguous chiral centres. Therefore they have constituted a set of versatile homochiral intermediates for the synthesis of a variety of highly functionalised, biologically interesting compounds.[4]

General Retrosynthetic Analysis.

The aim of this project was to synthesise polyfunctionalised cyclopentanes from sugar lactone precursors. The reaction central to this work was an intramolecular aldol cyclisation of a 5-formyl-1,5-lactone (**Scheme 2.1**).[5]

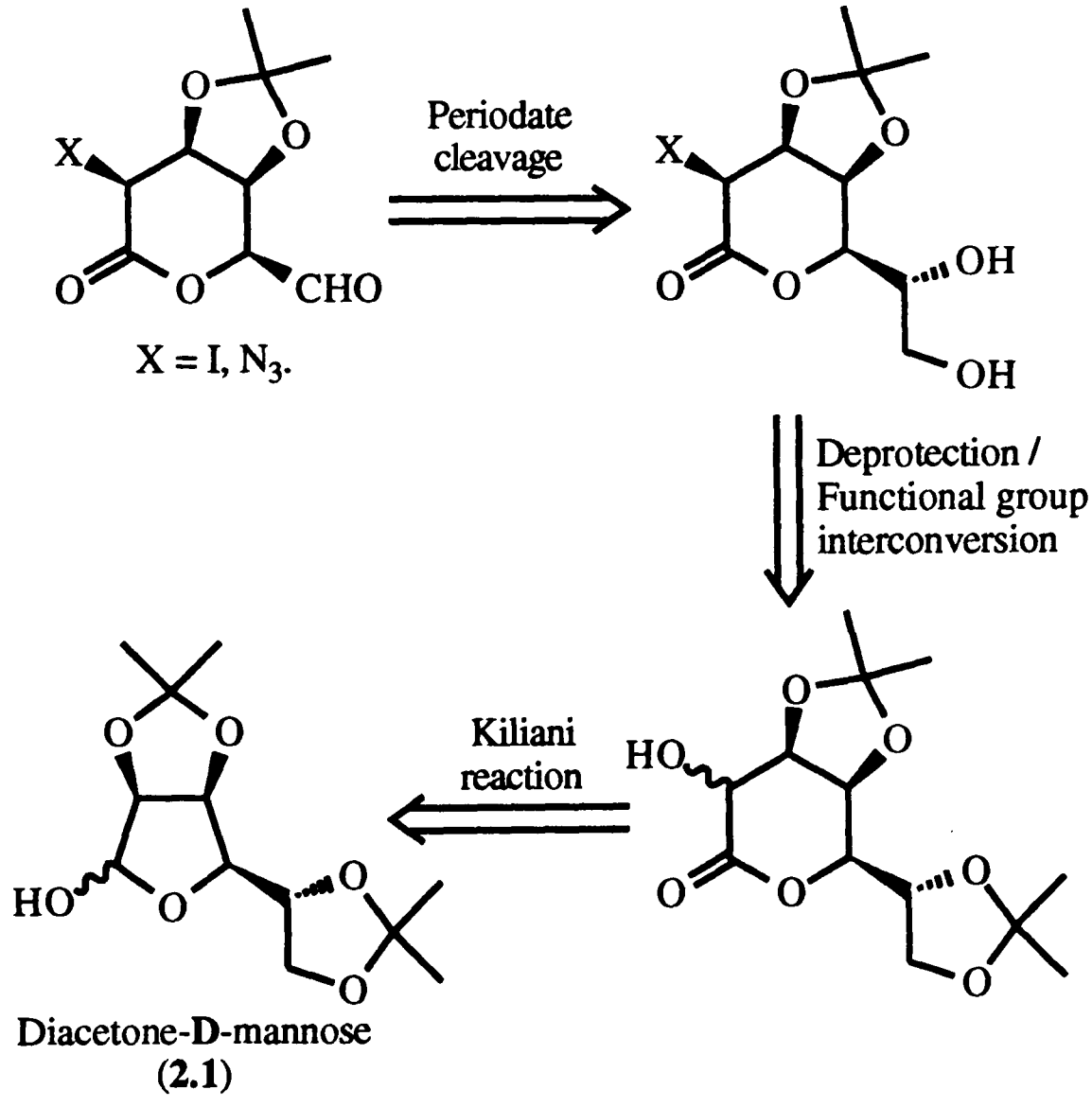


Scheme 2.1

Proton removal α to the lactone carbonyl would generate the required carbanion for aldol condensation. It was envisaged that the stability of such an α-carbanion would

be enhanced by the presence of an electron-withdrawing substituent at the C-2 position of the lactone. Previous work in this area has focused on the cyclisations of α-iodo and α-azido δ-lactones where the *cis*-3,4-diol has been protected as an acetonide.[6]

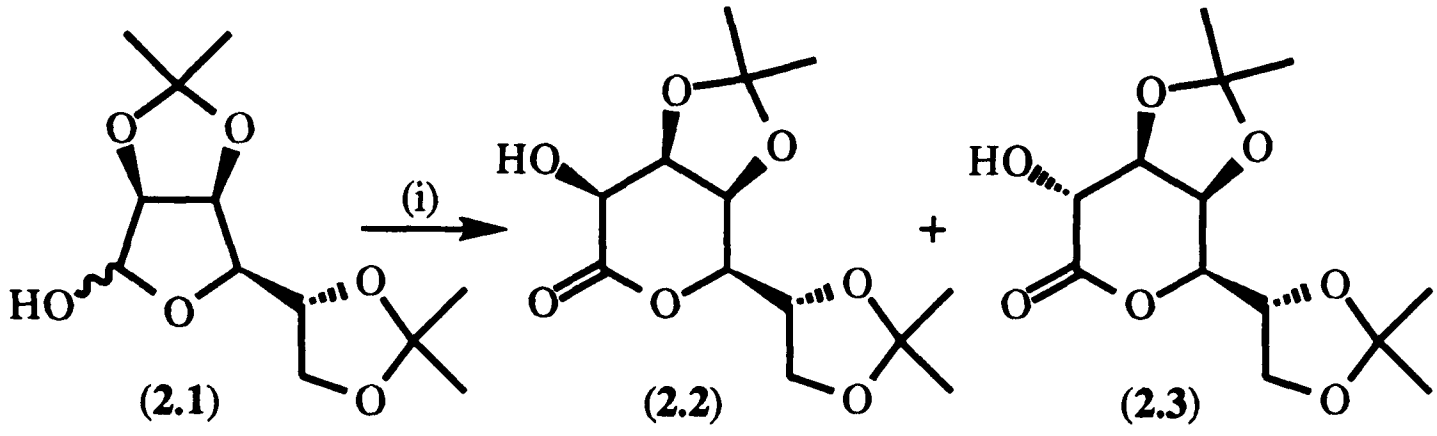
A retrosynthetic analysis of a generalised C-2 substituted 5-formyl-lactone is shown in **Scheme 2.2**. The aldehyde functionality may be derived from the periodate cleavage of an exposed terminal diol unit of a seven-carbon sugar lactone. Substitution at C-2 may be achieved, in turn, by initial conversion of a hydroxyl group into a leaving group, followed by nucleophilic displacement. The Kiliani ascension of a protected hexose, in this case diacetone-**D**-mannose (**2.1**), would provide the desired hydroxy-lactone intermediates.



Scheme 2.2

Previous Syntheses of α-Iodo and α-Azido Heptonolactones.

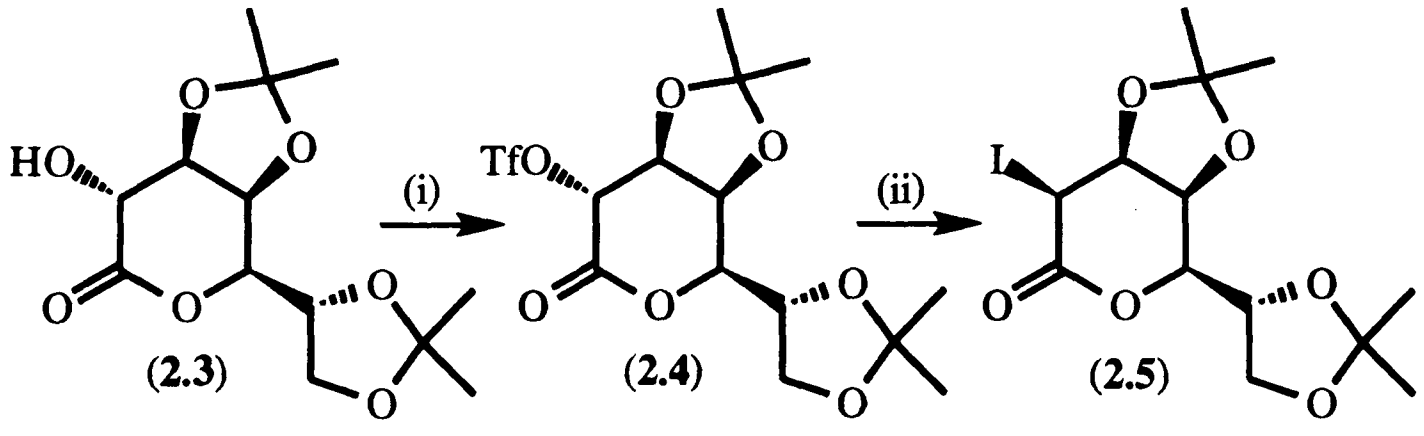
Treatment of diacetone-**D**-mannose (**2.1**) with aqueous sodium cyanide, followed by acidic work-up, gave the readily separable mixture of epimeric δ-lactones, (**2.2**) and (**2.3**), in moderate yields (**Scheme 2.3**).[3a] This reaction has been carried out on a multikilogram scale.



(i) NaCN, H_2O, then H_3O^+.

Scheme 2.3

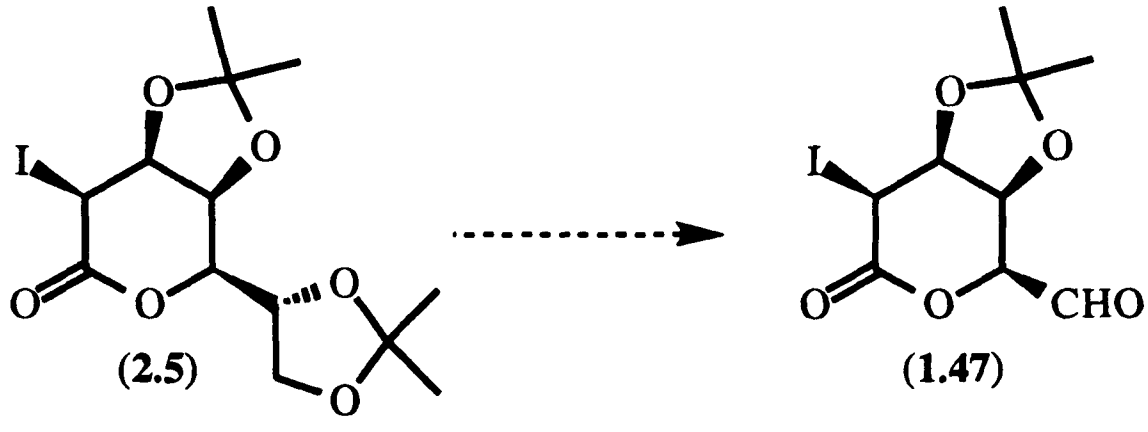
Possessing only acetonide protecting groups, the δ-lactones (**2.2**) and (**2.3**) allowed immediate access to a single hydroxyl group at C-2. Introduction of iodine at this position has been achieved *via* initial conversion of the minor lactone product (**2.3**) to its triflate (**2.4**). Subsequent nucleophilic displacement with tetra-*n*-butylammonium iodide produced the α-iodo-δ-lactone (**2.5**) (**Scheme 2.4**).[7]



(i) Tf_2O, Py, CH_2Cl_2, -30 to -20 °C, 2 h, 84%;
(ii) tetra-*n*-butylammonium iodide, THF, RT, 3 h, 88%.

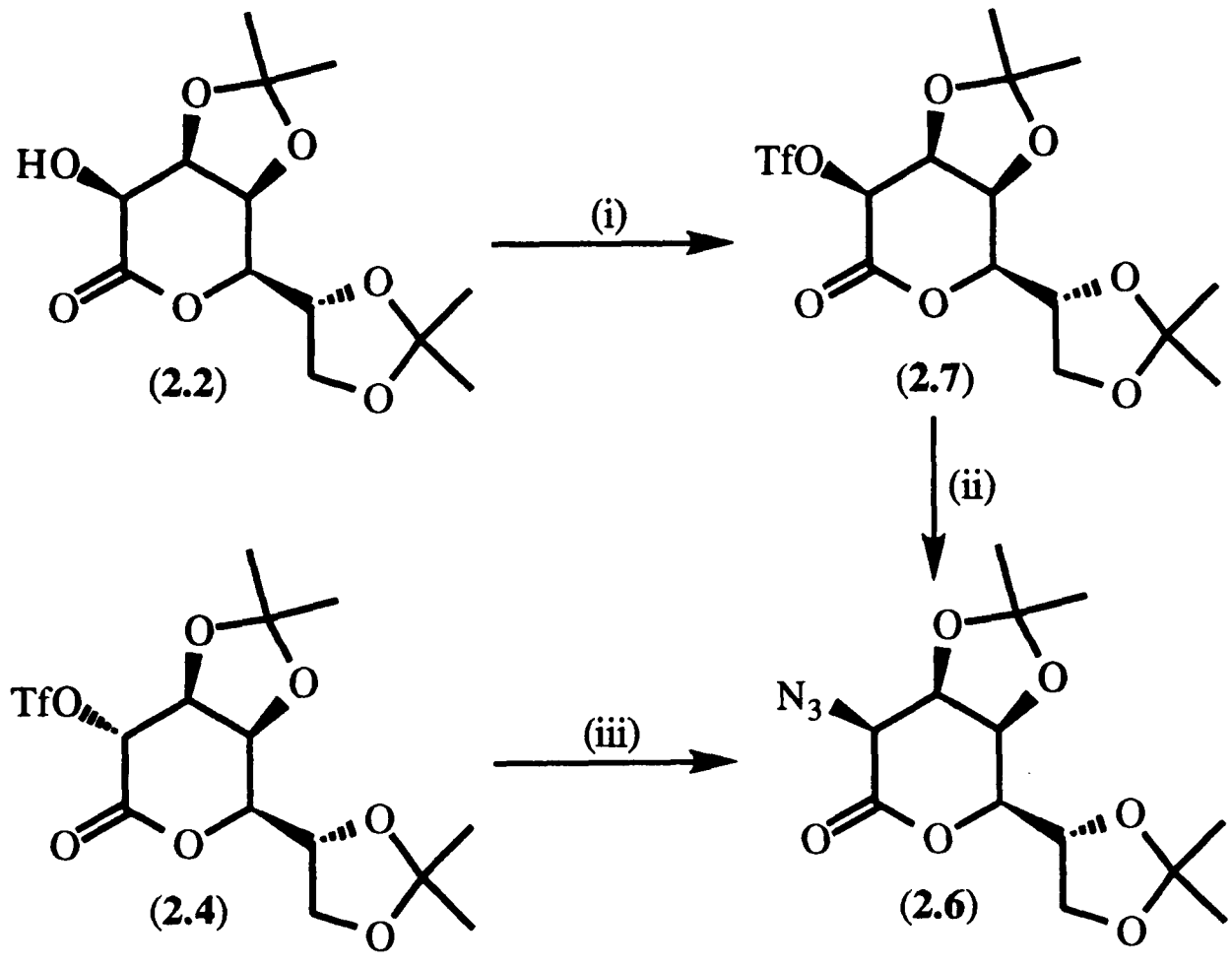
Scheme 2.4

Further elaboration would involve deprotection and periodate oxidation to give the iodo aldehyde (**1.47**) as the intramolecular aldol condensation precursor (**Scheme 2.5**).



Scheme 2.5

The α-azido-δ-lactone (**2.6**) has been prepared from both of the triflate esters, (**2.4**) and (**2.7**) (**Scheme 2.6**).[8] These, in turn, were derived from the products of the Kiliani reaction of diacetone-**D**-mannose (**2.3**) and (**2.2**) respectively.

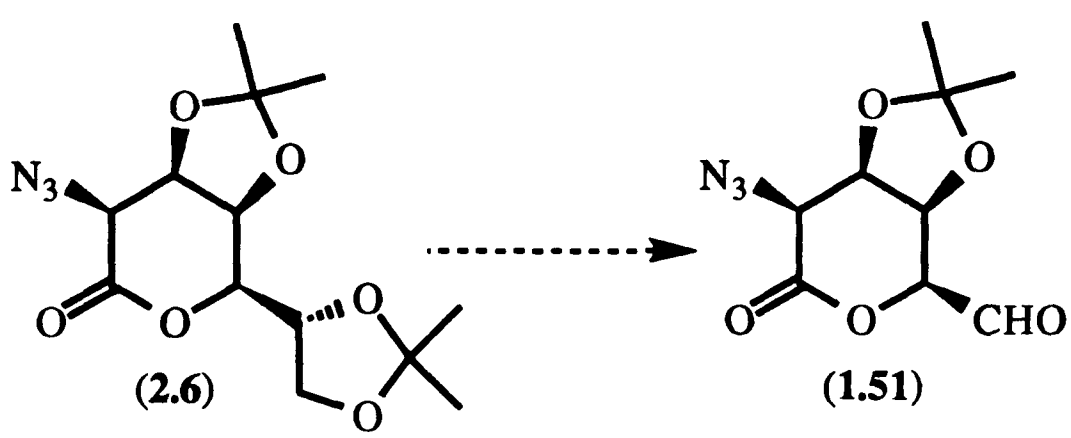


(i) Tf_2O, Py, CH_2Cl_2, -30 °C, 10 min, 93%;
(ii) NaN_3, DMF, RT, 4 h, 81%;
(iii) NaN_3, DMF, RT, 4 h, 82%.

Scheme 2.6

Sodium azide acted as a base, as well as a nucleophile, during the course of these reactions. Reversible deprotonation α to the lactone carbonyl occurred under conditions of thermodynamic control to produce exclusively the azido lactone (**2.6**). The efficiency of these reactions suggested that the carbanion intermediate did not undergo significant fragmentation of the β-oxygen substituent.

Conversion of the azido lactone (**2.6**) to the azido aldehyde (**1.51**) could again be achieved *via* a series of deprotection and oxidation reactions, analogous to the preparation of its α-iodo lactone analogue (**Scheme 2.7**).



Scheme 2.7

This chapter details the preparations of the α-iodo aldehyde (**1.47**) and the α-azido aldehyde (**1.51**), their intramolecular aldol cyclisations, and the subsequent syntheses of a number of polyfunctionalised cyclopentanes.

Results and Discussion.

The work can be divided into four sections:-

2.1 Preparation of the α-iodo aldehyde (**1.47**) and subsequent syntheses of polyfunctionalised cyclopentanes;

2.2 Preparation of the α-azido aldehyde (**1.51**) and subsequent syntheses of polyfunctionalised cyclopentanes;

2.3 Syntheses of tetrahydroxy-cyclopentane α-amino acids;

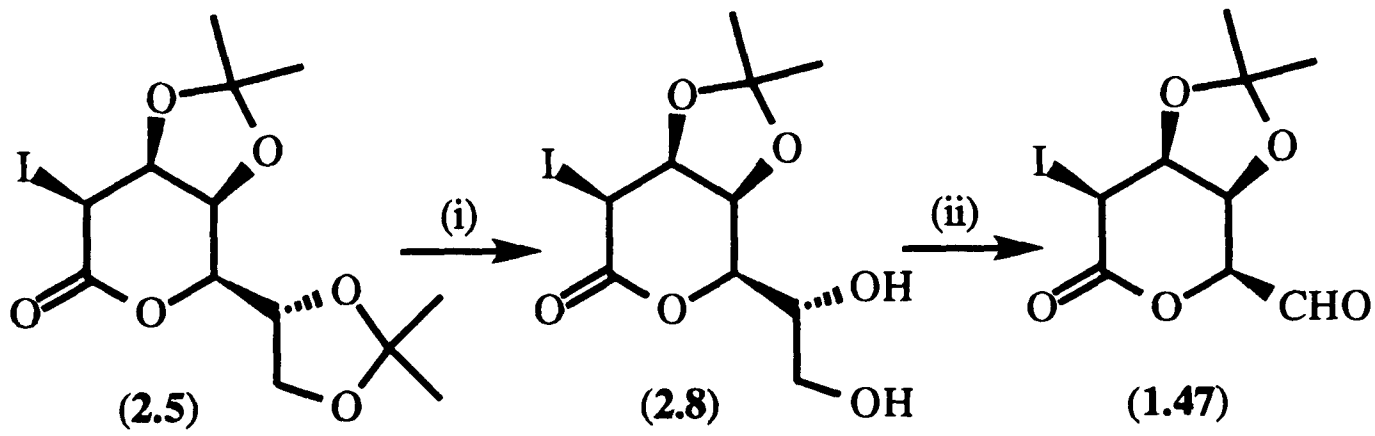
2.4 Incorporation of a tetrahydroxy-cyclopentane α-amino acid into peptides.

Each of these areas will now be discussed in turn.

2.1 Preparation of the α-Iodo Aldehyde (1.47) and Subsequent Syntheses of Polyfunctionalised Cyclopentanes.

The preparation of the α-iodo aldehyde (**1.47**) was carried out in accordance with the literature procedure, starting with the α-iodo-δ-lactone (**2.5**).[6a] This material is readily available from the minor product of the Kiliani reaction of diacetone-**D**-mannose (**2.3**) in two steps.[7]

Treatment of the iodolactone (**2.5**) with 80% aqueous acetic acid effected the selective removal of the primary ketal protecting group to give the iodo diol (**2.8**). Periodate cleavage of the diol moiety then produced the iodo aldehyde (**1.47**) in 97% yield (**Scheme 2.8**).

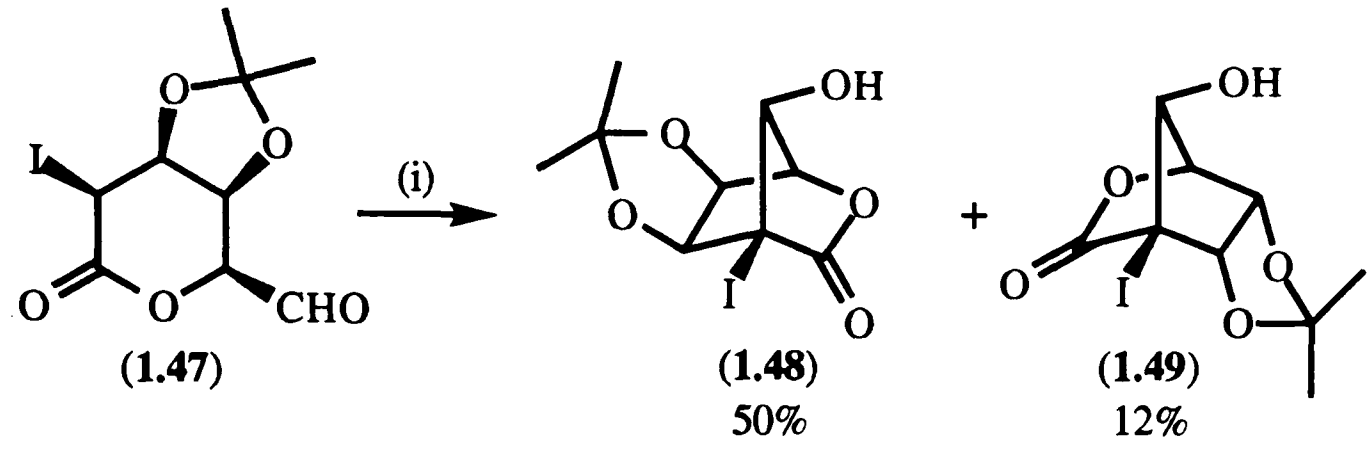


(i) 80% aqueous AcOH, 50 °C, 3 h, 88%;
(ii) H_5IO_6, THF, RT, 25 min, 97%.

Scheme 2.8

Base-induced aldol cyclisation was achieved by treatment of the iodo aldehyde (**1.47**) with potassium fluoride and 18-crown-6 in acetonitrile.[6a,9] This gave a mixture of

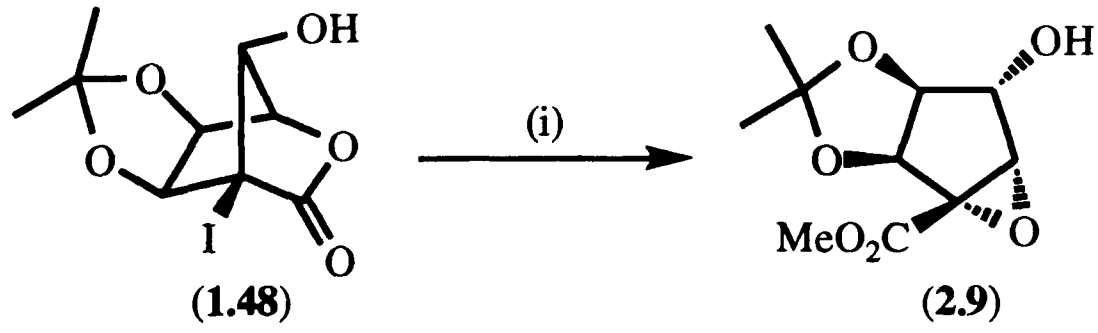
two bicyclic lactones (**1.48**) and (**1.49**), in 50% and 12% yields respectively (**Scheme 2.9**).



(i) KF, 18-crown-6, MeCN, 0 °C, 1 h.

Scheme 2.9

The major cyclisation product (**1.48**) was further elaborated to allow the introduction of nitrogen to the cyclopentane ring.[9,10] Firstly, base-catalysed methanolysis of the lactone ring, in the presence of one molar equivalent of potassium carbonate, resulted in the concomitant intramolecular displacement of iodide to afford the epoxide (**2.9**) in good yield (**Scheme 2.10**). Isolation of the intermediate iodide could be achieved under conditions of kinetic control with catalytic amounts of base.[9,10]

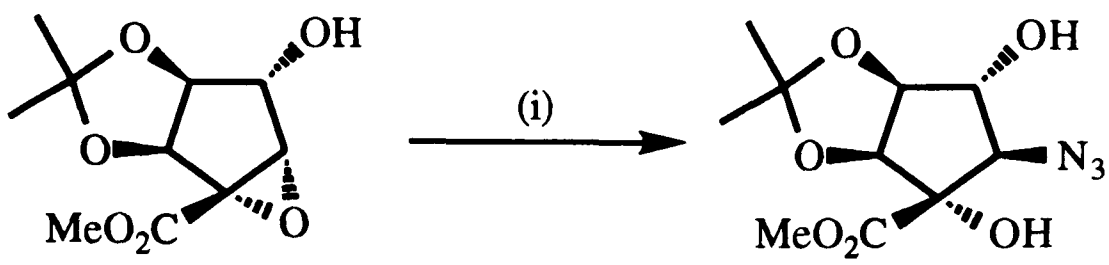


(i) K_2CO_3, MeOH, 0 °C - RT, 2 h, 93%.

Scheme 2.10

Treatment of the epoxide (**2.9**) with sodium azide in aqueous methanol then yielded the azido carbocycle (**2.10**) as the sole ring opened product (**Scheme 2.11**). The observed regioselectivity may be due to the difference in steric demand of the two

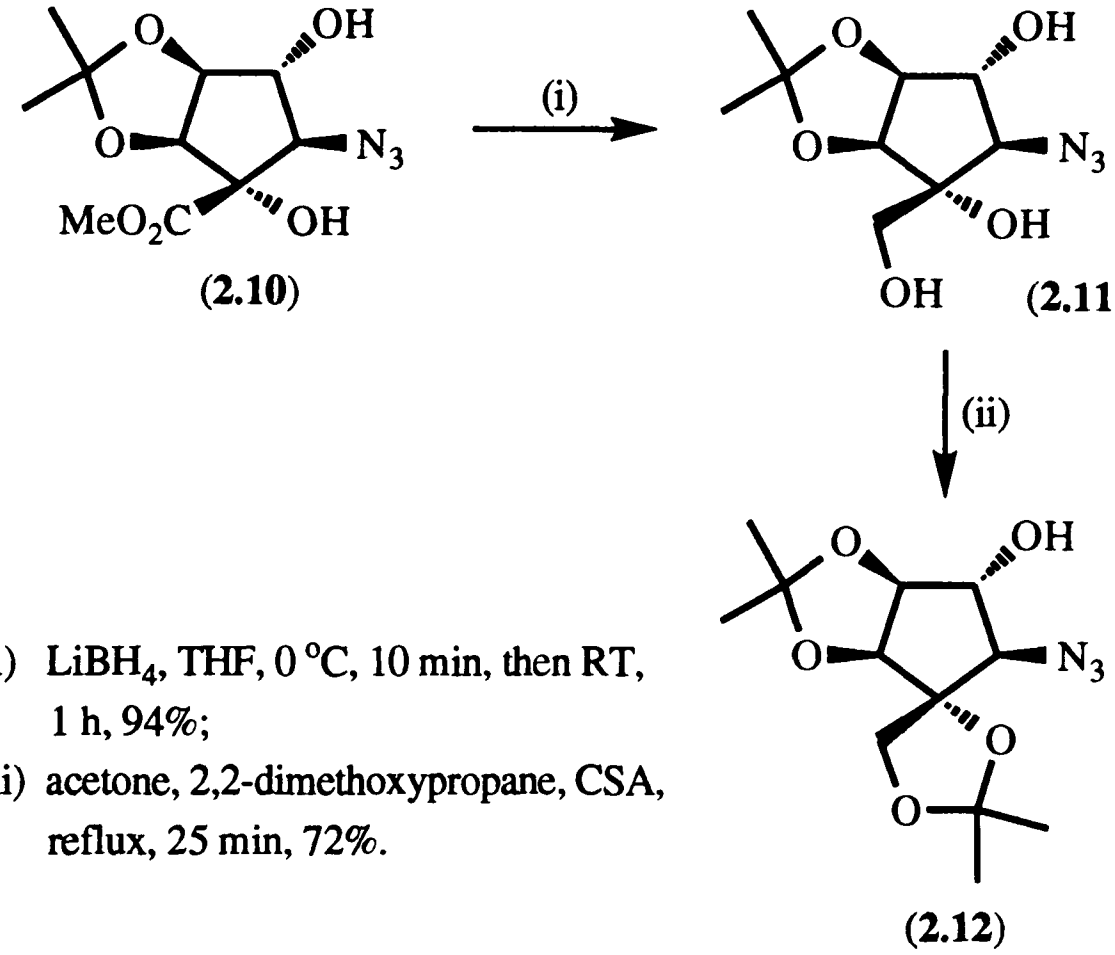
possible nucleophilic approaches. The structure of the azide (**2.10**) was confirmed by X-ray crystallographic analysis.[10]



(i) NaN_3, NH_4Cl, 80% aqueous MeOH, reflux, 18 h, 87%.

Scheme 2.11

Reduction of the methyl ester function of (**2.10**) was carried out with lithium borohydride in tetrahydrofuran to produce the azido triol (**2.11**) which was fully characterised as the diacetonide (**2.12**) (**Scheme 2.12**).

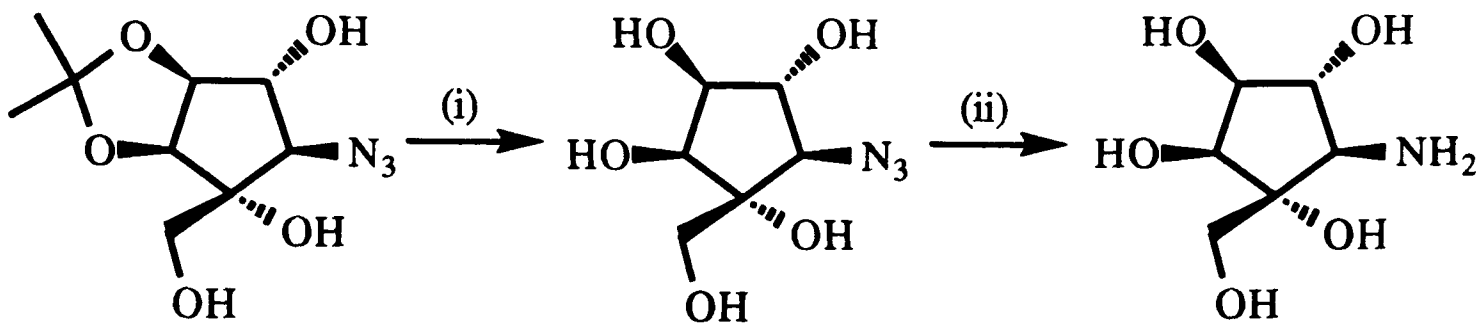


(i) $LiBH_4$, THF, 0 °C, 10 min, then RT, 1 h, 94%;
(ii) acetone, 2,2-dimethoxypropane, CSA, reflux, 25 min, 72%.

Scheme 2.12

Treatment of (**2.11**) with 40% aqueous trifluoroacetic acid effected deprotection to give the pentahydroxyazide (**2.13**) in 80% yield. Catalytic hydrogenation of the azide

functionality in the presence of palladium black afforded the amine (**2.14**) in quantitative yield (**Scheme 2.13**).

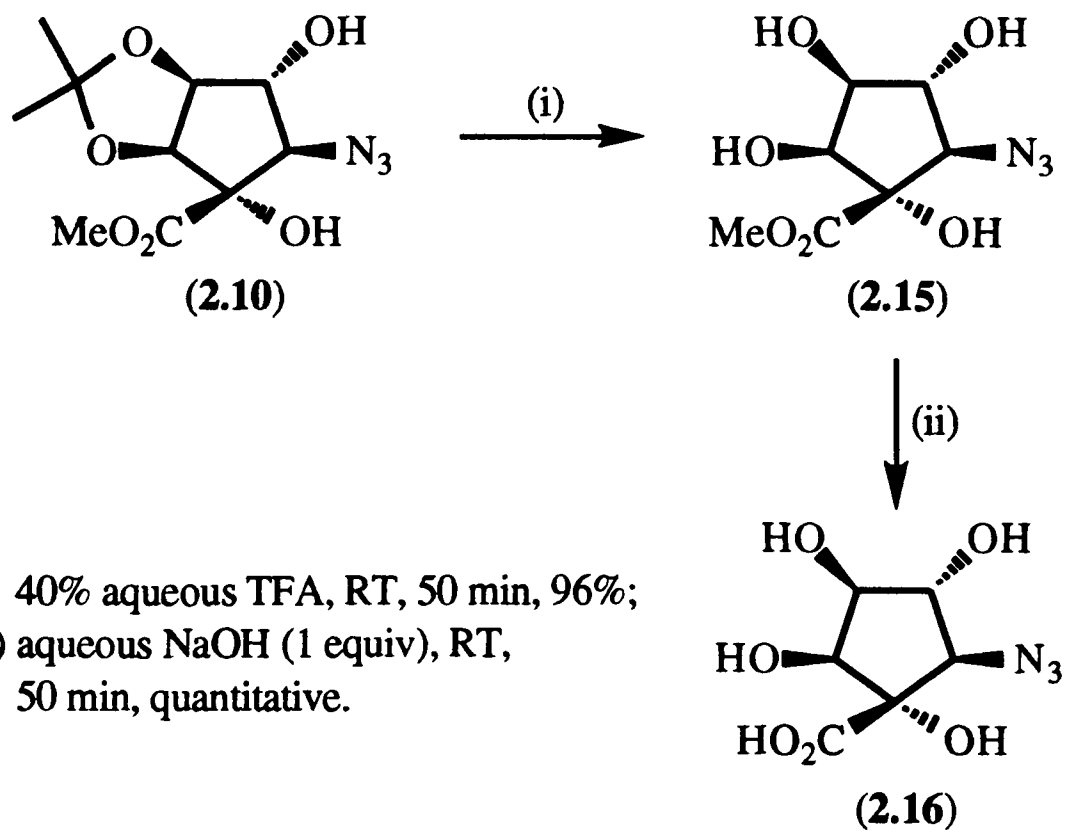


(2.11) **(2.13)** **(2.14)**

(i) 40% aqueous TFA, RT, 20 min 80%;
(ii) H_2, Pd black, water, RT, 7 h, quantitative.

Scheme 2.13

The azido ester (**2.10**) was also converted to the corresponding β-amino acid. Thus acid-catalysed hydrolysis of the ketal protecting group was achieved by treatment of the azido ester (**2.10**) with 40% aqueous trifluoroacetic acid to give the azido tetrol (**2.15**) in 96% yield. Exposure of this material to aqueous sodium hydroxide gave the corresponding β-azido carboxylate (**2.16**) upon purification by ion exchange chromatography (**Scheme 2.14**).

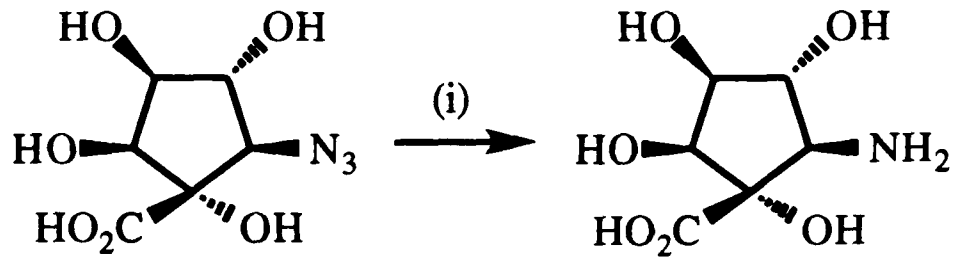


(2.10) **(2.15)** **(2.16)**

(i) 40% aqueous TFA, RT, 50 min, 96%;
(ii) aqueous NaOH (1 equiv), RT, 50 min, quantitative.

Scheme 2.14

Reduction of the azide function was accomplished by hydrogenation in the presence of palladium black to produce the β-amino acid (**2.17**) (**Scheme 2.15**).

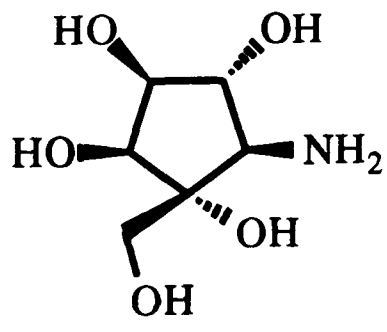


(2.16) **(2.17)**

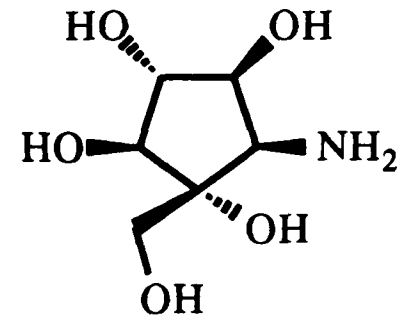
(i) H_2, Pd black, water, RT, 4 h, 98%.

Scheme 2.15

The amine (**2.14**) is a diastereomer of the degradation product of the trehalase inhibitor trehazolin (**2.18**).[11] Since some polyhydroxylated aminocyclopentanes have been shown to be potent mannosidase inhibitors,[12] the amine (**2.14**) was tested for inhibitory activity against human liver glycosidases using synthetic enzyme substrates.[13] No strong inhibition of any glycosidases was found, although (**2.14**) was a weak inhibitor of α-**L**-fucosidase (44% at 1 mM) and a weak activator of α-**D**-glucosidase (33% at 1 mM). The presence of the amine group did not lead to significant inhibition of β-hexoseaminidase (only 20% at 1 mM).[9]



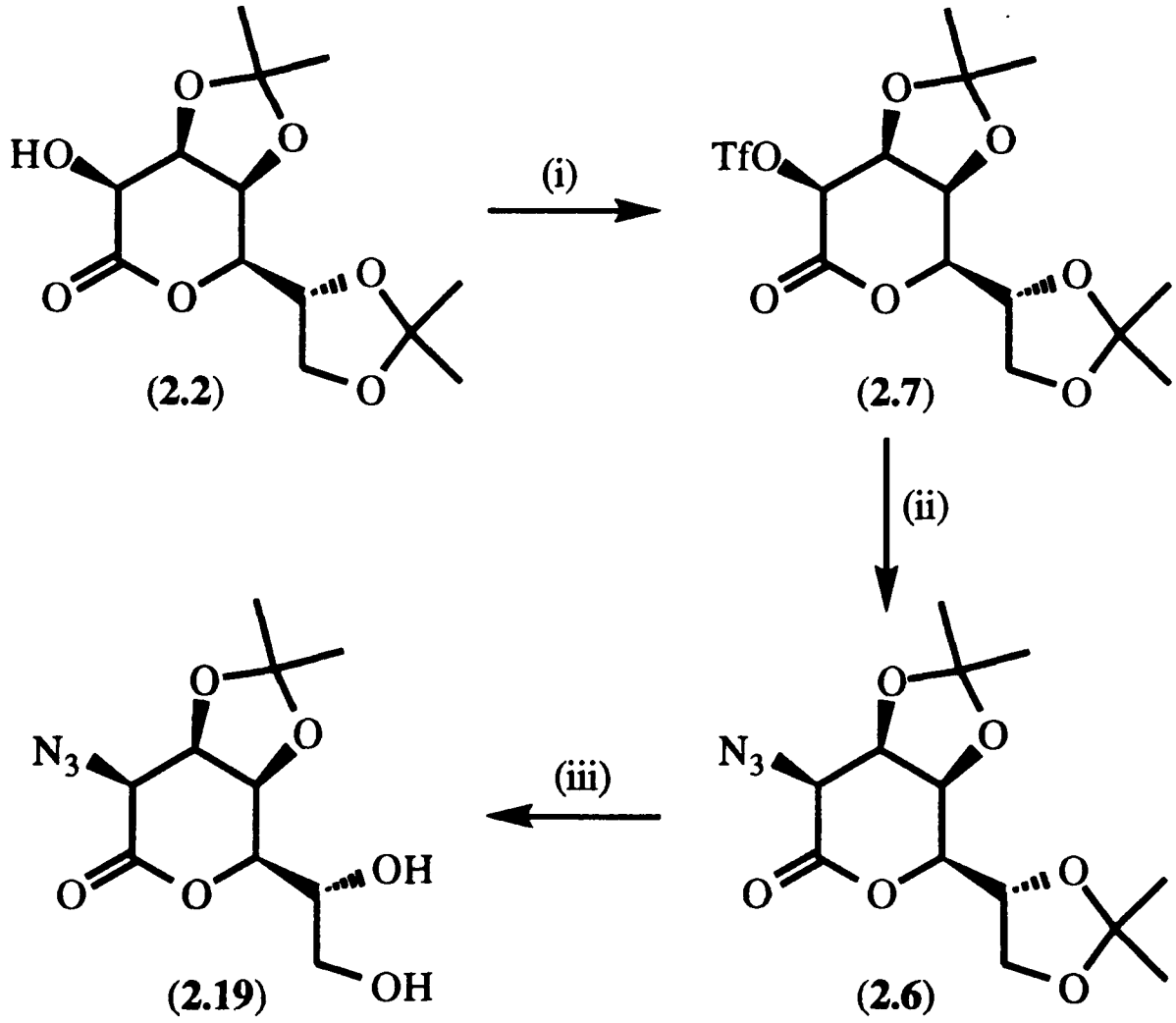
(2.14)



(2.18)

2.2 Preparation of the α-Azido Aldehyde (1.51) and Subsequent Syntheses of Polyfunctionalised Cyclopentanes.

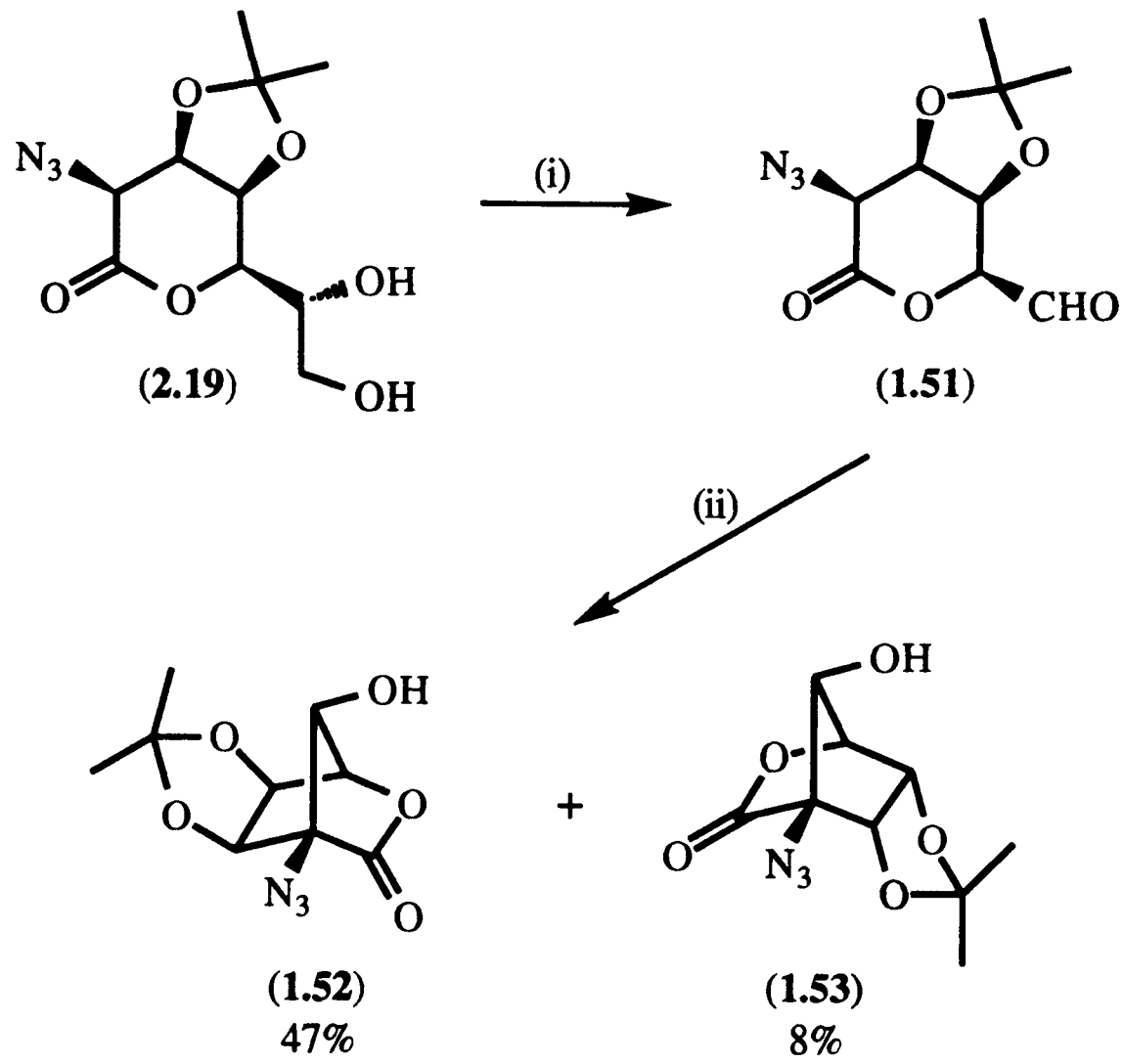
The preparation of the azido aldehyde (**1.51**) was carried out in accordance with the literature procedure.[6a,8,14] The synthesis began with the major product of the Kiliani ascension reaction of diacetone-**D**-mannose (**2.2**).[3a] Conversion of the alcohol (**2.2**) to the corresponding triflate ester was achieved by treatment with trifluoromethane-sulphonic anhydride and pyridine in dichloromethane. Reaction of the triflate (**2.7**) with sodium azide in *N,N*-dimethylformamide afforded the azido lactone (**2.6**) in 71% yield. Removal of the primary ketal protecting group was effected upon exposure of the azido lactone (**2.6**) to 80% aqueous acetic acid to give the diol (**2.19**) (**Scheme 2.16**).



(i) Tf_2O, Py, CH_2Cl_2, -30 °C to -20 °C over 2.5 h, 87%;
(ii) NaN_3, DMF, RT, 8 h, 71%;
(iii) 80% aqueous AcOH, 50 °C, 3 h, 93%.

Scheme 2.16

Periodate cleavage of the diol (**2.19**) gave the azido aldehyde (**1.51**), which was then converted to the two bicyclic lactones, (**1.52**) and (**1.53**), as described in Chapter 1 (**Scheme 2.17**).[6a,14]



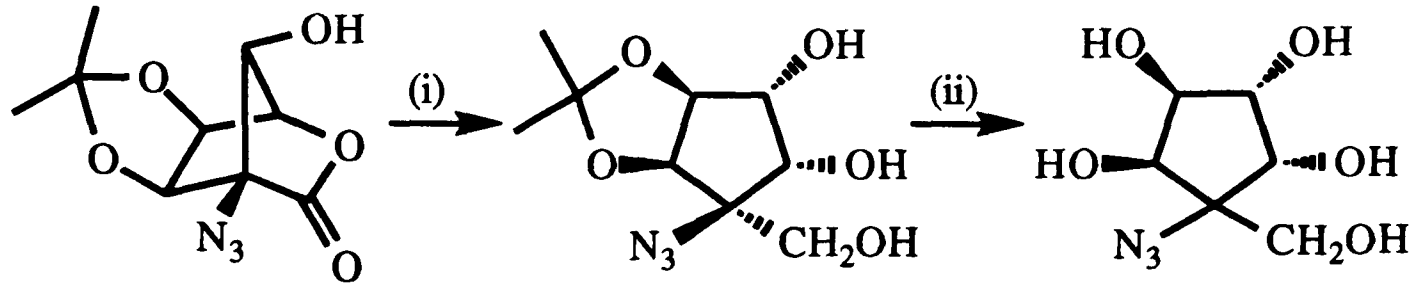
(i) H_5IO_6, THF, RT, 25 min, 92%;
(ii) KF, 18-crown-6, MeCN, 0 °C, 40 min.

Scheme 2.17

Further elaborations towards the syntheses of polyfunctionalised cyclopentanes were carried out using the major cyclisation product (**1.52**) obtained from the potassium fluoride induced aldol reaction.

Reaction of the azido lactone (**1.52**) with sodium borohydride in ethanol resulted in reductive opening of the lactone ring to give the azido triol (**2.20**). Acid-catalysed hydrolysis of the acetonide group was then achieved by treatment with 40% aqueous trifluoroacetic acid to produce the azido pentol (**2.21**) (**Scheme 2.18**). Symmetrically

protected or deprotected (2α,3α,4β,5β)-substituted cyclopentanes, such as (**2.21**), possess a pseudo C-2 rotational symmetry, which renders the C-1 atom pseudoasymmetric.

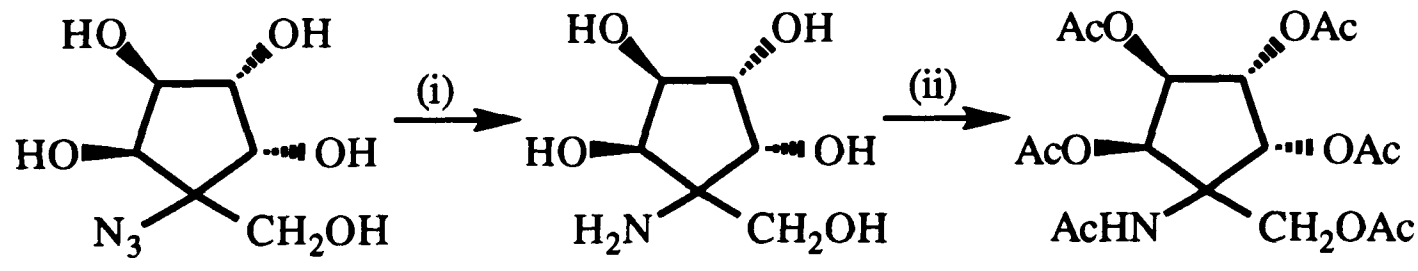


(1.52) **(2.20)** **(2.21)**

(i) $NaBH_4$, EtOH, RT, 50 min, 84%;
(ii) 40% aqueous TFA, RT, 20 min, 90%.

Scheme 2.18

Catalytic hydrogenation of the azido pentol (**2.21**) in the presence of palladium black produced the amino pentol (**2.22**) as a hygroscopic foam, which was fully characterised as its peracetate (**2.23**) (**Scheme 2.19**).

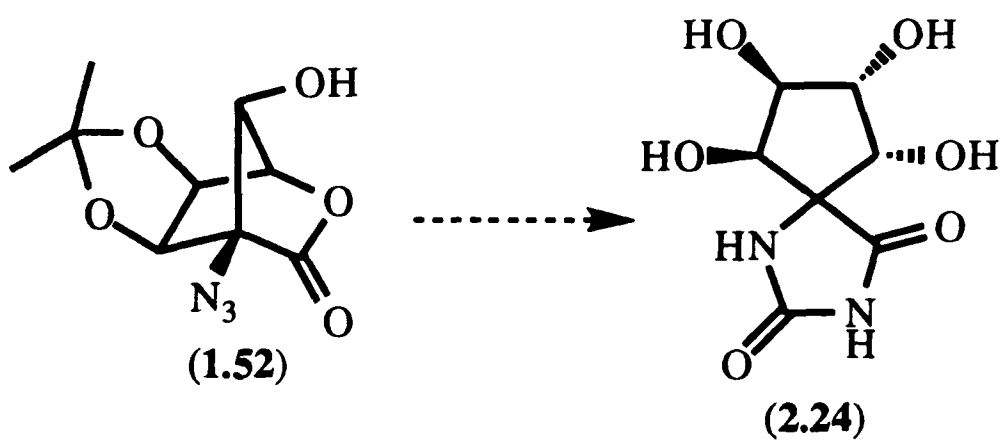


(2.21) **(2.22)** **(2.23)**

(i) H_2, Pd black, water, RT, 6 h, 99%;
(ii) Ac_2O, Py, DMAP, 0 °C, 2.5 h, 60%.

Scheme 2.19

Construction of a hydantoin ring between the nitrogen and the lactone carbonyl of the azido carbocycle (**1.52**) would provide access to a novel polyhydroxylated cyclopentane spirohydantoin (**2.24**) (**Scheme 2.20**). Two alternative synthetic strategies were investigated as detailed below.



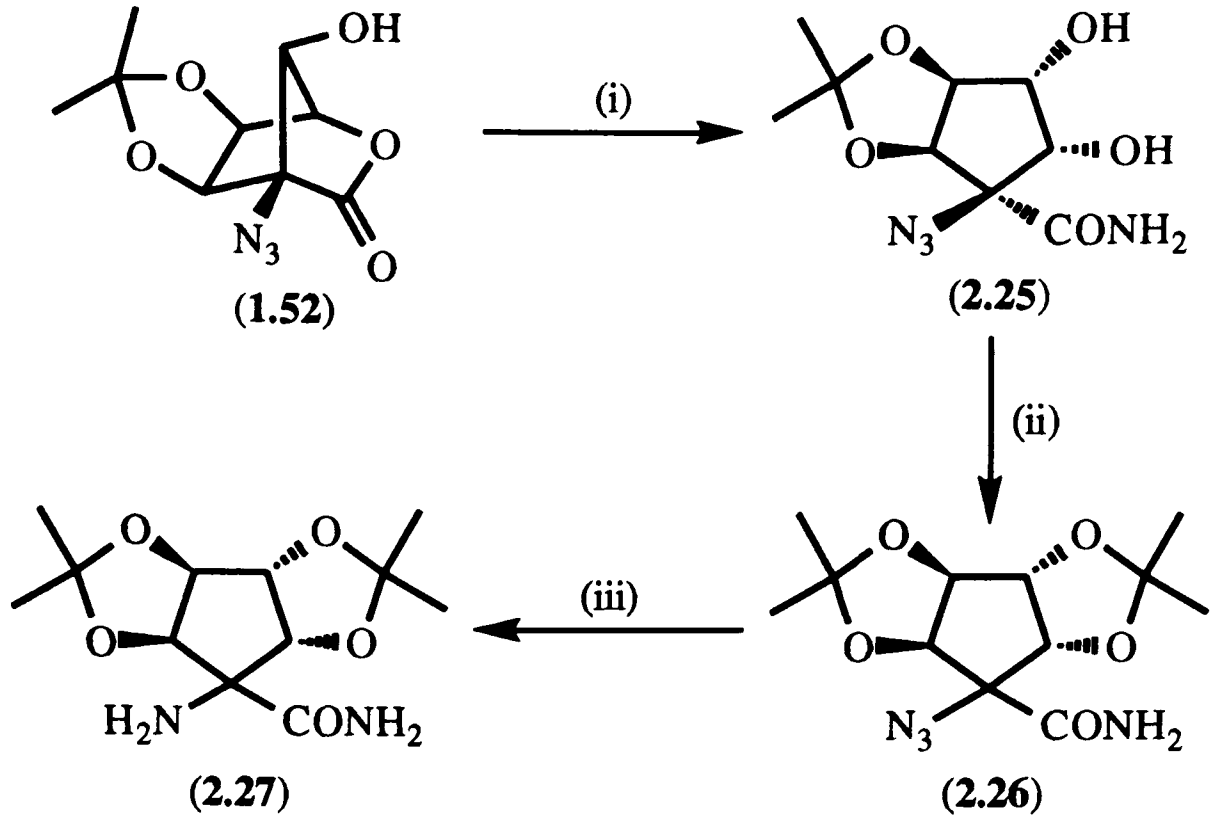
(1.52) **(2.24)**

Scheme 2.20

(i) Strategy 1

The first strategy adopted involved initial opening of the lactone ring to form an azido amide. Subsequent reduction of the azide moiety followed by reaction with a phosgene equivalent would result in the formation of a spirohydantoin ring.[10]

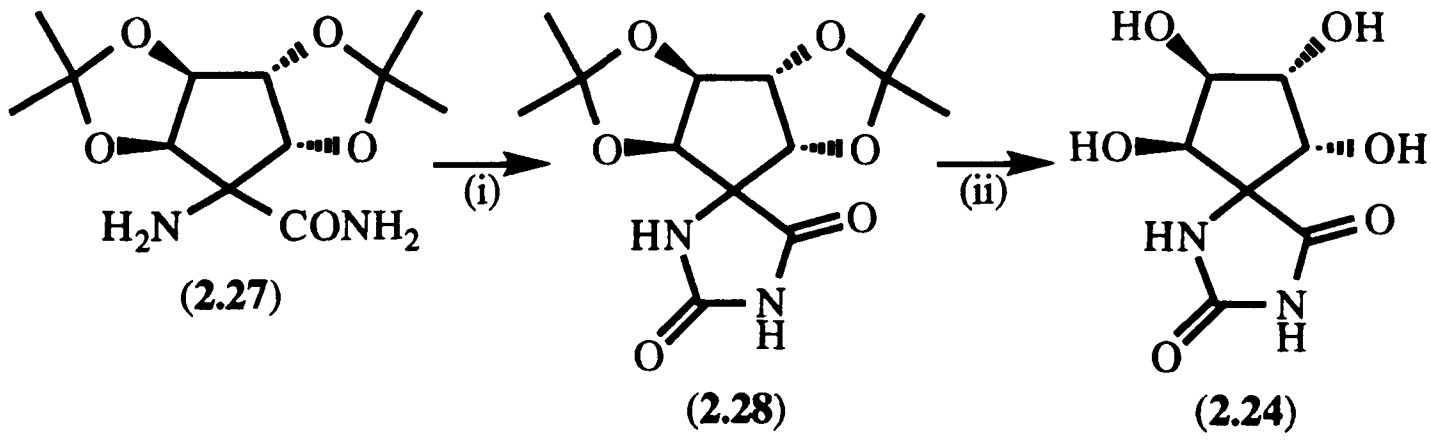
Treatment of the azido carbocycle (**1.52**) with a solution of ammonia in methanol produced the azido amide (**2.25**) in 92% yield. The resultant diol moiety was further protected by reaction with acetone and 2,2-dimethoxypropane, in the presence of (±)-10-camphorsulphonic acid, to give the diacetonide (**2.26**). Reduction of the azide functionality by hydrogenation in the presence of palladium black afforded the amino amide (**2.27**) (**Scheme 2.21**).



(i) NH_3 in MeOH, RT, 20 min, 92%;
(ii) acetone, 2,2-dimethoxypropane, CSA, reflux, 1.5 h, 71%;
(iii) H_2, Pd black, EtOH, RT, 10 h, 98%.

Scheme 2.21

Reaction of the amino amide (**2.27**) with 1,1-carbonyldiimidazole in refluxing toluene resulted in the formation of the protected spirohydantoin (**2.28**). Removal of the acetonide groups was achieved by treatment of (**2.28**) with 40% aqueous trifluoroacetic acid. The polarity of the product precluded purification by conventional chromatography; repeated recrystallisation gave the analytically pure spirohydantoin (**2.24**) in 40% yield [18% overall yield from the azido carbocycle (**1.52**)] (**Scheme 2.22**).



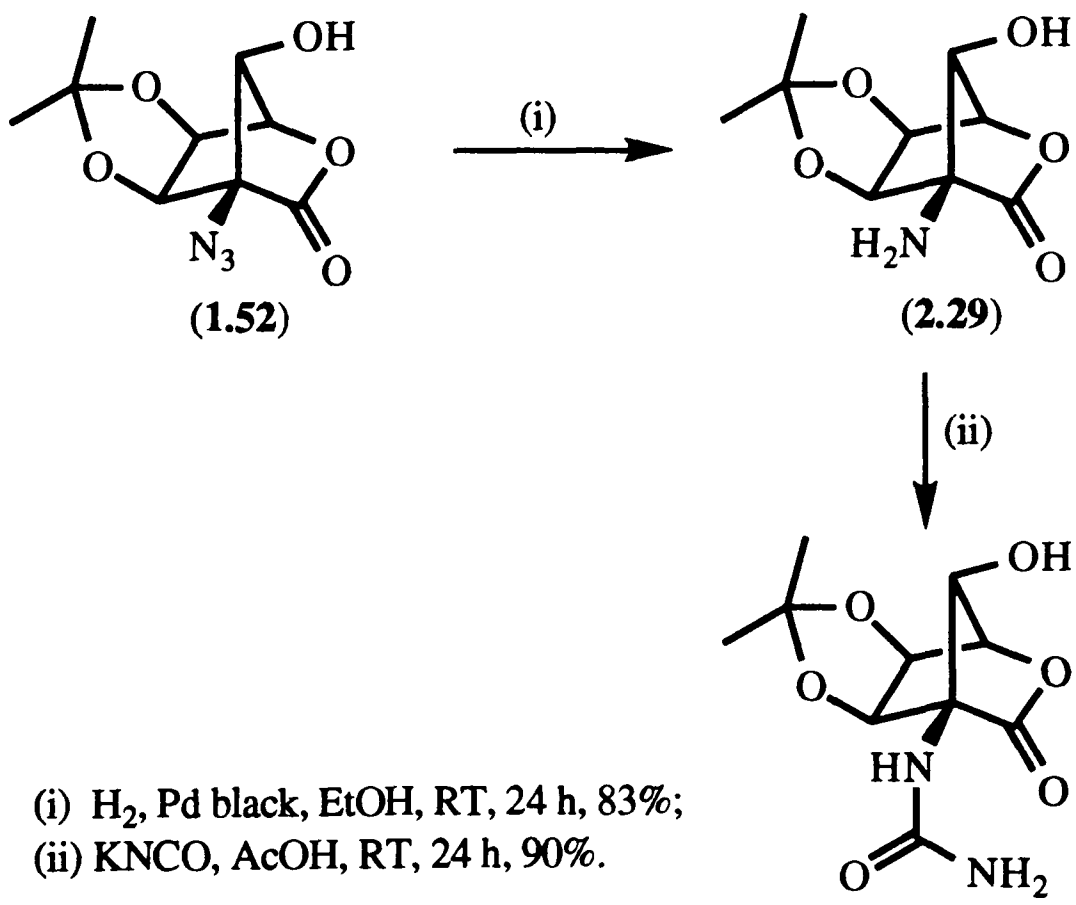
(i) 1,1-carbonyldiimidazole, toluene, reflux, 14 h, 71%;
(ii) 40% aqueous TFA, 40 min, 40% upon recrystallisation.

Scheme 2.22

(ii) Strategy 2

The second strategy adopted involved conversion of the azide functionality to its corresponding urea *via* an intermediate amine, followed by hydantoin ring closure between the urea primary nitrogen and the lactone carbonyl group.

Reduction of the azide moiety of the carbocycle (**1.52**) was achieved by hydrogenation in the presence of palladium black to give the amino carbocycle (**2.29**). Treatment of (**2.29**) with potassium cyanate in acetic acid afforded the urea (**2.30**) in good yield (**Scheme 2.23**).



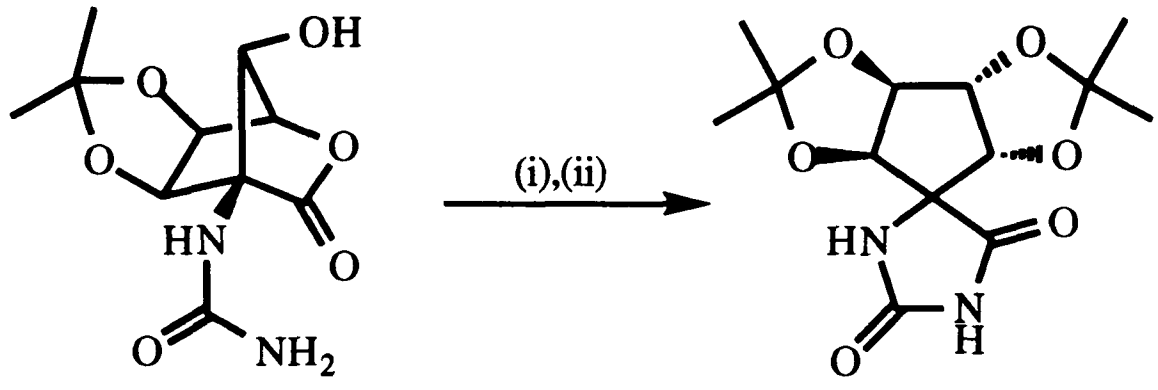
(1.52) **(2.29)** **(2.30)**

(i) H_2, Pd black, EtOH, RT, 24 h, 83%;
(ii) KNCO, AcOH, RT, 24 h, 90%.

Scheme 2.23

An initial attempt to induce hydantoin ring closure involved treatment of the urea (**2.30**) with potassium *tert*-butoxide in *N*,*N*-dimethylformamide.[15] Extensive decomposition was observed; when the product mixture was treated with acetone and

2,2-dimethoxypropane, only a trace amount of the diacetonide (**2.28**) was isolated. This would suggest that cyclisation did occur, albeit in low yield (**Scheme 2.24**).

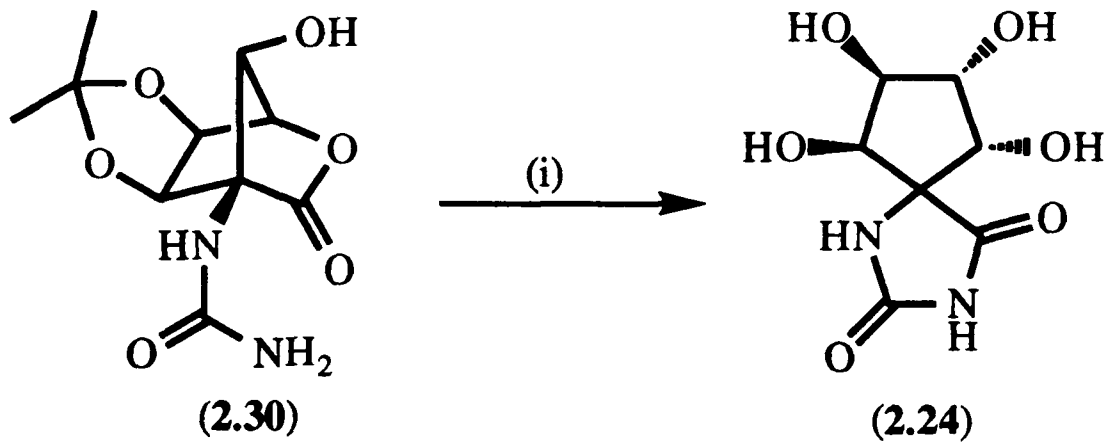


(2.30) **(2.28)**

(i) KO^{t}Bu, DMF, 0 °C - RT over 1 h;
(ii) acetone, 2,2-dimethoxypropane, CSA, 20% over 2 steps.

Scheme 2.24

Cyclisation and ketal deprotection were eventually achieved simultaneously by treatment of the urea (**2.30**) with a refluxing solution of methanolic HCl,[16] generated by the addition of acetyl chloride to anhydrous methanol. Analytically pure spirohydantoin (**2.24**) was again obtained by repeated recrystallisations in 36% yield [27% overall yield from the azido carbocycle (**1.52**)] (**Scheme 2.25**).



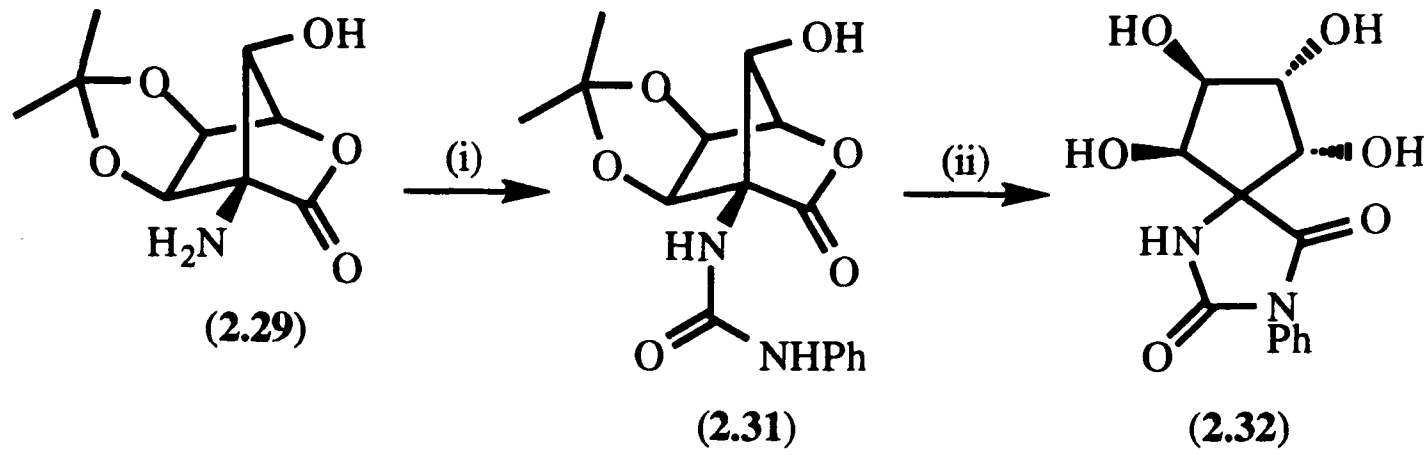
(2.30) **(2.24)**

(i) MeOH / HCl, reflux, 12 h, 36% upon recrystallisation.

Scheme 2.25

The second synthetic strategy described above would also allow access to *N'*-substituted spirohydantoins *via* the formation of *N'*-substituted urea precursors. Thus reaction of the amino carbocycle (**2.29**) with phenyl isocyanate in

tetrahydrofuran gave the phenyl urea (**2.31**). Cyclisation and deprotection were again achieved simultaneously by treatment of the phenyl urea (**2.31**) with methanolic HCl to produce the *N'*-phenyl spirohydantoin (**2.32**) in 82% yield (**Scheme 2.26**).



(2.29) **(2.31)** **(2.32)**

(i) PhNCO, THF, RT, 10 min, 69%;
(ii) MeOH / HCl, reflux, 3.5 h, 82%.

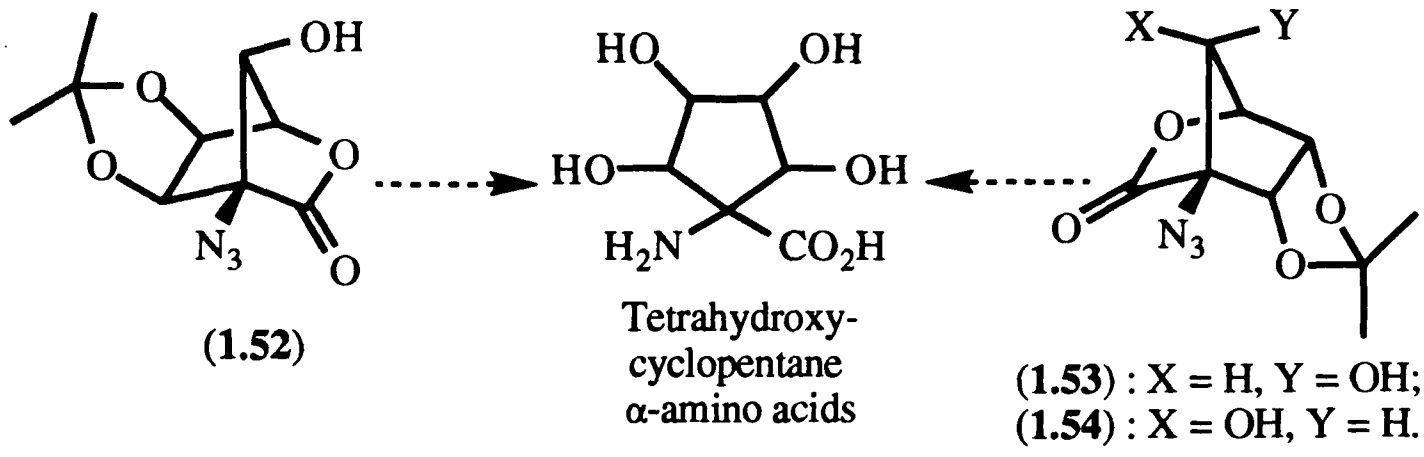
Scheme 2.26

Both the amine (**2.22**) and the spirohydantoin (**2.28**) were tested for their inhibitory activity against human liver glycosidases using synthetic enzyme substrates.[13] The amine (**2.22**) showed moderate inhibition of both α-**D**-mannosidase (IC_{50} 0.2 mM) and α-**L**-fucosidase (IC_{50} 0.25 mM); in contrast, the spirohydantoin (**2.28**) only inhibited α-**L**-fucosidase (IC_{50} 0.6 mM).[14]

2.3 Syntheses of Tetrahydroxy-Cyclopentane α-Amino Acids.

α,α-Disubstituted α-amino acids have attracted increasing attention in recent years. This group of nonproteinogenic amino acids induces dramatic conformational change when incorporated into peptides,[17] and renders them more resistant to protease hydrolysis.[18] They are found in natural peptide antibiotics,[19] and some are potent inhibitors of amino acid decarboxylases.[20] Chiral α,α-disubstituted α-amino acids are also important building blocks for the synthesis of pharmaceuticals and other biological agents.[21]

Each of the three azido bicyclic lactones, (**1.52**), (**1.53**) and (**1.54**), contains a quaternary carbon α to nitrogen (azide) and a carbonyl group. These bicyclic systems are therefore synthetic precursors to a set of novel α,α-disubstituted amino acids, namely tetrahydroxy-cyclopentane α-amino acids (**Scheme 2.27**). It was envisaged that simple sequences of reactions would produce the desired products.



Scheme 2.27

Work in this area can be divided into four sections:

(i) Synthesis from the bicyclic lactone (**1.52**);

(ii) Synthesis from the bicyclic lactones (**1.53**) and (**1.54**);

(iii) Investigation of the retro-aldol reactions;

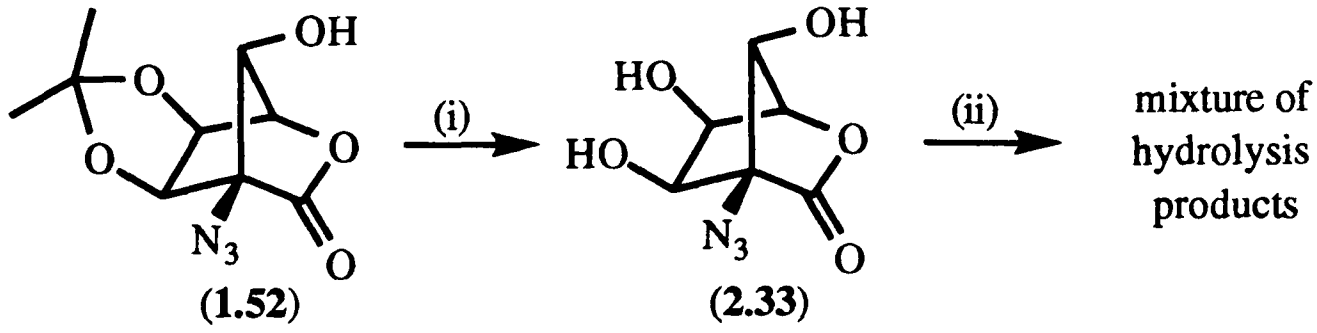
(iv) Synthesis of a fifth cyclopentane α-amino acid.

(i) Synthesis from the Bicyclic Lactone (1.52)

Conversion of the bicyclic lactone (**1.52**) to the corresponding carbocyclic α-amino acid required a combination of three steps, namely removal of the ketal group, opening of the lactone ring and reduction of the azide function. Four synthetic strategies were investigated as detailed below.

(a) Strategy 1

The first strategy adopted involved initial ketal hydrolysis, followed by lactone ring opening and reduction. Thus treatment of the bicyclic lactone (**1.52**) with 80% aqueous trifluoroacetic acid gave the azido triol (**2.33**) in 89% yield. Hydrolysis of the lactone ring was attempted using a number of aqueous bases. In all cases, a mixture of inseparable carboxylic acids was obtained, presumably arising from facile base-induced retro-aldol epimerisations at C-5 and / or C-7 (**Scheme 2.28**).



(1.52) **(2.33)**

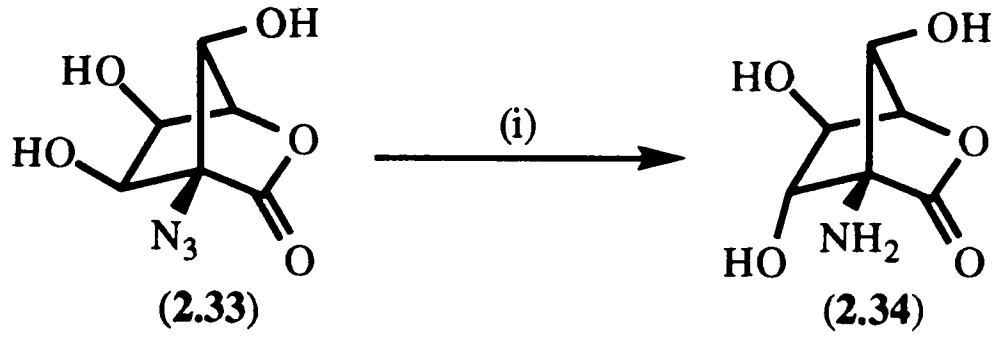
(i) 80% aqueous TFA, RT, 6 h, 89%;
(ii) Basic conditions: - aqueous NaOH (1 - 5 equiv);
- aqueous K_2CO_3 (1 equiv);
- aqueous Et_3N (15 equiv).

Scheme 2.28

(b) Strategy 2

It was postulated that the electron-withdrawing azide functionality contributed to the stabilisation of an α-carbanion, thus facilitating retro-aldol epimerisations. Hence the second synthetic strategy adopted involved reduction of the azide prior to lactone ring opening. Initial attempts to effect reduction of the azido triol (**2.33**) by catalytic hydrogenation in water resulted in the formation of an inseparable mixture of two amino lactone products, the ratio of which varied with reaction time, as adjudged by proton NMR spectroscopy. Prolonged reaction time led to the isolation of a single amino lactone product (**2.34**) in 93% yield (**Scheme 2.29**). Furthermore, an aqueous

solution of the amino lactone mixture equilibrated overnight to give the same amine product (**2.34**).

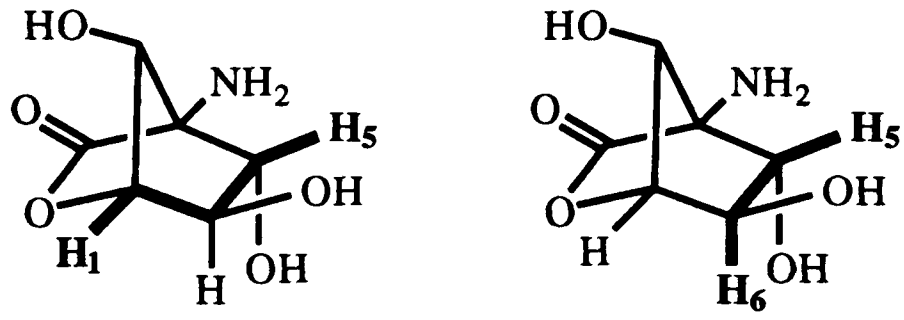


(2.33) **(2.34)**

(i) H_2, Pd black, water, RT, 24 h, 93%.

Scheme 2.29

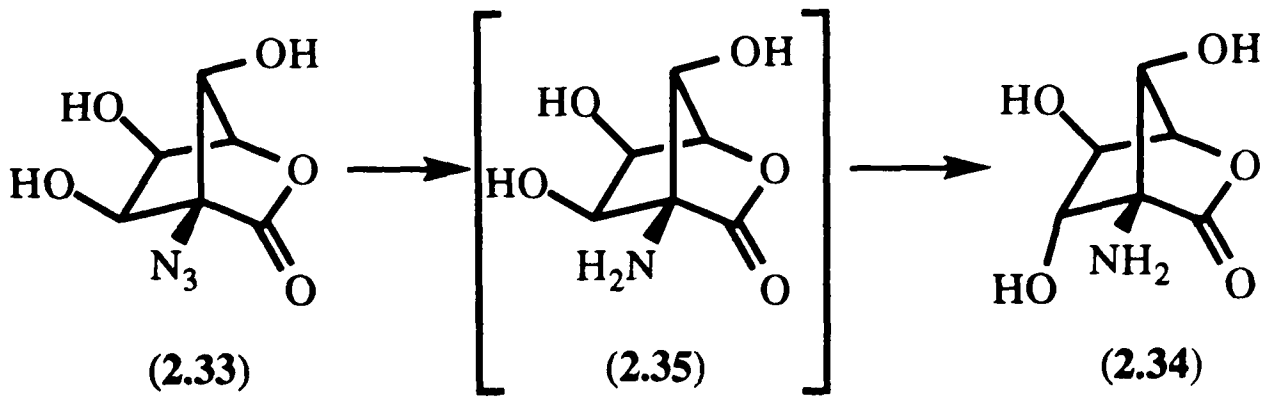
The relative stereochemistry of this material was initially assigned by proton NMR spectroscopy (**Scheme 2.30**). A small long range W-coupling ($J_{1,5}$ 1.5 Hz) was observed between H-1 and H-5; in addition, a small vicinal coupling ($J_{5,6}$ 1.5 Hz) would suggest a *trans* relationship between H-5 and H-6 in this bicyclic [2.2.1] ring system.



$J_{1,5}$ 1.5 Hz $J_{5,6}$ 1.5 Hz

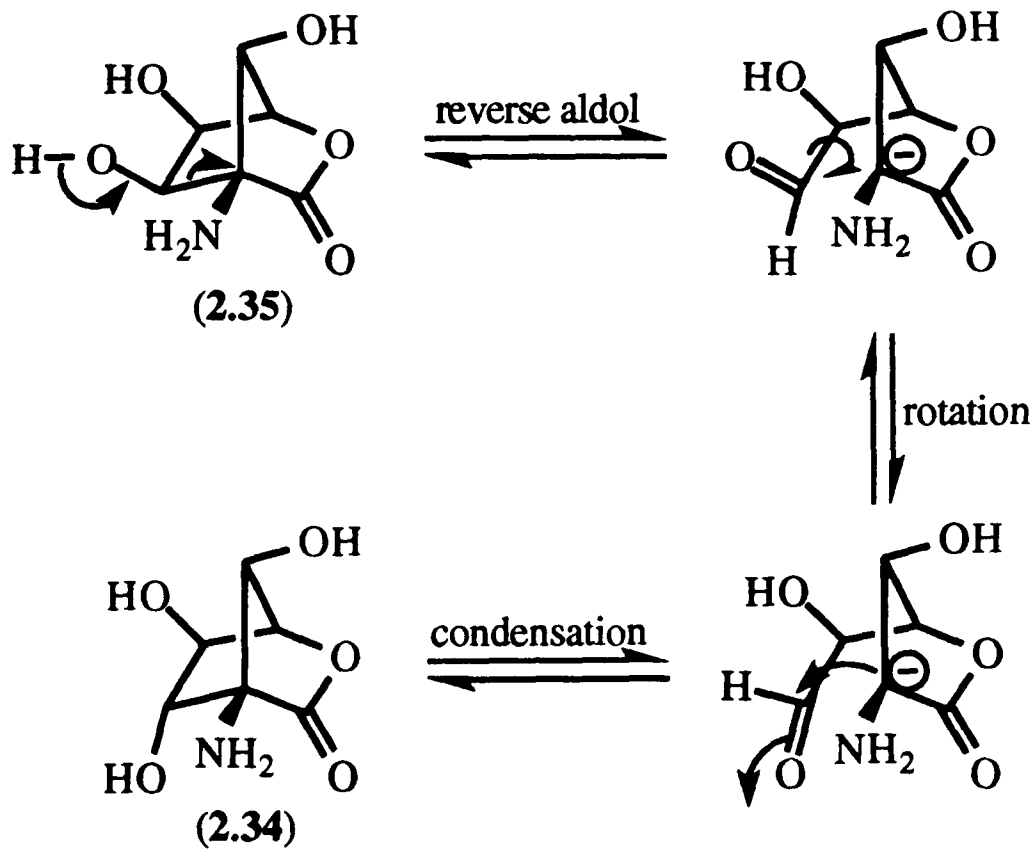
Scheme 2.30

It was decided to investigate whether the azido lactone (**2.33**) would undergo a similar isomerisation in aqueous solution. However, only the unreacted lactone (**2.33**) was recovered after exposure to water for 24 hours. Therefore, it would appear that the formation of the amino lactone (**2.34**) took place *via* an intermediate amine (**2.35**) which epimerised in aqueous solution to give the thermodynamically more stable amine (**2.34**) (**Scheme 2.31**).



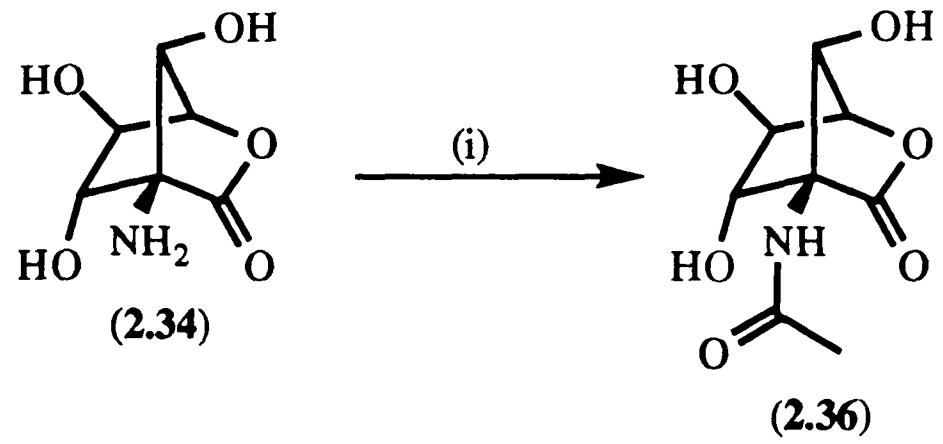
Scheme 2.31

Epimerisation of the hydroxyl group is thought to occur *via* an initial reverse aldol reaction. This is then followed by recondensation of the resultant carbanion onto the *si* face of the aldehyde (**Scheme 2.32**).



Scheme 2.32

The amino lactone (**2.34**) was found to be extremely hygroscopic. Therefore it was fully characterised as the corresponding *N*-acetate (**2.36**), which was formed by treatment of (**2.34**) with acetic anhydride in *N*,*N*-dimethylformamide (**Scheme 2.33**).



(2.34) **(2.36)**

(i) Ac_2O, DMF, 0 °C, 2 h, 75%.

Scheme 2.33

The relative configuration of (**2.36**) was established by single crystal X-ray analysis;[22] the crystal structure is shown in **Figure 2.1**. This further substantiates the postulated structure of the amino lactone (**2.34**).

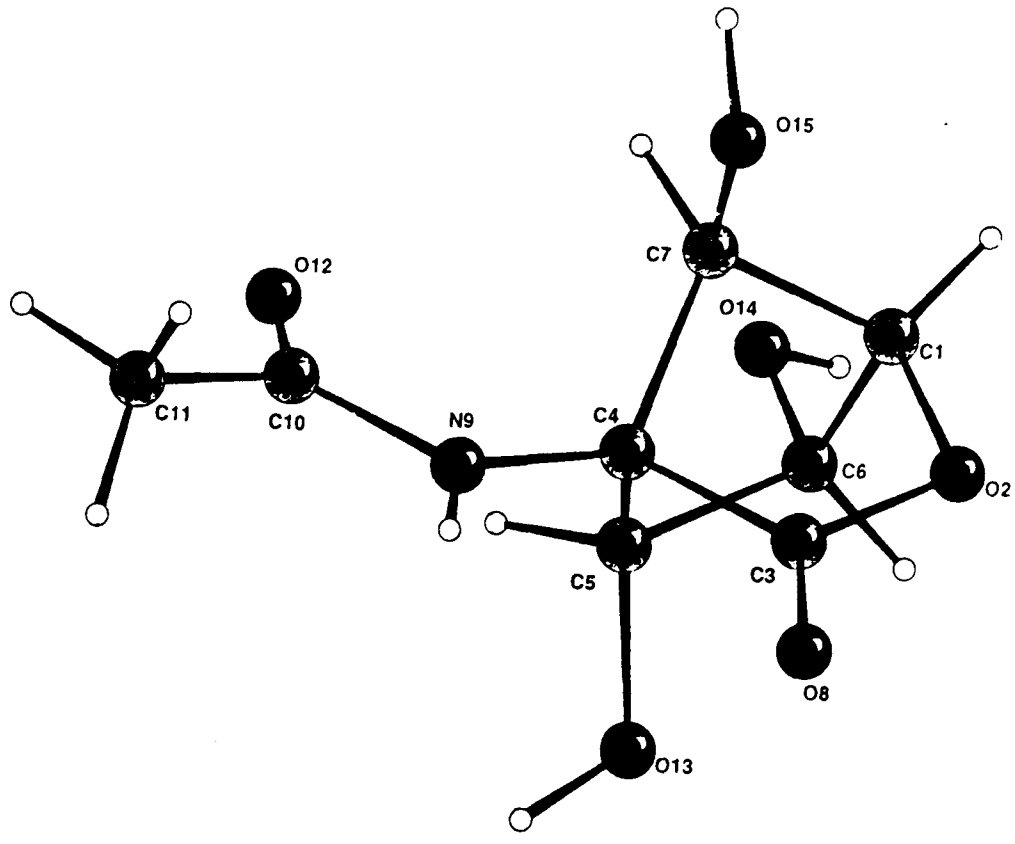


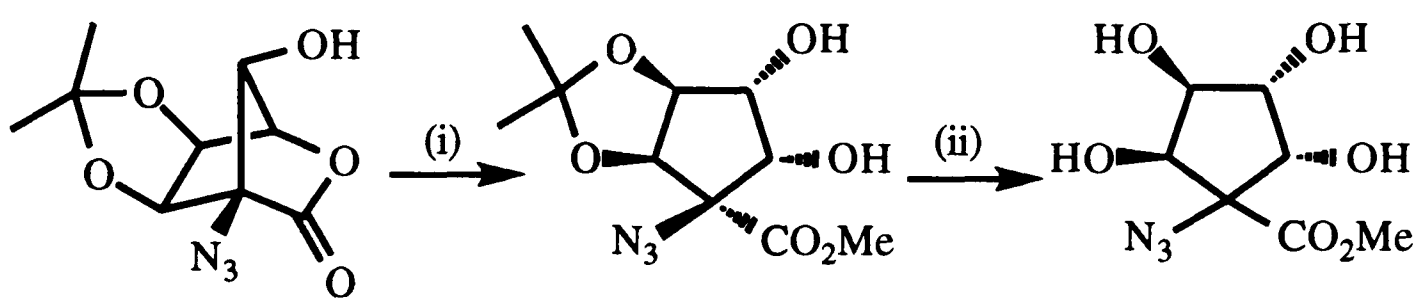
Figure 2.1

(c) Strategy 3

The third synthetic strategy adopted involved initial methanolysis of the bicyclic lactone (**1.52**) followed by ketal hydrolysis. Subsequent elaboration of the α-azido methyl ester functions would afford the desired α-amino acid. It was envisaged that

this reaction sequence would overcome the problematic tendency of the bicyclic lactone systems to undergo epimerisations.

It was decided to convert the lactone to its methyl ester, instead of the corresponding carboxylate *via* alkaline hydrolysis, because of the relative ease of purification of the intermediate compounds thereafter. Thus treatment of the bicyclic lactone (**1.52**) with potassium carbonate in methanol resulted in the formation of the azido ester (**2.37**).[10] Removal of the ketal group was then achieved by reaction with 80% aqueous trifluoroacetic acid to produce the deprotected methyl ester (**2.38**) in 84% yield (**Scheme 2.34**).

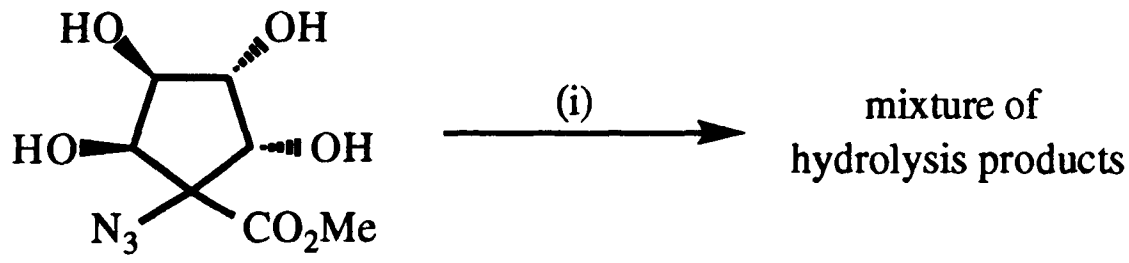


(1.52) **(2.37)** **(2.38)**

(i) K_2CO_3 (catalytic amount), MeOH, 0 °C, 20 min, 97%;
(ii) 80% aqueous TFA, RT, 1.5 h, 84%.

Scheme 2.34

Basic hydrolysis of the methyl ester (**2.38**) proved to be unsuccessful (**Scheme 2.35**). All attempts led to the formation of an inseparable mixture of carboxylate products, presumably as a result of facile retro-aldol reactions prior to hydrolysis.



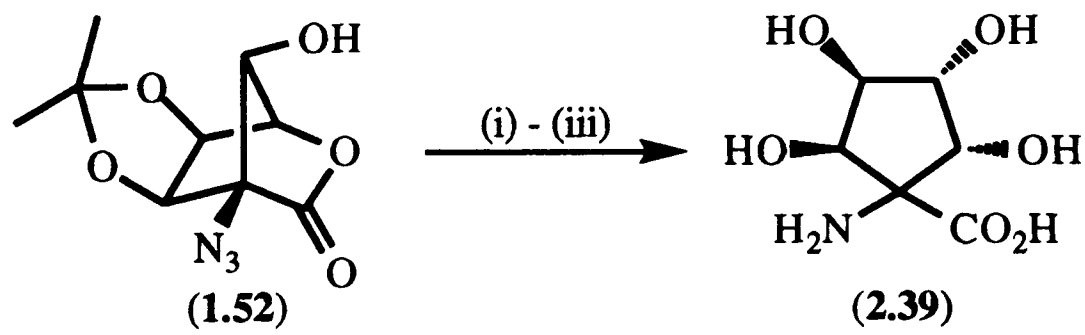
(i) Basic conditions: - aqueous NaOH (1 equiv);
- aqueous Et_3N (10 equiv).

Scheme 2.35

(d) Strategy 4

A fourth synthetic strategy was proposed based on the observation that removal of the acetonide group prior to basic hydrolysis of the carbonyl function had resulted in the formation of mixtures of products. Hence ketal deprotection was to be carried out as the last step in this reaction sequence.

Treatment of the azido bicyclic lactone (**1.52**) with aqueous potassium carbonate effected hydrolysis to produce a single azido carboxylate (as seen by proton and carbon NMR spectroscopy). This crude material was then reduced by hydrogenation in the presence of palladium black to give a single amino acid (again as seen by proton and carbon NMR spectroscopy). Further reaction with 40% aqueous trifluoroacetic acid caused the removal of the ketal protecting group. The amino acid (**2.39**) was thus isolated as the sole product upon purification by ion exchange chromatography (**Scheme 2.36**).



(1.52) **(2.39)**
98% over 3 steps

(i) K_2CO_3, water : dioxane (4 : 1), RT, 2 h;
(ii) H_2, Pd black, water, RT, 19 h;
(iii) 40% aqueous TFA, RT, 8 h.

Scheme 2.36

The relative configuration of (**2.39**) was confirmed by single crystal X-ray analysis,[23] and the crystal structure is shown in **Figure 2.2**. As can be seen, the four hydroxyl groups adopt a (2α,3α,4β,5β) relative configuration around the cyclopentane ring.

Therefore, no retro-aldol epimerisation had taken place in the course of this reaction sequence.

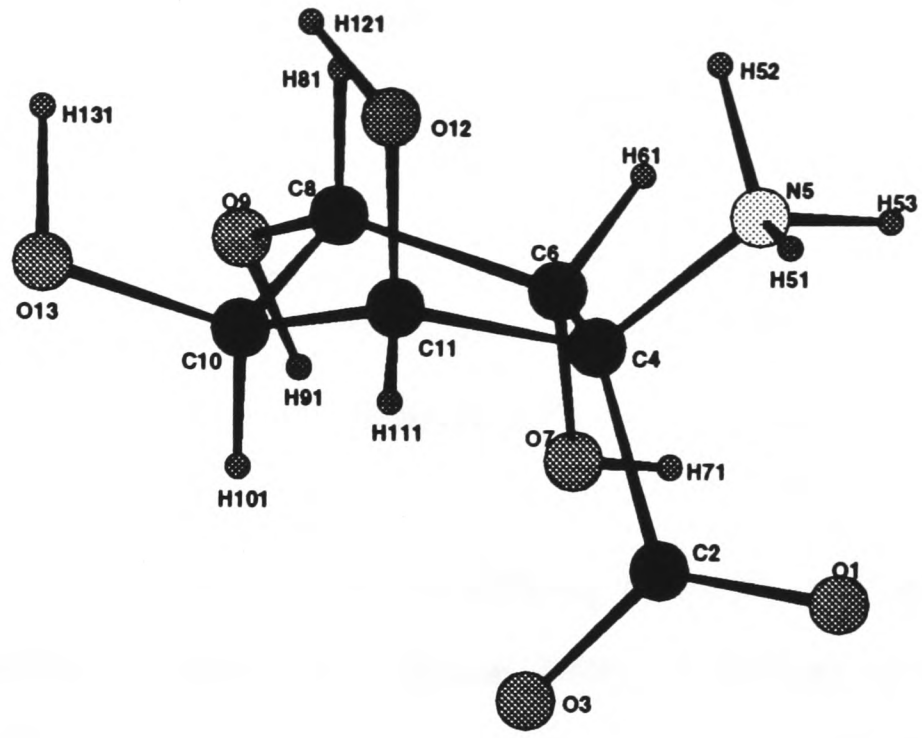


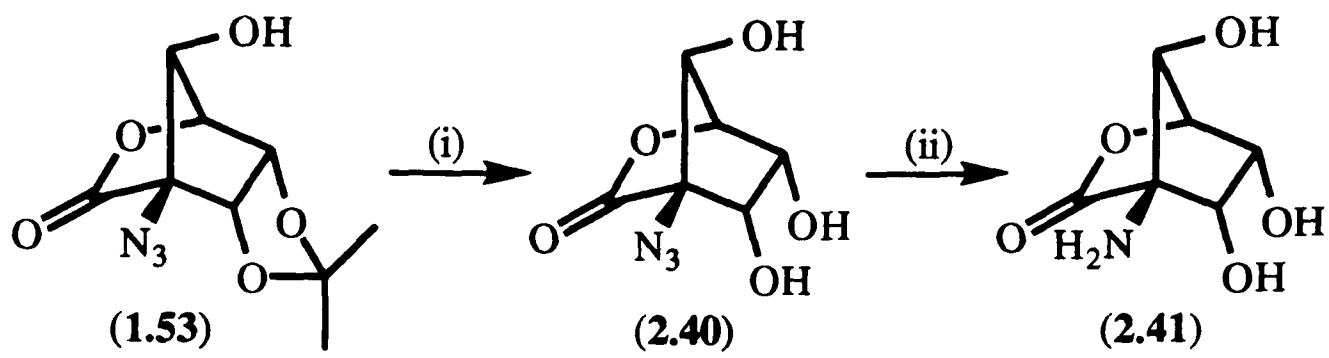
Figure 2.2

(ii) Synthesis from the Bicyclic Lactones (**1.53**) and (**1.54**)

Transformations of the bicyclic lactones (**1.53**) and (**1.54**) to the corresponding α-amino acids were investigated using the second synthetic approach described above, namely the initial ketal removal, followed by reduction of the azide functionality and ring opening of the resultant amino lactone.[24]

Treatment of the bicyclic lactone (**1.53**) with 40% aqueous trifluoroacetic acid yielded the azido triol (**2.40**). Reduction of the azide functionality was then achieved by hydrogenation in the presence of palladium black to give the amino triol (**2.41**)

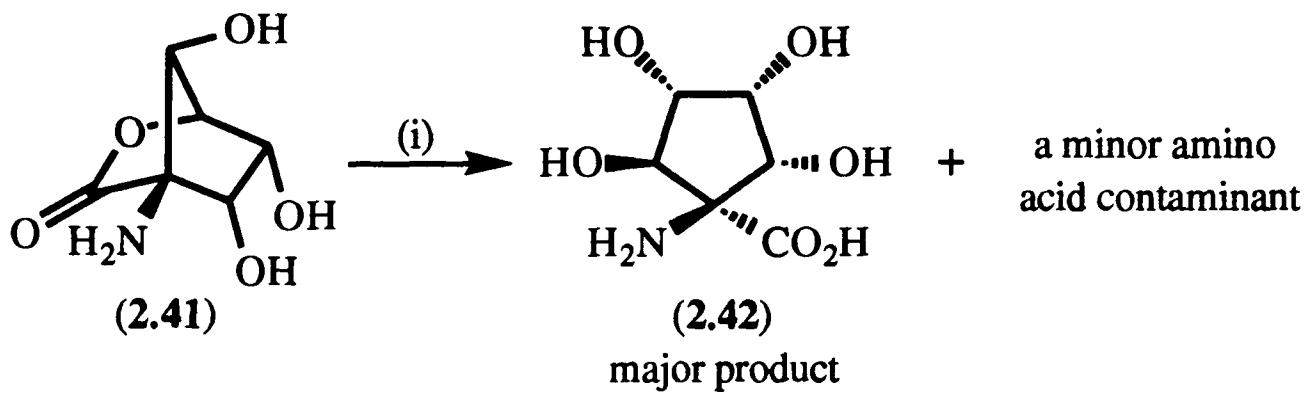
(**Scheme 2.37**). Although this material was found to be extremely hygroscopic, no retro-aldol epimerisation, analogous to that previous described, was observed.[24]



(i) 40% aqueous TFA, RT, 3 h, 97%;
(ii) H_2, Pd black, water, RT, 4.5 h, 88%.

Scheme 2.37

Basic hydrolysis of the lactone ring was effected by reaction of the amino lactone (**2.41**) with aqueous triethylamine (**Scheme 2.38**). A mixture of two amino acid products was isolated, in the ratio of 8 : 1, as adjudged by proton NMR spectroscopy.



(i) aqueous Et_3N (10 equiv), RT, 1.5 h, 86% combined yield.

Scheme 2.38

Separation of these materials by ion exchange chromatography proved unsuccessful. Repeated recrystallisations from an aqueous solution of the product mixture provided a pure sample of the major product (**2.42**), the absolute configuration of which was established by single crystal X-ray analysis (**Figure 2.3**).[25]

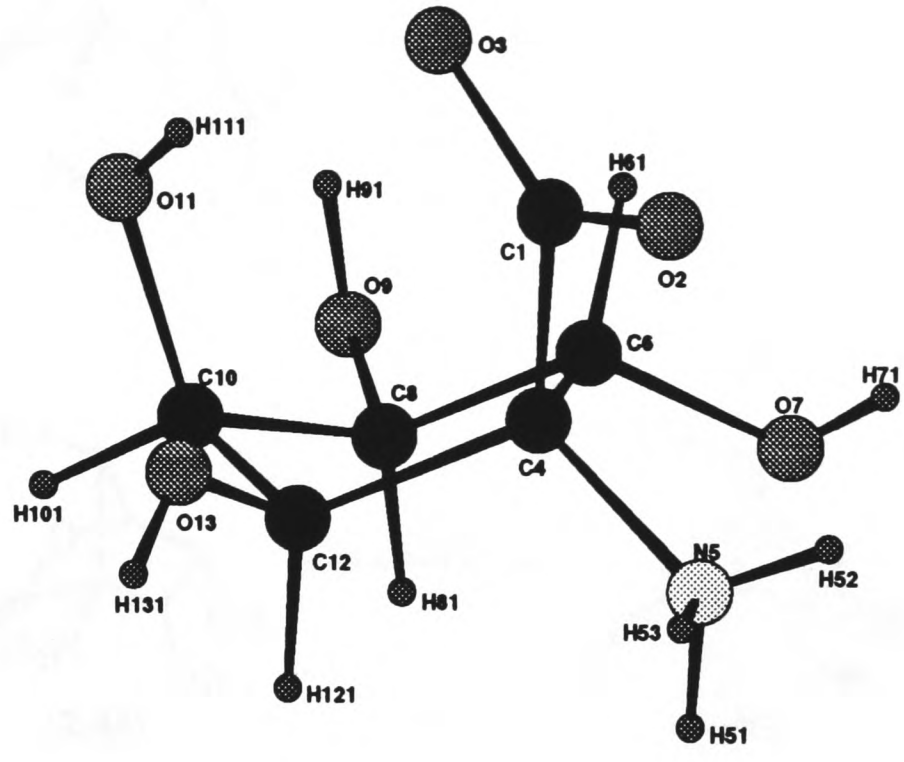
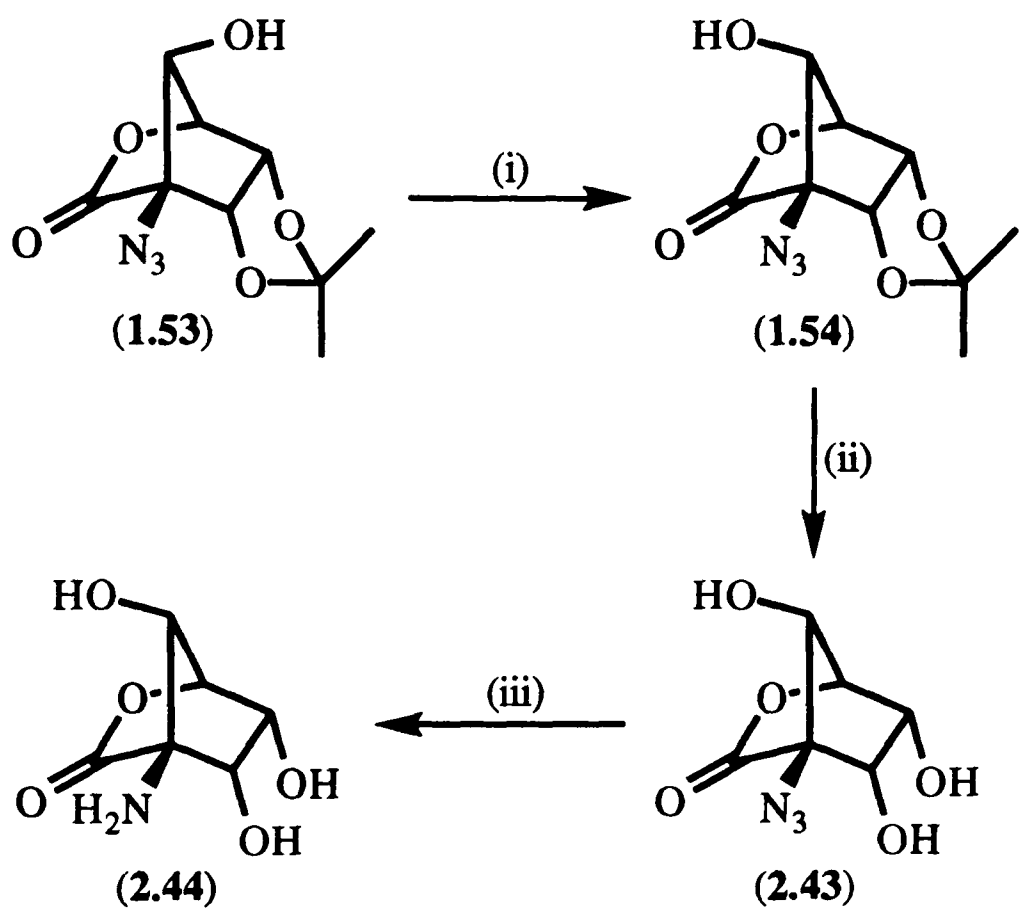


Figure 2.3

The formation of the major amino acid product (**2.42**) was the result of direct opening of the lactone ring of the amino triol (**2.41**), whilst the minor contaminant presumably arose from competing base-induced retro-aldol epimerisations.

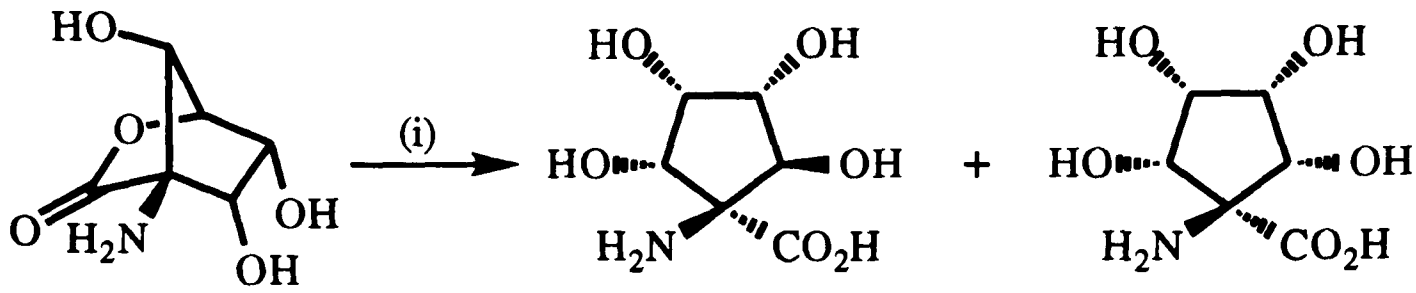
The third bicyclic lactone (**1.54**) was prepared by treatment of its epimer (**1.53**) with liquid ammonia, as described in Chapter 1.[24] Ketal hydrolysis with 40% aqueous trifluoroacetic acid then produced the azido triol (**2.43**) in 91% yield. Subsequent reduction of the azide moiety was achieved by hydrogenation in the presence of palladium black to give the amino triol (**2.44**); again, no evidence for retro-aldol epimerisation of this material in aqueous solution was found (**Scheme 2.39**).[24]



(i) liq. NH_3, -45 °C to RT over 30 min,
66% (82% based on recovered starting material);
(ii) 40% aqueous TFA, RT, 21 h, 91%;
(iii) H_2, Pd black, water, RT, 4.5 h, 88%.

Scheme 2.39

Treatment of the amino triol (**2.44**) with aqueous sodium hydroxide resulted in the formation of a mixture of two amino acid products, (**2.45**) and (**2.46**), in the ratio of 6 : 1, as adjudged by proton NMR spectroscopy (**Scheme 2.40**). Separation of these materials by ion exchange chromatography was again unsuccessful; a pure sample of the major product (**2.45**), the enantiomer of (**2.42**), was obtained by slow recrystallisation from an aqueous solution of the amino acid mixture. The minor, symmetric product (**2.46**) was later synthesised *via* an alternative route (see **Scheme 2.42**).[24]



(2.44) **(2.45)** : **(2.46)**

6 : 1

(i) aqueous NaOH (2 equiv), RT, 20 min, 59% combined yield.

Scheme 2.40

The enantiomeric relationship between the amino acids (**2.42**) and (**2.45**) was initially established by identical proton and carbon NMR spectra of the two compounds, and by comparison of the specific rotation of these materials at five different wavelengths, as shown in **Table 2.1**.

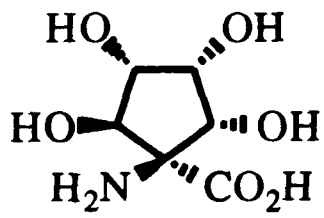
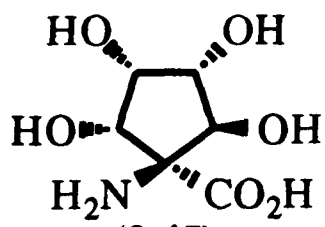
Wavelength / nm	589	578	546	436	365
 **(2.42)** (*c*, 0.75 in H_2O)	+3.7	+2.9	+3.2	+6.1	+10.0
 **(2.45)** (*c*, 0.75 in H_2O)	-4.4	-3.5	-4.0	-6.5	-9.6

Table 2.1 Optical rotation of the amino acids (**2.42**) and (**2.45**) at 25 °C at five different wavelengths.

Confirmation that the amino acids (**2.42**) and (**2.45**) were indeed enantiomers was provided by the circular dichroism (CD) spectra of the respective compounds, as shown in **Figures 2.4a** and **2.4b**. Since all available material was used for each

sample, the unequal concentrations had resulted in different intensities in the CD spectra.

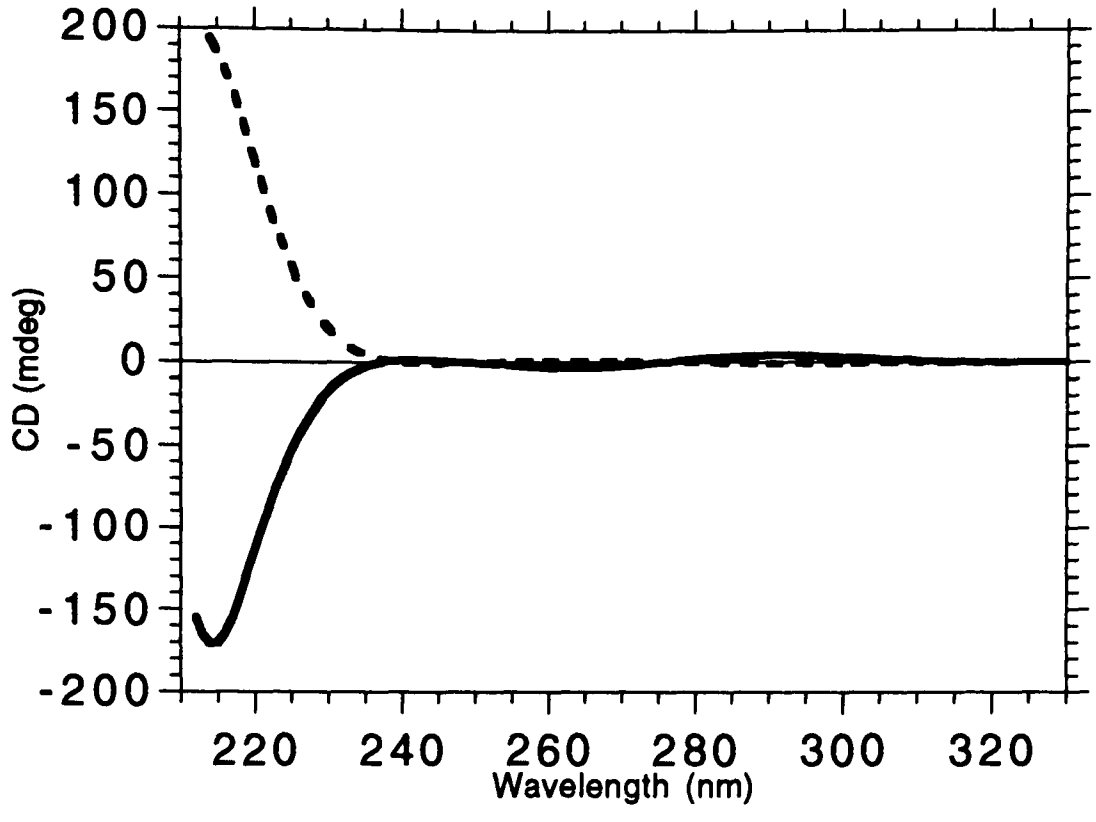


Figure 2.4a Solid line: CD spectrum of (**2.42**)
Dashed line: CD spectrum of (**2.45**)

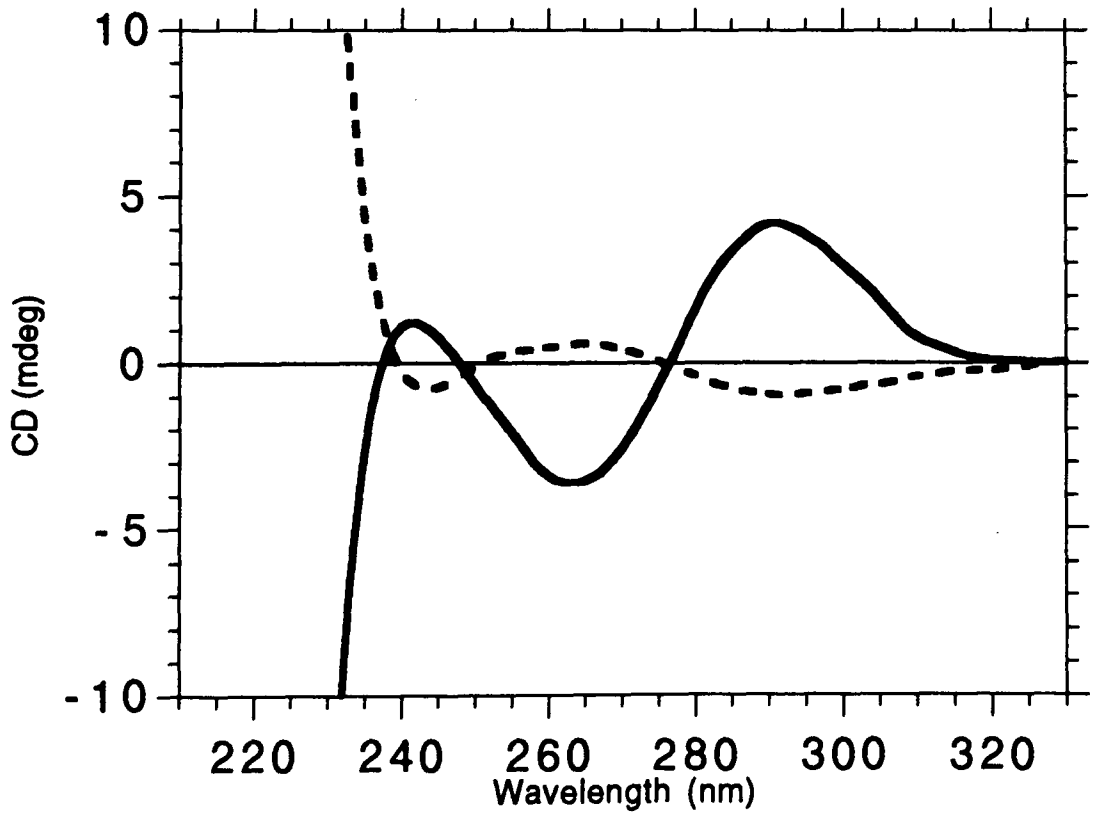
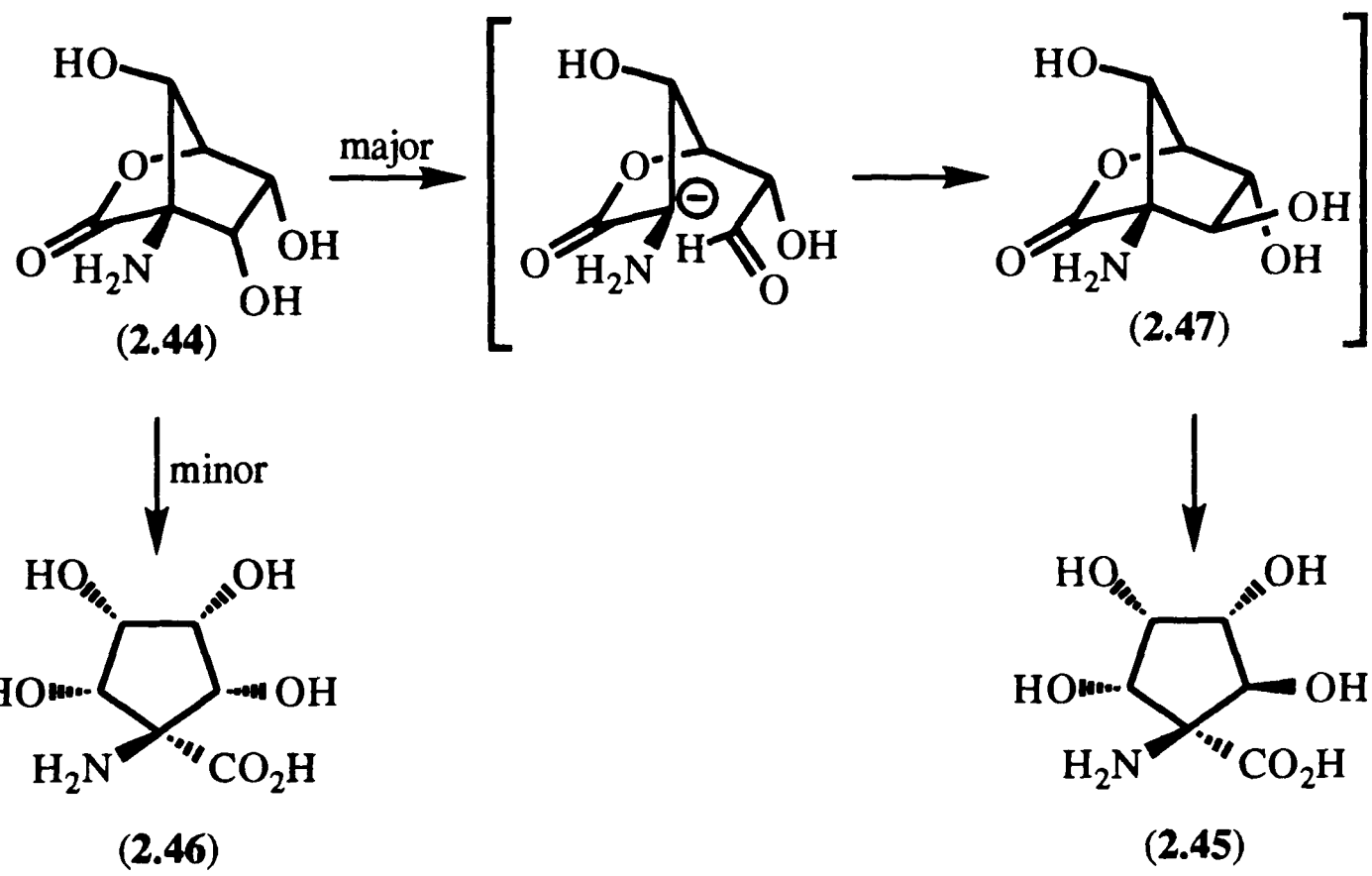


Figure 2.4b Solid line: CD spectrum of (**2.42**)
Dashed line: CD spectrum of (**2.45**)

The formation of the amino acid (**2.45**), as the major hydrolysis product of the amino triol (**2.44**), was thought to take place *via* an initial base-induced reverse aldol reaction. This was then followed by recondensation to produce the intermediate amino lactone (**2.47**), which was hydrolysed directly to yield the amino acid (**2.45**). The minor product (**2.46**) arose from direct opening of the lactone ring (**Scheme 2.41**).



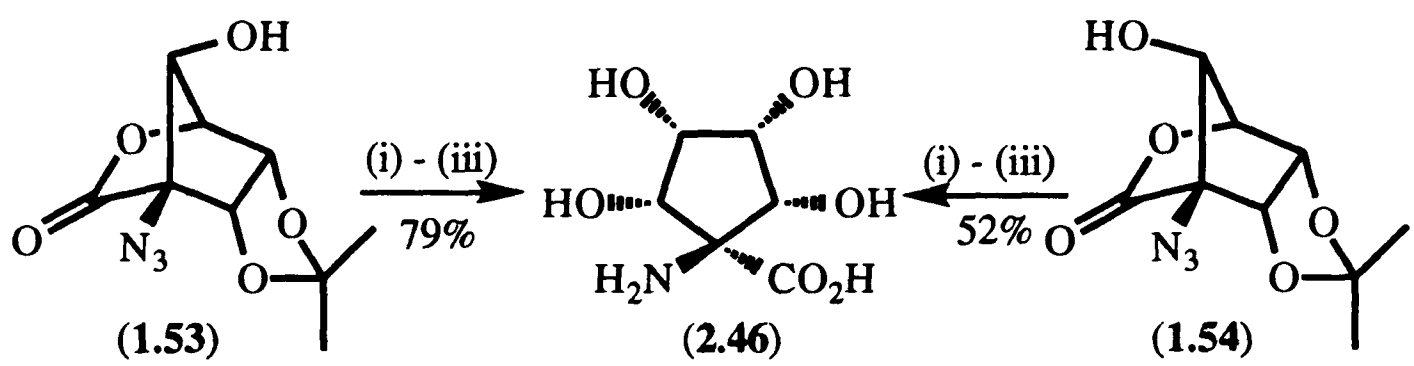
(**2.44**) (**2.47**) (**2.46**) (**2.45**)

Scheme 2.41

This is in contrast to the basic hydrolysis of the epimeric amino triol (**2.41**), where the major product (**2.42**) is formed by direct ring opening. A plausible explanation for these transformations has been proposed.[26] Direct ring opening of the amino lactone (**2.41**) takes place *via* the attack of an oxygen nucleophile from the least hindered *exo* face of the bicyclic lactone framework to give the amino acid (**2.42**), whilst the minor product arises from competing retro-aldol epimerisation reactions prior to hydrolysis. In contrast, nucleophilic approach from the *exo* face of the amino lactone (**2.44**) is hindered [relative to that of (**2.41**)] by the *syn* hydroxyl group at C-7. Therefore, direct hydrolysis represents the minor reaction pathway to yield (**2.46**), in competition

with initial base-induced retro-aldol epimerisation and subsequent hydrolysis to give (**2.45**) as the major product.

During the course of this work, it was found that when either of the bicyclic lactones (**1.53**) or (**1.54**) was treated with aqueous potassium carbonate, the same crude azido carboxylate was obtained. T.l.c. analysis of the reaction mixtures indicated equilibrations between the two bicyclic lactones (**1.53**) and (**1.54**). Subsequent reduction of the azide functionality followed by ketal hydrolysis gave the symmetrical amino acid (**2.46**) as the sole product (**Scheme 2.42**).[25] This firmly established (**2.46**) as the minor ring opening product of the amino lactone (**2.44**).



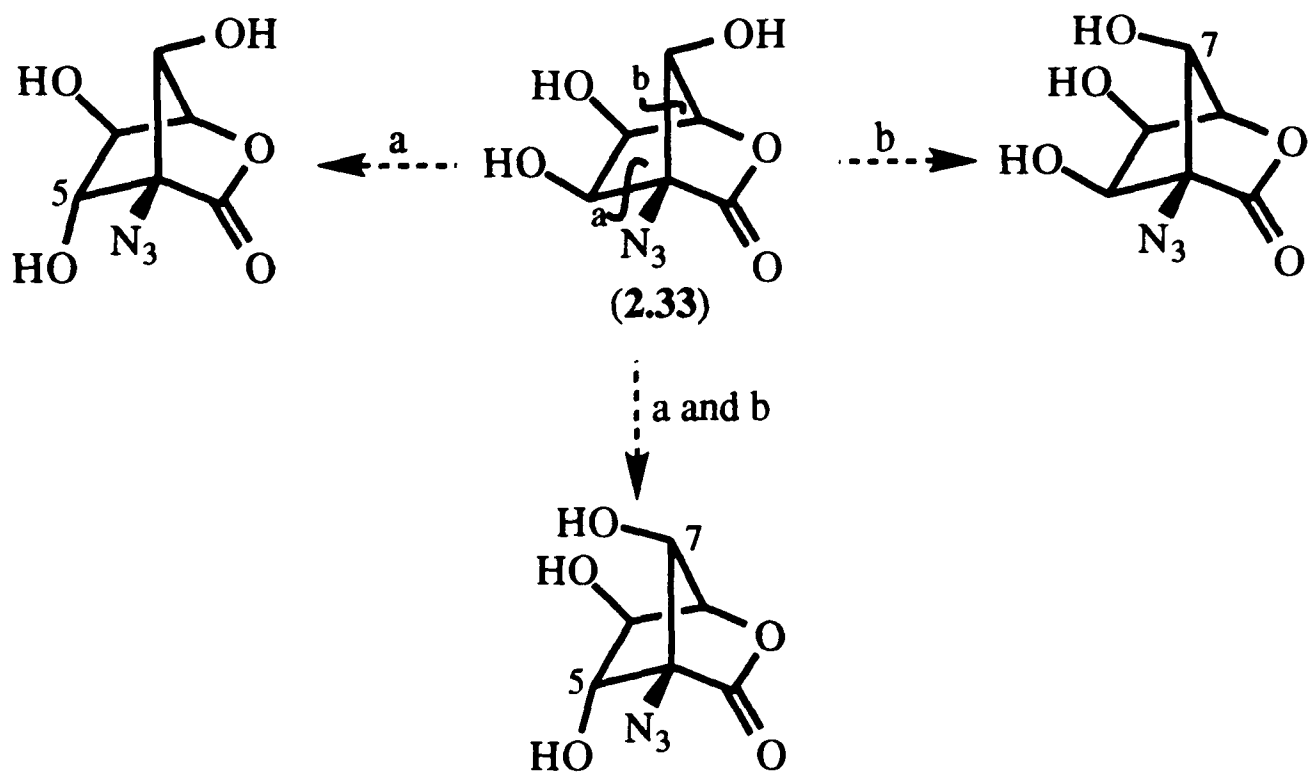
(i) K_2CO_3, water, RT, 16 h;
(ii) H_2, Pd black, water, RT, 4 h;
(iii) 40% aqueous TFA, RT, 16 h.

Scheme 2.42

(iii) Investigation of the Retro-Aldol Reactions

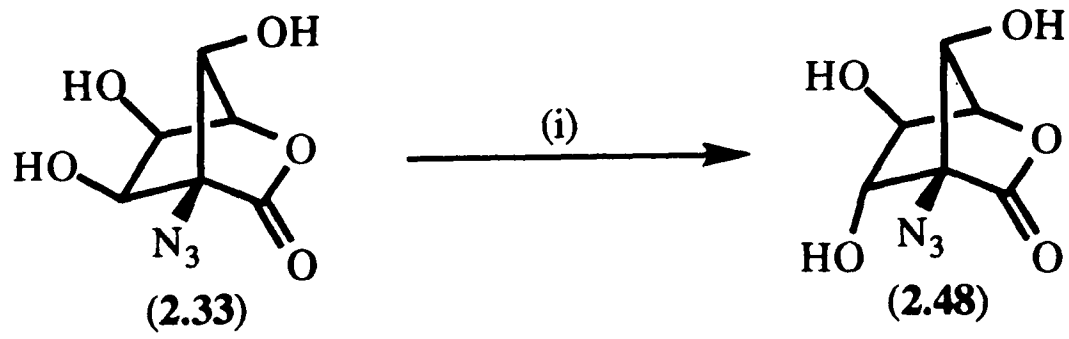
The propensity of the bicyclic lactone triol framework to undergo base-catalysed retro-aldol epimerisations during alkaline hydrolysis prompted an investigation into whether epimerisations could be induced in a controlled manner under non-aqueous conditions. The three azido lactone triols (**2.33**), (**2.40**) and (**2.43**), were chosen, instead of the corresponding amines, as starting materials for these studies because of the ease of purification of the compounds concerned.

The initial basic conditions examined were those which brought about the intramolecular aldol cyclisation in the formation of the bicyclic lactones (**1.52**) and (**1.53**), namely potassium fluoride or sodium azide in acetonitrile.[6a] It was envisaged that, under these conditions, the azido triol (**2.33**) could undergo epimerisation at C-5 (route a) and / or C-7 (route b) to give three possible lactone products (**Scheme 2.43**).



Scheme 2.43

Treatment of the azido triol (**2.33**) with potassium fluoride and 18-crown-6 in acetonitrile resulted in the formation of a single azido lactone (**2.48**) in 60% yield (**Scheme 2.44**). The absolute configuration of this material was established by X-ray crystallographic analysis;[27] the crystal structure is shown in **Figure 2.5**.



(i) KF, 18-crown-6, MeCN, RT, 12 h, 60%.

Scheme 2.44

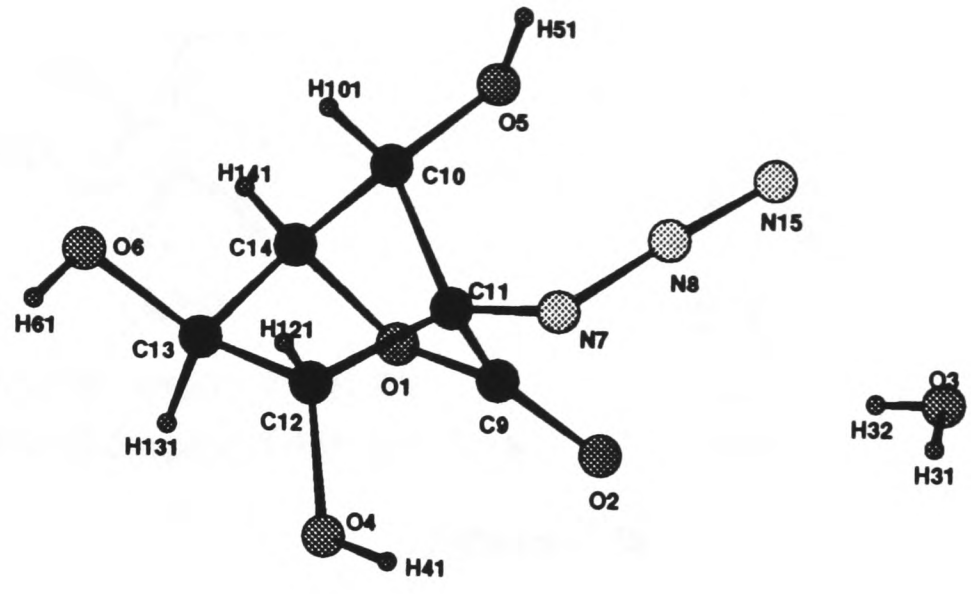
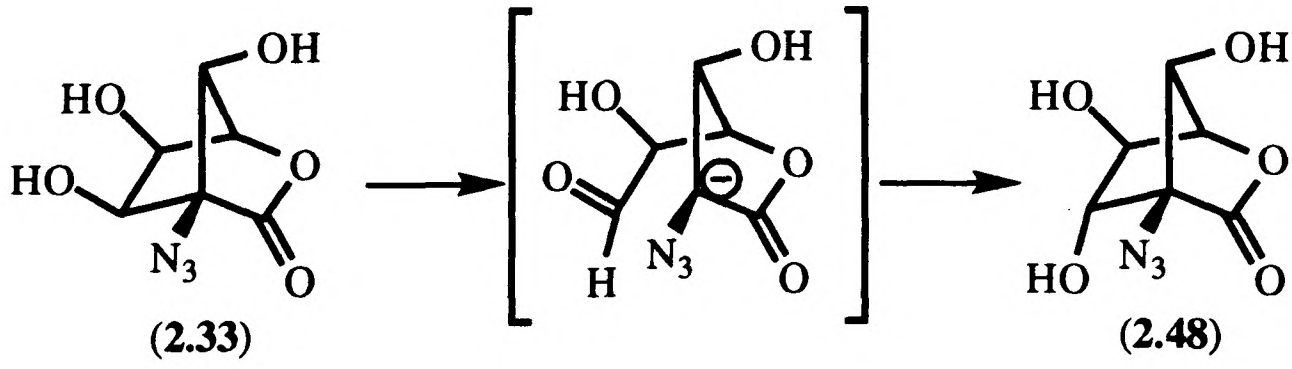


Figure 2.5

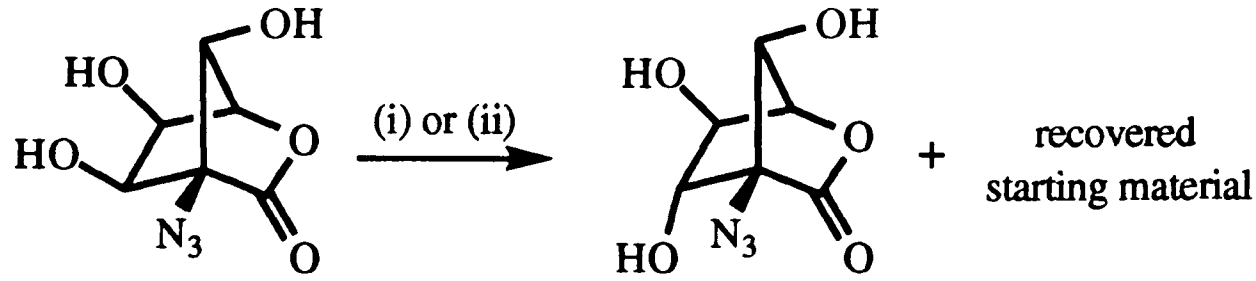
Analogous to the base-catalysed epimerisations described hitherto, the azido triol (**2.33**) underwent a reverse aldol reaction. Subsequent recondensation gave the thermodynamically more stable *trans*-isomer (**2.48**) (**Scheme 2.45**).



Scheme 2.45

Treatment of the azido triol (**2.33**) with sodium azide in acetonitrile did not induce epimerisation and the starting material was recovered. When a number of other basic

conditions were investigated, it was found that treatment of the azido triol (**2.33**) with sodium acetate in *N,N*-dimethylformamide resulted in the partial conversion to (**2.48**) (**Scheme 2.46**).



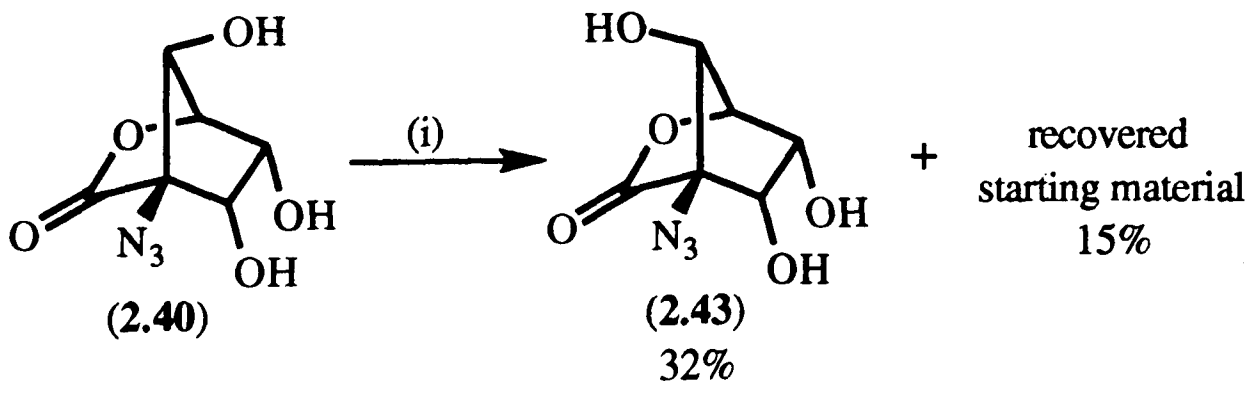
(2.33) **(2.48)**

(i) NaOAc (0.1 equiv), DMF, RT, 7 h:	50%	40%
(ii) NaOAc (0.5 equiv), DMF, RT, 7.5 h:	68%	8%

Scheme 2.46

It was then decided to investigate whether epimerisation could be induced in the opposite direction. However, treatment of the azido triol (**2.48**) with sodium acetate in *N,N*-dimethylformamide led only to the recovery of the starting material.

Attempts to effect epimerisation of the azido triols (**2.40**) and (**2.43**) were less successful. In most cases, extensive decompositions were observed. In particular, treatment of the azido triol (**2.40**) with potassium fluoride resulted in the isolation of the epimeric triol (**2.43**) in 32% yield (**Scheme 2.47**).



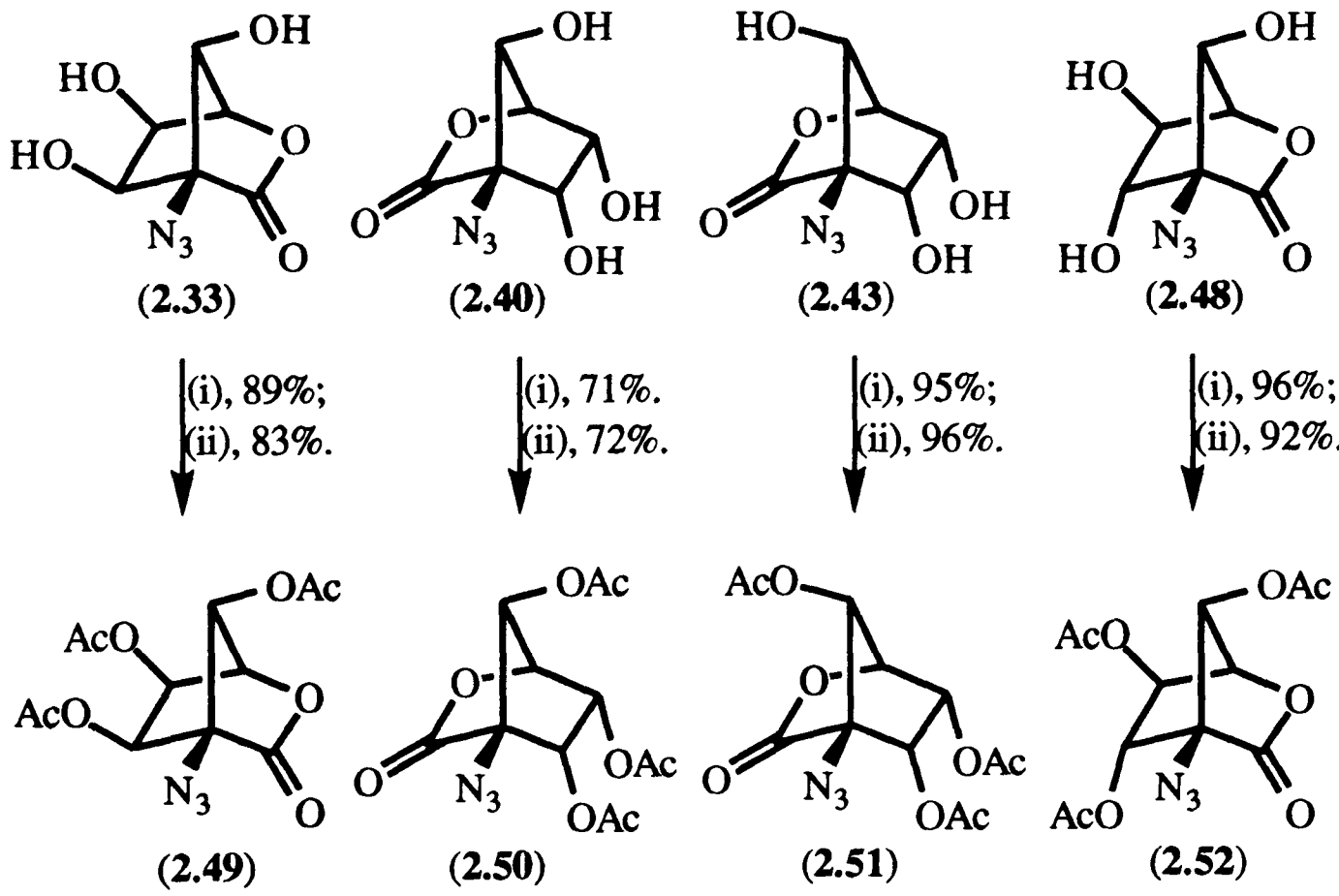
(2.40) **(2.43)**
32%

(i) KF, 18-crown-6, MeCN, RT, 10 h.

Scheme 2.47

Exposure of the azido triol (**2.43**) to a variety of basic conditions led only to the recovery of less than 40% of the starting material.

All four azido triols, (**2.33**), (**2.40**), (**2.43**) and (**2.48**), were further protected as the corresponding peracetates, (**2.49**), (**2.50**), (**2.51**) and (**2.52**), respectively, by reaction with acetic anhydride and pyridine. The absence of base-catalysed epimerisation in these reactions was confirmed by carrying out the parallel acetylations in acidic conditions (**Scheme 2.48**).



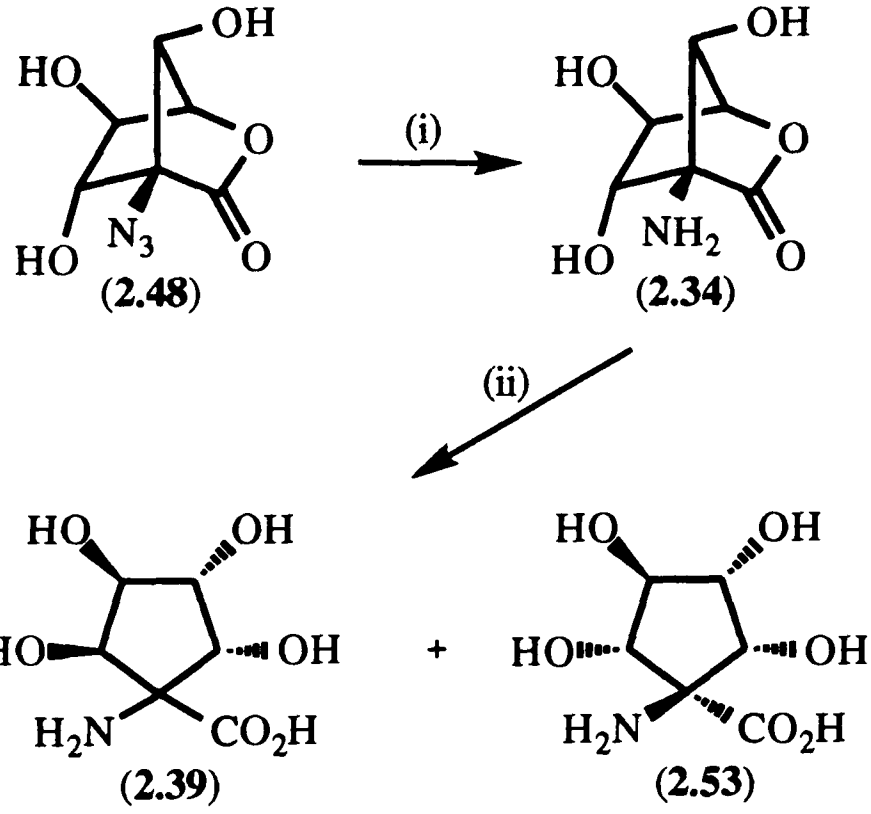
(i) Ac_2O, Py; (ii) Ac_2O, AcOH, c.H_2SO_4 (catalytic amount).

Scheme 2.48

(iv) Synthesis of a Fifth Polyhydroxylated Cyclopentane α-Amino Acid.

The controlled retro-aldol epimerisation of (**2.33**) provided the means of access to the azido triol (**2.48**). It was anticipated that conversion of this material to the corresponding amino acid could be achieved by a short reaction sequence.

Treatment of the azido triol (**2.48**) with aqueous sodium hydroxide again resulted in the formation of a mixture of two inseparable carboxylates. An alternative approach involved initial reduction of the azide functionality by hydrogenation in the presence of palladium black to give the amine (**2.34**). Unfortunately, basic hydrolysis of the lactone ring occurred with concomitant retro-aldol reaction to give a mixture of two amino acid products, (**2.39**) and (**2.53**) (**Scheme 2.49**). Other hydrolytic conditions investigated include aqueous pyridine, aqueous imidazole, and prolonged exposure to aqueous trifluoroacetic acid at 60 °C. In all these cases, no reaction was observed and only starting material was recovered.

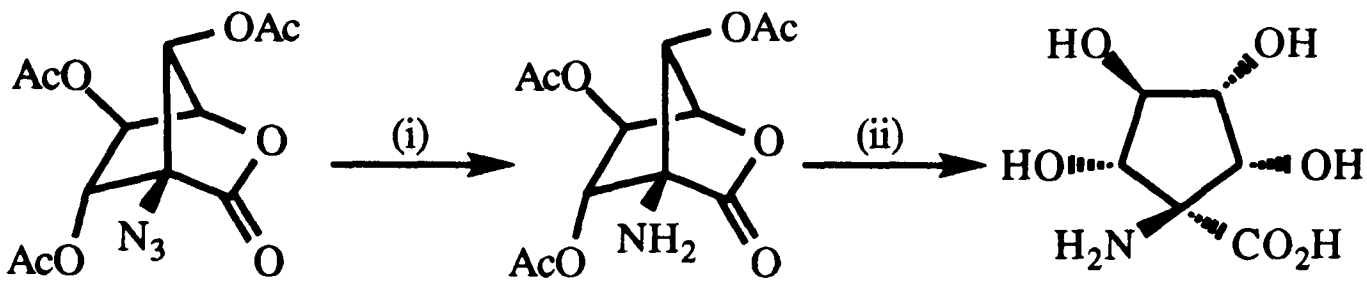


(i) H_2, Pd black, EtOH / H_2O, RT, 3.5 h, quant.;
(ii) Basic conditions: - aqueous NaOH (1 equiv);
- aqueous Et_3N (10 equiv);
- aqueous morpholine (10 equiv);
- Amberlite IRA - 400 ($^-$OH form), water.

Scheme 2.49

It was envisaged that base-induced retro-aldol reactions could be avoided by protection of the free hydroxyl groups prior to lactone ring opening. Thus the azido triacetate (**2.52**) was reduced by hydrogenation in the presence of palladium black to yield the amine (**2.54**). Treatment of (**2.54**) with aqueous triethylamine caused initial

ring opening as well as subsequent deprotection to give the amino acid (**2.53**) as the sole product upon purification by ion exchange chromatography (**Scheme 2.50**).

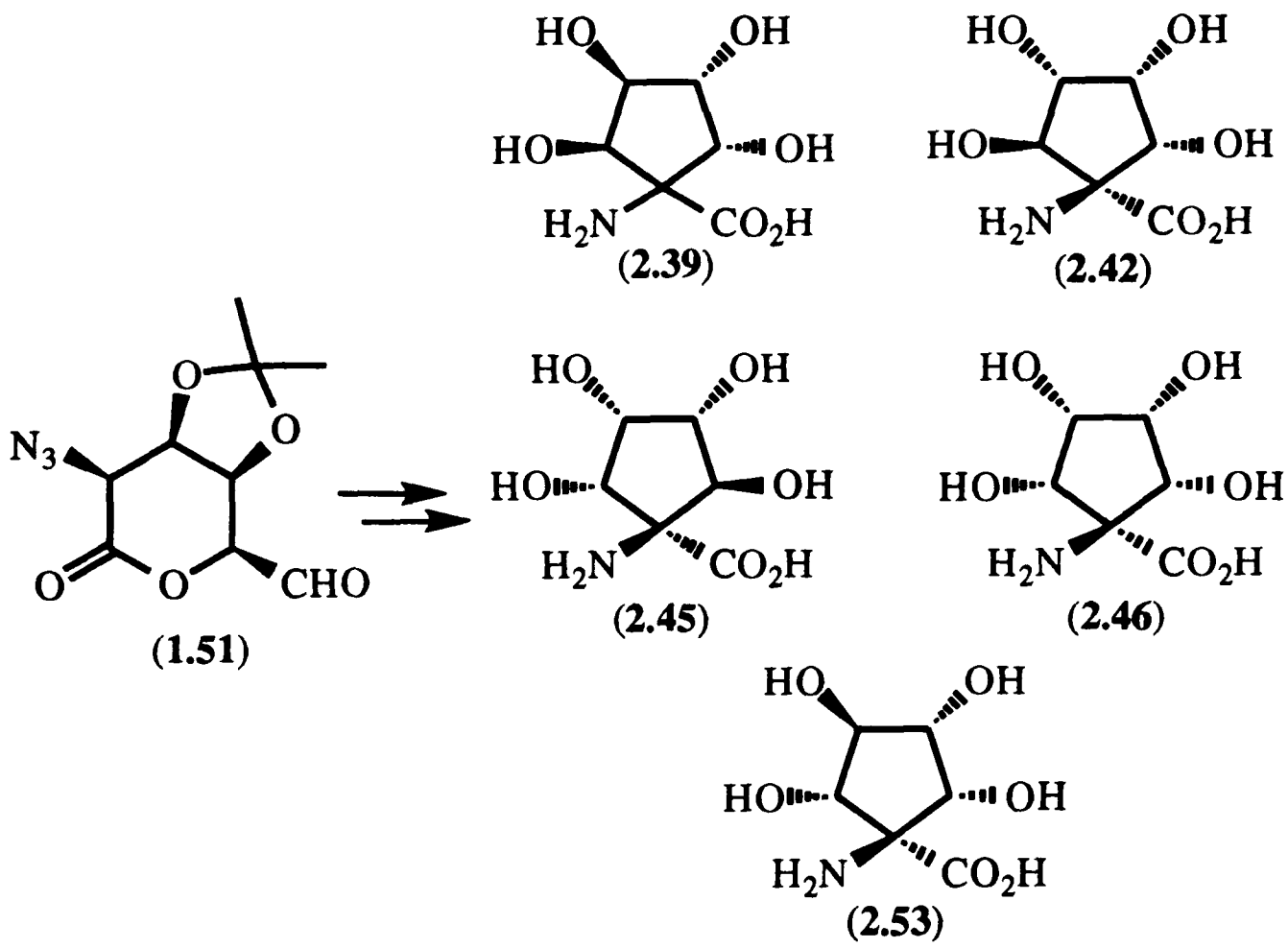


(2.52) (2.54) (2.53)

(i) H_2, Pd black, EtOH, RT, 18 h, 80%;
(ii) aqueous Et_3N (16 equiv), RT, 2 h, 62%.

Scheme 2.50

In summary, five tetrahydroxy-cyclopentane α-amino acids were synthesised, with good stereochemical control, from one azido aldehyde precursor (**1.51**) (**Scheme 2.51**). The flexibility in these syntheses is attributed to a series of intramolecular aldol and reverse aldol reactions towards the construction of the cyclopentane framework. These carbocyclic amino acids are currently being tested for biological activity.

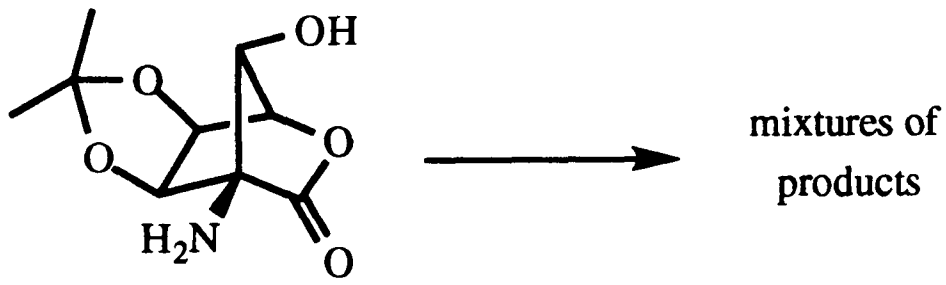


Scheme 2.51

2.4 Incorporation of a Tetrahydroxy-cyclopentane α-Amino Acid into Peptides.

One use of tetrahydroxy-cyclopentane α-amino acids would be their incorporation into short peptide sequences. This would provide an insight into the ability of these α,α-disubstituted amino acids to impose conformational restrictions on the secondary structure of a peptide backbone. Investigations into the assembly of oligopeptides have utilised the azido bicyclic lactone (**1.52**), as it is the most readily available carbocyclic starting material.

The initial approach involved prior attachment of the *N*-terminus of the bicyclic system to an *N*-protected amino acid. The lactone moiety could then be opened with a *C*-protected amino acid to give a tripeptide. Thus the amino lactone (**2.29**) was exposed to a range of peptide coupling conditions (**Scheme 2.52**). In all cases, reaction proceeded slowly to give mixtures of products which were often difficult to separate from each other.



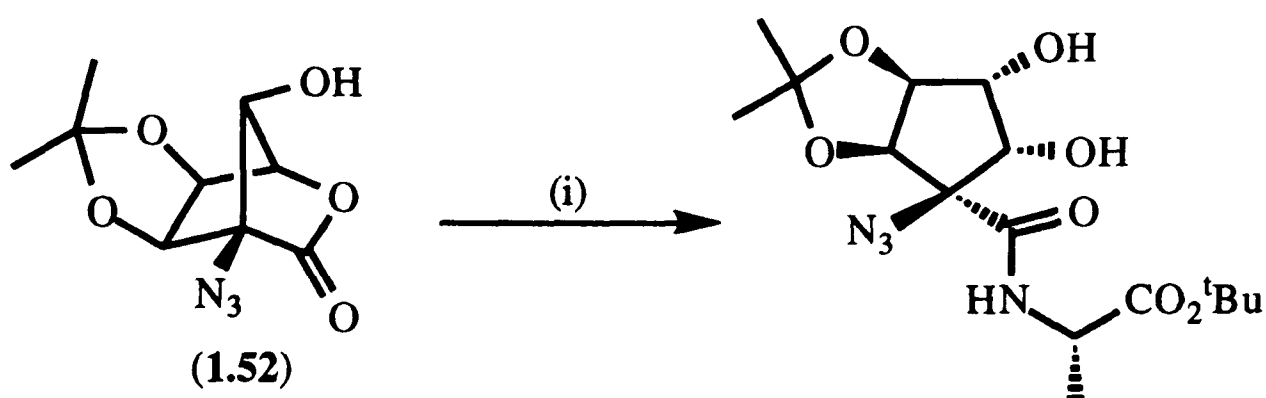
(2.29)

Conditions investigated:
- *N*-Z-Gly-OH, Et_3N, $ClCO_2Et$, THF, MeCN;
- *N*-Z-Gly-OH, DCCI, HOBT, DMF;
- *N*-Fmoc-Gly-OPfp, DMF;
- *N*-Fmoc-Gly-OPfp, HOBT, DMF;
- *N*-Boc-Gly-F, NMM, MeCN;
- *N*-Boc-**L**-Phe-OH, TBTU, HOBT, DIPEA, DMF.

Scheme 2.52

It was postulated that the poor selectivity of these reactions might be attributed to steric crowding around the primary amine of (**2.29**). This presumably led to competing reactions at the free hydroxyl group at C-7.

An alternative approach entailed reversing the order of peptide couplings onto the bicyclic system (**1.52**). Thus the bicyclic azide (**1.52**) was treated with L-phenylalanine *tert*-butyl ester in the presence of sodium acetate to give the coupled amide (**2.55**) in 91% yield (**Scheme 2.53**).



(i) L-Phe-O^{t}Bu, NaOAc, DMF, RT, 16 h, 91%.

Scheme 2.53

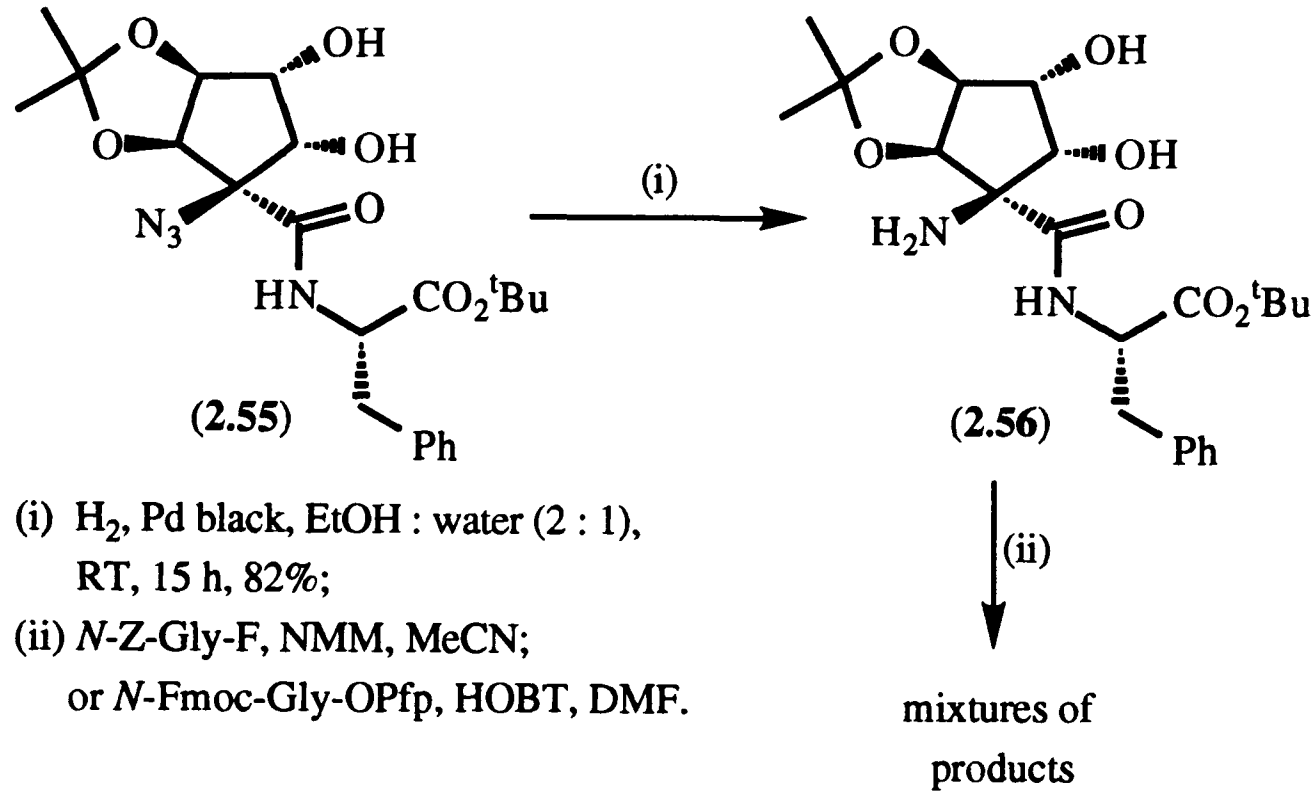
The choice of the *tert*-butyl ester protecting group over the methyl ester analogue was governed by two factors:

a) Subsequent linkage at the *N*-terminus of the peptide (**2.55**) would require the generation of the free amine base *via* reduction of the azide moiety. While unprotected dipeptide methyl esters are prone to cyclise to diketopiperazines, *tert*-butyl esters are more immune to such intramolecular nucleophilic attacks.[28]

b) Removal of the *tert*-butyl group could be achieved in acidic conditions. This would avoid the problematic base-induced retro-aldol reactions of the carbocyclic framework. Furthermore, the alkaline conditions necessary to

hydrolyse a methyl ester might cause other side reactions in the peptide chain, such as racemisation and hydantoin formation.[28]

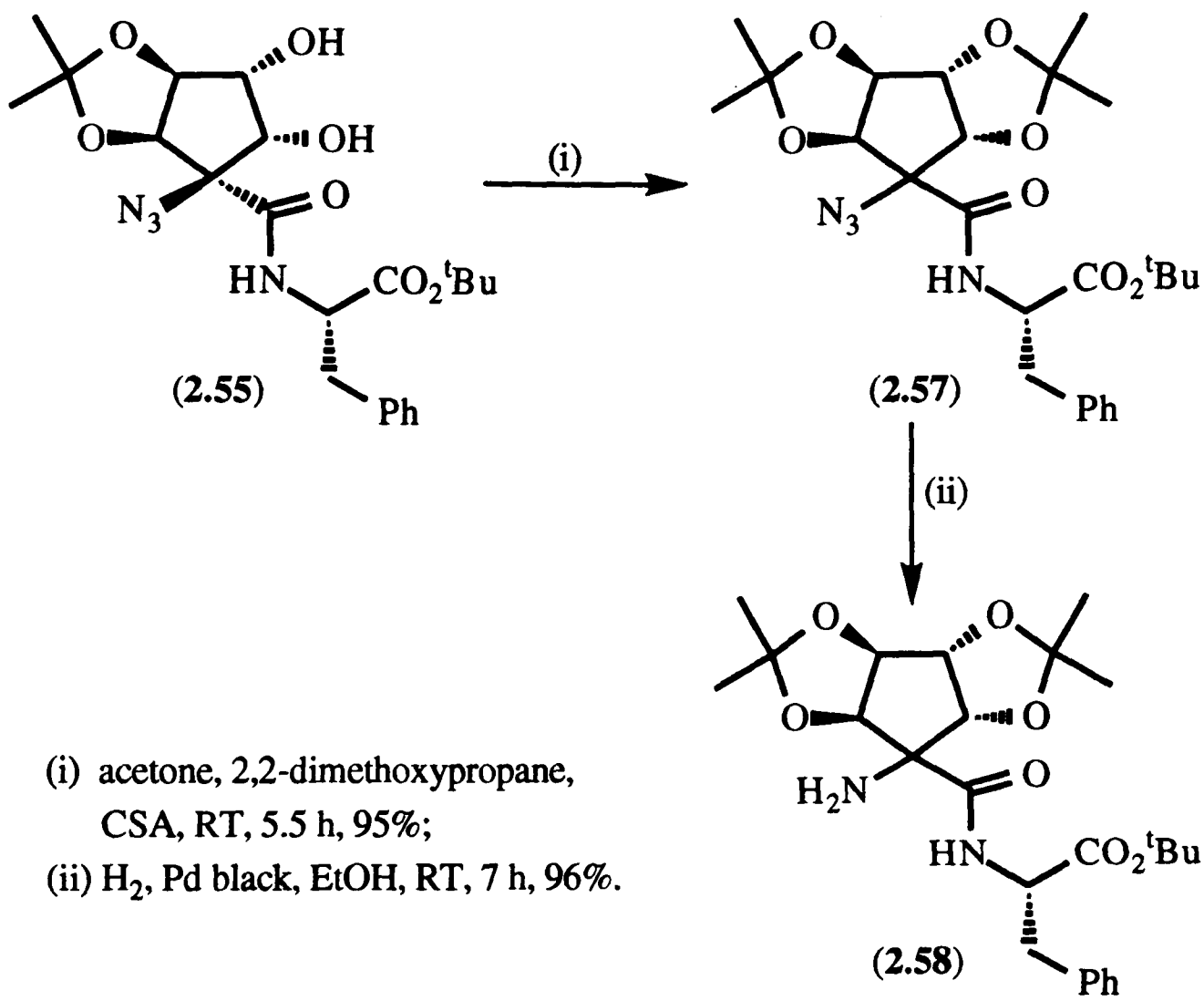
Reduction of the azide function of the peptide (**2.55**) *via* catalytic hydrogenation yielded the free amine (**2.56**). Exposure of (**2.56**) to various amino acid coupling conditions again resulted in competing reactions and the formation of product mixtures (**Scheme 2.54**).



(i) H_2, Pd black, EtOH : water (2 : 1), RT, 15 h, 82%;
(ii) *N*-Z-Gly-F, NMM, MeCN; or *N*-Fmoc-Gly-OPfp, HOBT, DMF.

Scheme 2.54

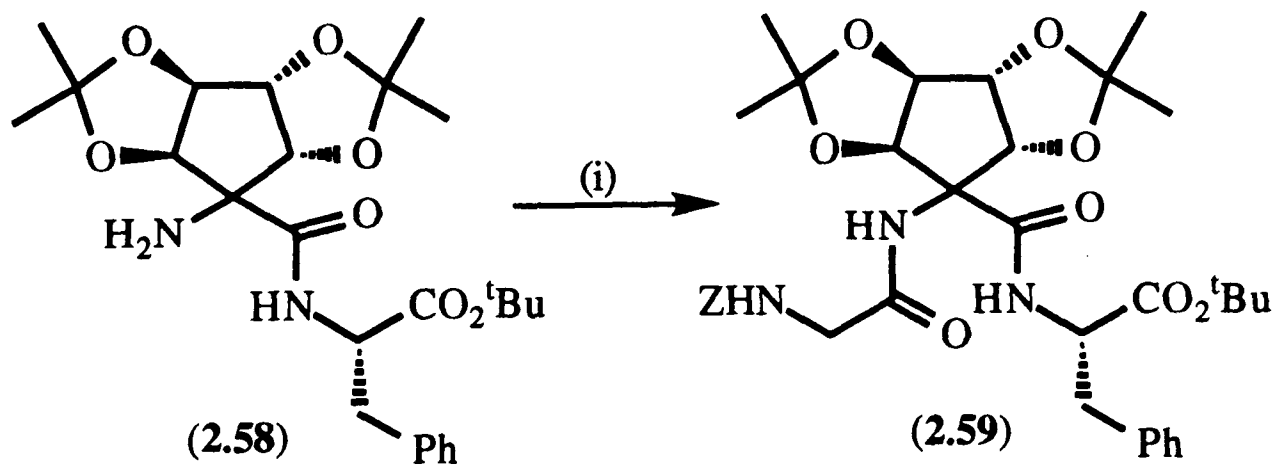
It was envisaged that protection of the diol unit would allow exclusive access to the primary amine in the subsequent coupling, thereby overcoming the problem of selectivity. Thus the azido diol (**2.55**) was treated with acetone and 2,2-dimethoxypropane, in the presence of (±)-10-camphorsulphonic acid, to produce the fully protected diacetonide (**2.57**). Generation of the free amine was then achieved *via* reduction of the azide function by hydrogenation in the presence of palladium black to give the dipeptide (**2.58**) (**Scheme 2.55**).



(i) acetone, 2,2-dimethoxypropane, CSA, RT, 5.5 h, 95%;
(ii) H_2, Pd black, EtOH, RT, 7 h, 96%.

Scheme 2.55

Reaction of the dipeptide (**2.58**) with *N*-benzyloxycarbonylglycine in the presence of *N,N'*-dicyclohexylcarbodiimide (DCCI) and 1-hydroxybenzotriazole (HOBT) for 48 hours gave the protected tripeptide (**2.59**) in good yield (**Scheme 2.56**). However, the isolation of this material from dicyclohexylurea, a co-product of the coupling reaction, proved to be difficult.

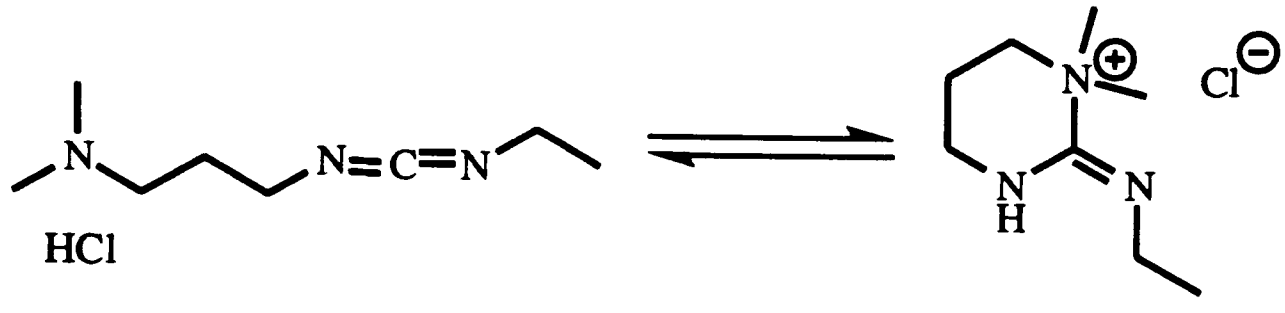


+ trace amounts of dicyclohexylurea

(i) *N*-Z-Gly-OH, DCCI, HOBT, DMF, RT, 48 h, 88% combined yield.

Scheme 2.56

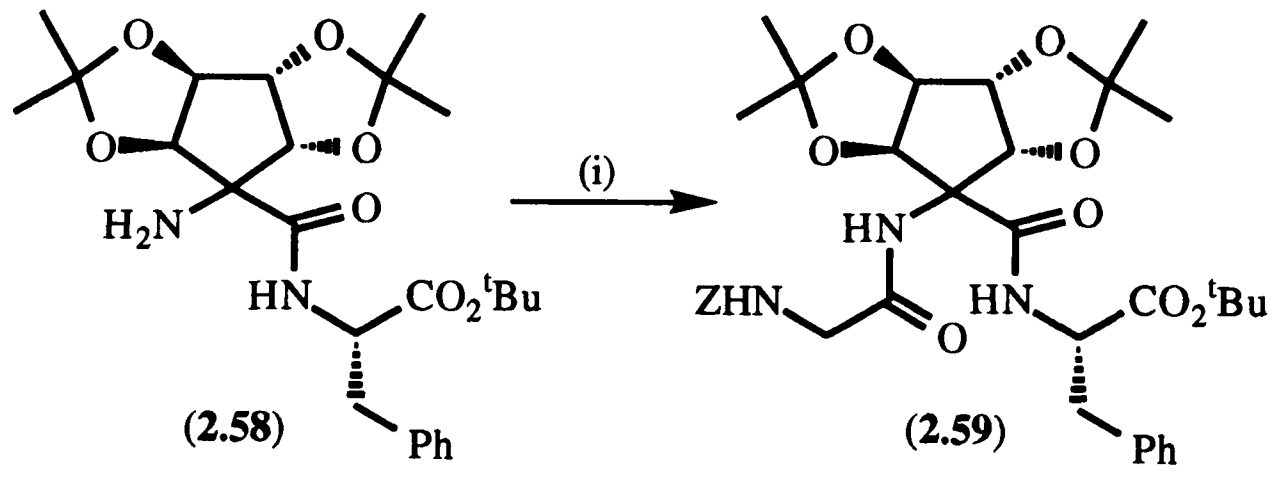
In order to facilitate purification of the tripeptide product (**2.59**), a water-soluble carbodiimide reagent, 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide (EDCI) (**2.60**),[29] was used in place of DCCI in the coupling reaction. The basic handle of EDCI would enable the urea co-product to be separated from the protected peptide products by extraction into an aqueous acidic phase (**Figure 2.6**).



1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, (EDCI)
(2.60)

Figure 2.6

As expected, treatment of the dipeptide (**2.58**) with *N*-benzyloxycarbonylglycine in the presence of EDCI and HOBT led to the ready isolation of the tripeptide (**2.59**) in 94% yield (**Scheme 2.57**).

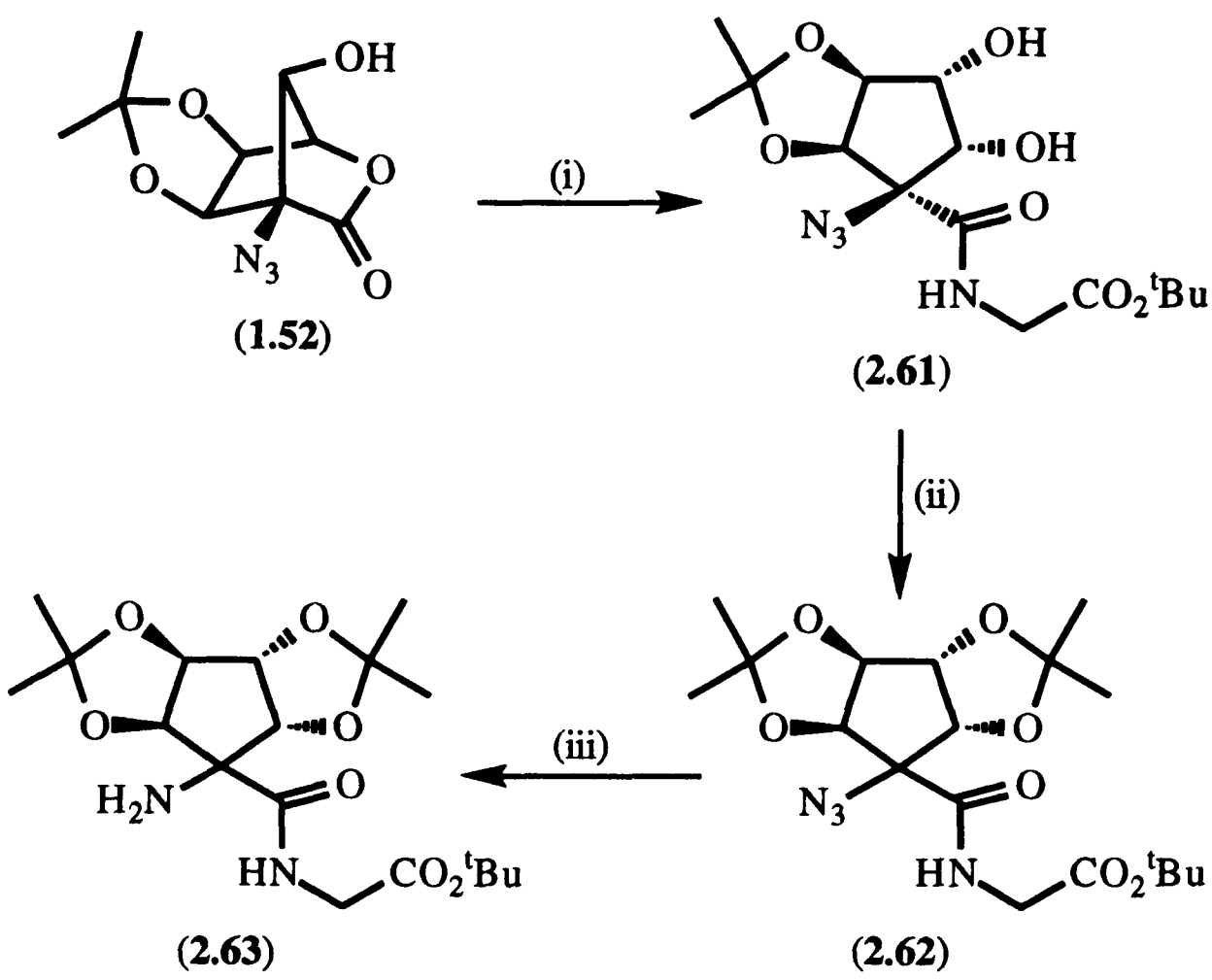


(i) *N*-Z-Gly-OH, EDCI, HOBT, CH_2Cl_2, RT, 48 h, 94%.

Scheme 2.57

An analogous series of reactions was carried out using glycine *tert*-butyl ester as the starting *C*-protected amino acid to open the bicyclic lactone (**1.52**). Thus the amide (**2.61**) was isolated in 95% yield. Further protection of the diol unit of the amide (**2.61**) was achieved by reaction with acetone and 2,2-dimethoxypropane to give the

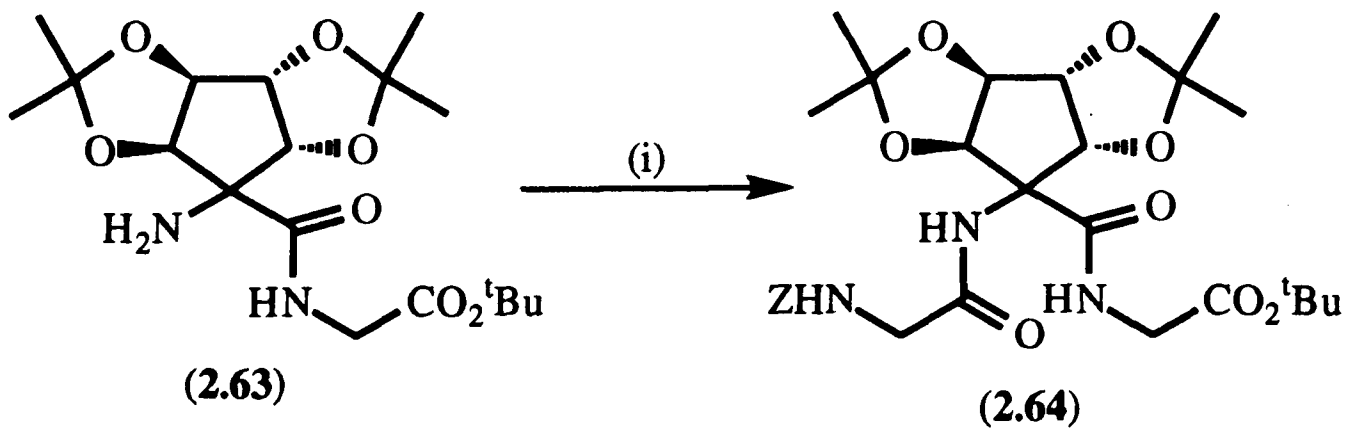
diacetonide (**2.62**). Reduction of the azide function by catalytic hydrogenation produced the amine (**2.63**) in 89% yield (**Scheme 2.58**).



(i) Gly-O^{t}Bu, NaOAc, DMF, RT, 17 h, 95%;
(ii) acetone, 2,2-dimethoxypropane, CSA, RT, 1 h, 95%;
(iii) H_2, Pd black, EtOH, RT, 17 h, 89%.

Scheme 2.58

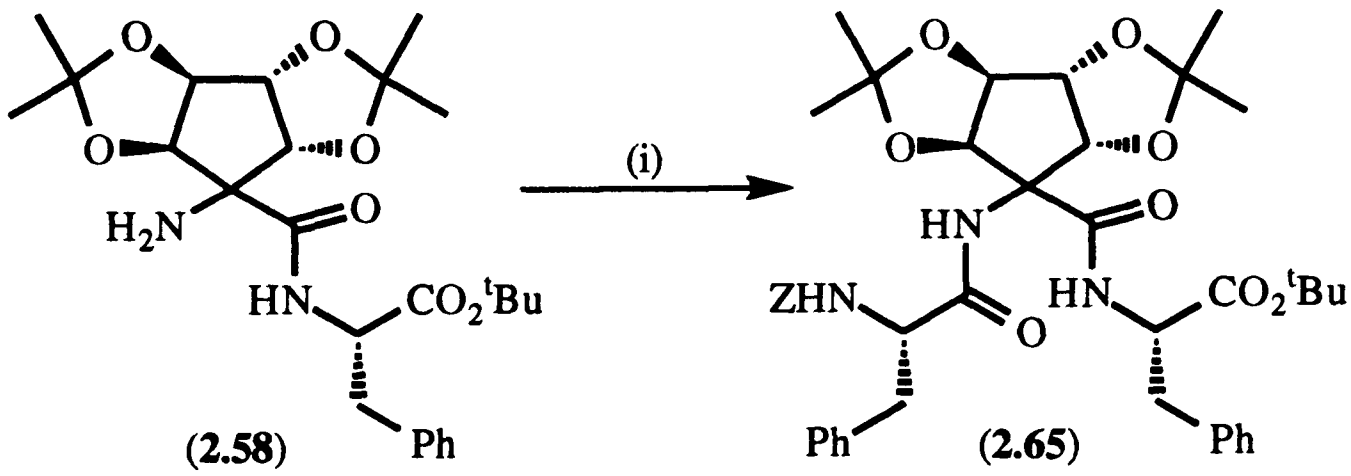
Treatment of the amine (**2.63**) with *N*-benzyloxycarbonylglycine in the presence of EDCI and HOBT gave a second tripeptide (**2.64**) in good yield (**Scheme 2.59**).



(i) *N*-Z-Gly-OH, EDCI, HOBT, CH_2Cl_2, RT, 45 h, 84%.

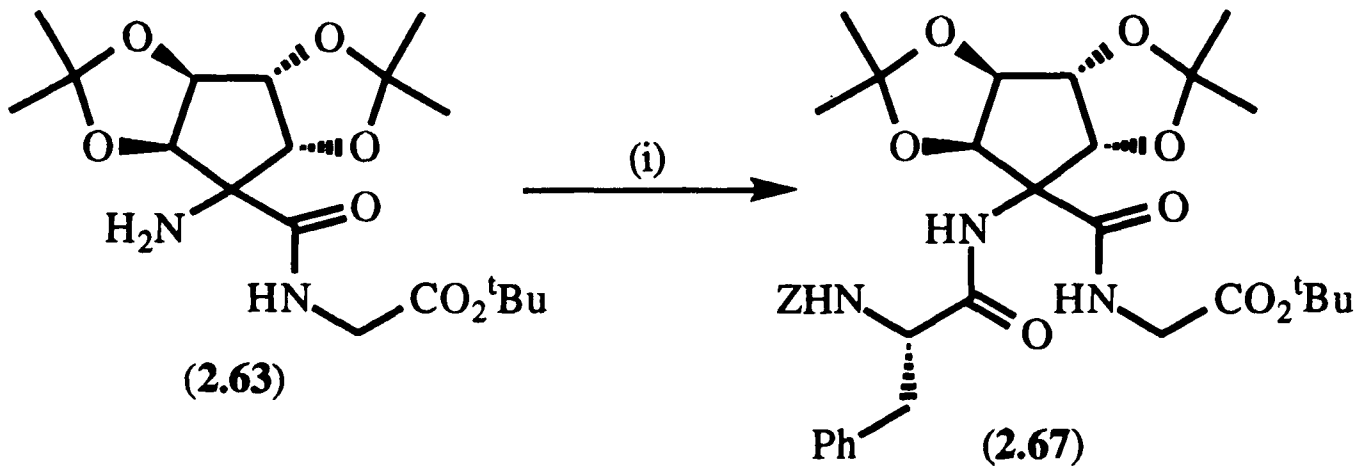
Scheme 2.59

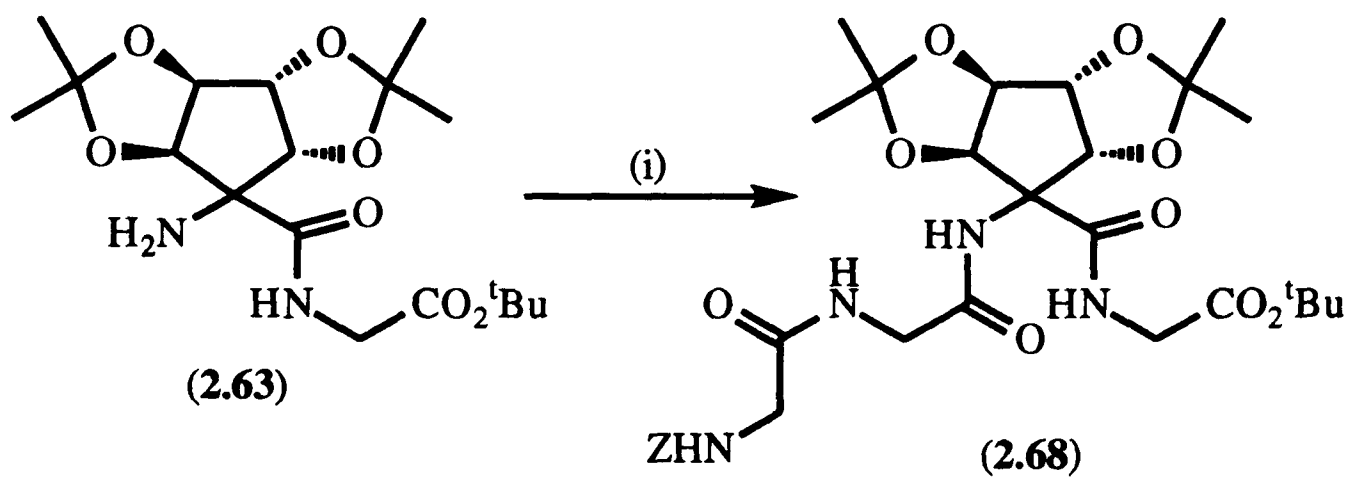
The efficiency of peptide bond formation at the *N*-termini of the dipeptides, (**2.58**) and (**2.63**), prompted a brief investigation to examine the scope of this reaction. Accordingly, each of the dipeptides, (**2.58**) and (**2.63**), was treated with two other *N*-protected amino acids, namely *N*-benzyloxycarbonyl-**L**-phenylalanine and *N*-benzyloxycarbonylglycylglycine, in the presence of EDCI and HOBT. These reactions are summarised in **Schemes 2.60** and **2.61**.



(i) *N*-Z-**L**-Phe-OH, EDCI, HOBT, CH_2Cl_2, RT, 120 h,
71% (89% based on recovered starting material);
(ii) *N*-Z-Gly-Gly-OH, EDCI, HOBT, CH_2Cl_2, RT, 125 h,
63% (79% based on recovered starting material).

Scheme 2.60





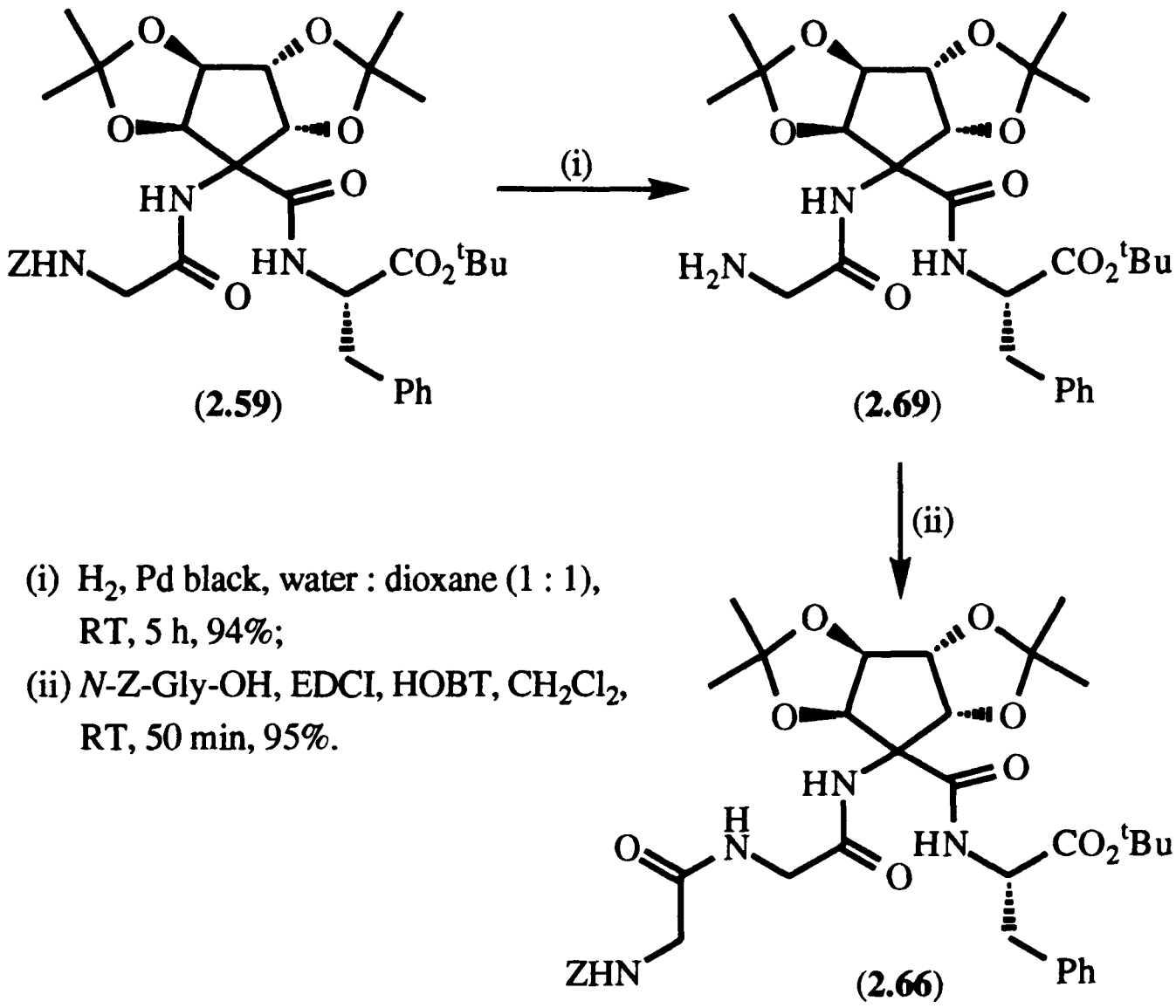
(i) *N*-Z-L-Phe-OH, EDCI, HOBT, CH_2Cl_2, RT, 46 h, 82%;
(ii) *N*-Z-Gly-Gly-OH, EDCI, HOBT, CH_2Cl_2, RT, 70 h, 93%.

Scheme 2.61

These results indicated that EDCI promoted relatively efficient peptide coupling reactions of the carbocyclic α-amino amide systems, (**2.58**) and (**2.63**), to give the readily isolable oligopeptides, (**2.65**) and (**2.66**), (**2.67**) and (**2.68**) respectively. Peptide chain extension of the amino-glycyl derivative (**2.63**) appeared to proceed with greater efficiency than that of its amino-phenylalanyl analogue (**2.58**). This may be due to the greater steric hindrance imposed by the bulky benzyl residue in the latter molecule (**2.58**).

An investigation to examine further chain extensions at the *N*-termini of these oligopeptide systems was carried out using the tripeptide (**2.59**). Thus removal of the benzyloxycarbonyl protecting group of (**2.59**) was achieved by hydrogenation in the

presence of palladium black to give the free amine (**2.69**). Treatment of this material with *N*-Z-benzyloxycarbonylglycine in the presence of EDCI and HOBT effected a smooth coupling to produce the tetrapeptide (**2.66**) in 95% yield (**Scheme 2.62**).

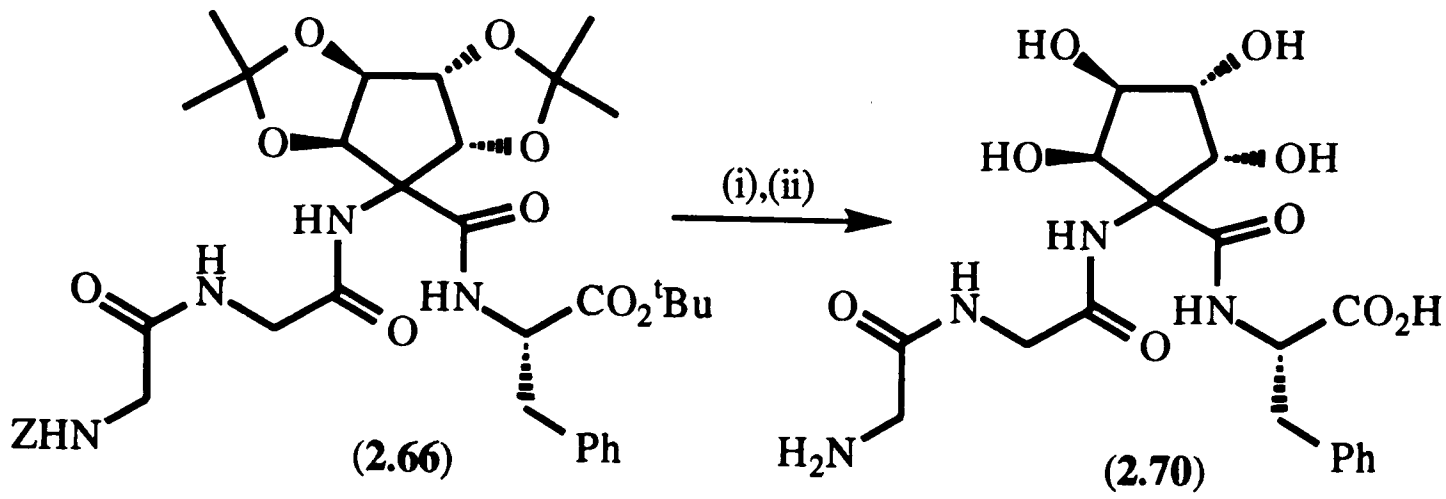


(i) H_2, Pd black, water : dioxane (1 : 1), RT, 5 h, 94%;
(ii) *N*-Z-Gly-OH, EDCI, HOBT, CH_2Cl_2, RT, 50 min, 95%.

Scheme 2.62

It is noteworthy that peptide coupling at the relatively exposed free amine of (**2.69**) required a much shorter reaction time than at the amine of the α-amino amides (**2.58**) and (**2.63**).

Treatment of the protected tetrapeptide (**2.66**) with 80% aqueous trifluoroacetic acid, followed by catalytic hydrogenation of the crude reaction mixture, caused complete deprotection to give the peptide (**2.70**) upon isolation by ion exchange chromatography (**Scheme 2.63**).



(i) 80% aqueous TFA, RT, 2 h;
(ii) H_2, Pd black, water, RT, 22 h, 99% yield over two steps.

Scheme 2.63

NMR spectroscopic studies of the deprotected tetrapeptide (**2.70**) are currently being carried out. Elucidation of the adopted conformations of this material in solution would provide an insight into the ability of the (2α,3α,4β,5β)-substituted cyclopentane α-amino acid (**2.39**) to impose conformational restrictions on the secondary structure in a peptide backbone.

References.

1. (a) Kiliani, H.; *Chem. Ber.*, 1885, **18**, 3066; (b) Hudson, C.S.; *Adv. Carbohydr. Chem.*, 1945, **1**, 5.
2. Brown, J.M.; Conn, A.D.; Pilcher, G.; Leitao, M.L.P.; Meng-Yan, Y.; *J. Chem. Soc. Chem. Commun.*, 1989, 1817.
3. (a) Beacham, A.R.; Bruce, I.; Choi, S.; Doherty, O.; Fairbanks, A.J.; Fleet, G.W.J.; Skead, B.M.; Peach, J.M.; Saunders J.; Watkins, D.J.; *Tetrahedron : Asymm.*, 1991, **2**, 883; (b) Bichard, C.J.F.; Wheatley, J.R.; Fleet, G.W.J.; *Tetrahedron : Asymm.*, 1994, **5**, 431.
4. Fleet, G.W.J.; Sugar Lactones as Useful Starting Materials in 'Antibiotics and Antiviral Compounds: Chemical Synthesis and Modification', (Ed. Krohn, E.; Kirst, H.; Maas, H.), pp. 333-342, VCH Verlagsgesellschaft, Weinheim, 1993, and references cited therein.
5. The numbering system adopted here refers to the lactone carbonyl as C-1. Strictly the aldehyde carbon should be referred to as C-1, rather than C-6. The correct convention has been used for naming all formyl-lactones (see note concerning nomenclature).
6. (a) Elliott, R.P. 'Sugars as Homochiral Starting Materials', D.Phil. Thesis, Oxford University, 1992, Chapter 3; (b) Fairbanks, A.J. 'Sugar Lactones in Synthesis', D.Phil. Thesis, Oxford University, 1993, Chapters 3 and 4.
7. Elliott, R.P.; Fleet, G.W.J.; Pearce, L.; Smith, C.; Watkin, D.J.; *Tetrahedron Lett.*, 1991, **43**, 6227.
8. Bruce, I.; Fleet, G.W.J.; Girdhar, A.; Haraldsson, M.; Peach, J.M.; Watkin, D.J.; *Tetrahedron*, 1990, **46**, 19.
9. Elliott, R.P.; Hui, A.; Fairbanks, A.J.; Nash, R.J.; Winchester, B.G.; Way, G.; Smith, C.; Lamont, R.B.; Storer, R.; Fleet, G.W.J.; *Tetrahedron Lett.*, 1993, **34**, 7949.

10. Elliott, R.P. 'Sugars as Homochiral Starting Materials', D.Phil. Thesis, Oxford University, 1992, Chapter 4.

11. Ando, O.; Nakajima, M.; Hamano, K.; Itoi, K.; Takahashi, S.; Takamatsu, Y.; Sato, A.; Enokita, R.; Okazaki, T.; Haruyama, H.; Kinoshita, T.; *J. Antibiot.*, 1993, **46**, 1116.

12. (a) Tropea, J.E.; Kaushal, G.P.; Pastuszak, I.; Mitchell, M.; Aoyagi, T.; Molyneux, R.; Elbein, A.D.; *Biochemistry*, 1990, **29**, 10062; (b) Farr, R.A.; Peet, N.P.; Kang, M.S.; *Tetrahedron Lett.*, 1990, **31**, 7109.

13. Cenci di Bello, I.; Fleet, G.W.J.; Namgoong, S.K.; Tadano, K.I.; Winchester, B.; *Biochem. J.*, 1989, **159**, 855.

14. Fairbanks, A.J.; Elliott, R.P.; Smith, C.; Hui, A.; Way, G.; Storer, R.; Taylor, H.; Watkin, D.J.; Winchester, B.G.; Fleet, G.W.J.; *Tetrahedron Lett.*, 1993, **34**, 7953.

15. (a) Fairbanks, A.J.; Fleet, G.W.J.; *Tetrahedron*, 1995, **51**, 3881; (b) Brandstetter, T.W.; Kim, Y.-H.; Son, J.C.; Taylor, H.M.; Lilley, P.M.de Q.; Watkin, D.J.; Johnson, L.N.; Oikonomakos, N.G.; Fleet, G.W.J.; *Tetrahedron Lett.*, 1995, **36**, 2149.

16. Lopez, C.A.; Trigo, G.C. 'The Chemistry of Hydantoins', *Adv. in Heterocyclic Chem.*, 1985, **38**, 177.

17. (a) Paul, P.K.C.; Di Blasio, B.; Pavone, V.; Pedone, C.; Balaram, P.; *J. Am. Chem. Soc.*, 1986, **108**, 6363; (b) Fauchere, J.-L., Elements for the Rational Design of Drugs in *Adv. Drug Res.*, 1986, **15**, 29; (c) Mutter, M.; *Angew. Chem.*; 1986, **97**, 639.

18. (a) Frauer, A.; Mehlführer, M.; Thirring, K.; Berner, H.; *J. Org. Chem.*, 1994, **59**, 4215; (b) Toniolo, C.; Crisma, M.; Pegoraro, S.; Valle, G.; Bonora, G.M.; Becker, E.L.; Polinelli, S.; Boesten, W.H.J.; Schoemaker, H.E.; Meijer, E.M.; Kamphuis, J.; Freer, R.; *Peptide Res.*, 1991, **4**, 66.

19. (a) Deeks, T.; Crooks, T.P.A.; Waigh, R.D.; *J. Med. Chem.*, 1983, **26**, 762; (b) Christensen, H.N.; Handlogten, M.E.; Vadgma, J.C.; de la Cuesta, E.; Ballesteros, P.; Trigo, G.C.; Avendano, C.; *J. Med. Chem.*, 1983, **26**, 1374.

20. (a) Bhattacharjee, M.K.; Snell, E.E.; *J. Biol. Chem.*, 1990, **265**, 6664; (b) Schirlin, D.; Gerhart, F.; Hornsperger, J.M.; Hamon, M.; Wagner, J.; Jung, M.J.; *J. Med. Chem.*, 1988, **31**, 30.

21. (a) Knudson, C.G.; Palkowitz, A.D.; Rapoport, H.; *J. Org. Chem.*, 1985, **50**, 325; (b) Lubell, W.D.; Rapoport, H.; *J. Am. Chem. Soc.*, 1987, **109**, 236.

22. see Appendix 1.

23. see Appendix 2.

24. Fairbanks, A.J. 'Sugar Lactones in Synthesis', D.Phil. Thesis, Oxford University, 1993, Chapter 4.

25. see Appendix 3.

26. Hui, A.; Fairbanks, A.J.; Nash, R.J.; Lilley, P.M.de Q.; Storer, R.; Watkin, D.J.; Fleet, G.W.J.; *Tetrahedron Lett.*, 1994, **35**, 8895.

27. see Appendix 4.

28. Jones, J.H. 'The Chemical Synthesis of Peptides' (International Series of Monographs on Chemistry; 23), pp. 33 - 35, Oxford University Press, 1994.

29. Sheehan, J.C.; Cruickshank, P.A.; Boshart, G.L.; *J. Org. Chem.*, 1961, **26**, 2525.

CHAPTER 3

Experimental Procedures

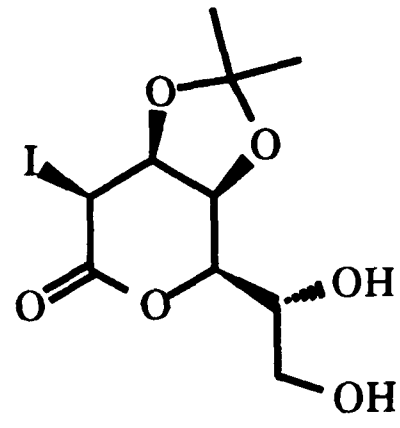
General Experimental Procedures.

Melting points were recorded on a Kofler hot block and are uncorrected. Proton nuclear magnetic resonance (δ_H) spectra were recorded on Varian Gemini 200 (at 200 MHz), or Bruker AC 200 (at 200 MHz), or Bruker AM 500 (at 500 MHz) spectrometers. Carbon nuclear magnetic resonance (δ_C) spectra were recorded on Varian Gemini 200 (at 50 MHz), or Bruker AC 200 (at 50 MHz), or Bruker AM 500 (at 125 MHz) spectrometers, and multiplicities were assigned using the DEPT sequence. All proton nuclear magnetic resonance spectra were recorded at 200 MHz, and carbon spectra at 50 MHz, unless otherwise stated. All chemical shifts are quoted on the δ-scale using residual solvent as an internal standard. Carbon spectra run in D_2O were referenced to methanol (δ_C 49.6 ppm) or 1,4-dioxane (δ_C 67.4 ppm) as internal standards. Infra-red spectra were recorded on a Perkin-Elmer 1750 IR Fourier Transform spectrophotometer. Mass spectra were recorded on a VG Micromass 30F, ZAB 1F, Masslab 20-250 spectrometers using desorption chemical ionisation (NH_3, DCI), chemical ionisation (NH_3, CI), or electrospray, as stated. Optical rotations were measured on a Perkin-Elmer 241 polarimeter with a path length of 1 dm. Concentrations are given in g / 100 ml. Circular dichroism spectra were performed on a JASCO J720 spectropolarimeter. In each case a water baseline has been subtracted, and the spectra have been smoothed. Microanalyses were performed by the microanalysis service of the Dyson-Perrins Laboratory. Thin layer chromatography (t.l.c.) was carried out on aluminium sheets coated with 60 F_{254} silica, and plates were developed using a solution of 0.2% w/v cerium (IV) sulphate and 5% w/v ammonium molybdate in 2 M sulphuric acid, or 0.5% w/v ninhydrin in methanol. Flash chromatography was carried out using Sorbsil C60 40/60 silica.

CMAW (chloroform / methanol / acetic acid / water), used as an eluent, was prepared in the following ratio:- $CHCl_3$: MeOH : AcOH : H_2O, 60 : 30 : 3 : 5. Ion exchange columns were packed with 'Dowex' 50W-X8 or 'Amberlite' CG-120 in the H^+ forms, or 'Amberlite' CG-400 in the HO^- form. Solvents and commercially available reagents were dried and purified before use according to standard procedures; dichloromethane was refluxed over and distilled from calcium hydride; pyridine was distilled from calcium hydride and stored over potassium hydroxide; tetrahydrofuran was distilled from a solution dried with sodium in the presence of benzophenone under nitrogen. *N,N*-Dimethylformamide was distilled under reduced pressure from calcium hydride or purchased anhydrous from the Aldrich Chemical Company in Sure-Seal™ bottles. Hexane was distilled at 68 °C before use to remove involatile fractions. All solvents were removed *in vacuo*.

Experimental Procedures for Results and Discussion Section 2.1.

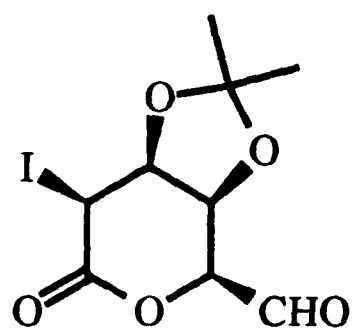
2-Deoxy-2-iodo-3,4-*O*-isopropylidene-**D**-*glycero*-**D**-*talo*-heptono-1,5-lactone (**2.8**)



2-Deoxy-2-iodo-3,4:6,7-di-*O*-isopropylidene-**D**-*glycero*-**D**-*talo*-heptono-1,5-lactone (**2.5**) (14.27 g, 35.9 mmol) was dissolved in aqueous acetic acid (80%, 250 ml) and the solution stirred at 50 °C in the dark for 3 h. After this time t.l.c. analysis (ethyl acetate) indicated complete conversion of starting material (R_f 0.65) to one major product (R_f 0.25). The solvent was removed and the residue co-evaporated with

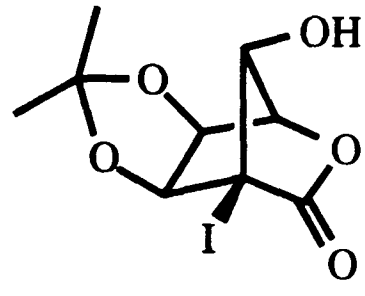
toluene (3 x 50 ml). Purification by dry flash chromatography (ethyl acetate) gave 2-deoxy-2-iodo-3,4-*O*-isopropylidene-**D**-*glycero*-**D**-*talo*-heptono-1,5-lactone (**2.8**) (11.31 g, 31.6 mmol, 88%) as a waxy solid. $[\alpha]_D^{20}$ +103.5 (*c*, 1.0 in acetone) [lit.[1] $[\alpha]_D^{20}$ +102.3 (*c*, 1.0 in acetone)]; δ_H ($CDCl_3$): 1.41, 1.47 (2 x 3H, 2 x s, $C(C\underline{H}_3)_2$), 2.50 (1H, br s ex in D_2O, OH), 2.99 (1H, br s ex in D_2O, OH), 3.87 (2H, m, H-7, H-7'), 4.04 (1H, m, H-6), 4.31 (1H, dd, $J_{5,4}$ 1.7 Hz, $J_{5,6}$ 8.6 Hz, H-5), 4.74 (1H, dd, $J_{4,3}$ 7.7 Hz, $J_{4,5}$ 1.7 Hz, H-4), 4.90 (1H, dd, $J_{3,2}$ 3.1 Hz, $J_{3,4}$ 7.7 Hz, H-3), 4.99 (1H, d, $J_{2,3}$ 3.1 Hz, H-2).

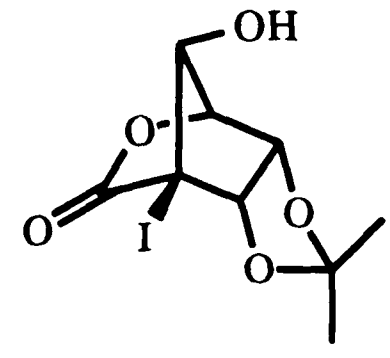
5-Iodo-5-deoxy-3,4-*O*-isopropylidene-**D**-*altrurono*-2,6-lactone (**1.47**)



Periodic acid (4.35 g, 19.1 mmol) was added to a stirred solution of 2-deoxy-2-iodo-3,4-*O*-isopropylidene-**D**-*glycero*-**D**-*talono*-heptono-1,5-lactone (**2.5**) (1.630 g, 4.55 mmol) in tetrahydrofuran (40 ml) at room temperature. After 5 min a thick white precipitate was formed, and after a further 20 min t.l.c. analysis (ethyl acetate) indicated complete conversion of starting material (R_f 0.3) to one product (R_f 0.45). The reaction mixture was preadsorbed onto silica gel and purification by dry flash chromatography (ethyl acetate / hexane, 3 : 1) gave 5-iodo-5-deoxy-3,4-*O*-isopropylidene-**D**-*altrurono*-2,6-lactone (**1.47**) (1.440 g, 4.42 mmol, 97%) as a colourless oil. δ_H ($CDCl_3$): 1.35, 1.37 (2 x 3H, 2 x s, $C(C\underline{H}_3)_2$), 4.54 (1H, m), 4.92 (2H, m), 5.14 (1H, m), 9.70 (1H, s, H-6). This material was used directly without further characterisation.

(1*R*,4*R*,5*S*,6*R*,7*S*)-5,6,7-Trihydroxy-4-iodo-5,6-*O*-isopropylidene-2-oxa-bicyclo[2.2.1]heptan-3-one (**1.48**) and (1*S*,4*S*,5*S*,6*R*,7*S*)-5,6,7-trihydroxy-4-iodo-5,6-*O*-isopropylidene-2-oxa-bicyclo[2.2.1]heptan-3-one (**1.49**)

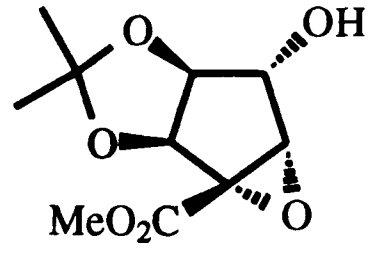




Potassium fluoride (512 mg, 8.83 mmol) and 18-crown-6 (466 mg, 1.77 mmol) were added to a stirred solution of 5-iodo-5-deoxy-3,4-*O*-isopropylidene-**D**-*altrurono*-2,6-lactone (**1.47**) (1.440 g, 4.42 mmol) in acetonitrile (50 ml) under nitrogen at 0 °C. After 1 h t.l.c. analysis (ethyl acetate / hexane, 1 : 1) showed little starting material (R_f 0.1) and two products (R_f 0.45 and R_f 0.35). Ethyl acetate (150 ml) and then water / brine (1 : 1, 10 ml) were added and the mixture stirred vigorously for 10 min to quench the reaction. The organic layer was decanted and the aqueous layer re-extracted with ethyl acetate (2 x 50 ml). The combined organic layers were dried (magnesium sulphate) and the solvent was removed. Purification by flash chromatography (ethyl acetate / hexane, 1 : 3) gave two main products, (1*R*,4*R*,5*S*,6*R*,7*S*)-5,6,7-trihydroxy-4-iodo-5,6-*O*-isopropylidene-2-oxa-bicyclo[2.2.1]heptan-3-one (**1.48**) (R_f 0.45) (725 mg, 2.22 mmol, 50%); m.p. 164 - 168 °C (diethyl ether / hexane) [lit.[1] m.p. 156 - 159 °C (diethyl ether / hexane)]; $[\alpha]_D^{20}$ +22.4 (*c*, 0.5 in chloroform) [lit.[1] $[\alpha]_D^{20}$ +24.4 (*c*, 0.5 in chloroform)]; δ_H ($CDCl_3$): 1.40, 1.56 (2 x 3H, 2 x s, $C(C\underline{H}_3)_2$), 2.55 (1H, d ex in D_2O, *J* 3.0 Hz, OH), 4.54 - 4.67 (3H, m), 4.80 (1H, s); and (1*S*,4*S*,5*S*,6*R*,7*S*)-5,6,7-trihydroxy-4-iodo-5,6-*O*-isopropylidene-2-oxa-bicyclo[2.2.1]heptan-3-one (**1.49**) (R_f 0.35) (170 mg, 0.52 mmol, 12%); m.p. 200 - 202 °C (diethyl ether / hexane) [lit.[1] m.p. 201 - 204 °C (diethyl ether / hexane)]; $[\alpha]_D^{20}$ +73.5 (*c*, 1.0 in chloroform) [lit.[1] $[\alpha]_D^{20}$ +83.6 (*c*, 1.0 in chloroform)]; δ_H [$(CD_3)_2SO$]: 1.30, 1.33 (2 x 3H, 2 x s, $C(C\underline{H}_3)_2$), 4.51 (1H, m,

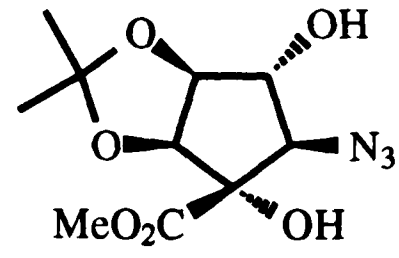
H-7), 4.78 (1H, m, H-4), 4.96, 4.99 (2H, 2 x dd, H-5, H-6), 7.03 (1H, d ex in D_2O, $J_{7,OH}$ 5.1 Hz, OH).

(1*S*,2*R*,3*S*,4*R*,5*S*)-Methyl [1,5-epoxy-2,3,4-trihydroxy-2,3-*O*-isopropylidene-cyclopentane] carboxylate (**2.9**)



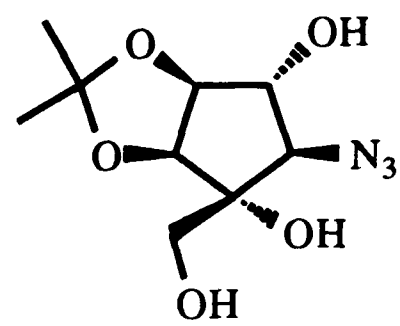
Potassium carbonate (192 mg, 1.39 mmol) was added to a solution of (1*R*,4*R*,5*S*,6*R*,7*S*)-5,6,7-trihydroxy-4-iodo-5,6-*O*-isopropylidene-2-oxa-bicyclo[2.2.1]heptan-3-one (**1.48**) (725 mg, 2.22 mmol) in methanol (60 ml) under nitrogen at 0 °C. The solution was stirred at 0 °C for 1 h, and was then allowed to warm up to room temperature for 1 h. After this time t.l.c. analysis (ethyl acetate / hexane, 1 : 1) indicated complete conversion of starting material (R_f 0.45) to one product (R_f 0.25). The solution was filtered to remove the excess solid bicarbonate and adjusted to pH 5 by dropwise addition of acetic acid. The solvent was removed and purification by flash chromatography (ethyl acetate / hexane, 1 : 1) gave (1*S*,2*R*,3*S*,4*R*,5*S*)-methyl [1,5-epoxy-2,3,4-trihydroxy-2,3-*O*-isopropylidene-cyclopentane] carboxylate (**2.9**) (476 mg, 2.07 mmol, 93%) as a colourless crystalline solid. M.p. 122 - 123 °C (diethyl ether / hexane) [lit.[2] m.p. 122 - 123 °C (diethyl ether / hexane)]; $[\alpha]_D^{20}$ -36.4 (*c*, 1.0 in chloroform) [lit.[2] $[\alpha]_D^{20}$ -36.1 (*c*, 1.0 in chloroform)]; δ_H ($CDCl_3$): 1.34, 1.47 (2 x 3H, 2 x s, $C(C\underline{H}_3)_2$), 2.28 (1H, d ex in D_2O, $J_{OH,4}$ 9.0 Hz, OH), 3.83 (3H, s, $CO_2C\underline{H}_3$), 4.10 (1H, m, H-5), 4.25 (1H, ddd, $J_{3,2}$ 5.5 Hz, $J_{3,4}$ 1.9 Hz, $J_{3,5}$ 1.2 Hz, H-3), 4.30 (1H, dd, $J_{4,OH}$ 9.0 Hz, $J_{4,3}$ 1.9 Hz, H-4), 4.90 (1H, dd, $J_{2,3}$ 5.5 Hz, $J_{2,5}$ 0.9 Hz, H-2).

(1*S*,2*R*,3*S*,4*R*,5*R*)-Methyl [5-azido-1,2,3,4-tetrahydroxy-2,3-*O*-isopropylidene-cyclopentane] carboxylate (**2.10**)



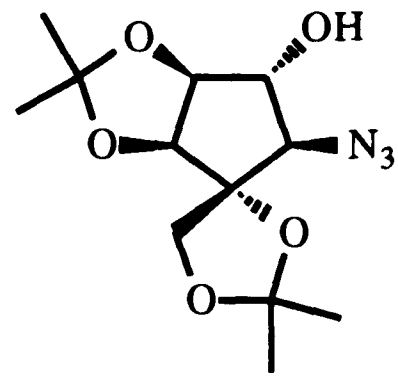
Sodium azide (319 mg, 4.90 mmol) and ammonium chloride (306 mg, 5.72 mmol) were added to a solution of (1*S*,2*R*,3*S*,4*R*,5*S*)-methyl [1,5-epoxy-2,3,4-trihydroxy-2,3-*O*-isopropylidene-cyclopentane] carboxylate (**2.9**) (188 mg, 0.82 mmol) in aqueous methanol (80%, 10 ml). The reaction mixture was heated under reflux for 18 h and was then allowed to cool to room temperature. The majority of the solvent was removed; ethyl acetate (40 ml) and then brine / water (1 : 1, 5 ml) were added. The organic layer was decanted and the aqueous layer re-extracted with ethyl acetate (2 x 20 ml). The combined organic layers were dried (magnesium sulphate) and purification by flash chromatography (ethyl acetate / hexane, 1 : 1) gave (1*S*,2*R*,3*S*,4*R*,5*R*)-methyl [5-azido-1,2,3,4-tetrahydroxy-2,3-*O*-isopropylidene-cyclopentane] carboxylate (**2.10**) (194 mg, 0.71 mmol, 87%) as a colourless crystalline solid. M.p. 89 - 90 °C (diethyl ether / hexane) [lit.[2] m.p. 91 - 92 °C (diethyl ether / hexane)]; $[\alpha]_D^{20}$ +102.2 (*c*, 1.0 in chloroform) [lit.[2] $[\alpha]_D^{20}$ +100.8 (*c*, 1.0 in chloroform)]; δ_H (C_6D_6): 0.96, 1.27 (2 x 3H, 2 x s, $C(C\underline{H}_3)_2$), 1.81 (1H, br s ex in D_2O, OH), 3.38 (3H, s, $CO_2C\underline{H}_3$), 3.67 (1H, d, *J* 10.0 Hz), 3.95 (1H, s ex in D_2O, OH), 4.10 (1H, dd, *J* 4.3 Hz, *J* 8.5 Hz), 4.26 (1H, d, *J* 8.5 Hz), 4.26 (1H, d, *J* 8.5 Hz), 4.40 (1H, dd, *J* 4.3 Hz, *J* 10.0 Hz).

(1*R*,2*R*,3*S*,4*R*,5*R*)-5-Azido-1,2,3,4-tetrahydroxy-1-(hydroxymethyl)-2,3-*O*-isopropylidene-cyclopentane (**2.11**)



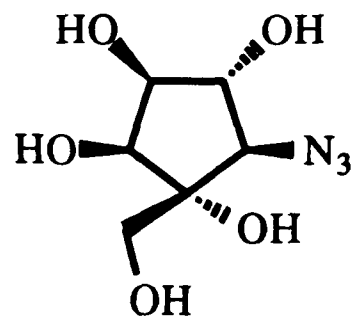
Lithium borohydride (2 M in tetrahydrofuran, 2.6 ml, 5.27 mmol) was added to a solution of (1*S*,2*R*,3*S*,4*R*,5*R*)-methyl [5-azido-1,2,3,4-tetrahydroxy-2,3-*O*-isopropylidene-cyclopentane] carboxylate (**2.10**) (626 mg, 2.29 mmol) in tetrahydrofuran (40 ml) under nitrogen at 0 °C. After 10 min the reaction mixture was allowed to warm up to room temperature and was stirred for 1 h. After this time t.l.c. analysis (methanol / dichloromethane, 1 : 9) indicated complete conversion of starting material (R_f 0.5) to one product (R_f 0.3). Ammonium chloride (200 mg, excess) was added to the reaction mixture which was stirred vigorously until evolution of nitrogen had ceased. Methanol was added dropwise to ensure complete consumption of excess reagent. The reaction mixture was preadsorbed onto silica gel and purification by flash chromatography (methanol in dichloromethane, 0 - 5%) gave (1*R*,2*R*,3*S*,4*R*,5*R*)-5-azido-1,2,3,4-tetrahydroxy-1-(hydroxymethyl)-2,3-*O*-isopropylidene-cyclopentane (**2.11**) (530 mg, 2.16 mmol, 94%) as a white foam. ν_{max} (KBr): 3425 (br, OH), 2106 cm^{-1} (azide); δ_H ($CDCl_3$, 500 MHz): 1.27, 1.45 (2 x 3H, 2 x s, $C(C\underline{H}_3)_2$), 3.71 (2H, AB system, $J_{A,B}$ 11.7 Hz, $C\underline{H}_2OH$), 3.77 (1H, dt, *J* 0.8 Hz, *J* 5.0 Hz, H-5), 4.03 (1H, dd, $J_{4,3}$ 2.5 Hz, $J_{4,5}$ 5.0 Hz, H-4), 4.47 (1H, dd, $J_{2,3}$ 6.8 Hz, $J_{2,5}$ 0.8 Hz, H-2), 4.54 (1H, ddd, $J_{3,2}$ 6.8 Hz, $J_{3,4}$ 2.5 Hz, $J_{3,5}$ 0.8 Hz, H-3); δ_C ($CDCl_3$): 22.8, 24.7 (2 x q, $C(\underline{C}H_3)_2$), 61.9 (t, $\underline{C}H_2OH$), 72.3, 78.7, 84.9, 85.1 (4 x d, C-2, C-3, C-4, C-5), 81.4 (s, C-1), 112.4 (s, $\underline{C}(CH_3)_2$); *m/z* (CI, NH_3): 263 [$(MNH_4)^+$, 100], 246 [$(MH)^+$, 40], 218 [$(MH-N_2)^+$, 30%].

(5*R*,6*S*,7*S*,8*R*,9*R*)-9-Azido-6,7,8-trihydroxy-6,7-*O*-isopropylidene-2,2-dimethyl-1,3-dioxa-spiro[4.4]nonane (**2.12**)



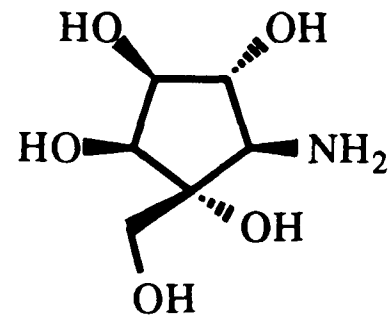
(1*R*,2*R*,3*S*,4*R*,5*R*)-5-Azido-1,2,3,4-tetrahydroxy-1-(hydroxymethyl)-2,3-*O*-isopropylidene-cyclopentane (**2.11**) (77 mg, 0.31 mmol) was dissolved in acetone / 2,2-dimethoxypropane (8 : 1, 9 ml), to which (±)-10-camphorsulphonic acid (10 mg, catalytic amount) was added. The reaction mixture was heated under reflux for 25 min, by which time t.l.c. analysis (methanol / dichloromethane, 1 : 9) indicated complete conversion of starting material (R_f 0.3) to one product (R_f 0.6). The reaction mixture was adjusted to pH 8 by dropwise addition of triethylamine. The solvent was removed and purification by flash chromatography (ethyl acetate / hexane, 1 : 4) gave (5*R*,6*S*,7*S*,8*R*,9*R*)-9-azido-6,7,8-trihydroxy-6,7-*O*-isopropylidene-2,2-dimethyl-1,3-dioxa-spiro[4.4]nonane (**2.12**) (64 mg, 0.22 mmol, 72%) as a colourless oil. $[\alpha]_D^{20}$ +6.8 (*c*, 1.0 in chloroform); (Found: C, 50.74; H, 6.90; N, 14.54%. $C_{12}H_{19}O_5N_3$ requires C, 50.52; H, 6.71; N, 14.73%); ν_{max} (thin film): 3437 (br, OH), 2109 cm^{-1} (azide); δ_H ($CDCl_3$, 500 MHz): 1.30, 1.43, 1.47, 1.48 (4 x 3H, 4 x s, 2 x $C(C\underline{H}_3)_2$), 2.63 (1H, br s ex in D_2O, OH), 3.87 (2H, br m), 4.16 (2H, AB system, $J_{A,B}$ 9.1 Hz, $C\underline{H}_2$), 4.53 - 4.57 (2H, m); δ_C ($CDCl_3$): 24.1, 25.6, 25.7, 26.0 (4 x q, 2 x $C(\underline{C}H_3)_2$), 65.0 (t, C-4), 70.3, 77.6, 82.8, 83.1 (4 x d, C-6, C-7, C-8, C-9), 87.5 (s, C-5), 110.8, 112.2 (2 x s, C-2, $\underline{C}(CH_3)_2$); *m/z* (CI, NH_3): 303 [$(MNH_4)^+$, 10], 286 [$(MH)^+$, 100], 258 [$(MH-N_2)^+$, 20%].

(1*R*,2*R*,3*S*,4*R*,5*R*)-5-Azido-1,2,3,4-tetrahydroxy-1-(hydroxymethyl)-cyclopentane (**2.13**)



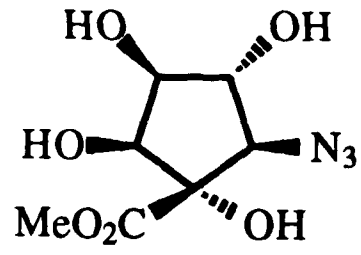
(1*R*,2*R*,3*S*,4*R*,5*R*)-5-Azido-1,2,3,4-tetrahydroxy-1-(hydroxymethyl)-2,3-*O*-isopropylidene-cyclopentane (**2.11**) (75 mg, 0.31 mmol) was stirred in aqueous trifluoroacetic acid (40%, 10 ml) at room temperature for 20 min. After this time t.l.c. analysis (methanol / chloroform, 1 : 9) indicated complete conversion of starting material (R_f 0.3) to one product (R_f 0.05). The solvent was removed and purification by flash chromatography (methanol / ethyl acetate, 1 : 9) gave (1*R*,2*R*,3*S*,4*R*,5*R*)-5-azido-1,2,3,4-tetrahydroxy-1-(hydroxymethyl)-cyclopentane (**2.13**) (50 mg, 0.24 mmol, 80%) as a colourless oil. $[\alpha]_D^{20}$ -25.7 (*c*, 1.2 in methanol); (Found: C, 35.02; H, 5.65; N, 20.20%. $C_6H_{11}O_5N_3$ requires C, 35.12; H, 5.40; N, 20.48%);ν_{max} (thin film): 3368 (br, OH), 2111 cm^{-1} (azide); δ_H (CD_3OD, 500 MHz): 3.47 (1H, d, *J* 6.9 Hz), 3.70 (2H, AB system, $J_{A,B}$ 11.4 Hz, CH_2OH), 3.82 (1H, dd, *J* 1.0 Hz, *J* 5.7 Hz), 3.95 (1H, dd, *J* 5.7 Hz, *J* 6.9 Hz), 3.99 (1H, t, *J* 6.9 Hz); δ_C (CD_3OD): 61.7 (t, CH_2OH), 73.2, 75.0, 75.9, 80.2 (4 x d, C-2, C-3, C-4, C-5), 79.9 (s, C-1); *m/z* (CI, NH_3): 223 [$(MNH_4)^+$, 100], 206 [$(MH)^+$, 10], 178 [$(MH-N_2)^+$, 15%].

(1*R*,2*R*,3*S*,4*R*,5*R*)-5-Amino-1,2,3,4-tetrahydroxy-1-(hydroxymethyl)-cyclopentane (**2.14**)



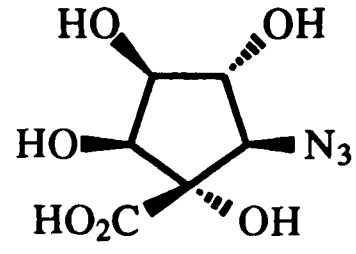
(1*R*,2*R*,3*S*,4*R*,5*R*)-5-Azido-1,2,3,4-tetrahydroxy-1-(hydroxymethyl)-cyclopentane (**2.13**) (317 mg, 1.55 mmol) was dissolved in water (20 ml) and palladium black (12 mg) added. The solution was degassed and the reaction mixture was stirred vigorously under hydrogen for 7 h. After this time t.l.c. analysis (methanol / ethyl acetate, 1 : 8) indicated complete conversion of starting material (R_f 0.5) to baseline materials. The reaction mixture was filtered through Celite (water elution, 70 ml) and the solvent was removed to give (1*R*,2*R*,3*S*,4*R*,5*R*)-5-amino-1,2,3,4-tetrahydroxy-1-(hydroxymethyl)-cyclopentane (**2.14**) (277 mg, 1.55 mmol, quant.) as a yellow oil. $[\alpha]_D^{20}$ -6.4 (*c*, 1.0 in water); (Found: C, 39.91; H, 7.09; N, 7.60%. $C_6H_{13}O_5N_1$ requires C, 40.22; H, 7.31; N, 7.82%); ν_{max} (thin film): 3339 cm^{-1} (br, OH, NH_2); δ_H (D_2O, 500 MHz): 2.81 (1H, dd, $J_{5,2}$ 1.3 Hz, $J_{5,4}$ 7.0 Hz, H-5), 3.67 (2H, AB system, $J_{A,B}$ 12.0 Hz, C$\underline{H}_2$OH), 3.74 (1H, t, $J_{4,3}$ 7.0 Hz, $J_{4,5}$ 7.0 Hz, H-4), 3.79 (1H, dd, $J_{3,2}$ 5.3 Hz, $J_{3,4}$ 7.0 Hz, H-3), 3.97 (1H, dd, $J_{2,3}$ 5.3 Hz, $J_{2,5}$ 1.3 Hz, H-2); δ_C (D_2O, 125 MHz): 62.9 (t, $\underline{C}H_2OH$), 64.9, 76.4, 77.2, 83.4 (4 x d, C-2, C-3, C-4, C-5), 80.9 (s, C-1); *m/z* (electrospray): 180 [$(MH)^+$, 100%].

(1*S*,2*S*,3*S*,4*R*,5*R*)-Methyl [5-azido-1,2,3,4-tetrahydroxy-cyclopentane] carboxylate (**2.15**)



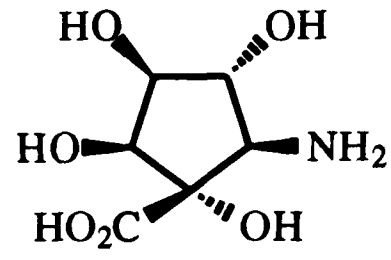
(1*S*,2*S*,3*S*,4*R*,5*R*)-Methyl [5-azido-1,2,3,4-tetrahydroxy-2,3-*O*-isopropylidene-cyclopentane] carboxylate (**2.10**) (232 mg, 0.85 mmol) was stirred in aqueous trifluoroacetic acid (40%, 15 ml) at room temperature for 50 min. After this time t.l.c. analysis (ethyl acetate) indicated complete conversion of starting material (R_f 0.7) to one product (R_f 0.15). The solvent was removed and purification by flash chromatography (ethyl acetate) gave (1*S*,2*S*,3*S*,4*R*,5*R*)-methyl [5-azido-1,2,3,4-tetrahydroxy-cyclopentane] carboxylate (**2.15**) (190 mg, 0.82 mmol, 96%) as a white crystalline solid. M.p. 156 - 157 °C (ethyl acetate / hexane); $[\alpha]_D^{20}$ +53.5 (*c*, 1.0 in methanol); (Found: C, 35.81; H, 4.66; N, 17.93%. $C_7H_{11}O_6N_3$ requires C, 36.06; H, 4.75; N, 18.02%); ν_{max} (KBr): 3450 (br, OH), 2110 (azide), 1733 cm^{-1} (ester); δ_H (CD_3OD, 500 MHz): 3.52 (1H, d, *J* 9.4 Hz), 3.78 (3H, s, $CO_2C\underline{H}_3$), 3.93 (1H, dd, *J* 5.8 Hz, *J* 8.7 Hz), 4.01 (1H, d, *J* 8.7 Hz), 4.22 (1H, dd, *J* 5.8 Hz, *J* 9.4 Hz); δ_C (CD_3OD): 51.5 (q, $CO_2\underline{C}H_3$), 70.9, 73.8, 75.7, 79.9 (4 x d, C-2, C-3, C-4, C-5), 85.5 (s, C-1), 171.5 (s, $\underline{C}O_2CH_3$); *m/z* (DCI, NH_3): 251 [$(MNH_4)^+$, 100], 234 [$(MH)^+$, 30%].

(1*S*,2*S*,3*S*,4*R*,5*R*)-5-Azido-1,2,3,4-tetrahydroxy-cyclopentane carboxylic acid (**2.16**)



(1*S*,2*S*,3*S*,4*R*,5*R*)-Methyl [5-azido-1,2,3,4-tetrahydroxy-cyclopentane] carboxylate (**2.15**) (90 mg, 0.39 mmol) was dissolved in water (3 ml). Aqueous sodium hydroxide (0.5 M, 0.8 ml, 1 equiv) was added dropwise and the reaction mixture was stirred at room temperature for 50 min. After this time t.l.c. analysis (ethyl acetate) indicated complete conversion of starting material (R_f 0.15) to baseline materials. Purification by ion exchange chromatography [CG-400(OH^-) 0.2 - 4 M aqueous acetic acid elution] gave (1*S*,2*S*,3*S*,4*R*,5*R*)-[5-azido-1,2,3,4-tetrahydroxy-cyclopentane] carboxylic acid (**2.16**) (85 mg, 0.39 mmol, quant.) as a hygroscopic foam. $[\alpha]_D^{20}$ +51.8 (*c*, 1.3 in water); (Found: C, 32.37; H, 4.72; N, 18.58%. $C_6H_9O_6N_3$ requires C, 32.88; H, 4.14; N, 19.17%); ν_{max} (KBr): 3400 (br, OH), 2117 (azide), 1730 cm^{-1} (COOH); δ_H (D_2O, 500 MHz): 3.62 (1H, d, *J* 9.3 Hz), 3.95 (1H, dd, *J* 5.6 Hz, *J* 8.7 Hz), 4.06 (1H, d, *J* 8.7 Hz), 4.19 (1H, dd, *J* 5.6 Hz, *J* 9.3 Hz); δ_C (D_2O): 70.9, 74.4, 76.0, 80.6 (4 x d, C-2, C-3, C-4, C-5), 86.6 (s, C-1), 174.4 (s, COOH); *m/z* (negative electrospray): 218 [$(M-H)^-$, 100%].

(1*S*,2*S*,3*S*,4*R*,5*R*)-5-Amino-1,2,3,4-tetrahydroxy-cyclopentane carboxylic acid (**2.17**)

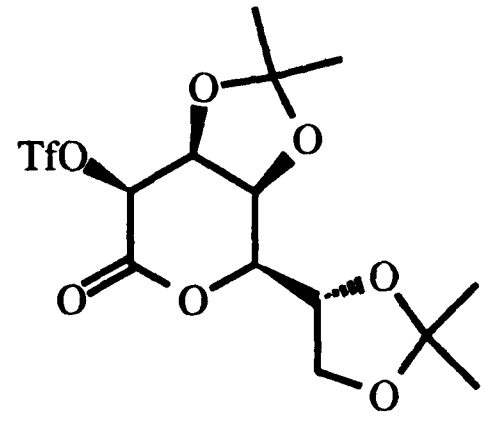


(1*S*,2*S*,3*S*,4*R*,5*R*)-5-Azido-1,2,3,4-tetrahydroxy-cyclopentane carboxylic acid (**2.16**) (44 mg, 0.20 mmol) was dissolved in distilled water (3 ml) and palladium black (3 mg) added. After degassing the solution, the reaction mixture was stirred

vigorously under hydrogen for 4 h. The reaction mixture was then filtered through Celite (water elution, 10 ml) and the solvent removed to give (1*S*,2*S*,3*S*,4*R*,5*R*)-5-amino-1,2,3,4-tetrahydroxy-cyclopentane carboxylic acid (**2.17**) (38 mg, 98%) as a white hygroscopic foam. ν_{max} (KBr): 3436 (br, OH, NH_2), 1626 cm^{-1} (COO^-); δ_H (D_2O, 500 MHz): 3.33 (1H, d, *J* 7.7 Hz), 4.04 - 4.08 (2H, m), 4.30 (1H, dd, *J* 7.7 Hz, *J* 4.9 Hz); δ_C (D_2O, 125 MHz): 62.4 (d, C-5), 76.1, 77.0, 79.8, 83.4 (3 x d, C-2, C-3, C-4), 83.1 (s, C-1), 175.6 (s, $\underline{C}OO^-$); *m/z* (electrospray): 194 [$(MH)^+$, 100%].

Experimental Procedures for Results and Discussion Section 2.2.

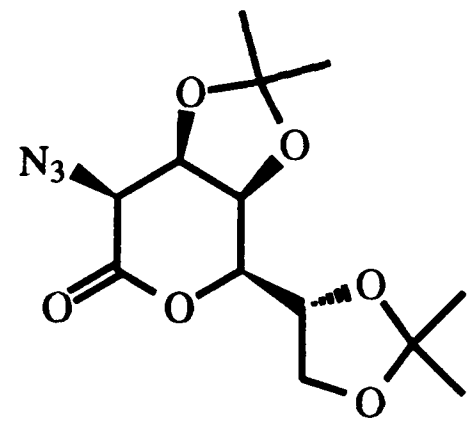
3,4:6,7-Di-*O*-isopropylidene-2-*O*-trifluoromethanesulphonyl-**D**-*glycero*-**D**-*talo*-heptono-1,5-lactone (**2.7**)



3,4:6,7-Di-*O*-isopropylidene-**D**-*glycero*-**D**-*talo*-heptono-1,5-lactone (**2.2**) (11.34 g, 39.4 mmol) was stirred in a solution of pyridine (7.34 ml, 90.8 mmol) and dichloromethane (40 ml) at -30 °C under nitrogen. Trifluoromethanesulphonic anhydride (7.30 ml, 43.3 mmol) in dichloromethane (20 ml) was added dropwise over 1.5 h. The reaction mixture was stirred at -20 °C for a further 1 h, by which time t.l.c. analysis (ethyl acetate / hexane, 1 : 1) indicated complete consumption of starting material (R_f 0.3) and one major product (R_f 0.8). The reaction was quenched by addition of dichloromethane (100 ml) and aqueous hydrochloric acid (2 M, 75 ml). The organic layer was washed with brine (50 ml) and dried (sodium sulphate); the

solvent was removed to give the crude triflate (**2.7**) (14.39 g, 34.3 mmol, 87%) as a creamy solid, which was used directly without further purification. A sample of the crude triflate was purified by recrystallisation to give 3,4:6,7-di-*O*-isopropylidene-2-*O*-trifluoromethanesulphonyl-**D**-*glycero*-**D**-*talo*-heptono-1,5-lactone (**2.7**) as a white crystalline solid. M.p. 119 - 121 °C (decomp., diethyl ether / hexane) [lit.[3] m.p. 118 - 119 °C (decomp., diethyl ether / hexane)]; $[\alpha]_D^{20}$ +39.7 (*c*, 1.0 in chloroform) [lit.[3] $[\alpha]_D^{20}$ +37.0 (*c*, 1.0 in chloroform)]; δ_H ($CDCl_3$): 1.39, 1.42, 1.48, 1.50 (4 x 3H, 4 x s, 2 x $C(CH_3)_2$), 4.07 (1H, dd, $J_{5,4}$ 1.7 Hz, $J_{5,6}$ 8.3 Hz, H-5), 4.10 (1H, dd, $J_{7,6}$ 3.6 Hz, $J_{7,7'}$ 9.5 Hz, H-7), 4.16 (1H, dd, $J_{7',6}$ 5.9 Hz, $J_{7',7}$ 9.5 Hz, H-7'), 4.42 (1H, ddd, $J_{6,5}$ 8.3 Hz, $J_{6,7}$ 3.6 Hz, $J_{6,7'}$ 5.9 Hz, H-6), 4.82 (1H, dd, $J_{4,3}$ 7.8 Hz, $J_{4,5}$ 1.7 Hz, H-4), 4.94 (1H, dd, $J_{3,2}$ 3.3 Hz, $J_{3,4}$ 7.8 Hz, H-3), 5.24 (1H, d, $J_{2,3}$ 3.3 Hz, H-2).

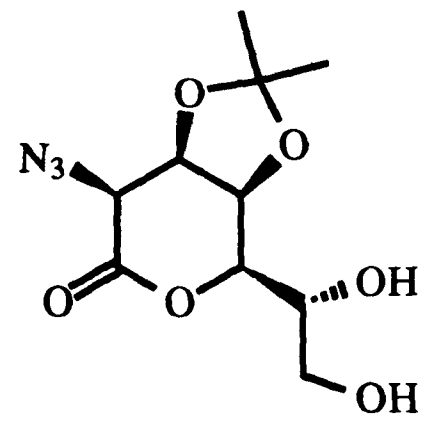
2-Azido-2-deoxy-3,4:6,7-di-*O*-isopropylidene-**D**-*glycero*-**D**-*talo*-heptono-1,5-lactone (**2.6**)



3,4:6,7-Di-*O*-isopropylidene-2-*O*-trifluoromethanesulphonyl-**D**-*glycero*-**D**-*talo*-heptono-1,5-lactone (**2.7**) (41.84 g, 99.6 mmol), in *N*,*N*-dimethylformamide (150 ml), was stirred with sodium azide (9.71 g, 149.4 mmol) at room temperature under nitrogen for 8 h. After this time t.l.c. analysis (ethyl acetate / hexane, 1 : 3) indicated complete consumption of starting material (R_f 0.25) and one major product (R_f 0.2). The solvent was removed and the residue then partitioned between dichloromethane (200 ml) and brine (200 ml). The organic layer was dried (sodium sulphate) and the solvent removed to give a yellow syrup. Recrystallisation (diethyl ether / hexane)

gave 2-azido-2-deoxy-3,4:6,7-di-*O*-isopropylidene-**D**-*glycero*-**D**-*talo*-heptono-1,5-lactone (**2.6**) (22.17 g, 70.8 mmol, 71%) as a white crystalline solid. M.p. 101 - 102 °C (diethyl ether / hexane) [lit.[3] m.p. 103 - 104 °C (diethyl ether / hexane)]; $[\alpha]_D^{20}$ +101.6 (*c*, 1.1 in chloroform) [lit.[3] $[\alpha]_D^{20}$ +96.7 (*c*, 1.1 in chloroform)]; δ_H ($CDCl_3$): 1.37, 1.40, 1.44, 1.48 (4 x 3H, 4 x s, 2 x $C(C\underline{H}_3)_2$), 3.86 (1H, d, $J_{2,3}$ 3.3 Hz, H-2), 3.98 (1H, dd, $J_{5,4}$ 1.5 Hz, $J_{5,6}$ 8.4 Hz, H-5), 4.07 (1H, dd, $J_{7,6}$ 3.8 Hz, $J_{7,7'}$ 9.3 Hz, H-7), 4.15 (1H, dd, $J_{7',6}$ 5.7 Hz, $J_{7',7}$ 9.3 Hz, H-7'), 4.41 (1H, ddd, $J_{6,5}$ 8.4 Hz, $J_{6,7}$ 3.8 Hz, $J_{6,7'}$ 5.7 Hz, H-6), 4.70 (1H, dd, $J_{4,3}$ 7.8 Hz, $J_{4,5}$ 1.5 Hz, H-4), 4.87 (1H, dd, $J_{3,2}$ 3.3 Hz, $J_{3,4}$ 7.8 Hz, H-3).

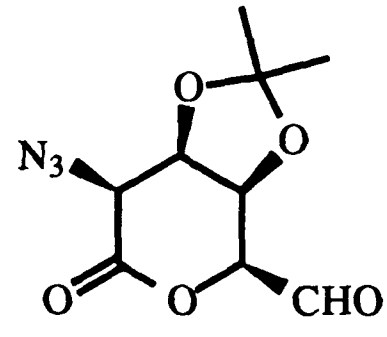
2-Azido-2-deoxy-3,4-*O*-isopropylidene-**D**-*glycero*-**D**-*talo*-heptono-1,5-lactone (**2.19**)



2-Azido-2-deoxy-3,4:6,7-di-*O*-isopropylidene-**D**-*glycero*-**D**-*talo*-heptono-1,5-lactone (**2.6**) (6.161 g, 19.7 mmol) was stirred with aqueous acetic acid (80%, 100 ml) at 50 °C for 3 h. After this time t.l.c. analysis (ethyl acetate) indicated complete conversion of starting material (R_f 0.7) to one product (R_f 0.2). The solvent was removed and the residue co-evaporated with toluene (3 x 60 ml). Purification by dry flash chromatography (ethyl acetate in hexane, 0 - 70%) gave 2-azido-2-deoxy-3,4-*O*-isopropylidene-**D**-*glycero*-**D**-*talo*-heptono-1,5-lactone (**2.19**) (5.009 g, 18.3 mmol, 93%) as a white crystalline solid. M.p. 124 - 125 °C (ethyl acetate) [lit.[3] m.p. 126 - 127 °C (ethyl acetate / hexane)]; $[\alpha]_D^{20}$ +133.8 (*c*, 1.1 in methanol) [lit.[3] $[\alpha]_D^{20}$ +131.5 (*c*, 1.1 in methanol)]; δ_H ($CDCl_3$): 1.41, 1.48 (2 x 3H, 2 x s, $C(C\underline{H}_3)_2$), 1.95 (1H, t, *J* 5.4 Hz, OH-7), 2.61 (1H, d, $J_{OH,6}$ 6.3 Hz, OH-6), 3.88 (3H, m), 4.07 (1H, m,

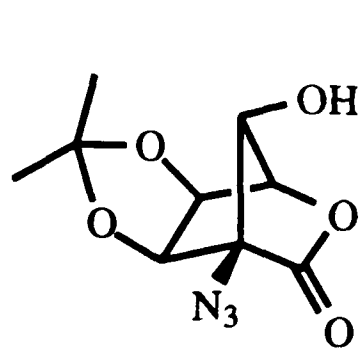
H-6), 4.20 (1H, dd, $J_{5,4}$ 1.4 Hz, $J_{5,6}$ 8.6 Hz, H-5), 4.81 (1H, dd, $J_{4,3}$ 7.8 Hz, $J_{4,5}$ 1.4 Hz, H-4), 4.88 (1H, dd, $J_{3,2}$ 3.0 Hz, $J_{3,4}$ 7.8 Hz, H-3).

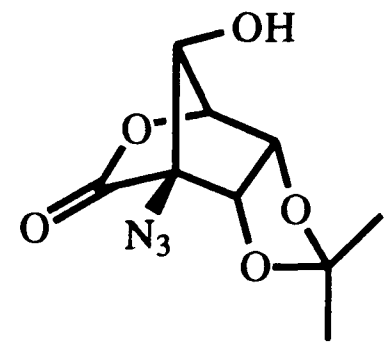
5-Azido-5-deoxy-3,4-*O*-isopropylidene-**D**-*altrurono*-2,6-lactone (**1.51**)



Periodic acid (3.20 g, 14.0 mmol) was added to a stirred solution of 2-azido-2-deoxy-3,4-*O*-isopropylidene-**D**-*glycero*-**D**-*talono*-heptono-1,5-lactone (**2.19**) (3.19 g, 11.7 mmol) in tetrahydrofuran (150 ml) at room temperature. After 5 min a thick white precipitate was formed, and after a further 20 min t.l.c. analysis (ethyl acetate) indicated complete conversion of starting material (R_f 0.2) to one product (R_f 0.4). The reaction mixture was preadsorbed onto silica gel and purification by flash chromatography (ethyl acetate / hexane, 2 : 3) gave 5-azido-5-deoxy-3,4-*O*-isopropylidene-**D**-*altrurono*-2,6-lactone (**1.51**) (2.581 g, 10.7 mmol, 92%) as a colourless oil. δ_H ($CDCl_3$): 1.35, 1.36 (2 x 3H, 2 x s, $C(C\underline{H}_3)_2$), 4.55 (1H, m), 4.98 (2H, m), 5.19 (1H, m), 9.7 (1H, s, H-6). This material was used directly without further characterisation.

(1*R*,4*R*,5*R*,6*R*,7*R*)-4-Azido-5,6,7-trihydroxy-5,6-*O*-isopropylidene-2-oxa-bicyclo[2.2.1]heptan-3-one (**1.52**) and (1*S*,4*S*,5*R*,6*R*,7*R*)-4-azido-5,6,7-trihydroxy-5,6-*O*-isopropylidene-2-oxa-bicyclo[2.2.1]heptan-3-one (**1.53**)

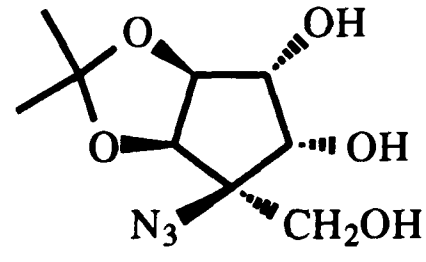




Potassium fluoride (651 mg, 11.20 mmol) and 18-crown-6 (592 mg, 2.24 mmol) were added to a solution of 5-azido-5-deoxy-3,4-*O*-isopropylidene-**D**-*altrurono*-2,6-lactone (**1.51**) (1.30 g, 5.40 mmol) in acetonitrile (100 ml) at 0 °C under nitrogen. After 40 min t.l.c. analysis (ethyl acetate / hexane, 1 : 1) showed a trace of starting material (R_f 0.1) and two products (R_f 0.45 and R_f 0.35). Ethyl acetate (250 ml) and then water / brine (1 : 1, 10 ml) were added, and the mixture was stirred vigorously for 10 min to quench the reaction. The organic layer was decanted and the aqueous layer was re-extracted with ethyl acetate (2 x 50 ml). The organic layers were combined and dried (magnesium sulphate). The solvent was removed and purification by flash chromatography (ethyl acetate / hexane, 1 : 3 then 1 : 2) gave (1*R*,4*R*,5*R*,6*R*,7*R*)-4-azido-5,6,7-trihydroxy-5,6-*O*-isopropylidene-2-oxa-bicyclo[2.2.1]heptan-3-one (**1.52**) (R_f 0.45) (608 mg, 2.52 mmol, 47%) as a colourless oil. $[\alpha]_D^{20}$ +42.8 (*c*, 1.0 in chloroform) [lit.[2] $[\alpha]_D^{20}$ +29.6 (*c*, 1.0 in chloroform)]; δ_H ($CDCl_3$): 1.37, 1.55 (2 x 3H, 2 x s, $C(CH_3)_2$), 3.20 (1H, br s ex in D_2O, OH), 4.51, 4.60 (2 x 1H, 2 x dd, $J_{5,6}$ 6.3 Hz, H-5, H-6), 4.72, 4.79 (2 x 1H, 2 x s, H-4, H-7); and (1*S*,4*S*,5*R*,6*R*,7*R*)-4-azido-5,6,7-trihydroxy-5,6-*O*-isopropylidene-2-oxa-bicyclo[2.2.1]heptan-3-one (**1.53**) (R_f 0.35) (103 mg, 0.4 mmol, 8%) as an oil which crystallised on standing; m.p. 104 - 107 °C (on standing) [lit.[2] m.p. 116 - 117 °C (on standing)]; $[\alpha]_D^{20}$ +165.9 (*c*, 1.0 in chloroform) [lit.[2] $[\alpha]_D^{20}$ +167.8 (*c*, 1.0 in chloroform)]; δ_H ($CDCl_3$): 1.39, 1.51 (2 x

3H, 2 x s, C(C<u>H</u>$_3$)$_2$), 3.62 (1H, br s ex in D_2O, OH), 4.62 (1H, d, *J* 2.5 Hz), 4.70 (1H, d, *J* 1.3 Hz), 5.07 (1H, dd, *J* 1.3 Hz, *J* 7.4 Hz), 5.14 (1H, dd, *J* 2.5 Hz, *J* 7.4 Hz).

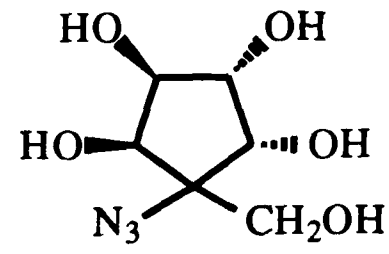
<u>(1*R*,2*R*,3*S*,4*R*,5*R*)-1-Azido-2,3,4,5-tetrahydroxy-1-(hydroxymethyl)-2,3-*O*-isopropylidene-cyclopentane (**2.20**)</u>



Sodium borohydride (46 mg, 2.12 mmol) was added to a solution of (1*R*,4*R*,5*R*,6*R*,7*R*)-4-azido-5,6,7-trihydroxy-5,6-*O*-isopropylidene-2-oxa-bicyclo[2.2.1]heptan-3-one (**1.52**) (232 mg, 0.96 mmol) in ethanol (15 ml) under nitrogen. The reaction mixture was stirred for 50 min at room temperature, by which time t.l.c. analysis (methanol / dichloromethane, 1 : 9) indicated complete conversion of starting material (R_f 0.55) to one product (R_f 0.3). Ammonium chloride (50 mg, excess) was added to the reaction mixture which was then stirred vigorously until evolution of nitrogen had ceased. Methanol was added dropwise to ensure complete consumption of excess reagent. The reaction mixture was preadsorbed onto silica gel and purification by flash chromatography (methanol / dichloromethane, 1 : 9) gave <u>(1*R*,2*R*,3*S*,4*R*,5*R*)-1-azido-2,3,4,5-tetrahydroxy-1-(hydroxymethyl)-2,3-*O*-isopropylidene-cyclopentane (**2.20**)</u> (198 mg, 0.81 mmol, 84%) as a colourless oil. $[\alpha]_D^{20}$ +69.3 (*c*, 1.0 in chloroform); (Found: C, 43.92; H, 6.26; N, 16.73%. $C_9H_{15}O_5N_3$ requires C, 44.08; H, 6.17; N, 17.13%); ν_{max} (thin film): 3401 (br, OH), 2111 cm^{-1} (azide); δ_H ($CDCl_3$, 500 MHz): 1.33, 1.52 (2 x 3H, 2 x s, C(C<u>H</u>$_3$)$_2$), 3.83 (2H, AB system, $J_{A,B}$ 11.5 Hz, C<u>H</u>$_2$OH), 4.16 (1H, d, *J* 5.5 Hz), 4.46 (1H, d, *J* 5.5 Hz), 4.51 (1H, d, *J* 6.4 Hz), 4.56 (1H, d, *J* 6.4 Hz); δ_C ($CDCl_3$): 23.8, 25.6 (2 x q, C(<u>C</u>H$_3$)$_2$), 62.5 (t, <u>C</u>H$_2$OH), 71.0 (s, C-1), 74.4, 75.1, 80.8, 83.3 (4 x d, C-2, C-3, C-4,

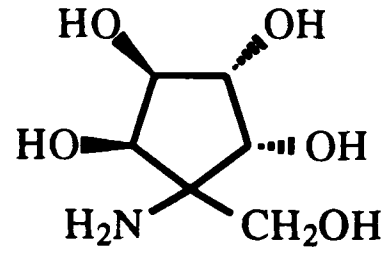
C-5), 112.4 (s, C(CH$_3$)$_2$); *m/z* (CI, NH$_3$): 263 [(MNH$_4$)$^+$, 15], 246 [(MH)$^+$, 5], 100 (100%).

(2*R*,3*R*,4*R*,5*R*)-1-Azido-2,3,4,5-tetrahydroxy-1-(hydroxymethyl)-cyclopentane (**2.21**)



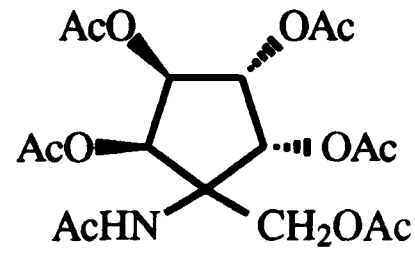
(1*R*,2*R*,3*S*,4*R*,5*R*)-1-Azido-2,3,4,5-tetrahydroxy-1-(hydroxymethyl)-2,3-*O*-isopropylidene-cyclopentane (**2.20**) (198 mg, 0.81 mmol) was stirred in aqueous trifluoroacetic acid (40%, 20 ml) at room temperature for 20 min. After this time t.l.c. analysis (methanol / chloroform, 1 : 4) indicated complete conversion of starting material (R_f 0.5) to one product (R_f 0.05). The solvent was then removed and purification by flash chromatography (methanol / chloroform, 1 : 9) gave (2*R*,3*R*,4*R*,5*R*)-1-azido-2,3,4,5-tetrahydroxy-1-(hydroxymethyl)-cyclopentane (**2.21**) (149 mg, 0.73 mmol, 90%) as a colourless oil. $[\alpha]_D^{20}$ +41.6 (*c*, 0.9 in methanol); (Found: C, 35.29; H, 5.66; N, 20.05%. $C_6H_{11}O_5N_3$ requires C, 35.12; H, 5.40; N, 20.48%); ν_{max} (thin film): 3369 (br, OH), 2111 cm^{-1} (azide); δ_H (CD$_3$OD, 500 MHz): 3.85 (2H, AB system, $J_{A,B}$ 11.7 Hz, CH$_2$OH), 3.92 (1H, dd, *J* 4.1 Hz, *J* 6.4 Hz), 3.97 (1H, dd, *J* 4.1 Hz, *J* 5.3 Hz), 4.05 (1H, d, *J* 5.3 Hz), 4.10 (1H, d, *J* 6.4 Hz); δ_C [(CD$_3$)$_2$SO]: 62.8 (t, CH$_2$OH), 73.5 (s, C-1), 72.6, 74.0, 75.6, 76.6 (4 x d, C-2, C-3, C-4, C-5); *m/z* (CI, NH$_3$): 223 [(MNH$_4$)$^+$, 100], 178 [(MH-N$_2$)$^+$, 40%].

(2*R*,3*R*,4*R*,5*R*)-1-Amino-2,3,4,5-tetrahydroxy-1-(hydroxymethyl)-cyclopentane (**2.22**)



(2*R*,3*R*,4*R*,5*R*)-1-Azido-2,3,4,5-tetrahydroxy-1-(hydroxymethyl)-cyclopentane (**2.21**) (149 mg, 0.73 mmol) was dissolved in water (10 ml) and palladium black (5 mg) was added. After degassing the solution, the reaction mixture was stirred vigorously under hydrogen for 6 h. After this time t.l.c. analysis (ethanol) indicated complete conversion of starting material (R_f 0.5) to baseline materials. The reaction mixture was filtered through Celite (water elution, 70 ml) and the solvent removed to give (2*R*,3*R*,4*R*,5*R*)-1-amino-2,3,4,5-tetrahydroxy-1-(hydroxymethyl)-cyclopentane (**2.22**) (129 mg, 0.72 mmol, 99%) as a colourless hygroscopic oil. $[\alpha]_D^{20}$ +11.9 (*c*, 1.0 in water); ν_{max} (KBr): 3402 cm^{-1} (br, OH, NH); δ_H (D_2O, 500 MHz): 3.58 (2H, AB system, $J_{A,B}$ 11.9 Hz, C$\underline{H}_2$OH), 3.90 - 4.02 (4H, m); δ_C (D_2O): 62.7 (s, C-1), 63.9 (t, $\underline{C}H_2OH$), 71.1, 75.2, 75.3, 76.7 (4 x d, C-2, C-3, C-4, C-5); *m/z* (electrospray): 180 [$(MH)^+$, 100%].

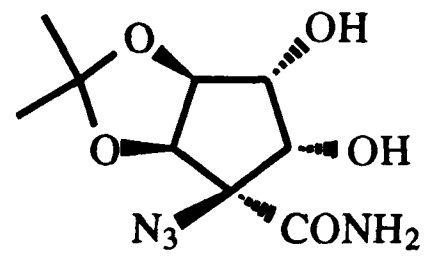
(2*R*,3*R*,4*R*,5*R*)-1-Acetamido-2,3,4,5-tetraacetoxy-1-(acetoxymethyl)-cyclopentane (**2.23**)



(2*R*,3*R*,4*R*,5*R*)-1-Amino-2,3,4,5-tetrahydroxy-1-(hydroxymethyl)-cyclopentane (**2.22**) (30 mg, 0.17 mmol) was stirred in a solution of acetic anhydride / pyridine (1 : 1, 4 ml) in the presence of 4-(*N,N*-dimethylamino)-pyridine (5 mg, catalytic amount)

at 0 °C under nitrogen for 2.5 h. After this time t.l.c. analysis (ethyl acetate) indicated complete conversion of starting material (baseline) to one product (R_f 0.3). The solvent was removed and the residue dissolved in ethyl acetate (25 ml), washed with aqueous hydrochloric acid (2 M, 10 ml), brine (10 ml), and then dried (magnesium sulphate). Purification by flash chromatography (ethyl acetate) gave (2*R*,3*R*,4*R*,5*R*)-1-acetamido-2,3,4,5-tetraacetoxy-1-(acetoxymethyl)-cyclopentane (**2.23**) (43 mg, 0.10 mmol, 60%) as a colourless oil. $[\alpha]_D^{20}$ +14.1 (*c*, 0.8 in methanol); (Found: C, 50.20; H, 6.03; N, 3.15%. $C_{18}H_{25}O_{11}N_1$ requires C, 50.12; H, 5.84; N, 3.25%); ν_{max} (thin film): 1751 (ester), 1682 cm^{-1} (amide); δ_H ($CDCl_3$, 500 MHz): 2.02, 2.05, 2.07, 2.08, 2.11, 2.13 (6 x 3H, 6 x s, 6 x $COCH_3$), 4.47 (2H, AB system, $J_{A,B}$ 11.7 Hz, CH_2OCOCH_3), 5.41 - 5.45 (2H, m), 5.67 (1H, d, *J* 5.5 Hz), 5.83 (1H, d, *J* 5.8 Hz); δ_C ($CDCl_3$): 20.3, 20.6 (2 x q, $OCOCH_3$), 23.7 (q, $NHCOCH_3$), 62.7 (s, C-1), 63.2 (t, C-6), 71.8, 73.1, 73.2, 74.0 (4 x d, C-2, C-3, C-4, C-5), 167.0, 168.6, 169.6, 169.8, 169.9, 170.4 (6 x s, 6 x CO); *m/z* (CI, NH_3): 449 [$(MNH_4)^+$, 60], 432 [$(MH)^+$, 100%].

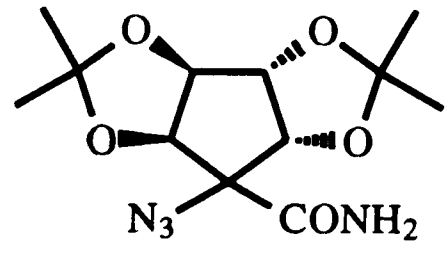
(1*R*,2*R*,3*S*,4*R*,5*R*)-[1-Azido-2,3,4,5-tetrahydroxy-2,3-*O*-isopropylidene-cyclopentane] carboxamide (**2.25**)



(1*R*,4*R*,5*R*,6*R*,7*R*)-1-Azido-5,6,7-trihydroxy-5,6-*O*-isopropylidene-2-oxa-bicyclo[2.2.1]heptan-3-one (**1.52**) (178 mg, 0.74 mmol) was added to methanol (15 ml), that has been saturated with ammonia, at room temperature. The solution was stirred for 20 min, by which time t.l.c. analysis (ethyl acetate / hexane, 1 : 1) indicated complete conversion of starting material (R_f 0.45) to one product (R_f 0.05). The solvent was removed and purification by flash chromatography (methanol / dichloromethane, 1 : 9) gave (1*R*,2*R*,3*S*,4*R*,5*R*)-[1-azido-2,3,4,5-tetrahydroxy-2,3-*O*-

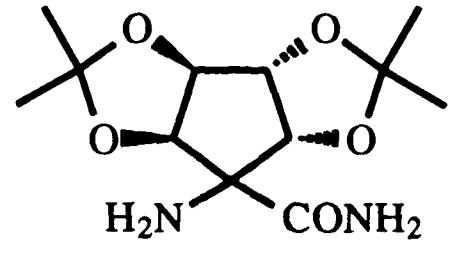
isopropylidene-cyclopentane] carboxamide (**2.25**) (176 mg, 0.68 mmol, 92%) as a colourless crystalline solid. M.p. 148 - 150 °C (ethyl acetate / hexane) [lit.[2] m.p. 147 - 150 °C (ethyl acetate / hexane)]; $[\alpha]_D^{20}$ +28.8 (*c*, 1.0 in acetonitrile) [lit.[2] $[\alpha]_D^{20}$ +30.7 (*c*, 1.0 in acetonitrile)]; δ_H ($CDCl_3$): 1.33, 1.51 (2 x 3H, 2 x s, $C(C\underline{H}_3)_2$), 3.30, 4.09 (2 x 1H, 2 x br s ex in D_2O, OH-4, OH-5), 4.53 (1H, d, *J* 6.3 Hz), 4.70 (2H, 2 x d, *J* 7.8 Hz), 4.94 (1H, s), 6.16, 7.03 (2 x 1H, 2 x br s ex in D_2O, $CON\underline{H}_2$).

(2*R*,3*R*,4*R*,5*R*)-[1-Azido-2,3,4,5-tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-cyclopentane] carboxamide (**2.26**)



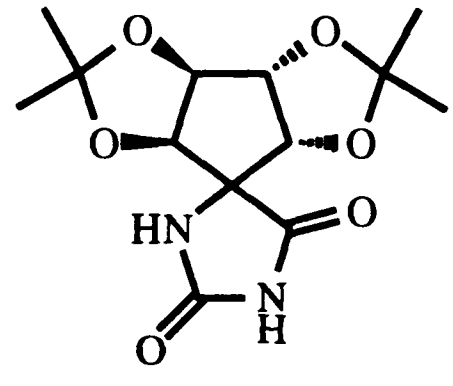
(1*R*,2*R*,3*S*,4*R*,5*R*)-[1-Azido-2,3,4,5-tetrahydroxy-2,3-*O*-isopropylidene-cyclopentane] carboxamide (**2.25**) (347 mg, 1.34 mmol) was dissolved in acetone / 2,2-dimethoxypropane (1 : 1, 30 ml) and the solution was adjusted to pH 2 by the addition of (±)-10-camphorsulphonic acid. The reaction mixture was heated under reflux for 1.5 h, by which time t.l.c. analysis (ethyl acetate / hexane, 1 : 1) indicated complete conversion of starting material (R_f 0.1) to one product (R_f 0.3). The reaction mixture was adjusted to pH 8 by dropwise addition of triethylamine. The solvent was removed and purification by flash chromatography (ethyl acetate / hexane, 1 : 3) gave (2*R*,3*R*,4*R*,5*R*)-[1-azido-2,3,4,5-tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-cyclopentane] carboxamide (**2.26**) (285 mg, 0.97 mmol, 71%) as a colourless oil. $[\alpha]_D^{20}$ +101.5 (*c*, 1.0 in chloroform) [lit.[2] $[\alpha]_D^{20}$ +114.2 (*c*, 1.0 in chloroform)]; δ_H ($CDCl_3$): 1.30, 1.35, 1.45, 1.58 (4 x 3H, 4 x s, 2 x $C(C\underline{H}_3)_2$), 4.65 (1H, d, $J_{5,4}$ 6.0 Hz, H-5), 4.70 (1H, d, $J_{4,5}$ 6.0 Hz, H-4), 4.74 (1H, d, $J_{3,2}$ 5.9 Hz, H-3), 5.18 (1H, d, $J_{2,3}$ 5.9 Hz, H-2), 6.15, 6.44 (2 x 1H, 2 x br s ex in D_2O, $CON\underline{H}_2$).

(2*R*,3*R*,4*R*,5*R*)-[1-Amino-2,3,4,5-tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-cyclopentane] carboxamide (**2.27**)



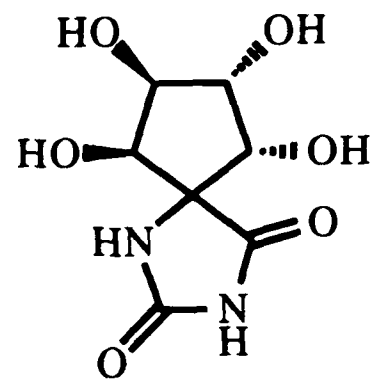
(2*R*,3*R*,4*R*,5*R*)-[1-Azido-2,3,4,5-tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-cyclopentane] carboxamide (**2.26**) (241 mg, 0.81 mmol) was dissolved in ethanol (10 ml) and palladium black (7 mg) added. After degassing the solution, the reaction mixture was stirred vigorously under hydrogen at room temperature for 10 h. After this time t.l.c. analysis (ethyl acetate / hexane, 1 : 1) indicated complete conversion of starting material (R_f 0.7) to baseline materials. The reaction mixture was filtered through Celite (methanol elution, 70 ml) and the solvent removed to give (2*R*,3*R*,4*R*,5*R*)-[1-amino-2,3,4,5-tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-cyclopentane] carboxamide (**2.27**) (215 mg, 0.79 mmol, 98%) as a colourless crystalline solid. M.p. 175 - 176 °C (ethyl acetate) [lit.[2] m.p. 179 - 182 °C (methanol / diethyl ether)]; $[\alpha]_D^{20}$ +48.2 (*c*, 1.0 in ethanol) [lit.[2] $[\alpha]_D^{20}$ +46.1 (*c*, 1.0 in ethanol)]; δ_H (CD_3OD): 1.27, 1.32, 1.42, 1.48 (4 x 3H, 4 x s, 2 x $C(CH_3)_2$), 4.52 (1H, d, *J* 5.6 Hz), 4.62 (1H, dd, *J* 6.3 Hz, *J* 1.0 Hz), 4.67 (1H, dd, *J* 1.0 Hz, *J* 5.6 Hz), 5.02 (1H, d, *J* 6.3 Hz).

(6*R*,7*R*,8*R*,9*R*)-1,3-Diaza-6,7,8,9-tetrahydroxy-6,7:8,9-di-*O*-isopropylidene-spiro[4.4]nonan-2,4-dione (**2.28**)



1,1-Carbonyldiimidazole (322 mg, 1.99 mmol) was added to a solution of (2*R*,3*R*,4*R*,5*R*)-[1-amino-2,3,4,5-tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-cyclopentane] carboxamide (**2.27**) (200 mg, 0.74 mmol) in toluene (25 ml) under nitrogen and the solution heated under reflux for 14 h. After this time t.l.c. analysis (methanol / dichloromethane, 1 : 9) indicated complete conversion of starting material (R_f 0.55) to one major product (R_f 0.6). The reaction was allowed to cool to room temperature and the solvent removed. Purification by flash chromatography (methanol / dichloromethane, 1 : 9) gave (6*R*,7*R*,8*R*,9*R*)-1,3-diaza-6,7,8,9-tetrahydroxy-6,7:8,9-di-*O*-isopropylidene-spiro[4.4]nonan-2,4-dione (**2.28**) (155 mg, 0.52 mmol, 71%) as a colourless crystalline solid. M.p. 222 - 223 °C (diethyl ether / hexane) [lit.[2] m.p. 203 - 205 °C (diethyl ether / hexane)]; $[\alpha]_D^{20}$ +46.1 (*c*, 1.0 in chloroform); δ_H ($CDCl_3$): 1.30, 1.34, 1.50, 1.51 (4 x 3H, 4 x s, 2 x $C(C\underline{H}_3)_2$), 4.64 (1H, d, *J* 6.4 Hz), 4.76 (1H, d, *J* 5.1 Hz), 4.79 (1H, d, *J* 5.1 Hz), 4.81 (1H, d, *J* 6.4 Hz), 5.87 (1H, br s ex in D_2O, NH-1), 8.02 (1H, br s ex in D_2O, NH-3).

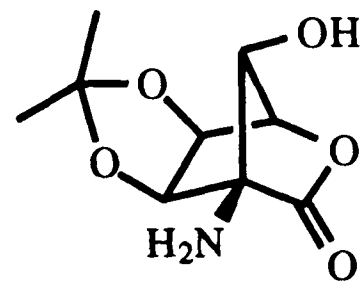
(6*R*,7*R*,8*R*,9*R*)-1,3-Diaza-6,7,8,9-tetrahydroxy-spiro[4.4]nonan-2,4-dione (**2.24**)



Method 1 - From (6*R*,7*R*,8*R*,9*R*)-1,3-diaza-6,7,8,9-tetrahydroxy-6,7:8,9-di-*O*-isopropylidene-spiro[4.4]nonan-2,4-dione (**2.28**).

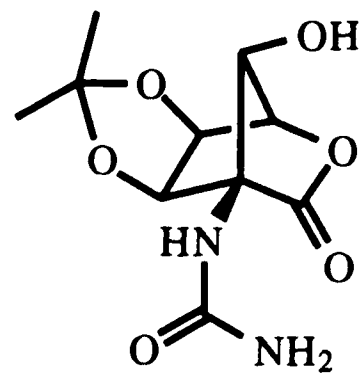
(6*R*,7*R*,8*R*,9*R*)-1,3-Diaza-6,7,8,9-tetrahydroxy-6,7:8,9-di-*O*-isopropylidene-spiro[4.4]nonan-2,4-dione (**2.28**) (138 mg, 0.46 mmol) was dissolved in aqueous trifluoroacetic acid (40%, 10 ml) and the reaction was stirred at room temperature for 40 min. After this time t.l.c. analysis (methanol / dichloromethane, 1 : 9) showed complete conversion of starting material (R_f 0.6) to one product (R_f 0.05). The solvent was removed and the residue was co-evaporated with toluene (3 x 10 ml). Purification by repeated recrystallisation (methanol) gave (6*R*,7*R*,8*R*,9*R*)-1,3-diaza-6,7,8,9-tetrahydroxy-spiro[4.4]nonan-2,4-dione (**2.24**) (39 mg, 0.18 mmol, 40%) as a colourless crystalline solid. M.p. 213 - 214 °C (methanol / dichloromethane); $[\alpha]_D^{20}$ +60.3 (*c*, 0.7 in water); (Found: C, 38.73; H, 4.66; N, 12.83%. $C_7H_{10}O_6N_2$ requires C, 38.54; H, 4.62; N, 12.84%); ν_{max} (KBr): 3284 (br, OH), 1761, 1736 cm^{-1} (hydantoin); δ_H (D_2O, 500 MHz): 3.99 (1H, dd, $J_{7,6}$ 6.0 Hz, $J_{7,8}$ 4.0 Hz, H-7), 4.19 (1H, dd $J_{8,7}$ 4.0 Hz $J_{8,9}$ 4.6 Hz, H-8), 4.26 (1H, d, $J_{9,8}$ 4.6 Hz, H-9), 4.34 (1H, d, $J_{6,7}$ 6.0 Hz, H-6); δ_C (D_2O, 125 MHz): 73.7, 74.2, 76.6, 76.9 (4 x d, C-6, C-7, C-8, C-9), 74.4 (s, C-5), 159.6 (s, C-2), 176.7 (s, C-4); *m/z* (FAB+): 311 [$(MH+Gly)^+$, 50], 219 [$(MH)^+$, 100%].

(1*R*,4*R*,5*R*,6*R*,7*R*)-1-Amino-5,6,7-trihydroxy-5,6-*O*-isopropylidene-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.29**)



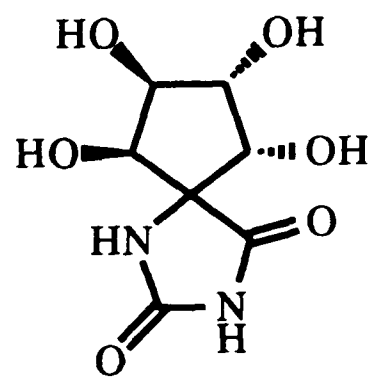
(1*R*,4*R*,5*R*,6*R*,7*R*)-1-Azido-5,6,7-trihydroxy-5,6-*O*-isopropylidene-2-oxa-bicyclo[2.2.1]heptan-3-one (**1.52**) (76 mg, 0.32 mmol) was dissolved in ethanol (5 ml) and palladium black (5 mg) added. The solution was degassed and the reaction mixture was stirred vigorously under hydrogen for 24 h. After this time t.l.c. analysis (ethyl acetate) indicated complete conversion of starting material (R_f 0.7) to one product (R_f 0.25). The reaction mixture was filtered through Celite (ethanol elution, 30 ml) and the solvent removed. Purification by flash chromatography (ethyl acetate) gave (1*R*,4*R*,5*R*,6*R*,7*R*)-1-amino-5,6,7-trihydroxy-5,6-*O*-isopropylidene-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.29**) (56 mg, 0.26 mmol, 83%) as a white solid. M.p. 193 - 196 ^{o}C (decomp., ethyl acetate); $[\alpha]_D^{20}$ -15.3 (*c*, 0.3 in methanol); (Found: C, 50.21; H, 6.06; N, 6.34%. $C_9H_{13}O_5N_1$ requires C, 50.23; H, 6.09; N, 6.51%); ν_{max} (KBr): 3429 (br, OH, NH), 1794 cm^{-1} (lactone); δ_H (CD_3OD, 500 MHz): 1.33, 1.46 (2 x 3H, 2 x s, $C(C\underline{H}_3)_2$), 3.98 (1H, d, *J* 4.6 Hz), 4.13 (1H, dd, *J* 4.6 Hz, *J* 2.4 Hz), 4.51 (1H, dd, *J* 7.1 Hz, *J* 2.4 Hz), 5.01 (1H, d, *J* 7.1 Hz); δ_C (CD_3OD, 125 MHz): 24.6, 26.4 (2 x q, $C(\underline{C}H_3)_2$), 67.9 (s, C-4), 76.9, 80.8, 82.5, 86.0 (4 x d, C-1, C-5, C-6, C-7), 113.7 (s, $\underline{C}(CH_3)_2$), 174.8 (s, C-3); *m/z* (CI, NH_3): 233 [$(MNH_4)^+$, 10], 216 [$(MH)^+$, 100%].

(1*R*,4*R*,5*R*,6*R*,7*R*)-5,6,7-Trihydroxy-5,6-*O*-isopropylidene-2-oxa-4-ureido-bicyclo[2.2.1]heptan-3-one (**2.30**)



(1*R*,4*R*,5*R*,6*R*,7*R*)-1-Amino-5,6,7-trihydroxy-5,6-*O*-isopropylidene-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.29**) (116 mg, 0.54 mmol) was dissolved in acetic acid (5 ml) and potassium cyanate (131 mg, 1.62 mmol) added. The reaction mixture was stirred under nitrogen at room temperature for 24 h and then preadsorbed onto silica gel. Purification by flash chromatography (ethyl acetate) gave (1*R*,4*R*,5*R*,6*R*,7*R*)-5,6,7-trihydroxy-5,6-*O*-isopropylidene-2-oxa-4-ureido-bicyclo[2.2.1]heptan-3-one (**2.30**) (125 mg, 0.48 mmol, 90%) as a white crystalline solid. M.p. 210 - 215 °C (decomp., ethanol); $[\alpha]_D^{20}$ -17.6 (*c*, 0.25 in methanol); (Found: C, 46.26; H, 5.40; N, 10.65%. $C_{10}H_{14}O_6N_2$ requires C, 46.51; H, 5.46; N, 10.85%); ν_{max} (KBr): 3446 (br, OH, NH), 1801 (lactone), 1677, 1537 cm^{-1} (urea); δ_H [$(CD_3)_2SO$, 500 MHz]: 1.30, 1.44 (2 x 3H, 2 x s, $C(C\underline{H}_3)_2$), 4.41 (1H, d, *J* 2.0 Hz), 4.57 (1H, dd, *J* 6.2 Hz, *J* 1.1 Hz), 4.66 (1H, s), 4.78 (1H, d, *J* 6.2 Hz), 5.97 (1H, br s ex in D_2O, OH), 6.76, 6.87 (3H, 2 x br s ex in D_2O, NH, NH_2); δ_C [$(CD_3)_2SO$, 125 MHz]: 24.2, 25.2 (2 x q, $C(\underline{C}H_3)_2$), 67.4 (s, C-4), 75.9, 76.0, 76.7, 79.4 (4 x d, C-1, C-5, C-6, C-7), 113.9 (s, $\underline{C}(CH_3)_2$), 159.2 (s, $NH\underline{C}ONH_2$), 174.8 (s, C-3); *m/z* (CI, NH_3): 276 [$(MNH_4)^+$, 10], 259 [$(MH)^+$, 100%].

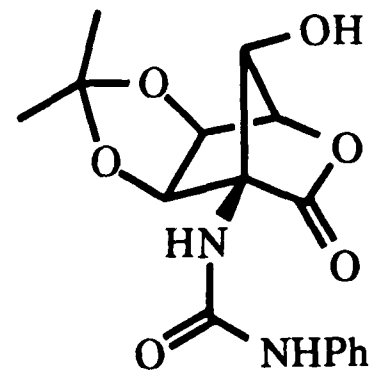
(6*R*,7*R*,8*R*,9*R*)-1,3-Diaza-6,7,8,9-tetrahydroxy-spiro[4,4]nonan-2,4-dione (**2.24**)



Method 2 - From (1*R*,4*R*,5*R*,6*R*,7*R*)-5,6,7-trihydroxy-5,6-*O*-isopropylidene-2-oxa-4-ureido-bicyclo[2.2.1]heptan-3-one (**2.30**).

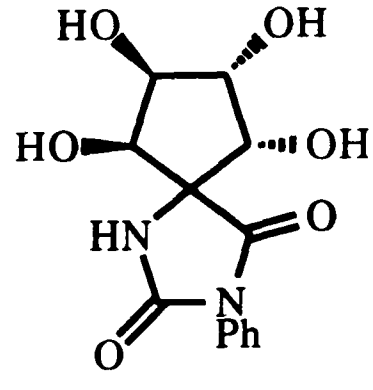
A 2 M solution of hydrochloric acid in methanol was generated by the addition of acetyl chloride (2.9 ml) to anhydrous methanol (17.1 ml), of which 5 ml was added to a suspension of (1*R*,4*R*,5*R*,6*R*,7*R*)-5,6,7-trihydroxy-5,6-*O*-isopropylidene-2-oxa-4-ureido-bicyclo[2.2.1]heptan-3-one (**2.30**) (91 mg, 0.35 mmol) in methanol (1 ml). The reaction mixture was heated under reflux for 12 h, by which time t.l.c. analysis (methanol / ethyl acetate, 1 : 1) indicated complete conversion of starting material (R_f 0.75) to one product (R_f 0.15). The solvent was removed and the residue co-evaporated with methanol (2 x 20 ml). Purification by repeated recrystallisation (methanol) gave (6*R*,7*R*,8*R*,9*R*)-1,3-diaza-6,7,8,9-tetrahydroxy-spiro[4,4]nonan-2,4-dione (**2.24**) as a colourless crystalline solid (27 mg, 0.12 mmol, 36%), identical to the authentic sample obtained in method 1.

(1*R*,4*R*,5*R*,6*R*,7*R*)-5,6,7-Trihydroxy-5,6-*O*-isopropylidene-2-oxa-4-*N'*-phenylureido-bicyclo[2.2.1]heptan-3-one (**2.31**)



(1*R*,4*R*,5*R*,6*R*,7*R*)-4-Amino-5,6,7-trihydroxy-5,6-*O*-isopropylidene-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.29**) (100 mg, 0.47 mmol) was dissolved in tetrahydrofuran (3 ml) and phenyl isocyanate (0.07 ml, 0.6 mmol) added. The reaction mixture was stirred under nitrogen at room temperature for 10 min. After this time t.l.c. analysis (ethyl acetate) indicated complete conversion of starting material (R_f 0.3) to one product (R_f 0.7). The solvent was removed and purification by flash chromatography (ethyl acetate / hexane, 1 : 1) gave (1*R*,4*R*,5*R*,6*R*,7*R*)-5,6,7-trihydroxy-5,6-*O*-isopropylidene-2-oxa-4-*N'*-phenylureido-bicyclo[2.2.1]heptan-3-one (**2.31**) (107 mg, 0.32 mmol, 69%) as a colourless crystalline solid. M.p. 210 - 212 °C (diethyl ether); $[\alpha]_D^{20}$ +51.3 (*c*, 0.4 in methanol); (Found: C, 57.61; H, 5.42; N, 8.29%. $C_{16}H_{18}O_6N_2$ requires C, 57.48; H, 5.43; N, 8.38%); ν_{max} (KBr): 3404 (br, OH, NH), 1793 (lactone), 1677, 1537 cm^{-1} (urea); δ_H [$(CD_3)_2SO$, 500 MHz]: 1.30, 1.44 (2 x 3H, 2 x s, $C(C\underline{H}_3)_2$), 4.49 (1H, d, *J* 4.0 Hz), 4.61 (1H, dd, *J* 6.2 Hz, *J* 1.4 Hz), 4.68 (1H, s), 5.06 (1H, d, *J* 6.2 Hz), 6.42 (1H, d, *J* 3.8 Hz, OH-7), 6.54, 8.81 (2 x 1H, 2 x br s, 2 x NH), 6.92 - 6.95 (1H, m, Ar-H), 7.23 - 7.27 (2H, m, Ar-H), 7.35 - 7.38 (2H, m, Ar-H); δ_C [$(CD_3)_2SO$, 125 MHz]: 24.0, 25.1 (2 x q, $C(\underline{C}H_3)_2$), 66.6 (s, C-4), 74.8, 75.7, 76.4, 79.0 (4 x d, C-1, C-5, C-6, C-7), 113.5 (s, $\underline{C}(CH_3)_2$), 117.8, 121.5, 128.6 (3 x d, Ar-CH), 139.7 (s, Ar-C), 154.4 (s, NH$\underline{C}$ONHPh), 172.4 (s, C-3); *m/z* (DCI, NH_3): 352 [$(MNH_4)^+$, 15], 335 [$(MH)^+$, 100%].

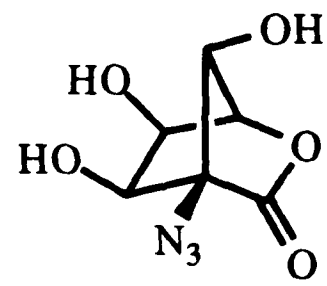
(6*R*,7*R*,8*R*,9*R*)-1,3-Diaza-6,7,8,9-tetrahydroxy-3-*N*-phenyl-spiro[4,4]nonan-2,4-dione (**2.32**)



A 2 M solution of hydrochloric acid in methanol was generated by the addition of acetyl chloride (2.9 ml) to anhydrous methanol (17.1 ml), of which 15 ml was added to a suspension of (1*R*,4*R*,5*R*,6*R*,7*R*)-5,6,7-trihydroxy-5,6-*O*-isopropylidene-2-oxa-4-*N'*-phenylureido-bicyclo[2.2.1]heptan-3-one (**2.31**) (143 mg, 0.43 mmol) in methanol (10 ml). The reaction mixture was heated to reflux under nitrogen for 3.5 h, by which time t.l.c. analysis (methanol / ethyl acetate, 1 : 1) indicated complete conversion of starting material (R_f 0.85) to one product (R_f 0.15). The solvent was removed and purification by flash chromatography (methanol / ethyl acetate, 1 : 9) gave (6*R*,7*R*,8*R*,9*R*)-1,3-diaza-6,7,8,9-tetrahydroxy-3-*N*-phenyl-spiro[4,4]nonan-2,4-dione (**2.32**) (103 mg, 0.35 mmol, 82 %) as a white crystalline solid. M.p. 199 - 200 °C; $[\alpha]_D^{20}$ +75.8 (*c*, 0.5 in methanol); (Found: C, 52.73; H, 5.08; N, 9.27%. $C_7H_{11}O_6N_3$ requires C, 53.06; H, 4.80; N, 9.52%); ν_{max} (KBr): 3350 (br, OH), 1775, 1714 cm^{-1} (hydantoin); δ_H (CD_3OD, 500 MHz): 3.97 (1H, dd, *J* 5.9 Hz, *J* 2.8 Hz), 4.15 (1H, dd, *J* 4.2 Hz, *J* 2.8 Hz), 4.42 (1H, d, *J* 4.3 Hz), 4.46 (1H, d, *J* 5.9 Hz), 7.35 - 7.48 (5H, m, Ar-H); δ_C (CD_3OD): 73.4 (s, C-5), 75.2, 75.3, 78.1, 79.1 (4 x d, C-6, C-7, C-8, C-9), 127.9, 129.2, 129.9 (3 x d, Ar-CH), 133.4 (s, Ar-C), 158.2 (s, C-2), 175.0 (s, C-4); *m/z* (DCI, NH_3): 312 [$(MNH_4)^+$, 100], 295 [$(MH)^+$, 100%].

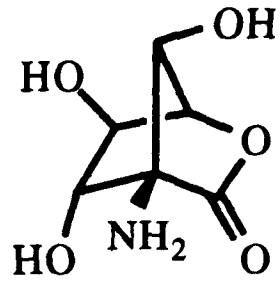
Experimental Procedures for Results and Discussion Section 2.3.

(1*R*,4*S*,5*R*,6*R*,7*R*)-4-Azido-5,6,7-trihydroxy-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.33**)



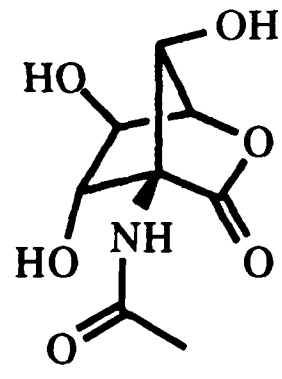
(1*R*,4*R*,5*R*,6*R*,7*R*)-4-Azido-5,6,7-trihydroxy-5,6-*O*-isopropylidene-2-oxa-bicyclo[2.2.1]heptan-3-one (**1.52**) (411 mg, 1.71 mmol) was stirred in aqueous trifluoroacetic acid (80%, 20 ml) at room temperature for 6 h. After this time t.l.c. analysis (ethyl acetate) indicated complete conversion of starting material (R_f 0.8) to one product (R_f 0.5). The solvent was removed and purification by flash chromatography (ethyl acetate / hexane, 3 : 2) gave (1*R*,4*S*,5*R*,6*R*,7*R*)-4-azido-5,6,7-trihydroxy-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.33**) (304 mg, 1.51 mmol, 89%) as a white crystalline solid. M.p. 134 - 135 °C (ethyl acetate / hexane); $[\alpha]_D^{20}$ +41.7 (*c*, 1.0 in methanol); (Found: C, 35.90; H, 3.40; N, 20.66%. $C_6H_7O_5N_3$ requires C, 35.83; H, 3.51; N, 20.89%); ν_{max} (KBr): 3384 (br, OH), 2130 (azide), 1811 cm^{-1} (lactone); δ_H (CD_3OD, 500 MHz): 3.96 (1H, d, $J_{6,5}$ 6.8 Hz, H-6), 4.04 (1H, dd, $J_{5,1}$ 1.1 Hz, $J_{5,6}$ 6.8 Hz, H-5), 4.44 (1H, t, H-4), 4.73 (1H, s, H-7); δ_C (CD_3CN): 66.6, 67.1, 76.6, 82.2 (4 x d, C-1, C-5, C-6, C-7), 73.1 (s, C-4), 171.7 (s, C-3); *m/z* (CI, NH_3): 219 [$(MNH_4)^+$, 40], 174 [$(MH\text{-}N_2)^+$, 10], 112 (100%).

(1*R*,4*S*,5*S*,6*R*,7*R*)-4-Amino-5,6,7-trihydroxy-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.34**)



(1*R*,4*S*,5*R*,6*R*,7*R*)-4-Azido-5,6,7-trihydroxy-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.33**) (48 mg, 0.24 mmol) was dissolved in water (6 ml) and palladium black (5 mg) added. The reaction mixture was degassed and stirred vigorously under hydrogen for 24 h. After this time t.l.c. analysis (ethyl acetate) indicated complete conversion of starting material (R_f 0.5) to baseline materials. The reaction mixture was filtered through Celite (water elution, 20 ml) and the solvent was removed to give (1*R*,4*S*,5*S*,6*R*,7*R*)-4-amino-5,6,7-trihydroxy-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.34**) (39 mg, 0.22 mmol, 93%) as a brown hygroscopic foam. $[\alpha]_D^{25}$ -4.6 (*c*, 1.9 in water); ν_{max} (KBr): 3428 (br, OH, NH), 1785 cm^{-1} (lactone); δ_H (CD_3OD, 500 MHz): 3.75, 3.87 (2 x 1H, 2 x t, $J_{5,1} = J_{6,1} = J_{5,6}$ 1.5 Hz, H-5, H-6), 4.22 (1H, s, H-7), 4.32 (1H, t, $J_{1,5} = J_{1,6}$ 1.5 Hz, H-1); δ_C (D_2O): 68.7 (s, C-4), 74.6, 76.8, 73.3, 82.3 (4 x d, C-1, C-5, C-6, C-7), 177.5 (s, C-3); *m/z* (CI, NH_3): 193 [$(MNH_4)^+$, 30], 176 [$(MH)^+$, 100%]. This material was used directly without further purification.

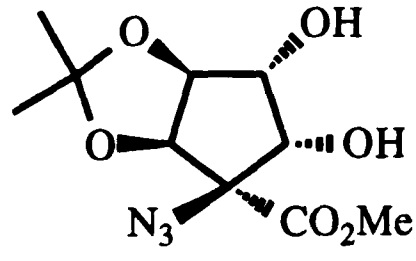
(1*R*,4*S*,5*S*,6*R*,7*R*)-4-Acetamido-5,6,7-trihydroxy-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.36**)



(1*R*,4*S*,5*S*,6*R*,7*R*)-4-Amino-5,6,7-trihydroxy-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.34**) (69 mg, 0.39 mmol) was dissolved in *N*,*N*-dimethylformamide (1 ml) under nitrogen.

Acetic anhydride (48 µl, 0.51 mmol) was added and the reaction mixture was stirred at 0 °C for 2 h. After this time t.l.c. analysis (methanol / ethyl acetate, 1 : 9) indicated the conversion of starting material (R_f 0.05) to one product (R_f 0.3). The solvent was removed and the residue was preadsorbed onto silica gel. Purification by flash chromatography (methanol / ethyl acetate, 1 : 19) gave (1*R*,4*S*,5*S*,6*R*,7*R*)-4-acetamido-5,6,7-trihydroxy-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.35**) (64 mg, 0.29 mmol, 75%) as a colourless crystalline solid. M.p. 192 - 194 °C (decomp., methanol / dichloromethane); $[\alpha]_D^{25}$ -27.3 (*c*, 1.0 in methanol); (Found: C, 44.21; H, 4.96; N, 6.20%. $C_8H_{11}O_6N_1$ requires C, 44.24; H, 5.11; N, 6.45%); ν_{max} (KBr): 3310 (br, OH, NH), 1791 (lactone), 1657, 1542 cm^{-1} (amide); δ_H (CD_3OD, 500 MHz): 2.03 (3H, s, CH_3), 3.73, 4.51 (2 x 1H, 2 x t, $J_{5,1} = J_{6,1} = J_{5,6}$ 1.5 Hz, H-5, H-6), 4.36 (1H, t, $J_{1,5} = J_{1,6}$ 1.5 Hz, H-1), 4.89 (1H, s, H-7); δ_C (CD_3OD): 23.0 (q, $CO\underline{C}H_3$), 72.0 (s, C-4), 75.1, 76.3, 76.4, 82.2 (4 x d, C-1, C-5, C-6, C-7), 173.9, 174.5 (2 x s, C-3, $\underline{C}OCH_3$); *m/z* (CI, NH_3): 235 [$(MNH_4)^+$, 30], 218 [$(MH)^+$, 100%].

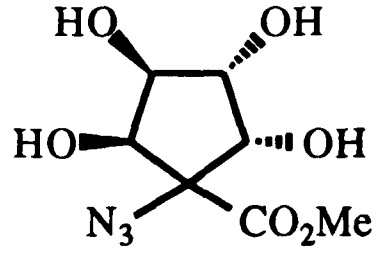
(1*R*,2*R*,3*S*,4*R*,5*R*)-Methyl [1-azido-2,3,4,5-tetrahydroxy-2,3-*O*-isopropylidene-cyclopentane] carboxylate (**2.37**)



Potassium carbonate (20 mg, catalytic amount) was added to a solution of (1*R*,4*R*,5*R*,6*R*,7*R*)-4-azido-5,6,7-trihydroxy-5,6-*O*-isopropylidene-2-oxa-bicyclo[2.2.1]heptan-3-one (**1.52**) (286 mg, 1.19 mmol) in dry methanol (20 ml) at 0 °C. The solution was stirred for 20 min, by which time t.l.c. analysis (ethyl acetate / hexane, 1 : 1) indicated complete conversion of starting material (R_f 0.5) to one product (R_f 0.3). The reaction mixture was filtered to remove the excess solid carbonate and the solution was adjusted to pH 5 by dropwise addition of acetic acid.

The solvent was removed and purification by flash chromatography (ethyl acetate / hexane, 1 : 1) gave (1*R*,2*R*,3*S*,4*R*,5*R*)-methyl [1-azido-2,3,4,5-tetrahydroxy-2,3-*O*-isopropylidene-cyclopentane] carboxylate (**2.37**) (315 mg, 1.15 mmol, 97%) as a colourless oil. $[\alpha]_D^{20}$ 102.8 (*c*, 0.5 in chloroform) [lit.[2] $[\alpha]_D^{20}$ +104.9 (*c*, 0.5 in chloroform)]; δ_H ($CDCl_3$): 1.35, 1.56 (2 x 3H, 2 x s, $C(C\underline{H}_3)_2$), 3.01 (1H, d ex in D_2O, $J_{OH,4}$ 8.1 Hz, OH-4), 3.44 (1H, d ex in D_2O, $J_{OH,5}$ 6.4 Hz, OH-5), 3.90 (3H, s, $CO_2C\underline{H}_3$), 4.17 (1H, ddd, $J_{4,OH}$ 8.1 Hz, $J_{4,3}$ 1.6 Hz, $J_{4,5}$ 4.9 Hz, H-4), 3.36 (1H, dd, $J_{5,OH}$ 6.4 Hz, $J_{5,4}$ 4.9 Hz, H-5), 4.60 (1H, dd, $J_{3,2}$ 6.5 Hz, $J_{3,4}$ 1.6 Hz, H-3), 4.99 (1H, d, $J_{2,3}$ 6.5 Hz, H-2).

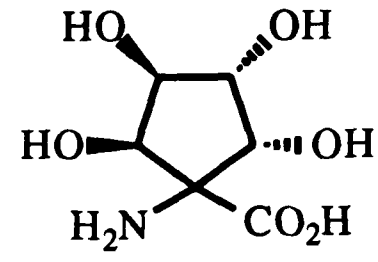
(2*R*,3*R*,4*R*,5*R*)-Methyl [1-azido-2,3,4,5-tetrahydroxy-cyclopentane] carboxylate (**2.38**)



(1*R*,2*R*,3*R*,4*R*,5*R*)-Methyl [1-azido-2,3,4,5-tetrahydroxy-2,3-*O*-isopropylidene-cyclopentane] carboxylate (**2.37**) (249 mg, 0.91 mmol) was stirred in aqueous trifluoroacetic acid (80%, 20 ml) at room temperature for 1.5 h. After this time t.l.c. analysis (ethyl acetate) showed a trace of starting material (R_f 0.5) and one product (R_f 0.25). The solvent was removed and purification by flash chromatography (ethyl acetate) gave (2*R*,3*R*,4*R*,5*R*)-methyl [1-azido-2,3,4,5-tetrahydroxy-cyclopentane] carboxylate (**2.38**) (178 mg, 0.76 mmol, 84%) as a white crystalline solid. M.p. 87 - 88 °C (ethyl acetate / hexane); $[\alpha]_D^{20}$ +73.4 (*c*, 1.0 in methanol); (Found: C, 36.29; H, 4.47; N, 17.93%. $C_7H_{11}O_6N_3$ requires C, 36.06; H, 4.75; N, 18.02%); ν_{max} (KBr): 3401 (br, OH), 2122 (azide), 1735 cm^{-1} (ester); δ_H [$(CD_3)_2SO$, 500 MHz]: 3.74 (3H, s, $CO_2C\underline{H}_3$), 3.76 - 3.83 (3H, m, H-3, H-4, H-5), 4.72 (1H, dd, *J* 6.3 Hz, *J* 7.3 Hz, H-2), 4.85 (1H, d, *J* 5.4 Hz, OH), 4.87 (1H, d, *J* 4.7 Hz, OH), 5.13 (1H, d, *J* 7.4 Hz, OH), 5.20 (1H, d, *J* 6.3 Hz, OH); δ_C (D_2O): 53.3 (q, $CO_2\underline{C}H_3$), 72.7, 74.8, 75.3, 75.8

(4 x d, C-2, C-3, C-4, C-5), 75.6 (s, C-1), 170.9 (s, $\underline{C}O_2CH_3$); *m/z* (CI, NH_3): 251 [$(MNH_4)^+$, 10], 206 [$(MH\text{-}N_2)^+$, 10], 118 (100%).

(2*R*,3*R*,4*R*,5*R*)-1-Amino-2,3,4,5-tetrahydroxy-cyclopentane carboxylic acid (**2.39**)



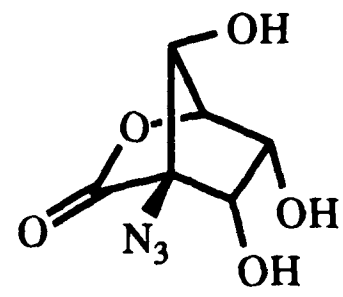
(1*R*,4*R*,5*R*,6*R*,7*R*)-4-Azido-5,6,7-trihydroxy-5,6-*O*-isopropylidene-2-oxa-bicyclo[2.2.1]heptan-3-one (**1.52**) (95 mg, 0.39 mmol) was dissolved in distilled water / dioxane (4 : 1, 5 ml), to which potassium carbonate (38 mg, 0.28 mmol) was added. The reaction mixture was stirred at room temperature for 2 h, by which time t.l.c. analysis (ethyl acetate) indicated complete conversion of starting material (R_f 0.8) to baseline materials. Removal of solvent gave a crude solid residue (141 mg). ν_{max} (KBr): 3439 (br, OH), 2112 (azide), 1598 cm^{-1} (COO^-); δ_H (D_2O): 1.16, 1.32 (2 x 3H, 2 x s, $C(C\underline{H}_3)_2$), 3.83 (1H, d, *J* 5.6 Hz), 4.11 (1H, d, *J* 5.6 Hz), 4.50 (1H, d, *J* 6.3 Hz), 4.75 (1H, d, *J* 6.3 Hz); δ_C (D_2O): 23.1, 24.7 (2 x q, $C(\underline{C}H_3)_2$), 74.2, 76.1, 80.6, 84.4 (4 x d, C-2, C-3, C-4, C-5), 76.3 (s, C-1), 112.6 (s, $\underline{C}(CH_3)_2$), 174.8 (s, COO^-); *m/z* (negative electrospray): 258 (M^-, 100%). This was used directly without further purification.

The crude solid residue (141 mg from the above reaction) was dissolved in distilled water (5 ml) and palladium black (6 mg) added. After degassing the solution, the reaction mixture was stirred vigorously under hydrogen for 19 h. The reaction mixture was then filtered through Celite (water elution, 20 ml) and the solvent removed to give a crude solid residue (126 mg). ν_{max} (KBr): 3410 (br, OH, NH_2), 1614 cm^{-1} (COO^-); δ_H (D_2O, 500 MHz): 1.26, 1.38 (2 x 3H, 2 x s, $C(C\underline{H}_3)_2$), 3.84 (1H, d, *J* 5.8 Hz), 3.94 (1H, d, *J* 5.8 Hz), 4.56 (2H, s); δ_C (D_2O, 125 MHz): 23.8,

25.8 (2 x q, C($\underline{C}H_3)_2$), 69.4 (s, C-1), 75.0, 78.8, 81.0, 85.1 (4 x d, C-2, C-3, C-4, C-5), 112.3 (s, $\underline{C}(CH_3)_2$, 179.0 (s, COO^-); *m/z* (electrospray): 180 [$(MH)^+$, 100%]. This was again used directly without further purification.

The crude solid residue (126 mg from the above reaction) was dissolved in aqueous trifluoroacetic acid (40%, 10 ml) and the reaction mixture was stirred at room temperature. After 8 h, crude proton NMR (D_2O) indicated the presence of a single compound. The solvent was removed, the residue co-evaporated with toluene (2 x 3 ml) and then purified by ion exchange chromatography [Dowex 50W-X8(H^+), 2 M aqueous pyridine elution] to give (2*R*,3*R*,4*R*,5*R*)-1-amino-2,3,4,5-tetrahydroxy-cyclopentane carboxylic acid (**2.39**) (75 mg, 98 % over three steps). M.p. >215 °C (decomp., water); $[\alpha]_D^{25}$ +22.0 (*c*, 0.15 in water); (Found: C, 37.58; H, 5.98; N, 7.39%. $C_6H_{11}O_6N_1$ requires C, 37.31; H, 5.74; N, 7.25%); ν_{max} (KBr): 3379 (br, OH, NH), 1636 cm^{-1} (COO^-); δ_H (D_2O, 500 MHz): 4.02 (1H, dd, *J* 6.1 Hz, *J* 3.4 Hz), 4.24 (1H, br t, *J* 4.0 Hz), 4.39 (1H, d, *J* 6.1 Hz), 4.54 (1H, d, *J* 4.6 Hz); δ_C (D_2O, 125 MHz): 69.9 (s, C-1), 72.8, 74.8, 75.3, 77.1 (4 x d, C-2, C-3, C-4, C-5), 173.3 (s, COO^-); *m/z* (electrospray): 194 [$(MH)^+$, 100%].

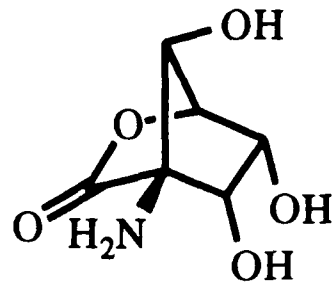
(1*S*,4*R*,5*R*,6*R*,7*R*)-4-Azido-5,6,7-trihydroxy-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.40**)



(1*S*,4*S*,5*R*,6*R*,7*R*)-4-Azido-5,6,7-trihydroxy-5,6-*O*-isopropylidene-2-oxa-bicyclo[2.2.1]heptan-3-one (**1.53**) (197 mg, 0.82 mmol) was stirred in aqueous trifluoroacetic acid (40%, 15 ml) at room temperature for 3 h. After this time t.l.c. analysis (ethyl acetate / hexane, 1 : 1) indicated complete conversion of starting material (R_f 0.5) to one product (R_f 0.15). The solvent was then removed and

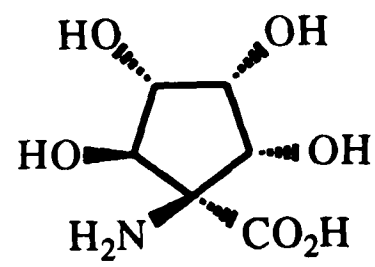
purification by flash chromatography (ethyl acetate / hexane, 1 : 1) gave (1*S*,4*R*,5*R*,6*R*,7*R*)-4-azido-5,6,7-trihydroxy-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.40**) (271 mg, 1.35 mmol, 97%) as a white crystalline solid. M.p. 99 - 101 °C (on standing) [lit.[4] m.p. 102 - 104 °C (on standing)]; $[\alpha]_D^{20}$ +184.9 (*c*, 1.0 in methanol) [lit.[4] $[\alpha]_D^{20}$ +186.7 (*c*, 1.0 in methanol)]; δ_H (CD_3CN): 3.50 (1H, d ex in D_2O, $J_{OH,6}$ 7.5 Hz, OH-6), 3.88 (1H, d ex in D_2O, $J_{OH,5}$ 5.4 Hz, OH-5), 4.29 (1H, dd, $J_{7,OH}$ 4.5 Hz, $J_{7,1}$ 2.6 Hz, H-7), 4.30 (1H, d, $J_{OH,7}$ 4.5 Hz, OH-7), 4.46 (1H, ddd, $J_{6,OH}$ 7.5 Hz, $J_{6,1}$ 2.3 Hz, $J_{6,5}$ 7.7 Hz, H-6), 4.55 (1H, ddd, $J_{5,OH}$ 5.4 Hz, $J_{5,1}$ 0.9 Hz, $J_{5,6}$ 7.7 Hz, H-5), 4.61 (1H, ddd, $J_{1,5}$ 0.9 Hz, $J_{1,6}$ 2.3 Hz, $J_{1,7}$ 2.6 Hz, H-1).

(1*S*,4*R*,5*R*,6*R*,7*R*)-4-Amino-5,6,7-trihydroxy-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.41**)



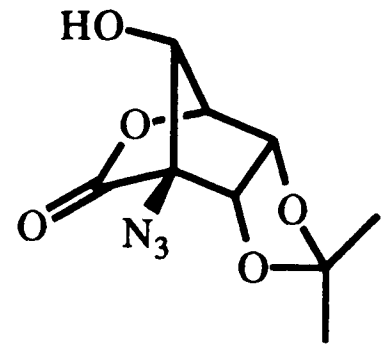
(1*S*,4*R*,5*R*,6*R*,7*R*)-4-Azido-5,6,7-trihydroxy-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.40**) (263 mg, 1.31 mmol) was dissolved in ethanol (25 ml) and palladium black (10 mg) added. The reaction mixture was degassed and stirred vigorously under hydrogen for 4.5 h. After this time t.l.c. analysis (ethyl acetate) indicated complete conversion of starting material (R_f 0.5) to baseline materials. The reaction mixture was filtered through Celite (ethanol elution, 40 ml) and the solvent removed to give (1*S*,4*R*,5*R*,6*R*,7*R*)-4-amino-5,6,7-trihydroxy-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.41**) (201 mg, 1.15 mmol, 88%) as a pale yellow hygroscopic solid. δ_H (CD_3OD): 4.01 (1H, d, $J_{7,1}$ 2.8 Hz, H-7), 4.24 (1H, br d, $J_{5,6}$ 8.0 Hz, H-5), 4.44 (1H, dd, $J_{6,1}$ 2.3 Hz, $J_{6,5}$ 8.0 Hz, H-6), 4.52 (1H, m, H-1). This material was used directly without further characterisation.

(1*S*,2*R*,3*R*,4*S*,5*R*)-1-Amino-2,3,4,5-tetrahydroxy-cyclopentane carboxylic acid (**2.42**)



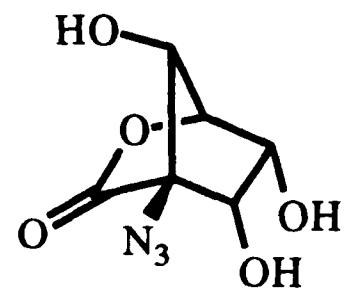
(1*S*,4*R*,5*R*,6*R*,7*R*)-4-Amino-2-oxa-5,6,7-trihydroxy-bicyclo[2.2.1]heptan-3-one (**2.41**) (195 mg, 1.11 mmol) was dissolved in water (10 ml). Triethylamine (1.5 ml, 11.14 mmol) was added and the resulting mixture stirred at room temperature. After 1.5 h t.l.c. analysis (CMAW) indicated complete conversion of starting material (R_f 0.5) to baseline materials. The solvent was removed and the residue purified by ion exchange chromatography [Dowex 50W-X8(H^+), 2 M aqueous pyridine elution] to yield (1*S*,2*R*,3*R*,4*S*,5*R*)-1-amino-2,3,4,5-tetrahydroxy-cyclopentane carboxylic acid (**2.42**), contaminated with small amounts of other amino acids (in the ratio of 8 : 1) (185 mg, 86% combined yield). Repeated recrystallisation from water furnished the pure material (**2.42**) as a colourless crystalline solid. M.p. >230 °C (decomp., water); $[\alpha]^{25}$ (*c*, 0.75 in water): +3.7 (589), +2.9 (578), +3.2 (546), +6.1 (436), +10.0 (365); ν_{max} (KBr) 3402 (br, OH, NH) cm^{-1}; δ_H (D_2O, 500 MHz): 3.85 (1H, dd, *J* 4.0 Hz, *J* 8.6 Hz), 3.89 (1H, m), 4.21 (1H, d, *J* 4.5 Hz), 4.41 (1H, d, *J* 8.6 Hz); δ_C (D_2O, 125 MHz): 69.0 (s, C-1), 72.1, 73.4, 76.4, 77.3 (4 x d, C-2, C-3, C-4, C-5), 173.8 (s, COOH).

(1*S*,4*S*,5*R*,6*R*,7*S*)-4-Azido-5,6,7-trihydroxy-5,6-*O*-isopropylidene-2-oxa-bicyclo[2.2.1]heptan-3-one (**1.54**)



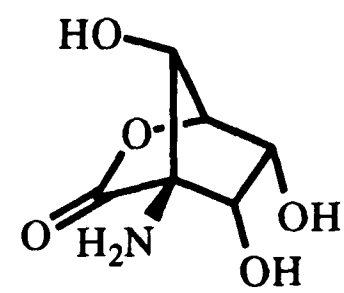
(1*S*,4*S*,5*R*,6*R*,7*R*)-4-Azido-5,6,7-trihydroxy-5,6-*O*-isopropylidene-2-oxa-bicyclo[2.2.1]heptan-3-one (**1.53**) (430 mg, 1.78 mmol) was stirred in liquid ammonia (10 ml) at -45 °C in a sealed Fischer-Porter Bottle. The reaction mixture was allowed to warm up to room temperature, under pressure, over a period of 30 min. The reaction vessel was then carefully vented and any remaining ammonia allowed to evaporate over a further period of 30 min. Ethyl acetate (20 ml) was added and the mixture transferred to a round bottomed flask. At this point t.l.c. analysis (ethyl acetate / hexane, 1 : 1) indicated a trace of starting material (R_f 0.3) and one major product (R_f 0.1). The solvent was then removed and the residue purified by flash chromatography (ethyl acetate / hexane, 1 : 1) to give (1*S*,4*S*,5*R*,6*R*,7*S*)-4-azido-5,6,7-trihydroxy-5,6-*O*-isopropylidene-2-oxa-bicyclo[2.2.1]heptan-3-one (**1.54**) (283 mg, 1.17 mmol, 66%, 82% based on recovered starting material) as a white crystalline solid. M.p. 127 - 129 °C (ethyl acetate / hexane) [lit.[4] m.p. 127 - 128 °C (ethyl acetate / hexane)]; $[\alpha]_D^{20}$ +47.1 (*c*, 1.0 in ethanol) [lit.[4] $[\alpha]_D^{20}$ +44.8 (*c*, 0.92 in ethanol)]; δ_H (CD_3CN): 1.29, 1.40 (2 x 3H, 2 x s, $C(CH_3)_2$), 4.31 (1H, d, $J_{7,OH}$ 4.2 Hz, H-7), 4.55 (1H, d ex in D_2O, $J_{OH,7}$ 4.2 Hz, OH-7), 4.60 (1H, dd, $J_{5,1}$ 1.5 Hz, $J_{5,6}$ 7.6 Hz, H-5), 4.68 (1H, m, H-1), 4.71 (1H, dd, $J_{6,1}$ 2.3 Hz, $J_{6,5}$ 7.6 Hz, H-6), and the recovered starting material (1*S*,4*S*,5*R*,6*R*,7*R*)-4-azido-5,6,7-trihydroxy-5,6-*O*-isopropylidene-2-oxa-bicyclo[2.2.1]heptan-23-one (**1.53**) (84 mg, 0.34 mmol).

(1*S*,4*R*,5*R*,6*R*,7*S*)-4-Azido-5,6,7-trihydroxy-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.43**)



(1*S*,4*S*,5*R*,6*R*,7*S*)-4-Azido-5,6,7-trihydroxy-5,6-*O*-isopropylidene-2-oxa-bicyclo[2.2.1]heptan-3-one (**1.54**) (194 mg, 0.80 mmol) was stirred in aqueous trifluoroacetic acid (40%, 15 ml) at room temperature for 21 h. After this time t.l.c. analysis (ethyl acetate) indicated complete conversion of starting material (R_f 0.6) to one product (R_f 0.2). The solvent was then removed and purification by flash chromatography (ethyl acetate) gave (1*S*,4*R*,5*R*,6*R*,7*S*)-4-azido-5,6,7-trihydroxy-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.43**) (148 mg, 0.74 mmol, 91%) as a white crystalline solid. M.p. >170 °C (decomp., methanol / diethyl ether) [lit.[4] m.p. >170 °C (decomp., methanol / diethyl ether)]; $[\alpha]_D^{20}$ +66.5 (*c*, 1.0 in methanol) [lit.[4] $[\alpha]_D^{20}$ +61.3 (*c*, 1.0 in methanol)]; δ_H (CD_3OD): 4.13 (1H, s, H-7), 4.17 (1H, dd, $J_{5,1}$ 1.1 Hz, $J_{5,6}$ 8.2 Hz, H-5), 4.20 (1H, dd, $J_{6,1}$ 1.9 Hz, $J_{6,5}$ 8.2 Hz, H-6), 4.56 (1H, m, H-1).

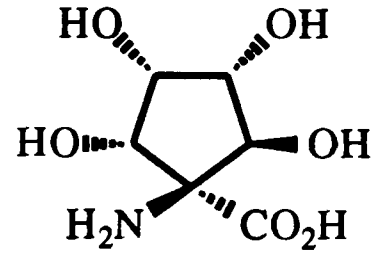
(1*S*,4*R*,5*R*,6*R*,7*S*)-4-Amino-5,6,7-trihydroxy-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.44**)



(1*S*,4*R*,5*R*,6*R*,7*S*)-4-Azido-5,6,7-trihydroxy-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.43**) (128 mg, 0.64 mmol) was dissolved in ethanol / water (4 : 1, 10 ml) to which palladium black (7 mg) was added. The reaction mixture was degassed and stirred vigorously under hydrogen for 4.5 h. After this time t.l.c. analysis (ethyl acetate) indicated complete conversion of starting material (R_f 0.2) to baseline materials. The

reaction mixture was filtered through Celite (ethanol elution, 40 ml) and the solvent removed to give (1*S*,4*R*,5*R*,6*R*,7*S*)-4-amino-5,6,7-trihydroxy-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.44**) (116 mg, crude, quant.) as a white hygroscopic foam; δ_H (CD_3OD): 3.95 (1H, br s, H-7), 4.08 (1H, dd, $J_{5,1}$ 0.8 Hz, $J_{5,6}$ 8.2 Hz, H-5), 4.21 (1H, dd, $J_{6,1}$ 2.0 Hz, $J_{6,5}$ 8.2 Hz, H-6), 4.50 (1H, m, H-1). This material was used directly without further characterisation.

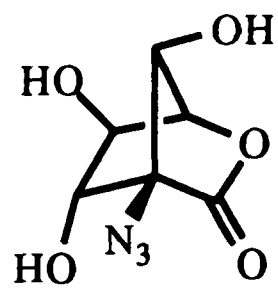
(1*S*,2*S*,3*R*,4*S*,5*S*)-1-Amino-2,3,4,5-tetrahydroxy-cyclopentane carboxylic acid (**2.45**)



(1*S*,4*R*,5*R*,6*R*,7*S*)-4-Amino-2-oxa-5,6,7-trihydroxy-bicyclo[2.2.1]heptan-3-one (**2.44**) (111 mg, 0.63 mmol) was dissolved in sodium hydroxide solution (0.4 M, 3 ml) and stirred at room temperature. After 20 min t.l.c. analysis (CMAW) indicated complete conversion of starting material (R_f 0.2) to baseline materials. The reaction mixture was adjusted to pH 7 by careful addition of aqueous hydrochloric acid. The solvent was then removed and the residue purified by ion exchange chromatography [Dowex 50W-X8(H^+), 2 M aqueous pyridine elution] to yield (1*S*,2*S*,3*R*,4*S*,5*S*)-1-amino-2,3,4,5-tetrahydroxy-cyclopentane carboxylic acid (**2.45**), contaminated with small amounts of other amino acids (in the ratio of 6 : 1) (76 mg, 59% combined yield). Repeated recrystallisation from water furnished the pure material (**2.45**) as a colourless crystalline solid. M.p. >230 °C (decomp., water); $[\alpha]_D^{25}$ (*c*, 0.75 in water): -4.4 (589), -3.5 (578), -4.0 (546), -6.5 (436), -9.6 (365); (Found: C, 37.25; H, 5.97; N, 7.08%. $C_6H_{11}O_6N_1$ requires C, 37.31; H, 5.74; N, 7.25%); ν_{max} (KBr) 3410 (br, OH, NH) cm^{-1} ; δ_H (D_2O, 500 MHz): 3.85 (1H, dd, *J* 4.0 Hz, *J* 8.6 Hz), 3.89 (1H, m), 4.21 (1H, d, *J* 4.5 Hz), 4.41 (1H, d, *J* 8.6 Hz); δ_C (D_2O, 125 MHz): 69.0 (s, C-1), 72.1,

73.4, 76.4, 77.3 (4 x d, C-2, C-3, C-4, C-5), 173.8 (s, COOH); *m/z* (electrospray): 194 [$(MH)^+$, 100%].

(1*R*,4*S*,5*S*,6*R*,7*R*)-4-Azido-5,6,7-trihydroxy-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.48**)



Method 1

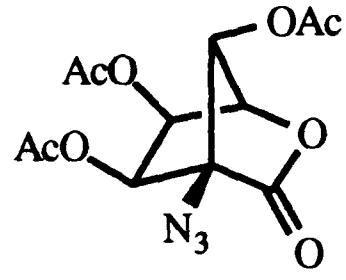
Potassium fluoride (69 mg, 1.19 mmol) and 18-crown-6 (63 mg, 0.24 mmol) were added to a solution of (1*R*,4*S*,5*R*,6*R*,7*R*)-4-azido-5,6,7-trihydroxy-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.33**) (120 mg, 0.60 mmol) in acetonitrile (10 ml) under nitrogen at room temperature. After 12 h t.l.c. analysis (methanol / chloroform, 1 : 9) showed complete conversion of the starting material (R_f 0.35) to a single product (R_f 0.25). Trifluoroacetic acid (0.15 ml) was added dropwise and the reaction mixture was preadsorbed onto silica gel. Flash chromatography (methanol / chloroform, 1 : 9) gave (1*R*,4*S*,5*S*,6*R*,7*R*)-4-azido-5,6,7-trihydroxy-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.48**) (72 mg, 0.36 mmol, 60%), as a white crystalline solid. M.p. 144 - 145 °C (methanol / chloroform); $[\alpha]_D^{20}$ +25.3 (*c*, 1.0 in methanol); (Found: C, 35.61; H, 3.35; N, 21.04%. $C_6H_7O_5N_3$ requires C, 35.83; H, 3.51; N, 20.89%); ν_{max} (KBr): 3401 (br, OH), 2127 (azide), 1790 cm^{-1} (lactone); δ_H (CD_3OD, 500 MHz): 3.76 (1H, t, *J* 1.6 Hz), 3.88 (1H, t, *J* 1.6 Hz), 4.36 (1H, s), 4.38 (1H, t, *J* 1.6 Hz); δ_C (CD_3CN, 125 MHz): 74.1 (s, C-4), 76.1, 77.8, 78.0, 83.3 (4 x d, C-1, C-5, C-6, C-7), 171.6 (s, C-3); *m/z* (DCI, NH_3): 219 [$(MNH_4)^+$, 90], 174 [$(MH-N_2)^+$, 30%], 112 (100%).

Method 2

(1*R*,4*S*,5*R*,6*R*,7*R*)-4-Azido-5,6,7-trihydroxy-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.33**) (52 mg, 0.26 mmol) was dissolved in *N*,*N*-dimethylformamide (1 ml) and sodium

acetate (2 mg, 0.03 mmol) added. The reaction mixture was stirred at room temperature under nitrogen for 7 h, by which time t.l.c. analysis (methanol / chloroform, 1 : 9) indicated partial conversion of the starting material (R_f 0.35) to a single product (R_f 0.25). Ethyl acetate (40 ml) was added and the mixture was filtered through a silica plug, with further elution of ethyl acetate (20 ml). Removal of solvent followed by flash chromatography (methanol / chloroform, 1 : 9) gave (1*R*,4*S*,5*S*,6*R*,7*R*)-4-azido-5,6,7-trihydroxy-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.48**) (R_f 0.25) (26 mg, 0.13 mmol, 50%, 84% based on recovered starting material), identical in all respects to that obtained in method 1; and the recovered starting material (1*R*,4*S*,5*R*,6*R*,7*R*)-4-azido-5,6,7-trihydroxy-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.33**) (R_f 0.35) (21 mg, 0.10 mmol).

(1*R*,4*S*,5*R*,6*R*,7*R*)-5,6,7-Triacetoxy-4-azido-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.49**)



Method 1

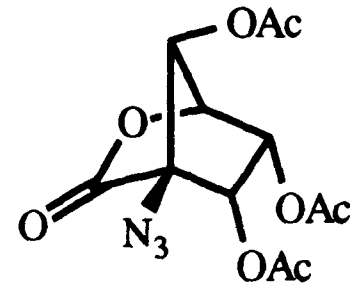
Acetic anhydride (0.7 ml) was added dropwise to a solution of (1*R*,4*S*,5*R*,6*R*,7*R*)-4-azido-5,6,7-trihydroxy-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.33**) (42 mg, 0.21 mmol) in pyridine (0.7 ml) under nitrogen. The reaction mixture was stirred at 0 °C for 2 h, by which time t.l.c. analysis (diethyl ether / hexane, 3 : 1) indicated the complete conversion of starting material (R_f 0.05) to a single product (R_f 0.35). The solvent was removed, and the residue was dissolved in ethyl acetate (10 ml), washed with aqueous hydrochloric acid (2 M, 5 ml), brine (5 ml), and dried (magnesium sulphate). Removal of solvent followed by flash chromatography (diethyl ether / hexane, 3 : 1) gave (1*R*,4*S*,5*R*,6*R*,7*R*)-5,6,7-triacetoxy-4-azido-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.49**) (61 mg, 0.19 mmol, 89%) as a colourless oil. $[\alpha]_D^{20}$ -5.5 (*c*, 1.6 in

chloroform); (Found: C, 44.23; H, 4.04; N, 12.86%. $C_{12}H_{13}O_8N_3$ requires C, 44.04; H, 4.00; N, 12.84%); ν_{max} (thin film): 2129 (azide), 1815 (lactone), 1758 cm^{-1} (ester); δ_H ($CDCl_3$, 500 MHz): 2.13, 2.14, 2.19 (3 x 3H, 3 x s, 3 x $COCH_3$), 4.85 (1H, t, *J* 1.1 Hz), 5.17 (1H, dd, *J* 1.6 Hz, *J* 6.7 Hz), 5.35 (1H, d, *J* 6.7 Hz), 5.58 (1H, s); δ_C ($CDCl_3$): 20.0, 20.4 (2 x q, $COCH_3$), 69.0 (s, C-4), 65.9, 67.7, 77.5, 78.0 (4 x d, C-1, C-5, C-6, C-7), 168.6, 168.8, 168.9, 169.9 (4 x s, C-3, 3 x $COCH_3$); *m/z* (CI, NH_3): 345 [$(MNH_4)^+$, 100], 328 [$(MH)^+$, 30%].

Method 2

Concentrated sulphuric acid (20 µl) was added to a solution of (1*R*,4*S*,5*R*,6*R*,7*R*)-4-azido-5,6,7-trihydroxy-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.33**) (65 mg, 0.32 mmol) in acetic acid / acetic anhydride (1 : 1, 3 ml) at room temperature under nitrogen. The reaction mixture was stirred for 30 min, by which time t.l.c. analysis (diethyl ether / hexane, 3 : 1) indicated the complete conversion of starting material (R_f 0.05) to a single product (R_f 0.35). Diethyl ether (10 ml) was added and the mixture washed with water (10 ml), the aqueous layer was then further extracted with diethyl ether (2 x 10 ml). The combined organic layers were dried (magnesium sulphate) and the solvent removed. Purification by flash chromatography (diethyl ether / hexane, 3 : 1) gave (1*R*,4*S*,5*R*,6*R*,7*R*)-5,6,7-triacetoxy-4-azido-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.49**) (88 mg, 0.27 mmol, 83%), identical in all respects to that obtained in method 1.

(1*S*,4*R*,5*R*,6*R*,7*R*)-5,6,7-Triacetoxy-4-azido-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.50**)



Method 1

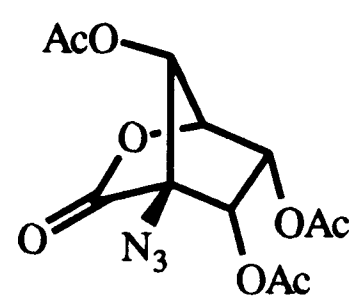
Acetic anhydride (0.4 ml) was added dropwise to a solution of (1*S*,4*R*,5*R*,6*R*,7*R*)-4-azido-5,6,7-trihydroxy-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.40**) (26 mg, 0.13 mmol) in pyridine (0.4 ml) under nitrogen. The reaction mixture was stirred at room temperature for 12 h, by which time t.l.c. analysis (ethyl acetate / hexane, 1 : 1) indicated the complete conversion of starting material (R_f 0.2) to a single product (R_f 0.5). The solvent was removed, and the residue was dissolved in ethyl acetate (20 ml), washed with aqueous hydrochloric acid (2 M, 10 ml), brine (10 ml), and dried (magnesium sulphate). Removal of solvent followed by flash chromatography (ethyl acetate / hexane, 1 : 1) gave (1*S*,4*R*,5*R*,6*R*,7*R*)-5,6,7-triacetoxy-4-azido-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.50**) (30 mg, 0.09 mmol, 71%) as a colourless oil. $[\alpha]_D^{20}$ +104.9 (*c*, 1.5 in chloroform); (Found: C, 44.18; H, 3.99; N, 13.14%. $C_{12}H_{13}O_8N_3$ requires C, 44.04; H, 4.00; N, 12.84%); ν_{max} (thin film): 2128 (azide), 1819 (lactone), 1758 cm^{-1} (ester); δ_H ($CDCl_3$, 500 MHz): 2.12, 2.15, 2.20 (3 x 3H, 3 x s, 3 x $COCH_3$), 4.97 (1H, m), 5.34 (1H, d, *J* 2.8 Hz), 5.45 (1H, dd, *J* 2.3 Hz, *J* 8.0 Hz), 5.63 (1H, d, *J* 8.0 Hz); δ_C ($CDCl_3$): 20.0, 20.1, 20.3 (3 x q, 3 x $COCH_3$), 68.4, 70.1, 74.3, 76.2 (4 x d, C-1, C-5, C-6, C-7), 71.1 (s, C-4), 166.3, 168.9, 169.7 (3 x s); *m/z* (CI, NH_3): 345 [$(MNH_4)^+$, 60], 302 (100%).

Method 2

Concentrated sulphuric acid (20 µl) was added to a solution of (1*S*,4*R*,5*R*,6*R*,7*R*)-4-azido-5,6,7-trihydroxy-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.40**) (85 mg, 0.42 mmol) in acetic acid / acetic anhydride (1 : 1, 4 ml) at room temperature under nitrogen. The

reaction mixture was stirred for 45 min, by which time t.l.c. analysis (ethyl acetate / hexane, 1 : 1) indicated the complete conversion of starting material (R_f 0.2) to a single product (R_f 0.5). Diethyl ether (10 ml) was added and the mixture washed with water (10 ml), the aqueous layer was then further extracted with diethyl ether (2 x 10 ml). The combined organic layers were dried (magnesium sulphate) and the solvent removed. Purification by flash chromatography (diethyl ether / hexane, 3 : 1) gave (1*S*,4*R*,5*R*,6*R*,7*R*)-5,6,7-triacetoxy-4-azido-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.50**) (100 mg, 0.31 mmol, 72%), identical in all respects to that obtained in method 1.

(1*S*,4*R*,5*R*,6*R*,7*S*)-5,6,7-Triacetoxy-4-azido-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.51**)



Method 1

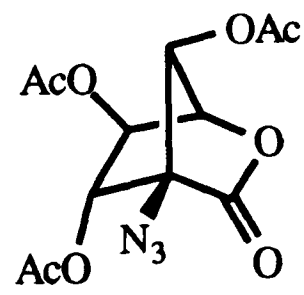
Acetic anhydride (0.7 ml) was added dropwise to a solution of (1*S*,4*R*,5*R*,6*R*,7*S*)-4-azido-5,6,7-trihydroxy-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.43**) (39 mg, 0.19 mmol) in pyridine (0.7 ml) under nitrogen. The reaction mixture was stirred at room temperature for 12 h, by which time t.l.c. analysis (diethyl ether) indicated the complete conversion of starting material (R_f 0.05) to a single product (R_f 0.6). The solvent was removed, and the residue was dissolved in ethyl acetate (25 ml), washed with aqueous hydrochloric acid (2 M, 10 ml), brine (10 ml), and dried (magnesium sulphate). Removal of solvent followed by flash chromatography (ethyl acetate / hexane, 1 : 1) gave (1*S*,4*R*,5*R*,6*R*,7*S*)-5,6,7-triacetoxy-4-azido-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.51**) (60 mg, 0.18 mmol, 95%) as a colourless oil. $[\alpha]_D^{20}$ +48.9 (*c*, 0.7 in chloroform); (Found: C, 43.74; H, 3.83; N, 12.77%. $C_{12}H_{13}O_8N_3$ requires C, 44.04; H, 4.00; N, 12.84%); ν_{max} (thin film): 2128 (azide),

1814 (lactone), 1762 cm^{-1} (ester); δ_H ($CDCl_3$, 500 MHz): 2.09, 2.12, 2.18 (3 x 3H, 3 x s, 3 x $COCH_3$), 4.99 (1H, t, *J* 1.0 Hz), 5.11 (1H, s), 5.34 (1H, dd, *J* 2.1 Hz, *J* 8.3 Hz), 5.41 (1H, d, *J* 8.3 Hz); δ_C ($CDCl_3$, 125 MHz): 20.1, 20.2, 20.4 (3 x q, 3 x $COCH_3$), 66.4, 68.6, 75.4, 78.5 (4 x d, C-1, C-5, C-6, C-7), 71.1 (s, C-4), 167.5, 169.2, 169.3 (3 x s); *m/z* (CI, NH_3): 345 [$(MNH_4)^+$, 100%].

Method 2

Concentrated sulphuric acid (20 µl) was added to a solution of (1*S*,4*R*,5*R*,6*R*,7*S*)-4-azido-5,6,7-trihydroxy-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.43**) (79 mg, 0.39 mmol) in acetic acid / acetic anhydride (1 : 1, 3 ml) at room temperature under nitrogen. The reaction mixture was stirred for 35 min, by which time t.l.c. analysis (diethyl ether / hexane, 3 : 1) indicated the complete conversion of starting material (R_f 0.05) to a single product (R_f 0.25). Diethyl ether (40 ml) was added and the mixture washed with water (10 ml), the aqueous layer was then further extracted with diethyl ether (2 x 10 ml). The combined organic layers were dried (magnesium sulphate) and the solvent removed. Purification by flash chromatography (ethyl acetate / hexane, 1 : 1) gave (1*S*,4*R*,5*R*,6*R*,7*S*)-5,6,7-triacetoxy-4-azido-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.51**) (123 mg, 0.38 mmol, 96%), identical in all respects to that obtained in method 1.

(1*R*,4*S*,5*S*,6*R*,7*R*)-5,6,7-Triacetoxy-4-azido-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.52**)



Method 1

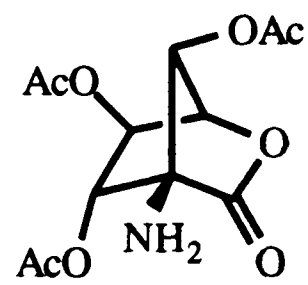
Acetic anhydride (0.5 ml) was added dropwise to a solution of (1*R*,4*S*,5*S*,6*R*,7*R*)-4-azido-5,6,7-trihydroxy-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.48**) (30 mg, 0.15 mmol)

in pyridine (0.5 ml) under nitrogen. The reaction mixture was stirred at 0 °C for 40 min, by which time t.l.c. analysis (diethyl ether / hexane, 3 : 1) indicated the complete conversion of starting material (R_f 0.05) to a single product (R_f 0.35). The solvent was removed, and the residue was dissolved in ethyl acetate (25 ml), washed with aqueous hydrochloric acid (2 M, 10 ml), brine (10 ml), and dried (magnesium sulphate). Removal of solvent followed by flash chromatography (diethyl ether / hexane, 55 : 45) gave (1*R*,4*S*,5*S*,6*R*,7*R*)-5,6,7-triacetoxy-4-azido-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.52**) (47 mg, 0.14 mmol, 96%) as a colourless oil. $[\alpha]_D^{20}$ +4.4 (*c*, 0.7 in chloroform); (Found: C, 43.90; H, 3.65; N, 12.65%. $C_{12}H_{13}O_8N_3$ requires C, 44.04; H, 4.00; N, 12.84%); ν_{max} (thin film): 2128 (azide), 1816 (lactone), 1758 cm^{-1} (ester); δ_H ($CDCl_3$, 500 MHz): 2.15, 2.16, 2.19 (3 x 3H, 3 x s, 3 x $COCH_3$), 4.80 (1H, d, *J* 1.2 Hz), 4.94 (1H, t, *J* 1.6 Hz), 5.29 (1H, t, *J* 1.6 Hz), 5.32 (1H, s); δ_C ($CDCl_3$): 20.4, 20.5 (2 x q, 3 x $COCH_3$), 69.1 (s, C-4), 73.7, 73.8, 77.0, 77.4 (4 x d, C-1, C-5, C-6, C-7), 167.6, 169.2, 169.4, 169.6 (4 x s, C-3, 3 x $COCH_3$); *m/z* (CI, NH_3): 345 [$(MNH_4)^+$, 100], 328 [$(MH)^+$, 30%].

Method 2

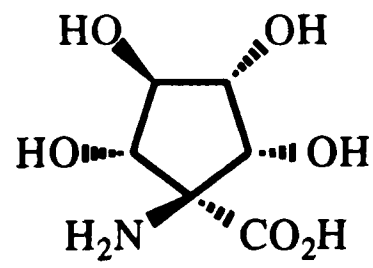
Concentrated sulphuric acid (20 µl) was added to a solution of (1*R*,4*S*,5*S*,6*R*,7*R*)-4-azido-5,6,7-trihydroxy-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.48**) (65 mg, 0.32 mmol) in acetic acid / acetic anhydride (1 : 1, 3 ml) at room temperature under nitrogen. The reaction mixture was stirred for 4 h, by which time t.l.c. analysis (methanol / chloroform, 1 : 9) indicated the complete conversion of starting material (R_f 0.25) to a single product (R_f 0.9). Diethyl ether (40 ml) was added and the mixture washed with water (10 ml), the aqueous layer was then further extracted with diethyl ether (2 x 20 ml). The combined organic layers were dried (magnesium sulphate) and the solvent removed. Purification by flash chromatography (diethyl ether / hexane, 55 : 45) gave (1*R*,4*S*,5*S*,6*R*,7*R*)-5,6,7-triacetoxy-4-azido-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.52**) (97 mg, 0.30 mmol, 92%), identical in all respects to that obtained in method 1.

(1*R*,4*S*,5*S*,6*R*,7*R*)-5,6,7-Triacetoxy-4-amino-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.54**)



(1*R*,4*S*,5*S*,6*R*,7*R*)-5,6,7-Triacetoxy-4-azido-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.52**) (145 mg, 0.44 mmol) and palladium black (5 mg) were stirred in ethanol (6 ml) at room temperature. The solution was degassed and stirred under hydrogen for 18 h. After this time t.l.c. analysis (ethyl acetate / hexane, 6 : 4) indicated complete consumption of starting material (R_f 0.4) and formation of a single product (R_f 0.15). The reaction mixture was filtered through Celite and the solvent was removed. Purification by flash chromatography (ethyl acetate) gave (1*R*,4*S*,5*S*,6*R*,7*R*)-5,6,7-triacetoxy-4-amino-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.54**) (107 mg, 0.36 mmol, 80%) as a colourless oil. $[\alpha]_D^{25}$ +7.9 (*c*, 1.0 in chloroform); ν_{max} (thin film): 3398 (NH), 1811 (lactone), 1752 cm^{-1} (ester); δ_H ($CDCl_3$, 500 MHz): 2.14, 2.16, 2.17 (3 x 3H, 3 x s, 3 x $COC\underline{H}_3$), 4.19 (1H, s), 4.75 (1H, t, *J* 1.7 Hz), 4.93 (1H, t, *J* 1.7 Hz), 5.22 (1H, t, *J* 1.7 Hz); δ_C ($CDCl_3$): 20.5 (q, $CO\underline{C}H_3$), 66.2 (s, C-4), 73.9 75.6, 76.9, 77.9 (4 x d, C-1, C-5, C-6, C-7), 169.1, 169.9, 170.2, 172.3 (4 x s, C-3, 3 x $\underline{C}OCH_3$); *m/z* (CI, NH_3): 302 [$(MH)^+$, 100%].

(1*S*,2*R*,3*R*,4*R*,5*S*)-1-Amino-2,3,4,5-tetrahydroxy-cyclopentane carboxylic acid (**2.53**)

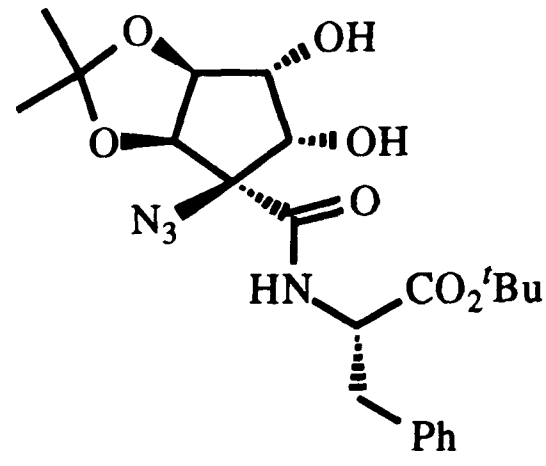


(1*R*,4*S*,5*S*,6*R*,7*R*)-5,6,7-Triacetoxy-4-amino-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.54**) (20 mg, 0.07 mmol) was dissolved in water (2 ml). Triethylamine (0.15 ml,

1.08 mmol) was added and the resulting mixture stirred at room temperature. After 2 h, crude proton NMR (D_2O) indicated the presence of one single compound. The solvent was removed and the residue purified by ion exchange chromatography [Dowex 50W-X8(H^+), 2 M aqueous pyridine elution] to yield (1*S*,2*R*,3*R*,4*R*,5*S*)-1-amino-2,3,4,5-tetrahydroxy-cyclopentane carboxylic acid (**2.53**) (8 mg, 0.04 mmol, 62%) as a brown hygroscopic foam. $[\alpha]_D^{25}$ +4.9 (*c*, 0.68 in water); ν_{max} (KBr): 3430 (br, OH, NH), 1631 cm^{-1} (COOH); δ_H (D_2O, 500 MHz): 3.94 (1H, dd, *J* 3.8 Hz, *J* 8.0 Hz), 3.95 (1H, d, *J* 7.4 Hz), 4.27 (1H, d, *J* 8.0 Hz), 4.33 (1H, dd, *J* 7.4 Hz, *J* 3.8 Hz); δ_C (D_2O, 125 MHz): 71.3, 75.2, 77.7, 83.0 (4 x d, C-2, C-3, C-4, C-5), 72.3 (s, C-1), 170.7 (s, COOH); *m/z* (electrospray): 194 [$(MH)^+$, 100%].

Experimental Procedures for Results and Discussion Section 2.4.

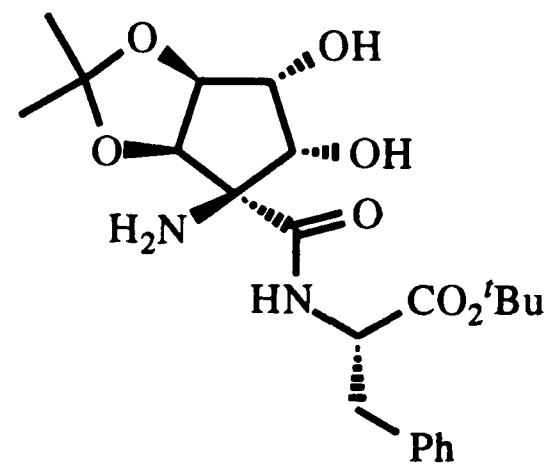
tert-Butyl [(1*R*,2*R*,3*S*,4*R*,5*R*)-1-azido-2,3,4,5-tetrahydroxy-2,3-*O*-isopropylidene-cyclopentane carboxyl] L-phenylalanate (**2.55**)



(1*R*,4*R*,5*R*,6*R*,7*R*)-4-Azido-5,6,7-trihydroxy-5,6-*O*-isopropylidene-2-oxa-bicyclo[2.2.1]heptan-3-one (**1.52**) (573 mg, 2.38 mmol) and sodium acetate (429 mg, 5.23 mmol) were dissolved in *N*,*N*-dimethylformamide (40 ml) under nitrogen. L-Phenylalanine *tert*-butyl ester (674 mg, 2.62 mmol) was added and the reaction mixture was stirred at room temperature for 16 h. After this time t.l.c. analysis (diethyl ether / hexane, 1 : 1) indicated the complete conversion of starting material

(R_f 0.2) to one product (R_f 0.3). The solvent was removed and the residue was purified by flash chromatography (diethyl ether / hexane, 1 : 1) to give *tert*-butyl [(1*R*,2*R*,3*S*,4*R*,5*R*)-1-azido-2,3,4,5-tetrahydroxy-2,3-*O*-isopropylidene-cyclopentane carboxyl] L-phenylalanate (**2.55**) (997 mg, 2.16 mmol, 91%) as a white crystalline solid. M.p. 95 - 96 °C (diethyl ether / hexane); $[\alpha]_D^{25}$ +33.5 (*c*, 1.0 in chloroform); (Found: C, 57.09; H, 6.54; N, 12.24%. $C_{22}H_{30}O_7N_4$ requires C, 57.13; H, 6.54; N, 12.11%); ν_{max} (KBr): 3341 (br, OH, NH), 2123 (azide), 1733 (ester), 1664, 1533 cm^{-1} (amide); δ_H ($CDCl_3$, 500 MHz): 1.30, 1.49 (2 x 3H, 2 x s, $C(C\underline{H}_3)_2$), 1.45 (9H, s, $C(C\underline{H}_3)_3$), 2.49 (1H, d, $J_{OH,4}$ 8.8 Hz, OH-4), 3.01, 3.16 (2 x 1H, 2 x dd, ABX system, AB part, $J_{A,B}$ 14.0 Hz, $J_{A,X}$ 7.3 Hz, $J_{B,X}$ 5.5 Hz, $PhC\underline{H}_2CH$), 4.00 (1H, dd, $J_{5,OH}$ 12.6 Hz, $J_{5,4}$ 6.3 Hz, H-5), 4.44 (1H, dd, $J_{4,OH}$ 8.8 Hz, $J_{4,5}$ 6.3 Hz, H-4), 4.63, 4.64 (2 x 1H, 2 x d, $J_{2,3} = J_{3,2}$ 6.2 Hz, H-2, H-3), 4.72 (1H, d, $J_{OH,5}$ 12.6 Hz, OH-5), 4.73 (1H, ddd, ABX system, X part, $J_{X,A}$ 7.3 Hz, $J_{X,B}$ 5.5 Hz, $J_{X,NH}$ 8.2 Hz, $PhCH_2C\underline{H}$), 7.22 - 7.34 (5H, m, Ar-H), 7.56 (1H, d, $J_{NH,X}$ 8.2 Hz, NH); δ_C ($CDCl_3$, 62.5 MHz): 23.6, 25.6 (2 x q, $C(\underline{C}H_3)_2$), 27.9 (q, $C(\underline{C}H_3)_3$), 38.3 (t, $Ph\underline{C}H_2CH$), 54.0 (d, $PhCH_2\underline{C}H$), 73.9, 74.3, 81.8, 84.8 (4 x d, C-2, C-3, C-4, C-5), 75.3 (s, C-1), 83.1 (s, $\underline{C}(CH_3)_3$), 111.4 (s, $\underline{C}(CH_3)_2$), 127.3, 128.5, 129.6 (3 x d, Ar-CH), 135.5 (s, Ar-C), 169.3, 170.4 (2 x s, 2 x CO); *m/z* (CI, NH_3): 463 [$(MH)^+$, 100], 435 [$(MH\text{-}N_2)^+$, 35%].

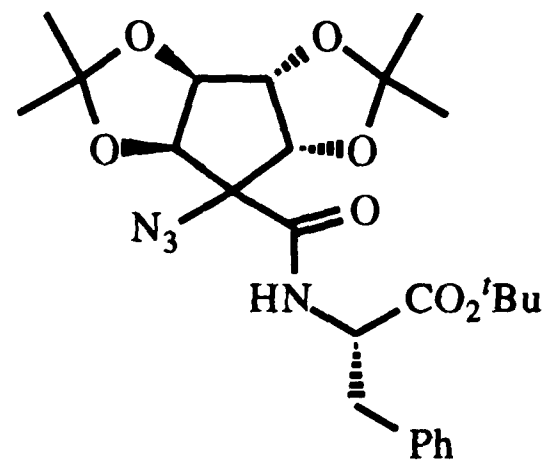
tert-Butyl [(1*R*,2*R*,3*S*,4*R*,5*R*)-1-amino-2,3,4,5-tetrahydroxy-2,3-*O*-isopropylidene-cyclopentane carboxyl] **L**-phenylalanate (**2.56**)



tert-Butyl [(1*R*,2*R*,3*S*,4*R*,5*R*)-1-Azido-2,3,4,5-tetrahydroxy-2,3-*O*-isopropylidene-cyclopentane carboxyl] **L**-phenylalanate (**2.55**) (118 mg, 0.26 mmol) and palladium black (5 mg) were stirred in ethanol / water (2 : 1, 6 ml) at room temperature. The solution was degassed and stirred under hydrogen for 15 h. After this time t.l.c. analysis (diethyl ether) indicated the complete consumption of starting material (R_f 0.7) and the formation of a single product (R_f 0.3). The reaction mixture was filtered through Celite and the solvent was removed. Purification by flash chromatography (diethyl ether) to yield *tert*-butyl [(1*R*,2*R*,3*S*,4*R*,5*R*)-1-amino-2,3,4,5-tetrahydroxy-2,3-*O*-isopropylidene-cyclopentane carboxyl] **L**-phenylalanate (**2.56**) (91 mg, 0.21 mmol, 82%) as a colourless oil, which solidified on standing. M.p. 64 - 65 °C (on standing); $[\alpha]_D^{25}$ +33.8 (*c*, 0.22 in chloroform); (Found: C, 60.51; H, 7.50; N, 6.13%. $C_{22}H_{32}O_7N_2$ requires C, 60.54; H, 7.39; N, 6.42%); ν_{max} (thin film): 3319 (br, OH, NH), 1736 (ester), 1643, 1530 cm^{-1} (amide); δ_H ($CDCl_3$, 500 MHz): 1.28, 1.44 (2 x 3H, 2 x s, $C(C\underline{H}_3)_2$), 1.43 (9H, s, $C(C\underline{H}_3)_3$), 2.50 (1H, br s, OH-4), 3.04, 3.15 (2 x 1H, 2 x dd, ABX system, AB part, $J_{A,B}$ 14.0 Hz, $J_{A,X}$ 7.0 Hz, $J_{B,X}$ 5.9 Hz, $PhC\underline{H}_2CH$), 3.93 (1H, dd, $J_{5,OH}$ 11.6 Hz, $J_{5,4}$ 6.0 Hz, H-5), 3.98 (1H, d, $J_{4,5}$ 6.0 Hz, H-4), 4.41, 4.60 (2 x 1H, 2 x d, $J_{2,3} = J_{3,2}$ 6.1 Hz, H-2, H-3), 4.70 (1H, ddd, ABX system, X part, $J_{X,A}$ 7.0 Hz, $J_{X,B}$ 5.9 Hz, $J_{X,NH}$ 8.2 Hz, $PhCH_2C\underline{H}$), 5.45 (1H, br d, $J_{OH,5}$ 12.0 Hz, OH-5), 7.21 - 7.32 (5H, m, Ar-H), 8.58 (1H, br d, $J_{NH,X}$ 8.2 Hz, NH); δ_C ($CDCl_3$): 23.8, 26.1 (2 x q, $C(\underline{C}H_3)_2$), 27.8 (q, $C(\underline{C}H_3)_3$), 38.0 (t,

PhCH$_2$CH), 53.6 (d, PhCH$_2$CH), 69.3 (s, C-1), 74.7, 80.2, 80.8, 85.1 (4 x d, C-2, C-3, C-4, C-5), 82.6 (s, C(CH$_3$)$_3$), 111.1 (s, C(CH$_3$)$_2$), 127.3, 128.6, 129.8 (3 x d, Ar-CH), 136.1 (s, Ar-C), 170.1, 175.4 (2 x s, 2 x CO); *m/z* (electrospray): 437 [(MH)$^+$, 100%].

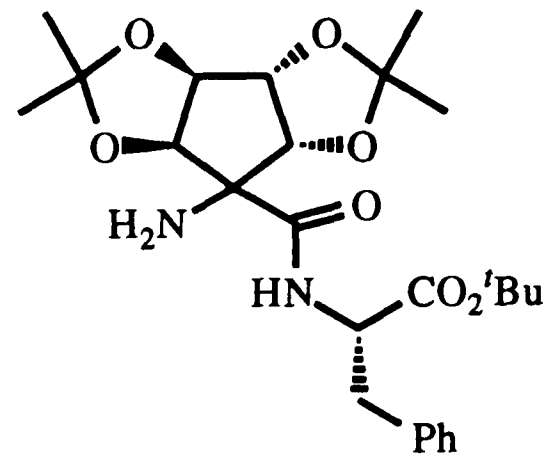
tert-Butyl [(2*R*,3*R*,4*R*,5*R*)-1-azido-2,3,4,5-tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-cyclopentane carboxyl] L-phenylalanate (**2.57**)



tert-Butyl [(1*R*,2*R*,3*R*,4*R*,5*R*)-1-azido-2,3,4,5-tetrahydroxy-2,3-*O*-isopropylidene-cyclopentane carboxyl] L-phenylalanate (**2.55**) (446 mg, 0.97 mmol) was dissolved in acetone / 2,2-dimethoxypropane (5 : 1, 18 ml), to which (±)-10-camphorsulphonic acid (22 mg, 0.10 mmol) was added. The reaction mixture was stirred at room temperature for 5.5 h, by which time t.l.c. analysis (diethyl ether / hexane, 1 : 1) indicated the complete conversion of starting material (R_f 0.1) to one product (R_f 0.35). The solution was adjusted to pH 8 by the careful dropwise addition of triethylamine. The solvent was removed and purification by flash chromatography (diethyl ether : hexane, 1 : 1) gave *tert*-butyl [(2*R*,3*R*,4*R*,5*R*)-1-azido-2,3,4,5-tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-cyclopentane carboxyl] L-phenylalanate (**2.57**) (459 mg, 0.91 mmol, 95%) as a white crystalline solid. M.p. 128 - 129 °C (diethyl ether / hexane); $[\alpha]_D^{25}$ 103.2 (*c*, 0.56 in chloroform); (Found: C, 59.55; H, 6.98; N, 11.11%. $C_{25}H_{34}O_7N_4$ requires C, 59.75; H, 6.82; N, 11.15%); ν_{max} (KBr): 3390 (br, NH), 2116 (azide), 1730 (ester), 1675, 1516 cm^{-1} (amide); δ_H ($CDCl_3$, 500 MHz): 1.30, 1.35, 1.42, 1.59 (4 x 3H, 4 x s, 2 x C(CH$_3$)$_2$), 1.41 (9H, s, C(CH$_3$)$_3$), 3.10, 3.17 (2 x 1H, 2 x dd, ABX system, AB part, $J_{A,B}$ 13.9 Hz, $J_{A,X}$ 6.2 Hz, $J_{B,X}$ 5.1

Hz, PhC$\underline{H}_2$CH), 4.65 (1H, d, *J* 6.0 Hz), 4.70 (1H, d, *J* 6.0 Hz), 4.74 (1H, d, *J* 5.9 Hz), 4.79 (1H, ddd, ABX system, X part, $J_{X,A}$ 6.2 Hz, $J_{X,B}$ 5.1 Hz, $J_{X,NH}$ 7.7 Hz, PhCH$_2$C$\underline{H}$), 5.12 (1H, d, *J* 5.9 Hz), 7.02 (1H, d, $J_{NH,X}$ 7.7 Hz, NH), 7.22 - 7.34 (5H, m, Ar-H); δ_C ($CDCl_3$): 24.9, 26.1, 26.2 (3 x q, 2 x C($\underline{C}H_3$)$_2$), 27.9 (q, C($\underline{C}H_3$)$_3$), 37.9 (t, Ph$\underline{C}$H$_2$CH), 53.6 (d, PhCH$_2\underline{C}$H), 74.3 (s, C-1), 82.6 (s, $\underline{C}$(CH$_3$)$_3$), 84.7, 85.3, 85.6 (3 x d, C-2, C-3, C-4, C-5), 113.1, 113.3 (2 x s, 2 x $\underline{C}$(CH$_3$)$_2$), 127.0, 128.3, 129.7 (3 x d, Ar-CH), 136.0 (s, Ar-C), 166.6, 169.8 (2 x s, 2 x CO); *m/z* (CI, NH_3): 503 [$(MH)^+$, 10], 475 [$(MH-N_2)^+$, 25], 228 (100%).

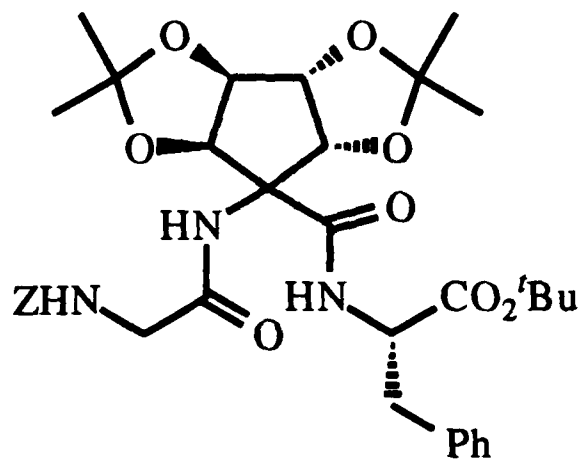
tert-Butyl [(2*R*,3*R*,4*R*,5*R*)-1-amino-2,3,4,5-tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-cyclopentane carboxyl] L-phenylalanate (**2.58**)



tert-Butyl [(2*R*,3*R*,4*R*,5*R*)-1-azido-2,3,4,5-tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-cyclopentane carboxyl] L-phenylalanate (**2.57**) (259 mg, 0.52 mmol) and palladium black (5 mg) were stirred in ethanol (10 ml) at room temperature. The solution was degassed and then stirred under hydrogen for 7 h. After this time t.l.c. analysis (diethyl ether / hexane, 7 : 3) indicated complete consumption of starting material (R_f 0.6) and formation of a single product (R_f 0.2). The reaction mixture was filtered through Celite and the solvent was removed. Purification by flash chromatography (diethyl ether / hexane, 7 : 3) gave *tert*-butyl [(2*R*,3*R*,4*R*,5*R*)-1-amino-2,3,4,5-tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-cyclopentane carboxyl] L-phenylalanate (**2.58**) (236 mg, 0.50 mmol, 96%) as a white crystalline solid. M.p. 139 - 140 °C (diethyl ether / hexane); $[\alpha]_D^{25}$ +89.0 (*c*, 0.64 in chloroform); (Found: C, 62.84; H,

7.66; N, 5.64%. $C_{25}H_{36}O_7N_2$ requires C, 63.01; H, 7.61; N, 5.88%); ν_{max} (KBr): 3373 (br, NH), 1732 (ester), 1670, 1499 cm^{-1} (amide); δ_H ($CDCl_3$, 500 MHz): 1.30, 1.33, 1.44, 1.50 (4 x 3H, 4 x s, 2 x $C(C\underline{H}_3)_2$), 1.41 (9H, s, $C(C\underline{H}_3)_3$), 3.13, 3.14 (2 x 1H, ABX system, AB part, $PhC\underline{H}_2CH$), 4.46 (1H, d, *J* 5.5 Hz), 4.65 (1H, d, *J* 6.3 Hz), 4.68 (1H, d, *J* 5.5 Hz), 4.75 - 4.79 (1H, m, $PhCH_2C\underline{H}$), 4.98 (1H, d, *J* 6.3 Hz), 7.21 - 7.29 (5H, m, Ar-H), 7.61 (1H, d, $J_{NH,X}$ 7.7 Hz, NH); δ_C (CD_3OD): 23.6, 25.0, 25.3 (3 x q, 2 x $C(\underline{C}H_3)_2$), 26.7 (q, $C(\underline{C}H_3)_3$), 37.0 (t, $Ph\underline{C}H_2CH$), 53.8 (d, $PhCH_2\underline{C}H$), 67.2 (s, C-1), 82.0 (s, $\underline{C}(CH_3)_3$), 83.2, 84.1, 85.9, 88.5 (4 x d, C-2, C-3, C-4, C-5), 112.2, 112.4 (2 x s, 2 x $\underline{C}(CH_3)_2$), 126.7, 128.2, 129.5 (3 x d, Ar-CH), 136.5 (s, Ar-C), 170.8, 172.6 (2 x s, 2 x CO); *m/z* (electrospray): 477 [$(MH)^+$, 100%].

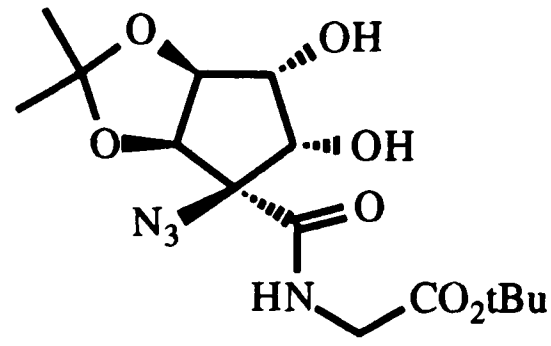
tert-Butyl {*N*-benzyloxycarbonylglycyl [(2*R*,3*R*,4*R*,5*R*)-1-amino-2,3,4,5-tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-cyclopentane carboxyl]} L-phenylalanate (2.59)



tert-Butyl [(2*R*,3*R*,4*R*,5*R*)-1-amino-2,3,4,5-tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-cyclopentane carboxyl] **L**-phenylalanate (**2.58**) (66 mg, 0.14 mmol), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (40 mg, 0.21 mmol), *N*-benzyloxycarbonylglycine (43 mg, 0.21 mmol) and 1-hydroxybenzotriazole (28 mg, 0.21 mmol) were dissolved in dichloromethane (2 ml) under nitrogen. The reaction mixture was stirred at room temperature for 48 h, by which time t.l.c. analysis (ethyl acetate / hexane, 3 : 2) indicated conversion of starting material (R_f 0.5) to one major product (R_f 0.45). The reaction mixture was quenched by

diluting with dichloromethane (10 ml), washed with aqueous hydrochloric acid (2 M, 5 ml), and the organic layer was dried (magnesium sulphate). Purification by flash chromatography (ethyl acetate / hexane, 2 : 3) afforded *tert*-butyl {*N*-benzyloxycarbonylglycyl [(2*R*,3*R*,4*R*,5*R*)-1-amino-2,3,4,5-tetrahydroxy-2,3;4,5-di-*O*-isopropylidene-cyclopentane carboxyl]} L-phenylalanate (**2.59**) (87 mg, 0.13 mmol, 94 %) as a white crystalline solid. M.p. 154 - 155 °C (diethyl ether / hexane); $[\alpha]_D^{25}$ +57.8 (*c*, 0.37 in chloroform); (Found: C, 63.08; H, 6.80; N, 6.38%. $C_{35}H_{45}O_{10}N_3$ requires C, 62.95; H, 6.79; N, 6.29%); ν_{max} (KBr): 3330 (br, NH), 1730 (ester), 1680, 1530 cm^{-1} (amide); δ_H ($CDCl_3$, 500 MHz): 1.30, 1.33, 1.40, 1.50 (4 x 3H, 4 x s, 2 x $C(C\underline{H}_3)_2$), 1.39 (9H, s, $C(C\underline{H}_3)_3$), 3.09, 3.17 (2 x 1H, 2 x dd, ABX system, AB part, $J_{A,B}$ 13.9 Hz, $J_{A,X}$ 6.1 Hz, $J_{B,X}$ 6.2 Hz, $PhC\underline{H}_2CH$), 3.87, 4.00 (2 x 1H, 2 x dd, ABX system, AB part, $J_{A,B}$ 16.9 Hz, $J_{A,X}$ 5.5 Hz, $J_{B,X}$ 5.2 Hz, $NHC\underline{H}_2CO$), 4.56 (1H, d, *J* 6.8 Hz), 4.62 (1H, br s), 4.74 (1H, ddd, ABX system, X part, $J_{X,A}$ 6.1 Hz, $J_{X,B}$ 6.2 Hz, $J_{X,NH}$ 7.3 Hz, $PhCH_2C\underline{H}$), 4.99 (1H, d, *J* 6.8 Hz), 5.08 - 5.15 (2H, m), 5.34 (1H, br d, *J* 4.3 Hz), 5.41 (1H, br s, $PhCH_2OCON\underline{H}$), 6.74 (1H, br s, $NHCH_2CON\underline{H}$), 7.19 - 7.38 (10H, m, Ar-H), 8.00 (1H, d, $J_{NH,X}$ 7.3 Hz, $N\underline{H}CH(CH_2Ph)$); δ_C ($CDCl_3$, 125 MHz): 23.9, 25.3, 25.7, 27.0 (4 x q, 2 x $C(\underline{C}H_3)_2$), 27.9 (q, $C(\underline{C}H_3)_3$), 37.8 (t, $Ph\underline{C}H_2CH$), 45.1 (t, $NH\underline{C}H_2CO$), 54.1 (d, $PhCH_2\underline{C}H$), 66.7 (s, C-1), 67.2 (t, $Ph\underline{C}H_2O$), 82.0 (s, $\underline{C}(CH_3)_3$), 82.6, 83.6, 84.2, 86.1 (4 x d, C-2, C-3, C-4, C-5), 112.6, 113.4 (2 x s, 2 x $\underline{C}(CH_3)_2$), 126.7, 128.1, 128.2, 128.5, 129.6 (5 x d, Ar-CH), 136.0, 136.6 (2 x s, 2 x Ar-C), 156.3 (s, $PhCH_2O\underline{C}ONH$), 168.2, 170.1 (2 x s); *m/z* (CI, NH_3): 668 [$(MH)^+$, 10], 91 ($C_7H_7^+$, 100%).

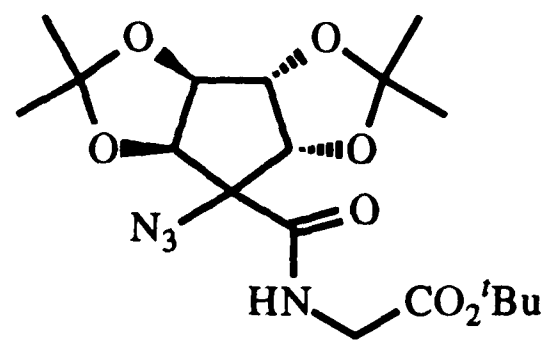
tert-Butyl [(1*R*,2*R*,3*S*,4*R*,5*R*)-1-azido-2,3,4,5-tetrahydroxy-2,3-*O*-isopropylidene-cyclopentane carboxyl] glycinate (**2.61**)



(1*R*,4*R*,5*R*,6*R*,7*R*)-4-Azido-5,6,7-trihydroxy-5,6-*O*-isopropylidene-2-oxa-bicyclo[2.2.1]heptan-3-one (**1.52**) (487 mg, 2.02 mmol) and sodium acetate (365 mg, 4.45 mmol) were dissolved in *N*,*N*-dimethylformamide (20 ml) under nitrogen. Glycine *tert*-butyl ester (373 mg, 2.22 mmol) was added and the reaction mixture was stirred at room temperature for 17 h. After this time t.l.c. analysis (ethyl acetate / hexane, 2 : 3) indicated the complete conversion of starting materials (R_f 0.25) to one product (R_f 0.2). The solvent was removed and the residue was purified by flash chromatography (ethyl acetate : hexane, 2 : 3) to give *tert*-butyl [(1*R*,2*R*,3*S*,4*R*,5*R*)-1-azido-2,3,4,5-tetrahydroxy-2,3-*O*-isopropylidene-cyclopentane carboxyl] glycinate (**2.61**) (712 mg, 1.91 mmol, 95%) as a white crystalline solid. M.p. 147 - 148 °C (ethyl acetate / hexane); $[\alpha]_D^{25}$ +1.38 (*c*, 0.87 in chloroform); (Found: C, 48.37; H, 6.62; N, 14.80%. $C_{15}H_{24}O_7N_4$ requires C, 48.38; H, 6.50; N, 15.05%); ν_{max} (KBr): 3402 (br, OH, NH), 2129 (azide), 1748 (ester), 1654, 1545 cm^{-1} (amide); δ_H ($CDCl_3$, 500 MHz): 1.33, 1.51 (2 x 3H, 2 x s, $C(C\underline{H}_3)_2$), 1.49 (9H, s, $C(C\underline{H}_3)_3$), 3.19 (1H, d, $J_{OH,4}$ 9.6 Hz, OH-4), 3.89, 3.95 (2 x 1H, 2 x dd, ABX system, AB part, $J_{A,B}$ 18.0 Hz, $J_{A,X}$ 5.6 Hz, $J_{B,X}$ 5.5 Hz, $NHC\underline{H}_2CO$), 4.07 (1H, dd, $J_{5,OH}$ 12.6 Hz, $J_{5,4}$ 6.2 Hz, H-5), 4.52 (1H, dd, $J_{4,OH}$ 9.6 Hz, $J_{4,5}$ 6.2 Hz, H-4), 4.64 (1H, d ex in D_2O, $J_{OH,5}$ 12.6 Hz, OH-5), 4.70 (2H, d (apparent), H-2, H-3), 7.47 (1H, br s, NH); δ_C ($CDCl_3$): 23.6, 25.6 (2 x q, $C(\underline{C}H_3)_2$), 27.9 (q, $C(\underline{C}H_3)_3$), 42.3 (t, $NH\underline{C}H_2CO$), 74.1, 74.3, 81.3, 84.6 (4 x d, C-2, C-3, C-4, C-5), 75.0 (s, C-1), 83.1 (s, $\underline{C}(CH_3)_3$), 111.4 (s, $\underline{C}(CH_3)_2$),

167.7, 171.5 (2 x s, 2 x CO); *m/z* (CI, NH_3): 373 [$(MH)^+$, 70], 317 [$(MH-C_4H_9)^+$, 100%].

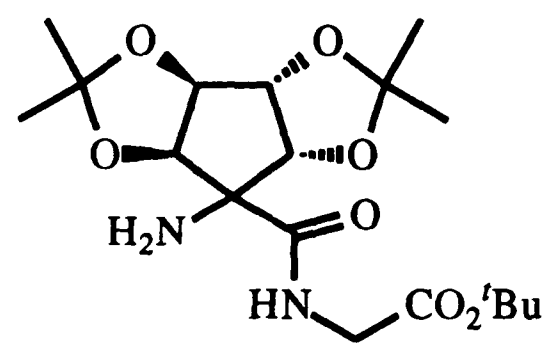
<u>*tert*-Butyl [(2*R*,3*R*,4*R*,5*R*)-1-azido-2,3,4,5-tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-cyclopentane carboxyl] glycinate (**2.62**)</u>



tert-Butyl [(1*R*,2*R*,3*S*,4*R*,5*R*)-1-azido-2,3,4,5-tetrahydroxy-2,3-*O*-isopropylidene-cyclopentane carboxyl] glycinate (**2.61**) (201 mg, 0.54 mmol) was dissolved in acetone / dimethoxypropane (5 : 1, 12 ml), to which (±)-10-camphorsulphonic acid (36 mg, 0.15 mmol) was added. The reaction mixture was stirred at room temperature for 1 h, by which time t.l.c. analysis (ethyl acetate / hexane, 2 : 3) indicated complete conversion of starting material (R_f 0.2) to one product (R_f 0.5). The solution was adjusted to pH 8 by dropwise addition of triethylamine. The solvent was removed and purification by flash chromatography (diethyl ether / hexane, 7 : 13) gave <u>*tert*-butyl [(2*R*,3*R*,4*R*,5*R*)-1-azido-2,3,4,5-tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-cyclopentane carboxyl] glycinate (**2.62**)</u> (459 mg, 0.91 mmol, 95%) as a colourless oil. ν_{max} (thin film): 3355 (br, NH), 2121 (azide), 1744 (ester), 1680, 1530 cm^{-1} (amide); δ_H ($CDCl_3$, 500 MHz): 1.29, 1.34, 1.42, 1.57 (4 x 3H, 4 x s, 2 x $C(CH_3)_2$), 1.48 (9H, s, $C(CH_3)_3$), 3.90, 4.03 (2 x 1H, 2 x dd, ABX system, AB part, $J_{A,B}$ 18.4 Hz, $J_{A,X}$ 4.7 Hz, $J_{B,X}$ 5.3 Hz, $NHCH_2CO$), 4.68 (1H, d, *J* 6.1 Hz), 4.70 (1H, d, *J* 6.1 Hz), 4.77 (1H, d, *J* 5.7 Hz), 5.14 (1H, d, *J* 5.7 Hz), 6.98 (1H, br s ex in D_2O, NH); δ_C ($CDCl_3$, 125 MHz): 24.8, 24.9, 26.1, 26.2 (4 x q, 2 x $C(CH_3)_2$), 28.0 (q, $C(CH_3)_3$), 42.1 (t, $NHCH_2CO$), 74.4 (s, C-1), 82.5 (s, $C(CH_3)_3$), 84.8, 84.9, 85.3, 85.5 (4 x d, C-2, C-3, C-4, C-5), 112.9, 113.4 (2 x s, 2 x $C(CH_3)_2$), 167.4, 168.3 (2 x

s, 2 x CO); *m/z* (CI, NH_3): 413 [$(MH)^+$, 30], 385 [$(MH-N_2)^+$, 100], 357 [$(MH-C_4H_9)^+$, 80%].

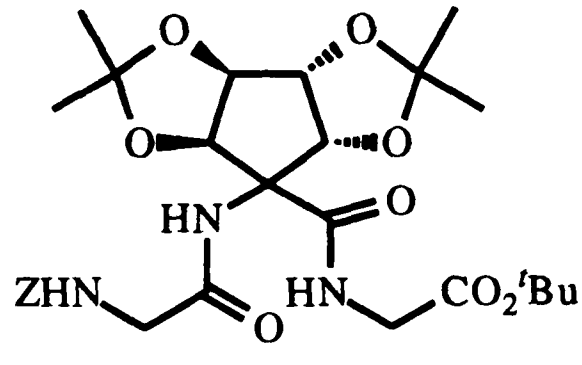
tert-Butyl [(2*R*,3*R*,4*R*,5*R*)-1-amino-2,3,4,5-tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-cyclopentane carboxyl] glycinate (**2.63**)



tert-Butyl [(2*R*,3*R*,4*R*,5*R*)-1-azido-2,3,4,5-tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-cyclopentane carboxyl] glycinate (**2.62**) (110 mg, 0.27 mmol) and palladium black (5 mg) were stirred in ethanol (8 ml) at room temperature. The solution was degassed and stirred under hydrogen for 17 h. After this time t.l.c. analysis (ethyl acetate / hexane, 1 : 1) indicated the complete conversion of starting material (R_f 0.6) to a single product (R_f 0.25). The reaction mixture was filtered through Celite and the solvent was removed. Purification by flash chromatography (diethyl ether / hexane, 7 : 3) gave *tert*-butyl [(2*R*,3*R*,4*R*,5*R*)-1-amino-2,3,4,5-tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-cyclopentane carboxyl] glycinate (**2.63**) (92 mg, 0.24 mmol, 89%) as a colourless oil. $[\alpha]_D^{25}$ +18.9 (*c*, 2.1 in chloroform); (Found: C, 55.80; H, 8.21; N, 7.39%. $C_{18}H_{30}O_7N_2$ requires C, 55.95; H, 7.82; N, 7.25%); ν_{max} (thin film): 3378 (br, NH), 1741 (ester), 1678, 1516 cm^{-1} (amide); δ_H ($CDCl_3$, 500 MHz): 1.29, 1.33, 1.426, 1.50 (4 x 3H, 4 x s, 2 x $C(CH_3)_2$), 1.48 (9H, s, $C(CH_3)_3$), 3.88, 4.05 (2 x 1H, 2 x dd, ABX system, AB part, $J_{A,B}$ 18.4 Hz, $J_{A,X}$ 4.7 Hz, $J_{B,X}$ 5.7 Hz, $NHCH_2CO$), 4.47 (1H, d, *J* 5.5 Hz), 4.68 (1H, d, *J* 6.1 Hz), 4.69 (1H, d, *J* 5.5 Hz), 5.03 (1H, d, *J* 6.1 Hz), 7.59 (1H, br s ex in D_2O, NH); δ_C ($CDCl_3$): 24.7, 24.9, 26.2, 26.6 (4 x q, 2 x $C(CH_3)_2$), 28.0 (q, $C(CH_3)_3$), 41.9 (t, $NHCH_2CO$), 67.5 (s, C-1), 82.0 (s, $C(CH_3)_3$), 83.6, 84.2, 85.6, 88.8 (4 x d, C-2, C-3, C-4, C-5), 112.2, 112.7 (2 x s, 2 x $C(CH_3)_2$),

168.9, 171.6 (2 x s, 2 x CO); *m/z* (electrospray): 387 [$(MH)^+$, 100], 331 [$(MH-C_4H_9)^+$, 60%].

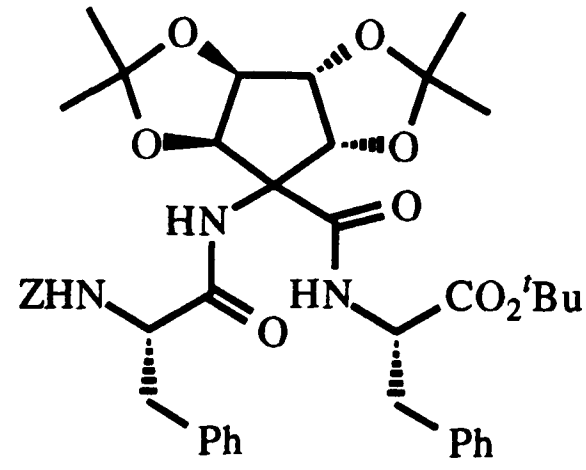
<u>*tert*-Butyl {*N*-benzyloxycarbonylglycyl [(2*R*,3*R*,4*R*,5*R*)-1-amino-2,3,4,5-tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-cyclopentane carboxyl]} glycinate (**2.64**)</u>



tert-Butyl [(2*R*,3*R*,4*R*,5*R*)-1-amino-2,3,4,5-tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-cyclopentane carboxyl] glycinate (**2.63**) (43 mg, 0.11 mmol), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (33 mg, 0.17 mmol), *N*-benzyloxycarbonylglycine (36 mg, 0.17 mmol) and 1-hydroxybenzotriazole (23 mg, 0.17 mmol) were dissolved in dichloromethane (3 ml) under nitrogen. The reaction mixture was stirred at room temperature for 45 h, by which time t.l.c. analysis (ethyl acetate / hexane, 3 : 2) indicated the complete conversion of starting material (R_f 0.4) and one major product (R_f 0.35). The reaction mixture was quenched by diluting with dichloromethane (20 ml), washed with aqueous hydrochloric acid (2 M, 10 ml), and the organic layer dried (magnesium sulphate). Purification by flash chromatography (ethyl acetate / hexane, 3 : 2) afforded <u>*tert*-butyl {*N*-benzyloxycarbonylglycyl [(2*R*,3*R*,4*R*,5*R*)-1-amino-2,3,4,5-tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-cyclopentane carboxyl]} glycinate (**2.64**)</u> (54 mg, 0.10 mmol, 84%) as a white crystalline solid. M.p. 147 - 148 °C (diethyl ether / hexane); $[\alpha]_D^{25}$ +49.7 (*c*, 0.15 in chloroform); (Found: C, 57.86; H, 6.99; N, 7.19%. $C_{28}H_{39}O_{10}N_3$ requires C, 58.27; H, 6.81; N, 7.27%); ν_{max} (KBr): 3354 (br, NH), 1728 (ester), 1680, 1530 cm^{-1} (amide); δ_H ($CDCl_3$, 500 MHz): 1.33, 1.49 (2 x 6H, 2 x s, 2 x $C(CH_3)_2$), 1.46 (9H, s, $C(CH_3)_3$), 3.78 - 3.92 (2H, m, ABX system, AB part, $NHCH_2CO$), 3.98 -

4.06 (2H, m, ABX system, AB part, NHC$\underline{H}_2$CO), 4.68 (2H, AB system, PhC$\underline{H}_2$O), 5.09 - 5.18 (2H, m), 5.21 - 5.27 (2H, m), 5.60 (1H, br s, PhCH$_2$OCON$\underline{H}$), 6.88 (1H, br s, NHCH$_2$CON$\underline{H}$), 7.30 - 7.38 (5H, m, Ar-H), 7.90 (1H, br t, *J* 4.9 Hz, N$\underline{H}$CH$_2$CO$_2$C(CH$_3$)$_3$); δ_C (CDCl$_3$): 24.0, 25.2, 25.7, 26.9 (4 x q, 2 x C($\underline{C}$H$_3$)$_2$), 28.0 (q, C($\underline{C}$H$_3$)$_3$), 42.4, 45.0 (2 x t, 2 x NH$\underline{C}$H$_2$CO), 67.0 (s, C-1), 67.2 (t, Ph$\underline{C}$H$_2$O), 82.0 (s, $\underline{C}$(CH$_3$)$_3$), 82.9, 83.9, 84.8, 85.8 (4 x d, C-2, C-3, C-4, C-5), 113.0, 113.3 (2 x s, 2 x $\underline{C}$(CH$_3$)$_2$), 128.2, 128.5 (2 x d, Ar-CH), 135.9 (s, Ar-C), 156.5 (s, PhCH$_2$O$\underline{C}$ONH), 168.7, 169.1, 170.6 (3 x s, 3 x CO); *m/z* (CI, NH$_3$): 578 [(MH)$^+$, 30], 522 [(MH-C$_4$H$_9$)$^+$, 40], 91 ($C_7H_7^+$, 100%).

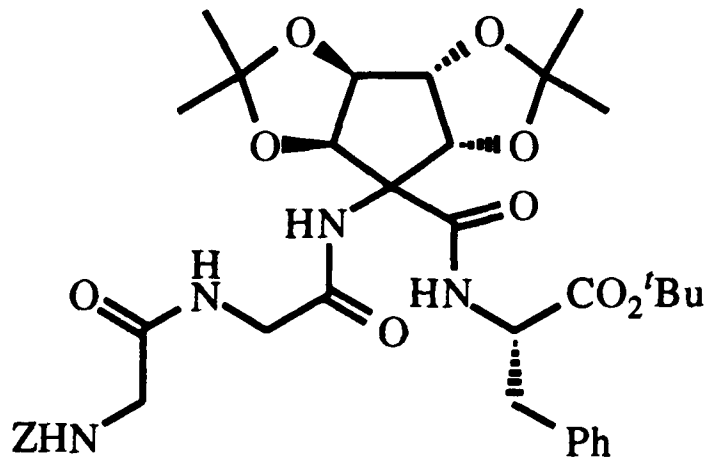
tert-Butyl {*N*-benzyloxycarbonyl-**L**-phenylalanyl [(2*R*,3*R*,4*R*,5*R*)-1-amino-2,3,4,5-tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-cyclopentane carboxyl]} **L**-phenylalanate (**2.65**)



tert-Butyl [(2*R*,3*R*,4*R*,5*R*)-1-amino-2,3:4,5-di-*O*-isopropylidene-2,3,4,5-tetrahydroxy-cyclopentane carboxyl] **L**-phenylalanate (**2.58**) (45 mg, 0.09 mmol), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (22 mg, 0.11 mmol), *N*-benzyloxycarbonyl-**L** -phenylalanine (34 mg, 0.11 mmol) and 1-hydroxybenzotriazole (15 mg, 0.11 mmol) were dissolved in dichloromethane (2 ml) under nitrogen. The reaction mixture was stirred at room temperature for 120 h, by which time t.l.c. analysis (ethyl acetate / hexane, 3 : 2) indicated a trace of starting material (R_f 0.5) and one major product (R_f 0.7). The reaction mixture was quenched by diluting with dichloromethane (15 ml), washed with aqueous

hydrochloric acid (2 M, 10 ml), and the organic layer dried (magnesium sulphate). Purification by flash chromatography (ethyl acetate / hexane, 3 : 7) afforded *tert*-butyl {*N*-benzyloxycarbonyl-**L**-phenylalanyl [(2*R*,3*R*,4*R*,5*R*)-1-amino-2,3,4,5-tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-cyclopentane carboxyl]} **L**-phenylalanate (**2.65**) (51 mg, 0.07 mmol, 71 %, 89% based on recovered starting material) as a white crystalline solid. M.p. 155 - 156 °C (diethyl ether / hexane); $[\alpha]_D^{25}$ +43.7 (*c*, 0.38 in chloroform); (Found: C, 66.58; H, 6.63; N, 5.28%. $C_{42}H_{51}O_{10}N_3$ requires C, 66.56; H, 6.78; N, 5.54%); ν_{max} (KBr): 3417 (br, NH), 1729 (ester), 1679, 1526 cm^{-1} (amide); δ_H ($CDCl_3$, 500 MHz): 1.29, 1.31, 1.39, 1.64 (4 x 3H, 4 x s, 2 x $C(CH_3)_2$), 1.38 (9H, s, $C(CH_3)_3$), 3.01, 3.19 (2 x 1H, 2 x dd, ABX system, AB part, $J_{A,B}$ 13.9 Hz, $J_{A,X}$ 7.3 Hz, $J_{B,X}$ 7.2 Hz, NHCH(CH_2Ph)CONH), 3.09, 3.18 (2 x 1H, 2 x dd, ABX system, AB part, $J_{A,B}$ 14.0 Hz, $J_{A,X}$ 6.0 Hz, $J_{B,X}$ 6.2 Hz, NHCH(CH_2Ph)$CO_2C(CH_3)_3$), 4.35 (1H, d, *J* 4.7 Hz), 4.41 (1H, ddd, ABX system, X part, $J_{X,A}$ 7.1 Hz, $J_{X,B}$ 7.2 Hz, $J_{X,NH}$ 7.3 Hz, NHCH(CH_2Ph)CONH), 4.47 (1H, d, *J* 6.9 Hz), 4.77 (1H, dd, ABX system, X part, $J_{X,A}$ 6.2 Hz, $J_{X,B}$ 6.0 Hz, NHCH(CH_2Ph)$CO_2C(CH_3)_3$), 4.96 (1H, d, *J* 6.9 Hz), 5.03 (2H, AB system, $J_{A,B}$ 12.2 Hz, PhCH_2O), 5.23 (1H, d, *J* 4.7 Hz), 5.32 (1H, d, $J_{NH,X}$ 7.1 Hz, NHCH(CH_2Ph)CONH), 6.74 (1H, br s, NHCH(CH_2Ph)CONH), 7.20 - 7.37 (15H, m, Ar-CH), 8.15 (1H, d, $J_{NH,X}$ 7.4 Hz, NHCH(CH_2Ph)$CO_2C(CH_3)_3$); δ_C ($CDCl_3$, 125 MHz): 23.8, 25.3, 25.6, 27.0 (4 x q, 2 x $C(CH_3)_2$), 27.9 (q, $C(CH_3)_3$), 37.9, 38.1 (2 x t, 2 x PhCH_2CH), 54.1, 57.2 (2 x d, 2 x PhCH$_2$CH), 66.8 (s, C-1), 67.1 (t, PhCH_2O), 82.0 (s, $C(CH_3)_3$), 82.3, 83.4, 84.0, 86.0 (4 x d, C-2, C-3, C-4, C-5), 112.4, 113.3 (2 x s, 2 x $C(CH_3)_2$), 126.7, 127.0, 128.1, 128.4, 128.7, 129.3, 129.6 (7 x d, Ar-CH), 135.9, 136.2, 136.6 (3 x s, 3 x Ar-C), 155.9 (s, PhCH$_2$OCONH), 168.1, 170.1, 171.9 (3 x s, 3 x CO); *m/z* (DCI, NH_3): 758 [$(MH)^+$, 20], 91 ($C_7H_7^+$, 100%); and recovered starting material *tert*-butyl [(2*R*,3*R*,4*R*,5*R*)-1-amino-2,3,4,5-tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-cyclopentane carboxyl] **L**-phenylalanate (**2.58**) (9 mg, 0.02 mmol).

tert-Butyl {*N*-benzyloxycarbonylglycylglycyl [(2*R*,3*R*,4*R*,5*R*)-1-amino-2,3,4,5-tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-cyclopentane carboxyl]} **L**-phenylalanate (**2.66**)

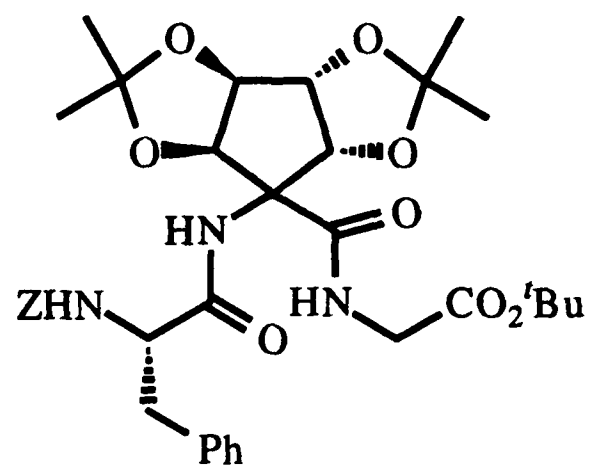


Method 1 - From *tert*-butyl [(2*R*,3*R*,4*R*,5*R*)-1-amino-2,3,4,5-tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-cyclopentane carboxyl] **L**-phenylalanate (**2.58**).

tert-Butyl [(2*R*,3*R*,4*R*,5*R*)-1-amino-2,3,4,5-tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-cyclopentane carboxyl] **L**-phenylalanate (**2.58**) (45 mg, 0.09 mmol), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (22 mg, 0.11 mmol), *N*-benzyloxycarbonylglycylglycine (30 mg, 0.11 mmol) and 1-hydroxybenzotriazole (15 mg, 0.11 mmol) were dissolved in dichloromethane (2 ml) under nitrogen. The reaction mixture was stirred at room temperature for 125 h, by which time t.l.c. analysis (ethyl acetate) indicated a trace of starting material (R_f 0.7) and one major product (R_f 0.2). The reaction mixture was quenched by diluting with dichloromethane (20 ml), washed with aqueous hydrochloric acid (2 M, 10 ml), and the organic layer was dried (magnesium sulphate). Purification by flash chromatography (ethyl acetate / hexane, 4 : 6, to ethyl acetate) afforded *tert*-butyl {*N*-benzyloxycarbonylglycylglycyl [(2*R*,3*R*,4*R*,5*R*)-1-amino-2,3,4,5-tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-cyclopentane carboxyl]} **L**-phenylalanate (**2.66**) (43 mg, 0.06 mmol, 63 %, 79% based on recovered starting material) as a white solid. M.p. 91 - 92 °C (diethyl ether / hexane); ν_{max} (KBr): 3328 (br, NH), 1728 (ester), 1676, 1576 cm^{-1} (amide); δ_H ($CDCl_3$, 500 MHz): 1.29, 1.34, 1.40, 1.56 (4 x 3H, 4 x s, 2 x $C(CH_3)_2$), 1.38 (9H, s, $C(CH_3)_3$), 3.08, 3.15 (2 x 1H, 2 x dd, ABX system, AB part,

$J_{A,B}$ 14.0 Hz, $J_{A,X}$ 6.0 Hz, $J_{B,X}$ 6.2 Hz, PhC$\underline{H}_2$CH), 3.89, 3.90 (2 x 1H, ABX system, AB part, NHC$\underline{H}_2$CO), 3.99 (2H, ABX system, AB part, NHC$\underline{H}_2$CO), 4.60 (1H, d, *J* 6.4 Hz), 4.61 (1H, d, *J* 5.1 Hz), 4.74 (1H, ddd, ABX system, X part, $J_{X,A}$ 6.0 Hz, $J_{X,B}$ 6.2 Hz, $J_{X,NH}$ 7.4 Hz, PhCH$_2$C$\underline{H}$), 4.97 (1H, d, *J* 6.4 Hz), 5.13 (2H, AB system, PhC$\underline{H}_2$O), 5.52 (1H, br s, PhCH$_2$OCON$\underline{H}$), 6.66, 6.79 (2 x 1H, 2 x br s, 2 x CH$_2$CON$\underline{H}$), 7.20 - 7.36 (10H, m, Ar-H), 7.79 (1H, br d, $J_{NH,X}$ 7.4 Hz, N$\underline{H}$CH(CH$_2$Ph)); δ_C (CDCl$_3$, 125 MHz): 24.1, 25.1, 26.1, 26.8 (4 x q, 2 x C($\underline{C}$H$_3$)$_2$), 27.9 (q, C($\underline{C}$H$_3$)$_3$), 37.9 (t, Ph$\underline{C}$H$_2$CH), 43.4, 44.4 (2 x t, 2 x NH$\underline{C}$H$_2$CO), 54.0 (d, PhCH$_2\underline{C}$H), 67.2 (t, Ph$\underline{C}$H$_2$O), 67.5 (s, C-1), 82.2 (s, $\underline{C}$(CH$_3$)$_3$), 82.8, 83.9, 84.5, 85.8 (4 x d, C-2, C-3, C-4, C-5), 112.7, 113.2 (2 x s, 2 x $\underline{C}$(CH$_3$)$_2$), 126.8, 128.1, 128.2, 128.5, 129.6 (5 x d, Ar-CH), 136.1, 136.5 (2 x s, 2 x Ar-C), 156.5 (s, PhCH$_2$O$\underline{C}$ONH), 168.2, 169.4, 169.5, 170.4 (4 x s, 4 x CO); *m/z* (DCI, NH$_3$): 725 [(MH)$^+$, 15], 699 [(MH-C$_4$H$_9$)$^+$, 50], 91 (C$_7$H$_7^+$, 70), 56 (100%); and recovered starting material *tert*-butyl [(2*R*,3*R*,4*R*,5*R*)-1-amino-2,3,4,5-tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-cyclopentane carboxyl] L-phenylalanate (**2.58**) (9 mg, 0.02 mmol).

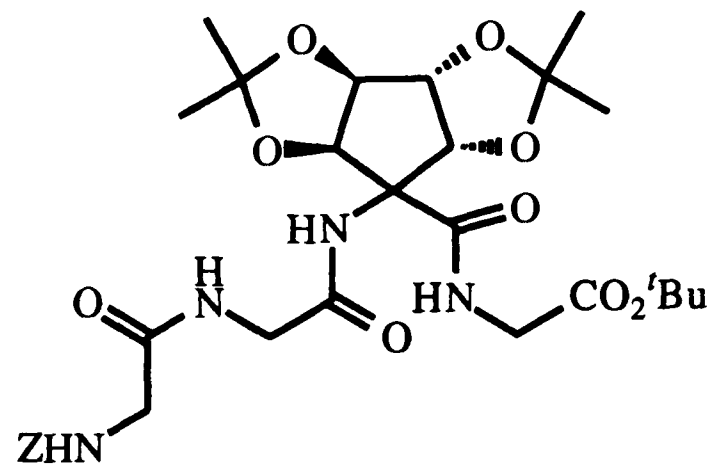
tert-Butyl {*N*-benzyloxycarbonyl-L-phenylalanyl [(2*R*,3*R*,4*R*,5*R*)-1-amino-2,3,4,5-tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-cyclopentane carboxyl]} glycinate (**2.67**)



tert-Butyl [(2*R*,3*R*,4*R*,5*R*)-1-amino-2,3,4,5-tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-cyclopentane carboxyl] glycinate (**2.63**) (38 mg, 0.10 mmol), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (29 mg, 0.15 mmol), *N*-benzyloxycarbonyl-L-phenylalanine (45 mg, 0.15 mmol) and

1-hydroxybenzotriazole (20 mg, 0.15 mmol) were dissolved in dichloromethane (3 ml) under nitrogen. The reaction mixture was stirred at room temperature for 46 h, by which time t.l.c. analysis (ethyl acetate / hexane, 3 : 2) indicated the complete conversion of starting material (R_f 0.4) to one major product (R_f 0.7). The reaction mixture was quenched by diluting with dichloromethane (25 ml), washed with aqueous hydrochloric acid (2 M, 10 ml), and the organic layer was dried (magnesium sulphate). Purification by flash chromatography (ethyl acetate / hexane, 5 : 7) afforded *tert*-butyl {*N*-benzyloxycarbonyl-L-phenylalanyl [(2*R*,3*R*,4*R*,5*R*)-1-amino-2,3,4,5-tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-cyclopentane carboxyl]} glycinate (**2.67**) (54 mg, 0.08 mmol, 82 %) as a white crystalline solid. M.p. 148 - 149 °C (diethyl ether / hexane); $[\alpha]_D^{25}$ +28.5 (*c*, 1.08 in chloroform); (Found: C, 63.23; H, 7.00; N, 6.13%. $C_{36}H_{45}O_{10}N_3$ requires C, 62.95; H, 6.79; N, 6.29%); ν_{max} (KBr): 3316 (br, NH), 1733 (ester), 1682, 1530 cm^{-1} (amide); δ_H ($CDCl_3$, 500 MHz): 1.30, 1.33, 1.40, 1.48 (4 x 3H, 4 x s, 2 x $C(C\underline{H}_3)_2$), 1.46 (9H, s, $C(C\underline{H}_3)_3$), 3.05, 3.22 (2 x 1H, 2 x dd, ABX system, AB part, $J_{A,B}$ 14.0 Hz, $J_{A,X}$ 7.2 Hz, $J_{B,X}$ 6.7 Hz, NHCH($C\underline{H}_2$Ph)CONH), 3.93, 4.00 (2 x 1H, 2 x dd, ABX system, AB part, $J_{A,B}$ 18.3 Hz, $J_{A,X}$ 5.0 Hz, $J_{B,X}$ 5.3 Hz, NH$C\underline{H}_2CO_2C(CH_3)_3$), 4.41 (1H, d, *J* 4.8 Hz), 4.46 (1H, br dd, ABX system, X part, $J_{X,A}$ 7.2 Hz, $J_{X,B}$ 6.7 Hz, NH$C\underline{H}$(CH_2Ph)CONH), 4.59 (1H, d, *J* 6.7 Hz), 5.05 (2H, AB system, $J_{A,B}$ 12.2 Hz, Ph$C\underline{H}_2$O), 5.15 (1H, d, *J* 4.8 Hz), 5.21 (1H, d, *J* 6.7 Hz), 5.35 (1H, br d, $J_{NH,X}$ 6.5 Hz, N$\underline{H}$CH(CH_2Ph)CONH), 6.84 (1H, br s, NHCH(CH_2Ph)CON$\underline{H}$), 7.21 - 7.36 (10H, m, Ar-CH), 7.96 (1H, br t, *J* 5.0 Hz, N$\underline{H}CH_2CO_2C(CH_3)_3$); δ_C ($CDCl_3$): 23.9, 25.3, 25.7, 27.0 (4 x q, 2 x $C(\underline{C}H_3)_2$), 28.0 (q, $C(\underline{C}H_3)_3$), 38.0 (t, Ph$\underline{C}H_2$CH), 42.4 (t, NH$\underline{C}H_2$CO), 57.0 (d, PhCH$_2\underline{C}$H), 66.8 (s, C-1), 67.2 (t, Ph$\underline{C}H_2$O), 81.9 (s, $\underline{C}(CH_3)_3$), 82.6, 83.7, 84.4, 85.9 (4 x d, C-2, C-3, C-4, C-5), 112.8, 113.3 (2 x s, 2 x $\underline{C}(CH_3)_2$), 127.1, 128.2, 128.5, 128.7, 129.3 (5 x d, Ar-CH), 135.8, 136.1 (2 x s, 2 x Ar-C), 156.0 (s, PhCH$_2$O$\underline{C}$ONH), 168.6, 168.9, 172.0 (3 x s, 3 x CO); *m/z* (DCI, NH_3): 668 [$(MH)^+$, 30], 612 [$(MH\text{-}C_4H_9)^+$, 10], 91 ($C_7H_7^+$, 100%).

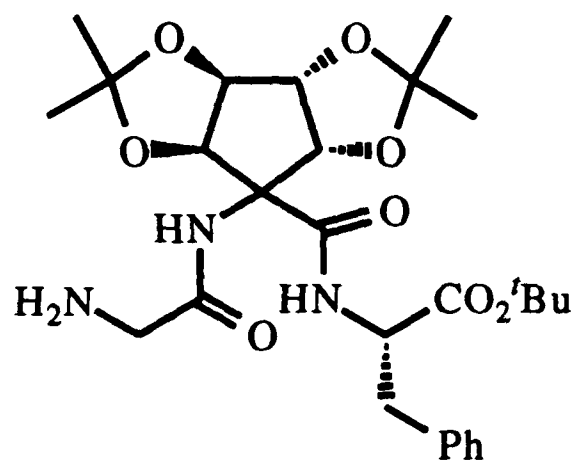
tert-Butyl {*N*-benzyloxycarbonylglycylglycyl [(2*R*,3*R*,4*R*,5*R*)-1-amino-2,3,4,5-tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-cyclopentane carboxyl]} glycinate (**2.68**)



tert-Butyl [(2*R*,3*R*,4*R*,5*R*)-1-amino-2,3,4,5-tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-cyclopentane carboxyl] glycinate (**2.63**) (61 mg, 0.16 mmol), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (45 mg, 0.24 mmol), *N*-benzyloxycarbonylglycylglycine (63 mg, 0.24 mmol) and 1-hydroxybenzotriazole (32 mg, 0.24 mmol) were dissolved in dichloromethane (1 ml) under nitrogen. The reaction mixture was stirred at room temperature for 70 h, by which time t.l.c. analysis (ethyl acetate) indicated complete conversion of starting material (R_f 0.5) to one major product (R_f 0.2). The reaction mixture was then quenched by diluting with dichloromethane (20 ml), washed with aqueous hydrochloric acid (2 M, 10 ml), and the organic layer was dried (magnesium sulphate). Purification by flash chromatography (methanol in chloroform, 0 - 2%) afforded *tert*-butyl {*N*-benzyloxycarbonyl-glycylglycyl [(2*R*,3*R*,4*R*,5*R*)-1-amino-2,3,4,5-tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-cyclopentane carboxyl]} glycinate (**2.68**) (93 mg, 0.15 mmol, 93%) as a white crystalline solid. M.p. 191 - 192 °C (ethyl acetate / hexane); $[\alpha]_D^{25}$ +46.3 (*c*, 0.10 in chloroform); (Found: C, 56.62; H, 6.73; N, 8.43%. $C_{30}H_{42}O_{11}N_4$ requires C, 56.27; H, 6.67; N, 8.83%); ν_{max} (KBr): 3334 (br, NH), 1727 (ester), 1680, 1531 cm^{-1} (amide); δ_H ($CDCl_3$, 500 MHz): 1.30, 1.32, 1.44, 1.52 (4 x 3H, 4 x s, 2 x $C(CH_3)_2$), 1.44 (9H, s, $C(CH_3)_3$), 3.87 - 4.02 (6H, m, 3 x $NHCH_2CO$), 4.62 (1H, d, *J* 5.6 Hz), 4.73 (1H, d, *J* 6.2 Hz), 5.12 (2H, AB system, $PhCH_2O$), 5.13 (1H, d, *J* 5.6 Hz), 5.20 (1H, d, *J* 6.2 Hz), 5.78 (1H, t, *J* 5.7 Hz,

PhCH$_2$OCONH), 6.99, 7.24 (2 x 1H, 2 x br s, 2 x CH$_2$CONH), 7.29 - 7.35 (5H, m, Ar-H), 7.69 (1H, br s, NHCH$_2$CO$_2$(CH$_3$)$_3$); δ_C (CDCl$_3$, 125 MHz): 24.3, 25.0, 26.3, 26.5 (4 x q, 2 x C(CH$_3$)$_2$), 28.0 (q, C(CH$_3$)$_3$), 42.2, 43.3, 44.4 (3 x t, 3 x NHCH$_2$CO), 67.2 (t, PhCH$_2$O), 68.2 (s, C-1), 82.2 (s, C(CH$_3$)$_3$), 83.1, 84.4, 85.2 (3 x d, C-2, C-3, C-4, C-5), 112.7, 113.1 (2 x s, 2 x C(CH$_3$)$_2$), 128.1, 128.2, 128.5 (3 x d, Ar-CH), 136.0 (s, Ar-C), 156.7 (s, PhCH$_2$OCONH), 169.1, 170.1 (2 x s); *m/z* (DCI, NH$_3$): 635 [(MH)$^+$, 35], 579 [(MH-C$_4$H$_9$)$^+$, 60], 91 (C$_7$H$_7^+$, 100%).

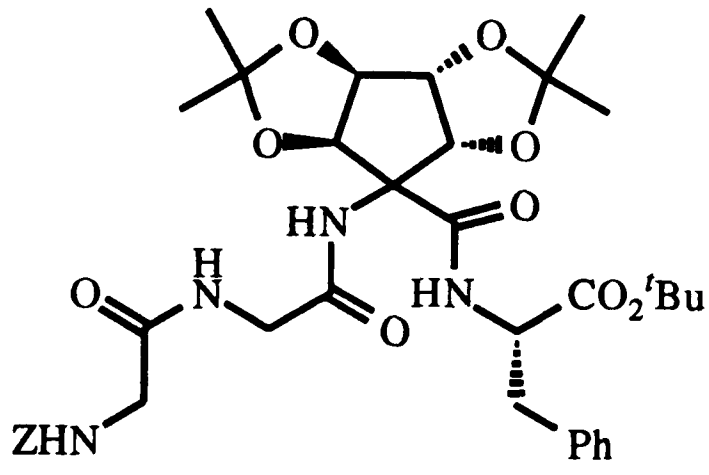
tert-Butyl [glycyl (2*R*,3*R*,4*R*,5*R*)-1-amino-2,3,4,5-tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-cyclopentane carboxyl] L-phenylalanate (**2.69**)



tert-Butyl {*N*-benzyloxycarbonylglycyl [(2*R*,3*R*,4*R*,5*R*)-1-amino-2,3,4,5-tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-cyclopentane carboxyl]} L-phenylalanate (**2.59**) (40 mg, 0.06 mmol) and palladium black (5 mg) were stirred in water / dioxane (1 : 1, 6 ml) at room temperature. The solution was degassed and stirred under hydrogen for 5 h. After this time t.l.c. analysis (ethyl acetate) indicated the complete conversion of starting material (R_f 0.6) to a single product (R_f 0.05). The reaction mixture was filtered through Celite, the solvent removed and the residue was then purified by flash chromatography (methanol / chloroform, 1 : 19) to yield *tert*-butyl [glycyl (2*R*,3*R*,4*R*,5*R*)-1-amino-2,3,4,5-tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-cyclopentane carboxyl] L-phenylalanate (**2.69**) (30 mg, 0.06 mmol, 94%) as a white crystalline solid. M.p. 157 - 158 °C (ethyl acetate / hexane); $[\alpha]_D^{25}$ +90.7 (*c*, 0.35 in chloroform); (Found: C, 61.07; H, 7.27; N, 7.77%. C$_{27}$H$_{39}$O$_8$N$_3$ requires C, 60.77;

H, 7.37; N, 7.87%); ν_{max} (KBr): 3317 (br, NH), 1733 (ester), 1675, 1548 cm^{-1} (amide); δ_H ($CDCl_3$, 500 MHz): 1.30, 1.37, 1.40, 1.67 (4 x 3H, 4 x s, 2 x $C(C\underline{H}_3)_2$), 1.38 (9H, s, $C(C\underline{H}_3)_3$), 3.10, 3.16 (2 x 1H, 2 x dd, ABX system, AB part, $J_{A,B}$ 14.0 Hz, $J_{A,X}$ 6.2 Hz, $J_{B,X}$ 6.1 Hz, $PhC\underline{H}_2CH$), 3.40 (2H, ABX system, AB part, $NHC\underline{H}_2CO$), 4.58 (1H, d, *J* 6.6 Hz), 4.59 (1H, d, *J* 4.8 Hz), 4.75 (1H, ddd, ABX system, X part, $J_{X,A}$ 6.2 Hz, $J_{X,B}$ 6.1 Hz, $J_{X,NH}$ 7.3 Hz, $PhCH_2C\underline{H}$), 5.24 (1H, d, *J* 6.6 Hz), 5.48 (1H, d, *J* 4.8 Hz), 7.19 - 7.28 (5H, m, Ar-H), 8.08 (1H, br s, $CH_2CON\underline{H}$), 8.26 (1H, d, $J_{NH,X}$ 7.3 Hz, $N\underline{H}CH(CH_2Ph)$); δ_C ($CDCl_3$, 125 MHz): 24.8, 25.1, 26.8 (3 x q, 2 x $C(\underline{C}H_3)_2$), 28.2 (q, $C(\underline{C}H_3)_3$), 38.9 (t, $Ph\underline{C}H_2CH$), 45.1 (t, $NH\underline{C}H_2CO$), 55.5 (d, $PhCH_2\underline{C}H$), 70.3 (s, C-1), 83.4 (s, $\underline{C}(CH_3)_3$), 84.5, 86.2, 86.4, 86.6 (4 x d, C-2, C-3, C-4, C-5), 113.5, 114.4 (2 x s, 2 x $\underline{C}(CH_3)_2$), 128.0, 129.4, 130.7 (3 x d, Ar-CH), 137.8 (s, Ar-C), 170.5, 171.8, 175.4 (3 x s, 3 x CO); *m/z* (electrospray): 534 [$(MH)^+$, 100], 478 [$(MH\text{-}C_4H_9)^+$, 15%].

tert-Butyl {*N*-benzyloxycarbonylglycylglycyl [(2*R*,3*R*,4*R*,5*R*)-1-amino-2,3,4,5-tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-cyclopentane carboxyl]} **L**-phenylalanate (**2.66**)

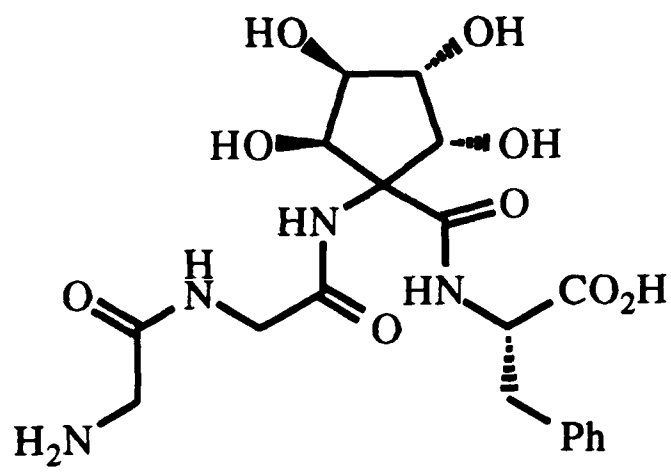


Method 2 - From *tert*-butyl [glycyl (2*R*,3*R*,4*R*,5*R*)-1-amino-2,3,4,5-tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-cyclopentane carboxyl] **L**-phenylalanate (**2.69**).

tert-Butyl [glycyl (2*R*,3*R*,4*R*,5*R*)-1-amino-2,3,4,5-tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-cyclopentane carboxyl] **L**-phenylalanate (**2.69**) (31 mg, 0.06 mmol),

1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (17 mg, 0.09 mmol), *N*-benzyloxycarbonylglycylglycine (18 mg, 0.09 mmol) and 1-hydroxybenzotriazole (12 mg, 0.09 mmol) were dissolved in dichloromethane (2 ml) under nitrogen. The reaction mixture was stirred at room temperature for 50 min, by which time t.l.c. analysis (methanol / ethyl acetate, 3 : 17) indicated the complete conversion of starting material (R_f 0.25) and one major product (R_f 0.7). The reaction mixture was quenched by diluting with dichloromethane (10 ml), washed with aqueous hydrochloric acid (2 M, 5 ml), and the organic layer was dried (magnesium sulphate). Purification by flash chromatography (ethyl acetate) afforded *tert*-butyl {*N*-benzyloxycarbonylglycylglycyl [(2*R*,3*R*,4*R*,5*R*)-1-amino-2,3,4,5-tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-cyclopentane carboxyl]} L-phenylalanate (**2.66**) (40 mg, 0.06 mmol, 95 %) identical in all respect to that obtained above in method 1.

Glycylglycyl [(2*R*,3*R*,4*R*,5*R*)-1-amino-2,3,4,5-tetrahydroxy-cyclopentane carboxyl] L-phenylalanate (**2.70**)



tert-Butyl {*N*-benzyloxycarbonylglycylglycyl [(2*R*,3*R*,4*R*,5*R*)-1-amino-2,3,4,5-tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-cyclopentane carboxyl]} L-phenylalanate (**2.66**) (42 mg, 0.06 mmol) was stirred in aqueous trifluoroacetic acid (80%, 5 ml) at room temperature for 2 h. After this time t.l.c. analysis (methanol / ethyl acetate, 3 : 17) indicated the complete conversion of starting material (R_f 0.7) to baseline materials. The solvent was removed and the crude residue was redissolved in water (5 ml) to which palladium black (3 mg) was added. The solution was degassed and

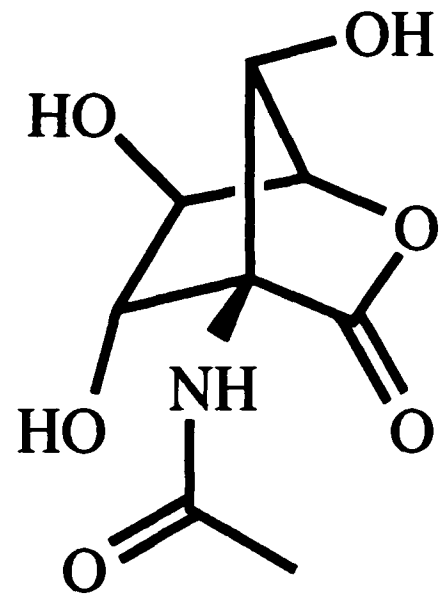
then stirred under hydrogen for 22 h. The solvent was removed and purification by ion exchange chromatography [Dowex 50W-X8(H^+), 2 M aqueous pyridine elution] gave glycylglycyl [(2*R*,3*R*,4*R*,5*R*)-1-amino-2,3,4,5-tetrahydroxy-cyclopentane carboxyl] L-phenylalanate (**2.70**) (26 mg, 0.06 mmol, 99% over 2 steps) as a hygroscopic foam. $[\alpha]_D^{25}$ +34.5 (*c*, 0.83 in water); ν_{max} (KBr): 3434 (br, NH), 1648, 1525 cm^{-1} (amide); δ_H (D_2O, 500 MHz): 3.00, 3.16 (2 x 1H, ABX system, AB part, $J_{A,B}$ 13.9 Hz, $J_{A,X}$ 7.7 Hz, $J_{B,X}$ 5.4 Hz, PhC$\underline{H}_2$CH), 3.88 (2H, ABX system, AB part, NHC$\underline{H}_2$CO), 3.97 - 3.98, 4.07 - 4.09 (2 x 1H, 2 x m, H-3, H-4), 4.01 (2H, ABX system, AB part, NHC$\underline{H}_2$CO), 4.36 (1H, d, *J* 5.7 Hz), 4.43 (1H, d, *J* 5.0 Hz), 4.48 (1H, dd, ABX system, X part, $J_{X,A}$ 7.7 Hz, $J_{X,B}$ 65.4 Hz, PhCH$_2$C$\underline{H}$), 7.26 - 7.37 (5H, m, Ar-H); δ_C (D_2O, 125 MHz): 37.98 (t, Ph$\underline{C}$H$_2$CH), 40.5, 43.0 (2 x t, 2 x NH$\underline{C}$H$_2$CO), 56.7 (d, PhCH$_2\underline{C}$H), 67.7 (s, C-1), 73.5, 75.1, 75.3, 76.1 (4 x d, C-2, C-3, C-4, C-5) 126.9, 128.6, 129.6 (3 x d, Ar-CH), 137.6 (s, Ar-C), 167.9, 171.0, 171.2 (3 x s, 3 x CO), 177.8 (s, COOH); *m/z* (electrospray): 455 [$(MH)^+$, 100%].

References.

1. Elliott, R.P. 'Sugars as Homochiral Starting Materials', D.Phil. Thesis, Oxford University, 1992, Chapter 3.
2. Elliott, R.P. 'Sugars as Homochiral Starting Materials', D.Phil. Thesis, Oxford University, 1992, Chapter 4.
3. Bruce, I.; Fleet, G.W.J.; Girdhar, A.; Haraldsson, M.; Peach, J.M.; Watkin, D.J.; *Tetrahedron*, 1990, **46**, 19.
4. Fairbanks, A.J. 'Sugar Lactones in Synthesis', D.Phil. Thesis, Oxford University, 1993, Chapter 4.

Appendix 1

Crystal Structure Data for
(1*R*,4*S*,5*S*,6*R*,7*R*)-4-Acetamido-5,6,7-trihydroxy-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.36**).

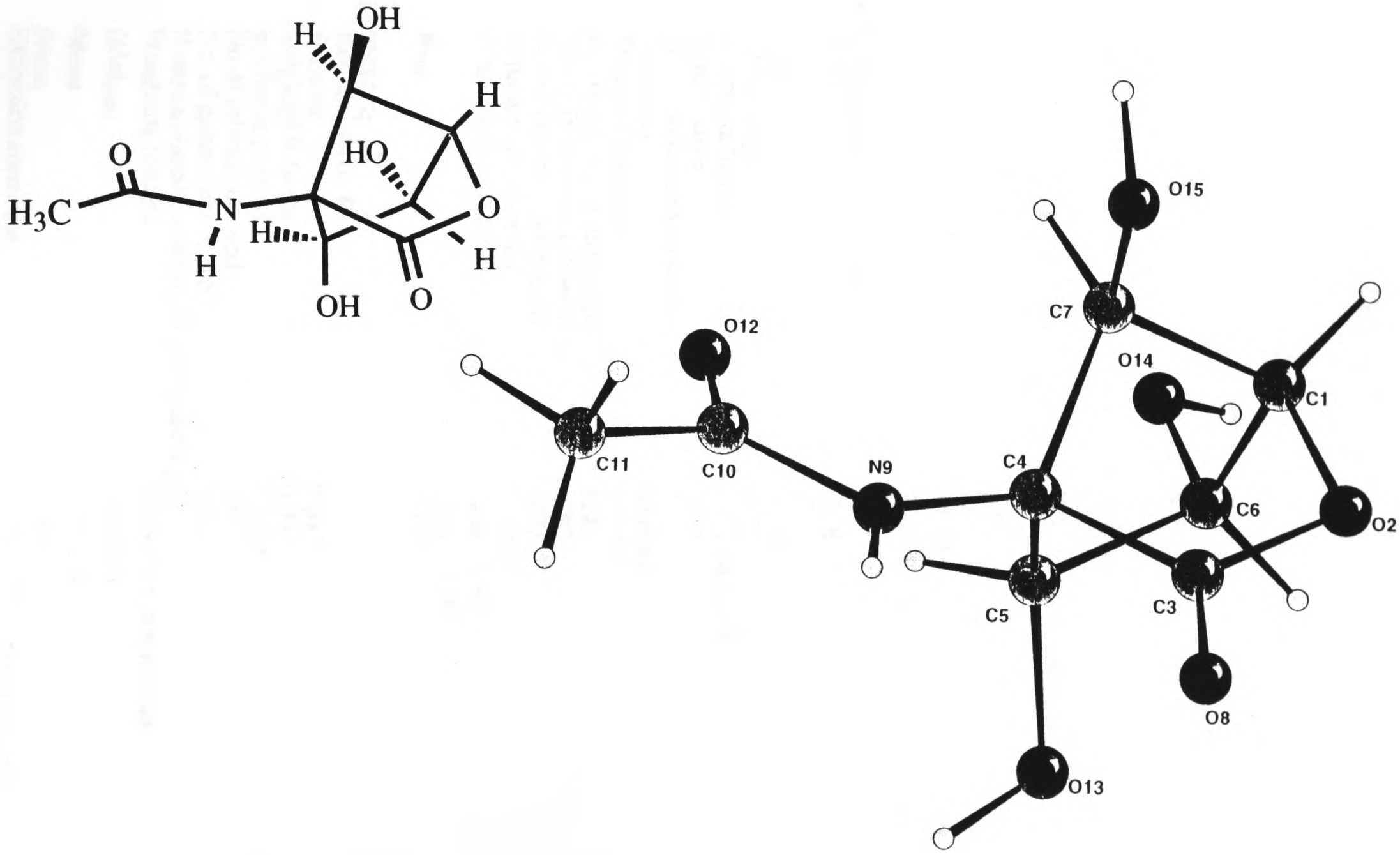


General X-Ray Crystal Structure Analysis.

Structures were established by single crystal X-ray analysis. Cell dimensions and intensity data were measured with an Enraf-Nonius CAD4-F diffractometer up to θ = 75° (Cu-Kα radiation). The data were corrected for absorption, Lorentz and polarisation effects. All calculations were carried out on a Microvax 3800 computer using SHELXS-86[1] for direct methods and CRYSTALS[2] for all other calculations. Atomic scattering factors were taken from International Tables.[3] Atomic coordinates for both compounds have been deposited at the Cambridge Crystallgraphic Data Centre.[4] The coordinates of all non-hydrogen atoms were given by SHELXS-86. The hydrogen atoms were placed geometrically except for the hydroxyl hydrogens which were found by Fourier difference maps. The structures were refined by full-matrix least-squares with isotropic temperature factors for the hydrogen atoms and anistropic temperature factors for all other atoms using data with merged Friedel pairs. Corrections for secondary extinction were applied,[5] and the models refined almost to convergence. The data were refined using Chebyshev[6] weighing schemes.

References.

1. Sheldrick, G.M.; Crystallographic Computing 3, ed. Sheldrick, G.M.; Kruger, C.; Goddard, R.; Oxford University Press, Oxford, 1985.
2. Watkin, D.J.; Carruthers, J.R.; Betteridge, P.W.; CRYSTALS User Guide, Chemical Crystallography Laboratory, Oxford University, 1985.
3. International Tables for X-ray Crystallography, Vol IV, Kynoch Press, Birmingham, 1974.
4. The atomic coordinates are available on request from the Cambridge Crystallographic Centre, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW.
5. Larson, A.C.; Crystallographic Computing Techniques, ed. Ahmed, F.R.; Munksgaard, Copenhagen, 1976.
6. Prince, E.; Mathematical Techniques in Crystallography and Material Sciences, Springer-Verlag Inc., New York, 1982.


H
OH
H
HO
O
H_3C
N
H
H
O
H
OH
O
O12
C11
C10
N9
C4
O15
C7
O14
C1
C6
O2
C5
C3
O8
O13

Crystal Structure Data for (1*R*, 4*S*, 5*S*, 6*R*, 7*R*)-4-Acetamido-5,6,7-trihydroxy-2-oxa-bicyclo[2.2.1]heptan-3-one (2.36)

Molecular formula	$C_8H_{11}O_6N$
Formula Weight	217.18
Crystal System	Orthorhombic
Space Group	$P2_12_12_1$

Unit Cell Parameters :-

a(Å)	7.641
b(Å)	8.072
c(Å)	15.243
Volume(Å^3)	940.28
Crystal dimensions (approx. mm)	0.9 x 0.6 x 0.4
Crystal description	Colourless Regular Block
No. of molecular units in the cell Z	4
Calculated Density (Mg m^{-3})	1.53
Reflections for cell parameters	25
Theta range for cell parameters (°)	18-28
Linear absorption coeff. (mm^{-1})	1.108

Data Collection Parameters :-

h range	-1, 9
k range	-1, 9
l range	-1, 18
Theta range (°)	0, 72
Copper radiation	λ = 1.54184 Å
Temperature	293K
No. of intensity standards	3
frequency	60 mins
Decay of standards	3.11%
No. of measured reflections	1543
No. of independent reflections	1087
No. of observed reflections	1002
Criterion for observed	$I > 3\sigma(I)$
Absorption correction :	T_{min} = 0.43
	T_{max} = 1.00
R_{int}	0.0255

Refinement :-

Refinement on F	
R-factor	0.047
weighted R-factor	0.061
goodness of fit (S)	1.1665
No.of reflections used	1002
No. of parameters refined	202
H atoms placed geometrically after each cycle	
Weighting scheme	Chebychev polynomial
$(\Delta/\sigma)_{max}$	0.000898
$\Delta\rho_{max}$	0.389 e Å^{-3}
$\Delta\rho_{min}$	-0.398 e Å^{-3}
Extinction correction	Larson 1970 Crystallographic Computing eq 22
Extinction coefficient	7.3(36)

Atomic coordinates and equivalent isotropic temperature factors

Atom	x/a	y/b	z/c	U(iso)	Occ
O(2)	-0.0556(3)	-0.9836(3)	-0.6889(2)	0.0331	1.0000
O(8)	-0.2003(3)	-1.2238(3)	-0.7032(2)	0.0382	1.0000
O(12)	-0.6449(4)	-0.8544(4)	-0.5666(2)	0.0473	1.0000
O(13)	-0.4197(3)	-0.9201(3)	-0.8060(1)	0.0329	1.0000
O(14)	-0.2574(3)	-0.5740(3)	-0.7065(2)	0.0355	1.0000
O(15)	-0.1819(4)	-0.9523(3)	-0.5123(1)	0.0416	1.0000
N(9)	-0.4882(3)	-1.0719(3)	-0.6149(1)	0.0273	1.0000
C(1)	-0.1063(4)	-0.8188(4)	-0.6548(2)	0.0310	1.0000
C(3)	-0.2000(4)	-1.0799(4)	-0.6832(2)	0.0284	1.0000
C(4)	-0.3474(3)	-0.9736(3)	-0.6484(2)	0.0255	1.0000
C(5)	-0.3879(4)	-0.8469(3)	-0.7233(2)	0.0261	1.0000
C(6)	-0.2183(4)	-0.7413(3)	-0.7271(2)	0.0290	1.0000
C(7)	-0.2430(4)	-0.8617(4)	-0.5852(2)	0.0315	1.0000
C(10)	-0.6264(4)	-1.0046(4)	-0.5713(2)	0.0311	1.0000
C(11)	-0.7484(4)	-1.1253(5)	-0.5292(2)	0.0406	1.0000
H(11)	-0.0054	-0.7484	-0.6328	0.0400	1.0000
H(51)	-0.5050	-0.7869	-0.7142	0.0400	1.0000
H(61)	-0.1577	-0.7394	-0.7877	0.0400	1.0000
H(71)	-0.2941	-0.7670	-0.5492	0.0400	1.0000
H(91)	-0.4962	-1.1744	-0.6207	0.0400	1.0000
H(111)	-0.8432	-1.0604	-0.4969	0.0400	1.0000
H(112)	-0.8045	-1.1965	-0.5738	0.0400	1.0000
H(113)	-0.6865	-1.1959	-0.4844	0.0400	1.0000
H(131)	-0.5234	-0.9724	-0.8161	0.0400	1.0000
H(141)	-0.2005	-0.5169	-0.7359	0.0400	1.0000
H(151)	-0.1730	-0.8983	-0.4654	0.0400	1.0000

Anisotropic temperature factors, standard deviations in brackets

Atom	U(11)	U(22)	U(33)	U(23)	U(13)	U(12)
O(2)	0.0246(9)	0.032(1)	0.047(1)	-0.0010(9)	0.0021(9)	0.0022(8)
O(8)	0.039(1)	0.031(1)	0.050(1)	-0.0058(9)	0.010(1)	0.0002(9)
O(12)	0.064(2)	0.039(1)	0.061(2)	-0.008(1)	0.033(1)	0.004(1)
O(13)	0.0355(9)	0.041(1)	0.0261(9)	0.0014(8)	-0.0006(8)	-0.0088(9)
O(14)	0.034(1)	0.0246(9)	0.055(1)	0.0031(9)	0.004(1)	-0.0020(8)
O(15)	0.061(1)	0.044(1)	0.029(1)	-0.000(1)	-0.013(1)	0.000(1)
N(9)	0.031(1)	0.027(1)	0.027(1)	0.0035(9)	0.0062(9)	-0.0027(9)
C(1)	0.026(1)	0.028(1)	0.041(2)	-0.001(1)	-0.004(1)	-0.001(1)
C(3)	0.027(1)	0.030(1)	0.028(1)	0.003(1)	0.002(1)	0.002(1)
C(4)	0.024(1)	0.026(1)	0.027(1)	-0.003(1)	0.002(1)	0.001(1)
C(5)	0.025(1)	0.028(1)	0.025(1)	0.000(1)	0.0017(9)	-0.002(1)
C(6)	0.025(1)	0.030(1)	0.034(1)	0.004(1)	0.003(1)	-0.001(1)
C(7)	0.034(1)	0.031(1)	0.031(1)	-0.000(1)	-0.005(1)	0.001(1)
C(10)	0.038(1)	0.035(1)	0.025(1)	-0.004(1)	0.008(1)	0.000(1)
C(11)	0.039(2)	0.052(2)	0.038(1)	0.006(1)	0.011(1)	-0.005(2)

Appendix 1

Inter-atomic distances (Å), standard deviations in brackets

O(2)	-	C(1)	1.480(3)
O(2)	-	C(3)	1.352(4)
O(8)	-	C(3)	1.201(4)
O(12)	-	C(10)	1.223(4)
O(13)	-	C(5)	1.413(3)
O(14)	-	C(6)	1.418(3)
O(15)	-	C(7)	1.409(4)
N(9)	-	C(4)	1.431(3)
N(9)	-	C(10)	1.361(4)
C(1)	-	C(6)	1.529(4)
C(1)	-	C(7)	1.529(4)
C(3)	-	C(4)	1.512(4)
C(4)	-	C(5)	1.564(4)
C(4)	-	C(7)	1.544(4)
C(5)	-	C(6)	1.552(4)
C(10)	-	C(11)	1.494(4)

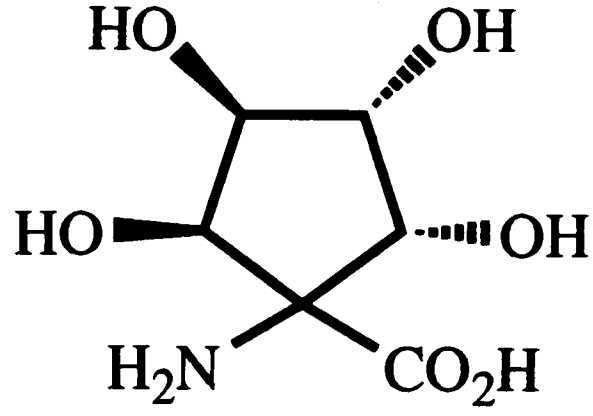
Inter-atomic angles in degrees, standard deviations in brackets

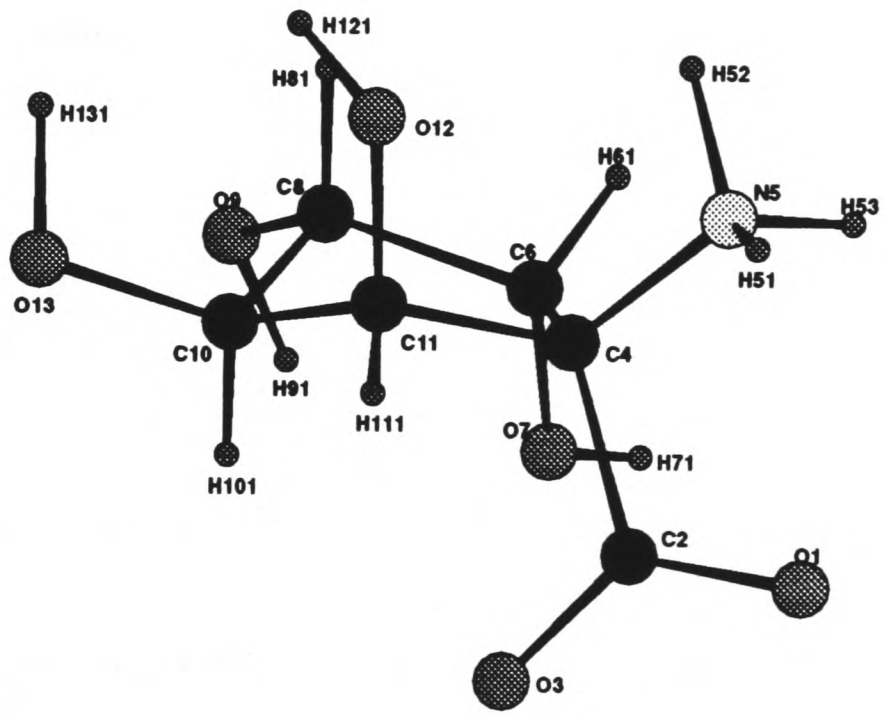
C(1)	-	O(2)	-	C(3)	106.3(2)
C(4)	-	N(9)	-	C(10)	122.4(2)
O(2)	-	C(1)	-	C(6)	105.1(2)
O(2)	-	C(1)	-	C(7)	102.6(2)
C(6)	-	C(1)	-	C(7)	102.2(2)
O(2)	-	C(3)	-	O(8)	122.8(3)
O(2)	-	C(3)	-	C(4)	107.7(2)
O(8)	-	C(3)	-	C(4)	129.5(3)
N(9)	-	C(4)	-	C(3)	111.8(2)
N(9)	-	C(4)	-	C(5)	118.4(2)
C(3)	-	C(4)	-	C(5)	105.2(2)
N(9)	-	C(4)	-	C(7)	119.3(2)
C(3)	-	C(4)	-	C(7)	99.6(2)
C(5)	-	C(4)	-	C(7)	100.1(2)
O(13)	-	C(5)	-	C(4)	114.3(2)
O(13)	-	C(5)	-	C(6)	109.9(2)
C(4)	-	C(5)	-	C(6)	102.8(2)
O(14)	-	C(6)	-	C(1)	110.3(3)
O(14)	-	C(6)	-	C(5)	109.8(2)
C(1)	-	C(6)	-	C(5)	102.5(2)
O(15)	-	C(7)	-	C(1)	116.0(3)
O(15)	-	C(7)	-	C(4)	111.1(2)
C(1)	-	C(7)	-	C(4)	93.0(2)
O(12)	-	C(10)	-	N(9)	121.0(3)
O(12)	-	C(10)	-	C(11)	123.3(3)
N(9)	-	C(10)	-	C(11)	115.7(3)

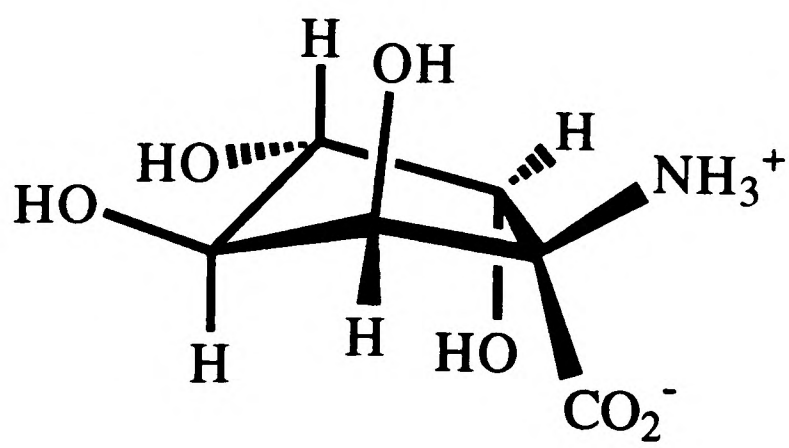
Appendix 2

Crystal Structure Data for

(2*R*,3*R*,4*R*,5*R*)-1-Amino-2,3,4,5-tetrahydroxy-cyclopentane carboxylic acid (**2.39**).




H121
H81
H131
O12
H52
H61
O8
C8
N5
H53
C6
H51
O13
C10
C11
C4
H91
H111
O7
H71
H101
C2
O1
O3


H
OH
HO
H
NH3+
HO
H
H
HO
CO2-

Crystal Structure Data for (2*R*, 3*R*, 4*R*, 5*R*)-1-Amino-2,3,4,5-tetrahydroxy-cyclopentane carboxylic acid (2.39)

Molecular formula	$C_6 H_{11} O_6 N$
Formula weight	193.1560
Crystal system	Primitive Monoclinic
Space Group	P 21

Unit Cell Parameters:-

a(Å)	6.5831	α(°)	90.0000
b(Å)	9.7294	β(°)	116.2779
c(Å)	6.5146	γ(°)	90.0000
Volume(Å^3)	373.9276		

Crystal dimensions (mm)	0.5 x 0.5 x 0.9
No. of molecular units in the cell Z	2
Calculated Density (g/cm^3)	1.7132
Reflections for lattice parameters	20
θ range for lattice parameters(°)	28.41 - 71.35
Linear absorption coeff.(cm^{-1})	13.015

Data Collection Parameters:-

h range		-8, 8
k range		-1, 1
l range		-1, 8
Theta range		0, 72
Copper radiation	λ(1)	1.540511
	λ(2)	1.544331
No. of automatic reorientations		0
Temperature (K)		294
No. of intensity standards		3
Decay of standards		-1.9%
Total data collected		778
Number of reflections used		773
Criterion for observed		I > 3sigma
Absorption empirical	min	1.356
	max	1.630
DIFABS	min	0.844
	max	1.140

Refinement:-

Number of data merged with Friedel pairs	778
Sheldrick merging R-factor	8.433
Maximum number of parameters	152
Ratio of data : parameters	5.09 : 1
Weighting scheme	Chebyshev with 3 terms
Flack enantiopole parameter	Not Refined
Del rho min	-0.25
Del rho max	0.48
Final R-factor	0.036
Final weighted R-factor	0.082

Atomic coordinates and equivalent isotropic temperature factors

Atom	x/a	y/b	z/c	U(iso)	Occ
O(1)	0.6023(5)	-0.0804(3)	-0.2391(6)	0.0270	1.0000
C(2)	0.4784(6)	0.0132(4)	-0.2259(6)	0.0188	1.0000
O(3)	0.5044(5)	0.1392(3)	-0.2427(6)	0.0263	1.0000
C(4)	0.2712(6)	-0.0315(4)	-0.1913(6)	0.0157	1.0000
N(5)	0.2406(5)	-0.1822(3)	-0.2302(5)	0.0176	1.0000
C(6)	0.2982(6)	0.0058(4)	0.0537(6)	0.0171	1.0000
O(7)	0.4998(4)	0.0814(3)	0.1827(4)	0.0226	1.0000
C(8)	0.0926(6)	0.0982(4)	0.0082(6)	0.0176	1.0000
O(9)	0.1270(4)	0.1910(3)	0.1879(4)	0.0227	1.0000
C(10)	0.0413(6)	0.1662(4)	-0.2209(6)	0.0173	1.0000
C(11)	0.0556(6)	0.0462(4)	-0.3654(6)	0.0163	1.0000
O(12)	-0.1405(4)	-0.0387(3)	-0.4528(4)	0.0204	1.0000
O(13)	-0.1640(4)	0.2416(3)	-0.3233(5)	0.0207	1.0000

Atom	x/a	y/b	z/c	U(iso)	Occ
H(131)	-0.2810	0.1856	-0.2921	0.0500	1.0000
H(121)	-0.2324	-0.0161	-0.3696	0.0500	1.0000
H(71)	0.5973	0.0421	0.2808	0.0500	1.0000
H(91)	0.2829	0.2132	0.2281	0.0500	1.0000
H(52)	0.0976	-0.2149	-0.2110	0.0500	1.0000
H(53)	0.3625	-0.2385	-0.1150	0.0500	1.0000
H(51)	0.2267	-0.2089	-0.3738	0.0500	1.0000
H(101)	0.1670	0.2263	-0.1875	0.0500	1.0000
H(111)	0.0805	0.0669	-0.4935	0.0500	1.0000
H(81)	-0.0420	0.0356	-0.0260	0.0500	1.0000
H(61)	0.2875	-0.0747	0.1475	0.0500	1.0000

Anisotropic temperature factors, standard deviations in brackets.

Atom	U(11)	U(22)	U(33)	U(23)	U(13)	U(12)
O(1)	0.024(1)	0.025(2)	0.059(2)	-0.002(1)	0.028(1)	0.000(1)
C(2)	0.015(2)	0.022(2)	0.020(2)	0.001(2)	0.007(1)	-0.001(2)
O(3)	0.025(1)	0.023(2)	0.050(2)	0.010(1)	0.023(1)	0.001(1)
C(4)	0.018(2)	0.012(2)	0.017(2)	-0.001(1)	0.007(1)	0.000(1)
N(5)	0.018(1)	0.013(1)	0.023(1)	-0.000(1)	0.010(1)	-0.001(1)
C(6)	0.018(2)	0.017(2)	0.015(2)	0.001(1)	0.005(1)	-0.003(1)
O(7)	0.020(1)	0.023(1)	0.021(1)	-0.000(1)	-0.001(1)	-0.003(1)
C(8)	0.019(2)	0.019(2)	0.016(2)	-0.003(1)	0.009(1)	-0.002(2)
O(9)	0.024(1)	0.030(1)	0.022(1)	-0.010(1)	0.012(1)	-0.003(1)
C(10)	0.015(2)	0.017(2)	0.021(2)	0.003(2)	0.008(1)	0.001(1)
C(11)	0.015(2)	0.019(2)	0.015(2)	0.003(1)	0.007(1)	0.000(1)
O(12)	0.014(1)	0.025(1)	0.020(1)	-0.003(1)	0.004(1)	-0.001(1)
O(13)	0.020(1)	0.021(1)	0.026(1)	0.007(1)	0.012(1)	0.007(1)

Appendix 2

Inter-atomic distances (Angstrom), with standard deviations in brackets.

O(1)	-	C(2)	1.250(5)
C(2)	-	O(3)	1.249(5)
C(2)	-	C(4)	1.541(5)
C(4)	-	N(5)	1.487(5)
C(4)	-	C(6)	1.568(5)
C(4)	-	C(11)	1.564(5)
N(5)	-	H(52)	1.053(3)
N(5)	-	H(53)	0.987(3)
N(5)	-	H(51)	0.935(3)
C(6)	-	O(7)	1.422(4)
C(6)	-	C(8)	1.540(5)
C(6)	-	H(61)	1.014(3)
O(7)	-	H(71)	0.776(3)
C(8)	-	O(9)	1.415(4)
C(8)	-	C(10)	1.527(5)
C(8)	-	H(81)	1.015(3)
O(9)	-	H(91)	0.965(3)
C(10)	-	C(11)	1.529(5)
C(10)	-	O(13)	1.419(4)
C(10)	-	H(101)	0.956(3)
C(11)	-	O(12)	1.422(4)
C(11)	-	H(111)	0.941(3)
O(12)	-	H(121)	0.999(3)
O(13)	-	H(131)	1.035(3)

Inter-atomic angles in degrees, with standard deviations in brackets.

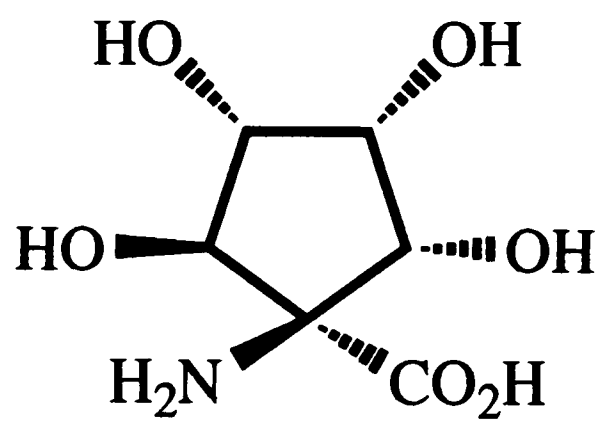
O(1)	-	C(2)	-	O(3)	126.1(4)
O(1)	-	C(2)	-	C(4)	116.9(3)
O(3)	-	C(2)	-	C(4)	117.0(3)
C(2)	-	C(4)	-	N(5)	108.4(3)
C(2)	-	C(4)	-	C(6)	112.0(3)
N(5)	-	C(4)	-	C(6)	110.3(3)
C(2)	-	C(4)	-	C(11)	109.6(3)
N(5)	-	C(4)	-	C(11)	110.0(3)
C(6)	-	C(4)	-	C(11)	106.5(3)
C(4)	-	N(5)	-	H(52)	109.8(3)
C(4)	-	N(5)	-	H(53)	114.5(3)
H(52)	-	N(5)	-	H(53)	102.2(3)
C(4)	-	N(5)	-	H(51)	113.0(3)
H(52)	-	N(5)	-	H(51)	109.8(3)
H(53)	-	N(5)	-	H(51)	107.0(3)
C(4)	-	C(6)	-	O(7)	112.1(3)
C(4)	-	C(6)	-	C(8)	104.2(3)
O(7)	-	C(6)	-	C(8)	108.8(3)
C(4)	-	C(6)	-	H(61)	115.3(3)
O(7)	-	C(6)	-	H(61)	109.8(3)
C(8)	-	C(6)	-	H(61)	106.1(3)
C(6)	-	O(7)	-	H(71)	116.6(3)
C(6)	-	C(8)	-	O(9)	114.0(3)
C(6)	-	C(8)	-	C(10)	103.7(3)
O(9)	-	C(8)	-	C(10)	114.6(3)
C(6)	-	C(8)	-	H(81)	107.4(3)
O(9)	-	C(8)	-	H(81)	111.6(3)
C(10)	-	C(8)	-	H(81)	104.6(3)

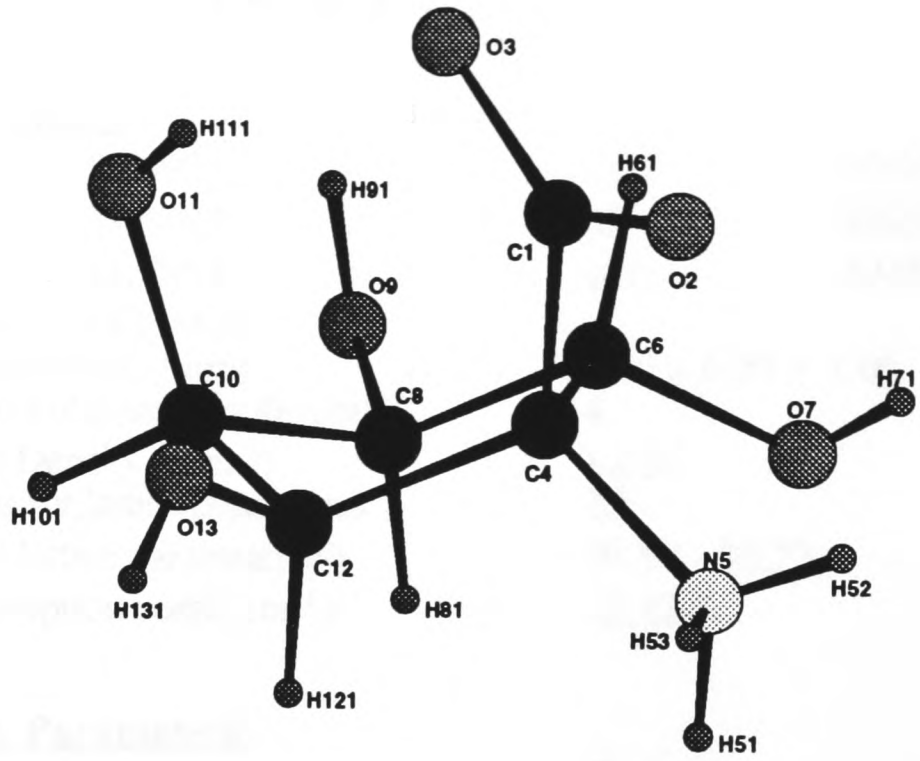
C(8)	- O(9)	- H(91)	97.4(2)
C(8)	- C(10)	- C(11)	102.9(3)
C(8)	- C(10)	- O(13)	115.9(3)
C(11)	- C(10)	- O(13)	114.3(3)
C(8)	- C(10)	- H(101)	104.4(3)
C(11)	- C(10)	- H(101)	108.9(3)
O(13)	- C(10)	- H(101)	109.8(3)
C(4)	- C(11)	- C(10)	101.9(3)
C(4)	- C(11)	- O(12)	112.4(3)
C(10)	- C(11)	- O(12)	113.4(3)
C(4)	- C(11)	- H(111)	106.7(3)
C(10)	- C(11)	- H(111)	117.7(3)
O(12)	- C(11)	- H(111)	104.6(3)
C(11)	- O(12)	- H(121)	108.4(2)
C(10)	- O(13)	- H(131)	105.8(2)

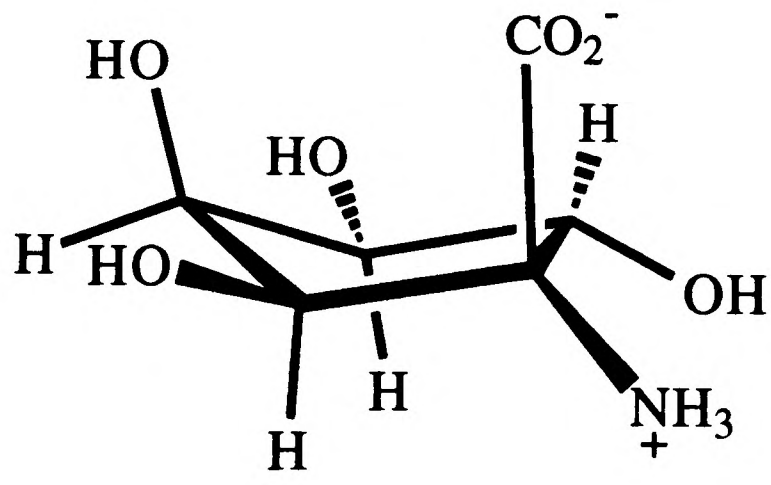
Appendix 3

Crystal Structure Data for

(1*S*,2*R*,3*R*,4*S*,5*R*)-1-Amino-2,3,4,5-tetrahydroxy-cyclopentane carboxylic acid (**2.42**).




O3
H111
O11
H91
H61
C1
O2
O9
C6
C10
C8
H71
O7
C4
H101
O13
C12
N5
H52
H131
H81
H53
H121
H51


HO
CO_2^-
H
HO
H
HO
OH
H
H
NH_3^+

Crystal Structure Data for (1*S*, 2*R*, 3*R*, 4*S*, 5*R*)-1-Amino-2,3,4,5-tetrahydroxy-cyclopentane carboxylic acid (2.42)

Molecular formula	$C_6 H_{11} O_6 N$
Formula weight	193.1550
Crystal system	Primitive orthorhombic
Space Group	P 21 21 21

Unit Cell Parameters:-

a(Å)	5.7499	α(°)	90.0000
b(Å)	11.5705	β(°)	90.0000
c(Å)	11.7953	γ(°)	90.0000
Volume(Å^3)	783.9919		
Crystal dimensions (mm)		0.15 x 0.95 x 1.00	
No. of molecular units in the cell Z		4	
Calculated Density (g/cm^3)		1.635	
Reflections for lattice parameters		25	
θ range for lattice parameters(°)		59.58 - 70.77	
Linear absorption coeff.(cm^{-1})		12.42	

Data Collection Parameters:-

h range		-7, 7
k range		-14, 14
l range		-14, 14
Theta range		0, 72
Copper radiation	λ(1)	1.540511
	λ(2)	1.544331
No. of automatic reorientations		0
Temperature (K)		294
No. of intensity standards		5
Decay of standards		0.5%
Total data collected		2643
Number of reflections used		1497
Criterion for observed		I > 3sigma
Absorption empirical	min	1.16
	max	1.54
DIFABS	min	0.92
	max	1.17

Refinement:-

Number of data merged, no Friedel	1533
Merging R-factor, no Friedel	2.84
Maximum number of parameters	120
Ratio of data : parameters	12.8 : 1
Weighting scheme	Chebyshev with 3 terms
Flack enantiopole parameter	0.00
esd	0.21
Del rho min	-0.277
Del rho max	0.327
Final R-factor	0.003
Final weighted R-factor	0.004

Atomic coordinates and equivalent isotropic temperature factors

Atom	x/a	y/b	z/c	U(iso)	Occ
O(9)	-0.1863(2)	-0.1387(1)	-0.51589(9)	0.0221	1.0000
O(7)	-0.2736(2)	-0.35010(9)	-0.35789(9)	0.0207	1.0000
O(13)	-0.0526(2)	-0.0251(1)	-0.1228(1)	0.0225	1.0000
O(11)	0.1022(2)	-0.0225(1)	-0.3536(1)	0.0255	1.0000
O(3)	0.3010(2)	-0.1883(1)	-0.2280(1)	0.0281	1.0000
O(2)	0.1747(2)	-0.2887(1)	-0.0794(1)	0.0250	1.0000
N(5)	-0.2662(2)	-0.2859(1)	-0.1397(1)	0.0185	1.0000
C(4)	-0.1074(3)	-0.2166(1)	-0.2109(1)	0.0149	1.0000
C(8)	-0.2312(3)	-0.1452(1)	-0.3976(1)	0.0177	1.0000
C(1)	0.1446(3)	-0.2326(1)	-0.1681(1)	0.0178	1.0000
C(6)	-0.1297(2)	-0.2521(1)	-0.3397(1)	0.0145	1.0000
C(12)	-0.1768(3)	-0.0872(1)	-0.2078(1)	0.0175	1.0000
C(10)	-0.1359(3)	-0.0438(1)	-0.3288(1)	0.0203	1.0000

Atom	x/a	y/b	z/c	U(iso)	Occ
H(81)	-0.4051	-0.1454	-0.4030	0.0139	1.0000
H(61)	0.0199	-0.2805	-0.3741	0.0112	1.0000
H(121)	-0.3392	-0.0711	-0.1820	0.0137	1.0000
H(101)	-0.2014	0.0344	-0.3464	0.0159	1.0000
H(52)	-0.2375	-0.3539	-0.1386	0.0500	1.0000
H(71)	-0.2331	-0.4008	-0.3606	0.0500	1.0000
H(91)	-0.0413	-0.1367	-0.5258	0.0500	1.0000
H(51)	-0.4244	-0.2742	-0.1606	0.0500	1.0000
H(53)	-0.2625	-0.2717	-0.0811	0.0500	1.0000
H(111)	0.1681	-0.0550	-0.3297	0.0500	1.0000
H(131)	-0.1300	0.0058	-0.0844	0.0500	1.0000

Anisotropic temperature factors, standard deviations in brackets.

Atom	U(11)	U(22)	U(33)	U(23)	U(13)	U(12)
O(9)	0.0255(6)	0.0292(6)	0.0154(5)	0.0046(4)	-0.0009(4)	0.0001(5)
O(7)	0.0268(6)	0.0153(5)	0.0244(5)	-0.0034(4)	-0.0072(5)	-0.0009(4)
O(13)	0.0262(6)	0.0239(6)	0.0248(5)	-0.0122(5)	0.0010(5)	-0.0030(5)
O(11)	0.0248(6)	0.0234(5)	0.0306(6)	0.0029(5)	0.0018(5)	-0.0053(5)
O(3)	0.0157(6)	0.0449(7)	0.0320(6)	0.0028(5)	0.0011(5)	-0.0021(5)
O(2)	0.0322(7)	0.0274(6)	0.0218(5)	-0.0012(5)	-0.0110(5)	0.0035(5)
N(5)	0.0202(7)	0.0197(6)	0.0161(6)	-0.0002(5)	0.0011(5)	-0.0011(5)
C(4)	0.0150(7)	0.0150(7)	0.0150(6)	-0.0014(6)	-0.0003(5)	-0.0011(5)
C(8)	0.0192(7)	0.0193(7)	0.0157(7)	0.0032(5)	-0.0015(6)	-0.0001(6)
C(1)	0.0179(7)	0.0204(7)	0.0190(7)	-0.0076(6)	-0.0037(6)	0.0033(6)
C(6)	0.0170(7)	0.0137(6)	0.0138(6)	-0.0025(5)	-0.0019(5)	0.0021(5)
C(12)	0.0183(7)	0.0153(7)	0.0205(7)	-0.0044(5)	0.0000(6)	-0.0012(6)
C(10)	0.0227(8)	0.0162(7)	0.0229(7)	-0.0000(6)	0.0011(7)	0.0008(6)

Inter-atomic distances in Angstroms, with standard deviations in brackets.

O(9)	-	C(8)	1.420(2)
O(9)	-	H(91)	0.843(1)
O(7)	-	C(6)	1.420(2)
O(7)	-	H(71)	0.632(1)
O(13)	-	C(12)	1.424(2)
O(13)	-	H(131)	0.729(1)
O(11)	-	C(10)	1.421(2)
O(11)	-	H(111)	0.603(1)
O(3)	-	C(1)	1.253(2)
O(2)	-	C(1)	1.243(2)
N(5)	-	C(4)	1.477(2)
N(5)	-	H(52)	0.804(1)
N(5)	-	H(51)	0.952(1)
N(5)	-	H(53)	0.710(1)
C(4)	-	C(1)	1.545(2)
C(4)	-	C(6)	1.579(2)
C(4)	-	C(12)	1.550(2)
C(8)	-	C(6)	1.527(2)
C(8)	-	C(10)	1.528(2)
C(8)	-	H(81)	1.002(2)
C(6)	-	H(61)	1.006(1)
C(12)	-	C(10)	1.530(2)
C(12)	-	H(121)	1.000(2)
C(10)	-	H(101)	1.001(2)

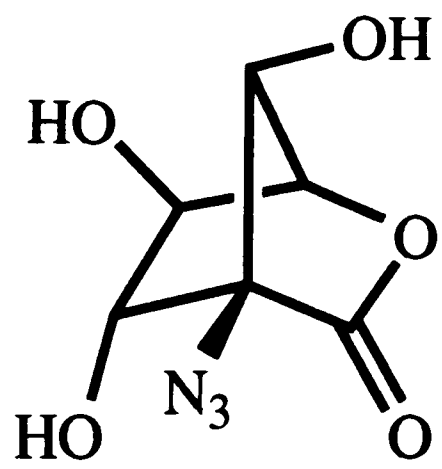
Inter-atomic angles in degrees, with standard deviations in brackets.

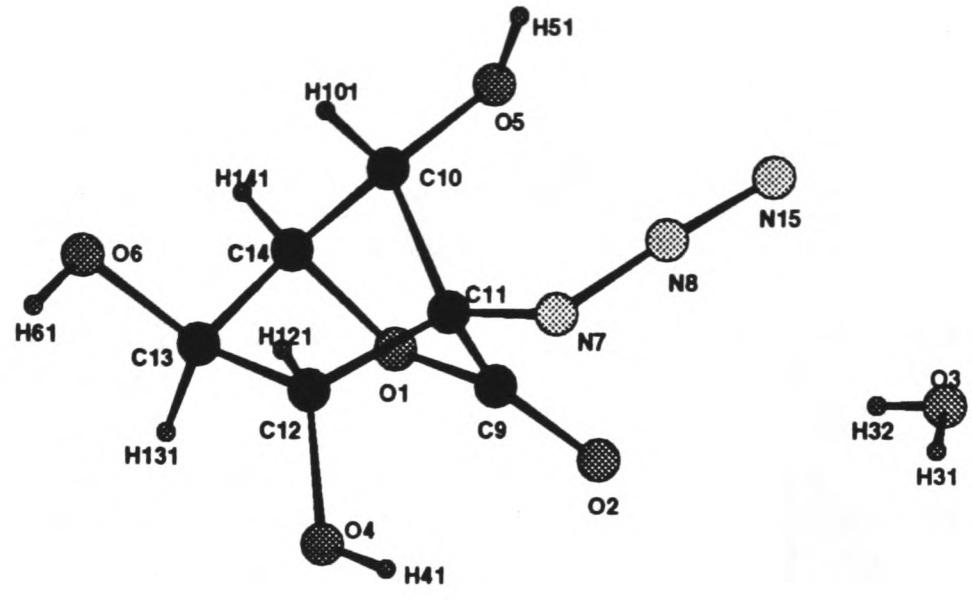
C(8)	-	O(9)	-	H(91)	108.5(1)
C(6)	-	O(7)	-	H(71)	122.3(1)
C(12)	-	O(13)	-	H(131)	112.3(1)
C(10)	-	O(11)	-	H(111)	113.6(2)
C(4)	-	N(5)	-	H(52)	114.4(1)
C(4)	-	N(5)	-	H(51)	111.5(1)
H(52)	-	N(5)	-	H(51)	109.8(1)
C(4)	-	N(5)	-	H(53)	114.1(1)
H(52)	-	N(5)	-	H(53)	101.8(1)
H(51)	-	N(5)	-	H(53)	104.3(1)
N(5)	-	C(4)	-	C(1)	109.2(1)
N(5)	-	C(4)	-	C(6)	110.8(1)
C(1)	-	C(4)	-	C(6)	111.1(1)
N(5)	-	C(4)	-	C(12)	110.6(1)
C(1)	-	C(4)	-	C(12)	110.5(1)
C(6)	-	C(4)	-	C(12)	104.6(1)
O(9)	-	C(8)	-	C(6)	114.4(1)
O(9)	-	C(8)	-	C(10)	114.5(1)
C(6)	-	C(8)	-	C(10)	104.3(1)
O(9)	-	C(8)	-	H(81)	96.8(1)
C(6)	-	C(8)	-	H(81)	114.1(1)
C(10)	-	C(8)	-	H(81)	113.1(1)
O(3)	-	C(1)	-	O(2)	126.0(2)
O(3)	-	C(1)	-	C(4)	116.1(1)
O(2)	-	C(1)	-	C(4)	117.9(1)
O(7)	-	C(6)	-	C(4)	113.6(1)
O(7)	-	C(6)	-	C(8)	110.9(1)
C(4)	-	C(6)	-	C(8)	104.5(1)

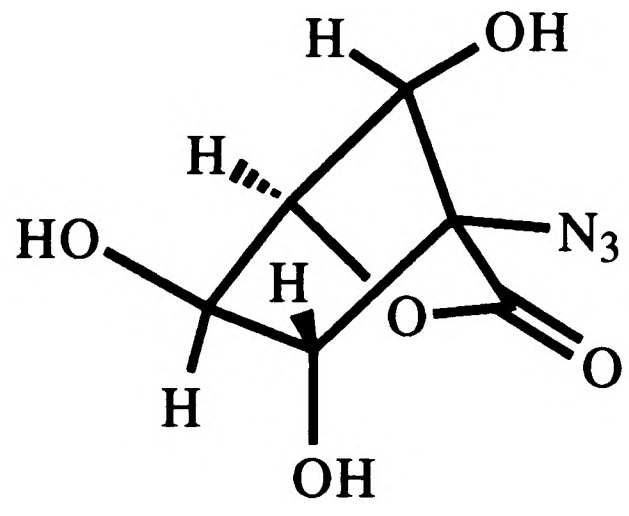
O(7)	- C(6)	- H(61)	100.2(1)
C(4)	- C(6)	- H(61)	113.8(1)
C(8)	- C(6)	- H(61)	114.3(1)
O(13)	- C(12)	- C(4)	112.0(1)
O(13)	- C(12)	- C(10)	114.4(1)
C(4)	- C(12)	- C(10)	104.8(1)
O(13)	- C(12)	- H(121)	99.2(1)
C(4)	- C(12)	- H(121)	115.3(1)
C(10)	- C(12)	- H(121)	111.5(1)
O(11)	- C(10)	- C(8)	111.7(1)
O(11)	- C(10)	- C(12)	113.4(1)
C(8)	- C(10)	- C(12)	100.9(1)
O(11)	- C(10)	- H(101)	99.4(1)
C(8)	- C(10)	- H(101)	116.7(1)
C(12)	- C(10)	- H(101)	115.5(1)

Appendix 4

Crystal Structure Data for
(1*R*,4*S*,5*S*,6*R*,7*R*)-4-Azido-5,6,7-trihydroxy-2-oxa-bicyclo[2.2.1]heptan-3-one (**2.48**).




H51
H101
O5
C10
H141
N15
O6
C14
N8
C11
H61
H121
N7
C13
O1
O3
C12
C9
H32
H131
O2
O4
H31
H41


H
OH
H
HO
N3
H
O
O
H
OH

Crystal Structure Data for (1*R*, 4*S*, 5*S*, 6*R*, 7*R*)-4-Azido-5,6,7-trihydroxy-2-oxa-bicyclo[2.2.1]heptan-3-one (2.48)

Molecular formula	$C_6 H_7 N_3 O_5$
Formula weight	213.15
Crystal system	Primitive orthorhombic
Space Group	P *2₁ 2₁ 2₁*

Unit Cell Parameters:-

	a	b	c	Volume
	6.0782	6.1754	23.285	951.49
Esd's	0.0007	0.009	0.004	

Crystal dimensions (approx mm)	0.25 x 0.30 x 0.75
No. of molecular units in the cell Z	4
Calculated Density (gcm^{-3})	1.62
Reflections for lattice parameters	25
Theta range for lattice parameters(°)	23.60 - 29.75
Linear absorption coeff.(cm^{-1})	11.70

Data Collection Parameters:-

h range			-7, 7
k range			-7, 7
l range			-28, 28
Theta range			0, 72°
Copper radiation		λ(1)	1.5405Å
		λ(2)	1.5443Å
No. of automatic reorientations			0
Temperature (K)			295
No. of intensity standards			4
Decay of standards			2.2%
Total data collected			2666
Number of reflections used			1555
Criterion for observed			$I > 3\sigma(I)$
Absorption	empirical	min	1.16
		max	1.35

Refinement:-

Number of data merged, no Friedel		1713
Merging R-factor, no Friedel		3.36
Maximum number of parameters		174
Ratio of data : parameters		9.8 : 1
Weighting scheme		Chebyshev with 3 terms
Flack enantiopole parameter		0.01
	esd	0.19
Del rho	min	-0.25
	max	0.23
Final R-factor		0.025
Final weighted R-factor		0.031

Atomic coordinates and equivalent isotropic temperature factors

Atom	x/a	y/b	z/c	U(iso)	Occ
O(1)	-0.2314(2)	-0.6296(2)	-0.07882(4)	0.0305	1.0000
O(2)	-0.5849(2)	-0.5677(2)	-0.10079(5)	0.0363	1.0000
O(4)	-0.5311(2)	-1.0452(2)	-0.03276(4)	0.0321	1.0000
O(5)	-0.1425(2)	-0.7310(2)	-0.19291(5)	0.0326	1.0000
O(6)	0.0265(2)	-1.1535(2)	-0.05618(5)	0.0349	1.0000
N(7)	-0.5811(2)	-0.9829(2)	-0.16292(6)	0.0308	1.0000
N(8)	-0.6050(2)	-0.8831(2)	-0.20860(5)	0.0315	1.0000
C(9)	-0.4280(2)	-0.6841(2)	-0.10166(6)	0.0251	1.0000
C(10)	-0.1624(2)	-0.8896(2)	-0.14968(6)	0.0259	1.0000
C(11)	-0.4009(2)	-0.9104(2)	-0.12686(5)	0.0222	1.0000
C(12)	-0.3665(2)	-1.0658(2)	-0.07562(6)	0.0253	1.0000
C(13)	-0.1396(2)	-0.9936(3)	-0.05140(6)	0.0281	1.0000
C(14)	-0.0792(2)	-0.8082(2)	-0.09188(6)	0.0282	1.0000
N(15)	-0.6468(3)	-0.8100(3)	-0.25127(8)	0.0506	1.0000
O(3)	-0.8844(3)	-0.3575(2)	-0.19848(5)	0.0434	1.0000
H(101)	-0.088(3)	-1.031(3)	-0.1594(7)	0.028(4)	1.0000
H(121)	-0.360(3)	-1.211(3)	-0.0909(8)	0.034(5)	1.0000
H(131)	-0.160(3)	-0.941(3)	-0.0123(8)	0.032(5)	1.0000
H(141)	0.077(3)	-0.745(3)	-0.0891(8)	0.037(5)	1.0000
H(61)	-0.008(4)	-1.251(4)	-0.035(1)	0.055(7)	1.0000
H(41)	-0.660(5)	-1.081(5)	-0.047(1)	0.069(8)	1.0000
H(31)	-0.981(5)	-0.489(6)	-0.193(1)	0.088(9)	1.0000
H(32)	-0.790(5)	-0.347(5)	-0.179(1)	0.077(9)	1.0000
H(51)	-0.133(4)	-0.789(5)	-0.225(1)	0.069(8)	1.0000

Anisotropic temperature factors, standard deviations in brackets.

Atom	U(11)	U(22)	U(33)	U(23)	U(13)	U(12)
O(1)	0.0324(5)	0.0280(5)	0.0342(5)	-0.0044(5)	-0.0070(4)	-0.0034(4)
O(2)	0.0351(6)	0.0302(5)	0.0464(6)	-0.0010(5)	0.0014(5)	0.0054(5)
O(4)	0.0268(5)	0.0498(7)	0.0291(5)	0.0117(5)	0.0049(4)	-0.0037(5)
O(5)	0.0440(6)	0.0341(6)	0.0267(5)	0.0068(5)	0.0068(5)	-0.0064(5)
O(6)	0.0272(5)	0.0439(7)	0.0455(6)	0.0202(6)	0.0021(4)	0.0045(5)
N(7)	0.0348(7)	0.0354(6)	0.0281(6)	0.0020(5)	-0.0077(5)	-0.0109(6)
N(8)	0.0301(6)	0.0362(6)	0.0303(6)	-0.0010(6)	-0.0047(5)	-0.0051(5)
C(9)	0.0277(7)	0.0247(6)	0.0234(6)	0.0017(5)	0.0002(5)	-0.0026(5)
C(10)	0.0258(6)	0.0273(7)	0.0267(7)	0.0041(6)	0.0051(5)	-0.0021(6)
C(11)	0.0229(6)	0.0228(6)	0.0217(6)	-0.0012(5)	-0.0006(5)	-0.0037(5)
C(12)	0.0244(7)	0.0247(7)	0.0278(7)	0.0038(5)	0.0013(5)	-0.0024(5)
C(13)	0.0252(7)	0.0352(7)	0.0261(7)	0.0058(6)	-0.0018(5)	0.0002(6)
C(14)	0.0244(7)	0.0291(7)	0.0329(7)	0.0033(5)	-0.0034(6)	-0.0037(6)
N(15)	0.053(1)	0.074(1)	0.0448(9)	0.0188(8)	-0.0202(7)	-0.0135(9)
O(3)	0.0545(8)	0.0484(7)	0.0366(6)	0.0057(6)	-0.0118(6)	-0.0155(7)

Inter-atomic distances (Å), standard deviations in brackets

O(1)	- C(9)	1.351(2)		N(8)	- N(15)	1.121(2)	
O(1)	- C(14)	1.471(2)		C(9)	- C(11)	1.524(2)	
O(2)	- C(9)	1.195(2)		C(10)	- C(11)	1.549(2)	
O(4)	- C(12)	1.419(2)		C(10)	- C(14)	1.523(2)	
O(5)	- C(10)	1.409(2)		C(11)	- C(12)	1.546(2)	
O(6)	- C(13)	1.417(2)		C(12)	- C(13)	1.555(2)	
N(7)	- N(8)	1.238(2)		C(13)	- C(14)	1.528(2)	
N(7)	- C(11)	1.451(2)					

Inter-atomic angles in degrees, standard devations in brackets

C(9)	- O(1)	- C(14)	106.7(1)		N(7)	- C(11)	- C(12)	110.9(1)	
N(8)	- N(7)	- C(11)	115.6(1)		C(9)	- C(11)	- C(12)	106.7(1)	
N(7)	- N(8)	- N(15)	171.6(2)		C(10)	- C(11)	- C(12)	100.9(1)	
O(1)	- C(9)	- O(2)	123.3(1)		O(4)	- C(12)	- C(11)	113.1(1)	
O(1)	- C(9)	- C(11)	106.5(1)		O(4)	- C(12)	- C(13)	110.1(1)	
O(2)	- C(9)	- C(11)	130.1(1)		C(11)	- C(12)	- C(13)	102.8(1)	
O(5)	- C(10)	- C(11)	112.5(1)		O(6)	- C(13)	- C(12)	113.8(1)	
O(5)	- C(10)	- C(14)	111.9(1)		O(6)	- C(13)	- C(14)	107.6(1)	
C(11)	- C(10)	- C(14)	92.0(1)		C(12)	- C(13)	- C(14)	101.8(1)	
N(7)	- C(11)	- C(9)	115.1(1)		O(1)	- C(14)	- C(10)	102.8(1)	
N(7)	- C(11)	- C(10)	122.2(1)		O(1)	- C(14)	- C(13)	106.5(1)	
C(9)	- C(11)	- C(10)	99.0(1)		C(10)	- C(14)	- C(13)	102.6(1)	