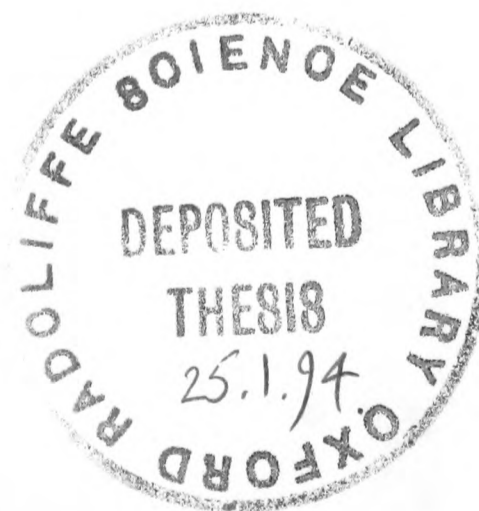


Sugar Lactones in Synthesis

by

Antony J. Fairbanks
Wadham College, Oxford
1993

A thesis submitted in partial fulfilment
of the requirements for the degree of D. Phil.



To my parents for everything.

Sugar Lactones in Synthesis.

Antony J. Fairbanks, Wadham College, Oxford

D. Phil., 1993.

Abstract.

This thesis describes the synthesis of some novel carbohydrate lactones and their uses as starting materials in (a) the syntheses of various polyfunctionalised cyclopentanes, via intramolecular aldol condensations, (b) the synthesis of 1-*epi*hydantocidin, in which the crucial synthetic step involves a novel transformation induced by tetra-*n*-propylammonium perruthenate, and (c) the syntheses of various tetrahydrofurans and tetrahydropyrans.

The syntheses of 3,4-*O*-isopropylidene and cyclohexylidene altrono and allono-1,5-lactones via Kiliani ascension of protected forms of D-ribose are described. The stereochemistry of the major reaction product, which was identified as 2,3-*O*-isopropylidene-D-altrono-1,5-lactone was confirmed by X-ray diffraction. Introduction of azide and iodide at C-2 is achieved via silyl protection of C-6 and formation of the 2-*O*-triflates. Nucleophilic displacement with azide or iodide produces mixtures of C-2 epimers. Desilylation is readily achieved by treatment with acetic acid to yield azido and iodo alcohols. Attempted oxidation of C-6 to an aldehyde functionality, in an attempt to effect cyclopentane formation via intramolecular aldol condensation of C-2 onto C-6 failed. Treatment of altrono and allono azido alcohols with tetrapropylammonium perruthenate unexpectedly results in the formation of a [2.2.2.] bicyclic hemiaminal, whose structure was confirmed by X-ray diffraction. Conversion of the amine functionality to a urea is effected by treatment with potassium cyanate. Cyclisation of the urea functionality onto the lactone carbonyl and subsequent deprotection effects the synthesis of 1-*epi*hydantocidin. Investigations into acid catalysed epimerisation of the spiro centre in both hydantocidin and 1-*epi*hydantocidin are described. Potassium carbonate induced ring contraction of 6-*O*-silyl altrono- and allono- 1,5-lactone-2-*O*-triflates yields tetrahydrofurans, the stereochemistry of which is confirmed by conversion to symmetric materials. Intramolecular Mitsunobu cyclisation of OH-2 onto C-6 of altrono-1,5-lactones effects tetrahydropyran formation.

Inversion of C-5 of the known 3,4:5,6-di-*O*-isopropylidene-D-glycero-D-galacto-heptono-1,5-lactone is described. Confirmation of product stereochemistry is achieved by conversion to 2,3-*O*-isopropylidene-L-altrono-1,5-lactone. Introduction of iodide and azide at C-2 is achieved via the formation of the 2-*O*-triflate. Selective deprotection of the 5,6 isopropylidene and subsequent periodate cleavage yields aldehyde lactones which undergo potassium fluoride induced intramolecular aldol cyclisation, to yield bicyclic [2.2.1.] azido and iodo carbocycles.

Sodium azide induced intramolecular aldol cyclisation of 5-azido-5-deoxy-3,4-*O*-isopropylidene-L-galacturono-2,6-lactone, which produces two [2.2.1.] bicyclic azido carbocycles, is described. The second azido carbocycle, which is found to be the major reaction product, readily undergoes a retro aldol reaction, resulting in the formation of a third azido carbocycle, the structure of which was confirmed by X-ray diffraction. Investigations into the equilibration of these three bicyclic [2.2.1.] azido carbocycles under the reaction conditions employed to effect their formation are described. Various ring opening reactions of the second and third materials, and their uses in the syntheses of a novel amino pentol, two novel tetrahydroxy cyclopentane spirohydantoins and two novel cyclopentane amino acids are described. The structure of the asymmetric amino acid was confirmed by X-ray diffraction. Under basic reaction conditions retro aldol equilibration is seen to compete effectively with ring opening.

ACKNOWLEDGEMENTS.

First and foremost, I would like to thank my supervisor Dr George Fleet, for his invaluable help and advice, constant support and ineffable enthusiasm over the past four years. I have enjoyed working with him immensely, and I shall leave the Perkin Lab with a twinge of sadness.

I would also like to thank Dr John Brown for all his help and advice, both during my undergraduate days and subsequently, and for pointing me on the right road towards the D.P.

A large amount of thanks must also go to all the technical staff of the D.P. for all of their help over the past four years, especially Val for all the micros, the Robins for the mass specs and Elizabeth for wonderful nmr spectra and dedication beyond the call of duty. Other 'official thanks' to Annabel, Ken, Joe, Ben and Andy for their proof-reading, I couldn't have done this without their help.

A general thanks to all the good friends I've made over the past four years. In particular to Dave for a great time in the States (especially lending me a dollar when I needed one) and for generally leading me astray (invariably to HH then St John's); Simon Leps for being such a good mate over the past seven years, driving even faster than Ken and Cropredy '93; to Jong, one of the nicest guys I've ever met, for being a miracle worker; Ben 'Skipper' Skead for great advice, introducing me to Richard Thompson and for forcing me to stop being so apathetic (remember the laundrette story); Ken 'sleepy boy' Hsia for tennis, badminton, drinking too quickly, superb driving (except where car transporters are concerned), being cool and explaining why the ERM cocked up; Mike for finishing my game of Space Rogue before I did and for being the master of the 'application'; Ben Davis for changing my outlook on the universe and many interesting discussions on 'matters of high importance'-perhaps if Nottingham Forest had scored that often last season they wouldn't have got relegated; Jon 'Nigel Havers' Burton for singing and nice fat boys after dinner; Jeremy for introducing me to Donaldson and Covent Garden Opera House; Helen Taylor for the

crystal structures and for telling me to 'Go away and recrystallise it properly!' and Simon 'I'm no fool' Mantell for putting me in my place; Joe for being a nice guy with a nice house and for putting up with frequent use of the lounge; Andy for advice and collaboration on matters chemical, not to mention amazing colour changes after two sips of beer; Sally for having excellent taste, punting at 4am on May morning and all the guitar strings; Lucy for the coolest Birthday card I've ever received; Sue for many a couch session (strictly from the psychiatric point of view); Tig for the France trip; Russ, Nigel, Ian, Francis and Philippa for help and advice when I was a mere novice Part II; to Ivor for all the liquid refreshment; to all the members of the glorious Wadham 2nd footy team (Cuppers winners 1991) especially Jaffa (you're not singing anymore), Steve Baxter and Southy (who will no doubt be running the country before long); to other special Wadhamites: Mac and Colin for longstanding service at the bar; to Tabby and Spencer / Theo / whoever...; to Steve, Jerry and all of 8 Essex St for putting up with sharing a house with me; and finally with affection to Rosie, for trips to Alton Towers, a memorable little soiree in the Gloucester Arms, a lift home, a stay in Sheffield and for being 'such a tease'.

CONTENTS

List of Abbreviations	i
Note concerning nomenclature	iii
CHAPTER 1 General Introduction	
General Introduction	1
References	21
CHAPTER 2 Synthesis and Investigations of Altrono-1,5-lactones	
Introduction	26
Results and Discussion	30
Experimental	55
References	92
CHAPTER 3 Synthesis and Investigations of D-glycero-L-altrono-1,5-lactones	
Introduction	94
Results and Discussion	98
Experimental	111
References	132
CHAPTER 4 Further Investigations of the Bicyclic Azido Carbocycles derived from D-glycero-D-talo and D-glycero-D-galacto-heptono-1,5-lactones	
Introduction	133
Results and Discussion	136
Experimental	153
References	174
APPENDIX 1	i
APPENDIX 2	i
APPENDIX 3	i
APPENDIX 4	i

ABBREVIATIONS

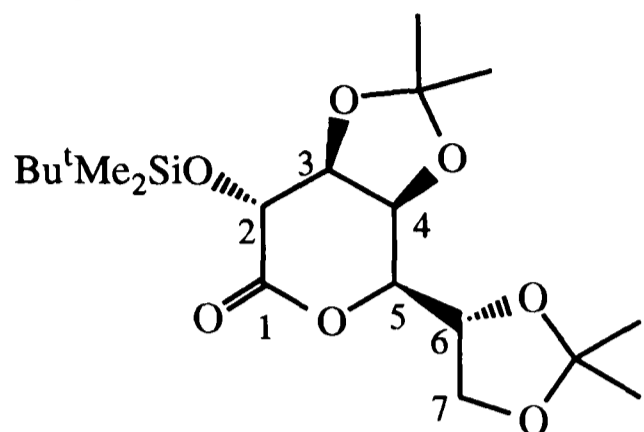
The following abbreviations are used in this thesis:-

Ac	acetyl
Bn	benzyl
br	broad
Bu ^t	<i>tert</i> -butyl
Cbz	benzyloxycarbonyl
CMAW	chloroform : methanol : acetic acid : water
18-crown-6	1,4,7,10,13,16-hexaoxacyclooctadecane
CSA	camphorsulphonic acid
d	doublet
dd	double doublet
DEAD	diethyl azodicarboxylate
DMAP	4-(<i>N,N</i> -dimethylamino)-pyridine
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulphoxide
Et	ethyl
<i>i</i> Pr	isopropyl
IR	infrared
m	multiplet
Me	methyl
NBS	<i>N</i> -bromosuccinimide
NMO	<i>N</i> -methylmorpholine- <i>N</i> -oxide
nmr	nuclear magnetic resonance
<i>n</i> Pr	<i>n</i> -propyl
n.O.e.	nuclear Overhauser effect
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate

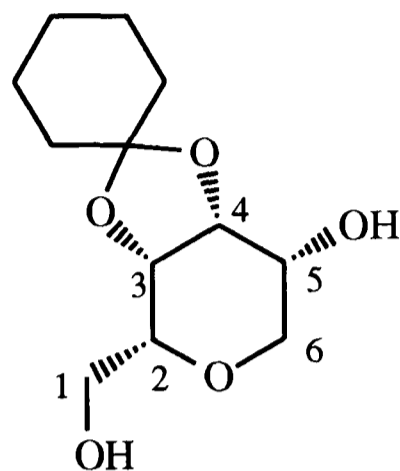
Ph	phenyl
Phth	phthalimide
PMB	<i>para</i> -methoxybenzyl
py	pyridine
q	quartet
s	singlet
t	triplet
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBDMS	<i>tert</i> -butyldimethylsilyl
TFA	trifluoroacetic acid
Tf	trifluoromethanesulphonyl
THF	tetrahydrofuran
THP	tetrahydropyran
t.l.c.	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetra- <i>n</i> -propylammonium perruthenate
Ts	<i>para</i> -toluenesulphonyl
triflate	trifluoromethanesulphonate

Note concerning nomenclature.

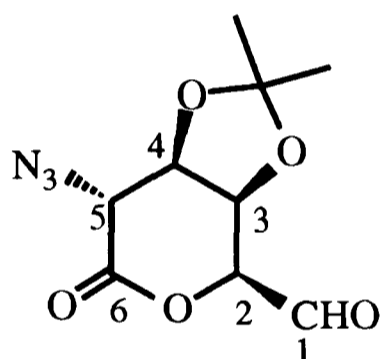
Spectroscopic data are assigned according to the numbering systems shown for the examples below.



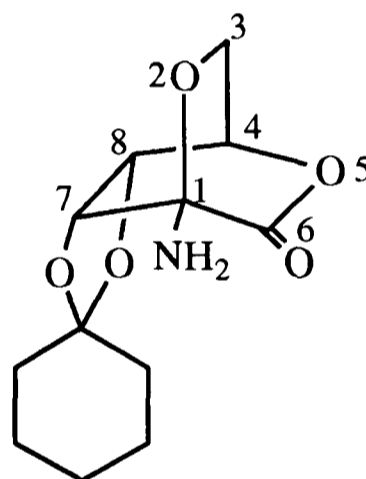
2-*O*-*tert*-Butyldimethylsilyl-3,4:6,7-di-*O*-isopropylidene-D-glycero-D-galactono-1,5-lactone



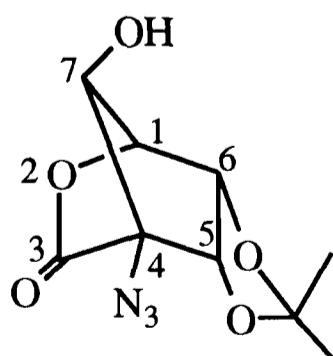
2,6-Anhydro-3,4-*O*-cyclohexylidene-D-altritol



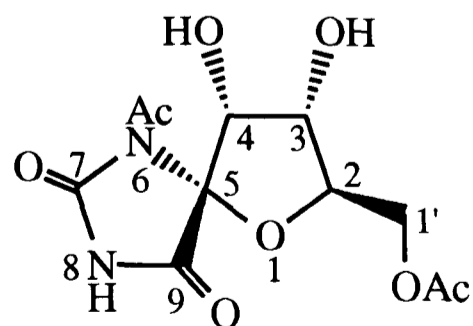
5-Azido-5-deoxy-3,4-*O*-isopropylidene-L-galacturono-2,6-lactone



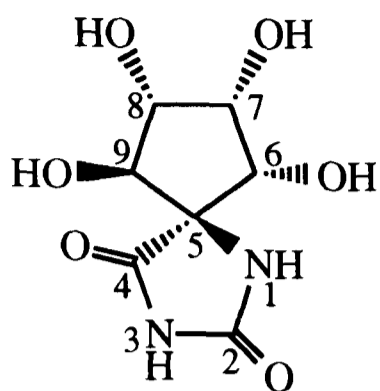
(1*S*,4*R*,7*R*,8*S*)-1-Amino-7,8-*O*-cyclohexylidene-7,8-dihydroxy-2,5-dioxa-bicyclo[2.2.2.]octan-6-one



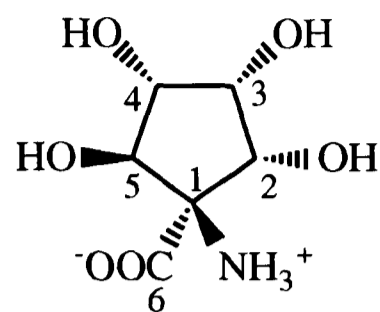
(1*S*,4*S*,5*R*,6*R*,7*R*)-4-Azido-5,6-*O*-isopropylidene-2-oxa-5,6,7-trihydroxybicyclo[2.2.1.]heptan-3-one



(2*R*,3*S*,4*R*,5*R*)-2-Acetoxymethyl-6-*N*-acetyl-6,8-diaza-3,4-dihydroxy-1-oxaspiro[4.4.]nonane-7,9-dione



(5S,6R,7R,8S,9R)-1,3-Diaza-6,7,8,9-tetrahydroxy-spiro[4.4.]nonane-2,4-dione

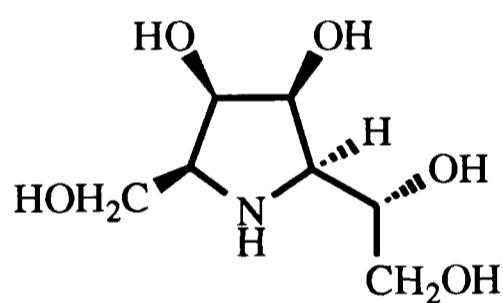


(1S,2R,3R,4S,5R)-1-Amino-2,3,4,5-tetrahydroxy-cyclopentane carboxylic acid

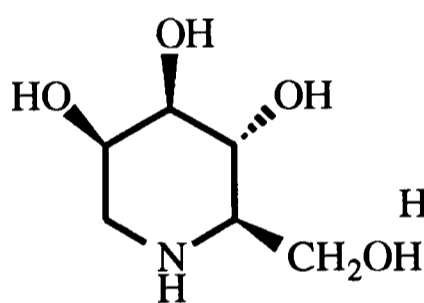
CHAPTER 1

General Introduction.

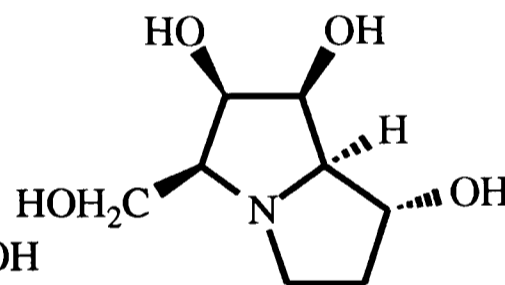
During recent years sugars have been used as starting materials for the synthesis of a wide range of natural products and biologically active analogues.¹ In particular, sugar lactones have been used in the syntheses of a large number of biologically interesting compounds. These include polyhydroxylated nitrogen heterocycles; e.g. pyrrolidines such as α -homoDIM (1.1),² piperidines such as deoxymannojirimicin (1.2),³ pyrrolizidines such as the alexine (1.3)⁴ and indolizidines such as 6-epicastanospermine (1.4),⁵ oxetanes such as norepioxetanocin (1.5)⁶ and polyfunctionalised tetrahydrofurans such as (+)-muscarine (1.6).⁷



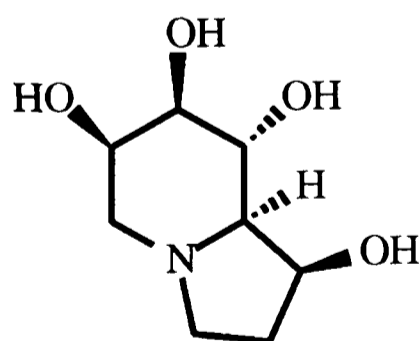
(1.1)



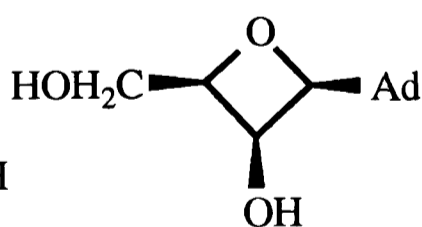
(1.2)



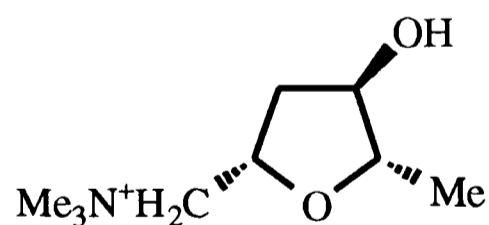
(1.3)



(1.4)



(1.5)



(1.6)

Major attractions in the use of carbohydrate lactones as starting materials are the absence of anomeric substituents and the ease of protection / deprotection of free hydroxyl groups. Novel carbohydrate lactones are readily synthesised via the Kiliani ascension of suitably protected sugar precursors. The products of these reactions can contain up to seven adjacent functional groups and five contiguous chiral centres and

have been demonstrated to be extremely versatile chirons for the synthesis of a variety of complex targets.

The two main objectives of the work detailed in this thesis were as follows:-

(1) The synthesis of some novel carbohydrate lactones, from either protected aldoses via Kiliani ascension, or other readily available lactones via selective inversion of hydroxyl groups.

(2) Use of these materials in the syntheses of several potentially biologically active compounds.

These synthetic targets can be divided up into two broad classes:

- (A) Polyfunctionalised Cyclopentanes
- (B) Polyhydroxylated Spirohydantoin.

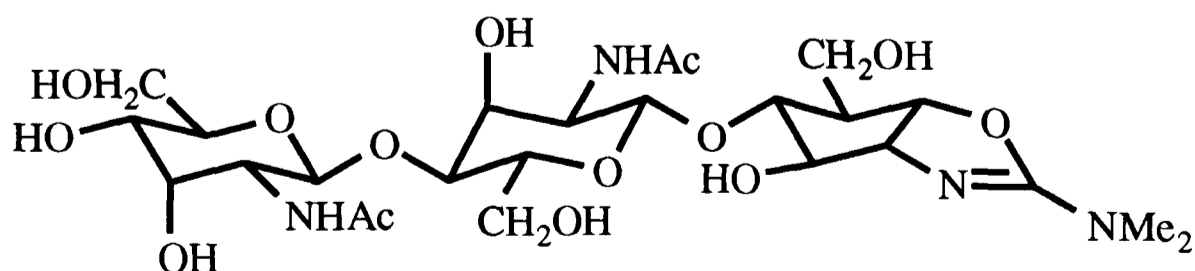
Each of these classes will now be discussed in turn, with reference to:-

- (a) Potential biological activity
- (b) Previous synthetic approaches.

(A) Polyhydroxylated Cyclopentanes.

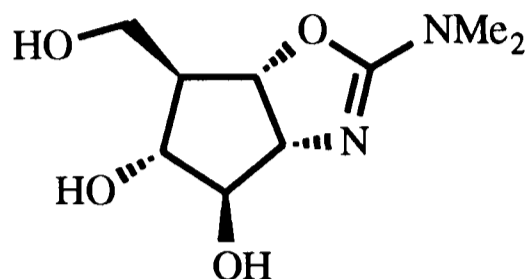
(a) Biological Activity.

The importance of chitin as one of the main components of insect cuticles⁸ and fungal cell walls⁹ generated an interest in the isolation and synthesis of compounds that may obstruct its biosynthesis. A screen for chitinase inhibitors resulted in the isolation of the novel pseudotrisaccharide allosamidin (1.7) in 1986.¹⁰



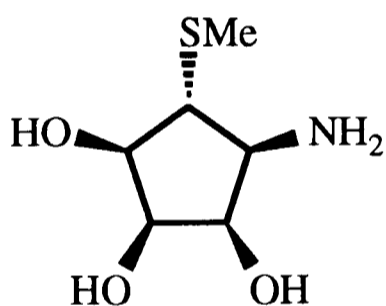
Allosamidin (1.7)

It was found to be a potent inhibitor of silkworm larvae chitinase¹¹ and also a potent inhibitor of the fungus *Candida albicans*.¹² Its structure was found to consist of two *N*-acetyl-allosamine units and the novel aminohydroxysubstituted cyclopentane allosamizoline (1.8).¹³

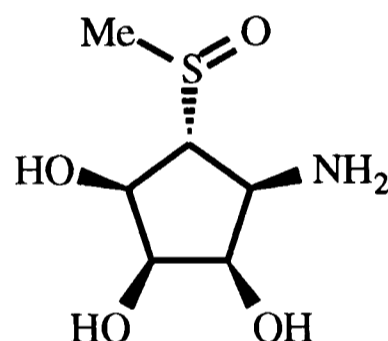


Allosamizoline (1.8)

This initial report opened the way to the recognition that aminohydroxy substituted cyclopentanes can have specific and powerful inhibitory activity against glycosidases that normally accept pyranoside substrates.



Mannostatin A (1.9)

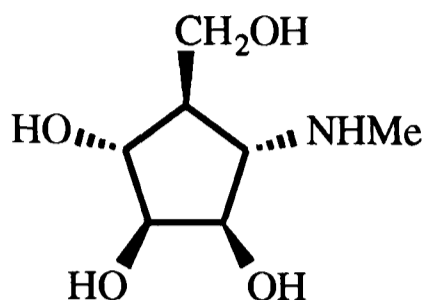


Mannostatin B (1.10)

In 1989 mannostatin A (1.9) and B (1.10) were isolated from the microorganism *Streptoverticillium verticulus var quintum* ME3-AG3.¹⁴ They are highly specific competitive inhibitors of jack bean, mung bean and rat liver lysosomal α -mannosidases and also of the glycoprotein processing enzyme mannosidase II.¹⁵ The structure and absolute stereochemistry were determined via crystallographic analysis of mannostatin B tetraacetate.¹⁶ To date they represent the only naturally occurring examples of carbocyclic mannosidase inhibitors.

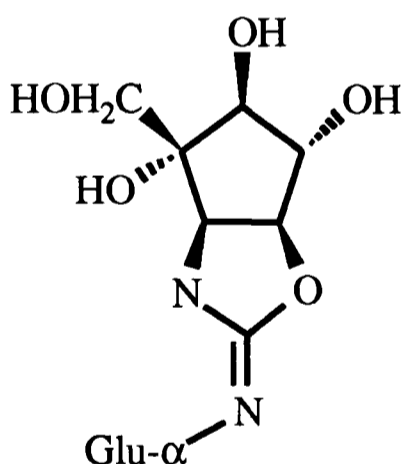
Another example of an aminohydroxycyclopentane that has been found to act as a potent α -mannosidase inhibitor is provided by the synthetic carbocyclic amine (1.11). This was first reported in 1990 by Farr and coworkers¹⁷ and was synthesised as a

result of molecular modelling studies during the course of a search for potential mannosidase inhibitors.



Merrel Dow cyclopentylamine (1.11)

The final example of a naturally occurring carbocyclic glycosidase inhibitor is provided by the pseudodisaccharide trehazolin / trehalostatin (1.12). These were isolated independently by two research groups during the course of screening for inhibitors of trehalase from the culture broths of *Micromonospora SANK 62390*¹⁸ and *Amycolatopsis trehalostatica* respectively.¹⁹



Trehazolin / trehalostatin (1.12)

Initially the two research groups assigned slightly different structures to their compounds but they have recently been shown to possess the same structure, the absolute configuration of which has been confirmed by total synthesis and chemical correlation with L-aspartic acid.²⁰ It was found to be a potent specific inhibitor of blowfly, silkworm and porcine trehalases.¹⁹

Much interest has been focused on the potential uses of glycosidase inhibitors; such as in the study of diabetes²¹, cancer²², and as antiviral agents.²³

In particular mannosidase inhibitors have been promulgated as potential anti-HIV agents.²⁴ Inhibition of viral infection is thought to arise from disruption of oligosaccharide processing of viral coat glycoproteins such as glycoprotein 120 (gp 120). Incomplete glycoprotein processing results in loss of recognition for the CD-4 receptor of the target white blood cell with consequential reduction in virus infectivity and inhibition of viral replication. Inhibitors of chitinases have potential uses as insect growth regulators²⁵ or as anti-fungal agents and inhibitors of trehalases as insecticides or insect antifeedants.²⁶

The four aminohydroxycyclopentanes detailed above are the most potent and specific known inhibitors of their respective enzymes; the superiority of these five membered inhibitors over six membered analogues (which more closely resemble the enzymatic substrates) is notable.

(b) Previous Synthetic Approaches.

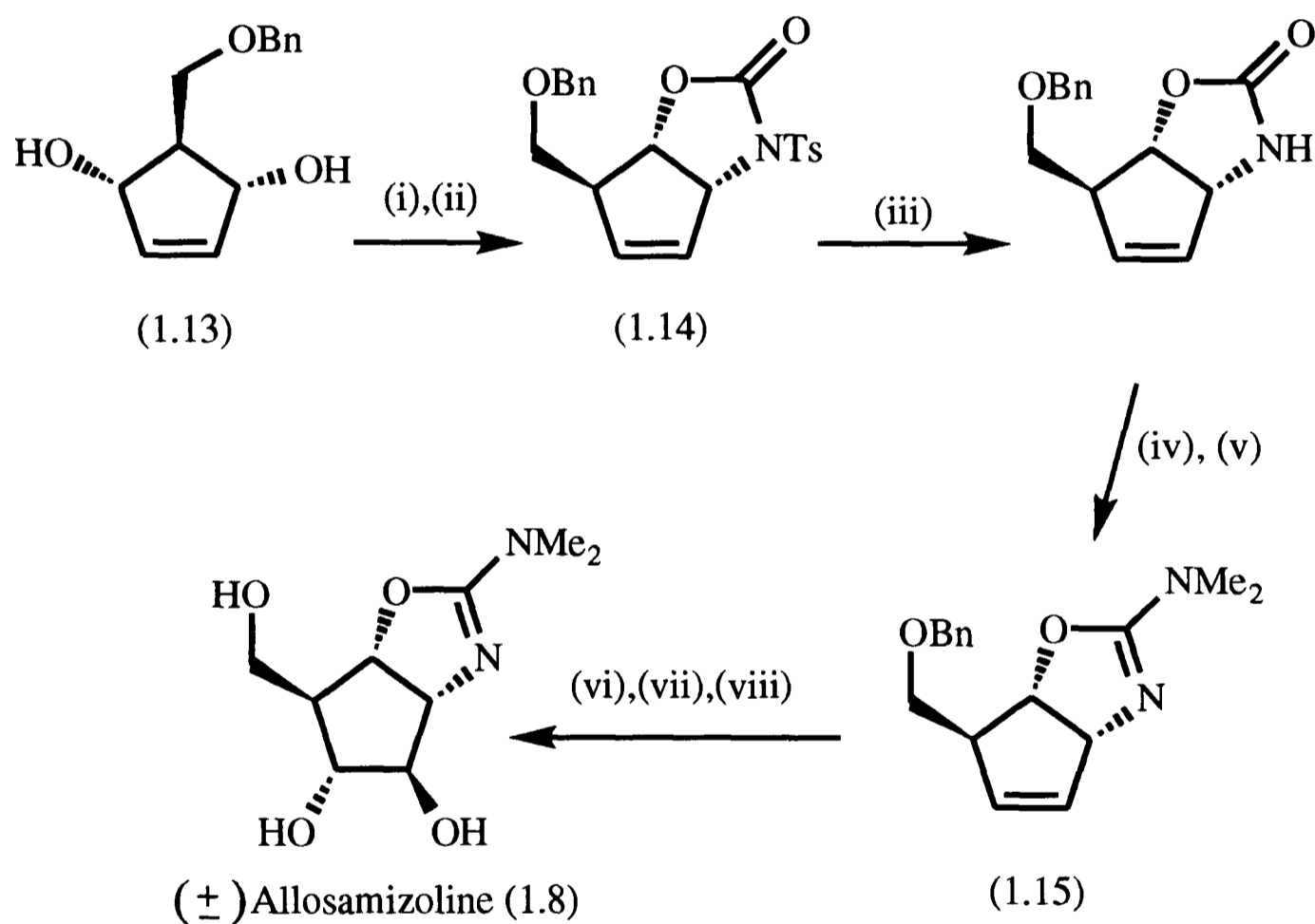
These can be divided into three broad categories:-

- (i) Previous syntheses from non-carbohydrate starting materials.
- (ii) Previous syntheses from carbohydrates.
- (iii) A novel intramolecular aldol approach to cyclopentanes from sugar lactones.

(i) Previous syntheses from non-carbohydrate starting materials.

The high density and juxtaposition of functionality of the amino hydroxycyclopentanes described above poses a difficult synthetic challenge to the chemist. Syntheses from non-carbohydrate starting materials require the stereoselective introduction of up to five adjacent functional groups.

Trost and co-workers have recently published a synthesis of racemic allosamizoline²⁷ starting from the known cyclopentenediol (1.13)²⁸ which can be derived in one operation from cyclopentadiene. The general strategy adopted involved application of palladium (0) catalysis to the formation of the oxazolidinone (1.14). Conversion of this material to the oxazolidene (1.15) and subsequent epoxidation / hydrolysis provided access to allosamizoline (1.8) (Scheme 1.1) as well as the diastereomeric *trans*-3,4-diol. The intermediate oxazolidene (1.15) was also used as a divergent intermediate for the synthesis of the *cis*-3,4-epimers of allosamizoline via *cis* dihydroxylation with osmium tetroxide.

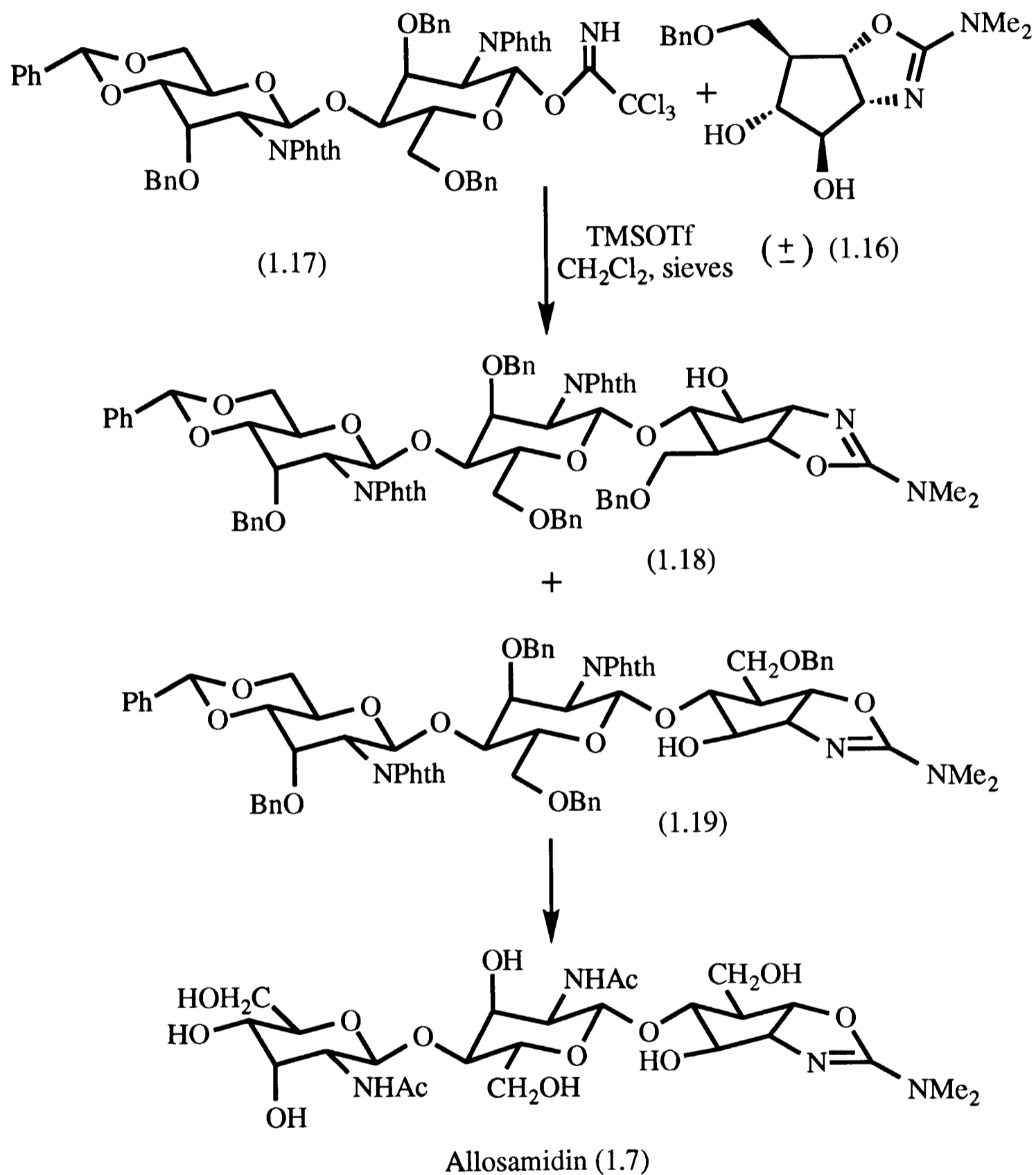


(i) 2 eq. TsNCO (ii) 1.5 mol% Pd[(O*i*Pr)₃P]₄ (iii) Na, naphthalene
 (iv) MeOTf (v) MeNH₂ (vi) 5.4M CF₃CO₃H, TFA, 0°C (vii) 10% aq TFA, 40°C (viii) H₂, Pd

Scheme 1.1

Coupling of racemic 6-*O*-benzylallosamizoline (1.16), synthesised by the above route, with the disaccharide (1.17) occurred with chemoselective glycosylation at the

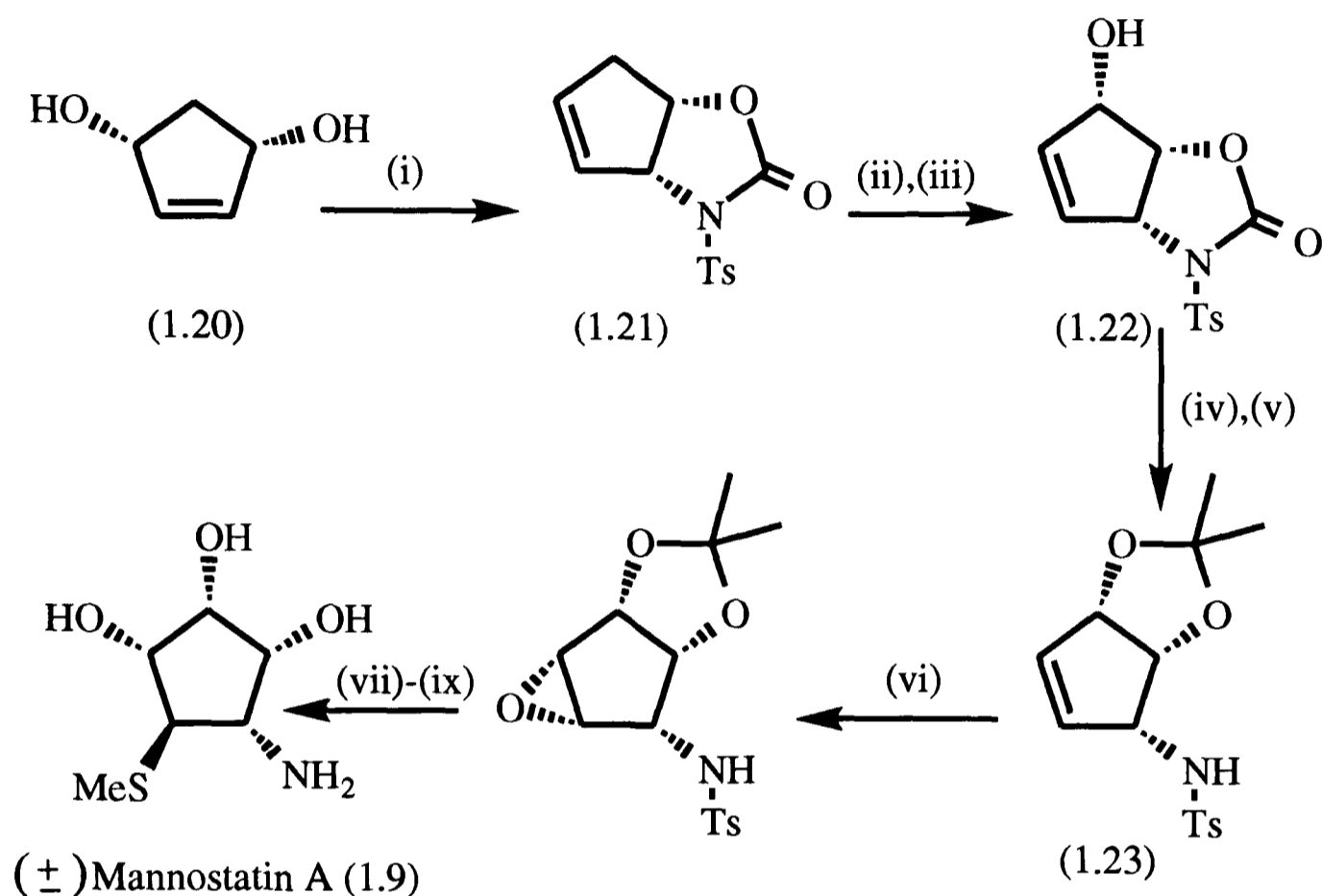
4-*O* position to give a mixture of pseudotrisaccharides (1.18) and (1.19). Separation, deprotection and acetylation of the correct isomer (1.19) provided the first total synthesis of allosamidin (1.7)²⁹ (Scheme 1.2).



Scheme 1.2

A similar strategy was adopted for the synthesis of mannostatin A³⁰ (1.9) starting from the cyclopentenediol (1.20),³¹ again derived from cyclopentadiene. Treatment with tosyl isocyanate under palladium (0) catalysis yielded the oxazolidinone (1.21).

Allylic oxidation followed by stereoselective reduction yielded the allylic alcohol (1.22) which was converted to the acetonide (1.23). Stereoselective epoxidation followed by regioselective opening by treatment with lithium thiomethoxide and deprotection yielded racemic mannostatin A (1.9).



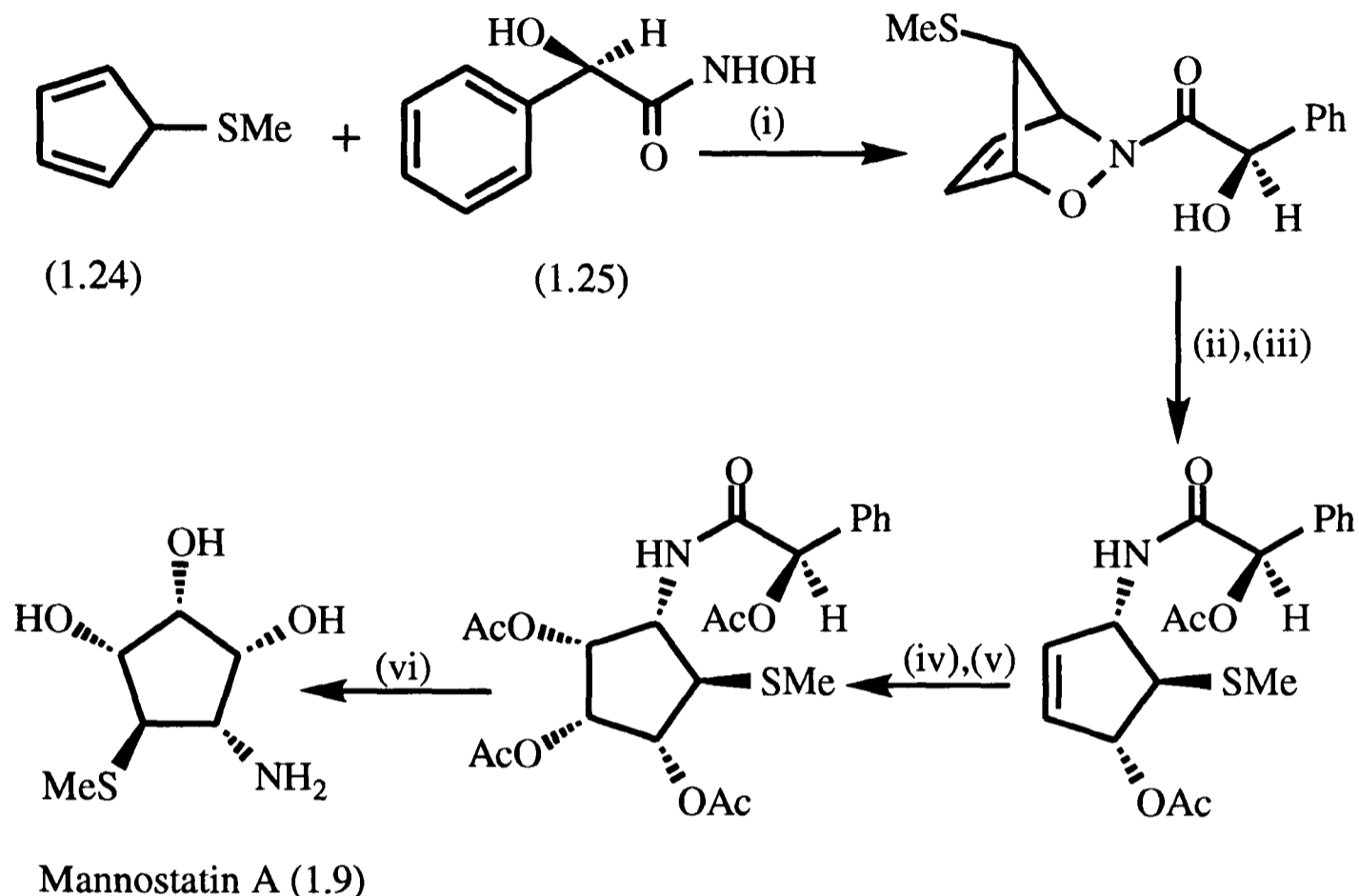
(i) 2 eq. TsNCO then 1.8 mol% Pd[(OiPr)₃P]₄ (ii) SeO₂ then Dess-Martin periodinane (iii) NaBH₄, CeCl₃ (iv) K₂CO₃ in MeOH / water (v) acetone, 2,2-dimethoxypropane, CSA (vi) CF₃CO₃H, Na₂HPO₄, CH₂Cl₂ (vii) MeSLi, THF (viii) Na, NH₃ (ix) 60% aq TFA.

Scheme 1.3

Conversion of both of these syntheses into asymmetric ones has been recently achieved via the use of chiral Pd(0) complexes.³²

Another synthesis of mannostatin A, published by Ganem,³³ is outlined in Scheme 1.4. Again the starting material is cyclopentadiene but this time the key synthetic step involves the asymmetric cycloaddition of methylthiocyclopentadiene (1.24) with the chiral acyl-nitroso compound derived *in situ* from the periodate oxidation of (R)-mandelohydroxamic acid (1.25). Reductive cleavage of the N-O bond followed by

diastereoselective *cis* dihydroxylation, achieved stoichiometrically with osmium tetroxide, furnished mannostatin A (1.9) in good yield.



(i) Bu_4NIO_4 , MeOH (ii) Al(Hg) (iii) Ac_2O , py, DMAP (iv) OsO_4 , py
 (v) Ac_2O , py, DMAP (vi) HCl, MeOH

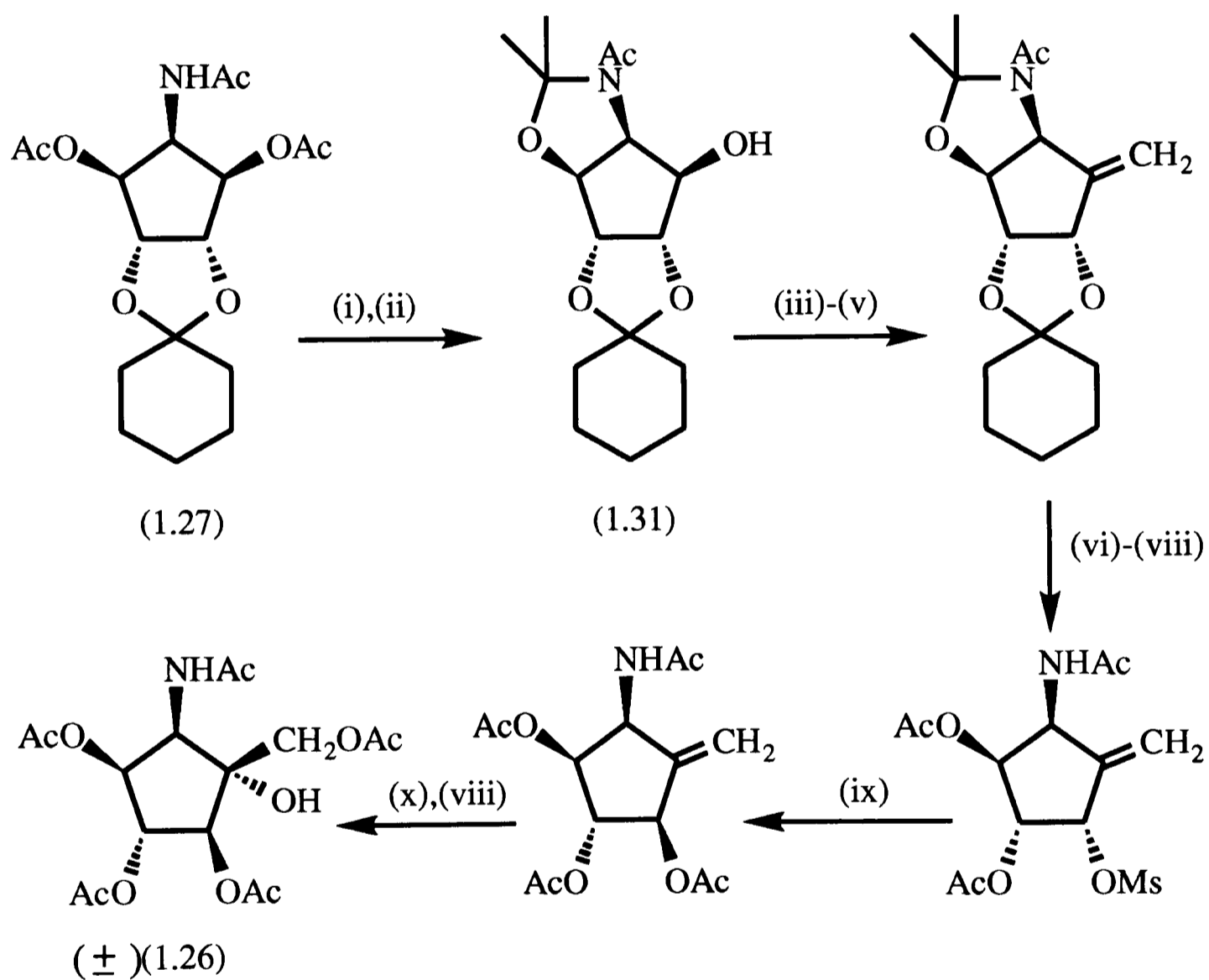
Scheme 1.4

(ii) Previous syntheses from carbohydrate starting materials.

Carbohydrates seem obvious precursors for the synthesis of polyhydroxylated aminocyclopentanes. The chirality and dense functionality of the starting material should facilitate stereoselective synthesis of such demanding synthetic targets. Several different strategies for the formation of a cyclopentane ring from a carbohydrate precursor are available including intramolecular radical cyclisations,³⁴ intramolecular cycloadditions,^{17,35} intramolecular Wittig³⁶ and aldol³⁷ reactions and nitro anion condensations.³⁸

Ogawa and co-workers have recently published the first total synthesis of trehazolin / trehalostatin.²⁰ The aminocyclitol portion was first synthesised³⁹ as its pentaacetate

(1.26) in a racemic form as shown in Scheme 1.5. The starting material for this sequence was the aminocyclopentane (1.27) which was derived from the minor product (5-10% yield) obtained from the base catalysed reaction of nitromethane with the dialdehyde derived from 1,2-*O*-cyclohexylidene-myoinositol.⁴⁰ The major product from this reaction is epimeric at the position of the nitrogen substituent and was used as the starting material for a racemic synthesis of mannostatin A by the same research group.⁴¹

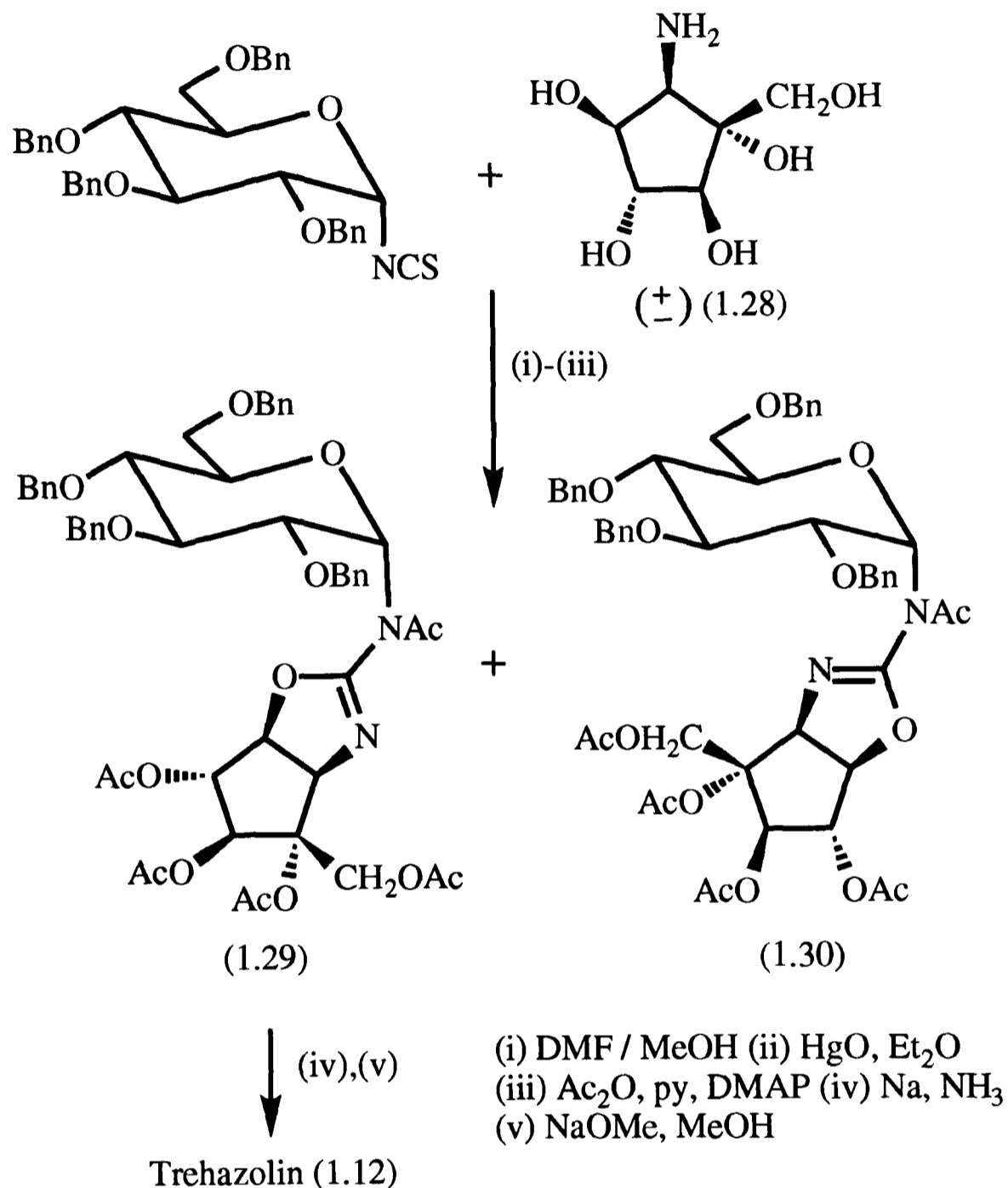


(i) NaOMe, MeOH (ii) 2,2-dimethoxypropane, TsOH, DMF (iii) PCC, CH₂Cl₂
 (iv) CH₂N₂, DMSO / Et₂O (v) P(OMe)₃ (vi) 80% aq. AcOH (vii) MsCl, py
 (viii) Ac₂O, py (ix) NaOAc, DMF (x) OsO₄, NMO, 80% aq. acetone

Scheme 1.5

Coupling of the racemic aminocyclitol (1.28) to α -glucose through an oxazoline ring produced a mixture of diastereomers that were separated as their pentaacetates (1.29)

and (1.30). Deprotection of one of these yielded trehazolin (1.12) as shown in Scheme 1.6.



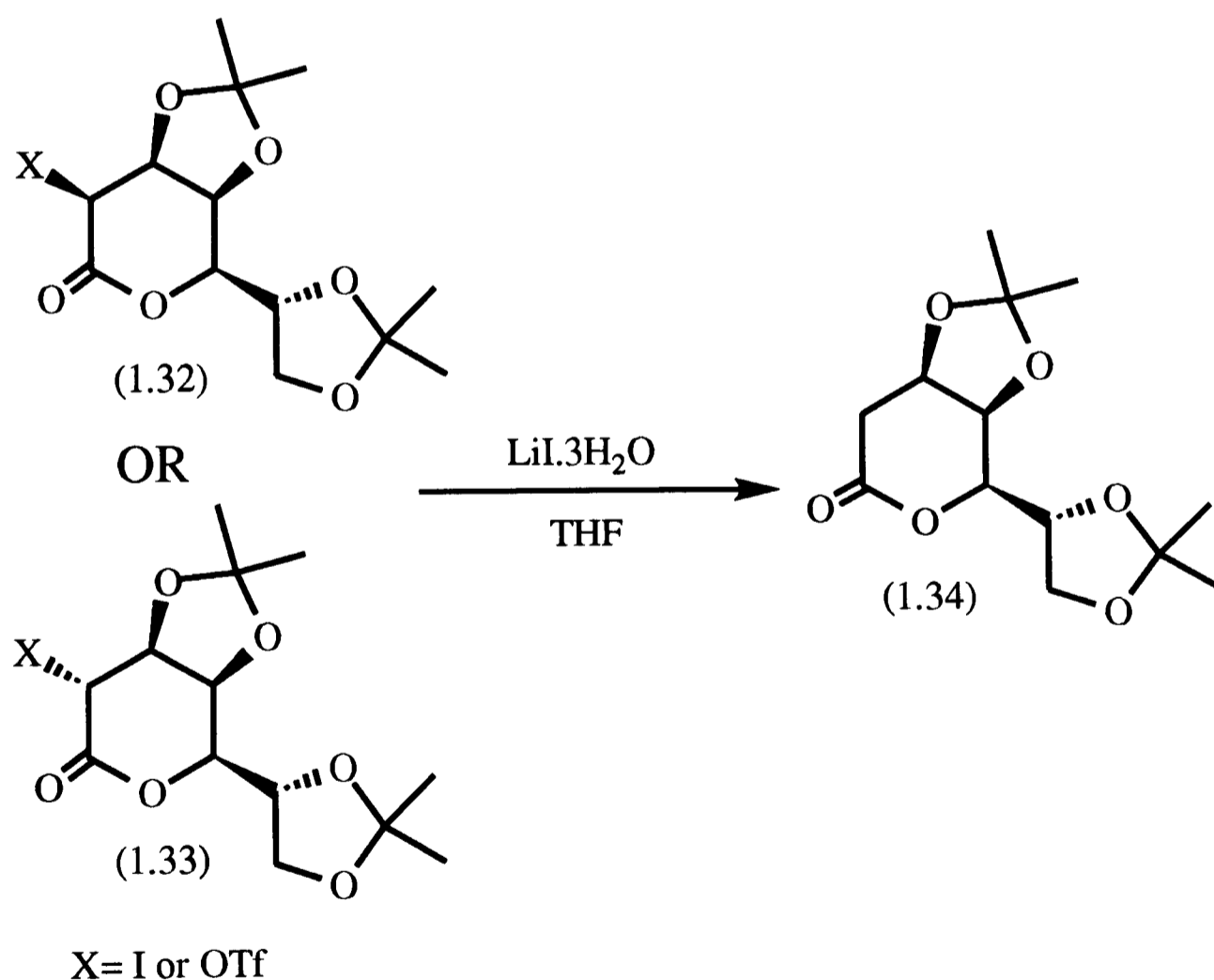
Scheme 1.6

The absolute configuration of the product was determined by optical resolution of the intermediate alcohol (1.31) (see Scheme 1.5) as its *O*-acetylmandelate and assignment of stereochemistry by chemical correlation with L-aspartic acid.²⁰ Trehazolin could be synthesised by coupling of optically active (1.28), derived from the correct enantiomer of the intermediate alcohol (1.31), thus establishing the absolute configuration of the natural product.

(iii) A novel intramolecular aldol approach to cyclopentanes from sugar lactones.

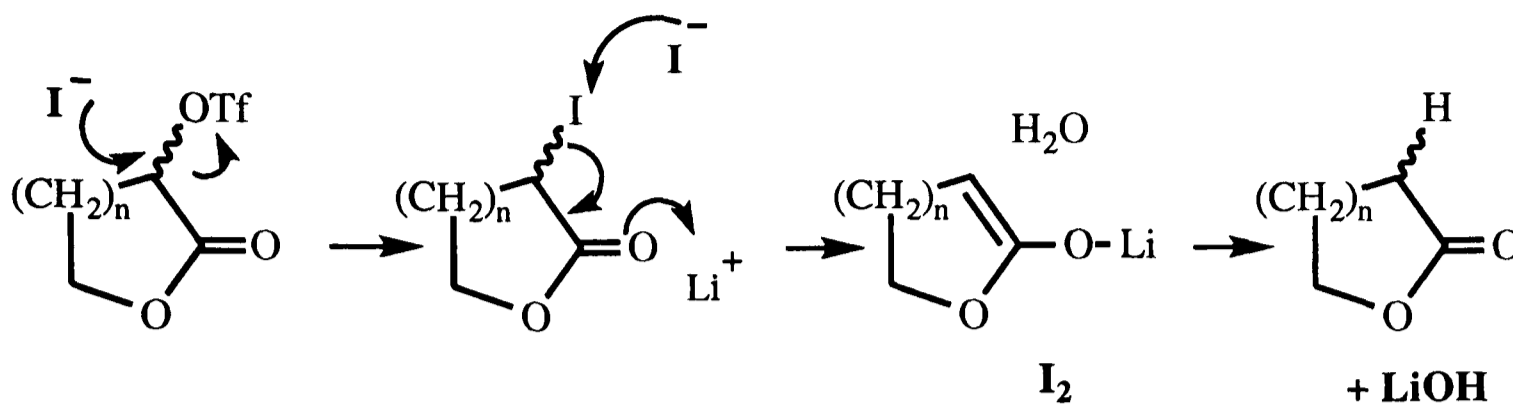
Aldol reactions have been relatively rarely used in the syntheses of cyclopentanes from carbohydrates. The Ferrier cyclisation,⁴² a widely used aldol reaction for the synthesis of 3-hydroxycyclohexanes from carbohydrates, cannot be used for the synthesis of cyclopentane counterparts.⁴³ These observations are consistent with Baldwin's rules of ring closure.⁴⁴

During the course of investigations into the displacement of α -triflates of carbohydrate lactones it was discovered that treatment of either the α -triflates or α -iodides of the δ -lactones (1.32) and (1.33) with lithium iodide trihydrate produced high yields of the corresponding reduced compound (1.34) (Scheme 1.7).⁴⁵



Scheme 1.7

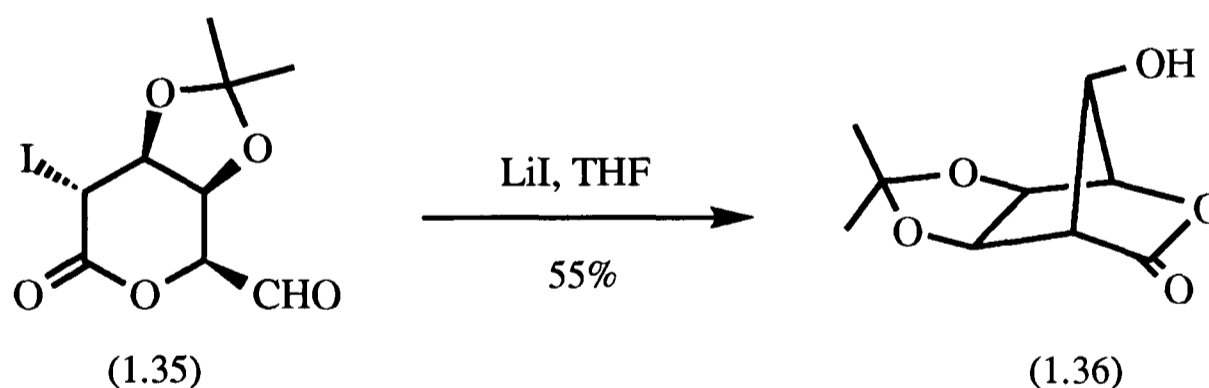
The proposed mechanism for this reaction involves initial $\text{S}_{\text{N}}2$ displacement of the triflate by iodide and subsequent abstraction of iodine via further attack by iodide to produce a lithium enolate which is then protonated by water (Scheme 1.8).



Scheme 1.8

This reaction has been shown to be quite general and has been used in the synthesis of a large number of 2-deoxy carbohydrate lactones.⁴⁶

Conversion of C-6 of suitable δ -lactone into an electrophilic centre, in this case an aldehyde, provided a plausible means of capturing the intermediate enolate ion via an intramolecular aldol reaction and thus a possible synthetic route to a polyhydroxylated cyclopentane. Indeed treatment of the iodo aldehyde (1.35) with anhydrous lithium iodide induced the expected reductive aldol reaction to afford the bicyclic carbocycle (1.36) in 55% yield as shown in Scheme 1.9.⁴⁷

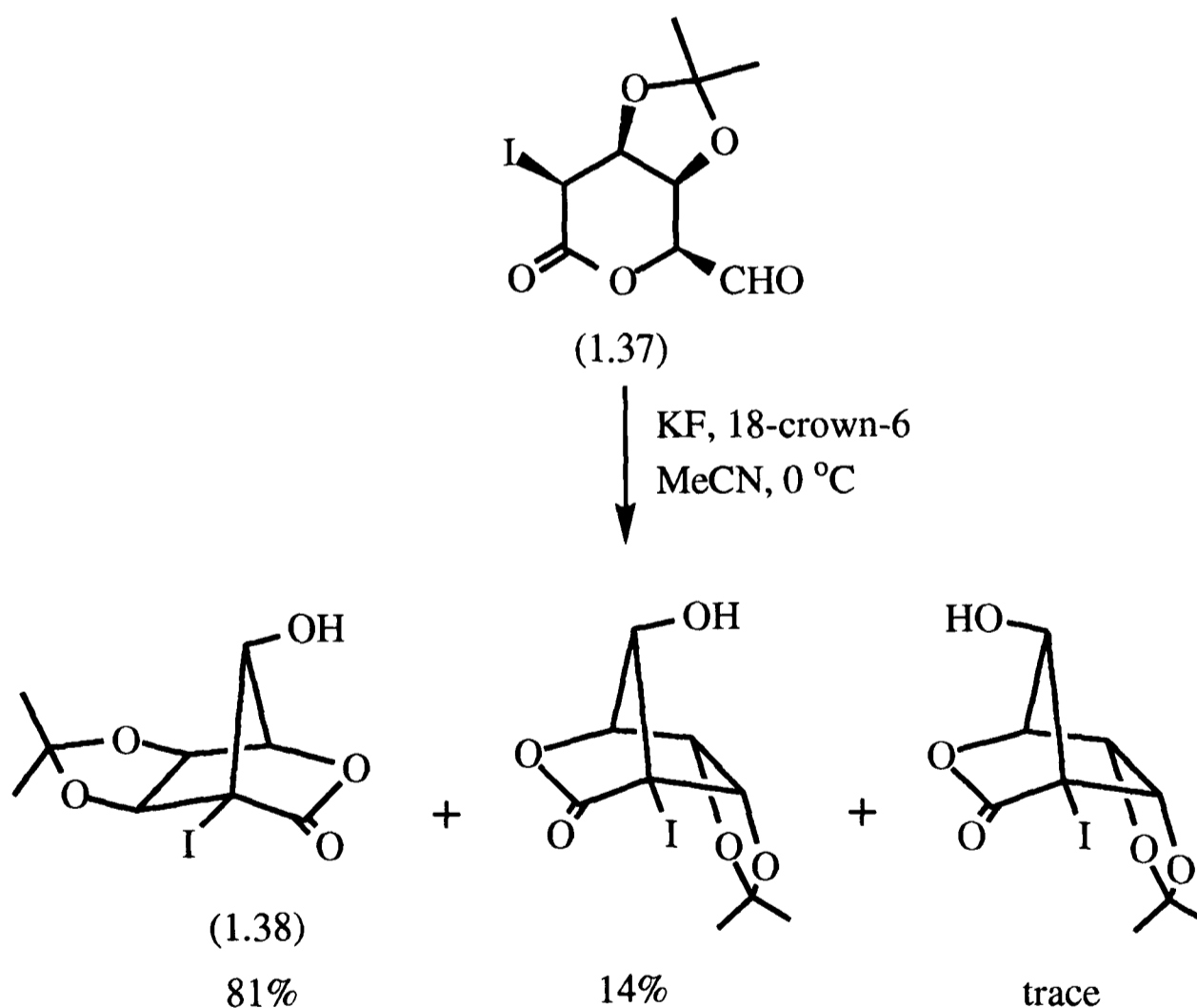


Scheme 1.9

During the course of this work, it became clear that the proton α -to the carbonyl group in both α -iodo⁴⁶ and α -azido⁴⁸ lactones was relatively acidic and could be removed and trapped again by protons without significant fragmentation of the β -oxygen substituent. Removal of this proton by treatment with a suitable base and cyclisation via a 'straight' aldol reaction onto an aldehyde derived from C-6 of a

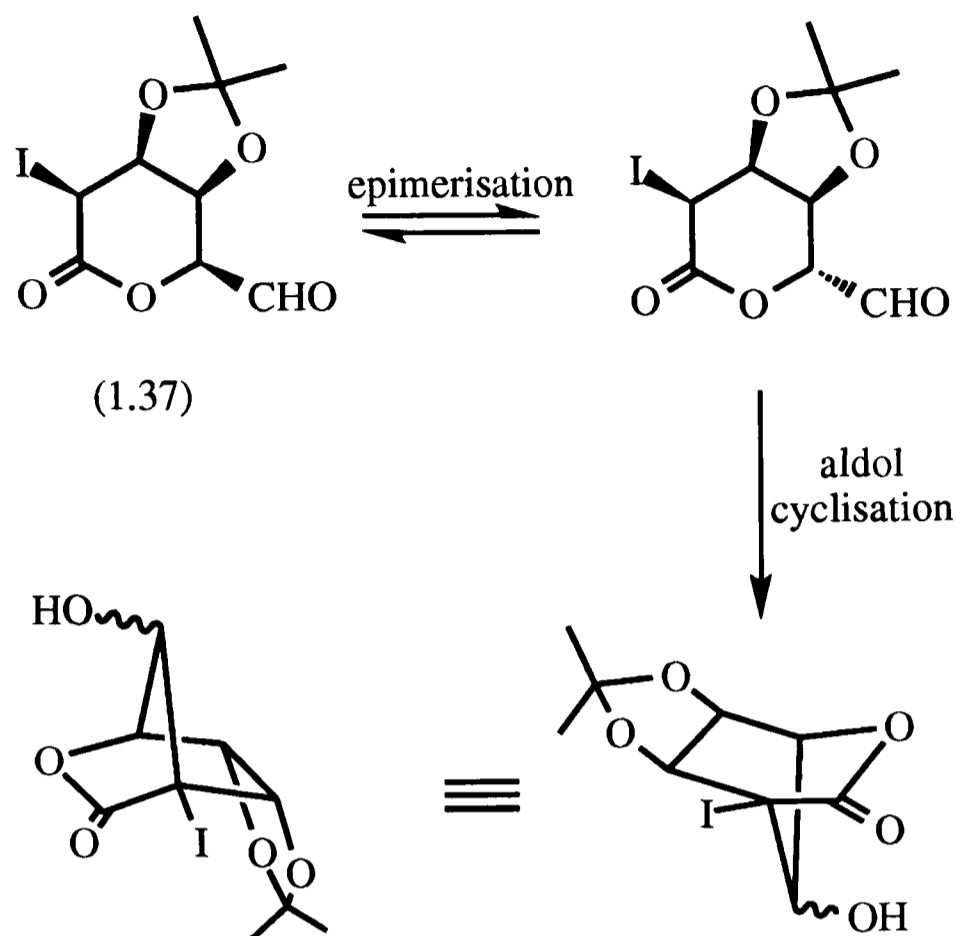
lactone precursor would provide a simple synthetic route to a number of heteroatom substituted polyhydroxylated cyclopentanes.

It was found that treatment of the iodo lactone (1.37) with potassium fluoride in acetonitrile produced a mixture of three products. All result from deprotonation α to the lactone and intramolecular cyclisation onto the aldehyde functionality (Scheme 1.10).⁴⁹ The structure of the major product (1.38) was confirmed by X-ray crystallographic analysis.⁴⁷ Reduction of the bridgehead iodide with tributyl tin hydride yielded the reduced carbocycle (1.36) (see Scheme 1.9), formed from the reductive aldol reaction detailed above, and thus confirmed the structure of this material.



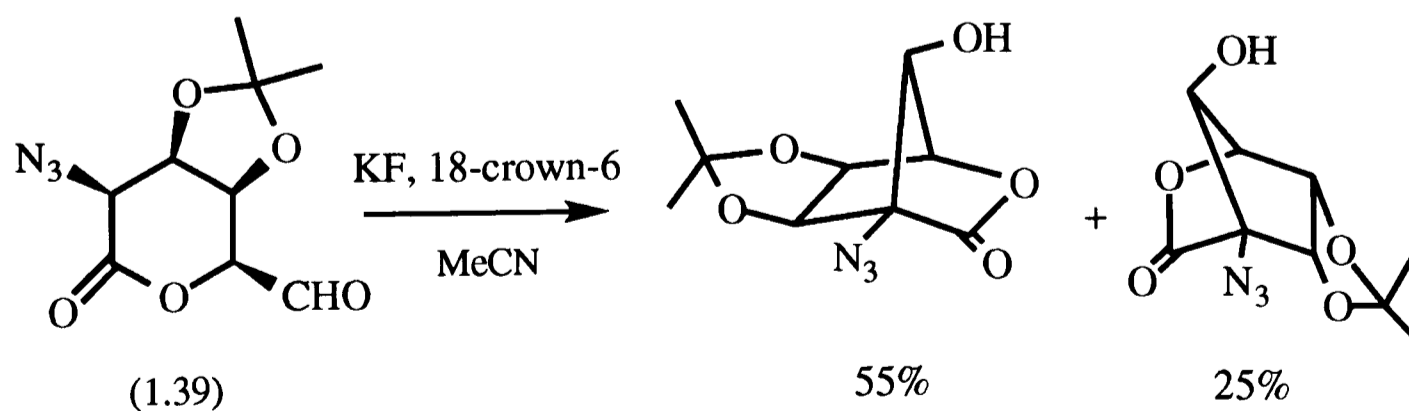
Scheme 1.10

The minor products formed during this reaction result from initial epimerisation α to the aldehyde which is then followed by intramolecular aldol cyclisation (Scheme 1.11).



Scheme 1.11

Treatment of the azido lactone (1.39) with potassium fluoride in acetonitrile was found to induce a similar intramolecular aldol reaction,⁵⁰ yielding a mixture of two carbocyclic products (Scheme 1.12). Again the major product arises from deprotonation α to the lactone and cyclisation onto the aldehyde; the minor product arising from initial epimerisation α to the aldehyde.



Scheme 1.12

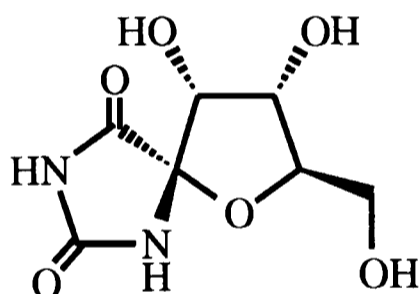
The high yields observed for these reactions prompted extensive investigations⁵¹ into the generality and applicability of such an intramolecular aldol approach towards the

synthesis of a variety of highly substituted cyclopentanes. Further investigations into this area constitute the main bulk of the work contained within this thesis.

(B) Polyhydroxylated Spirohydantoin.

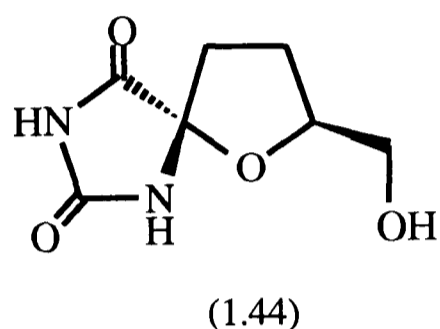
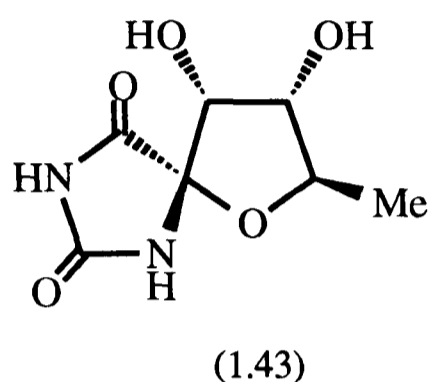
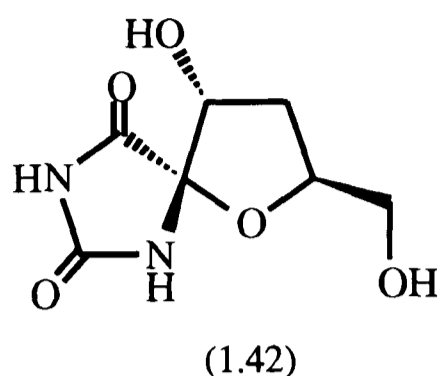
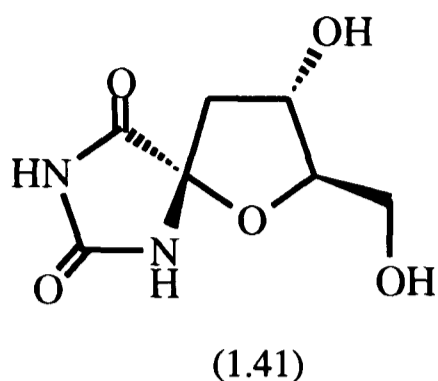
(a) Biological Activity.

During the course of a screening program for novel herbicides, hydantocidin (1.40) was isolated from the fermentation broth of *Streptomyces hygroscopicus* SANK 63584 and was found to possess potent herbicidal and plant growth regulatory activity, with no toxicity to micro-organisms or animals.⁵²



Hydantocidin (1.40)

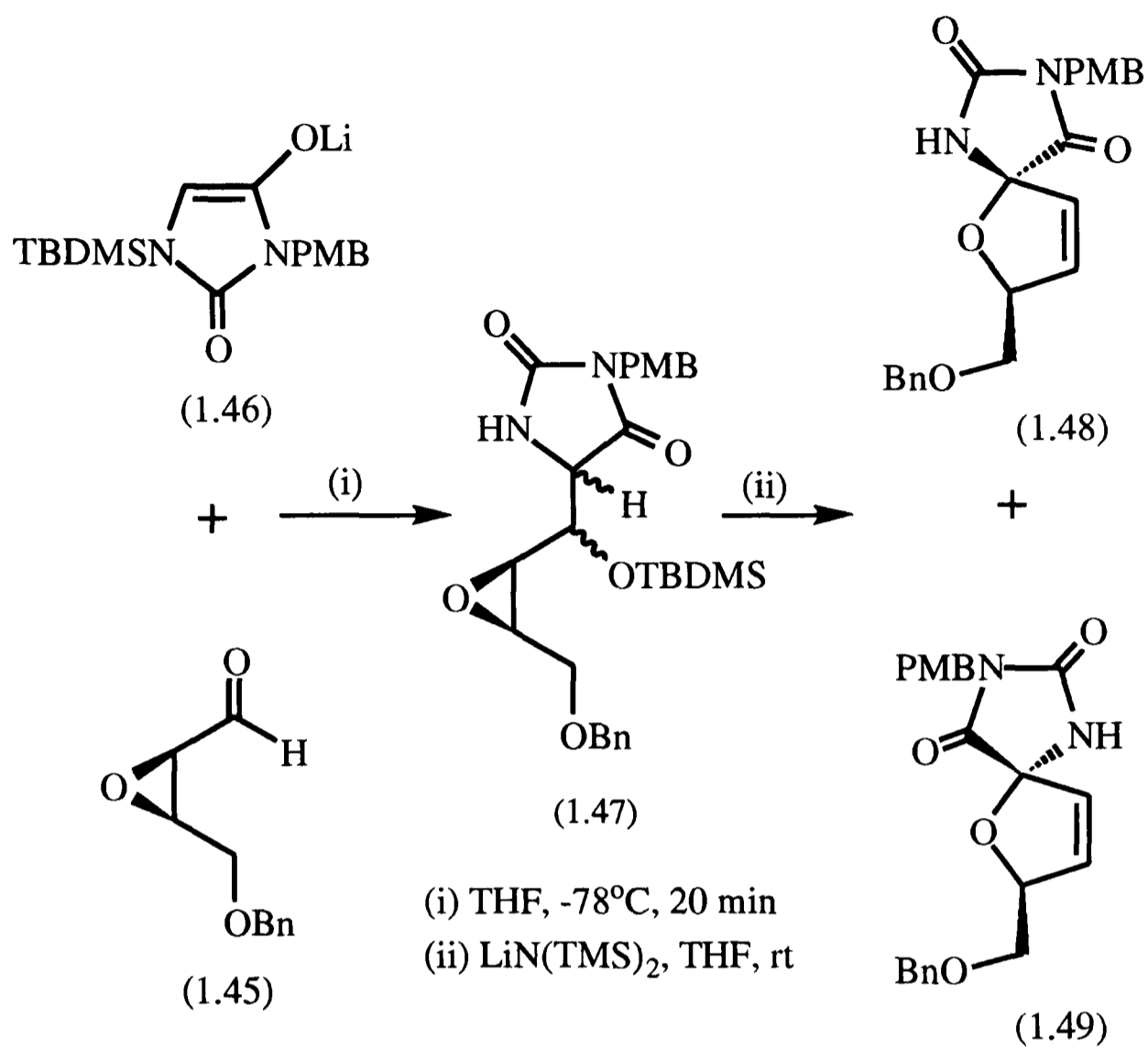
Its novel structure, which was initially elucidated⁵³ by a combination of mass, IR and ¹H and ¹³C nmr spectrometry and then confirmed by synthesis, consists of a spirohydantoin ring at the anomeric position of D-ribose. As yet, no mode of action for the observed herbicidal activity has been proposed. However, biological testing of the synthetic deoxyhydantocidins (1.41), (1.42), (1.43) and (1.44) revealed little or no herbicidal activity in all cases,⁵⁴ indicating that all the hydroxyl groups of hydantocidin are essential for biological activity.



(b) Previous synthetic approaches.

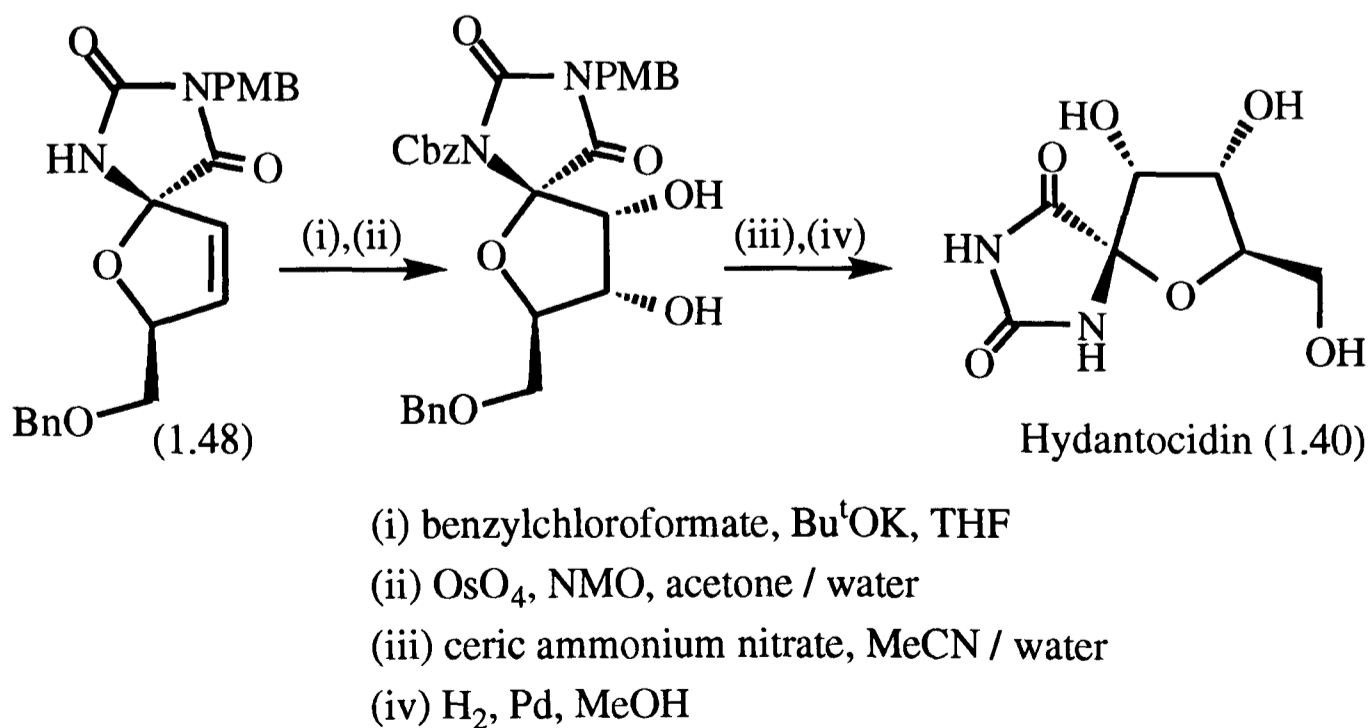
The potent herbicidal activity of hydantocidin has generated considerable interest in its synthesis. Mio and co-workers have published several syntheses using two different strategies.

The first approach⁵⁵ involved condensation of the epoxide (1.45) with the lithium enolate of the protected hydantoin (1.46) to yield a mixture of diastereomeric adducts (1.47). Treatment of the crude mixture with lithium bis(trimethylsilyl)amide induced cyclisation to yield a mixture of the two spirohydantoin (1.48) and (1.49) (Scheme 1.13). The stereochemistry of the spiro centre was determined by X-ray analysis of the ‘unnatural’ epimer (1.49).



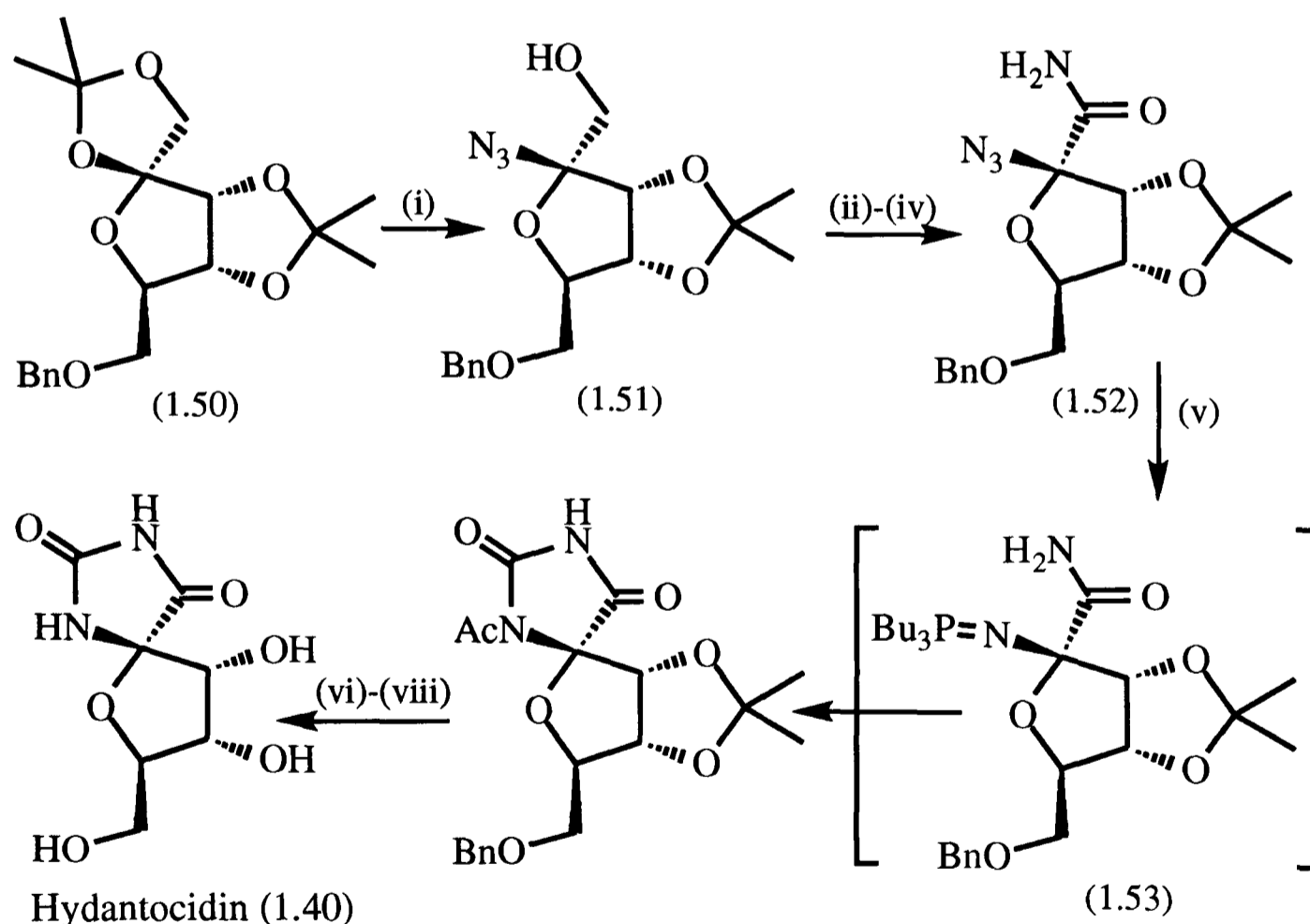
Scheme 1.13

Dihydroxylation of these intermediates followed by deprotection provided a simple synthetic route to hydantocidin and its 3-, 4-, 5- epimers.⁵⁶ The synthetic route to hydantocidin is shown in Scheme 1.14. The intermediate (1.48) was also used in the syntheses⁵⁴ of the deoxyhydantocidins (1.41), (1.42), (1.43) and (1.44).



Scheme 1.14

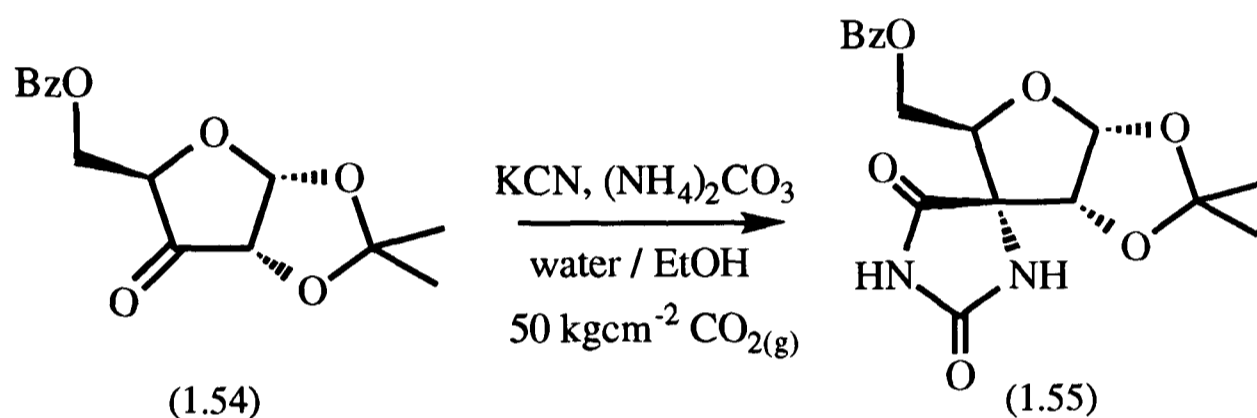
The other general synthetic approach⁵⁷ involved construction of a spirohydantoin ring at the anomeric position of D-ribofuranose. The starting material used was the psicofuranose (1.50) derived from D-fructose according to a literature procedure.⁵⁸ Lewis acid catalysed ring opening of the primary ketal and introduction of azide yielded the desired β -azide (1.51) as the major product. Conversion of the primary hydroxyl to an amide (1.52) allowed elaboration to a spirohydantoin. This was best achieved through the formation of an iminophosphoran (1.53) via an aza Wittig reaction, followed by the introduction of CO₂, to yield protected hydantocidin. Deprotection of the ketal protecting group without significant epimerisation at the spiro centre required initial *N*-acetylation of the hydantoin ring. Deacetylation via treatment with hydrazine and debenzoylation yielded hydantocidin (1.40) from D-fructose in 12 steps (19% overall yield) (Scheme 1.15).



- (i) TMSN₃, TMSOTf, MeCN, then aq NH₄Cl (ii) (COCl)₂, DMSO, Et₃N, CH₂Cl₂
 (iii) NaClO₂, NaH₂PO₄·2H₂O, 2-methylbutene, Bu^tOH / H₂O (iv) ClCO₂Et, Et₃N, THF then NH₃ gas (v) PBu₃, CO₂ gas, MeCN then Ac₂O, py, DMAP (vi) Dowex 50W(H⁺), MeOH / water (vii) NH₂NH₂·H₂O, MeOH (viii) H₂, Pd, MeOH

Scheme 1.15

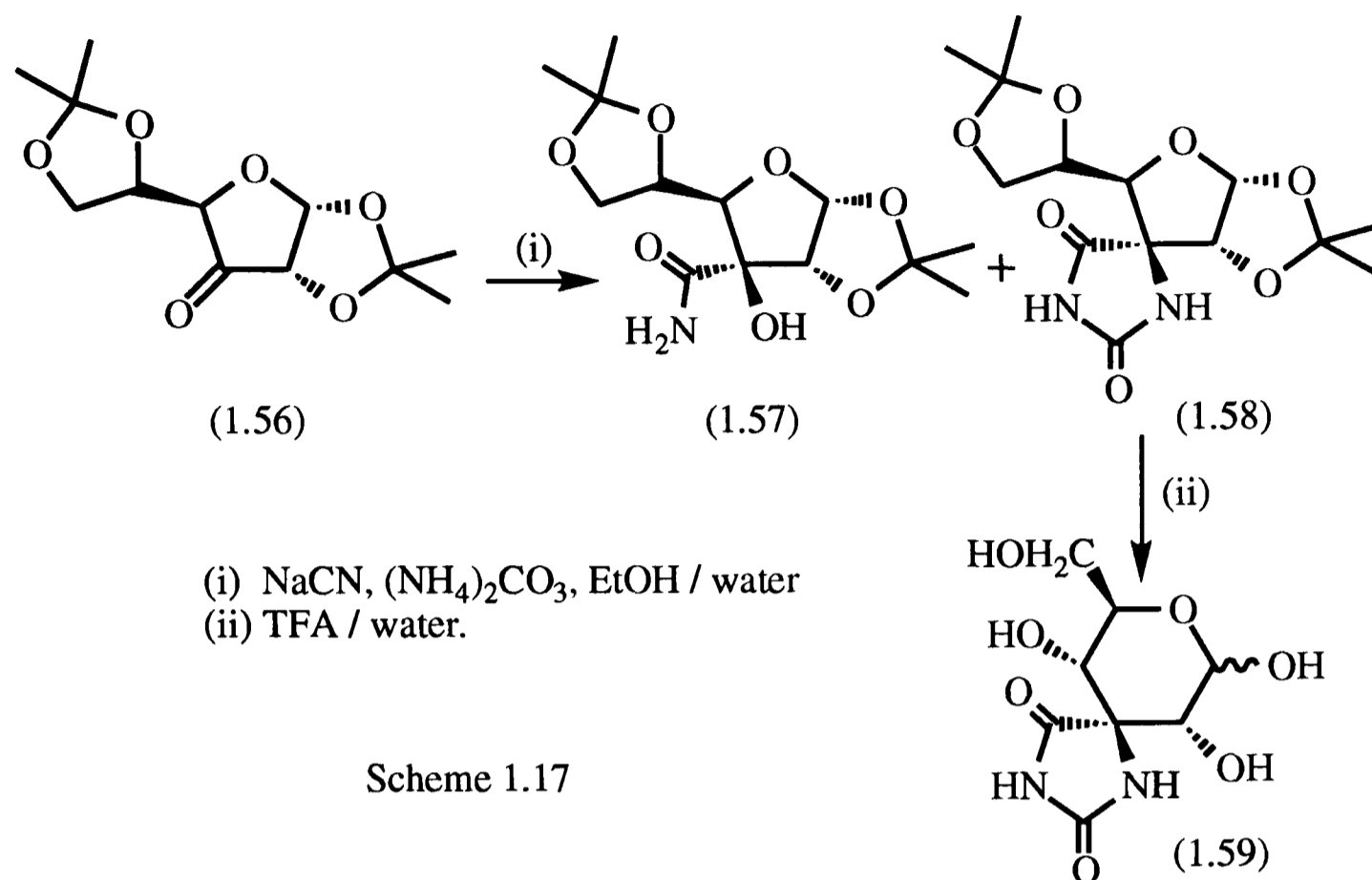
Several other polyhydroxylated spirohydantoins have been synthesised from sugars by use of the Bucherer reaction.⁵⁹ Reaction of protected aldehyde sugars having an isopropylidene protecting group in the α position often results in competing elimination processes.⁶⁰ However some keto derivatives have been found to give good yields of the corresponding hydantoins. For example treatment of the 3-pentosulose derivative (1.54) with aqueous potassium cyanide and ammonium carbonate under CO_2 resulted in the formation of the spirohydantoin (1.55) (Scheme 1.16).⁶¹



Scheme 1.16

Similarly the hexofuranulose (1.56) reacted smoothly under the normal Bucherer conditions to produce a 1 : 3 mixture of the amide (1.57) and the hydantoin (1.58), which was subsequently deprotected to give the free sugar derivative⁶⁰ (1.59) (Scheme 1.17).

At the time of writing no biological activity has been reported for these compounds. It was thought that the structural features of such materials, namely the nitrogen substituted polyhydroxylated framework, may result in either specific or generalised glycosidase inhibition.



Scheme 1.17

References.

- ¹For a review of recent work see 'Antibiotics and Anti-Viral Compounds: Chemical Synthesis and Modification', ed. by Krohn, K.; Kirst, H.A.; and Maag, H., VCH press, 1993, 327-403.
- ²Myerscough, P.M.; Fairbanks, A.J.; Jones, A.H.; Choi, S.S.; Fleet, G.W.J.; Al-Daher, S.S.; Cenci di Bello, I.; and Winchester, B. *Tetrahedron*, 1992, **48**, 10177.
- ³Fleet, G.W.J.; Ramsden, N.G.; and Witty, D.R. *Tetrahedron*, 1989, **45**, 319.
- ⁴Choi, S.S.; Bruce, I.; Fleet, G.W.J.; Jones, A.H.; Nash, R.J.; and Fellows, L.E. *Tetrahedron Lett.*, 1991, **32**, 5517.
- ⁵Fleet, G.W.J.; Ramsden, N.G.; Nash, R.J.; Fellows, L.E.; Jacob, G.S.; Cenci di Bello, I.; and Winchester, B. *Carbohydr. Res.*, 1990, **205**, 269.
- ⁶Wang, Y.; Fleet, G.W.J.; Storer, R.; Myers, P.L.; Wallis, C.J.; Doherty, O.; Watkin, D.J.; Vogt, K.; Witty, D.R.; Wilson, F.X.; and Peach, J.M. *Tetrahedron: Asymm.*, 1990, **1**, 527.
- ⁷Mantell, S.J.; Fleet, G.W.J.; and Brown, D. *J. Chem. Soc., Chem. Commun.*, 1992, 1605.

-
- 8 (a) Kramer, K.J.; Dziadik-Turner, C.; and Koga, D. *Comprehensive Insect Physiology Biochemistry and Pharmacology*; Vol 3, ed. by Kerkut, G.A.; and Gilbert, L.I.; Pergamon Press, Inc.; New York, 1985. (b) Andersen, S.D. *Annu. Rev. Entomol.*, 1979, **24**, 29.
- 9 (a) Barrett-Bee, K.; and Hamilton, M.J. *J. Gen. Microbiol.*, 1984, **130**, 1857. (b) Bartnicki-Garcia, S. *Annu. Rev. Microbiol.*, 1968, **22**, 87.
- 10 Sakuda, S.; Isogai, A.; Matsumoto, S.; and Suzuki, A. *Tetrahedron Lett.*, 1986, **27**, 2475.
- 11 Koga, D.; Isogai, A.; Sakuda, S.; Matsumoto, S.; Suzuki, A.; Kimura, S.; and Ide, A. *Agric. Biol. Chem.*, 1987, **51**, 471.
- 12 Dickinson, K.; Keer, V.; Hitchcock, C.A.; and Adams, D.J. *J. Gen. Microbiol.*, 1989, **136**, 1471.
- 13 (a) Sakuda, S.; Isogai, A.; Matika, T.; Matsumoto, S.; Koskei, K.; Kodama, H.; and Suzuki, A. *Agric. Biol. Chem.*, 1987, **51**, 3251. (b) Sakuda, S.; Isogai, A.; Matsumoto, S.; Suzuki, A.; Koskei, K.; Kodama, H.; and Yamada, Y. *Agric. Biol. Chem.*, 1988, **52**, 1615.
- 14 Aoyagi, T.; Yamamoto, T.; Kojiri, K.; Morishima, H.; Nagai, M.; Hamada, M.; Takeuchi, T.; and Umezawa, H. *J. Antibiot.*, 1989, **42**, 883.
- 15 Tropea, J.E.; Kaushal, G.P.; Pastuszak, I.; Mitchell, M.; Aoyagi, T.; Molyneux, R.J.; and Elbein, A.D. *Biochemistry*, 1990, **29**, 10062.
- 16 Morishima, H.; Kojiri, K.; Yamamoto, T.; Aoyagi, T.; Nakamura, H.; and Iitaka, Y. *J. Antibiot.*, 1989, **42**, 1008.
- 17 Farr, R.A.; Peet, N.P.; and Kang, M.S. *Tetrahedron Lett.*, 1990, **31**, 7109.
- 18 Ando, O.; Satake, H.; Itoi, K.; Sato, A.; Nakajima, M.; Takahashi, S.; Haruyama, H.; Ohkuma, Y.; Kinoshita, T.; and Enokita, R. *J. Antibiot.*, 1991, **44**, 1165.
- 19 Nakayama, T.; Amachi, T.; Murao, S.; Sakai, T.; Shin, T.; Kenny, P.T.M.; Iwashita, T.; Zagorski, M.; Komura, H.; and Nomoto, K. *J. Chem. Soc. Chem. Commun.*, 1991, 919.

-
- 20 Ogawa, S.; and Uchida, U. *Chem. Lett.*, 1993, 173.
- 21 (a) Rhinehart, B.L.; Robinson, K.M.; King, C.H., and Lui, P.S. *Biochem. Pharmacol.*, 1990, **39**, 1537. (b) Lui, P.S. *J. Org. Chem.*, 1987, **52**, 4717.
- 22 Woynarowska, B.; Wilkiel, H.; Sharma, M.; Carpenter, N.; Fleet, G.W.J.; and Bernacki, R.J. *Anticancer Res.*, 1992, **12**, 161.
- 23 (a) Fellows, L.E. *New Sci.*, 1989, **123**, 45. (b) Fellows, L.E. *Chem. Brit.*, 1987, **23**, 842.
- 24 Winkler, D.A.; and Holan, G. *J. Med. Chem.*, 1989, **32**, 2084 and references cited therein.
- 25 Chen, A.C.; and Mayer, R.T. *Comprehensive Insect Physiology Biochemistry and Pharmacology*; ed. by Kerkut, G.A.; and Gilbert, L.I.; Pergamon Press, Inc.; New York, 1985, **10**, Chapter 3.
- 26 (a) Murao, S; and Miyata, S. *Agric. Biol. Chem.*, 1980, **44**, 219. (b) Yamada, Y.; Asano, N.; Yamaguchi, T.; and Matsui, K. *J. Antibiot.*, 1987, **40**, 563. (c) Shigemoto, R.; Okuno, T.; and Matsuura, K. *Ann. Phytopath. Soc. Jpn.*, 1989, **55**, 238.
- 27 Trost, B.M.; and van Vranken, D.L. *J. Am. Chem. Soc.*, 1990, **112**, 1261.
- 28 Martin, J.C.; and Madhavan, G.V.B. *J. Org. Chem.*, 1986, **51**, 1287.
- 29 Maloisel, J.L.; Vasella, A.; Trost, B.M.; and van Vranken, D.L. *J. Chem. Soc. Chem. Commun.*, 1991, 1099.
- 30 Trost, B.M.; and van Vranken, D.L. *J. Am. Chem. Soc.*, 1991, **113**, 6317.
- 31 Kaneko, C.; Sugimoto, A.; and Tanaka, S. *Synthesis*, 1974, 876.
- 32 (a) Trost, B.M.; and van Vranken, D.L. *J. Am. Chem. Soc.*, 1993, **115**, 444. (b) Trost, B.M. in 'Antibiotics and Anti-Viral Compounds: Chemical Synthesis and Modification', ed. by Krohn, K.; Kirst, H.A.; and Maag, H. VCH press, 1993, 1.
- 33 King, S.B.; and Ganem, B. *J. Am. Chem. Soc.*, 1991, **113**, 5089.
- 34 Marco-Contelles, J.; Ruiz, P.; Martínez, L.; and Martínez-Grau, A. *Tetrahedron*, 1993, **49**, 6669 and references cited therein.

-
- 35 (a) Bernet, B.; and Vasella, A. *Helv. Chim. Acta*, 1979, **62**, 2400. (b) Kobayashi, Y.; Miyazaki, H.; and Shiozaki, M. *Tetrahedron Lett.*, 1993, **34**, 1505.
- 36 Borcharding, D.R.; Scholtz, S.A.; and Borchardt, R.T. *J. Org. Chem.*, 1987, **52**, 5457.
- 37 (a) Bélanger, P.; and Prasit, P. *Tetrahedron Lett.*, 1988, **29**, 5521. (b) Knapp, S.; and Murali Dhar, T.G. *J. Org. Chem.*, 1991, **56**, 4096.
- 38 Yoshikawa, M.; Nakae, T.; Cha, B.C.; Yokokawa, Y.; and Kitagawa, I. *Chem. Pharm. Bull.*, 1989, **37**, 545 and references cited therein.
- 39 Ogawa, S.; Uchida, C.; and Yuming, Y. *J. Chem. Soc. Chem. Commun.*, 1992, 886.
- 40 Suami, T.; Todano, K.; Nishiyama, S.; and Lichtenthaler, F.W. *J. Org. Chem.*, 1973, **38**, 3691.
- 41 Ogawa, S.; and Yuming, Y. *J. Chem. Soc. Chem. Commun.*, 1991, 890.
- 42 Ferrier, R.J.; and Prasit, P. *Pure Appl. Chem.*, 1983, **55**, 565.
- 43 Ferrier, R.J.; and Haines, S.R. *J. Chem. Soc. Perkin Trans. I*, 1984, 1689.
- 44 (a) Baldwin, J.E. *J. Chem. Soc. Chem. Commun.*, 1976, 734. (b) Baldwin, J.E.; and Lusch, M.J. *Tetrahedron*, 1982, **38**, 2939.
- 45 Elliott, R.P. 'Sugars as Homochiral Starting Materials', D.Phil Thesis, Oxford University, 1992, Chapter 2.
- 46 Elliott, R.P.; Fleet, G.W.J.; Gyoung, Y.S.; Ramsden, N.G.; and Smith, C. *Tetrahedron Lett.*, 1990, **31**, 3785.
- 47 Elliott, R.P.; Fleet, G.W.J.; Pearce, L.; Smith, C.; and Watkin, D.J. *Tetrahedron Lett.*, 1991, **43**, 6227.
- 48 Bruce, I.; Fleet, G.W.J.; Girdhar, A.; Haraldsson, M.; Peach, J.M.; and Watkin, D.J. *Tetrahedron*, 1990, **46**, 19.
- 49 Elliott, R.P.; Hui, A.; Fairbanks, A.J.; Nash, R.J.; Winchester, B.G.; Way, G.; Smith, C.; Lamont, R.B.; Storer, R.; and Fleet, G.W.J. *Tetrahedron Lett.*, 1993, **33**, submitted for publication.

-
- 50 Fairbanks, A.J.; Elliott, R.P.; Smith, C.; Hui, A.; Way, G.; Storer, R.; Taylor, H.; Watkin, D.J.; Winchester, B.G.; and Fleet, G.W.J. *Tetrahedron Lett.*, 1993, **33**, submitted for publication.
- 51 (a) Beacham, A.R. Part II Thesis, Oxford University, 1991. (b) Hsia, K.Y. Part II Thesis, Oxford University, 1991. (c) Burrows, J.N. Part II Thesis, Oxford University, 1993.
- 52 Nakajima, M.; Itoi, K.; Takamatsu, Y.; Kinoshita, T.; Okazaki, T.; Kawakubo, K.; Shindou, M.; Honma, T.; Tohjigamori, M.; and Haneishi, T. *J. Antibiot.*, 1991, **44**, 293.
- 53 Haruyama, H.; Takayama, T.; Kinoshita, T.; Kondo, M.; Nakajima, M.; and Haneishi, T. *J. Chem. Soc. Perkin Trans. I*, 1991, 1637.
- 54 Mio, S.; Sano, H.; Shindou, M.; Honma, T.; and Sugai, S. *Agric. Biol. Chem.*, 1991, **55**, 1105.
- 55 Mio, S.; Ichinose, R.; Goto, K.; and Sugai, S. *Tetrahedron*, 1991, **47**, 2111.
- 56 Mio, S.; Ueda, M.; Hamura, M.; Kitagawa, J.; and Sugai, S. *Tetrahedron*, 1991, **47**, 2145.
- 57 Mio, S.; Kumagawa, Y.; and Sugai, S. *Tetrahedron*, 1991, **47**, 2133.
- 58 Prisbe, E.J.; Smejkal, J.; Verheyden, J.P.H.; and Moffatt, J.G. *J. Org. Chem.*, 1976, **41**, 1836.
- 59 (a) Bucherer, H.T.; and Steiner, W. *J. Prakt. Chem.*, 1934, **140**, 291. (b) Bucherer, H.T.; and Leib, V.A. *J. Prakt. Chem.*, 1934, **141**, 5.
- 60 Kuzmann, J.; Marton-Meresz, M.; and Jerkovich, G. *Carbohydr. Res.*, 1988, **175**, 249.
- 61 Yanagisawa, H.; Kinoshita, M.; Nakada, S.; and Umezawa, S. *Bull. Chem. Soc. Jpn.*, 1970, **43**, 246.

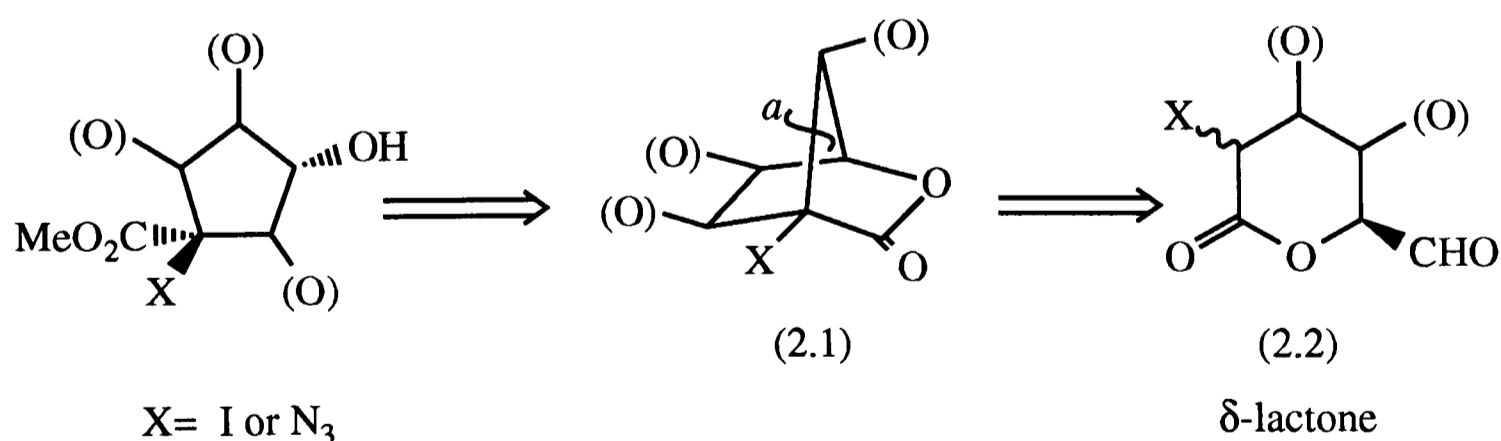
CHAPTER 2.

Synthesis and Investigations of Altrono-1,5-lactones.

Introduction.

The Kiliani reaction¹ of certain suitably protected sugars provides a simple synthetic route to sugar lactones that are not readily obtainable by other methods. In particular the formation of γ -hydroxy- δ -lactones, which are prone to isomerise to their thermodynamically more stable 5-ring counterparts,² can be achieved by the Kiliani ascension of substrates in which the C-3 hydroxyl group is protected. This approach has been used in the synthesis of several 6-ring heptonolactones³ which have proved to be useful intermediates for the synthesis of a wide range of biologically interesting compounds.

The principal aims of this project were the syntheses of polyhydroxylated cyclopentanes via intramolecular aldol cyclisations of sugar lactone starting materials. A retrosynthetic analysis of a generalised cyclopentane is shown in Scheme 2.1.



Scheme 2.1

The first step involves linking one of the free hydroxyl groups with a methyl ester to form a bicyclic lactone (2.1). This can then be disconnected by breaking bond *a*, via a

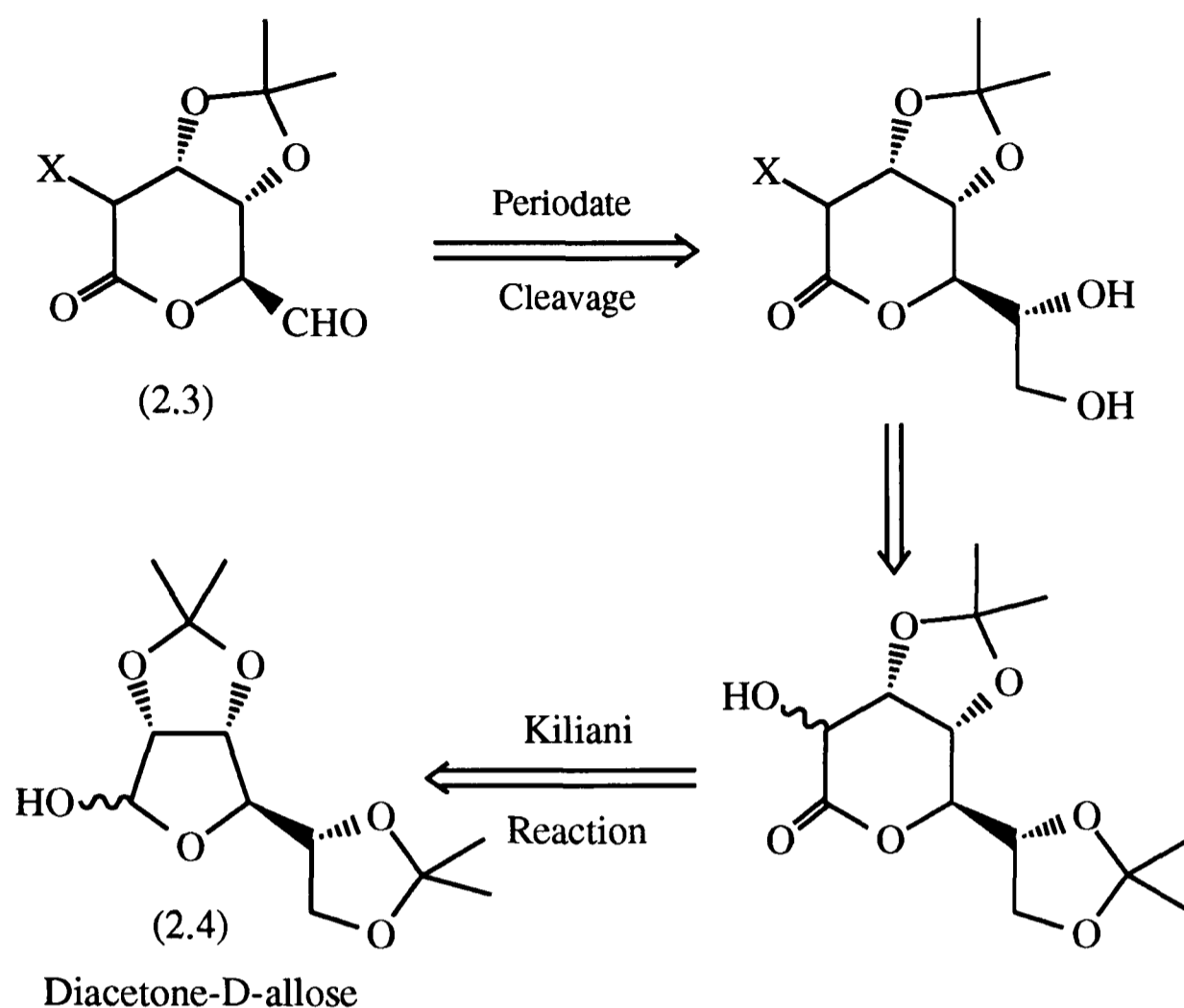
retro aldol condensation, to produce a δ -lactone precursor (2.2). An electron withdrawing substituent at C-2⁴ of the lactone precursor would facilitate proton removal for such an aldol reaction and initial investigations have concentrated on α -iodo or α -azido lactones.

The hydroxyl groups at C-3 and C-4 of the δ -lactone precursor (2.2) can be conveniently protected via an appropriate ketal thus necessitating *cis*-3,4-hydroxyl stereochemistry. The stereochemistry of the C-2 substituent depends on the stereoselectivity of both the Kiliani reaction by which the lactone is synthesised and also the stereochemical course of the subsequent nucleophilic displacement reactions used to introduce the substituent X.

This leaves only the cases where the formyl substituent at C-5 and the hydroxyl group at C-4 are either *cis* or *trans* to each other. Preliminary work by other workers⁵ focused on the case where these substituents were *cis* to each other using substrates derived from the Kiliani reaction of diacetone-D-mannose.⁶ Further work that has been carried out using azido aldehydes derived from this system is detailed in Chapter 4.

This Chapter and Chapter 3 detail investigations into the synthesis of carbocycles via intramolecular aldol condensations of aldehydo lactones in which the C-5 formyl substituent and the C-4 hydroxyl group are *trans* to each other.

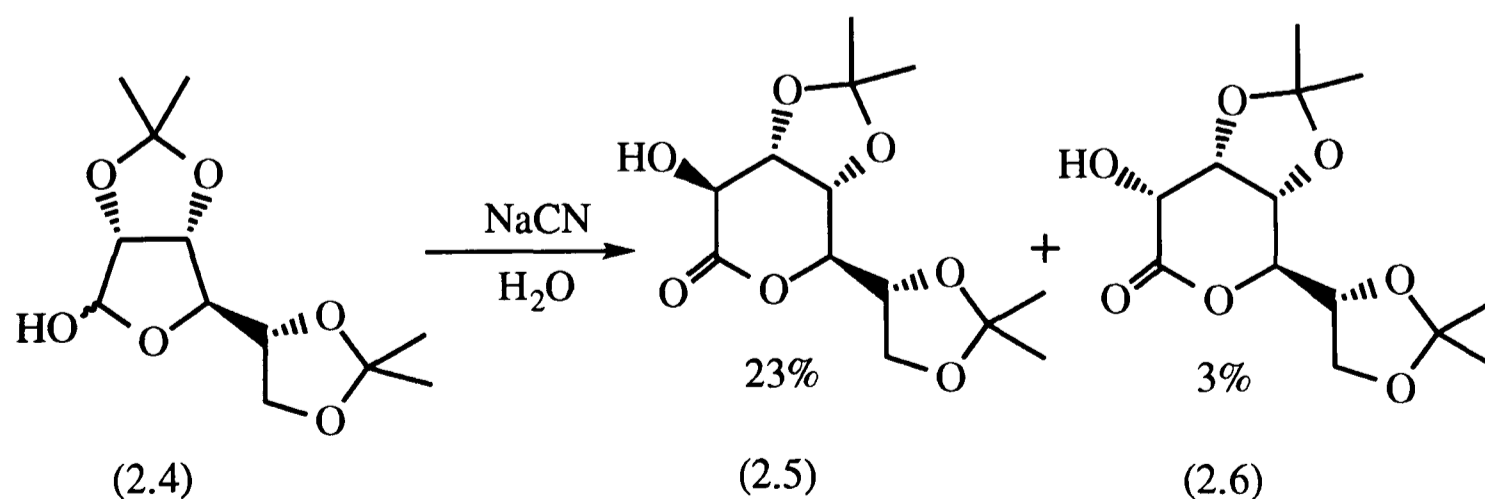
A retrosynthetic analysis of such an aldehydo lactone (2.3) is shown in Scheme 2.2.



Scheme 2.2

The aldehyde functionality at C-6 may be synthesised by periodate cleavage of an exposed diol unit of a seven carbon sugar lactone, which itself may be synthesised via a Kiliani reaction of a protected hexose precursor, in this case diacetone-D-allose (2.4).

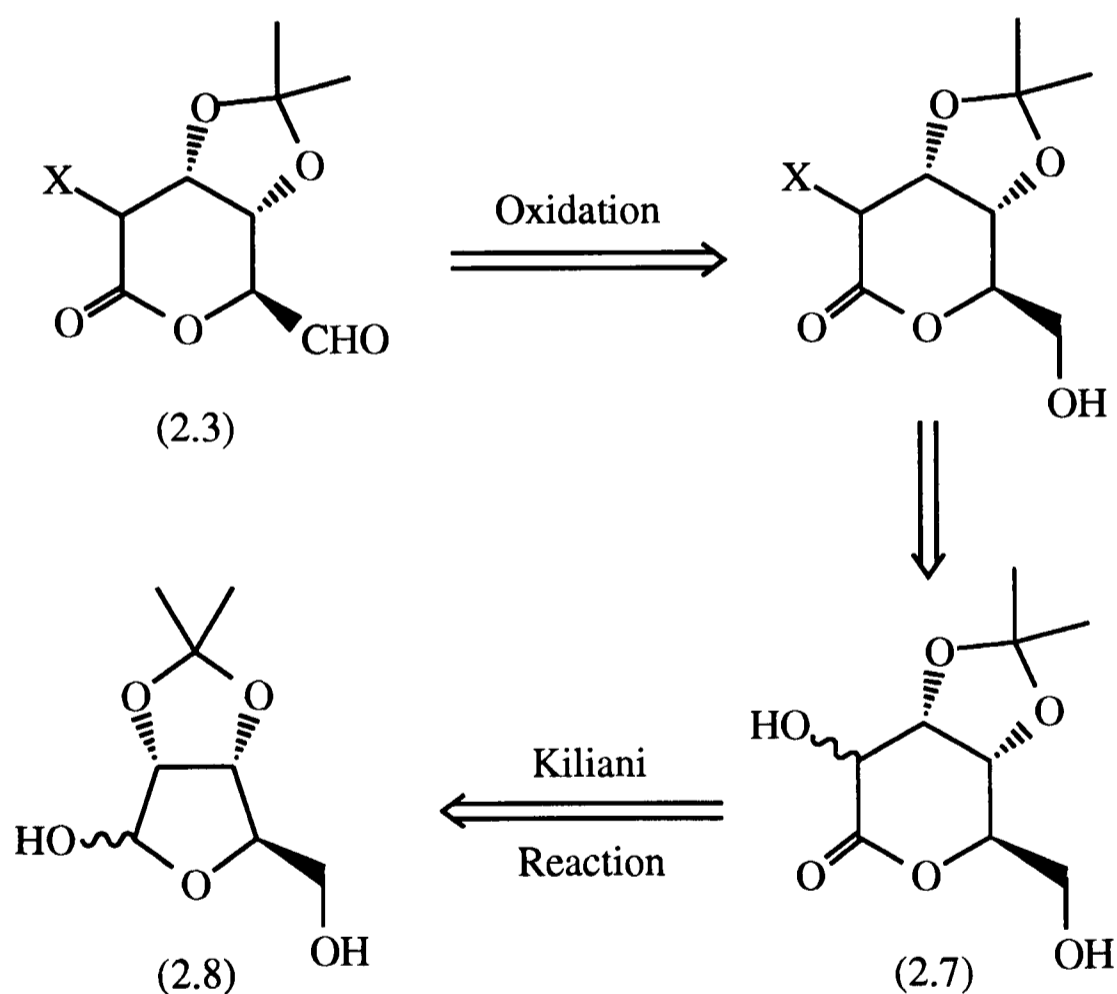
This Kiliani reaction has been found to proceed in modest yield to produce a mixture of D-glycero-D-altrono (2.5) and D-glycero-D-allono (2.6) heptono-1,5-lactones⁷ as shown in Scheme 2.3.



Scheme 2.3

However D-allose is not readily available⁸ and the starting material for this reaction must be synthesised from diacetone-D-glucose in 3 steps, via inversion of configuration at C-3 and migration of the acetonide protecting group.⁹ The modest yield observed for the Kiliani ascension combined with the protracted reaction sequence required for the synthesis of diacetone allose disfavour this reaction sequence as a practical approach to the precursors required for cyclopentane formation.

Alternative retrosynthetic analysis of the required aldehydo lactone (2.3) envisages formation of the aldehyde functionality via oxidation of a primary alcohol at C-6 of a hexose rather than periodate cleavage of a diol unit of a seven carbon sugar (Scheme 2.4).



Scheme 2.4

Subsequent analysis of the lactone (2.7) indicates simple disconnection to a protected pentose, in this case 2,3-*O*-isopropylidene-D-ribose (2.8), which is a readily available starting material.¹⁰ The Kiliani ascension of protected forms of D-ribose would provide simple access to such novel lactones. These would be expected to be useful synthetic

intermediates for the synthesis of a wide range of potentially biologically interesting compounds, most notably highly functionalised cyclopentanes formed via intramolecular aldol cyclisation of C-2 onto C-6.

Results and Discussion.

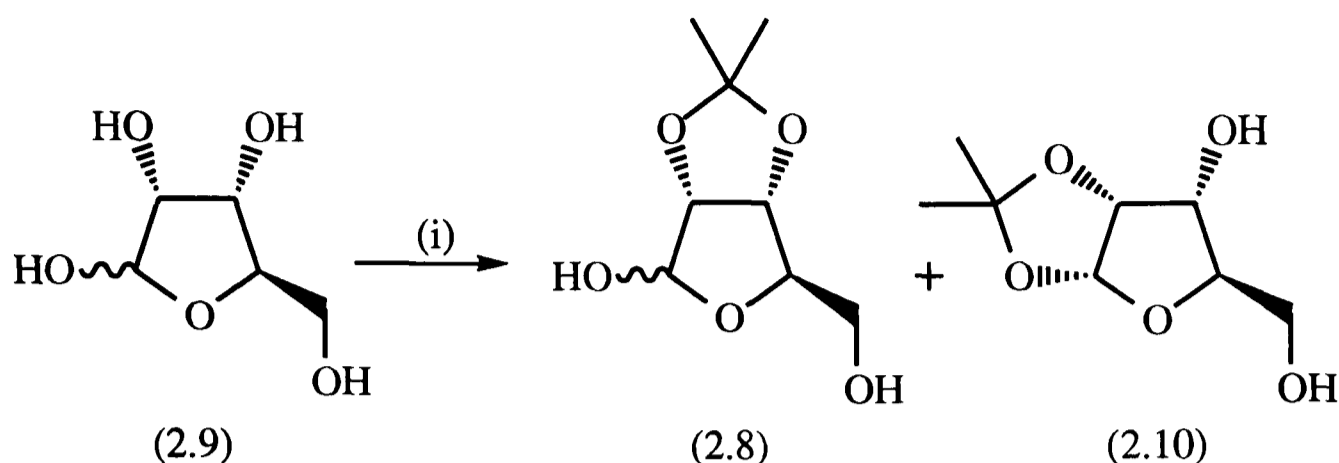
The work can be divided into the following four sections:-

- (i) Synthesis of altrono-1,5-lactones via Kiliani reactions of protected forms of D-ribose.
- (ii) Attempted synthesis of carbocycles via intramolecular aldol reactions.
- (iii) Synthesis of 1-*epi*hydantocidin.
- (iv) Investigations into tetrahydropyran and tetrahydrofuran ring formation.

Each of these will now be discussed in turn.

(i) Synthesis of altrono-1,5-lactones via Kiliani reactions of protected forms of D-ribose.

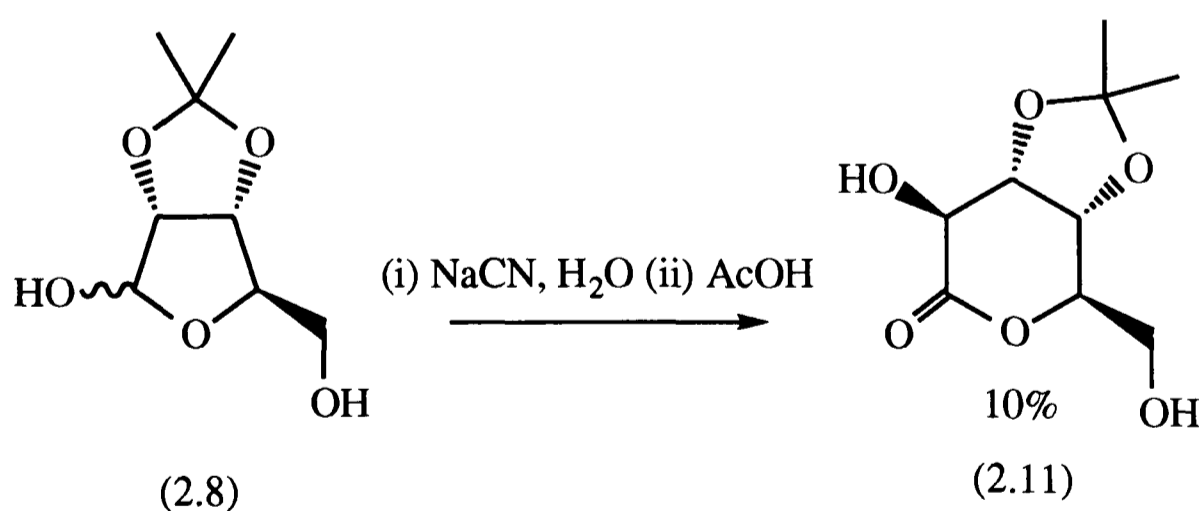
Initial investigations focused on the Kiliani reaction of 2,3-*O*-isopropylidene-D-ribose (2.8). This was synthesised by stirring D-ribose (2.9), together with acidic ion exchange resin as a catalyst, in dry acetone in the presence of molecular sieves. This reaction produced a mixture of products, the major component being the 2,3-acetonide (2.8) along with other contaminants¹¹ including some 1,2-acetonide (2.10) (Scheme 2.5). These were subjected to the Kiliani reaction as a crude mixture.



(i) acetone, Dowex 50X (H⁺), molecular sieves, 3 h, RT

Scheme 2.5

Stirring of this crude mixture with sodium cyanide in water overnight effected cyanohydrin formation. Cyanohydrin hydrolysis was achieved by heating to 60 °C with aeration until the production of ammonia ceased, as recommended by Isbell and co-workers.¹² Unreacted starting material and 1,2-acetonide were then removed by extraction with ethyl acetate, and lactonisation of the hydroxy acid achieved by removal of water and treatment with acetic acid to yield 3,4-*O*-isopropylidene-*D*-altrono-1,5-lactone (2.11) as the sole product in 10% yield (Scheme 2.6).



Scheme 2.6

The stereochemistry of the C-2 hydroxyl group was determined by single crystal X-ray diffraction. The crystal structure of 3,4-*O*-isopropylidene-*D*-altrono-1,5-lactone (2.11), which is seen to adopt a boat conformation, is shown in Figure 2.1.

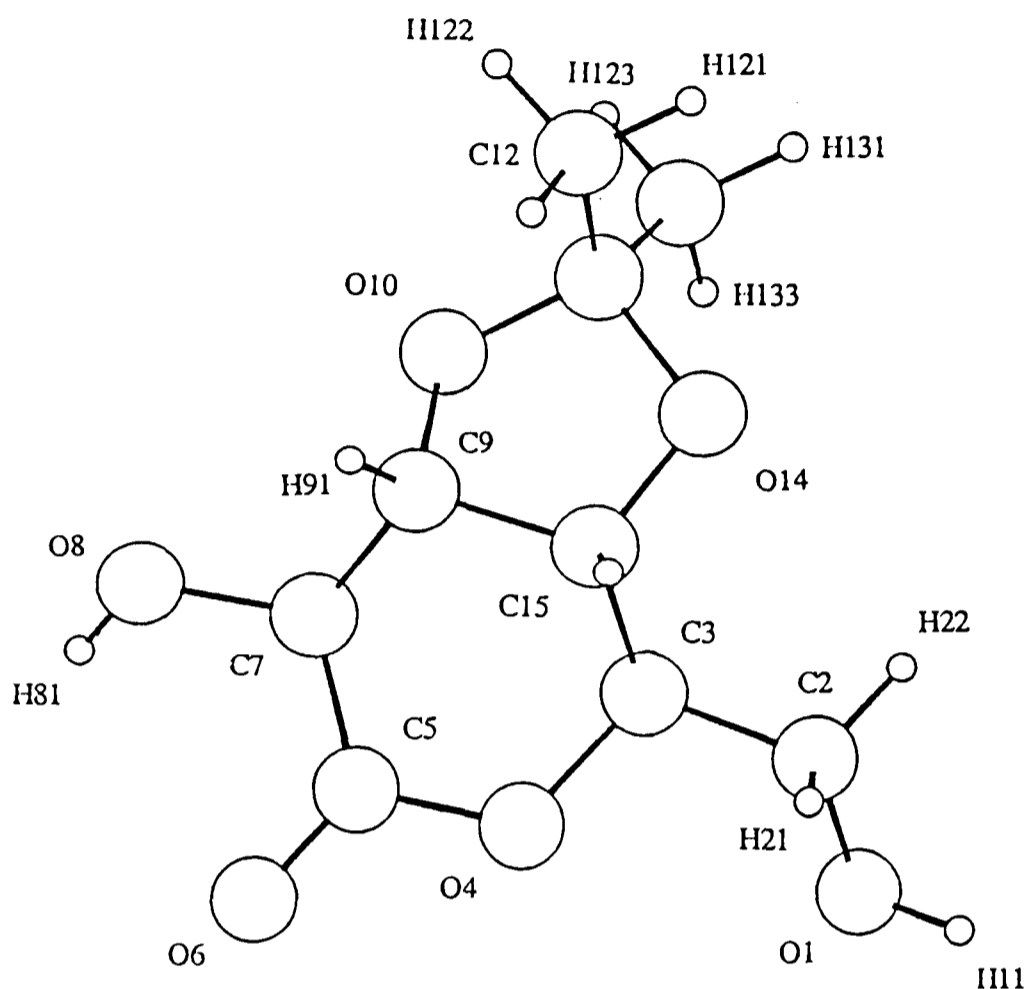
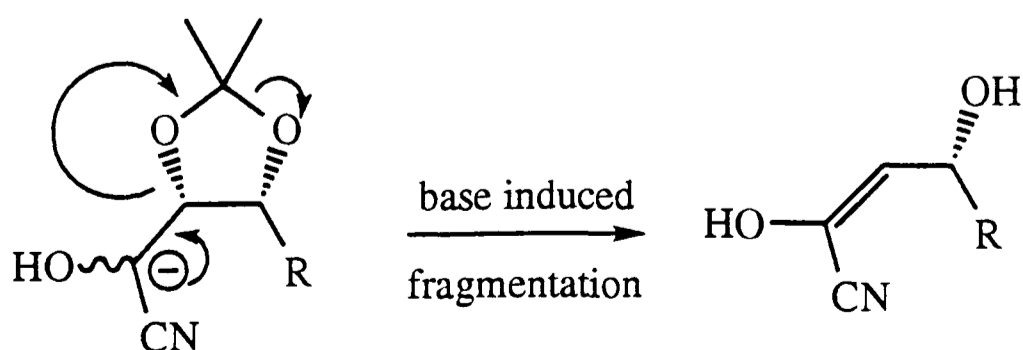


Figure 2.1.

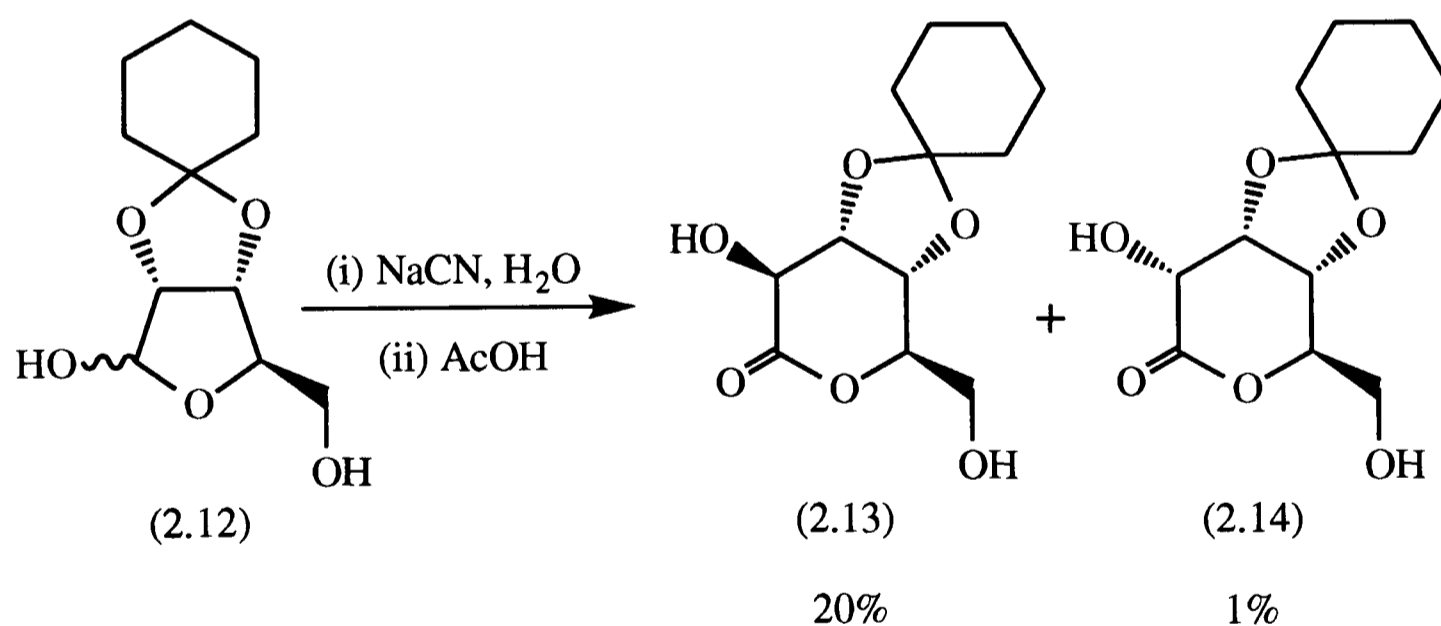
A literature study¹³ of the Kiliani reaction of a variety of unprotected sugars found that alternative mechanisms operated at varying pH's. Furthermore, a study¹⁴ of the Bucherer reaction of some aldoses with isopropylidene protecting groups α to the aldehyde functionality proposed that the low yields obtained from these reactions were due to facile elimination of the protecting group from the intermediate cyanohydrin, via deprotonation of the acidic proton α to the nitrile functionality (Scheme 2.7).



Scheme 2.7

For these reasons a variety of reaction conditions were investigated. These included the use of buffers, in order to control the reaction pH and reduce basic elimination of the acetonide protecting group, and also varying conditions for cyanohydrin hydrolysis. However, the use of buffers did not seem to increase the reaction yield and the use of more vigorous hydrolysis conditions simply caused deterioration of the product.

Due to the extremely poor yields observed for the Kiliani reaction of the 2,3-acetonide (2.8), the cyclohexylidene protecting group was chosen as an alternative. 2,3-*O*-Cyclohexylidene-D-ribose (2.12) was synthesised following a literature procedure¹⁵ and purified by chromatography. Treatment with sodium cyanide in water at room temperature overnight, followed by cyanohydrin hydrolysis at 70 °C and lactonisation of the resultant hydroxy acids by treatment with acetic acid, resulted in the formation of 2,3-*O*-cyclohexylidene-D-altrono-1,5-lactone (2.13) in 20% yield, together with a small amount of 2,3-*O*-cyclohexylidene-D-allono-1,5-lactone (2.14) as shown in Scheme (2.8).



Scheme 2.8

(ii) Attempted synthesis of carbocycles via intramolecular aldol reactions.

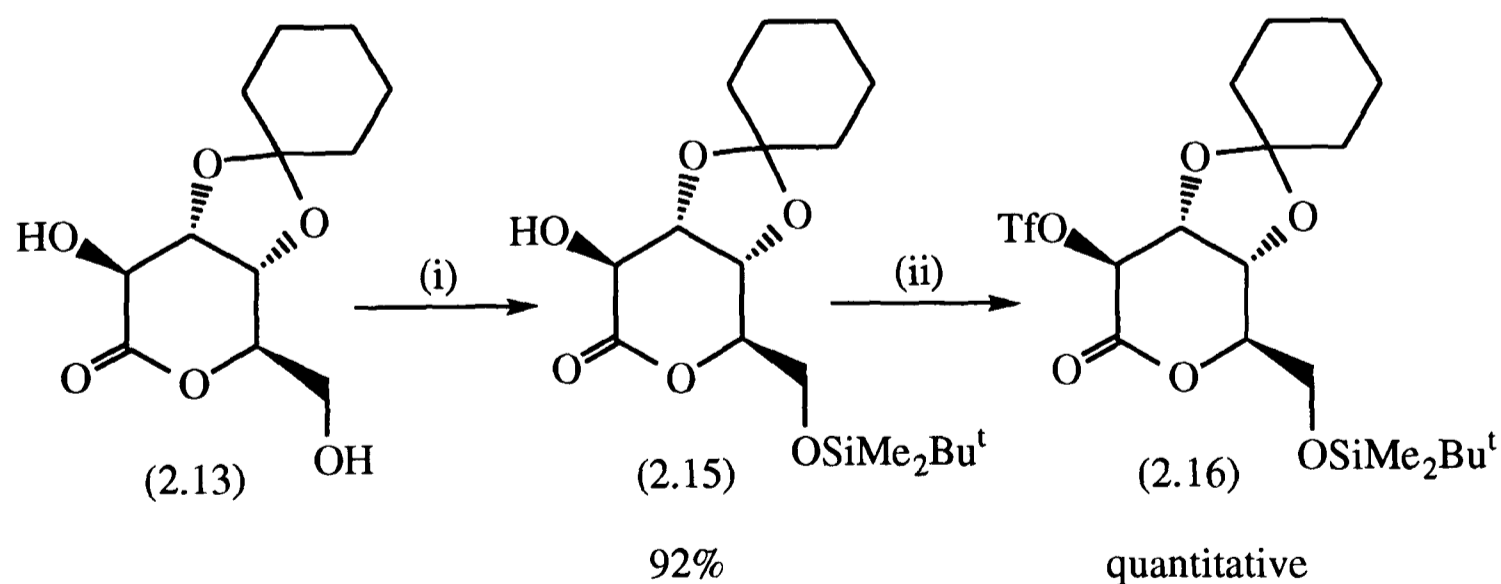
Synthetic efforts in this area concentrated on the use of 2,3-*O*-cyclohexylidene-D-altrono-1,5-lactone (2.13) as the starting material. The required reaction sequences

involve introduction of either azide or iodide at C-2 followed by oxidation of the primary hydroxyl group at C-6 to an aldehyde. Cyclisation of C-2 onto C-6 via a base induced aldol reaction would provide a synthetic route to highly functionalised cyclopentanes. Work in this area can be divided into two sections:-

- (a) Synthesis of azido and iodo alcohol precursors.
- (b) Attempted oxidations.

(a) Synthesis of azido and iodo alcohol precursors.

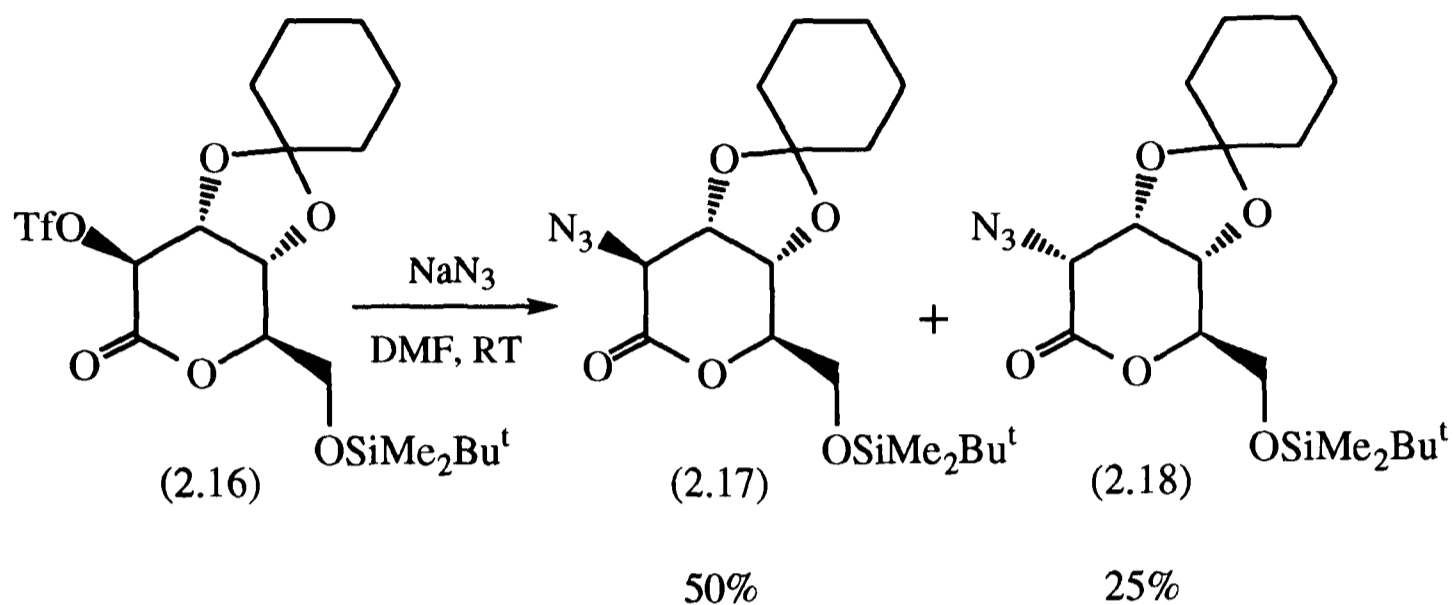
Introduction of a substituent at C-2 required initial protection of the primary hydroxyl group at C-6. This was achieved via a selective silylation using TBDMS chloride which produced mainly the required monosilylated compound (2.15) in 92% yield, together with a small amount of disilylated material. The hydroxyl group at C-2 was then converted to its triflate ester by treatment with triflic anhydride in dichloromethane, in the presence of an excess of pyridine, to yield the triflate (2.16) in quantitative yield (Scheme 2.9).



(i) TBDMSCl, imidazole, DMF, -20 °C (ii) Tf₂O, py, CH₂Cl₂, -20 °C

Scheme 2.9

Introduction of azide was achieved by treatment of the triflate (2.16) with sodium azide in DMF to produce a mixture of altrono (2.17) and allono (2.18) azides (Scheme 2.10).



Scheme 2.10

These were separated by chromatography and the stereochemistry of the azido substituent assigned by n.O.e. experiments. Irradiation of H-5 caused enhancement of the signal from H-2, and vice versa, only for the altrono azide (2.17). The probable preferred boat conformation^{6,16} of the altrono azide has both H-2 and H-5 in the flagpole position resulting in the observed n.O.e. enhancements (Figure 2.2).

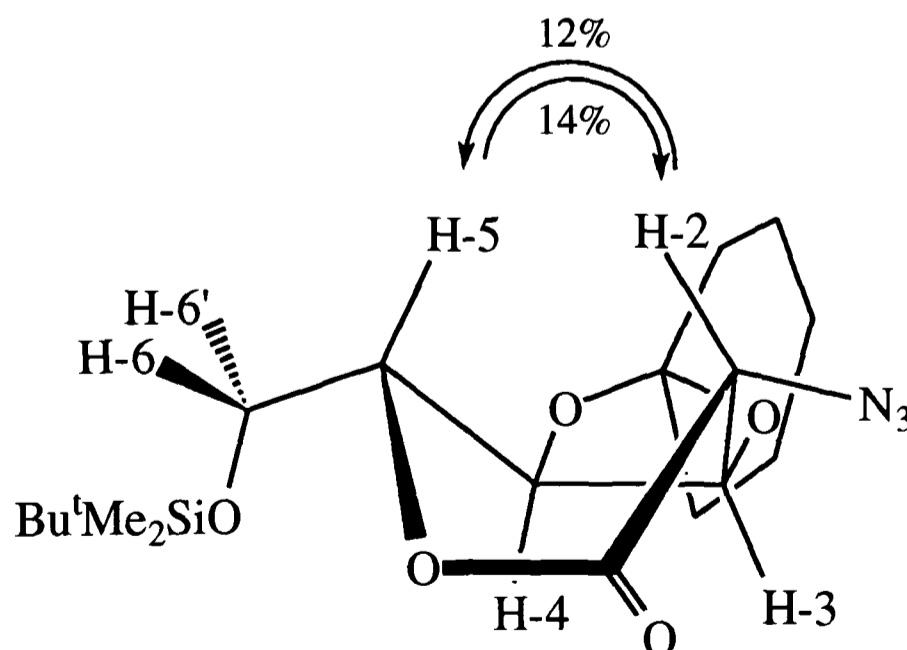
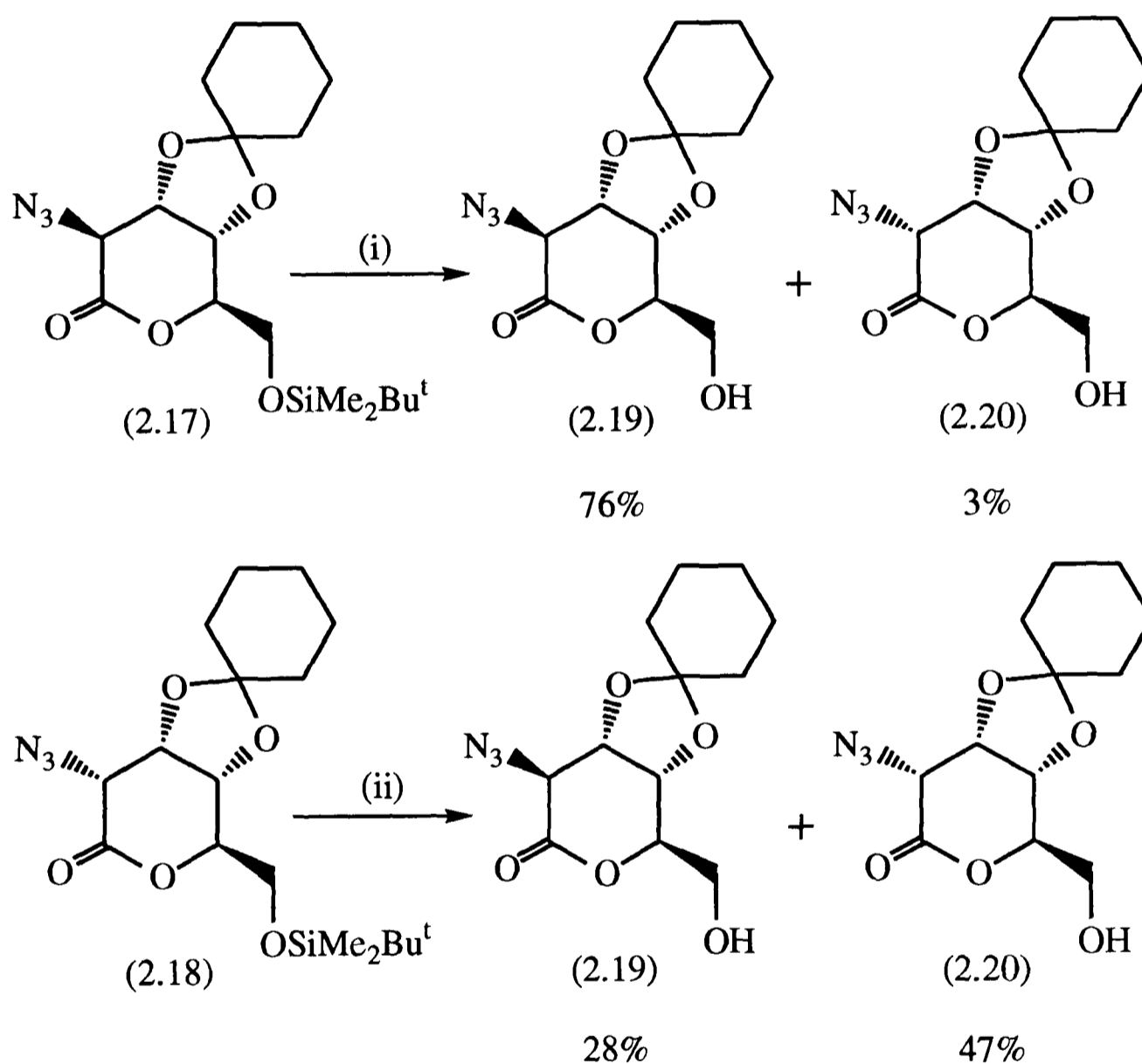


Figure 2.2

Deprotection of the C-6 hydroxyl group then yielded the required azido alcohols. Initial attempts to remove the silyl protecting group by treatment with tetra-*n*-butylammonium fluoride caused complete decomposition. Desilylation was achieved by treatment with 80% aqueous acetic acid to yield the altrono (2.19) and allono (2.20) azido alcohols. However in both cases some degree of epimerisation of the azido substituent was observed (Scheme 2.11).

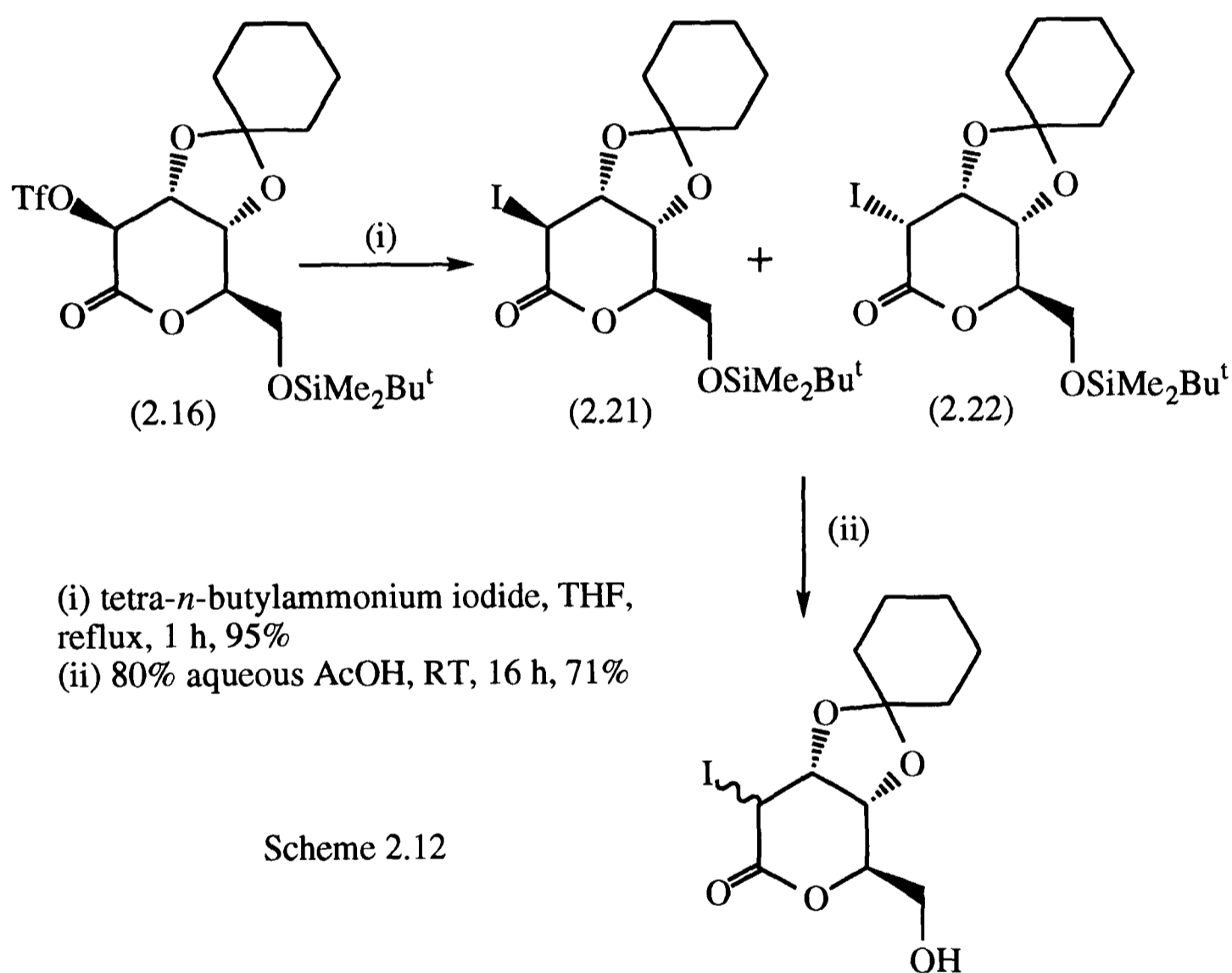


(i) 80% aqueous AcOH, 60 °C, 5 h (ii) 80% aqueous AcOH, 60 °C, 15 h

Scheme 2.11

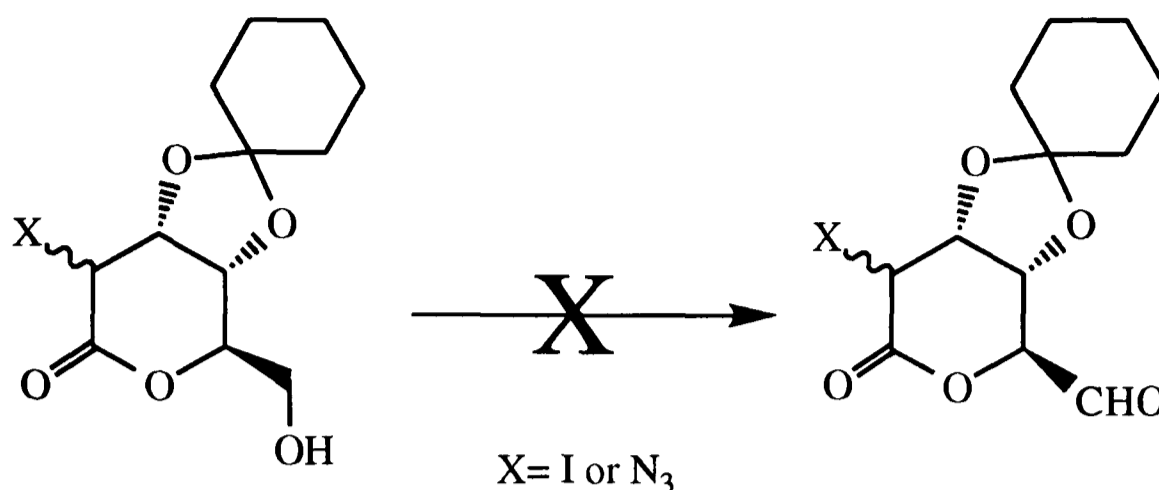
Introduction of iodide was achieved by treatment of the triflate (2.16) with tetra-*n*-butylammonium iodide in THF to yield a mixture of altrono (2.21) and allono (2.22) iodides, in a ratio of 2.2 : 1 as adjudged by ¹H nmr. These were found to be inseparable by chromatography and were used as a mixture in the subsequent

desilylation step. Small amounts of the altrono isomer (2.21) were crystallised out of a mixture of both epimers, thus facilitating product characterisation. The stereochemistry of the iodo substituent was assigned on the basis of coupling constants observed between H-2 and H-3. Desilylation of the mixture was again achieved by treatment with 80% aqueous acetic acid to yield an inseparable mixture of iodo alcohols which were used in subsequent attempted oxidations without further purification or characterisation. These reactions are summarised in Scheme (2.12).



(b) Attempted oxidations.

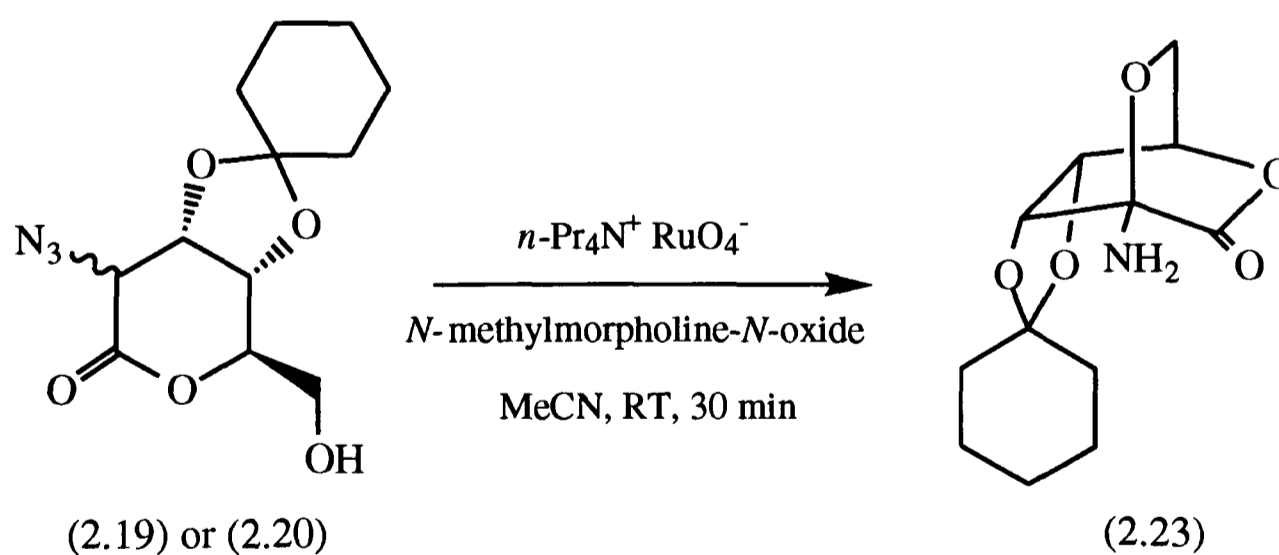
Unfortunately oxidation of the primary alcohol at C-6 to an aldehyde, in the cases of both of the azides and of the mixture of iodides, was unsuccessful (Scheme 2.13).



Scheme 2.13

A large number of different oxidants were tried including PCC, PDC, Jones, CrO₃ / dimethylpyrazole, Swern, Pfitzner-Moffatt, and the Dess-Martin periodinane¹⁷ but in all cases attempted oxidation resulted in either decomposition or recovery of starting material. No aldehyde products were obtained.

Attempted oxidation of either of the azido alcohols (2.19) or (2.20) with a catalytic amount of TPAP¹⁸ in the presence of *N*-methylmorpholine-*N*-oxide resulted in the unexpected formation of the bicyclic amine (2.23) in approximately 60% yield in both cases (Scheme 2.14).



Scheme 2.14

The structure of the bicyclic amine (2.23) was confirmed by crystallography and its X-ray structure is shown in Figure 2.3. A plausible mechanism for its formation involves

disproportionation of the azide functionality to produce nitrogen and an imine which is trapped intramolecularly by the free hydroxyl at C-6 to form a hemiaminal.

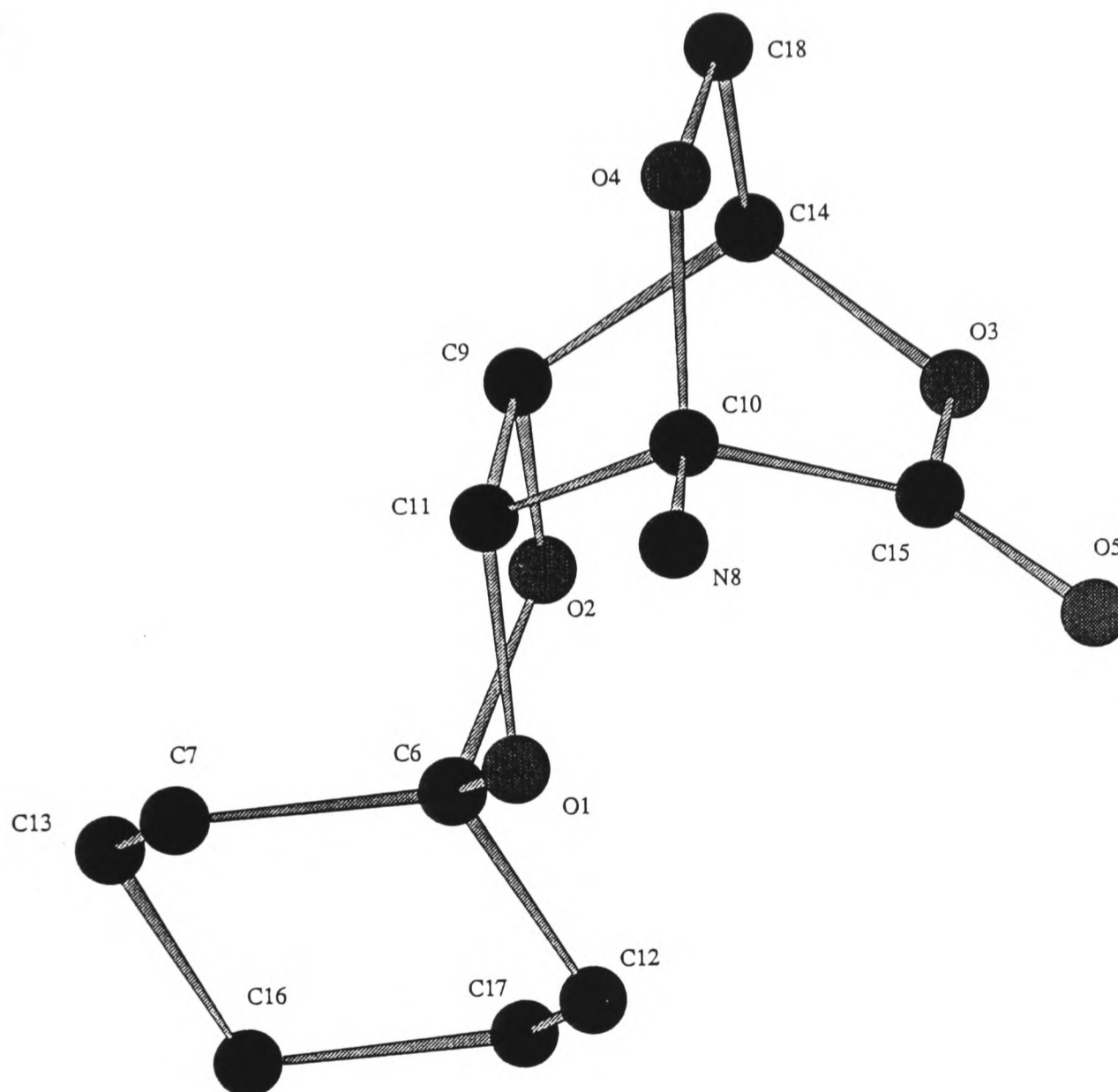
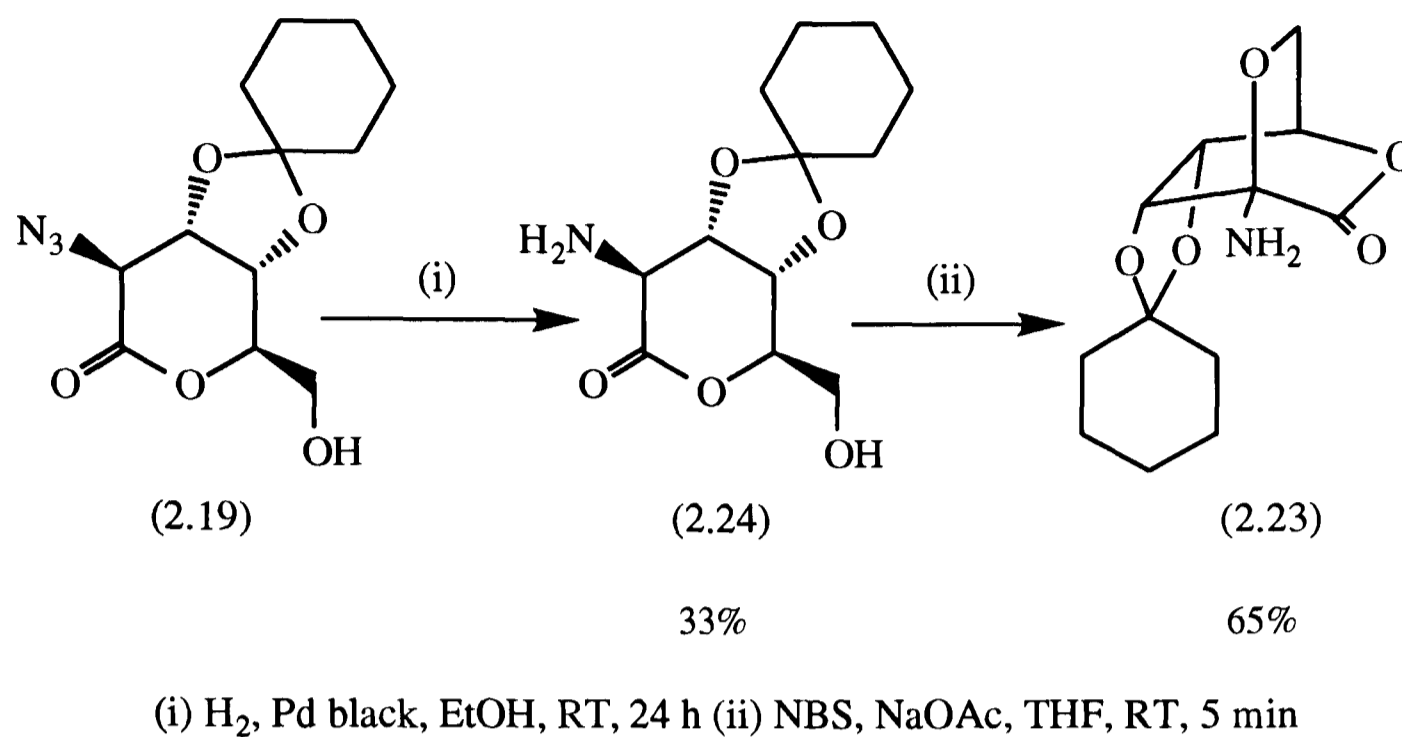


Figure 2.3

This synthetic transformation could also be induced in a two step process. Reduction of the altrono azido alcohol (2.19) with hydrogen and palladium black resulted in the formation of the altrono amino alcohol (2.24) in poor yield. Oxidation of the amine with *N*-bromosuccinimide in THF resulted in the formation of the bicyclic amine (2.23) in 65% yield, identical in all respects to the product of the TPAP reaction (Scheme 2.15).



Scheme 2.15

Due to the difficulties experienced with the crucial oxidation step an alternative strategy for the synthesis of the iodo and azido aldehyde precursors was required. This strategy and the observed results are discussed in Chapter 3.

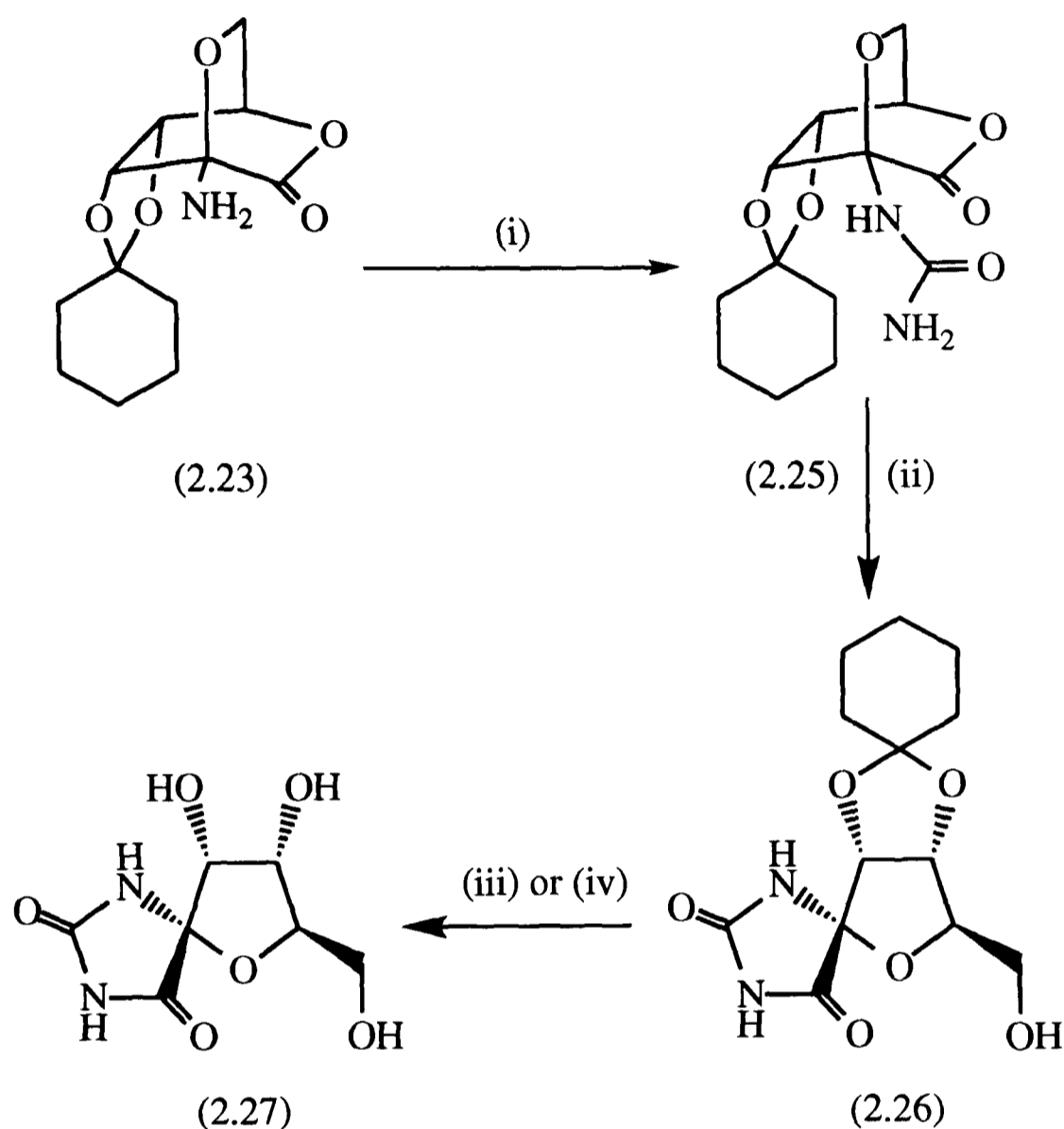
(iii) Synthesis of 1-*epi*Hydantocidin.¹⁹

The bicyclic amine (2.23), produced by the attempted TPAP oxidation described above, was thought to be a useful synthetic intermediate. In particular, construction of a hydantoin ring linking the amine functionality with the carbonyl carbon of the lactone would produce a pyranose analogue of the natural product hydantocidin (1.40).

The synthesis of a spirohydantoin from the bicyclic amine (2.23) was undertaken as follows.

Treatment of the amine (2.23) with potassium cyanate in acetic acid resulted in the formation of the urea (2.25). Cyclisation of the urea to the spirohydantoin (2.26) was achieved by treatment with potassium *tert*-butoxide in DMF. Deprotection of (2.26) with 40% aqueous trifluoroacetic acid, or methanol and acidic ion exchange resin, yielded 1-*epi*hydantocidin (2.27) as the sole product, with identical ¹H and ¹³C nmr

spectra to those of an authentic sample²⁰ of this material (Scheme 2.16). ¹H nmr spectra of both authentic and synthetic materials are shown in Appendix 1.

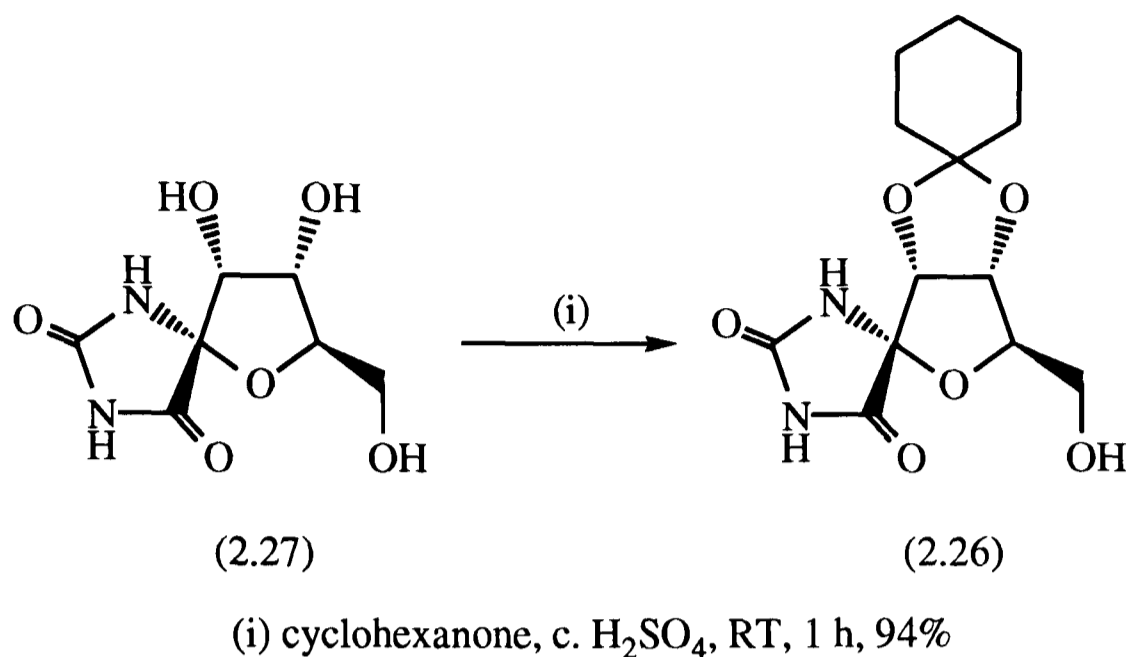


(i) KCNO, AcOH, 60 °C, 1.5 h (ii) KOBu^t, DMF, RT, 10 min, 61% over 2 steps (iii) 40% aqueous TFA, RT, 2 h, 98% (iv) MeOH, Dowex 50W-X8(H⁺), 40 °C, 16 h, 87%

Scheme 2.16

It is unclear as to whether the observed pyranose to furanose ring rearrangement occurs during the acidic urea formation or the subsequent base induced cyclisation. Attempts to grow crystals of the intermediate urea (2.25) suitable for X-ray analysis, in order to confirm the structure of this material, proved unsuccessful.

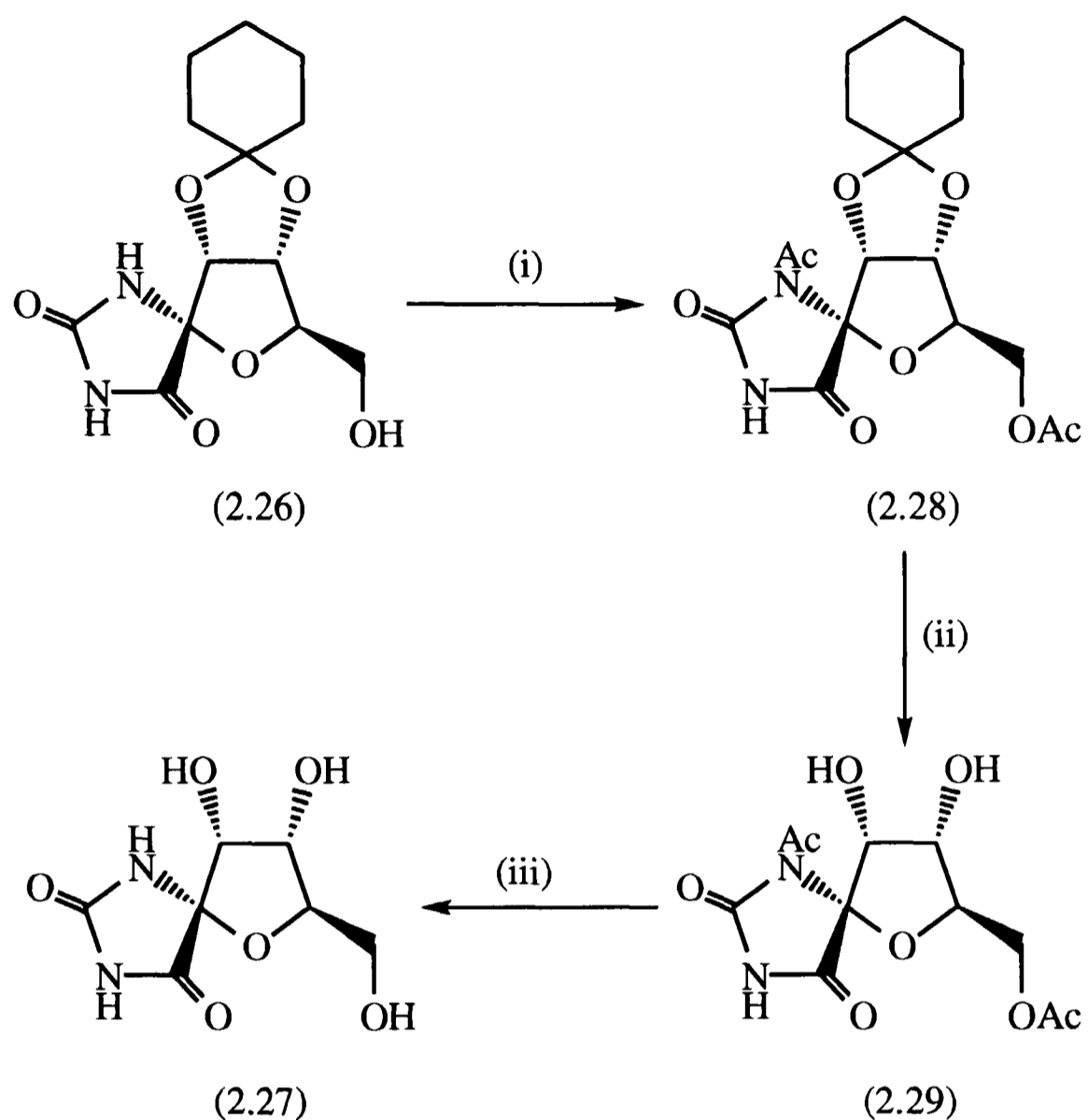
The stereochemistry of the protected spirohydantoin (2.26) was confirmed as follows. Treatment of 1-epihydantocidin (2.27) with cyclohexanone and sulphuric acid resulted in reformation of the protected spirohydantoin (2.26) (Scheme 2.17).



Scheme 2.17

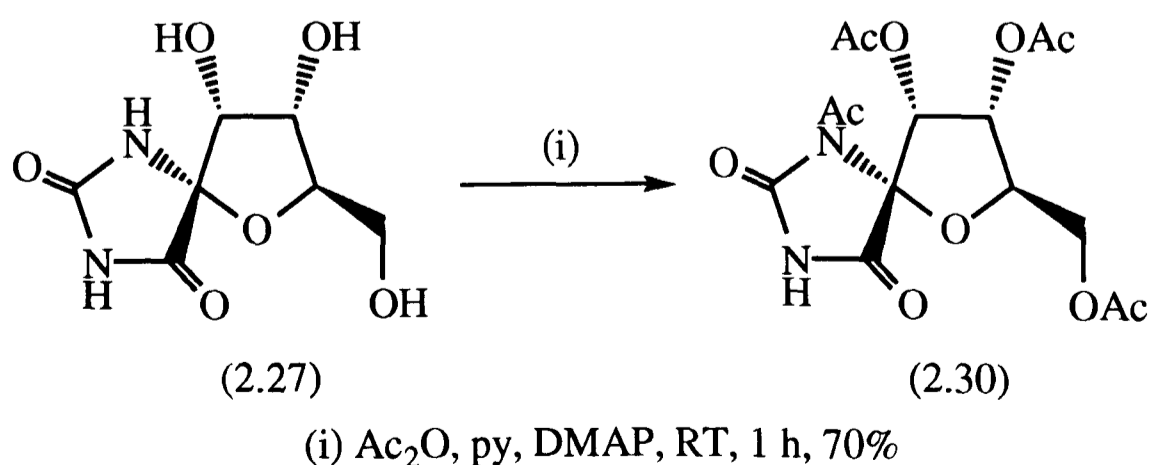
During a literature synthesis of hydantocidin,²¹ acidic hydrolysis of ketal protecting groups was found to cause some degree of epimerisation at the spiro centre. This problem was overcome by initial acetylation of the hydantoin ring and subsequent removal of the acetyl group with hydrazine. In order to avoid any possible epimerisation at the spiro position this strategy was also adopted for the deprotection of the protected spirohydantoin (2.26)

Treatment of the spirohydantoin (2.26) with acetic anhydride in pyridine in the presence of a catalytic amount of DMAP resulted in the formation of the cyclohexylidene diacetate (2.28). Removal of the cyclohexylidene protecting group was achieved by treatment with 40% aqueous trifluoroacetic acid to yield the diacetate (2.29). Treatment of this material with hydrazine in methanol resulted in the formation of 1-*epi*hydantocidin (2.27) as the sole product (Scheme 2.18).



Scheme 2.18

1-*epi*Hydantocidin (2.27) was further characterised as its tetraacetate (2.30) which was formed simply by treatment of (2.27) with acetic anhydride and pyridine in the presence of a catalytic amount of DMAP (Scheme 2.19).



Scheme 2.19

Due to the lack of epimerisation observed during the deprotection of cyclohexylidene-1-*epi*hydantocidin (2.26), and the literature precedent for the epimerisation of hydantocidin under similar conditions, a brief ^1H nmr study of the interconversion of hydantocidin (1.40)²⁰ and 1-*epi*hydantocidin (2.27) under the acidic conditions used for protecting group hydrolysis was undertaken. The two materials have readily discernible 500 MHz ^1H nmr spectra. Integration of the peaks corresponding to each, derived from mixtures obtained from acidic treatment of either of the pure starting materials, gave approximate ratios of materials. These results are summarised in Table 2.1.

Starting Material	Ratios of products observed		
		Hydantocidin	1- <i>epi</i> Hydantocidin
Hydantocidin (1.40)	(a)	1	: 2.2
	(b)	1	: 4
1- <i>epi</i> Hydantocidin (2.27)	(a)	1	: 10
	(b)	1	: 4.5

(a) 40% aqueous TFA , RT, 16 h
(b) 40% aqueous TFA , RT, 32 h

Table 2.1

Both materials are seen to equilibrate under the reaction conditions, though on a time scale longer than that required for the hydrolysis of cyclohexylidene-1-*epi*hydantocidin (2.26) as described above. The equilibrium mixture appears to be 1-*epi*hydantocidin : hydantocidin, in a ratio of approximately 4 : 1.

(iv) Investigations into tetrahydrofuran and tetrahydropyran ring formation.

Over recent years there has been much interest in the synthesis of a variety of tetrahydrofurans and tetrahydropyrans. In particular, there has been considerable

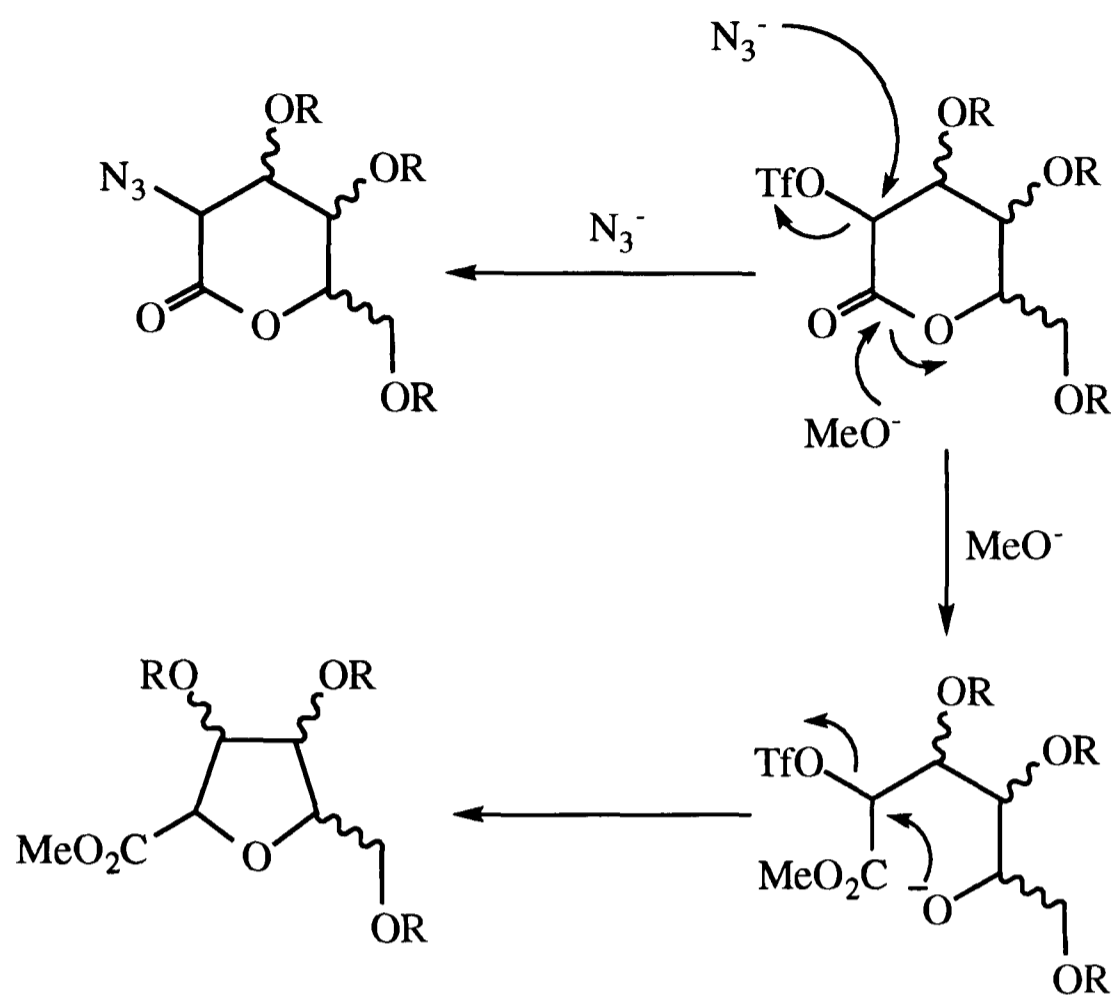
interest in the synthesis of both furanose and pyranose C-glycosides.²² Other synthetic interest has arisen as 2,5-disubstituted tetrahydrofurans and substituted tetrahydropyrans constitute the main structural features of a large number of natural products commonly known as the polyether antibiotics.²³ Many synthetic routes to THF and THP ring formation are available.²⁴

It was envisaged that the novel altrono and allono lactones, synthesised from the Kiliani reaction of protected forms of D-ribose, would be suitable precursors for investigations into THF and THP ring formation. Work in this area is divided into two sections, each of which will be discussed in turn:-

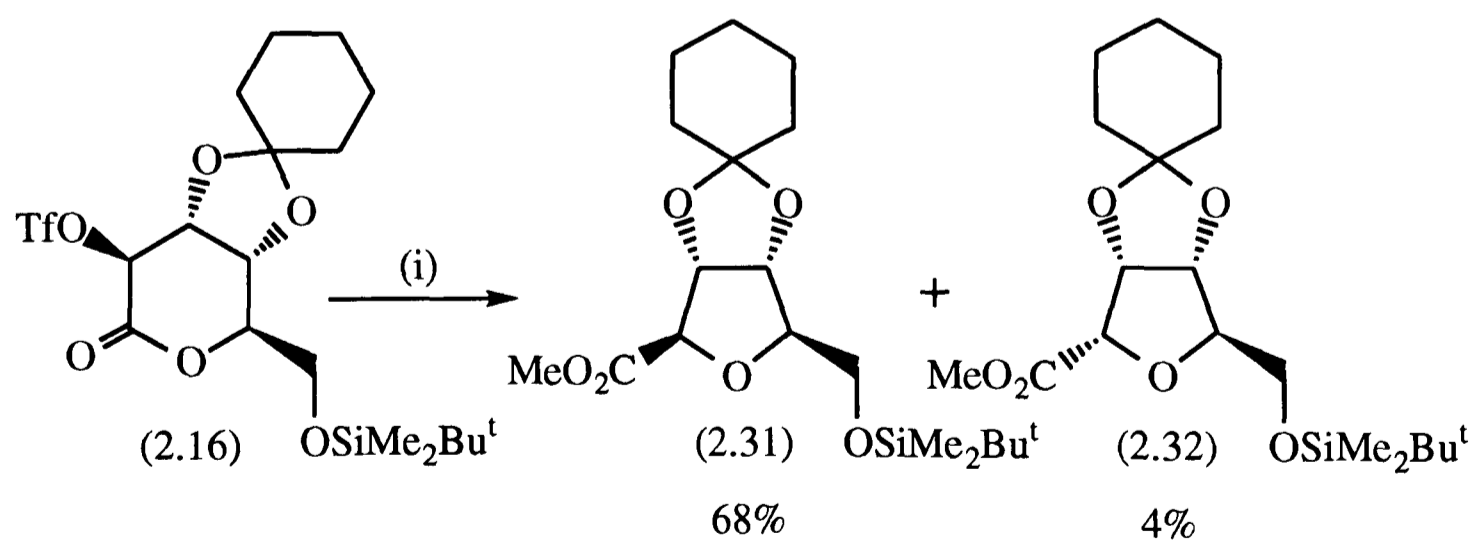
- (a) Tetrahydrofuran ring formation via base induced ring contractions.
- (b) Tetrahydropyran formation via Mitsunobu cyclisations.

(a) Tetrahydrofuran ring formation via base induced ring contractions.

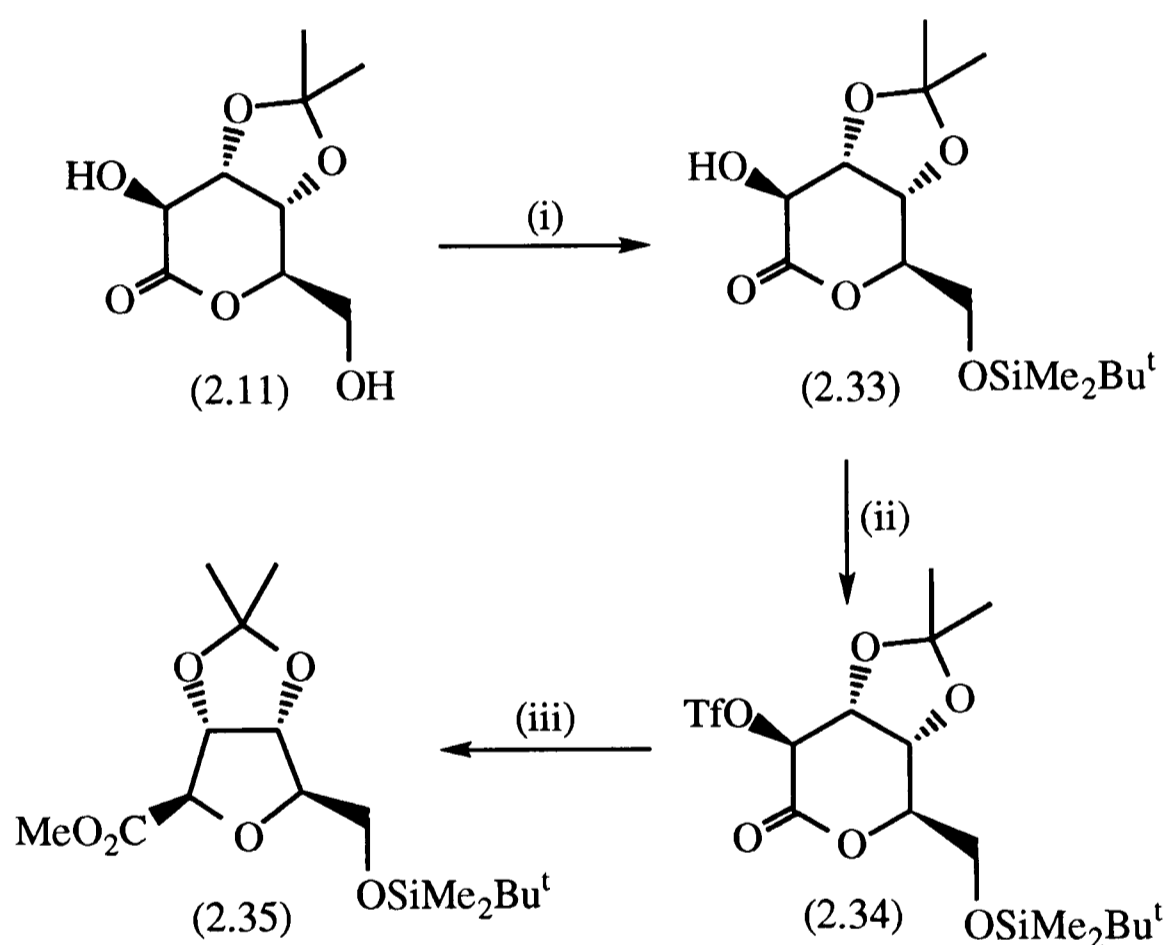
The ring contraction of δ -lactones with leaving group α -substituents provides a strategy for the synthesis of 2,5-disubstituted highly functionalised homochiral tetrahydrofurans.²⁵ Ring contraction of δ -lactone α -triflates can be effected by treatment of a methanolic solution of the triflate with potassium carbonate. Whereas treatment of δ -lactone α -triflates with sodium azide induces nucleophilic displacement of the leaving group, methoxide causes ring contraction by nucleophilic addition to the carbonyl group and ring opening; subsequent ring closure of the original ring oxygen onto C-2 with inversion of configuration results in formation of a tetrahydrofuran methyl ester (Scheme 2.20).



Treatment of the cyclohexylidene altrono silyl triflate (2.16) with potassium carbonate in methanol yielded the cyclohexylidene allo silyl tetrahydrofuran (2.31) as the major product, resulting from inversion of configuration at C-2 of the starting material, together with a small amount of the epimeric altro material (2.32) (Scheme 2.21).



A similar reaction sequence was performed on the isopropylidene altrono system derived from the Kiliani ascension of 2,3-*O*-isopropylidene ribose. Treatment of the altrono acetonide (2.11) with TBDMS chloride and imidazole in DMF yielded the silyl acetonide (2.33). The free hydroxyl at C-2 was converted to its triflate ester via treatment with triflic anhydride and pyridine in dichloromethane to yield the acetonide triflate (2.34). Ring contraction of this material was achieved by treatment with potassium carbonate in methanol to yield the allo tetrahydrofuran acetonide (2.35). This reaction sequence is summarised in Scheme 2.22.

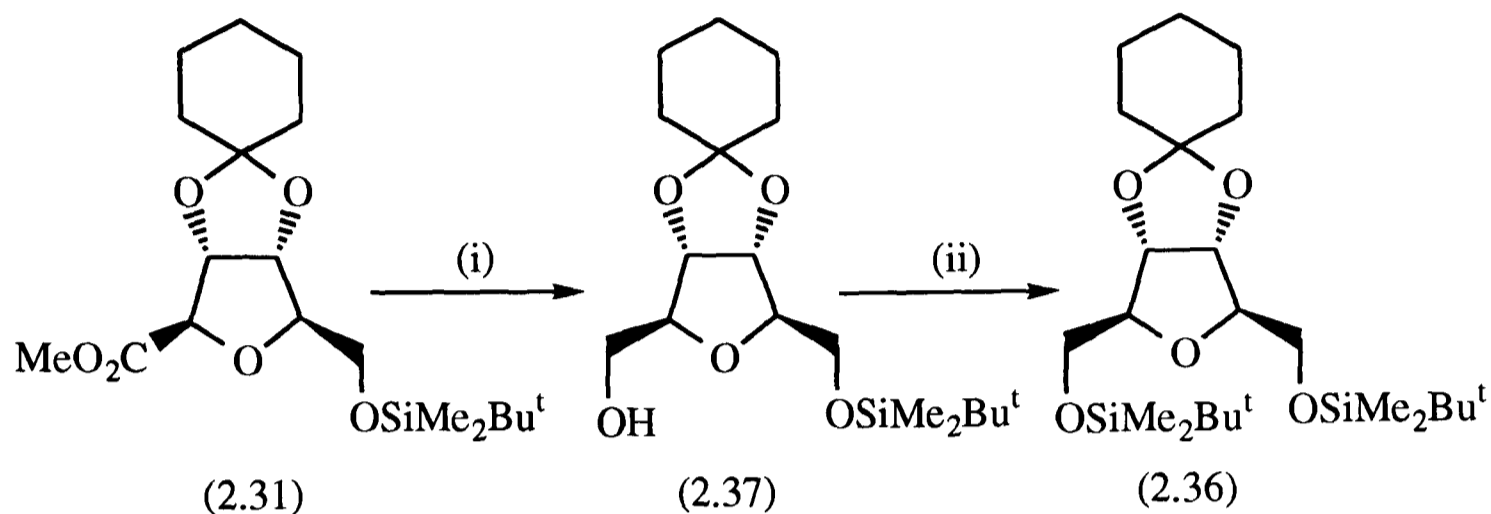


- (i) TBDMSCl, imidazole, DMF, RT, 30 min, 83%
(ii) Tf₂O, py, CH₂Cl₂, -20 °C, 10 min, quantitative
(iii) K₂CO₃, MeOH, RT, 10 min, 58%

Scheme 2.22

The stereochemistry of the cyclohexylidene ring contracted product (2.31) was confirmed by conversion to the symmetric disilyl THF (2.36) via a two step reaction sequence. Reduction of the methyl ester (2.31) to the alcohol (2.37) by treatment with lithium aluminium hydride followed by silylation with TBDMS chloride yielded the

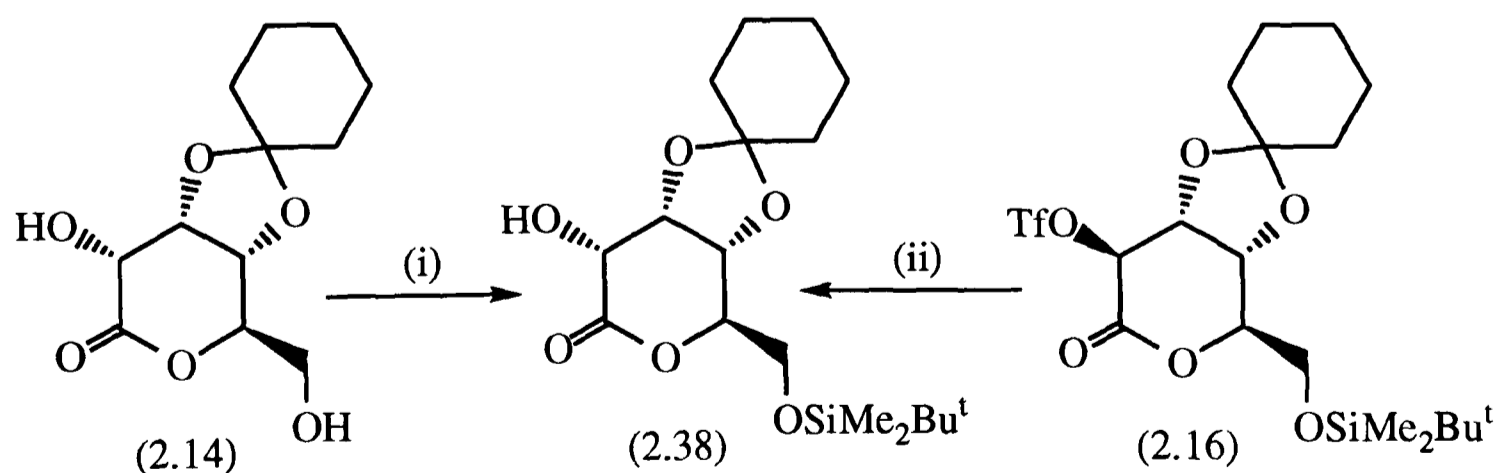
symmetric disilylated THF (2.36) which possessed a zero optical rotation and a characteristic ^{13}C nmr spectrum which contained only one carbohydrate CH_2 and two carbohydrate CH signals (Scheme 2.23).



(i) LiAlH_4 , THF, RT, 5 min, 94% (ii) TBDMSCl , imidazole, DMF, RT, 1 h, 88%

Scheme 2.23

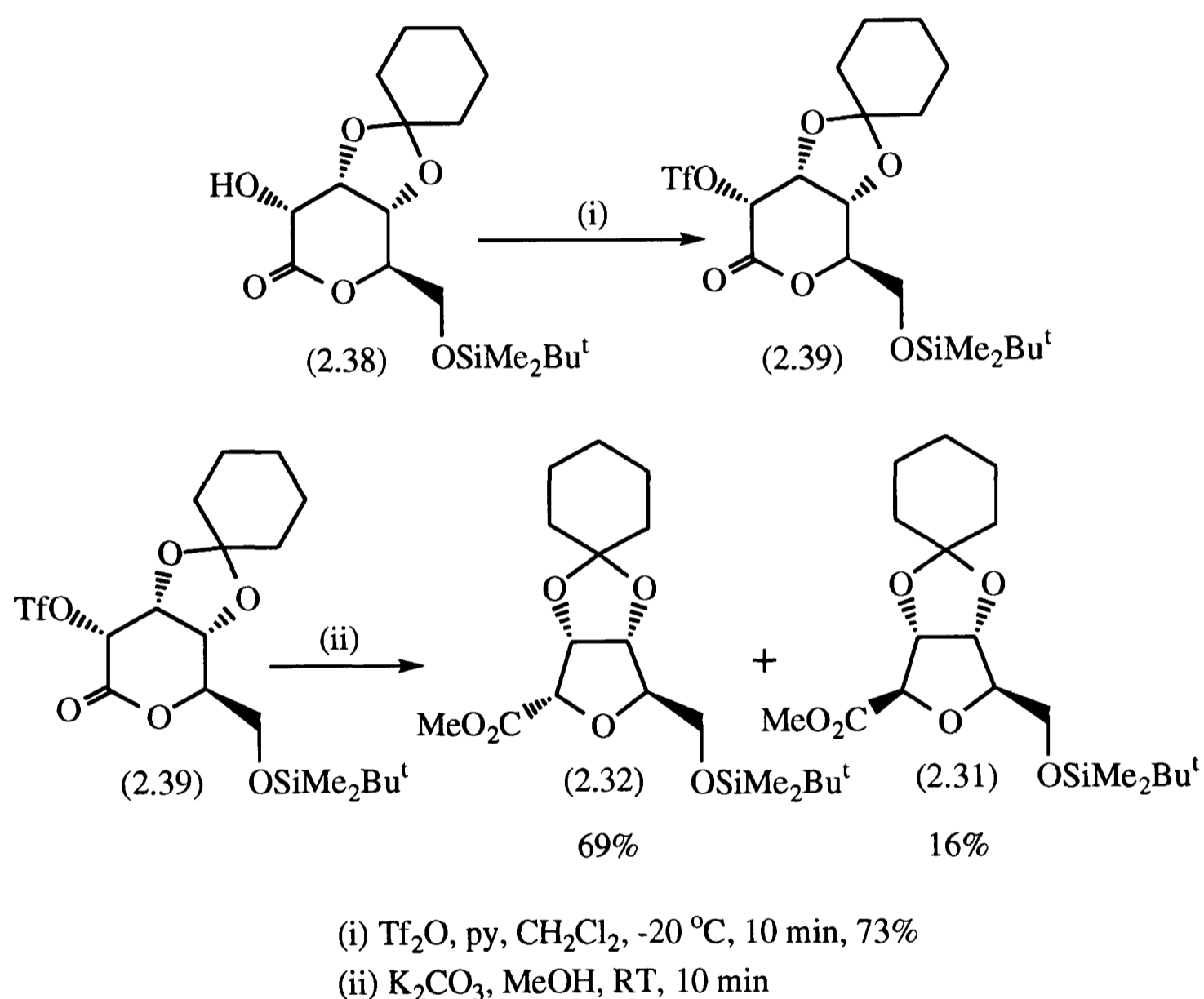
The ring contraction of the cyclohexylidene allono α -triflate (2.39) derived from the minor product of the Kiliani reaction was also investigated. Treatment of 3,4-*O*-cyclohexylidene-allono-1,5-lactone (2.14) with TBDMS triflate in pyridine produced the 6-*O*-silyl allono lactone (2.38). This could also be obtained by $\text{S}_{\text{N}}2$ nucleophilic displacement of the allono silyl triflate (2.16) with sodium trifluoroacetate in DMF (Scheme 2.24).



(i) TBDMSOTf , py, THF, $-20\text{ }^\circ\text{C}$, 30 min, 81%
(ii) $\text{CF}_3\text{CO}_2\text{Na}$, DMF, $70\text{ }^\circ\text{C}$, 2 h, then MeOH, 40%

Scheme 2.24

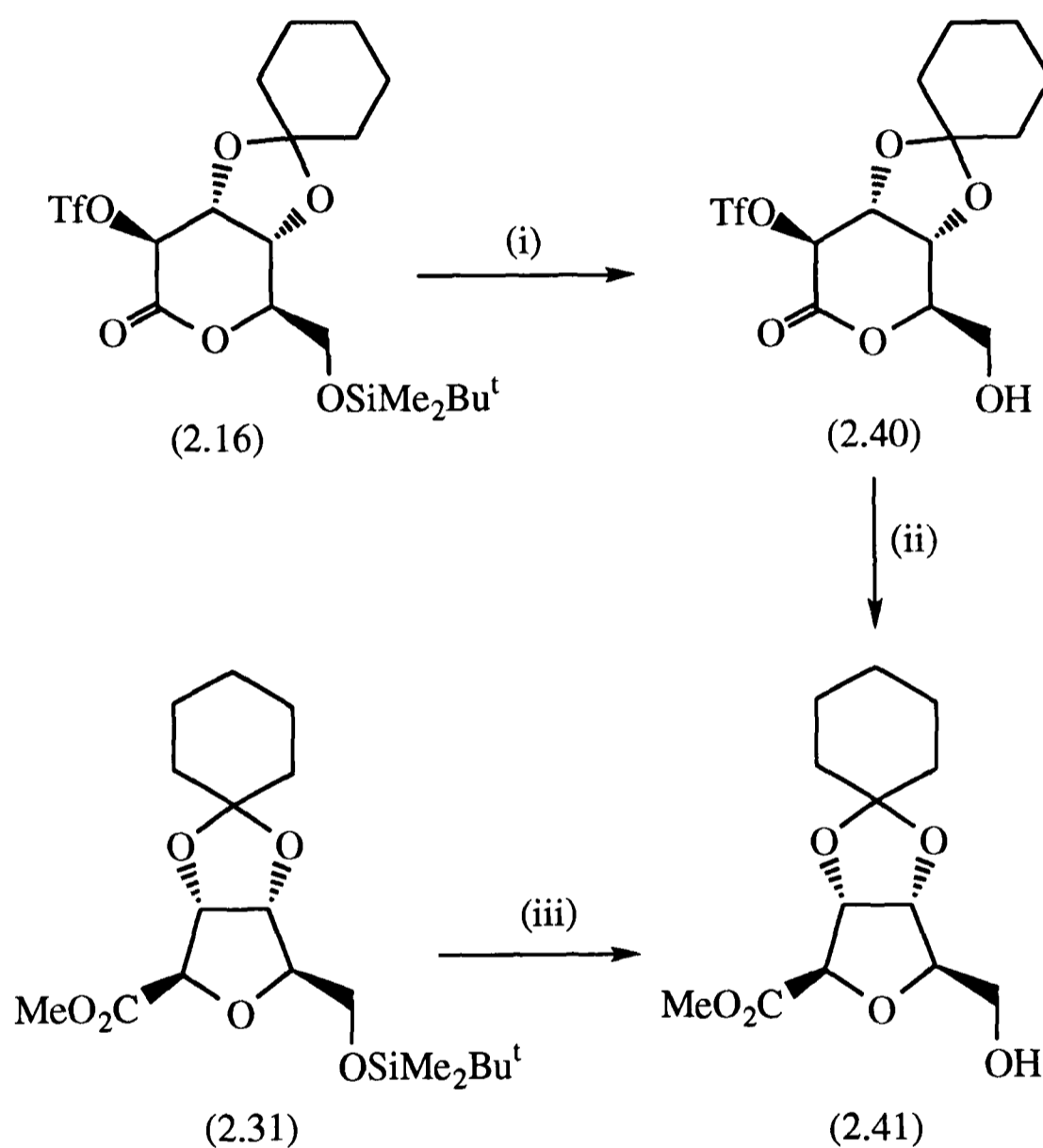
Treatment of the 6-*O*-silyl allono lactone (2.38) with triflic anhydride yielded the desired allo triflate (2.39). Ring contraction of the allo triflate (2.39) with potassium carbonate in methanol yielded the two ring contracted products observed previously, however this time the major product was found to be the altro tetrahydrofuran (2.32) again resulting from an inversion of configuration at C-2 (Scheme 2.25).



Scheme 2.25

Ring rearrangement of δ -lactones with a free hydroxyl group at C-6 and a leaving group at C-2, induced by similar reaction conditions, would provide a strategy for the synthesis of highly functionalised tetrahydropyrans. In order to investigate this possibility, desilylation of the silyl altrono triflate (2.16) was attempted. Initial efforts using tetra-*n*-butylammonium fluoride caused complete decomposition. Desilylation was achieved by treatment with 80% aqueous acetic acid to yield the alcohol (2.40).

Treatment of the alcohol (2.40) with potassium carbonate in methanol resulted in the formation of the ring contracted methyl ester (2.41) as the sole product. This material was synthesised unambiguously via desilylation of the ring contracted methyl ester (2.31) by treatment with 80% aqueous acetic acid. These reactions are summarised in Scheme 2.26.



- (i) 80% aqueous AcOH, RT, 13 h, 70%
(ii) K₂CO₃, MeOH, RT, 10 min, 94%
(iii) 80% aqueous AcOH, RT, 24 h, 60%

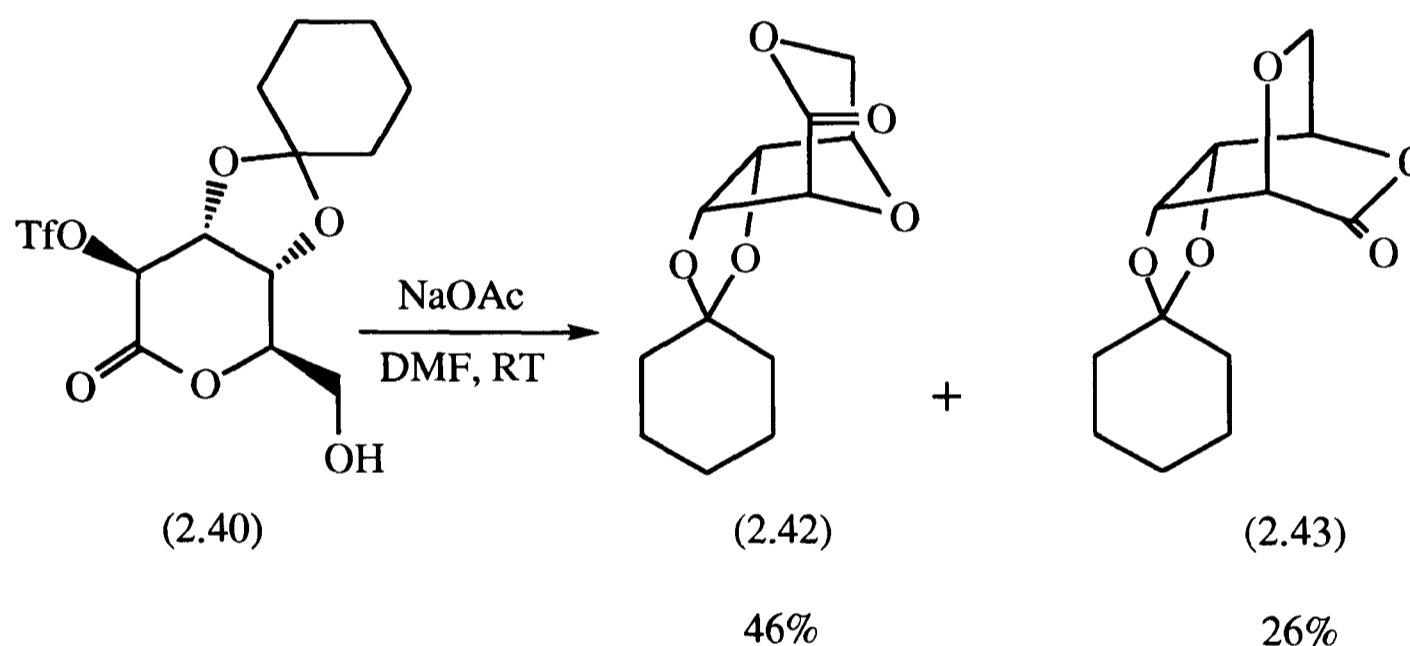
Scheme 2.26

The formation of this material as the sole reaction product shows that there is effectively no competition for the formation of a tetrahydropyran over a tetrahydrofuran in this system.

(b) Tetrahydropyran formation via Mitsunobu cyclisations.

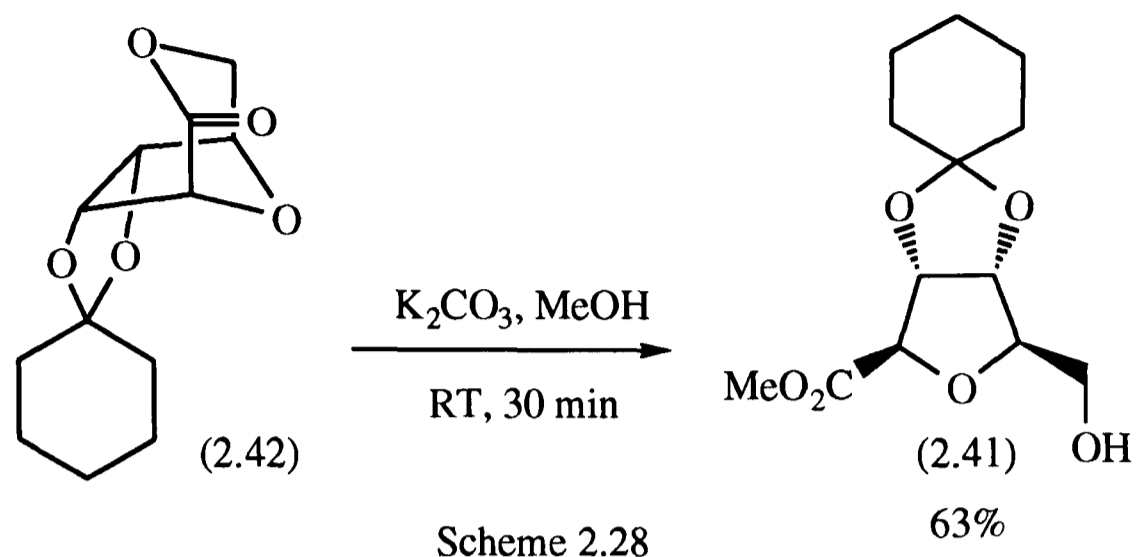
Due to the effective competition of THF over THP formation observed above, an alternative strategy for the synthesis of tetrahydropyrans was required. In particular, any attempts at formation of a tetrahydropyran ring from the altrono-1,5-lactone system must involve reaction conditions that leave the lactone ring intact.

The first strategy attempted involved treatment of the triflate alcohol (2.40) with sodium acetate in DMF in an attempt to induce base catalysed cyclisation of C-6 onto C-2 without opening of the lactone ring. A mixture of bicyclic products was obtained as shown in Scheme 2.27.



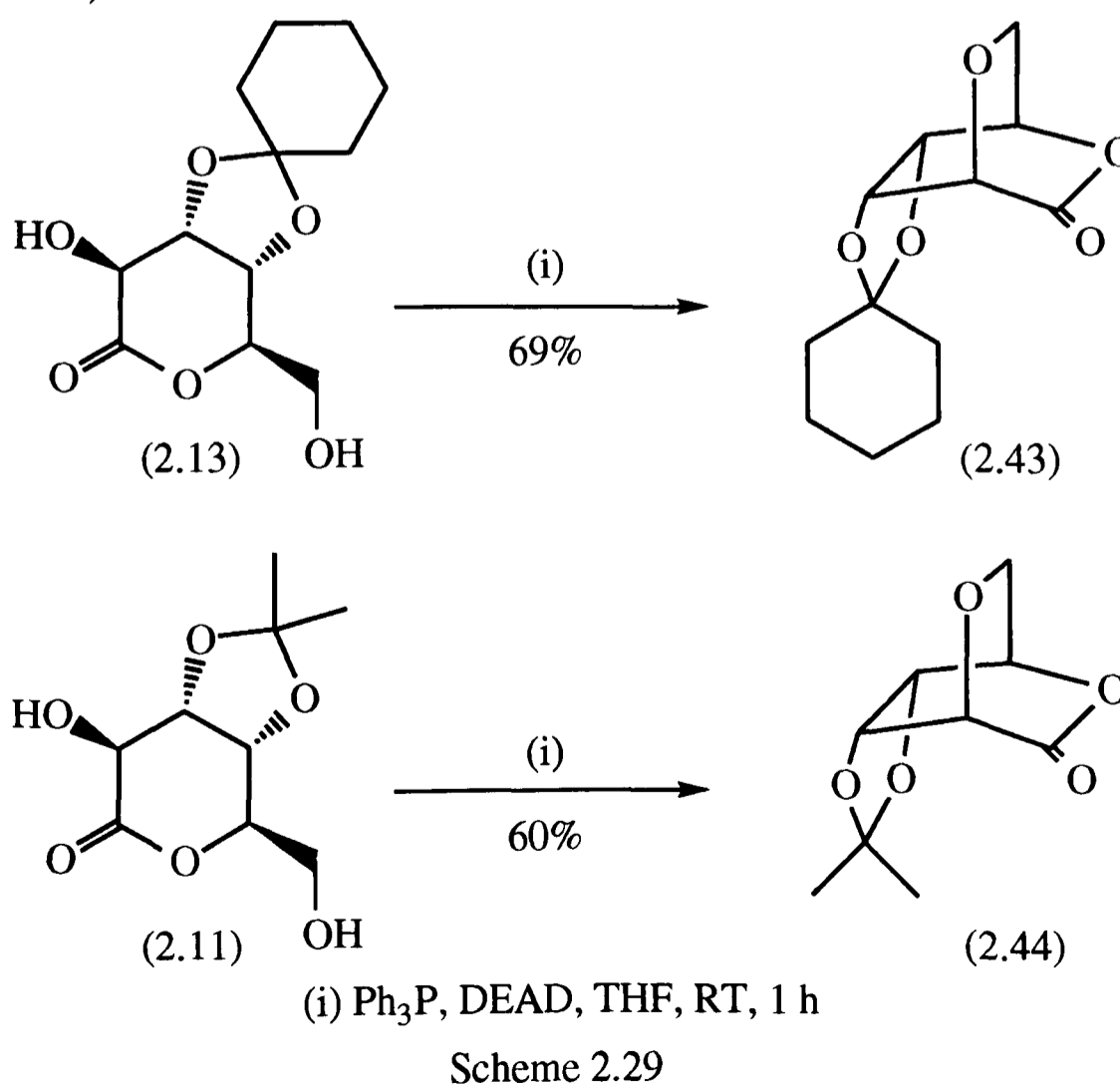
Scheme 2.27

The major product was identified as the bicyclic furan (2.42). Treatment of this material with potassium carbonate in methanol induced opening of the lactone to produce the furan methyl ester (2.41), identical with the material described earlier (Scheme 2.28). The minor product was later identified as the bicyclic pyran (2.43).

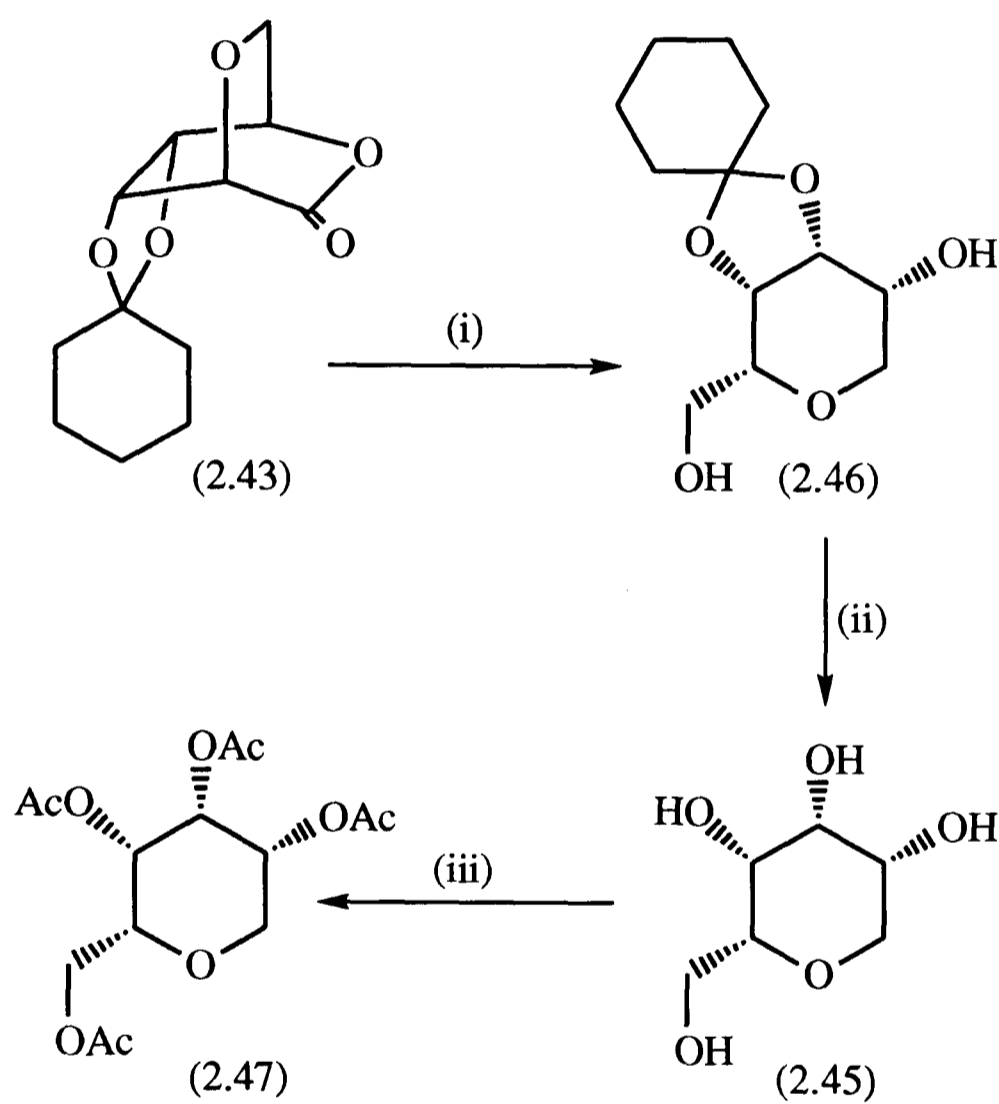


Cyclisation of C-6 onto C-2 in the altrono system requires epimerisation of the leaving group at C-2 before nucleophilic displacement can take place. An alternative strategy consisting of cyclisation of C-2 onto C-6, which also results in tetrahydropyran formation, was therefore adopted.

Simple treatment of the 3,4-*O*-cyclohexylidene-altrono-1,5-lactone (2.13) with triphenylphosphine and DEAD in THF²⁶ resulted in formation of the bicyclic pyran (2.43) as the sole reaction product in 69% yield. Similar treatment of the isopropylidene lactone (2.11) resulted in formation of the isopropylidene bicyclic pyran (2.44) (Scheme 2.29).



The identity of the bicyclic cyclohexylidene pyran (2.43) was confirmed by elaboration to 2,6-anhydro-D-altritol (2.45).²⁷ Reduction of the lactone with lithium borohydride produced the alcohol (2.46). Removal of the cyclohexylidene protecting group yielded 2,6-anhydro-D-altritol (2.45), with physical and spectral data in close agreement with literature values. Treatment of the tetrol (2.45) with acetic anhydride and pyridine in the presence of DMAP yielded the tetraacetate (2.47) which also possessed data in close agreement with literature values (Scheme 2.30).



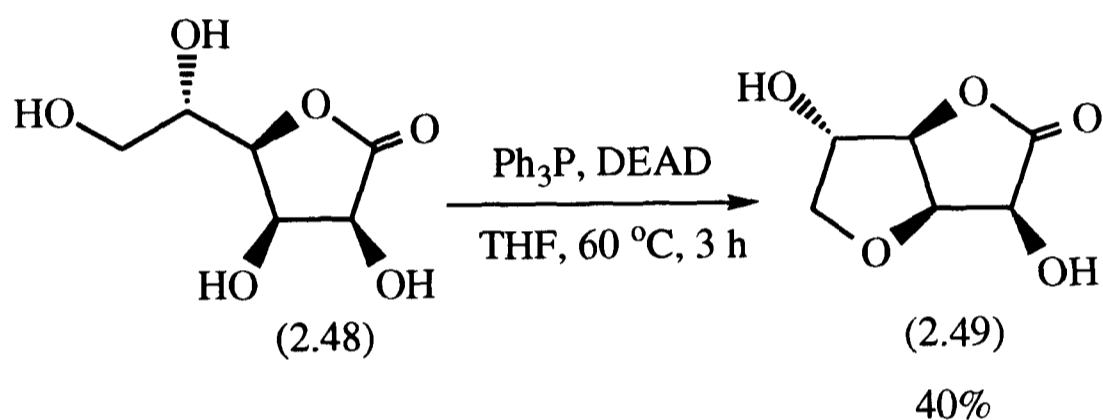
- (i) LiBH_4 , THF, 0°C , 4 h, 93%
(ii) 40% aqueous TFA, RT, 12 h, 89%
(iii) Ac_2O , py, DMAP, RT, 30 min, 50%

Scheme 2.30

The above reactions demonstrate that tetrahydropyran formation can be achieved simply by treatment of altrono-1,5-lactones under Mitsunobu type conditions. If such a methodology could be extended to seven carbon δ -lactones, which may be derived

from the Kiliani reaction of suitably protected hexoses, this would provide an efficient synthetic route to C-pyranosides.

In order to test the generality of this reaction, and in particular if Mitsunobu type conditions could lead to competitive THP formation in cases where THF formation was also possible, L-gulono-1,4-lactone (2.48) was subjected to similar reaction conditions. Again cyclisation to a bicyclic system occurred. However the sole reaction product was found to be the bicyclic furan (2.49),²⁸ resulting from cyclisation of C-3 onto C-6 (Scheme 2.31).

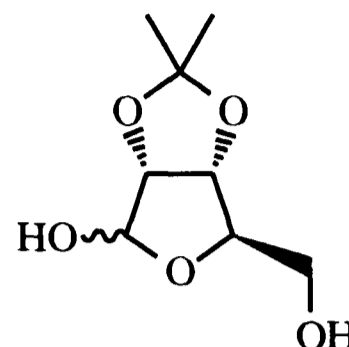


Scheme 2.31

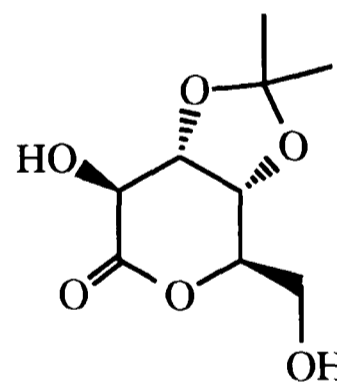
Again cyclisation to a furan is seen to compete effectively with the alternative cyclisation to a pyran and in this case also with possible epoxide formation. Such effective competition limits the applicability of such a strategy for the synthesis of polyhydroxylated tetrahydropyrans.

General Experimental Procedures.

Melting points were recorded on a Kofler hot block and are uncorrected. ^1H nuclear magnetic resonance (δ_{H}) spectra were recorded on Bruker WH 300 (300 MHz) or Bruker AM 500 (500 MHz) spectrometers. ^{13}C Nuclear magnetic resonance (δ_{C}) spectra were recorded on a Varian Gemini 200 (50.3 MHz) spectrometer and multiplicities were assigned using DEPT sequence. ^{13}C spectra run in D_2O were referenced to methanol (δ_{C} 49.6 ppm) as an internal standard. All chemical shifts are quoted on the δ -scale. Infra-red spectra were recorded on a Perkin-Elmer 1750 FT spectrophotometer. Mass spectra were recorded on VG Micromass 30F, ZAB 1F, Masslab 20-250 or Trio-1 GCMS (DB-5 column) spectrometers using desorption chemical ionisation (NH_3 , DCI), chemical ionisation (NH_3 , CI), electrospray, or electron impact (EI), 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. 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 60F₂₅₄ silica or glass plates coated with silica Blend 41. Plates were developed using a spray of 0.2% w/v cerium (IV) sulphate and 5% w/v ammonium molybdate in 2M sulphuric acid, or 0.5% w/v ninhydrin in methanol. All solvents were removed *in vacuo*. Flash chromatography was carried out using Sorbsil C60 40/60 silica. CMAW (chloroform / methanol / acetic acid / water) used as an eluant 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 in the H^+ 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; methanol was distilled from magnesium methoxide; pyridine was distilled from, and stored over, potassium hydroxide; tetrahydrofuran was distilled, under nitrogen, from a solution dried with sodium in the presence of benzophenone. Hexane was distilled at 68 °C before use to remove involatile fractions.

Experimental.2,3-O-Isopropylidene-D-ribose (2.8).

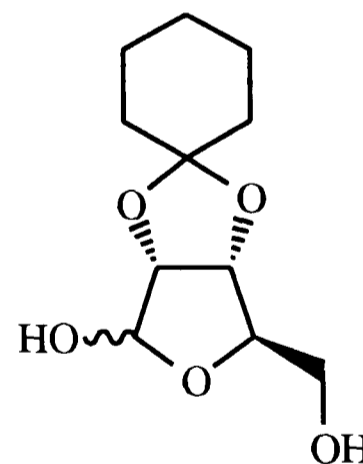
D-Ribose (2.9) (3.07 g, 20 mmol), Dowex 50W-X8 [H⁺] ion exchange resin (1.5 g) and dried 3Å molecular sieves (1.5 g, bead form) were stirred vigorously at room temperature in acetone (50 ml, dried over magnesium sulphate). After 3 h, t.l.c. (ethyl acetate) indicated complete consumption of starting material (R_f 0.1), and the formation of a major product (R_f 0.6), together with other minor products (R_f 0.8 and R_f 0.3). The suspension was then filtered, the solvent removed and the residue co-evaporated with acetonitrile (2 x 10 ml), to remove traces of acetone, to yield a crude syrup (2.1 g, 55%) which was used directly without further purification or characterisation.

3,4-O-Isopropylidene-D-altrono-1,5-lactone (2.11).

The crude syrup of (2.8) prepared above (2.1 g) was stirred with sodium cyanide (0.7 g, 14 mmol) in water (40 ml) at room temperature overnight. The mixture was then refluxed for 6 h. T.l.c. (ethyl acetate) indicated a major product at the baseline, together with some unreacted starting material (R_f 0.3). The solution was cooled and extracted with ethyl acetate (3 x 50 ml) to remove unreacted starting material. The aqueous extract was then adjusted to pH 4 by careful addition of concentrated sulphuric acid and the solvent then removed. The residue was co-evaporated with toluene (2 x 10 ml), dissolved in acetic acid (50 ml), and stirred at room temperature overnight. T.l.c. (ethyl

acetate) indicated the formation of a product (R_f 0.5) together with a large amount of baseline material. The solvent was removed, the residue co-evaporated with toluene (2 x 10 ml), and then dissolved in ethyl acetate by heating at reflux for several hours. The solution was cooled, filtered through a silica plug topped with Celite and the solvent removed to yield a residue that was purified by repeated flash chromatography (hexane : ethyl acetate, 1 : 1) to yield 3,4-*O*-isopropylidene-D-altrono-1,5-lactone (2.11) (223 mg, 10% based on crude isopropylidene ribose), as a white crystalline solid, m.p. 130-132 °C (ethyl acetate / hexane); $[\alpha]_D^{20} +101.3$ (c, 0.9 in EtOH); ν_{\max} (KBr) 3400 (br, OH), 1768 (C=O) cm^{-1} ; δ_{H} (CD_3OD) 1.37, 1.50 (6H, 2 x s, Me_2C), 3.72 (1H, dd, H-6, $J_{5,6}$ 5.0 Hz, $J_{6,6'}$ 12.8 Hz), 3.89 (1H, dd, H-6', $J_{5,6'}$ 2.1 Hz), 4.24 (1H, ddd, H-5, $J_{4,5}$ 9.5 Hz), 4.29 (1H, dd, H-3, $J_{2,3}$ 7.4 Hz, $J_{3,4}$ 8.0 Hz), 4.38 (1H, dd, H-4), 4.51 (1H, d, H-2); δ_{C} (CD_3OD) 24.2, 26.5 (2 x q, Me_2C), 61.2 (t, C-6), 71.2, 71.4, 78.5, 79.0 (4 x d, C-2, C-3, C-4, C-5), 112.6 (s, CMe_2), 173.7 (s, C-1); m/z (NH_3 , DCI) 236 (MNH_4^+ , 100%), 219 (MH^+). (Found: C, 49.20; H, 6.41; $\text{C}_9\text{H}_{14}\text{O}_6$ requires: C, 49.54; H, 6.47%).

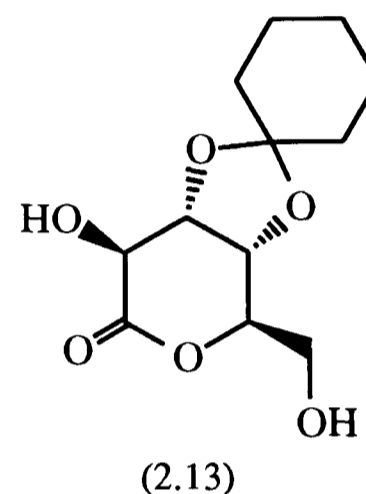
2,3-*O*-Cyclohexylidene-D-ribose (2.12).



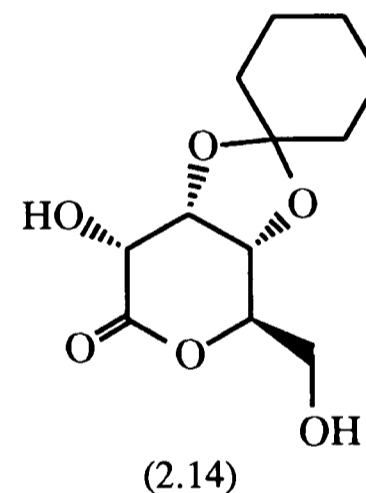
A mixture of D-ribose (2.9) (30.0 g, 0.2 mol) and *p*-toluenesulphonic acid (0.7 g, 3.7 mmol) was stirred in freshly distilled cyclohexanone (200 ml) under nitrogen. After 12 h, t.l.c. (ethyl acetate) indicated complete consumption of starting material (R_f 0.1), and the formation of a major product (R_f 0.7). Ethyl acetate (500 ml) was added and the mixture washed with sodium bicarbonate solution (300 ml), and water (300 ml). The organic extracts were dried (magnesium sulphate), filtered, the solvent removed and the residue purified by dry flash chromatography (chloroform : methanol, 20 : 1) to yield

2,3-O-cyclohexylidene-D-ribose (2.12) (44.5 g, 97%) as a colourless oil; $[\alpha]_D^{20}$ -20.0 (c, 1.1 in CHCl_3), [Lit -20.8 (c, 1.01 in CHCl_3)]¹⁵; δ_{H} (CDCl_3) 1.40-1.86 (10H, m, cyclohexylidene), 3.70-3.79 (2H, m, H-5, H-5'), 4.42 (1H, s, H-4), 4.58 (1H, dd, H-2, $J_{2,3}$ 5.9 Hz), 4.83 (1H, d, H-3), 5.43 (1H, d, H-1, $J_{1,2}$ 5.5 Hz); δ_{C} (CDCl_3) 23.5, 23.8, 24.8, 34.0, 35.7 (5 x t, cyclohexylidene), 63.4 (t, C-5), 81.2, 86.3, 87.8 (3 x d, C-2, C-3, C-4), 102.1 (d, C-1), 113.0 (s, cyclohexylidene).

3,4-O-Cyclohexylidene-D-altrono-1,5-lactone (2.13)



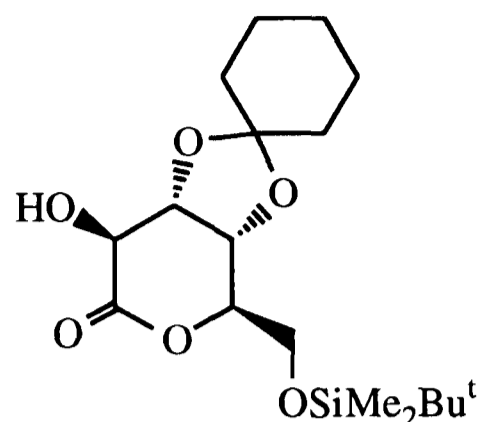
and 3,4-O-cyclohexylidene-D-allono-1,5-lactone (2.14).



2,3-O-Cyclohexylidene-D-ribose (2.12) (44.5 g, 0.19 mol) and sodium cyanide (8.53 g, 0.17 mol) were stirred together in water (500 ml) at room temperature overnight. The temperature of the reaction mixture was then raised to 70 °C and nitrogen was bubbled through the solution until evolution of ammonia had ceased (approx 6 h). At this point a test for cyanide was found to be negative and t.l.c. (ethyl acetate) indicated some starting material (R_f 0.7) together with a major product at the baseline. The mixture was allowed to cool to room temperature and then washed with ethyl acetate (4 x 400 ml) to remove unreacted starting material, which was reclaimed. The aqueous extract was adjusted to pH 7 by the addition of acetic acid, the solvent removed under reduced pressure and the residue co-evaporated with toluene (3 x 50 ml). Acetic acid

(200 ml) was added and the mixture heated at 70 °C. After 1.5 h, t.l.c. (ethyl acetate) indicated the formation of a major product (R_f 0.7) and a minor product (R_f 0.5). The solvent was removed and the residue co-evaporated with toluene (2 x 30 ml). The residue was then shaken with ethyl acetate (300 ml) and water (300 ml) and the aqueous layer further extracted with ethyl acetate (2 x 200 ml). The combined organic extracts were dried (magnesium sulphate), filtered, and the solvent removed to produce a residue which was purified by repeated flash chromatography (hexane : ethyl acetate, 1 : 1) to yield 3,4-*O*-cyclohexylidene-D-altrono-1,5-lactone (2.13) (7.92 g, 20% based on recovered starting material, R_f 0.7) as a white crystalline solid, m.p. 119-120 °C (ethyl acetate / methanol); $[\alpha]_D^{20} +80.4$ (*c*, 1.02 in EtOH); ν_{\max} (KBr) 3500-3200 (br, OH), 1773 (C=O) cm^{-1} ; δ_{H} (d_6 acetone) 1.40-1.70 (10H, m, cyclohexylidene), 3.72 (1H, dd, H-6, $J_{5,6}$ 4.9 Hz, $J_{6,6'}$ 12.6 Hz), 3.90 (1H, dd, H-6', $J_{5,6'}$ 2.1 Hz), 4.27 (1H, ddd, H-5, $J_{4,5}$ 9.4 Hz), 4.34 (1H, m, H-3, $J_{2,3}$ 6.9 Hz, $J_{3,4}$ 7.8 Hz), 4.42 (1H, dd, H-4), 4.55 (1H, d, H-2); δ_{C} (d_6 acetone) 24.2, 24.6, 25.6, 34.7, 37.4 (5 x t, cyclohexylidene), 61.5 (t, C-6), 71.0, 71.7, 78.3, 79.1 (4 x d, C-2, C-3, C-4, C-5), 112.9 (s, cyclohexylidene), 173.4 (s, C-1); m/z (NH_3 , DCI) 276 (MNH_4^+ , 100%), 259 (MH^+). (Found: C, 55.70; H, 7.26; $\text{C}_{12}\text{H}_{18}\text{O}_6$ requires: C, 55.81; H, 7.02%); and 3,4-*O*-cyclohexylidene-D-allono-1,5-lactone (2.14) (389 mg, 1% based on recovered starting material, R_f 0.5) as a white crystalline solid, m.p. 128-130 °C (ethyl acetate / hexane); $[\alpha]_D^{20} -68.1$ (*c*, 1.03 in EtOH); ν_{\max} (KBr) 3400 (br, OH), 1751 (C=O) cm^{-1} ; δ_{H} (d_6 acetone) 1.38-1.63 (10H, m, cyclohexylidene), 2.97 (2H, s, OH), 3.87-3.90 (2H, m, H-6, H-6'), 4.47 (1H, br t, H-5), 4.70-4.86 (3H, m, H-2, H-3, H-4); δ_{C} (d_6 acetone) 24.2, 24.5, 25.6, 34.5, 36.8 (5 x t, cyclohexylidene), 63.0 (t, C-6), 68.0, 74.3, 76.7, 84.0 (4 x d, C-2, C-3, C-4, C-5), 111.0 (s, cyclohexylidene), 172.5 (s, C-1); m/z (NH_3 , DCI) 276 (MNH_4^+), 259 (MH^+ , 100%). (Found: C, 55.58; H, 6.94; $\text{C}_{12}\text{H}_{18}\text{O}_6$ requires: C, 55.81; H, 7.02%).

6-*O*-*tert*-Butyldimethylsilyl-3,4-*O*-cyclohexylidene-D-altrono-1,5-lactone (2.15).



3,4-Cyclohexylidene-D-altrono-1,5-lactone (2.13) (4.72 g, 18.3 mmol) and imidazole (2.61 g, 38.4 mmol) were stirred under nitrogen in dry DMF (100 ml) at -20 °C. *tert*-Butyldimethylsilylchloride (2.90 g, 19.2 mmol) was added and the mixture stirred for 2.5 h when t.l.c. (hexane : ethyl acetate, 1 : 1) showed complete consumption of starting material (R_f 0.2) and the formation of a major product (R_f 0.8), together with a minor product (R_f 0.9). The solvent was removed and dichloromethane (75 ml) was added. The mixture was shaken with water (75 ml), which was further extracted with dichloromethane (2 x 50 ml). The combined organic extracts were then dried (magnesium sulphate), filtered, the solvent removed, and the residue purified by flash chromatography (hexane : ethyl acetate, 3 : 1) to yield 6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-cyclohexylidene-D-altrono-1,5-lactone (2.15) (6.28 g, 92%) as a white crystalline solid, m.p. 74-75 °C (methanol / water); $[\alpha]_D^{20} +71.3$ (c , 1.02 in CHCl_3); ν_{max} (KBr) 3400 (br, OH), 1767 (C=O) cm^{-1} ; δ_{H} (CDCl_3) 0.11 (6H, s, Me_2Si), 0.92 (9H, s, Bu^t), 1.40-1.76 (10H, m, cyclohexylidene), 3.36 (1H, d, OH, $J_{2,\text{OH}}$ 3.2 Hz), 3.88 (1H, dd, H-6, $J_{5,6}$ 4.5 Hz, $J_{6,6'}$ 12.0 Hz), 4.04 (1H, dd, H-6', $J_{5,6'}$ 2.0 Hz), 4.15 (1H, ddd, H-5, $J_{4,5}$ 9.0 Hz), 4.27-4.32 (1H, m, H-3), 4.36 (1H, dd, H-4, $J_{3,4}$ 7.8 Hz), 4.42 (1H, dd, H-2, $J_{2,3}$ 6.7 Hz); δ_{C} (CDCl_3) -5.6 (q, Me_2Si), 18.2 (s, Me_3CSi), 23.2, 23.7, 25.3 (3 x t, cyclohexylidene), 25.7 (q, Me_3C), 33.9, 36.6 (2 x t, cyclohexylidene), 61.8 (t, C-6), 69.7, 70.9, 77.1, 78.7 (4 x d, C-2, C-3, C-4, C-5), 113.0 (s, cyclohexylidene), 173.1 (s, C-1); m/z (NH_3 , DCI) 390 (MNH_4^+ , 100%), 373 (MH^+). (Found: C, 58.26; H, 8.90; $\text{C}_{18}\text{H}_{32}\text{O}_6\text{Si}$ requires: C, 58.03; H, 8.66%); and a small amount of disilylated material (0.414 g, 5%) as a colourless oil; δ_{H} (CDCl_3) 0.09 (6H, s, Me_2Si), 0.14, 0.18 (6H, 2 x s, Me_2Si), 0.90, 0.95 (18H, 2 x s,

2 x Bu^t), 1.40-1.75 (10H, m, cyclohexylidene), 3.83 (1H, dd, H-6, J_{5,6} 4.5 Hz, J_{6,6'} 11.8 Hz), 3.99 (1H, dd, H-6', J_{5,6'} 1.1 Hz), 4.08 (1H, m, H-5), 4.23-4.38 (3H, m); *m/z* (NH₃, DCI) 504 (MNH₄⁺), 487 (MH⁺).

6-*O*-*tert*-Butyldimethylsilyl-3,4-*O*-cyclohexylidene-2-*O*-trifluoromethanesulphonyl-D-altrono-1,5-lactone (2.16).

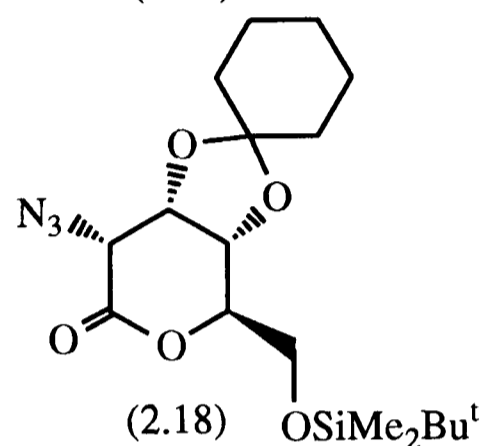
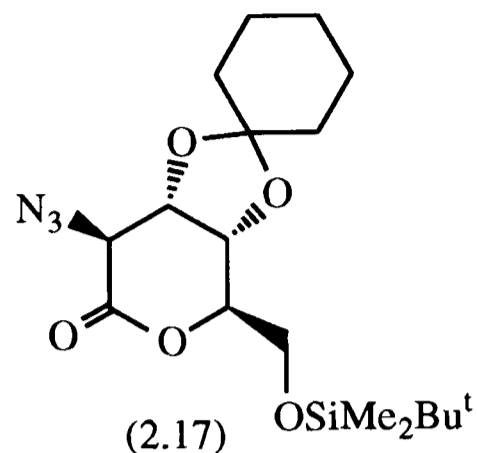


6-*O*-*tert*-Butyldimethylsilyl-3,4-*O*-cyclohexylidene-D-altrono-1,5-lactone (2.15) (1.53 g, 4.11 mmol) and dry pyridine (0.84 ml, 10.3 mmol) were stirred under nitrogen in dry dichloromethane (50 ml) at -20 °C. Trifluoromethanesulphonic anhydride (1.04 ml, 6.17 mmol) was added. After 10 min, t.l.c. (hexane : ethyl acetate, 3 : 1) indicated complete product formation (*R_f* 0.6) and further dichloromethane (20 ml) was added. The reaction mixture was shaken with water (30 ml, containing a few drops of 1M HCl) and then washed with water (30 ml) and brine (30 ml). The organic extracts were then dried (magnesium sulphate), filtered, the solvent removed and the residue purified by flash chromatography (hexane : ethyl acetate, 7 : 1) to yield 6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-cyclohexylidene-2-*O*-trifluoromethanesulphonyl-D-altrono-1,5-lactone (2.16) (2.06 g, quantitative) as a white crystalline solid, m.p. 76-78 °C (methanol / water); [α]_D²⁰ +19.1 (*c*, 1.1 in CHCl₃); ν_{max} (film) 1785 (C=O) cm⁻¹; δ_H (CDCl₃) 0.11 (6H, s, Me₂Si), 0.92 (9H, s, Bu^t), 1.41-1.77 (10H, m, cyclohexylidene), 3.90 (1H, dd, H-6, J_{5,6} 4.0 Hz, J_{6,6'} 11.9 Hz), 4.04 (1H, dd, H-6', J_{5,6'} 2.2 Hz), 4.25 (1H, m, H-5), 4.51-4.56 (2H, m, H-3, H-4), 5.22 (1H, d, H-2, J_{2,3} 7.0 Hz); δ_C (CDCl₃) -5.7 (q, Me₂Si), 18.2 (s, Me₃CSi), 23.3, 23.6, 24.7 (3 x t, cyclohexylidene), 25.6 (q, Me₃C), 34.1, 36.6 (2 x t, cyclohexylidene), 61.7 (t, C-6), 70.2, 73.9, 79.0, 82.0 (4 x d, C-2, C-3, C-4, C-5), 114.1 (s, cyclohexylidene), 164.3 (s, C-1); *m/z* (NH₃, DCI) 522 (MNH₄⁺, 100%), 505 (MH⁺). (Found: C, 45.19; H, 6.42; C₁₉H₃₁O₈F₃SSi requires: C, 45.23; H, 6.19%).

2-Azido-6-O-tert-butyltrimethylsilyl-3,4-O-cyclohexylidene-2-deoxy-D-altrono-1,5-lactone (2.17)

and

2-azido-6-O-tert-butyltrimethylsilyl-3,4-O-cyclohexylidene-2-deoxy-D-allono-1,5-lactone (2.18).



6-O-tert-Butyltrimethylsilyl-3,4-O-cyclohexylidene-2-O-trifluoromethanesulphonyl-D-altrono-1,5-lactone (2.16) (850 mg, 1.69 mmol) and sodium azide (329 mg, 5.06 mmol) were stirred at room temperature in DMF (10 ml). After 10 min t.l.c. (hexane : ethyl acetate, 5 : 1) indicated complete consumption of starting material (R_f 0.7), and the formation of two products (R_f 0.6 and R_f 0.5). The solvent was removed and ethyl acetate (50 ml) added. The mixture was then washed with water (50 ml), brine (50 ml), dried (magnesium sulphate), filtered, the solvent removed and the residue purified by flash chromatography (hexane : ethyl acetate, 7 : 1) to yield 2-azido-6-O-tert-butyltrimethylsilyl-3,4-O-cyclohexylidene-2-deoxy-D-altrono-1,5-lactone (2.17) (340 mg, 50%, R_f 0.6) as a white crystalline solid, m.p. 67-68 °C (methanol / water); $[\alpha]_D^{20} +18.2$ (c , 1.06 in CHCl_3); ν_{max} (KBr) 2125 (N_3), 1757 ($\text{C}=\text{O}$) cm^{-1} ; δ_{H} (CDCl_3) 0.11, 0.12 (6H, 2 x s, Me_2Si), 0.92 (9H, s, Bu^t), 1.41-1.74 (10H, m, cyclohexylidene), 3.89 (1H, dd, H-6, $J_{5,6}$ 4.4 Hz, $J_{6,6'}$ 11.9 Hz), 4.03 (1H, dd, H-6', $J_{5,6'}$ 2.1 Hz), 4.15 (1H, ddd, H-5, $J_{4,5}$ 9.2 Hz), 4.27-4.30 (2H, m, H-2, H-3), 4.37 (1H, m, H-4); δ_{C} (CDCl_3) -5.6, -5.5 (2 x q, Me_2Si), 18.3 (s, $\text{Me}_3\text{C-Si}$), 23.3, 23.7, 24.8 (3 x t, cyclohexylidene), 25.7 (q, Me_3C), 33.9, 36.7 (2 x t, cyclohexylidene),

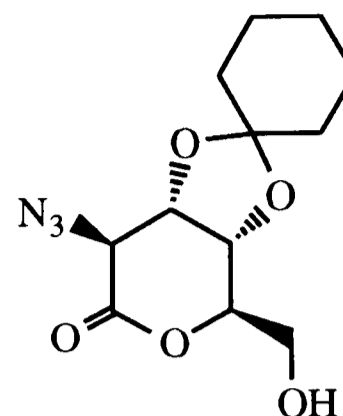
61.9 (t, C-6), 62.4 (d, C-2), 70.0, 75.2, 79.0 (3 x d, C-3, C-4, C-5), 113.4 (s, cyclohexylidene), 167.4 (s, C-1); m/z (NH₃, DCI) 415 (MNH₄⁺, 100%), 398 (MH⁺), 370 (MH⁺-N₂, 100%). (Found: C, 54.60; H, 7.97; N, 10.56; C₁₈H₃₁O₅SiN₃ requires: C, 54.38; H, 7.86; N, 10.57%).

n.O.e. Data. Irradiate δ 4.15 (H-5) ; enhancements : 3.89 (H-6, 3.4%), 4.03 (H-6', 3.4%), 4.28 (H-2, H-3, 14%).
Irradiate δ 4.28 (H-2, H-3) ; enhancements : 4.15 (H-5, 12%), 4.37 (H-4, 7.9%).

and 2-azido-6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-cyclohexylidene-2-deoxy-D-allono-1,5-lactone (2.18) (160 mg, 25%, R_f 0.5) as a white crystalline solid, m.p. 160-162 °C (ether / hexane); $[\alpha]_D^{20}$ -77.2 (*c*, 1.08 in CHCl₃); ν_{\max} (KBr) 2115 (N₃), 1743 (C=O) cm⁻¹ ; δ_H (d₆ benzene) -0.20, -0.19 (6H, 2 x s, Me₂Si), 0.75 (9H, s, Bu^t), 1.41-1.75 (10H, m, cyclohexylidene), 3.07 (1H, dd, H-6, J_{5,6} 3.2 Hz, J_{6,6'} 11.9 Hz), 3.34 (1H, dd, H-6', J_{5,6'} 3.3 Hz), 4.14 (1H, dd, H-4, J_{3,4} 7.3 Hz, J_{4,5} 1.9 Hz), 4.23 (1H, dt, H-5), 4.44 (1H, d, H-2, J_{2,3} 4.0 Hz), 4.51 (1H, dd, H-3); δ_C (CDCl₃) -5.9 (q, Me₂Si), 18.0 (s, Me₃C_{Si}), 23.5, 23.7, 24.8 (3 x t, cyclohexylidene), 25.7 (q, Me₃C), 33.9, 36.0 (2 x t, cyclohexylidene), 58.4 (d, C-2), 64.9 (t, C-6), 73.7, 76.2, 82.8 (3 x d, C-3, C-4, C-5), 111.6 (s, cyclohexylidene), 167.4 (s, C-1); m/z (NH₃, DCI) 415 (MNH₄⁺, 100%), 398 (MH⁺), 370 (MH⁺-N₂, 100%). (Found: C, 54.37; H, 7.93; N, 10.52; C₁₈H₃₁O₅SiN₃ requires: C, 54.38; H, 7.86; N, 10.57%).

n.O.e. Data. Irradiate δ 4.24 (H-5) ; enhancements : 3.07 (H-6, 7.8%), 3.34 (H-6', 6.7%). No enhancement seen to H-2.
Irradiate δ 4.44 (H-2) ; enhancements : 4.51 (H-3). No enhancement seen to H-5.
Irradiate δ 4.51 (H-3) ; enhancements : 4.44 (H-2, 7.2%).

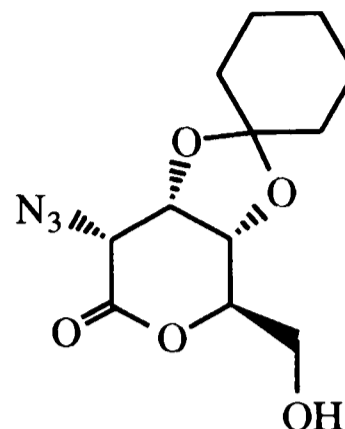
2-Azido-3,4-O-cyclohexylidene-2-deoxy-D-altrono-1,5-lactone (2.19).



2-Azido-6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-cyclohexylidene-2-deoxy-D-altrono-1,5-lactone (2.17) (210 mg, 0.53 mmol) was stirred in acetic acid : water, 4 : 1 (10 ml) at 60 °C. After 5 h, t.l.c. (hexane : ethyl acetate, 1 : 1) indicated complete consumption of starting material and the formation of two products (R_f 0.5 and 0.3). The solvent was removed and the residue co-evaporated with toluene (2 x 5 ml). Ethyl acetate (10 ml) was added, the mixture preabsorbed onto silica and then purified by flash chromatography (hexane : ethyl acetate, 3 : 2) to yield 2-azido-3,4-*O*-cyclohexylidene-2-deoxy-D-altrono-1,5-lactone (2.19) (114 mg, 76%, R_f 0.5) as a white crystalline solid, m.p. 97-99 °C (ether / hexane); $[\alpha]_D^{20} +28.9$ (c , 1.01 in CHCl_3); ν_{max} (KBr) 3472 (OH), 2119 (N_3), 1762 (C=O) cm^{-1} ; δ_{H} (CDCl_3) 1.43-1.78 (10H, m, cyclohexylidene), 3.87 (1H, dd, H-6, $J_{5,6}$ 4.6 Hz, $J_{6,6'}$ 12.8 Hz), 4.06 (1H, dd, H-6', $J_{5,6'}$ 2.6 Hz), 4.21 (1H, ddd, H-5, $J_{4,5}$ 9.4 Hz), 4.30-4.32 (2H, m, H-2, H-3), 4.42 (1H, m, H-4); δ_{C} (CDCl_3) 23.3, 23.7, 24.7, 33.9, 36.6 (5 x t, cyclohexylidene), 61.3 (t, C-6), 62.3 (d, C-2), 69.9, 75.2, 78.8 (3 x d, C-3, C-4, C-5), 113.8 (s, cyclohexylidene), 167.5 (s, C-1); m/z (NH_3 , DCI) 301 (MNH_4^+ , 100%), 284 (MH^+), 256 ($\text{MH}^+ - \text{N}_2$, 100%);

and 2-azido-3,4-*O*-cyclohexylidene-2-deoxy-D-allono-1,5-lactone (2.20) (4 mg, 3%, R_f 0.3) identical in all respects to the material described below.

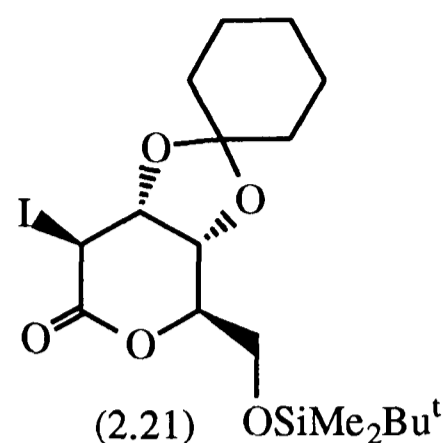
2-Azido-3,4-O-cyclohexylidene-2-deoxy-D-allono-1,5-lactone (2.20).



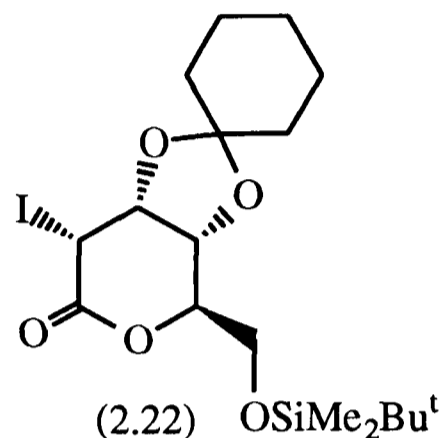
2-Azido-6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-cyclohexylidene-2-deoxy-D-allono-1,5-lactone (2.18) (160 mg, 0.4 mmol) was stirred in acetic acid : water, 4 : 1 (10 ml) at 60 °C. After 15 h, t.l.c. (hexane : ethyl acetate, 1 : 1) indicated complete consumption of starting material and the formation of two products (R_f 0.5 and 0.3). The solvent was removed, the residue co-evaporated with toluene (2 x 5 ml) and then purified by flash chromatography (hexane : ethyl acetate, 2 : 1) to yield 2-azido-3,4-*O*-cyclohexylidene-2-deoxy-D-allono-1,5-lactone (2.20) (55 mg, 47%, R_f 0.3) as a white crystalline solid, m.p. 110-112 °C (ether / hexane); $[\alpha]_D^{20}$ -68.8 (c , 1.03 in EtOH); ν_{\max} (KBr) 3438 (OH), 2116 (N₃), 1757 (C=O) cm⁻¹; δ_H (d₆-acetone) 1.40-1.77 (10H, m, cyclohexylidene), 3.94 (2H, br, d, H-6, H-6', J 4.0 Hz), 4.58 (1H, t, H-5, J 4.1 Hz), 4.67 (1H, d, H-2, J_{2,3} 4.1 Hz), 4.79 (1H, d, H-4, J_{3,4} 7.3 Hz), 4.97 (1H, dd, H-3); δ_C (d₆-acetone) 23.3, 23.6, 24.6, 33.4, 35.9 (5 x t, cyclohexylidene), 58.3 (d, C-2), 62.3 (t, C-6), 73.5, 76.1, 82.8 (3 x d, C-3, C-4, C-5), 110.4 (s, cyclohexylidene), 167.2 (s, C-1); m/z (NH₃, DCI) 301 (MNH₄⁺, 100%), 284 (MH⁺), 256 (MH⁺-N₂, 100%). (Found: C, 51.00; H, 5.99; N, 14.70; C₁₂H₁₇O₅N₃ requires: C, 50.88; H, 6.05; N, 14.83%);

and 2-azido-3,4-*O*-cyclohexylidene-2-deoxy-D-altrono-1,5-lactone (2.19) (32 mg, 28%, R_f 0.5) identical in all respects to the material described previously.

6-*O*-*tert*-Butyldimethylsilyl-3,4-*O*-cyclohexylidene-2-deoxy-2-iodo-D-altrono-1,5-lactone (2.21) and



6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-cyclohexylidene-2-deoxy-2-iodo-D-allono-1,5-lactone (2.22)

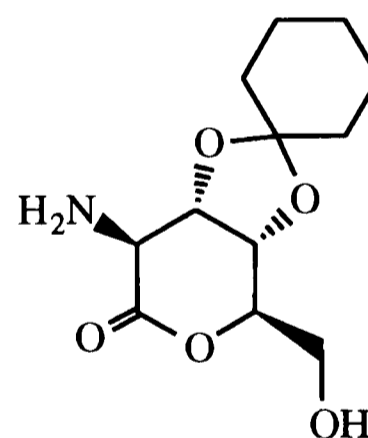


6-*O*-*tert*-Butyldimethylsilyl-3,4-*O*-cyclohexylidene-2-*O*-trifluoromethanesulphonyl-D-altrono-1,5-lactone (2.16) (125 mg, 0.25 mmol) and tetra-*n*-butylammonium iodide (275 mg, 0.74 mmol) were stirred in dry THF (5 ml) in the dark. The reaction mixture was then heated to reflux and after 1 h, t.l.c. (hexane : ethyl acetate, 5 : 1) indicated the formation of two products (R_f 0.6 and R_f 0.5). The reaction mixture was cooled to room temperature, the solvent removed, the residue dissolved in dichloromethane (5 ml) and flushed through a short silica plug (eluant ether) to yield a mixture of 6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-cyclohexylidene-2-deoxy-2-iodo-D-altrono-1,5-lactone (2.21) and 6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-cyclohexylidene-2-deoxy-2-iodo-D-allono-1,5-lactone (2.22) as an oil (113 mg, 95%, in a ratio of 2.2 : 1 as indicated by ¹H nmr). Recrystallisation from hexane yielded pure 6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-cyclohexylidene-2-deoxy-2-iodo-D-allono-1,5-lactone (2.22) (R_f 0.5) as a white crystalline solid, m.p. 123-125 °C (hexane); $[\alpha]_D^{20}$ -28.5 (*c*, 0.63 in CHCl₃); ν_{\max} (KBr) 1752 (C=O) cm⁻¹; δ_H (CDCl₃) 0.10, 0.11 (6H, 2 x s, Me₂Si), 0.91 (9H, s, Bu^t), 1.42-1.83 (10H, m, cyclohexylidene), 3.90 (1H, dd, H-6, $J_{5,6}$ 3.3 Hz, $J_{6,6'}$ 12.0 Hz), 4.04 (1H, dd, H-6', $J_{5,6'}$ 2.3 Hz), 4.35 (1H, dd, J 4.9 Hz, J' 7.5 Hz), 4.54 (1H, dd, J 4.9 Hz, J' 7.7 Hz), 4.71 (1H, m, H-5), 5.30 (1H, d, H-2, $J_{2,3}$ 5.0 Hz); δ_C (CDCl₃) -5.8, -5.7 (2 x q, Me₂Si), 18.1 (s, Me₃CSi), 20.6 (d, C-2), 23.4, 23.7, 24.8

(3 x t, cyclohexylidene), 25.7 (q, Me_3C), 34.3, 35.8 (2 x t, cyclohexylidene), 63.7 (t, C-6), 71.5, 74.0, 81.2 (3 x d, C-3, C-4, C-5), 112.0 (s, cyclohexylidene), 166.7 (s, C-1); m/z (NH_3 , DCI) 500 (MNH_4^+ , 100%), 483 (MH^+). (Found: C, 44.93; H, 6.46; $\text{C}_{18}\text{H}_{31}\text{O}_5\text{Si}$ requires: C, 44.81; H, 6.48%);

and 6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-cyclohexylidene-2-deoxy-2-iodo-*D*-altrono-1,5-lactone (2.21) (R_f 0.6) as a colourless oil (still contaminated with a small amount of epimeric material); ν_{max} (film) 1764 (C=O) cm^{-1} ; δ_{H} (CDCl_3) 0.08, 0.11 (6H, 2 x s, Me_2Si), 0.92 (9H, s, Bu^t), 1.41-1.75 (10H, m, cyclohexylidene), 3.92 (1H, dd, H-6, $J_{5,6}$ 4.4 Hz, $J_{6,6'}$ 11.8 Hz), 4.05 (1H, dd, H-6', $J_{5,6'}$ 2.8 Hz), 4.22 (1H, ddd, H-5, $J_{4,5}$ 8.4 Hz), 4.38 (1H, dd, H-4, $J_{3,4}$ 7.4 Hz), 4.65 (1H, dd, H-3, $J_{2,3}$ 8.3 Hz), 4.78 (1H, d, H-2); δ_{C} (CDCl_3) -5.6, -5.5 (2 x q, Me_2Si), 18.2 (s, Me_3CSi), 23.0 (d, C-2), 23.3, 23.7, 24.8 (3 x t, cyclohexylidene), 25.7 (q, Me_3C), 34.0, 36.7 (2 x t, cyclohexylidene), 61.9 (t, C-6), 70.9, 79.8, 80.0 (3 x d, C-3, C-4, C-5), 112.5 (s, cyclohexylidene), 165.9 (s, C-1); m/z (NH_3 , DCI) 500 (MNH_4^+ , 100%), 483 (MH^+).

2-Amino-3,4-*O*-cyclohexylidene-2-deoxy-*D*-altrono-1,5-lactone (2.24).

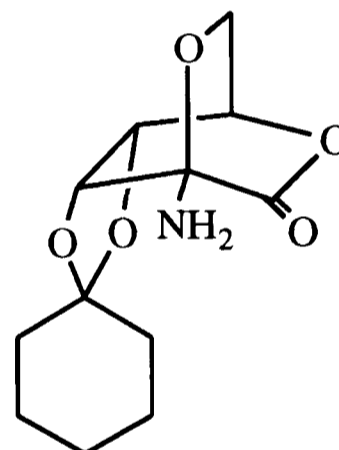


2-Azido-3,4-*O*-cyclohexylidene-2-deoxy-*D*-altrono-1,5-lactone (2.19) (110 mg, 0.39 mmol) and palladium black (4 mg, 0.04 mmol) were in stirred ethanol (5 ml) at room temperature. The solution was degassed and then stirred under an atmosphere of hydrogen for 24 h after which time t.l.c. (chloroform : methanol, 10 : 1) indicated complete consumption of starting material (R_f 0.8) and the formation of three products (R_f 0.5, 0.3 and 0.1). The reaction mixture was filtered through a Celite plug (washing with methanol, 5 ml), the solvent removed and the residue purified by flash chromatography (chloroform : methanol, 10 : 1) to yield 2-amino-3,4-*O*-cyclohexylidene-2-deoxy-*D*-altrono-1,5-lactone (2.24) (R_f 0.5, 33 mg, 33%) as a

white crystalline solid, m.p. 127-129 °C (ethyl acetate / hexane); $[\alpha]_D^{20}$ -58.5 (c, 0.2 in CHCl_3); ν_{max} (KBr) 3400 (br, OH), 3357, 3305 (NH), 1785 (C=O) cm^{-1} ; δ_{H} (CDCl_3) 1.40-1.76 (10H, m, cyclohexylidene), 3.79 (1H, d, H-2, $J_{2,3}$ 7.8 Hz), 3.85 (1H, dd, H-6, $J_{5,6}$ 4.8 Hz, $J_{6,6'}$ 12.7 Hz), 4.03 (1H, dd, H-6', $J_{5,6'}$ 2.6 Hz), 4.18 (1H, t, H-3, $J_{3,4}$ 7.8 Hz), 4.21 (1H, ddd, H-5, $J_{4,5}$ 9.4 Hz), 4.36 (1H, dd, H-4); δ_{C} (CD_3OD) 23.1, 23.5, 24.7, 33.6, 36.4 (5 x t, cyclohexylidene), 54.6 (d, C-2), 60.4 (t, C-6), 70.2, 77.4, 78.6 (3 x d, C-3, C-4, C-5), 112.3 (s, cyclohexylidene), 173.2 (s, C-1); m/z (NH_3 , DCI) 258 (MH^+ , 100%). (Found: C, 56.10; H, 7.32; N, 5.35; $\text{C}_{12}\text{H}_{19}\text{O}_5\text{N}$ requires: C, 56.02; H, 7.44; N, 5.44%);

together with a material identified as 2-amino-3,4-*O*-cyclohexylidene-2-deoxy-D-allono-1,5-lactone (R_f 0.3, 15 mg, 15%) and some baseline material (30 mg, 30%).

(1S,4R,7R,8S)-1-Amino-7,8-*O*-cyclohexylidene-7,8-dihydroxy-2,5-dioxa-bicyclo[2.2.2.]octan-6-one (2.23).



Method 1.

2-Azido-3,4-*O*-cyclohexylidene-2-deoxy-D-allono-1,5-lactone (2.19) (1.04 g, 3.67 mmol) and *N*-methylmorpholine-*N*-oxide (646 mg, 5.51 mmol) were stirred in dry acetonitrile (20 ml) at room temperature under nitrogen. Tetra-*n*-propylammonium perruthenate (65 mg, 0.18 mmol, 5%) was added and after 20 min t.l.c. (hexane : ethyl acetate, 1 : 1) indicated complete consumption of starting material (R_f 0.5) and the formation of a major product (R_f 0.1). The solvent was removed, the residue dissolved in a small volume of dichloromethane and purified by flash chromatography (ethyl acetate : hexane, 2 : 1) to yield (1S,4R,7R,8S)-1-amino-7,8-*O*-cyclohexylidene-7,8-dihydroxy-2,5-dioxa-bicyclo[2.2.2.]octan-6-one (2.23) (593 mg, 63%) as a white crystalline solid, m.p. 161-163 °C (ethyl acetate / hexane); $[\alpha]_D^{20}$ -54.2 (c, 1.1 in CHCl_3); ν_{max} (KBr) 3428, 3346 (NH), 1767 (C=O) cm^{-1} ; δ_{H} (CDCl_3) 1.36-1.67

(10H, m, cyclohexylidene), 3.89 (1H, d, H-3, $J_{3,3'}$ 10.6 Hz), 4.09 (1H, dd, H-3', $J_{3,4}$ 2.8 Hz), 4.38 (1H, d, H-7, $J_{7,8}$ 7.6 Hz), 4.49 (1H, dd, H-8, $J_{4,8}$ 2.1 Hz), 4.82 (1H, t, H-4); δ_C (CDCl₃) 23.4, 23.6, 24.8, 34.0, 35.3 (5 x t, cyclohexylidene), 63.7 (t, C-3), 73.2, 74.2, 77.1 (3 x d, C-4, C-7, C-8), 83.7 (s, C-1), 112.1 (s, cyclohexylidene), 169.2 (s, C-6); m/z (NH₃, DCI) 273 (MNH₄⁺), 256 (MH⁺, 100%). (Found: C, 56.78; H, 6.40; N, 5.33; C₁₂H₁₇O₅N requires: C, 56.46; H, 6.71; N, 5.49%).

Method 2.

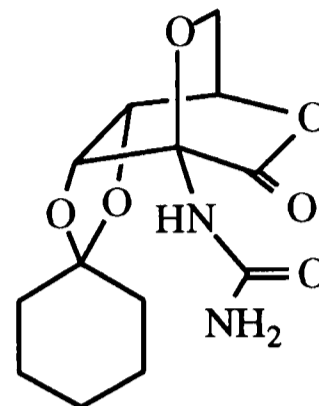
2-Azido-3,4-*O*-cyclohexylidene-2-deoxy-D-allono-1,5-lactone (2.20) (648 mg, 2.29 mmol) and *N*-methyilmorpholine-*N*-oxide (402 mg, 5.51 mmol) were stirred in dry acetonitrile (20 ml) at room temperature under nitrogen. Tetra-*n*-propylammonium perruthenate (40 mg, 0.11 mmol, 5%) was added and after 1 h t.l.c. (hexane : ethyl acetate, 1 : 1) indicated complete consumption of starting material (R_f 0.4) and the formation of a major product (R_f 0.1). The solvent was removed, the residue dissolved in a small volume of dichloromethane and purified by flash chromatography (ethyl acetate : hexane, 2 : 1) to yield (1S,4R,7R,8S)-1-amino-7,8-*O*-cyclohexylidene-7,8-dihydroxy-2,5-dioxa-bicyclo[2.2.2.]octan-6-one (2.23) (355 mg, 61%), identical in all respects to the material described above.

Method 3.

2-Amino-3,4-*O*-cyclohexylidene-2-deoxy-D-altrono-1,5-lactone (2.24) (25 mg, 0.1 mmol) and sodium acetate (24 mg, 0.3 mmol) were stirred in dry THF (3 ml) at room temperature under nitrogen. *N*-Bromosuccinimide (23 mg, 0.13 mmol) was added and after 5 min t.l.c. (ethyl acetate) indicated the formation of a single product (R_f 0.6). Ethanol (3 ml) was then added and the reaction mixture stirred for 5 min. The solvent was removed and the residue purified by flash chromatography (ethyl acetate : hexane, 2 : 1) to yield (1S,4R,7R,8S)-1-amino-7,8-*O*-cyclohexylidene-7,8-dihydroxy-2,5-

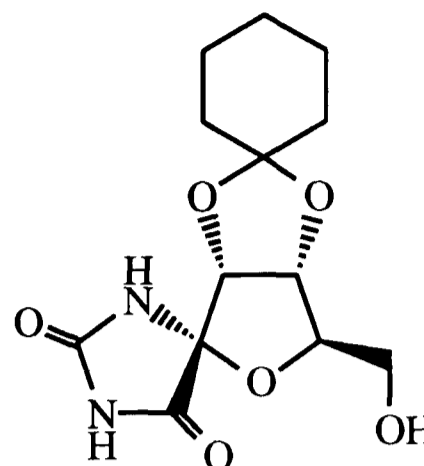
dioxa-bicyclo[2.2.2.]octan-6-one (2.23) (16 mg, 65%) identical to the material described above.

(1S,4R,7R,8S)-7,8-O-Cyclohexylidene-7,8-dihydroxy-2,5-dioxa-1-ureido-bicyclo[2.2.2.]octan-6-one (2.25).



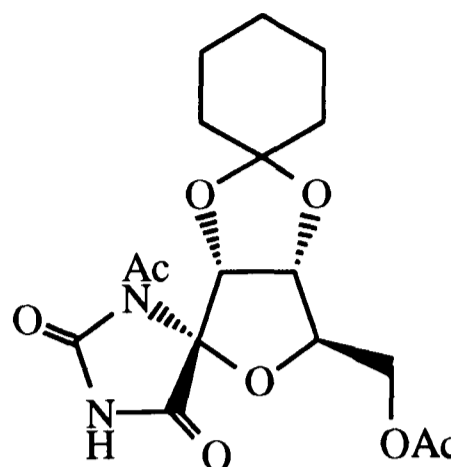
(1S,4R,7R,8S)-1-Amino-7,8-O-cyclohexylidene-7,8-dihydroxy-2,5-dioxa-bicyclo[2.2.2.]octan-6-one (2.23) (160 mg, 0.63 mmol) and potassium cyanate (152 mg, 1.88 mmol) were stirred in acetic acid (10 ml) at 60 °C. After 1.5 h, t.l.c. (ethyl acetate) indicated complete consumption of starting material (R_f 0.5) and the formation of a major product (R_f 0.3). The solvent was removed, the residue co-evaporated with toluene (2 x 5 ml) and purified by flash chromatography (THF) to yield (1S,4R,7R,8S)-7,8-O-cyclohexylidene-7,8-dihydroxy-2,5-dioxa-1-ureido-bicyclo[2.2.2.]octan-6-one (2.25) (142 mg, 76%) as a white crystalline solid, m.p. 258-262 °C (decomp, methanol); $[\alpha]_D^{20}$ -46.9 (c , 0.7 in MeOH); ν_{\max} (KBr) 3439, 3390, 3347 (NH), 1780 (C=O), 1658 (urea) cm^{-1} ; δ_{H} (d_6 -DMSO) 1.26-1.61 (10H, m, cyclohexylidene), 3.92 (2H, m), 4.65 (1H, dd, J 2.1 Hz, J' 7.7 Hz), 5.01 (1H, d, J 1.9 Hz), 5.56 (1H, d, J 7.7 Hz), 6.03 (2H, br s, NH_2), 6.92 (1H, s, NH); δ_{C} (d_6 -DMSO) 23.5, 23.8, 24.7, 35.8, 36.4 (5 x t, cyclohexylidene), 63.0 (t, C-3), 72.6, 73.3, 74.2 (3 x d, C-4, C-7, C-8), 82.5 (s, C-1), 110.7 (s, cyclohexylidene), 157.3 (s, urea), 168.3 (s, C-6); m/z (NH_3 , DCI) 299 (MH^+ , 100%), 256 ($\text{MNH}_4^+ - \text{H}_2\text{NCONH}_2$). (Found: C, 52.03; H, 5.82; N, 9.19; $\text{C}_{13}\text{H}_{18}\text{O}_6\text{N}_2$ requires: C, 52.35; H, 6.08; N, 9.39%). In later experiments this material was used directly without isolation.

(2R,3R,4R,5R)-3,4-O-Cyclohexylidene-6,8-diaza-3,4-dihydroxy-2-(hydroxymethyl)-1-oxa-spiro[4.4.]nonane-7,9-dione (2.26).



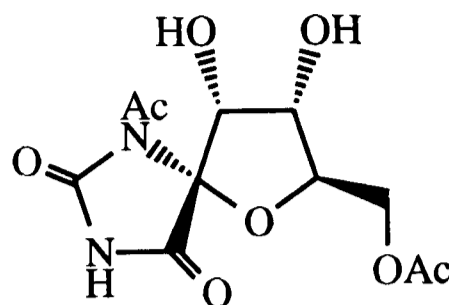
(1S,4R,7R,8S)-1-Amino-7,8-O-cyclohexylidene-7,8-dihydroxy-2,5-dioxabicyclo[2.2.2.]octan-6-one (2.23) (340 mg, 1.3 mmol) and potassium cyanate (324 mg, 4.2 mmol) were stirred in acetic acid (20 ml) at 60 °C. After 1.5 h, t.l.c. (ethyl acetate) indicated complete consumption of starting material (R_f 0.5) and the formation of a major product (R_f 0.3). The solvent was removed, the residue co-evaporated with toluene (2 x 5 ml) and flushed through a short silica plug (eluant THF). The solvent was then removed, the residue dissolved in dry DMF (10 ml) and stirred at room temperature under nitrogen. Potassium *tert*-butoxide (346 mg, 3.1 mmol) was added and after 10 min t.l.c. (ethyl acetate) indicated complete consumption of starting material (R_f 0.3) and the formation of a single product (R_f 0.8). Acetic acid (5 ml) was added, the solvent removed, the residue co-evaporated with toluene (2 x 5 ml), preabsorbed onto silica and purified by flash chromatography (ethyl acetate : hexane, 1 : 1) to yield (2R,3R,4R,5R)-3,4-O-cyclohexylidene-6,8-diaza-3,4-dihydroxy-2-(hydroxymethyl)-1-oxa-spiro[4.4.]nonane-7,9-dione (2.26) (243 mg, 61% over two steps) as a white foam; $[\alpha]_D^{20}$ -59.4 (*c*, 1.18 in CHCl_3); ν_{max} (film) 3370 (br, OH, NH), 1791, 1735 (hydantoin) cm^{-1} ; δ_{H} (CDCl_3) 1.41-1.78 (10H, m, cyclohexylidene), 3.67 (1H, dd, H-1, $J_{1',2}$ 2.8 Hz, $J_{1',1''}$ 13.0 Hz), 3.87 (1H, dd, H-1'', $J_{1'',2}$ 1.6 Hz), 4.50 (1H, br s), 4.90 (1H, d, J 5.9 Hz), 5.02 (1H, d, J 5.9 Hz), 5.92 (1H, br s, NH), 8.14 (1H, br s, NH); δ_{C} (CDCl_3) 23.4, 23.8, 24.7, 33.5, 35.9 (5 x t, cyclohexylidene), 63.7 (t, C-1'), 80.7, 81.9, 85.2 (3 x d, C-2, C-3, C-4), 94.3 (s, C-5), 115.0 (s, cyclohexylidene), 155.4, 175.4 (2 x s, C-7, C-9); m/z (NH_3 , DCI) 316 (MNH_4^+ , 100%), 299 (MH^+). (Found: C, 52.53; H, 6.39; N, 9.18; $\text{C}_{13}\text{H}_{18}\text{O}_6\text{N}_2$ requires: C, 52.35; H, 6.08; N, 9.39%).

(2R,3R,4R,5R)-2-(Acetoxymethyl)-6-N-acetyl-3,4-O-cyclohexylidene-6,8-diaza-3,4-dihydroxy-1-oxa-spiro[4.4.]nonane-7,9-dione (2.28).



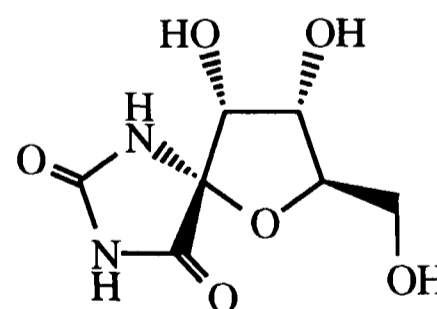
(2R,3R,4R,5R)-3,4-O-Cyclohexylidene-6,8-diaza-3,4-dihydroxy-2-(hydroxymethyl)-1-oxa-spiro[4.4.]nonane-7,9-dione (2.26) (80 mg, 0.27 mmol) was stirred in a mixture of dry pyridine (2 ml) and acetic anhydride (2 ml) at room temperature under nitrogen. DMAP (2 mg) was added and after 10 min t.l.c. (hexane : ethyl acetate, 1 : 1) indicated complete consumption of starting material (R_f 0.2) and the formation of a single product (R_f 0.5). The solvent was removed and ethyl acetate (15 ml) added. The mixture was then washed sequentially with 1M HCl (10 ml), water (10 ml) and brine (10 ml). The organic extracts were then dried (magnesium sulphate), filtered, the solvent removed, and the residue purified by flash chromatography (hexane : ethyl acetate, 2 : 1) to yield (2R,3R,4R,5R)-2-(acetoxymethyl)-6-N-acetyl-3,4-O-cyclohexylidene-6,8-diaza-3,4-dihydroxy-1-oxa-spiro[4.4.]nonane-7,9-dione (2.28) (74 mg, 72%), as a white crystalline solid, m.p. 135-136 °C (ether / hexane); $[\alpha]_D^{20} +36.8$ (c, 0.53 in CHCl_3); ν_{max} (film) 3226 (br, NH), 1807 (hydantoin), 1762 (br, C=O) cm^{-1} ; δ_{H} (CDCl_3) 1.38-1.78 (10H, m, cyclohexylidene), 2.14, 2.56 (6H, 2 x s, 2 x Ac) 4.09 (1H, dd, H-1', $J_{1',2}$ 4.8 Hz, $J_{1',1''}$ 12.2 Hz), 4.60 (1H, dd, H-1'', $J_{1',2}$ 3.4 Hz), 4.88-4.91 (2H, m, H-3, H-4), 4.99 (1H, m, H-2), 7.63 (1H, br s, NH); δ_{C} (CDCl_3) 20.8, 26.1 (2 x q, 2 x Ac), 23.3, 23.7, 24.7, 33.6, 34.2 (5 x t, cyclohexylidene), 63.6 (t, C-1'), 81.8, 82.9, 85.7 (3 x d, C-2, C-3, C-4), 96.0 (s, C-5), 118.3 (s, cyclohexylidene), 152.7 (s, hydantoin), 169.1, 170.1, 171.6 (3 x s, hydantoin, 2 x Ac); m/z (NH_3 , DCI) 400 (MNH_4^+ , 100%), 383 (MH^+). (Found: C, 53.43; H, 5.76; N, 7.08; $\text{C}_{17}\text{H}_{22}\text{O}_8\text{N}_2$ requires: C, 53.40; H, 5.80; N, 7.33%).

(2R,3S,4R,5R)-2-(Acetoxymethyl)-6-N-acetyl-6,8-diaza-3,4-dihydroxy-1-oxa-spiro[4.4.]nonane-7,9-dione (2.29).



(2R,3R,4R,5R)-2-(Acetoxymethyl)-6-N-acetyl-3,4-O-cyclohexylidene-6,8-diaza-3,4-dihydroxy-1-oxa-spiro[4.4.]nonane-7,9-dione (2.28) (71 mg, 0.19 mmol) was stirred in a mixture of trifluoroacetic acid and water, (2 : 3, 5 ml) at room temperature. After 20 min, t.l.c. (hexane : ethyl acetate, 1 : 1) indicated complete conversion to a single product (R_f 0.1). The solvent was removed, the residue co-evaporated with toluene (2 x 2 ml) and purified by flash chromatography (ethyl acetate) to yield (2R,3S,4R,5R)-2-(acetoxymethyl)-6-N-acetyl-6,8-diaza-3,4-dihydroxy-1-oxa-spiro[4.4.]nonane-7,9-dione (2.29) (53 mg, 94%) as a colourless hygroscopic oil; ν_{\max} (film) 3270 (br, OH, NH), 1793 (hydantoin), 1762 (br, C=O) cm^{-1} ; δ_{H} (CD_3OD) 2.08, 2.15 (6H, 2 x s, 2 x Ac), 4.07 (1H, dd, H-1', $J_{1',2}$ 9.7 Hz, $J_{1',1''}$ 12.0 Hz), 4.22 (1H, m, H-2), 4.39 (1H, dd, H-1'', $J_{1'',2}$ 3.6 Hz), 4.45 (1H, m, H-3, $J_{3,4}$ 5.0 Hz), 5.19 (1H, d, H-4); δ_{C} (CD_3OD) 18.9, 19.2 (2 x q, 2 x Ac), 63.1 (t, C-1'), 70.7, 73.5, 81.4 (3 x d, C-2, C-3, C-4), 91.7 (s, C-5), 157.0 (s, hydantoin), 170.5, 171.4, 173.0 (3 x s, hydantoin, 2 x Ac); m/z (NH_3 , DCI) 320 (MNH_4^+ , 100%), 303 (MH^+).

(2R,3S,4R,5R)-6,8-Diaza-3,4-dihydroxy-2-(hydroxymethyl)-1-oxa-spiro[4.4.]nonane-7,9-dione (2.27).



Method 1.

(2R,3R,4R,5R)-3,4-O-Cyclohexylidene-6,8-diaza-3,4-dihydroxy-2-(hydroxymethyl)-1-oxa-spiro[4.4.]nonane-7,9-dione (2.26) (61 mg, 0.2 mmol) was stirred in a mixture of trifluoroacetic acid and water (2 : 3, 5 ml) at room temperature. After 2 h, t.l.c. (ethyl acetate) indicated complete product formation (R_f 0.1). The solvent was removed, the residue co-evaporated with toluene (2 x 1 ml) and purified by flash

Chapter 2-Experimental

chromatography (dichloromethane : methanol, 6 : 1) to yield (2R,3S,4R,5R)-6,8-diaza-3,4-dihydroxy-2-(hydroxymethyl)-1-oxa-spiro[4.4.]nonane-7,9-dione (2.27) (44 mg, 98%) as a white amorphous solid; $[\alpha]_D^{20}$ -7.0 (*c*, 0.52 in MeOH)[Lit -11.0 (*c*, 0.3 in MeOH)²⁹]; ν_{\max} (film) 3333 (br, OH, NH), 1783, 1736 (hydantoin) cm^{-1} ; δ_{H} (CD_3OD) 3.59 (1H, dd, H-1', $J_{1',2}$ 5.2 Hz, $J_{1',1''}$ 12.1 Hz), 3.66 (1H, dd, H-1'', $J_{1'',2}$ 4.3 Hz), 4.09 (1H, ddd, H-2, $J_{2,3}$ 3.2 Hz), 4.17 (1H, dd, H-3, $J_{3,4}$ 4.9 Hz), 4.25 (1H, d, H-4); δ_{C} (CD_3OD) 63.6 (t, C-1'), 73.1, 74.3, 87.1 (3 x d, C-2, C-3, C-4), 94.4 (s, C-5), 158.2, 175.7 (2 x s, C-7, C-9); *m/z* (NH_3 , DCI) 236 (MNH_4^+ , 100%), 219 (MH^+). (Found: C, 38.56; H, 4.63; N, 12.47; $\text{C}_7\text{H}_{10}\text{O}_6\text{N}_2$ requires: C, 38.54; H, 4.62; N, 12.84%).

Method 2.

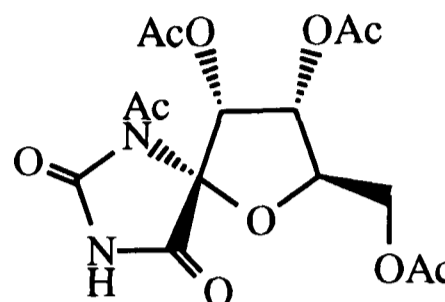
(2R,3R,4R,5R)-3,4-*O*-Cyclohexylidene-6,8-diaza-3,4-dihydroxy-2-(hydroxymethyl)-1-oxa-spiro[4.4.]nonane-7,9-dione (2.26) and Dowex 50W-X8(H^+) ion exchange resin (30 mg) were stirred in methanol (3 ml) at 40 °C. After 16 h, t.l.c. (dichloromethane : methanol, 4 : 1) indicated the formation of a major product (R_f 0.3). The reaction mixture was filtered, the solvent removed and the residue purified by flash chromatography (dichloromethane : methanol, 4 : 1) to yield (2R,3S,4R,5R)-6,8-diaza-3,4-dihydroxy-2-(hydroxymethyl)-1-oxa-spiro[4.4.]nonane-7,9-dione (2.27) (16 mg, 66%, 87% based on recovered starting material, R_f 0.3) identical to the material described previously, together with unreacted starting material (8 mg, 24 %, R_f 0.8).

Method 3.

(2R,3S,4R,5R)-2-(Acetoxymethyl)-6-*N*-acetyl-6,8-diaza-3,4-dihydroxy-1-oxa-spiro[4.4.]nonane-7,9-dione (2.29) (44 mg, 0.15 mmol) was stirred at room temperature in methanol (2 ml). Hydrazine monohydrate (18 μl , 0.36 mmol) was added and the reaction mixture stirred for 2 h after which time t.l.c. (ethyl acetate) indicated complete consumption of starting material (R_f 0.5) and formation of a single product (R_f 0.1). The solvent was removed and the residue purified by flash chromatography

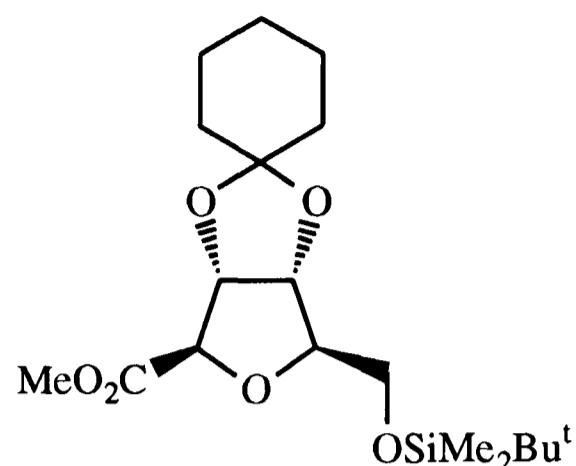
(dichloromethane : methanol, 6 : 1) to yield (2R,3S,4R,5R)-6,8-diaza-3,4-dihydroxy-2-(hydroxymethyl)-1-oxa-spiro[4.4.]nonane-7,9-dione (2.27) (22 mg, 70 %) identical to the material described previously.

(2R,3R,4R,5R)-2-(Acetoxymethyl)-6-N-acetyl-3,4-diacetoxy-6,8-diaza-1-oxa-spiro[4.4.]nonane-7,9-dione (2.30).



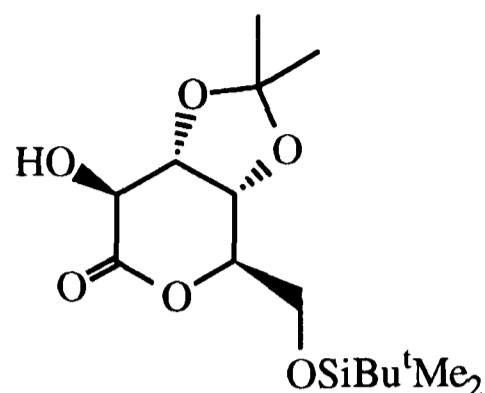
(2R,3S,4R,5R)-6,8-Diaza-3,4-dihydroxy-2-(hydroxymethyl)-1-oxa-spiro[4.4.]nonane-7,9-dione (2.27) (30 mg, 0.14 mmol) was stirred in a mixture of dry pyridine (2 ml) and acetic anhydride (2 ml) at room temperature under nitrogen. DMAP (2 mg) was added and after 1 h t.l.c. (hexane : ethyl acetate, 1 : 1) indicated the formation of a single product (R_f 0.4). The solvent was removed and ethyl acetate (10 ml) was added. The mixture was then washed sequentially with 1M HCl (10 ml), water (5 ml) and brine (5 ml). The organic extracts were then dried (magnesium sulphate), filtered, the solvent removed and the residue purified by flash chromatography (hexane : ethyl acetate, 1 : 1) to yield (2R,3R,4R,5R)-2-(acetoxymethyl)-6-N-acetyl-3,4-diacetoxy-6,8-diaza-1-oxa-spiro[4.4.]nonane-7,9-dione (2.30) (37 mg, 70%) as a colourless oil; $[\alpha]_D^{20} +96.2$ (c , 0.6 in CHCl_3); ν_{max} (film) 3228 (br, NH), 1810 (hydantoin), 1752 (br, C=O) cm^{-1} ; δ_{H} (CDCl_3) 2.06, 2.15, 2.16, 2.54 (12H, 4 x s, 4 x Ac) 4.05 (1H, dd, H-1', $J_{1',2}$ 4.2 Hz, $J_{1',1''}$ 12.5 Hz), 4.69 (1H, dd, H-1'', $J_{1'',2}$ 2.6 Hz), 4.95 (1H, ddd, H-2, $J_{2,3}$ 6.6 Hz), 5.34 (1H, dd, H-3, $J_{3,4}$ 8.7 Hz), 5.43 (1H, d, H-4), 8.78 (1H, br s, NH); δ_{C} (CDCl_3) 19.9, 20.3, 20.7, 25.7 (4 x q, 4 x Ac), 62.4 (t, C-1'), 70.8, 72.8, 83.7 (3 x d, C-2, C-3, C-4), 94.9 (s, C-5), 152.3 (s, hydantoin), 168.5, 169.0, 170.4, 170.6, 171.3 (5 x s, hydantoin, 4 x Ac); m/z (NH_3 , DCI) 404 (MNH_4^+ , 100%), 387 (MH^+). (Found: C, 46.38; H, 4.39; N, 6.96; $\text{C}_{15}\text{H}_{18}\text{O}_{10}\text{N}_2$ requires: C, 46.64; H, 4.70; N, 7.25%).

Methyl 2,5-anhydro-6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-cyclohexylidene-D-allonate (2.31).



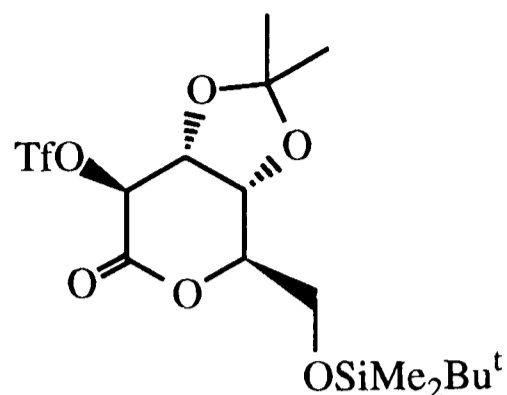
6-*O*-*tert*-Butyldimethylsilyl-3,4-*O*-cyclohexylidene-2-*O*-trifluoromethanesulphonyl-D-altrono-1,5-lactone (2.16) (2.06 g, 4.1 mmol) was dissolved in methanol (80 ml). Potassium carbonate (566 mg, 4.1 mmol) was added and the resultant mixture stirred at room temperature. After 10 min, t.l.c. (hexane : ethyl acetate, 3 : 1) indicated complete consumption of starting material (R_f 0.7) and the formation of a major product (R_f 0.6), together with a small amount of more polar material (R_f 0.5). The solvent was removed and the residue shaken with dichloromethane (75 ml). The resultant suspension was filtered, the solvent removed and the residue purified by flash chromatography (hexane : ethyl acetate, 7 : 1) to yield methyl 2,5-anhydro-6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-cyclohexylidene-D-allonate (2.31) (1.07 g, 68%, R_f 0.6) as a colourless oil; $[\alpha]_D^{20}$ -36.7 (c , 1.2 in CHCl_3); ν_{max} (film) 1761, 1741 (C=O) cm^{-1} ; δ_{H} (CDCl_3) 0.05, 0.07 (6H, 2 x s, Me_2Si), 0.89 (9H, s, Bu^t), 1.39-1.79 (10H, m, cyclohexylidene), 3.73 (2H, d, H-6, H-6', J 3.9 Hz), 3.77 (3H, s, Me), 4.30 (1H, m, H-5), 4.50 (1H, d, H-2, $J_{2,3}$ 3.3 Hz), 4.69 (1H, dd, H-4, $J_{3,4}$ 6.1 Hz, $J_{4,5}$ 1.2 Hz), 4.96 (1H, dd, H-3); δ_{C} (CDCl_3) -5.8, -5.7 (2 x q, Me_2Si), 18.2 (s, $\text{Me}_3\text{C-Si}$), 23.5, 23.8, 24.8 (3 x t, cyclohexylidene), 25.7 (q, Me_3C), 34.6, 36.8 (2 x t, cyclohexylidene), 52.1 (q, MeO), 61.4 (t, C-6), 82.2, 83.3, 84.8, 86.2 (4 x d, C-2, C-3, C-4, C-5), 114.1 (s, cyclohexylidene), 171.2 (s, C-1); m/z (NH_3 , DCI) 404 (MNH_4^+), 387 (MH^+ , 100%). (Found: C, 59.24; H, 8.98; $\text{C}_{19}\text{H}_{34}\text{O}_6\text{Si}$ requires: C, 59.04; H, 8.87%); together with methyl 2,5-anhydro-6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-cyclohexylidene-D-altronate (2.32) (68 mg, 4%, R_f 0.5) identical to the material described later.

6-*O*-*tert*-Butyldimethylsilyl-3,4-*O*-isopropylidene-D-altrono-1,5-lactone (2.33).



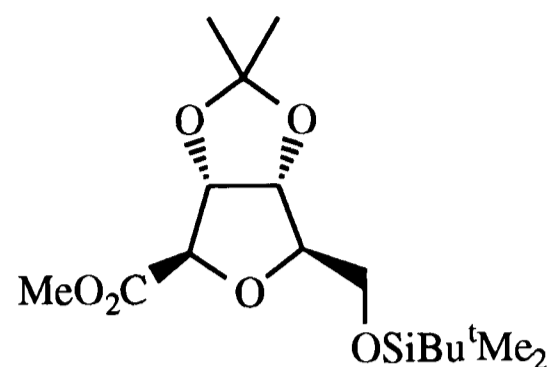
3,4-*O*-Isopropylidene-D-altrono-1,5-lactone (2.11) (300 mg, 1.4 mmol) and imidazole (247 mg, 3.6 mmol) were stirred under nitrogen in dry DMF (15 ml) at 0 °C. *tert*-Butyldimethylsilylchloride (300 mg, 2.0 mmol) was added and the mixture allowed to warm to room temperature. After 30 min, t.l.c. (hexane : ethyl acetate, 1 : 1) showed complete consumption of starting material (R_f 0.3) and the formation of a single product (R_f 0.7). The solvent was removed and ether (20 ml) added. The mixture was shaken with water (20 ml), which was then further extracted with ether (2 x 20 ml). The combined organic extracts were then dried (magnesium sulphate), filtered, the solvent removed and the residue purified by flash chromatography (hexane : ethyl acetate, 3 : 1) to yield 6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-isopropylidene-D-altrono-1,5-lactone (2.33) (378 mg, 83%), as a white crystalline solid, m.p. 140-143 °C (ether / hexane); $[\alpha]_D^{20} +78.2$ (c , 1.04 in CHCl_3); ν_{max} (CHCl_3) 3500 (br, OH), 1760 (C=O) cm^{-1} ; δ_{H} (CDCl_3) 0.11 (6H, s, Me_2Si), 0.92 (9H, s, Bu^t), 1.39, 1.54 (6H, 2 x s, Me_2C), 3.35 (1H, br, OH), 3.88 (1H, dd, H-6, $J_{5,6}$ 4.5 Hz, $J_{6,6'}$ 12.0 Hz), 4.03 (1H, dd, H-6', $J_{5,6'}$ 2.0 Hz), 4.16 (1H, m, H-5), 4.28-4.30 (2H, m, H-3, H-4), 4.42 (1H, d, H-2, $J_{2,3}$ 7.7 Hz); δ_{C} (CDCl_3) -5.6 (q, Me_2Si), 18.2 (s, SiCMe_3), 24.3, 26.6 (2 x q, Me_2C), 25.7 (q, Me_3C), 61.8 (t, C-6), 70.0, 70.8, 77.4, 78.5 (4 x d, C-2, C-3, C-4, C-5), 112.2 (s, CMe_2), 172.9 (s, C-1); m/z (NH_3 , DCI) 350 (MNH_4^+ , 100%), 333 (MH^+). (Found: C, 54.37; H, 8.72; $\text{C}_{15}\text{H}_{28}\text{O}_6\text{Si}$ requires: C, 54.19; H, 8.49%).

6-*O*-*tert*-Butyldimethylsilyl-3,4-*O*-isopropylidene-2-*O*-trifluoromethanesulphonyl-D-altrono-1,5-lactone
(2.34).



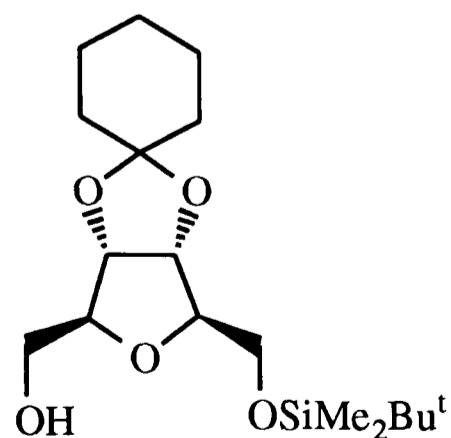
6-*O*-*tert*-Butyldimethylsilyl-3,4-*O*-isopropylidene-altrono-1,5-lactone (2.33) (303 mg, 0.9 mmol) and dry pyridine (0.180 ml, 2.3 mmol) were stirred under nitrogen in dry dichloromethane (2ml) at -20 °C. Trifluoromethanesulphonic anhydride (0.23 ml, 1.4 mmol) was added. After 10 min, t.l.c. (hexane : ethyl acetate, 3 : 1) indicated complete product formation (R_f 0.7) and further dichloromethane (5 ml) was added. The reaction mixture was then shaken with water (5 ml containing a few drops of 1M HCl). The aqueous layer was then further extracted with dichloromethane (2 x 5 ml). The combined organic extracts were then dried (magnesium sulphate), filtered, the solvent removed, and the residue purified by flash chromatography (hexane : ethyl acetate, 4 : 1) to yield 6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-isopropylidene-2-*O*-trifluoromethane sulphonyl-altrono-1,5-lactone (2.34) (420 mg, quantitative) as a colourless oil; ν_{\max} (film) 1784 (C=O) cm^{-1} ; δ_{H} (CDCl_3) 0.11 (6H, s, Me_2Si), 0.92 (9H, s, Bu^t), 1.41, 1.55 (6H, 2 x s, Me_2C), 3.89 (1H, dd, H-6, $J_{5,6}$ 4 Hz, $J_{6,6'}$ 12.0 Hz), 4.03 (1H, dd, H-6', $J_{5,6'}$ 2.2 Hz), 4.25 (1H, m, H-5), 4.51-4.56 (2H, m, H-3, H-4), 5.23 (1H, d, H-2, $J_{2,3}$ 7.0 Hz); δ_{C} (CDCl_3) -5.7 (q, Me_2Si), 18.2 (s, Me_3CSi), 24.5, 26.5 (2 x q, Me_2C), 25.6 (q, Me_3C), 61.7 (t, C-6), 70.4, 74.2, 78.8, 81.7 (4 x d, C-2, C-3, C-4, C-5), 113.2 (s, CMe_2), 164.2 (s, C-1); m/z (NH_3 , DCI) 482 (MNH_4^+ , 100%).

Methyl 2,5-anhydro-6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-isopropylidene-D-allonate (2.35).



6-*O*-*tert*-Butyldimethylsilyl-3,4-*O*-isopropylidene-2-*O*-trifluoromethanesulphonyl-D-altrono-1,5-lactone (2.34) (119 mg, 0.26 mmol) and potassium carbonate (36 mg, 0.26 mmol) were stirred in dry methanol (10 ml) at room temperature under nitrogen. After 10 min the solvent was removed and the residue purified by flash chromatography (hexane : ether, 3 : 1) to yield methyl 2,5-anhydro-6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-isopropylidene-D-altrunate (2.35) (51 mg, 58%, R_f 0.6) as a white crystalline solid, m.p. 33-34 °C (ether / hexane); $[\alpha]_D^{20}$ -32.8 (c , 1.0 in CHCl_3); ν_{max} (film) 1762, 1740 (C=O) cm^{-1} ; δ_{H} (CDCl_3) 0.06, 0.07 (6H, 2 x s, Me_2Si), 0.89 (9H, s, Bu^t), 1.38, 1.56 (6H, 2 x s, Me_2C), 3.70-3.76 (2H, m, H-6, H-6'), 3.77 (3H, s, Me), 4.29 (1H, dt, H-5, $J_{4,5}$ 1.7 Hz, $J_{5,6}$ 4.0 Hz, $J_{5,6'}$ 4.0 Hz), 4.51 (1H, d, H-2, $J_{2,3}$ 3.4 Hz), 4.71 (1H, dd, H-4, $J_{3,4}$ 6.1 Hz), 4.96 (1H, dd, H-3); δ_{C} (CDCl_3) -5.9, -5.7 (2 x q, Me_2Si), 18.2 (s, Me_3CSi), 25.1, 27.0 (2 x q, Me_2C), 25.7 (q, Me_3C), 52.2 (q, MeO), 64.1 (t, C-6), 82.6, 82.7, 84.6, 86.2 (4 x d, C-2, C-3, C-4, C-5), 113.4 (s, CMe_2), 171.1 (s, C-1); m/z (NH_3 , DCI) 364 (MNH_4^+), 347 (MH^+ , 100%). (Found: C, 55.24; H, 8.84; $\text{C}_{16}\text{H}_{30}\text{O}_6\text{Si}$ requires: C, 55.46; H, 8.73%).

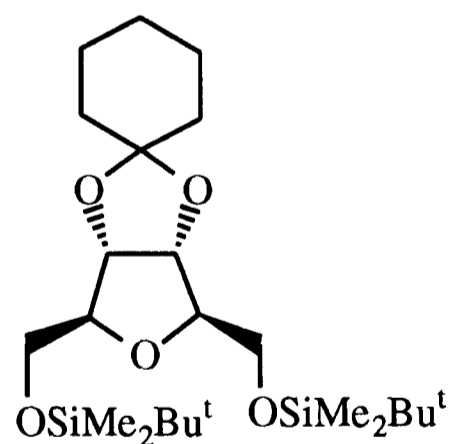
2,5-Anhydro-1-*O*-*tert*-butyldimethylsilyl-3,4-*O*-cyclohexylidene-L-allitol (2.37).



Methyl 2,5-anhydro-6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-cyclohexylidene-D-allonate (2.31) (112 mg, 0.29 mmol) was stirred in THF (3 ml) at room temperature under

nitrogen. Lithium aluminium hydride (12 mg, 0.29 mmol) was added and after 5 min t.l.c. (hexane : ethyl acetate, 3 : 1) indicated complete consumption of starting material (R_f 0.6) and formation of a single product (R_f 0.4). The reaction was quenched by addition of ethyl acetate (1 ml), the resulting solution filtered through a silica plug (eluant hexane : ethyl acetate, 3 : 1) and the solvent removed to yield 2,5-anhydro-1-*O*-*tert*-butyldimethylsilyl-3,4-*O*-cyclohexylidene-L-allitol (2.37) (98 mg, 94%) as a colourless oil; $[\alpha]_D^{20} +13.6$ (c , 1.04 in CHCl_3); ν_{max} (film) 3435 (br, OH) cm^{-1} ; δ_{H} (CDCl_3) 0.11 (6H, 2 x s, Me_2Si), 0.93 (9H, s, Bu^t), 1.40-1.77 (10H, m, cyclohexylidene), 3.00 (1H, br, OH), 3.62 (1H, br m, H-6), 3.79-3.84 (2H, m, H-6', H-1'), 3.90 (1H, dd, H-1, $J_{1,2}$ 2.7 Hz, $J_{1,1'}$ 11.2 Hz), 4.08 (1H, m, H-2), 4.23 (1H, dd, H-5, $J_{4,5}$ 2.6 Hz), 4.70 (1H, dd, H-4, $J_{3,4}$ 6.1 Hz), 4.74 (1H, dd, H-3, $J_{2,3}$ 4.2 Hz); δ_{C} (CDCl_3) -5.8 (q, Me_2Si), 18.3 (s, $\text{Me}_3\text{C-Si}$), 23.5, 23.9, 24.8 (3 x t, cyclohexylidene), 25.7 (q, Me_3C), 34.8, 37.3 (2 x t, cyclohexylidene), 63.9 (t, C-1, C-6), 80.6, 82.3, 85.0, 85.8 (4 x d, C-2, C-3, C-4, C-5), 113.8 (s, cyclohexylidene); m/z (NH_3 , DCI) 376 (MNH_4^+), 359 (MH^+ , 100%). (Found: C, 60.28; H, 9.74; $\text{C}_{18}\text{H}_{34}\text{O}_5\text{Si}$ requires: C, 60.30; H, 9.56%).

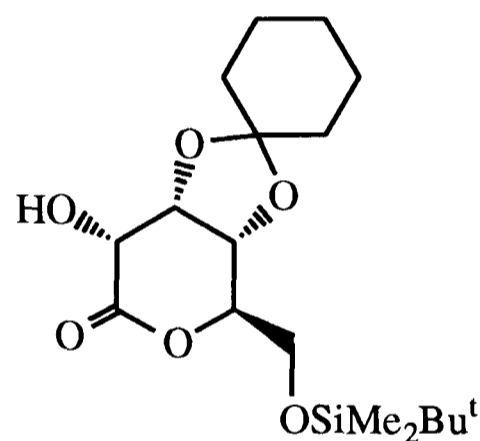
2,5-Anhydro-3,4-*O*-cyclohexylidene-1,6-di-*O*-*tert*-butyldimethylsilyl-allitol (2.36).



2,5-Anhydro-1-*O*-*tert*-butyldimethylsilyl-3,4-*O*-cyclohexylidene-L-allitol (2.37) (56 mg, 0.16 mmol) and imidazole (43 mg, 0.63 mmol) were stirred under nitrogen in dry DMF (3 ml) at 0 °C. *tert*-Butyldimethylsilylchloride (47 mg, 0.31 mmol) was added and the reaction mixture was allowed to warm to room temperature. After 1 h, t.l.c. (hexane : ethyl acetate, 3 : 1) indicated complete consumption of starting material (R_f 0.4) and formation of a single product (R_f 0.8). The solvent was removed and ether (10 ml) was added. The mixture was shaken with water (10 ml) and the aqueous layer

further extracted with ether (10 ml). The combined organic extracts were dried (magnesium sulphate), filtered, the solvent removed and the residue purified by flash chromatography (hexane : ether, 4 : 1) to yield 2,5-anhydro-3,4-*O*-cyclohexylidene-1,6-di-*O*-*tert*-butyldimethylsilyl-allitol (2.36) (65 mg, 88%) as a colourless oil; $[\alpha]_{\text{D}}^{20} +0.0$ (*c*, 1.98 in CHCl_3); δ_{H} (CDCl_3) 0.07 (12H, s, 2 x Me_2Si), 0.91 (18H, s, 2 x Bu^t), 1.38-1.77 (10H, m, cyclohexylidene), 3.68 (4H, m, H-1, H-1', H-6, H-6'), 4.05 (2H, m, H-2, H-5), 4.54 (2H, d, H-3, H-4, $J_{2,3}$ 2.2 Hz); δ_{C} (CDCl_3) -5.6 (q, Me_2Si), 18.2 (s, Me_3CSi), 23.5, 23.9, 24.9 (3 x t, cyclohexylidene), 25.8 (q, Me_3C), 35.0, 37.2 (2 x t, cyclohexylidene), 64.1 (t, C-1, C-6), 81.7, 85.3 (2 x d, C-2, C-3, C-4, C-5), 114.0 (s, cyclohexylidene); *m/z* (NH_3 , DCI) 490 (MNH_4^+), 473 (MH^+ , 100%). (Found: C, 60.86; H, 10.15; $\text{C}_{24}\text{H}_{48}\text{O}_5\text{Si}_2$ requires: C, 60.97; H, 10.23%).

6-*O*-*tert*-Butyldimethylsilyl-3,4-*O*-cyclohexylidene-D-allono-1,5-lactone (2.38).



Method 1.

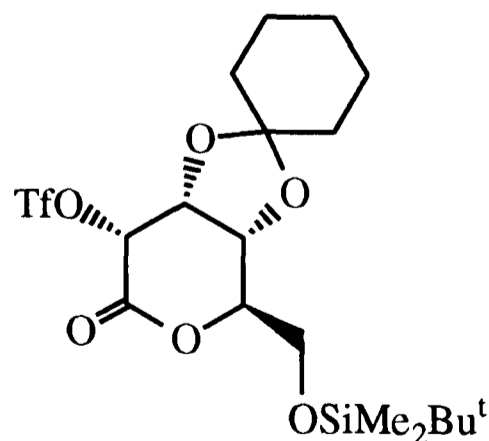
3,4-Cyclohexylidene-D-allono-1,5-lactone (2.14) (57 mg, 0.22 mmol) and pyridine (37 μl , 0.46 mmol) were stirred under nitrogen in dry THF (2ml) at $-70\text{ }^\circ\text{C}$. *tert*-Butyldimethylsilyltrifluoromethanesulphonate (56 μl , 0.24 mmol) was added and the mixture was allowed to warm to $-20\text{ }^\circ\text{C}$. After 0.5 h t.l.c. (hexane : ethyl acetate, 1 : 1) indicated the formation of a major product (R_f 0.7), together with some starting material (R_f 0.1) and a small amount of less polar material (R_f 0.9). Methanol (1 ml) was added and the mixture allowed to warm to room temperature. The solvent was removed and the residue purified by flash chromatography (hexane : ethyl acetate, 2 : 1) to yield 6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-cyclohexylidene-D-allono-1,5-lactone (2.38) (47 mg, 57%; 81% based on unrecovered starting material) as a white crystalline solid, m.p. $101\text{-}103\text{ }^\circ\text{C}$ (ether / hexane); $[\alpha]_{\text{D}}^{20} -50.1$ (*c*, 0.58 in CHCl_3); ν_{max} (KBr) 3460 (br,

OH), 1747 (C=O) cm^{-1} ; δ_{H} (CDCl_3) 0.09, 0.10 (6H, 2 x s, Me_2Si), 0.91 (9H, s, Bu^t), 1.40-1.66 (10H, m, cyclohexylidene), 3.10 (1H, d, OH, $J_{2,\text{OH}}$ 6.7 Hz), 3.91 (1H, dd, H-6, $J_{5,6}$ 3.2 Hz, $J_{6,6'}$ 12.0 Hz), 3.97 (1H, dd, H-6', $J_{5,6'}$ 3.1 Hz), 4.58-4.63 (2H, m, H-4, H-5), 4.80 (1H, dd, H-3, $J_{2,3}$ 4.2 Hz, $J_{3,4}$ 7.1 Hz), 4.91 (1H, dd, H-2); δ_{C} (CDCl_3) -5.9 (q, Me_2Si), 18.0 (s, Me_3CSi), 23.4, 23.7, 24.8 (3 x t, cyclohexylidene), 25.7 (q, Me_3C), 33.9, 36.0 (2 x t, cyclohexylidene), 64.5 (t, C-6), 67.1, 73.5, 75.3, 83.1 (4 x d, C-2, C-3, C-4, C-5), 111.2 (s, cyclohexylidene), 172.4 (s, C-1); m/z (NH_3 , DCI) 390 (MNH_4^+), 373 (MH^+ , 100%). (Found: C, 58.10; H, 8.63; $\text{C}_{18}\text{H}_{32}\text{O}_6\text{Si}$ requires: C, 58.03; H, 8.66%).

Method 2.

6-*O*-*tert*-Butyldimethylsilyl-3,4-*O*-cyclohexylidene-2-*O*-trifluoromethanesulphonyl-D-alltrono-1,5-lactone (2.16) (286 mg, 0.57 mmol) and sodium trifluoroacetate (232 mg, 1.70 mmol) were stirred together in DMF (10 ml) at 70 °C. After 2 h, t.l.c. (hexane : ethyl acetate, 3 : 1) indicated the formation of a major product (R_f 0.3). The solvent was removed and the residue co-evaporated with toluene (2 x 3 ml). Methanol (10 ml) was added and the mixture was preabsorbed onto silica. Purification by flash chromatography (hexane : ethyl acetate, 3 : 1) yielded 6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-cyclohexylidene-D-allono-1,5-lactone (2.38) (83 mg, 40%), identical in all respects to the material prepared above.

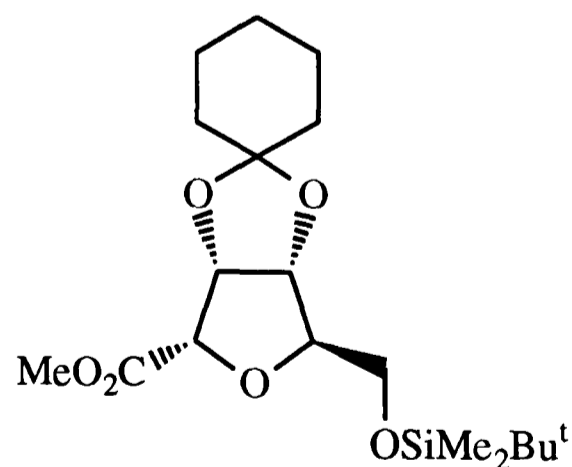
6-*O*-*tert*-Butyldimethylsilyl-3,4-*O*-cyclohexylidene-2-*O*-trifluoromethanesulphonyl-D-allono-1,5-lactone (2.39).



6-*O*-*tert*-Butyldimethylsilyl-3,4-*O*-cyclohexylidene-D-allono-1,5-lactone (2.38) (81 mg, 0.22 mmol) and dry pyridine (44 μl , 0.54 mmol) were stirred under nitrogen in dry dichloromethane (5 ml) at -20 °C. Trifluoromethanesulphonic anhydride (55 μl ,

0.33 mmol) was then added. After 10 min t.l.c. (hexane : ethyl acetate, 3 : 1) indicated complete product formation (R_f 0.6) and further dichloromethane (10 ml) was added. The reaction mixture was then shaken with water (10 ml, containing a few drops of 1M HCl) and then washed with water (10 ml) and brine (10 ml). The organic extracts were then dried (magnesium sulphate) and filtered. The solvent was removed and the residue purified by flash chromatography (hexane : ethyl acetate, 5 : 1) to yield 6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-cyclohexylidene-2-*O*-trifluoromethanesulphonyl-D-allono-1,5-lactone (2.39) (80 mg, 73%) as a white crystalline solid, m.p. 157-159 °C (ether / hexane); $[\alpha]_D^{20}$ -32.3 (*c*, 0.9 in CHCl_3); ν_{max} (KBr) 1766 (C=O) cm^{-1} ; δ_{H} (CDCl_3) 0.13, 0.14 (6H, 2 x s, Me_2Si), 0.92 (9H, s, Bu^t), 1.40-1.69 (10H, m, cyclohexylidene), 3.92 (1H, dd, H-6, $J_{5,6}$ 2.4 Hz, $J_{6,6'}$ 12.0 Hz), 4.09 (1H, dd, H-6', $J_{5,6'}$ 2.0 Hz), 4.64-4.67 (2H, m, H-4, H-5), 4.88 (1H, dd, H-3, $J_{2,3}$ 4.3 Hz, $J_{3,4}$ 6.9 Hz), 6.03 (1H, d, H-2); δ_{C} (CDCl_3) -5.6, -5.9 (2 x q, Me_2Si), 18.4 (s, Me_3CSi), 23.4, 23.6, 24.7 (3 x t, cyclohexylidene), 25.8 (q, Me_3C), 34.1, 35.9 (2 x t, cyclohexylidene), 65.4 (t, C-6), 74.0, 74.2, 78.0, 83.1 (4 x d, C-2, C-3, C-4, C-5), 112.4 (s, cyclohexylidene), 163.8 (s, C-1); m/z (NH_3 , DCI) 522 (MNH_4^+ , 100%), 505 (MH^+). (Found: C, 45.19, H, 6.31; $\text{C}_{19}\text{H}_{31}\text{O}_8\text{F}_3\text{SSi}$ requires: C, 45.23; H, 6.19%).

Methyl 2,5-anhydro-6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-cyclohexylidene-D-altronate (2.32).

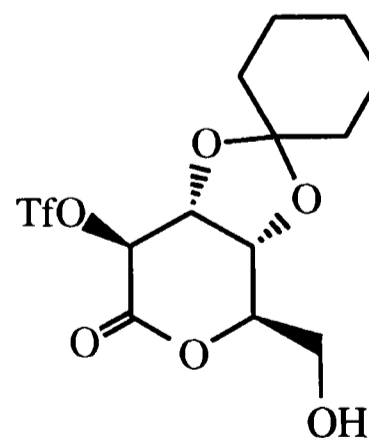


6-*O*-*tert*-Butyldimethylsilyl-3,4-*O*-cyclohexylidene-2-*O*-trifluoromethanesulphonyl-D-allono-1,5-lactone (2.39) (40 mg, 0.08 mmol) was dissolved in methanol (3 ml). Potassium carbonate (11 mg, 0.08 mmol) was added and the resultant mixture stirred at

room temperature for 10 min at which point t.l.c. (hexane : ethyl acetate, 3 : 1) indicated the formation of a major product (R_f 0.5) together with a small amount of less polar material (R_f 0.6). Camphorsulphonic acid (5 mg) was added and the solvent removed. Ethyl acetate (5 ml) was added and the mixture shaken with water (5 ml). The organic extracts were dried (magnesium sulphate), filtered, the solvent removed and the residue purified by flash chromatography (hexane : ethyl acetate, 7 : 1) to yield methyl 2,5-anhydro-6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-cyclohexylidene-D-altronate (2.32) (21 mg, 69%, R_f 0.5) as a white crystalline solid, m.p. 80-81 °C (pentane); $[\alpha]_D^{20}$ -31.3 (c , 0.8 in CHCl_3); ν_{max} (KBr) 1765 (C=O) cm^{-1} ; δ_{H} (CDCl_3) 0.06, 0.07 (6H, 2 x s, Me_2Si), 0.90 (9H, s, Bu^t), 1.35-1.71 (10H, m, cyclohexylidene), 3.73 (1H, dd, H-6, $J_{5,6}$ 2.4 Hz, $J_{6,6'}$ 11.0 Hz), 3.80 (3H, s, Me), 3.82 (1H, dd, H-6', $J_{5,6'}$ 2.6 Hz), 4.36 (1H, m, H-5), 4.81-4.84 (2H, m), 5.00 (1H, t, J 5.5 Hz); δ_{C} (CDCl_3) -6.0, -5.9 (2 x q, Me_2Si), 17.9 (s, Me_3CSi), 23.6, 23.8, 24.9 (3 x t, cyclohexylidene), 25.7 (q, Me_3C), 34.6, 35.6 (2 x t, cyclohexylidene), 51.9 (q, MeO), 65.6 (t, C-6), 82.2, 82.3, 82.9, 85.4 (4 x d, C-2, C-3, C-4, C-5), 113.7 (s, cyclohexylidene), 169.3 (s, C-1); m/z (NH_3 , DCI) 404 (MNH_4^+), 387 (MH^+ , 100%). (Found: C, 59.33; H, 9.07; $\text{C}_{19}\text{H}_{34}\text{O}_6\text{Si}$ requires: C, 59.04; H, 8.87%);

and methyl 2,5-anhydro-6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-cyclohexylidene-D-allonate (2.31) (5 mg, 16%, R_f 0.6) identical in all respects to the material described previously.

3,4-*O*-Cyclohexylidene-2-*O*-trifluoromethanesulphonyl-D-altrono-1,5-lactone (2.40)



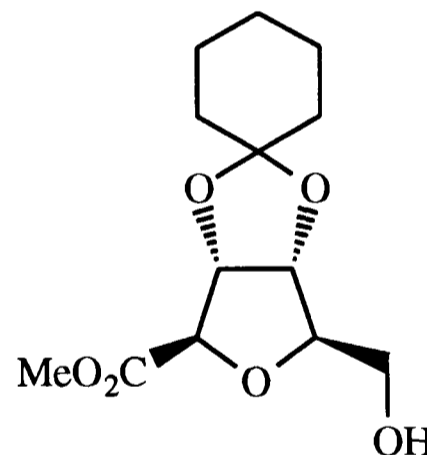
6-*O*-*tert*-Butyldimethylsilyl-3,4-*O*-cyclohexylidene-2-*O*-trifluoromethanesulphonyl-D-altrono-1,5-lactone (2.16) (492 mg, 0.98 mmol) was stirred in a mixture of acetic acid (8 ml) and water (2 ml) at room temperature. After 13 h, t.l.c. (hexane : ethyl acetate, 3 : 1) indicated the formation of a single product (R_f 0.2). The solvent was removed,

the residue co-evaporated with toluene (2 x 5 ml) and purified by flash chromatography (hexane : ethyl acetate, 2 : 1) to yield 3,4-*O*-cyclohexylidene-2-*O*-trifluoromethanesulphonyl-D-altrono-1,5-lactone (2.40) (267 mg, 70%) as a white crystalline solid, m.p. 109-111 °C (ether / hexane); $[\alpha]_D^{20} +29.0$ (*c*, 0.9 in CHCl₃); ν_{\max} (KBr) 3614 (OH), 1786 (C=O) cm⁻¹; δ_H (CDCl₃) 1.39-1.76 (10H, m, cyclohexylidene), 2.93 (1H, br, OH), 3.85 (1H, br d, H-6, $J_{6,6'}$ 12.3 Hz), 4.09 (1H, br d, H-6'), 4.27-4.32 (1H, m, H-5), 4.54-4.63 (2H, m, H-3, H-4), 5.26 (1H, d, H-2, $J_{2,3}$ 7.2 Hz); δ_C (CDCl₃) 23.3, 23.6, 24.6, 34.0, 36.5 (5 x t, cyclohexylidene), 61.0 (t, C-6), 69.9, 73.8, 79.1, 81.9 (4 x d, C-2, C-3, C-4, C-5), 114.5 (s, cyclohexylidene), 165.0 (s, C-1); *m/z* (NH₃, DCI) 408 (MNH₄⁺, 100%), 390 (MNH₄⁺-H₂O). (Found: C, 40.09; H, 4.43; C₁₃H₁₇O₈F₃S requires: C, 40.00; H, 4.39%).

Methyl 2,5-anhydro-3,4-*O*-cyclohexylidene-D-allonate

(2.41)

Method 1.



Methyl 2,5-anhydro-6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-cyclohexylidene-D-allonate (2.31) (90 mg, 0.23 mmol) was stirred in a mixture of acetic acid (4 ml) and water (1 ml) at room temperature. After 24 h, t.l.c. (hexane : ethyl acetate, 1 : 1) indicated the formation of a single product (R_f 0.4). The solvent was removed, the residue co-evaporated with toluene (2 x 5 ml) and purified by flash chromatography (hexane : ethyl acetate, 1 : 1) to yield methyl 2,5-anhydro-3,4-*O*-cyclohexylidene-D-allonate (2.41) (36 mg, 60%) as a colourless oil; $[\alpha]_D^{20} -58.3$ (*c*, 0.47 in CHCl₃); ν_{\max} (film) 3400-3200 (br, OH) 1741 (C=O) cm⁻¹; δ_H (CDCl₃) 1.39-1.79 (10H, m, cyclohexylidene), 3.55 (1H, dd, H-6, $J_{5,6}$ 3.7 Hz, $J_{6,6'}$ 12.6 Hz), 3.82 (3H, s, Me), 3.85 (1H, dd, H-6', $J_{5,6'}$ 2.7 Hz), 4.40-4.43 (1H, m, H-5), 4.61 (1H, d, H-2, $J_{2,3}$ 3.1 Hz), 4.75 (1H, dd, H-4, $J_{3,4}$ 6.0 Hz, $J_{4,5}$ 1.6 Hz), 4.86 (1H, dd, H-3); δ_C (CDCl₃) 23.5, 23.8, 24.8,

34.5, 36.7 (5 x t, cyclohexylidene), 52.7 (q, MeO), 63.1 (t, C-6), 82.0, 84.3, 84.4, 87.6 (4 x d, C-2, C-3, C-4, C-5), 114.4 (s, cyclohexylidene), 173.9 (s, C-1); m/z (NH₃, DCI) 290 (MNH₄⁺), 273 (MH⁺). (Found: C, 57.30; H, 7.47; C₁₃H₂₀O₆ requires: C, 57.34; H, 7.40%)

Method 2.

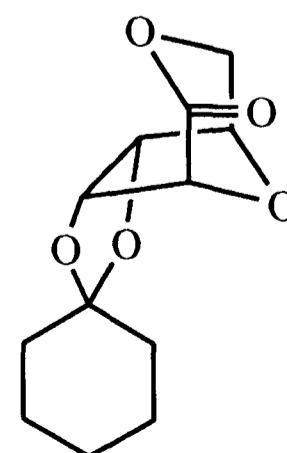
3,4-*O*-Cyclohexylidene-2-*O*-trifluoromethanesulphonyl-D-altrono-1,5-lactone (2.40) (82 mg, 0.21 mmol) and potassium carbonate (29 mg, 0.21 mmol) were stirred in dry methanol (4 ml) at room temperature under nitrogen. After 10 min, t.l.c. (hexane : ethyl acetate, 1 : 1) indicated complete consumption of starting material (R_f 0.5) and the formation of a single product (R_f 0.4). Acetic acid (0.5 ml) was added, the solvent removed and the residue purified by flash chromatography (hexane : ethyl acetate, 2 : 1) to yield methyl 2,5-anhydro-3,4-*O*-cyclohexylidene-D-allonate (2.41) (52 mg, 94%) as a colourless oil, identical to the material described above.

Method 3.

2,5-Anhydro-3,4-*O*-cyclohexylidene-D-allono-1,6-lactone (2.42) (19 mg, 0.08 mmol) and potassium carbonate (11.5 mg, 0.08 mmol) were stirred together in dry methanol (2 ml). After 30 min, acetic acid (0.1 ml) was added, the solvent removed and the residue purified by flash chromatography (hexane : ethyl acetate, 2 : 1) to yield methyl 2,5-anhydro-3,4-*O*-cyclohexylidene-D-allonate (2.41) (13 mg, 63%) as a colourless oil, identical to the material described above.

2,5-Anhydro-3,4-*O*-cyclohexylidene-D-allono-1,6-lactone (2.42).

3,4-*O*-Cyclohexylidene-2-*O*-trifluoromethanesulphonyl-D-altrono-1,5-lactone (2.40) (50 mg, 0.13 mmol) and sodium

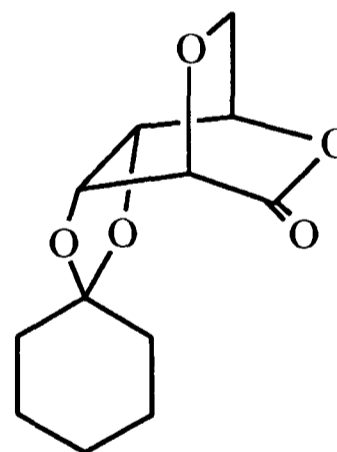


acetate (53 mg, 0.64 mmol) were stirred in dry DMF (3 ml) at room temperature under nitrogen. After 3 h, t.l.c. (hexane : ethyl acetate, 2 : 1) indicated the formation of two products (R_f 0.5 and R_f 0.4). The solvent was removed and the residue purified by flash chromatography (hexane : ethyl acetate, 3 : 1) to yield 2,5-anhydro-3,4-*O*-cyclohexylidene-D-allono-1,6-lactone (2.42) (14 mg, 46%, R_f 0.5) as a white crystalline solid, m.p. 76-80 °C (ethyl acetate / hexane); $[\alpha]_D^{20} +40.9$ (c , 0.64 in CHCl_3); ν_{max} (KBr) 1751 (C=O) cm^{-1} ; δ_{H} (CDCl_3) 1.40-1.78 (10H, m, cyclohexylidene), 4.22 (1H, d, H-6, $J_{6,6'}$ 11.5 Hz), 4.44 (1H, d, J 4.1 Hz), 4.56 (1H, dd, H-6', $J_{5,6}$ 4.2 Hz), 4.65 (1H, s), 4.80-4.87 (2H, m); δ_{C} (CDCl_3) 23.5, 23.8, 24.6, 34.3, 35.5 (5 x t, cyclohexylidene), 69.7 (t, C-6), 77.6, 81.0, 81.9, 82.9 (4 x d, C-2, C-3, C-4, C-5), 115.0 (s, cyclohexylidene), 165.8 (s, C-1); m/z (NH_3 , DCI) 258 (MNH_4^+ , 100%), 240 ($\text{MH}^+ - \text{H}_2\text{O}$);

together with 2,6-anhydro-3,4-*O*-cyclohexylidene-D-altrono-1,5-lactone (2.43) (8 mg, R_f 0.4, 26%) identical to the material described below.

2,6-Anhydro-3,4-*O*-cyclohexylidene-D-altrono-1,5-lactone

(2.43).

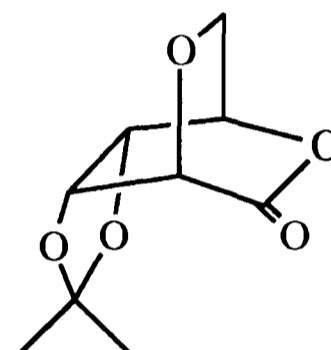


3,4-*O*-Cyclohexylidene-D-altrono-1,5-lactone (2.13) (1.26 g, 4.8 mmol) and triphenylphosphine (1.92 g, 7.3 mmol) were stirred in dry THF (40 ml) at room temperature under nitrogen. Diethyl azodicarboxylate (3.5 ml, 38% soln in toluene) was added and after 1 h t.l.c. (hexane : ethyl acetate, 1 : 1) indicated the consumption of starting material and the formation of a major product (R_f 0.6). The solvent was removed and the residue purified by flash chromatography (hexane : ethyl acetate, 2 : 1) to yield 2,6-anhydro-3,4-*O*-cyclohexylidene-D-altrono-1,5-lactone (2.43) (813 mg, 69%) as a white crystalline solid, m.p. 204-205 °C (ethyl acetate / hexane); $[\alpha]_D^{20}$

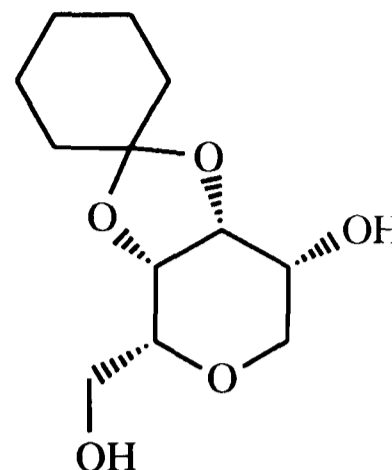
-43.8 (c, 1.1 in CHCl_3); ν_{max} (KBr) 1765 (C=O) cm^{-1} ; δ_{H} (CDCl_3) 1.39-1.74 (10H, m, cyclohexylidene), 3.78 (1H, d, H-6, $J_{6,6'}$ 10.5 Hz), 4.03 (1H, dd, H-6', $J_{5,6'}$ 2.5 Hz), 4.36 (1H, dd, H-4, $J_{3,4}$ 7.4 Hz, $J_{4,5}$ 2.3 Hz), 4.44 (1H, d, H-2, $J_{2,3}$ 4.4 Hz), 4.59 (1H, dd, H-3), 4.85 (1H, m, H-5); δ_{C} (CDCl_3) 23.5, 23.7, 24.8, 33.9, 35.2 (5 x t, cyclohexylidene), 62.8 (t, C-6), 70.6, 72.4, 73.5, 73.6 (4 x d, C-2, C-3, C-4, C-5), 112.1 (s, cyclohexylidene), 168.0 (s, C-1); m/z (NH_3 , DCI) 258 (MNH_4^+ , 100%), 241 (MH^+). (Found: C, 59.88; H, 6.67; $\text{C}_{12}\text{H}_{16}\text{O}_5$ requires: C, 59.99; H, 6.71%).

2,6-Anhydro-3,4-O-isopropylidene-D-altrono-1,5-lactone

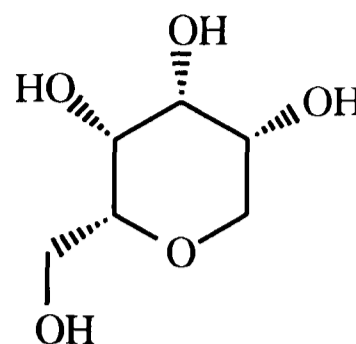
(2.44).



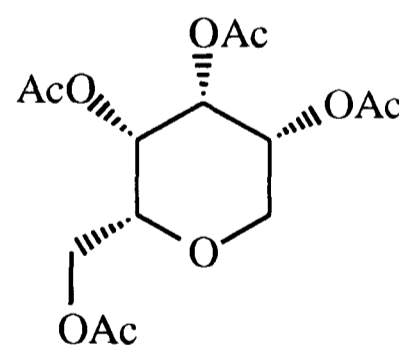
3,4-*O*-Isopropylidene-*D*-altrono-1,5-lactone (2.11) (80 mg, 0.37 mmol) and triphenylphosphine (144 mg, 0.55 mmol) were stirred in dry THF (4 ml) at room temperature under nitrogen. Diethyl azodicarboxylate (0.26 ml, 38% soln in toluene) was added and after 1 h, t.l.c. (hexane : ethyl acetate, 1 : 1) indicated the disappearance of starting material and the formation of a major product (R_f 0.5). The solvent was removed and the residue purified by flash chromatography (hexane : ethyl acetate, 2 : 1) to yield 2,6-anhydro-3,4-*O*-isopropylidene-*D*-altrono-1,5-lactone (2.44) (44 mg, 60%) as a white crystalline solid, m.p. 190-192 °C (ethyl acetate / hexane); $[\alpha]_{\text{D}}^{20}$ -46.0 (c, 0.88 in CHCl_3); ν_{max} (KBr) 1772 (C=O) cm^{-1} ; δ_{H} (CDCl_3) 1.37, 1.48 (6H, 2 x s, Me_2C), 3.81 (1H, d, H-6, $J_{6,6'}$ 10.5 Hz), 4.03 (1H, dd, H-6', $J_{5,6'}$ 2.8 Hz), 4.37 (1H, dd, H-4, $J_{3,4}$ 7.4 Hz, $J_{4,5}$ 2.2 Hz), 4.44 (1H, d, H-2, $J_{2,3}$ 4.4 Hz), 4.61 (1H, dd, H-3), 4.85 (1H, t, H-5); δ_{C} (CD_3CN) 23.4, 23.6 (2 x q, Me_2C), 62.5 (t, C-6), 70.3, 72.5, 73.7, 73.8 (4 x d, C-2, C-3, C-4, C-5), 110.5 (s, CMe_2), 168.6 (s, C-1); m/z (NH_3 , DCI) 218 (MNH_4^+ , 100%). (Found: C, 54.06; H, 6.01; $\text{C}_9\text{H}_{12}\text{O}_5$ requires: C, 54.00; H, 6.04%).

2,6-Anhydro-3,4-O-cyclohexylidene-D-altritol (2.46).

2,6-Anhydro-3,4-O-cyclohexylidene-D-altrono-1,5-lactone (2.43) (111 mg, 0.46 mmol) was dissolved in dry THF (10 ml) and stirred at 0 °C under nitrogen. Lithium borohydride (0.46 ml, 2.0 M solution in THF) was added and the mixture allowed to warm to room temperature. After 4 h, t.l.c. (ethyl acetate) indicated complete consumption of starting material (R_f 0.8) and the formation of a single product (R_f 0.2). Ammonium chloride (50 mg) was added carefully, followed by methanol (10 ml) and the mixture stirred for 10 min. The solvent was removed, the residue co-evaporated with methanol (2 x 10 ml), preabsorbed onto silica and purified by flash chromatography (ethyl acetate) to yield 2,6-anhydro-3,4-O-cyclohexylidene-D-altritol (2.46) (105 mg, 93%) as a colourless oil; $[\alpha]_D^{20} +21.9$ (c , 1.13 in CHCl_3); ν_{max} (film) 3600-3200 (br, OH) cm^{-1} ; δ_{H} (CDCl_3) 1.38-1.89 (10H, m, cyclohexylidene), 3.50 (1H, dd, H-6, $J_{5,6}$ 2.0 Hz, $J_{6,6'}$ 10.5 Hz), 3.74 (1H, m, H-2), 3.79 (2H, m, H-1, H-5), 3.98 (1H, dd, H-1', $J_{1,1'}$ 11.8 Hz, $J_{1',2}$ 7.4 Hz), 4.07 (1H, dd, H-6', $J_{5,6'}$ 3.9 Hz), 4.20 (1H, dd, H-3, $J_{2,3}$ 2.6 Hz, $J_{3,4}$ 6.3 Hz), 4.28 (1H, dd, H-4, $J_{4,5}$ 5.1 Hz); δ_{C} (CDCl_3) 23.6, 23.9, 24.9, 34.3, 35.3 (5 x t, cyclohexylidene), 62.8, 68.0 (2 x t, C-1, C-6), 64.1, 71.7, 72.4, 75.9 (4 x d, C-2, C-3, C-4, C-5), 110.7 (s, cyclohexylidene); m/z (NH_3 , DCI) 262 (MNH_4^+ , 100%), 245 (MH^+). (Found: C, 59.28; H, 8.53; $\text{C}_{12}\text{H}_{20}\text{O}_5$ requires: C, 59.00; H, 8.25%).

2,6-Anhydro-D-altritol (2.45)

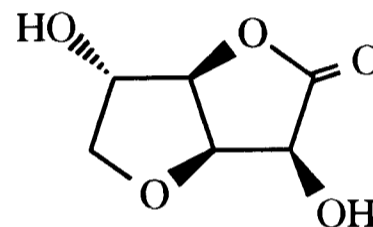
2,6-Anhydro-3,4-*O*-cyclohexylidene-D-altritol (2.46) (105 mg, 0.43 mmol) was stirred in a mixture of trifluoroacetic acid (4 ml) and water (6 ml) at room temperature. After 12 h, t.l.c. (ethyl acetate) indicated complete consumption of starting material (R_f 0.2) and the formation of a single product (R_f 0.0). The solvent was removed, the residue co-evaporated with toluene (2 x 5 ml) and then purified by flash chromatography (ethyl acetate : methanol, 9 : 1) to yield 2,6-anhydro-D-altritol (2.45) (63 mg, 89%) as a viscous gum; $[\alpha]_D^{20}$ -7.5 (c , 0.72 in H₂O)[Lit -11.5 (c , 4.85 in H₂O)]²⁷; ν_{\max} (film) 3600-3200 (br, OH) cm⁻¹; δ_H (D₂O) 3.46 (1H, ddd, J 1.0 Hz, J' 4.0 Hz, J'' 8.0 Hz), 3.56 (1H, dd, J 1.2 Hz, J' 12.7 Hz), 3.62 (1H, dd, J 4.0 Hz, J' 11.8 Hz), 3.69 (1H, d, J 3.4 Hz), 3.71 (1H, dd, J 8.0 Hz, J' 11.8 Hz), 3.80 (1H, m), 3.85 (1H, m), 3.94 (1H, dd, J 2.2 Hz, J' 12.7 Hz); δ_C (CD₃OD) 61.6, 70.9 (2 x t, C-1, C-6), 68.8, 69.8, 70.1, 79.9 (4 x d, C-2, C-3, C-4, C-5); m/z (NH₃, CI) 182 (MNH₄⁺), 165 (MH⁺, 100%).

2,6-Anhydro-1,3,4,5-tetra-*O*-acetyl-D-altritol (2.47)

2,6-Anhydro-D-altritol (2.45) (31 mg, 0.19 mmol) and DMAP (2 mg) were stirred in a mixture of dry pyridine (2 ml) and acetic anhydride (2 ml) at room temperature under nitrogen. After 30 min, t.l.c. (ethyl acetate : hexane, 1 : 1) indicated the formation of a single product (R_f 0.4). The solvent was removed and ethyl acetate (10 ml) was added. The crude mixture was then washed sequentially with 1M HCl (5 ml), water (5 ml) and brine (5 ml), dried (magnesium sulphate), filtered, the solvent removed and the residue

purified by flash chromatography (ethyl acetate : hexane, 1 : 1) to yield 2,6-anhydro-1,3,4,5-tetra-O-acetyl-D-altritol (2.47) (30 mg, 50%) as a white crystalline solid, m.p. 108 °C (ether / hexane) [Lit 108 °C]²⁷; $[\alpha]_{\text{D}}^{20}$ -18.1 (*c*, 0.31 in CHCl₃) [Lit -16.2 (*c*, 5.0 in CHCl₃)]²⁷; δ_{H} (CDCl₃) 2.02, 2.07 (6H, 2 x s, 2 x Ac), 2.16 (6H, s, 2 x Ac), 3.74 (1H, dd, *J* 1.8 Hz, *J'* 13.3 Hz), 3.86 (1H, dt, *J* 1.6 Hz, *J'* 5.9 Hz), 4.16 (1H, dd, *J* 2.2 Hz, *J'* 13.3 Hz), 4.18-4.23 (2H, m), 5.12 (1H, t, *J* 3.5 Hz), 5.18 (1H, m), 5.33 (1H, m); δ_{C} (CDCl₃) 20.5, 20.6, 20.9 (3 x q, 4 x Ac), 62.2, 75.1 (2 x t, C-1, C-6), 66.1, 66.6, 67.8, 75.1, (4 x d, C-2, C-3, C-4, C-5), 170.0, 170.5, 170.6, 170.9 (4 x s, 4 x Ac); *m/z* (NH₃, DCI) 182 (MNH₄⁺), 165 (MH⁺, 100%).

3,6-Anhydro-L-gulono-1,5-lactone (2.49).



L-Gulono-1,5-lactone (2.48) (197 mg, 1.1 mmol) and triphenylphosphine (435 mg, 1.66 mmol) were stirred in dry THF (10 ml) at room temperature under nitrogen. Diethyl azodicarboxylate (0.80 ml, 38% soln in toluene) was added and the reaction mixture heated at 60 °C. After 3 h, t.l.c. (ethyl acetate) indicated the formation of a major product (*R_f* 0.4). The solvent was removed and the residue purified by flash chromatography (ethyl acetate) to yield 3,6-anhydro-L-gulono-1,5-lactone (2.49) (71 mg, 40%) as a white crystalline solid, m.p. 137-138 °C (ethyl acetate / hexane) [Lit 137-138 °C]²⁸; $[\alpha]_{\text{D}}^{20}$ +64.7 (*c*, 0.66 in acetone)[Lit +64.6 (*c*, 2.0 in acetone)]²⁸; ν_{max} (KBr) 3400-3200 (br, OH) 1778 (C=O) cm⁻¹; δ_{H} (CD₃CN) 3.51 (1H, d, OH, *J* 4.2 Hz), 3.64 (1H, dd, *J* 1.0 Hz, *J'* 9.0 Hz), 3.82 (1H, dd, *J* 1.0 Hz, *J* 10.2 Hz), 3.95 (1H, dd, *J* 3.8 Hz, *J'* 10.2 Hz), 4.40-4.43 (2H, m), 4.66 (1H, dd, *J* 3.5 Hz, *J'* 5.1 Hz), 4.76 (1H, d, OH, *J* 3.6 Hz); δ_{C} (CD₃OD) 69.3, 74.0, 77.9, 84.6 (4 x d, C-2, C-3, C-4, C-5), 74.5 (t, C-6), 176.3 (s, C-1); *m/z* (NH₃, DCI) 178 (MNH₄⁺, 100%), 160 (MNH₄⁺-H₂O). (Found: C, 45.19; H, 5.17; C₆H₈O₅ requires: C, 45.01; H, 5.04%).

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. and Meng-Yan, Y. *J. Chem. Soc. Chem. Commun.*, 1989, 1817.
- ³ Beacham, A.R.; Bruce, I.; Choi, S.; Doherty, O.; Fairbanks, A.J.; Fleet, G.W.J.; Skead, B.M.; Peach, J.M.; Saunders, J.; and Watkin, D.J. *Tetrahedron: Asymm.*, 1991, **2**, 883.
- ⁴ For clarity, the numbering system adopted here refers to the lactone carbon 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 aldehydo lactones (see note concerning nomenclature).
- ⁵ Elliott, R.P. 'Sugars as Homochiral Starting Materials', D. Phil Thesis, Oxford University, 1992.
- ⁶ Bruce, I.; Fleet, G.W.J.; Girdhar, A.; Haraldsson, M.; Peach, J.M.; and Watkin, D.J. *Tetrahedron*, 1990, **46**, 19.
- ⁷ Bichard, C.J.F.; Fairbanks, A.J.; Fleet, G.W.J.; Ramsden, N.G.; Vogt, K.; Doherty, O.; Pearce, L.; and Watkin, D.J. *Tetrahedron: Asymm.*, 1991, **2**, 901.
- ⁸ 1993 Sigma Catalogue price: 1g of D-allose costs £ 101.90.
- ⁹ (a) Haga, M.; Takano, M.; and Tejima, S.; *Carbohydr. Res.*, 1970, **14**, 237. (b) Ballard, J.M., and Stacey, B. *Carbohydr. Res.*, 1970, **12**, 37.
- ¹⁰ Kaskar, B.; Heise, G.L.; Michalak, R.S.; and Vishnuvajjala, B.R. *Synthesis*, 1990, 1031.
- ¹¹ Hughes, N.A.; and Speakman, P.R.H. *Carbohydr. Res.*, 1965, **1**, 171.
- ¹² Isbell, H.S.; Karabinos, J.V.; Frush, H.L.; Holt, N.B.; Schwebel, A.; and Galkowski, T.T. *J. Res. NBS*, 1952, **48**, 163.
- ¹³ Serianni, A.S.; Nunez, H.A.; and Barker, R. *J. Org. Chem.*, 1980, **45**, 3329.

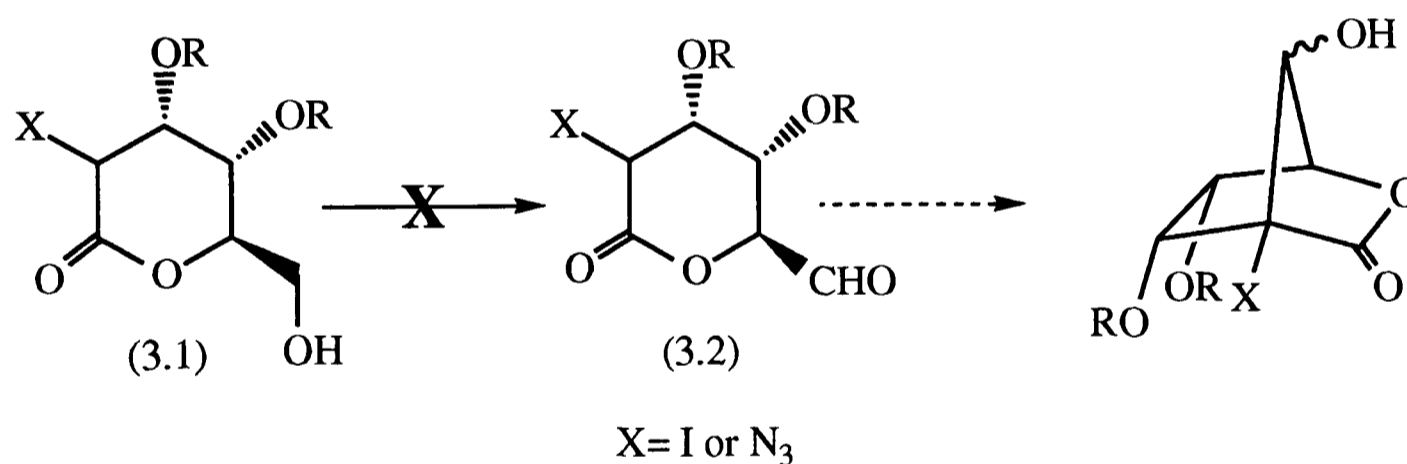
-
- 14 Kuzmann, J.; Marton-Meresz, M.; and Jerkovich, G. *Carbohydr. Res.*, 1988, **175**, 249.
- 15 Mori, K.; and Kikuchi, H. *Liebigs Ann. Chem.*, 1989, 1267.
- 16 Baird, P.D.; Dho, J.C.; Fleet, G.W.J.; Peach, J.M.; Prout, K.; and Smith, P.W. *J. Chem. Soc., Perkin Trans. 1*, 1987, 1785.
- 17 (a) Dess, D.B.; and Martin, J.C. *J. Org. Chem.*, 1983, **48**, 4156. (b) Ireland, R.E.; and Lui, L. *J. Org. Chem.*, 1993, **58**, 2899.
- 18 Griffith, W.P.; and Ley, S.V. *Aldrichimica Acta*, 1990, **23**, 13.
- 19 The numbering system used for the trivial name 1-epihydantocidin refers to the spiro centre as C-1. This should strictly be referred to as C-5 (see note concerning nomenclature).
- 20 Authentic nmr spectra and a sample of hydantocidin were kindly provided by Dr S. Mirza of CIBA GEIGY, Basle.
- 21 Mio, S.; Kumagawa, Y.; and Sugai, S. *Tetrahedron*, 1991, **47**, 2133.
- 22 Postema, M.H.D. *Tetrahedron*, 1992, **48**, 8545.
- 23 Westley, J.W. *Polyether Antibiotics: Naturally Occurring Acid Ionophores*, Vols. I and II, 1982, Marcel Dekker, New York.
- 24 Boivin, T.L.B. *Tetrahedron*, 1987, **43**, 3309.
- 25 Choi, S.S.; Myerscough, P.M.; Fairbanks, A.J.; Skead, B.M.; Bichard, C.J.F.; Mantell, S.J.; Son, J.C.; Fleet, G.W.J.; Saunders, J.; and Brown, D. *J. Chem. Soc. Chem. Commun.*, 1992, 1605.
- 26 Mitsunobu, O. *Synthesis*, 1981, 1.
- 27 Rosenfeld, D.A.; Richtmyer, N.K.; and Hudson, C.S. *J. Am. Chem. Soc.*, 1948, **70**, 2201.
- 28 Heyns, K.; Alpers, E.; and Weyer, J. *Chem. Ber.*, 1968, **101**, 4199.
- 29 Mio, S.; Ueda, M.; Hamura, M.; Kitagawa, J.; and Sugai, S. *Tetrahedron*, 1991, **47**, 2145.

CHAPTER 3

Synthesis and Investigations of D-glycero-L-alto-heptono-1,5-lactones.

Introduction.

The crucial synthetic step in the attempted cyclopentane synthesis detailed in Chapter 2 involved oxidation of the alcohols (3.1) to the aldehydes (3.2) (Scheme 3.1). It was envisaged that the aldehydes (3.2) would be useful synthetic intermediates which could provide access to polyhydroxylated cyclopentanes via intramolecular aldol cyclisation. The difficulties experienced in effecting the synthesis of these materials via the oxidation route attempted in Chapter 2 necessitated an alternative synthetic strategy.

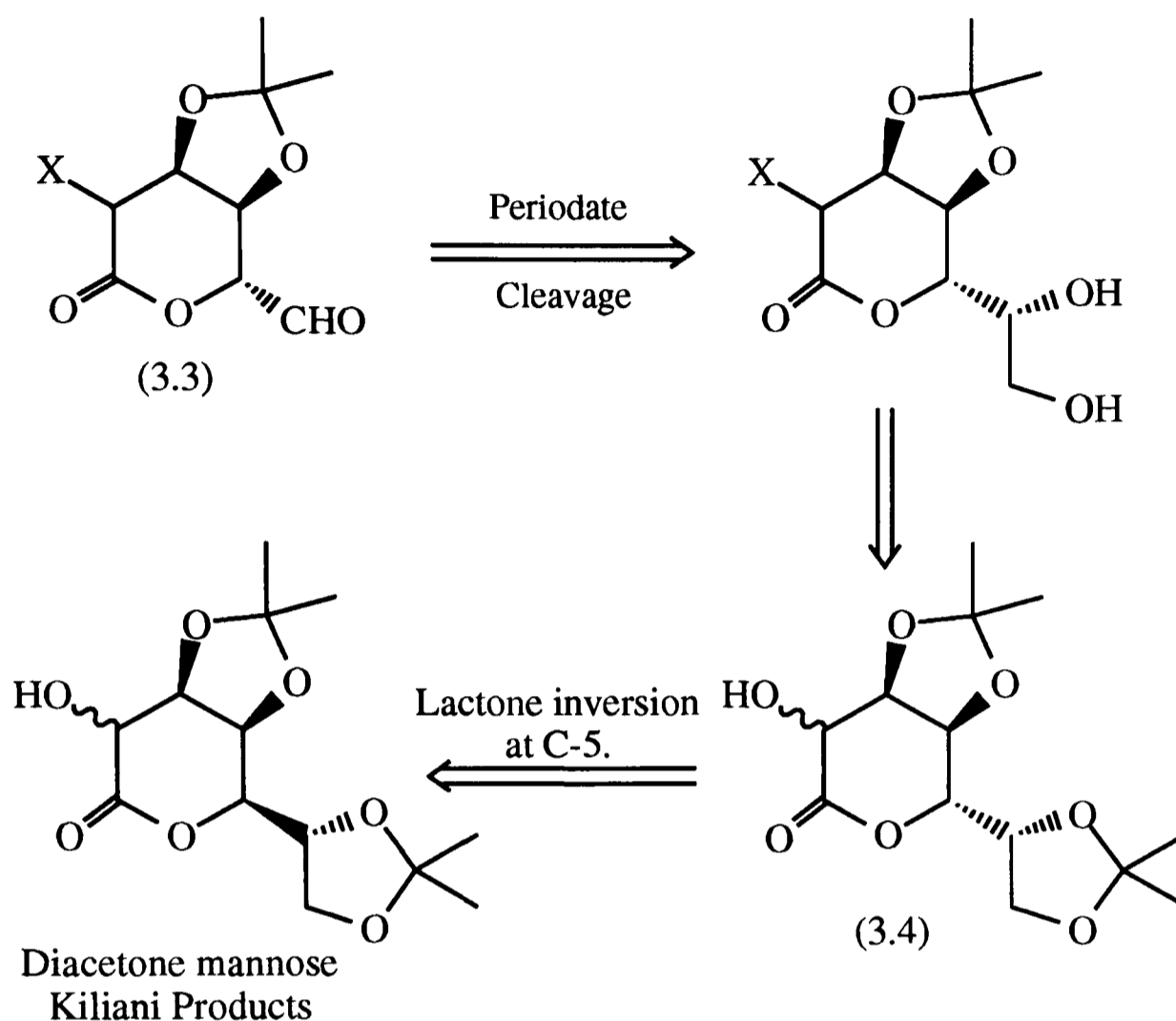


Scheme 3.1

As detailed in Chapter 2, alternative retrosynthesis of the aldehydes (3.2) via periodate cleavage, rather than oxidation, leads to the Kiliani product derived from diacetone-D-allose (2.4) (Scheme 2.2). Due to the low yield of the allose Kiliani reaction, and the protracted reaction sequence required for the synthesis of the starting material, this was not considered to be a viable synthetic route.

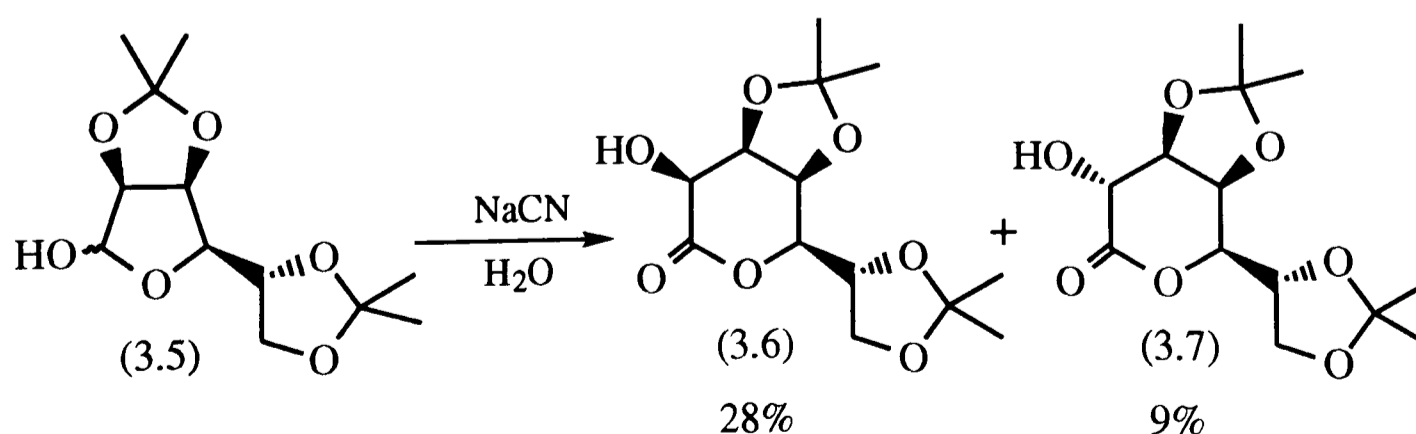
However retrosynthetic analysis of the enantiomeric aldehyde (3.3), via periodate cleavage, leads to the lactone (3.4) (Scheme 3.2). Further analysis of this material

indicates that it could be readily synthesised from the products of the Kiliani reaction of diacetone-D-mannose (3.5) simply by an inversion of configuration at C-5.



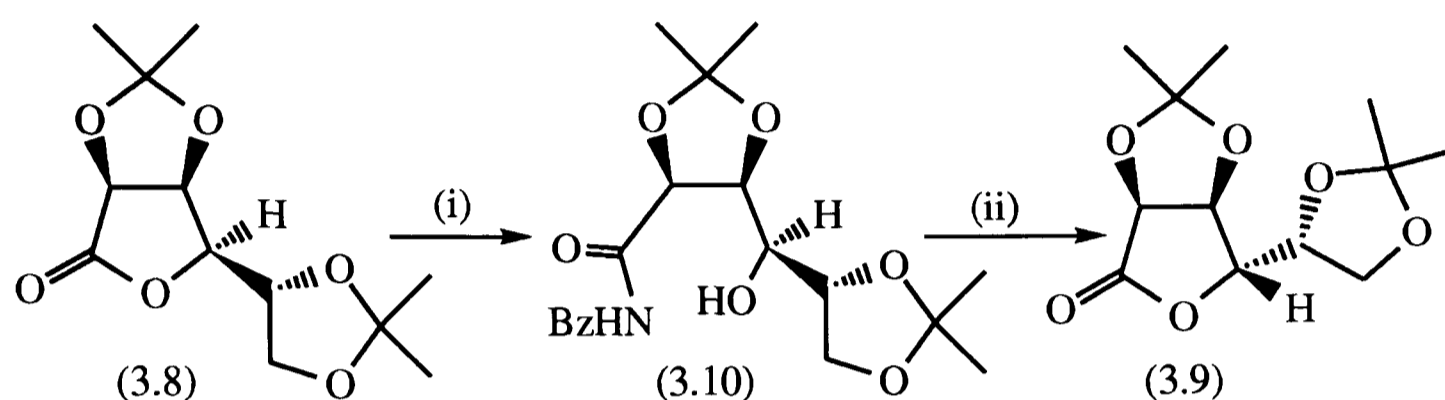
Scheme 3.2

Diacetone-D-mannose (3.5) is a cheap and readily available starting material. The Kiliani ascension, which has been performed on a multikilogram scale,¹ proceeds in moderate yield to produce a readily separable mixture of epimeric lactones (3.6) and (3.7) (Scheme 3.3).



Scheme 3.3

The inversion of several carbohydrate lactones at the stereocentre to which the oxygen of the lactone ring is attached has been achieved by a two step reaction process.² Scheme 3.4 details the inversion of the diacetonide of D-mannono-1,4-lactone (3.8) at C-4, which proceeds in good yield, to produce the diacetonide of D-talono-1,4-lactone (3.9).



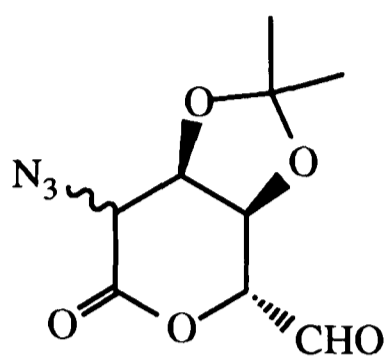
(i) BzNH₂, THF, RT, 22 h, 98% (ii) Tf₂O, py,
CH₂Cl₂, -10 °C, then aqueous work-up, 73%.

Scheme 3.4

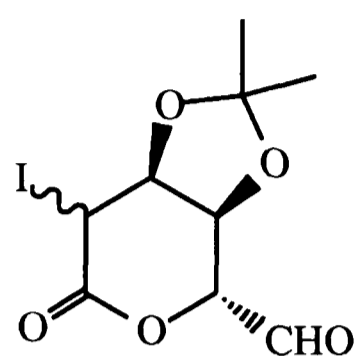
The strategy adopted involved initial opening of the lactone ring by treatment with a suitable amine, in this case benzylamine, to produce the amide (3.10). Treatment of this amide with a threefold excess of triflic anhydride induced relactonisation with a corresponding inversion of configuration at the carbon atom bearing the lactone ring oxygen. This step precludes the use of substrates possessing free hydroxyl groups, which must be initially protected. The precise mechanism of the relactonisation step is not entirely clear. It seems certain that triflation of the free hydroxyl derived from the lactone ring is crucial to obtaining inverted products, though this does not appear to be the site of initial triflation as the use of only 1 equivalent of triflic anhydride results in the formation of lactone products in which the configuration at the carbon atom bearing the lactone ring oxygen has been retained.²

Application of such a synthetic transformation to the heptonolactones (3.6) and (3.7) would allow access to the azido (3.11) and iodo (3.12) aldehydes. Except for the replacement of a cyclohexylidene protecting group with an acetonide, these materials are enantiomeric with the crucial intermediates which could not be synthesised via the

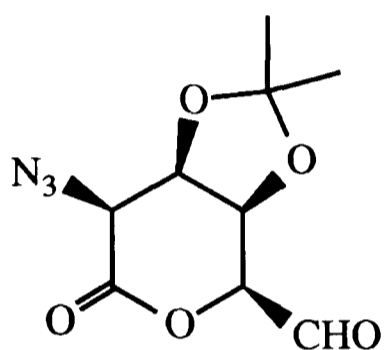
oxidation of the α -azido and α -iodo-D-altrono-1,5-lactones detailed in Chapter 2 (Scheme 2.13). Deprotonation α to the lactone followed by intramolecular aldol cyclisation would then result in cyclopentane formation.



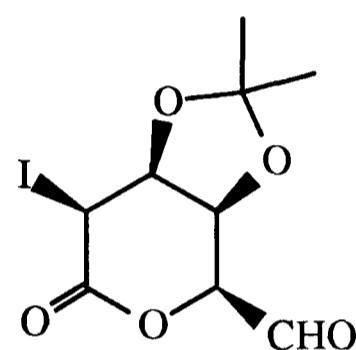
(3.11)



(3.12)



(1.39)



(1.37)

Cyclisation of the azido (1.39) and iodo (1.37) aldehydes was found to produce a mixture of carbocycles in both cases as detailed in Chapter 1 (Schemes 1.10 and 1.12). The minor products formed during these reactions were found to result from initial epimerisation α to the aldehyde functionality before intramolecular aldol cyclisation occurred (Scheme 1.11).

Cyclisation of the azido and iodo aldehydes (3.11) and (3.12), which are epimeric α to the aldehyde functionality as compared to (1.39) and 1.37), would provide further insight into the stereochemical course of these cyclisation reactions. In particular cyclisation of (3.11) and (3.12) would be expected to yield some, or all, of the same set of carbocyclic products that were obtained from (1.39) and (1.37).

Results and Discussion.

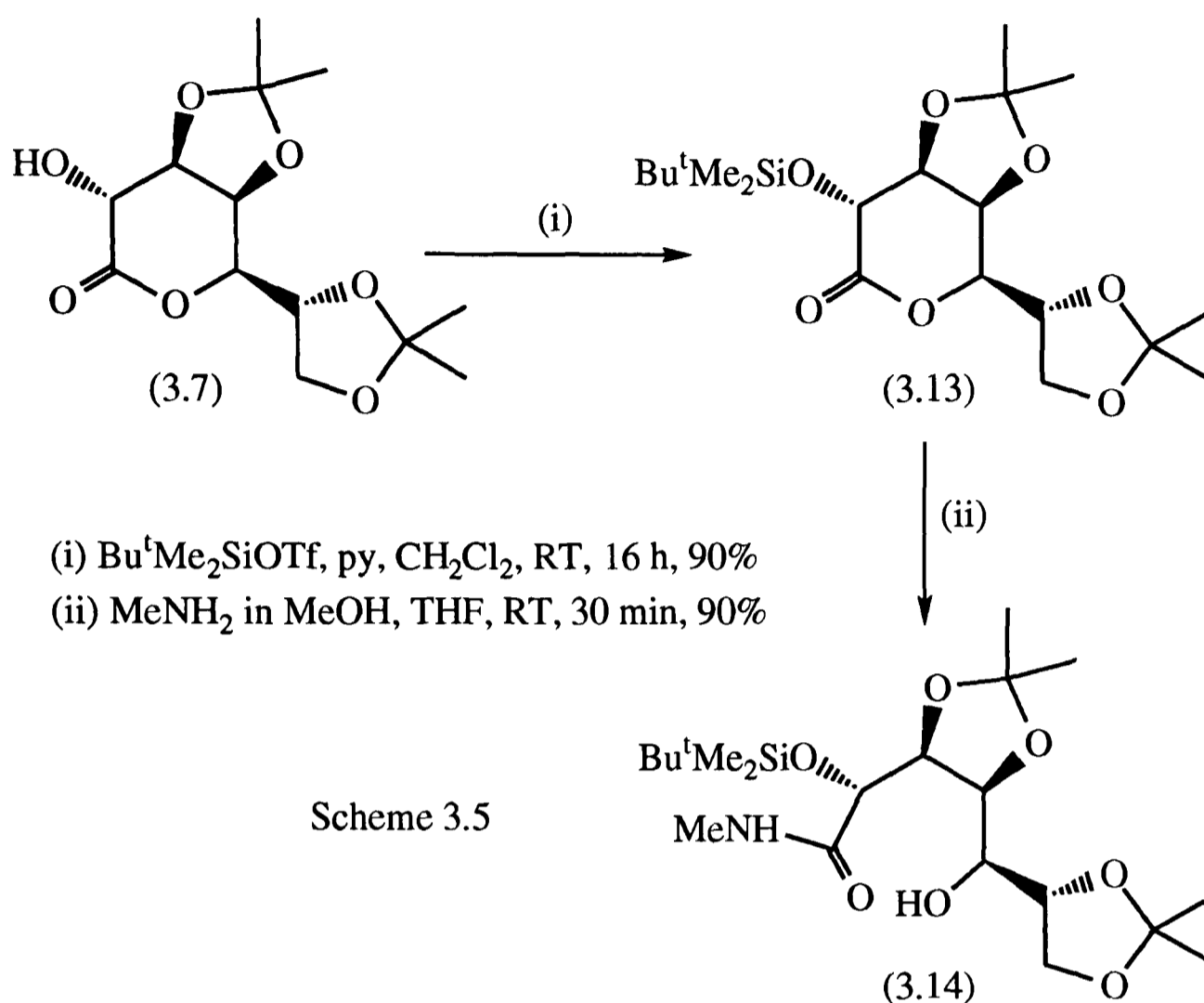
Work in this chapter is divided into four areas:-

- (i) Investigations into the inversion at C-5 of D-glycero-D-galacto-heptono-1,5-lactones.
- (ii) Confirmation of the stereochemical identity of the inverted lactone product.
- (iii) Synthesis of iodo carbocycles.
- (iv) Synthesis of azido carbocycles.

(i) Investigations into the inversion at C-5 of D-glycero-D-galacto-heptono-1,5-lactones.

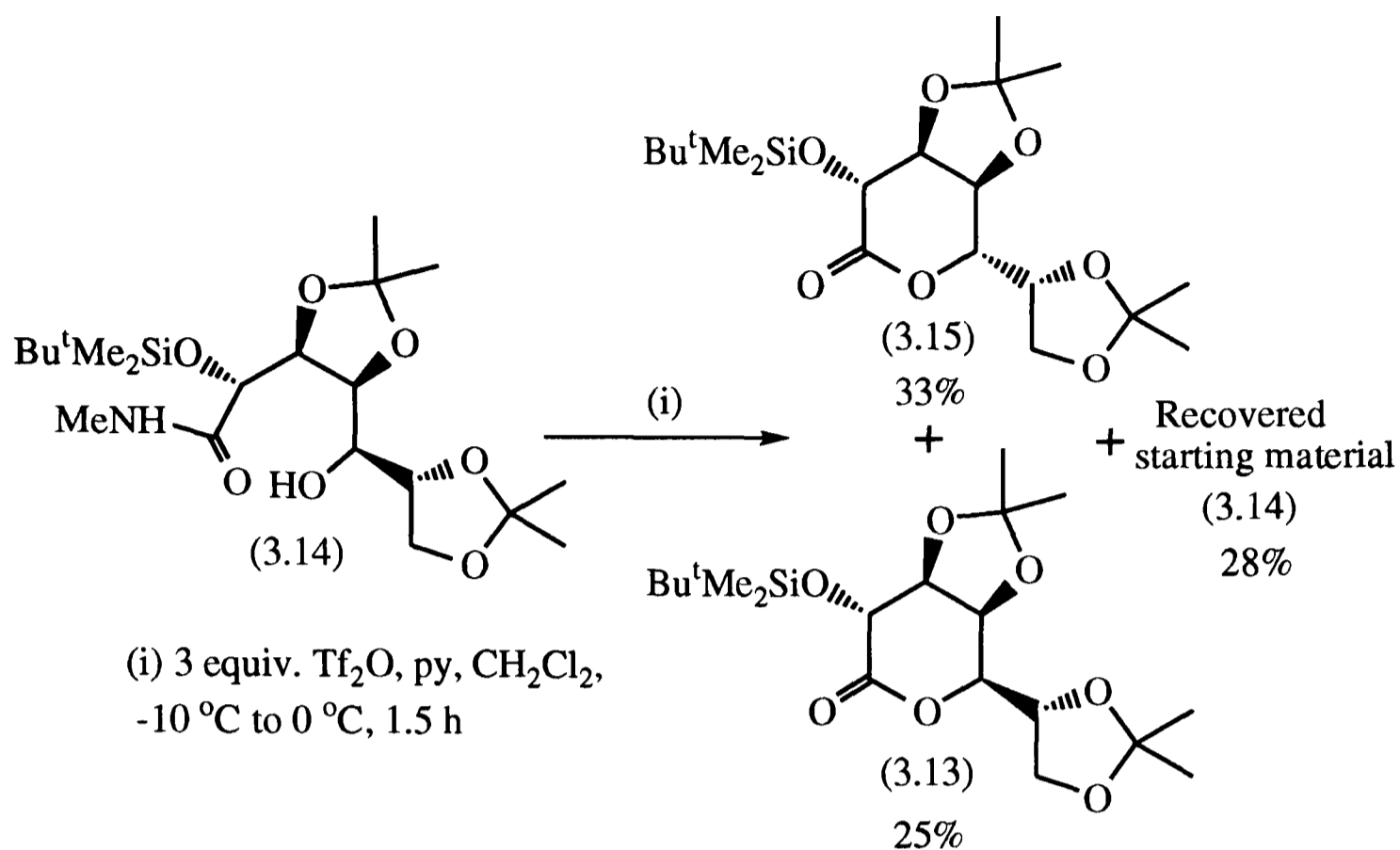
Synthetic efforts concentrated upon the attempted C-5 inversion of the diacetone of D-glycero-D-galacto-heptono-1,5-lactone (3.7), which is the minor product of the Kiliani reaction of diacetone-D-mannose (3.5), but once inverted at C-5 is enantiomeric with the major product (2.5) obtained from the Kiliani reaction of diacetone-D-allose (2.4) (Chapter 2, Scheme 2.3).

The synthetic route employed was directly analogous to the reaction sequence used for the inversion of C-4 of the diacetone of D-mannono-1,4-lactone (Scheme 3.4). The reaction conditions employed for the relactonisation step necessitated protection of the free C-2 hydroxyl of the starting material. This was achieved simply by treatment of (3.7) with TBDMS triflate and pyridine in dichloromethane to yield the completely protected lactone (3.13). Treatment of this material with a methanolic solution of methylamine in THF produced the open chain amide (3.14) in 90% yield (Scheme 3.5).



Scheme 3.5

Relactonisation of the amide (3.14) was achieved by treatment with 3 equivalents of triflic anhydride and an excess of pyridine in dichloromethane. Following aqueous work up, three reaction products were isolated. These were identified as the required lactone (3.15), which had undergone an inversion of configuration at C-5, unreacted amide (3.14), and the initial silyl lactone (3.13), which had relactonised with retention of configuration at C-5 (Scheme 3.6).

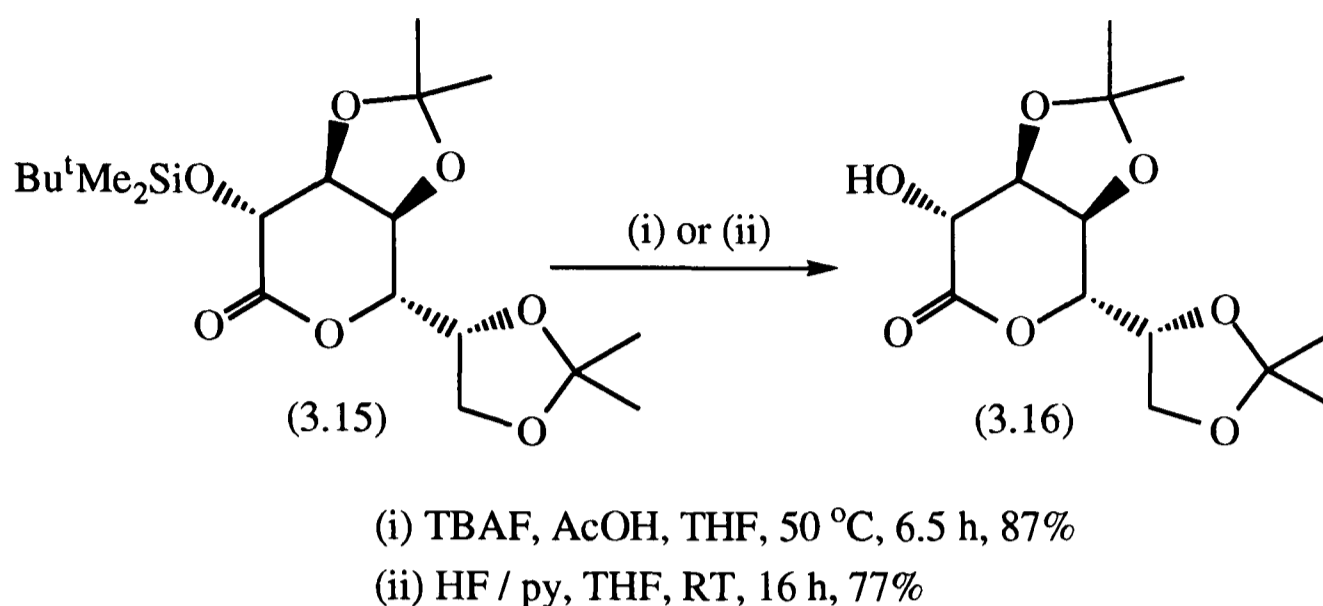


Scheme 3.6

Investigations into the synthetic transformation of (3.13) into (3.15), via other intermediate amides and by employing various reaction conditions, have been carried out by other co-workers.³ The best yield obtained for the C-5 inverted product (3.15) was in the region of 50%, based on recovered starting material.

Initial attempts to desilylate the inverted lactone (3.15) with TBAF caused a large degree of product decomposition, probably via base induced elimination of the secondary acetonide protecting group. Attempts to remove the silyl group with acid proved unsuccessful as reaction conditions forcing enough to induce desilylation caused hydrolysis of both the primary and secondary acetonides, resulting in isomerisation to the thermodynamically more stable γ -lactone.⁴

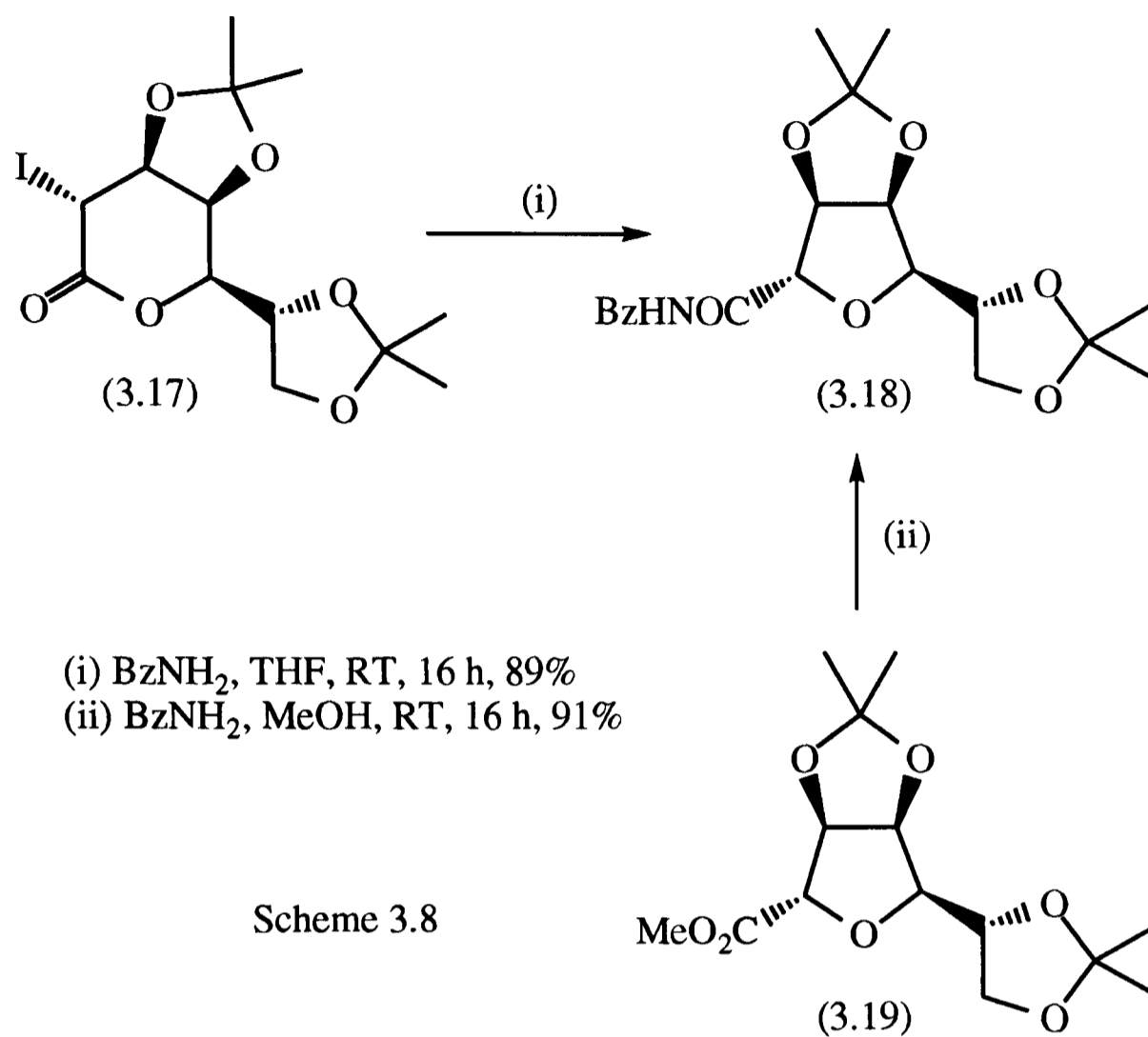
Successful desilylation was achieved in two ways, either by treatment with TBAF in THF in the presence of an excess of acetic acid, or by treatment with HF / pyridine complex.⁵ Both produced good yields of the diacetonide of D-glycero-L-altro heptono-1,5-lactone (3.16) (Scheme 3.7).



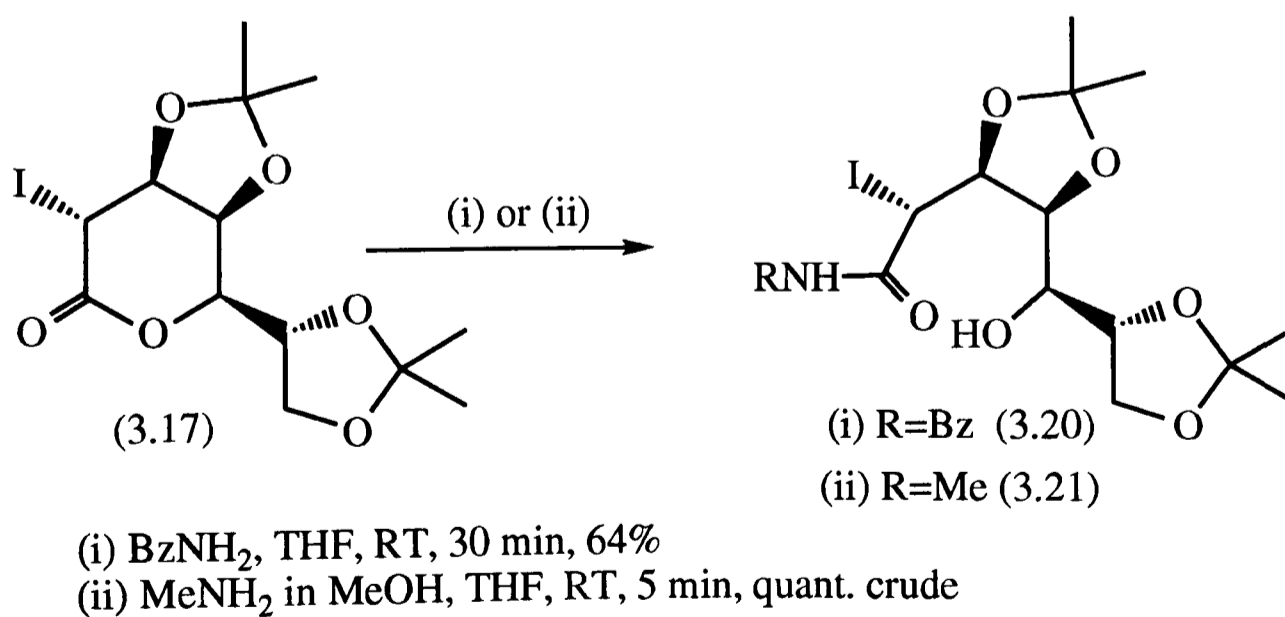
Scheme 3.7

The above reaction sequence, though successful, is rather long. Since subsequent manipulations of the D-glycero-L-altro-heptono-lactone (3.16) would involve introduction of iodide or azide at C-2 a shorter synthetic route can be envisaged. The two additional steps of silylation and desilylation, which are necessitated by the presence of the free hydroxyl group at C-2, could be avoided if a similar inversion of C-5 could be performed on a substrate in which the C-2 hydroxyl has already been substituted by either azide or iodide.

Efforts in this area concentrated on the attempted C-5 inversion of the α -iodo lactone (3.17),⁶ which is readily available from the iodide displacement of the 2-O-triflate derived from the major product (3.6) of the Kiliani reaction of diacetone-D-mannose. Treatment of this iodo lactone with benzylamine in THF for protracted reaction times resulted in the formation of the ring contracted amide (3.18). The identity of this material was confirmed by treatment of the known methyl ester (3.19)⁷ with an excess of benzylamine in methanol, which also resulted in the formation of (3.18) (Scheme 3.8).



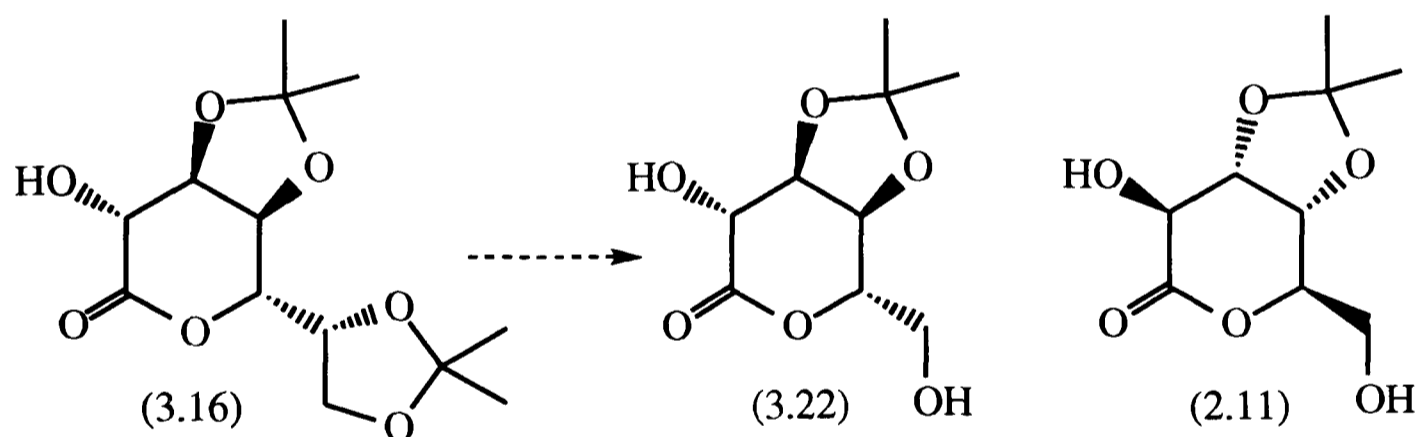
Treatment of the iodo lactone (3.17) with benzylamine or methylamine for short periods of time resulted in the formation of the open-chain benzylamide (3.20) and methylamide (3.21) respectively (Scheme 3.9).



The presence of the α -iodo substituent was confirmed both by mass spectrometry and by the characteristic ^{13}C signal for the C-2 CH at around 20 ppm. However all attempts to induce either material to relactonise with inversion of configuration at C-5, using the methodology adopted above, proved unsuccessful.

(ii) Confirmation of the stereochemical identity of the inverted lactone product.

In order to be entirely certain of the stereochemical integrity of the C-5 inverted lactone product, it was decided to chemically correlate the D-glycero-L-altrio heptonolactone (3.16) with a compound of known structure. Degradation of the carbon side chain of the lactone (3.16) by one unit would produce the L-altrono lactone (3.22) as shown in Scheme 3.10.

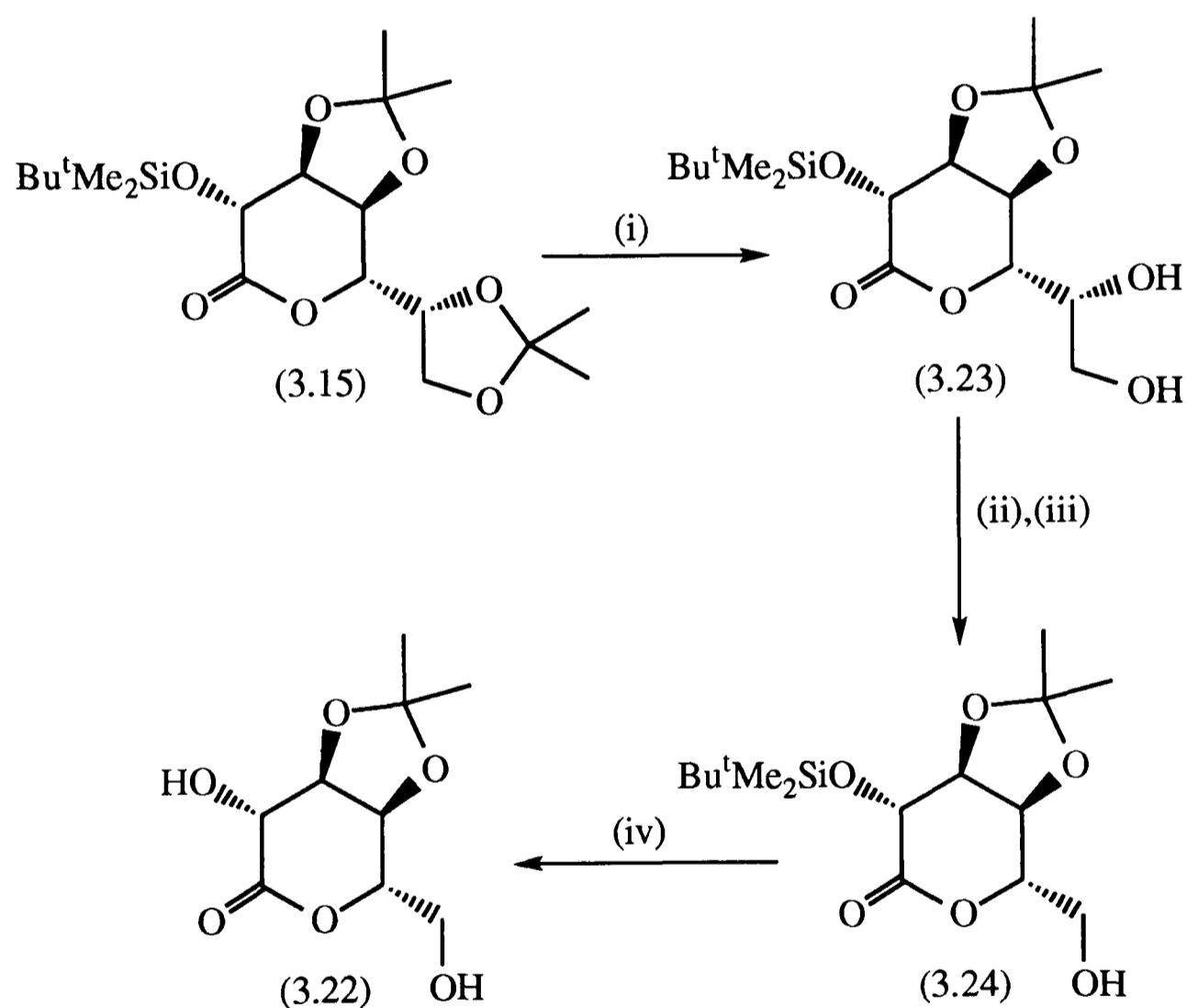


Scheme 3.10

This material is enantiomeric with the D-altrono-lactone (2.11) which was synthesised from the Kiliani reaction of the 2,3-acetonide of D-ribose (2.8) as detailed in Chapter 2 (Scheme 2.6) and whose structure was confirmed by X-ray crystallography.

The synthetic strategy adopted involved use of the silyl D-glycero-L-altrio-heptonolactone (3.15) as starting material. Selective removal of the primary acetonide was achieved by treatment with 80% aqueous acetic acid to produce the silyl diol (3.23). Periodate cleavage followed by reduction with sodium borohydride at low

temperature produced a moderate yield of the degraded silyl L-altrono-lactone (3.24). Removal of the silyl protecting group with TBAF in the presence of acetic acid produced the L-altrono lactone (3.22) which possessed a melting point and ^1H and ^{13}C nmr spectra identical with those of the enantiomeric lactone (2.11). The measured optical rotation (-96.2 c, 0.53 in EtOH) was also in close agreement with the value obtained for its enantiomer ($+101.3$ c, 0.9 in EtOH). This reaction sequence is summarised in Scheme 3.11.



(i) 80% aqueous AcOH, RT, 20 h, 82%

(ii) H_5IO_6 , THF, RT, 10 min, 66%

(iii) NaBH_4 , EtOH / H_2O , -10 °C, 10 min, 40%

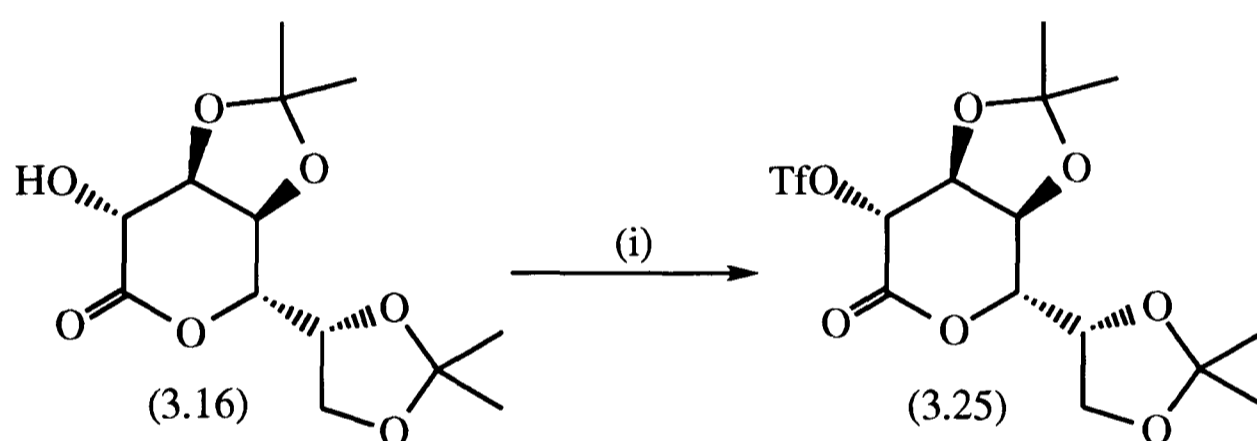
(iv) TBAF, AcOH, THF, 50 °C, 2 h, 74%

Scheme 3.11

(iii) Synthesis of iodo carbocycles.

The general synthetic strategy adopted for the formation of iodo carbocycles followed the pathway indicated by the retrosynthetic analysis outlined in Scheme 3.2. Introduction of iodine at C-2, followed by removal of the side chain acetonide and periodate cleavage, would produce iodo aldehydes which could then be cyclised via an intramolecular aldol condensation.

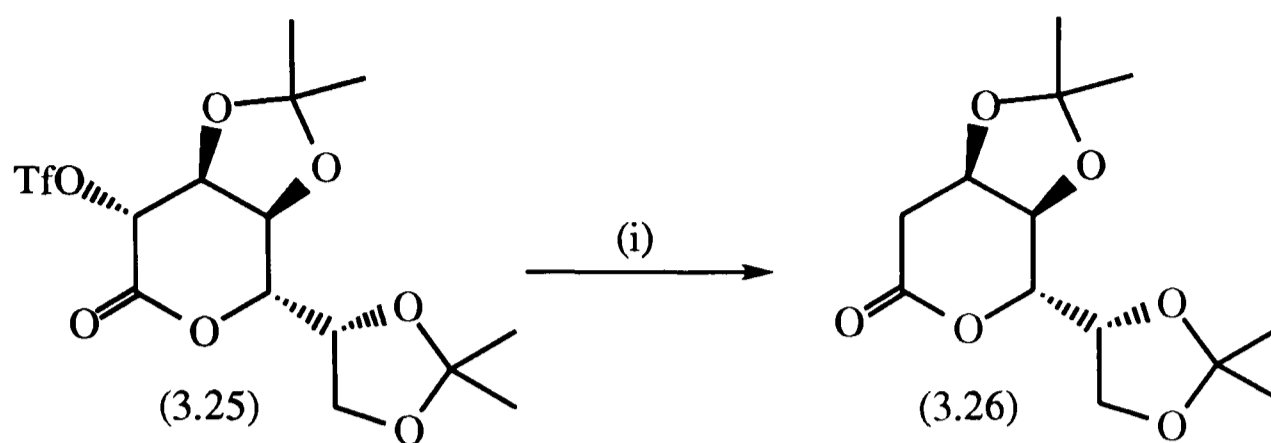
Introduction of iodine at C-2 of the D-glycero-L-althro-heptono lactone (3.16) was achieved via formation of the triflate (3.25) (Scheme 3.12).



(i) Tf_2O , py, CH_2Cl_2 , $-20\text{ }^\circ\text{C}$, 30 min, 76%

Scheme 3.12

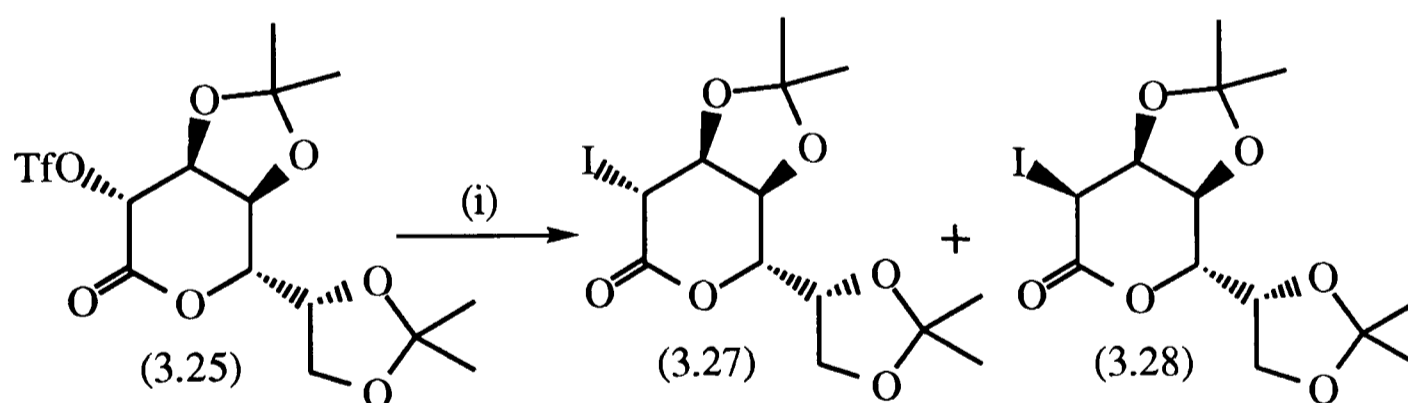
An initial attempt to introduce iodine at C-2 involved treatment of triflate (3.25) with sodium iodide in acetone. T.l.c. indicated the formation of a mixture of products. Washing with aqueous thiosulphate solution resulted in the conversion of these materials to a single product (as seen by t.l.c.) which was identified as the reduced material (3.26) in 80% yield (Scheme 3.13).



(i) NaI, acetone, 40 °C, 2 h, then aq. Na₂S₂O₃

Scheme 3.13

Subsequent attempts to introduce iodine involved treatment of the triflate (3.25) with tetra-*n*-butylammonium iodide in THF, and avoided an aqueous thiosulphate wash. These reactions produced an inseparable mixture of epimeric iodides (3.27) and (3.28) (Scheme 3.14). These materials were characterised as a mixture and used as such for the next synthetic step.

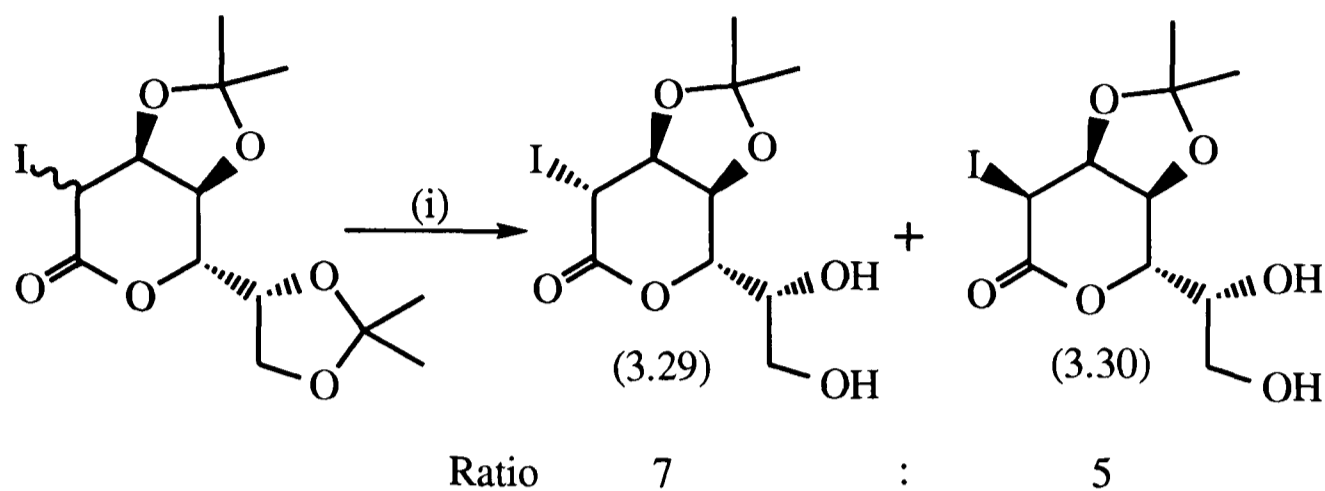


(i) tetra-*n*-butylammonium iodide, THF, RT, 1.5 h, 71%

Scheme 3.14

Removal of the primary acetonide was achieved by treatment with 80% aqueous acetic acid to produce a mixture of epimeric iodo diols (3.29) and (3.30) (in a ratio of 7 : 5, as adjudged by ¹H nmr, Scheme 3.15). These materials were again found to be inseparable by chromatography and again were used as a mixture for the next

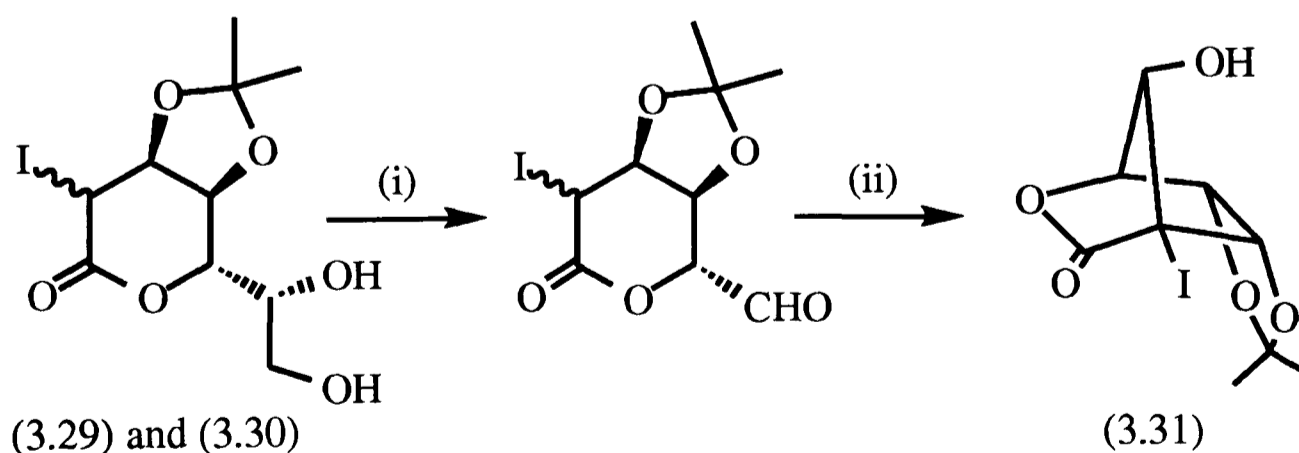
synthetic step. Small amounts of the minor D-glycero-L-allo isomer (3.30) could be crystallised out of a solution of the mixture, thus facilitating characterisation.



(i) 80% aqueous AcOH, RT, 20 h, 67%

Scheme 3.15

Periodate cleavage of the mixture of iodo diols (3.29) and (3.30) produced a mixture of aldehydes which were used without isolation or characterisation. Treatment of these aldehydes with potassium fluoride and 18-crown-6 in dry acetonitrile produced the iodo carbocycle (3.31) as the sole reaction product (Scheme 3.16). This material was identical to an authentic sample which had been isolated⁸ as one of the minor carbocyclic products from the aldol cyclisation of the iodo aldehyde (1.37) detailed in Chapter 1 (Scheme 1.10).



(i) H_5IO_6 , THF, RT, 10 min

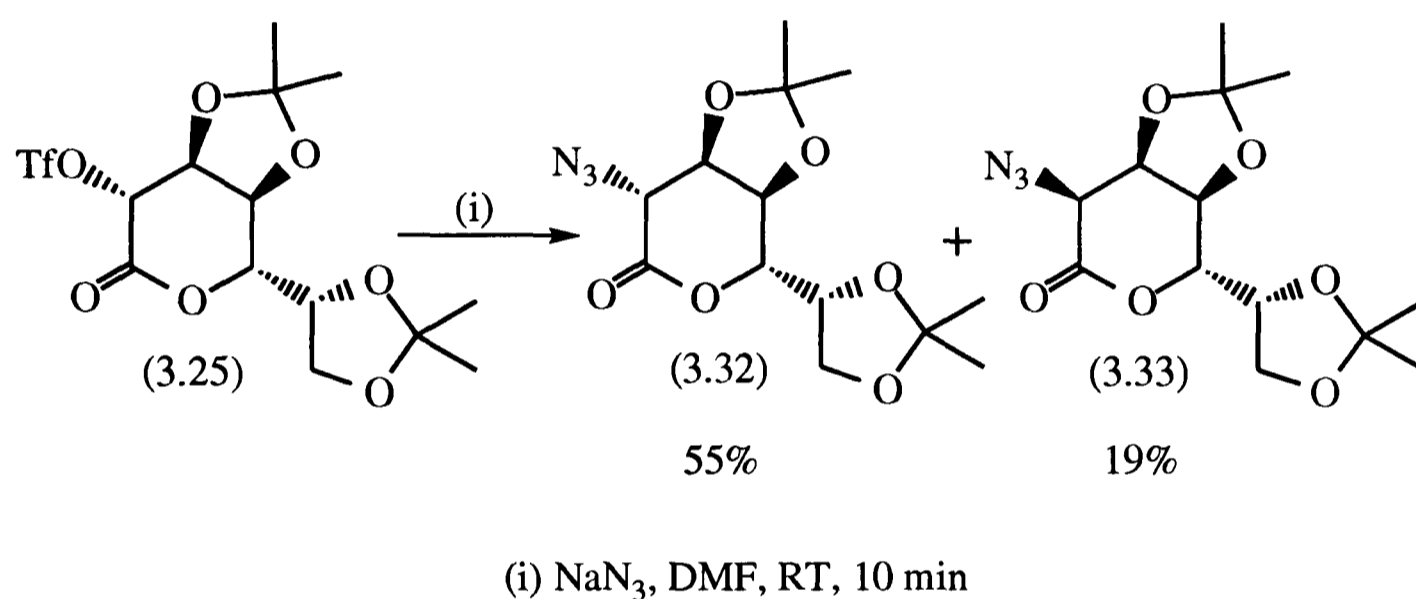
(ii) KF, 18-crown-6, MeCN, 0 °C, 30 min, 30% over 2 steps

Scheme 3.16

(iv) Synthesis of azido carbocycles.

The synthesis of azido carbocycles, using the D-glycero-L-alto-heptono-1,5-lactone (3.16) as a starting material, followed a route directly analogous to the one described above for the iodo carbocycle synthesis.

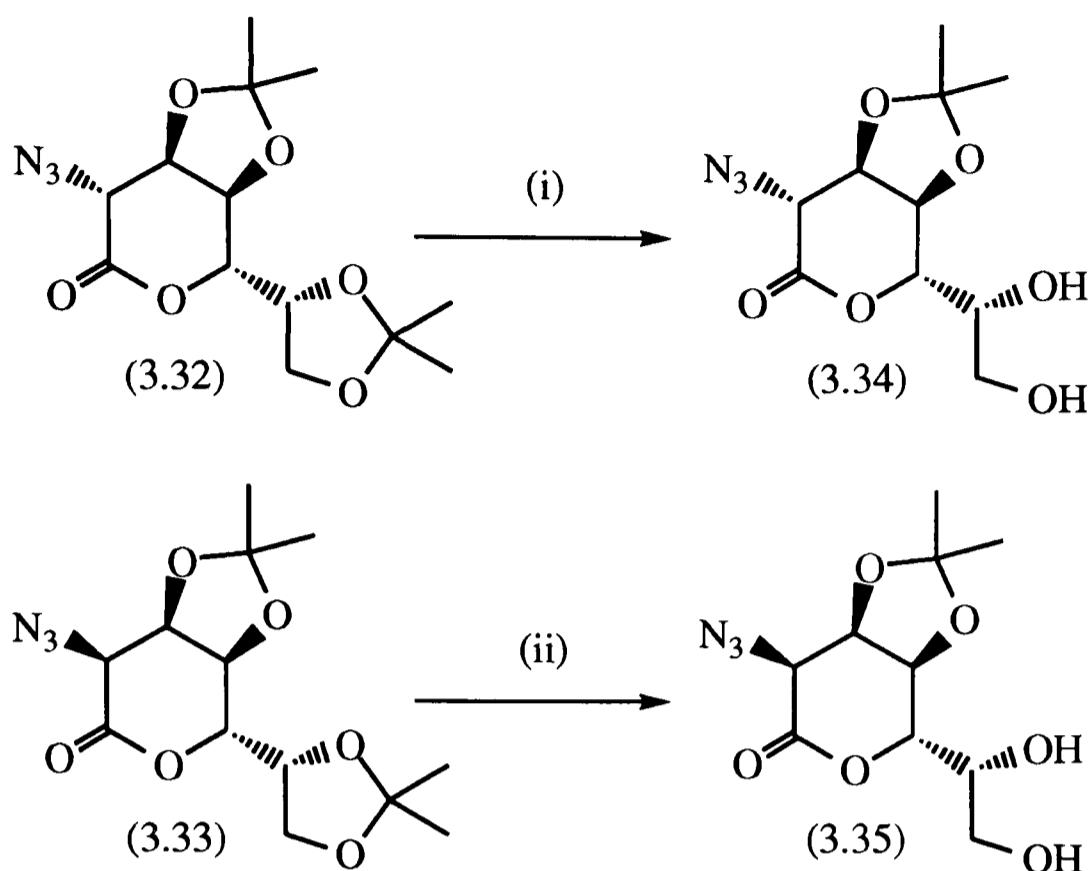
Introduction of azide at C-2 was achieved via treatment of the triflate (3.25) with sodium azide in DMF. This produced a separable mixture of D-glycero-L-alto (3.32) and D-glycero-L-allo (3.33) azides (Scheme 3.17).



Scheme 3.17

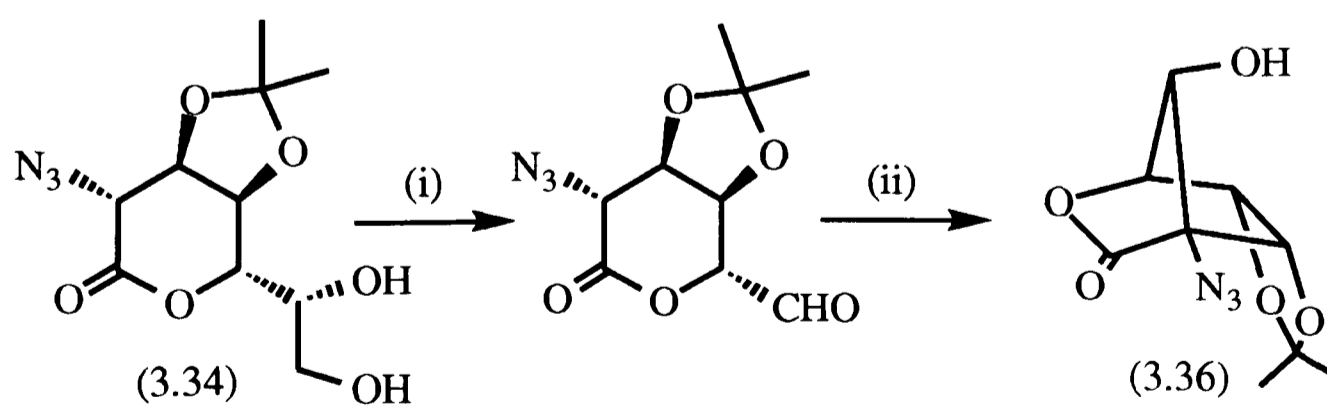
The stereochemistry of the azide substituent was assigned via n.O.e. experiments in a manner directly analogous to that described for the D-altrono (2.17) and D-allono (2.18) azides detailed in Chapter 2. Enhancements between H-2 and H-5 were only observed for the major alto epimer in which both occupy flagpole positions in the preferred boat conformation (see Chapter 2, Fig 2.2).

Removal of the primary acetonide was achieved in both cases via treatment with 80% aqueous acetic acid to produce the two azido diols (3.34) and (3.35) (Scheme 3.18). No significant epimerisation of the azido substituent was observed during this deprotection step.



Scheme 3.18

Treatment of the D-glycero-L-altro azido diol (3.34) with periodic acid produced an azido aldehyde which was used directly without characterisation. Treatment of this material with potassium fluoride and 18-crown-6 in dry acetonitrile yielded the azido carbocycle (3.36) as the sole reaction product (Scheme 3.19).

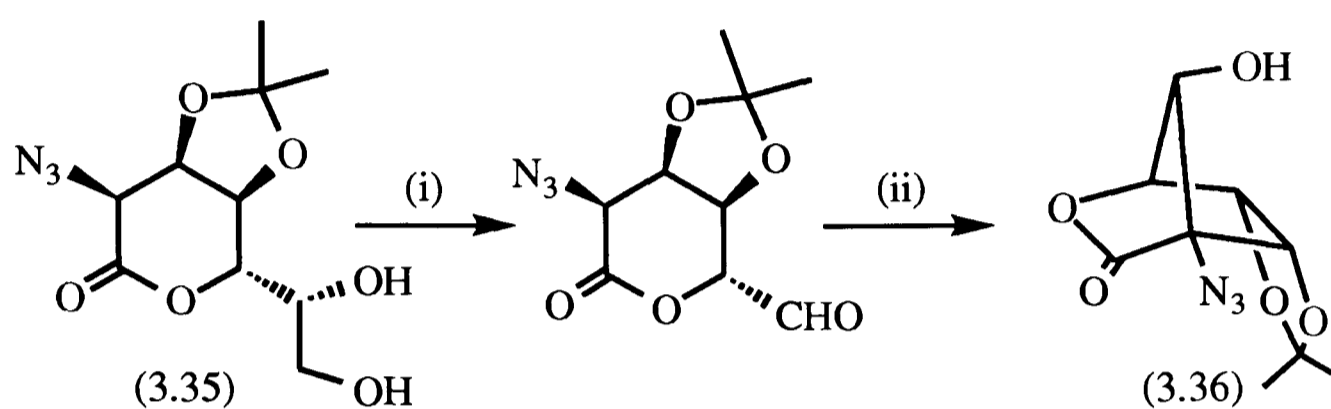


(i) H_5IO_6 , THF, RT, 5 min
(ii) KF, 18-crown-6, MeCN, 0 °C, 20 min, 52% over 2 steps

Scheme 3.19

This material was identical with an authentic sample which was isolated⁸ as the minor product of the cyclisation of the azido aldehyde (1.39) detailed in Chapter 1 (Scheme 1.12).

Similar treatment of the D-glycero-L-allo azido diol (3.35) again produced the azido carbocycle (3.36) as the sole reaction product (Scheme 3.20).

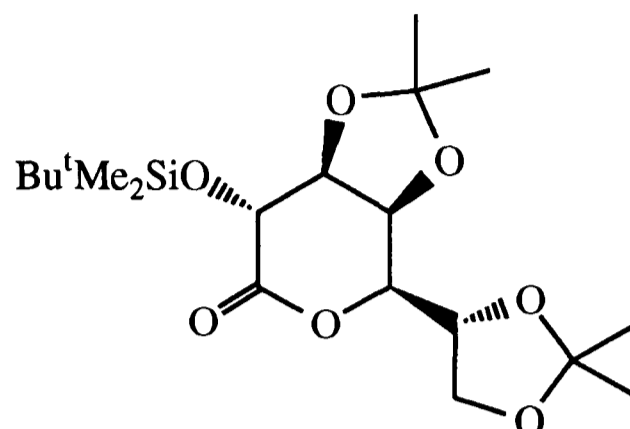


(i) H_5IO_6 , THF, RT, 5 min

(ii) KF, 18-crown-6, MeCN, 0 °C, 20 min, 48% over 2 steps

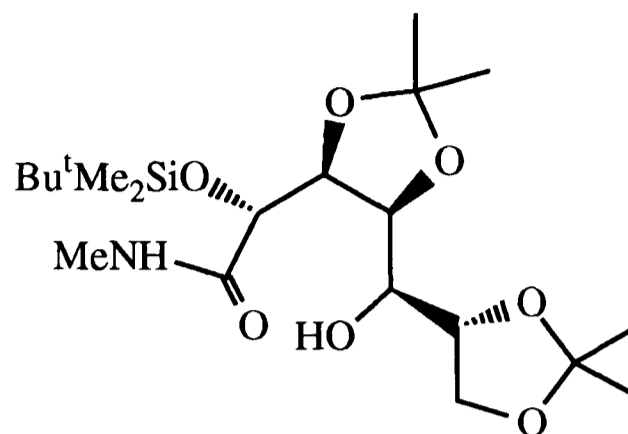
Scheme 3.20

The formation of the azido (3.36) and iodo (3.31) carbocycles as the sole reaction product in each case indicates that potassium fluoride induced deprotonation at C-2 and subsequent cyclisation occurs rapidly. In the D-glycero-D-talo derived aldehydes (Schemes 1.10 and 1.12), competitive epimerisation α to the aldehyde functionality occurs, resulting in the formation of a mixture of products. However, cyclisation of the D-glycero-L-allo and D-glycero-L-altro derived aldehydes, detailed in this Chapter, is seen to compete effectively with epimerisation α to the aldehyde functionality, resulting in the formation of a single product in all cases. The equilibration experiments detailed in Chapter 4 (Table 4.1) indicate that this is probably a kinetic rather than thermodynamic effect. Further investigations into the formation of azido carbocycles and their uses for the syntheses of a variety of potentially biologically active polyhydroxylated cyclopentanes are detailed in Chapter 4.

Experimental.2-O-tert-Butyldimethylsilyl-3,4:6,7-di-O-isopropylidene-D-glycero-D-galactono-1,5-lactone (3.13).

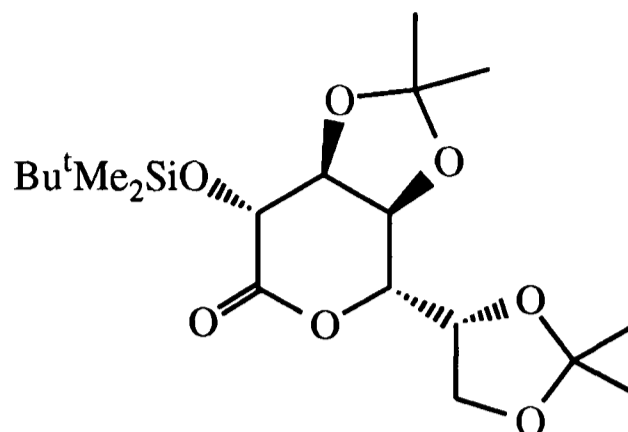
3,4:6,7-Di-*O*-isopropylidene-D-glycero-D-galactono-1,5-lactone (3.7) (14.79 g, 51.3 mmol) and pyridine (10.3 ml, 0.13 mol) were stirred in dry dichloromethane (250 ml) at 0 °C under nitrogen. *tert*-Butyldimethylsilyl trifluoromethanesulphonate (11.8 ml, 77.0 mmol) was added and the reaction mixture allowed to warm to room temperature. After 16 h, t.l.c. (hexane : ethyl acetate, 2 : 1) indicated the complete consumption of starting material (R_f 0.2) and formation of a single product (R_f 0.6). Dichloromethane (200 ml) was added and the mixture washed with dilute aqueous hydrochloric acid (2 M, 200 ml), water (200 ml), and brine (200 ml). The organic extracts were dried (magnesium sulphate), filtered, the solvent removed and the residue purified by flash chromatography (hexane : ethyl acetate, 4 : 1) to yield 2-O-tert-butyl dimethylsilyl-3,4:6,7-di-O-isopropylidene-D-glycero-D-galactono-1,5-lactone (3.13) (18.5 g, 90%) as white crystalline solid, m.p. 64-65 °C (ether / hexane) [Lit 51-52 °C]³; $[\alpha]_D^{20}$ +63.5 (*c*, 1.0 in CHCl₃) [Lit +63.8 (*c*, 1.0 in CHCl₃)]³; δ_H (C₆D₆) -0.02, 0.06 (6H, 2 x s, Me₂Si), 0.83 (9H, s, Bu^t), 1.15, 1.38 (12H, 2 x s, 2 x Me₂C), 3.92 (1H, dd, H-7, $J_{6,7}$ 6.1 Hz, $J_{7,7'}$ 9.0 Hz), 4.10 (1H, dd, H-7', $J_{6,7'}$ 4.4 Hz), 4.28 (1H, dd, H-3, $J_{2,3}$ 2.6 Hz, $J_{3,4}$ 7.5 Hz), 4.46 (1H, d, H-2), 4.48 (1H, ddd, H-6, $J_{5,6}$ 8.6 Hz), 4.57 (1H, dd, H-4, $J_{4,5}$ 1.6 Hz), 4.89 (1H, dd, H-5).

N-Methyl-2-*O*-*tert*-butyldimethylsilyl-3,4:6,7-di-*O*-isopropylidene-D-glycero-D-galacto-heptonamide (3.14).



2-*O*-*tert*-Butyldimethylsilyl-3,4:6,7-di-*O*-isopropylidene-D-glycero-D-galacto-heptono-1,5-lactone (3.13) (17.0 g, 42.2 mmol) was stirred in a mixture of methylamine (0.78 g / ml in methylated spirit, 100 ml) and THF (100 ml) at room temperature under nitrogen. After 0.5 h, t.l.c. (hexane : ethyl acetate, 2 : 1) indicated complete consumption of starting material (R_f 0.6) and formation of a single product (R_f 0.3). The solvent was removed and the residue recrystallised from hot hexane to yield N-methyl-2-*O*-*tert*-butyldimethylsilyl-3,4:6,7-di-*O*-isopropylidene-D-glycero-D-galacto-heptonamide (3.14) (16.4 g, 90%) as a white crystalline solid, m.p. 122-123 °C (hexane); $[\alpha]_D^{20}$ -25.0 (c , 0.66 in CHCl_3); ν_{max} (KBr) 3491, 3274 (OH, NH), 1655 (amide) cm^{-1} ; δ_{H} (CDCl_3) 0.15, 0.16 (6H, 2 x s, Me_2Si), 0.94 (9H, s, Bu^t), 1.35, 1.36, 1.48, 1.52 (12H, 4 x s, 2 x Me_2C), 2.25 (1H, d, D_2O exch, OH, $J_{5,\text{OH}}$ 7.7 Hz), 2.85 (3H, d, MeN, J 5.0 Hz), 4.02-4.09 (3H, m), 4.19-4.26 (2H, m), 4.43 (1H, dd, J 1.0, J' 6.8 Hz), 4.73 (1H, d, H-2, $J_{2,3}$ 8.5 Hz), 6.76 (1H, br t, NH); δ_{C} (CDCl_3) -5.4, -4.5 (2 x q, Me_2Si), 18.2 (s, CMe_3), 24.4, 25.3, 25.5, 26.2, 26.6 (5 x q, 2 x Me_2C and MeNH), 25.8 (q, Me_3C), 66.7 (t, C-7), 70.1, 72.2, 76.3, 78.0 (4 x d, C-2, C-3, C-4, C-5, C-6), 108.1, 109.2 (2 x s, 2 x CMe_2), 172.5 (s, C-1); m/z (DCI, NH_3) 434 (MH^+ , 100%). (Found: C, 55.32; H, 9.39; N, 3.31; $\text{C}_{20}\text{H}_{39}\text{NO}_7\text{Si}$ requires: C, 55.40; H, 9.07; N, 3.23%).

2-O-tert-Butyldimethylsilyl-3,4:6,7-di-O-isopropylidene-D-glycero-L-altro-heptono-1,5-lactone (3.15).



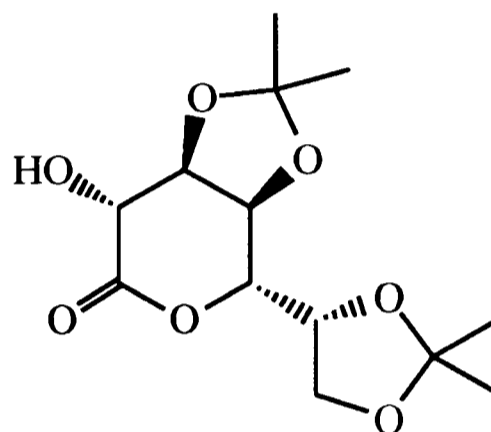
N-Methyl-2-*O*-*tert*-butyldimethylsilyl-3,4:6,7-di-*O*-isopropylidene-*D*-glycero-*D*-galacto-heptonamide (3.14) (10.53 g, 24.3 mmol) and dry pyridine (11.7 ml, 0.15 mol) were stirred in dry dichloromethane (100 ml) under nitrogen at 0 °C. Trifluoromethanesulphonic anhydride (12.4 ml, 73 mmol) was added slowly over a period of 10 min. After 1.5 h, t.l.c. (hexane : ethyl acetate, 2 : 1) indicated the partial conversion of the starting material (R_f 0.3) to a major product (R_f 0.55) and a minor product (R_f 0.6). The reaction was quenched by addition of saturated aqueous sodium bicarbonate solution (40 ml) at 0 °C and stirred for 1 min. The reaction mixture was diluted with dichloromethane (100 ml), dilute aqueous hydrochloric acid (2 M, 100 ml) added cautiously, and the resulting mixture shaken. The organic extracts were separated and washed with saturated sodium bicarbonate solution (100 ml), and brine (50 ml), dried (magnesium sulphate), filtered, and the solvent removed to yield a yellow syrup which was purified by flash chromatography (hexane : ethyl acetate, 4 : 1) to afford 2-*O*-*tert*-butyldimethylsilyl-3,4:6,7-di-*O*-isopropylidene-*D*-glycero-*L*-altro-heptono-1,5-lactone (3.15) (3.25 g, 33%, 46% based on recovered starting material) as a white crystalline solid, m.p. 99-100 °C (methanol / water); $[\alpha]_D^{20}$ -26.5 (c , 1.0 in CHCl_3); ν_{max} (KBr) 1773 (C=O) cm^{-1} ; δ_{H} (C_6D_6) 0.20, 0.31 (6H, 2 x s, Me_2Si), 0.95, 1.27, 1.33, 1.49 (12H, 4 x s, 2 x Me_2C), 1.10 (9H, s, Bu^t), 3.58 (1H, dd, H-7, $J_{6,7}$ 3.7 Hz, $J_{7,7'}$ 9.4 Hz), 3.74 (1H, dd, J 6.8, J' 8.4 Hz), 3.84-3.90 (2H, m), 4.01 (1H, dd, H-7', $J_{6,7'}$ 8.0 Hz), 4.09-4.12 (1H, m), 4.25 (1H, d, H-2, $J_{2,3}$ 7.2 Hz); δ_{C} (CDCl_3) -5.6, -5.1 (2 x q, Me_2Si), 18.3 (s, CMe_3), 24.5, 26.0, 26.7 (3 x q, 2 x Me_2C), 25.5 (q, Me_3C), 65.0 (t, C-7), 71.5, 72.0, 74.6, 76.1, 78.3 (5 x d, C-2, C-3, C-4, C-5, C-6), 110.2, 112.0 (2 x s, 2 x CMe_2), 170.2 (C-1); m/z (CI, NH_3) 420 (MNH_4^+ , 25%),

403 (MH⁺, 65%). (Found: C, 56.74; H, 8.49; C₁₉H₃₄O₇Si requires: C, 56.69; H, 8.51%),

together with 2-*O*-*tert*-butyldimethylsilyl-3,4:6,7-di-*O*-isopropylidene-D-glycero-D-galacto-heptono-1,5-lactone (3.13) (2.41 g, 25%, 34% based on recovered starting material);

and *N*-methyl-2-*O*-*tert*-butyldimethylsilyl-3,4:6,7-di-*O*-isopropylidene-D-glycero-D-galacto-heptonamide (3.14) (2.97 g, 28%, unreacted starting material).

3,4:6,7-Di-*O*-isopropylidene-D-glycero-L-altro-heptono-1,5-lactone (3.16).



Method 1.

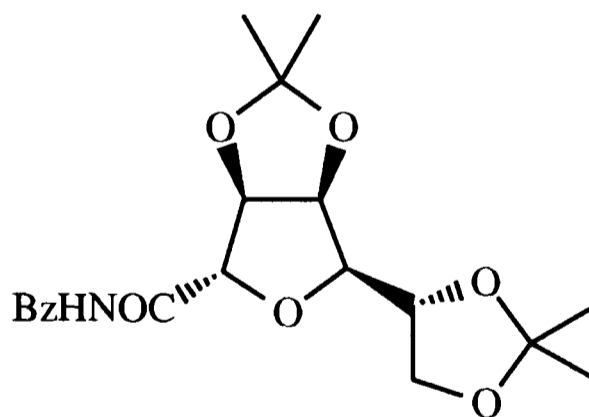
2-*O*-*tert*-Butyldimethylsilyl-3,4:6,7-di-*O*-isopropylidene-D-glycero-L-altro-heptono-1,5-lactone (3.15) (760 mg, 1.89 mmol) and acetic acid (1.1 ml, 18.9 mmol) were stirred in THF (20 ml) at room temperature under nitrogen. Tetra-*n*-butylammonium fluoride (4.7 ml, 1.0 M soln in THF) was added and the reaction mixture warmed to 50 °C. After 6.5 h, t.l.c. (hexane : ethyl acetate, 2 : 1) indicated complete consumption of starting material (R_f 0.7) and the formation of a single product (R_f 0.1). The residue was preabsorbed onto silica and purified by flash chromatography (hexane : ethyl acetate, 1 : 1) to yield 3,4:6,7-di-*O*-isopropylidene-D-glycero-L-altro-heptono-1,5-lactone (3.16) (476 mg, 87%), m.p. 167-168 °C (ether / hexane); $[\alpha]_D^{20}$ -93.5 (c , 0.95 in CHCl₃); ν_{\max} (KBr) 3435 (OH), 1773 (C=O) cm⁻¹; δ_H (CDCl₃) 1.39, 1.41, 1.46, 1.54 (12H, 2 x Me₂C), 3.40 (1H, d, OH, $J_{2,OH}$ 3.2 Hz), 4.01 (1H, dd, H-7, $J_{6,7}$ 6.8, $J_{7,7'}$ 8.6 Hz), 4.09 (1H, dd, H-5, $J_{4,5}$ 9.4, $J_{5,6}$ 3.9 Hz), 4.13 (1H, dd, H-7', $J_{6,7'}$ 6.8 Hz), 4.32 (1H, t, J 7.7 Hz), 4.38 (1H, dt, H-6), 4.40-4.44 (2H, m); δ_C (CDCl₃) 24.4, 25.4, 26.0, 26.6 (4 x q, 2 x Me₂C), 65.0 (t, C-7), 70.7, 71.3, 74.2, 76.8, 77.5, (5 x d, C-2, C-3, C-4, C-5, C-6), 110.4, 112.6 (2 x s, 2 x CMe₂), 171.5

(s, C-1); m/z (NH_3 , DCI) 306 (MNH_4^+), 289 (MH^+). (Found: C, 54.12; H, 6.96; $\text{C}_{13}\text{H}_{20}\text{O}_7$ requires: C, 54.16; H, 6.99%).

Method 2.

2-*O*-*tert*-Butyldimethylsilyl-3,4:6,7-di-*O*-isopropylidene-D-glycero-L-altro-heptono-1,5-lactone (3.15) (109 mg, 0.27 mmol) was stirred in THF (3 ml) at 0 °C under nitrogen. Pyridine / HF complex (0.4 ml) was added and the mixture allowed to warm to room temperature. After 16 h, t.l.c. (hexane : ethyl acetate, 2 : 1) indicated complete consumption of starting material (R_f 0.7) and the formation of a single product (R_f 0.1). The reaction mixture was cooled in an ice bath and ethyl acetate (10 ml) added. Saturated aqueous sodium bicarbonate solution was added dropwise until effervescence ceased. The organic extracts were separated, washed with brine (5 ml), dried (magnesium sulphate), filtered, the solvent removed and the residue purified by flash chromatography (hexane : ethyl acetate, 1 : 1) to yield 3,4:6,7-di-*O*-isopropylidene-D-glycero-L-altro-heptono-1,5-lactone (3.16) (60 mg, 77%) identical to the material described above.

N-Benzyl-2,5-anhydro-3,4:6,7-di-*O*-isopropylidene-D-glycero-D-talo-heptonamide (3.18)



Method 1.

2-Deoxy-3,4:6,7-di-*O*-isopropylidene-2-iodo-D-glycero-D-galacto-heptono-1,5-lactone (3.17) (1.11 g, 12.8 mmol) and benzylamine (1.8 ml, 16.7 mmol) were stirred in dry THF (10 ml) at room temperature in the dark. After 16 h, t.l.c. (hexane : ethyl acetate, 1 : 1) indicated the formation of a major product (R_f 0.4). The solvent was removed and ethyl acetate (30 ml) added. The resulting solution was washed with 1M HCl (30 ml), brine (40 ml), dried (magnesium sulphate), filtered, the solvent removed and the residue purified by flash chromatography (hexane : ethyl acetate, 2 : 1) to yield *N*-

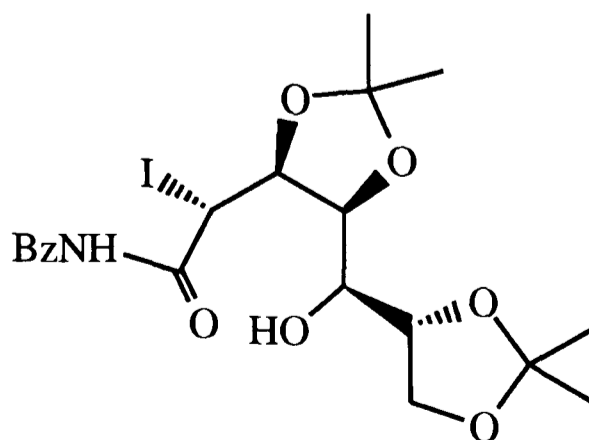
benzyl-2,5-anhydro-3,4:6,7-di-O-isopropylidene-D-glycero-D-talo-heptonamide (3.18) (934 mg, 89%) as a colourless oil; $[\alpha]_{\text{D}}^{20}$ -16.8 (*c*, 1.02 in CHCl_3); ν_{max} (film) 3327 (NH), 1667 (amide) cm^{-1} ; δ_{H} (CDCl_3) 1.35, 1.38, 1.41, 1.50 (12H, 4 x s, 2 x Me_2C), 3.81 (1H, dd, *J* 3.7 Hz, *J'* 6.2 Hz), 4.03 (1H, dd, H-7, *J*_{6,7} 5.0 Hz, *J*_{7,7'} 8.8 Hz), 4.10 (1H, dd, H-7', *J*_{6,7'} 6.4 Hz), 4.41-4.51 (3H, m), 4.52 (1H, s), 4.74 (1H, dd, *J* 3.7 Hz, *J'* 6.2 Hz), 5.27 (1H, dd, *J* 1.0 Hz, *J'* 6.2 Hz), 6.79 (1H, br t, NH), 7.25-7.37 (5H, m, Ph); δ_{C} (CDCl_3) 24.4, 24.9, 25.8, 26.5 (4 x q, 2 x Me_2C), 42.6 (t, CH_2Ph), 66.2 (t, C-7), 73.0, 80.2, 82.3, 83.3, 89.0 (5 x d, C-2, C-3, C-4, C-5, C-6), 108.9, 112.7 (2 x s, 2 x CMe_2), 127.4, 128.7 (2 x d, Ph), 138.4 (s, Ph), 169.5 (s, C-1); *m/z* (NH_3 , DCI) 378 (MH^+ , 100%). (Found: C, 63.75; H, 6.68; N, 3.47; $\text{C}_{20}\text{H}_{27}\text{NO}_6$ requires: C, 63.64; H, 7.21; N, 3.71%).

Method 2.

Methyl 2,5-anhydro-3,4:6,7-di-O-isopropylidene-D-glycero-D-talo-heptonate (3.19) (50 mg, 0.17 mmol) and benzylamine (0.11 ml, 0.99 mmol) were stirred in dry methanol (2 ml) at room temperature under nitrogen. After 16 h, the solvent was removed and ethyl acetate (10 ml) added. The resulting solution was washed with 1M HCl (10 ml), water (10 ml), brine (10 ml), dried (magnesium sulphate), filtered, the solvent removed and the residue purified by flash chromatography (hexane : ethyl acetate, 2 : 1) to yield *N*-benzyl-2,5-anhydro-3,4:6,7-di-O-isopropylidene-D-glycero-D-talo-heptonamide (3.18) (57 mg, 91%) as a colourless oil, identical to the material described above.

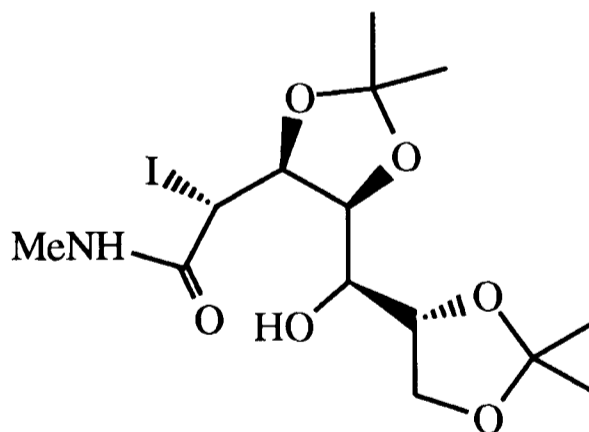
N-Benzyl-2-deoxy-3,4:6,7-di-O-isopropylidene-2-iodo-D-glycero-D-talo-heptonamide (3.20).

2-Deoxy-3,4:6,7-di-O-isopropylidene-2-iodo-D-glycero-D-galacto-heptono-1,5-lactone (3.17) (2.0 g, 5.0 mmol) and



benzylamine (11 ml, 0.10 mol) were stirred in dry THF (20 ml) at room temperature under nitrogen. After 0.5 h, t.l.c (hexane : ethyl acetate, 1 : 1) indicated complete consumption of starting material (R_f 0.8) and formation of a major product (R_f 0.7). The reaction mixture was diluted with ether (100 ml) and washed with 1M HCl (2 x 50 ml) and water (50 ml). The organic extracts were dried (magnesium sulphate), the solvent removed and the residue purified by flash chromatography (hexane : ethyl acetate, 2 : 1) to give *N*-benzyl-2-deoxy-3,4:6,7-di-*O*-isopropylidene-2-iodo-*D*-glycero-*D*-talo-heptonamide (3.20) (1.63 g, 64%) as a colourless oil; $[\alpha]_D^{20} +30.4$ (c , 1.0 in CHCl_3); ν_{max} (film) 3300 (OH, NH) 1651 (amide) cm^{-1} ; δ_{H} (CDCl_3) 1.34, 1.39, 1.43, 1.51 (4 x s, 2 x Me_2C), 3.47 (1H, m), 3.87-4.11 (3H, m), 4.48 (3H, m), 4.81-4.96 (2H, m), 6.28 (1H, br t, NH, J 5.9 Hz), 7.24-7.40 (5H, m, Ph); δ_{C} (CDCl_3) 23.2 (d, C-2), 24.2, 25.2, 26.5, 26.8 (4 x q, 2 x Me_2C), 43.6 (t, CH_2Ph), 66.4 (t, C-7), 69.6, 75.0, 76.3, 78.4 (4 x d, C-3, C-4, C-5, C-6), 107.6, 109.4 (2 x s, 2 x CMe_2), 127.8, 127.9, 128.9 (3 x d, Ph) 137.8 (s, Ph), 170.0 (s, C-1); m/z (NH_3 , DCI) 506 (MH^+). (Found: C, 47.31; H, 5.54; N, 2.66; $\text{C}_{20}\text{H}_{28}\text{NO}_6\text{I}$ requires: C, 47.54; H, 5.58; N, 2.77%).

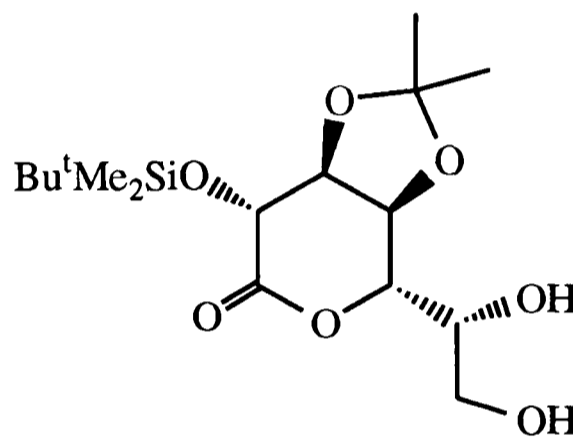
N-Methyl-2-deoxy-3,4:6,7-di-*O*-isopropylidene-2-iodo-*D*-glycero-*D*-galacto-heptonamide (3.21).



2-Deoxy-3,4:6,7-di-*O*-isopropylidene-2-iodo-*D*-glycero-*D*-galacto-heptono-1,5-lactone (3.17) (490 mg, 1.26 mmol) was stirred in dry THF (3 ml) at room temperature in the dark. Methylamine (3 ml, 33% solution in methanol) was added and the mixture stirred for 5 min, after which time the solvent was removed to yield *N*-methyl-2-deoxy-3,4:6,7-di-*O*-isopropylidene-2-iodo-*D*-glycero-*D*-galacto-heptonamide (3.21) (532 mg, crude, quantitative) as a white crystalline solid, which was purified by recrystallisation (ether / hexane), m.p. 130-132 °C (ether / hexane); $[\alpha]_D^{20} +50.3$ (c , 0.6 in CHCl_3);

ν_{\max} (KBr) 3400-3300 (br, OH, NH), 1666 (amide) cm^{-1} ; δ_{H} (CDCl_3) 1.34, 1.39, 1.43, 1.52 (12H, 4 x s, 2 x Me_2C), 2.86 (3H, d, MeN, J 4.9 Hz), 3.43 (1H, dd, J 7.2 Hz, J' 9.5 Hz), 3.94-4.04 (3H, m), 4.50 (1H, d, J 6.7 Hz), 4.82 (1H, dd, J 6.7 Hz, J' 10.1 Hz), 4.87 (1H, d, J 10.1 Hz), 5.78 (1H, m, NH); δ_{C} (CDCl_3) 22.3 (d, C-2), 24.1, 25.2, 26.4, 28.8 (4 x q, 2 x Me_2C and MeNH), 66.3 (t, C-7), 68.5, 74.9, 76.3, 78.3 (4 x d, C-3, C-4, C-5, C-6), 107.8, 109.4 (2 x s, 2 x CMe_2), 170.5 (s, C-1); m/z (NH_3 , DCI) 430 (MH^+ , 100%), 302 (MH^+-HI). (Found: C, 39.41; H, 5.76; N, 3.23; $\text{C}_{14}\text{H}_{24}\text{NO}_6\text{I}$ requires: C, 39.17; H, 5.64; N, 3.26%).

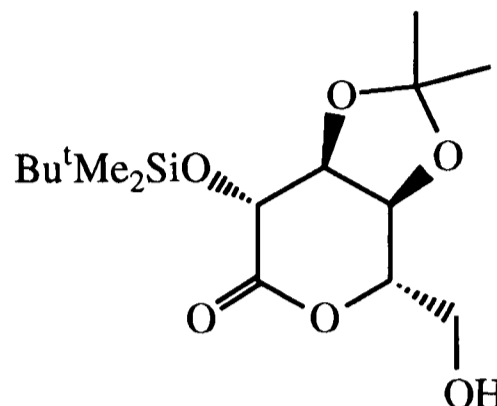
2-O-tert-Butyldimethylsilyl-3,4-O-isopropylidene-D-glycero-L-altro-heptono-1,5-lactone (3.23)



2-O-tert-Butyldimethylsilyl-3,4:6,7-di-O-isopropylidene-D-glycero-L-altro-heptono-1,5-lactone (3.15) (645 mg, 1.6 mmol) was stirred in a mixture of water (5 ml) and acetic acid (20 ml) at room temperature. After 16 h, t.l.c. (hexane : ethyl acetate, 2 : 1) indicated the complete consumption of starting material (R_f 0.6) and the formation of a major product (R_f 0.1). The solvent was removed, the residue co-evaporated with toluene (2 x 5 ml) and purified by flash chromatography (hexane : ethyl acetate, 1 : 1) to yield 2-O-tert-butylidimethylsilyl-3,4-O-isopropylidene-D-glycero-L-altro-heptono-1,5-lactone (3.23) (308 mg, 53%) as a white foam; $[\alpha]_{\text{D}}^{20}$ -34.5 (c , 1.05 in CHCl_3); ν_{\max} (film) 3400-3200 (br, OH), 1767 (C=O) cm^{-1} ; δ_{H} (CDCl_3) 0.14, 0.18 (6H, 2 x s, Me_2Si), 0.96 (9H, s, Bu^t), 1.38, 1.52 (6H, 2 x s, Me_2C), 3.80 (1H, dd, H-7, $J_{6,7}$ 5.1 Hz, $J_{7,7'}$ 11.6 Hz), 3.85 (1H, dd, H-7', $J_{6,7'}$ 5.6 Hz), 3.91 (1H, m, H-6), 4.16 (1H, dd, H-5, $J_{4,5}$ 9.3 Hz, $J_{5,6}$ 3.9 Hz), 4.32 (1H, t, H-3), 4.40 (1H, d, H-2, $J_{2,3}$ 7.2 Hz), 4.46 (1H, dd, H-4, $J_{3,4}$ 7.9 Hz); δ_{C} (CDCl_3) -5.5, -5.1 (2 x q, Me_2Si), 18.2 (s, CMe_3), 24.5, 26.7 (2 x q, Me_2C), 25.5 (q, Me_3C), 63.0 (t, C-7), 70.3, 70.5,

72.1, 77.0, 78.1 (5 x d, C-2, C-3, C-4, C-5, C-6), 111.9 (s, $\underline{\text{C}}\text{Me}_2$), 171.4 (s, C-1); m/z (NH_3 , DCI) 380 (MNH_4^+), 363 (MH^+ , 100%). (Found: C, 52.74; H, 8.49; $\text{C}_{16}\text{H}_{30}\text{O}_7\text{Si}$ requires: C, 53.01; H, 8.34%).

2-O-tert-Butyldimethylsilyl-3,4-O-isopropylidene-L-altrono-1,5-lactone (3.24)

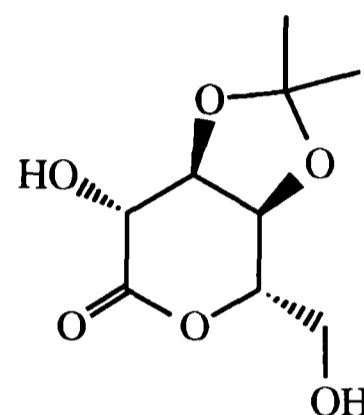


2-O-tert-Butyldimethylsilyl-3,4-O-isopropylidene-D-glycero-L-altro-heptono-1,5-lactone (3.23) (223 mg, 0.62 mmol) and periodic acid (169 mg, 0.74 mmol) were stirred together in THF (10 ml) at room temperature. After 10 min, t.l.c. (hexane : ethyl acetate, 1 : 1) indicated complete consumption of starting material (R_f 0.5) and the formation of a single product (R_f 0.7). The crude reaction mixture was preabsorbed onto silica and purified by flash chromatography (hexane : ethyl acetate, 1 : 1) to yield the aldehyde (135 mg, 66%) which was used in next step directly, without further purification or characterisation.

The aldehyde (135 mg, 0.41 mmol) was dissolved in a mixture of water (4 ml) and ethanol (4 ml) and stirred at $-10\text{ }^\circ\text{C}$. Sodium borohydride (5.1 mg, 0.12 mmol) was then added. After 10 min, acetic acid (1 ml) and ethyl acetate (20 ml) were added and the mixture allowed to warm to room temperature. The reaction mixture was then washed with brine (20 ml), which was further extracted with ethyl acetate (2 x 10 ml). The organic extracts were combined, dried (magnesium sulphate), filtered, the solvent removed and the residue purified by flash chromatography (hexane : ethyl acetate, 1 : 1) to yield 2-O-tert-butyl dimethylsilyl-3,4-O-isopropylidene-L-altrono-1,5-lactone (3.24) (53 mg, 40%, R_f 0.6) as a white crystalline solid, m.p. $94\text{-}95\text{ }^\circ\text{C}$ (pentane); $[\alpha]_D^{20}$ -43.2 (c , 1.05 in CHCl_3); ν_{max} (film) 3400-3200 (br, OH), 1771 (C=O) cm^{-1} ; δ_{H} (CDCl_3) 0.14, 0.19 (6H, 2 x s, Me_2Si), 0.97 (9H, s, Bu^t), 1.37, 1.52 (6H, 2 x s, Me_2C), 3.82 (1H, dd, H-6, $J_{5,6}$ 4.8 Hz, $J_{6,6'}$ 12.6 Hz), 3.99 (1H, dd, H-6', $J_{5,6'}$ 2.5

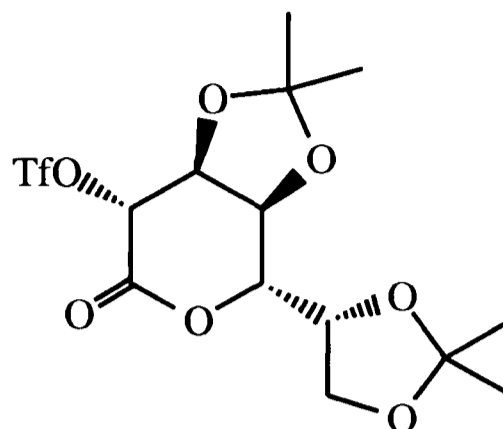
Hz), 4.18 (1H, ddd, H-5, $J_{4,5}$ 8.6 Hz), 4.30-4.36 (2H, m, H-3, H-4), 4.40 (1H, d, H-2, $J_{2,3}$ 6.5 Hz); δ_C (CDCl₃) -5.5, -5.1 (2 x q, Me₂Si), 18.3 (s, CMe₃), 24.5, 26.7 (2 x q, Me₂C), 25.5 (q, Me₃C), 61.6 (t, C-6), 70.5, 72.2, 77.7, 78.2 (4 x d, C-2, C-3, C-4, C-5), 112.0 (s, CMe₂), 171.0 (s, C-1); m/z (NH₃, DCI) 333 (MH⁺, 100%). (Found: C, 53.95; H, 8.63; C₁₅H₂₈O₆Si requires: C, 54.19; H, 8.49%).

3,4-O-Isopropylidene-L-altrono-1,5-lactone (3.22).



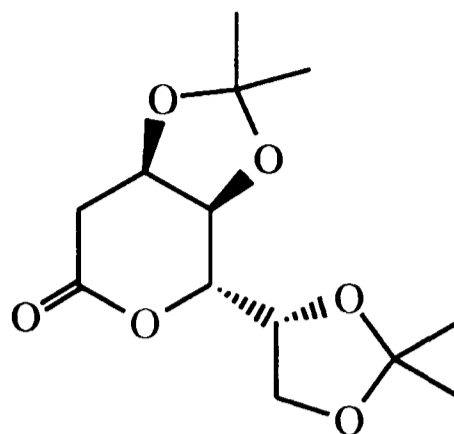
2-*O*-*tert*-Butyldimethylsilyl-3,4-*O*-isopropylidene-L-altrono-1,5-lactone (3.24) (37 mg, 0.11 mmol) and acetic acid (64 μ l, 1.1 mmol) were stirred in THF (5 ml) at room temperature under nitrogen. Tetra-*n*-butylammonium fluoride (0.28 ml, 1.0 M soln in THF) was added and the reaction mixture warmed to 50 °C. After 2 h, t.l.c. (hexane : ethyl acetate, 1 : 1) indicated complete consumption of starting material (R_f 0.6) and the formation of a single product (R_f 0.1). The solvent was then removed and the residue purified by flash chromatography (hexane : ethyl acetate, 1 : 2) to yield 3,4-*O*-isopropylidene-L-altrono-1,5-lactone (3.22) (18 mg, 74%) as a white crystalline solid, m.p. 131-133 ° C (ethyl acetate / hexane)[Enantiomer 130-132 °C]; $[\alpha]_D^{20}$ -96.2 (*c*, 0.53 in EtOH)[Enantiomer +101.3 (*c*, 0.9 in EtOH)]; all spectral data identical with that of the enantiomeric compound (2.11), described in Chapter 2.

3,4:6,7-Di-O-isopropylidene-2-O-trifluoromethanesulphonyl-D-glycero-L-altro-heptono-1,5-lactone (3.25).



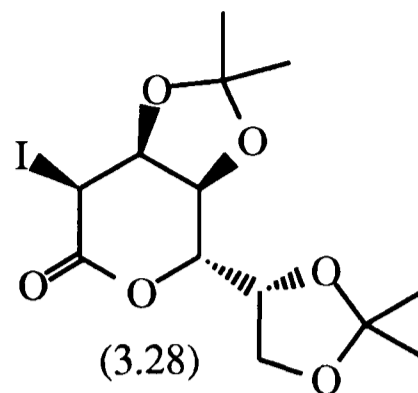
3,4:6,7-Di-O-isopropylidene-D-glycero-L-altro-heptono-1,5-lactone (3.16) (907 mg, 3.15 mmol) and dry pyridine (0.63 ml, 7.88 mmol) were stirred at -20 °C in dichloromethane (50 ml) under nitrogen. Trifluoromethanesulphonic anhydride (0.80 ml, 4.72 mmol) was added and the reaction mixture stirred at -20 °C. After 30 min, t.l.c. (hexane : ethyl acetate, 3 : 1) indicated the formation of a single product (R_f 0.5). Further dichloromethane (20 ml) was added and the mixture allowed to warm to room temperature. The crude mixture was then shaken successively with 1M HCl (20 ml), water (20 ml) and brine (20 ml). The organic extracts were then dried (magnesium sulphate), filtered, the solvent removed and the residue purified by flash chromatography (hexane : ethyl acetate, 3 : 1) to yield 3,4:6,7-di-O-isopropylidene-2-O-trifluoromethanesulphonyl-D-glycero-L-altro-heptono-1,5-lactone (3.25) (1.01 g, 76%) as a white crystalline solid, m.p. 100-102 °C (ether / hexane); $[\alpha]_D^{20}$ -15.5 (c , 1.01 in CHCl_3); ν_{max} (KBr) 1785 (C=O) cm^{-1} ; δ_{H} (CDCl_3) 1.41, 1.42, 1.47, 1.56 (12H, 4 x s, 2 x Me_2C), 4.04 (1H, dd, H-7, $J_{6,7}$ 6.7, $J_{7,7'}$ 8.6 Hz), 4.14 (1H, dd, H-7', $J_{6,7'}$ 6.8 Hz), 4.19 (1H, dd, H-5, $J_{4,5}$ 8.3 Hz, $J_{5,6}$ 3.5 Hz), 4.38 (1H, dt, H-6), 4.55-4.62 (2H, m, H-3, H-4), 5.23 (1H, d, H-2, $J_{2,3}$ 7.4 Hz); δ_{C} (CDCl_3) 24.5, 25.3, 25.8, 26.5 (4 x q, 2 x Me_2C), 64.8 (t, C-7), 71.6, 73.9, 74.3, 77.1, 81.6, (5 x d, C-2, C-3, C-4, C-5, C-6), 110.6, 113.6 (2 x s, 2 x CMe_2), 164.0 (s, C-1); m/z (NH_3 , DCI) 438 (MNH_4^+ , 100%), 421 (MH^+). (Found: C, 40.26; H, 4.30; $\text{C}_{14}\text{H}_{19}\text{O}_9\text{SF}_3$ requires: C, 40.00; H, 4.56%).

2-Deoxy-3,4:6,7-di-*O*-isopropylidene-D-talo-heptono-1,5-lactone (3.26).

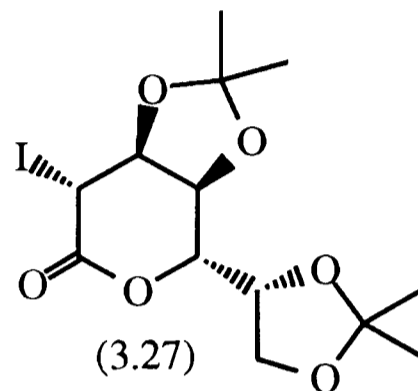


3,4:6,7-Di-*O*-isopropylidene-2-*O*-trifluoromethanesulphonyl-D-glycero-L-altro-heptono-1,5-lactone (3.25) (62 mg, 0.15 mmol) and sodium iodide (110 mg, 0.74 mmol) were stirred together in dry acetone (5 ml) at 40 °C. After 2 h, t.l.c. (hexane : ethyl acetate, 2 : 1) indicated complete consumption of starting material (R_f 0.6) and the formation of a mixture of products (R_f 0.5 and R_f 0.4). At this point the solvent was removed and the residue dissolved in ethyl acetate (20 ml). The crude mixture was then washed with aqueous sodium thiosulphate solution (1.0 M, 20 ml), which resulted in decolourisation of the organic layer. T.l.c. (hexane : ethyl acetate, 2 : 1) at this point revealed the formation of a single product (R_f 0.3). The organic extracts were then washed with water (10 ml), brine (10 ml), dried (magnesium sulphate), filtered, the solvent removed and the residue purified by flash chromatography (hexane : ethyl acetate, 3 : 1) to yield 2-deoxy-3,4:6,7-di-*O*-isopropylidene-D-talo-heptono-1,5-lactone (3.26) (32 mg, 80%), as a white crystalline solid, m.p. 138-140 °C (ether / hexane); $[\alpha]_D^{20}$ -45.3 (c , 0.6 in CHCl_3); ν_{max} (CHCl_3) 1755 (C=O) cm^{-1} ; δ_{H} (CDCl_3) 1.37, 1.39, 1.42, 1.49 (12H, 4 x s, 2 x Me_2C), 2.69 (1H, dd, H-2, $J_{2,2'}$ 16.0 Hz, $J_{2,3}$ 5.7 Hz), 3.13 (1H, dd, H-2', $J_{2',3}$ 6.0 Hz), 4.02 (1H, t, H-7), 4.11 (1H, dd, H-7', $J_{6,7'}$ 6.6 Hz, $J_{7,7'}$ 8.4 Hz), 4.22 (1H, dd, H-5, $J_{4,5}$ 5.8 Hz, $J_{5,6}$ 3.0 Hz), 4.34 (1H, ddd, H-6, $J_{6,7}$ 7.6 Hz), 4.39 (1H, dd, H-4, $J_{3,4}$ 7.3 Hz), 4.63 (1H, dt, H-3); δ_{C} (CDCl_3) 24.5, 25.5, 25.8, 26.7 (4 x q, 2 x Me_2C), 34.7 (t, C-2), 65.1 (t, C-7), 70.7, 72.4, 75.3, 78.0, (4 x d, C-3, C-4, C-5, C-6), 110.4, 110.7 (2 x s, 2 x CMe_2), 169.4 (s, C-1); m/z (NH_3 , DCI) 290 (MNH_4^+), 273 (MH^+ , 100%). (Found: C, 57.57; H, 7.41; $\text{C}_{13}\text{H}_{20}\text{O}_6$ requires: C, 57.34; H, 7.40%).

2-Deoxy-3,4:6,7-di-*O*-isopropylidene-2-iodo-D-glycero-L-*allo*-heptono-1,5-lactone (3.28) and

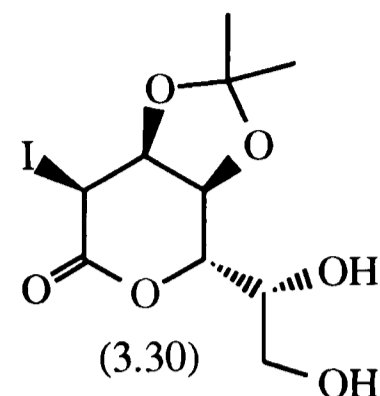


2-deoxy-3,4:6,7-di-*O*-isopropylidene-2-iodo-D-glycero-L-*altro*-heptono-1,5-lactone (3.27).

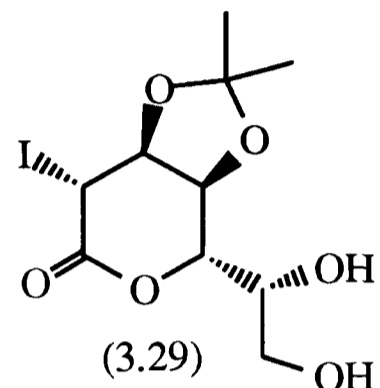


3,4:6,7-Di-*O*-isopropylidene-2-*O*-trifluoromethanesulphonyl-D-glycero-L-*altro*-heptono-1,5-lactone (3.25) (270 mg, 0.64 mmol) and tetra-*n*-butylammonium iodide (240 mg, 0.64 mmol) were stirred together in dry THF (70 ml) at room temperature in the dark. After 1.5 h, t.l.c. (hexane : ethyl acetate, 2 : 1) indicated complete consumption of starting material (R_f 0.6) and the formation of a mixture of products (R_f 0.5 and R_f 0.4). At this point the solvent was removed and the residue purified by flash chromatography (hexane : ether, 1 : 1) to yield 2-deoxy-3,4:6,7-di-*O*-isopropylidene-2-iodo-D-glycero-L-*allo*-heptono-1,5-lactone (3.28) and 2-deoxy-3,4:6,7-di-*O*-isopropylidene-2-iodo-D-glycero-L-*altro*-heptono-1,5-lactone (3.27) (182 mg, 71%), as an inseparable mixture of epimers (2D t.l.c. indicating interconversion on silica); a colourless oil; ν_{\max} (film) 1752 (br, C=O) cm^{-1} ; δ_{H} (CDCl_3) 1.38 (15H, br s, 5 x Me), 1.43, 1.52, 1.57 (9H, 3 x s, 3 x Me), 3.74-3.77 (m), 3.96-4.17 (m), 4.27-4.42 (m), 4.49-4.81 (m), 5.21-5.25 (1H, m), 5.27 (1H, d, J 4.8 Hz); δ_{C} (CDCl_3) 19.5, 23.1 (2 x d, 2 x C-2), 24.5, 24.9, 25.4, 25.8, 26.0, 26.5, 26.8, 30.9 (8 x q, 4 x Me_2C), 64.9, 65.2 (2 x t, 2 x C-7), 72.5, 72.7, 74.0, 74.2, 75.6, 78.0, 78.8, 80.3 (8 x d, 2 x C-3, 2 x C-4, 2 x C-5, 2 x C-6), 110.4, 110.7, 111.7, 112.1 (4 x s, 4 x CMe_2), 165.5, 166.4 (2 x s, 2 x C-1); m/z (NH_3 , DCI) 416 (MNH_4^+), 399 (MH^+). (Found: C, 39.41; H, 4.55; $\text{C}_{13}\text{H}_{19}\text{O}_6\text{I}$ requires: C, 39.21; H, 4.81%).

2-Deoxy-2-iodo-3,4-*O*-isopropylidene-D-glycero-L-allo-heptono-1,5-lactone (3.30) and



2-deoxy-2-iodo-3,4-*O*-isopropylidene-D-glycero-L-altro-heptono-1,5-lactone (3.29).

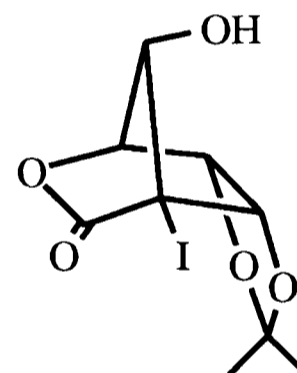


2-Deoxy-3,4:6,7-di-*O*-isopropylidene-2-iodo-D-glycero-L-allo-heptono-1,5-lactone (3.28) and 2-deoxy-3,4:6,7-di-*O*-isopropylidene-2-iodo-D-glycero-L-altro-heptono-1,5-lactone (3.27) (130 mg, 0.33 mmol, mixture of epimers as described above) were stirred in a mixture of acetic acid (8 ml) and water (2 ml) at room temperature in the dark. After 20 h, t.l.c. (ethyl acetate) indicated the formation of a mixture of products (R_f 0.6 and R_f 0.55). The solvent was removed, the residue co-evaporated with toluene (2 x 3 ml) and then purified by flash chromatography (ethyl acetate : hexane, 2 : 1) to yield a mixture of 2-deoxy-2-iodo-3,4-*O*-isopropylidene-D-glycero-L-allo-heptono-1,5-lactone (3.30) and 2-deoxy-2-iodo-3,4-*O*-isopropylidene-D-glycero-L-altro-heptono-1,5-lactone (3.29) (78 mg, 67%, ratio of 5 : 7 indicated by ^1H nmr), as a colourless oil. These materials were found to be inseparable by chromatography (2D t.l.c. again indicating interconversion on silica). Recrystallisation from ethyl acetate / hexane yielded pure 2-deoxy-2-iodo-3,4-*O*-isopropylidene-D-glycero-L-allo-heptono-1,5-lactone (3.30) as a white crystalline solid, m.p. 144-146 °C (ethyl acetate / hexane); $[\alpha]_D^{20}$ -17.2 (c , 0.93 in EtOH); ν_{max} (KBr) 3400-3200 (br, OH), 1728 (C=O) cm^{-1} ; δ_{H} (CD_3CN) 1.36, 1.48 (6H, 2 x s, Me_2C), 3.03 (1H, br t, J 5.9 Hz), 3.12 (1H, br t, J 5.7 Hz), 3.50-3.59 (1H, m), 3.68 (1H, d, J 5.3 Hz), 4.51-4.55 (2H, m), 5.47 (1H, d, H-2, $J_{2,3}$ 4.7 Hz); δ_{C} (CD_3CN) 22.4 (d, C-2), 25.1, 26.6 (2 x q,

Me_2C), 62.9 (t, C-7), 72.7, 73.6, 76.1, 81.8 (4 x d, C-3, C-4, C-5, C-6), 111.1 (s, CMe_2), 166.8 (s, C-1); m/z (NH_3 , DCI) 376 (MNH_4^+). (Found: C, 33.35; H, 4.15; $\text{C}_{10}\text{H}_{15}\text{O}_6\text{I}$ requires: C, 33.54; H, 4.22%);

and 2-deoxy-2-iodo-3,4-*O*-isopropylidene-D-glycero-L-alto-heptono-1,5-lactone (3.29) as a colourless oil (still contaminated with a small amount of epimeric material); ν_{max} (film) 3400-3200 (br, OH), 1752 (C=O) cm^{-1} ; δ_{H} (CD_3CN) 1.36, 1.48 (6H, 2 x s, Me_2C), 3.40 (1H, d, J 6.7 Hz), 3.50-3.59 (3H, m), 3.76 (1H, dq, J 2.3 Hz, J' 6.6 Hz), 3.85 (1H, dq, J 3.0 Hz, J' 6.4 Hz), 4.30 (1H, dd, J 2.3 Hz, J' 9.3 Hz), 4.62 (1H, dd, J 4.1 Hz, J' 7.5 Hz), 5.03 (1H, d, H-2, $J_{2,3}$ 9.0 Hz); δ_{C} (CD_3CN) 24.6 (d, C-2), 23.8, 26.0 (2 x q, Me_2C), 61.8 (t, C-7), 69.6, 71.4, 77.8, 80.2 (4 x d, C-3, C-4, C-5, C-6), 111.4 (s, CMe_2), 166.3 (s, C-1); m/z (NH_3 , DCI) 376 (MNH_4^+).

(1*S*,4*S*,5*S*,6*R*,7*S*)-4-Iodo-5,6-*O*-isopropylidene-2-oxa-5,6,7-trihydroxy-bicyclo[2.2.1]heptan-3-one (3.31)

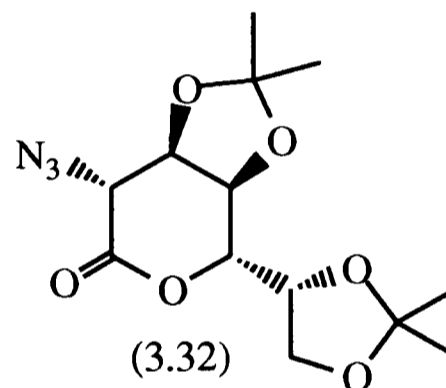


A mixture of 2-deoxy-2-iodo-3,4-*O*-isopropylidene-D-glycero-L-allo-heptono-1,5-lactone (3.30) and 2-deoxy-2-iodo-3,4-*O*-isopropylidene-D-glycero-L-alto-heptono-1,5-lactone (3.29) (65 mg, 0.18 mmol, mixture of epimers as prepared above) and periodic acid (50 mg, 0.22 mmol) were stirred in THF at room temperature. After 10 min, t.l.c. (ethyl acetate) indicated complete consumption of starting materials. The crude mixture was preabsorbed onto silica and flushed through a short silica plug (eluant ethyl acetate). The solvent was then removed to yield a mixture of aldehydes (47 mg, 80%) which was used directly without further purification or characterisation

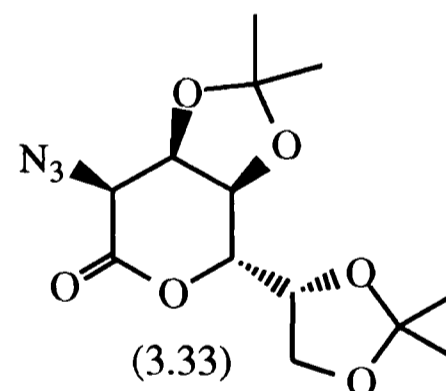
The mixture prepared above and 18-crown-6 (10 mg, 0.04 mmol) were dissolved in dry acetonitrile (3 ml) and stirred at 0 °C under nitrogen. Potassium fluoride (21 mg, 0.36 mmol) was added and the mixture stirred for 30 min. At this point t.l.c. (hexane : ethyl acetate, 1 : 1) indicated the formation of a product (R_f 0.2), together with some baseline material. Ethyl acetate (20 ml) and semi-saturated brine (20 ml) were added

and the mixture stirred at 0 °C for a further 5 min. The organic layer was removed and the aqueous layer further extracted with ethyl acetate (2 x 10 ml). The organic extracts were then combined, dried (magnesium sulphate), filtered, the solvent removed and the residue purified by flash chromatography to yield (1S,4S,5S,6R,7S)-4-iodo-5,6-O-isopropylidene-2-oxa-5,6,7-trihydroxy-bicyclo[2.2.1]heptan-3-one (3.31) (18 mg, 30% over two steps) identical to an authentic sample of this material;⁸ ν_{\max} (film) 3400-3200 (br, OH), 1791 (C=O) cm^{-1} ; δ_{H} (CDCl_3) 1.38, 1.52 (6H, 2 x s, Me_2C), 4.63 (1H, d, J 2.5 Hz), 4.75 (1H, dd, J 2.2 Hz, J' 3.8 Hz), 5.08 (2H, m); m/z (NH_3 , DCI) 344 (MNH_4^+ , 100%), 327 (MH^+).

2-Azido-2-deoxy-3,4:6,7-di-O-isopropylidene-D-glycero-L-altro-heptono-1,5-lactone (3.32) and



2-azido-2-deoxy-3,4:6,7-di-O-isopropylidene-D-glycero-L-allo-heptono-1,5-lactone (3.33).



3,4:6,7-Di-O-isopropylidene-2-O-trifluoromethanesulphonyl-D-glycero-L-altro-heptono-1,5-lactone (3.25) (390 mg, 0.92 mmol) and sodium azide (181 mg, 2.78 mmol) were stirred in dry DMF (10 ml) at room temperature. After 10 min, t.l.c. (hexane : ethyl acetate, 2 : 1) indicated the formation of two products (R_f 0.5 and R_f 0.3). The solvent was removed and ethyl acetate (50 ml) and water (50 ml) were added. The crude mixture was shaken and the organic extracts were washed with brine (50 ml), dried (magnesium sulphate), filtered, the solvent removed and the residue purified by flash chromatography (hexane : ethyl acetate, 3 : 1) to yield 2-azido-2-deoxy-3,4:6,7-di-O-isopropylidene-D-glycero-L-altro-heptono-1,5-lactone (3.32) (160 mg,

55%, R_f 0.5), as a white crystalline solid, m.p. 111-112 °C (ether / hexane); $[\alpha]_D^{20}$ -18.7 (*c*, 0.99 in CHCl_3); ν_{max} (CHCl_3) 2121 (N_3), 1772 ($\text{C}=\text{O}$) cm^{-1} ; δ_{H} (CD_3CN) 1.35 (6H, s, Me_2C), 1.40, 1.50 (6H, 2 x s, Me_2C), 3.95 (1H, dd, H-7, $J_{6,7}$ 6.1 Hz, $J_{7,7'}$ 8.6 Hz), 4.10 (1H, dd, H-7', $J_{6,7'}$ 6.9 Hz), 4.18 (1H, dd, H-5, $J_{4,5}$ 9.3 Hz, $J_{5,6}$ 4.2 Hz), 4.31-4.34 (2H, m, H-3, H-6), 4.39 (1H, dd, H-4, $J_{3,4}$ 7.7 Hz), 4.48 (1H, d, H-2, $J_{2,3}$ 8.1 Hz); δ_{C} (CDCl_3) 24.4, 25.4, 26.0, 26.7 (4 x q, 2 x Me_2C), 62.0 (d, C-2), 64.9 (t, C-7), 71.4, 74.0, 75.5, 77.0, (4 x d, C-3, C-4, C-5, C-6), 110.4, 112.8 (2 x s, 2 x CMe_2), 166.8 (s, C-1); m/z (NH_3 , DCI) 331 (MNH_4^+), 314 (MH^+), 303 ($\text{MNH}_4^+-\text{N}_2$), 286 (MH^+-N_2 , 100%). (Found: C, 49.93; H, 6.09; N, 13.59; $\text{C}_{13}\text{H}_{19}\text{O}_6\text{N}_3$ requires: C, 49.84; H, 6.11; N, 13.41%);

n.O.e. Data. Irradiate δ 4.18 (H-5) ; enhancements : 3.95 (H-7, 2.5%), 4.3 (H-6, 3.6%), 4.48 (H-2, 11.2%)
Irradiate δ 4.48 (H-2) ; enhancements : 4.18 (H-5, 9%)

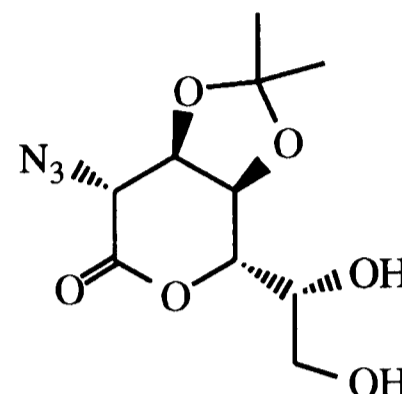
and 2-azido-2-deoxy-3,4:6,7-di-*O*-isopropylidene-D-glycero-L-allo-heptono-1,5-lactone (3.33) (54 mg, 19%, R_f 0.3), as a white crystalline solid, m.p. 132-134 °C (ether / hexane); $[\alpha]_D^{20}$ +87.6 (*c*, 0.98 in CHCl_3); ν_{max} (CHCl_3) 2118 (N_3), 1764 ($\text{C}=\text{O}$) cm^{-1} ; δ_{H} (CDCl_3) 1.36, 1.37, 1.39, 1.50 (12H, 4 x s, 2 x Me_2C), 4.01 (1H, t, H-7, J 8.3 Hz), 4.11 (1H, dd, H-7', $J_{6,7'}$ 6.6 Hz, $J_{7,7'}$ 8.5 Hz), 4.27 (1H, m, H-6, $J_{5,6}$ 1.6 Hz), 4.51 (1H, m, H-5), 4.62 (1H, dd, H-4, $J_{3,4}$ 7.2 Hz, $J_{4,5}$ 0.6 Hz), 4.74 (1H, d, H-2, $J_{2,3}$ 4.0 Hz), 4.87 (1H, dd, H-3); δ_{C} (CDCl_3) 24.4, 25.3, 25.5, 26.2 (4 x q, 2 x Me_2C), 58.2 (d, C-2), 65.5 (t, C-7), 74.6, 76.0, 76.4, 79.8, (4 x d, C-3, C-4, C-5, C-6), 111.1 (s, 2 x CMe_2), 167.0 (s, C-1); m/z (NH_3 , DCI) 331 (MNH_4^+), 314 (MH^+), 303 ($\text{MNH}_4^+-\text{N}_2$), 286 (MH^+-N_2 , 100%). (Found: C, 50.04; H, 6.11; N, 13.52; $\text{C}_{13}\text{H}_{19}\text{O}_6\text{N}_3$ requires: C, 49.84; H, 6.11; N, 13.41%).

n.O.e. Data. Irradiate δ 4.50 (H-5) ; enhancements : 4.01 (H-7, 2.4%), 4.27 (H-6, 5.2%), 4.62 (H-4, 2%). No enhancement seen to H-2.

Irradiate δ 4.74 (H-2) ; enhancements : 4.87 (H-3, 3%). No enhancement seen to H-5.

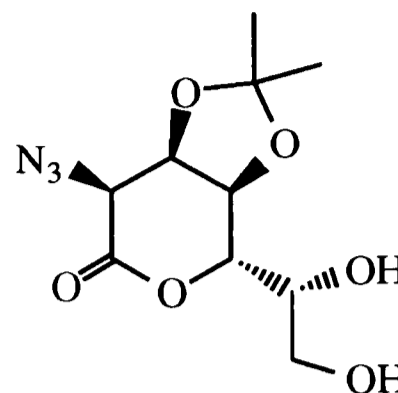
Irradiate δ 4.87 (H-3) ; enhancements : 4.74 (H-2, 5.7%).

2-Azido-2-deoxy-3,4-O-isopropylidene-D-glycero-L-altro-heptono-1,5-lactone (3.34).



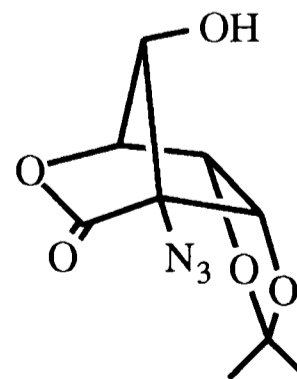
2-Azido-2-deoxy-3,4:6,7-di-O-isopropylidene-D-glycero-L-altro-heptono-1,5-lactone (3.32) (92 mg, 0.3 mmol) was stirred at room temperature in a mixture of acetic acid (4 ml) and water (1 ml). After 20 h, t.l.c. (hexane : ethyl acetate, 2 : 1) indicated complete consumption of starting material (R_f 0.6) and the formation of a major product (R_f 0.1). The solvent was removed, the residue co-evaporated with toluene (2 x 5 ml) and then purified by flash chromatography (ethyl acetate) to yield 2-azido-2-deoxy-3,4-O-isopropylidene-D-glycero-L-altro-heptono-1,5-lactone (3.34) (74 mg, 92%), as colourless oil; $[\alpha]_D^{20}$ -25.9 (c , 1.04 in CHCl_3); ν_{max} (film) 3400 (br, OH) 2120 (N_3), 1765 ($\text{C}=\text{O}$) cm^{-1} ; δ_{H} (CD_3OD) 1.41, 1.56 (6H, 2 x s, Me_2C), 3.79 (1H, dd, H-7, $J_{6,7}$ 5.2 Hz, $J_{7,7'}$ 11.5 Hz), 3.86 (1H, dd, H-7', $J_{6,7'}$ 6.0 Hz), 3.96 (1H, dt, J 3.4 Hz, J' 5.5 Hz), 4.23 (1H, dd, J 3.4 Hz, J' 9.3 Hz), 4.31-4.35 (2H, m), 4.56 (1H, ddd, J 1.4 Hz, J' 6.0 Hz, J'' 9.3 Hz); δ_{C} (CD_3OD) 24.4, 26.6 (2 x q, Me_2C), 62.1 (d, C-2), 62.8 (t, C-7), 70.1, 70.5, 75.4, 78.0, (4 x d, C-3, C-4, C-5, C-6), 112.8 (s, CMe_2), 168.3 (s, C-1); m/z (NH_3 , DCI) 291 (MNH_4^+ , 100%), 274 (MH^+), 263 ($\text{MNH}_4^+-\text{N}_2$), 246 (MH^+-N_2). (Found: C, 44.32; H, 5.51; N, 15.03; $\text{C}_{10}\text{H}_{15}\text{O}_6\text{N}_3$ requires: C, 43.96; H, 5.53; N, 15.38%).

2-Azido-2-deoxy-3,4-*O*-isopropylidene-D-glycero-L-
allo-heptono-1,5-lactone (3.35).



2-Azido-2-deoxy-3,4:6,7-di-*O*-isopropylidene-D-glycero-L-allylo-heptono-1,5-lactone (3.33) (80 mg, 0.26 mmol) was stirred at 50 °C in a mixture of acetic acid (4 ml) and water (1 ml). After 2 h, t.l.c. (hexane : ethyl acetate, 1 : 1) indicated complete consumption of starting material (R_f 0.6) and the formation of a major product (R_f 0.1). The solvent was removed, the residue co-evaporated with toluene (2 x 2 ml) and then purified by flash chromatography (ethyl acetate) to yield 2-azido-2-deoxy-3,4-*O*-isopropylidene-D-glycero-L-allylo-heptono-1,5-lactone (3.35) (48 mg, 69%), as a white crystalline solid, m.p. 138-140 °C (decomp, ethyl acetate / hexane); $[\alpha]_D^{20}$ -6.1 (c , 0.53 in EtOH); ν_{\max} (KBr) 3369 (br, OH), 2119 (N_3), 1737 (C=O) cm^{-1} ; δ_H (CD_3OD) 1.38, 1.43 (6H, 2 x s, Me_2C), 3.53-3.61 (2H, m, H-7, H-7'), 3.88 (1H, dt, J 2.7 Hz, J' 6.7 Hz), 4.68-4.73 (2H, m), 4.83-4.94 (2H, m); δ_C (CD_3OD) 23.0, 25.1 (2 x q, Me_2C), 58.3 (d, C-2), 61.8 (t, C-7), 72.5, 74.7, 76.6, 82.2, (4 x d, C-3, C-4, C-5, C-6), 109.9 (s, CMe_2), 168.8 (s, C-1); m/z (NH_3 , DCI) 291 (MNH_4^+), 274 (MH^+), 263 ($MNH_4^+-N_2$), 246 (MH^+-N_2 , 100%). (Found: C, 43.63; H, 5.49; N, 15.21; $C_{10}H_{15}O_6N_3$ requires: C, 43.96; H, 5.53; N, 15.38%).

(1*S*,4*S*,5*R*,6*R*,7*R*)-4-Azido-5,6-*O*-isopropylidene-2-oxa-
5,6,7-trihydroxy-bicyclo[2.2.1]heptan-3-one (3.36).



Method 1.

2-Azido-2-deoxy-3,4-*O*-isopropylidene-D-glycero-L-allylo-heptono-1,5-lactone (3.34) (50 mg, 0.18 mmol) and periodic acid (50 mg, 0.22 mmol) were stirred in THF (2 ml) at room temperature. After 5 min, a white precipitate was formed and t.l.c. (ethyl

acetate) indicated complete consumption of starting material (R_f 0.6). The mixture was preabsorbed onto silica and flushed through a short silica plug (eluant ethyl acetate). The solvent was then removed and the residue stirred with 18-crown-6 (10 mg, 0.03 mmol) in dry acetonitrile (2 ml) at 0 °C under nitrogen. Potassium fluoride (20 mg, 0.33 mmol) was added and after 20 min t.l.c. (hexane : ethyl acetate, 1 : 1) indicated the formation of a product (R_f 0.3), together with some baseline material. Ethyl acetate (15 ml) and semi-saturated brine (10 ml) were added and the mixture stirred at 0 °C for a further 5 min. The organic layer was then removed and the aqueous layer washed with ethyl acetate (2 x 10 ml). The organic extracts were then combined, dried (magnesium sulphate), filtered, the solvent removed and the residue purified by flash chromatography (hexane : ethyl acetate, 1 : 1) to yield (1S,4S,5R,6R,7R)-4-azido-5,6-O-isopropylidene-2-oxa-5,6,7-trihydroxy-bicyclo[2.2.1.]heptan-3-one (3.36) (23 mg, 52% over two steps) as an oil which crystallised on standing, m.p. 116-117 °C (on standing); $[\alpha]_D^{20} +167.8$ (c, 1.0 in CHCl_3); ν_{max} (film) 3600 (br, OH), 2124 (N_3), 1800 (C=O) cm^{-1} ; δ_{H} (CDCl_3) 1.39, 1.51 (6H, 2 x s, Me_2C), 3.62 (1H, br s, D_2O exch, 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); δ_{C} (CDCl_3) 25.1, 25.5 (2 x q, Me_2C), 75.2 (s, C-4), 76.6, 79.4, 80.1, 82.2 (4 x d, C-1, C-5, C-6, C-7), 117.9 (s, CMe_2), 169.0 (s, C-3); m/z (NH_3 , DCI) 259 (MNH_4^+ , 100%), 214 (MH^+-N_2). (Found: C, 45.09; H, 4.52; N, 17.30; $\text{C}_9\text{H}_{11}\text{O}_5\text{N}_3$ requires: C, 44.82; H, 4.60; N, 17.42%)

Method 2.

2-Azido-2-deoxy-3,4-O-isopropylidene-D-glycero-L-allo-heptono-1,5-lactone (3.35) (38 mg, 0.14 mmol) and periodic acid (38 mg, 0.17 mmol) were stirred in THF (2 ml) at room temperature. After 5 min, a white precipitate was formed and t.l.c. (ethyl acetate) indicated complete consumption of starting material (R_f 0.4). The mixture was preabsorbed onto silica and flushed through a short silica plug (eluant ethyl acetate). The solvent was removed and the residue stirred with 18-crown-6 (8 mg, 0.03 mmol) in dry acetonitrile (2 ml) at 0 °C under nitrogen. Potassium fluoride (17 mg, 0.3 mmol)

was added and after 20 min t.l.c. (hexane : ethyl acetate, 1 : 1) indicated the formation of a product (R_f 0.3), together with some baseline material. Ethyl acetate (15 ml) and semi-saturated brine (10 ml) were added and the mixture stirred at 0 °C for a further 5 min. The organic layer was then removed and the aqueous layer washed with ethyl acetate (2 x 10 ml). The organic extracts were then combined, dried (magnesium sulphate), filtered, the solvent removed and the residue purified by flash chromatography (hexane : ethyl acetate, 1 : 1) to yield (1S,4S,5R,6R,7R)-4-azido-5,6-O-isopropylidene-2-oxa-5,6,7-trihydroxy-bicyclo[2.2.1]heptan-3-one (3.36) (16 mg, 48% over two steps) identical to the material described above.

References

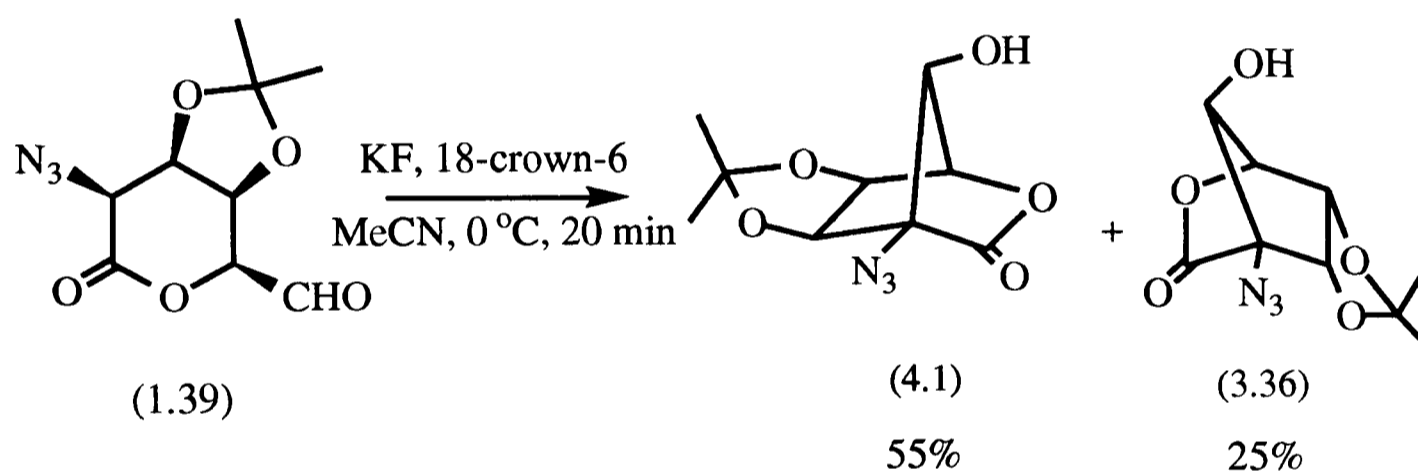
- ¹ Beacham, A.R.; Bruce, I.; Choi, S.; Doherty, O.; Fairbanks, A.J.; Fleet, G.W.J.; Skead, B.M.; Peach, J.M.; Saunders, J.; and Watkin, D.J. *Tetrahedron: Asymm.*, 1991, **2**, 883.
- ² Burley, D.A. Part II Thesis, 1992, Oxford University.
- ³ Hui, A. Part II Thesis, 1992, Oxford University.
- ⁴ Brown, J.M.; Conn, A.D.; Pilcher, G.; Leitao, M.L.P.; and Meng-Yan, Y. *J. Chem. Soc. Chem. Commun.*, 1989, 1817.
- ⁵ Nicolaou, K.C.; and Webber, S.E. *Synthesis*, 1986, 453.
- ⁶ Elliott, R.P.; Fleet, G.W.J.; Pearce, L.; Smith, C.; and Watkin, D.J. *Tetrahedron Lett.*, 1991, **43**, 6227.
- ⁷ Choi, S.S.; Myerscough, P.M.; Fairbanks, A.J.; Skead, B.M.; Bichard, C.J.F.; Mantell, S.J.; Son, J.C.; Fleet, G.W.J.; Saunders, J.; and Brown, D. *J. Chem. Soc. Chem. Commun.*, 1992, 1605.
- ⁸ Elliott, R.P. 'Sugars as Homochiral Starting Materials', D. Phil Thesis, 1992, Oxford University.

CHAPTER 4

Further Investigations of the Bicyclic Azido Carbocycles derived from D-glycero-D-talo- and D-glycero-D-galacto-heptono-1,5-lactones.

Introduction.

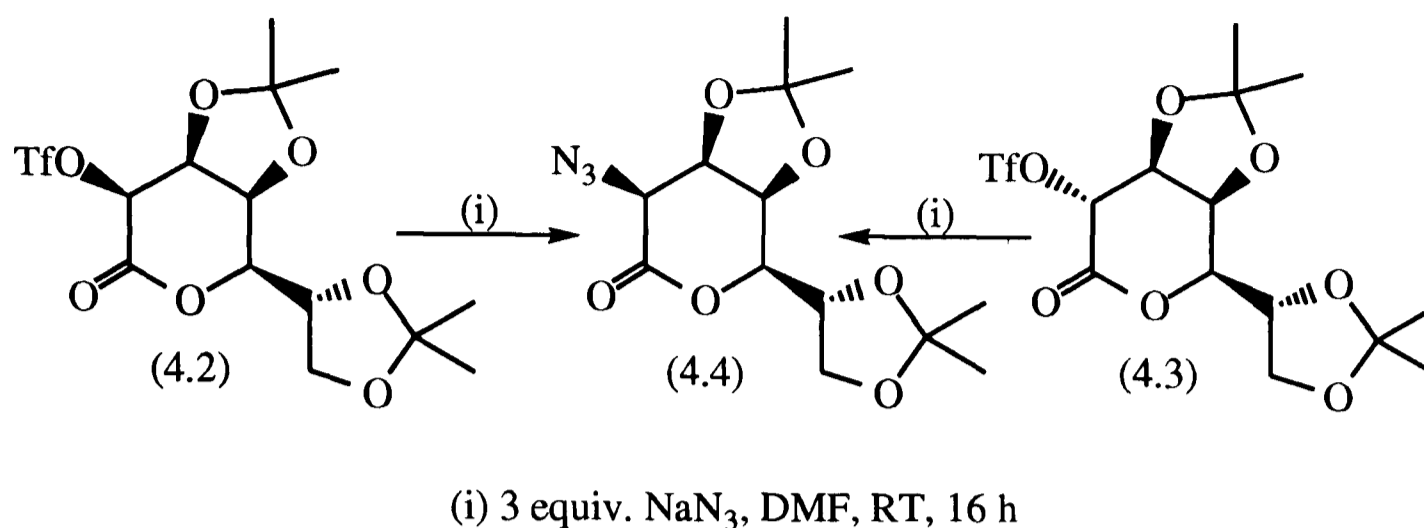
Cyclisation of the azido aldehyde (1.39), with potassium fluoride in acetonitrile, yielded a mixture of two carbocyclic products (4.1) and (3.36) as described previously (Scheme 1.12), and shown again in Scheme 4.1.



Scheme 4.1

Previous work¹ in this area has concentrated on the use of the major azido carbocyclic product (4.1) as the starting material for the synthesis of a variety of polyhydroxylated cyclopentanes. Further investigations into the synthetic uses of this material are currently in progress.

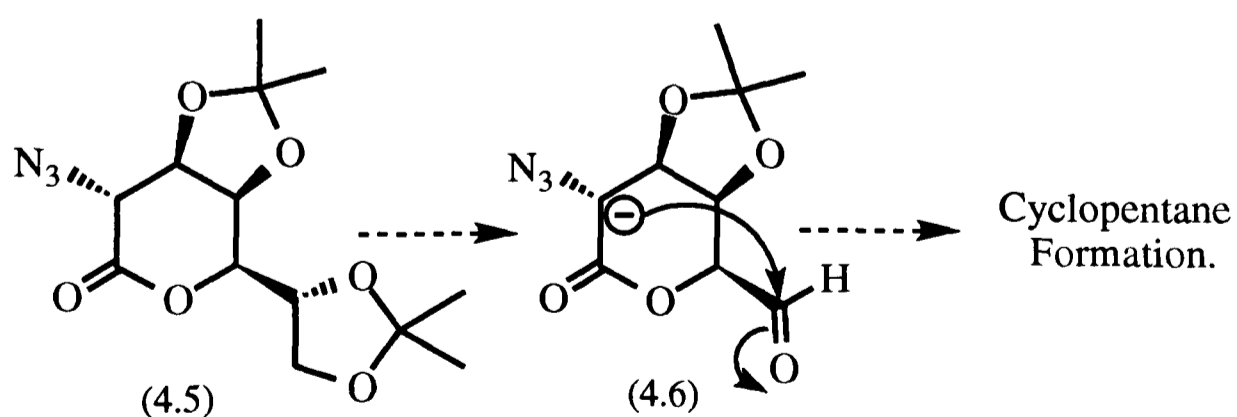
The azido aldehyde (1.39), used as the starting material for this cyclisation, is derived in four steps from the products of the Kiliani reaction of diacetone-D-mannose.¹ The azide functionality is introduced via displacement of either the D-glycero-D-talo (4.2) or D-glycero-D-galacto (4.3) triflates (Scheme 4.2).



Scheme 4.2

Sodium azide can act as a base during the course of these reactions and deprotonation α to the lactone occurs readily. Performing the reaction under conditions of thermodynamic control leads to formation of the thermodynamically more stable D-glycero-D-talo azide (4.4) as the sole reaction product.² The high yields observed for these reactions indicate that proton removal at C-2 occurs without causing significant fragmentation of the β -oxygen substituent.

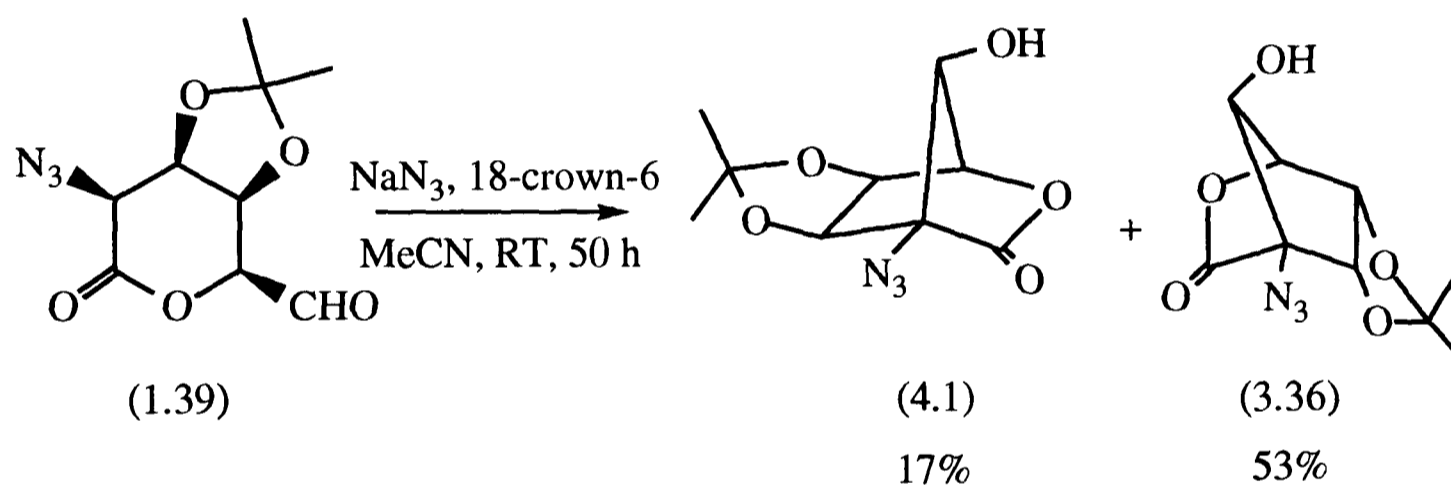
The D-glycero-D-galacto azide (4.5) can be isolated from the azide displacement of the D-glycero-D-talo triflate (4.2) if the reaction is not allowed to reach equilibrium.^{2,3} Selective removal of the primary acetone, followed by periodate cleavage, would produce the azido aldehyde (4.6). Intramolecular aldol cyclisation of this material would also lead to cyclopentane formation (Scheme 4.3).



Scheme 4.3

Further investigations into the cyclisation of the azido aldehyde (1.39) found that treatment with sodium azide in acetonitrile resulted in the formation of the same two carbocyclic products obtained from the potassium fluoride induced cyclisation, but in opposite ratios (Scheme 4.4). The major product of the sodium azide induced cyclisation is the second azido carbocycle (3.36).¹ This material is the sole product from the cyclisation reactions of the azido aldehydes described in Chapter 3 (Schemes 3.19 and 3.20).

Thus the use of sodium azide as a base to induce cyclisation of the readily available azido aldehyde (1.39) provides an efficient synthetic route to the second azido carbocycle (3.36).



Scheme 4.4

Results and Discussion.

This chapter details investigations into ring opening reactions of the second carbocycle (3.36), and its use in the synthesis of a variety of novel polyhydroxylated cyclopentane products. It was envisaged that some of these compounds may shown activity as glycosidase inhibitors. Also detailed are the synthesis and cyclisations of the azido aldehyde (4.6), derived from the D-glycero-D-galacto azido lactone (4.5).

The work is divided into five sections:-

- (i) Synthesis and cyclisation of the azido aldehyde (4.6).
- (ii) Equilibration experiments of azido carbocycles.

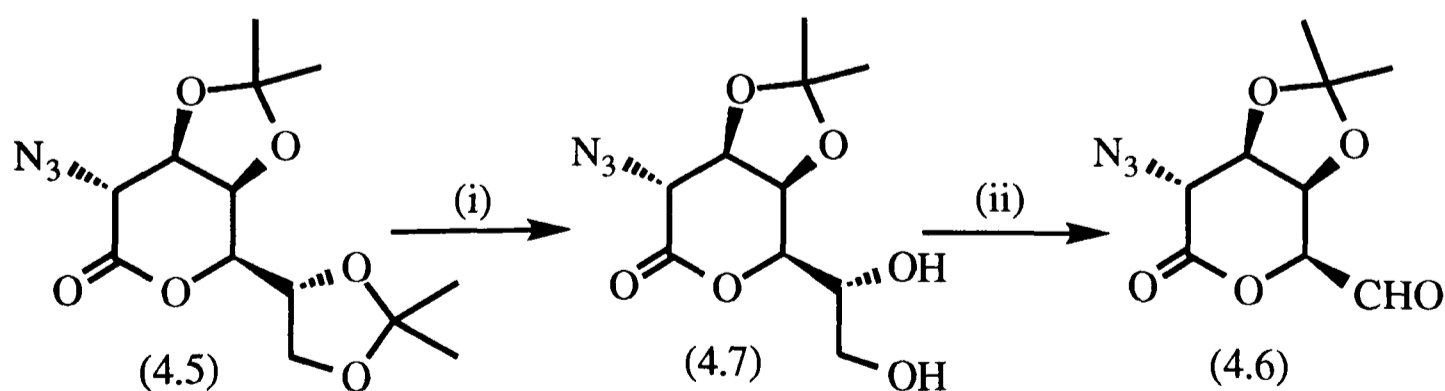
- (iii) Synthesis of a cyclopentane amino pentol.
- (iv) Syntheses of polyhydroxylated cyclopentane spirohydantoins.
- (v) Syntheses of polyhydroxylated cyclopentane amino acids.

Each of these will now be discussed in turn.

(i) Synthesis and cyclisation of the azido aldehyde (4.6).

The starting material used for this synthetic route was the D-glycero-D-galacto azide (4.5),² which is readily available from the kinetically controlled azide displacement of the D-glycero-D-talo triflate (4.2), itself derived from the major product of the Kiliani ascension of diacetone-D-mannose. Treatment of the D-glycero-D-talo triflate (4.2) with 0.9 equivalents of sodium azide, in DMF at room temperature for 3 h, produced a mixture of compounds, the major component of which was found to be the D-glycero-D-galacto azide (4.5).³

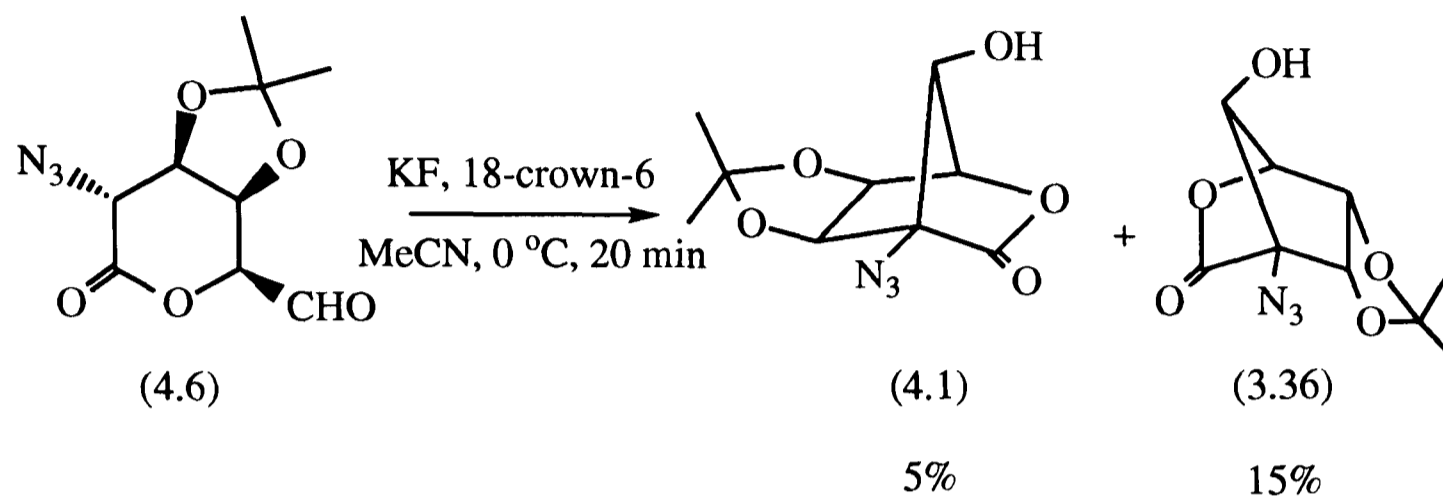
Conversion of this material to the azido aldehyde (4.6) was achieved via a synthetic route directly analogous to that described for the synthesis of the azido aldehydes described in Chapter 3. Selective removal of the primary acetonide group was achieved by treatment with 80% aqueous acetic acid to produce the diol (4.7). Treatment of this material with periodic acid in THF at room temperature produced the required azido aldehyde (4.6) (Scheme 4.5).



- (i) 80% aqueous AcOH, RT, 21 h, 80%
- (ii) H₅IO₆, THF, RT, 5 min, 84%

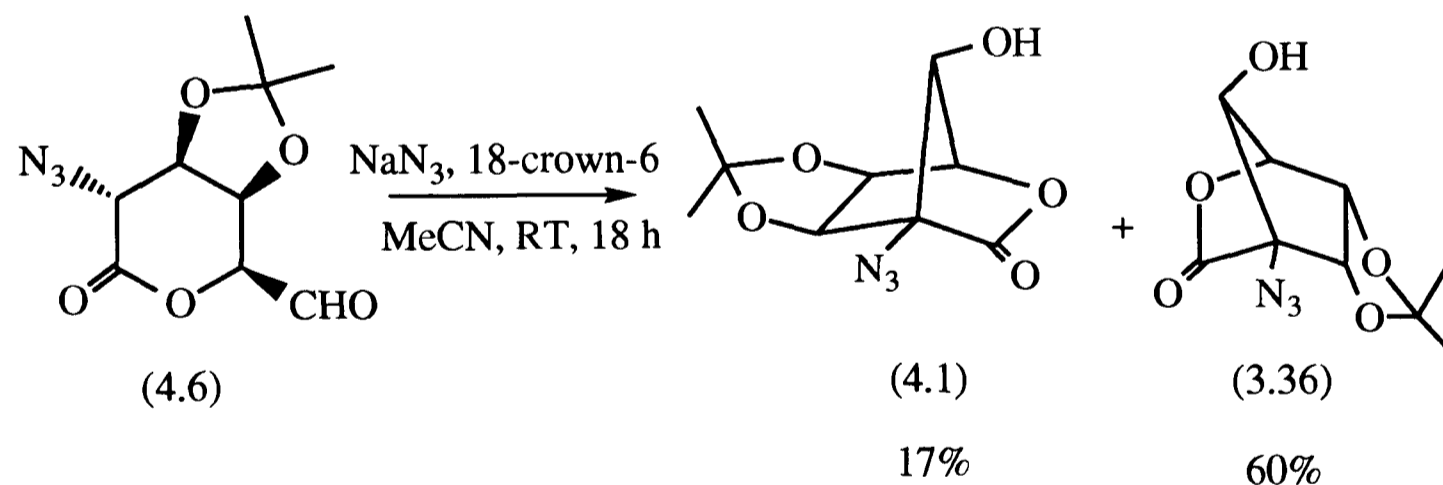
Scheme 4.5

Cyclisation of this material was attempted under two sets of reaction conditions. Treatment with potassium fluoride and 18-crown-6 at 0 °C in dry acetonitrile produced a poor yield of the two carbocyclic products (4.1) and (3.36) (Scheme 4.6).



Scheme 4.6

Alternatively, cyclisation induced by treatment with sodium azide and 18-crown-6 in acetonitrile at room temperature produced a mixture of the two carbocyclic products, but in good yield (Scheme 4.7).

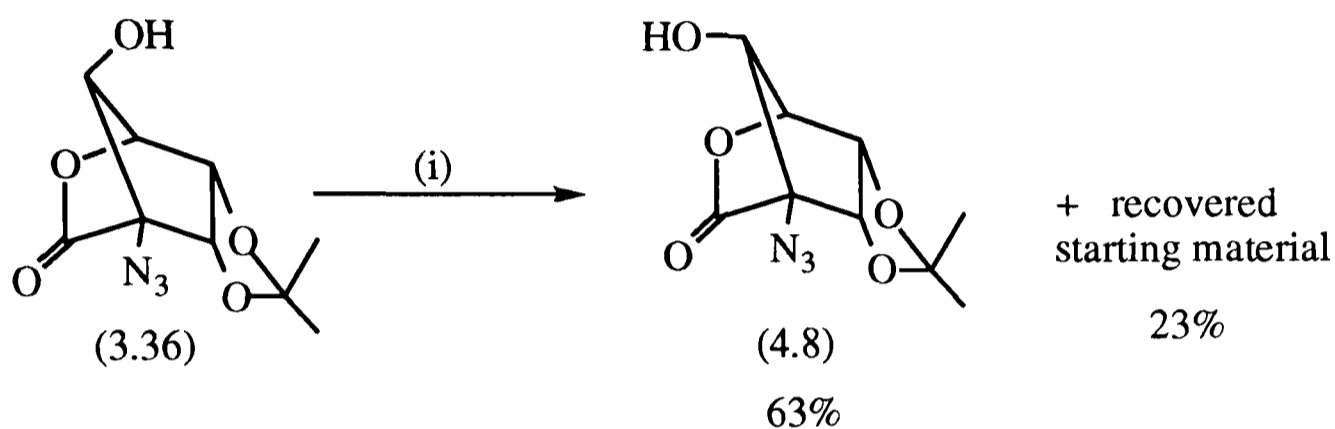


Scheme 4.7

The major product was found to be the second azido carbocycle (3.36), resulting from initial epimerisation of the starting material α to the aldehyde functionality, directly analogous to the sodium azide induced cyclisation of the azido aldehyde (1.39) detailed in Scheme 4.4.

(ii) Equilibration experiments on the azido carbocycles.

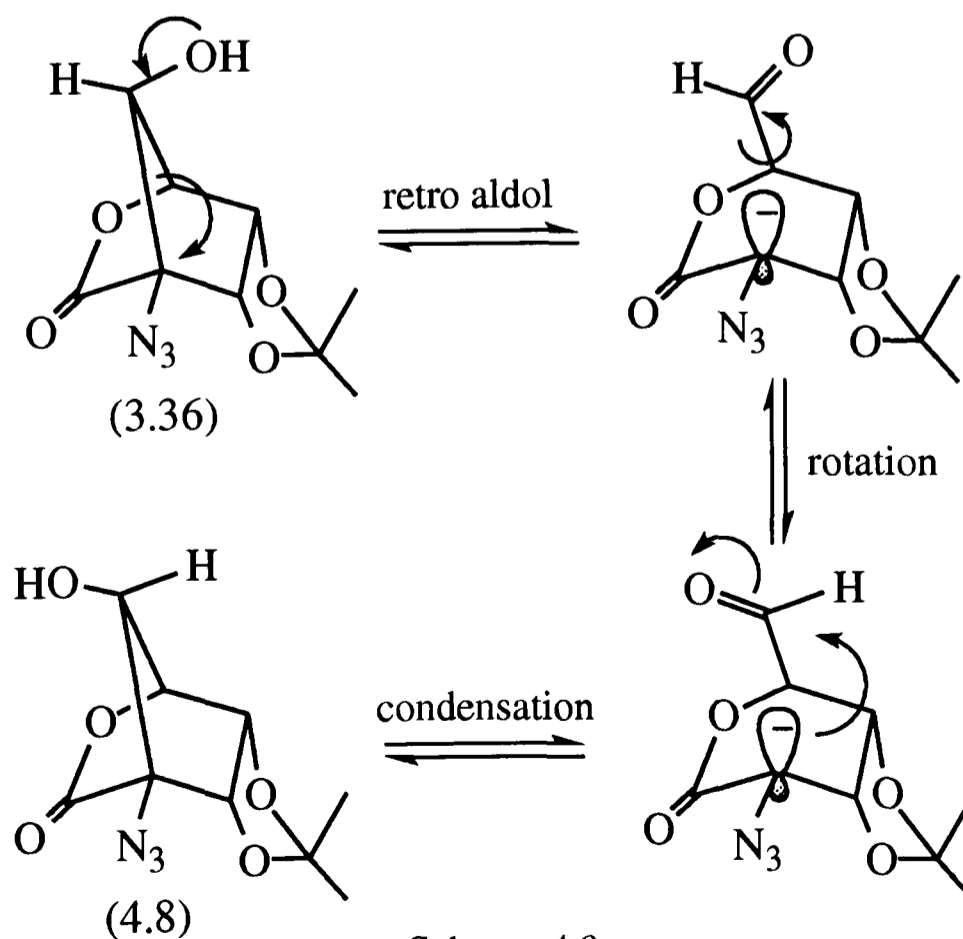
During investigations into the ring opening of the second azido carbocycle (3.36), it was found that treatment of this material with liquid ammonia caused epimerisation of the free hydroxyl group and production of a third azido carbocycle (4.8), instead of ring opening (Scheme 4.8).



(i) liq. NH₃, -45 °C to RT over 30 min

Scheme 4.8

Epimerisation of the hydroxyl group occurs via a facile base catalysed retro aldol reaction. This is then followed by re-condensation of the enolate ion onto the opposite face of the aldehyde (Scheme 4.9).



Scheme 4.9

The structure of this material was confirmed by single crystal X-ray analysis and its crystal structure is shown in Figure 4.1.

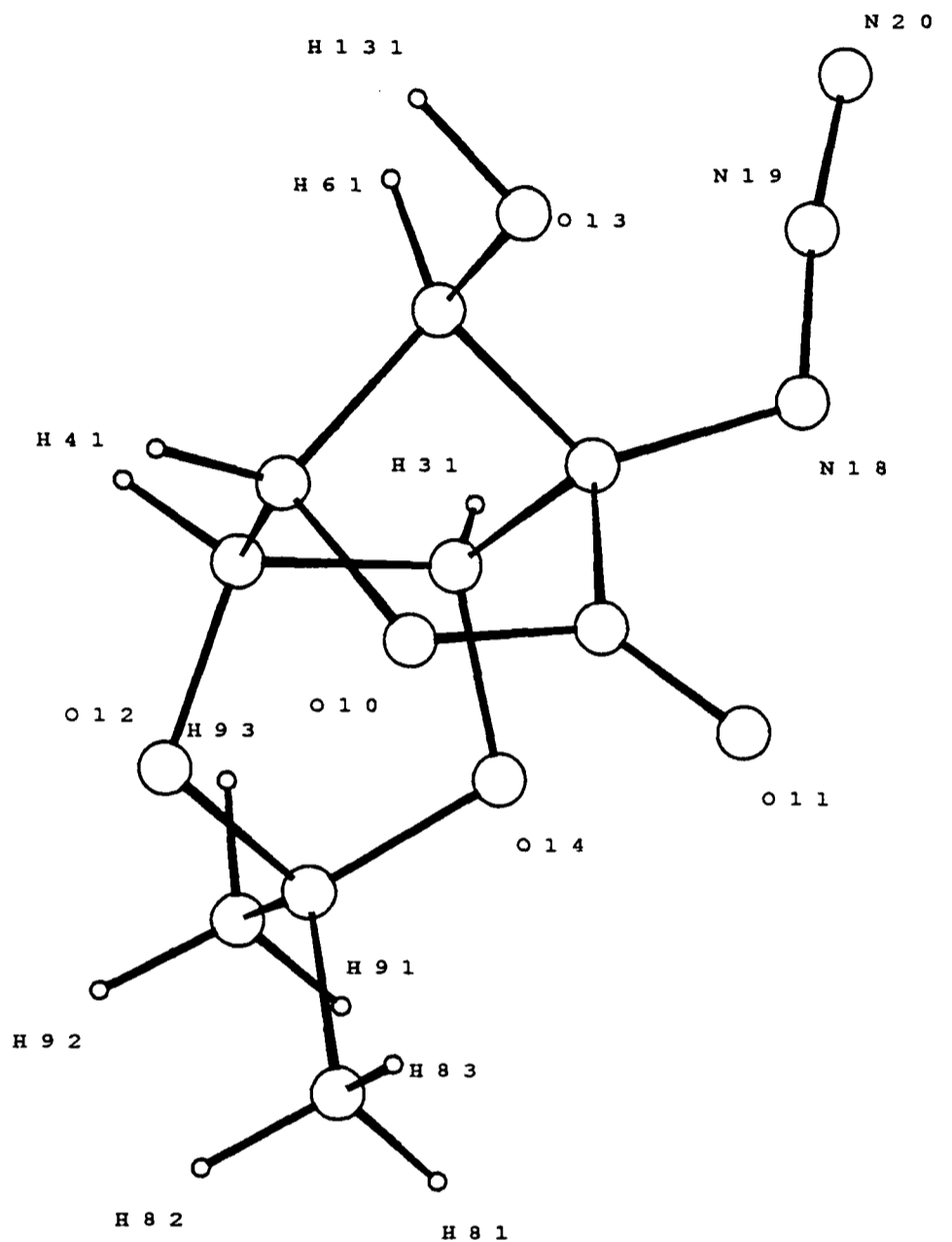
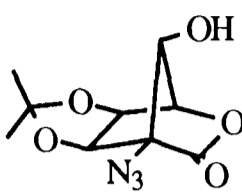
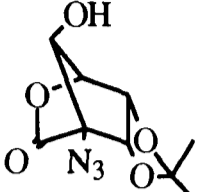
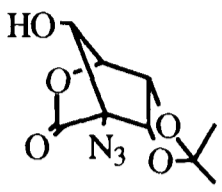
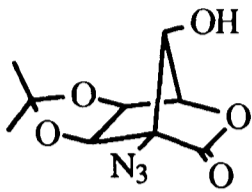
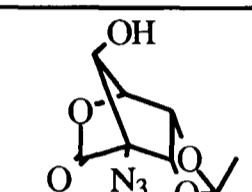
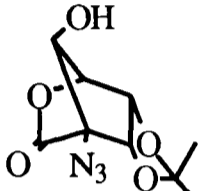
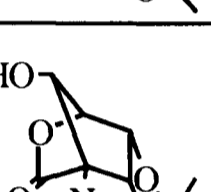
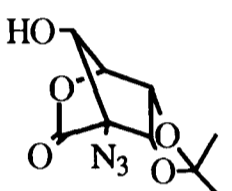
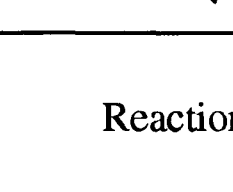


Fig 4.1.

Due to the facile interconversion observed between the two carbocycles (3.36) and (4.8) under basic conditions, it was decided to investigate whether any or all of the carbocyclic products were equilibrated by the basic reaction conditions used to induce their formation. A brief study of the interconversions of all three carbocycles under both sets of reaction conditions, namely potassium fluoride or sodium azide in acetonitrile, was carried out. The results obtained are summarised in Table 4.1. The left hand column denotes the pure starting material used and the percentages refer to the percentage yields of each of the three carbocycles obtained after exposure to the reaction conditions described.

Products Starting Material		1st	2nd	3rd
				
1st		(a) No epimerisation	—	—
		(b) No epimerisation	—	—
2nd		(a) 8%	17%	54%
		(b) 4%	42%	50%
3rd		(a) 6%	19%	44%
		(b) —	22%	78%

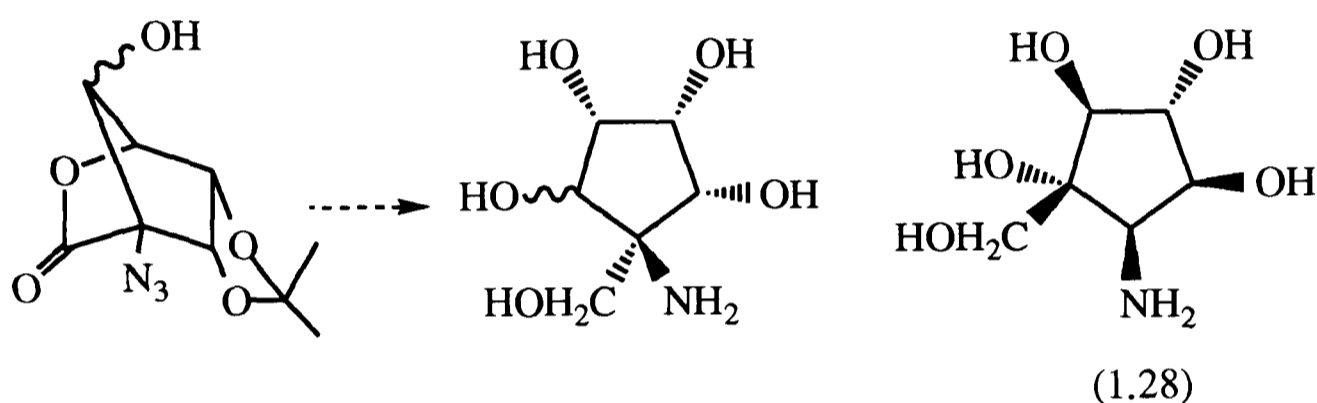
Reaction conditions:- (a) KF, 18-crown-6, MeCN, RT, 24 h
 (b) NaN₃, 18-crown-6, MeCN, RT, 48 h

Table 4.1.

As can be seen, the first carbocycle (4.1) is not equilibrated, i.e. it does not undergo a retro aldol reaction under either set of reaction conditions. Both of the other two carbocycles (3.36) and (4.8) are converted into a mixture of carbocycles by retro aldol reactions induced by either set of basic reaction conditions. The fact that the third carbocycle (4.8) was not isolated from any of the cyclisation reactions may be explained by the observation that this material is chromatographically inseparable from the starting aldehydes (1.39) and (4.6); in all of the cyclisation reactions some starting aldehyde persisted thus obscuring production and isolation of trace amounts of (4.8). It may be that (3.36) is formed kinetically, but that (4.8) is thermodynamically more stable.

(iii) Synthesis of a cyclopentane amino pentol.

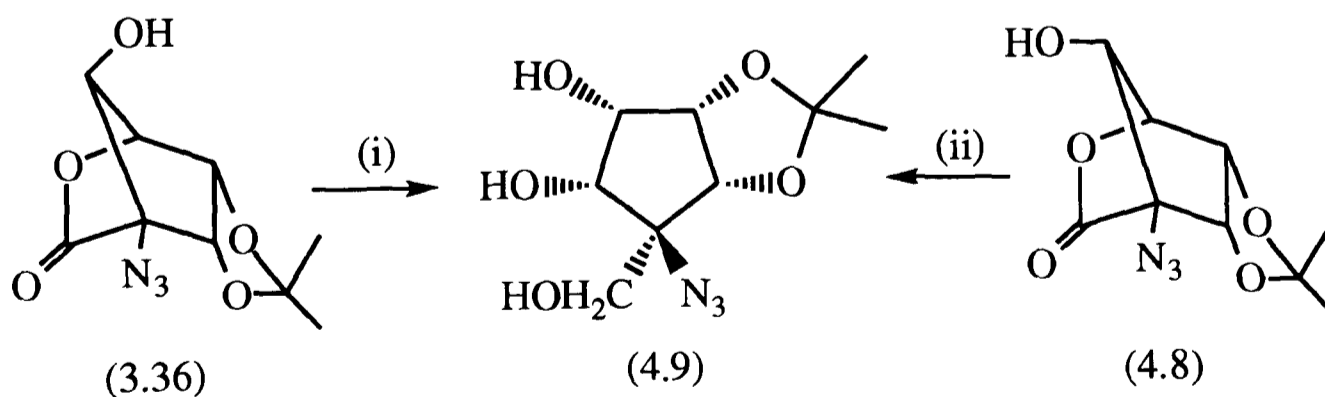
The second and third azido carbocycles (3.36) and (4.8) are ideal precursors for the synthesis of a wide range of nitrogen substituted polyhydroxylated cyclopentane targets. In particular, reductive opening of the lactone ring followed by removal of the acetonide protecting group and reduction of the azide functionality would provide access to analogues of the cyclopentane moiety of the trehalase inhibitor trehazolin (1.28) (Scheme 4.10).



Scheme 4.10

Cyclopentane moiety
of trehazolin

Attempts to reductively open the two carbocycles (3.36) and (4.8) with sodium borohydride lead to the formation of the same azido triol (4.9) in high yield in both cases (Scheme 4.11).

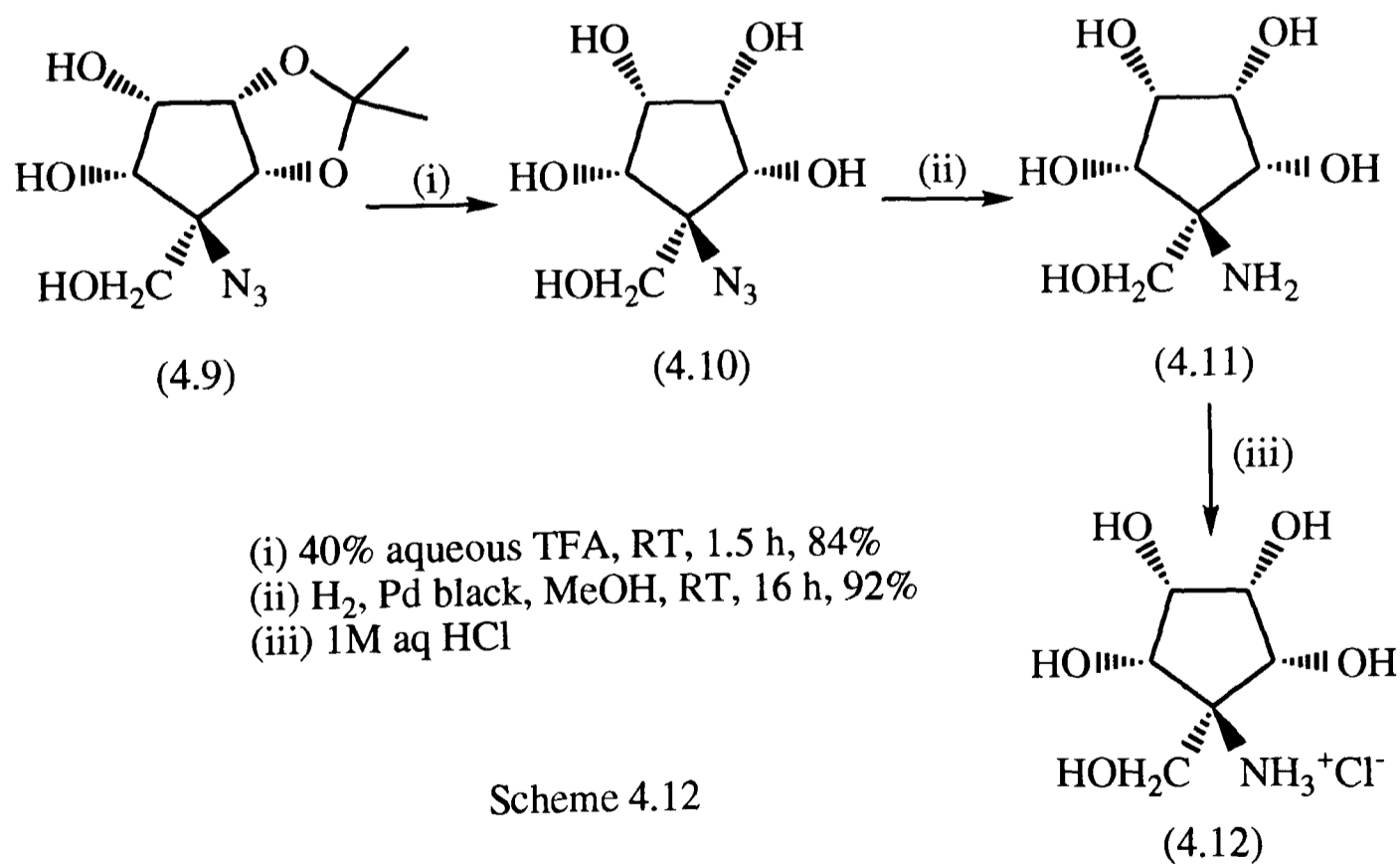


(i) NaBH₄, EtOH, RT, 16 h, 83%
(ii) NaBH₄, EtOH, RT, 12 h, 89%

Scheme 4.11

A plausible explanation for the formation of the same product in both cases is that again the two carbocycles are equilibrated under the basic reaction conditions. Interconversion via retro aldol reactions occurs more rapidly than reduction. The third carbocycle (4.8) must be reduced preferentially leading to displacement of the equilibrium and the formation of a single product (4.9). No material corresponding to reduction of the monocyclic aldehyde via which the two carbocycles equilibrate was isolated.

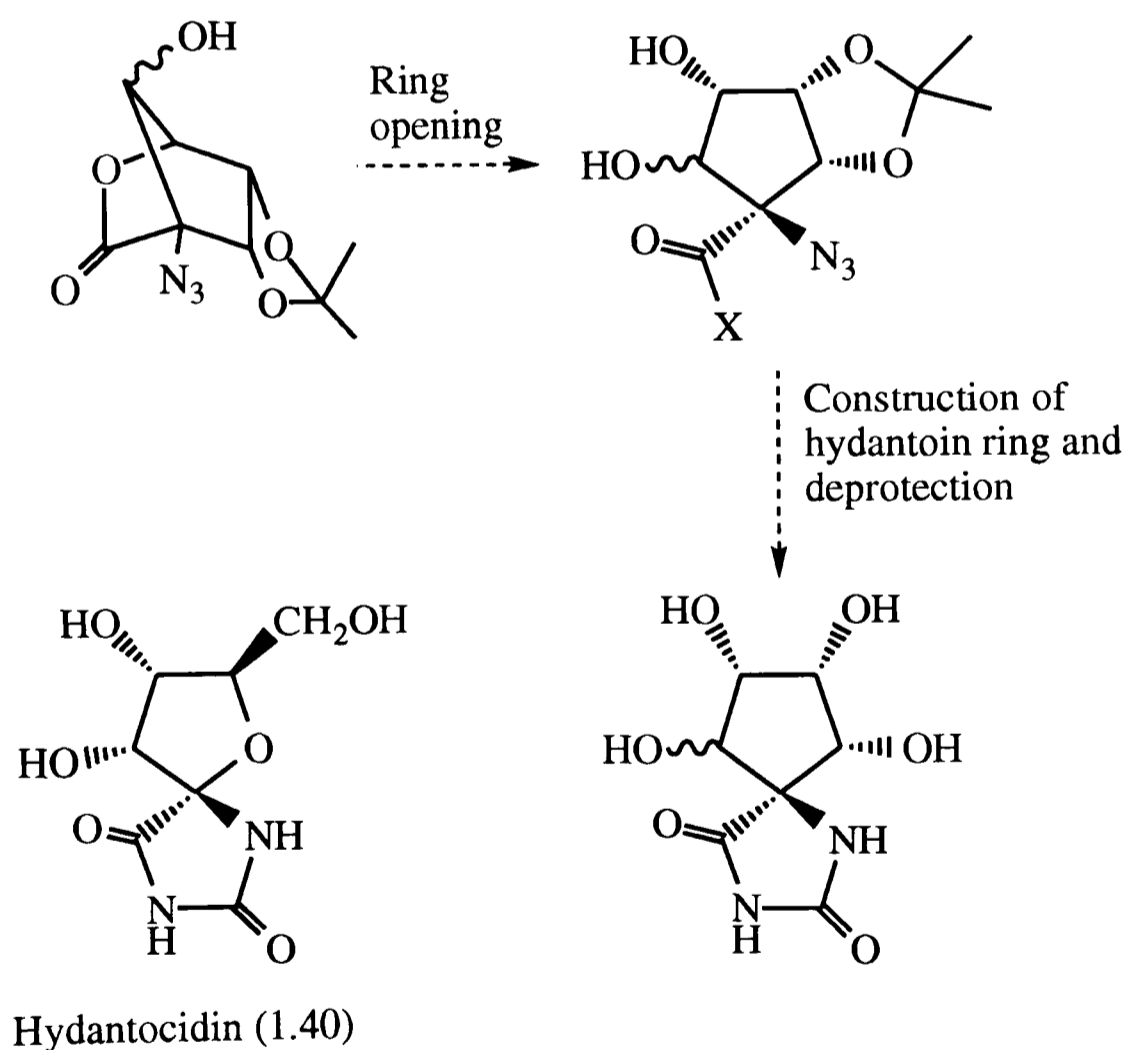
Confirmation of the stereochemistry of the azido triol (4.9) was achieved simply by removal of the acetonide group with 40% aqueous TFA to produce the symmetrical azido pentol (4.10), which possessed a zero optical rotation and characteristic ^1H and ^{13}C nmr spectra. Reduction of the azide functionality was achieved by hydrogenation in the presence of palladium black to produce the amino pentol (4.11) which was further characterised as its hydrochloride salt (4.12) (Scheme 4.12). This material was tested for potential glycosidase inhibition but showed little activity against a range of enzymes.⁴



(iv) Syntheses of polyhydroxylated cyclopentane spirohydantoins.

Non-reductive ring opening of the bicyclic azido carbocycles followed by construction of a hydantoin ring between the nitrogen and carbonyl functionalities would provide access to novel polyhydroxylated cyclopentane spirohydantoins (Scheme 4.13). Such materials can be considered to be carbocyclic analogues of the potent herbicide hydantocidin (1.40), and may display herbicidal activity.

Construction of a hydantoin ring may be achieved via many different synthetic routes.⁵ Two alternative synthetic strategies for the conversion of the bicyclic azido carbocycles (3.36) and (4.8) into spirohydantoins were attempted, and each will now be discussed in turn.



Scheme 4.13

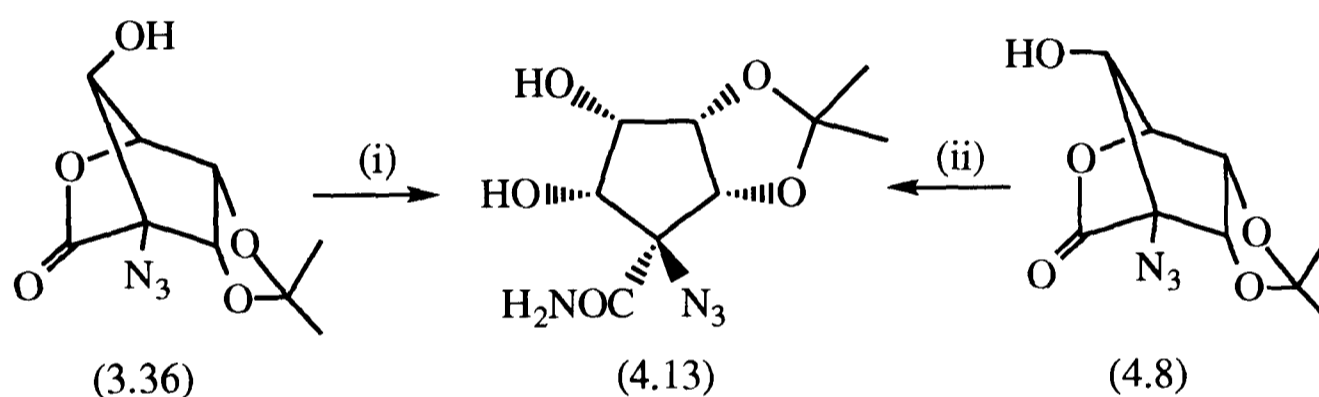
(a) Strategy 1.

The first synthetic strategy adopted involved opening of the lactone ring to produce an azido amide. Reduction of the azide functionality would then produce an amino

amide and treatment of this material with a phosgene equivalent would result in the formation of a spirohydantoin ring.

Initial attempts to open the second carbocycle (3.36) with liquid ammonia resulted only in equilibration to the third carbocycle (4.8) as described previously and shown in Scheme 4.8.

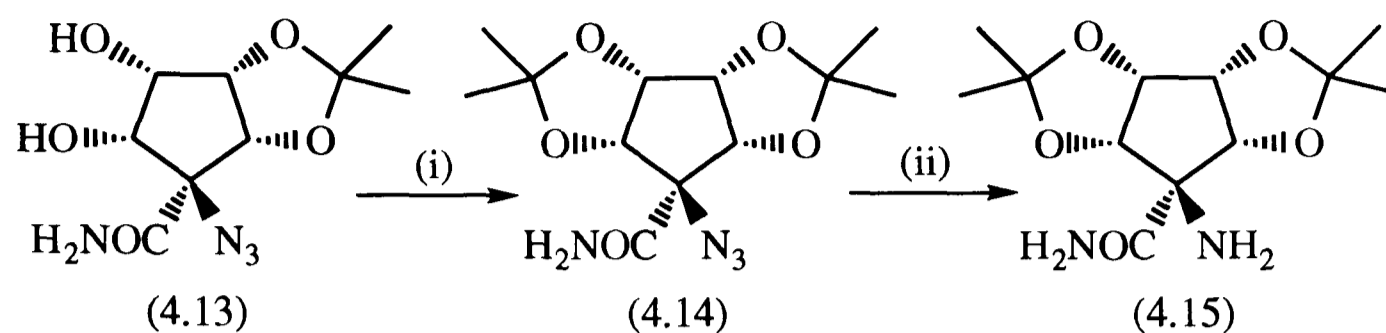
Successful ring opening of both carbocycles (3.36) and (4.8) was achieved by treatment with a saturated solution of ammonia in methanol. In both cases the same azido amide (4.13) was obtained as the sole reaction product, in moderate yield (Scheme 4.14). Formation of this material results from retro aldol equilibration and preferential ring opening of the third carbocycle (4.8), directly analogous to the reductive ring opening outlined in Scheme 4.11.



(i) NH₃ in MeOH, RT, 30 min, 31%
(ii) NH₃ in MeOH, RT, 30 min, 48%

Scheme 4.14

The stereochemistry of the azido amide (4.13) was confirmed by conversion to the symmetric diacetonide (4.14), which possessed a zero optical rotation and characteristic ¹H and ¹³C nmr spectra, by treatment with acetone and 2,2-dimethoxypropane in the presence of a catalytic amount of camphorsulphonic acid. Reduction of the azide functionality by hydrogenation in the presence of palladium black yielded the amino amide (4.15) as a precursor for the formation of a spirohydantoin (Scheme 4.15).



(i) acetone, 2,2-dimethoxypropane, CSA, 40 °C, 3.5 h, 80%

(ii) H₂, Pd black, EtOH, RT, 19 h, quantitative

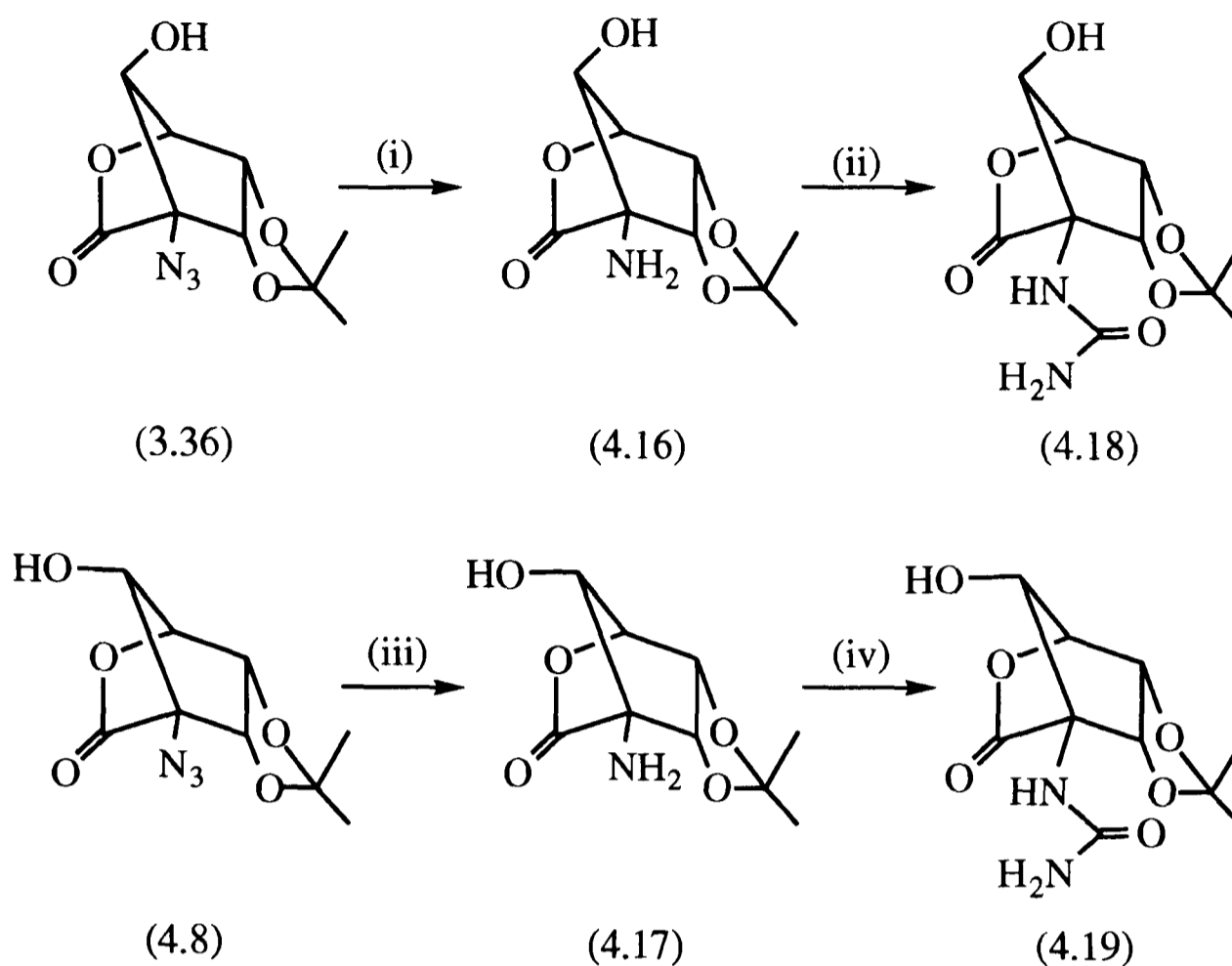
Scheme 4.15

Unfortunately treatment of the amino amide (4.15) with carbonyl diimidazole in refluxing toluene produced only trace amounts of the required spirohydantoin. The poor yield observed for this reaction, combined with the low yields observed during the ring opening step detailed above, and the fact that this route would only allow access to one of the two possible epimeric hydantoin targets, necessitated an alternative synthetic strategy.

(b) Strategy 2.

The second synthetic strategy adopted was analogous to that used for the synthesis of 1-*epi*hydantocidin (2.27) described in Chapter 2. Reduction of the bridgehead azide functionality would produce an amine which could be converted to a urea by treatment with potassium cyanate. Cyclisation of the urea onto the carbonyl group of the lactone would then result in the formation of a spirohydantoin.

Smooth reduction of the bridgehead azide functionality of the two carbocycles (3.36) and (4.8) was achieved by hydrogenation in the presence of palladium black to yield the two epimeric carbocyclic amines (4.16) and (4.17) respectively. No epimerisation of the free hydroxyl was observed during these reactions. Conversion of these amines into their corresponding ureas (4.18) and (4.19) was achieved by treatment with potassium cyanate in acetic acid to yield the two epimeric precursors required for spirohydantoin formation. These reactions are summarised in Scheme 4.16.

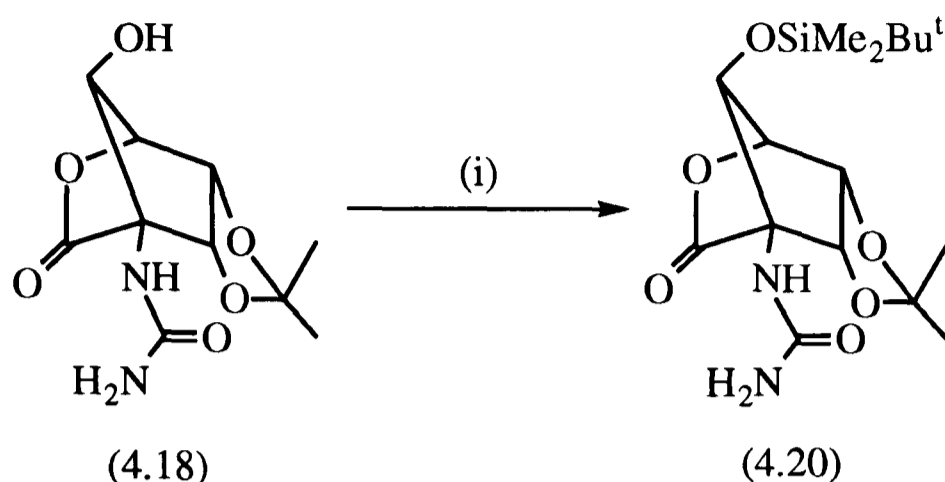


- (i) H₂, Pd black, EtOH / water, RT, 2 h, 97%
(ii) KCNO, AcOH, RT, 1 h, 72%
(iii) H₂, Pd black, EtOH / water, RT, 3 h, 76%
(iv) KCNO, AcOH, RT, 20 min, 78%

Scheme 4.16

Initial attempts to induce cyclisation of these materials involved treatment with potassium *tert*-butoxide in DMF in a manner analogous to that used for the synthesis of 1-*epi*hydantocidin (2.27) as described in Chapter 2, but these proved unsuccessful. At temperatures above 0 °C complete decomposition occurred in both cases, and at lower temperatures either of the pure ureas, (4.18) or (4.19), was simply converted into a mixture of both epimers via retro aldol reactions.

Silylation of the free hydroxyl group of the urea (4.18), derived from the second carbocycle (3.36), was achieved by treatment with TBDMS triflate in pyridine to produce the silyl urea (4.20) (Scheme 4.17). T.l.c. analysis of the reaction mixture did not indicate the formation of any of the epimeric urea (4.19), and hence it was assumed that no epimerisation of the hydroxyl substituent had occurred during this reaction.



(i) TBDMSOTf, py, 0 °C, 10 min, 58%

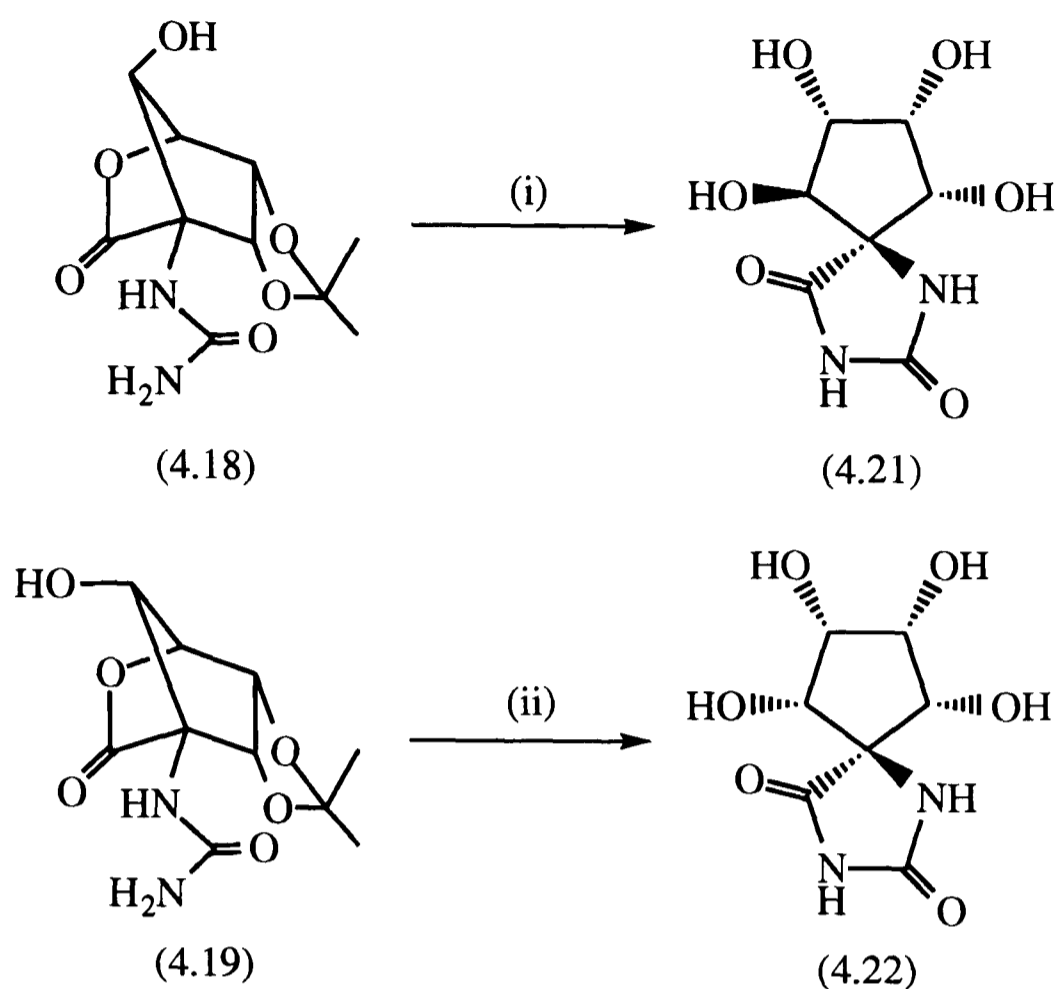
Scheme 4.17

Treatment of this material with potassium *tert*-butoxide did not induce retro aldol reactions but neither did it induce cyclisation to a spirohydantoin; only starting material was recovered in all cases.

Due to these difficulties, an alternative acid catalysed cyclisation approach was applied to the ureas (4.18) and (4.19). This approach was not attempted initially since it would necessarily induce removal of the acetonide protecting group and purification of any reaction products by conventional chromatography would be difficult.

Successful cyclisation and deprotection was achieved in both cases by refluxing the urea in a solution of methanolic HCl, produced by the addition of acetyl chloride to dry methanol. Good yields of the two tetrahydroxy spirohydantoins (4.21) and (4.22) were obtained (Scheme 4.18).

The symmetric hydantoin (4.22), derived from the third carbocycle (4.8) was found to possess a zero optical rotation and characteristic ^1H and ^{13}C nmr spectra as expected. These materials will be tested against a range of glycosidases and for potential herbicidal activity.



(i) MeOH / HCl, reflux, 32 h, 90%

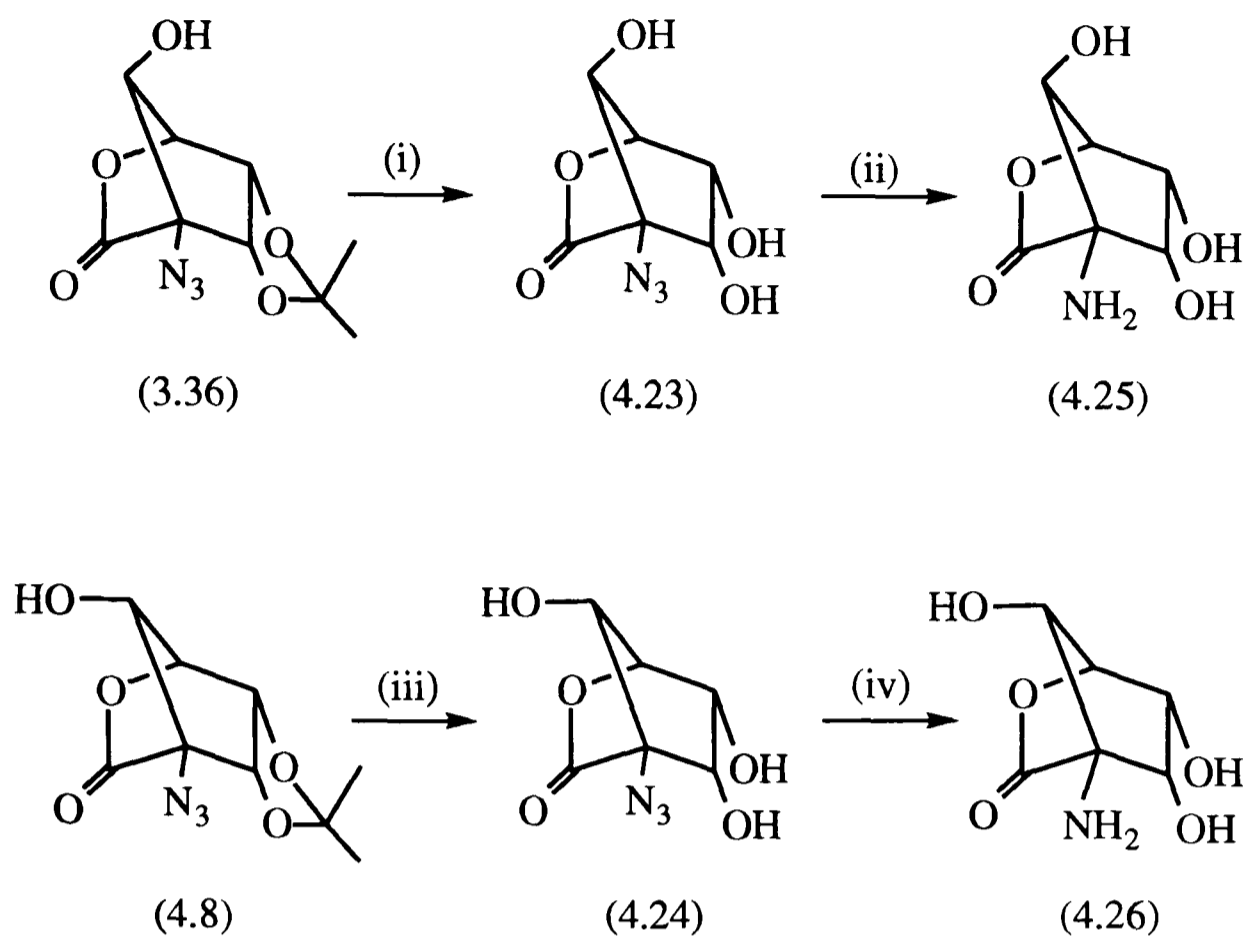
(ii) MeOH / HCl, reflux, 72 h, 81%

Scheme 4.18

(v) Syntheses of polyhydroxylated cyclopentane amino acids.

It was envisaged that conversion of the two azido carbocycles (3.36) and (4.8) into their corresponding cyclopentane α -amino acids could be achieved by a short reaction sequence. The general synthetic strategy initially adopted involved removal of the acetonide protecting group followed by reduction of the azide functionality and ring opening of the resultant amino lactone to produce the corresponding amino acid.

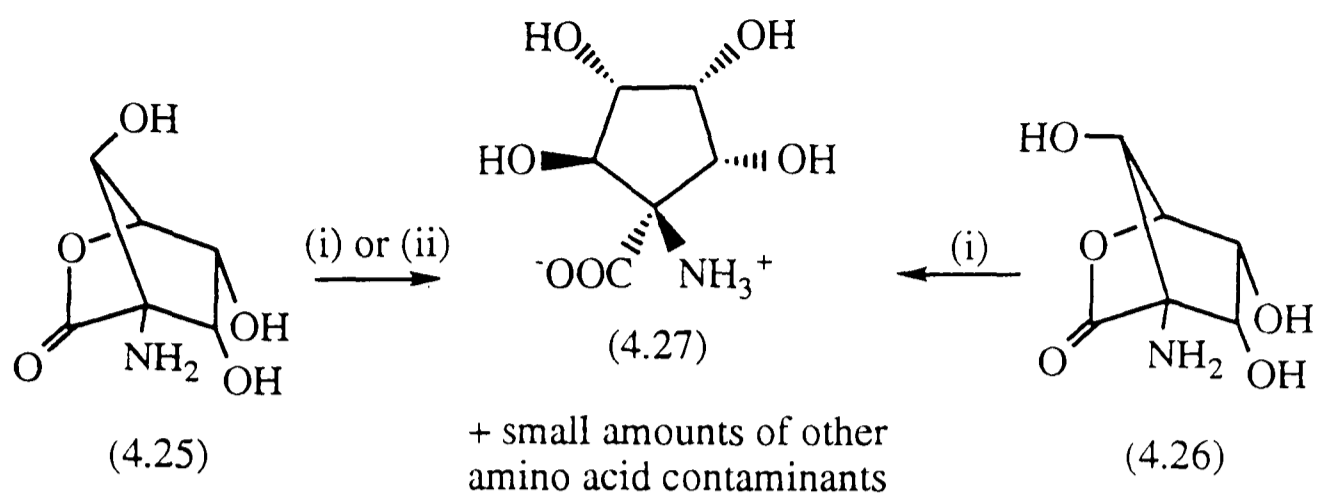
Treatment of the two azido carbocycles (3.36) and (4.8) with 40% aqueous TFA resulted in the formation of the corresponding triols (4.23) and (4.24). Reduction of the bridgehead azide functionality was then achieved in both cases to yield two epimeric amino triols (4.25) and (4.26) (Scheme 4.19). These materials were found to be extremely hygroscopic.



- (i) 40% aqueous TFA, RT, 3 h, 94%
(ii) H₂, Pd black, EtOH, RT, 4 h, quantitative
(iii) 40% aqueous TFA, RT, 6 h, 81%
(iv) H₂, Pd black, EtOH, RT, 3 h, quantitative

Scheme 4.19

Several ring opening reactions were attempted on both amino triols (4.25) and (4.26). It was found that ring opening could be achieved by treatment with aqueous sodium hydroxide or aqueous triethylamine. In all cases a mixture of either two or three amino acid products was obtained, presumably as a result of base catalysed retro aldol epimerisation. In all cases the major product was found to be the amino acid (4.27) (Scheme 4.20).



(i) 0.4 M aqueous NaOH, RT, 10 min
 (ii) 10 equiv. Et₃N in water, RT, 2 h

Scheme 4.20

The ratio of this material to the side products was in excess of 5 : 1, as adjudged by ¹H nmr. Separation of the mixtures of amino acids by ion exchange chromatography proved extremely difficult. Pure samples of the amino acid (4.27) were obtained by recrystallisation from an aqueous solution of the mixtures of amino acids. The low optical activity of this material makes it unclear as to whether either any, partial or complete racemisation occurs during the final ring opening step. The relative configuration of (4.27) was confirmed by single crystal X-ray analysis; the crystal structure is shown in Fig 4.2.

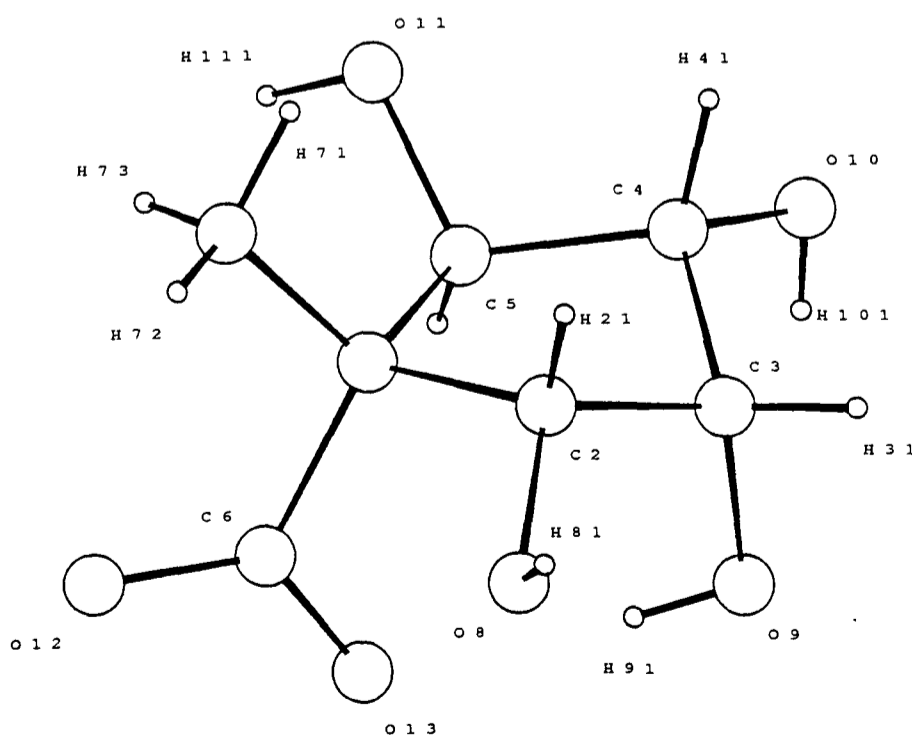
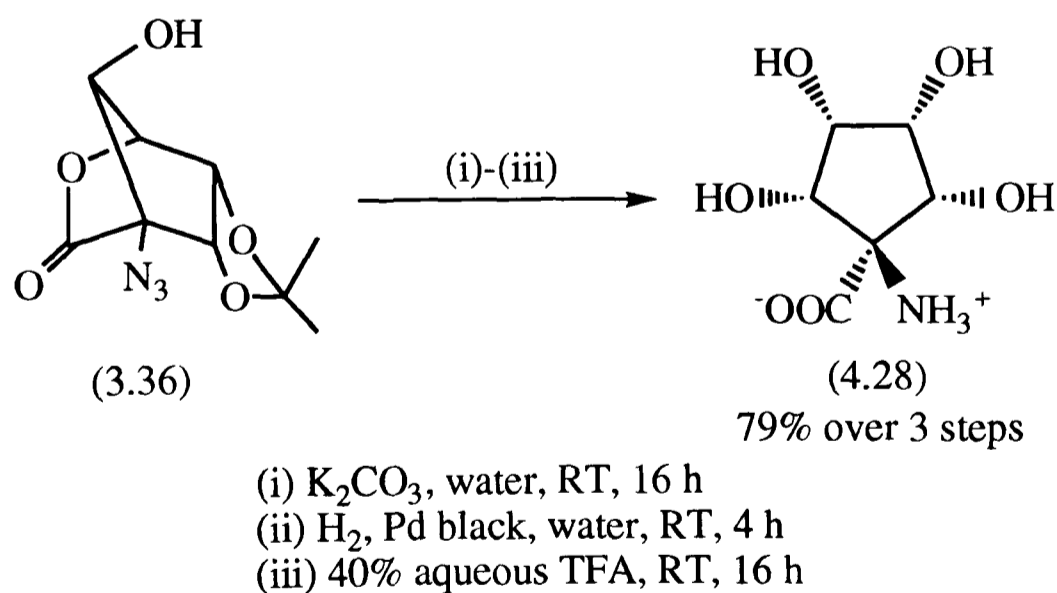


Fig 4.2.

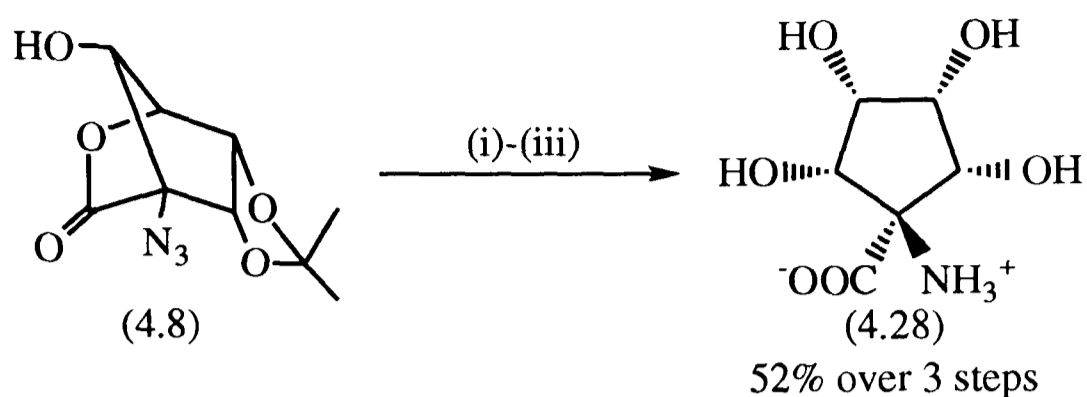
During the later stages of this work it became clear that removal of the acetonide protecting group from any of the azido carbocycles (4.1),⁶ (3.36) or (4.8), before ring opening of these materials was attempted, resulted in the formation of a mixture of products during the ring opening step. These products presumably arise from facile retro aldol reactions, which are unexpectedly found to occur even after the bridgehead azide functionality has been reduced, allowing in these cases epimerisation of both OH-7 and OH-5.⁷ Therefore an alternative synthetic route to cyclopentane amino acids was attempted in which ring opening was achieved before the removal of the acetonide protecting group.

Treatment of the second azido carbocycle (3.36) with aqueous potassium carbonate caused ring opening to give a single azido carboxylate (as seen by crude ¹H nmr). T.l.c. analysis of the reaction mixture indicated equilibration of the starting material (3.36) with the third azido carbocycle (4.8). The crude reaction material was then reduced with hydrogen in the presence of palladium black to produce a single amino acid (again as seen by ¹H nmr) and treatment with 40% aqueous TFA caused removal of the acetonide protecting group to yield the symmetric amino acid (4.28) as the sole reaction product (Scheme 4.21).



Scheme 4.21

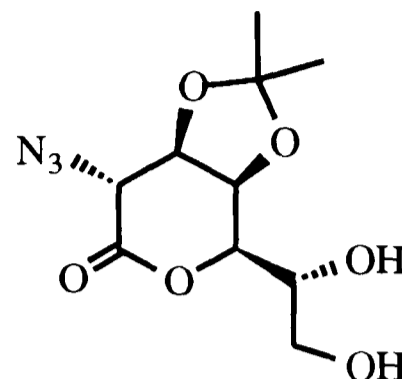
The third carbocycle (4.8) was subjected to an identical three step reaction sequence, and again the symmetric amino acid (4.28) was isolated as the sole reaction product (Scheme 4.22).



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

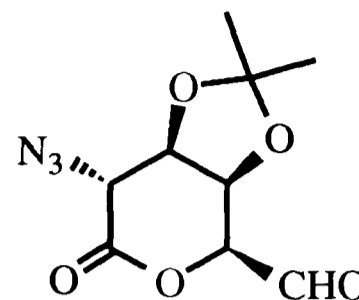
Scheme 4.22

The amino acid (4.28) was purified simply by ion exchange chromatography and possessed a zero optical rotation and characteristic 1H and ^{13}C nmr spectra as expected. Comparison of its 1H nmr spectra with those obtained from the mixtures of amino acids produced by the previous synthetic route confirmed this material to be one of the two minor contaminants. The formation of this material as the sole product from both the second (3.36) and third (4.8) azido carbocycles is consistent with the ring opening reactions described earlier (Schemes 4.11 and 4.14). Both of the amino acids (4.27) and (4.28) will be tested for potential biological activity.

Experimental.2-Azido-2-deoxy-3,4-O-isopropylidene-D-glycero-D-galacto-heptono-1,5-lactone (4.7).

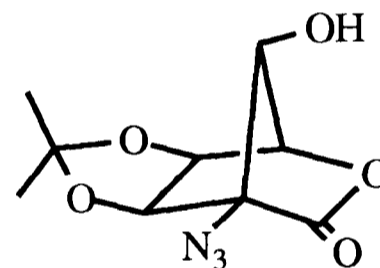
2-Azido-2-deoxy-3,4:5,6-di-O-isopropylidene-D-glycero-D-galacto-heptono-1,5-lactone (4.5) (1.74 g, 5.6 mmol) was stirred in a mixture of acetic acid (32 ml) and water (8 ml) at room temperature overnight. After 21 h, t.l.c. (hexane : ethyl acetate, 1 : 1) indicated complete consumption of starting material (R_f 0.9) and the formation of a single product (R_f 0.2). The solvent was removed, the residue co-evaporated with toluene (2 x 10 ml) and purified by flash chromatography (hexane : ethyl acetate, 1 : 1) to yield 2-azido-2-deoxy-3,4-O-isopropylidene-D-glycero-D-galacto-heptono-1,5-lactone (4.7) (1.20 g, 80%), as a white crystalline solid, m.p. 81-82 °C (ethyl acetate / hexane); $[\alpha]_D^{20} +184.0$ (c , 1.05 in CHCl_3); ν_{max} (KBr) 3430 (OH), 2114 (N_3), 1752 ($\text{C}=\text{O}$) cm^{-1} ; δ_{H} (CDCl_3) 1.37, 1.43 (6H, 2 x s, Me_2C), 3.85 (1H, dd, H-7, $J_{6,7}$ 4.5 Hz, $J_{7,7'}$ 11.4 Hz), 3.94 (1H, dd, H-7', $J_{6,7'}$ 3.1 Hz), 4.04 (1H, ddd, H-6, $J_{5,6}$ 8.6 Hz), 4.35 (1H, d, H-2, $J_{2,3}$ 2.2 Hz), 4.55 (1H, dd, H-3, $J_{3,4}$ 7.4 Hz), 4.66 (1H, dd, H-5, $J_{4,5}$ 1.8 Hz), 4.72 (1H, dd, H-4); δ_{C} (CDCl_3) 24.0, 25.7 (2 x q, Me_2C), 60.4 (d, C-2), 62.7 (t, C-7), 69.1, 70.5, 74.1, 75.5 (4 x d, C-3, C-4, C-5, C-6), 110.7 (s, CMe_2), 165.9 (s, C-1); m/z (NH_3 , DCI) 291 (MNH_4^+ , 100%), 274 (MH^+), 246 (MH^+-N_2). (Found: C, 44.20; H, 5.41; N, 15.00; $\text{C}_{10}\text{H}_{15}\text{O}_6\text{N}_3$ requires: C, 43.96; H, 5.53; N, 15.38%)

5-Azido-5-deoxy-3,4-*O*-isopropylidene-L-galacturono-2,6-lactone (4.6).

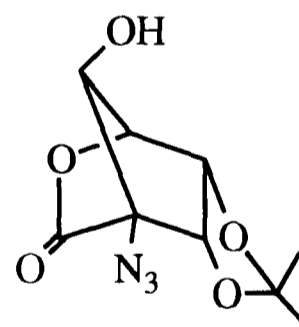


2-Azido-2-deoxy-3,4-*O*-isopropylidene-D-glycero-D-galacto-heptono-1,5-lactone (4.7) (492 mg, 1.80 mmol) and periodic acid (493 mg, 2.16 mmol) were stirred at room temperature in THF (30 ml). After 5 min a white precipitate had formed. The mixture was then preabsorbed onto silica and flushed through a short silica plug (eluant hexane : ethyl acetate, 1 : 1) to yield 5-azido-5-deoxy-3,4-*O*-isopropylidene-L-galacturono-2,6-lactone (4.6) (366 mg, 84%) as a white foam. This material was used in subsequent cyclisations without further purification or characterisation.

(1R,4R,5R,6R,7R)-4-Azido-5,6-*O*-isopropylidene-2-oxa-5,6,7-trihydroxy-bicyclo[2.2.1]heptan-3-one (4.1) and



(1S,4S,5R,6R,7R)-4-azido-5,6-*O*-isopropylidene-2-oxa-5,6,7-trihydroxy-bicyclo[2.2.1]heptan-3-one (3.36).



Method 1.

5-Azido-5-deoxy-3,4-*O*-isopropylidene-L-galacturono-2,6-lactone (4.6) (90 mg, 0.37 mmol), 18-crown-6 (20 mg, 0.07 mmol) and sodium azide (49 mg, 0.74 mmol) were stirred at room temperature in dry acetonitrile (5 ml) under nitrogen. After 18 h, t.l.c. (hexane : ethyl acetate, 1 : 1) indicated the formation of two products (R_f 0.6 and R_f 0.5). Ethyl acetate (20 ml) and brine (20 ml) were added and the mixture stirred for a further 5 min. The organic layer was removed and the aqueous layer washed with further ethyl acetate (2 x 40 ml). The organic extracts were combined, dried (magnesium sulphate), filtered, the solvent removed and the residue purified by flash

chromatography (hexane : ethyl acetate, 3 : 1) to yield (1R,4R,5R,6R,7R)-4-azido-5,6-O-isopropylidene-2-oxa-5,6,7-trihydroxy-bicyclo[2.2.1.]heptan-3-one (4.1) (15 mg, 17%, R_f 0.6) as an oil which crystallised on standing, m.p. 72 °C (on standing); $[\alpha]_D^{20}$ +29.6 (*c*, 1.0 in CHCl_3); ν_{max} (film) 3600 (br, OH), 2126 (N_3), 1800 ($\text{C}=\text{O}$) cm^{-1} ; δ_{H} (CDCl_3) 1.37, 1.55 (6H, 2 x s, Me_2C), 3.20 (1H, br s, D_2O exch, OH), 4.51, 4.60 (2H, 2 x d, H-5, H-6, $J_{5,6}$ 6.3 Hz), 4.72, 4.79 (2H, 2 x s, H-1, H-7); δ_{C} (CDCl_3) 23.9, 25.0 (2 x q, Me_2C), 71.6 (s, C-4), 75.7, 76.0, 76.4, 79.5 (4 x d, C-1, C-5, C-6, C-7), 115.8 (s, CMe_2), 170.4 (s, C-3); m/z (NH_3 , DCI) 259 (MNH_4^+ , 100%), 214 ($\text{MH}^+ - \text{N}_2$). (Found: C, 45.00; H, 4.87; N, 16.99; $\text{C}_9\text{H}_{11}\text{O}_5\text{N}_3$ requires: C, 44.82; H, 4.60; N, 17.42%);

and (1S,4S,5R,6R,7R)-4-azido-5,6-O-isopropylidene-2-oxa-5,6,7-trihydroxy-bicyclo[2.2.1.]heptan-3-one (3.36) (54 mg, 60%, R_f 0.5) identical in all respects to the material described in Chapter 3.

Method 2.

5-Azido-5-deoxy-3,4-O-isopropylidene-L-galacturono-2,6-lactone (4.6) (102 mg, 0.42 mmol) and 18-crown-6 (22 mg, 0.08 mmol) were stirred in dry acetonitrile (5 ml) at 0 °C under nitrogen. Potassium fluoride (50 mg, 0.84 mmol) was added and after 20 min t.l.c. (hexane : ethyl acetate, 1 : 1) indicated the formation of two products (R_f 0.6 and R_f 0.5), together with some baseline material. Ethyl acetate (15 ml) and semi-saturated brine (10 ml) were added and the mixture stirred at 0 °C for a further 5 min. The organic layer was removed and the aqueous layer washed with ethyl acetate (2 x 10 ml). The organic extracts were then combined, dried (magnesium sulphate), filtered, the solvent removed and the residue purified by flash chromatography (hexane : ethyl acetate, 1 : 1) to yield (1R,4R,5R,6R,7R)-4-azido-5,6-O-isopropylidene-2-oxa-5,6,7-trihydroxy-bicyclo[2.2.1.]heptan-3-one (4.1) (5 mg, 5%, R_f 0.6);

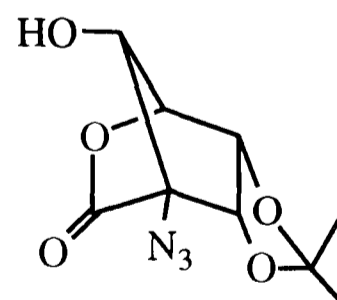
and (1S,4S,5R,6R,7R)-4-azido-5,6-O-isopropylidene-2-oxa-5,6,7-trihydroxy-bicyclo[2.2.1.]heptan-3-one (3.36) (17 mg, 17%, R_f 0.5), both identical to the materials described above.

Method 3.

5-Azido-5-deoxy-3,4-O-isopropylidene-D-alturono-2,6-lactone (1.39) (438 mg, 1.8 mmol), 18-crown-6 (50 mg, 0.19 mmol) and sodium azide (240 mg, 3.6 mmol) were stirred at room temperature in dry acetonitrile (20 ml) under nitrogen. After 50 h, t.l.c. (hexane : ethyl acetate, 1 : 1) indicated the formation of two products (R_f 0.6 and R_f 0.5) together with some starting material (R_f 0.1). Ethyl acetate (50 ml) and brine (30 ml) were added and the mixture stirred for a further 5 min. The organic layer was removed and the aqueous layer washed with further ethyl acetate (2 x 40 ml). The organic extracts were combined, dried (magnesium sulphate), filtered, the solvent removed and purified by flash chromatography (hexane : ethyl acetate, 3 : 1) to yield (1R,4R,5R,6R,7R)-4-azido-5,6-O-isopropylidene-2-oxa-5,6,7-trihydroxy-bicyclo[2.2.1.]heptan-3-one (4.1) (75 mg, 17%, R_f 0.6);

and (1S,4S,5R,6R,7R)-4-azido-5,6-O-isopropylidene-2-oxa-5,6,7-trihydroxy-bicyclo[2.2.1.]heptan-3-one (3.36) (230 mg, 53%, R_f 0.5), both identical to the materials described above.

(1S,4S,5R,6R,7S)-4-Azido-5,6-O-isopropylidene-2-oxa-5,6,7-trihydroxy-bicyclo[2.2.1.]heptan-3-one (4.8).

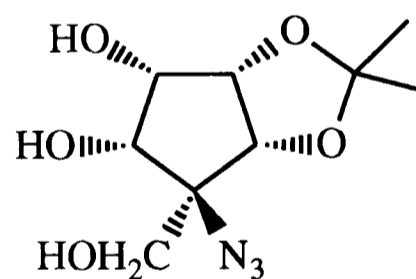


(1S,4S,5R,6R,7R)-4-Azido-5,6-O-isopropylidene-2-oxa-5,6,7-trihydroxy-bicyclo[2.2.1.]heptan-3-one (3.36) (700 mg, 2.9 mmol) was stirred in liquid ammonia (20 ml) at $-45\text{ }^{\circ}\text{C}$ in a sealed Fischer-Porter Bottle. The reaction mixture was allowed to warm to room temperature, under pressure, 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 (30 ml) was added and the mixture transferred to a round bottomed flask. At this point t.l.c. (hexane : ethyl acetate, 1 : 1) indicated the formation of a major product (R_f 0.15) together with some remaining starting material (R_f 0.5). The solvent was then removed and the residue purified by flash chromatography to yield (1S,4S,5R,6R,7S)-4-azido-5,6-O-isopropylidene-2-oxa-5,6,7-trihydroxy-bicyclo[2.2.1.]heptan-3-one (4.8) (443 mg, 63%, 82% based on recovered starting material, R_f 0.15) as a white crystalline solid, m.p. 127-128 °C (ethyl acetate / hexane); $[\alpha]_D^{20}$ +44.8 (*c*, 0.92 in EtOH); ν_{\max} (KBr) 3519 (br, OH), 2143 (N₃), 1790 (C=O) cm⁻¹; δ_H (CD₃CN) 1.29, 1.40 (6H, 2 x s, Me₂C), 4.31 (1H, d, H-7, $J_{7,OH}$ 4.2 Hz), 4.55 (1H, d, D₂O exch, OH), 4.60 (1H, dd, H-5, $J_{1,5}$ 1.5 Hz, $J_{5,6}$ 7.6 Hz), 4.68 (1H, m, H-1), 4.71 (1H, dd, H-6, $J_{1,6}$ 2.3 Hz); δ_C (CD₃CN) 24.2, 24.7 (2 x q, Me₂C), 74.7, 77.0, 78.6, 80.4 (4 x d, C-1, C-5, C-6, C-7), 75.8 (s, C-4), 114.9 (s, CMe₂), 170.2 (s, C-3); *m/z* (NH₃, DCI) 259 (MNH₄⁺), 231 (MNH₄⁺-N₂), 214 (MH⁺-N₂, 100%). (Found: C, 44.86; H, 4.57; N, 17.56; C₉H₁₁O₅N₃ requires: C, 44.82; H, 4.60; N, 17.42%);

together with some recovered starting material (3.36) (160 mg, 23%).

(1S,2R,3S,4S,5S)-1-Azido-1-(hydroxymethyl)-2,3-O-isopropylidene-2,3,4,5-tetrahydroxy-cyclopentane (4.9).



Method 1.

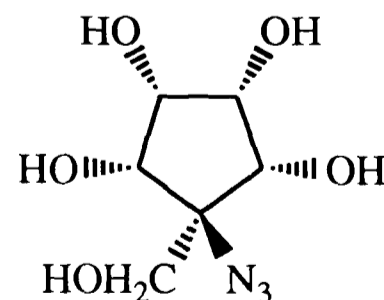
(1S,4S,5R,6R,7R)-4-Azido-5,6-O-isopropylidene-2-oxa-5,6,7-trihydroxy-bicyclo[2.2.1.]heptan-3-one (3.36) (51 mg, 0.21 mmol) and sodium borohydride (16 mg, 0.42 mmol) were stirred together in ethanol (4 ml) at room temperature. After 16 h, ammonium chloride (30 mg) and then methanol (5 ml) were added. The reaction mixture was stirred for a further 10 min and then co-evaporated with methanol (2 x 5 ml). At this point t.l.c. (hexane : ethyl acetate, 1 : 2) indicated the formation of a single product (R_f 0.5). The residue was then preabsorbed onto silica and purified by flash chromatography (hexane : ethyl acetate, 1 : 2) to yield (1S,2R,3S,4S,5S)-1-

azido-1-(hydroxymethyl)-2,3-*O*-isopropylidene-2,3,4,5-tetrahydroxy-cyclopentane (4.9) (43 mg, 83%) as a colourless oil; $[\alpha]_D^{20}$ -7.0 (*c*, 0.63 in CHCl₃); ν_{\max} (film) 3392 (br, OH), 2104 (N₃) cm⁻¹; δ_H (CDCl₃) 1.33, 1.51 (6H, 2 x s, Me₂C), 3.96 (1H, d, J 4.7 Hz), 4.15 (1H, d, H-6, J_{6,6'} 12.2 Hz), 4.22 (1H, m), 4.25 (1H, d, H-6'), 4.40 (1H, dd, J 1.3 Hz, J' 5.8 Hz), 4.70 (1H, t, J 5.7 Hz); δ_C (CDCl₃) 23.8, 25.9 (2 x q, Me₂C), 62.1 (t, C-6), 71.5, 76.2, 79.4, 82.6 (4 x d, C-2, C-3, C-4, C-5), 71.6 (s, C-1), 112.5 (s, CMe₂); *m/z* (NH₃, DCI) 263 (MNH₄⁺), 246 (MH⁺), 218 (MH⁺-N₂, 100%). (Found: C, 44.22; H, 6.37; N, 16.89; C₉H₁₅O₅N₃ requires: C, 44.08; H, 6.17; N, 17.13%).

Method 2.

(1*S*,4*S*,5*R*,6*R*,7*S*)-4-Azido-5,6-*O*-isopropylidene-2-oxa-5,6,7-trihydroxy-bicyclo[2.2.1.]heptan-3-one (4.8) (41 mg, 0.17 mmol) and sodium borohydride (13 mg, 0.34 mmol) were stirred together in ethanol (5 ml) at room temperature. After 12 h, ammonium chloride (30 mg) and then methanol (5 ml) were added. The reaction mixture was stirred for a further 10 min and then co-evaporated with methanol (2 x 5 ml). At this point t.l.c. (hexane : ethyl acetate, 1 : 2) indicated the formation of a single product (R_f 0.5). The residue was then preabsorbed onto silica and purified by flash chromatography (hexane : ethyl acetate, 1 : 2) to yield (1*S*,2*R*,3*S*,4*S*,5*S*)-1-azido-1-(hydroxymethyl)-2,3-*O*-isopropylidene-2,3,4,5-tetrahydroxy-cyclopentane (4.9) (37 mg, 89%) as a colourless oil, identical to the material described above.

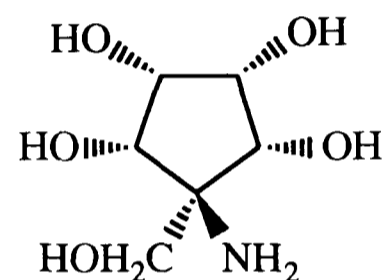
1β-Azido-1α-(hydroxymethyl)-2α,3α,4α,5α-tetrahydroxy-cyclopentane (4.10).



(1*S*,2*R*,3*S*,4*S*,5*S*)-1-Azido-1-(hydroxymethyl)-2,3-*O*-isopropylidene-2,3,4,5-tetrahydroxy-cyclopentane (4.9) (106 mg, 0.43 mmol) was stirred in a mixture of trifluoroacetic acid (2 ml) and water (3 ml) at room temperature. After 1.5 h, t.l.c. (chloroform : methanol, 4 : 1) indicated complete consumption of starting material

(R_f 0.8) and the formation of a single product (R_f 0.3). The solvent was removed, the residue co-evaporated with toluene and purified by flash chromatography (chloroform : methanol, 4 : 1) to yield 1 β -azido-1 α -(hydroxymethyl)-2 α ,3 α ,4 α ,5 α -tetrahydroxy-cyclopentane (4.10) (75 mg, 84%) as a colourless oil; $[\alpha]_D^{20} +0.0$ (c , 1.0 in MeOH); ν_{\max} (film) 3369 (br, OH), 2101 (N_3) cm^{-1} ; δ_H (CD_3OD) 3.88 (2H, dd, J 2.1 Hz, J' 3.8 Hz), 4.05 (2H, dd, J 2.1 Hz, J' 3.8 Hz), 4.06 (2H, s, H-6, H-6'); δ_C (CD_3OD) 61.9 (t, C-6), 71.4, 76.1 (2 x d, C-2, C-3, C-4, C-5), 73.0 (s, C-1); m/z (NH_3 , DCI) 223 (MNH_4^+ , 100%), 206 (MH^+), 178 (MH^+-N_2). (Found: C, 35.38; H, 5.48; N, 20.25; $C_6H_{11}O_5N_3$ requires: C, 35.12; H, 5.40; N, 20.48%).

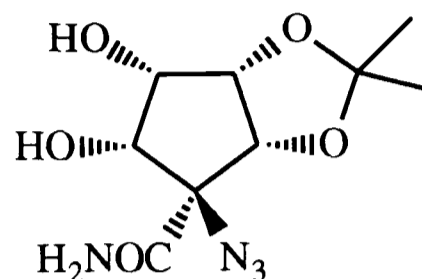
1 β -Amino-1 α -(hydroxymethyl)-2 α ,3 α ,4 α ,5 α -tetrahydroxy-cyclopentane (4.11).



1 β -Azido-1 α -(hydroxymethyl)-2 α ,3 α ,4 α ,5 α -tetrahydroxy-cyclopentane (4.10) (45 mg, 0.22 mmol) and palladium black (2 mg) were stirred at room temperature in methanol (3 ml). The solution was degassed and stirred under an atmosphere of hydrogen for 16 h. After this time t.l.c. (chloroform : methanol, 4 : 1) indicated complete consumption of starting material (R_f 0.3) and formation of a product at the baseline. The reaction mixture was filtered through Celite, the solvent removed and the residue purified by ion exchange chromatography (Dowex 50W-X8[H⁺], eluant 1.0 M aqueous ammonia) to yield 1 β -amino-1 α -(hydroxymethyl)-2 α ,3 α ,4 α ,5 α -tetrahydroxy-cyclopentane (4.11) (36 mg, 92%) as a very hygroscopic amorphous solid; ν_{\max} (KBr) 3400 (br, OH) cm^{-1} ; δ_H (D_2O) 3.71 (2H, s, H-6, H-6'), 3.74 (2H, dd, J 2.1 Hz, J' 3.8 Hz), 4.09 (2H, dd, J 2.1 Hz, J' 3.8 Hz); δ_C (D_2O) 63.7 (t, C-6), 64.5 (s, C-1), 72.3, 78.7 (2 x d, C-2, C-3, C-4, C-5); m/z (NH_3 , DCI) 180 (MH^+ , 100%). A small portion of this material was then converted to the hydrochloride salt (4.12) as follows: 1M aqueous HCl (1ml) was added and the mixture shaken. The solvent was removed and the residue freeze-dried to yield the hydrochloride salt (4.12), as a hygroscopic colourless solid; δ_H (D_2O) 3.91 (2H, s, H-6, H-6'), 4.02 (2H,

dd, J 2.1 Hz, J' 4.2 Hz), 4.05 (2H, dd, J 2.1 Hz, J' 4.2 Hz); δ_C (D₂O) 60.4 (t, C-6), 67.7 (s, C-1), 71.7, 75.3 (2 x d, C-2, C-3, C-4, C-5). (Found: C, 33.76; H, 6.68; N, 6.13; C₆H₁₄O₅NCl requires: C, 33.42; H, 6.54; N, 6.50%).

(1S,2R,3S,4S,5S)-1-Azido-2,3-O-isopropylidene-2,3,4,5-tetrahydroxy-cyclopentane carboxamide
(4.13).



Method 1.

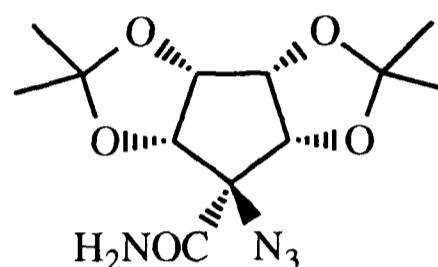
(1S,4S,5R,6R,7R)-4-Azido-5,6-O-isopropylidene-2-oxa-5,6,7-trihydroxy-bicyclo [2.2.1.] heptan-3-one (3.36) (108 mg, 0.45 mmol) was added to methanol (10 ml), that had been saturated with ammonia, and stirred at room temperature under nitrogen. After 30 min, t.l.c. (ethyl acetate) indicated complete consumption of starting material (R_f 0.8), and the formation of a major product (R_f 0.7). The crude reaction mixture was preabsorbed onto silica and purified by flash chromatography (hexane : ethyl acetate, 1 : 2) to yield (1S,2R,3S,4S,5S)-1-azido-2,3-O-isopropylidene-2,3,4,5-tetrahydroxy-cyclopentane carboxamide (4.13) (36 mg, 31%) as a white crystalline solid, m.p. 147-148 °C (ethyl acetate / hexane); $[\alpha]_D^{20}$ +0.4 (c, 1.02 in MeOH); ν_{max} (KBr) 3430-3200 (br, OH, NH), 2109 (N₃), 1676 (amide) cm⁻¹; δ_H (CD₃CN) 1.31, 1.46 (6H, 2 x s, Me₂C), 3.46 (1H, d, OH, J 10.0 Hz), 3.78 (1H, d, OH, J 5.3 Hz), 3.96 (1H, br t, J 4.9 Hz), 4.15 (1H, m), 4.52 (1H, dd, J 1.5 Hz, J' 5.9 Hz), 4.68 (1H, dd, J 0.5 Hz, J' 5.9 Hz); δ_C (CD₃OD) 22.9, 24.5 (2 x q, Me₂C), 71.1 (s, C-1), 71.5, 76.4, 79.1, 83.0 (4 x d, C-2, C-3, C-4, C-5), 112.6 (s, CMe₂), 172.0 (s, C-6); m/z (NH₃, DCI) 259 (MH⁺, 100%). (Found: C, 41.97; H, 5.49; N, 21.66; C₉H₁₄O₅N₄ requires: C, 41.86; H, 5.46; N, 21.70%).

Method 2.

(1S,4S,5R,6R,7S)-4-Azido-5,6-O-isopropylidene-2-oxa-5,6,7-trihydroxy-bicyclo[2.2.1.]heptan-3-one (4.8) (110 mg, 0.45 mmol) was added to a solution of

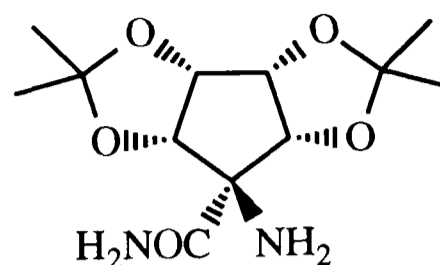
methanol (10 ml), that had been saturated with ammonia, and stirred at room temperature under nitrogen. After 30 min, t.l.c. (ethyl acetate) indicated the formation of a major product (R_f 0.7). The crude reaction mixture was preabsorbed onto silica and purified by flash chromatography (hexane : ethyl acetate, 1 : 1) to yield (1S,2R,3S,4S,5S)-1-azido-2,3-O-isopropylidene-2,3,4,5-tetrahydroxy-cyclopentane carboxamide (4.13) (57 mg, 48%), identical in all respects to the material described above.

(1 β ,2 α ,3 α ,4 α ,5 α)-1-Azido-2,3:4,5-di-O-isopropylidene-2,3,4,5-tetrahydroxy-cyclopentane carboxamide (4.14).



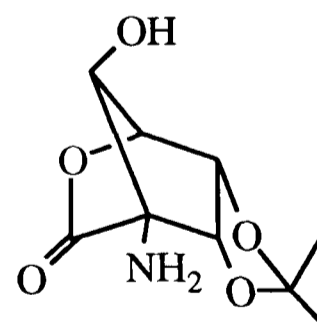
(1S,2R,3S,4S,5S)-1-Azido-2,3-O-isopropylidene-2,3,4,5-tetrahydroxy-cyclopentane carboxamide (4.13) (109 mg, 0.42 mmol) and camphorsulphonic acid (10 mg, 0.04 mmol) were stirred in dry acetone (20 ml) at 40 °C under nitrogen. 2,2-Dimethoxypropane (0.26 ml, 2.1 mmol) was added and the mixture stirred for 3.5 h. After this time, t.l.c. (hexane : ethyl acetate, 1 : 1) indicated complete consumption of starting material (R_f 0.1) and the formation of a single product (R_f 0.6). Triethylamine (1 ml) was added, the solvent removed and the residue purified by flash chromatography (hexane : ethyl acetate, 2 : 1) to yield (1 β ,2 α ,3 α ,4 α ,5 α)-1-azido-2,3:4,5-di-O-isopropylidene-2,3,4,5-tetrahydroxy-cyclopentane carboxamide (4.14) (101 mg, 80%) as a white crystalline solid, m.p. 218-220 °C (decomp, chloroform / hexane); $[\alpha]_D^{20}$ +0.0 (c , 0.93 in CHCl_3); ν_{max} (KBr) 3438, 3321 (NH_2), 2105 (N_3), 1694 (amide) cm^{-1} ; δ_{H} (CDCl_3) 1.45, 1.63 (12H, 2 x s, 2 x Me_2C), 4.55 (2H, dd, J 1.9 Hz, J' 3.8 Hz), 4.67 (2H, dd, J 1.9 Hz, J' 3.8 Hz), 6.42 (1H, br, NH), 7.16 (1H, br, NH); δ_{C} (CDCl_3) 24.2, 25.3 (2 x q, 2 x Me_2C), 69.4 (s, C-1), 79.1, 85.3 (2 x d, C-2, C-3, C-4, C-5), 113.9 (s, 2 x CMe_2), 169.6 (s, C-6); m/z (NH_3 , DCI) 316 (MNH_4^+), 299 (MH^+ , 100%). (Found: C, 48.56; H, 5.99; N, 18.87; $\text{C}_{12}\text{H}_{18}\text{O}_5\text{N}_4$ requires: C, 48.32; H, 6.08; N, 18.78%).

(1 β ,2 α ,3 α ,4 α ,5 α)-1-Amino-2,3:4,5-di-*O*-isopropylidene-2,3,4,5-tetrahydro-cyclopentane carboxamide (4.15).



(1 β ,2 α ,3 α ,4 α ,5 α)-1-Azido-2,3:4,5-di-*O*-isopropylidene-2,3,4,5-tetrahydro-cyclopentane carboxamide (4.14) (96 mg, 0.32 mmol) and palladium black (3 mg) were stirred in ethanol (10 ml) at room temperature. The solution was degassed and then stirred under hydrogen for 19 h. After this time, t.l.c. (ethyl acetate) indicated the formation of a single product at the baseline. The reaction mixture was filtered through Celite and the solvent removed to yield (1 β ,2 α ,3 α ,4 α ,5 α)-1-amino-2,3:4,5-di-*O*-isopropylidene-2,3,4,5-tetrahydro-cyclopentane carboxamide (4.15) (87 mg, crude, quantitative) as a hygroscopic white solid, m.p. >236 °C (decomp, methanol / ether); $[\alpha]_D^{20} +0.0$ (c, 0.65 in MeOH); ν_{\max} (KBr) 3378 (NH), 1681 (amide) cm^{-1} ; δ_{H} (CD₃OD) 1.34, 1.58 (12H, 2 x s, 2 x Me₂C), 4.45 (2H, dd, J 1.9 Hz, J' 3.8 Hz), 4.69 (2H, dd, J 1.9 Hz, J' 3.8 Hz); δ_{C} (CD₃OD) 23.0, 24.5 (2 x q, 2 x Me₂C), 62.8 (s, C-1), 79.3, 87.2 (2 x d, C-2, C-3, C-4, C-5), 113.0 (s, 2 x CMe₂), 174.3 (s, C-6); *m/z* (NH₃, DCI) 273 (MH⁺, 100%).

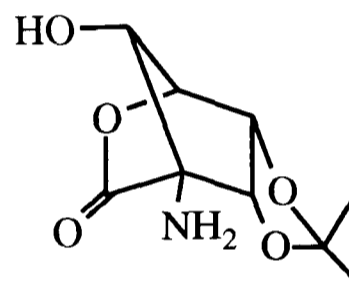
(1S,4S,5R,6R,7R)-4-Amino-5,6-*O*-isopropylidene-2-oxa-5,6,7-trihydroxy-bicyclo[2.2.1]heptan-3-one (4.16).



(1S,4S,5R,6R,7R)-4-Azido-5,6-*O*-isopropylidene-2-oxa-5,6,7-trihydroxy-bicyclo[2.2.1]heptan-3-one (3.36) (490 mg, 2.0 mmol) and palladium black (11 mg) were stirred in a mixture of ethanol (10 ml) and water (2 ml) at room temperature. The solution was degassed and then stirred under hydrogen for 2 h. After this time, t.l.c. (chloroform : methanol, 7 : 1) indicated the formation of a single product (*R_f* 0.4). The reaction mixture was filtered through Celite, preabsorbed onto silica, and purified by flash chromatography (chloroform : methanol, 7 : 1) to yield

(1S,4S,5R,6R,7R)-4-amino-5,6-O-isopropylidene-2-oxa-5,6,7-trihydroxy-bicyclo[2.2.1.]heptan-3-one (4.16) (426 mg, 97%) as a white crystalline solid, m.p. 185-186 °C (methanol / ether); $[\alpha]_{\text{D}}^{20} +113.5$ (*c*, 0.55 in MeOH); ν_{max} (KBr) 3330-3200 (br, OH, NH), 1793 (C=O) cm^{-1} ; δ_{H} (d_6 -DMSO) 1.27, 1.31 (6H, 2 x s, Me_2C), 2.10 (2H, br s, NH_2), 4.12 (1H, m, H-7), 4.55 (1H, m, H-1), 4.64 (1H, dd, H-5, $J_{1,5}$ 1.2 Hz, $J_{5,6}$ 7.4 Hz), 4.91 (1H, dd, H-6, $J_{1,6}$ 2.4 Hz), 6.32 (1H, d, OH, $J_{7,\text{OH}}$ 3.6 Hz); δ_{C} (d_6 -DMSO) 24.5, 25.1 (2 x q, Me_2C), 70.4 (s, C-4), 75.5, 78.6, 81.5, 82.4 (4 x d, C-1, C-5, C-6, C-7), 114.4 (s, CMe_2), 172.7 (s, C-3); m/z (NH_3 , CI) 233 (MNH_4^+ , 100%), 216 (MH^+). (Found: C, 50.04; H, 6.09; N, 6.51; $\text{C}_9\text{H}_{13}\text{O}_5\text{N}$ requires: C, 50.23; H, 6.09; N, 6.51%).

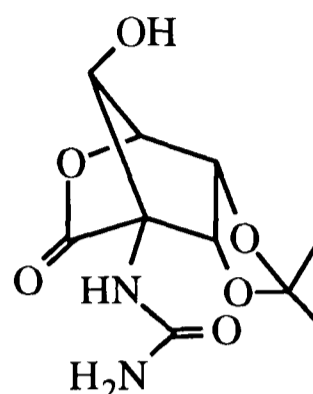
(1R,4S,5R,6R,7S)-4-Amino-5,6-O-isopropylidene-2-oxa-5,6,7-trihydroxy-bicyclo[2.2.1.]heptan-3-one (4.17).



(1S,4S,5R,6R,7S)-4-Azido-5,6-O-isopropylidene-2-oxa-5,6,7-trihydroxy-bicyclo[2.2.1.]heptan-3-one (4.8) (178 mg, 0.74 mmol) and palladium black (4 mg) were stirred in a mixture of ethanol (10 ml) and water (2 ml) at room temperature. The solution was degassed and then stirred under hydrogen for 3 h. After this time, t.l.c. (ethyl acetate) indicated complete consumption of starting material (R_f 0.7) and the formation of a single product (R_f 0.1). The reaction mixture was filtered through Celite, preabsorbed onto silica, and purified by flash chromatography (ethyl acetate : methanol, 9 : 1) to yield (1R,4S,5R,6R,7S)-4-amino-5,6-O-isopropylidene-2-oxa-5,6,7-trihydroxy-bicyclo[2.2.1.]heptan-3-one (4.17) (120 mg, 76%) as a white crystalline solid, m.p. 188-190 °C (methanol / ethyl acetate); $[\alpha]_{\text{D}}^{20} +82.7$ (*c*, 0.66 in MeOH); ν_{max} (KBr) 3470-3270 (br, OH, NH), 1791 (C=O) cm^{-1} ; δ_{H} (CD_3OD) 1.29, 1.39 (6H, 2 x s, Me_2C), 4.05 (1H, s, H-7), 4.55 (1H, dd, H-5, $J_{1,5}$ 1.2 Hz, $J_{5,6}$ 7.5 Hz), 4.56 (1H, dd, H-1, $J_{1,6}$ 2.2 Hz), 4.72 (1H, dd, H-6); δ_{C} (CD_3OD) 23.8, 24.4 (2 x q, Me_2C), 71.5 (s, C-4), 75.2, 78.2, 79.1, 80.0 (4 x d, C-1, C-5, C-6, C-7), 114.3 (s,

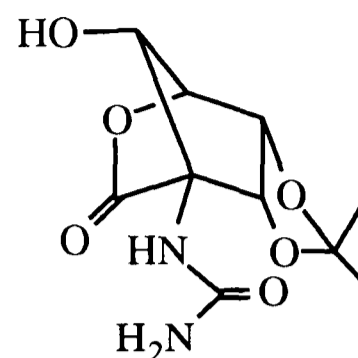
$\underline{\text{CMe}_2}$), 175.7 (s, C-3); m/z (NH_3 , DCI) 233 (MNH_4^+ , 100%), 216 (MH^+). (Found: C, 50.16; H, 6.01; N, 6.71; $\text{C}_9\text{H}_{13}\text{O}_5\text{N}$ requires: C, 50.23; H, 6.09; N, 6.51%).

(1S,4S,5R,6R,7R)-5,6-O-Isopropylidene-2-oxa-5,6,7-trihydroxy-4-ureido-bicyclo[2.2.1]heptan-3-one (4.18).



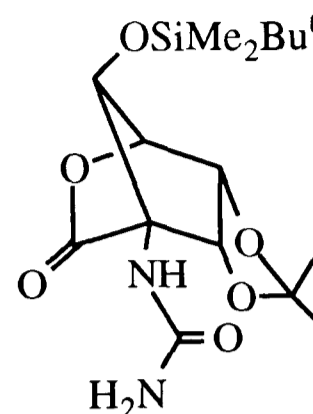
(1S,4S,5R,6R,7R)-4-Amino-5,6-O-isopropylidene-2-oxa-5,6,7-trihydroxy-bicyclo[2.2.1]heptan-3-one (4.16) (426 mg, 2.0 mmol) and potassium cyanate (554 mg, 6.8 mmol) were stirred in acetic acid (20 ml) at room temperature under nitrogen. After 1 h, t.l.c. (ethyl acetate) indicated complete consumption of starting material (R_f 0.2) and the formation of a single product (R_f 0.4). The crude reaction mixture was preabsorbed onto silica and the residue purified by flash chromatography (ethyl acetate : hexane, 2 : 1) to yield (1S,4S,5R,6R,7R)-5,6-O-isopropylidene-2-oxa-5,6,7-trihydroxy-4-ureido-bicyclo[2.2.1]heptan-3-one (4.18) (370 mg, 72%) as a white crystalline solid, m.p. 208-212 °C (decomp, methanol / ether); $[\alpha]_D^{20} +100.3$ (c , 0.39 in MeOH); ν_{max} (KBr) 3450-3200 (br, OH, NH), 1791 (C=O), 1655 (urea) cm^{-1} ; δ_{H} (CD_3CN) 1.34, 1.39 (6H, 2 x s, Me_2C), 4.59 (1H, d, H-7, $J_{1,7}$ 2.6 Hz), 4.70 (1H, dt, H-1, $J_{1,5}$ 1.3 Hz, $J_{1,6}$ 2.5 Hz), 5.11 (1H, dd, H-5, $J_{5,6}$ 7.4 Hz), 5.17 (1H, dd, H-6), 5.23 (2H, br, NH_2), 6.14 (1H, br s, OH), 6.65 (1H, br s, NH); δ_{C} (d_6 -DMSO) 25.4, 26.0 (2 x q, Me_2C), 71.2 (s, C-4), 76.7, 79.1, 80.1, 80.6 (4 x d, C-1, C-5, C-6, C-7), 116.1 (s, $\underline{\text{CMe}_2}$), 159.0 (s, urea), 170.8 (s, C-3); m/z (NH_3 , CI) 276 (MNH_4^+), 259 (MH^+ , 100%). (Found: C, 46.69; H, 5.22; N, 10.84; $\text{C}_{10}\text{H}_{14}\text{O}_6\text{N}_2$ requires: C, 46.51; H, 5.46; N, 10.85%).

(1S,4S,5R,6R,7S)-5,6-O-Isopropylidene-2-oxa-5,6,7-trihydroxy-4-ureido-bicyclo[2.2.1]heptan-3-one (4.19).



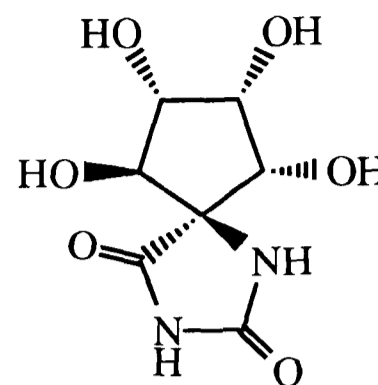
(1S,4S,5R,6R,7S)-4-Amino-5,6-O-isopropylidene-2-oxa-5,6,7-trihydroxy-bicyclo[2.2.1]heptan-3-one (4.17) (120 mg, 0.56 mmol) and potassium cyanate (136 mg, 1.7 mmol) were stirred in acetic acid (10 ml) at room temperature under nitrogen. After 20 min, t.l.c. (ethyl acetate) indicated complete consumption of starting material (R_f 0.15) and the formation of a single product (R_f 0.35). The crude reaction mixture was preabsorbed onto silica and the residue purified by flash chromatography (ethyl acetate : methanol, 20 : 1) to yield (1S,4S,5R,6R,7S)-5,6-O-isopropylidene-2-oxa-5,6,7-trihydroxy-4-ureido-bicyclo[2.2.1]heptan-3-one (4.19) (112 mg, 78%) as a white crystalline solid, m.p. >230 °C (decomp, methanol / ether); $[\alpha]_D^{20} +69.1$ (c, 0.47 in DMSO); ν_{\max} (KBr) 3448-3378 (br, OH, NH), 1790 (C=O), 1683 (urea) cm^{-1} ; δ_{H} (d_6 -DMSO) 1.22, 1.30 (6H, 2 x s, Me_2C), 4.56 (1H, d, H-7, $J_{7,\text{OH}}$ 4.3 Hz), 4.61 (1H, br m, H-1), 4.73 (1H, dd, H-6, $J_{1,6}$ 2.3 Hz, $J_{5,6}$ 7.7 Hz), 5.07 (1H, dd, H-5, $J_{1,5}$ 1.1 Hz), 5.94 (2H, s, NH_2), 6.33 (1H, d, OH, D_2O exch), 6.48 (1H, br s, NH); δ_{C} (d_6 -DMSO) 25.3, 25.8 (2 x q, Me_2C), 72.2 (s, C-4), 74.3, 75.3, 76.7, 80.8 (4 x d, C-1, C-5, C-6, C-7), 113.5 (s, CMe_2), 158.5 (s, urea), 173.3 (s, C-3); m/z (NH_3 , CI) 276 (MNH_4^+), 259 (MH^+ , 100%). (Found: C, 46.66; H, 5.59; N, 10.83; $\text{C}_{10}\text{H}_{14}\text{O}_6\text{N}_2$ requires: C, 46.51; H, 5.46; N, 10.85%).

(1R,4R,5R,6R,7R)-7-O-tert-Butyldimethylsilyl-5,6-O-isopropylidene-2-oxa-5,6,7-trihydroxy-4-ureido-bicyclo[2.2.1]heptan-3-one (4.20).



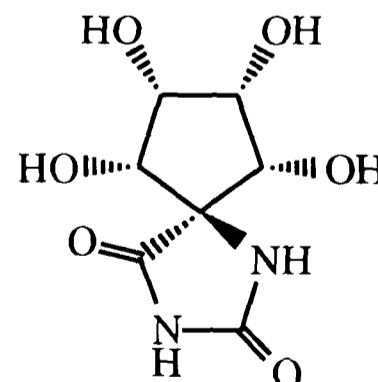
(1S,4S,5R,6R,7R)-5,6-O-Isopropylidene-2-oxa-5,6,7-trihydroxy-4-ureido-bicyclo[2.2.1]heptan-3-one (4.18) (78 mg, 0.3 mmol) was stirred in dry pyridine (4 ml) at 0 °C under nitrogen. *tert*-Butyldimethylsilyltrifluoromethanesulphonate (76 µl, 0.33 mmol) was added and the reaction mixture allowed to warm to room temperature. After 10 min, t.l.c. (hexane : ethyl acetate, 1 : 1) indicated complete consumption of starting material (R_f 0.1) and the formation of a major product (R_f 0.3). The solvent was removed and the residue dissolved in ethyl acetate (10 ml). This was then washed sequentially with 1M HCl (10 ml), water (10 ml), brine (10 ml), dried (magnesium sulphate), filtered, the solvent removed and the residue purified by flash chromatography (hexane : ethyl acetate, 1 : 1) to yield (1R,4R,5R,6R,7R)-7-O-tert-butyl dimethylsilyl-5,6-O-isopropylidene-2-oxa-5,6,7-trihydroxy-4-ureido-bicyclo[2.2.1]heptan-3-one (4.20) (65 mg, 58%) as a white crystalline solid, m.p. 125-130 °C (chloroform / hexane); $[\alpha]_D^{20} +69.7$ (c , 0.74 in CHCl_3); ν_{max} (KBr) 3386-3200 (br, NH), 1804 (C=O), 1672 (urea) cm^{-1} ; δ_{H} (d_6 -DMSO) 0.05, 0.07 (6H, 2 x s, Me_2Si), 0.85 (9H, s, Bu^t), 1.31, 1.33 (6H, 2 x s, Me_2C), 4.69 (1H, m, H-1), 4.77 (1H, dd, H-5, $J_{1,5}$ 1.0 Hz, $J_{5,6}$ 7.4 Hz), 4.91 (1H, dd, H-6, $J_{1,6}$ 2.5 Hz), 5.09 (1H, d, H-7, $J_{1,7}$ 2.5 Hz), 5.63 (2H, br, NH_2), 7.06 (1H, br s, NH); δ_{C} (CDCl_3) -5.7, -5.2 (2 x q, Me_2Si), 17.6 (s, Me_3CSi), 25.1, 25.6 (2 x q, Me_2C), 25.4 (q, Me_3C), 71.4 (s, C-4), 77.0, 79.4, 80.4, 80.9 (4 x d, C-1, C-5, C-6, C-7), 117.4 (s, CMe_2), 158.3 (s, urea), 171.7 (s, C-3); m/z (NH_3 , DCI) 373 (MH^+ , 100%). (Found: C, 51.84; H, 7.37; N, 7.52; $\text{C}_{16}\text{H}_{28}\text{O}_6\text{N}_2$ requires: C, 51.59; H, 7.58; N, 7.52%).

(5S,6R,7R,8S,9R)-1,3-Diaza-6,7,8,9-tetrahydroxy-spiro[4.4.]nonane-2,4-dione (4.21).



(1S,4S,5R,6R,7R)-5,6-*O*-Isopropylidene-2-oxa-5,6,7-trihydroxy-4-ureido-bicyclo[2.2.1.]heptan-3-one (4.18) (109 mg, 0.4 mmol) was stirred at room temperature in dry methanol (5 ml). To this was added a methanolic solution of HCl (5 ml) formed by the careful addition of acetyl chloride (0.1 ml) to dry methanol (5 ml). The reaction mixture was then heated at 65 °C for 8 h. After this time t.l.c. (CMAW) indicated the formation of a major product (R_f 0.2). The reaction mixture was cooled to room temperature, the solvent removed and the residue purified by flash chromatography (CMAW) to yield (5S,6R,7R,8S,9R)-1,3-diaza-6,7,8,9-tetrahydroxy-spiro[4.4.]nonane-2,4-dione (4.21) as a hygroscopic white foam; $[\alpha]_D^{20} +33.0$ (c , 0.93 in MeOH); ν_{max} (KBr) 3400-3200 (br, OH), 1769, 1719 (hydantoin) cm^{-1} ; δ_H (D₂O) 3.78 (1H, dd, J 4.3 Hz, J' 9.2 Hz), 3.93 (1H, t, J 4.4 Hz), 4.16 (1H, d, J 4.1 Hz), 4.24 (1H, d, J 9.1 Hz); δ_C (D₂O) 73.0 (s, C-5), 70.9, 75.8, 76.0, 77.5 (4 x d, C-6, C-7, C-8, C-9), 159.9, 177.7 (2 x s, C-2, C-4); m/z (EI) 263 ($[MNa_2-H]^+$), 241 (MNa^+).

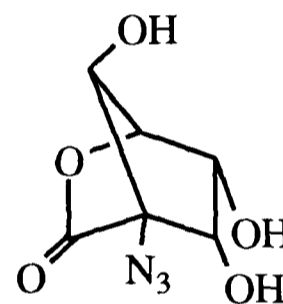
(5 β ,6 α ,7 α ,8 α ,9 α)-1,3-Diaza-6,7,8,9-tetrahydroxy-spiro[4.4.]nonane-2,4-dione (4.22).



(1S,4S,5R,6R,7S)-5,6-*O*-isopropylidene-2-oxa-5,6,7-trihydroxy-4-ureido-bicyclo[2.2.1.]heptan-3-one (4.19) (119 mg, 0.4 mmol) was stirred at room temperature in dry methanol (5 ml). To this was added a methanolic solution of HCl (5 ml) formed by the careful addition of acetyl chloride (0.25 ml) to dry methanol (5

ml). The reaction mixture was then heated at 65 °C for 72 h. After this time, t.l.c. (CMAW) indicated the formation of a major product (R_f 0.15). The reaction mixture was cooled to room temperature, the solvent removed and the residue purified by flash chromatography (CMAW) to yield (5 β ,6 α ,7 α ,8 α ,9 α)-1,3-diaza-6,7,8,9-tetrahydro-spiro[4.4.]nonane-2,4-dione (4.22) as a white powder; $[\alpha]_D^{20}$ +0.0 (*c*, 0.54 in H₂O); ν_{\max} (KBr) 3400-3200 (br, OH, NH), 1765, 1719 (hydantoin) cm⁻¹; δ_H (D₂O) 4.05 (2H, dd, *J* 2.2 Hz, *J'* 4.7 Hz), 4.10 (2H, dd, *J* 2.2 Hz, *J'* 4.7 Hz); δ_C (D₂O) 70.9, 74.3 (2 x d, C-6, C-7, C-8, C-9), 78.0 (s, C-5), 160.1, 176.6 (2 x s, C-2, C-4); *m/z* (EI) 263 ([MNa₂-H]⁺, 100%), 241 (MNa⁺).

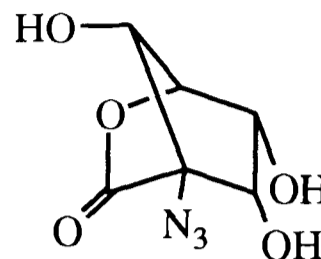
(1S,4R,5R,6R,7R)-4-Azido-2-oxa-5,6,7-trihydroxy-
bicyclo[2.2.1.]heptan-3-one (4.23).



(1S,4S,5R,6R,7R)-4-Azido-5,6-*O*-isopropylidene-2-oxa-5,6,7-trihydroxy-bicyclo[2.2.1.]heptan-3-one (3.36) (212 mg, 0.88 mmol) was stirred in a mixture of water (3 ml) and trifluoroacetic acid (2 ml) at room temperature. After 3 h, t.l.c. (hexane : ethyl acetate, 1 : 1) indicated complete consumption of starting material (R_f 0.6) and the formation of a single product (R_f 0.2). The solvent was removed, the residue co-evaporated with toluene (2 x 5 ml), and purified by flash chromatography (hexane : ethyl acetate, 1 : 1) to yield (1S,4R,5R,6R,7R)-4-azido-2-oxa-5,6,7-trihydroxy-bicyclo[2.2.1.]heptan-3-one (4.23) (166 mg, 94%) as a pale red solid, m.p. 102-104 °C (on standing); $[\alpha]_D^{20}$ +186.7 (*c*, 1.05 in MeOH); ν_{\max} (KBr) 3400-3200 (br, OH), 2131 (N₃), 1790 (C=O) cm⁻¹; δ_H (CD₃CN) 3.50 (1H, d, OH-6, *J*_{6,OH} 7.5 Hz, D₂O exch), 3.88 (1H, d, OH-5, *J*_{5,OH} 5.4 Hz, D₂O exch), 4.29 (1H, dd, H-7, *J*_{1,7} 2.6 Hz, *J*_{7,OH} 4.5 Hz), 4.30 (1H, d, OH-7), 4.46 (1H, dt, H-6, *J*_{1,6} 2.3 Hz, *J*_{5,6} 7.7 Hz), 4.55 (1H, ddd, H-5, *J*_{1,5} 0.9 Hz), 4.61 (1H, dt, H-1); δ_C (CD₃OD) 68.3, 70.2, 75.1, 80.7 (4 x d, C-1, C-5, C-6, C-7), 75.4 (s, C-4), 170.6 (s, C-3); *m/z* (NH₃, DCI)

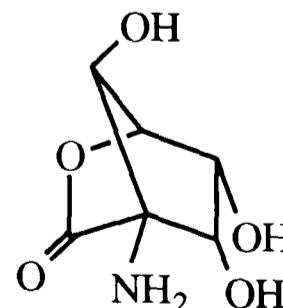
219 (MNH_4^+ , 100%), 191 ($\text{MNH}_4^+-\text{N}_2$) (Found: C, 35.88; H, 3.24; N, 20.70; $\text{C}_6\text{H}_7\text{O}_5\text{N}_3$ requires: C, 35.83; H, 3.51; N, 20.89%).

(1S,4R,5R,6R,7S)-4-Azido-2-oxa-5,6,7-trihydroxy-
bicyclo[2.2.1.]heptan-3-one (4.24).



(1S,4S,5R,6R,7S)-4-Azido-5,6-*O*-isopropylidene-2-oxa-5,6,7-trihydroxy-bicyclo[2.2.1.]heptan-3-one (4.8) (138 mg, 0.57 mmol) was stirred in a mixture of water (3 ml) and trifluoroacetic acid (2 ml) at room temperature. After 6 h, t.l.c. (ethyl acetate) indicated complete consumption of starting material (R_f 0.7) and the formation of a single product (R_f 0.3). The solvent was removed, the residue co-evaporated with toluene (2 x 5 ml), and purified by flash chromatography (hexane : ethyl acetate, 1 : 3) to yield (1S,4R,5R,6R,7S)-4-azido-2-oxa-5,6,7-trihydroxy-
bicyclo[2.2.1.]heptan-3-one (4.24) (93 mg, 81%) as a white crystalline solid, m.p. >170 °C (decomp methanol / ether); $[\alpha]_D^{20} +61.3$ (c , 1.05 in MeOH); ν_{max} (KBr) 3400-3200 (br, OH), 2136 (N_3), 1795 (C=O) cm^{-1} ; δ_{H} (CD_3OD) 4.13 (1H, s, H-7), 4.17 (1H, dd, H-5, $J_{1,5}$ 1.1 Hz, $J_{5,6}$ 8.2 Hz), 4.20 (1H, dd, H-6, $J_{1,6}$ 1.9 Hz), 4.56 (1H, H-1, m); δ_{C} (CD_3OD) 66.0, 69.2, 74.9, 84.1 (4 x d, C-1, C-5, C-6, C-7), 76.5 (s, C-4), 171.7 (s, C-3); m/z (NH_3 , DCI) 219 (MNH_4^+ , 100%). (Found: C, 35.86; H, 3.22; N, 21.03; $\text{C}_6\text{H}_7\text{O}_5\text{N}_3$ requires: C, 35.83; H, 3.51; N, 20.89%).

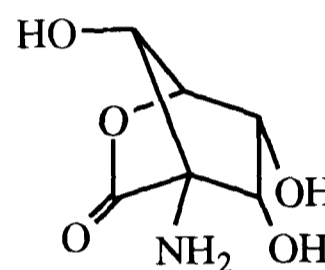
(1S,4R,5R,6R,7R)-4-Amino-2-oxa-5,6,7-trihydroxy-
bicyclo[2.2.1.]heptan-3-one (4.25).



(1S,4R,5R,6R,7R)-4-Azido-2-oxa-5,6,7-trihydroxy-bicyclo[2.2.1.]heptan-3-one (4.23) (84 mg, 0.42 mmol) and palladium black (3 mg) were stirred in ethanol (8 ml) at room temperature. The solution was degassed and then stirred under hydrogen for 4 h. After this time, t.l.c. (ethyl acetate) indicated complete consumption of starting

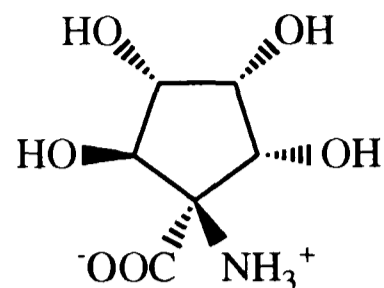
material (R_f 0.5) and the formation of a single product (R_f 0.0). The reaction mixture was filtered through Celite and the solvent removed to yield (1S,4R,5R,6R,7R)-4-amino-2-oxa-5,6,7-trihydroxy-bicyclo[2.2.1]heptan-3-one (4.25) (73 mg, crude, quant) as a hygroscopic pale yellow solid; ν_{\max} (KBr) 3400-3200 (br, OH, NH), 1805 (C=O) cm^{-1} ; δ_{H} (CD_3OD) 4.01 (1H, d, H-7, $J_{1,7}$ 2.8 Hz), 4.24 (1H, br d, H-5, $J_{5,6}$ 8.0 Hz), 4.44 (1H, dd, H-6, $J_{1,6}$ 2.3 Hz), 4.52 (1H, m, H-1, $J_{1,5}$ 0.9 Hz); δ_{C} (D_2O) 69.0, 72.0, 76.3, 81.8 (4 x d, C-1, C-5, C-6, C-7), 71.2 (s, C-4), 177.1 (s, C-3); m/z (NH_3 , CI) 193 (MNH_4^+), 176 (MH^+).

(1S,4R,5R,6R,7S)-4-Amino-2-oxa-5,6,7-trihydroxy-bicyclo[2.2.1]heptan-3-one (4.26).



(1S,4R,5R,6R,7S)-4-Azido-2-oxa-5,6,7-trihydroxy-bicyclo[2.2.1]heptan-3-one (4.24) (115 mg, 0.57 mmol) and palladium black (5 mg) were stirred in a mixture of ethanol (8 ml) and water (2 ml) at room temperature. The solution was degassed and stirred under hydrogen for 3 h. After this time, t.l.c. (ethyl acetate) indicated the formation of a single product (R_f 0.0). The reaction mixture was filtered through Celite and the solvent removed to yield (1S,4R,5R,6R,7S)-4-amino-2-oxa-5,6,7-trihydroxy-bicyclo[2.2.1]heptan-3-one (4.26) (100 mg, crude, quant) as a white hygroscopic amorphous solid; ν_{\max} (KBr) 3400-3200 (br, OH, NH), 1786 (C=O) cm^{-1} ; δ_{H} (CD_3OD) 3.95 (1H, br s, H-7), 4.08 (1H, dd, H-5, $J_{1,5}$ 0.8 Hz, $J_{5,6}$ 8.2 Hz), 4.21 (1H, dd, H-6, $J_{1,6}$ 2.0 Hz), 4.49-4.50 (1H, m, H-1); δ_{C} (CD_3OD) 66.3, 69.6, 74.2, 84.2 (4 x d, C-1, C-5, C-6, C-7), 71.5 (s, C-4), 175.4 (s, C-3); m/z (NH_3 , CI) 193 (MNH_4^+), 176 (MH^+ , 100%).

(1S,2R,3R,4S,5R)-1-Amino-2,3,4,5-tetrahydroxy-cyclopentane carboxylic acid (4.27).



Method 1.

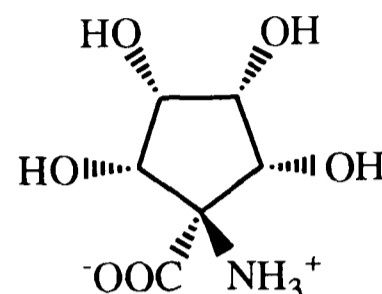
(1S,4R,5R,6R,7R)-4-Amino-2-oxa-5,6,7-trihydroxy-bicyclo[2.2.1.]heptan-3-one (4.25) (106 mg, 0.61 mmol) was dissolved in water (5 ml). Triethylamine (0.8 ml, 6.0 mmol) was added and the resulting mixture stirred at room temperature. After 2 h, t.l.c. (CMAW) indicated complete consumption of starting material (R_f 0.5) and the formation of a single product at the baseline. The solvent was removed and the residue purified by ion exchange chromatography (Dowex 50W-X8[H⁺], eluant 2M aqueous pyridine) and then recrystallised from water to yield (1S,2R,3R,4S,5R)-1-amino-2,3,4,5-tetrahydroxy-cyclopentane carboxylic acid (4.27), contaminated with small amounts of other amino acids, (70 mg, 60%). Repeated recrystallisation from water furnished pure material as a colourless crystalline solid, m.p. >230 °C (decomp, water); $[\alpha]_D^{20} +3.9$ (c, 0.23 in H₂O); ν_{\max} (KBr) 3400-3300 (br, OH, NH) cm⁻¹; δ_H (D₂O) 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 (D₂O) 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, C-6); m/z (electrospray) 194 (MH⁺, 100%). (Found: C, 37.31; H, 5.62; N, 7.15; C₆H₁₁O₆N requires: C, 37.31; H, 5.74; N, 7.25%).

Method 2.

(1S,4R,5R,6R,7S)-4-Amino-2-oxa-5,6,7-trihydroxy-bicyclo[2.2.1.]heptan-3-one (4.26) (40 mg, 0.23 mmol) was dissolved in 0.4 M sodium hydroxide solution (3 ml) and stirred at room temperature. After 10 min, t.l.c. (CMAW) indicated complete consumption of starting material (R_f 0.2) and the formation of a product at the baseline. The reaction mixture was adjusted to pH 7 by careful addition of 1M aqueous HCl. The solvent was then removed and the residue purified by ion exchange chromatography (Dowex 50W-X8[H⁺], eluant 2M aqueous pyridine) to yield

(1S,2R,3R,4S,5R)-1-amino-2,3,4,5-tetrahydroxy-cyclopentane carboxylic acid (4.27) (22 mg, 50%), identical to the material described above, together with small amounts of inseparable epimeric amino acids.

(1 β ,2 α ,3 α ,4 α ,5 α)-1-Amino-2,3,4,5-tetrahydroxy-cyclopentane carboxylic acid (4.28).



Method 1.

(1S,4S,5R,6R,7R)-4-Azido-5,6-*O*-isopropylidene-2-oxa-5,6,7-trihydroxy-bicyclo[2.2.1]heptan-3-one (3.36) (67 mg, 0.28 mmol) and potassium carbonate (37 mg, 0.27 mmol) were stirred in water (3 ml) at room temperature. After 16 h, t.l.c. (ethyl acetate) indicated complete consumption of starting material (R_f 0.8) and the formation of a single product at the baseline. Palladium black (3 mg) was added, the solution degassed and the resulting mixture stirred under hydrogen for 5 h. At this point ^1H nmr (D_2O) indicated conversion to a single product. The mixture was filtered through Celite and the solvent removed. The crude residue was dissolved in a mixture of water (3 ml) and trifluoroacetic acid (2 ml) and stirred at room temperature overnight. After 12 h, crude ^1H nmr (D_2O) again indicated conversion to a single product. The solvent was removed, the residue co-evaporated with toluene (2 x 1 ml) and then purified by ion exchange chromatography (Dowex 50W-X8[H^+], eluant 2M aqueous pyridine) and recrystallised from water to yield (1 β ,2 α ,3 α ,4 α ,5 α)-1-amino-2,3,4,5-tetrahydroxy-cyclopentane carboxylic acid (4.28) (42 mg, 79%) as a colourless crystalline solid; m.p. >225 $^\circ\text{C}$ (decomp, water); $[\alpha]_{\text{D}}^{20}$ +0.0 (c , 0.45 in H_2O); ν_{max} (KBr) 3500-3200 (br, OH, NH) cm^{-1} ; δ_{H} (D_2O) 4.10 (2H, dd, J 2.2 Hz, J' 5.0 Hz), 4.15 (2H, dd, J 2.2 Hz, J' 5.0 Hz); δ_{C} (D_2O , with TFA at pH 1) 74.5 (s, C-1), 71.8, 74.7 (2 x d, C-2, C-3, C-4, C-5), 169.2 (s, C-6); m/z (electrospray) 194 (MH^+ , 100%). (Found: C, 37.60; H, 5.56; N, 7.41; $\text{C}_6\text{H}_{11}\text{O}_6\text{N}$ requires: C, 37.31; H, 5.74; N, 7.25%).

Method 2.

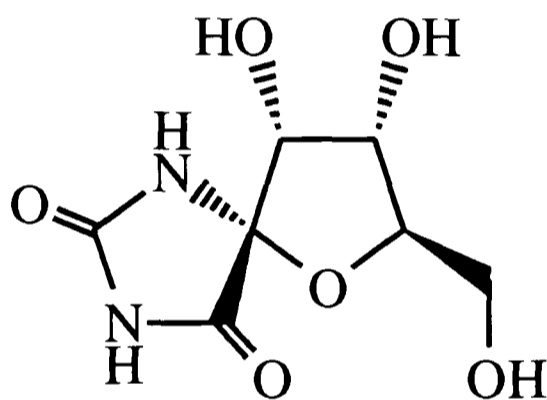
(1S,4S,5R,6R,7S)-4-Azido-5,6-*O*-isopropylidene-2-oxa-5,6,7-trihydroxy-bicyclo[2.2.1.]heptan-3-one (4.8) (239 mg, 0.99 mmol) and potassium carbonate (137 mg, 0.99 mmol) were stirred in water (10 ml) at room temperature. After 24 h, t.l.c. (ethyl acetate) indicated complete consumption of starting material (R_f 0.5) and the formation of a single product at the baseline. Palladium black (5 mg) was added, the solution degassed and the resulting mixture stirred under hydrogen for 12 h. The mixture was then filtered through Celite and the solvent removed. The crude residue was dissolved in a mixture of water (6 ml) and trifluoroacetic acid (4 ml) and stirred at room temperature for 12 h. The solvent was then removed, the residue co-evaporated with toluene (2 x 5 ml) and purified by ion exchange chromatography (Dowex 50W-X8[H⁺], eluant 2M aqueous pyridine) and recrystallised from water to yield (1 β ,2 α ,3 α ,4 α ,5 α)-1-amino-2,3,4,5-tetrahydroxy-cyclopentane carboxylic acid (4.28) (99 mg, 52%) identical to the material described above.

References.

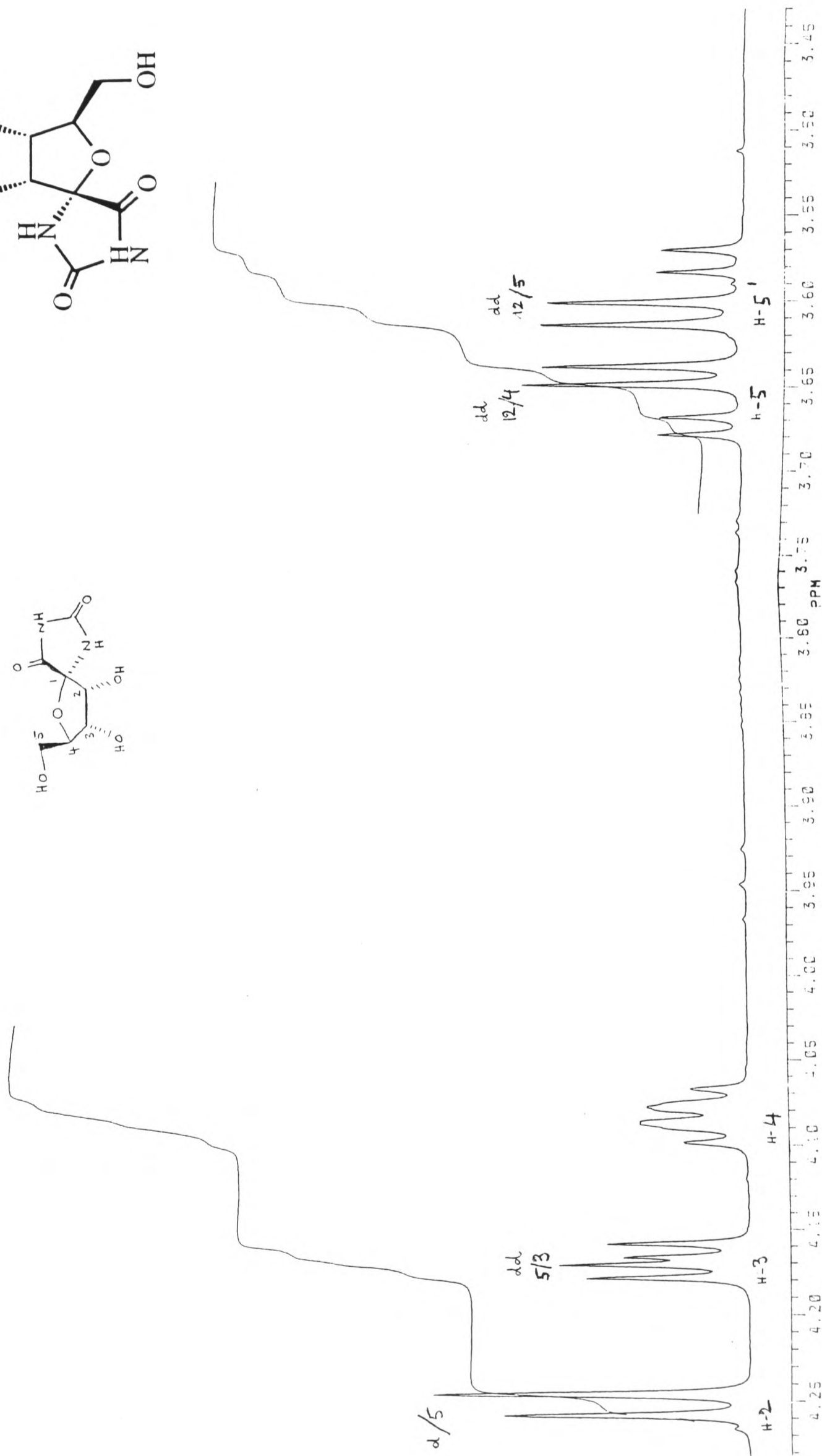
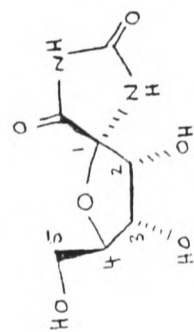
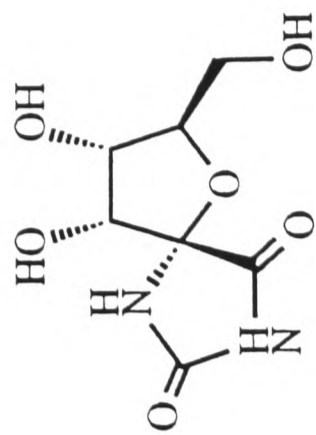
- ¹ Elliott, R.P. 'Sugars as Homochiral Starting Materials', D. Phil Thesis, 1992, Oxford University, Chapter 4.
- ² Bruce, I.; Fleet, G.W.J.; Girdhar, A.; Haraldsson, M.; Peach, J.M.; and Watkin, D.J. *Tetrahedron*, 1990, **46**, 19.
- ³ Burton, J.W. Part II Thesis, 1993, Oxford University.
- ⁴ Fairbanks, A.J.; Elliott, R.P.; Smith, C.; Hui, A.; Way, G.; Storer, R.; Taylor, H.E.; Watkin, D.J.; Winchester, B.G.; and Fleet, G.W.J. *Tetrahedron Lett.*, 1993, submitted for publication.
- ⁵ Lopez, C.A.; and Trigo, G.C. 'The Chemistry of Hydantoins', *Adv. in Heterocyclic Chem.*, 1985, **38**, 177.
- ⁶ Hui, A. personal communication.
- ⁷ Fairbanks, A.J.; Skead, B.M.; Nash, R.J.; Taylor, H.E.; Hui, A.; Storer, R.; Saunders, J.; Watkin, D.J.; and Fleet, G.W.J. paper in preparation.

APPENDIX 1

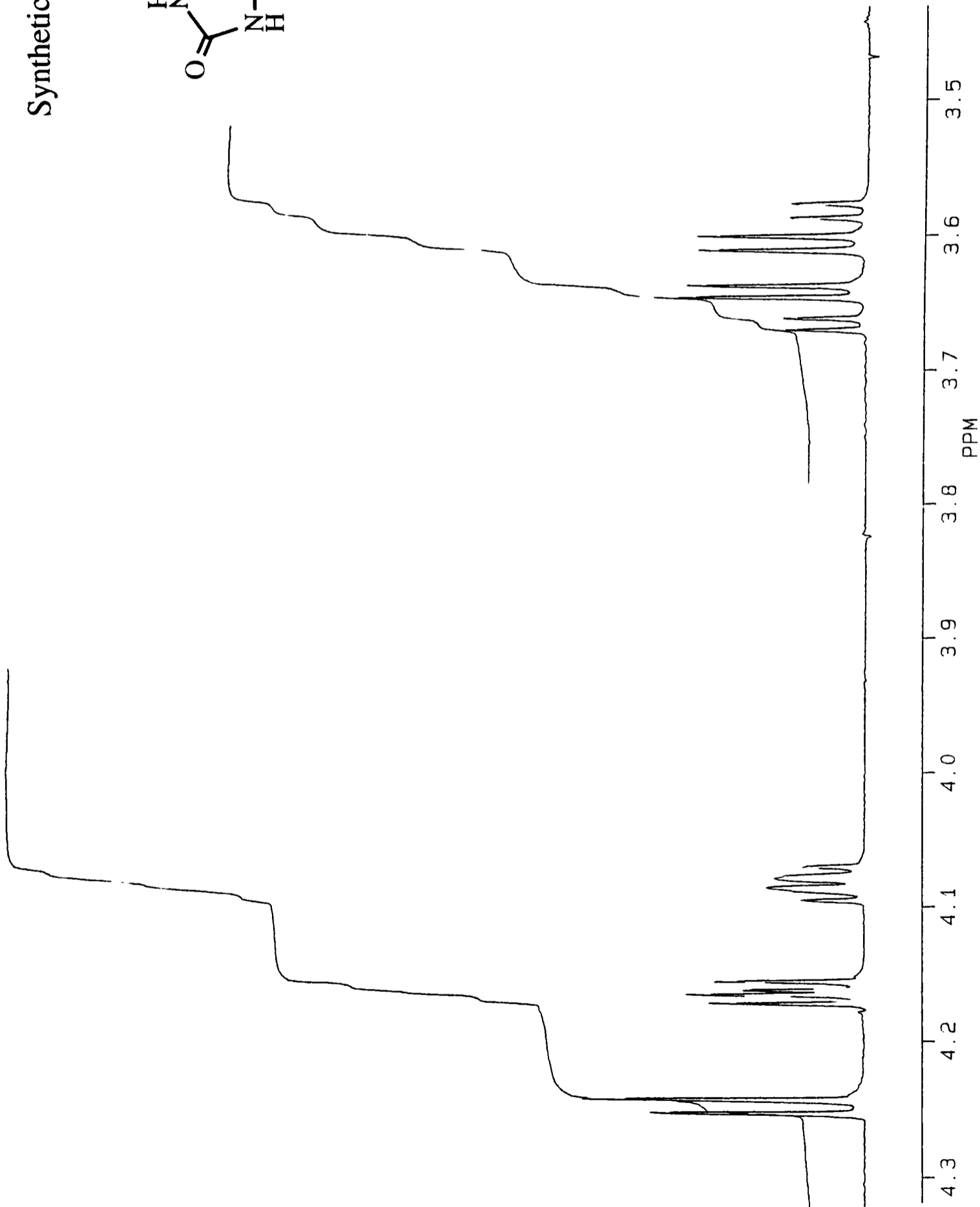
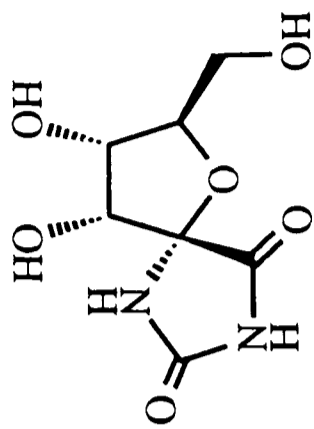
^1H Nmr spectra of synthetic and authentic 1-*epi*hydantocidin (2.27)



Authentic 1-epihydantocidin.

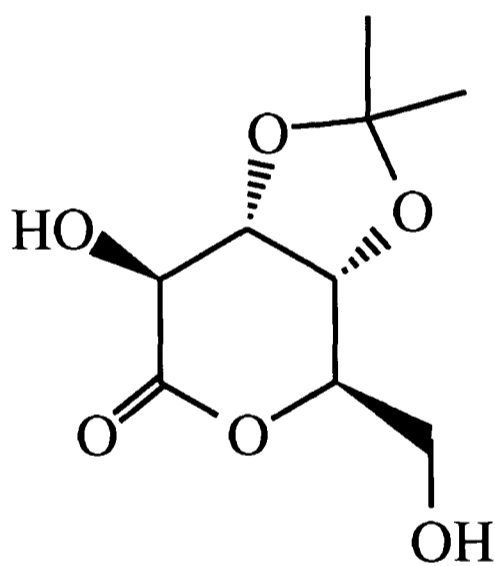


Synthetic 1-epihydantocidin.



APPENDIX 2

Crystal Structure Data for
3,4-*O*-Isopropylidene-D-altrono-1,5-lactone (2.11).

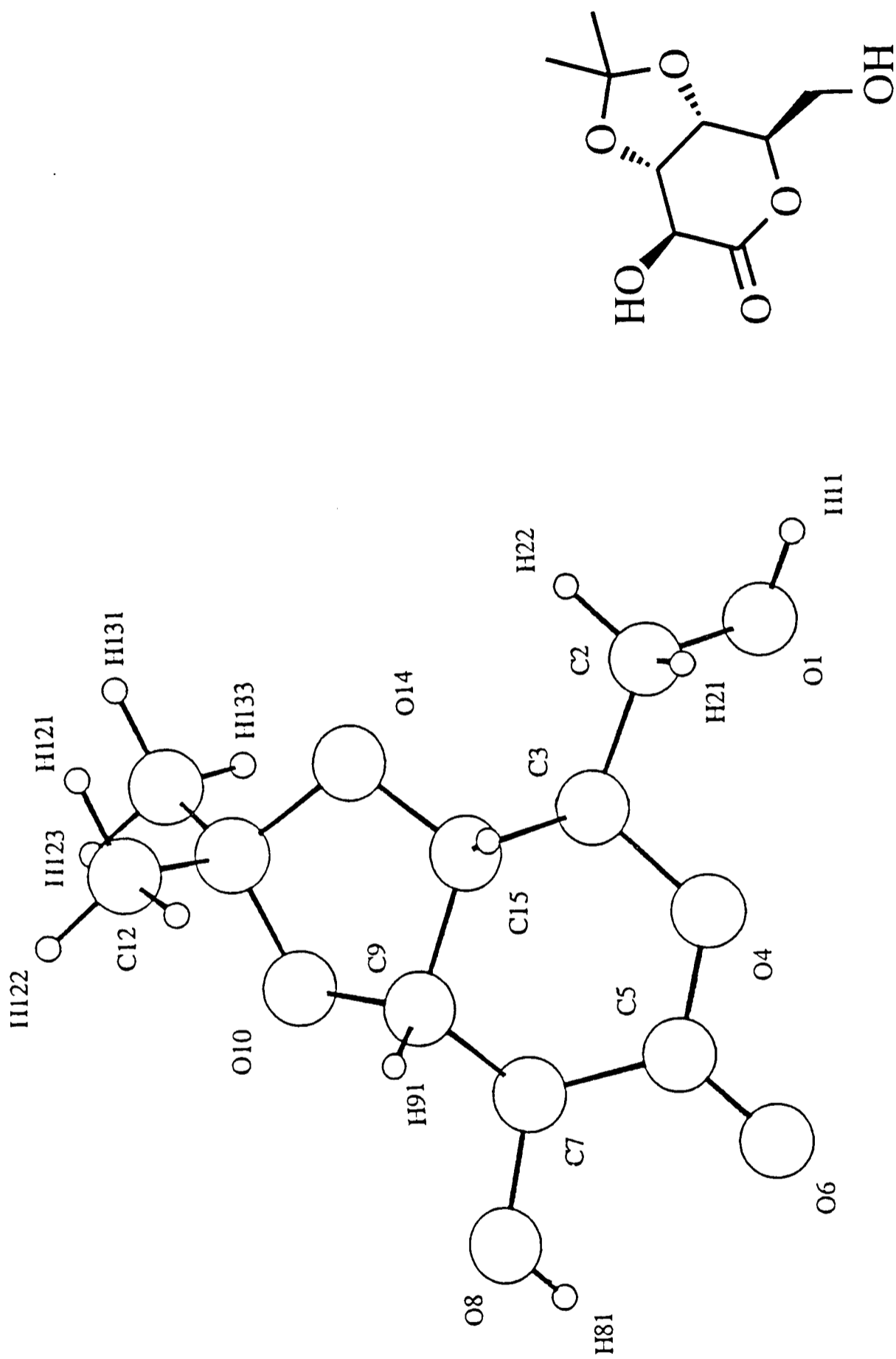


General X-Ray Crystal Structure Analyses.

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 $\theta = 75^\circ$ (Cu-K α radiation). The data were corrected for absorption, Lorentz and polarisation effects. All calculations were carried out on a Microvax 3800 computer using SHELXS-86¹ for direct methods and CRYSTALS² for all other calculations. Atomic scattering factors were taken from International Tables.³ Atomic coordinates for both compounds have been deposited at the Cambridge Crystallographic 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 anisotropic 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 Chebyshev⁶ weighting schemes.

References

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



Crystal Data for 3,4-O-isopropylidene-D-altrono-1,5-lactone (2.11).

Molecular formula $C_9H_{14}O_6$ Formula weight 218.206

Crystal data:

Crystal system orthorhombic

$a/\text{\AA}$ 7.004(4) $\alpha/^\circ$ 90

$b/\text{\AA}$ 8.954(6) $\beta/^\circ$ 90

$c/\text{\AA}$ 16.738(3) $\gamma/^\circ$ 90

space group P 2₁2₁2₁ $D_c/g\text{ cm}^{-3}$ 1.385

linear absorption coeff. / cm^{-1} 9.65

Crystal size /mm 0.1 x 0.2 x 0.6

Data collection:

X-radiation $\lambda = 1.5418\text{ \AA}$ Cu-K α

θ min., max. / $^\circ$ 0, 75

ω -scan parameters: A, B ($^\circ$) (A + B tan θ) A = 0 B = 0

Horizontal aperture parameters: A, B (mm) (A + B tan θ) A = 0.6 B = 0.15

Scan speed/ $^\circ\text{ min}^{-1}$ 1.1 (min.) to 1.7 (max.)

Total data 1823 Total unique data 1211

Observed data 838, for $[I > n\sigma(I)]$ where n =

Absorption correction, Psi scan: min 1.00, max 1.12 Sheldrick Merging R 3.36%

Refinement: Solved by SHELXS-86

Weighting Scheme type Chebyshev 4 coefficients, 2.00, -1.35, 1.25, -0.859

Extinction parameter 47(4)

Maximum residual electron density/ $e\text{\AA}^{-3}$ 1.4

Final R 3.62% R_w 4.13%

Fractional atomic coordinates and equivalent isotropic temperature factors $U(\text{eq})$ with standard deviations in parentheses for 3,4-di-*O*-isopropylidene-*D*-altrono-1,5-lactone (9).

Atom	x/a	y/b	z/c	U(iso)
O(1)	0.0062(4)	-0.2930(3)	-0.2993(1)	0.0422
C(2)	-0.0056(6)	-0.1379(4)	-0.3163(2)	0.0412
C(3)	0.1331(5)	-0.1002(3)	-0.3818(2)	0.0347
O(4)	0.0656(4)	-0.1753(3)	-0.4535(1)	0.0402
C(5)	0.1542(5)	-0.1433(4)	-0.5233(2)	0.0381
O(6)	0.1029(4)	-0.2077(3)	-0.5829(1)	0.0497
C(7)	0.3166(5)	-0.0327(4)	-0.5194(2)	0.0364
O(8)	0.3712(4)	0.0144(3)	-0.5963(1)	0.046
C(9)	0.2670(5)	0.1043(3)	-0.4699(2)	0.0340
O(10)	0.4371(4)	0.1576(3)	-0.4328(1)	0.0448
C(11)	0.3880(5)	0.2246(4)	-0.3590(2)	0.0431
C(12)	0.3339(7)	0.3870(4)	-0.3692(3)	0.0597
C(13)	0.5476(8)	0.2012(8)	-0.3004(3)	0.0834
O(14)	0.2215(4)	0.1418(3)	-0.3326(1)	0.0452
C(15)	0.1367(5)	0.0672(4)	-0.3989(2)	0.0366

Final anisotropic temperature factors with standard deviations in parentheses for 3,4-di-*O*-isopropylidene-*D*-altrono-1,5-lactone (9).

Atom	U(11)	U(22)	U(33)	U(23)	U(13)	U(12)
O(1)	0.065(2)	0.038(1)	0.033(1)	0.002(1)	0.010(1)	-0.010(1)
C(2)	0.060(2)	0.038(2)	0.034(2)	-0.003(1)	0.014(2)	-0.006(2)
C(3)	0.045(2)	0.035(2)	0.028(1)	-0.005(1)	0.006(1)	-0.002(2)
O(4)	0.058(1)	0.041(1)	0.031(1)	-0.0052(9)	0.007(1)	-0.015(1)
C(5)	0.049(2)	0.034(2)	0.033(2)	-0.001(1)	0.004(1)	0.001(2)
O(6)	0.069(2)	0.053(1)	0.036(1)	-0.008(1)	0.002(1)	-0.010(1)
C(7)	0.047(2)	0.036(2)	0.030(2)	-0.001(1)	0.009(1)	-0.001(2)
O(8)	0.078(2)	0.042(1)	0.038(1)	-0.001(1)	0.024(1)	-0.003(1)
C(9)	0.043(2)	0.032(1)	0.030(1)	0.001(1)	0.004(1)	-0.000(2)
O(10)	0.044(1)	0.053(1)	0.044(1)	-0.013(1)	0.010(1)	-0.007(1)
C(11)	0.051(2)	0.044(2)	0.037(2)	-0.006(1)	0.005(2)	-0.003(2)
C(12)	0.077(3)	0.039(2)	0.084(3)	-0.009(2)	0.028(3)	-0.011(2)
C(13)	0.083(3)	0.128(5)	0.063(3)	-0.009(4)	-0.026(3)	0.009(4)
O(14)	0.074(2)	0.049(1)	0.038(1)	-0.015(1)	0.021(1)	-0.024(2)
C(15)	0.042(2)	0.034(2)	0.036(2)	-0.002(1)	0.009(2)	0.002(2)

Bond lengths (in Å) for the non-hydrogen atoms with standard deviations in parentheses for 3,4-di-*O*-isopropylidene-*D*-altrono-1,5-lactone (9).

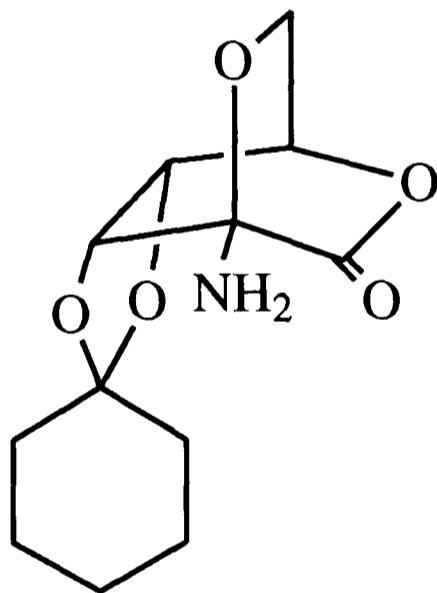
O(1) - C(2)	1.418(4)	C(2) - C(3)	1.503(4)
C(3) - O(4)	1.452(3)	C(3) - C(15)	1.524(5)
O(4) - C(5)	1.353(4)	C(5) - O(6)	1.206(4)
C(5) - C(7)	1.508(5)	C(7) - O(8)	1.407(4)
C(7) - C(9)	1.518(4)	C(9) - O(10)	1.424(4)
C(9) - C(15)	1.533(4)	O(10) - C(11)	1.415(4)
C(11) - C(12)	1.510(5)	C(11) - C(13)	1.501(6)
C(11) - O(14)	1.449(4)	O(14) - C(15)	1.423(4)

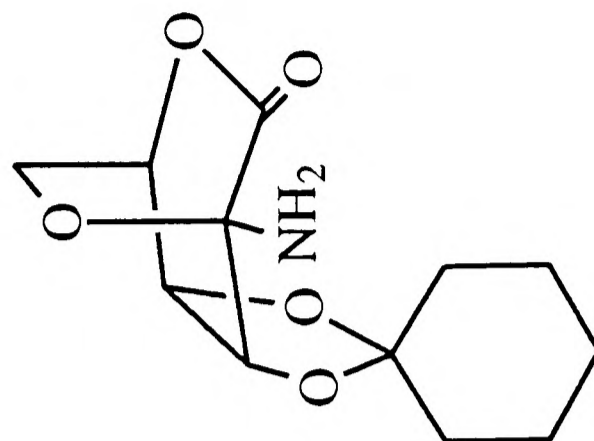
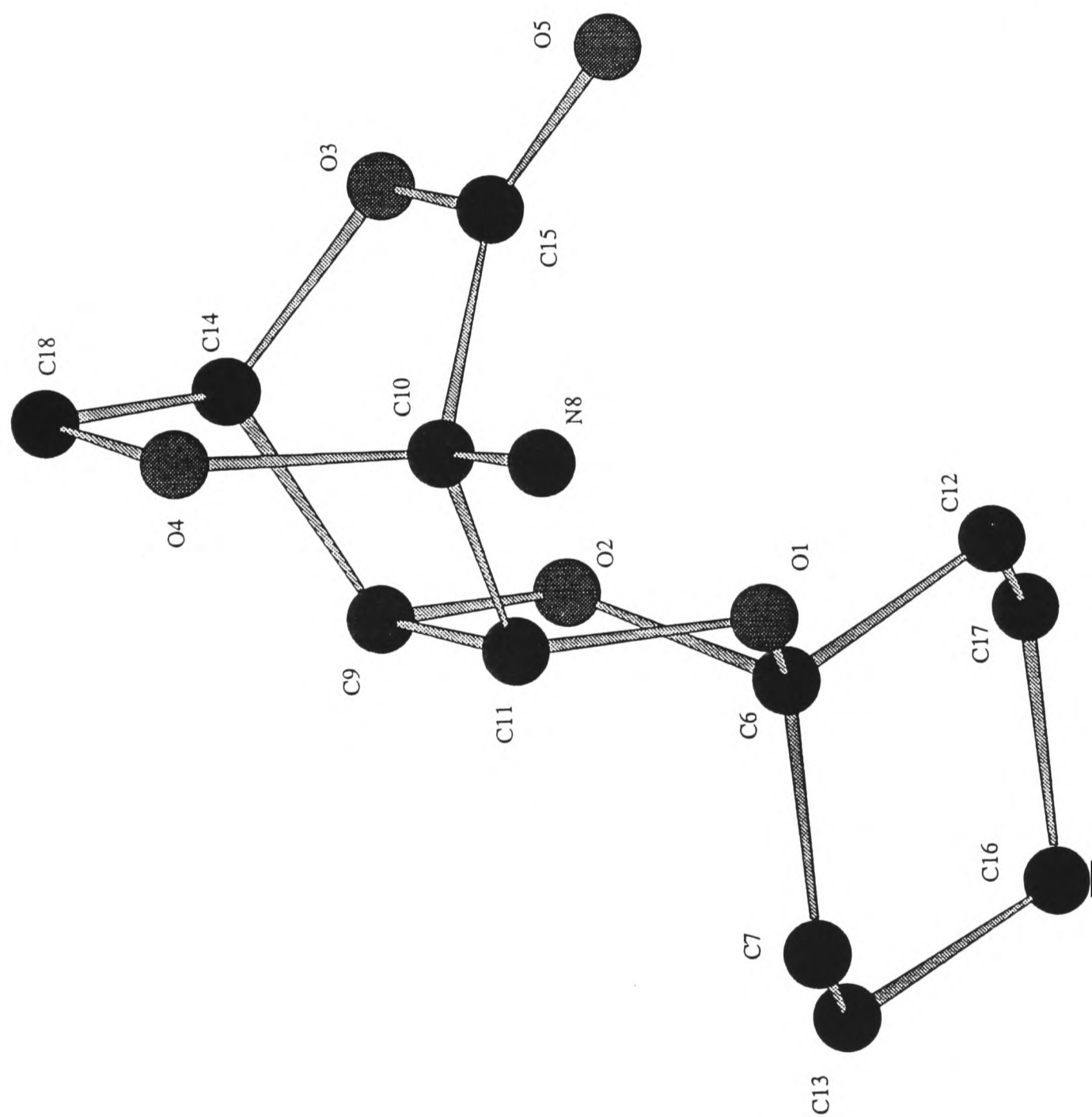
Bond angles (in degrees) for the non-hydrogen atoms with standard deviations in parentheses for 3,4-di-*O*-isopropylidene-*D*-altrono-1,5-lactone (9).

C(3) - C(2) - O(1)	109.1(3)	O(4) - C(3) - C(2)	106.7(3)
C(15) - C(3) - C(2)	111.6(3)	C(15) - C(3) - O(4)	107.8(3)
C(5) - O(4) - C(3)	117.7(2)	O(6) - C(5) - O(4)	118.4(3)
C(7) - C(5) - O(4)	116.5(3)	C(7) - C(5) - O(6)	125.0(3)
O(8) - C(7) - C(5)	111.2(3)	C(9) - C(7) - C(5)	112.4(3)
C(9) - C(7) - O(8)	108.6(3)	O(10) - C(9) - C(7)	108.4(3)
C(15) - C(9) - C(7)	112.6(3)	C(15) - C(9) - O(10)	103.5(2)
C(11) - O(10) - C(9)	108.6(3)	C(12) - C(11) - O(10)	111.7(3)
C(13) - C(11) - O(10)	109.3(3)	C(13) - C(11) - C(12)	113.3(4)
O(14) - C(11) - O(10)	104.1(3)	O(14) - C(11) - C(12)	108.9(3)
O(14) - C(11) - C(13)	109.2(3)	C(15) - O(14) - C(11)	109.7(2)
C(9) - C(15) - C(3)	111.5(3)	O(14) - C(15) - C(3)	108.7(3)
O(14) - C(15) - C(9)	104.7(3)		

APPENDIX 3

Crystal Structure Data for
(1*S*,4*R*,7*R*,8*S*)-1-Amino-7,8-*O*-cyclohexylidene-7,8-dihydroxy-2,5-
dioxo-bicyclo[2.2.2.]octan-6-one (2.23).





Crystal Data for (1S,4R,7R,8S)-1-Amino-7,8-O-cyclohexylidene-7,8-dihydroxy-2,5-dioxa-bicyclo[2.2.2]octan-6-one (2,23)

Crystal Data

Chemical formula $C_{12}H_{18}O_5N$

M_r 255.27

Cell dimensions:

a (Å) 5.9642

α (°) 90

b (Å) 21.1527

β (°) 90

c (Å) 9.6350

γ (°) 90

Volume (Å³) 1215.5

Density (g cm⁻³) 1.3945

Crystal system: Orthorhombic

Spacegroup: $P 2_1 2_1 2_1$

$Z = 4$

Crystal colour: Colourless

Crystal size (mm) 1.0 x 0.2 x 0.2

Data Collection

Diffractometer type: Enraf Nonius CAD4-F

Collection method $\omega/2\phi$

ϕ_{\min}, ϕ_{\max} (°) 0, 75

X-radiation Cu - K α : λ (Å) = 1.5418

Temperature (K) 300

No. of reflections for lattice parameters:

25

No. and interval for standard reflections:

3, 60 minutes

Variation of standards:

None

No. of measured reflections: 3125

h_{\min}, h_{\max} -6, 6

No. of unique reflections : 2128

k_{\min}, k_{\max} -1, 21

No. of observed reflections: 2694

l_{\min}, l_{\max} -1, 10

Condition for observed reflections: $I \geq n\sigma(I)$ where $n=3$

Merging R 4.65%

Absorption correction type: Spherical

Absorption correction (T_{\min}, T_{\max}) 1.00, 1.06

Refinement

Solution software: SHELXS-86

Refinement software: CRYSTALS/TURBOEX

Atomic scattering factors taken from International Tables, Volume 4

No. of parameters refined 170

Refinement of F

Hydrogen atom placing: Calculated using CRYSTALS, except amine placed by difference fourier.

Extinction parameter 39.617

Weighting scheme, type: Chebychev polynomial, 3 parameters

Weighting coefficients: 4.80, -0.631, 3.93

Final R 4.32%

R_w 5.29%

Atom	x/a	y/b	z/c	U(iso)
O(1)	0.0827(4)	-0.8484(1)	-0.4670(3)	0.0395
O(2)	-0.1070(3)	-0.9000(1)	-0.6351(3)	0.0386
O(3)	-0.3167(4)	-0.9455(1)	-0.3908(3)	0.0449
O(4)	0.0698(4)	-1.0007(1)	-0.2891(3)	0.0489
O(5)	-0.2875(5)	-0.8850(2)	-0.2046(3)	0.0607
C(6)	0.0172(5)	-0.8432(2)	-0.6084(3)	0.0339
C(7)	0.2158(6)	-0.8376(2)	-0.7047(4)	0.0426
N(8)	0.1713(7)	-0.9059(2)	-0.1883(4)	0.0585
C(9)	-0.0070(5)	-0.9488(2)	-0.5536(4)	0.0361
C(10)	0.0530(6)	-0.9317(2)	-0.3010(4)	0.0425
C(11)	0.1308(5)	-0.9140(2)	-0.4455(4)	0.0366
C(12)	-0.1441(6)	-0.7883(2)	-0.6251(4)	0.0442
C(13)	0.1451(6)	-0.8305(2)	-0.8548(4)	0.0468
C(14)	-0.1830(6)	-0.9868(2)	-0.4787(4)	0.0443
C(15)	-0.1957(6)	-0.9170(2)	-0.2912(4)	0.0444
C(16)	-0.0116(7)	-0.7742(2)	-0.8722(4)	0.0499
C(17)	-0.2106(7)	-0.7801(2)	-0.7762(5)	0.0483
C(18)	-0.0690(7)	-1.0341(2)	-0.3863(4)	0.0540

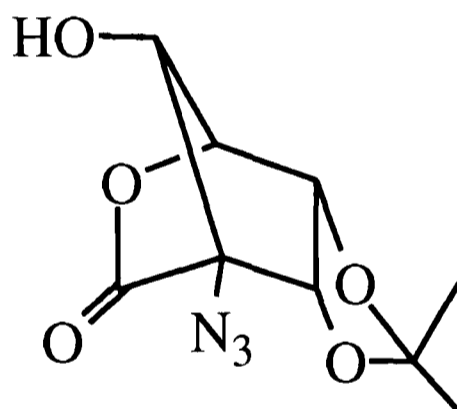
Atom	x/a	y/b	z/c	U(iso)
H(71)	0.3094	-0.8766	-0.6956	0.0430
H(72)	0.3062	-0.7999	-0.6771	0.0430
H(91)	0.0794	-0.9771	-0.6178	0.0366
H(111)	0.2960	-0.9216	-0.4554	0.0385
H(121)	-0.2813	-0.7966	-0.5692	0.0447
H(122)	-0.0697	-0.7488	-0.5921	0.0447
H(131)	0.0663	-0.8698	-0.8852	0.0477
H(132)	0.2810	-0.8237	-0.9133	0.0477
H(141)	-0.2864	-1.0074	-0.5471	0.0442
H(161)	-0.0681	-0.7734	-0.9707	0.0529
H(162)	0.0703	-0.7345	-0.8519	0.0529
H(171)	-0.3006	-0.8176	-0.8047	0.0491
H(172)	-0.3022	-0.7409	-0.7842	0.0491
H(181)	0.0266	-1.0628	-0.4441	0.0545
H(182)	-0.1832	-1.0595	-0.3355	0.0545
H(81)	0.104(6)	-0.882(2)	-0.126(4)	0.0500
H(82)	0.284(7)	-0.891(2)	-0.207(5)	0.0500

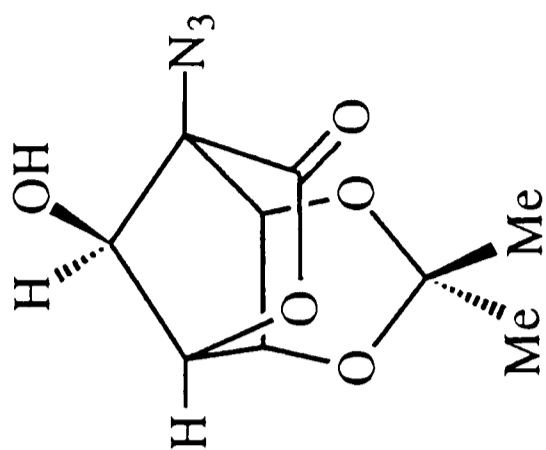
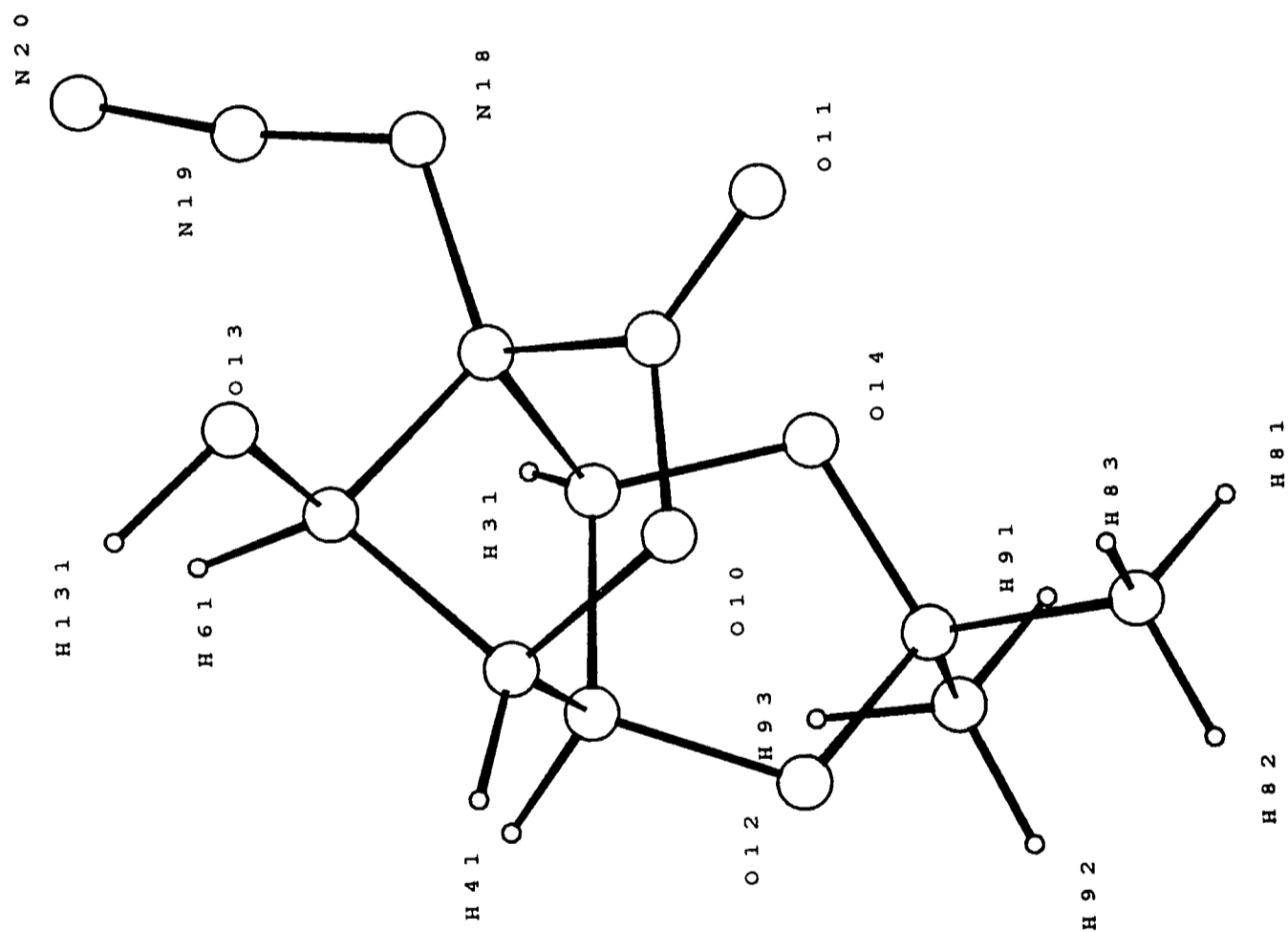
Atom	U(11)	U(22)	U(33)	U(23)	U(13)	U(12)
O(1)	0.043(1)	0.040(1)	0.036(1)	0.001(1)	-0.003(1)	-0.005(1)
O(2)	0.042(1)	0.035(1)	0.043(1)	0.004(1)	-0.009(1)	-0.007(1)
O(3)	0.029(1)	0.055(2)	0.057(2)	-0.001(2)	0.003(1)	0.002(1)
O(4)	0.053(2)	0.049(1)	0.054(2)	0.015(1)	-0.005(1)	0.012(1)
O(5)	0.067(2)	0.070(2)	0.060(2)	-0.009(2)	0.023(2)	0.012(2)
C(6)	0.034(2)	0.035(2)	0.033(2)	-0.002(2)	-0.002(1)	-0.002(2)
C(7)	0.038(2)	0.047(2)	0.044(2)	-0.002(2)	-0.002(2)	0.001(2)
N(8)	0.061(3)	0.092(3)	0.039(2)	-0.003(2)	-0.009(2)	-0.013(2)
C(9)	0.038(2)	0.037(2)	0.034(2)	-0.000(2)	-0.001(2)	0.004(2)
C(10)	0.042(2)	0.049(2)	0.039(2)	0.004(2)	-0.004(2)	0.005(2)
C(11)	0.025(2)	0.048(2)	0.047(2)	0.006(2)	-0.003(2)	0.010(2)
C(12)	0.044(2)	0.038(2)	0.055(2)	0.002(2)	0.007(2)	0.007(2)
C(13)	0.053(2)	0.056(3)	0.037(2)	0.003(2)	0.010(2)	-0.002(2)
C(14)	0.051(2)	0.043(2)	0.040(2)	0.000(2)	-0.004(2)	-0.003(2)
C(15)	0.051(2)	0.049(2)	0.038(2)	0.007(2)	0.009(2)	0.005(2)
C(16)	0.057(2)	0.052(2)	0.050(2)	0.019(2)	0.001(2)	-0.008(2)
C(17)	0.047(2)	0.042(2)	0.063(3)	0.012(2)	-0.005(2)	0.009(2)
C(18)	0.070(2)	0.039(2)	0.059(3)	0.005(2)	0.006(2)	0.005(2)

C(11) - O(1) - C(6)	105.6(3)		
C(9) - O(2) - C(6)	106.9(2)		
C(15) - O(3) - C(14)	113.0(3)		
C(18) - O(4) - C(10)	113.5(3)	O(1) - C(6)	1.422(4)
O(2) - C(6) - O(1)	104.4(3)	O(1) - C(11)	1.433(4)
C(7) - C(6) - O(1)	112.3(3)	O(2) - C(6)	1.436(4)
C(7) - C(6) - O(2)	111.1(3)	O(2) - C(9)	1.426(4)
C(12) - C(6) - O(1)	109.6(3)	O(3) - C(14)	1.455(4)
C(12) - C(6) - O(2)	107.1(2)	O(3) - C(15)	1.344(5)
C(12) - C(6) - C(7)	111.9(3)	O(4) - C(10)	1.466(4)
C(13) - C(7) - C(6)	112.1(3)	O(4) - C(18)	1.435(5)
C(11) - C(9) - O(2)	104.7(3)	O(5) - C(15)	1.206(4)
C(14) - C(9) - O(2)	111.0(3)	C(6) - C(7)	1.509(5)
C(14) - C(9) - C(11)	107.9(3)	C(6) - C(12)	1.516(5)
N(8) - C(10) - O(4)	107.0(3)	C(7) - C(13)	1.514(5)
C(11) - C(10) - O(4)	107.2(3)	N(8) - C(10)	1.405(5)
C(11) - C(10) - N(8)	117.4(3)	C(9) - C(11)	1.517(5)
C(15) - C(10) - O(4)	105.5(3)	C(9) - C(14)	1.507(5)
C(15) - C(10) - N(8)	111.3(4)	C(10) - C(11)	1.515(5)
C(15) - C(10) - C(11)	107.8(3)	C(10) - C(15)	1.518(5)
C(9) - C(11) - O(1)	105.2(3)	C(12) - C(17)	1.518(6)
C(10) - C(11) - O(1)	108.1(3)	C(13) - C(16)	1.522(6)
C(10) - C(11) - C(9)	110.2(3)	C(14) - C(18)	1.502(5)
C(17) - C(12) - C(6)	110.8(3)	C(16) - C(17)	1.510(6)
C(16) - C(13) - C(7)	110.7(3)		
C(9) - C(14) - O(3)	109.9(3)		
C(18) - C(14) - O(3)	107.6(3)		
C(18) - C(14) - C(9)	108.9(3)		
O(5) - C(15) - O(3)	120.1(3)		
C(10) - C(15) - O(3)	112.9(3)		
C(10) - C(15) - O(5)	127.0(4)		
C(17) - C(16) - C(13)	110.6(3)		
C(16) - C(17) - C(12)	113.0(3)		
C(14) - C(18) - O(4)	108.7(3)		

APPENDIX 4

Crystal Structure Data for
(1*S*,4*S*,5*R*,6*R*,7*S*)-4-Azido-5,6-*O*-isopropylidene-2-oxa-5,6,7-
trihydroxy-bicyclo[2.2.1.]heptan-3-one (4.8).





Crystal Data for (1S,4S,5R,6R,7S)-4-Azido-5,6-O-isopropylidene-2-oxa-5,6,7-trihydroxy-bicyclo[2.2.1]heptan-3-one (4.8).

Molecular formula	C ₉ H ₁₁ N ₃ O ₅	Formula weight	241.2
Crystal system	Orthorhombic	Space group	C 2 2 2 ₁
a (Å)	11.090(6)	a/°	90
b (Å)	5.836(1)	b/°	90
c (Å)	32.509(3)	g/°	90
V (Å ³)	2105.4	D _c /g cm ⁻³	1.52
Z	8		
Reflections for lattice parameters		25	
Linear absorption coeff. μ (cm ⁻¹)		10.37	
q range for lattice parameters (°)		16.13 - 24.10	
Crystal size (mm)		0.05 x 0.25 x 0.30	

Data collection

h _{min}	0	h _{max}	13
k _{min}	0	k _{max}	7
l _{min}	-1	l _{max}	32
Abs ⁿ correction type	Psi scan	Abs ⁿ corr ⁿ (T _{min} , T _{max})	1.00-1.12
Total data collected	2393	Criterion for observed	I > 3σ
Total observed data			
Merged Friedel pairs	1535	Merging R _{factor}	2.27%
Unmerged Friedel pairs	1192	Merging R _{factor}	2.20%

Refinement

No. of parameters		169	
Ratio of data : parameters		7.1	
Weighting scheme		Tukey & Prince	
W = weight x [1-(dF/6σF) ²] ²			
(Dr) _{min} (eÅ ⁻³)	-0.221	(Dr) _{max} (eÅ ⁻³)	+0.23
Final R _{factor}	0.36	Final R _w	0.043
Flack enantiopole parameter	0.02(35)		

Interatomic distances (Å) with e.s.d.'s in parentheses

N(18)	N(19)	1.238(3)	N(18)	C(2)	1.457(3)
N(19)	N(20)	1.117(3)	O(10)	C(1)	1.348(3)
O(10)	C(5)	1.472(3)	O(11)	C(1)	1.195(3)
O(12)	C(4)	1.414(3)	O(12)	C(7)	1.432(3)
O(13)	C(6)	1.409(3)	O(14)	C(3)	1.412(3)
O(14)	C(7)	1.428(3)	C(1)	C(2)	1.512(3)
C(2)	C(3)	1.558(3)	C(2)	C(6)	1.539(3)
C(3)	C(4)	1.538(3)	C(4)	C(5)	1.513(4)
C(5)	C(6)	1.517(4)	C(7)	C(8)	1.502(4)
C(7)	C(9)	1.512(5)			

Interatomic angles (°) with e.s.d.'s in parentheses

C(2)	N(18)	N(19)	114.0(2)	N(20)	N(19)	N(18)	171.7(3)
C(5)	O(10)	C(1)	106.9(2)	C(7)	O(12)	C(4)	109.3(2)
C(7)	O(14)	C(3)	108.5(2)	O(11)	C(1)	O(10)	123.6(2)
C(2)	C(1)	O(10)	106.6(2)	C(2)	C(1)	O(11)	129.8(2)
C(1)	C(2)	N(18)	110.0(2)	C(3)	C(2)	N(18)	117.3(2)
C(3)	C(2)	C(1)	104.3(2)	C(6)	C(2)	N(18)	122.1(2)
C(6)	C(2)	C(1)	99.8(2)	C(6)	C(2)	C(3)	100.7(2)
C(2)	C(3)	O(14)	111.0(2)	C(4)	C(3)	O(14)	104.4(2)
C(4)	C(3)	C(2)	102.7(2)	C(3)	C(4)	O(12)	105.4(2)
C(5)	C(4)	O(12)	114.5(2)	C(5)	C(4)	C(3)	102.3(2)
C(4)	C(5)	O(10)	108.1(2)	C(6)	C(5)	O(10)	102.6(2)
C(6)	C(5)	C(4)	100.7(2)	C(2)	C(6)	O(13)	111.0(2)
C(5)	C(6)	O(13)	115.0(2)	C(5)	C(6)	C(2)	92.6(2)
O(14)	C(7)	O(12)	105.6(2)	C(8)	C(7)	O(12)	108.1(3)
C(8)	C(7)	O(14)	108.5(2)	C(9)	C(7)	O(12)	111.0(3)
C(9)	C(7)	O(14)	109.8(2)	C(9)	C(7)	C(8)	113.6(3)

Fractional atomic co-ordinates and equivalent isotropic temperature factors, U(equ),

(with e.s.d.'s in parentheses)

Atom	x/a	y/b	z/c	U(equ)
N(18)	-0.0734(2)	-0.2968(4)	-0.29540(6)	0.0528
N(19)	-0.1550(2)	-0.3626(4)	-0.27223(6)	0.0473
N(20)	-0.2242(3)	-0.4019(5)	-0.24826(9)	0.0671
O(10)	0.0984(2)	-0.5871(3)	-0.37200(6)	0.0506
O(11)	0.1412(2)	-0.2514(4)	-0.34173(6)	0.0570
O(12)	-0.0775(2)	-0.5601(3)	-0.43323(5)	0.0558
O(13)	0.0330(2)	-0.7784(4)	-0.29512(7)	0.0679
O(14)	-0.0970(2)	-0.2393(3)	-0.39384(4)	0.0430
C(1)	0.0737(2)	-0.4081(4)	-0.34718(7)	0.0427
C(2)	-0.0517(2)	-0.4479(4)	-0.33031(7)	0.0396
C(3)	-0.1359(2)	-0.4209(4)	-0.36838(7)	0.0390
C(4)	-0.1086(2)	-0.6384(4)	-0.39345(7)	0.0437
C(5)	-0.0054(2)	-0.7440(4)	-0.36963(8)	0.0472
C(6)	-0.0491(2)	-0.7104(5)	-0.32585(8)	0.0476
C(7)	-0.0963(3)	-0.3177(4)	-0.43547(7)	0.0506
C(8)	0.0101(4)	-0.2132(6)	-0.4571(1)	0.0730
C(9)	-0.2157(4)	-0.2630(7)	-0.4556(1)	0.0794

Fractional atomic co-ordinates and isotropic temperature factors, U(iso) (With e.s.d.'s in parentheses)

Atom	x/a	y/b	z/c	U(iso)
H(131)	-0.024(7)	-0.96(1)	-0.294(2)	0.21(3)
H(31)	-0.2214	-0.3851	-0.3612	0.070(9)
H(41)	-0.1732	-0.7537	-0.3991	0.065(9)
H(51)	0.0174	-0.9008	-0.3790	0.069(9)
H(61)	-0.1203	-0.8021	-0.3158	0.09(1)
H(81)	-0.0011	-0.0434	-0.4590	0.11(1)
H(82)	0.0169	-0.2790	-0.4854	0.09(1)
H(83)	0.0854	-0.2471	-0.4413	0.12(2)
H(91)	-0.2266	-0.0928	-0.4569	0.10(1)
H(92)	-0.2168	-0.3270	-0.4842	0.09(1)
H(93)	-0.2827	-0.3322	-0.4392	0.08(1)

Final anisotropic temperature factors
(with standard deviations in parentheses)

Atom	U(11)	U(22)	U(33)	U(23)	U(13)	U(12)
N(18)	0.067(1)	0.055(1)	0.044(1)	-0.006(1)	0.009(1)	-0.014(1)
N(19)	0.057(1)	0.044(1)	0.043(1)	0.0025(9)	0.005(1)	0.0024(9)
N(20)	0.080(2)	0.066(2)	0.064(1)	0.001(1)	0.024(1)	-0.000(1)
O(10)	0.0413(9)	0.045(1)	0.076(1)	0.0023(9)	0.0149(8)	0.0021(8)
O(11)	0.048(1)	0.058(1)	0.079(1)	0.008(1)	-0.0037(9)	-0.020(1)
O(12)	0.089(2)	0.0428(9)	0.0481(9)	0.0039(8)	0.0132(9)	-0.003(1)
O(13)	0.075(1)	0.065(1)	0.078(1)	0.026(1)	-0.016(1)	0.001(1)
O(14)	0.0582(9)	0.0326(8)	0.0428(8)	0.0029(7)	-0.0005(7)	0.0054(8)
C(1)	0.038(1)	0.040(1)	0.054(1)	0.010(1)	0.002(1)	-0.004(1)
C(2)	0.041(1)	0.038(1)	0.041(1)	0.002(1)	0.0028(9)	-0.006(1)
C(3)	0.038(1)	0.034(1)	0.046(1)	-0.001(1)	0.0048(9)	-0.0021(9)
C(4)	0.055(1)	0.032(1)	0.050(1)	-0.005(1)	0.005(1)	-0.006(1)
C(5)	0.050(1)	0.031(1)	0.070(2)	0.002(1)	0.009(1)	-0.002(1)
C(6)	0.049(1)	0.042(1)	0.058(1)	0.015(1)	-0.001(1)	-0.005(1)
C(7)	0.071(2)	0.044(1)	0.042(1)	0.001(1)	-0.004(1)	-0.001(1)
C(8)	0.12(3)	0.070(2)	0.062(2)	0.010(2)	0.026(2)	-0.020(2)
C(9)	0.098(3)	0.091(3)	0.068(2)	-0.011(2)	-0.031(2)	0.017(2)

