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A New Methodology for the Synthesis of Carbafuranoses and Related Carbanucleosides

by

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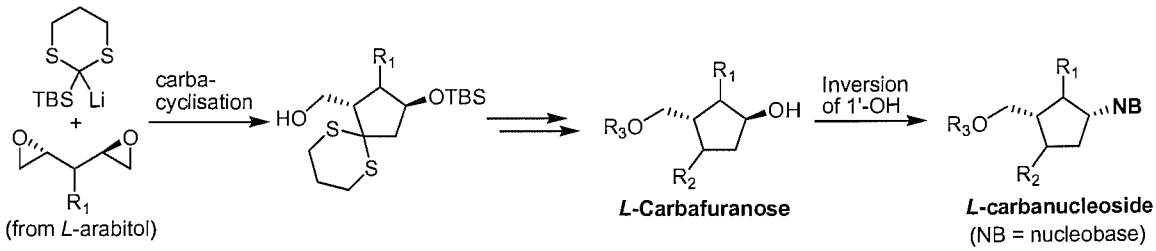
Abstract

Carbocyclic nucleosides (carbanucleosides) are mimetics of natural nucleosides and have been the subject of intense research in recent years. Many analogues of carbanucleosides have exhibited potent anti-viral and anti-tumour properties. Thus, there is a continuing interest for synthetic methodologies to access carbanucleoside analogues in enantiomerically pure form.



This thesis describes the development of a novel approach for the enantiospecific synthesis of carbafuranose analogues and the conversion of the synthesised carbafuranoses into the corresponding carbanucleosides. The core of the methodology concerns the construction of the cyclopentane moiety of the carbanucleoside by a Brook rearrangement-mediated domino carbacyclisation. Hence, the coupling of a lithio-*tert*-butyldimethyl-1,3-dithiane linchpin with chiral symmetric bis-epoxide substrates led to highly functionalised spiro-thioketals which could be converted to a range of carbafuranose analogues in straightforward transformations. The symmetric bis-epoxide building blocks were synthesised from arabitol, which is available in both enantiomeric forms. The hetereonucleobase of the carbanucleoside was then introduced to the suitably protected cycloalkanols to afford the corresponding carbanucleoside targets.

Acknowledgements

First of all, I would like to thank the University of Southampton for the PhD opportunity. Many thanks to CMS chemicals for the financial support and also to Vicky, who have had to make several trips to the department about my work. I would also like to pay tribute to the MS and the NMR services at Southampton as they have been absolutely marvellous, and the same can be said for the rest of the staff in the department.

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Abbreviations

Ac	Acetyl
9-BBN	9-Borabicyclo[3.3.1]nonane
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
BSA	Benzeneseleninic anhydride
BTI	Bis-(trifluoroacetoxy)iodobenzene
Bu	Butyl
Bz	Benzoyl
CAN	Cerium ammonium nitrate
CSA	Camphor sulfonic acid
DAIB	Diacetoxyiodobenzene
DAST	Diethylaminosulfur trifluoride
DBBQ	2,6-Di-tert-butyl-1,4-benzoquinone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
de	Diastereomeric excess
DEAD	Diethyl azodicarboxylate
DHP	Dihydropyran
DIAD	Diisopropylazodicarboxylate
DIBAL-H	Diisobutylaluminium hydride
DIPEA	Diisopropylethylamine
DMAP	Dimethylaminopyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMP	Dess-Martin Periodate
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMS	Dimethylsulfide
DMSO	Dimethylsulfoxide
Ee	Enantiomeric excess
Ent-	Enantiomer of
Et	Ethyl
HMPA	Hexamethylphosphoramide
HWE	Horner-Wadsworth-Emmons
IBDA	Iodobenzene diacetate
IBX	Iodoxybenzoic acid
IPA	Propan-2-ol
Ipc	Isopinocamphenyl
LDA	Lithium diispropylamide
***m*-CPBA**	*meta*-Chloroperoxybenzoic acid
Me	Methyl
MEM	Methoxyethoxy-methyl
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NIS	*N*-Iodosuccinimide
PCC	Pyridinium chlorochromate
P.E.	Petroleum ether 40-60
Ph	Phenyl
Pr	Propyl
***p*-TSA**	*para*-Toluenesulfonic acid
py	Pyridine
RCM	Ring closing metathesis
TBAB	Tetrabutylammonium bromide
TBAF	Tetrabutylammonium fluoride
THF	Tetrahydrofuran
THP	Tetrahydropyran
TMEDA	Tetramethylethylenediamine
Ts	Tosyl
Tris	Triisopropylbenzenesulfonyl

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Chapter 1 - Introduction

1.1 Carbasugars and Carbanucleosides

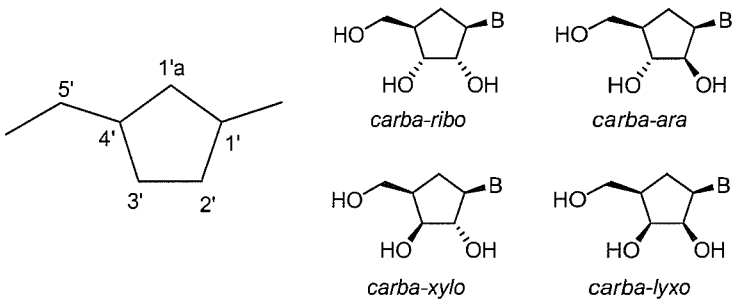
Carbohydrates are important biomolecules that have vital roles in many biological processes as well as being simply a form of the body's energy storage.[1-9] Nucleosides, derivatives of carbohydrates, are of particular importance as they can be sequentially phosphorylated by kinases and processed by polymerases into nucleic acids which are essential in all biological systems. Nucleoside analogues display a wide range of biological activities and the search for nucleosides as non-toxic, selective inhibitors of cellular enzymes for the control of viral diseases and cancer has been the subject of intense research.[10-17] This consequently led to the discovery of novel synthetic nucleoside analogues with extensive modifications both on the heterocyclic base and on the sugar moiety.

As part of the research and development of nucleoside-based therapeutic agents, the endocyclic ring oxygen of the sugar moiety of nucleosides was replaced by a carbon atom to form analogues of **carbocyclic nucleosides,** also called **carbanucleosides**. These so-called **carbohydrate mimetics** were anticipated to replace the hydrolytically and enzymatically scissile glycosidic bond of conventional nucleosides with a stable C-N bond, while causing minimal structural disturbances. Up until now, a large number of biologically active carbanucleosides has been reported, but the search for more potent analogues as suitable drug candidates continues.

1.1.1 Nomenclature for Carbanucleosides

The nomenclature for carbanucleosides closely resembles that of the conventional nucleoside system. In addition, the replacement of the ring oxygen by carbon is termed 'carba', which is also used as a prefix (*carba*) when incorporated into the name of the compound (Figure 1.1). The conventional numbering system for nucleosides is preserved and the number for the additional carbon atom is designated as 1'a.[10]

Figure 1.1 – Carbanucleoside Nomenclature



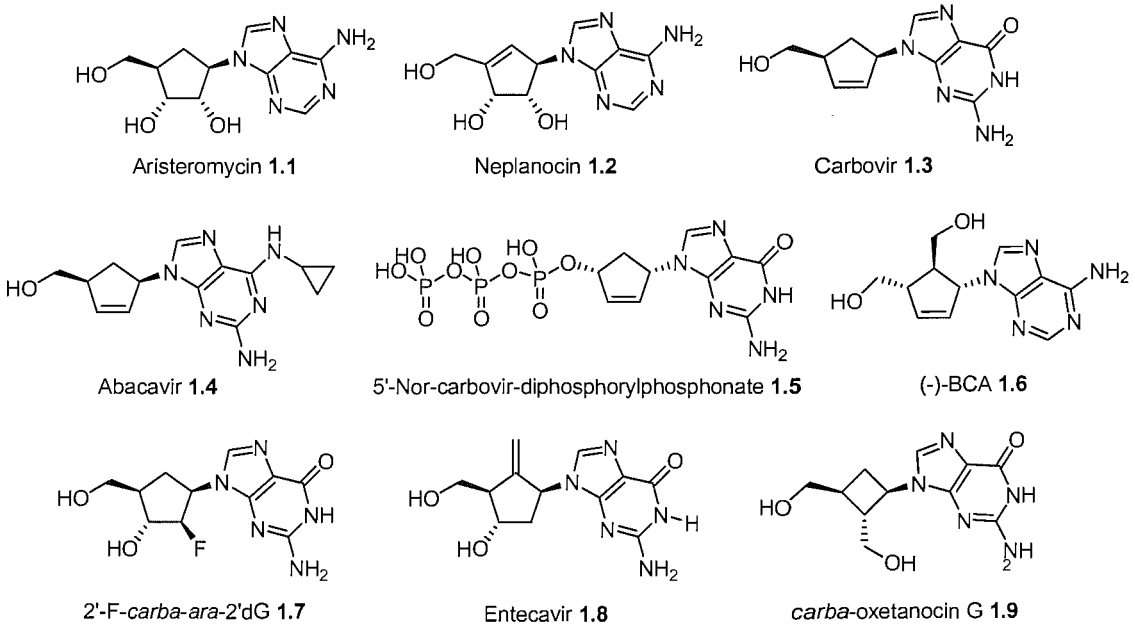
1.1.2 Examples of Carbanucleosides

Aristeromycin **1.1**[18] and neplanocin A **1.2**[19] (Figure 1.2) were the first natural carbanucleoside analogues isolated and the broad spectrum of biological activities displayed by these compounds sparked the search for other biologically active carbanucleosides by the means of chemical synthesis. Consequently, several synthetic carbanucleoside analogues with important therapeutic properties were discovered.

Several synthetic carbocyclic nucleoside analogues have been found to display a broad spectrum of anti-viral and anti-bacterial activities. The triphosphate of the antiretroviral agent carbovir **1.3** is a potent and selective inhibitor of HIV reverse transcriptase.[20] Abacavir **1.4**,[21,22] a prodrug of carbovir with improved

pharmacokinetics, is currently employed in the treatment of HIV. Intriguingly, (-)-5'-nor-carbovir-diphosphorylphosphonate **1.5**, with the unnatural configuration, is a more potent inhibitor of HIV-RT than carbovir triphosphate itself.[23] This is one of the examples where the unnatural carbanucleoside analogue exhibits biological activities equal to or higher than its natural enantiomer. A second example of such analogues is the 1'a-substituted (-)-BCA **1.6** which also exhibits potent anti-HIV activity.[24] It is therefore essential to have access to optically pure carbanucleoside analogues in both enantiomeric forms.

Figure 1.2



Other biologically active carbanucleosides include the fluorine containing 2'-F-*carba-ara*-2'dG **1.7** which is exceptionally effective against herpes simplex virus (HSV) 1 and HSV 2.[25] In addition, this compound established carbocyclic nucleosides as more than simply metabolically stable versions of active furanose nucleosides since its furanose parent only displayed weak anti-herpes activity. Another successful

example, entecavir **1.8**, is currently undergoing phase III clinical trials for the treatment of chronic hepatisis B infections (HBV).[22,26] Furthermore, several cyclobutyl and cyclohexyl carbanucleosides have been developed, with the former showing particularly promising anti-viral properties. For example, carbocyclic oxetanocin G **1.9** displays broad-spectrum anti-viral activity against HIV and herpes viruses.[27,28]

1.1.3 Conformational Aspects of Carbanucleosides

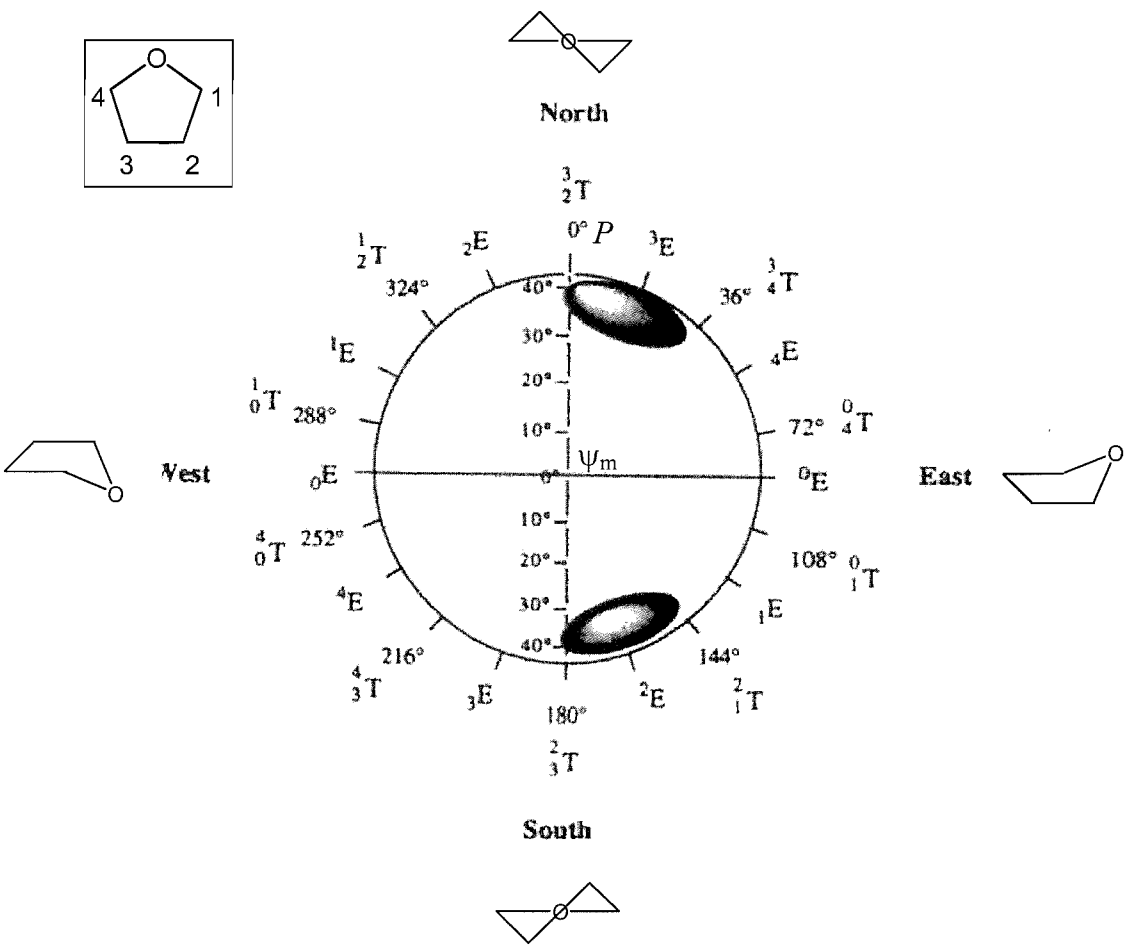
The replacement of the ring oxygen by a carbon atom should in principle cause minimal changes to the structure of the original nucleoside molecule. In many cases however, carbocyclic nucleosides have displayed poorer activities than the furanose counterparts. Since the conformation of the five-membered ring is believed to play a critical role in modulating biological activity, conformational changes caused by the replacement of the ring oxygen is a possible reason for the observed difference in bioactivity.

In a furanose nucleoside, steric as well as stereoelectronic effects such as the **anomeric effect** and **gauche interactions** force the sugar into two preferred conformations in the pseudorotational cycle.[29] In carbasugars and carbanucleosides, the loss of the tetrahydrofuran oxygen abolishes the anomeric effect as well as the gauche interaction between the ring oxygen and the hydroxyl groups. In the absence of these stereoelectronic effects, it is possible for the cyclopentane ring to adopt conformations significantly deviated from those of the furanose ring, resulting in the loss (or gain) in biological activities. In addition to conformational differences, removal of the ring oxygen in carbanucleosides can induce further changes in physical parameters such as bond lengths and bond angles as well as the basicity of the molecule.

1.1.3.1 Factors Influencing the Pseudorotational Equilibrium of the Furanose Moiety of Nucleosides

The pseudorotational wheel[29] (Figure 1.3) describes the interconversions of puckered forms of the cyclopentane/furanose ring, in which *P* defines the phase angle of pseudorotation (position of puckering) and ψ_m indicates the extent of puckering. The wheel consists of 20 distinct twist (T) and envelope (E) conformations, where T and E are the two lowest energy conformations adopted by a five-membered ring. This is further divided into north (N), south (S), east (E) and west (W) regions as depicted in Figure 1.3.

Figure 1.3



A survey of 178 crystal structures of nucleosides and nucleotides by Altona *et al.* revealed the majority of these compounds to adopt the north ($P \sim 18^{\circ}$) and south ($P \sim 162^{\circ}$) conformations.[30] For these 178 β-D-furanosides, the ratio between the N and S states in ribonucleosides was found to be approximately 1:1, while a 1:3 ratio favouring the S conformation was observed for 2'-deoxyribonucleosides (Figure 1.4). The conformational preferences of the pentofuranose moiety are controlled by a combination of steric interactions between substituents, and stereoelectronic effects such as the anomeric effect and gauche interactions. The gauche effect, in this context, is the stabilisation of the gauche relative to the *trans* formation of the O-C-C-O fragment by electronegative elements. In nucleosides, the anomeric effect corresponds to the tendency of the lone pair on the furanose oxygen to orient antiperiplanar to the heteronucleobase.

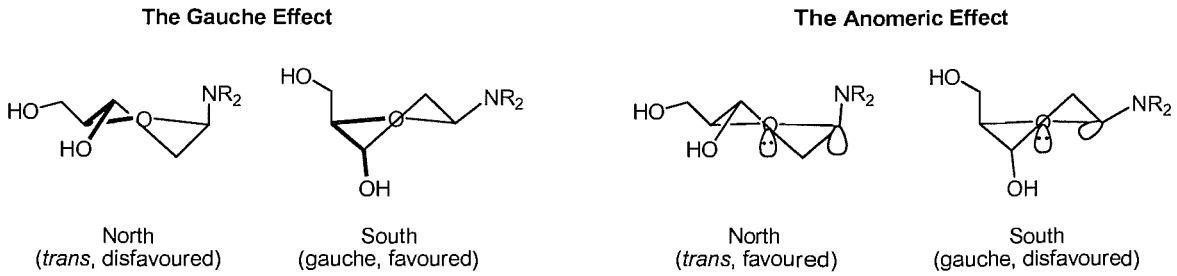
Figure 1.4

Ribofuranoside **2'-Deoxyribofuranoside**

Qualitative assessment of the steric interactions between the substituents of the furanose moiety alone suggests nucleosides prefer conformations with $P = 0^{\circ}$, 18° (N) and 162°, 180° (S).[31,32] In these conformations, steric repulsion between the 1'-nucleobase and the 4'-hydroxymethyl substituent is minimal. Stereoelectronically, the preference of the O4'-C4'-C3'-O3' torsion angle for the gauche rather than the *trans* staggered conformation in 2'-deoxyribonucleosides (Figure 1.5) explains the higher

population of S conformers observed.[33,34] Substitution of the 3'-hydroxyl by a more electronegative substituent has a similar effect.[35,36]

Figure 1.5

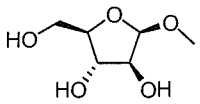


In ribonucleosides, two additional torsional angles (O4'-C1'-C2'-O2' and O2'-C2'-C3'-O3') also prefer the gauche conformations. The net effect would lead to an approximately equal population of the S and N conformers.

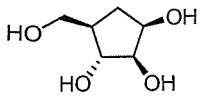
The anomeric effect is most favourable in W conformations, but few W nucleoside conformers have been found due to disfavourable steric interactions between the 1'- and the 4'-substituents. The N-type conformation is energetically favoured over S in terms of the anomeric effect (Figure 1.5) due to a more efficient orbital overlapping between the oxygen lone pair and the C-N anti-bonding orbital.

In carbocyclic nucleoside analogues, the anomeric effect is abolished and gauche interactions corresponding to the endocyclic oxygen are also eliminated, resulting in changes in the conformation of the cyclopentane moiety. This was demonstrated by comparing the conformations of β-methyl glycoside **1.10a** and β-carbafuranose **1.10b** (Figure 1.6).[37-39] In both cases, the northern conformations predominate. However, furanoside **1.10a** has a higher proportion of N conformers due to additional stabilisation by the anomeric effect.

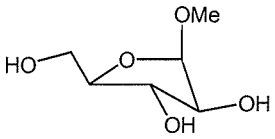
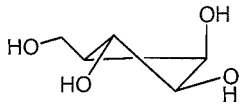
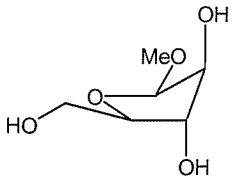
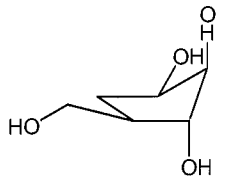
Figure 1.6



1.10a



1.10b

N conformer	$_2E$		^3_2T	
X_N (%)	99		75	
S conformer	^2E		^2E	
X_S (%)	1		25	

1.2 Major Synthetic Routes to Carbafuranoses

Up to now, numerous carbanucleoside analogues have been synthesised and it would be difficult to encompass all the reported syntheses in this report. Fortunately, several excellent reviews dealing with the synthetic strategies for these compounds are available in the literature.[11,13-17] In this Chapter, we therefore provide a brief overview of the major synthetic routes for carbafuranose analogues closely related in structure to the ones involved in our project. The formation of carbanucleosides from the corresponding carbafuranose analogues will be discussed in the subsequent Chapter.

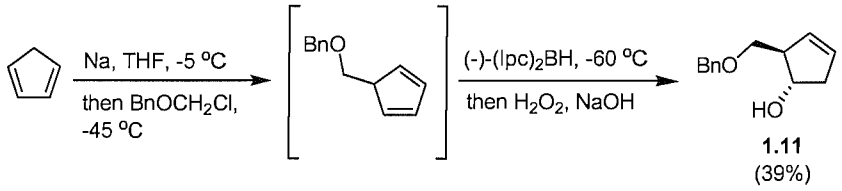
1.2.1 Cyclopentadiene-Based Strategies

With the cyclopentane ring already present, cyclopentadiene has proved to be a popular starting material for the synthesis of the carbafuranose moiety of carbanucleosides. However, the major drawback with cyclopentadiene-based methodologies is the lack of intrinsic stereochemical information within cyclopentadiene itself. Consequently, the main focus of this strategy is on introducing the necessary functionalities with the correct stereochemistry as well as inducing the required enantioselectivity. The latter can be achieved by processes such as asymmetric synthesis and enzymatic resolution.

In the first example, an impressively facile synthesis of chiral cyclopentenol **1.11** from cyclopentadiene (Scheme 1.1) was reported by Biggadike *et al.*[40] Alkylation of the sodium salt of cyclopentadiene with benzylchoromethyl ether followed by *in-situ* asymmetric hydroboration using (-)-diisopinocamphenylborane ((-)-$(Ipc)_2BH$) afforded

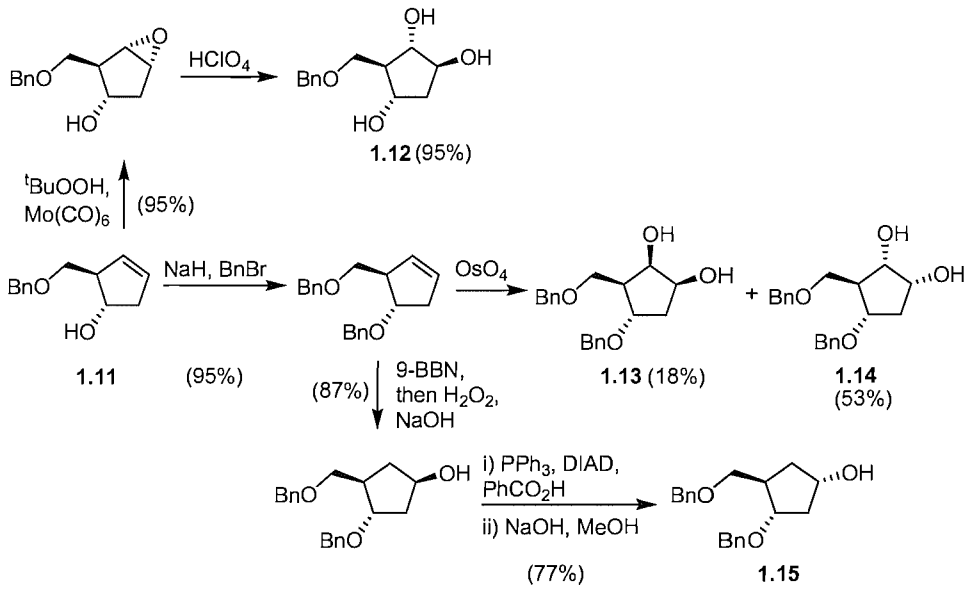
cyclopentenol **1.11** in 39% yield (>98% ee).

Scheme 1.1



Chiral cyclopentenol intermediate **1.11** could be converted into the corresponding 1'a-hydroxycarbafuranose analogues **1.12-1.14** by a stereoselective dihydroxylation or an epoxidation/epoxide opening sequence (Scheme 1.2).[41] On the other hand, the conventional 2'-deoxycarbanucleosides **1.15** could be obtained by the stereoselective hydroboration of the same intermediate.[42]

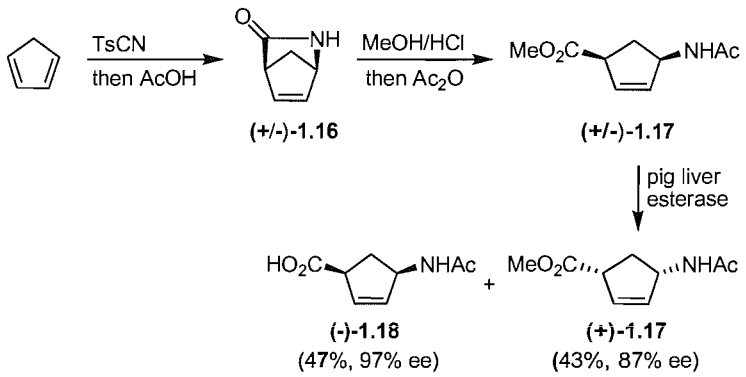
Scheme 1.2



The above example is one of only a few that utilised an asymmetric synthesis process to generate optically enriched cyclopentane analogues. The majority of cyclopentadiene-based routes generally involved enzymatic resolution of racemic building blocks derived from cyclopentadiene. Sicsic *et al.* utilised pig liver esterase to

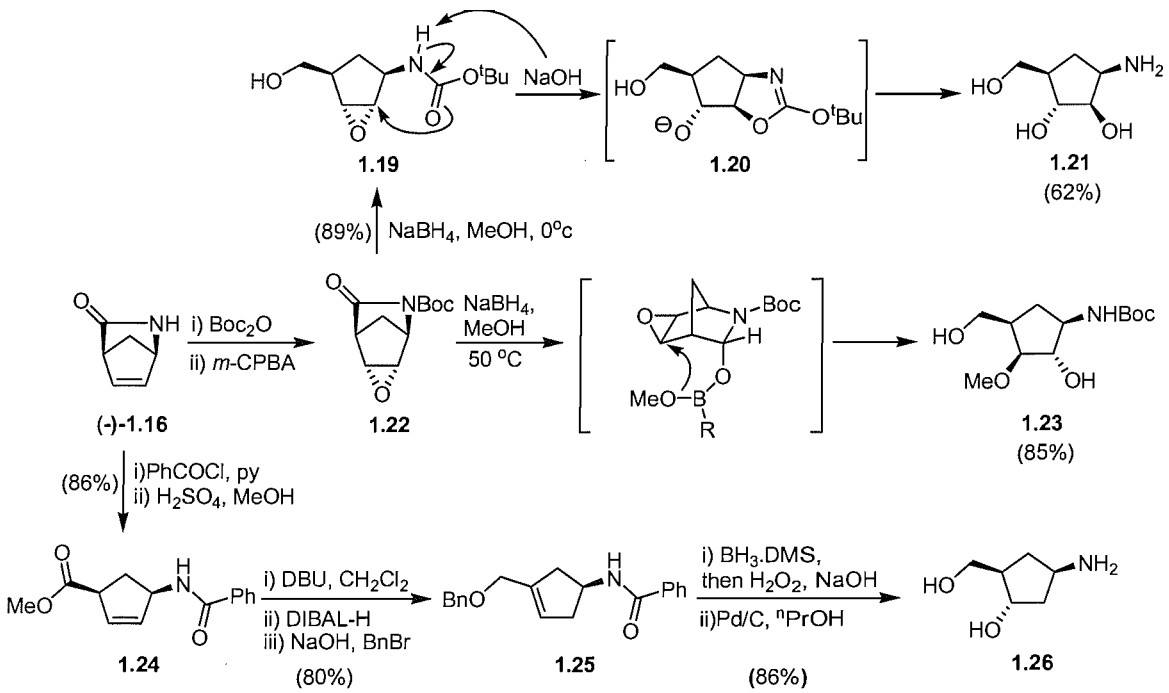
effect enantioselective hydrolysis of acetamidoester **1.17** to afford the optically enriched acid **(-)-1.18** in 47% yield (97% ee) (Scheme 1.3), with the unreacted ester **(+)-1.17** recovered in 43% yield (87% ee).[43,44]

Scheme 1.3



Enantiopure bicyclic lactam **(-)-1.16** later became commercially available (Chiroscience) and several syntheses of carbafuranoses have since been developed starting from enantiopure lactam **1.16** (Scheme 1.4) and ester **1.17** (Scheme 1.5).

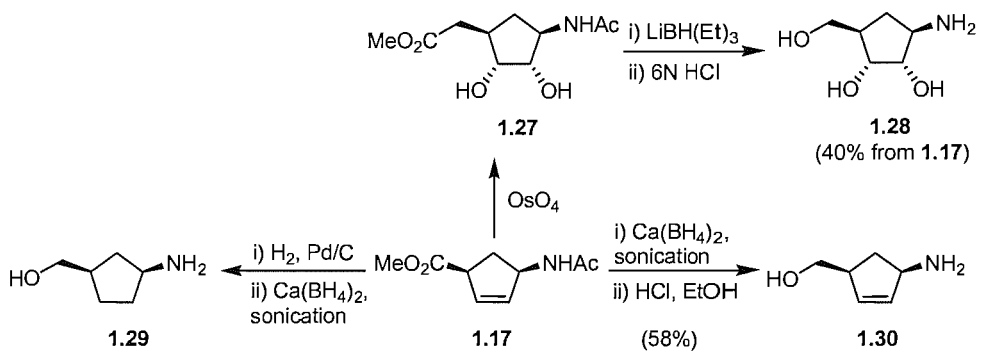
Scheme 1.4



Cullis *et al.* established the syntheses of enantiopure carbaxylose derivative **1.23** and carbaarabinose derivative **1.21** *via* chiral epoxide **1.22** (Scheme 1.4), which was obtained from the stereoselective epoxidation of chiral lactam **(-)-1.16**.[45,46] Treatment of lactam **1.22** with sodium borohydride in methanol at 0 °C readily afforded epoxide **1.19**. This was converted into carbaarabinose derivative **1.21** *via* intermediate **1.20** which was formed from the regioselective opening of epoxide **1.19**. Alternatively, treatment of lactam **1.22** with sodium borohydride in methanol at 50 °C led not only to the reductive cleavage of the lactam, but also to the regioselective methanolysis of the epoxide functionality to give carbaxylose derivative **1.23**. Bray and Dolan have also utilised lactam **(-)-1.16** in the synthesis of enantiopure 2'-deoxycarbafuranose derivative **1.26** by a sequence of transformations involving an alkene isomerisation and a stereoselective hydroboration (Scheme 1.4).[47]

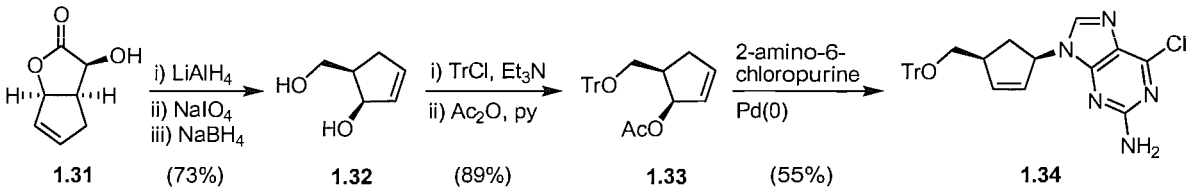
Enantiopure ester **(-)-1.17** (Scheme 1.5), obtained from the hydrolysis and protection of chiral lactam **1.16**, was converted to carbaribose derivative **1.28** *via* the dihydroxylation product **1.27**.[43] Furthermore, the 2',3'-dideoxycarbafuranose derivative **1.29** and cyclopentene **1.30** were both derived from ester **(-)-1.17** in straightforward operations,[48,49] the latter being a precursor of the biologically active carbovir **1.3** (Figure 1.2).[49]

Scheme 1.5



The racemic cycloaddition product **1.31** (Scheme 1.6) derived from glyoxalic acid and cyclopentadiene was resolved by Roberts *et al.* using the enzyme pseudomonas fluorescens lipase (pfl).[50] In addition, Roberts also demonstrated the conversion of hydroxylactone **1.31** into allylic acetate **1.33** in straightforward operations. The heteronucleobase could be subsequently introduced by a palladium catalysed cross coupling process.[51] Enantiopure hydroxylactone **1.31** thus served as another invaluable building block in carbocyclic nucleoside synthesis.

Scheme 1.6



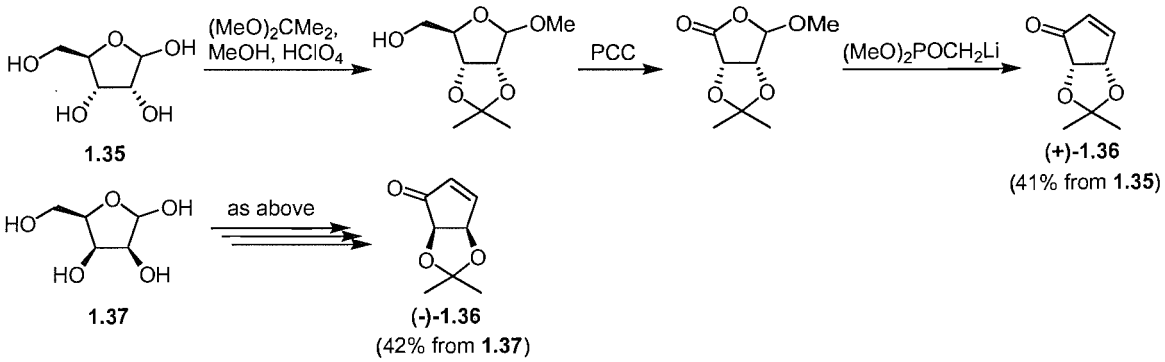
1.2.2 From Chiral Starting Materials

In contrast to the cyclopentadiene-based methodologies, chiral starting materials already containing the required stereogenic centres can be utilised in the synthesis of carbafuranoses. Carbohydrates, with several isomeric analogues available commercially in both enantiomeric forms, are especially suited to this purpose. With the majority of the stereocentres already defined, carbohydrate-based methodologies focus on the formation of the cyclopentane ring.

The chiral cyclopentenones **(+)-1.36** and **(-)-1.36** (Scheme 1.7) derived from carbohydrate-based materials have been commonly employed in the synthesis of carbanucleosides. They have been synthesised by various methods,[52,53] the most efficient of which was reported by Borchardt.[53] Starting from D-ribose **1.35**, cyclopentenone **(+)-1.36** was obtained in three operations in 41% overall yield in which

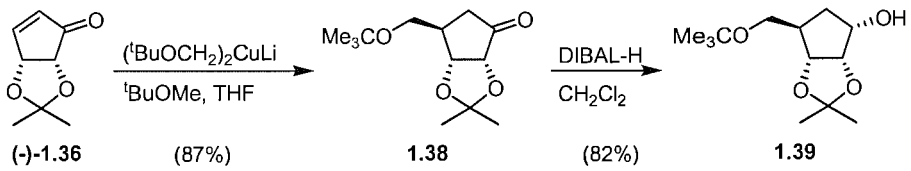
the five-membered ring was formed by an intramolecular HWE cyclisation. Lactone **(-)-1.36** was obtained in 42% overall yield from D-lyxose **1.37** in a similar manner.

Scheme 1.7



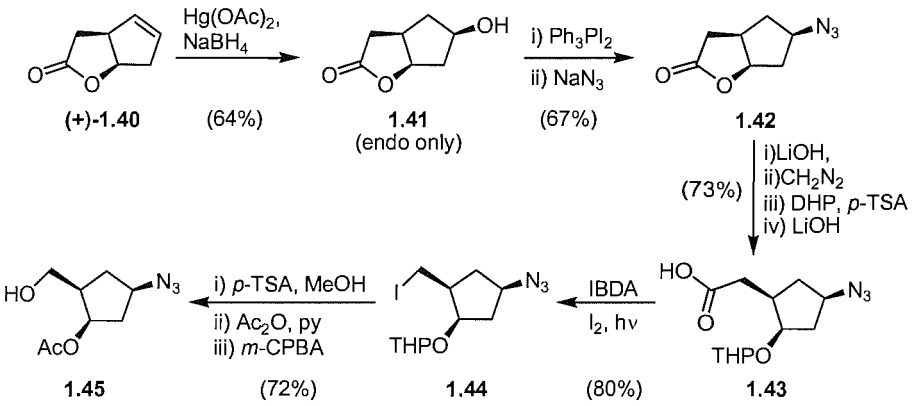
Enone **1.36** could be converted to the 1,4-addition product **1.38**, which was subsequently reduced to α-carbafuranose **1.39** using DIBAL-H (Scheme 1.8).[54] Several other carbohydrate-based methods for the synthesis of carbafuranose analogues have been reported, but many of them are relatively lengthy and practically inefficient.[55-59]

Scheme 1.8



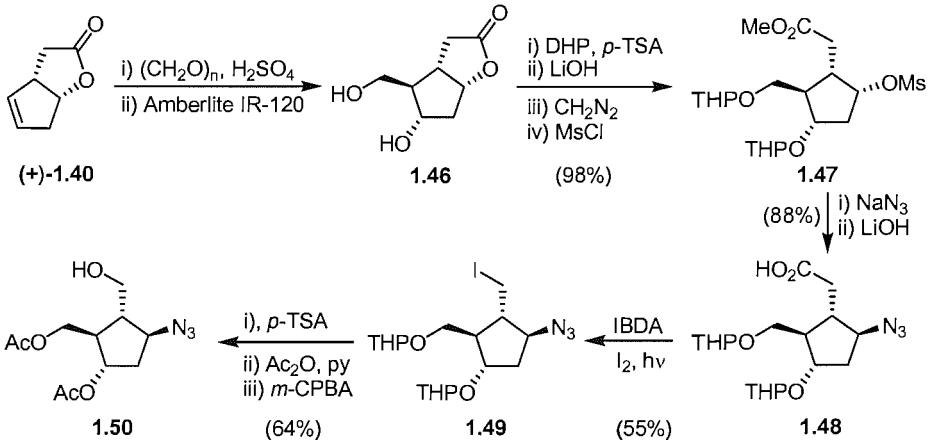
Commercially available chiral scaffolds with suitable structural features have occasionally been utilised as building blocks for carbanucleosides. Ötvös *et al.* have developed two synthetic routes to 2'-deoxycarbafuranose analogues starting from the commercially available chiral lactone **1.40** (Scheme 1.9 and 1.10).

Scheme 1.9



The first method involved a highly regio- and stereoselective hydroxylation employing $Hg(OAc)_2$ to afford alcohol **1.41** (Scheme 1.9).[60] Subsequent introduction of azide occurred with net retention of configuration (i.e. double inversion) *via* the corresponding iodo derivative. Hydrolysis of lactone **1.42** and protection of the hydroxyl functionality led to azido-acid **1.43**. Carboxylic acid **1.43** was then converted into iodide **1.44** in an iododecarboxylation process utilising iodobenzene diacetate IBDA (also named diacetoxyiodobenzene DAIB). Exchange of the THP protecting group with an acetate group, followed by the introduction of the 5'-hydroxyl substituent by *m*-CPBA furnished carbafuranose derivative **1.45**.

Scheme 1.10



The second method commenced with a regio- and stereospecific Prins addition of formaldehyde to cyclopentene **1.40** (Scheme 1.10). The resultant diol from the hydrolysis of the Prins adduct **1.46** was protected as the bis-THP ether.[61] Lactone opening and methylation of acid followed by sulfonylation of the secondary hydroxyl afforded mesylate **1.47**. Displacement of mesylate with NaN_3 and then ester hydrolysis led to azido-acid **1.48**. Carboxylic acid **1.48** was converted into iodide **1.49** by iododecarboxylation. Exchange of protecting groups and subsequent introduction of the 1'a-hydroxymethyl functionality furnished carbafuranose derivative **1.50**. The 1'a-hydroxylmethyl substituent could be removed by oxidation to the corresponding carboxylic acid followed by a second iodo-decarboxylation process. This method was originally employed by Ötvös in the synthesis of conventional carbanucleosides, but the large number of steps involved would certainly restrict its synthetic applications. It would be much more suitable for the synthesis of 1'a-substituted carbanucleoside analogues.

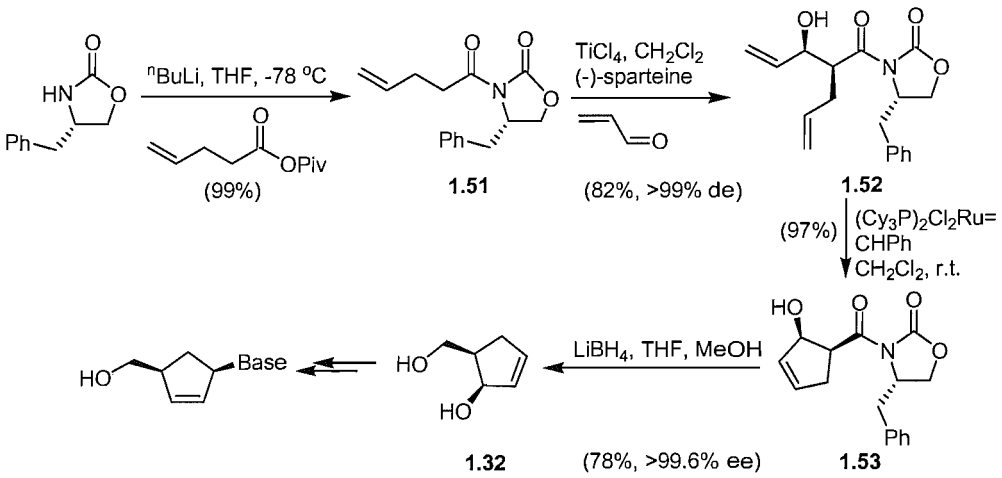
1.2.3 Metathesis-Based Strategies[14,17]

The olefin metathesis reaction was first reported in 1955 by Anderson and Merckeling describing the polymerisation of norbornene by titanium(II) species. It was not until the early 1990s that the metathesis reaction found wide-spread applications in organic synthesis, largely due to the discovery of several well defined and functional group-tolerant catalysts by Schrock, Nolan and Grubbs during that period.[62] More recently, a large number of metathesis-based routes to carbanucleosides have been reported and they ultimately incorporated the ring closing metathesis (RCM) process as a key transformation for the construction of the cyclopentane moiety.[14,17] With several

practical advantages such as functional group tolerance and the ease of product isolation and purification, the RCM process has emerged as a powerful tool in the synthesis of carbanucleoside analogues as well as in organic synthesis in general.

The first metathesis-based carbanucleoside synthesis was by Crimmins *et al.*[63,64] and this involved a combination of an asymmetric aldol addition using chiral (*S*)-4-benzyl-2-oxazolidinone auxiliaries and an RCM process to construct the cyclopentane ring (Scheme 1.11). Diene **1.52**, the product of the asymmetric aldol reaction from compound **1.51** and acrolein (82%, >99% de), was cyclised in the presence of the Grubbs catalyst to cyclopentenol **1.53** which was subsequently reduced to diol **1.32** (>99.6% ee). The nucleobase could then be introduced by a palladium-catalysed cross coupling to the bis-acetate derived from diol **1.32**.

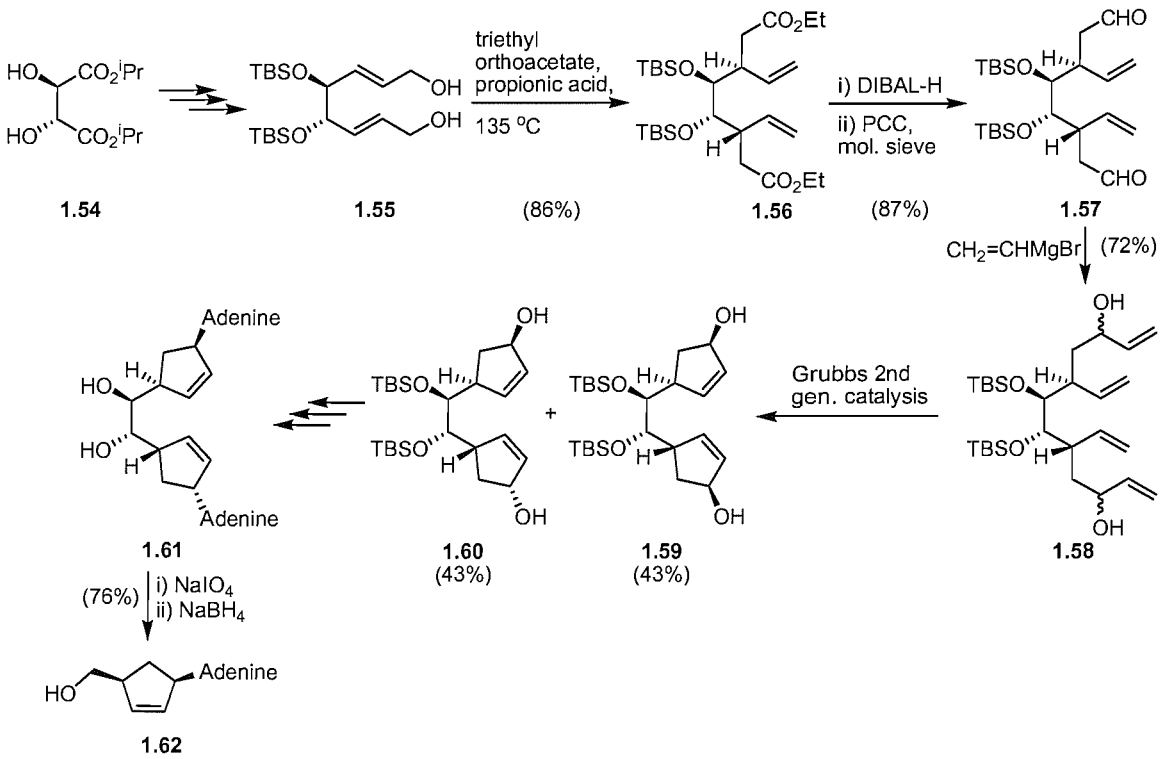
Scheme 1.11



A remarkable dis-symmetric synthesis of carbovir analogues from L-tartrate was reported by Hong *et al.*, involving the combined used of a double sigmatropic rearrangement and a double RCM process.[65] L-tartrate **1.54** was converted into diol **1.55** in straightforward operations (Scheme 1.12). This was followed by a double [3,3]-sigmatropic rearrangement to give bis-ester **1.56**, which was subsequently converted

into the corresponding bis-aldehyde **1.57** by DIBAL-H reduction and oxidation with PCC. Addition of vinylmagnesium bromide afforded bis-diene **1.58**, which underwent subsequent RCM to afford a mixture of non-symmetrical bis-cyclopentenol **1.59** and C_2-symmetric bis-cyclopentenol **1.60** (43% each). After desilylation of compound **1.60**, introduction of adenine followed by treatment with $NaIO_4$ and then $NaBH_4$ furnished the desired carbanucleoside **1.62**. Other metathesis-based routes have been reported and the majority of them concerned the synthesis of cyclopentene nucleosides and analogues of carbaribose/carbalyxose nucleosides.[14]

Scheme 1.12



1.3 Formation of Carbanucleosides from Carbafuranose Analogues[16]

There are several different ways in which a heteronucleobase can be introduced to a carbafuranose analogue. These are broadly divided into the two major approaches. The **linear** approach concerns the construction of the heteronucleobase moiety from the corresponding cyclopentamine in a stepwise manner. The **convergent** approach involves the direct attachment of a heteronucleobase with an appropriately functionalised carbafuranose fragment and there are various ways in which this can be achieved. While the convergent approach involves fewer numbers of synthetic steps, mixtures of regioisomers are obtained. On the other hand, the linear approach only produces the desired regioisomer, but the additional transformations involved greatly reduce the efficiency of the synthesis.

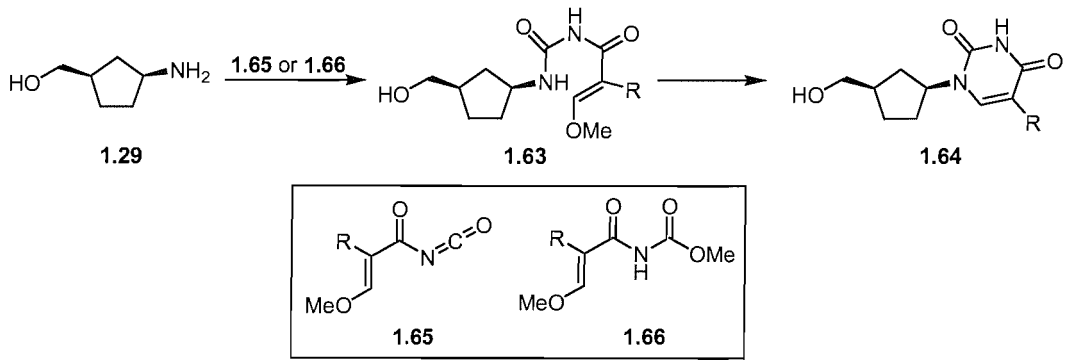
1.3.1 The Linear Approach

1.3.1.1 Construction of Pyrimidine Carbanucleosides

The construction of uracil and thymine bases from the corresponding amine is mainly based upon methodologies developed by Shaw and Warrener.[66,67] Hence, treatment of amine **1.29** with *in-situ* generated isocyanate **1.65** would lead to acryloyl urea **1.63**, which could be subsequently cyclised to the carbanucleoside analogue **1.64** (Scheme 1.13). Alternatively, reaction of amine **1.29** with acryloyl carbamate **1.66** at elevated temperature would lead to the same urea **1.63**. The use of carbamate **1.66** can sometimes be more convenient as it is a solid that can be recrystallised and stored over a

long period of time. Cytidine analogues can be derived from the corresponding uridines (R = H) with additional transformations. Applications of such syntheses have been demonstrated by Roberts[49] and Chu.[58]

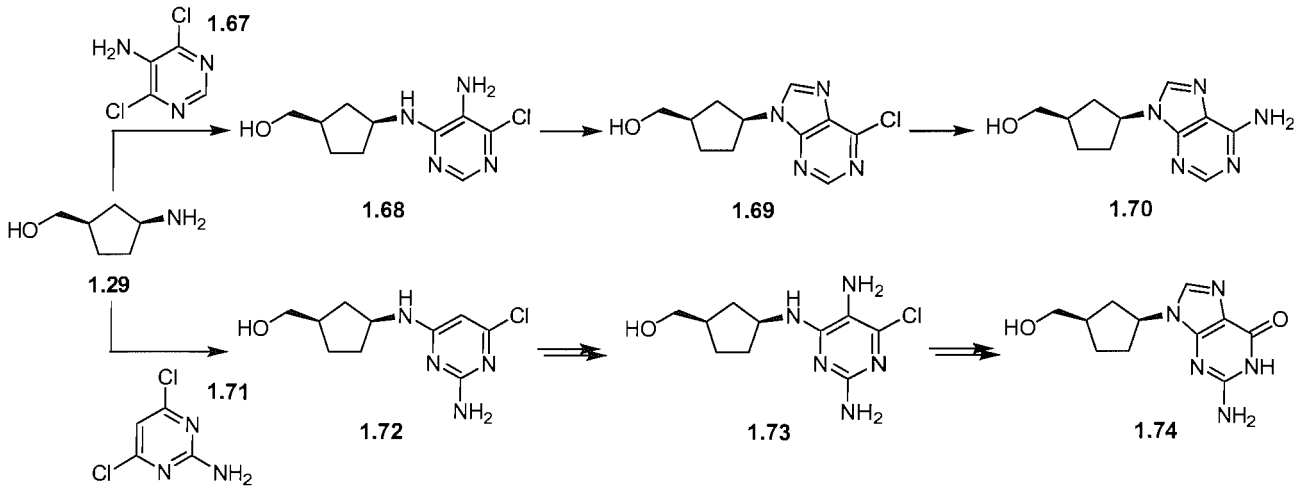
Scheme 1.13



1.3.1.2 Construction of Purine Carbanucleosides

Construction of the purine bases is based on the Traube synthesis.[16] Adenine analogues are prepared from cyclopentamine **1.29** to afford compound **1.68** (Scheme 1.14). Cyclisation with triethylorthoformate and subsequent ammonolysis of the chloro function afford the carbaadenosine analogue **1.70**.

Scheme 1.14



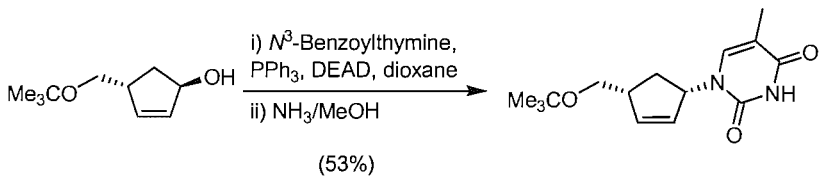
Synthesis of the guanidine analogues involved two additional steps. After the formation of compound **1.72**, the 5-amino group is introduced by a diazotisation/reduction sequence. Cyclisation of compound **1.73** followed by hydrolysis of the chloro function furnished the carbaguanosine analogue **1.74**. Applications of such syntheses have been demonstrated by Ötvös.[61]

1.3.2 The Convergent Approach

1.3.2.1 Mitsunobu Coupling with a Cycloalkanol

The Mitsunobu condensation reaction between a cyclopentanol and a heteronucleobase is mediated by a triphenylphosphine/dialkylazodicarboxylate mixture and proceeds with inversion of configuration (Scheme 1.15).[58] The conditions involved are remarkably mild and several functional groups are tolerated. This is therefore often the method of choice for the attachment of nucleobases to the carbafuranose moiety.[68-74] However, like all S_N2 processes, the Mitsunobu reaction is strongly influenced by the steric environment of the alcohol and this will be discussed in detail in Chapter 5.2.1.

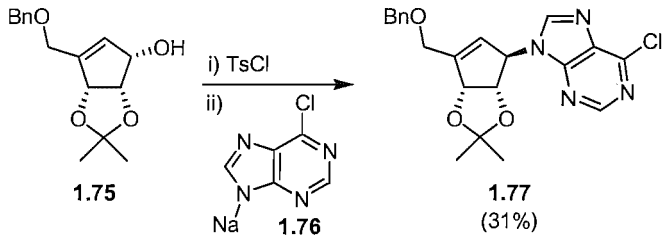
Scheme 1.15



1.3.2.2 Nucleophilic Displacement of an Activated Hydroxyl

The heteronucleobase, or its metal salt, can undergo nucleophilic displacement of a mesylate or triflate formed from the corresponding cyclopentanol with inversion of configuration. This was demonstrated by Marquez in the first convergent synthesis of neplanocin A **1.2**.[75] Chiral alcohol **1.75**, derived from D-ribonolactone, was converted to the corresponding tosylate and treatment with the sodium salt of 6-chloropurine **1.76** afforded carbanucleoside **1.77** in 31% yield (Scheme 1.16).

Scheme 1.16

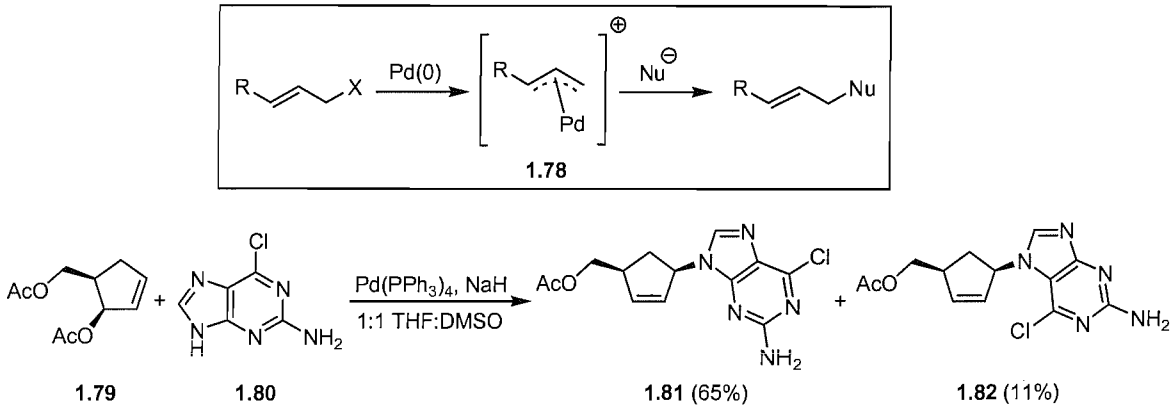


1.3.2.3 Pd-Catalysed Displacement of an Allyic Ester or Carbonate

The palladium-catalysed allylation of nucleophiles is another method often employed in the synthesis of cyclopentene nucleosides.[17] The so-called Tsuji-Trost allylation occurs *via* the η^3-allylpalladium(II) complex **1.78** (Scheme 1.17), formed from the oxidative addition of allylic esters (or carbonates, halides, epoxides etc.) to Pd(0), and this can be attacked by a nucleophile at its less hindered site. Crimmins *et al.* have demonstrated the application of such allyation in the synthesis of carbanucleoside analogue **1.81**, which served as a common synthetic intermediate for the biologically active carbovir **1.3** and abacavir **1.4** (Figure 1.2).[64] It is also

noteworthy to mention that the oxidative addition of allylic acetates to Pd(0) is reversible and must be performed in the presence of a base.

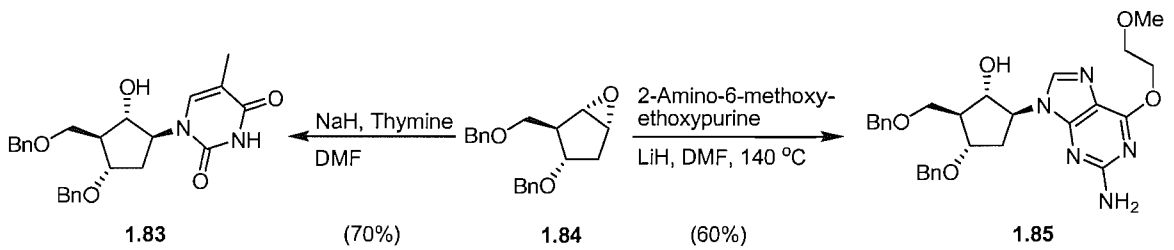
Scheme 1.17



1.3.2.4 Ring Opening of an Epoxide or a Cyclic Sulfate

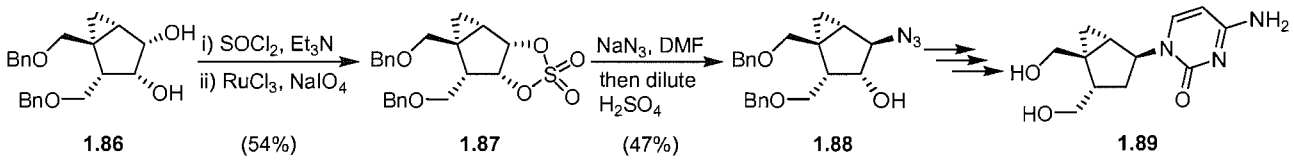
Nucleophilic opening of an epoxide enabled the stereospecific introduction of a heteronucleobase, as demonstrated by Borthwick *et al.*.[76] As previously described, chiral cyclopentyl epoxide **1.84** was readily obtained from cyclopentadiene (Scheme 1.2). Regioselective opening of epoxide **1.84** with the lithium salt of 2-amino-6-methoxyethoxypurine led to the purine carbanucleoside **1.85** in 60% yield (Scheme 1.18). Epoxide opening with the sodium salt of thymine also furnished a good yield of the thymidine analogue **1.83**.

Scheme 1.18



Likewise, nucleophilic opening of a cyclic sulfite or sulfate derived from the corresponding *cis*-1,2-diol has been applied to the synthesis of carbanucleoside analogues. *Cis*-diol **1.86** was converted to the corresponding cyclic sulfite by treatment with $SOCl_2$ and Et_3N and then oxidised further to cyclic sulfate **1.87** using $RuCl_3$ and $NaIO_4$ (Scheme 1.19).[77] Opening of the cyclic sulfate with NaN_3 followed by hydrolytic cleavage of the resulting sulfate afforded azide **1.88**, which was subsequently converted into the cyclopropyl-fused carbanucleoside **1.89**.

Scheme 1.19

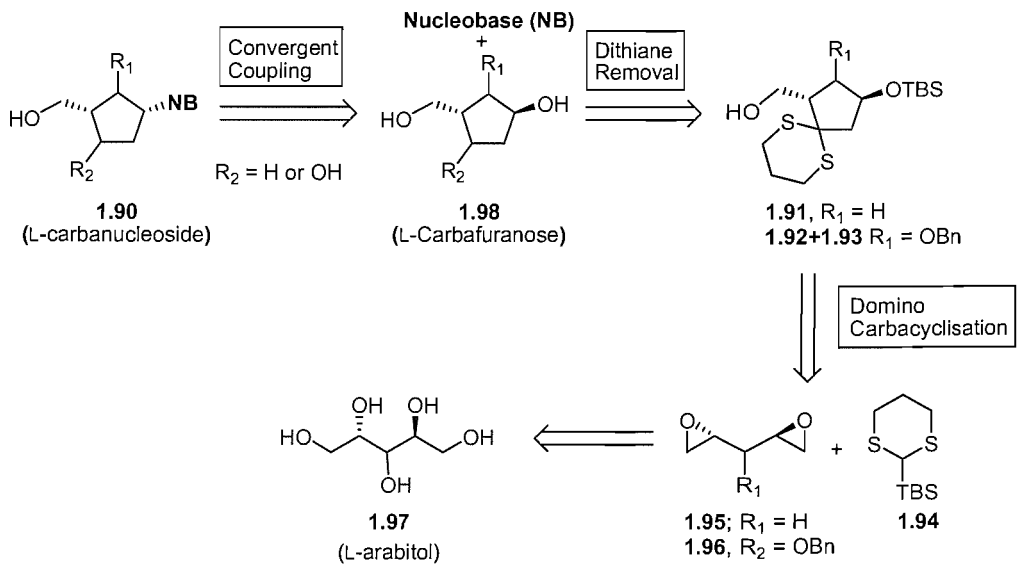


1.86 (54%) **1.87** (47%) **1.88** **1.89**

1.4 Aim of this Project

The aim of the project is to develop a versatile methodology for the enantiospecific synthesis of optically pure carbocyclic nucleoside analogues with the general structure of **1.90** (Scheme 1.20). The nucleus of the synthetic methodology concerns the construction of the carbocylic moiety of carbanucleosides *via* a Brook rearrangement-mediated domino carbacyclisation sequence between silyl dithiane linchpin **1.94** and symmetric bis-epoxides **1.95** and **1.96**, leading to highly functionalised cyclopentanes with the desired functionalities and stereochemistries. Enantiopure bis-epoxide analogues **1.95** and **1.96** will be obtained by literature methods from the commercially available arabitol **1.97**, which is available in both enantiomeric forms at similar costs (L-arabitol used for this project).

Scheme 1.20



The nature of the R_1 substituent of **1.90** is governed by the choice of the bis-epoxide substrate in the carbacyclisation process. Thus, the use of C_2-symmetric bis-

epoxide **1.95** should lead to the 1'a-unsubstituted product **1.91**, whilst the desymmetrisation of the *pseudo*-C_2-symmetric bis-epoxide **1.96** during the carbacyclisation process should eventually lead to the formation of the product as a pair of diastereoisomers **1.92** and **1.93**. Removal of the dithiane moiety of the carbacyclisation products **1.91-1.93** is anticipated to be achieved by reduction using Raney nickel to afford the 2',3'-dideoxycarbafuranose analogues (**1.98**, R_2 = H). Alternatively, hydrolysis of the thioketal functionality and reduction of the resultant ketone should furnish the 2'-deoxycarbafuranose analogues (**1.98**, R_2 = OH). After suitable protection/deprotection processes, it should be possible to convert the carbafuranoses to the corresponding carbanucleoside analogues **1.90** by the convergent coupling with a nucleobase *via* the inversion of the 1'-hydroxyl functionality.

The project will therefore begin with the synthesis of bis-epoxide **1.95** and **1.96** (Chapter 2) followed by detailed investigations of the key carbacyclisation process (Chapter 3). The carbacyclisation products will then be converted to the carbanucleoside precursors *via* a series of transformations (Chapter 4) and the project will eventually conclude with the investigation of the introduction of nucleobases to the synthesised carbanucleoside precursors (Chapter 5).

1.5 Literature Precedence

The centre of the current project is undoubtedly the domino carbacyclisation sequence that ultimately produces the skeletal backbone of the carbanucleoside targets. The underlying principles within the carbacyclisation process evolved from a combination of synthetic methodologies previously developed. These include mainly the utilisation of a *1,3-dithiane linchpin in the formation of carbon-carbon bonds* and the incorporation of the *Brook rearrangement in the construction of domino reaction sequences*. In this Chapter, a brief introduction to these two concepts and their combined applications in synthesis is provided. In addition, existing chemical processes closely related to the carbacyclisation process employed in this project are described.

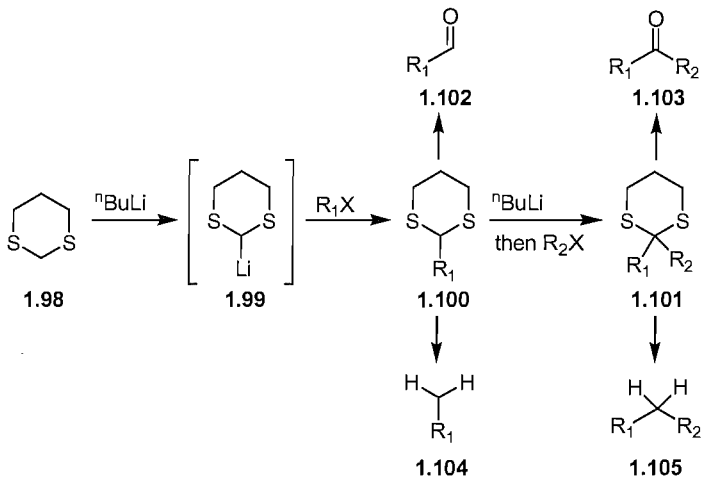
1.5.1 The Role of 1,3-Dithiane in Organic Synthesis[78]

As a protecting group - thioketals and thioacetals formed from ketones and aldehydes exhibit high stability towards acidic and basic conditions. They can be converted back into the corresponding carbonyl compounds by metal-induced hydrolysis, oxidative and alkylative hydrolysis and have commonly served as protecting groups for the carbonyl function.[79]

As acyl anion equivalents in C-C bond formation - 2-lithio-1,3-dithiane (or 2-lithiated-1,3-dithiane) **1.99** and its derivatives are so-called **umpolung acyl anion equivalents** and have been widely employed as masked nucleophilic acylating agents.[80,81] Lithio-dithiane **1.99** can be easily prepared by deprotonation of 1,3-dithaine **1.98** with alkyl lithium reagents and it exhibits reverse reactivity of the carbonyl group

(Scheme 1.21). After reaction with an electrophile (R_1X), the dithiane moiety of **1.100** can be subsequently hydrolysed to reveal the carbonyl functionality or catalytically reduced to the methylene unit. Alternatively, a second lithiation/alkylation affords difunctionalised thioketal **1.101** and the dithiane group thus acts as a linchpin connecting the R_1 and R_2 functionalities.

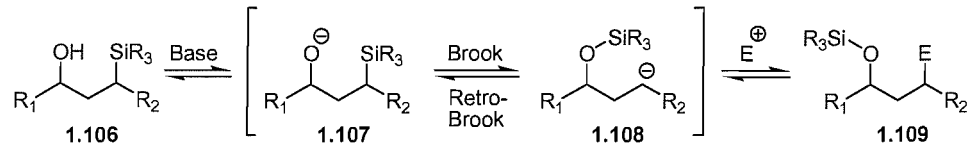
Scheme 1.21



1.5.2 The Brook Rearrangement

The intramolecular 1,2-anionic migration of a silyl group from a carbon atom to an oxygen atom was first reported by A. G. Brook and a family of [1,n]-carbon to oxygen silyl migrations has been observed since.[82] These were commonly referred to as Brook rearrangements and the reverse processes, silyl migrations from oxygen to carbon, were termed retro-Brook rearrangements. The direction of silyl migration depends mainly on the stability of the species present in equilibrium (Scheme 1.22).

Scheme 1.22



When a sub-stoichiometric amount of base is added, the position of the equilibrium is governed by the relative stabilities of carbinol **1.106** and silyl ether **1.109** (E = H). Hence, providing that an electron withdrawing group is present (R_2 = EWG) to kinetically facilitate carbanion formation, the difference in energy between the O-Si bond (120-130 kcal mol^{-1}) and the C-Si bond (75-85 kcal mol^{-1}) provides sufficient driving force for a complete Brook rearrangement to occur.[83]

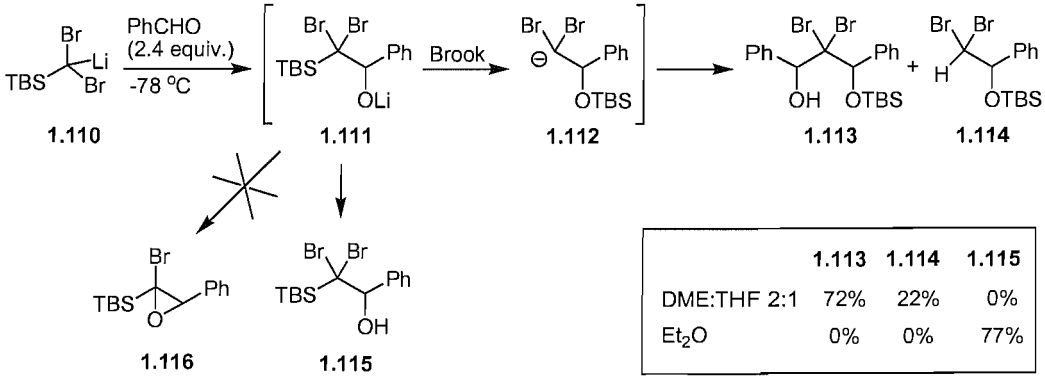
In contrast, the equilibrium position of a fully deprotonated system is governed by the relative stabilities of the intermediate alkoxide **1.107** and carbanion **1.108**. The stability of carbanion **1.108** depends on the ability of the R_2 substituent to stabilise the anionic charge. Hence, if the R_2 substituent is electron withdrawing, carbon to oxygen migration is favoured. The stability of alkoxide **1.107** is influenced by the nature of the counterions. The highly aggregated state and tight ion pairing characteristic of lithium alkoxides favour oxygen to carbon migration, whereas the weaker ion-pairing characteristics of potassium and sodium alkoxides shift the equilibrium in favour of the silyl ether. Similarly, destabilisation of alkoxides can also be achieved by the addition of reagents that chelate metal counterions (e.g. crown ether, TMEDA) or through the solvation of the cations with polar aprotic solvents (e.g. dimethoxyethane, HMPA, DMPU).

1.5.2.1 Solvent-Dependency of Brook Rearrangement

The Brook rearrangement is often incorporated into domino reaction sequences in which an alkoxide is initially formed. *In-situ C-* to *O-* silyl migration generates a carbanion that can undergo further transformation with an electrophile. This is a widely used strategy allowing the successive formation of carbon-carbon bonds in a single pot. In such strategies, it is essential to be able to control the direction and the rate of silyl migration.

Utimoto and Oshima had observed the relative sensitivity of the Brook rearrangement to reaction solvent in the alkylation of *tert*-butyldimethylsilyldibromomethyllithium **1.110** (Scheme 1.23).[84,85] Treatment of dibromolithium **1.111** with benzaldehyde in DME:THF (2:1) at -78 °C led to hydroxy-silyl ether **1.113** and silyl ether **1.114** in 72% and 22% yield respectively. Intriguingly, the expected oxirane side-product **1.116** was not observed, indicating the much faster rate of silyl migration over epoxide formation. Replacement of DME:THF with Et_2O afforded alcohol **1.115** in 77% yield, with no silyl migration products isolated (i.e. compounds **1.113** and **1.114**).

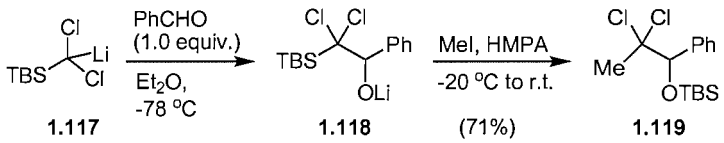
Scheme 1.23



	1.113	1.114	1.115
DME:THF 2:1	72%	22%	0%
Et_2O	0%	0%	77%

Utimoto *et al.* pursued with the investigations and accomplished the one-pot synthesis of silyl ether **1.119** by successive additions of two different electrophiles to silyldichloromethyllithium **1.117** (Scheme 1.24). Dichloromethyllithium **1.117** was initially treated with benzaldehyde in Et_2O to afford the alkoxide intermediate **1.118,** with the Brook rearrangement completely suppressed. After the complete consumption of benzaldehyde, HMPA was added to trigger silyl migration and methyl iodide alkylation of the resultant carbanion afforded silyl ether **1.119** in 71% yield.

Scheme 1.24



1.117 **1.118** (71%) **1.119**

1.5.3 The Utilisation of Dithiane Linchpins within Brook Rearrangements

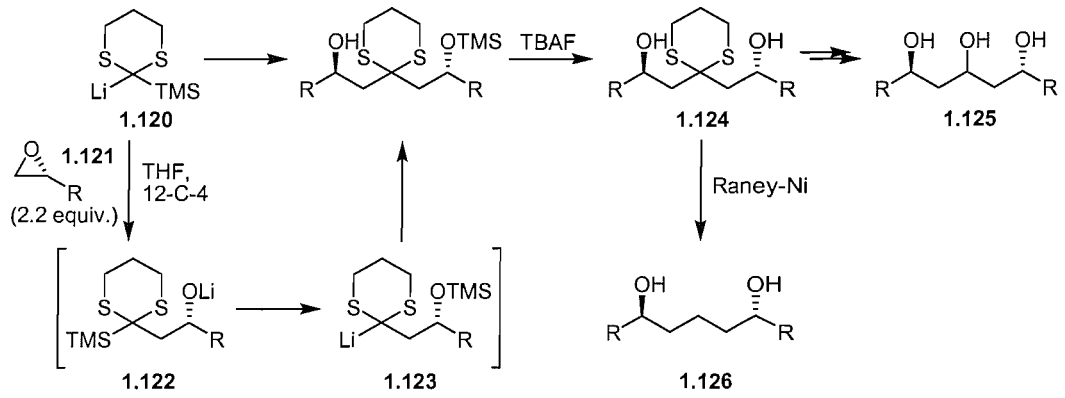
2-Silyl-1,3-dithiane analogues, obtained from the silylation of 1,3-dithiane, can be deprotonated with alkyllithium reagents to afford the corresponding lithiated silyl-dithianes. These have been employed in various Brook rearrangement-mediated domino reaction strategies, particularly in bidirectional synthesis, one-pot multi-component coupling and domino cyclisation processes.

1.5.3.1 Silyl Migration/Alkylation Sequences

Nucleophilic opening of chiral epoxides by lithiated-dithiane nucleophiles enables the construction of masked aldol linkages in a stereospecific manner. The incorporation of a Brook rearrangement in the process thus enables the facile one-pot construction of

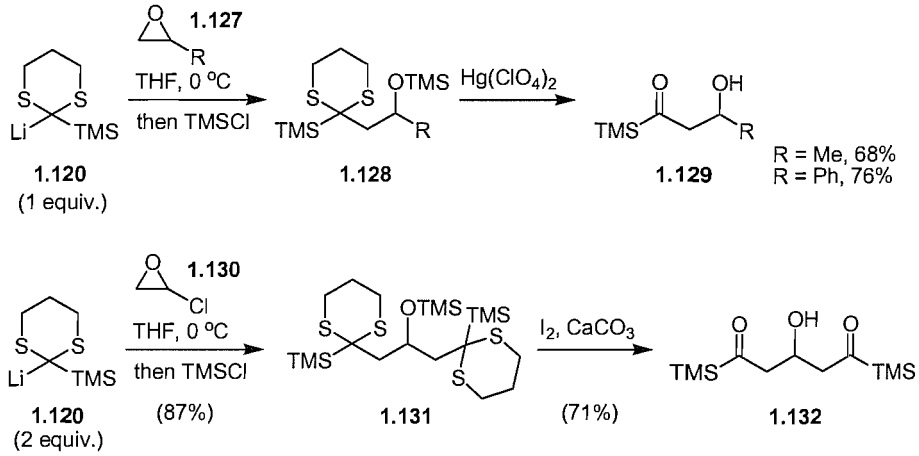
highly oxygenated chiral building blocks. Tietze *et al.* demonstrated the application of such a domino strategy in the synthesis of C_2-symmetric 1,5-diols **1.126** and *pseudo*-C_2-symemtric 1,3,5-triols **1.125** (Scheme 1.25).[86] Opening of chiral epoxide **1.121** by lithiated-dithiane **1.120** led to alkoxide **1.122**, which underwent silyl migration to regenerate the active carbanion **1.123**. A second alkylation followed by desilylation furnished diol **1.124** which could be converted to triol **1.125** or diol **1.126** in straightforward operations.

Scheme 1.25



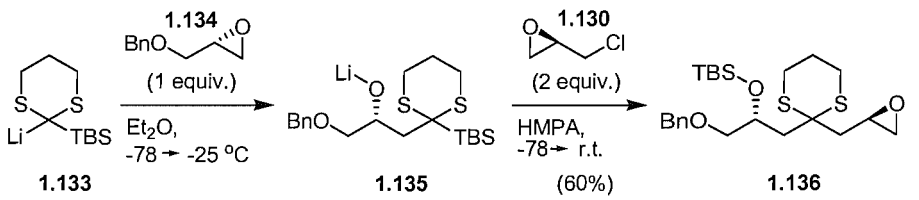
Portella applied similar strategies in the synthesis of acylsilanes and bis-acylsilanes from lithiated-dithiane **1.120** and epoxide substrates (Scheme 1.26).[87] Hence, treatment of **1.120** with epoxide **1.127** in THF at 0 °C followed by silylation with TMSCl afforded silyl ether **1.128**. Hydrolysis of the thioketal functionality of **1.128** proceeded with concomitant silyl ether cleavage to afford acylsilane **1.129**. When epichlorohydrin **1.130** (1 equivalent) was treated with 2 equivalents of lithiated dithiane **1.120** under the same conditions,[88] the corresponding carbanion was silylated using TMSCl to furnish bis-silane **1.131**. Hydrolysis of both the thioketal groups led to bis-acylsilane **1.132** in good yield.

Scheme 1.26



Smith *et al.* accomplished the one-pot unsymmetric dialkylation of 2-silyl-1,3-dithianes by using the solvent-controlled Brook rearrangement tactic reported by Utimoto.[89] Hence, treatment of lithiated silyl-dithiane **1.133** with chiral epoxide **1.134** in Et_2O led exclusively to alkoxide **1.135** (Scheme 1.27). After the complete consumption of epoxide **1.134**, HMPA and epichlorohydrin **1.130** were added to generate the desired silyl ether **1.136** in 60% yield.

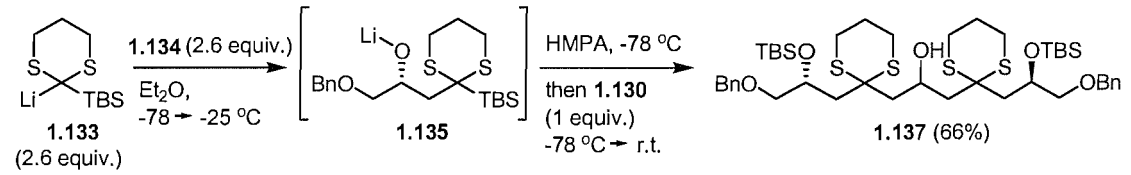
Scheme 1.27



Furthermore, Smith *et al.* extended this methodology further by assembling the five-component coupling product **1.137** in a single pot using the same set of starting materials (Scheme 1.28). In the former case, two different substituents were attached to the dithiane moiety to give compound **1.136**, whereas the latter case involved the addition of two equivalents of alkoxide **1.135** to epichlorohydrin **1.130**. The

regeneration of an active carbanion from an alkoxide product by Brook rearrangement and subsequent alkylation of the anionic species was later termed *anion relay chemistry* by Smith. They successfully applied this type of multi-component coupling in the synthesis of several natural products.[90-93]

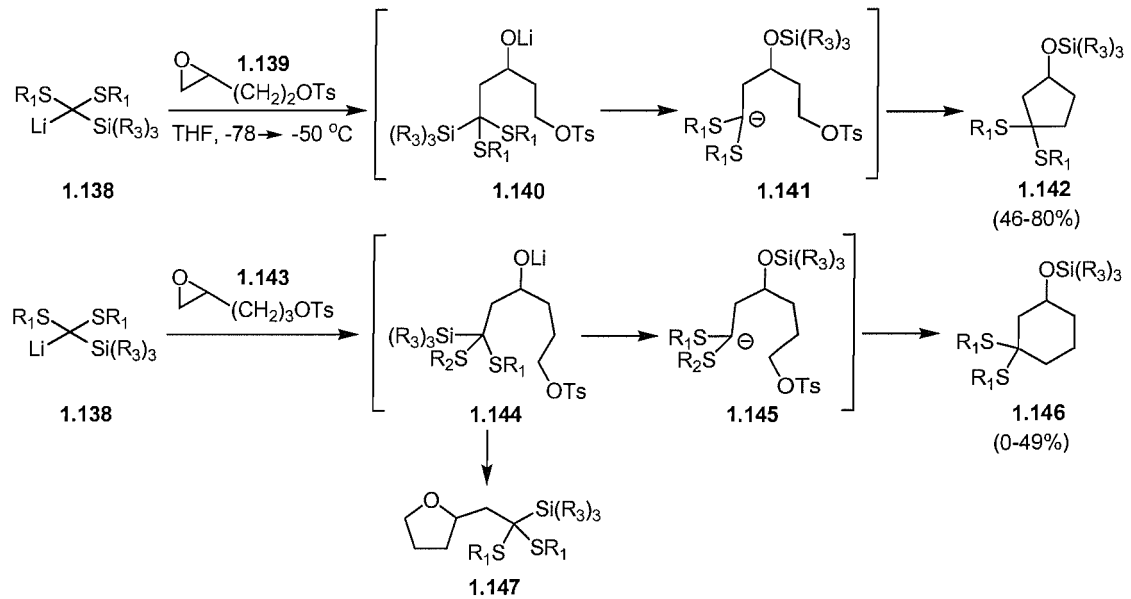
Scheme 1.28



1.5.3.2 Silyl Migration/Cyclisation Sequences

When dielectrophiles are treated with lithiated silyl-dithianes such as **1.138**, carbocycles are the ultimate products.

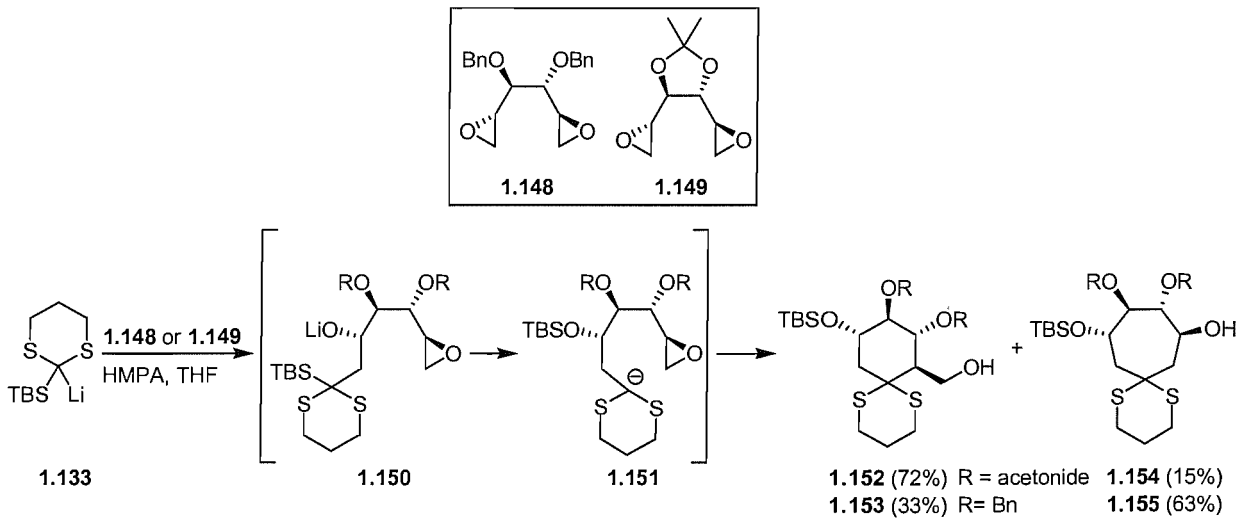
Scheme 1.29



Schaumann *et al.* reported the first transformations of this type in which cyclopentanes **1.142** were obtained in modest to good yields from epoxyhomoallyl tosylates **1.139** and lithiated silyl-dithianes **1.138** (Scheme 1.29).[94,95] Under similar conditions, the corresponding cyclohexanes **1.146** were obtained in much lower yields due to competing cyclisations of alkoxide intermediates **1.144** to give tetrahydrofuran derivatives **1.147**. Construction of cycloheptanes by this method also resulted in low yields due to the formations of the corresponding tetrahydropyran derivatives in significant quantities.

In a similar type of domino carbacyclisation, Le Merrer *et al.* gained access to both cyclohexyl and cycloheptyl carbocycles in good yields starting from lithiated dithiane **1.133** and enantiomerically pure 1,5-bis-epoxides **1.148** and **1.149** derived from L-iditol (Scheme 1.30).[96,97] When propylidenyl bis-epoxide **1.149** was used, 6-*exo-tet* cyclisation was favoured and cyclohexane **1.152** was formed as the major product. In contrast, the regioselectivity was reversed when larger protecting groups were employed. Hence, carbacyclisation utilising benzyl-protected bis-epoxide **1.148** led to cycloheptane **1.155** as the major product as a result of epoxide opening at the less hindered side (see **1.151**).

Scheme 1.30



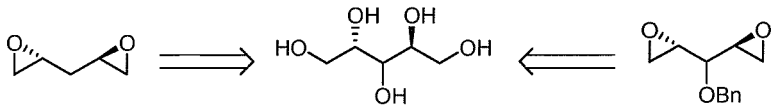
The aforementioned methodologies laid the foundations for the carbacyclisation sequence in this project and the aim was to further expand the scope of this type of domino processes by application to the synthesis of carbafuranose and carbanucleoside analogues.

Results and Discussion

Chapter 2 - Synthesis of Bis-Epoxide Building Blocks

The bis-epoxide building blocks **1.95** and **1.96** were synthesised from enantiopure arabitol **1.97**, which is available commercially in both enantiomeric forms at similar cost. The L-enantiomer was used exclusively throughout this project (Scheme 2.1).

Scheme 2.1



1.95 **1.97** **1.96**

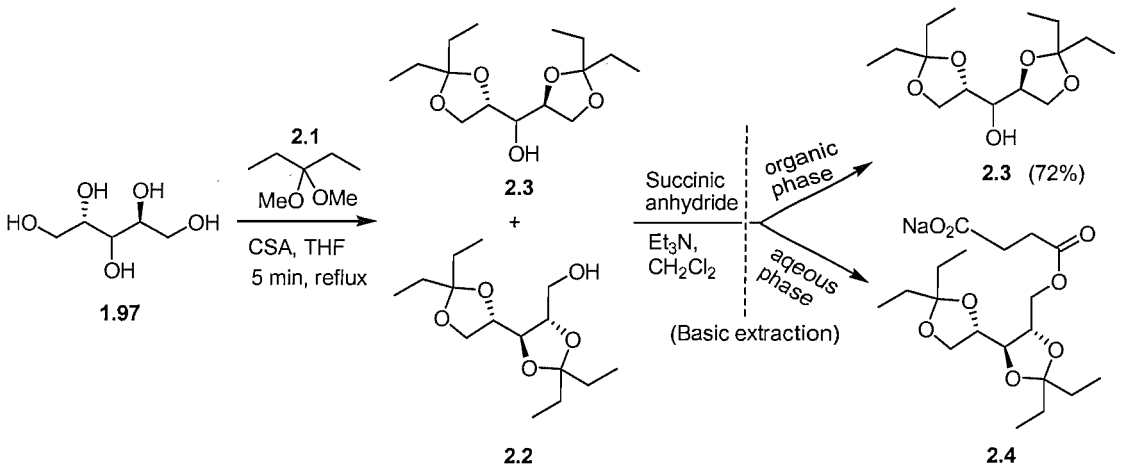
2.1 C_2-Symmetric Bis-Epoxide 1.95

Bis-epoxide **1.95** has been synthesised by various methods,[98-100] the shortest of which was reported by Rychnovsky (5 steps from pentane-1,3-dione).[98] In this project however, bis-epoxide **1.95** was synthesised by the method previously developed in our laboratory due to practical reasons (Scheme 2.1).[100,101]

Acetal protection of L-arabitol employing 3,3-dimethoxypentane **2.1** and CSA would ultimately lead to the formation of the more stable bis-acetal **2.2** under thermodynamic conditions. The desired kinetic product **2.3** could be formed as the major product under carefully controlled conditions. Thus, heating a mixture of L-arabitol **1.97**, dimethoxypentane **2.1** (4.4 equiv.) and CSA (0.3 equiv.) in THF at reflux for exactly 5 minutes afforded a mixture of bis-acetals consisting mainly of the desired isomer **2.3**.[101] To facilitate the separation of **2.2** and **2.3**, the mixture was treated with

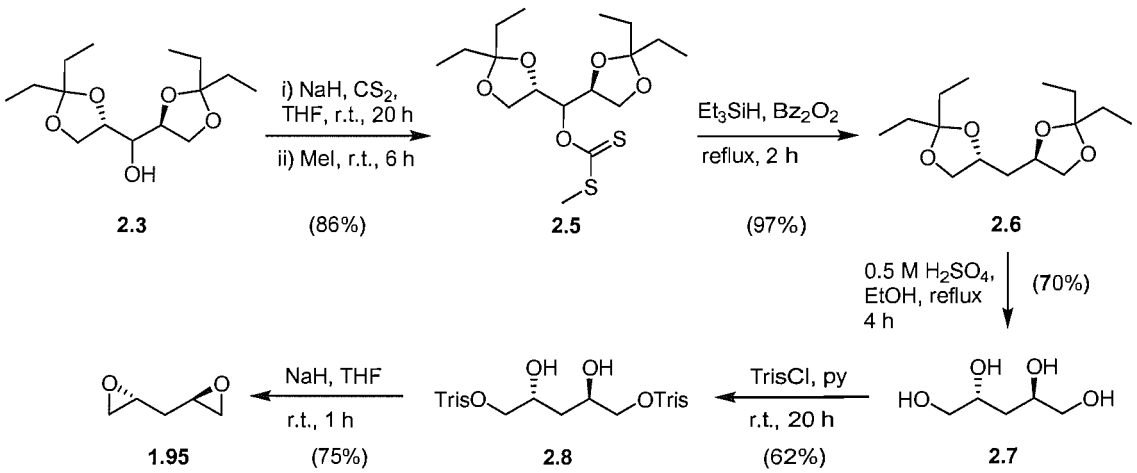
succinic anhydride to selectively convert the undesired **2.2** into carboxylate **2.4**, which was subsequently removed by an aqueous extraction process (Scheme 2.2) to afford pure bis-acetal **2.3** in 72% yield (20 gram scale) after filtration through silica gel.

Scheme 2.2



Bis-acetal **2.3** was then converted into the corresponding xanthate **2.5** (Scheme 2.3) and subsequently reduced with benzoyl peroxide and triethylsilane in a Barton-McCombie-type deoxygenation to afford bis-acetal **2.6** in good yields.

Scheme 2.3



The terminal hydroxyl groups of pentane-1,2,4,5-tetraol **2.7**, obtained from the acid-catalysed deprotection of **2.6**, were selectively sulfonylated using triisopropylbenzenesulfonyl chloride (TrisCl) in pyridine to afford bis-sulfonate **2.8**. Intramolecular displacement of the sulfonate groups of **2.8** mediated by the treatment with sodium hydride afforded bis-epoxide **1.95**, which was purified by Kügelrohr distillation before benig subjected to further synthetic transformations.

2.1.1 Practical Modifications

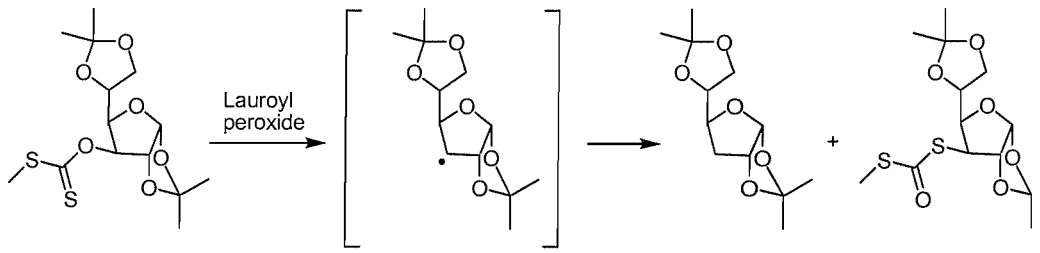
Although the synthetic route described above was practically consistent, there were certain aspects of this methodology that could be improved in order to raise the overall efficiency. These included a difficult and time-consuming filtration during the isolation of tetraol **2.7**, and the use of an expensive silane as the reaction solvent for the reduction of xanthate **2.5**.

i) Xanthate Reduction

The radical mediated reduction of xanthate in the Barton-McCombie deoxygenation traditionally employed the highly toxic tributyltin hydride as the source of the hydrogen atom. As a result, several methods have been developed to replace the organotin reagent,[102-107] including the aforementioned reduction of xanthate **2.5** with a benzoyl peroxide/triethylsilane system. The major drawback with this system was the need of large quantities of the expensive triethylsilane (£77.70/100 mL; Aldrich), as it was used as the reaction solvent. Therefore, a more cost effective system reported by Zard was investigated.[108]

Zard *et al.* reported the rapid conversion of xanthate **2.9** to the corresponding deoxygenated product **2.11** employing lauroyl peroxide in the protic solvent propan-2-ol (Scheme 2.4). The *O*- to *S*- rearranged product **2.12** was also isolated as the minor product in 20% yield. Intriguingly, the selectivity between **2.11** and **2.12** was reversed when the aprotic solvent benzene was used, leading to the formation of **2.12** as the major product. An apparent rationale for the above observations was that upon the cleavage of the C-O bond, the alkyl radical **2.10** would undergo hydrogen abstraction if a hydrogen source (propan-2-ol) was present. However, in the absence of a hydrogen source, alkyl radical **2.10** could react with a second molecule of xanthate to yield the rearrangement product **2.12**.

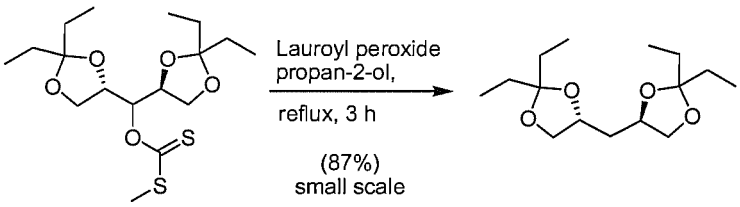
Scheme 2.4



Based upon Zard's observation, we decided to subject xanthate **2.5** to treatment with a sub-stoichiometric amount of lauroyl peroxide in propan-2-ol (Scheme 2.5). In the initial investigations, we were pleased to find that xanthate **2.5** was converted cleanly to bis-acetal **2.6** in excellent yield. When the reaction was performed on a multi-gram scale, large quantities of a solid by-product, believed to be derivatives of lauroyl peroxide were isolated. The by-product was found to cause significant problems with chromatographic purification. In fact, the majority of this solid could not be

separated from the desired product and therefore investigations involving this system were terminated.

Scheme 2.5



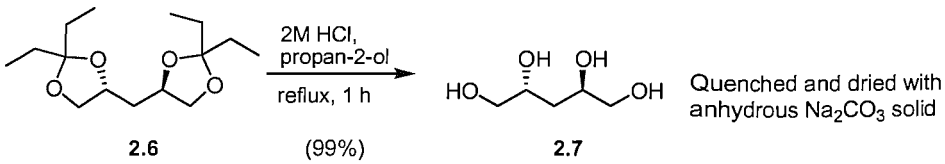
2.5 **2.6**

ii) Acetal Deprotection

Deprotection of bis-acetal **2.6** was originally performed using dilute H_2SO_4 in ethanol. Neutralisation of the acidic solution with solid barium carbonate afforded tetraol **2.7** in good yield. However, subsequent filtration of the barium carbonate solid from the solution proved to be very difficult and time consuming (up to 2 hours). In order to avoid the laborious filtration, the development of a more effective method was undertaken.

It was found that acids in alcoholic solvents generally effected highly efficient deprotection. However, the use of organic acid catalysts in the deprotection or organic bases in quenching led to the formation of organic salts which were difficult to separate from the water-soluble tetraol product. To that end, deprotection of **2.6** employing dilute HCl in propan-2-ol (Scheme 2.6) followed by neutralisation/drying of the reaction mixture with anhydrous sodium carbonate afforded tetraol **2.7** in quantitative yield without the formation of inseparable organic salts. Moreover, the filtration was now much easier to carry out.

Scheme 2.6

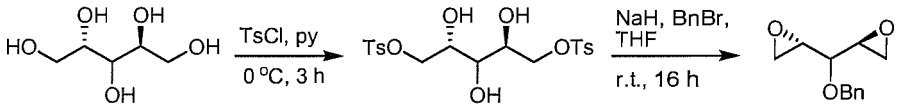


2.6 (99%) **2.7**

2.2 *Pseudo-C_2*-Symmetric Bis-Epoxide 1.96

The second bis-epoxide building block **1.96** was again synthesised from L-arabitol and several synthetic methods were available in the literature.[109-111] The shortest of these methods was reported by Dreyer in which bis-epoxide **1.96** was obtained from arabitol **1.97** in 3 steps *via* the intermediate bis-tosylate **2.9** in 30% overall yield (Scheme 2.7). In our hands however, a consistent yield of **1.96** has not been obtained by this method even after several attempts. We therefore decided to carry out a series of optimisation experiments based on the conditions reported by Dreyer.[110]

Scheme 2.7



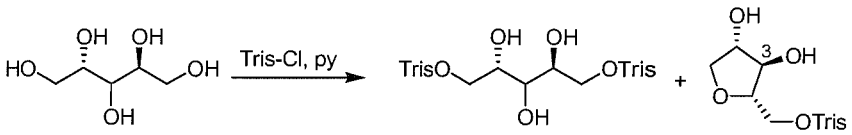
1.97 (74%) **2.9** (40%) **1.96**

2.2.1 Optimisation of Bis-Sulfonate Formation

The two potential problems associated with the initial bis-tosylation step were anticipated to be i) the intramolecular cyclisation of bis-tosylate intermediate **2.9** to form tetrahydrofuran derivative **2.10** under basic conditions; ii) regioselectivity of tosylation between the primary and secondary hydroxyl groups. While the first issue

would be difficult to address, replacement of the tosyl group by the more sterically demanding 2,4,6-triisopropylbenzenesulfonyl (Tris) group was anticipated to increase the selectivity of sulfonate formation. The optimisation results are summarised in Table 2.1.

Table 2.1



1.97 **2.11** **2.10**

Entry	Conc. (M)	TrisCl (equiv.)	Time (h)	Temp (°C)	Yield of **2.11** (%)	Yield of **2.10** (%)
1	0.44	2.2	18	r.t.	48	32
2	1.31	2.2	18	r.t.	44	27
3	0.22	2.2	18	r.t.	32	39
4	0.44	2.4	5	r.t.	55	13
5	0.44	2.4	20	0	73	7
6	0.44	2.2[a]	24	0	80	10

[a] 10 mol % DMAP added.

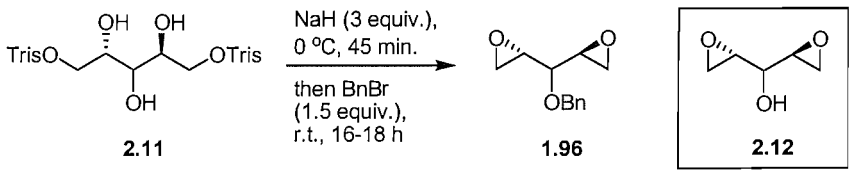
First, the reaction of L-arabitol with TrisCl at ambient temperature for 18 hours yielded the desired bis-sulfonate **2.11** as the major product in modest yield together with a side product which was identified as tetrahydrofuran derivative **2.10** (Table 2.1, Entry 1). Note that **2.10** was isolated as a single diastereoisomer and the relative stereochemistry at C3 was assigned based on related examples.[112-114] Increasing or decreasing the concentration led to decreased yields of **2.11** with equally unacceptable high returns of **2.10** (Entries 2-3). As **2.10** clearly originated from the intramolecular cyclisation of **2.11** a shorter reaction time was investigated (Entry 4). This led to a considerable reduction in the yield of side-product **2.10**, but unfortunately this did not

lead to a significant increase in yield for **2.11** (Entry 4 vs 1). Finally, it was found that the reaction temperature was a decisive parameter with the cyclisation being largely suppressed at 0 °C (Entry 5). Addition of DMAP to facilitate the sulfonylation further improved the yield of **2.11** to 80% together with 10% of cyclised by-product **2.10** (Entry 6) also being formed. This therefore completed the first part of the optimisation process.

2.2.2 Optimisation of Bis-Epoxide Formation

The double intramolecular sulfonate displacement process was investigated using purified bis-sulfonate **2.11** (Table 2.2). Dreyer's original conditions involved the treatment of **2.11** with sodium hydride in THF to initiate bis-epoxide formation followed by benzylation of the resulting alkoxide with benzyl bromide. In our hands, a yield of 46% was obtained for the formation of bis-epoxide **1.96** from **2.11** following conditions which were similar to Dreyer's results for this reaction starting from the corresponding bis-tosylate **2.9** (Table 2.2, Entry 1).

Table 2.2



2.11 **1.96** **2.12**

Entry	Conc. (M)	Solvent	NaI (equiv.)	Yield of **1.96** (%)
1	0.061	THF	0	46
2	0.073	DMF	0	62
3	0.050	DMF	0	74
4	0.033	DMF	0	77
5	0.033	DMF	1.5	83

When **2.11** was treated with NaH in THF and then quenched with H_2O, instead of undergoing further benzylation, the intermediate alcohol **2.12** could be isolated in 80% yield. This indicated that the observed low yield was largely due to ineffective benzylation of the alkoxide generated after the initial bis-epoxide formation. The optimisation therefore began with the use of the polar aprotic solvent DMF instead of THF to enable a more effective benzylation process and this led to an increase in yield to 62% (Entry 2). Further increases in yield were observed at increased dilution (Entries 3 and 4). Finally, the efficiency of the benzylation step was further enhanced by the addition of sodium iodide, leading to an excellent 83% yield of **1.96** (Entry 5).

2.2.3 Large-Scale Optimisation

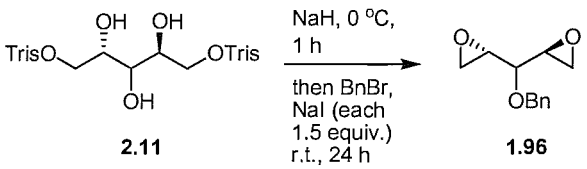
Having determined high yielding conditions for both of the individual processes, further optimisations for the large-scale synthesis of bis-epoxide **1.96** were necessary as a few drawbacks soon became apparent upon performing the reaction on a multi-gram scale. First, with the significant gain in mass after the initial bis-sulfonate formation, purification of the bis-sulfonate intermediate **2.11** by column chromatography was found to be very difficult.

To address this problem, crude **2.11** obtained from the bis-sulfonate formation process was subjected directly to the bis-epoxide formation/benzylation sequence. Although an overall yield of 61% for bis-epoxide **1.96** was obtained starting with 1 gram of arabitol, the overall yield decreased to 47% on a 10-gram scale. The decrease in yield was found to be related to the residual TrisCl after the initial bis-sulfonate formation. With 2.2 equivalents of TrisCl added in the initial operation, the residual TrisCl could react with the alkoxide formed in the bis-epoxide formation process. This

problem could simply be eliminated by reducing the amount of TrisCl utilised to 2.05 equivalents, and thus leaving behind the minimum amount of TrisCl in the crude mixture.

Secondly, a more practical problem was that no less than 2.2 L of DMF would be required for the bis-epoxide formation/benzylation sequence starting with 10 grams of arabitol. The use of large quantities of anhydrous DMF could lead to various problems including costs, safety and ease of removal (by aqueous extraction). In order to reduce the amount of DMF required for this process, the use of solvent mixtures was investigated (Table 2.3).

Table 2.3



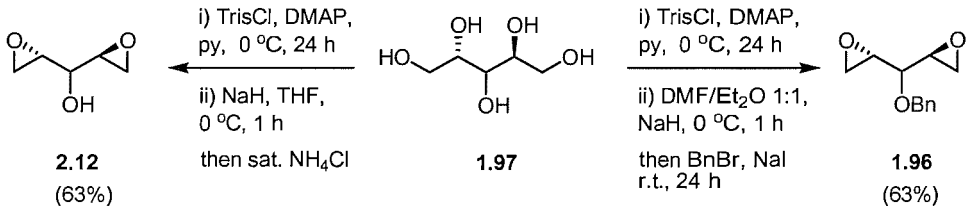
Entry	**Solvent** (0.03 M)	**Yield** (%)
1	DMF/THF 5:5	83
2	DMF/THF 3.7:6.3	81
3	DMF/THF 2.7:7.3	66
4	DMF/Et_2O 5:5	85

Starting from purified bis-sulfonate **2.11**, it was found that a 1:1 mixture of DMF/THF afforded yields similar to those recorded when DMF was used as the reaction solvent (Entry 1). Reducing the amount of DMF further led to reductions in yield (Entries 2 and 3). In addition, the use of water-soluble solvents in the mixture (i.e. DMF + THF) did not facilitate the aqueous extraction process. However, the employment of a 1:1 DMF/Et_2O solvent mixture afforded yields comparable to the corresponding DMF/THF mixture (Entry 4 vs 1) and the use of the water-immiscible Et_2O greatly simplified the subsequent aqueous extraction procedures.

The large scale synthesis of bis-epoxide **1.96** was re-attempted with the new DMF/Et_2O mixed-solvent system. The amount of TrisCl in the initial bis-sulfonate

formation step was also reduced to 2.05 equivalents to minimise side reactions. Consequently, bis-epoxide was obtained in an overall 63% yield starting from 10 grams of arabitol and no chromatographic purification of the intermediate bis-sulfonate **2.11** was necessary (Scheme 2.8). Moreover, the water-soluble hydroxy-bis-epoxide **2.12** could be synthesised under similar conditions with slight modification to the procedures to avoid the aqueous extraction process. Hence, the bis-epoxide formation process was carried out using THF as solvent. Quenching with a small amount of sat. NH_4Cl and drying with $MgSO_4$ led to bis-epoxide **2.12** in 63% yield from arabitol (Scheme 2.8).

Scheme 2.8



2.12 (63%) **1.97** **1.96** (63%)

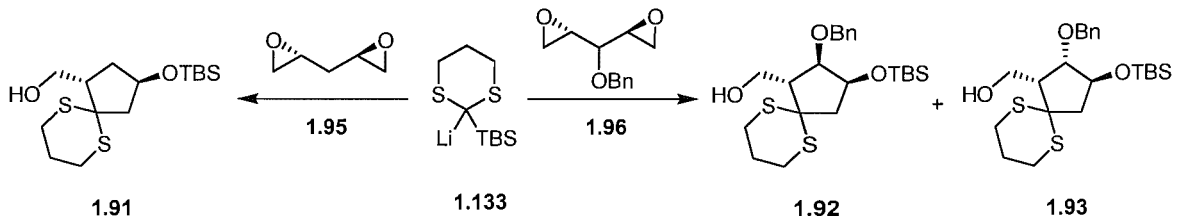
2.3 Conclusion

In conclusion, C_2-symmetric bis-epoxide **1.95** was synthesised by literature methods (6 steps, 19%) from L-arabitol. For *pseudo*-C_2-symmetric bis-epoxide **1.96**, a consistent yield was not obtained using conditions reported by Dreyer. Consequently, a reproducible and efficient methodology suitable for the multi-gram production of bis-epoxide analogues **1.96** and **2.12** was developed.[115]

Chapter 3 - The Brook Rearrangement-Mediated Carbacyclisation

With the bis-epoxide building blocks synthesised, the next part of the project was to investigate a domino reaction sequence involving the desymmetrisation of the previously synthesised bis-epoxide building blocks with a lithiated silyl-dithiane nucleophile to produce the key carbacyclisation products **1.91**, **1.92** and **1.93** which contain the carbafuranose backbone (Scheme 3.1).

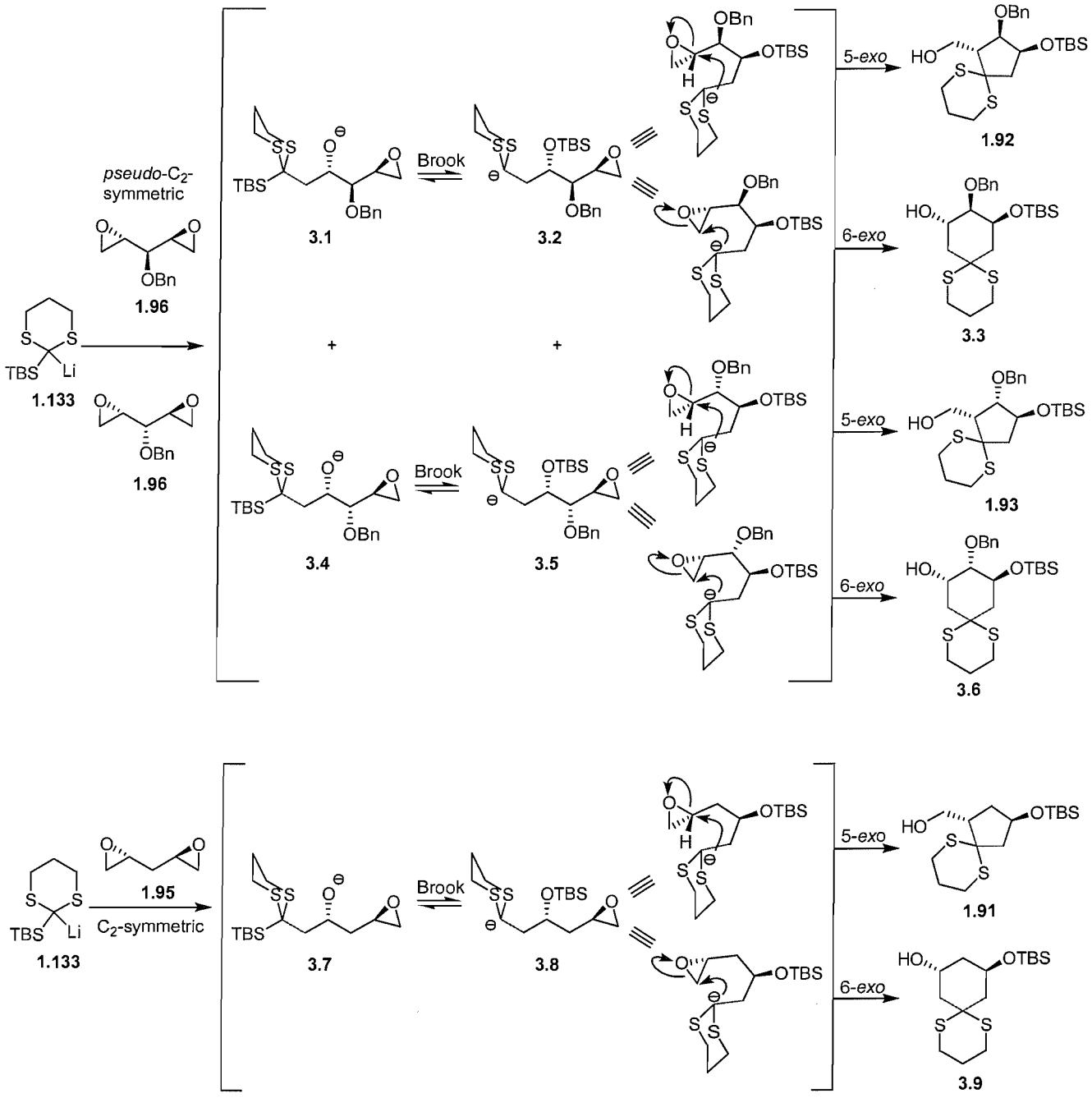
Scheme 3.1



3.1 Mechanistic and Stereochemical Considerations

The domino carbacyclisation sequence consists of 3 individual operations (Scheme 3.2) – i) stereoselective nucleophilic opening of the first epoxide functionality by lithiated 2-*tert*-butyldimethylsilyl-1,3-dithiane; ii) HMPA-promoted 1,4-Brook rearrangement (*C*- to *O*- migration of the TBS group) to regenerate the carbanion; and iii) 5-*exo* (or 6-*exo*) cyclisation of the carbanion on the second epoxide functionality. The processes are illustrated in Scheme 3.2, in which the reaction between lithiated dithiane **1.133** and bis-epoxides **1.95** and **1.96** in the presence of HMPA is expected to give a mixture of the corresponding 5-*exo* and 6-*exo* cyclisation products.

Scheme 3.2



When the C_2-symmetric bis-epoxide **1.95** is employed as the substrate, the 5-*exo* and 6-*exo* cyclisation products are expected to form as single diastereomers (**1.91** and **3.9**), while mixtures of diastereoisomers are expected from the carbacyclisation process using the *pseudo*-C_2-symmetric bis-epoxide **1.96** (**1.92** and **1.93** for 5-*exo*; **3.3** and **3.6**

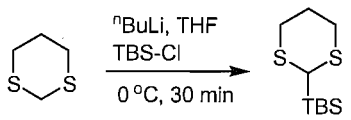
for 6-*exo*). In both cases, the rate of 5-*exo* cyclisation is expected to be faster than the 6-*exo* process.[116-119] Since the intramolecular cyclisation is irreversible, 5-*exo* cyclisation products **1.91-1.93** are expected to form as the major products.

3.2 Preliminary Experiments

3.2.1 Preparation of 2-*tert*-(Butyldimethylsilanyl)-1,3-Dithiane 1.94

Silyl-dithiane **1.94** was easily obtained in large quantities (~50 g) by the procedure of Chuang *et al.* (Scheme 3.3).[120] Deprotonation of 1,3-dithiane **1.98** with ^{n}BuLi followed by treatment with *tert*-butyldimethylsilyl chloride afforded **1.94** in an excellent 97% yield after purification by column chromatography and vacuum distillation.

Scheme 3.3



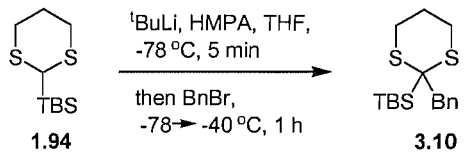
1.98 (97%) **1.94**

3.2.2 Model Studies of the Initial Deprotonation

Initial attempts of the carbacyclisation process gave very low yields of the desired products with large return of the starting materials. This led us to perform a series of model experiments to ensure the complete deprotonation of silyl-dithiane **1.94** and efficient alkylation of the generated silyl-dithiane anion. To achieve the above objectives, silyl-dithiane **1.94** was deprotonated with ^{t}BuLi and benzylated with the

simple electrophile benzyl bromide in order to determine the efficiency of the deprotonation and alkylation processes. The results are summarised in Table 3.1.

Table 3.1



1.94 **3.10**

Entry	^{t}BuLi (equiv.)	HMPA:THF	Yield of **3.10** (%)	Recovered **1.94** (%)
1	1.5	0:10	0	100
2	1.5	1:9	69	27
3	2.0	1:9	84	16
4	1.2	1:9	80	a

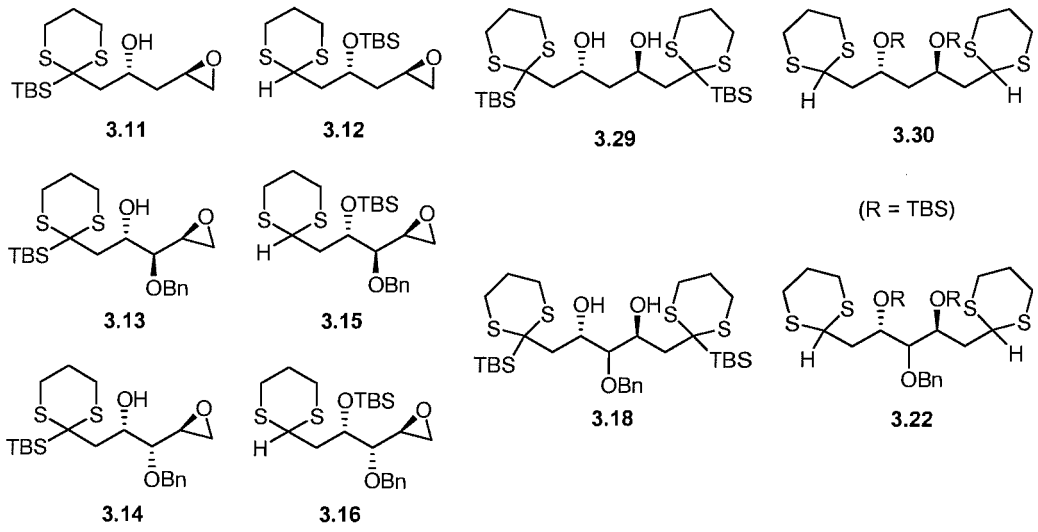
a - not isolated

The results suggested that an ineffective deprotonation was the main problem as more than 2.0 equivalents of ^{t}BuLi were required for complete deprotonation of **1.94** (Entries 2 and 3). The study also illustrated the important role of HMPA in the initial deprotonation and alkylation processes (Entry 1). The ineffective deprotonation was found to be the result of a vigorous reaction between ^{t}BuLi and the THF used in rinsing the syringe. It is well documented in the literature that THF reacts with various organolithium reagents at room temperature and most rapidly with ^{t}BuLi, leading to acetaldehyde enolate.[121] This could explain the effervescence observed when ^{t}BuLi was taken up into a THF-rinsed syringe. Consequently, only 1.2 equivalents of ^{t}BuLi were required to effectively deprotonate **1.94** using a syringe rinsed with distilled pentane (Entry 4).

3.3 Independent Synthesis of the Possible Carbacyclisation Side-Products

The carbacyclisation process could potentially produce several side-products if the sequence is interrupted (Figure 3.1). These side-products **3.11-3.16** are essentially the protonated alkoxide and carbanion intermediates depicted in the carbacyclisation mechanism (Scheme 3.2, compounds **3.1**, **3.2**, **3.4**, **3.5**, **3.7**, **3.8**). Moreover, if both the epoxide functionalities on the bis-epoxide molecule are alkylated by two molecules of lithiated-dithiane **1.133**, bis-addition products such as diols **3.18**, **3.29** and bis-silyl ethers **3.22**, **3.30** will be formed. In order to fully investigate the carbacyclisation sequence, these side-products were independently synthesised.

Figure 3.1

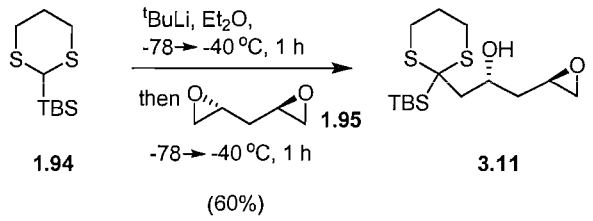


3.3.1 Side-Products Arising from Bis-Epoxide 1.95

If the carbacyclisation process terminates immediately after the initial opening of the first epoxide functionality, alcohol **3.11** would be isolated as the side-product

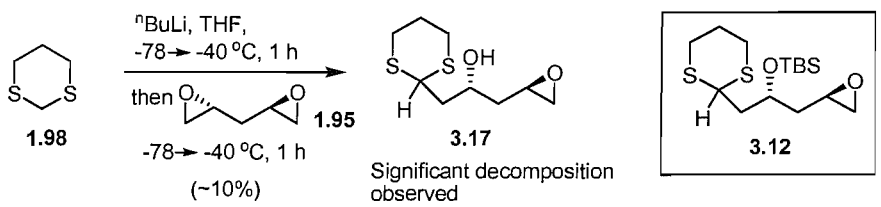
(Scheme 3.4). Hence, independent synthesis of alcohol **3.11** would require the suppression of the Brook rearrangement after the initial epoxide opening. Thus, silyl-dithiane **1.94** was deprotonated with ^{t}BuLi and then treated with bis-epoxide **1.95** (1 equivalent) in Et_2O in the absence of HMPA at -40 °C (Scheme 3.4), as no silyl migration was expected after the initial epoxide opening under such conditions.[84] Indeed, alcohol **3.11** was obtained in 60% yield.

Scheme 3.4



If the carbacyclisation sequence terminates after migration of the silyl group, silyl ether **3.12** would be the expected side-product. Silyl ether **3.12** cannot be synthesised directly from the available starting materials, but should be accessible *via* silylation of alcohol **3.17** (Scheme 3.5). Unfortunately, treatment of lithiated **1.98** with bis-epoxide **1.95** led to a poor yield (~10%) of the corresponding alcohol **3.17**. Rapid decomposition of alcohol **3.17** during the reaction prevented its use in the subsequent transformation to silyl ether **3.12**.

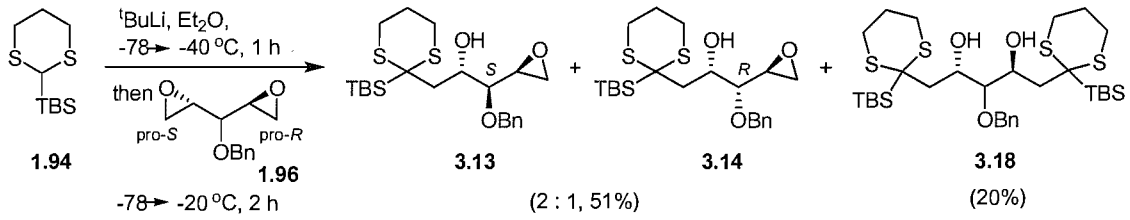
Scheme 3.5



3.3.2 Side Products Arising from Bis-Epoxide 1.96

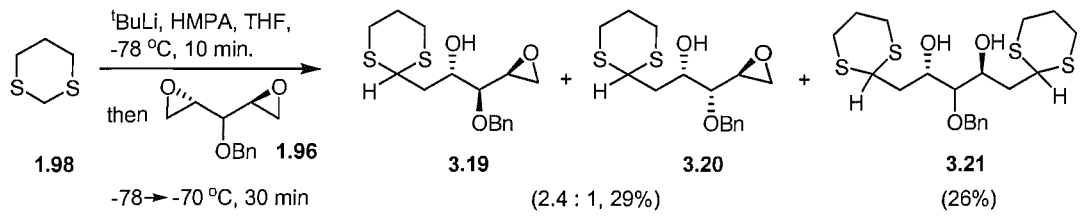
When bis-epoxide **1.96** was treated with 1 equivalent of lithiated **1.94** in the absence of HMPA in Et_2O (Scheme 3.6), the desired alcohols **3.13** and **3.14** were formed in 51% yield (2:1) as an inseparable mixture together with 20% of the *pseudo*-C_2-symmetric bis-addition product **3.18**. The ratio of **3.13**:**3.14** was somewhat surprising as it indicated a significant selectivity for the attack of **1.94** on the pro-*S* epoxide group (Confirmation of stereochemistry will be discussed later).

Scheme 3.6



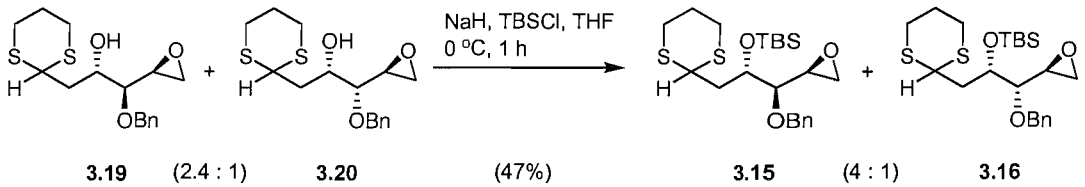
Unlike silyl ether **3.12**, silyl ethers **3.15** and **3.16** were successfully synthesised *via* alcohols **3.19** and **3.20** respectively (Scheme 3.7 and 3.8). Treatment of 1 equivalent of lithiated **1.98** with bis-epoxide **1.96** (Scheme 3.7) afforded a stable, but inseparable, mixture of the diastereomeric alcohols **3.19** and **3.20** (2.4:1, 29%), together with the *pseudo*-C_2-symmetric bis-addition product **3.21** in 26% yield. Again, it was noted that the opening of **1.96** occurred with a significant diastereoselectivity in favour of attack on the pro-*S* epoxide group.

Scheme 3.7



Silyl protection of **3.19** and **3.20** employing TBSCl and imidazole failed and the starting materials were recovered. Alternatively, when treated with NaH and TBSCl in THF, **3.19** and **3.20** were converted into the desired silyl ethers **3.15** and **3.16** in 47% combined yield as an inseparable mixture (Scheme 3.8).

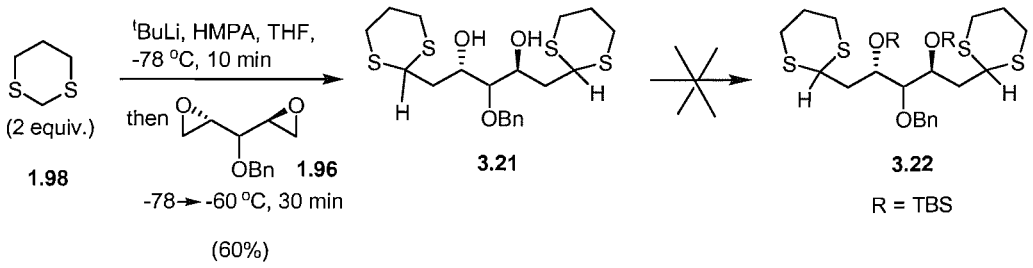
Scheme 3.8



3.3.3 Bis-Addition Reactions

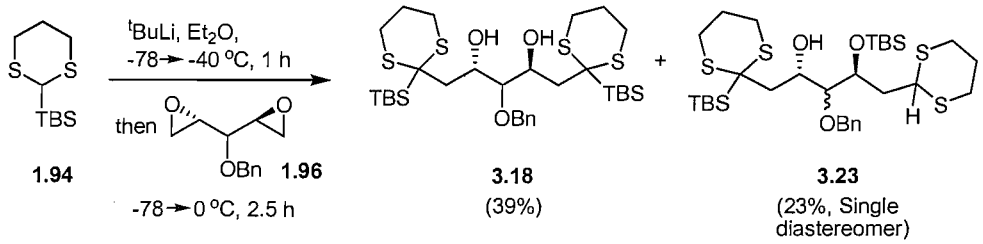
Apart from intermediates **3.11-3.16**, bis-silyl ether **3.22** resulting from the bis-addition of silyl-dithiane followed by bis-silyl migration could also be present in the reaction mixture. Furthermore, reactions between silyl-dithiane derivatives and epoxide electrophiles serve as an excellent method to construct protected aldol linkages in a stereocontrolled manner. Small, chiral building blocks such as **3.22** may find potentially useful applications in the synthesis of natural products, in particular ones that contain polyketide sub-units. Therefore, synthesis of **3.22** was attempted *via* the silylation of the bis-addition product **3.21** (Scheme 3.9).

Scheme 3.9



First, bis-epoxide **1.96** was treated with two equivalents of lithiated **1.98** in the presence of HMPA. Although the reaction proceeded smoothly to yield bis-adduct **3.21** in 60% yield without any mono-adduct, subsequent silylation failed to yield the desired bis-silyl ether **3.22**. Treatment of bis-epoxide **1.96** with two equivalents of lithiated **1.94** (Scheme 3.10) led to the formation of bis-adduct **3.18** in only 39% yield. Interestingly, no mono-adduct was detected.

Scheme 3.10



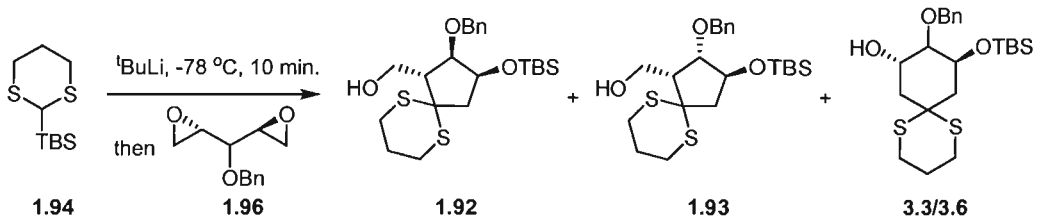
A second product with the same molecular mass as **3.18** was isolated as a single diastereoisomer, and was later found to be the mono-migration product **3.23** with the relative C3 stereochemistry unconfirmed. The formation of **3.23** was surprising as no Brook rearrangement was expected under the reaction conditions. The isolation of **3.23** as a single diastereoisomer was also very surprising, as a pair of diastereomers was expected from the desymmetrisation of the *pseudo*-C_2 symmetric **3.18**. The investigation, however, was terminated here due to time limitation and no conclusion

could be drawn, although bis-silyl ether **3.22** was indeed found to be a side product in the carbacyclisation reaction (see later).

3.4 Carbacyclisation – Optimisation[122]

The domino carbacyclisation sequence using bis-epoxide **1.96** as substrate was thoroughly investigated, including the observed diastereoselectivity. The general procedures for the investigation involved first the deprotonation of dithiane **1.94** with ^{t}BuLi (concentration determined by titration against diphenylacetic acid) in a mixture of co-solvent HMPA and a major solvent (usually THF) at -78 °C for 10 minutes. Bis-epoxide **1.96** was then added either neat or as a solution in THF. The -78 °C cold bath was then switched to a second bath of the appropriate temperature and the mixture was stirred at a constant temperature for the length of time indicated. The results are summarised in Table 3.2 and they are discussed in greater details in the corresponding sub-Chapters that follow. It is also noteworthy to mention that the colour of the reaction mixture changed from bright yellow after initial ^{t}BuLi addition to deep green when the reaction was completed.

Table 3.2 –Domino Carbacyclisation Investigation



1.94 **1.96** **1.92** **1.93** **3.3/3.6**

Entry	1.94 (equiv.)	^{t}Buli (equiv.)	Conc. (M)	HMPA:THF	Temp. (°C)	Time (min.)	Mol. Sieve	1.92 + 1.93 (%)	1.92 : 1.93[a]	3.3/3.6[b] (%)	1.96[b] (%)
1	1.1	1.0	0.1	1:10	-75	4.63	n	44	5.3:1	1	23
2	1.0	1.0	0.1	1:10	-45	30	n	56	3.3:1	4	7
3	1.0	1.0	0.1	1:10	-18	15	n	61	2.6:1	4	0
4	1.0	1.0	0.1	1:10	0	10	n	51	1.8:1	7	0
5	1.0	1.0	0.05	1:10	-45	40	n	61	4.1:1	4	13
6	1.1	1.0	0.033	1:10	-45	180	n	53	4.9:1	3	24
7	1.1	1.0	0.030	1:10	-45	180	n	53	4.9:1	1	17
8	1.1	1.0	0.030	1:30	-45	120	n	39	2.3:1	4	0
9	1.1	1.0	0.030	HMPA:Et_2O 1:10	-45	120	n	55	5.9:1	3	2
10	1.1	1.0	0.030	TMEDA:THF 1:10	-45	120	n	0	\	0	~100
11[c]	1.1	1.0	0.030	DMPU :THF 1:3.3	-45	120	n	0	\	0	~100
12	1.1	1.0	0.030	1:10	-30	100	n	64	3.6:1	5	0
13	1.1	1.0	0.030	1:10	-30	75	y	76	3.5:1	6	0
14	1.1	1.0	0.030	1:10	-45	120	y	69	3.6:1	6	0
15	1.1	1.0	0.030	1:9	-30	75	y	77	4.1:1	4	0
16	1.4	1.3	0.050	1:9	-30	90	Y	76	2.9:1	7	0
17	1.4	1.3	0.030	1:9	-30	90	y	80	3.2:1	8	0
18[d]	1.4	1.3	0.030	1:9	-30	120	y	0	0	0	~100

a – isolated yields of **1.92** and **1.93** after purification by HPLC; *b* – compounds **3.3/3.6** and **1.96** not separated. Ratio estimated by ^{1}H NMR integrations; *c* – addition of DMPU before or after the initial deprotonation both effected no carbacyclisation; *d* - a solution of lithiated **1.94** added to bis-epoxide **1.96**

3.4.1 Optimisation Parameters

Temperature – a high diastereoselectivity between the 5-*exo* cyclisation products **1.92** and **1.93** was observed at -75 °C, though a low overall yield was obtained (Entry 1). In contrast, performing the experiment at 0 °C resulted in poor diastereoselectivity (**1.92** vs **1.93**) as well as poor regioselectivity (**1.92**+**1.93** vs **3.3**/**3.6**) (Entry 4). The optimum temperature was found to be between -45 to -18 °C, effecting good overall yields with reasonable diastereo- and regioselectivity (Entries 2 and 3). The 6-*exo* product **3.3**/**3.6** was isolated as a single diastereoisomer but the relative stereochemistry of the benzyloxy substituent was not confirmed (see also Chapter 3.4.2).

Concentration - decreasing the reaction concentration led to increases both in yield (by minimising bis-addition of lithiated dithiane) and diastereoselectivity (Entry 5 vs 2). Reducing the concentration further led to a decrease in yield, but with a higher recovery of bis-epoxide **1.96** (Entries 6 and 7).

Solvents + Co-solvents – lowering the amount of HMPA in THF led to a significant drop in yield, again emphasising the crucial role played by HMPA (Entry 8). Switching the solvent from THF to diethyl ether led to a similar yield with moderately increased diastereoselectivity (Entry 9 vs 7). Replacement of the carcinogenic HMPA with TMEDA or DMPU led to no carbacyclisation (Entries 10 and 11). In the case of DMPU, a side reaction with ^{t}BuLi was present even at -78 °C, as evidenced by the disappearance of the bright yellow colouring of the reaction mixture. This agreed with Seebach's observations which stated, "for a carbonyl compound, DMPU is remarkably unreactive: although a vigorous, exothermic reaction takes place when a hexane solution of butyllithium is added to a (THF/DMPU)-mixture at -78 °C, only a slow

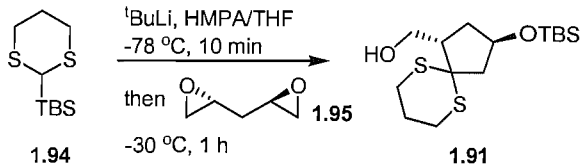
reaction was noticed at -90 °C.".[123] Although he also stated, "if a more reactive substrate is present in the solution, the DMPU cosolvent does not interfere", and "DMPU can so be added to a THF solution of a reagent generated under conventional metallation conditions, just prior to the reaction with an electrophile.". This would of course only be true if the metallated species itself does not react with DMPU.

Addition of 4Å Molecular Sieves – the presence of 4Å molecular sieves in the reaction mixture increased the overall of yield of the process by almost 10% (Entries 13 vs 12). This clearly indicated the need for thoroughly dried reagents and solvent when operating with a stoichiometric amount of ^{t}BuLi.

Finally, the *temperature* and *concentration* parameters were carefully adjusted to complete the optimisation process (Entries 14 - 16). Using a slight excess of the lithiated silyl-dithiane nucleophile, 5-*exo* carbacyclisation products **1.92** and **1.93** were eventually obtained in 80% yield (3.2:1) together with 8% of the 6-*exo* products **3.3/3.4** almost entirely as a single diastereoisomer (Entry 17), though its relative stereochemistry at the carbon centre bearing the benzyloxy substituent could not be confirmed (by analysis of the observed ^{1}H NMR coupling constants). Furthermore, the addition of a solution of the lithiated silyl-dithiane nucleophile to a THF solution of bis-epoxide **1.96** did not lead to any conversion (Entry 18).

When bis-epoxide **1.95** was subjected to small-scale carbacyclisation under the optimised conditions, the expected 5-*exo* cyclisation product **1.91** was formed in 83% yield (Scheme 3.11) and the corresponding 6-*exo* cyclisation product was not isolated.

Scheme 3.11



3.4.2 Carbacyclisation – Major Observations

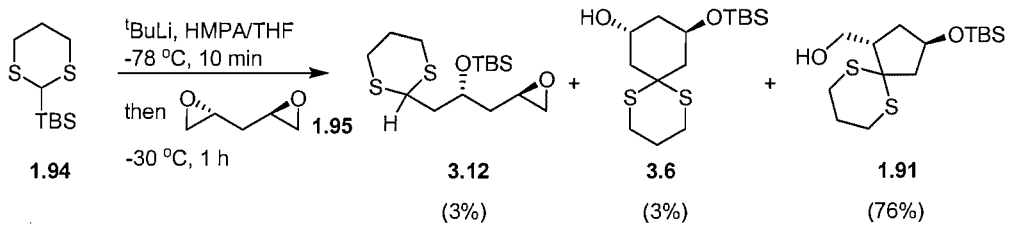
Other than the yields and diastereoselectivities listed in Table 3.1, there were several other findings from the investigation that aided the understanding of the carbacyclisation process. The main observations are listed below (Note that all the aforementioned optimisation experiments were conducted using 100 – 200 mg of bis-epoxide **1.96**):

	Observations	**Comments**
1)	Little or virtually no side-products **3.13-3.16** were detected by TLC (spotting against reference compounds) or isolated after column chromatography under the optimised conditions	i) The initial epoxide opening step, which was inter-molecular in nature, was found to be rate-determining. ii) The intramolecular cyclisations to all cyclisation products were complete.
2)	The 6-*exo* cyclisation product **3.3/3.6** was isolated as a single diastereomer, but the stereochemistry of the OBn substituent was not confirmed.	The observed diastereoselectivity between the 5-*exo* products originated mainly, but not entirely, from the initial epoxide opening process as it was also affected by the competing 6-*exo* cyclisation.
3)	The only unwanted side-product occasionally isolated in small amounts was the bis-silyl ether **3.22**.	The only significant side reaction present was the bis-addition/silyl migration process. This undesired process was minimal under the optimised conditions.

3.5 Carbacyclisation – Large-Scale Syntheses

Having determined suitable conditions for the carbacyclisation processes on a small scale, it was important to ensure the process was suitable for on a multi-gram scale. Carbacyclisation experiments employing multi-gram quantities of bis-epoxide substrates were therefore conducted. When bis-epoxide **1.95** was subjected to carbacyclisation under the optimised conditions, 5-*exo* cyclisation product **1.91** was formed in yields comparable to the corresponding small scale experiments (Scheme 3.12). Moreover, it was now possible to isolate small amounts of the uncyclised intermediate **3.12** and the 6-*exo* cyclisation product **3.6** (3% each).

Scheme 3.12

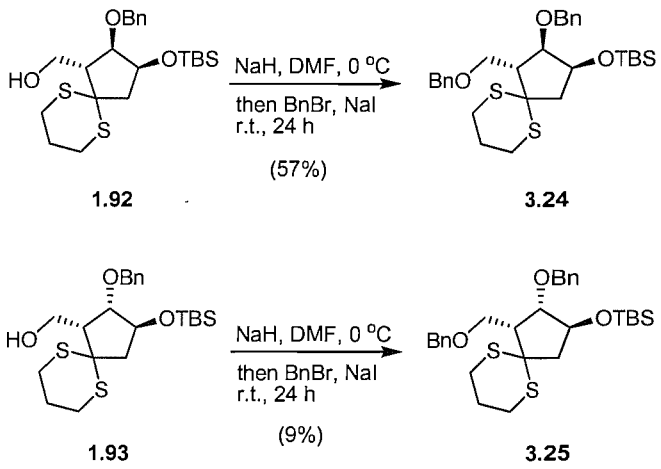


Similarly, large-scale carbacyclisation employing bis-epoxide **1.96** again afforded yields comparable to the corresponding small scale process, with the 5-*exo* products **1.92**, **1.93** and the 6-*exo* product **3.3** obtained in 64%, 13% and 4% respectively. The greater diastereoselectivity observed compared with the corresponding small-scale process presumably was due to a less efficient heat transfer process within the flask. Hence, a larger amount of solvent would take longer to warm from -78 to -30 °C. 5-*exo* cyclisation products **1.92** and **1.93** could only be separated by preparative HPLC which was only suitable for small scale separations. Hence, an efficient separation method had to be developed in order for the process to be of practical use on a larger scale.

3.5.1 Separation of Diastereoisomers

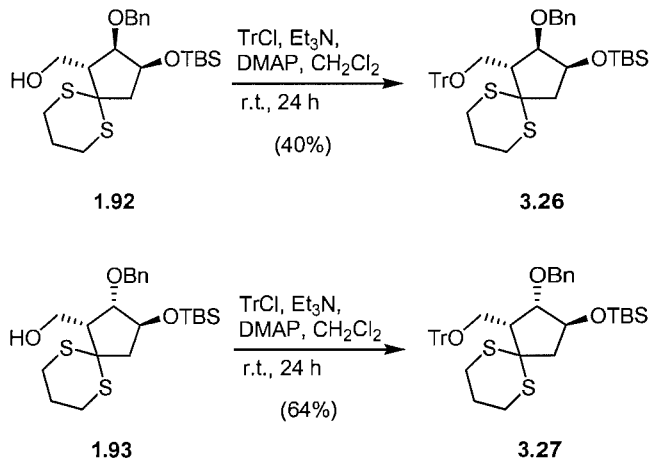
A practically efficient strategy for the large scale separation of the 5-*exo* products **1.92**, **1.93** and also the 6-*exo* product **3.3** was found to be possible through the functionalisation of the primary hydroxyl group, in which the difference in the steric environments between the pair of diastereoisomers could be exploited. This was demonstrated by the benzylation of the cyclisation product **1.92** and **1.93** to afford the respective benzyl ethers **3.24** and **3.25** (Scheme 3.13). Treatment of **1.92** with NaH followed by benzyl bromide afforded **3.24** in 57% yield, whilst only 9% of benzyl ether **3.25** was obtained when alcohol **1.93** was benzylated under the same conditions. In both cases, the majority of the unreacted starting material could be recovered. Steric influence from the adjacent benzyloxy group was the probable rationale for the observed difference in reactivity, as S_N2 reactions are known to be sensitive to steric hindrance. The difference in rate between the two benzylation reactions could be investigated to facilitate separation of the two diastereoisomers **1.92** and **1.93**.

Scheme 3.13



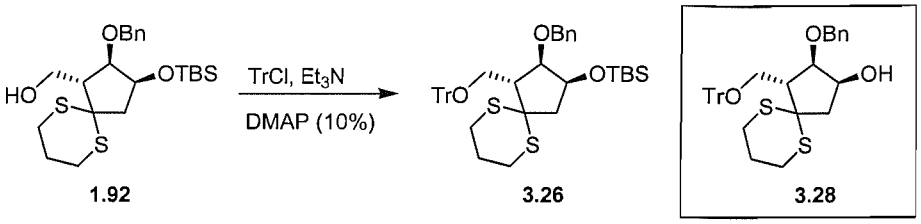
On the other hand, tritylation of both alcohols **1.92** and **1.93** by treatment with trityl chloride and triethylamine led to similar yields of the corresponding trityl ether **3.26** and **3.27** (Scheme 3.14). Although only modest yields were obtained for the transformation initially, the diastereomeric trityl ethers **3.26** and **3.27** could be separated by careful column chromatography using dichloromethane and petroleum ether as eluent. Moreover, we were delighted to discover that when a mixture of trityl ethers **3.26** and **3.27** were recrystallised from ethanol, only crystals of trityl ether **3.26** were formed. Although a small amount of **3.26** remained in the filtrate and had to be separated from **3.27** by column chromatography, this proved to be the most practical and effective way to separate the two diastereomers.

Scheme 3.14



Having established the appropriate recrystallisation procedures for the separation of trityl ether diastereoisomers, optimisation of the tritylation process was conducted using purified alcohol **1.92** and the results are summarised in Table 3.3.

Table 3.3



1.92 **3.26** **3.28**

Entry	TrCl (equiv.)	Et_3N (equiv.)	Conc. (M)	Solvent	Temp. (°C)	Time (h)	1.92 (%)	3.26 (%)
1	1.2	/	0.04	Pyridine	70	24	\	26[a]
2	1.4	1.5	0.03	DMF	r.t	110	74	18
3	1.4	1.5	0.10	DMF	r.t.	110	53	36
4	1.4	4.0	0.10	DMF	r.t	110	73	12
5	1.4	1.5	0.10	DMF	60	23	traces	77
6	2.0	2.0	0.10	DMF	60	24	7	86
7	2.0	2.0	0.10	DMF	90	22	9	72
8	1.1	1.2	0.10	DMF	Reflux	1.5	traces	56
9	2.0	2.0	0.20	DMF	60	16	traces	90[b]

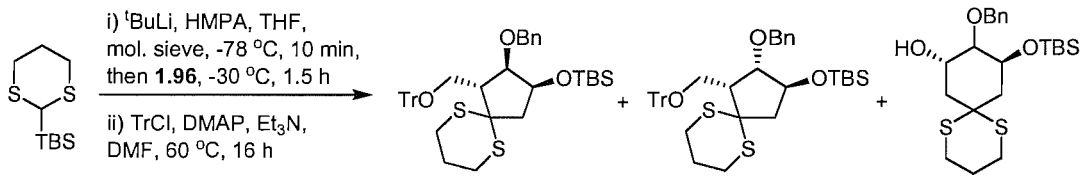
a – 21% of alcohol **3.28** also isolated; *b* – performed on a mixture of **1.92** and **1.93** to give 90% of a mixture of **3.26** and **3.27**

Tritylation of alcohol **1.92** in pyridine at 70 °C afforded a poor 26% yield of **3.26** with the starting material completely consumed (Table 3.3, Entry 1). Significant quantities of two other compounds were isolated, one of which was thought to be alcohol **3.28** resulting from the cleavage of the silicon protecting group (not fully characterised). Performing the tritylation process in a dilute DMF solution led to low yields of trityl ether **3.26**, with the majority of the starting material recovered (Entry 2). A higher yield was obtained in a more concentrated DMF solution, whilst increasing the amount of triethylamine led to a decreased yield of **3.26** (Entries 3 and 4 respectively). Critically, elevating the temperature to 60 °C led to a much better conversion (Entry 5) and the use of 2.0 equivalents of trityl chloride at 60 °C in DMF furnished the desired **3.26** in 86% yield (Entry 6). At temperatures above 60 °C, the overall yield was found

to be reduced (Entries 7 and 8), probably as a result of silicon protecting group cleavage as observed in the earlier experiment involving pyridine. To complete the optimisation, a mixture of **1.92** and **1.93** was subjected to tritylation at an increased concentration (0.2M) at 60 °C in DMF to afford a mixture of **3.26** and **3.27** in an excellent 90% yield (Entry 9).

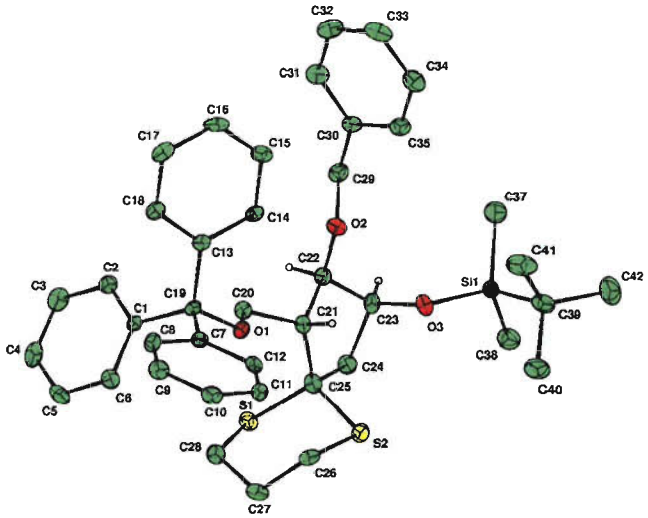
To apply this in a large scale process, the crude carbacyclisation products, which were not purified by column chromatography, were subjected to tritylations under the optimised conditions (Scheme 3.15). This afforded a mixture of trityl ethers **3.26** and **3.27** (56% and 20% from bis-epoxide **1.96**) together with the unreacted 6-*exo* carbacyclisation product **3.3/3.6** (7%). The majority of **3.26** was isolated as pure crystals, whilst the remaining mixture was purified by column chromatography. Hence, the tritylation/recrystallisation process not only greatly facilitated the separation of the diastereomeric 5-*exo* carbacyclisation products **1.92** and **1.93**, but also the separation of the 6-*exo* cyclisation product **3.3/3.6** from the 5-*exo* counterparts.

Scheme 3.15



The X-ray structure of **3.26** was obtained (Figure 3.2) which allowed for unambiguous assignment of the relative stereochemistries **3.26**, and hence of **1.92**, **1.93** and **3.27**.

Figure 3.2 – Crystal Structure of 3.26



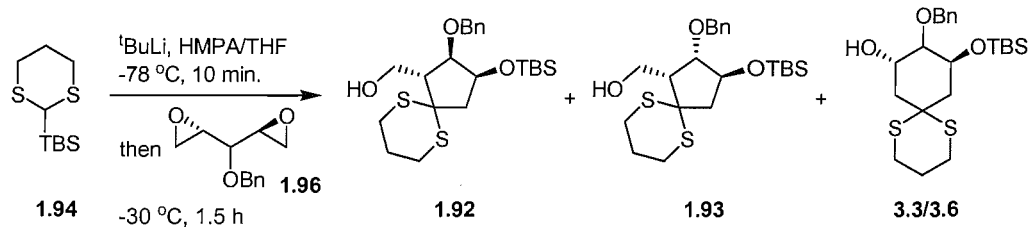
3.6 Carbacyclisation - Additional Results

3.6.1 Investigating the Effect of Li^+ Ion on Carbacyclisation

The observed diastereoselectivity of the carbacyclisation process was found to originate mainly from the selective opening of one of the two diastereotopic epoxide functionalities. The differentiation between the epoxide functionalities by the dithiane nucleophile was likely due to steric reasons. However, the presence of lithium cations could influence the stereochemical outcome as well as the rate of the reaction through coordination to the oxygen atoms of the bis-epoxide **1.96**. The role of HMPA in the carbacyclisation process was to fully chelate the Li^+ cations, thus increasing the reactivity of the nucleophiles by liberating the free anions from tight ion-pairing with the lithium cations. Therefore, lithium cations should neither affect the diastereoselectivity nor accelerate the carbacyclisation by direct lithium catalysis in the presence of HMPA.

In seeking evidence supporting the above theory, a pair of parallel carbacyclisation experiments was conducted under the usual carbacyclisation conditions, one of which contains an additional 1.0 equivalent of $LiClO_4$ (Table 3.4).

Table 3.4

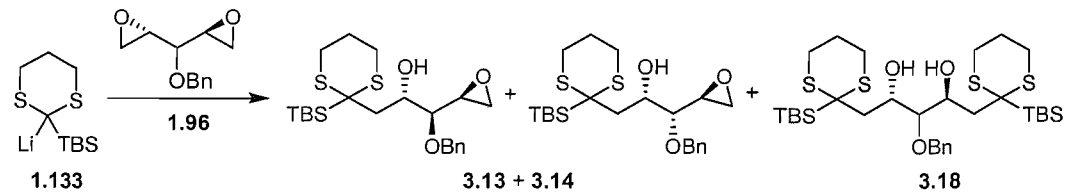


Entry	$LiClO_4$ (equiv.)	Yield of 1.92+1.93 (%)	Ratio of 1.92:1.93	Yield of 3.3/3.6 (%)	Recovd. 1.96 (%)
1	0	78	4.0:1	6	0
2	1.0	55	3.8:1	6	14

The results were very much as expected with the additional Li^+ cations having virtually no effect on the diastereomeric ratio between **1.92** and **1.93** (Entry 2 vs 1). However, the overall yield was lower when an addition 1.0 equivalent of $LiClO_4$ was present. This was due to a reduced HMPA vs Li^+ ratio, thus lowering the chelating effect of HMPA. The pair of experiments thus provided further evidence for the fact that the carbacyclisation diastereoselectivity originated solely from the initial bis-epoxide opening, and that it was purely a steric phenomenon.

Secondly, the effect of Li^+ cations on the initial epoxide opening process in the absence of HMPA was also examined. A pair of parallel experiments involving the treatment of bis-epoxide **1.96** with one equivalent of the dithiane anion **1.133** was conducted and an additional 1.0 equivalent of $LiClO_4$ was added to one of the two experiments. In both the experiments, Brook rearrangement was suppressed by the use of Et_2O as solvent and the exclusion of HMPA in the reaction mixture (Table 3.5).

Table 3.5



Entry	$LiClO_4$ (equiv.)	Temp (°C)	Time (h)	Yield of 3.13+3.14 (%)	Ratio of 3.13:3.14	Yield of 3.18 (%)	Recovd. 1.96 (%)
1	\	-40 to -30	2.0	36	1.3:1	18	6
2	1.0	-40 to -30	2.0	31	3.1:1	0	48
3	1.0	-78	4.0	94	2.7:1	0	5

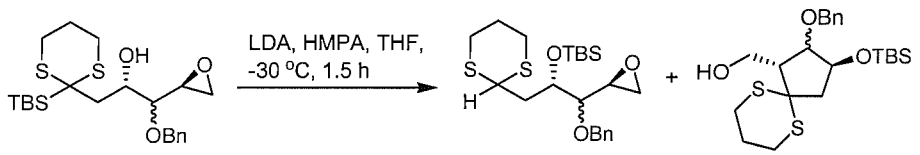
In the absence of lithium perchlorate, alcohols **3.13** and **3.14** were obtained in 36% yield (1.3:1) together with 18% of the bis-adduct **3.18** (Table 3.5, Entry 1). On the other hand, when 1.0 equivalent of lithium perchlorate was present, equally low yields of **3.13** and **3.14** were obtained (Entry 2) and a large amount of unreacted bis-epoxide **1.96** was recovered in this case. More interestingly, the bis-adduct **3.18** was not detected in the latter experiment. Unfortunately, it would be difficult to relate the observed diastereoselectivity to the effect of Li^+ ions as the subsequent reaction of **1.133** with **3.13/3.14** is likely to proceed with different reaction rates (Entry 1). When the second experiment was repeated at a lower temperature (Entry 3), a much higher conversion was achieved with similar diastereoselectivity (Entry 3 vs 2). The much higher conversion here could be the result of working under a much drier environment or the use of better quality alkyllithium reagent. A much clearer conclusion could be drawn if more experimental data were available, but the investigation was terminated here due to time limitations.

3.6.2 Confirmation of Relative Stereochemistry

So far, the relative stereochemistries of the pre-cyclisation intermediates **3.13**, **3.14**, **3.15** and **3.16** were deduced from the carbacyclisation mechanism based on the confirmed stereochemistry of the cyclised structures **1.92** and **1.93**. To ensure the relative stereochemistry of the intermediates were correctly assigned, it was necessary to relate the intermediates to the cyclisation products by simply converting the intermediate directly into the corresponding cyclisation products **1.92** and **1.93**. This could be achieved, in theory, by conversion of alcohols **3.13** and **3.14** into the corresponding alkoxide in the presence of HMPA. Under these conditions, the alkoxides should undergo Brook rearrangement and then subsequently cyclise to furnish the cyclisation products **1.92** and **1.93**.

Carbacyclisation using a 2.7:1 mixture of alcohols **3.13** and **3.14** was first attempted by treatment with *in-situ* generated lithium diisopropylamine (LDA) with HMPA in THF. This led to the formation of silyl ethers **3.15** and **3.16** as the major products of the reaction (66%, 2.8:1), whereas the desired carbacyclisation products **1.92** and **1.93** were only formed in very small quantities (Scheme 3.16).

Scheme 3.16



3.13 + 3.14
(2.7 : 1.0)

3.15 + 3.16
(2.8 : 1.0)
(66%)

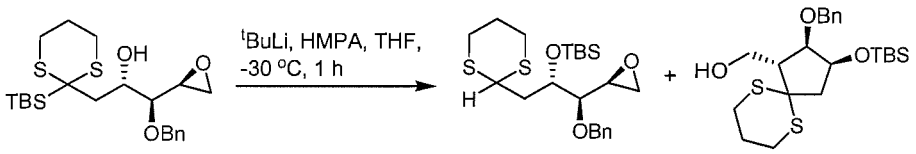
1.92 + 193
(9.9 : 1.0)
(3%)

The formation of silyl ethers **3.15** and **3.16** as the major products could be explained by the release of diisopropylamine after the deprotonation of the hydroxyl

group by LDA. The diisopropylamine was subsequently deprotonated by the carbanion formed after the Brook rearrangement of the alkoxides. In the next attempt, replacing LDA with LiH led to no conversion at all.

Fortunately, it was later found that the alcohol mixture **3.13** and **3.14** could be separated by careful HPLC purification using ethyl acetate/toluene as the eluent and alcohol **3.13** was successfully isolated in diastereomerically pure form. When alcohol **3.13** was treated with ^{t}BuLi in an HMPA/THF solution (Scheme 3.17), silyl ether **3.15** and the 5-*exo* cyclisation product **1.92** were formed in 35% and 26% yields respectively, both as a single diastereoisomer. This unambiguously confirmed the stereochemical assignments for both sets of diastereoisomers **3.13/3.14** and **3.15/3.16**, and that it was the pro-*S* epoxide of bis-epoxide **1.96** which was opened preferentially.

Scheme 3.17



3.13

3.15 (35%)

1.92 (26%)

3.7 Conclusion

The carbacyclisation sequence was thoroughly investigated and experimental conditions were fully optimised. Both bis-epoxide substrates **1.95** and **1.96** exhibited good regioselectivity towards the 5-*exo* cyclisation process. Desymmetrisation of the *pseudo*-C_2-symmetric bis-epoxide **1.96** led to a mixture of diastereomeric cyclisation products **1.92** and **1.93** with marked selectivity. The observed diastereoselectivity was found to originate mainly, but not entirely, from the initial epoxide opening by the

dithiane anion, despite the two diastereotopic epoxide functionalities of **1.96** were thought to be rather similar. A similar selectivity was also observed in the synthesis of alcohols **3.13** and **3.14**, possible side-products of the carbacyclisation process.

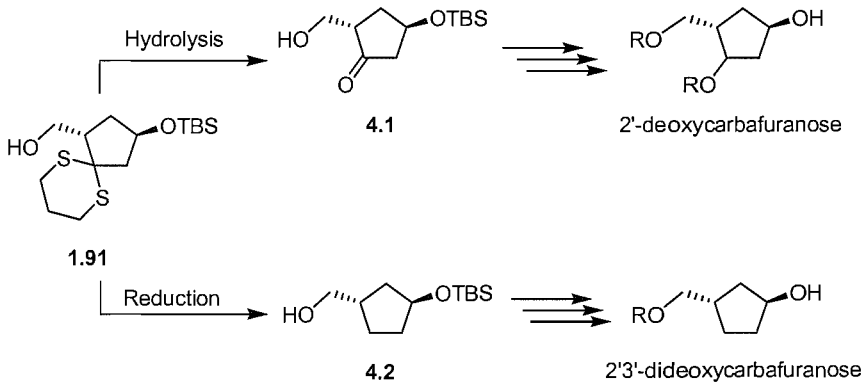
Large scale carbacyclisation experiments afforded products in yields comparable to the small scale experiments. Separation of large quantities of the diastereomeric 5-*exo* products **1.92** and **1.93** as well as the 6-*exo* product **3.3/3.6** could be easily achieved *via* conversion of **1.92** and **1.93** to the corresponding trityl ethers **3.26** and **3.27**. Recrystallisation followed by chromatographic purification enabled the isolation of trityl ethers **3.26** and **3.27** in diastereomerically pure forms. The relative configuration of the newly formed stereocentre of **1.92** was unambiguously confirmed by X-ray crystallography.

Chapter 4 - Carbafuranose Synthesis

4.1 Removal of the Thioketal Group

The thioketal group present in the cyclisation products could be removed by hydrolysis to afford the corresponding ketone (Chapter 4.1.1), which could then be used for the synthesis of 2'-deoxycarbafuranose analogues (Scheme 4.1). Alternatively, reduction using Raney nickel should convert the thioketal moiety into the corresponding methylene group (Chapter 4.1.3). These precursors could then be used for the synthesis of 2',3'-dideoxycarbafuranose analogues.

Scheme 4.1



4.1.1 Thioketal Hydrolysis

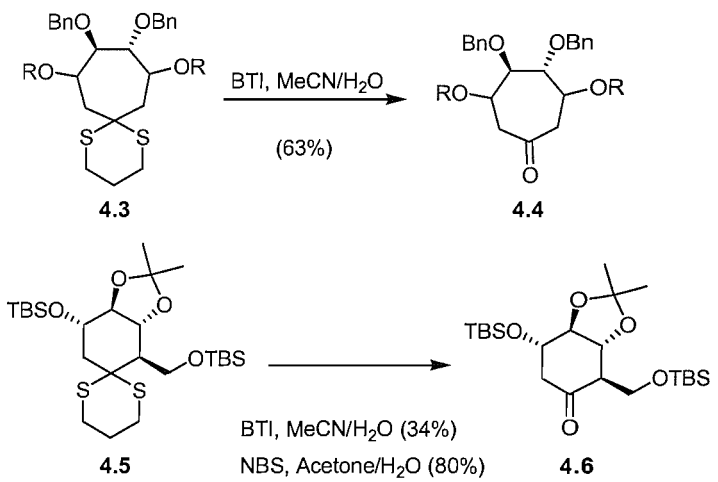
Cyclic and acyclic thioketals exhibit high stability towards relatively strong acids and bases, and have therefore found numerous applications in synthesis as protecting groups for the aldehyde and ketone functionalities. Several methods have been developed in the literature for the hydrolysis of thioacetals and thioketals to reform the corresponding aldehydes and ketones.[79] Traditionally, the transformation is mediated by oxidation, alkylation (MeI) or metallation (Hg^{2+}) of sulfur. However, the harsh

conditions involved in the cleavage of thioketals are often incompatible with other functional groups present in the molecule, thus hampering its use in the synthesis of more sensitive natural products.

4.1.1.1 Literature Examples – Hydrolysis of Spiro-Thioketal

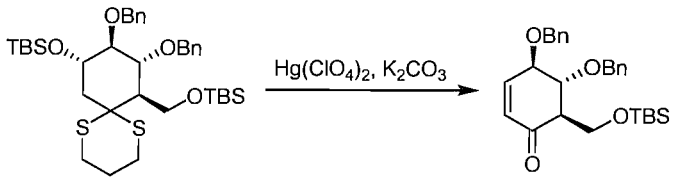
While the hydrolysis of numerous thioketal containing compounds afforded the corresponding ketone products in good yields, deprotection of spiro-thioketals with structures similar to the carbacyclisation products **1.91-1.93** was often reported to be problematic. Le Merrer *et al.* reported the use of bis-trifluoroacetoxyiodobenzene (BTI) in the hydrolysis of spiro-dithioketal **4.3** to give cycloheptanone **4.4** in good yield (Scheme 4.2), whereas cyclohexanone **4.6** was only formed in 34% yield from the corresponding thioketal **4.5** under the same conditions.[97] Having failed to obtain satisfactory results with several other reagents including Et_3OBF_4, DDQ, $HgCl_2$ and $Hg(ClO_4)_2$, Le Merrer eventually found the best conditions to be the use of 8 equivalents of NBS in acetone/H_2O at -30 °C. Under these conditions, ketone **4.6** was synthesised in 80% yield.

Scheme 4.2



The isolation of enone **4.8** by Le Merrer in the $HgClO_4$-mediated hydrolysis of spiro-dithioketal **4.7** (Scheme 4.3)[96] suggested that the decomposition of ketone **4.6** by a β-elimination process might have accounted for the observed low yield in the BTI-mediated hydrolysis of thioketal **4.5**.

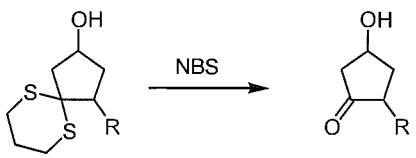
Scheme 4.3



4.7 **4.8**

While Le Merrer, with considerable effort, managed to find good conditions for the thioketal hydrolysis process, Schaumann *et al.* also reported difficulties with the hydrolysis of spiro-thioketals to the corresponding cyclopentanones.[95] Intriguingly, NBS-mediated hydrolysis of thioketal **4.9** led to the cyclopentanone **4.10** in good yields (Scheme 4.4). However, hydrolysis of the analogous thioketal **4.11** bearing an α-methyl substituent afforded **4.12** in only 27% yield. An unambiguous rationale was not provided for the observed poor yield.

Scheme 4.4



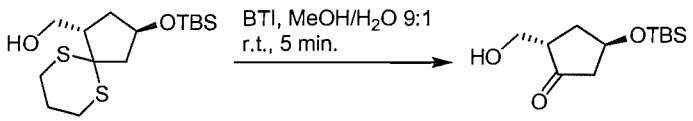
R = H, **4.9**
R = Me, **4.11**

R = H, **4.10**; (64%)
R = Me, **4.12**; (27%)

4.1.1.2 Thioketal Hydrolysis – Hypervalent Iodine Reagents

In 1989, Stork *et al.* reported the hydrolysis of a series of 1,3-dithianes using BTI.[124] The reagent has since found numerous applications in synthesis because of its tolerance to several functional groups, with good yields often obtained in reaction time of less than 10 minutes. Due to the above advantages, the conversion of thioketal **1.91** into the corresponding ketone **4.1** was initially attempted using this hypervalent iodine reagent (Scheme 4.5).

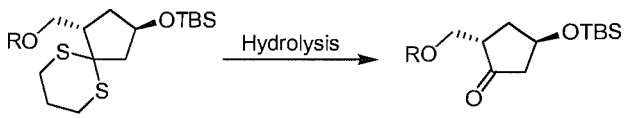
Scheme 4.5



1.91 (32%) **4.1**

When BTI was added to a solution of thioketal **1.91** in $MeOH/H_2O$, the complete consumption of starting material was observed within the first 5 minutes. However, only a poor yield (32%) of the desired ketone **4.1** was obtained after purification by column chromatography, and decomposition was sometimes observed after purification. To ensure that side reactions did not occur on the primary hydroxyl group, protected thioketals **4.13** (R = Bz) and **4.14** (R = Bn) were also subjected to BTI mediated hydrolysis (Table 4.1).

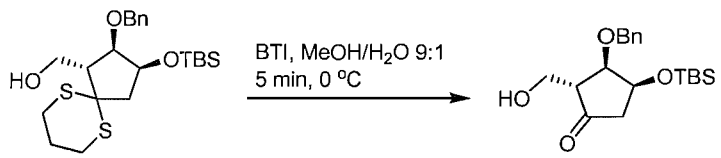
Table 4.1



Entry	R	Reagent	Time	Temp.	Solvent	Yield
1	Bz (**4.13**)	BTI (1.5 equiv.)	5 min.	r.t.	MeOH/H_2O 9:1	12%
2	Bn (**4.14**)	BTI (1.5 equiv.)	15 min.	0 °C	MeOH:CH_2Cl_2:H_2O (8:1:1)	28%
3	Bz (**4.13**)	DMP (2.0 equiv.)	2 d	r.t.	MeCN:CH_2Cl_2:H_2O (8:1:1)	Failed
4	Bn (**4.14**)	IBX (2.0 equiv.)	1 d	r.t.	DMSO:H_2O (9:1)	Failed

Hydrolysis of benzoate **4.13** and benzyl ether **4.14** did not lead to an improved yield of the corresponding ketones (Entries 1 and 2) and it was apparent that the low yield for the transformation was not related to potential side reactions on the primary hydroxyl group. Thioketal hydrolysis using other hypervalent iodine reagents such as iodoxybenzoic acid[125] (IBX) and Dess-Martin periodate[126] (DMP) were also attempted, but they failed to yield detectable amounts of the desired ketones when added to compounds **4.13** and **4.14** (Entries 3 and 4).

Scheme 4.6

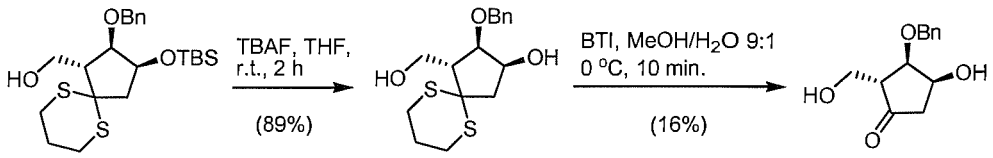


1.92 (15%) **4.15**

BTI-mediated hydrolysis of the 1'a-substituted thioketal **1.92** also afforded the desired ketone **4.15** in very poor yield (Scheme 4.6). Furthermore, thioketal **4.16**, obtained from the treatment of thioketal **1.92** with tetrabutylammonium fluoride (Scheme 4.7), was subjected to hydrolysis using BTI under conditions described

previously, but no improvement was observed for the transformation. This suggested that the decomposition of ketone by β-*tert*-butyldimethylsilyloxy elimination was not the major cause for the poor yield observed.

Scheme 4.7

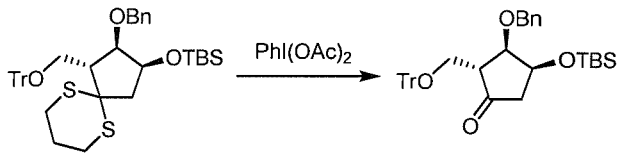


1.92 **4.16** **4.17**

In addition, a second hydrolysis experiment was conducted using diol **4.16**, with 2,6-lutidine incorporated in the reaction mixture as a scavenger for the trifluoroacetic acid formed during the reaction. The experiment began at a temperature of -30 °C at which no reaction was observed. On warming to 0 °C, the starting material was quickly consumed but not a trace of the desired product was observed. It was therefore clear that the TFA produced in the reaction was also not the cause for the observed low yield.

The next set of conditions investigated was based on the hypervalent iodine reagent diacetoxyiodobenzene (DAIB) using trityl-protected thioketal **3.26**. The DAIB reagent was reported as a cheaper variant of BTI, with the much milder acetic acid produced as the by-product.[127] When DAIB was used in small excess (Table 4.2, Entry 1) and in large excess (Entry 2), formation of ketone **4.18** could be detected initially by TLC analysis, but decomposition was observed at longer reaction time. Reducing the reaction time enabled ketone **4.18** to be isolated in 13% and 16% yields respectively when 2.5 and 10 equivalents of DAIB were used (Entries 3 and 4). Needless to say, these yields were still unacceptable.

Table 4.2

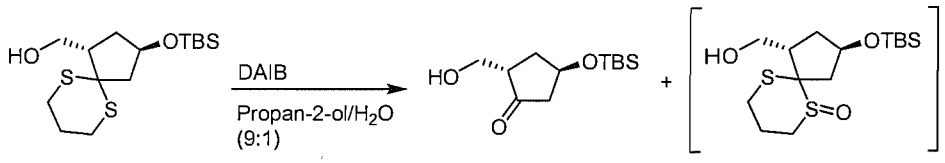


3.26 **4.18**

Entry	Reagent	Solvent	Temp.	Time	Yield / Observation
1	DAIB (2.5 equiv)	Acetone/H_2O 9:1	r.t.	1 day	Small amount of product forming initially, decomposed later
2	DAIB (10 equiv)	Acetone/H_2O 9:1	r.t.	3 h	As above
3	DAIB (2.5 equiv)	Acetone/Buffer 9:1	r.t.	3 h	13%
4	DAIB (10 equiv)	MeCN/Buffer 8:2	r.t.	25 min	16%

The investigation continued with the use of 1'a-unsubstituted thioketal **1.91**. Similar to the previous example, treatment of **1.91** with DAIB in propan-2-ol/H_2O at ambient temperature afforded the desired ketone in 18% yield (Table 4.3, Entry 1). Intriguingly, a second compound anticipated to be the corresponding sulfoxide diastereoisomers **4.19** (based on NMR and mass spectrometry analysis) was isolated in approximately 30% yield.

Table 4.3



1.91 **4.1** **4.19**
Structure not confirmed

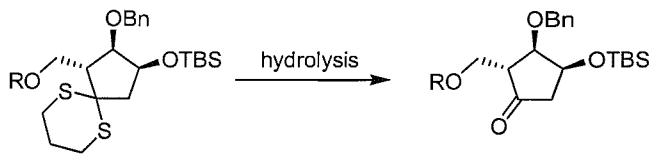
Entry	Reagent	Additive	Yield of 4.1	Other products
1	DAIB	\	18%	~30% sulfoxide **4.19**
2	DAIB	HBF_4	21%	No sulfoxide
3	DAIB	AcOH	20%	No sulfoxide

Sulfoxides derived from dithioketals can be converted to the corresponding ketone by either i) using an excess of the initial oxidant in the presence of water; or ii) acidic hydrolysis with HBF_4.[128] Since the amount of DAIB used was already in excess, the *in-situ* conversion of the undesired sulfoxide **4.19** into the desired ketone was attempted by the incorporation of HBF_4 in the reaction mixture in the following hydrolysis experiment (Entry 2). Although dramatic acceleration in reaction rate was observed when HBF_4 was incorporated into the reaction mixture, the yield of ketone **4.1** did not improve. Furthermore, sulfoxide **4.19** was no longer detected. Replacing HBF_4 with the milder AcOH led to very similar results (Entry 3).

4.1.1.3 Thioketal Hydrolysis – Other Methods

With the exception of $HgCl_2$[129] (Table 4.4, Entry 4), which did not initiate the hydrolysis process, other reagents such as pyridinium hydrobromide perbromide (Entry 1),[130] benzeneseleninic anhydride (Entries 2 and 3),[131] MeI (Entry 5), $AgNO_3$ (Entry 6), DMSO at reflux (Entry 7) and cerium ammonium nitrate (Entry 8)[132] all led to decomposition into unknown products, few of which could be isolated and identified. Moreover, thioketal hydrolysis experiments employing neat trichloroisocyanuric acid,[133] mercury(II) nitrate trihydrate[134] or chlorinated silica gel[135] also led to decompositions.

Table 4.4



1.92, R = H
3.26, R = Tr

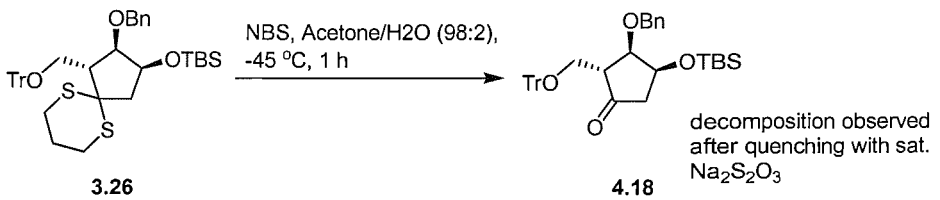
4.15, R = H
4.18, R = Tr

Entry	Thioketal	Reagent	Solvent	Temp.	Time	Observation
1	**3.26**	HBr.Br.py, TBAB, py	CH_2Cl_2/H_2O 5:1	r.t.	1 day	Small amounts of two unknown products
2	**3.26**	BSA (1.1 equiv)	THF	reflux	3 h	Decomposition
3	**1.92**	BSA (1.1 equiv)	THF	reflux	3 h	Decomposition
4	**3.26**	$HgCl_2$ (2 equiv) + $CaCO_3$ (2 equiv)	$MeCN/H_2O$ 8:2	reflux	3.5 h	No reaction
5	**3.26**	MeI (1 equiv)	$EtOH/H_2O$ 95:5	reflux	1 day	Decomposition
6	**3.26**	$AgNO_3$ (2 equiv)	EtOH	50 °C	1 h	Decomposition
7	**3.26**	\	DMSO	reflux	1 day	Decomposition
8	**3.26**	CAN	Acetone/H_2O 3:1	r.t.	16 h	Decomposition

4.1.1.4 *N*-Halosuccinimide-Mediated Thioketal Hydrolysis

The search for suitable conditions for this transformation continued with the use of *N*-halosuccinimides. First, hydrolysis of thioketal **3.26** was attempted under conditions reported by Le Merrer.[97] Hence, upon treatment of **3.26** with 8 equivalents of NBS at -45 °C (Scheme 4.8), formation of the desired ketone was observed by TLC analysis. However, the ketone product was no longer present after quenching with saturated $Na_2S_2O_3$ solution.

Scheme 4.8



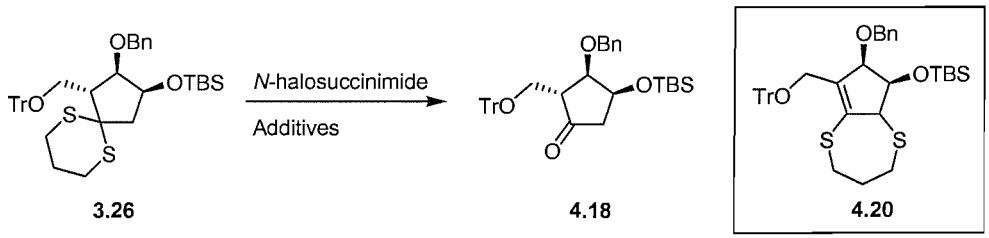
3.26 **4.18**

The use of saturated $Na_2S_2O_4$ solution in work-up was considered as a possible cause for the decomposition observed. Therefore, *in-situ* reduction of ketone **4.18** into

the corresponding alcohol was attempted. Hence, $NaBH_4$ was added to the reaction mixture after 1 hour at -45 °C, which led to vigorous effervescence. However, neither the desired alcohol nor the unreduced ketone was isolated after the usual aqueous work-up.

Next, the incorporation of additives within the system was investigated. Silver(I) salts have been reported by Corey to enhance the efficiency of NBS- and NCS-mediated hydrolysis of thioketal, both in increasing the yield and in reducing the amount of halosuccinimide required for the process.[129] Furthermore, the addition of strong acid salts such as $LiClO_4$ was found to effectively promote NBS-mediated glycosidation reactions with thioglycosides under mild and neutral reaction conditions.[136] An unambiguous rationale for the observed enhancing effects was not provided in either case. Nevertheless, the hydrolysis of thioketal **3.26** employing NBS or NCS in conjunction with either $LiClO_4$ or $AgNO_3$ (or both) was investigated (Table 4.5).

Table 4.5



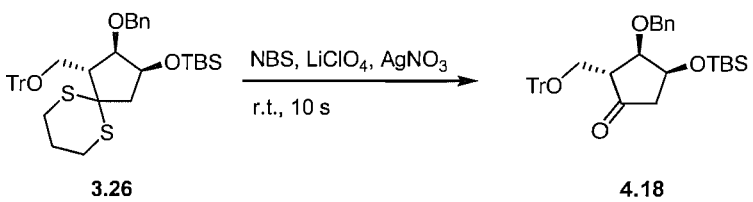
3.26 **4.18** **4.20**

Entry	Reagent	Solvent	Temp.	Time	Yield of **4.18**	Observation
1	NCS (4 equiv.) $AgNO_3$ (4.5 equiv.)	MeCN/H_2O 8:2	r.t.	3 min	12%	No other compound isolated
2	NCS (4 equiv.) $AgNO_3$ (4.5 equiv.)	Acetone/H_2O 9:1	r.t.	1 min	14%	Small amount of one unknown isolated
3	NCS (4 equiv.) $AgNO_3$ (4.5 equiv.)	Acetone/H_2O 9:1	-30 °C	5 min	0	Some starting material recovered
4	NBS (1.5 equiv.) $LiClO_4$ (0.5 equiv.)	THF/H_2O 97:3	-30 °C	1 h	19%	Intermediate **4.20** isolated as major product

In the initial investigations, although all the starting material was consumed within 5 minutes, hydrolysis of **3.26** using NCS and $AgNO_3$ at room temperature led to low yields of the corresponding ketone **4.18** (Entries 1 and 2). Reducing the temperature to -30 °C did not afford the desired ketone at all (Entry 3). Intriguingly, when $LiClO_4$ was employed as the additive, ketone **4.18** was formed as the minor compound in low yield (Entry 4). The major compound formed in the reaction was a relatively stable solid later found to be the ring-expanded product **4.20**. Further details on the ring-expansion process can be found in Chapter 4.1.2. It is noteworthy that the ring-expansion product **4.20** was only formed under specific conditions, usually when $LiClO_4$ was added or the reaction performed at very low temperature when hydrolysis was not possible. It was never observed in experiments in which $AgNO_3$ was present in the reaction mixture.

Further optimisation experiments of this process were then conducted in order to improve the formation of the desired ketone **4.18** in preference to the ring-expansion product **4.20** (Table 4.6). The optimisation procedures involved the use of a large excess of the reagents (15 equivalents) to accelerate the rate of ketone formation and the significant reduction in reaction time (~10 seconds) to minimise the decomposition of ketone **4.18** after its formation. In addition, the amount of water vs solvent was increased to 1:4 to ensure effective dissolution of $AgNO_3$.

Table 4.6



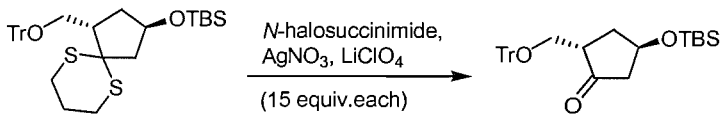
3.26 **4.18**

Entry	NBS (equiv.)	$AgNO_3$ (equiv.)	$LiClO_4$ (equiv.)	Solvent	Time	Yield of 4.18	Others
1	15	15	\	Acetone/H_2O 4:1	10 s	16%	One unknown compound (unstable) isolated
2	15	15	\	THF/H_2O 4:1	10 s	14%	One unknown compound (unstable) isolated
3	15	\	15	THF/H_2O 4:1	10 s	28%	Contained a large amount of ring expanded products **4.20**
4	15	\	4.0 M soln.	THF/H_2O 4:1	10 s	20%	Contained a large amount of ring expanded products **4.20**
5	15	15	15	THF/Buffer 4:1	10 s	45%	Nothing isolated other than ketone
6	15	15	15	THF/Buffer 4:1	10 s	37%	(Repeating Entry 5)
7	4	4	4	THF/Buffer 4:1	10 s	31%	Nothing isolated other than ketone

Thioketal hydrolysis employing 15 equivalents of NBS and $AgNO_3$ in acetone/H_2O led to poor yields as observed in the previous experiments (Table 4.6, Entry 1). Changing the reaction solvent to THF did not lead to an increase in yield (Entry 2). On the other hand, the use of 15 equivalents of NBS with the same amount of $LiClO_4$ seemed to lead to an apparent increase in yield (Entry 3), although performing the hydrolysis in a concentrated $LiClO_4$ solution (4.0 M; ~130 equivalents) did not lead to a further yield enhancement (Entry 4). In both cases, although the ketone formation process was improved, the major product isolated was still the ring expansion product **4.20**. Surprisingly, the combined use of both $LiClO_4$ and $AgNO_3$ with NBS seemed to have inhibited the formation of the ring expansion product and led to further increased yields of the desired ketone (Entries 5 and 6). Note that a pH 7.0 buffer was used instead of H_2O for these two experiments, but similar results were later obtained using H_2O without additional buffering. Reducing the amount of reagents led to a decreased yield of ketone **4.18** (Entry 7), indicating the need for the large excess of each reagent.

With the yield of this transformation still unsatisfactory, optimisation of the hydrolysis process continued by using the 1'a-unsubstituted thioketal **4.21** (synthesised from carbacyclisation product **1.91** by treatment with TrCl and Et_3N in DMF (90%)). NCS-mediated hydrolysis led to slightly lower yield of ketone **4.22** compared with the corresponding NBS experiment, but a small increase in yield was observed when NIS was employed (Table 4.7, Entries 2 and 3 vs 1). However, it was difficult to draw unambiguous conclusions from experimental yields which were only marginally different. In addition, it was found that an additional acid catalyst did not facilitate ketone formation (Entry 4 vs 3) and the use of a different solvent system also did not improve the yield of the transformation (Entry 5 vs 1).

Table 4.7



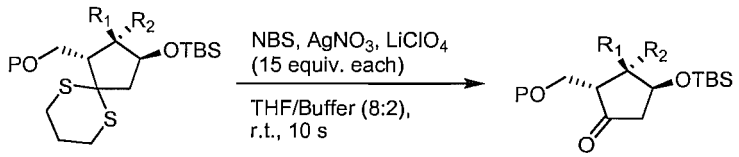
4.21 **4.22**

Entry	Reagent	Solvent	Additive	Yield of 4.22
1	NBS	THF:H_2O 8:2	\	48%
2	NCS	THF:H_2O 8:2	\	41%
3	NIS	THF:H_2O 8:2	\	53%
4	NIS	THF:H_2O 8:2	AcOH	23%
5	NBS	MeCN:CH_2Cl_2:H_2O 6:3:1	\	49%

Although the yields obtained from the above experiments were only modest, they were the best that have been observed to date. The cocktail of NBS, $AgNO_3$ and $LiClO_4$ were then applied to the hydrolysis of several thioketal analogues generated

from the carbacyclisation experiments (Table 4.8). Typical experimental procedures involved the addition of a solution of thioketal in THF to a vigorously stirred mixture of NBS, $LiClO_4$ and $AgNO_3$ in THF/H_2O. After 10 seconds, the reaction mixture was poured into a conical flask containing saturated $NaHCO_3$ solution and then extracted with Et_2O. In general, yields of between 40-50% were obtained for the hydrolysis of various thioketal analogues

Table 4.8



Entry	Thioketal	P	R_1	R_2	Ketone	Yield
1	**3.26**	Tr	OBn	H	**4.18**	45%
2	**3.27**	Tr	H	OBn	**4.23**	40%
3	**4.21**	Tr	H	H	**4.22**	49%
4	**1.92**	H	OBn	H	**4.15**	44%
5	**1.93**	H	H	OBn	**4.24**	43%
6	**1.91**	H	H	H	**4.1**	55%

Some noteworthy observations for the hydrolysis process are listed below:

1. The order of addition of the reagents was first NBS, followed by $LiClO_4$ and then $AgNO_3$. Hence, when $LiClO_4$ was added to a solution of NBS in THF/H_2O, the colour of the solution became an intense orange (possibly due to the formation of Br_2) and the addition was exothermic. Subsequent addition of $AgNO_3$ decolourised the solution. When a solution of thioketal in THF was subsequently added to this mixture, the colour temporarily turned blue and instantaneous precipitation was observed. Eventually a yellow suspension was obtained.

2. The corresponding ketones obtained from the hydrolysis experiments were found to be stable to mildly acidic conditions, but were very base labile. Thus, the presence of even weak bases in significant concentration could lead to decomposition of ketones through β-elimination

3. Problems with quenching were previously mentioned and clarification is provided here. The NBS reagent was quenched by saturated $NaHCO_3$ solution. If the amount of $NaHCO_3$ solution was insufficient, significant decomposition was observed after concentration *in vacuo* and sometimes even after purification by column chromatography. However, excess $NaHCO_3$ would lead to ketone decomposition due to its base-labile nature, but to a smaller extent. Therefore, the ketones synthesised by this method were either used immediately or purified further by HPLC after the initial chromatographic purification.

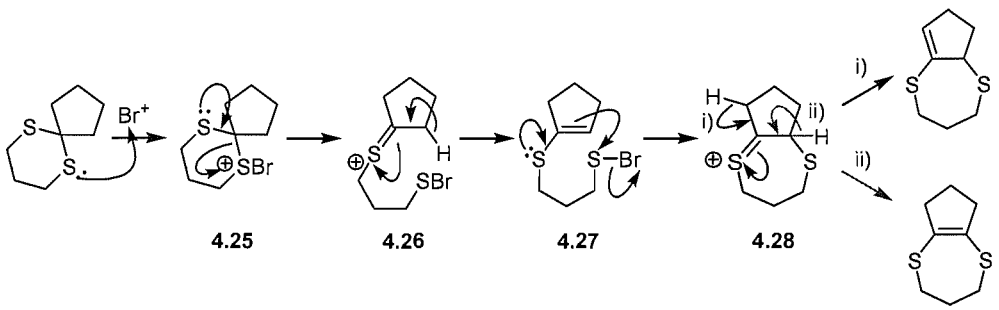
In conclusion, severe difficulties were encountered in the hydrolysis of spiro-thioketals with structures resembling carbacyclisation products **1.91** and **1.92**. Performing the transformation using several literature methods mostly resulted in decomposition either during the hydrolysis process or after the formation of the ketone product. There were several possible decomposition pathways and some were identified based on experimental evidence. These included 1.) thioketal ring expansion; 2.) oxidation of sulfur to sulfoxide; 3.) base-catalysed β-elimination (see Chapter 4.2.2); and 4.) over-bromination (see Chapter 4.2.1). Although the use of a cocktail of NBS, $LiClO_4$ and $AgNO_3$ in excess had minimised the side-reactions/decompositions described above, only modest yields of the desired ketones could be achieved.

4.1.2 Thioketal Ring Expansion

4.1.2.1 Mechanistic Considerations

As mentioned previously, when thioketal **3.26** was treated with a mixture of NBS and $LiClO_4$, an unexpected compound was isolated. The compound was later identified to be the ring expansion product **4.20**. A plausible mechanism for its formation is shown in Scheme 4.9.

Scheme 4.9

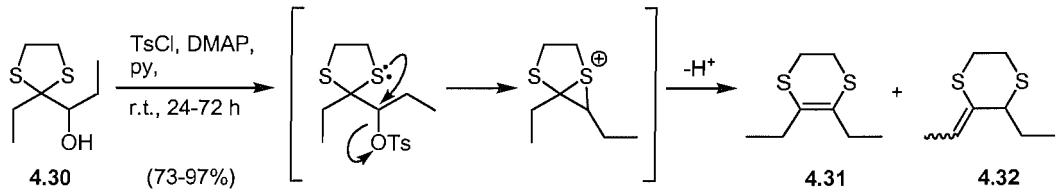


C-S bond scission after the initial bromination on the sulfur atom would be followed by the loss of a proton (instead of H_2O attack) to afford intermediate **4.27**. Subsequent intramolecular displacement of bromide and loss of a second proton should lead to the formation of either expansion product **4.20** or **4.29**, depending on the position of the second proton being lost. Initially, it was not certain as to whether the ring expansion product resembled the structure of **4.20** or **4.29**. Since **4.29** could find potentially useful applications in the synthesis of cyclopentene carbanucleosides, the ring expansion process was investigated in greater detail.

4.1.2.2 Literature Precedence

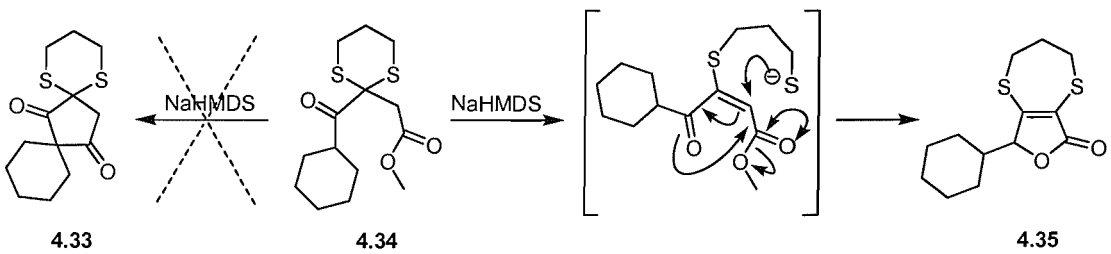
Very few transformations of this type had been reported in the literature and some examples are briefly described here. In the first example, tosylation of hydroxy-thioketal **4.30** led to the formation of the unexpected ring expansion products **4.31** and **4.32** (Scheme 4.10).[137] The formation of **4.31** and **4.32** were anticipated to proceed *via* the displacement of tosylate by the sulfur atom followed by the loss of a proton.

Scheme 4.10



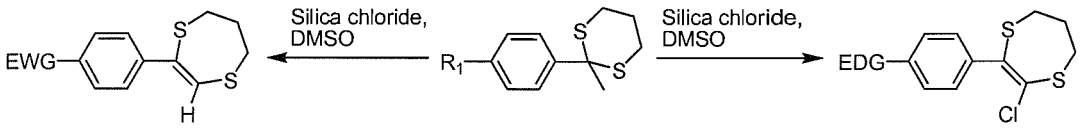
Fetizon *et al.* also reported a similar thioketal ring expansion mediated by NaHMDS (Scheme 4.11).[138] Instead of the desired cyclopentane-dione **4.33**, unsaturated lactone **4.35** was obtained as the major product. The mechanism of its formation was postulated to be *via* an intramolecular Michael addition after the initial C-S bond scission. Concomitant intramolecular lactonisation to form the β,γ-unsaturated lactone followed by alkene isomerisation led to the α,β-unsaturated lactone **4.35**.

Scheme 4.11



While these two examples are clearly mechanistically different, the final example was very closely related to the ring expansion process observed in our case. Iranpoor reported the use of "silica chloride" (chlorinated silica gel) as a source of Cl^+ in the deprotection of thioketals[139] and the transdithioacetalisation of acetals.[140] In a separate account, a series of ring expansions of α-aryl-thioketals mediated by silica chloride was also reported (Scheme 4.12).[135] When R_1 was an electron-withdrawing substituent, ring expansion product **4.37** was obtained. Conversely, when R_1 was electron donating in nature, chloride **4.38** was formed as the major product. The mechanism of the transformation would probably be similar to the one shown in Chapter 4.1.2.1.

Scheme 4.12



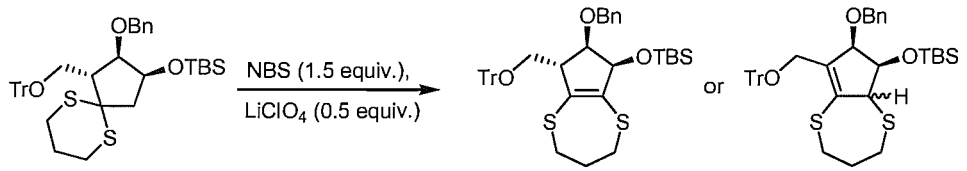
4.37 **4.36** **4.38**

4.1.2.3 Investigation of Thioketal Ring Expansion

Unlike the thioketal hydrolysis, the ring expansion process did not require the incorporation of water. Moreover, only 1.5 equivalents of NBS and 0.5 equivalent of $LiClO_4$ were required (Table 4.9). The investigation thus began by the treatment of **3.26** (~50 mg) with NBS and $LiClO_4$ in THF at -78 °C (Table 4.9, Entry 1). This led to formation of the ring expansion product as a single compound in modest yield. It is noteworthy to mention that compound **4.29** would exist as a single isomer, whereas compound **4.20** could be formed as either of the two possible diastereoisomers. Two other unstable compounds were isolated and the same two compounds were found in other experiments. The structures of these compounds were not identified, but it was

quite possible for these two compounds to be regio- or diastereoisomers of the expected ring expansion product.

Table 4.9 (NBS-Mediated Thioketal Expansion Based on 50 mg of 3.26)



3.26 4.29 4.20

Entry	Solvents	Conc. (M)	Temp. (°C)	Yield of 4.29/4.20	Others
1	THF	0.08	-78	41%	2 unknown compounds – 13 mg
2	Acetone	0.08	-78	48%	1 unknown compound – 17mg
3	Acetone	0.02	-78	54%	2 unknown compounds – 13 mg
4	Acetone	0.02	-45	35%	2 unknown compounds – 11 mg
5	MeCN[a]	0.02	-45	54%	2 unknown compounds – 9 mg
6	CH_2Cl_2	0.02	-45	16%	2 unknown compounds – 4 mg
7	MeCN:CH_2Cl_2 (1:3)	0.02	-45	65%	2 unknown compounds – 4 mg

a – a few drops of CH_2Cl_2 added to aid dissolution

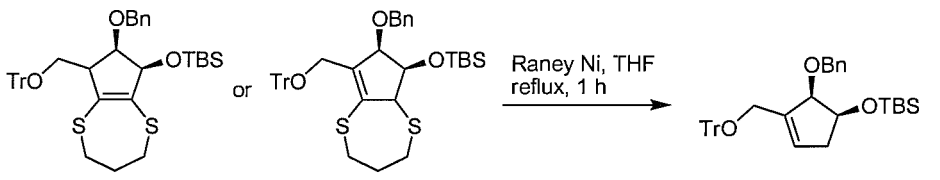
Changing the reaction solvent to acetone afforded a slightly increased yield of the ring expansion product (Entry 2), whilst decreasing the concentration to 0.02 M led to a further increase in yield (Entry 3). However, increasing the temperature to -45 °C led to a decreased yield of the product (Entry 4). Although the transformation seemed to be favoured at -78 °C, the experiment had to be conduct at -45 °C when acetonitrile was used as the solvent. This led to equally good yields of the expansion product comparing with the corresponding experiment carried out at -78 °C in acetone (Entry 5 vs 3). On the other hand, although a much lower 16% yield was observed when acetonitrile was replaced by dichloromethane (Entry 6), a combination of the two solvents afforded the

desired product as a single compound in good yield (Entry 7). Only a small amount of a second compound was isolated under this set of conditions.

4.1.2.4 Structural Identification of the Ring Expansion Product

The ring expansion product was then subjected to treatment with Raney nickel to afford the corresponding cyclopentene (Scheme 4.13). Although a low yield was obtained, the amount obtained was sufficient for the full characterisation of the compound. ^{1}H NMR spectroscopic analysis revealed the structure of the cyclopentene product to be **4.39**, as only a single alkene proton signal was present. This suggested the structure of the ring expansion compound to be one of the two diastereoisomers of **4.20**, although the possibility of double bond migration would also have to be taken into consideration. In addition, it could be envisaged that the two unknown compounds isolated from the expansion process might be the epimer of **4.20** and the regioisomer **4.29** from alkene isomerisation. Further optimisation process was terminated due to time limitations.

Scheme 4.13



4.29 **4.20** **4.39**

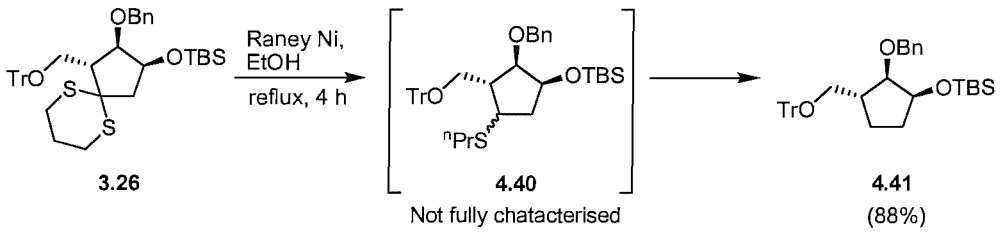
(29%)
+ 9% starting material

4.1.3 Raney Nickel Reduction of the Thioketal Functionality

Reduction of the dithiane functionality to the methylene unit using Raney nickel was investigated next. In contrast to the hydrolysis process, Raney nickel mediated

reduction of thioketal **3.26** proceeded smoothly to afford the corresponding cyclopentane **4.41** *via* the intermediate thioether **4.40** in excellent yield (Scheme 4.14). The two diastereomers of thioether **4.40** were not separated and were therefore not fully characterised, although analysis by mass spectrometry and ^{1}H NMR provided good evidence for the anticipated structure. The thioether diastereomers **4.40** were often isolated as by-products when the reduction was incomplete. Therefore, careful monitoring of the reduction process by TLC analysis was very important.

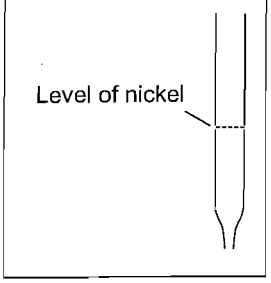
Scheme 4.14



3.26 **4.40** Not fully chatacterised **4.41** (88%)

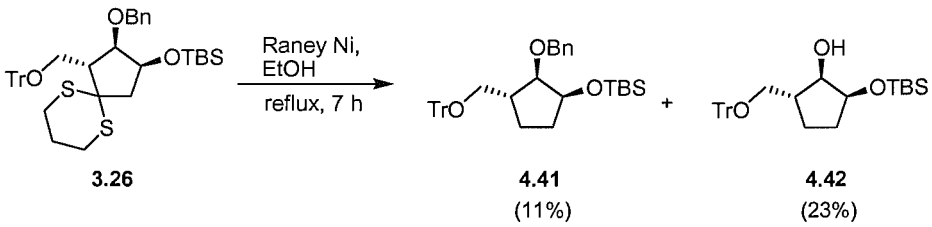
Transfer of Raney nickel was accomplished using a Pasteur pipette with a shortened tip (Figure 4.1). The catalyst was allowed to settle to the bottom and the quantity of nickel being added was estimated by calibration of the pipette against a known volume of liquid. This provided a sufficiently accurate estimation for the process as the amount of nickel needed not to be precise.

Figure 4.1



When a large excess of Raney nickel was added, the over-reduction product **4.42** was obtained at a longer reaction time (Scheme 4.15). This could be avoided by the addition of Raney nickel in small portions and careful monitoring of the process by TLC analysis.

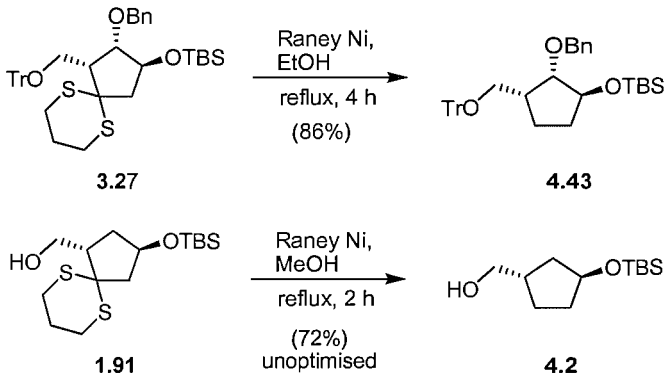
Scheme 4.15



3.26 **4.41** (11%) **4.42** (23%)

Finally, reduction of thioketals **3.27** and **1.91** employing Raney nickel in alcoholic solvents at reflux also proceeded smoothly to afford cyclopentanes **4.43** and **4.2** respectively in excellent yields (Scheme 4.16).

Scheme 4.16



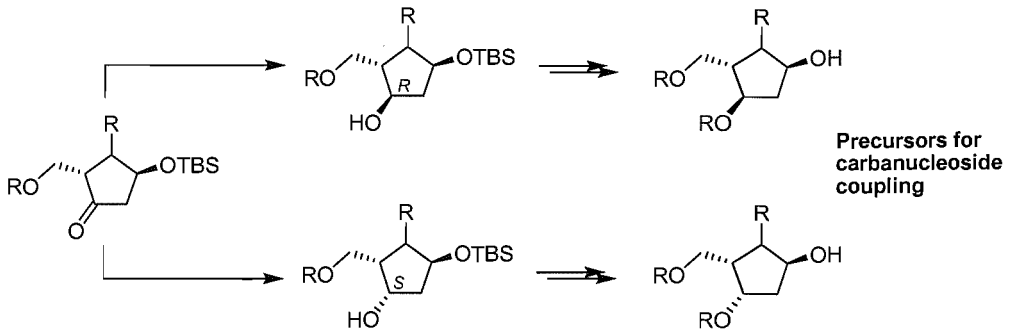
3.27 **4.43**

1.91 **4.2**

4.2 Synthesis of 2'-Deoxycarbanucleoside Precursors

The cyclopentanones obtained from the hydrolysis of the various carbacyclisation products could be selectively reduced to both of the corresponding alcohol epimers. Protection of the alcohols and subsequent removal of the silicon protecting group should furnish the corresponding carbanucleoside coupling precursors (Scheme 4.17). These precursors could then undergo further coupling with nucleobases *via* the inversion of the secondary alcohol to afford the carbanucleoside targets.

Scheme 4.17



4.2.1 Synthesis of β-3'-Hydroxycarbafuranose Analogues

4.2.1.1 β-Selective Ketone Reduction

The stereoselectivity of the ketone reduction process could be controlled by coordination with the 5-OH group. For instance, coordination of a borohydride species to the C5 hydroxyl group of ketone **4.1** could potentially direct hydride transfer to the ketone from the bottom face.[141-144] Therefore, selective reduction of cyclopentanones **4.1**, **4.15** and **4.24** were attempted using tetramethylammonium triacetoxyborohydride in AcOH/THF.[145] Treatment of ketone **4.1** with $Me_4NBH(OAc)_3$ in AcOH/THF at 0 °C for 4 hours afforded the desired crystalline diol **4.44** as the major diastereomer in 76% yield (Scheme 4.18), whilst the undesired diastereomer **4.45** was isolated in 5% yield. Diols **4.44** and **4.45** could easily be separated by column chromatography. The relative stereochemistry of diol **4.44** was confirmed by the determination of its crystal structure (Figure 4.2)

Scheme 4.18

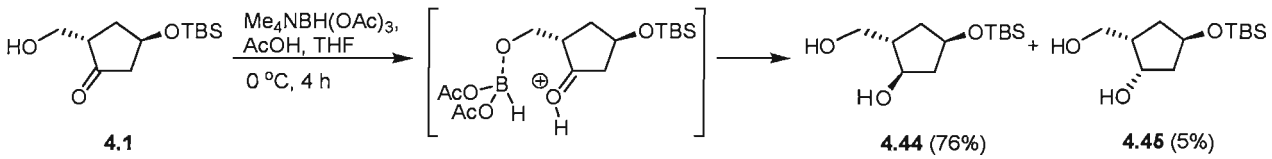
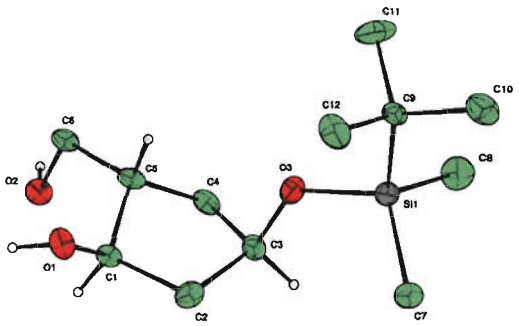
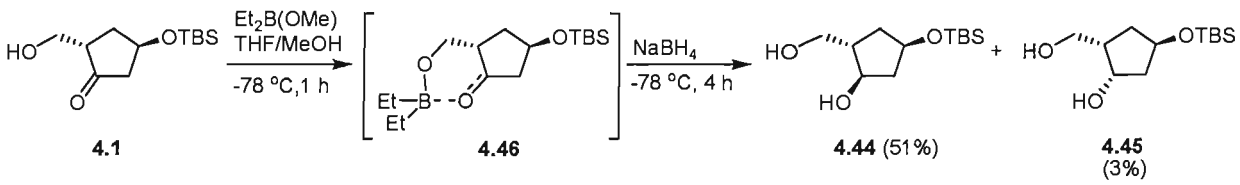


Figure 4.2 – Crystal Structure of Diol 4.44



Diol **4.44** was also obtained from ketone **4.1** by Shapiro's alkoxy-dialkylborane method.[146] Hence, formation of alkoxyborane **4.46** from treatment of ketone **4.1** with diethylmethoxyborane in THF/MeOH and should direct the subsequent borohydride reduction from the top phase to afford diol **4.45**. However, the β-epimer **4.44** was unexpectedly obtained as the major product (Scheme 4.19).

Scheme 4.19



Cyclopentanones **4.15** and **4.24** were also selectively reduced. Treatment of ketone **4.15** with tetramethylammonium triacetoxyborohydride led to the desired alcohol **4.47** as a single diastereoisomer in 81% yield (Scheme 4.20). Intriguingly, when ketone **4.24** was reduced using this method, the desired alcohol **4.48** was formed

as a crystalline solid in 77% as a single diastereoisomer together with 5% of bromo-carbafuranose **4.49**. The formation of by-product **4.49** was envisaged to be the result of an over-bromination side-reaction that occurred during the previous thioketal hydrolysis step. Although ketone **4.24** was purified by HPLC, the over-bromination side-product was clearly not separated from the desired product. The relative C2 and C3 stereochemistry of **4.49** was not confirmed.

Scheme 4.20

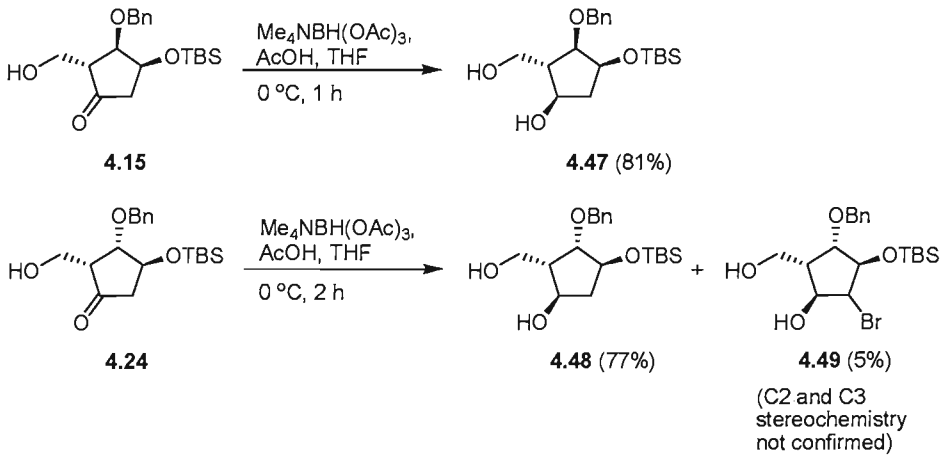
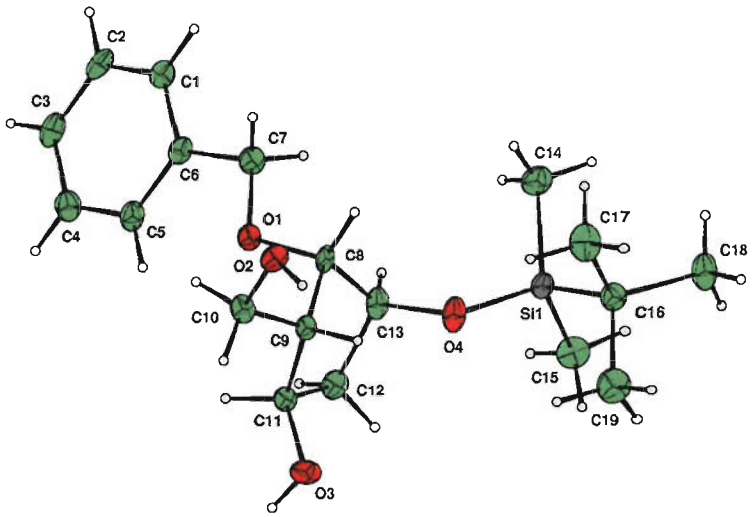


Figure 4.3 – Crystal Structure of Diol 4.48

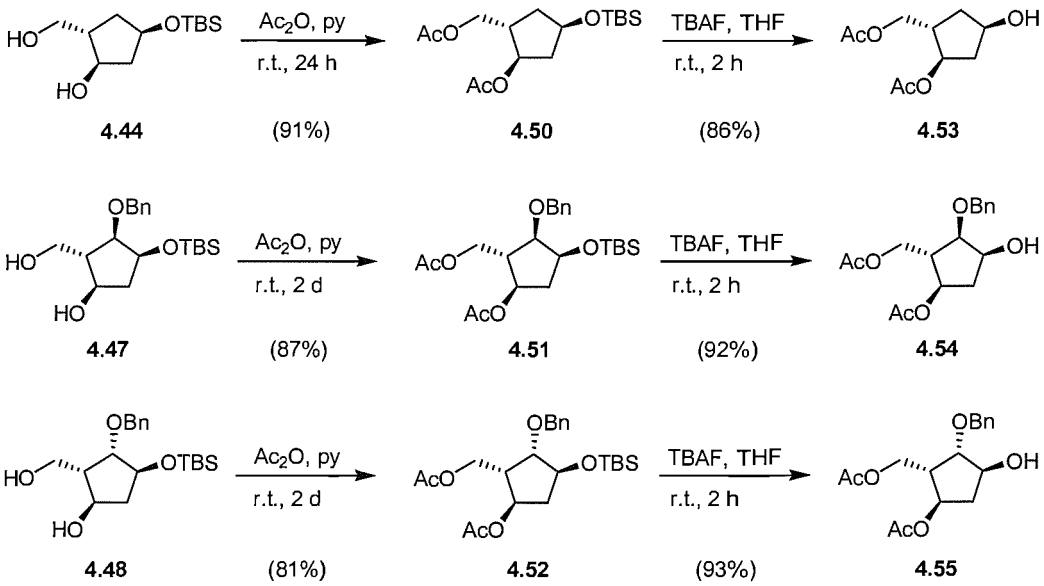


The relative configuration of diol **4.48** was confirmed by the crystal structure shown in Figure 4.3. Crystals of diol **4.47** could not be obtained and the C3 stereochemistry therefore remains unassigned. However, based on the confirmed structures of diols **4.44** and **4.48**, the relative C3 stereochemistry of **4.47** was anticipated to be similar to that observed in the analogous **4.44** and **4.48** (i.e. 3'-β).

4.2.1.2 Conversion to the Precursors for Nucleoside Synthesis

The diols obtained from the reduction processes were converted into the corresponding bis-acetates **4.50-4.52** in excellent yields by treatment with acetic anhydride in pyridine (Scheme 4.21). Subsequent removal of the silicon protecting group with tetrabutylammonium fluoride led to the carbafuranose targets **4.53-4.55** also in excellent yields.

Scheme 4.21

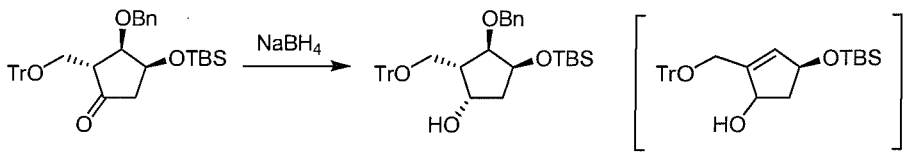


4.2.2 Synthesis of α-3'-Hydroxycarbafuranose Analogues

4.2.2.1 α-Selective Ketone Reduction

The stereochemical outcome of the ketone reduction process could be reversed by the functionalisation of the C5 hydroxyl group with a much more bulky reagent in order to inhibit the hydride attack from occurring at the bottom phase. This was initially attempted by the treatment of trityloxy-ketone **4.18** with sodium borohydride (Scheme 4.22), but low yields were obtained. A few by-products were also isolated from the experiments, one of which was identified as the α,β-unsaturated alcohol **4.57** (based on mass spectrometry and ^{1}H NMR spectroscopic analysis). As mentioned in the previous chapter, all cyclopentanone analogues generated from the hydrolysis of carbacyclisation products were base-labile. Naturally, the use of the relatively basic sodium borohydride would lead to significant β-elimination as observed above. Furthermore, the same elimination product was also observed in the sodium borohydride reduction of ketone **4.23** (see Table 4.10, Entry 1). This suggested the elimination to occur *via* an E1cB mechanism following enolate formation.

Scheme 4.22



4.18 **4.56** **4.57**

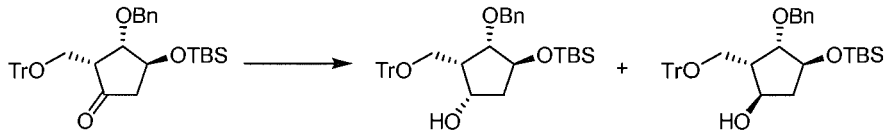
i) MeOH/THF (2:98) - 40%
ii) Propan-2-ol - 16%

(structure not confirmed)

To avoid elimination, reduction of the ketone under non-basic conditions were investigated (Table 4.10). When ketone **4.18** was treated with $Me_4NBH(OAc)_3$ and AcOH in THF (Entry 2), no reaction was observed due to the size of

triacetoxyborohydride molecule being too large to reach the sterically hindered ketone moiety. The same result was observed when $NaBH_4$ was added to ketone **4.23** and AcOH in THF (Entry 3), as triacetoxyborohydride was generated *in-situ* from the reaction between $NaBH_4$ and AcOH.

Table 4.10



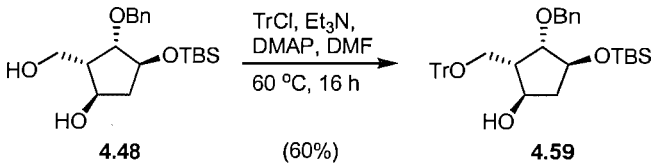
4.23 **4.58** **4.59**

Entry	Reagent	Solvent	Additives	Yield of 4.58	Yield of 4.59	Observations
1	$NaBH_4$	THF/MeOH (98:2)	none	37%	12%	Significant elimination
2	$Me_4NBH(OAc)_3$	THF	AcOH	\	\	No conversion
3	$NaBH_4$	THF	AcOH	\	\	No conversion
4	$NaCNBH_3$	THF	AcOH	46%	\	\
5	BH_3.THF	THF	\	43%	33%	No elimination
6	9-BBN	THF	\	\	\	No conversion
7	$BEt_2(OMe)$, then BH_3.THF	THF/MeOH	\	\	\	No conversion

Sodium cyanoborohydride on the other hand has been reported for the reduction of ketones in the presence of various inorganic and organic acids. However, a modest 46% yield was achieved using a large excess of $NaCNBH_3$ in THF at reflux after 1 day (Entry 4). Eventually, it was found that ketone reduction employing borane-tetrahydrofuran complex proceeded in good yields without the formation of any elimination products (Entry 5). The low selectivity between the formation of alcohols **4.58** and **4.59** was largely attributed to a possible coordination of BH_3 to the benzyloxy substituent. Although further experiments were performed in attempting to increase the diastereoselectivity of the process (Entries 6 and 7), no conversion was observed in

either cases. The relative C3 stereochemistry of alcohols **4.58** and **4.59** were confirmed by the selective tritylation of the previously obtained diol **4.48** (Figure 4.3) to give alcohol **4.59** (Scheme 4.23).

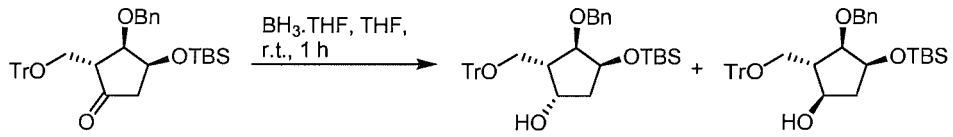
Scheme 4.23



4.48 (60%) **4.59**

Fortunately, reduction of ketone **4.18** employing BH_3.THF led to alcohols **4.56** and **4.60** in 56% and 29% (1.93:1) yield respectively (Scheme 4.24). The diastereoselectivity could be improved to 4:1 when the reduction was performed at 0 °C with slow addition of the BH_3.THF solution. The relative C3 stereochemistries of **4.56** and **4.60** were unconfirmed.

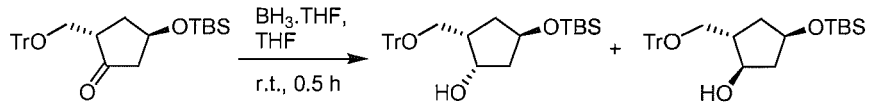
Scheme 4.24



4.18 **4.56** (56%) **4.60** (29%)

As a result, trityloxy ketone **4.22** previous synthesised was treated with BH_3.THF under conditions described to afford the corresponding alcohols **4.61** and **4.62** in 80% and 16% yields respectively (Scheme 4.25). The two diastereoisomers were easily separated by column chromatography. However, the relative C3 stereochemistries of **4.61** and **4.62** were unconfirmed.

Scheme 4.25

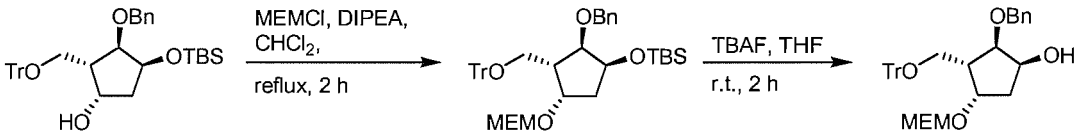


4.22 **4.61** (80%) **4.62** (16%)

4.2.2.2 Conversion to the Precursors for Nucleoside Synthesis

Alcohol **4.56** was converted into the corresponding MEM ether **4.63** by treatment with MEMCl and diisopropylethylamine in refluxing dichloromethane in excellent yield (Scheme 4.26). Subsequent TBS-removal afforded the carbafuranose target **4.64** in almost quantitative yield.

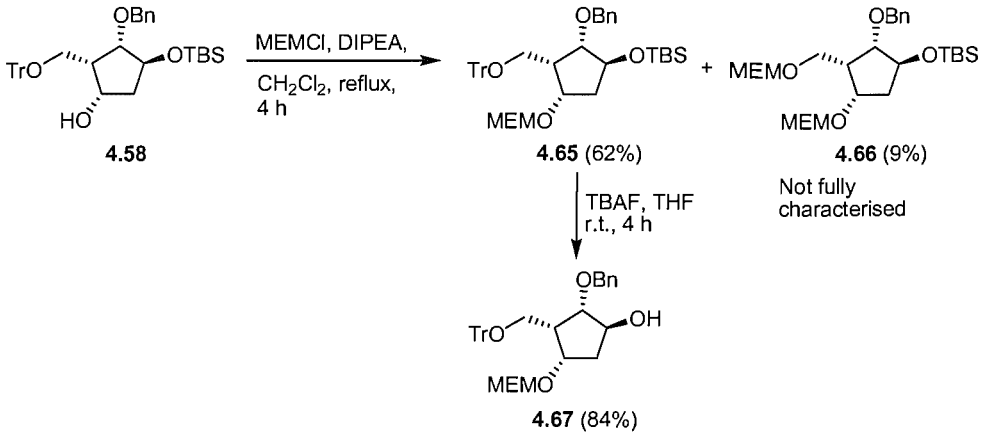
Scheme 4.26



4.56 (92%) **4.63** (99%) **4.64**

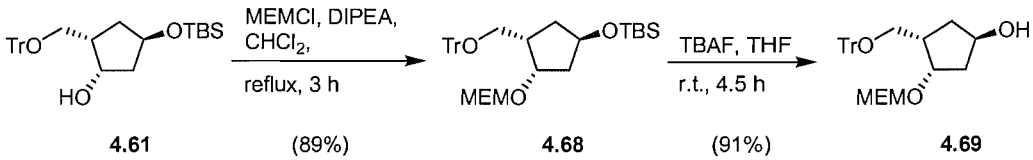
However, when alcohol **4.58** was subjected to alkylation under the same conditions, MEM ether **4.65** was only formed in 62% yield (Scheme 4.27). The isolation of a small but significant amount of the bis-MEM ether **4.66** indicated cleavage of the trityl group under the reaction conditions, leading to the reduced yield. MEM ether **4.65** was desilylated using TBAF to afford the desired carbafuranose target **4.67** in 84% yield.

Scheme 4.27



Finally, the 1'a-unsubstituted alcohol **4.61** was converted to MEM ether **4.68** in excellent yield using the same method (Scheme 4.28). Subsequent treatment with TBAF afforded carbafuranose target **4.69** in an excellent 91% yield.

Scheme 4.28

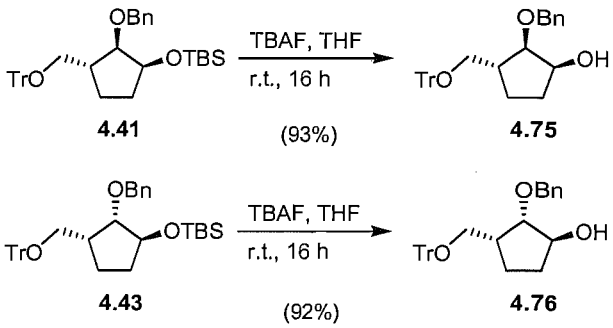


4.3 Synthesis of the Remaining Carbafuranose Targets

4.3.1 Synthesis of 2',3'-Dideoxcarbafuranose Analogues

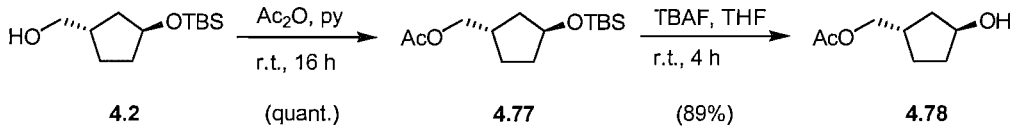
Cyclopentanes **4.41** and **4.43** previously synthesised from the Raney nickel reduction of thioketal (see Chapter 4.1.3) were treated with TBAF in THF to afford the carbafuranose target **4.75** and **4.76** in 93% and 92% yield respectively (Scheme 4.29).

Scheme 4.29



The final carbafuranose target **4.78** was obtained in 89% overall yield from alcohol **4.2** (also from Raney nickel reduction) by acetylation with acetic anhydride in pyridine and subsequent TBAF desilylation (Scheme 4.30).

Scheme 4.30

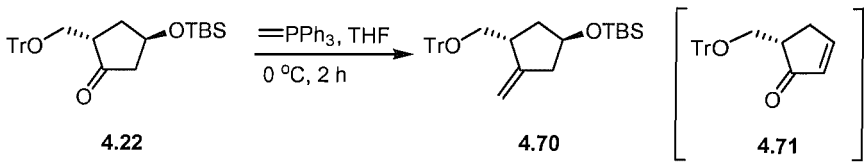


4.3.2 Synthesis of 3-Methylene Carbafuranose

We became interested in carbafuranose analogues containing an *exo*-methylene unit as these have been found in biologically active carbanucleosides such as Entecavir, and yet very few carbafuranose analogues of this type have been reported in the literature. To this end, the 3-methylene carbafuranose **4.70** was considered to be a potentially useful synthetic target. Initially, conversion of cyclopentanone **4.22** into alkene **4.70** was attempted by the conventional Wittig homologation process.[147-149] Treatment of ketone with methylenetriphenylphosphorane, generated *in situ* from methyltriphenyl-phosphonium bromide and butyllithium, failed to deliver alkene **4.70** (Scheme 4.31). The isolation of what was anticipated to be enone **4.71** in a significant

quantity suggested the decomposition of ketone **4.22** in a similar manner to that described in the previous Chapter.

Scheme 4.31

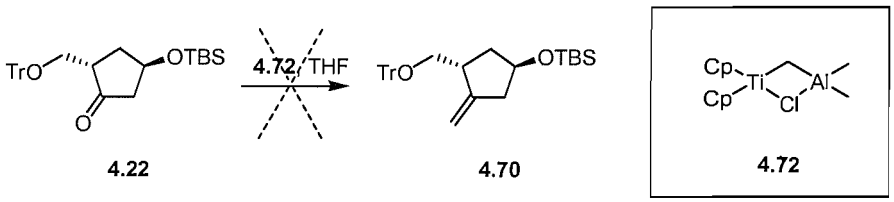


4.22 **4.70** **4.71**

Anticipated structure based on ^{1}H NMR and M.S. spectroscopic analysis

Next, methylenation of **4.22** using the Tebbe reagent[150-152] was investigated. The Tebbe reagent was originally synthesised from Cp_2TiCl_2 and $AlMe_3$ over a period of 3 days. The resultant aluminium-titanium complex **4.72** was, however, known to be air sensitive and could only be handled with air-sensitive techniques.[152] Therefore, complex **4.72** was prepared *in situ* immediately prior to use by procedures described by Grubbs.[152] Cp_2TiCl_2 was first treated with $AlMe_3$ (2.0 M solution in hexanes) for 72 hours, followed by the addition of ketone **4.22** in THF (Scheme 4.32) to the preformed complex. However, no reactivity was observed and ketone **4.22** was recovered.

Scheme 4.32

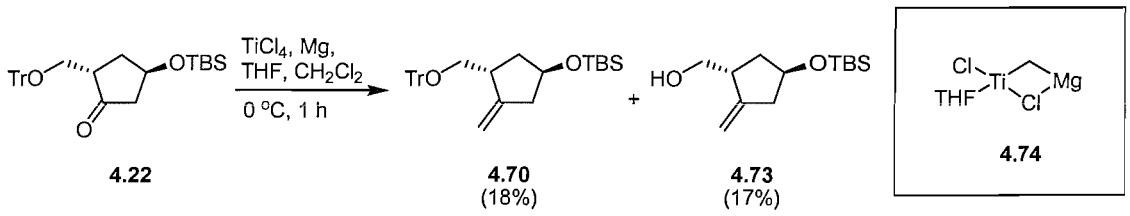


4.22 **4.70** **4.72**

The next attempt involved the use of a titanium-magnesium bimetallic organometallic reagent **4.74** which was similar in structure to the Tebbe complex. The experimental procedures involved here were much simpler and the reagents were much easier to handle.[153] It was found that addition of ketone **4.22** to a mixture consisting of

titanium tetrachloride, magnesium metal and dichloromethane afforded only 18% of the desired alkene **4.70**, together with 17% of the detritylated alkene **4.73** (Scheme 4.33). Performing the reaction at a lower temperature (from -45 °C to 0 °C over 3 hours) prevented cleavage of the trityl group and afforded alkene **4.70** in 34% yield, with no other products isolated. This was clearly unsatisfactory, but further investigation into this transformation was terminated due to time limitations.

Scheme 4.33



4.22 **4.70** (18%) **4.73** (17%) **4.74**

4.4 Conclusion

The carbacyclisation products were successfully converted to a range of 2'-deoxycarbafuranose analogues *via* cyclopentanone intermediates obtained from the hydrolysis of the thioketal group. Major difficulties were encountered with the thioketal hydrolysis process due to various competing side-reactions and only modest yields could be achieved. One of the side-reactions was identified to be an unexpected ring expansion process with little literature precedence. On the other hand, Raney nickel reduction of the thioketal functionality led to cyclopentane intermediates which could be transformed to a range of 2',3'-dideoxycarbafuranoses.

Chapter 5 - Carbanucleoside Synthesis

5.1 Synthesis of 1'a-Unsubstituted Carbanucleosides

The final part of the project involved the conversion of the synthesised carbafuranose analogues into the corresponding carbanucleoside targets. The nucleobase moiety of the carbanucleosides can be introduced by direct coupling of commercially available nucleobases with the carbafuranoses synthesised. Alternatively, the heterocyclic nucleobase can be constructed from the 1'-amino group derived from the corresponding carbafuranose. The former convergent coupling method involves fewer synthetic steps, though a mixture of the *N*- and *O*-carbanucleoside regioisomers are typically formed. On the other hand, the construction of the nucleobase is more laborious, but it ensures formation of the *N*-nucleoside only.

The direct coupling method was chosen initially for this project. With the absence of an endocylic oxygen, traditional glycosidation coupling methods are not suitable for the carbanucleoside coupling process. The most commonly used methods for carbanucleoside coupling include the Mitsunobu coupling, opening of cyclic sulfate, and nucleophilic displacement of mesylates/triflates. Of all the methods available, the Mitsunobu coupling involves very mild conditions and is often the method of choice for this process due to its tolerance of a large number of functional groups.[68-74]

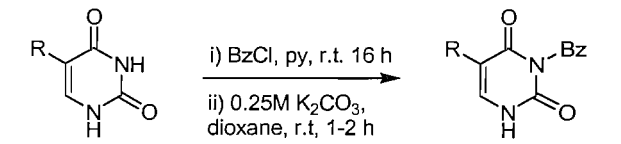
5.1.1 Carbanucleoside Formation – the Mitsunobu Reaction

Investigation of the carbanucleoside formation process began with the direct coupling of 1'a-unsubstituted carbafuranose **4.78** and suitable protected pyrimidine nucleobases **5.3** and **5.4**.

5.1.1.1 Synthesis of ^{3}N-Benzoylthymine and ^{3}N-Benzoyluracil

The pyrimidine bases were selectively protected on the ^{3}N-position by literature methods to ensure coupling occurred at the ^{1}N position only.[154,155] Thus, thymine and uracil were converted to the corresponding dibenzoylpyrimidines, which were subsequently hydrolysed to ^{3}N-benzoyluracil **5.3** and ^{3}N-benzoylthymine **5.4** respectively (Scheme 5.1).

Scheme 5.1



uracil **5.1**; R = H
thymine **5.2**; R = Me

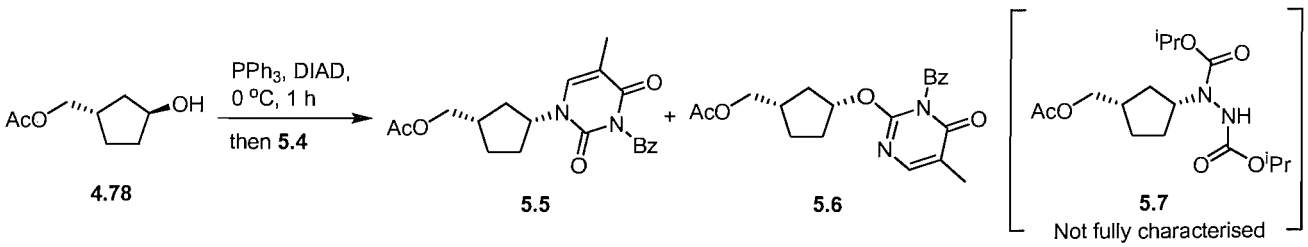
5.3; R = H (30%)
5.4; R = Me (63%)

5.1.1.2 Mitsunobu Coupling - Optimisation

Coupling of carbafuranose **4.78** and ^{3}N-benzoylthymine **5.4** under conventional Mitsunobu conditions were then investigated (Table 5.1). Typical experimental procedures involved the preformation of the DIAD-PPh_3 adduct at 0 °C for 1 hour, followed by the addition of alcohol **4.78** followed by ^{3}N-benzoylthymine. The investigation began with the use of 2.5 equivalents of PPh_3 and DIAD and 1.5

equivalents of ^{3}N-benzoylthymine **5.4** in DMF (Entry 1). This led to the formation of the *N*- and *O*-carbanucleosides **5.5** and **5.6** in 53% and 8% yield respectively. Replacing DMF with the less polar THF led to an increased overall yield, but an increased amount of the undesired *O*-carbanucleoside was also obtained (Entry 2). Similarly, switching the solvent to dichloromethane led to a further improved conversion, but the regioselectivity was reduced further (Entry 3). This was consistent with Meier's observations in a series of experiments that determined the influence of solvent polarity on the Mitsunobu coupling of ^{3}N-benzoylthymine **5.4** and cyclopentanol.[156-158] He concluded in his findings that the Mitsunobu coupling between carbasugars and pyridimine bases should be performed in DMF or MeCN to favour *N*-alkylation.

Table 5.1



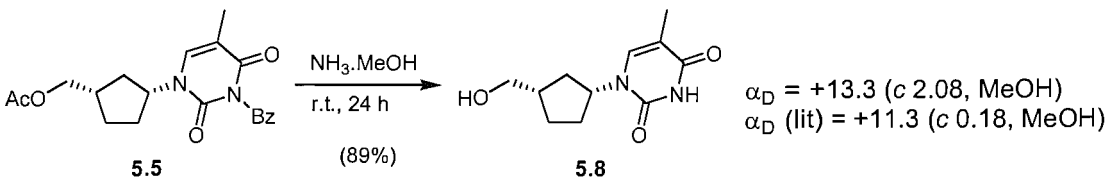
Entry	PPh_3 (equiv.)	DIAD (equiv.)	5.4 (equiv.)	Solvent (0.05 M)	Temp (°C)	Yield of **5.5** (%)	Yield of **5.6** (%)
1	2.5	2.5	1.5	DMF	r.t.	53	8
2	2.5	2.5	1.5	THF	r.t.	47	22
3	2.5	2.5	1.5	CH_2Cl_2	r.t.	49	35
4[a]	2.5	2.5	1.5	DMF	0	33	12
5	1.5	1.5	3.0	DMF	r.t.	64	25
6	1.5	1.5	3.0	DMF	0	48	20

a – 43% of compound **5.7** isolated

In an attempt to increase the regioselectivity of the coupling process in DMF, the reaction temperature after the addition of ^{3}N-benzoylthymine was reduced to 0 °C. However, the isolation of compound **5.7** as the major coupling product indicated an apparent competitive side-reaction involving alcohol **4.78** and a diamide side-product derived from the reduction of DIAD (Entry 4). Although side-product **5.7** was not isolated in the previous experiments, it was believed that this side-reaction was occurring, but to a much smaller extent. Fortunately, this side-reaction could be minimised by reducing the amount of DIAD in the reaction mixture to 1.5 equivalents and increasing the amount of benzoylthymine to 3.0 equivalents at the same time (Entry 5). This furnished the desired *N*-carbanucleoside **5.5** in 64% yield, together with approximately 25% of the *O*-carbanucleoside. Finally, reducing the temperature again did not lead to better regioselectivity, but instead hampered the overall coupling efficiency (Entry 6).

The protected *N*-carbanucleoside was treated with ammonia in methanol to afford the final target 2',3'-dideoxycarbathymidine **5.8** in good yield (Scheme 5.2). The optical rotation of carbanucleoside **5.8** corresponded to the literature value.[58] Previously, carbanucleoside **5.8** was synthesised by a linear approach.[58,159]

Scheme 5.2



5.5 **5.8**

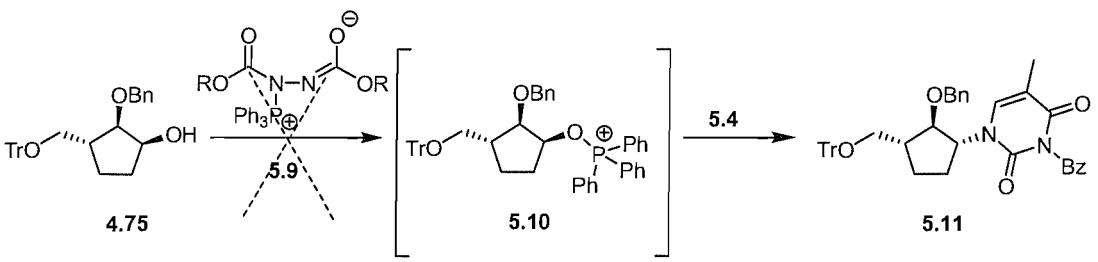
5.2 Synthesis of 1'a-Substituted Carbanucleosides

Having completed the synthesis of 1'a-unsubtituted carbanucleoside **5.8**, we next focused on the synthesis of carbanucleosides bearing a benzyloxy substituent on the 1'a-position. This type of carbanucleosides is very rarely reported in the synthetic literature and if successful, our methodology would allow potential access to several carbanucleoside analogues of this type. Once again, the direct Mitsunobu coupling process was preferred and alcohol **4.75** was initially employed as the carbafuranose substrate.

5.2.1 Carbanucleoside Formation – Mitsunobu Coupling

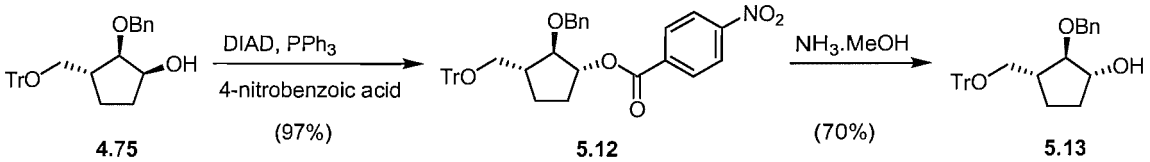
The investigation began with the treatment of β-benzyloxyalcohol **4.75** and ^{3}N-benzoyltymine **5.4** under Mitsunobu conditions previously described (Scheme 5.3). Unlike the previous case, no conversion was observed and alcohol **4.75** was recovered in quantitative yield. Similarly, Mitsunobu coupling of **4.75** with 6-chloropurine or unprotected thymine both failed to react and complete recovery of alcohol **4.75** was observed. It was apparent that the additional steric presence of the 1'a-substituent prevented the formation of the alkoxyphosphonium intermediate **5.10**.

Scheme 5.3



The main limitations of the Mitsunobu reaction are the need to use an acidic substrate and the process' inherent sensitivity to the steric environment of the alcohol.[160,161] As a result, various modifications have been made to the original Mitsunobu conditions to enable the use of more sterically hindered alcohol substrates.[160-163] For example, Tsunoda *et al.* had replaced the traditional PPh_3/DEAD system by PBu_3 and (azodicarbonyl)dipiperidine (ADDP).[160] The use of PBu_3 would increase the electrophilicity of the initial azocarboxylate/phosphine adduct, thus facilitating the formation of the alkoxyphosphonium intermediate (c.f. **5.10**). Replacement of DEAD with ADDP would increase the basicity of the initial azocarboxylate-phosphine adduct, thus facilitating the protonation of the azocarboxylate/phosphine adduct. In our hands however, treatment of alcohol **4.75** and ^3N-benzoylthymine **5.4** with the preformed adduct from ADDP and PBu_3 led again to the complete return of starting material.

Scheme 5.4

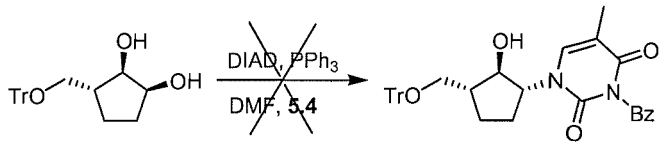


4.75 **5.12** **5.13**

Carboxylic acids with pK_a values lower than benzoic acid (pk_a ~4.2) such as 4-nitrobenzoic acid and chloroacetic acid have been reported to significantly improve the efficiency of the Mitsunobu esterification process compared with acids of higher pK_a values.[160,164] Indeed, when alcohol **4.75** and 4-nitrobenzoic acid were subjected to coupling under Mitsunobu conditions, the corresponding ester **5.12** was formed in an excellent 97% yield (Scheme 5.4). Subsequent basic hydrolysis of ester **5.12** afforded diastereomeric alcohol **5.13**, indicating an inversion of stereochemistry during the esterification process.

Furthermore, subjection of diol **5.14**, which contained a less sterically hindered alcohol, and ^{3}N-benzoylthymine **5.4** to Mitsunobu coupling conditions led once again to the complete recovery of starting material **5.14** (Scheme 5.5). It was certain at this point that the formation of carbanucleosides of this type would have to proceed by alternative methods.

Scheme 5.5

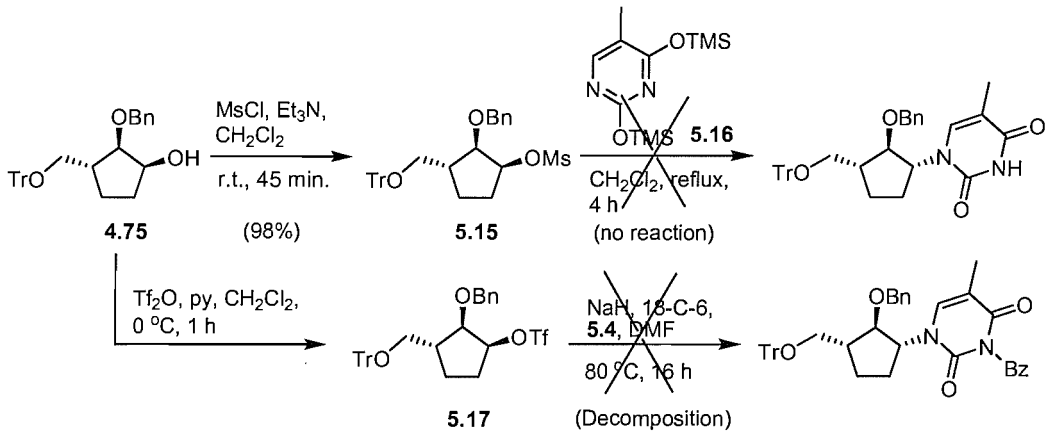


5.14 (recovery of starting material)

5.2.2 Displacement of Sulfonates

Another method commonly employed for the direct coupling of carbasugars with nucleobases is *via* the displacement of a sulfonate leaving group formed from the corresponding alcohol.[165,166]

Scheme 5.6



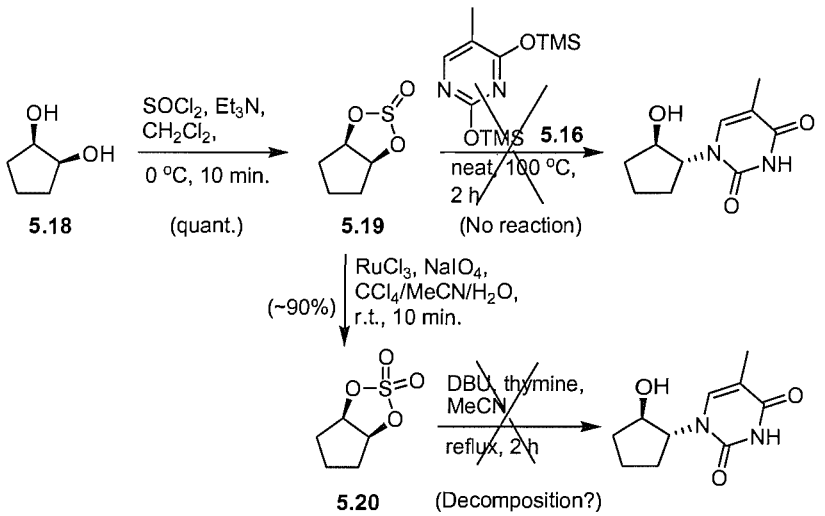
In our initial attempt, carbafuranose **4.75** was converted into the corresponding mesylate **5.15** in excellent yield (Scheme 5.6). However, subjection of mesylate **5.15** to the silylated thymine **5.16** led again to the complete return of starting material. Then,

conversion of alcohol **4.75** to triflate **5.17** followed by immediate treatment of the crude triflate with the sodium salt of ^{3}N-benzoylthymine in DMF led only to decomposition. Having failed in both cases, alternative methods were sought for this transformation.

5.2.3 Cyclic Sulfate Activation

The pyrimidine nucleobase could also be introduced *via* the ring opening of the cyclic sulfate or sulfite formed from the corresponding cis-1,2-diol and this method was initially attempted using commercially available cyclopentane-1,2-diol **5.18**.[77] Thus treatment of diol **5.18** with $SOCl_2$ and Et_3N in CH_2Cl_2 afforded cyclic sulfite **5.19** as a pair of inseparable diastereoisomers in quantitative yield (Scheme 5.7). At this point, the cyclic sulfite could either be oxidised further to the cyclic sulfate **5.20** or it could be immediately subjected to ring opening by a nucleophile. Although the cyclic sulfate was often found to be a more reactive electrophile, the sulfite sometimes produces a better yield because of the increased stability.[77] To this end, both sulfite **5.19** and sulfate **5.20** were subjected to ring opening by activated thymine nucleophiles.

Scheme 5.7



Treatment of sulfite **5.19** with neat silylated thymine **5.16** at 100 °C resulted once again in the recovery of starting material (Scheme 5.7). On the other hand, oxidation of sulfite **5.19** to the corresponding sulfate **5.20** proceeded in excellent yield. Subsequent treatment of cyclic sulfate **5.20** with DBU and thymine afforded very polar products which could not be isolated by column chromatography. As the initial studies using the model diol **5.18** failed to produce any meaningful results, alternative coupling methods were attempted.

5.2.4 The Mukaiyama Condensation

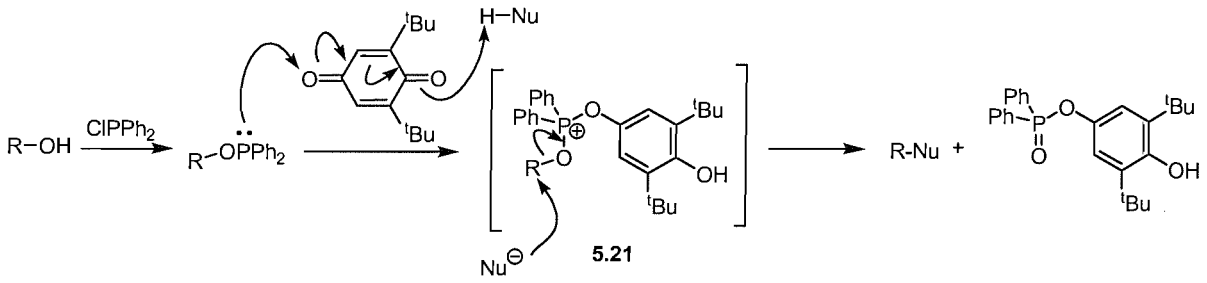
Mukaiyama recently reported a series of quinone-mediated oxidative-reductive condensation reactions that were mechanistically similar to the Mitsunobu coupling. This new type of condensation reaction was applied to the coupling of alcohols, *via* the corresponding alkoxyphosphines, with substrates containing acidic protons with complete inversion of stereochemistry. It was reported that even sterically hindered alcohols were tolerated and a wide range of substrates including phenols,[167] benzothiazoles,[168] carboxylic acids,[169] phthalimide[170] etc. have been demonstrated to successfully undergo this type of coupling.

5.2.4.1 Mechanistic Aspects

Mechanistically, the main difference between the Mukaiyama-type and the Mitsunobu reaction lies in the formation of the alkoxyphosphonium ion (**5.10** vs **5.21**). In the Mitsunobu reaction, the alkoxyphosphonium ion (i.e. **5.10**, Scheme 5.3) is formed from the attack of alcohol on the bulky DIAD/PPh_3 adduct. Naturally, the use of

sterically hindered alcohols in the process will be strongly disfavoured and consequently lead to the return of the starting material.

Scheme 5.8



On the other hand, alkoxyphosphonium formation in the Mukaiyama-type coupling occurs *via* the attack of a phosphinite, formed from the corresponding alcohol, on the electrophilic oxygen atom of an unsymmetrical quinone analogue (Scheme 5.8). As a result, the steric presence of the neighbouring substituents on the alcohol substrate will have far less influence on the alkoxyphosphonium formation process and thus enables the use of sterically hindered secondary alcohols and even tertiary alcohols.

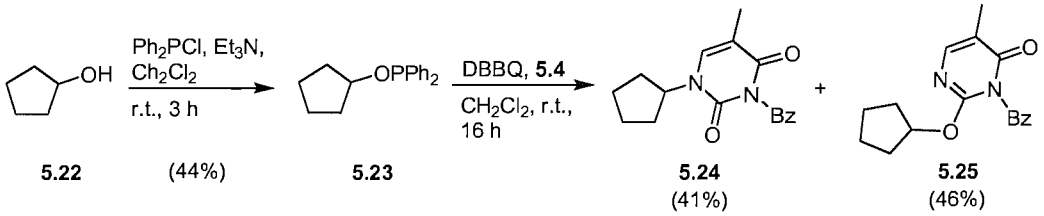
Another noteworthy point about the mechanism is that the use of 2,6-disubstituted benzoquinone derivatives such as 2,6-di-*tert*-butyl-1,4-benzoquinone (DBBQ) is essential in the process. The presence of the 2- and 6-substituents ensures protonation of the phenoxide from the initial addition to give phenol **5.21** instead of undergoing further nucleophilic substitution.

5.2.4.2 Model Studies

As the Mukaiyama method had never been applied to carbanucleoside coupling, the commercially available cyclopentanol **5.22** was chosen as the substrate for a preliminary model study. Cyclopentanol **5.22** was converted to the corresponding

diphenylphosphinite **5.23** by treatment with chlorodiphenylphospine and Et_3N (Scheme 5.9). We were pleased to find that subjection of phosphinite **5.23** and ^3N-benzoylthymine **5.4** under Mukaiyama coupling conditions using DBBQ afforded the corresponding *N*- and *O*-alkylated products **5.24** and **5.25** in excellent yields, although little selectivity was evident.

Scheme 5.9

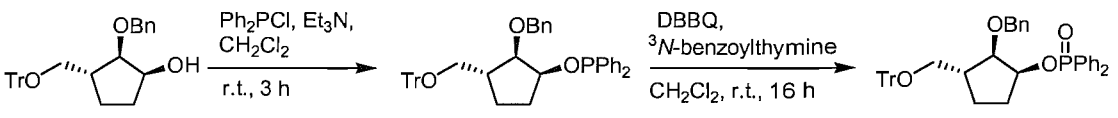


5.22 (44%) **5.23** **5.24** (41%) **5.25** (46%)

5.2.4.3 Carbanucleoside Coupling

Encouraged by the success observed in the model study, coupling of carbafuranose **4.75** with ^3N-benzoylthymine **5.4**, which had failed by every method so far, was attempted under the Mukaiyama coupling conditions. Initial conversion of alcohol **4.75** into phosphinite **5.26** under conditions previously described was accomplished in good yield (Scheme 5.10). However, when phosphinite **5.26** and ^3N-benzoylthymine **5.4** were treated with DBBQ, the expected carbanucleoside was not observed. Instead, phosphinate **5.27,** resulting from the oxidation of phosphinite **5.26,** was isolated as the major product in 87% yield.

Scheme 5.10



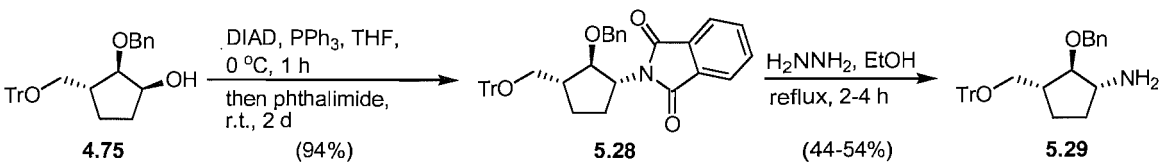
4.75 (76%) **5.26** (87%) **5.27**

5.2.5 The Linear Strategy

5.2.5.1 Synthesis of Cyclopentamine Precursor

As little success was achieved with the direct convergent coupling strategy, construction of carbanucleosides from amine **5.29** was attempted. Despite the failure in coupling alcohol **4.75** with ^{3}N-benzoylthymine by the Mitsunobu method, treatment of alcohol **4.75** and phthalimide under similar conditions surprisingly afforded the coupled product **5.28** in excellent yield (Scheme 5.11). An interesting observation on the aforementioned Mitsunobu process is as follows – when DIAD was added to a solution of PPh_3 in THF at 0 °C, precipitation was often observed indicating the formation of the zwitter-ionic DIAD/PPh_3 adduct. The reaction mixture remained heterogeneous after the addition of alcohol **4.75**, and only became homogeneous upon the addition of phthalimide solid. This suggested the need for the protonation of the DIAD/PPh_3 adduct by an acidic substrate (phthalimide) in order to mediate alkoxyphosphonium ion formation, at least in the case when the hindered alcohol **4.75** was employed.

Scheme 5.11

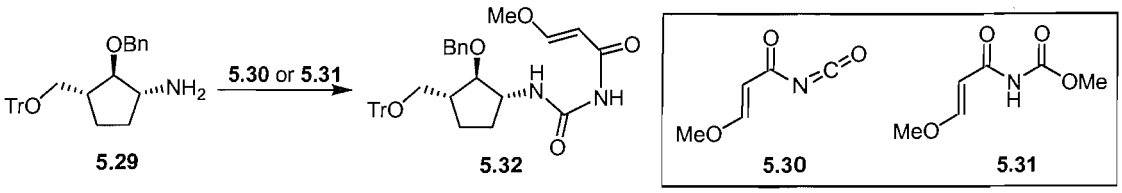


4.75 (94%) **5.28** (44-54%) **5.29**

Phthalimide derivative **5.28** was then treated with hydrazine monohydrate in ethanol at reflux to furnish cyclopentamine **5.29** in 44-54% yield, together with significant amounts of a structurally related side-product that was not identified. Increasing the the amount of hydrazine did not improve the yield of the reaction.

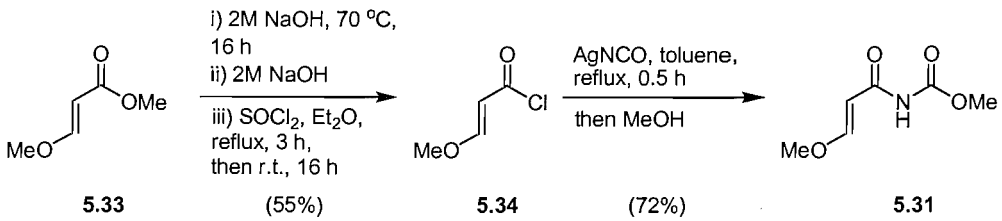
5.2.5.2 Synthesis of Uracil Precursors 5.30 and 5.31

Scheme 5.12



The pyrimidine moiety of the desired carbanucleoside could be constructed by the reaction of either isocyanate **5.30** or carbamate **5.31** with amine **5.29** followed by intramolecular cyclisation of the resulting nucleoside precursor **5.32** (Scheme 5.12).[58,159,171] Isocyanate **5.30** and carbamate **5.31** could be obtained *via* the common acid chloride **5.34**, which was synthesised in a 3-step sequence from the commercially available (*E*)-methyl 3-methoxyacrylate **5.33** (Scheme 5.13).[66,67]

Scheme 5.13

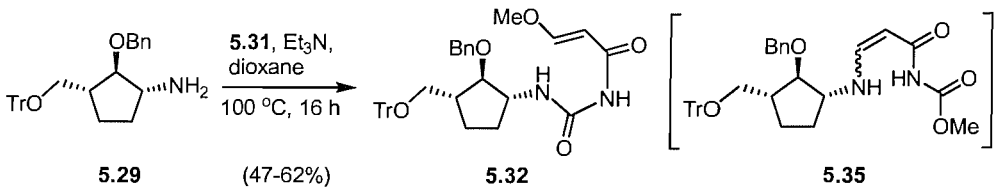


Treatment of acid chloride **5.34** with silver isocyanate in toluene at reflux afforded the air sensitive isocyanate **5.30** which was immediately treated with methanol to give carbamate **5.31** in 72% yield. Due to its unstable nature, isocyanate **5.30** would be generated *in-situ* immediately prior to use in the synthesis of precursor **5.32**. On the other hand, carbamate **5.31** is a stable solid that can be recrystallised from dichloromethane and petroleum ether.

5.2.5.3 Carbanucleoside Formation

Initially, synthesis of nucleoside precursor **5.32** from the coupling of amine **5.29** and *in-situ* generated isocyanate **5.30** under conventional conditions[159,172-175] led to cleavage of the trityl protecting group. On the other hand, treatment of amine **5.29** with carbamate **5.31** in dioxane[171] afforded varying yields of uracil precursor **5.32** (Scheme 5.14). Significant amounts of a few structurally similar compounds were also observed and two of them were anticipated to be the regioisomer **5.35** and the corresponding tautomers of **5.32** and **5.35**, based on NMR, MS and IR data.

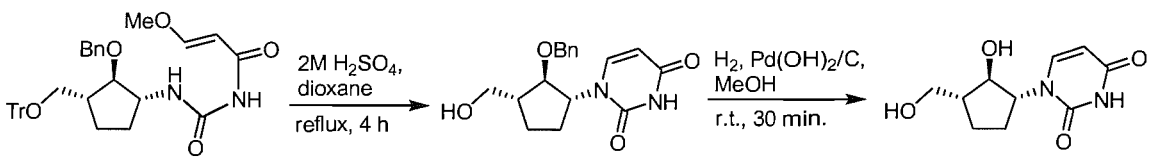
Scheme 5.14



5.29 (47-62%) **5.32** **5.35**

In the subsequent ring closure step, the base-catalysed cyclisation of precursor **5.32** led to the complete recovery of starting material. Fortuitously, treatment of **5.32** with dilute H_2SO_4 in dioxane mediated simultaneous cyclisation and trityl group removal to afford the desired carbanucleoside analogue **5.36** in good yield (Scheme 5.15). Finally, removal of the benzyl protecting group by catalytic hydrogenolysis furnished the carbanucleoside target **5.37** in excellent yield.

Scheme 5.15

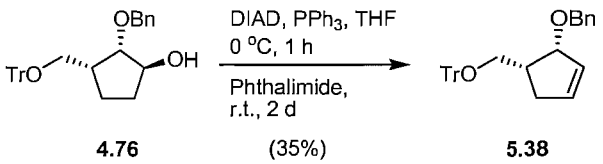


5.32 (69%) **5.36** (86%) **5.37**

Finally, it should be mentioned that the synthetic sequence starting from the phthalimide derivative **5.28** to the protected carbanucleoside **5.36** was only poorly understood. Further research would be necessary to fully establish the best conditions for these transformations.

The final part of the project concerned the synthesis of α-1'a-carbanucleoside analogues from carbafuranose **4.76**. To begin the investigation, coupling of **4.76** with ^{3}N-benzoylthymine **5.4** was again attempted under Mitsunobu conditions, but led only to the complete recovery of starting material as expected. Furthermore, Mitsunobu coupling of alcohol **4.76** with phthalimide under conditions which previously furnished excellent yields of amine precursor **5.28** led to the formation of the dehydration product **5.38** (Scheme 5.16).

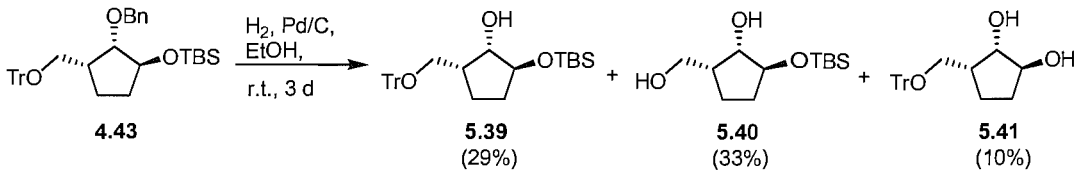
Scheme 5.16



4.76 (35%) **5.38**

The isolation of cyclopentene **5.38** suggested that although alkoxyphosphonium ion formation was successful, subsequent loss of a β-proton was much more favourable than the nucleophilic attack of phthalimide. As this was considered to be related to the steric hindrance on the bottom face of the molecule, removal of the two large protecting groups should facilitate the nucleophilic substitution process. To this end, benzyl ether **4.43** was subjected to hydrogenolysis using hydrogen gas and palladium on carbon in an attempt to removal both the trityl and the benzyl protecting group (Scheme 5.17).

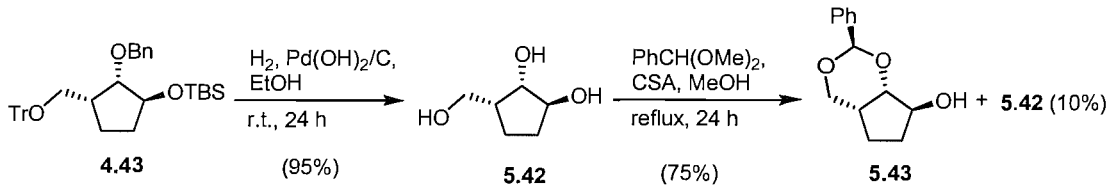
Scheme 5.17



4.43 **5.39** (29%) **5.40** (33%) **5.41** (10%)

It was somewhat surprising to find that not only a large amount of the trityl group remained uncleaved (**5.39**), but significant loss of the silicon protecting group was also observed (**5.41**). It was equally surprising to find that hydrogenolysis of benzyl ether **4.43** using hydrogen gas and palladium hydroxide on carbon led to complete silyl ether cleavage to afforded triol **5.42** in excellent yield (Scheme 5.18). The original aim in the synthetic sequence was to perform the subsequent acetal protection using diol **5.40**. However, a good selectivity for acetal formation from *cis*-1,3-diol over *trans*-1,2-diol was anticipated. Thus, triol **5.42** was directly treated with benzaldehyde dimethyl acetal and CSA in methanol and this afforded acetal **5.43** in good yield together with 10% of the starting triol **5.42**.

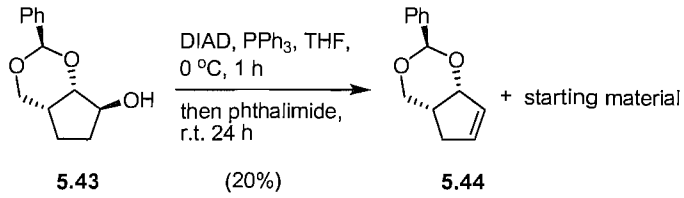
Scheme 5.18



4.43 (95%) **5.42** (75%) **5.43**

Nevertheless, subjection of alcohol **5.43** and phthalimide under Mitsunobu coupling conditions afforded alkene **5.44** instead of the desired carbanucleoside product (Scheme 5.19). This indicated that the replacement of the trityl and benzyl protecting groups by an acetal was insufficient to relieve the steric congestion present at the bottom face of the molecule. Unfortunately, we were unable to carry the synthesis further due to time restrictions.

Scheme 5.19



5.43 (20%) **5.44**

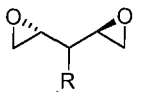
5.3 Conclusion

1'a-unsubstituted carbanucleoside **5.8** was successfully synthesised in high yield by the convergent coupling of cyclopentanol **4.78** with ^{3}N-benzoylthymine **5.4** under Mitsunobu conditions. In contrast, carbanucleoside formation by various convergent approaches failed to deliver the corresponding 1'a-substituted carbanucleosides targets. Synthesis of β-1'a-substituted carbanucleoside **5.37** was eventually achieved by the linear approach *via* the cyclopentamine intermediate **5.29**, although the corresponding α-carbanucleoside analogues could not be obtained.

Chapter 6 - Project Summary

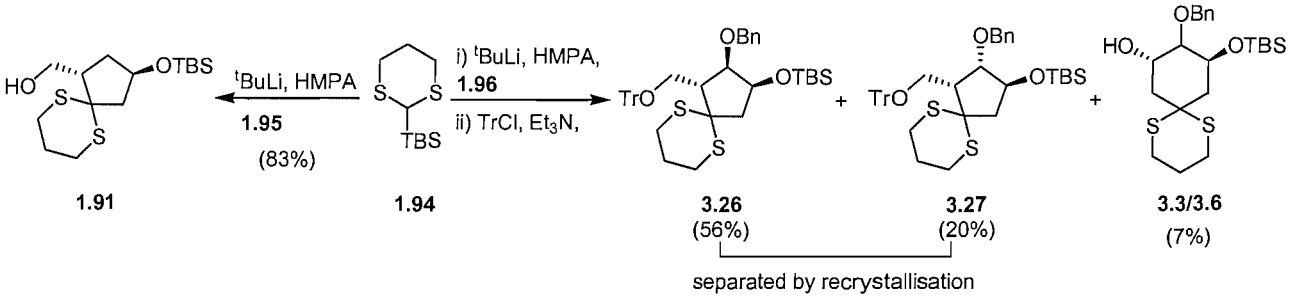
At the end of this project, the following goals were achieved:

1. The large scale synthesis of bis-epoxide **1.95** from arabitol by literature methods.
2. The development of an effective method for the large scale syntheses of bis-epoxides **1.96** and **2.12.**



R = H, **1.95**
R = OBn, **1.96**
R = OH, **2.12**

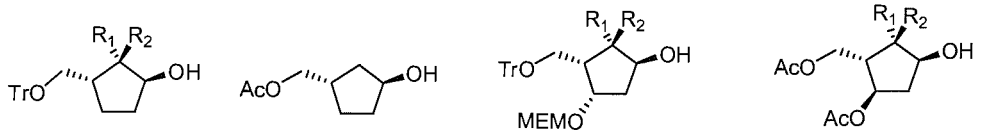
3. Thorough investigation of the carbacyclisation process, including optimisation of yield, determination of the origin of the observed diastereoselectivity, and development of a practical method for the separation of the two diastereomeric carbacyclisation products.



1.91 **1.94** **3.26** (56%) **3.27** (20%) **3.3/3.6** (7%)

separated by recrystallisation

4. Transformation of the carbacyclisation products into suitable carbafuranose analogues for the subsequent carbanucleoside formation process.



R_1 = H, R_2 = OBn, **4.75**
R_1 = OBn, R_2 = H, **4.76**

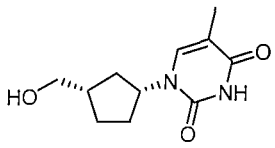
4.78

R_1 = H, R_2 = H, **4.69**
R_1 = H, R_2 = OBn, **4.64**
R_1 = OBn, R_2 = H, **4.67**

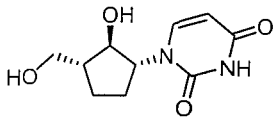
R_1 = H, R_2 = H, **4.53**
R_1 = H, R_2 = OBn, **4.54**
R_1 = OBn, R_2 = H, **4.55**

5. Establishment of a completed synthetic route to the 1'a-unsubstituted carbanucleoside target **5.8**.

6. Successful synthesis of the β-1'a-substituted carbanucleoside target **5.37**, although further research would be required to improve the efficiency of the synthetic route.



5.8



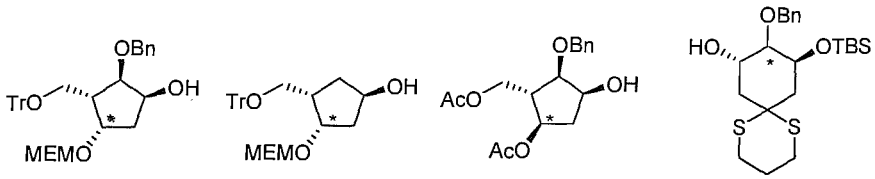
5.37

7. Finally, the unsuccessful synthesis of α-1'a-substituted carbanucleoside analogues from carbafuranose **4.76.**

Chapter 7 – Future Work

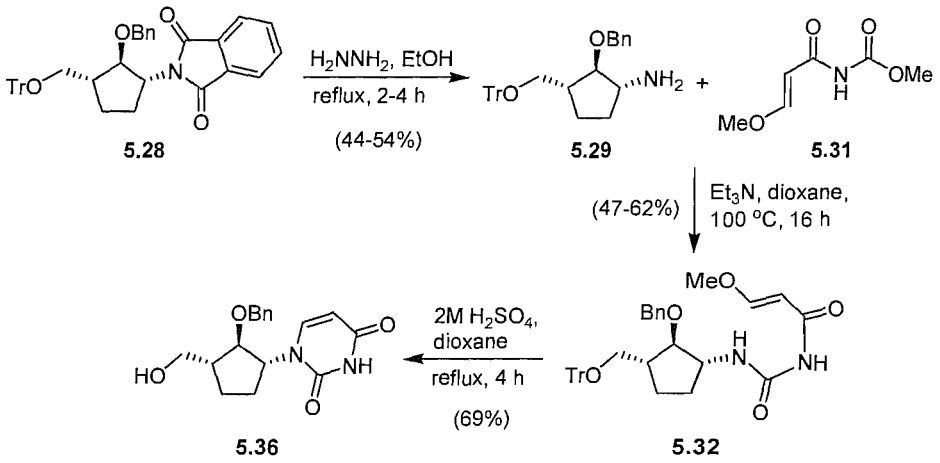
Short term - to fully complete the project, the followings will be required:

1.) The determination of the relative C3 stereochemistry of carbafuranoses **4.54**, **4.64** and **4.69**.



2.) The determination of the relative stereochemistry at the carbon centre bearing the benzyloxy substituent of the 6-*exo* cyclisation product **3.3/3.6**.

3.) Obtain better yields for the transformation sequence below:



Long term – for further development of the project, the following improvements are recommended:

1.) Submission of carbfuranoses **5.8** and **5.37** for biological testings.

2.) As the removal of the thioketal functionality proved to be the major drawback of the project, the replacement of the dithiane group with another acyl anion equivalent could largely improve the efficiency of the methodology.

3.) The establishment of a synthetic route to optically active α-1'a-carbanucleosides, which could not be obtained by the current methodology.

Chapter 8 - Experimental

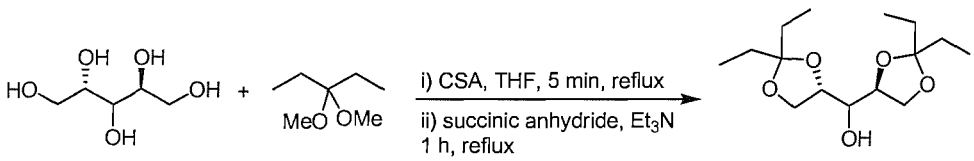
General Methods

All melting points were uncorrected and were recorded on a Gallekamp electrothermal melting point apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded on Brüker AV 300 and Brüker DPX 400 spectrometers. IR spectra were recorded as neat solids or liquids on a Thermo Nicolet 380 spectrometer. Optical rotations were recorded on an Optical Activity Polaar 2001 polarimeter. Low resolution ES and EI/CI mass spectra were recorded on Waters ZMD and ThermoQuest TraceMS spectrometers respectively. High resolution mass spectra were recorded on the Brüker Apex III FT-ICR-MS.

Column chromatography was performed on Fischer's Davisil grade silica gel (60 Å, 35-70 μm). Preparative HPLC was carried out using Biorad Bio-Sil D 90-10 columns (250 × 22 mm at 20 mL min^{-1} and 250 × 10 mm at 5 mL min^{-1}). TLC analyses were performed on Merck silica gel 60 F_{254} aluminium plates and were developed with $KMnO_4$, anisaldehyde and ninhydrin dyes.

Anhydrous solvents were distilled immediately prior to use, with the exception of anhydrous DMF which was purchased in seal containers containing molecular sieves from commercial sources. Pyridine was distilled from CaH_2 and stored in a Schlenk flask. Triethylamine was distilled from CaH_2 immediately prior to use. Arabitol was obtained from CMS Chemicals, and used without further purification. HMPA was distilled from CaH_2 and stored under molecular sieves. ^{t}BuLi was purchased from Acros Chemicals and the actual concentration (nearest 0.1 M) was determined by titration against 1 mole equivalent of diphenylacetic acid. All other reagents were purchased from commercial sources and used without further purification unless specifically stated.

8.1 (2*S*,4*S*)-1,2:4,5-Di-*O*-(3,3-pentylidene)arabitol (2.3)



1.97 **2.1** (72%) **2.3**

A mixture of L-arabitol **1.97** (20.0 g, 0.131 mol) and dimethoxypentane **2.1** (92.0 mL, 0.581 mol) in THF (200 mL) was stirred at reflux for 15 minutes. CSA (9.33 g, 0.040 mol) was added and the mixture was stirred at reflux for 5 minutes, followed by the addition of NaOH solution (2 M; 40 mL). Et_2O (300 mL) and H_2O (300 mL) were added and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 150 ml). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*.

The crude mixture was dissolved in CH_2Cl_2 (400 mL). Triethylamine (20.0 mL, 0.145 mol) and succinic anhydride (3.45 g, 0.0345 mol) were added and the mixture was stirred at reflux for 1 hour before quenching with $NaHCO_3$ (5%; 200 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 200 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by column chromatography (EtOAc/petroleum ether 2:8) to yield **2.3** as a clear oil (27.3 g, 72%).

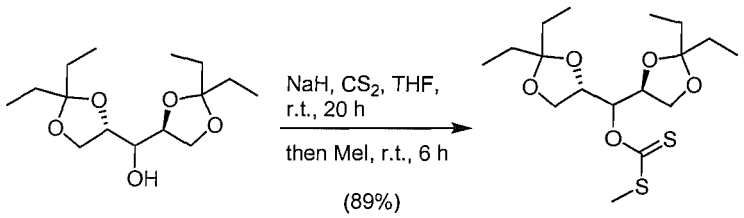
M.W. 288.4 (288.1937)

^{1}H NMR (300 MHz, $CDCl_3$) 4.05-4.23 (3H, m, $CH_2C\underline{H}$ + $C\underline{H}_aH_bCH$ + $C\underline{H}_cH_dCH$), 3.82-4.01 (3H, m, $CH_2C\underline{H}$ + $CH_a\underline{H}_bCH$ + $CH_c\underline{H}_dCH$), 3.45 (1H, m, $C\underline{H}OH$), 2.40 (1H, d, J = 5.5 Hz, OH), 1.55-1.70 (8H, m, $CH_3C\underline{H}_2$ × 4), 0.84-0.94 (12H, m, $C\underline{H}_3CH_2$ × 4)

^{13}C NMR (75 MHz, $CDCl_3$) 113.3 (OCO), 112.9 (OCO), 76.9 ($CH_2\underline{C}H$), 76.5 ($CH_2\underline{C}H$), 73.1 (CHOH), 68.0 ($\underline{C}H_2CH$), 66.7 ($\underline{C}H_2CH$), 29.7 × 2 ($CH_3\underline{C}H_2$ × 2), 29.1 × 2 ($CH_3\underline{C}H_2$ × 2), 8.4 × 2 ($\underline{C}H_3CH_2$ × 2), 8.2 × 2 ($\underline{C}H_3CH_2$ × 2)

^{1}H NMR and **^{13}C NMR** corresponded to the previously reported values.[92]

8.2 (2*S*,4*S*)-1,2:4,5-Di-*O*-(3,3-pentylidene)-3-(methylthiothiocarbonyl oxy)arabitol (2.5)



2.3 **2.5**

NaH (5.61 g, 0.140 mol) was added to a solution of **2.3** (31.1g, 0.108 mol) in THF (415 ml) at 0°C. The solution was stirred at 0 °C for 1 hour and this was followed by the addition of CS_2 (78 mL, 1.29 mol). The solution was stirred at room temperature for 20 hours. MeI (8.7 mL, 0.140 mmol) was added and the mixture was stirred at room temperature for 6 hours. Sat. NH_4Cl (100 mL) was added followed by H_2O (300 mL) and Et_2O (500 mL). The aqueous layer was extracted with Et_2O (2 × 400 mL). The organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by column chromatography (EtOAc/petroleum ether 5:95) to yield a yellow oil **2.5** (36.2 g, 89%).

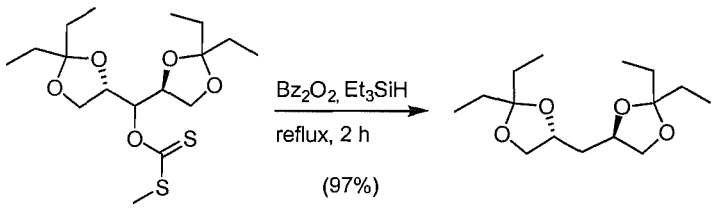
M.W. 378.55 (378.1535)

^{1}H NMR (300 MHz, $CDCl_3$) 6.13 (1H, dd, J = 5.5, 2.5 Hz, C$\underline{H}$OCS), 4.36-4.45 (2H, m, $CH_2C\underline{H}$ × 2), 4.10 (1H, dd, J = 8.5, 6.5 Hz, C$\underline{H_a}H_b$CH), 4.02 (1H, dd, J = 8.5, 6.5 Hz, C$\underline{H_c}H_d$CH), 3.98 (1H, dd, J = 8.5, 6.5 Hz, $CH_a\underline{H_b}$CH), 3.69 (1H, dd, J = 8.5, 7.5 Hz, $CH_c\underline{H_d}$CH), 2.59 (3H, s, SCH_3), 1.57-1.66 (8H, m, $CH_3C\underline{H_2}$ × 4), 0.85-0.94 (12H, m, $C\underline{H_3}CH_2$ × 4)

^{13}C NMR (75 MHz, $CDCl_3$) 113.4 × 2 (OCO × 2), 79.5 (C$\underline{H}$OCS), 75.7 ($CH_2\underline{C}H$), 75.5 ($CH_2\underline{C}H$), 66.5 ($\underline{C}H_2CH$), 65.8 ($\underline{C}H_2CH$), 29.7 ($CH_3\underline{C}H_2$), 29.5 ($CH_3\underline{C}H_2$), 29.2 ($CH_3\underline{C}H_2$), 29.1 ($CH_3\underline{C}H_2$), 19.4 × 2 ($\underline{C}H_3CH_2$ × 2), 8.3 × 2 ($\underline{C}H_3CH_2$ × 2)

^{1}H NMR and **^{13}C NMR** corresponded to the previously reported values.[93]

8.3 (2*R*,4*R*)-1,2:4,5-Di-*O*-(3,3-pentylidene)-3-deoxyarabitol (2.6)



2.5 **2.6**

Benzoyl peroxide (4.40 g, 18.2 mmol) was added to a solution of xanthate **2.5** (34.5 g, 91.1 mmol) in triethylsilane (455 mL) at reflux. The solution was stirred at reflux for 2 hours with similar quantities of benzoyl peroxide (4.40 g, 18.2 mmol × 3) added after 30, 60 and 90 minutes. The mixture was cooled, concentrated *in vacuo* and purified by column chromatography (EtOAc/petroleum ether 5:95) to yield **2.6** as a clear oil (24.0 g, 97%).

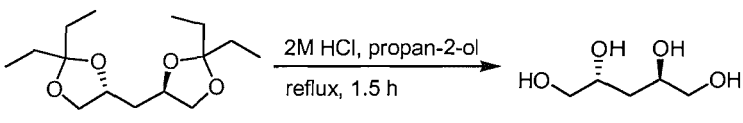
M.W. 272.38 (272.1988)

^{1}H NMR (300 MHz, $CDCl_3$) 4.07-4.20 (4H, m, $CH_2C\underline{H}$ × 2 + $C\underline{H}_aH_bCH$ × 2), 3.49 (2H, t, J = 7.5 Hz, $CH_a\underline{H}_bCH$ × 2), 1.79 (2H, t, J = 6.0 Hz, $CHC\underline{H}_2CH$), 1.55-1.64 (8H, m, $C\underline{H}_3CH_2$ × 4), 0.87 (6H, t, J = 7.5 Hz, $C\underline{H}_3CH_2$ × 2), 0.86 (6H, t, J = 7.5 Hz, $C\underline{H}_3CH_2$ × 2)

^{13}C NMR (75 MHz, $CDCl_3$) 112.7 × 2 (O$\underline{C}$O × 2), 74.1 × 2 ($CH_2\underline{C}H$ × 2), 70.6 × 2 ($\underline{C}H_2CH$ × 2), 37.8 ($CH\underline{C}H_2CH$), 30.0 × 2 ($CH_3\underline{C}H_2$ × 2), 29.8 × 2 ($CH_3\underline{C}H_2$ × 2), 8.4 × 2 ($\underline{C}H_3CH_2$ × 2), 8.1 × 2 ($\underline{C}H_3CH_2$ × 2)

^{1}H NMR and **^{13}C NMR** corresponded to the previously reported values.[93]

8.4 (2*R*,4*R*)-Pentane-1,2,4,5-tetraol (2.7)



2.6 (99%) **2.7**

HCl (2.0 M; 50 μL, 0.10 mmol) was added to a solution of bis-acetal **2.6** (89.0 mg, 0.327 mmol) in propan-2-ol (3.27 ml). The mixture was stirred at reflux for 1.5 hours followed by the addition of anhydrous Na_2CO_3 until neutral. Concentration *in vacuo* and purification by column chromatography ($MeOH/CH_2Cl_2$ 25:75) afforded a white soild (40 mg, 99%) which could be recrystallised from EtOH/petroleum ether.

M.W. 136.15 (136.0736)

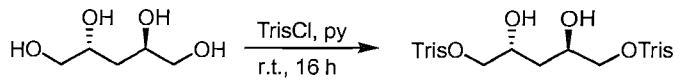
mp 104-105 °C (EtOH/petroleum ether); lit. 106-107 °C

^{1}H NMR (300 MHz, D_2O) 3.89 (2H, tdd, J = 7.0, 5.5, 4.0 Hz, $CH_2C\underline{H}$ × 2), 3.59 (2H, dd, J = 11.5, 4.0 Hz, $C\underline{H}_aH_bCH$ × 2), 3.48 (2H, dd, J = 11.5, 7.0 Hz, $CH_a\underline{H}_bCH$ × 2), 1.52 (2H, dd, J = 7.5, 5.5 Hz, $CHC\underline{H}_2CH$)

^{13}C NMR (75 MHz, D_2O) 69.0 × 2 ($CH_2\underline{C}H$ × 2), 66.6 × 2 ($\underline{C}H_2CH$ × 2), 36.4 ($CH\underline{C}H_2CH$)

^{1}H NMR and **^{13}C NMR** corresponded to the literature values.[168]

8.5 (2*R*,4*R*)-2,4-Dihydroxypentane-1,5-diyl bis-(2,4,6-triisopropyl-benzenesulfonate) (2.8)



2.7 (75%) **2.8**

Triisopropylbenzenesulfonyl chloride (222 mg, 0.732 mmol) was added to a solution of tetraol **2.7** (48.6 mg, 0.357 mmol) in pyridine (0.45 mL). The reaction mixture was stirred at room temperature for 16 hours. The solvent was removed *in vacuo* and the crude was purified by column chromatography (acetone/petroleum ether 25:75) to afford **2.8** as a white solid (179 mg, 75%) which could be recrystallised from acetone /petroleum ether to give small white needles.

M.W. 668.94 (668.3417)

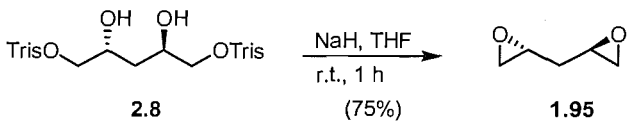
mp 146-148 °C (acetone/petroleum ether); lit. 154-155 °C (CH_2Cl_2/hexane)

^{1}H NMR (300 MHz, $CDCl_3$) 7.19 (2H, s, ArH), 7.18 (2H, s, ArH), 3.94-4.25 (6H, m, $C\underline{H}_2CH \times 2 + CH_2C\underline{H} \times 2$), 2.84 (2H, septet, J = 7.0 Hz, $C\underline{H}(CH_3)_2 \times 2$), 2.09 (2H, br, OH), 1.63 (2H, dd, J = 7.0, 5.5 Hz, $CHC\underline{H}_2CH$), 1.26 (12H, d, J = 7.0 Hz, $CH(C\underline{H}_3)_2 \times 2$), 1.25 (24H, d, J = 7.0 Hz, $CH(C\underline{H}_3)_2 \times 4$)

^{13}C NMR (75 MHz, $CDCl_3$) 154.2 × 2 ($C_{Ar} \times 2$), 151.0 × 4 ($C_{Ar} \times 4$), 128.9 × 2 ($C_{Ar} \times 2$), 124.0 × 4 ($CH_{Ar} \times 4$), 72.7 × 2 ($\underline{C}H_2CH \times 2$), 66.7 × 2 ($CH_2\underline{C}H \times 2$), 35.0 ($CH\underline{C}H_2CH$), 34.4 × 2 ($\underline{C}H(CH_3)_2 \times 2$), 29.8 × 4 ($\underline{C}H(CH_3)_2 \times 4$), 24.9 × 4 ($CH(\underline{C}H_3)_2 \times 4$), 23.7 × 4 ($CH(\underline{C}H_3)_2$)

^{1}H NMR and **^{13}C NMR** corresponded to the literature values.[168]

8.6 (2*R*,4*R*)-1,2,4,5-Diepoxypentane (1.95)



2.8 (75%) **1.95**

A solution of **2.8** (11.5 g, 0.0172 mol) in THF (150 mL) was added to a suspension of NaH (60% dispersion in mineral oil, 7.50 g, 0.188 mol) in THF (250 mL) rinsed with pentane. The mixture was stirred for 1 hour at room temperature, filtered through $MgSO_4$, washed with pentane and concentrated by fractional distillation. The crude bis-epoxide was purified by column chromatography (Et_2O/pentane 4:1), concentrated by fractional distillation and was further purified by Kügelrohr distillation (16 mmHg, 105 °C) to yield **1.95** as a colourless liquid (1.29 g, 75%).

M.W. 100.12 (100.0524)

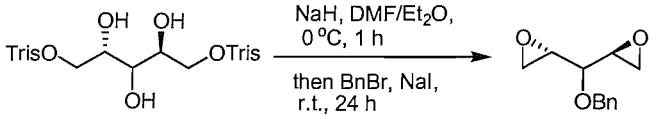
bp 105 °C/ 16 mmHg

^{1}H NMR (300 MHz, $CDCl_3$) 3.01-3.07 (2H, m, $CH_2C\underline{H} \times 2$), 2.76 (2H, dd, J = 5.0, 4.0 Hz, $C\underline{H}_aH_bCH \times 2$), 2.48 (2H, dd, J = 5.0, 2.5 Hz, $CH_a\underline{H}_bCH \times 2$), 1.70 (2H, t, J = 5.5 Hz, $CHC\underline{H}_2CH$)

^{13}C NMR (75 MHz, $CDCl_3$) 49.3 × 2 ($CH_2\underline{C}H$ × 2), 46.8 × 2 ($\underline{C}H_2CH$ × 2), 36.0 ($CH\underline{C}H_2CH$)

^{1}H NMR and **^{13}C NMR** all corresponded to the literature values.[169]

8.7 (2S,4*S*)-1,2:4,5-Dianhydro-3-(benzyloxy)-arabitol (1.96)



2.11 (85%) **1.96**

NaH (60% dispersion in mineral oil; 0.120 g, 3.00 mmol) was added to a solution of **2.11** (0.503 g, 0.734 mmol) in DMF/Et_2O (1:1, 24.4 mL) at 0 °C. The mixture was stirred at 0 °C for 1 hour. BnBr (0.14 mL, 1.18 mmol) was added and the reaction mixture was warmed to room temperature. NaI (0.164 g, 1.10 mmol) was added and the reaction was stirred for 24 hours. Sat. NH_4Cl (10 mL) was added followed by H_2O (10 mL) and Et_2O (10 mL). The aqueous layer was extracted with Et_2O (2 × 10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (EtOAc/petroleum ether 2:8) gave **1.96** (0.128 g, 85%) as a colourless liquid.

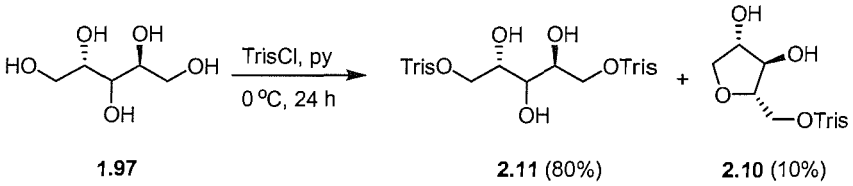
M.W. 206.24 (206.0943)

^{1}H NMR (300 MHz, $CDCl_3$) 7.16-7.28 (5H, m, ArH), 4.97 (1H, d, J = 12.0 Hz, $C\underline{H}_aH_bPh$), 4.56 (1H, d, J = 12.0 Hz, $CH_a\underline{H}_bPh$), 3.09 (1H, ddd, J = 5.5, 4.0, 2.5 Hz, $CH_2C\underline{H}$), 2.99 (1H, ddd, J = 5.5, 4.0, 2.5 Hz, $CH_2C\underline{H}$), 2.91 (1H, dd, J = 6.0, 5.5 Hz, $C\underline{H}OBn$), 2.74 (1H, dd, J = 5.0, 4.0 Hz, $C\underline{H}_aH_bCH$), 2.72 (1H, dd, J = 5.0, 4.0 Hz, $C\underline{H}_cH_dCH$), 2.59 (1H, J = 4.5, 2.5 Hz, $CH_a\underline{H}_bCH$), 2.57 (1H, dd, J = 4.5, 2.5 Hz, $CH_c\underline{H}_dCH$)

^{13}C NMR (75 MHz, $CDCl_3$) 138.0 (C_{Ar}), 128.5 (CH_{Ar}), 127.9 (CH_{Ar}), 79.8 (CHOBn), 72.3 (CH_2Ph), 52.8 ($CH_2\underline{C}H$), 51.1 ($CH_2\underline{C}H$), 45.5 ($\underline{C}H_2CH$), 43.3 ($\underline{C}H_2CH$)

^{1}H NMR and **^{13}C NMR** corresponded to the previously reported values.[107]

8.8 (2*S*,4*S*)-2,3,4-Trihydroxypentane-1,5-diyl bis(2,4,6-triisopropyl-benzenesulfonate (2.11)



1.97 **2.11** (80%) **2.10** (10%)

Triisopropylbenzenesulfonyl chloride (4.47 g, 14.8 mmol) was added to a solution of L-arabitol **1.97** (1.06 g, 6.70 mmol) in pyridine (15 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 24 h. 2 M HCl (92 mL) and Et_2O (80 mL) were added. The aqueous layer was extracted with Et_2O (2 × 60 mL). The organic layer was washed with 2 M HCl (30 mL), 3% $NaHCO_3$ (30 mL) and brine (30 mL). The solution was dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography (acetone/petroleum Ether 3:7) to yield **2.11** (3.84 g, 80%) and **2.10** (256 mg, 10%) as white solids.

Data for 2.11

M.W. 684.95 (684.3366)

mp 127-128 °C

$[\alpha]_D$ = -1.36 (*c* = 1.1, $CHCl_3$, 23 °C)

IR ν_{max}/cm^{-1} 3517 br, 2959 m, 1600 m, 1341 m, 1173 s

^{1}H NMR (400 MHz, $CDCl_3$) 7.19 (4H, s, ArH), 4.33 (1H, dd, *J* = 11.0, 3.0 Hz, $C\underline{H}_aH_bCH$), 4.27-4.06 (8H, m, $C\underline{H}_2CH$ + $CH_a\underline{H}_bCH$ + $CH_2C\underline{H}$ + $C\underline{H}(CH_3)_2$ × 4), 3.98 (1H, ddd, *J* = 8.5, 6.0, 3.0 Hz, $CH_2C\underline{H}$), 3.60 (1H, dd, *J* = 8.0, 1.0 Hz, $CHC\underline{H}CH$), 2.91 (2H, sept, *J* = 7.0 Hz, $C\underline{H}(CH_3)_2$ × 2), 2.67 (3H, s, OH × 3), 1.26 (24H, d, *J* = 7.0 Hz, $CH(C\underline{H}_3)_2$ × 4), 1.25 (12H, d, *J* = 7.0 Hz, $CH(C\underline{H}_3)_2$ × 2)

^{13}C NMR (100 MHz, $CDCl_3$) 154.3 (C_{Ar}), 151.1 × 2 (C_{Ar} × 2), 129.0 (C_{Ar}), 124.1 × 2 (CH_{Ar} × 2), 70.9 ($\underline{C}H_2CH$), 70.5 ($\underline{C}H_2CH$), 70.2 ($CH_2\underline{C}H$), 70.0 ($CH_2\underline{C}H$), 68.3 ($CH\underline{C}HCH$), 34.4 × 2 ($\underline{C}H(CH_3)_2$ × 2), 29.8 × 4 ($\underline{C}H(CH_3)_2$ × 4), 24.8 × 8 ($CH(\underline{C}H_3)_2$ × 4), 23.6 × 4 ($CH(\underline{C}H_3)_2$ × 2)

ES$^+$ ***m/z*** (%) 707 ($M+Na^+$, 100)

HRMS (ES^+) for $C_{35}H_{56}O_9S_2Na$ $(M+Na)^+$: Calculated 707.3258; Measured 707.3259

Data for (2*S*,3*R*,4*S*)-(tetrahydro-3,4-dihydroxyfuran-2-yl)methyl 2,4,6-triisopropylbenzenesulfonate (2.10)

M.W. 400.5 (400.1920)

mp 163-164 °C

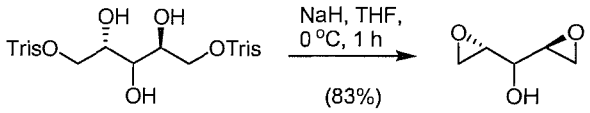
^{1}H NMR (400 MHz, acetone) 7.36 (1H, s, ArH), 7.35 (1H, s, ArH), 4.47 (1H, m, OH), 4.08-4.23 (3H, m, CH + CH_2), 4.01 (1H, m, CH), 3.91-3.96 (2H, m, $C\underline{H}_a\underline{H}_bCH$ + CH), 3.72 (1H, dt, J = 9.5, 2.0 Hz, $CH_a\underline{H}_b$), 2.99 (2H, septet, J = 7.0 Hz, $C\underline{H}(CH_3)_2 \times 2$), 2.98 (1H, septet, J = 7.0 Hz, $C\underline{H}(CH_3)_2$), 2.87 (1H, m, OH), 1.26 (12H, d, J = 7.0 Hz, $CH(C\underline{H}_3)_2 \times 2$), 1.25 (6H, d, J = 7.0 Hz, $CH(C\underline{H}_3)_2$)

^{13}C NMR (100 MHz, $CDCl_3$) 154.9 (C_{Ar}), 151.7 × 2 ($C_{Ar} \times 2$), 130.5 (C_{Ar}), 124.8 × 2 ($CH_{Ar} \times 2$), 84.1 ($\underline{C}HCH_2OS$), 79.6 (CH), 78.3 (CH), 74.7 (CH_2OS), 70.4 ($O\underline{C}H_2CH$), 35.0 × 2 ($\underline{C}H(CH_3)_2 \times 2$), 30.4 ($\underline{C}H(CH_3)_2$), 25.0 × 4 ($CH(\underline{C}H_3)_2 \times 2$), 23.8 × 2 ($CH(\underline{C}H_3)_2$)

ES$^+$ ***m/z*** (%) 423 ($M+Na^+$, 100)

Anal Calcd for $C_{20}H_{32}O_6S$: C, 59.98; H, 8.05. Found: C, 60.14; H, 8.21

8.9 (2*S*,4*S*)-1,2;4,5-Diepoxypentanol (2.12)



2.11 **2.12**

NaH (60% dispersion in mineral oil, 0.120 g, 3.00 mmol) was added to a solution of **2.11** (0.477g, 0.697 mmol) in THF (24.3 mL) at 0 °C and the mixture was stirred at 0 °C for 1 hour. Sat. NH_4Cl (0.5 mL) was added and the slurry was filtered through a column of Na_2SO_4. Concentration *in vacuo* and purification by column chromatography (EtOAc/toluene 3:7) afforded **2.12** as a colourless liquid (67.0 mg, 83%).

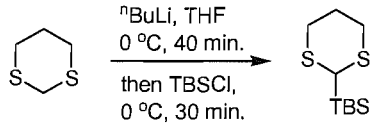
M.W. 116.12 (116.0473)

^{1}H NMR (300 MHz, $CDCl_3$) 3.52 (1H, q, J = 5.0 Hz, C<u>H</u>OH), 3.14 (1H, td, J = 4.0, 2.5 Hz, $CH_2C\underline{H}$), 3.09 (1H, ddd, J = 4.5, 4.0, 2.5 Hz, $CH_2C\underline{H}$), 2.75-2.85 (4H, m, $C\underline{H_2}CH$ × 2), 2.62 (1H, d, J = 5.0 Hz, OH)

^{13}C NMR (75 MHz, $CDCl_3$) 70.2 (CHOH), 52.6 ($CH_2\underline{C}H$), 52.1 ($CH_2\underline{C}H$), 44.6 ($\underline{C}H_2CH$), 44.1 ($\underline{C}H_2CH$)

^{1}H NMR and **^{13}C NMR** corresponded to the previously reported values.[101]

8.10 2-(*tert*-Butyldimethylsilyl)-1,3-dithiane (1.94)



1.98 (97%) **1.94**

^{n}BuLi (2.5 M solution in hexanes; 100 ml, 0.250 mol) was added to a stirred solution of 1,3-dithiane **1.98** (22.4 g, 0.186 mol) in THF (150 mL) over 30 minutes at 0 °C. The solution was stirred for 10 minutes at 0 °C and TBSCl (29.3 g, 0.195 mol) in THF (30 mL) was added. The mixture was stirred at 0 °C for 30 minutes followed by the addition of sat. NH_4Cl (250 mL). EtOAc (500 mL) was added and the layers were separated. The organic layer was washed with brine (2 × 250 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (toluene/petroleum ether 2:8) to yield **1.94** as a clear oil (42.2 g, 97 %).

M.W. 234.50 (234.0932)

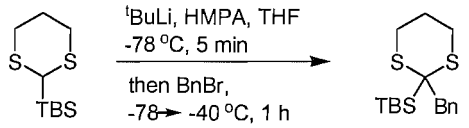
bp 124 °C/5 mm Hg

^{1}H NMR (300 MHz, $CDCl_3$) 3.81 (1H, s, SC<u>H</u>S), 2.85-2.94 (2H, m, $SCH_a\underline{H_b}$+$SCH_c\underline{H_d}$), 2.66-2.74 (2H, m, $SCH_a\underline{H_b}$+$SCH_c\underline{H_d}$), 1.96-2.15 (2H, m, $CH_2C\underline{H_2}CH_2$), 0.98 (9H, s, $SiC(C\underline{H_3})_3$), -0.12 (6H, s, $Si(C\underline{H_3})_2$)

^{13}C NMR (75 MHz, $CDCl_3$) 32.7 (SCS), 31.7 (2 × SCH_2), 27.2 × 3 ($SiC(\underline{C}H_3)_3$), 26.4 ($CH_2\underline{C}H_2CH_2$), 17.6 (SiC), -7.0 × 2 ($SiCH_3$ × 2)

^{1}H NMR and **^{13}C NMR** corresponded to the literature values.[170]

8.11 2-Benzyl-2-(*tert*-butyl-dimethyl-silanyl)-1,3-dithiane (3.10)



1.94 (85%) **3.10**

^{t}BuLi (1.7 M in pentane; 1.0 mL, 1.70 mmol) was added to a solution of dithiane **1.94** (0.204 g, 0.870 mmol) and HMPA (0.60 mL) in THF (6 mL) at -78 °C and the mixture was stirred at -78 °C for 5 minutes. Benzyl bromide (0.11 mL, 0.883 mmol) was added and the reaction was warmed to -40 °C over a period of 30 minutes. The reaction was stirred for an additional 30 minutes at -40 °C followed by the addition of sat. NH_4Cl (8 mL). The aqueous layer was extracted with Et_2O (2 × 10 mL). The organic layer was dried over Na_2SO_4, concentrated *in vacuo* and purified by column chromatography (toluene/petroleum ether 1:9) to yield **3.10** as a colourless oil (239 mg, 85%).

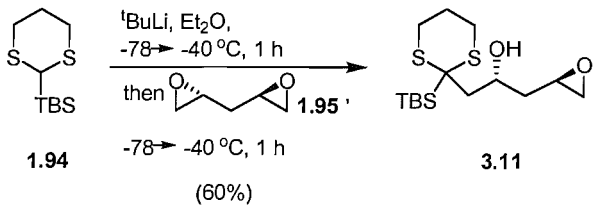
^{1}H NMR (300 MHz, $CDCl_3$) 7.61-7.64 (2H, m, ArH), 7.27-7.30 (3H, m, ArH), 3.44 (2H, s, CH_2Ph), 2.18-2.23 (4H, m, SCH_2 × 2), 1.53-1.76 (2H, m, $CH_2C\underline{H}_2CH_2$), 1.10 (9H, s, $C(C\underline{H}_3)_3$), 0.22 (6H, s, $Si(C\underline{H}_3)$ × 2)

^{13}C NMR (75 MHz, $CDCl_3$) 139.3 (C_{Ar}), 131.6 × 2 (CH_{Ar} × 2), 128.0 × 2 (CH_{Ar} × 2), 126.8 (CH_{Ar}), 48.6 (CH_2Ph), 38.7 (SCS), 29.0 × 3 ($C(\underline{C}H_3)_3$), 25.4 (SCH_2 × 2), 23.5 ($CH_2\underline{C}H_2CH_2$), 20.3 ($Si\underline{C}$)

* ^{13}C NMR signals for $SiCH_3$ groups were offscale.

^{1}H NMR and **^{13}C NMR** corresponded to the literature values.[171,172]

8.12 (2*R*,4*R*)-1-[2-(*tert*-Butyl-dimethyl-silanyl)-1,3-dithian-2-yl]-3-oxiranyl-propan-2-ol (3.11)



^{t}BuLi (1.7 M solution in pentane, 0.64 mL, 1.09 mmol) was added to a solution of dithiane **1.94** (0.196 g, 0.837 mmol) in Et_2O (6 mL) at -78 °C and the mixture was warmed to -40 °C over 1 hour. The reaction mixture was recooled to -78 °C and bis-epoxide **1.95** (0.084 mL. 0.783 mmol) was added. The mixture was warmed to -40 °C over 1 hour, followed by the addition of sat. NH_4Cl (8 mL). The aqueous layer was extracted with Et_2O (3 × 10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography (EtOAc/petroleum ether 35:65) to afford **3.11** (0.166 g, 60%) as a colourless oil.

M.W. 334.62 (334.1456)

$[\alpha]_D$ = +3.00 (*c* = 0.8, $CHCl_3$, 23 °C)

IR ν_{max}/cm^{-1} 3414 br, 2929 m, 2856 w, 1470 w, 1413 w, 1362 w, 1301 w, 1251 m

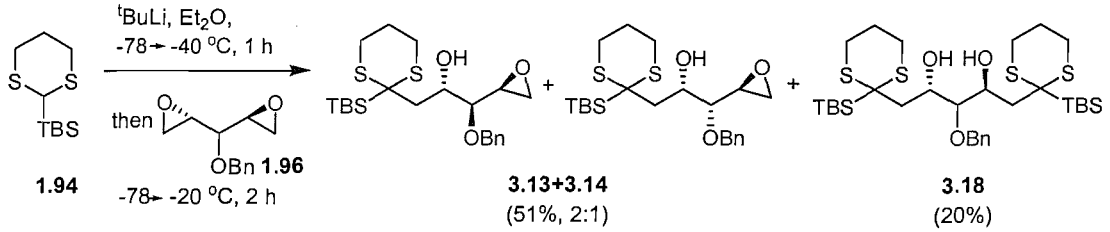
^{1}H NMR (400 MHz, $CDCl_3$) 4.44 (1H, d, *J* = 1.0 Hz, OH), 4.23-4.29 (1H, m, CHOH), 3.20 (1H, ddd, *J* = 14.5, 12.5, 3.0 Hz, SCH_aH_b), 3.16-3.09 (2H, m, SCH_cH_d+CH_2CH), 2.80 (1H, dd, *J* = 5.0, 4.0 Hz, CH_aH_bCH), 2.76 (1H, dd, *J* = 15.5, 10.0 Hz, $SCSCH_aH_b$), 2.50 (1H, dd, *J* = 5.0, 2.5 Hz, CH_aH_bCH), 2.49 (2H, m, SCH_aH_b + SCH_cH_d), 2.30 (1H, dd, *J* = 15.5, 0.5 Hz, $SCSCH_aH_b$), 2.04 (1H, m, $SCH_2CH_aH_b$), 1.90 (1H, m, $SCH_2CH_aH_b$), 1.81 (1H, ddd, *J* = 14.0, 8.5, 4.5 Hz, $CHCH_aCH_bCH$), 1.46 (1H, dddd, *J* = 14.0, 7.0, 4.0, 1.5 Hz, $CHCH_aH_bCH$), 1.03 (9H, s, $SiC(CH_3)_3$), 0.32 (3H, s, $Si(CH_3)$), 0.23 (3H, s, $Si(CH_3)$)

^{13}C NMR (100 MHz, $CDCl_3$) 68.9 (CHOH), 49.7 (CH_2CH), 47.5 (CH_2CH), 44.1 ($SiCCH_2$), 41.2 ($CHCH_2CH$), 39.5 (SCS), 28.5 × 3 ($SiC(CH_3)_3$), 24.5 (SCH_2), 24.2 (SCH_2), 23.6 (SCH_2CH_2), 20.0 ($SiC(CH_3)_3$), -4.8 ($Si(CH_3)$), -5.5 ($Si(CH_3)$)

ES$^+$ *m/z* (%) 357 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{15}H_{30}O_2S_2SiNa$ $(M+Na)^+$: Calcd 357.1348; Measured 357.1346

8.13 (1*S*,2*S*)- and (1*R*,2*S*)-1-Benzyloxy-3-(2-*tert*-butyldimethylsilanyl-1,3-dithian-2-yl)-1-((*S*)-oxiran-2-yl)propan-2-ol) (3.13) and (3.14)



^{t}BuLi (1.5M solution in pentane; 0.37 mL, 0.555 mmol) was added to a solution of dithiane **1.94** (0.101 g, 0.431 mmol) in Et_2O (4.9 mL) at –78 °C and the mixture was warmed to -40 °C over 1 hour. Bis-epoxide **1.96** (0.0927 g, 0.453 mmol) was added at -78 °C and the temperature was warmed to -20 °C over 2 hours before the reaction was quenched by the addition of sat. NH_4Cl (2 mL) and H_2O (5 mL). The aqueous phase was extracted with Et_2O (3 × 10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by column chromatography (EtOAc/petroleum ether 2:8) to afford a mixture of diastereoisomers **3.13** and **3.14** (96 mg, 51%, 2:1) and diol **3.18** (29 mg, 20%), all as oils.

Data for a mixture of 3.13 + 3.14

M.W. 440.74 (440.1875)

IR ν_{max}/cm^{-1} 3405 br, 2930 w, 2896 w, 2857 w, 1471 w, 1416 w, 1390 w

ES$^+$ *m/z* (%) 464 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{22}H_{36}O_3S_2SiNa$ $(M+Na)^+$: Calcd 463.1767; Measured 463.1770

NMR data for major isomer 3.13 (isolated after HPLC)

^{1}H NMR (400 MHz, $CDCl_3$) 7.26-7.40 (5H, m, ArH), 4.91 (1H, d, J = 12.0 Hz, CH_aH_bPh), 4.65 (1H, d, J = 12.0 Hz, CH_aH_bPh), 4.28 (1H, d, J = 1.5 Hz, OH), 4.21 (1H, tdd, J = 7.0, 5.0, 1.5 Hz, CHOH), 3.12-3.20 (2H, m, $CHCH_2$ + SCH_aH_b), 3.07 (1H, ddd, J = 14.5, 12.0, 3.0 Hz, SCH_cH_d), 2.97 (1H, t, J = 7.0 Hz, CHOBn), 2.87 (1H, dd, J

= 5.0, 4.0 Hz, $CHC\underline{H}_aH_b$), 2.69 (1H, dd, J = 5.0, 3.0 Hz, $CHCH_a\underline{H}_b$), 2.61-2.63 (2H, m, $SCSCH_2$), 2.44-2.53 (2H, m, $SCH_a\underline{H}_b$ + $SCH_c\underline{H}_d$), 2.04 (1H, m, $SCH_2C\underline{H}_aH_b$), 1.90 (1H, dtt, J = 14.0, 12.5, 3.0 Hz, $SCH_2CH_a\underline{H}_b$) 1.06 (9H, s, $SiC(CH_3)_3$), 0.32 (3H, s, $SiCH_3$), 0.24 (3H, s, $SiCH_3$)

^{13}C NMR (100 MHz, $CDCl_3$) 138.4 (C_{Ar}), 128.4 × 2 (CH_{Ar} × 2), 128.0 × 2 (CH_{Ar} × 2), 127.7 (CH_{Ar}), 83.9 (CHOBn), 72.5 (CH_2Ph), 71.7 (CHOH), 53.3 ($\underline{C}HCH_2$), 44.2 ($CH\underline{C}H_2$), 40.5 ($SCS\underline{C}H_2$), 39.5 (SCS), 28.6 × 3 ($SiC(\underline{C}H_3)_3$), 24.5 (SCH_2), 24.4 (SCH_2), 23.8 ($SCH_2\underline{C}H_2$), 20.0 (SiC), -4.8 ($SiCH_3$), -5.7 ($SiCH_3$)

NMR data for 3.14 (from a mixture of 3.13 and 3.14)

^{1}H NMR (400 MHz, $CDCl_3$) 7.27-7.40 (5H, m, ArH), 4.77 (1H, d, J = 12.0 Hz, $C\underline{H}_aH_bPh$), 4.58 (1H, d, J = 12.0 Hz, $CH_a\underline{H}_bPh$), 4.28 (1H, m, $C\underline{H}OH$), 3.92 (1H, d, J = 3.0 Hz, OH), 3.28 (1H, dd, J = 5.0, 3.5 Hz, CHOBn), 3.25 (1H, m, $C\underline{H}CH_2$), 3.04-3.21 (2H, m, $SC\underline{H}_aH_b$ + $SC\underline{H}_cH_d$), 2.81-2.87 (2H, m, $CHC\underline{H}_aH_b$ + $SCSC\underline{H}_aH_b$), 2.79 (1H, dd, J = 5.5, 2.5 Hz, $CHCH_a\underline{H}_b$), 2.43-2.53 (2H, m, $SCH_a\underline{H}_b$ + $SCH_c\underline{H}_d$), 2.36 (1H, dd, J = 15.5, 1.5 Hz, $SCSCH_a\underline{H}_b$), 1.85-2.08 (2H, m, $SCH_2C\underline{H}_2$), 1.04 (9H, s, $SiC(CH_3)_3$), 0.31 (3H, s, $SiCH_3$), 0.23 (3H, s, $SiCH_3$)

^{13}C NMR (100 MHz, $CDCl_3$) 138.1 (C_{Ar}), 128.5 × 2 (CH_{Ar} × 2), 128.2 × 2 (CH_{Ar} × 2), 128.0 (CH_{Ar}), 80.5 (CHOBn), 73.3 (CH_2Ph), 71.2 (CHOH), 51.1 ($\underline{C}HCH_2$), 45.8 ($CH\underline{C}H_2$), 40.7 ($SCS\underline{C}H_2$), 39.3 (SCS), 28.6 × 3 ($SiC(\underline{C}H_3)_3$), 24.5 (SCH_2), 24.4 (SCH_2), 23.8 ($SCH_2\underline{C}H_2$), 20.0 (SiC), -5.1 ($SiCH_3$), -5.6 ($SiCH_3$)

Data for (2*S*,4*S*)-3-Benzyloxy-1,5-bis-(2-(*tert*-butyl-dimethyl-silanyl)-1,3-dithian-2-yl)-pentane-2,4-diol (3.18)

M.W. 675.24 (674.2807)

$[\alpha]_D$ = -41.0 (c = 2.3, $CHCl_3$, 24 °C)

IR ν_{max}/cm^{-1} 3497 br, 3373 br, 2922 w, 2896 w, 2856 w, 1471 w, 1423 w, 1392 w, 1363 w

^{1}H NMR (400 MHz, $CDCl_3$) 7.27-7.39 (5H, m, ArH), 4.73 (1H, d, J = 11.5 Hz, $C\underline{H}_aH_bPh$), 4.68 (1H, d, J = 1.5 Hz, OH), 4.65 (1H, d, J = 11.5 Hz, $CH_a\underline{H}_bPh$), 4.36-

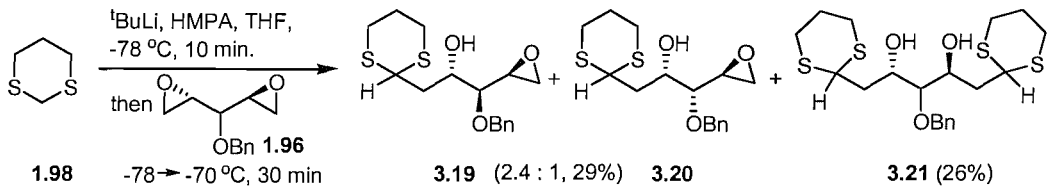
4.42 (2H, m, C<u>H</u>OH × 2), 3.92 (1H, d, J = 7.5 Hz, OH), 3.33 (1H, dd, J = 7.5, 2.5 Hz, CHOBn), 3.18 (1H, ddd, J = 15.0, 12.5, 2.5 Hz, SC<u>H</u>$_a$H$_b$), 3.05-3.13 (2H, m, SC<u>H</u>$_c$H$_d$ + SC<u>H</u>$_e$H$_f$), 2.98 (1H, ddd, J = 14.5, 12.0, 2.5 Hz, SC<u>H</u>$_g$H$_h$), 2.59-2.66 (4H, m, C<u>H</u>$_2$CHOH × 2), 2.43-2.52 (3H, m, SCH$_a$<u>H</u>$_b$ + SCH$_c$<u>H</u>$_d$ + SCH$_g$<u>H</u>$_h$), 2.27 (1H, dt, J = 14.0, 3.5 Hz, SCH$_e$<u>H</u>$_f$), 1.79-2.09 (4H, m, SCH$_2$C<u>H</u>$_2$ × 2), 1.062 (9H, s, SiC(CH$_3$)$_3$), 1.058 (9H, s, SiC(CH$_3$)$_3$), 0.32 (3H, s, SiC<u>H</u>$_3$), 0.28 (3H, s, SiC<u>H</u>$_3$), 0.26 (3H, s, SiC<u>H</u>$_3$), 0.24 (3H, s, SiCH$_3$)

^{13}C NMR (100 MHz, $CDCl_3$) 138.0 (C_{Ar}), 128.5 × 2 (CH_{Ar} × 2), 128.4 × 2 (CH_{Ar} × 2), 127.9 (CH_{Ar}), 83.4 (CHOBn), 73.0 (CH_2Ph), 71.5 (CHOH), 69.7 (CHOH), 41.4 (<u>C</u>H$_2$CHOH), 40.8 (<u>C</u>H$_2$CHOH), 39.7 (2 × SCS), 28.9 × 3 (SiC(<u>C</u>H$_3$)$_3$), 28.7 × 3 (SiC(<u>C</u>H$_3$)$_3$), 24.7 (SCH_2), 24.5 (SCH_2), 24.3 (SCH_2), 23.7 (SCH_2), 20.2 (SCH_2CH_2), 20.0 (SCH_2CH_2), -4.9 (Si<u>C</u>H$_3$), -5.2 (Si<u>C</u>H$_3$), -5.6 (Si<u>C</u>H$_3$), -5.7 (Si<u>C</u>H$_3$)

ES$^+$ ***m/z*** (%) 697 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{32}H_{58}O_3S_4Si_2Na$ $(M+Na)^+$: Calcd. 697.2700; Measured 697.2694

8.14 (2*S*,4*S*)-3-Benzyloxy-1,5-bis-(1,3-dithian-2-yl)-pentane-2,4-diol (3.21)



^{t}BuLi (1.5 M solution in pentane; 0.85 mL, 1.28 mmol) was added to a solution of 1,3-dithiane **1.98** (0.106 g, 0.882 mmol) in THF (8.5 mL) at –78 °C and the mixture was stirred for 10 minutes. Bis-epoxide **1.96** (0.175 g, 0.849 mmol) was added and the mixture was warmed to -70 °C over 30 minutes. The reaction was quenched by the addition of sat. NH_4Cl (10 mL) and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by column chromatography (acetone/petroleum ether 25:75) to

afford a 2.4:1 mixture of diastereoisomers **3.19** and **3.20** (colourless oil, 82.0 mg, 29%) which were not separated by HPLC, and diol **3.21** (white solid, 99.0 mg, 26%).

Data for 3.21

M.W. 446.71 (446.1078)

$[\alpha]_D$ = -16.5 (c = 3.2, $CHCl_3$, 24 °C)

IR ν_{max}/cm^{-1} 3436 br, 2930 w, 2897 w, 1496 w, 1454 w, 1421 m

^{1}H NMR (400 MHz, $CDCl_3$) 7.29-7.38 (5H, m, ArH), 4.68 (1H, d, J = 11.5 Hz, $C\underline{H}_aH_bPh$), 4.60 (1H, d, J = 11.5 Hz, $CH_a\underline{H}_bPh$), 4.27 (1H, dd, J = 9.5, 5.0 Hz, SCHS), 4.15-4.27 (2H, m, $C\underline{H}OH$ × 2), 4.15 (1H, dd, J = 9.5, 5.0 Hz, SCHS), 3.45 (1H, d, J = 4.0 Hz, OH), 3.25-3.28 (2H, m, CHOBn + OH; simplified to 3.27 (1H, dd, J = 5.5, 3.0 Hz, CHOBn) upon D_2O exchange), 2.80-2.94 (8H, m, SCH_2 × 4), 1.82-2.17 (8H, m, $SCH_2C\underline{H}_2$ × 2 + $SCSC\underline{H}_2$ × 2)

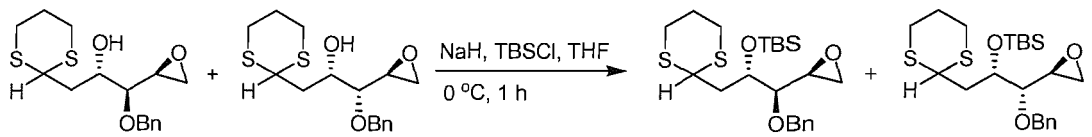
^{13}C NMR (100 MHz, $CDCl_3$) 137.5 (C_{Ar}), 128.5 × 2 (CH_{Ar} × 2), 128.3 × 2 (CH_{Ar} × 2), 128.0 (CH_{Ar}), 81.4 (CHOBn), 72.9 (CH_2Ph), 68.8 (CHOH), 68.1 (CHOH), 43.9 (SCHS), 43.7 (SCHS), 39.3 ($SCS\underline{C}H_2$), 39.0 ($SCS\underline{C}H_2$), 30.2 (SCH_2), 30.1 (SCH_2), 29.8 (SCH_2), 29.7 (SCH_2), 25.9 ($SCH_2\underline{C}H_2$), 25.8 ($SCH_2\underline{C}H_2$)

ES$^+$ ***m/z*** (%) 469 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{20}H_{30}O_3S_4Na$ $(M+Na)^+$: Calcd 469.0970; Measured 469.0970

The structure of alcohols 3.19 and 3.20 were confirmed by the characterisation of silyl ethers 3.15 and 3.16 which were derived from 3.19 and 3.20 respectively.

8.15 (1*S*,2*S*)- and (1*R*,2*S*)-1-Benzyloxy-3-(1,3-dithian-2-yl)-1-((*S*)-oxiran-2-yl)propan-2-yloxy)-*tert*-butyldimethylsilane (3.15) and (3.16)



3.19 (2.4 : 1) **3.20** **3.15** (4 : 1, 47%) **3.16**

A mixture of **3.19** and **3.20** (70.0 mg, 0.214 mmol) in THF (1.0 mL) was added to a suspension of NaH (60% dispersion in mineral oil; 0.237 g, 0.593 mmol) and TBSCl (56.0 mg, 0.372 mmol) in THF (1.7 mL) at 0 °C. The reaction was stirred at 0 °C for 1 hour. 5% $NaHCO_3$ (10 mL) and Et_2O (10 mL) were added. The aqueous layer was extracted with Et_2O (2 × 10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by column chromatography (EtOAc/ petroleum ether 1:9) to afford a 4:1 mixture of **3.15** and **3.16** (colourless oil, 44.0 mg, 47%).

Data for a mixture of 3.15 and 3.16

M.W. 440.74 (440.1875)

IR ν_{max}/cm^{-1} 2950 w, 2903w, 2855 w, 1457 w, 1421 w, 1389 w, 1359 w, 1318 w

ES$^+$ *m/z* (%) 463 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{22}H_{36}O_3S_2SiNa$ $(M+Na)^+$: Calcd 463.1767; Measured 463.1776

NMR data for major isomer 3.15

^{1}H NMR (400 MHz, $CDCl_3$) 7.27-7.41 (5H, m, ArH), 4.84 (1H, d, J = 11.5 Hz, CH_aH_bPh), 4.65 (1H, d, J = 11.5 Hz, CH_aH_bPh), 4.13-4.18 (2H, m, CHOSi + SCHS), 3.12 (1H, ddd, J = 7.5, 4.0, 2.5 Hz, $CHCH_2$), 3.04 (1H, dd, J = 7.5, 4.0 Hz, CHOBn), 2.73-2.89 (5H, m, SCH_2 × 2 + $CHCH_aH_b$), 2.59 (1H, dd, J = 5.0, 2.5 Hz, $CHCH_aH_b$), 2.10 (1H, m, $SCH_2CH_aH_b$), 2.06 (1H, ddd, J = 14.5, 8.0, 5.5 Hz, $SCSCH_aH_b$), 1.82-1.93 (2H, m, $SCH_2CH_aH_b$ + $SCSCH_aH_b$), 0.91 (9H, s, $SiC(CH_3)_3$), 0.14 (3H, s, $SiCH_3$), 0.10 (3H, s, $SiCH_3$)

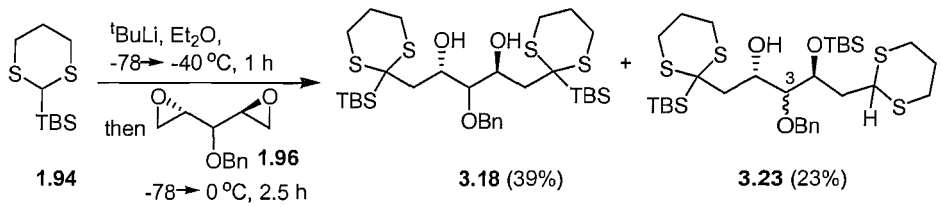
^{13}C NMR (100 MHz, $CDCl_3$) 138.5 (C_{Ar}), 128.4 × 2 (CH_{Ar} × 2), 128.1 × 2 (CH_{Ar} × 2), 127.7 (CH_{Ar}), 84.3 (CHOBn), 72.4 (CH_2Ph), 70.5 (CHOSi), 52.8 ($CHCH_2$), 44.1 ($CHCH_2$), 43.7 (SCHS), 40.3 (CH_2CHOSi), 30.7 (SCH_2), 30.3 (SCH_2), 26.1 × 3 ($SiC(CH_3)_3$), 26.0 (SCH_2CH_2), 18.3 (SiC), -4.1 ($SiCH_3$), -4.5 ($SiCH_3$)

NMR data for minor isomer 3.16 (from a mixture of 3.15 and 3.16)

^{1}H NMR (400 MHz, $CDCl_3$) 7.27-7.40 (5H, m, ArH), 4.65 (1H, d, J = 12.0 Hz, CH_aH_bPh), 4.50 (1H, d, J = 12.0 Hz, CH_aH_bPh), 4.13-4.20 (1H, m, CHOSi), 4.00 (1H, dd, J = 10.0, 5.0 Hz, SCHS), 3.58 (1H, dd, J = 4.0, 2.5 Hz, CHOBn), 3.24 (1H, dt, J = 5.5, 2.5 Hz, $CHCH_2$), 2.91 (1H, dd, J = 5.5, 2.5 Hz, $CHCH_aH_b$), 2.73-2.86 (5H, m, $SCH_2 \times 2 + CHCH_aH_b$), 2.15 (1H, ddd, J = 14.0, 10.0, 4.0 Hz, $SCHCH_aH_b$), 1.80-2.13 (3H, m, $SCH_2CH_2 + SCSCH_aH_b$), 0.90 (9H, s, $SiC(CH_3)_3$), 0.09 (3H, s, $SiCH_3$), 0.01 (3H, s, $SiCH_3$)

^{13}C NMR (100 MHz, $CDCl_3$) 138.4 (C_{Ar}), 128.5 × 2 ($CH_{Ar} \times 2$), 128.0 × 2 ($CH_{Ar} \times 2$), 127.8 (CH_{Ar}), 77.0 (CHOBn), 73.2 (CH_2Ph), 69.0 (CHOSi), 50.9 ($CHCH_2$), 44.5 ($CHCH_2$), 43.8 (SCHS), 37.9 (CH_2CHOSi), 30.4 (SCH_2), 29.8 (SCH_2), 26.2 (SCH_2CH_2), 26.0 × 3 ($SiC(CH_3)_3$, 18.1 (SiC), -4.2 ($SiCH_3$), -4.6 ($SiCH_3$)

8.16 (2*S*,4*S*)-3-Benzyloxy-1-(2-*tert*-butyldimethylsilanyl-1,3-dithian-2-yl)-4-*tert*-butyldimethylsilanyloxy-5-(1,3-dithian-2-yl)-pentan-2-ol (3.23)



^{t}BuLi (1.5 M solution in pentane; 1.78 mL, 2.67 mmol) was added to a solution of dithiane **1.94** (0.419 g, 1.78 mmol) in Et_2O (8.5 mL) at –78 °C and the mixture was warmed to –40 °C over 1 hour. After recooling to –78 °C, bis-epoxide **1.96** (0.175 g, 0.846 mmol) was added and the mixture was warmed to 0 °C over 2.5 hours. The reaction was quenched by the addition of sat. NH_4Cl (10 mL) and the aqueous layer was extracted with Et_2O (3 × 10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by column chromatography (EtOAc/petroleum ether 25:75) to afford diol **3.18** (white solid, 222 mg, 39%) and the rearranged product **3.23** as a single diastereoisomer (colourless oil, 131 mg, 23%).

M.W. 675.24 (674.2807)

$[\alpha]_D$ = +9.0 (c = 0.75, $CHCl_3$, 24 °C)

IR ν_{max}/cm^{-1} 3420 br, 2951 w, 2929 w, 2896 w, 2856 w, 1471 w, 1422 w, 1390 w, 1362 w

^{1}H NMR (400 MHz, $CDCl_3$) 7.27-7.43 (5H, m, ArH), 4.93 (1H, d, J = 11.5 Hz, CH_aH_bPh), 4.59 (1H, d, J = 11.5 Hz, CH_aH_bPh), 4.39 (1H, ddd, J = 8.0, 4.5, 2.0 Hz, CHOSi), 4.17 (1H, dd, J = 9.0, 5.5 Hz, SCHS), 4.16 (1H, m, CHOH), 3.82 (1H, d, J = 2.0 Hz, OH), 3.45 (1H, dd, J = 6.0, 4.5 Hz, CHOBn), 3.05 (1H, ddd, J = 15.0, 12.0, 3.0 Hz, SCH_aH_b), 2.82-2.94 (4H, m, SCH_2 × 2), 2.75 (1H, ddd, J = 14.0, 11.0, 2.5 Hz, SCH_cH_d), 2.61 (1H, dd, J = 15.0, 8.5 Hz, CH_aH_bCHOH), 2.43 (1H, dt, J = 14.0, 4.0 Hz, SCH_aH_b), 2.35 (1H, dd, J = 15.0, 1.5 Hz, CH_aH_bCHOH), 2.35 (1H, m, SCH_cH_d), 1.69-2.15 (6H, m, CH_2CHOSi + SCH_2CH_2 × 2), 1.04 (9H, s, $SiC(CH_3)_3$), 0.95 (9H, s, $SiC(CH_3)_3$), 0.28 (3H, s, $SiCH_3$), 0.22 (3H, s, $SiCH_3$), 0.19 (3H, s, $SiCH_3$), 0.16 (3H, s, $SiCH_3$)

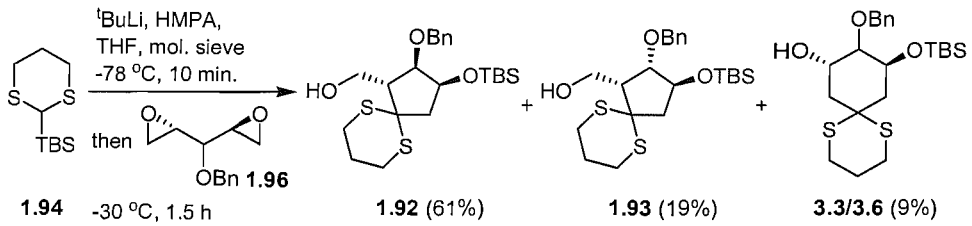
^{13}C NMR (100 MHz, $CDCl_3$) 138.4 (C_{Ar}), 128.5 × 4 (CH_{Ar} × 4), 127.9 (CH_{Ar}), 85.0 (CHOBn), 7.7 (CH_2Ph), 70.5 (CHOSi), 70.1 (CHOH), 44.2 (SCHS), 42.2 (CH_2CHOH), 39.6 (CH_2CHOSi), 39.5 (SCS), 30.4 (SCH_2), 30.0 (SCH_2), 28.8 × 3 ($SiC(CH_3)_3$), 26.2 (SCH_2), 26.1 × 3 ($SiC(CH_3)_3$), 24.6 (SCH_2), 24.4 (SCH_2CH_2), 24.0 (SCH_2CH_2), 20.1 (SiC), 18.1 (SiC), -3.9 ($SiCH_3$), -4.5 ($SiCH_3$), -5.2 ($SiCH_3$), -5.4 ($SiCH_3$)

ES^+ ***m/z*** (%) 697 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{32}H_{59}O_3S_4Si_2$ $(M+H)^+$: Calcd 675.2880; Measured 675.2904

* Note that the relative stereochemistry at C3 was not confirmed.

8.17 (1*R*,2*R*,3*S*)- and (1*R*,2*S*,3*S*)-[2-Benzyloxy-3-(*tert*-butyldimethyl silanyloxy)-6,10-dithiaspiro[4,5]dec-1-yl]-methanol (1.92) and (1.93)



^{t}BuLi (1.5 M solution in pentane, titrated conc. 1.3 M; 0.53 mL, 0.689 mmol) was added to a solution of dithiane **1.94** (0.170 g, 0.725 mmol) and HMPA (1.78 mL) in THF (16.0 mL) containing 4 Å molecular sieves (~4 g) at –78 °C and the mixture was stirred for 10 minutes. Bis-epoxide **1.96** (0.110 g. 0.533 mmol) in THF (1 mL) was added and the mixture was stirred at –30 °C (dry ice in acetonitrile/*o*-xylene 2:8) for 90 minutes. The reaction was quenched by the addition of sat. NH_4Cl (10 mL) and H_2O (10 mL) and the aqueous layer was extracted with Et_2O (3 × 10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was purified by column chromatography (EtOAc/petroleum ether 2:8) to afford a mixture of diastereoisomers which were separated by HPLC (EtOAc/hexane 2:8) to give the 5-*exo* cyclisation products **1.92** (144 mg, 61%), **1.93** (44.0 mg, 19%) and the 6-*exo* cyclisation product **3.3/3.6** (20.0 mg, 9%), all as colourless oils.

M.W. 440.73 (440.1875)

Major isomer 1.92

$[\alpha]_D$ = +88.7 (*c* 0.60, $CHCl_3$, 25 °C)

IR ν_{max}/cm^{-1} 3530 w, 2952 s, 2928 s, 2898 s, 1471 w, 1253 m

^{1}H NMR (400 MHz, $CDCl_3$) 7.25-7.35 (5H, m, ArH), 4.75 (1H, d, *J* = 12.0 Hz, C$\underline{H}_a$H$_b$Ph), 4.45 (1H, d, *J* = 12.0 Hz, CH$_a$$\underline{H}_b$Ph), 4.40 (1H, q, *J* = 5.0 Hz, CHOSi), 3.91-4.03 (2H, m, C$\underline{H}_2$OH; simplifies to 3.99 (1H, dd, *J* = 12.0, 7.0 Hz) and 3.94 (1H, dd, *J* = 12.0, 6.0 Hz) upon treatment with D_2O), 3.79 (1H, dd, *J* = 9.0, 5.0 Hz, CHOBn), 3.10 (1H, ddd, *J* = 14.5, 12.0, 2.5 Hz, SC$\underline{H}_a$H$_b$), 2.97 (1H, ddd, *J* = 14.5, 11.5, 3.0 Hz, SC$\underline{H}_c$H$_d$), 2.84 (1H, dd, *J* = 14.0, 5.5 Hz, SCSC$\underline{H}_a$H$_b$), 2.74-2.87 (2H, m, SCH$_a$$\underline{H}_b$ + SCH$_c$$\underline{H}_d$), 2.68 (1H, dt, *J* = 9.0, 6.5 Hz, C$\underline{H}$CH$_2$OH), 2.52 (1H, t, *J* = 6.5, OH; signal disappears after treatment with D_2O), 2.49 (1H, dd, *J* = 14.0, 4.0 Hz, SCSCH$_a$$\underline{H}_b$), 2.10 (1H, m, SCH$_2C\underline{H}_aH_b$), 1.92 (1H, m, SCH$_2CH_a$$\underline{H}_b$), 0.93 (9H, s, SiC(CH$_3$)$_3$), 0.11 (3H, s, SiCH$_3$), 0.10 (3H, s, SiCH$_3$)

^{13}C NMR (100 MHz, $CDCl_3$) 138.3 (C_{Ar}), 128.5 × 2 (CH_{Ar} × 2), 127.8 × 3 (CH_{Ar} × 3), 81.7 (CHOBn), 72.1 (CH_2Ph), 70.3 (CHOSi), 62.2 (CH_2OH), 56.2 (C$\underline{H}$CH$_2$OH), 52.2

(SCS), 51.0 ($SCSCH_2$), 28.8 (SCH_2), 27.2 (SCH_2), 26.0 × 3 ($SiC(\underline{C}H_3)_3$), 25.7 (SCH_2CH_2), 18.3 (SiC), -4.3 ($SiCH_3$), -4.6 ($SiCH_3$)

CIMS *m/z* (%) 441 ($(M+H)^+$, 10), 291 (8), 197 (20), 171 (41), 106 (36)

Anal Calcd for $C_{22}H_{36}O_3S_2Si$: C, 59.96; H, 8.23. Found: C, 60.11; H, 8.45.

Minor isomer 1.93

$[\alpha]_D$ = +33.7 (*c* 1.3, $CHCl_3$, 25 °C)

IR ν_{max}/cm^{-1} 3495 w, 2951 s, 2928 s, 2897 s, 2855 s, 1471 w, 1254 m

^{1}H NMR (400 MHz, $CDCl_3$) 7.25-7.38 (5H, m, ArH), 4.75 (1H, d, *J* = 12.0 Hz, $C\underline{H}_aH_bPh$), 4.57 (1H, d, *J* = 12.0 Hz, $CH_a\underline{H}_bPh$), 4.41 (1H, dt, *J* = 8.0, 5.5 Hz, CHOSi), 4.28 (1H, dd, *J* = 7.0, 4.5Hz, CHOBn), 3.88-3.99 (2H, m, $C\underline{H}_2OH$; simplifies upon D_2O treatment), 2.84-2.97 (4H, m, SCH_2 × 2), 2.69-2.76 (2H, m, $C\underline{H}CH_2OH$ + $SCSC\underline{H}_aH_b$), 2.61 (1H, t, *J* = 6.5 Hz, OH; signal disappears upon treatment with D_2O), 2.04 (1H, dd, *J* = 14.5, 5.5 Hz, $SCSCH_a\underline{H}_b$), 1.96-2.01 (2H, m, $SCH_2C\underline{H}_2$), 0.91 (9H, s), 0.10 (3H, s), 0.08 (3H, s)

^{13}C NMR (100 MHz, $CDCl_3$) 138.3 (C_{Ar}), 128.6 × 2 (CH_{Ar} × 2), 127.9 (CH_{Ar}), 127.7 × 2 (CH_{Ar} × 2), 87.8 (CHOBn), 76.7 (CHOSi), 72.8 (CH_2Ph), 60.8 (CH_2OH), 53.8 (SCS), 52.3 ($\underline{C}HCH_2OH$), 49.1 ($SCSCH_2$), 28.9 (SCH_2), 28.1 (SCH_2), 25.9 × 3 ($SiC(CH_3)_3$), 25.0 ($SCH_2\underline{C}H_2$), 18.0 (SiC), -4.3 ($SiCH_3$), -4.6 ($SiCH_3$)

CIMS *m/z* (%) 441 ($(M+H)^+$, 100)

Anal Calcd for $C_{22}H_{36}O_3S_2Si$: C, 59.96; H, 8.23. Found: C, 59.75; H, 8.36.

Data for (8*S*,10*S*)-9-Benzyloxy-10-(*tert*-butyldimethylsilanyloxy)-1,5-dithiaspiro[5.5] undecan-8-ol (3.3/3.6)

$[\alpha]_D$ = +14.7 (*c* = 1.3, $CHCl_3$, 24 °C)

IR ν_{max}/cm^{-1} 3460 br, 2949 w, 2929 w, 2898 w, 2856 w, 1471 w, 1454 w, 1361 w

^{1}H NMR (400 MHz, $CDCl_3$) 7.29-7.36 (5H, m, ArH), 4.71 (1H, d, *J* = 12.0 Hz, $C\underline{H}_aH_bPh$), 4.63 (1H, d, *J* = 12.0 Hz, $CH_a\underline{H}_bPh$), 4.14-4.21 (2H, m, $C\underline{H}OH$ + CHOSi), 3.38 (1H, dd, *J* = 6.5, 3.5 Hz, CHOBn), 2.91-3.03 (2H, m, $SC\underline{H}_aH_b$ + $SC\underline{H}_cH_d$), 2.70-2.78 (3H, m, $SCH_a\underline{H}_b$ + $SCH_c\underline{H}_d$ + OH), 2.40 (1H, dd, *J* = 14.0, 7.0 Hz, $C\underline{H}_aH_bCHOH$), 2.29 (1H, dd, *J* = 14.0, 3.0 Hz, $C\underline{H}_aH_bCHOSi$), 2.23 (1H, dd, *J* = 14.0, 3.5 Hz,

CH_aH_bCHOH), 2.03 (1H, m, $SCH_2CH_aH_b$), 1.91 (1H, m, $SCH_2CH_aH_b$), 1.85 (1H, dd, J = 14.0, 7.5 Hz, CH_aH_bCHOSi), 0.91 (9H, s, $SiC(CH_3)_3$), 0.09 (3H, s, $SiCH_3$), 0.07 (3H, s, $SiCH_3$)

^{13}C NMR (100 MHz, $CDCl_3$) 138.5 (C_{Ar}), 128.6 × 2 (CH_{Ar} × 2), 128.0 × 2 (CH_{Ar} × 2), 127.9 (CH_{Ar}), 82.4 (CHOBn), 72.9 (CH_2Ph), 68.1 (CH), 67.4 (CH), 47.7 (SCS), 43.4 (CH_2), 40.6 (CH_2), 26.8 × 2 (SCH_2 × 2), 26.0 × 3 ($SiC(CH_3)_3$), 25.4 (SCH_2CH_2), 18.1 (SiC), -4.6 ($SiCH_3$), -4.7 ($SiCH_3$)

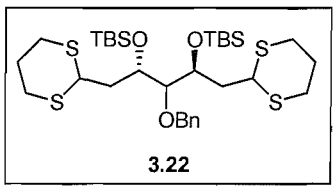
ES$^+$ ***m/z*** (%) 463 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{22}H_{36}O_3S_2SiNa$ $(M+Na)^+$: Calcd 463.1767; Measured 463.1771

1.) The relative stereochemistry at C9 was not determined and it was not possible to distinguish between the CH and the CH_2 groups on the ^{13}C NMR spectrum.

2.) A small amount of compound **3.22** was sometimes isolated in carbcacyclisation experiments (see below).

Data for (2*S*,4*S*)-3-Benzyloxy-2,4-di-*tert*-butyldimethylsilanyloxy-1,5-bis-(1,3-dithian-2-yl)-pentane (3.22)



3.22

$[\alpha]_D$ = -19.0 (c = 0.65, $CHCl_3$, 24 °C)

IR ν_{max}/cm^{-1} 2950 m, 2930 m, 2897 m, 2855 m, 1472 m, 1462 m, 1360 m

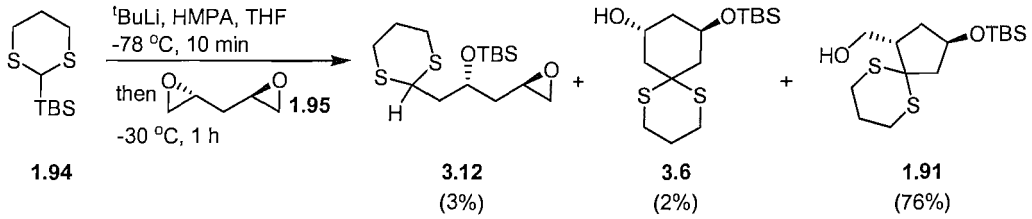
^{1}H NMR (400 MHz, $CDCl_3$) 7.29-7.36 (5H, m, ArH), 4.84 (1H, d, J = 11.5 Hz, CH_aH_bPh), 4.61 (1H, d, J = 11.5 Hz, CH_aH_bPh), 4.26 (1H, dt, J = 10.0, 2.0 Hz, CHOSi), 4.15 (1H, dd, J = 11.0, 3.5 Hz, SCHS), 4.05-4.09 (2H, m, CHOSi + SCHS), 3.43 (1H, dd, J = 6.0, 2.0 Hz, CHOBn), 2.71-2.92 (8H, m, SCH_2 × 4), 2.04-2.25 (4H, m, SCH_2CH_2 × 2), 1.84-1.97 (4H, m, CH_2CHOSi × 2), 0.93 (9H, s, $SiC(CH_3)_3$), 0.90 (9H, s, $SiC(CH_3)_3$), 0.16 (3H, s, $SiCH_3$), 0.12 (3H, s, $SiCH_3$), 0.10 (3H, s, $SiCH_3$), -0.02 (3H, s, $SiCH_3$)

^{13}C NMR (100 MHz, $CDCl_3$) 138.9 (C_{Ar}), 128.3 × 2 (CH_{Ar} × 2), 127.9 × 2 (CH_{Ar} × 2), 127.5 (CH_{Ar}), 85.3 (CHOBn), 73.8 (CH_2Ph), 70.5 (CHOSi), 69.9 (CHOSi), 44.3 (SCHS), 43.8 (SCHS), 40.0 ($\underline{C}H_2CHOSi$), 39.3 ($\underline{C}H_2CHOSi$), 30.7 (SCH_2), 30.4 (SCH_2), 29.9 (SCH_2), 29.8 (SCH_2), 26.3 × 3 ($SiC(\underline{C}H_3)_3$), 26.2 × 3 ($SiC(\underline{C}H_3)_3$), 26.2 ($SCH_2\underline{C}H_2$), 26.1 ($SCH_2\underline{C}H_2$), 18.4 × 2 (SiC × 2), -3.4 ($SiCH_3$), -3.6 ($SiCH_3$), -4.5 ($SiCH_3$), -4.7 ($SiCH_3$)

ES$^+$ ***m/z*** (%) 697 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{32}H_{58}O_3S_4Si_2Na$ $(M+Na)^+$: Calcd 697.2699; Measured 697.2696

8.18 (1*S*,3*R*)-[3-(*tert*-Butyl-dimethyl-silanyloxy]-6,10-dithia-spiro[4.5] dec-1-yl]-methanol (1.91)



^{t}BuLi (1.5 M solution in pentane, titrated conc. 1.1 M; 4.7 mL, 5.2 mmol) was added to a solution of dithiane **1.94** (1.50 g, 6.38 mmol) and HMPA (17.0 mL) in THF (149 mL) containing 4 Å molecular sieves (20 g) at -78 °C and the mixture was stirred for 10 minutes. Bis-epoxide **1.95** (0.471 g, 4.70 mmol) in THF (1 mL) was added and the mixture was stirred at -30 °C for 1 hour. Sat. NH_4Cl (50 mL) was added and the aqueous layer was extracted with Et_2O (3 × 100 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by column chromatography (EtOAc/petroleum ether 2:8) to afford **1.94** as a colourless oil (1.19 g, 76%) together with small amounts of **3.12** (52.0 mg, 3%) and **3.6** (39.0 mg, 2%), both as colourless oils.

M.W. 350.52

Data for 1.91

$[\alpha]_D$ = +2.5 (*c* 0.85, $CHCl_3$, 25 °C)

IR ν_{max}/cm^{-1} 3444 m, 2952 s, 2928 s, 2899 s, 2854 s, 1471 m, 1254 s, 1087 s, 835 s

^{1}H NMR (400 MHz, $CDCl_3$) 4.40 (1H, m, CHOSi), 3.90 (1H, ddd, *J* = 12.0, 8.0, 4.0 Hz, $C\underline{H}_aH_bOH$; simplifies to dd, *J* = 12.0, 8.0 Hz upon D_2O treatment), 3.70 (1H, ddd, *J* = 12.0, 8.5, 5.5 Hz, $CH_a\underline{H}_bOH$; simplifies to dd, *J* = 12.0, 5.5 upon D_2O treatment), 3.05 (1H, ddd, *J* = 14.5, 11.5, 3.0 Hz, $SC\underline{H}_aH_b$), 2.99 (1H, dd, *J* = 14.0, 7.5 Hz, $SCC\underline{H}_aH_b$), 2.97 (1H, ddd, *J* = 14.5, 11.5, 3.0 Hz, $SC\underline{H}_cH_d$), 2.74-2.83 (2H, m, $SCH_a\underline{H}_b$ + $SCH_c\underline{H}_d$), 2.62 (1H, qd, *J* = 8.5, 5.5 Hz, $C\underline{H}CH_2OH$), 2.33 (1H, m, OH; disappears upon D_2O treatment), 2.13 (1H, dd, *J* = 14.0, 5.5 Hz, $SCCH_a\underline{H}_b$), 2.10 (1H, m, $SCH_2C\underline{H}_aH_b$), 1.82-1.98 (3H, m, $SCH_2CH_a\underline{H}_b$ + $CHC\underline{H}_2CH$), 0.87 (9H, s, $SiC(CH_3)_3$), 0.03 (6H, s, $SiCH_3$ × 2)

^{13}C NMR (100 MHz, $CDCl_3$) 71.1 (CHOSi), 63.4 (CH_2OH), 56.6 (SCS), 52.8 ($SCCH_2$), 51.4 ($\underline{C}HCH_2OH$), 37.4 ($CH\underline{C}H_2CH$), 28.9 (SCH_2), 26.9 (SCH_2), 25.8 ($SCH_2\underline{C}H_2$), 25.7 × 3 ($SiC(\underline{C}H_3)_3$), 18.0 (SiC), -4.8 × 2 ($SiCH_3$ × 2)

CIMS *m/z* (%) 335 ($(M+H)^+$, 22), 317 (14), 277 (28), 259 (100), 203 (100), 185 (85)

Anal Calcd for $C_{15}H_{30}O_2S_2Si$: C, 53.84; H, 9.04. Found: C, 54.20; H, 9.39.

Data for (2*R*)-3-(1,3-dithian-2-yl)-1-((*R*)-oxiran-2-yl)propan-2-yloxy-*tert*-butyl dimethylsilane (3.12)

$[\alpha]_D$ = -9.8 (*c* = 1.2, $CHCl_3$, 25 °C)

IR ν_{max}/cm^{-1} 2951 w, 2928 w, 2896 w, 2855 w, 1507 w, 1472 w, 1463 w, 1423 w, 1414 w, 1388 w, 1372 w

^{1}H NMR (400 MHz, $CDCl_3$) 4.18 (1H, ddt, *J* = 7.5, 6.5, 5.0 Hz, CHOSi), 4.07 (1H, dd, *J* = 8.5, 6.5 Hz, SCHS), 3.01 (1H, dddd, *J* = 6.5, 5.5, 4.0, 3.0 Hz, $CH_2C\underline{H}$), 2.77-2.92 (5H, m, SCH_2 × 2 + $C\underline{H}_aH_bCH$), 2.49 (1H, dd, *J* = 5.5, 3.0 Hz, $CH_a\underline{H}_bCH$), 2.08-2.15 (2H, m, $SCH_2C\underline{H}_2$), 1.83-1.98 (2H, m, $SCCH_2$), 1.73 (1H, ddd, *J* = 14.0, 6.0, 5.5 Hz, $CHC\underline{H}_aH_bCH$), 1.66 (1H, ddd, *J* = 14.0, 6.5, 5.0 Hz, $CHCH_a\underline{H}_bCH$), 0.91 (1H, s, $SiC(CH_3)_3$), 0.14 (3H, s, $SiCH_3$), 0.11 (3H, s, $SiCH_3$)

^{13}C NMR (100 MHz, $CDCl_3$) 67.1 (CHOSi), 49.4 ($CH_2\underline{C}H$), 47.7 ($\underline{C}H_2CH$), 43.8 (SCHS), 43.5 ($SCCH_2$), 40.8 ($CH\underline{C}H_2CH$), 30.6 (SCH_2), 30.3 (SCH_2), 26.1 ($SCH_2\underline{C}H_2$),

26.0 × 3 ($SiC(\underline{C}H_3)_3$), 18.0 (SiC), -4.8 × 2 ($SiCH_3$ × 2)

ES$^+$ ***m/z*** (%) 357 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{15}H_{31}O_2S_2Si$ $(M+H)^+$: Calcd 335.1529; Measured 335.1525.

Data for (8*R*,10*R*)-10-*tert*-butyldimethylsilanyloxy-1,5-dithiaspiro[5.5]undecan-8-ol (3.6)

$[\alpha]_D$ = +2.3 (*c* = 0.95, $CHCl_3$, 25 °C)

IR ν_{max}/cm^{-1} 3555 br, 2949 m, 2929 m, 2092 w, 2855 m, 1471 w, 1462 w, 1435 w, 1423 w, 1377 w

^{1}H NMR (400 MHz, $CDCl_3$) 3.88-3.97 (2H, m, C<u>H</u>OH + CHOSi), 2.73-2.91 (3H, m, SCH_2 + $SC\underline{H_a}H_b$), 2.66 (1H, ddd, *J* = 14.5, 7.0, 4.0 Hz, $SCH_a\underline{H_b}$), 2.55 (1H, ddt, *J* = 13.0, 4.5, 2.0 Hz, $C\underline{H_a}H_b$)*, 2.44 (1H, ddt, *J* = 13.5, 4.5, 2.0 Hz, $C\underline{H_c}H_d$), 2.23 (1H, ddt, *J* = 12.0, 4.5, 2.0 Hz, $C\underline{H_e}H_f$), 1.84-1.98 (2H, m, $SCH_2C\underline{H_2}$), 1.48-1.66 (3H, m, OH + $CH_a\underline{H_b}$ + $CH_c\underline{H_d}$), 1.35 (1H, q, *J* = 11.5 Hz, $CH_e\underline{H_f}$), 0.90 (9H, s, $SiC(CH_3)_3$), 0.09 (3H, s, $SiCH_3$), 0.08 (3H, s, $SiCH_3$)

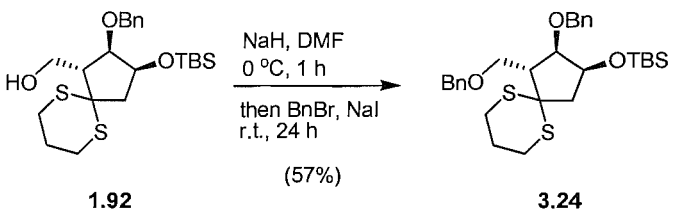
^{13}C NMR (100 MHz, $CDCl_3$) 66.0 (CH), 65.8 (CH), 47.6 (SCS), 46.1 (CH_2), 45.4 × 2 (CH_2 × 2), 26.6 (SCH_2), 26.1 (SCH_2), 26.0 × 3 ($SiC(\underline{C}H_3)_3$), 25.8 ($SCH_2\underline{C}H_2$), 18.3 (SiC), -4.6 × 2 ($SiCH_3$ × 2)

ES$^+$ ***m/z*** (%) 357 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{15}H_{30}O_2S_2SiNa$ $(M+Na)^+$: Calcd 357.1349; Measured 357.1352.

*It was not possible to distinguish between the ^{1}H and ^{13}C NMR signals of the three CH_2 groups and the two CH groups.

8.19 (2*S*,3*R*,4*R*)-(3-Benzyloxy-4-benzyloxymethyl-6,10-dithiaspiro[4.5]dec-2-yloxy)-*tert*-butyldimethylsilane (3.24)



1.92 **3.24**

NaH (60% dispersion in mineral oil; 12.0 mg, 0.30 mmol) was added to a solution of **1.92** (42.0 mg, 0.095 mmol) in DMF (1.0 mL) at 0 °C. The mixture was stirred at 0 °C for 1 hour. BnBr (20 μL, 0.168 mmol) was added and the reaction mixture was warmed to room temperature. NaI (21.0 mg, 0.140 mmol) was added and the mixture was stirred for 24 hours. Sat. NH_4Cl (10 mL) was added, followed by H_2O (10 mL) and Et_2O (10 mL). The aqueous layer was extracted with Et_2O (2 × 10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by column chromatography (EtOAc/petroleum ether 1:9) to give **3.24** as a clear oil (29.0 mg, 57%).

M.W. 530.86

$[\alpha]_D$ = +35.3 (c = 0.6, $CHCl_3$, 24 °C)

IR ν_{max}/cm^{-1} 2951 w, 2898 w, 2856 w, 1497 w, 1472 w, 1362 w

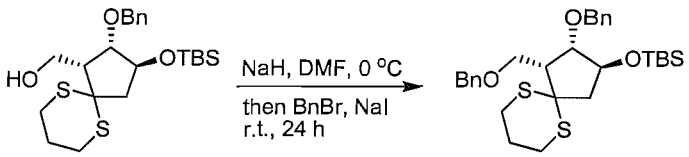
^{1}H NMR (400 MHz, $CDCl_3$) 7.28-7.40 (10H, m, ArH), 4.76 (1H, d, J = 12.0 Hz, $C\underline{H}_aH_bPh$), 4.63 (1H, d, J = 12.0 Hz, $C\underline{H}_cH_dPh$), 4.58 (1H, d, J = 12.0 Hz, $CH_c\underline{H}_dPh$), 4.56 (1H, d, J = 12.0 Hz, $CH_a\underline{H}_bPh$), 4.40 (1H, dt, J = 6.5, 5.0 Hz, CHOSi), 3.90 (1H, dd, J = 10.0, 6.0 Hz, $C\underline{H}_aH_bOBn$), 3.84 (1H, dd, J = 7.0, 5.0 Hz, CHOBn), 3.74 (1H, dd, J = 10.0, 6.0 Hz, $CH_a\underline{H}_bOBn$), 3.08 (1H, ddd, J = 14.0, 11.0, 3.0 Hz, $SC\underline{H}_aH_b$), 2.95 (1H, ddd, J = 14.0, 10.5, 3.0 Hz, $SC\underline{H}_cH_d$), 2.79-2.92 (2H, m, $SCH_a\underline{H}_b$ + $SCH_c\underline{H}_d$), 2.78 (1H, dd, J = 13.5, 5.5 Hz, $SCSC\underline{H}_aH_b$), 2.69 (1H, dt, J = 7.0, 6.0 Hz, $C\underline{H}CH_2OBn$), 2.48 (1H, dd, J = 13.5, 6.5 Hz, $SCSCH_a\underline{H}_b$), 2.08 (1H, m, $SCH_2C\underline{H}_aH_b$), 1.94 (1H, m, $SCH_2CH_a\underline{H}_b$), 0.97 (9H, s, $SiC(CH_3)_3$), 0.14 (6H, s, $SiCH_3$ × 2)

^{13}C NMR (100 MHz, $CDCl_3$) 139.0 (C_{Ar}), 138.6 (C_{Ar}), 128.4 × 2 (CH_{Ar} × 2), 128.3 × 2 (CH_{Ar} × 2), 127.8 × 4 (CH_{Ar} × 4), 127.5 (CH_{Ar}), 127.4 (CH_{Ar}), 81.2 (CHOBn), 73.0 (CH_2Ph), 72.0 (CH_2Ph), 71.2 (CHOSi), 68.4 (CH_2OBn), 56.4 ($\underline{C}HCH_2OBn$), 52.5 (SCS), 49.6 ($SCS\underline{C}H_2$), 28.8 (SCH_2), 27.7 (SCH_2), 26.1 × 3 ($SiC(\underline{C}H_3)_3$), 25.5 ($SCH_2\underline{C}H_2$), 18.4 (SiC), -4.5 × 2 ($SiCH_3$ × 2)

ES$^+$ *m/z* (%) 553 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{29}H_{43}O_3S_2Si$ $(M+H)^+$: Calcd 531.2418; Measured 531.2420.

8.20 (2*S*,3*S*,4*R*)-(3-Benzyloxy-4-benzyloxymethyl-6,10-dithiaspiro[4.5] dec-2-yloxy)-*tert*-butyldimethylsilane (3.25)



1.93 **3.25**

NaH (60% dispersion in mineral oil; 18.0 mg, 0.450 mmol) was added to a solution of **1.93** (97.0 mg, 0.220 mmol) in DMF (2.2 mL) at 0 °C. The mixture was stirred at 0 °C for 1 hour. BnBr (40.0 μL, 0.336 mmol) was added and the reaction mixture was warmed to room temperature. NaI (63.0 mg, 0.420 mmol) was added and the mixture was stirred for 24 hours. Sat. NH_4Cl (10 mL) was added followed by H_2O (10 mL) and Et_2O (10 mL). The aqueous layer was extracted with Et_2O (2 × 10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by column chromatography (EtOAc/petroleum ether 1:9) to give **3.25** as a clear oil (10.0 mg, 9%).

M.W. 530.86

$[\alpha]_D$ = +14.1 (*c* = 0.4, $CHCl_3$, 24 °C)

IR ν_{max}/cm^{-1} 2952 w, 2898 w, 2857 w, 1491 w, 1449 w, 1362 w

^{1}H NMR (400 MHz, $CDCl_3$) 7.29-7.39 (10H, m, ArH), 4.71 (1H, d, *J* = 12.0 Hz, $C\underline{H}_aH_bPh$), 4.66 (1H, d, *J* = 12.0 Hz, $CH_a\underline{H}_bPh$), 4.60 (1H, d, *J* = 12.0 Hz, $C\underline{H}_cH_dPh$), 4.56 (1H, d, *J* = 12.0 Hz, $CH_c\underline{H}_dPh$), 4.39 (1H, ddd, *J* = 7.5, 5.5, 3.0 Hz, CHOSi), 4.18 (1H, dd, *J* = 7.0, 5.0 Hz, CHOBn), 4.02 (1H, dd, *J* = 9.5, 7.5 Hz, $C\underline{H}_aH_bOBn$), 3.84 (1H, dd, *J* = 9.5, 4.5 Hz, $CH_a\underline{H}_bOBn$), 3.05 (1H, ddd, *J* = 14.5, 10.0, 3.0 Hz, $SC\underline{H}_aH_b$), 2.86-2.97 (4H, m, $SCH_a\underline{H}_b$ + SCH_2 + $SCSC\underline{H}_aH_b$), 2.78 (1H, td, *J* = 7.0, 4.5 Hz, $C\underline{H}CH_2OBn$), 2.14 (1H, dd, *J* = 14.5, 5.5 Hz, $SCSCH_a\underline{H}_b$), 2.07 (1H, m, $SCH_2C\underline{H}_aH_b$), 1.95 (1H, m, $SCH_2CH_a\underline{H}_b$), 0.93 (9H, s, $SiC(CH_3)_3$), 0.10 (6H, s, $SiCH_3$ × 2)

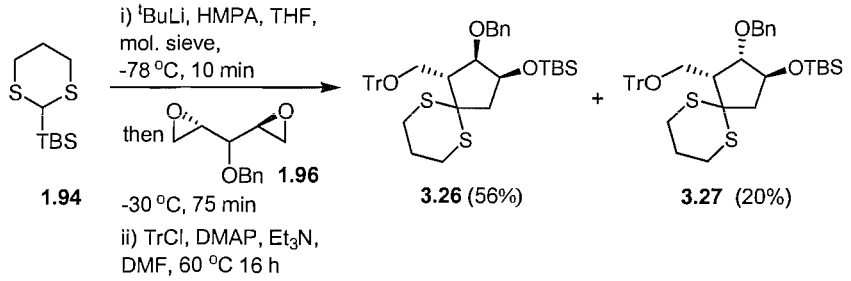
^{13}C NMR (100 MHz, $CDCl_3$) 139.0 (C_{Ar}), 138.7 (C_{Ar}), 128.4 × 2 (CH_{Ar} × 2), 128.3 × 2 (CH_{Ar} × 2), 127.8 × 2 (CH_{Ar} × 2), 127.5 × 3 (CH_{Ar} × 3), 127.4 (CH_{Ar}), 86.9 (CHOBn), 77.0 (CHOSi), 73.4 (CH_2Ph), 72.6 (CH_2Ph), 66.9 (CH_2OBn), 55.0 (SCS), 52.9

(CHCH$_2$OBn), 50.2 (SCSCH$_2$), 28.8 (SCH$_2$), 27.9 (SCH$_2$), 25.9 × 3 (SiC(CH$_3$)$_3$), 25.2 (SCH$_2$CH$_2$), 18.1 (SiC), -4.4 (SiCH$_3$), -4.6 (SiCH$_3$)

ES$^+$ ***m/z*** (%) 553 ((M+Na)$^+$, 100)

HRMS (ES$^+$) for $C_{29}H_{43}O_3S_2Si$ (M+H)$^+$: Calcd 531.2418; Measured 531.2412.

8.21 (2*S*,3*R*,4*R*)- and (2*S*,3*S*,4*R*)-(3-Benzyloxy-4-trityloxymethyl-6,10-dithiaspiro[4.5]dec-2-yloxy)-*tert*-butyldimethylsilane (3.26) and (3.27)



^{t}BuLi (1.5 M solution in pentane, titrated conc. 1.3 M; 2.70 mL, 3.51 mmol) was added to a solution of dithiane **1.94** (0.851 g, 3.63 mmol) and HMPA (8.9 mL) in THF (80.0 mL) containing 4Å molecular sieves (~20 g) at –78 °C and the mixture was stirred for 10 minutes. Bis-epoxide **1.96** (0.555 g. 2.69 mmol) was added as a solution in THF (2 mL) and the mixture was stirred for 90 minutes at –30 °C (dry ice in acetonitrile/*o*-xylene 2:8). The reaction was quenched by the addition of sat. NH_4Cl (30 mL) and H_2O (50 mL) and the aqueous phase was extracted with Et_2O (3 × 80 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was dissolved in DMF (13.3 mL). Et_3N (0.74 mL, 5.31 mmol) and DMAP (40.0 mg, 0.327 mmol) were added followed by TrCl (1.50 g, 5.38 mmol). The mixture was stirred at 60 °C for 16 hours. After cooling to room temperature, sat NH_4Cl (5 mL) and H_2O (15 mL) were added. The aqueous phase was extracted with Et_2O (3 × 30 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by chromatography (EtOAc/petroleum ether 5:95) afforded solids which were recrystallised from ethanol to give pure crystals of **3.26** (0.944 g). Concentration of the residual solution and purificaton by chromatography (EtOAc/petroleum ether 3:97) afforded a mixture of **3.26/3.27** (0.467 g, 1:4.5) to give net yields of **3.26** and **3.27** in 56% and 20%

respectively. (Note that **3.26** and **3.27** can be separated by column chromatography using CH_2Cl_2/petroleum ether 30:70 as eluent).

M.W. 683.05 (683.2971)

Major isomer 3.26

mp 102-105 °C (EtOH)

$[\alpha]_D$ +37.5 (c = 0.65, $CHCl_3$, 24 °C)

IR ν_{max}/cm^{-1} 2949 w, 2929 w, 2898 w, 2855 w, 1491 w, 1462 w

^{1}H NMR (400 MHz, $CDCl_3$) 7.29-7.59 (20H, m, ArH), 4.76 (1H, d, J = 12.0 Hz, $C\underline{H}_aH_bPh$), 4.51 (1H, d, J = 12.0 Hz, $CH_a\underline{H}_bPh$), 4.37 (1H, dt, J = 7.5, 6.0 Hz, CHOSi), 3.73 (1H, t, J = 6.0 Hz, CHOBn), 3.61 (1H, dd, J = 9.5, 6.0 Hz, $C\underline{H}_aH_bOTr$), 3.38 (1H, dd, J = 9.5, 6.0 Hz, $CH_a\underline{H}_bOTr$), 3.08 (1H, ddd, J = 14.0, 10.5, 3.0 Hz, $SC\underline{H}_aH_b$), 2.84-2.92 (2H, m, SCH_2), 2.84 (1H, dd, J = 13.0, 6.0 Hz, $SCSC\underline{H}_aH_b$), 2.73 (1H, q, 6.0 Hz, $C\underline{H}CH_2OTr$), 2.68 (1H, ddd, J = 14.0, 6.0, 3.0 Hz, $SCH_a\underline{H}_b$), 2.43 (1H, dd, J = 13.0, 8.0 Hz, $SCSCH_a\underline{H}_b$), 2.04 (1H, m, $SCH_2C\underline{H}_aH_b$), 1.90 (1H, m, $SCH_2CH_a\underline{H}_b$), 0.99 (9H, s, $SiC(CH_3)_3$), 0.15 (3H, s, $SiCH_3$), 0.14 (3H, s, $SiCH_3$)

^{13}C NMR (100 MHz, $CDCl_3$) 144.3 × 3 (C_{Ar} × 3), 139.0, 129.1 × 6 (CH_{Ar} × 6), 128.2 × 2 (CH_{Ar} × 2), 127.8 × 6 (CH_{Ar} × 6), 127.6 × 2 (CH_{Ar} × 2), 127.2 (CH_{Ar}), 127.0 × 3 (CH_{Ar} × 3), 87.6 (CPh_3), 81.7 (CHOBn), 72.1 (CH_2Ph), 71.3 (CHOSi), 62.1 (CH_2OTr), 57.3 ($\underline{C}HCH_2OTr$), 52.4 (SCS), 50.0 ($SCS\underline{C}H_2$), 28.8 (SCH_2), 27.8 (SCH_2), 26.1 × 3 ($SiC(\underline{C}H_3)_3$), 25.4 ($SCH_2\underline{C}H_2$), 18.4 (SiC), -4.5 × 2 ($SiCH_3$ × 2)

ES$^+$ ***m/z*** (%) 705 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{41}H_{50}O_3S_2SiNa$ $(M+Na)^+$: Calcd 705.2863; Measured 705.2864.

Minor isomer 3.27

mp 50-54 °C

$[\alpha]_D$ = +20.8 (c = 1.3, $CHCl_3$, 24 °C)

IR ν_{max}/cm^{-1} 2950 w, 2929 w, 2898 w, 2856 w, 1497 w, 1472 w, 1453 w, 1363 w

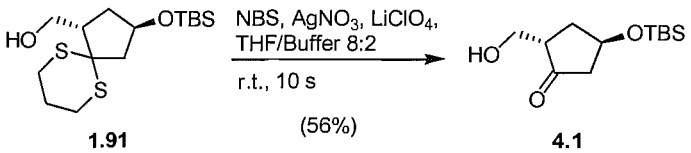
^{1}H NMR (400 MHz, $CDCl_3$) 7.26-7.56 (20H, m, ArH), 4.63 (1H, d, J = 12.5 Hz, CH_aH_bPh), 4.58 (1H, d, J = 12.5 Hz, CH_aH_bPh), 4.45 (1H, ddd, J = 7.0, 5.5, 3.0 Hz, CHOSi), 4.21 (1H, dd, J = 6.0, 3.0 Hz, CHOBn), 3.69 (1H, dd, J = 9.5, 4.5 Hz, CH_aH_bOTr), 3.60 (1H, dd, J = 9.5, 8.0 Hz, CH_aH_bOTr), 3.04 (1H, ddd, J = 14.0, 10.5, 3.0 Hz, SCH_aH_b), 2.97 (1H, dd, J = 14.0, 7.0 Hz, $SCSCH_aH_b$), 2.75-2.88 (3H, m, SCH_aH_b + SCH_cH_d + $CHCH_2OTr$), 2.68 (1H, ddd, J = 14.0, 6.0, 3.5 Hz, SCH_cH_d), 2.16 (1H, dd, J = 14.0, 5.5 Hz, $SCSCH_aH_b$), 2.03 (1H, m, $SCH_2CH_aH_b$), 1.87 (1H, m, $SCH_2CH_aH_b$), 0.98 (9H, s, $SiC(CH_3)_3$), 0.13 (6H, s, $SiCH_3$ × 2)

^{13}C NMR (100 MHz, $CDCl_3$) 144.4 × 3 (C_{Ar} × 3), 138.9 (C_{Ar}), 129.1 × 6 (CH_{Ar} × 6), 128.3 × 2 (CH_{Ar} × 2), 127.8 × 6 (CH_{Ar} × 6), 127.6 × 2 (CH_{Ar} × 2), 127.3 (CH_{Ar}), 127.0 × 3 (CH_{Ar} × 3), 87.5 (CPh_3), 87.0 (CHOBn), 77.4 (CHOSi), 72.6 (CH_2Ph), 59.9 (CH_2OTr), 55.1 (SCS), 53.9 ($CHCH_2OTr$), 50.3 ($SCSCH_2$), 28.9 (SCH_2), 27.7 (SCH_2), 26.0 × 3 ($SiC(CH_3)_3$), 25.1 (SCH_2CH_2), 18.1 (SiC), -4.4 ($SiCH_3$), -4.6 ($SiCH_3$)

ES$^+$ ***m/z*** (%) 705 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{41}H_{50}O_3S_2SiNa$ $(M+Na)^+$: Calcd 705.2863; Measured 705.2859.

8.22 (2*S*,4*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-2-hydroxymethyl cyclopentanone (4.1)



1.91 **4.1**

A solution of thioketal **1.91** (57.0 mg, 0.170 mmol) in THF (1.0 mL) was added to a solution of NBS (430 mg, 2.42 mmol), $LiClO_4$ (257 mg, 2.42 mmol) and $AgNO_3$ (412 mg, 2.43 mmol) in THF/pH 7.0 buffer (8:2; 4.4 mL). The mixture was stirred at room temperature for 10 seconds and was then poured into a mixture of sat. $NaHCO_3$ (20 mL) and Et_2O (20 mL). The aqueous layer was extracted with Et_2O (3 × 20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was

purified by column chromatography (EtOAc/petroleum ether 35:65) to afford **4.1** as a clear oil that crystallised upon storage in the fridge (23.0 mg, 55 %).

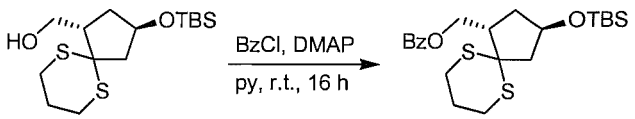
M.W. 244.40 (244.1495)

^{1}H NMR (300 MHz, $CDCl_3$) 4.54-4.56 (1H, m, CHOSi), 3.89 (1H, dd, J = 11.0, 4.5 Hz, $C\underline{H}_aH_bOH$), 3.68 (1H, dd, J = 11.0, 6.0 Hz, $CH_a\underline{H}_bOH$), 2.70 (1H, m, $C\underline{H}CH_2OH$), 2.30-2.32 (2H, m, $C\underline{H}_2CO$), 2.13 (1H, m, $CHC\underline{H}_aH_bCH$), 1.94 (1H, ddd, J = 13.0, 11.5, 4.0 Hz, $CHCH_a\underline{H}_bCH$), 0.86 (9H, s, $C(CH_3)_3$), 0.07 (3H, s, $SiCH_3$), 0.06 (3H, s, $SiCH_3$)

^{13}C NMR (75 MHz, $CDCl_3$) 217.1 (C=O), 68.4 (CHOSi), 61.8 (CH_2OH), 48.9 ($\underline{C}H_2CO$), 47.7 ($\underline{C}HCH_2OH$), 35.8 ($CH\underline{C}H_2OH$), 25.8 × 3 ($SiC(\underline{C}H_3)_3$), 18.1 (SiC), -4.7 ($SiCH_3$), -4.8 ($SiCH_3$)

^{1}H NMR and **^{13}C NMR** corresponded to the previously reported values.[174]

8.23 (1*S*,3*R*) Benzoic acid 3-(tert-butyl-dimethyl-silanyloxy)-6,10-dithia-spiro[4.5]dec-1-ylmethyl ester (4.13)



1.91 **4.13**

BzCl (0.085 mL, 0.732 mmol) and DMAP (~5 mg, 0.041mmol) were added to a solution of **1.91** (0.198 g, 0.591 mmol) in pyridine (3.2 mL). The reaction was stirred at room temperature for 16 hours. Concentration *in vacuo* and purification by column chromatography (EtOAc/petroleum ether 1:9) yielded **4.13** as a colourless oil (0.241 g, 93%).

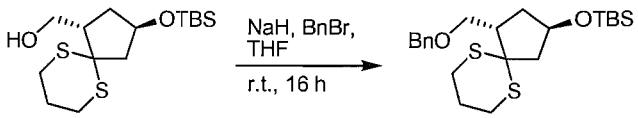
^{1}H NMR (300 MHz, $CDCl_3$) 8.06-8.09 (2H, m, ArH), 7.52-7.58 (1H, m, ArH), 7.41-7.47 (2H, m, ArH), 4.64 (1H, dd, J = 11.5, 5.5 Hz, $C\underline{H}_aH_bOBz$), 4.39 (1H, ddt, J = 7.5, 5.5, 3.5 Hz, CHOSi), 4.39 (1H, dd, J = 11.5, 7.5 Hz, $CH_a\underline{H}_bOBz$), 2.78-3.08 (6H, m,

$SCH_2 \times 2$ + $C\underline{H}CH_2OBz$ + $CHC\underline{H_a}H_bCH$), 1.86-2.23 (5H, m, $SCH_2C\underline{H_2}$ + $SCCH_2$ + $CHCH_a\underline{H_b}CH$), 0.88 (9H, s, $SiC(CH_3)_3$), 0.05 (6H, s, $SiCH_3 \times 2$)

^{13}C NMR (75 MHz, $CDCl_3$) 166.6 (C=O), 133.0 (CH_{Ar}), 130.4 (C_{Ar}), 129.8 × 2 ($CH_{Ar} \times 2$), 128.5 (CH_{Ar}), 128.4 (CH_{Ar}), 71.0 (CHOSi), 65.3 (CH_2OBz), 56.7 (SCS), 52.8 ($SC\underline{C}H_2$), 48.6 ($\underline{C}HCH_2OBz$), 38.5 ($CH\underline{C}H_2CH$), 28.9 (SCH_2), 27.4 (SCH_2), 26.0 × 3 ($SiC(\underline{C}H_3)_3$), 25.6 ($SCH_2\underline{C}H_2$), 18.2 (SiC), -4.6 × 2 ($SiCH_3 \times 2$)

^{1}H NMR and **^{13}C NMR** corresponded to the previously reported values.[174]

8.24 (2*R*,4*S*)-(4-Benzyloxymethyl-7,9-dithiaspiro[4.5]dec-2-yloxy)-*tert*-butyldimethylsilane (4.14)



1.91 **4.14**

NaH (60% dispersion in mineral oil; 0.0490 g, 1.23 mmol) was added to a solution of **1.91** (0.270 g, 0.807 mmol) in THF (5.4 mL) at 0 °C and the mixture was stirred at 0 °C for 1 hour. BnBr (0.144 mL, 1.21 mmol) was added and the reaction was stirred at room temperature for 16 hours. H_2O (5 mL) and Et_2O (10 mL) were then added and the aqueous layer was extracted with Et_2O (2 × 10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography gave **4.14** as a colourless oil (0.179 g, 52%).

M.W. 424.74 (424.1926)

$[\alpha]_D$ = -10.8 (*c* = 0.6, $CHCl_3$, 24 °C)

IR ν_{max}/cm^{-1} 2952 m, 2928 m, 2859 m, 1471 m, 1422 m, 1253 m, 1087 s

^{1}H NMR (400 MHz, $CDCl_3$) 7.26-7.35 (5H, m, ArH), 4.58 (1H, d, *J* = 12.0 Hz, $C\underline{H_a}H_bPh$), 4.53 (1H, d, *J* = 12.0 Hz, $CH_a\underline{H_b}Ph$), 4.38-4.44 (1H, m, CHOSi), 3.81 (1H, dd, *J* = 9.0, 5.0 Hz, $C\underline{H_a}H_bOBn$), 3.52 (1H, t, *J* = 9.0 Hz, $CH_a\underline{H_b}OBn$), 2.87-3.04 (3H,

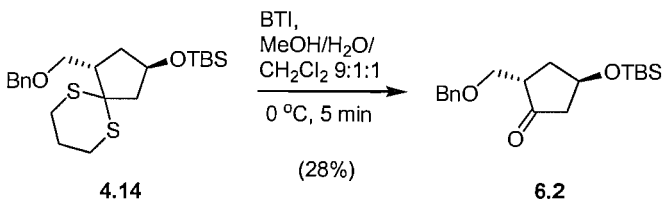
m, SCH_aH_b + SCH_cH_d + $SCCH_aH_b$), 2.65-2.84 (3H, m, SCH_aH_b + SCH_cH_d + $CHCH_2OBn$), 2.00-2.14 (4H, m, $SCH_2CH_aH_b$ + $SCCH_aH_b$ + $CHCH_2CH$), 1.83-1.94 (1H, m, $SCH_2CH_aH_b$), 0.88 (9H, s, $SiC(CH_3)_3$), 0.04 (6H, s, $SiCH_3 \times 2$)

^{13}C NMR (100 MHz, $CDCl_3$) 138.7 (C_{Ar}), 128.5 × 2 ($CH_{Ar} \times 2$), 127.7 × 2 ($CH_{Ar} \times 2$), 127.6 (CH_{Ar}), 73.3 (CH_2Ph), 71.3 (CH_2OBn), 71.2 ($CHOSi$), 56.7 (SCS), 52.7 ($SCCH_2$), 49.5 ($CHCH_2OBn$), 39.2 ($CHCH_2CH$), 28.8 (SCH_2), 27.4 (SCH_2), 26.0 × 3 ($SiC(CH_3)_3$), 25.8 (SCH_2CH_2), 18.2 (SiC), -4.6 × 2 ($SiCH_3 \times 2$)

ES$^+$ *m/z* (%) 447 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{22}H_{36}O_2S_2SiNa$ $(M+Na)^+$: Calcd 447.1818; Measured 447.1809.

8.25 (2*S*,4*R*)-4-[(*tert*-Butyl-dimethyl-silanyloxy)-2-benzyloxymethyl cyclopentanone (6.2)



4.14 **6.2**

Bis-(trifluoroacetoxy)iodobenzene (0.148 g, 0.344 mmol) was added to a solution of **4.14** (0.100 g, 0.236 mmol) in $MeOH/CH_2Cl_2/H_2O$ (9:1:1, 1 ml) and the solution was stirred at 0 °C in the dark for 15 minutes. The reaction mixture was then poured into sat. $NaHCO_3$ (2 mL), extracted with Et_2O (3 × 5 mL), dried over Na_2SO_4, concentrated *in vacuo* and purified by column chromatography (EtOAc/petroleum ether 1:9) to yield **6.2** as a colourless oil (22.0 mg, 28%).

M.W. 334.53 (334.1964)

$[\alpha]_D$ = -72.6 (*c* = 0.9, $CHCl_3$, 23 °C)

IR ν_{max}/cm^{-1} 2953 m, 2929 m, 2856 m, 1746 s, 1496 m, 1390 m

^{1}H NMR (400 MHz, $CDCl_3$) 7.21-7.30 (5H, m, ArH), 4.51 (1H, m, CHOSi), 4.47 (1H, d, *J* = 12.5 Hz, CH_aH_bPh), 4.43 (1H, d, *J* = 12.5 Hz, CH_aH_bPh), 3.70 (1H, dd, *J* = 9.5,

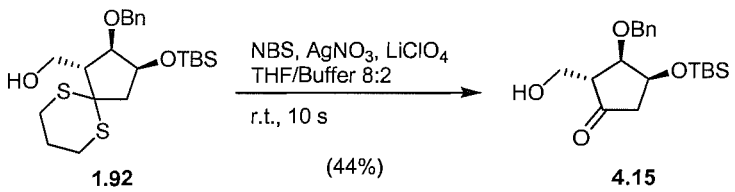
5.0 Hz, C<u>H</u>$_a$H$_b$OBn), 3.56 (1H, dd, J = 9.5, 4.0 Hz, CH$_a$<u>H</u>$_b$OBn), 2.63 (1H, tt, J = 9.5, 4.0 Hz, C<u>H</u>CH$_2$OBn), 2.29 (1H, dd, J = 18.0, 4.5 Hz, C<u>H</u>$_a$H$_b$CO), 2.21 (1H, d, J = 18.0 Hz, CH$_a$<u>H</u>$_b$CO), 2.10-2.15 (2H, m, CHC<u>H</u>$_2$CH), 0.82 (9H, s, SiC(CH$_3$)$_3$) 0.02 (3H, s, SiCH$_3$), 0.01 (3H, s, SiCH$_3$)

^{13}C NMR (100 MHz, $CDCl_3$) 218.1 (C=O), 138.4 (C_{Ar}), 128.5 × 2 (CH_{Ar} × 2), 127.7 × 2 (CH_{Ar} × 2), 127.6 (CH_{Ar}), 73.4 (CH_2Ph), 69.0 (CH_2OBn), 68.7 (CHOSi), 49.0 (CO<u>C</u>H$_2$), 46.6 (<u>C</u>HCH$_2$OBn), 36.7 (CH<u>C</u>H$_2$CH), 25.9 × 3 (SiC(<u>C</u>H$_3$)$_3$), 18.1 (SiC), -4.7 × 2 ($SiCH_3$ × 2)

ES$^+$ ***m/z*** (%) 357 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{19}H_{30}O_3SiNa$ $(M+Na)^+$: Calcd 357.1856; Measured 357.1850.

8.26 (2*R*,3*R*,4*S*)-3-Benzyloxy-4-*tert*-butyldimethylsilanyloxy-2-hydroxymethyl-cyclopentanone (4.15)



1.92 **4.15**

A solution of thioketal **1.92** (72.0 mg, 0.163 mmol) in THF (1.0 mL) was added to a solution of NBS (436 mg, 2.45 mmol), $LiClO_4$ (261 mg, 2.45 mmol) and $AgNO_3$ (416 mg, 2.45 mmol) in THF/pH 7.0 buffer (8:2, 4.5 mL). The mixture was stirred at room temperature for 10 seconds followed by the addition of sat. $NaHCO_3$ (5 mL) and H_2O (5 mL). The aqueous layer was extracted with Et_2O (3 × 5 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was purified by column chromatography (EtOAc/petroleum ether 35:65) to afford **4.15** as a white solid (25.0 mg, 44 %).

M.W. 350.52 (350.1913)

mp 54-58 °C

$[\alpha]_d$ = +3.8 (c = 0.55, $CHCl_3$, 23 °C)

IR ν_{max}/cm^{-1} 3460 br, 2952 m, 2928 m, 2884 w, 2856 m, 1746 s, 1462 m, 1390 m

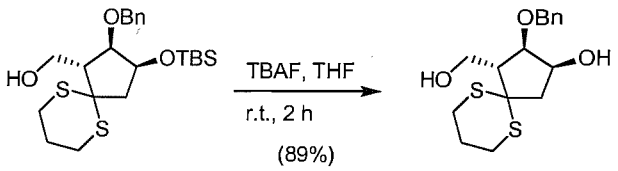
^{1}H NMR (400 MHz, $CDCl_3$) 7.26-7.34 (5H, m, ArH), 4.80 (1H, d, J = 11.5 Hz, CH_aH_bPh), 4.61 (1H, m, CHOSi), 4.51 (1H, d, J = 11.5 Hz, CH_aH_bPh), 4.01 (1H, dd, J = 11.5, 4.0 Hz, CH_aH_bOH), 3.97 (1H, dd, J = 10.5, 3.5 Hz, CHOBn), 3.73 (1H, dd, J = 11.5, 4.5 Hz, CH_aH_bOH), 2.76 (1H, m, $CHCH_2OH$), 2.43 (1H, dt, J = 18.5, 1.5 Hz, CH_aH_bCO), 2.25 (1H, dd, J = 18.5, 4.0 Hz, CH_aH_bCO), 1.72 (1H, s, OH), 0.89 (9H, s, $SiC(CH_3)_3$), 0.12 (3H, s, $SiCH_3$), 0.10 (3H, s, $SiCH_3$)

^{13}C NMR (100 MHz, $CDCl_3$) 215.0 (C=O), 138.1 (C_{Ar}), 128.6 × 2 (CH_{Ar} × 2), 128.0 (CH_{Ar}), 127.9 × 2 (CH_{Ar} × 2), 79.4 (CHOBn), 71.5 (CH_2Ph), 67.8 (CHOSi), 59.3 (CH_2OH), 53.1 ($CHCH_2OH$), 47.8 (CH_2CO), 25.8 × 3 ($SiC(CH_3)_3$), 18.2 (SiC), -4.3 × 2 ($SiCH_3$ × 2)

ES$^+$ ***m/z*** (%) 373 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{19}H_{30}O_4SiNa$ $(M+Na)^+$: Calculated 373.1805; Measured 373.1801

8.27 (1*S*,3*R*,4*R*)-3-Benzyloxy-4-hydroxymethyl-6,10-dithiaspiro[4.5] decano-2-ol (4.16)



1.92 **4.16**

TBAF (1.0 M solution in THF; 2.16 mL, 2.16 mmol) was added to a solution of **1.92** (635 mg, 1.44 mmol) in THF (10 mL) and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated *in vacuo* and the crude was purified by column chromatography (acetone/petroleum ether 3:7) to afford **4.16** (0.412 g, 89%) as a white foam.

M.W. 326.48 (326.1010)

$[\alpha]_D$ = +37.3 (c = 2.5, $CHCl_3$, 24 °C)

IR ν_{max}/cm^{-1} 3436 br, 2930 w, 2903 w, 1454 w, 1421 w, 1355 w

^{1}H NMR (400 MHz, $CDCl_3$) 7.30-7.39 (5H, m, ArH), 4.65 (1H, d, J = 11.5 Hz, CH_aH_bPh), 4.61 (1H, d, J = 11.5 Hz, CH_aH_bPh), 4.28 (1H, quintet, J = 5.5 Hz, CHOH;

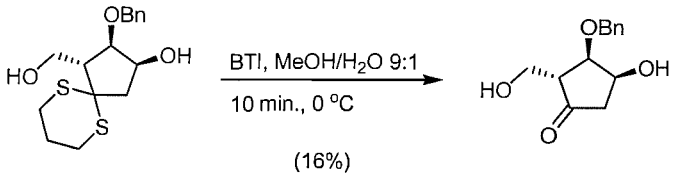
simplifies to quartet after D_2O exchange), 3.90-4.04 (3H, m, $C\underline{H}_2OH$ + CHOBn), 3.11 (1H, ddd, J = 15.0, 12.5, 2.5 Hz, $SC\underline{H}_aH_b$), 2.99 (1H, ddd, J = 14.5, 11.5, 2.5 Hz, $SC\underline{H}_cH_d$), 2.98 (1H, dd, J = 14.0, 6.0 Hz, $SCSC\underline{H}_aH_b$), 2.73-2.81 (3H, m, $SCH_a\underline{H}_b$ + $SCH_c\underline{H}_d$ + OH), 2.47-2.55 (2H, m, $C\underline{H}CH_2OH$ + OH), 2.46 (1H, dd, J = 14.0, 4.5 Hz, $SCSCH_a\underline{H}_b$), 2.13 (1H, m, $SCH_2C\underline{H}_aH_b$), 1.90 (1H, m, $SCH_2CH_2\underline{H}_b$)

^{13}C NMR (100 MHz, $CDCl_3$) 137.5 (C_{Ar}), 128.7 × 2 (CH_{Ar} × 2), 128.2 (CH_{Ar}), 128.0 × 2 (CH_{Ar} × 2), 81.2 (CHOBn), 72.7 (CH_2Ph), 69.1 (CHOH), 61.5 (CH_2OH), 56.6 ($\underline{C}HCH_2OH$), 52.6 (SCS), 49.9 ($SCS\underline{C}H_2$), 28.7 (SCH_2), 27.0 (SCH_2), 25.5 ($SCH_2\underline{C}H_2$)

ES$^+$ ***m/z*** (%) 349 ($(M+Na)^+$, 100), 675 ($(2M+Na)^+$, 12)

HRMS (ES^+) for $C_{16}H_{22}O_3S_2Na$ $(M+Na)^+$: Calcd 349.0908; Measured 349.0908.

8.28 (2*R*,3*R*,4*S*)-3-Benzyloxy-4-hydroxy-2-hydroxymethyl-cyclopentanone (4.17)



4.16 **4.17**

Bis-(trifluoroacetoxy)iodobenzene (0.337 g, 0.782 mmol) was added to a solution of **4.16** (0.161 g, 0.493 mmol) in $MeOH/H_2O$ (9:1, 2.5 ml) and the mixture was stirred at 0 °C in the dark for 10 minutes. It was then poured into sat. $NaHCO_3$ (5 mL) and the aqueous layer was extracted with Et_2O (3 × 5 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by column chromatography ($MeOH/CH_2Cl_2$ 5:95) to yield **4.17** as a crystalline solid (19.0 mg, 16%).

M.W. 236.26 (236.1049)

mp 82-84 °C

$[\alpha]_D$ = -87.5 (c = 0.4, $CHCl_3$, 24 °C)

IR ν_{max}/cm^{-1} 3241 br, 3185 br, 2878 br, 1743 s, 1497 w, 1455 w, 1427w

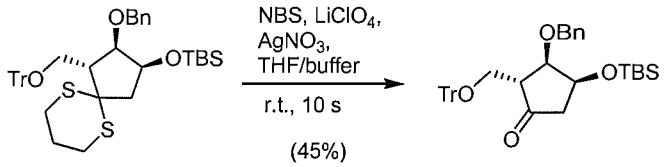
^{1}H NMR (400 MHz, $CDCl_3$) 7.33-7.40 (5H, m, ArH), 4.74 (1H, d, J = 11.5 Hz, $C\underline{H}_aH_bPh$), 4.69 (1H, d, J = 11.5 Hz, $CH_a\underline{H}_bPh$), 4.47 (1H, t, J = 4.0 Hz, $C\underline{H}OH$), 4.14 (1H, dd, J = 9.5, 4.0 Hz, CHOBn), 4.04 (1H, ddd, J = 11.0, 6.0, 4.0 Hz, $C\underline{H}_aH_bOH$), 3.73 (1H, dt, J = 11.0, 5.0 Hz, $CH_a\underline{H}_bOH$), 2.60-2.65 (2H, m, $C\underline{H}CH_2OH$ + OH), 2.58 (1H, d, J = 19.0 Hz, $C\underline{H}_aH_bCO$), 2.24 (1H, ddd, J = 19.0, 5.0, 1.5 Hz, $CH_a\underline{H}_bCO$), 1.93 (1H, t, J = 6.0 Hz)

^{13}C NMR (100 MHz, $CDCl_3$) 214.5 (C=O), 137.5 (C_{Ar}), 128.9 × 2 (CH_{Ar} × 2), 128.6 (CH_{Ar}), 128.1 × 2 (CH_{Ar} × 2), 79.1 (CHOBn), 72.4 (CH_2Ph), 66.7 (CHOH), 59.1 (CH_2OH), 53.0 ($\underline{C}HCH_2OH$), 46.0 (CH_2CO)

ES$^+$ ***m/z*** (%) 259 ($(M+Na)^+$, 70)

HRMS (ES^+) for $C_{13}H_{16}O_4Na$ $(M+Na)^+$: Calcd 259.0941; Measured 259.0941

8.29 (2*R*,3*R*,4*S*)-(3-Benzyloxy-4-(*tert*-butyldimethylsilanyloxy)-2-trityloxymethyl-cyclopentanone (4.18)



3.26 **4.18**

A solution of thioketal **3.26** (49.2 mg, 0.0720 mmol) in THF (1.0 mL) was added to a solution of NBS (190 mg, 1.07 mmol), $LiClO_4$ (115 mg, 1.08 mmol) and $AgNO_3$ (180 mg, 1.06 mmol) in THF/pH 7.0 buffer (8:2; 2.5 mL). The mixture was stirred at room temperature for 10 seconds followed by the addition of sat. $NaHCO_3$ (3 mL) and Et_2O (5 mL). The aqueous layer was extracted with Et_2O (2 × 5 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was purified by column chromatography (EtOAc/petroleum ether 5:95) to afford **4.18** as a white foam (19.0 mg, 45 %).

M.W. 592.84 (592.3009)

$[\alpha]_D$ = -6.3 (c = 1.1, $CHCl_3$, 24 °C)

IR ν_{max}/cm^{-1} 3058 w, 3030 w, 2947 w, 2926 w, 2882 w, 2854 w, 1748 m, 1490 w, 1448 w, 1389 w, 1359 w

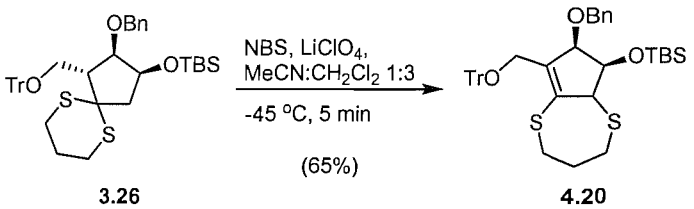
^{1}H NMR (400 MHz, $CDCl_3$) 7.26-7.45 (20H, m, ArH), 4.73 (1H, m, CHOSi), 4.67 (1H, d, J = 11.5 Hz, $C\underline{H}_aH_bPh$), 4.44 (1H, d, J = 11.5Hz, $CH_a\underline{H}_bPh$), 4.31 (1H, dd, J = 9.0, 3.5 Hz, CHOBn), 3.82 (1H, dd, J = 9.0, 3.0 Hz, $C\underline{H}_aH_bOTr$), 3.28 (1H, dd, J = 9.0, 3.0 Hz, $CH_a\underline{H}_bOTr$), 2.69 (1H, m, $C\underline{H}CH_2OTr$), 2.59 (1H, m, $COC\underline{H}_aH_b$), 2.51 (1H, dd, J = 17.5, 4.0 Hz, $COCH_a\underline{H}_b$), 0.93 (9H, s, $SiC(CH_3)_3$), 0.14 (6H, s, $SiCH_3 \times 2$)

^{13}C NMR (100 MHz, $CDCl_3$) 213.7 (C=O), 143.9 × 3 (C_{Ar} × 3), 138.2 (C_{Ar}), 128.8 × 6 (CH_{Ar} × 6), 128.4 × 2 (CH_{Ar} × 2), 128.0 × 6 (CH_{Ar} × 6), 127.8 × 2 (CH_{Ar} × 2), 127.7 (CH_{Ar}), 127.2 × 3 (CH_{Ar} × 3), 86.8 (CPh_3), 80.2 (CHOBn), 71.9 (CH_2Ph), 68.9 (CHOSi), 59.2 (CH_2OTr), 52.4 ($\underline{C}HCH_2OTr$), 47.9 ($COCH_2$), 25.9 × 3 ($SiC(\underline{C}H_3)_3$), 18.2 (SiC), -4.5 × 2 ($SiCH_3 \times 2$)

ES$^+$ ***m/z*** (%) 615 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{38}H_{44}O_4SiNa$ $(M+Na)^+$: Calcd 615.2901; Measured 615.2891.

8.30 (6*R*,7*R*)-7-Benzyloxy-8-trityloxymethyl-3,4,6,7-tetrahydro-2*H*,5a*H*-cyclopenta[b][1,4]dithiepin-6-yloxy-*tert*-butyldimethylsilane (4.20)



3.26 **4.20**

NBS (20.0 mg, 0.112 mmol) was added to a solution of **3.26** (51.2 mg, 0.0750 mmol) and $LiClO_4$ (4.0 mg, 0.0376 mmol) in CH_2Cl_2/MeCN (3:1, 3.6 mL) at –45 °C. The mixture was stirred for 5 minutes before quenching with sat. $Na_2S_2O_3$ (3 mL). H_2O (3 mL) and Et_2O (5 mL) were added and the aqueous layer was extracted with Et_2O (2 × 5 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The

crude was purified by column chromatography to afford **4.20** as a white solid (33.0 mg, 65%).

M.W. 592.84

mp 42-46 °C

$[\alpha]_D$ = -6.3 (*c* = 1.1, $CHCl_3$, 24 °C)

IR ν_{max}/cm^{-1} 3085 w, 3057 w, 2948 w, 2925 w, 2853 w, 1596 w, 1489 w, 1446 m

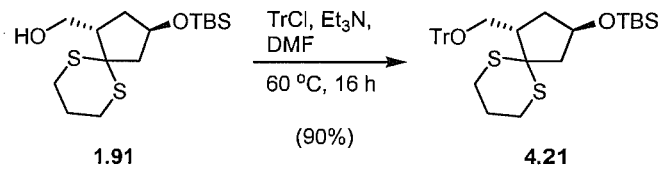
^{1}H NMR (400 MHz, $CDCl_3$) 7.26-7.45 (20H, m, ArH), 4.73 (1H, td, *J* = 4.0, 3.5 Hz, CHOSi), 4.67 (1H, d, *J* = 11.5 Hz, CH_aH_bPh), 4.44 (1H, d, *J* = 11.5 Hz, CH_aH_bPh), 4.31 (1H, dd, *J* = 9.0, 3.5 Hz, CHOBn), 3.82 (1H, dd, *J* = 9.0, 3.0 Hz, CH_aH_bOTr), 3.28 (1H, dd, *J* = 9.0, 3.0 Hz, CH_aH_bOTr), 2.69 (1H, m, $CHCH_2OTr$), 2.59 (1H, ddd, *J* = 17.5, 2.5, 1.5 Hz, $COCH_aH_b$), 2.51 (1H, dd, *J* = 17.5, 4.0 Hz, $COCH_aH_b$), 0.93 (9H, s, $SiC(CH_3)_3$), 0.14 (6H, s, $SiCH_3 \times 2$)

^{13}C NMR (100MHz, $CDCl_3$) 213.7 (C=O), 143.9 × 3 ($C_{Ar} \times 3$), 138.2 (C_{Ar}), 128.8 × 6 ($CH_{Ar} \times 6$), 128.4 × 6 ($CH_{Ar} \times 2$), 128.0 × 6 ($CH_{Ar} \times 6$), 127.8 × 6 ($CH_{Ar} \times 2$), 127.7 (CH_{Ar}), 127.2 × 3 ($CH_{Ar} \times 3$), 86.8 (CPh_3), 80.2 (CHOBn), 71.9 (CH_2Ph), 68.9 (CHOSi), 59.2 (CH_2OTr), 52.4 ($CHCH_2OTr$), 47.9 ($COCH_2$), 25.9 × 3 ($SiC(CH_3)_3$), 18.2 (SiC), -4.5 × 2 ($SiCH_3 \times 2$)

ES$^+$ ***m/z*** (%) 703 ($(M+Na)^+$, 10)

HRMS (ES^+) for $C_{41}H_{48}O_3S_2SiNa$ $(M+Na)^+$: Calcd 703.2706; Measured 703.2697.

8.31 (2*R*,4*S*)-(4-Trityloxymethyl-6,10-dithiaspiro[4.5]dec-2-yloxy)-*tert*-butyldimethylsilane (4.21)



1.91 **4.21**

TrCl (0.875 g, 3.14 mmol) was added to a solution of **1.91** (0.525 g, 1.57 mmol) and Et_3N (0.46 mL) in DMF (7.8 mL). The mixture was stirred at 60 °C for 16 hours and

then cooled to room temperature. Sat. NH_4Cl (5 mL) followed by H_2O (10 mL) and Et_2O (15 mL) were added. The aqueous phase was extracted with Et_2O (2 × 15 mL). The organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was purified by column chromatography to afford **4.21** as a white solid (0.814 g, 90%).

M.W. 576.93 (576.2552)

mp 43 - 47 °C

$[\alpha]_D$ = -16.6 (c = 0.67, $CHCl_3$, 26 °C)

IR ν_{max}/cm^{-1} 3058 w, 2952 w, 2927 m, 2901 w, 2855 m, 1490 m, 1471 m, 1462 w, 1448 m, 1422 w

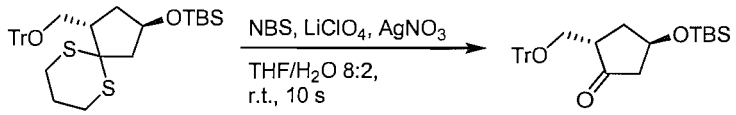
^{1}H NMR (400 MHz, $CDCl_3$) 7.21-7.50 (15H, m, ArH), 4.36 (1H, m, CHOSi), 3.52 (1H, dd, J = 9.0, 5.0 Hz, $C\underline{H}_aH_bOTr$), 3.10 (1H, t, J = 9.0 Hz, $CH_a\underline{H}_bOTr$), 2.94 (1H, ddd, J = 14.0, 10.5, 3.0 Hz, $SC\underline{H}_aH_b$), 2.87 (1H, dd, J = 14.0, 7.5 Hz, $SCSC\underline{H}_aH_b$), 2.72-2.81 (2H, m, $SCH_a\underline{H}_b$ + $SC\underline{H}_cH_d$), 2.67 (1H, qd, J = 9.0, 4.5 Hz, $C\underline{H}CH_2OTr$), 2.57 (1H, ddd, J = 14.0, 6.0, 3.0 Hz, $SCH_c\underline{H}_d$), 2.01-2.08 (3H, $C\underline{H}_2CHOSi$ + $SCSCH_a\underline{H}_b$), 1.97 (1H, m, $SCH_2C\underline{H}_aH_b$), 1.82 (1H, m, $SCH_2CH_a\underline{H}_b$), 0.90 (9H, s, $SiC(CH_3)_3$), 0.06 (3H, s, $SiCH_3$), 0.05 (3H, s, $SiCH_3$)

^{13}C NMR (100 MHz, $CDCl_3$) 144.4 × 3 (C_{Ar} × 3), 129.0 × 6 (CH_{Ar} × 6), 127.9 × 6 (CH_{Ar} × 6), 127.0 × 3 (CH_{Ar} × 3), 87.1 (CPh_3), 71.1 (CHOSi), 64.2 (CH_2OTr), 56.6 (SCS), 52.7 ($SCS\underline{C}H_2$), 50.0 ($\underline{C}HCH_2OTr$), 39.1 ($\underline{C}H_2CHOSi$), 28.8 (SCH_2), 27.4 (SCH_2), 26.1 × 3 ($SiC(\underline{C}H_3)_3$), 25.6 ($SCH_2\underline{C}H_2$), 18.3 (SiC), -4.5 × 2 ($SiCH_3$ × 2).

ES$^+$ ***m/z*** (%) 599 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{34}H_{44}O_2S_2SiNa$ $(M+Na)^+$: Calcd 599.2444; Measured 599.2438.

8.32 (2*S*,4*R*)-4-(*tert*-Butyldimethylsilanyloxy)-2-trityloxymethyl-cyclopentanone (4.22)



4.21 (48%) **4.22**

A solution of thioketal **4.21** (365 mg, 0.632 mmol) in THF (5.0 mL) was added to a solution of NBS (1.69 g, 9.49 mmol), $LiClO_4$ (1.01 g, 9.49 mmol) and $AgNO_3$ (1.61 g, 9.49 mmol) in THF/H_2O (8:2, 16 mL). The mixture was stirred at room temperature for 10 seconds and was poured into a mixture of $NaHCO_3$ (20 mL) and Et_2O (20 mL). The aqueous layer was extracted with Et_2O (3 × 20 mL). The organic phases were washed with sat. $NaHCO_3$ (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was purified by column chromatography (EtOAc/petroleum ether 1:9) to afford **4.22** as a clear oil that crystallised upon storage in the fridge (148 mg, 48 %).

M.W. 486.72 (486.2590)

$[\alpha]_D$ = -48.7 (*c* = 1.1, $CHCl_3$, 26 °C)

IR ν_{max}/cm^{-1} 3059 w, 2954 m, 2928 m, 2883 w, 2856 m, 1747 s, 1490 m, 1471 w, 1448 m, 1389 w

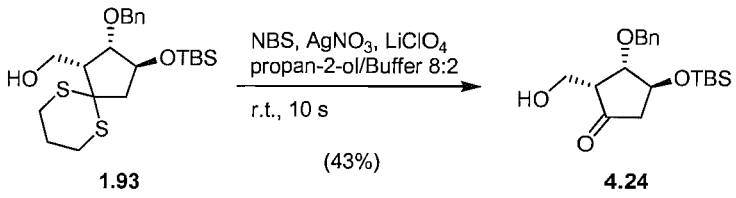
^{1}H NMR (400 MHz, $CDCl_3$) 7.21-7.43 (20H, m, ArH), 4.64 (1H, tt, *J* = 4.5, 2.5 Hz, CHOSi), 3.52 (1H, dd, *J* = 9.0, 5.0 Hz, $C\underline{H}_aH_bOTr$), 3.17 (1H, dd, *J* = 9.0, 3.5 Hz, $CH_a\underline{H}_bOTr$), 2.63 (1H, m, $C\underline{H}CH_2OTr$), 2.48 (1H, dd, *J* = 18.0, 5.0 Hz, $COC\underline{H}_aH_b$), 2.30 (1H, dtd, *J* = 18.0, 2.5, 1.0 Hz, $COCH_a\underline{H}_b$), 2.13-2.23 (2H, m, $C\underline{H}_2CHOSi$), 0.88 (9H, s, $SiC(CH_3)_3$), 0.09 (3H, s, $SiCH_3$), 0.08 (3H, s, $SiCH_3$)

^{13}C NMR (100 MHz, $CDCl_3$) 218.0 (C=O), 144.1 × 3 (C_{Ar} × 3), 128.8 × 6 (CH_{Ar} × 6), 127.9 × 6 (CH_{Ar} × 6), 127.1 × 3 (CH_{Ar} × 3), 86.7 (CPh_3), 68.9 (CHOSi), 62.3 (CH_2OTr), 49.2 ($COCH_2$), 46.6 ($\underline{C}HCH_2OTr$), 36.9 ($\underline{C}H_2CHOSi$), 25.9 × 3 ($SiC(\underline{C}H_3)_3$), 18.2 (SiC), -4.6 ($SiCH_3$), -4.7 ($SiCH_3$)

ES$^+$ ***m/z*** (%) 509 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{31}H_{38}O_3SiNa$ $(M+Na)^+$: Calcd 509.2482; Measured 509.2470.

8.33 (2*R*,3*S*,4*S*)-3-Benzyloxy-4-(*tert*-butyldimethylsilanyloxy)-2-hydroxymethyl-cyclopentanone (4.24)



1.93 **4.24**

A solution of thioketal **1.93** (480 mg, 1.09 mmol) in propan-2-ol (6.3 mL) was added to a solution of NBS (2.91 g, 16.3 mmol), $LiClO_4$ (1.74 g, 16.3 mmol) and $AgNO_3$ (2.78 g, 16.3 mmol) in propan-2-ol/pH 7.0 buffer (8:2; 30 mL). The mixture was stirred at room temperature for 10 seconds followed by the addition of sat. $NaHCO_3$ (50 mL) and H_2O (50 mL). The aqueous layer was extracted with Et_2O (3 × 80 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by column chromatography (EtOAc/petroleum ether 3:7) to afford **4.24** as a white solid (166 mg, 43%).

M.W. 350.52 (350.1913)

$[\alpha]_D$ = -88.3 (*c* = 0.35, $CHCl_3$, 26 °C)

IR ν_{max}/cm^{-1} 3460 br, 2953 m, 2929 m, 2886 w, 2857 m, 1743 s, 1497 w, 1471 w

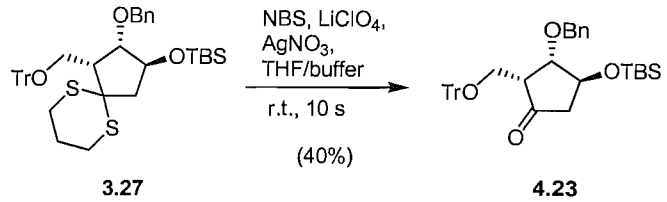
^{1}H NMR (400 MHz, $CDCl_3$) 7.30-7.40 (5H, m, ArH), 4.63 (1H, d, *J* = 12.0 Hz, $C\underline{H}_aH_bPh$), 4.51 (1H, d, *J* = 12.0 Hz, $CH_a\underline{H}_bPh$), 4.38 (1H, dt, *J* = 5.5, 1.5 Hz, CHOSi), 4.05 (1H, dt, *J* = 5.5, 2.0 Hz, CHOBn), 3.93 (1H, ddd, *J* = 11.5, 6.0, 3.5 Hz, $C\underline{H}_aH_bOH$), 3.82 (1H, ddd, *J* = 11.5, 9.0, 6.0 Hz, $CH_a\underline{H}_bOH$), 2.72 (1H, qd, *J* = 6.0, 1.5 Hz, $C\underline{H}CH_2OH$), 2.53 (1H, dd, *J* = 18.5, 5.5 Hz , $C\underline{H}_aH_bCHOSi$), 2.39 (1H, dd, *J* = 9.0, 3.5 Hz, OH), 2.14 (1H, dq, *J* = 18.5, 1.5 Hz, $CH_a\underline{H}_bCHOSi$), 0.87 (9H, s, $SiC(CH_3)_3$), 0.09 (3H, s, $SiCH_3$), 0.08 (3H, s, $SiCH_3$)

^{13}C NMR (100 MHz, $CDCl_3$) 216.9 (C=O), 137.7 (C_{Ar}), 128.8 × 2 (CH_{Ar} × 2), 128.3 (CH_{Ar}), 127.8 × 2 (CH_{Ar} × 2), 83.9 (CHOBn), 72.4 (CH_2Ph), 70.1 (CHOSi), 59.2 (CH_2OH), 52.3 ($\underline{C}HCH_2OH$), 45.6 ($\underline{C}H_2CHOSi$), 25.8 × 3 ($SiC(\underline{C}H_3)_3$), 18.1 (SiC), -4.7 × 2 ($SiCH_3$ × 2)

ES$^+$ ***m/z*** (%) 373 ($(M+Na)^+$, 100), 723 ($(2M+Na)^+$, 90)

HRMS (ES^+) for $C_{19}H_{30}O_4SiNa$ $(M+Na)^+$: Calcd 373.1805; Measured 373.1805.

8.34 (2*R*,3*R*,4*S*)-(3-Benzyloxy-4-(*tert*-butyldimethylsilanyloxy)-2-trityloxymethyl-cyclopentanone (4.23)



3.27 **4.23**

A solution of thioketal **3.27** (560 mg, 0.823 mmol) in THF (7.4 mL) was added to a solution of NBS (2.20 g, 12.4 mmol), $LiClO_4$ (1.30 g, 12.4 mmol) and $AgNO_3$ (2.10 g, 12.4 mmol) in THF/pH 7.0 buffer (8:2, 20 mL). The mixture was stirred at room temperature for 10 seconds before it was poured into a mixture of sat. $NaHCO_3$ (50 mL) and H_2O (50 mL). The aqueous layer was extracted with Et_2O (3 × 40 mL). The organic layer was washed with sat. $NaHCO_3$ (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was purified by column chromatography (CH_2Cl_2/petroleum ether 6:4) to afford **4.23** as a colourless oil (195 mg, 40%).

M.W. 592.84 (592.3009)

$[\alpha]_D$ = -23.7 (*c* = 0.45, $CHCl_3$, 28 °C)

IR ν_{max}/cm^{-1} 3060 w, 3031 w, 2928 m, 2856 m, 1747 s, 1491 m, 1471 w, 1449 m, 1388 w, 1361 w

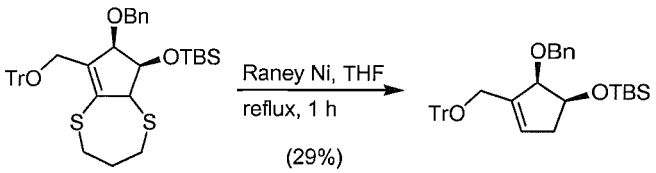
^{1}H NMR (400 MHz, $CDCl_3$) 7.09-7.36 (20H, m, ArH), 4.50 (1H, d, *J* = 12.0 Hz, $C\underline{H}_aH_bPh$), 4.46 (1H, d, *J* = 12.0 Hz, $CH_a\underline{H}_bPh$), 4.41 (1H, dt, *J* = 5.5, 2.0 Hz, CHOSi), 4.11 (1H, m, CHOBn), 3.57 (1H, dd, *J* = 9.5, 4.0 Hz, $C\underline{H}_aH_bOTr$), 3.28 (1H, t, *J* = 9.5, Hz, $CH_a\underline{H}_bOTr$), 2.85 (1H, m, $C\underline{H}CH_2OTr$), 2.46 (1H, dd, *J* = 18.5, 6.0 Hz , $C\underline{H}_aH_bCHOSi$), 2.07 (1H, dq, *J* = 18.5, 1.5 Hz , $CH_a\underline{H}_bCHOSi$), 0.85 (9H, s, $SiC(CH_3)_3$), 0.03 (3H, s, $SiCH_3$), 0.00 (3H, s, $SiCH_3$)

^{13}C NMR (100 MHz, $CDCl_3$) 215.0 (C=O), 144.2 × 3 (C_{Ar} × 3), 138.3 (C_{Ar}), 128.9 × 6 (CH_{Ar} × 6), 128.5 × 2 (CH_{Ar} × 2), 127.9 × 6 (CH_{Ar} × 6), 127.8 (CH_{Ar}), 127.7 × 2 (CH_{Ar} × 2), 127.1 × 3 (CH_{Ar} × 3), 87.1 (CPh_3), 82.7 (CHOBn), 72.5 (CH_2Ph), 70.9 (CHOSi), 58.6 (CH_2OTr), 52.2 ($\underline{C}HCH_2OTr$), 45.5 ($\underline{C}H_2CHOSi$), 25.9 × 3 ($SiC(\underline{C}H_3)_3$), 18.2 (SiC), -4.6 ($SiCH_3$), -4.7 ($SiCH_3$)

ES$^+$ ***m/z*** (%) 615 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{38}H_{44}O_4SiNa$ $(M+Na)^+$: Calcd 615.2901; Measured 615.2886.

8.35 (1*S*,2*R*)-2-Benzyloxy-3-trityloxymethylcyclopent-3-enyloxy-*tert*-butyldimethylsilane (4.39)



4.20 **4.39**

Raney Ni (slurry in water, rinsed with THF; ~2cm^3), was added to a solution of **4.20** (45.0 mg, 0.0661 mmol) in THF (0.66 mL). The mixture was stirred at reflux for 1 hour, with the addition of the same portion of catalyst every 15 minutes. After cooling to room temperature, the mixture was filtered through celite, washed with Et_2O, concentrated *in vacuo* and purified by column chromatography (EtOAc/petroleum ether 5:95) and then by HPLC (EtOAc/hexane 5:95) to afford **4.39** as a colourless oil (11 mg, 29%).

M.W. 576.84 (576.3060)

$[\alpha]_D$ = +8.4 (c = 0.4, $CHCl_3$, 26 °C)

IR ν_{max}**/cm^{-1}** 3086 w, 3060 w, 3031 w, 2952 w, 2827 w, 2855 w, 1491 w, 1471 w, 1462 m, 1361 w

^{1}H NMR (400 MHz, $CDCl_3$) 7.21-7.50 (20H, m, ArH), 6.02 (1H, m, C=CH), 4.80 (1H, d, J = 11.5 Hz, C$\underline{H}_a$H$_b$Ph), 4.55 (1H, d, J = 11.5 Hz, CH$_a\underline{H}_b$Ph), 4.45 (1H, td, J = 7.0, 6.0 Hz, CHOSi), 4.26 (1H, dd, J = 6.0, 1.0 Hz, CHOBn), 3.78 (1H, dd, J = 13.0, 1.5 Hz, C$\underline{H}_a$H$_b$OTr), 3.68 (1H, dq, J = 13.0, 2.5 Hz, CH$_a\underline{H}_b$OTr), 2.44-2.63 (2H, m, C$\underline{H}_2$CHOSi), 1.00 (9H, s, $SiC(CH_3)_3$), 0.19 (6H, s, $SiCH_3 \times 2$)

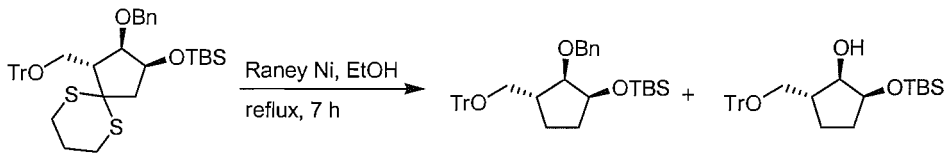
^{13}C NMR (100 MHz, $CDCl_3$) 144.3 × 3 (C_{Ar} × 3), 140.5 and 139.4 (C_{Ar} + $\underline{C}$=CH), 128.8 × 6 (CH_{Ar} × 6), 128.3 × 3 (CH_{Ar} × 3), 128.0 × 3 (CH_{Ar} × 3), 127.9 × 7 (CH_{Ar} × 6 +

C=CH), 127.3 (CH_{Ar}), 127.1 × 2 (CH_{Ar} × 2), 86.8 (CPh_3), 81.5 (CHOBn), 73.8 (CHOSi), 71.5 (CH_2Ph), 62.0 (CH_2OTr), 39.3 (CH_2CHOSi), 26.1 × 3 ($SiC(CH_3)_3$), 18.4 (SiC), -4.5 ($SiCH_3$), -4.6 ($SiCH_3$)

ES$^+$ ***m/z*** (%) 599 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{38}H_{44}O_3SiNa$ $(M+Na)^+$: Calcd 599.2952; Measured 599.2944.

8.36 (1*S*,2*R*,3*R*)-(2-Benzyloxy-3-trityloxymethyl-cyclopentyloxy)-*tert*-butyldimethylsilane (4.41)



3.26 **4.41** (11%) **4.42** (23%)

Raney nickel (slurry in water, rinsed with EtOH; ~3 cm^3) was added to a solution of **3.26** (1.17 g, 1.71 mmol) in ethanol (3.7 mL). The mixture was stirred at reflux for 2 hours with the addition of Raney nickel (~3 cm^3) every 30 minutes. After stirring for a further 5 hours, the suspension was cooled and filtered through celite. The resulting solution was concentrated *in vacuo* and purified by column chromatography (EtOAc/petroleum ether 5:95) to afford cyclopentanol **4.42** (193 mg, 23%) and benzyl ether **4.41** (110 mg, 11%), both as oils.

Data for 4.41

M.W. 578.86 (578.3216)

$[\alpha]_D$ = +36.0 (*c* = 0.50, $CHCl_3$, 24 °C)

IR ν_{max}/cm^{-1} 3085 w, 3058 w, 3027 w, 2950 w, 2853 w, 1489 w, 1447 w, 1358 w

^{1}H NMR (400 MHz, $CDCl_3$) 7.14-7.36 (20H, m, ArH), 4.60 (1H, d, *J* = 12.0 Hz, CH_aH_bPh), 4.40 (1H, d, *J* = 12.0 Hz, CH_aH_bPh), 4.07 (1H, m, CHOSi), 3.52 (1H, dd, *J* = 6.0, 4.0 Hz, CHOBn), 3.02 (1H, dd, *J* = 9.0, 6.0 Hz, CH_aH_bOTr), 3.00 (1H, dd, *J* =

9.0, 5.5 Hz, CH_aH_bOTr), 2.32 (1H, m, $CHCH_2OTr$), 1.87 (1H, m, $CH_aH_bCH_2CHOSi$), 1.64-1.69 (2H, m, CH_2CHOSi), 1.29 (1H, m, $CH_aH_bCH_2CHOSi$), 0.84 (9H, s, $SiC(CH_3)_3$), 0.00 (3H, s, $SiCH_3$), -0.01 (3H, s, $SiCH_3$)

^{13}C NMR (100 MHz, $CDCl_3$) 144.5 × 3 (C_{Ar} × 3), 139.3 (C_{Ar}), 128.9 × 6 (CH_{Ar} × 6), 128.3 × 2 (CH_{Ar} × 2), 127.8 × 6 (CH_{Ar} × 6), 127.7 × 2 (CH_{Ar} × 2), 127.3 (CH_{Ar}), 127.0 × 3 (CH_{Ar} × 3), 86.4 (CPh_3), 83.1 (CHOBn), 73.5 (CHOSi), 71.8 (CH_2Ph), 64.9 (CH_2OTr), 42.6 ($CHCH_2OTr$), 31.5 (CH_2CHOSi), 26.1 × 3 ($SiC(CH_3)_3$), 23.2 (CH_2CH_2CHOSi), 18.4 (SiC), -4.4 ($SiCH_3$), -4.5 ($SiCH_3$)

ES$^+$ ***m/z*** (%) 601 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{38}H_{46}O_3SiNa$ $(M+Na)^+$: Calcd 601.3108; Measured 601.3119.

Data for (1*R*,2*S*,5*R*)-2-*tert*-Butyldimethylsilanyloxy-5-trityloxymethyl-cyclopentanol (4.42)

M.W. 488.73 (488.2747)

$[\alpha]_D$ = +34.9 (*c* = 0.78, $CHCl_3$, 27 °C)

IR ν_{max}/cm^{-1} 3546 br, 3086 w, 3032 w, 3023 w, 2953 m, 2928 m, 2903 m, 2857 m, 1597 w, 1490 m, 1471 w, 1463 w, 1448 m

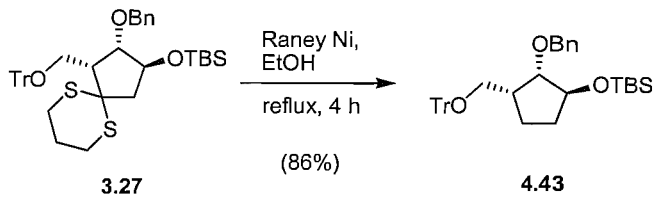
^{1}H NMR (400 MHz, $CDCl_3$) 7.21-7.46 (15H, m, ArH), 4.11 (1H, q, *J* = 5.5 Hz, CHOSi), 3.73 (1H, q, *J* = 5.5 Hz, CHOH), 3.15 (1H, dd, *J* = 9.0, 5.0 Hz, CH_aH_bOTr), 3.10 (1H, dd, *J* = 9.0, 6.0 Hz, CH_aH_bOTr), 2.54 (1H, d, *J* = 5.5 Hz, OH), 2.17 (1H, m, $CHCH_2OTr$), 1.96 (1H, dtd, *J* = 13.0, 8.5, 4.0 Hz, $CH_aH_bCH_2CH$), 1.85 (1H, m, CH_aH_bCHOH), 1.66 (1H, m, CH_aH_bCHOH), 1.34 (1H, dq, *J* = 13.0 8.5 Hz, $CH_aH_bCH_2CH$)

^{13}C NMR (100 MHz, $CDCl_3$) 144.5 × 3 (C_{Ar} × 3), 128.9 × 6 (CH_{Ar} × 6), 127.9 × 6 (CH_{Ar} × 6), 127.0 × 3 (CH_{Ar} × 3), 86.5 (CPh_3), 76.2 (CHOH), 74.6 (CHOSi), 65.3 (CH_2OTr), 45.0 ($CHCH_2OTr$), 31.6 (CH_2CHOH), 26.0 × 3 ($SiC(CH_3)_3$), 24.1 (CH_2CH_2CH), 18.3 (SiC), -4.4 ($SiCH_3$), -4.8 ($SiCH_3$)

ES$^+$ ***m/z*** (%) 511 ($(M+Na)^+$, 20)

HRMS (ES^+) for $C_{31}H_{40}O_3SiNa$ $(M+Na)^+$: Calcd 511.2639; Measured 511.2653.

8.37 (1*S*,2*S*,3*R*)-(2-Benzyloxy-3-trityloxymethyl-cyclopentyloxy)-*tert*-butyldimethylsilane (4.43)



3.27 **4.43**

Raney nickel (slurry in water, rinsed with EtOH; ~2 cm^3) was added to a solution of **3.27** (126.0 mg, 0.184 mmol) in ethanol (1.85 mL). The mixture was stirred at reflux with the addition of Raney nickel (~2 cm^3) every 30 minutes until complete conversion was evident by TLC (~4 hours). The suspension was cooled and filtered through celite. The resulting solution was concentrated *in vacuo* and purified by column chromatography (EtOAc/petroleum ether 3:97) to afford **4.43** as a colourless oil (92.0 mg, 86%).

M.W. 578.86

$[\alpha]_D$ = +11.6 (*c* = 2.1, $CHCl_3$, 24 °C)

IR ν_{max}/cm^{-1} 3084 w, 3057 w, 3029 w, 2949 w, 2854 w, 1490 w, 1447 w, 1359 w

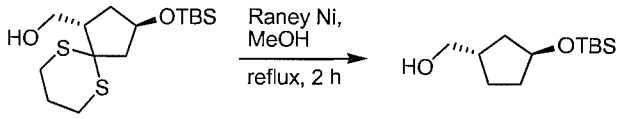
^{1}H NMR (400 MHz, $CDCl_3$) 7.07-7.42 (20H, m, ArH), 4.46 (1H, d, *J* = 12.0 Hz, $C\underline{H}_aH_bPh$), 4.36 (1H, d, *J* = 12.0 Hz, $CH_a\underline{H}_bPh$), 4.14 (1H, dt, *J* = 6.0, 2.5 Hz, CHOSi), 3.72 (1H, dd, *J* = 5.0, 2.5 Hz, CHOBn), 3.18 (1H, dd, *J* = 9.0, 7.5 Hz, $C\underline{H}_aH_bOTr$), 3.16 (1H, dd, *J* = 9.0, 6.5 Hz, $CH_a\underline{H}_bOTr$), 2.45 (1H, m, $C\underline{H}CH_2OTr$), 1.95 (1H, m, $C\underline{H}_aH_bCHOSi$), 1.80 (1H, m, $C\underline{H}_aH_bCH_2CHOSi$), 1.44 (1H, m, $CH_a\underline{H}_bCHOSi$), 1.34 (1H, m, $CH_a\underline{H}_bCH_2CHOSi$), 0.85 (9H, s, $SiC(CH_3)_3$), 0.01 (3H, s, $SiCH_3$), 0.00 (3H, s, $SiCH_3$)

^{13}C NMR (100 MHz, $CDCl_3$) 144.7 × 3 (C_{Ar} × 3), 139.2 (C_{Ar}), 129.0 × 6 (CH_{Ar} × 6), 128.3 × 2 (CH_{Ar} × 2), 128.0 × 6 (CH_{Ar} × 6), 127.5 × 2 (CH_{Ar} × 2), 127.4 (CH_{Ar}), 126.9 × 3 (CH_{Ar} × 3), 86.7 (CHOBn), 86.6 ($\underline{C}Ph_3$), 76.9 (CHOSi), 71.9 (CH_2Ph), 63.2 (CH_2OTr), 41.7 ($\underline{C}HCH_2OTr$), 32.4 ($\underline{C}H_2CHOSi$), 26.0 × 3 ($SiC(\underline{C}H_3)_3$), 25.2 ($\underline{C}H_2CH_2CHOSi$), 18.4 (SiC), -4.5 × 2 ($SiCH_3$ × 2)

ES$^+$ ***m/z*** (%) 601 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{38}H_{46}O_3SiNa$ $(M+Na)^+$: Calcd 601.31084; Measured 601.31186.

8.38 (1*S*,3*S*)-[3-(*tert*-Butyl-dimethyl-silanyloxy)-cyclopentyl]-methanol (4.2)



1.91 4.2

Raney Ni (50% slurry in water, rinsed with MeOH; ~1 cm^3) was added to a solution of **1.91** (0.0964 g, 0.288 mmol) in MeOH (3.5 mL) at reflux. Similar quantities of Raney Ni were added after 30, 60 and 90 minutes. The reaction mixture was cooled and then filtered through celite, washed with EtOH, concentrated *in vacuo* and purified by column chromatography (EtOAc/petroleum ether 25:75) to give **4.2** as a colourless oil (47.0 mg, 72%).

M.W. 230.42 (230.1702)

$[\alpha]_D$ = +0.9 (*c* = 0.8, $CHCl_3$, 23 °C)

IR ν_{max}/cm^{-1} 3338 br, 2954 m, 2928 m, 2895 w, 2857 m, 1471 w, 1361 w

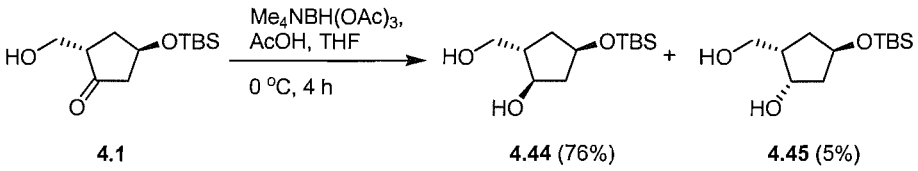
^{1}H NMR (400 MHz, $CDCl_3$) 4.27 (1H, m, CHOSi), 3.51 (2H, d, *J* = 7.0 Hz, $C\underline{H}_2OH$), 2.37 (1H, septet, *J* = 7.5 Hz, $C\underline{H}CH_2OH$), 1.91 (1H, dtd, *J* = 12.5, 8.5, 6.0 Hz, $C\underline{H}_aH_bCH_2CHOSi$), 1.79 (1H, m, $CH_2C\underline{H}_aH_bCHOSi$), 1.71 (1H, m, $CHC\underline{H}_aH_bCH$), 1.57 (1H, m, $CH_2CH_a\underline{H}_bCHOSi$), 1.42 (1H, ddd, *J* = 13.5, 8.5, 6.0 Hz, $CHCH_a\underline{H}_bCH$), 1.34 (1H, s, OH), 1.24 (1H, ddt, *J* = 12.5, 8.5, 7.0 Hz, $CH_a\underline{H}_bCH_2CHOSi$), 0.87 (9H, s, $SiC(CH_3)_3$), 0.04 (6H, s, $SiCH_3 \times 2$)

^{13}C NMR (100 MHz, $CDCl_3$) 74.1 (CHOSi), 67.5 (CH_2OH), 39.8 ($\underline{C}HCH_2OH$), 39.1 ($CH\underline{C}H_2CH$), 35.6 ($CH_2\underline{C}H_2CHOSi$), 26.6 ($\underline{C}H_2CH_2CHOSi$), 26.0 × 3 ($SiC(\underline{C}H_3)_3$), 18.3 (SiC), -4.6 × 2 ($SiCH_3$) × 2)

EIMS *m/z* (%) 173 ($(M-^tBu)^+$, 80)

HRMS (EI) for $C_8H_{17}O_2Si$ $(M-^tBu)^+$: Calcd 173.0998; Measured 173.0998.

8.39 (1*R*,2*S*,4*R*)-4-(*tert*-Butyldimethylsilanyloxy)-2-hydroxymethyl-cyclopentanol (4.44)



4.1 **4.44** (76%) **4.45** (5%)

A solution of ketone **4.1** (39.0 mg, 0.160 mmol) in THF (0.74 mL) was added to a solution of $Me_4NBH(OAc)_3$ (0.181 g, 0.654 mmol) in THF/acetic acid (1:1, 1.26 mL) at 0 °C and the mixture was stirred for 4 hours. 1 M NaOH (15 mL) was added and the aqueous layer was extracted with Et_2O (3 × 8 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was filtered through silica gel and purified by HPLC (acetone/hexane 1:3) to give the crystalline *trans*-diol **4.44** (30.0 mg, 76%) and the minor epimer **4.45** (1.9 mg, 5%).

Data for 4.44

M.W. 246.42 (246.4651)

mp 56-59 °C (CH_2Cl_2/hexane)

$[\alpha]_D$ = -7.9 (*c* = 0.98, $CHCl_3$, 26 °C)

IR ν_{max}/cm^{-1} 3350 br, 2954 m, 2928 m, 2885 w, 2856 m, 1472 w, 1463 w, 1408 w

^{1}H NMR (400 MHz, $CDCl_3$) 4.36 (1H, m, CHOSi), 4.03 (1H, br, C<u>H</u>OH), 3.65 (1H, dd, *J* = 10.5, 5.5 Hz, C<u>H$_a$</u>H$_b$OH), 3.50 (1H, dd, *J* = 10.5, 8.0 Hz, CH$_a$<u>H$_b$</u>OH), 3.05 (1H, d, *J* = 7.5 Hz, CHO<u>H</u>), 2.40 (1H, qdd, *J* = 8.5, 6.0, 3.5 Hz, C<u>H</u>CH$_2$OH), 1.87-1.97 (3H, m, C<u>H$_a$</u>H$_b$CHOSi + HOCHCH$_a$<u>H$_b$</u> + CH$_2$O<u>H</u>), 1.80 (1H, m, HOCHCH$_a$<u>H$_b$</u>), 1.41 (1H, ddd, *J* = 14.0, 8.5, 5.0 Hz, CH$_a$<u>H$_b$</u>CHOSi), 0.89 (9H, s, SiC(CH$_3$)$_3$), 0.08 (6H, s, SiCH$_3$ × 2)

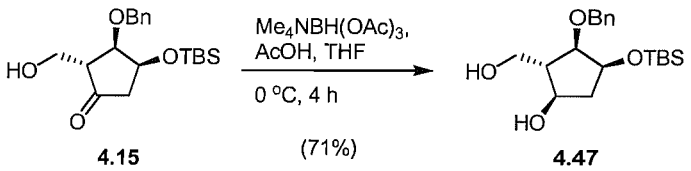
^{13}C NMR (100 MHz, $CDCl_3$) 76.7 (CHOSi), 74.1 (CHOH), 65.7 (CH_2OH), 49.8 (<u>C</u>HCH$_2$OH), 43.9 (HOCH<u>C</u>H$_2$), 37.8 (<u>C</u>H$_2$CHOSi), 26.0 × 3 (SiC(<u>C</u>H$_3$)$_3$), 18.1 (SiC), -4.7 ($SiCH_3$), -4.8 ($SiCH_3$)

ES$^+$ ***m/z*** (%) 269 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{12}H_{26}O_3SiNa$ $(M+Na)^+$: Calcd 269.1543; Measured 269.1546.

The amount of compound **4.45** isolated was insufficient for full characterisation

8.40 (1*R*,2*S*,3*R*,4*S*)-3-Benzyloxy-4-(*tert*-butyldimethylsilanyloxy)-2-hydroxymethyl-cyclopentanol (4.47)



4.15 4.47

A solution of **4.15** (42.0 mg, 0.120 mmol) in THF (0.92 mL) was added to a solution of $Me_4NBH(OAc)_3$ (0.139 g, 0.502 mmol) in THF/acetic acid (1:1, 0.84 mL) at 0 °C and the mixture was stirred for 4 hours. 1 M NaOH (8.5 mL) was added and the aqueous layer was extracted with Et_2O (3 × 6 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was filtered through silica gel and purified by HPLC (acetone/hexane 3:7) to give **4.47** as a crystalline solid (30.0 mg, 71%).

M.W. 352.54 (352.2070)

$[\alpha]_D$ = +82.0 (*c* = 1.5, $CHCl_3$, 27 °C)

IR ν_{max}/cm^{-1} 3395 br, 2952 m, 2928 m, 2884 m, 2856 m, 1497 w, 1471 m, 1462 m, 1360 m

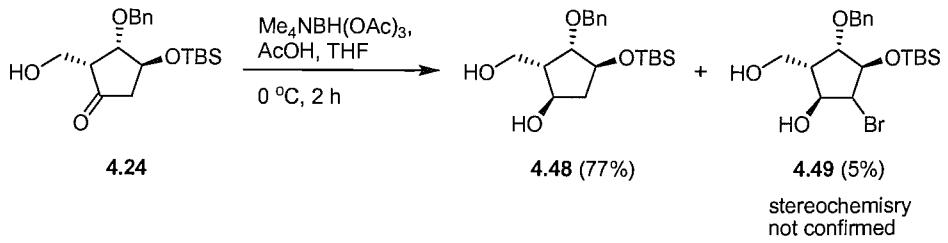
^{1}H NMR (400 MHz, $CDCl_3$) 7.27-7.35 (5H, m, ArH), 4.72 (1H, d, *J* = 12.0 Hz, CH_aH_bPh), 4.44 (1H, d, *J* = 12.0 Hz, CH_aH_bPh), 4.31 (1H, m, CHOSi), 3.92 (1H, m, CHOH), 3.80 (1H, dd, *J* = 10.5, 5.5 Hz, CH_aH_bOH), 3.65 (1H, m, CH_aH_bOH), 3.45 (1H, dd, *J* = 8.5, 3.5 Hz, CHOBn), 2.73 (1H, d, *J* = 10.0 Hz, CHOH), 2.32 (1H, m, $CHCH_2OH$), 1.89-1.95 (2H, m, CH_2OH + CH_aH_bCHOSi) 1.80 (1H, dtd, *J* = 14.5, 2.5, 1.0 Hz, CH_aH_bCHOSi), 0.93 (9H, s, $SiC(CH_3)_3$), 0.132 (3H, s, $SiCH_3$), 0.126 (3H,s, $SiCH_3$)

^{13}C NMR (100 MHz, $CDCl_3$) 138.4 (C_{Ar}), 128.5 × 2 (CH_{Ar} × 2), 127.8 × 3 (CH_{Ar} × 3), 82.7 (CHOBn), 73.4 (CHOH), 72.2 (CHOSi), 72.0 (CH_2Ph), 63.3 (CH_2OH), 54.4 ($CHCH_2OH$), 41.1 (CH_2CHOSi), 26.0 × 3 ($SiC(CH_3)_3$), 18.2 (SiC), -4.5 ($SiCH_3$), -4.6 ($SiCH_3$)

ES$^+$ ***m/z*** (%) 375 ($(M+Na)^+$, 100), 727 ($(2M+Na)^+$, 18)

HRMS (ES^+) for $C_{19}H_{32}O_4SiNa$ $(M+Na)^+$: Calcd 375.1962; Measured 375.1952.

8.41 (1*R*,2*S*,3*S*,4*S*)-3-Benzyloxy-4-(*tert*-butyldimethylsilanyloxy)-2-hydroxymethyl-cyclopentanol (4.48)



4.24 **4.48** (77%) **4.49** (5%) stereochemisry not confirmed

A solution of ketone **4.24** (63.0 mg, 0.180 mmol) in THF (0.75 mL) was added to a solution of $Me_4NBH(OAc)_3$ (0.199 g, 0.719 mmol) in THF/acetic acid (1:1; 1.28 mL) at 0 °C and the mixture was stirred for 4 hours. 1 M NaOH (13 mL) was added and the aqueous layer was extracted with Et_2O (3 × 10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was filtered through silica gel and purified by HPLC (acetone/hexane 25:75) to give the desired diol **4.48** (crystalline solid; 49.0 mg, 77%) and the bromo-diol **4.49** (oil; 4.0 mg, 5%).

Data for 4.48

M.W. 352.54 (352.2070)

$[\alpha]_D$ = -29.8 (*c* = 1.2, $CHCl_3$, 28 °C)

IR ν_{max}/cm^{-1} 3371 br, 2953 m, 2928 m, 2885 m, 2856 m, 1497 w, 1471 w, 1462 w, 1361 w

^{1}H NMR (400 MHz, $CDCl_3$) 7.27-7.38 (5H, m, ArH), 4.65 (1H, d, *J* = 12.0 Hz, $C\underline{H}_aH_bPh$), 4.49 (1H, d, *J* = 12.0 Hz, $CH_a\underline{H}_bPh$), 4.29 (1H, m, C<u>H</u>OH), 4.25 (1H, m, CHOSi), 3.99 (1H, m, CHOBn), 3.93 (1H, dt, *J* = 11.5, 4.0 Hz, $C\underline{H}_aH_bOH$), 3.85 (1H, ddd, *J* = 11.5, 8.5, 5.5 Hz, $CH_a\underline{H}_bOH$), 2.47 (1H, dd, *J* = 8.5, 4.0 Hz, $CH_2O\underline{H}$), 2.41 (1H, d, *J* = 8.0 Hz, CHO<u>H</u>), 2.32 (1H, m, C<u>H</u>CH_2OH), 2.29 (1H, ddd, *J* = 13.5, 7.0, 5.5 Hz , $C\underline{H}_aH_bCHOSi$), 1.67 (1H, dt, *J* = 13.5, 4.0 Hz, $CH_a\underline{H}_bCHOSi$), 0.90 (9H, s, $SiC(CH_3)_3$), 0.10 (6H, s, $SiCH_3 \times 2$)

^{13}C NMR (100 MHz, $CDCl_3$) 138.0 (C_{Ar}), 128.7 × 2 (CH_{Ar} × 2), 128.1 (CH_{Ar}), 127.7 × 2 (CH_{Ar} × 2), 87.9 (CHOBn), 76.2 (CHOSi), 73.8 (CHOH), 72.5 (CH_2Ph), 61.4

(CH_2OH), 52.8 ($\underline{C}HCH_2OH$), 42.2 ($\underline{C}H_2CHOSi$), 25.9 × 3 ($SiC(\underline{C}H_3)_3$), 18.0 (SiC), -4.5 ($SiCH_3$), -4.7 ($SiCH_3$)

ES$^+$ *m/z* (%) 375 ($(M+Na)^+$, 100), 727 ($(2M+Na)^+$, 77)

HRMS (ES^+) for $C_{19}H_{32}O_4SiNa$ $(M+Na)^+$: Calcd 375.1962; Measured 375.1970.

Data for (2*S*,3*S*,4*R*)-3-benzyloxy-5-bromo-4-*tert*-butyldimethylsilanyloxy-2-hydroxymethyl-cyclopentanol (4.49)

M.W. 430.44 (430.1175)

$[\alpha]_D$ = +13.6 (*c* = 0.35, $CHCl_3$, 28 °C)

IR ν_{max}/cm^{-1} 3408 br, 2952 m, 2928 m, 2885 w, 2856 m, 1471 w, 1463 w, 1361 w

^{1}H NMR (400 MHz, $CDCl_3$) 7.27-7.40 (5H, m, ArH), 4.73 (1H, d, *J* = 11.5 Hz, $C\underline{H}_aH_bPh$), 4.56 (1H, d, *J* = 11.5 Hz, $CH_a\underline{H}_bPh$), 4.44 (1H, dd, *J* = 5.0, 4.0 Hz, CHBr), 4.16-4.25 (3H, m, CHOSi + CHOH + CHOBn), 3.94 (1H, dt, *J* = 12.0, 3.0 Hz, $C\underline{H}_aH_bOH$), 3.79 (1H, ddd, *J* = 12.0, 9.5, 4.5 Hz, $CH_a\underline{H}_bOH$), 2.39-2.46 (2H, m, $C\underline{H}CH_2OH$ + $O\underline{H}$), 2.34 (1H, d, *J* = 11.0 Hz, $O\underline{H}$), 0.95 (9H, s, $SiC(CH_3)_3$), 0.17 (3H, s, $SiCH_3$), 0.14 (3H, s, $SiCH_3$)

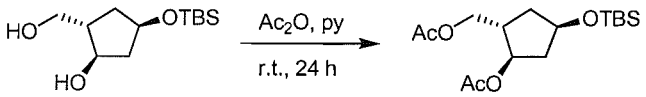
^{13}C NMR (100 MHz, $CDCl_3$) 137.5 (C_{Ar}), 128.8 × 2 (CH_{Ar} × 2), 128.3 (CH_{Ar}), 127.8 × 2 (CH_{Ar} × 2), 85.2 (CHOBn), 78.5 (CH*), 73.9 (CH*), 71.8 (CH_2Ph), 61.5 (CHBr), 60.5 (CH_2OH), 50.2 ($\underline{C}HCH_2OH$), 25.9 × 3 ($SiC(\underline{C}H_3)_3$), 18.2 (SiC), -4.4 ($SiCH_3$), -4.7 ($SiCH_3$)

ES$^+$ *m/z* (%) 431 ($(M+H)^+$, 100)

HRMS (ES^+) for $C_{19}H_3BrO_4SiNa$ $(M+Na)^+$: Calcd 453.1067; Measured 453.1060.

*Note that it was not possible to distinguish between the ^{13}C NMR signals for CHOSi and CHOH from the HMQC spectrum

8.42 (1*R*,2*S*,4*R*)-Acetic acid 2-acetoxymethyl-4-(*tert*-butyldimethyl-silanyloxy)-cyclopentyl ester (4.50)



4.44 (91%) **4.50**

Acetic anhydride (30.7 μL, 0.391 mmol) was added to a solution of diol **4.44** (20.0 mg, 0.0812 mmol) in pyridine (0.81 mL). The mixture was stirred at room temperature for 24 hours. The solvent was evaporated *in vacuo*. The crude was filtered through silica gel and purified by HPLC (acetone/hexane 22:78) to afford **4.50** as a colourless oil (24.4 mg, 91%).

M.W. 330.49 (330.1863)

$[\alpha]_D$ = -42.6 (*c* = 0.46, $CHCl_3$, 26 °C)

IR ν_{max}/cm^{-1} 2954 w, 2930 w, 2896 w, 2857 w, 1738 s, 1472 w, 1463 w, 1364 m

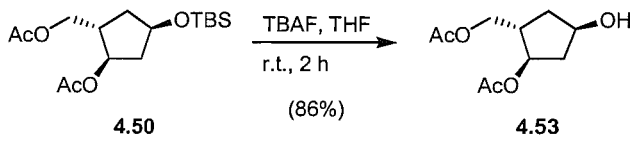
^{1}H NMR (400 MHz, $CDCl_3$) 4.88 (1H, ddd, *J* = 8.0, 6.0, 5.0 Hz, CHOAc), 4.27 (1H, tt, *J* = 5.5, 3.5 Hz, CHOSi), 4.11 (1H, dd, *J* = 11.0, 6.0 Hz, CH_aH_bOAc), 4.07 (1H, dd, *J* = 11.0, 6.0 Hz, CH_aH_bOAc), 2.62 (1H, ddq, *J* = 9.5, 8.0, 6.0 Hz, $CHCH_2OAc$), 2.32 (1H, ddd, *J* = 14.0, 8.0, 5.5 Hz, $AcOCHCH_aH_b$), 2.05 (3H, s, $COCH_3$), 2.04 (3H, s, $COCH_3$), 1.87 (1H, dddd, *J* = 13.5, 8.0, 5.0, 2.0 Hz, CH_aH_bCHOSi), 1.66 (1H, dddd, *J* = 14.0, 5.0, 3.5, 2.0 Hz, $AcOCHCH_aH_b$), 1.54 (1H, ddd, *J* = 13.5, 9.5, 5.5 Hz, CH_aH_bCHOSi), 0.89 (9H, s, $SiC(CH_3)_3$), 0.05 (3H, s, $SiCH_3$), 0.04 (3H, s, $SiCH_3$)

^{13}C NMR (100 MHz, $CDCl_3$) 171.2 (C=O), 171.1 (C=O), 76.3 (CHOAc), 71.4 (CHOSi), 65.4 (CH_2OAc), 42.7 ($CHCH_2OAc$), 42.5 ($AcOCHCH_2$), 37.8 (CH_2CHOSi), 25.9×3 ($SiC(CH_3)_3$), 21.3 ($COCH_3$), 21.0 ($COCH_3$), 18.1 (SiC), -4.7 × 2 ($SiCH_3$ × 2)

ES$^+$ ***m/z*** (%) 353 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{16}H_{30}O_5SiNa$ $(M+Na)^+$: Calcd 353.1755; Measured 353.1749.

8.43 (1*R*,2*S*,4*R*)-Acetic acid 2-acetoxymethyl-3-benzyloxy-4-hydroxy-cyclopentyl ester (4.53)



4.50 4.53

TBAF (1.0 M solution in THF; 88.0 μL, 0.0880 mmol) was added to a solution of **4.50** (13.7 mg, 0.0439 mmol) in THF (0.44 mL). The mixture was stirred at room temperature for 2 hours and the solvent was evaporated *in vacuo*. The crude was filtered through silica gel and purified by HPLC (acetone/hexane 36:64) to afford **4.53** as a clear oil (7.7 mg, 86%).

M.W. 216.23 (216.0998)

$[\alpha]_D$ = -40.0 (*c* = 0.34, $CHCl_3$, 26 °C)

IR ν_{max}/cm^{-1} 3450 br, 2943 br, 1732 vs, 1432 w, 1367 m, 1238 vs, 1046 m

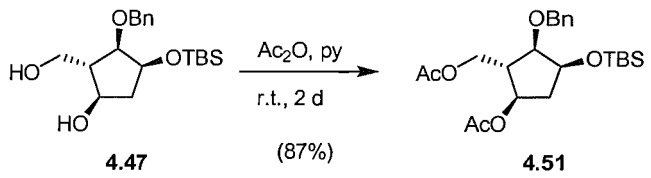
^{1}H NMR (400 MHz, $CDCl_3$) 5.00 (1H, ddd, *J* = 8.0, 5.5, 4.0 Hz, CHOAc), 4.38 (1H, qt, *J* = 5.5, 2.5 Hz, C<u>H</u>OH), 4.09-4.11 (2H, m, C<u>H$_2$</u>OAc), 2.66 (1H, ddq, *J* = 9.5, 8.0, 5.5 Hz, C<u>H</u>CH$_2$OAc), 2.34 (1H, ddd, *J* = 15.0, 7.5, 5.5 Hz, AcOCHC<u>H$_a$</u>H$_b$), 2.07 (3H, s, $COCH_3$), 2.06 (3H, s, $COCH_3$), 1.99 (1H, ddt, *J* = 14.0, 8.0, 2.5 Hz , C<u>H$_a$</u>H$_b$CHOH), 1.77 (1H, ddt, *J* = 15.0, 4.0, 2.5 Hz, AcOCHCH$_a$<u>H$_b$</u>), 1.68 (1H, d, *J* = 5.5 Hz, OH), 1.63 (1H, ddd, *J* = 14.0 , 9.5, 5.5 Hz, CH$_a$<u>H$_b$</u>CHOH)

^{13}C NMR (100 MHz, $CDCl_3$) 171.1 (C=O), 170.8 (C=O), 77.0 (CHOAc), 72.1 (CHOH), 65.2 (CH_2OAc), 43.2 (<u>C</u>HCH$_2$OAc), 41.8 (AcOCH<u>C</u>H$_2$), 37.7 (<u>C</u>H$_2$CHOH), 21.4 ($CO\underline{C}H_3$), 21.0 ($CO\underline{C}H_3$)

ES$^+$ ***m/z*** (%) 239 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{10}H_{16}O_5Na$ $(M+Na)^+$: Calcd 239.0889; Measured 239.0888.

8.44 (1*R*,2*S*,3*R*,4*S*)-Acetic acid 2-acetoxymethyl-3-benzyloxy-4-(*tert*-butyldimethylsilanyloxy)-cyclopentyl ester (4.51)



4.47 4.51

Acetic anhydride (39.0 μL, 0.413 mmol) was added to a solution of **4.47** (24 mg, 0.0681 mmol) in pyridine (0.7 mL). The mixture was stirred at room temperature for 2 days. 1 M HCl (4.3 mL) was then added. The aqueous layer was extracted with Et_2O (3 × 8 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was purified by column chromatography (acetone/petroleum ether 2:8) to afford **4.51** as a colourless oil (26 mg, 87%).

M.W. 436.61 (436.2281)

$[\alpha]_D$ = +61.6 (*c* = 0.45, $CHCl_3$, 27 °C)

IR ν_{max}/cm^{-1} 2953 w, 2929 w, 2896 w, 2856 w, 1739 s, 1472 w, 1380 w, 1362 m

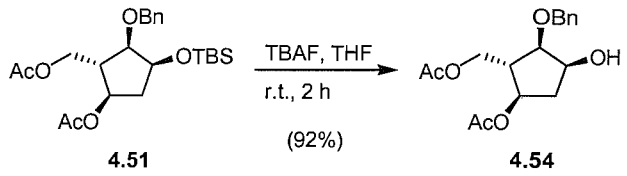
^{1}H NMR (400 MHz, $CDCl_3$) 7.27-7.34 (5H, m, ArH), 4.87 (1H, ddd, *J* = 8.5, 6.0, 3.5 Hz, CHOAc), 4.73 (1H, d, *J* = 12.0 Hz, $C\underline{H}_aH_bPh$), 4.43 (1H, d, *J* = 12.0 Hz, $CH_a\underline{H}_bPh$), 4.22 (1H, q, *J* = 4.0 Hz, CHOSi), 4.19-4.22 (2H, m, CH_2OAc), 3.46 (1H, dd, *J* = 9.0, 4.0 Hz, CHOBn), 2.63 (1H, m, $C\underline{H}CH_2OAc$), 2.14 (1H, ddd, *J* = 15.0, 8.0, 4.5 Hz, $C\underline{H}_aH_bCHOSi$), 2.03 (3H, s, $COCH_3$), 1.94 (3H, s, $COCH_3$), 1.78 (1H, dt, *J* = 15.0, 3.5 Hz, $CH_a\underline{H}_bCHOSi$), 0.93 (9H, s, $SiC(CH_3)_3$), 0.11 (3H, s, $SiCH_3$), 0.09 (3H, s, $SiCH_3$)

^{13}C NMR (100 MHz, $CDCl_3$) 171.1 (C=O), 171.0 (C=O), 138.4 (C_{Ar}), 128.5 × 2 (CH_{Ar} × 2), 127.8 × 3 (CH_{Ar} × 3), 80.3 (CHOBn), 72.9 (CHOAc), 71.8 (CH_2Ph), 70.2 (CHOSi), 62.8 (CH_2OAc), 47.4 ($\underline{C}HCH_2OAc$), 38.8 ($\underline{C}H_2CHOSi$), 25.9 × 3 ($SiC(\underline{C}H_3)_3$), 21.2 ($CO\underline{C}H_3$), 20.9 ($CO\underline{C}H_3$), 18.2 (SiC), -4.46 ($SiCH_3$), -4.53 ($SiCH_3$)

ES$^+$ ***m/z*** (%) 459 ($(M+Na)^+$, 100), 895 ($(2M+Na)^+$, 28)

HRMS (ES^+) for $C_{23}H_{36}O_6SiNa$ $(M+Na)^+$: Calcd 437.2384; Measured 437.2360.

8.45 (1*R*,2*S*,3*R*,4*S*)-Acetic acid 2-acetoxymethyl-3-benzyloxy-4-hydroxy-cyclopentyl ester (4.54)



4.51 4.54

TBAF (1.0 M solution in THF; 114 μL, 0.114 mmol) was added to a solution of **4.51** (25 mg, 0.0573 mmol) in THF (0.57 mL). The mixture was stirred at room temperature for 2 hours and the solvent was evaporated *in vacuo*. The crude was filtered through silica gel and purified by HPLC (acetone/hexane 35:65) to afford **4.54** as a clear oil (17.0 mg, 92%).

M.W. 322.35 (322.1419)

$[\alpha]_D$ = +23.6 (*c* = 0.55, $CHCl_3$, 27 °C)

IR ν_{max}/cm^{-1} 3501 br, 2944 w, 2897 w, 1735 s, 1497 w, 1455 w, 1430 w, 1381 w, 1364 m

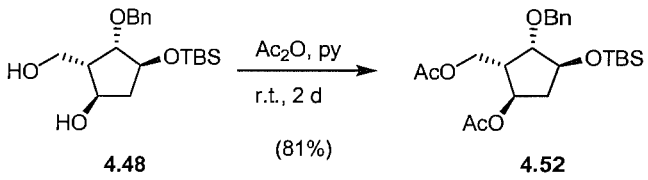
^{1}H NMR (400 MHz, $CDCl_3$) 7.30-7.39 (5H, m, ArH), 4.90 (1H, ddd, *J* = 8.5, 6.5, 4.0 Hz, CHOAc), 4.64 (1H, d, *J* = 12.0 Hz, $C\underline{H}_aH_bPh$), 4.56 (1H, d, *J* = 12.0 Hz, $CH_a\underline{H}_bPh$), 4.19-4.20 (2H, m, CH_2OAc), 4.13 (1H, m, $C\underline{H}OH$), 3.61 (1H, dd, *J* = 9.0, 4.5 Hz, CHOBn), 2.55 (1H, ddt, *J* = 9.0, 6.5, 4.5 Hz, $C\underline{H}CH_2OAc$), 2.46 (1H, dd, *J* = 3.0, 1.0 Hz, OH), 2.26 (1H, dddd, *J* = 15.5, 8.5, 5.0, 1.0 Hz , $C\underline{H}_aH_bCHOH$), 2.05 (3H, s, $COCH_3$), 1.98 (3H, s, $COCH_3$), 1.85 (1H, m, $CH_a\underline{H}_bCHOH$)

^{13}C NMR (100 MHz, $CDCl_3$) 171.0 (C=O), 170.9 (C=O), 137.6 (C_{Ar}), 128.8 × 2 (CH_{Ar} × 2), 128.4 (CH_{Ar}), 128.1 × 2 (CH_{Ar} × 2), 80.5 (CHOBn), 72.7 (CHOAc), 72.4 (CH_2Ph), 69.4 (CHOH), 62.4 (CH_2OAc), 47.3 ($\underline{C}HCH_2OAc$), 37.7 ($\underline{C}H_2CHOH$), 21.2 ($CO\underline{C}H_3$), 20.9 ($CO\underline{C}H_3$)

ES$^+$ ***m/z*** (%) 345 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{17}H_{22}O_6Na$ $(M+Na)^+$: Calcd 345.1309; Measured 345.1316.

8.46 (1*R*,2*S*,3*S*,4*S*)-Acetic acid 2-acetoxymethyl-3-benzyloxy-4-(*tert*-butyldimethylsilanyloxy)-cyclopentyl ester (4.52)



4.48 4.52

Acetic anhydride (23.0 μL, 0.243 mmol) was added to a solution of diol **4.48** (21.0 mg, 0.0596 mmol) in pyridine (0.6 mL). The mixture was stirred at room temperature for 2 days. 1 M HCl (10 mL) was then added. The aqueous layer was extracted with Et_2O (3 × 5 mL). The organic layer was washed with H_2O (5 mL) and brine (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was filtered through silica gel and purified by HPLC (acetone/hexane 17:83) to afford **4.52** as a colourless oil (21.0 mg, 81%).

M.W. 436.61 (436.2281)

$[\alpha]_D$ = -41.3 (*c* = 0.6, $CHCl_3$, 27 °C)

IR ν_{max}/cm^{-1} 2954 m, 2929 m, 2897 w, 2857 m, 1740 s, 1472 w, 1463 w, 1364 m

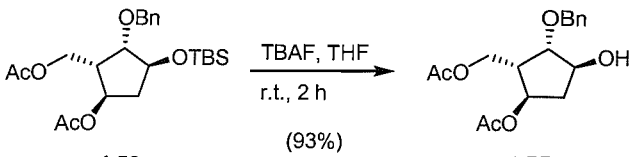
^{1}H NMR (400 MHz, $CDCl_3$) 7.27-7.36 (5H, m, ArH), 5.02 (1H, ddd, *J* = 8.5, 7.5, 4.5 Hz, CHOAc), 4.58 (1H, d, *J* = 12.0 Hz, $C\underline{H}_aH_bPh$), 4.48 (1H, d, *J* = 12.0 Hz, $CH_a\underline{H}_bPh$), 4.30 (1H, dd, *J* = 11.0, 8.0 Hz, $C\underline{H}_aH_bOAc$), 4.24 (1H, dd, *J* = 11.0, 6.5 Hz, $CH_a\underline{H}_bOAc$), 4.18 (1H, dt, *J* = 6.0, 2.5 Hz, CHOSi), 3.78 (1H, m, CHOBn), 2.66 (1H, m, $C\underline{H}CH_2OAc$), 2.59 (1H, ddd, *J* = 14.5, 8.5, 6.0 Hz, $C\underline{H}_aH_bCHOSi$), 2.03 (3H, s, $COCH_3$), 2.00 (3H, s, $COCH_3$), 1.54 (1H, dddd, *J* = 14.5, 4.0, 2.5, 1.5 Hz, $CH_a\underline{H}_bCHOSi$), 0.89 (9H, s, $SiC(CH_3)_3$), 0.060 (3H, s, $SiCH_3$), 0.057 (3H, s, $SiCH_3$)

^{13}C NMR (100 MHz, $CDCl_3$) 171.0 × 2 (C=O × 2), 138.2 (C_{Ar}), 128.5 × 2 (CH_{Ar} × 2), 127.8 (CH_{Ar}), 127.7 × 2 (CH_{Ar} × 2), 84.8 (CHOBn), 75.8 (CHOAc), 74.2 (CHOSi), 72.1 (CH_2Ph), 62.0 (CH_2OAc), 46.2 ($\underline{C}HCH_2OAc$), 40.2 ($\underline{C}H_2CHOSi$), 25.9 × 3 ($SiC(\underline{C}H_3)_3$), 21.3 ($CO\underline{C}H_3$), 21.1 ($CO\underline{C}H_3$), 18.1 (SiC), -4.57 ($SiCH_3$), -4.64 ($SiCH_3$)

ES$^+$ ***m/z*** (%) 459 ($(M+Na)^+$, 28), 895 ($(2M+Na)^+$, 100)

HRMS (ES^+) for $C_{23}H_{37}O_6Si$ $(M+H)^+$: Calcd 437.2354; Measured 437.2348.

8.47 (1*R*,2*S*,3*S*,4*S*)-Acetic acid 2-acetoxymethyl-3-benzyloxy-4-hydroxy-cyclopentyl ester (4.55)



4.52 **4.55**

TBAF (1.0 M solution in THF; 87.0 μL, 0.0870 mmol) was added to a solution of **4.52** (19.0 mg, 0.0435 mmol) in THF (0.44 mL). The mixture was stirred at room temperature for 2 hours and the solvent was evaporated *in vacuo*. The crude was filtered through silica gel and purified by HPLC (acetone/hexane 35:65) to afford **4.55** as a clear oil (13.0 mg, 93%).

M.W. 322.35 (322.1419)

$[\alpha]_D$ = -55.7 (*c* = 0.45, $CHCl_3$, 28 °C)

IR ν_{max}/cm^{-1} 3464 br, 2940 br, 1736 s, 1455 w, 1367 m, 1241 s

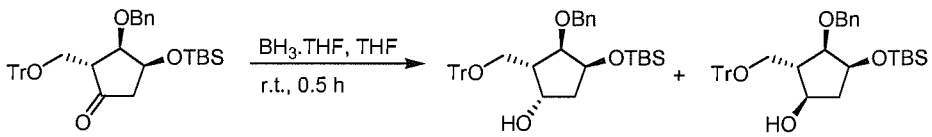
^{1}H NMR (400 MHz, $CDCl_3$) 7.27-7.37 (5H, m, ArH), 5.06 (1H, ddd, *J* = 8.5, 7.0, 4.0 Hz, CHOAc), 4.60 (1H, d, *J* = 12.0 Hz, $C\underline{H}_aH_bPh$), 4.52 (1H, d, *J* = 12.0 Hz, $CH_a\underline{H}_bPh$), 4.31 (1H, dd, *J* = 11.0, 8.0 Hz, $C\underline{H}_aH_bOAc$), 4.27 (1H, m, C<u>H</u>OH), 4.23 (1H, dd, *J* = 11.0, 6.5 Hz, $CH_a\underline{H}_bOAc$), 3.90 (1H, m, CHOBn), 2.69 (1H, m, C<u>H</u>CH_2OAc), 2.67 (1H, ddd, *J* = 15.0, 8.5, 6.5 Hz , $C\underline{H}_aH_bCHOH$), 2.05 (3H, s, $COCH_3$), 2.00 (3H, s, $COCH_3$), 1.82 (1H, d, *J* = 4.5 Hz, OH), 1.61 (1H, m, $CH_a\underline{H}_bCHOH$)

^{13}C NMR (100 MHz, $CDCl_3$) 171.0 (C=O), 170.8 (C=O), 138.1 (C_{Ar}), 128.6 × 2 (CH_{Ar} × 2), 128.0 (CH_{Ar}), 127.8 × 2 (CH_{Ar} × 2), 84.4 (CHOBn), 75.6 (CHOAc), 74.2 (CHOH), 72.3 (CH_2Ph), 61.7 (CH_2OAc), 46.3 (<u>C</u>HCH_2OAc), 39.2 (<u>C</u>H_2CHOH), 21.3 ($CO\underline{C}H_3$), 21.0 ($CO\underline{C}H_3$)

ES$^+$ ***m/z*** (%) 345 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{17}H_{22}O_6Na$ $(M+Na)^+$: Calcd 345.1309; Measured 345.1316.

8.48 (1*S*,2*S*,3*R*,4*S*)- and (1*R*,2*S*,3*R*,4*S*)-3-Benzyloxy-4-(*tert*-butyl dimethylsilanyloxy)-2-trityloxymethyl-cyclopentanol (4.56) and (4.60)



4.18 **4.56** (56%) **4.60** (29%)

BH_3 (1.0 M solution in THF; 0.21 mL, 0.210 mmol) was added to a solution of ketone **4.18** (63.4 mg, 0.107 mmol) in THF (1.1 mL) and the mixture was stirred at room temperature for 1 hour. 2 M NaOH (6 mL) was then added and the aqueous layer was extracted with Et_2O (3 × 8 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was purified by column chromatography (EtOAc/petroleum ether 1:9) to afford **4.56** (35.8 mg, 56%) and **4.60** (18.2 mg, 29%) as white foams.

M.W. 594.85 (594.3165)

Data for major isomer 4.56

$[\alpha]_D$ = +42.6 (*c* = 0.95, $CHCl_3$, 27 °C)

IR ν_{max}/cm^{-1} 3446 br, 3059 w, 3031 w, 2953 m, 2927 m, 2856 m, 1491 w, 1471 w, 1462 w, 1449 m

^{1}H NMR (400 MHz, $CDCl_3$) 7.21-7.42 (20H, m, ArH), 4.58 (1H, d, *J* = 11.5 Hz, $C\underline{H}_aH_bPh$), 4.35 (1H, d, *J* = 11.5 Hz, $CH_a\underline{H}_bPh$), 4.32 (1H, q, *J* = 3.5 Hz, CHOSi), 4.02 (1H, m, C<u>H</u>OH), 3.62 (1H, dd, *J* = 8.0, 4.0 Hz, CHOBn), 3.40 (1H, dd, *J* = 9.0, 4.0 Hz, $C\underline{H}_aH_bOTr$), 3.19 (1H, dd, *J* = 9.0, 5.5 Hz, $CH_a\underline{H}_bOTr$), 2.76 (1H, d, *J* = 10.0 Hz, OH), 2.35 (1H, m, $C\underline{H}CH_2OTr$), 1.99 (1H, ddd, *J* = 14.0, 6.5, 4.0 Hz , $C\underline{H}_aH_bCHOSi$), 1.86 (1H, m, $CH_a\underline{H}_bCHOSi$), 0.92 (9H, s, $SiC(CH_3)_3$), 0.12 (3H, s, $SiCH_3$), 0.10 (3H, s, $SiCH_3$)

^{13}C NMR (100 MHz, $CDCl_3$) 144.2 × 3 (C_{Ar} × 3), 138.6 (C_{Ar}), 128.9 × 6 (CH_{Ar} × 6), 128.3 × 2 (CH_{Ar} × 2), 127.9 × 6 (CH_{Ar} × 6), 127.7 × 2 (CH_{Ar} × 2), 127.5 (CH_{Ar}), 127.1 × 3 (CH_{Ar} × 3), 86.7 (CPh_3), 82.8 (CHOBn), 74.2 (CHOH), 73.0 (CHOSi), 72.1 (CH_2Ph),

63.0 (CH_2OTr), 53.3 ($\underline{C}HCH_2OTr$), 41.0 ($\underline{C}H_2CHOSi$), 26.0 × 3 ($SiC(\underline{C}H_3)_3$), 18.3 (SiC), -4.5 ($SiCH_3$), -4.6 ($SiCH_3$)

ES$^+$ *m/z* (%) 617 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{38}H_{46}O_4SiNa$ $(M+Na)^+$: Calcd 617.3057; Measured 617.3063.

Data for minor isomer 4.60

$[\alpha]_D$ = +66.1 (*c* = 0.80, $CHCl_3$, 27 °C)

IR ν_{max}/cm^{-1} 3490 br, 3060 w, 3031 w, 2951 w, 2928 w, 2884 w, 2855 w, 1491 w, 1471 w, 1448 m

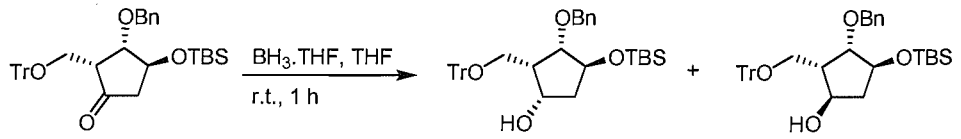
^{1}H NMR (400 MHz, $CDCl_3$) 7.23-7.43 (20H, m, ArH), 4.66 (1H, d, *J* = 12.0 Hz, $C\underline{H}_aH_bPh$), 4.50 (1H, tt, *J* = 7.0, 4.0 Hz, $C\underline{H}OH$), 4.39 (1H, m, CHOSi), 4.36 (1H, d, *J* = 12.0 Hz, $CH_a\underline{H}_bPh$), 3.69 (1H, dd, *J* = 9.0, 4.5 Hz, CHOBn), 3.51 (1H, dd, *J* = 9.5, 4.5 Hz, $C\underline{H}_aH_bOTr$), 3.24 (1H, dd, *J* = 9.5, 8.0 Hz, $CH_a\underline{H}_bOTr$), 2.57 (1H, d, *J* = 3.5 Hz, OH), 2.54 (1H, m, $C\underline{H}CH_2OTr$), 2.11 (1H, ddd, *J* = 14.0, 7.0, 3.5 Hz , $C\underline{H}_aH_bCHOSi$), 1.80 (1H, dt, *J* = 14.0, 4.5 Hz, $CH_a\underline{H}_bCHOSi$), 0.91 (9H, s, $SiC(CH_3)_3$), 0.09 (3H, s, $SiCH_3$), 0.08 (3H, s, $SiCH_3$)

^{13}C NMR (100 MHz, $CDCl_3$) 143.8 × 3 (C_{Ar} × 3), 138.8 (C_{Ar}), 128.6 × 6 (CH_{Ar} × 6), 128.3 × 2 (CH_{Ar} × 2), 128.1 × 6 (CH_{Ar} × 6), 127.6 × 2 (CH_{Ar} × 2), 127.5 (CH_{Ar}), 127.3 × 3 (CH_{Ar} × 3), 87.3 (CPh_3), 81.2 (CHOBn), 71.7 (CH_2Ph), 70.7 (CHOSi), 70.4 (CHOHi), 62.0 (CH_2OTr), 46.8 ($\underline{C}HCH_2OTr$), 42.5 ($\underline{C}H_2CHOSi$), 26.0 × 3 ($SiC(\underline{C}H_3)_3$), 18.3 (SiC), -4.4 ($SiCH_3$), -4.5 ($SiCH_3$)

ES$^+$ *m/z* (%) 617 ($(M+Na)^+$, 20)

HRMS (ES^+) for $C_{38}H_{46}O_4SiNa$ $(M+Na)^+$: Calcd 617.3058; Measured 617.3064.

8.49 (1*S*,2*S*,3*S*,4*S*) and (1*R*,2*S*,3*S*,4*S*)-3-Benzyloxy-4-(*tert*-butyl-dimethylsilanyloxy)-2-trityloxymethyl-cyclopentanol (4.58) and (4.59)



4.23 **4.58** (43%) **4.59** (33%)

BH_3 (1.0 M solution in THF; 0.245 mL, 0.245 mmol) was added to a solution of ketone **4.23** (98.0 mg, 0.165 mmol) in THF (1.7 mL) at 0 °C and the mixture was stirred at room temperature for 1 hour. 1 M NaOH (0.5 mL) was then added, followed by H_2O (3 mL). The aqueous layer was extracted with Et_2O (3 × 5 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was purified by column chromatography (EtOAc/petroleum ether 15:85) to afford **4.58** (37.0 mg, 43%) and **4.59** (28.0 mg, 33%), both as colourless oils.

M.W. 594.85 (594.3165)

Data for major isomer 4.58

$[\alpha]_D$ = +13.3 (*c* = 0.45, $CHCl_3$, 28 °C)

IR ν_{max}/cm^{-1} 3544 br, 3059 w, 3031 w, 2928 m, 2856 m, 1491 m, 1471 w, 1449 m, 1361 w

^{1}H NMR (400 MHz, $CDCl_3$) 7.09-7.45 (20H, m, ArH), 4.54 (1H, d, *J* = 12.0 Hz, CH_aH_bPh), 4.39 (1H, d, *J* = 12.0 Hz, CH_aH_bPh), 4.38 (1H, m, CHOSi), 4.32 (1H, m, CHOH), 3.85 (1H, d, *J* = 4.5 Hz, CHOBn), 3.53 (1H, dd, *J* = 9.5, 7.0 Hz, CH_aH_bOTr), 3.41 (1H, dd, *J* = 9.5, 7.5 Hz, CH_aH_bOTr), 2.45 (1H, tt, *J* = 7.5, 5.0 Hz, $CHCH_2OTr$), 2.35 (1H, d, *J* = 10.0 Hz, OH), 2.17 (1H, ddd, *J* = 15.0, 6.5, 2.0 Hz , CH_aH_bCHOSi), 1.96 (1H, ddd, *J* = 15.0, 6.5, 3.0 Hz , CH_aH_bCHOSi), 0.90 (9H, s, $SiC(CH_3)_3$), 0.08 (3H, s, $SiCH_3$), 0.06 (3H, s, $SiCH_3$)

^{13}C NMR (100 MHz, $CDCl_3$) 144.4 × 3 (C_{Ar} × 3), 138.2 (C_{Ar}), 128.9 × 6 (CH_{Ar} × 6), 128.5 × 2 (CH_{Ar} × 2), 127.9 × 6 (CH_{Ar} × 6), 127.8 (CH_{Ar}), 127.5 × 2 (CH_{Ar} × 2), 127.1 × 3 (CH_{Ar} × 3), 87.5 (CHOBn), 86.8 (CPh_3), 75.0 (CHOSi), 73.5 (CHOH), 72.2 (CH_2Ph),

59.4 (CH_2OTr), 46.9 ($\underline{C}HCH_2OTr$), 45.6 ($\underline{C}H_2CHOSi$), 26.0 × 3 ($SiC(\underline{C}H_3)_3$), 18.2 (SiC), -4.5 ($SiCH_3$), -4.6 ($SiCH_3$)

ES$^+$ ***m/z*** (%) 617 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{38}H_{46}O_4SiNa$ $(M+Na)^+$: Calcd 617.3057; Measured 617.3054.

Data for minor isomer 4.59

$[\alpha]_D$ = +23.6 (*c* = 0.35, $CHCl_3$, 28 °C)

IR ν_{max}/cm^{-1} 3450 br, 3060 w, 3031 w, 2953 m, 2928 m, 2856 m, 1491 m, 1471 w, 1449 m, 1361 m

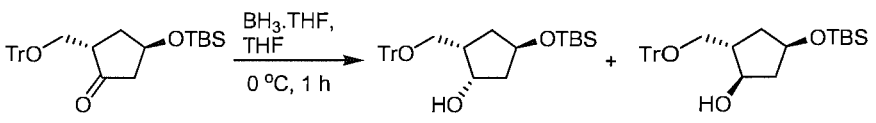
^{1}H NMR (400 MHz, $CDCl_3$) 7.05-7.44 (20H, m, ArH), 4.46 (1H, d, *J* = 12.0 Hz, $C\underline{H}_aH_bPh$), 4.32 (1H, d, *J* = 12.0 Hz, $CH_a\underline{H}_bPh$), 4.14 (1H, ddd, *J* = 5.5, 3.0, 2.0 Hz, CHOSi), 4.05 (1H, tt, *J* = 7.5, 5.5 Hz, $C\underline{H}OH$), 3.80 (1H, m, CHOBn), 3.41 (1H, dd, *J* = 9.0, 7.0 Hz, $C\underline{H}_aH_bOTr$), 3.38 (1H, dd, *J* = 9.0, 8.0 Hz, $CH_a\underline{H}_bOTr$), 2.47 (1H, m, $C\underline{H}CH_2OTr$), 2.39 (1H, d, *J* = 5.5 Hz, OH), 2.36 (1H, ddd, *J* = 14.0, 8.0, 5.5 Hz , $C\underline{H}_aH_bCHOSi$), 1.56 (1H, dddd, *J* = 14.0, 5.0, 3.5, 1.0 Hz , $CH_a\underline{H}_bCHOSi$), 0.90 (9H, s, $SiC(CH_3)_3$), 0.06 (6H, s, $SiCH_3$ × 2)

^{13}C NMR (100 MHz, $CDCl_3$) 144.3 × 3 (C_{Ar} × 3), 138.6 (C_{Ar}), 128.9 × 6 (CH_{Ar} × 6), 128.4 × 2 (CH_{Ar} × 2), 128.0 × 6 (CH_{Ar} × 6), 127.5 (CH_{Ar}), 127.4 × 2 (CH_{Ar} × 2), 127.1 × 3 (CH_{Ar} × 3), 87.2 (CPh_3), 86.4 (CHOBn), 75.8 (CHOSi), 75.5 (CHOH), 72.1 (CH_2Ph), 63.0 (CH_2OTr), 51.0 ($\underline{C}HCH_2OTr$), 42.2 ($\underline{C}H_2CHOSi$), 26.0 × 3 ($SiC(\underline{C}H_3)_3$), 18.2 (SiC), -4.5 ($SiCH_3$), -4.6 ($SiCH_3$)

ES$^+$ ***m/z*** (%) 617 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{38}H_{46}O_4SiNa$ $(M+Na)^+$: Calcd 617.3058; Measured 617.3050.

8.50 (1*S*,2*S*,4*R*)- and (1*R*,2*S*,4*R*)-4-(*tert*-Butyldimethylsilanyloxy)-2-trityloxymethyl-cyclopentanol (4.61) and (4.62)



4.22 **4.61** (70%) **4.62** (12%)

BH_3 (1.0 M solution in THF; 0.190 mL, 0.190 mmol) was added to a solution of ketone **4.22** (47.3 mg, 0.0971 mmol) in THF (0.97 mL) at 0 °C and the mixture was stirred for 1 hour. 2 M NaOH (6 mL) was then added and the aqueous layer was extracted with Et_2O (3 × 8 mL). The organic layer was washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude (5.73:1 of **4.61**:**4.62** by NMR) was filtered through silica gel and purified by HPLC (EtOAc/hexane 1:9) to afford the major diastereomer **4.61** (33.1 mg, 70 %) and the minor diastereomer **4.62** (5.6 mg, 12%) as foams.

M.W. 488.73 (488.2747)

Data for 4.61

$[\alpha]_D$ = +1.7 (*c* = 1.1, $CHCl_3$, 26 °C)

IR ν_{max}/cm^{-1} 3452 br, 3058 w, 3032 w, 2954 m, 2928 m, 2856 m, 1490 m, 1471 w, 1448

^{1}H NMR (400 MHz, $CDCl_3$) 7.22-7.45 (15H, m, ArH), 4.35 (1H, m, CHOSi), 4.01 (1H, ddt, *J* = 8.5, 6.5, 3.5 Hz, C<u>H</u>OH), 3.17 (1H, dd, *J* = 9.0, 6.0 Hz, C<u>H$_a$</u>H$_b$OTr), 3.06 (1H, d, *J* = 8.5 Hz, OH), 2.99 (1H, dd, *J* = 9.0, 7.0 Hz, CH$_a$<u>H$_b$</u>OTr), 2.53 (1H, m, C<u>H</u>CH$_2$OTr), 1.86-1.96 (2H, m, C<u>H$_a$</u>H$_b$CHOSi + OCHC<u>H$_a$</u>H$_b$CHO), 1.79 (1H, m, OCHCH$_a$<u>H$_b$</u>CHO), 1.47 (1H, ddd, *J* = 14.0, 8.5, 5.5 Hz, CH$_a$<u>H$_b$</u>CHOSi), 0.90 (9H, s, SiC(CH$_3$)$_3$), 0.08 (6H, s, SiCH$_3$ × 2)

^{13}C NMR (100 MHz, $CDCl_3$) 144.3 × 3 (C_{Ar} × 3), 128.8 × 6 (CH_{Ar} × 6), 127.9 × 6 (CH_{Ar} × 6), 127.1 × 3 (CH_{Ar} × 3), 86.7 (CPh_3), 77.1 (CHOSi), 74.3 (CHOH), 66.1 (CH_2OTr), 47.7 (<u>C</u>HCH$_2$OTr), 43.8 (HOCH<u>C</u>H$_2$), 38.2 (TrOCH$_2$CHCH$_2$), 26.0 × 3 (SiC(<u>C</u>H$_3$)$_3$), 18.1 (SiC), -4.7 ($SiCH_3$), -4.8 ($SiCH_3$)

ES$^+$ ***m/z*** (%) 511 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{31}H_{40}O_3SiNa$ $(M+Na)^+$: Calcd 511.2639; Measured 511.2628.

Data for 4.62

$[\alpha]_D$ = +30.5 (*c* = 0.32, $CHCl_3$, 26 °C)

IR ν_{max}/cm^{-1} 3448 br, 3086 w, 3059 w, 3032 w, 2954 m, 2928 m, 2855 m, 1490 m, 1471 w, 1448 m

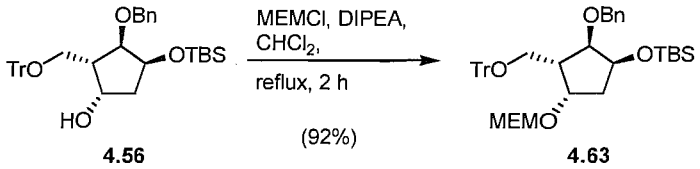
^{1}H NMR (400 MHz, $CDCl_3$) 7.23-7.45 (15H, m, ArH), 4.35 (1H, tt, J = 5.0, 2.5 Hz, CHOH), 4.43 (1H, tdd, J = 6.5, 4.5, 2.5 Hz, CHOSi), 3.41 (1H, dd, J = 9.0, 5.0 Hz, $C\underline{H_a}H_bOTr$), 3.06 (1H, t, J = 9.0 Hz, $CH_a\underline{H_b}OTr$), 2.55 (1H, m, $C\underline{H}CH_2OTr$), 2.05 (1H, dd, J = 2.5, 1.0 Hz, OH), 1.97 (1H, ddd, J = 14.5, 6.5, 2.5 Hz, $OCHC\underline{Ha}HbCHO$), 1.86 (1H, m, $OCHCH_a\underline{H_b}CHO$), 1.68 (1H, ddd, J = 13.0, 11.0, 6.5 Hz, $C\underline{H_a}H_bCHOSi$), 1.56 (1H, ddd, J = 13.0, 8.0, 2.5 Hz, $CH_a\underline{H_b}CHOSi$), 0.88 (9H, s, $SiC(CH_3)_3$), 0.031 (3H, s, $SiCH_3$), 0.030 (3H, s, $SiCH_3$)

^{13}C NMR (100 MHz, $CDCl_3$) 144.1 × 3 (C_{Ar} × 3), 128.6 × 6 (CH_{Ar} × 6), 128.1 × 6 (CH_{Ar} × 6), 127.3 × 3 (CH_{Ar} × 3), 87.0 (CPh_3), 73.7 (CHOH), 72.5 (CHOSi), 63.3 (CH_2OTr), 45.4 ($OCH\underline{C}H_2CHO$), 42.8 ($\underline{C}HCH_2OTr$), 36.7 ($\underline{C}H_2CHOSi$), 26.1 × 3 ($SiC(\underline{C}H_3)_3$), 18.3 (SiC), -4.6 ($SiCH_3$ × 2)

ES$^+$ ***m/z*** (%) 511 ($(M+Na)^+$, 10)

HRMS (ES^+) for $C_{31}H_{40}O_3SiNa$ $(M+Na)^+$: Calcd 511.2639; Measured 511.2632

8.51 (1*S*,2*R*,3*S*,4*S*)-(2-Benzyloxy-4-(2-methoxyethoxy-methoxy)-3-trityloxymethyl-cyclopentyloxy)-*tert*-butyldimethylsilane (4.63)



4.56 **4.63**

MEMCl (20.0 μL, 0.158 mmol) was added to a solution of **4.56** (18 mg, 0.030 mmol) and DIPEA (25.0 μL, 0.151 mmol) in CH_2Cl_2 (0.3 mL). The mixture was stirred at reflux for 2 hours and the solvent was evaporated *in vacuo*. The crude was purified by column chromatography (acetone/petroleum ether) to afford **4.63** as a colourless oil (19 mg, 92%).

M.W. 682.96 (682.3690)

$[\alpha]_D$ = +23.7 (c = 0.35, $CHCl_3$, 27 °C)

IR ν_{max}/cm^{-1} 2927 m, 2883 m, 2856 m, 1490 w, 1471 w, 1449 m, 1361 w

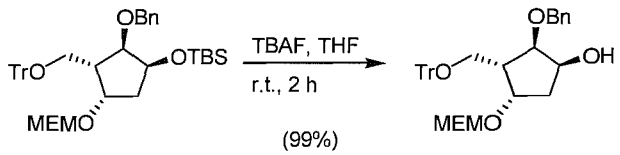
^{1}H NMR (400 MHz, $CDCl_3$) 7.25-7.46 (20H, m, ArH), 4.75 (1H, d, J = 12.5 Hz, CH_aH_bPh), 4.71 (1H, d, J = 7.0 Hz, OCH_aH_bO), 4.65 (1H, d, J = 7.0 Hz, OCH_aH_bO), 4.59 (1H, d, J = 12.5 Hz, CH_aH_bPh), 4.19 (1H, m, CHOSi), 4.01 (1H, q, J = 7.0 Hz, CHOMEM), 3.68-3.75 (2H, m, CHOBn + $OCH_aH_bCH_2O$), 3.60 (1H, dt, J = 11.0, 4.5 Hz, $OCH_aH_bCH_2O$), 3.41 (3H, s, OMe), 3.34 (1H, dd, J = 9.5, 4.0 Hz, CH_aH_bOTr), 3.23 (1H, dd, J = 9.0, 4.5 Hz, CH_aH_bOTr), 2.41 (1H, m, $CHCH_2OTr$), 2.28 (1H, ddd, J = 13.0, 7.5, 5.5 Hz , CH_aH_bCHOSi), 1.99 (1H, dt, J = 13.0, 7.0 Hz, CH_aH_bCHOSi), 0.97 (9H, s, $SiC(CH_3)_3$), 0.13 (3H, s, $SiCH_3$), 0.12 (3H, s, $SiCH_3$)

^{13}C NMR (100 MHz, $CDCl_3$) 144.2 × 3 (C_{Ar} × 3), 139.1 (C_{Ar}), 128.9 × 6 (CH_{Ar} × 6), 128.3 × 2 (CH_{Ar} × 2), 127.9 × 6 (CH_{Ar} × 6), 127.7 × 2 (CH_{Ar} × 2), 127.4 (CH_{Ar}), 127.1 × 3 (CH_{Ar} × 3), 95.1 (OCH_2O), 86.6 (CPh_3), 81.0 (CHOBn), 75.8 (CHOMEM), 71.8 and 71.7 (OCH_2CH_2O + CH_2Ph), 71.6 (CHOSi), 66.8 (OCH_2CH_2O), 61.8 (CH_2OTr), 59.1 (OCH_3), 50.7 ($CHCH_2OTr$), 39.0 (CH_2CHOSi), 26.0 × 3 ($SiC(CH_3)_3$), 18.4 (SiC), -4.5 ($SiCH_3$), -4.6 ($SiCH_3$)

ES$^+$ ***m/z*** (%) 705 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{42}H_{54}O_6SiNa$ $(M+Na)^+$: Calcd 705.3581; Measured 705.3588.

8.52 (1*S*,2*R*,3*S*,4*S*)-2-Benzyloxy-4-(2-methoxyethoxy-methoxy)-3-trityloxymethyl-cyclopentanol (4.64)



4.63 **4.64**

TBAF (1.0 M solution in THF; 94.0 µL, 0.0940 mmol) was added to a solution of **4.63** (28.0 mg, 0.0471 mmol) in THF (0.47 mL). The mixture was stirred at room temperature for 2 hours and the solvent was evaporated *in vacuo*. The crude was filtered through silica gel and purifed by HPLC (acetone/hexane 35:65) to afford **4.64** as a clear oil (23.0 mg, 99%).

M.W. 568.70 (568.2825)

$[\alpha]_D$ = +16.5 (c = 0.65, $CHCl_3$, 27 °C)

IR ν_{max}/cm^{-1} 3467 br, 3058 w, 3031 w, 2925 m, 2878 m, 1490 m, 1449 m, 1363 w

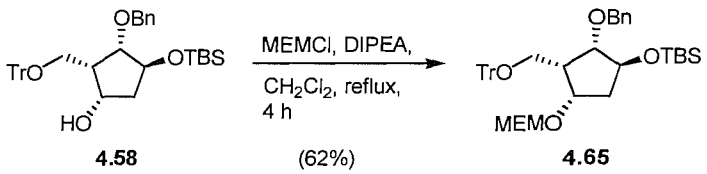
^{1}H NMR (400 MHz, $CDCl_3$) 7.24-7.45 (20H, m, ArH), 4.70 (1H, d, J = 11.0 Hz, $OC\underline{H}_aH_bO$), 4.69 (1H, d, J = 11.0 Hz, $OCH_a\underline{H}_bO$), 4.56 (1H, d, J = 12.0 Hz, $C\underline{H}_aH_bPh$), 4.55 (1H, d, J = 12.0 Hz, $CH_a\underline{H}_bPh$), 4.13 (1H, quintet, J = 5.0 Hz, $C\underline{H}OH$), 4.07 (1H, ddd, J = 7.5, 5.5, 5.0 Hz, CHOMEM), 3.80 (1H, dd, J = 7.5, 5.0 Hz, CHOBn), 3.68 (1H, ddd, J = 11.0, 5.5, 4.5 Hz, $OC\underline{H}_aH_bCH_2O$), 3.59 (1H, ddd, J = 11.0, 5.0, 4.5 Hz, $OCH_a\underline{H}_bCH_2O$), 3.47-3.50 (2H, m, $OCH_2C\underline{H}_2O$) , 3.38 (3H, s, OMe), 3.31 (1H, dd, J = 9.5, 4.5 Hz, $C\underline{H}_aH_bOTr$), 3.28 (1H, dd, J = 9.5, 4.5 Hz, $CH_a\underline{H}_bOTr$), 2.58 (1H, d, J = 5.0 Hz, OH), 2.40 (1H, m, $C\underline{H}CH_2OTr$), 2.20 (1H, ddd, J = 14.0, 7.5, 5.0 Hz , $C\underline{H}_aH_bCHOH$), 1.94 (1H, dt, J = 14.0, 4.5 Hz, $CH_a\underline{H}_bCHOH$)

^{13}C NMR (100 MHz, $CDCl_3$) 144.1 × 3 (C_{Ar} × 3), 138.1 (C_{Ar}), 128.9 × 6 (CH_{Ar} × 6), 128.6 × 2 (CH_{Ar} × 2), 127.9 × 9 (CH_{Ar} × 9), 127.2 × 3 (CH_{Ar} × 3), 94.9 (OCH_2O), 86.7 (CPh_3), 81.6 (CHOBn), 76.5 (CHOMEM), 72.0 and 71.8 (CH_2Ph + $O\underline{C}H_2CH_2O$), 70.3 (CHOH), 67.0 ($OCH_2\underline{C}H_2O$), 61.8 (CH_2OTr), 59.1 (OCH_3), 50.3 ($\underline{C}HCH_2OTr$), 38.3 ($\underline{C}H_2CHOH$)

ES$^+$ ***m/z*** (%) 591 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{36}H_{40}O_6Na$ $(M+Na)^+$: Calcd 591.2717; Measured 591.2707.

8.53 (1*S*,2*S*,3*S*,4*S*)-(2-Benzyloxy-4-(2-methoxyethoxy-methoxy)-3-trityloxymethyl-cyclopentyloxy)-*tert*-butyldimethylsilane (4.65)



4.58 (62%) **4.65**

MEMCl (90%, 46 μL, 0.363 mmol) was added to a solution of **4.58** (51.1 mg, 0.0859 mmol) and DIPEA (61 μL, 0.369 mmol) in CH_2Cl_2 (0.92 mL). The mixture was stirred at reflux for 4 hours and the solvent was evaporated *in vacuo*. The crude was purified

by column chromatography (acetone/petroleum ether 15:85) to afford **4.65** as a colourless oil (36.5 mg, 62%).

M.W. 682.96 (682.3690)

$[\alpha]_D$ = +28.1 (*c* = 0.26, $CHCl_3$, 26 °C)

IR ν_{max}/cm^{-1} 3060 w, 3031 w, 2928 m, 2884 m, 2856 m, 1490 w, 1471 w, 1449 m, 1362 w, 1254 m, 1089 s, 1044 vs

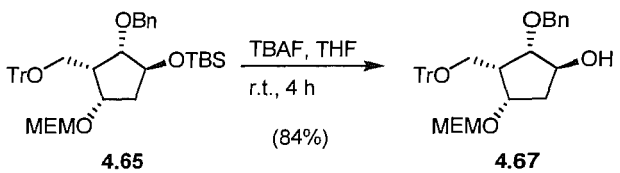
^{1}H NMR (400 MHz, $CDCl_3$) 7.20-7.50 (20H, m, ArH), 4.67 (1H, d, *J* = 7.0 Hz, $OC\underline{H}_aH_bO$), 4.60 (1H, d, *J* = 12.5 Hz, $C\underline{H}_aH_bPh$), 4.59 (1H, d, *J* = 7.0 Hz, $OCH_a\underline{H}_bO$), 4.50 (1H, d, *J* = 12.5 Hz, $CH_a\underline{H}_bPh$), 4.40 (1H, td, *J* = 6.5, 4.0 Hz, CHOMEM), 4.33 (1H, ddd, *J* = 6.5, 4.0, 2.5 Hz, CHOSi), 3.82 (1H, dd, *J* = 6.0, 2.5 Hz, CHOBn), 3.62 (1H, m, $OC\underline{H}_aH_bCH_2O$), 3.43-3.55 (3H, m, $OCH_a\underline{H}_bCH_2O$ + $OCH_2C\underline{H}_2O$), 3.39 (3H, s, OCH_3), 3.36-3.42 (2H, m, $C\underline{H}_2OTr$), 2.59 (1H, quintet, *J* = 6.5 Hz, $C\underline{H}CH_2OTr$), 2.17 (1H, ddd, *J* = 14.0, 6.5, 4.0 Hz , $C\underline{H}_aH_bCHOSi$), 1.91 (1H, ddd, *J* = 14.0, 6.5, 4.0 Hz, $CH_a\underline{H}_bCHOSi$), 0.93 (9H, s, $SiC(CH_3)_3$), 0.083 (3H, s, $SiCH_3$), 0.076 (3H, s, $SiCH_3$)

^{13}C NMR (100 MHz, $CDCl_3$) 144.6 × 3 (C_{Ar} × 3), 139.0 (C_{Ar}), 128.9 × 6 (CH_{Ar} × 6), 128.3 × 2 (CH_{Ar} × 2), 128.0 × 6 (CH_{Ar} × 6), 127.6 × 2 (CH_{Ar} × 2), 127.4 (CH_{Ar}), 127.0 × 3 (CH_{Ar} × 3), 95.0 (OCH_2O), 87.0 (CPh_3), 86.2 (CHOBn), 77.2 (CHOMEM), 77.0 (CHOSi), 72.1 (CH_2Ph), 71.9 ($O\underline{C}H_2CH_2O$), 66.8 ($OCH_2\underline{C}H_2O$), 59.5 (CH_2OTr), 59.1 (OCH_3), 45.8 ($\underline{C}HCH_2OTr$), 41.5 ($\underline{C}H_2CHOSi$), 26.0 × 3 ($SiC(\underline{C}H_3)_3$), 18.1 (SiC), -4.5 ($SiCH_3$), -4.7 ($SiCH_3$)

ES$^+$ ***m/z*** (%) 705 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{42}H_{54}O_6SiNa$ $(M+Na)^+$: Calcd 705.3581; Measured 705.3565.

8.54 (1*S*,2*S*,3*S*,4*S*)-2-Benzyloxy-4-(2-methoxyethoxy-methoxy)-3-trityloxymethyl-cyclopentanol (4.67)



4.65 **4.67**

TBAF (1.0 M solution in THF; 70.0 μL, 0.070 mmol) was added to a solution of **4.65** (23.6 mg, 0.0346 mmol) in THF (0.35 mL). The mixture was stirred at room temperature for 4 hours and the solvent was evaporated *in vacuo*. The crude was filtered through silica gel and purifed by HPLC (acetone/hexane 36:64) to afford **4.67** as a clear oil (16.5 mg, 84%).

M.W. 568.70 (568.2825)

$[\alpha]_D$ = +16.9 (*c* = 0.54, $CHCl_3$, 26 °C)

IR ν_{max}/cm^{-1} 3440 br, 3059 w, 3031 w, 2931 m, 2885 m, 1490 m, 1449 m, 1363 w

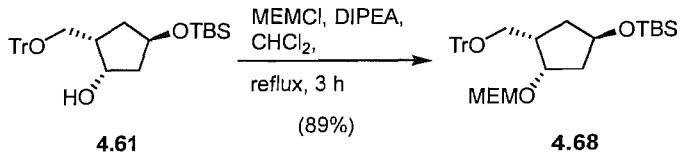
^{1}H NMR (400 MHz, $CDCl_3$) 7.19-7.42 (20H, m, ArH), 4.63 (1H, d, *J* = 7.0 Hz, OCH_aH_bO), 4.56 (1H, d, *J* = 7.0 Hz, OCH_aH_bO), 4.55 (1H, d, *J* = 12.5 Hz, CH_aH_bPh), 4.51 (1H, d, *J* = 12.5 Hz, CH_aH_bPh), 4.32-4.38 (2H, m, CHOH + CHOMEM), 3.82 (1H, dd, *J* = 6.5, 3.0 Hz, CHOBn), 3.57 (1H, dt, *J* = 11.0, 5.0 Hz, $OCH_aH_bCH_2O$), 3.35-3.50 (5H, m, $OCH_aH_bCH_2O$ + OCH_2CH_2O + CH_2OTr), 3.34 (3H, s, OCH_3), 2.60 (1H, quintet, *J* = 6.5 Hz, $CHCH_2OTr$), 2.23 (1H, ddd, *J* = 14.5, 7.0, 3.5 Hz , CH_aH_bCHOH), 1.82 (1H, ddd, *J* = 14.5, 6.0, 5.0 Hz, CH_aH_bCHOH), 1.42 (1H, d, *J* = 3.5 Hz, OH)

^{13}C NMR (100 MHz, $CDCl_3$) 144.5 × 3 (C_{Ar} × 3), 138.8 (C_{Ar}), 128.9 × 6 (CH_{Ar} × 6), 128.4 × 2 (CH_{Ar} × 2), 127.83 × 6 (CH_{Ar} × 6), 127.76 × 2 (CH_{Ar} × 2), 127.6 (CH_{Ar}), 127.0 × 3 (CH_{Ar} × 3), 94.9 (OCH_2O), 87.0 (CPh_3), 85.9 (CHOBn), 77.1 and 76.9 (CHOMEM + CHOH), 72.3 (CH_2Ph), 71.8 (OCH_2CH_2O), 66.8 (OCH_2CH_2O), 59.3 (CH_2OTr), 59.1 (OCH_3), 46.3 ($CHCH_2OTr$), 40.5 (CH_2CHOH)

ES$^+$ ***m/z*** (%) 591 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{36}H_{40}O_6Na$ $(M+Na)^+$: Calcd 591.2717; Measured 591.2727.

8.55 (1*S*,2*S*,4*R*)-(4-(2-Methoxyethoxy-methoxy)-3-trityloxymethyl-cyclopentyloxy)-*tert*-butyldimethylsilane (4.68)



4.61 **4.68**

MEMCl (90%; 25 μL, 0.194 mmol) was added to a solution of **4.61** (18.8 mg, 0.0385 mmol) and DIPEA (32.0 μL, 0.194 mmol) in CH_2Cl_2 (0.39 mL). The mixture was stirred at reflux for 3 hours and the solvent was evaporated *in vacuo*. The crude was filtered through silica gel and purified by HPLC (acetone/hexane 15:85) to afford **4.68** as a colourless oil (19.7 mg, 89%).

M.W. 576.84 (576.3271)

$[\alpha]_D$ = -6.7 (*c* = 0.90, $CHCl_3$, 26 °C)

IR ν_{max}/cm^{-1} 3059 w, 3033 w, 2954 m, 2928 m, 2884 m, 2856 m, 1490 w, 1471 w, 1449 m, 1362 w

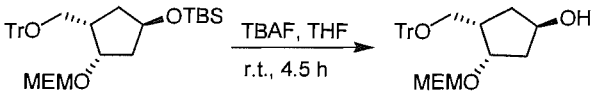
^{1}H NMR (400 MHz, $CDCl_3$) 7.24-7.47 (20H, m, ArH), 4.69 (1H, d, *J* = 7.0 Hz, $OC\underline{H}_aH_bO$), 4.65 (1H, d, *J* = 7.0 Hz, $OCH_a\underline{H}_bO$), 4.25 (1H, m, CHOSi), 3.91 (1H, q, *J* = 7.0 Hz, CHOMEM), 3.66 (1H, m, $OC\underline{H}_aH_bCH_2O$), 3.57 (1H, m, $OCH_a\underline{H}_bCH_2O$), 3.48-3.49 (2H, app. t, *J* = 4.5 Hz, $OCH_2C\underline{H}_2O$), 3.39 (3H, s, OCH_3), 3.18 (1H, dd, *J* = 9.0, 5.0 Hz, $C\underline{H}_aH_bOTr$), 3.09 (1H, dd, *J* = 9.0, 6.0 Hz, $CH_a\underline{H}_bOTr$), 2.44 (1H, m, $C\underline{H}CH_2OTr$), 2.33 (1H, dt, *J* =13.5, 7.0 Hz, $MEMOCHC\underline{H}_aH_b$), 1.88 (1H, ddd, *J* = 13.5, 9.0, 5.0 Hz , $C\underline{H}_aH_bCHOSi$), 1.76 (1H, ddd, *J* = 13.5, 7.0, 6.5 Hz, $CH_a\underline{H}_bCHOSi$), 1.66 (1H, dtd, *J* = 13.5, 6.0, 1.0 Hz, $MEMOCHCH_a\underline{H}_b$), 0.93 (9H, s, $SiC(CH_3)_3$), 0.091 (3H, s, $SiCH_3$), 0.084 (3H, s, $SiCH_3$)

^{13}C NMR (100 MHz, $CDCl_3$) 144.4 × 3 (C_{Ar} × 3), 128.9 × 6 (CH_{Ar} × 6), 127.8 × 6 (CH_{Ar} × 6), 127.0 × 3 (CH_{Ar} × 3), 95.0 (OCH_2O), 86.4 (CPh_3), 79.1 (CHOMEM), 71.9 ($O\underline{C}H_2CH_2O$), 71.3 (CHOSi), 66.8 ($OCH_2\underline{C}H_2O$), 64.5 (CH_2OTr), 59.1 (OCH_3), 44.4 ($\underline{C}HCH_2OTr$), 42.7 ($MEMOCH\underline{C}H_2$), 37.6 ($\underline{C}H_2CHOSi$), 26.1 × 3 ($SiC(\underline{C}H_3)_3$), 18.3 (SiC), -4.6 × 2 ($SiCH_3$ × 2)

ES$^+$ ***m/z*** (%) 599 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{35}H_{48}O_5SiNa$ $(M+Na)^+$: Calcd 599.3163; Measured 599.3174.

8.56 (1*S*,2*S*,4*R*)-4-(2-Methoxyethoxy-methoxy)-3-trityloxymethyl-cyclopentanol (4.69)



4.68 (91%) **4.69**

TBAF (1.0 M solution in THF; 64 μL, 0.064 mmol) was added to a solution of **4.68** (18.7 mg, 0.0324 mmol) in THF (0.32 mL). The mixture was stirred at room temperature for 4.5 hours and the solvent was evaporated *in vacuo*. The crude was filtered through silica gel and purifed by HPLC (acetone/hexane 4:6) to afford **4.69** as a clear oil (13.7 mg, 91%).

M.W. 462.58 (462.2406)

$[\alpha]_D$ = +2.9 (*c* = 0.60, $CHCl_3$, 26 °C)

IR ν_{max}/cm^{-1} 3441 br, 3057 w, 3032 w, 2928 m, 2884 m, 1490 m, 1449 m

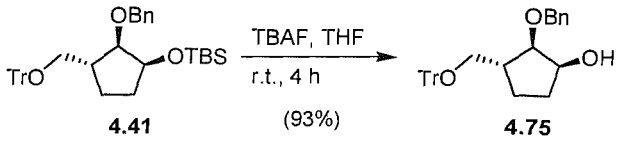
^{1}H NMR (400 MHz, $CDCl_3$) 7..21-7.44 (20H, m, ArH), 4.75 (1H, d, *J* = 7.0 Hz, $OC\underline{H}_aH_bO$), 4.73 (1H, d, *J* = 7.0 Hz, $OCH_a\underline{H}_bO$), 4.26 (1H, br, $C\underline{H}OH$), 4.15 (1H, dt, *J* = 5.5, 3.5 Hz, CHOMEM), 3.70 (1H, m, $OC\underline{H}_aH_bCH_2O$), 3.63 (1H, dt, *J* = 11.0, 4.5 Hz, $OCH_2CH_a\underline{H}_bO$), 3.50 (2H, app. t, *J* = 4.5 Hz, $OC\underline{H}_2CH_2O$), 3.37 (3H, s, OCH_3), 3.08 (1H, dd, *J* = 9.0, 6.0 Hz, $C\underline{H}_aH_bOTr$), 2.97 (1H, dd, *J* = 9.0, 7.0 Hz, $CH_a\underline{H}_bOTr$), 2.57 (1H, m, $C\underline{H}CH_2OTr$), 2.28 (1H, d, *J* = 7.0 Hz, OH), 2.00 (1H, ddt, *J* = 14.0, 8.5, 2.0 Hz, $C\underline{H}_aH_bCHOH$), 1.84-1.94 (2H, m, $MEMOCHC\underline{H}_2$), 1.56 (1H, ddd, *J* = 14.0, 8.0, 5.5 Hz, $CH_a\underline{H}_bCHOH$)

^{13}C NMR (100 MHz, $CDCl_3$) 144.3 × 3 (C_{Ar} × 3), 128.9 × 6 (CH_{Ar} × 6), 127.9 × 6 (CH_{Ar} × 6), 127.1 × 3 (CH_{Ar} × 3), 94.4 (OCH_2O), 86.6 (CPh_3), 80.8 (CHOMEM), 73.4 (CHOH), 71.9 ($OCH_2\underline{C}H_2O$), 67.1 ($O\underline{C}H_2CH_2O$), 65.1 (CH_2OTr), 59.1 (OCH_3), 45.1 ($\underline{C}HCH_2OTr$), 41.1 ($MEMOCH\underline{C}H_2$), 38.2 ($\underline{C}H_2CHOH$)

ES$^+$ ***m/z*** (%) 485 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{29}H_{34}O_5Na$ $(M+Na)^+$: Calcd 485.2298; Measured 485.2291.

8.57 (1*S*,2*R*,3*R*)-2-Benzyloxy-3-trityloxymethyl-cyclopentanol (4.75)



4.41 (93%) **4.75**

TBAF (1.0 M solution in THF, 93.0 μL, 0.0930 mmol) was added to a solution of **4.41** (24.0 mg, 0.0415 mmol) in THF (0.42 mL). The mixture was stirred at room temperature for 4 hours. The solvent was removed *in vacuo* and the residue was purified by column chromatography (EtOAc/petroleum ether 3:7) to afford **4.75** as a white foam (18.0 mg, 93%).

M.W. 464.59 (464.2351)

[α]$_D$ = +19.0 (*c* = 1.7, $CHCl_3$, 24 °C)

IR ν_{max}/cm^{-1} 3466 br, 3086 w, 3058 w, 3031 w, 2968 w, 2924 w, 2866 w, 1489 w, 1448 m, 1381 w

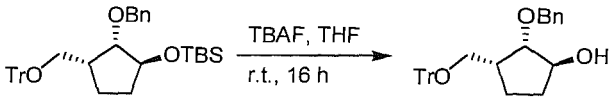
^{1}H NMR (400 MHz, $CDCl_3$) 7.24-7.48 (20H, m, ArH), 4.59 (1H, d, *J* = 11.5 Hz, C$\underline{H}_a$H$_b$Ph), 4.54 (1H, d, *J* = 11.5 Hz, CH$_a\underline{H}_b$Ph), 4.11 (1H, quintet, *J* = 4.5 Hz, C$\underline{H}$OH), 3.73 (1H, dd, *J* = 6.5, 4.5 Hz, CHOBn), 3.17 (1H, dd, *J* = 9.0, 5.5 Hz, C$\underline{H}_a$H$_b$OTr), 3.14 (1H, dd, *J* = 9.0, 6.0 Hz, CH$_a\underline{H}_b$OTr), 2.38 (1H, m, C$\underline{H}$CH$_2$OTr), 2.01 (1H, m, C$\underline{H}_a$H$_b$CH$_2$CH), 1.73-1.88 (2H, m, C$\underline{H}_2$CHO), 1.42 (1H, dddd, *J* = 14.5, 9.0, 8.0, 7.0 Hz, CH$_a\underline{H}_b$CH$_2$CH)

^{13}C NMR (100 MHz, $CDCl_3$) 144.4 × 3 (C_{Ar} × 3), 138.2 (C_{Ar}), 128.9 × 6 (CH_{Ar} × 6), 128.6 × 2 (CH_{Ar} × 2), 127.9 × 7 (CH_{Ar} × 7), 127.8 × 2 (CH_{Ar} × 2), 127.1 × 3 (CH_{Ar} × 3), 86.5 (CPh_3), 83.6 (CHOBn), 72.0 (CH_2Ph), 71.7 (CHOH), 64.7 (CH_2OTr), 42.6 ($\underline{C}$HCH$_2$OTr), 30.8 ($\underline{C}$H$_2$CHO), 23.8 ($\underline{C}$H$_2$CH$_2$CHO)

ES$^+$ *m/z* (%) 487 ((M+Na)$^+$, 100)

HRMS (ES$^+$) for $C_{32}H_{32}O_3Na$ (M+Na)$^+$: Calcd 487.2243; Measured 487.2253.

8.58 (1*S*,2*S*,3*R*)-2-Benzyloxy-3-trityloxymethyl-cyclopentanol (4.76)



4.43 (92%) **4.76**

TBAF (1.0 M solution in THF; 0.285 mL, 0.285 mmol) was added to a solution of **4.43** (110 mg, 0.190 mmol) in THF (1.9 mL). The mixture was stirred at room temperature for 16 hours. The solvent was removed *in vacuo* and the residue was purified by column chromatography (EtOAc/petroleum ether 3:7) to afford **4.76** as a white solid (81.0 mg, 92%).

M.W. 464.59

mp 38-40 °C

$[\alpha]_D$ = +9.2 (*c* = 0.80, $CHCl_3$, 24 °C)

IR ν_{max}/cm^{-1} 3388 br, 3086 w, 3059 w, 3031 w, 2931 w, 2873 w, 1490 m, 1448 m, 1386 w, 1351 w

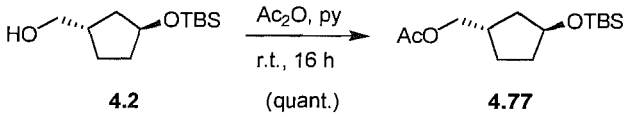
^{1}H NMR (400 MHz, $CDCl_3$) 7.13-7.48 (20H, m, ArH), 4.52 (1H, d, *J* = 12.0 Hz, $C\underline{H}_aH_bPh$), 4.46 (1H, d, *J* = 12.0 Hz, $CH_a\underline{H}_bPh$), 4.25 (1H, m, C<u>H</u>OH), 3.87 (1H, dd, *J* = 5.5, 2.5 Hz, CHOBn), 3.27 (1H, dd, *J* = 9.0, 7.5 Hz, $C\underline{H}_aH_bOTr$), 3.21 (1H, dd, *J* = 9.0, 6.5 Hz, $CH_a\underline{H}_bOTr$), 2.57 (1H, m, C<u>H</u>CH_2OTr), 2.11 (1H, m, $C\underline{H}_aH_bCH_2CHOH$), 1.88 (1H, m, $C\underline{H}_aH_bCHOH$), 1.43-1.55 (3H, m, $CH_a\underline{H}_bCH_2CHOH$ + $CH_a\underline{H}_bCHOH$ + OH)

^{13}C NMR (100 MHz, $CDCl_3$) 144.6 × 3 (C_{Ar} × 3), 138.8 (C_{Ar}), 128.9 × 6 (CH_{Ar} × 6), 128.4 × 2 (CH_{Ar} × 2), 127.8 × 6 (CH_{Ar} × 6), 127.6 × 2 (CH_{Ar} × 2), 127.5 (CH_{Ar}), 127.0 × 3 (CH_{Ar} × 3), 86.6 (CHOBn), 86.4 (CPh_3), 76.5 (CHOH), 72.0 (CH_2Ph), 62.8 (CH_2OTr), 41.8 (<u>C</u>HCH_2OTr), 31.7 (<u>C</u>H_2CHOH), 24.9 (<u>C</u>H_2CH_2CHOH),

ES$^+$ ***m/z*** (%) 487 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{32}H_{32}O_3Na$ $(M+Na)^+$: Calcd 487.2243; Measured 487.2232.

8.59 (1*S*,3*S*)-Acetic acid 3-(*tert*-butyldimethylsilanyloxy)-cyclopentyl methyl ester (4.77)



4.2 (quant.) **4.77**

Acetic anhydride (39 μL, 0.413 mmol) was added to a solution of alcohol **4.2** (48 mg, 0.208 mmol) in pyridine (1.0 mL). The mixture was stirred at room temperature for 16 hours and the solvent was evaporated *in vacuo*. The crude was purified by column chromatography (EtOAc/petroleum ether 5:95) to afford **4.77** as a colourless oil (57 mg, quant.).

M.W. 272.46 (272.1808)

$[\alpha]_D$ = +7.7 (*c* = 1.08, $CHCl_3$, 26 °C)

IR ν_{max}/cm^{-1} 2954 m, 2929 m, 2893 w, 2856 m, 1743 s, 1472 w, 1463 w, 1435 w, 1387 w, 1364 m, 1235 s

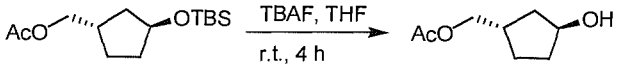
^{1}H NMR (400 MHz, $CDCl_3$) 4.29 (1H, tt, *J* = 5.5, 3.5 Hz, CHOSi), 3.95 (2H, app. d, *J* = 7.0 Hz, $C\underline{H}_2OAc$), 2.48 (1H, m, $C\underline{H}CH_2OAc$), 2.05 (3H, s, $COCH_3$), 1.93 (1H, m, $C\underline{H}_aH_bCH_2CHOSi$), 1.81 (1H, m, $CH_2C\underline{H}_aH_bCHOSi$), 1.73 (1H, dddd, *J* = 13.0, 8.0, 3.0, 1.5 Hz, $CHC\underline{H}_aH_bCH$), 1.57 (1H, m, $CH_2CH_a\underline{H}_bCHOSi$), 1.41 (1H, ddd, *J* = 13.0, 8.5, 5.5 Hz, $CHCH_a\underline{H}_bCH$), 1.25 (1H, ddt, *J* = 13.0, 9.0, 7.0 Hz, $CH_a\underline{H}_bCH_2CHOSi$), 0.88 (9H, s, $SiC(CH_3)_3$), 0.04 (6H, s, $SiCH_3 \times 2$)

^{13}C NMR (100 MHz, $CDCl_3$) 171.4 (C=O), 73.9 (CHOSi), 68.6 (CH_2OAc), 39.5 ($CH\underline{C}H_2CH$), 36.3 ($\underline{C}HCH_2OAc$), 35.5 ($CH_2\underline{C}H_2CHOSi$), 26.9 ($\underline{C}H_2CH_2CHOSi$), 26.0 × 3 ($SiC(\underline{C}H_3)_3$), 21.1 ($CO\underline{C}H_3$), 18.2 (SiC), -4.6 × 2 ($SiCH_3 \times 2$)

ES$^+$ ***m/z*** (%) 295 ($(M+Na)^+$, 70), 567 ($(2M+Na)^+$, 100)

HRMS (ES^+) for $C_{14}H_{28}O_3SiNa$ $(M+Na)^+$: Calcd 295.1670; Measured 295.1699.

8.60 (1*S*,3*S*)-Acetic acid 3-hydroxy-cyclopentylmethyl ester (4.78)



4.77 (89%) **4.78**

TBAF (1.0 M solution in THF; 0.15 mL, 0.150 mmol) was added to a solution of acetate **4.77** (27.0 mg, 0.0991 mmol) in THF (1.0 mL). The mixture was stirred at room temperature for 4 hours and the solvent was evaporated *in vacuo*. The crude was filtered through silica gel and purified by HPLC (acetone/hexane 34:66) to afford **4.78** as a colourless oil (14.0 mg, 89%).

M.W. 158.20 (158.0943)

$[\alpha]_D$ = +9.4 (*c* = 0.41, $CHCl_3$, 26 °C)

IR ν_{max}/cm^{-1} 3411 br, 2954 br, 1740 s, 1718 s, 1437 w, 1388 w, 1367 m, 1241 s

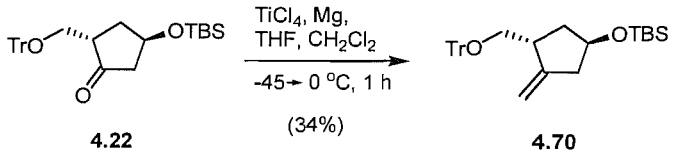
^{1}H NMR (400 MHz, $CDCl_3$) 4.39 (1H, m, C<u>H</u>OH), 3.99 (1H, dd, *J* = 11.0, 7.0 Hz, C<u>H$_a$</u>H$_b$OAc), 3.96 (1H, dd, *J* = 11.0, 4.5 Hz, CH$_a$<u>H$_b$</u>OAc), 2.53 (1H, m, C<u>H</u>CH$_2$OAc), 2.06 (3H, s, $COCH_3$), 1.88-2.02 (2H, m, C<u>H$_a$</u>H$_b$CH$_2$CHO + CH$_2$C<u>H$_a$</u>H$_b$CHO), 1.80 (1H, ddt, *J* = 14.0, 8.0, 2.0 Hz, CHC<u>H$_a$</u>H$_b$CH), 1.61 (1H, m, CH$_2$CH$_a$<u>H$_b$</u>O), 1.50 (1H, ddd, *J* = 14.0, 9.0, 5.0 Hz, CHCH$_a$<u>H$_b$</u>CH), 1.38 (1H, d, *J* = 1.5 Hz, OH), 1.33 (1H, m, CH$_a$<u>H$_b$</u>CH$_2$CHo)

^{13}C NMR (100 MHz, $CDCl_3$) 171.4 (C=O), 73.7 (CHOH), 68.3 (CH_2OAc), 39.3 (CH<u>C</u>H$_2$CH), 36.4 (<u>C</u>HCH$_2$OAc), 35.1 (CH$_2$<u>C</u>H$_2$CHO), 27.0 (<u>C</u>H$_2$CH$_2$CHO), 21.1 (CO<u>C</u>H$_3$)

ES$^+$ ***m/z*** (%) 181 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_8H_{14}O_3Na$ $(M+Na)^+$: Calcd 181.0835; Measured 181.0837.

8.61 (1*R*,4*R*)-(3-Methylene-4-trityloxymethyl-cyclopentyloxy)-*tert*-butyldimethylsilane (4.70)



4.22 **4.70**

A solution of ketone **4.22** (27.8 mg, 0.0571 mmol) in THF/CH_2Cl_2 (2:3, 0.23 mL) was added to a suspension of magnesium turnings (ca. 12 mg, 8-9 equiv.) and $TiCl_4$ (1.0 M solution in CH_2Cl_2; 0.11 mL, 0.11 mmol) in CH_2Cl_2 (0.11 mL) at -45 °C. The reaction was stirred at -45 °C for 1 hour and then warmed to 0 °C over 3 hours before quenching with sat. K_2CO_3 (5 mL). The aqueous layer was extracted with Et_2O (3 × 8 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was purified by column chromatography (EtOAc/petroleum ether 5:95) to afford **4.70** as a clear oil (9.3 mg, 34 %).

M.W. 484.74 (484.2798)

$[\alpha]_D$ = -14.5 (*c* = 0.80, $CHCl_3$, 26 °C)

IR ν_{max}/**cm**$^{-1}$ 3089 w, 3060 w, 3025 w, 2954 w, 2927 w, 2856 w, 1493 m, 1471 w, 1448 m, 1361 w

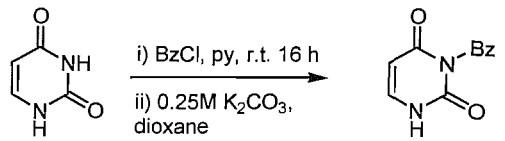
^{1}H NMR (400 MHz, $CDCl_3$) 7.28-7.54 (20H, m, ArH), 4.98 (1H, m, C=C$\underline{H}_a$H$_b$), 4.87 (1H, m, C=CH$_a\underline{H}_b$), 4.38 (1H, quintet, *J* = 4.5 Hz, CHOSi), 3.24 (1H, dd, *J* = 9.0, 5.5 Hz, C$\underline{H}_a$H$_b$OTr), 3.10 (1H, dd, *J* = 9.0, 7.5 Hz, CH$_a\underline{H}_b$OTr), 3.00 (1H, m, C$\underline{H}$CH$_2$OTr), 2.60 (1H, m, C$\underline{H}_a$H$_b$CHOSi), 2.36 (1H, ddq, *J* = 16.5, 4.0, 2.0 Hz, CH$_a\underline{H}_b$CHOSi), 2.00 (1H, dddd, *J* = 13.0, 8.0, 4.5, 1.5 Hz, CHC$\underline{H}_a$H$_b$CH), 1.83 (1H, dddd, *J* = 13.0, 7.5, 5.0, 1.0 Hz, CHCH$_a\underline{H}_b$CH), 0.96 (9H, s, SiC(CH$_3$)$_3$), 0.13 (3H, s, SiCH$_3$), 0.12 (3H, s, SiCH$_3$)

^{13}C NMR (100 MHz, $CDCl_3$) 151.5 (C=CH$_2$), 144.5 × 3 (C$_{Ar}$ × 3), 128.9 × 6 (CH$_{Ar}$ × 6), 127.8 × 6 (CH$_{Ar}$ × 6), 127.0 × 3 (CH$_{Ar}$ × 3), 107.1 (C=CH$_2$), 86.5 (CPh$_3$), 72.3 (CHOSi), 66.8 (CH$_2$OTr), 43.8 (CH$_2$CHOSi), 41.9 (CHCH$_2$OTr), 40.2 (CHCH$_2$CH), 26.1 × 3 (SiC(CH$_3$)$_3$), 18.3 (SiC), -4.5 (SiCH$_3$), -4.6 (SiCH$_3$)

ES$^+$ ***m/z*** (%) 507 ((M+Na)$^+$, 22)

HRMS (ES$^+$) for $C_{32}H_{40}O_2SiNa$ (M+Na)$^+$: Calcd 507.2690; Measured 507.2680.

8.62 3-Benzoyluracil (5.3)



5.1 (30%) **5.3**

BzCl was added to a solution of uracil **5.1** (2.01 g, 17.8 mmol) in pyridine (18.0 mL) and the mixture was stirred at room temperature for 16 hours. 2 M HCl (120 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 80 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was then stirred in a mixture of dioxane and 0.25 M K_2CO_3 (1:1, 135 mL) at room temperature for 3 hours. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 80 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was purified by column chromatography (acetone/petroleum ether 1:1) to afford white crystals of **5.3** (1.18 g, 30%).

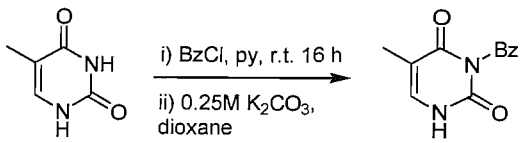
M.W. 216.19

^{1}H NMR (400 MHz, DMSO) 11.58 (1H, br, NH), 7.94-7.97 (2H, m, CH_{Ar} × 2), 7.77 (1H, tt, J = 7.5, 1.5 Hz, CH_{Ar}), 7.65 (1H, d, J = 8.0 Hz, C<u>H</u>=CH), 7.58-7.62 (2H, m, CH_{Ar} × 2), 5.74 (1H, d, J = 8.0 Hz, CH=C<u>H</u>)

^{13}C NMR (100 MHz, DMSO) 170.0 (C=O), 162.9 (C=O), 150.0 (C=O), 143.2 (<u>C</u>H=CH), 135.3 (CH_{Ar}), 131.3 (C_{Ar}), 130.2 × 2 (CH_{Ar} × 2), 129.4 × 2 (CH_{Ar} × 2), 100.1 (CH=<u>C</u>H)

^{1}H NMR and **^{13}C NMR** corresponded to the previously reported values.[147]

8.63 3-Benzoylthymine (5.4)



5.2 (65%) **5.4**

BzCl was added to a solution of thymine **5.2** (1.11 g, 8.80 mmol) in pyridine (8.8 mL) and the mixture was stirred at room temperature for 16 hours. 2 M HCl (60 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 80 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was then stirred in a mixture of dioxane and 0.25 M K_2CO_3 (1:1, 80 mL) at room temperature for 1 hour. Sat. NH_4Cl (30 mL) and H_2O (50 mL) were added and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was dissolved in acetone and precipitated by the addition of petroleum ether to afford white crystals of **5.4** (1.32 g, 65%).

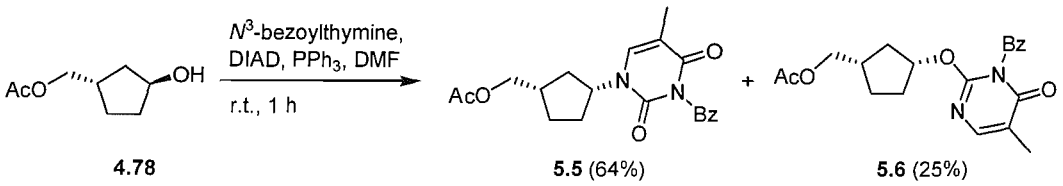
M.W. 230.22

^{1}H NMR (400 MHz, DMSO) 11.34 (1H, br, NH), 7.91-7.95 (2H, m, CH_{Ar} × 2), 7.77 (1H, ddt, J = 8.0, 7.0, 1.5 Hz, CH_{Ar}), 7.57-7.62 (2H, m, CH_{Ar} × 2), 7.52 (1H, q, J = 1.5 Hz, CH=C), 1.82 (1H, d, J = 1.5 Hz, CH_3)

^{13}C NMR (100 MHz, DMSO) 170.1 (C=O), 163.5 (C=O), 149.9 (C=O), 138.7 (CH=C), 135.2 (CH_{Ar}), 131.4 (C_{Ar}), 130.2 × 2 (CH_{Ar} × 2), 129.4 × 2 (CH_{Ar} × 2), 107.8 (CH=C), 11.6 (CH_3)

^{1}H NMR and **^{13}C NMR** corresponded to the previously reported values.[147]

8.64 (1*S*,3*R*)-Acetic acid 3-(3-benzoyl-5-methyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-cyclopentylmethyl ester (5.5)



4.78 **5.5** (64%) **5.6** (25%)

DIAD (64 μL, 0.304 mmol) was added to a solution of PPh_3 (80.0 mg, 0.304 mmol) in DMF (2.0 mL) at 0 °C and the mixture was stirred for 1 hour. A solution of 3-benzoylthymine (140 mg, 0.609 mmol) and alcohol **4.78** (32.1 mg, 0.203 mmol) in DMF (2.0 mL) was then added and the mixture was stirred at room temperature for 1 hour. H_2O (10 mL) was added and the aqueous layer was extracted with Et_2O (3 × 10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was purified by column chromatography (acetone/petroleum ether 35:65) then by HPLC (EtOAc/hexane 6:4) to afford **5.5** (48.0 mg, 64%) and **5.6** (18.6 mg, 25%) as colourless oils.

M.W. 370.40 (370.1529)

Data for 5.5

$[\alpha]_D$ = +23.5 (*c* = 0.66, $CHCl_3$, 26 °C)

IR ν_{max}/cm^{-1} 3072 w, 2954 w, 2874 w, 1741 s, 1695 s, 1648 vs, 1599 w, 1441 m, 1389 w, 1367 m, 1240 s

^{1}H NMR (400 MHz, $CDCl_3$) 7.91-7.94 (2H, m, CH_{Ar}), 7.64 (1H, tt, *J* = 7.0, 1.5 Hz, CH_{Ar}), 7.47-7.52 (2H, m, CH_{Ar}), 7.14 (1H, q, *J* = 1.0 Hz, C=CH), 4.91 (1H, dtd, *J* = 11.0, 9.0, 7.5 Hz, C<u>H</u>N), 4.09 (2H, app. d, *J* = 6.5 Hz, C<u>H$_2$</u>OAc), 2.24-2.42 (2H, m, C<u>H</u>CH$_2$OAc + CHC<u>H$_a$</u>H$_b$CH), 2.15 (1H, m, CH$_2$C<u>H$_a$</u>H$_b$CH), 2.08 (3H, s, $COCH_3$), 2.00 (3H, s, CH_3), 1.91 (1H, m, C<u>H$_a$</u>H$_b$CH$_2$CH), 1.77 (1H, m, CH$_2$CH$_a$<u>H$_b$</u>CH), 1.61 (1H, dddd, *J* = 13.0, 9.5, 7.5, 6.0 Hz, CH$_a$<u>H$_b$</u>CH$_2$CH), 1.45 (1H, dt, *J* = 12.0, 10.0 Hz, CHCH$_a$<u>H$_b$</u>CH)

^{13}C NMR (100 MHz, $CDCl_3$) 171.2 (C=O), 169.3 (C=O), 162.8 (C=O), 150.1 (C=O), 136.4 (C=$\underline{C}$H), 135.0 (CH_{Ar}), 131.9 (C_{Ar}), 130.6 × 2 (CH_{Ar} × 2), 129.2 × 2 (CH_{Ar} × 2), 111.3 ($\underline{C}$=CH), 67.9 (CH_2OAc), 56.6 (CHN), 36.8 ($\underline{C}HCH_2OAc$), 35.1 ($CH\underline{C}H_2CH$), 29.8 ($CH_2\underline{C}H_2CH$), 27.0 ($\underline{C}H_2CH_2CH$), 21.0 ($CO\underline{C}H_3$), 12.8 (CH_3)

ES$^+$ ***m/z*** (%) 393 ($(M+Na)^+$, 82), 371 ($(M+H)^+$, 100)

HRMS (ES^+) for $C_{20}H_{22}N_2O_5Na$ $(M+Na)^+$: Calcd 393.1421; Measured 393.1417

Data for ((1*S*,3*R*)-(1-benzoyl-1,6-dihydro-5-methyl-6-oxopyrimidin-2-yloxy)cyclopentyl)methyl acetate (5.6)

IR ν_{max}/cm^{-1} 2960 br, 1737 s, 1611 m, 1552 m, 1429 s, 1335 m

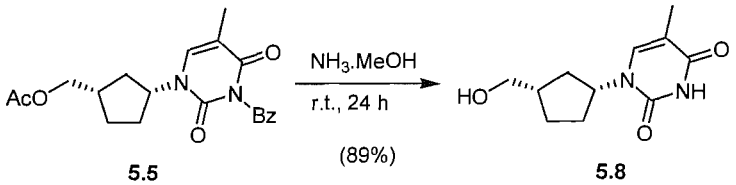
^{1}H NMR (400 MHz, $CDCl_3$) 8.39 (1H, d, J = 1.0 Hz, CH=C), 8.18-8.21 (2H, m, CH_{Ar}), 7.67 (1H, m, CH_{Ar}), 7.51-7.55 (2H, m, CH_{Ar}), 5.37 (1H, tt, J = 6.0, 4.0 Hz, C$\underline{H}$O), 4.08 (1H, dd, J = 11.0 6.5 Hz, C$\underline{H}_a$H$_b$OAc), 4.05 (1H, dd, J = 11.0, 6.5 Hz, CH$_a\underline{H}_b$OAc), 2.25-2.37 (2H, m, C$\underline{H}$CH$_2$OAc + CHC$\underline{H}_a$H$_b$CH), 2.15 (3H, d, J = 1.0 Hz, CH_3), 2.04 (3H, s, $COCH_3$) 1.92-2.00 (2H, m, C$\underline{H}_a$H$_b$CHO), 1.84 (1H, m, C$\underline{H}_a$H$_b$CH$_2$CH), 1.57-1.70 (2H, m, CHCH$_a\underline{H}_b$CH + CH$_a\underline{H}_b$CH$_2$CH)

^{13}C NMR (100 MHz, $CDCl_3$) 171.2 (C=O), 165.4 (C=O), 164.0 (C=O), 163.3 (C=O), 161.9 (C=$\underline{C}$H), 134.3 (CH_{Ar}), 130.6 × 2 (CH_{Ar} × 2), 129.2 × 2 (CH_{Ar} × 2), 128.6 (C_{Ar}), 115.5 ($\underline{C}$=CH), 79.5 (CHO), 68.6 (CH_2OAc), 37.4 ($\underline{C}HCH_2OAc$), 35.9 ($CH\underline{C}H_2CH$), 32.4 ($\underline{C}H_2CHO$), 27.4 ($\underline{C}H_2CH_2CH$), 21.1 ($CO\underline{C}H_3$), 12.3 (CH_3)

ES$^+$ ***m/z*** (%) 371 ($(M+H)^+$, 88), 393 ($(M+Na)^+$, 70)

HRMS (ES^+) for $C_{20}H_{22}N_2O_5Na$ $(M+Na)^+$: Calcd 371.1601; Measured 371.1603.

8.65 (1'*R*,4'*S*)-1-(4-hydroxymethyl-cyclopentan-1-yl)thymine (5.8)



5.5 5.8

A mixture of **5.5** (38.2 mg, 0.103 mmol) and NH_3 (7 N solution in MeOH; 1.5 mL, 10.5 mmol) was stirred at room temperature for 24 hours. The solvent was evaporated *in vacuo* and the crude was purified by column chromatography (acetone/petroleum ether 6:4) to afford **5.8** as white crystals (20.6 mg, 89%).

M.W. 224.26 (224.1161)

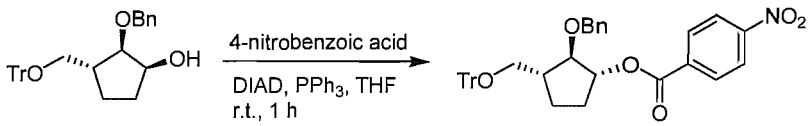
$[\alpha]_D$ = +13.3 (c = 2.08, MeOH, 29 °C)

^{1}H NMR (400 MHz, DMSO) 11.14 (1H, s), 7.55 (1H, s), 4.72 (1H, m), 4.53 (1H, t, J = 5.5 Hz), 3.39 (2H, t, J = 5.5 Hz), 2.06 (1H, m), 2.08 (3H, s), 1.95 (1H, dt, J = 12.0, 7.5 Hz), 1.86 (1H, m), 1.62-1.75 (2H, m), 1.53 (1H, m), 1.37 (1H, m)

^{13}C NMR (100 MHz, DMSO) 163.7 (C=O), 150.9 (C=O), 137.6 (CH), 109.0 (CH), 64.8 (CH_2), 55.3 (CH), 39.5 (CH), 33.9 (CH_2), 29.1 (CH_2), 26.1 (CH_2), 12.0 (CH_3)

^{1}H NMR corresponded to the previously reported values.[50]

8.66 (1*R*,2*R*,3*R*)-2-Benzyloxy-3-trityloxymethyl-cyclopentyl 4-nitro-benzoate (5.12)



4.75 (97%) **5.12**

DIAD (21.0 µL, 0.0980 mmol) was added to a solution of PPh_3 (25.5 mg, 0.0972 mmol) in THF (0.65 mL) at 0 °C and the mixture was stirred for 1 hour. A solution of 4-nitrobenzoic acid (16.2 mg, 0.0972 mmol) and alcohol **4.75** (30.1 mg, 0.0648 mmol) in THF (0.65 mL) was then added at 0 °C and the mixture was stirred at room temperature for 1 hour. The solvent was evaporated *in vacuo* and the crude was purified by column chromatography (acetone/petroleum ether 15:85) to afford **5.12** as a white foam (38.5 mg, 97%).

M.W. 613.70 (613.2464)

$[\alpha]_D$ = -30.4 (*c* = 1.35, $CHCl_3$, 27 °C)

IR ν_{max}/cm^{-1} 3085 w, 3057 w, 3031 w, 2869 w, 2829 w, 1723 s, 1607 w, 1527 s, 1490 w, 1449 m

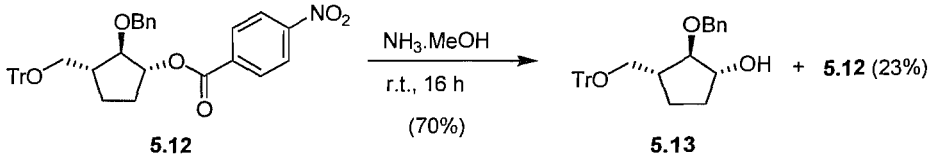
^{1}H NMR (400 MHz, $CDCl_3$) 8.24 (2H, dt, *J* = 9.0 2.0 Hz, CH_{Ar}), 8.02 (2H, dt, *J* = 9.0, 2.0 Hz, CH_{Ar}), 7.20-7.45 (20H, m, ArH), 5.40 (1H, quintet, *J* = 3.0 Hz, CHOC=O), 4.67 (1H, d, *J* = 12.0 Hz, $C\underline{H}_aH_bPh$), 4.60 (1H, d, *J* = 12.0 Hz, $CH_a\underline{H}_bPh$), 3.93 (1H, ddd, *J* = 5.0, 2.5, 1.0 Hz, CHOBn), 3.24 (1H, dd, *J* = 9.0, 6.0 Hz, $C\underline{H}_aH_bOTr$), 3.17 (1H, dd, *J* = 9.0, 6.5 Hz, $CH_a\underline{H}_bOTr$), 2.41 (1H, m, $C\underline{H}CH_2OTr$), 2.20 (1H, dddd, *J* = 14.0, 10.0, 8.0, 6.0 Hz, $C\underline{H}_aH_bCHO$), 2.03 (1H, m, $C\underline{H}_aH_bCH_2CH$), 1.85 (1H, m, $CH_a\underline{H}_bCHO$), 1.68 (1H, dddd, *J* = 13.0, 10.0, 9.0, 7.0 Hz, $CH_a\underline{H}_bCH_2CH$)

^{13}C NMR (100 MHz, $CDCl_3$) 164.0 (C=O), 150.6 (C_{Ar}), 144.2 × 3 (C_{Ar} × 3), 138.4 (C_{Ar}), 135.8 (C_{Ar}), 130.8 × 2 (CH_{Ar} × 2), 128.9 × 6 (CH_{Ar} × 6), 128.5 × 2 (CH_{Ar} × 2), 127.9 × 6 (CH_{Ar} × 6), 127.8 × 2 (CH_{Ar} × 2), 127.7 (CH_{Ar}), 127.1 × 3 (CH_{Ar} × 3), 123.6 × 2 (CH_{Ar} × 2), 86.6 (CPh_3), 86.2 (CHOBn), 81.5 (CHOC=O), 72.1 (CH_2Ph), 64.8 (CH_2OTr), 45.6 ($\underline{C}HCH_2OTr$), 30.3 ($\underline{C}H_2CHO$), 26.0 ($\underline{C}H_2CH_2CH$)

ES$^+$ ***m/z*** (%) 636 ($(M+Na)^+$, 5)

HRMS (ES^+) for $C_{39}H_{35}NO_6Na$ $(M+Na)^+$: Calcd 636.2357; Measured 636.2365.

8.67 (1*R*,2*R*,3*R*)-2-Benzyloxy-3-trityloxymethyl-cyclopentanol (5.13)



5.12 **5.13**

A mixture of **5.12** (22.9 mg, 0.0373 mmol) and NH_3 (7 N solution in MeOH; 0.74 mL, 5.18 mmol) was stirred at room temperature for 16 hours. The solvent was evaporated *in vacuo* and the crude was purified by column chromatography (acetone/petroleum ether 2:8) to afford **5.13** as a white foam (12.2 mg, 70%) and starting material **5.12** (5.2 mg, 23%).

M.W. 464.59 (464.2351)

$[\alpha]_D$ = +25.3 (*c* = 0.48, $CHCl_3$, 27 °C)

IR ν_{max}/cm^{-1} 3458 br, 3058 w, 3030 w, 2914 br, 2868 w, 1597 w, 1490 w, 1449 w, 1362 w

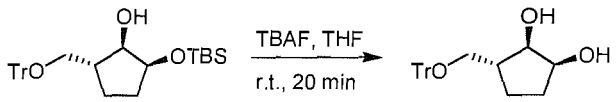
^{1}H NMR (400 MHz, $CDCl_3$) 7.22-7.46 (20H, m, ArH), 4.54 (2H, s, CH_2Ph), 4.16(1H, m, C<u>H</u>OH), 3.58 (1H, dd, *J* = 5.0, 4.0, Hz, CHOBn), 3.22 (1H, dd, *J* = 9.0, 5.5 Hz, C<u>H$_a$</u>H$_b$OTr), 3.19 (1H, dd, *J* = 9.0, 5.5 Hz, CH$_a$<u>H$_b$</u>OTr), 2.22 (1H, m, C<u>H</u>CH$_2$OTr), 1.83-1.97 (2H, m, C<u>H$_a$</u>H$_b$CH$_2$CH + C<u>H$_a$</u>H$_b$CHOH), 1.60-1.74 (3H, m, CH$_a$<u>H$_b$</u>CHOH + CH$_a$<u>H$_b$</u>CH$_2$CH + OH)

^{13}C NMR (100 MHz, $CDCl_3$) 144.3 × 3 (C_{Ar} × 3), 138.8 (C_{Ar}), 128.9 × 6 (CH_{Ar} × 6), 128.5 × 2 (CH_{Ar} × 2), 127.9 × 6 (CH_{Ar} × 6), 127.73 × 2 (CH_{Ar} × 2), 127.65 (CH_{Ar}), 127.1 × 3 (CH_{Ar} × 3), 89.1 (CHOBn), 86.9 (CPh_3), 77.8 (CHOH), 72.0 (CH_2Ph), 65.2 (CH_2OTr), 44.7 (<u>C</u>HCH$_2$OTr), 32.2 (<u>C</u>H$_2$CHOH), 24.7 (<u>C</u>H$_2$CH$_2$CH)

ES$^+$ ***m/z*** (%) 487 ($(M+Na)^+$, 18)

HRMS (ES^+) for $C_{32}H_{32}O_3Na$ $(M+Na)^+$: Calcd 487.2244; Measured 487.2250.

8.68 (1*S*,2*R*,3*R*)-3-Trityloxymethyl-cyclopentane-1,2-diol (5.14)



4.42 (96%) **5.14**

TBAF (1.0 M solution in THF; 0.68 mL, 0.680 mmol) was added to a solution of **4.42** (138 mg, 0.282 mmol) in THF (1.8 mL). The mixture was stirred at room temperature for 20 minutes. The solvent was removed *in vacuo* and the residue was purified by column chromatography (acetone/petroleum ether 4:6) to afford **5.14** as a white solid (102 mg, 96%).

M.W. 374.47 (374.1882)

mp 133-134 °C

$[\alpha]_D$ = -13.8 (*c* = 0.26, $CHCl_3$, 27 °C)

IR ν_{max}/cm^{-1} 3381 br, 3086 w, 3057 w, 3032 w, 2928 br, 2870 w, 1713 br m, 1597 w, 1490 m, 1466 w, 1443 m

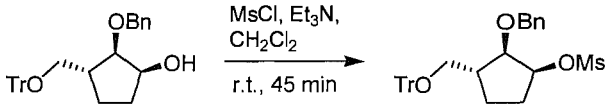
^{1}H NMR (400 MHz, $CDCl_3$) 7.24-7.44 (15H, m, ArH), 4.09 (1H, tt, J = 4.5, 2.5 Hz, HOC$\underline{H}$CH$_2$), 3.73 (1H, ddd, J = 8.5, 4.5, 2.5 Hz, CHC$\underline{H}$CH), 3.42 (1H, dd, J = 9.0, 5.0 Hz, C$\underline{H}_a$H$_b$OTr), 3.04 (1H, t, J = 9.0 Hz, CH$_a\underline{H}_b$OTr), 2.99 (1H, d, J = 2.5 Hz, OH), 2.47 (1H, dd, J = 2.0, 1.0 Hz, OH), 2.36 (1H, quintet of doublet, J = 8.5, 5.0 Hz, C$\underline{H}$CH$_2$OTr), 1.79-1.93 (2H, m, HOCHC$\underline{H}_a$H$_b$ + C$\underline{H}_a$H$_b$CH$_2$CH), 1.72 (1H, m, HOCHCH$_a\underline{H}_b$), 1.13 (1H, m, CH$_a\underline{H}_b$CH$_2$CH)

^{13}C NMR (100 MHz, $CDCl_3$) 144.0 × 3 (C_{Ar} × 3), 128.8 × 6 (CH_{Ar} × 6), 128.1 × 6 (CH_{Ar} × 6), 127.3 × 3 (CH_{Ar} × 3), 87.3 (CPh_3), 79.3 (CH$\underline{C}$HCH), 73.3 (HO$\underline{C}$HCH$_2$), 67.2 (CH_2OTr), 43.2 ($\underline{C}$HCH$_2$OTr), 30.0 (HOCH$\underline{C}$H$_2$), 25.1 ($\underline{C}$H$_2$CH$_2$CH)

ES$^+$ ***m/z*** (%) 397 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{25}H_{26}O_3Na$ $(M+Na)^+$: Calcd 397.1774; Measured 397.1782.

8.69 (1*S*,2*R*,3*R*)-2-Benzyloxy-3-trityloxymethyl-cyclopentylmethane sulfonate (5.15)



4.75 (98%) **5.15**

MsCl (5.3 μL, 0.0678 mmol) was added to a solution of **4.75** (21.0 mg, 0.0452 mmol) and Et_3N (9.5 μL, 0.0678 mmol) in CH_2Cl_2 (0.45 mL). The mixture was stirred at room temperature for 45 minutes. The solvent was evaporated *in vacuo* and the crude was purified by column chromatography (acetone/petroleum ether 25:75) to afford **5.15** as white crystals (24 mg, 98%).

M.W. 542.69 (542.2127)

mp 139-140 °C (CH_2Cl_2/petroleum ether)

$[\alpha]_D$ = +54.1 (c = 0.61, $CHCl_3$, 26 °C)

IR ν_{max}/cm^{-1} 3058 w, 3031 w, 2937 w, 2871 w, 1490 w, 1449 m, 1354 s

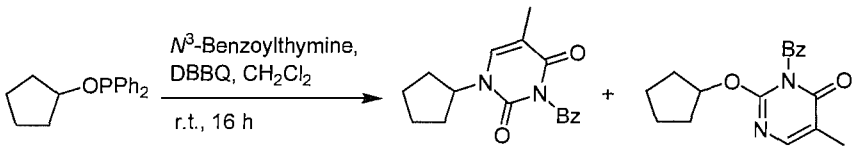
^{1}H NMR (400 MHz, $CDCl_3$) 7.22-7.44 (20H, m, ArH), 5.19 (1H, m, CHOS), 4.65 (1H, d, J = 11.5 Hz, $C\underline{H}_aH_bPh$), 4.43 (1H, d, J = 11.5 Hz, $CH_a\underline{H}_bPh$), 3.81 (1H, dd, J = 9.0, 4.0 Hz, CHOBn), 3.23 (1H, dd, J = 9.0, 4.5 Hz, $C\underline{H}_aH_bOTr$), 3.16 (1H, dd, J = 9.0, 5.5 Hz, $CH_a\underline{H}_bOTr$), 2.97 (3H, s, SO_2CH_3), 2.38 (1H, m, $C\underline{H}CH_2OTr$), 1.94-2.11 (3H, m, $C\underline{H}_2CHOS$ + $C\underline{H}_aH_bCH_2CHOS$), 1.63 (1H, m, $CH_a\underline{H}_bCH_2CHOS$)

^{13}C NMR (100 MHz, $CDCl_3$) 144.2 × 3 (C_{Ar} × 3), 137.9 (C_{Ar}), 128.9 × 6 (CH_{Ar} × 6), 128.5 × 2 (CH_{Ar} × 2), 128.1 × 2 (CH_{Ar} × 2), 127.9 × 7 (CH_{Ar} × 7), 127.1 × 3 (CH_{Ar} × 3), 86.6 (CPh_3), 81.9 × 2 (CHOBn + CHOS), 72.6 (CH_2Ph), 63.5 (CH_2OTr), 42.0 ($\underline{C}HCH_2OAc$), 39.0 (SO_2CH_3), 28.9 ($\underline{C}H_2CHOS$), 22.9 ($\underline{C}H_2CH_2CHOS$)

ES$^+$ ***m/z*** (%) 565 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{33}H_{34}O_5S$ $(M+Na)^+$: Calcd 565.2019; Measured 565.2032.

8.70 3-Benzoyl-1-cyclopentyl-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (5.24) and 3-benzoyl-2-cyclopentyloxy-5-methylpyrimidin-4(3*H*)-one and (5.25)

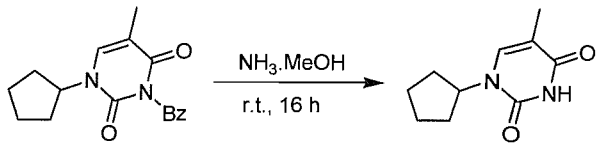


5.22 **5.24** (41%) **5.25** (46%)

A mixture of di-*tert*-butylbenzoquinone (DBBQ; 45.0 mg, 0.203 mmol), cyclopentanol **5.22** (50.0 mg, 0.185 mmol) and N^3-benzoylthymine **5.4** (47.0 mg, 0.203 mmol) in CH_2Cl_2 (1.85 mL) was stirred at room temperature for 16 hours. The solution was concentrated *in vacuo* and purified by column chromatography (EtOAc/petroleum ether 3:7) to afford **5.24** (22.7 mg, 41%) and **5.25** (25.4 mg, 46%) as oils.

See compounds 6.5 and 6.6 for characterisation data

8.71 1-Cyclopentyl-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (6.5)



5.24 **6.5**

A mixture of **5.24** (14.3 mg, 0.0479 mmol) and NH_3 (7 N solution in MeOH; 0.45 mL, 3.15 mmol) was stirred at room temperature for 16 hours. The solvent was evaporated *in vacuo* and the crude was purified by column chromatography ($MeOH/CH_2Cl_2$ 5:95) to afford **6.5** as a colourless oil (8.1 mg, 87%).

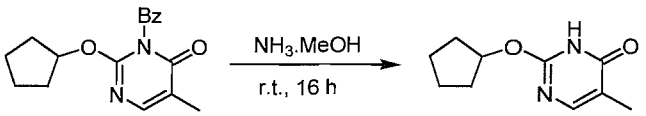
M.W. 194.23 (194.1055)

^{1}H NMR (400 MHz, $CDCl_3$) 11.13 (1H, s, NH), 7.51 (1H, s, CH=C), 4.72 (1H, quintet, J = 8.5 Hz, CHN), 1.85-1.94 (2H, m, CH_2), 1.78 (3H, s, CH_3), 1.52-1.80 (6H, m, CH_2)

^{13}C NMR (100 MHz, $CDCl_3$) 163.7 (C=O), 150.9 (C=O), 137.8 (<u>C</u>H=C), 109.1 (CH=<u>C</u>), 55.7 (CHN), 30.3 × 2 (CH_2CHN × 2), 23.6 × 2 (<u>C</u>H_2CH_2CHN × 2), 12.0 (CH_3)

^{1}H NMR and **^{13}C NMR** corresponded to the previously reported values.[149]

8.72 2-(Cyclopentyloxy)-5-methylpyrimidin-4(3*H*)-one (6.6)



5.25 **6.6**

A mixture of **5.25** (15.3 mg, 0.0513 mmol) and NH_3 (7 N solution in MeOH; 0.51 mL, 3.57 mmol) was stirred at room temperature for 16 hours. The solvent was evaporated *in vacuo* and the crude was purified by column chromatography ($MeOH/CH_2Cl_2$ 5:95) to afford **6.6** as a colourless oil (7.0 mg, 70%).

M.W. 194.23 (194.1055)

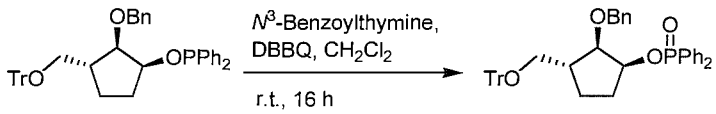
^{1}H NMR (400 MHz, $CDCl_3$) 12.00 (1H, s, NH), 7.54 (1H, s, CH=C), 5.30 (1H, tt, J = 6.0, 2.5 Hz, CHO), 1.84-1.93 (2H, m, CH_2), 1.81 (3H, s, CH_3), 1.52-1.75 (6H, m, CH_2)

^{13}C NMR (100 MHz, $CDCl_3$) 164.0 (C=O), 156.0 (NCN), 116.1 (CH=C), 79.6 (CHO), 32.1 × 2 (CH_2CHO × 2), 23.2 × 2 (CH_2CH_2CHO × 2), 12.2 (CH_3)

*Note that the ^{13}C NMR signal for CH=C was not present in the spectrum.

^{1}H NMR and **^{13}C NMR** corresponded to the previously reported values.[149]

8.73 (1*S*,2*R*,3*R*)-Diphenylacetic acid 2-benzyloxy-3-trityloxymethyl-cyclopentyl ester (5.27)



5.26 (87%) **5.27**

A mixture of di-*tert*-butylbenzoquinone (DBBQ; 6.4 mg, 0.0290 mmol), **5.26** (17.1 mg, 0.0264 mmol) and N^3-benzoylthymine **5.4** (25.1 mg, 0.109 mmol) in CH_2Cl_2 (0.53 mL) was stirred at room temperature for 16 hours. The solution was concentrated *in vacuo* and purified by column chromatography (acetone/petroleum ether 2:8) to afford **5.27** (15.2 mg, 87%) as a white solid.

M.W. 664.77 (664.2742)

mp 48-51 °C

$[\alpha]_D$ = +49.6 (c = 1.8, $CHCl_3$, 26 °C)

IR ν_{max}/cm^{-1} 3057 w, 3031 w, 2948 w, 2867 w, 1594 w, 1489 w, 1448 m, 1439 m

^{1}H NMR (400 MHz, $CDCl_3$) 7.79-7.87 (4H, m, ArH), 7.19-7.55 (26H, m, ArH), 4.94 (1H, m, CHOP), 4.57 (1H, d, J = 12.0 Hz, CH_aH_bPh), 4.39 (1H, d, J = 12.0 Hz, CH_aH_bPh), 3.76 (1H, dd, J = 8.0, 4.0 Hz, CHOBn), 3.19 (1H, dd, J = 9.0, 5.0 Hz, CH_aH_bOTr), 3.15 (1H, dd, J = 9.0, 4.0 Hz, CH_aH_bOTr), 2.53 (1H, m, $CHCH_2OTr$),

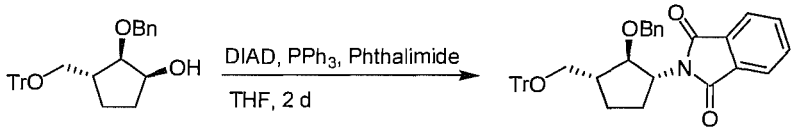
1.99-2.08 (2H, m, $C\underline{H}_aH_bCHO$ + $C\underline{H}_aH_bCH_2CH$), 1.86 (1H, m, $C\underline{H}_2CHO$), 1.52 (1H, m, $CH_a\underline{H}_bCH_2CH$)

^{13}C NMR (100 MHz, $CDCl_3$) 144.4 × 3 (C_{Ar} × 3), 138.5 (C_{Ar}), 132.9 (d, J = 137.0 Hz, C_{Ar}), 132.3 (d, J = 125.0 Hz, C_{Ar}), 132.10 (d, J = 2.5 Hz, CH_{Ar}), 132.01 (d, J = 2.5 Hz, CH_{Ar}), 131.94 × 2 (d, J = 10.0 Hz, CH_{Ar} × 2), 131.76 × 2 (d, J = 10.0 Hz, CH_{Ar} × 2), 128.9 × 6 (CH_{Ar} × 6), 128.54 × 2 (d, J = 13.0 Hz, CH_{Ar} × 2), 128.46 × 2 (d, J = 13.0 Hz, CH_{Ar} × 2), 128.3 × 2 (CH_{Ar} × 2), 127.9 × 6 (CH_{Ar} × 6), 127.8 × 2 (CH_{Ar} × 2), 127.5 (CH_{Ar}), 127.0 × 3 (CH_{Ar} × 3), 86.5 (CPh_3), 82.3 (CHOBn), 75.9 (CHOP), 71.9 (CH_2Ph), 64.2 (CH_2OTr), 42.3 ($\underline{C}HCH_2OTr$), 30.0 ($\underline{C}H_2CHO$), 23.1 ($\underline{C}H_2CH_2CH$)

ES$^+$ ***m/z*** (%) 687 ($(M+Na)^+$, 12)

HRMS (ES^+) for $C_{44}H_{41}O_3PNa$ $(M+Na)^+$: Calcd 687.2635; Measured 687.2639.

8.74 2-((1*R*,2*R*,3*R*)-2-Benzyloxy-3-trityloxymethyl-cyclopentyl) isoindoline-1,3-dione (5.28)



4.75 (94%) **5.28**

DIAD (70.0 μL, 0.333 mmol) was added to a solution of PPh_3 (87.3 mg, 0.333 mmol) in THF (2.2 mL) at 0 °C and the mixture was stirred for 0.5 hour. Alcohol **4.75** (103 mg, 0.222 mmol) in THF (2.2 mL) was then added, followed by phthalimide (98.0 mg, 0.666 mmol) and the mixture was stirred at room temperature for 2 days. The solvent was evaporated *in vacuo* and the crude was purified by column chromatography (EtOAC/petroleum ether 2:8) to afford **5.28** as a white solid (124 mg, 94%).

M.W. 593.71 (593.2566)

mp 52-55 °C

$[\alpha]_D$ = -13.6 (c = 0.54, $CHCl_3$, 27 °C)

IR ν_{max}/cm^{-1} 3085 w, 3059 w, 3031 w, 2946 w, 2915 w, 2872 w, 1770 w, 1708 vs, 1612 w, 1596 w, 1490 w, 1467 w, 1448 w, 1387 m

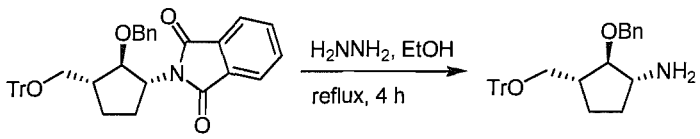
^{1}H NMR (400 MHz, $CDCl_3$) 7.74-7.79 (2H, m, ArH), 7.66-7.71 (2H, m, ArH), 6.91-7.53 (20H, m, ArH), 4.60 (1H, dt, J = 9.5, 8.0 Hz, CHN), 4.44 (1H, t, J = 8.0 Hz, CHOBn), 4.39 (1H, d, J = 12.0 Hz, $C\underline{H}_aH_bPh$), 4.23 (1H, d, J = 12.0 Hz, $CH_a\underline{H}_bPh$), 3.35 (1H, dd, J = 9.0, 5.0 Hz, $C\underline{H}_aH_bOTr$), 3.24 (1H, dd, J = 9.0, 6.0 Hz, $CH_a\underline{H}_bOTr$), 2.31 (1H, m, $C\underline{H}CH_2OTr$), 1.94-2.11 (4H, m, $CH_2 \times 2$)

^{13}C NMR (100 MHz, $CDCl_3$) 168.2 × 2 (C=O × 2), 144.4 × 3 (C_{Ar} × 3), 138.7 (C_{Ar}), 133.8 × 2 (CH_{Ar} × 2), 132.2 × 2 (C_{Ar} × 2), 129.0 × 6 (CH_{Ar} × 6), 128.2 × 2 (CH_{Ar} × 2), 127.9 × 8 (CH_{Ar} × 8), 127.3 (CH_{Ar}), 127.1 × 3 (CH_{Ar} × 3), 123.2 × 2 (CH_{Ar} × 2), 86.6 (CPh_3), 82.8 (CHOBn), 72.4 (CH_2Ph), 64.5 (CH_2OTr), 56.5 (CHN), 45.1 ($\underline{C}HCH_2OTr$), 26.1 (CH_2), 25.1 (CH_2)

ES$^+$ ***m/z*** (%) 616 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{40}H_{35}NO_4Na$ $(M+Na)^+$: Calcd 616.2458; Measured 616.2466.

8.75 (1*R*,2*R*,3*R*)-2-Benzyloxy-3-trityloxymethyl-cyclopentamine (5.29)



5.28 (44%) **5.29**

Hydrazine (28.0 μL, 0.570 mmol) and **5.28** (84.7 mg, 0.143 mmol) in EtOH (1.4 mL) were stirred at reflux for 4 hours. The mixture was cooled, filtered and concentrated *in vacuo*. The crude was purified by column chromatography (acetone/petroleum ether 2:8) to afford a mixture of compounds which was purified further by HPLC ($MeOH/CH_2Cl_2$ 5:95) to afford amine **5.29** as a clear oil (26.1 mg, 44%).

M.W. 463.61 (463.2511)

$[\alpha]_D$ = +5.7 (c = 1.1, $CHCl_3$, 27 °C)

IR ν_{max}/cm^{-1} 3059 w, 3030 w, 2948 w, 2867 w, 1662 w, 1597 w, 1491 m, 1449 m

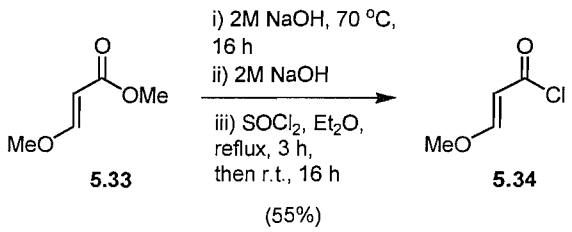
^{1}H NMR (400 MHz, $CDCl_3$) 7.23-7.50 (20H, m, ArH), 4.55 (1H, d, J = 12.0 Hz, $C\underline{H}_aH_bPh$), 4.48 (1H, d, J = 12.0 Hz, $C\underline{H}_aH_bPh$), 3.36 (1H, t, J = 6.0 Hz, CHOBn), 3.27 (1H, m, CHN), 3.22 (1H, dd, J = 9.0, 6.0 Hz, $C\underline{H}_aH_bOTr$), 3.16 (1H, dd, J = 9.0, 6.5 Hz, $CH_a\underline{H}_bOTr$), 2.26 (1H, m, $C\underline{H}CH_2OTr$), 1.85-1.97 (2H, m, $C\underline{H}_aH_bCH_2CH$ + $C\underline{H}_aH_bCHN$), 1.60 (1H, m, $CH_a\underline{H}_bCH_2CH$), 1.28-1.41 (3H, m, $CH_a\underline{H}_bCHN + NH_2$)

^{13}C NMR (100 MHz, $CDCl_3$) 144.4 × 3 (C_{Ar} × 3), 139.0 (C_{Ar}), 128.9 × 6 (CH_{Ar} × 6), 128.5 × 2 (CH_{Ar} × 2), 127.9 × 6 (CH_{Ar} × 6), 127.7 × 2 (CH_{Ar} × 2), 127.6 (CH_{Ar}), 127.1 × 3 (CH_{Ar} × 3), 90.6 (CHOBn), 86.7 (CPh_3), 72.3 (CH_2Ph), 65.5 (CH_2OTr), 58.7 (CHN), 45.1 ($\underline{C}HCH_2OTr$), 32.2 ($\underline{C}H_2CHN$), 25.2 ($\underline{C}H_2CH_2CH$)

ES$^+$ ***m/z*** (%) 504 ($(M+MeCN)^+$, 25)

HRMS (ES^+) for $C_{32}H_{34}NO_2$ $(M+H)^+$: Calcd 464.2584; Measured 464.2577.

8.76 (*E*)-3-Methoxyacryloyl chloride (5.34)



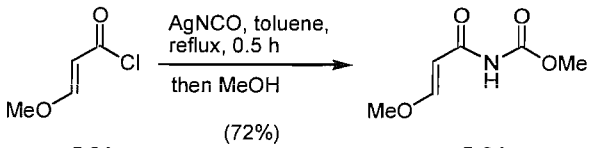
2M NaOH (90 mL) was added to (*E*)-Methyl-3-methoxyacrylate **5.33** (36.9 mL, 0.343 mol). NaOH solid was then added to the mixture until a deep red solution was obtained. The solution was then stirred at 70 °C for 16 hours before it was cooled and acidified with 2M HCl to precipitate the methoxyacrylic acid (21.2 g, 61%).

The carboxylic acid was then neutralised with 2M NaOH, concentrated *in vacuo* and dried in a dessicator under high vacuum for 4 hours. Et_2O (342 mL) was added to the solid, followed by $SOCl_2$ (16.2 mL 0.222 mol) dropwise. The mixture was stirred at reflux for 3 hours and at room temperature for a further 16 hours. The resultant suspension was filtered, concentrated *in vacuo* (beware when concentrating $SOCl_2$) and purified by distillation under vacuum (100 °C, 35 mmHg)* to afford acyl chloride **5.34** as a clear liquid (2.15 g, 90%; 55% overall).

* Acyl chloride **5.34** was very moisture senstive. Although it could be stored in a sealed container in the freezer for a certain period of time, it was used immediately in the in the next transformation.

* Polymerisation was observed at temperature above 100 °C. Therefore the distillation should be performed at a vacuum stronger than 35 mmHg.

8.77 Methyl (*E*)-3-methoxyacryloylcarbamate (5.31)



5.34 **5.31**

A mixture of **5.34** (1.55 g, 12.9 mmol) and AgNCO (2.50 g, 16.7 mmol) in toluene (42.9 mL) was stirred at reflux for 30 minutes. The suspension was cooled and MeOH (3 mL) was added. The resultant mixture was stirred for a further 5 minutes, filtered, concentrated *in vacuo* and recrystallised from CH_2Cl_2/petroleum ether to afford carbamate **5.31** (1.47 g, 72%) as yellow crystals.

M.W. 159.14 (159.0532)

mp 123-124 °C (CH_2Cl_2/petroleum ether)

IR ν_{max}/cm^{-1} 3208 w, 3127 w, 2987 w, 1759 s, 1684 s, 1617 s, 1497 m, 1457 w, 1439 w, 1206 vs

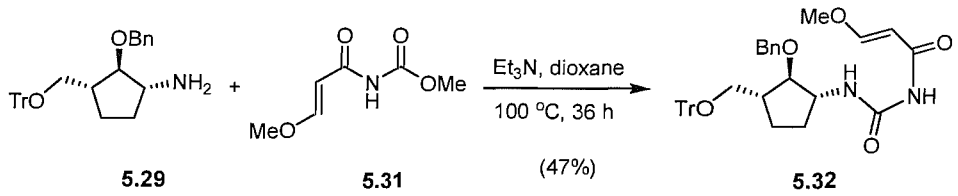
^{1}H NMR (300 MHz, $CDCl_3$) 7.83 (1H, d, J = 12.5 Hz, C<u>H</u>=CH), 7.50 (1H, br, NH), 6.46 (1H, d, J = 12.5 Hz, CH=C<u>H</u>), 3.78 (6H, s, CH_3 × 2)

^{13}C NMR (75MHz, $CDCl_3$) 167.3 (C=O), 165.5 (C=O), 152.7 (<u>C</u>=C), 96.4 (C=<u>C</u>), 57.8 (CH_3), 53.0 (CH_3)

ES$^+$ ***m/z*** (%) 182 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_6H_9NO_4Na$ $(M+Na)^+$: Calcd 182.0424; Measured 182.0425

8.78 1-((1*R*,2*R*,3*R*)-2-Benzyloxy-3-trityloxymethyl-cyclopentyl)-3-((*E*)-3-methoxyacryloyl)urea (5.32)



5.29 **5.31** **5.32**

A mixture of amine **5.29** (36.9 mg, 0.0796 mmol), Et_3N (13.3 μl, 0.0955 mmol) and carbamate **5.31** (14.3 mg, 0.0955 mmol) in dioxane (0.8 mL) was stirred at 100 °C for 36 hours. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (acetone/petroleum ether 3:7) to afford carbanucleoside precursor **5.32** as a white foam (22.3 mg, 47%).

M.W. 590.71 (590.2781)

$[\alpha]_D$ = -5.9 (*c* = 0.67, $CHCl_3$, 27 °C)

IR ν_{max}/cm^{-1} 3233 br, 3087 w, 3061 w, 2958 br, 2868 w, 1701 m, 1677 s, 1616 m, 1549 s, 1491 m, 1449 m

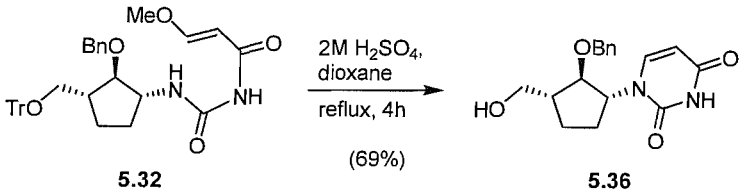
^{1}H NMR (400 MHz, $CDCl_3$) 9.96 (1H, s, NH), 8.81 (1H, d, *J* = 12.5 Hz, NH), 7.65 (1H, d, *J* = 12.5 Hz, C<u>H</u>=CH), 7.20-7.45 (20H, m, ArH), 5.39 (1H, d, *J* = 12.5 Hz, CH=C<u>H</u>), 4.66 (1H, d, *J* = 11.5 Hz, C<u>H$_a$</u>H$_b$Ph), 4.54 (1H, d, *J* = 11.5 Hz, CH$_a$<u>H$_b$</u>Ph), 4.24 (1H, tt, *J* = 7.5, 5.0 Hz, CHN), 3.71 (1H, m, CHOBn), 3.61 (3H, s, OMe), 3.15 (2H, app. d, *J* = 6.0 Hz, CH_2OTr), 2.29 (1H, tq, *J* = 8.5, 6.0 Hz, C<u>H</u>CH$_2$OTr), 2.11 (1H, m, C<u>H$_a$</u>H$_b$CHN), 1.96 (1H, m, C<u>H$_a$</u>H$_b$CH$_2$CH), 1.54-1.66 (2H, m, CH$_a$<u>H$_b$</u>CHN + CH$_a$<u>H$_b$</u>CH$_2$CH)

^{13}C NMR (100 MHz, $CDCl_3$) 168.1 (C=O), 163.4 (C=O), 155.1 (<u>C</u>H=CH), 144.3 × 3 (C_{Ar} × 3), 138.7 (C_{Ar}), 128.9 × 6 (CH_{Ar} × 6), 128.4 × 2 (CH_{Ar} × 2), 127.9 × 6 (CH_{Ar} × 6), 127.7 × 2 (CH_{Ar} × 2), 127.5 (CH_{Ar}), 127.0 × 3 (CH_{Ar} × 3), 97.8 (CH=<u>C</u>H), 87.6 (CHOBn), 86.6 (CPh_3), 72.1 (CH_2Ph), 65.0 (CH_2OTr), 57.8 (OCH_3), 56.5 (CHN), 45.6 (<u>C</u>HCH$_2$OTr), 30.3 (<u>C</u>H$_2$CHN), 25.8 (<u>C</u>H$_2$CH$_2$CH)

ES$^+$ ***m/z*** (%) 613 ($(M+Na)^+$, 12)

HRMS (ES^+) for $C_{17}H_{20}N_2O_4Na$ $(M+Na)^+$: Calcd 613.2673; Measured 613.2684.

8.79 1-((1*R*,2*R*,3*R*)-2-Benzyloxy-3-hydroymethyl-cyclopentyl)-pyrimidine-2,4(1*H*,3*H*)dione (5.36)



5.32 5.36

A solution of urea **5.32** (53.2 mg, 0.0901 mmol) in 2M H_2SO_4/dioxane (1:1; 1.8 mL) was stirred at reflux for 4 hours. 2M NaOH (0.9 mL) was added and neutralisation was completed by the addition of sat. $NaHCO_3$. The solvent was evaporated *in vacuo* and the residue was suspended in EtOH (5 mL) and sonicated (or vigorously stirred) for 5 minutes. The ethanolic suspension was filtered, concentrated *in vacuo* and purified by column chromatography (MeOH/CH_2Cl_2 4:96) to afford carbanucleoside derivative **5.36** as a white solid (19.7 mg, 69%).

M.W. 316.35 (316.1423)

mp 115-116 °C

$[\alpha]_D$ = -5.1 (*c* = 0.87, $CHCl_3$, 27 °C)

IR ν_{max}/cm^{-1} 3412 br, 3197 br, 3059 w, 2947 w, 2876 w, 1678 vs, 1464 m, 1421 w, 1380 m

^{1}H NMR (400 MHz, $CDCl_3$) 7.22-7.31 (5H, m, ArH), 7.11 (1H, d, *J* = 8.0 Hz, C<u>H</u>=CH), 5.62 (1H, d, *J* = 8.0 Hz, CH=C<u>H</u>), 4.57 (1H, d, *J* = 12.0 Hz, C<u>H</u>$_a$H$_b$Ph), 4.56 (1H, td, *J* = 9.5, 7.5 Hz, CHN), 4.50 (1H, d, *J* = 12.0 Hz, CH$_a$<u>H</u>$_b$Ph), 4.17 (1H, t, *J* = 7.0 Hz, CHOBn), 3.77 (1H, dd, *J* = 10.5, 5.5 Hz, C<u>H</u>$_a$H$_b$OH), 3.74 (1H, dd, *J* = 10.5, 6.0 Hz, CH$_a$<u>H</u>$_b$OH), 2.26 (1H, m, C<u>H</u>CH$_2$OH), 2.08 (1H, m, C<u>H</u>$_a$H$_b$CHN), 1.87-1.99 (2H, m, C<u>H</u>$_a$H$_b$CH$_2$CH + CH$_a$<u>H</u>$_b$CHN), 1.71 (1H, m, CH$_a$<u>H</u>$_b$CH$_2$CH)

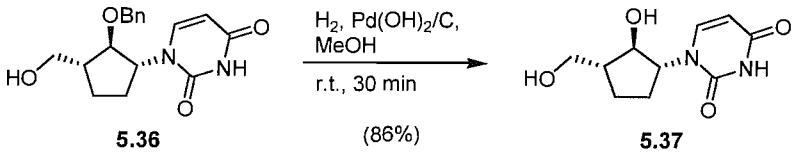
^{13}C NMR (100 MHz, $CDCl_3$) 163.6 (C=O), 151.1 (C=O), 143.1 (<u>C</u>=C), 138.1 (C_{Ar}), 128.6 × 2 (CH_{Ar} × 2), 128.1 × 3 (CH_{Ar} × 3), 102.7 (C=<u>C</u>), 83.2 (CHOBn), 72.2 (CH_2Ph), 66.4 (CHN), 64.1 (CH_2OH), 45.8 (<u>C</u>HCH$_2$OH), 27.7 (<u>C</u>H$_2$CHN), 24.3 (<u>C</u>H$_2$CH$_2$CH)

ES$^+$ ***m/z*** (%) 317 ($(M+H)^+$, 100)

HRMS (ES$^+$) for $C_{17}H_{20}N_2O_4Na$ $(M+Na)^+$: Calcd 339.1315; Measured 339.1323.

*Note that the ^{1}H NMR signals for OH and NH seemed to be a very broad signal between 3.7-4.6 ppm, presumably due to significant hydrogen bonding.

8.80 1-((1*R*,2*R*,3*R*)-2-Hydroxy-3-hydroxymethyl-cyclopentyl)-pyrimidine-2,4(1*H*,3*H*)-dione (5.37)



A mixture of $Pd(OH)_2$ on carbon (20% Pd; 10.0 mg, 0.0142 mmol) and **5.36** (22.4 mg, 0.0709 mmol) in MeOH (0.7 mL) was stirred under a hydrogen atmosphere (balloon) at room temperature for 30 minutes. The mixture was then filtered through celite, concentrated *in vacuo* and purified by HPLC ($MeOH/CH_2Cl_2$ 2:8) to afford carbanucleoside **5.37** (13.8 mg, 86%) as a white solid.

M.W. 226.23 (226.0954)

$[\alpha]_D$ = -6.0 (*c* = 0.47, $CHCl_3$, 27 °C)

IR ν_{max}/cm^{-1} 3367 br, 3052 w, 2952 w, 2879 w, 1662 vs, 1468 m, 1417 m, 1383 m

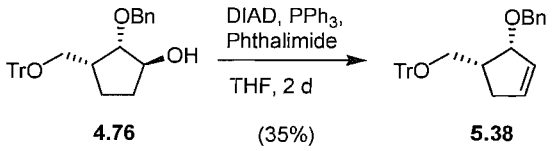
^{1}H NMR (400 MHz, MeOD) 7.63 (1H, d, *J* = 8.0 Hz, C<u>H</u>=CH), 5.69 (1H, d, *J* = 8.0 Hz, CH=C<u>H</u>), 4.59 (1H, q, *J* = 9.0 Hz, CHN), 4.04 (1H, t, *J* = 9.0 Hz, C<u>H</u>OH), 3.73 (1H, dd, *J* = 11.0, 4.5 Hz, C<u>H$_a$</u>H$_b$OH), 3.60 (1H, dd, *J* = 11.0, 6.5 Hz, CH$_a$<u>H$_b$</u>OH), 1.89-2.12 (3H, m, C<u>H</u>CH$_2$OH + C<u>H$_a$</u>H$_b$CHN + C<u>H$_a$</u>H$_b$CH$_2$CH), 1.66-1.83 (2H, m, CH$_a$<u>H$_b$</u>CHN + CH$_a$<u>H$_b$</u>CH$_2$CH)

^{13}C NMR (100 MHz, MeOD) 166.5 (C=O), 153.3 (C=O), 144.5 (<u>C</u>=C), 102.6 (C=<u>C</u>), 76.6 (CHOH), 65.7 (CHN), 64.2 (CH_2OH), 47.1 (<u>C</u>HCH$_2$OH), 26.6 (<u>C</u>H$_2$CHN), 23.8 (<u>C</u>H$_2$CH$_2$CH)

ES$^+$ ***m/z*** (%) 227 ($(M+H)^+$, 100)

HRMS (ES^+) for $C_{10}H_{15}N_2O_4$ $(M+H)^+$: Calcd 227.1026; Measured 227.1028.

8.81 (((1*R*,2*R*)-2-Benzyloxy-cyclopent-3-enyl)methoxy)triphenyl methane (5.38)



4.76 (35%) **5.38**

DIAD (65.0 μL, 0.310 mmol) was added to a solution of PPh_3 (81.4 mg, 0.310 mmol) in THF (2.1 mL) at 0 °C and the mixture was stirred for 30 minutes. A solution of alcohol **4.76** (96.1 mg, 0.207 mmol) in THF (2.1 mL) followed by phthalimide (91.3 mg, 0.621 mmol) was added and the mixture was stirred at room temperature for 1 day. The solvent was evaporated *in vacuo* and the crude was purified by column chromatography (acetone/petroleum ether 15:85) to afford **5.38** as a colourless oil (32.1 mg, 35%).

M.W. 446.58 (446.2246)

$[\alpha]_D$ = -25.0 (*c* = 1.1, $CHCl_3$, 27 °C)

IR ν_{max}/cm^{-1} 3085 w, 3058 w, 3030 w, 2930 w, 2873 w, 1597 w, 1491 m, 1448 m, 1389 w

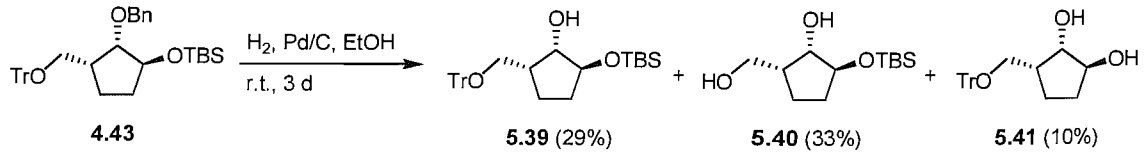
^{1}H NMR (400 MHz, $CDCl_3$) 7.22-7.50 (20H, m, ArH), 6.03 (1H, dt, *J* = 6.0, 2.5 Hz, C<u>H</u>=CH), 5.92 (1H, dq, *J* = 6.0, 2.5 Hz, CH=C<u>H</u>), 4.53 (1H, dt, *J* = 6.5, 2.0, Hz, CHOBn), 4.49 (1H, d, *J* = 12.0 Hz, C<u>H</u>$_a$H$_b$Ph), 4.42 (1H, d, *J* = 12.0 Hz, CH$_a$<u>H</u>$_b$Ph), 3.48 (1H, dd, *J* = 9.0, 7.5 Hz, C<u>H</u>$_a$H$_b$OTr), 3.28 (1H, dd, *J* = 9.0, 7.5 Hz, CH$_a$<u>H</u>$_b$OTr), 2.60 (1H, sextet, *J* = 7.5 Hz, C<u>H</u>CH$_2$OTr), 2.44 (1H, dddd, *J* = 16.5, 7.5, 2.5, 2.0 Hz, C<u>H</u>$_a$H$_b$C=C), 2.28 (1H, ddq, *J* = 16.5, 7.0, 2.0 Hz, CH$_a$<u>H</u>$_b$C=C)

^{13}C NMR (100 MHz, $CDCl_3$) 144.7 × 3 (C_{Ar} × 3), 139.2 (C_{Ar}), 135.7 (<u>C</u>=C), 131.1 (C=<u>C</u>), 129.0 × 6 (CH_{Ar} × 6), 128.3 × 2 (CH_{Ar} × 2), 127.8 × 6 (CH_{Ar} × 6), 127.6 × 2 (CH_{Ar} × 2), 127.3 (CH_{Ar}), 127.0 × 3 (CH_{Ar} × 3), 86.7 (CPh_3), 83.2 (CHOBn), 71.6 (CH_2Ph), 63.2 (CH_2OTr), 42.9 (<u>C</u>HCH_2OTr), 35.3 (CH_2C=C)

ES$^+$ ***m/z*** (%) 469 ($(M+Na)^+$, 50)

HRMS (ES^+) for $C_{32}H_{30}O_2Na$ $(M+Na)^+$: Calcd 469.2138; Measured 469.2144.

8.82 (1*S*,2*S*,5*R*)-2-*tert*-Butyldimethylsilanyloxy-5-trityloxymethyl-cyclopentanol (5.39), (1*S*,2*S*,5*R*)-2-*tert*-butyldimethylsilanyloxy-5-hydroxymethyl-cyclopentanol (5.40) and (1*S*,2*S*,3*R*)-3-trityloxymethyl-cyclopentane-1,2-diol (5.41)



4.43 **5.39** (29%) **5.40** (33%) **5.41** (10%)

A mixture of palladium on carbon (5% Pd; ~90 mg, 0.0424 mmol) and **4.43** (123 mg, 0.212 mmol) in THF (2.1 mL) was stirred under hydrogen atmosphere (balloon) at room temperature for 3 days (the same amount of Pd catalyst was added after 16, 24 and 40 hours). The mixture was filtered through celite, concentrated *in vacuo* and purified by column chromatography (acetone/petroleum ether 3:7) to afford **5.39** (foam; 29.9 mg, 29%), **5.40** (solid; 17.4 mg, 33%) and **5.41** (solid; 8.0 mg, 10%).

Data for 5.39

M.W. 488.73 (488.2747)

$[\alpha]_D$ = +1.4 (*c* = 0.90, $CHCl_3$, 27 °C)

IR ν_{max}/cm^{-1} 3493 br, 3059 w, 2952 m, 2928 m, 2856 w, 1490 m, 1471 w, 1462 w, 1448 m

^{1}H NMR (400 MHz, $CDCl_3$) 7.23-7.46 (15H, m, ArH), 4.02-4.06 (2H, m, CHOSi + C<u>H</u>OH), 3.40 (1H, dd, *J* = 9.0, 4.5 Hz, C<u>H$_a$</u>H$_b$OTr), 3.19 (1H, dd, *J* = 9.0, 7.5 Hz, CH$_a$<u>H$_b$</u>OTr), 2.44 (1H, qt, *J* = 7.5, 4.5 Hz, C<u>H</u>CH$_2$OTr), 2.04 (1H, m, C<u>H$_a$</u>H$_b$CHO), 1.78 (1H, m, C<u>H$_a$</u>H$_b$CH$_2$CH), 1.47-1.60 (2H, m, CH$_a$<u>H$_b$</u>CHO + CH$_a$<u>H$_b$</u>CH$_2$CH), 0.90 (9H, s, SiC(CH$_3$)$_3$), 0.08 (3H, s, SiCH$_3$), 0.07 (3H, s, SiCH$_3$)

^{13}C NMR (100MHz, $CDCl_3$) 144.0 × 3 (C_{Ar} × 3), 128.7 × 6 (CH_{Ar} × 6), 128.1 × 6 (CH_{Ar} × 6), 127.3 × 3 (CH_{Ar} × 3), 87.1 (<u>C</u>Ph$_3$), 80.6* and 79.3* (CHOSi + CHOH), 63.5 (CH_2OTr), 41.6 (<u>C</u>HCH$_2$OTr), 32.5 (<u>C</u>H$_2$CHO), 26.0 × 3 (SiC(<u>C</u>H$_3$)$_3$), 24.1 (<u>C</u>H$_2$CH$_2$CH), 18.2 (SiC), -4.55 (SiCH$_3$), -4.59 (SiCH$_3$)

ES$^+$ ***m/z*** (%) 511 ((M+Na)$^+$, 60)

HRMS (ES^+) for $C_{31}H_{40}O_3SiNa$ $(M+Na)^+$: Calcd 511.2639; Measured 511.2640.

* It was not possible to distinguish between the CHOSi and CHOH signals in the HMQC spectrum.

Data for 5.40

M.W. 246.42 (246.1651)

mp 47-48 °C

$[\alpha]_D$ = +8.2 (*c* = 0.51, $CHCl_3$, 27 °C)

IR ν_{max}/cm^{-1} 3354 br, 2953 m, 2929 m, 2895 m, 2857 m, 1472 w, 1463 w, 1389 w

^{1}H NMR (400 MHz, $CDCl_3$) 4.05 (1H, dt, *J* = 6.0, 3.5 Hz, C<u>H</u>OH), 4.01 (1H, m, CHOSi), 3.84 (1H, ddd, *J* = 11.0, 5.0, 4.5 Hz, C<u>H</u>$_a$H$_b$OH), 3.76 (1H, ddd, *J* = 11.0, 7.0, 5.5 Hz, CH$_a$<u>H</u>$_b$OH), 2.43 (1H, d, *J* = 3.5 Hz, OH), 2.32-2.40 (2H, m, C<u>H</u>CH$_2$OH + OH), 1.98 (1H, m, C<u>H</u>$_a$H$_b$CHO), 1.79 (1H, m, C<u>H</u>$_a$H$_b$CH$_2$CH), 1.46-1.59 (2H, m, CH$_a$<u>H</u>$_b$CHO + CH$_a$<u>H</u>$_b$CH$_2$CH), 0.89 (9H, s, SiC(CH$_3$)$_3$), 0.08 (3H, s, SiCH$_3$), 0.07 (3H, s, SiCH$_3$)

^{13}C NMR (100MHz, $CDCl_3$) 81.2 (CHOH), 79.6 (CHOSi), 63.6 (CH_2OH), 41.5 (<u>C</u>HCH$_2$OH), 31.8 (<u>C</u>H$_2$CHO), 26.0 × 3 (SiC(<u>C</u>H$_3$)$_3$), 23.0 (<u>C</u>H$_2$CH$_2$CH), 18.2 (SiC), -4.49 ($SiCH_3$), -4.56 ($SiCH_3$)

ES^+ ***m/z*** (%) 269 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{12}H_{26}O_3SiNa$ $(M+Na)^+$: Calcd 269.1543; Measured 269.1537.

Data for 5.41

M.W. 374.47 (374.1882)

$[\alpha]_D$ = -16.9 (*c* = 0.21, $CHCl_3$, 27 °C)

IR ν_{max}/cm^{-1} 3414 br, 3086 w, 3058 w, 3032 w, 2929 w, 2876 w, 1490 w, 1448 m

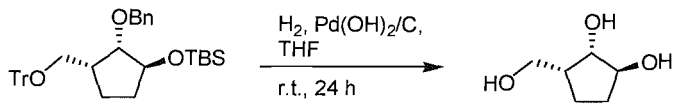
^{1}H NMR (400 MHz, $CDCl_3$) 7.23-7.49 (15H, m, ArH), 4.10-4.12 (2H, m, C<u>H</u>OH × 2), 3.39 (1H, dd, *J* = 9.5, 5.0 Hz, C<u>H</u>$_a$H$_b$OTr), 3.16 (1H, dd, *J* = 9.5, 8.0 Hz, CH$_a$<u>H</u>$_b$OTr), 2.52 (1H, d, *J* = 3.5 Hz, OH), 2.50 (1H, m, C<u>H</u>CH$_2$OTr), 2.11 (1H, m, C<u>H</u>$_a$H$_b$CHO), 1.81 (1H, m, C<u>H</u>$_a$H$_b$CH$_2$CH), 1.47-1.60 (3H, m, CH$_a$<u>H</u>$_b$CHO + CH$_a$<u>H</u>$_b$CH$_2$CH + OH)

^{13}C NMR (100MHz, $CDCl_3$) 143.9 × 3 (C_{Ar} × 3), 128.7 × 6 (CH_{Ar} × 6), 128.1 × 6 (CH_{Ar} × 6), 127.3 × 3 (CH_{Ar} × 3), 87.2 ($\underline{C}Ph_3$), 80.3 (CHOH), 78.9 (CHOH), 63.4 (CH_2OTr), 41.5 ($\underline{C}HCH_2OTr$), 31.6 ($\underline{C}H_2CHO$), 24.0 ($\underline{C}H_2CH_2CH$)

ES$^+$ ***m/z*** (%) 397 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{25}H_{26}O_3Na$ $(M+Na)^+$: Calcd 397.1174; Measured 397.1782.

8.83 (1*S*,2*S*,3*R*)-3-Hydroxymethyl-cyclopentane-1,2-diol (5.42)



4.43 (95%) **5.42**

A mixture of $Pd(OH)_2$ on carbon (20% Pd; 233 mg, 0.332 mmol) and **4.43** (96.2 mg, 0.166 mmol) in THF (1.7 mL) was stirred under hydrogen atmosphere (balloon) at room temperature for 24 hours. The mixture was then filtered through celite, concentrated *in vacuo* and purified by column chromatography ($MeOH/CH_2Cl_2$ 15:85) to afford a white solid **5.42** (20.9 mg, 95%).

M.W. 132.16 (132.0786)

mp 80-81 °C

$[\alpha]_D$ = -83.3 (*c* = 0.60, $CHCl_3$, 27 °C)

IR ν_{max}/cm^{-1} (shows a broad signal at 3322; no further information could be extracted)

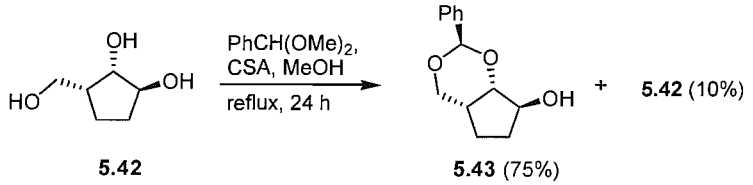
^{1}H NMR (400 MHz, acetone) 3.93-4.01 (2H, m, $C\underline{H}OH$ × 2), 3.69-3.75 (2H, m, $C\underline{H_2}OH$), 2.27 (1H, m, $C\underline{H}CH_2OH$), 2.01 (1H, m, $C\underline{H_a}H_bCHO$), 1.73 (1H, m, $C\underline{H_a}H_bCH_2CH$), 1.42-1.55 (2H, m, $CH_a\underline{H_b}CHO$ + $CH_a\underline{H_b}CH_2CH$)

^{13}C NMR (100MHz, acetone) 80.3 (CHOH), 79.3 (CHOH), 62.7 (CH_2OH), 44.0 ($\underline{C}HCH_2OH$), 32.1 ($\underline{C}H_2CHO$), 24.4 ($\underline{C}H_2CH_2CH$)

ES$^+$ ***m/z*** (%) 155 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_6H_{12}O_3Na$ $(M+Na)^+$: Calcd 155.0679; Measured 155.0677.

8.84 (5R,6S,7S)-2-Phenyl-hexahydro-cyclopenta[1,3]dioxin-7-ol (5.43)



5.42 **5.43** (75%)

A mixture of triol **5.42** (83.2 mg, 0.630 mmol), $PhCH(OMe)_2$ (0.567 mL, 3.78 mmol) and CSA (14.6 mg, 0.0630 mmol) in MeOH (6.3 mL) was stirred at reflux for 24 hours. Upon cooling to room temperature, the reaction mixture was neutralised with anhydrous Na_2CO_3, filtered and concentrated *in vacuo*. The crude was purified by column chromatography (acetone.petroleum ether, then MeOH) to afford **5.43** as a crystalline solid (96.9 mg, 75%) and starting material **5.42** (8.3 mg, 10%).

M.W. 220.26 (220.1099)

mp 73-75 °C

$[\alpha]_D$ = -8.9 (*c* = 0.42, $CHCl_3$, 27 °C)

IR ν_{max}/cm^{-1} 3422 br, 2949 br, 1456 w, 1393 w

^{1}H NMR (400 MHz, $CDCl_3$) 7.32-7.48 (5H, m, ArH), 5.45 (1H, s, OCHO), 4.27 (1H, m, C<u>H</u>OH), 4.22 (1H, dd, *J* = 12.0, 3.0 Hz, C<u>H$_a$</u>H$_b$O), 4.13-4.17 (2H, m, CH$_a$<u>H$_b$</u>O + CHOBn), 2.37 (1H, dddd, *J* = 14.5, 10.5, 6.0, 4.5 Hz, C<u>H$_a$</u>H$_b$CHOH), 2.07-2.23 (2H, m, C<u>H</u>CH$_2$O + C<u>H$_a$</u>H$_b$CH$_2$CH), 1.96 (1H, dtd, *J* = 12.5, 8.5, 4.5 Hz, C<u>H$_a$</u>H$_b$CH$_2$CH), 1.51-1.68 (2H, m, CH$_a$<u>H$_b$</u>CHO + OH)

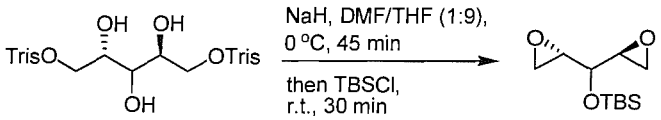
^{13}C NMR (100MHz, $CDCl_3$) 138.8 (C_{Ar}), 129.0 (CH_{Ar}), 128.4 × 2 (CH_{Ar} × 2), 126.2 × 2 (CH_{Ar} × 2), 100.2 (OCO), 84.6 (CHOBn), 77.7 (CHOH), 67.9 (CH_2O), 36.3 (<u>C</u>HCH$_2$O), 33.4 (<u>C</u>H$_2$CHOH), 24.8 (<u>C</u>H$_2$CH$_2$CH)

ES$^+$ ***m/z*** (%) 221 ($(M+H)^+$, 80)

HRMS (ES^+) for $C_{13}H_{16}O_3H$ $(M+H)^+$: Calcd 221.1172; Measured 221.1172.

Additional Compounds

8.85 (2S,4*S*)-1,2:4,5-Diepoxy-3-*tert*-butyl-dimethyl-silanyloxypentane (6.1)



2.11 (38%) **6.1**

NaH (60% dispersion in mineral oil; 0.132 g, 3.30 mmol) was added to a solution of **2.11** (0.523 g, 0.763 mmol) in DMF/THF (1:9, 30 mL) at 0 °C. The mixture was stirred at 0 °C for 45 minutes. TBSCl (0.17 g, 1.13 mmol) was added and the reaction mixture was stirred at room temperature for 30 minutes. Sat. $NaHCO_3$ (10 mL) and Et_2O (10 mL) was added. The aqueous layer was extracted with Et_2O (2 × 10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (Et_2O/petroleum ether 15:85) afforded **6.1** as clear oil (66.0 mg, 38%).

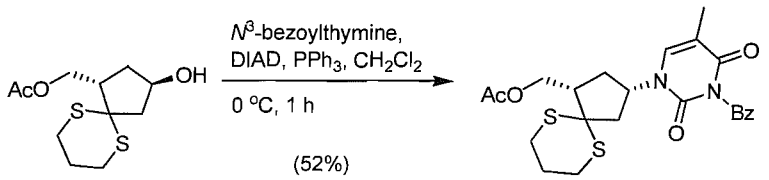
M.W. 230.38 (230.1338)

^{1}H NMR (300 MHz, $CDCl_3$) 3.30 (1H, dd, J = 6.0, 4.5 Hz, CHOSi), 3.06 (1H, ddd, J = 6.0, 4.0, 3.0 Hz, $CH_2C\underline{H}$), 3.00 (1H, ddd, J = 4.5, 4.0, 2.5 Hz, $CH_2C\underline{H}$), 2.82 (1H, dd, J = 5.0, 4.0 Hz, $C\underline{H}_aH_bCH$), 2.75 (1H, dd, J = 5.5, 4.0 Hz, $C\underline{H}_cH_dCH$), 2.70 (1H, dd, J = 5.5, 3.0 Hz, $CH_c\underline{H}_dCH$), 2.69 (1H, dd, J = 5.0, 2.5 Hz, $CH_a\underline{H}_bCH$), 0.89 (9H, s, $SiC(CH_3)_3$), 0.09 (3H, s, $SiCH_3$), 0.05 (3H, s, $SiCH_3$)

^{13}C NMR (75 MHz, $CDCl_3$) 73.6 (CHOSi), 53.9 ($CH_2\underline{C}H$), 52.2 ($CH_2\underline{C}H$), 44.6 ($\underline{C}H_2CH$), 44.2 ($\underline{C}H_2CH$), 25.8 × 3 ($SiC(\underline{C}H_3)_3$), 18.3 (SiC), -4.7 ($SiCH_3$), -4.8 ($SiCH_3$)

^{1}H NMR and **^{13}C NMR** corresponded to the previously reported values.[173]

8.86 (1*S*,3*S*)-Acetic acid 3-(3-benzoyl-5-methyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-6,10-dithiaspiro[4.5]dec-1-ylmethyl ester (6.4)



6.3 **6.4**

DIAD (80 μL, 0.384 mmol) was added to a solution of PPh_3 (101 mg, 0.384 mmol) in CH_2Cl_2 (3.1 mL) at 0 °C and the mixture was stirred for 1 hour. A suspension of 3-benzoylthymine (53.0 mg, 0.230 mmol) and alcohol **6.3** (24.3 mg, 0.154 mmol) in CH_2Cl_2 (0.5 mL) was then added at 0 °C and the mixture was stirred at room temperature for 16 hours. The solvent was evaporated *in vacuo* and the crude was purified by column chromatography (acetone/petroleum ether 25:75) to afford **6.4** as a white foam (29.6 mg, 52%).

M.W. 474.60 (474.1283)

[α]$_D$ = -5.4 (*c* = 1.0, $CHCl_3$, 26 °C)

IR ν_{max}/cm^{-1} 2952 w, 2903 w, 1742 s, 1697 s, 1653 vs, 1598 w, 1441 m, 1389 w

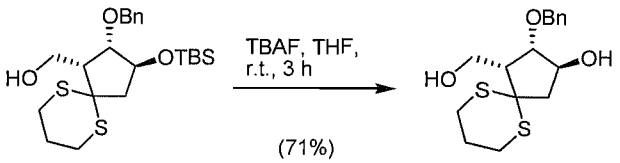
^{1}H NMR (400 MHz, $CDCl_3$) 7.91-7.93 (2H, m, CH_{Ar}), 7.65 (1H, tt, *J* = 7.5, 1.5 Hz, CH_{Ar}), 7.61 (1H, m, CH=C), 7.48-7.52 (2H, m, CH_{Ar}), 5.34 (1H, m, CHN), 4.47 (1H, dd, *J* = 11.5, 4.5 Hz, C$\underline{H}_a$H$_b$OAc), 4.38 (1H, dd, *J* = 11.5, 8.0 Hz, CH$_a\underline{H}_b$OAc), 3.03 (1H, ddd, *J* = 14.5, 11.0, 2.5 Hz, SC$\underline{H}_a$H$_b$), 2.92 (1H, dd, *J* = 14.5, 10.5 Hz, SCSC$\underline{H}_a$H$_b$), 2.91-3.00 (2H, m, SCH_2), 2.82 (1H, ddd, *J* = 14.5, 5.5, 3.5 Hz, SCH$_a\underline{H}_b$), 2.68 (1H, dd, *J* = 14.5, 7.5 Hz, SCSCH$_a\underline{H}_b$), 2.47-2.55 (2H, m, C$\underline{H}$CH$_2$OAc + CHC$\underline{H}_a$H$_b$CH), 2.15 (1H, m, $SCH_2C\underline{H}_aH_b$), 2.09 (3H, s, $COCH_3$), 1.98 (3H, s, CH_3), 1.93-2.05 (2H, m, $SCH_2CH_a\underline{H}_b$ + $CHCH_a\underline{H}_bCH$)

^{13}C NMR (100 MHz, $CDCl_3$) 170.8 (C=O), 169.2 (C=O), 162.7 (C=O), 150.2 (C=O), 137.0 (C=$\underline{C}$H), 135.1 (CH_{Ar}), 131.8 (C_{Ar}), 130.6 × 2 (CH_{Ar} × 2), 129.3 × 2 (CH_{Ar} × 2), 111.9 ($\underline{C}$=CH), 64.3 (CH_2OAc), 56.0 (SCS), 53.2 (CHN), 49.2 ($\underline{C}HCH_2OAc$), 48.2 ($SCSCH_2$), 34.3 ($CH\underline{C}H_2CH$), 28.7 (SCH_2), 27.0 (SCH_2), 25.4 ($SCH_2\underline{C}H_2$), 21.1 ($CO\underline{C}H_3$), 12.9 (CH_3)

ES$^+$ *m/z* (%) 497 ($(M+Na)^+$, 100)

HRMS (ES^+) for $C_{23}H_{26}N_2O_5S_2Na$ $(M+Na)^+$: Calcd 497.1175; Measured 497.1175

8.87 (1*S*,3*S*,4*R*)-3-Benzyloxy-4-hydroxymethyl-6,10-dithiaspiro[4.5] decan-2-ol (6.7)



1.93 **6.7**

TBAF (1.0 M solution in THF; 0.95 mL, 0.95 mmol) was added to a solution of **1.93** (0.278 g, 0.631 mmol) in THF (6.3 mL) and the mixture was stirred at room temperature for 3 hours. The solvent was removed *in vacuo* and the crude was purified by column chromatography (acetone/petroleum ether 3:7) to afford **6.7** (0.143 g, 71%) as a white solid.

M.W. 326.48 (326.1010)

mp 66-70 °C

$[\alpha]_D$ = +15.7 (*c* = 1.65, $CHCl_3$, 24 °C)

IR ν_{max}/cm^{-1} 3391 br, 2931 w, 2900 w, 1496 w, 1453 w, 1422 w, 1398 w

^{1}H NMR (400 MHz, $CDCl_3$) 7.28-7.39 (5H, m, ArH), 4.74 (1H, d, *J* = 11.5 Hz, $C\underline{H}_aH_bPh$), 4.61 (1H, d, *J* = 11.5 Hz, $CH_a\underline{H}_bPh$), 4.40 (1H, m, $C\underline{H}OH$), 4.32 (1H, dd, *J* = 7.0, 4.5 Hz, CHOBn), 3.96 (1H, dd, *J* = 12.0, 6.5 Hz, $C\underline{H}_aH_bOH$), 3.91 (1H, dd, *J* = 12.0, 6.5 Hz, $CH_a\underline{H}_bOH$), 2.99 (1H, ddd, *J* = 14.5, 8.5, 3.5 Hz, $SC\underline{H}_aH_b$), 2.83-2.92 (3H, m, $SCH_a\underline{H}_b$ + SCH_2), 2.72-.2.82 (3H, m, $SCSC\underline{H}_aH_b$ + $C\underline{H}CH_2OH$ + OH; simplified to 2.77 (1H, dd, *J* = 14.5, 8.0 Hz, $SCSC\underline{H}_aH_b$) and 2.76 (1H, dd, *J* = 12.0, 6.0Hz, $C\underline{H}CH_2OH$) upon D_2O exchange), 2.68 (1H, d, *J* = 6.0 Hz, OH), 2.25 (1H, dd, *J* = 14.5, 4.5 Hz, $SCSCH_a\underline{H}_b$), 1.92-2.08 (2H, m, $SCH_2C\underline{H}_2$)

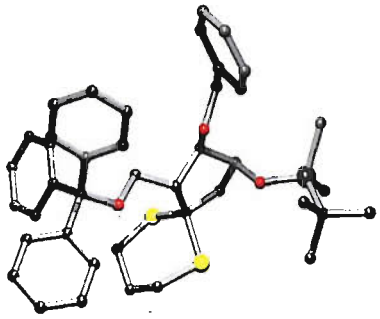
^{13}C NMR (100 MHz, $CDCl_3$) 138.0 (C_{Ar}), 128.6 × 2 (CH_{Ar} × 2), 127.9 (CH_{Ar}), 127.7 × 2 (CH_{Ar} × 2), 87.7 (CHOBn), 76.3 (CHOH), 72.5 (CH_2Ph), 60.1 (CH_2OH), 54.1 (SCS), 53.0 ($\underline{C}HCH_2OH$), 46.7 ($SCS\underline{C}H_2$), 28.8 (SCH_2), 27.8 (SCH_2), 24.9 ($SCH_2\underline{C}H_2$)

ES$^+$ ***m/z*** (%) 349 ((M+Na)$^+$, 100)

HRMS (ES$^+$) for $C_{16}H_{22}O_3S_2Na$ (M+Na)$^+$: Calcd 349.0902; Measured 349.0907.

Crystallographic Data for Compound 3.26

Table 1. Crystal data and structure refinement details.



Identification code	**2005sot0231**
Empirical formula	$C_{41}H_{50}O_3S_2Si$
Formula weight	683.02
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 12.791(5) Å
	b = 11.2002(17) Å β = 112.75(2)°
	c = 14.029(4) Å
Volume	1853.4(9) Å^3
Z	2
Density (calculated)	1.224 Mg / m^3
Absorption coefficient	0.213 mm^{-1}
$F(000)$	732
Crystal	Rod; Colourless
Crystal size	0.14 × 0.04 × 0.02 mm^3
θ range for data collection	3.15 – 27.48°
Index ranges	$-16 \le h \le 16$, $-14 \le k \le 14$, $-18 \le l \le 18$
Reflections collected	27463
Independent reflections	8377 [R_{int} = 0.1296]
Completeness to θ = 27.48°	99.7 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9958 and 0.9708
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8377 / 1 / 474
Goodness-of-fit on F^2	0.987
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0656, $wR2$ = 0.1051
R indices (all data)	$R1$ = 0.1446, $wR2$ = 0.1279
Absolute structure parameter	0.09(8)
Largest diff. peak and hole	0.311 and –0.348 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit*). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement:** *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: Sheldrick, G. M. SADABS - Bruker Nonius area detector scaling and absorption correction - V2.10 **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model. C21=R; C22=R; C23=S

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
S1	1179(1)	3741(1)	6568(1)	27(1)	1
S2	2235(1)	1459(1)	7621(1)	27(1)	1
Si1	3786(1)	2338(1)	11204(1)	24(1)	1
O1	−1099(2)	1707(2)	7047(2)	21(1)	1
O2	434(2)	2995(2)	9780(2)	25(1)	1
O3	2677(2)	2422(2)	10095(2)	27(1)	1
C1	−2749(3)	2623(3)	5756(3)	19(1)	1
C2	−3058(3)	3723(4)	6000(3)	26(1)	1
C3	−3348(4)	4661(4)	5305(4)	34(1)	1
C4	−3334(4)	4500(4)	4342(4)	35(1)	1
C5	−3013(4)	3421(4)	4079(4)	31(1)	1
C6	−2725(3)	2469(4)	4784(3)	27(1)	1
C7	−2561(4)	383(3)	6082(3)	21(1)	1
C8	−3618(4)	106(4)	5328(3)	26(1)	1
C9	−3848(4)	−1023(4)	4910(3)	28(1)	1
C10	−3034(4)	−1898(4)	5225(3)	28(1)	1
C11	−1989(4)	−1660(4)	5991(3)	24(1)	1
C12	−1746(3)	−516(4)	6424(3)	21(1)	1
C13	−2837(3)	1672(3)	7391(3)	20(1)	1
C14	−2177(3)	1526(4)	8437(3)	21(1)	1
C15	−2672(4)	1517(4)	9159(3)	28(1)	1
C16	−3829(4)	1613(4)	8843(4)	33(1)	1
C17	−4496(4)	1753(4)	7815(4)	30(1)	1
C18	−4005(4)	1785(3)	7097(4)	25(1)	1
C19	−2318(3)	1624(4)	6570(3)	20(1)	1
C20	−621(3)	2849(3)	7497(3)	22(1)	1
C21	616(3)	2638(3)	8191(3)	20(1)	1
C22	952(3)	3460(3)	9135(3)	22(1)	1
C23	2240(3)	3504(3)	9572(3)	25(1)	1
C24	2479(4)	3637(4)	8597(3)	28(1)	1
C25	1559(4)	2858(4)	7750(3)	25(1)	1
C26	1124(4)	808(4)	6507(3)	28(1)	1
C27	851(4)	1538(4)	5515(3)	31(1)	1
C28	314(4)	2742(4)	5553(3)	32(1)	1
C29	375(4)	3826(4)	10541(3)	28(1)	1
C30	−232(4)	3228(4)	11131(3)	24(1)	1
C31	−1126(4)	3783(4)	11274(3)	30(1)	1
C32	−1670(4)	3227(4)	11835(4)	38(1)	1
C33	−1308(4)	2131(4)	12279(4)	39(1)	1
C34	−406(4)	1563(4)	12161(3)	33(1)	1

C35	122(4)	2111(4)	11581(3)	30(1)	1
C37	3520(4)	3137(4)	12250(4)	36(1)	1
C38	5055(4)	3023(5)	11076(4)	38(1)	1
C39	3971(4)	684(4)	11443(3)	32(1)	1
C40	4209(4)	80(4)	10559(4)	36(1)	1
C41	2876(5)	156(4)	11464(4)	48(2)	1
C42	4964(5)	429(5)	12464(4)	58(2)	1

Table 3. Bond lengths [Å] and angles [°].

S1–C28	1.812(4)
S1–C25	1.827(4)
S2–C26	1.810(4)
S2–C25	1.832(4)
Si1–O3	1.654(3)
Si1–C37	1.858(5)
Si1–C38	1.866(5)
Si1–C39	1.882(5)
O1–C19	1.443(4)
O1–C20	1.452(4)
O2–C22	1.412(5)
O2–C29	1.440(5)
O3–C23	1.415(5)
C1–C2	1.377(6)
C1–C6	1.387(5)
C1–C19	1.540(5)
C2–C3	1.383(6)
C3–C4	1.370(6)
C4–C5	1.372(6)
C5–C6	1.403(6)
C7–C8	1.391(6)
C7–C12	1.395(5)
C7–C19	1.528(6)
C8–C9	1.377(6)
C9–C10	1.373(6)
C10–C11	1.378(6)
C11–C12	1.400(6)
C13–C14	1.390(5)
C13–C18	1.394(5)
C13–C19	1.537(5)
C14–C15	1.388(5)
C15–C16	1.375(6)
C16–C17	1.372(6)
C17–C18	1.378(6)
C20–C21	1.522(5)
C21–C22	1.531(5)
C21–C25	1.574(5)
C22–C23	1.520(6)
C23–C24	1.520(6)
C24–C25	1.573(6)
C26–C27	1.534(6)
C27–C28	1.523(6)

C29–C30	1.495(6)
C30–C31	1.382(6)
C30–C35	1.395(6)
C31–C32	1.385(6)
C32–C33	1.373(6)
C33–C34	1.382(6)
C34–C35	1.385(6)
C39–C42	1.530(7)
C39–C41	1.531(6)
C39–C40	1.543(6)

C28–S1–C25	104.3(2)
C26–S2–C25	100.8(2)
O3–Si1–C37	111.32(19)
O3–Si1–C38	110.3(2)
C37–Si1–C38	108.0(2)
O3–Si1–C39	103.09(18)
C37–Si1–C39	112.5(2)
C38–Si1–C39	111.6(2)
C19–O1–C20	117.1(3)
C22–O2–C29	114.1(3)
C23–O3–Si1	124.0(3)
C2–C1–C6	118.2(4)
C2–C1–C19	121.4(4)
C6–C1–C19	120.1(4)
C1–C2–C3	122.0(4)
C4–C3–C2	119.5(5)
C3–C4–C5	120.0(4)
C4–C5–C6	120.3(4)
C1–C6–C5	119.9(4)
C8–C7–C12	118.6(4)
C8–C7–C19	120.9(4)
C12–C7–C19	120.5(4)
C9–C8–C7	120.9(4)
C10–C9–C8	120.5(4)
C9–C10–C11	119.9(4)
C10–C11–C12	120.1(4)
C7–C12–C11	120.0(4)
C14–C13–C18	117.8(4)
C14–C13–C19	121.7(3)
C18–C13–C19	120.4(4)
C15–C14–C13	120.6(4)
C16–C15–C14	120.2(4)
C17–C16–C15	120.1(4)
C16–C17–C18	119.8(4)

C17–C18–C13	121.4(4)
O1–C19–C7	105.2(3)
O1–C19–C13	110.7(3)
C7–C19–C13	107.2(3)
O1–C19–C1	108.1(3)
C7–C19–C1	112.1(3)
C13–C19–C1	113.3(3)
O1–C20–C21	107.5(3)
C20–C21–C22	109.6(3)
C20–C21–C25	119.3(3)
C22–C21–C25	104.1(3)
O2–C22–C23	117.2(3)
O2–C22–C21	106.7(3)
C23–C22–C21	105.5(3)
O3–C23–C22	109.3(3)
O3–C23–C24	111.9(3)
C22–C23–C24	101.7(3)
C23–C24–C25	105.9(3)
C24–C25–C21	104.7(3)
C24–C25–S1	104.1(3)
C21–C25–S1	117.8(3)
C24–C25–S2	107.8(3)
C21–C25–S2	111.6(3)
S1–C25–S2	110.1(2)
C27–C26–S2	113.3(3)
C28–C27–C26	112.9(4)
C27–C28–S1	115.3(3)
O2–C29–C30	107.9(3)
C31–C30–C35	118.6(4)
C31–C30–C29	120.9(4)
C35–C30–C29	120.4(4)
C30–C31–C32	120.4(5)
C33–C32–C31	120.3(5)
C32–C33–C34	120.5(5)
C33–C34–C35	119.1(5)
C34–C35–C30	121.1(4)
C42–C39–C41	110.2(5)
C42–C39–C40	108.7(4)
C41–C39–C40	108.3(4)
C42–C39–Si1	110.6(3)
C41–C39–Si1	109.3(3)
C40–C39–Si1	109.8(3)

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

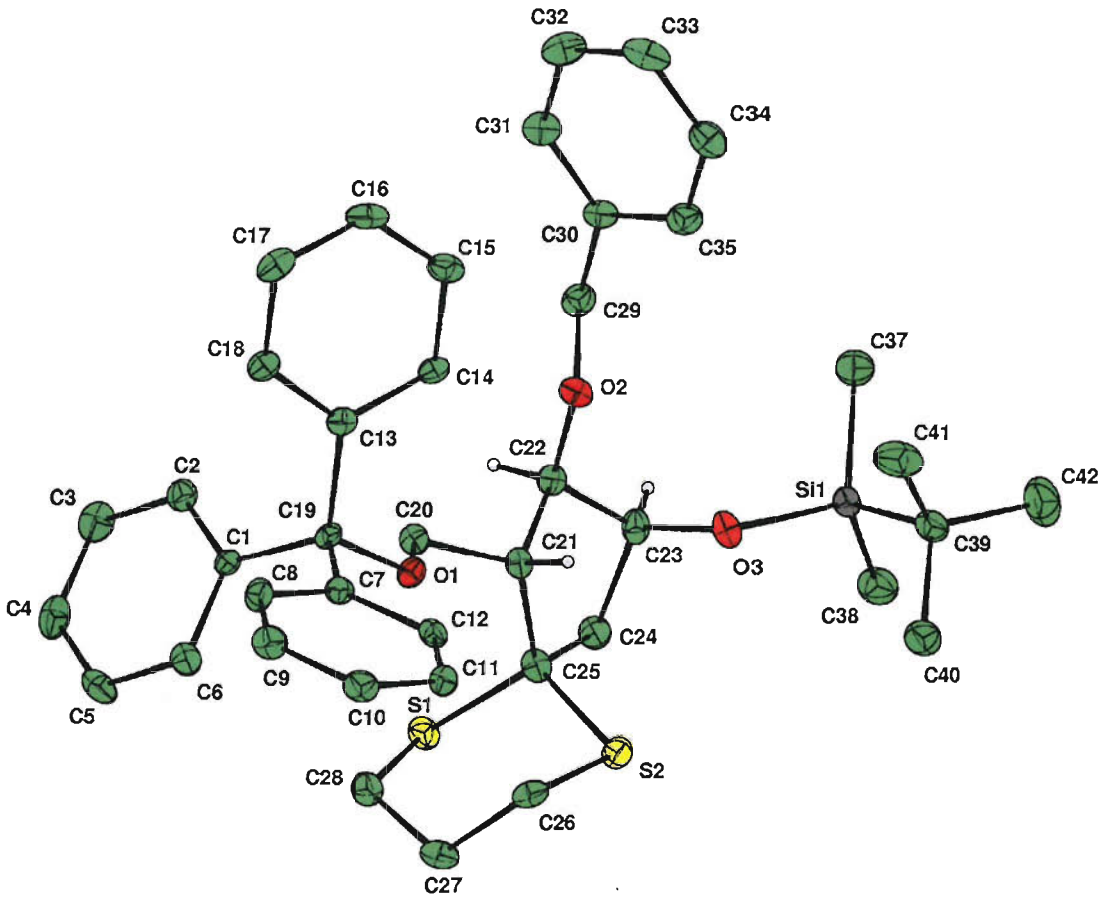
Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S1	29(1)	30(1)	25(1)	6(1)	11(1)	−1(1)
S2	24(1)	29(1)	29(1)	4(1)	11(1)	3(1)
Si1	22(1)	28(1)	20(1)	1(1)	7(1)	2(1)
O1	16(2)	21(2)	24(2)	−2(1)	6(1)	−1(1)
O2	32(2)	23(2)	22(2)	−1(1)	12(2)	−3(1)
O3	29(2)	25(2)	21(2)	4(1)	3(1)	−2(1)
C1	12(2)	24(2)	20(2)	0(2)	7(2)	−1(2)
C2	27(3)	24(2)	28(3)	4(2)	12(2)	3(2)
C3	27(3)	30(3)	45(3)	6(2)	14(3)	−3(2)
C4	24(3)	32(3)	45(3)	14(3)	10(2)	1(2)
C5	29(3)	46(3)	18(3)	3(2)	8(2)	−9(2)
C6	24(2)	30(3)	25(3)	3(2)	8(2)	−2(2)
C7	25(3)	18(2)	21(3)	1(2)	11(2)	1(2)
C8	21(3)	28(3)	26(3)	0(2)	5(2)	3(2)
C9	26(3)	29(3)	26(3)	−9(2)	7(2)	−7(2)
C10	36(3)	22(3)	25(3)	−7(2)	12(2)	0(2)
C11	25(3)	23(3)	23(3)	2(2)	9(2)	4(2)
C12	19(2)	27(2)	16(2)	−1(2)	5(2)	−4(2)
C13	26(2)	12(2)	24(2)	0(2)	13(2)	0(2)
C14	19(2)	21(2)	27(3)	−1(2)	13(2)	−1(2)
C15	41(3)	22(2)	26(3)	−2(2)	18(2)	1(2)
C16	44(3)	30(3)	37(3)	−4(2)	31(3)	−3(2)
C17	27(3)	21(2)	48(3)	−2(2)	20(3)	0(2)
C18	21(3)	25(2)	31(3)	−1(2)	12(2)	−2(2)
C19	14(2)	25(2)	24(2)	3(2)	10(2)	1(2)
C20	16(2)	26(2)	23(3)	1(2)	7(2)	−6(2)
C21	19(2)	19(2)	21(2)	2(2)	6(2)	−3(2)
C22	24(2)	18(2)	24(3)	2(2)	9(2)	0(2)
C23	26(3)	18(2)	24(3)	0(2)	4(2)	2(2)
C24	21(3)	35(3)	28(3)	3(2)	11(2)	−4(2)
C25	23(2)	25(2)	25(3)	2(2)	7(2)	−4(2)
C26	24(3)	31(3)	33(3)	−3(2)	17(2)	0(2)
C27	36(3)	36(3)	28(3)	0(2)	20(2)	−4(2)
C28	25(3)	42(3)	25(3)	2(2)	7(2)	2(2)
C29	27(3)	27(3)	30(3)	−5(2)	11(2)	1(2)
C30	23(3)	28(3)	24(3)	−7(2)	11(2)	−7(2)
C31	31(3)	28(3)	33(3)	−5(2)	14(2)	−8(2)
C32	40(3)	33(3)	46(3)	−10(2)	25(3)	−3(2)
C33	52(3)	41(3)	30(3)	−9(2)	24(3)	−17(3)
C34	41(3)	30(3)	26(3)	−5(2)	10(2)	−8(3)
C35	30(3)	31(3)	28(3)	−8(2)	11(2)	−2(2)

C37	41(3)	35(3)	33(3)	−6(2)	14(3)	0(2)
C38	35(3)	48(4)	33(3)	−4(2)	13(3)	−6(2)
C39	41(3)	33(3)	22(3)	−2(2)	12(2)	7(2)
C40	48(4)	30(3)	31(3)	−1(2)	17(3)	6(2)
C41	72(4)	36(3)	49(4)	5(3)	40(4)	−1(3)
C42	78(5)	47(4)	37(4)	4(3)	9(3)	25(3)

Table 5. Hydrogen coordinates [× 10^4] and isotropic displacement parameters [$Å^2$ × 10^3].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H2	−3071	3841	6665	27(12)	1
H3	−3556	5412	5493	40(14)	1
H4	−3546	5136	3855	57(16)	1
H5	−2986	3317	3417	51(15)	1
H6	−2514	1720	4595	37(13)	1
H8	−4188	704	5098	6(9)	1
H9	−4577	−1197	4400	37(13)	1
H10	−3190	−2667	4916	31(12)	1
H11	−1434	−2273	6225	39(13)	1
H12	−1025	−353	6951	6(9)	1
H14	−1379	1432	8659	5(9)	1
H15	−2211	1444	9874	32(12)	1
H16	−4167	1581	9339	48(14)	1
H17	−5295	1828	7598	9(10)	1
H18	−4472	1887	6387	24(12)	1
H20A	−1038	3174	7904	25(12)	1
H20B	−677	3428	6946	27(12)	1
H21	690	1795	8444	16(10)	1
H22	647	4279	8903	0(8)	1
H23	2532	4207	10041	11(10)	1
H24A	3251	3349	8715	43(14)	1
H24B	2416	4484	8379	37(13)	1
H26A	1355	−6	6396	30(12)	1
H26B	428	736	6653	7(9)	1
H27A	1558	1670	5401	46(14)	1
H27B	326	1075	4922	41(14)	1
H28A	−407	2600	5641	25(11)	1
H28B	127	3146	4879	57(16)	1
H29A	−38	4554	10198	18(10)	1
H29B	1149	4059	11016	28(12)	1
H31	−1367	4551	10985	35(13)	1
H32	−2297	3606	11914	73(18)	1
H33	−1681	1761	12670	39(13)	1
H34	−154	807	12472	27(12)	1
H35	736	1721	11490	14(10)	1
H37A	3403	3988	12078	36(13)	1
H37B	4175	3039	12903	64(17)	1
H37C	2843	2808	12318	80(20)	1
H38A	5149	2691	10468	52(15)	1
H38B	5731	2847	11696	64(17)	1

H38C	4953	3890	10996	90(20)	1
H40A	4241	–788	10654	73(18)	1
H40B	4936	366	10566	28(12)	1
H40C	3603	282	9895	40(14)	1
H41A	2947	–714	11530	50(15)	1
H41B	2239	361	10822	64(18)	1
H41C	2741	485	12054	53(16)	1
H42A	4804	768	13037	80(20)	1
H42B	5656	790	12450	100(30)	1
H42C	5069	–436	12560	66(17)	1



Thermal ellipsoids drawn at the 35% probability level. Only hydrogens at chiral centres are shown.

Crystallographic Data for Compound 4.44

Table 1. Crystal data and structure refinement details.

Identification code	**2006sot0271 (44844/4/2)**
Empirical formula	$C_{12}H_{26}O_3Si$
Formula weight	246.42
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 6.4302(5) Å
	b = 6.7027(8) Å
	c = 34.516(4) Å
Volume	1487.6(3) Å^3
Z	4
Density (calculated)	1.100 Mg / m^3
Absorption coefficient	0.151 mm^{-1}
F(000)	544
Crystal	Lath; Colourless
Crystal size	0.3 × 0.04 × 0.02 mm^3
θ range for data collection	3.10 – 27.57°
Index ranges	$-7 \le h \le 5$, $-8 \le k \le 8$, $-44 \le l \le 36$
Reflections collected	6716
Independent reflections	1939 [R_{int} = 0.0762]
Completeness to θ = 27.50°	95.6 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9970 and 0.9461
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1939 / 0 / 152
Goodness-of-fit on F^2	1.099
Absolute structure parameter	Not reliably determined
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0709, $wR2$ = 0.1479
R indices (all data)	$R1$ = 0.1087, $wR2$ = 0.1635
Largest diff. peak and hole	0.299 and –0.311 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit*). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: Sheldrick, G. M. SADABS - Bruker Nonius area detector scaling and absorption correction - V2.10 **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model. Relative Chirality: C1=R, C3=R, C5=S

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
Si1	6588(2)	9229(2)	1513(1)	28(1)	1
O2	1011(4)	4036(6)	189(1)	29(1)	1
O1	6981(5)	3613(5)	369(1)	33(1)	1
C7	8605(8)	10800(8)	1281(2)	37(1)	1
O3	5705(6)	7576(5)	1200(1)	39(1)	1
C9	7683(7)	7662(7)	1916(1)	29(1)	1
C10	8619(8)	8967(8)	2236(2)	43(1)	1
C5	3704(7)	4809(7)	660(1)	26(1)	1
C1	5478(7)	5177(7)	380(1)	24(1)	1
C6	2084(7)	3332(8)	533(1)	30(1)	1
C12	9405(10)	6295(9)	1758(2)	55(2)	1
C3	4990(8)	8019(8)	818(1)	31(1)	1
C4	2966(8)	6917(7)	750(2)	31(1)	1
C8	4439(8)	10857(9)	1690(2)	48(2)	1
C11	5936(10)	6377(9)	2092(2)	60(2)	1
C2	6492(8)	7133(7)	519(2)	35(1)	1

Table 3. Bond lengths [Å] and angles [°].

Si1–O3	1.649(4)
Si1–C7	1.854(5)
Si1–C8	1.863(6)
Si1–C9	1.879(5)
O2–C6	1.453(6)
O1–C1	1.426(5)
O3–C3	1.427(6)
C9–C10	1.531(7)
C9–C12	1.537(7)
C9–C11	1.539(7)
C5–C6	1.502(6)
C5–C1	1.517(6)
C5–C4	1.522(7)
C1–C2	1.541(6)
C3–C4	1.515(7)
C3–C2	1.534(7)
O3–Si1–C7	109.8(2)
O3–Si1–C8	110.6(2)
C7–Si1–C8	109.1(2)
O3–Si1–C9	103.8(2)
C7–Si1–C9	112.1(2)
C8–Si1–C9	111.3(3)
C3–O3–Si1	125.2(3)
C10–C9–C12	108.2(4)
C10–C9–C11	108.9(4)
C12–C9–C11	109.4(5)
C10–C9–Si1	111.1(4)
C12–C9–Si1	109.9(3)
C11–C9–Si1	109.3(3)
C6–C5–C1	116.3(4)
C6–C5–C4	117.1(4)
C1–C5–C4	102.3(4)
O1–C1–C5	114.0(4)
O1–C1–C2	110.3(3)
C5–C1–C2	104.9(4)
O2–C6–C5	110.7(4)
O3–C3–C4	108.7(4)
O3–C3–C2	109.8(4)
C4–C3–C2	104.3(4)
C3–C4–C5	102.5(4)
C3–C2–C1	105.9(4

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

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Si1	27(1)	29(1)	27(1)	0(1)	−2(1)	−4(1)
O2	13(2)	41(2)	32(2)	−1(2)	−1(1)	−2(2)
O1	17(2)	46(2)	35(2)	−11(2)	−2(2)	3(2)
C7	36(3)	39(3)	38(3)	3(3)	2(3)	−3(3)
O3	60(2)	31(2)	26(2)	5(2)	−20(2)	−8(2)
C9	31(3)	36(3)	19(3)	2(2)	−3(2)	−5(2)
C10	38(3)	57(4)	32(3)	−6(3)	−5(3)	−3(3)
C5	18(2)	40(3)	21(2)	4(2)	0(2)	−2(2)
C1	14(2)	34(3)	22(3)	1(2)	0(2)	0(2)
C6	20(3)	42(3)	27(3)	1(2)	8(2)	−2(2)
C12	84(5)	46(4)	36(3)	5(3)	−9(3)	29(3)
C3	42(3)	29(3)	23(3)	0(2)	−6(2)	3(2)
C4	27(3)	42(3)	24(3)	0(2)	4(2)	6(2)
C8	34(3)	54(4)	56(4)	−7(3)	1(3)	−1(3)
C11	69(4)	62(4)	49(4)	28(3)	−12(4)	−32(4)
C2	26(3)	38(3)	42(3)	2(2)	−3(3)	−8(2)

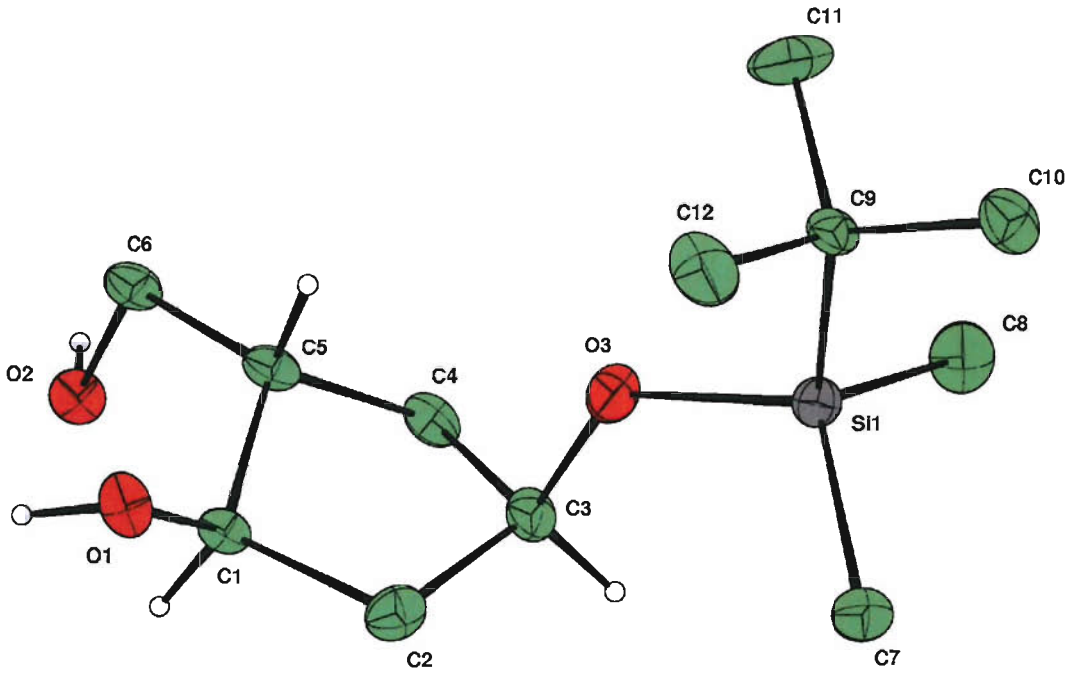
Table 5. Hydrogen coordinates [× 10^4] and isotropic displacement parameters [$Å^2$ × 10^3].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H92	−279	4000	227	43	1
H91	6688	2817	189	49	1
H7A	9733	9949	1185	56	1
H7B	9160	11748	1470	56	1
H7C	7989	11534	1064	56	1
H10A	7538	9839	2343	64	1
H10B	9741	9783	2127	64	1
H10C	9176	8115	2442	64	1
H5	4335	4273	903	31	1
H1	4900	5379	113	28	1
H6A	2754	2034	478	35	1
H6B	1066	3131	745	35	1
H12A	9953	5467	1969	83	1
H12B	10528	7111	1650	83	1
H12C	8831	5436	1555	83	1
H3	4815	9488	780	38	1
H4A	2191	7493	528	37	1
H4B	2073	6943	983	37	1
H8A	3802	11549	1469	72	1
H8B	4995	11842	1872	72	1
H8C	3388	10038	1820	72	1
H11A	6507	5541	2299	90	1
H11B	5336	5526	1890	90	1
H11C	4853	7247	2198	90	1
H2A	7863	6863	638	42	1
H2B	6686	8065	299	42	1

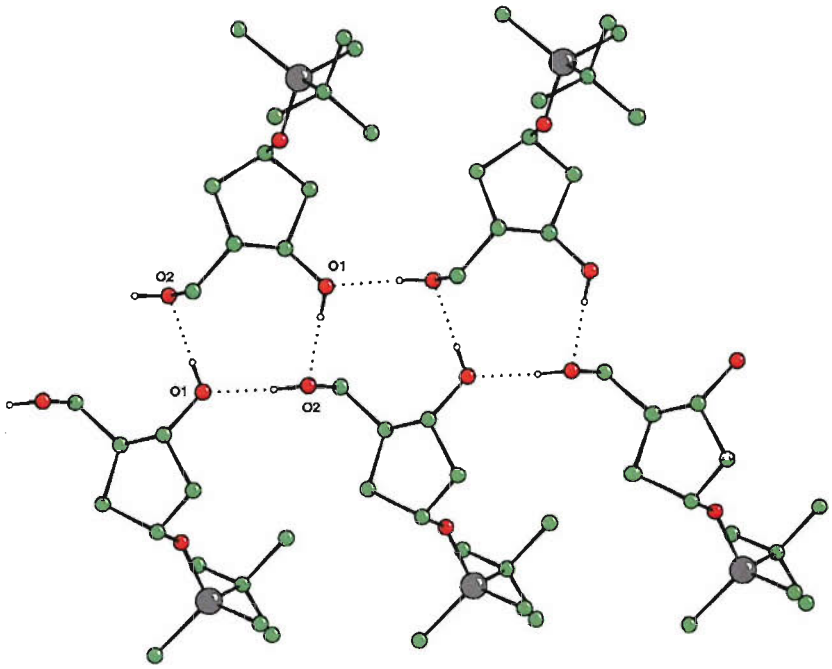
Table 6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*DHA*)
O2–H92···O1^{i}	0.84	1.85	2.680(4)	170.7
O1–H91···O2^{ii}	0.84	1.85	2.693(5)	177.1

Symmetry transformations used to generate equivalent atoms:
(i) x−1,y,z (ii) x+1/2,−y+1/2,−z



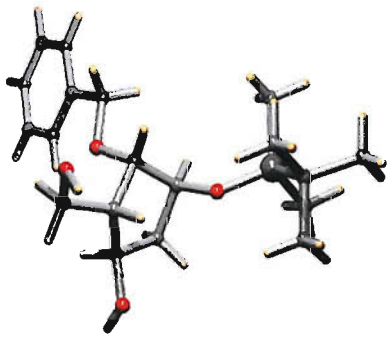
Thermal ellipsoids drawn at the 35% probability level. Non hetero hydrogen atoms and hydrogen atoms not at a chiral centre omitted for clarity.



Part of a hydrogen bonded tape that extends along the *a* axis

Crystallographic Data for Compound 4.48

Table 1. Crystal data and structure refinement details.



Identification code	**2005sot1556 (LL4413/68/2H)**
Empirical formula	$C_{19}H_{32}O_4Si$
Formula weight	352.54
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 6.2980(3) Å
	b = 13.7691(10) Å
	c = 23.2242(15) Å
Volume	2014.0(2) Å^3
Z	4
Density (calculated)	1.163 Mg / m^3
Absorption coefficient	0.135 mm^{-1}
F(000)	768
Crystal	Needle; Colourless
Crystal size	0.2 × 0.02 × 0.02 mm^3
θ range for data collection	2.96 – 27.48°
Index ranges	$-8 \le h \le 7$, $-17 \le k \le 17$, $-29 \le l \le 30$
Reflections collected	26317
Independent reflections	4444 [R_{int} = 0.1154]
Completeness to θ = 27.48°	97.9 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9973 and 0.9635
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4444 / 0 / 224
Goodness-of-fit on F^2	1.028
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0620, $wR2$ = 0.1124
R indices (all data)	$R1$ = 0.1198, $wR2$ = 0.1301
Absolute structure parameter	–0.15(19)
Largest diff. peak and hole	0.227 and –0.268 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit*). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: Sheldrick, G. M. SADABS - Bruker Nonius area detector scaling and absorption correction - V2.10 **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model. Chirality, C8=S, C9=S, C11=R, C13=S

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
Si1	8476(1)	3177(1)	2239(1)	28(1)	1
O1	8498(4)	5556(1)	647(1)	31(1)	1
O2	6604(3)	3572(1)	–312(1)	34(1)	1
O3	12963(3)	3326(2)	324(1)	41(1)	1
O4	9213(4)	3462(2)	1586(1)	39(1)	1
C1	6383(6)	7999(2)	946(1)	32(1)	1
C2	7002(6)	8948(2)	888(1)	37(1)	1
C3	9024(6)	9176(2)	694(1)	40(1)	1
C4	10394(6)	8436(2)	548(1)	38(1)	1
C5	9759(6)	7464(2)	611(1)	35(1)	1
C6	7772(5)	7243(2)	815(1)	29(1)	1
C7	7083(6)	6209(2)	919(2)	35(1)	1
C8	8280(6)	4573(2)	842(1)	29(1)	1
C9	9377(5)	3935(2)	393(1)	26(1)	1
C10	8593(5)	4035(2)	–223(1)	31(1)	1
C11	11734(5)	4160(2)	481(1)	29(1)	1
C12	11938(5)	4424(2)	1123(1)	37(1)	1
C13	9711(5)	4408(2)	1370(1)	33(1)	1
C14	6420(6)	4031(2)	2493(2)	42(1)	1
C15	10756(5)	3249(3)	2743(2)	44(1)	1
C16	7482(5)	1897(2)	2167(1)	32(1)	1
C17	5628(6)	1860(3)	1740(2)	51(1)	1
C18	6742(6)	1525(2)	2753(2)	47(1)	1
C19	9282(7)	1241(3)	1946(2)	56(1)	1

Table 3. Bond lengths [Å] and angles [°].

Si1–O4	1.634(2)
Si1–C14	1.846(4)
Si1–C15	1.855(3)
Si1–C16	1.877(3)
O1–C7	1.415(4)
O1–C8	1.434(3)
O2–C10	1.421(4)
O3–C11	1.432(4)
O4–C13	1.431(4)
C1–C2	1.371(5)
C1–C6	1.392(4)
C2–C3	1.387(5)
C3–C4	1.378(5)
C4–C5	1.404(5)
C5–C6	1.373(5)
C6–C7	1.508(4)
C8–C9	1.529(4)
C8–C13	1.538(4)
C9–C10	1.518(4)
C9–C11	1.530(4)
C11–C12	1.541(4)
C12–C13	1.515(5)
C16–C18	1.527(5)
C16–C17	1.533(5)
C16–C19	1.538(5)
O4–Si1–C14	110.01(14)
O4–Si1–C15	110.65(15)
C14–Si1–C15	107.91(16)
O4–Si1–C16	103.75(13)
C14–Si1–C16	113.14(16)
C15–Si1–C16	111.38(16)
C7–O1–C8	113.5(2)
C13–O4–Si1	127.4(2)
C2–C1–C6	120.9(3)
C1–C2–C3	120.6(3)
C4–C3–C2	119.2(3)
C3–C4–C5	120.1(3)
C6–C5–C4	120.4(3)
C5–C6–C1	118.8(3)
C5–C6–C7	121.8(3)
C1–C6–C7	119.4(3)

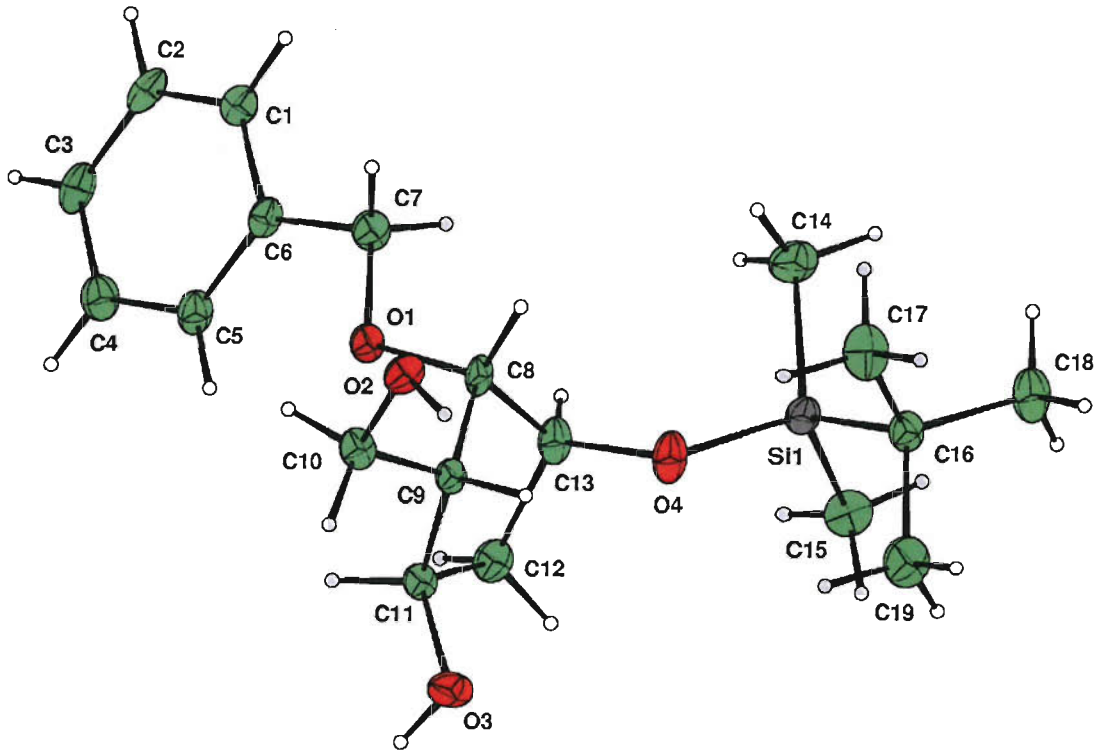
O1–C7–C6	110.4(3)
O1–C8–C9	106.4(2)
O1–C8–C13	109.6(3)
C9–C8–C13	101.2(3)
C10–C9–C8	116.3(3)
C10–C9–C11	115.0(3)
C8–C9–C11	103.4(3)
O2–C10–C9	112.6(2)
O3–C11–C9	109.1(2)
O3–C11–C12	113.0(3)
C9–C11–C12	105.0(3)
C13–C12–C11	106.5(3)
O4–C13–C12	110.4(3)
O4–C13–C8	106.6(2)
C12–C13–C8	103.9(3)
C18–C16–C17	109.4(3)
C18–C16–C19	109.0(3)
C17–C16–C19	109.0(3)
C18–C16–Si1	109.7(2)
C17–C16–Si1	110.1(2)
C19–C16–Si1	109.6(2)

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

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Si1	34(1)	21(1)	28(1)	0(1)	0(1)	0(1)
O1	43(1)	16(1)	34(1)	−1(1)	11(1)	2(1)
O2	40(1)	21(1)	40(1)	−4(1)	−3(1)	0(1)
O3	35(1)	21(1)	66(2)	−5(1)	13(1)	2(1)
O4	66(2)	20(1)	33(1)	0(1)	4(1)	−6(1)
C1	37(2)	30(2)	29(2)	−1(1)	−3(2)	1(2)
C2	53(3)	21(2)	35(2)	−1(2)	−12(2)	8(2)
C3	62(3)	22(2)	35(2)	2(2)	−9(2)	−3(2)
C4	44(2)	31(2)	38(2)	1(2)	2(2)	−6(2)
C5	47(2)	23(2)	34(2)	1(2)	4(2)	−1(2)
C6	41(2)	22(2)	23(2)	−1(1)	−2(2)	2(2)
C7	44(2)	22(2)	41(2)	−1(2)	10(2)	2(2)
C8	41(2)	12(2)	34(2)	5(1)	3(2)	−4(2)
C9	32(2)	15(2)	30(2)	0(1)	5(1)	−2(1)
C10	37(2)	23(2)	32(2)	−4(1)	3(2)	−7(2)
C11	34(2)	15(2)	38(2)	−1(1)	7(2)	−4(2)
C12	43(2)	26(2)	42(2)	0(2)	−2(2)	−3(2)
C13	51(2)	18(2)	30(2)	−1(2)	3(2)	−7(2)
C14	42(2)	27(2)	57(2)	−1(2)	0(2)	1(2)
C15	45(2)	41(2)	45(2)	−9(2)	−7(2)	−3(2)
C16	38(2)	23(2)	35(2)	0(2)	4(2)	−3(2)
C17	62(2)	40(2)	51(2)	−4(2)	−8(2)	−21(2)
C18	64(2)	28(2)	50(2)	6(2)	5(2)	−14(2)
C19	71(3)	26(2)	70(3)	−1(2)	14(2)	−1(2)

Table 5. Hydrogen coordinates [× 10^4] and isotropic displacement parameters [$Å^2$ × 10^3].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H92	6792	2972	–351	51	1
H93	14119	3507	178	61	1
H1	4989	7854	1076	38	1
H2	6038	9454	982	44	1
H3	9460	9835	663	48	1
H4	11769	8583	404	45	1
H5	10712	6956	512	41	1
H7A	7052	6077	1338	42	1
H7B	5632	6112	765	42	1
H8	6769	4383	912	35	1
H9	9149	3244	510	31	1
H10A	8457	4733	–318	37	1
H10B	9656	3749	–487	37	1
H11	12154	4728	238	35	1
H12A	12850	3947	1324	44	1
H12B	12573	5078	1167	44	1
H13	9504	4922	1668	40	1
H14A	7051	4676	2545	63	1
H14B	5842	3802	2860	63	1
H14C	5278	4070	2207	63	1
H15A	11808	2754	2640	65	1
H15B	10258	3137	3137	65	1
H15C	11405	3894	2717	65	1
H17A	5106	1191	1710	76	1
H17B	6112	2082	1362	76	1
H17C	4481	2283	1876	76	1
H18A	5555	1923	2890	71	1
H18B	7917	1565	3029	71	1
H18C	6281	848	2717	71	1
H19A	10434	1226	2229	84	1
H19B	9820	1498	1580	84	1
H19C	8738	582	1887	84	1



Thermal ellipsoids drawn at the35% probability level

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