PROBING STEREOSELECTIVITY WITH CARBOHYDRATES

by

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Department of Chemistry
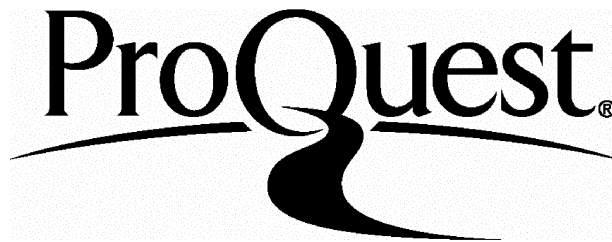
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ABBREVIATIONS

$A^{1,3}$ strain	1, 3 Allylic strain
Ac	Acetyl
AIBN	Azoisobutyronitrile
ax	Axial
bd	Broad doublet
Bn	Benzyl
bs	Broad singlet
d	Doublet
ddd	Doublet of a doublet of a doublet
DAST	Diethylaminosulfur trifluoride
DMSO	Dimethyl sulfoxide
eq	Equatorial
ether	Diethyl ether
HPLC	High performance liquid chromatography
^{i}Pr	2-Propyl
IR	Infra-red
J	Scalar coupling constant
LDA	Lithium diisopropylamide
LN	Lithium naphthalenide
m-cpba	Meta-chloroperbenzoic acid
mmpp	Magnesium monoperoxyphthalate
MS	Mass spectrum
NIS	N-Iodo succinimide
NMO	N-Methylmorpholine N-oxide
nmr	Nuclear magnetic resonance
n. O. e.	Nuclear Overhausser effect

OTf	Triflate
s	Singlet
THF	Tetrahydrofuran
t. l. c.	Thin layer chromatography
TMS	Trimethylsilyl

Abstract

This thesis describes the use of carbohydrates to probe the effects of oxygenated substituents on the stereoselectivity of free radical and osmium tetroxide dihydroxylation reactions.

The first, introduction, chapter briefly surveys literature methods employed in the synthesis of 2-deoxy-β-glycosidic linkages in carbohydrate chemistry. The use of O-acyl thiohydroxamate chemistry on ulosonic acid derivatives in the <u>arabino</u>-series is then presented as a method for the preparation of β-C- and β-O-glycosides. The evidence for an accelerating or stabilizing β-oxygen effect in radical reactions is then outlined. Finally, the stereodirecting effect of an allylic alcohol or ether on the osmylation of alkenes is discussed with particular reference to glycal derivatives.

In the second chapter, on the basis of chemical correlation with products of known absolute configuration and/or of proton coupled ^{13}C-nmr spectroscopy, the anomeric configuration of a number of 3-deoxyheptulosonic acid derivatives previously prepared in this laboratory is reassigned. The effect of temperature and of axial substituents in the 3-position on the stereoselectivity of alkoxyglycosyl radical reactions is then briefly examined.

The third chapter describes a series of probes designed to identify any stereochemical component to the β-oxygen effect in free radical reactions. By comparison with non-oxygenated analogues it is determined that β-oxygen bonds do indeed accelerate radical reactions. However, competition between stereoisomers reveals that the stereoelectronic component, while real is very small.

The fourth chapter outlines a brief investigation into the stereochemistry of osmylation reactions of glycals. In <u>arabino</u>-glycals reaction occurs on the α-face and it is postulated that this is a function of the lone pairs on the ring oxygen. This chapter describes the reversal of this stereoselectivity in going to the <u>ribo</u>-series. Some attempts at the reversal of stereoselectivity by use of chiral ligands for osmium are described.

The final chapter is the complete experimental part.

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CHAPTER 1

INTRODUCTION

Many natural products which show biological activity, such as esperamicin,[1] calicheamicin,[1] sporavidin[2] and orthosomycin[3] contain a 2-deoxy-β-glycosidic linkage, figure 1:

Figure 1: β-Glycosidic linkage in the 2-deoxy series.
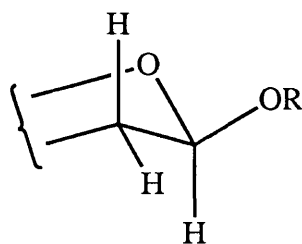
The preparation of such linkages has therefore been of considerable interest to carbohydrate chemists. This coupling involves the joining of two functionalised monosaccharide units. The glycosyl acceptor must have all the hydroxy groups protected, except one, whilst the glycosyl donor must have an activated anomeric group and the other hydroxy groups must be protected. To obtain such a linkage, the coupling step must be able to provide diastereoselectivity in favour of the β-linkage.

1.1. Synthesis of 2-deoxy-β-glycosides:

The preparation of such linkages has generally been approached in two main ways:

(i) The directed Koenigs-Knorr[4,5] glycosylation method which involves the activation of the anomeric centre via glycosyl halide formation followed by coupling and then the removal (reduction) of the directing group at C-2. Sinaÿ[4,5] used an adaptation of this methodology to transform the 1,2-trans-di-O-acetyl derivative (1) into the 2-deoxy-β-product (3β) via (2), scheme 1.

OBn

BnO

CH₂OBn

AcO⁗

OAc

(1)

ROH,

TMS-OTf, -20 °C

OBn

BnO

CH₂OBn

AcO⁗

OR

(2)

(i) NaOMe/MeOH
(ii) NaH, imidazole,
    CS₂, IMe,
(iii) Bu₃SnH, AIBN,
    Toluene, reflux

OBn

BnO

CH₂OBn

O

OR

(3β)
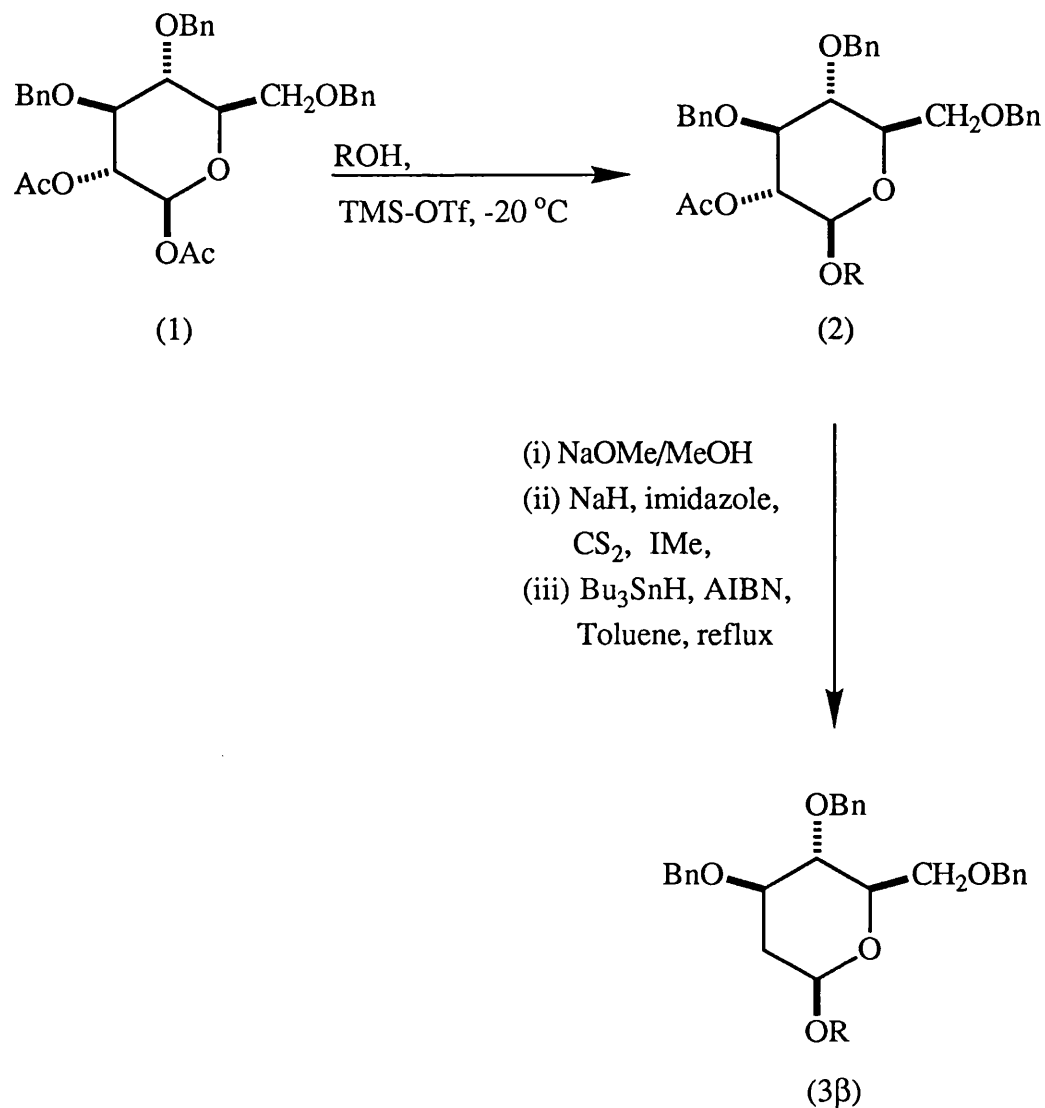
Scheme 1 : Synthesis of 2-deoxy-β-linkage by Sinaÿ.

In another example, Nicolaou[6] activated the anomeric centre in (4) by treatment with DAST, resulting in a 1,2-migration of the thiophenol group from C-1 to C-2. The fluoride (5) then acted as a glycosyl donor and coupled with (6) to give (8) via the intermediate (7). Removal of the thiophenol group by treatment with Raney nickel in ethanol gave the 2-deoxy-β-product (9β), scheme 2.
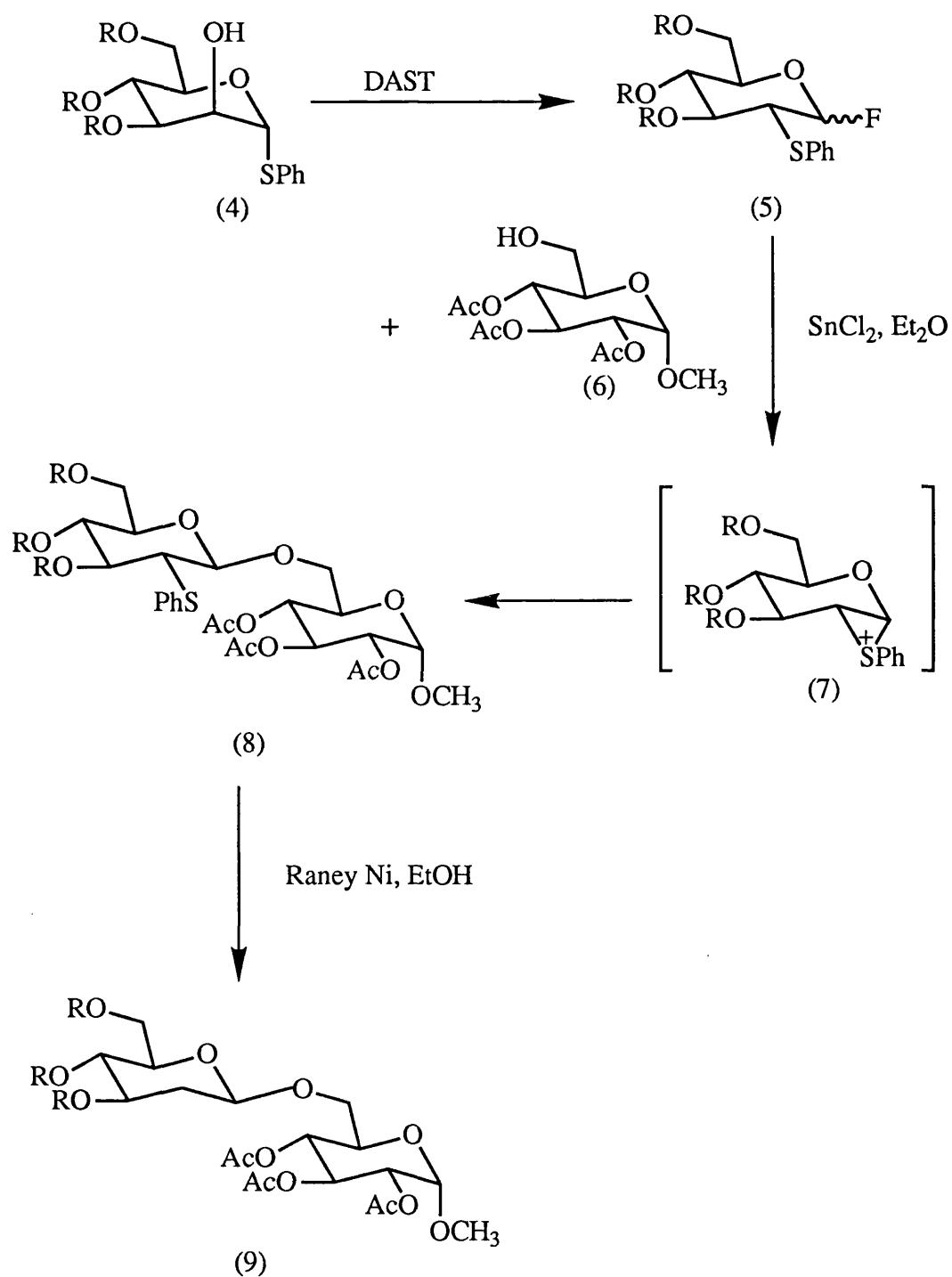
Scheme 2 : Synthesis of 2-deoxy-β-glycoside by Nicolaou.

(ii) The second method involves introducing a stereodirecting moiety in the course of the glycosylation reaction by addition across a double bond.[7] In Thieme's study,[7] the pyranoside (10) and 4-*O*-acetyl-L-livomycal (11) were treated with NIS to give the β-

product (12β). Removal of the iodo-substituent with 10% palladium/charcoal gave the 2-deoxy-β-glycoside but only as the minor product, scheme 3.

(10)   (11)

NIS

12α : major
12β : minor

(12)
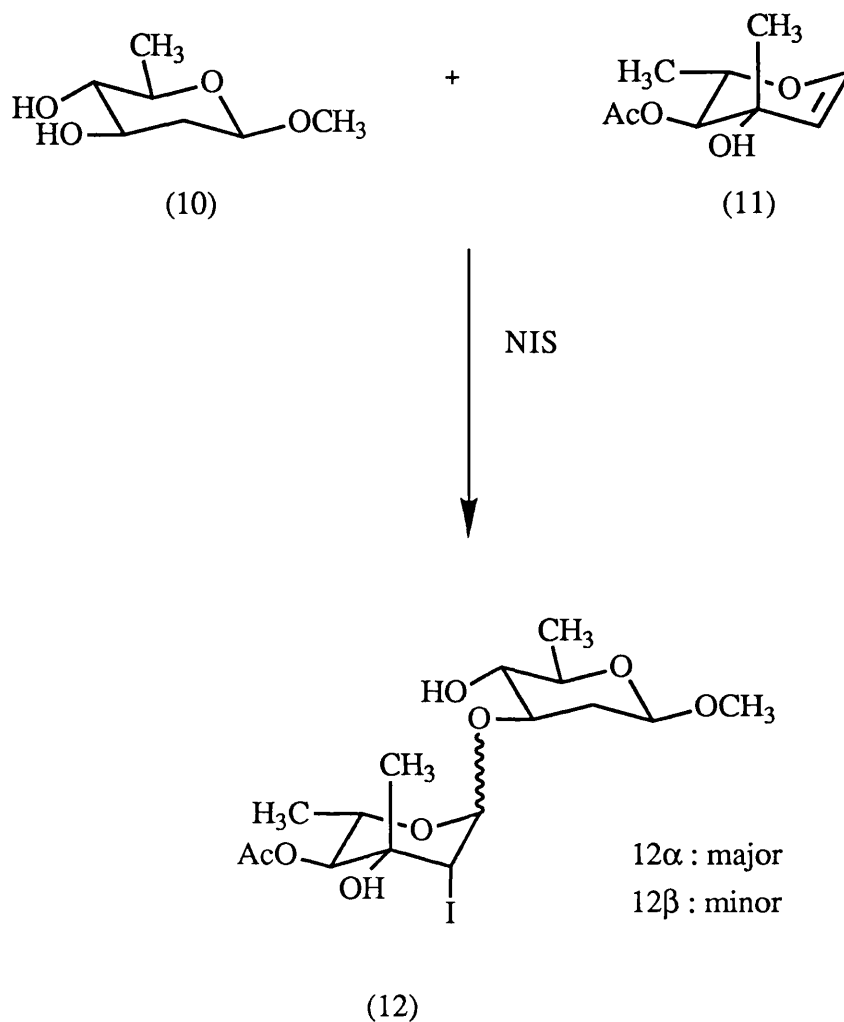
Scheme 3 : Synthesis of 2-deoxy-β-glycoside linkage by addition across a double bond.

Another variation of this method involved the use of benzene sulfenate esters,[8] (13) in the presence of Lewis acids such as BF₃·OEt₂. In this method, addition across the double bond took place to give the β-anomer as the major product (14β), scheme 4.

R^{1}OSPh   +   [structure: RO, RO, RO tetrahydropyran with terminal alkene, R = Ac, Bn] $\xrightarrow[\text{-15 °C}]{\text{TMSOTf, (ClCH}_2\text{)}_2}$

(13)

R^1 = Me, ^{i}Pr   R = Ac, Bn

$\left[\text{RO, RO, RO sugar ring with } \overset{+}{\text{SPh}} \right]$

(7)

[structure 14α: RO, RO, RO sugar with SPh, O, OR^1]   +   [structure 14β: RO, RO, RO sugar with O, OR^1, SPh]

(14α)   (14β)
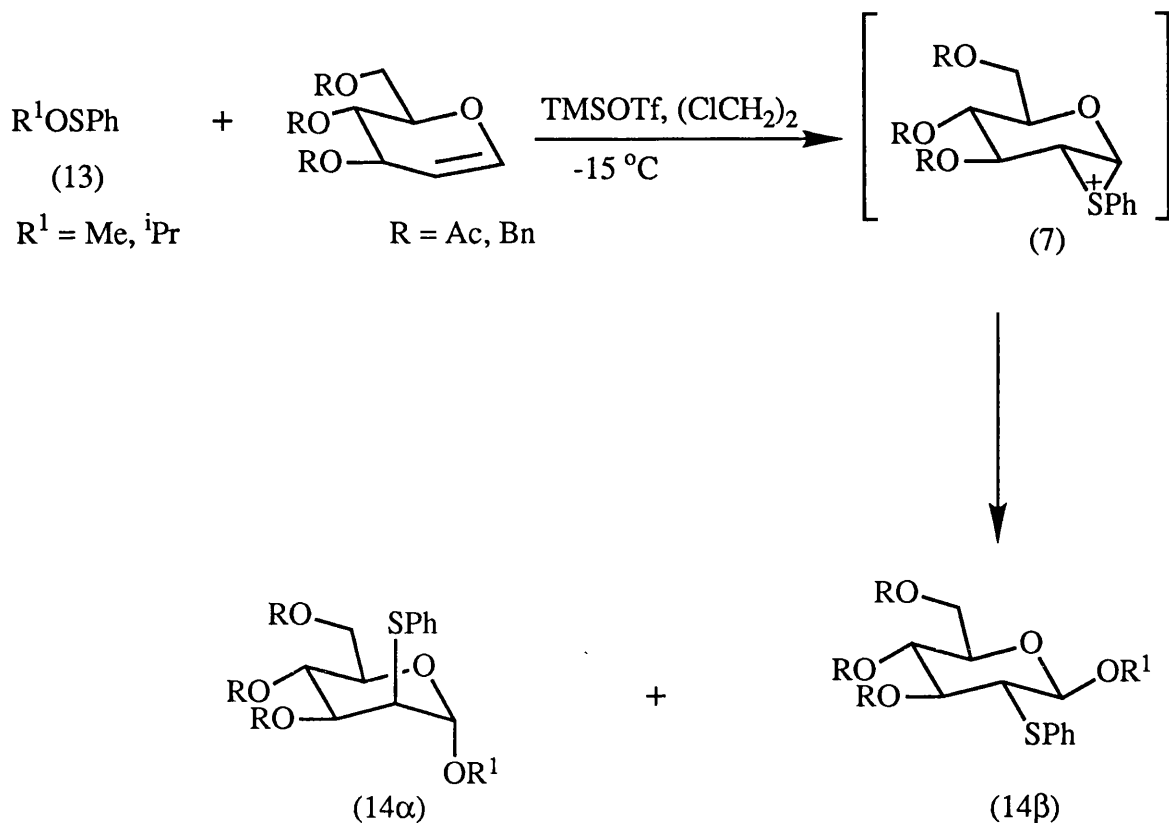
Scheme 4 : Synthesis of 2-arylthio-β-D-glycosides using benzene sulfenate esters.

This work was later extended by Franck[9] who found that better face-selectivity was achieved in the presence of the complex sulfonium reagent (16), scheme 5. It was found that the p-tolyl reagent gave the best β-selectivity (17β) with tri-O-benzyl-D-glucal (15) as the substrate. After obtaining the product, desulfurisation of the 2-arylthio-group was achieved by using Raney nickel.

BnO—⌐⌐O
BnO—⌐⌐
BnO—⌐   + CH₃OH $\xrightarrow{\text{+ (16), -60 °C, CH}_2\text{Cl}_2}$

(15)

BnO—⌐
BnO—⌐   O
BnO—⌐   ⌐—OCH₃
       ArS

(17β)

+

| Ar——S ——S⁺——S—Ar |
| | |
| Ar |

(16)

BnO—⌐   SAr
BnO—⌐   ⌐-O
BnO—⌐
              OCH₃
(17α)
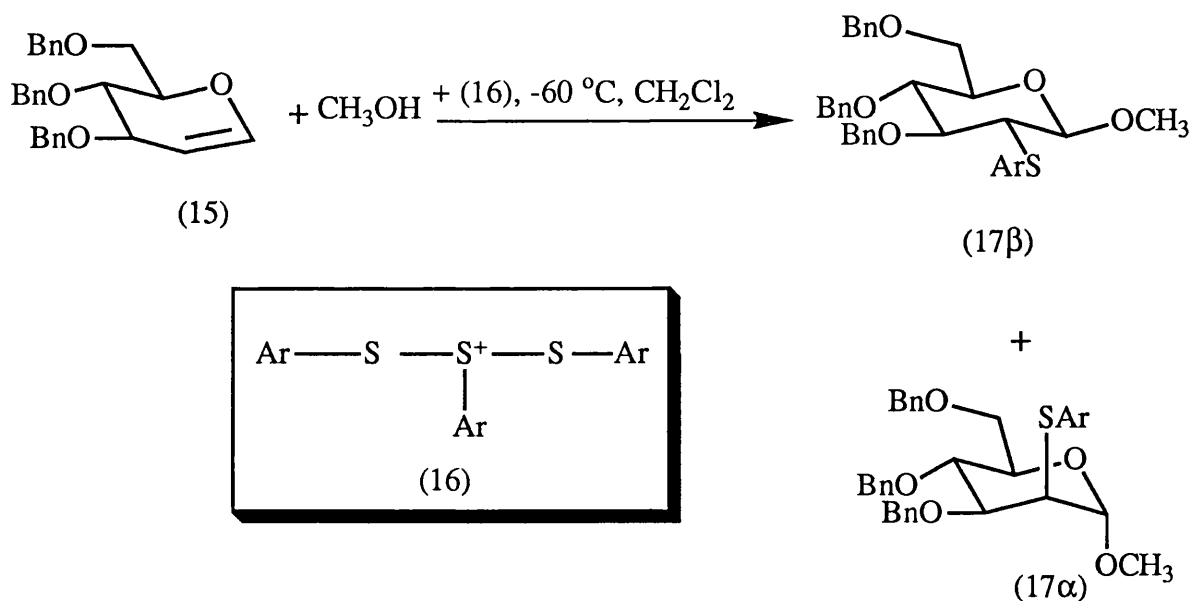
Scheme 5 : Synthesis of 2-arylthio-β-D-glycoside.

The chemistry of simple anomeric radicals has been explored _inter alia_ by Baldwin and Giese.[10] In Giese's work, the anomeric radical (19) derived from tetra-O-acetyl-glucopyranoside (18) was allowed to react with acrylonitrile in competition with D-trapping (from tributyltin deuteride). The major product from reaction with acrylonitrile was the α-anomer (20α) and a small amount of the competition product having the deuterium atom in the α-position was also obtained, scheme 6.

AcO—⌐
AcO—⌐   O
AcO—⌐   ⌐
   AcO ⌐
        Br

(18)

$\xrightarrow{\text{Bu}_3\text{SnD, AIBN}}$

AcO—⌐
AcO—⌐   O
AcO—⌐   ⌐
     AcO •

(19)

CH₂=CHCN

AcO—⌐
AcO—⌐   O
AcO—⌐   ⌐
   AcO CH₂CHDCN

(20α)

AcO—⌐
AcO—⌐   O
AcO—⌐   ⌐
   AcO D
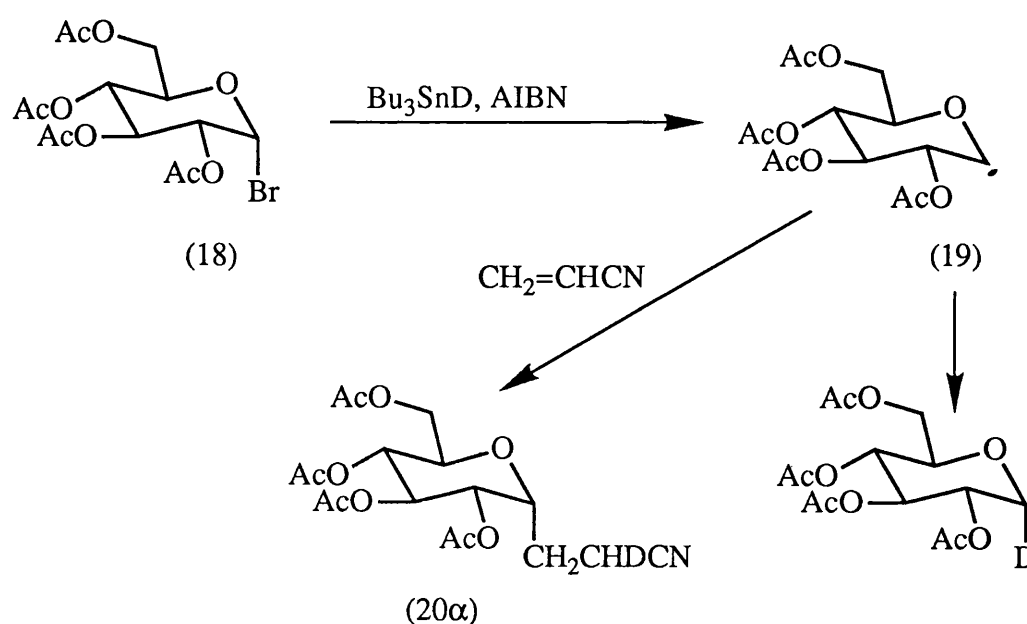
Scheme 6 : Quenching of the anomeric radical mainly from the axial direction.

Baldwin also observed[10] similar selectivity on quenching (19) with methyl acrylate, to give mainly the α-product (21α) scheme 7.

$$CH_2=CHCO_2CH_3$$

(19)   (21α)
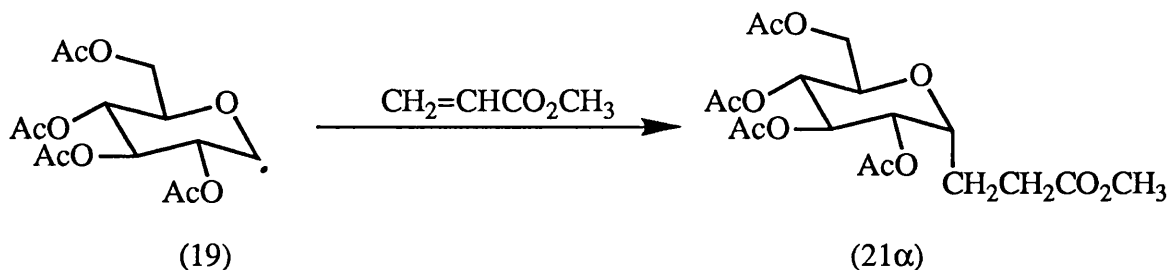
Scheme 7 : Quenching of the anomeric radical from the axial direction.

These observations are supported by the work of the Sustmann group[11] who found that this stereoselectivity is due to the boat conformation adopted by the sp^2 hybridised glycosyl radical (19). In this conformation the singly occupied orbital containing the radical is periplanar with and stabilised by the interaction with the β-C-O bond, thereby reducing the dipole moment of the radical. Quenching takes place from the exo-face of the boat structure.

Esr measurements[12] on the common 2-deoxyalkoxyl radical (23), generated by hydrogen abstraction from cis- and trans-2-deoxy-4-methyltetrahydropyran (22a) and (22b), show that the anomeric carbon is sp^3 hybridised i. e,that the radical is σ in nature, scheme 8.
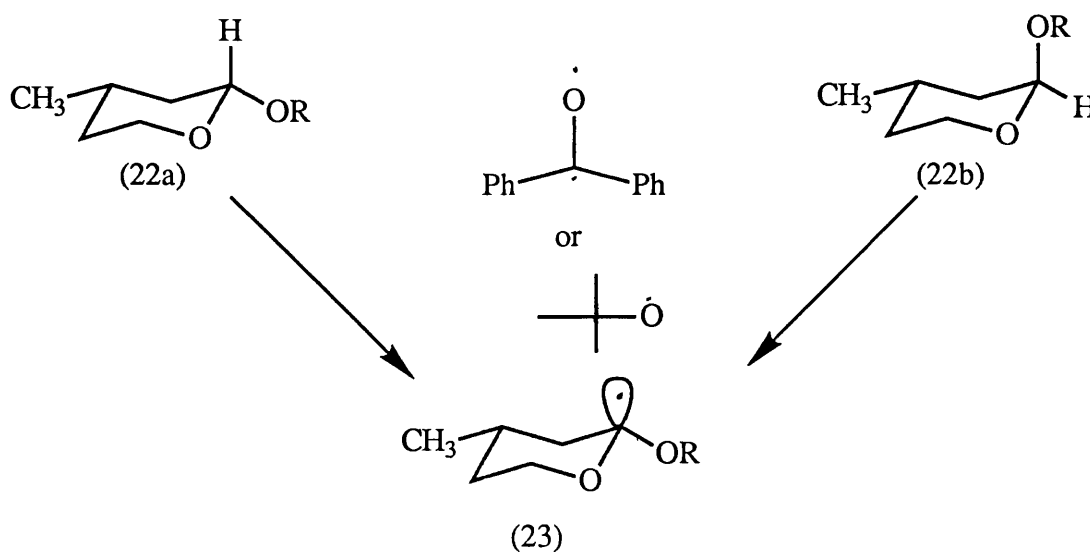
Scheme 8 : Generation of a σ-radical from either *cis*- or *trans*-2-alkoxy-4-

methyltetrahydropyran.

Esr measurements also showed[12] that the single electron is in an axial position. Therefore

it can be predicted that in pyranosides, which are closely related to tetrahydropyrans, the

radical formed at the anomeric centre would be axial. Thus quenching of this radical (A)

from the α-face with a thiol would lead to the synthesis of a β-glycoside linkage (B)

scheme 9.
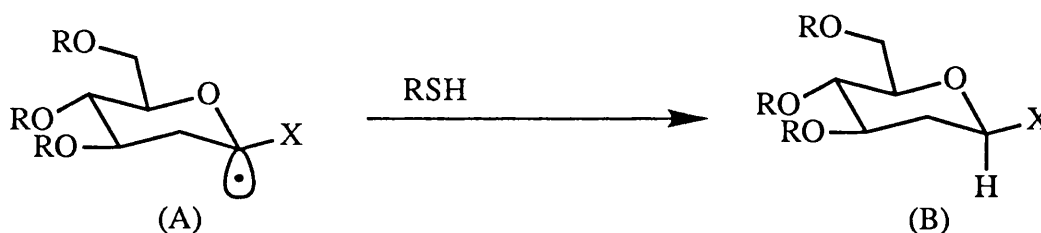
Scheme 9 : Axial radical at C-1 would lead to a β-product.

This also suggests that the radical chemistry at the anomeric centre would not be affected

by the presence or by the absence of substituents at C-2. The substituent at C-1, however

would affect the outcome of the radical reaction due to stereoelectronic effects.

This concept was developed in this laboratory employing Barton's thiohydroxamate chemistry[13] to generate 1-alkoxyglycosyl radicals (24), figure 2 from ulosonic acid glycosides.

Figure 2 : 1-Alkoxylglycosyl radical (24) derived from a ulosonic acid glycoside.
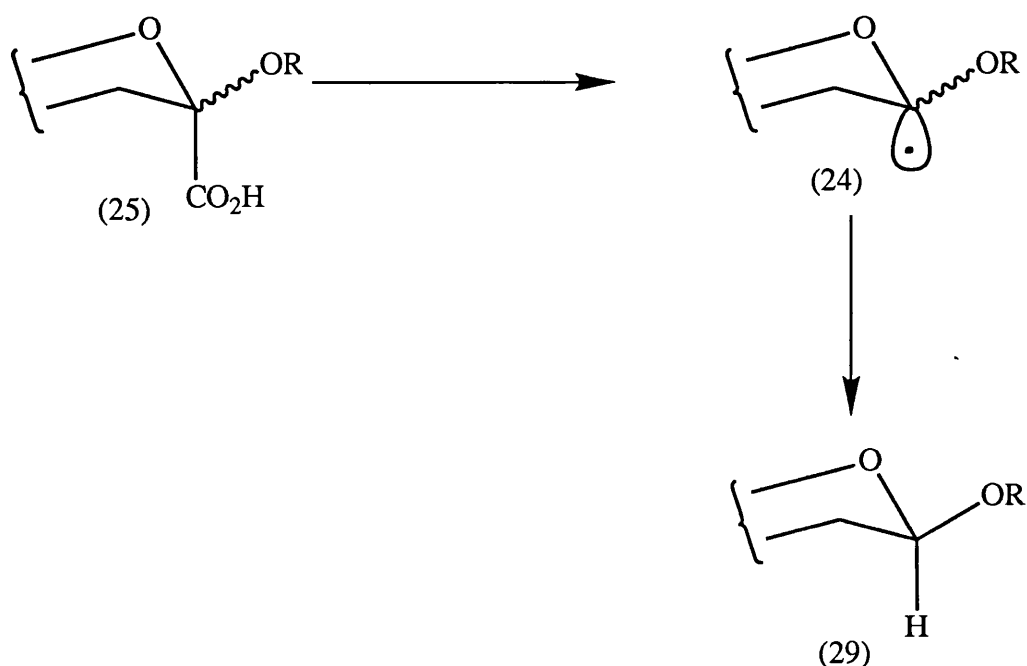
The idea underlying this methodology was to combine the ulosonic acid functionality (25) with the thiohydroxamate chemistry to generate the O-acyl thiohydroxamate ester (27) by condensation with thiohydroxamic acid (26). Decarboxylation under photolytic or thermal conditions would produce the glycosyl radical (28). This radical, being axial in nature, would be trapped by a tertiary thiol, leading to the formation of a β-glycoside product (29) scheme 10.

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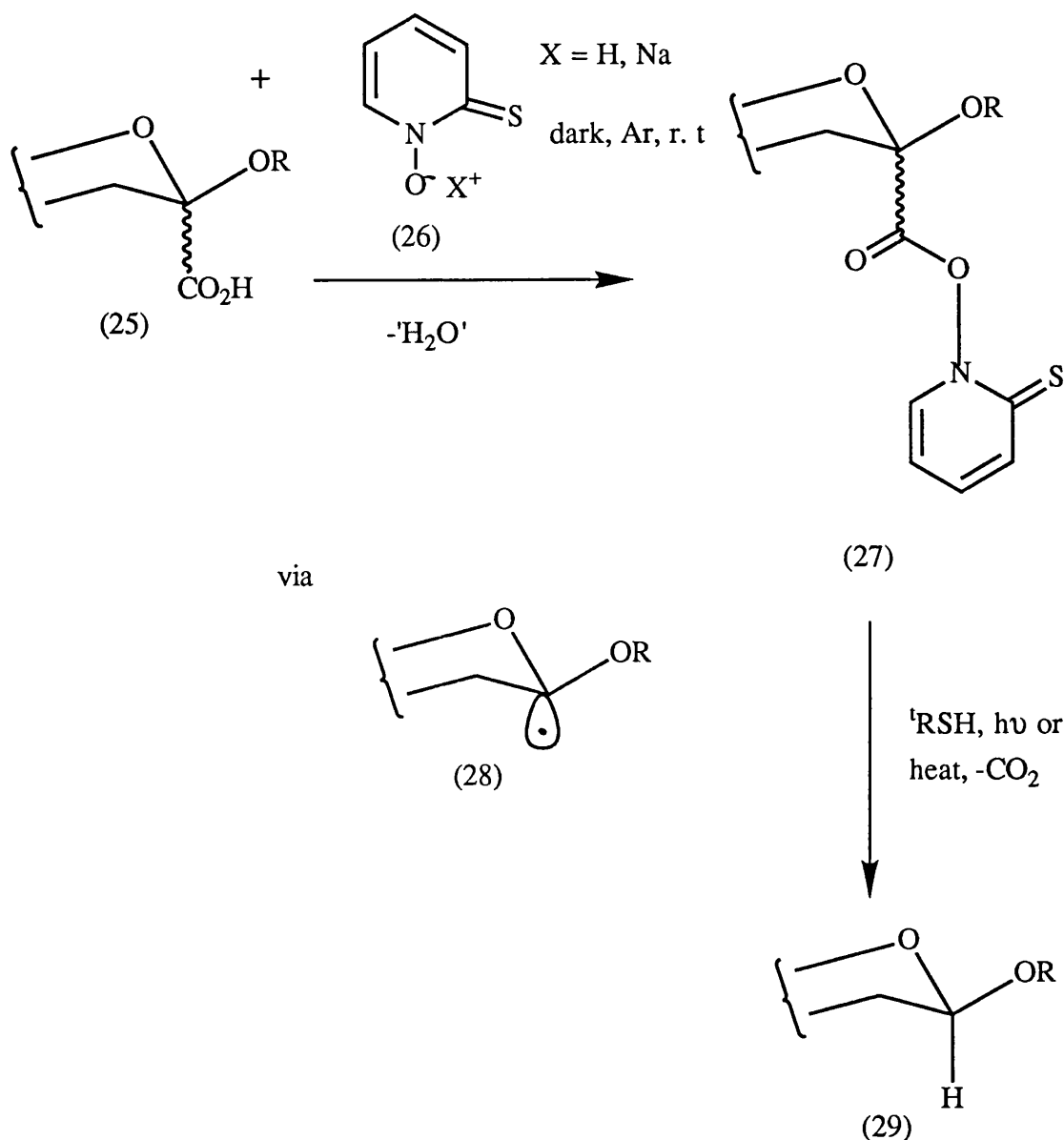
Scheme 10 : Decarboxylation of ulosonic acid derivatives.

Results obtained in this laboratory[14] in the synthesis of 2-deoxy-β-O-glycoside linkages using this protocol gave very good diastereoselectivities - between 8 : 1 and 95 : 5 (β : α). Similar results, involving H-atom transfer to alkoxyglycos-1-yl radicals, generated by an alternative protocol, were obtained by Kahne.[15]

This work was further extended to the preparation of 2-deoxy-C-glycosides and then β-glucosides.[16] In the study for preparation of 2-deoxy-C-glycosides, the heterocyclic salt

(30) figure 3, was used and the decarboxylation was carried out under photolytic conditions.

Figure 3 : Heterocyclic salt (30) used for decarboxylation.

(30)
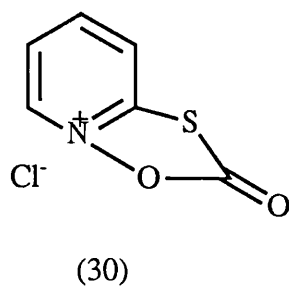
Excellent diastereoselectivities (>95 : 5, β : α) were obtained. This showed that in such radical chemistry, the α-radical in scheme 11 is more face-selective than the α-radical in scheme 12.
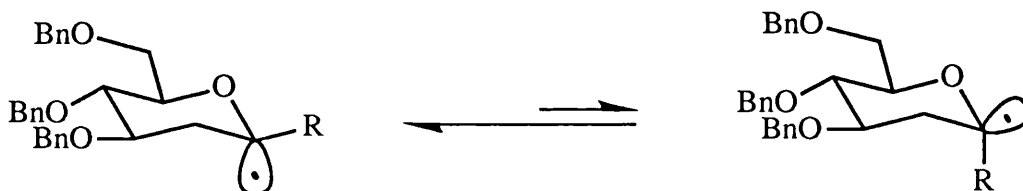
Scheme 11
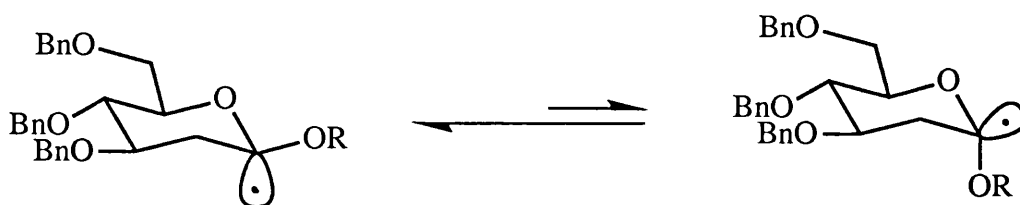
Scheme 12

These results are in direct agreement with those reported by Vasella[17] for the related reaction of the nitroglycoside (31) with tributyltin hydride with the exclusive formation of compound (32), scheme 13.
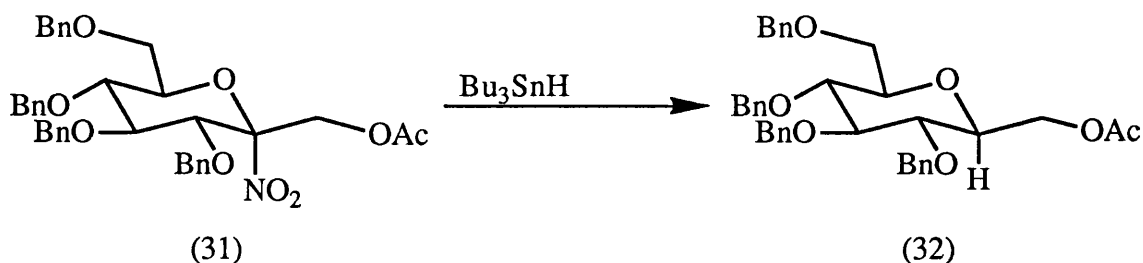
Scheme 13 : α-Radical trapped by H-atom abstraction from tributyltin hydride.

Decarboxylation of the two glycosides (33) and (34) figure 4, was also investigated.[16]

Figure 4 : The two glycosides (33) and (34).
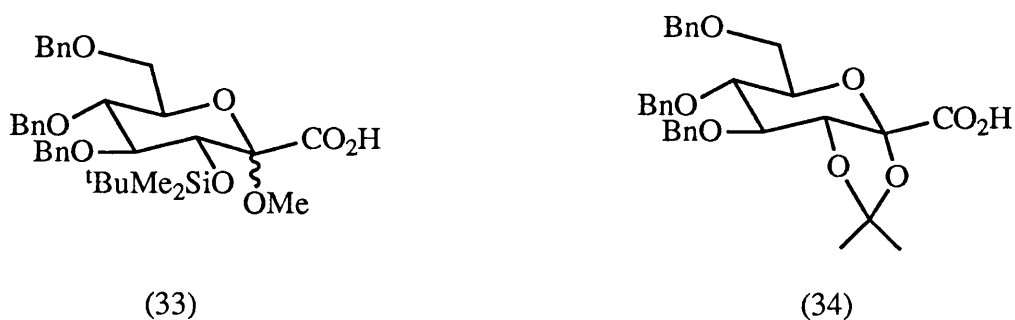
Upon decarboxylation of (33), the ^1H nmr spectrum of the purified product showed that the selectivity of this radical reaction was at least 25 : 1 in favour of reaction on the α-face. Compound (34) is a special case that probably represents a conformation imposed by the fused dioxolane ring. Decarboxylation of (34) showed a reversal of selectivity with highly selective β-quenching.

More recently,[18] a diacid (35) was subjected to the Barton reductive decarboxylation protocol, scheme 14. The product (36) was obtained in 76% yield.

CH$_3$
BnO
BnO
O
CO$_2$H
BnO
CH$_3$
O
O
CO$_2$H
OMe

(35)

decarboxylate

CH$_3$
BnO
BnO
O
CH$_3$
BnO
O
O
OMe
H
H

(36)
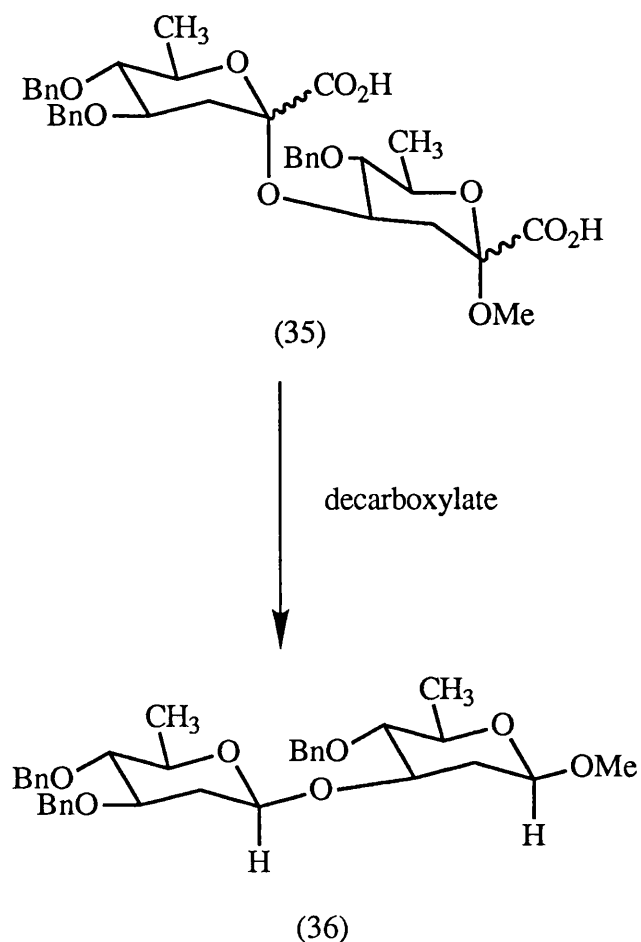
Scheme 14 : Double decarboxylation on the disaccharide (35).

The aim in this thesis was to further study alkoxyglycosyl radicals, and in particular, the effect of substituents on the stereochemistry of quenching and the effect of temperature on stereoselectivity.

1.2. Effect of a β-oxygen bond on the rate of radical reactions.

Stereoelectronic effects in free-radicals reactions have also been discussed in terms of the β-oxygen effect. The Barton group[19] found that thionoformate esters and isonitriles having an alkoxy and/or acyloxy group in the β-position underwent deoxygenation and deamination respectively on treatment with tributyltin hydride at lower temperatures than

the corresponding unsubstituted species. Thus the thionoformate (37) underwent

reductive deoxygenation in toluene at reflux to give the corresponding deoxy product (38)

in 29% yield, scheme 15.
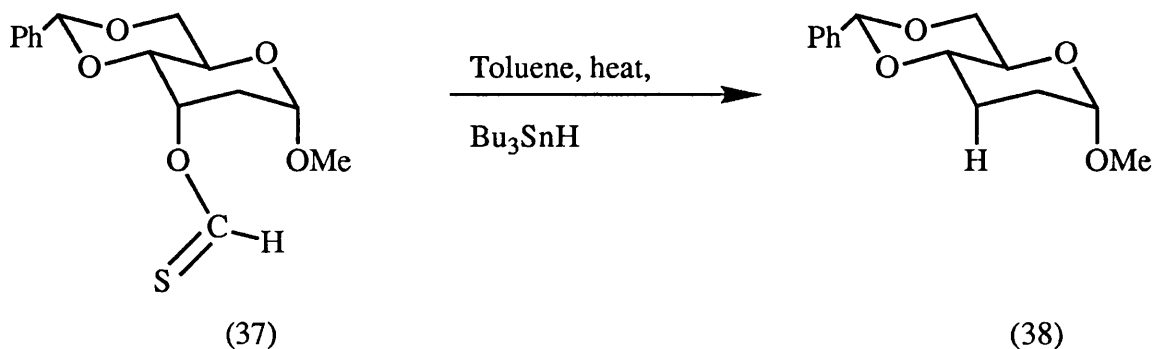
Scheme 15 : Deoxygenation of the thionoformate ester (37) to give (38).

When the same reaction was carried out with cholestanyl thioformate (39) a low yield

(9%) of cholestane (40) was obtained, scheme 16.
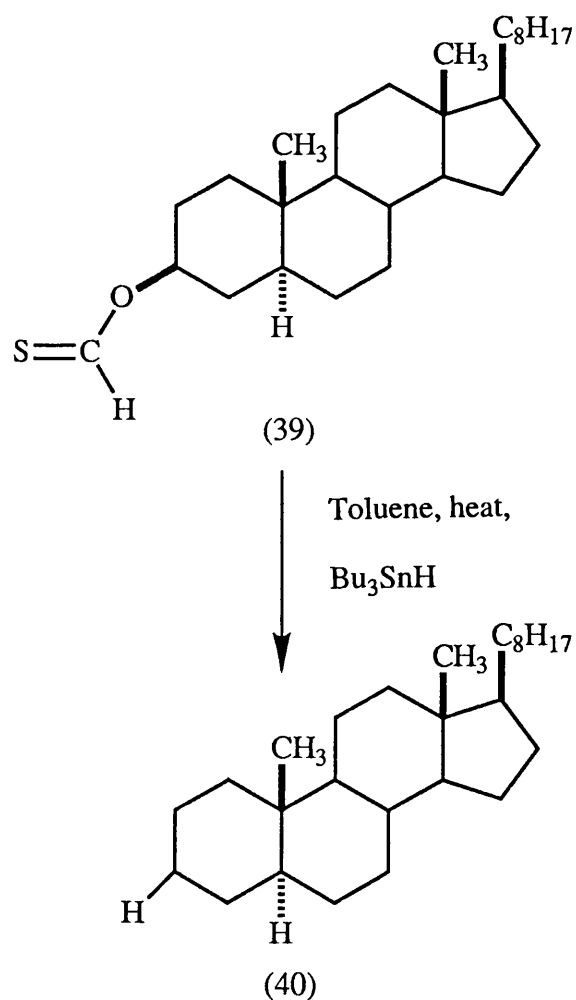
Scheme 16 : Deoxygenation of cholestanyl thioformate (39).

From these studies Barton concluded that the presence of an oxygen atom in the β-position "has a marked effect in stabilising carbon radicals, thus permitting homolytic fission not seen otherwise." However esr studies have shown that there is no bridging. Therefore there must be another effect in operation which allows such radicals to be somewhat stabilised or the reaction to be accelerated. It is thought that stability is achieved by the radical adopting a conformation in which the single electron is in a p-orbital, synclinal to the β-oxygen bond.[20]

More recently Gleicher[21] observed that the radical reaction of epichlorohydrin with triphenyltin hydride was 2 times faster than that of cyclohexyl chloride at 70 °C. In the same report, it was noted that under the same conditions cis-2-chloro-7-oxabicyclo[4.1.0]heptane reacted twice as fast as compared to its trans isomer, suggesting that the presence of an oxygen atom β to the radical centre not only affects the rate of reaction but also that the acceleration has a stereoelectronic component.

As discussed above, Giese and Sustmann[22] found that tetraacetylglucopyranos-1-yl radicals are quenched from the axial direction with high stereoselectivity by many radical traps. Low temperature esr studies have shown that the singly occupied orbital was periplanar to the β-acetoxy bond which would result in overlap possibly suggesting a stabilising interaction.

On the basis of these observations, a further aim of this thesis was to determine whether the increase in the rate of reaction in molecules containing a β-bond involves a stereoelectronic component. However, in order to examine such an effect the conformational mobility of the molecule must be taken into account. These reactions are carried out at high temperatures which might allow the molecule to adopt a higher energy conformation, thereby rendering the results ambiguous. To prevent the molecule from adopting a higher energy conformation at the reflux temperature, "rigid" molecules would

have to be synthesised in order to determine how much an effect the presence of a β-oxygen atom has on the rate of a radical reaction.

Any understanding gained from these experiments could then be used in possibly predicting diastereoselective radical reactions in sugars in which the ring oxygen is β to the radical reaction taking place at the anomeric centre.

1.3. Osmylation of glycals.

Another aim of this thesis was to study osmylation reactions of glycals in the ribo- and the arabino-series with a view to determining the effect, either steric or electronic or both, of allylic alcohols or ethers. This problem has extensively been researched by a number of investigators such as Kishi[23, 24] and Brimacombe[25] (see chapter 4 for detailed discussion) but no compelling conclusion has been reached. The ready availability of the glycals and of all possible diastereoisomeric products makes them ideal models with which to study this problem.

Kishi's[23] group carried out a number of osmylation reactions on allylic alcohols and ethers. The results from these experiments were analysed and an empirical rule was formulated. This rule states that upon osmylation the *relative stereochemistry between the pre-existing hydroxy or alkoxy group and the adjacent, newly introduced hydroxy group of the major product in all cases is erythro*. Previous work carried out in this laboratory[16] on osmylation of glycals gave interesting results. Osmylation reactions were separately carried out on tri-O-benzyl-D-glucal (15) and on the 1-carbomethoxy glucal (41). According to Kishi's empirical rule, *cis*-dihydroxylation should have given the *erythro*-product at C-2 as the major isomer i.e both glycals should have the *manno*-stereochemistry at C-2 upon osmylation. Instead the only product from these reactions had the *gluco*-stereochemistry at C-2, (42) and (43), scheme 17.
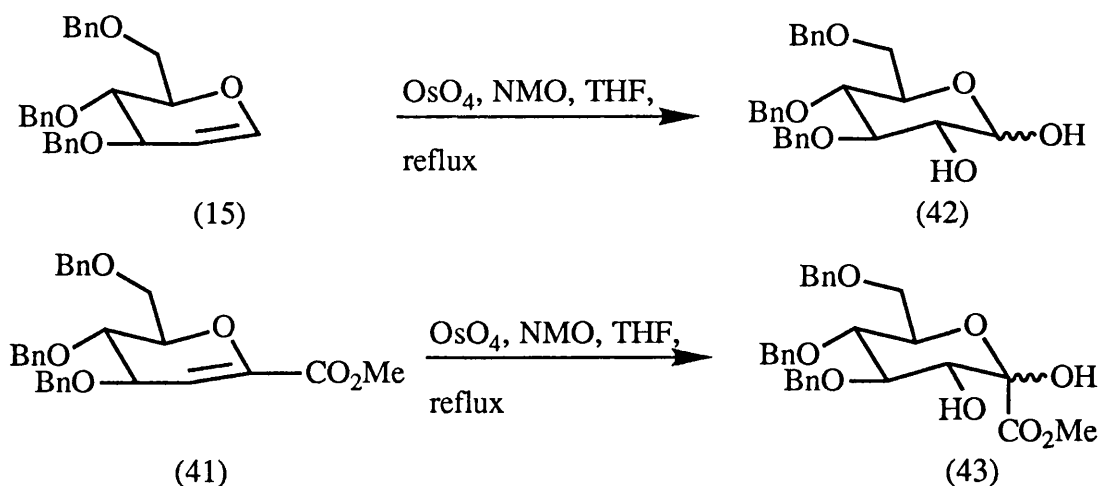
Scheme 17 : Osmylation of the glycals (15) and (41) gave the *gluco*-adduct.

A further object in the thesis was to try to reverse the stereochemistry of osmɣlation observed at C-2 in these glycals. This could be carried out in two ways. One method would be to examine the use of alkaloids as asymmetric catalysts. Sharpless[26, 27] and Griffith[28] both have used amines to enhance the rates of such reactions. Sharpless and co-workers[30] have also explored the use of the diastereomeric cinchona alkaloids, quinine and quinidine, which effectively act like enantiomers. Therefore the use of such catalysts might result in a rate enhancement and/or reversal in stereoselectivity. Another method could be to try to block the bottom face of the π-bond so that OsO_4 would be forced to approach the double bond from the top face. This type of hindrance could be achieved by placing an axial substituent at C-3 i.e. a glycal having the ribo-stereochemistry.

CHAPTER 2

DETERMINATION OF CONFIGURATION AT THE ANOMERIC CENTRE OF VARIOUS 3-DEOXYULOSONIC ACID DERIVATIVES

Chapter 2

2.1. Preparation of the sulfone ester (50)

Recent work in this laboratory[14, 16] has concentrated on the synthesis of 3-deoxyulosonic acid derivatives which serve as precursors for the 2-deoxy-O-and 2-deoxy-C-glycopyranos-1-yl radicals and so for the corresponding β-glycosides, scheme 18:
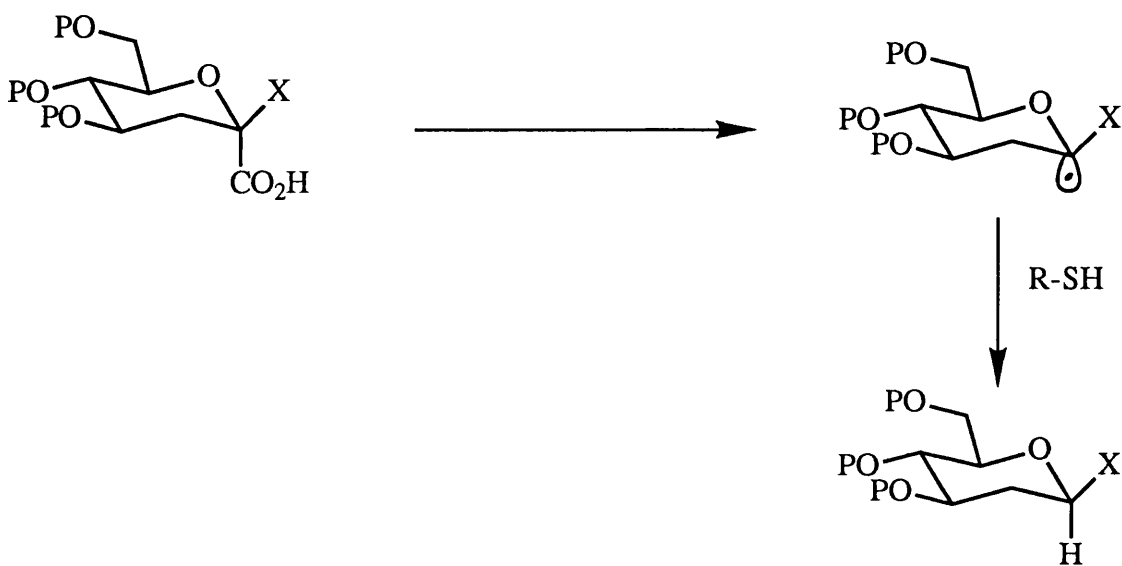
Scheme 18 : Degradation of ulosonic acids via an anomeric radical.

The assignment of configuration at the anomeric centre of some of these sugar derivatives has been difficult due to the absence of an anomeric proton. This chapter concentrates primarily on the synthesis of various 3-deoxyulosonic acid derivatives and the assignment of their anomeric configuration via chemical and physical methods.

The starting material for the synthesis was tri-O-benzyl-D-glucal (15) which was prepared by the standard protocol employed in this laboratory, scheme 19:
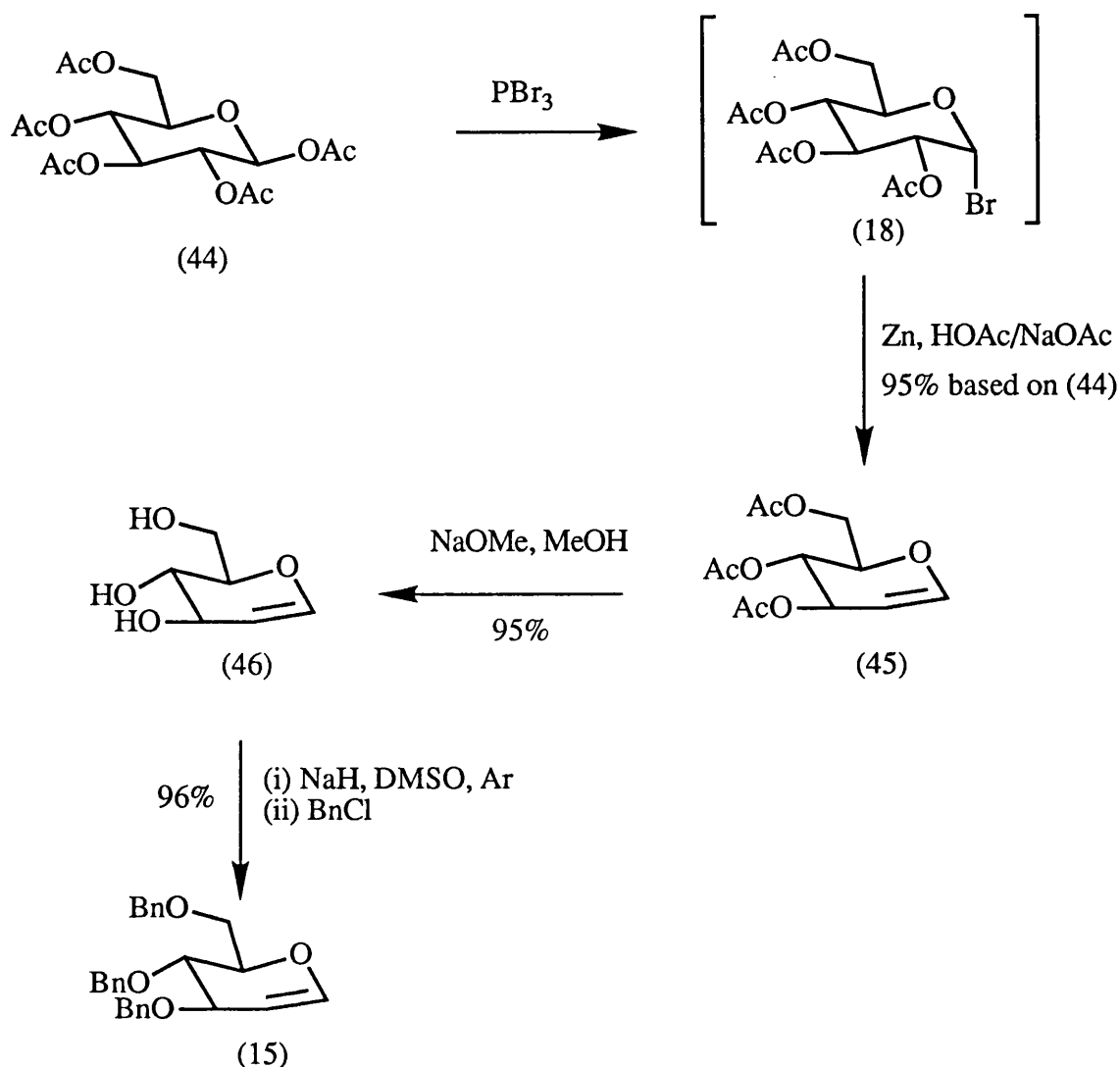
Scheme 19 : Synthesis of tri-*O*-benzyl-D-glucal (15).

The glucal (15) was converted to the sulfone ester (50) according to Crich and Ritchie[14] via the chlorides (47α) and (47β) which were not isolated but converted directly to the phenyl thioglycosides (48α) and (48β). The sulfides (48α) and (48β) were obtained in a ratio of α : β, 1 : 5. On oxidation with mmpp in ethanol at room temperature, the sulfides (48α) and (48β) were converted to the sulfones (49α) and (49β), which were obtained in a ratio α : β, 1 : 5. After deprotonation of the mixture of sulfones (49α) and (49β) with LDA and quenching with dimethyl carbonate, the sulfone ester (50) was obtained as a white solid following purification by column chromatography, scheme 20:
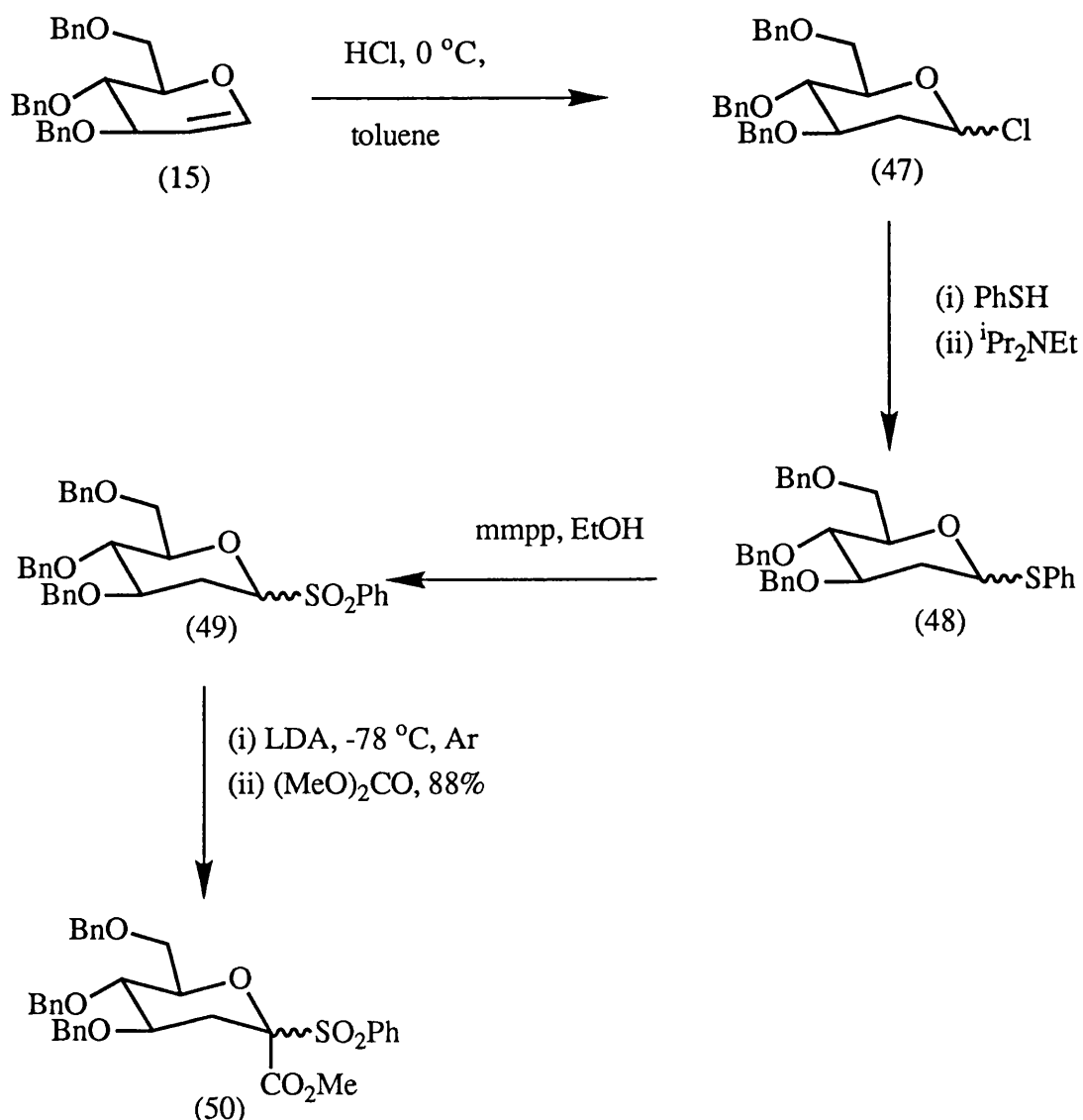
Scheme 20 : Synthesis of the sulfone ester (50).

As alluded to above, the assignment of configuration of the sulfone ester (50) was difficult since there is no anomeric proton. Previously, the configuration of the sulfone ester (50) had been assigned so as to place the sulfone group in the equatorial position, i. e. as the β-sulfone ester. This assignment was based on work carried out by Ley[29] on related tetrahydropyranyl systems.

The Ley study involved deprotonation of 2-arylsulfonyltetrahydropyrans (51) at low temperature, followed by quenching with a diverse range of electrophiles. On warming to

room temperature, spontaneous elimination of benzenesulfinic acid occurred to give the

alkene (52) with no evidence of any addition product, scheme 21:
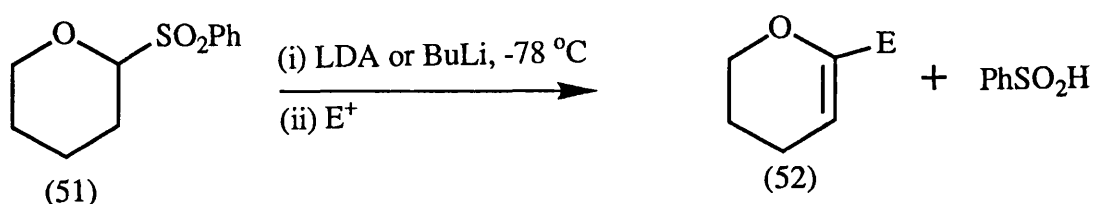
Scheme 21 : Alkylation of 2-phenylsulfonyl tetrahydropyran with elimination of benzene

sulfinic acid.

However, the study also revealed that the reaction of the anion derived from (51) with

alkyl and aryl chlorformates gave the addition product (53), scheme 22.
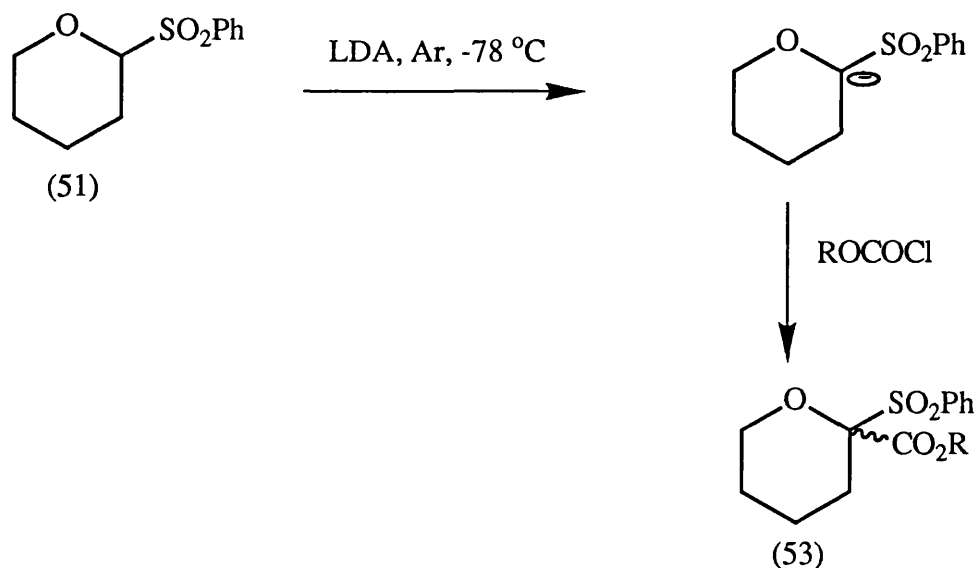
Scheme 22 : Formation of 2-alkoxycarbonyl-2-sulfonyltetrahydropyrans.

These acylated sulfones were isolated as stable crystalline solids. X-ray crystallographic

structure determination of one such compound showed the sulfonyl moiety to be in the

equatorial position. Further, in this laboratory, attempts at the base-promoted elimination

of benzenesulfinic acid from the sulfone ester (50) were unsuccessful. Similarly, the use

of Lewis acids such as magnesium bromide etherate, $MgBr_2.OEt_2$, as suggested by Ley[30] for the formation of glycoside bonds using glycosyl sulfones as donors were unsuccessful when applied to the sulfone ester (50). This lack of reactivity and the Ley crystal structure had suggested that (50) had the sulfone group in the equatorial position. In order to continue with the synthesis of β-linkages, the sulfone ester (50) was "reduced" according to Crich and Ritchie[14] to give the separable phenyl thioglycosides (54) and (55), scheme 23. The ^1H nmr spectral data of these compounds were identical to data reported in the literature by Crich and Ritchie.

The phenyl thioglycoside (55) was the faster eluting anomer and was obtained in crystalline form from methanol. Again assignment of anomeric configuration was difficult. Previously, assignment of configuration was directed by the observation of a n.O.e. between the *ortho*-hydrogens of the phenylthio group and the 3β-hydrogen in (55) showing that the phenylthio group was in the equatorial position.

$$(54) : (55)$$
$$0.7 : 1$$
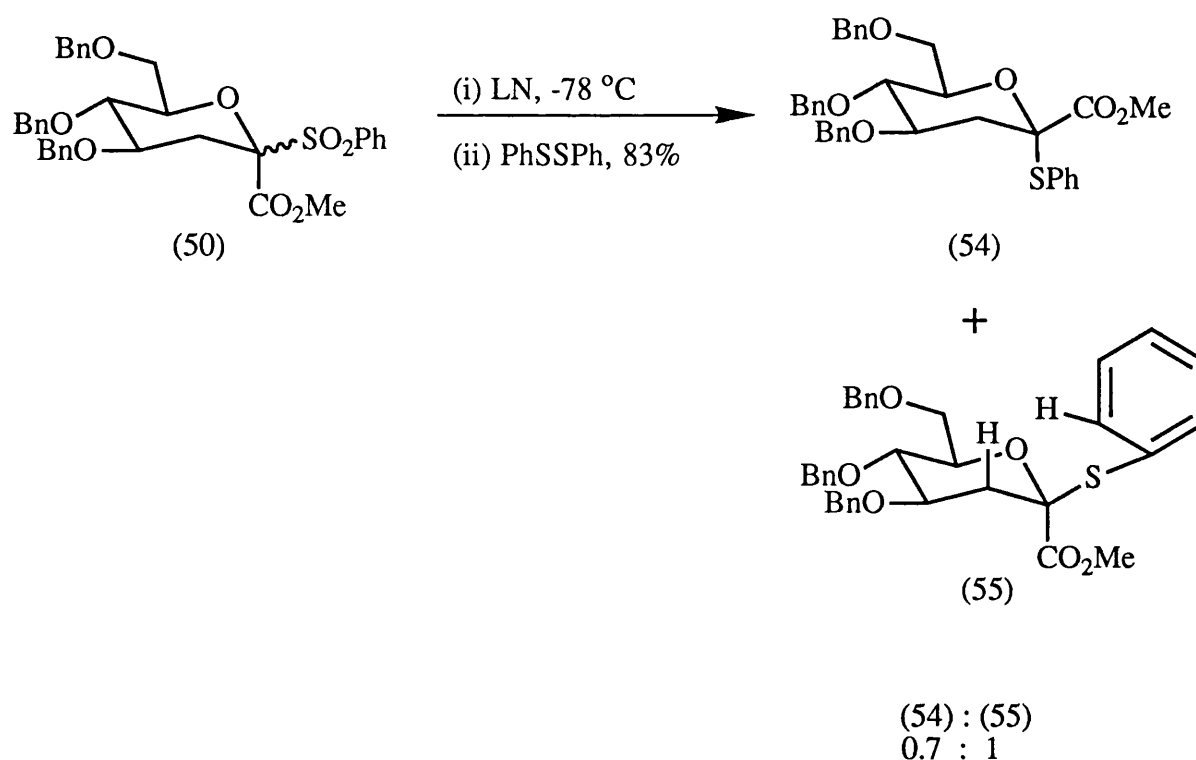
Scheme 23 : "Reduction" of the sulfone ester (50).

The mixture of the sulfides (54) and (55) was converted to the separable O-methyl glycosides (56) and (57), scheme 24. The major isomer was obtained as a white solid, m. pt (76-78) °C, whereas in the literature it was reported as a colourless oil.
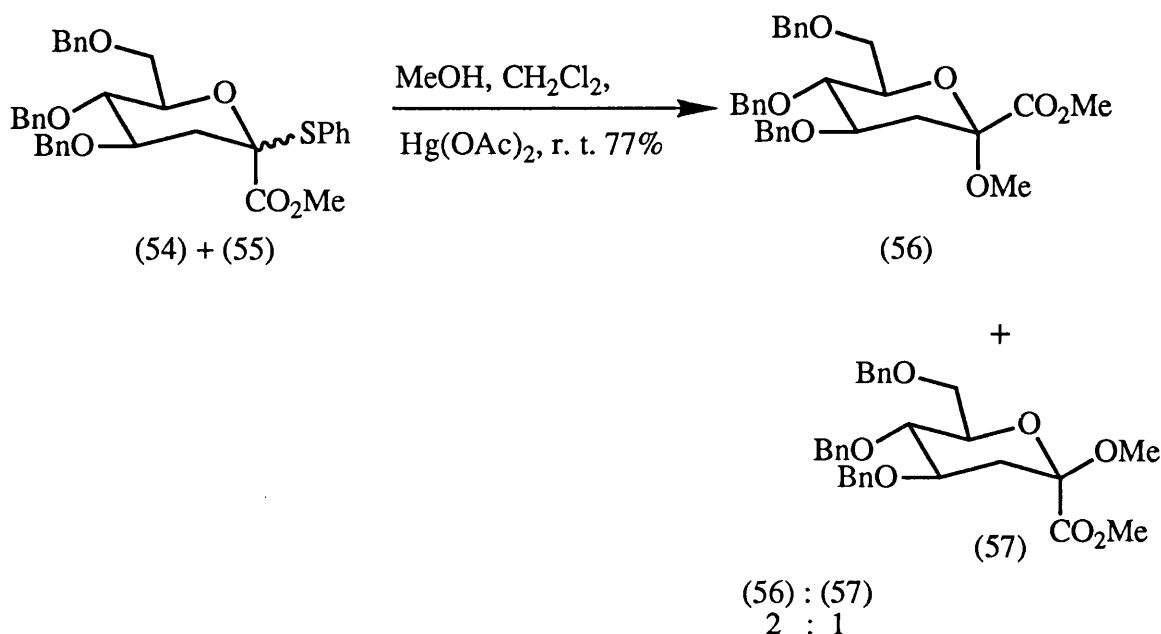
Scheme 24 : Preparation of O-methyl glycosides (56) and (57).

Again, the original assignments of (56) and (57) could possibly be reversed since they were not previously rigorously determined for the same reasons outlined above for the sulfone ester (50).

2.2. Assignment of Configuration of the sulfone ester (50) and other derivatives.

So far the anomeric configuration of these sugars had not been assigned with complete certainty. Ley's[29] compounds had been assigned according to evidence obtained from X-ray crystal structure data. However, these compounds are probably conformationally mobile since the ring is not otherwise substituted. Thus the X-ray structure of (53) could simply represent the lowest energy conformation with the most bulky sulfonyl group equatorial, figure 5. On the other hand, with the relatively conformationally rigid (50),

the observed configuration probably reflects the stereoelectronic preference for reactivity of the intermediate anion.

Figure 5 : Conformational equilibrium of unsubstituted sulfone ester (53a) showing 1,3-diaxial interactions.
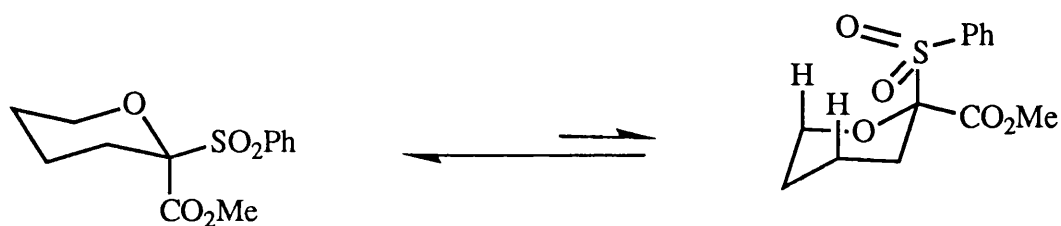
Hence, the diastereoisomer obtained in the reaction is likely to reflect either the kinetic selectivity of the possible pyramidal anion, if it is rapidly interconverting, or if the anion is configurationally stable under the reaction conditions employed then the product ratio formed would reflect the ratio of the starting sulfones. The experiments revealed that one major product is obtained starting from a 1 : 5, α : β ratio of (49α) and (49β), suggesting that there is rapid inversion of the anions and that one reacts significantly faster than the other, giving one major product.

Comparison of the anomeric configuration of the sulfone ester (50) was also made to related compounds described by Beau and Sinaÿ.[31] This group employed the substituted 1-sulfonyl-2-deoxypyranose system (58) with different protecting groups. These sulfones (58) were deprotonated with LDA or n-BuLi at low temperature and quenched with D2O. The products were isolated and it was found that the major product (59) had the bulky sulfonyl group in the axial position, scheme 25.

OR

RO,,,

(i) LDA or n-BuLi, -78 °C
(ii) D₂O

RO

O

SO₂Ph

R = TBDMS, Bn, Me

(58)

OR

RO,,,

RO

O

D

SO₂Ph

(59)

+

OR

RO,,,

RO

O

SO₂Ph

D

(60)

α : β
4 : 1
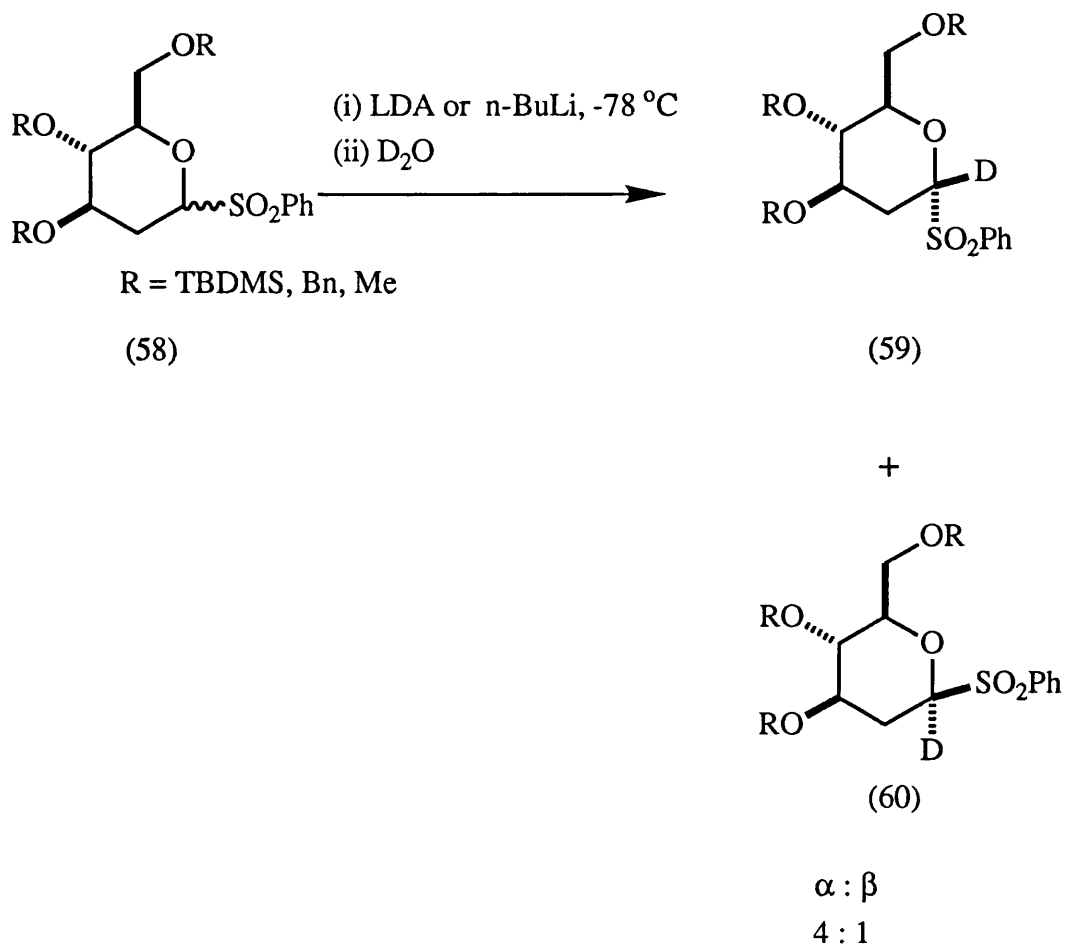
Scheme 25 : Deprotonation of substituted 1-sulfonyl-2-deoxypyranose systems followed by quenching with D₂O.

Regardless of the starting anomeric mixture of (58), the same anomeric composition of α–deuterated sulfones (59) and (60) was obtained. This result indeed suggests that the following equilibrium exists, scheme 26.

RO
RO
RO
O
H
SO$_2$Ph

(49α)

RO
RO
RO
O
SO$_2$Ph
H

(49β)

-H$^+$

-H$^+$

RO
RO
RO
O
SO$_2$Ph

RO
RO
RO
O
SO$_2$Ph
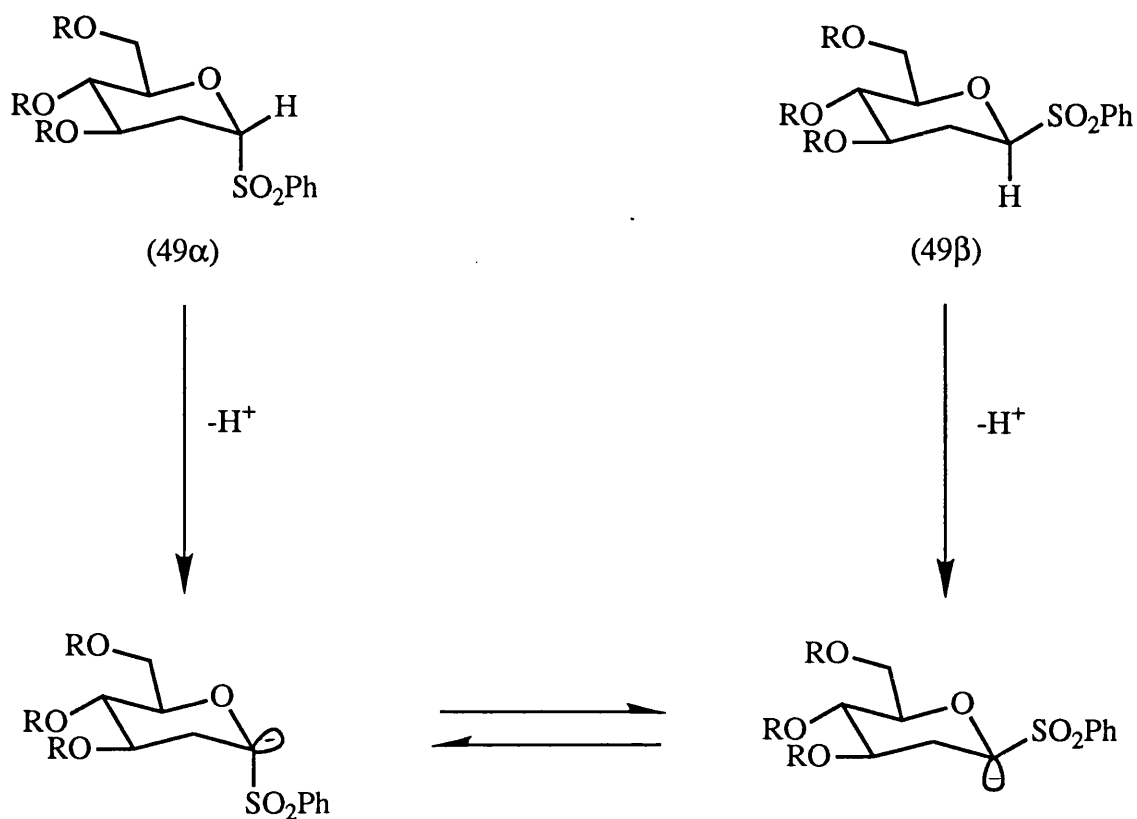
Scheme 26 : Equilibrium between α- and β- anions of (58).

Kinetic anions formed by equatorial and/or axial deprotonation of the corresponding sulfones equilibrate so as to allow the lone pair at C-1 to adopt an equatorial orientation. This results in the formation of the α-sulfone as the major product on quenching with D$_2$O.

However, studies on "chiral" α-sulfonyl anions[32] show that these species are planar or nearly planar (61) rather than pyramidal and the lone pair in Cα bisects the O-S-O angle, figure 6.

Figure 6 : Planar versus pyramidal α-sulfonyl anions.

$$R^1\underset{R^2}{\overset{O}{\underset{\diagdown}{\overset{\|}{C}}}}SO_2R \qquad \text{or} \qquad R^2\overset{R^1}{\underset{O}{\overset{\diagdown}{\underset{\|}{C}}}}SO_2R$$

(61a)   (61b)

vs

$$R^1\underset{R^2}{\overset{\diagdown}{\diagup}}C=S\overset{O^-}{\underset{O}{\diagup\diagdown}}R$$

(62)
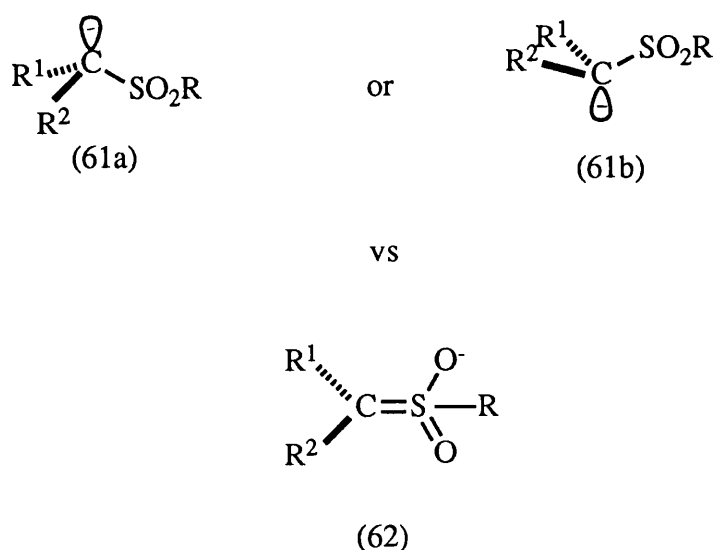
Spectroscopic evidence also suggests that the anion is planar. In benzylic anions like (63) and (64), figure 7, ^{13}C nmr spectrum coupling constants for $^1J_{C-H}$ for C_α are very large (160-168 Hz). This is in good agreement with a nearly planar configuration at this C atom. IR spectroscopic studies on $PhSO_2CH_2Li$ indicate an increase in the S-C_α and a decrease in the S-O force constant relative to the corresponding values for methyl phenyl sulfone. This suggests that the S-C_α bond is shortened in the "anion", and the S-O bond is lengthened. The X-ray structure of (65) revealed that the S-C_α distance is 164.1 pm which is considerably shorter than the corresponding lengths in sulfones (average bond length in similar compounds is 180.6 pm) and that the C atom was planar.

Figure 7 : Spectroscopically studied α-sulfonyl species.

$$PhSO_2\bar{C}HPh\ Li^+ \qquad\qquad {}^tBuSO_2\bar{C}HPhLi^+$$
(63)   (64)

$$[PhSO_2\bar{C}HPhLi^+.TMEDA]$$
(65)
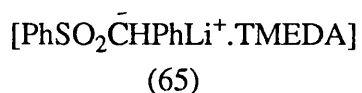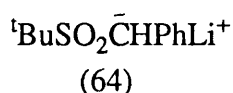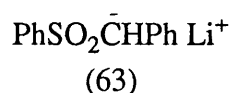
Despite this body of spectroscopic and crystallographic information, acyclic sulfones having a chiral α-carbon atom retain their configuration upon deprotonation and quenching with an electrophile, scheme 27, or by H/D exchange,[33] as shown in scheme 25.

$$
\underset{(66)}{\overset{\displaystyle H}{\underset{R^2}{\overset{R^1\cdots}{\big|}}}\hspace{-0.5em}SO_2R}
\quad
\xrightarrow[\text{(ii) } E^+]{\text{(i) LDA, -75 °C}}
\quad
\underset{(67)}{\overset{\displaystyle E}{\underset{R^2}{\overset{R^1\cdots}{\big|}}}\hspace{-0.5em}SO_2R}
$$
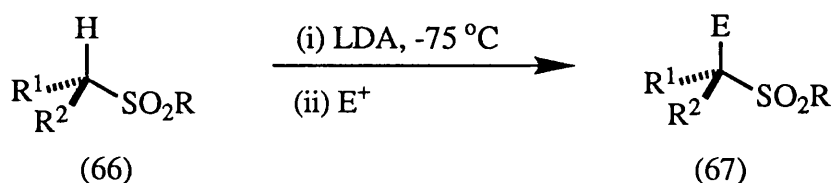
Scheme 27: Deprotonation and quenching of α-sulfones results in retention of configuration.

In (49), the anions formed upon deprotonation are probably pyramidal with the ring oxygen exerting an additional effect.

In the same series of reports by Beau and Sinaÿ,[31] using R=Si+, quenching of the anion of (68) with dimethyl carbonate gave two products. The major product was assigned as the isomer having a twist-boat ($^OS_3$) conformation while the minor isomer had the chair ($^4C_1$) conformation. In both cases, the sulfonyl group was in the equatorial or "pseudo-equatorial" position, scheme 28.
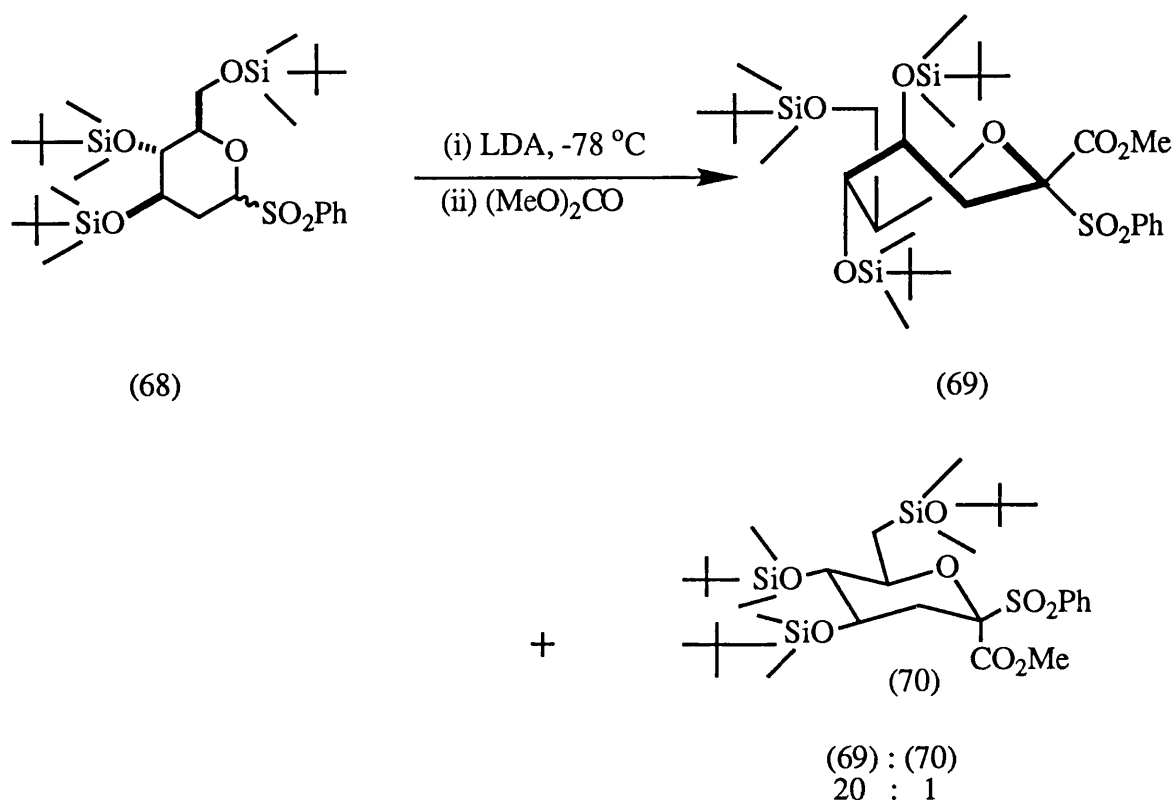
Scheme 28 : Deprotonation and quenching gives the sulfone group in the equatorial or "pseudo-equatorial" position.

Similar work by Claesson[34] involved a pyranose (71) with a carbomethoxy group at C-1 with deprotonation at low temperature and quenching with $^{13}CO_2$. Measurement of the three bond coupling constants of ^{13}C nmr spectrum of (73) of the carboxylic acid group to the protons at C-3 gave proof of the structure of (73), scheme 29.

$$\text{(71)} \quad \xrightarrow[\text{(ii) } ^{13}CO_2]{\text{(i) LDA, -75°C}} \quad \text{(72)}$$

$$+$$

(73)

(72) : (73)
3 : 7
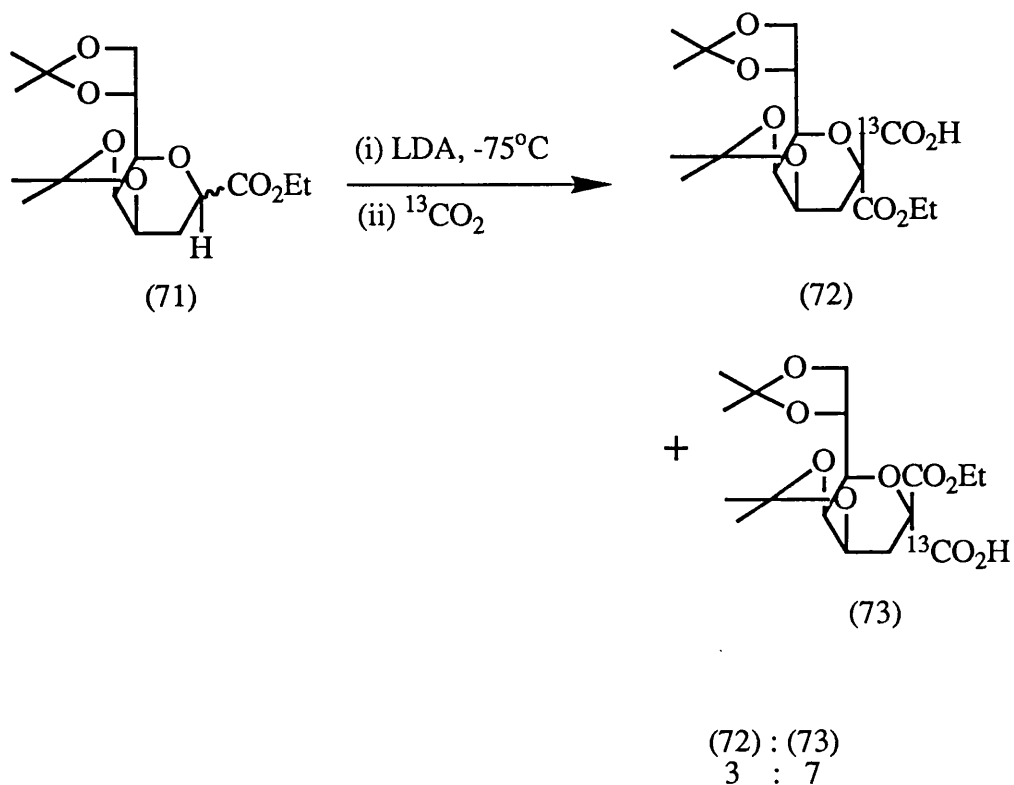
Scheme 29 : Deprotonation of 1-carboethoxypyranose and quenching with $^{13}CO_2$.

Originally, as indicated above, the sulfone group in (50) was assigned to the the β-position, in accordance with the Ley X-ray structure and in apparent agreement with its lack of reactivity. Elimination was achieved by pyrolysis and this was explained in terms of the higher temperature promoting a conformation from which elimination was more facile, scheme 30.

BnO—
BnO—
BnO— SO₂Ph
CO₂Me

(50)

heat
⟶

BnO— SO₂Ph
OBn
CO₂Me
-O
OBn

-H⁺, -PhSO₂⁻

BnO—
BnO—
BnO— CO₂Me

(41)
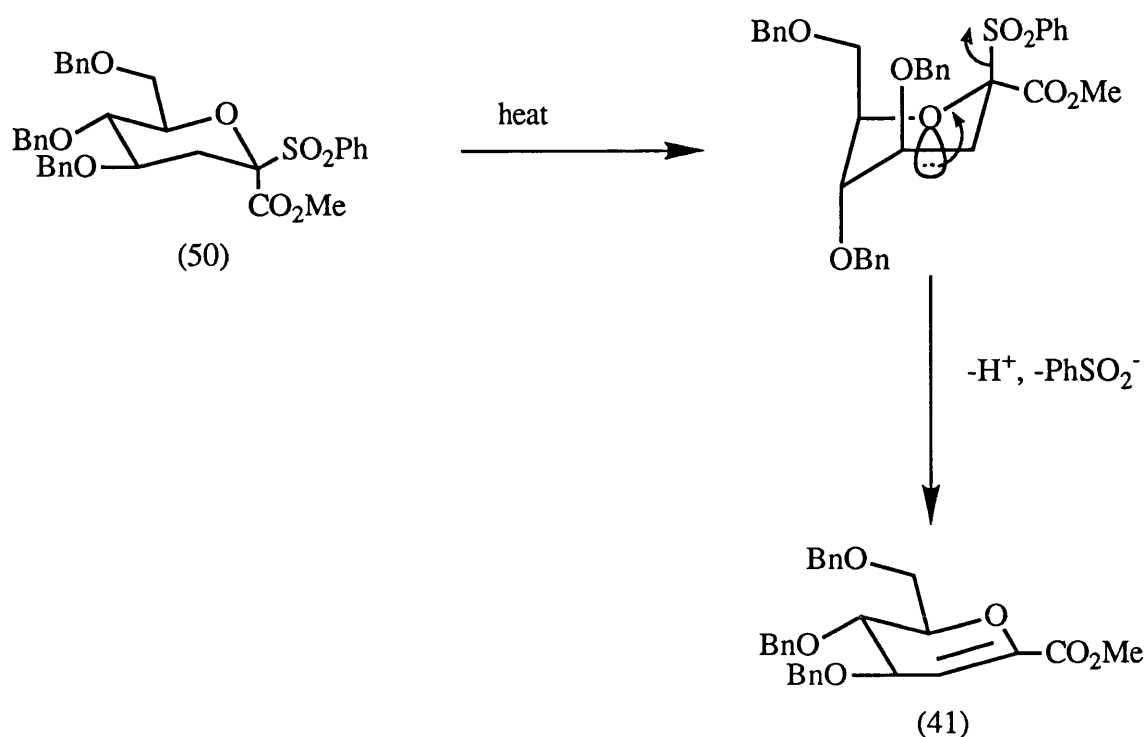
Scheme 30 : Possible mechanism for elimination of benzenesulfinic acid.

Due to the unknown position of the phenyl sulfone group in (50), it was decided to correlate the sulfone ester with the phenyl thioglycosides (54) and (55). The phenyl thioglycosides (54) and (55) were prepared and separated chromatographically. The faster migrating sulfide ester (55) was assigned (vide supra) by Crich and Ritchie[14] as having the phenylthio group in the β-position by n. O e measurements. It was oxidised with 2.5 molar equivalents of mmpp in ethanol at room temperature. In a separate experiment, the sulfide ester (55) was oxidised again, but this time m-cpba in CH₂Cl₂ at 0 °C was used as the oxidant. The results are shown in scheme 31.

BnO—
BnO⌐
BnO— ⟩O
        ⟩—SPh
     CO₂Me
  (55)

mmpp, EtOH,
————————————→
r.t, 77%

m-cpba, CH₂Cl₂,
————————————→
0 °C, 73%

BnO—
BnO⌐ O
BnO—   ⟩—CO₂Me
       (41)
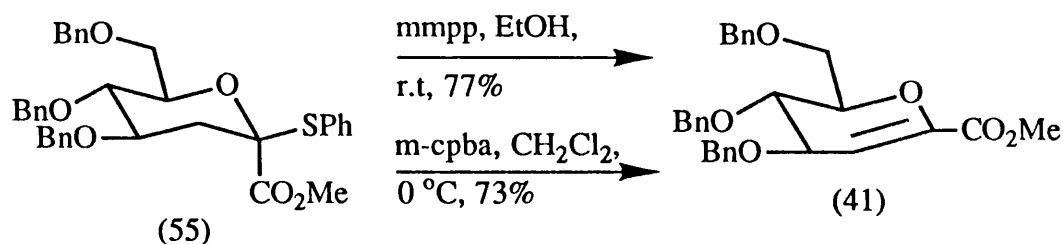
Scheme 31 : Oxidation of the sulfide ester (55).

The other anomer (54) was also subjected to oxidation under the same reaction
conditions. In this instance the sulfone ester (50) could be isolated. The results are
shown in scheme 32.

BnO—
BnO⌐
BnO— ⟩O
        ⟩—CO₂Me
       SPh
      (54)

mmpp, EtOH,   m-cpba,
r.t   CH₂Cl₂, 0 °C

BnO—
BnO⌐ O
BnO—   ⟩—CO₂Me
     (50) SO₂Ph
     21%

+

BnO—
BnO⌐ O
BnO—   ⟩—CO₂Me
       (41)
       54%

BnO—
BnO⌐
BnO— ⟩O
        ⟩—CO₂Me
     (50) SO₂Ph
     70%
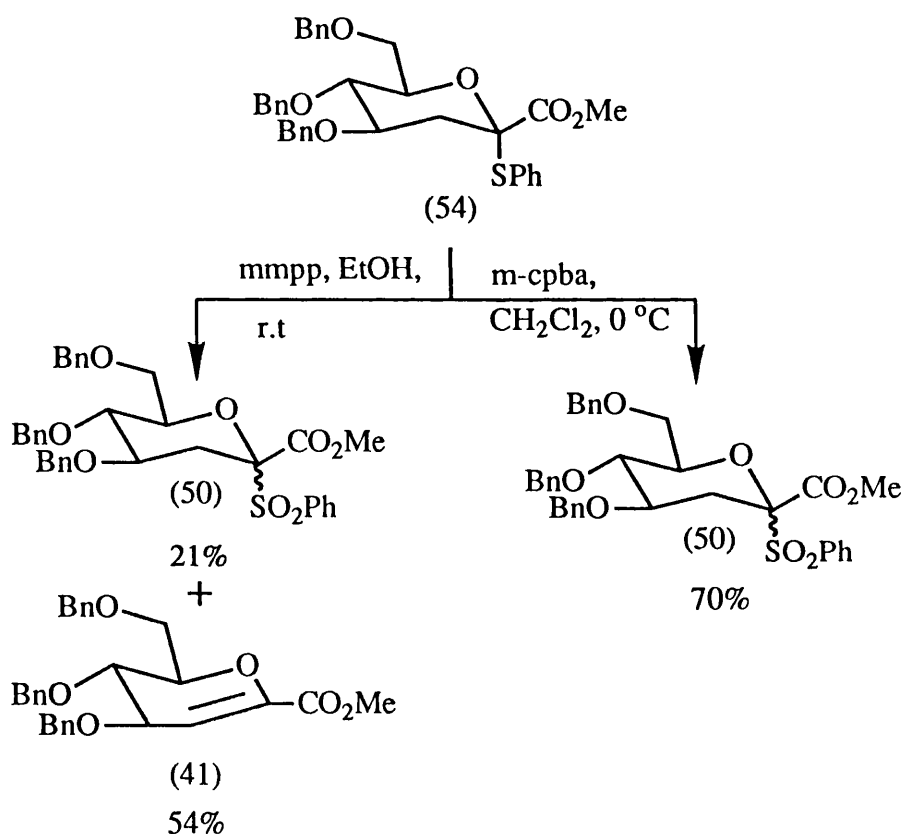
Scheme 32 : Oxidation of the sulfide ester (54).

The experimental results show that the sulfide ester (54), having the -SPh group in the α
position gave the sulfone ester (50) which was previously assigned as having the -SO₂Ph

group in the β position. The sulfide ester (55), having the -SPh group in the β position gave exclusively the carbomethoxy glucal (41). These observations clearly indicate that either the α-sulfide ester (54) or the β-sulfone ester (50) had been misassigned. It would appear that in the oxidation of (54) with mmpp, the glucal (41) must have come from the intermediate sulfoxide (74), figure 8, possibly via syn-elimination or more likely, given the reaction temperature, by simple acid-catalysed elimination as described by Kahne.[15] The other sulfoxide (55) gave exclusively the carbomethoxy glucal (41). It would appear that this glucal (41) comes from the intermediate sulfoxide (75), figure 8. It is less stable than its diastereoisomeric counterpart (74), and therefore readily eliminates benzenesulfinic acid to give the more stable glucal (41).

Figure 8 : The intermediate sulfoxides.

(74)   (75)
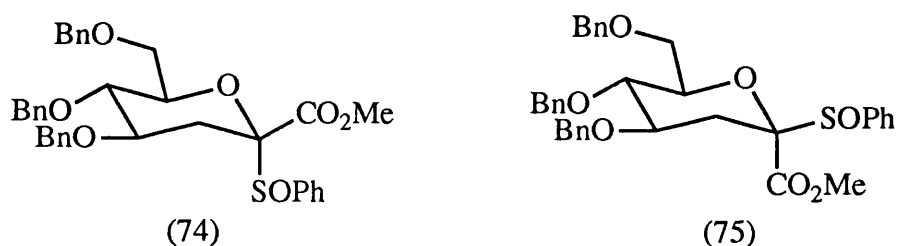
In a related study by Sinaÿ[35] on 2- thioglycosides of N-acetylneuraminic acid, the two glycosides (76) and (77) were prepared, figure 9.

Figure 9 : 2-Thioglycosides of N-acetylneuraminic acid.

(76)   (77)
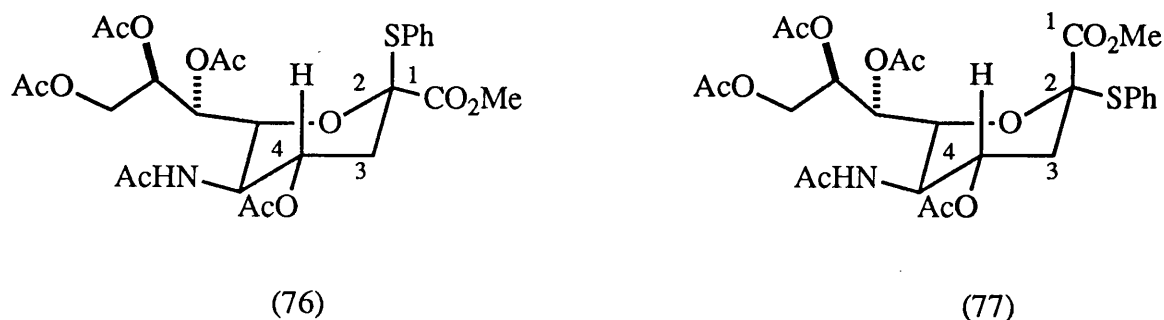
The basis for the assignment of configuration of (76) and (77) was not given. However, the structures of the above acetylated 2-thioglycosides were distinguishable by ^{1}H nmr spectroscopy (C_6D_6). The signal for H-4 in (77), figure 10 is reported at significantly higher field (δ 4.81 ppm) than that for the corresponding β-glycoside (76), (δ 5.35 ppm).

Figure 10 : The sulfide esters (54) and (55).

(54)   (55)
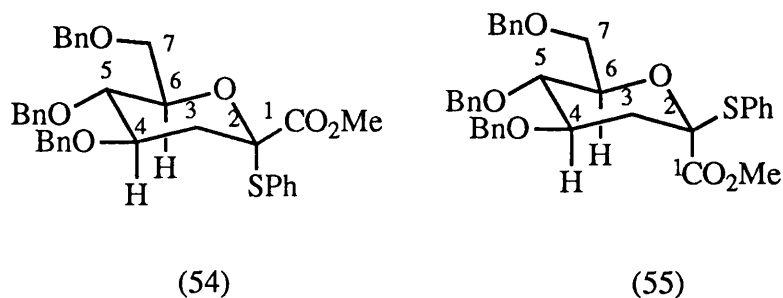
In (54) H-4 and H-6 have a 1,3 -diaxial relationship to the axial substituent at C-2. H-4 and H-6 are both ddd and are found at δ 4.08 ppm and δ 4.48 ppm. H-4 and H-6 can be distinguished by decoupling experiments, in particular by irradiation at H-3.

In (55) both H-4 and H-6 are part of a 3H unresolved multiplet which includes H-5. This multiplet is centered on δ 3.55 ppm.

From the ^{1}H nmr spectrum data both signals in (54) are shifted substantially downfield from the corresponding signals in the Ritchie β-sulfide (55). This is clearly the same effect observed by Sinaÿ where the compound with the axial -SPh group has the more downfield shift for H-4.

A more detailed analysis of ^{1}H nmr spectrum data of (54) and of (55) and of Sinaÿ's compounds (76) and (77) is presented in the table below.

Table 1:

(54)	(55)	(76)	(77)
δ 2.12 1H, dd, H-3ax	δ 1.83 1H, dd, H-3ax $J_{3ax-4} = 11.1$ Hz	δ 2.01, 1H, dd, H-3ax $J_{3ax-4} = 11.7$ Hz	δ 2.03, 1H, dd, H-3ax $J_{3ax-4} = 12.0$ Hz
δ 2.80 1H, dd, H-3eq $J_{3ax-3eq} = 13.9$ Hz	δ 2.96 1H, dd, H-3eq $J_{3ax-eq} = 12.8$ Hz $J_{3eq-4} = 5.0$ Hz	δ 2.80, 1H, dd, H-3eq $J_{3ax-3eq} = 14.0$ Hz $J_{3eq-4} = 4.8$ Hz	δ 2.98, 1H, dd, H-3eq $J_{3ax-3eq} = 12.8$ Hz $J_{3eq-4} = 4.7$ Hz
δ 4.08 1H, ddd, H-4 or H-6 $J_{3ax-4} = 11.1$ Hz $J_{3eq-4} = 4.7$ Hz	δ 3.55 3H, m, H-4, H-5 and H-6	δ 4.61, 1H, m, H-6	δ 3.94, 1H, dd, H-6 $J_{5-6} = 10.7$ Hz $J_{6-7} = 2.2$ Hz
δ 4.48 1H, ddd, H-4 or H-6		δ 5.35, 1H, ddd, H-4 $J_{4-5} = 10.2$ Hz	δ 4.81, 1H, ddd, H-4 $J_{4-5} = 10.5$ Hz

From the coupling constant values to H-3axial and H-3equatorial, it can be safely concluded that all the four thioglycosides are in the $^5C_2$ chair conformation (or $^4C_1$ conformation, glucose numbering).

Re-examining the sulfone ester's (50) ^{1}H nmr spectral data:

δ 2.83 2H, ddd,

2 x H-3

$J_{3ax-3eq}$ = 15.2 Hz

J_{3ax-4} = 6.0 Hz

J_{3eq-4} = 4.2 Hz
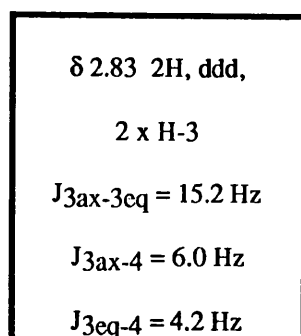
It can be concluded that the sulfone ester (50) is not in a chair conformation but probably adopts a twist-boat $^0S_3$ conformation, figure 11.

Figure 11 : Possible room temperature conformation of the sulfone ester (50).
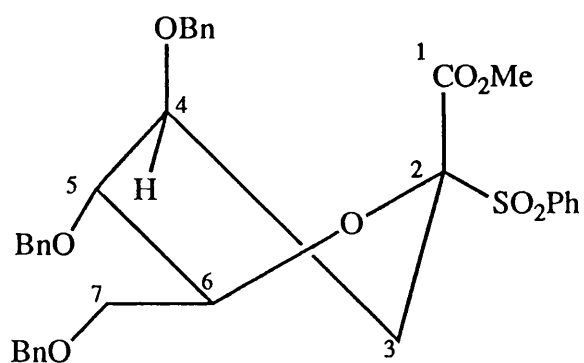
The oxidation of the phenyl thioglycosides (54) and (55) can thus be rationalised as follows: when (55) is oxidised, there is no change in 1, 3-diaxial interactions, scheme 37.
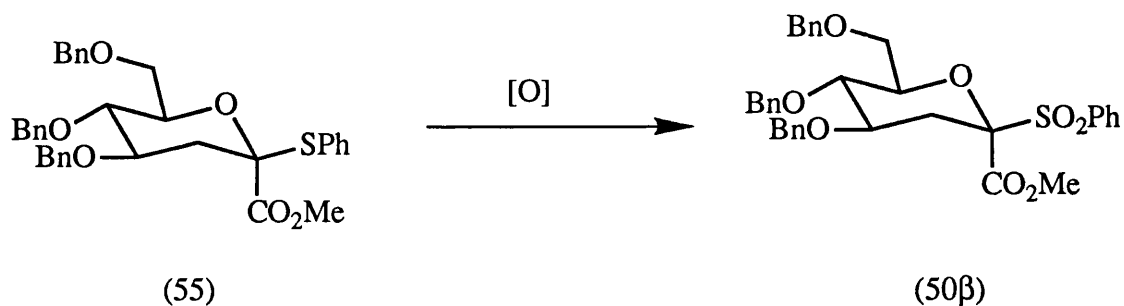
Scheme 37 : Oxidation of the β-sulfide ester (55).

However, (50β) was not observed: instead the carbomethoxyglucal (41) was observed. This suggests that the intermediate sulfoxide (75) is not stable and elimination occurs before the formation of (50β) to give (41). On oxidation of (54), the 1,3-diaxial interactions are increased upon oxidation to first the sulfoxide (74) and then to the sulfone (50), and a twist-boat structure results, scheme 38.
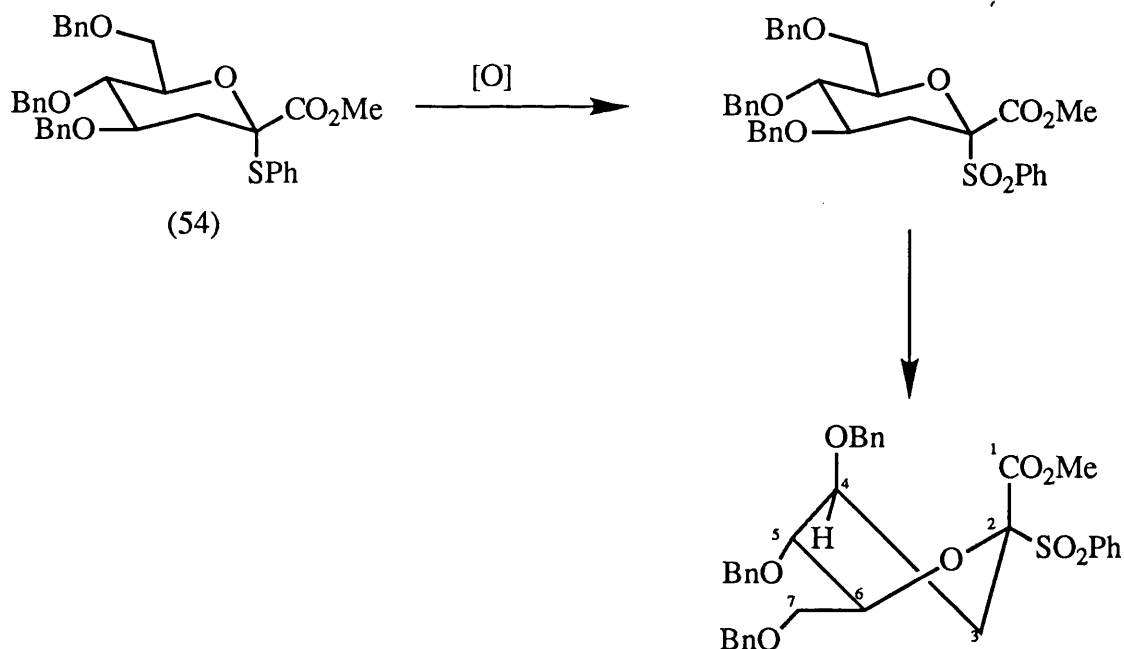
Scheme 38 : Oxidation of the sulfide ester (54).

To confirm these findings, it was decided to employ a spectroscopic method pioneered by Japanese workers, Ohrui and Meguro,[36] in order to determine the anomeric configuration. This method is based on the Karplus assumption of a relationship of $^3J_{C-H,H-3ax}$ of sialic acid (78), figure 11.

Figure 11 : Configuration of sialic acid (78).

(78)
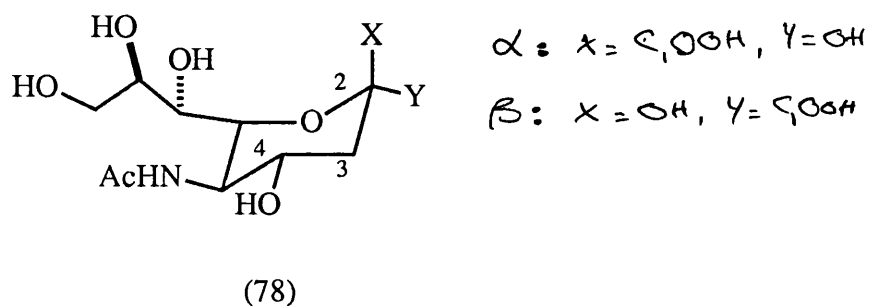
The dihedral angles of C-1-C-2-C-3-H-3ax of the α and β anomers are close to 180° and 60° respectively in the $^2C_5$ chair conformation. Therefore it is expected that the $J_{C-1, H-3ax}$ value of the α anomer is larger than that of the β-anomer, figure 12.

Figure 12 : Angles derivable from coupling constants.
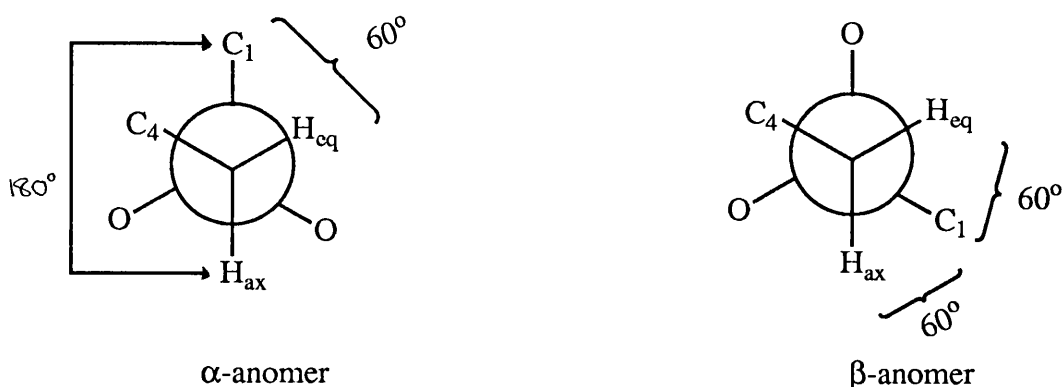
α-anomer

β-anomer

The Japanese workers measured the <u>gated proton - coupled</u> ^{13}C nmr spectrum in D_2O of (78). The signal for C-1 of the α-anomer was a doublet ($J_{C-1,H-3ax} = 6.1$ Hz) at δ 175.3

ppm and the corresponding signal of the β-anomer was a singlet at δ 176.1 ppm, indicating that the synclinal coupling was virually zero.

It was then decided to use this method and apply it firstly to the phenyl thioglycosides (54) and (55). In (55), the proton-coupled carbonyl signal of the methyl ester was centred at δ 168.21 ppm, as a doublet of quartet with $W_{1/2} = 26$ Hz, figure 13. In this J_1 ~ $2J_2$. In (54), the carbonyl signal of the methyl ester is centred around δ 169.49 ppm with $W_{1/2} = 19$ Hz. In theory this should be a triplet of quartet. Therefore nmr spectroscopy supports the previous assignments for the sulfide esters (54) and (55) and hence the reversed assignment for the sulfone ester (50).

The ^{13}C nmr gated proton-coupled spectrum of the sulfone ester (50) was then measured. The spectrum showed a superficial quartet at δ 167.28 ppm. This can be interpreted as a quartet with a poorly resolved second coupling which suggests that the dihedral angle is small. $W_{1/2}$ here is ~19 Hz. This leads to the conclusion that in the absence of other data, the ^{13}C $^3J_{H-C}$ coupling method should be treated with caution and should only be applied when the chair conformation is proven.

The ^{13}C nmr method was then applied to the diastereoisomeric O-methylglycosides (57) and (56). The table below shows selected ^1H nmr data.

Table 2

(57)	(56)
δ 1.76 1H, dd, H-3ax	δ 1.80 1H, dd, H-3ax
δ 2.53 1H, dd, H-3eq $J_{3ax-3eq} = 12.83$ Hz $J_{3ax-4} = 11.18$ Hz $J_{3eq-4} = 5.10$ Hz	δ 2.73 1H, dd, H-3eq $J_{3ax-3eq} = 12.89$ Hz $J_{3ax-4} = 11.29$ Hz $J_{3eq-4} = 4.53$ Hz

The spectral data shows that the O-methyl glycosides (57) and (56) are clearly both in the $^5C_2$ chair conformation. In the ^{13}C gated proton-coupled spectrum for (56), figure 13 the carbonyl signal of the carbomethoxy group is centred at δ 169.58 ppm with $W_{1/2} = 16.88$ Hz. The corresponding signal for (57) is a broad doublet centred at δ 169.51 ppm with $W_{1/2} = 11.25$ Hz. This suggests that in (56) because of a bigger $W_{1/2}$ value, the CO_2Me group should be axial. Therefore on this basis the O-methyl glycosides were originally misassigned. The faster eluting anomer is now in fact β-O-methyl glycoside. This also correlates with the phenyl thioglycosides in which the faster eluting anomer is the β-phenyl thioglycoside.

Figure 13 : ^{13}C gated proton coupled nmr spectra.

(50)

$w_{1/2} = \sim 19$ Hz

(54)

$w_{1/2} = 19$ Hz

(55)

$w_{1/2} = 26$ Hz

BnO

BnO
BnO
O
CO₂Me
OMe
(56)
w₁/₂ = 11.25 Hz

BnO
BnO
BnO
O
OMe
(57)
CO₂Me
w₁/₂ = 16.88 Hz

Ph
O
O
O
OBn
CO₂Me
SO₂Ph
(100)

w₁/₂ ~ 13 Hz

169   168   167   166
PPM
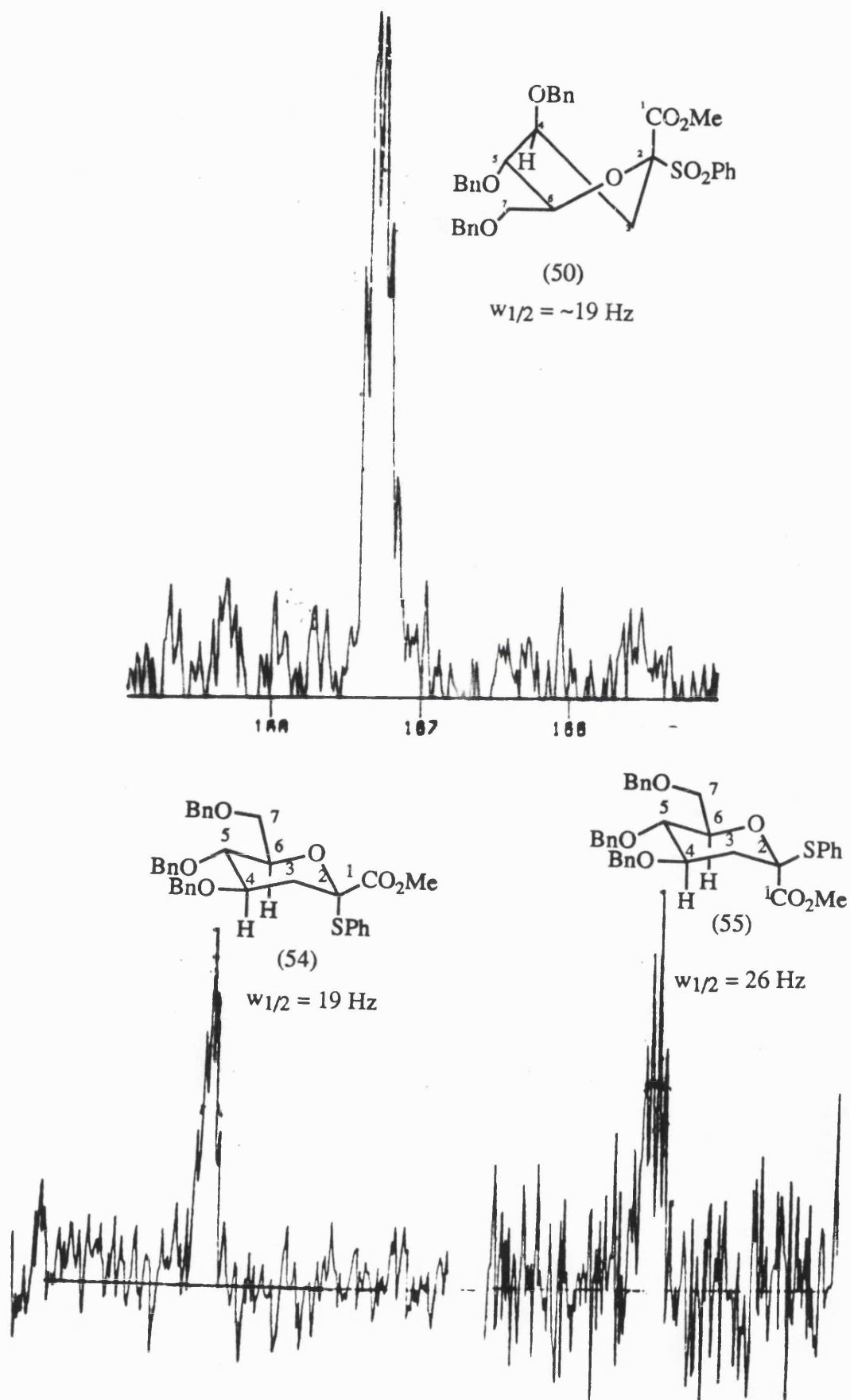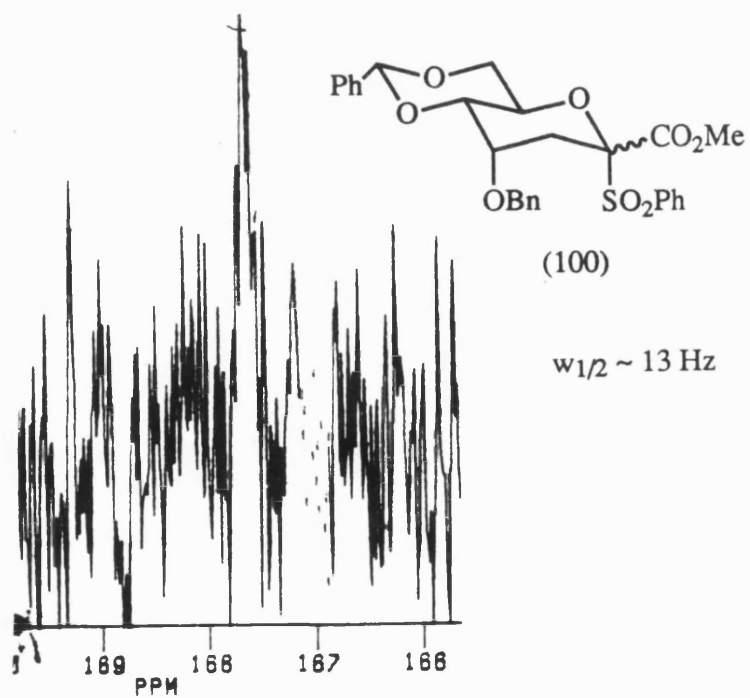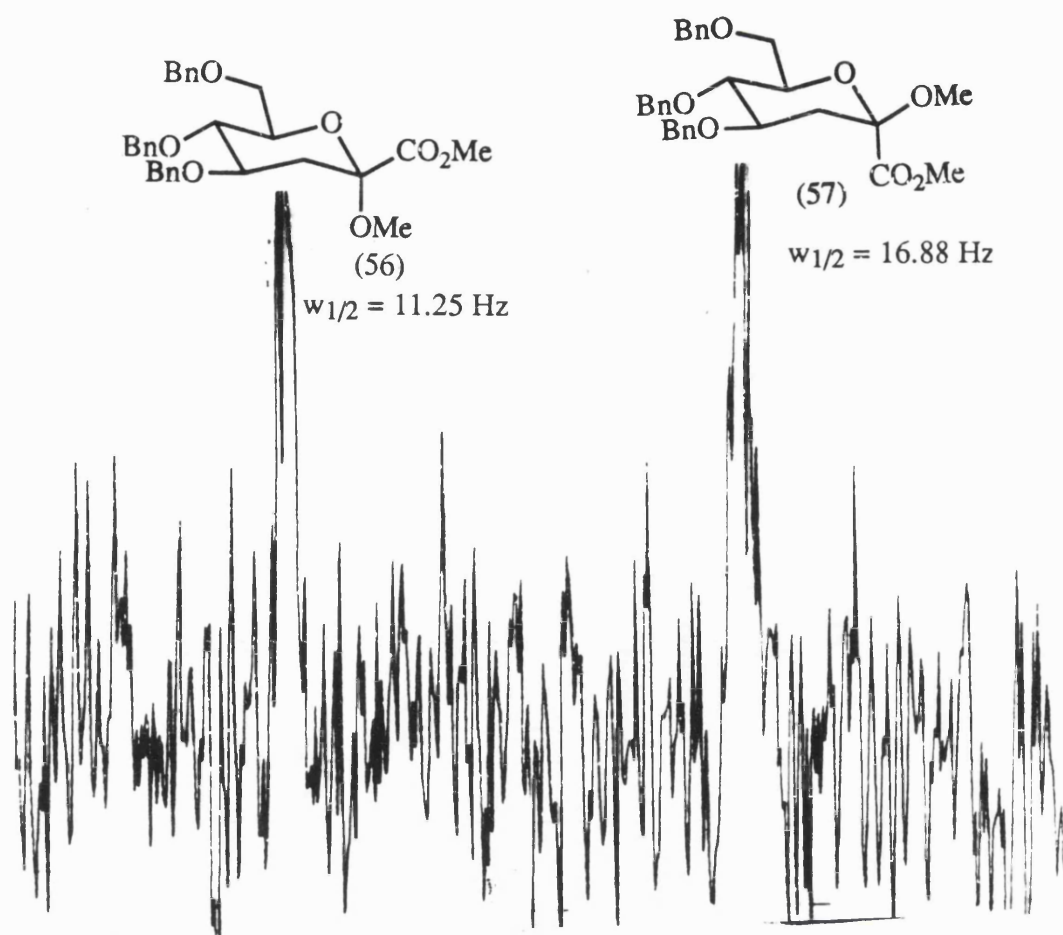
Therefore in order to assign the anomeric configuration using the gated proton-coupled method, the molecule must be in a chair conformation. Looking at the sulfone ester (50), the molecule is not in the chair conformation. This is deduced from the ^{1}H nmr coupling constant values. Both phenyl thioglycosides (54) and (55) were first assigned by physical methods (n.O.e) and then by ^{13}C gated proton-coupled nmr spectra. The O-methyl glycosides (57) and (56) were reassigned using the nmr method. The assignment of these O-methyl glycosides (57) and (56) also correlates to the phenyl thioglycosides: the faster eluting phenyl thioglycoside (54) gives the faster eluting O-methyl glycoside (56). Hence a consistent pattern is obtained for the whole series. The $^3J_{C-H}$ coupling method can only be applied with confidence when the conformation is known and works best when the molecule is in the chair conformation.

Now a possible mechanism for elimination of benzenesulfinic acid from (50) can be proposed to give (41). Because the sulfonyl group is in the equatorial or 'pseudo-equatorial' position, the twist-boat structure does not allow the molecule to act as a glycosyl donor when it is treated with Lewis acids. The earlier mechanism (scheme 30), based on the incorrect anomeric configuration for (50), proposed for the elimination of benzenesulfinic acid to give the carbomethoxy glucal (41) can also be adapted to the correct anomeric configuration. Thus, on heating, the room temperature twist-boat confomer is brought into equilibrium with the $^5C_2$ chair in which the sulfone group is axial and antiperiplanar with a ring oxygen lone pair leading to the explusion and, after proton loss, formation of the glucal (41), scheme 39.
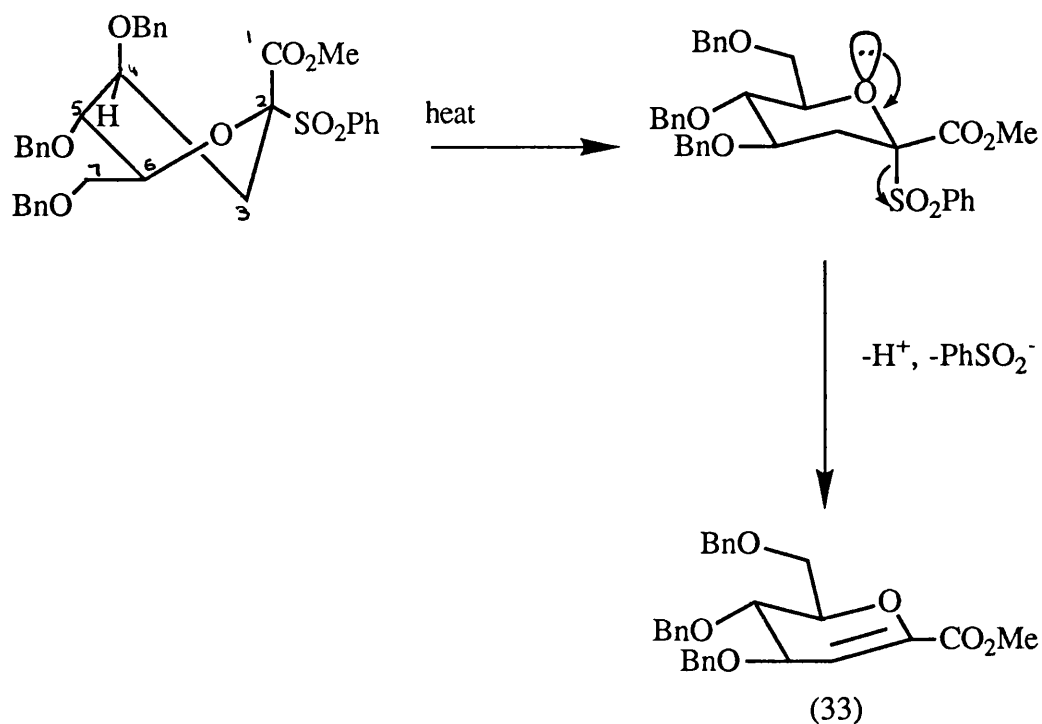
Scheme 39 : Possible mechanism for elimination of benzenesulfinic acid from the twist-

boat structure of the sulfone ester (50).

2.3. Reductive Decarboxylation using Barton O-acyl Thiohydroxamate Chemistry.

The O-methyl glycosides (57) and (56) were prepared as described above. These were

obtained as a mixture and saponified with potassium hydroxide to give the corresponding

ulosonic acid glycosides, scheme 40.

BnO—

BnO—
BnO—

OMe

CO$_2$Me

KOH/THF,

MeOH/H$_2$O

92%

BnO—

BnO—
BnO—

OMe

CO$_2$H

(56) and (57)

(79)
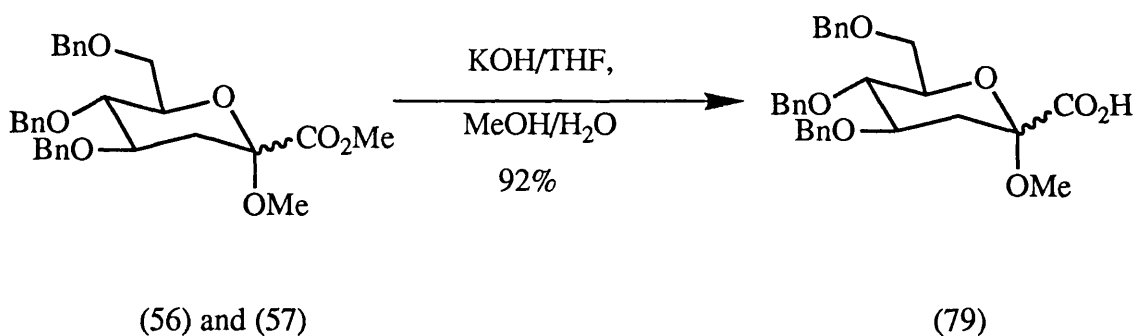
Scheme 40 : Saponification of O-methyl glycosides (57) and (56).

The ulosonic acid (79) was not purified but used immediately in the reductive decarboxylation step, according to Barton's methodology.[13] This involved reacting the acid (79) with the heterocyclic salt (30) and triethylamine under an inert atmosphere in dry dichloromethane. The reaction mixture was stirred in the dark at room temperature until a bright yellow intermediate, the O-acyl thiohydroxamate ester (80) was observed, scheme 41. This ester was decomposed on treatment with 5 molar equivalents of t-butylmercaptan, followed by photolysis with a 300W tungsten lamp to give (81). The photolysis step was carried out at three different temperatures.
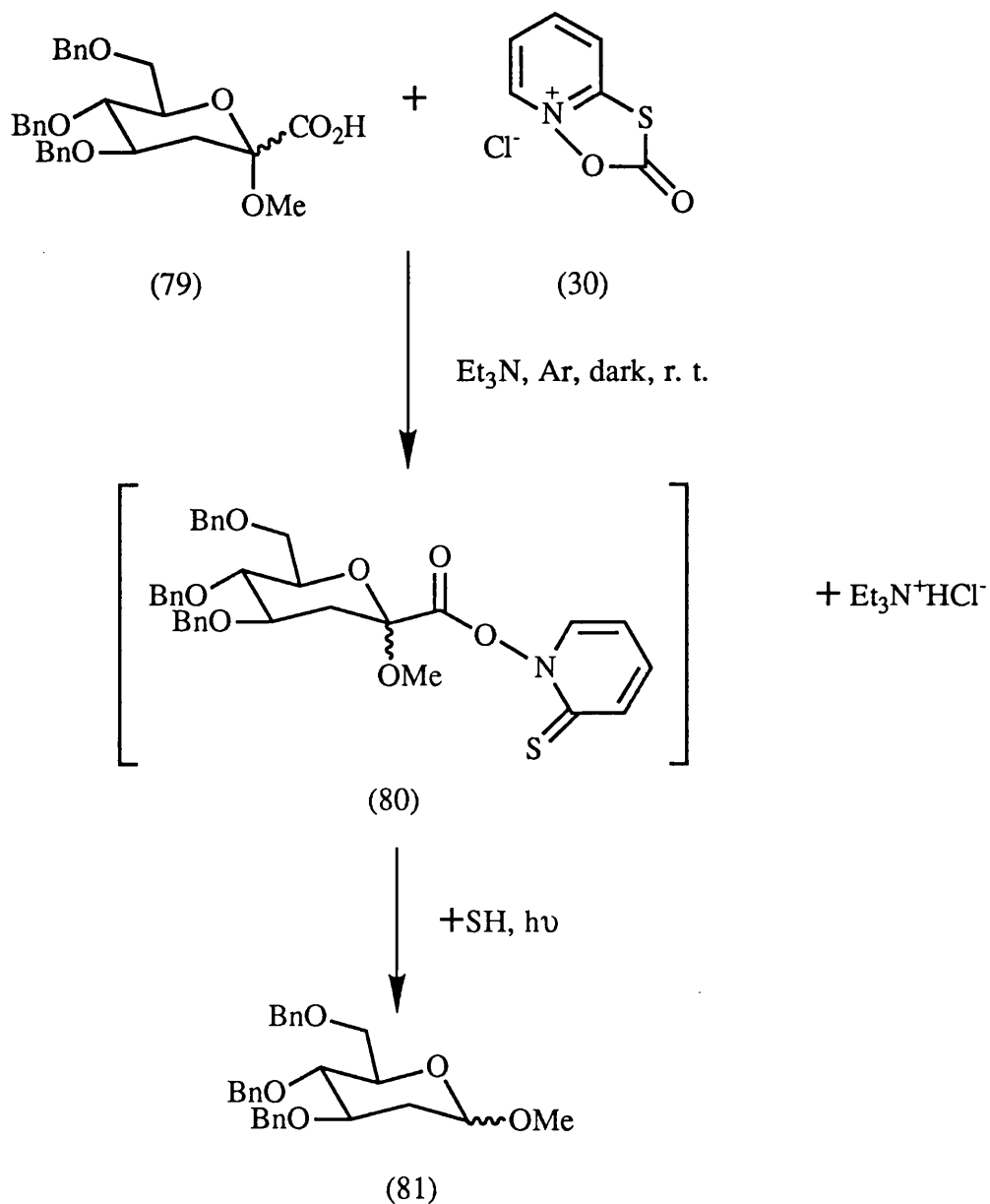
Scheme 41 : Reductive decarboxylation of ulosonic acid glycoside (٦٩).

The table below shows the yield and the anomeric ratio of products obtained at various temperatures.

Table 3

Temperature (°C)	Product yield*	Anomeric ratio α : β
13	30%	1 : 10
0	25%	1 : 11
(-13-->-10)	40%	1 : 15

* yield determined after purification.

From the table above, the α : β ratio increases from 1 : 10 at 13 °C to 1 : 15 at about -13 °C. This result is in accordance with the usual reactivity-selectivity relationship. Presumably, if the temperature was lowered even more, a further increase in selectivity would ensue. Unfortunately, given the limitations of the photochemical set-up, this was not practical.

2.4 The Ribo-Problem

Previous work in this laboratory[14, 16] on diastereoselective free-radical reactions in the 2-deoxy-arabino-heptulosonate esters showed that the anomeric radicals are quenched mainly from the axial direction leading to a β-product in high selectivity. These esters have an equatorial substituent at C-3 (glucose numbering). Thus it was decided to prepare analogous compounds in the ribo-series to compare and contrast the effect of an axial C-3 substituent on the diastereoselective free-radical reaction.

The synthetic strategy to be adopted for the formation of the 2-deoxy-D-ribo-heptulosonic acid derivatives required the preparation of a glycal with the ribo-stereochemistry (82), figure 14:

Figure 14 : ribo-Stereochemistry at C-3 required.

PO
PO O

OP

P : Protecting group.

(82)
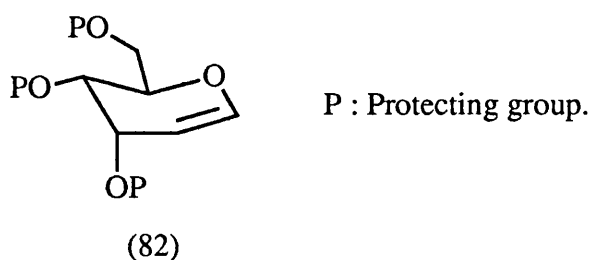
From this glycal the corresponding 2-deoxy-D-ribo-heptulosonic acid could be synthesised according to literature procedures[14] and then Barton's O-acyl thiohydroxamate[13] chemistry could be used to carry out a radical decarboxylation at C-1 enabling comparison with the quenching ratio obtained in the arabino-series.

For the synthesis of a ribal derivative, a sugar with an axial hydroxy group at C-3 was required. Either D-allose (83) or D-altrose (84) could have been used to synthesize the glycal (87). All the hydroxy groups in either D-allose (83) or D-altrose (84) could first be protected as the acetate esters, followed by forming the bromides at C-1 to give (85) and (86) respectively. Reductive elimination of either bromide (85) and (86) with zinc and acetic acid would give the desired glucal (87), scheme 42.
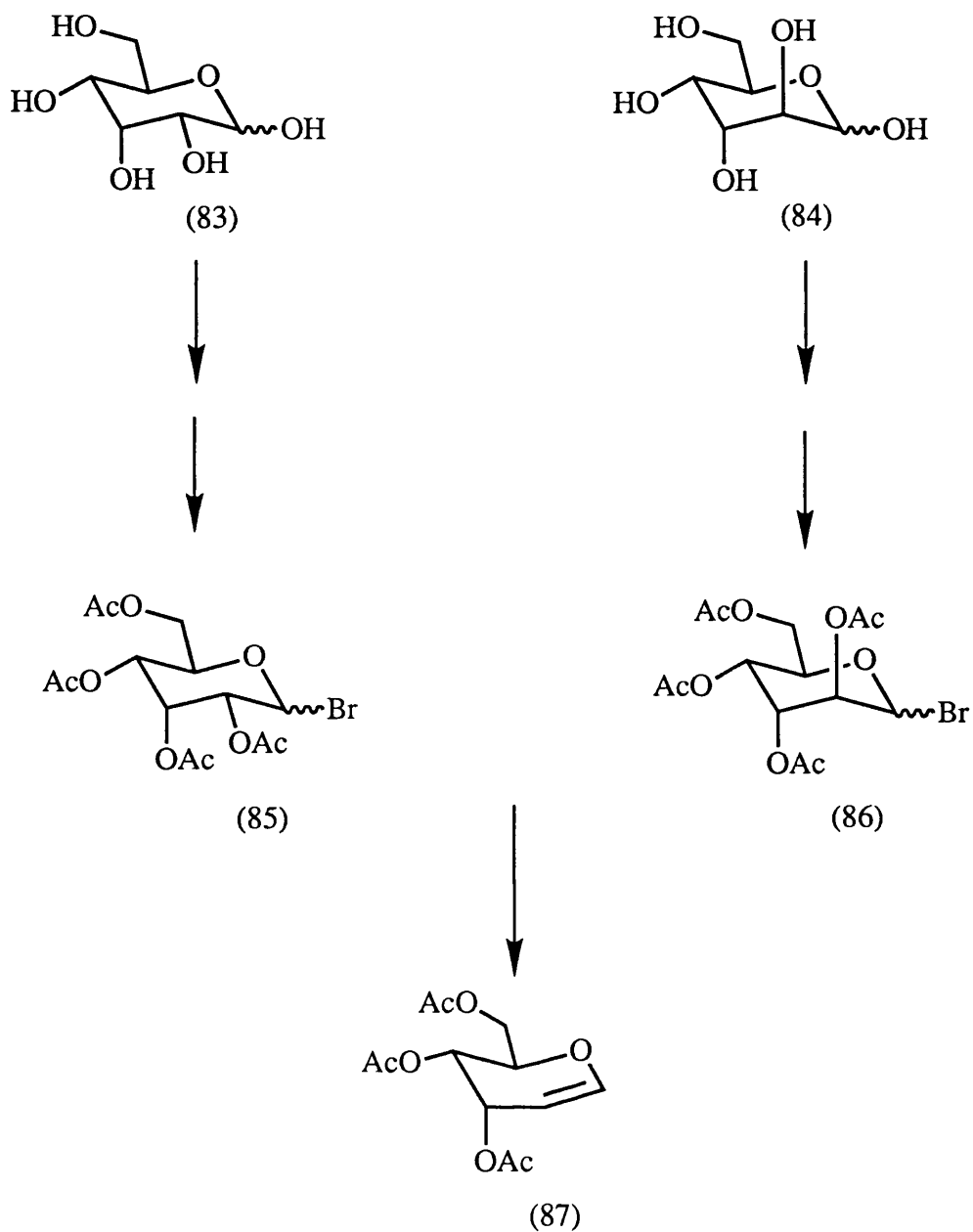
Scheme 42 : Possible synthesis of the glucal (87).

D-Allose (83) and D-altrose (84) are both commercially available by synthesis from D-ribose. However, using large quantities of either of these two sugars is not economically viable. Both of these rare sugars may also be extracted from plants in low yield, but this is not a viable source.

Therefore, a method which used a more common sugar such as D-glucose (88), figure 15, as the starting material was required. In this approach, the double bond between C-1 and C-2 would be formed by elimination of the hydroxy groups from these positions. The stereochemistry at C-3 would have to be inverted and the hydroxy groups at C-3, C-4 and C-6 would have to be protected in the course of the synthesis.

Figure 15 : Operations required on D-glucose (88).
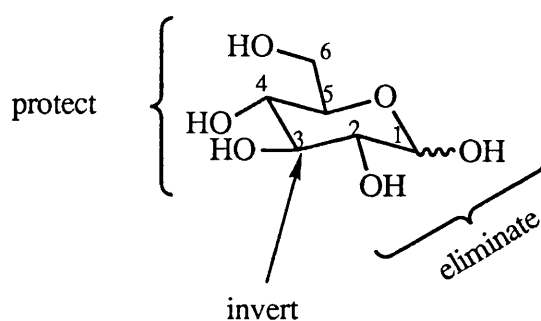
Thus it was decided to start from the readily available starting material (89), α-methyl-D-glucopyranoside, an inexpensive sugar. This sugar (89) was protected as the benzylidene acetal (90) with zinc chloride in benzaldehyde according to the literature procedure.[37] The acetal (90) was converted to the 2,3-di-O-tosylate (91) with excess of tosyl chloride. Treatment of this ditosylate (91) with sodium methoxide in dichloromethane gave the 2,3-anhydro-allose derivative (92).[37] These reactions are summarised in scheme 43.
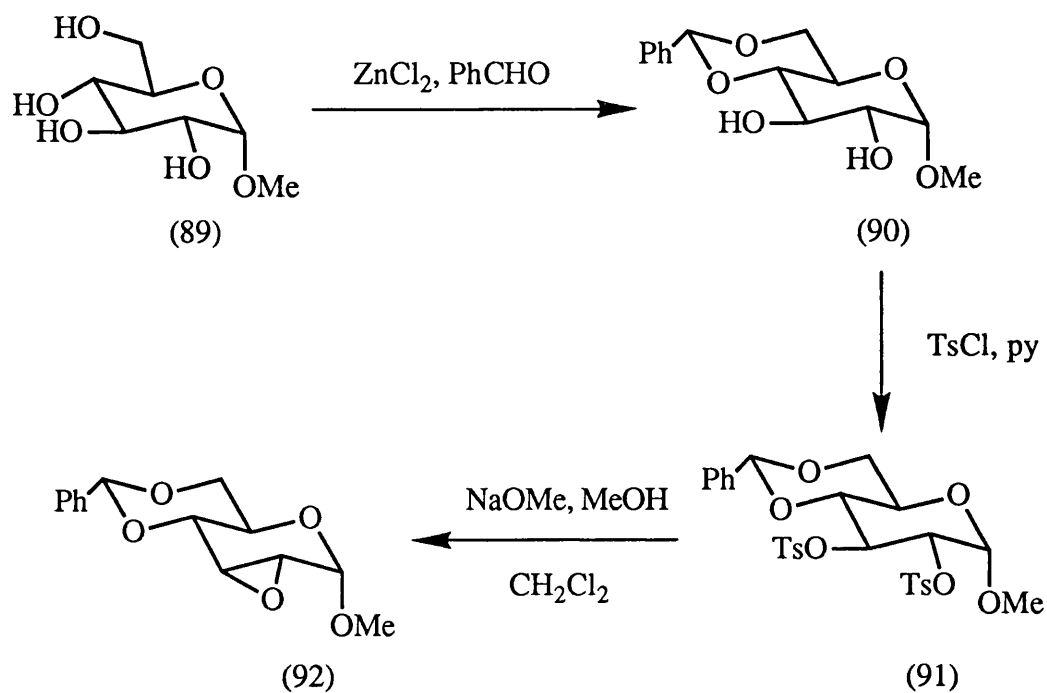
Scheme 43 : Synthesis of the 2,3-anhydroallose derivative (92).

There is a change in configuration from the ditosylate (91) to the epoxide, (92) i. e. from

the D-glucose to the D-allose configuration. This change in configuration is shown by the

coupling constant values obtained from ^{1}H nmr spectroscopy data. The relevant coupling

constant values are shown in table 4.

Table 4

(91)	(92)
δ 3.50 1H, t, H-4 $J_{4-3} \sim J_{4-5} \sim 9.58$ Hz	δ 3.50 1H, dd, H-3 $J_{3-2} = 4.20$ Hz $J_{3-4} = 2.78$ Hz
δ 4.43 1H, dd, H-2 $J_{2-3} = 9.55$ Hz $J_{2-1} = 3.65$ Hz	δ 3.53 1H, bd, H-2
δ 5.09 1H, t, H-3 $J_{3-2} = J_{3-4} = 9.56$ Hz	δ 3.95 1H, dd, H-4 $J_{4-5} = 9.11$ Hz $J_{4-3} = 2.78$ Hz

The coupling constant values of H-4 proton to H-3 proton in the two compounds is important. From the table it can be seen that the coupling constant value of H-4 proton to H-3 proton changes from 9.58 Hz in (91) to 2.78 Hz in (92). For a $^{4}C_1$ chair configuration, axial-axial coupling constant value is typically between 7-10 Hz. This is seen for compound (91) which is in the D-glucose configuration. Compound (92) is in a different configuration in which the angle between H-4 and H-3 is about 60° and typical coupling constant values are between 3 and 5 Hz. Thus by measuring the coupling constant value of H-4 with H-3, it can be seen that the epoxide (92) is in the D-allose configuration.

The crude epoxide (92) was converted to the <u>altro</u>-iodide (93) using lithium iodide in dry

ether,[38] scheme 44.
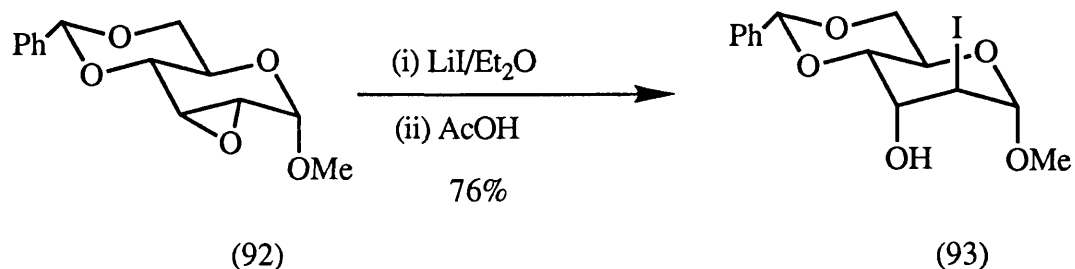
Scheme 44 : Synthesis of the <u>altro</u>-iodide (93).

The iodide (93) was found to be unstable in solutions such as chloroform, reverting back

to the epoxide (92).

The iodide (93) was used to prepare the glucal (94). One literature procedure[39] describes

a one pot synthesis for making (94) directly from the epoxide (92). This synthesis

involved using ethylmagnesium bromide to which copper (I) iodide was added slowly at

low temperature under an inert atmosphere. A solution of the epoxide (92) in dry THF

was then slowly added to the reaction mixture. On warming to 0 °C and work-up, the

glucal (94) was obtained after chromatography in 75% yield. This reaction was

performed according to the literature but after many attempts this procedure was

abandoned because the only identifiable compound after the reaction was carried out was

the epoxide (92).

From the above literature synthesis, it appears that formation of the glucal (94) from the

epoxide (92) occurs via an electron transfer mechanism. Thus it was decided to allow the

iodide (93) to react with four equivalents of lithium naphthalenide (LN) at -78 °C under

an inert atmosphere, scheme 45.
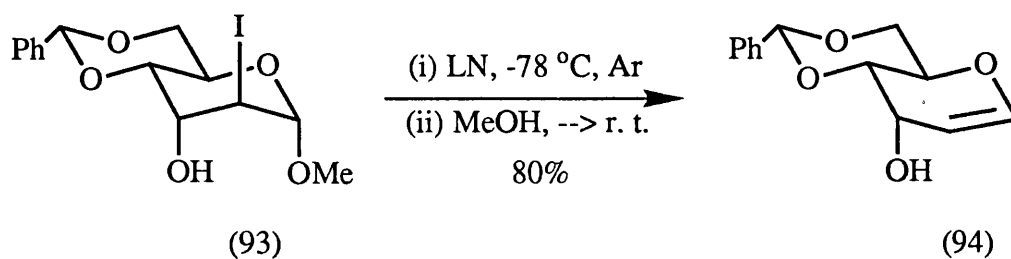
Scheme 45 : Synthesis of the glycal (94).

After quenching with methanol and work-up, excess naphthalene was removed by sublimation in a Kugelrohr apparatus and the glycal was purified by column chromatography. This procedure, using deliberate electron transfer is much more efficient than the serendipitously discovered literature approach. A possible mechanism for the formation of the glycal (94) is shown in scheme 46.
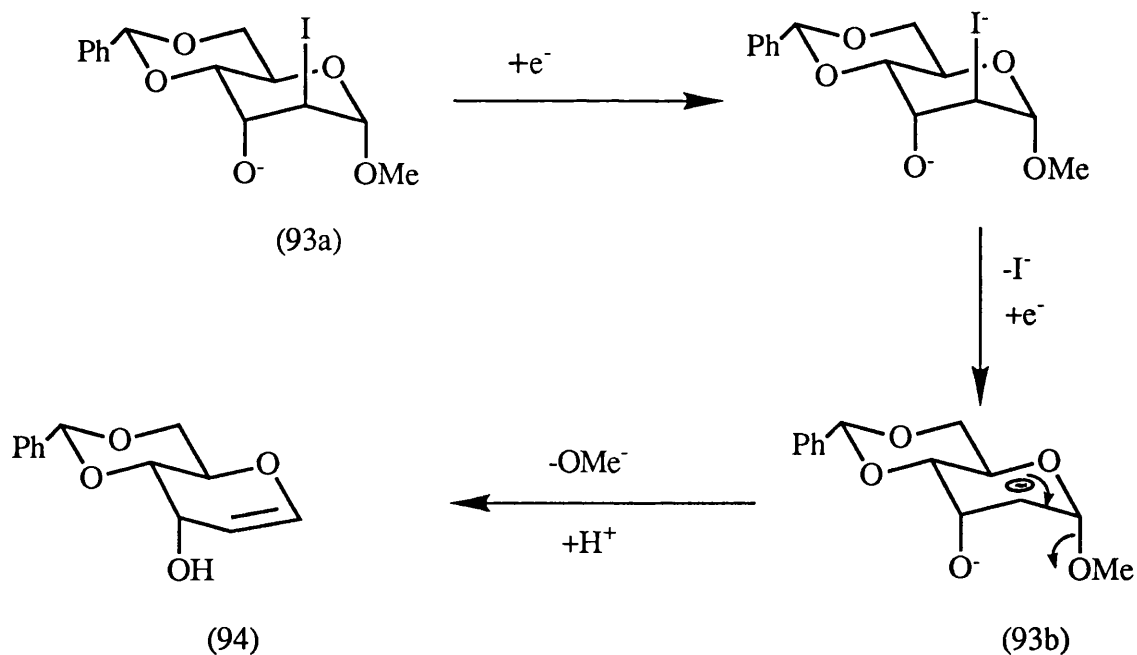
Scheme 46 : Possible mechanism for formation of the glycal (94).

The reaction proceeds via the intermediate (93a) which eliminates OMe⁻ rather than O²⁻ because OMe⁻ is a better leaving group than O²⁻.

The free hydroxy group of the glycal (94) at C-3 was protected as the benzyl ether under standard conditions, to give (95), scheme 47.
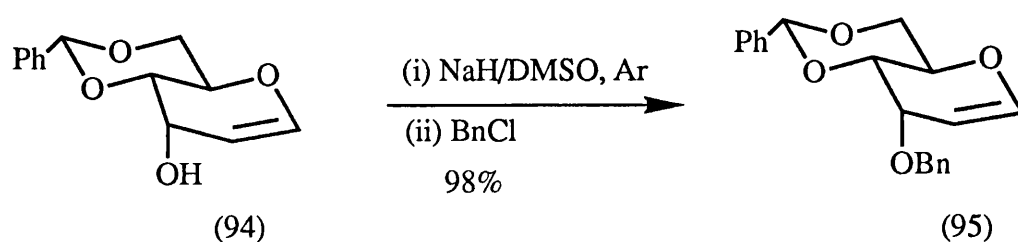
Scheme 47 : Protection of the hydroxy group in (94).

After the synthesis of the glycal (95) was completed, an alternative entry involving a 2,3-sigmatropic rearrangement from (96) has been described by Danishifsky,[40] scheme 48.
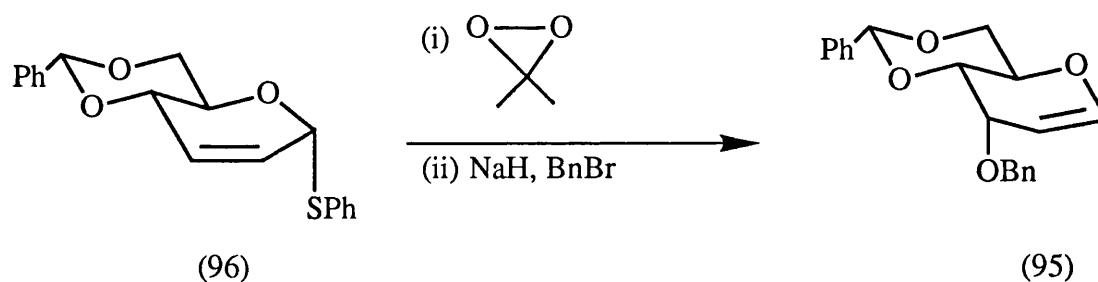
Scheme 48 : Synthesis of the benzylated glycal (95) via a 2,3-sigmatropic shift.

With the protected ribo-glycal in hand, its elaboration to the ulosonic acid functionality was investigated. The first step in functionalising C-1 was to place a sulfur function as in the arabino-series. It was decided to use the same methodology for the preparation of the sulfides (98α) and (98β) in the ribo-series : addition of dry HCl gas across the double bond followed by displacement of the chlorine atom at C-1 by thiophenate ion and/or

direct acid catalysed addition of thiophenol using camphor sulfonic acid (CSA). Both procedures gave the starting material (95) and there was very little evidence for the formation of the sulfides (98α) and (98β).

^{1}H nmr experiments with TFA in CDCl$_3$ and in C$_6$D$_6$ followed by addition of Hunig's base and thiophenol indicated that the glycal (95) was readily protonated but that nucleophilic attack by the thiophenate ion was slow, scheme 49.
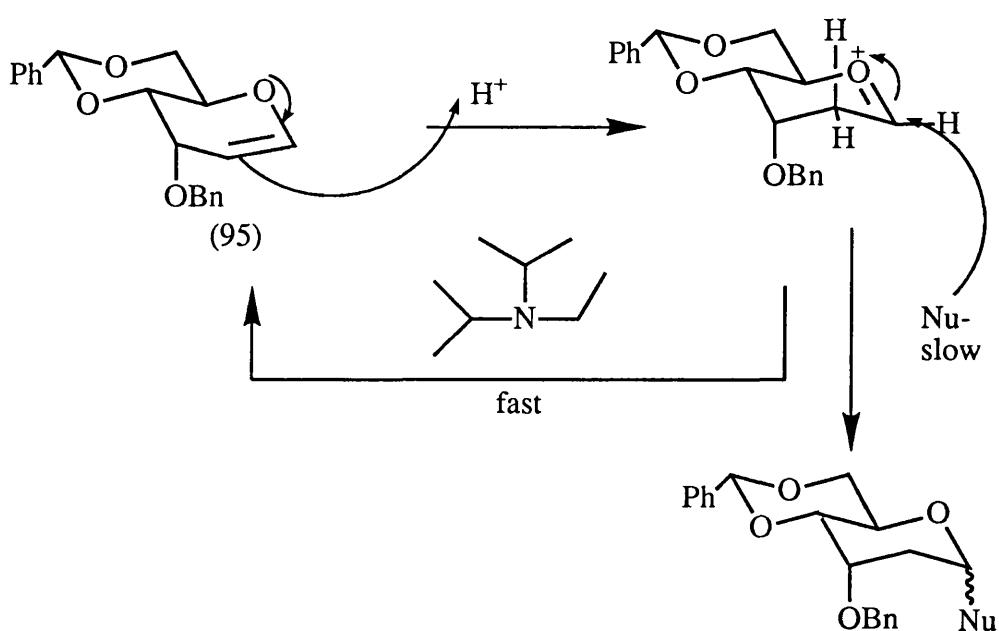
Scheme 49 : Protonation of (95) followed by slow attack of nucleophile.

Eventually, armed with this knowledge, the preparation of the sulfides, (98α) and (98β) was attempted again, using a modification of the first method. The glycosyl chlorides (97α) and (97β), prepared as before, were treated with a preformed solution of the lithium salt of thiophenol, scheme 50.

(97α) and (97β)   (98α) and (98β)
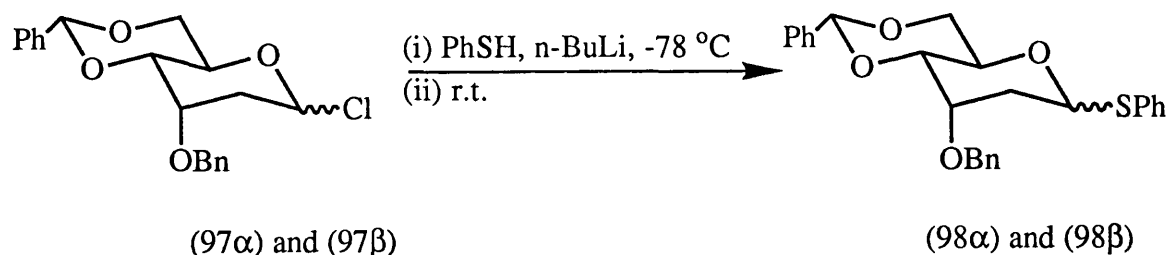
Scheme 50 : Preparation of the sulfides (98α) and (98β).

After work-up and purification by chromatography on silica gel, the sulfides (98α) and

(98β) were obtained as white solids in 77% yield in an anomeric ratio of α : β, 4 : 1.

Assignment of configuration at the anomeric centre of these sulfides (98α) and (98β) as

based on coupling constant values obtained for protons at C-2.

The α- and β- sulfides (98α) and (98β) were oxidised in almost quantitative yield to the

corresponding sulfones, (99α) and (99β) with mmpp (2.5 molar equivalents) at room

temperature in ethanol, scheme 51.

(98α) and (98β)   (99α) and (99β)
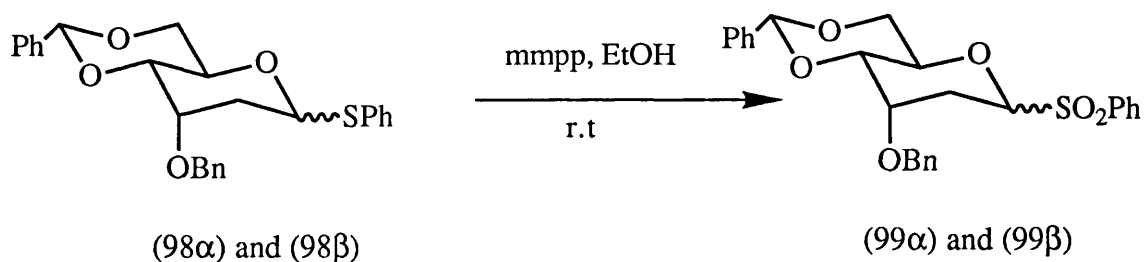
Scheme 51 : Oxidation of the sulfides (98α) and (98β) to give the corresponding

sulfones.

After many attempts, the sulfone ester (100) was prepared by deprotonation of the sulfone

(99α) with LDA at -78 °C, followed by quenching with dimethyl carbonate, scheme 52.

After work-up and purification, the sulfone ester (100) was obtained as a white solid as a

single anomer, but in only 19% yield. Despite repeated attempts this yield could not be improved.
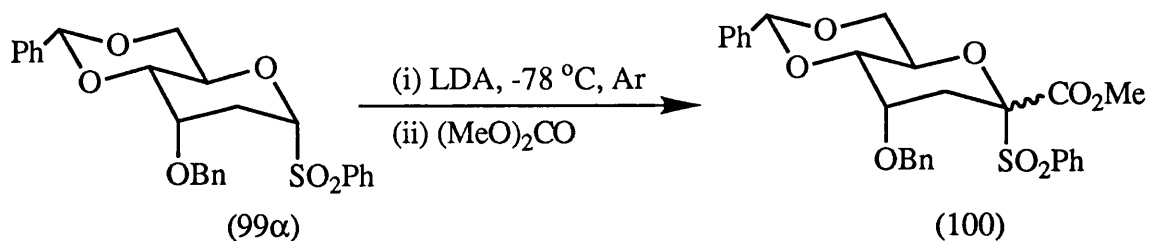
Scheme 52 : Synthesis of the sulfone ester (100).

This difficulty in acylation is obviously due to the axial substituent and 1,3-diaxial strain between either the incoming electrophile or the sulfone group.

2.5 Decarboxylation of the sulfone ester (100).

The sulfone ester (100) was saponified with aqueous potassium hydroxide in methanol, scheme 53, to give the sulfone acid (101).
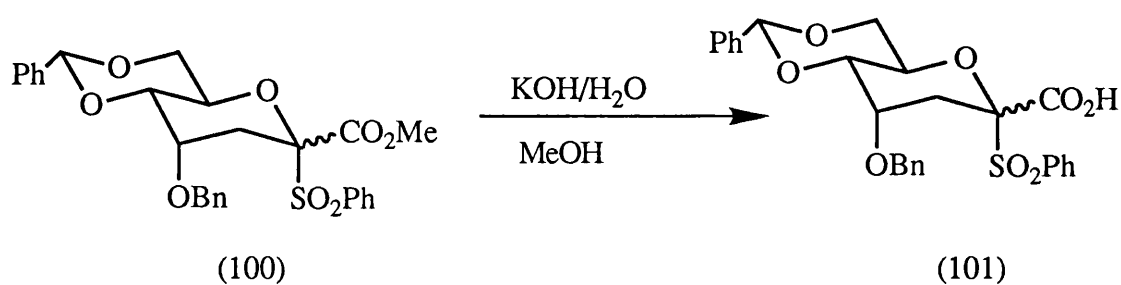
Scheme 53 : Saponification of the sulfone ester (100).

The ^{1}H nmr spectrum showed slight decomposition of this crude acid (101) as indicated by a singlet at δ 10.2ppm (PhCHO). The crude acid (101) was used without purification in the reductive decarboxylation step. This was carried out as in the arabino-series.

Unfortunately, due to the small scale, meaningful results were not available for this experiment.

Thus a method of comparing radical selectivity of the arabino-series with the ribo-series was needed. It was decided to use the glycals (95) and (94) in the ribo-series and (15) in the arabino-series, respectively as starting materials for the investigation. As before, the chlorides (97), (102) and (47) were prepared, scheme 54. The chlorides would then be allowed to react separately with first tributyltin hydride (Bu3SnH) and then with tributyltin deuteride (Bu3SnD) and the anomeric ratios compared.

It was found that the ribo-chlorides (97) and (102) were both unstable at room temperature and therefore could not be isolated.
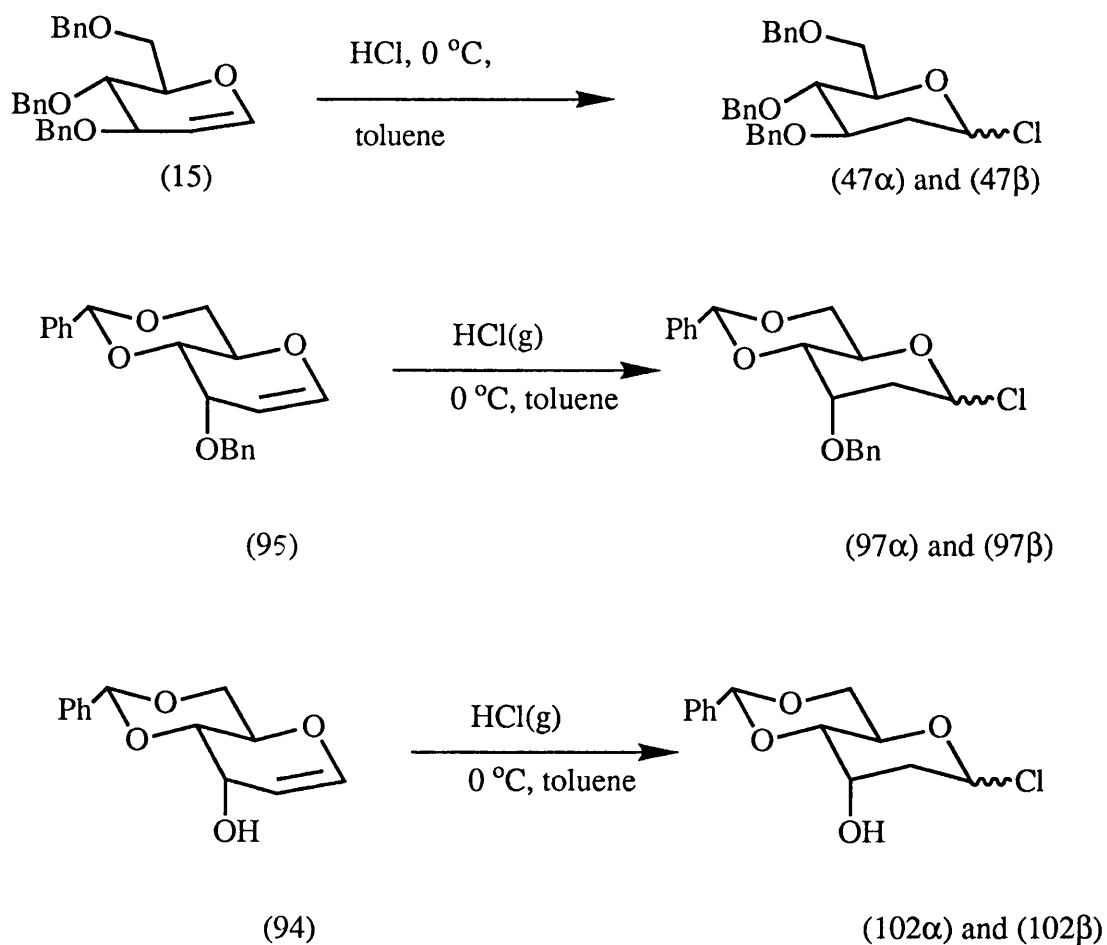
Scheme 54 : Synthesis of the various chlorides.

It was then decided to synthesise the corresponding phenyl thioglycosides of the glycosides (94), (95) and (15) to give (103), (98) and (48) respectively, scheme 55.

(102α) and (102β)

(103α) and (103β)

(47α) and (47β)

(48α) and (48β)

(97α) and (97β)

(98α) and (98β)
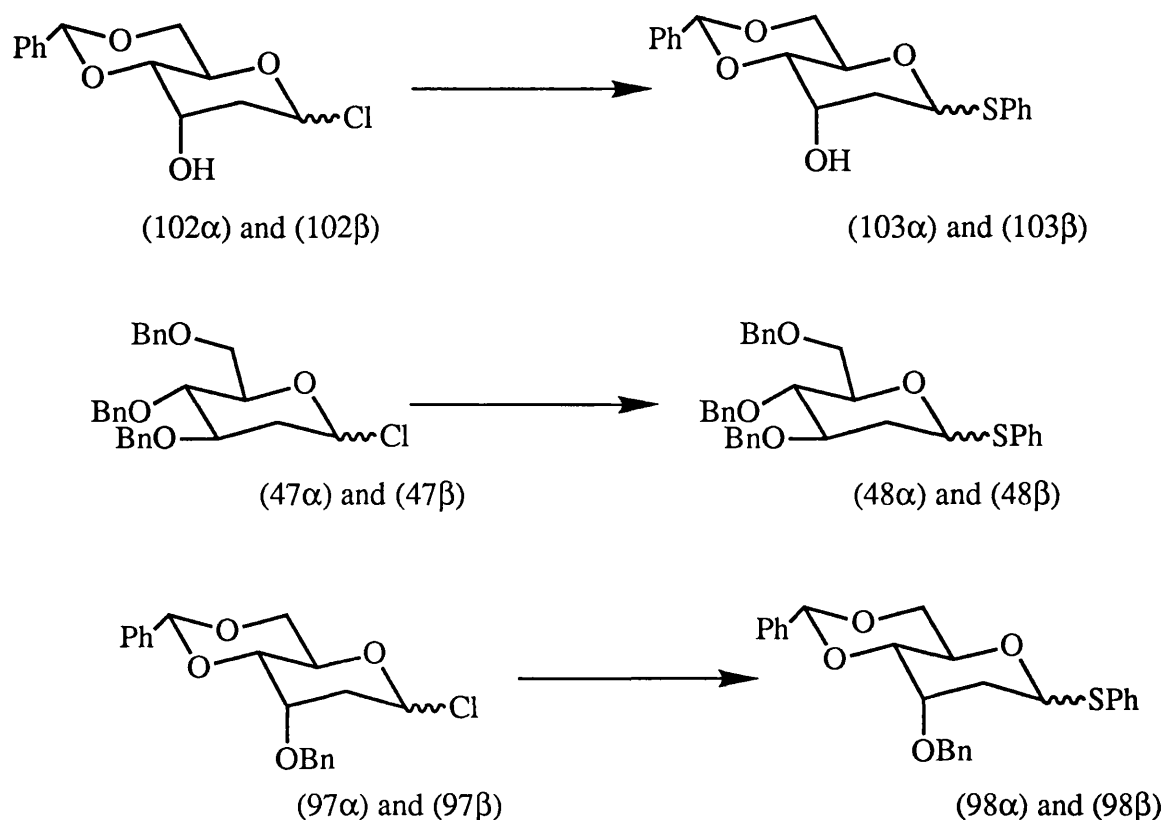
Scheme 55 : Synthesis of the various sulfides.

The phenyl thioglycoside (103) was prepared using preformed lithium thiophenate.The sulfide (48) was subjected to photolysis with Bu3SnH and AIBN in dry benzene. This radical reaction proved extremely slow. This lack of reactivity of a phenyl thioglycoside is in fact well known. This was also observed by Keck[41] and co-workers in the following reaction, scheme 56.
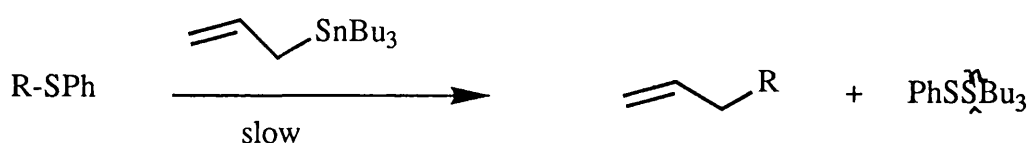
Scheme 56 : Lack of reactivity of phenyl thioglycosides.

This study found that the reactivity of the thioether is increased if the phenyl group was replaced by a methyl group.

However, instead of conducting an obvious synthesis of the corresponding methyl thioglycosides, it was decided to prepare the more reactive seleno-derivatives. These were prepared by from the corresponding glycosyl chlorides by immediately reacting them with the phenylseleno anion, generated in an ultrasound bath from diphenyl diselenide and sodium dispersion in dry THF under argon,[42] scheme 57.

BnO, BnO, BnO ... Cl → PhSe⁻Na⁺ → BnO, BnO, BnO ... SePh

(47α) and (47β)   (104α) and (104β)

Ph, O, O ... Cl with OH → PhSe⁻Na⁺ → Ph, O, O ... SePh with OH

(102α) and (102β)   (105α) and (105β)

Ph, O, O ... Cl with OBn → PhSe⁻Na⁺ → Ph, O, O ... SePh with OBn

(97α) and (97β)   (106α) and (106β)
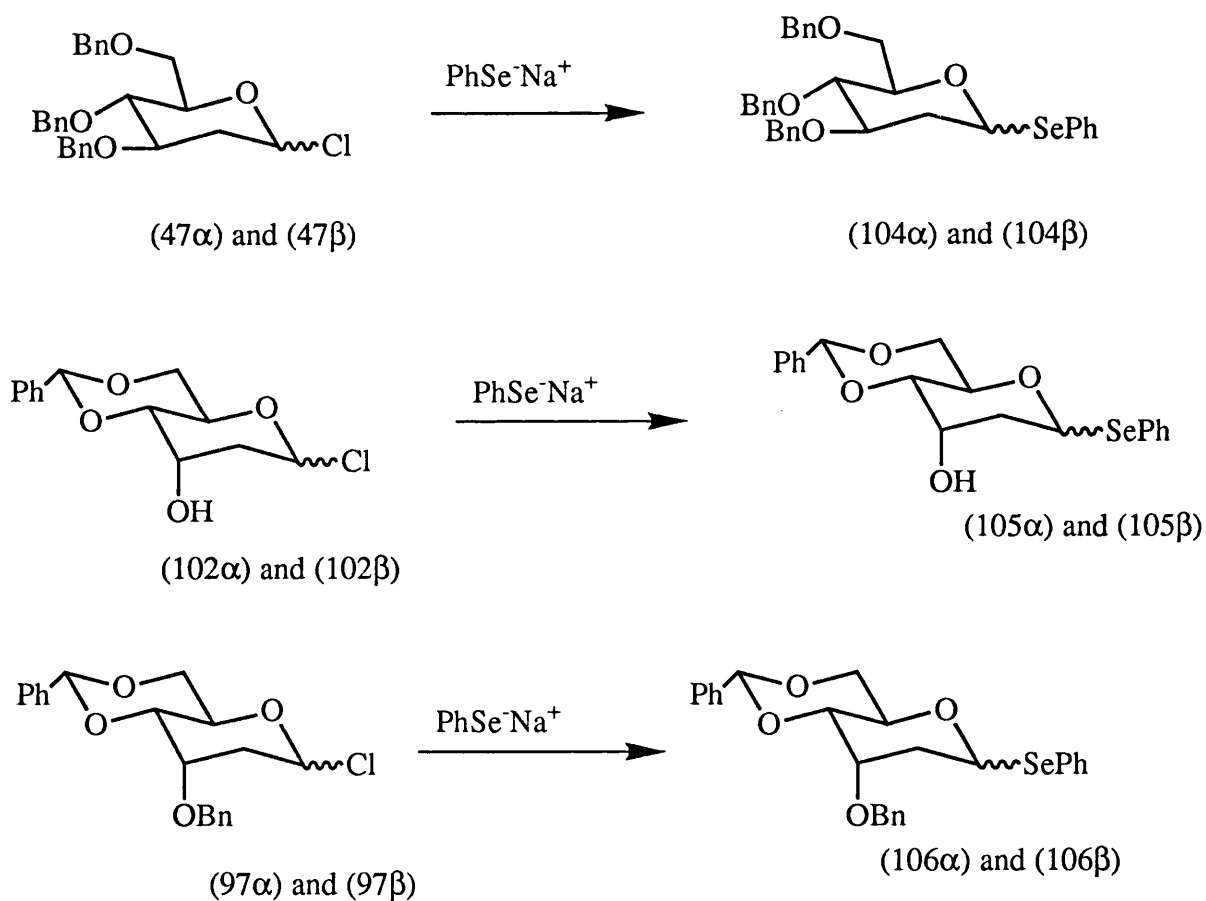
Scheme 57 : Synthesis of phenyl selenoglycosides.

It was found that (106) was unstable to storage at room temperature. Therefore it was decided to use (104) and (105) for the comparison study.

The selenoglycoside (104) was first subjected to photolysis with tributyltin hydride and AIBN in dry benzene under argon, scheme 58. The product (107) was purified and the anomeric protons were assigned in the ^{1}H nmr spectrum.

BnO
BnO
BnO
BnO—SePh
$Bu_3SnH, AIBN, h\upsilon$
benzene, Ar

BnO
BnO
BnO

(104α) and (104β)   (107)
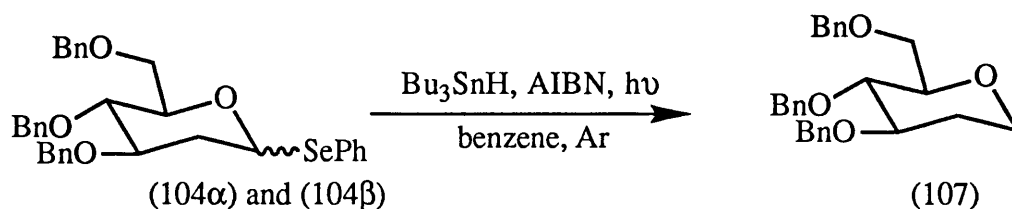
Scheme 58 : Reaction of phenyl selenoglycosides (104) with Bu3SnH.

The phenyl selenoglycosides (104) were then photolysed in the presence of tributyltin deuteride with AIBN in benzene under argon, scheme 59.

BnO
BnO
BnO
BnO—SePh
$Bu_3SnD, AIBN, h\upsilon$
benzene, Ar

BnO
BnO
BnO
D

(104α) and (104β)   (108)
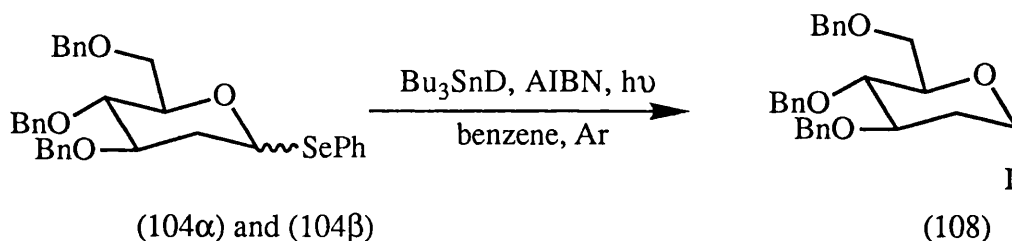
Scheme 59 : Reaction of phenyl selenoglycosides (104) with Bu3SnD.

This reaction was slower, presumably due to a 'primary' kinetic isotope effect. After purification, the ^{1}H nmr spectrum of the product (108) was analysed. It was found that one anomeric signal disappeared completely, and this signal was assigned to the axial proton in the spectrum of compound (107). Thus in the arabino-series as anticipated, there is exclusive quenching of the radical from the axial direction.

The phenyl selenoglycoside (105) in the ribo-series was then photolysed, first with tributyltin hydride and AIBN in dry benzene under argon, scheme 60. The reaction was much slower compared to the analogous reaction of (104) with Bu3SnH. The product

(109) was purified and the ^{1}H nmr spectrum was run in CDCl$_3$. The signals were assigned using decoupling experiments. It was found that there was much overlap of the anomeric proton signals with signals of other protons in the ring. Therefore the ^{1}H nmr spectrum was run in C$_6$D$_6$. This resolved the anomeric proton signals and assignment of protons was made again by decoupling experiments.

$$Bu_3SnH, AIBN, h\upsilon$$
$$benzene, Ar$$

(105α) and (105β) (109)
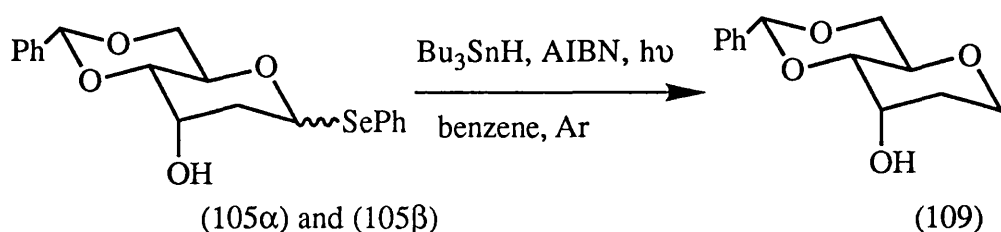
Scheme 60 : Reaction of phenyl selenoglycosides (105) with Bu$_3$SnH.

Next, the <u>ribo</u>-phenyl selenoglycosides (105) were photolysed in the presence of tributyltin deuteride and AIBN in dry benzene under argon. The reaction was extremely slow but eventually went to completion, scheme 61.

$$Bu_3SnD, AIBN, h\upsilon$$
$$benzene, Ar$$

(105α) and (105β) (110)
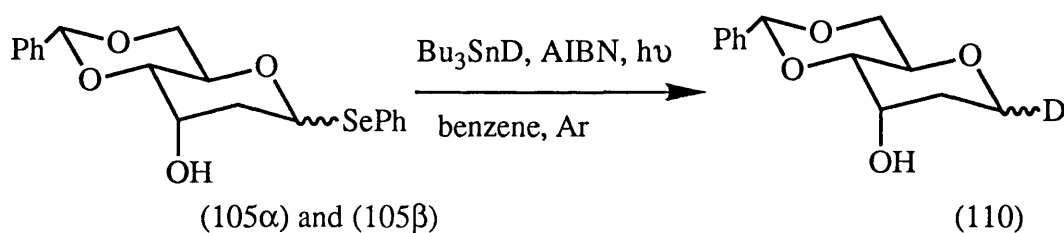
Scheme 61 : Reaction of phenyl selenoglycosides (105) with Bu$_3$SnD.

The product (110) was isolated and the ^{1}H nmr spectrum was run in C$_6$D$_6$. On analysis, it was found that signals for both anomeric protons were affected. Thus quenching had occured from both the axial and equatorial directions. The ratio of quenching from the axial face was however greater than 10 : 1 as found by integration of the appropriate protons in the proton spectrum run in C$_6$D$_6$.

It is known that carbohydrate molecules which undergo radical addition and atom abstraction reactions[17, 43] having equatorial substituents (β-substitutents) adjacent to the radical centre result in axial quenching. Axial substituents at C-2 lead to an increase in axial product formation. Stereoelectronic effects on the diastereoselectivity of radical reactions have also been investigated by le Noble.[44] In carbohydrate radical reactions, quenching from the axial direction is usually observed to give mainly β-products. This axial quenching has been attributed to the influence of the lone pair of electrons on the ring oxygen which is adjacent to the anomeric radical reaction centre. This effect of the ring oxygen is best illustrated by comparison with the recent work of Giese and Houk[45] who studied the effect of ring substitution at various positions on mono- and disubstituted cyclohexyl radicals.

These authors first investigated the addition of acrylonitrile to the 4-*tert*-butylcyclohexyl radical using tributyltin hydride to generate the radical. It was found that both axial and equatorial products were formed in almost equal amount. Giese assumed that the transition state for the axial radical would be attained at a higher energy due to 1,3-diaxial interactions with the "bottom" face of the cyclohexyl ring.

The effect of a γ-substituent was also investigated by Giese and Houk.[45] Interestingly, with the *trans*-10-methyldecalin-2-yl radical (axial γ-substituent), the major product was from quenching from the equatorial direction. When an axial substituent is present at the γ-position, there is almost equal amount of axial and equatorial quenched product.

Comparison of the results presented above and those of Giese leads to the conclusion that the ring oxygen has a major effect on the stereochemistry of quenching of 6-membered cyclic radicals, changing the prefential mode of attack from the equatorial to the axial position. Moreover, the effect is large enough to substantially overcome the unfavourable steric interactions due to an axial substituent in the 3-position.

CHAPTER 3

STEREOELECTRONIC EFFECTS IN FREE RADICAL CHEMISTRY : THE β-OXYGEN EFFECT

3.1 Introduction and background

In 1982 the Barton group published a series of observations on the effect of β-oxygen substituents in radical deoxygenation and deamination reactions.[19] Their principal findings were that thionoformate esters and isonitriles bearing alkoxy and/or acyloxy groups in the β-position underwent deoxygenation and deamination respectively on treatment with tri-n-butyltin hydride at lower temperatures than the corresponding unsubstituted species. For example the thionoformate (111) gave 29% of the corresponding deoxy compound (112) in toluene at reflux whereas cholestanyl thioformate (113) gave only 9% of cholestane (114) under the same conditions, and only 24% in xylene at reflux, scheme 62.
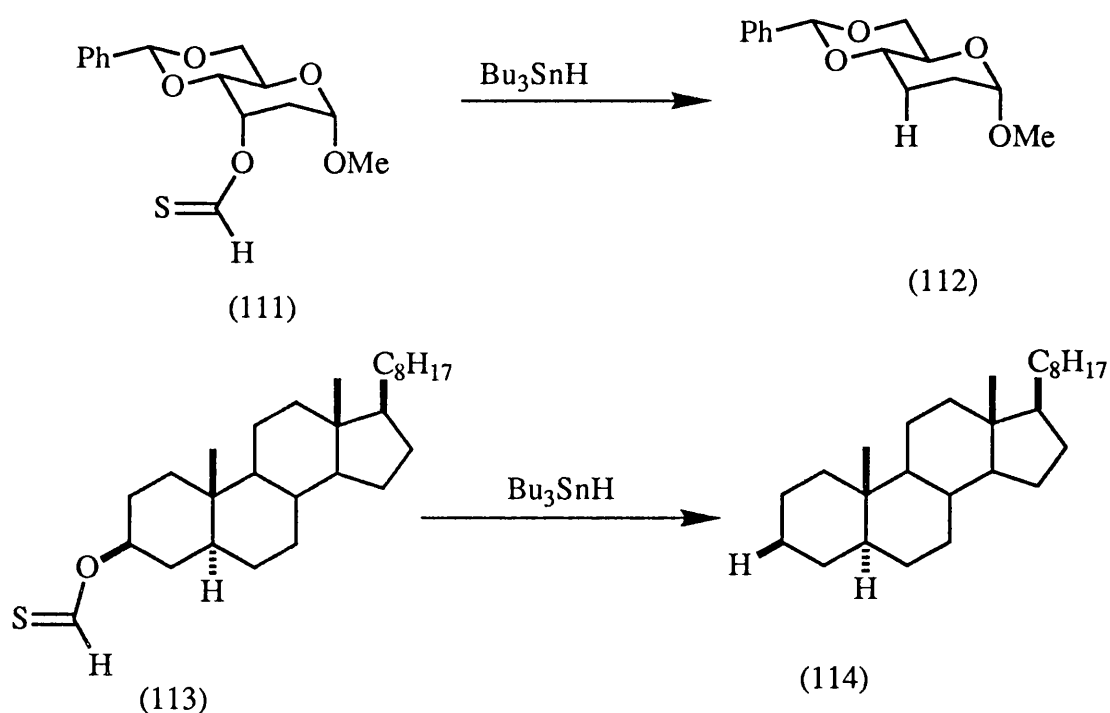
Scheme 62 : Reaction of two thionoformates to give the corresponding deoxy products.

The conclusion drawn from these studies was that "β-bonded oxygen has a marked effect in stabilising carbon radicals thus permitting homolytic fission not seen otherwise". However, as noted by Barton, esr spectroscopic studies on β-alkoxyethyl radicals do not

indicate stabilization by bridging and even suggest a prefered conformation in which the singly occupied p-orbital is synclinal rather than periplanar to the β-oxygen bond, figure 16.[46]

Figure 16 : Prefered comformation of a β-Alkoxyethyl Radical.
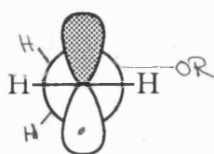
More recently Gleicher has published a related observation in which epichlorohydrin was reduced by triphenyltin hydride some 2.00 times faster than cyclohexyl chloride at 70 ^{0}C.[21] Furthermore, Gleicher demonstrated that cis-2-chloro-7-oxabicyclo[4.1.0]heptane (115) was approximately twice as reactive as its trans-isomer (116) under the same conditions thus pointing to a stereoelectronic component to the β-oxygen effect, figure 17.

Figure 17 : Epichlorohydrins used in Gleicher's study.

(115)   (116)
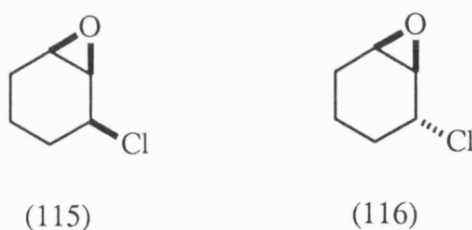
In betweentimes Giese and Sustmann have proposed, on the basis of low temperature esr studies, that the tetraacetylglucopyranos-1-yl radical (117), figure 18, adopts a boat like conformation in which the radical is stabilized by overlap with a periplanar β-acetoxy bond, and that this conformation satisfactorily accounts for the high α-selectivity in the quenching of this radical by a number of radical traps.[11a]

Figure 18 : Boat conformation of the tetraacetylglucopyranos-1-yl radical as proposed by

Giese and Sustmann.

(117) .
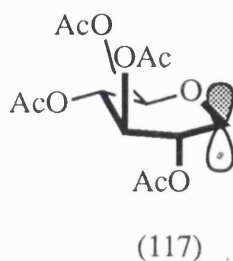
This chapter concentrates on a study conducted in this laboratory with conformationally

rigid β-alkoxythiocarbonyl esters which indicate that, at least in rigid systems, there is a

distinct but small stereoelectronic component to the β-oxygen effect. The origin of this

effect is discussed in terms of the Cieplak effect[47] as previously applied to radicals by le

Noble[44] following the suggestion of Cieplak.[48]

The Gleicher experiments with probes (115) and (116) provided a strong indication of the

existence of a small but measureable stereoelectronic component to the β-oxygen effect.

However, the exact interpretation of these experiments was complicated by concerns

about the reactive conformations of both (115) and (116) and so the exact orientation of

the β-oxygen bonds with respect to the scissile C-Cl bonds. In principle, it is possible to

extract valuable information on any stereoelectronic effect due to β-oxygen bonds from

the extensive literature on the reactions of carbohydrate based thiocarbonyl esters with

tributyltin hydride under free radical conditions.[13c] The very through and comprehensive

work of Stick and coworkers is particularly attractive in this light.[49] Unfortunately, the

widely differing steric environments encountered in the various carbohydrates series

introduce considerable ambiguity into the interpretation of this body of data.

3.2 Preparation of Substrates and Competition Reactions

In order to probe the β-oxygen effect, the aim was first to prepare the four xanthate esters

(118), (119), (120) and (121) and to conduct a series of competition experiments. Thus a

competition reaction between (118) and (120) [and (119) and (121)] would reveal any overall accelerating effect of a β-oxygen bond whereas competition between (120) and (121) would expose any stereoelectronic effect. Thiocarbonyl esters were chosen as substrates in this study because of their efficient reaction with tin hydrides,[50] because their use would allow maximum approach to the original work of Barton,[19] and importantly because the mechanism of their reaction with stannyl radicals is relatively well understood,[51] figure 19.

Figure 19 : Various xanthate esters prepared to examine the effect of a β-oxygen bond on the rate of deoxygenation reaction.

(118)

(119)

(120)

(121)
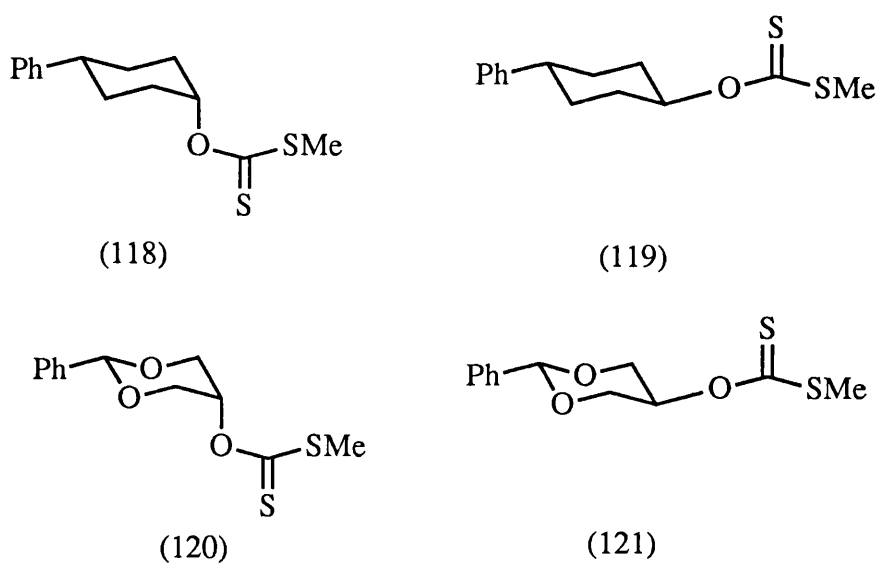
The accepted mechanism involves rapid, reversible addition of the stannyl radical to the thiocarbonyl group followed by slower fragmentation of the adduct radical with cleavage of the carbon oxygen bond, scheme 63. Thus, any β-oxygen effect observed in the proposed competition experiments (where X, which does affect the reactivity of C=S, is constant) can be taken to be the result of perturbation of the scissile C-O in the adduct radical rather than of the reactivity of the thiocarbonyl bond.
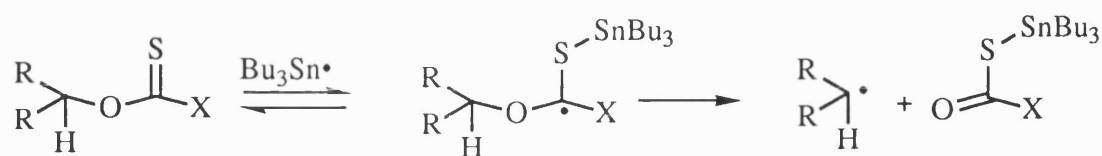
Scheme 63 : Mechanism of the Barton-McCombie Reaction.

Initially (118) and (119) were prepared from the corresponding alcohols by standard techniques and a 1 : 1 mixture heated to reflux under nitrogen in toluene in the presence of 4-dimethylaminopyridine (DMAP) as convenient internal standard then treated with a deficiency of tributyltin hydride (TBTH) (ratio (118) : (119) : TBTH 1 : 1 : 1) and 5 mole % of azoisobutyronitrile (AIBN) as radical in initiator.[52] After 30 min at reflux the solvent was removed in vacuo and the crude reaction mixture examined by ^{1}H nmr at 300 MHz. The cis-xanthate (118) was found to have reacted approximately twice as fast as its trans-isomer (119). This experiment is in effect the microscopic reverse of the le Noble experiment in which the 5-phenyladamantan-2-yl radical (122) was quenched with bromine with 57 : 43 selectivity from the zu-face, and demonstrates the effect of a 4-phenyl group on the reactivity of conformationally locked cyclohexyl radicals. It seems apparent that both radical formation and quenching occurs preferentially from the direction opposite to the most electron rich bond (bold) as indicated in, figure 20, and in agreement with the Cieplak hypothesis.

Figure 20 : Quenching of the 5-phenyladamantan-2-yl radical mainly from the zu-face.

Faster reaction
(le Noble[44])
zu face

Ph

H

(122)
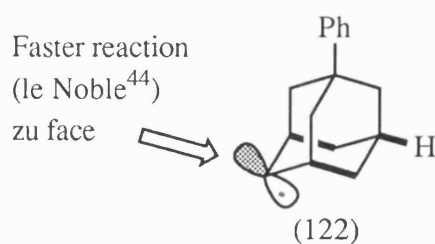
The xanthates (120) and (121), each having two β-oxygen bonds, were prepared from the corresponding alcohols (123) and (124), figure 21, in the standard manner.

Figure 21 : Alcohols used for the preparation of the two xanthates, (120) and (121).

OH   OH

(123)   (124)
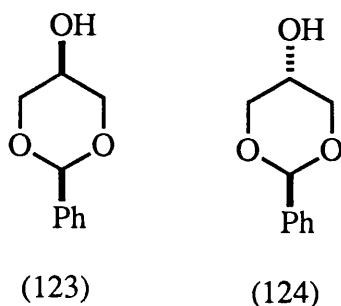
Synthesis of the cis-alcohol (123) was straightforward, simply requiring heating of glycerol and benzaldehyde in toluene in a Dean-Stark apparatus with catalysis by *p*-toluenesulfonic acid followed by removal of solvent and recrystallization. For the obtention of diastereoisomerically pure (123) this Dean-Stark procedure is superior to literature processes which give mixtures with (124) and the two isomeric dioxolanes.[53] The isolation of a pure sample of the less stable *trans*-isomer (124) was more problematic. In principle[53] (124) was available by chromatography of the mother liquers from the crystallization of (123), but in practice a satisfactory separation could not be achieved owing to apparent epimerization on the column. Ultimately (123) was oxidized to the known ketone (125),[54] figure 22, by the Swern protocol then reduced with sodium borohydride. In accordance with the calculations of Houk[55] an excellent ratio of 10 : 1 of (123) : (124) was obtained in this reduction.

Figure 22 : Ketone (125) obtained by Swern Oxidation of the alcohol (123).

O

(125)
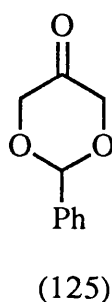
Reaction of a 1 :1 mixture of the two *cis*-phenyl xanthates (118) and (120), again with

DMAP as an internal standard, in toluene at reflux with a deficiency of tributyltin hydride

[(118) : (120) : TBTH 1 : 1 : 1] clearly demonstrated the accelerating effect of the two β-

oxygens with the ratio of remaining substrates found to be 1 : 2 in support of the original

work of Barton and the more recent work of Gleicher. Subsequently, a 1 : 1 mixture of

(120) and (121) was reacted with a deficiency of tin hydride [(120) : (121) : TBTH 1 : 1 :

1)] in a similar manner. The axial xanthate (120) was found to react approximately twice

as rapidly as the equatorial isomer (121) similar to the result found for (118) and (119)

and to that found for (115) and (116) by Gleicher. 2-Phenyl-1,3-dioxane was readily

isolated from these reactions indicating that the measured ratios were indeed the result of

the desired deoxygenation reaction. Whilst these latter experiments clearly support the

existence of an accelerating β-oxygen effect the interpretation of the stereoelectronics of

the process is open to doubt due to the possibility of (120) and (121) undergoing

conformational change in toluene at reflux.

Evidently a more rigid probe along the lines the 5-phenyladamantyl derivatives pioneered

by Whiting[55] and elegantly exploited by le Noble[44] in his work but containing β-oxygen

bonds was required. *myo*-Inositol-1,3,5-orthoformate (126)[57, 58] was a convenient

starting point. Thus, (126) was converted to the *myo*- and *scyllo*-inositol dibenzyl ethers

(127) and (128) respectively according to the literature procedure[57] and these were then

transformed into the corresponding monothiocarbonyl esters (129) and (130), by reaction

with *p*-tolyl chlorothioformate essentially according to the Robins modification[59] of the

Barton-McCombie reaction, with their two synclinal and antiperiplanar β-oxygen bonds

respectively. For convenience, in the series of compounds (129)-(138), the base (as

drawn) of the trioxaadamantane is considered as the framework formed from the original

six inositol carbons, as a chair and the bonds extending from it as either axial or

equatorial. Thus, for example, compound (129) has two axial benzyl ethers and an

equatorial thiocarbonate moiety, whilst (130) has its thiocarbonate axial, figure 23.

Under the standard conditions (129) was found to react some two times as rapidly as

(130) with tributyltin hydride.

Figure 23 : Inositol derivatives used as rigid probes to examine selectivity in

deoxygenation reactions.
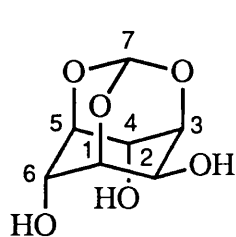
(126)
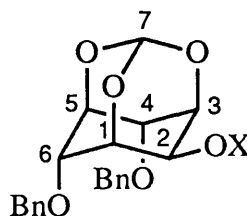
(127) X = H
(129) X = C(=S)OC$_6$H$_4$Me
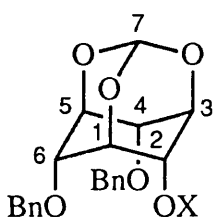
(128) X = H
(130) X = C(=S)OC$_6$H$_4$Me
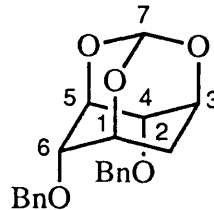
(131)

Preparative t. l. c. enabled isolation of the dibenzyl ether (131) of scylloquercitol

(desoxyscyllitol) again indicating that the substrates were being consumed by the

anticipated reaction. This result is grossly the same as that observed with the xanthates

(120) and (121), namely that the xanthate with the two synclinal β-oxygens was cleaved

most readily. However it could still be said that (130) was less reactive than (129) owing

to a possible steric hindrance of its thiocarbonyl group by the two benzyl ethers. X-ray

crystallographic analysis of (130), figure 24, indicated that this was not the case, at least

in the crystalline phase. In deuteriochloroform solution the two 2'-hydrogens of the tolyl

group in (130) are shifted somewhat upfield with respect to their counterparts in (129) indicating shielding by the benzyl ethers. Similarly, the thiocarbonyl carbon in (130) is shifted upfield up 3.8 ppm in the ^{13}C nmr spectrum from that in (129) indicative either of shielding by the benzyl groups in (130) or possibly of the influence of the antiperiplanar β-oxygen bonds. In view of this possible ambiguity we elected to prepare a second rigid probe based on the trioxaadamantane framework but lacking the possible steric bias of (130).

Figure 24 : X-ray crystallographic structure of (130).
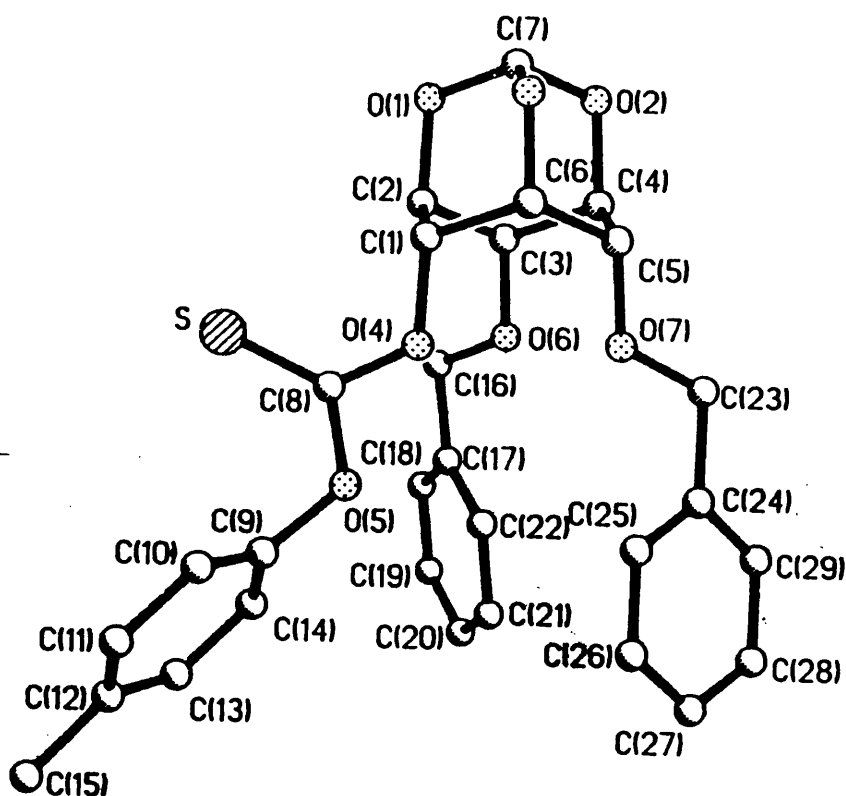
Reaction of (126) with benzoyl chloride in pyridine gave the dibenzoate (132) in 92% yield. Barton-McCombie deoxygenation of the derived xanthate (133) gave the 6-deoxy-*myo*-inositol derivative (134) in 56% overall yield. Saponification then gave (135) and finally reaction with sodium hydride then carbon disulfide and methyl iodide the dixanthate (136), figure 25. In the dixanthate (136) one xanthate group has two synclinal

β-oxygen bonds and the other two antiperiplanar β-oxygen bonds; neither xanthate group

is subject to severe 1,3-diaxial type steric interactions.

Figure 25 : Difunctionalized inositol probes
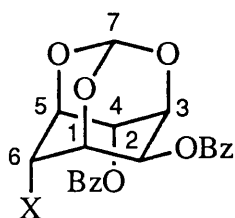
(132) X = OH
(133) X = OC(=S)-1-imidazolyl
(134) X = H
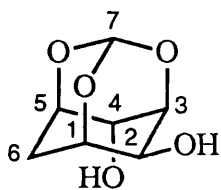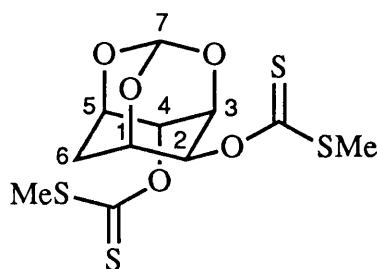
(135)   (136)

Treatment of (136) with half an equivalent of tributyltin hydride under the standard

conditions followed by inspection of the crude reaction mixture by ^{1}H nmr spectroscopy

immediately revealed that as in the cases of (121) and (122), and (129) and (130), the

xanthate with the synclinal β-oxygen bonds was cleaved most rapidly. Chromatography

on silica gel led to the isolation of two very major products (137) and (138) in 32 and

47% yields respectively. The ratio of (137) to (138) in the crude reaction mixture was 1 :

1.5, as determined by ^{1}H nmr spectroscopy. The former and less important product is

readily explained by the simple reductive deoxygenation of the xanthate antiperiplanar to

two β-oxygen bonds, scheme 64, path a. The latter, major product is explained by the

mechanism outlined in path b of scheme 64 in which the xanthate with the synclinal β-

oxygen bonds is cleaved first followed by migration of the remaining xanthate group and

eventual trapping by the tin hydride.
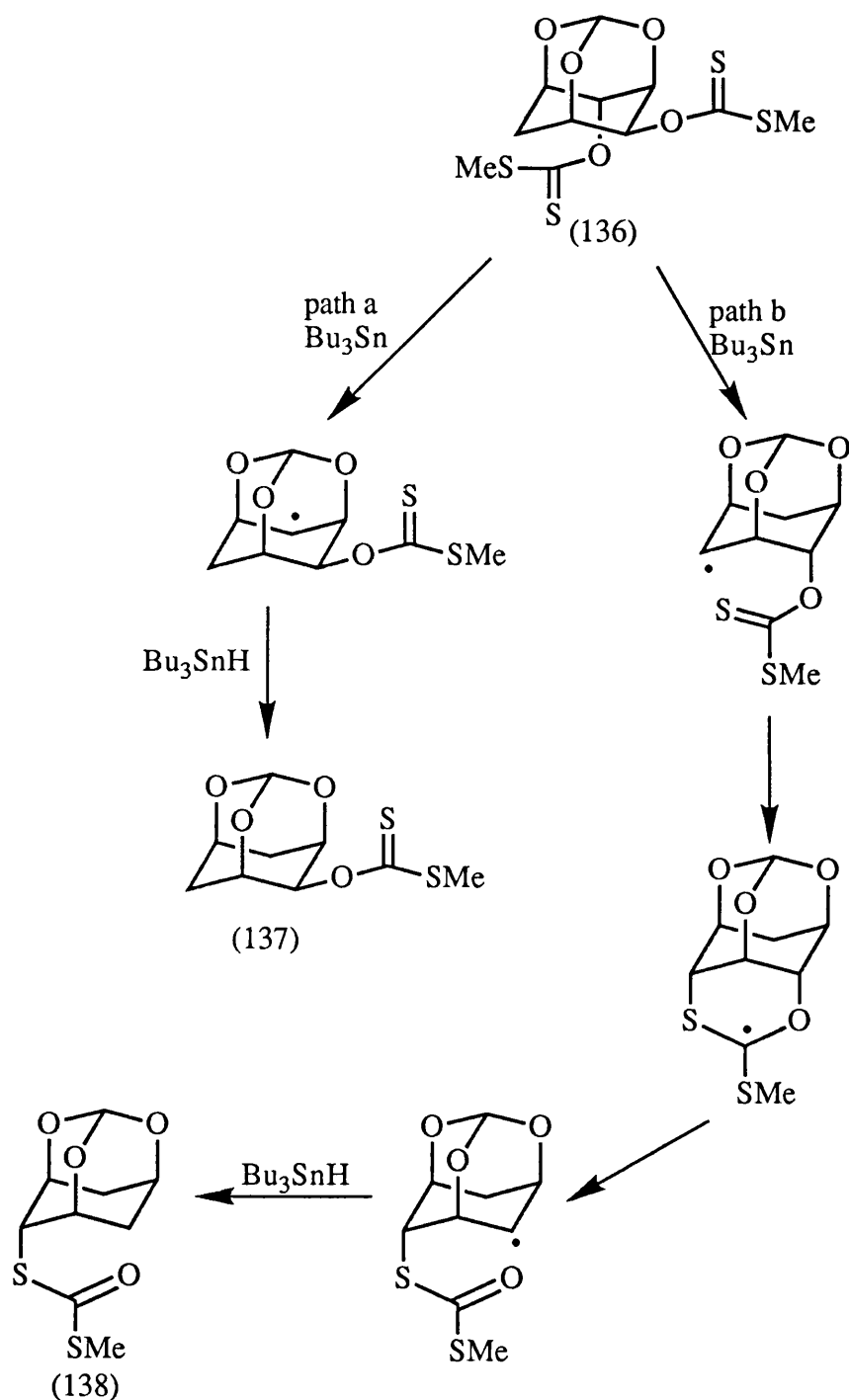
Scheme 64 : Reduction of (136) with substoichiometric tributyltin hydride.

Similar migrations have been previously implied in the chemistry of related dixanthate esters.[13c, 50, 60]

Evidently (136) conforms with the pairs (120) and (121), (129) and (130), and (115) and (116) with the bond synclinal to the β-oxygen is more readily cleaved than the antiperiplanar one, suggesting that fears of conformational mobility in (120) and (121) and of steric hindrance in (130) were unfounded. In a final experiment (136) was partially reduced with tris(trimethylsilyl)silane[61] with virtually identical results to the stannane reduction indicating that the observed difference in reaction rates is not the result of preco-ordination of the stannane to the synclinal β-oxygen bond.[62]

The correct structural elucidation of compounds (137) and especially (138) is crucial to the argument and deserves comment. In the series (129)-(138) the three bond coupling constants within the axial and equatorial hydrogen atoms are all reduced below the normal for 60° torsion angles owing to the electronegativity of the multiple oxygen substituents. Thus, most of the hydrogen atoms attached to the various trioxaadamantanes described appear, in the 300 MHz ^{1}H nmr spectrum, as poorly resolved multiplets. Even if better resolution were available it would not permit rigourous determination of stereochemistry in (137) and (138) owing to the more or less perfect 60° torsion angles in all of the three bond coupling systems. Fortuitously, each equatorial hydrogen also has the ideal W spacial relationship to enable four bond coupling to at least one other equatorial hydrogen whereas the axial hydrogens have no such possibility. In practice two types of multiplet are observed, those involved only in simple three bond coupling, and those involved in both three and four bond couplings, with the latter being correspondingly broader. It is this additional breadth of the equatorial multiplets, with respect to the axial ones, that enables them to be distinguished by simple comparison of the widths at half height ($w_{1/2}$). Interestingly ^4J W coupling (≥ 1 Hz) is also observed between H-7 and the equatorial hydrogens on the base of the trioxaadamantane framework resulting in each case in slight broadening of the H-7 signal. All the chemical shifts and $w_{1/2}$ values of the

skeletal hydrogens of (129)-(138), with the exception of (125) whose spectra were recorded in other solvents, are set out in the table 5.

Table 5: Distinguishing ^{1}H nmr Features in Inositol Orthoformates

Cmpd	Chemical Shift δ^a (width at half height in Hz)						
	H-1	H-2	H-3	H-4	H-5	H-6	H-7
(132)	4.62^b	5.67^b	4.50	5.84	4.62^b	4.74^d	5.67^c
			(6.8)	(9.8)			
(133)	4.69-4.75^b	5.77	5.20	5.89	4.69-4.75^b	6.17	5.61
		(2.0)	(7.8)	(10.2)		(10.1)	(4.6)
(134)	4.47-4.52^b	5.30	4.63	5.83	4.47-4.52^b	2.15$_{ax}$	5.70
		(4.3)	(8.5)	(10.2)		(5.1)^e	(2.6)
						+ 2.82$_{eq}$	
						(10.2)^e	
(136)	4.51^b	5.74	4.73	6.28	4.51^b	2.04$_{ax}$	5.64
		(6.0)	(10.2)	(12.7)		(5.1)^e	(2.6)
						+ 2.79$_{eq}$	
						(12.0)^e	
(137)	4.53	5.66	4.53	1.82$_{ax}$	4.37	1.82$_{ax}$	5.60
	(8.6)	(4.5)	(8.6)	(5.1)^e	(9.3)	(5.1)^e	(4.3)
				+		+ 2.86$_{eq}$	
				2.86$_{eq}$		(12.7)^e	
				(12.7)^e			
(138)	4.29^f	4.70	4.29^f	1.84$_{ax}$	4.25^f	1.84$_{ax}$	5.65
		(9.3)		(4.2)^e		(4.2)^e	(2.6)
				+		+ 2.61$_{eq}$	
				2.61$_{eq}$		(10.0)^e	
				(10.0)			
(129)	4.69	5.89	4.69	4.45	4.53	4.45	5.60
	(5.5)	(3.4)	(5.5)	(8.1)	(6.5)	(8.1)	(2.6)
(130)	4.88	5.82	4.88	4.42	4.64	4.42	5.89
	(6.5)	(7.0)	(6.5)	(7.0)	(6.5)	(7.0)	(1.2)
(131)	4.21^b	4.21^b	4.50	4.21^b	4.21^b	2.38^c	5.54
			(7.6)				(3.5)

a) Axial hydrogens are identified by boldface chemical shifts; b) Unresolved multiplet; c) Unresolved multiplet; d) Coupled to OH; e) $w_{1/2}$ in one wing of a geminal doublet; f) Insufficiently resolved for estimation of $w_{1/2}$.

When the resolution enabled determination of coupling constants this information is given in the experimental part. It can readily be seen that the H-2 signal of (137) is a narrow multiplet representative of an axial hydrogen, whilst the corresponding signal in (138) is much broader indicating an equatorial hydrogen atom. The existence of ^4J coupling between H-2 and H-4/6-eq in (138), and its absence in (137), was further confirmed by spin decoupling experiments. Of course it is also possible to deduce the stereochemistry at C-2 in (137) simply from chemical shift values but this is not the case for (138) owing to the lack of related compounds for comparison.

From the ensemble of the above results it is apparent that, as demonstrated by Barton and Gleicher, β-oxygens do indeed accelerate radical bond cleavage reactions. It is also apparent that there is a small but definite stereoelectronic component whereby synclinal β-oxygen bonds have a greater accelerating effect than antiperiplanar ones. Thus, it can be proposed that two different effects are required to explain these results. First, there is a definite accelerating effect due to the presence of a β-alkoxy group. Inductive stabilisation of a polarised transition state, similar to that suggested by Gleicher for chloroepoxides, is a possible explanation, scheme 65. The stereochemical component of this acceleration is small or non-existant as is evident from the diversity of systems studied by Barton.

X = SCH₃ or OAr, etc
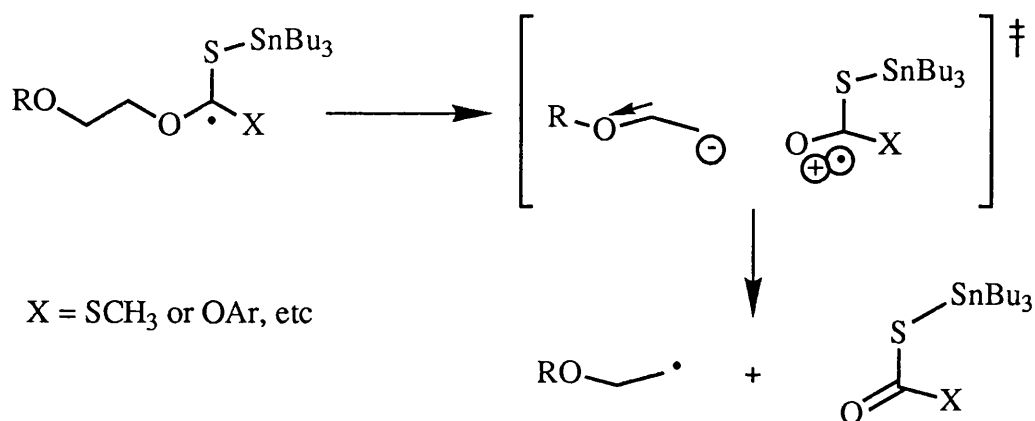
Scheme 65 : Inductive stabilization of a polarised transition state.

The second, and smaller, effect governing the more rapid reaction of (118) than (119),

(120) than (122), (129) than (130), of the synclinal rather than the antiperiplanar bond of

(136), and of (115) than (116) could possibly be a simple manifestation of the Cieplak

effect. Thus the xanthate (or chloride) having the more electron rich antiperiplanar bond

is cleaved more rapidly with the observed results (Scheme 66) in good agreement with the

order of σ-bond donor abilities σ CH > σ CC > σ CO.

σ C-H > σ C-C

σ C-H > σ C-O

σ C-C > σ C-O
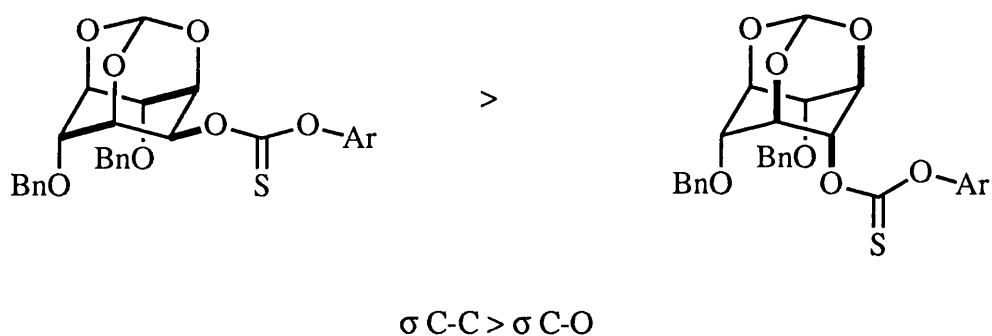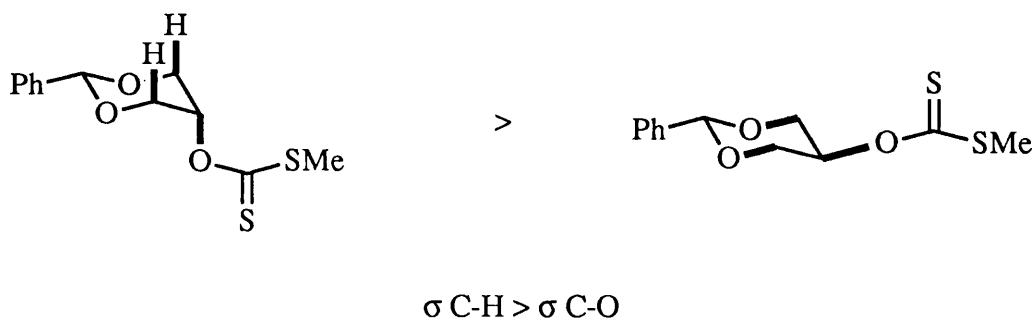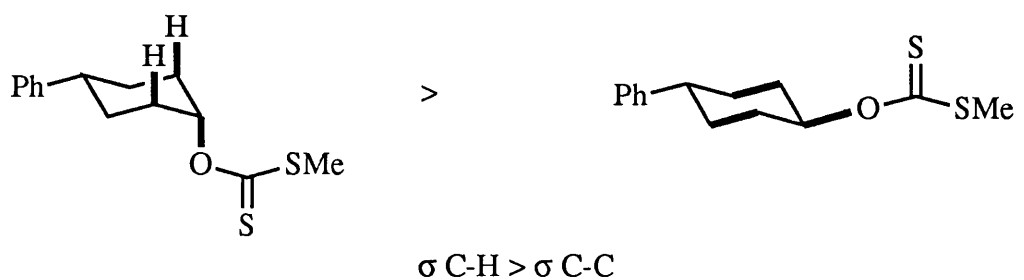
Scheme 66 : Competitive cleavage reactions.

$$\sigma\text{ C-C} > \sigma\text{ C-O}$$

$$2 \times \sigma\text{ C-C} > 1 \times \sigma\text{ C-O} + 1 \times \sigma\text{ C-H}$$
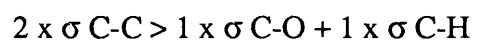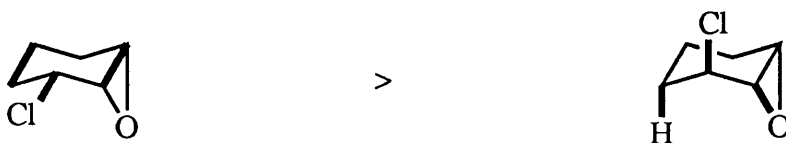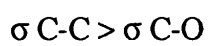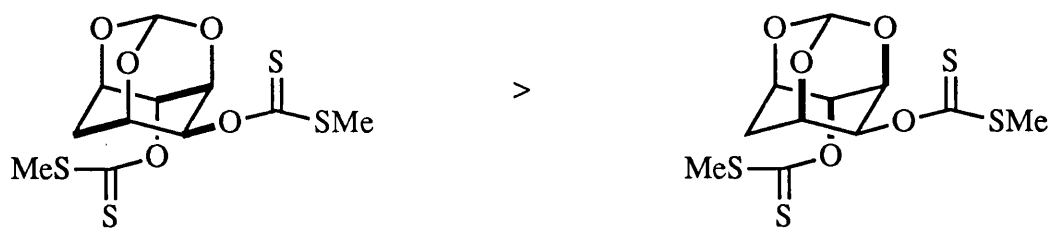
Scheme 66 (cont.) : Competitive cleavage reactions.

CHAPTER 4

OSMYLATION OF GLYCALS

Chapter 4

4.1 Introduction and background

The stereospecific *syn*-hydroxylation of alkenes, scheme 67, whether in its stoichiometric or less expensive and more environmentally benign catalytic version, is a widely applied process in organic synthesis.[64] The reaction has been reviewed several times and as such the discussion here is limited to those aspects of immediate relevance to the work described, namely the influence of adjacent stereocentres on the stereoselectivity of the reaction.
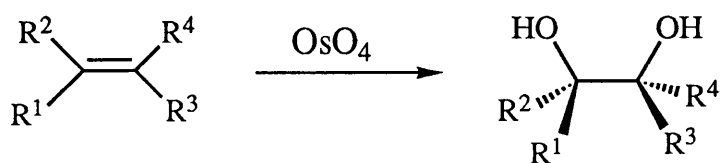
Scheme 67 : *cis*-Dihydroxylation using osmium tetraoxide.

A few words about the mechanism of OsO_4 *syn*-hydroxylation are appropriate. Although, it is not known with certainty OsO_4 hydroxylation is widely considered to take place via what may be viewed as a formal [3+2] cycloaddition reaction leading to a 5-membered metallocycle (139) scheme 68, path a. Indeed, in the stoichiometric version, this species (139) may be isolated and has to cleaved by treatment with a reducing agent, typically the metabisulfite ion. An alternative mechanism, proposed by Sharpless[26, 65] involves formal [2+2] cycloaddition to give a 4-membered metallocycle (140) followed by rearrangement leading to the observed addition product (141) scheme 68, path b.
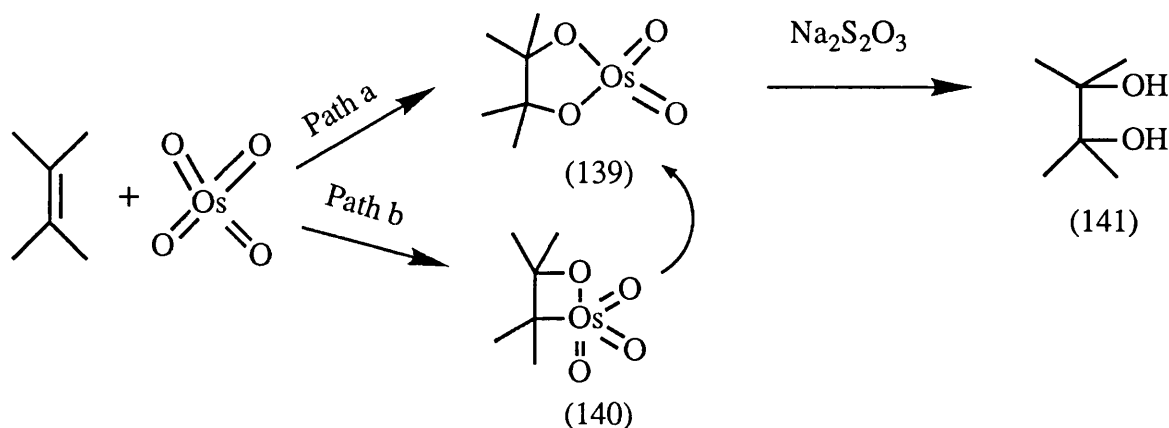
Scheme 68 : Two possible mechanisms for *cis*-dihydroxylation using osmium tetraoxide.

In the absence of other directing influences OsO_4 dihydroxylation is widely considered to occur from the least hindered face of any alkene. This is entirely reasonable in view of the evident steric bulk of the reagent, whether reaction occurs by either the [3+2] or [2+2] type addition. In recent years much interest in OsO_4 hydroxylations has stemmed from a 1984 paper by Kishi,[23, 24] in which following a careful study with a number of allylic alcohols and ethers, an empirical rule is formulated whereby *the relative stereochemistry between the preexisting hydroxyl or alkoxyl group (142) and the adjacent newly introduced hydroxyl group of the major product in all cases is erythro (143)* , scheme 69.

(142)   (143)
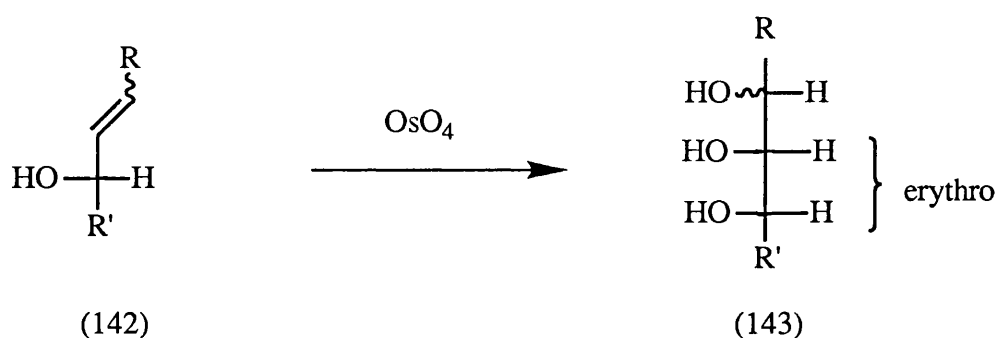
Scheme 69 : Erythro product (143) is formed upon *cis*-dihydroxylation of an allylic double bond using OsO_4.

This empirical rule, aside from its obvious predictive value, has aroused much interest and a number of conflicting rationalizations have been put forward. It was felt that, in keeping with the general theme of the project, that carbohydrates and particularly glycals would be ideal substrates for probing further any stereoelectronic influences underlying Kishi's observations and predictions. In the light of Kishi's predictions, a number of authors, but most notably Brimacombe,[25] have studied the stereochemistry of OsO_4 dihydroxylation of carbohydrate derived alkenes but, previous to this study, glycals had not been investigated in depth.[66] This chapter summarises the various rationalizations to date and describes the outcome of our researches in this area.

Kishi originally rationalized his observations in terms of the alkene adopting such a conformation as to minimise $A^{1,3}$ strain[67, 68] with the hydroxyl or alkoxyl group roughly perpendicular to the plane of the alkene and with attack occuring antiperiplanar to the C-O bond (Scheme 70).
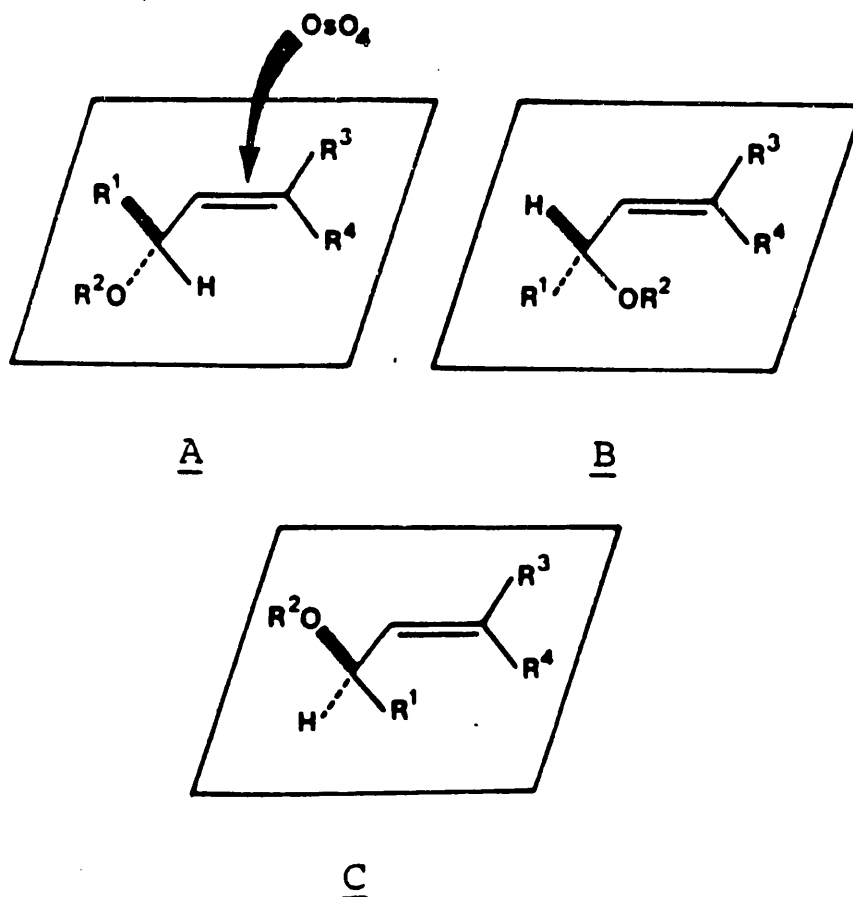
Scheme 70 : Approach of OsO_4 on the double bond from the sterically least compressed side.

Alternative transition states for the OsO_4 dihydroxylation of allylic alcohols have been proposed by Stork[69] (for γ-hydroxy-α,β-unsaturated esters) and by Vedejs[70] for the general case. Both proposals are essentially based on simple steric arguments and attribute no special directing effect to the allylic hydroxyl or alkoxyl group. Calculations by Houk[71] support the notion that attack takes place opposite the most electron rich bond and suggest that this may be explained by a σ-π electron density stabilization of the transition state. This is now generally known as the Cieplak Hypothesis and suggests that, as proposed by Stork[69] and Vedejs,[70] any such stereoelectronic effect would be

easily overruled by pure steric effects. A number of experimental systems have been devised in an attempt to probe the requirements of the reaction. Thus, Cieplak and Johnson[48] studied osmylation of 3-substituted methylene-cyclohexanes, and although the system contains a steric bias that predisposes it towards axial attack, it was noted that as the remote equatorial 3-substituent was made a better electron donor, the amount of equatorial attack increased. This result was interpreted as being in accordance with the general Cieplak hypothesis.[47] On the other hand Vedejs[72] later studied osmylation of 2-substituted-4-t-butylmethylene-cyclohexane derivatives. Variation of the electronic nature of the 2-substituent was apparently not correlated with stereochemistry of the reaction which was best interpreted in simple steric terms.

In the light of these conflicting observations the recent study of Halterman[73] is especially interesting and valuable. In the system outlined in scheme 71, which has no inherent steric bias for either face, the nature of the group X in (144) was systematically varied from electron withdrawing through to electron donating and face selectivity in the osmylation reaction studied. When X was electron withdrawing the major product in each case was the cis-product (145b) whereas when X was electron donating the trans-isomer (145a) predominated. These experiments provided the first clear-cut evidence of the existence of a definite stereoelectronic effect in the osmylation of alkenes. Furthermore, the effect is in perfect agreement with the postulates of the Cieplak hypothesis with reaction taking place antiperiplanar to the most electron rich bond.

X = NO$_2$, Cl, Br, OCH$_3$, N(CH$_3$)$_3$.

(144)

(CH$_3$)$_3$NO

3% OsO$_4$

acetone : water
8 : 1

+

(145a)
Trans

(145b)
Cis
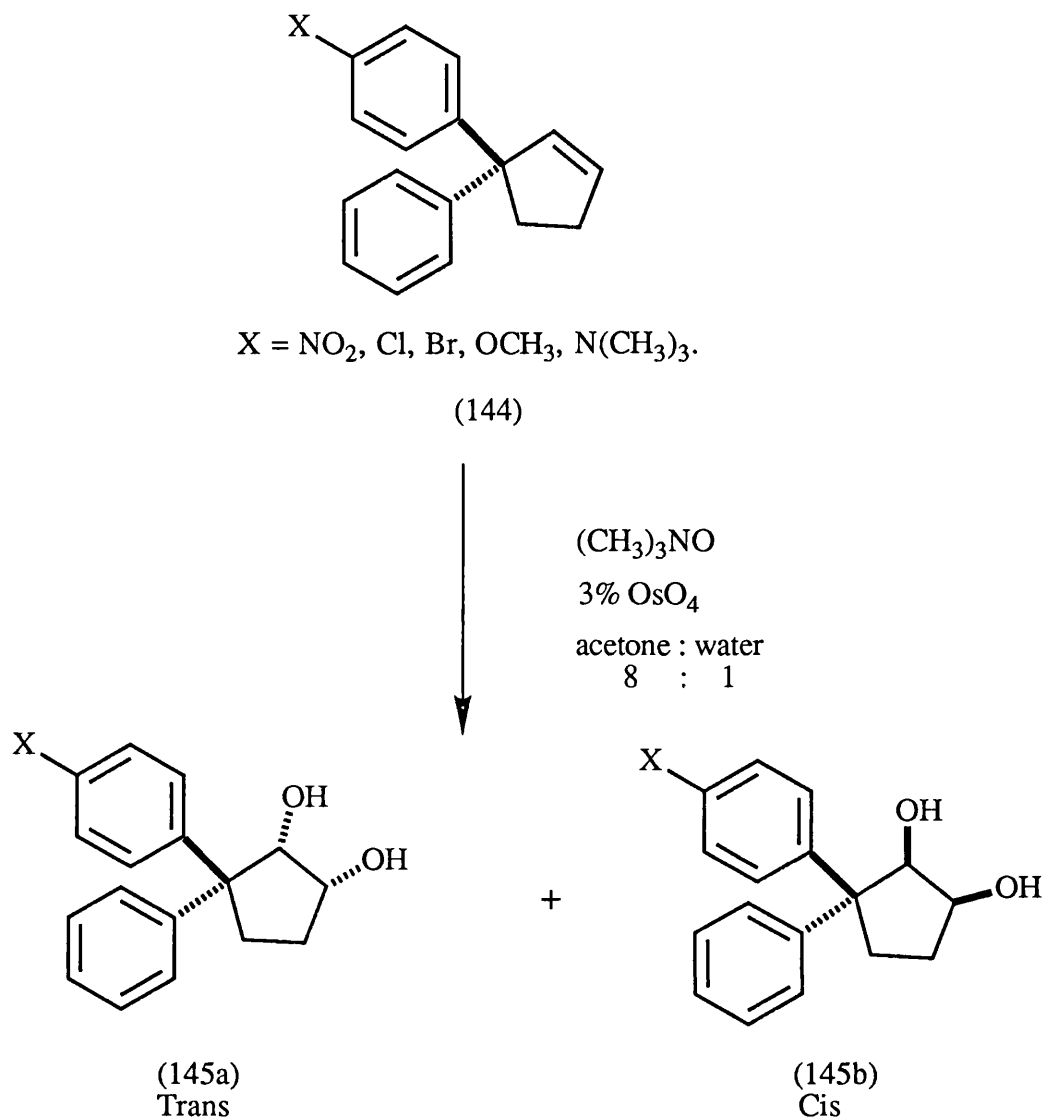
Scheme 71 : Stereoselectivity in osmylation reaction involving a sterically unbiased

system.

A further informative system has been described by Gandolfi.[74] This system exploits

3,4-disubstituted cyclobutenes and studies their face selectivity as a function of the

pyramidalization (distortion from planarity) of the sp^2 carbons and the nature of the

substituents. Initially, [3+2] cycloaddition of diazomethane with the three systems in

scheme 72 was studied. In system C attack occurred exclusively anti to the fused 5-

membered ring, on the convex face of the pyramidalized alkene. With the almost planar

alkene of system D a mixture of syn- and anti-adducts were obtained whereas with system

E only the syn-adduct was obtained resulting again from attack on the convex face of the

distorted alkene. The propensity of distorted alkenes and more especially of enol ethers to undergo attack on the convex face has also been noted and used by Seebach[75] to explain stereoselectivity in certain classes of reaction.

(C)	(D)	(E)
syn-bent	co-planar	anti-bent
α is positive	$\alpha \sim 0^\circ$	α is negative
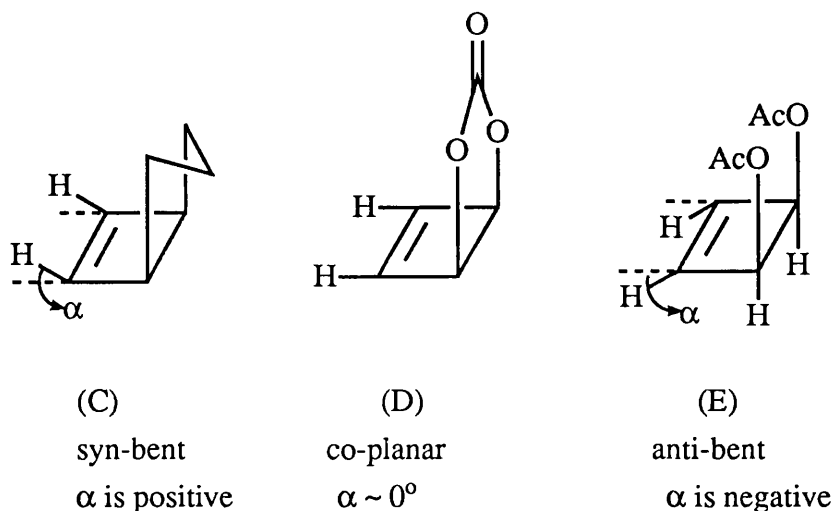
Scheme 72 : Types of systems considered in terms of position of the olefinic C-H bonds.

Related systems were then used to probe osmylation scheme 73. In (146) when X was Cl, OAc, and OSO_2Me, high *syn*-selectivity was observed (147) whereas with X = OCH_2Ph low *anti*-selectivity (148) was noted and with cyclic substituents attack took place exclusively *anti*. Both Kishi's model and the Vedejs steric model predict attack on the *anti*-face in each of these systems and are thus found to be oversimplifications. However, if it is assumed that the sense of pyramidalization of the alkene is determined by the nature, electron donating or electron withdrawing, of the allylic bonds it is readily seen that these results provide further support for the existence of a "Cieplak Effect" in the osmylation of alkenes.

Chapter 4

(146)   (147)   (148)

Syn   Anti
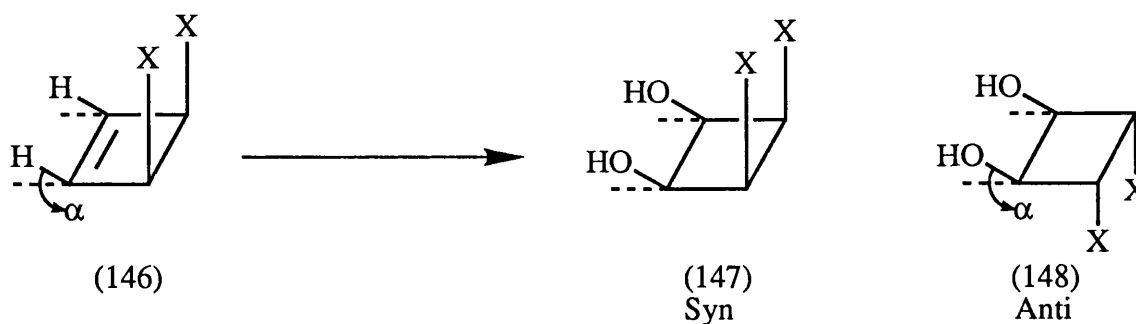
Scheme 74 : Rigid system used by Gandolfi to probe stereoselectivity in osmylation.

4.1 cis-Dihydroxylation of Glycals

The hydroxylation of glycals was investigated in 1970 by Bilik and Kucar[76] with a number of different oxidizing systems. (First report of hydroxylation of tri-*O*-acetyl-D-glucal was by Hockett[77]). In particular, these authors noted that oxidation of free D-galactal (149) by OsO_4 and hydrogen peroxide gave a 4 : 1 ratio of D-galactose (150) and D-talose (151), scheme 75.

(149)   (150)   (151)

4   :   1

D-galactose   D-talose
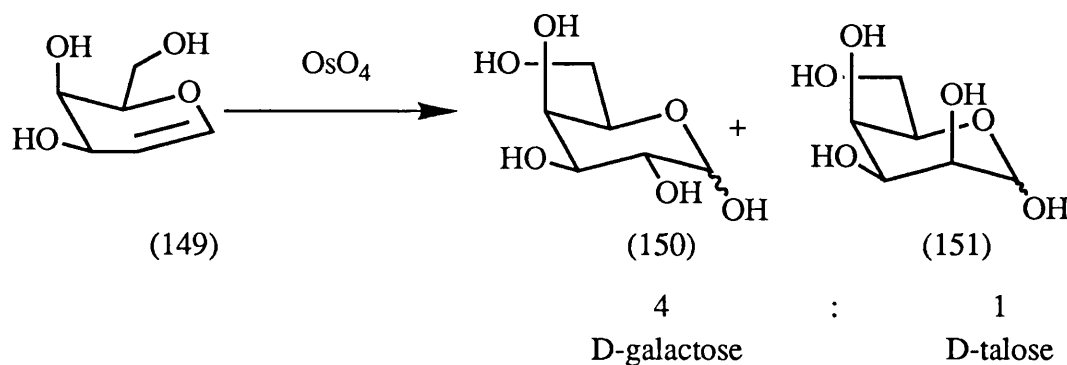
Scheme 75 : Osmylation of D-galactal (149).

When selenium dioxide, vanadium pentoxide or chromium trioxide were used as oxidant D-galactose was again the major product. However, tungsten trioxide and molybdenum trioxide gave preferentially D-talose. When applied to D-glucal, D-arabinal and D-xylal the MoO_3 system gave D-mannose, D-ribose and D-lyxose respectively. Although these

systems and their selectivity are interesting, it is probable that they proceed by epoxide formation and subsequent ring opening and so they are of little relevance to the present study since a different mechanism operates in this system. Reaction of OsO_4 and chloramine-T with tri-O-acetyl-D-glucal[78] provides a mixture of regioisomers but which all have the *gluco*-stereochemistry. In this laboratory,[16b] reaction of both tri-O-benzyl-D-glucal (15) and of 1-carbomethoxytri-O-benzyl-D-glucal (41) with catalytic OsO_4 in the presence of NMO had been found to occur cleanly from the α-face with formation of the *gluco*-stereochemistry (42) and (43) respectively, in excellent yield, scheme 76. In fact oxidation of tri-O-benzyl-D-glucal (15) in this manner can be described as a very efficient preparation of 3,4,6-tri-O-benzyl D-glucopyranose (42) that compares very favourably with the literature route as described by Gigg.[79] This was subsequently rediscovered by a Canadian group.[80]

$$OsO_4, NMO, THF, \text{ reflux}$$

$$OsO_4, NMO, THF, \text{ reflux}$$

(15)   (42)

(41)   (43)
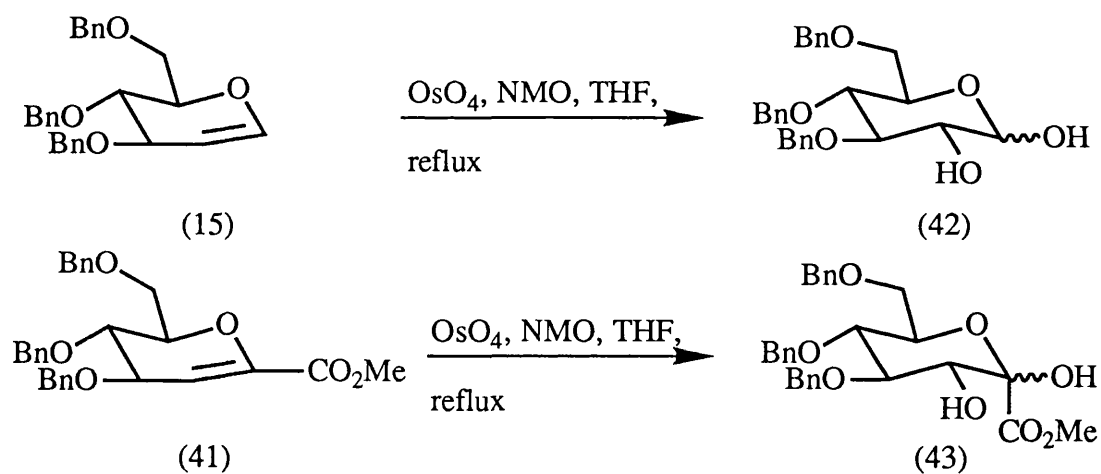
Scheme 76 : Osmylation of (15) and (41) gave the *gluco*-adducts.

The *threo*-disposition of the 2,3-hydroxy groups in glucose leads to the conclusion that osmylation of glucal, and indeed of D-galactal, and of their various protected forms, is in exception to Kishi's empirical rule. Indeed this is strictly correct. However, closer inspection of Kishi's paper reveals that it too contains a class of exception although provision is not made for it in the rule. Thus, it is noted that osmylation of cyclic allylic alcohols (152), eg scheme 77, occurs preferentially on the face opposite to the hydroxyl

group, i. e with formation of the *threo*-geometry (153) between the preexisting hydroxyl and the newly introduced adjacent hydroxyl group.
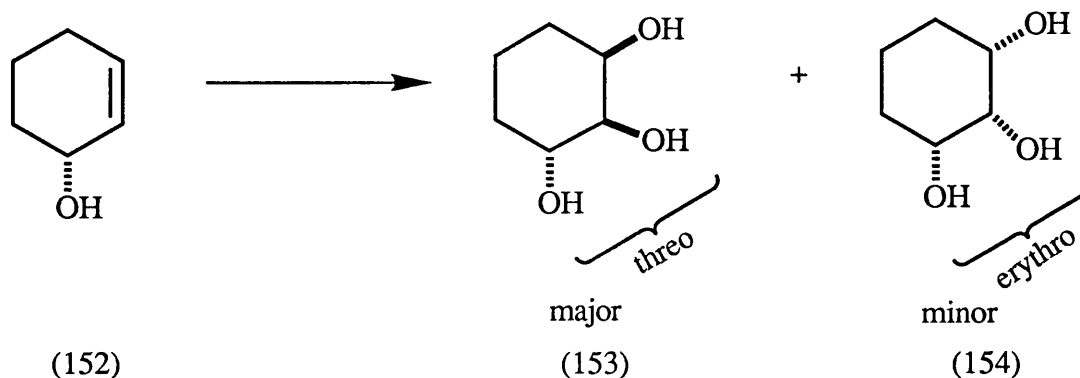
Scheme 77 : Osmylation of cyclic alcohols (152) gives mainly the *threo*-isomer.

Further consideration of the cyclohexenol system leads to the conclusion that the anomalous result is a consequence of the imposed conformation. By extension it can thus be concluded that acyclic *cis*-allylic alcohols which obey the rule react via an extended conformation of the carbon chain and antiperiplanar to the allylic hydroxyl group rather than via a folded conformation which would lead to the *threo*-isomer, scheme 78.
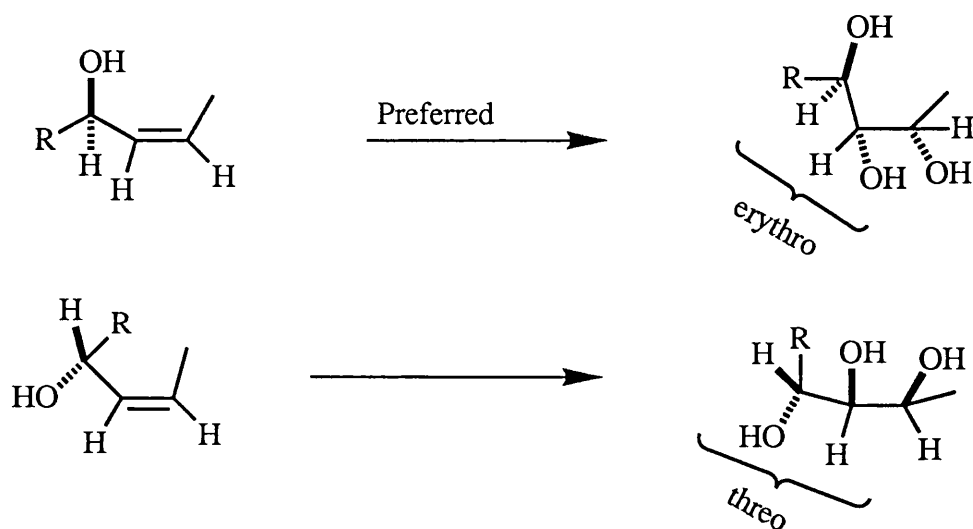
Scheme 78 : Acyclic *cis*-allylic alcohols give the *erythro*-isomer.

At first sight the glucal (149) may simply be viewed as a further example of the cyclohexenol type system. However, the ring oxygen and its lone pairs cannot be neglected. In fact, the pseudoaxial lone pair can be interpreted as a region of very high electron density in the allylic position. If reaction occurs through the known $^4H_5$ ground state conformation,[81] figure 25, osmylation of the glucal can then be seen to occur antiperiplanar to this region of high allylic electron density as would be predicted by the Cieplak hypothesis. Furthermore, examination of the literature X-ray crystal structure of tri-O-acetyl-D-glucal (45)[81] revealed the alkene moiety to be distorted from planarity with the two olefinic hydrogens being displaced towards the β-face of the molecule. This is consistent with Gandolfi's observations that attack takes place on the convex side of a distorted alkene.

Figure 25 : $^4H_5$ conformation of glucal (149).

slight distortion of the alkene

pseudoaxial lone pair
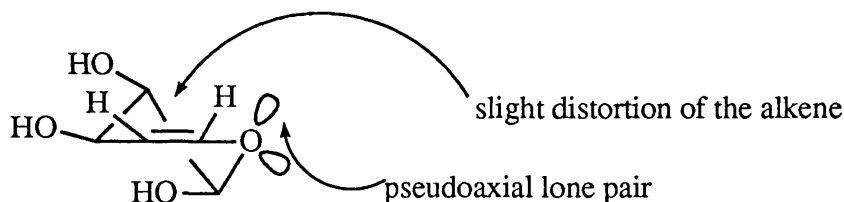
The ideal molecule with which to probe the osmylation of glycals and to differentiate between the directing effect of the hydroxy group at C-3 and that of the pseudoaxial lone pair is a conformationally locked derivative of a ribal (155) derived leading to either allose (156) or altrose (157), scheme 79. In this system the pseudoaxial lone pair would still direct hydroxylation onto the α-face resulting in the formation of an allose derivative, whereas the pseudoaxial C-3 hydroxyl group would direct reaction to the β-face, in contravention of a literal interpretation of Kishi's rule but in agreement with the example of scheme 77, and so formation of an altrose derivative.

Ribal
(155)

Allose
(156)

Altrose
(157)
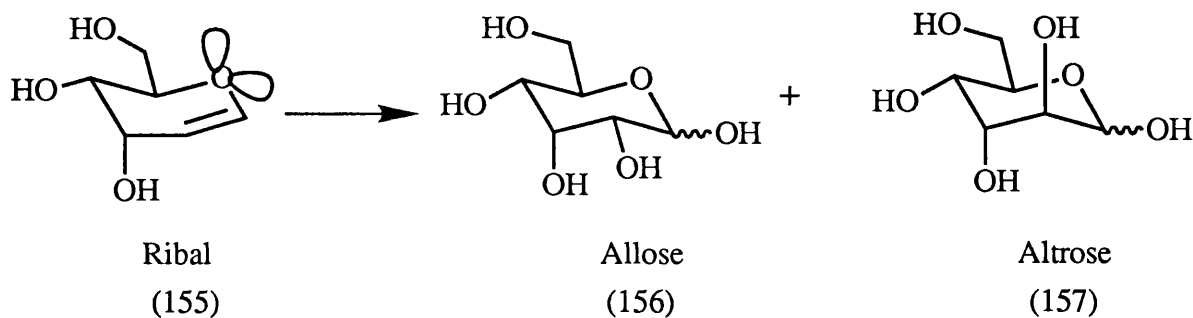
Scheme 79 : Possible products from osmylation of (155).

The 4,6-benzylidene-D-ribal (94) was prepared as previously described and converted to its benzyl ether (95) by standard methods and the dihydroxylation of both species attempted with a catalytic amount of OsO_4 and NMO. In the case of the hydroxy derivative (94) the reaction was both clean and relatively rapid with the dihydroxylation product obtained in 41% yield after 4 hours at reflux, scheme 80.

OsO_4/NMO

4hrs, reflux, 41%

(94)

(158)
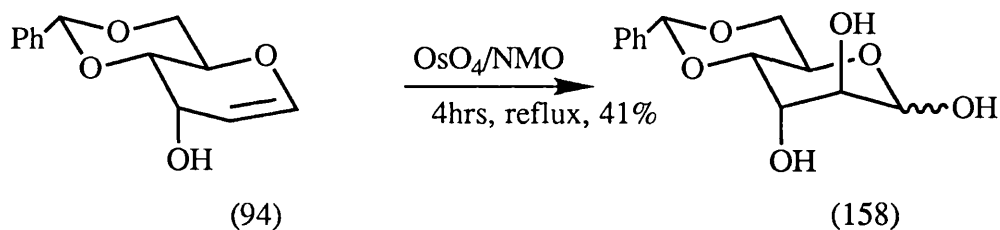
Scheme 80 : cis-Dihydroxylaytion of (94) gives the altro-adduct.

Assignment of stereochemistry by ^1H nmr spectroscopy was severely hampered by poor resolution of the various ring hydrogens and owing to the presence of seemingly two compounds, be they anomers of the one substance or epimers at C-2. Microscale acetylation improved things somewhat such that it was possible to discern two distinct anomeric doublets at δ 6.01 and 5.49 ppm. The more downfield, and major, isomer was a doublet with a coupling constant of 1.45 Hz whilst the upfield, minor isomer was a broad singlet indicating that $J_{1,2}$ was less than 1 Hz. The ratio of the two isomers was

approximately 4 : 1. Assuming the $^4C_1$ conformation for all possible isomers, as seems entirely reasonable particularly in the light of a recent X-ray structure for methyl 4,6-*O*-benzylidene-α-D-altropyranoside[82] which clearly indicates this conformation, the four possible products may be formulated as in figure 26.

The small value of the ^3J coupling to H-1 in both isomers ruled out the possibility of the β-*allo* derivative in which the torsion angle H(1)-C(1)-C(2)-H(2) would be anticipated to be approximately 180° with a correspondingly large coupling constant. On the basis of the apparent absence of ^4J W-coupling from H-1 to H-3 it would appear that the two α-anomers could also be ruled out. On this basis only one structure fits the data, namely the β-*altro*-derivative but clearly, from the ^1H nmr spectrum, two substances are formed. It has to be concluded therefore that either ^4J W coupling was not resolved or that the $^4C_1$ conformation is not adopted by one of the compounds. In the face of this problem it was decided to to fully deprotect the mixture of products and to identify the free sugars by comparison with authentic samples of D-allose and D-altrose. Thus, hydrogenolysis of the dihydroxylation mixture gave a free carbohydrate that was subsequently analysed by HPLC on silica gel eluting with aqueous acetonitrile mixtures. Authentic samples of D-allose and D-altrose, purchased from Aldrich, were sufficiently well resolved with the system used to enable easy distinction but the anomers of each were not. In this manner the carbohydrate from the OsO_4 reaction was readily identified as >95% pure altrose, figure 27. Evidently, the two triacetates observed by ^1H nmr were anomers of *altro*-pyranoside. That mixtures of anomers are obtained simply reflects the mutarotation of the initially formed products both in the reaction mixture and on acetylation.

Figure 26 : Possible products which may be obtained after osmylation and acetylation of (94).

β-allose

(159)

α-allose

(160)

β-altrose

(161)

α-altrose

(162)
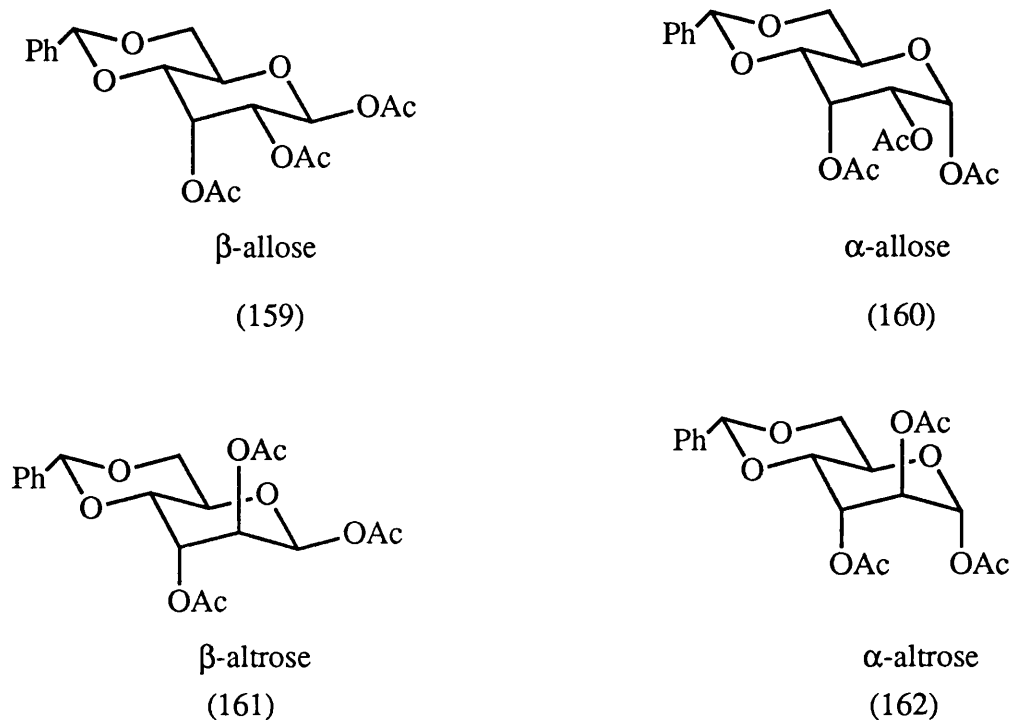
In a similar manner dihydroxylation of the benzylated ribal (95) was examined. In contrast to the above reaction this species only reacted very sluggishly with OsO_4 and the reaction mixture was complex owing to the prolonged reaction time required. Nevertheless, the anticipated diol was isolated by preparative tlc in 36% yield. ^{1}H nmr spectroscopic examination of the purified diol or its diacetate suffered from the same problems described above for the triol and its triacetate. Hence, deprotection was again resorted to and the product again identified as pure altrose containing less than 5% allose by HPLC.

   Chapter 4

Figure 27 : Identifcation of Dihydroxylation Product of Ribal as Altrose by HPLC.

allose + altrose

allose

altrose

Compound (95) after hydrogenation

(95) + allose
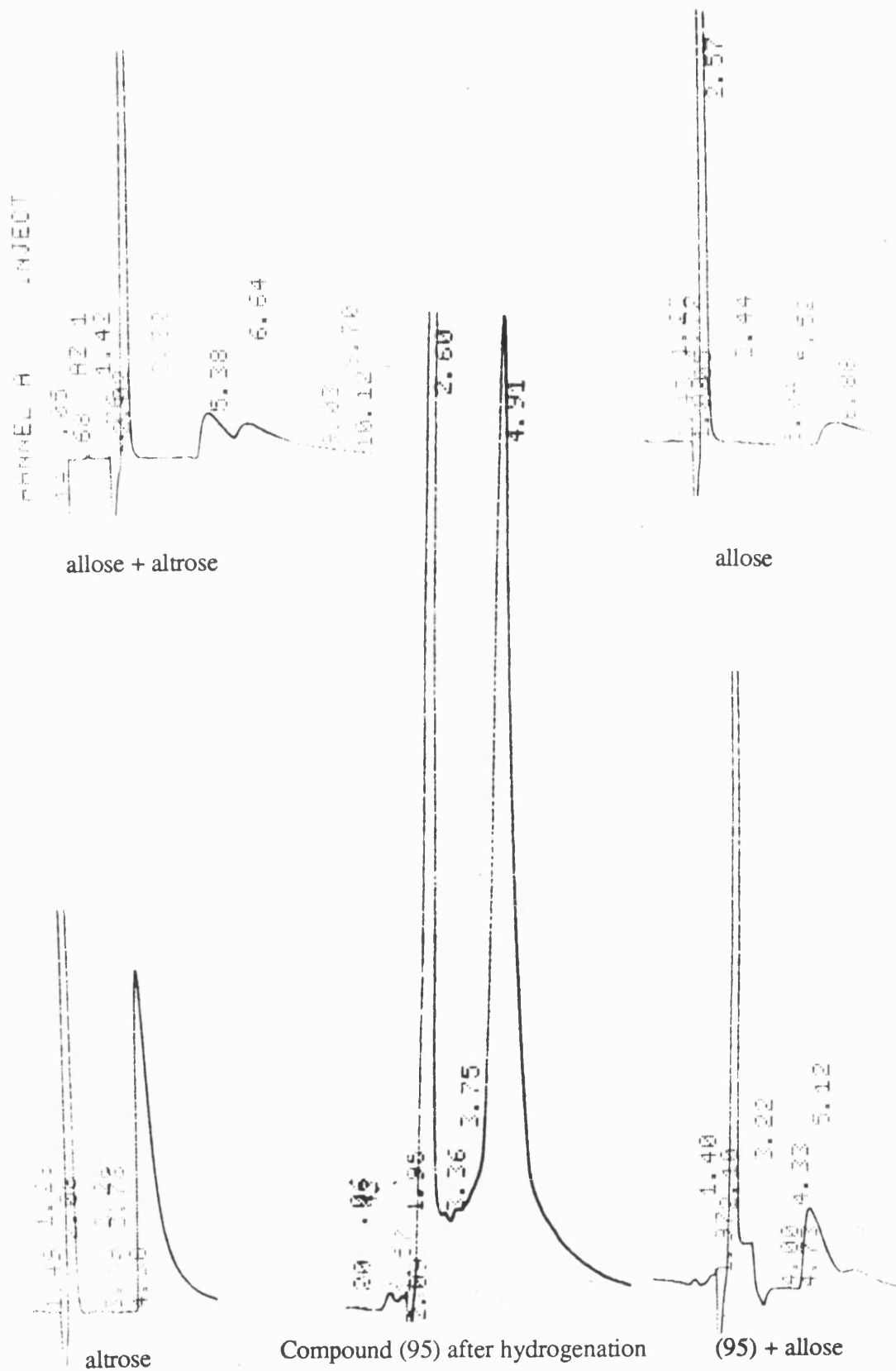
These results clearly demonstrate that in the osmylation of glycals the directing effect of the pseudoaxial lone pair on the ring oxygen is readily overridden by that of any alkoxyl or hydroxyl substituent at C-3. The effect of the axial hydroxy and benzyloxy substituents might be due to acceleration of reaction from the antiperiplanar direction or simply due to steric retardation of attack on the α-face. Unfortunately, due to the constraints of time, we have been unable to conduct the obvious experiments to differentiate between these factors. The significant, and reproducible, difference in rate between the benzyloxy compound (95) and the hydroxy compound (94) is puzzling. It is possibly indicative of the very bulky benzyl ether imposing a different and less reactive conformation on the glycal. Were suitable crystals available this could be probed crystallographically.

Attention was next turned to the possibility of reversing the stereoselectivity of osmoylation of glycals with the aid of chiral catalysts. In recent years much attention has been devoted to the design of chiral amine catalysts for use in ligand accelerated enantiospecific dihydroxylation of alkenes by OsO_4.[27, 83] A number of systems have been developed but by the far the most successful, in terms of catalytic turnover, chemical yield and availability, are the derivatives of the cinchona alkaloids described by the Sharpless group.[27] Thus, various esters of dihydroquinine and dihydroquinidine catalyse the enantiospecific dihydroxylation of trans-alkenes with excellent yields and enantiomeric excesses and opposite face selectivity. cis-Alkenes give somewhat lower ee's with these catalysts and it was only after the completion of this study that derivatives were developed that gave routinely high enantioselectivities for this class of alkene[84] and also for the dihydroxylation of enols.[85]

Application of the standard Sharpless catalysts to the dihydroxylation of allylic alcohols has been studied, mainly in carbohydrate derivatives by a number of authors as in figure 27, and it has been demonstrated that with the correct choice of catalyst the normal selectivity, as predicted by Kishi's rule, can be overturned and useful yields of the

alternative diastereoisomer obtained.[25, 86] This constitutes a case of double asymmetric

induction with a mismatched pair according to the Masamune[87] formalism.

Figure 27 : Two chiral catalysts used in osmylation reactions.

(163)   (164)

dihydroquinine 4-chlorobenzoate   dihydroquinidine 4-chlorobenzoate
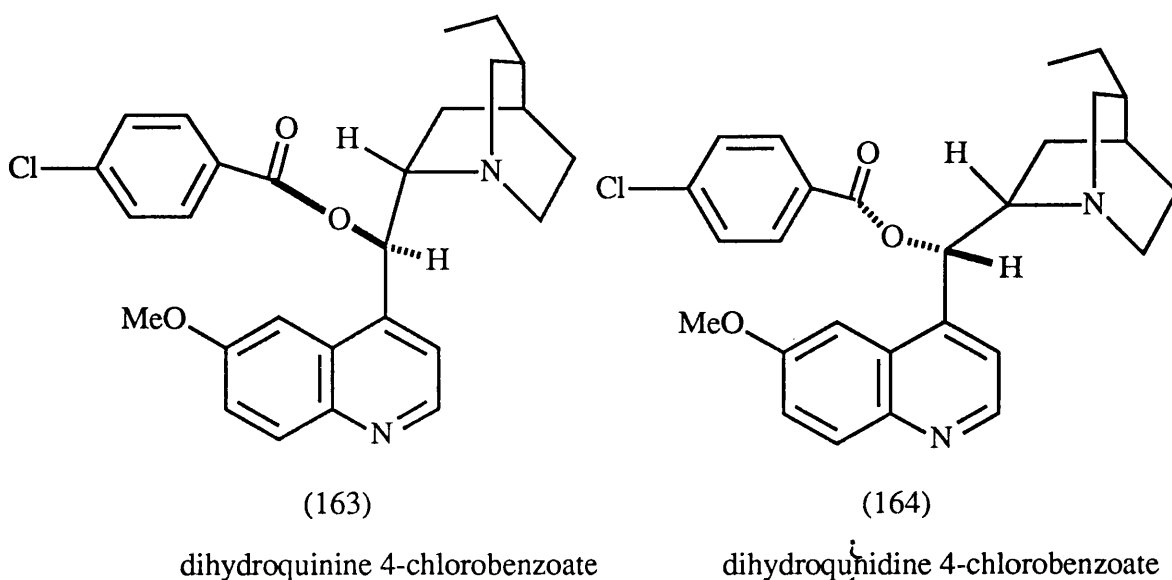
Osmylation of tri-O-benzyl-D-glucal (15) was examined with the usual system of catalytic

OsO$_4$ and NMO together with 5 mole % of one or the other of the commercial Sharpless

catalysts (163) or (164). After completion the reactions were worked up in the normal

way, the diols were acetylated to facilitate analysis, and the stereochemistry determined by

^{1}H nmr. With the dihydroquinidine catalyst (164) the reaction was significantly faster

than the uncatalysed process and led to the clean formation, after acetylation of an

anomeric mixture of gluco acetates, scheme 81, as determined by comparison with

authentic samples. No evidence was found for the formation of the manno-isomers.

With the dihydroquinine catalyst (163) the reaction was slower than the corresponding

reaction with (164), but nevertheless, analysis as above leads to the conclusion that only

the gluco-isomers were formed. Therefore, both catalysts accelerate the rate of reaction

but to differing extent such that one must be a matched pair (OsO$_4$-164) and the other

must be a mismatched pair (OsO$_4$-163). As in the case of the osmylations of ribals

described above it is evident that the reaction occurs exclusively from the α-face and that

mutarotation then results in the formation of anomeric mixtures.
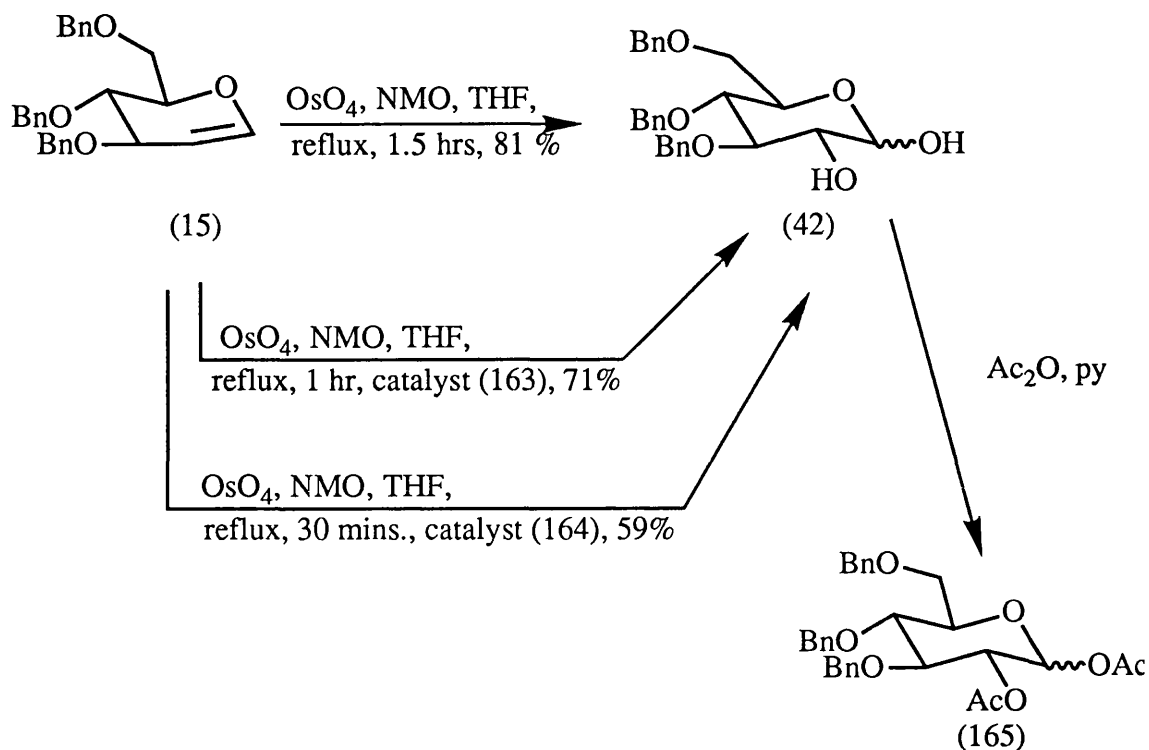
Scheme 81 : Comparison of catalysed and uncatalysed osmylation of tri-O-benzyl-D-

glucal (15).

It is evident that, for the case of osmylation of glycals, D-glucal and the dihydroquinidine

(164) form a matched pair resulting in accelerated reaction and excellent stereoselectivity,

whereas D-glucal and the dihydroquinine (163) constitute a mismatched pair resulting in

retarded reaction compared with reaction of (164) under the same reaction conditions. In

another reaction, the ribal (95) was subjected to osmylation with catalyst (164). There

was no similar increase in the rate of reaction possibly due to the increased steric

bulkiness of the complex OsO_4-164.

Unfortunately it appears that the directing influence of the glucal oxygen is still

significantly stronger than than that of the catalyst resulting in isolation of only the gluco-

isomer of the product, hence no reversal if stereochemistry at C-2 was observed. It is possible that one of the two catalysts now recommended for dihydroxylation[84] of *cis*-alkenes might be able to reverse the face selectivity but this remains to be investigated at a later date.

CHAPTER 5

EXPERIMENTAL

Chapter 5

General Methods :

Melting points are uncorrected and were determined with a Kofler hot-stage microscope. Optical rotations were measured with a Perkin Elmer 241 polarimeter, $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded on a Perkin-Elmer 983 or on a 1605 spectrophotometer. ^1H nmr spectra were recorded at 300 MHz with a Bruker AC 300 instrument. ^{13}C nmr spectra were recorded at 75 MHz with the same instrument operating in the ^{13}C mode. ^1H nmr spectra were also recorded on a Varian VXR-400 MHz or Varian XL-200 MHz spectrometer. Chemical shifts (δ) are in ppm downfield from tetramethylsilane as internal standard, J values are given in Hz. All spectra were run in $CDCl_3$ as the solvent unless otherwise stated. 70 eV EIMS mass spectra were recorded with an AEI MS-30 mass spectrometer or on a VG 7007H mass spectrometer with Finnigan INCOS II data system. Microanalyses were performed by the microanalytical section of the Department of Chemistry at University College London or by Midwest Microanalytical, Indianapolis. All solvents were dried and distilled by standard techniques. Tetrahydrofuran (THF) was distilled under nitrogen from sodium benzophenone ketyl before use. Ether refers to diethyl ether and light petroleum to the fraction boiling in the range (40-60) °C. HPLC analyses were conducted with the aid Rheodyne injector valve and of a Spectra Physics Spectra 100 isocratic pump coupled to a Shodex RI SE-61 differential refractometer and a Spectra Physics SP 4270 integrator.

S-Phenyl 3,4,6-tri-*O*-benzyl-1,2-dideoxy-1-thio-α/β-D-arabinopyranoside (48α) and (48β).

A stream of dry HCl (g) was bubbled into a stirred solution of the glycal (45) (10.0 g, 24 mmol) in dry toluene (3 mL) at 0 °C for 10 minutes. After a further 15 minutes, the solvent was evaporated under reduced pressure. The residual sirrup was dissolved in dry toluene (25 mL) and treated at room temperature with thiophenol (3.7 mL, 36 mmol) followed by Hunig's base (6.5 mL, 36 mmol). When the reaction was complete as indicated by t. l. c, it was washed with 2M KOH, 2M HCl, water, brine, dried (MgSO₄) and concentrated under reduced pressure to give the title products in a α : β ratio of 1 : 5, lit[14] α : β, 1 : 5. The spectral data was consistent with that in the literature.

S-Phenyl 3,4,6-tri-*O*-benzyl-1,2-dideoxy-1-sulfonyl-α/β-D-arabino-pyranoside (49α) and (49β).

To a solution of the starting material (48α) and (48β) (12.52 g, 0.024 mol) in absolute ethanol (430 mL) at room temperature, mmpp (24.68 g, 0.048 mol) was added portionwise. The resulting heterogenous mixture was stirred overnight. After the reaction was complete as indicated by t. l. c., the solvent was evaporated under reduced pressure. Crystallisation gave the title products as a mixture of anomers in a ratio α : β, 1 : 5 lit[14] α : β, 1 : 5. The spectral data was consistent with that in the literature.

Methyl [Phenyl 4,5,7-Tri-*O*-benzyl-3-deoxy-2-sulfonyl-β-D-arabino-2-heptulopyranosid]onate (50).

To a colourless solution of the starting material (49α) and (49β) (2.020 g, 0.36 mmol) in dry THF (5.0 mL) at -78 °C under argon, LDA (1M, 4.32 mL, 0.43 mmol) was added. The reaction mixture was stirred at -78 °C for 15 minutes before dimethyl carbonate (1.30 mL, 0.0154 mol) was added dropwise. The reaction mixture was stirred at -78 °C until

t. l. c. (ether : petroleum, 1 : 1) showed complete loss of starting material. The reaction mixture was then allowed to warm to room temperature before pouring onto a mixture of saturated ammonium chloride and brine solutions. The reaction mixture was repeatedly extracted with ether. The combined ethereal layers were washed with water and brine, dried (MgSO$_4$), filtered and the filtrate was concentrated under reduced pressure to give a yellow gum. Chromatography on silica gel (ether : petroleum, 1 : 1) gave the sulfone ester as a white solid which was crystallised from ether in 88% yield (1.945 g). M. pt 88 ºC, lit[14] 88 ºC. δ (300 MHz) 2.83 (2H, ddd, J = 15.2, 6.0 and 4.2 Hz, 2xH-3), 3.40 (3H, s, OCH$_3$), 3.55 (1H, dd, J = 9.70 and 2.55 Hz, H-4), 3.70-3.37 (2H, m, 2xH-7), 4.05 (1H, m, H-6), 4.34-4.70 (7H, m, 3xOC$\underline{H}$$_2$Ph, H-5), 7.17-7.50 (20H, m, aromatic).

Methyl [Phenyl 4,5,7-Tri-O-benzyl-3-deoxy-2-thio-α/β-D-arabino-2-heptulopyranosid]oate (54) and (55).

To a colourless solution of the starting material (50) (0.250 g, 0.04 mmol) in dry THF (2.5 mL) at -78 ºC under argon, LN (1M, 1.1 mL, 0.11 mmol) was added. The resulting dark brown mixture was stirred at -78 ºC for 10 minutes before diphenyl disulfide (0.180 g, 0.082 mmol) in dry THF was added. The reaction mixture was then slowly allowed to warm to 2 ºC before it was poured onto brine and repeatedly extracted with ether. The organic layer was separated and washed with dilute HCl, water and brine. The organic layer was separated, dried (MgSO$_4$), filtered, and the filtrate was evaporated under reduced pressure to give a yellow oil. Chromatography on silica gel (eluent, ether : petroleum, 1 : 2) gave the title products in 83% yield (0.278 g). δ (200 MHz) one anomer 1.84 (1H, dd, J = 13 and 12 Hz, H-2ax), 2.96 (1H, dd, J = 12 and 5 Hz, H-2eq), 3.48 (3H, s, CO$_2$CH$_3$), 3.42-3.65 (3H, m), 3.79 (2H, m), 4.56-4.66 (5H, m), 4.88 (1H, d, J = 10.8 Hz), 7.18-7.38 (18H, m, aromatic), 7.58 (2H, m, aromatic). Another anomer δ (200 MHz) 2.12 (1H, dd, J = 14 and 10 Hz, H-2ax), 2.87 (1H, dd, J = 14 and 5 Hz, H-2eq), 3.51 (3H, s, CO$_2$CH$_3$), 3.30-3.84 (4H, m), 3.98 (1H, m),

4.35-4.68 (5H, m), 4.90 (1H, d, J = 10.9 Hz), 7.18-7.47 (20H, m, aromatic). These data were identical to those of a authentic samples.[14]

Methyl [Methyl 4,5,7-Tri-*O*-benzyl-3-deoxy-α/β-D-arabino-2-heptulo-pyranosid]onate (56) and (57).

To a solution of the sulfide esters (54) and (55) (0.285 g, 0.05 mmol) in methanol (3.46 mL) and dichloromethane (1.15 mL), $Hg(OAc)_2$ (0.156 g, 0.05 mmol) was added. The reaction mixture was allowed to stir at room temperature for 2 nights until t. l. c. (ether : petroleum, 3 : 7) showed complete loss of starting material. Sodium sulfide nonahydrate (0.176 g, 0.07 mmol) was added and the reaction mixture was stirred at room temperature for 1 hour. The dark coloured solution was filtered on Celite to remove the black precipitate and after concentration, the residue was purified by chromatography on silica gel (ether : petroleum, 3 : 7) to give the products in 75% yield (0.184 g). δ (300 MHz) one anomer 1.79 (1H, dd, J = 13 and 12 Hz, H-3ax), 2.73 (1H, dd, J = 13 and 4.4 Hz, H-3eq), 3.38 (3H, s, OCH_3), 3.78 (3H, s, CO_2CH_3), 3.44-3.84 (5H, m), 4.51-4.73 (5H, m), 4.89 (1H, d, J = 10 Hz), 7.18- 7.39 (15H, m). The other anomer δ (300 MHz) 1.75 (1H, dd, J = 12 and 11 Hz, H-3ax), 2.56 (1H, dd, J = 12 and 4 Hz, H-3eq), 3.23 (3H, s, OCH_3), 3.81 (3H, s, CO_2CH_3), 3.50-3.82 (4H, m), 4.00 (1H, m, H-4), 4.52-4.70 (5H, m), 4.90 (1H, d, J = 10.8 Hz), 7.17-7.36 (15H, m, aromatic). These data were identical to those of authentic samples.[14]

Methyl 4,5,7-Tri-*O*-benzyl-2-deoxy-b-D-arabino-2-heptulopyranosidonic acid (79).

To a pale yellow coloured solution of the starting material (56) and (57) (0.059 g, 0.012 mmol) in methanol (0.3 mL), a solution of potassium hydroxide (0.013 g, 0.023 mmol) in water (1.0 mL) was added. The reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was then poured onto dilute hydrochloric acid and

repeatedly extracted with ether. The organic layer was separated, dried (MgSO$_4$), filtered and the solvent was evaporated under reduced pressure. The crude acid (0.053 mg, 93%) (79) was used in the next step without purification.

General procedure for decarboxylation using (30): Methyl 3,4,6-Tri-O-benzyl-2-deoxy-α/β-D-gluco-pyranoside (81).

To a stirred solution of the acid (79) (0.014 g, 0.003 mmol) in dry CH$_2$Cl$_2$ (0.20 mL), under an atmosphere of argon, the cyclic salt (30) (0.0058 g, 0.003 mmol) was added, followed by triethylamine (6 μL, 0.004 mmol). The reaction mixture was stirred in the dark for 35 minutes. Tertiary-butylthiol (0.03 mL) was then added and the reaction mixture was photolysed at 13 °C under argon with a 300W tungsten lamp for 1.5 hours. The reaction mixture was then taken up in ether, washed with dilute sodium hydroxide solution, dilute hydrochloric acid and finally with water. The organic layer was separated, dried (MgSO$_4$), filtered and the solvent was evaporated under reduced pressure. Chromatography on silica gel (ether : petroleum, 3 : 7) gave the title product as a mixture of anomers in a ratio, α : β, 1 : 10, in 30% yield (0.0035 g).

This reaction was repeated at 0 °C and between -10 and -13 °C. The yields and anomeric ratios from these experiments are collated in table 3, page 57.

Reaction of the "α" sulfide ester (54) with oxidising agents.

(i) With mmpp:

To a solution of the starting material (54) (0.005 g, 0.009 mmol) in ethanol (0.5 mL), mmpp (0.013 g, 80%, 0.02 mmol) was added. The resulting reaction mixture was stirred at room temperature for 4 hours. The reaction was complete as indicated by t. l. c. (ether : petroleum, 1 : 1). The solvent was removed under reduced pressure and the resulting

white solid was taken up in $CHCl_3$. The organic layer was washed with sodium bicarbonate solution and water. The organic layer was separated, dried ($MgSO_4$), filtered, and the filtrate was removed by evaporation under reduced pressure. The solvent was evaporated under reduced pressure and the white residue was purified by thin layer preparative chromatography on silica gel (ether : petroleum, 1 : 1) to give the sulfone ester (50), (1.1 mg, 21%) and also the carbomethoxy glucal (41), (2.2 mg, 54%) both of which were identical with authentic samples.[14]

(ii) With mcpba:

The starting material (54) (0.0041 g, 0.007 mmol) was dissolved in CH_2Cl_2 (0.25 mL) at 0 °C. A solution of mcpba (0.0058 g, 0.0017 mmol) in CH_2Cl_2 (0.04 mL) was added. The reaction mixture was stirred at 0 °C until t. l. c. (ether : petroleum, 1 : 1) showed complete loss of starting material. The solvent was removed under reduced pressure and the resulting white solid was purified by thin layer preparative chromatography (ether : petroleum, 1 : 1) to give the sulfone ester (50) in 70% yield (0.0030 g) which was identical to an authentic sample.[14]

Reaction of the "β" sulfide ester (55) with oxidising agents.

(i) With mmpp:

To a pale yellow coloured solution of the "β" sulfide ester (55) (0.010 g, 0.002 mmol) in ethanol at room temperature, mmpp (0.026 g, 80%, 0.004 mmol) was added. The reaction mixture was stirred at room temperature overnight. Ethanol was evaporated and the white residue was taken up in chloroform, washed with sodium bicarbonate solution and water. The organic layer was separeted, dried ($MgSO_4$), filtered, and the solvent was evaporated under reduced pressure to give a white solid. Thin layer preparative

chromatography (ether : petroleum, 1 : 1) gave the carbomethoxy glucal (41) in 77% yield (0.062 g) which was identical to an authentic sample.[14]

(ii) With mcpba:

To a stirred solution of the sulfide ester (55) (0.0106 g, 0.002 mmol) in CH_2Cl_2 (0.30 mL) at 0 °C, a solution of mcpba (0.0149 g, 0.004 mmol) in CH_2Cl_2 (0.55 mL) was added slowly. The reaction mixture was stirred at 0 °C until t. l. c. (ether : petroleum, 1 : 1) showed complete loss of starting material. The solvent was evaporated under reduced pressure and thin layer preparative chromatography gave the carbomethoxy glucal (41) in 73% yield (0.0063 g) which was identical to an authentic sample.[14]

Methyl 4,6-*O*-Benzylidene-α-D-glucopyranoside (90).

Zinc chloride (32.44 g, 0.238 mol) was added portionwise at room temperature to a mechanically stirred suspension of methyl-α-D-glucopyranoside (89), (40.55 g, 0.210 mol) in benzaldehyde (103 mL). The resulting mixture was stirred overnight. The reaction mixture was then poured into water (300 mL) and stirred for 25 minutes. Petroleum spirit (100 mL) was added and the resulting white solid was filtered, washed with water (100 mL), petroleum spirit (100 mL) and again with water (100 mL). Yield 59.00 g, (99%). M. pt (163-164) °C, lit[37] (161-163) °C. δ(400 MHz) 3.43 (3H, s, OCH_3), 3.47 (1H, t, J = 9.27 Hz, H-4), 3.61 (1H, bd, H-2), 3.75 (2H, m, H-5, H-6ax), 3.91 (1H, t, J = 9.27 Hz, H-3), 4.27 (1H, dd, J = 9.64 and 4.27 Hz, H-6eq), 4.77 (1H, d, J = 3.93 Hz, H-1), 5.51 (1H, s, PhC$\underline{H}$), 7.15-7.98 (5H, m, aromatic).

Methyl 4,6-O-Benzylidene-2,3-di-O-p-tolylsulfonyl-α-D-glucopyranoside (91).

To a cold solution of the starting material (90), (10.17 g, 0.036 mol) in pyridine (105 mL), p-toluenesulfonyl chloride (34.56 g, 0.181 mol) was added portionwise. The flask was stoppered and left at room temperature for 3-4 days. The reaction mixture was then poured onto cracked ice. When most of the ice had melted, the solution was decanted into a separatory funnel and extracted with CH_2Cl_2 (6 x 40 mL). The organic layer was separated and extracted with dilute HCl (7 x 40 mL). The organic layer was then washed with water (50 mL), saturated sodium carbonate solution (50 mL) and again with water (50 mL). The organic layer was separated, dried over $MgSO_4$ and treated with charcoal. The solution was filtered and reduced under vacuum to a thin sirrup. Petroleum spirit was added to effect recrystallisation. The white solid was isolated by filtration under suction. Yield 20.63 g, (97%). M. pt (147-149) °C lit[37] (147-148) °C. δ (400 MHz) 2.25 (3H, s, CH_3), 2.45 (3H, s, CH_3), 3.40 (3H, s, OCH_3), 3.50 (1H, t, J = 9.58 Hz, H-4), 3.66 (1H, t, J = 10.37 Hz, H-6ax), 3.85 (1H, ddd, J = 2x10.05 and 4.02 Hz, H-5), 4.24 (1H, dd, J = 10.05 and 4.85 Hz, H-6eq), 4.43 (1H, dd, J = 9.52 and 3.65 Hz, H-2), 5.03 (1H, d, J = 3.66 Hz, H-1), 5.09 (1H, t, J = 9.57 Hz, H-3), 5.20 (1H, s, PhCH), 6.9-7.82 (15H, m, aromatic).

Methyl 2,3-Anhydro-4,6-O-Benzylidene-α-D-allopyranoside (92).

To a cold solution of the ditosyl compound (91), (7.385 g, 0.013 mol) in CH_2Cl_2 (123 mL), a cold solution of sodium (1.470 g, 0.064 mol) in methanol (20 mL) was added. The flask was stoppered and left in the refrigerator for 3-4 days and then at room temperature for 1-2 days. The reaction mixture was diluted with water and extracted with CH_2Cl_2 (3 x 70 mL). The organic layer was separated, dried over $CaCl_2$, filtered and the filtrate was reduced under pressure. The title compound was recrystallised from $CHCl_3$/ether in 97% yield (3.343 g). M. pt 114 °C, lit[37] 115 °C. δ (400 MHz) 3.47

(3H, s, OCH$_3$), 3.50 (1H, dd, J = 4.24 and 2.78 Hz, H-3), 3.53 (1H, bd, H-2), 3.69

(1H, t, J = 10.32 Hz, H-6ax), 3.95 (1H, dd, J = 9.11 and 2.78 Hz, H-4), 4.09 (1H,

ddd, J = 10.39, 9.23 and 5.05 Hz, H-5), 4.24 (1H, dd, J = 9.55 and 5.05 Hz, H-6eq),

4.90 (1H, J = 2.25 Hz, H-1), 5.55 (1H, s, PhC$\underline{H}$), 7.20-7.52 (5H, m, aromatic).

Methyl 4,6-*O*-Benzylidene-2-deoxy-2-iodo-α-D-altropyranoside (93).

To a suspension of the epoxide (92), (3.511 g, 0.013 mol) in ether (510 mL), lithium

iodide (8.952 g, 0.067 mol) was added. The resulting pale yellow coloured solution was

stirred magnetically until no more starting material was visible by t. l. c. (petroleum :

ether, 1 : 1). Glacial acetic acid (2 mL) was added and the reaction mixture was washed

with water (2 x 100 mL), sodium thiosulfate solution (5%, 2 x 50 mL) and water (50

mL). The organic layer was separated, dried over CaCl$_2$, filtered and the filtrate was

reduced under pressure to give a white solid in 76% yield (3.958 g). M. pt (105-106)

^{o}C, lit[37] (105-106) ^{o}C. δ (200 MHz) 3.44 (3H, s, OCH$_3$), 3.97 (1H, m, H-6), 4.30

(5H, m, H-2, H-3, H-4, H-5, H-6), 5.00 (1H, bs, H-1), 5.67 (1H, s, PhC$\underline{H}$), 7.15-

7.50 (5H, m, aromatic).

4,6-*O*-Benzylidene-D-allal (94).

To a suspension of lithium (0.340 g, 0.049 mol), in dry THF (49 mL), naphthlene

(6.280 g, 0.049 mol) was added. The reaction mixture was placed in a sonic bath under

an argon atmosphere for 1.5 hours. In a separate flask, a solution of the iodide (93),

(2.407 g, 6.14 mmol), in dry THF (24 mL) was cooled to -78 ^{o}C with stirring under

argon. The lithium naphthalenide solution was added via a syringe to the iodide solution

at -78 ^{o}C until a permeanant dark green coloured was obtained. The reaction mixture was

allowed to stir for 20 minutes at -78 ^{o}C. Glacial acetic acid (0.7 mL) was added and the

reaction mixture was allowed to warm to room temperature. The solution was diluted

with ether (100 mL) and washed with water (3 x 60 mL). The organic layer was

separated, dried over $CaCl_2$, filtered and the filtrate was reduced under vacuum. Naphthalene was sublimed out on a Kugelrohr apparatus (150 °C/0.3 mmHg) and the glycal (94) was obtained as a white solid by chromatography on silica gel (eluant : ether : petroleum spirit, 1 : 1). Yield 80% (1.150 g). M. pt (ethanol) 85 °C, lit[39] 83.5 °C. δ (200 MHz) 2.48 (1H, d, J = 1.6 Hz, O$\underline{H}$), 3.95 (2H, m, H-4, H-6), 4.30 (2H, m, H-6eq), 5.04 (1H, t, J = 6 Hz, H-2), 5.68 (1H, s, PhC$\underline{H}$), 6.47 (1H, d, J = 6 Hz, H-1), 7.20-7.65 (5H, m, aromatic).

3-*O*-Benzyl-4,6-*O*-benzylidene-D-allal (95).

To a solution of starting material (94), (0.546 g, 2.33 mol), in DMSO (5.5 mL), sodium hydride (80%, 0.105 g, 3.50 mmol) was slowly added under argon. The resulting brown coloured solution was stirred at room temperature for 1.5 hours. Benzyl chloride (0.40 mL, 2.80mol) was added under an argon atmosphere and the reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with ether (50 mL) and washed with water (3 x 30 mL). The organic layer was separated, washed, dried over $CaCl_2$, filtered and the filtrate was reduced under vacuum. Chromatography on silica gel (eluant : ether : petroleum, 1 : 1) afforded the product (95) as a white solid (0.700 g, 92%). M. pt (ethanol) 107-108 °C, lit[40] 103-105 °C. $[\alpha]_{20}^D$ = +132.0° (c = 1, $CHCl_3$). δ (400 MHz) 3.82 (1H, t, J = 10.39 Hz, H-6ax), 3.95 (1H, dd, J = 10.48 and 3.51 Hz, H-4), 4.04 (1H, dd, J = 5.92 and 3.49 Hz, H-3), 4.33 (1H, ddd, J = 10.48 and 5.43 Hz, H-5), 4.45 (1H, dd, J = 10.39 and 5.34 Hz, H-6eq), 4.80 (3H, m, OC$\underline{H}_2$Ph, H-2), 5.58 (1H, s, PhC$\underline{H}$), 6.38, d, J = 6.02 Hz, H-1), 7.22-7.53 (10H, m, aromatic). Anal. $C_{20}H_{20}O_4$ requires: C, 74.06; H, 6.21%. Found: C, 74.05; H, 6.48%.

S-Phenyl 3-O-Benzyl-4,6-O-benzylidene-1,2-dideoxy-1-thio-β-D-ribo-pyranoside (98β) and the α-$\underline{D}$-anomer(98α).

HCl (g) was slowly bubbled through a solution of the glycal (95), (1.447 g, 4.46 mmol) in dry toluene at 0 °C until t. l. c. (ether : petroleum, 1 : 1) showed complete loss of starting material. The reaction mixture was then evaporated in vacuo at room temperature to remove the solvent and excess HCl (g). In a separate flask under argon, thiophenol (1.17 mL, 0.0114 mol) in dry THF (10 mL), was cooled to -78 °C and n-BuLi in hexane (2.33M, 3.83 mL, 8.92 mmol) was added. The resulting solution was allowed to stir at -78 °C for 30 minutes. This solution (8 mL) was added to the above prepared chloride at room temperature and the reaction mixture was stirred at room temperature for 1.5 hours. Ether (100 mL) was added and the reaction mixture was washed with saturated sodium bicarbonate solution (3 x 30 mL) and then with water (30 mL). The organic layer was separated, dried over $CaCl_2$, filtered and the filtrate was reduced under vacuum. Chromatography of the crude residue on silica gel (eluant : ether : petroleum, 1 : 7) gave first the β-sulfide (98β) as a white solid (0.358 g, 18.5%). M. pt (ethanol) (76-78) °C with $[\alpha]_D^{22}$ = +23° (c = 1, CHCl$_3$). δ (400 MHz) 1.97 (1H, ddd, J = 16.82, 12.29 and 2.28Hz, H-2ax), 2.28 (1H, ddd, J = 16.07, 3.34 and 2.25 Hz, H-2eq), 3.69 (1H, dd, J = 9.58 and 2.34 Hz, H-4), 3.75 (1H, t, J = 10.39 Hz, H-6ax), 4.05 (1H, bd, H-3), 4.20 (1H, ddd, J = 2 x 9.83 and 6.03 Hz, H-5), 4.36 (1H, dd, J = 10.39 and 5.34 Hz, H-6eq), 4.80 (2H, AB quartet, OC$\underline{H}_2$Ph), 5.30 (1H, dd, J = 12.07 and 2.24 Hz, H-1), 5.52 (1H, s, PhC$\underline{H}$), 7.26-7.60 (15H, m, aromatic). IR (film) $\bar{\upsilon}_{max}$ 2970, 2925, 2861, 1465, 1361 and 1259 cm^{-1}. Anal. $C_{26}H_{26}O_4S$ requires: C, 71.86; H, 6.03%. Found C, 71.44; H, 6.08%. Further elution gave the α-sulfide (98α) (1.136 g, 58.7%). M. pt (ethanol) (76-78) °C with $[\alpha]_D^{20}$ = +218° (c = 1, CHCl$_3$). δ (400 MHz) 2.38 (1H, ddd, J = 14.85, 6.54 and 2.74 Hz, H-2ax), 2.47 (1H, ddd, J = 14.91, 3.34 and 0.95 Hz, H-2eq), 3.74 (2H, m, H-6ax, H-6eq), 4.04 (1H, dd, J = 5.65 and 2.78 Hz, H-3), 4.32 (1H, dd, J = 10.22 and 5.19 Hz, H-4), 4.88 (3H, m, OC$\underline{H}_2$Ph, H-5), 5.51 (1H, bd, H-1), 5.57 (1H, s, PhC$\underline{H}$), 7.23-7.55 (15H, m, aromatic). IR (film) $\bar{\upsilon}_{max}$ 2979, 2929,

2858, 1465, 1364 and 1258 cm^{-1}. Anal. $C_{26}H_{26}O_4S$ requires: C, 71.86; H, 6.03%. Found: C, 71.89; H, 5.61%.

S-Phenyl 3-O-Benzyl-4,6-O-benzylidene-1,2-dideoxy-1-sulfonyl-α-D-ribopyranoside (99α) and the β-anomer (99β).

The α-sulfide (98α), (0.0.63 g, 0.144 mmol) was dissolved in ethanol (7 mL). mmpp (0.151 g, 0.303 mmol) was added portionwise at room temperature and the resulting reaction mixture was stirred at room temperature until there was no more starting material visible by t. l. c. (ether : petroleum, 1 : 1). The solvent was reduced under vacuum and the resulting white solid was dissolved in CH_2Cl_2 (25 mL). The organic layer was washed with saturated sodium bicarbonate solution (3 x 5 mL) and then with water (10 mL). The organic layer was separated, dried over Na_2SO_4, filtered and the filtrate was reduced under vacuum to give a white solid in 89% yield (0.60 g). M. pt (methanol) (130-131) °C $[α]_D^{20}$ = +28° (c = 0.2, CHCl$_3$). δ (400 MHz) 2.16 (1H, ddd, J = 16, 8 and 4 Hz, H-2ax), 3.08 (1H, ddd, J = 16 and 4 Hz, H-2eq), 3.52 (2H, m, H-6ax, H-6eq), 4.00 (1H, m, H-3), 4.29 (1H, dd, J = 10 and 4 Hz, H-4), 4.72 (1H, d, J = 8 Hz, H-1), 4.83 (2H, AB quartet, OCH$_2$Ph), 5.00 (1H, ddd, J = 2 x 10 and 4 Hz, H-5), 5.50 (1H, s, PhCH), 7.23-7.94 (15H, m, aromatic). IR (film) $\bar{v}_{max}$ 3063, 2975 2927, 2871, 1745, 1475, 1390 and 1229 cm^{-1}. Anal. $C_{26}H_{26}O_6S$ requires: C, 66.93; H, 5.62%. Found: C, 66.57; H, 6.06%. A similar procedure was applied to obtain the β-sulfone (99β) in 98% yield. M. pt (methanol) melts at room temperature. $[α]_D^{24}$ = +34° (c = 1, CHCl$_3$). δ (400 MHz) 1.98 (1H, ddd, J = 13.69, 12.03 and 2.71 Hz, H-2ax), 2.46 (1H, ddd, J = 13.74, 3.78 and 2.48 Hz, H-2eq), 3.64 (2H, m, H-6ax, H-6eq), 4.03 (1H, ddd, J = 14.84, 9.73 and 4.66 Hz, H-5), 4.32 (2H, m, H-3, H-4), 4.61-4.81 (3H, m, OCH$_2$Ph, H-1), 5.43 (1H, s, PhCH), 7.20-7.89 (15H, m,aromatic). IR (film) $\bar{v}_{max}$ 3063, 2981, 2925, 2866, 1809, 1475, 1389 and 1230 cm^{-1}. Anal. $C_{26}H_{26}O_6S$ requires: C, 66.93; H, 5.62%. Found: C, 66.75; H, 5.49%.

Methyl [5,7-*O*-Benzylidene-3-*O*-Benzyl-3-deoxy-2-sulfonyl-α-D-ribo-2-heptulopyranoside]oate (100).

To a colourless solution of the α-sulfone (99α), (0.175 g, 0.0375 mmol) in dry THF (1.75 mL), 4 Å molecular sieves were added. The reaction mixture was cooled to -78 °C under an atmosphere of argon. After 10 minutes, 1M LDA solution (0.45 mL, 0.045 mmol) was added dropwise. The yellow coloured reaction mixture was allowed to stir at -78 °C for 10 minutes. Dimethyl carbonate (0.50 mL, 0.63 mmol) was added dropwise and the reaction mixture was stirred at -78 °C for 15 minutes before being allowed to warm to room temperature over a period of 1 hour. The reaction mixture was poured onto brine and diluted with ether. The organic layer was separated and the aqueous layer was repeatedly extracted with ether. The combined etheral layers were washed with water and then brine. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was removed by concentration under reduced pressure. Thin layer preparative chromatography (ether : petroleum, 2 : 1) gave the product as a white solid (m. pt (63.5-64.5) °C) in 19% yield (0.038 g). δ (400 MHz) 2.24 (1H, dd, J = 16.00 and 3.96 Hz, H-3ax), 3.36 (1H, dd, J = 16.14 and 3.34 Hz, H-3eq), 3.51 (3H, s, OC$\underline{H}$3), 3.65 (1H, dd, J = 9.88 and 2.81 Hz, H-7eq), 3.75 (1H, t, J = 10.29 Hz, H-7ax), 4.02 (1H, dt, J = 5.36 and 3.42 Hz, H-4), 4.39 (1H, dd, J = 10.33 and 5.24 Hz, H-5), 4.85 (3H, m, OC$\underline{H}$2Ph, H-6), 5.50 (1H, s, PhC$\underline{H}$O), 7.25-7.95 (15H, m, aromatic). ^{13}C δ (75 MHz) 19.07, 32.96, 53.92, 59.08, 64.14, 69.80, 69.97, 72.97, 78.02, 78.97, 96.44, 102.76, 126.95, 128.11, 128.20, 128.35, 128.95, 129.31, 129.48, 130.91, 134.90, 137.97, 139.02, 167.71.

S-Phenyl 4,6-O-Benzylidene-1,2-dideoxy-1-thio-α/β-D-ribopyranoside (103).

HCl (g) was slowly bubbled through a solution of the starting material (0.069 g, 0.029 mmol), in dry toluene (0.85 mL) at 0 °C, until all the starting material was consumed as

indicated by t. l. c. (ether : petroleum, 1 : 1). Dry nitrogen gas was then bubbled through the reaction mixture. To this solution of the chloride, a preformed solution of lithium thiophenate solution (0.547M, 0.40 mL, 0.044 mmol) was added. After 3 hours of stirring at room temperature there was no further change in t. l. c. (ether : petroleum, 1 : 1). The reaction mixture was diluted with ether, washed with saturated sodium bicarbonate solution and then with water. The organic layer was separated, dried (Na_2SO_4), filtered and the filtrate was evaporated under reduced pressure to give a yellow oil. Thin layer preparative chromatography (ether : petroleum, 1 : 1) gave the title product (103) as a colourless gum in 30% yield. δ (300 MHz) 2.62 (1H, ddd, J = 15.31, 2.84 and <1 Hz, H-2eq), 2.86 (1H, ddd, J = 15.53, 6.72 and 3.73 Hz, H-2ax), 3.78 (1H, t, J = 10.36 Hz, H-6ax), 3.87 (1H, dd, J = 9.31 and 3.41 Hz, H-4), 4.33 (1H, dd, J = 10.43 and 5.28 Hz, H-6eq), 4.55 (1H, dd, J = 6.43 and 3.15 Hz, H-3), 4.77 (1H, ddd, J = 9.83, 9.83 and 5.25 Hz, H-5), 5.56 (1H, dd J = 6.65 and 3.15 Hz, H-1), 5.66 (1H, s, PhC$\underline{H}$O), 7.23-7.67 (10H, m, aromatic). IR (film) υ_{max} 3500, 2978, 2915, 2862, 1453, 1369 and 1245 cm^{-1}.

Se-Phenyl 3,4,6-tri-O-benzyl-1,2-dideoxy-1-seleno-α/β-D-arabino-pyranoside (104).

The chlorides (47) (0.013 mmol) were prepared as before and taken up in dry THF (1.3 mL) under an argon atmosphere. The preformed sodium phenylselenate solution (yellow/orange suspension, 0.13 mL, 1.6M, 0.02 mmol) was added. After 2 minutes of stirring at room temperature a clear orange coloured solution had formed. The reaction mixture was allowed to stir for a further 20 minutes at room temperature until there was no change in t. l. c. (ether : petroleum, 1 : 2). The reaction mixture was then diluted with ether (10 mL) and washed with water (2 x 7mL). The organic layer was separated, dried (Na_2SO_4), filtered and the filtrate was evaporated under reduced pressure to give a yellow solid. Thin layer preparative chromatography (ether : petroleum, 1 : 3) gave the title compound (104) as a sticky, colourless oil in 40% yield (0.030 g). δ (300 MHz) 1.81-

1.93 (1H, m, H-2eq), 2.5-2.55 (1H, ddd, J = 10.90, 8.46 and <1 Hz, H-2ax), 3.43-3.81 (5H, m), 4.52-5.00 (7H, m, 3 x C$\underline{H}_2$Ph, H-1), 7.15-7.70 (20H, m, aromatic). IR (film) $\bar{\upsilon}_{max}$ 2970, 2910, 2850, 1465, 1375 and 850 cm^{-1}.

3,4,6-Tri-O-benzyl-1,2-dideoxy-D-arabinopyranoside (107).

A solution of the starting material (104) (0.0137 g, 0.002 mmol) in dry benzene (0.12 mL) was treated with tributyltin hydride (13 µL, 0.003 mmol, 67% purity) and AIBN (5mol%, 0.0002 g) at room temperature under argon. The resulting pale yellow coloured solution was photolysed with a 300W tungsten lamp for 5.5 hours under argon until t. l. c. (ether : petroleum, 1 : 2) showed almost complete loss of starting material. The solvent was removed under reduced pressure. Thin layer preparative chromatography (ether : petroleum, 1 : 2) gave the product as a colourless oil in 74% yield (0.0043 g) based on recovered starting material. δ (400 MHz) 1.74-1.77 (1H, m, H-2eq), 2.07-2.12 (1H, m, H-2ax), 3.32-3.42 (2H, m, H-1ax, H-3), 3.50 (1H, t, J = 8.82 Hz, H-4), 3.62-3.73 (3H, m, H-5, 2xH-6)), 4.00-4.03 (1H, ddd, J = 11.67, 4.85 and 3.24 Hz, H-1eq), 4.5-4.92 (6H, m, 3 x OC$\underline{H}_2$Ph), 7.15-7.4 (15H, m, aromatic).

3,4,6-Tri-O-benzyl-1,2-dideoxy-1-α-deuterio-D-arabinopyranoside (108).

The reaction was carried out on the same scale as above but this time tributyltin deuteride (9 µL, 0.003 mmol) was added. The reaction mixture was photolysed for a total of 11 hours and 15 minutes. Work-up as before followed by thin layer preparative chromatography gave the title compound as a colourless oil in 48% yield (0.0083 g). δ (400 MHz) : the signal for H-1ax at δ 3.35 disappeared completely and the multiplets for H-2eq and H-2ax had simplified.

Se-Phenyl 4,6-*O*-Benzylidene-1,2-dideoxy-1-seleno-β-D-ribopyranoside (105).

To a solution of the chlorides (102) (0.03 mmol) in dry THF (1.00 mL) at room temperature under argon, a solution of sodium phenylselenate (0.3 mL, 1.2M, 0.05 mmol), was added. The resulting orange/brown solution was stirred at room temperature for 25 minutes until there was no change in t. l. c (ether : hexanes, 1 : 2). Thin layer preparative chromatography (ether : hexanes, 1 : 2) gave the title compound as a colourless glass (0.021 g), 17% yield. δ (400 MHz) 2.4 (2H, m, H-2ax, H-2eq), 3.79 (2H, m, H-6ax, H-6eq), 4.14 (1H, ddd, J = 9.50, 9.48 and 5.30 Hz, H-5), 4.36 (1H, dd, J = 10.56 and 5.23 Hz, H-4), 4.51 (1H, bd, J = 2.94 Hz, H-3), 5.60 (2H, m, PhCHO, H-1ax), 7.23-7.89 (10H, m, aromatic). ^{13}C δ (75 MHz) 15.20, 40.55,57.04, 65.79, 67.60, 68.78, 75.01, 77.73, 101.87, 126.22, 128.17, 128.09, 128.30, 129.21, 134.51. IR (film) $\tilde{\upsilon}_{max}$ 3500, 2911, 2855, 1455, 1370 and 820 cm^{-1}.

4,6-*O*-Benzylidene-1,2-dideoxy-1-D-ribopyranose (109).

To a colourless solution of the starting material (105) (0.0047 g, 0.001 mmol) in dry benzene (0.12 mL) under argon, tributyltin hydride (5 μL, 0.002 mmol) was added together with a small amount of AIBN (5mol%). The reaction mixture was photolysed for a total of 8 hours until all starting material was consumed as indicated by t. l. c. (ether : hexanes, 1 :1). The solvent was evaporated under reduced pressure. Thin layer preparative chromatography (ether : hexanes, 1 : 1) gave the title product as a colourless oil in 46% yield (0.0013 g). δ (400 MHz) (C$_6$D$_6$) 1.65 (1H, m, H-2ax), 2.1 (1H, m, H-2eq), 3.18 (1H, dd, J = 9.08 and 3.15 Hz, H-4), 3.31 (1H, m, H-1eq), 3.47 (1H, t, J = 10.19 Hz, H-6ax), 3.72 (1H, ddd, J = 12.00, 11.96 and 2.26 Hz, H-1ax), 3.98 (1H, m, H-5), 4.11 (1H, dd, J = 3.11 and 2.10 Hz, H-3), 4.21 (1H, dd, J = 10.25 and 5.15 Hz, H-6eq), 5.35 (1H, s, PhCHO), 6.85-7.7 (5H, m, aromatic).

4,6-O-Benzylidene-1,2-dideoxy-1-α/β-deuterio-D-ribopyranoside (110).

To a solution of starting material (105) (0.0030 g, 0.0008 mmol) in dry benzene (0.08 mL) under argon at room temperature, tributyltin deuteride (3 µL, 0.001 mmol) was added together with a small amount of AIBN (5mol%). The reaction mixture was photolysed for a total of 15 hours and 35 minutes until there was no change in t. l. c. (ether : hexanes, 1 : 1). Work-up as before followed by thin layer preparative chromatography (ether : hexanes, 1 : 1) gave the product in 66% yield (0.0012 g). δ (400 MHz) (C_6D_6) the ratio of axial : equatorial quenching (found from integration of the appropriate protons) was greater than 10 : 1.

O-(cis-4-Phenylcyclohexyl) S-Methyl Dithiocarbonate (118).

cis-4-Phenylcyclohexanol (57 mg, 0.32 mmol) was dissolved in THF (0.6 mL) under an argon atmosphere and treated with sodium hydride (80%, 14 mg, 0.48 mmol). When the evolution of gas was complete carbon disulfide (0.1 mL, 1.6 mmol) was added and the reaction mixture stirred at room temperature for 30 minutes. Methyl iodide (0.2 mL, 3.2 mmol) was then added and the reaction mixture heated to reflux for 40 minutes before cooling to room temperature and addition of water (5 mL). The reaction mixture was extracted with ether (3 x 15 mL), and the extracts dried ($MgSO_4$), concentrated and purified by thin layer preparative chromatography (SiO_2, petroleum : ether, 50 : 1) to give the xanthate (118) (60 mg, 92%) as a pale yellow solid with m.pt. (44-46) °C. δ (300 MHz) 1.7-1.9 (6H, m), 2.5 (2H, m), 2.59 (3H, s), 2.61 (1H, m), 5.90 (1H, m), 7.1-7.35 (5H, m); ^{13}C δ (75 MHz) 18.74, 28.67, 29.84, 43.22, 78.99, 126.15, 126.75, 128.43, 146.75, 214.79; IR (film) $\bar{v}_{max}$ 3132, 2970, 1724, 1424, 1238, 1215, 1094, 1042 cm^{-1}. Anal. $C_{14}H_{18}OS_2$ requires: C, 63.12; H, 6.81; O, 6.01; S, 24.06%. Found: C, 62.87; H, 7.00%.

O-(trans-4-Phenylcyclohexyl) S-Methyl Dithiocarbonate (119).

trans-4-Phenylcyclohexanol was converted to the xanthate (119) as described for the cis-isomer in 99% isolated yield. The xanthate (118) was a pale yellow solid with m.pt. (108-109) °C. δ (300 MHz) 1.6–1.75 (4 H, m), 2.00 (2H, m), 2.32(2H, m), 2.56 (4H, m, SC$\underline{H}_3$, H-4), 5.60 (1H, m), 7.1-7.35 (5H, m); ^{13}C δ (75MHz) 18.87, 31.37, 32.09, 43.28, 82.70, 126.28, 128.47, 145.94; IR (film) $\bar{\upsilon}_{max}$ 3130, 1645, 1226, 1042, 997 cm^{-1}. Anal. C$_{14}$H$_{18}$OS$_2$ requires: C, 63.12; H, 6.81%. Found: C, 62.87; H, 7.00%.

cis-5-Hydroxy-2-phenyl-1,3-dioxane (123).

To a mixture of glycerol (55.07 g, 0.60 mmol) and benzaldehyde (50.0 g, 0.47 mmol) in toluene (69 mL) was added concentrated sulfuric acid (3 drops) and the resulting mixture heated to reflux in a Dean-Stark water separator under nitrogen. When the separation of water was complete (7.3 mL, 86%) the reaction mixture was allowed to cool to room temperature and the solvent removed under reduced pressure to give a white solid which was recrystallized from ether/petroleum ether. Repeated recrystallization from the same solvent gave the pure cis-alcohol (47.7 g, 56%) with m.pt. (62-63.5) °C, lit.^{53} m.pt.(62.5-63) °C. δ (300MHz) 3.20 (1H, bs), 3.60 (1H, m), 4.15 (4H, m), 5.55 (1H, s), 7.37 (3H, m), 7.48 (2H, m).

2-Phenyl-1,3-dioxan-5-one (125).

To a solution of oxalyl chloride (0.20 mL, 2.3 mmol) in CH$_2$Cl$_2$ (10 mL) under an argon atmosphere at -78 °C DMSO (0.35 mL, 4.9 mmol) was added slowly. After 5 minutes a solution of the alcohol (123) (0.37 g, 2.1 mmol) in CH$_2$Cl$_2$ (5.0 mL) was added. After consumption of (123) (t. l. c. control) triethylamine (1.0 mL, 7.1 mmol) was added. The yellow reaction mixture was then allowed to warm to room temperature before it was

quenched with water (5 mL) and diluted with ether (30 mL). The organic layer was repeatedly washed with water, dried (MgSO₄), filtered and concentrated to give the ketone (125) (0.355 g, 97%) as an oil that solidified to a white solid on standing at -18 °C under argon. It had m.pt. (67-68) °C, lit[54] m.pt. (68-69) °C. δ (300 MHz) 4.50 (4H, m), 5.90 (1H, s), 7.40 (3H, m), 7.50 (2H, m).

trans-5-Hydroxy-2-phenyl-1,3-dioxane (124).

To a solution of the ketone (125) (0.91 g, 5.1 mmol) in methanol (30 mL) at 0 °C sodium borohydride (0.965 g, 26 mmol) was added portionwise and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with ether (70 mL) and the organic phase washed with water (3 x 25 mL), dried (MgSO₄), filtered and evaporated to yield the alcohol (124) (0.352 g, 38%), as a 1 : 10, cis : trans mixture with (113), with m.pt.(64-65) °C, lit[53] m.pt.(63-64) °C. δ (300MHz) 3.55 (2H, m), 3.85 (1H, m), 4.25 (2H, m), 5.40 (1H, s), 7.35 (3H, m), 7.45 (2H, m).

O-(cis-2-Phenyl-1,3-dioxan-5-yl) S-Methyl Dithiocarbonate (120).

The xanthate (120) was prepared from the alcohol (123) in 91% yield as described for the preparation of (118) above. It was a pale yellow solid with m.pt. 94 °C. δ (300 MHz) 2.61 (3H, s), 4.24 (2H, m), 4.48(2H, m), 5.54 (1H, m), 5.59 (1H, s), 7.38 (3H, m), 7.50 (2H, m); ^{13}C δ (75 MHz) 18.71, 68.65, 74.00, 101.40, 126.15, 128.38, 129.19, 138.00, 215.10; IR (film) $\bar{\upsilon}_{max}$ 3136, 2250, 1645, 1451, 1388, 1240, 1219, 1135, 1103, 1050, 1008 cm⁻¹. Anal. for $C_{12}H_{14}O_3S_2$ requires: C, 53.31; H, 5.22; S, 23.72%. Found: C, 53.52; H, 5.29; S, 23.89%.

O-(trans-2-Phenyl-1,3-dioxan-5-yl) S-Methyl Dithiocarbonate (121).

The xanthate (121) was prepared from the alcohol (124) but in only 11% yield as described for the preparation of (118) above. It was a pale yellow solid with m.pt. 74 °C. δ (300MHz) 2.58 (3H, s), 3.84 (3H, m), 4.55 (2H, m), 5.51 (1H, s), 5.80 (1H, m), 7.38 (3H, m), 7.50(2H, m); ^{13}C δ (75 MHz) 19.48, 67.70, 70.29, 101.44, 126.15, 128.38, 129.19, 137.10, 215.10; IR (film) $\bar{\upsilon}_{max}$ 3125, 2450, 1645, 1456, 1377, 1271, 1192, 1150, 1066 cm^{-1}.

Partial Reduction of a Mixture of (118) and (119) with Tributyltin Hydride.

To an equimolar solution of xanthates (118) and (119) (23.7 mg, 0. 089 mmol) in toluene (24 mL), containing DMAP (2.9 mg) as a convenient internal standard, at reflux under argon was added tributyltin hydride (0.2M, 0.12 mL, 0.023 mmol) in toluene containing 5 mol% AIBN was added over a period of 2 minutes. The reaction mixture was maintained at reflux for 35 minutes and then cooled to room temperature. The solvent was removed under reduced pressure and the residue taken up in deuteriochloroform and analysed by ^{1}H nmr at 300 MHz. The ratio of residual 118 : 119 was 1 : 1.8 for a total conversion of 9.3%.

Partial Reduction of a Mixture of (120) and (121) with Tributyltin Hydride: Isolation of 2-Phenyl-1,3-dioxane.

To an equimolar solution of xanthates (120) and (121) (20.8 mg, 0. 077 mmol) in toluene (0.21 mL), containing DMAP (2.4 mg) as a convenient internal standard, at reflux under argon was added an 0.2M solution of tributyltin hydride containing AIBN (5 mol%) in toluene (0.1 mL, 0.025 mmol). After heating to reflux for 35 minutes the reaction mixture was cooled to room temperature and the solvent removed in vacuo. The crude

reaction mixture was examined by ^{1}H nmr spectroscopy at 300 MHz. At 71% conversion the ratio of residual 120 : 121 was 1 : 2. A sample of 2-phenyl-1,3-dioxane could be isolated by thin layer preparative chromatography (SiO$_2$, ether : petroleum, 3 : 1). It had m.pt. (49-51) °C, lit.[88] m.pt.(49-51) °C. δ (300 MHz) 1.45 (1H, m), 2.25 (1H, m), 3.98 (1H, m), 4.28 (2 H, m), 5.51 (1 H, s), 7.28-7.52 (5 H, m).

Partial Reduction of a Mixture of (119) and (120) with Tributyltin Hydride.

To a mixture of (119) (8.8 mg, 0.039 mmol) and (120) (10.5 mg, 0.039 mmol) and DMAP (10 mg) in toluene (0.21 mL) at reflux under argon was added an 0.2M solution of tributyltin hydride containing AIBN (5 mol%) in toluene (0.1 mL, 0.025 mmol). After a further 30 minutes at reflux the reaction mixture was cooled to room temperature and the solvent removed in vacuo. The crude reaction mixture was examined by ^{1}H nmr spectroscopy at 300 MHz. At 50% conversion the ratio of residual 119 : 120 was 2.2 : 1.

Partial Reduction of a Mixture of (119) and (121) with Tributyltin Hydride.

To a mixture of (119) (8.8 mg, 0.039 mmol) and (120) (10.5 mg, 0.039 mmol) and DMAP (15 mg) in toluene (0.21 mL) at reflux under argon was added an 0.2M solution of tributyltin hydride containing AIBN (5 mol%) in toluene (0.1 mL, 0.025 mmol). After a further 30 minutes at reflux the reaction mixture was cooled to room temperature and the solvent removed in vacuo. The crude reaction mixture was examined by ^{1}H nmr spectroscopy at 300 MHz. At 15% conversion the ratio of residual 119 : 121 was 1 : 0.92.

Partial Reduction of a Mixture of (118) and (120) with Tributyltin Hydride.

To a solution of (118) (11 mg, 0.049 mmol) and (120) (13.2 mg, 0.049 mmol) at reflux under argon in toluene (0.26 mL) containing DMAP (3.7 mg) was added a solution of tributyltin hydride (0.2M, 0.13 mL, 0.025 mmol) in toluene containing AIBN (5mol%) over 2.5 minutes. After a further 30 minutes at reflux the reaction mixture was cooled to room temperature, the solvent removed under reduced pressure and the ratio of 118 : 120 determined to be 1 : 2 for 66% overall conversion.

4,6-Di-O-benzyl-2-O-(4-O-tolylthiocarbonyl)-*myo*-inositol-1,3,5-orthoformate (129).

The *myo*-inositol orthoformate (127) (176 mg, 0.48 mmol) was dissolved in pyridine (3 mL) and treated with DMAP (73 mg, 0.59 mmol) and 4-O-tolyl chlorothioformate (210 mg, 1.13 mmol) and then stirred at room temperature for 48 hours. The reaction mixture was then diluted with ether (50 mL) and washed sequentially with 2M HCl (2 x 50 mL), water (50 mL) and brine (50 mL), then dried (MgSO$_4$) and evaporated to dryness under vacuum to give a pale green solid from which the thiocarbonate (119) (122 mg, 49%) was obtained, by crystallization from hot ether, as needles with m.pt. (150-1) °C. δ (300 MHz) 2.37 (3H, s), 4.45 (2H, t, J = 3.91 Hz), 4.53 (1H, m), 4.66 (4H, ABquartet), 4.69 (2H, m), 5.60 (1H, d, J = 1.39 Hz), 5.89 (1H, m), 7.05 (2H, d, J = 9.0 Hz), 7.23 (2H, d, J = 9.0 Hz), 7.27 (10H, bs); ^{13}C δ (75 MHz) 20.99, 68.31, 69.68, 71.57, 72.98, 73.59, 103.18, 120.69, 121.50, 127.91, 128.44, 130.04, 136.48, 137.24, 151.28, 194.70. Anal. C$_{29}$H$_{28}$O$_7$S requires: C, 66.91; H, 5.42% Found: C, 66.69; H, 5.13%.

4,6-Di-O-benzyl-2-O-(4-O-tolylthiocarbonyl)-*scyllo*-inositol-1,3,5-orthoformate (130).

The alcohol (128) (200 mg, 0.54 mmol) was treated in pyridine (1 mL) with 4-O-tolyl chlorothioformate (140 mg, 0.75 mmol) and then stirred at room temperature for 72 hours. The reaction mixture was then diluted with ether (50 mL) and washed sequentially with 2M HCl (2 x 50 mL), water (50 mL) and brine (50 mL), then dried (MgSO$_4$) and evaporated to dryness under vacuum to give a pale green solid from which the thiocarbonate (129) (126 mg, 45%) was obtained, by crystallization from hot ether, as rhombs with m.pt. (121-2) °C. δ (300 MHz) 2.35 (3H, s), 4.42 (2H, m), 4.64 (1H, m), 4.68 (bs, 4 H), 4.88 (2H, m), 5.59 (1H, s), 5.82 (1H, m), 6.64 (2H, d, J = 8.0 Hz), 7.08 (2H, d, J = 8.0 Hz), 7.22 (6H, m), 7.38 (4H, m); ^{13}C δ (75 MHz) 22.19, 66.89, 68.49, 71.32, 72.16, 73.77, 103.13, 121.43, 127.56, 128.26, 129.94, 130.18, 136.58, 137.69, 151.50, 190.90. Anal. C$_{29}$H$_{28}$O$_7$S requires: C, 66.91; H, 5.42% . Found: C, 67.03; H, 5.37.%

Partial Reduction of a Mixture of (129) and (130) with Tributyltin Hydride: Isolation of (131).

To a solution of a 1:1 mixture of (129) and (130) (18.4 mg, 0.035 mmol) in toluene (0.18 mL) containing DMAP (6.8 mg) at reflux under argon was added tributyltin hydride (0.2M, 0.1 mL, 0.019 mmol) in toluene containing AIBN (5 mol%) over 2.5 minutes. After heating to reflux for a further 30 minutes the reaction mixture was cooled to room temperature and the solvent removed under vacuum. The ratio of residual 129 : 130 was determined to be 1 : 1.8 by ^{1}H nmr at 300MHz for a total conversion of 62%. A sample of the reduction product, 2,4-di-O-benzyl-scylloquercitol 1,3,5-orthoformate, (131) was isolated by thin layer preparative chromatography (SiO$_2$, ether : petroleum , 2 : 3). It had m.pt. (113-114.5) °C. δ (300 MHz) 2.38 (2H, m), 4.21 (4H, m), 4.50 (1H, m), 4.58 (2H, d, ^{2}J = 11.4 Hz, C$\underline{H}_2$Ph), 4.69 (2H, d, ^{2}J = 11.4 Hz, C$\underline{H}_2$Ph), 5.54 (1H, s), 7.3-

7.4 (10H, m); ^{13}C δ (75 MHz) 23.17, 68.20, 68.52, 71.44, 72.51, 103.74, 127.66, 127.78, 128.41.

(±)-2,4-Di-O-benzoyl-*myo*-inositol-1,3,5-orthoformate (132).

myo-inositol-1,3,5-orthoformate (190 mg, 1.0 mmol) was dissolved in pyridine (1.0 mL) and treated dropwise at room temperature with benzoyl chloride (308 mg, 2.2 mmol). After stirring at room temperature for 1 hour the reaction mixture was diluted with ether (10 mL) and then water (4 mL). The aqueous layer was further extracted with ether (2 x 10 mL) and the combined organic phases dried (MgSO$_4$) and concentrated under vacuum. Column chromatography (SiO$_2$, EtOAc : hexanes, 1 : 9) gave a colourless oil (358 mg, 90%) which solidified on standing. White crystals, obtained from hexane/ether, had m.pt. (173-4) °C. δ (300 MHz) 2.70 (1H, m, O<u>H</u>), 4.50 (1H, m, H-3), 4.62 (2H, m, H-1, H-5), 4.74 (1H, m, H-6), 5.66 (2H, m , H-2, H-7), 5.84 (1 H, dt, ^4J = 1.7, ^3J = 3.9 Hz, H-4), 7.44-7.50 (4H, m), 7.57-7.63 (2H, m), 8.07 (2H, m), 8.16 (2 H, m); ^{13}C δ (75 MHz) 63.74, 67.46, 68.51, 68.58, 69.67, 71.83, 102.98, 128.53(2 C), 128.71(2 C), 128.89, 129.43, 129.91, 129.98, 133.56 (2 C), 133.78(2 C), 166.21; IR (film) $\bar{v}_{max}$ 3496, 3072, 2968, 2902, 1724, 1602 cm^{-1}. Anal. C$_{21}$H$_{18}$O$_8$ requires: C, 63.3a; H, 4.55% Found: C, 63.30; H, 4.53%.

(±)-2,4-Di-O-benzoyl-6-O-(1-imidazolylthiocarbonyl)-*myo*-inositol-1,3,5-orthoformate (133).

The alcohol (132) (3.98 g, 10 mmol) in 1,2-dichloroethane (80 mL) under an argon atmosphere was treated with 1,1-thiocarbonyl diimidazole (2.97 g of 90%, 15 mmol) and the reaction mixture heated to reflux for 10 hours before cooling to room temperature and quenching with water (50 mL). The aqueous phase was extracted with dichloromethane (2 x 50 mL) and the combined organic phases dried (MgSO$_4$) and concentrated under vacuum. Column chromatography (SiO$_2$, EtOAc : hexanes, 1 : 1) gave (133) (4.06 g,

80%) as a white crystalline solid with m.pt. (156-157) °C. δ(300 MHz) 4.69-4.75 (2H,

m, H-1, H-5), 5.20 (1H, m, H-3), 5.61 (1H, q, ^4J = 1.6 Hz, H-7), 5.77 (1H, m, H-2),

5.89 (1H, dt, ^4J = 1.6, ^3J = 3.9 Hz, H-4), 6.17 (1H, dt, ^4J = 1.6, ^3J = 3.9 Hz, H-6),

6.87 (1H, dd, J = 0.8, 1.7 Hz), 7.28 (2H, tt, J = 1.7, 7.8 Hz), 7.44 (1H, dd, J = 0.8

Hz), 7.49 (2H, tt, J = 1.7, 7.8 Hz), 7.51 (2H, tt, J = 1.4, 7.4 Hz), 7.62 (1 H, dt, J =

1.4, 7.4 Hz), 7.75 (2 H, dt, J = 1.3, 7.9 Hz), 8.17 (2H, dt, J = 1.4, 7.7 Hz), 8.22 (1H,

t, J = 0.8 Hz); ^{13}C δ (75 MHz) 63.50, 65.76, 67.89, 68.62, 69.15, 74.51, 103.24,

117.47, 128.03, 128.60, 128.65, 128.98, 129.32, 129.97, 131.26, 133.79, 134.02,

137.25, 164.95, 166.14, 181.58; IR (film) $\tilde{v}_{max}$ 3132, 2966, 1723, 1602, 1452, 1396,

1287, 1263, 1164 cm^{-1}. Anal. $C_{25}H_{20}N_2O_8S$ requires : C, 59.05; H, 3.96%; N,

5.51%. Found: C, 58.95; H, 3.89; N, 5.49%.

(±)-6-Deoxy-2,4-di-O-benzoyl-*myo*-inositol-1,3,5-orthoformate (134).

Tri-n-butyltin hydride (2.14 g, 7.4 mmol) and AIBN (52 mg) in toluene (40 mL) were

added dropwise over 40 min to a solution of (133) (3.40 g, 6.69 mmol) in toluene (100

mL) at reflux under argon. After a further 1 hour at reflux the reaction mixture was

allowed to cool to room temperature, the solvent removed under vacuum, and the deoxy-

inositol derivative (132) isolated (2.00 g, 78%) by chromatography on silica gel (EtOAc :

hexanes, 1 : 4). It was a white crystalline solid with m.pt. (190-1) °C. δ (300 MHz)

2.15 (1H, d, ^2J = 13.9 Hz, H-6ax.), 2.82 (1H, d, ^2J = 13.9 Hz, H-6eq.), 4.47-4.52

(2H, m, H-1, H-5), 4.63 (1H, dt, ^4J = 1.8, ^3J = 3.7 Hz, H-3), 5.30 (1H, t, J = 1.3Hz,

H-2), 5.70 (1H, bs, H-7), 5.83 (1H, dt, ^4J = 1.6, ^3J = 4.2 Hz, H-4), 7.46 (2H, tt, J =

1.4, 7.8 Hz,), 7.58 (1H, tt, J = 1.2, 7.4 Hz), 7.62 (1H, tt, J = 1.2, 7.4 Hz), 8.04 (2H,

dt, J = 0.7), 8.15 (1H, dt, J = 0.7, 7.9 Hz); ^{13}C δ (75 MHz) 27.92, 66.78, 67.05,

67.69, 67.96, 69.86, 104.09, 128.50(2 C), 128.65, 128.73(2 C), 129.40, 129.79(2 C),

129.97(2 C), 133.52, 133.08, 164.95, 166.23; IR (film) $\tilde{v}_{max}$ 3061, 2974, 1727, 1601,

1584, 1492, 1452, 1370, 1346 cm^{-1}; HRMS (EI, 70eV) calcd. for $C_{21}H_{18}O_7$ 382.1053,

found: 382.1047 (M$^+$).

Chapter 5

(±)-6-Deoxy-*myo*-inositol-1,3,5-orthoformate (135).

The dibenzoate (134) (200 mg, 0.52 mmol) was dissolved in THF (5 mL) and ethanol (1 mL) and treated with 10% aqueous sodium hydride (2 mL) and vigourously stirred at room temperature for 1 hour. The solvents were then removed under vacuum and the residue dissolved in methanol, filtered, evaporated and purified by column chromatography (SiO$_2$, EtOAc) to give the orthoester (135) (78 mg, 86%) as a white crystalline solid with m.pt. (250-251) ^{o}C. δ (300 MHz) (CD$_3$COCD$_3$) 2.01 (1H, bd, ^2J = 13.5 Hz, H-6ax.), 2.45 (1H, dm, ^2J = 13.5 Hz, H-6eq), 3.61 (1H, m, H-2), 4.01 (3 H, m, H-1, H-3, H-5), 4.41 (1H, m, H-4), 5.36 (1H, bs, H-7); ^{13}C δ (75 MHz) (CD$_3$OD) 27.15, 64.08, 65.97, 69.60, 71.53, 75.17, 104.29; IR (film) $\bar{\upsilon}_{max}$ 3504, 2950, 2930, 2856, 1469, 1256 1162 cm^{-1}. Anal. C$_7$H$_{10}$O$_5$ requires : C, 48.28; H, 5.79%. Found: C, 48.27; H, 5.71%.

(±)-6-Deoxy-2,4-di-O-(S-methyl dithiocarbonyl)-*myo*-inositol-1,3,5-orthoformate (136).

The diol (136) (52 mg, 0.3 mmol) was dissolved in THF (5 mL) and treated under argon at room temperature with sodium hydride (36 mg of 80%, 1.2 mmol). After stirring for 5 minutes carbon disulfide (0.12 mL, 2 mmol) was added and stirring continued for a further 30 minutes before methyl iodide (0.125 mL, 2 mmol) was added. After stirring for 30 more minutes at room temperature water (5 mL) was added and the reaction mixture extracted with benzene (2 x 30 mL). The extracts were dried (Na$_2$SO$_4$), concentrated and purified by column chromatography (SiO$_2$, EtOAc : hexanes, 1 : 9) to give the dixanthate ester (136) (80 mg, 75%) as a colourless oil which could be crystallized from ether. The crystals had m.pt. (114-116) ^{o}C. δ (300 MHz) 2.04 (1H, d, ^2J = 14.1 Hz, H-6ax.), 2.60 (3 H, s), 2.62 (3 H, s), 2.79 (1H, dm, ^2J = 14.1 Hz, H-6eq), 4.51 (2H, m, H-1, H-5), 4.73 (1H, m, H-3), 5.64 1H,bs, H-7), 5.74 (1H, m, H-2), 6.28 (1H, m, H-4); ^{13}C δ (75 MHz) 19.19, 19.58, 27.94, 66.12, 67.37, 68.62,

74.10, 74.25, 103.68, 214.02, 215.47; IR (film) $\bar{\upsilon}_{max}$ 2963, 2923, 2856, 1424, 1283, 1199, 1161, 1082 cm^{-1}. Anal. $C_{11}H_{14}O_5S_4$ requires : C, 37.27; H, 3.98%. Found: C, 37.46; H, 4.09%.

Partial Reduction of (136) with Tributyltin Hydride: Isolation of (137) and (138).

To a stirred solution of the bisxanthate (136) (100 mg, 0.28 mmol) in toluene at reflux under argon was added a solution of tri-n-butyltin hydride (81 mg, 0.28 mmol) and AIBN (2.5 mg) in toluene (0.5 mmol). The reaction mixture was heated to reflux for a further 1 hour before cooling to room temperature, removal of the solvent under vacuum and chromatograhy on silica gel. Elution with EtOAc : hexanes, 1 : 3 gave first the 2,4,6-trideoxy-2-thio-2-(S-methylthiocarbonyl)-*scyllo*-inositol-1,3,5-orthoformate (138) (32 mg, 47%) with m.pt. (125-128)^{o}C (ether/hexanes). δ (300 MHz) 1.84 (2H, d, ^2J = 13.9 Hz, H-4ax, H-6eq.), 2.46 (3H, s), 2.61 (2H, dm, ^2J = 13.9 Hz, H-4eq, H-6eq.), 4.25 (1H, m, H-5), 4.29 (2 H, m, H-1, H-3), 4.70 (1H, m, H-2), 5.65 (1H, bs, H-7); ^{13}C δ (75 MHz) 17.52, 29.65(2 C), 43.94, 66.08, 69.43(2 C), 104.83, 186.85; IR υ_{max} (film) 2959, 2929, 2855, 1718, 1648, 1443, 1379, 1306, 1207, 1163, 1113 cm^{-1}; HRMS (EI, 70eV) calcd. for $C_9H_{12}O_4S_2$ 248.0177, found: 248.0172 (M$^+$, 2.6%). Further elution with the same solvent gave the 4,6-dideoxy-2-(S-methyldithiocarbonyl)-*myo*-inositol-1,3,5-orthoformate (137) (22 mg, 32%) with m.pt. (116-8) ^{o}C (ether/hexanes). δ (300 MHz) 1.82 (2H, bd, ^2J = 13.5 Hz, H-4ax,H-6ax.), 2.62 (3H, s), 2.86 (2H, dm, ^2J = 13.5 Hz, H-4eq, H-6eq.), 4.37 (1H, m, H-5), 4.53(2H, m, H-1, H-3), 5.60 (1H, dt, ^4J = 1.1, 1.3 Hz), 5.66 (1H, bs, H-2); ^{13}C δ (300 MHz) 19.11, 32.53(2 C), 65.70, 68.62(2 C), 77.67, 105.02, 215.80; IR (film) $\bar{\upsilon}_{max}$ 2962, 2927, 1221, 1165, 1070, 981, 912, 817 cm^{-1}. Anal. $C_9H_{12}O_4S_2$ requires : C, 43.53; H, 4.87; S, 25.83%. Found: C, 43.73; H, 4.74; S, 25.94%.

Partial Reduction of (136) with Tris(trimethylsilyl)silane.

The bis xanthate (136) (18 mg, 0.05 mmol) was heated to reflux under argon in toluene (2 mL) and treated dropwise with a solution of tris(trimethylsilyl)silane (13.5 mg, 0.055 mmol) over 10 minutes. After a further 2 hour at reflux the solvent was removed at reduced pressure and the ratio of (137) and (138) determined by ^{1}H nmr spectroscopy of the crude reaction mixture in CDCl$_3$ (1 : 1.4).

4,6-O-Benzylidene-α/β-altropyranoside (158).

The starting material (94) (0.150 g, 0.64 mmol) was dissolved in THF (0.76 mL) and t-butyl alcohol (1.02 mL) and treated with pyridine (2 drops) and water (0.34 mL). NMO (0.142 g, 1.41 mmol) was added followed by osmium tetraoxide (1 crystal). The resulting browm coloured reaction mixture was refluxed for a total of 10 hours until t. l. c. (ether : hexanes , 9 : 1), showed complete loss of starting material. After cooling to room temperature, the reaction mixture was treated with sodium metabisulphite solution (20%, 2.5 ml), and stirred at room temperature for 30 minutes. The bulk of t-butyl alcohol and THF were removed under reduced pressure. After dilution with aqueous sodium chloride, the reaction mixture was repeatedly extracted with hot ether, hot ethyl acetate and finally with methyl ethyl ketone. The combined extracts were washed with brine, dried (MgSO$_4$) and concentrated under reduced pressure. Thin layer preparative chromatography (ether : petroleum, 9 : 1) gave the title compound as a white foam as a mixture of two anomers in a ratio of 4 : 1 (0.56 g, 41%). The major had δ (300 MHz) 2.10 (3H, s, CH$_3$), 2.18 (3H, s, CH$_3$), 2.21 (1H, s, CH$_3$), 3.72 (1H, t, J = 8.7 Hz, H-6ax), 4.04 (2H, m, H-5, H-6eq), 4.37 (1H, dd, J = 11.6 and 5.8 Hz, H-4), 5.14 (1H, dd, J = 5.8 and 1.45 Hz, H-3), 5.36 (1H, t, J = 1.45 Hz, H-2), 5.51 (1H, s , OCH$_2$Ph), 6.01 (1H, d, J = 1.45 Hz, H-1), 7.35-7.5 (5H, m, aromatic). The minor anomer had δ (300MHz) 4.83 (1H, d J = 4.76 Hz), 5.25 (1H, t, J = 1.56 Hz), 5.61 (1H, s , OCH$_2$Ph), 5.83 (1H, s, H-1).

3-*O*-Benzyl-4,6-*O*-Benzylidene-α/β-altropyranoside (166).

The starting material (95) (0.090 g, 0.28 mmol) was dissolved in THF (0.34 mL) and t-butyl alcohol (0.44 mL) and treated with pyridine (1 drop) and water (0.17 mL). N-methylmorpholine N-oxide (0.060 g, 0.58 mmol) was added followed by osmium tetraoxide (1 crystal). The resulting brown coloured reaction mixture was refluxed for a total of 15 hours until all the starting material was consumed as indicated by t. l. c. (petroleum : ether, 4 : 1). After cooling to room temperature, the reaction mixture was treated with sodium metabisulphite solution (20%, 1.01 mL) and the mixture was stirred at room temperature for 5 minutes before the bulk of t-butyl alcohol and THF were removed under reduced pressure. After dilution with aqueous sodium chloride the reaction mixture was repeatedly extracted first with ether then with methanol. The combined extracts were washed with brine, dried (MgSO$_4$) and concentrated under reduced pressure. Thin layer preparative chromatography (ether : petroleum 1 : 4) gave a white foam (0.036 g, 36%). δ (300 MHz): 3.7 (1H, t, J = 12 Hz, H-6ax), 4.26 (2H, m, H-3, H-4), 4.25 (1H, m, H-5), 4.38 (1H, dd, J = 12 and 8.9 Hz, H-6eq), 4.82 (2H, AB quartet, OCH$_2$Ph), 5.25 (1H, dd, J = 1.57 and 3.79 Hz, H-2), 5.58 (1H, s, PhCHO), 6.19 (1H, d, J = 1.58Hz, H-1), 7.16-59 (10H, m, aromatic).

D-Altrose by Hydrogenolysis of Dihydroxylation Products (HPLC Analysis):

(i) From (158)

To a solution of the starting material (158) (11.0 mg, 0.004 mmol) in ethanol (0.11 ml), Pd(OH)$_2$ (5 mol%, 20%, 0.0002 g, 0.002 mmol) was added. The reaction mixture was stirred at room temperature under an atmosphere of hydrogen until all the starting material was consumed by t. l. c. (ether : petroleum, 2 : 1). The reaction mixture was then filtered under gravity and the filtrate was evaporated under vacuum.

(ii) From (166)

To a solution of the starting material (166) (16.8 mg, 0.005 mmol) in ethanol (0.7 ml),

Pd(OH)$_2$ (5 mol%, 20%, 0.0003 g, 0.0025 mmol) was added. The reaction mixture was

stirred at room temperature under an atmosphere of hydrogen until all the starting material

was consumed by t. l. c. (ether : petroleum, 2 : 1). The reaction mixture was then filtered

under gravity and the filtrate was evaporated under vacuum. ^{1}H nmr spectrum indicated

the presence of possibly two compounds.

HPLC Analysis

HPLC analysis was conducted with an 5μ normal phase 25 cm Spherisorb silica column

eluting with 5% water in acetonitrile with a flow rate of 1.5 mL/min. Altrose had a

retention time of 4.9 min. and allose of 6.9 min. The experimentally derived sample co-

migrated with authentic altrose and was resolved from authentic allose.

Dihydroxylation of (15) with chiral ligands: 3,4,6-Tri-O-Benzyl-α/β-D-

glucopyranoside (42).

Using Dihydroquinidine 4-chlorobenzoate :

The staring material (15) (0.1005 g, 0.24 mmol) was dissolved in THF (0.5 mL) and

treated with pyridine (1drop) and water (0.25 mL). NMO (0.0643 g,0.59 mmol) was

added followed by osmiun tetraoxide (1 crystal) and Dihydroquinidine 4-chlorobenzoate

(5 mole%, 0.0057 g 0.012 mmol) The resulting brown coloured reaction mixture was

refluxed for 30 minutes until all the starting material was consumed by t. l.c. (ether :

petroleum 1 : 1). After cooling to room temperature, work-up and purification gave (42)

in 59% yield. Microacetalytion (1drop of pyridine, 2 drops of acetic anhydride, stir

overnight) was carried out. The spectra of the purified diol and of the diacetalyted sugar were identical to those reported in the literature.[16]

Using Dihydroquinine-4-chlorobenzoate:

The same reaction conditions were used. In this experiment reflux time for complete consumption of starting material was 1 hour. After cooling to room temperature, work-up and purification gave (42) in 71% yield. Spectra of the purified diol and of the diacetylated product were identical to those reported in the literature.[16]

REFERENCES

References

1. a). J. Golik, J. Clardy, G. Dubray, G. Groenewald, H. Kawaguchi, M. Konishi,

    B. H. Ohkuma, K. Saitoh and T. Doyle, *J. Am. Chem. Soc.*, 1987, 109, 3461;

    b). M. Dee, T. S. Dunne, M. M. Siegel, C. C. Chang, G. O. Morton and D. B.

    Borders, *J. Am. Chem. Soc.*, 1987, 109, 3464.

2. I. Kimura, K. Yamamoto, K. Tempaku and M. Suzuki, *Tetrahedron Lett.*, 1987,

    28, 1917, 1921.

3. D. E. Wright, *Tetrahedron*, 1979, 35, 1207.

4. a). M. Trumtel, A. Veyrieres and P. Sinaÿ, *Tetrahedron Lett.*, 1989, 30, 2529;

    b). P. Tavecchia, M. Trumtel, A. Veyrieres and P. Sinaÿ, *ibid*; 1989, 30, 2533.

5. R. Preuss and R. R. Schmidt, *Synthesis*, 1988, 694.

6. K. C. Nicolaou, T. Ladduwahetty, J. L. Randall and A. Chucholowski, *J. Am.

    Chem. Soc.*, 1986, 108, 2466.

7. a). J. Thieme and M. Gerken, *J. Org. Chem.*, 1985, 50, 954;

    b). M. Perez and J. M. Beau, *Tetrahedron Lett.*, 1989, 30, 75;

    c). J. Thiem and S. Köpper, *Topics in Current Chemistry*, 1990, 154, 285.

8. a). Y. Ito and T. Ogawa, *Tetrahedron Lett.*, 1987, 28, 2723;

    b). Y. Ito and T. Ogawa, *Tetrahedron Lett.*, 1988, 29, 3987.

9. G. Grewal, N. Kaila and R. W. Franck, *J. Org. Chem.*, 1992, 57, 2084.

10. a). R. M. Adlington, J. E. Baldwin, A. Basak and R. P. Kozyrod, *J. Chem. Soc.,

    Chem. Commun.*, 1983, 944;

    b). B. Giese and J. Dupuis, *Angew. Chem., Int. Ed. Engl.*, 1983, 22, 622;

    c). idem, *Tetrahedron Lett.*, 1984, 25, 1349.

11. a). H. G. Korth, R. Sustmann, B. Giese and J. Dupuis, *J. Chem. Soc., Perkin

    Trans. 2*, 1986, 615;

    b). K. S. Gröninger, K. F. Jäger and B. Giese, *Liebigs Ann. Chem.*, 1987, 5731;

    c). B. Giese, K. S. Gröninger, T. Witzel, H. G. Groth and R. Sustmann, *Angew.

    Chem., Intl. Edn. Engl.*, 1987, 26, 233;

d). B. Giese, S. Giles, K. S. Gröninger, C. Lamberth and T. Witzel, *Liebigs Ann. Chem.*, 1988, 615;

e). H. G. Korth, R. Sustmann, K. S. Gröninger, M. Leisung and B. Giese, *J. Org. Chem.*, 1988, 53, 4364.

12. a). A. L. J. Beckwith and C. J. Easton, *J. Am. Chem. Soc.*, 1981, 103, 615;

b). K. Hayday and R. D. McKelvey, *J. Org. Chem.*, 1976, 41, 2222;

c). A. L. J. Beckwith and S. Brumby, *J. Chem. Soc., Perkin Trans. 2*, 1987, 1801;

d). V. Malatesta, R. D. McKelvey, B. W. Babcock and K. U. Ingold, *J. Org. Chem.*, 1979, 44, 1872;

e). A. R. Gregory and V. Malesta, *J. Org. Chem.*, 1980, 45, 122.

13. a). D. H. R. Barton, D. Crich and W. B. Motherwell, *Tetrahedron*, 1985, 41, 3901;

b). D. H. R. Barton, D. Crich and G. Kretzschmar, *J. Chem. Soc., Perkin Trans. 1*, 1986, 39;

c). For a comprehensive review see: D. Crich and L. Quintero, *Chem. Rev.*, 1989, 89, 413.

14. D. Crich and T. J. Ritchie, *J. Chem. Soc., Perkin Trans. 1*, 1990, 945.

15. D. Kahne, D. Yang, J. J. Lim, R. Miller and E. Paguaga, *J. Am. Chem. Soc.*, 1988, 110, 8716.

16. a). D. Crich and L. B. L. Lim, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2205;

b). D. Crich and L. B. L. Lim, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2209.

17. F. Baumberger and A. Vasella, *Helv. Chim. Acta,* 1983, 66, 2210.

18. D. Crich and F. Hermann, *Tetrahedron Lett.,* 1993, 34, 3385.

19. D. H. R. Barton, W. Hartwig and W. B. Motherwell, *J. Chem. Soc., Chem. Commun.*, 1982, 447.

20. K. S. Chen and J. K. Kochi, *J. Am. Chem. Soc.*, 1974, 96, 1383.

21   K. W. Krosley, G. J. Gleicher and G. E. Clapp, *J. Org. Chem.*, 1992, 52, 840.

22. B. Giese and R. Sustmann, *J. Chem. Soc., Perkin Trans. 2*, 1986, 1453.

23. a). J. K. Cha, W. J. Christ and Y. Kishi, *Tetrahedron Lett.,* 1983, 24, 3943.

    b). W. J. Christ, J. K. Cha and Y. Kishi, *Tetrahedron Lett.,* 1983, 24, 3947.

24. J. K. Cha, W. J. Christ and Y. Kishi, *Tetrahedron,* 1984, 40, 2247.

25. a). J. S. Brimacombe, R. Hanna, A. K. M. S. Kabir and I. D. Taylor, *J. Chem. Soc., Perkin Trans. 1,* 1986, 815;

    b). J. S. Brimacombe, R. Hanna and A. K. M. S. Kabir, *J. Chem. Soc., Perkin Trans. 1,* 1986, 823;

    c). J. C. Barnes, J. S. Brimacombe and G. McDonald, *J. Chem. Soc., Perkin Trans. 1,* 1989, 1483;

    d). J. S. Brimacombe, and A. K. M. S. Kabir, *Carbohydr. Res.,* 1988, 179, 21.

26. S. G. Hentges and K. B. Sharpless, *J. Chem. Soc.,* 1980, 102, 4263.

27. a). E. N. Jacobsen, I. Markó, W. S. Mungall, G. Schröder and K. B. Sharpless, *J. Am. Chem. Soc.,* 1988, 110, 1968;

    b). E. N. Jacobsen, I. Markó, M. B. France, J. S. Svendsen and K. B. Sharpless, *J. Am.Chem. Soc.,* 1989, 111, 737.

28. M. J. Cleare, P. C. Hydes, W. P. Griffith and M. J. Wright, *J. Chem. Soc., Dalton Trans.,* 1977, 941.

29. S. V. Ley, B. Lygo, F. Sternfeld and A. Wonnacott, *Tetrahedron,* 1986, 42, 4333.

30. D. S. Brown, S. V. Ley and S. Vile, *Tetrahedron Lett.,* 1988, 29, 4873.

31. J. M. Beau and P. Sinaÿ, *Tetrahedron Lett.,* 1985, 26, 6185, 6189 and 6193.

32. P. Magnus, *Tetrahedron,* 1977, 33, 2019.

33 G. Boche, *Angew. Chem., Int. Ed. Engl.,* 1989, 28, 277.

34. K. Luthman, M. Orbe, T. Waglund and A. Claesson, *J. Org. Chem.,* 1987, 52, 3777.

35. A. Amara and P. Sinaÿ, *Carbohydr. Res.,* 1989, 187, 35.

36. H. Hari, T. Nakajima, Y. Nishidi, H. Ohuri and H. Meguro, *Tetrahedron Lett.,* 1988, 29, 6317.

37. N. K. Richmeyer in "Methods in Carbohydrate Chemistry" vol. 1, page 107, R. L. Whistler and M. L. Wolfrom Eds., Academic Press, 1962.

38. R. Lemieux, E. Fraga and K. Watanabe, *Can. J. Chem.*, 1968, 46, 61.

39. N. Tsudu, S. Tokota, T. Kudo and O. Mitsonubu, *Chem. Letts.*, 1983, 289.

40. D. A. Griffith and S. J. Danishefsky, *J. Am. Chem. Soc.*, 1991, 113, 5863.

41. G. E. Keck, E. J. Enholm, J. B. Yates and M. Wiley, *Tetrahedron*, 1985, 41, 4079.

42. S. V. Ley, I. A. O'Neil and C. M. R. Low, *Tetrahedron*, 1986, 42, 5363.

43. B. Giese, *Angew. Chem. Int. Ed. Engl.*, 1989, 28, 969 and references therein.

44. V. R. Bodepudi and W. J. le Noble, *J. Org. Chem.*, 1991, 56, 2001.

45. W. Damm, B. Giese, J. Hartung, T. Hasskerl, K. N. Houk, O. Hutrt and H. Zipse, *J. Am. Chem. Soc.*, 1992, 114, 4067.

46. K. S. Chen and J. K. Kochi, *J. Am. Chem. Soc.*, 1974, 96, 1383.

47. A. S. Cieplak, *J. Am. Chem. Soc.*, 1981, 103, 4540.

48. A. S. Cieplak, B. D. Tait, and C. R. Johnson, *J. Am. Chem. Soc.*, 1987, 109, 5875.

49. a). C. Copeland and R. V. Stick, *Aust. J. Chem.*, 1978, 31, 449;

    b). J. J. Patroni and R. V. Stick, *Aust. J. Chem.*, 1979, 32, 411;

    c). R. J. Conway, J. P. Nagel, R. V. Stick and D. M. G. Tilbrook, *Aust. J. Chem.*, 1985, 38, 939;

    d). T. S. Fuller and R. V. Stick, *Aust. J. Chem.*, 1980, 33, 2509.

50. D. H. R. Barton and S. W. McCombie, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1574.

51. a). P. J. Barker and A. L. J. Beckwith, *J. Chem. Soc., Chem. Commun.*, 1988, 683;

    b). D. H. R. Barton, D. Crich, A. Löbberding and S. Z. Zard, *Tetrahedron*, 1986, 42, 2329;

    c). M. D. Bachi and E. Bosch, *J. Chem. Soc., Perkin Trans. 1*, 1988, 1517;

    d). D. H. R. Barton, D. O. Jang and J. Cs. Jaszberenyi, *Tetrahedron Lett.*, 1990, 31, 3991; 4681;

    e). D. Crich, *Tetrahedron Lett.*, 1988, 29, 5805;

f). M. D. Bachi, E. Bosch, D. Denenmark and D. Girsh, *J. Org. Chem.*, 1992, <u>57</u>, 6803.

52. In a separate experiment it was demonstrated that in the absence of DMAP qualitatively identical results were obtained.

53. a). N. Baggett, J. S. Brimacombe, A. B. Foster, M. Stacey and D. H. Whitten, *J. Chem. Soc.*, 1960, 2574;

    b). E. Juaristi and S. Antúnez, *Tetrahedron*, 1992, <u>48</u>, 5941.

54. M. O. Chang, and R. J. Crawford, *Can. J. Chem.*, 1981, <u>59</u>, 2556.

55. Y-D. Wu and K. N. Houk, *J. Am. Chem. Soc.*, 1987, <u>109</u>, 908.

56. M. L. Sinnott and M. C. Whiting, *J. Chem. Soc., Perkin Trans. 2*, 1975, 1446.

57. a). H. W. Lee and Y. Kishi, *J. Org. Chem.*, 1985, <u>50</u>, 4402;

    b). G. Baudin, B. I. Glänzer, K. S. Swaminathan and A. Vasella, *Helv. Chim. Acta*, 1988, <u>71</u>, 1367;

    c). D. C. Billington, R. Baker, J. J. Kulagowski, I. M. Mawer, J. P. Vacca, S. J. deSolms and J. R. Huff, *J. Chem. Soc., Perkin Trans. 1*, 1989, 1423;

58. For the trivial nomenclature of cyclitols see: Th. Posternak, "The Cyclitols", Holden-Day, San Francisco, 1965.

59. M. J. Robins, J. S. Wilson and F. Hansske, *J. Am. Chem. Soc.*, 1983, <u>105</u>, 4059.

60. C. J. France, I. M. McFarlane, C. G. Newton, P. Pritchen and D. H. R. Barton, *Tetrahedron*, 1991, <u>48</u>, 6381.

61. M. Ballestri, C. Chatgillialoglu, K. B. Clark, D. Griller, B. Giese and B. Kopping, *J. Org. Chem.*, 1991, <u>56</u>, 678.

62. Dr W. B. Motherwell, Imperial College London, is thanked for pointing out this possibility

63. a). H. Sano, T. Takeda and T. Migita, *Chem. Lett.*, 1988, 119;

    b). A. V. R. Rao, K. A. Reddy, M. K. Gurjar and A. C. Kunwar, *J. Chem. Soc., Chem. Commun.*, 1988, 1273;

c). P. Boquel, C. L. Cazalet, Y. Chapleur, S. Samreth and F. Bellamy, *Tetrahedron Lett.*, 1992, 33, 1997;

64. For a general review on osmylation, see A. G. Haines, *Comprehensive Organic Chemistry*, volume 7, page 439.

65. K. B. Sharpless, A. Y. Teranishi and J. E. Backvall, *J. Am. Chem. Soc.*, 1977, 99, 3120.

66. R. Dyong, G. Schulte, Q. Lam-Chi and H. Friege, *Carbohydr. Res.*, 1979, 68, 257.

67. F. Johnson, *Chem. Rev.*, 1968, 68, 375.

68. R. W. Hoffmann, *Chem. Rev.*, 1989, 89, 1841.

69. G. Stork and M. Kahn, *Tetrahetron Lett.*, 1983, 24, 3951.

70. E. Vedejs and K. C. McClure, *J. Am. Chem Soc.*, 1986, 108, 1094.

71. a). K. N. Houk, S. R. Moses, Y.-D. Wu, N. G. Randon, V. Jages, R. Schohe and F. R. Fronczek, *J. Am. Chem. Soc.*, 1984, 106, 3880;

    b). K. N. Houk, H.-Y. Duh, Y. -D. Wu and S. R. Moses, *J. Am Chem. Soc.*, 1986, 108, 2754.

72. E. Vedejs and W. H. Dent III, *J. Am. Chem. Soc.*, 1989, 111, 6861.

73. R. L. Halterman and M. A. McEnvoy, *J. Am. Chem. Soc.*, 1992, 114, 980.

74. M. Burdisso, R. Gandolfi and A. Rastelli, *Tetrahedron Lett.*, 1991, 32, 2659.

75. D. Seebach, T. Maetzke, W. Petter, B. Klotzer and D. A. Plattner, *J. Am. Chem. Soc.*, 1991, 113, 1781.

76. V. Bilik and S. Kucar, *Carbohydr. Res.*, 1970, 13, 311.

77. R. C. Hockett, A. C. Sapp and S. R. Millman, *J. Am. Chem. Soc.*, 1941, 63, 2051.

78. a).K. B. Sharpless and E. Herranz, *J. Org. Chem.*, 1978, 43, 2544;

    b). K. B. Sharpless, D. W. Patrick, L. K. Truesdale and S. A. Biller, *J. Am. Chem. Soc.*, 1975, 97, 2305.

79. P. A. Dent and R. Gigg, *Carbohydr. Res.*, 1976, 49, 325.

80. A. B. Charette, J-F. Marcoux and B. Côté, *Tetrahedron Lett.*, 1991, 32, 7215.

81. a). K. Vangehr, P. Luger and H. Paulsen, *Carbohydr.Res.*, 1979, 70, 1;

    b). W. Korytnky and O. Dodson-Simmons, *Carbohydr.Res.*, 1984, 131, 157.

82. E. Bozo and A. Vasella , *Helv. Chim. Acta,* 1992, 75, 2613.

83. a). M. J. Cleare, P. C. Hydes, W. P. Griffith and M. J. Wright, *J. Chem. Soc., Dalton Trans.* 1977, 941;

    b).K. Akashi, R. E. Palermo and K. B. Sharpless, *J. Org. Chem.*, 1978, 43, 2063;

    c). M. Tokles and J. K. Snyder, *Tetrahedron Lett.*, 1986, 34, 3951.

84. L. Wang and K. B. Sharpless, *J. Am. Chem. Soc.*, 1992, 114, 7568.

85. T. Hashiyama, K. Morikawa and K. B. Sharpless, *J. Org. Chem.*, 1992, 57, 5067.

86. R. Amunziata, M. Cinquini, F. Cozzi and L. Raimondi, *Tetrahedron*, 1988, 44, 6897.

87. S. Masamune, W. Choy, J. S. Petersen and L. R. Sita, *Angew. Chem., Intl. Edn. Engl.*, 1985, 24, 1.

88. E. Fischer, *Ber. Deut. Chem. Ges.,* 1894, 27, 1524.

APPENDIX

X-RAY CRYSTALLOGRAPHIC STRUCTURE PARAMETERS FOR (130)

X-ray analysis of 4,6-Di-O-benzyl-2(4-O-tolylthiocarbonyl)-*scyllo*-inositol-1,3,5-orthoformate (130).

Crystals of (130) were obtained from diethyl ether.

Crystal Data: $C_{29}H_{28}O_7S$, FW = 520.61; Monoclinic space group $P\ 2_1/n$; a = 16.527 (9), b = 8.915 (2), c = 18.268 (3) Å; α = 90.00 (0), β = 107.21 (2), γ = 90.00 (0)°; V = 2571.3 (0) Å^3 (for least squares refinement on diffractometer angles for 30 automatically centered reflections λ = 0.71073 Å); Z = 4; $\rho_{calcd.}$ 1.34 g.cm^{-3} ; $F(000)$ = 1096; T = 292 K, irregular 0.37 x 0.37 x 0.1 mm colorless crystal, μ(Mo-Kα) = 0.16 cm^{-1}.

Data Collection and Processing

Nicolet R3m/V diffractometer, $\omega/2\theta$ mode, graphite monochromated Mo-Kα radiation (5 $\leq 2\theta \leq 50°$), 3288 unique data giving 1601 with $I \geq 3\sigma(I)$.

Structure analysis and refinement

The structure was solved by direct methods and refined by full least-squares methods. Hydrogen atoms were placed in calculated positions (C-H 0.96 Å) and assigned a common fixed isotropic thermal parameter (U = 0.08 Å^2). The least-squares refinement included 149 parameters for 1601 variables, gave R = 0.0855, R_w = 0.0889 (weighing scheme w^{-1} = σ^2(F) + 0.001 001 F^2) and did not shift any parameter by more than 0.002 times its estimated standard deviation. The final difference-Fourier map was featureless with the largest peak 0.36 e/Å^3.
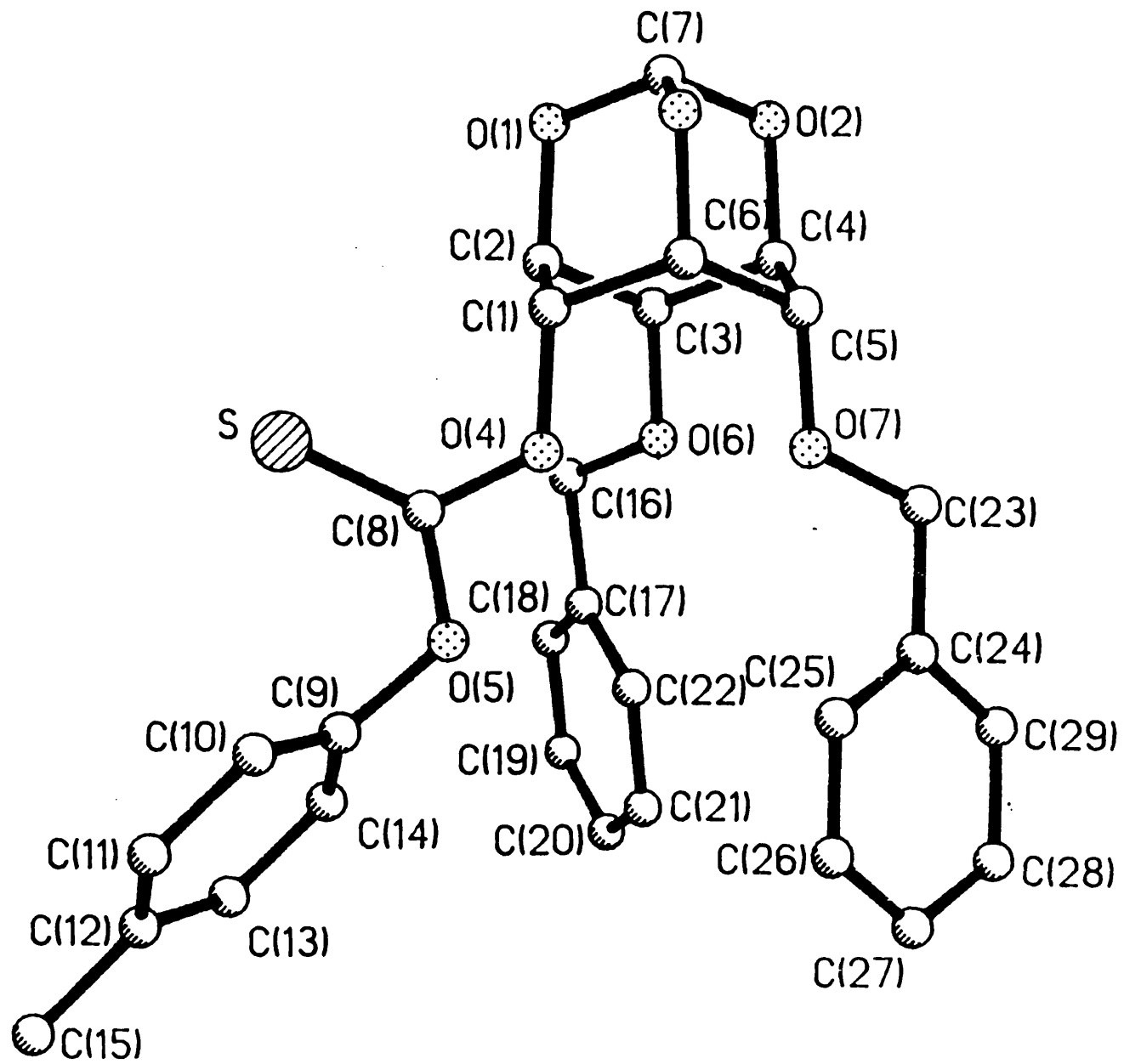
Table 1. Fractional Atomic Coordinates (x10^4) for (130)

Atom	x	y	z	Atom	x	y	z
S	345 (2)	2164 (3)	5396 (1)	C (12)	-1805 (6)	2473 (10)	2789 (5)
O (1)	1233 (4)	1257 (7)	7879 (3)	C (13)	-1970 (6)	1286 (11)	3192 (5)
O (2)	497 (4)	1219 (8)	8770 (3)	C (14)	-1775 (6)	1338 (11)	3989 (5)
O (3)	744 (4)	3452 (7)	8242 (3)	C (15)	-2031 (7)	2429 (12)	1931 (5)
O (4)	-584 (3)	2629 (6)	6327 (3)	C (16)	-785 (7)	-1430 (12)	6486 (6)
O (5)	-1285 (4)	2674 (7)	5162 (3)	C (17)	-1621 (6)	-1885 (10)	5949 (5)
O (6)	-889 (3)	-308 (6)	6988 (3)	C (18)	-1722 (7)	-3323 (11)	5672 (5)
O (7)	-1455 (4)	2595 (7)	7365 (3)	C (19)	-2491 (7)	-3730 (12)	5166 (5)
C (1)	162 (6)	2601 (9)	6977(4)	C (20)	-3128 (8)	-2774 (12)	4948 (6)
C (2)	483 (6)	1032 (10)	7241 (5)	C (21)	-3043 (7)	-1327 (13)	5214 (6)
C (3)	-120 (6)	79 (10)	7551 (4)	C (22)	-2268 (6)	-878 (12)	5729 (5)
C (4)	-306 (6)	975 (10)	8189 (5)	C (23)	-2155 (6)	2051 (11)	7579 (5)
C (5)	-671 (6)	2523 (9)	7949 (5)	C (24)	-2940 (6)	2209 (10)	6910 (5)
C (6)	-50 (6)	3383 (10)	7642 (5)	C (25)	-2972 (7)	3067 (11)	6278 (5)
C (7)	1059 (8)	2019 (13)	8474 (6)	C (26)	-3693 (7)	3164 (12)	5669 (6)
C (8)	-508 (7)	2487 (9)	5628 (5)	C (27)	-4405 (7)	2380 (11)	5688 (6)
C (9)	-1420 (6)	2600 (10)	4365 (5)	C (28)	-4399 (8)	1544 (12)	6312 (6)
C (10)	-1247 (6)	3810 (11)	3990 (5)	C (29)	-3661 (7)	1479 (12)	6931 (6)
C (11)	-1440 (6)	3736 (11)	3191 (5)				

Table 2. Bond Lengths (Å) for (130)

S-C (8)	1.614 (12)	O (5)-C (8)	1.325 (11)
O (1)-C (7)	1.382 (14)	O (6)-C (3)	1.421 (9)
O (2)-C (7)	1.401 (15)	O (7)-C (5)	1.415 (10)
O (3)-C (7)	1.397 (13)	C (1)-C (6)	1.526
O (4)-C (8)	1.325 (11)	C (2)-C (3)	1.537 (14)
O (5)-C (9)	1.408 (10)	C (3)-C (4)	1.519 (13)
O (6)-C (16)	1.402 (12)	C (4)- C(5)	1.518 (12)
O (7)-C (23)	1.412 (13)	C (5)-C (6)	1.515 (14)
C (1)-C (2)	1.523 (12)	C (13)-C (12)	1.361 (13)
C (13)-C (14)	1.396 (12)	C (14)-C (9)	1.358 (12)
C (16)-C (17)	1.496 (13)	C (15)-C (12)	1.501 (13)
C (17)-C (22)	1.361 (14)	C (17)-C (18)	1.370 (13)
C (18)-C (19)	1.380 (13)	C (29)-C (28)	1.399 (14)
C (29)-C (24)	1.369 (15)	C (19)-C (20)	1.322 (15)
C (24)-C (25)	1.373 (13)	C (20)-C (21)	1.370 (16)
C (25)-C (26)	1.372 (13)	C (21)-C (22)	1.405 (13)
C (26) -C (27)	1.377 (17)	C (23)-C (24)	1.502 (12)
C (27)-C (28)	1.360 (15)	C (9)-C (10)	1.352 (14)
O (1)-C (2)	1.443 (9)	C (10)-C (11)	1.400 (12)
O (2)-C (4)	1.449 (10)	C (11)-C (12)	1.382 (13)
O (3)-C (6)	1.441 (9)	O (4)-C 1)	1.437 (9)

Table 3. Bond Angles (°) for (130)

C (2)-O (1)-C (7)	111.9 (7)	O (6)-C (3)-C (2)	114.0 (6)
C (6)-O (3)-C (7)	111.4 (7)	C (2)-C (3)-C (4)	107.0 (7)
C (8)-O (5)-C (9)	119.1 (8)	O (2)-C (4)-C (3)	106.9 (8)
C (5)-O (7)-C (23)	114.8 (7)	C (3)-C (4)-C (5)	114.2 (7)
O (4)-C (1)-C (2)	114.2 (6)	O (7)-C (5)-C (4)	117.1 (7)
O (4)-C (1)-C (6)	107.9 (7)	C (4)-C (5)-C (6)	108.2 (8)
O (2)-C (1)-C (6)	107.9 (7)	O (3)-C (6)-C (1)	104.7 (7)
O (1)-C (2)-C (3)	106.0 (6)	C (1)-C (6)-C (5)	113.8 (7)
O (6)-C (3)-C (4)	110.0 (8)	C (14)-C (13)-C (12)	121.1 (8)
O (2)-C (4)-C (5)	106.0 (7)	C (13)-C (14)-C (9)	119.1 (9)
O (7)-C (5)-C (6)	105.5 (7)	C (16)-C (17)-C (18)	118.9 (9)
O (3)-C (6)-C (5)	107.7 (6)	C (18)-C (17)-C (22)	120.6 (8)
O (6)-C (16)-C (17)	110.7 (8)	C (17)-C (18)-C (19)	118.7 (9)
C (16)-C (17)-C (22)	120.5 (8)	C (24)-C (29)-C (28)	121.1 (10)
C (19)-C (20)-C (21)	120.8 (10)	C (18)-C (19)-C (20)	121.7 (10)
C (29)-C (24)-C (23)	118.8 (8)	C (20)-C (21)-C (22)	118.9 (10)
C (23)-C (24)-C (25)	123.0 (9)	C (17)-C (22)-C (21)	119.4 (9)
C (24)-C (25)-C (26)	121.7 (11)	O (7)-C (23)-C (24)	108.9 (8)
C (26)-C (27)-C (28)	120.4 (9)	C (29)-C (24)-C (25)	118.2 (8)
C (29)-C (28)-C (27)	119.3 (11)	C (25)-C (26)-C (27)	119.4 (10)
O (1)-C (7)-O (3)	110.9 (9)	O (1)-C (7)-O (2)	111.7 (8)
S-C(8)-O (5)	127.6 (7)	O (2)-C (7)-O (3)	110.6 (10)
O (5)-C (9)- C (14)	118.3 (8)	S-C (8)-O (4)	127.5 (7)
C (14)-C (9)-C (10)	122.0 (8)	O (4)-C (8)-O (5)	104.9 (9)
C (9)-C (10)-C (11)	118.3 (8)	O (5)-C (9)-C (10)	119.6 (7)
C (4)-O (2)-C (7)	111.2 (7)	C (10)-C (11)-C (12)	121.4 (9)
C (1)-O (4)-C (8)	119.6 (7)	C (13)-C (12)-C (11)	118.2 (8)
C (3)-O (6)-C (16)	112.9 (7)	C (13)-C (12)-C (15)	121.1 (8)
O (1)-C (2)-C (1)	105.3 (6)	C (15)-C (12)-C (11)	120.7 (8)
C (1)-C (2)-C (3)	114.9 (8)		