A STUDY OF ACTIVATED KETAL REDUCTION WITH BORANE DIMETHYL SULPHIDE

by Birgit Bartels

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Supervisor: Professor Roger Hunter

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ABSTRACT

Carbonyl reduction to secondary alcohols is a fundamentally important reaction in organic chemistry and many reagents have been developed for achieving this transformation efficiently, with regard to both the optical and material yield. An alternative approach, popularized in recent times, is the dissociative reduction of ketals to afford ethers as protected secondary alcohol derivatives and a number of approaches accomplishing a high degree of stereoselectivity have been developed.

This thesis describes a study of a novel reagent combination, namely borane dimethyl sulphide and trimethylsilyl trifluoromethanesulphonate (TMSOTf) for reductive ketal cleavage. The thesis begins with a review of the reaction in organic synthesis.

The reagent combination was found to chemoselectively reduce 1,3-dioxane ketals at low temperature in dichloromethane in high yield, whereas reduction of simple 1,3-dioxolanes resulted in a significant amount of side reaction. This can be attributed to the advanced oxocarbenium ion character of these silylated ketals in the transition state of the reduction step. The study was extended to include the regioselectivity of reduction of unsymmetrical vicinal diols as models for carbohydrate derivatives. The reduction was found to exhibit a solvent and structure dependent regioselectivity, which reflects strongly on the nature of the silylated complex in the reaction. In THF, there was a preference for reduction via silylation of the oxygen attached to the primary carbon resulting in overall protection of a secondary hydroxyl group in the presence of a primary hydroxyl group. A mechanism is postulated to explain the observed regioselectivities in the light of a recent hypothesis by Denmark *et al.*

Stereochemical studies of the reaction reveal intermediate selectivities and are consistent with hydride delivery *anti* to the C-O bond cleaved. As an extension of the application of the reagent the chemo- and regioselectivity of reduction of ketals of

various cyclic carbohydrate derivatives was studied in the context of selective protection group methodology. For these derivatives it was found that reduction proceeds via an intermediate derived from the more chelation orientated silyloxonium ion. The benzylidene acetal functionality of the open chain ribo sugar 1-benzyloxyimino-4,5-*O*-benzylidene-2,3-*O*-isopropylidene-D-ribose was reduced chemo- and regioselectively to afford the 5-benzyloxy 4-hydroxy derivative. This result is also consistent with a chelation controlled pathway.

ABBREVIATIONS:

$[\alpha]_D$	optical rotation
9-BBN	9-borabicyclo[3.3.1]nonane
Ac	acetate or acetyl
Ar	aryl
ax	axial
Bn	benzyl
bp	boiling point
br. s.	broad singlet
Bu	butyl
Bz	benzoyl
c-hex	cyclohexyl
cat.	catalytic
cf.	*confer*
CHN	elementary analysis
d	dextrorotatory
d	doublet
d.e.	diastereomeric excess
DEE	diethyl ether
DIBAH	diisobutylaluminium hydride
DIPE	diisopropyl ether
DMF	dimethylformamide
exch.	exchangeable (NMR signal)
e.e.	enantiomeric excess
eq	equivalents or equatorial
Et	ethyl
EtOAc	ethyl acetate
EtOH	ethanol
g	grams
gc	gas chromatography
GC-MS	gas chromatography-mass spectrometry
hex	hexyl
hr	hour
HRMS	high resonance mass spectrometry
i-Pr	iso-propyl
IR	infra red spectroscopy
J	coupling constant(s)
m	meta

M	molar
m/z	mass-to-charge ratio
Me	methyl
MeOH	methanol
mg	milligrams
MHz	Megahertz
min	minute
ml	milliliter(s)
mmHg	millimeter mercury, torr
mmol	millimole(s)
mol	mole(s)
mp	melting point
MS	mass spectrometry
nmr	nuclear magnetic resonance spectroscopy
o	ortho
p	para
pet ether	petroleum ether (boiling point range: 60°C-70°C)
Ph	phenyl
ppm	parts per million
pyr	pyridine
q	quartet
quin	quintet
R	alkyl radical
R	rectus
RT	room temperature
s	singlet
S	sinister
t	triplet
t-But	*t*-butyl
TBDMS	*t*-butyl dimethylsilyl
Thexyl	1,1,2-trimethylpropyl
THF	tetrahydrofuran
THP	tetrahydropyran
t.l.c.	thin layer chromatography
TMS	tetramethylsilane
TMSOTf	trimethylsilyl trifluoromethanesulphonate
*p*TsOH	*p*-toluenesulphonic acid

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CHAPTER 1

REVIEW

This thesis constitutes a study of the use of borane dimethyl sulphide, in conjunction with the Lewis acid trimethylsilyl trifluoromethane sulphonate (TMSOTf), as a novel reagent combination for the reduction of acetals and ketals in order to extend the use of $BH_3{\cdot}SMe_2$ in organic synthesis[1a]. The reducing ability of $BH_3{\cdot}SMe_2$ is well documented in the synthetic organic literature[1b], and from the outset it was envisaged that the use of this reagent for ketal reduction offered the attractive features of stability and availability of the reagent. In addition to this, it offered the possibility of anchoring the borane to a suitable site in the molecule via metal-hydrogen exchange or hydroboration for intramolecular reduction[2]. In order to put these ideas into perspective, the thesis begins with a literature review of the utility of acetals and ketals in organic synthesis and the reduction of this functional group by various reagents.

1.1. The Chemistry of Acetals and Ketals

Acetals and ketals are classically known for their use as temporary protecting groups of aldehydes and ketones[3] and fulfil the major requirements for a good protecting group[4], namely:

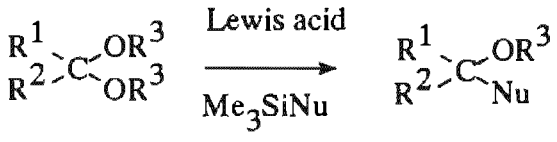
(a) general accessibility of cheap reagents

(b) availability of protection procedures, which lead quickly to the substrate and in good yield[5,6].

(c) inertness of the protecting group towards a range of reagents, thus making structural modifications possible in another part of the substrate, and

(d) availability of methods for deprotection in good yield[7,8].

Apart from their use as protecting groups, acetals and ketals are very useful functional groups in their own right. It has been known for some time that acetals undergo carbon-carbon bond forming reactions by formal nucleophilic addition at the carbonyl carbon. Most of the examples before 1976 required harsh reaction conditions[9] and are not synthetically useful. However, over the past two decades the utility of acetals in synthesis has been enhanced by the use of Lewis acidic promoters in conjunction[10] with nucleophilic reagents, in particular silicon-based nucleophiles (scheme 1.1). This reaction has evolved in parallel with the related addition of organosilicon nucleophiles to aldehydes and ketones in the presence of Lewis acids[10].



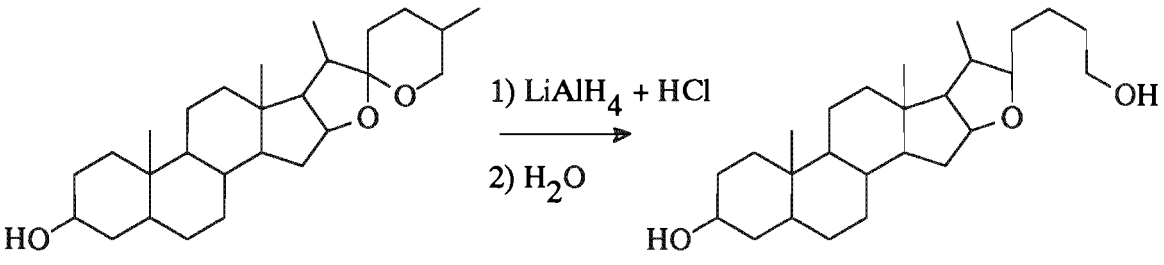
Scheme 1.1.

A recent review by Mukaiyama[10] outlines advances made in cross-coupling reactions based on acetals and emphasizes the use of organosilicon nucleophiles. It is beyond the scope of this thesis to review the whole spectrum of nucleophilic substitution reactions involving acetals. Therefore, the following chapter will concentrate on the reaction involving nucleophilic hydride species. This reaction developed into an important dissociative alternative to direct carbonyl reduction for both asymmetric and non-asymmetric substrates. These reactions will be classified according to the metal in the reducing agent.

1.2. Reduction of Acetals and Ketals by Organoaluminium Reagents

Acetals and ketals are stable towards lithium aluminium hydride in alkaline media and advantage has been taken of this fact to protect carbonyl groups from reduction. The first reduction of a ketal was reported in 1951[11] when diosgenine, a spiroketal, was

reduced by $LiAlH_4$ to dihydrodiosgenine (scheme 1.2), by the addition of the reagent to a solution of the starting material in anhydrous ether saturated with hydrogen chloride (or bromide) gas.



Scheme 1.2.

This report was noteworthy at the time for two reasons. Firstly, the combination of the reagent was unusual, as neither reagent affects the spiroketal by itself and secondly, because no procedure affording acceptable yields was available at that time for the transformation.

Subsequent work by Eliel *et al*[12-15] established that the reducing properties of $LiAlH_4$ may be considerably altered by the addition of Lewis acids, in particular $AlCl_3$. In 1958, they established that acetals and ketals would be reduced with a mixture of $LiAlH_4$ and $AlCl_3$ in a ratio of 1:4 but did not clearly understand the exact nature of the reducing agent, and concluded that the reduction proceeded via a "mixed reagent" or "mixed hydride". Later, it was shown by Brown *et al*[16], that the species responsible for reduction in a mixture of $LiAlH_4$ and $AlCl_3$ are AlH_3, AlH_2Cl or $AlHCl_2$, depending upon the molar proportions of $LiAlH_4$ to $AlCl_3$ according to the following equations:

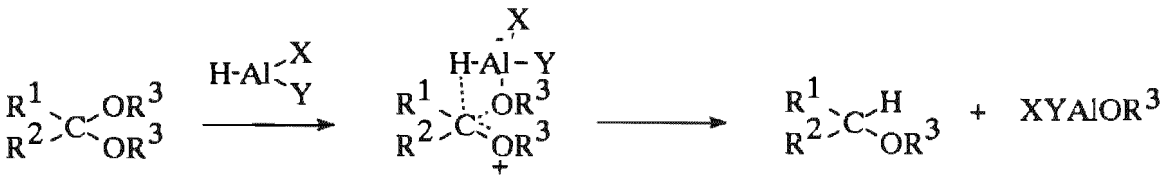
(a) $AlCl_3 + 3LiAlH_4 \rightarrow 4AlH_3 + 3LiCl$

(b) $AlCl_3 + LiAlH_4 \rightarrow 2AlH_2Cl + LiCl$

(c) $3AlCl_3 + LiAlH_4 \rightarrow 4AlHCl_2 + LiCl$

$AlCl_3$ is converted stepwise to AlH_3 via $AlHCl_2$ and AlH_2Cl and this process is reversible.

The nature of aluminium in the reducing agent was further exemplified by Zakharkin *et al*[17] when they showed that diisobutylaluminium hydride (DIBAH) is also able to reduce acetals and ketals to the corresponding ethers. Reduction with these reagents reflects the ability of aluminium to act as both electrophile (i.e. Lewis acid) and nucleophile (i.e. reducing agent) (scheme 1.3), and H. Yamamoto[18,19] has coined the phrase "ambiphilicity" for this property.



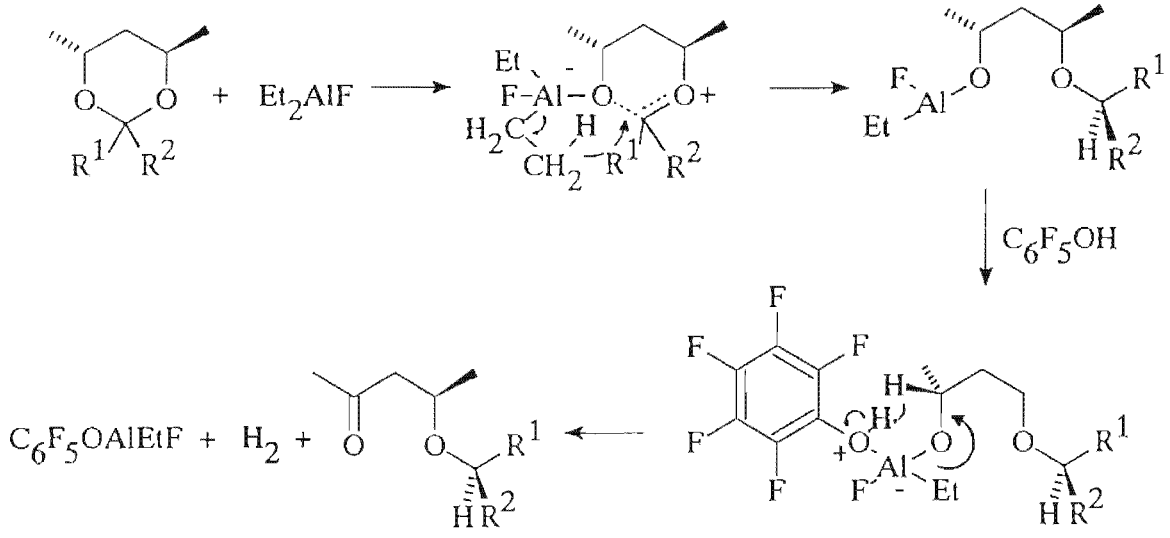
X=Y= iBu for DIBAH
X=Cl, Y=H for 1:1 ratio of $LiAlH_4$:$AlCl_3$
X=Y=Cl for 1:3 ratio of $LiAlH_4$:$AlCl_3$

Scheme 1.3.

$LiAlH_4$ can also be used in conjunction with other Lewis acids such as $BF_3{\cdot}OEt_2$[20], $B(Hal)_2H$[21] and $ZrCl_2$[22]. Eliel *et al*[14] also demonstrated that reduction occurred with a mixture of lithium hydride and aluminium chloride with only a catalytic amount of $LiAlH_4$ in which LiH and $AlCl_3$ form $LiAlH_4$ *in situ*[23].

Recently in an attempt to enhance the nucleophilicity of organoaluminium reagents, H. Yamamoto *et al*[24] have found that treatment of trialkylaluminium with 2,6-difluorophenol increases the reactivity of the aluminium reagent as an alkylation agent. Further studies revealed that ketals of optically active 1,3 diols can be reduced to ß-alkoxyketones in high yield and diastereoselectivity (see Chapter 3) with the combined

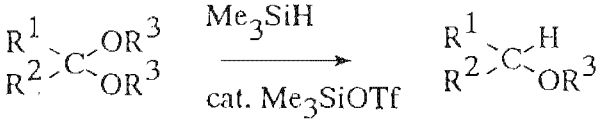
use of diethylaluminium fluoride (1.2 eq) and pentafluorophenol (2.4 eq). The product in this case is a result of an unique intramolecular Meerwein-Ponndorf-Verley-Oppenauer reaction (scheme 1.4).



Scheme 1.4.

1.3. Reduction of Acetals and Ketals by Organosilicon Reagents

The first time trialkylsilane was reported as a reducing agent was in 1962 by Frainnet *et al*[25], who discovered that triethylsilane in conjunction with the Lewis acid $ZnCl_2$ reduced acyclic acetals and ketals to their corresponding ethers. The same transformation can be achieved by triethylsilane in trifluoroacetic acid at 50°C[26] while lower temperatures (0°C → RT) for the reduction can be achieved by the use of TMSOTf as a catalyst[27] (scheme 1.5).



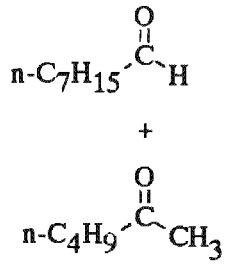
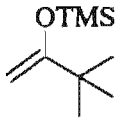
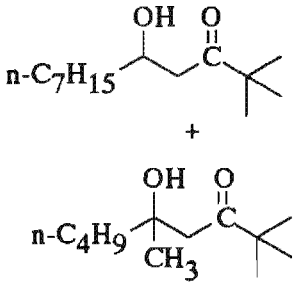
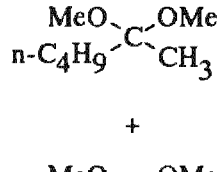
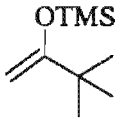
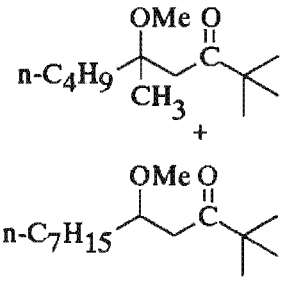
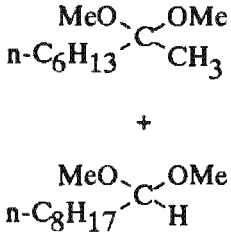
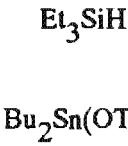
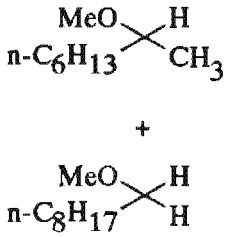
Scheme 1.5.

In their search for a useful asymmetric reduction of ketals derived from chiral diols, H. Yamamoto *et al*[28] reported on the use of triethylsilane with a variety of Lewis acids at -78°C. Among the Lewis acids examined, $TiCl_4$ was highly effective giving high yields and stereochemical outcome (see Chapter 3). The use of $BF_3{\cdot}OEt_2$ and $SnCl_4$ also resulted in high yields, but with $AlCl_3$ the yields of the reduction were lower.

Olah *et al*[29] have shown that Nafion-H, (a registered trademark of the DuPont Company and a superacidic perfluorosulphonic acid resin) is an effective catalyst for the reductive cleavage of acyclic acetals and ketals with triethylsilane in refluxing dichloromethane solution. Both benzylic as well as aliphatic substrates are reduced in high yields and the catalyst can be recovered and regenerated into an active form after the reaction. Unlike Lewis acids, Nafion-H is stable in the presence of moisture and its catalytic activity improves with small amounts of water.

Recently, Sato *et al*[30] reported that dibutyltin bis(triflate) catalyses the reaction between ketals and silicon-based nucleophiles such as Et_3SiH in dichloromethane. This report was significant because the authors showed that at -78°C the Lewis acid chemoselectively catalyses the reaction of aldehydes with a variety of silyl-nucleophiles in the presence of ketones. Moreover, ketals are activated under the same conditions in preference to acetals towards the addition of nucleophiles (Table 1.1). This selectivity is not observed with other Lewis acids such as $TiCl_4$, $SnCl_4$, $AlCl_3$ and TMSOTf and the authors ascribed the unique catalytic activity of dibutyltin bis(triflate) to its mild reactivity and reduced oxygenophilicity compared to other Lewis acids.

Table 1.1.

substrates/ 1equivalent each	Nucleophile/ 1 equivalent	Products	
	 $Bu_2Sn(OTf)_2$, cat.		85% 0%
	 $Bu_2Sn(OTf)_2$, cat		100% 0%
	 Et_3SiH $Bu_2Sn(OTf)_2$, cat		87% 5%

1.4. Reduction of Acetals and Ketals with Boron Reagents

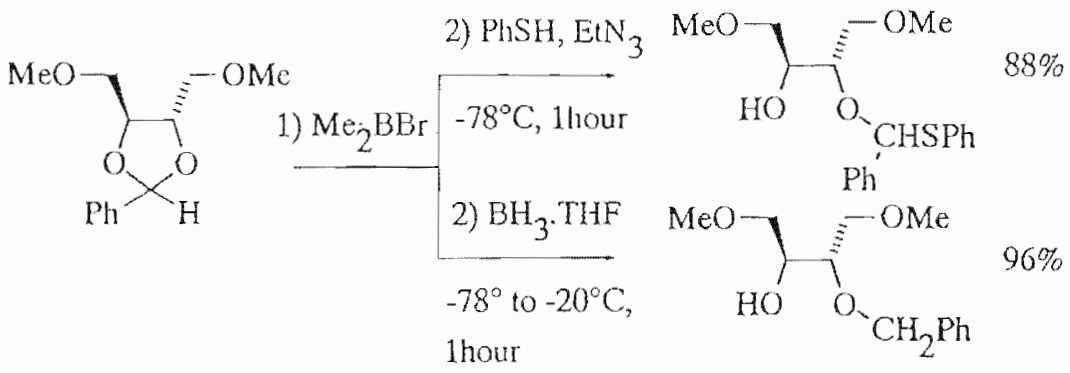
As is the case with $LiAlH_4$, $NaBH_4$ does not reduce acetals and ketals in alkaline media, although Gribble *et al*[31] have demonstrated that $NaBH_4$ and trifluoroacetic acid in THF at 20°C reduce benzylic acetals and ketals in high yield. However, this reaction only gives low yields with aliphatic acetals and ketals even after refluxing for 24 hours.

Horne and Jordan[32] reported on the reduction of dimethoxy acetals and ketals by $NaBH_3CN$, which is more stable than $NaBH_4$ in acidic media, in methanol at O°C after HCl had been bubbled through the solution. When a cyclic ketal was used the only

product was the methoxy ether which is presumably derived via ketal exchange with solvent, followed by reduction.

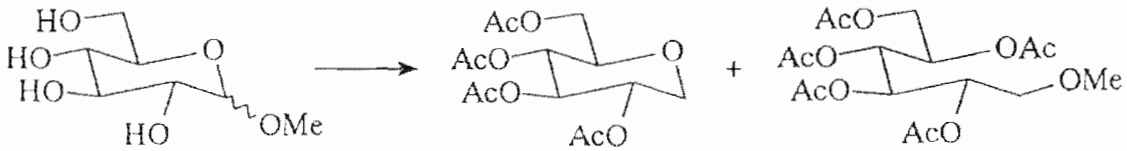
Similarly, $Zn(BH_4)_2$[33] in conjunction with TMSCl is effective for the reductive cleavage of aromatic acetals and ketals. 0.5 Equivalents of $Zn(BH_4)_2$ and 1.2 equivalents of the TMSCl are needed at 25°C in ether as solvent and once again aliphatic ketals react more sluggishly in lower yield. The use of other Lewis acids such as $BF_3{\cdot}OEt_2$ and $ZnCl_2$ was not successful. In these cases there may be reduction of the Lewis acid occurring (ie. transmetallation).

In 1974, Fleming and Bolker[34] reported that borane tetrahydrofuran complex in tetrahydrofuran reduces acetals and ketals to their corresponding ethers. The reactions were carried out at ambient temperatures and involved long reaction times (15 hours). For aromatic acetals the yields were excellent, but for acyclic ketals the yields were much lower and cyclic ketals required elevated temperatures (35°-50°C) for the reaction to occur. As with AlH_3 mentioned previously, the borane is acting ambiphilically. Hence, the reagent by itself has limited chemoselectivity for ketal reduction. More recently, Guindon *et al*[35] have shown that the tandem use of dimethyl (or diphenyl) boron bromide and borane THF complex effects the regioselective reduction (discussed in detail in Chapter 4) of benzylidene acetals to their corresponding hydroxybenzyl ethers. They have proposed that the acetals react with the dialkyl (or diaryl) bromoborane at -78°C to form the corresponding α-bromoethers[36]. This species can be trapped by a nucleophile such as thiophenol to form the corresponding hydroxy-O,S-acetal or by BH_3.THF, Super-hydride or DIBAH to form ethers (scheme 1.6).



Scheme 1.6.

In contrast to borane, alkyldiboranes do not reduce acetals even up to temperatures of 130°C. Köster and Dahlhoff *et al*[37] have used alkyldiboranes in the presence of sulphonic acid derivatives such as 9-methanesulphonato-9-borabicyclo(3.3.1)nonane (MSBBN) for the reduction of open chain and cyclic acetals and glycosides to ethers (scheme 1.7).



α	45	:	55
β	10	:	90

a: Activated triethylborane and ethyl diborane, 4 eq.

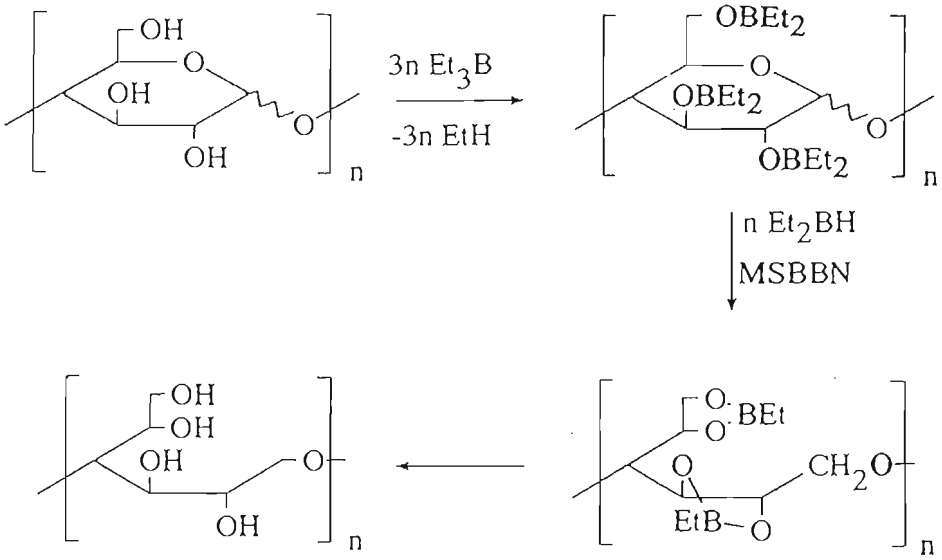
b: MSBBN, reflux 120°C, 4 hours

c: Methanol, glycol

d: Acetylation with acetic anhydride, pyridine

Scheme 1.7.

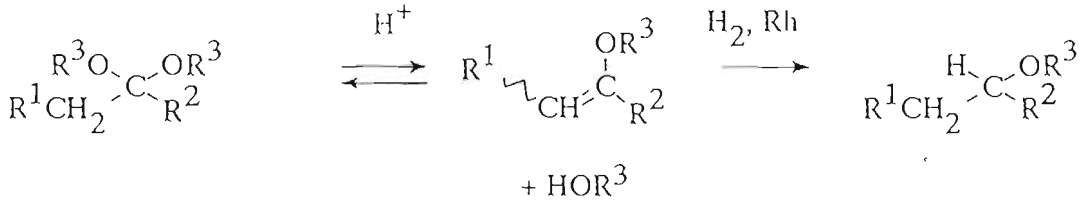
An interesting feature of the reaction here, is the selectivity shown by the ß-anomer towards endocyclic C-O bond cleavage (see chapter 5). This methodology has been used in the regioselective reduction of amylose and cellulose to afford a novel polymer, poly-1,4-anhydroglucitol with the retention of the polymer backbone[37d] (scheme 1.8).



Scheme 1.8.

1.5. Miscellaneous Reductions of Acetals and Ketals

The literature contains several references to the hydrogenolysis of aldehyde acetals to ethers and alcohols, usually under conditions of high temperature and pressure[38]. By hydrogenation, Gorin *et al*[39] cleaved some cyclic ketals of sugars and obtained ether derivatives. Howard and Brown *et al*[40] found that hydrogenation of acidified ketals over a rhodium catalyst gives high yields of saturated ethers and alcohols under mild conditions (scheme 1.9).



Scheme 1.9.

If R^3 is a primary alkyl group (e.g. methyl or ethyl), the reaction proceeds at 50°- 80°C, whereas if R^3 is a secondary alkyl group (e.g. *iso*propyl or cyclohexyl) the reaction proceeds rapidly to completion at room temperature. The authors propose that the reaction proceeds via hydrogenation of an enol ether intermediate formed when the ketal is subjected to acid.

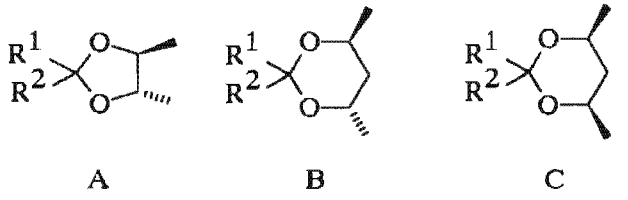
In addition to allylic and benzylic ethers it is possible to reductively cleave acetals and to a lesser extent alcohols in metal ammonia solutions[41], but there is a tendency for over-reduction to occur, particularly in the presence of an added proton source such as ethanol. The reductions are carried out at -33°C and need long reaction times.

H. Yamamoto *et al*[28] in their study of the effects of different Lewis acids on the stereochemical outcome of the reduction of ketals by triethylsilane, also report that *t*BuMgCl (5.0 equivalents) in conjunction with $TiCl_4$ (1.2 equivalents) reduces ketals. They do not, however, comment on the mechanism of the reduction[19], but it is consistent with the known ß-hydride transfer from the *t*Bu group.

1.6. Discussion of the Mechanism of Nucleophilic Addition to Acetals/Ketals

The following section will focus on the mechanism of nucleophilic substitution to acetals and ketals. A great deal of information in the literature on this subject stems from investigations on the cross-coupling reactions of nucleophiles with chiral acetals where mechanism relates closely to stereoselectivity. This is discussed in Chapter 3.

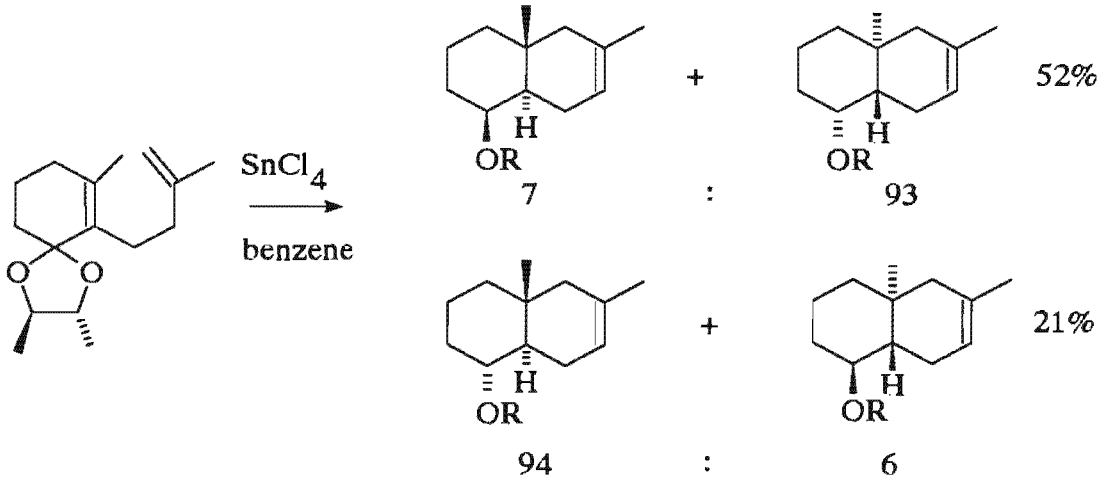
The most prevalent types of acetals and ketals used in these studies are of type A, B and C (scheme 1.10)[42].



A B C

Scheme 1.10.

Chiral acetals of type A were first used by Johnson *et al*[43] in a $SnCl_4$ catalyzed alkene cyclisation (scheme 1.11), and later by the same group[44] in conjunction with stereoselective substitutions by allylsilane.



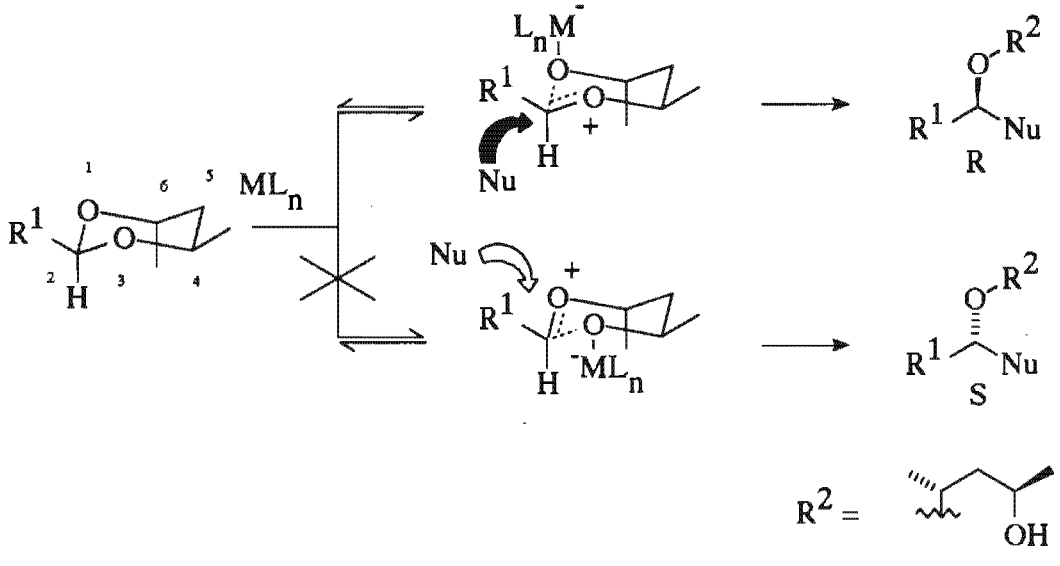
Scheme 1.11.

The acetals can be cleaved by various organometallic nucleophiles in conjunction with Lewis acids with varying degrees of success[45-48], resulting in a hydroxy ether substituent in the product. This group may be removed by oxidation (e.g. Swern[49]) to the keto-ether, followed by α-elimination to the corresponding alcohol (lithium in ethylamine, reflux, 5 hours, or sodium in diethyl ether, 25°C, 22 hours).

The use of this class of acetal has largely given way to the dioxane acetal of type B, due to the fact that the structures are generally more rigid leading to improved stereoselectivities and the removal of the chiral auxiliary can easily be carried out by

oxidation (Swern), followed by facile base-catalysed ß-elimination to form the unprotected alcohol[45].

The fundamental issue in the mechanism of nucleophilic addition to acetals and ketals, concerns the timing of the C-O bond breaking and the C-Nu (in this instance C-H) bond formation steps[50]. This feature strongly impacts on the stereoselectivity. In addition, stereoselectivity is dependent on which C-O bond is cleaved (ie. site selectivity of complexation of the Lewis acid), and on the direction of attack by the nucleophile (*syn* or *anti*). In explaining the high stereoselectivities observed in the reaction of dioxane-acetals B or C with organometallic nucleophiles in the presence of Lewis acids, Johnson *et al*[45] proposed that complexation of the Lewis acid to the sterically more accessible oxygen atom of the acetal (α to axial methyl group), followed by *anti* attack of the nucleophile in an S_N2-like transition state, resulting in inversion of configuration at the acetal carbon, occurred (scheme 1.12).



Scheme 1.12.

The complexation of the Lewis acid to the oxygen α to the axial methyl group is favoured, as it lengthens the C^2-O^1 bond and, by the anomeric effect, shortens the C^2-

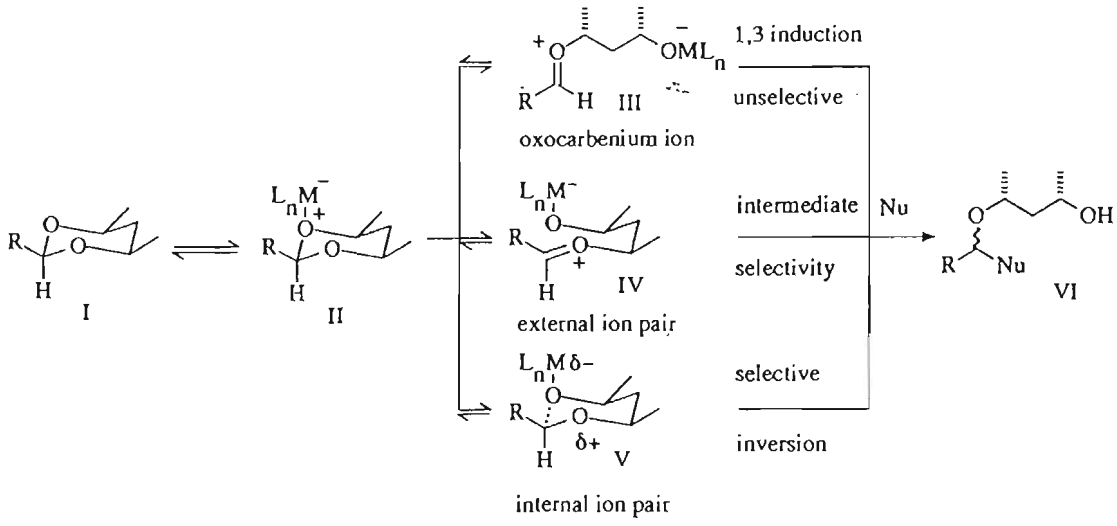
O^3 bond. Chelation to the other oxygen would lengthen the C^2-O^3 bond and shorten the C^2-O^1 bond, thus increasing the 1,3-diaxial interaction between the axial methyl group and the axial substituent on C^2, leading to a more strained complex.

Denmark *et al*[51] have shown by variable temperature ^{13}C nmr that upon complexation with various Lewis acids, the dioxane ring is not opened to any great extent and a single complex is formed. In this paper, Denmark *et al.* assume an electronic preference for the complexation of O^1 with its rehybridization towards sp^2, giving a planar or weakly pyramidal complex. In this configuration the Lewis acid experiences eclipsing interactions with the equatorial group α to the oxygen, and thus prefers coordination next to the axial methyl group.

Most explanations of the stereoselectivities observed, involving nucleophilic substitutions at acetal centres, up until the year 1990, are based on S_N2-type substitutions involving a closed transition state. However, Y. Yamamoto *et al*[52] showed though a strong dependence on the nucleophilicity of the reagent. With strong nucleophiles, such as allyltributylstannane, stereoselectivity was determined by the configuration of the acetal, while with weaker nucleophiles, such as allylsilanes, the addition stereoselectivity was independent of acetal configuration following a Cram, ie S_N1-type, pathway.

Recently, Heathcock, Bartlett and H. Yamamoto *et al*[53] examined the stereochemical course of opening of meso acetals (type C) to distinguish between the limiting S_N1 and S_N2 mechanisms. They concluded that the reactions proceed largely via an S_N1 (oxocarbenium ion) mechanism. However, to rationalize the high stereoselectivities observed with chiral acetals, the authors modified their proposal to involve oxocarbenium ion pairs that maintain some of the structural features of the intact six-membered rings.

These studies have culminated recently in a new unified mechanism put forward by Denmark *et al*[50] which incorporates both limiting scenarios in addition to the ones mentioned above (scheme 1.13).

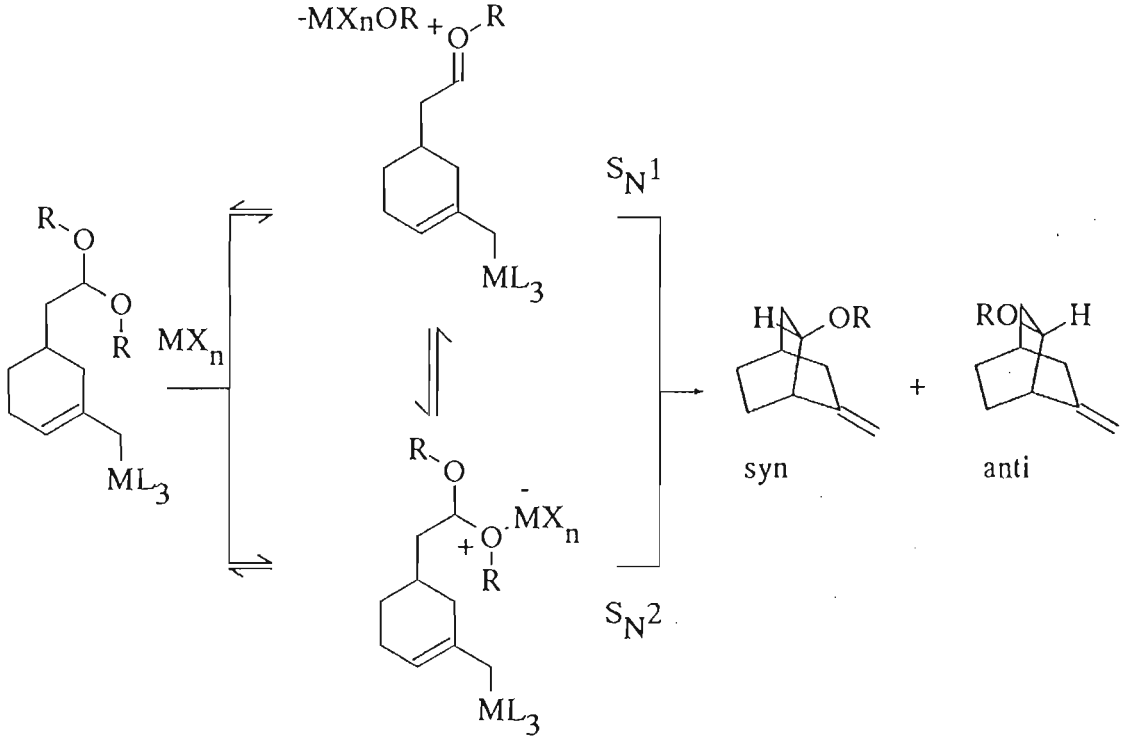


Scheme 1.13.

According to this scheme, the initially formed Lewis acid complex, though spectroscopically detectable, is not the reactive intermediate, and is in equilibrium with the true reactive species, the intimate ion pair, the external ion pair and the oxocarbenium ion. These two limiting species react with completely different stereochemical profiles. For the intimate ion pair, the reaction would be stereospecific with inversion of configuration at C^2 while for the oxocarbenium ion, the reaction would be stereo-random. The external ion pair is suggested to exhibit intermediate selectivities between the two extremes. Thus the overall stereochemical result depends on the equilibrium composition of the reactive species and their relative rates of reactivity. This is strongly dependent on the structure and experimental conditions.

(a) Acetal structure:

Previous investigations by Denmark *et al*[54] established a strong dependence on acetal structure in an intramolecular version of the reaction. They demonstrated that methyl, ethyl and isobutyl acetals react via a common synchronous ("S_N1-like") mechanism with bi-coordinate Lewis acids ($TiCl_4$, $SnCl_4$). Bulky diisopropyl acetals reacted via the latter mechanism with all Lewis acids (scheme 1.14).



Scheme 1.14.

Heathcock *et al*[53] and his colleagues also showed that with increasing steric bulk of the acetal alkoxy group, nucleophilic substitution proceeds via an oxocarbenium ion.

(b) C-2 Substituent Dependence

Denmark *et al*[50] showed that there was a dependence on the substituent at C-2 whereby, if one moves from R = n-hexyl to R = cyclohexyl or phenyl, the

stereoselectivities decrease substantially. The authors explain this by the increased concentration of the oxocarbenium ion **III** and the external ion pair **IV** in the latter, due to increased resonance stabilization of charge.

(c) Lewis acid Dependence

A systematic study of Lewis acids has not yet been undertaken but the above results (scheme 1.14) by Denmark *et al*[50] show a strong dependence on the Lewis acid used. They also indicate that with $TiCl_4$, acetals apparently react via a reactive species which is close to external ion pair **IV** in nature, whereas the more Lewis acidic BF_3 reacts unselectively via the oxocarbenium ion **III**.

These findings may be supported by H. Yamamoto's work[28] where it was established that, in the reduction of chiral acetals, the highest stereoselectivities were observed with the $Et_3SiH/TiCl_4$ combination, and lower selectivities in conjunction with other Lewis acids such as $BF_3{\cdot}OEt_2$, $SnCl_4$ and $AlCl_3$.

(d) Nucleophile Dependence

In addition to Y. Yamamoto's[52] observations mentioned previously, Denmark and Almstead[55] reported in another publication that the nucleophilicity of the reagent has a significant impact on the stereoselectivity of the reaction. Thus, generally tin-nucleophiles react with higher selectivity than silicon-nucleophiles.

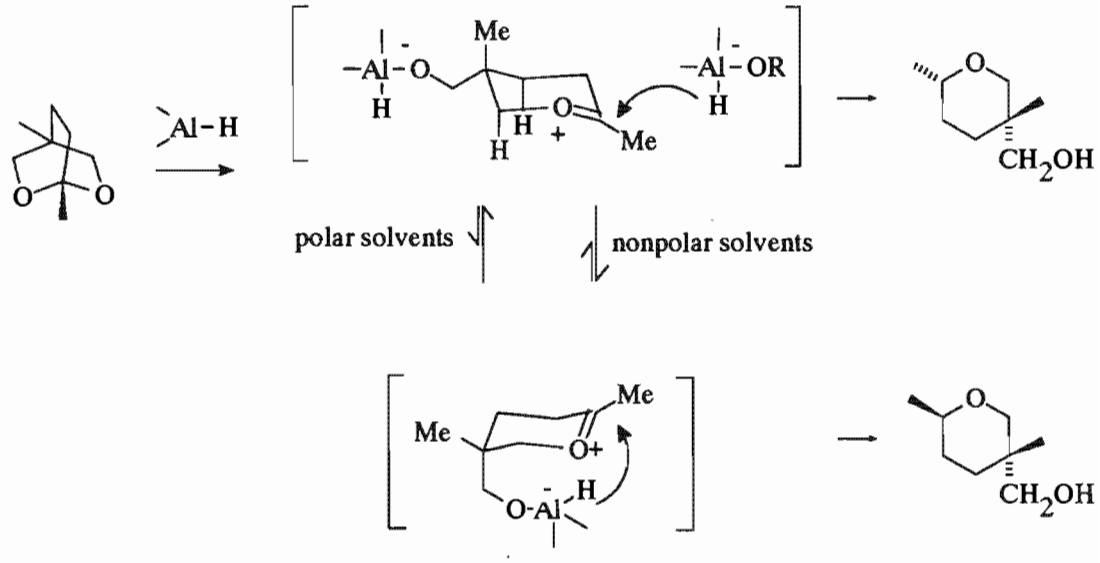
(e) Stoichiometry and Concentration

It has been demonstrated by Denmark *et al*[50] that stereoselectivity is independent of the stoichiometry of both the nucleophile and the Lewis acid, indicating that the equilibration of the reactive intermediates is faster than the nucleophile attack, and that always the same number of Lewis acids are coordinated.

(f) Solvent Dependence

Perhaps the least understood aspect of the reaction is the solvent effect on the equilibrium in scheme 1.13.

Conceptually, it can be envisaged that an increase in solvent polarity will increase the proportion of oxocarbenium ion **III**, while in nonpolar solvents an increase in the proportion of the internal ion pair **V** will result. This was confirmed by Heathcock *et al*[53], whereby reactions in acetonitrile proceeded via an S_N-1-type oxocarbenium ion and reactions in CH_2Cl_2 via a "mixture of S_N2 and S_N1" ie. via external ion pair **IV**. H. Yamamoto *et al*[56] have observed the same trend in their study of the reduction of bicyclic acetals (scheme 1.15).



Scheme 1.15.

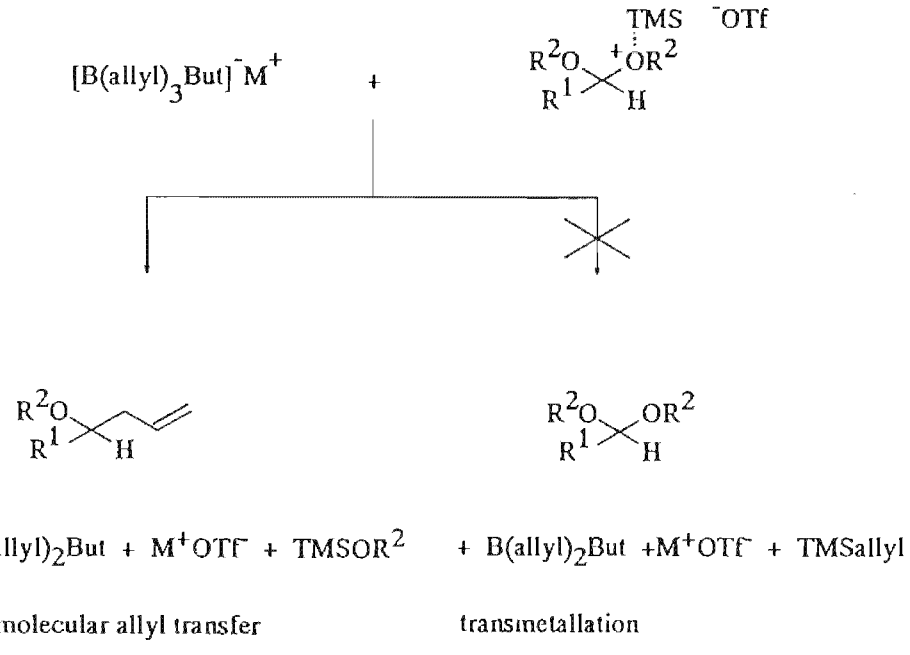
Denmark *et al*[50] also showed a similar trend in their studies. Yet, in all these three studies mentioned above there seems to be a mechanistic divergence when non-polar solvents such as hexane and CCl_4 are used. Heathcock *et al*[53] indicated that in these solvents the reaction could occur via both limiting mechanisms, whereas H. Yamamoto *et al*[56] had no explanation for the low selectivities observed in hexane and proposed a complex association of the aluminium reagents. Denmark *et al*[50] rationalized the low stereoselectivities observed in CCl_4 and hexane by the possibility of forming agglomerations of the charged complexes to distribute charge in these solvents. Another possibility would involve an alternative mechanism via a neutral intermediate, such as an α-chloroether (for $TiCl_4$ as Lewis acid).

CHAPTER 2

Results and Discussion

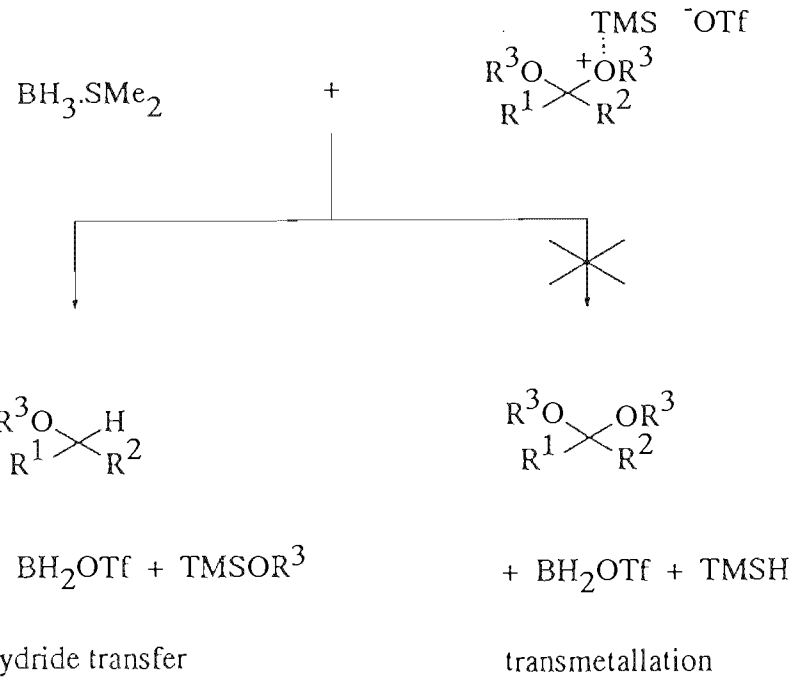
2.1. Ketal Reduction Model Studies using the Reagent $BH_3 \cdot SMe_2$/TMSOTf[57]

The experimental part of the thesis begins with the initial study carried out on the reduction of some model acetals and ketals in order to gain some insight into the chemoselectivity of the reagent combination (TMSOTf/$BH_3 \cdot SMe_2$). As mentioned in Chapter 1, acetal and ketal reductive opening using borane tetrahydrofuran complex in tetrahydrofuran is known to afford moderate yields in the absence of a Lewis acid[34]. Furthermore, it is known from other studies[58] that TMSOTf is compatible at low temperatures (-78°C) with boron reagents such as lithium *n*-butyltriallylborate and that no transmetallation occurs at this temperature (scheme 2.1).



Scheme 2.1.

Thus, it was anticipated that the Lewis acid would not be transmetallated by borane dimethyl sulphide (scheme 2.2).

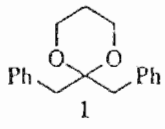
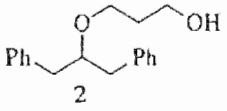
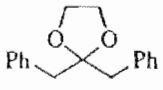
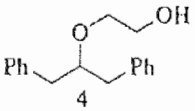
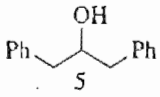
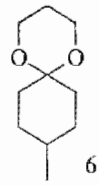
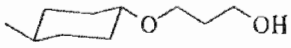
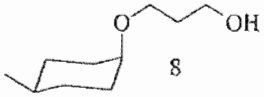
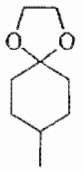
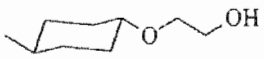
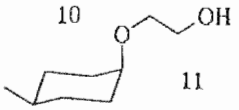
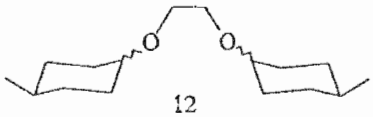
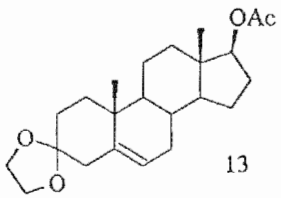
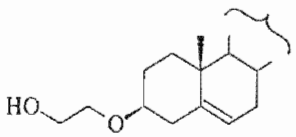
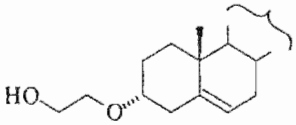
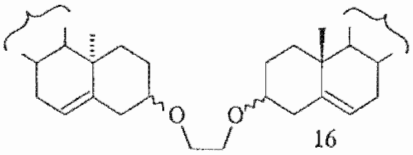


Scheme 2.2.

Borane dimethyl sulphide was chosen over borane·THF as this reagent is available as a neat liquid (10M), 1.0 M solution in CH_2Cl_2 or 2.0 M solution in THF. Furthermore the reductions with borane·THF proceeded sluggishly. The results of the model study are summarised in table 2.1.

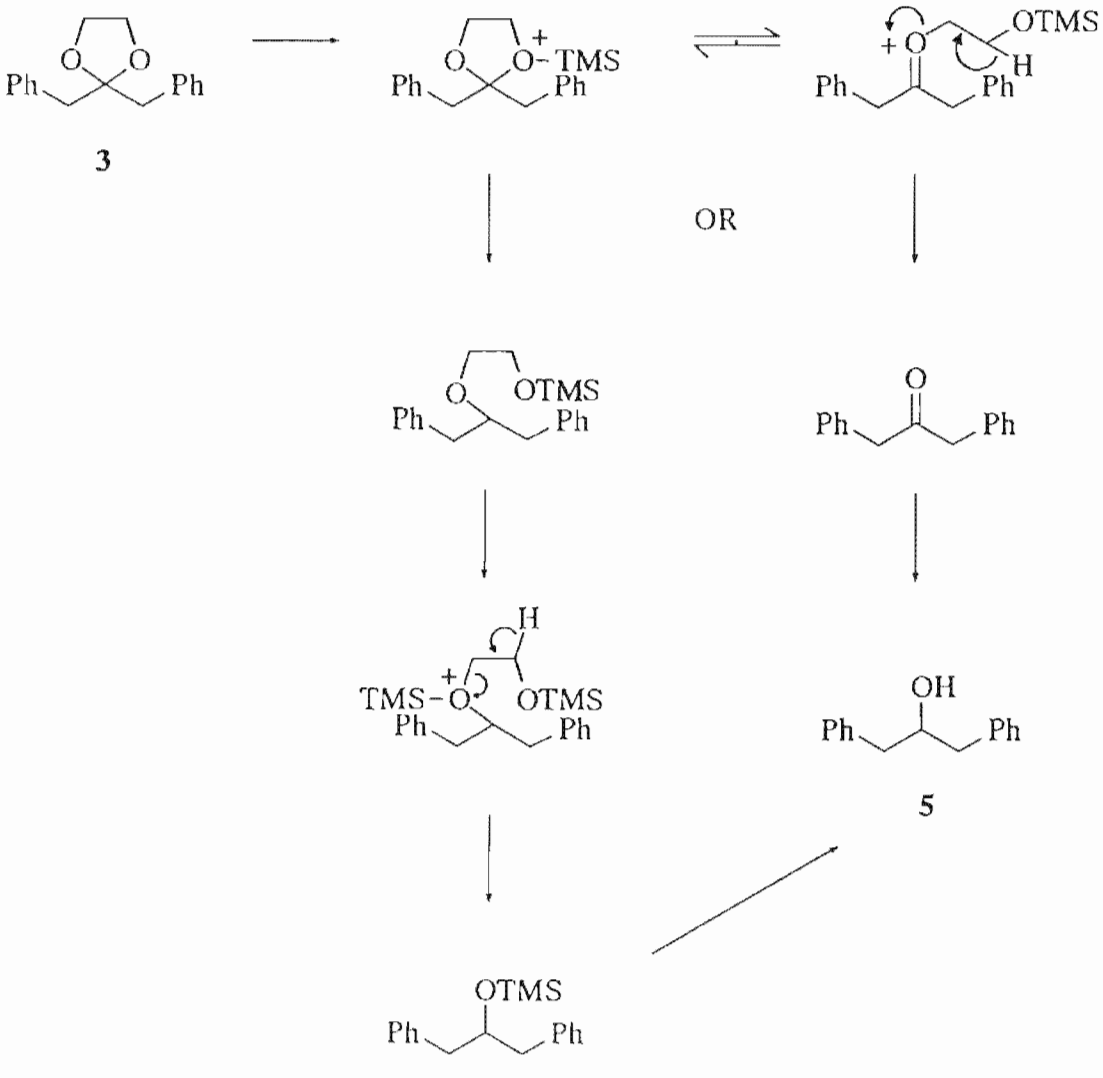
The first ketal studied, 2,2-dibenzyl-1,3-dioxane 1 was completely reduced to 2 in very high yield in one hour at -78°C in dichloromethane as solvent. Dichloromethane is a convenient solvent to use for the reaction as it is easily dried, has a medium range polarity and readily dissolved the substrates studied. Other solvents such as hexane, diethyl ether and THF were also screened. THF deserves special mention because reductions in this solvent were considerably slower, requiring higher temperatures. Above 0°C, complications arose owing to solvent polymerisation resulting in difficulties with product isolation. The lower reaction rate is probably due to the fact that THF, being Lewis basic[59], competes with the substrate for complexation of the Lewis acid.

TABLE 2.1.

Substrate	Product(s)	Yield
 1	 2	95%
 3	 4	51%
	 5	20%
 6	 7	83%
	 8	14%
 9	 10	13%
	 11	7%
	 12	71%
 13	 14	82.7%
	 15	0.9%
	 16	16.2%

It was established that at least 1 mol equivalent of both TMSOTf and $BH_3{\cdot}SMe_2$ was needed for optimum yield. However, most reductions were carried out with 2 mol equivalents of both reagents without adverse side reactions occurring.

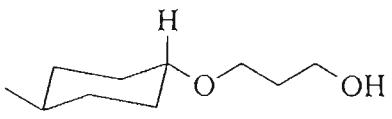
In comparison with dioxane **1**, the corresponding five-membered ring ketal **3**, 2,2-dibenzyl-1,3-dioxolane, gave the product of reductive cleavage **4** (51%) together with a significant yield of dibenzylmethanol **5** (20%). This product could have been formed in one of two ways (scheme 2.3).



Scheme 2.3.

The formation of the unprotected secondary alcohol side-product **5** from dioxolane **3** at this stage of the study indicated a significant mechanistic difference in reactivity of the dioxolane ring compared with its dioxane counterpart.

The next substrate studied was the ketal **6** derived from 4-methylcyclohexane and 1,3-propanediol for which simple diastereoselectivity became an issue. As before, the reduction proceeded at -78°C in dichloromethane in one hour to afford the individual cis **8** and trans 7 isomers in a ratio of 6:1 after column chromatography. The structures of the two products were established by the nmr signals for H-1. For the trans-isomer **7**, this signal was a triplet of triplets with coupling constants 4.2 Hz and 10.7 Hz indicative of axial-equatorial and axial-axial coupling, respectively. The total width of the signal was 30 Hz. By comparison, the signal for H-1 of the minor cis-product **8** was a multiplet with a total width of 16 Hz.



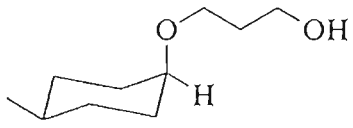
7

triplet of triplets

$J_{ax\text{-}ax}$ = 10.7 Hz

$J_{ax\text{-}eq}$ = 4.2 Hz

width of signal = 30 Hz



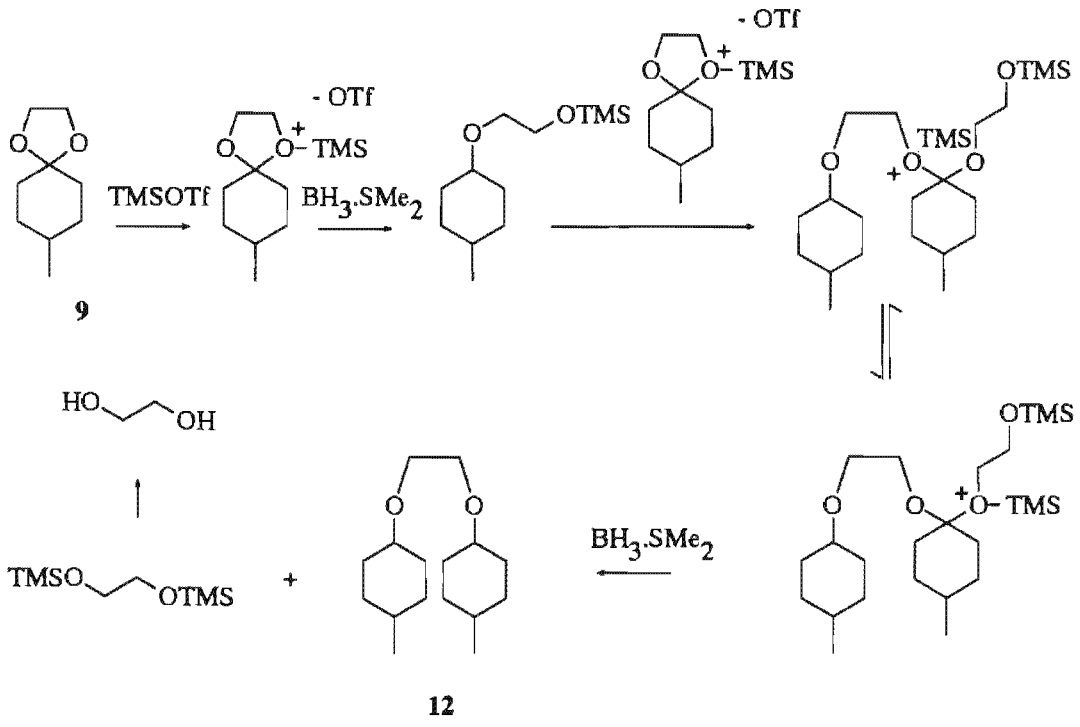
8

multiplet

width of signal = 16 Hz

The dioxolane ketal of 4-methylcyclohexanone and 1,2-ethanediol reduced in dichloromethane at -78°C to give the unexpected dimeric product **12** in 71% yield as a mixture of 3 isomers with very similar chromatographic properties. One of these was isolated in a pure form and was found to be the trans-trans isomer of **12** with similar coupling constants for H-1 as compound **10**.

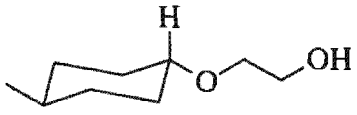
A possible mechanism of formation of the dimeric product is shown in scheme 2.4.



Scheme 2.4.

In this scheme, the opened ketal species competes with hydride as a nucleophile in attack on an activated ketal complex as a result of activation to the silyl ether. Again, the different product selectivities obtained from the five and six membered ketals indicate that the structures of the activated ketal complexes of the two ring systems in the nucleophilic addition step are different.

The expected reduced products **10** and **11** were isolated in 20% yield in a ratio of approximately 2:1. Once again, the configurations of the isomers were established by the nmr signal for H-1. H-1 of **10** is a triplet of triplets with coupling constants of 4.2 Hz and 10.8 Hz while H-1 of **11** shows a multiplet of total width of signal of 9 Hz. The last two examples demonstrate that there is some degree of simple diastereoselection in the reduction of cyclic ketals with this reagent combination.

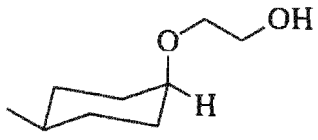


10

triplet of triplets

$J_{ax\text{-}ax}$ = 10.8 Hz

$J_{ax\text{-}eq}$ = 4.2 Hz

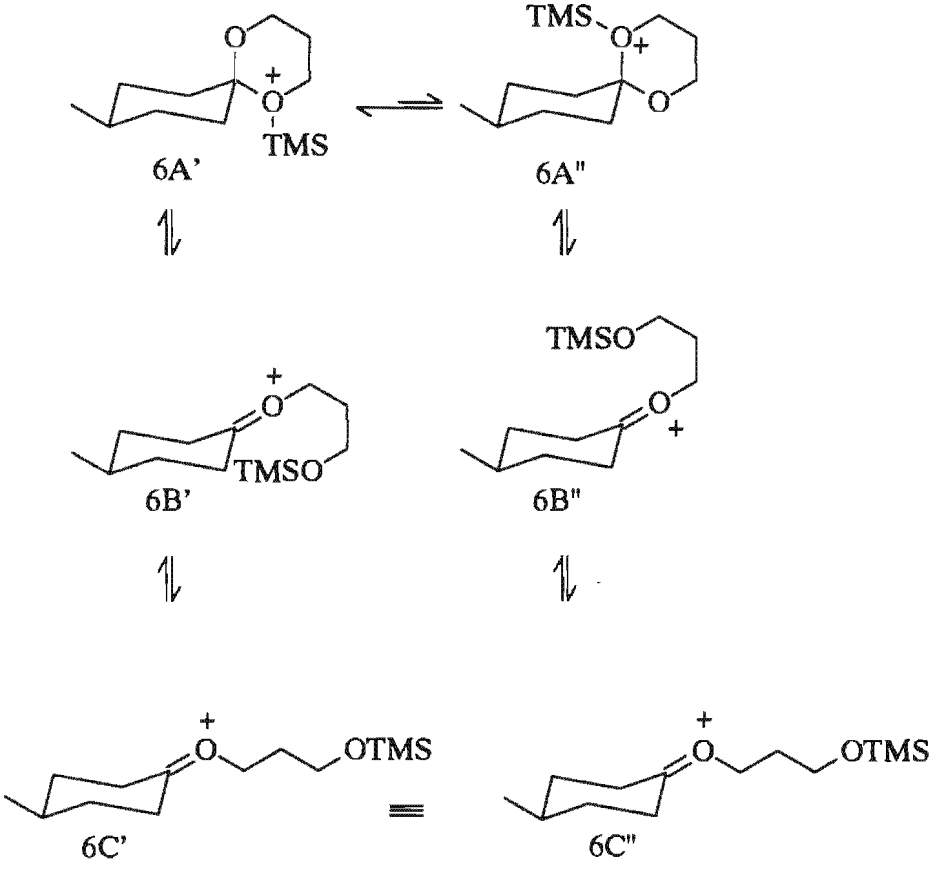


11

multiplet

width of signal = 9 Hz

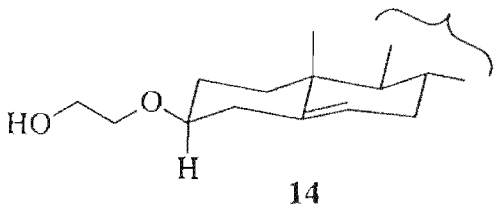
The observed diastereoselectivity is consistent with two mechanistic scenarios. At the one extreme of possible transition states, a spectrum hypothesised recently by Denmark, the reactive complex could be a closed silylated oxonium ion **6A'** or **6A"** and the observed stereoselectivity can be explained by kinetically favoured equatorial O-silylation to afford **6A'**, followed by invertive hydride attack on the ketal carbon to give an equatorial oxygen substituent (scheme 2.5).



Scheme 2.5.

At the other extreme, the reaction could proceed via an open oxocarbenium ion followed by stereoelectronically favoured pseudo-axial hydride delivery as postulated for diastereoselective ring carbonyl reductions[60], using sterically unhindered reducing agents such as sodium borohydride. This method of reduction is complementary, therefore, to reductions of carbonyls with large reducing agents such as super-hydride, in which equatorial attack of the carbonyl group is favoured for steric reasons. However , as Denmark *et al.*[50] and Heathcock *et al.*[53] have commented, it is unlikely that nucleophilic additions to activated ketals goes via a strictly closed transition state with S_N2-type inversion of configuration, but rather that the reactive complex is an external ion pair as depicted by **6B'** and **6B"**.

Another example where simple diastereoselection is demonstrated is with the androstane derivative **13**, 3,3(ethylenedioxy)-androst-5-on-17ß-yl acetate. The reduction of this ketal in dichloromethane occurred at -20°C to afford the α and ß isomers in a ratio of 1:99, assigned by the nmr signal for H-3. Again, it is evident that axial-hydride attack is preferred, which is consistent with the previous example.

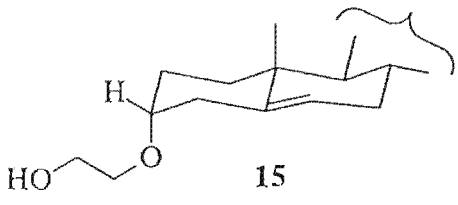


14

triplet of triplets

$J_{ax\text{-}ax}$ = 11.1 Hz

$J_{eq\text{-}ax}$ = 4.1 Hz



15

triplet of triplets

$J_{eq\text{-}ax}$ = 4.7 Hz

$J_{eq\text{-}eq}$ = 1.4 Hz

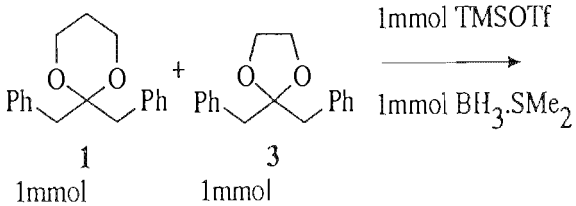
The third product isolated was again a dimeric product formed by the mechanism depicted in scheme 2.4. The percentage yield of the dimeric product of the steroid **13** is much lower than that of **3**, and is likely to be due to the greater steric bulk of the steroid

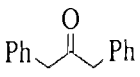
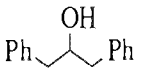
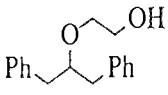
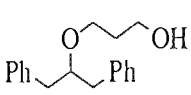
being unfavourable for dimer formation. It is noteworthy that the double bond at position C5-C6 and the acetate at position C17 were unaffected by the reagents at -20°C.

2.2. Relative Reactivity of Dioxane vs Dioxolane

As a result of the different behaviour of dioxolane and dioxane ketals towards the reagent combination, competition experiments were carried out to gather more mechanistic information about their reactivity. In this experiment, 1 mmol each of 2,2-dibenzyl-1,3-dioxane **1** and 2,2-dibenzyl-1,3-dioxolane **3** were reduced in dichloromethane by 1 mmol each of the reagent combination. The latter were introduced into a solution of the two substrates at -78°C via a graduated 1.0ml syringe. In this step the possibility of the introduction of a 5-10% error did exist. A more dilute solution of the reagents could have been used to be more accurate, but the results obtained provided enough information. TMSOTf was first added at -78°C, followed by the borane after 15 minutes. The length of time and the temperature was varied and the results are depicted in table 2.2.

Table 2.2



Temp	Time	1	3		 5	 4	 2
-78°C	1 hour	-	0.95mmol	0.33mmol	-	-	0.67mmol
-78°C	3 hours	-	0.74mmol	0.52mmol	0.19mmol	-	0.57mmol
-78° to -40°C	2 hours	-	0.86mmol	0.47mmol	0.18mmol	-	0.46mmol

In none of the experiments was there any starting dioxane ketal **1** isolated or any product of ketal opening of the dioxolane **3**. In all experiments there were significant amounts of dibenzylketone isolated, and in each case some of this product must have been a result of reaction of both the dioxane and dioxolane ketals. Furthermore, in entries 2 and 3, dibenzylmethanol was isolated and less of the product **2** of reductive cleavage of the dioxane ketal **1**.

The following conclusions may be drawn from these experiments:

(a) Although $BH_3{\cdot}SMe_2$ contains 3 mol equivalents of hydride, only one of them appears to be important as a nucleophile indicating that H_2BOTf is not a competitive reducing species under these reaction conditions.

(b) The most likely pathway for the production of dibenzylmethanol is via the ketone (scheme 2.3), although the pathway via the reduction of reduced dioxane cannot be ruled out.

(c) When borane is the limiting reagent, as in this case, the dioxane is reduced chemoselectively in the presence of the dioxolane. Furthermore, under these limiting conditions, some cleavage of the dioxane ring to ketone and/or alcohol directly is possible. This was not observed in the model studies using 2 mol equivalents of reagent (see table 2.1.)

A possible explanation of the chemoselectivity, consistent with recent thinking[42] in this field, is that silylation of one of the dioxane ring oxygens with concomitant C-O bond lengthening relieves the 1,3-diaxial strain between the C_2 ketal carbon axial substituent (benzyl in this case), and the axial hydrogens at C-4 and C-6. This non-bonded interaction is less severe in the dioxolane case. Moreover, the chemoselectivity is consistent with seminal results obtained by Leggetter and Brown in the 1960's on the

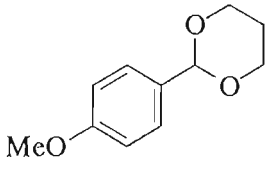
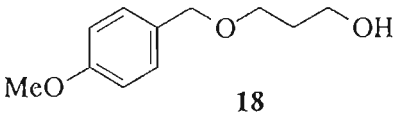
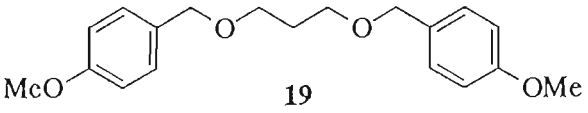
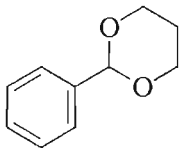
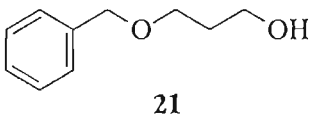
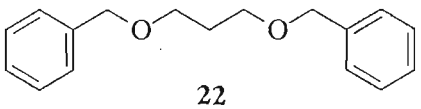
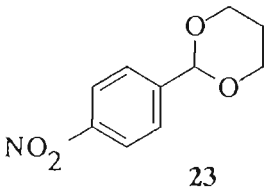
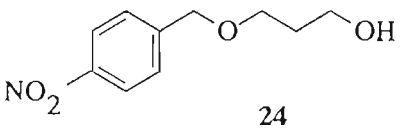
relative rates of reductive ring cleavage using $LiAlH_4/AlCl_3$ as the reducing agent. These authors concluded that the relief of 1,3 diaxial strain was a more important factor in ring opening than the stereoelectronic requirements for oxocarbenium ion formation which were more favourable in the dioxolane case.

In the present scenario, the reduction proceeded at a much lower temperature and, as already discussed, the reaction might not proceed via a truly opened oxocarbenium ion, but rather via an external ion pair. The difference in the reactivity and the outcome of the reaction of the two substrates points towards a difference in the structure of the transition states involving nucleophilic hydride delivery. The most plausible explanation at this stage was that the dioxolane has a more opened reactive complex (more S_N1-like) in the reduction step while the dioxane has a more closed transition state (more S_N2-like).

2.3. Reduction of Aromatic Acetals

The reactivity of aromatic acetals towards reduction was studied, since benzylidene acetals are of major importance in carbohydrate chemistry[62] and reduction of these leads to benzyl protected hydroxy groups.

Table 2.3.

Substrate	Product(s)	Yield
 **17**	 **18**	33%
	 **19**	35%
 **20**	 **21**	75%
	 **22**	25%
 **23**	 **24**	77%

The regioselectivity of their reduction will be dealt with in detail in Chapter 5, but initially from a mechanistic point of view, it was interesting to study the relative reactivity of acetals **17**, **20** and **23**, in which the aromatic substituents (-OMe, -H and -NO_2) were anticipated to have a rate effect (table 2.3).

Acetals **17** and **20** both reacted rapidly at -78°C to give significant amounts of dimeric product. The percentage of this side product was higher for acetal **17**, but the lower overall yield of products from acetal **17** may be attributed to the instability of the *p*-methoxybenzyl group in the products[63,64]. This possibility is supported by the result of a model study, in which it was found that this hydroxyl protecting group was cleaved by the reagents at -50°C (section 2.5). The reduction of acetal **23** proceeded to completion only at 0°C and there was no evidence of a dimeric product.

Thus, it can be concluded that the formation of the dimeric product is enhanced by the ability of the aryl group attached to the acetal centre to stabilise an oxocarbenium ion. The methoxy group of acetal **17** is able to donate electron density mesomerically into the aromatic ring to stabilise the incipient positive charge at the acetal carbon, while the electron-withdrawing group of acetal **23** retards the formation of the oxocarbenium ion.

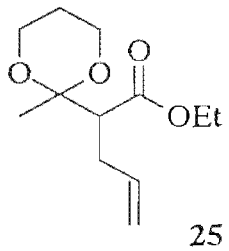
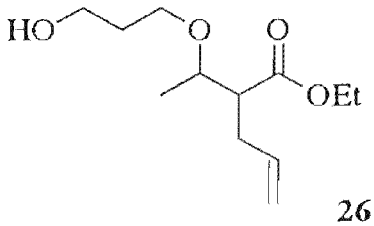
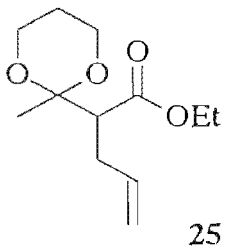
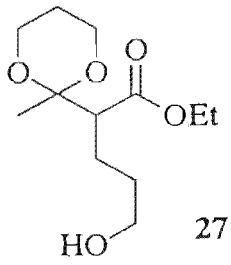
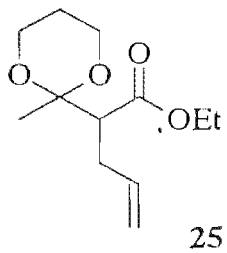
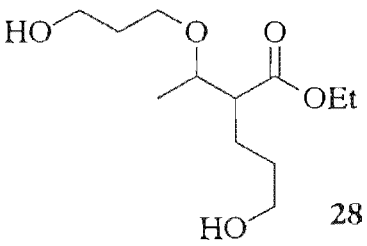
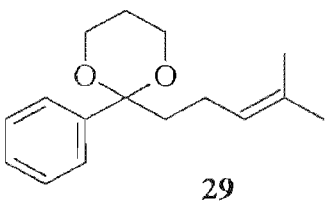
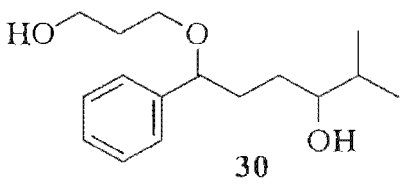
2.4. Chemoselectivity Studies

In order to demonstrate that under these conditions reduction of ketals could occur chemoselectively to double bond hydroboration and vice-versa, the ketal of ethyl allylacetoacetate and 1,3-propanediol **25** was studied (table 2.4). Cooling the substrate to -78°C before adding the TMSOTf and $BH_3{\cdot}SMe_2$ resulted in chemoselective reduction of the ketal at -20°C to give product **26**. By comparison, selective hydroboration of substrate **25** could be achieved by reaction of **25** at 0°C with $BH_3{\cdot}SMe_2$ without Lewis acid followed by oxidative workup with basic peroxide[65] to afford compound **27**.

Finally, intramolecular reduction of **25** could be accomplished by firstly hydroborating at 0°C followed by cooling to -78°C and addition of TMSOTf. Allowing the mixture to warm to -20°C resulted in ketal reduction and the diol **28** was obtained after the normal oxidative workup as a 3:2 mixture of diastereomers.

A similar reaction sequence was performed on substrate **29** and product **30** was isolated as a 1:1 mixture of diastereomers. Thus, it appears that intramolecular reduction of these systems is viable but proceeds with low diastereoselectivity, hence the concept of intramolecular reduction via anchoring of the borane by hydroboration was not pursued further at this point.

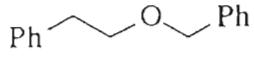
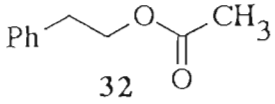
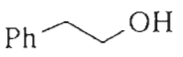
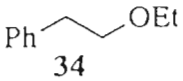
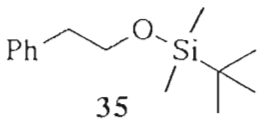
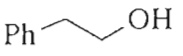
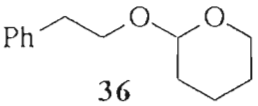
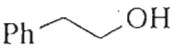
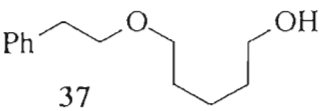
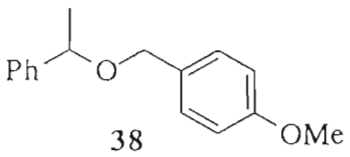
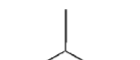
Table 2.4.

Substrate	Product	Yield
 **25**	 **26**	77%
 **25**	 **27**	80%
 **25**	 **28**	36%
 **29**	 **30**	72%

2.5. Protecting Group Studies

As an extension of the chemoselectivity studies in the context of multifunctionalised substrates, the reduction of common protecting groups[4] with $TMSOTf/BH_3{\cdot}SMe_2$ was examined. The results are summarised in table 2.5.

Table 2.5

Substrate	Product(s)	Conditions	Yield
 **31**	no reaction	-78°C to RT	-a
 **32**	 **33**  **34**	-78° to 0°C	57% 40%
 **35**	 **33**	-78°C	70%
 **36**	 **33**  **37**	-78° to -20°C	83% 10%
 **38**	 **39**	-78° to -50°C	60%

a: 98% of starting material recovered

As can be seen, the benzyl group **31** is stable towards the reagents even up to room temperature. The acetate functionality **32** was stable at -78°C and reaction only occurred

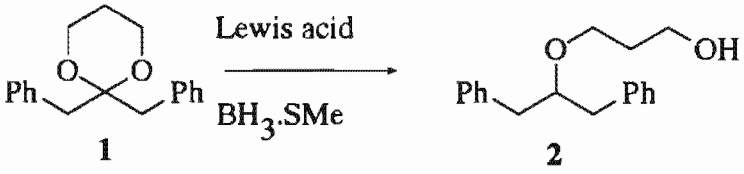
above -20°C with carbonyl reduction to the ethyl ether and cleavage to the alcohol. As evidenced by examples **13** and **25**, esters are far less reactive than a ketal centre towards reduction under these conditions. The *t*-butyldimethylsilyl protecting group in **35** was completely removed to afford the alcohol at -78°C within 30 minutes. The tetrahydropyranyl protecting group in **36**, an acetal itself, was of interest in order to ascertain the direction of cleavage, i.e. exo with loss of the tetrahydropyran ring **33** or endo with opening of the ring **37**, see chapter 5. 2-Phenylethanol was the major product together with traces of **37**. Difficulty was experienced in the purification of **37** as there were other unidentifiable products with similar chromatographic properties.

The *p*-methoxybenzyl group, a common protecting group in carbohydrate chemistry, and usually cleaved by cerium ammonium nitrate, CAN[63c], was reduced at -50°C to the alcohol even though the unsubstituted benzyl protecting group is stable. Again, this is presumably due to the mesomeric release of electron density from the methoxy group to activate the group towards reduction.

2.6. Study of Different Lewis Acids

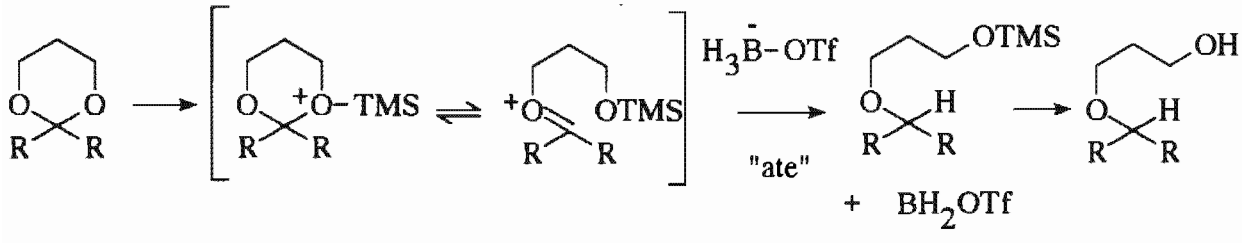
Besides TMSOTf, other Lewis acids were also used as activators and the results are summarised in table 2.6.

Table 2.6.



Lewis acid/CH_2Cl_2	temperature	Yield
TMSOTf	-78°C, 1hour	95%
$TiCl_4$	-78° to 0°C, 2hours	70%
$SnCl_4$	-78° to 0°C, 2hours	88%
$BF_3.OEt_2$	-78°C to RT	-

From this table, it may be concluded that TMSOTf is the Lewis acid of choice regarding efficiency and selectivity. Although $TiCl_4$ is a stronger Lewis acid than TMSOTf[66], a plausible explanation for the reversed reactivity is that upon complexation with the Lewis basic ketal, TMSOTf dissociates and the triflate ion plays an activating role in the hydride delivery step by priming the borane dimethylsuphide to form an "ate" complex. By comparison, $TiCl_4$ may well retain its four chlorine ligands up to a much higher temperature thus retarding the reduction step via an "ate" complex (scheme 2.6).

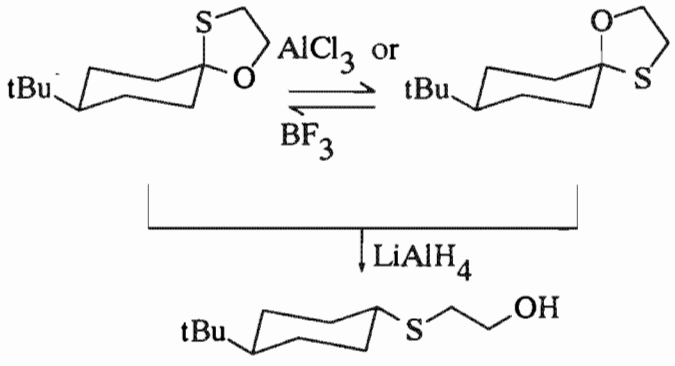


Scheme 2.6.

2.7. Reduction of Mixed O,S Ketals and S,S Acetals

Monothioacetals and dithioacetals are very important and useful carbonyl derivatives[67] in organic synthesis, providing carbanions for use in alkylation reactions. Otera *et al.*[68] have recently reported that a monothioacetal can be converted by nucleophilic displacement into either ethers or a thioether selectively using the Lewis acid catalysts $BF_3{\cdot}OEt_2$ or $TiCl_4$ respectively. The authors explained the reaction outcome by the high affinity of $TiCl_4$ towards oxygen. This prompted us to carry out an investigation into the effect of the reagent combination $BH_3{\cdot}SMe_2$/TMSOTf on an O,S ketal. It is known that TMSOTf is a highly oxygenophilic Lewis acid and it was anticipated that only C-O bond cleavage would occur in the reduction.

Reductions of O,S ketals were studied by Eliel *et al.*[15] in 1962, when they reported on the reduction of cyclic 1,3 oxathiolanes with a mixture of $LiAlH_4/AlCl_3$. They found that with this reagent selective cleavage of the carbon-oxygen bond occurred. Leggetter and Brown[69] showed that BF_3 could also be used in conjunction with $LiAlH_4$ to effect this transformation. Eliel *et al.*[15] also reported that these Lewis acids isomerised 1,3 oxathiolanes via a thionium ion and this step was faster than the reduction as the product of both isomers was the thermodynamically favoured trans-isomer (scheme 2.7).



Scheme 2.7.

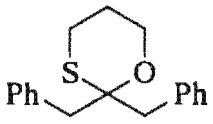
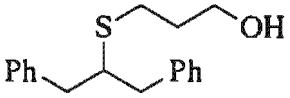
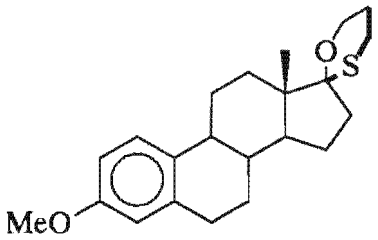
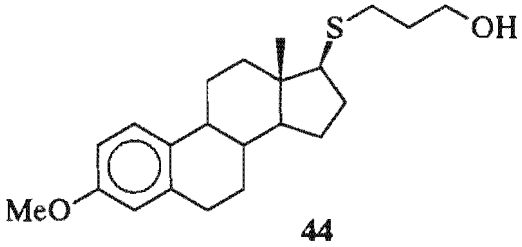
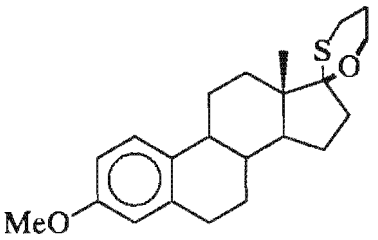
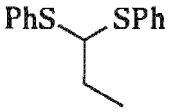
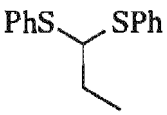
The results of the present study are summarised in table 2.7.

The first mixed O,S ketal studied was that of dibenzylketone and 3-mercaptopropanol **40**. It was found that only C-O bond cleavage occurred and this was verified by the ^{13}C nmr spectrum in which the signal for the reduced ketal centre was at 49.4 ppm compared to 82.6 ppm for that of 2,2-dibenzyl-1,3-dioxane.

The next substrates studied were the mixed O,S ketals **42** and **43**. Both ketals were formed on ketalisation of 3-methoxyestra-1,3,5(10)-triene-17-one with 3-mercaptoethanol. The isomers were separated by chromatography, but it was not possible to assign the stereochemistry of the C-17 position. The reduction of both isomers resulted in an identical product **44**, tentatively assigned to be the 17ß-derivative, which is consistent with Eliel's findings[15] on the isomerisation of this type of compound and clearly shows that for O,S ketals the reduction goes via an open thionium ion (S_N1). However, this does not prove that the identical mechanism operates for O,O ketals.

A simple S,S acetal **45** was also subjected to the reagent combination and some reduction (37%) did occur at -78°C with 1.1 eq. of both reagents but, optimum yields could not be obtained with excess reagent or higher reaction temperature. Further studies on the use of other Lewis acids are warranted for this reaction.

Table 2.7

Substrate	Product(s)	Yield
 **40**	 **41**	72%
 **42**	 **44**	84% from 42
 **43**		97% from 43
 **45**	 **46**	37%
	 **45**	42%

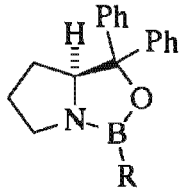
In Conclusion

The reagent combination TMSOTf/BH_3·SMe_2 is a potent reducing agent for acetals and ketals. The reduction generally occurs at low temperatures (-78°C) and in good yield for 6-membered-ring dioxane ketals. However, with 5-membered dioxolane ketals and acetals with electron-donating groups, side reactions occur to give products of dimerisation or ketal ring fragmentation to afford ketone or alcohol. The former pathway appears to be favoured over the latter for spiroketals except where steric hindrance plays a major role. Conversely, the latter pathway is favoured for acyclic ketals. The difference in reactivity is most likely due to the transition state for dioxolane hydride reduction, being more open and thus having more oxocarbenium character than its six membered ring counterpart.

CHAPTER 3

The Stereochemical Aspect of Ketal Reduction

The stereoselective addition of nucleophiles to carbonyl groups, in particular the asymmetric reduction of ketones is a very important reaction in synthetic organic chemistry[70]. The direct formation of optically active alcohols with high enantiomeric purities is difficult using classical synthetic reactions and many studies have focussed on modifying aluminium or boron hydrides with chiral ligands and on the transfer of chirality by delivery of a hydride ion attached to a chiral centre (e.g. Meerwein-Ponndorf-Verley reduction). However, one of the major drawbacks of these methods is their lack of general application as they are effective only for aromatic or α,ß-unsaturated ketones. Recently, E.J. Corey *et al.*[71] have reported on the use of a chiral oxazaborolidine VII as a catalyst in the presence of borane for the enantioselective reduction of ketones in high enantiomeric excess, (scheme 3.1).



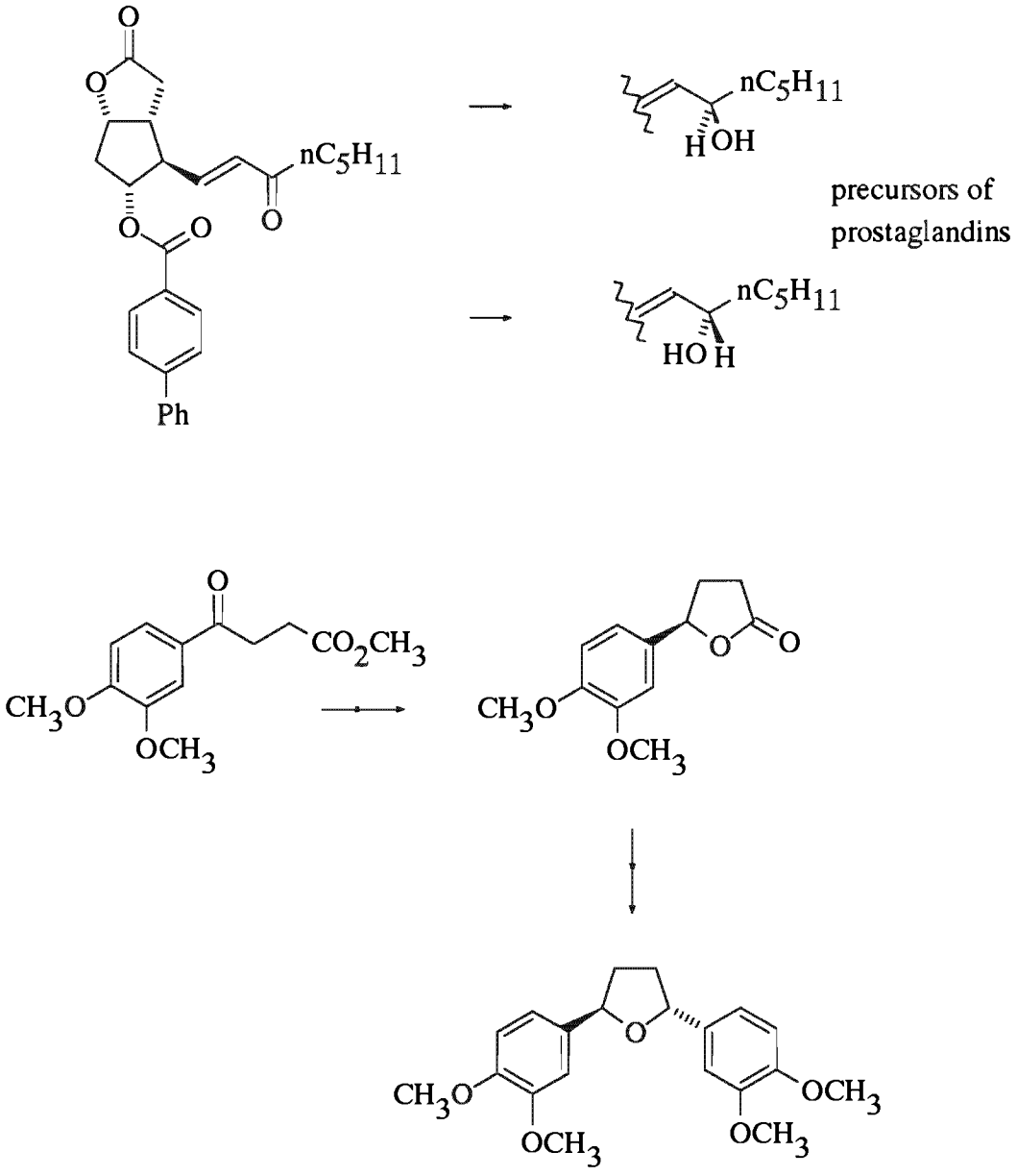
VII

R = H or CH_3

$$2R_1R_2CO + BH_3 \xrightarrow[2\text{ mins}]{\text{VII, THF}} (R_1R_2CHO)_2BH \longrightarrow 2R_1R_2CHOH$$

Scheme 3.1.

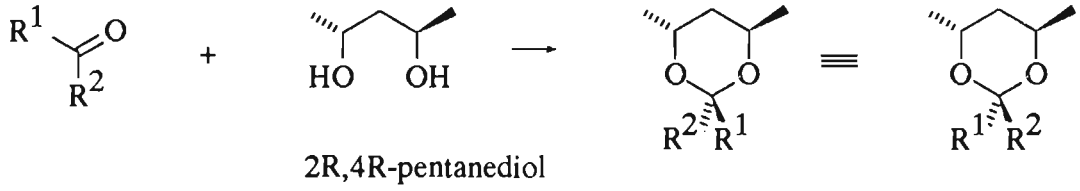
The same authors[72] illustrate the utility of this catalytic reagent by using it for several reductions to produce synthetically useful intermediates, (scheme 3.2).



Scheme 3.2.

A key feature of these reagents is that they all contain the chirality in the reducing agent. From a stereochemical perspective the unique advantage of using acetals and ketals in nucleophilic addition reactions is the possibility of using the acetal functionality as a chiral auxiliary by using optically active diols. During the past decade there have been a growing number of papers in the literature on the use of chiral acetals and a recent review by Alexakis and Mangeney[42] describes the usefulness of these auxiliaries in asymmetric synthesis. With this in mind, it was decided to examine the

use of the reagent combination for the stereoselective reduction of ketals prepared from diols having a C_2 axis of symmetry, (scheme 3.3). These "masked" carbonyls form a single diastereomer.

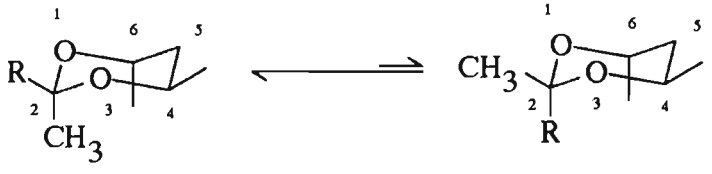


2R,4R-pentanediol

R^1 = cyclohexyl or n-hexyl
R^2 = methyl

Scheme 3.3.

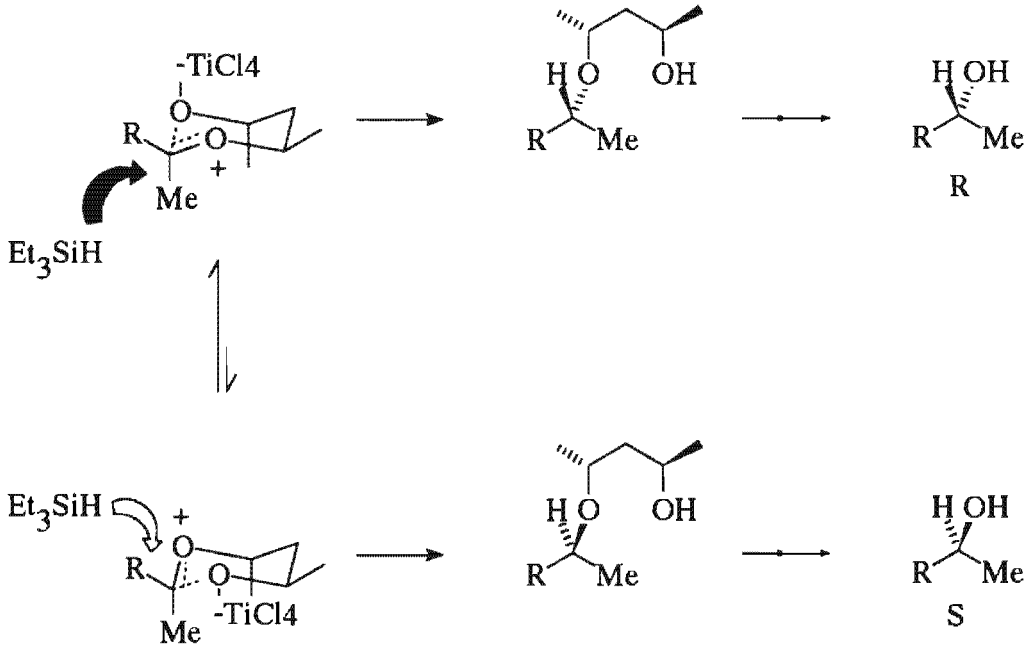
The reasons for choosing 2R,4R-pentanediol as a chiral auxiliary were threefold, namely that it is readily accessible and comparatively cheap, a lot of information is available in the literature on these ketals and the dioxane-type derivatives had so far given satisfactory results concerning yield and lack of side-products. The ketals of 2-octanone and cyclohexylmethyl ketone were of particular interest, since H. Yamamoto *et al.*[28,73-78] have used these ketals in their study of asymmetric reductions and have shown that $TiCl_4$ (1.2 eq) and triethylsilane (1.2 eq) at -78°C in CH_2Cl_2 reduce them with high diastereoselectivity (98:2, R:S). In rationalising the high stereoselectivity they assumed that the difference in steric bulk between the cyclohexyl group (or n-hexyl) and the methyl group is sufficiently large to fix the cyclic ketal as its lowest energy conformer, (scheme 3.4).



R = cyclohexyl or n-hexyl

Scheme 3.4.

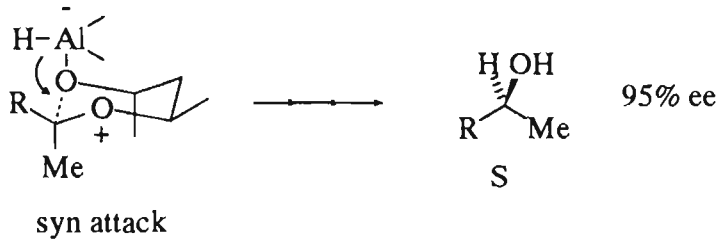
The observed stereoselectivity was rationalised as involving specific coordination of the Lewis acid to the sterically more accessible oxygen, O^1, adjacent to the axial methyl group followed by attack of hydride from the Si-face of the masked carbonyl in an S_N2-type inversion reaction. The complexation of the Lewis acid to O^1 has also been invoked by other workers[42] and is explained by the anomeric effect whereby complexation to O^1 leads to a lengthening of the O^1-C^2 bond and subsequent shortening of the O^3-C^2 bond. This relieves the 1,3 diaxial interaction between the axial methyl group and the substituent on C^2, (scheme 3.5).



Scheme 3.5.

However, the same authors[78] have shown that using $SnCl_4$ or $AlCl_3$ as the Lewis acid in the presence of triethylsilane results in lower stereoselectivities (65:35, R:S and 66:34, R:S). The authors do not comment on the reasons for this, but it is consistent with Denmark's hypothesis[50] that it is a consequence of a different reactive complex in the transition state with these Lewis acids, i.e. the transition state may be more like an external ion pair resulting in moderate stereoselectivities with $SnCl_4$ and $AlCl_3$ and

more like a closed transition state with $TiCl_4$. As a complementary reaction they have also reported that organoaluminium reagents such as DIBAH or Br_2AlH produce the opposite stereoisomer which they rationalise in terms of *syn* hydride delivery with retention of ketal configuration, (scheme 3.6).

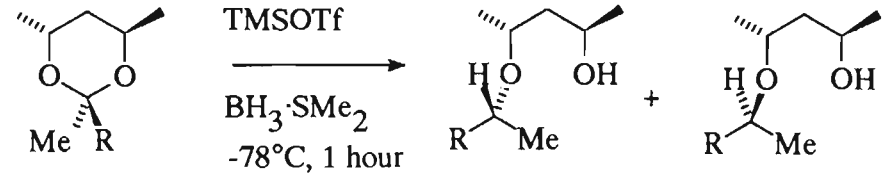


syn attack

Scheme 3.6.

The following table summarises the results obtained using $BH_3{\cdot}SMe_2$/TMSOTf.

Table 3.1



46, R=cyclohexyl

47, R= n-hexyl

R S

R	solvent	Yield[a]	Ratio[b] R:S
cyclohexyl	hexane	96%	60:40 (62:38)[c]
cyclohexyl	CH_2Cl_2	92%	79:21
cyclohexyl	THF	98%	79:21 (78:22)[c]
n-hexyl	hexane	37%	50:50
n-hexyl	CH_2Cl_2	51%	64:36
n-hexyl	THF	63%	75:25

a: isolated yield after column chromatography

b: diastereomeric ratio determined by gc

c: diastereomeric ratio determined by quantitative ^{13}C nmr

The cyclohexylmethyl ketal was prepared by initial ketalisation of the ketone with trimethylorthoformate followed by transketalisation with the chiral diol in the presence of pyridinium *p*-toluenesulphonate (PPTS). In this way unreacted diol can be retrieved after the reaction by simple filtration. The n-hexylmethyl ketal was prepared by reacting the ketone with the chiral diol with azeotropic removal of water, followed by a non-aqueous workup. All reactions were carried out at -78°C for one hour and after standard workup and chromatography only traces of starting material were present. In the case of the ketal of 2-octanone the low yields can be ascribed to the volatility of the products. The diastereomeric ratios were determined by gc (Hewlett Packard 588OA Series), using a supelcowax 10 fused silica capillary column of length 30 m, inner diameter 0,25 mm and film thickness 0,25 m with nitrogen as the carrier gas. The values quoted in table 3.1 were averaged from two experiments. The retention times for the cyclohexylmethyl derivative were 22.1 min for the minor and 22.5 min for the major diastereomer and for the n-hexylmethyl derivative 16.8 min for the minor and 17.4 min for the major diastereomer with good baseline separation. For the cyclohexyl derivative H. Yamamoto *et al.*[76] obtained retention times of 10.9 min and 14.0 min for syn and anti products respectively and for the *n*-hexyl 11.4 min and 12.3 min for the syn and anti products respectively. It can be deduced that major products in this case are thus a result of anti addition of hydride to the activated ketals.

The use of ^{1}H nmr for the determination of the diastereomeric ratios was unsatisfactory. The signals for both isomers overlapped in the 200MHz spectrum. The addition of trichloroacetyl-isocyanate (TAI) to the diastereomeric mixture which contain hydroxy groups, reported in the literature[79] to give separated N-H signals, in this case gave no resolution. Fortunately, the signals in the ^{13}C nmr were well resolved and quantitative ^{13}C nmr could also be used for the determination of the ratios. This is a practical source of quantitative analytical information from mixtures containing carbon[80]. In this method, in order to allow for the different T_1 relaxation times for the ^{13}C in each

molecule, a sufficiently long delay is introduced after data acquisition. For this the decoupler is only gated on during acquisition and off during a recovery time chosen to be at least four times as long as the longest T_1 (estimated in this case to be 4 seconds). Alternatively, the addition of small amounts of $Cr(AcAc)_3$, a paramagnetic substance soluble in $CDCl_3$, shortens all T_1 values thus quenching all NOE effects, but was not necessary in this case. Quantitative data was thus obtained by numerical integration of the transformed spectra and the results obtained from this corresponded well with the gc analysis.

To determine the absolute configuration of the newly created chiral centre, one of the cyclohexylmethyl derivatives was subjected to Swern oxidation followed by base catalysed ß-elimination to afford the unprotected chiral alcohol. The determination of the specific rotation revealed a negative value, which corresponds to the R enantiomer being the major isomer (literature value: $[\alpha]^{25}_D$ +4.58° (neat, d= 0.92) for the S-enantiomer for 92% ee).[76]

The results obtained for the reductions performed in dichloromethane and THF compare favourably with the results obtained by H. Yamamoto's group[78] with triethylsilane and $SnCl_4$ or $AlCl_3$, but unfortunately the diastereoselectivities are not good enough to be synthetically useful. This raises the question as to whether the same mechanism is operating as with the $TiCl_4/Et_3SiH$ combination and whether the difference in steric bulk of the two substituents on the ketal centre is large enough to shift the equilibrium in scheme 3.3. towards conformer A. This may also be affected by the temperature of the reaction.

An interesting effect observed in these results is the difference in diastereoselectivities obtained using different solvents. As seen before from Denmark's[50] as well as Heathcock, Bartlett and H. Yamamoto's[53] work, the solvent may play a key role in

determining the nature of the transition state. In addition, THF may have a significant effect on the reagents (see Chapter 4).

A decrease of diastereoselectivity was also observed by Denmark *et al.*[50] in the study of nucleophilic addition of allylsilanes to acetals in the presence of $TiCl_4$ in less polar solvents such as hexane. The authors attributed this to the possibility that in these solvents the reactive complexes agglomerate to distribute charge. A similar scenario could be envisaged in this study. The intermediate selectivities observed with the more polar solvents is consistent with Denmark's external ion pair reactive complex, but further studies using different boranes and auxiliaries would be necessary to exploit the full use of this methodology in asymmetric reduction.

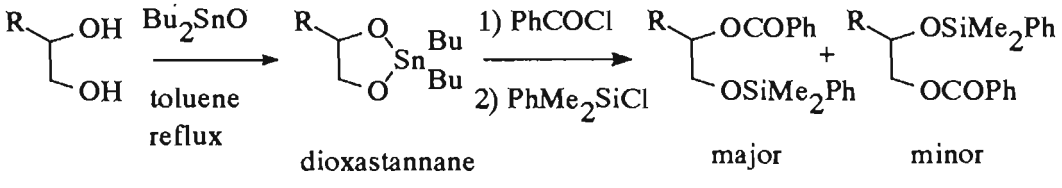
CHAPTER 4

The Regioselectivity of Reduction of Acetals and Ketals[81]

It is of great importance in organic synthesis to be able to distinguish between hydroxyl groups of various polyhydroxy compounds. Selective etherification of primary hydroxyl groups in the presence of secondary hydroxyl groups using trityl chloride[82] has been accomplished and extensive effort has been directed at achieving the selective acylation of unsymmetrical diols and polyols, with varying degrees of success[83]. Recently, Yamada[84] has reported on the selective acylation of the primary hydroxyl group in di- and polyhydroxyl compounds using 3-acylthiazolidine-2-thiones in the presence of NaH. Most methods make use of the difference in reactivity of the hydroxyl groups towards the particular reagent based on the greater acidity of primary hydroxyl groups. Steric factors also play an important role.

Considerable effort has been directed at achieving chemoselective protection of unsymmetrical vicinal 1°,2° diols to afford the thermodynamically and kinetically less stable secondary protected derivative. All of the procedures involve cyclic intermediates.

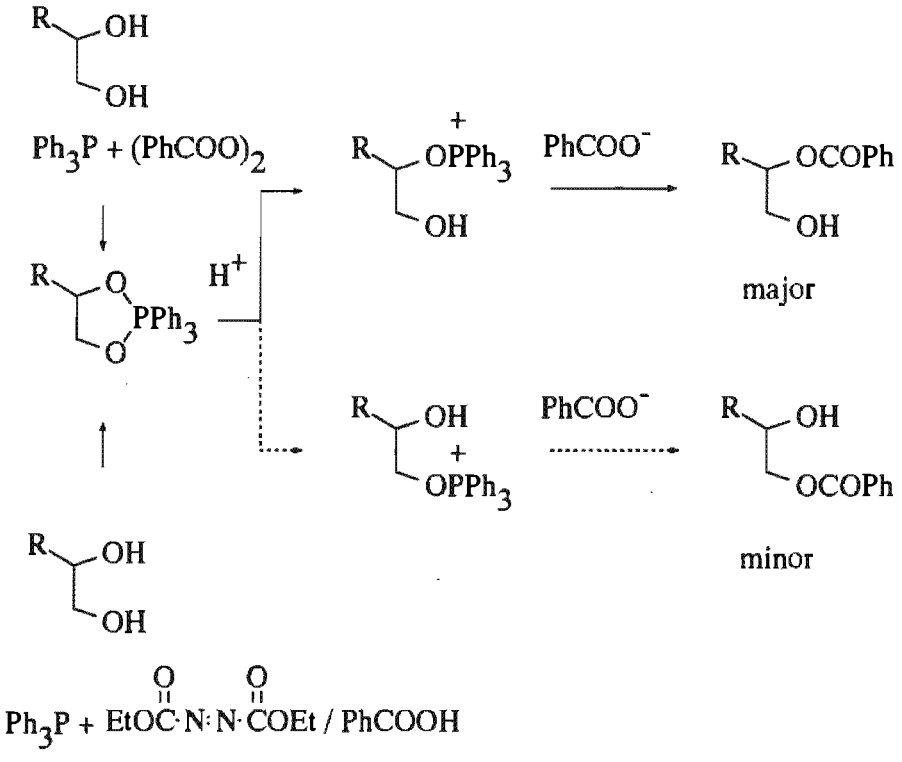
Roelens *et al.*[85,86] have shown that benzoylation of dioxastannanes involves functionalisation of the hydroxyl group attached to the more substituted position (scheme 4.1).



Scheme 4.1.

Previous work involving organotin derivatives[87] for regioselective manipulation of hydroxyl groups had indicated that hydroxyl group reactivity follows the order primary > secondary >> tertiary. This is caused by enhancement of the nucleophilicity of the oxygen in the Sn-O bond for stereoelectronic reasons and is accentuated by small differences in electronegativity between two oxygens in a diol. However, the reactivity of dioxastannylenes is strongly affected by steric factors and experimental conditions.

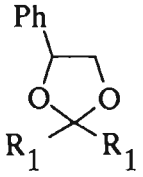
Another method reported in the literature for the reversed esterification of unsymmetrical 1,2-diols is via dioxaphospholanes[88], derived from the reaction of triphenyl phosphine, benzoyl peroxide or diethyl azodicarboxylate/benzoic acid and an unsymmetrical glycol. These phosphorus intermediates protonate with ring cleavage followed by S_N2 substitution to afford the less stable regioisomer (scheme 4.2).



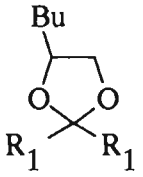
Scheme 4.2.

Up to now in this thesis, the reduction of acetals and ketals has been discussed only from the point of view of the reduced ketal centre, whereas the reduction of acetals can

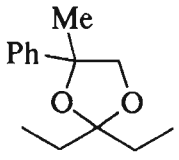
be used in carbohydrate chemistry for overall mono-protection of vicinal diols where the interest lies in the diol part of the acetal[62]. It was of interest, therefore, to study the influence of structure and reaction conditions on the outcome of the reduction of ketals derived from unsymmetrical vicinal diols using $BH_3{\cdot}SMe_2$ and TMSOTf. The diols chosen were 1,2-hexanediol, 1-phenyl-1,2-ethanediol, 2-phenylpropane-1,2-diol, 2,3-heptanediols and substituted glycerols (scheme 4.3).



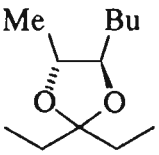
48, R_1 = Me
51, R_1 = Et
54, R_1 = CH_2Ph



57, R_1 = Et
60, R_1 = CH_2Ph



63



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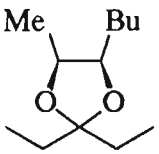

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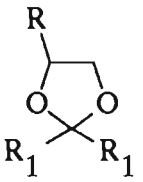
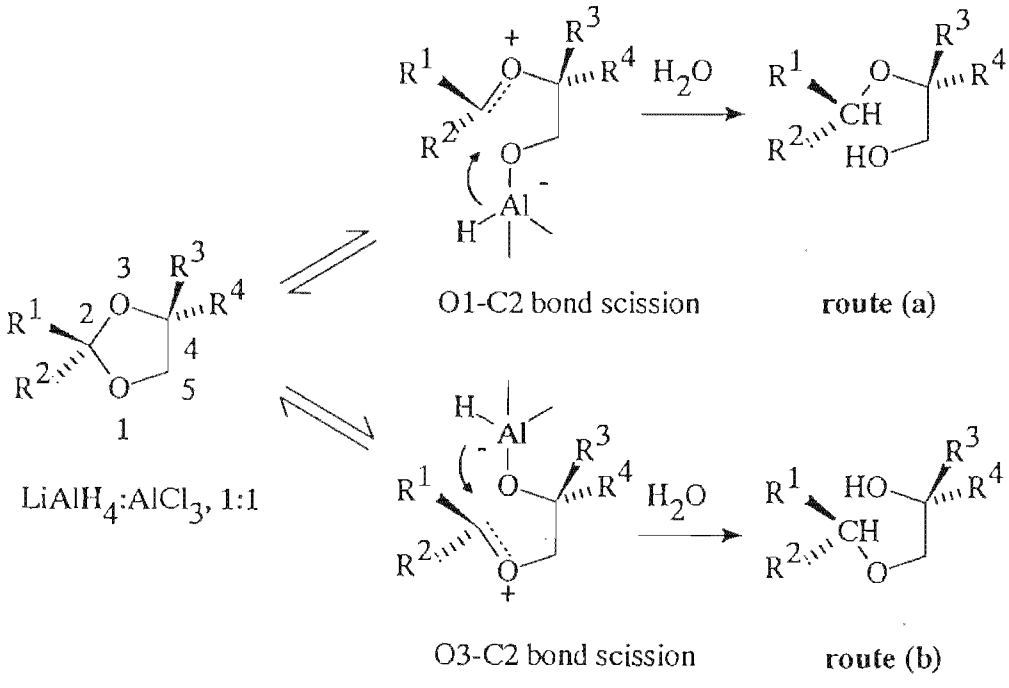


74, R = CH_2OCH_2Ph, R_1 = Me
77, R = CH_2OCH_2Ph, R_1 = CH_2Ph
80, R = CH_2OH, R_1 = CH_2Ph
82, R = CH_2OSi-t-$BuMe_2$, R_1 = CH_2Ph
83, R = CH_2OCOCH_3, R_1 = CH_2Ph

Scheme 4.3.

An important regioselectivity study on the reduction of ketal derivatives of unsymmetrical vicinal diols by Brown and Leggetter[89,90,91,92] using the reagent $LiAlH_4/AlCl_3$ was carried out in the early 1960's.

The authors[90,92] established that in the reductive ring cleavage of 1,3-dioxolanes with an equimolar mixture of $LiAlH_4$ and $AlCl_3$ in ether solution, substituents on C4 of the dioxolane ring exerted a marked control over the direction of the ring opening. Electron donating substituents, (eg. R= methyl), resulted in predominant cleavage of the C2-O1 bond remote from C4, while electron attracting groups, (eg. R=CH_2Cl), attached to C4 resulted in a higher proportion of cleavage of the C2-O3 bond nearest to the C4 substituted position. This selectivity was rationalized on the basis of the stabilizing or destabilizing effect that the C4-substituents exerted on the two possible intermediate oxocarbenium ions, the formation of which was considered to be the rate-determining step (scheme 4.4).



Scheme 4.4.

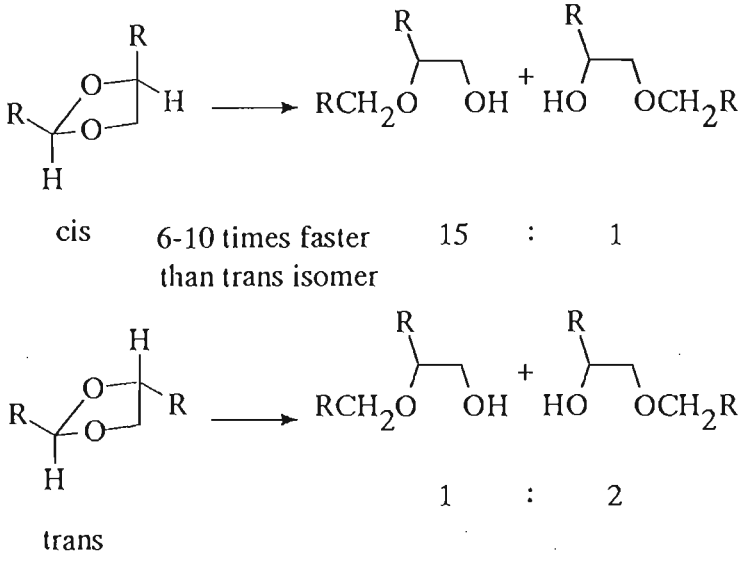
R^3 or R^4 as Me would stabilize the oxocarbenium ion shown in route (a) to a greater extent, hence the reduction would largely follow this route. Conversely, R^3 or R^4 as CH_2Cl would destabilize the oxocarbenium ion from route (a) and the reduction would largely go via route (b).

It should be noted here that Brown and Leggetter[89] initially proposed that, for the reduction using $LiAlH_4/AlCl_3$, the acetal was complexed to $AlCl_3$ and hydride delivery occurred intermolecularly from $LiAlH_4$. Subsequently[92], they suggested that a mixed hydride was the active species in the reduction, as discussed before. At that time, oxocarbenium ions were invoked as intermediates since they accounted for the results obtained. In related research carried out more recently, H. Yamamoto[73] does not rule out this possibility and proposes that with DIBAH and AlH_xCl_y, aluminium behaves as an ambiphilic species delivering the hydride syn to the breaking bond. His research has been directed at investigating the stereoselectivity of reduction at the ketal carbon and he did not study the regioselectivity of the reaction.

Brown and Leggetter[91] also established that the tetrasubstituted dioxolane (R^1=R^2=R^3=R^4=Me) reduced via route (b). This unexpected result was rationalised in terms of the relief of steric strain, due to non-bonded interactions between the four methyl groups and favoured by C2-O3 bond breaking as in route (b), outweighing inductive stabilization of the oxocarbenium ion from route (a). Indeed, the latter in this case was destabilised by steric interactions between the C2 and C4 substituents.

These arguments were supported by the fact that 2,4,4 trimethyl-1,3-dioxolane (R^1=R^3=R^4=Me, R^2=H) and 2,2,4 trimethyl-1,3-dioxolane (R^1=R^2=R^4=Me, R^3=H) both reduced predominantly via route (a) to give the primary alcohols in 90% and 82% yields respectively of total reduction product.

Brown and Leggetter[93] also studied the relative rates and regioselective opening of the cis and trans isomers of 2,4-dialkyl-substituted-1,3-dioxolanes, (ie. R^1=R^3= alkyl, R^2=R^4=H for cis and R^1=R^4= alkyl, R^2=R^3=H for trans), and found that the cis isomer reduced 6 to 10 times faster than the corresponding trans isomer. Furthermore, the ratio between products from route (a) to products from route (b) was 15:1 in the case of the cis isomer and 1:2 in the case of the trans isomer. They gave no clear explanation for this and ruled out an equilibration of the cis and the trans isomers under the reaction conditions (scheme 4.5).

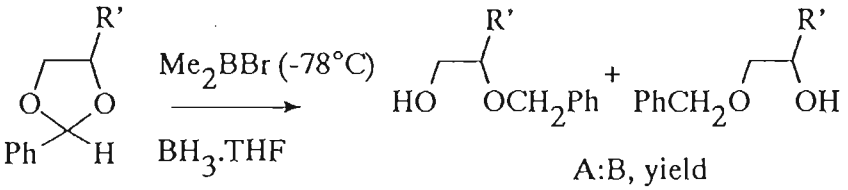


Scheme 4.5.

An example[90] which may be considered as a carbohydrate model is the case where R^1=R^2=Me and R^3 or R^4= -$CH_2OCH(CH_3)_2$ or -CH_2OH. The latter reduced to give a ratio of 19:81 and 14:86 respectively of the products from route (a) and from route (b). Once again this was explained by the influence of the electronic character of the substituent on C4. However, no mention was made of the possibility of chelation of the Lewis acidic aluminium species, with both O3 and the O on the C4 substituent.

More recently, Guindon[35] has studied the regioselectivity of reductive cleavage of benzylidene acetals of unsymmetrical glycols with Me_2BBr/BH_3.THF and established a

preference for primary alcohol, (again via route (a) in scheme 4.4.), rather than secondary alcohol formation. The selectivity was attributed to the preferential complexation of the less hindered oxygen with the boron reagent and subsequent formation of the α-bromo ether, followed by substitution with hydride to give the secondary alcohol protected as a benzyl ether. The trans-disubstituted dioxolane showed a greater selectivity for the primary alcohol than the corresponding cis-disubstitued dioxolane. This was explained by steric congestion of the substituents on both the α and the ß faces in the case of the trans isomer thus maximising the importance of steric considerations. The use of bulkier ligands on boron (eg. Ph_2BBr), enhanced regioselectivity while the presence of chelating groups proximal to the reactive acetal reduced selectivity for the secondary protected alcohol A. In the case of a methoxymethyl group, anchimeric participation (or chelation) competes with steric factors and this increases the amount of undesired primary alcohol (scheme 4.6).



	A:B, yield
R' = $(CH_2)_5CH_3$, trans isomer	14:1, 83%
R' = $(CH_2)_5CH_3$, cis isomer	6:1, 93%
R' = CH_2OCH_3	2:1, 80%
R' = $CH_2CH_2OCH_3$	4:1, 98%

Scheme 4.6.

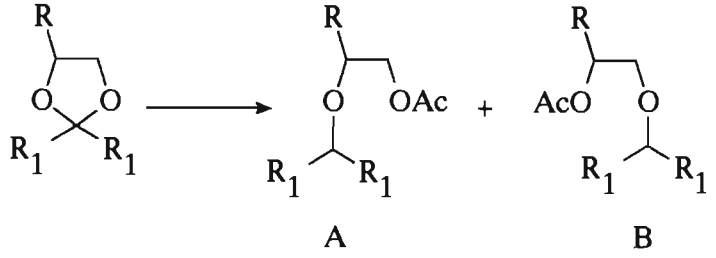
Hence, in the case where R'=CH_2OCH_3, the substituent encourages the complexation of boron to the sterically more hindered oxygen attached to the secondary carbon. This may be attributed to the substituent's influence on the relative stabilities of the two oxocarbenium ions, as proposed by Brown and Leggetter[89-93], as well as the

possibility of anchimeric assistance in favouring the approach of the Lewis acid towards the secondary oxygen.

Regarding studies related to the thesis, it was initially decided to study ketals derived from the unsymmetrical diols 1-phenyl-1,2-ethanediol and 1,2-hexanediol (**48, 51, 54, 57** and **60** of scheme 4.3). The effect of the ketal structure and different reaction conditions on the ratio of secondary protected product A : primary protected product B is summarized in table 4.1.

From the outset it should be mentioned that compared with the dioxolane model systems studied in chapter 2, the reaction in this section proceeded in good to high yields with only traces of dimer formation. In the case of R^1=CH_2Ph, a minor amount of dibenzylmethanol was isolated. This indicates as mentioned before that with increasing steric bulk and complexity of the ketal system the degree of side reactions is reduced.

Table 4.1.



Product yields and isomer ratios from reductive cleavage of ketals **48, 51, 54, 57** and **60** using borane dimethyl sulphide and TMSOTf (2 equivalents) followed by acetylation.

entry	R	R_1	solvent	temp (°C)	ratio A:B	yield (%)
1	Ph	Me	CH_2Cl_2	-78	63:37	60
2	Ph	Me	THF	-78 to +10	81:19	67
3	Ph	Et	CH_2Cl_2	-78 to -30	63:37	84
4	Ph	Et	THF	-78 to +10	98:2	88
5	Ph	Et	diethyl ether	-78 to 0	63:37	76
6	Ph	Et	diisopropyl ether	-78 to 0	62:38	84
7	Ph	CH_2Ph	CH_2Cl_2	-78 to -20	48:52	69
8	Ph	CH_2Ph	THF	-78 to RT	99: 1	56[a]
9	Bu	Et	CH_2Cl_2	-78 to -20	29:71	73
10	Bu	Et	THF	-78 to +4	83:17	72
11	Bu	Et	dioxane	RT	67:33	70
12	Bu	Et	THP	-50 to -30	51:49	80
13	Bu	CH_2Ph	CH_2Cl_2	-78 to -20	31:69	91
14	Bu	CH_2Ph	THF	-78 to RT	90:10	87
15	Bu	CH_2Ph	diethyl ether	-78 to RT	38:62	83

a: THF polymerised, yield is of unacetylated product

The yields quoted in the table are those of the products isolated after acetylation and column chromatography. Except for entries 5, 6, 11 and 12 relating to solvent influence, all experiments were carried out in duplicate and the ratios averaged. In most cases, (except for R=Ph and R_1=Me, **48**), the product regioisomers could not be separated by column chromatography nor was gc analysis on a packed column (OV225) satisfactory, giving no baseline separation. Therefore, product ratios were obtained from the ^1H nmr

spectrum of the mixed products. Acetylation resulted in a downfield shift of the protons attached to the acetoxy group and ratios were obtained by integration. It was found that slightly higher ratios of A:B were obtained by adding borane dimethyl sulphide first, followed by TMSOTf at -78°C. The amount of B was increased significantly when the reaction was carried out at 0°C in CH_2Cl_2 (A:B, 10:90 for **48**, ratio by gc, 30% yield). The gc trace showed a significant amount (40%) of unidentified products and acetylated 1-phenyl-1,2-ethanediol (30%). Therefore, the reactions were all carried out by adding all reagents at -78°C before allowing the mixture to warm slowly to the temperature at which reaction occurred. The reactions were all monitored by t.l.c. of aliquots (0.1ml) of the mixture quenched with saturated $NaHCO_3$ solution. Reactions in THF were all sluggish and care had to be taken not to leave the reaction for too long at temperatures greater than 0°C, as this resulted in polymerization of the solvent, making product isolation difficult (entry 8). From table 4.1, various trends may be identified and these are summarised as follows:

1) The effect of the group on the ketal carbon (R_1) was studied and the results are illustrated in table 4.2.

Table 4.2. Effect of R_1

entry	R	R_1	solvent	temp (°C)	ratio A:B	yield(%)
2	Ph	Me	THF	-78 to +10	81:19	67
4	Ph	Et	THF	-78 to +10	98:2	88
10	Bu	Et	THF	-78 to +4	83:17	72
14	Bu	CH_2Ph	THF	-78 to RT	90:10	87
1	Ph	Me	CH_2Cl_2	-78	63:37	60
3	Ph	Et	CH_2Cl_2	-78 to -30	63:37	84
9	Bu	Et	CH_2Cl_2	-78 to -20	29:71	73
13	Bu	CH_2Ph	CH_2Cl_2	-78 to -20	31:69	91

As can be seen, the isomer ratio improves in favour of the secondary protected derivative A with increasing steric bulk of R_1 when the reaction is performed in THF, but in CH_2Cl_2 R_1 has only a slight influence on the outcome of the reaction.

2) The importance of the group on C4, R, in steering the regiochemistry of the ketal reduction is shown in table 4.3.

Table 4.3. Effect of R

entry	R	R_1	solvent	temp (°C)	ratio A:B	yield (%)
3	Ph	Et	CH_2Cl_2	-78 to -30	63:37	84
9	Bu	Et	CH_2Cl_2	-78 to -20	29:71	73
4	Ph	Et	THF	-78 to +10	98:2	88
10	Bu	Et	THF	-78 to +4	83:17	72

In this case phenyl directs the opening of the ketal more towards isomer A. This effect is more pronounced in CH_2Cl_2 than in THF.

3) Table 4.4 shows the results of using a bulkier Lewis acid eg. *tert*-butyldimethylsilyl trifluoromethanesulphonate (TBDMSOTf) or a bulkier reducing agent, eg. 1,1,2-trimethylpropylborane (thexylborane).

Table 4.4. Effect of bulkier reagents on the reduction of ketal **48**, R = Ph and R_1 = Me

Entry	Solvent	Lewis acid	Borane	temp (°C)	ratio A:B	Yield (%)
1	CH_2Cl_2	TMSOTf	$BH_3{\cdot}SMe_2$	-78	63:37	60
2	THF	TMSOTf	$BH_3{\cdot}SMe_2$	-78 to +10	81:19	67
16	CH_2Cl_2	TBDMSOTf	$BH_3{\cdot}SMe_2$	-78 to -20	26:74	38
17	CH_2Cl_2	TMSOTf	Thexyl	-78 to +5	20:80	-[a]

a: no isolated yield, ratio obtained from gc

4) The most pronounced difference in regioselectivity was observed on changing from CH_2Cl_2 to THF as solvent. In THF there is a greater regioselectivity for the desired isomer A compared with CH_2Cl_2 in spite of the higher temperature required for the reaction (table 4.5).

Table 4.5. Effect of THF vs CH_2Cl_2

entry	R	R_1	solvent	temp (°C)	ratio A:B	yield (%)
1	Ph	Me	CH_2Cl_2	-78	63:37	60
2	Ph	Me	THF	-78 to +10	81:19	67
3	Ph	Et	CH_2Cl_2	-78 to -30	63:37	84
4	Ph	Et	THF	-78 to +10	98:2	88
9	Bu	Et	CH_2Cl_2	-78 to -20	29:71	73
10	Bu	Et	THF	-78 to +4	83:17	72
13	Bu	CH_2Ph	CH_2Cl_2	-78 to -20	31:69	91
14	Bu	CH_2Ph	THF	-78 to RT	90:10	87

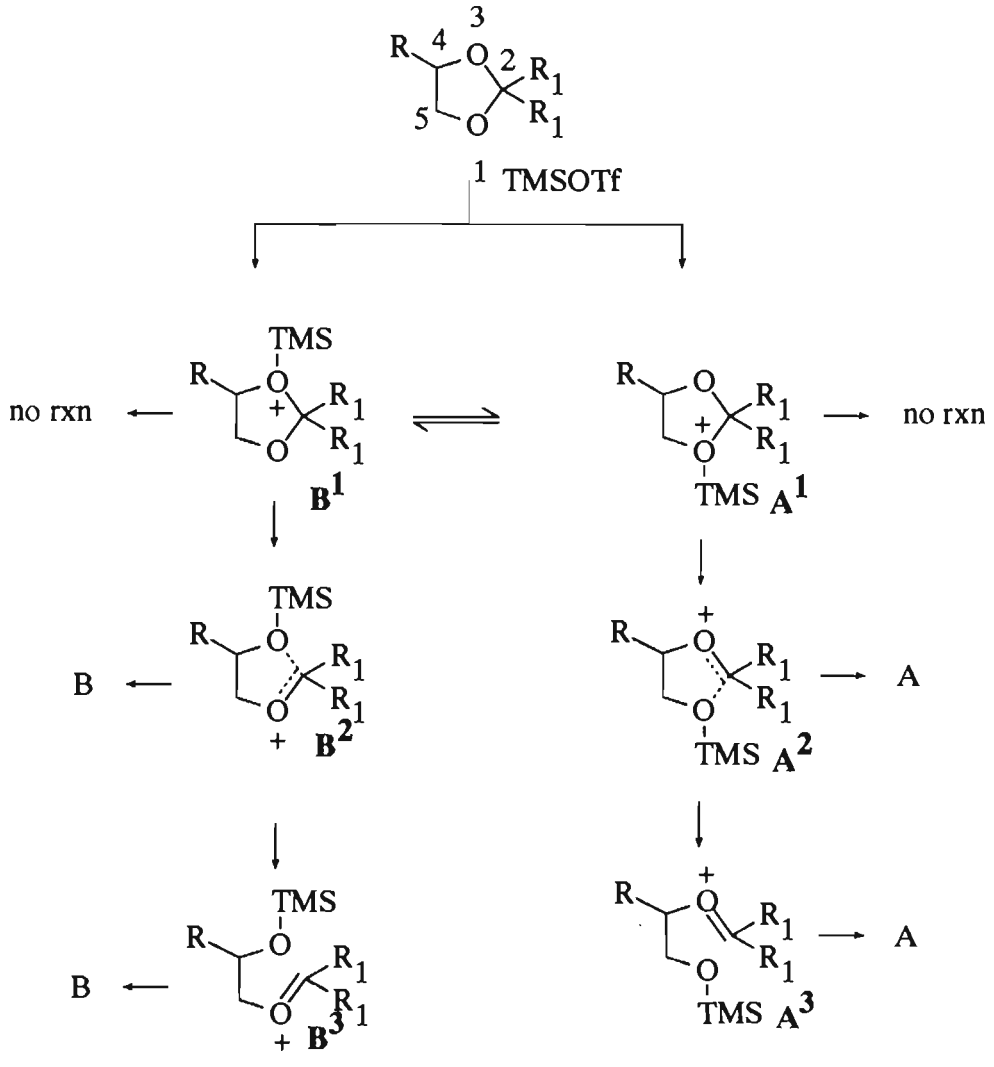
5) Other ethereal solvents, such as diethyl ether and diisopropyl ether, did not significantly alter the ratio of A:B compared with CH_2Cl_2. With dioxane and tetrahydropyran (THP) the ratio of A:B increased in favour of A, but not as much as in THF. For both of these solvents the reaction could not be performed at -78°C, because of their relatively high melting points. Therefore, the reaction in dioxane was carried out at room temperature and that in THP between -50 and -30°C.

Table 4.6. Effect of other solvents

entry	R	R_1	solvent	temp (°C)	ratio A:B	yield (%)
5	Ph	Et	diethyl ether	-78 to 0	63:37	76
6	Ph	Et	diisopropyl ether	-78 to 0	62:38	84
11	Bu	Et	dioxane	RT	67:33	70
12	Bu	Et	THP	-50 to -30	51:49	80
15	Bu	CH_2Ph	diethyl ether	-78 to RT	38:62	83

From the tables above one may conclude that the more Lewis basic the solvent, the greater the regioselectivity shifts in favour of A, particularly for THF. Furthermore, this regioselectivity is more pronounced for R=Ph over R=Bu and for bulky R_1.

The following mechanism is postulated to rationalize the above observations (scheme 4.7).



Scheme 4.7.

There are two possible pathways in the reduction step, which are depicted by A and B. These are analogous to routes (a) and (b) in Brown and Leggetter's mechanism (scheme

4.4). The first step in both pathways is the silylation of the ketal oxygens. Pathway A is initiated by silylation of the sterically less hindered oxygen and thus kinetically favoured and pathway B by silylation of the sterically more hindered oxygen. One has to realize at the outset that it is the site selectivity of the silylation which ultimately controls the regiochemistry of the opening of the cyclic ketal. The two species A^1 and B^1 will exist in equilibrium, which is biased towards A^1 for steric reasons. It is conceivable that these initial complexes are not the reactive species, much in the same way as Denmark *et al.*[50] point out in their hypothesis, depicted in scheme 1.13.

In order for hydride delivery to occur, there must be bond perturbation to A^2 and B^2 at one end of the mechanistic spectrum or A^3 and B^3 at the other. It is this subtle difference in the nature of the reactive species which will control the regiochemistry of the cleavage.

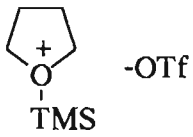
For pathway A to occur, reaction has to proceed via bond lengthening of C2-O1 to form A^2. This step is energetically less favourable than the same step in pathway B, since lengthening of C2-O1 results in simultaneous shortening of C2-O3 which decreases the distance between the substituents on the ketal, R_1, and C4, R. Compared to A^2, formation of B^2 is energetically less demanding because lengthening of C2-O3 relieves the 1,3-strain in the molecule. Once the C2-O1 bond has broken, the energetically more favoured species A^3 is formed. This oxocarbenium ion is favoured over B^3 because of the electronic influence of the electron donating substituents on C4 being able to stabilize the positive charge and will be dominant at higher temperatures.

Thus, when A is formed as a major isomer in the product, reduction proceeds via the thermodynamically favoured oxocarbenium ion pathway A^2 and A^3, whereas when B is formed as a major isomer, the reactive species B^2, for which 1,3-steric strain relief is important, plays a leading role in the reaction pathway.

The above mechanism can be used to explain the influence of the solvent in this reaction. This, as mentioned before, is the least understood effect in nucleophilic substitutions of acetals and ketals and has not been examined in detail in studies on the regiochemistry of this reaction.

In order to explain how the solvent controls the regioselectivity of the ring opening the above mechanism proposes that the two possible silylated oxonium ions A^1 and B^1 may interconvert through silyl transfer and that the pathway followed, A or B, depends on the relative rates of ring opening of A^1 and B^1 which is controlled by the temperature at which silylation occurs. Furthermore, since the possibility of the relative reduction rates of the closed silyloxonium ions A^1 and B^1 being solvent controlled appears to be unlikely, the mechanism proposes that no significant reduction occurs at the A^1/B^1 complex level.

For the results in THF, where isomer A is the major product, the regioselectivity can be explained via the thermodynamically more stable oxocarbenium ion pathway, involving A^2 and A^3. The reductions in THF were always found to occur at higher temperatures than in CH_2Cl_2 suggesting that the solvent plays a mediating role in the silylation step via silylated THF.



The bulky THF silylating agent would be more discriminating than TMSOTf and therefore also favourably influences the initial ratio of complex A^1 to B^1 towards the former silyloxonium ion. The regioselectivity results in THF indicate that ring opening of A^1 to a suitably electrophilic point in the Denmark-type[50] mechanistic spectrum followed by hydride delivery occurs faster than the interconversion to B_1 and the subsequent reduction via pathway B. This is presumably due to A^1 being sufficiently

energetic to pass to A^2 and beyond towards A^3 on account of the higher temperature at which the silylation occurs. The regioselectivities are particularly good for R=Ph in which inductive stabilization of the developing positive charge at the carbon helps to counteract unfavourable 1,3-steric strain due to C2-O3 bond compression on passing from A^1 to A^3 via A^2.

In the solvent CH_2Cl_2 the regioselectivity ratios indicate that more reduction occurs via the B pathway than in THF to varying degrees depending particularly on the R group on C4. Since silylation may proceed unimpeded at -78°C, as evidenced by reduction at this temperature, the results indicate that opening of B^1 to B^2, in which there is 1,3 steric strain relief competes favourably with the conversion of A^1 to A^2. The regioselectivity ratio of B:A is higher for R=Bu compared with R=Ph indicating the greater steric strain relief and reduced inductive stabilization for the former.

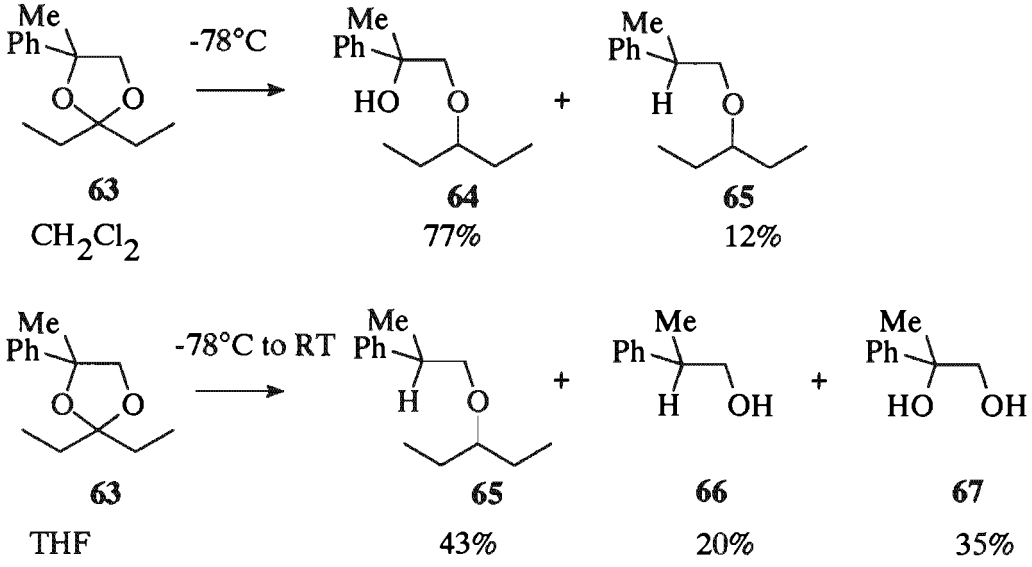
The effect of the other solvents, diethyl ether and diisopropyl ether, can be explained along the same lines as CH_2Cl_2 and it is evident that they do not influence the reagents in the same way as THF does. The results obtained for dioxane and THP are tending towards the same pathway as THF. This might be due to the Lewis basicity and the higher reaction temperature at which the reaction had to be carried out.

The results depicted in table 4.2, where R_1 influences the regioselectivity more in THF as a solvent than CH_2Cl_2 suggests that silylation in the former solvent is more sensitive to the steric factors in the substrate. The interaction of THF with the Lewis acid is proposed as the cause of this.

The results with the bulky reagents TBDMSOTf and thexylborane in separate experiments (entries 16 and 17, table 4.4) are interesting. Both results show a significant shift towards isomer B and are the only instances when the dioxolane **48**, (R=Ph, R_1=Me) gives a greater percentage of B than A. The most likely reason for the

predominance of pathway B is that the B intermediates involve the sterically least demanding trajectory for hydride delivery from a borate species if an anti-mechanism is operating. This is particularly important for the thexylborane case. With the bulky TBDMSOTf the greater relief of 1,3-steric strain for B compared to A may also be a contributing factor. Yields for 16 and 17, however, were much lower than for the $BH_3{\cdot}SMe_2$/TMSOTf combination, and hence not synthetically useful.

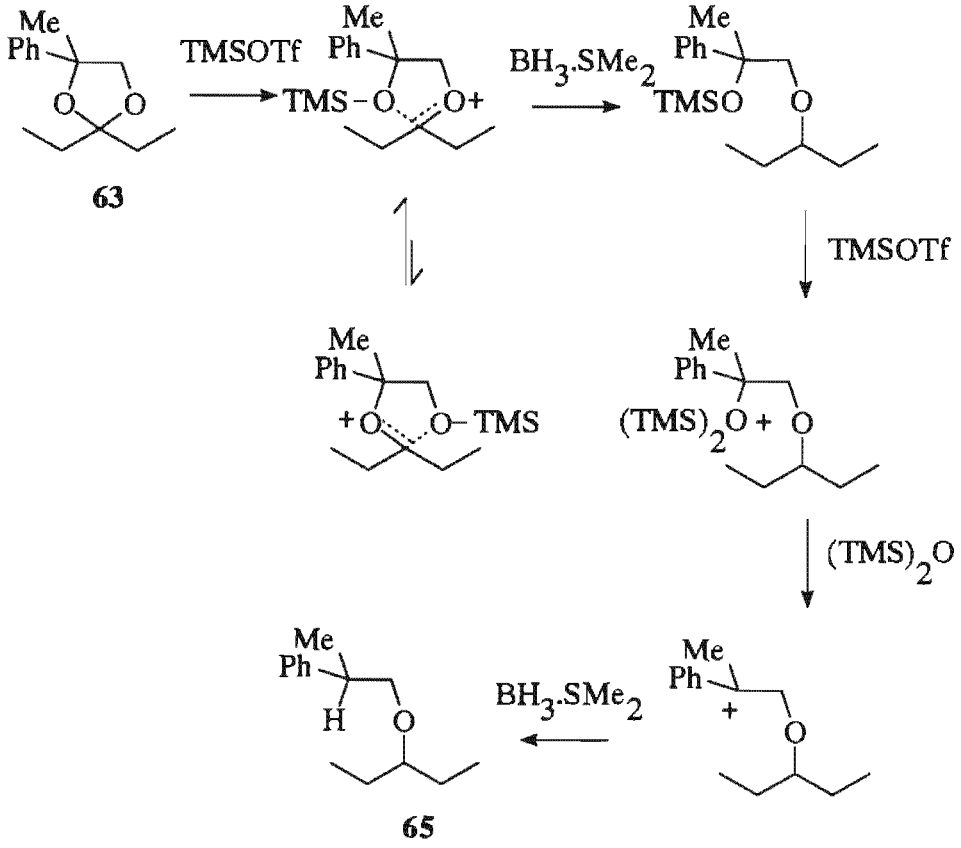
In order to extend the regioselectivity study and to gain more mechanistic insight into the reaction, a ketal derived from a 1°,3°-diol, 2-phenyl-1,2-propanediol was studied and the results are depicted in scheme 4.8.



Scheme 4.8.

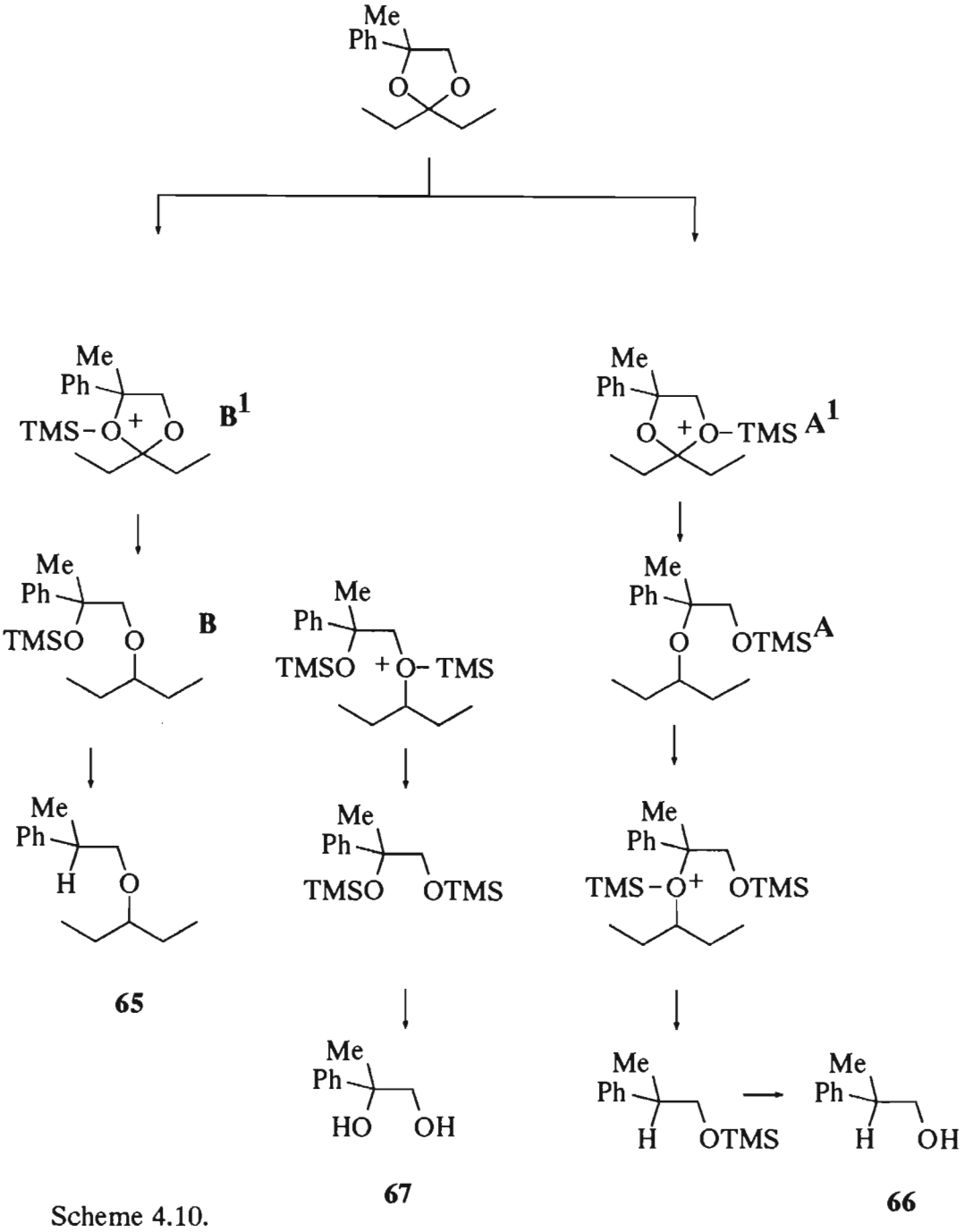
Reduction in CH_2Cl_2 favoured the primary derivative indicating that the reaction proceeded via pathway B with no trace of the secondary protected alcohol. This result highlights the importance of 1,3-strain relief in the substrate and is similar to Brown and Leggetter's findings[91] on 2,2,4,4-tetrasubstituted dioxolanes mentioned earlier. The unexpected and previously unobserved product (**65**, 12%) can be related to the same

silylation process and may be explained by the mechanism depicted in scheme 4.9. Silylation of the ketal occurs and the formation of the reactive complex B^2 is strongly favoured over A^2. Reduction, followed by a second silylation results in a good oxygen leaving group which is displaced by hydride possibly via the carbocation.



Scheme 4.9.

In THF, none of the secondary product was isolated. An attempt at rationalizing the formation of the products is depicted in scheme 4.10.

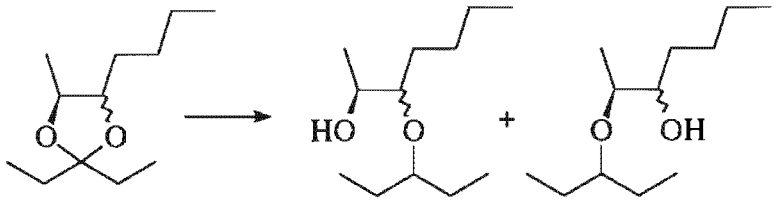


Scheme 4.10.

In this scheme the major pathway followed is via B^1 as a result of 1,3-strain relief. In the reduced species from both A^1 and B^1, a second silylation and subsequent carbocation formation leads to products **65, 66** and **67**.

The next set of substrates studied were the ketals derived from the 2°,2° diols, ±2R,3R-heptanediol and ±2R,3S-heptanediol and the results are summarised in table 4.7.

Table 4.7.



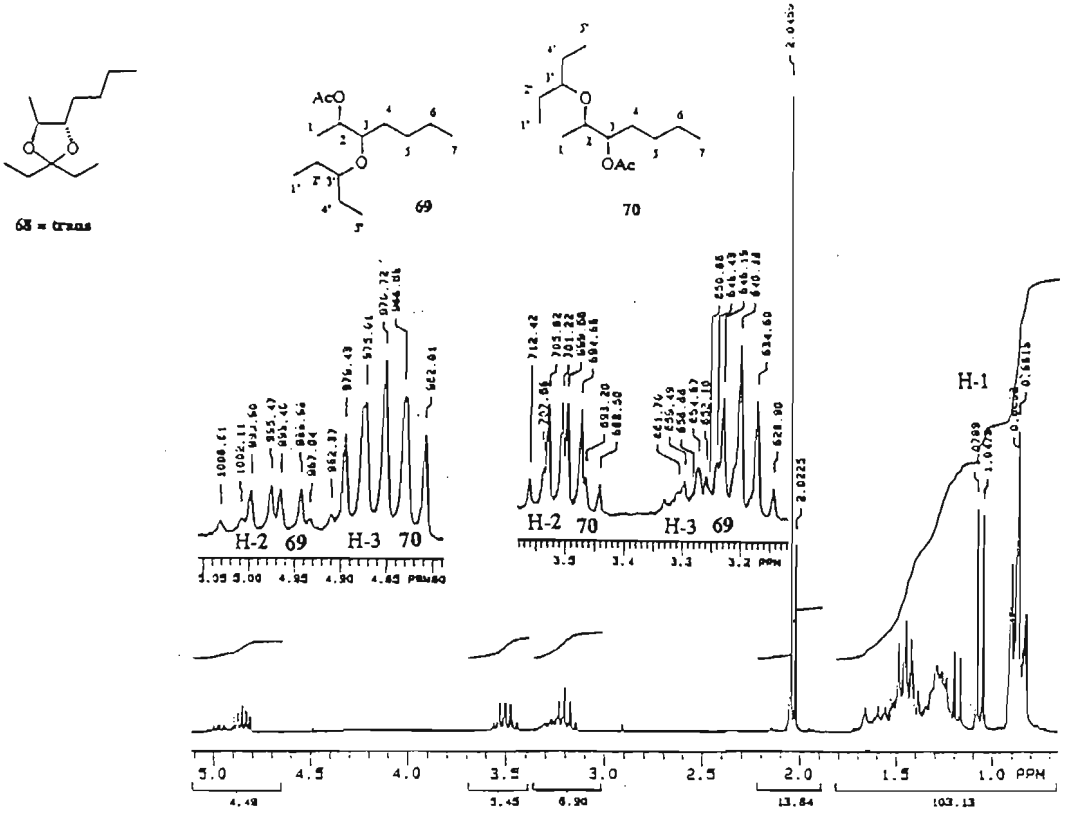
68 = TRANS
71 = CIS

C D

Entry	Ketal	Solvent	temp (°C)	Ratio C:D[a]	Yield (%)[b]
1	trans	CH_2Cl_2	-78 to -50	25:75	31[c]
2	trans	THF	-78 to +4	74:26	50[c]
3	cis	CH_2Cl_2	-78 to -50	25:75(27:73)	92
4	cis	THF	-78 to RT	70:30(68:32)	83[d]

a: ratio determined by ^1H nmr, ratio in (paranthesis) from gc-ms (Cape Technicon)
b: isolated yield after chromatography
c: acetylated products (acetic anhydride, pyridine, DMAP)
d: 14% of starting material recovered

The product isomer ratios were determined by ^1H nmr spectroscopy. In the trans ketal cases the hydroxyl signals in the products were not clearly resolved and each product had to be acetylated to determine the ratios, resulting in lower overall yields. The ratio was determined by integration of the signals for H-2 and H-3 (assigned on the basis of the coupling constants and COSY nmr) of each isomer. The ^1H nmr spectrum of the reaction in CH_2Cl_2 is depicted in figure 4.1. The signal of the proton attached to the acetylated position is shifted downfield. Therefore, the signal H-2 of **69** and H-3 of **70** appear at 4.97ppm and 4.85ppm respectively. H-2 of **69** is coupled in the COSY spectrum to the doublet for H-1 of **69** at 1.18ppm. The coupling of H-2 to H-3 of **69** is not seen in this COSY spectrum. The latter signal coincides with H-3' of the 3'-pentoxy-group. On the other hand H-3 of **70** is coupled to H-2 of **70** at 3.50ppm and H-4 of **70** in the multiplet at approx. 1.5ppm. The ratio of the diastereomers is confirmed by the relative heights of the singlets of the acetoxy groups at 2.02 and 2.05ppm. for **69** and **70** respectively.


AcO
OAc
69
70
H-2 69
H-3 70
H-2 70
H-3 69
H-1
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0 PPM

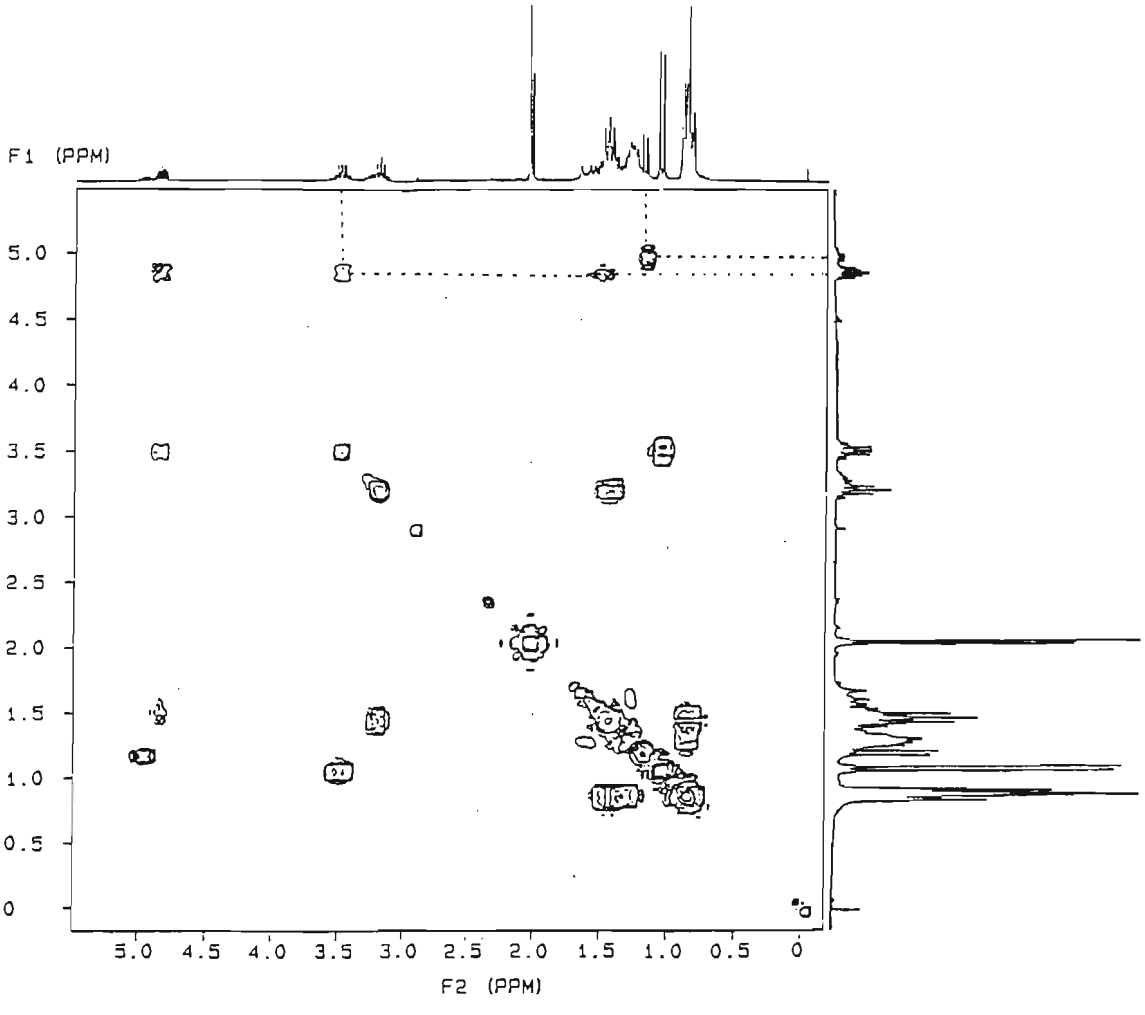

F1 (PPM)
F2 (PPM)
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0

Figure 4.1.

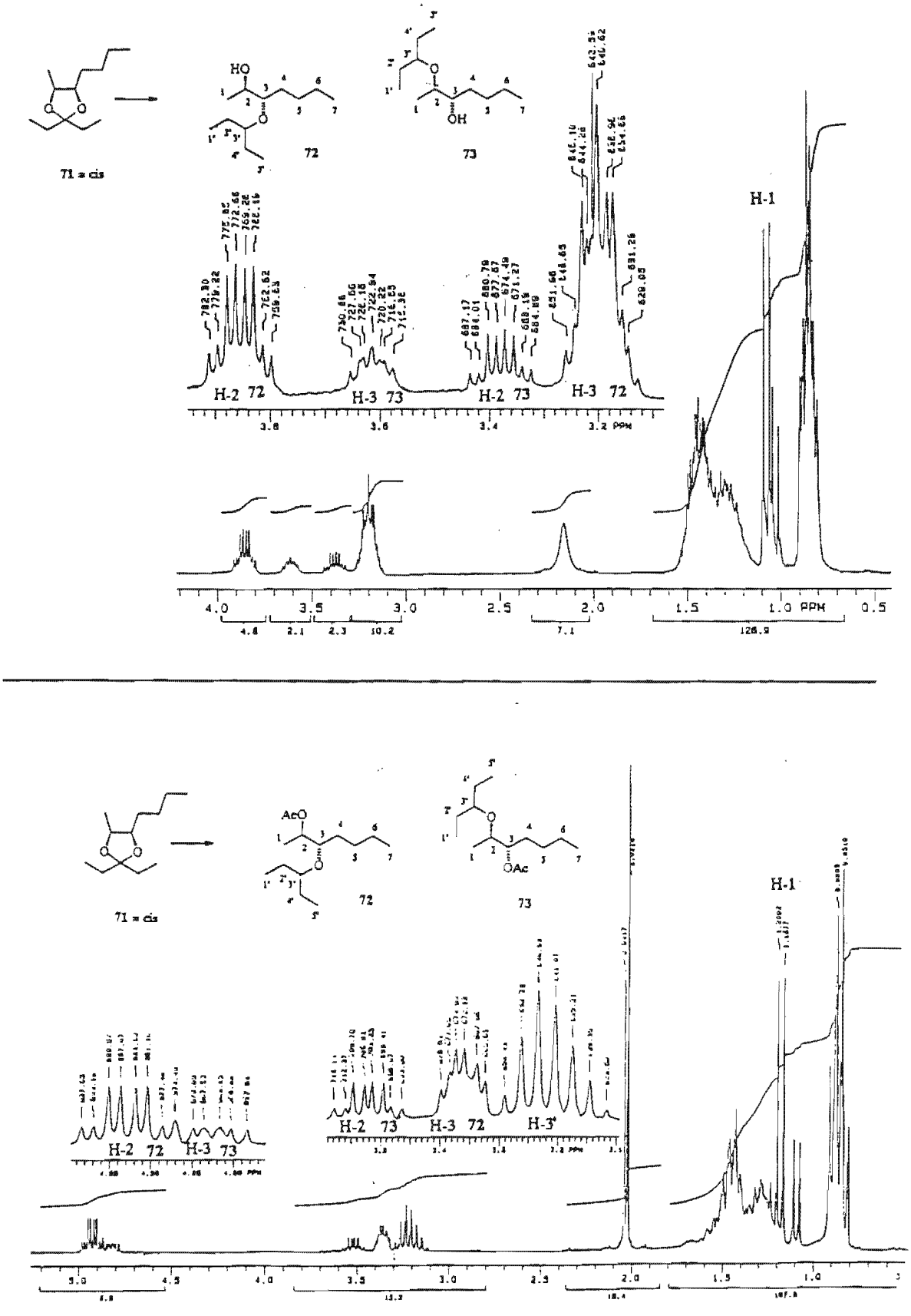

71 = cis
72
73
H-2 72
H-3 73
H-2 73
H-3 72
H-1
4.0
3.5
3.0
2.5
2.0
1.5
1.0 PPM
0.5
AcO
OAc
H-2 72
H-3 73
H-2 73
H-3 72
H-3'
H-1

Figure 4.2.

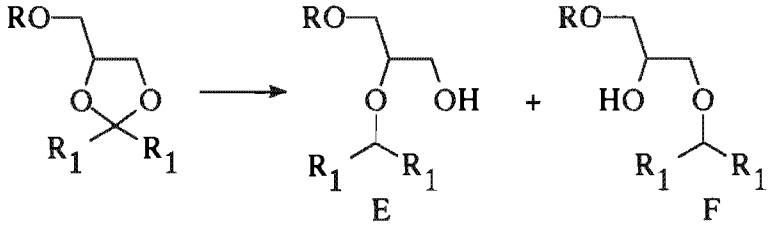
By comparison, the hydroxyl protons in the cis ketal products **72** and **73** were well resolved. The assignment of the signals of the two diastereomers was done on the basis of the coupling pattern and confirmed by the acetylation of the product mixture. The nmr spectra are depicted in figure 4.2. H-2 of **72** is coupled to H-1 and H-3 as a quartet of doublets with coupling constants of 6.5 Hz and 3.0 Hz respectively. This signal is shifted downfield in the acetoxy derivative. H-3 of **72** coincides with H-3' of the 3-pentoxy group for the free hydroxyl derivative, but shifts slightly downfield in the acetoxy derivative. In this case it is displayed as a multiplet. Similar assignments can be made for **73**. The determination of the ratio is done by integration and can be confirmed by the acetoxy signals.

From the results it is clear again that the solvent plays an important role in steering the direction of ring opening with complete reversal of selectivity on changing from CH_2Cl_2 to THF. These results are consistent with the results obtained previously for dioxolane **57**, entries 9 and 10 in table 4.1 and can be rationalized by the same subtle effects in the transition state of the different reactive complexes, as depicted in scheme 4.7. In THF, the reduction occurs via complexation of the less sterically hindered oxygen leading to the thermodynamically favoured oxocarbenium ion pathway A, while in CH_2Cl_2 reaction occurs via the B pathway in which 1,3-strain dominates bond perturbation in generating the electrophile.

As opposed to Brown and Leggetter's[93] observations (scheme 4.5) in the *cis* and *trans* systems, there was no difference in the rate of the reduction in the two isomers **68** and **71**. An attempt was made at examining the effect of the reagent combination of the two possible *cis* and *trans* isomers of the acetal of benzaldehyde and 1-*O*-benzyl-glycerol, but difficulties were experienced in the separation of the isomers and in addition both compounds were found to be very labile with decomposition occurring at room temperature.

In order to extend this study of the regioselective opening of ketals to the carbohydrate series, the next set of substrates investigated were derivatives of glycerol. In these substrates, there exists the possibility of chelation controlled silylation of the ketal oxygen in a similar manner to the way vicinal oxygen functionality might influence the site selectivity of complex formation in sugar molecules. The results are summarised in table 4.8.

Table 4.8.



Entry	R	R_1	solvent	Temp(°C)	Ratio E:F[a]	Yield (%)
1	CH_2Ph	Me	CH_2Cl_2	-78 to -70	5:95	86
2	CH_2Ph	Me	THF	-78 to -30	27:73	69
3	CH_2Ph	CH_2Ph	CH_2Cl_2	-78 to -70	5:95	72
4	H	CH_2Ph	CH_2Cl_2	-78 to -15	only F[c]	74
5	Si*t*BuMe$_2$	CH_2Ph	CH_2Cl_2	-78	only F[c] (R = H)[d]	88
6	Ac	CH_2Ph	CH_2Cl_2	-78 to -40	only F[c] (R = H)[e]	59
7	Ac	CH_2Ph	CH_2Cl_2	-78 to -15	47:53 (R = Et)[f]	49

a: Ratio obtained from ^{1}H nmr

b: Isolated yield after chromatography

c: No evidence of isomer E from nmr spectrum

d: Silyl protecting group is hydrolysed under reaction conditions

e: The acetate was hydrolysed for identification

f: Reduction of acetate to ethoxy ether occurred. 25% of isomer F[c] where R = H was also isolated.

The results obtained for the reductions in CH_2Cl_2 show a high selectivity for the primary protected hydroxyl group. This indicates high site selectivity for the complexation of the oxygen proximal to C4 and is consistent with results obtained by

Brown and Leggetter[90] as well as Guindon *et al.*[35] Anchiomeric assistance by the proximal oxygen functionality may steer the complexation, in spite of TMSOTf being a mono-chelating Lewis acid. The electronic effect of the group may also be a reason for the good regioselectivity observed, because its electron withdrawing effect would destabilize the formation of an oxocarbenium ion proximal to it.

However, when the reaction is carried out in THF (entry 2) the solvent is able to override the anchiomeric (or chelation) effect to some extent. This is further evidence that silylation in THF occurs via silylated THF which, being sterically more demanding than TMSOTf and less Lewis acidic, results in a more selective silylation at a higher temperature. However, as mentioned before, equilibration may occur to the oxygen attached to the more substituted carbon. It is interesting to note that with these glycerol derivatives the reduction in THF proceeded at a lower temperature compared with the unsymmetrical 1,2-diols. This can be explained by the enhanced nucleophilicity of the oxygen in the substrate being able to complex the silyl group at a lower temperature in the presence of THF than in the previous substrates. Unfortunately, substrates **77, 80, 82** and **83** where R_1=CH_2Ph, did not react in THF at room temperature and polymerisation of the solvent occurred.

In summarising, the regioselectivity of reduction of unsymmetrical vicinal diols using the reagent combination has been studied and it is concluded that in THF the reaction proceeds via a thermodynamically favoured oxocarbenium ion pathway resulting in the formation of the more substituted protected alcohol as a major product. By comparison in the less polar and less Lewis basic solvents such as CH_2Cl_2, the reaction via a more closed transition state becomes an important competing pathway. In this pathway the relief of 1,3-strain is a determining factor resulting in an increased proportion of the primary isomer as a major product. The presence of proximal oxygen functionality in the unsymmetrical ketal has a strong directing influence in favour of the primary protected alcohol.

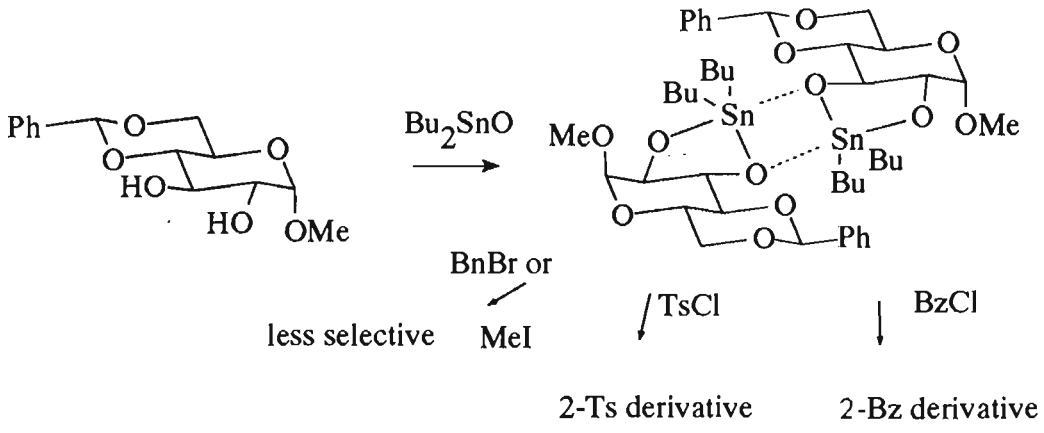
The results of this study establish the important role played by the solvent in the reduction reaction as well as the idea of a mechanistic spectrum of electrophilic intermediates from a closed silyloxonium ion through to a fully opened oxocarbenium ion as discussed recently by Denmark *et al.*[50] In these regards, the work differs significantly from that of Brown and Leggetter[89-93].

CHAPTER 5

The Chemo- and Regioselective Aspects of Reductive Cleavage of Carbohydrate Acetals/Ketals

As mentioned in Chapter 4, a continuing goal in synthetic organic chemistry, particularly in the carbohydrate area is the development of reactions that occur at only one of two or more hydroxyl groups which are in similar environments. An abundance of papers in the literature[94] deal with the chemoselective reactions of carbohydrate substrates, and in functional group methodology one of the methods which shows considerable promise involves the use of distannylene acetals as intermediates in regio-controlled substitution reactions[87,95]. Di-*n*-butylstannylene acetals derived from many different carbohydrates have been shown to predominantly monosubstitute with reactive electrophiles, such as benzoyl chloride, tosyl chloride and benzyl bromide and often in a highly regioselective manner. The stannylene acetals react much faster with electrophiles than do the free diols owing to the enhanced nucleophilicity of the tin-oxygen bond. Unfortunately, however, it is difficult to predict the reaction regioselectivity, since its origin is not fully understood. An example[87] of observed regioselectivities is given in scheme 5.1:

For example:

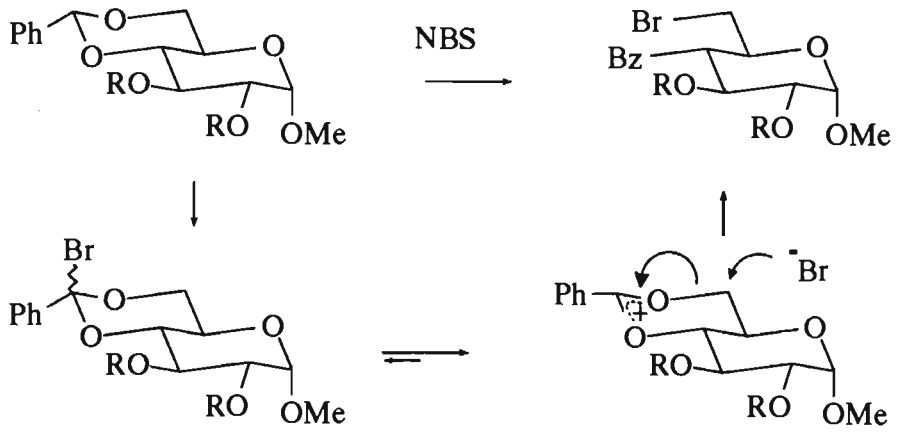


Scheme 5.1.

There is evidence that the regioselectivity of the reaction is related to the substrate's specific oligomeric structure in solution, and it has been shown that carbohydrate stannylene acetals in the solid state may exist as dimers or higher oligomers, depending on the molecule (scheme 5.1). In solution, the structure of the stannylene acetal depends on the temperature, the concentration and on the absence or presence of added nucleophiles, e.g. methanol. In any event, the large number of parameters makes it extremely difficult to predict the regioselectivity for any particular substrate.

Similarly, a reagent combination mentioned in Chapter 4 which can also be used to chemoselectively functionalize one OH of a vicinal diol is Ph_3P and benzoyl peroxide[88], but this methodology has not been applied to the carbohydrate area.

Another reaction, which is extremely useful to the carbohydrate chemist, and has been used in many syntheses is the oxidative cleavage of cyclic acetals by *N*-bromosuccinimide (NBS). Hanessian[96] demonstrated in 1968 that treatment of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside with NBS in refluxing carbon tetrachloride in the presence of barium carbonate gives a good yield of methyl-4-*O*-benzoyl-6-bromo-6-deoxy-α-D-glucopyranoside. The reaction may also take place in the presence of free radical initiators or acid scavengers[97]. The regioselectivity observed is general of 4,6-benzylidene acetals for which there is no possibility of rearrangement of the intermediate benzoxonium ion resulting in benzoyl migration. The most probable mechanism of the reaction involves initial attack of NBS to give the *gem*-bromo acetal by either a free radical process or an ionic one, followed by rearrangement to the benzoxonium ion which is then attacked by bromide ion (scheme 5.2).



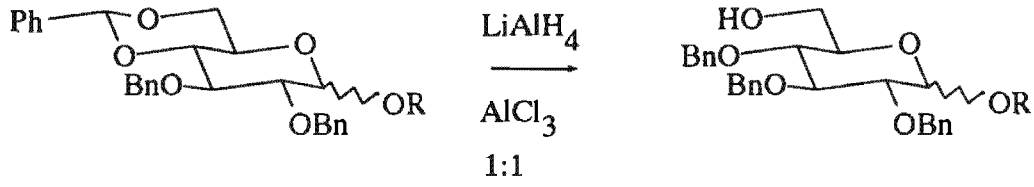
Scheme 5.2.

The literature[62] on this subject is vast and a review of it is beyond the scope of this thesis. It is important to mention, however, that in many cases the reaction is regioselective, but once again (especially in 1,3-dioxolane derivatives) the direction of cleavage depends on the specific structure of the substrate.

Thus, it is evident that the chemistry of acetals and ketals forms an integral part of carbohydrate chemistry. Since the discovery in 1895 by Emil Fischer[98] that glucoses react with aldehydes and ketones, these important derivatives have often been used in the synthetic chemistry of monosaccharides either for routine protection or for use in an original synthesis. A review in 1981 by Gelas[62] discussed the reactivity of 1,3-dioxolane and 1,3-dioxane derivatives of aldoses and aldosides towards oxidation, photolysis, halogenation, action of strong bases and reduction. This chapter discusses the reduction of a number of carbohydrate substrates using the reagent combination TMSOTf and $BH_3 \cdot SMe_2$ with regards to regio- and chemoselectivity. The principles involved in the regioselective reduction of cyclic acetals in the carbohydrate series can be adequately demonstrated by glucopyranosides and glucofuranosides.

The first direct application of acetal reduction involving the use of "mixed hydride" reagents, eg. aluminium reagents, in the carbohydrate series was described by

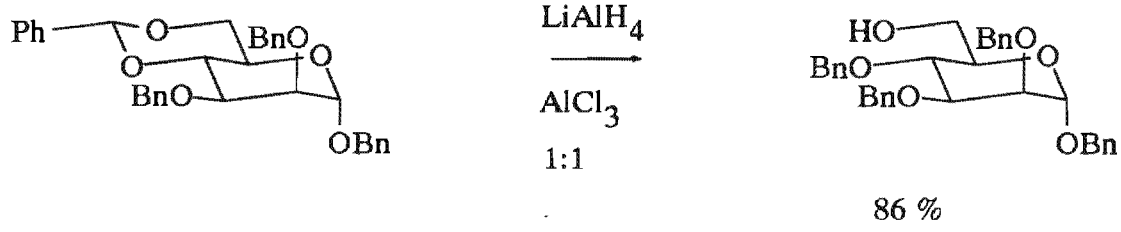
Bhattacharjee and Gorin[99] in 1969. They investigated the reaction between lithium aluminium hydride and aluminium chloride in a 1:1 ratio (i.e. AlH_2Cl as the reactive species) and methyl-4,6-*O*-benzylidene-2,3-di-*O*-benzyl-ß-D-glucopyranose. This reduction was highly regioselective forming the 6-hydroxy derivative exclusively in a 64% yield (scheme 5.3).



R = Me, β	64%
R = Bn, β	90%
R = Ph, α	68%
R = Me, α	94%

Scheme 5.3

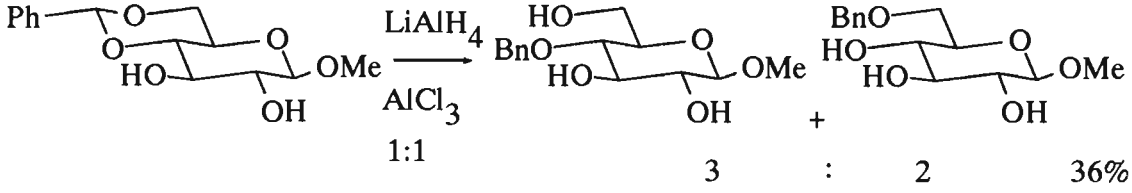
This result was later confirmed (1975) by Lipták *et al.*[100], who demonstrated that the high regioselectivity was independent of the stereochemistry at the anomeric position and the substituent at C-2 as shown for the mannopyranoside in scheme 5.4.



86 %

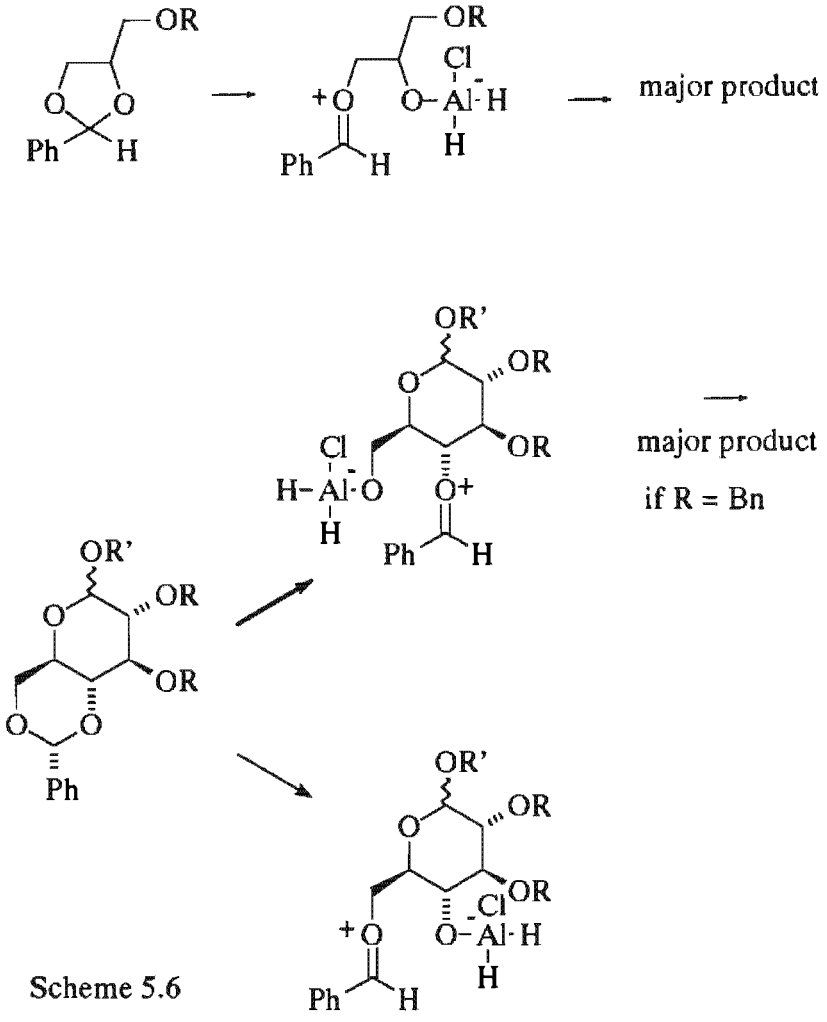
Scheme 5.4

However, Bhattacharjee and Gorin[99] found that when the unprotected methyl 4,6-*O*-benzylidene-ß-D-glucopyranoside was reacted with the same reagent the 6-hydroxy and 4-hydroxy derivatives were obtained in a 3:2 ratio and in low yield (scheme 5.5).



Scheme 5.5

Lipták *et al.*[100] concluded that for this reagent the regioselectivity of reduction of 4,6-*O*-benzylidene acetals in the pyranoside series was controlled by the size of the group at O-3. The free OH at C-3 promoted some reduction via activation of O-4 while protection at this centre steered the reaction to follow a sterically controlled activation to give the 4-protected derivative exclusively. This is in contrast to Brown and Leggetter's[90] findings on the reductions of glycerol acetals, for which the direction of the acetal reduction was controlled by electronic factors and regioselectivity was determined by formation of the more stable oxocarbenium ion, i.e. route (b) in scheme 4.4. The conclusions about the relative stability of oxocarbenium ions in sugar molecules is more tentative, but the following argument is proposed (scheme 5.6). As shown in this scheme the major product observed from the reduction of the glucose benzylidene acetal using AlH_2Cl is formed via the oxocarbenium ion on position O-4. This oxocarbenium ion should be less favoured than the oxocarbenium ion on O-6, because the latter has only one ß (O-5) oxygen functionality adjacent to it, whereas the oxocarbenium ion O-4 has two ß (O-3 and O-5) interactions, which are destabilizing via inductive withdrawal. However, the relative influence of the aluminate group in the two ions should not be neglected and thus, as noted above, the situation is more complex than the model study. One is left to conclude that, for R = Bn, the reaction is steered by kinetically controlled activation of O-6 for steric reasons.

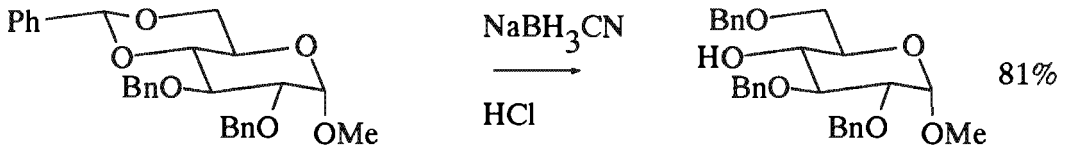


Scheme 5.6

More recently, Guindon *et al.*[35] have reported on the reduction of methyl 4,6-*O*-benzylidene-2,3-di-*O*-methyl-α-D-glucopyranoside with the diphenylboron bromide/ BH_3.THF reagent combination. The 6-hydroxy derivative was formed exclusively in high yield (88%) with no anomeric reduction. Furthermore, the regioselectivity was independent of the configuration at the anomeric position. Thus, it is evident that anchimeric participation of the group at O-3 does not play a dominating role in directing the regioselectivity of this particular reduction, as was proposed by these authors for the glycerol derivative (scheme 4.6). This result, along with that obtained by Bhattacharjee and Gorin[99], indicates that 4,6-*O*-benzylidene glucopyranosides reduce via a sterically controlled activation process. As the authors point out, a potential limitation of the

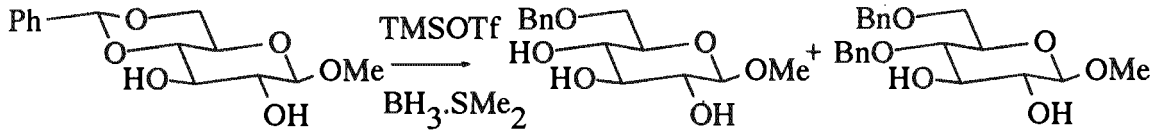
reagent Ph_2BBr is the necessity to work with protected hydroxyl groups in order to avoid hydrolysis of the boron halide to a Brønsted acid.

By comparison, a reagent combination which complements this result and described by Garegg *et al.*[101], is $NaBH_3CN$-HCl. Reduction of methyl-4,6-*O*-benzylidene-2,3-di-*O*-benzyl-α-D-glucopyranoside with this reagent resulted in the formation of the 4-hydroxy derivative exclusively. The authors attributed this result to the small size of the proton, which allows the attack at the O-4 of the benzylidene acetal to be governed by the relative nucleophilicities of the acetal oxygens (scheme 5.7).



Scheme 5.7

At this point, it is interesting to introduce the results obtained for the reagent combination $TMSOTf/BH_3{\cdot}SMe_2$ (1.1 equivalents). The reaction products were characterized by ^1H and ^{13}C nmr spectroscopy and compared with literature values (scheme 5.8).



95 **94**

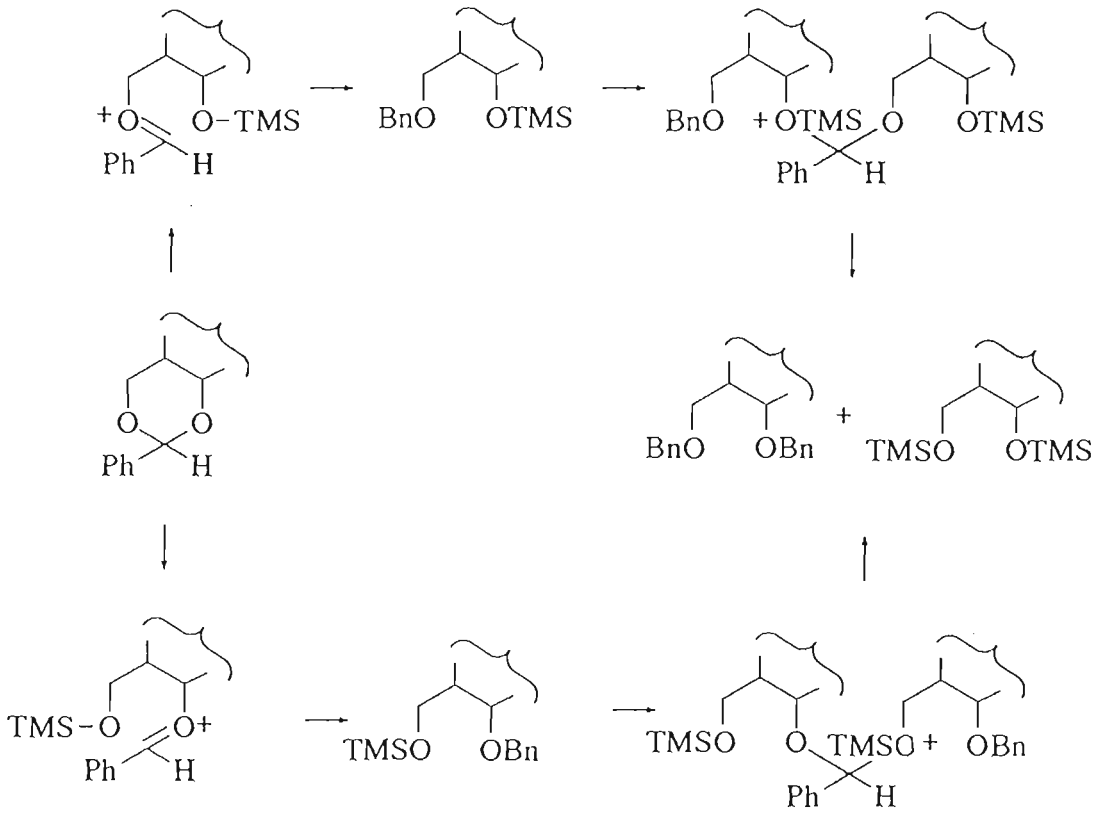
CH_2Cl_2, -78°C, 0.5hours — 75% — 6%

THF, -78°C to RT — complex mixture

Scheme 5.8

From the results obtained in the study of the glycerol derivatives (Chapter 4), the major product of the reduction of methyl-4,6-*O*-benzylidene-α-D-glucopyranose in CH_2Cl_2 was expected to be the 6-benzyloxy derivative **95**, on the basis of silylation occurring adjacent to the proximal functionality O-3.

Indeed, in CH_2Cl_2 as solvent, the reduction occurred at -78°C in 0.5 hours with 1.1 equivalents of reagents to form this product **95** in 75% yield. In addition, 6% of the 4,6-*O*-benzylidene derivative **94** was also formed in a similar way to the formation of the dimeric products discussed in Chapter 2 (scheme 5.9).



Scheme 5.9.

The signals for C-6 in the ^{13}C nmr spectra of compounds **94** and **95** were shifted downfield, which indicated the C-6 oxygen to be alkylated as a benzyl ether. The

200MHz ^{1}H nmr of these compounds was complex and did not permit unambiguous assignment of the position of the benzyl group.

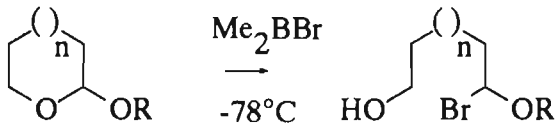
The yield (75%) is an improvement on the result of Bhattacharjee and Gorin[99] (36%) and there was no evidence of 6-hydroxy derivative formation. The regioselectivity is the same as that obtained using $NaBH_3CN/HCl$ reduction of the 2,3-*O*-dibenzyl derivative, ie via O-4 activation, in which the low steric demand of H^+ was a contributing factor. It is plausible that with the unprotected OH at C-3, the reduction proceeds via an anchored borane intermediate produced via boron-hydrogen exchange and that this plays a role in controlling regioselectivity. Alternatively, in view of the low temperature of reaction and in line with ideas outlined in Chapter 4, the regioselectivity may be due to equilibration of the silyl group from O-6 (sterically favoured) to O-4 (chelation controlled) before C-O bond perturbation to advanced oxocarbenium ion character. Opening with silyl at O-4 would then lead to the more stable oxocarbenium ion.

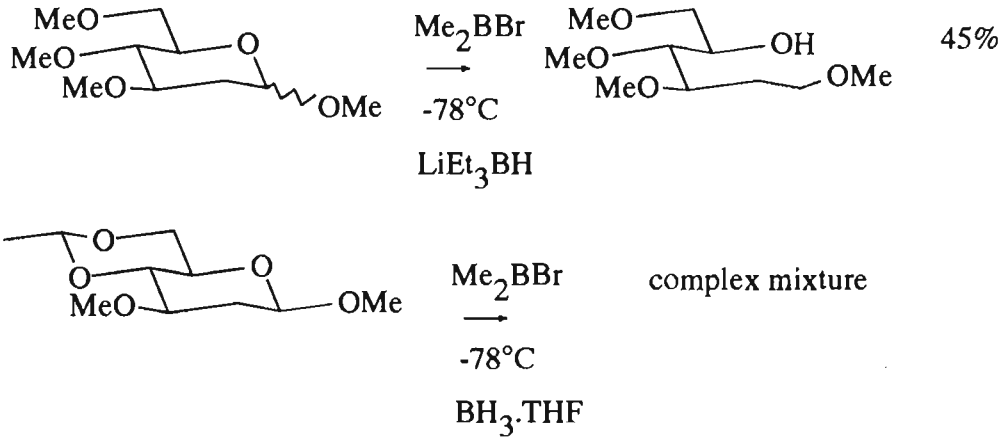
In THF, as expected the reaction required a higher temperature (>0°C) and gave a complex mixture of products. No attempt was made to identify all of the products, as this was clearly not an efficient and selective reduction.

In the light of this result it was decided to determine the reaction of a fully protected methyl-α-D-glucopyranoside with $TMSOTf/BH_3{\cdot}SMe_2$.

Guindon *et al.*[102] have reported that the endocyclic C-O bond in THP and THF ethers can be cleaved selectively by dimethylboron bromide at -78°C to give acyclic α-bromoethers. In an extension of the study[103], the authors showed that methyl-2-deoxy-3,4,6-tri-*O*-methyl-D-glucopyranoside (α and ß) can be reduced by Me_2BBr (2eq) in CH_2Cl_2 and $LiEt_3BH$ (3eq) at -78°C to form only the ring opened products and independent of the configuration at the anomeric position. When the same authors applied this reagent combination to methyl-4,6-*O*-benzylidene-2-deoxy-3-*O*-methyl-ß-

D-glucopyranoside the product of the reaction was a complex mixture of compounds as a consequence of non-chemoselective reduction at the anomeric position as well as of the benzylidene acetal. Guindon offers no explanation as to why a 2-deoxy-glucopyranoside derivative is reduced more readily at the anomeric position than a glucopyranoside derivative (cf. page 81)[35] (scheme 5.10).

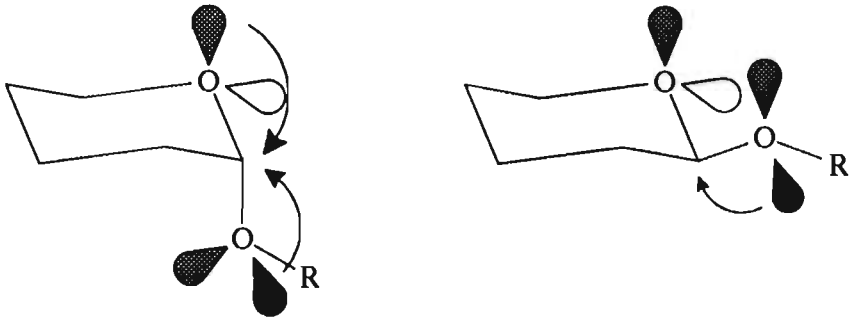




Scheme 5.10.

In order to explain the selectivity for ring cleavage in both the α and the ß anomers Guindon *et al.*[103] have proposed that the relative basicities of the endo and exocyclic oxygens affects the regioselectivity of the reaction and that activation of the ring oxygen is kinetically controlled. As has been pointed out by Deslongchamps[104], the relative basicities of the ring versus the exocyclic oxygen atom should be affected by their participation in the endo and exo anomeric effects respectively (scheme 5.11). Only the ring oxygen of the ß-anomer is not involved in an anomeric effect and it is therefore more basic, so that ring cleavage can occur with stereoelectronic assistance from the exocyclic oxygen. In the α-anomer, both oxygens are involved in an anomeric effect, but Guindon[103] ascribes the observed regioselectivity to the fact that the exo-

anomeric effect is stronger and that complexation of Me_2BBr may also be sterically controlled.

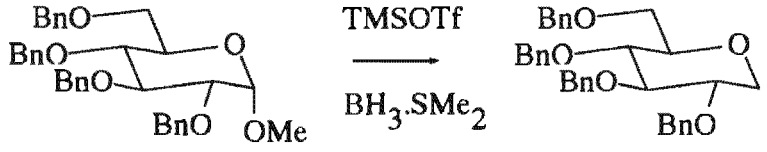


α β

Scheme 5.11.

In contrast to the above observations, Köster and Dahlhoff[103] have established that the anomeric configuration has a strong influence on the selectivity of ring opening in the reduction of glucosides with ethyl diboranes and MSBBN (see scheme 1.6, chapter 1). In their case the α-anomer gave a 55:45 ratio of endocyclic to exocyclic bond cleavage for glucose and the ß-anomer a 90:10 ratio. This selectivity can therefore be attributed to the relative basicities of the oxygen as described in scheme 5.11.

As described in Chapter 2 (table 2.5), reduction of a THP ether with TMSOTf/BH_3·SMe_2 resulted in exocyclic ring cleavage as the major pathway. In the case of methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside no reaction occurred at -78°C and the reaction had to be warmed up to room temperature. The use of an excess (3eq) of the reagent did not increase the reaction rate. In THF, the disappearance of starting material took 6 days and resulted in a mixture of compounds. The only compound which was identified was the ring compound **107** in low yield. These were variable and ranged from 20-50%. The reaction was repeated in CH_2Cl_2 and proceeded to completion in 3 days. The highest yield was obtained with 1.1eq of the reagent combination (64%) (scheme 5.12).



107
variable yields

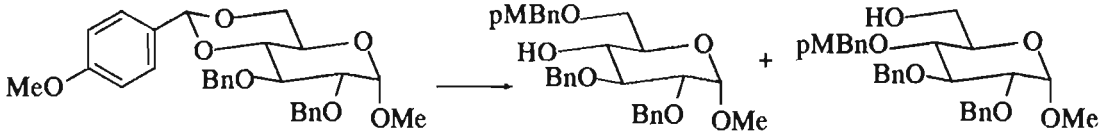
Scheme 5.12.

Clearly, the anomeric position in glucopyranosides is reactive enough to be reduced but chemoselectivity may be controlled by temperature.

The observed regioselectivity[see also 14c,105] can be explained as follows: Silylation of the ring oxygen must be the kinetically favoured process on the basis of stereoelectronic factors, but there exists the possibility of equilibration to the exocyclic silyloxonium ion. Development of sufficient oxocarbenium ion character for hydride delivery is more readily attained via the exocyclic silyloxonium ion than the endocyclic one resulting in retention of ring integrity. The higher temperature of reaction indicates that this development is more difficult for the glycosidic acetals than for the 4,6-*O*-benzylidene acetal derivatives.

The next set of substrates studied were methyl-4-methoxybenzylidene-2,3-di-*O*-benzyl-α-D-glucopyranoside and methyl-4-methoxybenzylidene-α-D-glucopyranoside. As described in Chapter 2, 4-methoxybenzyl ethers are common protecting groups in carbohydrate chemistry and can be cleaved by CAN (cerium ammonium nitrate)[63] and, as shown recently by Just *et al.*[64], by Me_2BBr. 4-Methoxybenzyl ethers can also be cleaved to the free hydroxyl group by the reagent combination TMSOTf/BH_3·SMe_2. Furthermore, 4-methoxybenzylidene acetals are also more reactive towards reduction and acid hydrolysis than their benzylidene counterparts.

Johannsson and Samuelsson[106] have demonstrated that methyl-4,6-*O*-(4-methoxy-benzylidene)-2,3-di-*O*-benzyl-α-D-glucopyranoside can be reductively cleaved with $NaBH_3CN/CF_3COOH$ in dimethyl formamide (DMF) as solvent to give the free 4-hydroxy derivative in 76% yield together with 13% of the free 6-hydroxy derivative. Conversely, reduction with $NaBH_3CN$ and TMSCl in acetonitrile resulted in the free 6-hydroxy derivative as the major product. In DMF, a 1:1 mixture of regioisomers was obtained. In the reduction using $NaBH_3CN/CF_3COOH$ in DMF, the latter was needed to stabilize the intermediate 4-methoxybenzyl cation and to avoid hydrolysis of acid labile acetal (scheme 5.13). The regioselectivity observed was again attributed to the difference in sizes of the H^+ and TMSCl. The authors did not offer an explanation for the solvent effect, but a possible one is that DMF helps to stabilize the more stable 6-oxocarbenium ion formed by equilibration from the kinetically favoured 4-oxocarbenium ion or silyloxonium ion intermediate. They did not comment on the possibility of equilibration nor speculate about the degree of bond breaking in the transition state.

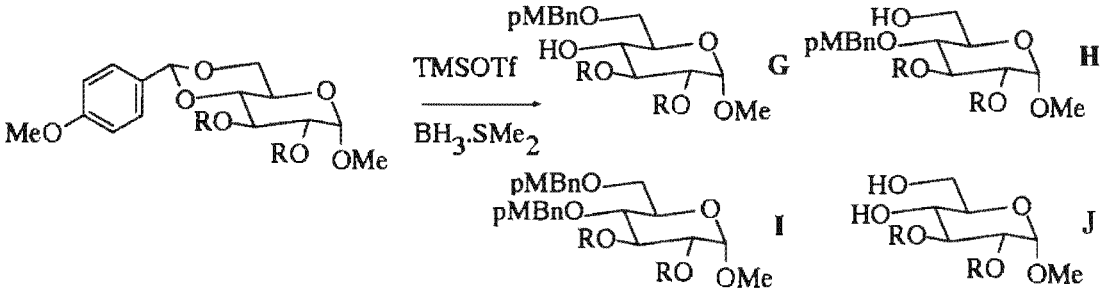


$NaBH_3CN$, CF_3COOH, DMF, 0°C	76%	13%
$NaBH_3CN$, TMSCl, CH_3CN, 0°C	9%	88%
$NaBH_3CN$, TMSCl, DMF, 0°C		1:1 mixture

Scheme 5.13.

The results obtained for the reagent combination $TMSOTf/BH_3{\cdot}SMe_2$ (1.1 equivalents) are summarized in table 5.1.

Table 5.1



pMBn = p-methoxybenzyl

entry	R	solvent	temp	G	H	I	J
1	H	CH_2Cl_2	-78	45	22	-	-[a]
2	H	THF	-78 to -30	33	26	11	-[a]
3	CH_2Ph	CH_2Cl_2	-78	19	-	-	61
4	CH_2Ph	THF	-78 to -30	72	-	-	28

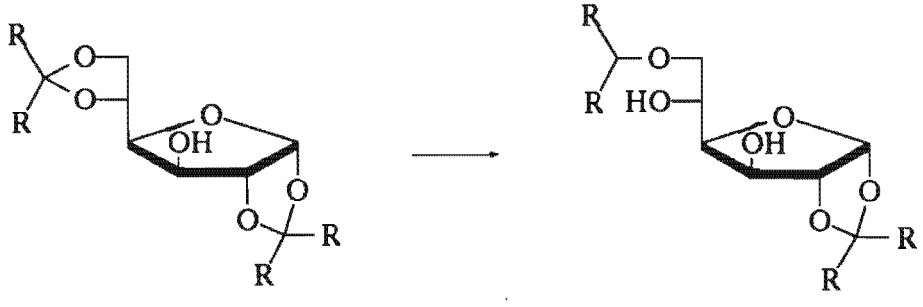
a: product of hydrolysis or reduction of 4-methoxbenzyl ether not observed due to solubility in H_2O

The results obtained for R=CH_2Ph are consistent with results obtained by Johannsson and Samuelsson[106] for the reagent combination $NaBH_3CN/CF_3COOH$. The low yield in CH_2Cl_2 can be attributed to the acid lability of the 4-methoxybenzylidene group and the possibility of cleavage of the product to the free hydroxyl. The most striking observation is the complete reversal in regioselectivity in going from $TMSCl/NaBH_3CN/CH_3CN/0°C$ to $TMSOTf/BH_3{\cdot}SMe_2/-78°C$ (R = CH_2Ph, THF or CH_2Cl_2) ie. scheme 5.13 vs entry 4/table 5.1. Given that the only significant difference between the two is temperature of reaction and since both must proceed through an initial silyloxonium ion, the most plausible explanation is as follows. Under Johannsson's conditions kinetic silylation is favoured at O-6 at a high enough temperature (apparently around 0°C) for C-O bond cleavage to occur faster than silyloxonium ion equilibration to O-4. Thus, the 6-hydroxy derivative is obtained. Conversely, with the more reactive TMSOTf, silylation may occur at much lower

temperature and equilibration followed by ring opening may be faster than direct ring opening. With R = CH_2Ph this rationale would imply that oxocarbenium ion character involving O-6 is favoured over that involving O-4. With R = H in THF one observes some of the hydroxy derivative as a result of kinetic silylation at O-6 followed by C-O bond perturbation and reduction before equilibration. This theme has been dominant in both Chapters 4 and 5, further studies are required to fully investigate the importance of order of addition of reagents when R = H.

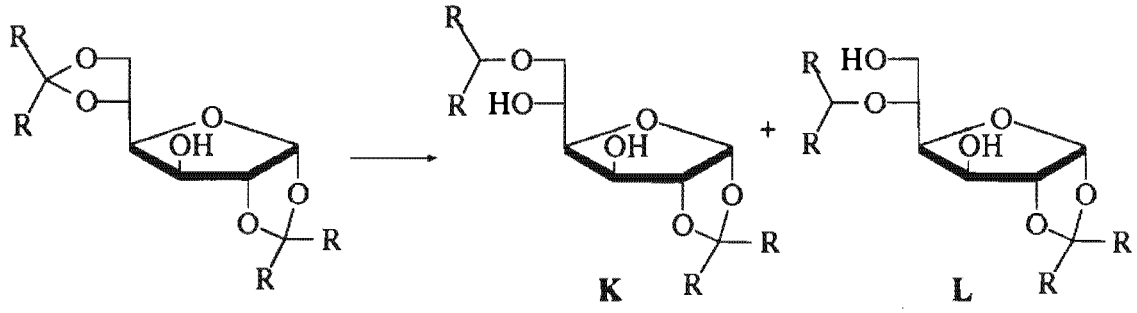
In these glucopyranoside cases, solvent does not affect the direction of the ring opening as significantly as described in Chapter 4. However, these acetals are examples of 1,3-dioxanes and as seen in Chapter 2, may react at a different point in the Denmark type mechanistic spectrum to 1,3-dioxolanes. Furthermore, the presence of so many oxygen functionalities makes site selectivity a difficult issue to predict.

The next set of substrates to be studied were derivatives of glucofuranose. Diacetal derivatives of glucofuranose are particularly interesting substrates, as they contain two possible sites of reactivity. Examples in the literature[99] have shown that the ketal at the 5,6 position is more reactive towards reaction with mixed aluminium hydrides than that at the 1,2 position and that the 5-hydroxy derivatives are obtained regioselectively. 1,2-*O*-linked acetals in the glucofuranose series are also particularly resistant to hydrolysis when compared to their 5,6-*O*-linked counterparts (scheme 5.14).



Scheme 5.14.

Table 5.2. summarizes the results obtained for TMSOTf/BH_3·SMe_2 (1.1 equivalents).



Entry	R	R^1	solvent	temperature (°C)	K:L	yield (%)
1	Me	H	CH_2Cl_2	-78	only K	54
2	Me	H	THF	-78 to RT	2:1	58
3	-$CH_2(CH_2)_4CH_2$-	H	CH_2Cl_2	-78	only K	61
4	-$CH_2(CH_2)_4CH_2$-	H	CH_2Cl_2	a	only K	65
5	-$CH_2(CH_2)_4CH_2$-	Bn	CH_2Cl_2	-78	only K	65

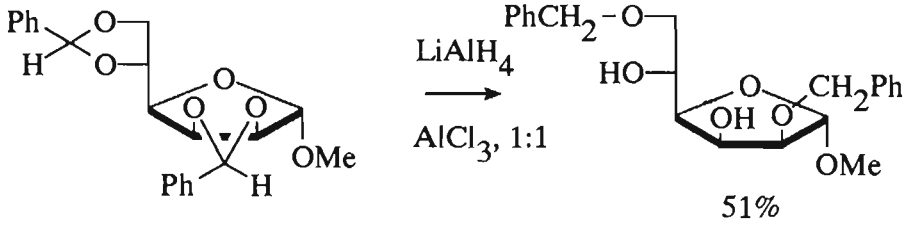
a: BH_3·SMe_2 added at -78°C, allowed to warm to 0°C, 10 min, cooling to -78°C before adding TMSOTf.

The results in CH_2Cl_2 are consistent with the results of Bhattacharjee and Gorin[99] using $LiAlH_4/AlCl_3$ and are also the expected product from the model study on the glycerol system, discussed in Chapter 4. Entry 4 in table 5.2. shows that in this system anchoring the borane reducing agent does not influence the regioselectivity in any way.

The effect of THF in these 1,3-dioxolanes can also be explained along the same lines as in Chapter 4. The reduction in THF occurs at a higher temperature than in CH_2Cl_2 indicating the possibility that THF interacts with the silylating agent to form a bulkier Lewis acid. The approach of the silylating agent is significantly impeded at O-5 such that silylation at O-6 may compete with the chelating effect of O-3 as well as O-4 and the stability of the oxocarbenium ion factors.

To further investigate the chemoselectivity of the reduction when two acetals are present, 2.3:5,6-di-*O*-isopropylidene-D-mannofuranose was reduced. This compound was synthesized by reaction of D-mannose with acetone in the presence of acid and the resultant diacetal was isolated as a mixture of anomers[107]. This made the ^{1}H and ^{13}C nmr spectra complicated so that analysis of the products of the reduction was difficult.

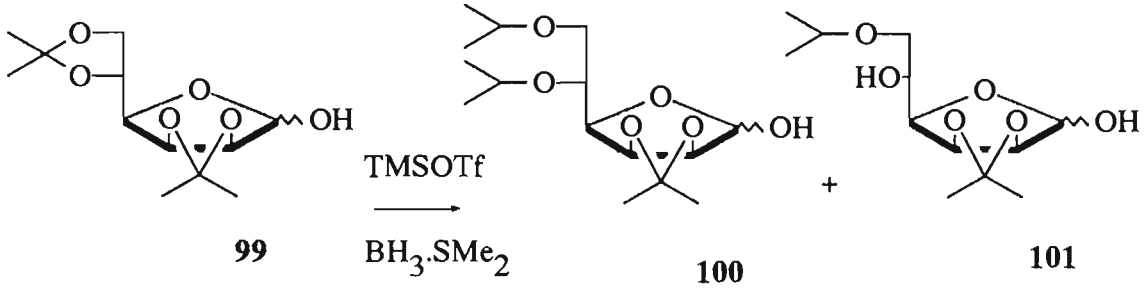
Bhattacharjee and Gorin[99] have studied the effect of 2 equivalents of the reagent combination $LiAlH_4/AlCl_3$, 1:1, on methyl 2,3:5,6-di-*O*-benzylidene-α-D-mannofuranoside and the resultant product was identified to be methyl 2,6-di-*O*-benzyl-α-D-mannofuranoside (scheme 5.15).



Scheme 5.15.

The results of the reduction of 2,3:5,6-di*O*-isopropylidene-D-mannofuranose with $TMSOTf/BH_3{\cdot}SMe_2$ in CH_2Cl_2 are summarized in table 5.3.

Table 5.3



99 **100** **101**

Entry	Equivalents	**100**	**101**
1	1.1 eq. of reagents	15%	47%+7% **99**
2	2.0 eq of reagents	10%	38%

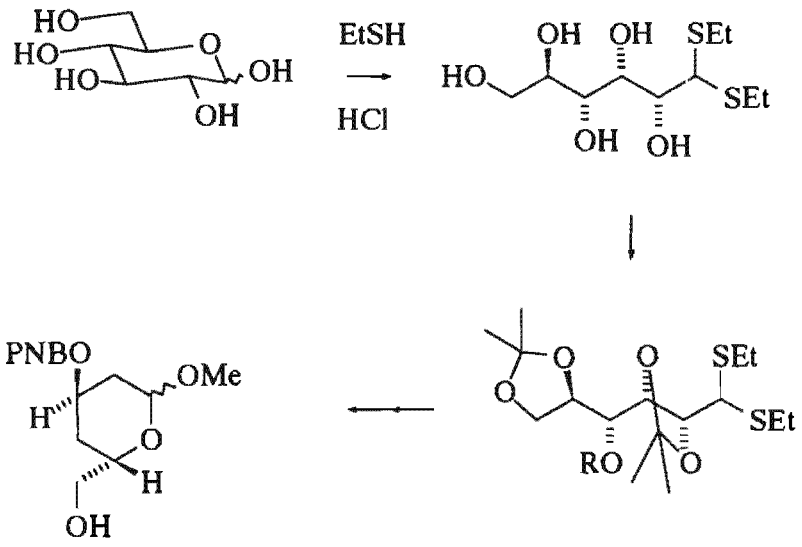
When 2 equivalents of reagent were used the yield of **101** was lower, but no triol was isolated. However, this could have been due to loss in the aqueous workup, in spite of the products being extracted several times with ethyl acetate. This result is promising though, as it shows that reduction of this diacetal derivative is both chemo- and regioselective. For future studies, it would be necessary to form the methyl-mannofuranoside to overcome the solubility problems of the products. The assignment of compound **100** is tentative and is based on the doubling of isopropyl CH_3 signals in both the ^1H and the ^{13}C nmr spectra. The assignment of compound **101** was based on the downfield shift of C-6 in the ^{13}C nmr spectrum compared to D-mannose, indicating that O-6 was still alkylated. The signal for C-5 is shifted upfield compared to **99** indicating attachment to a free hydroxyl group[108].

The significance of this result is that with 1.1 equivalents of reagent there is chemoselective reduction of the 5,6-*O*-linked acetal. This is due to this group (and especially O-5) being sterically and electronically favoured for silylation. The effect of the free hydroxyl group at the anomeric position seems negligible.

The above study, although only covering a limited scenario, has indicated the following: In 4,6-*O*-linked acetals of glucopyranosides the reduction with TMSOTf/BH_3·SMe_2 is chemoselective for the acetal at low temperature with no reduction of the anomeric position occurring. For benzylidene acetals the direction of cleavage is via silylation at O-4. For 4-methoxybenzylidene acetals, when there is a free hydroxy at O-3, the regioselectivity of ring cleavage is lower because of the increased reactivity of these derivatives. In the latter case where O-3 is protected by a benzyl group there is good regioselectivity in the reduction, but the yields in CH_2Cl_2 are lowered by the possibility of hydrolysis.

In diacetal derivatives of furanoses the order of reactivity can be generalized as 5,6-*O*-linked ketal > 1,2-*O*-linked ketal for glucofuranosides and 5,6-*O*-linked ketal > 2,3-*O*-linked ketal for mannofuranosides.

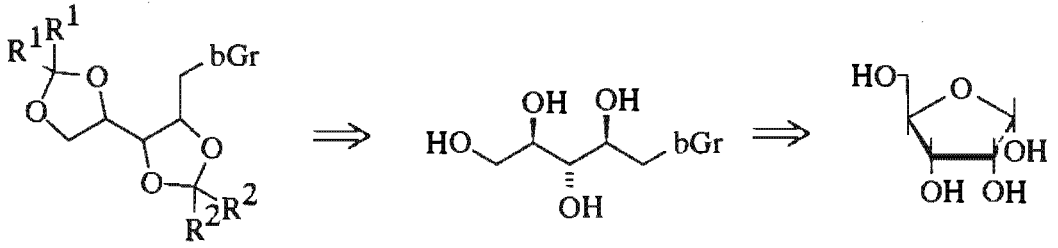
A final study undertaken, particularly in view of the one carried out on acyclic derivatives pertaining to chapter 4, was to involve taking advantage of the fact that carbohydrates may be opened up to give acyclic ketal derivatives. It was felt that such a substrate would offer the opportunity of studying the reduction of an acyclic polyketalised substrate[109] as an extension of ideas delineated in Chapter 4. Of crucial importance was whether both chemo- and regioselectivity aspects would operate in tandem. Selectively protected open chain forms of sugars have been used in synthesis. D-Glucose may be readily ring-opened by treatment with ethanethiol in the presence of concentrated HCl to afford D-glucose diethyl dithioacetal[110], with five unprotected hydroxyl groups. Treatment with acetone results in the 2,3:5,6-di-*O*-isopropylidene derivative, with the 4-position unprotected and this compound has been used recently in a synthesis of an intermediate of the lactone moiety of Mevinic acids in an enantiomerically pure form[111]. In the present study difficulties were envisaged in the glucose series in obtaining two different acetal groups in the molecule and with the effect of the free hydroxyl group (scheme 5.16).



PBNO = p-nitrobenzoyl

Scheme 5.16.

In order to have two different ketals in the same molecule with a terminal blocking group, it was conceptualized that a pentose-sugar would be a good model substrate (scheme 5.17).

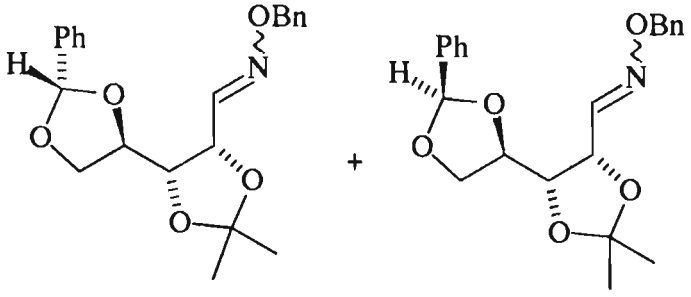


bGr = blocking group

Scheme 5.17

Ribose may be readily ring opened with ethanethiol and conc. HCl to form the diethyl dithioacetal, but treatment of the resulting tetraol with acetone under acidic conditions leads to a mixture of 2,3:4,5-di-*O*-isopropylidene and 2,4:3,5-di-*O*-isopropylidene derivatives which have to be separated chromatographically[112].

Alternatively, protection of ribose as a ketal followed by ring opening with protection of C-1, would lead to a diol. Ketalisation of this would offer the possibility of having two different ketal functionalities. The acid-catalyzed opening of 2,3-isopropylidene ribofuranose to form the thio-acetal was considered problematic in view of the acid-sensitivity of the ketal centre. Furthermore, there existed the possibility of the thioacetal competing in the reduction step so an alternative ring-opening was considered. The possibilities included reduction of the aldehyde at O-1 to the ribitol derivative or trapping of the aldehyde with a Wittig reagent, but the reaction which was chosen ultimately was oxime formation by an O-protected hydroxylamine. Hence, the model compounds chosen for this study were **109** and **110** (scheme 5.18). It was hoped firstly, that the benzylidene group would be more reactive as indicated by the model study and secondly, that the oxime would not be affected in the reduction with the TMSOTf/BH_3·SMe_2 reagent combination.

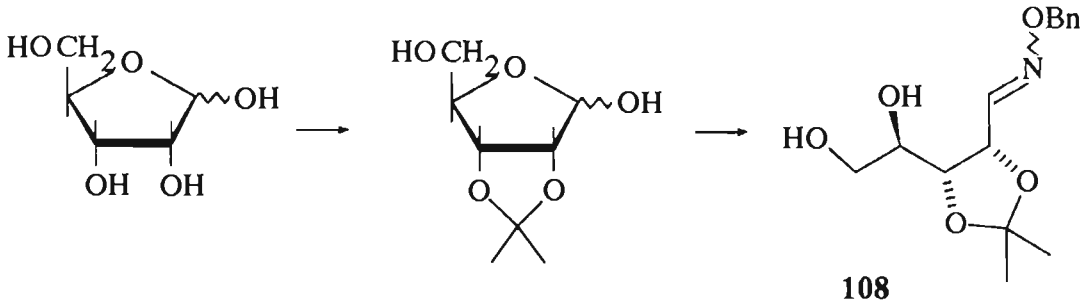


isomers 109 & 110

Scheme 5.18.

For the synthesis of **109** and **110**, Ribose was reacted with acetone in the presence of acid at 0°C to form 2,3-*O*-isopropylidene-D-ribofuranose in 97% yield (scheme 5.19). The small amount of the 1,2-isomer was removed at the diol-oxime stage by chromatography. The 2,3-*O*-isopropylidene derivative was opened up with *O*-benzyl hydroxylamine in 85% yield after column chromatography and the product isolated was a mixture of geometrical isomers of 1-(*O*-benzyloxyimino)-2,3-*O*-isopropylidene-D-ribose **108** (scheme 5.19). The diol **108** gave satisfactory elemental analysis, but the

signals in the ^{1}H nmr were complicated by the presence of two geometrical isomers. The signals for the oxime-H were at 6.90ppm and at 7.52ppm and it was not possible to fully assign all of the signals in the spectrum. The ^{13}C nmr was also complicated but it was possible to assign signals due to C-5 and C-4, which appeared upfield (63.9 and 69.6 ppm for the major geometrical isomer, respectively) compared to the other carbons.



108

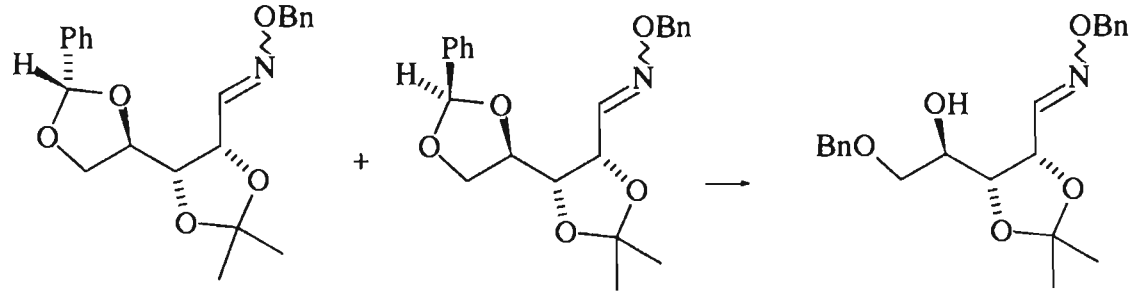
Scheme 5.19.

The formation of the benzylidene derivative from **108** was problematic. Problems were envisaged using conventional method of acetalisation, so transacetalisation with dimethoxyphenylmethane was considered. The best results were obtained by the use of $BF_3{\cdot}OEt_2$ at -78°C, in CH_2Cl_2 as solvent.

Warming of the reaction to -20°C was required and not all of the starting material was consumed. After chromatography of the reaction products, two fractions were isolated. The minor fraction was isolated as a single spot on t.l.c. as an oil and the ^{1}H nmr showed it to be a mixture of compounds. The signals for the oxime protons of both geometrical isomers were doubled up indicating that the fraction existed as a mixture of diastereomers **109** and **110** as geometrical isomers. An accurate mass determination (Found M^+ 383.1725, $C_{22}H_{25}NO_5$ requires 383.1733) revealed the molecular mass to be correct for structures **109** and **110**.

The major isomer was isolated as a more gummy substance as a single spot on t.l.c. which later solidified and had a melting point of 120-126°C. An accurate mass

determination showed that this fraction was also an isomer with a molecular weight of 383.1718. The signals in the 200MHz nmr spectra were complicated and further work is required to determine the exact structure of this compound, before a conclusion can be drawn as to the nature of the major fraction. It was disappointing that the transacetalisation was inefficient, and further work needs to be carried out to optimise this step (eg. Noyori's[6] acetalisation). However, it was decided to carry out the reduction with TMSOTf/BH_3·SMe_2 on the minor fraction, because the compounds in this fraction are interesting in that they have at least four possible sites where silylation can occur and two possible sites of attack for the reduction (excluding the oxime).



isomers 109 & 110 **111**

Scheme 5.20

The mixture of compounds **109** and **110** was reacted with 1.1 equivalents of TMSOTf/BH_3·SMe_2 in CH_2Cl_2 at -78°C and monitoring by t.l.c. showed that the reaction did not go to completion. Warming the reaction to -30°C resulted in the formation of unwanted polar products. The reaction was repeated at -78°C with 2 equivalents of reagent and stirred at that temperature for 3 hours. All of the starting material was consumed and the reaction quenched. The product which was isolated after chromatography was identified to be **111** in 61% yield (scheme 5.20), on the following basis:

An accurate mass determination showed M^+ to be 385.1878($C_{22}H_{27}NO_5$ requires 385.1889) which indicates the addition of 1 equivalent of H_2 to **109** and **110** (ie. mono-reduction. The ^1H nmr spectrum showed that there was an oxime functionality present,

still as a mixture of geometrical isomers (δ 6.80 and 7.52 ppm). The spectrum was run in DMSO and showed the OH signal (exchangeable) as a doublet (*J* 6.0 Hz) indicating it to be a secondary centre. The isopropylidene signals had not changed relative to the starting material and therefore this ketal centre was still intact. The other proton signals could be assigned on the basis of their coupling constants. The ^{13}C nmr showed the signal for C-5 to be downfield (71.4 ppm) compared to the diol **108** (63.9 ppm)indicating it to be O-alkylated. The signal for C-4 was at 68.7 ppm compared with 69.6 ppm in **108.** Furthermore, the benzylidene acetal centre had vanished (cf. 104.0 and 104.5 ppm for **109** and **110**).

This result indicates the following:

The reduction of **109/110** is chemoselective for the benzylidene acetal and even at higher temperatures (-30°C) the isopropylidene group and the oxime group are not affected by the reagent. The reduction of the benzylidene acetal is regioselective giving rise to the 5-protected derivative, and is independent of the benzylidene stereochemistry. This regioselectivity is in agreement with results in the model study (Chapter 4).

A detailed study, particularly regarding acetal formation from diol and possibly using different blocking groups (eg. reduced oxime), is required to fully elucidate the potential of this methodology in natural product synthesis. However, the approach is noteworthy in that it appears possible to chemo- and regioselectively differentiate acetal and ketal centres in the same molecule and thus selectively functionalise different hydroxyl groups in a complex system. The resultant products could be used as building blocks in synthetic organic chemistry.

CONCLUSIONS:

The study of the mechanism of Lewis acid catalysed nucleophilic substitution at acetal centres remains a topical subject in organic chemistry, as it has a strong bearing on the outcome of the reaction. It has been identified that the timing of the C-O bond cleavage and C-nucleophile bond formation is of crucial importance in controlling the stereochemistry of this class of reaction. The reduction of ketals is an important and viable alternative to direct carbonyl reduction and in the present study it has been demonstrated that trimethylsilyl trifluoromethanesulphonate and borane dimethyl sulphide is a potent reagent combination for the reduction of acetals and ketals at low temperature.

With this reagent combination the nature of the substrate is important in determining the extent to which the initial silyloxonium ion is opened in the transition state of the reduction step (ie. closed transition state, open transition state or an intermediate of the two extremes). This feature controls the regio- and stereochemistry of bond cleavage. It is apparent that the silyloxonium ions equilibrate and the timing of the hydride delivery depends strongly on the degree of C-O bond cleavage, in that attack can only occur once the acetal/ketal centre has sufficient electrophilic character.

With simple 1,3-dioxanes the reaction is fast at low temperature and occurs in high yield, whereas with simple 1,3-dioxolanes reduction with TMSOTf/$BH_3 \cdot SMe_2$ results in a significant amount of side reaction indicating that for these structures the transition state in the reduction step has advanced oxocarbenium ion character. Furthermore, the reaction has been shown to be chemoselective for ketals in the presence of other functionalities.

Studies on the stereoselectivity of the reaction of chiral derivatives have revealed that the hydride delivery occurs anti to the breaking C-O bond, but the selectivities were

only moderate and therefore not of practical use. A crucial observation was that solvent has a marked effect on the nature of the transition state.

A model study on the regiochemistry of reduction of ketals derived from vicinal diols has revealed that structure has a strong influence on the nature of the transition state, but more importantly that the nature of the solvent and thus the temperature at which reduction occurs are crucial factors in determining the point in the mechanistic spectrum at which hydride delivery will occur. In this regard, it was found that the Lewis basic THF changes the electronic and steric nature of the silylating agent and this causes an increase of the products formed via sterically controlled activation of the ketal. The effect of proximal oxygen functionality has the strongest influence on the regiochemistry and causes activation of the C-O bond closest to it. These findings have led to a study of regioselective reduction of acetals and ketals in the carbohydrate series and it has been found that the information gleaned from the model studies holds for these complex systems. Furthermore, reduction of a benzylidene acetal occurred chemo- and regioselectively in the presence of an isopropylidene acetal in an acyclic ribose derivative.

Thus, the study has extended the use of borane dimethyl sulphide in organic synthesis and a contribution has been made towards a better understanding of the mechanism of dissociative ketal reduction. The results of this thesis point towards the need for more selective silylating agents, by changing the nature of the leaving group, as well as a better understanding of the features influencing Lewis acid complexation in complex, polyoxygenated molecules. This would lead to a more regioselective process, as it is this application which holds the greatest promise, particularly with acyclic carbohydrate intermediates.

CHAPTER 6

Experimental Section

6.1. General

6.1.1. Characterization of compounds:

All melting points (mp.) were determined on a Reichert Jung hot stage microscope and are uncorrected.

Infra-red spectra were recorded in chloroform or carbon tetrachloride using a Perkin-Elmer 983 Spectrophotometer.

Routine proton nuclear magnetic resonance (^{1}H nmr) were recorded on a Varian EM 360 (60MHz spectrometer) or a Bruker90 (90MHz spectrometer). High resolution proton (^{1}H nmr) and carbon-13 (^{13}C nmr) were recorded on a Varian VXR-200 (200.057MHz and 50.31MHz respectively) in deuteriochloroform, unless otherwise stated. The chemical shifts (δ) are given in ppm relative to the signal of tetramethylsilane TMS (δ 0.00) or the residual chloroform in the deuteriochloroform (δ 7.24).

Mass spectra were recorded on a VG micromass 16F mass-spectrometer (UCT) or at the mass-spectrometry unit (Cape Technicon). Optical rotations were determined in chloroform solution at 20°C with a Perkin Elmer 141 polarimeter. The concentration *c* refers to g/100ml.

Microanalyses for C, H and N were carried out using a Heraeus CHN-rapid combustion analyser (UCT) or submitted to MATECH (CSIR, Pretoria).

All reactions were monitored by thin layer chromatography (TLC) using Merck TLC aluminium sheets, silica gel 60 F_{254}, layer thickness 0.2mm. Detection was done by one of the following methods:

(a) using an ultraviolet lamp (wavelength 254 nm),

(b) by placing the plate in iodine vapour for 5-10 mins,

(c) by heating the plate at 100°C after spraying with a 1% solution of cerium ammonium sulphate in 6N sulphuric acid or

(d) by heating the plate at 100°C after spraying with a mixture of 1ml conc. sulphuric acid and 10ml 2.5% anisaldehyde in ethanol.

Column chromatography was carried out on silica gel (Merck, silica gel 60, particle size 0.063-0.200mm (70-230 mesh ASTM)). Usually the amount of silica gel used was 100fold of the crude product weight. The eluents are specified in each experiment.

6.1.2. Solvents:

Commonly used solvents were purified as described below: Purification of other solvents is described in the experimental procedure.

Tetrahydrofuran: Dried over sodium wire and then distilled from sodium and benzophenone under a nitrogen atmosphere immediately before use.

Benzene: Distilled from sodium wire and stored over sodium wire.

Dichloromethane: Stored over phosphorus pentoxide and distilled immediately before use.

Diethyl ether: Distilled from sodium and stored over sodium wire.

Pyridine: Distilled from potassium hydroxide and stored over molecular sieves 4Å.
Pet. ether (boiling range 60-70°C), hexane, dichloromethane and ethyl acetate for column chromatography were distilled.

6.1.3. Experimental conditions:

All non-aqueous reactions were done under a nitrogen atmosphere and the reagents were introduced into the reaction flask via syringe.

The standard workup procedure refers to the addition of an aqueous solution of a salt, specified in parenthesis, and extraction with a solvent, also specified in parenthesis (usually three times the equivalent volume of the aqueous phase). The organic fractions were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*, which refers to the removal of the solvent under reduced pressure on a Buchi rotary evaporator.

6.2. Synthesis of acetals/ketals

Acetals and ketals were synthesised by one of the following methods:

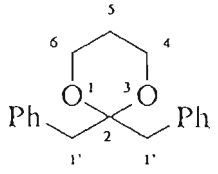
Method A:

To a stirred solution of aldehyde/ketone in dry benzene were added diol (1.1eq.-2eq.) and *p*-TsOH (cat amount). The mixture was refluxed in a Dean-Stark apparatus for the azeotropic removal of water. The reaction was normally followed by t.l.c. unless the R_f of the starting material coincided with the product. In this case the reaction was followed by nmr spectroscopy (60MHz). Upon completion, the reaction was cooled to room temperature, poured onto a saturated aqueous $NaHCO_3$ solution and the product extracted with a suitable solvent (CH_2Cl_2 or diethyl ether). The organic fractions were combined, dried over $MgSO_4$, filtered and the solvent evaporated *in vacuo*. The purification of the residue is specified in each experiment.

Method B:

The same as Method A except no aqueous workup was used. The acid was destroyed by the addition of solid Na_2CO_3 and the product obtained by filtration and removal of the benzene *in vacuo*.

6.2.1. Ketalisation of dibenzyl ketone with 1,3-propanediol



1

Method A was used on a 25mmol scale. The crude product was recrystallised from methanol to give 2,2-dibenzyl-1,3-dioxane **1** (3.91g, 59%), melting point: 63-65°C as a white crystalline solid (Found: C, 80.5; H, 7.3. $C_{18}H_{20}O_2$ requires C, 80.6; H, 7.5%);

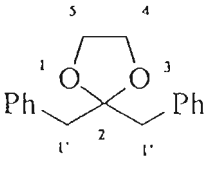
$\nu_{max.}$ ($CHCl_3$) 3005, 2960, 2870, 1605, 1125, 1100, 740 and 700 cm^{-1};

δ_H (200MHz) 1.69 (2H, quin, *J* 5.7 Hz, H-5), 2.97 (4H, s, H-1'), 4.05 (4H, t, *J* 5.7 Hz, H-4 and H-6) and 7.23 (10H, m, Ph-H);

δ_C (50MHz) 25.1 (C-5), 40.3 (C-1'), 59.7 (C-4 and C-6), 100.4 (C-2), 126.1, 127.8, 130.6 and 136.8 (Ph-C);

m/z 268 (M^+, 3%), 210 (4%), 177 (95%), 119 (13%) and 91 (100%).

6.2.2. Ketalisation of dibenzyl ketone with 1,2 ethanediol



3

Method A was used on a 20mmol scale:

The crude 2,2-dibenzyl-1,3-dioxolane **3** was purified by recrystallisation from methanol (3.53g, 73%), m.p. 62-64°C[31];

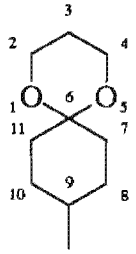
$\nu_{max.}$ ($CHCl_3$) 3060, 3030, 2950, 2925, 1490, 1450, 1325, 1190, 1140, 1120, 1045, 1035, 755, 740 and 695 cm^{-1};

δ_H (200MHz) 2.93 (4H, s, H-1'), 3.43 (4H, s, H-5 and H-4), 7.26 (10H, m, Ph-H);

δ_C (50MHz) 44.7 (C-1'), 65.4 (C-4 and C-5), 110.8 (C-2), 126.2, 127.7 and 130.7 (Ph-CH), 136.5 (Ph-C);

m/z 163 (M^+-91, 87%), 91 (100%), 83 (30%) and 55 (32%).

6.2.3 Ketalisation of 4-methyl-1-cyclohexanone with 1,3-propanediol



6

Method A was used on an 89mmol scale. The residual liquid was distilled *in vacuo* (61-64°C, 1mmHg) to yield 9-methyl-1,5-dioxaspiro[5.5]undecane **6** (7.77g, 51.2%) as a clear liquid. (Found: C, 70.1; H, 10.3. $C_{10}H_{18}O_2$ requires C, 70.5; H, 10.6%);

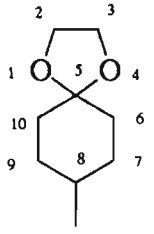
$\nu_{max.}$ ($CHCl_3$) 2950, 2870, 1445, 1370 and 1105 cm^{-1};

δ_H (200MHz) 0.74 (3H, d, *J* 6.2 Hz, 9-Me), 0.94-1.46 (7H, m, H-8, H-9, H-10, H-7eq and H-11eq), 1.53 (2H, m, H-3), 2.05 (2H, m, H-7ax and H-11ax), 3.73 (4H, quin, *J* 5.6 Hz, H-2 and H-4);

δ_C (50MHz) 21.5 (9-Me), 25.6 (C-3), 30.6, 31.8, 32.2 (C-7, C-8, C-9, C-10, C-11), 58.8, 59.1 (C-2, C-4), 97.6 (C-6);

m/z 113 (M^+-57, 100%), 103 (25%), 97 (10%), 83 (15%), 69 (18%) and 55 (38%)[113].

6.2.4 Ketalisation of 4-methyl-cyclohexanone with 1,2-ethanediol



9

Method A was used on a 100mmol scale. The crude product was purified by vacuum distillation (41-44°C, 1.0mmHg) to yield 8-methyl-1,4-dioxaspiro[4.5]decane **9** (10.58g, 68%).

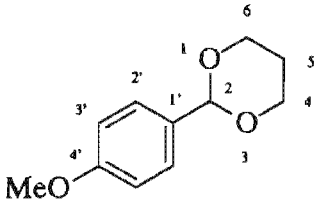
$\nu_{max.}$ ($CHCl_3$) 2950, 2870, 1450, 1365, 1270, 1250, 1160, 1105, 1080, 1030, 975, 935, 895 and 660 cm^{-1};

δ_H (200MHz) 0.91 (3H, d, *J* 6.2 Hz, 8-Me), 1.12-1.77 (9H, m, H-6, H-7, H-8, H-9 and H-10), 3.92 (4H, s, H-2 and H-3);

δ_C (50MHz) 21.5 (8-Me), 31.3 (C-8), 32.1 and 34.4 (C-6, C-7, C-9 and C-10), 63,9 and 64.0 (C-2 and C-3), 108.7 (C-5);

m/z 156 (M^+, 5%), 113 (8%), 105 (50%), 99 (100%) and 87 (20%)[113].

6.2.5. Acetalisation of *p*-Anisaldehyde with 1,3-propanediol



17

To *p*-methoxyphenyldimethoxymethane (9.8g, 54mmol) was added 1,3-propanediol (6.3g, 83mmol), pTsOH (100mg) (no solvent) and the mixture stirred for 3 hours at room temperature. The methanol was then removed under reduced pressure and the product obtained by standard work up procedure ($NaHCO_3/CH_2Cl_2$). The residue was distilled to afford 2-*p*-methoxyphenyl-1,3-dioxane **17** (10.1g, 96.7%) as a solid, mp. 39-42°C (pet ether (boiling range 60-70°C)) (Found: C, 68.25; H, 7.1. $C_{11}H_{14}O_3$ requires C, 68.0; H, 7.2%)

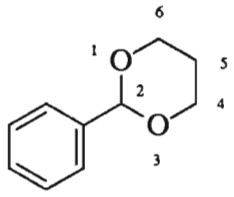
$\nu_{max.}$ ($CHCl_3$) 2955, 2845, 1615, 1515, 1465, 1375, 1245, 1170, 1145, 1105, 1040, 790 and 755 cm^{-1};

δ_H (200 MHz) 1.44 (1H, d, *J* 13.5 Hz, H-5_{eq}), 2.23 (1H, m, H-5_{ax}), 3.81 (3H, s, -OMe), 3.99 (2H, t, H-4_{eq} and H-6_{eq}), 4.27 (2H, d, H-4_{ax} and H-6_{ax}), 5.48 (1H, s, H-2), 6.91 (2H, d, *J* 8.8 Hz, H-3'), 7.43 (2H, d, *J* 8.8 Hz, H-2');

δ_C (50 MHz) 26.4 (C-5), 55.9 (C-OMe), 70.0 (C-4 and C-6), 102.1 (C-2), 114.1 (C-3'), 127.8 (C-2'), 131.9 (C-1'), 160.4 (C-4');

m/z 194(M^+, 45%), 193 (70%), 163 (12%), 135 (100%), 108 (16%) and 77 (25%).

6.2.6. Acetalisation of benzaldehyde with 1,3-propanediol



20

Method A was used on a 100mmol scale:

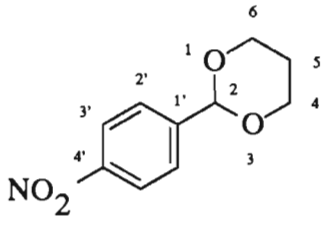
The crude product was distilled under vacuum to yield 2-phenyl-1,3-dioxane **20** (11.70g, 71.3%) as a white solid, mp. 39-42°C.

$\nu_{max.}$ ($CHCl_3$) 3005, 2975, 2930, 2855, 2725, 1600, 1490, 1465, 1450, 1390, 1375, 1276, 1235, 1145, 1105, 1025, 1005, 985, 735 and 695 cm^{-1};

δ_H (60MHz) 1.3 (1H, d, *J* 11 Hz, H-5_{eq}), 2.0 (1H, m, H-5_{ax}), 3.6 (2H, m, H-4_{eq} and H-6_{eq}), 4.1 (2H, m, H-4_{ax} and H-6_{ax}), 5.3 (1H, s, H-2), 7.1 (5H, m, Ph-H);

m/z 164 (M^+, 60%), 163 (92%), 105 (100%), 87 (28%), 77 (44%).

6.2.7. Acetalisation of *p*-Nitrobenzaldehyde with 1,3-propanediol



23

Method A was used on a 10mmol scale:

The resulting product was pure by t.l.c. (1.26g, 60.3%), but was recrystallised from pet ether (boiling range 60-70°C) to obtain 2-*p*-nitrophenyl-1,3-dioxane **23** (0.91g, 43.5%), mp. 108-110°C as yellow crystals (Found: C, 57.6; H, 5.5; N, 6.6. $C_{10}H_{11}NO_4$ requires C, 57.4; H, 5.3; N, 6.7%)

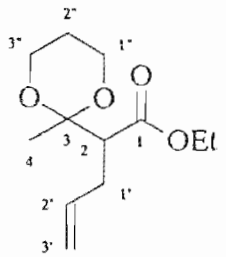
$\nu_{max.}$ ($CHCl_3$) 3005, 2975, 2930, 2855, 2725, 1600, 1490, 1465, 1450, 1390, 1375, 1275, 1235, 1145, 1105, 1025, 1005, 985, 735 and 695 cm^{-1};

δ_H (200MHz) 1.51 (1H, d, *J* 13.6 Hz, H-5_{eq}), 22.5 (1H, m, H-5_{ax}), 4.03 (2H, t, H-4_{eq} and H-6_{eq}), 4.32 (2H, d, H-4_{ax} and H-6_{ax}), 5.59 (1H, s, H-2), 7.68 (2H, d, H-2'), 8.26 (2H, d, H-3');

δ_C (50MHz) 26.3 (C-5), 68.0 (C-4 and C-6), 100.4 (C-2), 123.9 (C-3'), 127.7 (C-2'), 145.7 (C-4' and C1');

m/z 209 (M^+, 32%), 208 (62%), 150 (100%), 107 (91%), 105 (28%), 104 (24%), 87 (57%) and 77 (65%).

6.2.8. Ketalisation of Ethyl allyl acetoacetate with 1,3-propanediol



25

Method A was used on a 58.8mmol scale.

The residue was distilled *in vacuo* (93-95°C, 2.0mmHg) to afford ethyl 2-allyl-3,3-(1',3'-propanedioxy)butanoate **25** (10.77g 80.3%) as a clear liquid. R_f= 0.67 (1:1, ethyl acetate:Pet ether) (Found: C, 63.0; H. 8.5. $C_{12}H_{20}O_4$ requires C, 63.1; H, 8.8%);

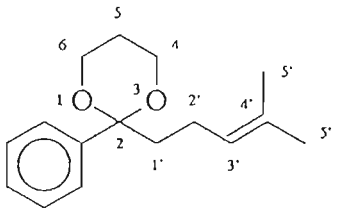
$\nu_{max.}$ ($CHCl_3$) 2980, 2875, 1725, 1640 and 1185 cm^{-1};

δ_H (200MHz) 1.10 (3H, t, *J* 7.2 Hz, Eth-CH_3), 1.30 (3H, s, H-4), 1.53 (2H, quin, *J* 5.6 Hz, H-2"), 2.25 (2H, m, H-1'), 3.05 (1H, dd, *J* 3.7 and 11.2 Hz, H-2), 3.75 (4H, m, H-1" and C-3"), 4.00 (2H, q, *J* 7.2 Hz, Eth-CH_2), 4.82 (1H, m, *J* 12.1 Hz, H-3' trans), 4.87 (1H, m, *J* 18.8 Hz, H-3' cis), 5.60 (1H, m, H-2');

δ_C (50MHz) 13.8 (Eth-CH_3), 18.9 (C-4), 24.8 (C-2"), 31.4 (C-1'), 50.5 (C-2), 59.2 and 59.3 (C-1" and C-3"), 59.9 (Eth-CH_2), 98.91 (C-2), 116.0 (C-3'), 135.3 (C-2'), 171.7 (ester C=O);

m/z 213 (M^+-15, 12%), 101 (100%), 73 (12%) and 43 (58%).

6.2.9. Ketalisation of 1-phenyl-5-methylhex-4-en-1-one with 1,3-propanediol



29

Method A as used on a 20mmol scale:

The crude product was distilled *in vacuo* (117°C-124°C, 1.0mmHg) to obtain 2-phenyl-2-(4-methyl-3-pentenyl)-1,3-dioxane **29** (3.97g, 80.7%) as a white solid.

$\nu_{max.}$ ($CHCl_3$) 2965, 2920, 2870, 1460, 1445, 1429, 1375, 1245, 1185, 1140, 1085, 1010, 970, 940 and 705 cm^{-1};

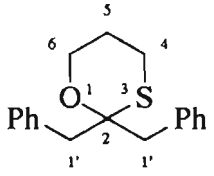
δ_H (200MHz) 1.14 (2H, m, H-5), 1.47 and 1.57 (6H, 2xs, H-5'), 1.70 (2H, m, H-1'), 2.12 (2H, m, H-2'), 3.81 (4H, m, H-4 and H-6), 4.96 (1H, t, *J* 7.1 Hz, H-3'), 7.37 (5H, m, Ph-H);

δ_C (50MHz) 17.4 and 25.4 (C-5'), 21.6 (C-2'), 25.6 (C-1'), 44.5 (C-5), 60.8 (C-4 and C-6), 101.5 (C-2), 123.9 (C-3'), 127.1, 127.4, 128.2 and 131.0 (Ph-C), 139.9 (C-4');

m/z 246 (M^+, 10%), 187 (6%), 169 (6%), 163 (100%), 105 (96%) and 77 (34%).

Found: M^+, 246.1604, $C_{16}H_{22}O_2$ requires *M*, 246.1620.

6.2.10. Ketalisation of dibenzylketone with 3-mercaptopropanol



39

Method A was used on a 5mmol scale. After column chromatography this resulted in 2,2-dibenzyl-3-thio-1-oxane **39** (1.12g, 63%). R_f=0.42 (pet ether : ethyl acetate, 9:1) mp: 68-69°C (methanol) (Found: C, 75.6; H, 7.2. $C_{18}H_{20}OS$ requires C, 76.1; H, 7.0%)

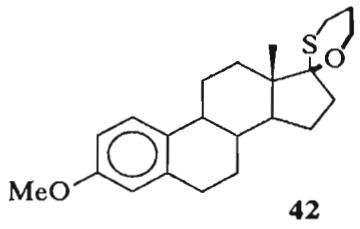
$\nu_{max.}$ ($CHCl_3$) 3065, 3000, 2335, 1605, 1495, 1450, 1205, 1080, 1030, 775, 725 and 700cm^{-1};

δ_H (200MHz) 1.79 (2H, m, H-5), 2.84 (2H, dd, *J* 5.9 and 7.6 Hz, H-6), 3.10 (2H, d, *J* 14.5 Hz, H-1'), 3.29 (2H, d, *J* 14.4 Hz, H-1'), 4.08 (2H, t, *J* 5.6 Hz, H-4), 7.29 (10H, s, Ph-H);

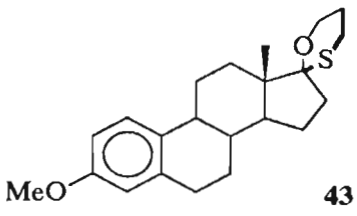
δ_C (50MHz) 24.1 (C-5), 24.7 (C-6), 43.8 (C-1'), 61.8 (C-4), 84.9 (C-2), 126.5, 127.6 and 130.8 (Ph-CH), 136.6 (Ph-C);

m/z: 193 (M^+-91, 95%), 91 (100%).

6.2.11. Ketalisation of 3-Methoxyestra-1,3,5(10)-trien-17-one with 3-mercaptopropanol



42



43

Method A was used on a 3.6mmol scale:

Column chromatography of the crude material gave the starting material (0.129g, 13%), diastereomer **42** (0.565g, 44%) and diastereomer **43** (0.409g, 32%).

42:

mp.: 139-143°C, (Found: C, 73.6; H, 8.6. $C_{22}H_{30}O_2S$ requires C, 73.7; H, 8.4%); $[\alpha]_D$ ($CHCl_3$) +54.7° (c= 1.00),

$\nu_{max.}$ ($CHCl_3$) 3015, 2945, 1605, 1495, 1215, 735 and 665 cm^{-1};

δ_H (200MHz) 0.86 (3H, s, H-18), 1.26-2.42 (12H, steroidal backbone), 2.58-3.08 (5H, m, H-3' and H-2'), 3.77 (3H, s, 3-OMe), 3.87-3.97 (2H, m, H-1'), 6.62 (1H, d, *J* 2.7 Hz, H-4), 6.70 (1H, dd, *J* 2.7 and 8.6 Hz, H-2), 7.22 (1H, d, *J* 8.5 Hz, H-1);

δ_C (50MHz) 15.4 (C-18), 24.3, 24.8, 26.3, 26.3, 27.9, 29.8, 30.0, 33.6, 39.1 (3-OMe), 43.6, 47.8, 49.7 (C-1'), 55.2, 62.1 (C-13), 93.0 (C-17), 111.3, 126.3, 132.7, 137.9, 157.2 (C-3);

m/z 358 (M^+, 43%), 284 (18%), 266 (46%) and 129 (100%).

43:

mp.: 124-125°C, (Found: C, 73.4; H, 8.6. $C_{22}H_{30}O_2S$ requires C, 73.7; H, 8.4%); $[\alpha]_D$ ($CHCl_3$) +1.3° (c= 1.00);

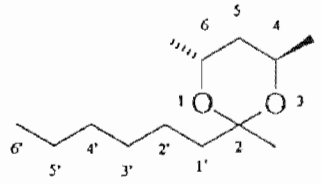
$\nu_{max.}$ ($CHCl_3$) 3015, 2940, 1605, 1495, 1215, 782, 734 and 665 cm^{-1};

δ_H (200MHz) 0.91 (3H, s, H-18), 1.21-2.55 (13H, steroidal backbone), 2.78-3.05 (4H, m, H-2', H-3'), 3.76 (3H, s, 3-OMe), 3.79-4.2 (2H, m, H-1'), 6.61 (1H, d, *J* 2.7 Hz, H-4), 6.70 (1H, dd, *J* 2.8 Hz, *J* 8.5 Hz, H2), 7.19 (1H, d, *J* 8.6 Hz, H1)

δ_C (50MHz) 13.9 (C-18), 23.2, 25.3, 25.9, 26.7, 27.4, 29.9, 34.2, 36.0, 39.3 (3-OMe), 43.5, 48.5, 49.4 (C-1'), 55.2, 65.0 (C-13), 95.5 (C-17), 111.4, 113.7, 126.2, 132.5, 137.8, 157.2 (C-3);

m/z: 358 (M^+, 43%), 284 (18%), 266 (46%) and 129 (100%).

6.2.12. Ketalisation of 2-octanone with 2R,4R-pentanediol



47

Method B was used on a 13.9mmol scale:

Column chromatography afforded 2,4R,6R-trimethyl-2-hexyl-1,3-dioxane (1.80g, 60%)[76].

$\nu_{max.}$ ($CHCl_3$) 2930, 2855, 1455, 1440, 1380, 1355, 1265, 1210, 1150, 1120, 1035, 970 and 760 cm^{-1};

δ_H (200MHz) 0.82 (3H, t, *J* 6.7 Hz, H-6'), 1.05-1.36 (17H, m, 2-Me, 4-Me, 6-Me, H-5', H-4', H-3' and H-2'), 1.40-1.70 (4H, m, H-5, H-1'), 3.88 (2H, m, H-4 and H-6);

δ_C (50MHz): 14.1 (C-6'), 21.8 (4-Me and 6-Me), 22.7 (2-Me), 22.6, 24.1, 29.6, 31.8, 38.3 and 41.5 (C-5, C-1', C-2', C-3', C-4' and C-5'), 62.3 and 62.5 (C-4 and C-6), 101.4 (C-2);

m/z 199 (M^+-15, 6%), 152 (26%), 129 (100%), 123 (21%), 110 (35%), 87 (18%), 69 (62%), 58(12%), 43 (58%).

6.2.13. Synthesis of 1-cyclohexylethanone

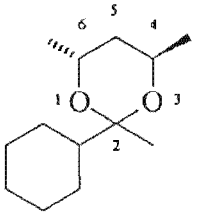
To a stirred suspension of magnesium (14.6g, 0.6mol) in dry diethyl ether (200ml) was added slowly over 1hr cyclohexyl bromide (49ml, 0.4mol) dissolved in diethyl ether (50ml). Freshly distilled ethanal (31ml, 0.6mol) dissolved in diethyl ether (50ml) was then added slowly over 1 hr and the reaction stirred for 24 hrs. Water (200ml) was added to this followed by HCl (300ml, 0.3mol). When hydrolysis was complete the product was extracted with diethyl ether (3x200ml). The organic fraction was reduced to 150ml, before being washed with NaOH (100ml, 200mmol). The organic layer was dried over $MgSO_4$ and the diethyl ether evaporated *in vacuo* to yield 1-cyclohexylethanol (40.9g, 80%). This was confirmed by 60MHz ^1H nmr.

δ_H (60MHz), neat: 1.2-2.1 (12H, m), 1.4 (3H, d), 3.2 (1H, m);

This material was used further without purification. To a stirred solution of 1-cyclohexylethanol (10.24g, 80mmol) in acetone (50ml) at 0°C was added dropwise Jones reagent (50ml, 100mmol) and the solution left stirring for 1hr at room temperature before adding solid sodium meta bisulphite slowly until no more effervescence occurred. The mixture was poured into a separating funnel, diluted with water (100ml) and the product extracted with diethyl ether (3x150ml). The organic layers were dried over $MgSO_4$, filtered and evaporated to yield 1-cyclohexylethanone (6.65g, 66%) (bp. 44-47°C, 1mmHg) after distillation.

δ_H (60MHz), neat: 1.2-2.1 (10H, m), 2.2 (3H, s), 2.5 (1H, m);

6.2.14. Ketalisation of 1-cyclohexylethanone with 2R,4R-pentanediol



A mixture of 1-cyclohexylethanone (3.33g, 26.4mmol), trimethyl orthoformate (6.1ml, 55.4mmol) and *p*TsOH (20mg) was stirred at room temperature for 5 hrs. Methyl formate was then removed *in vacuo*, solid $NaHCO_3$ (0.5g, large excess) added and the mixture filtered. The crude product was distilled under reduced pressure (bp. 145-150°C, 20mmHg) to obtain 1,1-dimethoxy-1-cyclohexyl ethane (3.81g, 84%). To the latter (2.91g, 16.9mmol) in dry benzene (10ml) was added 2R,4R-pentanediol (1.94g, 18.7mmol) and pyridinium-*p*-toluene sulphonate (PPTS) (20mg). The mixture was heated under reflux in a Dean-Stark apparatus for 5 hrs, cooled and solid $NaHCO_3$ (0.5g, large excess) added. The mixture was filtered, the filtrate washed with diethyl ether and the ether evaporated under reduced pressure. The residue was dissolved in pet ether and refiltered to recover unreacted (2R,4R-pentanediol). Removal of the solvent and purification by column chromatography on silica gel gave 2-cyclohexyl-2,4R,6R-trimethyl-1,3-dioxane (2.91g, 61%)[76].

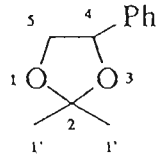
$\nu_{max.}$ ($CHCl_3$) 2970, 2930, 2850, 1450, 1440, 1375, ,1230, 1165, 1145, 1100, 1035, 960, 760 and 740 cm^{-1};

δ_H (200MHz) 1.09 (3H, d, *J* 6.4 Hz, 4-Me or 6-Me), 1.12 (3H, d, *J* 6.5 Hz, 4-Me or 6-Me), 1.13 (3H, s, 2-Me), 0.75-1.87 (13H, m, cyclohexyl-H and H-5), 3.90 (2H, m, H-4 and H-6);

δ_C (50MHz) 19.1, 21.8 and 21.8 (2-Me, 4-Me and 6-Me), 26.5, 26.7 and 27.5 (cyclohexyl-CH_2), 41.2 (C-5), 45.4 (cyclohexyl-CH), 62.0 and 62.2 (C-4 and C-6), 102.5 (C-2);

m/z 197 (M^+-15, 4%), 129 (100%), 87 (18%), 83 (8%), 69 (55%), 55 (10%) and 43 (50%).

6.2.15. Ketalisation of acetone with 1-phenyl-1,2-ethanediol



48

A solution of 1-phenyl-1,2-ethanediol (5.0g, 36mmol) and *p*TsOH (50mg) in dry acetone (150ml) was refluxed for 4 hrs. After a standard workup ($NaHCO_3/CH_2Cl_2$) the residue was purified by vacuum distillation to afford 2,2-dimethyl-4-phenyl-1,3-dioxolane **48** (4.0g, 62%).

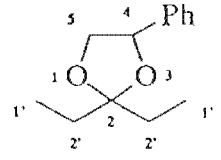
$\nu_{max.}$ ($CHCl_3$) 2985, 2935, 2880, 1490, 1450, 1380, 1370, 1225, 1155, 1055, 1025, 860 and 700cm^{-1};

δ_H (200MHz) 1.50 (3H, s, H-1'), 1.56 (3H, s, H-1'), 3.70 (1H, t, *J* 8.1 Hz, H-5), 4.28 (1H, dd, *J* 6.2 and 8.2 Hz, H-4), 5.07 (1H, dd, *J* 6.2 and 8.1 Hz, H-5), 7.36 (5H, m, Ph-H);

δ_C (50MHz) 26.4 and 27.0 (C-1'), 72.1 (C-5), 78.4 (C-4), 110.2 (C-2), 126.6, 128.4, 128.9 and 139.6 (Ph-H);

m/z 178 (M^+, 5%), 177 (31%),163 (35%), 120 (24%), 119 (22%), 107 (28%), 105 (56%), 91 (34%), 77 (42%), 72 (62%) and 43 (100%).

6.2.16. Ketalisation of 3-pentanone with 1-phenyl-1,2-ethanediol



51

Method A was used on a 35mmol scale. The crude product was purified by vacuum distillation to afford 2,2-diethyl-4-phenyl-1,3-dioxolane **51** (5.3g, 73%)

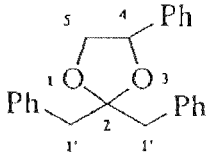
$\nu_{max.}$ ($CHCl_3$) 2975, 2940, 2880, 1460, 1170, 1075, 1055, 1035, 915, 775 and 700cm^{-1};

δ_H (200MHz) 1.03 (6H, m, H-2'), 1.77 (4H, m, H-1'), 3.66 (1H, dd, *J* 8.0 and 8.8 Hz, H-5), 4.30 (1H, dd, *J* 6.1 and 8.0 Hz, H-4), 5.08 (1H, dd, *J* 6.0 and 8.9 Hz, H-5), 7.39 (5H, m, Ph-H);

δ_C (50MHz) 8.0 (C-2'), 29.5 and 29.8 (C-1'), 71.9 (C-5), 78.1 (C-4), 113.4 (C-2), 126.1, 127.9, 128.4 and 138.7 (Ph-C);

m/z 206 (M^+, 2%), 205 (11%), 177 (36%), 105 (35), 91 (16%), 77 (19%) and 57 (100%).

6.2.17. Ketalisation of dibenzylketone with 1-phenyl-1,2-ethanediol



54

Method A was used on a 10mmol scale:

The crude product was purified by column chromatography to yield 2,2- dibenzyl-4-phenyl-1,3-dioxolane **54** (2.63g, 80%), mp. 75-78°C. (Found: C, 83.6; H, 6.7. $C_{23}H_{22}O_2$ requires C, 83.6; H, 6.7%)

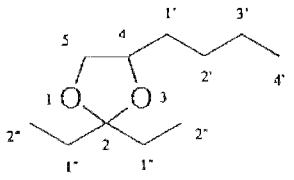
$\nu_{max.}$ ($CHCl_3$) 3085, 3065, 3030, 2920, 2880, 1490, 1450, 1250, 1180, 1130, 1030, 765 and 695 cm^{-1};

δ_H (200MHz) 3.06 (2H, s, H-1'), 3.13 (2H, s, H-1'), 3.25 (1H, dd, *J* 7.7 and 9.3 Hz, H-5), 4.01 (1H, dd, *J* 6.0 and 7.6 Hz, H-4), 4.38 (1H, dd, *J* 6.1 and 9.3 Hz, H-5), 6.94-7.00 (2H, m, Ph-H), 7.20-7.42 (13H, m, Ph-H);

δ_C (50MHz) 15.6 (C-1'), 28.9 (C-5), 78.6 (C-4), 111.8 (C-2), 126.5, 126.8, 127.9, 128.0, 128.2, 128.4, 130.9, 131.2, 136.5, 136.6 and 137.6 (Ph-C);

m/z 239 (M^+-91, 55%), 119 (17%), 91 (100%) and 77 (5%).

6.2.18. Ketalisation of 3-pentanone with 1,2-hexanediol



57

Method A was used on a 20mmol scale:

The crude product was distilled *in vacuo* to yield 2,2-diethyl-4-butyl-1,3-dioxolane **57** (1.73g, 47%) (bp. 44°C, 0.5mmHg).

$\nu_{max.}$ ($CHCl_3$) 2965, 2935, 2870, 1460, 1440, 1375, 1350, 1195, 1170, 1135, 1120, 1075, 1055, 1035, 925, 790 and 770 cm^{-1};

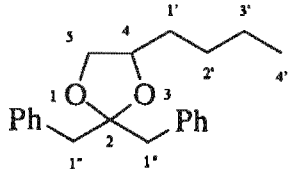
δ_H (200MHz) 0.84 and 0.85 (9H, 2xt, *J* 7.4 and 7.5 Hz respectively, H-4' and H2"), 1.16-1.70 (10H, m, H-1', H-2', H-3', H-1"), 3.40 (1H, m, H-5), 4.00 (2H, m, H-4 and H-5);

δ_C (50MHz) 7.9, 8.2 and 13.9 (C-2" and C-4'), 22.7, 28.0, 29.8, 30.0 and 33.2 (C-1', C-2', C-3' and C-1"), 70.2 (C-5), 76.3 (C-4), 112.3 (C-2);

m/z 157 (M^+-29, 30%), 143 (38%), 103 (10%), 87 (82%), 83 (51%), 69 (49%), 55 (46%) and 43 (100%).

Found: M^+-*29*, 157.1216. $C_9H_{17}O_2$ requires *M-29,* 157.1228.

6.2.19. Ketalisation of dibenzyl ketone with 1,2-hexanediol



60

Method A was used on a 20mmol scale:

The crude product was purified by column chromatography (pet ether/ethyl acetate) to afford 2,2-dibenzyl-4-butyl-1,3-dioxolane **60** (3.76g, 61%). mp. 43-46°C, (Found: C, 80.3; H, 8.4. $C_{21}H_{26}O_2$ requires C, 81.3; H, 8.4%)

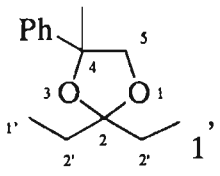
$\nu_{max.}$ ($CHCl_3$) 3060, 3030, 2955, 2930, 1490, 1450, 1180, 1125, 1080, 1060, 1030, 765, 740 and 695 cm^{-1};

δ_H (200MHz) 0.84 (3H, t, *J* 6.8 Hz, H-4'), 1.00-1.34 (6H, m, H-1', H-2', H-3'), 2.77 (1H, t, *J* 7.9 Hz, H-5), 2.93 (4H, s, H1"), 3.42 (1H, m, H-4), 3.65 (1H, dd, *J* 5.9 and 7.2 Hz, H-5), 7.3 (10H, m, Ph-H);

δ_C (50MHz) 14.0 (C-4'), 22.6 (C-3'), 27.9 (C-2'), 32.3 (C-1'), 45.1 and 45.2 (C-1"), 70.5 (C-5), 76.7 (C-4), 110.8 (C-2), 126.2, 127.5, 127.7 130.7 131.0, 136.5 and 136.6 (Ph-C);

m/z 219 (M^+-91, 100%), 137 (12%), 91 (90%), 83 (50%), 55 (40%).

6.2.20. Ketalisation of 3-pentanone with 2-phenyl-propane-1,2-diol



63

Method A was used on a 20mmol scale:

The crude product was purified by column chromatography (pet ether/ethyl acetate) to yield 2,2-diethyl-4-methyl-4-phenyl-1,3-dioxolane **63** (2.95g, 67%)

$\nu_{max.}$ ($CHCl_3$) 3085, 3060, 3025, 2975, 2940, 2880, 1490, 1460, 1440, 1165, 1070, 1055, 985, 930, 765 and 700 cm^{-1};

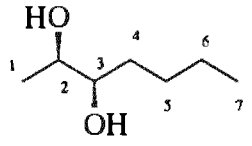
δ_H (200MHz) 0.89 (3H, t, *J* 7.5 Hz, H2'), 1.00 (3H, t, *J* 7.4 Hz, H2'), 1.57 (3H, s, 4-Me), 1.58 (2H, q, *J* 7.7 Hz, H-1'), 1.79 (2H, q, *J* 7.6 Hz, H-1'), 4.09 (2H, s, H-5), 7.23-7.49 (5H, m, Ph-H);

δ_C (50MHz) 8.2 and 8.7 (C-2'), 29.1 and 29.3 (C-1'), 29.6 (4-Me), 75.5 (C-5), 82.2 (C-4), 113.8 (C-2), 124.5, 126.6, 128.1 and 146.5 (Ph-C);

m/z 191 (M^+-29, 32%), 163 (31%), 135 (20%), 117 (42%), 105 (54%) and 57 (100%).

Found: M^+-*29*, 191.1044. $C_{12}H_{15}O_7$ requires *M-29*, 191.1072.

6.2.21. Hydroxylation of *cis*-hept-2-ene



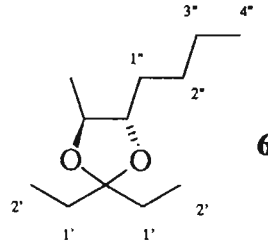
To a solution of *cis*-hept-2-ene (1.00ml, 7.1mmol) in formic acid (10ml) was added at 0°C hydrogen peroxide (0.65ml, 7.1mmol). After 24 hrs, during which the mixture was allowed to warm up to RT, the formic acid was removed on the rotary evaporator. NaOH solution (5M, 10ml) was then added and the mixture heated to 50°C for 1 hr. The mixture was poured into H_2O (20ml) and the product extracted with warm ethyl acetate (5x50ml). The organic fractions were combined, dried over $MgSO_4$ and the ethyl acetate evaporated. This resulted in 0.92g (98%) of ±2R,3R-heptanediol, which was used further without purification.

$\nu_{max.}$ 3420, 2955, 2930, 2870, 1455, 1375, 1180, 1050 and 730cm^{-1};

δ_H (200MHz) 0.91 (3H, t, *J* 6.7 Hz, H-7), 1.17 (3H, d, *J* 6.2 Hz, H-1), 1.35 (6H, m, H-4, H-5, H-6), 3.31 (1H, m, H-3), 3.45 (2H, br. s., exch., -OH), 3.57 (1H, quin, *J* 6.5 Hz, H-2);

δ_C (50MHz) 14.0 (C-7), 19.4 (C-1), 22.7 (C-6), 27.7 (C-5), 32.9 (C-4), 70.8 (C-2), 76.1 (C-3).

6.2.22. Ketalisation of pentan-3-one with ±2R,3R-heptanediol



68

Method B was used on a 7.0mmol scale:

The crude product was purified by column chromatography (pentane:diethyl ether, 95:5), to yield *trans*-4-butyl-2,2-diethyl-5-methyl-1,3-dioxolane **68** (1.30g, 92%).

$\nu_{max.}$ ($CHCl_3$) 2970, 2930, 2870, 1460, 1380, 1170, 1090, 940 and 735cm^{-1};

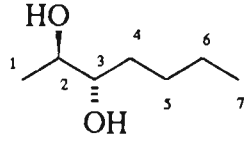
δ_H (200MHz) 0.86 (9H, m, H-2', H-4"), 1.20 (3H, d, *J* 5.9 Hz, 5-Me), 1.24-1.51 (6H, m, H1", H2", H3"), 1.58 (2H, q, *J* 7.4 Hz, H-1'), 1.59 (2H, q, *J* 7.4 Hz, H-1'), 3.45 (1H, td, *J* 5.6 and 8.5 Hz, H4), 3.65 (1H, qd, *J* 5.9 and 8.9 Hz, H5);

δ_C (50MHz) 7.9 and 8.0 (C2'), 13.8 (C4"), 17.5 (5-Me), 22.8 (C3"), 28.2, 30.7, 30.8 and 32.0 (C1', C1" and C2"), 77.1 and 82.8 (C4 and C5), 111.2 (C2);

m/z 171 (M^+-29, 27%), 97 (30%) and 57 (100%);

Found: *M^+-29*, 171.1380. $C_{10}H_{19}O_2$ requires *M-29*, 171.1380.

6.2.23. Hydroxylation of *trans*-hept-2-ene



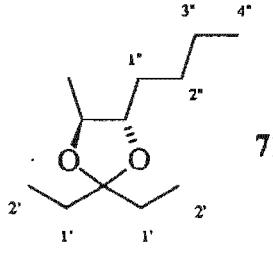
To a solution of *trans*-hept-2-ene (1.00ml, 7.1mmol) in formic acid (10ml) was added at 0°C hydrogen peroxide (0.65ml, 7.1mmol). After 24 hrs, during which time the mixture was allowed to warm up to RT, the formic acid was removed on the rotary evaporator, NaOH solution (10ml, 50mmol) added and the solution heated to 50°C for 1 hr. The mixture was poured into H_2O (20ml) and the product extracted with ethyl acetate (5x50ml, warmed to 50°C). The combined organic fractions were dried over $MgSO_4$, filtered and the solvent evaporated to afford ±2R,3S-heptanediol (0.93g, 98%), which was used without further purification.

$\nu_{max.}$ ($CHCl_3$) 3590, 3430, 2960, 2930, 2870, 1450, 1380, 1340, 1205, 1050, 765 and 730cm^{-1};

δ_H (200MHz) 0.87 (3H, t, *J* 7.0 Hz, H-7), 1.09 (3H, d, *J* 6.5 Hz, H-1), 1.17-1.52 (6H, m, H-4, H-5 and H-6), 2.98 (2H, br. s., exch., -OH), 3.56 (1H, dt, *J* 3.1 and 5.9 Hz, H-3), 3.73 (1H, dq, *J* 3.1 and 6.4 Hz, H-2);

δ_C (50MHz) 13.9 (C-7), 16.4 (C-1), 22.7 (C-6), 28.2 (C-5), 31.5 (C-5), 70.4 (C-2), 74.9 (C-3);

6.2.24. Ketalisation of pentan-3-one with ±2R,3S-heptanediol



71

Method B was used on a 7.0mmol scale:

The crude product was purified by column chromatography (pentane:diethyl ether, 95:5), to yield *cis*-4-butyl-2,2-diethyl-5-methyl-1,3-dioxolane **71** (1.30g, 92%).

$\nu_{max.}$ ($CHCl_3$) 2965, 2935, 2875, 1460, 1375, 1175, 1080, 945 and 755 cm^{-1};

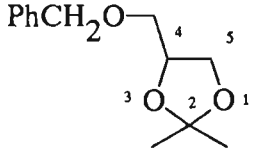
δ_H (200MHz) 0.83 (9H, m, H-2', H-4"), 1.04 (3H, d, *J* 6.4 Hz, 5-Me), 1.18-1.44 (6H, m, H-1", H-2", H-3"), 1.54 (4H, quin, *J* 7.4 Hz, H-1'), 3.95 (1H, m, H-4), 4.16 (1H, quin, *J* 6.4 Hz, H-5);

δ_C (50MHz) 8.0 and 8.6 (C-2'), 13.9 (C-4"), 15.7 (5-Me), 22.7 (C-3"), 28.6, 29.1, 29.7 and 30.1 (C-1', C-1" and C-2"), 73.4 and 77.7 (C-4 and C-5), 110.8 (C-2);

m/z 171 (M^+-29, 5%), 171 (45%), 143 (2%), 115 (8%), 114 (9%), 97 (35%), 86 (13%), 57 (100%) and 55 (45%).

Found: M^+-29, 171.1373; $C_{10}H_{19}O_2$ requires *M-29*, 171.1380;

6.2.25. Benzylation of 2,2-Dimethyl-1,3-dioxolane-4-methanol



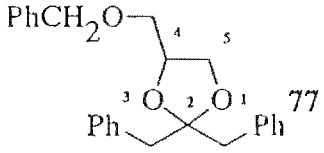
74

To a solution of solketal (20ml, 162mmol) in glyme (50ml) were added NaH (6.5g, 191mmol), benzyl bromide (23.1ml, 190mmol) and $Bu_4N^+I^-$ (100mg, phase transfer catalyst). After 3 days at room temperature, standard workup afforded the crude product, which was purified by distillation (87-90°C, 2mmHg) to obtain 2,2-dimethyl-4-benzyloxymethyl-1,3-dioxolane **74** (28.25g, 79%)[114]

δ_H (60MHz) 1.40 and 1.48 (6H, 2s, 2-Me), 3.36-4.33 (5H, m, H-4, H-5, 4-CH_2), 4.45 (2H, s, benzyl-CH_2), 7.20 (5H, s, Ph-H);

δ_C (50MHz) 25.4 and 26.8 (2-Me), 66.9 (C-5), 71.2 (4-CH_2), 73.5 (Bn-CH_2), 74.8 (C-4), 109.4 (C-2), 126.2, 127.7, 128.4 and 138.1 (Ph-C).

6.2.26. Benzylation of 2,2-dibenzyl-1,3-dioxolane-4-methanol **80**



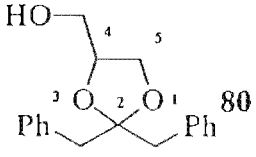
77

To a solution of 2,2-dibenzyl-1,3-dioxolane-4-methanol **80** (1.54g, 5.4mmol) in THF (20ml) at 0°C was added NaH (0.25g, 8.1mmol), benzyl bromide (0.71ml, 5.9mmol) and $Bu_4N^+I^-$ (100mg, phase transfer catalyst). This was left to warm up to room temperature and stirred for 24 hours before quenching with ice. The crude product was obtained by standard workup (H_2O, ethyl acetate) to yield 4-benzyloxymethyl-2,2-dibenzyl-1,3-dioxolane 77 (1.48g, 73%)

δ_H (200MHz) 2.86 (1H, dd, *J* 9.7 and 5.7 Hz, H-5), 2.95 (4H, s, H-1'), 3.07 (2H, m, 4-CH_2), 3.61 (1H, dd, *J* 7.5 and 6.3 Hz, H-5), 3.77 (1H, quintet, *J* 6.2, H-4), 4.32 (1H, d, *J* 12.2 Hz, benzyl-CH_2), 4.43 (1H, d, *J* 12.3 Hz, benzyl-CH_2), 7.25 (15H, m, Ph-H);

δ_C (50MHz) 44.9 and 45,0 (C-1'), 68.0 (C-5), 70.7 (4-CH_2), 73.2 (benzyl-CH_2), 75.4 (C-4), 111.9 (C-2), 126.2, 126.2, 126.3, 127.6, 127.6, 128.3, 130.7, 131.0 (Ph-CH), 136.2, 136.5 and 137.8 (Ph-C).

6.2.27. Transketalisation of 2,2-dimethyl-1,3-dioxolane-4-methanol



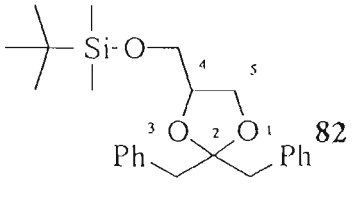
80

To a solution of solketal (10g, 76mmol) in CH_2Cl_2 (50ml) at 0°C were added pyridine (10.0ml, 124mmol) and acetic anhydride (10.0ml, 106mmol). After 15hrs at RT the reaction was quenched with a saturated solution of $NaHCO_3$ and a crude product was obtained by standard workup ($NaHCO_3$, ethyl acetate). To the crude product were added dibenzyl ketone (15.9g, 76mmol) and *p*TsOH (50mg, cat. amount) and the reaction stirred under reduced pressure for 5 hrs. The reaction was quenched with water and standard workup (water, ethyl acetate) resulted in a residue which was hydrolysed with a solution of KOH (5.0g, 88mmol) in aqueous methanol (85%) for 3 hours. Standard workup (water, ethyl acetate) afforded a crude product which was purified by column chromatography to yield dibenzyl ketone (3.81g, 24% recovery) and 2,2-dibenzyl-1,3-dioxolane-4-methanol **80** (8.20g, 38%) mp. 52-57°C, (Found: C, 76.1; H, 7.2. $C_{18}H_{20}O_3$ requires C, 76.1; H, 7.0%)

δ_H (200MHz) 1.85 (1H, br.s., -OH), 3.05 and 3.08 (4H, 2s, Bn-CH_2), 3.20-3.83 (5H, m, C-4, C-5, 4-CH_2), 7.25 (10H, m, Ph-H);

δ_C (50MHz) 44.5 (Bn-CH_2), 63.2 (4-CH_2), 68.0 (C-5), 76.5 (C-4), 11.6 (C-2), 126.4, 127.7, 127.9, 128.1, 130.7 and 131.1 (Ph-CH), 136.5 and 136.6 (Ph-C).

6.2.28. Silylation of 2,2-Dibenzyl-1,3-dioxolane-4-methanol **80**



82

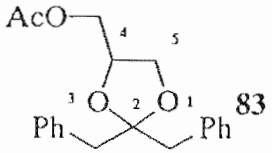
To a solution of 2,2-dibenzyl-1,3-dioxolane-4-methanol (1.00g, 3.52mmol) in DMF (20ml) were added imidazole (0.27g, 4.0mmol) and *t*butyldimethylsilyl chloride (0.58g, 8.8mmol). The reaction was stirred at room temperature for 15 hours before adding water (50ml). Standard workup (H_2O, CH_2Cl_2) and column chromatography afforded

4-(*t*butyldimethylsiloxy)methyl-2,2-dibenzyl-1,3-dioxolane **83** (1.12g, 80%) as a solid (mp. 31-32°C) (Found: C, 72.5; H,8.9; N, 0.3. $C_{24}H_{34}O_3Si$ requires C, 72.4; H, 8.5%);

δ_H (200MHz) -0.04 (3H, s, Si-CH_3), -0.03 (3H, s, Si-CH_3), 0.83 (9H, s, *t*Bu-CH_3), 2.90 (1H, m), 2.94 (2H, s, Bn-CH_2), 2.97 (2H, s, Bn-CH_2), 2.97 2H, s, Bn-CH_2), 3.22-3.45 (2H, m), 3.68 (2H, m), 7.27 (10H, m, Ph-H);

δ_C (50MHz) -5.5 (Si-CH_3), 18.2 (*t*Bu-C), 25.8 (*t*Bu-CH_3), 44.8 (Bn-CH_2), 63.6 (4-CH_2), 68.1 (C-5), 76.9 (C-4), 111.6 (C-2), 126.3, 127.7, 127.9, 130.7 and 131.1 (Ph-CH), 136.4 and 136.6 (Ph-C).

6.2.29. Acetylation of 2,2-Dibenzyl-1,3-dioxolane-4-methanol **80**



83

To a solution of 2,2-dibenzyl-1,3-dioxolane-4-methanol **80** (1.20g, 4.2mmol), in CH_2Cl_2 (20ml) were added pyridine (1.5ml, 18.6mmol) and acetic anhydride (1.0ml, 10.6mmol). After 3 hours at room temperature the crude product was obtained by standard workup (NH_4Cl, CH_2Cl_2) and purified by column chromatography to afford 2,2-dibenzyl-1,3-dioxolane-4-methyl ethanoate **83** (0.95g, 69%) as a solid and starting material (0.03g, 25%) (Found: C, 72.6; H, 6.8. $C_{20}H_{22}O_4$ requires C, 73.6; H, 6.7%)

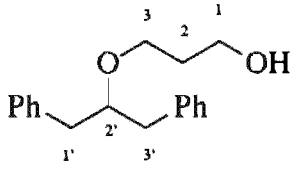
$\nu_{max.}$ 3010, 2925, 1740, 1495, 1450, 1370, 1235, 1042, 760, 735 and 700cm^{-1};

δ_H (200MHz) 2.01 (3H, s, Ac-CH_3), 2.95 (2H, s, Bn-CH_2), 2.97 (2H, s, Bn-CH_2), 3.07 (1H, m, H-4), 3.66 (4H, m, H-5 and 4-CH_2), 7.26 (10H, m, Ph-H);

δ_C (50MHz) 20.7 (Ac-CH_3), 44.8 (Bn-CH_2), 44.9 (BnCH_2), 64.2 (4-CH_2), 67.5 (C-5), 74.3 (C-4). 112.3 (C-2), 126.5, 127.8, 127.9, 129.5, 130.7 and 131.0 (Ph-CH), 136.0 and 136.3 (Ph-C), 170.5 (Ac-C=O).

6.3. Reduction of acetals/ketals

6.3.1. Reduction of 2,2-dibenzyl-1,3-dioxane 1



2

To a stirred solution of 2,2-dibenzyl-1,3-dioxane 1 (264.9mg, 0.99mmol) in THF (5ml) at -78°C were added TMSOTf (0.20ml, 1.1mmol) and after 10 min. $BH_3{\cdot}SMe_2$ (0.11ml of 10M solution, 1.1mmol). The reaction mixture was stirred at -78°C to -75°C for 50 min before a saturated $NaHCO_3$ solution (4ml) was added. The mixture was allowed to warm up to room temperature and the crude product obtained by the standard workup ($NaHCO_3$/ethyl acetate). This was purified by column chromatography to yield 3-dibenzylmethoxy-propan-1-ol **2** (253.8mg, 95%). R_f= 0.52 (ethyl acetate : pet ether, 3:7);

$\nu_{max.}$ ($CHCl_3$) 3515, 3000, 2940, 2870, 1600, 1090, 780 and 700cm^{-1};

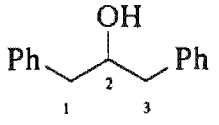
δ_H (200MHz) 1.64 (2H, quin, *J* 5.7 Hz, H-2), 2.22 (1H, br. s, exch., OH), 2.82 (4H, d, *J* 6.4 Hz, H-1' or H-3'), 3.41 (2H, t, *J* 5.7 Hz, H-3), 3.54 (2H, t, *J* 5.6 Hz, H-1), 3.72 (1H, quin, *J* 6.4, H-2'), 7.25 (10H, m, Ph-H);

δ_C (50MHz) 32.1 (C-2), 40.8 (C-1' or C-3'), 61.1 (C-1), 68.6 (C-3), 82.6 (C-2'), 126.1, 128.2 and 129.2 (Ph-CH), 138.7 (Ph-C);

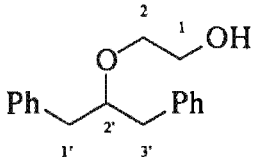
m/z 179 (M^+-91, 100%), 121 (92%), 105 (77%), 103 (32%), 91 (80%) and 59 (51%).

Found: M^+, 270.1590. $C_{18}H_{22}O_2$ requires *M*, 270.1620.

6.3.2. Reduction of 2,2-dibenzyl-1,3-dioxolane **3**



4



5

To a solution of 2,2-dibenzyl-1,3-dioxolane **3** (0.2540g, 1.0mmol) in CH_2Cl_2 at -78°C were added TMSOTf (0.21ml, 1.1eq) and $BH_3{\cdot}SMe_2$ (1.10ml of 1M solution in CH_2Cl_2, 1.1eq). The reaction was allowed to warm up to -60°C and then quenched with a saturated solution of $NaHCO_3$. After the standard workup ($NaHCO_3$, ethyl acetate) the crude product was purified by column chromatography (pet ether, ethyl acetate) to yield dibenzyl methanol **4** (41.6mg, 20%) and 2-dibenzylmethoxy-ethan-1-ol **5** (131.1mg, 51%)[31].

dibenzylmethanol **4**:

δ_H (200MHz) 1.58 (1H, br.s., -OH), 2.67 (2H, dd, *J* 7.9 and 13.7 Hz, H-1 and H-3), 2.80 (2H, dd, *J* 4.9 and 13.6 Hz, H-1 and H-3), 3.99 (1H, tt, *J* 4.8 and 7.9 Hz, H-2), 7.20 (10H, m, Ph-H);

δ_C (50MHz) 43.3 (C-1 and C-3), 73.6 (C-2), 126.5, 128.5 and 129.4 (Ph-CH), 138.4 (Ph-C);

2-dibenzylmethoxy-ethan-1-ol **5**:

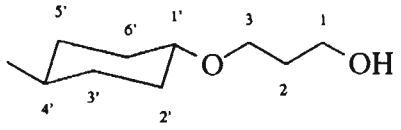
$\nu_{max.}$ ($CHCl_3$) 3555, 3000, 2920, 2870, 1600, 1495, 1450, 1370, 1245, 1100, 1045, 745, 700 and 665cm^{-1};

δ_H (200MHz) 1.59 (1H, br., exch., O-H), 2.79 (4H, d, *J* 6.3 Hz, H-1' and H-3'), 3.36 (4H, m, H-1 and H-2), 3.70 (1H, quin, *J* 6.3 Hz, H-2'), 7.20 (10H, m, Ph·H);

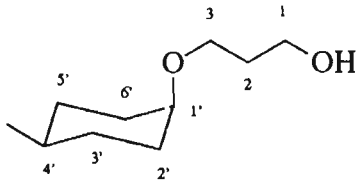
δ_C (50MHz) 41.1 (C-1' and C-3'), 61.7 (C-1), 71.1 (C-2), 82.8 (C-2'), 126.2, 128.3, 129.2 and 138.7 (Ph-H);

m/z 165 (M^+-91, 100%), 121 (75%), 91 (42%).

6.3.3. Reduction of 9-Methyl-1,5-dioxaspiro[5.5]undecane **6**



7



8

To a solution of 9-methyl-1,5-dioxaspiro[5.5]undecane **6** (0.1750g, 1.0mmol) in THF (5ml) at -78°C were added TMSOTf (0.20ml, 1.1mmol) and $BH_3{\cdot}SMe_2$ (0.11ml of 10 M, 1.1mmol). After 1 hr the reaction was quenched with a saturated $NaHCO_3$ solution and the crude products obtained by the standard workup procedure (NH_4Cl/ethyl acetate) and purified by column chromatography (pet ether/ethyl acetate/98:2) to afford the cis isomer **8** (24.7 mg, 14%)

$\nu_{max.}$ ($CHCl_3$) 3470, 2930, 2855, 1450, 1355, 1095, 1075, 795 and 745cm^{-1};

δ_H (200MHz) 0.84 (3H, d, *J* 5.9 Hz, 4'-Me), 1.12-1.48 (7H, m, H-3', H-4', H-5', H-2'$_{eq}$ and H-6'$_{eq}$), 1.76 (2H, m, H-2'$_{ax}$ and H-6'$_{ax}$), 1.79 (2H, quin, *J* 5.5 Hz, H-2), 2.90 (1H, br. s., -OH), 3.45 (1H, m, H-1'), 3.57 (2H, t, *J* 5.5Hz, H-3), 3.75 (2H, t, *J* 5.5 Hz, H-1);

δ_C (50MHz): 21.9 (4'-Me), 29.3 (C-2', C-3', C-5' and C-6'), 31.5 (C-2), 32.0 (C-4'), 63.0 (C-1), 67.9 (C-3), 74.5 (C-1');

and the trans isomer **7** (147.7mg, 83.4%);

$\nu_{max.}$ ($CHCl_3$) 3450, 2925, 2855, 1450, 1365, 1095, 1075, 795 and 745cm^{-1};

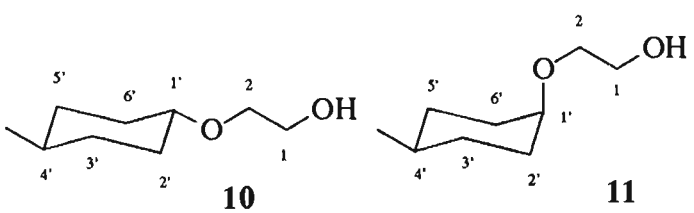
δ_H (200MHz): 0.74 (3H, d, *J* 5.8 Hz, 4'-Me), 0.87 (2H, m, H-3'$_{eq}$ and H-5'$_{eq}$), 1.00-1.38 (3H, m, H-3'$_{ax}$, H-5'$_{ax}$ and H-4'), 1.63 (2H, m, H-2'$_{eq}$ and H-6'$_{eq}$), 1.72 (2H, quin, *J* 5.7 Hz, H-2), 1.93 (2H, m, H-2'$_{ax}$ and H-6'$_{ax}$), 2.79 (1H, br. s., -OH), 3.10 (1H, tt, *J* 10.7 and 4.2 Hz, H-1'), 3.57 (2H, t, *J* 5.7 Hz, H-3), 3.67 (2H, t, *J* 5.7 Hz, H-1);

δ_C (50MHz): 21.8 (4'-Me), 31.9 (C-2), 32.1 (C-3' and C-5'), 32.2 (C-4'), 33.2 (C-2' and C-6'), 61.9 (C-1), 67.1 (C-3), 78.5 (C-1');

m/z 172 (M^+, 2%), 115 (100%), 113 (38%), 97 (37%), 59 (47%) and 57 (67%);

Found: M^+, 172.1442. $C_{10}H_{20}O_2$ requires *M*, 172.1463.

6.3.4. Reduction of 8-methyl-1,4-dioxaspiro[4.5]decane **9**



10 **11** **12**

To a solution of 8-methyl-1,4-dioxaspiro[4.5]decane **9** (0.1563g, 1.00mmol) in CH_2Cl_2 at -78°C were added TMSOTf (0.39ml, 2eq) and $BH_3{\cdot}SMe_2$ (2.0ml of 1M solution in CH_2Cl_2, 2eq). After 2hrs at -78°C the reaction was quenched with a saturated solution of $NaHCO_3$ and after standard workup the crude products were purified by column chromatography to afford 1-(*trans*-4'-methyl-cyclohexyl-1-oxy)-2-(*cis*-4'-methyl-cyclohexyl-1-oxy)ethane **12**, 1,2-bis(*cis*-4'-methyl-cyclohexyl-1-oxy)ethane **12** and 1,2-bis(*trans*-4'-methyl-cyclohexyl-1-oxy)ethane **12** (90.9mg, 71%) as a mixture of

1,2-bis(*trans*-4'-methyl-cyclohexyl-1-oxy)ethane **12**:

(Found: C, 75.0; H, 11.5. $C_{16}H_{30}O_2$ requires C, 75.6; H, 11.8%)

$\nu_{max.}$ ($CHCl_3$) 2995, 2930, 2865, 1455, 1370, 1350, 1205, 1095, 730 and 665cm^{-1};

δ_H (200MHz) 0.87 (6H, d, *J* 6.4 Hz, 4'-Me), 0.94-2.01 (16H, m, cyclohexyl-H), 3.20 (2H, tt, *J* 4.2 and 10.7 Hz, H-1'), 3.59 (4H, s, H-1 and H-2);

δ_C (50MHz) 22.8 (4'-Me), 32.8 (C-4'), 33.0, 34.2 (C-2', C-5' and C-6'), 68.3 (C-1 and C-2), 79.4 (C-1');

2-(*cis*-4'-methyl-cyclohexyl-1-oxy)ethan-1-ol **11**:

$\nu_{max.}$ ($CHCl_3$) 3445, 2995, 2930, 2860, 1450, 1350, 1110, 1100, 1050, 890 and 725cm^{-1}

δ_H (200MHz) 0.88 (3H, t, *J* 5.9 Hz, 4'-Me), 1.20-1.90 (10H, m, cyclohexyl-H and -OH), 3.52 (3H, m, H-2 and H-1'), 3.71 (3H, m, H-1);

δ_C (50MHz) 22.6 (4'-Me), 30.1 (cyclohexyl-CH_2), 32.1 (C-4'), 62.9 (C-1), 69.4 (C-2), 75.2 (C-1');

m/z 158 (M^+, 2%), 101 (36%), 97 (65%), 96 (25%), 81 (11%), 57 (65%), 55 (100%) and 45 (40%);

Found: M^+, 158.1300. $C_9H_{18}O_2$ requires *M*, 158.1307.

2-(*trans*-4'-methyl-cyclohexyl-1-oxy)ethan-1-ol **10**:

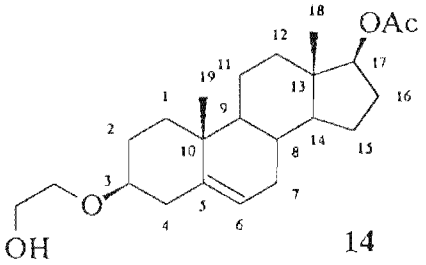
$\nu_{max.}$ ($CHCl_3$) 3580, 2925, 2860, 1455, 1350, 1215, 1205, 1110, 1050, 890 and 725cm^{-1};

δ_H (200MHz) 0.85 (3H, t, *J* 6.4 Hz, 4'-Me), 0.88-2.06 (9H, m, cyclohexyl-H), 2.24 (1H, br., exch., -OH), 3.19 (1H, tt, *J* 4.2 and 10.8 Hz, H-1'), 3.54 (2H, m, H-2), 3.68 (2H, m, H-1);

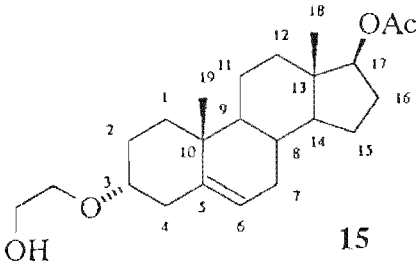
δ_C (50MHz) 22.7 (4'-Me), 32.8 (C-4'), 33.0 and 34.0 (cyclohexyl-CH_2), 62.8 (C-1), 69.7 (C-2), 79.4 (C-1');

Found: M^+, 158.1336. $C_9H_{18}O_2$ requires *M*, 158.1307.

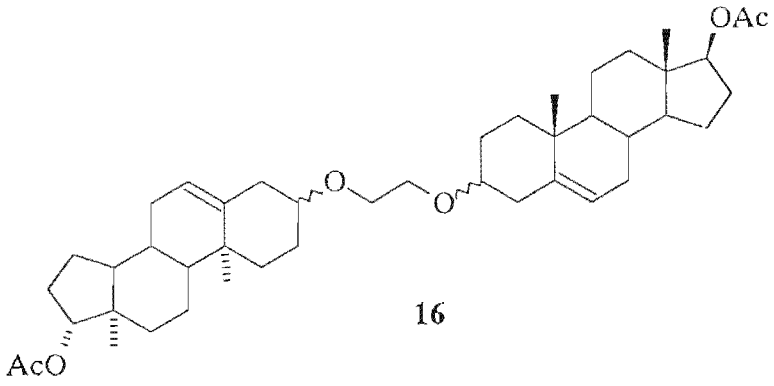
6.3.5. Reduction of 3,3(ethylenedioxy)-androst-5-en-17ß-yl acetate



14



15



16

To a solution of (3,3(ethylenedioxy)-androst-5-en-17ß-yl acetate) **13** (0.3666g, 0.98mmol) in CH_2Cl_2 at -78°C under nitrogen were added TMSOTf (0.20ml, 1.1mmol) and $BH_3 \cdot SMe_2$ (0.11ml of 10M, 1.1mmol). The reaction was monitored by t.l.c., before it was quenched at -60°C with a saturated $NaHCO_3$ solution in water. The crude products were obtained by the standard workup procedure ($NaHCO_3$/ethyl acetate) and the products separated by column chromatography to afford **16** 63.0mg (16.2%): mp. 142-147°C, R_f= 0.85 (pet ether:ethyl acetate 1:1)

$\nu_{max.}$ ($CHCl_3$): 2935, 2855, 1720, 1370, 1255, 1205, 1030, 780 and 730cm^{-1};

δ_H (200MHz) 0.72 (s, Me), 0.76 (s, Me), 0.87 (s, Me). 0.96 (s, Me), 1.00-2.40 (steroid backbone), 1.99 (s, -OAc), 2.00 (s, -OAc), 3.15 (2H, m, H-3 and H-3'), 3.57 (4H, s, H of ethylene bridge), 4.56 (2H, m, H-17 and H-17'), 5.30 (2H, d of d, H-6 and H-6')

m/z 690 (M^+, 1%), 346 (28%), 316 (81%), 277 (100%), 256 (83%), 99 (95%0, 43 (80%);

Found: M^+, 690.4862, $C_{44}H_{66}O_6$ requires *M*, 690.4849.

3α(2'-hydroxyethoxy)-androst-5(6)-en-17ß-yl acetate **15**: 3.2mg (0.9%): R_f= 0.36 (pet ether:ethyl acetate 1:1)

δ_H (200MHz): 0.74 (3H, s, Me), 0.91 (3H, s, Me), 1.00-2.32 (19H, m, steroid backbone), 2.00 (3H, s, -OAc), 3.45 (2H, tt, *J* 1.4 Hz, *J* 4.7 Hz, H-3_{eq}), 3.50-3.73 (5H, m, ethylene H and O-H), 4.55 (1H, m, H-17), 5.31 (1H, m, H-6).

3ß(2'-hydroxyethoxy)-androst-5(6)-en-17ß-yl **14**: 304.7mg (82.7%): R_f= 0.30 (pet ether:ethyl acetate 1:1) $[\alpha]_D$= -55.3° (c=0.988)

(Found: C, 73.1; H,9.65. $C_{23}H_{36}O_4$ requires C, 73.4; H, 9.64%)

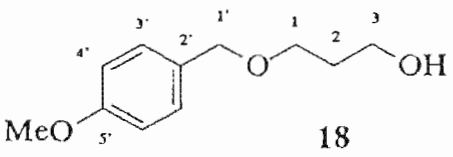
$\nu_{max.}$ ($CHCl_3$) 3585, 2940, 1725, 1665, 1625, 1465, 1375, 1255, 1210, 1110, 1045 and 1035 cm^{-1};

δ_H (200MHz) 0.68 (3H, s, Me), 0.89 (3H, s, Me), 0.78-2.32 (19H, m, steroid backbone), 1.91 (3H, s, -OAc), 2.68 (1H, br. s., -OH), 3.08 (1H, tt, *J* 11.1 and *J* 4.1 Hz, H-3_{ax}), 3.45 (2H, m, H-1'), 3.58 (2H, m, H-2'), 4.47 (1H, dd, *J* 9.0 and 7.6 Hz, H-17), 5.22 (1H, m, H6);

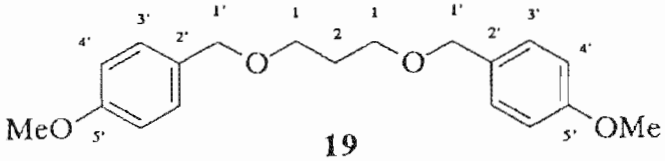
δ_C (50MHz) 11.6, 19.1, 20.3, 20.8, 23.3, 27.2, 28.1, 31.2, 31.4, 36.5, 36.6, 36.9, 38.8, 42.1, 49.9, 50.8, 61.7, 68.9, 79.0, 82.5, 121.0, 140.5, 170.9;

m/z 315 (M^+-62, 22%) and 314 (100%).

6.3.6. Reduction of 2-*p*-Methoxyphenyl-1,3-dioxane **17**



18



19

To a solution of 2-*p*-methoxyphenyl-1,3-dioxane **17** (0.3784g, 1.95mmol) in CH_2Cl_2 cooled to -78°C were added TMSOTf (0.41ml, 1.1eq) and $BH_3 \cdot SMe_2$ (2.15ml, 1.1eq). After 10 min the reaction was quenched with a saturated solution of $NaHCO_3$ in water, worked up standard procedure ($NaHCO_3/CH_2Cl_2$) and the products separated by column chromatography to yield 1,3-di-*p*-methoxybenzyloxypropane **19** (0.1085g, 35.2%) and 1-*p*-methoxybenzyloxy-3-propanol **18** (0.1254g, 32.8%)

1,3-di-*p*-methoxybenzyloxypropane **19**:

$\nu_{max.}$ ($CHCl_3$) 3010, 2950, 2935, 2910, 2860, 2835, 1610, 1585, 1510, 1460, 1360, 1300, 1245, 1170, 1085, 1035, 845, 820 and 730 cm^{-1};

δ_H (200MHz) 1.84 (2H, quin, *J* 6.3 Hz, H-2), 3.49 (4H, t, *J* 6.3 Hz, H-1 and H-3), 3.73 (6H, s, -OMe), 4.36 (4H, s, H-1'), 6.81 (4H, d, *J* 8.6 Hz, H-3'), 7.18 (4H, d, *J* 8.5 Hz, H-4');

δ_C (50MHz) 30.2 (C-2), 55.2 (O-Me), 67.1 (C-1 and C-3), 72.6 (C-1'), 113.7 and 129.1 (C-3' and C-4'), 130.6 (C-2'), 159.0 (C-5');

m/z 316 (M^+, 5%), 196 (18%), 195 (100%), 137 (70%) and 121 (90%).

1-*p*-methoxybenzyloxy-3-propanol **18**:

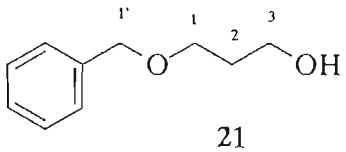
$\nu_{max.}$ ($CHCl_3$ 3485, 3000, 2935, 2865, 2835, 1610, 1510, 1460, 1360, 1300, 1245, 1170, 1070, 1035, 845, 820, 765 and 745cm^{-1}

δ_H (200MHz) 1.82 (2H, quin, *J* 5.8 Hz, H-2), 3.60 (2H, t, *J* 5.9 Hz, H-1), 3.70 (2H, t, *J* 5.8 Hz, H-3), 3.78 (3H, s, -OMe), 4.43 (2H, s, H-1') 6.86 (2H, d, *J* 8.8 Hz, H-3'), 7.24 (2H, d, *J* .8. Hz, H-4');

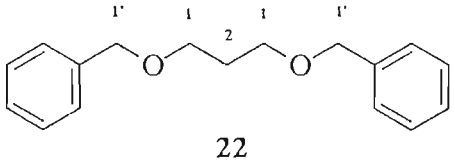
δ_C (50MHz) 32.1 (C-2), 55.2 (-OMe), 61.5 (C-3), 68.8 (C-1), 72.8 (C-1'), 113.8 and 129.1 (Ph-C), 130.1 (C-2'), 159.1 (C-5');

m/z 197 (2%), 196 (M^+, 19%), 137 (75%) and 121 (100%)

6.3.7. Reduction of 2-Phenyl-1,3-dioxane **20**



21



22

To a solution of 2-phenyl-1,3-dioxane **20** (0.32447g, 2.0mmol) in CH_2Cl_2 at -78°C were added TMSOTf (0.42ml, 1.1eq) and $BH_3 \cdot SMe_2$ (2.20ml, 1.1eq). After 10 min the reaction was quenched with 4ml of a saturated solution of $NaHCO_3$ in water and the mixture allowed to warm to room temperature. The crude reaction mixture was obtained by the standard workup procedure ($NaHCO_3/CH_2Cl_2$) and purified by column chromatography to afford 1,3 dibenzyloxypropane **22** (63.9mg, 25.2%) and 1-benzyloxy-3-propanol **21** (244.2mg, 74.3%)

1,3 dibenzyloxypropane **22**:

$\nu_{max.}$ ($CHCl_3$) 3065, 3025, 3000, 2950, 2925, 2860, 1600, 1490, 1450, 1360, 1265, 1205, 1090, 905, 725 and 695, cm^{-1};

δ_H (200MHz) 1.96 (2H, quin, *J* 6.3 Hz, H-2), 3.62 (4H, t, *J* 6.3 Hz, H-1 and H-3), 4.53 (4H, s, H-1'), 7.35 (10H, m, Ph-H);

δ_C (50MHz): 30.3 (C-2), 67.3 (C-1), 73.0 (C-1'), 127.4, 127.58 and 138.47 (Ph-C);

m/z 165 (M^+-91, 70%), 107 (72%) and 91(100%).

1-benzyloxy-3-propanol **21**:

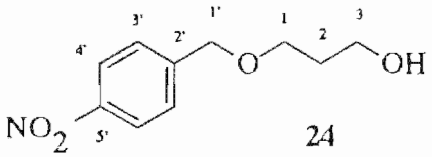
$\nu_{max.}$ ($CHCl_3$) 3485, 3065, 3000, 2945, 2865, 1600, 1490, 1450, 1365, 1235, 1070, 741 and 695 cm^{-1};

δ_H (200 MHz) 1.83 (2H, quin, *J* 6.0Hz, H-2), 2.97 (1H, br. s, O-H), 3.61 (2H, t, *J* 6.0 Hz, H-1), 3.71 (2H, t, *J* 6.0 Hz, H-3), 4.49 (2H, s, H-1'), 7.32 (5H, m, Ph-H);

δ_C (50 MHz): 32.1 (C-2), 60.8 (C-3), 68.5 (C-1), 73.0 (C-1'), 127.4, 128.15 and 137.90 (Ph-C);

m/z 166 (M^+, 8%), 167 (M^++1, 12%), 107 (78%) and 91 (100%).

6.3.8. Reduction of 2-*p*-Nitrophenyl-1,3-dioxane **23**



24

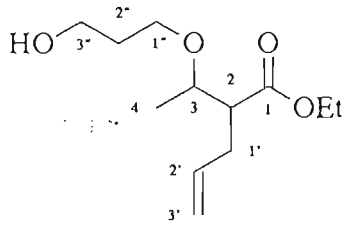
To a stirred solution of 2-*p*-nitrophenyl-1,3-dioxane **23** (0.2038g, 0.98 mmol) in CH_2Cl_2 at -78°C was added TMSOTf (0.21 ml, 1.1 eq.) and $BH_3{\cdot}SMe_2$ (1.08 ml of 1M solution in CH_2Cl_2). T.l.c. monitoring of the reaction indicated that reduction proceeded at 0°C and thus was quenched at this temperature with a saturated solution of $NaHCO_3$ in water after 10 min. Standard workup ($NaHCO_3/CH_2Cl_2$) followed by column chromatography (solvent: 1:1 petether:ethyl acetate) of the residue yielded 1-*p*-nitrobenzyloxy-3-propanol **24** (158.4 mg, 77%).

δ_H (200MHz) 1.95 (2H, quin, *J* 6.0 Hz, H-2), 2.61 (1H, br. s., -OH), 3.74 (2H, t, *J* 5.9 Hz, H-3), 4.67 (2H, s, H-1'), 7.54 (2H, d, *J* 8.9 Hz, H-3'), 8.23 (2H, d, *J* 8.9 Hz, H-4');

δ_C (50MHz) 32.9 (C-2), 61.3 (C-3), 69.7 (C-1), 72.4 (C-1'), 124.1 (C-3'), 128.2 (C-4'), 146.5 (C-2'), 147.8 (C-5');

m/z 212 (M^++1, 8%), 211 (M^+, 10%), 152 (100%), 136 (65%), 107 (45%), 106 (30%), 89 (50%) and 78 (60%).

6.3.9. Reduction of Ethyl 2-allyl-3,3-(1',3'-propanedioxy)-butanoate **25**



26

To a stirred solution of ethyl 2-allyl-3,3-(1',3'-propanedioxy)butanoate **25** (239.3mg, 1.01mmol) in THF (5ml) at -78°C were added TMSOTf (0.20ml, 1.1mmol) and after 10 min $BH_3{\cdot}SMe_2$ (0.11ml of 10M, 1.1mmol). The reaction was stirred at -78°C for 1 hour and then left to warm up to -20°C before a basic peroxide mixture (5ml ethanol, H_2O_2 (1.5ml, 1.5mmol), KOH (0.28g, 5mmol)) was added. After 3 hours at RT the crude product was obtained by the standard workup conditions (NH_4Cl/ethyl acetate). The product was purified by column chromatography to furnish a mixture of two diastereomers (approx. 2:1 ratio) **26** (185.2mg, 76.7%).

$\nu_{max.}$ ($CHCl_3$) 3510, 2980, 2940, 2870, 1720, 1640 and 1185cm^{-1};

δ_H (200MHz) 1.03 (3H, d, *J* 6.3 Hz, H-4 minor), 1.04 (3H, d, *J* 6.2 Hz, H-4 major), 1.11 (3H, t, *J* 7.2 Hz, Eth-CH_3 both isomers), 1.62 (2H, m, H-2" both isomers), 2.14

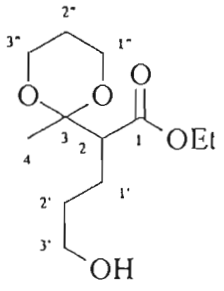
(2H, m, H-1' major), 2.24 (2H, m, H-1' minor), 2.40 (1H, m, H-2 both isomers), 2.67 (1H, br.s., O-H minor), 2.90 (1H, br.s., O-H major), 3.37 (2H, m, H-1" both isomers), 3.54 (3H, m, H-3 and H-3", both isomers), 3.99 (2H, q, *J* 7.2 Hz, Eth-CH_2 minor), 4.00 (2H, q, *J* 7.2 Hz, Eth-CH_2 major), 4.86 (1H, m, *J* 8.5 Hz, H-3'trans both isomers), 4.92 (1H, m, *J* 17.1 Hz, H-3'cis both isomers), 5.60 (1H, m, H-2' both isomers);

δ_C (50MHz): major isomer: 14.0 (Eth-CH_3), 16.6 (C-4), 32.2 (C-2"), 32.4 (C-1'), 51.7 (C-2), 60.1 (Eth-CH_2), 60.6 (C-3"), 67.2 (C-1"), 76.3 (C-3), 116.6 (C-3'), 134.7 (C-2'), 173.7 (ester C=O); minor isomer: 14.0 (Eth-CH_3), 16.8 (C-4), 32.1 (C-2"), 32.5 (C-1'), 50.9 (C-2), 60.1 (Eth-CH_2), 60.7 (C-3"), 67.2 (C-1"), 75.8 (C-3), 116.3 (C-3'), 135.2 (C-2'), 173.2 (ester C=O);

m/z 215 (M^+-15, 0.2%), 189 (2%), 156 (7%), 143 (5%), 128 (25%), 115 (29%), 103 (74%), 87 (18%), 67 (12%) and 59 (100%).

Found: M^+, 230.1487. $C_{12}H_{22}O_4$ requires *M*, 230.1518.

6.3.10. Hydroboration of Ethyl 2-allyl-3,3-(1',3'-propanedioxy)-butanoate **25**



27

To a stirred solution of ethyl 2-allyl-3,3-(1',3'-propanedioxy)butanoate **25** (0.2278g, 1.0mmol) in THF (5ml) at -78°C was added $BH_3{\cdot}SMe_2$ (0.11ml of 10M, 1.1mmol) and the reaction left to warm up to 0°C over 2 hours. After a further hour at 0°C an oxidation mixture (ethanol (5ml), H_2O_2 (5ml, 5mmol) and $NaHCO_3$ (0.14g, 1.7mmol)) was added. This mixture was left stirring for 15 hours and then worked up as usual

($NaHCO_3$/ethyl acetate) to furnish the crude product. Column chromatography gave starting material (13.5mg, 5.9%) and of the hydroborated product **27** (196.5mg, 79.9%) as an oil.

(Found: C, 58.3; H, 8.6. $C_{12}H_{22}O_5$ requires C, 58.5; H, 9.0%)

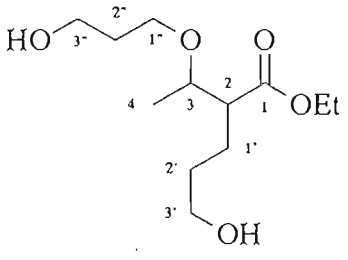
$\nu_{max.}$ ($CHCl_3$) 3616, 3000, 2960, 2875, 1720, 1475, 1445, 1430, 1370, 1245, 1220, 1190, 1145, 1120, 1095 and 1055 cm^{-1};

δ_H (200MHz) 1.16 (3H, t, *J* 7.1 Hz, Eth-CH_3), 1.34 (3H, s, H-4), 1.38-1.70 (6H, m, H-2", H-1', H-2'), 2.38 (1H, br. s., -OH), 3.01 (1H, dd, *J* 3.8 and 10.7 Hz, H-2), 3.51 (2H, t, *J* 6.4 Hz, H-3'), 3.78 (3H, m, H-1" and H-3"), 3.93 (1H, m, H-1" or H-3"), 4.07 (2H, q, *J* 7.1 Hz, Eth-CH_2);

δ_C (50MHz) 14.1 (Eth-CH_3), 18.8 (C-4), 23.6, 24.9, 30.8 (C-1', C-2' and C-2"), 51.1 (C-2), 59.4, 59.5, 60.3, 62.1 (Eth-CH_2, C-3", C-1", C-3'), 99.3 (C-3), 172.8 (C-1);

m/z 245 (M^+-H, 0.5%), 231 (4%), 173 (5%), 127 (6%), 101 (100%) and 73 (10%).

6.3.11. Hydroboration/Reduction of Ethyl 2-allyl-3,3-(1',3'-propanedioxy)butanoate **25**



28

To a stirred solution of ethyl 2-allyl-3,3-(1',3'-propanedioxy)butanoate **25** (0.2302, 1.01mmol)in dry THF at 0°C was added $BH_3{\cdot}SMe_2$ (0.11ml of 10M, 1.1mmol) and the reaction left to stir for 2 hrs at 0°C. The mixture was then cooled to -78°C and TMSOTf (0.20ml, 1.1mmol) added. The reaction was left to warm up slowly to 0°C before adding

the oxidation mixture (0.49g $NaHCO_3$, 1.7ml H_2O_2, 10ml EtOH). After 15 hrs at room temperature the standard workup procedure (NH_4Cl/ethyl acetate) afforded the crude product which was purified by column chromatography to yield a diol **28** (89.9mg, 36%) as a ~3:2 mixture of diastereomers.

$\nu_{max.}$ ($CHCl_3$) 3530, 2935, 2870, 1730, 1445, 1375, 1180, 1070, 900 and 740cm^{-1};

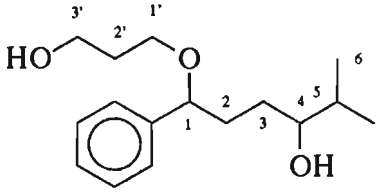
δ_H (200MHz) 1.13 (3H, d, *J* 6.2 Hz, H-4), 1.23 (3H, t, *J* 7.1 Hz, Eth-CH_3), 1.41-1.83 (5H, m, H-2, H-1' and H-2'), 2.46 (3H, m, H-2" and O-H), 3.33-3.77 (8H, m, H-1", H-3", H-3, H-3' and O-H), 4.12 (2H, q, *J* 7.0 Hz, Eth-CH_2 of major), 4.12 (2H, q, *J* 7.1 Hz, Eth-CH_2 of minor);

δ_C (50MHz) 14.4 (Eth-CH_3), 17.0 (C-4, major), 17.3 (C-4, minor), 24.4 and 30.5 (C-1' and C-2', major), 24.9 and 30.6 (C-1' and C-2', minor), 32.3 (C-2"), 51.3 (C-2, minor), 51.9 (C-2 major), 60.6, 61.3, 62.2 (major) and 62.3 (minor) (Eth-CH_2, C-3' and C-3"), 67.7 (C-1", minor), 67.7 (C-1", major), 76.6 (C-3, minor), 77.1 (C-3, major), 174.1 (C-1, minor), 174.8 (C-1, major);

m/z 248 (M^+, 1%), 145 (M^+-105, 30%), 103 (75%), 59 (100%).

Found: M^+, 248.1660. $C_{12}H_{24}O_5$ requires *M*, 248.1624.

6.3.12. Hydroboration/Reduction of 2-Phenyl-2-(4-methyl-pent-3-enyl)-1,3-dioxane **29**



30

To a stirred solution of 2-phenyl-2-(4-methyl-pent-3-enyl)-1,3-dioxane **29** (0.2409g, 0.98mmol) in THF (5ml) at 0°C under nitrogen was added $BH_3{\cdot}SMe_2$ (0.11ml of 10M, 1.1mmol). After 1.5hrs the reaction flask was cooled to -78°C, TMSOTf (0.20ml, 1.1mmol) added and the reaction left to warm up to -65° over 1.5hrs. The reaction was quenched by adding an oxidation mixture (EtOH (25ml), H_2O_2 (0.38ml, 3.8mmol), and solid $NaHCO_3$ (1.0g, excess)). After 15hrs the crude product was obtained by the standard workup procedure and was purified by column chromatography to give (3-hydroxy-propan-1-yl)-1-(1-phenyl-5methyl-hexan-4-ol) ether **30** (0.2605g, 72%) as a 1:1 mixture of diastereomers. R_f= 0.32 (petether:ethyl acetate 1:3)

$\nu_{max.}$ ($CHCl_3$) 3435, 3085, 3065, 3000, 2960, 2870, 1725, 1605, 1490, 1465, 1450, 1370, 1245, 1090. 1065. 910, 750. 730, 700 and 660cm^{-1};

δ_H (200MHz) 0.83 (3H, d, *J* 6.7 Hz, H-6 or 5-Me), 0.84 (3H, d, *J* 6.9 Hz, H-6 or 5-Me), 1.20-1.98 (7H, m, H-5, H-2, H-3, H-2'), 2.05 (2H, br. s., -OH), 3.30 (1H, m, H-4), 3.42 (2H, m, H-1'), 3.68 (2H, m, H-3'), 4.20 (1H, m, H-1), 7.24 (5H, m, Ph-H);

δ_C (50MHz) 17.2 (C-6), 17.3 (C-6), 18.7 (C-2'), 30.2, 30.5, 33.4, 33.5, 34.6, 34.9, (C-5, C-3, C-2), 61.2 (C-3'), 67.3 (C-1'), 76.4 (C-4), 76.5 (C-4), 82.8 (C-1), 82.9 (C-1), 126.4, 127.5, 127.5, 128.4 and 142.3 (Ph-C);

m/z 207 (M^+-59, 11%), 189 (3%), 165 (100%) and 107 (76%).

Found: *M^+-101*, 165.0899. $C_{16}H_{26}O_3$ requires *M-101*, 165.0915

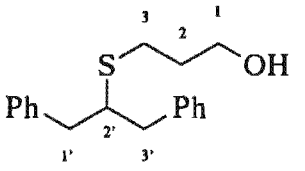
6.3.13. T.l.c. experiments of the reduction of 2,2 dibenzyl-1,3-dioxane **1** with other Lewis Acids

(i) The same procedure was used as in 6.3.1., but with $BF_3{\cdot}OEt_2$ (0.14ml, 1.1mmol) instead of TMSOTf. Aliquots were removed from the reaction flask and quenched in a saturated $NaHCO_3$ solution. EtOAc was added to this and a t.l.c. done of the organic layer. It was found that the reaction did not go to completion until it reached RT.

(ii) The same procedure as above was used, but with $TiCl_4$ (1.10ml of a 1M solution, 1.1mmol) as a Lewis acid. The reaction proceeded at 0°C. The reaction was quenched and the products isolated as in 6.3.1. 3-dibenzylmethoxy-propan-1-ol (70%) was isolated, as well as dibenzylmethanol (13%).

(iii) The same procedure as above was used, but with $SnCl_4$ (1.10ml of a 1M solution, 1.1mmol) as a Lewis acid. The reaction proceeded at 0°C. The reaction was quenched and the products isolated as in 6.3.1. 3-dibenzylmethoxy-propan-1-ol (88%) was isolated.

6.3.14. Reduction of 2,2-Dibenzyl-3-thio-1-oxane **39**



40

To a stirred solution of 2,2-dibenzyl-3-thio-1-oxane **39** (0.1371g, 0.48mmol) in CH_2Cl_2 (10ml) at -78°C under nitrogen were added TMSOTf (0.20ml, 0.95mmol) and $BH_3{\cdot}SMe_2$ (0.97ml of 1M in CH_2Cl_2, 0.97mmol). The reaction was left to stir at -78° for 4.5 hrs. before being worked up ($NaHCO_3$, CH_2Cl_2). The crude product (0.1376g) was purified by column chromatography (pet ether:ethyl acetate 4:1) to afford 3-

dibenzylmethylthio-propan-1-ol **40** (98.9mg, 71.6%) and starting material (34.6mg, 25.2%).

3-dibenzylmethylthio-propan-1-ol **40**

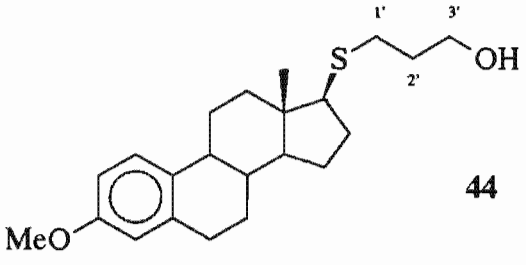
$\nu_{max.}$ ($CHCl_3$) 3620, 3450, 3000, 2935, 1600, 1495, 1450, 1440, 1235, 1205, 1030, 1005, 760, 730, 700cm^{-1};

δ_H (200MHz) 1.46 (1H, br. s., exch., -OH), 1.64 (2H, quin, *J* 6.5 Hz, H-1), 2.40 (2H, t, *J* 7.0 Hz, H-3), 2.95 (5H, m, H-1' and H-2'), 3.54 (2H, t, *J* 6.0 Hz, H-1), 7.25 (10H, m, Ph-H);

δ_C (50MHz) 28.1 (C-2), 31.9 (C-3), 41.9 (C-1'), 49.4 (C-2'), 61.6 (C-1), 126.3, 128.2, 129.2, 139.4 (Ph-C);

m/z (3%), 286 (M^+, 16%), 195 (64%), 151 (26%), 137 (43%), 135 (26%), 121 (48%), 105 (82%) and 91 (100%).

6.3.15. Reduction of (3-Methoxyestra-1,3,5(10)-triene)-17-spiro-2'(3-thio-1-oxane) **42** and **43**



44

To a stirred solution of (3-methoxyestra-1,3,5(10)-triene)-17-spiro-2'(3-thio-1-oxane) **42** (87.7mg, 0.24mmol) in CH_2Cl_2 at -78°C were added TMSOTf (0.089ml, 0.48mmol) and $BH_3{\cdot}SMe_2$ (0.48ml of 1M in CH_2Cl_2, 0.48mmol). After 3 hrs at -78°C the reaction

was quenched with water (5ml) and warmed up to room temperature. After the standard workup (Na_2CO_3, CH_2Cl_2) the crude product was isolated and purified by column chromatography (pet ether:ethyl acetate, 4:1) to afford 3-methoxyestra-1,3,5(10)-triene 17ß-sulfanyl-3'-hydroxypropyl ether **44** (85.1mg, 97%) as an oil.

$\nu_{max.}$ ($CHCl_3$) 3410, 2995, 2935, 2870, 1605, 1570, 1495, 1465, 1255, 1235, 1035, 900 and 740cm^{-1};

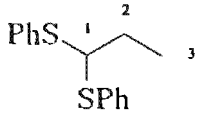
δ_H (200MHz) 0.77 (3H, s, H-18), 1.21-2.38 (17H, m), 2.66 (1H, t, *J* 9.3 Hz, H-16), 2.68 (2H, t, *J* 7.0 Hz, H-1'), 2.83 (1H, m, H-17), 3.76 (2H, t, *J* 6.0 Hz, H-3'), 3.77 (3H, s, 3-0Me), 6.63 (1H, d, *J* 2.7 Hz, H-4), 6.70 (1H, dd, *J* 2.9 and 8.5 Hz, H-2), 7.20 (1H, dm *J* 8.3 Hz, H-1);

δ_C (50MHz) 13.4 (C-18), 24.3 (C-15), 26.5 (C-11), 27.7 (C-7), 29.3 (C-6), 29.9 (C-2'), 31.1 (C-12), 32.6 (C-16), 37.7 (C-1'), 39.3 (C-8), 43.9 (C-9), 44.5 (C-13), 53.7 and 56.6 (C-14 and C-17), 55.2 (3-OMe), 62.0 (C-3'), 111.34 (C-2), 113.7 (C-4), 126.2 (C-1), 132.4 (C-10), 137.7 (C-5), 157.2 (C-3);

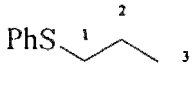
m/z 360 (M^+, 80%), 301 (32%), 227 (67%), 137 (87%), 121 (100%), 57 (43%).

Found: M^+, 360.2151. $C_{22}H_{32}O_2S$ requires *M*, 360.2123.

6.3.16. Reduction of 1,1-Diphenylthiopropane **45**



45



46

To a solution of 1,1-diphenylthiopropane **45** (0.2355g, 0.91mmol) in dry CH_2Cl_2 (5ml) at -78°C were added TMSOTf (0.19ml, 0.99mmol) and $BH_3{\cdot}SMe_2$ (0.99ml of 1M in CH_2Cl_2, 0.99mmol). The progress of the reaction was followed by t.l.c. revealing that some reaction did occur at -78°C, but that full consumption of the starting material did not occur even at room temperature. The reaction was therefore quenched with a saturated $NaHCO_3$ solution (80ml) and the products extracted with CH_2Cl_2 (3x80ml), according to the standard workup. The crude oil was purified by column chromatography to yield 1-phenylthiopropane **46** (0.0572g, 37%) and 1,1-diphenylthiopropane **45** (0.0985g, 42%).

1-phenylthiopropane **46**:

$\nu_{max.}$ ($CHCl_3$) 3075, 2965, 2930, 2870, 1585, 1480, 1435, 1375, 1290, 1235, 1090, 1025, 760, 735 and 690cm^{-1};

δ_H (200MHz) 1.02 (3H, t, *J* 7.3 Hz, H-3), 1.67 (2H, sestet, *J* 7.3 Hz, H-2), 2.89 (2H, t, *J* 7.3 Hz, H-1), 7.10-7.37 (5H, m, Ph-H);

δ_C (50MHz): 13.5 (C-3), 22.6 (C-2), 35.7 (C-1), 125.6, 128.7, 128.9 and 136.9 (Ph-C);

m/z 218 (42%, PhSSPh), 152 (68%, M^+), 123 (46%), 110 (100%), 109 (42%), 65 (20%) and 43 (30%).

1,1-diphenylthiopropane **45**:

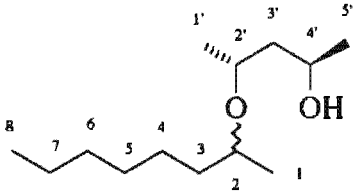
$\nu_{max.}$ ($CHCl_3$) 3060, 2965, 2930, 2870, 1580, 1475, 1435, 1375, 1165, 1085, 1025, 795, 765, 745 and 690cm^{-1}

δ_H (200MHz): 1.15 (3H, t, *J* 7.6 Hz, H-3), 1.90 (2H, quin, *J* 7.1, H-2), 4.37 (1H, t, *J* 6.5 Hz, H-1), 7.24-7.36 (6H, m, Ph-H), 7.44-7.51 (4H, m, Ph-H);

δ_C (50MHz): 11.8 (C-3), 29.0 (C-2), 60.0 (C-1), 127.5, 128.7, 132.5 and 134.3 (Ph-C);

m/z 260 (M^+, 10%), 152 (35%), 151 (100%), 123 (30%), 110 (32%), 109 (32%), 77 (8%) and 73 (12%);

6.3.17.a. Reduction of 2,4R,6R-trimethyl-2-hexyl-1,3-dioxane in CH_2Cl_2



To a solution of 2,4R,6R-trimethyl-2-hexyl-1,3-dioxane (0.1093g, 0.51mmol) in CH_2Cl_2 (5ml) at -78°C under nitrogen were added $BH_3{\cdot}SMe_2$ (1.02ml of 1M solution in CH_2Cl_2, 2.0eq) and TMSOTf (0.20ml, 2.0eq). After 1hr at -78°C the reaction was quenched with a saturated solution of $NaHCO_3$. The mixture was allowed to warm up to room temperature and standard workup procedure ($NaHCO_3/CH_2Cl_2$) resulted in the crude product which was purified by column chromatography to yield 2R-(2-octyloxy)-4R-pentanol (74.6mg, 67.6%) as a 64:36 mixture of diastereomers.

both diastereomers: $\nu_{max.}$ ($CHCl_3$) 3445, 2970. 2930, 2855, 1450, 1375, 1330, 1110, 1070, 1010 and 750cm^{-1};

both diastereomers: δ_H (200MHz): 0.83 (3H, t, *J* 6.5 Hz, H-8), 1.08 (3H, d, *J* 6.1 Hz, H-1), 1.12 (3H, d, *J* 6.2 Hz, H-1' or H-5'), 1.14 (3H, d, *J* 6.3 Hz, H-1' or H-5'), 1.23 (10H, m, H-3, H-4, H-5, H-6, and H-7), 1.53 (2H, m, H-3'), 3.15 (1H, br., exch., O-H), 3.44 (1H, sestet, *J* 6.2 Hz, H-2), 3.80 (1H, m, H-2'), 4.05 (1H, m, H-4');

major diastereomer: δ_C (50MHz) 14.0 (C-8), 19.4, 19.8 and 23.4 (C-1', C-5' and C-1), 22.5 (C-7), 25.5 (C-6), 29.3 (C), 31.7 (C-4), 37.4 (C-3), 44.4 (C-3'), 64.5 (C-4'), 70.2 and 72.7 (C-2 and C-2');

minor diastereomer: δ_C (50MHz) 14.0 (C-8), 20.2, 20.9 and 23.6 (C-1', C-5' and C-1), 22.5 (C-7), 25.3 (C-6), 29.4 (C-5), 31.7 (C-4), 36.6 (C-3), 44.4 (C-3'), 64.4 (C-4'), 71.4 and 73.8 (C-2 and C-2');

major diastereomer: *m/z* 217 (M^++1, 0.1%), 201 (M^+-15, 1.3%), 157 (4.3%), 131 (70%), 113 (19%), 89 (35%), 87 (30%), 73 (14%), 71 (34%), 69 (58%), 57 (30%), 55 (17%), 45 (100%).

minor diastereomer: *m/z* 201 (M^+, 0.8%), 157 (4.3%), 131 (51%), 113 (18%), 103 (8%), 89 (32%), 87 (29%), 73 (11%), 71 (31%), 69 (57%), 57 (30%), 55 (15%), 45 (100%).

Found: M^+-*15,* 201.1868. $C_{12}H_{25}O_2$ requires *M-15,* 201.1854.

6.3.17.b. Reduction of 2,4R,6R-trimethyl-2-hexyl-1,3-dioxane in THF

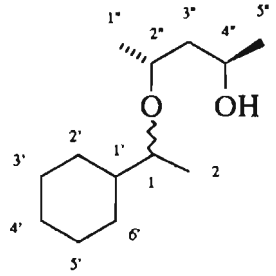
Same procedure as above. The amounts of reagents used were as follows: 2,4R,6R-Trimethyl-2-hexyl-1,3-dioxane (0.1017g, 0.48mmol), THF (5ml), $BH_3 \cdot SMe_2$ (0.48ml of 2M solution in THF, 2.0eq) and TMSOTf (0.18ml, 2.0eq). After purification a 75:25 mixture of diastereomers was isolated (51.5mg, 50.2%). The spectroscopic data was identical with the above products.

6.3.17.c. Reduction of 2,4R,6R-trimethyl-2-hexyl-1,3-dioxane in hexane

Same procedure as above. The amounts of reagents used were as follows:

2,4R,6R-Trimethyl-2-hexyl-1,3-dioxane (0.2152g, 1.01mmol), hexane (5ml), $BH_3{\cdot}SMe_2$ (0.11ml of 10M, 1.1mmol) and TMSOTf (0.21ml, 1.1mmol). After purification a 50:50 mixture of diastereomers was isolated (79.7mg, 36.7%). The spectroscopic data was identical with the above products.

6.3.18.a. Reduction of 2-cyclohexyl-2,4R,6R-trimethyl-1,3-dioxane in CH_2Cl_2



To a solution of 2-cyclohexyl-2,4R,6R-trimethyl-1,3-dioxane (0.1083g, 0.51mmol) in CH_2Cl_2 (5ml) at -78°C under nitrogen was added $BH_3{\cdot}SMe_2$ (1.02ml of 1M solution in CH_2Cl_2, 2.0eq) and TMSOTf (0.20ml, 2.0eq). After 1hr at -78°C the reaction was quenched with a saturated solution of $NaHCO_3$. The mixture was allowed to warm up to RT and the product mixture obtained by the standard workup procedure ($NaHCO_3/CH_2Cl_2$). The crude mixture was purified by column chromatography to yield 2R-cyclohexylmethylmethoxy-4R-pentanol (0.1058g, 97%) as a 79:21 mixture of diastereomers.

both diastereomers: $\nu_{max.}$ ($CHCl_3$) 3500, 2970, 2930, 2850, 1445, 1375, 1260, 1150, 1120, 1065 and 780cm^{-1};

both diastereomers: δ_H (200MHz) 1.11-1.20 (15H, m, H-1", H-5", H-2, H-3', H-4', H-5'), 1.48-1.87 (7H, m, H-3", H-1', H-2', H-6'), 3.22 (1H, m, H-1), 3.30 (1H, br. s., exch., O-H), 3.80 (1H, m, H-2"), 4.06 (1H, m, H-4");

major diastereomer: δ_C (50MHz) 16.6, 19.3 and 23.4 (C-1", C-5", C-2), 26.3, 26.3, 26.6, 28.1 and 28.1 (C-2', C-3', C-4', C-5', C-6'), 43.7 (C-1'), 44.4 (C-3"), 64.5 (C-4"), 70.3 and 76.9 (C-1, C-2");

minor diastereomer: δ_C (50MHz) 17.9, 20.1 and 23.7 (C-1", C-5", C-2), 26.4, 26.4, 26.7, 28.1 and 29.1 (C-2', C-3', C-4', C-5', C-6'), 43.4 (C1'), 44.5 (C-3"), 64.3 (C-4"), 72.5 and 78.3 (C-1, C-2");

major diastereomer: *m/z* 215 (M^+-1, 0.3%). 131 (33%), 111 (21%), 110 (4%), 89 (31%), 87 (32%), 73 (16%), 69 (79%), 55 (25%), 45 (100%);

minor diastereomer: *m/z* 131 (M^+-83, 57%), 111 (17%), 89 (26%), 87 (27%), 73 (11%), 69 (70%), 55 (22%) and 45 (100%);

Found: *M^+-83*, 131.1070. $C_7H_{15}O_2$ requires *M-83*, 131.1072.

6.3.18.b. Reduction of 2-cyclohexyl-2,4R,6R-trimethyl-1,3-dioxane in THF

Same procedure as above. The amounts of reagents used were as follows: 2-cyclohexyl-2,4R,6R-trimethyl-1,3-dioxane (0.1214g, 0.57mmol), THF (5ml), $BH_3{\cdot}SMe_2$ (0.57ml of 2M solution in THF, 2.0eq) and TMSOTf (0.22ml, 2.0eq). After purification a 79:21 mixture of diastereomers was isolated (123.3mg, 99%). The spectroscopic data was identical with the above products.

6.3.18.c. Reduction of 2-cyclohexyl-2,4R,6R-trimethyl-1,3-dioxane in hexane

Same procedure as above. The amounts of reagents used were as follows: 2-cyclohexyl-2,4R,6R-trimethyl-1,3-dioxane (0.0770g, 0.36mmol), hexane (5ml), $BH_3{\cdot}SMe_2$ (0.07ml, 2.0eq) and TMSOTf (0.14ml, 2.0eq). After purification a 60:40

mixture of diastereomers was isolated (74.2mg, 95%). The spectroscopic data was identical with the above products.

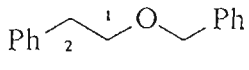
6.3.18.d. Removal of chiral auxiliary

To a solution of oxalyl chloride (0.10ml, 1.20mmol) in dichloromethane (1ml) was added DMSO (0.18ml, 2.60mmol) in dichloromethane (0.2ml) at -78°C. The mixture was stirred for 2 min and the alcohol (from 6.3.18.a.) (95.5mg, 0.45mmol) was added. Stirring was contined for an additional 15 min. Triethylamine (0.38ml, 2.77mmol) was added and the mixture stirred at -78°C for 5 min and at RT for 30 min. Water (10ml) was added and the aqueous layer was extracted with dichloromethane. The dried organic layers were concentrated in vacuo to afford the crude ketone, which was redissolved in methanol (5ml) and treated with K_2CO_3 (1.38g, 10mmol) for 36 hours. The crude product was obtained by standard workup (H_2O, ethyl acetate) and purified by column chromatography (pet ether/ ethyl acetate) to give 1-cyclohexyl ethanol as a colourless oil (35.1mg, 61%) with an identical 60MHz nmr to an authentic sample.

$[\alpha]_D$= -5.1° (c = 0.988)

6.3.19. Protective group studies

6.3.19.1. Reduction of 1-benzyloxy-2-phenyl ethane



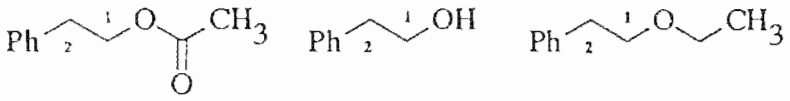
31

To a solution of 1-benzyloxy-2-phenyl ethane **31** (0.2312, 1.1mmol), prepared by benzylation of 2-phenylethanol with benzylbromide in the presence of sodium hydride, in CH_2Cl_2 at-78°C were added TMSOTf (0.25ml, 1.2mmol) and $BH_3{\cdot}SMe_2$ (1.20ml,

1.2mmol).The reaction was left to warm up to +5°C over 2 hrs before being quenched with a saturated solution of $NaHCO_3$. A standard workup resulted in the recovery of the starting material (0.2276, 98%)

δ_H (90MHz) 2.87 (2H, t, *J* 7.2 Hz, H-2), 3.63 (2H, t, *J* 7.2 Hz, H-1), 4.48 (2H, s, benzyl-CH_2), 7.16 (5H, s, Ph-H), 7.22 (5H, s, Ph-H).

6.3.19.2. Reduction of 2-phenylethyl ethanoate **32**



32 **33** **34**

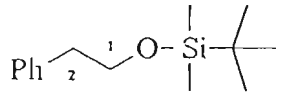
To a solution of 2-phenylethyl ethanoate **32**, prepared by the acetylation of 2-phenylethanol with acetic anhydride in the presence of pyridine and catalytic amount of dimethylaminopyridine (bp 60-63°C, 0.3mmHg), in CH_2Cl_2 at -78°C were added TMSOTf (0.68ml, 3.0eq) and $BH_3 \cdot SMe_2$ (3.20ml of 1M solution in CH_2Cl_2, 3.0eq). The reaction was left to warm up to room temperature and stirred for 70 hrs before a standard workup ($NaHCO_3$, CH_2Cl_2) afforded the crude product. This was purified by column chromatography to yield 2-phenylethyl ethyl ether **34** (65.8mg, 40%) and 2-phenylethanol **33** (73.9mg, 57%)

2-phenylethyl ethyl ether **34**:

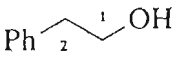
δ_H (90MHz) 1.20 (3H, t, *J* 7.2 Hz, H-2'), 2.88 (2H, t, *J* 7.2 Hz, H-2), 3.55 (4H, m, H-1 and H-1'), 7.22 (5H, m, Ph-H);

2-phenylethanol **33** was compared to an authentic sample and gave the identical nmr spectrum.

6.3.19.3. Reduction of 1-*t*-butyldimethylsilyloxy-2-phenyl ethane **35**



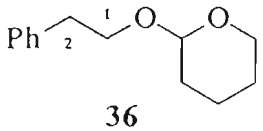
35



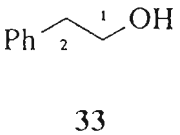
33

To a solution of 1-*t*-butyldimethylsilyloxy-2-phenyl ethane **35** (0.2319g, 0.98mmol), prepared by silylation of 2-phenylethanol with *t*-butyldimethylsilyl chloride in the presence of imidazole, in CH_2Cl_2 at -78°C were added TMSOTf (0.23ml, 1.1mmol) and $BH_3{\cdot}SMe_2$ (1.1ml, 1.1mmol). After 4.5hrs at -78°C the reaction was quenched with a saturated solution of $NaHCO_3$. A standard workup resulted in a crude product which was purified by column chromatography to afford 2-phenylethanol **33** (84.4mg, 70%) which gave an identical nmr spectrum to an authentic sample.

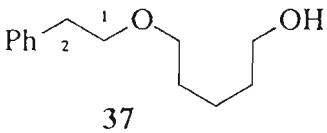
6.3.19.4. Reduction of 2-Phenylethyl 1-tetrahydropyranyl ether **36**



36



33



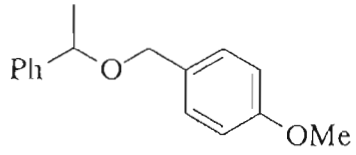
37

To a solution of 2-phenylethyl 1-tetrahydropyranyl ether **36** (0.2045g, 1.0mmol) in CH_2Cl_2 at -78°C were added TMSOTf (0.21ml, 1.0mmol) at $BH_3{\cdot}SMe_2$ (1.0ml, 1.0mmol). After 3hours at -78°C the reaction was quenched with a saturated solution of $NaHCO_3$. A standard workup and column chromatography resulted in 2-phenylethanol **33** (100.0mg, 83%) and impure 1-(2-phenylethoxy)-hexan-6-ol **37** together with traces of starting material (20mg, 10%).

1-(2-phenylethoxy)-hexan-6-ol **37**:

δ_H (200MHz) 0.8-2.0 (8H, m), 2,8-4.2 (7H, m), 7.29 (5H, s, Ph-H).

6.3.19.5. Preparation of 1-*p*-methoxybenzyl 1-phenylethyl ether **38**



38

To a solution of 1-phenylethanol **39** (5.0ml, 42mmol) in glyme (20ml) was added slowly NaH (2.0g, 2eq) followed by *p*-methoxybenzylchloride (6.2ml, 1.1eq) and $Bu_4N^+I^-$ (cat. amount). After 5 hrs at room temperature the product was obtained by standard workup (H_2O, CH_2Cl_2) and purified by distillation in a Kugelrohr apparatus (150°C, 1mmHg) to afford *p*-methoxybenzyl 1-phenylethyl ether **38** (9.14g, 90%)

δ_H (200MHz) 1.44 (3H, d, *J* 6.5 Hz, H-2), 3.76 (3H, s, -OMe), 4.21 (1H, d, *J* 11.4 Hz, H-1'), 4.37 (1H, d, *J* 11.4 Hz, H-1'), 4.46 (1H, q, *J* 6.5 Hz, H-1), 6.85 (2H, d, *J* 8.7 Hz, H-4'), 7.22 (2H, d, *J* 8.7 Hz, H-3'), 7.33 (5H, s, Ph-H);

δ_C (50MHz) 24.9 (C-1), 55.9 (O-Me), 70.6 (C-1'), 77.5 (C-1), 11.4 (C-4'), 126.9 (C-3'), 128.0, 129.0, 129.8 and 144.4 (Ph-C), 131.3 (C-2'), 159.7 (C-5');

m/z: 242 (M^+, 8%), 137 (47%), 121 (100%), 106 (32%), 105 (33%), 91 (19%) and 77 (26%).

6.3.19.6. Reduction of *p*-methoxybenzyl 1-phenylethyl ether **38**

39

To a stirred solution of 1-*p*-methoxybenzyl 1-phenylethyl ether **38** (0.257g, 1.06mmol) at -78°C was added TMSOTf (0.23ml, 1.1eq) and $BH_3 \cdot SMe_2$ (0.11ml of 10M, 1.10mmol). The reaction was left to warm up to -50°C and quenched with a saturated

solution of $NaHCO_3$. After standard workup ($NaHCO_3$, ethyl acetate) the crude product was purified by column chromatography. This resulted in 1-phenylethanol **39** (77.0mg, 60%) and starting material (79.6mg, 31%)

The 60MHz nmr spectrum of 1-phenylethanol was compared to that of an authentic sample.

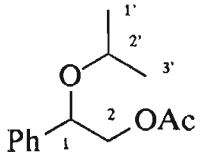
δ_H (60MHz), CCl_4 1.35 (3H, d, *J* 6.0 Hz, H-2), 3.05 (1H, br. s., OH), 4.65 (1H, q, *J* 6.0 Hz, H-1), 7.05 (5H, s, Ph-H);

6.4. Regioselectivity studies

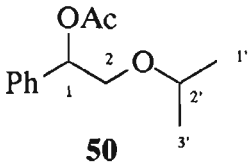
6.4.1. General procedure

To a stirred solution of the substituted dioxolane (1mmol) in a solvent at -78°C were added $BH_3 \cdot SMe_2$ (2eq) followed by TMSOTf (0.40ml, 2eq). The reaction was left to warm up until it had gone to completion (followed by t.l.c.) before it was quenched with a saturated solution of $NaHCO_3$ (5ml). After the standard workup ($NaHCO_3$, CH_2Cl_2) the crude product was dissolved in CH_2Cl_2 and pyridine (1.0ml, 12.4mmol), acetic anhydride (1.0ml, 10.6mmol) and dimethylaminopyridine (20mg) were added. After 15 hrs the acetylated product was isolated by the standard workup ($NaHCO_3$, CH_2Cl_2 followed by 0.1M HCl, CH_2Cl_2) to yield a mixture of regioisomers.

6.4.2. Reduction of 2,2-Dimethyl-4-phenyl-1,3-dioxolane **48**



49



50

The general procedure for regioselective reduction was used.

a) In CH_2Cl_2 the temperature at which the reaction went to completion was -78°C. After chromatography a 63:37 mixture of 2-acetoxy-1-isopropoxy-1-phenylethane : 1-acetoxy-2-isopropoxy-1-phenylethane **49:50** (60%) was isolated.

b) In THF the temperature at which the reaction went to to completion was +10°C. After chromatography a 81:19 mixture of 2-acetoxy-1-isopropoxy-1-phenylethane : 1-acetoxy-2-isopropoxy-1-phenylethane **49:50** (67%) was isolated.

2-acetoxy-1-isopropoxy-1-phenylethane **49:**

δ_H (200MHz) 1.12 (3H, d, *J* 6.3 Hz, H-1' or H-3'), 1.17 (3H, d, *J* 6.0 Hz, H-1' or H-3'), 2.06 (3H, s, Ac-Me), 3.56 (1H, sestet, *J* 6.1 Hz, H-2'), 4.15 (2H, m, H-2), 4.63 (1H, dd, *J* 4.5 and 7.5 Hz, H-1), 7.34 (5H, m, Ph-H);

δ_C (50MHz) 21.0 and 21.3 (C-1' and C-3'), 23.3 (Ac-Me), 68.3 (C-2), 69.9 (C-2'), 77.0 (C-1), 126.8, 127.9, 128.4 and 137.9 (Ph-C), 170.1 (Ac-C=O);

Found: M^+-*73*, 149.0973. $C_{10}H_{13}O$ requires *M-73,* 149.0966.

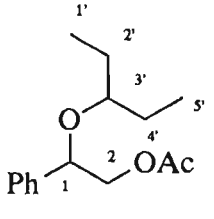
1-acetoxy-2-isopropoxy-1-phenylethane **50**:

δ_H (200MHz) 1.13 (3H, d, *J* 6.1 Hz, H-1' or H-3'), 1.14 (3H, d, *J* 6.1 Hz, H-1' or H-3'), 2.09 (3H, s, Ac-Me), 3.51-3.75 (3H, m, H-2' and H-2), 5.91 (1H, dd, *J* 4.3 and 7.8 Hz, H-1), 7.34 (5H, m, Ph-H);

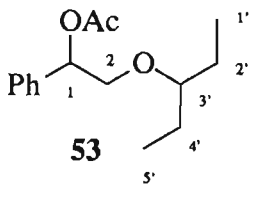
δ_C (50MHz) 21.3 and 22.0 (C-1' and C-3'), 22.1 (Ac-Me), 71.0 (C-2), 72.2 (C-2'), 75.0 (C-1), 126.7, 128.1, 128.4 and 137.9 (Ph-C), 170.1 (Ac-C=O);

Found: M^+-*60*, 162.1025. $C_{11}H_{14}O$ requires *M-60,* 162.1045.

6.4.3. Reduction of 2,2-diethyl-4-phenyl-1,3-dioxolane



52



53

The general procedure for regioselective reduction was used:

a) In CH_2Cl_2 the temperature at which the reaction went to completion was -30°C. After chromatography a 63:37 mixture of 2-acetoxy-1-(3'-pentoxy)-1-phenylethane : 1-acetoxy-2-(3'-pentoxy)-1-phenylethane **52:53** (84%) was isolated.

b) In THF the temperature at which the reaction went to completion was +10°C. After chromatography a 98:2 mixture of 2-acetoxy-1-(3'-pentoxy)-1-phenylethane : 1-acetoxy-2-(3'-pentoxy)-1-phenylethane **52:53** (88%) was isolated.

c) In diethyl ether the temperature at which the reaction went to completion was 0°C. After chromatography a 63:37 mixture of 2-acetoxy-1-(3'-pentoxy)-1-phenylethane : 1-acetoxy-2-(3'-pentoxy)-1-phenylethane **52:53** (76%) was isolated.

d) In diisopropyl ether the temperature at which the reaction went to completion was 0°C. After chromatography a 62:38 mixture of 2-acetoxy-1-(3'-pentoxy)-1-phenylethane : 1-acetoxy-2-(3'-pentoxy)-1-phenylethane **52:53** (84%) was isolated.

2-acetoxy-1-(3'-pentoxy)-1-phenylethane **52**:

δ_H (200MHz) 0.77 (3H, t, *J* 7.5 Hz, H-1' or H-5'), 0.93 (3H, t, *J* 7.4 Hz, H-1' or H-5'), 1.33-1.74 (4H, m, H-2' and H-4'), 2.04 (3H, s, Ac-Me), 3.19 (1H, quin, *J* Hz, H-3'), 4.05-4.20 (2H, m, H-2), 4.61 (1H, dd, *J* 5.5 and 6.8 Hz, H-1), 7.34 (5H, m, Ph-H);

δ_C (50MHz) 8.7 and 10.0 (C-1' and C-5'), 20.9 (Ac-Me). 24.9 and 26.5 (C-2' and C-4'), 68.3 (C-2), 77.4 and 79.8 (C-3' and C-1), 127.1, 128.0, 128.3 and 136.4 (Ph-C), 170.7 (Ac-C=O);

m/z 177 (M^+-73, 29%), 163 (3%), 149 (8%), 107 (15%), 58 (9%), 43 (100%)

Found: M^+-*73*, 177.1261. $C_{12}H_{17}O$ *M-73*, 177.1279.

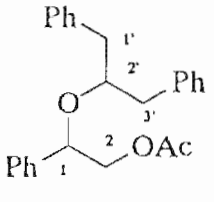
1-acetoxy-2-(3'-pentoxy)-1-phenylethane **53**:

δ_H (200MHz) expand 0.77 (3H, t, *J* 7.5 Hz, H-1' or H-5'), 0.93 (3H, t, *J* 7.4 Hz, H-1' or H-5')1.35-1.72 (4H, m, H-2' and H-4'), 2.08 (3H, s, Ac-Me), 3.17 (1H, quintet, *J* 5.8 Hz, H-3'), 3.64 (1H, dd, *J* 4.4 and 10.8 Hz, H-2), 3.72 (1H, dd, *J* 7.7 and 10.8 Hz, H-2), 5.93 (1H, dd, *J* 4.4 and 7.7 Hz, H-1), 7.34 (5H, m, Ph-H);

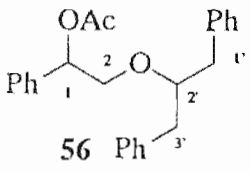
δ_C (50MHz) 9.5 (C-1' and C-5'), 21.1 (Ac-Me), 25.9 and 26.0 (C-2' and C-4'), 71.6)C-2), 75.0 and 82.6 (C-3' and C-1), 126.6, 127.8, 128.0 and 137.9 (Ph-C), 170.1 (Ac-C=O);

m/z 190 (M^+-60, 4%), 163 (3%, 149 (8%0, 107 (15%), 58 (9%), 43 (100%).

6.4.4. Reduction of 2,2-dibenzyl-4-phenyl-1,3-dioxolane **54**



55



56

The general procedure for regioselective reduction was used:

a) In CH_2Cl_2 the temperature at which the reaction went to completion was -20°C. After chromatography a 48:52 mixture of 2-acetoxy-1-dibenzylmethoxy-1-phenylethane : 1-acetoxy-2-dibenzylmethoxy-1-phenylethane **55:56** (69%) was isolated.

(b) In THF the temperature at which the reaction went to completion was RT. The THF polymerised and the products were obtained by column chromatography without acetylation to afford 1-dibenzylmethoxy-1-phenyl-2-ethanol which was characterised by acetylation and identified with the product (**55**) obtained in (a). Only traces of **56** were observed.

2-acetoxy-1-dibenzylmethoxy-1-phenylethane **55:**

δ_H (200MHz) 20.7 (3H, s, Ac-Me), 2.70-2.95 (4H, m, H-1' and H-3'), 3.80 (1H, quin, *J* 5.9 Hz, H-2'), 4.12 (1H, d, *J* 4.9 Hz, H-2), 4.14 (1H, d, *J* 6.9 hz, H-2), 4.60 (1H, dd, *J* 4.9 and 6.7 Hz, H-1)

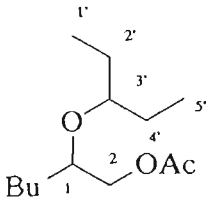
δ_C (50MHz) 21.2 (Ac-Me), 40.0 and 40.7 (C-1' and C-3'), 67.9 (C-2), 74.9 and 82.9 (C-2' and C-1), 126.2, 126.3, 126.8, 128.4, 129.7, 138.9 (Ph-C), 170.1 (Ac-C=O);

1-acetoxy-2-dibenzylmethoxy-1-phenylethane **56:**

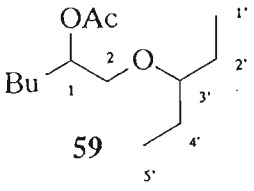
δ_H (200MHz) 2.06 (3H, s, Ac-Me), 2.70-2.95 (4H, m, H-1' and H-3'), 3.55 (1H, dd, *J* 4.2 and 9.4 Hz, H-2), 3.68 (1H, dd, *J* 7.6 and 9.4 hz, H-2), 3.80 (1H, quin, *J* 5.9 hz, H-2'), 5.85 (1H, dd, *J* 4.1 and 7.4 Hz, H-1), 7.00-7.33 (15H, m, Ph-H);

δ_C (50MHz) 21.0 (Ac-Me), 40.6 and 41.4 (C-1' and C-3'), 72.6 (C-2), 78.0 and 79.7 (C-2' and C-1), 126.2, 126.3 126.8, 128.4, 129.7, 138.9 (Ph-H), 170.8 (Ac-C=O).

6.4.5. Reduction of 2,2-diethyl-4-butyl-1,3-dioxolane



58



59

The general procedure for regioselective reduction was used:

a) In CH_2Cl_2 the temperature at which the reaction had gone to completion was -20°C. After chromatography a 73:27 mixture of 2-acetoxy-1-(3'-pentoxy)hexane : 1-acetoxy-2-(3'-pentoxy)hexane **59:58** (73%) was isolated.

b) In THF the temperature at which the reaction had gone to completion was +4°C. After chromatography a 17:83 mixture of 2-acetoxy-1-(3'-pentoxy)hexane : 1-acetoxy-2-(3'-pentoxy)hexane **59:58** (72%) was isolated.

Both regioisomers:

$\nu_{max.}$ ($CHCl_3$) 2960, 2935, 2875, 1740, 1455, 1375, 1365, 1240, 1095, 1040, 795 and 745cm^{-1};

m/z 201 (M^+-29, 1%), 157 (26%), 143 (37%), 87 (70%), 83 (35%), 69 (29%), 55 (29%) and 43 (100%).

Found: *M*$^+$*-29*, 201.1515. $C_{11}H_{21}O_3$ requires *M-29*, 201.1490.

2-acetoxy-1-(3'-pentoxy)hexane **59**:

δ_H (200MHz) 0.82 (9H, t, *J* 7.3 Hz, H-1', H-5' and H-6), 1.15-1.60 (10H, m, H-2', H-3, H-4, H-4' and H-5), 1.98 (3H, s, Ac-Me) 3.05 (1H, quin, *J* 5.9 Hz, H-3'), 3.44 (2H, m, H-1), 4.90 (1H, m, H-2);

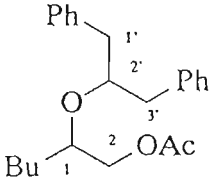
δ_C (50MHz) 9.5 and 9.6 (C-1' and C-5'), 13.9 (C-6), 21.1 (Ac-Me), 22.5, 25.9, 27.4, 30.5 and 30.6 (C-3, C-4, C-5, C-2' and C-4'), 69.7 (C-2), 73.3 (C-1), 82.3 (C-3'), 170.5 (Ac-C=O);

1-acetoxy-2-(3'-pentoxy)hexane **59**:

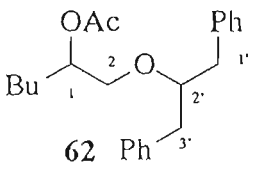
δ_H (200MHz) 0.84 (9H, t, *J* 7.4 Hz, H-1', H-5' and H-6), 1.18-1.53 (10H, m, H-2', H-3, H-4, H-4' and H-5), 2.00 (3H, s, Ac-Me), 3.18 (1H, quin, *J* 5.7 Hz, H-3'), 3.45 (1H, quin, *J* 5.5 Hz, H-2), 3.98 (1H, d, *J* 2.1 Hz, H-1) 4.00 (1H, d, *J* 1.4 Hz, H-1);

δ_C (50MHz) 9.4 and 9.5 (C-1' and C-5'), 13.8 (C-6), 20.7 (Ac-Me), 22.7, 27.4, 32.0 (C-3, C-4 and C-5), 26.1 and 26.2 (C-2' and C-4'), 66.4 (C-2), 74.9 (C-1), 80.6 (C-3'), 170.8 (Ac-C=O);

6.4.6. Reduction of 2,2-dibenzyl-4-butyl-1,3-dioxolane **60**



61



62

The general procedure for the regioselective reduction was used:

a) In CH_2Cl_2 the reaction had gone to completion at -20°C. After column chromatography a 31:69 mixture of 2-acetoxy-1-(dibenzylmethoxy)hexane : 1-acetoxy-2-(dibenzylmethoxy)hexane **62:61** (91%) was isolated.

b) In THF the reaction had gone to completion at room temperature. After column chromatography a 90:10 mixture of 2-acetoxy-1-(dibenzylmethoxy)hexane : 1-acetoxy-2-(dibenzylmethoxy)hexane **62:61** (87%) was isolated.

c) In diethyl ether the reaction had gone to completion at room temperature. After column chromatography a 38:62 mixture of 2-acetoxy-1-(dibenzylmethoxy)hexane : 1-acetoxy-2-(dibenzylmethoxy)hexane **62:61** (82%) was isolated.

2-acetoxy-1-(dibenzylmethoxy)hexane **62**:

δ_H (200MHz) 0.89 (3H, t, *J* 7.3 Hz, H-6), 1.05-1.52 (6H, m, H-3, H-4, H-5), 2.00 (3H, s, Ac-Me), 2.79 (4H, m, H-1', H-3'), 3.42 (1H, m, H-2), 3.72 (1H, quin, H-2'), 3.83 (2H, d, *J* 5.0 Hz, H-1), 7.26 (10H, m, Ph-H);

δ_C (50MHz) 14.0 (C-6), 20.9 (Ac-Me), 22.9, 27.3 and 31.9 (C-3, C-4 and C-5), 41.4 (C-1' and C-3'), 66.3 (C-1), 76.1 (C-2), 81.6 (C-2'), 126.1, 128.3, 129.5 and 139.0 (Ph-H), 170.6 (Ac-C=O);

1-acetoxy-2-(dibenzylmethoxy)hexane **61**:

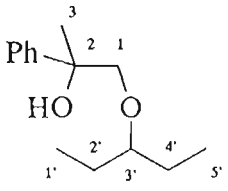
δ_H (200MHz) 0.89 (3H, t, *J* 7.3 Hz, H-6), 1.05-1.52 (6H, m, H-3, H-4, H-5), 2.00 (3H, s, Ac-Me), 2.79 (4H, m, H-1', H-3'), 3.36 (2H, d, *J* 4.9 Hz, H-1), 3.72 (1H, quin, H-2'), 4.81 (1H, quin, *J* 6.0 Hz, H-2), 7.26 (10H, m, Ph-H);

δ_C (50MHz) 14.1 (C-6), 21.2 (Ac-Me), 22.6, 27.5 and 30.6 (C-3, C-4 and C-5), 40.8 (C-1' and C-3'), 70.7 (C-1), 73.1 (C-2), 82.7 (C-2'), 126.1, 127.0, 129.6 and 138.9 (Ph-H), 170.4 (Ac-C=O);;

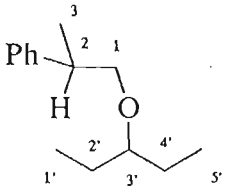
m/z 263 (M^+-91, 6%), 143 (73%), 83 (39%), 55 (32%), 43 (100%);

Found: M^+, 354.2239. $C_{23}H_{30}O_3$ requires *M*, 354.2195.

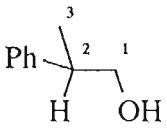
6.4.7. Reduction of 2,2-diethyl-4-methyl-4-phenyl-1,3-dioxolane **63**



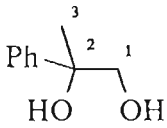
64



65



66



67

To a stirred solution of 2,2-diethyl-4-methyl-4-phenyl-1,3-dioxolane **63** (0.2300g, 1.05mmol) in CH_2Cl_2 at -78°C was added $BH_3{\cdot}SMe_2$ (2.10ml of 1M in CH_2Cl_2, 2.0eq) and TMSOTf (0.40ml, 2.0eq). After 2hrs at -78°C the reaction is quenched with a saturated solution of $NaHCO_3$. Standard workup ($NaHCO_3$, ethyl acetate) afforded the crude product which was purified by column chromatography (pet. ether, ethyl acetate) to yield 1-(3'-pentoxy)-2-phenylpropane **65** (26.1mg, 12%) and 1-(3'-pentoxy)-2-phenylpropan-2-ol **64** (179.3mg, 77%).

1-(3'-pentoxy)-2-phenylpropane **65**:

$\nu_{max.}$ ($CHCl_3$) 3060, 3025, 2965, 2875, 1600, 1490, 1450, 1375, 1140, 1075, 1015, 800 and 700cm^{-1};

δ_H (200MHz) 0.81 (3H, t, *J* 7.4 Hz, H-1' or H-5'), 0.88 (3H, t, *J* 7.4 Hz, H-1' or H-5'), 1.31 (3H, d, *J* 7.0 Hz, H-3), 1.37-1.57 (4H, m, H-4' and H-2'), 3.00 (1H, septet, *J* 6.9

Hz, H-2), 3.08 (1H, quin, *J* 5.8 Hz, H-3'), 3.41 (1H, dd, *J* 7.9 and 9.1 Hz, H-1), 3.56 (1H, dd, *J* 5.9 and 9.1 Hz, H-1), 7.25 (5H, m, Ph-H);

δ_C (50MHz) 10.3 and 10.4 (C-1' and C-5'), 19.3 (C-3), 26.7 (C-2' and C-4'), 41.2 (C-2), 75.6 (C-1), 82.9 (C-3'), 126.8, 127.9, 128.8 and 145.4 (Ph-C);

m/z 191 (M^+-15, 22%), 117 (18%) and 57 (100%);

Found: *M^+-15*, 191.1047, $C_{14}H_{22}O$ requires *M-15*, 191.1072.

1-(3'-pentoxy)-2-phenylpropan-2-ol **64**:

$\nu_{max.}$ ($CHCl_3$) 3555, 3060, 3000, 2965, 2930, 2875, 1600, 1490, 1460, 1445, 1370, 1325, 1125, 1090, 1060, 950, 870 and 700cm^{-1};

δ_H (200MHz), DMSO-D_6 0.76 (6H, dt, *J* 5.1 and 7.4 Hz, H-1' and H-5'), 1.29-1.47 (4H, m, H-2' and H-4'), 1.45 (3H, s, H-3), 3.07 (1H, quin, *J* 5.7 Hz, H-3'), 3.40 (2H, s, H-1), 4.88 (1H, s, exch., -OH), 7.13-7.52 (5H, m, Ph-H);

δ_C (50MHz) $CDCl_3$ 10.1 and 10.2 (C-1' and C-5'), 26.5 (C-2' and C-4'), 27.4 (C-3), 77.4 (C-1), 83.1 (C-3'), 125.5, 127.2, 128.5 and 146.3 (Ph-C);

m/z 222 (M^+, 2%), 193 (1%), 121 (100%), 91 (10%) and 43 (57%);

Found: *M^+-29*, 193.1220, $C_{12}H_{17}O_2$ requires *M-29*, 193.1228.

b) Same procedure as a) but THF was used as a solvent. The reaction was warmed up to room temperature before quenching. Column chromatography of the crude product

afforded 1-(3'-pentoxy)-2-phenylpropane (89,8mg, 43%) **65**, 2-phenylpropan-1-ol **66** (26.8mg, 20%) and 2-phenyl-1,2-propandiol **67** (58.5mg, 35%)

1-(3'-pentoxy)-2-phenylpropane exhibited the identical spectral features as above.

2-phenylpropan-1-ol **66**:

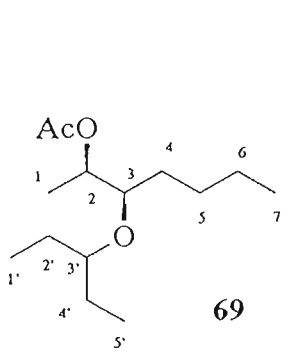
δ_H (200MHz) 1.30 (3H, d, *J* 7.0Hz, H-3), 1.60 (1H, br. s., O-H), 2.97 (1H, sestet, *J* 6.9 Hz, H-2), 3.72 (2H, d, *J* 6.8 Hz, H-1), 7.29 (5H, m, Ph-H);

δ_C (50MHz) 18.3 (C-3), 42.8 (C-2), 68.7 (C-1), 126.0, 126.8, 128.0 and 142.9 (Ph-C);

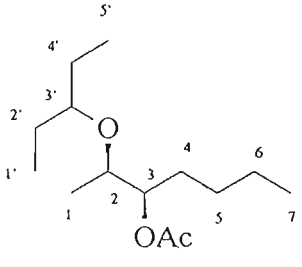
m/z 136 (M^+, 19%), 106 (27%), 79 (23%), 78 (10%), 77 (28%);

Found: M^+, 136.0908. $C_9H_{12}O$ requires *M*, 136.0888.

6.4.8. Reduction of *trans*-4-butyl-2,2-diethyl-5-methyl-1,3-dioxolane **68**



69



70

The general procedure for the regioselective reduction was used on a 0.50mmol scale.

a) In CH_2Cl_2 the temperature at which the reaction was complete was -50°C. After chromatography a 25:75 mixture of ±2R-acetoxy-3R-(3-pentoxy)heptane : ±3R-acetoxy-2R-(3-pentoxy)heptane **69:70** (31%) was isolated.

b) In THF the temperature at which the reaction was complete was +4°C. After chromatography a 81:19 mixture of ±2R-acetoxy-3R-(3-pentoxy)heptane : ±3R-acetoxy-2R-(3-pentoxy)heptane **69:70** (50%) was isolated.

Both regioisomers (unacetylated):

$\nu_{max.}$ ($CHCl_3$) 3550, 2960, 2935, 2875, 1455, 1375, 1105, 1070, 1010 and 980cm^{-1};

m/z 173 (M^+-29, 4%), 157 (42%), 115 (66%), 97 (28%), 87 (100%), 71 (76%), 69 (74%), 59 (14%), 57 (17%), 55 (31%), 45 (40%) and 43 (72%);

Found: M^+-*29*, 173.1536. $C_{10}H_{21}O_2$ requires *M-29*, 173.1541.

±2R-acetoxy-3R-(3-pentoxy)heptane **69**:

δ_H (200MHz) 0.87 (9H, m, H-7, H-1' and H-5'), 1.18 (3H, d, *J*, 6.5 Hz, H-1), 1.21-1.67 (10H, m, H-4, H-5, H-6, H-2' and H-4'), 2.02 (3H, s, Ac-Me), 3.20 (1H, quin, *J* 5.8 Hz, H-3'), 3.26 (1H, m, H-3), 4.97 (1H, m, H-2);

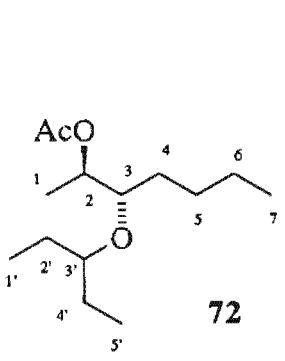
δ_C (50MHz) 9.4 and 10.0 (C-1 and C-7), 14.0 and 14.7 (C-1' and C-5'), 21.4 (Ac-Me), 23.0, 26.1, 26.2, 27.9 and 29.6 (C-4, C-5, C-6, C-2' and C-4'), 70.9, 77.7 and 80.8 (C-2, C-3 and C-3'), 170.5 (Ac-C=O);

±3R-acetoxy-2R-(3-pentoxy)heptane **70**:

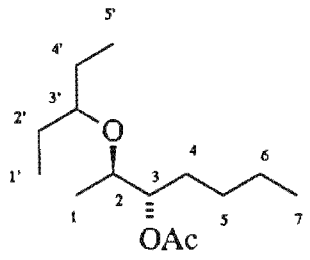
δ_H (200MHz) 0.87 (9H, m, H-7, H-1' and H-5'), 1.06 (3H, d, *J*, 6.4 Hz, H-1), 1.21-1.67 (10H, m, H-4, H-5, H-6, H-2' and H-4'), 2.05 (3H, s, Ac-Me), 3.20 (1H, quin, *J* 5.8, H-3'), 3.50 (1H, m, H-3), 4.85 (1H, m, H-2);

δ_C (50MHz) 9.7 and 9.8 (C-1 and C-7), 14.0 and 16.1 (C-1' and C-5'), 21.3 (Ac-Me), 22.7, 26.4, 26.4, 27.9 and 28.8 (C-4, C-5, C-6, C-2' and C-4'), 73.4, 76.0 and 80.6 (C-2, C-3 and C-3'), 170.8 (Ac-C=O);

6.4.9. Reduction of *cis*-4-butyl-2,2-diethyl-5-methyl-1,3-dioxolane **71**



72



73

The general procedure for the regioselective reduction was used on a 0.50mmol scale.

a) In CH_2Cl_2 the temperature at which the reaction was complete was -50°C. After chromatography a 25:75 mixture of ±3R-(3-pentoxy)heptan-2S-ol : ±2S-(3-pentoxy)heptan-3R-ol **72:73** (92%) was isolated.

b) In THF the temperature at which the reaction was complete was +4°C. After chromatography a 70:30 mixture of ±3R-(3-pentoxy)heptan-2S-ol : ±2S-(3-pentoxy)heptan-3R-ol **72:73** (83%) was isolated.

Both regioisomers:

$\nu_{max.}$ ($CHCl_3$) 2955, 2920, 2860, 1740, 1455, 1380, 1120, 1070, 1005 and 960cm^{-1};

±3R-(3-pentoxy)heptan-2S-ol **72**:

δ_H (200MHz) 0.82-0.94 (9H, m, H-7, H-1' and H-5'), 1.10 (3H, d, *J* 6.5 Hz, H-1), 1.23-1.55 (10H, m, H-4, H-5, H-6, H-2' and H-4'), 3.21 (2H, m, H-3 and H-3'), 3.88 (1H, dq, *J* 3.0 and 6.5 Hz, H-2);

δ_C (50MHz) 9.4 and 9.8 (C-1 and C-7), 17.4 (C-1' and C-5'), 23.0, 26.1, 26.1, 28.0, and 28.6 (C-4, C-5, C-6, C-2' and C-4'), 68.0 (C-2), 79.9 (C-3'), 80.2 (C-3);

m/z 173 (M^+-29, 1%), 157 (21%), 115 (9%), 97 (11%), 87 (100%), 71 (25%), 69 (73%) and 55 (24%).

±2S-(3-pentoxy)heptan-3R-ol **73**:

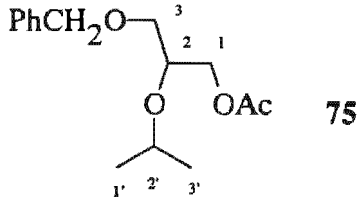
δ_H (200MHz) 0.82-0.94 (9H, m, H-7, H-1' and H-5'), 1.05 (3H, d, *J*, 6.4 Hz, H-1), 1.23-1.55 (10H, m, H-4, H-5, H-6, H-2' and H-4'), 3.21 (1H, quin, *J* 5.8 Hz, H-3'), 3.41 (1H, dq, *J* 3.0 and 6.5 Hz, H-2), 3.64 (1H, ddd, *J* 3.1, 4.7 and 7.7 Hz, H-3);

δ_C (50MHz) 9.6 and 9.7 (C-1 and C-7), 13.7 and 14.0 (C-1' and C-5'), 22.8, 26.4, 26.5, 28.3 and 31.8 (C-4, C-5, C-6, C-2' and C-4'), 73.3 (C-2), 75.6 (C-3) and 79.8 (C-3');

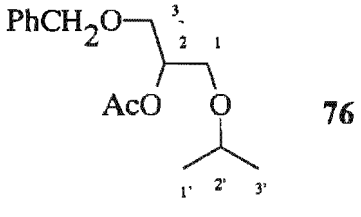
m/z 173 (M^+-29, 3%), 115 (65%), 97 (31%), 87 (10%), 71 (100%), 69 (34%), 55 (25%).

Found: M^+-29, 173.1527; $C_{10}H_{21}O_2$ requires *M-29*, 173.1541.

6.4.10.. Reduction of 4-benzyloxymethyl-2,2-dimethyl-1,3-dioxolane **74**



75



76

The general procedure for regioselective reduction was used:

a) In CH_2Cl_2 the temperature at which the reaction had gone to completion was -70°C. After chromatography a 5:95 mixture of 1-acetoxy-3-benzyloxy-2-isopropoxy-propane : 2-acetoxy-3-benzyloxy-1-isopropoxy-propane **75:76** (86%) was isolated.

b) In THF the temperature at which the reaction had gone to completion was -70°C. After chromatography a 27:73 mixture of 1-acetoxy-3-benzyloxy-2-isopropoxy-propane : 2-acetoxy-3-benzyloxy-1-isopropoxy-propane **75:76** (72%) was isolated.

1-acetoxy-3-benzyloxy-2-isopropoxy-propane **75**:

δ_H (200MHz) 1.12 (6H, d, *J* 6.3 Hz, H-1' and H-3'), 2.01 (Ac-Me), 3.45-3.64 (3H, m, H-1' and H-3), 3.72 (1H, m, H-2), 4.08 (1H, dd, *J* 5.9 and 11.5 Hz, H-1), 4.19 (1H, dd, *J* 4.5 and 11.4 Hz, H-1), 4.53 (2H, dd, Bn-CH_2, ab system), 7.31 (5H, m, Ph-H);

δ_C (50MHz) 20.8 (Ac-C), 22.6 (C-1'), 22.7 (C-3'), 64.4 (C-1), 70.1 (C-3), 71.5 (C-2'), 73.4 (Bn-CH_2), 74.0 (C-2), 127.5, 127.7, 128.3 and 138.0 (Ph-C), 170.3 (Ac-C);

2-acetoxy-3-benzyloxy-1-isopropoxy-propane **76**:

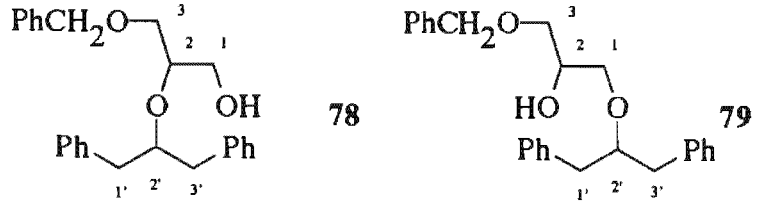
δ_H (200MHz) 1.26 (6H, d, *J* 6.1 Hz, H-2'), 2.07 (3H, s, Ac-CH_3), 3.49-3.68 (5H, m, H-1', H-1, H-3), 4.54 (2H, dd, Bn-CH_2, ab system), 5.12 (1H, quin, *J* 2.6 Hz, H-2), 7.32 (5H, m, Ph-H);

δ_C (50MHz) 21.2 (Ac-C), 22.1 (C-1'), 22.0 (C-3'), 66.5 (C-1), 68.7 (C-3), 71.9 (C-2), 72.1 (C-2'), 73.2 (Bn-CH_2), 127.5, 127.7, 128.3 and 138.0 (Ph-C), 170.3 (Ac-C);

m/z 266 (M^+, 0.2%), 159 (3%), 117 (10%), 107 (15%), 92 (13%), 91 (84%), 73 (13%), 58 (40%), 57 (14%) and 43 (100%);

Found: M^+, 266.1492. $C_{15}H_{22}O_4$ requires *M*, 266.1518.

6.4.11. Reduction of 4-benzyloxymethyl-2,2-dibenzyl-1,3-dioxolane **77**



To a solution of 4-benzyloxymethyl-2,2-dibenzyl-1,3-dioxolane (0.3747g, 1.00mmol) in CH_2Cl_2 at -78°C were added TMSOTf (0.47ml, 2.2eq) and $BH_3{\cdot}SMe_2$ (2.20ml of 1M, 2.2eq). The reaction mixture was stirred for 4 hours at -78°C before quenching with a saturated $NaHCO_3$ solution. A standard workup ($NaHCO_3$, ethyl acetate) afforded the crude product which was purified by column chromatography to yield starting material (43.9mg, 12%), dibenzylmethanol **4** (29.8mg, 14%) and 3-benzyloxy-1-dibenzylmethoxy-2-propanol **79** (198.4mg, 56%) together with traces of 3-benzyloxy-2-dibenzylmethoxy-1-propanol **78** (~ 95:5 ratio)

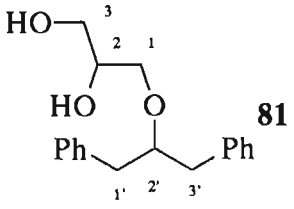
$\nu_{max.}$ ($CHCl_3$) 3550, 3065, 3000, 2920, 2865, 1600, 1585, 1495, 1360, 1325, 1225, 1210, 1095, 1025, 725, 700 and 660cm^{-1};

δ_H (200MHz) 2.12 (1H, br.s, -OH), 2.76 (4H, d, *J* 6.2 Hz, H-1' and H-3'), 3... (2H, d, *J* 5.5 Hz, H-3), 3.30 (1H, dd, *J* 6.0 and 9.7 Hz, H-1), 3.39 (1H, dd, *J* 4.6 and 9.8 Hz, H-1) 3.69 (2H, m, H-2 and H-2'), 4.39 (2H, s, benzyl-CH_2), 7.24 (15H, m, Ph-H);

δ_C (50MHz) 40.8 (C-1' and C-3'), 69.4 (C-2), 70.9, 71.0 and 73.2 (C-1, C-3 and benzyl-CH_2), 83.0 (C-2'), 126.1, 127.4, 128.1, 128.2 and 129.2 (Ph-CH), 137.9 and 138.5 (Ph-C).

Found: M^+-*91*, 327.1594. $C_{20}H_{23}O_4$ requires *M-91*, 327.1596.

6.4.12. Reduction of 2,2-dibenzyl-1,3-dioxolane-4-methanol **80**



81

To a solution of 2,2-dibenzyl-1,3-dioxolane-4-methanol **80** (0.2936g, 1.03mmol) in CH_2Cl_2 at -78°C was added $BH_3{\cdot}SMe_2$ (1.14ml of 1M solution in CH_2Cl_2, 1.14mmol) and warmed to 0°C for 1 hour. After cooling to -78°C, TMSOTf (0.24ml, 1.14mmol) was added. The reaction was stirred for 24 hours at -15°C, before it was quenched with a saturated solution of NH_4Cl. Standard workup (NH_4Cl, ethyl acetate) and column chromatography afforded dibenzylmethanol **4** (50.5mg, 23%) and 1-dibenzylmethoxy-propan-2,3-diol **81** (218.3mg, 74%).

$\nu_{max.}$ 3680, 3560, 3065, 3015, 2920, 2870, 1600, 1515, 1495, 1450, 1215, 1105, 1055, 925, 740, 700 and 665cm^{-1};

δ_H (200MHz) 1.93 (2H, br.s., -OH), 2.77 (4H, dd, *J* 2.2 and 6.4 Hz, H-1' and H-3'), 3.34 (4H, m, H-1 and H-3), 3.56 (1H, m, H-2), 3.72 (1H, quintet, *J* 6.3 Hz, H-2'), 7.26 (10H, m, Ph-H);

δ_C (50MHz) 40.8 (C-1' and C-3'), 63.5 (C-3), 70.5 (C-2), 71.3 (C-1), 83.1 (C-2'), 126.1, 128.2 and 129.1 (Ph-CH), 138.3 and 138.4 (Ph-C);

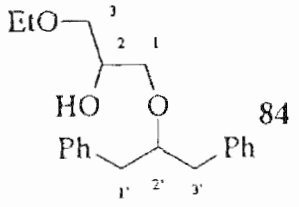
m/z 286 (M^+, 0.75%), 287 (M^++1, 0.55%), 195 (100%), 121 (78%), 117 (10%), 105 (12%), 103 (32%), 91 (78%), 75 (92%) and 57 (12%);

Found: M^+-*91*, 195.1021. $C_{11}H_{15}O_3$ requires *M-91*, 195.1021.

6.4.13. Reduction of 4-(*t*-Butyldimethylsilyloxy)methyl-2,2-dibenzyl-1,3-dioxolane **82**

To a solution of 4-(*t*-butyldimethylsilyloxy)methyl-2,2-dibenzyl-1,3-dioxolane **82** (0.2000g, 0.50mmol) in CH_2Cl_2 at -78°C were added TMSOTf (0.32ml, 1.51mmol) and $BH_3.SMe_3$ (1.50ml of 1M solution in CH_2Cl_2, 1.50mmol). After 3 hours at -78°C the reaction was quenched with a saturated solution of $NaHCO_3$. Standard workup ($NaHCO_3$, ethyl acetate) and column chromatography afforded 1-dibenzylmethoxy-propan-2,3-diol **81** (125.7mg, 88%) with the same properties as in 6.4.12.

6.4.14. Reduction of 2,2-dibenzyl-1,3-dioxolane-4-methyl ethanoate **83**



84

To a solution of 2,2-dibenzyl-1,3-dioxolane-4-methyl ethanoate **83** (0.1409g, 0.43mmol) in CH_2Cl_2 at -78°C were added TMSOTf (0.27ml, 1.30mmol) and $BH_3{\cdot}SMe_2$ (1.30ml of 1M solution in CH_2Cl_2, 1.30mmol). After 6 hours at -40°C the reaction was quenched with water. Standard workup (H_2O, CH_2Cl_2) resulted in a crude product mixture which was dissolved in ethanol (96%, 10ml). To this was added potassium hydroxide (1.0g, 18mmol) and stirred at room temperature for 18 hours. Standard workup (2M HCl, 20ml, 40mmol, ethyl acetate) and column chromatography resulted in 1-dibenzylmethoxy propan-2,3-diol **81** (72.8mg, 59%) with the same spectral properties as in 6.4.12.

The reaction was repeated as before on a 0.39mmol scale and stirred at -15°C for 20 hours. Column chromatography afforded 1-dibenzylmethoxy-3-ethoxy-2-propanol **84** (28.4mg, 23%), 2-dibenzylmethoxy-1-ethoxy-3-propanol **85** (31.7mg, 26%) and 1-dibenzylmethoxy-propan-2,3-diol **81** (27.3mg, 25%).

$\nu_{max.}$ both isomers 3545, 3005, 2925, 1495, 1450, 1225, 1180, 1125, 1105, 1080, 1040, 1015, 765 and 700cm^{-1};

1-dibenzylmethoxy-3-ethoxy-2-propanol **84**:

δ_H (200MHz) 1.15 (3H, t, *J* 7.0 Hz, Et-CH_3), 1.80 (1H, brs., -OH), 2.79 (4H, d, *J* 6.3 Hz, H-1' and H-3'), 3.23 (2H, d, *J* 5.6 Hz, H-3), 3.31 (1H, dd, *J* 6.3 and 9.4 Hz, H-1), 3.41 (2H, q, *J* 7.0 Hz, Et-CH_2), 3.41 (1H, dd, *J* 4.4 and 9.9 Hz, H-1), 3.70 (2H, m, H-2' [illegible] 7.25-(10H, m, Ph-H);

δ_H (200MHz) DMSO-d_6, 1.07 (6H, d, *J* 6.1 Hz, H-1'), 1.21 (3H, s, H-1"), 1.35 (3H, s, H-1"), 3.35 (1H, septet, *J* 6.9 Hz, H-2'), 3.50 (1H, m, H-6), 3.55 (1H, m, H-6), 3.74 (1H, m, H-5), 3.83 (1H, dd, *J* 8.7 and 2.4 Hz, H-4), 4.01 (1H, d, *J* 2.4 Hz, H-3), 4.36 (1H, d, *J* 3.5 Hz, H-2), 4.50 (1H, d, exch., *J* 5.4 Hz, -OH), 5.37 (1H, d, exch., *J* 4.9 Hz, -OH), 5.76 (1H, d, *J* 3.7 Hz, H-1);

δ_C (50MHz) 22.0 (C-1'), 26.2 and 26.8 (C-1"), 69.1 (C-2'), 69.2 (C-6), 72.5 (C-5),,,,, 75.3 (C-3), 80.0 (C-4), 85.0 (C-2), 104.8 (C-1), 111.5 (C-2");

b) The same method as a) on a 1.0 mmol scale in THF as a solvent, -78°C to RT. Column chromatography resulted in a 2:1 mixture of 6-*O*-isopropyl-1,2-*O*-isopropylidene-D-glucofuranose **97** and 5-*O*-isopropyl-1,2-*O*-isopropylidene-D-gluco-furanose (0.1505g, 58%) **98**:

δ_C (200MHz) signals for both isomers coincide, no resolution could be achieved.

δ_C (50MHz) 22.4 and 22.5 (C-1'), 26.1 and 26.7 (C-1"), 62.6 (C-6), 73.4 (C-2'), 75.5 (C-3), 76.8 (C-5), 78.9 (C-4), 85.3 (C-2), 104.3 (C-1), 111.5 (C-2");

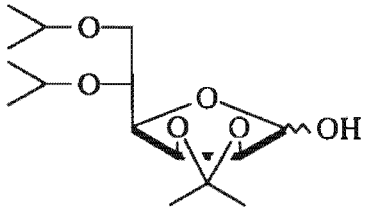
36%) **99** as a mixture of anomers, mp.: 117-120°C, R_f= 0.49 (ethyl acetate : pet ether 1:1), (Found: C, 55.7; H, 7.55. $C_{12}H_{20}O_6$ requires C, 55.4; H, 7.75%)[107];

$\nu_{max.}$ ($CHCl_3$) 3595, 3365, 2990, 2950, 1455, 1380, 1370, 1205, 1065, 840 and 730cm^{-1};

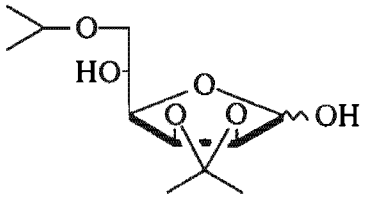
δ_H (200MHz) 1.31, 1.37 and 1.45 (12H, 3s, Me, major anomer), 1.38, 1.43 and 1.52 (3s, Me, minor anomer) 2.75 (1H, br.s., -OH), 3.46 (1H of minor, dd, *J* 3.1 and 8.31Hz), 3.98-4.13 (2H, m), 4.17 (1H of major anomer, dd, *J* 3.6 7.3 Hz), 4.38 (1H, m), 4.52 (1H, of minor anomer, dd, *J* 3.5 and 5.9 Hz), 4.61 (1H of major anomer, d, *J* 5.9 Hz), 4.75 (1H of minor anomer, dd, *J* 3.3 and 6.1 Hz), 4.80 (1H of major anomer, dd, J= 3.6 Hz and 5.9 Hz), 4.99 (1H of minor anomer, dd, J= 3.6 Hz and 12.2 Hz), 5.36 (1H of major anomer, s, H1);

m/z 245 (M^+-15, 50%), 187 (15%), 101 (80%), 59 (55%) and 43 (100%).

6.5.9. Reduction of 2,3-5,6-di-*O*-isopropylidene-D-mannofuranose **99**



100



101

To a solution 2,3-5,6-di-*O*-isopropylidene-D-mannofuranose (0.2600g, 1.00mmol) **99** in CH_2Cl_2 at -78°C were added TMSOTf (0.21ml, 1.1eq) and $BH_3{\cdot}SMe_2$ (1.10ml of 1M in CH_2Cl_2, 1.1eq). The reaction was quenched after 2 hours at -78°C with saturated aqueous $NaHCO_3$ solution. After a standard workup ($NaHCO_3$, ethyl acetate) the crude product mixture was isolated and purified by column chromatography (pet ether, ethyl acetate). This afforded 5,6-di-*O*-isopropyl-2,3-*O*-isopropylidene-D-mannofuranose

(22.3mg, 15%) **100**, 6-*O*-isopropyl-2,3-*O*-isopropylidene-D-mannofuranose (122.6mg, 47%) **101** and starting material (18.7mg, 7%).

5,6-di-*O*-isopropyl-2,3-*O*-isopropylidene-D-mannofuranose **100**:

δ_H (200MHz) 1.14-1.52 (18H, m, isopropyl-CH_3 and isopropylidene-CH_3), 1.95 (1H, br., -OH), 3.39-4.18 (7H, m), 4.47 (1H of minor, dd, *J* 3.7 and 6.0 Hz), 4.56 (1H of major, dd, *J* 2.4 and 5.9 Hz), 4.74 (1H of minor, dd, *J* 3.0 and 5.9 Hz), 4.79 (1H of major, dd, *J* 3.3 and 5.8 Hz), 4.86 (1H of major, dd, *J* 3.4 and 5.9 Hz), 4.93 (1H of minor, m), 5.11 (1H, s.), 5.33 (1H, s.);

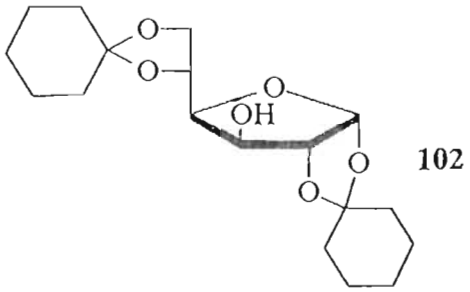
δ_C (50MHz) 21.5, 22.1, 22.2, 22.5, 23.4, 24.7, 25.0, 26.0 and 26.2 (isopropyl-CH_3 and isopropylidene-CH_3), 68.9, 69.0, 69.4 and 69.5 (C-6), 72.1, 72.2, 74.5, 74.6, 74.7,78.13, 78.8, 79.4, 79.5, 79.9, 80.1, 85.2, 85.4, 96.7, 101.4, 104.4, 112.1, 112.3, 112.7;

6-*O*-isopropyl-2,3-*O*-isopropylidene-D-mannofuranose (mixture of anomers) **101**:
δ_H (200MHz) 1.13 (6H, d, *J* 6.0 Hz, isopropyl-CH_3), 1.28 and 1.41 (6H, 2s, isopropylidene-CHz), 2.85 (2H, br., -OH), 3.40-3.69 (3H, m, H-6 and isopropyl-CH)m, 3.96-4.11 (2H, m, H-4 and H-5), 4.47 (1H of minor, dd., *J* 3.5 and 6.1 Hz, H-2), 4,54 (1H of major, d, *J* 5.9 Hz, H-2), 4.78 (1H of minor, dd. *J* 3.4 and 6.1 Hz, H-3), 4.83 (1H of major, dd., *J* 3.3 and 6.0 Hz, H-3), 4.94 (1H of minor, d, *J* 3.5 Hz, H-1), 5.32 (1H of major, s., H-1);

δ_C (50MHz) 22.0 and 22.1 (isopropyl-CH_3), 24.6 and 26.0 (isopropylidene-CH_3), 68.3, 70.5, 75.2, 78.4 and 79.6 (C-2, C-3, C-4, C-5 and isopropyl-CH of minor), 69.5 (C-6 of minor), 68.9, 72.3, 79.3, 80.2 and 85.4 (C-2, C-3, C-4, C-5 and isopropyl-CH of major), 69.7 (C-6 of major), 97.0 (C-1 of minor), 101.0 (C-1 of major), 112.5 (isopropylidene-C of major), 112.9 (isopropylidene-C of minor);

The reaction was repeated on a 1mmol scale and 2 equivalents of TMSOTf and BH_3·SMe_2 and the same products were obtained. 5,6-di-*O*-isopropyl-2,3-*O*-isopropylidene-D-mannofuranose (15.0mg, 10%) **100** and 6-*O*-isopropyl-2,3-*O*-isopropylidene-D-mannofuranose (99.7mg, 38%) **101**.

6.5.10. Synthesis of 1,2:5,6-Di-*O*-cyclohexyl-α-D-glucofuranose **102**



102

To a flask containing cyclohexanone (21.14ml, 200mmol), cooled to 0°C, was added dropwise H_2SO_4 (conc., 1.25ml) followed by glucose (9.0g, 50mmol). The reaction was left to warm up to RT and stirred for 18 hrs. A solid off-white crystalline mass precipitated. 50ml of heptane was added followed by a saturated solution of Na_2CO_3 in water (15ml) and the mixture heated on a boiling water bath. The heptane layer was decanted and another 50ml of heptane added to the aqueous layer. The mixture was heated again and the heptane layer decanted. The organic fractions were combined and cooled in a refrigerator overnight. The crystalline product was filtered off and recrystallised from heptane to yield 1,2:5,6-di-*O*-cyclohexylidene-α-D-glucofuranose (7.65g, 45%) **102**, mp.: 112°C-117°C. (Found: C, 63.8; H, 8.3; $C_{18}H_{28}O_6$ requires C, 63.5; H, 8.3%)[115]

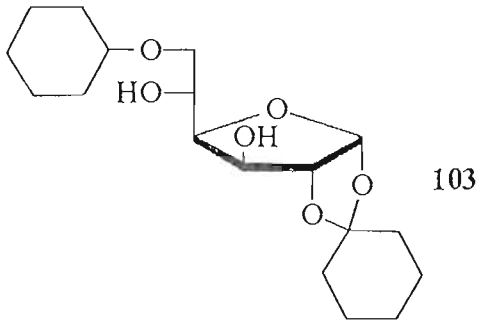
$\nu_{max.}$ ($CHCl_3$) 3460, 2940, 2860, 1445, 1365, 1230, 1205, 1160, 1110, 1075, 925, 745 and 730cm^{-1};

δ_H (200MHz) 1.20-2.35 (20H, m, cyclohexyl-H), 2.52 (1H, br., -OH), 3.62-4.51 (6H, m, H-2, H-3, H-4, H-5, H-6), 5.91 (1H, d, *J* 3.6 Hz, H-1);

δ_C (50MHz): 23.7, 23.9, 24.0, 24.1, 25.0 and 25.2 (C-3', C-4', C-5'), 35.8, 35.8, 36.5 and 36.6 (C-2', C-6'), 67.4 (C-6), 73.3, 75.4, 81.2 and 84,6 (C-2, C-3, C-4, C-5), 104.8 (C-1), 110.2 and 112.4 (C-1');

m/z 340 (M^+, 33%), 297 (59%), 199 (37%), 127 (34%), 99 (45%), 81 (32%) and 55 (100%).

6.5.11. Reduction of 1,2-5,6-di-*O*-cyclohexylidene-α-D-glucofuranose **102**[99]



103

Method a

To a solution of 1,2-5,6-di-*O*-cyclohexylidene-α-D-glucofuranose (0.3400g, 1.00mmol) **102** in CH_2Cl_2 at -78°C were added TMSOTf (0,21ml, 1.1eq) and $BH_3 \cdot SMe_2$ (1.10ml, 1.1eq). The reaction was quenched after 0.5 hour at -78°C with saturated aqueous $NaHCO_3$. After a standard workup ($NaHCO_3$, ethyl acetate) the crude product mixture was isolated and purified by column chromatography (pet ether, ethyl acetate). This afforded starting material (31.9mg, 9.4%), and 6-*O*-cyclohexyl-1,2-*O*-cyclohexylidene-α-D-glucofuranose. (208.6mg, 61%) **103**;

$\nu_{max.}$ 3450, 2940, 2855, 1445, 1365, 1230, 1165, 1115, 1075, 1015, 925 and 730cm^{-1};

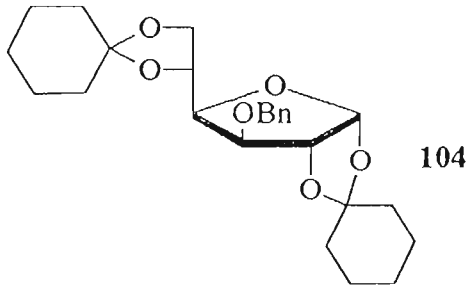
δ_H (200MHz) 1.13-1.95 (20H, m, cyclohexyl-CH_2), 3.31 (1H, m, cyclohexyl-CH), 3.32 (2H, br., exch., -OH), 3.52 (1H, dd, *J* 5.4 and 9.9 Hz, H-6), 3.71 (1H, dd, *J* 3.1 and 9.8 Hz, H-6), 4.02 (1H, dd, *J* 2.5 and 6.3 Hz, H-4), 4.07 (1H, m, H-5), 4.31 (1H, d, *J* 2.3 Hz, H-3), 4.47 (1H, d, *J* 3.7, H-2), 5.91 (1H, d, *J* 3.7, H-1);

δ_C (50MHz) 23.5, 23.8, 23.9, 24.9, 25.7, 31.9, 32.0, 35.7, 36.5 (cyclohexyl-CH_2), 68.8 (C-6), 69.3 (C-5), 75.7 (C-3), 78.2 (cyclohexyl-C-H), 80.0 (C-4), 84.7 (C-2), 104.4 (C-1), 112.2 (cyclohexyl-C).

Method b

To a solution of 1,2-5,6-di-*O*-cyclohexylidene-α-glucofuranose (0.3408g, 1.00mmol) **102** in CH_2Cl_2 at -78°C was added $BH_3 \cdot SMe_2$ (1.10ml, 1.1eq). The solution was warmed up to 0°C for 0.5 hours and cooled to -78°C before adding TMSOTf (0.21ml, 1.1eq). The reaction was left to warm to -50°C before quenching with $NaHCO_3$ solution. After a standard workup ($NaHCO_3$, ethyl acetate) the product mixture was isolated and purified by column chromatography (pet ether, ethyl acetate). This afforded starting material (10.0mg, 3%) and 6-*O*-cyclohexyl-1,2-*O*-cyclohexylidene-α-D-glucofuranose (223.5mg, 65%) **103**. The product gave the same spectroscopic data as in method a.

6.5.12. Synthesis of 3-*O*-benzyl-1,2-5,6-di-*O*-cyclohexylidene-α-D-glucofuranose **104**[115]



104

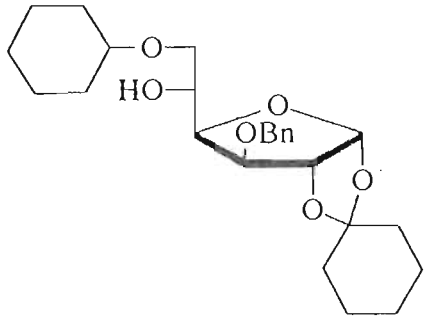
The compound was synthesized according to a known procedure and was purified by column chromatography.

δ_H (200MHz) 1.39 (16H, m, cyclohexylidene-CH_2), 1.61 (4H, m, cyclohexylidene-CH_2), 3.95-4.19 (4H, m), 4.38 (1H, m), 4.58 (1H, d, *J* 3.9Hz, H-2), 4.65 (1H, d, *J* 12.0 Hz, benzyl-CH_2, ab system), 4.72 (1H, d, *J* 12.0 Hz, benzyl-CH_2, ab system), 5.90 (1H, d, *J* 3.7 Hz, H-1), 7.14-7.43 (5H, m, Ph-H);

δ_C (50MHz) 23.7, 24.0, 24.2, 25.0, 25.3, 35.0, 35.8, 36.6 (cyclohexylidene-CH_2), 67.3 (C-6), 72.2 (C-5), 72.4 (benzyl-CH_2), 81.5 (C-4), 81.8 (C-3), 82.4 (C-2), 104.9 (C-1), 109.6 and 112.5 (cyclohexylidene-C), 127.6, 127.7 and 128.4 (Ph-C-H), 137.7 (Ph-C)

m/z 430 (M^+, 17%) and 91 (100%).

6.5.13. Reduction of 3-*O*-benzyl-1,2-5,6-di-*O*-cyclohexylidene-α-D-glucofuranose **104**



105

To a stirred solution of 3-*O*-benzyl-1,2-5,6-di-*O*-cyclohexylidene-α-D-glucofuranose (0.4297g, 1.00mmol) in CH_2Cl_2 at -78°C were added TMSOTf (0.21ml, 1.1eq) and $BH_3 \cdot SMe_2$ (1.10ml, 1.1eq). After 1 hour at -78°C the reaction was quenched with saturated $NaHCO_3$ solution and standard workup resulted in a crude product which was purified by column chromatography. This yielded starting material (1.79mg, 4%) and 3-*O*-benzyl-6-*O*-cyclohexyl-1,2-di-*O*-cyclohexylidene-α-D-glucofuranose (282.6g, 65%) **105**.

$\nu_{max.}$ 3560, 3000, 2935, 2855, 1450, 1365, 1160, 1075, 1020, 905, 775 and 695cm^{-1};

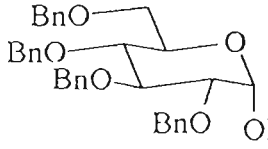
3-*O*-benzyl-6-*O*-cyclohexyl-1,2-di-*O*-cyclohexylidene-α-D-glucofuranose **105**:

δ_H (200MHz) 1.11-1.90 (20H, m, cyclohexyl-CH_2 and cyclohexylidene-CH_2), 2.84 (1H, br.s., -OH), 3.26 (1H, m, cyclohexyl-C-H), 3.51 (1H, dd, *J* 5.0 and 9.9 Hz, H-4), 3.70 (1H, dd, *J* 2.6 and 9.6 Hz, H5), 4.10 (2H, s, benzyl-CH_2), 4.10 (1H, m, H3), 4.55 (1H, d, *J* 3.8 Hz, H-2), 4.64 (2H, d, *J* 2.7 Hz, H-6), 5.89 (1H, d, *J* 3.8 Hz, H-1), 7.26-7.33 (5H, m, Ph-H);

δ_C (50MHz) 23.6, 23.9, 24.9, 25.8, 32.0, 32.2, 35.9 and 36.5 (cyclohexyl-CH_2 and cyclohexylidene-CH_2), 67.9 (C-5), 69.6 (C-6), 72.4 (benzyl-CH_2), 77.9, 80.0, 82.0 and

82.1 (C-2, C-3, C-4 and cyclohexyl-CH), 104.7 (C-1), 112.3 (cyclohexylidene-C), 127.7, 127.8 and 128.4 (Ph-CH), 137.7 (Ph-C).

6.5.14. Synthesis of Methyl 2,3,5,6-tetra-*O*-benzyl-α-D-glucopyranoside **106**



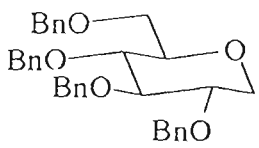
106

To a suspension of methyl-α-D-glucopyranoside (10.0g, 51mmol) in glyme (50ml, distilled from Na, stored over 4Å molecular sieves) were added NaH (10.0g, 410mmol), benzyl bromide (35ml, 255mmol) and $Bu_4N^+I^-$ (100mg, phase transfer catalyst). The mixture was heated up to reflux for 48hours. Standard workup (H_2O, CH_2Cl_2) and removal of excess benzyl bromide and oil from NaH by distillation resulted in a crude product which was purified by column chromatography (pet ether, ethyl acetate) to yield methyl 2,3:5,6-tetra-*O*-benzyl-α-D-glucopyranoside (18.0g, 63%) as an oil.

δ_H (200MHz) 3.42 (3H, s, 1-OMe), 3.56-3.85 (5H, m), 4.04 (1H, dd, *J* 8.6 and 9.5), 4.47-5.06 (9m), 7.30 (20H, m, Ph-H);

δ_C (50MHz) 55.1 (1-OMe), 69.4 (C-6), 70.0, 73.3, 73.4, 74.9, 75.7, 77.6, 79.8, 82.0, 98.1 (C-1), 127.5, 127.6, 127.6, 127.8, 127.8, 127.9, 128.0, 128.3, 128.3, 128.4 (Ph-CH), 137.8, 138.1, 138.2, 138.7 (Ph-C);

6.5.15. Reduction of Methyl 2,3,5,6-tetra-*O*-benzyl-α-D-glucopyranoside **106**[105]



107

To a solution of methyl 2,3,5,6-tetra-*O*-benzyl-α-D-glucopyranoside (0.2848g, 0.51mmol) **106** in CH_2Cl_2 at -78°C was added TMSOTf (0.11ml, 1.1eq) and $BH_3 \cdot SMe_2$ (0.57ml of 1m solution in CH_2Cl_2, 1.1eq). The reaction was left to warm to room temperature and stirred for 6 days. After a standard workup ($NaHCO_3$, ethyl acetate) and column chromatography 1,5-anhydro-2,3,4,6-tetra-*O*-benzyl-D-glucitol (0.1648g, 62%) **107** and starting material (30.0mg, 11%) were isolated.

The reaction was repeated on a 1.07mmol scale and 3 equivalents of TMSOTf (0.62ml) and $BH_3 \cdot SMe_2$ (3.21ml). The reaction was stirred at room temperature for 24 hours. The reaction was repeated on a 1mmol scale using THF as a solvent and 3 equivalents of TMSOTf and $BH_3 \cdot SMe_2$. The reaction was stirred at room temperature for 6 days.

1,5-anhydro-2,3,4,6-tetra-*O*-benzyl-D-glucitol **107**

$\nu_{max.}$ ($CHCl_3$) 3065, 3025, 3000, 2905, 2865, 1495, 1450, 1355, 1090, 1025, 750 and 695cm^{-1};

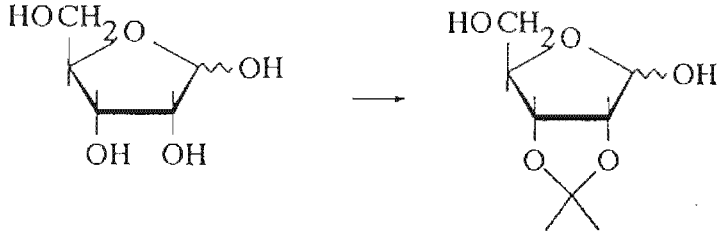
δ_H (200MHz) 3.20 (1H, m), 3.36 (1H, m), 3.51-3.71 (5H, m), 4.04 (1H, dd, *J* 4.5 and 11.2 Hz), 4.45-5.00 (8H, m, benzyl-CH_2), 7.11-7.35 (20H, m, Ph-H);

δ_C (50MHz) 68.1 and 68.9 (C-1 and C-6), 73.1, 73.5, 75.0 and 75.4 (benzyl-CH_2), 77.7, 78.4, 79.2 and 86.3 (C-2, C-3, C-4 and C-5), 127.5, 127.6, 127.7, 127.8, 128.3 and 128.4 (Ph-CH), 137.8, 138.1 and 138.7 (Ph-C).

m/z 524 (M^+, 0.1%), 433 (M^+-91, 13%), 342 (4%), 181 (17%) and 91 (100%);

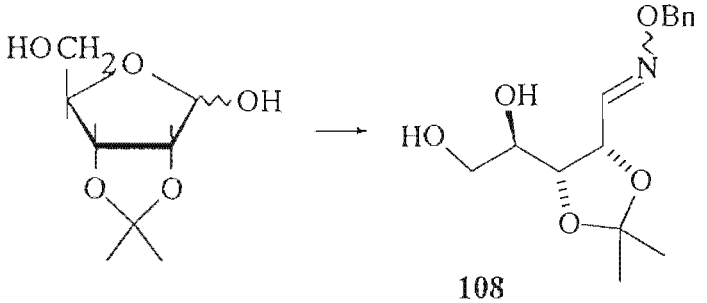
Found *M^+-91*, 433.2052. $C_{27}H_{29}O_5$ requires *M-91*, 433.2027.

6.5.16. Synthesis of 2,3-*O*-Isopropylidene-D-ribose



To a suspension of D-ribose (5.0g, 33mmol) in acetone (150ml) at 0°C was added conc. H_2SO_4 (1ml, 18mmol). Once the solid was all dissolved the reraction was stirred for a further hour before being quenched with a solution of KOH (1.7g, 35mmol) in methanol (20ml). The volume of solvent was reduced *in vacuo* and standard workup (H_2O, ethyl acetate) afforded crude 2,3-*O*-isopropylidene-D-ribose (6.15g, 97%) which was used further without purification.

6.5.17. Formation of 1-(*O*-benzyloxyimino)-2,3-*O*-isopropylidene-D-ribose



108

To a solution of 2,3-*O*-isopropylidene-D-ribose (6.0g, 31.6mmol) in pyridine (10ml) was added *O*-benzylhydroxyamine hydrochloride (5.5g, 3.5mmol). The mixture was stirred at room temperature for 18 hours before an icecold solution of HCl (approx. 5M) was added until the mixture became acidic. The product was extracted into ethyl acetate (3x50ml) and the organic phase washed with a saturated solution of $NaHCO_3$ (50ml) before being dried over $MgSO_4$, filtered and evaporated to afford the crude product (11.6g) which was purified by chromatography (ethyl acetate, methanol). This yielded 1-*O*-benzyloxyimino-2,3-*O*-isopropylidene-D-ribose **108** (7.9g, 85%) as a white solid and a

a mixture of geometrical isomers, (mp. 85-88°C, recrystallised from pet ether, ethyl acetate) (Found: C, 60.8; H, 7.1; N, 4.7. $C_{15}H_{21}NO_5$ requires C, 61.0; H, 7.1; N, 4.7%)

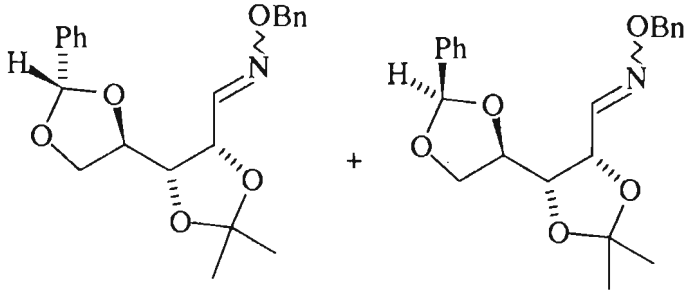
δ_H (200MHz) 1.34 (3H, s, H-1', major and minor), 1.44 (3H, s, H-1', major), 1.47 (3H, s, H-1', minor), 2.60 (1H, br.s., -OH), 3.05 (1H, br.s., -OH), 3.62 (3H, m), 4.13 (1H, dd, *J* 6.3 and 8.5 Hz, major), 4.24 (1H, t, *J* 1.6 and 5.9 Hz, minor), 4.75 (1H, t, *J* 6.7 Hz, major and minor), 5.09 (2H, s, Bn-CH_2 of major), 5.13 (2H, d, *J* 2.8 Hz, Bn-CH_2 of minor), 5.28 (1H, t, *J* 6.2 Hz, minor), 6.90 (1H, d, *J* 5.6 Hz, H-1, minor), 7.33 (5H, m, Ph-H), 7.52 (1H, d, *J* 7.3 Hz, H-1 major);

δ_C (50MHz), major: 25.3 and 27.6 (C-1'), 63.9 (C-5), 69.6 (C-4), 74.9 and 77.6 (C-2 and C-3), 76.0 (Bn-CH_2), 110.0 (C-2'), 127.8, 128.1, 128.3 and 136.9 (Ph-C), 148.6 (C-1);

δ_C (50MHz), minor: 25.0 and 27.3 (C-1'), 63.7 (C-5), 70.5, 71.5 and 78.4 (C-2, C-3, C-4), 76.8 (Bn-CH_2), 109.6 (C-2'), 127.8, 128.1, 128.3 and 136.2 (Ph-C);

m/z 280 (M^+-15, 1%), 173 (5%) and 91 (100%).

6.5.18. Acetalisation of 1-benzyloxyimino-2,3-*O*-isopropylidene-D-ribose



isomers 109 & 110

To a solution of 1-benzyloxyimino-2,3-*O*-isopropylidene-D-ribose (2.55g, 8.6mmol) and 1,1-dimethoxyphenylmethane (1.55ml, 10.4mmol) in CH_2Cl_2 at -78°C was added

$BF_3{\cdot}OEt_2$ (1.28ml, 10.4mmol) and the solution allowed to warm to -20°C over 4 hours. It was then quenched with a solution of KOH (0.85g, 15mmol) in methanol (10ml). H_2O was added and the product extracted with ethyl acetate (3x50ml). The organic fractions were dried, filtered and evaporated. The crude products were separated by column chromatography to give a minor product **109** and **110** (0.515g, 17%), a major product (1.30g, 39%) and starting material (0.740g, 29%)

109 and **110**:

$\nu_{max.}$ 2990, 2935, 2880, 1495, 1450, 1381, 1370, 1240, 1220, 1090, 1065, 1025, 980 and 695cm^{-1}

δ_H (200MHz) 1.37 and 1.49 (6H, s, isopropylidene-CH_3), 3.92-5.39 (5H, m, C-2, C-3, C-4, C-5), 5.13 (2H, d, *J* 2.2 Hz, Bn-CH_2), 5.74, 5.78, 5.96 and 5.98 (1H, 4s, benzylidene-CH of 4 isomers), 6.88 (1H of 1 isomer, d, *J* 5.1 Hz, H-1), 6.92 (1H of 1 isomer, d, *J* 5.4 Hz, H-1), 7.31 (10H, m, Ph-H), 7.53 (1H of 1 isomer, d, *J* 8.1 Hz, H-1), 7.59 (1H of 1 isomer, d, *J* 8.1 Hz, H-1);

δ_C (50MHz) 25.4 and 27.7 (isopropylidene-CH_3), 68.2 and 68.5 (C-5), 73.6, 74.0, 75.0, 78.3 and 78.4 (C-2, C-3 and C-4), 76.4 (benzyl-CH_2), 104.0, 104.4 and 104.5 (benzylidene-CH), 109.7 and 110.0 (isopropylidene-C), 126.2, 126.4, 126.8, 127.9, 128.0, 128.2, 128.3, 128.4, 129.1 and 129.3 (Ph-CH), 137.1, 137.3 and 137.9 (Ph-C), 146.7 and 147.9 (C-1)

m/z 383 (M^+, 0.2%), 292 (M^+-91, 2%), 247 (1%), 181 (2%), 149 (18%), 105 (13%), 91 (100%), 77 (11%) and 43 (15%);

Found: M^+, 383.1725. $C_{22}H_{25}NO_5$ requires *M*, 383.1733.

major product, mp:121-126°C:

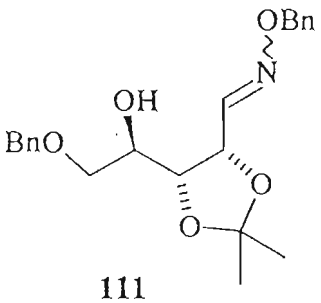
$\nu_{max.}$ 3065, 3005, 2955, 2935, 2870, 1495, 1450, 1381, 1372, 1270, 1230, 1205, 1200, 1155, 1110, 1095, 1055, 1015, 915, 855, 750 and 695cm^{-1};

δ_H (200MHz) 1.36 and 1.54 (6H, m, isopropylidene-CH_3), 3.60-5.38 (8H, m), 6.89-7.90 (11H, m, Ph-H and C-1);

m/z 383 (M^+, 1%), 292 (M^+-91, 5%), 247 (12%), 181 (5%), 157 (4%), 105 (15%), 91 (100%), 85 (13%), 77 (22%), 69 (16%), 59 (15%) and 43 (42%);

Found: M^+, 383.1718, $C_{22}H_{25}NO_5$ requires *M*, 383.1733.

6.5.19. Reduction of **109** and **110**



111

To a solution of **109** and **110** (0.1586g, 0.41mmol) in CH_2Cl_2 at -78°C were added TMSOTf (0.16ml, 0.82mmol) and $BH_3 \cdot SMe_2$ (0.82ml, 0.82mmol). After 2.5 hours at -78°C the reaction was quenched with a saturated solution of $NaHCO_3$ and standard workup ($NaHCO_3$, ethyl acetate) resulted in a crude product which was purified by column chromatography (pet ether:ethyl acetate) to yield 5-*O*-benzyl-1-*O*-benzylhydroxyimino-2,3-*O*-isopropylidene-D-ribose **111** (98.7mg, 62%).

$\nu_{max.}$ 3460, 3060, 2990, 2930, 2830, 2865, 1600, 1495, 1450, 1380, 1370, 1220, 1065, 1010, 860, 730 and 695cm^{-1};

δ_H (200MHz) 1.35 and 1.44 (6H, 2s, isopropylidene-$CH_3$0, 2.53 (1H, of major, br.d, -OH), 2.72 (1H of minor, br.d., -OH), 3.55 (1H of major, dd, *J* 6.3 and 9.7 Hz, H-5), 3.50-3.64 (2H, of minor, m, H-5), 3.69 (1H of major, dd, *J* 2.9 and 9.7 \, H-5), 3.82 (1H of major and minor, m, H-4), 4.18 (1H of major, dd, *J* 6.1 and 8.9 Hz, H-3), 4.32 (1H of minor, dd, *J* 6.4 and 7.7 Hz, H-3), 4.55 (2H, of major and minor, s, 5-Bn-CH_2), 4.77 (1H of major, dd, *J* 6.1 and 7.5 Hz, H-2), 5.10 (2H of major, s, oxime benzyl-CH_2), 5.12 (2H of minor, ab system, *J* 1.6 Hz, oxime benzyl-CH_2), 5.32 (1H of minor, t, *J* 6.2 Hz, H-2), 6.90 (1H of minor, d, *J* 6.0 Hz, H-1), 7.33 (10h, m, Ph-H), 7.53 (1H of major, d, 7.5 Hz, H-1); The spectrum was repeated in DMSO-d_6: exchangeable signals: 5.05 (1H of minor, d, *J* 6.0 Hz, -OH), 5.14 (1H of major, d, *J* 6.0 Hz, H-1);

δ_C (50MHz) major isomer: 25.4 and 27.7 (isopropylidene-CH_3), 68.7 (C-4), 71.4, 73.4 and 76.4 (C-5 and benzyl-CH_2), 75.2 and 76.6 (C-2 and C-3), 110.0 (isopropylidene-C), 127.2, 127.3, 127.6, 127.7, 127.8, 128.1 and 128.2 (Ph-CH), 137.5 and 138.4 (Ph-C), 147.8 (C-1); minor isomer: 25.2 and 27.5 (isopropylidene-CH_3), 69.8 (C-4), 71.3 and 78.1 (C-2 and C-3), 71.3, 73.4 and 76.7 (C-5 and Bn-CH_2), 109.6 (isopropylidene-C), 127.2, 127.3, 127.6, 127.7, 127.8, 128.1 and 128.2 (Ph-CH), 136.9 and 137.9 (Ph-C), 150.1 (C-1);

m/z 385 (M^+,, 0.1%), 370 (M^+-15, 0.2%), 294 (M^+-91, 0.3%), 107 (11%), 91 (100%), 79 (14%), 77 (12%) and 43 (13%);

Found: M^+, 385.1878. $C_{22}H_{29}NO_5$ requires *M* 385.1889.

References:

1. (a) Brown, H.C. In "*Boranes in Organic Chemistry*", Cornell University Press, Ithaca, New York, **1972**. (b) Pelter, A.; Smith, K.; Brown, H.C. In "*Borane Reagents, Best Synthetic Methods"* Academic Press, London, **1988**, pp.125-164.
2. For an example of intramolecular hydroboration: Still, W.C.; Darst, K.P. *J. Am. Chem. Soc.* **1980,** *102*, 7387-7389.
3. For general reviews on the chemistry of acetals, see: (a) Meerwein, H. In *Houben-Weyl: Methoden der organischen Chemie,* Müller, E.; Ed.; Georg Thieme Verlag: Stuttgart, **1965**; Band VI/3a, pp 199-204. (b) Schmitz, E.; Eichorn, I. In *The Chemistry of the Ether Linkage;* Patai, S.; Ed.; Wiley: New York, **1967**; Chapter 7. (c) Bergstrom, R.G. In *Supplement E: The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulfur Analogues, Part 2;* Patai, S.; Wiley: New York, **1980;** Chapter 20.
4. Green, T.W. In *Protective Groups in Organic Synthesis;* Wiley-Interscience: New York, **1981**, pp 116-141.
5. Meskens, F.A.J. *Synthesis,* **1981,** 501-522
6. (a) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1979,** *21*, 1357-1358. (b) Chan, T.H.; Brook, M.A.; Chaly, B.T. *Synthesis* **1983,** 203-205. (c) Sakurai, H.; Sasaki, K.; Hayashi, J.; Hosomi, A. *J. Org. Chem.* **1984,** *49*, 2808-2809.
7. Ford, K.L.; Roskamp, E.J. *Tetrahedron Lett.* **1992**, *33*, 1135-1138.
8. Sterzycki, R. *Synthesis* **1979,** 724-725.
9. (a) Westara, G.; Blomberg, C.; Bickelhaupt, F. *J. Organomet. Chem.* **1978,** *144,* 285. (b) Ishikawa, H.; Mukaiyama, T.; Ikeda, S. *Bull. Chem. Soc. Jpn.* **1981,** *54,* 776.
10. Review: (a) Mukaiyama, T.; Murakami, M. *Synthesis* **1987,** 1043. (b) Hosomi, A.; Endo, M.; Sakurai, H. *Chem. Lett.* **1976,** 941.
11. Doukas, H.M.; Fontaine, T.D. *J. Am. Chem. Soc.* **1951,** *73,* 5917.
12. Eliel, E.L.; Rerick, M.N. *J. Org. Chem.* **1958,** *23,* 1088.
13. Eliel, E.L.; Badding, V.G. *J. Am. Chem. Soc.* **1959,** *81,* 6087.

14. (a) Eliel, E.L.; Badding, V.G.; Rerick, M.N. *J. Am. Chem. Soc.* ***1962,*** *84,* 2371. (b) Eliel, E.L. *Red. Chem. Prog.* **1961,** *23,* 129. (c) Eliel, E.L.; Novak, B.E.; Daignauet, R.A.; Badding, V.G. *J. Org. Chem.* **1965,** *30,* 2441.

15. Eliel, E.L.; Pilato, L.A.; Badding, V.G. *J. Am. Chem. Soc.* **1962,** *84,* 2377.

16. Diner, U.E.; Davis, H.A.; Brown, R.K. *Can. J. Chem.* **1967,** *45,* 207.

17. Zakharkin, L.I.; Khorlina, I.M. *Bull. Acad. Sci. USSR, Div. Chem. Sci.,* **1959,** 2156. Takano, S.; Akiyama, M.; Saho, S.; Ogasawara, K. *Chem. Lett.,* **1983,** 1593.

18. Matsumura, Y.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1982,** *23,* 1929.

19. Maruoka, K.; Sakurai, M.; Yamamoto, H. *Tetrahedron Lett.* **1985,** *26,* 3853.

20. Abdun-Nur, A.R.; Issidorides, C.H. *J. Org. Chem.* **1962,** *27,* 67.

21. Bonner, T.G.; Lewis, D.; Rutter, K. *J. Chem. Soc., Perkin Trans I.* **1981,** 1807.

22. Shaozu, W.; Tianhui, R.; Ning, C.; Yulan, Z. *OPPI Briefs,* **1991,** *23,* 427.

23. Finholt, A.E.; Bond, A.C.; Schlesinger, H.I. *J. Am. Chem. Soc.* **1947,** *69,* 1199.

24. Ishihara, K.; Hanaki, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1991,** *113,* 7074-7075.

25. Frainnet, E.; Esclamadon, C. *Compt. rend.* **1962,** ***254,*** 1814.

26. (a) Loim, N.M.; Parnes, Z.N.; Vasil'eva, S.P.; Kursanov, D.N. *Zh. Org. Khim.* **1972,** *8,* 896. (b) For a review on the ionic hydrogenation with silanes, see Kursanov, D.N.; Parnes, Z.N.; Loim, N.M. *Synthesis* **1974,** 633.

27. Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1979,** *21,* 4679-4680.

28. Mori, A.; Ishihara, K.; Yamamoto, H. *Tetrahedron Lett.* **1986,** *27,* 987-990.

29. Olah, G.A.; Yamato, T.; Iyer, P.S.; Prakash, G.K.S. *J. Org. Chem.* **1986,** *51,* 2826.

30. Sato, T.; Otera, J.; Nozaki, H. *J. Am. Chem. Soc.* **1990,** *112,* 901.

31. Nutaitis, C.F.; Gribble, G.W. *Org. Prep. Proc. Int.* **1985,** *17,* 11-16.

32. Horne, D.A.; Jordan, A. *Tetrahedron Lett.* **1978,** *16,* 1357.

33. Kotsuki, H.; Ushio, Y.; Yoshimura, N.; Ochi, M. *J. Org. Chem.* **1987,** *52,* 2594.

34. Fleming, B.; Bolker, H.I. *Can. J. Chem.* **1974,** *52,* 888.

35. Guindon, Y.; Girard, Y.; Berthiaume, S.; Gorys, V.; Lemieux, R.; Yoakim, C. *Can. J. Chem.* **1990,** *68,* 897.

36. Guindon, Y.; Morton, H.E. *J. Org. Chem.* **1985,** *50,* 5379.

37. (a) Köster, R.; Penades-Ullate, S.; Dahlhoff, W.V. *Angew. Chem. Int. Ed. Engl.* **1985,** *24,* 6, 519. (b) Bernabe, M.; Martin-Lomas, M.; Penades, S.; Köster, R.; Dahlhoff, W.V. *J. Chem. Soc., Chem. Comm.* **1985,** 1001. (c) Dahlhoff, W.V. *Z. Naturforsch.* **1988,** *43b,* 136. (d) Dahlhoff, W.V.; Imre, J.; Köster, R. *Macromolecules* **1988,** *21,* 3342. (e) Dahlhoff, W.V. *Z. Naturforsch.*, **1989,** *44b,* 1105. (f) Dahlhoff, W.V. *Liebigs Ann. Chem.* **1990,** 811.

38. Sigmund, F.; Marchart, G. *Monatsh.* **1927,** *48,* 267.

39. Gorin, P.A.J. *J. Org. Chem.* **1959,** *24,* 49.

40. Howard, W.L.; Brown, J.H., Jr. *J. Org. Chem.* **1961,** *26,* 1026.

41. Abell, A.D.; Massy-Westropp, R.A. *Tetrahedron* **1985**, *41*, 2451-2464 and references cited therein.

42. Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1990,** *1,* 477.

43. (a) Johnson, W.S.; Harbert, C.A.; Stipanovic, R.D. *J. Am. Chem. Soc.* **1968**, *90*, 5279-5280. (b) Johnson, W.S.; Harbert, C.A.; Ratcliffe, B.E.; Stipanovic, R.O. *J. Am. Chem. Soc.* **1976**, *98*, 6188-6193. (c) Bartlett, P.A.; Johnson, W.S.; Elliott, J.D. *J. Am. Chem. Soc.* **1983,** *105,* 2088.

44. Johnson, W.S.; Crackett, P.H.; Elliott, J.D.; Jagodzinski, J.J.; Lindell, S.D.; Natarajan, S. *Tetrahedron Lett.* **1984,** *25,* 3951.

45. (a) Elliott, J.D.; Choi, V.M.F.; Johnson, W.S. *J. Org. Chem.* **1983,** *48,* 2295. (b) Johnson, W.S.; Edington, C.; Elliott, J.D.; Silverman, I.R. *J. Am. Chem. Soc.* **1984,** *106,* 7588. (c) Lindell, S.D.; Elliott, J.D.; Johnson, W.S. *Tetrahedron Lett.* **1984,** *25,* 3947. (d) Choi, V.M.F.; Elliott, J.D.; Johnson, W.S. *Tetrahedron Lett.* **1984,** *25,* 591. (e) Elliott, J.D.; Steele, J.; Johnson, W.S. *Tetrahedron Lett.* **1985,** *26,* 2535. (f) Silverman, R.I.; Edington, C.; Elliott, J.D.; Johnson, W.S. *J. Org. Chem.* **1987,** *52,* 180.

46. McNamara, J.M.; Kishi, Y. *J. Am. Chem. Soc.* **1982,** *104,* 7371.

47. (a) For copper nucleophiles: Ghribi, A.; Alexakis, A.; Normant, J.F. *Tetrahedron Lett.* **1984,** *25,* 3075. (b) Ghribi, A.; Alexakis, A.; Normant, J.F. *Tetrahedron Lett.* **1984,** *25,* 3083.

48. Richter, W.J. *J. Org. Chem.* **1981**, *46*, 5119-5124.

49. Omura, K.; Shama, A.K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 957-962.

50. Denmark, S.E.; Almstead, N.G. *J. Am. Chem. Soc.* **1991**, *113*, 8089. See also: Sammakia, T.; Smith, R.S. *J. Org. Chem.* **1992**, *57*, 2997-3000.

51. (a) Denmark, S.E.; Wilson, T.; Willson, T.M. *J. Am. Chem. Soc.* **1988**, *110*, 984. (b) Denmark, S.E.; Willson, T.M.; Almstead, N.G. *J. Am. Chem. Soc.* **1989**, *111*, 9258.

52. Yamamoto, Y.; Nishii, S.; Yamada, J. *J. Am. Chem. Soc.* **1986**, *108*, 7116.

53. Mori, I.; Ishihara, K.; Flippin, L.A.; Nozaki, K.; Yamamoto, H.; Bartlett, P.A.; Heathcock, C.H. *J. Org. Chem.* **1990**, *55*, 6107.

54. Denmark, S.E.; Willson, T.M. *J. Am. Chem. Soc.* **1989**, *111*, 3475.

55. Denmark, S.E.; Almstead, N.G. *J. Org. Chem.* **1991**, *56*, 6485.

56. Ishihara, K.; Mori, A.; Yamamoto, H. *Tetrahedron* **1990**, *46*, 4595.

57. This is published in part: Hunter, R.; Bartels, B.; Michael, J.P. *Tetrahedron Lett.* **1991**, *32*, 1095-1098.

58. Hunter, R,; Tomlinson, G.D. *Tetrahedron Lett.* **1989**, *30*, 2013.

59. Maria, P-C.; Gal, J-F. *J. Phys. Chem.*, **1985**, *89*, 1296-1304.

60. Pelter, A.; Smith, K. In "*Comprehensive Organic Synthesis*" **1979** Vol 3, Pergamon, Oxford pp 689-940.

61. Leggetter, B.E.; Diner, U.E.; Brown, R.K. *Can. J. Chem.* **1964**, *42*, 2113.

62. Gelas, J. *Adv. Carbohydr. Chem. Biochem.* **1981**, *39*, 71.

63. (a) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885. (b) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 889. (c) Classon, B.; Garegg, P.J.; Samuelsson, B.; *Acta Chem. Scand.* **1984**, *B 38*, 419-422.

64. Hébert, N.; Beck, A.; Lennox, R.B.; Just, G. *J. Org. Chem.* **1992**, *57*, 1777-1783.

65. Reference 1 (b), pp246-248.

66. Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981**, *37*, 3899.

67. Block, In "*Reactions of Organosulfur Compounds*" Academic Press, New York, **1978.**

68. (a) Sato, T.; Otera, J.; Nozaki, H. *J. Org. Chem.* **1990**, *55*, 6116-6121. (b) Sato, T.; Okura, S.; Otera, J.; Nozaki, H. *Tetrahedron Lett.* **1987**, *28*, 6299-6302.

69. Leggetter, B.E.; Brown, R.K. *Can. J. Chem.* **1963**, *41*, 2671.

70. There are many reviews on this subject, For example: Nógrádi, M. In "*Stereoselective Synthesis*" **1987**, pp 105-148. VCH Verlagsgesellschaft.

71. Corey, E.J.; Bakshi, R.K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551-5553.

72. Corey, E.J.; Bakshi, R.K.; Shibata, S.; Chen, C-P.; Singh, V.K. *J. Am. Chem. Soc.* **1987**, *109*, 7925-7926.

73. Mori, A.; Furiwara, J.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1983**, *24*, 4581.

74. Mori, A.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1984**, *25*, 4421.

75. Mori, A.; Yamamoto, H. *J. Org. Chem.* **1985**, *50*, 5444.

76. Mori, A.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *J. Organomet. Chem.* **1985**, *285*, 83.

77. Ishihara, K.; Mori, A.; Arai, I.; Yamamoto, H. *Tetrahedron Lett.* **1986**, *26*, 983.

78. Mori, A.; Ishihara, K.; Arai, I.; Yamamoto, H. *Tetrahedron* **1987**, *43*, 755.

79. Roos, G.H.P.; Watson, M.C. *S. Afr. J. Chem.***1991**, *44*, 95.

80. Shoolery, J.N. *Prog NMR Spectroscopy*, **1977**, *11*, 79-93.

81. This has been published in part: Bartels, B.; Hunter, R. *J. Chem. Soc.; Perkin Trans. I* **1991**, 2887-2888.

82. Green, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis*, 2nd ed. Wiley: New York, 1991, Chapter2.

83. (a) Posner, G.H.; Oda, M. *Tetrahedron. Lett.* **1981**, *22*, 5003-5006. (b) Sekine, M.; Kume, A.; Hata, T. *Tetrahedron Lett.* **1987**, *22*, 3617-3620.

84. Yamada, S. *J. Org. Chem.* **1992**, *57*, 1591-1592.

85. Reginato, G.; Ricci, A.; Roelens, S.; Scapecchi, S. *J. Org. Chem.* **1990**, *55*, 5132-5139.

86. Ricci, A.; Roelens, S.; Vannuchi, A. *J. Chem. Soc., Chem. Comm.* **1985**, 1457.

87. David, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 643-663.

88. Pautard, A.M.; Evans Jr., S.A. *J. Org. Chem.* **1988**, *53*, 2300.

89. (a) Diner, U.E.; Brown, R.K. *Can. J. Chem.* **1967**, *45*, 2547. (b) Diner, U.E.; Brown, R.K. *Can. J. Chem.* **1967**, *45*, 1297.

90. Leggetter, B.E.; Brown, R.K. *Can. J. Chem.* **1964**, *42*, 990.

91. Leggetter, B.E.; Brown, R.K. *Can. J. Chem.* **1964**, *42*, 1005.

92.(a) Davis, H.A.; Brown, R.K. *Can. J. Chem.* **1971**, *49*, 2166. (b) Davis, H.A.; Brown, R.K. *Can. J. Chem.* **1971**, *49*, 2563.

93. Leggetter, B.E.; Brown, R.K. *Can. J. Chem.* **1966**, *43*, 1030.

94. (a) Haines, A.H. *Adv. Carbohydr. Chem. Biochem.* **1976**, *33*, 11-109. (b) Therisod, M.; Klibanov, A.M. *J. Am. Chem. Soc.* **1986**, *108*, 5638-5640.

95. (a) Holzapfel, C.W.; Koekemoer, J.M.; Marais, C.F.; Kuger, G.J.; Pretorius, J.A. *S. Afr. J. Chem.* **1982**, *35*, 80-88. (b) Holzapfel, C.W.; Koekemoer, J.M.; Marais, C.F. *S. Afr. J. Chem.* **1984**, *37*, 19. (c) Bredenkamp, M.W.; Holzapfel, C.W.; Toerien, F. *S. Afr. J. Chem.* **1991**, *44*, 97.

96. Hanessian, S. *Carbohydr. Res.* **1966**, *2*, 86.

97. Chrétien, F.; Khaldi, M.;, Chapleur, Y. *Synth. Comm.*, **1990**, *20*, 1589-1596.

98. Fischer, E. *Ber.* **1895**, *28*, 1145-1167.

99. (a) Bhattacharjee, S.A.; Gorin, P.A.J. *Can. J. Chem.* **1969**, *47*, 1195. (b) Bhattacharjee, S.S.; Gorin, P.A.J. *Can. J. Chem.* **1969**, *47*, 1207. (c) Gorin, P.A.J.; Finlayson, A.J. *Carbohydr. Res.* **1971**, *18*, 269.

100. (a) Lipták, A.; Jodal, I.; Nanasi, P. *Carbohydr. Res.* **1975**, *44*, 1. (b) Lipták, A. *Tetrahedron Lett.* **1976**, 3557. (c) Lipták, A. *Carbohydr. Res.* **1978**, *63*, 69. (d) Lipták, A.; Fügedi, P.; Nanasi, P. *Carbohydr. Res.* **1976**, *51*, C19. (e) Lipták, A.; Fügedi, P.; Nanasi, P. *Carbohydr. Res.* **1978**, *65*, 209. (f) Hajko, J.; Borbas, A.; Lipták, A.; Kajtar-Peredy. M. *Carbohydr. Res.* **1991**, *216*, 413.

101. (a) Garegg, P.J.; Hultberg, H.; Wallin, S. *Carbohydr. Res.* **1982**, *108*, 97. (b) Garegg, P.J.; Hultberg, H. *Carbohydr. Res.* **1981**, *93*, C10.

102. Guindon, Y.; Bernstein, M.A.; Anderson, P.C. *Tetrahedron Lett.* **1987**, *28*, 2225-2228.

103. Guindon, Y.; Anderson, P.C. *Tetrahedron Lett.* **1987,** *28,* 2485-2488.

104. Deslongchamps, P. In "*Stereoelectronic Effects in Organic Chem.*" **1983,** Pergamon Press, Oxford.

105. (a) Jun, J.G.; Gray, G.R. *Carbohydr. Res.* **1987,** *163,* 247-261. (b) Rolf, D.; Gray, G.P. *J. Am. Chem. Soc.* **1982,** *104,* 3539-3541.

106. (a) Johansson, R.; Samuelsson, B. *J. Chem. Soc. Perkin Trans. I* **1984,** 2371. (b) Joniák, D.; Kosiková, B.; Kosáková, L. *Collect. Czech. Chem. Comm.* **1978,** *43,* 769. For an application see (c) Pozsgay, V.; Brisson, J-R.; Jennings, H.J.; Allen, S.; Paulson, J.C. *J. Org. Chem.* **1991,** *56,* 3377-3385.

107. (a) Ghosh, K.A.; McKee, S.P.; Thompson, W.J. *J. Org. Chem.* **1991,** 6500-6503. (b) Freudenberg, K.; Wolf, A. *Ber.* **1927,** *66,* 232.

108. Ashry, E.S.H.E; Kilany, Y, Y.E.; Mousaad, A. *Carbohydr. Res.* **1987,** *163,* 265-268.

109. Cha, J.K.; Christ, W.J.; Kishi, Y. *Tetrahedron* **1984,** *40,* 2247-2255.

110. Wolfrom, M.L.; Thompson, A. *Methods Carbohydr. Chem.* **1963,** *2,* 427.

111. Valverde, S.; López, J.C.; Gómez, A.M.; Garcia-Ochoa, S. *J. Org. Chem.* **1992,** *57,* 1613-1615.

112. Blumberg, K.; Fucello, A.; van Es, T. *Carbohydr. Res.* **1979,** *70,* 217-232.

113. Audier, H.E.; Tabet, J.C.; Fetizon, M. *Helv. Chim. Acta* **1982,** *68,* 4, 903-911.

114. Hirth, G.; Barner, R. *Helv. Chim. Acta* **1982,** *65,* 3, 1059-1084.

115. Vogel's "Textbook of Practical Organic Chemistry" 5thed, Longman Scientific & Technical, pp653-657.