PHD

Synthesis Of The Herbicidin Glycoside

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SYNTHESIS OF THE HERBICIDIN GLYCOSIDE

Submitted by Nicholas John Newcombe

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To Jill

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ABSTRACT

Chapter 1 introduces C-glycosides and encompasses a review on methods available for introducing C-C bonds at the anomeric carbon of pyranoses. This is followed by an introduction to the herbicidin family of natural products and our proposed strategy for their synthesis.

The synthesis and reactivity of three related bridged 2-keto sugar derivatives (79a-c) is then described and their usefulness in C-glycoside synthesis evaluated. It was found that the ether-bridged system (79a) could be used to generate anionic reactivity at the "anomeric" carbon and this allowed the synthesis of various C-glycosyl derivatives.

Condensation of ketone (79a) with the furanoside aldehyde (122) gave enone (126) which, upon hydrogenation afforded diol (127), a compound possessing the core furo-pyrano-pyran ring system present in the herbicidins. This derivative could then be rapidly converted to methyl ester (145), the glycoside portion of the herbicidin class of natural products.

Ester (145) will hopefully prove to be a useful building block for elaboration to members of the herbicidin family.

ABBREVIATIONS

The following abbreviations are used in the text:

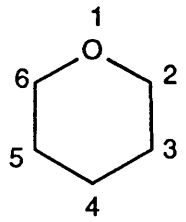
AB	AB quartet
Ac	acetyl
AIBN	azobisisobutyronitrile
Bn	benzyl
Boc	*tert*-butoxycarbonyl
b.p.	boiling point
br	broad
BTCEAD	bis(trichloroethyl)azodicarboxylate
Bu	butyl
Bz	benzoyl
cat.	catalytic
cf.	compare
m-CPBA	*meta*-chloroperbenzoic acid
C.I.	chemical ionisation
conc.	concentrated
d	doublet
DCC	dicyclohexyl carbodiimide
DCU	dicyclohexyl urea
DDQ	dichlorodicyano quinone
dec.	decomposition
DIBAL-H	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMPU	*N*,*N*'-dimethyl-*N*,*N*'-propylene urea

DMSO	dimethyl sulphoxide
$E^{\oplus}$	electrophile
E.I.	electron ionisation
Et	ethyl
FT	Fourier transform
HMPA	hexamethylphosphoric triamide
HOBT	hydroxybenztriazole
HPLC	high performance liquid chromatography
hυ	light
Im	imidazole
IR	infrared
Iso-but.	isobutane
J	coupling constant
LDA	lithium diisopropylamide
LDMAN	lithium-1-(dimethylamino) naphthalenide
Lit.	literature
LN	lithium napthalenide
LUMO	lowest unoccupied molecular orbital
m	multiplet
M	molar
M^+	molecular ion
Me	methyl
MHz	megahertz
m.p.	melting point
MPM	*p*-methoxyphenylmethyl
MS	mass spectrum
Ms	methanesulphonyl
n	straight chain
N	normal

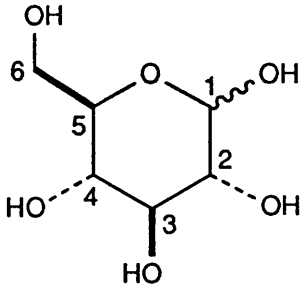
NMR	nuclear magnetic resonance
n.O.e.	nuclear Overhauser effect
Nu	nucleophile
p	para
PCC	pyridinium chlorochromate
Ph	phenyl
Pr	propyl
Py	pyridine
q	quartet
ref.	reference
r.t.	room temperature
s	singlet
s	secondary
SOMO	singly occupied molecular orbital
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
tert(*t*)	tertiary
Tf	trifluoromethanesulphonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
t.l.c.	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Ts	*para*-toluenesulphonyl
UV	ultraviolet
w	weak
Δ	heat
δ	chemical shift

NUMBERING CONVENTIONS

There are two numbering systems which are commonly used in the literature with regard to pyranose rings. The first is derived from tetrahydropyran nomenclature and labels the ring oxygen 1 as in Structure (I).

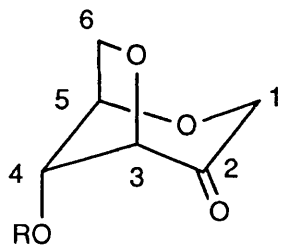


(I)

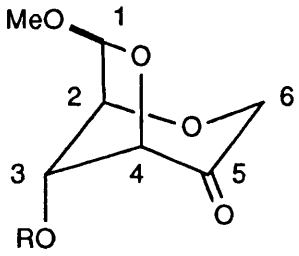


(II)

The second numbering convention used is based on carbohydrate nomenclature where the anomeric carbon is labelled 1 as in Structure (II). To simplify the following discussion the latter convention [i.e. Structure (II)] has been used throughout this thesis when referring to substituted pyran derivatives.



(79a)



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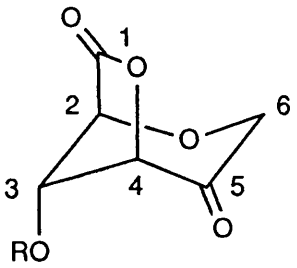
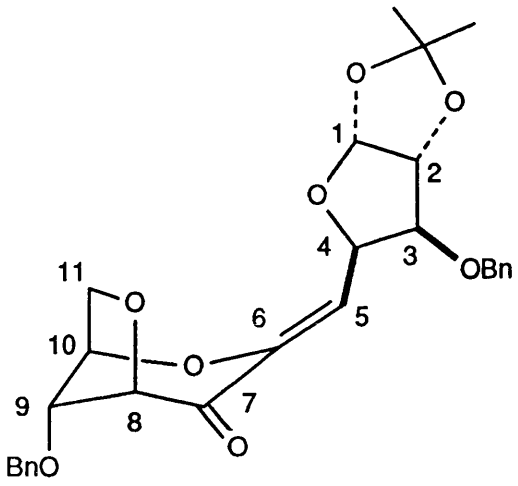


(79c)

The bridged bicyclic ketones (79a-c) are numbered according to their systematic names as illustrated below. Similarly, simple derivatives of these bridged systems are numbered based on this method.

The other numbering scheme used in this thesis is that derived from the numbering of the herbicidins[66] as illustrated.



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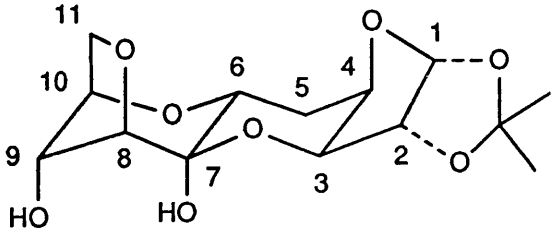


(127)

It should also be noted that the numbering systems above are the same as those used in the systematic naming of these derivatives.

When referring to a given structure the following abbreviations have been used.

C(1) - Carbon at position 1.

1-H - Proton at carbon 1.

5a-H - Proton at carbon 5 with axial (5e-H, equatorial) configuration.

These abbreviations have been used extensively in the Experimental Section when interpreting NMR spectra.

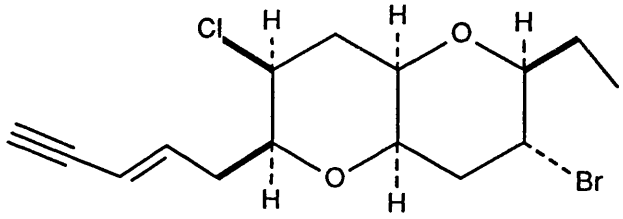
CONTENTS

1. INTRODUCTION

INTRODUCTION

1.1 THE IMPORTANCE OF C-GLYCOSIDES

Polyhydroxylated tetrahydropyrans bearing a carbon-bonded substituent at C(1) may be formally classified as C-pyranosides, or more generally C-glycosides. Such C-pyranosyl units constitute an important structural feature of a diversity of natural products including dactomelyne[1], which has a cis-fused pyranopyran ring system and palytoxin[2], possessing no less than eight C-pyranoside fragments. The structural complexity and biological properties of such naturally occurring C-pyranosides has led to considerable effort being directed towards their synthesis.

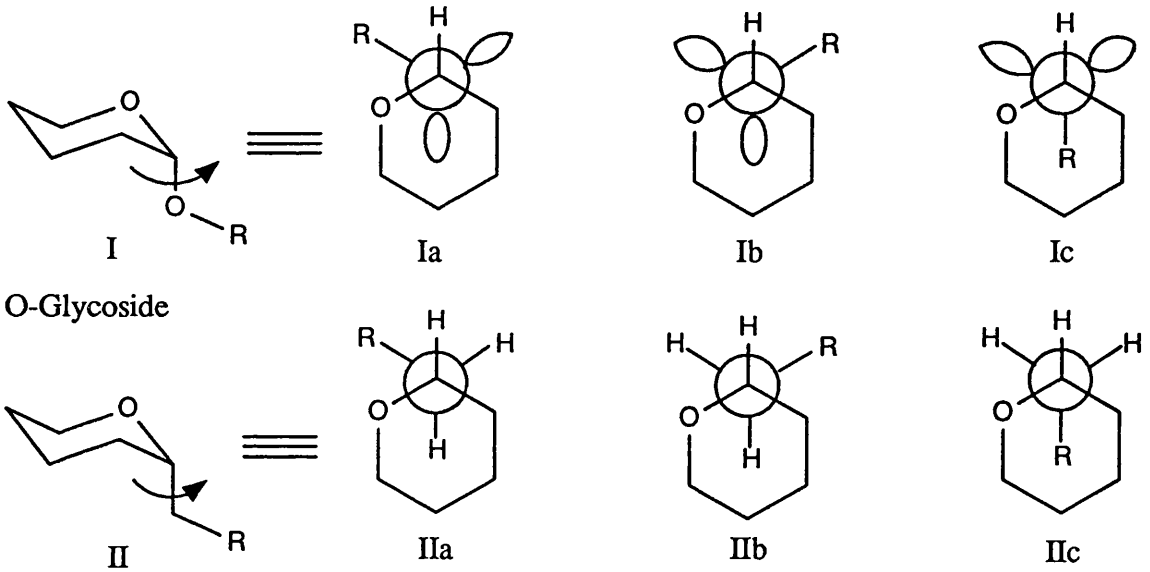


3(E)-Dactomelyne

Other areas of importance are the employment of C-glycosides as hydrolytically stable analogues of their parent O-glycosides and as conformational probes for oligosaccharide structures. This latter use has become very important recently since the role of glycoconjugates in the regulation of functions such as cell recognition, signal transduction and membrane transport is central to many areas of biology[3]. The possibility that such processes depend on the recognition of the three-dimensional structure of oligosaccharides has placed the conformational analysis of these units to the forefront of such studies[4]. However, due to the inherent difficulties in deriving reliable information about the solution conformations of oligosaccharides from experimental data alone this analysis remains elusive[5].

Kishi[6] has recently demonstrated, by application of the Karplus equation[7] to the protons of the C(1)-C(α) C-glycoside bond of simple C-glycosides, that the conformation about this bond is essentially identical to that adopted by the parent O-glycoside (Scheme 1).

Scheme 1



Conformers Ia and IIa are preferred.

These results show that the conformational behaviour of both O- and C-glycosides can be accounted for by steric effects as a first approximation, although the existence of a stereoelectronic stabilisation (the "exo-anomeric effect")[8] cannot be excluded in the oxygen case. Kishi has further extended this work to encompass C-disaccharides[9] and found that the observed conformational preference matched that obtained for simple C-glycosides.

These observations, showing the similarities in conformation between carbon-linked analogues and their parent O-glycosides, suggest that such carbon analogues may prove useful as experimental probes for the conformational analysis of

more complex oligosaccharides. This information will have an important part to play in our understanding of the diverse biological functions mediated by oligosaccharides.

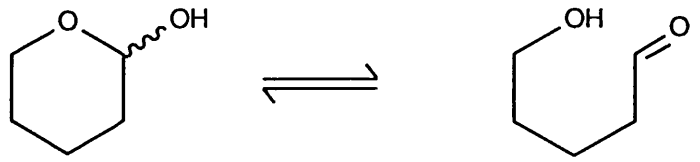
In summary, C-glycosides are important residues not only by virtue of their occurrence in many structurally diverse and biologically active natural products, but also because of their inherent potential as stable analogues of, and as tools for probing the conformations of biologically important oligosaccharides. The following section will discuss approaches to the synthesis of such C-glycosides.

1.2 SYNTHESIS OF C-GLYCOSIDES

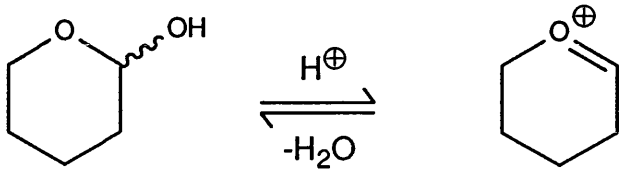
As previously mentioned, C-glycosides are important targets for synthesis due firstly to their biological importance, either as natural products or carbon analogues thereof, and secondly because many possess unique structural features making them interesting targets in their own right. Fortunately, useful reviews covering the areas of C-nucleosides,[10] polyether antibiotic synthesis[11] and the use of chain-extended carbohydrates as chiral templates[12] have appeared recently. This review will therefore concentrate on the methods available for the synthesis of C-pyranosides by the formation of a carbon-carbon bond at the anomeric centre of pyranoses and especially on the generation and reactivity of anions at the "anomeric site".

1.3 INTRODUCTION OF CARBON NUCLEOPHILES AT THE ANOMERIC CENTRE

The reactivity of the hemiacetal function of a pyranose is usually regarded as that of an electrophile. This is partly due to the aldehyde equivalence of the anomeric carbon (1), but also as a result of the ease with which the oxonium ion (2) can be generated. As a consequence of this reactivity, many methods for the introduction of a wide variety of carbon nucleophiles at the anomeric centre of pyranose rings have been developed.



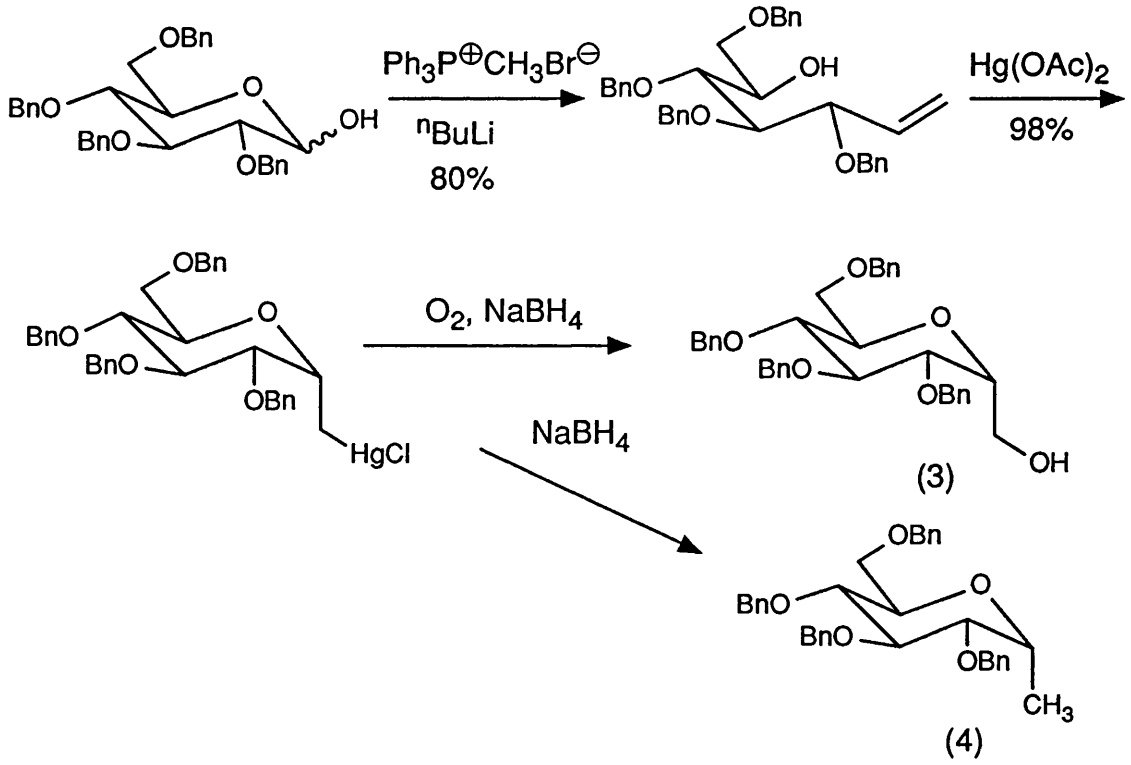
(1)



(2)

For example, the aldehyde reactivity of pyranoses has been exploited by the use of the Wittig reaction[13] to introduce the carbon substituent at the anomeric centre.

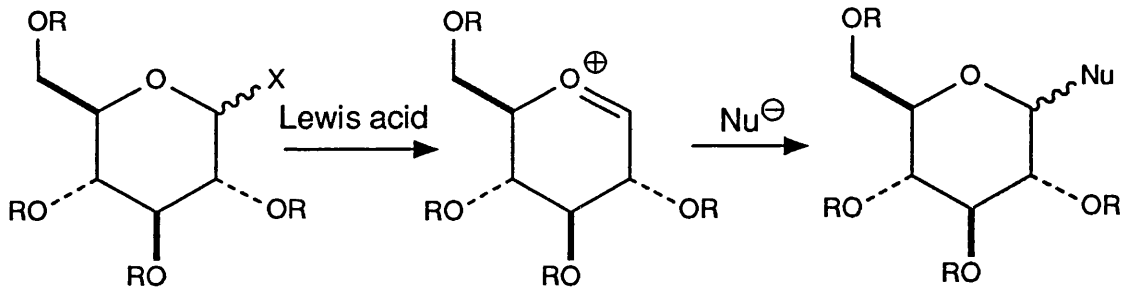
Scheme 2



Sinay[14] used the Wittig reaction to create a new carbon-carbon bond at C(1) and then a mercury(II)-mediated cyclisation regenerated the tetrahydropyran ring. This methodology provided a stereocontrolled route to the α-D-C-glycopyranosyl derivatives (3) and (4) shown in good overall yield (Scheme 2).

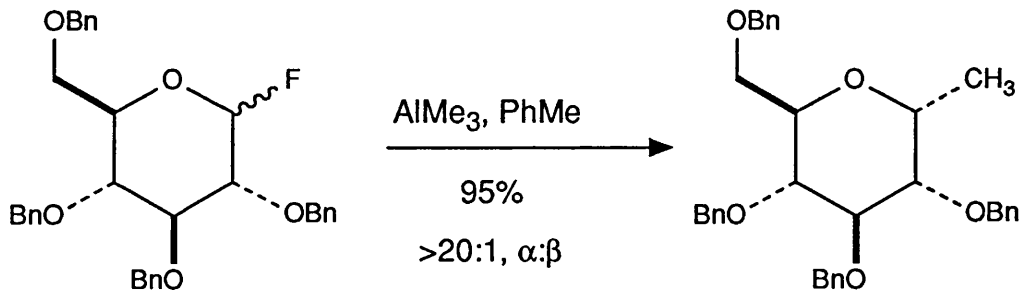
The reactivity of the oxonium ion (2) (above) can also be exploited directly for the synthesis of C-glycosides. In this respect, by analogy with O-glycoside terminology oxonium ion (2) can be regarded as a C-glycosyl donor, since reaction with a carbon nucleophile would give a C-glycoside. This reactivity is observed in the reaction of a glycosyl halide with a suitable carbon nucleophile such as an allyl silane or enol ether, often in the presence of a Lewis acid[15] (Scheme 3).

Scheme 3



Nicolaou[16] has demonstrated that glycosyl fluorides are useful substrates in these processes and are compatible with organoaluminium reagents[17] (Scheme 4).

Scheme 4

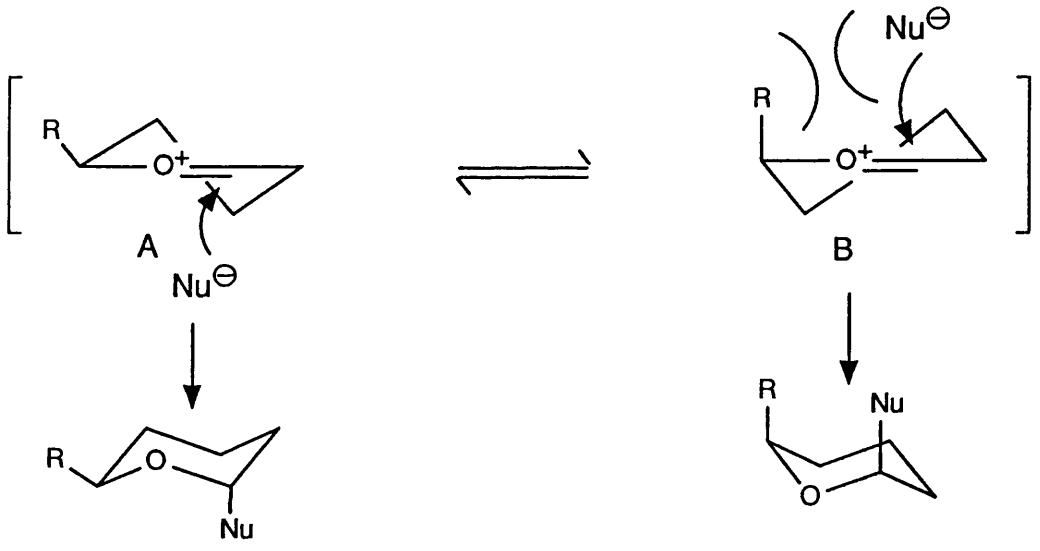


In general, these reactions give predominantly α-C-glycosides and in many cases the α-anomer is the sole product. Kishi[18] explained this selectivity by considering both electronic and steric factors, i.e.

1) A stereoelectronic effect whereby the nucleophile is introduced in an anti-periplanar orientation to one of the ring oxygen long pairs .

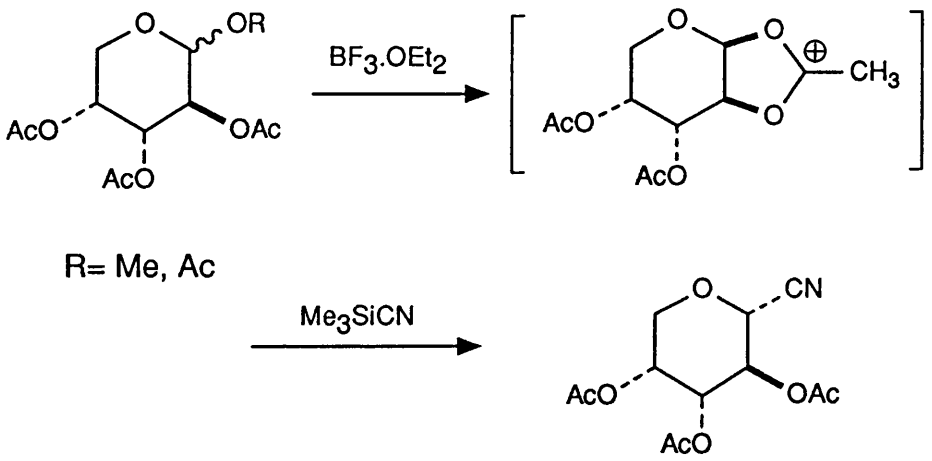
2) Steric hindrance, arising from the R group in conformer B (Scheme 5), thus providing compound (5), having the experimentally observed stereochemistry.

Scheme 5



The stereoselectivity of these reactions can also be controlled *via* neighbouring group participation of an acyl group at C(2) and this chemistry is well established[10]. An example of such a procedure is outlined below which shows that the intermediacy of an acetoxonium ion leads to the observed facial selectivity for the attack of the carbon nucleophile, in this case trimethylsilyl cyanide[19] (Scheme 6).

Scheme 6

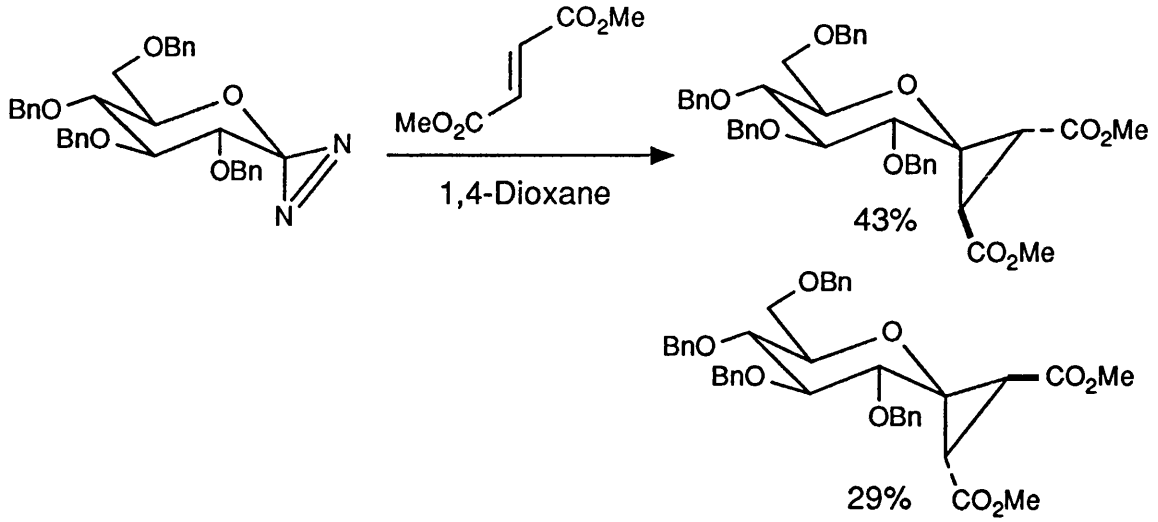


There are many other examples of the pyranose ring functioning as an electrophile and C-glycosides being formed by the attack of carbon nucleophiles[20]. However, an alternative strategy for carbon-carbon bond formation at the anomeric centre of pyranoses which is more relevant to this thesis is the generation of "umpolung" reactivity at C(1). That is, the generation of an anion or nucleophilic radical at the anomeric site which can then be reacted with a variety of carbon electrophiles to generate C-glycosides. More recently, Vasella[21] has demonstrated that carbenoid reactivity can also be obtained at C(1) and that such reactivity can be utilised in carbon-carbon bond formation. These alternative modes of reactivity will be discussed in the remainder of this review.

1.4 C-GLYCOSIDE SYNTHESIS USING ANOMERIC CARBENES

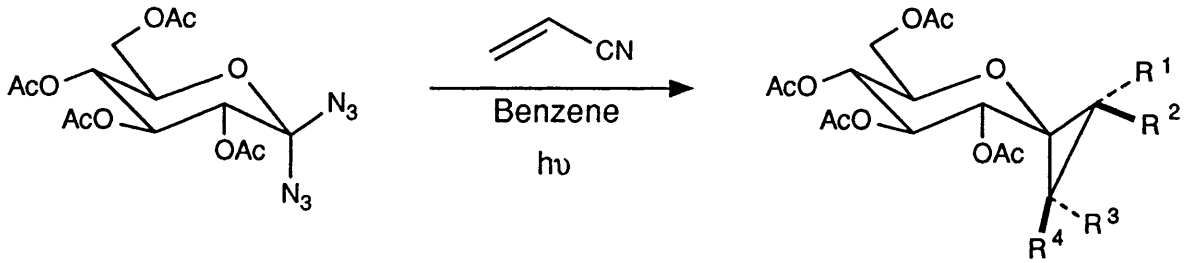
As eluded to in the previous section, the generation and reactivity of anomeric carbenes has recently been demonstrated. Vasella[21] has described the synthesis of glycosylidene derived diazirines and their use as precursors to anomeric carbenes. Such carbenes are expected to form spirocyclopropanes by cycloaddition to acceptor substituted alkenes which is indeed the case (Scheme 7).

Scheme 7



Descotes[22] has also demonstrated this cycloaddition reaction of an anomeric carbene with, in this case, acrylonitrile (Scheme 8). Photolysis of the anomeric diazide (7) in the presence of acrylonitrile thus afforded the four possible diastereomeric anomeric cyclopropanes (8a-d). An extension of this work has recently been published that utilises the sodium salt of D-glucono-1,5 -lactone tosylhydrazone as a more convenient source of the required carbenoid intermediate[23].

Scheme 8



(7)

(8) a. R^1=CN, R^2=H, R^3=H, R^4=H
b. R^1=H, R^2=CN, R^3=H, R^4=H
c. R^1=H, R^2=H, R^3=CN, R^4=H
d. R^1=H, R^2=H, R^3=H, R^4=CN

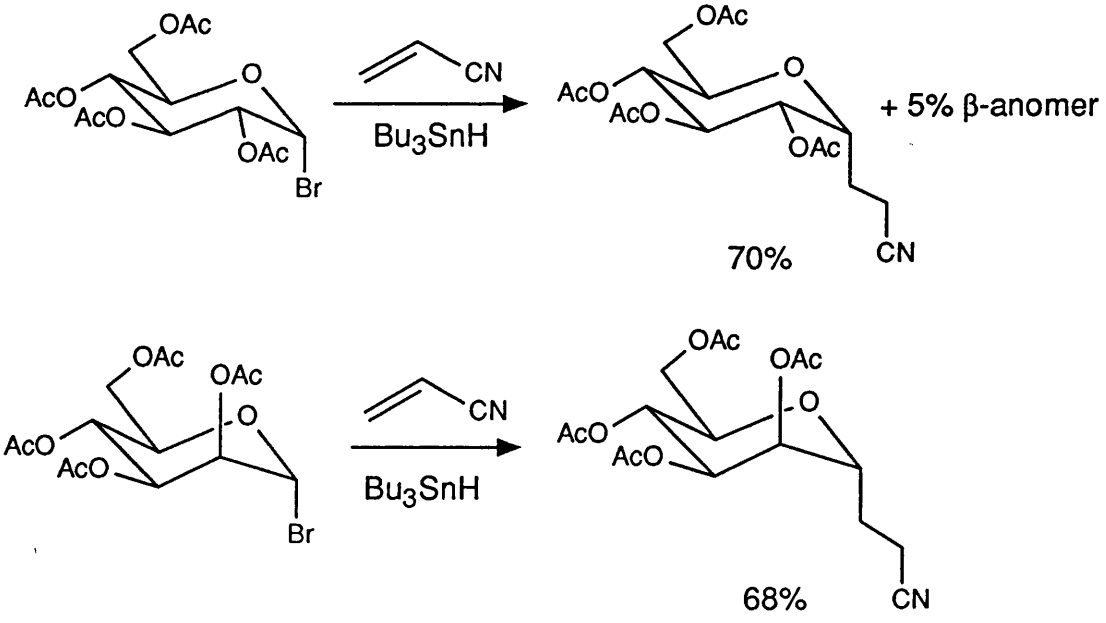
To date, the reactivity of such anomeric carbenes as a method for C-glycoside formation is limited to the synthesis of anomeric spirocyclopropane derivatives.

1.5 GENERATION AND REACTIVITY OF FREE RADICALS AT THE ANOMERIC CARBON

The use of radicals for the formation of carbon-carbon bonds is widespread in organic synthesis and the reactivity displayed by these species often gives rise to differences in chemo- and regioselectivity compared to that of the corresponding ionic reaction[24]. Hence, the formation of carbon-carbon bonds at the anomeric centre of pyranoses *via* a radical at C(1) has been extensively studied.

Such anomeric radicals are most often generated from the corresponding glycosyl bromide or chloride *via* photolysis or thermolysis in the presence of tributyltin hydride[25]. The anomeric radical so generated can then be trapped with a suitable carbon electrophile, common examples being acrylonitrile and enones (Scheme 9).

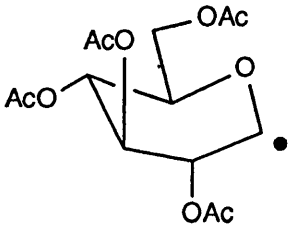
Scheme 9



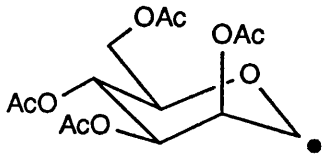
It is well known that a radical generated at the anomeric site is nucleophilic in nature[26]. This is due to the π-donor effect of the neighbouring alkoxy residue (i.e. the ring oxygen) overcoming the inductive, electron-withdrawing effect of this oxygen. This can

best be explained by a planar structure of the alkoxyalkyl radical in which the interaction of the singularly occupied molecular orbital (SOMO) of the radical carbon atom with the orbitals of the alkoxy group is most effective. Thus, such anomeric radicals display nucleophilic character at C(1) compared to pyranoses which are generally electrophilic at the anomeric carbon, that is anomeric radicals possess a level of "umpolung" reactivity.

As illustrated in Scheme 9, C-glycosides having the α-configuration at C(1) were the major products obtained from the alkylation of both glucose and mannose-derived C(1) radicals[25]. This selectivity can be explained by considering the preferred conformations of the corresponding glucosyl (9) and mannosyl (10) radical species.



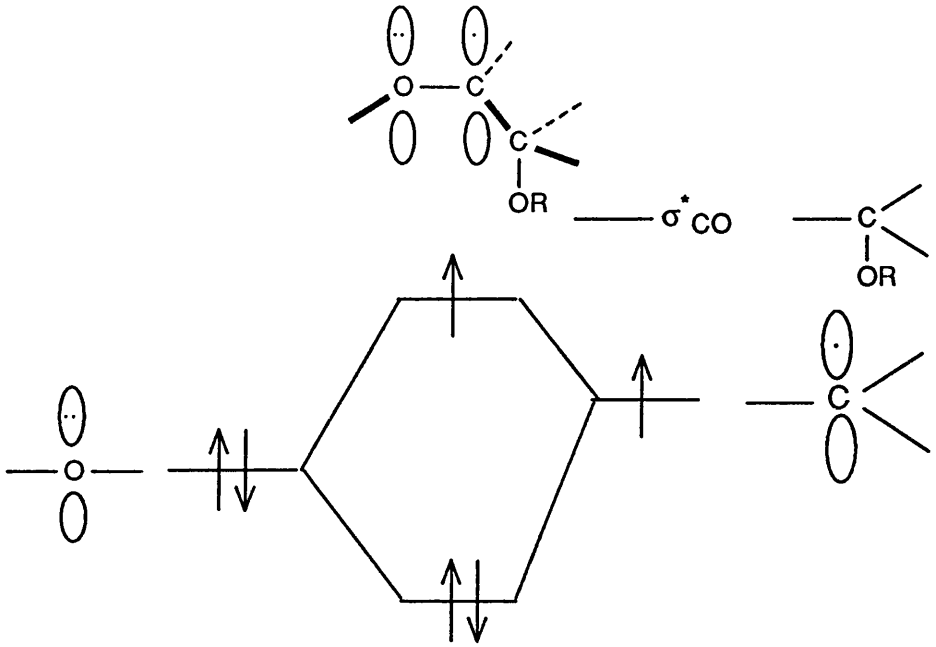
(9)



(10)

The mannosyl radical (10) exists in the chair form as shown. In this case approach of the electrophilic component is axial, since the overlap between the unpaired electron (or the newly formed bond) and the non-bonded electron pair on oxygen previously mentioned is maintained. The glucosyl radical (9), however, prefers to exist in a boat conformation which again leads to α-products *via* the "exo-anomeric" effect. The preferred conformations of these radicals were obtained by Giese using ESR and this work suggested that these radicals are stabilised by the effect of β-CO bonds[27] (Scheme 10).

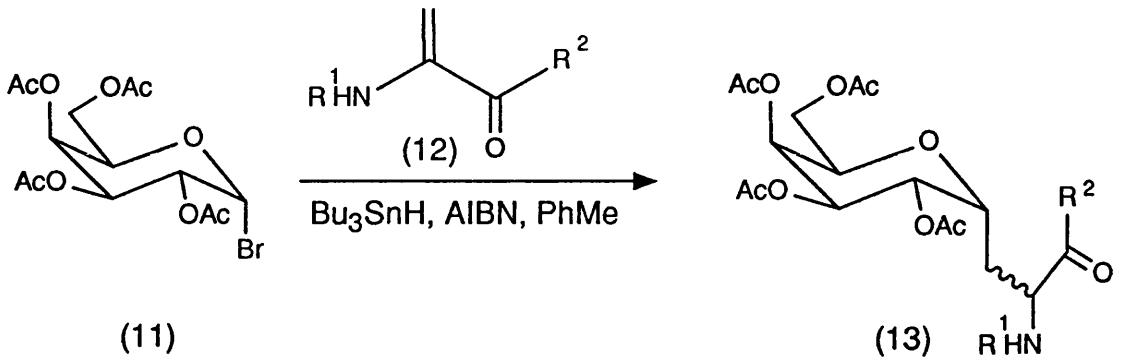
Scheme 10



As previously mentioned the SOMO of the anomeric radical overlaps with the non-bonded electron pair on the ring oxygen. This results in a higher SOMO energy, making the stabilising interaction of this SOMO with the LUMO of the neighbouring axial carbon-oxygen σ-bond possible. It is this extra stabilisation which overcomes the steric repulsion which occurs during the chair-boat interconversion of the glucosyl radical (9)[28]. In the case of the mannosyl radical (10) no conformational change is necessary since the acetoxy group at C(2) is axial.

The use of glycosyl radicals for the stereoselective synthesis of α-C-glycosides has recently been extended to the production of C-disaccharides and Kessler[29] has also demonstrated the application of this method to the formation of C-glycopeptides (Scheme 11).

Scheme 11



R^1=Boc, R^2=OBz; 3.8:1, R:S

Treatment of various glycosyl bromides such as the galactose example (11) with dehydroalanine derivatives (12) in the presence of AIBN and tributyltin hydride afforded the diastereomeric C-glycopeptides (13) shown with predominantly α-stereochemistry at the anomeric centre. Although this selectivity is high, the stereochemical induction at the β-carbon was less efficient, the best selectivity obtained being 3.8:1 (R:S).

In summary, glycosyl radicals are useful precursors for the synthesis of C-glycosides having the α-configuration, although their usefulness is limited by the range of electrophiles that can be used and by the fact that the corresponding β-anomers cannot easily be obtained.

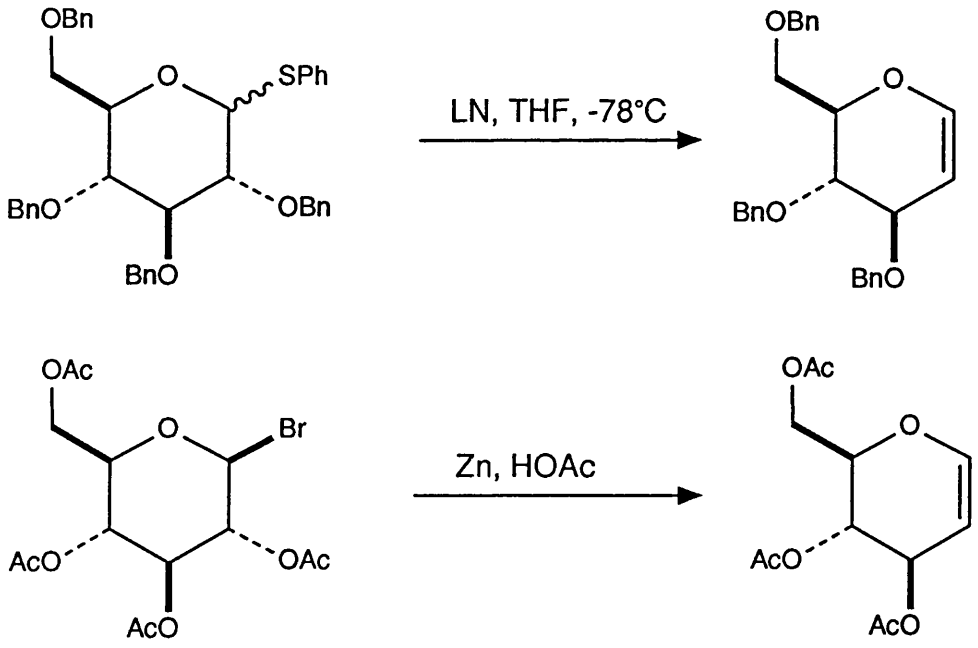
1.6 ANIONIC REACTIVITY AT THE ANOMERIC CENTRE

Of direct relevance to our programme of research is the generation of anionic reactivity at the anomeric centre of pyranoses and the remainder of this review will concentrate on this topic. Such an anomeric anion could, in principle be generated through lithiation of the corresponding tetrahydropyran with a strong alkyl lithium base, since it is well known that the acidity of a proton on an sp^3 hybridised carbon is increased by an α-heteroatom. Lehn[30] has attributed this increase in C-H acidity to the polarisation

effect of the α-oxygen atom due to the high electronegativity of oxygen. However, such a procedure has been shown to be unsuitable, since the relatively high temperature required to deprotonate the cyclic ether and generate the sp^3 alkyl lithium species resulted in the decomposition of this latter moiety[31]. Milder methods for the formation of such anomeric anions are therefore required.

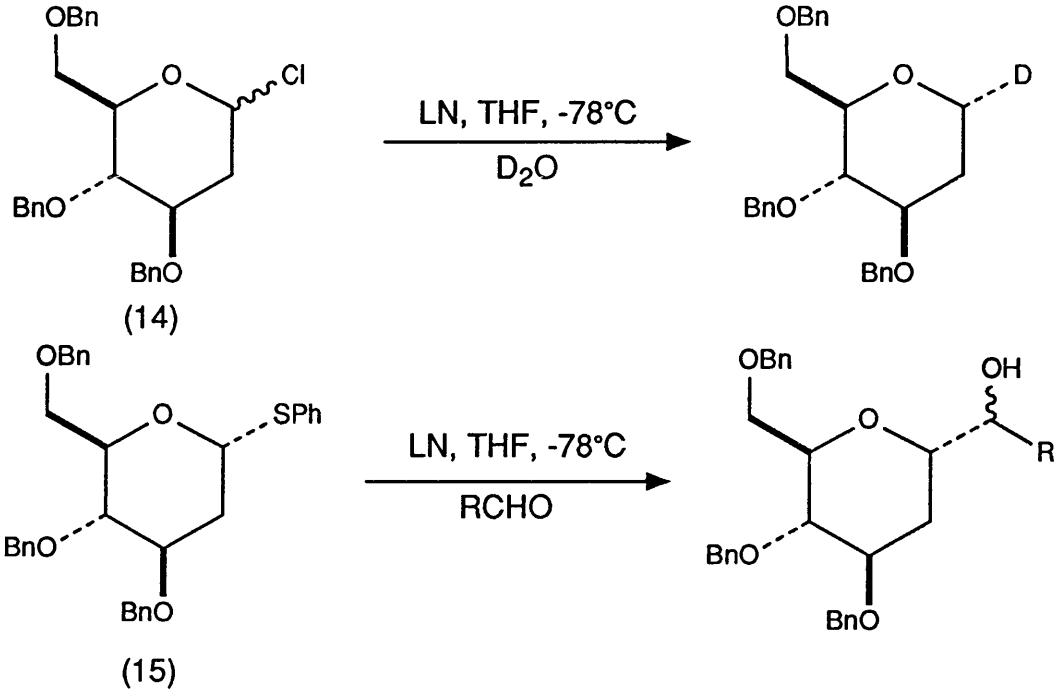
One such method involves the reductive lithiation of a glycosyl sulphide or chloride with two equivalents of a single-electron transfer agent, such as lithium naphthalenide (LN). Early work by Sinay[32], however, showed that if the substrate possessed a C(2) oxygen substituent, the glycosyl lithium species generated underwent a facile β-elimination to give a glycal (Scheme 12). This reactivity is analogous to the well-known reductive elimination of acetobromo-glucose to give triacetoxy-D-glucal as shown[33].

Scheme 12



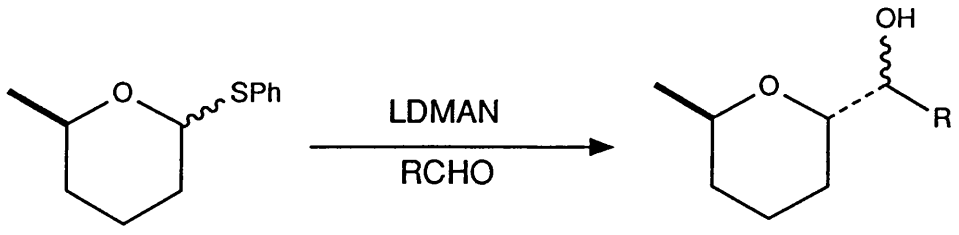
This method has however, been applied successfully to the reductive lithiation of 2-deoxy sugar derivatives as shown (Scheme 13).

Scheme 13

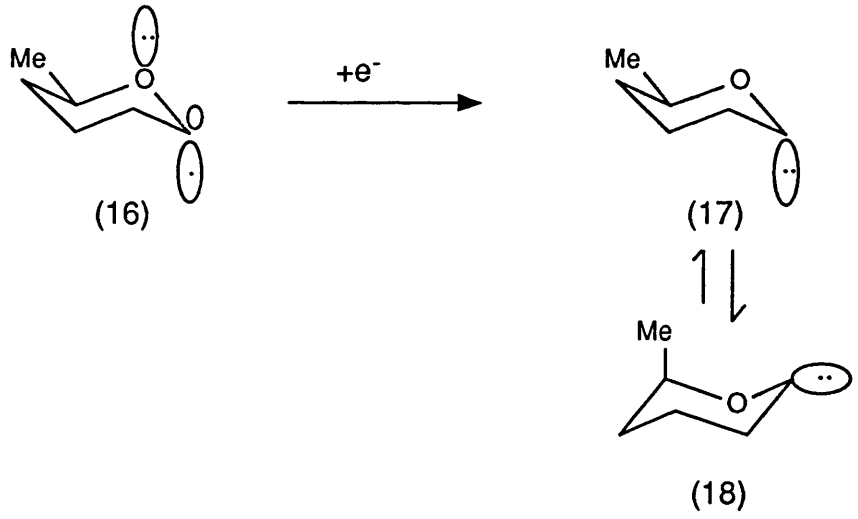


Thus, treatment of either glycosyl chloride (14) or glycosyl sulphide (15) with two equivalents of LN followed by the addition of an electrophile gave the 1-substituted products shown. Of particular interest is the observation that substituents are introduced exclusively in the axial configuration giving rise to α-C-glycosides stereoselectively from either α- or β- precursors. These results concur with those obtained by Cohen, who carried out similar studies on simple tetrahydropyran substrates using lithium 1-(dimethylamino) naphthalenide (LDMAN) as the single-electron transfer agent[34] (Scheme 14).

Scheme 14



This stereoselectivity can be explained by recognising the formation of an anomeric radical (16) as an intermediate[35]. Such a radical species would then adopt the preferred axial configuration by a rapid equilibration between the equatorial and axial epimers[36]. This preference for the axial configuration is due to the favourable orbital overlap of the axial oxygen lone pair with the SOMO of the radical as mentioned previously (Scheme 10). This radical then accepts another electron from the LDMAN to generate an organolithium species, which is configurationally stable at -78°C. This simple tetrahydropyran-derived species (17) can then undergo a chair-chair interconversion to put the C-Li bond in an equatorial orientation, thus eliminating the driving force for epimerisation at this centre.

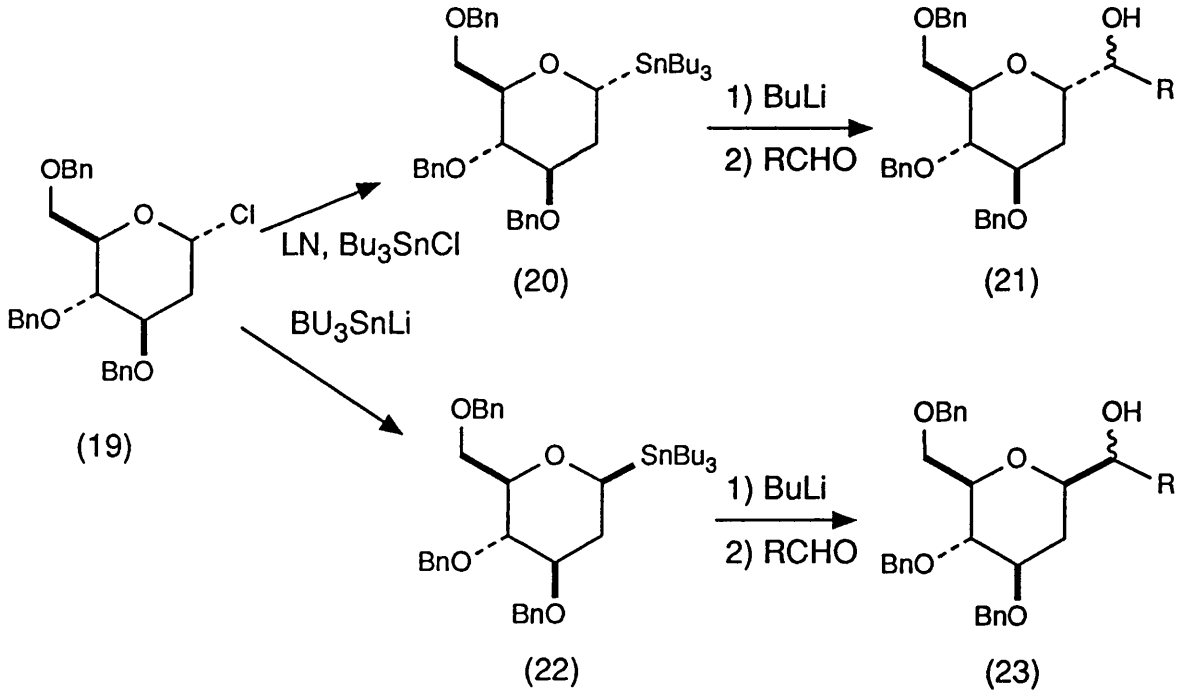


Alkylation of this tetrahydropyran (18) then leads to the observed products, alkylation occurring with overall retention of configuration at C(1). Similarly, in the case of carbohydrate-derived organolithiums, alkylation of the configurationally stable axial glycosyl lithium species gave α-C-pyranosides in good overall yield.

A second method for the generation of a C(1) glycosyl lithium species under mild conditions is the transmetalation of a glycosyl stannane. Beau and Sinay[37] have applied this method to the synthesis of both α- and β-C-glycosides (Scheme 15). The 2-deoxy

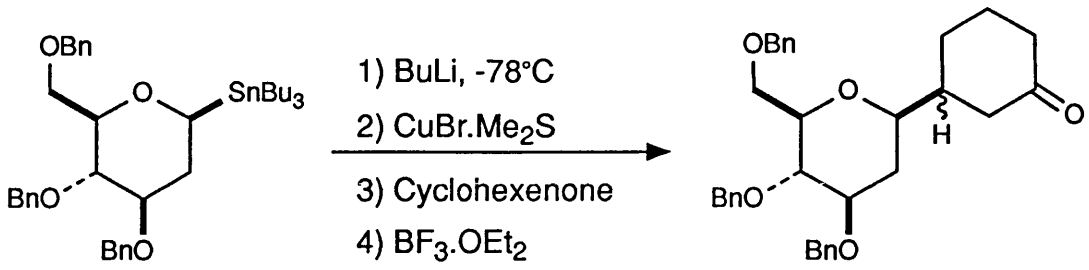
α-glycosyl chloride (19) was used as a common intermediate for the generation of both the α-glycosyl stannane (20), by the single electron transfer mechanism previously discussed, and for the formation of the β-glycosyl stannane (22) by displacement of the anomeric chloride by tri-n-butylstannyl lithium. Treatment of the glycosyl stannanes (20) and (22) with butyl lithium at low temperature gave rise to a rapid and stereoselective tin-lithium exchange which occurred with retention of configuration as previously demonstrated by Clark Still[38]. The resultant, configurationally stable organolithium species then underwent alkylation, again with retention of configuration at C(1) to afford the alkylated products (21) and (23) in good yield.

Scheme 15



Glycosyl cuprates can also be generated by an adaptation of this transmetalation methodology[39] (Scheme 16).

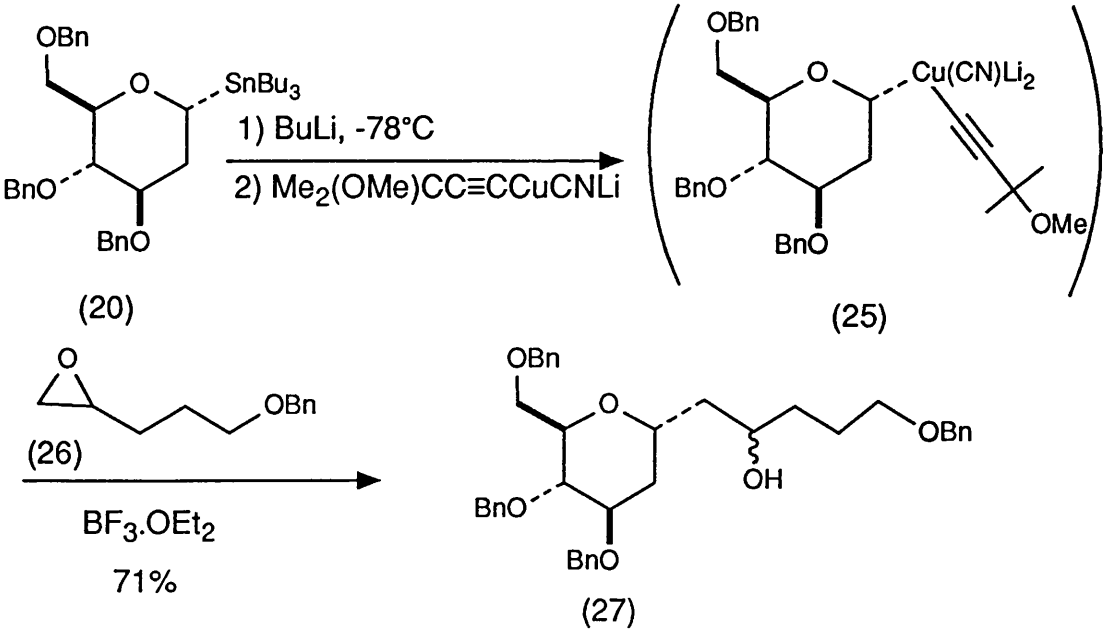
Scheme 16



(22) 78% (24)

The glycosyl stannane (22) was first transmetalated by treatment with butyl lithium and subsequent addition of a copper(I) salt gave rise to a glycosyl cuprate, both transmetalations occurring rapidly with retention of configuration about the anomeric carbon. Fuchs demonstrated that under Lewis acid catalysis this species afforded, upon treatment with cyclohexenone, the alkylated derivative (24), resulting from a 1,4-addition to the enone with the initial stereochemistry at C(1) being retained. Beau, in a further extension of this work generated the higher order cuprate (25) from the α-glycosyl stannane (20) in an analogous manner[40] (Scheme 17). Lewis acid catalysed ring opening of epoxide (26) with this reagent furnished the α-C-glycoside (27) in good overall yield.

Scheme 17

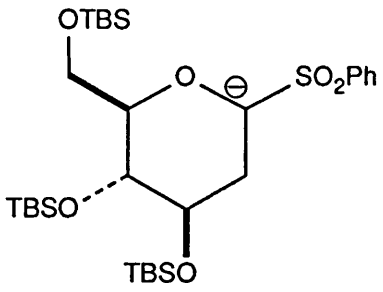


(20) (25) (27)

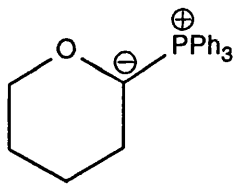
Thus the formation and subsequent alkylation of a C(1) lithiated glycosyl compound has been successfully applied to C-glycoside synthesis. However, this chemistry is somewhat limited in that oxygen functionality at C(2) is not compatible with the generation of the glycosyl lithium species due to the problem of β-elimination previously discussed.

An alternative method for forming an anion at the anomeric position is to incorporate an electron-withdrawing substituent at C(1) to facilitate the deprotonation and to stabilise the resulting anion[41-45]. Some representative examples of such stabilised anions are illustrated below (Scheme 18).

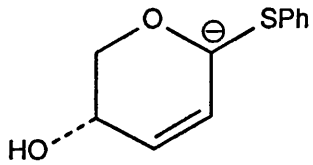
Scheme 18



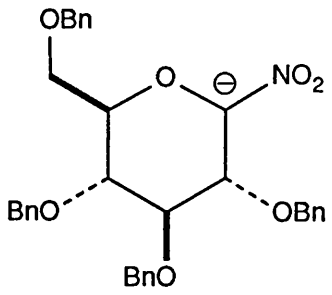
(28a) ref.41



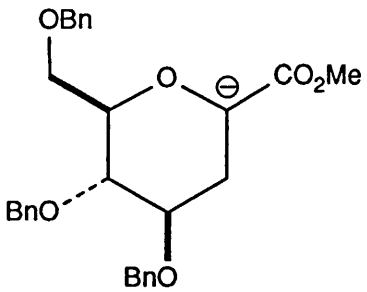
(29) ref.42



(32) ref.45



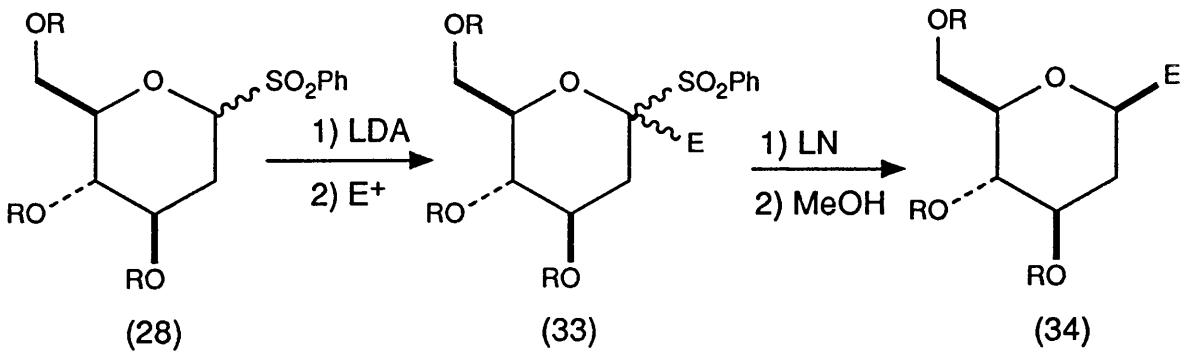
(30) ref.43



(31) ref.44

Glycosyl sulphones have been used extensively in C-pyranoside synthesis as illustrated (Scheme 19).

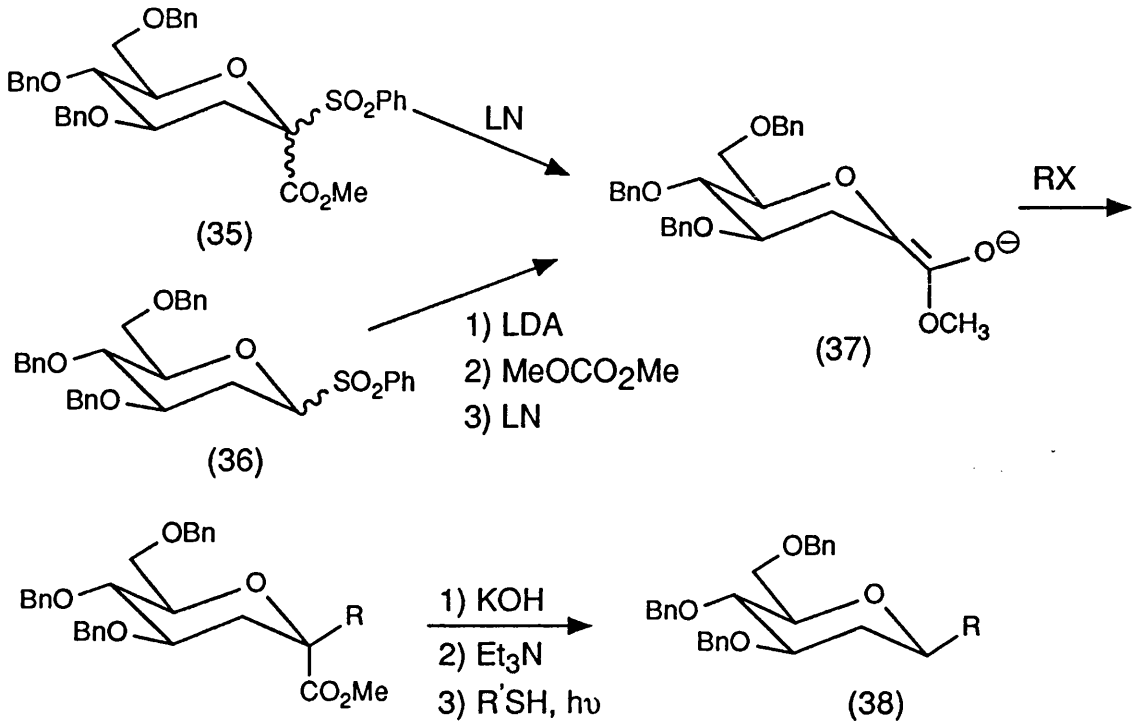
Scheme 19



(28) (33) (34)

Deprotonation at the anomeric centre of sulphone (28), followed by trapping with an electrophile gave a mixture of α- and β-C-glycosides (33) which, upon treatment with two equivalents of LN and quenching with methanol, afforded β-C-glycopyranosyl derivatives (34)[41a]. The stereochemical outcome of this sequence results from the intermediacy of an anomeric radical in the sulphone-cleavage step which has a preference for the axial configuration as previously stated. It is interesting to note that this method gives complementary selectivity to the reductive lithiation of glycosyl sulphides as previously discussed.

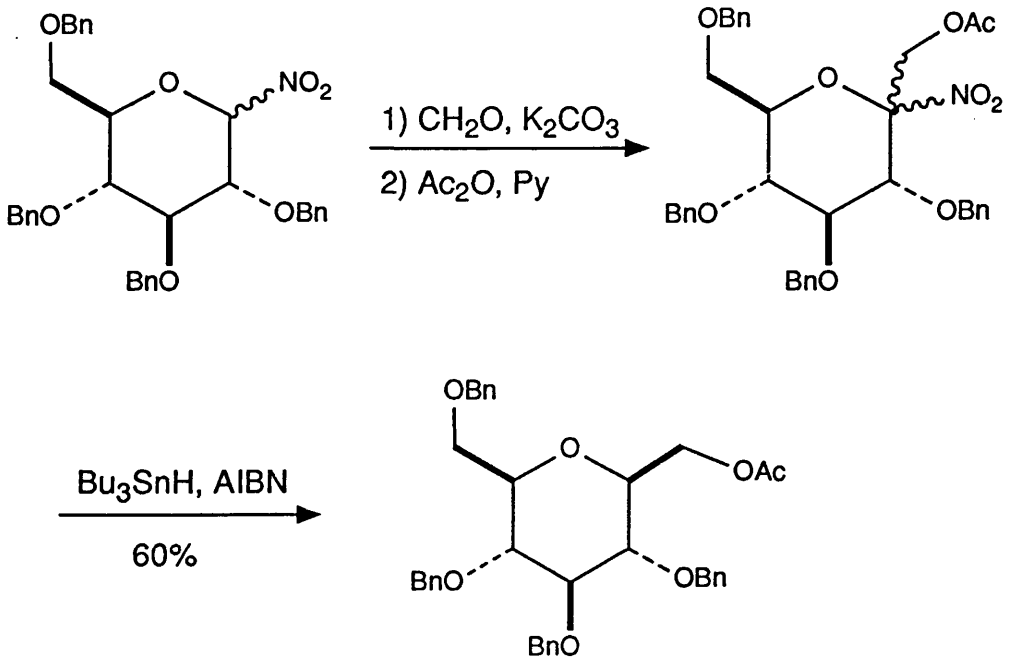
Scheme 20



In similar fashion, Crich[44] has generated the anomeric ester enolate (37) from the glycosyl sulphones (35) and (36) as shown (Scheme 20). Alkylation of this enolate with an alkyl halide followed by transformation of the ester moiety to the intermediate O-acyl thiohydroxamate and subsequent photolysis afforded the β-C-glycoside (38) in moderate yield. Again, the stereoselectivity obtained for the product β-C-glycoside is determined by hydrogen atom transfer to an axial glycosyl radical.

However, these methods are still limited by the reactivity of the anomeric anion formed which prevents oxygen functionality being present at C(2) due to competing β-elimination. Only Vasella[43] has successfully applied this methodology to a carbohydrate possessing an alkyloxy residue at C(2) by incorporating a nitro group at C(1) (Scheme 21).

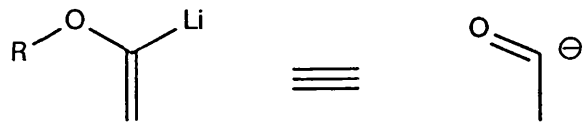
Scheme 21



(39)

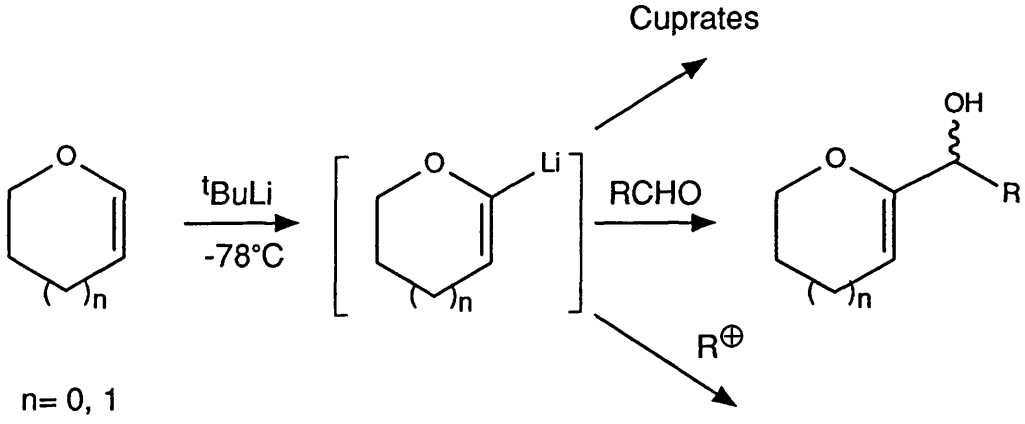
As illustrated, this route furnished the β-C-glycoside (39) in moderate yield, the stereochemistry at C(1) being set during the subsequent homolytic cleavage of the C-NO_2 bond *via* the glycosyl radical. The observation that the benzyloxy substituent at C(2) could be tolerated is due to the greater stabilisation afforded to the anomeric anion by the nitro group compared to for example, that of the sulphone function (NB: CH_3NO_2, pKa = 17.2; $CH_3SO_2CH_3$, pKa = 31.1, solvent: DMSO[46]).

The generation of anionic reactivity at the anomeric carbon of pyranoses has so far concentrated on the metalation of sp^3 hybridised carbon atoms. However, it is known that the stability of a carbanion increases relative to the proportion of s-character at this carbon, thus the more s-character the closer the electrons are to the nucleus and hence the lower their energy. The acidity of a proton attached to a carbon therefore increases in the order $sp>sp^2>sp^3$. A heteroatom α- to an sp^2 centre is also known to increase the acidity of the α-proton through inductive effects and thus heteroatom-facilitated lithiations of enol ethers, enamines and aromatic tertiary amines are well-established[47].



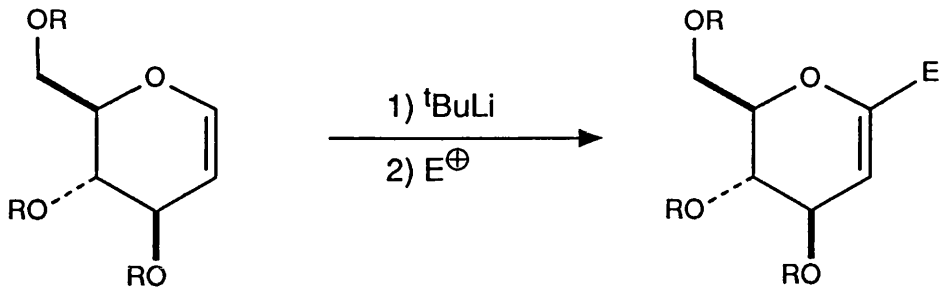
Early work on the lithiation of vinyl ethers and their utility as acyl anion equivalents was independently carried out by Schöllkopf[48] and Baldwin[49]. Since these pioneering studies, Boeckmann[50] has successfully adapted this methodology to the lithiation and alkylation of simple dihydropyrans and dihydrofurans (Scheme 22). Lithiation of simple cyclic vinyl ethers with *tert*-butyl lithium followed by reaction with an electrophile, such as an aldehyde, gave the alkylated dihydropyran or dihydrofuran in good yield.

Scheme 22



The extension of this method to encompass the field of C-glycoside synthesis has been carried out primarily by Sinay[51] (Scheme 23).

Scheme 23

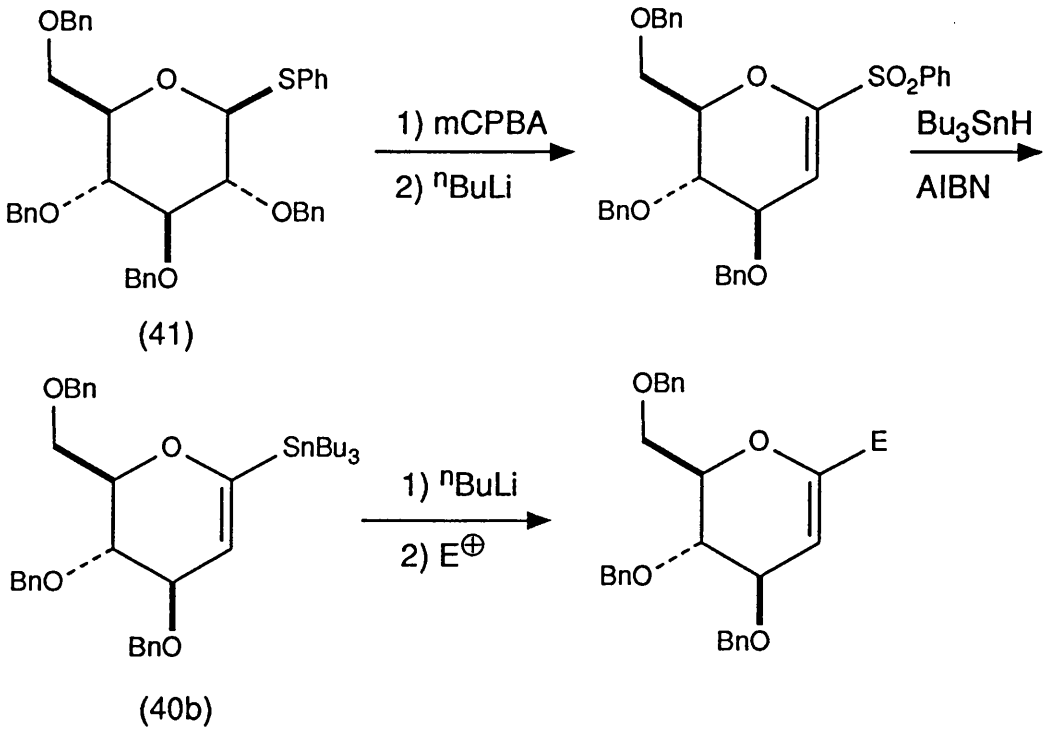


(40) a) R=TBS
b) R=Bn

$E^{\oplus}$	E	Yield
MeI	Me	86%
Allyl iodide	Allyl	70%
CO_2	CO_2H	60%

Deprotonation of glycal (40a) at C(1) using the procedure developed by Boeckman[50], followed by reaction with the carbon electrophiles shown gave the alkylated products in good yield. However, direct lithiation of tri-O-benzyl-D-glycal (40b) was unsatisfactory and therefore a transmetalation protocol was devised (Scheme 24).

Scheme 24

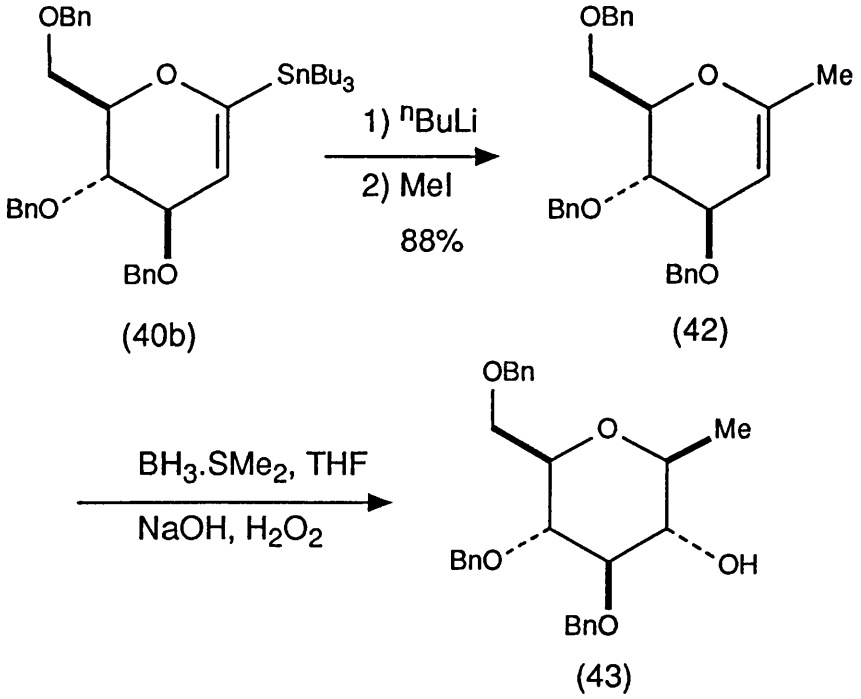


A series of standard manipulations afforded stannylated glycal (40b) from sulphide (41) which could then be smoothly transmetalated with n-butyl lithium to give the desired C(1) lithiated glycal intermediate. Quenching of this lithiated derivative with carbon electrophiles furnished C-glycals in good yields[51].

These results demonstrated that anionic reactivity could be generated at C(1) of glycals and that such lithiated species could be intercepted with carbon electrophiles. However, the extension of this method to the synthesis of 2-hydroxy-C-glycosides requires the regio- and stereospecific introduction of an oxygen function at C(2) of the C-glycal derivative and also control of the configuration at the anomeric position.

Such a procedure has been demonstrated by Hanessian[52] who carried out a highly regio- and stereoselective oxygenation of alkylated glycal (42) using a hydroboration/oxidation sequence (Scheme 25).

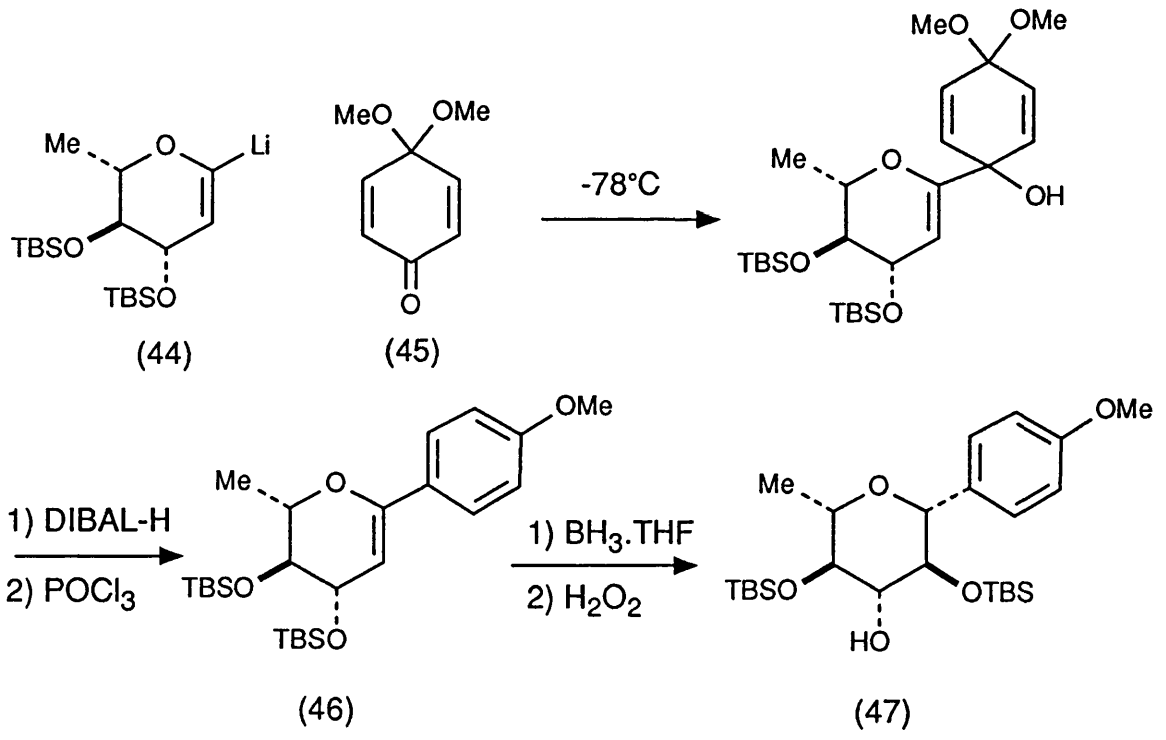
Scheme 25



Alkylation of the stannylated glycal (40b) with methyl iodide using the previously described transmetalation procedure gave the methylated derivative (42) in high overall yield. Subsequent hydroboration/oxidation of this compound afforded the 2-hydroxy-β-D-C-glucoside (43) in a highly regio- and stereocontrolled fashion.

This alkylation/hydroboration/oxidation approach has recently been adopted by Parker[53] in a novel synthesis of C-aryl glycosides from the lithiated rhamnal derivative (44) (Scheme 26).

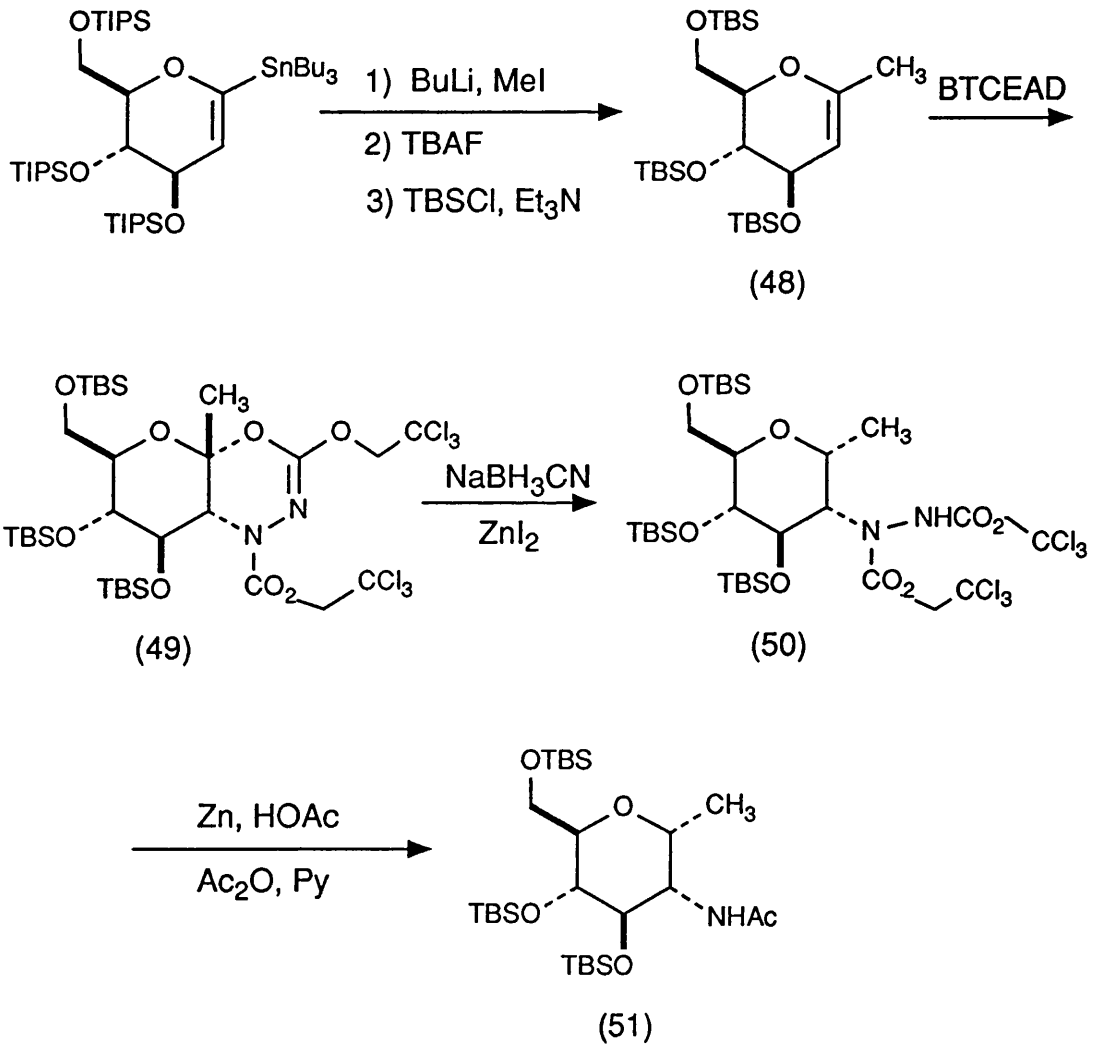
Scheme 26



Alkylation of this lithiated glycal with quinone ketal (45) followed by a reductive aromatisation furnished the C-aryl glycal (46). Hydroboration of the glycal double bond and subsequent oxidation then served to give the desired C-aryl glycoside (in which silyl group migration had also occurred) in good overall yield.

Leblanc[54] has recently demonstrated that amine functionality can also be introduced at C(2) of C(1) alkylated glycals in a stereoselective manner (Scheme 27). Thus methylated glycal (48), efficiently prepared by the standard alkylation procedure, underwent a [4+2] cycloaddition reaction with bis(trichloroethyl)azodicarboxylate (BTCEAD) to give adduct (49) as a single isomer. The ketal function generated at C(1) was then reduced with sodium cyanoborohydride/zinc iodide and the resultant hydrazide (50) converted to the 2-acetamido-C-glucoside (51) by a standard procedure.

Scheme 27

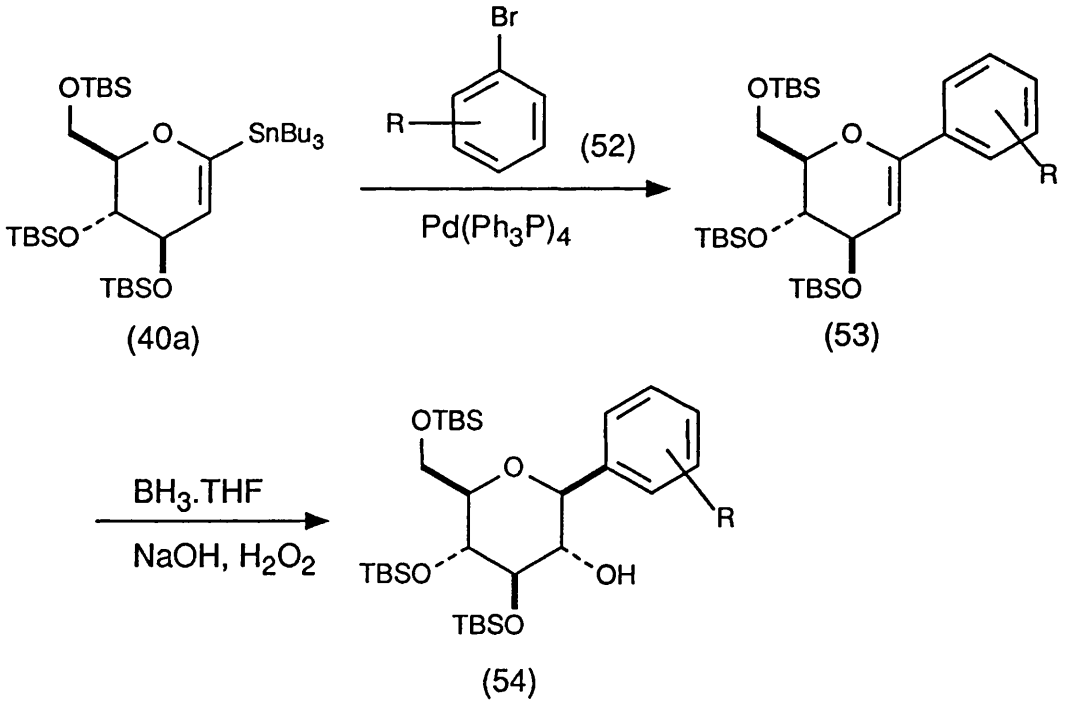


The reactivity of stannylated glycals can also be exploited for C-glycoside synthesis in a somewhat different manner. Stille[55] has shown that vinyl tin reagents undergo a facile, palladium(0)-catalysed cross-coupling reaction with aryl halides to give

functionalised styrenes and this coupling reaction has recently been used to synthesise C-aryl glycosides[56].

A solution of stannylated glycal (40a) and the bromobenzene derivative (52) in refluxing toluene underwent a smooth cross-coupling reaction to give the C-aryl glycal (53) under palladium(0) catalysis. Hydroboration/oxidation of the glycal double bond then gave the corresponding C-aryl glycoside possessing the β-D-gluco configuration as the major product[56a] (Scheme 28).

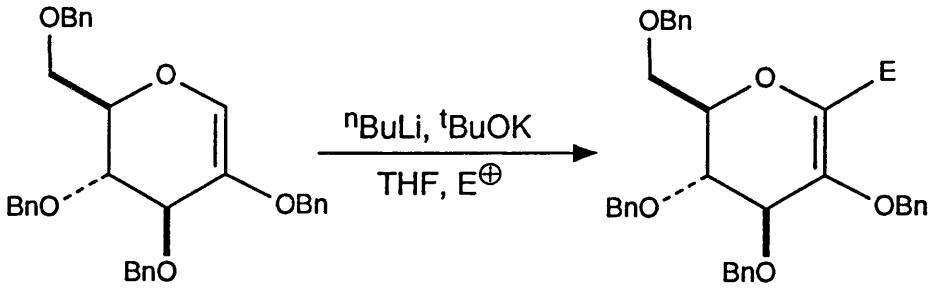
Scheme 28



Until now, no attempt has been made to generate an anion at C(1) of a glycal in the presence of an oxygen function at C(2). Such an oxygen substituent would be expected to facilitate the deprotonation at C(1), by both an inductive effect and an intramolecular complexation of the resultant lithium glycal[47]. Schmidt has shown that deprotonation of the 2-benzyloxyglycal (55) is indeed possible[57] (Scheme 29).

Treatment of glycal (55) with Schlosser's base[58] and subsequent trapping of the lithium glycal with the electrophiles shown resulted in low to moderate yields of the desired products. Side reactions, such as competing lithiation of the benzyl methylenes (mainly at C(2)) were proposed as being the cause of the problems encountered and the low yields obtained.

Scheme 29

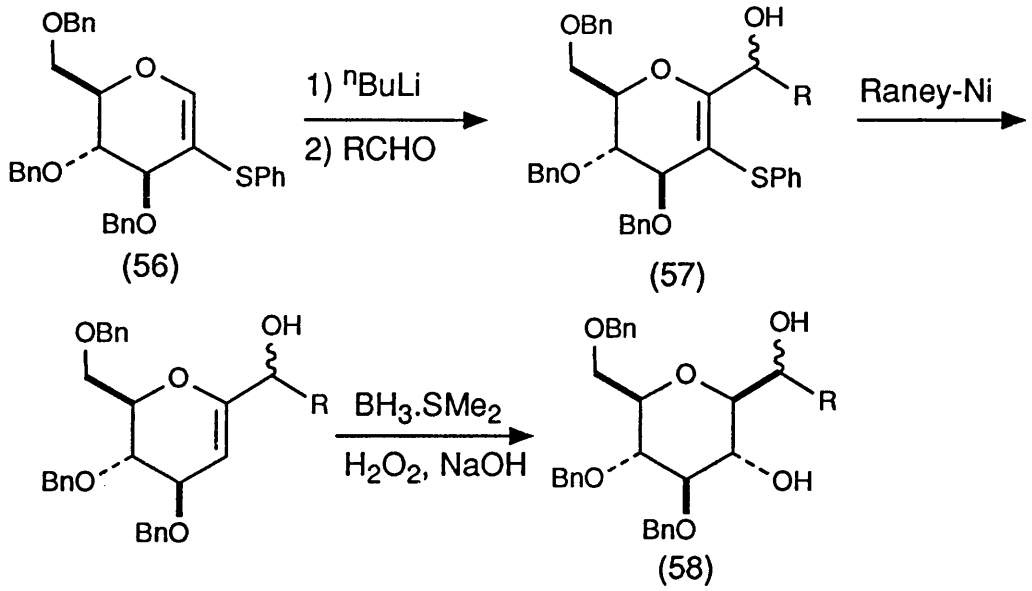


(55)

$E^{\oplus}$	E	Yield
D_2O	D	63%
MeI	Me	47%
MeSSMe	SMe	49%
ClCOOMe	COOMe	35%

When the benzyloxy substituent at C(2) was replaced by a phenylthio moiety however, no such difficulties were encountered (Scheme 30).

Scheme 30



Deprotonation of the 2-phenylthio-glycal (56) and subsequent alkylation gave the alkylated glycal (57) in good yield. Reductive removal of the phenylthio moiety and subsequent hydroboration of the glycal double bond followed by oxidation gave β-D-C-glucoside (58) in high overall yield. This approach however, offers no significant advantage over the previously described methodology, since the functionality at C(2) has to be removed prior to elaboration to the desired C-glycoside.

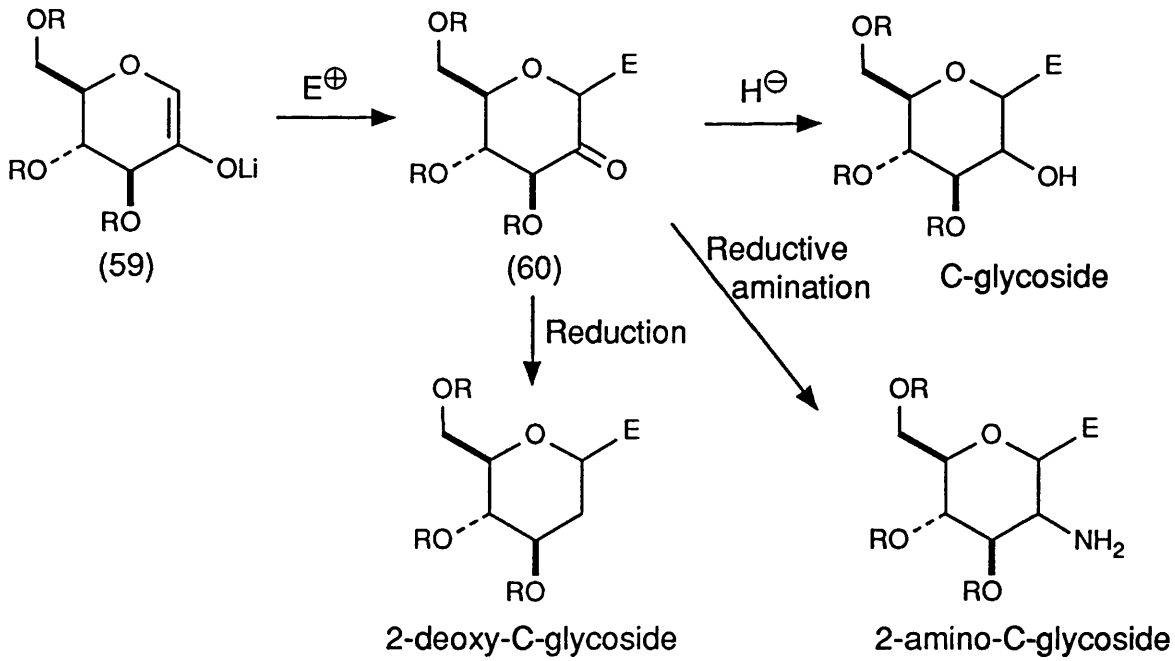
In summary, anomeric anions have been generated in a number of ways and their application to the synthesis of C-glycosides has been widely demonstrated. However, the synthetic flexibility of the methods discussed is limited by the fact that oxygen functionality cannot often be tolerated at C(2), i.e. adjacent to the anomeric anion formed. To date, only Vasella[43] has successfully carried through an oxygen function at this position whilst generating an anion at C(1) and this methodology is limited to the synthesis of simple β-C-glycoside derivatives. The lithiated glycal approach however, although intolerant of a C(2) oxygen substituent can still be applied to the synthesis of 2-hydroxy-C-glycosides by a subsequent hydroboration/oxidation of the glycal double bond. However, this hydroboration step is a necessity and thus puts a constraint on the flexibility of this method.

In order to provide a general solution to this problem, a carbohydrate-derived synthon possessing a C(2) oxygen function and anionic reactivity at C(1) is required. The following section discusses the viability of such an approach and the possible applications to the synthesis of naturally occurring C-glycosides.

1.7 ENOLATE REACTIVITY AT THE ANOMERIC CENTRE

As discussed in the earlier review on anomeric anions, the major limitation of current methods is in carrying through an oxygen functionality at C(2) whilst generating an anion at C(1). One possible synthon that could offer a solution to this problem is the carbohydrate-derived enolate (59) shown below.

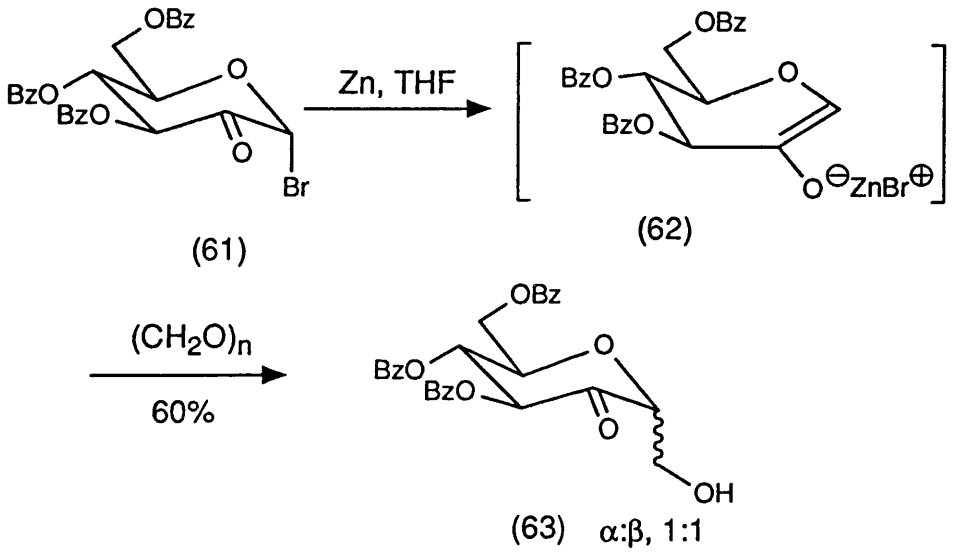
Scheme 31



If this enolate can be generated, then alkylation with a carbon electrophile would yield the 2-keto C-glycoside (60). The ketone moiety could then be further manipulated to allow the synthesis of both D-manno- and D-gluco-C-pyranosides *via* stereoselective reduction of this function or, the corresponding 2-amino-C-glycosides resulting from

reductive amination procedures or, a complete reductive removal of the ketone to give 2-deoxy derivatives (Scheme 31). Obviously, the presence of the ketone as a functional "handle" at C(2) would allow significant flexibility in approaches to a large range of C-glycosyl derivatives. Lichtenthaler has recently demonstrated the potential of such a synthon for the synthesis of C-glycosides[59] (Scheme 32).

Scheme 32



Treatment of the glycos-2-ulosyl bromide (61) with zinc in THF under Reformatsky conditions generated the zinc enolate (62). This species then underwent reaction with formaldehyde to give the hydroxymethyl compound (63) as a mixture of anomers (α:β, 1:1). This reaction, although illustrating the potential of anomeric enolate reactivity in C-glycoside synthesis, is somewhat limited in its applications. For example, the compatibility of this Reformatsky process with aldehydes and ketones is known but other electrophiles, such as alkyl halides would not be suitable. Also, the method allows only the generation of the zinc enolate (62), whereas, to fully explore the reactivity of enolates such as (59) other counter-ions would require investigation. Therefore, in order to carry out such studies, alternative methods for generating enolate (59) are required which would offer the necessary flexibility.

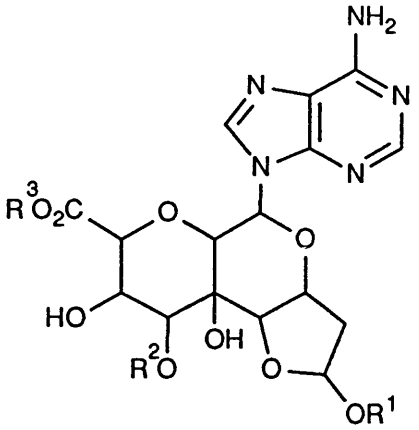
As we have previously stated, there are many biologically important C-pyranosides, and one such group are the herbicidins. The next section will discuss the structure and biological importance of these natural products and one possible synthetic strategy based on our carbohydrate-derived enolate (59).

1.8 THE HERBICIDINS

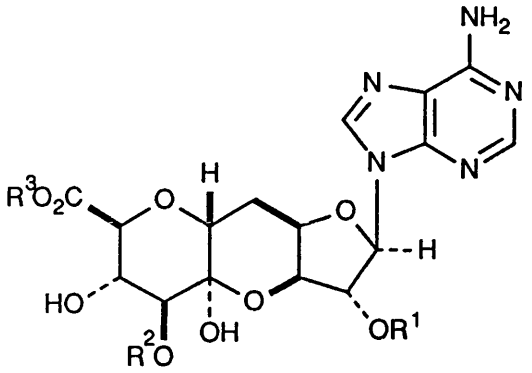
The herbicidin family of natural products constitute a small but structurally unique class of C-pyranosides. Originally isolated[60] from a fermentation broth containing *Streptomyces saganonensis*[61], the structure of the herbicidins was originally proposed as (64) based on chemical degradation studies and spectroscopic evidence[62]. However, on obtaining X-ray crystallographic data of chemically modified derivatives, these structures were later revised to (65a-e), confirming the presence of the unusual furo-pyrano-pyran ring system[63].

A structurally very similar compound which has recently been reported is aureonuclemycin (65f). In common with the herbicidins this molecule was isolated from cultures of *Streptomyces*, in this case, *Streptomyces aureus suzhouneusian*[64]. As illustrated, the structure of aureonuclemycin is essentially the same as that of herbicidin G but without an O-acyl substituent at the C(8) hydroxyl.

The herbicidins exhibit herbicidal activity and more specifically aureonuclemycin is an efficient inhibitor of *Xanthomonas oryzae*, a bacterium that infects rice crops[64]. However, no member of the herbicidin family has exhibited any other significant antimicrobial activity[61] which is in marked contrast to the known nucleoside antibiotics, eg. sinefungin[65]. In spite of this observation, these molecules are still of great interest due firstly to their unusual structure, which makes them attractive targets for synthesis and secondly that their biological mechanism of action is as yet unknown.



(64)



(65)

	R^1	R^2	R^3
a. Herbicidin A	CH_3	$CO(CH_2OH)C=CHCH_3$	CH_3
b. Herbicidin B	CH_3	H	CH_3
c. Herbicidin E	CH_3	$COCH(CH_3)_2$	CH_3
d. Herbicidin F	CH_3	$CO(CH_3)C=CHCH_3$	CH_3
e. Herbicidin G	H	$CO(CH_3)C=CHCH_3$	H
f. Aureonuclemycin	H	H	H

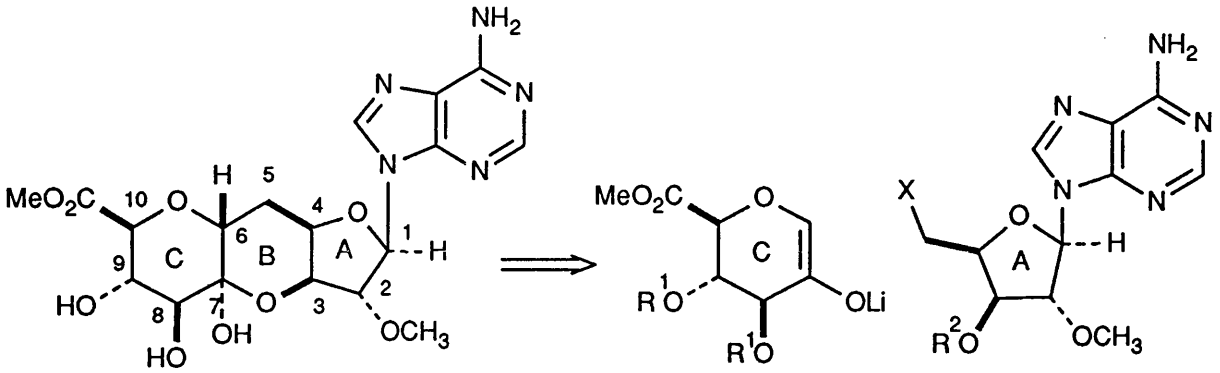
(Note all alkenes possess E- geometry)

The aim of this project is therefore to develop versatile synthetic methodology which will allow rapid assembly of the herbicidin skeleton and be flexible enough to accommodate modifications to the parent structure.

1.9 SYNTHETIC APPROACHES TO THE HERBICIDINS

Our proposed approach to this synthetic problem is outlined in Scheme 33 which illustrates in this case, one possible disconnection of herbicidin B (65b). The first disconnection to be made is at the C-pyranoside bond between C(5) and C(6)[66] which is adjacent to a hemiketal functionality at C(7).

Scheme 33



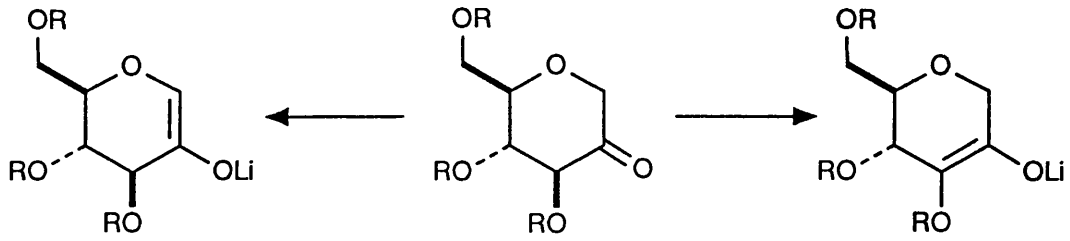
Recognition of the carbonyl equivalence of this hemiketal reveals the carbohydrate enolate (66) and the furanoside electrophile (67) as synthons for what would constitute a highly convergent synthetic approach.

The adenine moiety at C(1) could be incorporated into the structure either before (as in Scheme 33) or after the coupling reaction between enolate (66) and a suitably protected furanoside derivative. Indeed, methodology for the stereoselective introduction of both purine and pyrimidine bases into the anomeric position of furanoses is well established[67]. Thus, the coupling reaction could be carried out first to establish the herbicidin tricyclic skeleton and the adenine unit could then be introduced at a later point in the synthesis. This approach would also facilitate variation in substitution at C(1), allowing the synthesis of analogues possessing different or modified bases at this position.

The protected furanoside electrophile (67) could be synthesised from either D-xylose[68] or, after a one carbon degradation, from D-glucose. The required carbohydrate enolate would most likely be generated from a glucose (or mannose)-derived ketone rather than from the corresponding uronate ester due to possible complications arising from the acidity of the proton α- to the ester function at C(5). Thus, our carbohydrate enolate (59)

emerges as a logical precursor for ring C of the herbicidins.

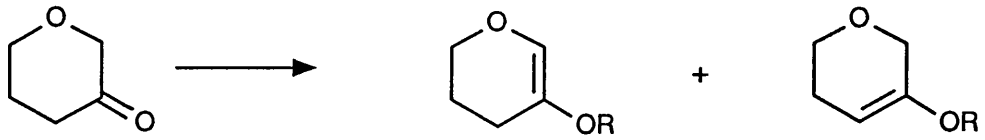
In summary, we have proposed that enolate (59), discussed in the previous section, could find use in a synthesis of the herbicidin class of natural products. However, if we wish to generate such a species directly, then the unsymmetrical nature of the corresponding ketone (68) must be taken into consideration. Thus treatment of ketone (68) with a suitable base could generate two possible enolates, whereby enolisation could occur either towards or away from the ring-constrained oxygen.



(59) (68) (69)

Obviously, we would wish to form enolate (59) exclusively, so that introduction of our furanoside electrophile would only occur at the anomeric carbon of ketone (68) to form the required C-pyranoside linkage. Unfortunately, the preferred mode of enolisation of pyranoside ketones such as (68) has not been studied in great detail. However, theoretical calculations and empirical studies of the enolisation of simple tetrahydropyran-3-one (70) have been carried out[69]. The experimental results obtained by Goldsmith[69] indicate that under conditions of both thermodynamic and kinetic control, the simple tetrahydropyran-3-one (70) will preferentially enolise away from the ring constrained oxygen which concurs with the previous observations made by Hirsch[70] (Scheme 34).

Scheme 34



(70) (71) (72)

a. R=Ac	Kinetic	24%	76%
	Thermodynamic	-	100%
b. $R=SiMe_3$	Kinetic	25-12%	75-88%
	Thermodynamic	11%	89%

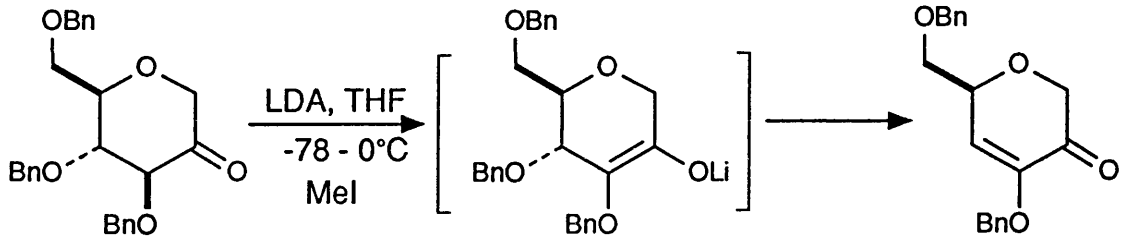
Considering inductive effects alone, an adjacent oxygen function has been predicted by Lehn[71] to provide 10-15 KCal/mole additional stabilisation to an adjacent carbanion relative to a methylene group. Goldsmith has also shown that MM2 conformational analysis of the isomeric enol acetates (71a) and (72a) favours the "endiol" isomer (71a) as the more stable[69].

The unexpected experimental observations are thought to arise from an unfavourable interaction between the enolate anion and the antiperiplanar lone pair of the ring oxygen overcoming the inductive and steric effects discussed above. In the case of the carbohydrate ketone (68), both enolates (59) and (69) would suffer similar destabilising effects from adjacent oxygen functionality. However, Hine[72] has shown that this effect can be minimised through rotation about the C-O bond. Thus enolate (69) could lessen this destabilisation, whereas the constraining influence of the pyranose ring prevents any significant minimisation of this effect for enolate (59). Therefore, a carbohydrate derived ketone such as (68) would be expected to undergo enolisation away from the ring oxygen.

Indeed, an example of such an enolisation process has recently been

communicated to us by colleagues at the University of East Anglia[73]. Treatment of ketone (73) with LDA at low temperature led, on warming, to enone (75), which is the consequence of β-elimination *via* the "undesired" enolate (74) (Scheme 35).

Scheme 35

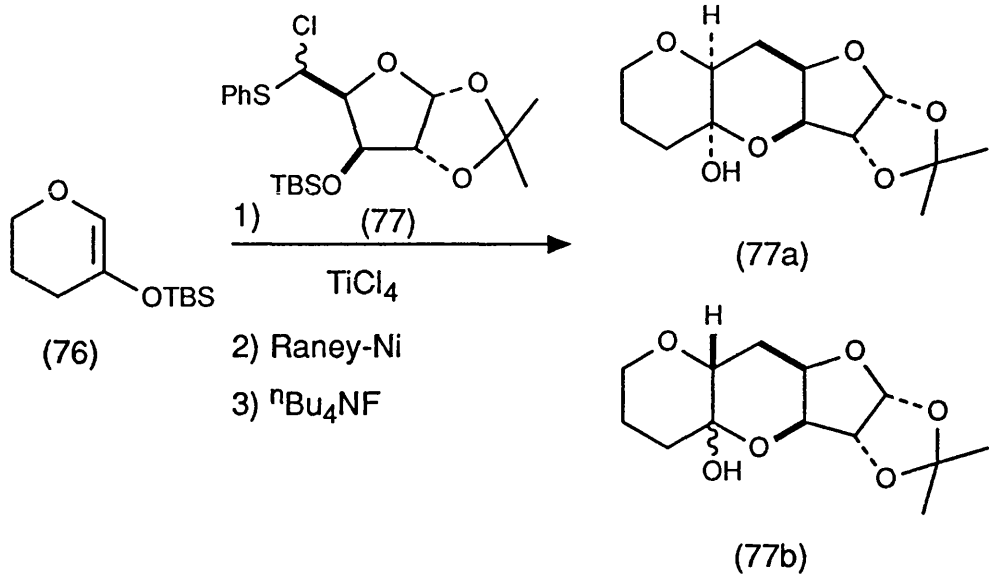


(73) (74) (75)

In conclusion, both simple tetrahydropyran-3-ones and our carbohydrate-derived ketone (68) would be expected to enolise in the opposite sense to that required, that is, away from the ring-constrained oxygen. Therefore, in order to put into practise our proposed synthetic strategy directed towards the herbicidins, alternative methods for the generation of the required enolate (59) are required.

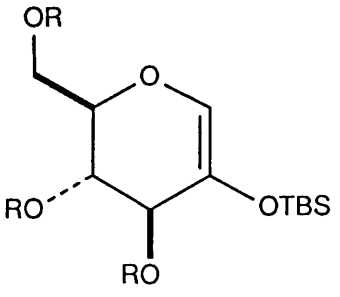
Solutions to this general problem have been devised within the Gallagher group for the simple tetrahydropyran-3-one system[74,75]. Cox and Gallagher demonstrated that the enol silane (76), prepared by an indirect method, could be unmasked in the presence of a Lewis acid *in situ* to generate the desired regiospecific enolate which then underwent alkylation with the α-chlorosulphide furanoside (77) (Scheme 36)[75].

Scheme 36



Subsequent transformations then led to the two tricycles (77a) and 77b) which are useful model systems for the herbicidins.

The success of this early work prompted us to investigate such reactivity with a polyhydroxylated tetrahydropyran bearing the functionality that would be required for ring C of the herbicidin nucleus. However, if we wished to use the chemistry described above we would still need to synthesise, by an indirect method, the enol silane (78) having the general structure shown.



(78)

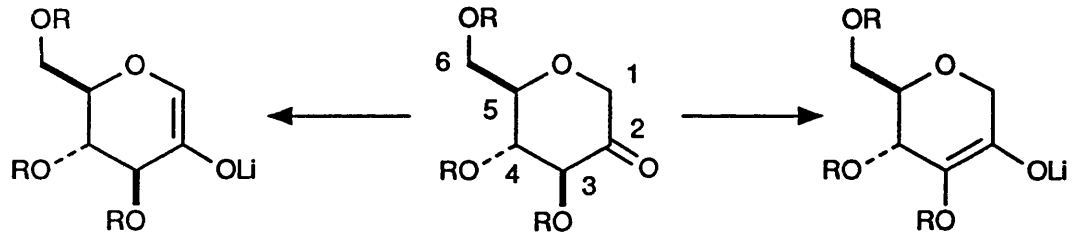
Therefore, a somewhat different, and potentially more flexible approach to the synthesis of C-glycosides was attempted which will be discussed in the next section.

2.. RESULTS AND DISCUSSION

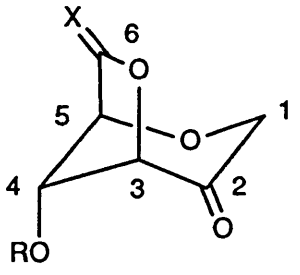
2 RESULTS AND DISCUSSION

2.1 INTRODUCTION

As previously discussed in Section 1.9., deprotonation of ketone (68) would be expected to generate the C(3) enolate (69) rather than the desired C(1) enolate (59), thus ketone (68) would not be a suitable precursor for C-glycoside synthesis in general, or for elaboration to the herbicidins (65) in particular.



In order to overcome this regiochemical problem and to retain the synthetically flexible ketone moiety at C(2), a novel approach to C-glycoside synthesis was proposed based on the bridged derivatives (79a-c) shown below.



(79)

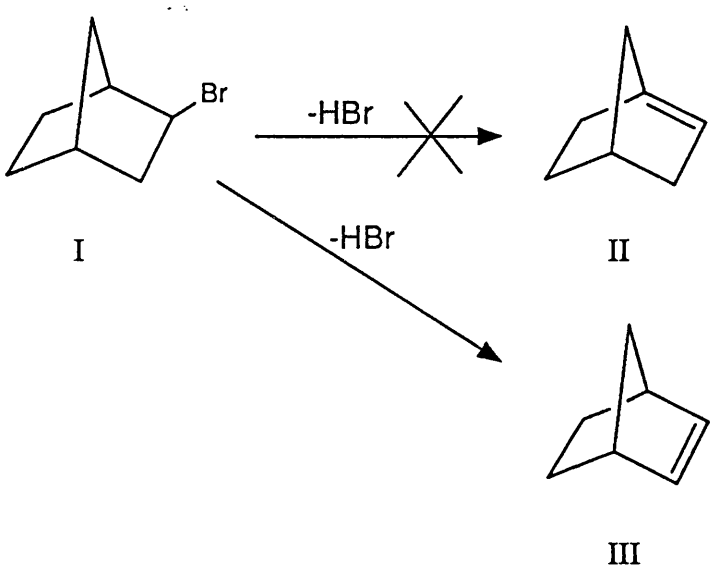
a. X=H, H

b. X=H, OMe

c. X=O

Ketones of type (79) are both highly functionalised and potentially very flexible intermediates for elaboration into C-glycosides. The enolisation of such ketones would be expected to occur at C(1) (carbohydrate numbering), i.e. towards

the six-membered ring oxygen. Enolisation towards the bridgehead carbon is precluded by Bredt's rule[76] which states that, in general terms, a bridgehead double bond would not be possible in a bicyclo [a.b.c] ring system where S(=a+b+c) ≤ 7, due to the strain involved. The practical limitations of this rule stem from studies by Prelog[77] and an example that illustrates the general principle is shown below.



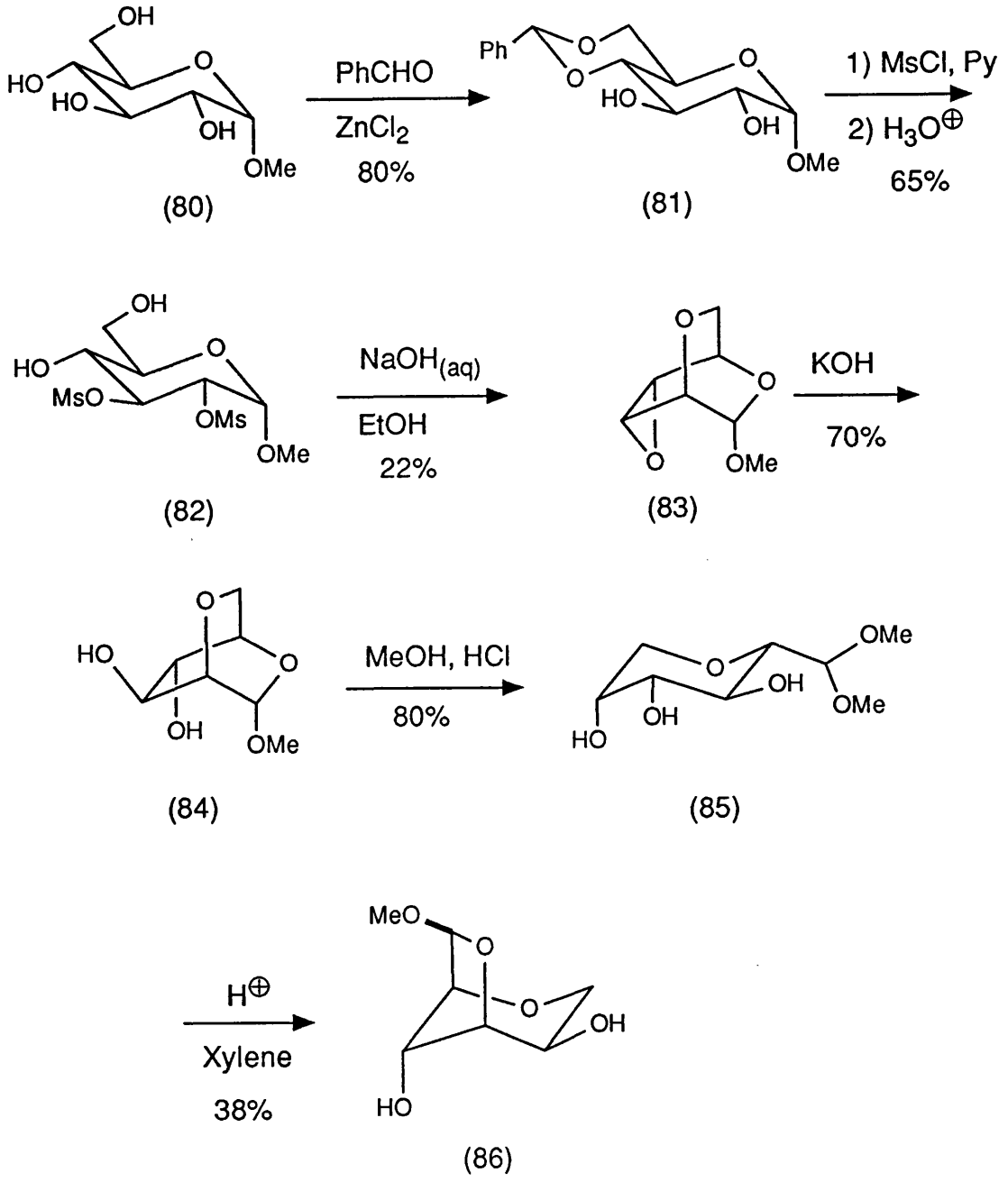
Elimination of HBr from bromide I gave alkene III rather than the bridgehead isomer II, since a bridgehead double bond is not possible in such a bicyclo[2.1.2] system. Therefore, the bridged bicyclo[3.2.1] ketones (79a-c) illustrated above would be expected to generate C(1) "anomeric" enolate anions upon deprotonation. Subsequent alkylation of these C(1) enolates with suitable electrophiles would then give access to a large range of C-glycosyl derivatives, the herbicidin family being of particular interest to this study.

As shown, various bridged systems are available with differing oxidation level at C(6). Ketones having either an ether bridge (79a), an acetal bridge (79b) or a lactone bridge (79c) are all potentially useful molecules within this context and the aim of this study was twofold.

1. To demonstrate that our prediction about the mode of enolisation of the bridged ketones (79a-c) is indeed correct.

2. To use these bridged ketones for the synthesis of C-glycosides with an overall aim of synthesising a member of the herbicidin class of natural products.

Scheme 37


OH
HO
HO
O
OH
OMe
PhCHO
$ZnCl_2$
80%
Ph
O
O
HO
O
OH
OMe
1) MsCl, Py
2) $H_3O^{\oplus}$
65%
(80)
(81)
OH
HO
MsO
O
OMs
OMe
$NaOH_{(aq)}$
EtOH
22%
O
O
O
OMe
KOH
70%
(82)
(83)
O
HO
O
OH
OMe
MeOH, HCl
80%
OMe
O
OH
OH
OMe
HO
(84)
(85)
$H^{\oplus}$
Xylene
38%
MeO
O
O
OH
HO
(86)

2.2 SYNTHESIS AND REACTIVITY OF AN ACETAL-BRIDGED KETONE

The presence in the literature of the bicyclic diol, methyl 2,6-anhydro-α-D-mannofuranoside (86)[78] prompted us to begin our study of the bridged ketones (79a-c) with the acetal-bridged derivative (79b). The synthesis of diol (86) is illustrated in Scheme 37.

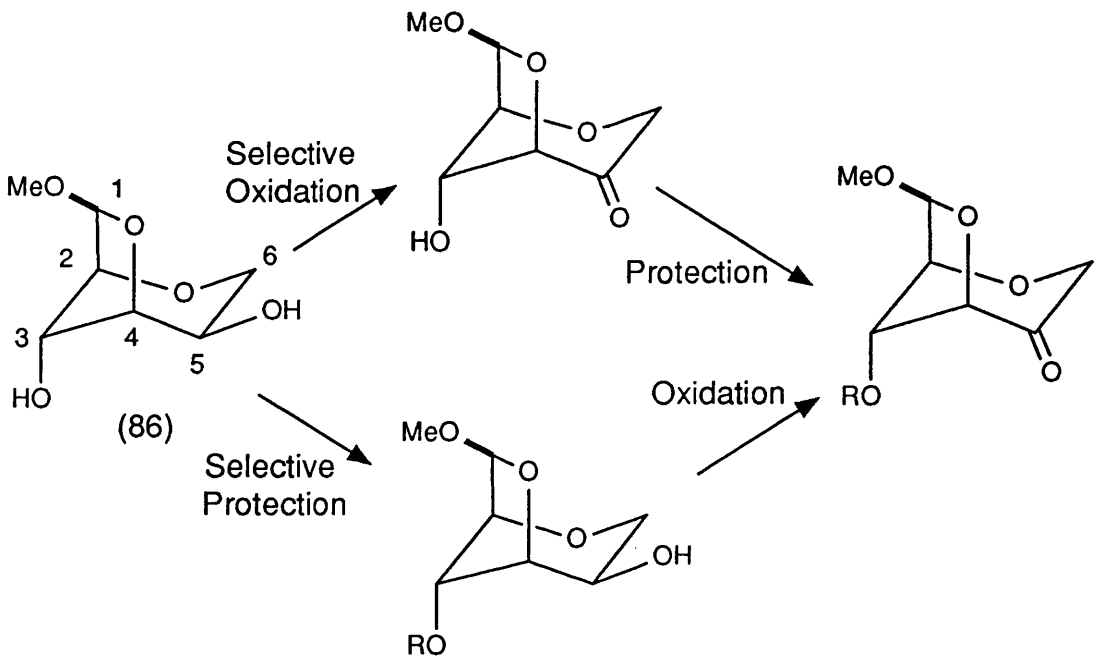
Treatment of methyl-α-D-glucopyranoside (80) with benzaldehyde and zinc chloride using a standard procedure[79] gave benzylidene acetal (81). Dimesylation of (81) and subsequent acid-catalysed hydrolysis of the benzylidene acetal protecting group using the procedure of Sinclair[80], gave diol (82) in good overall yield. Exposure of diol (82) to ethanolic sodium hydroxide for four days at ambient temperature and then one hour at reflux afforded dianhydride (83) in 22% yield[81]. The epoxide function of this molecule was then opened in a regioselective manner with aqueous potassium hydroxide at elevated temperature to furnish diol (84) {the methyl pyranoside isomer of the desired diol (86)} in moderate yield. Subsequent acid-catalysed methanolysis of diol (84) gave dimethyl acetal (85)[82] in high yield. Addition of a catalytic amount of ρ-toluenesulphonic acid to a solution of acetal (85) in xylene at reflux then afforded the required furanoside diol (86) in 38% yield along with pyranoside (84) and its β-anomer in a combined yield of 25% using a modification of the literature procedure[78].

In carrying out this rearrangement of dimethyl acetal (85), Köll allowed the reaction mixture to reflux under Dean and Stark conditions for thirty hours and obtained diol (86) in 32% yield. However, in our hands we found that the dimethyl acetal (85) was consumed within one hour of the reflux commencing and that subsequent work up gave the required diol (86) in slightly improved yields. This result may be explained by a slow, acid-catalysed equilibration of the furanoside (86) to the pyranoside (84) resulting in a higher proportion of (84) in the product

mixture with increasing reflux time.

With bicyclic diol (86) in hand elaboration to the required ketone (79b) was then attempted. Our strategy was to affect either a selective oxidation of the C(5) hydroxyl followed by protection of the C(3) hydroxyl or to selectively protect the C(3) hydroxyl with a subsequent oxidation to give ketone (79b) as shown in Scheme 38 below (NB. The numbering of diol (86) is derived from the systematic name, see Numbering Conventions section).

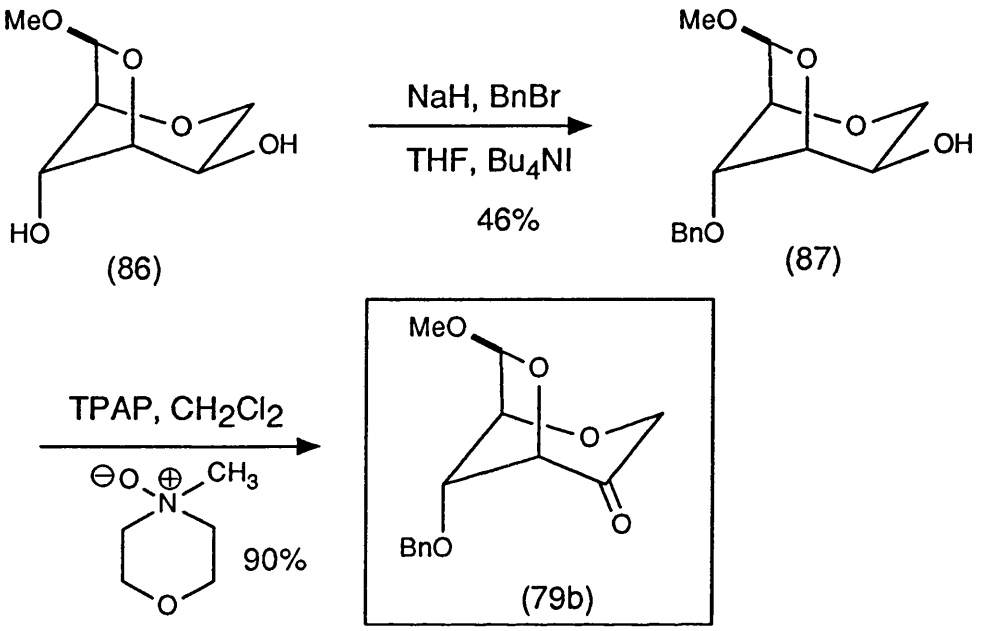
Scheme 38



The selective oxidation of the C(5) hydroxyl of diol (86) met with little success. Similarly, attempts at a selective protection of the C(3) hydroxyl of (86) under standard silylating or acylating conditions[83] were also unproductive, although it should be noted that under such conditions equilibration of the reaction products can occur. However, treatment of diol (86) with a slight excess of sodium hydride and one equivalent of benzyl bromide in the presence of tetrabutylammonium iodide[84] afforded the C(3)-*O*-benzyl derivative (87) in 46% yield (Scheme 39). Also

isolated were the corresponding bis(benzyl) derivative in 18% yield and the C(5)-*O*-benzylated alcohol in 5% yield, along with 18% of recovered diol (86).

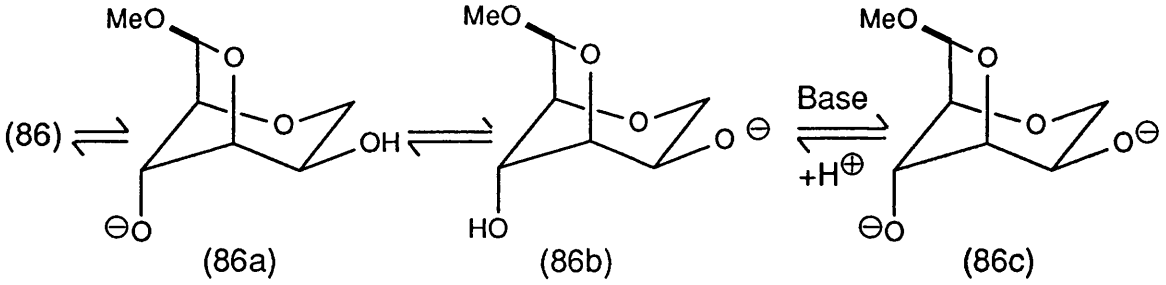
Scheme 39



The reason for the high selectivity of this protection step is not immediately obvious and appears to be inconsistent with the observed reactivity of equatorial versus axial hydroxyls on pyranose rings. In general, equatorial hydroxyls in such systems are more reactive than the corresponding axial hydroxyls and are thus easier to esterify and alkylate[85]. However, the bicyclic nature of diol (86) makes a direct extrapolation of this behaviour difficult and, since the steric and electronic environments of the hydroxyl groups at C(3) and C(5) are very similar, the observed difference in reactivity is difficult to explain.

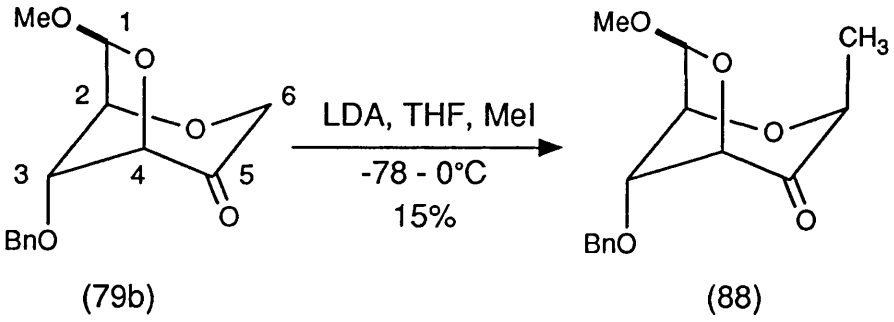
Upon addition of sodium hydride to a solution of alcohol (86) the species likely to be present in solution are the alkoxides (86a), (86b) and (86c) along with diol (86). Assuming that all of these species are in equilibrium then either the

activation energy for alkylation of alkoxide (86a) must be lower than that for alkoxides (86b) and (86c) or, alkoxide (86c) undergoes a kinetic reaction at the C(3) hydroxyl upon addition of benzyl bromide giving rise to the observed selectivity[86].

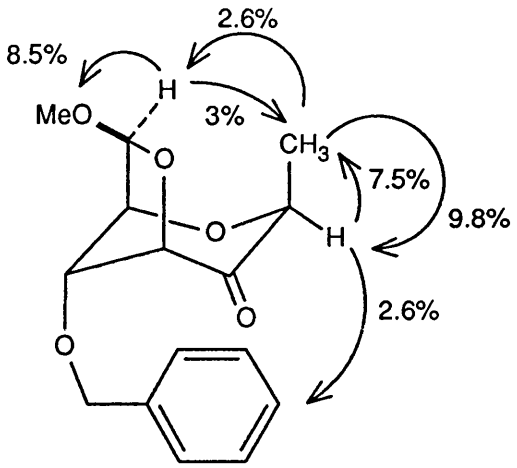


After this selective benzylation, the C(5) hydroxyl group of alcohol (87) was then oxidised using tetrapropylammonium perruthenate (TPAP)[87] in the presence of N-methylmorpholine-N-oxide as co-oxidant to furnish ketone (79b) in good yield with the structure of ketone (79b) and also that of alcohol (87) being confirmed by examination of their ^1H NMR spectra. With ketone (79b) in hand, the alkylation chemistry of this compound was then investigated (Scheme 40).

Scheme 40

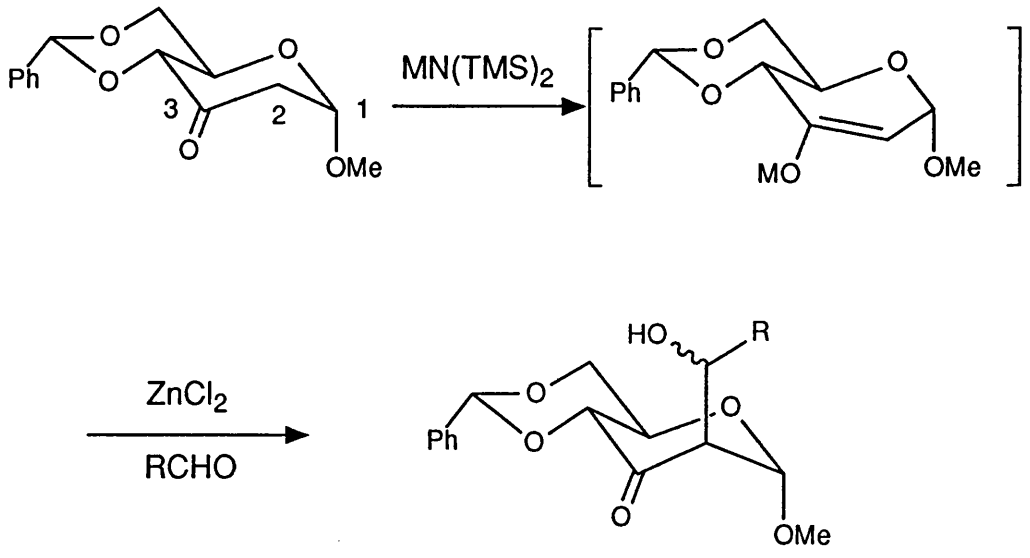


Treatment of ketone (79b) with LDA in THF at -78°C followed by addition of methyl iodide gave, after work up, a low yield of the methylated derivative (88). The axial stereochemistry of the newly-formed chiral centre at C(6) was ascertained by n.O.e. experiments[88], the results of which are illustrated below.



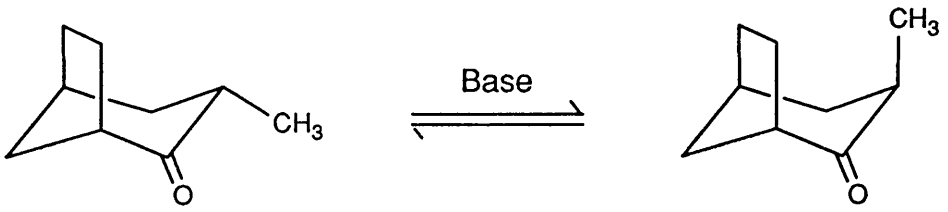
(88)

These studies demonstrate that the major product of this alkylation was the axial methylated ketone (88) shown. In support of these findings, Fraser-Reid[89] had observed that enolisation of the 3-keto sugar derivative shown below under kinetic conditions, followed by alkylation with various aldehydes afforded mixtures of the corresponding axially-oriented C(2)-alkylated aldol products in good yield.



Interestingly, studies by McKinney on the epimerisation of either epimer of the simple carbocyclic analogue of ketone (79b) (3-methyl bicyclo[3.2.1]

-octan-2-one) resulted in a 70:30 ratio of exo:endo isomers as shown below[90].



Exo
70%

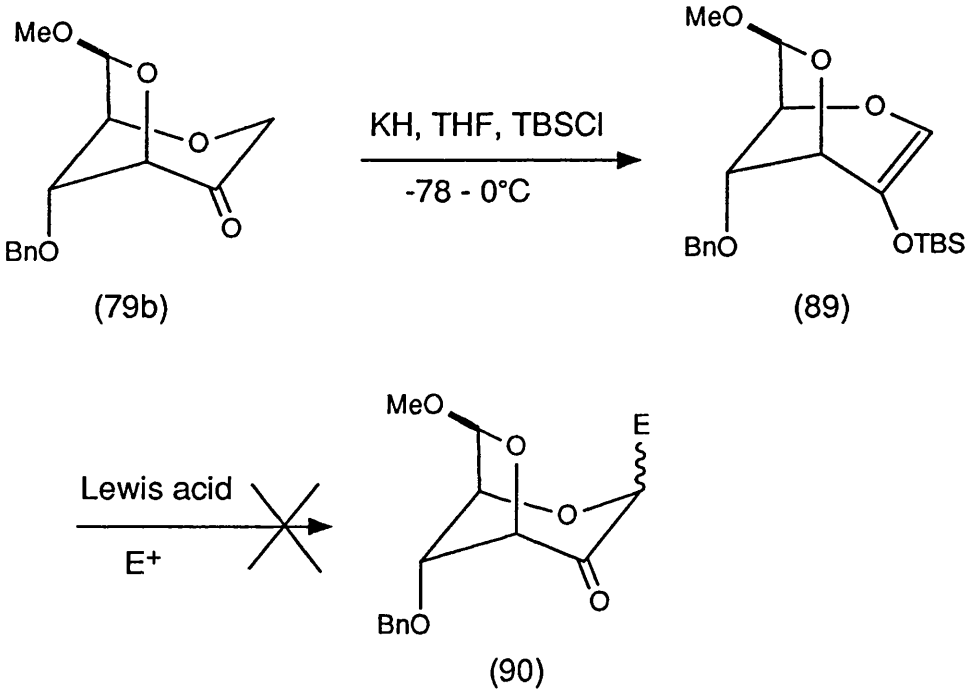
Endo
30%

By analogy, this implies that the thermodynamic product of the alkylation of ketone (79b) would be expected to have an equatorially-oriented alkyl group at C(6) (Scheme 40). Thus, the axially-methylated ketone (88) obtained is likely to be the product arising from kinetic control during this alkylation reaction. However, despite the observation that methylation of ketone (79b) was possible, albeit in low yield, interception of the enolate generated by treatment with LDA in THF with other electrophiles, such as allyl bromide or benzyl bromide failed to give alkylated products. This low reactivity of enolates derived from ketone (79b) was also observed when potassium hydride or potassium hexamethyldisilazide were used as bases. Similarly, changing the reaction solvent from THF to dimethoxyethane, toluene or ether still failed to provide any alkylation products. Due to the difficulties associated with enolate generation and/or reactivity the silyl enol ether (89) was synthesised and its reactivity under Lewis acid-mediated alkylation conditions[91] was studied.

Enolisation of ketone (79b) with potassium hydride in the presence of *tert*-butyldimethylsilyl chloride[92] afforded silyl enol ether (89) in good yield (Scheme 41). Following the success of the Lewis acid-mediated phenylthio alkylation procedure[93] used by Cox for model studies of the herbicidins (Scheme 36), attempts were made at applying this methodology to the alkylation of silyl enol

ether (89). As shown in Scheme 41, efforts to alkylate silyl enol ether (89) with the simple α-chlorosulphide (91)[94] using either zinc bromide or titanium tetrachloride as the Lewis acid resulted in decomposition of the silyl enol ether (89) and no products of alkylation were obtained. Similar results were noted using a Mukaiyama aldol procedure with trimethylsilyl triflate and benzaldehyde[91c].

Scheme 41



(79b) (89) (90)

Reagents and conditions

(i) $PhSCH_2Cl$ (91), $ZnBr_2$, 20°C.

(ii) (91), $TiCl_4$, -78°C

(iii) $PhCH(OMe)_2$, TMSOTf.

These disappointing results were thought to be due to the reactivity of the methyl acetal moiety of silyl enol ether (89) towards Lewis acids. Indeed, to demonstrate the high reactivity of (89) a control experiment was carried out using zinc bromide in the absence of an electrophile. A solution of silyl enol ether (89) in dichloromethane was cooled to -78°C and zinc bromide was added. The reaction

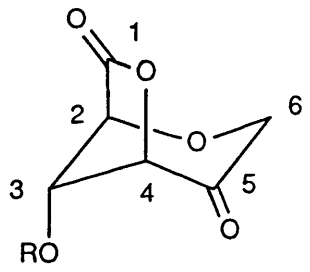
mixture was then allowed to warm slowly to 0°C and at this temperature, rapid decomposition of (89) was noted.

Therefore, the complications involved in the Lewis acid-mediated reactions of silyl enol ether (89) and the low reactivity of ketone (79b) towards alkylation put limitations on the usefulness of the acetal-bridged system for the synthesis of C-glycosides. However, despite the incompatibility of silyl enol ether (89) with the Lewis acid-mediated alkylation chemistry, the C(6) enolate (refer to Numbering Conventions section) generated from ketone (79b) still offers potential in this area. The low reactivity of this enolate species towards alkylation might be overcome by the addition of cosolvents such as DMPU[95] and HMPA[96] to the alkylation mixture. Similarly, a silyl enol ether derivative such as (89) could be used to generate the required enolate by treatment with either fluoride ion[97] or methyl lithium[98]. However, the major problem encountered with the acetal-bridged system (79b) was the availability of a sufficient quantity of this material to enable the full scope of the alkylation chemistry to be evaluated. As illustrated (Scheme 37 and Scheme 39), the synthesis of ketone (79b) required eight steps from methyl α-D-glucopyranoside (80), the overall yield being ≤1% and subsequent attempts at improving the yields of key, low-yielding steps, such as the formation of epoxide (83) from dimesylate (82) were unsuccessful. Also, the acid-catalysed rearrangement of dimethyl acetal (85) to the furanoside diol (86) proved to be a capricious reaction. We found that it was necessary to keep the concentration of substrate (85) in xylene very low (typically ≤0.005M) for reproducible yields of diol (86) to be obtained, which put practical limitations on the scale at which this process could be carried out.

In summary, we have successfully completed our first goal which was to demonstrate that ketones such as (79b) will enolise in the required sense, towards the ring oxygen as expected by application of Bredt's rule. However, due to the reactivity of the acetal bridge of silyl enol ether (89) towards Lewis acid-mediated

2.3 SYNTHESIS AND REACTIVITY OF A LACTONE-BRIDGED KETONE

As discussed in the previous section, our attempts at using the Lewis acid-mediated phenylthioalkylation procedure with ketone (79b), previously used with simple tetrahydropyran-3-ones by Cox was compromised by the high reactivity of the acetal bridge. It was therefore proposed that the silyl enol ether derivative of lactone-bridged ketone (79c), as well as possessing the correct oxidation level at C(1) (see Numbering Conventions) necessary for the herbicidins, would also be less susceptible to side reactions under these Lewis acid conditions. Ketone (79c) could also be used to generate the "anomeric" enolate at C(6) required for the synthesis of C-glycosyl compounds by a direct deprotonation and alkylation strategy, enolisation towards the ring oxygen again being enforced by the restraints associated with Bredt's rule.

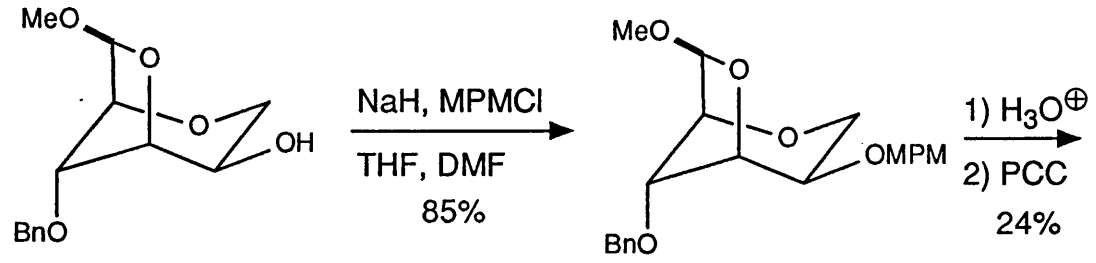


(79c)

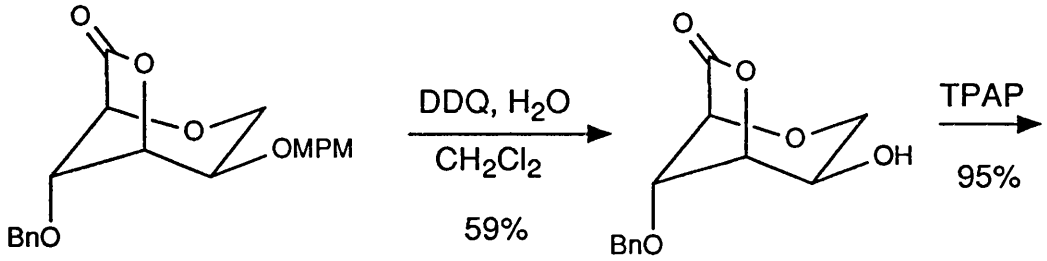
Our initial synthetic efforts directed towards the synthesis of ketone (79c) were based on the oxidation of the acetal function of ketone (79b) which would give our desired lactone-bridged derivative (79c) in a single step (see below).

However, treatment of ketone (79b) with either ozone[99] or *m*-chloroperbenzoic acid/boron trifluoride etherate[100] to effect the oxidation of the acetal function failed to give any of the desired ketone (79c), complex mixtures of products being obtained in both cases. Similarly, acid hydrolysis of the acetal

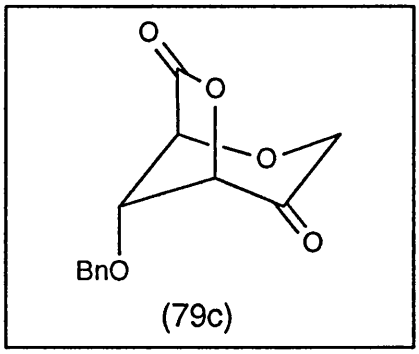
Scheme 42



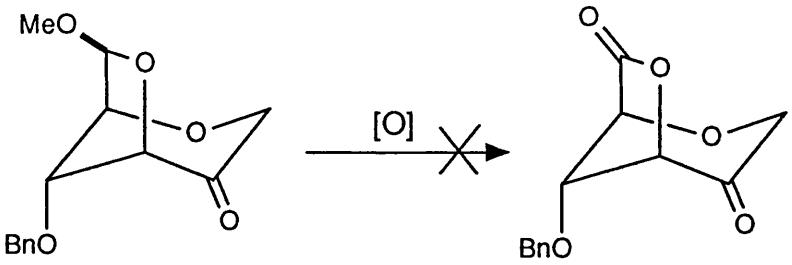
(87) (92)



(93) (94)



(79c)



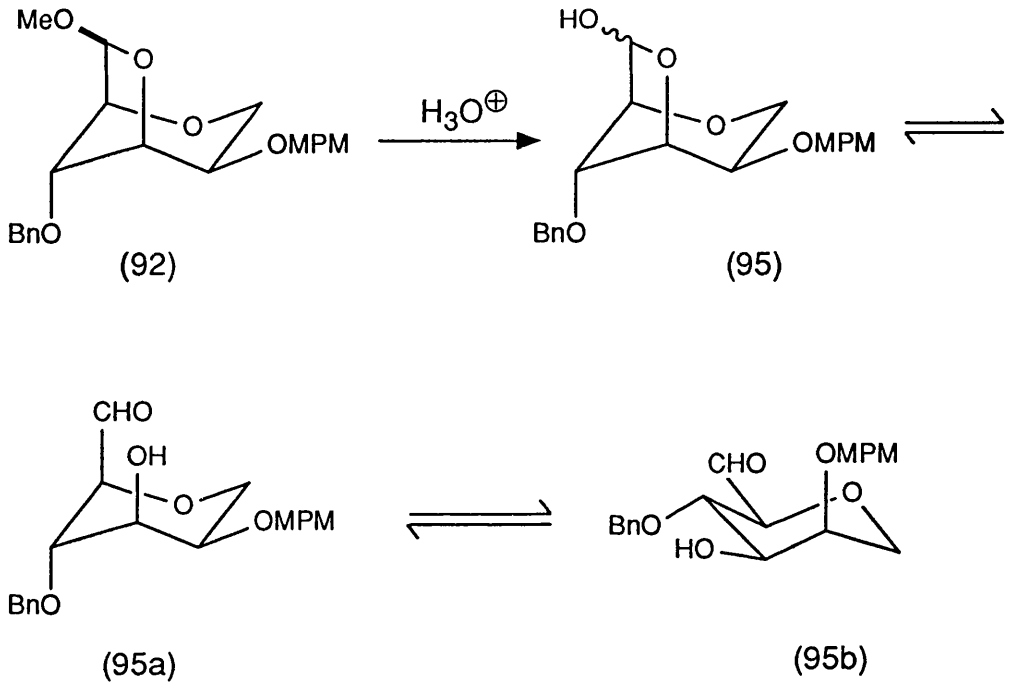
(79b) (79c)

moiety of ketone (79b) followed by hemiacetal oxidation with PCC[101] again resulted in multiple products. A protected version of alcohol (87) was therefore synthesised and elaboration to the required lactone-bridged ketone (79c) carried out as shown in Scheme 42.

Alcohol (87) was treated with sodium hydride in DMF/THF and then alkylated with *p*-methoxybenzyl chloride (MPMCl) to give the *p*-methoxybenzyl ether (92) in good yield. Hydrolysis of the acetal function of the protected derivative (92) was then achieved with dilute sulphuric acid in THF at room temperature; stronger acidic conditions resulted in accompanying loss of the *p*-methoxybenzyl protecting group. Attempted hydrolysis of this acetal function in the presence of lithium tetrafluoroborate[103] also resulted in some loss of the *p*-methoxybenzyl ether moiety.

The product obtained from the hydrolysis of acetal (92) was initially thought to possess the closed hemiacetal structure (95). However, examination of the ^{1}H NMR spectrum of this hydrolysis product revealed an aldehyde proton resonance at δ9.5 and no signal corresponding to the expected hemiacetal proton. Therefore (95) is presumed to exist in solution as an equilibrium mixture of the open, hydroxyaldehyde forms (95a) and (95b), conformer (95b) being favoured since three out of the four functional groups adopt equatorial orientations about the six-membered ring (Scheme 43).

Scheme 43



Subsequent oxidation of hemiacetal (95) with PCC[101] gave lactone (93) in a low yield (Scheme 42). This low yield can be explained by considering the species present in solution during this oxidation reaction. Thus, in dichloromethane, hemiacetal (95) would be expected to exist to a large extent as the open, hydroxyaldehyde form (95b) and so competitive oxidation of both the aldehyde and alcohol functions of this species would be possible, leading to acidic and ketonic by-products. However, since (95b) is also in equilibrium with hemiacetal (95), oxidation to lactone (93) is also possible, the product ratio of lactone to other oxidised products being solely dependant on the relative oxidation rates of these species rather than the proportion of each isomer present in solution.

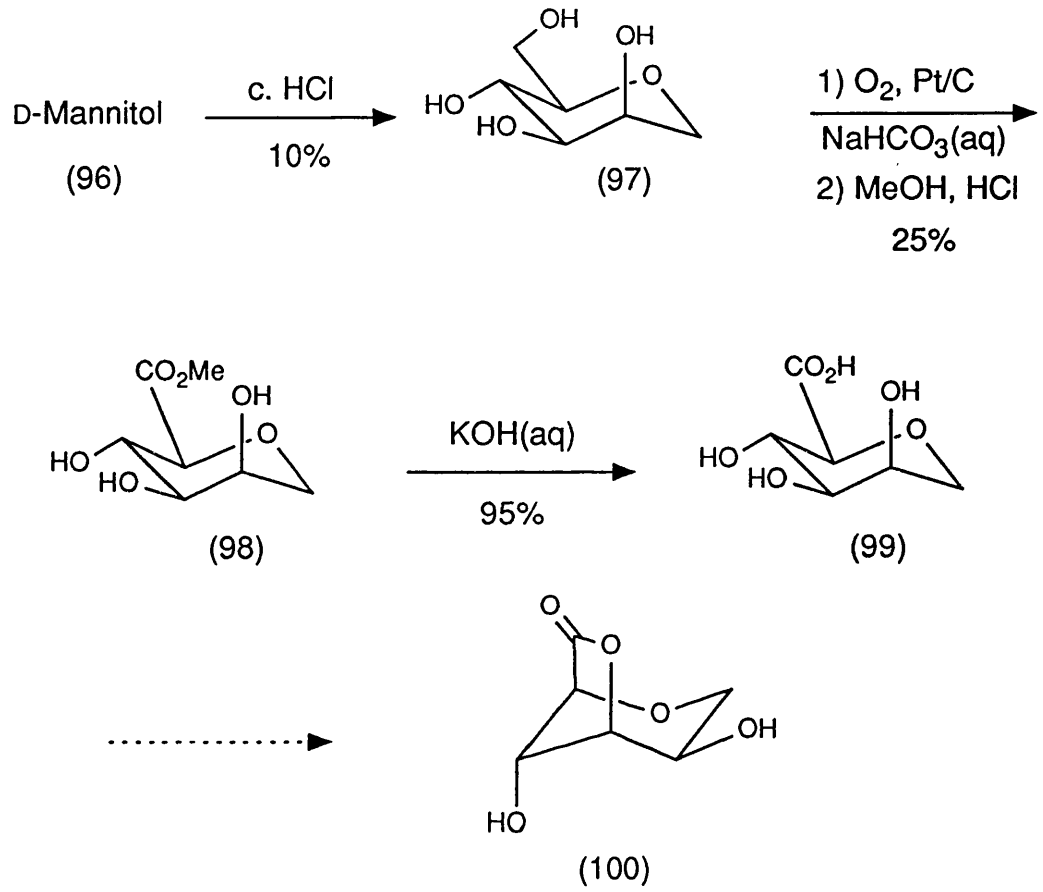
With the lactone bridge now in place removal of the *p*-methoxybenzyl protecting group from lactone (93) was accomplished using DDQ[102] and furnished alcohol (94) in moderate yield. Subsequent oxidation of alcohol (94) with TPAP in the presence of N-methylmorpholine-N-oxide as co-oxidant gave, after an aqueous

work up, essentially pure ketone (79c). However, attempts to obtain an analytically pure sample of ketone (79c) using flash chromatography resulted in decomposition of this substrate.

We have demonstrated that the required lactone-bridged ketone (79c) can be synthesised from acetal (87), although the stability of ketolactone (79c) towards silica gel was low and a complicating factor. However, the major problem encountered with this route was, once again the low yields that were obtained throughout the sequence and the large number of steps required to make the lactone-bridged ketone (79c) (11 steps, overall yield ≈ 0.1%). In order to fully explore the chemistry of ketone (79c) we would require a <u>much</u> shorter and less time-consuming route which would enable multi-gram quantities of ketone (79c) to be produced. With this rationale in mind, a more direct synthesis of lactone-bridged ketone (79c) was accomplished, using D-mannitol as a cheap and readily available starting material (Scheme 44).

Heating a solution of D-mannitol (96) in concentrated hydrochloric acid for two days under reflux using the procedure of Hewitt and Fletcher gave 1,5-anhydro-D-mannitol (97) in low yield[104]. The yield of this reaction, although poor, was relatively unimportant since the above procedure was carried out on up to a 2 mole scale and D-mannitol is very inexpensive. The primary alcohol function of 1,5-anhydro-D-mannitol (97) was then oxidised selectively using an air oxidation protocol catalysed by platinum on carbon[105].

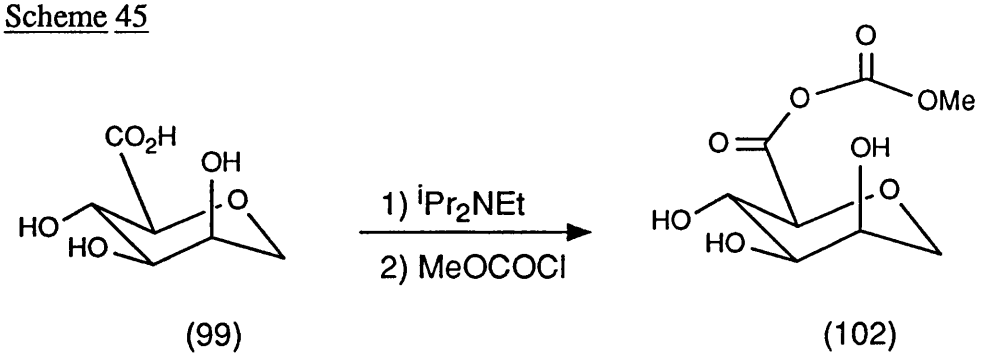
Scheme 44



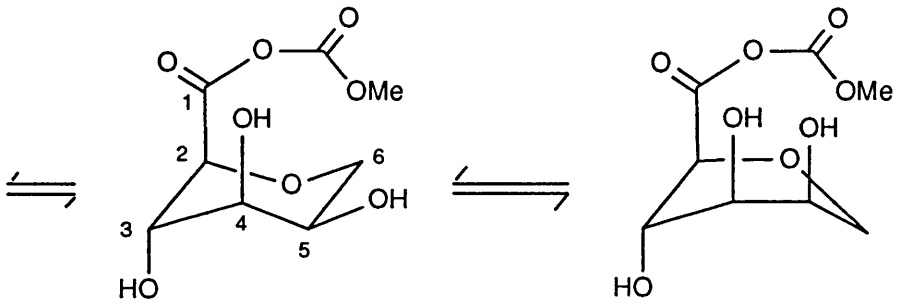
Thus, bubbling oxygen into an aqueous solution of 1,5-anhydro-D-mannitol (97) containing sodium bicarbonate and a catalytic amount of platinum on carbon served to perform the required oxidation. To allow for convenient purification of the oxidised product, we found that prior conversion of the crude reaction product to methyl ester (98) by treatment with HCl in methanol was necessary. Subsequent chromatography and recrystallisation then afforded methyl ester (98) in 25% overall yield.

Methyl ester (98) was then saponified by treatment with aqueous potassium hydroxide solution to give acid (99) in good yield and lactonisation of this acid to the required dihydroxy 1,4-lactone (100) was then attempted. Our initial efforts involved adding Hünig's base to acid (99) and after dissolving the ammonium salt

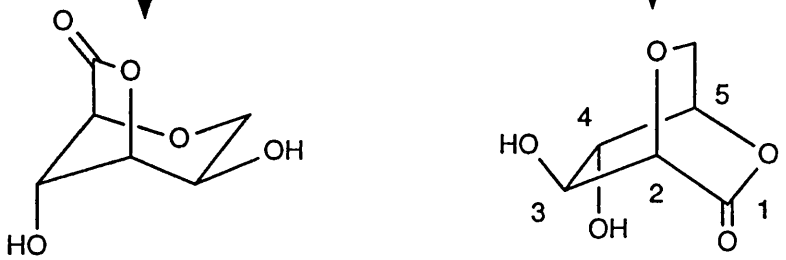
Scheme 45



(99) (102)



(102a) (102b)



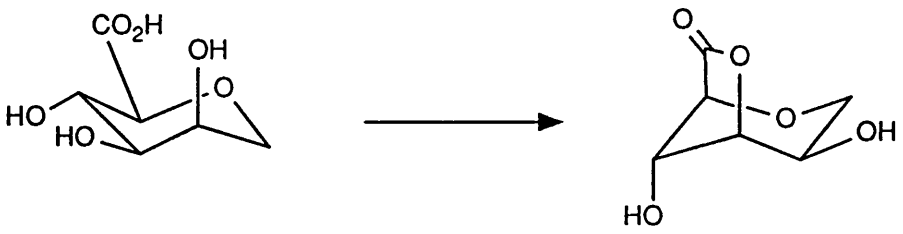
(100) (103)

so formed in dichloromethane, reaction with methyl chloroformate gave the mixed anhydride (102) which then cyclised to form lactone (100) (Scheme 45).

However, this procedure resulted in very low yields (typically 15%) of the required lactone (100) (the formation of (103) will be discussed later). A modification of this procedure which involved diluting the solution of mixed anhydride (102) with chlorobenzene followed by heating gave somewhat better results with the yield of lactone (100) increasing to 30%. In order to make this route more efficient, a higher yield for this lactonisation step was required and so other methods for this transformation were investigated (see Table 1).

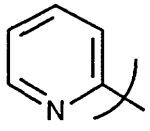
Addition of dicyclohexylcarbodiimide (DCC) to a solution of acid (99) in THF at room temperature gave lactone (100) in a low yield (Entry 3)[106]. Furthermore, this procedure was complicated by the dicyclohexylurea (DCU) by-product which proved to be difficult to separate from the lactone product. In an attempt to simplify the purification procedure, the water-soluble carbodiimide, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride was used to affect lactonisation. However, the relatively high water solubility of dihydroxy lactone (100) led to a substantial loss of product upon work-up. Application of the Yamaguchi lactonisation procedure to acid (99) resulted in the decomposition of the substrate, no lactone (100) being isolated. In an attempt to improve the yield of lactone (100) obtained the double activation method developed by Corey was implemented[108] (Scheme 46).

TABLE 1

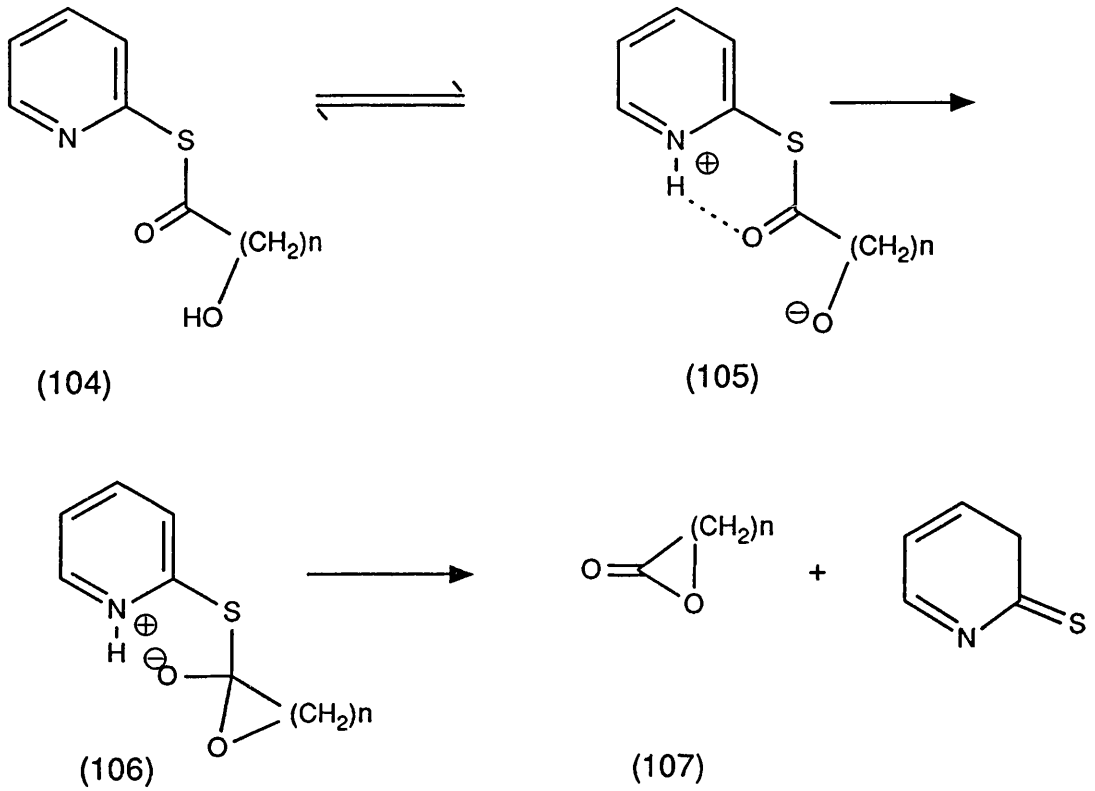


(99) (100)

Conditions	Yield/%
1) $^{i}Pr_2NEt$, CH_2Cl_2; MeOCOCl	15
2) As 1) then PhCl, Δ	30
3) DCC, HOBT, THF	15
4) Et_3N, THF; 2,4,6-$Cl_3C_6H_2COCl$, DMAP	0
5) $Me_2NC_3H_6N{=}C{=}NC_2H_5$.HCl, HOBT, THF	15
6) a. $(R'S)_2$, PPh_3, $PhCH_3$	5
b. $(R'S)_2$, PPh_3, DMF	18
7) $H^{\oplus}$, $PhCH_3$	0
8) $^{i}Pr_2NEt$, THF; MeOCOCl	71

Where R'= 

Scheme 46



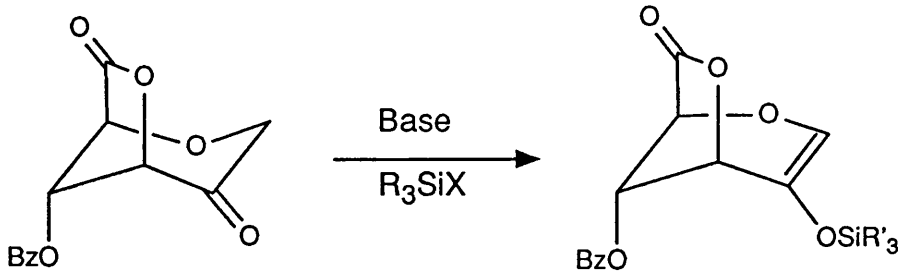
For the 2-pyridinethiol ester (104), proton-transfer from the hydroxyl to the carbonyl is facilitated by the pyridine nitrogen. Such an internal proton-transfer would generate the dipolar intermediate (105) which would undergo an electrostatically-driven cyclisation to (106) which would then give lactone (107) by elimination of 2-pyridthione.

The application of Corey's standard conditions for the synthesis and subsequent lactonisation of the 2-pyridinethiol ester of acid (99) gave a very poor yield of lactone (100) (Entry 6a, Table 1). However, when this reaction was carried out in DMF as the solvent, formation of the desired lactone (100) was observed on standing at room temperature. Subsequent work up and chromatography gave the lactone (100) in 18% yield. However, in order to separate the product lactone (100) from the 2-pyridthione by-product a methanol/dichloromethane solvent system was used in the chromatography step and these conditions were later shown to cleave

lactone (100) to give methyl ester (98). Indeed, in a repeat of this reaction, upon work-up and chromatographic purification lactone (100) and methyl ester (98) were obtained in a combined yield of 35%.

With this solvent effect in mind we repeated the Hünig's base/methyl chloroformate lactonisation method (Entry 1, Table 1) but with DMF in place of dichloromethane. After stirring at room temperature for six hours t.l.c. indicated that acid (99) had been consumed and, after work-up, lactone (100) was isolated in 70% overall yield. In order to simplify the work up procedure, this reaction was then repeated using THF as solvent which resulted in lactone (100) being isolated in 71% yield along with a minor component, thought to be lactone (103) in 4% yield. The formation of this six-membered lactone (103) can be explained by consideration of the mechanism illustrated in Scheme 45. If the mixed anhydride conformer (102a) undergoes a chair-boat interconversion to generate conformer (102b) then C(5)-OH could compete with C(4)-OH and cyclisation to give 1,5-lactone (103) could occur. This competition reaction is analogous to the formation of both furanoside (86) and the pyranoside isomer (84) from the cyclisation of dimethyl acetal (85) under acid catalysis (see Scheme 37). With an effective lactonisation method now in hand, we sought to convert dihydroxy-lactone (100) to ketone (79c). Using the selective benzylation procedure that had been successfully applied to diol (86) (Scheme 39) in the acetal-bridged series resulted in decomposition of the lactone starting material. This is most likely explained by the attack of an alkoxide function of one molecule on the lactone bridge of another, resulting in dimeric and higher polymeric materials being formed. However, treatment of a solution of dihydroxy-lactone (100) in dichloromethane with one equivalent of DMAP followed by dropwise addition of one equivalent of benzoyl chloride gave, after standing at 20°C for eighteen hours, monobenzoate lactone (108) in 46% yield along with dibenzoate (109) in 18% yield and recovered lactone (100) in 19% yield. The reason for the high selectivity observed in this benzoylation procedure is not entirely

TABLE 2



(79d) (110)

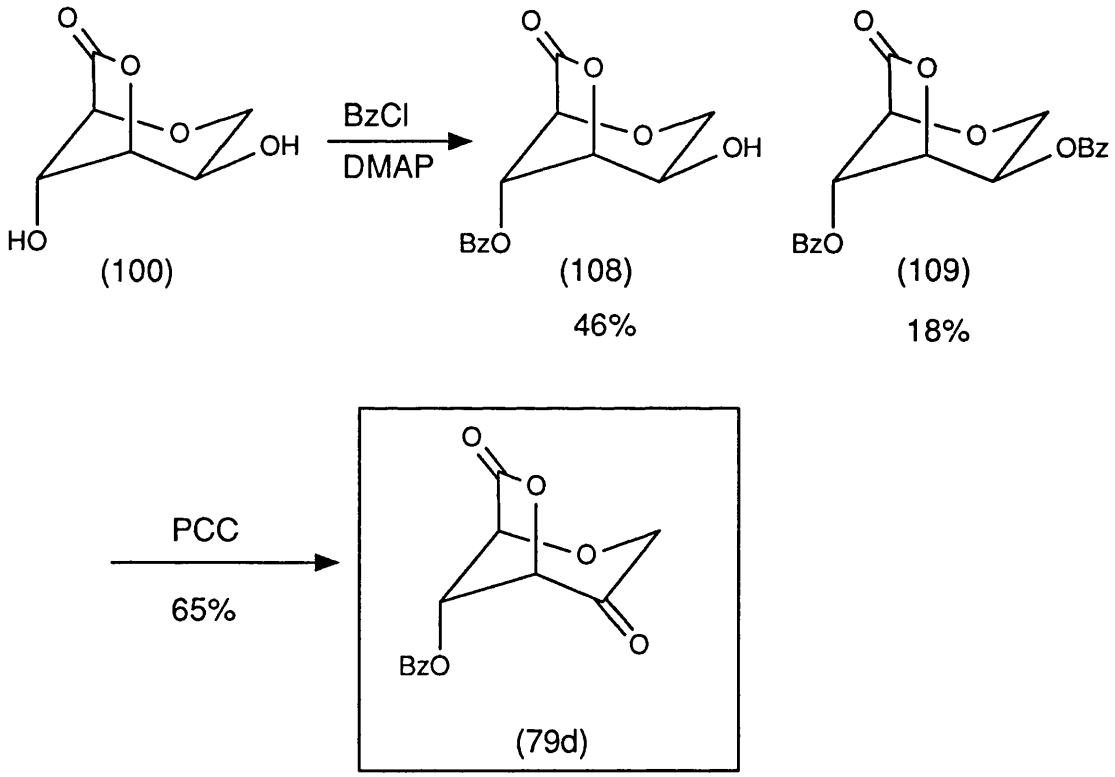
NOT ISOLATED

Conditions	Result	Reference to procedure
LDA, THF, TBSCl -78°C	Decomposition of substrate	109
KH, TBSCl, THF -78 - 20°C	No silyl enol ether, ketone decomposed at 20°C	92
TMSCl, DMF, Et_3N	Decomposition of substrate	110
TBSOTf, 2,6-lutidine 0 - 20°C	Complex mixture of products	111
$Me_3SiCH_2CO_2Et$ Bu_4NF 0 - 20°C	No reaction at 0°C, decomposition on warming	112

clear, since both alcohol functions at C(3) and C(5) experience similar steric and electronic interactions with neighbouring groups.

Subsequent oxidation of monobenzoate (108) was then achieved with PCC which gave, after a simple filtration through Florisil, essentially pure lactone-bridged ketone (79d) in moderate yield (Scheme 47).

Scheme 47



With our required lactone-bridged ketone (79d) now available we proceeded to investigate the synthesis and reactivity of the silyl enol ether derivative (110). However, all attempts at synthesising silyl enol ether (11) were unsuccessful as shown (Table 2). Notably, treatment of ketone (79d) with a strong, but non-nucleophilic base, (LDA) (Entry 1, Table 2) immediately decomposed the ketolactone (79d). These disappointing results were thought to be indicative of the inherent reactivity of the lactone-bridged ketone (79d) which is due largely to

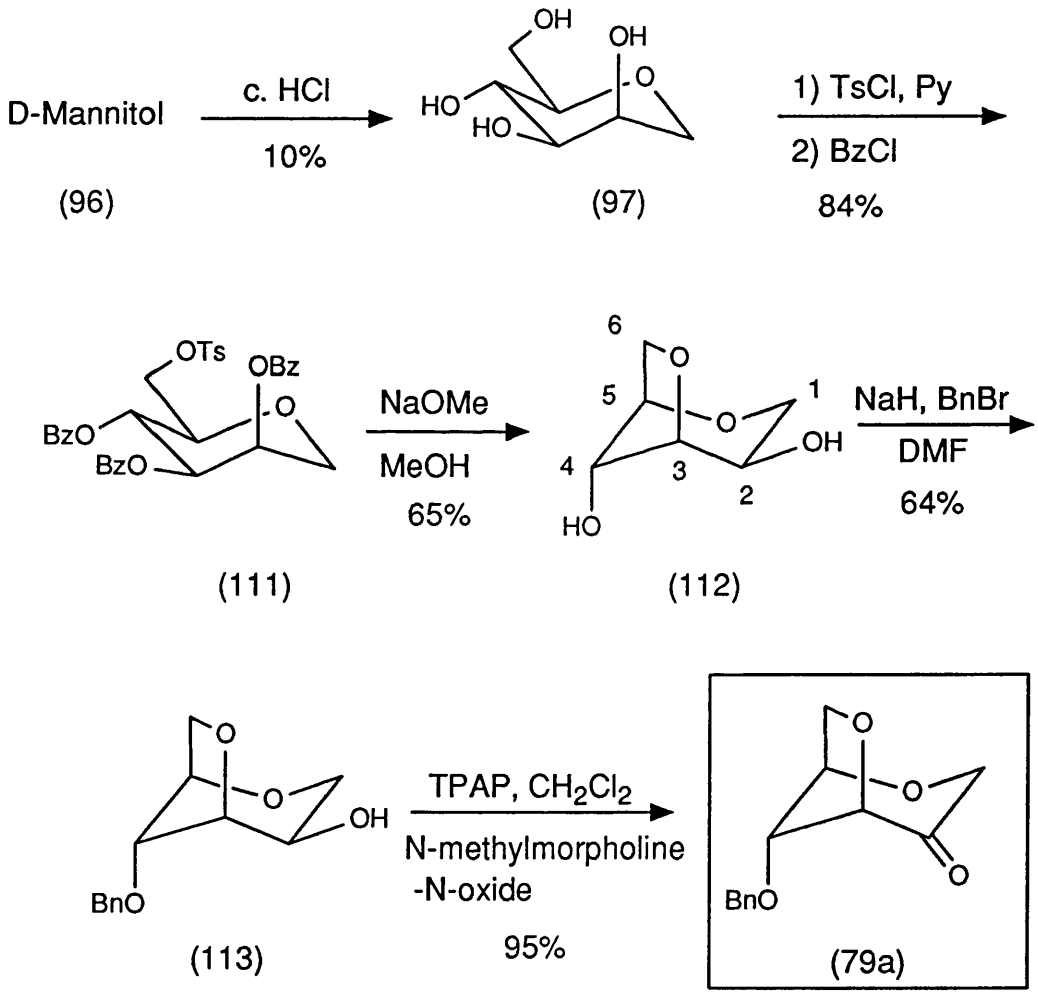
ring-strain, the instability of (79d) towards silica having been previously noted. The strained nature of ketone (79d) was confirmed by the examination of the infrared spectrum (IR) of this compound. If ketone (79d) possessed no extra strain by virtue of its bicyclic nature, then the six-ring ketone carbonyl would be expected to absorb at around 1715 cm^{-1} and the lactone carbonyl at 1770 cm^{-1}. However, the measured value for the ketone carbonyl was 1750 cm^{-1}, a value usually associated with the strained cyclopentanone ring. Similarly, the carbonyl stretch of the lactone function of ketone (79d) absorbed at 1820 cm^{-1} which is close to the value expected for a four-membered saturated lactone (typically 1840 cm^{-1})[113]. Thus, the effect of putting two sp^2-hybridised carbon atoms into a bicyclo [3.2.1] system such as ketone (79d), is to introduce severe strain into the molecule which, in this specific example results in an unstable and highly reactive compound.

To summarise, the lactone-bridged ketone (79d) was initially an attractive molecule from the point of view of being a flexible precursor for C-glycoside synthesis and for the herbicidins in particular due to the presence of the correct oxidation level at C(1). However, this combination of functional groups proved to be unsuitable due to its highly reactive nature and more detailed studies of ketone (79d) were postponed at this stage in favour of pursuing more thoroughly the chemistry of the ether-bridged ketone (79a). The results of this study will be discussed in detail in the next section.

2.4 SYNTHESIS AND REACTIVITY OF AN ETHER-BRIDGED KETONE

As previously stated, concurrent with our synthetic studies based on the lactone-bridged ketone (79d) we also undertook a study of the chemistry of the ether-bridged derivative (79a). The synthesis of this ketone is illustrated below (Scheme 48).

Scheme 48



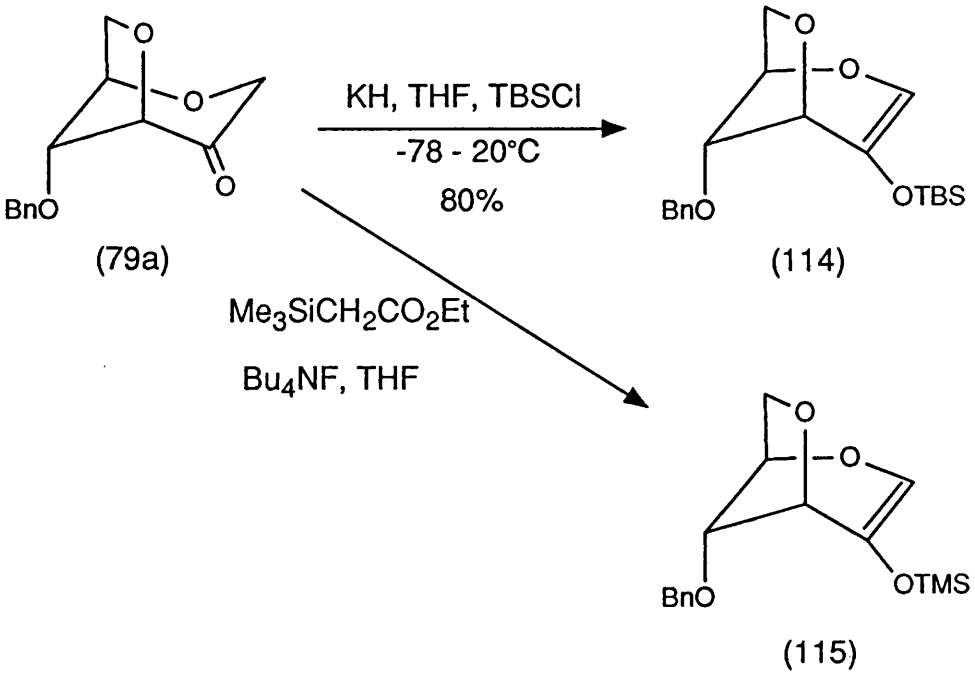
Our approach was based on the selective protection and oxidation of the ether-bridged diol (112), a strategy which had proved to be successful in both the acetal- and lactone-bridged series. The requisite diol, 1,5:3,6-dianhydro-D-mannitol ("neomannide") (112) was readily available from D-mannitol (96) using the

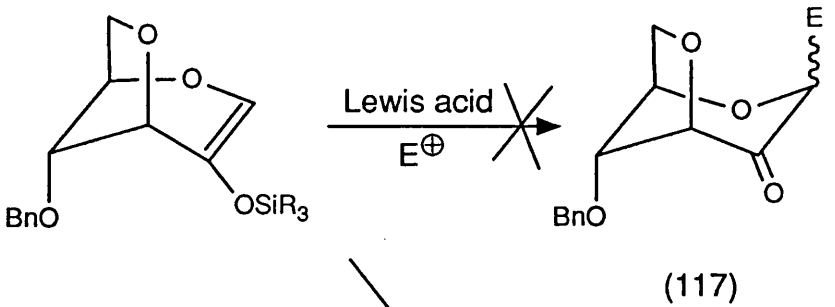
literature procedures shown[104,112]. Cyclisation of D-mannitol (96) to the corresponding 1,5-anhydride (97) could be achieved, albeit in low yield, by treatment of D-mannitol (96) with concentrated hydrochloric acid as previously described[104]. Subsequent selective tosylation of the primary alcohol function of anhydride (97) and benzoylation of the secondary hydroxyls using the procedure of Hockett and Sheffield gave bicycle (111) as a crystalline solid in high yield, no chromatographic purification being required[114]. Cyclisation of this material to 1,5:3,6-dianhydro-D-mannitol (112) was affected by heating a solution of tosylate (111) in methanol containing sodium methoxide under reflux which also served to remove the benzoate protecting groups[114]. Upon work up, diol (112) could be obtained pure in moderate yield upon crystallisation of the crude product without resorting to a chromatographic separation.

With diol (112) in hand, a selective protection of the C(4) hydroxyl function was attempted using the benzylation conditions which had successfully been applied to the acetal-bridged diol (86). This procedure[84] proved to be useful but the reaction was sluggish when THF was employed as solvent and we found that optimum yields of the monobenzyl derivative (113) and much shorter reaction times could be obtained when the solvent was changed to DMF. In this way, the monobenzylated alcohol (113) could be obtained in 64% yield, the only other components isolated being the corresponding dibenzyl derivative and recovered diol (112)[115]. To complete the synthesis, the benzyl protected derivative (113) was then oxidised to give our required ketone (79a). Initial efforts using PCC as the oxidising agent gave an optimum yield of 75% of ketone (79a) from alcohol (112)[115] but, the use of TPAP as oxidant afforded ketone (79a) in excellent yield, demonstrating that our required ether-bridged ketone could be synthesised in high overall yield from a readily available starting material (32% from 1,5-anhydro- D-mannitol (97)).

Our initial strategy for the synthesis of the herbicidins was to apply the

Scheme 49





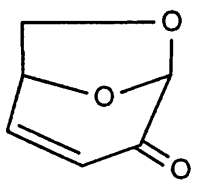
R_3 = TMS, TBS

Conditions

(i) $PhSCH_2Cl$ (91), $ZnBr_2$, CH_2Cl_2, 0°C

(ii) (91), AgOTf, CH_2Cl_2, -78 - 0°C

(iii) PhCHO, $TiCl_4$, CH_2Cl_2, -78°C



(116)

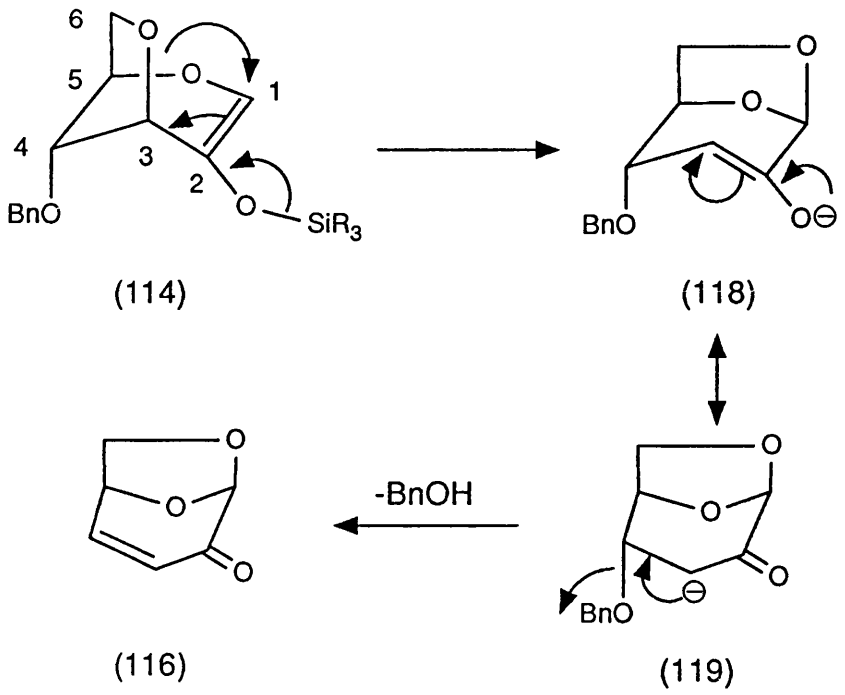
"levoglucosenone"

Lewis acid-mediated phenylthio-alkylation procedure used by Cox in the model study previously described (see Scheme 36) to a silyl enol ether derivative of the ether-bridged ketone (79a). If such an alkylation could be carried out then the issue of an oxidative cleavage of the ether bridge would need to be considered. However, we chose initially to focus our efforts on the Lewis acid-mediated alkylation chemistry previously described, the results of this study are shown in Scheme 49.

The ether bridged ketone (79a) was converted to the silyl enol ether (114) by treatment with potassium hydride and *tert*-butyldimethylsilyl chloride. This silyl enol ether derivative (114) was quite stable and a purification by flash chromatography was possible with no noticeable hydrolysis being observed.

Subsequent treatment of silyl enol ether (114) with α-chlorosulphide (91) in the presence of zinc bromide at 0°C gave one major component upon work up. However, examination of the ^{1}H NMR spectrum of this product indicated that it was not the required alkylated derivative (117) and furthermore, loss of the benzyl protecting group had also taken place under these reaction conditions. This had presumably occurred via a β-elimination since vinyl proton signals were also observed in the ^{1}H NMR spectrum. Closer examination revealed that the coupling pattern of the methylene group at C(6) of this compound was substantially different from that of silyl enol ether (114) and this evidence prompted us to speculate that a skeletal rearrangement had also taken place. This ^{1}H NMR evidence, along with mass spectral data and an IR spectrum suggested enone (116) (known as levoglucosenone) as the major product of this reaction, a product that is also derived from the degradation of cellulose. The proposed mechanism of formation of levoglucosenone from (114) is illustrated below (Scheme 50).

Scheme 50



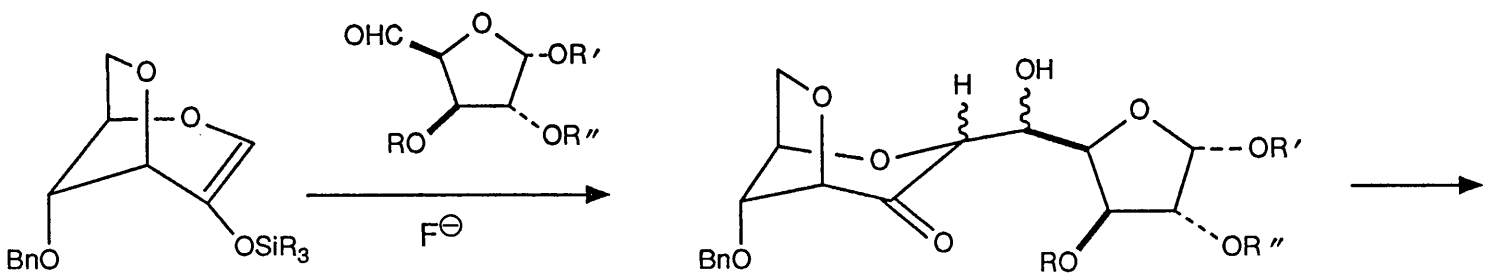
(114) (118) (116) (119)

Migration of the bridge from C(3) to C(1) accompanied by isomerisation of the intermediate enolate (118) to the 1,6-anhydro derivative (119) would be followed by β-elimination of benzyl alcohol to generate enone (116) having the preferred (Z) double bond geometry. To confirm our prediction, the published ^{1}H NMR data for levoglucosenone[116] matched the spectrum obtained for our product, thus proving our assignment.

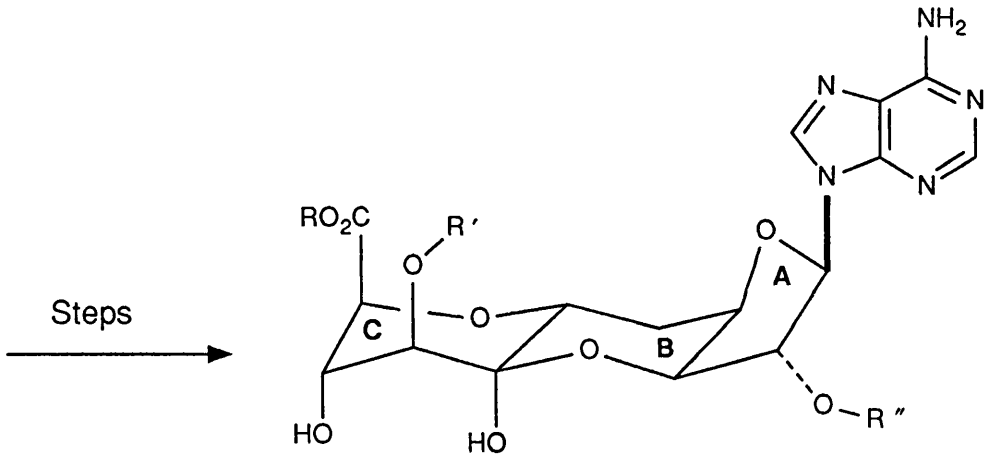
A similar rearrangement was also noted when silver triflate was used as the Lewis acid and an attempted titanium tetrachloride-mediated aldol reaction with benzaldehyde[91a] also gave levoglucosenone (116) as the only product.

In an attempt to increase the reactivity of the silyl enol ether component, the trimethylsilyl enol ether (115) was prepared from ketone (79a) by treatment with ethyl (trimethylsilyl) acetate with tetrabutylammonium fluoride as catalyst according to the procedure described by Noyori[118]. However, under the Lewis acid conditions previously applied to enol ether (114), the trimethylsilyl derivative (115)

Scheme 51



(114a)



Herbicidin (65)

afforded levoglucosenone (116) as the sole product even at low temperatures. The chemistry of this silyl enol ether (115) was further compromised by its ease of hydrolysis and so further studies on this material were not carried out.

These preliminary results conclusively demonstrated that a Lewis acid-mediated coupling of the type previously used by Cox[75] would not be a suitable approach for C-glycoside synthesis, since the silyl enol ether derivatives (114) and (115) underwent a facile skeletal rearrangement. However, the synthetic utility of (114) and (115) is not limited solely to their Lewis acid-mediated alkylation chemistry. The generation of the required C(1) "anomeric" enolate could be carried out by treatment of a suitable silyl enol ether derivative with methyl lithium[98] or tetrabutylammonium fluoride[97] and the application of this methodology to the aldol reaction for example is well documented[117]. Such an approach could be applied to the synthesis of the herbicidins, using a suitably protected furanoside aldehyde as the ring A portion (Scheme 51).

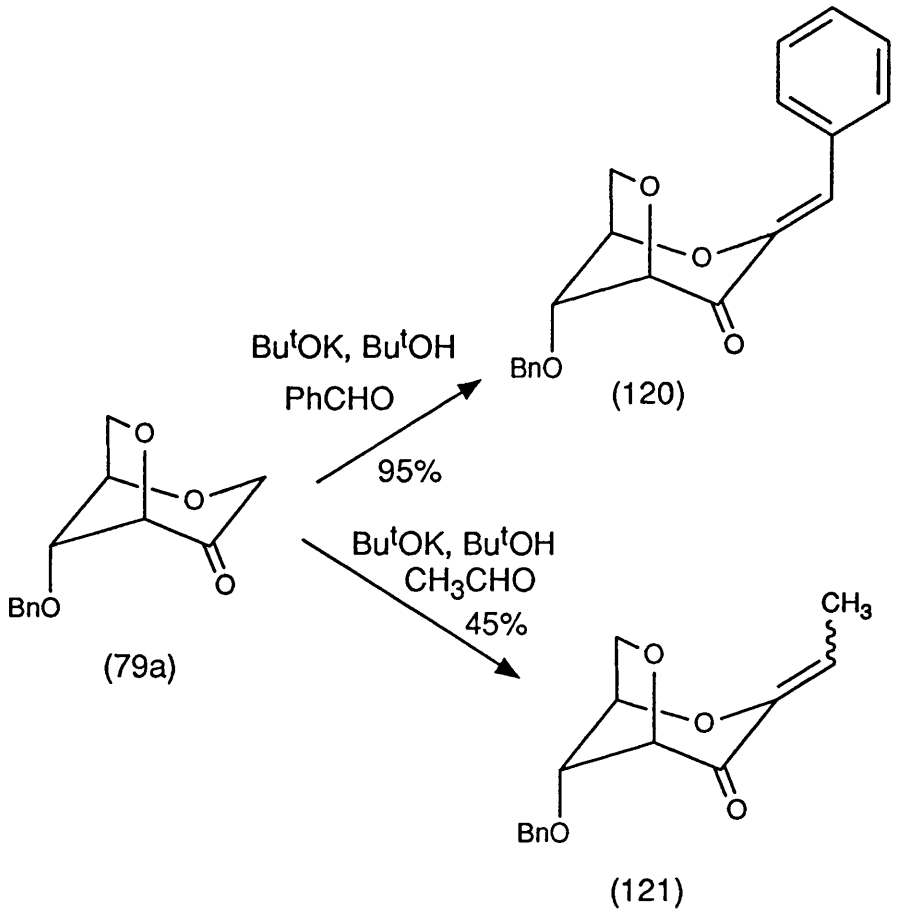
An aldol reaction between silyl enol ether (114a) and a furanoside derived aldehyde would give access to the coupled products shown. Subsequent transformations would then allow elaboration to members of the herbicidin family of natural products.

In tandem with the Lewis acid-mediated chemistry of the silyl enol ether derivatives (114) and (115), simple alkylations of ketone (79a) were also studied. The success of these reactions led to a suspension of work on the silyl enol ether chemistry and the commencement of studies on the aldol reactions of ketone (79a). The preliminary results of some of these aldol reactions are illustrated in Scheme 52.

Treatment of a solution of ketone (79a) containing benzaldehyde in *tert*-butanol with potassium *tert*-butoxide gave, after work up and chromatography,

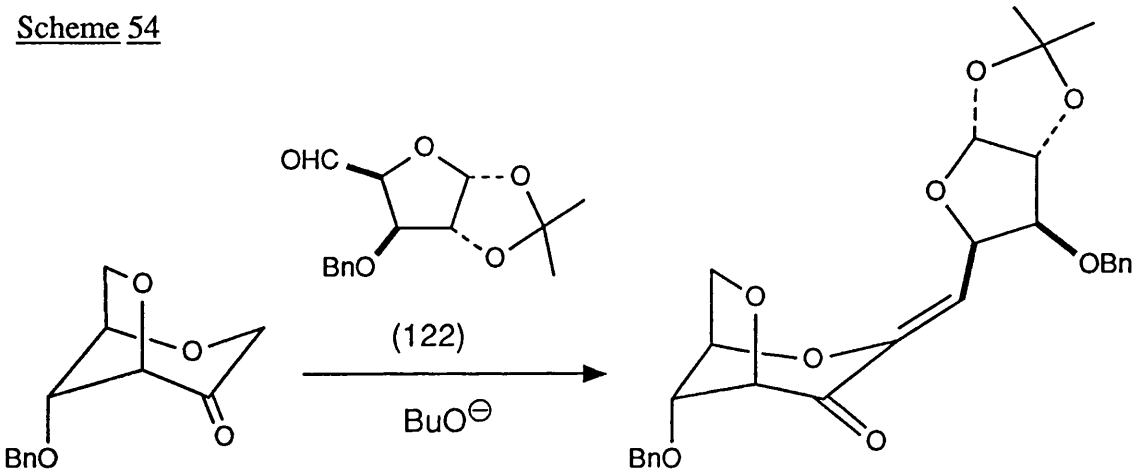
enone (120) as a single geometrical isomer in excellent yield. The geometry about the enone double bond of (120) was not determined, but would be expected to adopt the (Z)-geometry as shown since the (E)-isomer would suffer an unfavourable steric interaction between the phenyl ring and the carbonyl oxygen. A similar reaction with acetaldehyde gave enone (121) as a mixture of (E)- and (Z)- isomers in moderate yield.

Scheme 52

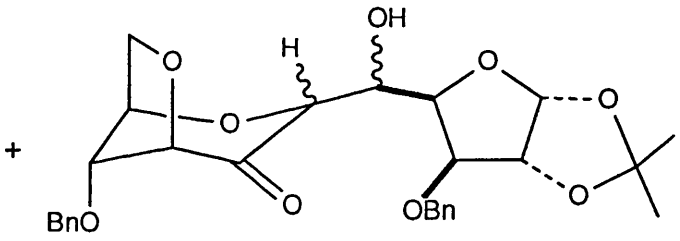


The success of these preliminary reactions prompted us to investigate the coupling of a furanoside aldehyde derivative with ketone (79a) as a facile route to the herbicidin core. The requisite aldehyde (122) was conveniently synthesised using the literature procedures[118] outlined in Scheme 53. Protection of the alcohol function of diacetonide (123) as a benzyl ether was accomplished in good yield

Scheme 54



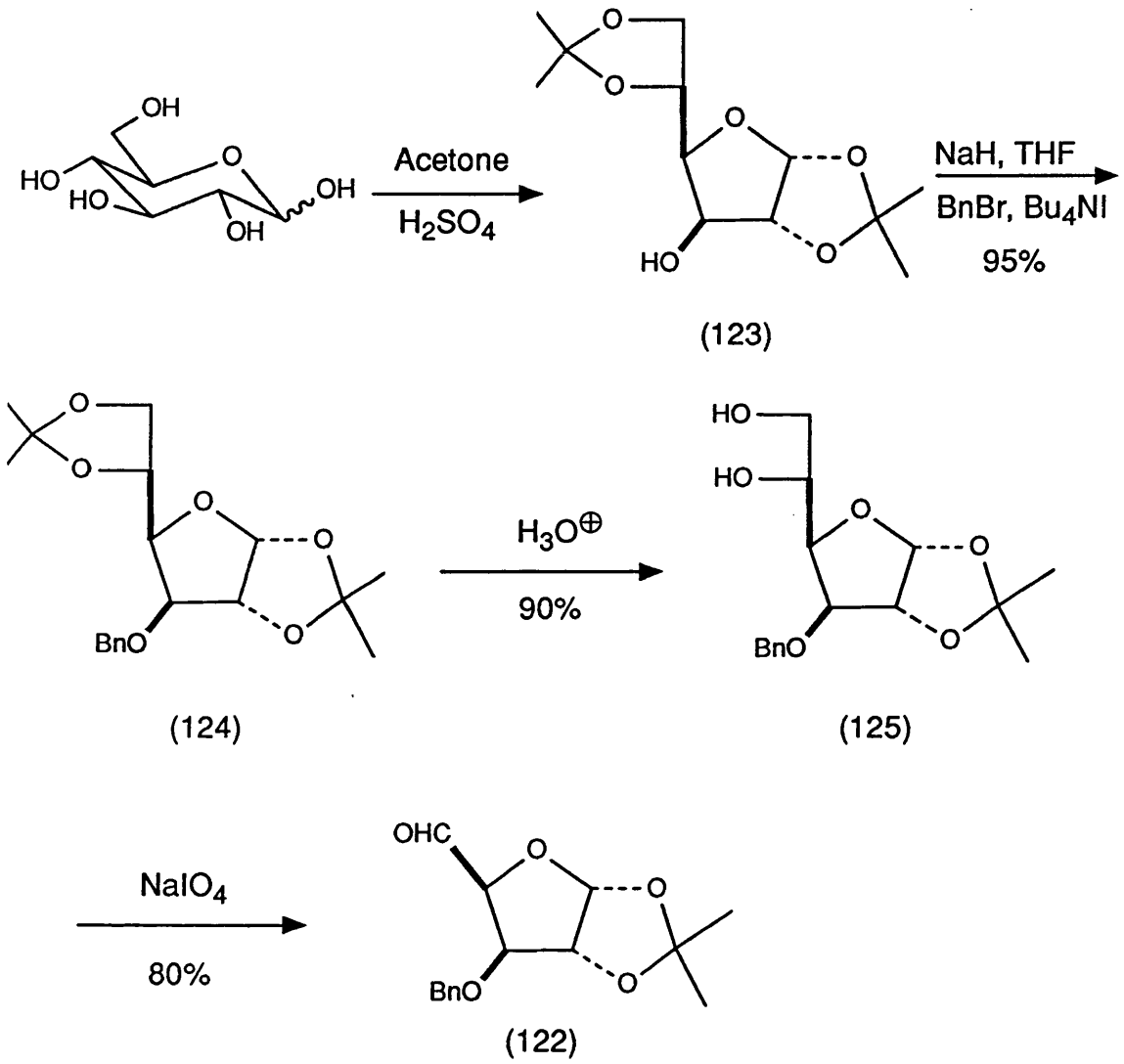
(79a) (126)



Conditions	Results
Bu^tOK, Bu^tOH, 25°C	Complex mixture of products, some (126) present
Bu^tOK, THF, 0°C	60% yield of (126) + aldol products

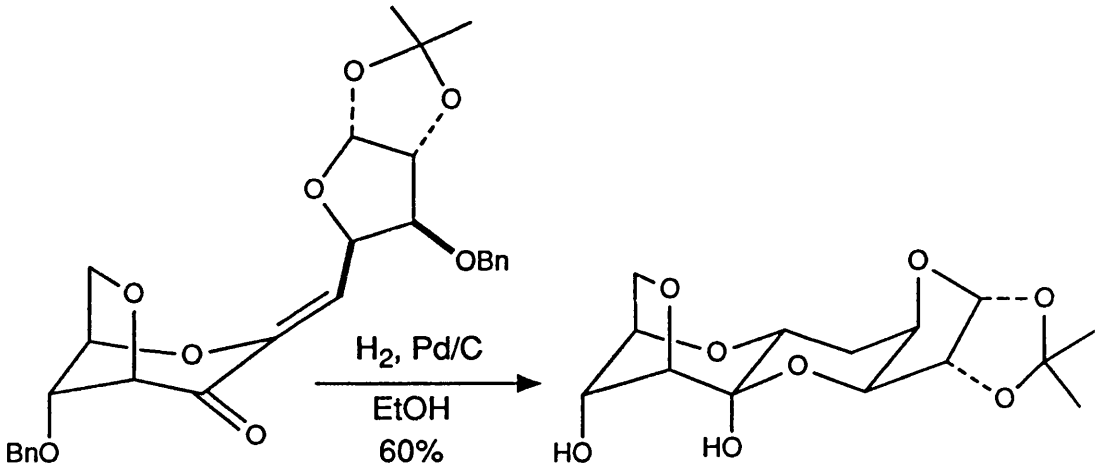
using the previously described procedure[84]. The selective hydrolysis of the C(5)-C(6) acetonide protecting group of (124) was then carried out by warming in aqueous acetic acid which served to furnish diol (125) in good overall yield.

Scheme 53



Diol (125) was then cleaved with sodium periodate using the procedure of Fraser-Reid[118] to give the hydrate of the required aldehyde (122). Azeotropic drying in a Dean-Stark trap using toluene as solvent then gave the free aldehyde (122) as an oil which was used in the subsequent aldol condensations without any further purification (Scheme 54).

Scheme 55



(126) (127)

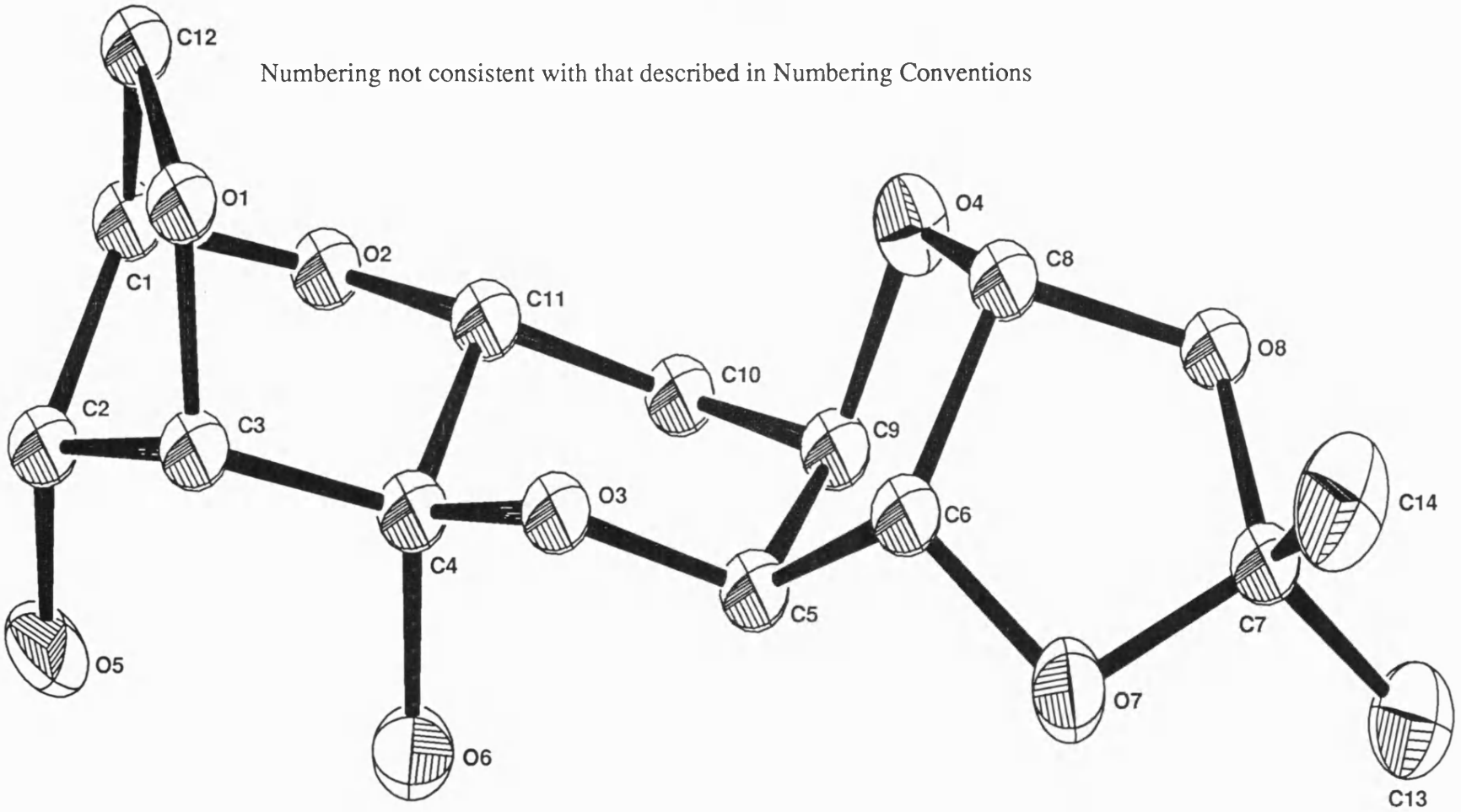
Reaction of aldehyde (122) and ketone (79a) in *tert*-butanol with potassium *tert*-butoxide at 25°C afforded a major, strongly UV active spot. However ^{1}H NMR studies of this product indicated that it consisted of at least three major components, one of which being the required enone (126). When this condensation reaction was carried out at 0°C with THF as the solvent there were no such complications and enone (126) could be isolated in up to 60% yield after purification by flash chromatography. The mass balance of material from this reaction was made up of aldol products, although at this stage the structure and reactivity of these compounds was not further investigated.

Again, the geometry of the enone double bond would be expected to be (Z) as shown due to an unfavourable steric interaction between the benzyloxy substituent on the furanose ring and the ketone moiety at C(7), although this has yet to be determined. The gross structure of enone (126) was confirmed by 400 MHz ^{1}H NMR studies (and COSY for assignments) and ^{13}C NMR spectroscopy since it proved impossible to obtain crystalline material suitable for an X-ray structural analysis.

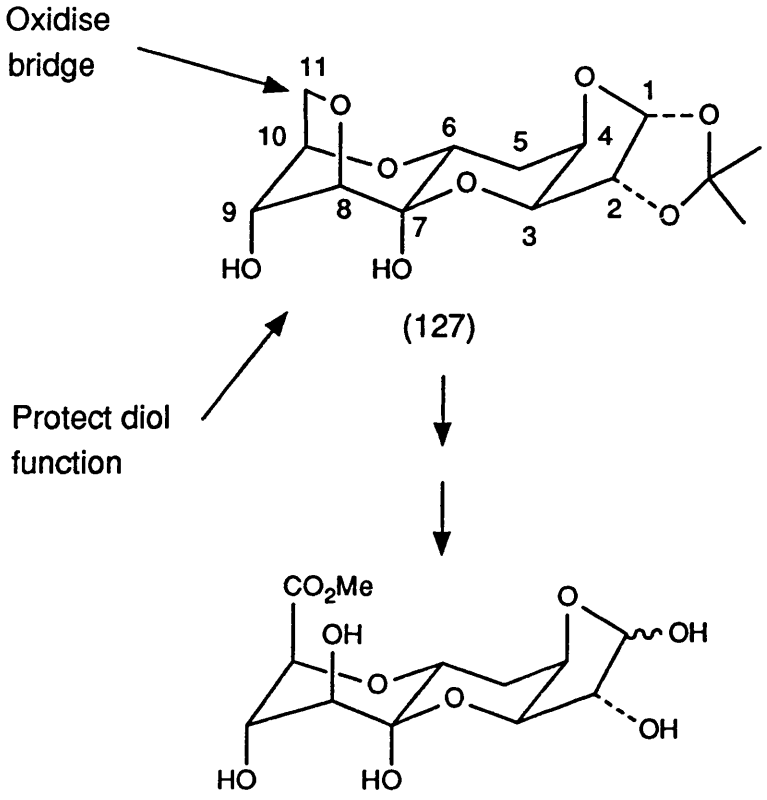
With enone (126) in hand reduction of the enone double bond was achieved by hydrogenation over palladium on carbon (Scheme 55). As shown, face-selective reduction was accompanied by O-debenzylation to give hemiketal (127) containing the furo-pyrano-pyran core of the herbicidins in moderate yield. The structure of (127) was determined by X-ray crystallographic analysis which served to confirm the stereochemistry at C(6) and C(7) and the presence of the hemiketal function as shown.

ORTEP diagram of diol (127)

Numbering not consistent with that described in Numbering Conventions

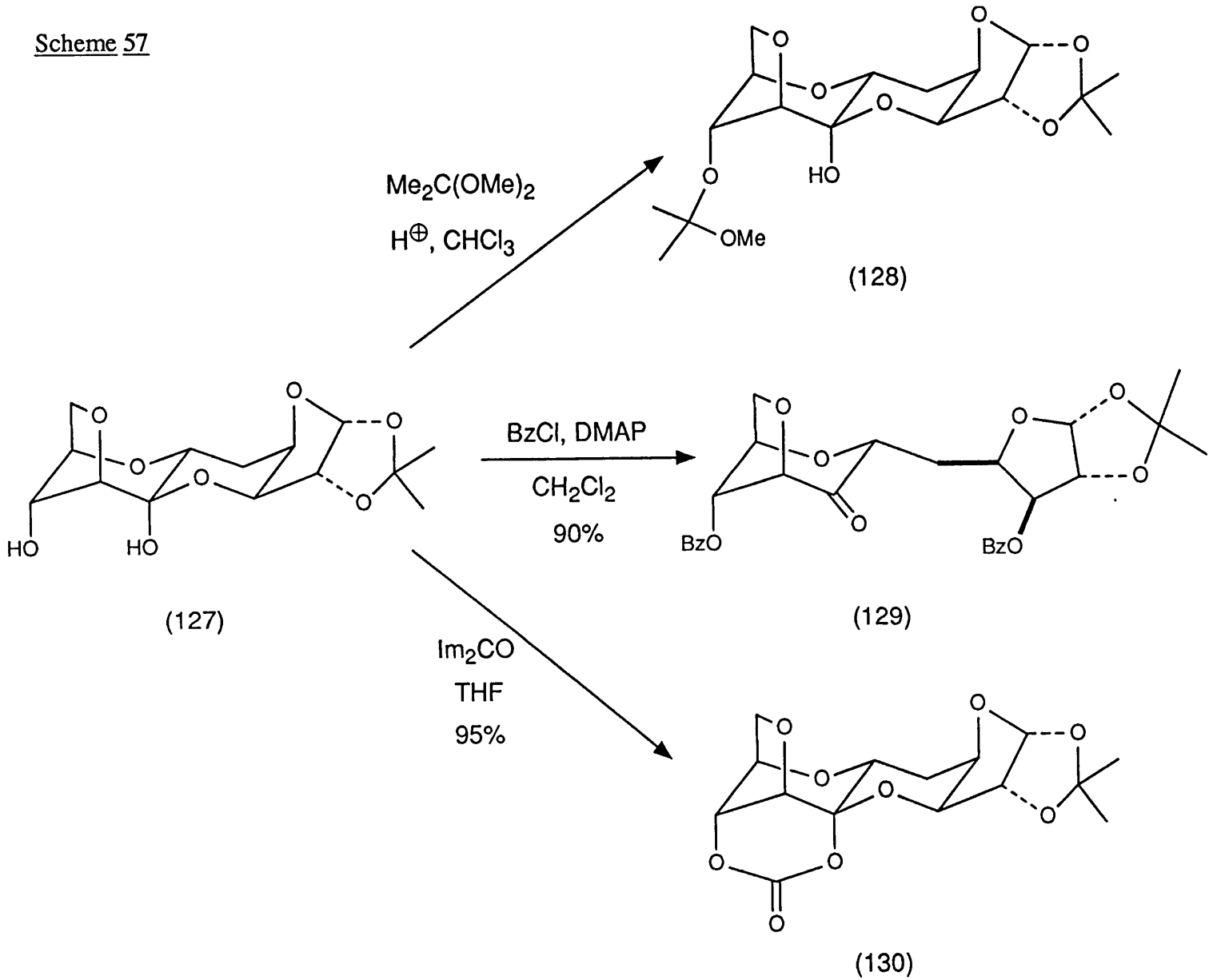


Scheme 56



Conversion of hemiketal (127) to the herbicidin skeleton (151) would require an oxidation of the C(11) methylene to the corresponding lactone (or ester) and to achieve this transformation, prior protection of the C(7)\C(9) diol function would also be necessary. This strategy is outlined in Scheme 56 and the results of our synthetic studies will be discussed in the next section.

Scheme 57

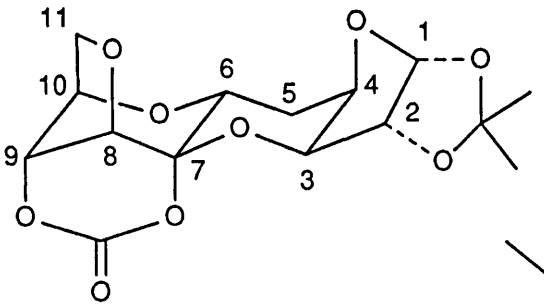

Me2C(OMe)2
H⊕, CHCl3
HO
OMe
(128)
BzCl, DMAP
CH2Cl2
90%
HO
HO
(127)
BzO
BzO
(129)
Im2CO
THF
95%
(130)

2.5 SYNTHESIS OF THE C-11 UNDECOSE CORE OF THE HERBICIDINS

As illustrated in Scheme 56, the first step in our proposed conversion of tricycle (127) to the herbicidin glycoside core required the protection of the diol functionality, however, preliminary attempts at protecting the C(7) and C(9) hydroxyls as an acetonide group proved unrewarding. Treatment of diol (127) with an excess of dimethoxypropane in chloroform at reflux containing *p*-toluenesulphonic acid afforded one major product. The structure of this product has been assigned as (128) on the basis of spectral data (see Scheme 57). An attempt at a cyclisation of (128) to the required acetonide by treatment with *p*-toluenesulphonic acid in toluene resulted in cleavage back to diol (127). Reaction of (127) with acetone in the presence of either mineral acid or a Lewis acid also failed to give the required diacetonide. These results can be explained by the low nucleophilicity of the hemiketal hydroxyl at C(7) since it is both tertiary and electron-deficient due to the neighbouring ring oxygen atom. Also, upon examination of a molecular model of the required C(7)-C(9) acetonide derivative of diol (127), the observation was made that the six-membered ring of the acetonide function would be forced to adopt the disfavoured boat conformation.

As an alternative to acetonide protection the diol (127) was reacted with a large excess of benzoyl chloride in the presence of DMAP to give a dibenzoylated derivative in good overall yield. However, close examination of the ^{1}H NMR spectrum of this compound revealed a significant change in the coupling pattern between the methylene protons at C(5) and the methine proton at C(6) compared to that of diol (127). This change was attributed to the bis(benzoate) isolated having the "open" structure (129) (Scheme 57). Loss of the hemiketal function would remove the conformational lock about the C(5)-C(6) bond and the couplings between the C(5) methylene and the C(6) methine would therefore be significantly altered, although the large $J_{5e,5a}$ geminal coupling would remain relatively

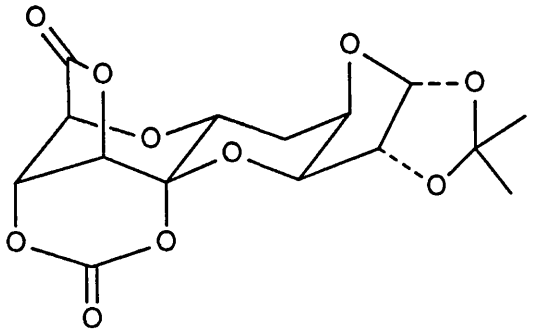
Scheme 58



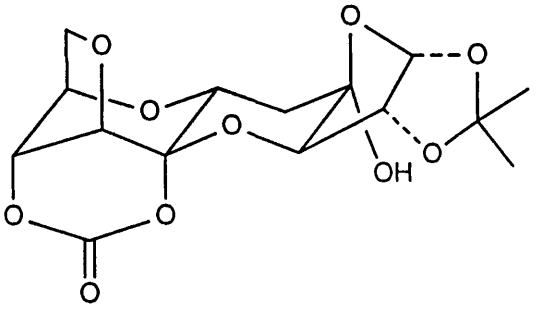
(130)

[O]

Mn_2O_7
CCl_4, Me_2CO
10%



(131)



(132)

Oxidants

RuO_4,CCl_4

$RuCl_3(RuO_2)$, $NaIO_4$, CH_3CN, CCl_4, H_2O

H_2CrO_4, Me_2CO

$Bn(Et)_3N^{\oplus}MnO_4^{\ominus}$

Mn_2O_7, CCl_4, Me_2CO

unchanged. Benzoate (129) would arise as a result of the secondary alcohol function of the open form of hemiketal (127) reacting at a faster rate than the tertiary alcohol of the closed form, the open and closed forms being in equilibrium in solution.

This benzoylation reaction, although succeeding in our primary aim of protecting the C(7) and C(9) alcohol functions of diol (127) was not used in our proposed synthesis of the herbicidins since a protected derivative retaining the tricyclic skeleton of (127) would be preferable. This would lessen the chance of any complications at latter points in the synthesis arising from, for example, epimerisation at C(6) adjacent to the ketone moiety of an open chain compound such as bis(benzoate) (129).

To address this problem, diol (127) was treated with phosgene in the presence of pyridine[119] in an attempt at forming a cyclic carbonate derivative. However, this reaction proved to be slow and so alternative methods for the introduction of the carbonate protecting group were tried. The best method involved treating diol (127) in THF with an excess of carbonyl diimidazole[120] at ambient temperature which furnished the required cyclic carbonate (130) in excellent yield as a highly crystalline material (Scheme 57).

With carbonate (130) in hand we examined a variety of methods for the selective oxidation of the C(11) methylene. The most widely used oxidant for this type of transformation is ruthenium tetroxide which is known to favour the oxidation of a $-CH_2-O-$ over that of a >CH-O- group[121]. However, treatment of carbonate (130) with a solution of ruthenium tetroxide in carbon tetrachloride[122] failed, even after prolonged reflux, to give the required lactone (131) with only starting material being recovered (Scheme 58). Similarly, using a catalytic amount of either ruthenium trichloride or ruthenium dioxide with sodium periodate as co-oxidant in the two phase system (CCl_4\H_2O) containing acetonitrile as developed by

Sharpless[123], no oxidation of the ether bridge of carbonate (130) was observed, even after prolonged heating with a very large excess of oxidant.

The lack of reactivity of the ether bridge of carbonate (130) towards these ruthenium-based oxidation prompted us to investigate other strong oxidants (Scheme 58). Efforts to achieve an oxidation of carbonate (130) with a large excess of Jone's reagent according to the method of Henbest[124] gave essentially unchanged starting material. A similar result was also obtained upon using the strong oxidant, benzyltriethylammonium permanganate[125]. In a final attempt at oxidising the C(11) methylene of carbonate (130), a solution of the highly reactive oxidant, dimanganese heptoxide in carbon tetrachloride was prepared using the procedure of Trömel[126]. This powerful oxidant is known to react rapidly with alcohols and alkenes at temperatures as low as -78°C and to oxidise ethers cleanly at -40°C[126].

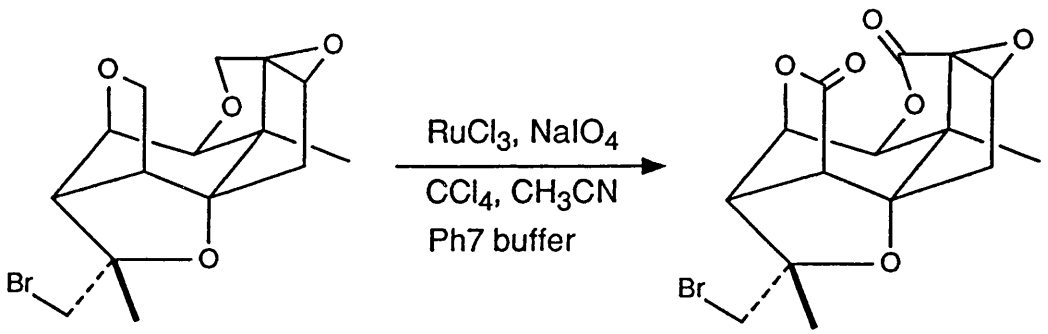
A solution of carbonate (130) in acetone\carbon tetrachloride (1:1) was treated with two equivalents of a solution of dimanganese heptoxide in carbon tetrachloride at -78°C; the dimanganese heptoxide solution having been freshly titrated to determine the concentration of oxidant present. The resulting purple-coloured solution was then allowed to warm slowly to -20°C and at this temperature a brown precipitate was noted. A more polar spot was observed by t.l.c. and work-up and chromatographic separation gave recovered carbonate (130) as the major component and the tertiary alcohol (132).

The assignment of (132) is based on examination of the ^{1}H NMR spectrum. It was observed that the splitting pattern of the C(5) methylene protons had been simplified to two double doublets, the large $J_{5a,5e}$ geminal coupling and the couplings of both protons to 6-H being retained. Also, the signal corresponding to 3-H was now a singlet, whereas in the ^{1}H NMR spectrum of carbonate (130) this proton was observed as a doublet. This spectroscopic evidence suggested tertiary

alcohol (132) and in the absence of other gross structural changes we have tentatively assigned the stereochemistry at C(4) as shown.

The lack of reactivity observed for the C(11) -CH_2-O- group of ether (130) was unexpected, especially in the light of the result obtained by Yamada and co-workers[121] on the oxidation of the related bicyclic ether (133) to the bis-lactone (134) (Scheme (59).

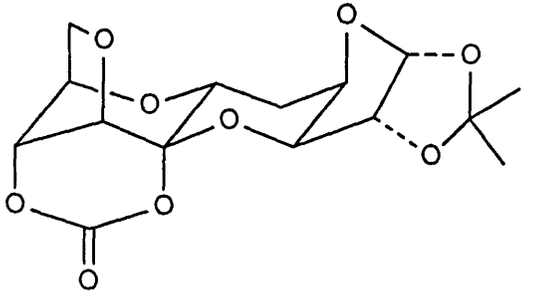
Scheme 59



(133) (134)

However, our results can be rationalised by considering the mechanism of the ruthenium tetroxide-mediated oxidation of ethers[127] (Scheme 60). As shown, the first step involves hydride transfer from the ether, in this example THF, to the Ru(VIII) species. This abstraction step might be disfavoured for compound (130) due to the proximity of the electron-withdrawing carbonate group to the ether bridge which may destabilise an intermediate oxonium ion. Assuming a similar mechanism for the oxidation of ethers by dimanganese heptoxide, then this oxidant would oxidise the next most reactive centre of carbonate (130), which in this case is the tertiary site at C(4).

Scheme 61

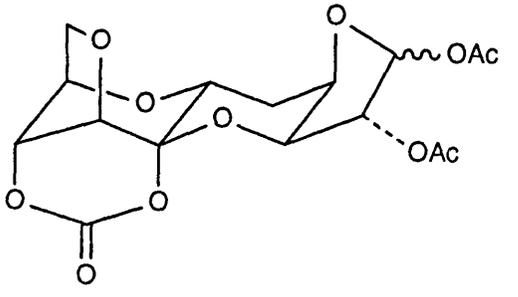


(130)

1) TFA, H_2O

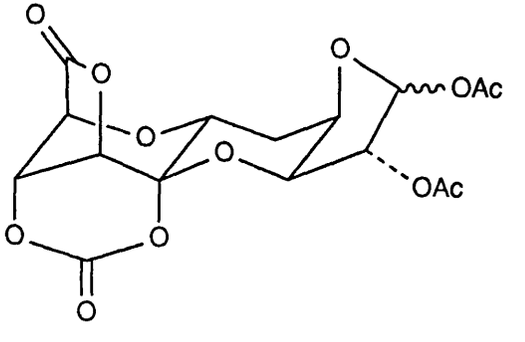
2) Ac_2O, Py

89%



(135)

[O]



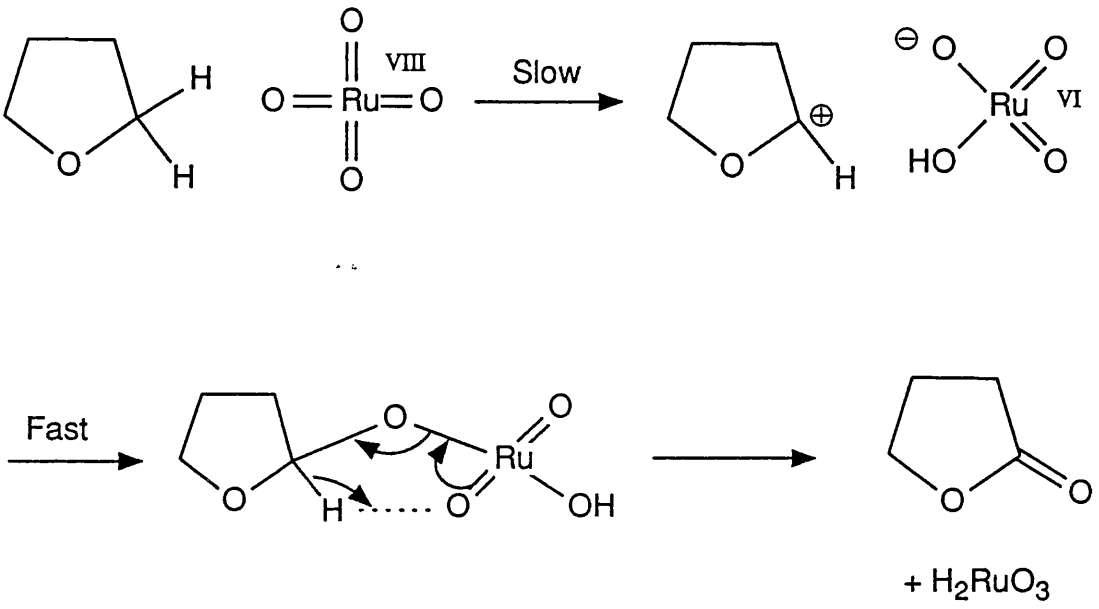
Oxidant

RuO_4,CCl_4

$RuCl_3(RuO_2)$, $NaIO_4$, CH_3CN, CCl_4, H_2O

Mn_2O_7, CCl_4, Me_2CO

Scheme 60



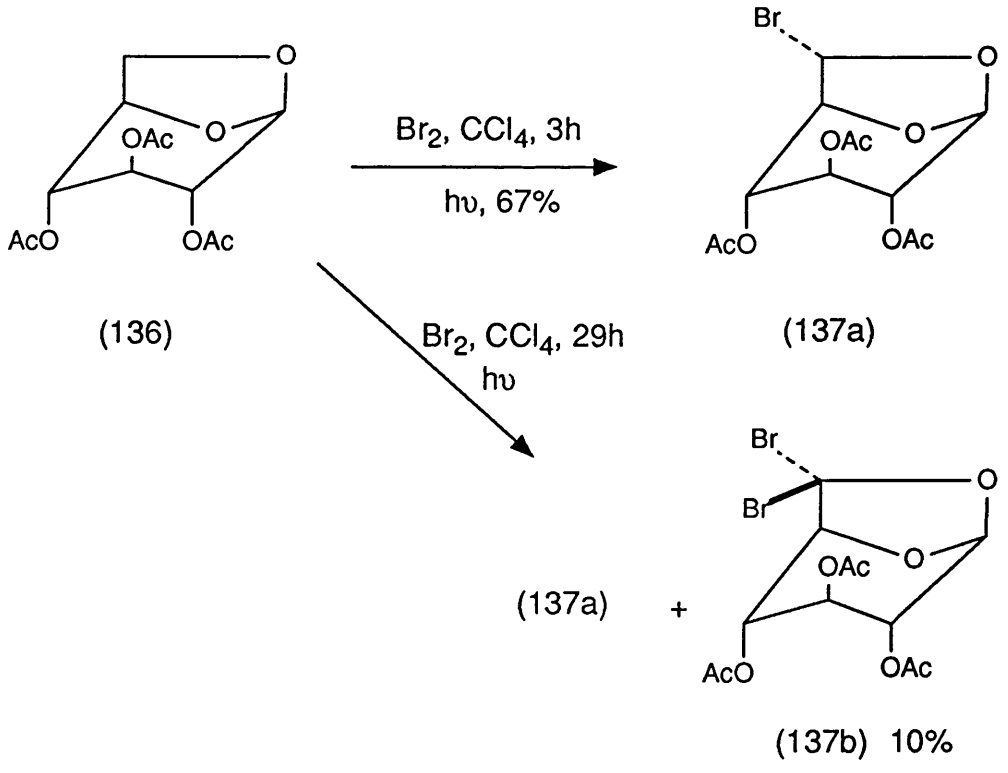
In an attempt to encourage oxidation to occur at C(11) of carbonate (130) we sought initially to synthesise diacetate (135) in order to try and balance the electronic environment of the two sites [C(4) and C(11)] of (135) (Scheme 61).

In order to synthesise diacetate (135), prior hydrolysis of the acetonide function of carbonate (130) was required. Initial attempts using aqueous mineral acid resulted in substantial loss of the cyclic carbonate function. However, brief treatment of carbonate (130) with aqueous trifluoroacetic acid resulted in a clean, selective hydrolysis of the acetonide group and subsequent treatment of the crude product of this reaction with acetic anhydride in pyridine gave diacetate (135) as a mixture of anomers (2(α):1(β)) (Scheme 61).

Unfortunately, no reaction was observed upon extended treatment of diacetate (135) with either dimanganese heptoxide[126] or ruthenium tetroxide[123], even at elevated temperatures. Although we succeeded in deactivating the C(4) position of diacetate (135) towards oxidation, C(11) was still unreactive.

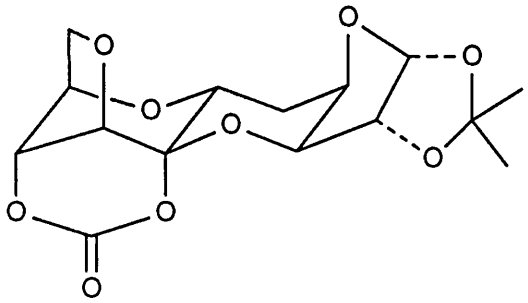
The selective oxidation of the C(11) methylene of carbonate (130) had thus far proved unrewarding and an alternative strategy was required. One possible solution would have been to make a derivative of diol (127) having a non electron-withdrawing protecting group at C(7)-C(9), such as an acetonide. However, the difficulties previously encountered in the synthesis of such an acetonide prevented such a study. We were, however, successful in applying the photobromination method as developed by Ferrier to the oxidation of the ether bridge of (130). Ferrier had shown that photolysis of a solution of tri-O-acetyl-1,6-anhydro-β-D-glucopyranose (136) and bromine in carbon tetrachloride at reflux afforded bromide (137a) in good yield. Dibromide (137b) was isolated as a minor component when the reaction was allowed to proceed for an extended period (Scheme 62)[128].

Scheme 62



The possibility of applying this chemistry to (130) offered the opportunity to

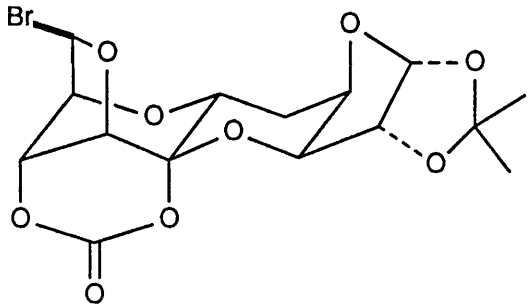
Scheme 63



(130)

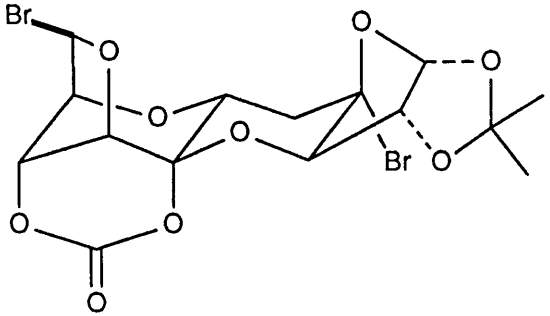
Br_2, CCl_4

$h\upsilon$



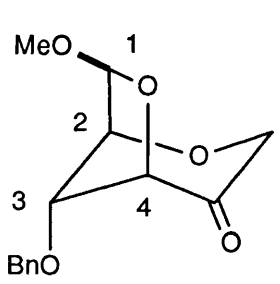
(138) 20%

+ 70% recovered starting material



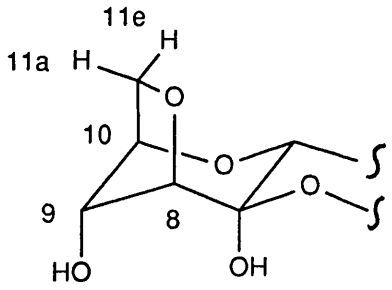
(139) 5%

go to the aldehyde oxidation level or directly to the lactone oxidation level at C(11). In the event, treatment of a solution of carbonate (130) in carbon tetrachloride with an excess of bromine under bright visible light (200W lamp) at reflux gave a mixture of compounds from which the C(11) monobromide (138) could be isolated in low yield (Scheme 63). The stereochemistry of the newly-created chiral centre at C(11) was determined by examination of the ^{1}H NMR spectrum of bromide (138). By analogy to the acetal-bridged ketone (79b) and ether (127), the absence of a coupling between 10-H and 11-H served to confirm the stereochemistry at C(11) of (138) as shown below.



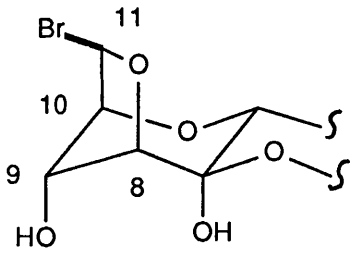
(79b)

$J_{1,2} = 0$



(127)

$J_{10,11a} = 3$; $J_{10,11e} = 0$

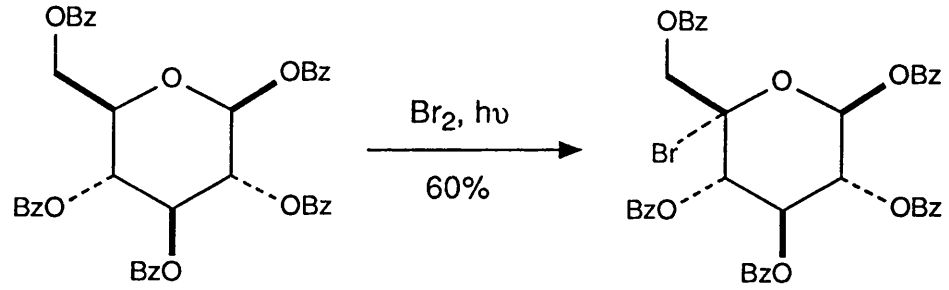


(138)

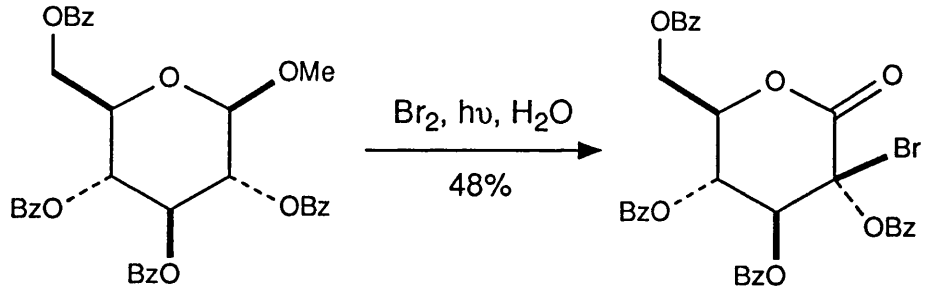
$J_{10,11} = 0$

In order to optimise the bromination, careful control of the amount of bromine used (one equivalent being optimal) was required. Also, monitoring the reaction by t.l.c. allowed the reaction to be stopped as soon as the appearance of by-products was detected. In this way, bromide (138) could be obtained in yields of 20-30% along with bis(bromide) (139) in 5-10% yield. A substantial amount of starting carbonate was also recovered (up to 60%). The fact that the second bromination of carbonate (130) occurred at C(4) was disappointing since a second bromination at C(11) to give the required oxidation level at this centre had been expected, 11-H being activated by the adjacent oxygen and bromine in (138). However, 11-H is too hindered compared to 4-H for such a reaction to take place

but, the reactivity of 4-H was surprising since the acetal centre at C(1) would be expected to be a more reactive site towards this radical bromination process, as demonstrated by Ferrier[128]. Treatment of perbenzoylated β-D-glucopyranosides [possessing a methyl glycoside at C(1)] with bromine, under the conditions described above, gave products resulting from radical bromination at C(1). However, the corresponding C(1)-benzoylated derivatives were preferentially brominated at C(5) with this difference in reactivity being attributed to the destabilisation of an intermediate radical at C(1) by the electron-withdrawing benzoate function at this position.



Penta-O-benzoyl-β-D-glucopyranose

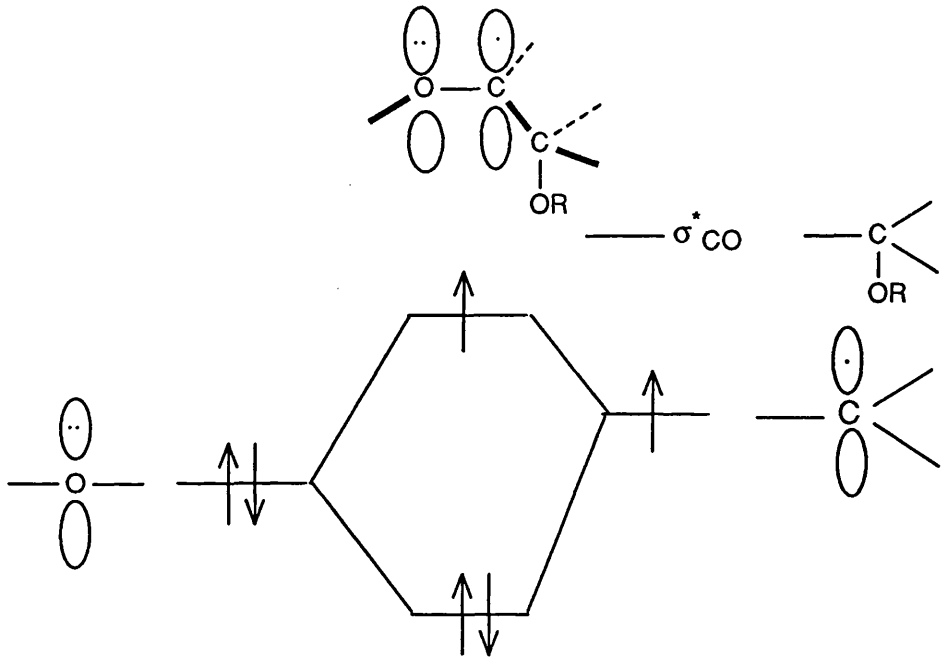


Methyl tetra-O-benzoyl-β-D-glucopyranoside

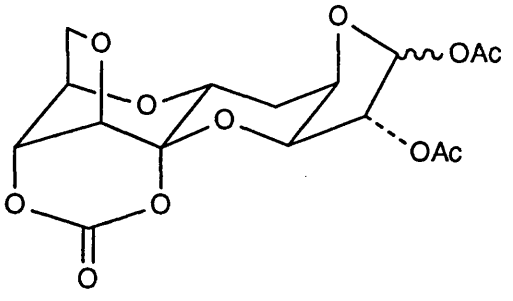
However, in all of these examples the abstracted hydrogen atom is in the axial configuration, antiperiplanar to one of the lone pairs of the neighbouring oxygen atom. This then leads to a stabilisation of the radical formed by an orbital overlap of the radical SOMO with this lone pair. In the case of carbonate (130) however, 1-H is in a pseudo-equatorial orientation and would therefore be less

susceptible to abstraction than 4-H which is antiperiplanar to one of the lone pairs of the furanose ring oxygen. Furthermore, such a C(4) radical species would also be stabilised by an interaction with the LUMO of the β-CO bond at C(3) in a similar manner to that described by Giese[27] (Scheme 10). These factors may then account for the observed competing bromination of carbonate (130) at C(4).

Scheme 10



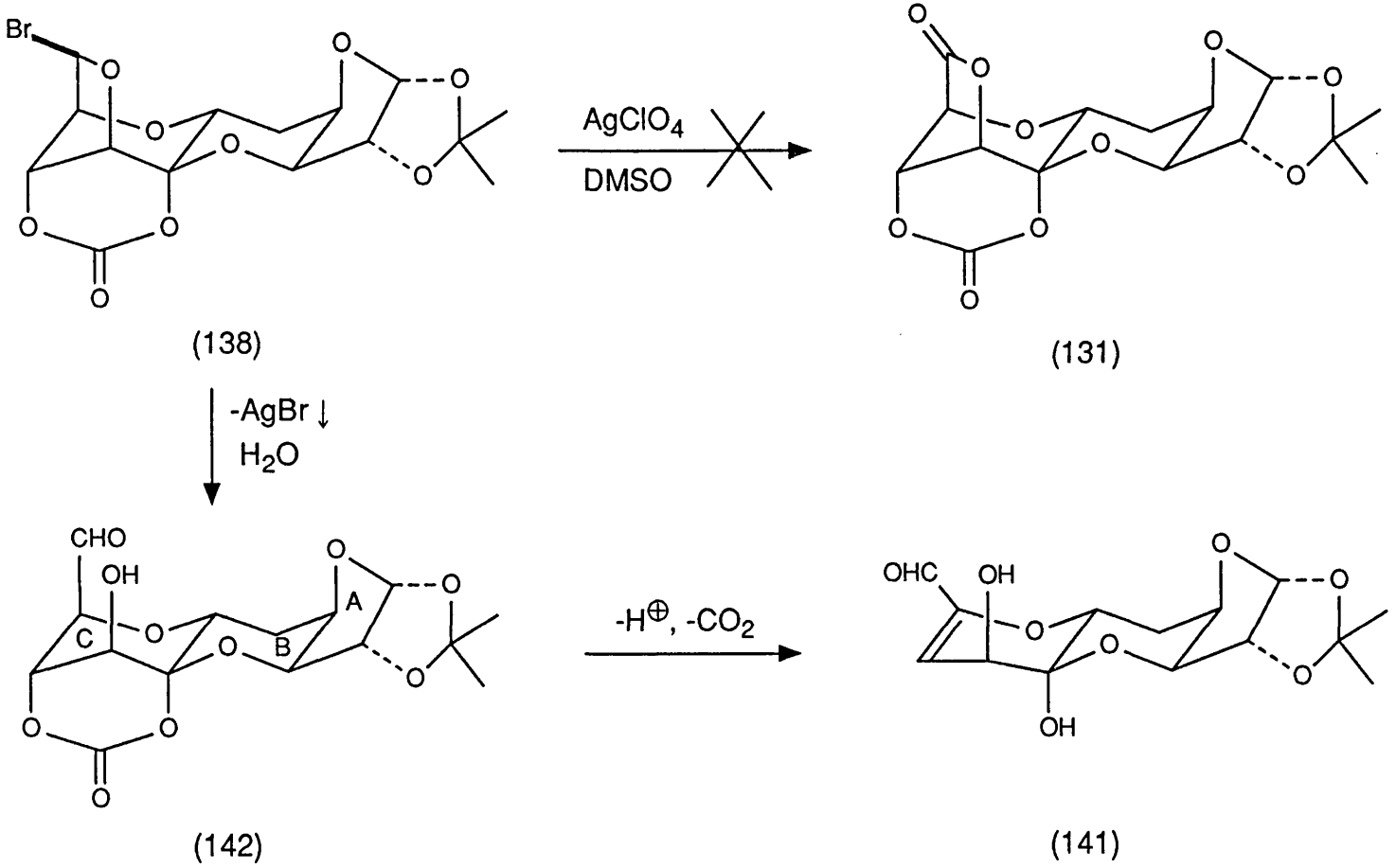
We did consider the use of diacetate (135) to overcome this problem but, due to a lack of time this was not pursued.



(135)

With bromide (138) in hand we would require a second oxidation at C(11) to

Scheme 64a


Br
AgClO4
DMSO
(138)
(131)
-AgBr ↓
H2O
CHO
OH
A
B
C
-H⊕, -CO2
OHC
OH
OH
(142)
(141)

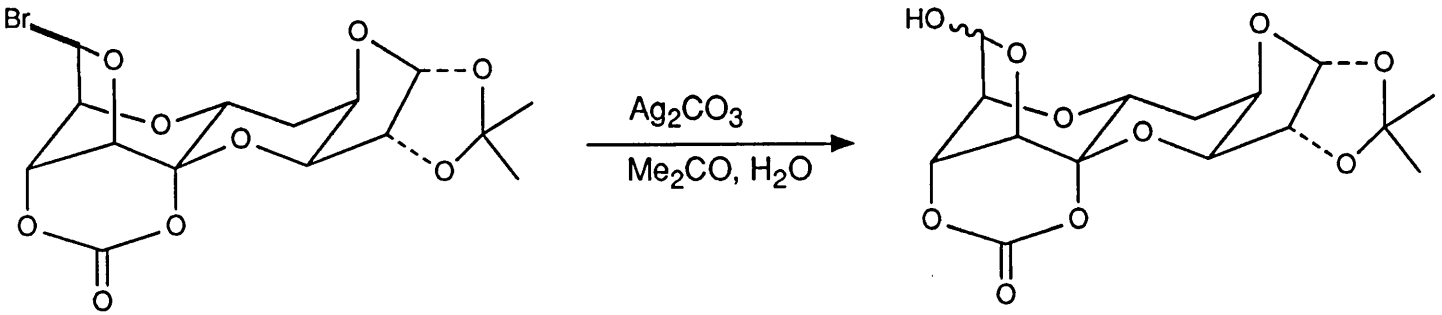
attain the oxidation level present in the herbicidins. In order to realise this aim we examined both a direct oxidation of bromide (138) to lactone (131) and also a route based on the hydrolysis of the α-bromoether function to give a hemiacetal followed by an oxidation at C(11). The results of these preliminary studies are shown in Scheme 64a and Scheme 64b.

Ganem and Boeckman have reported that an Ag(I) modified Kornblum[129] reaction will oxidise primary and secondary alkyl halides to the corresponding aldehydes and ketones respectively[130]. Under these conditions bromide (138) gave only enal (141) (Scheme 64a). The formation of (141) is presumably via a β-elimination of the carbonate protecting group from hydroxyaldehyde (142), formed on hydrolysis of the intermediate oxysulphonium ion, either by traces of moisture in the reaction medium or upon exposure to the aqueous work-up conditions. A result which confirmed this mechanistic hypothesis relates to the attempted hydrolysis of bromide (138) to hydroxyaldehyde (142) with silver(I) carbonate in the presence of aqueous acetone which resulted in the exclusive formation of enal (141) in nearly quantitative yield (Scheme 64b). Again we presume that the desired hydroxyaldehyde (142) is an intermediate in this process but the facility with which the β-elimination occurs must be due to the geometrical constraint and leaving group ability imposed on the system by the carbonate function.

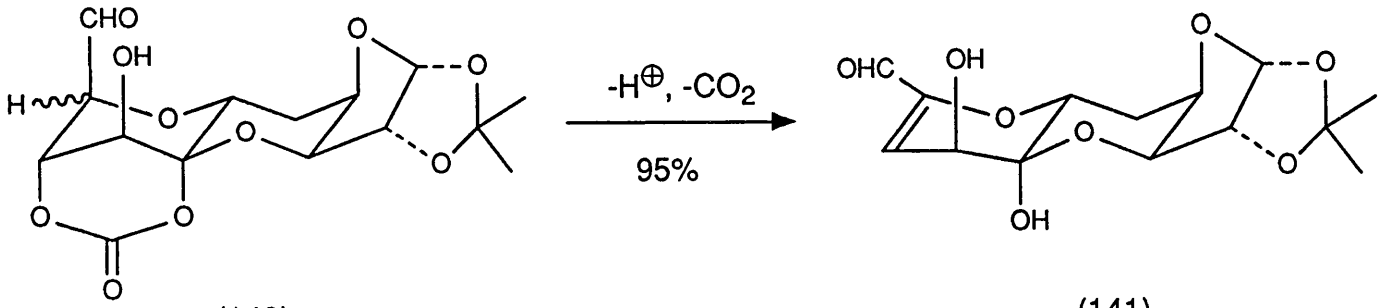
Similarly, treatment of bromide (138) with either silver(I) acetate or silver(I) trifluoroacetate in aqueous acetone gave only enal (141) in both cases. However, upon addition of an excess of silver(I) nitrate to a solution of bromide (138) in wet acetone, the appearance of a grey precipitate was noted and t.l.c. indicated conversion to a single, more polar compound.

Examination of the ^{1}H NMR spectrum of the crude product from this

Scheme 64b



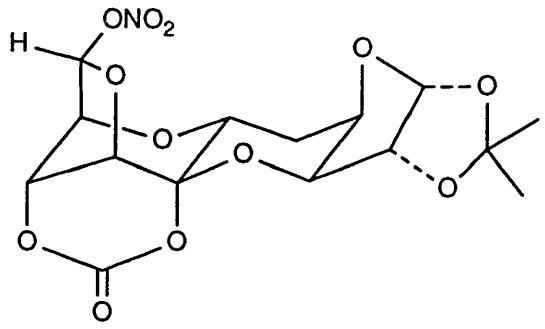
(138)



(142)

(141)

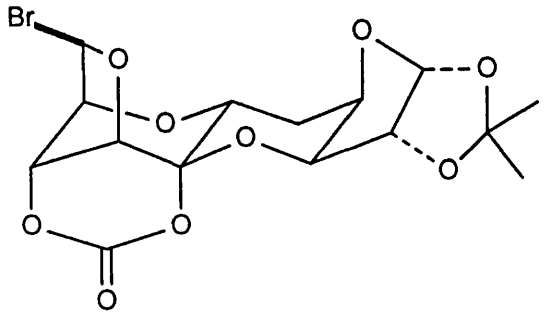
reaction revealed little evidence for the presence of either the required aldehyde (142) or enal (141). Indeed, upon initial observation it appeared that little change to the starting bromide (138) had occurred except for an inversion of stereochemistry at C(11). This is suggested since the crude product possessed a coupling between 10-H and 11-H usually absent for bromide (138). Further spectroscopic investigation of this material revealed a strong carbonate stretch in the IR spectrum at 1775cm^{-1} and an additional strong band at 1680cm^{-1}. This additional band can be explained by the presence of a nitrate ester adjacent to an electron-withdrawing group at C(11)[133]. This spectroscopic evidence, along with the appearance of the silver(I) bromide precipitate led us to tentatively assign the product of this reaction as the C(11) nitrate ester (150) shown.



(150)

Therefore, in order to hydrolyse bromide (138) a different approach was required to prevent these side reactions and these problems were subsequently overcome by removal of the carbonate protecting group prior to the hydrolysis of the α-bromoether moiety. The first step, removal of the carbonate function, was achieved by treatment of bromide (138) with sodium methoxide in methanol which gave diol (143) in good overall yield (Scheme 65). Hydrolysis of this material with silver carbonate in aqueous acetone then served to give hydroxyaldehyde (144) in nearly quantitative yield. However, an attempted chromatographic purification of this material led to a small amount of enal (141) also being formed, presumably due to a β-elimination occurring on the silica. As a result hydroxyaldehyde (144) was

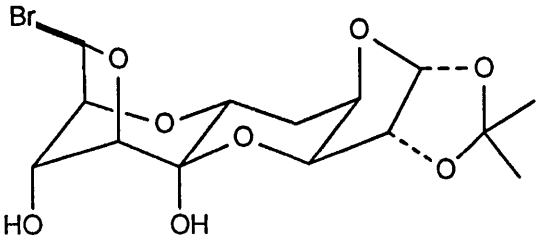
Scheme 65



(138)

NaOMe, MeOH

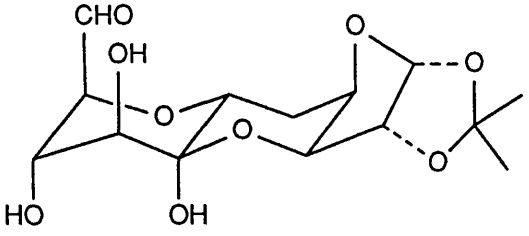
90%



(143)

Ag_2CO_3

Me_2CO, H_2O



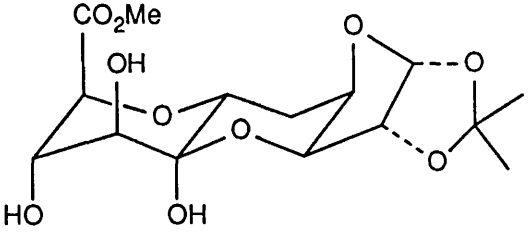
(144)

I_2, KOH

MeOH

40-50%

from (143)

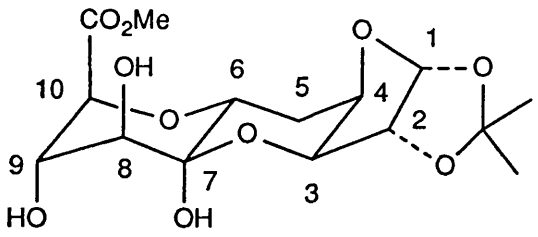


(145)

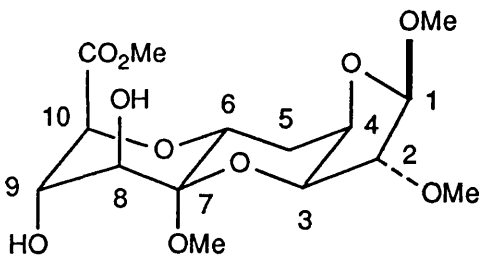
used without further purification in the subsequent reaction.

On examination of the ^1H NMR spectrum of hydroxy-aldehyde (144) there was no evidence for the closed, hemiacetal form and the presence of an aldehyde resonance at δ9.80 was noted. This presumably reflects the conformational relaxation required in the C-ring of aldehyde (144) in order to accommodate four axial substituents.

Finally, in order to selectively oxidise the aldehyde function of compound (144) to the required methyl ester, a recent adaptation[132] of the classical halogen oxidation of aldoses[131] was used. Reaction of aldehyde (144) with iodine and potassium hydroxide in methanol afforded crystalline methyl ester (145) in moderate yield. The ^1H NMR spectrum of methyl ester (145) was correlated with that of methyl glycoside (146), a derivative obtained upon the acid-catalysed methanolysis of herbicidin B, the structure of compound (146) having been confirmed by an X-ray crystallographic analysis of the corresponding bis *p*-bromobenzoate [63].



(145)



(146)

^{1}H NMR data for (145) and (146) in $CDCl_3$

Chemical Shift (δ)

	1-H	2-H	3-H	4-H	5a-H	5e-H	6-H	8-H	9-H	10-H
(145)	5.88	4.51	4.33	4.42	2.12	2.32	4.49	3.68	4.48	4.42
(146)	4.87	3.75	3.99	4.47	2.13	2.18	4.61	3.96	4.35	4.39

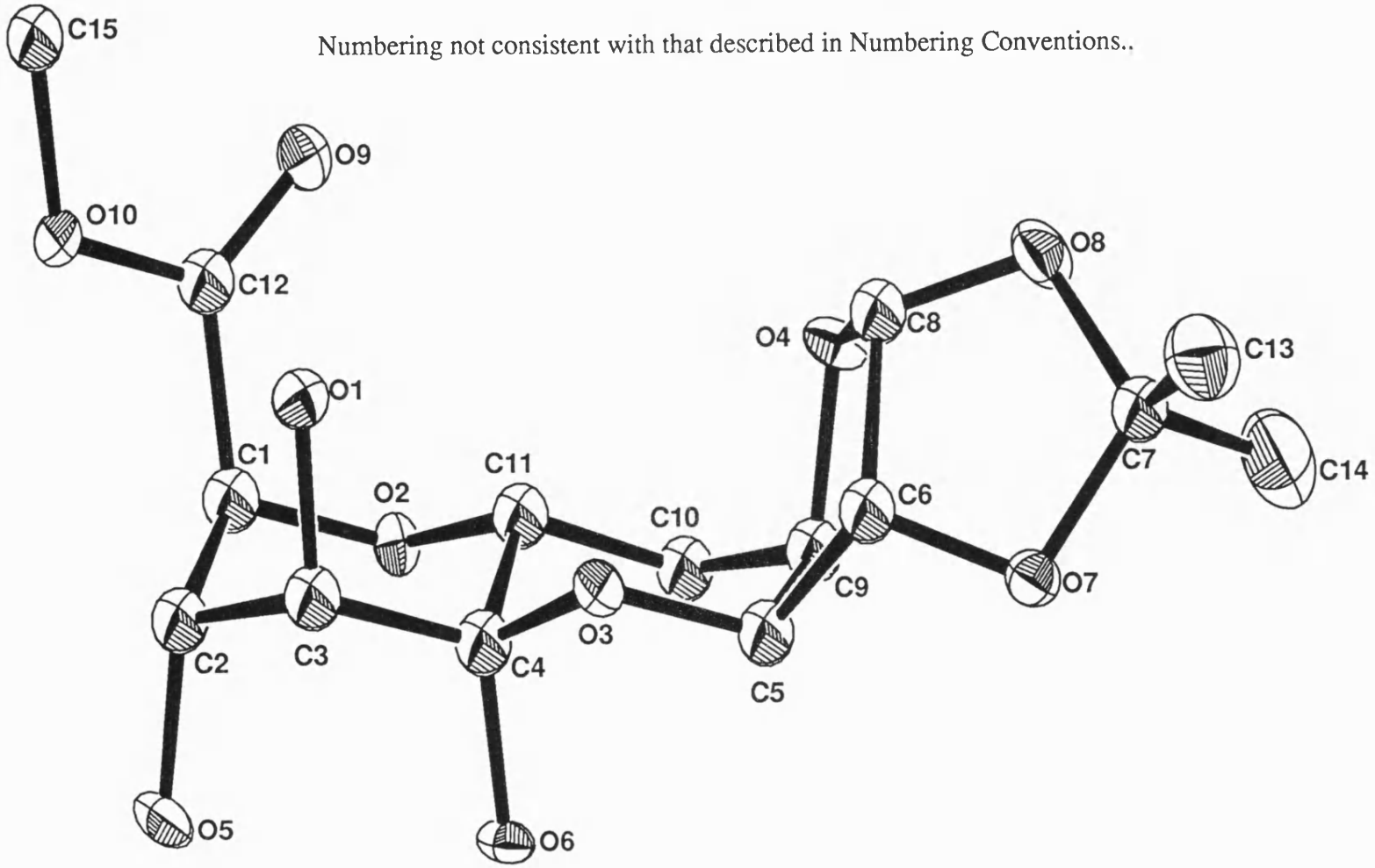
Coupling Constants *J* (Hz)

	2,3	3,4	5a,5e	4,5a	4,5e	6,5a	6,5e	8,9	9,10
(145)	0	2	14	4	*	11.5	4	3	1.5
(146)	0	3	14	3	3	10.5	7	3	1.5

*- Not determined

ORTEP diagram of ester (145)

Numbering not consistent with that described in Numbering Conventions..



The results of this study show that the chemical shifts of the 3-H - 10-H protons of ester (145) and those of the degradation product (146) have very similar values, the large discrepancies between the corresponding shifts of 1-H and 2-H of these compounds arising from ester (145) having the opposite anomeric configuration to that of derivative (146). Similarly, observation of the proton coupling constants of these two compounds shows a good agreement and the values about the A and B rings also correlating independently with those of diol (127), a compound whose structure we have independently confirmed by X-ray crystallographic studies (see previous chapter). Also, the coupling constants between 9-H and both 8-H and 10-H of ester (145) are in good agreement with those of (146), evidence that epimerisation at C(10) had not occurred during the oxidation reaction.

We have subsequently obtained an X-ray crystal structure for ester (145) that confirms the absolute stereochemistry as that of the herbicidin glycoside as shown.

In summary, we have demonstrated that the ether-bridged ketone (79a) can be used to generate anionic reactivity at the anomeric carbon and can be alkylated to give access to C-glycosyl compounds. Furthermore, condensation of ketone (79a) with furanoside aldehyde (122) gave enone (126) which could be rapidly converted to methyl ester (145) having the required tricyclic core and overall stereochemistry of the glycoside portion of the herbicidin class of natural products. This constitutes the first synthesis of the herbicidin glycoside core and we have achieved this in a highly convergent and efficient manner [7 steps, 10% yield from ketone (79a)]. The elaboration of ester (145) to the corresponding nucleoside is currently being actively pursued within our group.

3. EXPERIMENTAL

3 EXPERIMENTAL

INSTRUMENTATION AND EXPERIMENTAL TECHNIQUES

Infrared spectra were recorded in the range 4000-600 cm^{-1} using a Perkin-Elmer 1310 grating spectrophotometer and a Nicolet 510P FT-IR spectrometer and peaks are reported (υ_{max}) in wave numbers (cm^{-1}). Spectra of liquid samples were taken as thin films or as solutions in chloroform. Spectra of solid samples were taken in chloroform solution unless otherwise stated.

Routine mass spectra were obtained in the electron impact mode (E.I.) with an ionising potential of 70eV and in the chemical ionisation mode (C.I.) with *iso*-butane as reagent gas. These, along with high resolution accurate mass determinations in the E.I. mode were recorded with a VG Analytical 7070E instrument and a VG 2000 data system. High resolution accurate mass determinations in the C.I. mode were recorded at the SERC facility at Swansea with either *iso*-butane or ammonia as reagent gas. Where possible, the molecular ion is indicated along with all sizeable fragments.

Proton magnetic resonance (^1H NMR) spectra were recorded at 60MHz on Hitachi Perkin-Elmer high resolution R-24B and Varian Anaspect EM-360 spectrometers, at 250 MHz on a Bruker AM250 spectrometer, at 270 MHz on a Jeol GNM GX FT 270 spectrometer, at 300 MHz on a Nicolet AT300 spectrometer and at 400 MHz on a Jeol GNM GX FT 400 spectrometer. Carbon 13 magnetic resonance (^{13}C NMR) spectra were recorded on a Jeol GNM GX FT 270 spectrometer operating at 68 MHz and using 90 and 135 DEPT pulse sequences to aid in multiplicity determination. ^1H and ^{13}C NMR spectra are expressed in parts per million (ppm) downfield (δ) from internal tetramethylsilane. Multiplicities are given as follows: singlet (s), doublet (d),

triplet (t), quartet (q) and multiplet (m). The abbreviation "br" is appended to a multiplet to indicate significant broadening.

Melting points (m.p.) were determined on commercially available apparatus (Gallenkamp) and are uncorrected. Elemental microanalyses were carried out using a Carlo Erba 1106 Elemental Analyser. Optical rotations were measured using a Perkin-Elmer 141 polarimeter with concentration (c) expressed in g/100 ml.

Thin layer chromatography (t.l.c.) was used extensively as a qualitative guide for monitoring the course of reactions and for assessing the purity of compounds. Merck DC-alufolien Kieselgel 60 F_{254} sheets containing fluorescent indicator were used for this purpose. Visualisation of reaction components was achieved by illumination under short wavelength (254 nm) ultraviolet light (where possible) and/or using a reagent (typically potassium permanganate) that would give a colour change with the functional groups present, as described in "Dyeing Reagents for Thin Layer and Paper Chromatography", E. Merck, Darmstadt, 1980.

Unless otherwise stated, petrol refers to that fraction of petroleum spirit boiling in the range 60-80°C. Solvents used as eluants in chromatography were dried and distilled prior to use.

Medium pressure flash column chromatography was routinely employed using Kieselgel 60 (Merck 9385) and 60H silica gel (Merck 7736) for reaction component separations. A pressure gradient was developed using a small, commercially available hand bellows (Gallenkamp). In all cases columns were prepared in the least polar solvent of the eluant mixture and chromatography was carried out with the least polar solvent as initial eluant, then eluting with

solvent mixtures of steadily increasing polarity. Material to be chromatographed was pre-adsorbed onto the column support and applied as a thin layer to the top of the column. Preparative thin layer chromatography was performed using Merck 60 F_{524} silica gel, glass supported plates.

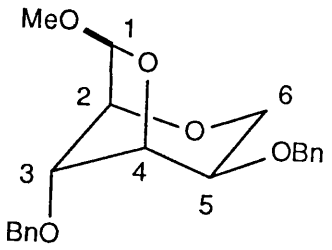
Tetrahydrofuran (THF) was pre-dried over sodium wire, then refluxed over sodium benzophenone ketyl under dry nitrogen until anhydrous. This was redistilled immediately prior to use.

DOWEX-50W-X8 (H^+) ion-exchange resin was washed repeatedly with distilled water and ethanol immediately before use.

Glassware used for water sensitive reactions was baked in an oven at 160°C for approximately 12h and allowed to cool in a desiccator over $CaCl_2$. Flasks and stirrer bars were, however, additionally flame-dried under a stream of dry nitrogen. In all experiments the excess solvent was removed with a Büchi rotary evaporator using a water aspirator at room temperature to avoid unnecessary decomposition. All yields quoted are of purified products and are uncorrected.

All other general reagents and solvents were purified and dried as required, using the methods described in: D.D. Perrin, W.L.F. Armarego and D.R. Perrin, "Purification of Laboratory Chemicals", 2nd Edn., Pergamon Press, Oxford, 1990.

For a brief description of the systematic numbering used herein see the Numbering Convention section at the beginning of this thesis.



(87a)

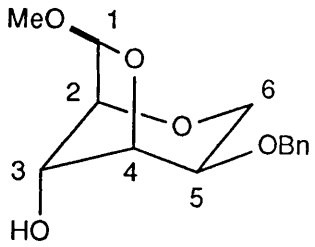
Methyl 2,6-anhydro-α-D-mannofuranoside (86)

A solution of acetal (85) (450 mg, 2.16 mmol) in xylene (300 cm^3) was heated to reflux and a solution of freshly dried *p*-toluenesulphonic acid (20 mg, 0.11 mmol) in xylene (10 cm^3) was added. After 1 hour, t.l.c. (EtOAc\acetone, 3:1) showed that acetal (85) had been consumed. The reaction mixture was cooled and extracted with 10% sodium hydrogen carbonate solution (6 x 25 cm^3) and the combined aqueous phases evaporated. The residue was then extracted with EtOAc (5 x 25cm^3) and the extracts evaporated to give a colourless gum. Purification by flash chromatography with EtOAc/acetone (4:1) as the eluant afforded the title compound (86) (143 mg, 38%) as colourless plates, m.p. 83-84°C (isopropyl ether) (Lit.,[82] m.p. 84°C). This compound gave identical spectral data to that described in the literature[82].

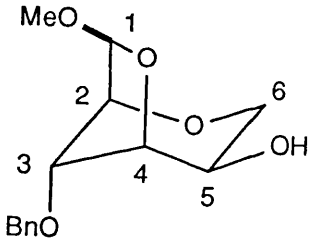
Methyl 2,6-anhydro-3-*O*-benzyl-α-D-mannofuranoside (87)

To a solution of diol (86) (176 mg, 1.0 mmol) in THF (2 cm^3) at 0°C was added sodium hydride (36 mg, 1.50 mmol) and the resultant suspension stirred at 0°C for 10 minutes. To this mixture was added benzyl bromide (171 mg, 1.0 mmol) followed by tetrabutylammonium iodide (37 mg, 0.1 mmol) and the reaction mixture stirred at room temperature for 19 hours. The reaction mixture was then concentrated *in vacuo* and the residue chromatographed on silica with EtOAc/petrol (1:1) as eluant to give three fractions:

(i) The first component, methyl 2,6-anhydro-3,5-di-*O*-benzyl-α-D-mannofuranoside (87a) (65 mg, 18%) as a colourless oil. (Found: C, 70.80; H, 6.86. $C_{21}H_{24}O_5$ requires C, 70.77; H, 6.78%); υ_{max}/cm^{-1} 2900, 1590, 1490; δ_H (270 MHz, $CDCl_3$) 3.40 (3H, s, OCH_3), 3.62 (1H, brd, $J_{6a,6e}$ and $J_{6a,5}$ 10, 6a-H), 3.96 (3H, m, 2-H, 5-H and 6e-H), 4.17 (1H, dd, $J_{3,2}$ 3, $J_{3,4}$ 6, 3-H), 4.42 (1H, d,



(87b)

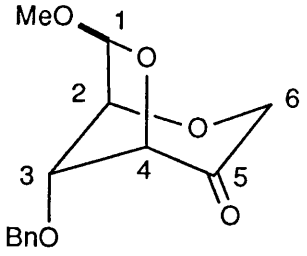


(87)

$J_{4,3}$ 6, 4-H), 4.44 (1H, d, J 12, part of AB), 4.46 (1H, d, J 12, part of AB), 4.53 (1H, d, J 12, part of AB), 4.66 (1H, d, J 12, part of AB), 5.05 (1H, s, 1-H) and 7.32 (10H, m, 2 x C_6H_5); m/z (Iso-but. C.I.), 325 (M^++H-32, 5%).

(ii) The second component, methyl 2,6-anhydro-5-*O*-benzyl-α-D-mannofuranoside (87b) (6 mg, 6%) as a colourless viscous oil. (Found: C, 63.10; H, 6.81. $C_{14}H_{18}O_5$ requires C, 63.14; H, 6.81%); υ_{max}/cm^{-1} 3700, 1600, δ_H (270 MHz, CD_3OD) 3.39 (3H, s, OCH_3), 3.56 (1H, dd, J 12, J 13.5, 6a-H), 3.73 (1H, d, $J_{2,3}$ 3, 2-H), 3.93 (2H, m, 5-H and 6e-H), 4.32 (1H, dd, $J_{3,2}$ 3, $J_{3,4}$ 6, 3-H), 4.41 (1H, brd, $J_{4,3}$ 6, 4-H), 4.58 (1H, d, J 12, part of AB), 4.60 (1H, d, J 12, part of AB), 5.04 (1H, s, 1-H) and 7.30-7.36 (5H, m, C_6H_5); m/z (Iso-but. C.I.) 267 (M^++H, 3%).

(iii) The third component, methyl 2,6-anhydro-3-*O*-benzyl-α-D-mannofuranoside (87) (122 mg, 46%) as a colourless viscous oil. (Found: C, 62.90; H, 6.81. $C_{14}H_{18}O_5$ requires C, 63.14; H, 6.81%); υ_{max}/cm^{-1} 3550, 1600; δ_H (270 MHz, CD_3OD) 3.38 (3H, s, OCH_3), 3.49 (1H, dd, $J_{6a,6e}$ 9, $J_{6a,5}$ 10, 6a-H), 3.92 (1H, dd, $J_{6e,5}$ 7, $J_{6e,6a}$ 9, 6e-H), 3.94 (1H, d, $J_{2,3}$ 3, 2-H), 4.04 (1H, m, 5-H), 4.16 (1H, dd, $J_{3,2}$ 3, $J_{3,4}$ 6, 3-H), 4.28 (1H, dd, $J_{4,3}$ 6, $J_{4,5}$ 1, 4-H), 4.54 (1H, d, J 12, part of AB), 4.66 (1H, d, J 12, part of AB), 5.04 (1H, s, 1-H) and 7.30-7.38 (5H, m, C_6H_5); m/z (Iso-but. C.I.) 267 (M^++H, 2%).



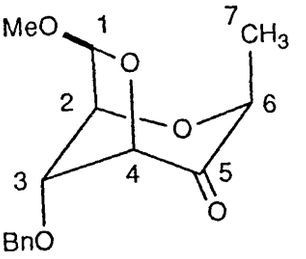
(79b)

Methyl 2,6-anhydro-3-*O*-benzyl-α-D-*lyxo*-hexofuranosid-5-ulose (79b)

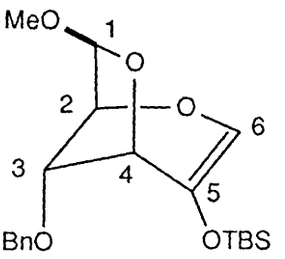
To a solution of alcohol (87) (67 mg, 0.25 mmol) in CH_2Cl_2 (2.5 cm^3) containing powdered 4Å molecular sieves was added 4-methylmorpholine N-oxide (44 mg, 0.37 mmol) and the mixture stirred at room temperature for 10 minutes. Tetrapropylammonium perruthenate (4.5 mg, 0.012 mmol) was then added and the reaction mixture stirred at room temperature for 1 hour. Removal of solvent *in vacuo* followed by chromatography of the residue with EtOAc/petrol (1:4) as the eluant gave the ketone (79b) (65 mg, 99%) as a colourless oil. (Found: M^++H, 265.108. $C_{14}H_{17}O_5$ requires M^+, 265.107); υ_{max}/cm^{-1} 3150, 1760, 1500; δ_H (270 MHz, CD_3OD) 3.40 (3H, s, OCH_3), 4.12 (1H, d, *J* 17, part of AB), 4.26 (1H, d, $J_{4,3}$ 6, 4-H), 4.27 (1H, d, $J_{2,3}$ 3, 2-H), 4.54 (1H, d, *J* 17, part of AB), 4.57 (1H, d, *J* 12, part of AB), 4.64 (1H, dd, $J_{3,4}$ 6, $J_{3,2}$ 3, 3-H), 4.67 (1H, d, *J* 12, part of AB), 5.22 (1H, s, 1-H) and 7.30-7.40 (5H, m, C_6H_5); m/z (Iso-but. C.I.) 265 (M^++H, 3%).

Methyl 2,6-anhydro-3-*O*-benzyl-α-D-*manno*-heptofuranosid-5-ulose (88)

To a solution of diisopropylamine (30 mg, 0.3 mmol) in THF (2 cm^3) at -10°C was added n-butyl lithium (1.6M solution in THF, 187 µl, 0.3 mmol) and the resulting solution stirred for 10 minutes before being cooled to -78°C. A solution of the ketone (79b) (66 mg, 0.25 mmol) in THF (1 cm^3) was then added dropwise over 5 minutes and the resulting mixture stirred at -78°C for 30 minutes. Methyl iodide (55 mg, 0.39 mmol) was added and the mixture allowed to warm to room temperature over 20 minutes. After this time saturated ammonium chloride solution (0.5 cm^3) was added and the mixture extracted with CH_2Cl_2 (5 x 2 cm^3). The organic extracts were dried (Na_2SO_4), evaporated and the residue chromatographed with EtOAc/petrol (4:1) as eluant



(88)

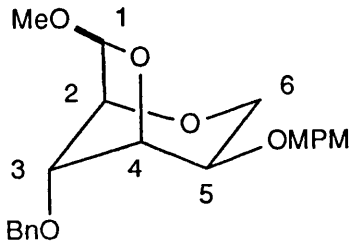


(89)

to give the methylated ketone (88) (7 mg, 15%) as a colourless viscous oil; υ_{max}/cm^{-1} 2700, 1730; δ_H (270 MHz, CD_3OD) 1.40 (3H, d, *J* 7.5, $CHCH_3$), 3.36 (3H, s, OCH_3), 4.18 (1H, d, $J_{4,3}$ 6, 4-H), 4.25 (1H, d, $J_{2,3}$ 3, 2-H), 4.36 (1H, q, *J* 7.5, 6-H), 4.58 (1H, d, *J* 12, part of AB), 4.67 (1H, d, *J* 12, part of AB), 4.68 (1H, dd, $J_{3,2}$ 3, $J_{3,4}$ 6, 3-H), 5.02 (1H, s, 1-H) and 7.35 (5H, m, C_6H_5); m/z (Iso-but. C.I.) 279 (M^++H, 2.5%).

Methyl 2,6-anhydro-3-*O*-benzyl-5,6-dehydro-5-*O*-*tert*-butyldimethylsilyl -α-D-*lyxo*-hexofuranoside (89)

To a suspension of potassium hydride (68 mg, 1.70 mmol) in THF (2.5 cm^3) at -78°C under nitrogen was added a solution of the ketone (79b) (112 mg, 0.42 mmol) in THF (1.5 cm^3), followed by solid *tert*-butyldimethylsilyl chloride (83 mg, 0.55 mmol). The resulting mixture was allowed to warm to room temperature over 2 hours. After this time saturated ammonium chloride solution (1 cm^3) was added and the mixture was extracted with CH_2Cl_2 (5 x 5 cm^3). The organic extracts were dried (Na_2SO_4) and evaporated to an oil which was purified by chromatography with EtOAc/petrol (5:1) as eluant to give the silyl enol ether (89) (126 mg, 80%) as a colourless oil. (Found: M^+, 378.183. $C_{20}H_{30}O_5Si$ requires M^+, 378.186); υ_{max}/cm^{-1} 2900, 1450; δ_H (270 MHz, CD_3OD) 0.18 (6H, s, $(CH_3)_2Si$), 0.92 (9H, s, ^tBu), 3.32 (3H, s, OCH_3), 4.01 (1H, m, 4-H), 4.10 (2H, m, 2-H and 3-H), 4.62 (1H, d, *J* 12, part of AB), 4.70 (1H, d, *J* 12, part of AB), 4.97 (1H, s, 1-H), 6.08 (1H, d, *J* 1.5, 6-H) and 7.30-7.40 (5H, m, C_6H_5); m/z (70eV E.I.) 378 (M^+, 100%).



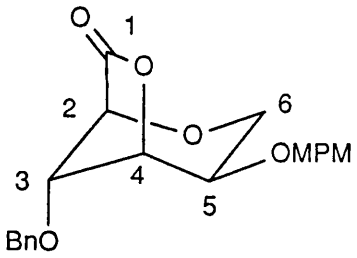
(92)

Methyl 2,6-anhydro-3-*O*-benzyl-5-*O*-p-methoxybenzyl-α-D -mannofuranoside (92)

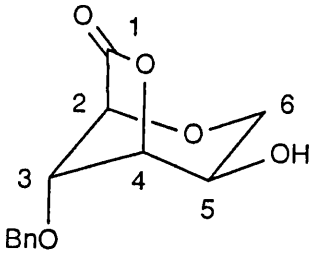
To a suspension of sodium hydride (68 mg of 80%, 2.26 mmol) in DMF (3 cm^3) was added a solution of alcohol (87) (429 mg, 1.61 mmol) in THF (6 cm^3) and the resultant suspension stirred at room temperature for 45 minutes. *p*-Methoxybenzyl chloride (0.26 cm^3, 1.94 mmol) was added dropwise and the reaction mixture stirred at room temperature for 2 days. Saturated aqueous ammonium chloride solution (1 cm^3) was added and the reaction mixture extracted with CH_2Cl_2 (4 x 20 cm^3). The combined organic extracts were washed with brine (10 cm^3), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography with EtOAc/petrol (1:4) as eluant to give the title compound (92) (505 mg, 81%) as a colourless oil. (Found: M^+, 386.1707. $C_{22}H_{26}O_6$ requires M^+, 386.1728); υ_{max}/cm^{-1} 2900, 1610, 1500; δ_H (300 MHz, $CDCl_3$) 3.41 (3H, s, 1-OCH_3), 3.62 (1H, dd, $J_{6a,5}$ 7.5, $J_{6a,6e}$ 9, 6a-H), 3.83 (3H, s, C_6H_4-OCH_3), 3.90 (1H, m, 5-H), 3.94 (1H, d, $J_{6e,6a}$ 9, 6e-H), 4.00 (1H, d, $J_{4,3}$ 6, 4-H), 4.18 (1H, dd, $J_{3,2}$ 3, $J_{3,4}$ 6, 3-H), 4.40 (1H, d, *J* 11.5, part of AB), 4.42 (1H, d, $J_{2,3}$ 3 , 2-H), 4.48 (1H, d, *J* 11.5, part of AB), 4.49 (1H, d, *J* 11.5, part of AB), 4.68 (1H, d, *J* 11.5, part of AB), 5.07 (1H, s, 1-H) and 6.90-7.35 (9H, m, $C_6H_5CH_2$ and CH_3O $C_6H_4CH_2$); m/z (70eV E.I.) 386 (M^+, 5%).

2,6-Anhydro-3-*O*-benzyl-5-*O*-p-methoxybenzyl-D-mannono-1 ,4-lactone (93)

A solution of acetal (92) (53 mg, 0.14 mmol) in THF (5 cm^3) was treated with 75mM sulphuric acid (5 cm^3) at room temperature for 3 days. Solid sodium bicarbonate was added until no further effervescence was observed and the THF was then removed *in vacuo*. The residual suspension was extracted with EtOAc (3 x 15 cm^3) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the hemiacetal (95)



(93)



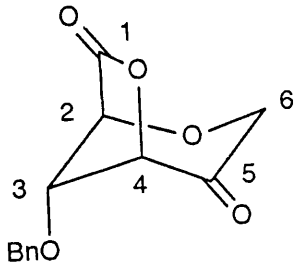
(94)

which was used without further purification.

The crude hemiacetal (95) was dissolved in CH_2Cl_2 (2 cm^3) PCC (44 mg, 0.21 mmol), sodium acetate (113 mg, 1.37 mmol) and powdered 3Å molecular sieves (45 mg) were added sequentially and the resultant suspension stirred at room temperature for 2 hours. The reaction mixture was filtered through Florisil and the filtrate concentrated *in vacuo*. The residue was purified by chromatography with EtOAc/petrol (1:4) as eluant to give the title compound (93) (12 mg, 24%) as a colourless oil. (Found: M^+, 370.1399. $C_{21}H_{22}O_6$ requires M^+, 370.1414); υ_{max}/cm^{-1} 1800, 1600, 1550; δ_H (300 MHz, $CDCl_3$) 3.60 (1H, m, 6a-H), 3.83 (3H, s, C_6H_4-OCH_3), 4.05 (1H, dd, $J_{3,2}$ 3, $J_{3,4}$ 6, 3-H), 4.08-4.18 (3H, m, 6e-H, 5-H and 4-H), 4.45 (1H, d, J 11.5, part of AB), 4.52 (1H, d, J 11.5, part of AB), 4.53 (1H, d, J 11.5, part of AB), 4.71 (1H, d, J 11.5, part of AB), 4.74 (1H, d, $J_{2,3}$ 3, 2-H) and 6.90-7.38 (9H, m, $C_6H_5CH_2$ and C_6H_4-OCH_3); m/z (70eV E.I.) 370 (M^+, 33%).

2,6-Anhydro-3-*O*-benzyl-D-mannono-1,4-lactone (94)

A solution of lactone (93) (7.5 mg, 0.05 mmol) in CH_2Cl_2 (0.5 cm^3) containing water (1 drop) was treated with DDQ (16 mg, 0.07 mmol) at room temperature for 17 hours. Saturated aqueous sodium bicarbonate (1 cm^3) was added and the resultant suspension was extracted with CH_2Cl_2 (5 x 5 cm^3). The combined organic extracts were washed with saturated aqueous sodium bicarbonate (2 x 5 cm^3), brine (5 cm^3) and dried (Na_2SO_4). The solvent was evaporated *in vacuo* and the residue purified by chromatography with EtOAc/petrol (1:1) as eluant to afford the title compound (94) (7 mg, 59%) as a colourless gum. (Found: M^+, 250.0838. $C_{13}H_{14}O_5$ requires M^+, 250.0840); υ_{max}/cm^{-1} 3570, 1800; δ_H (300 MHz, $CDCl_3$) 3.46 (1H, dd, $J_{6a,6e}$ 11.5, $J_{6a,5}$ 9, 6a-H), 4.10 (1H, dd, $J_{3,4}$ 6, $J_{3,2}$ 3, 3-H), 4.19 (1H, dd, $J_{4,3}$ 6, $J_{4,5}$ 1, 4-H), 4.27



(79c)

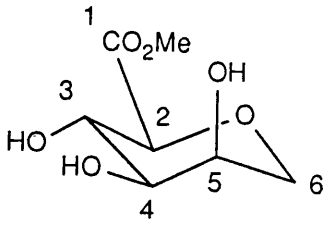
(1H, dd, $J_{6e,6a}$ 11.5, $J_{6e,5}$ 7, 6e-H), 4.40 (1H, ddd, $J_{5,4}$ 1, $J_{5,6e}$ 7, $J_{5,6a}$ 9, 5-H), 4.60 (1H, d, J 12, part of AB), 4.74 (1H, d, J 12, part of AB), 4.75 (1H, d, $J_{2,3}$ 3, 2-H) and 7.40 (5H, m, $CH_2C_6H_5$); m/z (70eV E.I.) 250 (M^+, 30%).

2,6-Anhydro-3-*O*-benzyl-D-*lyxo*-5-hexulosono-1,4-lactone (79c)

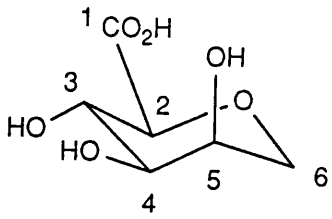
A solution of alcohol (94) (6 mg, 0.02 mmol) in CH_2Cl_2 (0.5 cm^3) was treated with N-methyl morpholine N-oxide (4 mg, 0.03 mmol) and powdered 4Å molecular sieves (10 mg) and stirred at room temperature for 10 minutes. Solid TPAP (1 mg, cat.) was then added and the resultant suspension stirred at room temperature for 30 minutes. The reaction mixture was diluted with CH_2Cl_2 (10 cm^3), filtered and washed with 1N sodium sulphite solution (5 cm^3), brine (5 cm^3) and saturated copper (II) sulphate solution (5 cm^3). The organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to give the title ketone (79c) (5 mg, 95%) as a colourless oil. (Found: M^+, 248.0675. $C_{13}H_{12}O_5$ requires M^+, 248.0683); υ_{max}/cm^{-1} 2950, 1815, 1750; δ_H (250 MHz, C_6D_6) 3.26 (1H, dd, $J_{3,2}$ 3, $J_{3,4}$ 6, 3-H), 3.84 (1H, d, $J_{2,3}$ 3, 2-H), 3.89 (1H, d, J 17, part of AB, 6a-H), 3.91 (1H, d, J 12, part of AB), 4.00 (1H, d, J 17, part of AB, 6e-H), 4.07 (1H, d, J 12, part of AB), 4.11 (1H, d, $J_{4,3}$ 6, 4-H) and 7.10 (5H, m, $CH_2C_6H_5$); m/z (70eV E.I.) 248 (M^+, 15%).

Methyl 2,6-anhydro-D-mannonate (98)

Oxygen was bubbled through a fine glass frit into a solution of 1,5-anhydro-D-mannitol (97) (9.83 g, 59.94 mmol) in water (750 cm^3) containing sodium bicarbonate (5.04 g, 59.94 mmol) and 5% platinum on carbon (7.86 g, 80% w/w) which was stirred vigorously at room temperature for 15 hours. The mixture was filtered to remove the catalyst and the filtrate was then freeze dried. The crude acid obtained was used without further purification



(98)



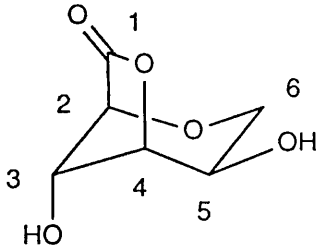
(99)

in the next step.

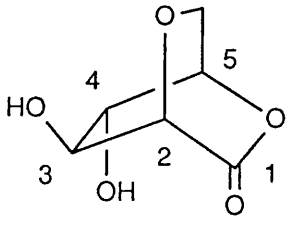
Acetyl chloride (7 cm^3) was added dropwise to dry methanol (250 cm^3) kept at 0°C and to this solution was added the crude acid obtained by the procedure above. The resultant solution was stirred at room temperature for 24 hours. Solid sodium bicarbonate was added until no further effervescence was observed and the resultant suspension was filtered. The filtrate was concentrated *in vacuo* and the residue purified by chromatography with methanol/CH_2Cl_2 (1:9) as eluant to give the methyl ester (98) (2.85 g, 25%) as colourless needles, m.p. 102-104°C (EtOAc/petrol). (Found: C, 43.60; H, 6.44. $C_7H_{12}O_6$ requires C, 43.75; H, 6.44%); υ_{max}/cm^{-1} (Nujol) 3300, 1730; δ_H (270 MHz, CD_3OD) 3.55-3.62 (2H, m, 6e-H and 4-H), 3.74 (3H, s, CH_3), 3.75 (1H, d, $J_{2,3}$ 7.5, 2-H), 3.87-3.98 (3H, m, 6a-H, 5-H and 3-H); m/z (70eV E.I.) 192 (M^+, 8%).

2,6-Anhydro-D-mannonic acid (99)

A solution of methyl ester (98) (1.58 g, 8.21 mmol) in water/methanol (4:1, 80 cm^3) was cooled to 0°C and 1N potassium hydroxide (9 cm^3) was added dropwise over 30 minutes. The resultant solution was stirred at 0°C for a further 30 minutes and then neutralised by addition of DOWEX-50W-X8 ion exchange resin. The resin was removed by filtration and the filtrate concentrated *in vacuo*. The residue was triturated with isopropanol (5 cm^3) and filtered to afford the title acid (99) (1.31 g, 90%) as colourless plates, m.p. 158-159°C (EtOH/Et_2O). (Found: C, 40.20; H, 5.85. $C_6H_{10}O_6$ requires C, 40.45; H, 5.66%); υ_{max}/cm^{-1} (Nujol) 3200, 1715; δ_H (270 MHz, CD_3OD) 3.56 (1H, dd, $J_{4,3}$ 8, $J_{4,5}$ 4, 4-H), 3.58 (1H, dd, $J_{6e,6a}$ 13.5, $J_{6e,5}$ 2, 6e-H), 3.72 (1H, d, $J_{2,3}$ 8, 2-H), 3.87 (1H, ddd, $J_{5,6e}$ 2, $J_{5,6a}$ 4, $J_{5,4}$ 4, 5-H), 3.90 (1H, brt, $J_{3,4}$ and $J_{3,2}$ 8, 3-H) and 3.95 (1H, dd, $J_{6a,6e}$ 13.5, $J_{6a,5}$ 4, 6a-H); m/z (70eV E.I.) 178 (M^+, 2%),



(100)



(103)

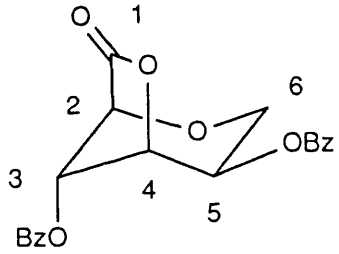
160 (M^+-18, 8%).

2,6-Anhydro-D-mannono-1,4-lactone (100)

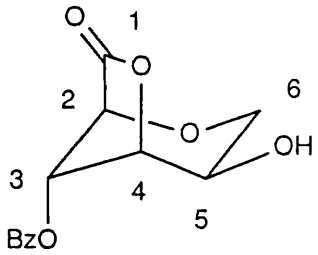
To the solid acid (99) (688 mg, 3.86 mmol) was added diisopropyl-ethylamine (0.81 cm^3, 4.64 mmol) followed by dry THF (70 cm^3) and the resultant solution cooled to 0°C. Methyl chloroformate (0.33 cm^3, 4.25 mmol) was added dropwise over 5 minutes and the reaction mixture was stirred at room temperature for 36 hours. Solvent was removed *in vacuo* and the residue purified by chromatography with EtOAc/petrol (7:3) as eluant to afford two fractions:

(i) The first component, 1,4-lactone (100) (440 mg, 71%) as colourless needles, m.p. 112-114°C (EtOAc). (Found: C, 45.40; H, 5.13. $C_6H_8O_5$ requires C, 45.00; H, 5.04%); υ_{max}/cm^{-1} 3300, 1780; δ_H (270 MHz, CD_3OD) 3.40 (1H, dd, $J_{6a,6e}$ 11, $J_{6a,5}$ 10, 6a-H), 3.97 (1H, brd, $J_{4,3}$ 6, 4-H), 4.12 (1H, dd, $J_{6e,6a}$ 11, $J_{6e,5}$ 7.5, 6e-H), 4.27 (1H, m, 5-H), 4.36 (1H, dd, $J_{3,2}$ 3, $J_{3,4}$ 6, 3-H) and 4.66 (1H, d, $J_{2,3}$ 3, 2-H); m/z (70eV E.I.) 160 (M^+, 3%).

(ii) The second component 1,5-lactone (103) (26 mg, 4%) as a colourless gum. (Found: M^+, 160.0371. $C_6H_8O_5$ requires M^+, 160.0372); υ_{max} 3400, 1750; δ_H (270 MHz, CD_3OD) 3.85-3.89 (2H, m, 5-H and 3-H), 4.01 (1H, dd, $J_{6a,6e}$ 9.5, $J_{6a,5}$ 3, 6a-H), 4.06 (1H, dd, $J_{6e,6a}$ 9.5, $J_{6e,5}$ 1, 6e-H), 4.20 (1H, dd, J 1.5, J 2, 4-H), 4.79 (1H, s, 2-H); m/z (70eV E.I.) 160 (M^+, 2%).



(109)



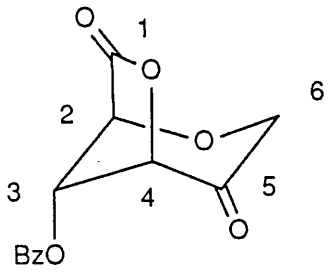
(108)

2,6-Anhydro-3-*O*-benzoyl-D-mannono-1,4-lactone (108)

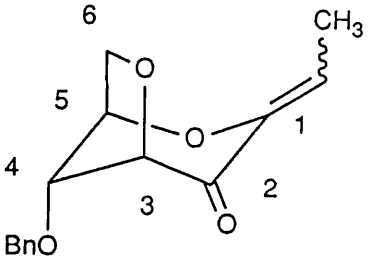
A solution of lactone (100) (84 mg, 0.52 mmol) in CH_2Cl_2 (2 cm^3) containing DMAP (64 mg, 0.52 mmol) was cooled to 0°C and treated with benzoyl chloride (61 µl, 0.52 mmol) and the resultant solution stirred at room temperature for 24 hours. Dry methanol (one drop) was added and the reaction mixture concentrated *in vacuo*. The residue was purified by chromatography with EtOAc/petrol (1:1) as eluant to afford two fractions:

(i) The first component, bis(benzoate) (109) (34 mg, 18%) as colourless needles, m.p. 144-146°C (EtOAc/petrol). (Found: C, 64.90; H, 4.28. $C_{20}H_{16}O_7$ requires C, 65.21; H, 4.38%); υ_{max}/cm^{-1} 1800, 1720; δ_H (270 MHz, $CDCl_3$) 3.85 (1H, dd, $J_{6a,6e}$ 12, $J_{6a,5}$ 10, 6a-H), 4.45 (1H, dd, $J_{6e,6a}$ 12, $J_{6e,5}$ 7, 6e-H), 4.59 (1H, d, $J_{2,3}$ 3, 2-H), 5.26 (1H, brd, $J_{4,3}$ 6, 4-H), 5.41 (1H, dd, $J_{3,2}$ 3, $J_{3,4}$ 6, 3-H), 5.68 (1H, ddd, $J_{5,6a}$ 10, $J_{5,6e}$ 7, $J_{5,4}$ 1, 5-H), 7.41-8.20 (10H, m, 2 x C_6H_5CO); m/z (Iso-but. C.I.) 369 (M^++H, 100%).

(ii) The second component, monobenzoate (108) (63 mg, 46%) as a colourless solid, m.p. 120-121°C (EtOAc/petrol). (Found: C, 59.10; H, 4.49. $C_{13}H_{12}O_6$ requires C, 59.09; H, 4.58%); υ_{max}/cm^{-1} 3400, 1800, 1705; δ_H (270 MHz, $CDCl_3$) 3.54 (1H, dd, $J_{6a,6e}$ 11.5, $J_{6a,5}$ 9, 6a-H), 4.28 (1H, dd, $J_{6e,6a}$ 11.5, $J_{6e,5}$ 7, 6e-H), 4.40 (1H, m, 5-H), 4.50 (1H, d, $J_{4,3}$ 6, 4-H), 5.08 (1H, d, $J_{2,3}$ 3, 2-H), 5.34 (1H, dd, $J_{3,4}$ 6, $J_{3,2}$ 3, 3-H), 7.40-8.10 (5H, m, C_6H_5CO); m/z (Iso-but. C.I.) 265 (M^++H, 70%).



(79d)



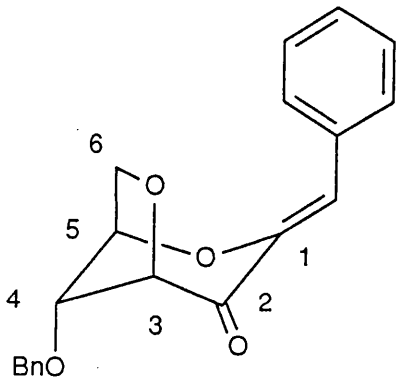
(121)

2,6-Anhydro-3-*O*-benzoyl-D-*lyxo*-5-hexulosono-1,4-lactone (79d)

A solution of alcohol (108) (8 mg, 0.03 mmol) in CH_2Cl_2 (0.5 cm^3) was treated with powdered 4Å molecular sieves (10 mg) followed by PCC (15 mg, 0.07 mmol) and the reaction mixture stirred at room temperature for 2.5 hours. The supernatant was decanted and the residue extracted with dry Et_2O (5 x 5 cm^3). The combined organic extracts were filtered through Florisil and concentrated *in vacuo* to give the ketone (79d) (5 mg, 65%) as a colourless gum. (Found: M^++H, 263.0560. $C_{13}H_{11}O_6$ requires M^+, 263.0554); υ_{max}/cm^{-1} 1820, 1760, 1740; δ_H (270 MHz, $CDCl_3$) 4.42 (1H, d, *J* 17.5, part of AB), 4.60 (1H, d, *J* 17.5, part of AB), 4.79 (1H, d, $J_{2,3}$ 3, 2-H), 4.98 (1H, d, $J_{4,3}$ 6, 4-H), 5.67 (1H, dd, $J_{3,2}$ 3, $J_{3,4}$ 6, 3-H), 7.43-8.00 (5H, m, C_6H_5CO); m/z (Iso-but. C.I.) 263 (M^++H, 70%).

(Z)-1,5:3,6-Dianhydro-4-*O*-benzyl-1-ethylidene-D-*arabino*-hexulose (121)

A solution of ketone (79a) (53 mg, 0.22 mmol) in *tert*-butanol (2 cm^3) containing acetaldehyde (15 µl, 0.27 mmol) was treated with potassium *tert*-butoxide (38 mg, 0.34 mmol) at room temperature for 10 minutes. Saturated aqueous ammonium chloride (1 cm^3) was added and the resultant emulsion was extracted with CH_2Cl_2 (3 x 20 cm^3). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by chromatography with EtOAc/petrol (3:7) as eluant to afford enone (121) (26 mg, 43%) as a colourless oil. (Found: M^+, 260.1016. $C_{15}H_{16}O_4$ requires M^+, 260.1049); υ_{max}/cm^{-1} 2900, 1720, 1610; δ_H (270 MHz, $CDCl_3$) 1.69 (3H, d, *J* 7, CH_3), 4.10 (2H, brs, 6a and 6e-H), 4.16 (1H, d, $J_{3,4}$ 6, 3-H), 4.32 (1H, dd, $J_{4,3}$ 6, $J_{4,5}$ 3, 4-H), 4.58 (2H, brd, *J* 12, $CH_2C_6H_5$), 4.66 (1H, m, 5-H), 5.91 (1H, q, *J* 7, CH_3CH) and 7.28 (5H, m, $CH_2C_6H_5$); m/z (70eV E.I.) 260 (M^+, 10%).



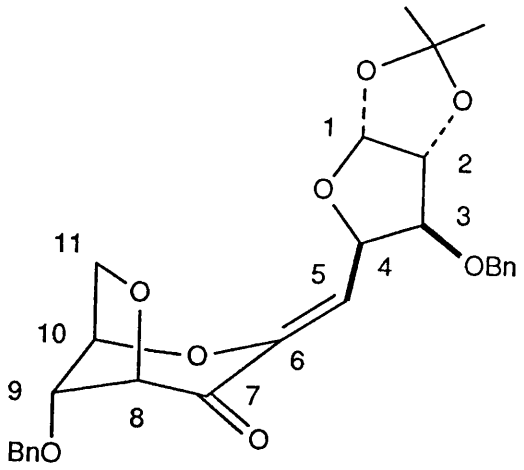
(120)

(Z)-1,5:3,6-Dianhydro-4-*O*-benzyl-1-benzylidene-D-*arabino*-hexulose (120)

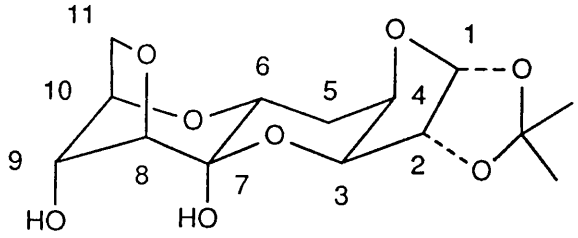
A solution of ketone (79a) (56 mg, 0.24 mmol) in *tert*-butanol (2 cm^3) containing benzaldehyde (29 µl, 0.29 mmol) was treated with potassium *tert*-butoxide (40 mg, 0.36 mmol) and the resultant solution stirred at room temperature for 20 minutes. Saturated aqueous ammonium chloride solution (1 cm^3) was added and the resultant emulsion was extracted with CH_2Cl_2 (3 x 20 cm^3). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by chromatography with EtOAc/petrol (1:1) as eluant to afford the title enone (120) (70 mg, 91%) as a colourless oil. (Found: M^+, 322.1254. $C_{20}H_{18}O_4$ requires M^+, 322.1205); υ_{max}/cm^{-1} 3100, 1710, 1600, 1500; δ_H (270 MHz, $CDCl_3$) 4.18 (2H, brs, 6e and 6a-H), 4.27 (1H, d, $J_{3,4}$ 6, 3-H), 4.41 (1H, dd, $J_{4,5}$ 3, $J_{4,3}$ 6, 4-H), 4.61 (1H, d, *J* 12, part of AB), 4.67 (1H, d, *J* 12, part of AB), 4.81 (1H, m, 5-H), 6.67 (1H, s, C_6H_5 *CH*) and 7.20-7.75 (10H, m, 2 x C_6H_5); m/z (70eV E.I.) 322 (M^+, 10%).

6,10:8,11-Dianhydro-3,9-di-*O*-benzyl-5,6-didehydro-5-deoxy-1,2-*O*-isopropylidene-D-*erythro*-L-*ido*-7-undeculo-α-D-1,4-furanose (126)

A solution of ketone (79a) (236 mg, 1.01 mmol) in THF (8 cm^3) containing aldehyde (122) (336 mg, 1.21 mmol) was cooled to 0°C and treated with potassium *tert*-butoxide (170 mg, 1.51 mmol) for 20 minutes. Saturated aqueous ammonium chloride (2 cm^3) was added and the resultant emulsion was extracted with CH_2Cl_2 (3 x 20 cm^3). The combined organic extracts were washed with brine (10 cm^3), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by chromatography with EtOAc/petrol (3:7) as eluant to afford the title enone (126) (296 mg, 59%) as a foam. (Found: M^++H, 495.2020. $C_{28}H_{31}O_8$ requires M^+, 495.2016); υ_{max}/cm^{-1} 3000, 1720, 1630; δ_H (400 MHz, $CDCl_3$) 1.32 (3H, s, CH_3), 1.53 (3H, s, CH_3), 3.97 (1H, d, $J_{3,4}$ 3,



(126)

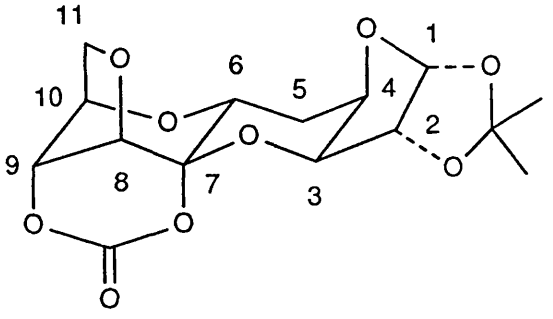


(127)

3-H), 4.18 (1H, dd, $J_{11a,10}$ 3, $J_{11a,11e}$ 11, 11a-H), 4.24 (1H, d, $J_{11e,11a}$ 11, 11e-H), 4.29 (1H, d, $J_{8,9}$ 6, 8-H), 4.43 (1H, dd, $J_{9,10}$ 3, $J_{9,8}$ 6, 9-H), 4.46 (1H, d, J 12, part of AB), 4.49 (1H, d, J 12, part of AB), 4.60 (1H, d, $J_{2,1}$ 4, 2-H), 4.71 (2H, brs, $CH_2C_6H_5$), 4.75 (1H, d, $J_{10,11a}$ and $J_{10,9}$ 3, 10-H), 5.14 (1H, dd, $J_{4,5}$ 8, $J_{4,3}$ 3, 4-H), 5.97 (1H, d, $J_{1,2}$ 4, 1-H), 6.12 (1H, d, $J_{5,4}$ 8, 5-H) and 7.25 (10H, m, 2 x CH_2 C_6H_5); δ_C (67.80 MHz, $CDCl_3$) 26.14 (CH_3), 26.79 (CH_3), 72.46 (CH_2), 72.75 (CH_2), 73.14 (CH_2), 74.73 (CH), 75.09 (CH), 77.55 (CH), 77.91 (CH), 83.19 (CH), 83.55 (CH), 104.80 (CH), 104.86 (C), 109.63 (CH), 127.73 (CH), 128.31 (CH), 128.38 (CH), 128.57 (CH), 136.26 (C), 137.46 (C), 148.42 (C) and 187.86 (C); m/z (Iso-but. C.I.) 495 (M^++H, 65%).

6,10:8,11-Dianhydro-1,2-*O*-isopropylidene-D-*arabino*-L-*ido*-7-undeculo-(7R) -3,7-pyrano-α-D-1,4-furanose (127)

A solution of enone (126) (80 mg, 0.16 mmol) in absolute ethanol (4 cm^3) containing 10% palladium on carbon (40 mg, 40% w/w) was stirred under an atmosphere of hydrogen for 1 hour at room temperature. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography, eluting with EtOAc afforded the title compound (127) (33 mg, 65%) as colourless cubes, m.p. 197-198°C (Et_2O). (Found: C, 53.20; H, 6.54. $C_{14}H_{20}O_8$ requires C, 53.16; H, 6.37%); υ_{max}/cm^{-1} 3250, 1700 (wk); δ_H (270 MHz, $CDCl_3$) 1.33 (3H, s, CH_3), 1.51 (3H, s, CH_3), 2.15 (1H, ddd, $J_{5e,5a}$ 12.5, $J_{5e,4}$ 4, $J_{5e,6}$ 2, 5e-H), 2.28 (1H, dt, $J_{5a,4}$ 4, $J_{5a,6}$ and $J_{5a,5e}$ 12.5, 5a-H), 3.87 (1H, d, $J_{8,9}$ 5, 8-H), 4.02 (1H, dd, $J_{11a,10}$ 3, $J_{11a,11e}$ 10.5, 11a-H), 4.26 (3H, m, 6-H, 9-H and 10-H), 4.27 (1H, d, $J_{11e,11a}$ 10.5, 11e-H), 4.31 (1H, d, $J_{3,4}$ 2.5, 3-H), 4.45 (1H, dt, $J_{4,3}$ 2.5, $J_{4,5a}$ and $J_{4,5e}$ 4, 4-H), 4.63 (1H, d, $J_{2,1}$ 4, 2-H) and 5.98 (1H, d, $J_{1,2}$ 4, 1-H); δ_C (67.80 MHz, $CDCl_3$) 24.91 (CH_2), 26.10 (CH_3), 26.49 (CH_3), 68.24 (CH), 68.63 (CH_2), 73.30 (CH), 74.27 (CH), 75.54 (CH), 75.96 (CH), 76.51 (CH), 83.95 (CH), 94.35 (C), 104.80 (CH)



(130)

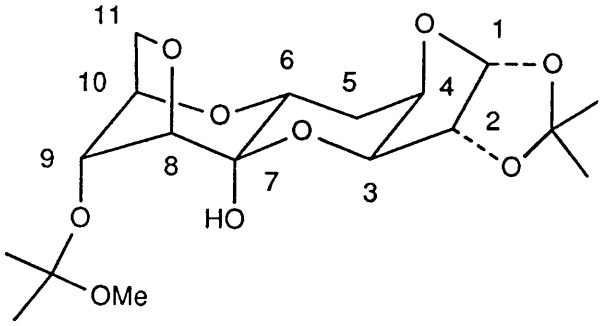
and 111.38 (C); m/z (Iso-but. C.I.) 317 (M^++H, 40%), 299 (M^++H-18, 100%).

6,10:8,11-Dianhydro-7,9-*O*-carbonyl-1,2-*O*-isopropylidene-D-*arabino*-L-*ido*-7-undeculo-(7R)-3,7-pyrano-α-D-1,4-furanose (130)

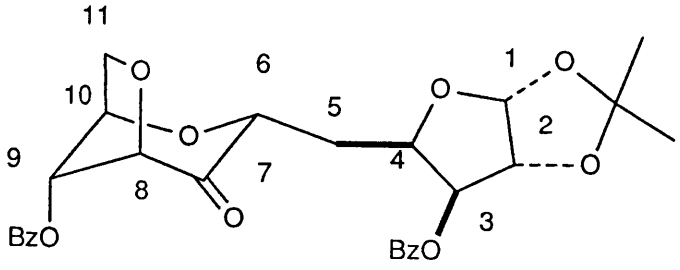
A solution of diol (127) (292 mg, 0.92 mmol) in THF (15 cm^3) was treated with carbonyl diimidazole (450 mg, 2.77 mmol) for 18 hours at room temperature. The solution was concentrated *in vacuo* and the residue purified by chromatography with EtOAc/petrol (1:1) as eluant to afford the title carbonate (130) (294 mg, 94%) as colourless crystals, m.p. 239-241°C (dec.). (Found: C, 52.80; H, 5.53. $C_{15}H_{18}O_9$ requires C, 52.64; H, 5.30%); υ_{max}/cm^{-1} 1790; δ_H (270 MHz, $CDCl_3$) 1.30 (3H, s, CH_3), 1.49 (3H, s, CH_3), 2.15 (1H, dt, $J_{5a,4}$ 3, $J_{5a,5e}$ and $J_{5a,6}$ 12, 5a-H), 2.31 (1H, ddd, $J_{5e,4}$ 3, $J_{5e,6}$ 5, $J_{5e,5a}$ 12, 5e-H), 4.10 (1H, dd, $J_{11a,11e}$ 11.5, $J_{11a,10}$ 3, 11a-H), 4.19 (1H, d, $J_{8,9}$ 6, 8-H), 4.26 (1H, d, $J_{11e,11a}$ 11.5, 11e-H), 4.34 (1H, dd, $J_{6,5a}$ 12, $J_{6,5e}$ 5, 6-H), 4.49 (3H, m, 3-H, 4-H and 10-H), 4.60 (1H, d, $J_{2,1}$ 4, 2-H), 4.83 (1H, dd, $J_{9,8}$ 6, $J_{9,10}$ 3, 9-H) and 5.92 (1H, d, $J_{1,2}$ 4, 1-H); m/z (Iso-but. C.I.) 343 (M^++H, 100%), 299 (M^++H-44, 5%).

6,10:8,11-Dianhydro-1,2-*O*-isopropylidene-9-*O*-(2-methoxy-isopropyl)-D-*arabino*-L-*ido*-7-undeculo-(7R)-3,7-pyrano-α-D-1,4-furanose (128)

A solution of diol (127) (46 mg, 0.15 mmol) in $CHCl_3$ (10 cm^3) was treated with 2,2-dimethoxy propane (9 μl, 0.74 mmol) and ρ-toluenesulphonic acid (1 mg) and the resultant solution was then refluxed for 7 hours. Saturated aqueous sodium bicarbonate solution (2 cm^3) was added and the resultant emulsion extracted with CH_2Cl_2 (3 x 10 cm^3). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by chromatography, eluting with EtOAc/petrol (1:1) to afford the title compound


11
O
10
O
6
5
O
1
O
4
2
O
9
8
7
3
O
HO
O
OMe

(128)


11
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5
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O
2
9
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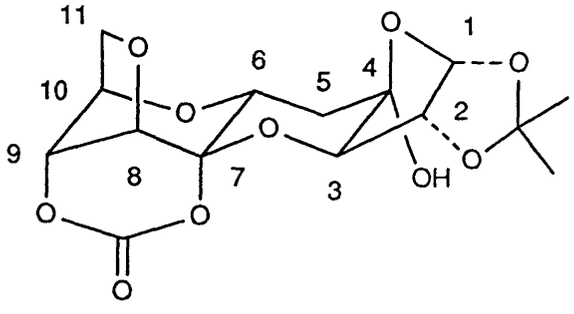
7
4
O
BzO
O
BzO
3

(129)

(128) (27 mg, 46%) as an oil. υ_{max}/cm^{-1} 3450, 1720 (wk); δ_H (270 MHz, $CDCl_3$) 1.28 (3H, s, CH_3), 1.45 (3H, s, CH_3), 1.47 (6H, s, 2 x CH_3), 2.10 (1H, brd, $J_{5e,5a}$ 12, 5e-H), 2.24 (1H, dt, $J_{5a,4}$ 4, $J_{5a,6}$ 12, $J_{5a,5e}$ 12, 5a-H), 3.28 (3H, s, OCH_3), 3.85 (1H, d, $J_{8,9}$ 5.5, 8-H), 3.98 (1H, dd, $J_{11a,10}$ 3, $J_{11a,11e}$ 11, 11a-H), 4.21 (1H, dd, $J_{6,5a}$ 12, $J_{6,5e}$ 5, 6-H), 4.23 (1H, m, 9-H), 4.24 (1H, d, $J_{11e,11a}$ 11, 11e-H), 4.35 (1H, brs, 10-H), 4.38 (1H, d, $J_{3,4}$ 2.5, 3-H), 4.42 (1H, dd, $J_{4,3}$ 2.5, $J_{4,5e}$ and $J_{4,5a}$ 4, 4-H), 4.56 (1H, d, $J_{2,1}$ 4, 2-H) and 5.93 (1H, d, $J_{1,2}$ 4, 1-H); m/z (Iso-but. C.I.) 389 (M^++H, 5%), 357 (M^++H-32, 12%).

6,10:8,11-Dianhydro-3,9-di-*O*-benzoyl-1,2-*O*-isopropylidene-D-*arabino*-L-*ido*-7-undeculo-α-D-1,4-furanose (129)

A solution of the diol (127) (10 mg, 0.03 mmol) in CH_2Cl_2 (1 cm^3) at 0°C was treated with 4-dimethyl aminopyridine (16 mg, 0.13mmol) followed by benzoyl chloride (115 µl, 0.13 mmol) and the resultant solution stirred at room temperature for 48 hours. The reaction mixture was concentrated *in vacuo* and the residue purified by chromatography, eluting with EtOAc/petrol (1:4) to afford the title compound (129) (16 mg, 90%) as a colourless oil. υ_{max}/cm^{-1} 1760, 1720; δ_H (270 MHz, $CDCl_3$) 1.24 (3H, s, CH_3), 1.52 (3H, s, CH_3), 1.79 (1H, ddd, $J_{5a,5e}$ 9.5, $J_{5a,6}$ 10.5, $J_{5a,4}$ 4, 5a-H), 2.50 (1H, ddd, $J_{5e,5a}$ 9.5, $J_{5e,6}$ 12.5, $J_{5e,4}$ 2, 5e-H), 4.36 (1H, dd, $J_{11a,11e}$ 11, $J_{11a,10}$ 3, 11a-H), 4.45 (1H, d, $J_{8,9}$ 6, 8-H), 4.53 (1H, d, $J_{11e,11a}$ 11, 11e-H), 4.60 (2H, m, 2-H and 4-H), 4.71 (1H, dd, $J_{6,5e}$ 12.5, $J_{6,5a}$ 10.5, 6-H), 4.77 (1H, brt, $J_{10,11a}$ and $J_{10,9}$ 3, 10-H), 5.34 (1H, d, $J_{3,4}$ 3, 3-H), 5.51 (1H, dd, $J_{9,8}$ 6, $J_{9,10}$ 3, 9-H), 5.95 (1H, d, $J_{1,2}$ 4, 1-H) and 7.40-8.00 (10H, m, 2 x C_6H_5CO). We were unable to obtain a molecular ion or satisfactory analytical data for this compound.



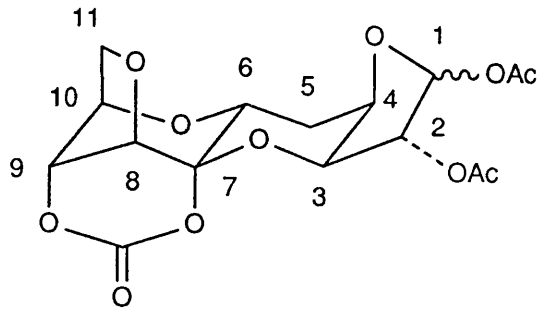
(132)

6,10:8,11-Dianhydro-7,9-*O*-carbonyl-4-hydroxy-1,2-*O*-isopropylidene-D-*arabino*-L-*ido*-7-undeculo-(7R)-3,7-pyrano-α-D-1,4-furanose (132)

A solution of carbonate (130) (13 mg, 0.04 mmol) in CCl_4 (0.5 cm^3) and acetone (0.5 cm^3) at -78°C was treated with a 0.5N solution of dimanganese heptoxide in CCl_4 (152 μl, 0.076 mmol). The resultant solution was allowed to warm to -10°C and stirred at this temperature for 5 minutes. Isopropyl alcohol (1 drop) was added and the mixture filtered through celite. The filtrate was concentrated *in vacuo* and the residue purified by chromatography with EtOAc/petrol (1:1) as eluant to afford alcohol (132) (1 mg, 7%) as a colourless oil. (Found: M^++NH_4, 376.1244. $C_{15}H_{22}O_{10}N$ requires M^+, 376.1244); υ_{max}/cm^{-1} 3700, 1774; δ_H (270 MHz, $CDCl_3$) 1.30 (3H, s, CH_3), 1.60 (3H, s, CH_3), 2.21 (1H, dd, $J_{5a,5e}$ 13, $J_{5a,6}$ 12, 5a-H), 2.45 (1H, dd, $J_{5e,5a}$ 13, $J_{5e,6}$ 5, 5e-H), 3.85 (1H, s, 4-OH), 4.11 (1H, dd, $J_{11a,11e}$ 11.5, $J_{11a,10}$ 3, 11a-H), 4.13 (1H, dd, $J_{6,5a}$ 12, $J_{6,5e}$ 5, 6-H), 4.23 (1H, d, $J_{8,9}$ 6.5, 8-H), 4.26 (1H, d, $J_{11e,11a}$ 11.5, 11e-H), 4.52 (1H, brt, $J_{10,11a}$ 3, $J_{10,9}$ 3, 10-H), 4.56 (1H, s, 3-H), 4.67 (1H, d, $J_{2,1}$ 3.5, 2-H), 4.86 (1H, dd, $J_{9,8}$ 6.5, $J_{9,10}$ 3, 9-H) and 5.96 (1H, d, $J_{1,2}$ 3.5, 1-H); m/z (Iso-but. C.I.) 359 (M^++H, 10%).

6,10:8,11-Dianhydro-1,2-di-*O*-acetyl-7,9-*O*-carbonyl-D-*arabino*-L-*ido*-7-undeculo-(7R)-3,7-pyrano-α(and β)-D-1,4-furanose (135)

Carbonate (130) (10 mg, 0.029 mmol) was treated with TFA/water (9:1, 1 cm^3) for 45 minutes at room temperature. The mixture was concentrated *in vacuo* and then freeze-dried. The residue was dissolved in pyridine (1 cm^3) and treated with acetic anhydride (0.1 cm^3) for 18 hours at room temperature. The reaction mixture was poured into water (10 cm^3) and the resultant solution extracted with EtOAc (3 x 10 cm^3). The combined organic extracts were washed with 2N hydrochloric acid (10 cm^3), water (10 cm^3), saturated aqueous


11
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OAc
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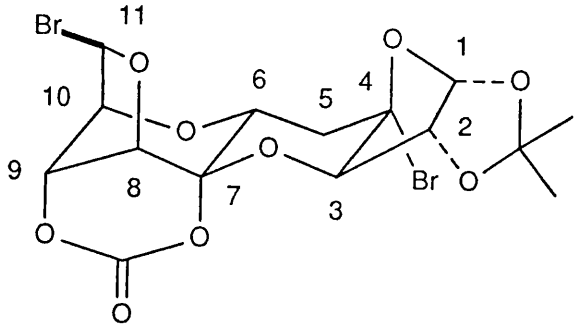
O
2
O
9
8
7
3
OAc
O
O
O

(135)


Br
11
O
1
6
5
4
10
O
O
2
O
9
8
7
3
Br
O
O
O
O

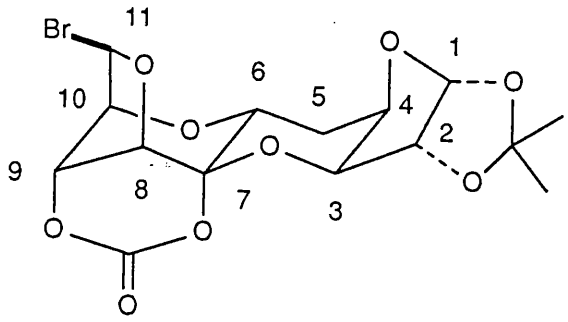
(139)

sodium bicarbonate (10 cm^3), brine (10 cm^3) and dried (Na_2SO_4). The organic phase was concentrated *in vacuo* to afford the title compound (135) (10 mg, 89%) as a mixture of anomers (α:β, 2:1). (Found: M^++H, 387.0927. $C_{16}H_{19}O_{11}$ requires M^+, 387.0927); υ_{max} /cm^{-1} 1770, 1750; δ_H (270 MHz, $CDCl_3$) 2.07-2.11 (6H, m, 2 x $COCH_3$), 2.12 (2H, m, 5a-H and 5e-H), 4.10 (1H, m, 11a-H), 4.22 (2H, m, 11e-H and 8-H), 4.35 (1H, m, 6-H), 4.50-4.61 (3H, m, 3-H, 4-H and 10-H), 4.83 (1H, dd, $J_{9,8}$ 6, $J_{9,10}$ 3, 9-H), 5.24 (0.33H, s, 2β-H), 5.30 (0.66H, d, $J_{2\alpha,1\alpha}$ 5, 2α-H), 6.07 (0.33H, s, 1β-H) and 6.45 (0.66H, d, $J_{1\alpha,2\alpha}$ 5, 1α-H); m/z (Iso-but. C.I.) 387 (M^++H, 3%).

6,10:8,11-Dianhydro-(11R)-11-bromo-7,9-*O*-carbonyl-1,2-*O*-isopropylidene-D-*arabino*-L-*ido*-7-undeculo-(7R)-3,7-pyrano-α-D-1,4-furanose (138)

A solution of carbonate (130) (52 mg, 0.15 mmol) in CCl_4 (5 cm^3) was treated with bromine (10 μl, 0.18 mmol) and the resultant solution was then refluxed and irradiated with a 200W heat lamp for 15 minutes. The solution was concentrated *in vacuo* and the residue purified by chromatography with EtOAc/CH_2Cl_2 (1:19) as eluant to afford three fractions.

(i) The first component bis(bromide) (139) (4 mg, 5%) as a colourless solid, m.p. 140-142°C(dec.). (Found: M^++H, 500.922. $C_{15}H_{17}O_9Br_2$ requires M^+, 500.922; ^{79}Br, ^{81}Br); ν_{max}/cm^{-1} 3410, 1788; δ_H (270 MHz, $CDCl_3$) 1.33 (3H, s, CH_3), 1.71 (3H, s, CH_3), 2.77 (1H, dd, $J_{5a,5e}$ 13.5, $J_{5a,6}$ 12, 5a-H), 3.06 (1H, dd, $J_{5e,5a}$ 13.5, $J_{5e,6}$ 5, 5e-H), 3.98 (1H, dd, $J_{6,5a}$ 12, $J_{6,5e}$ 5, 6-H), 4.54 (1H, d, $J_{8,9}$ 6.5, 8-H), 4.67 (1H, d, $J_{10,9}$ 3, 10-H), 4.71 (1H, d, $J_{2,1}$ 4, 2-H), 5.03 (1H, s, 3-H), 5.55 (1H, dd, $J_{9,8}$ 6.5, $J_{9,10}$ 3, 9-H), 6.05 (1H, d, $J_{1,2}$ 4, 1-H) and 6.40 (1H, s, 11-H); m/z (Iso-but. C.I.) 501 (M^++H, 5%; ^{79}Br, ^{81}Br).



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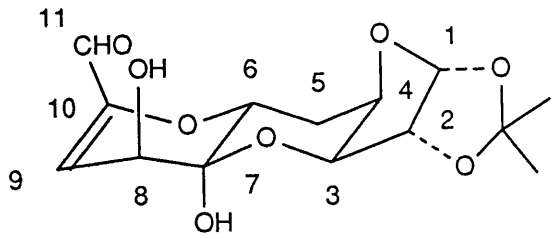


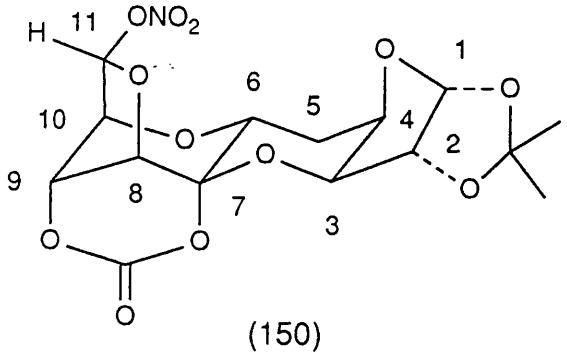
(141)

(ii) The second component bromide (138) (11 mg, 17%) as a colourless solid, m.p. 224-225°C (dec.) (EtOAc/petrol). (Found: M^++H, 421.0130. $C_{15}H_{18}O_9Br$ requires M^+, 421.0134; ^{79}Br); υ_{max}/cm^{-1} 1780, 1076; δ_H (270 MHz, $CDCl_3$) 1.31 (3H, s, CH_3), 1.48 (3H, s, CH_3), 2.14 (1H, dt, $J_{5a,4}$ 3, $J_{5a,5e}$ and $J_{5a,6}$ 12, 5a-H), 2.33 (1H, brd, $J_{5a,5e}$ 12, 5e-H), 4.25 (1H, dd, $J_{6,5a}$ 12, $J_{6,5e}$ 5, 6-H), 4.48 (2H, m, 3-H and 4-H), 4.50 (1H, d, $J_{8,9}$ 6.5, 8-H), 4.58 (1H, d, $J_{2,1}$ 4, 2-H), 4.65 (1H, d, $J_{10,9}$ 3, 10-H), 5.53 (1H, dd, $J_{9,8}$ 6.5, $J_{9,10}$ 3, 9-H), 5.89 (1H, d, $J_{1,2}$ 4, 1-H) and 6.43 (1H, s, 11-H); m/z (Iso-but. C.I.) 421 (M^++H, 10%; ^{79}Br), 423 (M^++H, 10%; ^{81}Br).

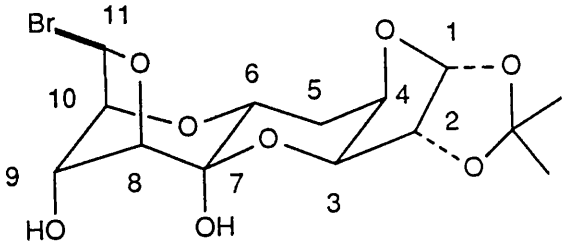
(iii) The third component, recovered carbonate (130) (37 mg, 71%) which gave identical spectral data to that previously described.

6,10-Anhydro-9,10-didehydro-9-deoxy-1,2-*O*-isopropylidene-L-*glycero*-L-*ido*-7-undeculodialdo-(7R)-3,7-pyrano-α-D-1,4-furanose (141)

A solution of bromide (138) (5 mg, 0.01 mmol) in acetone (1 cm^3) was treated with water (one drop) and silver carbonate (5 mg, 0.02 mmol) and the resultant suspension stirred at room temperature for 3 days. The mixture was filtered and the filtrate concentrated *in vacuo* to afford the title compound (141) (3 mg, 95%) as a colourless oil. υ_{max}/cm^{-1} 3580, 1709; δ_H (270 MHz, $CDCl_3$) 1.32 (3H, s, CH_3), 1.51 (3H, s, CH_3), 2.23 (1H, ddd, $J_{5a,5e}$ 15, $J_{5a,6}$ 12, $J_{5a,4}$ 3.5, 5a-H), 2.58 (1H, brd, $J_{5e,5a}$ 15, 5e-H), 3.98 (1H, d, $J_{8,9}$ 5.5, 8-H), 4.25 (1H, dd, $J_{6,5a}$ 12, $J_{6,5e}$ 5.5, 6-H), 4.38 (1H, d, $J_{3,4}$ 2, 3-H), 4.49 (1H, m, 4-H), 4.57 (1H, d, $J_{2,1}$ 4, 2-H), 5.90 (1H, d, $J_{1,2}$ 4, 1-H), 5.93 (1H, d, $J_{9,8}$ 5.5, 9-H) and 9.26 (1H, s, RCHO). This compound was not characterised further.



(150)



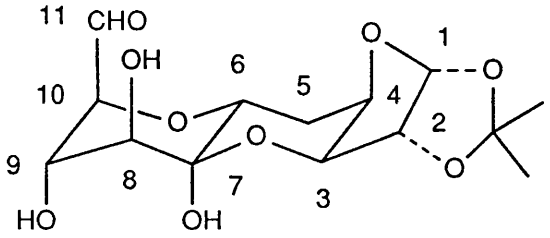
(143)

6,10:8,11-Dianhydro-7,9-*O*-carbonyl-1,2-*O*-isopropylidene-(11S)-11-*O*-nitrato-D-*arabino*-L-*ido*-7-undeculo-(7R)-3,7-pyrano-α-D-1,4-furanose (150)

To a solution of bromide (138) (5 mg, 0.012 mmol) in moist acetone (0.5 cm^3) was added silver(I) nitrate (4 mg, 0.024 mmol) and the mixture stirred at room temperature for 3 hours. The mixture was filtered through Celite and the filtrate concentrated *in vacuo* to afford the title compound (150) (4.5 mg, 90%) as a colourless gum. υ_{max}/cm^{-1} 1775, 1690; δ_H (270MHz, $CDCl_3$) 1.25 (3H, s, CH_3), 1.49 (3H, s, CH_3), 2.15 (1H, m, 5a-H), 2.41 (1H, brd, $J_{5e,5a}$ 13, 5e-H), 4.41 (1H, d, $J_{8,9}$ 6, 8-H), 4.51 (2H, m, 3-H and 4-H), 4.55 (1H, brt, $J_{10,9}$ 3 and $J_{10,11}$ 3, 10-H), 4.59 (1H, d, $J_{2,1}$ 4, 2-H), 4.68 (1H, dd, $J_{6,5a}$ 11.5, $J_{6,5e}$ 5, 6-H), 4.96 (1H, dd, $J_{9,8}$ 6, $J_{9,10}$ 3, 9-H), 5.94 (1H, d, $J_{1,2}$ 4, 1-H) and 6.49 (1H, d, $J_{11,10}$ 3, 11-H). This compound was not characterised further.

6,10:8,11-Dianhydro-(11R)-11-bromo-1,2-*O*-isopropyliden e-D-*arabino*-L-*ido*-7-undeculo-(7R)-3,7-pyrano-α-D-1,4-furanose (143)

A solution of bromide (138) (6 mg, 0.01 mmol) in methanol (1 cm^3) at 0°C was treated with sodium methoxide (1 mg, 0.02 mmol) for 20 minutes. The reaction mixture was quenched with DOWEX 50W-X8 ion exchange resin and the mixture filtered. The filtrate was concentrated *in vacuo* and the residue purified by chromatography with EtOAc/petrol (1:1) as eluant to afford the diol (143) (5 mg, 95%) as a colourless solid. υ_{max}/cm^{-1} 3410, 1730 (wk), 1082; δ_H (270 MHz, $CDCl_3$) 1.31 (3H, s, CH_3), 1.48 (3H, s, CH_3), 2.16 (1H, brd, $J_{5e,5a}$ 12, 5e-H), 2.25 (1H, dt, $J_{5a,4}$ 4, $J_{5a,5e}$ and $J_{5a,6}$ 12, 5a-H), 4.12 (1H, dd, $J_{6,5a}$ 12, $J_{6,5e}$ 5, 6-H), 4.22 (1H, d, $J_{8,9}$ 6, 8-H), 4.31 (1H, d, $J_{3,4}$ 2.5, 3-H), 4.40 (1H, d, $J_{10,9}$ 3, 10-H), 4.44 (1H, dd, $J_{4,3}$ and $J_{4,5e}$ 2.5, $J_{4,5a}$4, 4-H), 4.56 (1H, d, $J_{2,1}$ 4, 2-H), 5.05 (1H, dd, $J_{9,10}$ 3, $J_{9,8}$ 6, 9-H), 5.91 (1H, d, $J_{1,2}$ 4, 1-H) and 6.57 (1H, s,



(144)

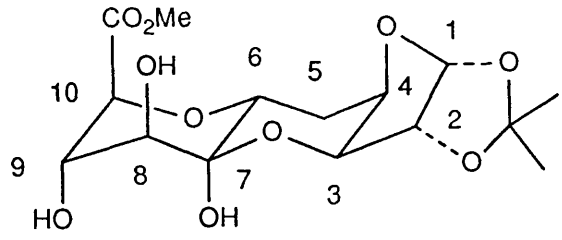
11-H). We were unable to obtain satisfactory mass spectral data for this compound.

6,10-Anhydro-1,2-*O*-isopropylidene-D-*arabino*-L-*ido*-7-undeculodialdo-(7R)-3, 7-pyrano-α-D-1,4-furanose (144)

A solution of bromide (143) (5 mg, 0.01 mmol) in acetone (1 cm^3) containing water (1 drop) was treated with silver carbonate (5 mg, 0.02 mmol) for 25 minutes at room temperature. The mixture was filtered through Celite and concentrated *in vacuo* to give the crude aldehyde (144) (4.5 mg, 95%) as a colourless gum. υ_{max}/cm^{-1} 3440, 2930, 1732, 1087; δ_H (270 MHz, $CDCl_3$) 1.32 (3H, s, CH_3), 1.49 (3H, s, CH_3), 2.09 (1H, dt, $J_{5a,b}$ and $J_{5a,5e}$ 12, $J_{5a,4}$ 4, 5a-H), 2.32 (1H, brd, $J_{5e,5a}$ 12, 5e-H), 3.72 (1H, d, $J_{8,9}$ 2.5, 8-H), 4.25 (1H, brs, 10-H), 4.30 (1H, dd, $J_{6,5a}$ 12, $J_{6,5e}$ 5, 6-H), 4.34 (1H, d, $J_{3,4}$ 2, 3-H), 4.37-4.45 (2H, m, 4-H and 9-H), 4.52 (1H, d, $J_{2,1}$ 4, 2-H), 5.87 (1H, d, $J_{1,2}$ 4, 1-H) and 9.80 (1H, s, RCHO). This compound was not characterised further.

Methyl 6,10-anhydro-1,2-*O*-isopropylidene-D-*arabino*-L-*ido*-7 -undeculo-(7R)-3,7-pyranose-α-D-1,4-furanuronate (145)

A solution of aldehyde (144) (7 mg, 0.02 mol) in methanol (0.5 cm^3) at 0°C was treated sequentially with a solution of iodine in methanol (0.1 cm^3 of a 7% w/v solution) followed by a solution of potassium hydroxide in methanol (0.1 cm^3 of a 3% w/v solution) and the resultant solution stirred at 0°C for 2.5 hours. Further portions of iodine solution (0.1 cm^3) followed by potassium hydroxide solution (0.1 cm^3) were added and the reaction mixture stirred at 0°C for a further 1.5 hours. Saturated aqueous ammonium chloride solution (1 cm^3) was added and the reaction mixture extracted with EtOAc (3 x 5 cm^3). The combined organic extracts were washed with 0.1N sodium thiosulphate solution



(145)

($5\ cm^3$) and dried (Na_2SO_4). Solvent was removed *in vacuo* and the residue purified by chromatography with EtOAc/petrol (3:1) as eluant to afford the title compound, ester (145) (3 mg, 40%) as colourless needles, m.p. 208-209°C (benzene). υ_{max}/cm^{-1} 3410, 1734, 1084; δ_H (270 MHz, $CDCl_3$) 1.24 (3H, s, CH_3), 1.43 (3H, s, CH_3), 2.12 (1H, ddd, $J_{5a,5e}$ 14, $J_{5a,6}$ 11.5, $J_{5a,4}$ 4, 5a-H), 2.32 (1H, brd, $J_{5e,5a}$ 14, 5e-H), 3.68 (1H, d, $J_{8,9}$ 3, 8-H), 3.77 (3H, s, CO_2CH_3), 4.33 (1H, d, $J_{3,4}$ 2, 3-H), 4.42 (2H, m, 4-H and 10-H), 4.48 (1H, dd, $J_{9,8}$ 3, $J_{9,10}$ 1.5, 9-H), 4.49 (1H, dd, $J_{6,5a}$ 11.5, $J_{6,5e}$ 4, 6-H), 4.51 (1H, d, $J_{2,1}$ 4, 2-H) and 5.88 (1H, d, $J_{1,2}$ 4, 1-H).

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APPENDIX

X-RAY CRYSTAL DATA

1. Diol (127) crystallised (EtOH\Et$_2$O) in the space group $P2_1$ with a = 7.203(2), b = 10.636(4), c = 9.346(2) Å , β = 100.66(2) , U = 703.65 Å^3, μ(Mo-K_α) = 0.78 cm^{-1}, F(000) = 336 and D_c = 1.49 gcm^{-3} for Z = 2 at room temperature. The structure was solved by direct methods using 915 unique reflections with $I \geq 3\sigma(I)$ and refined by full-matrix least squares to final residuals of R = 6.87 and R_w = 0.0718.

2. Ester (145) crystallised (benzene) in the space group $P2_12_12_1$ with a = 6.592(1), b = 24.161(1), c = 10.666(1) Å, U = 1698.6 Å^3, μ(Mo-K_α) = 1.1 cm^{-1}, F(000) = 784 and D_c= 1.41 gcm^{-3} for Z = 4 at room temperature. The structure was solved by direct methods using 1059 unique reflections with $I \geq 2\sigma(I)$ and refined by full-matrix least squares to final residuals of $R = R_w$ = 0.0369.

Atomic coordinates, bond lengths and angles and thermal parameters are deposited at the Cambridge Crystallographic Data Centre.