THE APPLICATION OF DIASTEREOSELECTIVE FREE RADICAL REACTIONS IN CARBOHYDRATE CHEMISTRY

by

Linda Lim Biaw Leng

A thesis submitted to the University of London

for a Doctor of Philosophy

November 1990

Department of Chemistry

University College London

20 Gordon Street

London WC1H 0AJ

Dedicated with love to

my parents

ACKNOWLEDGEMENT

I thank the Brunei government for awarding me the Brunei Scholarship.

I also wish to thank Dr. H. S. Dang for the calligraphy, Dr. T. Ritchie for helping me when I first started this project, Claude for looking after me and cheering me up throughout my PhD years, Dr. P. Garratt for his help and advice, all members of staff at the general office of Chemistry department, Jill Maxwell and P. Leighton for being very helpful.

I wish to express my sincere thanks to Simon Thorn for occasionally buying, when given no choice, the famous Nyholm Room's "tea and toast", helping with my write-up, keeping me up to date with the latest gossip and for being a good friend.

I am grateful to my brother, Dr. D. K. K. Lim, and my cousins especially Miss L. K. Lee and Miss C. M. Chan for always being there when I needed them.

I wish to express my sincere thanks to Prof. A. Davies FRS for his understanding, invaluable help and advice throughout my university years.

This thesis would not have been possible without the constant help, encouragement and advice from my excellent supervisor, Prof. D. Crich. I therefore wish to take this opportunity to convey my thanks to him not only for his help with my PhD but also for his support whenever I needed it.

Another person whom I wish to thank wholeheartedly is "Dr." Simon Doherty for his constant help, encouragement and support, for putting up with my moods, for keeping me sane and for all the happy and wonderful times we shared.

Lastly, I am indebted to both my wonderful parents, Mr. E. H. Lim and Mdm. Pauline Liew, for their neverending love, encouragement, support, understanding and help throughout my life and it is to them that I dedicate this thesis.

萬里長城是一
磚一磚砌成的
汪洋大海是一
滴一滴滙成的

ABBREVIATIONS

AIBN	Azoisobutyronitrile
DAST	Diethylaminosulphur trifluoride
DCC	Dicyclohexyl carbodiimide
DCU	Dicyclohexyl urea
DMF	Dimethyl formamide
DMSO	Dimethyl sulphoxide
LDA	Lithium diisopropylamide
LN	Lithium naphthalenide
MMPP	Magnesium Monoperoxyphthalate
NMO	*N*-methylmorpholine-*N*-oxide
SEM-Cl	ß-Trimethylsilylethoxymethyl chloride
TBAF	Tetra-n-butylammonium fluoride
TBDMS-OTf	*tert*-Butyldimethylsilyl triflate
THF	Tetrahydrofuran

ABSTRACT

This thesis focuses essentially on the application of diastereoselective radical reactions to the preparation of *O*- and *C*-glycosidic linkages. As such, the introduction surveys both the general area of glycoside synthesis and diastereoselective radical reactions and in particular, their use in carbohydrate chemistry.

Methyl [Phenyl 4,5,7-tri-*O*-benzyl-3-deoxy-2-sulphonyl-ß-D-*arabino*-2-heptulopyranoside]onate (sulphone ester) was prepared from tri-*O*-benzyl-D-glucal according to a method previously developed in the laboratory. The highly diastereoselective preparation of ß-*C*-glycosides was achieved by reductive desulphonylation of the sulphone ester with lithium naphthalenide followed by quenching with an alkyl halide and ultimately by Barton reductive decarboxylation. Diastereoselectivities in excess of 95:5 were routinely observed.

Thermal elimination of phenylsulphinic acid from the sulphone ester gave the corresponding 1-carbomethoxy glycal. *cis*-Hydroxylation with osmium tetroxide gave exclusively the *gluco*-isomer. Acetonation, saponification and reductive decarboxylation gave 1,2-*O*-isopropylidene-3,4,6-tri-*O*-benzyl-ß-D-*gluco*-pyranose as a single anomer and the first example of a 1,2-*trans*-isopropylidene derivative of a pyranose sugar. Other ß-*O*-*gluco*-pyranosides were prepared as single anomers by related process. The extension of the methodology to the preparation of ß-*O*-*manno*-pyranosides was investigated.

The extrapolation of the method to the preparation of furanosidic linkages was investigated. 2,3:4,6-Di-*O*-isopropylidene-2-*keto*-L-gulonic acid was chosen as starting material and methods were developed for its selective deprotection and

protection. The stereoselectivity of the radical decarboxylation step was investigated.

Finally, in the context of the *C*-glycoside synthesis, ß-trimethylsilylethoxymethyl chloride (SEM-Cl) was developed as a practical equivalent to formaldehyde in low temperature, non-aqueous aldol type reactions.

TABLE OF CONTENTS

CHAPTER 1

INTRODUCTION

1. Introduction

In the last few decades the increased understanding of the mechanism of biological events and the constant search for antibiotics have led to enormous effort being put into the synthesis and chemical modification of sugar units. Furthermore, not only are carbohydrates a relatively cheap source of chiral carbon compounds but they also possess a vast variety of functional, stereochemical and conformational features open to chemical exploitation. With an abundance of stereochemical attributes, carbohydrates[1] have captured the attention of organic chemists and at the same time present a major challenge in the quest of conquering enantiomerically pure synthetic targets.

In spite of enormous progress in the chemistry of carbohydrates over the years, several problems still remain to be solved in this area of natural products. Of these the two most common but often difficult-to-reach goals in carbohydrate chemistry are the selective functionalisation of the ring system and the stereocontrolled synthesis of glycosidic bonds, especially in the 2-deoxy series. The latter problem is especially important and crucial in the medicinal field because a specific glycosidic linkage might be biologically active and important whilst the corresponding diastereoisomer is biologically inactive. Much attention has therefore been focused on diastereoselective glycosidic linkage synthesis in carbohydrate chemistry.

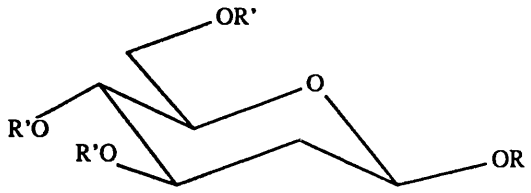
The synthesis of a disaccharide involves the linkage of two polyfunctional sugar components. In order for this synthesis to be regioselective, the glycosylating component (i.e. the glycosyl donor) must possess selectively protected hydroxyl groups and an activating anomeric group, whilst the glycosyl acceptor with the free hydroxyl group must have all other hydroxyl groups protected. These strategies therefore demand complicated protecting group tactics

as well as a suitable method for activation of the anomeric C-centre. In addition, the coupling step must ensure diastereoselectivity with respect to the formation of an α- or β-glycosidic bond.

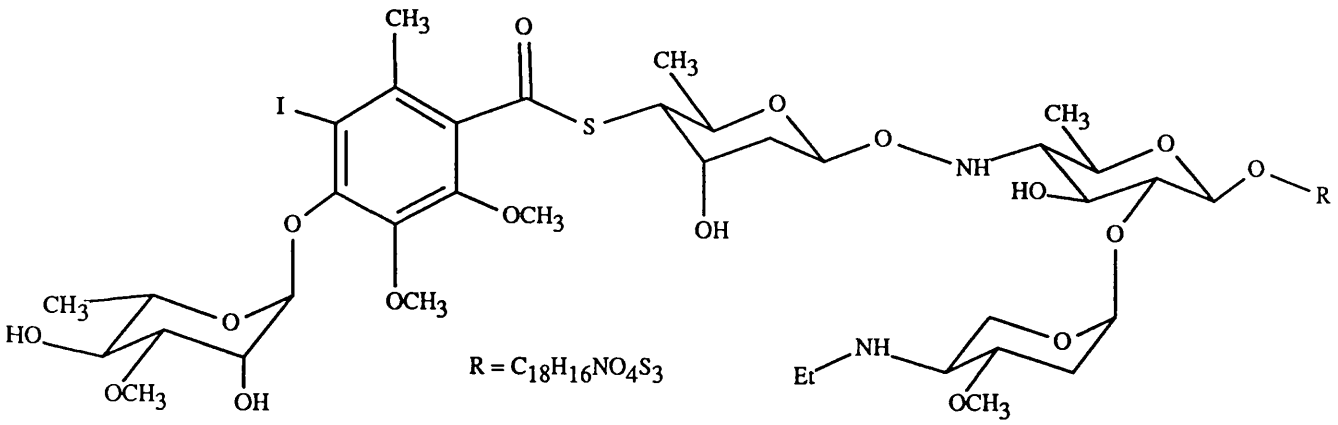
In a classical Koenigs-Knorr method, activation of the anomeric centre is achieved through the formation of glycosyl halides (chlorides or bromides). The Koenigs-Knorr glycosylation involves a 2-step reaction: the introduction of a leaving group at the anomeric centre and catalytic nucleophilic substitution of this leaving group. The coupling reactions are facilitated by use of heavy-metal salts, preferably silver salts. Diastereoselectivity in the coupling reaction is attained by neighbouring-participating groups; *in situ* anomerisation of the α-glycosyl halide to the more reactive β-glycosyl halides which then reacts preferentially to give the more stable α-glycosides; and by the use of catalysts. Hence, as a general rule, the reactivity of the glycosyl donor can be varied over relatively wide ranges by the choice of halogens, the catalyst promoter and the protecting group pattern. The reactivity of the glycosyl acceptor is controlled by the choice of protecting groups with appropriate steric and electronic effects. Although the application of these generalisations have led to excellent results, several disadvantages of the classical Koenigs-Knorr glycosylation still persist. The generation of glycosyl halides requires relatively harsh conditions. They exhibit low thermal stability and are highly sensitive to hydrolysis, hence requiring extremely carefully controlled experimental conditions. The use of heavy-metal salts in the coupling reactions meant that these reactions were limited to small scale synthesis as large scale preparation is often hazardous owing to the toxicity of mercuric salts and explosive nature of some silver salts. Furthermore, heavy-metal salts are expensive. As a result, many attempts have been made to improve on this method.

1.1 Synthesis of 2-deoxy-β-glycosides

In this laboratory, interests lie specifically in the diastereoselective synthesis of 2-deoxy-β-glycosidic linkages (**1**) found widely in Nature, for example in the aureolic acid group of antitumor antibiotics,[2] in certain cardiac glycosides[3] and in recently isolated potent antitumor agents[4] such as calichemicin γ_1^I (**2**).



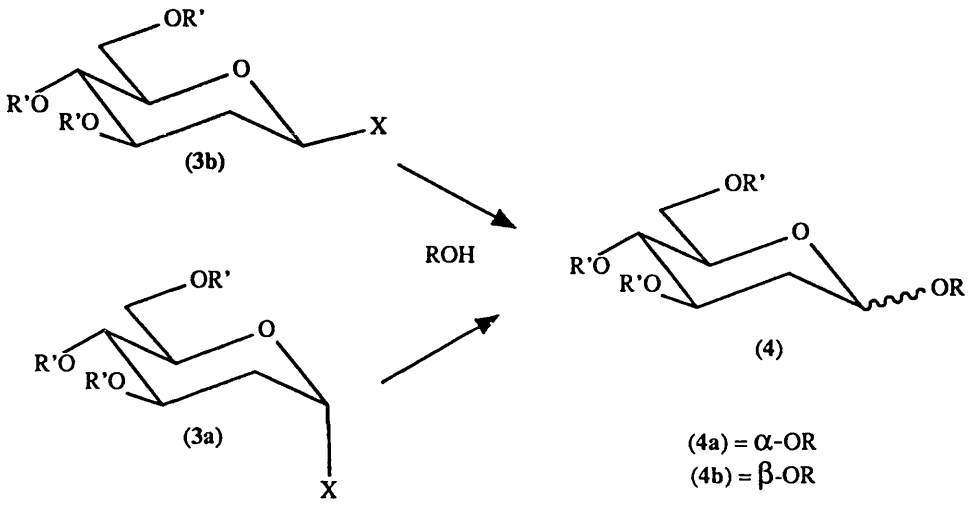
(1)



Calichemicin γ_1^I (2)

Synthesis of such glycosidic linkages is achieved with the aid of a glycosyl donor. It is known that as a result of the anomeric effect,[5] treatment of both α- and β-glycosyl halides (**3a**) and (**3b**) leads preferentially to the α-product (**4a**) [Scheme 1].

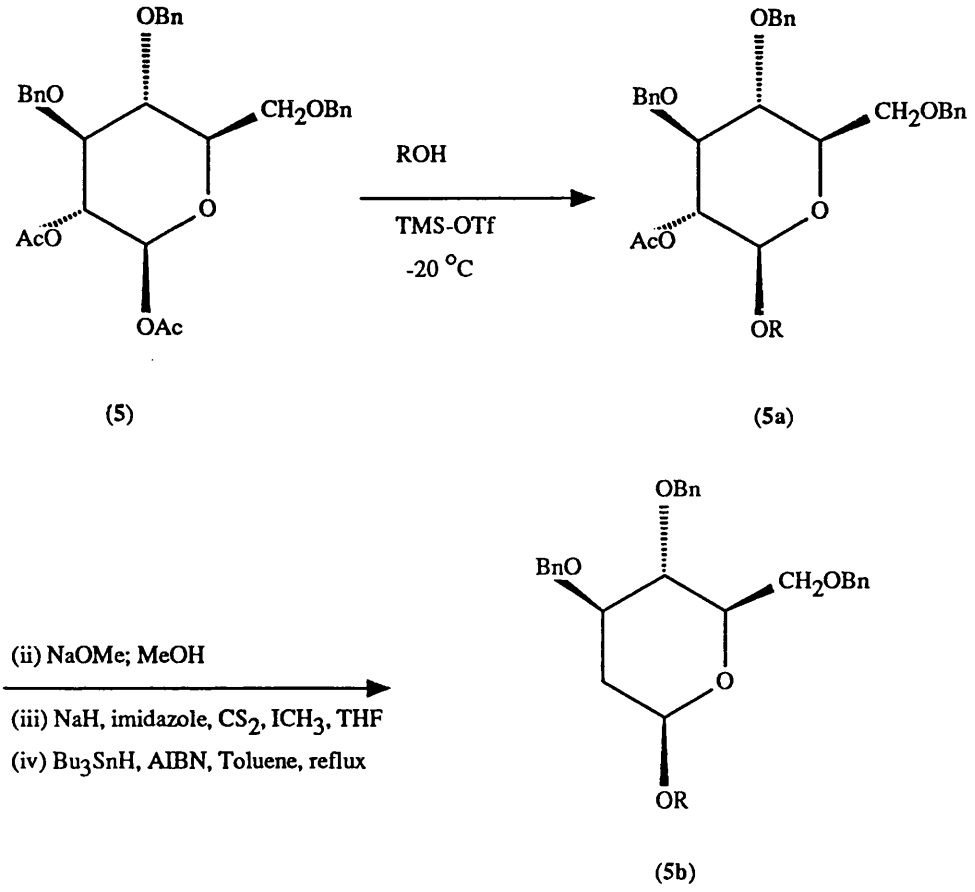
Scheme 1



The stereocontrolled construction of β-glycosidic bonds in the 2-deoxy series is often difficult to achieve owing to the lack of neighbouring-active group at C-2. This problem can be overcome with the aid of a glycosyl donor bearing an equatorially positioned substituent at C-2 capable of providing anchimeric assistance in the glycosylation step. Once this synthesis of β-glycosidic linkages is accomplished, this auxiliary is then reductively removed in a subsequent reaction. Two such approaches to the synthesis of β-glycosidic linkages could be identified in the literature. The first is use of the classical Koenigs-Knorr glycosidation.[6] An example of such methodology was elegantly illustrated by

Sinaÿ in which the 1,2-*trans*-di-*O*-acetyl derivative (**5**) was transformed, in the presence of trimethylsilyl triflate (TMS-OTf), into the β-product (**5b**). The reductive removal of the acetate group at C-2 [steps (ii), (iii) and (iv)] subsequently transformed (**5a**) to the desired 2-deoxy-β-product (**5b**) [Scheme 2].

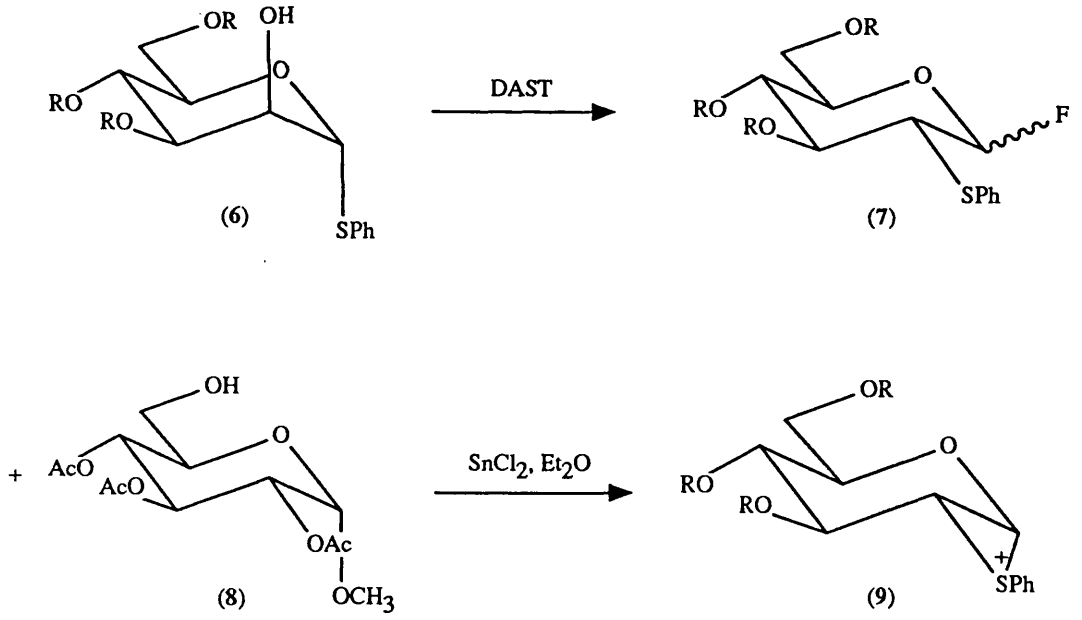
Scheme 2

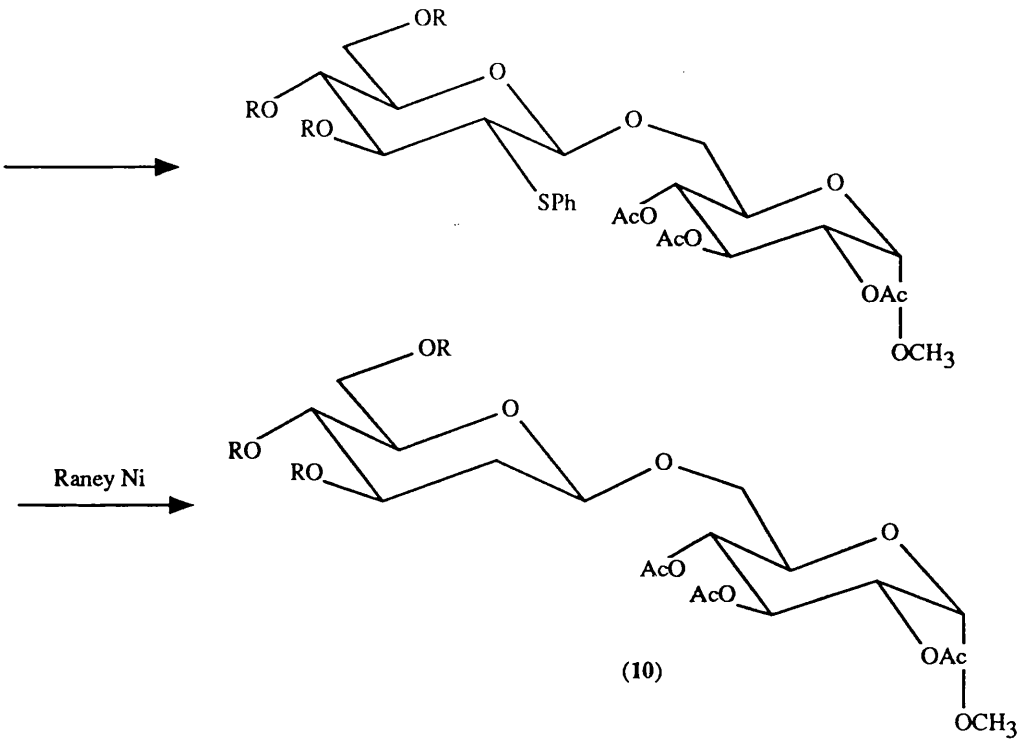


Another example making use of the Koenigs-Knorr methodology was illustrated by Nicolaou based on the stereospecific 1,2-migration in carbohydrates to direct diastereoselective synthesis of the glycosidic linkage. Activation of the

anomeric centre with fluoride by the treatment of (**6**) with diethylaminosulphur trifluoride (DAST) resulted in the migratory group at C-1 (SPh) being induced to shift to the neighbouring position at C-2 as a result of the departure of the leaving hydroxyl group at C-2. This glycosyl fluoride, compound (**7**), then undergoes coupling to the glycosyl acceptor (**8**) in the presence of tin(II) chloride ($SnCl_2$) in diethyl ether (Et_2O) to give the β-product in 92% yield. This diastereoselectivity was explained in terms of the action of a tin-complexing solvent such that the SPh group on C-2 remains free to direct the glycosylation *via* a transient intermediate (**9**) [Scheme 3]. Desulphurisation with Raney nickel in ethanol gave the desired 2-deoxy-β-glycoside (**10**) in 94% yield.

Scheme 3



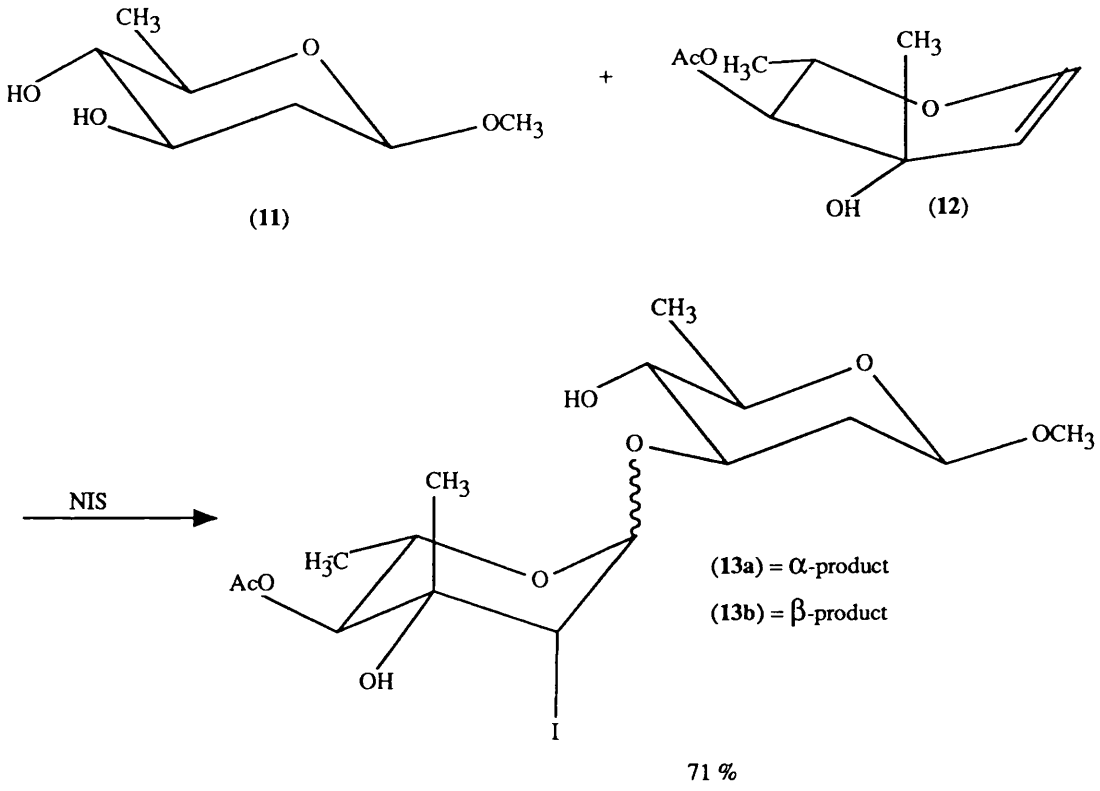


(10)

The second method[7] involves introducing the stereodirecting entity in the course of the glycosylation reaction by addition across a glycal double bond. For example, in recent studies by Thiem, acceptable* yields of 2-deoxy-β-glycosides were obtained by *N*-iodo-succinimide (NIS) mediated condensation reactions. Treatment of methyl 2,6-dideoxy-β-D-*arabino*-hexopyranoside (**11**) and 4-*O*-acetyl-L-livomycal (**12**) with NIS gave, after 3 days, the β-product (**13b**) in 71% yield. Hydrogenolytic cleavage of the iodo-substituent with 10% palladium/charcoal completed the synthesis of the 2-deoxy-β-glycoside [Scheme 4]. However, the α-anomer was the major product.

*acceptable in terms of yields obtained from classical Koenigs-Knorr glycosylation reactions.

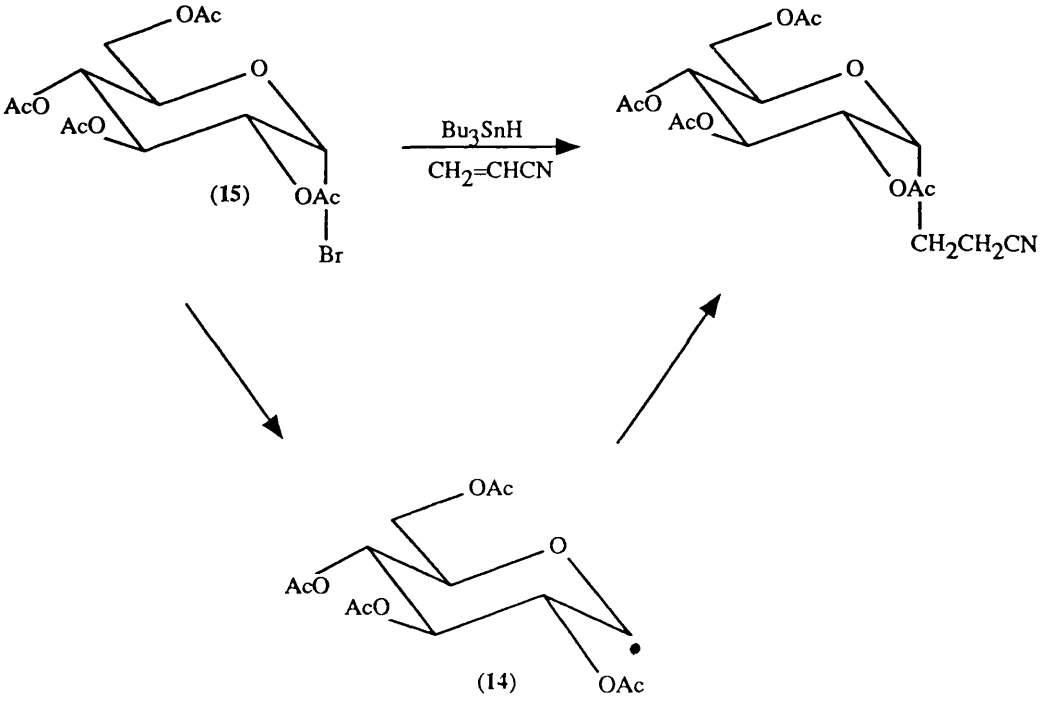
Scheme 4



The results obtained in this laboratory are based on a new method, independent of any stereodirecting auxiliary, ruling out the need for further manipulation of the product after glycosylation. This new method approaches the synthesis of 2-deoxy-β-glycosides *via* a free radical chain mechanism. The use of free radical reactions in organic synthesis has received increased interest in recent years and can be of great value for the synthesis of natural products and, we believe, for their stereoselective synthesis. Unlike ionic reactions, free radical reactions are relatively insensitive to the presence of functional groups, a feature vital in the synthesis of carbohydrates. Recently, free radical reactions have been applied to C-C coupling reactions of carbohydrate derivatives with alkenes.

The highly diastereoselective quenching of an anomeric radical has been demonstrated by Giese.[8] In his report, predominant attack at the α-position by both acrylonitrile (and tributyltin deuteride) on tetra-*O*-acetyl-glucos-1-yl radical (**14**) was observed [Scheme 5] with diastereoselectivities of between 82:18 to 98:2 (α:β).

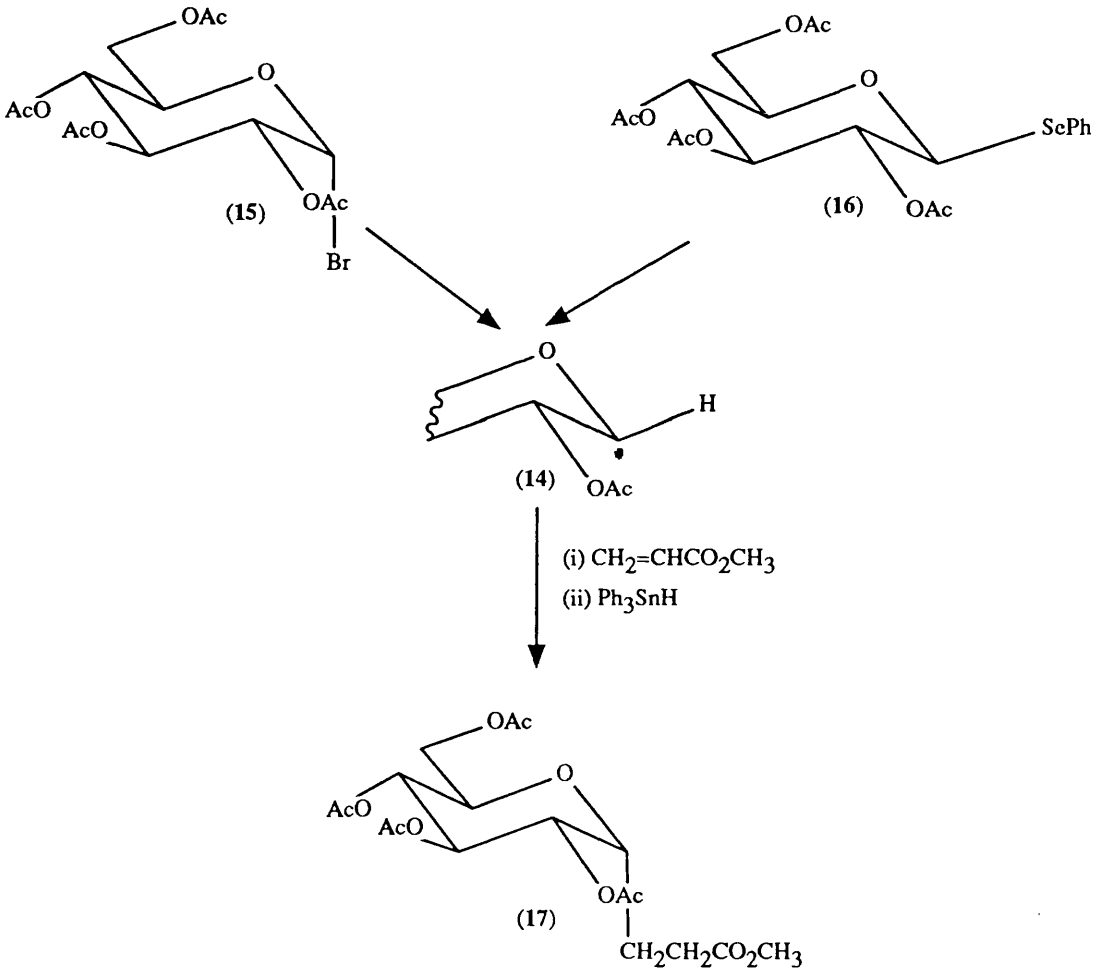
Scheme 5



This α-trapping of glucos-1-yl radical (**14**) was also observed by Baldwin[9] who demonstrated the generation of the radical (**14**) from the β-phenylseleno-glycoside. Thus when a mixture of phenyl tetraacetyl-β-D-selenoglucoside (**16**) and 10 molar equivalents of methyl acrylate in refluxing toluene was treated with triphenyltin hydride by slow addition over 13

h, the α-product (**17**) was obtained in 40% yield. Similarly with acetobromo-glucose (**15**), again the α-product (**17**) was obtained in 35% yield. The glucos-1-yl radical (**14**) appears preferentially to couple to give the axial product [Scheme 6].

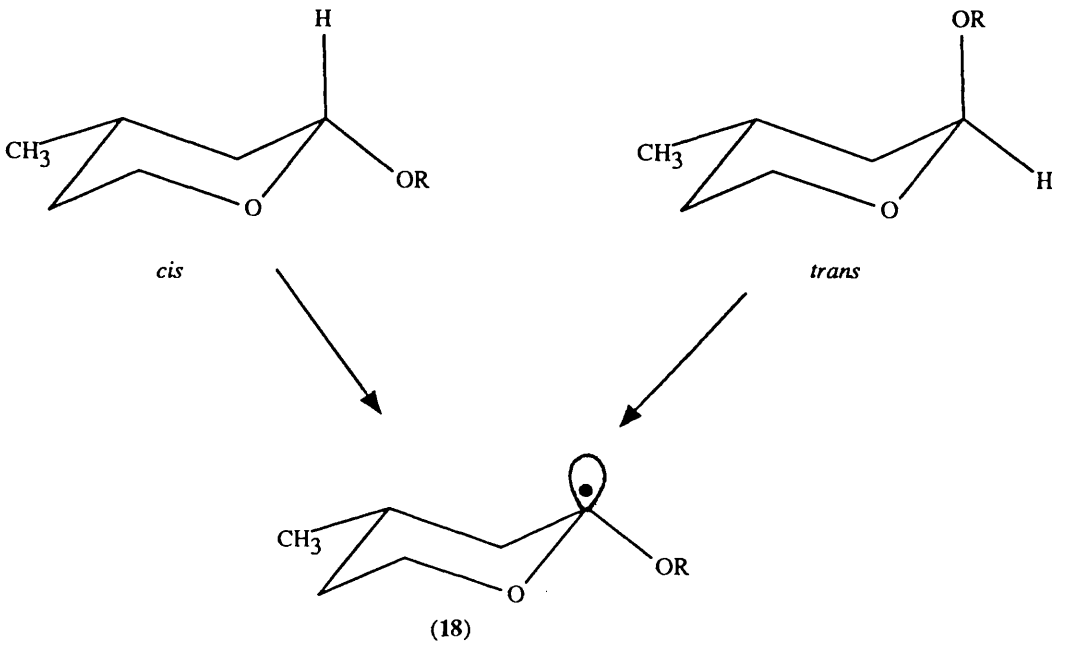
Scheme 6



Esr measurements[10] have shown that a common intermediate radical (**18**) is formed as a result of hydrogen abstraction from *cis*- and

trans-2-alkoxy-4-methyltetrahydropyran. Similar observations have been made with other related diastereoisomers [Scheme 7]. This radical has been shown, again by esr, to be sp^3 in nature i.e. the radical is a σ-radical.

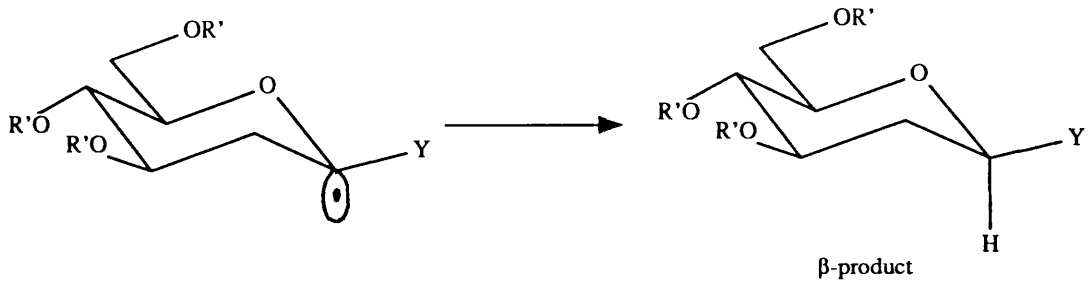
Scheme 7



(18)

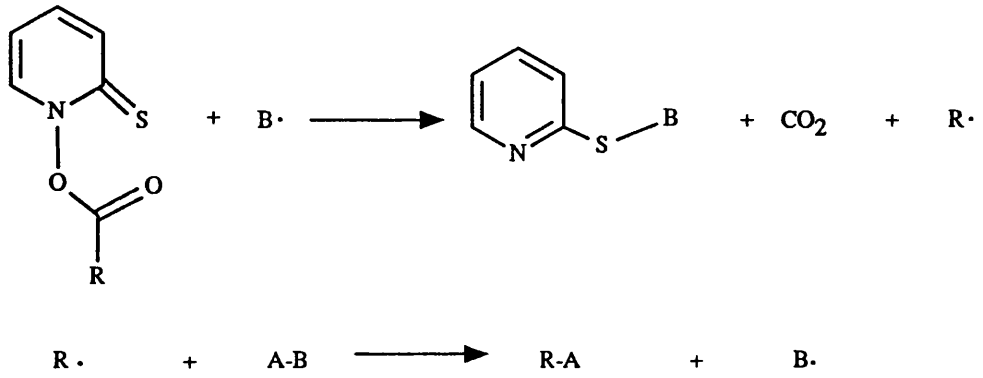
Based on esr measurements, the single electron of such radicals in tetrahydropyran and related systems is thought to be axially positioned. Pyranosides, being closely related in structure, were predicted to form an anomeric radical with the single electron similarly axially placed. This hypothesis thus provided a route to the synthesis of a β-glycosidic linkage. As the intermediate radical is being axially positioned, it favours hydrogen atom transfer to the α-face, resulting in the desired β-anomer [Scheme 8].

Scheme 8

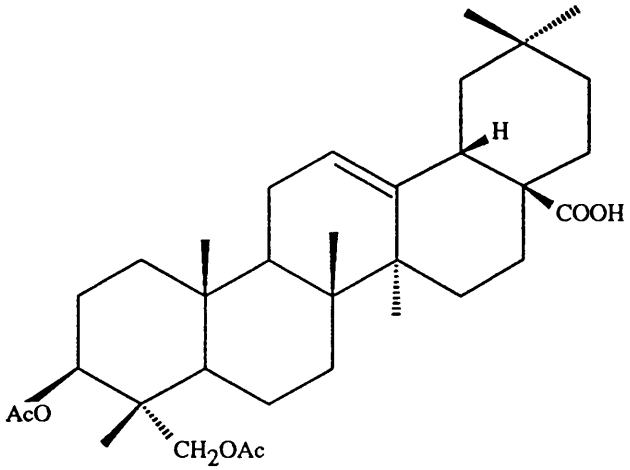


It was therefore necessary to find a way of generating such intermediate radicals as well as to develop a synthetically useful and applicable methodology. Barton's group has developed an excellent method of reducing carboxylic acids *via* the reaction of *O*-acyl thiohydroxamates[11] with thiols by a free radical chain mechanism. The presence of radicals in the closely related decarboxylative rearrangement has been confirmed by esr spectroscopy.[12] As illustrated by Scheme 9, the reaction of *O*-acyl thiohydroxamates with a molecule A-B is synthetically useful in that A-B can serve both as a donor of an atom or group A such that when quenched with the alkyl radical R•, the product R-A is formed as well as the thiophilic radical B• which can propagate a chain reaction by addition to the thiocarbonyl group.

Scheme 9

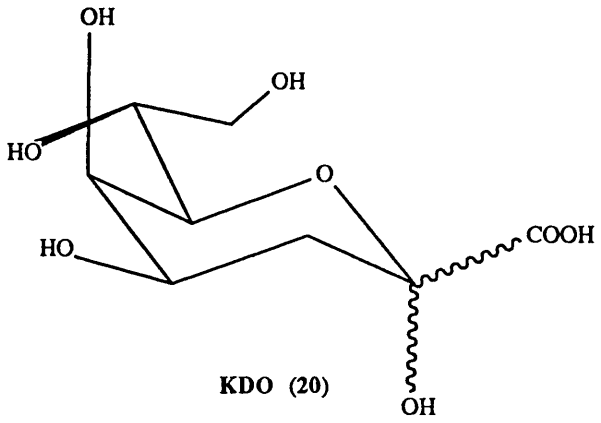


It has also been shown that this powerful method of thiohydroxamate chemistry is not limited to simple carboxylic acids. When applied to highly hindered carboxylic acids, such as (**19**), this methodology still gave excellent yields.



(**19**)

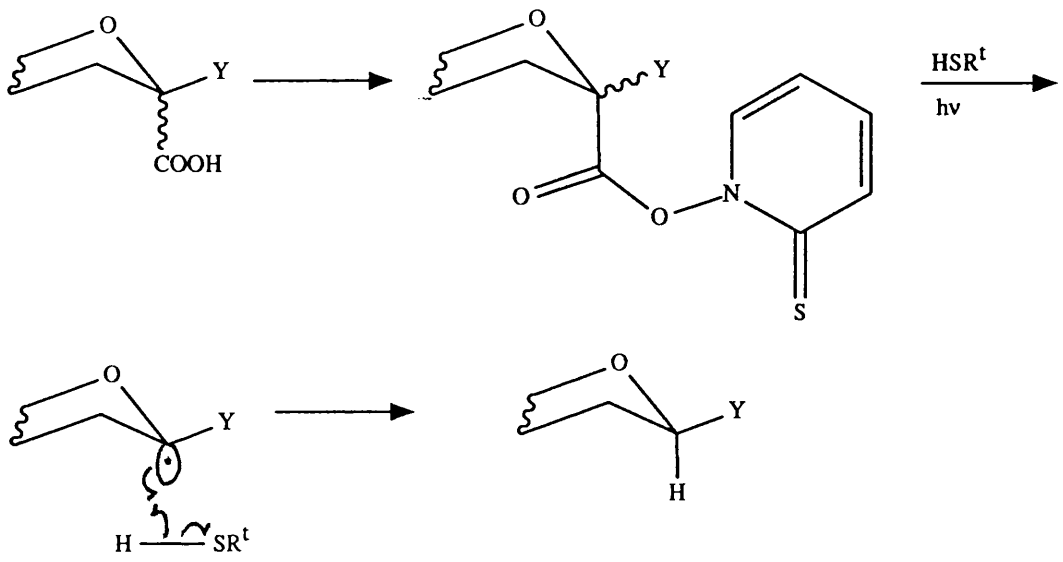
Consequently attention was turned to the use of ulosonic acid derivatives as radical precursors in so far as various 3-deoxyulosonic acids occur in nature and are stable and isolable, e.g. 3-deoxy-D-*manno*-2-octulosonic acid (KDO) (**20**), a characteristic sugar component of lipopolysaccharides which occurs in the cell surface of Gram-negative bacteria and carry important biological functions.



KDO (20)

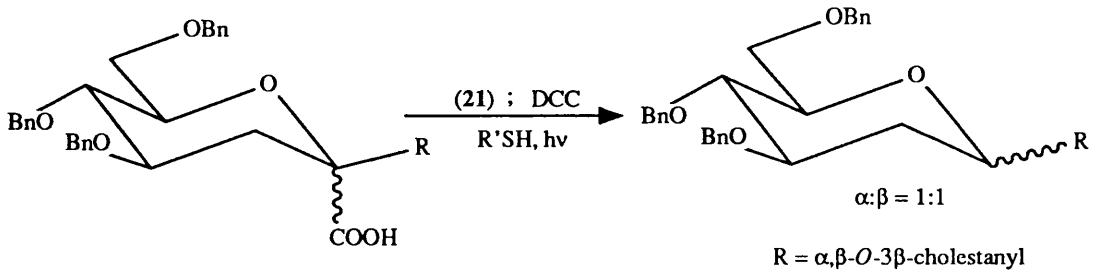
The generation of radicals from these ulosonic acid derivatives was envisaged using one of Barton's thiohydroxamate protocols. Thus combining the ulosonic acid function with the thiohydroxamate chemistry should generate the intermediate *O*-acyl thiohydroxamate ester which on photolysis should result in the glycosyl radical. This radical when trapped axially with a tertiary thiol should result in the β-glycoside product [Scheme 10].

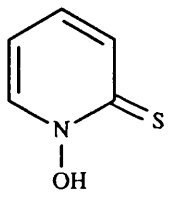
Scheme 10



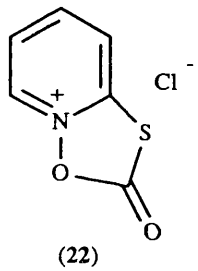
This idea has already been put to test in this laboratory[13] and shown to function as predicted [Scheme 11]. The *O*-acyl thiohydroxamate was readily prepared by coupling *N*-hydroxypyridine-2-thione (**21**) and the ulosonic acid by means of dicyclohexyl carbodiimide (DCC). However, although the thiohydroxamate ester was formed readily, the by-product in this reaction, dicyclohexyl urea (DCU), meant that filtration of the reaction mixture was required prior to photolysis. This problem was easily overcome by the use of the heterocyclic salt (**22**) which is formed almost quantitatively as a white crystalline solid from the treatment of *N*-hydroxypyridine-2-thione (**21**) with phosgene. This salt couples directly with carboxylic acids without the requirement of any external reagents hence filtration was not required prior to photolysis. The use of a tertiary thiol as hydrogen donor is preferred over stannanes for reasons of simplicity of work-up.

Scheme 11





(21)



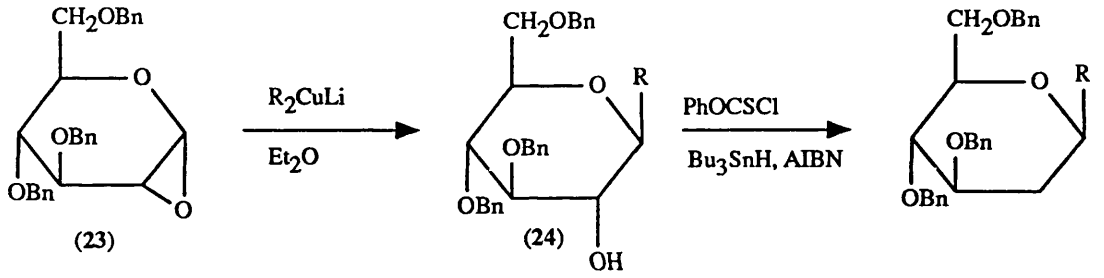
(22)

In the synthesis of 2-deoxy-β-*O*-glycosidic linkages *via* this methodology, very good diastereoselectivities of between 8:1 to 95:5 (β:α) were observed both in the *arabino*-series as well as in the *lyxo*-series at room temperature. This encouraging observation prompted us, in this thesis, into extending this synthesis to the 2-deoxy-*C*-glycosides and to study the effect on diastereoselectivity of varying the anomeric substituent group.

The recent isolation of potent anticancer agents[14] such as nogalamycin[15] as well as the discovery of a wide variety of medicinally important *C*-nucleosides[16] has led to an increased interest in C-C bond formation at the anomeric centre of carbohydrates. As a result several diverse and elegant

solutions[16] have emerged in recent years. For example Czernecki[16] has made use of oxirane ring opening using organocuprates which proceeds *anti* to the oxygen atom. By treatment of 3,4,6-tri-*O*-benzyl-1,2-anhydro-α-D-*gluco*-pyranose (**23**) with lithium dimethyl- or diphenyl-cuprate in anhydrous diethyl ether at low temperature, the β-D-glycopyranoside (**24**) was obtained in moderate yield [Scheme 12].

Scheme 12

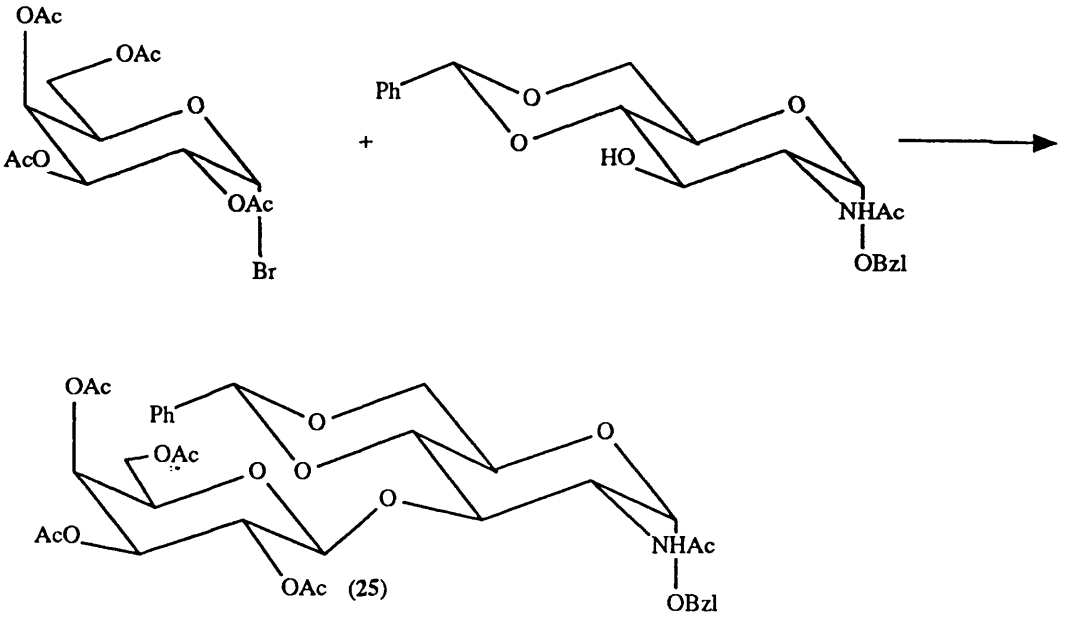


1.2 β-*manno*- and β-*gluco*-pyranosides

Apart from the synthesis of 2-deoxy-β-pyranosides, this laboratory was also interested in extending this methodology to the study of diastereoselectivities when the C-2 position bears an *O*-substituent group; i.e. the synthesis of β-*O*-*manno*- or β-*O*-*gluco*-pyranosides. In the classical Koenigs-Knorr reaction, α- or β-*gluco*-pyranosyl halides in which the H-atom on 2-OH is replaced by a neighbouring-participating group undergo glycosylation to form the β-glycosidic linkage. Such diastereoselective reactions can be achieved by the use of a catalyst such as silver silicate. The only disadvantage is the formation of water

in the course of the reaction which therefore requires the addition of drying agents. Often the yields obtained from such reactions are low. However, this problem could be overcome by the use of the Helferich catalyst, $Hg(CN)_2$, whereby hydrogen cyanide produced during the reaction is able to escape and so cause no interference with the glycosylation. A good example[18] of an $Hg(CN)_2$-catalysed glycosylation reaction is illustrated in Scheme 13 where the β-*galacto*-product (**25**) was obtained in 80% yield.

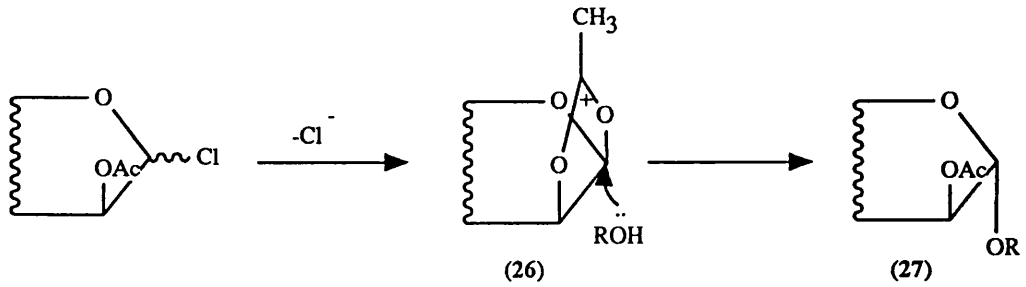
Scheme 13



The β-*manno* linkage, on the other hand, is one of the most difficult types of linkage to prepare. Unlike the situation with *gluco*- and *galacto*-derivatives, the hydroxyl group on C-2, important for guiding the glycosidic linkages, is positioned axially in *manno*-derivatives. As a result the presence of a neighbouring-group active substituent, such as acetate, at the 2-OH

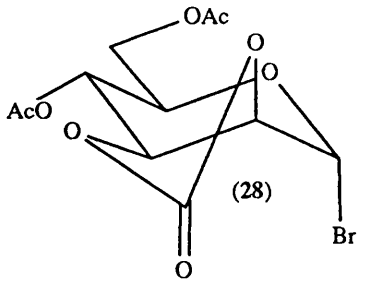
results in an acetoxonium ion intermediate (**26**) which stereodirects glycosylation to the α-face leading to the formation of a α-*manno*-product (**27**) [Scheme 14].

Scheme 14



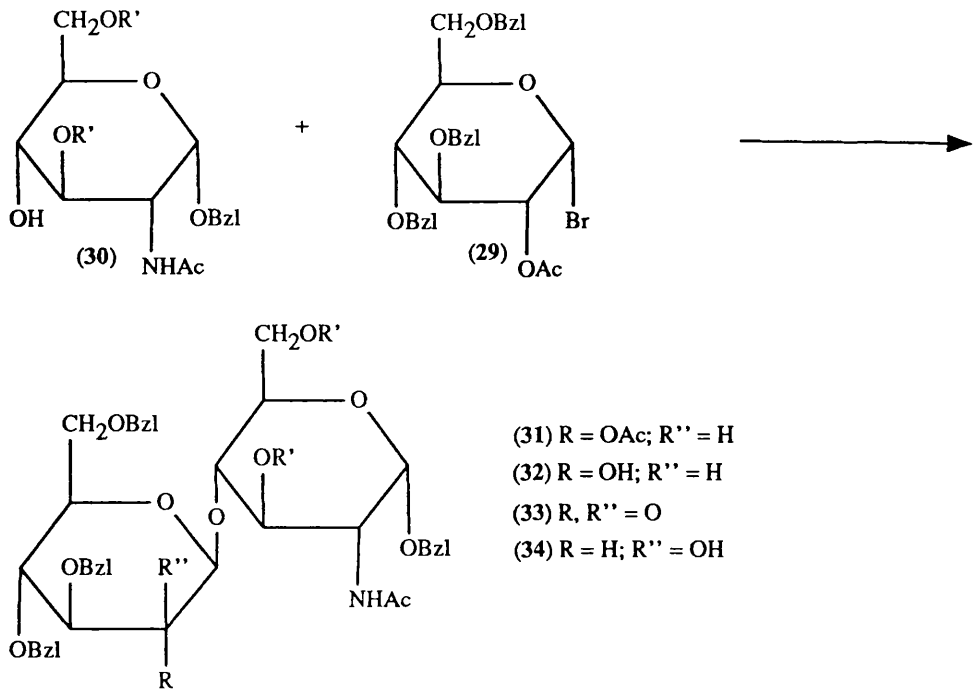
Even in the absence of a neighbouring-active substituent at the 2-position, an α-glycoside is still often the preferred product. The difficult problem lies in the conversion of a relatively stable α-halide, with inversion, into a non-stabilised β-glycoside. Hence, the synthesis of β-*manno* linkages presents a great challenge to synthetic organic chemists.

As a result these last few years have seen many attempts to elaborate synthetic routes[19] for the preparation of such linkages. Gorin and Perlin[20] successfully prepared them in a Koenigs-Knorr reaction using 4,6-di-*O*-acetyl-2,3-di-*O*-carbonate-α-D-mannosyl bromide (**28**), which itself had to be prepared through a multiple step synthesis.



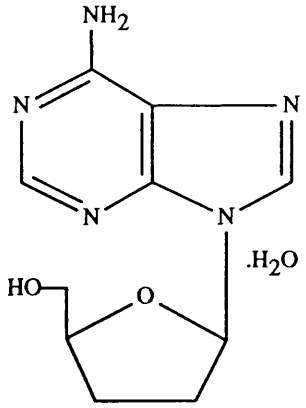
The synthesis of β-*manno*-pyranosides by stereoreduction, using hydrogenation over platinum catalyst, of methyl β-D-*arabino*-hexopyranosidulose has also been demonstrated by both Theander[21] and Longren.[22] Another[23] long and complex route made use of an activated D-*gluco*-pyranosyl derivative to introduce the β-*gluco* linkage. Once the β-linkage is achieved, the 2-OH of this β-*gluco* product is selectively deblocked, oxidised to the keto group and then selectively reduced. In this way the desired β-*manno*-pyranoside could be obtained either exclusively or as a mixture of *gluco*- and *manno*-products. An example to illustrate such methodology is shown in Scheme 15. Jeanloz and co-workers[22] carried out glycosylation of glucosyl bromide (**29**) with (**30**) using silver triflate, AgOTf, as the catalyst to form the β-*gluco*-derivative (**31**). *O*-Deacetylation gave the *gluco*-product (**32**) which was then oxidised with dimethyl sulphoxide (DMSO)/acetic anhydride (Ac_2O) to the corresponding keto product (**33**). Reduction of this ketone with sodium borohydride ($NaBH_4$) gave the desired β-*manno*-product (**34**).

Scheme 15

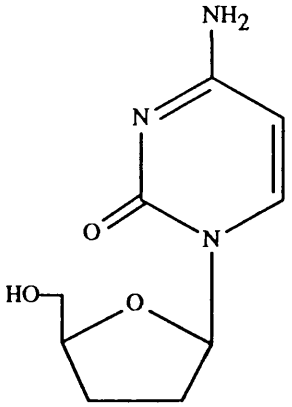


1.3 Furanosides

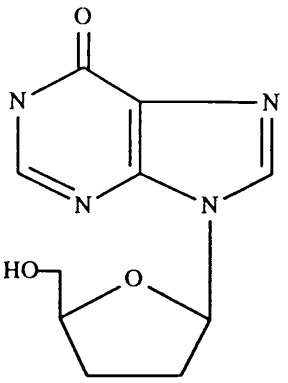
The discovery of naturally occurring furanosides which exhibit potent antibiotic properties has attracted growing interest in this area of natural products. Much attention has been focused on the synthesis of these medicinally important nucleoside analogues. For example, 2',3'-dideoxynucleosides[24] such as (**35**), (**36**) and (**37**) were recently reported to be potent inhibitors of human acquired immune deficiency syndrome (AIDS) virus.



(35)



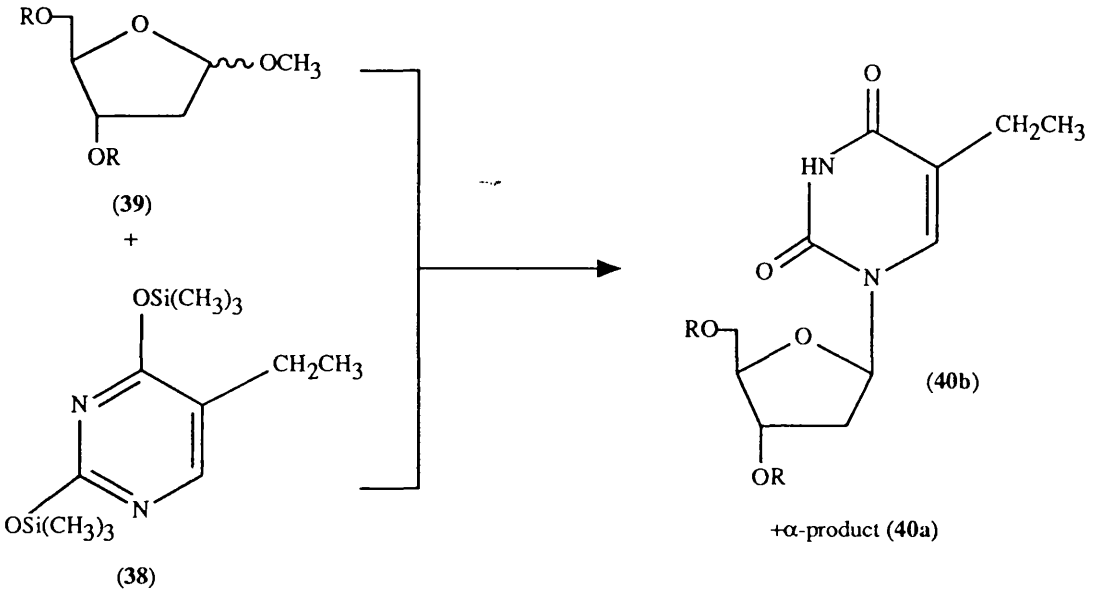
(36)



(37)

The stereoselective glycosylation reactions of such furanose systems have not been as widely studied as that of the corresponding pyranosides. Such syntheses usually result in a mixture of anomeric products. For example,[25] the synthesis of 2'-deoxynucleoside (**40**) did not proceed with very high diastereoselectivity. As seen from Scheme 16 below, coupling of furanose (**39**) with 5-ethyluracil (**38**) in the presence of $Me_3SiOSO_2CF_3$ gave 27% of β- and 15% of α-nucleoside [(**40b**) and (**40a**) respectively].

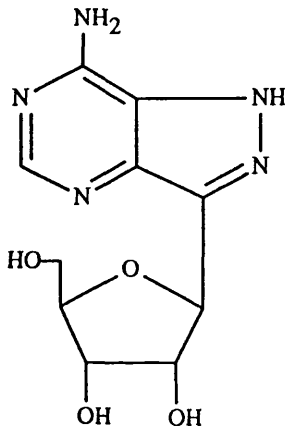
Scheme 16



(39) + (38)

(40b) +α-product (40a)

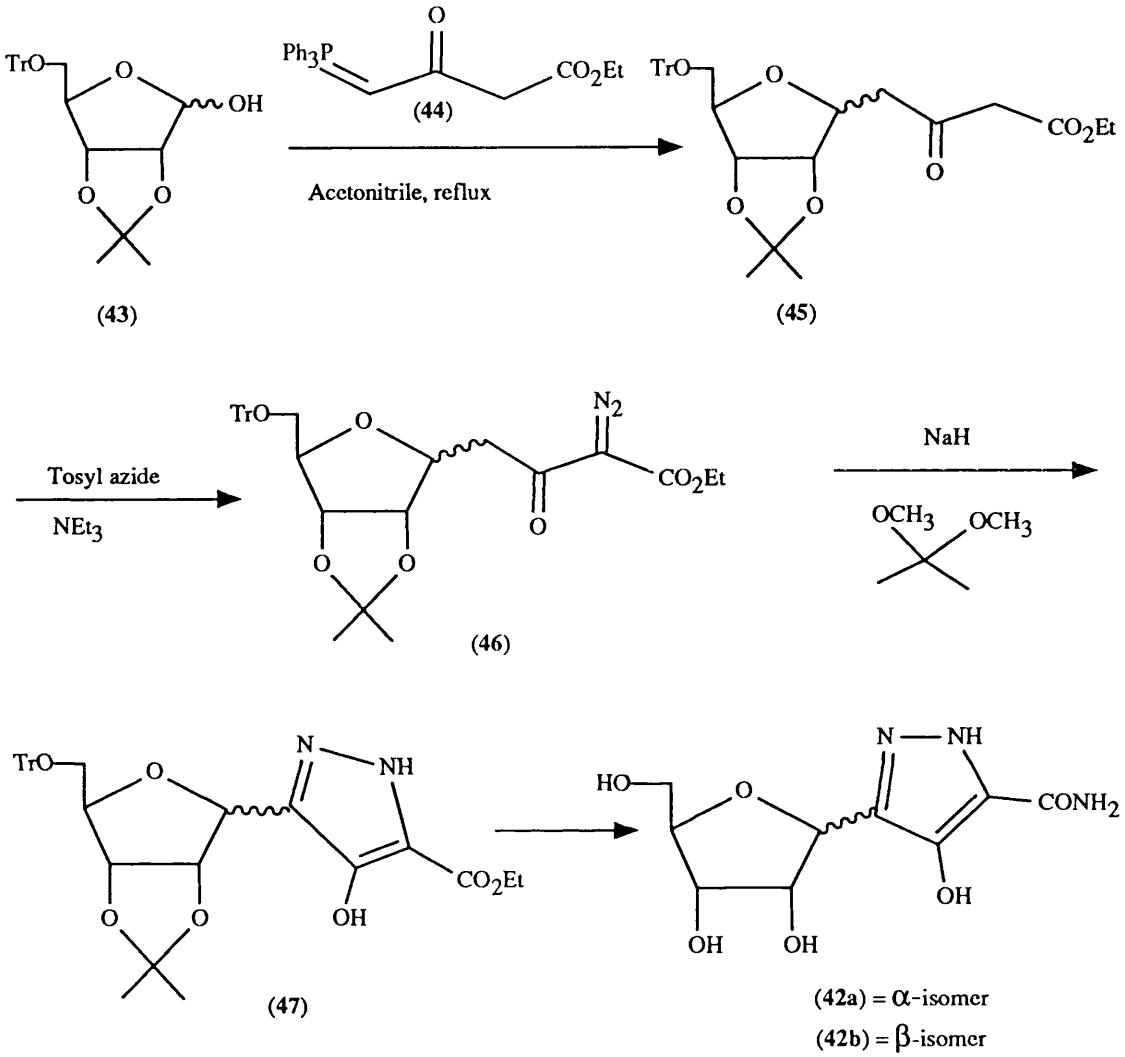
Also present in nature are C-nucleosides[26] in which a glycon (carbohydrate) and an aglycon (noncarbohydrate) are linked *via* a stable C-C bond. Most of these naturally occurring C-nucleosides appear to exhibit antibiotic properties e.g. the antibiotic formycin (**41**).[27]



(41)

As a result their synthesis has also gained growing popularity over the last few years. For example, a Japanese research group led by T. Kato[28] synthesised pyrazofurin (**42b**) and pyrazofurin B (**42a**) from β-keto ester (**45**), obtained by Wittig reaction of the protected D-ribose (**43**) with phosphorane (**44**) in acetonitrile under reflux for 90 h. Product (**45**) was obtained as an anomeric mixture (β:α = 2:1) in 95% yield. Treatment of these compounds with tosyl azide in the presence of triethylamine (Et_3N) gave the diazo product (**46**) (β:α = 1:1). This compound on treatment with sodium hydride (NaH) in 1,2-dimethoxyethane cyclised to form the pyrazole (**47a**) (42%) and its α-epimer (**47b**) (21%). Subsequent reactions transform (**47a**) and (**47b**) to (**42a**) and (**42b**) respectively [Scheme 17].

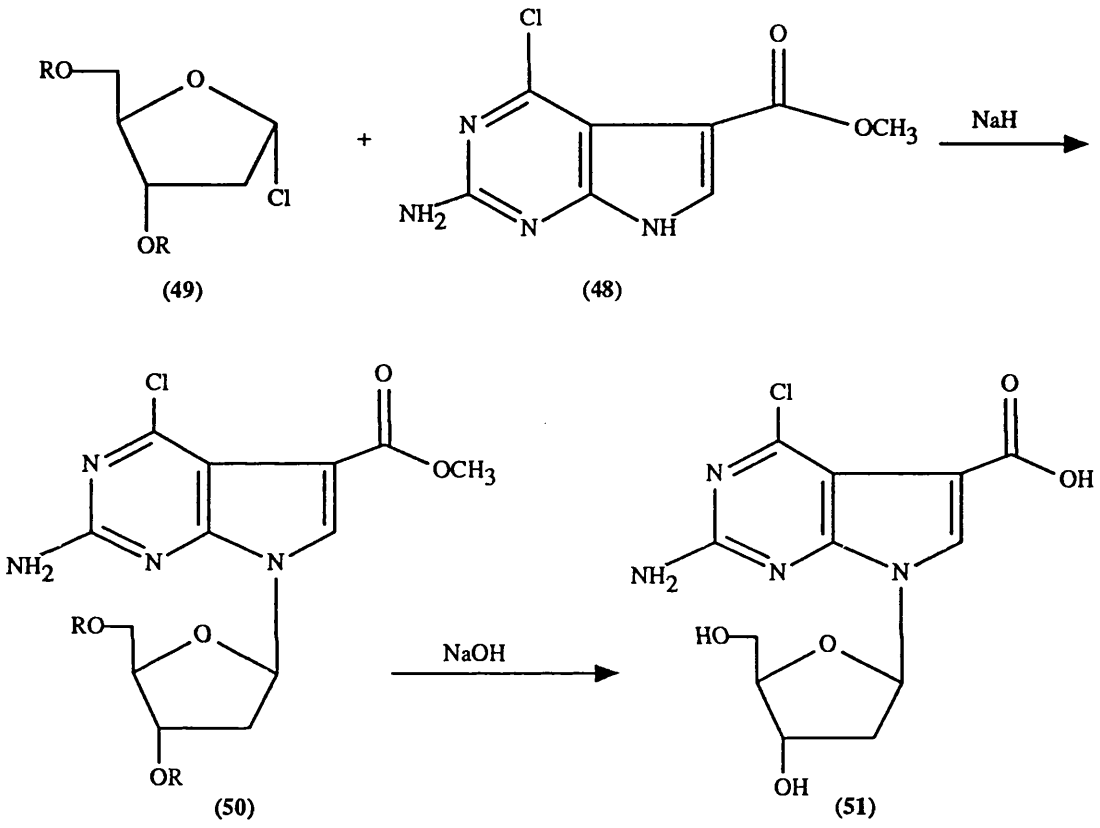
Scheme 17



However, a recent report by Revankar[29] illustrated an efficient and stereospecific synthesis of 2'-deoxycadeguomycin (**51**) from pyrrolo [2,3-*d*] pyrimidines (**48**). Glycosidation of the sodium salt of (**48**), generated *in situ* by treatment of 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranose (**49**) with sodium hydride, gave the protected nucleoside (**50**). Saponification with sodium hydroxide (NaOH) followed by neutralisation led to the desired product

(**51**) [Scheme 18].

Scheme 18



R = toluoyl

Thus, given the relative importance of glycosidic linkages to furanose sugars and the relative sparsity of information on radical reactions of such derivatives, the final section in this thesis is directed towards the preparation of appropriate radical precursors.

CHAPTER 2

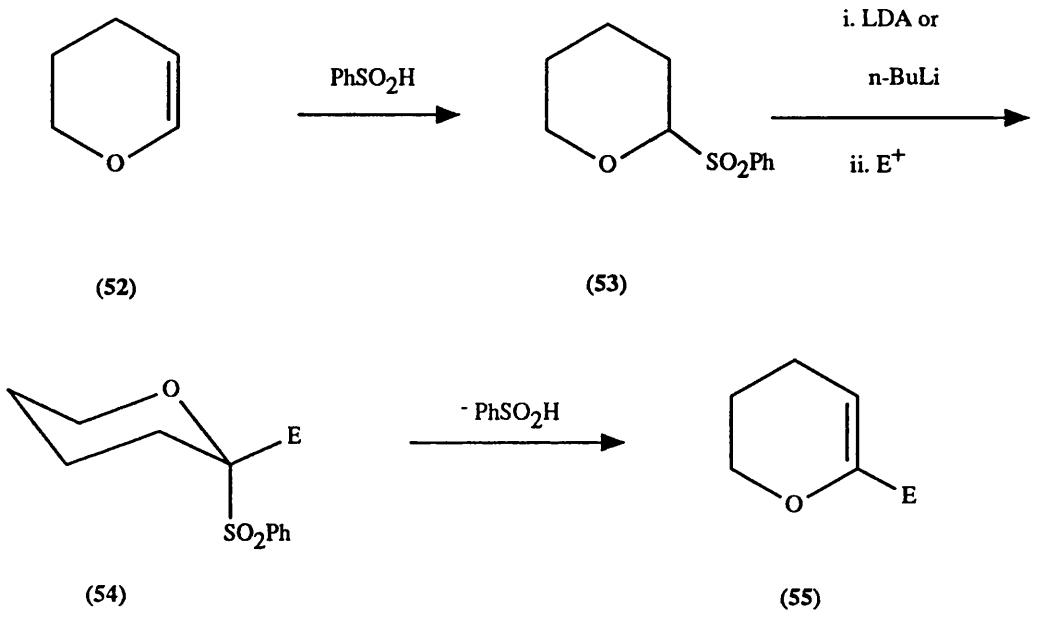
DIASTEREOSELECTIVE SYNTHESIS OF 2-DEOXY-ß-*C*-GLYCOSIDES

2. Diastereoselective synthesis of 2-deoxy-β-*C*-glycosides

Previously it has been shown[13] in this group that the synthesis of 2-deoxy-β-*O*-glycosides can be achieved with high diastereoselectivity by radical methodology. As an extension to this work, it was decided to investigate the effect on diastereoselectivity of variation of the anomeric substituent group from *O*- to *C*-. The synthesis of 2-deoxy-β-*C*-glycosides was thus envisaged using a diastereoselective free radical chain reaction as the ultimate stereodirecting step. As in the previous work, ulosonic acid derivatives were thought to be suitable radical precursors using the Barton[11] *O*-acyl thiohydroxamate chemistry. These ulosonic acid derivatives themselves could be synthesised from glycosyl sulphones by an extension of the work of Ley and Beau as outlined below.

In his studies on the reactions of 2-benzenesulphonyl tetrahydropyran, Ley[30] illustrated the ease of introducing a sulphone moiety at the α-position by direct addition of benzenesulphinic acid across the olefinic bond of 3,4-dihydro-2-H-pyran (**52**). Deprotonation of this sulphone (**53**) with either n-butyllithium (n-BuLi) or lithium diisopropylamide (LDA) at -78 °C, followed by alkylation with carbonyl compounds or alkyl halides, gave cyclic enol ether products (**55**). These were the result of spontaneous elimination of benzenesulphinic acid from the intermediate alkylated product (**54**) as the reaction warmed to room temperature [Scheme 19].

Scheme 19

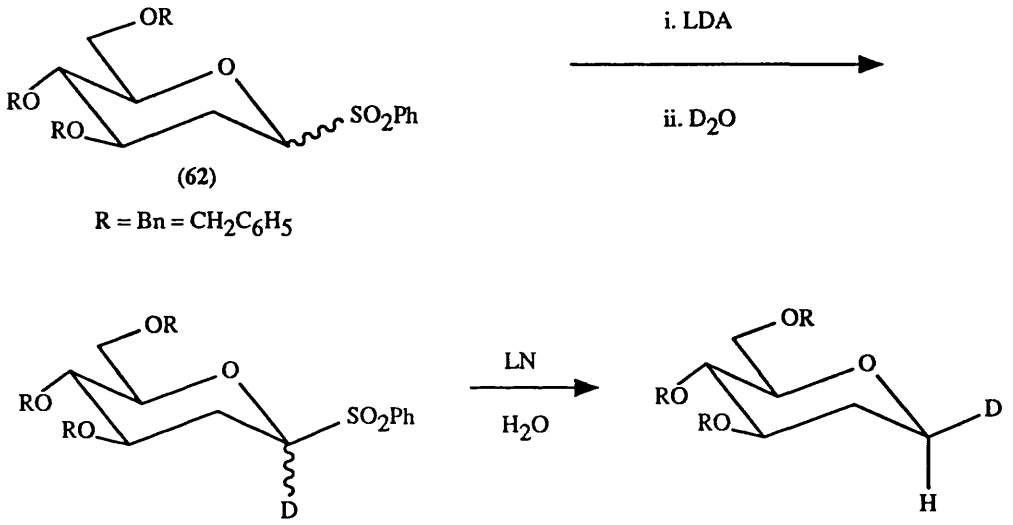


(52) (53) (54) (55)

Similar reactions were studied by Beau[31] on sugar derivatives whereby 2-deoxy-D-*gluco*-pyranosyl phenylsulphone (**62**) was synthesised from commercially available tri-*O*-acetyl-D-glucal (**57**). Saponification of the acetate groups to hydroxyl groups gave D-glucal (**58**) which was then protected as the tri-benzyl ether by treatment with sodium hydride (NaH) and benzyl chloride. Hydrochlorination followed by treatment with thiophenol and Hunig's base (diisopropylethylamine) gave the corresponding phenylthio glycoside (**61**) which on oxidation with *meta*-chloroperbenzoic acid gave sulphone (**62**). Unlike the simple tetrahydropyran derivative, attempts at direct addition of the sulphone moiety to the glycal by treatment with benzenesulphinic acid failed to introduce sulphone at the anomeric position. However as with the simple tetrahydropyran derivative, the sulphone glycoside (**62**) underwent deprotonation with LDA or n-BuLi at -78 °C followed by quenching with deuterium oxide (D_2O) to give an anomeric mixture of deuterated sulphones in the ratio 4:1 (α:β). Reductive

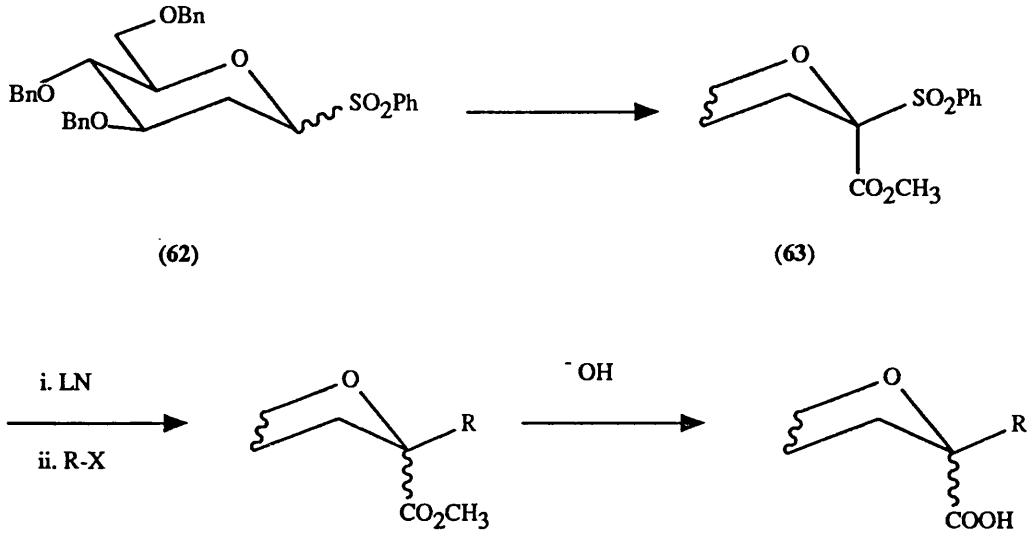
lithiation of the anomeric deuterated sulphone with two molar equivalents of lithium naphthalenide (LN) at -78 °C and quenching of the anion gave exclusively the β-deuterio derivative [Scheme 20]. Hence, as seen from the above reports, anomeric sulphones could be used in stereoselective synthesis of α-D-*C*-glycosides using a reductive lithiation-alkylation reaction.

Scheme 20



This provided a possible route for the rational design of a synthesis of 2-deoxy-*C*-glycosides. Sulphones (**62**) would undergo deprotonation with LDA and by the use of an appropriate electrophile, a carboxyl group could then be introduced at the anomeric position giving sulphone ester (**63**). Reductive desulphonylation with two molar equivalents of LN followed by quenching with alkyl halide (R-X) would then result in the formation of alkyl ester. Saponification of these esters would lead to the required ulosonic acid derivatives [Scheme 21].

Scheme 21



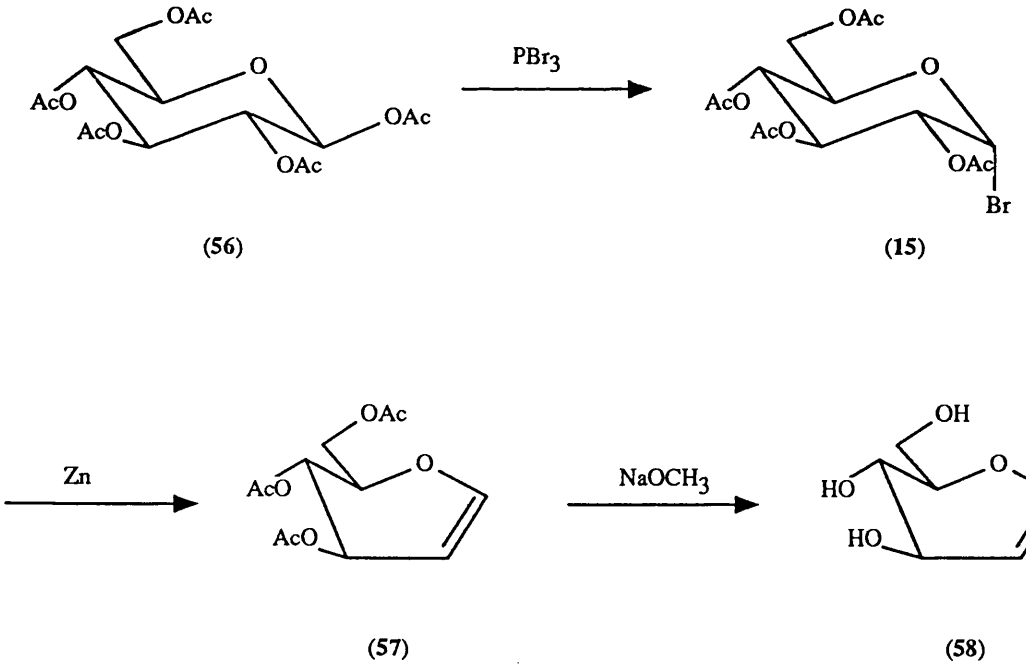
A single example using this methodology had been reported[13] whereby sulphone (**62**) was converted to sulphone ester (**63**) by initial deprotonation of (**62**) with LDA and quenching of the anion with dimethyl carbonate. Reductive desulphonylation of (**63**) with LN and alkylation of the resultant lithium salt with allyl bromide then gave the *C*-glycoside (**64**) as a single unassigned stereoisomer. This methodology thus provides a route to the synthesis of the required 3-deoxy-*C*-ulosonic acid precursors.

2.1. Synthesis of tri-*O*-benzyl-D-glucal

In view of the high cost of commercially available tri-*O*-benzyl-D-glucal[32] (**59**) as well as the amount which would be required for the

preparation of *C*- (and later *O*-) glycosides, it was decided to synthesise (**59**) from the commercially inexpensive and readily available β-D-*glucose* pentaacetate (**56**). The conversion of (**56**) to tri-*O*-acetyl-D-glucal (**57**) was carried out on a large scale (200 g) *via* a modified literature[33] procedure [Scheme 22]. Treatment of (**56**) with phosphorus tribromide, used in place of red phosphorus and bromine, gave the intermediate tetra-*O*-acetyl-α-D-*gluco*-pyranosyl bromide (**15**). Isolation of this intermediate bromide (**15**) was not attempted but it was used immediately in the reduction reaction with zinc at room temperature to give the white crystalline product (**57**), m.p. 54 °C, in an overall yield of 86% (cf. lit. m.p. 54-55 °C, 60-70% yield).

Scheme 22



(56) (15) (57) (58)

Zemplen deacetylation using sodium methoxide (NaOMe) in

methanol (MeOH) to deprotect the acetate groups gave D-glucal (**58**). The reaction was complete in a day, as indicated by thin layer chromatography (t.l.c.), giving an excellent yield of 92% (cf. lit. 73% yield: 3-4 days reaction time). An alternative deprotonation procedure, using ammonia in methanol, has recently been reported by Kozikowski[34] for the cleavage of the acetate groups from tri-*O*-acetyl-D-galactal. After attempting standard methods (e.g. $Ba(OH)_2$ in MeOH; Et_3N/H_2O/MeOH; NaOMe in MeOH), Kozikowski claimed the use of ammonia-methanol to be the best deprotecting method. However this route had been previously tried[13] in our laboratory and found to be less satisfactory than the Zemplen method.

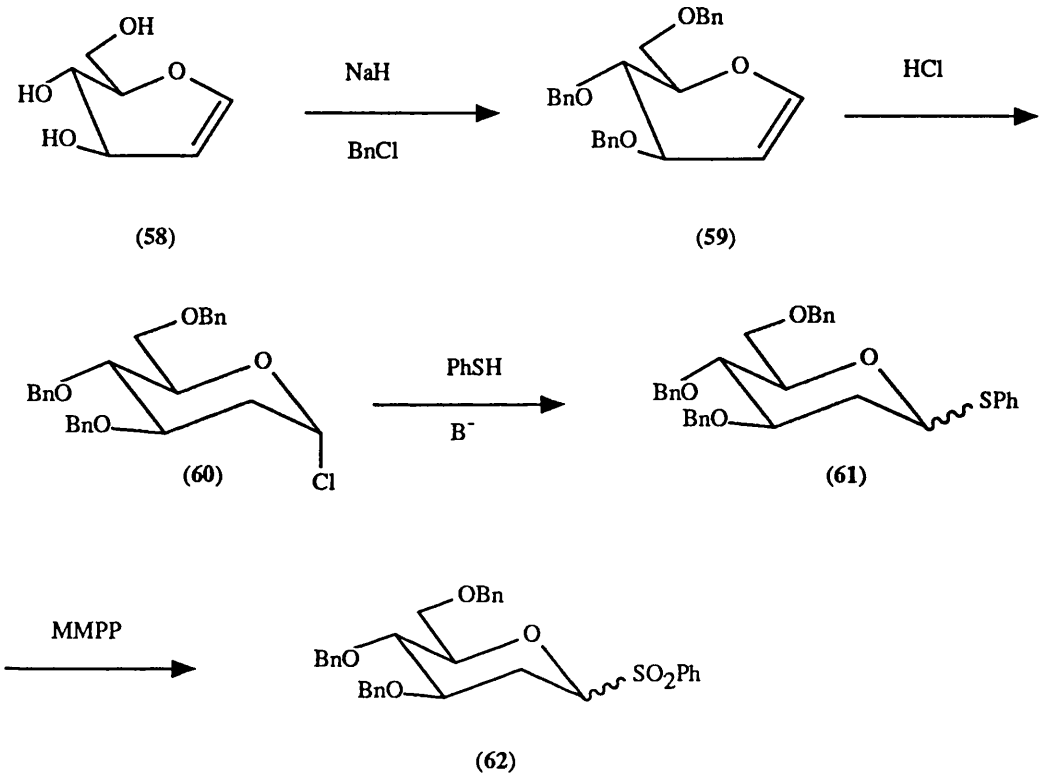
Having obtained the D-glucal (**58**), the free hydroxyl groups were then subjected to protection with benzyl groups. This was achieved by deprotonation of D-glucal (**58**) with sodium hydride (NaH) in dimethyl sulphoxide (DMSO) at room temperature and quenching the trianion thus formed with benzyl chloride (BnCl) to give tri-*O*-benzyl-D-glucal (**59**) as a white crystalline solid, m.p. 57 °C, in 87% yield. This preparation could be carried out on a 25 gram scale with no chromatographic purification. Hence tri-*O*-benzyl-D-glucal (**59**) was available on a multigram scale from glucose pentaacetate without recourse to chromatography.

2.1.1 Preparation of sulphone ester (63)

The glycal (**59**) (10 g scale), in dry toluene at 0 °C, was subjected to hydrochlorination by bubbling a slow stream of HCl gas into the solution. The intermediate chloride (**60**) formed in this reaction was not isolated but converted immediately to the corresponding thiophenyl glycoside (**61**) by treatment with

thiophenol and Hunig's base at room temperature [Scheme 23]. The product (**61**), a white crystalline solid with m.p. 57 °C, was obtained as a mixture of anomers (α:β = 1:5) in an overall yield of 99%.

Scheme 23

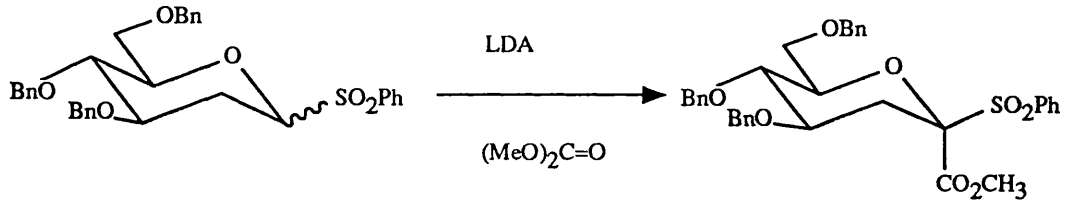


Oxidation of phenylthio glycoside (**61**) to the corresponding sulphone (**62**) with the magnesium salt of monoperoxyphthalic acid (MMPP)[35] in ethanol at room temperature gave, after extractive work up, the white crystalline product (**62**) (71%), m.p. 102-104 °C as a mixture of α:β (1:5) anomers. Sulphone (**62**) could therefore be prepared from β-D-*glucose* pentaacetate (**56**) in gram quantities

without recourse to any chromatographic purification step.

With gram quantities of the sulphone (**62**) in hand the next step was to find a way of introducing a carboxyl group at the anomeric position. Adopting Beau's idea of deprotonation-alkylation of sulphone derivatives, sulphone (**62**) was deprotonated with LDA at -78 °C, under an inert atmosphere of argon, and the anion subsequently quenched with dimethyl carbonate. Extractive work up followed by chromatographic purification gave a white crystalline product (**63**), m.p. 88 °C, in 76% yield [Scheme 24].

Scheme 24



(62) (63)

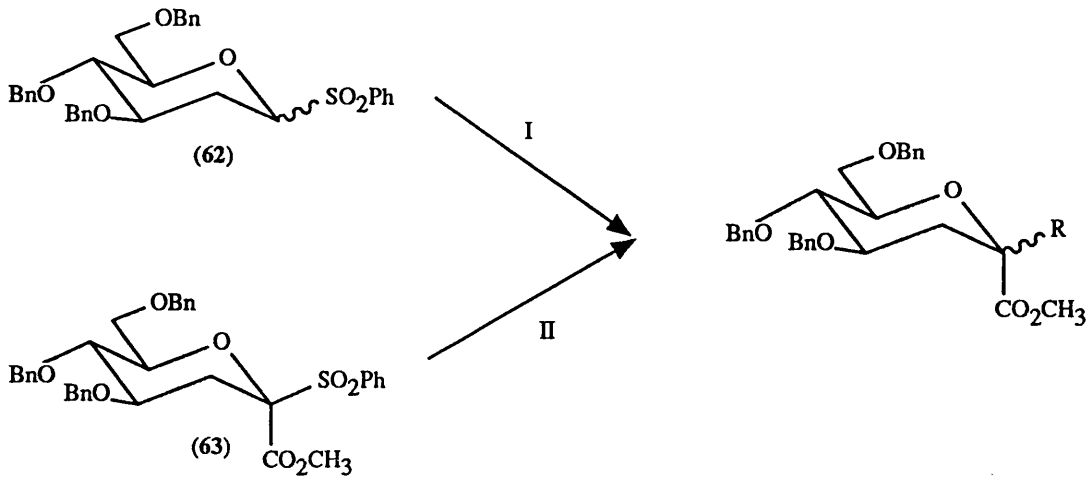
The assignment of the configuration of the sulphone ester (**63**) was based on a report by Ley.[30] Whilst investigating the alkylation reactions of anions derived from 2-benzenesulphonyl tetrahydropyran (**53**), Ley observed spontaneous elimination of benzenesulphinic acid from the intermediate alkylated products as the reaction warmed up to room temperature. The only exception to this rule was the reaction with alkyl and aryl chloroformates. The crystalline acylated sulphones were isolated and in all cases their X-ray crystal structure determinations showed

the sulphone to be in the equatorial position. The β-configuration of the sulphone moiety was further supported by studies of the coupling constant, $J_{1,2}$ (^{1}H nmr), of the simple sulphone, obtained from deprotonation of (**62**) with LDA followed by quenching with water (H_2O). From its ^{1}H nmr spectrum the coupling constants, $J_{1,2}$, of the anomeric proton led to the assignment of the sulphone moiety as equatorially positioned. Hence, in accordance with Ley's results, the sulphone ester (**63**) was assigned the β-configuration (with the sulphone moiety adopting an equatorial position).

2.2 Synthesis of alkyl ester and ulosonic acid derivatives

Having successfully introduced the carboxyl group at the anomeric position, the next step was to seek a method of replacing the sulphone moiety with an alkyl group. Two methods (methods I and II) were adopted for the synthesis of *C*-glycosyl ester [Scheme 25]. The first (Method I) involved the deprotonation of sulphone (**62**) with LDA at -78 °C followed by quenching the anion formed with dimethyl carbonate to form the sulphone ester (**63**). This substance was then subjected to reductive desulphonylation with two molar equivalents of LN and alkylation of the resulting anion with alkyl halide (R-X). Although this involved several steps, the reaction itself was carried out by a one-pot procedure without the isolation of the intermediate sulphone ester (**63**), giving reasonable overall yield. The second (Method II), on the other hand, started out from the sulphone ester (**63**) which on reductive decarboxylation with LN followed by alkylation with R-X gave the alkyl-substituted product.

Scheme 25



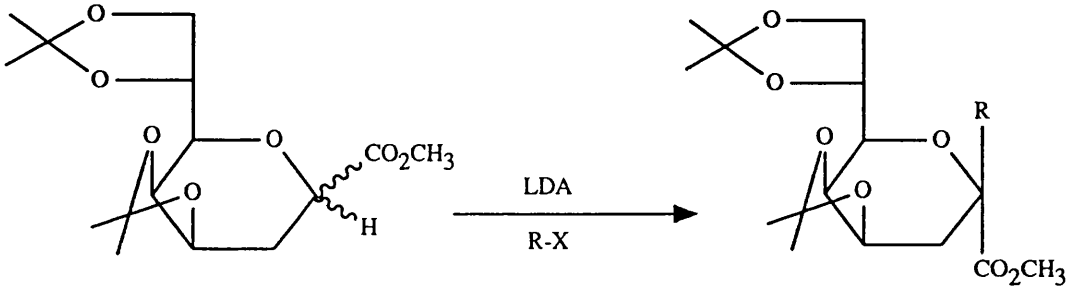
The following table [Table 1] summarises the results obtained from the above synthesis.

Table 1

R-X	Method	Product	Yield
CH_2=$CHCH_2Br$	I	**(64)**	44 %
$C_6H_5CH_2Cl$	I	**(65)**	56 %
SEM-Cl	II	**(66)**	70 %
CH_3I	II	**(67)**	50 %

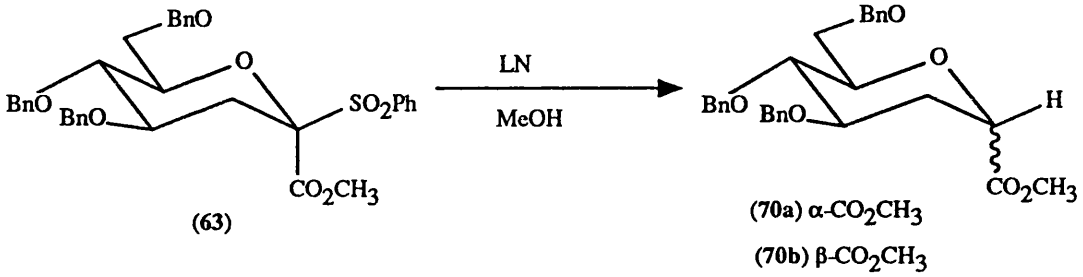
With the exception of alkylation with methyl iodide whereby the product (**67**) was obtained as a mixture of anomers in the ratio 3:5, alkylation with benzyl chloride, allyl bromide and β-trimethylsilylethoxymethyl chloride (SEM-Cl) all gave products (**64**), (**65**) and (**66**) respectively as single anomers. The lack of an anomeric proton ruled out the widely used ^1H nmr method of measuring vicinal $J_{1,2}$ coupling constants to determine the anomeric configuration of these compounds.

In order to attempt assignment of configuration of these products, careful studies were made on related compounds. Work by Claesson[36] on the deprotonation of (**68**) with LDA followed by quenching with various carbon electrophiles showed that in all cases the quenching with carbon electrophiles took place predominantly from the β-face thereby resulting in the β-products as the major anomers with ratios varying from (α:β) 70:30 to >95:5. The α- and β-configurations were assigned either by X-ray crystallography on the nitrile (**69**) or on the basis of chemical correlation with (**69**).



(**68**) (**69**) R = CN

Another reaction[13] based on the reductive desulphonylation of sulphone ester (**63**) with two molar equivalents of LN followed by quenching of the anion with methanol gave product (**70**) as a mixture of two separable anomers (α:β = 2:1) in 76% combined yield, the α-anomer (**70a**) being the less polar of the two isomers. The chemical shifts of H-3 axial and H-3 equatorial were identified.



(**63**)

(**70a**) α-CO_2CH_3

(**70b**) β-CO_2CH_3

On the basis of Claesson's report, the products formed from quenching the anion derived from reductive desulphonylation of (**63**), with alkyl halide, would be predicted to occur at the β-face. Combining this observation with careful examination on the chemical shifts of H-3 axial and H-3 equatorial of products (**64**), (**65**), (**66**) and of the anomeric mixtures (**67a**) and (**67b**), it was hoped that chemical shifts derived from (**70a**) and (**70b**) would help assign the anomeric configuration. The table [Table 2] below summarises the chemical shifts of axial and equatorial H-3 protons.

Table 2

Compound	δ H-3a	δ H-3e
(70b)	1.71	2.50
(70a)	1.88	2.56
(64)	1.54	2.66
(65)	1.55	2.65
(66)	1.57	2.75
(67a)	1.49	2.77
(67b)	1.52	2.73

As seen from the above table, the chemical shifts of both H-3a and H-3e of the β-ester (**70b**) appear slightly upfield (δ 1.71 and 2.50 ppm respectively) of that of the corresponding α-anomer (**70a**) (δ 1.88 and 2.56 ppm). The less polar α-anomer was isolated prior to the β-anomer from column chromatography. However, a comparison with the methyl-substituted products (**67a**) and (**67b**), obtained from the alkylation with methyl iodide, contradicted the above observations. The first product (**67a**) obtained from column chromatography, when based on the above observation, would be expected to be of α-ester configuration. Its H-3 chemical shifts, according to the chemical shifts for the "α-ester" are 1.52 and 2.73 ppm while the other anomer, supposedly the

corresponding "β-ester", has chemical shifts of 1.49 and 2.77 ppm. The observed trend is therefore opposite to that predicted. Furthermore, the chemical shifts of H-3a and H-3e are both upfield whereas for products (**64**) to (**67**) only the chemical shift of H-3a is close to that of H-3a of the α-product (**70a**). The chemical shifts of the H-3e are all nearer to those observed for the H-3e of the β-anomer (**70b**).

Hence, the unambiguous assignment of configurations to these products from desulphonylation-alkylation of sulphone ester (**63**) could not simply be based on the above data. A possible solution to this problem of assignment of anomeric configuration lies in a recent report[37] whereby the 3-bond coupling constant between CO_2CH_3 and the H-3 (axial and equatorial) is measured and related to dihedral angle. However at the present time we have not attempted this method.

The next step of this synthesis was to convert the alkyl esters to the corresponding ulosonic acid derivatives (**B**). Saponification (KOH) of esters [(**64**) to (**67**)] [Scheme 26] gave the corresponding 3-deoxy-ulosonic acid derivatives [(**71**) to (**74**)] in good yields [Table 3]; where necessary the temperature was elevated to facilitate the reaction.

Scheme 26

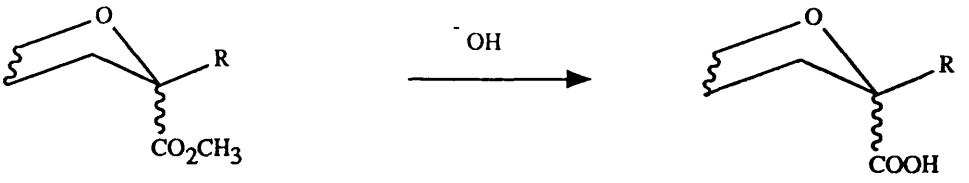


Table 3

Ester	Acid	Yield
(64)	**(71)**	77 %
(65)	(72)	72 %
(66)	(73)	82 %
(67)	(74)	88 %

2.2.1 Reductive decarboxylation reaction

The free ulosonic acid derivatives [(**71**) to (**74**)] were not purified but were used immediately in the folowing step. They were converted to the intermediate *O*-acyl thiohydroxamate (**75**) by stirring in dry dichloromethane under argon at room temperature in the dark, with the heterocyclic salt (**22**) and triethylamine (Et_3N) [Scheme 27]. When all the acid had been converted to (**75**), 5 molar equivalents of *t*-dodecylmercaptan were then added to the reaction mixture. Photolysis was then carried out at 0 °C under argon for 1 h using a 500W tungsten lamp. The product was purified by column chromatography on silica gel. In all cases, a single anomer was obtained (within the limits of high field ^1H nmr spectroscopy) in good to excellent yields [Table 4].

Scheme 27

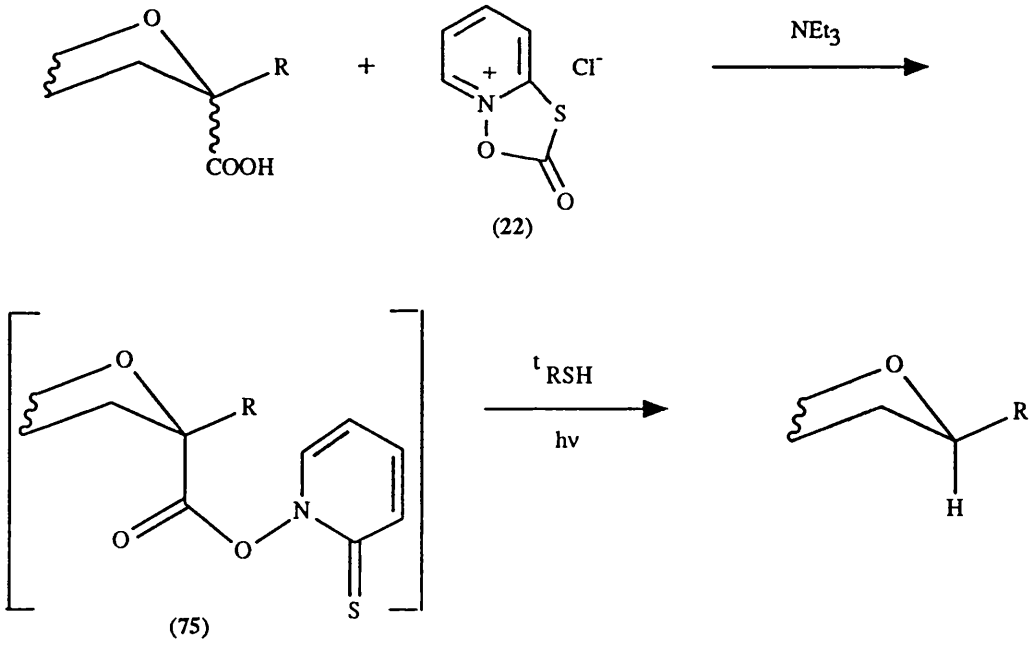


Table 4

Acid	Product	Yield
(71)	(76)	73 %
(72)	(77)	92 %
(73)	(78)	58 %
(74)	(79)	56 %

2.2.2 Assignment of anomeric configuration

Normally careful studies on the vicinal $J_{1,2}$ coupling constants would enable the assignment of anomeric configuration to be made. However in the case of products (**76**) to (**79**), overlapping of the methylene protons in the benzyl protecting groups and complex multiplet splittings of the anomeric proton due to adjacent alkyl and H-2 protons resulted, in all cases, in difficulties in spectral analysis of the anomeric proton. Therefore it was more convenient to focus attention on the protons at C-2 and to analyse their vicinal coupling constants ($J_{2,3}$ and $J_{2,1}$) to both H-3 and H-1, and their geminal coupling constant, $J_{2a,2e}$.

Product (**76**), whose ^1H nmr spectrum is typical and is shown [Spectrum 1], has been chosen as an example to illustrate this analysis. This

analysis is based on the product being the β-anomer with the alkyl group adopting an equatorial position [Diagram A and B] and the pyranose ring remaining in the favoured $^4C_1$ conformation.

Diagram A and B

Diagram A

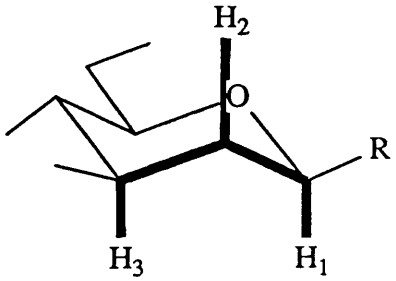
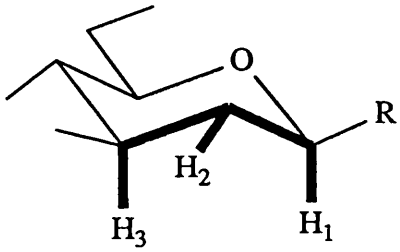
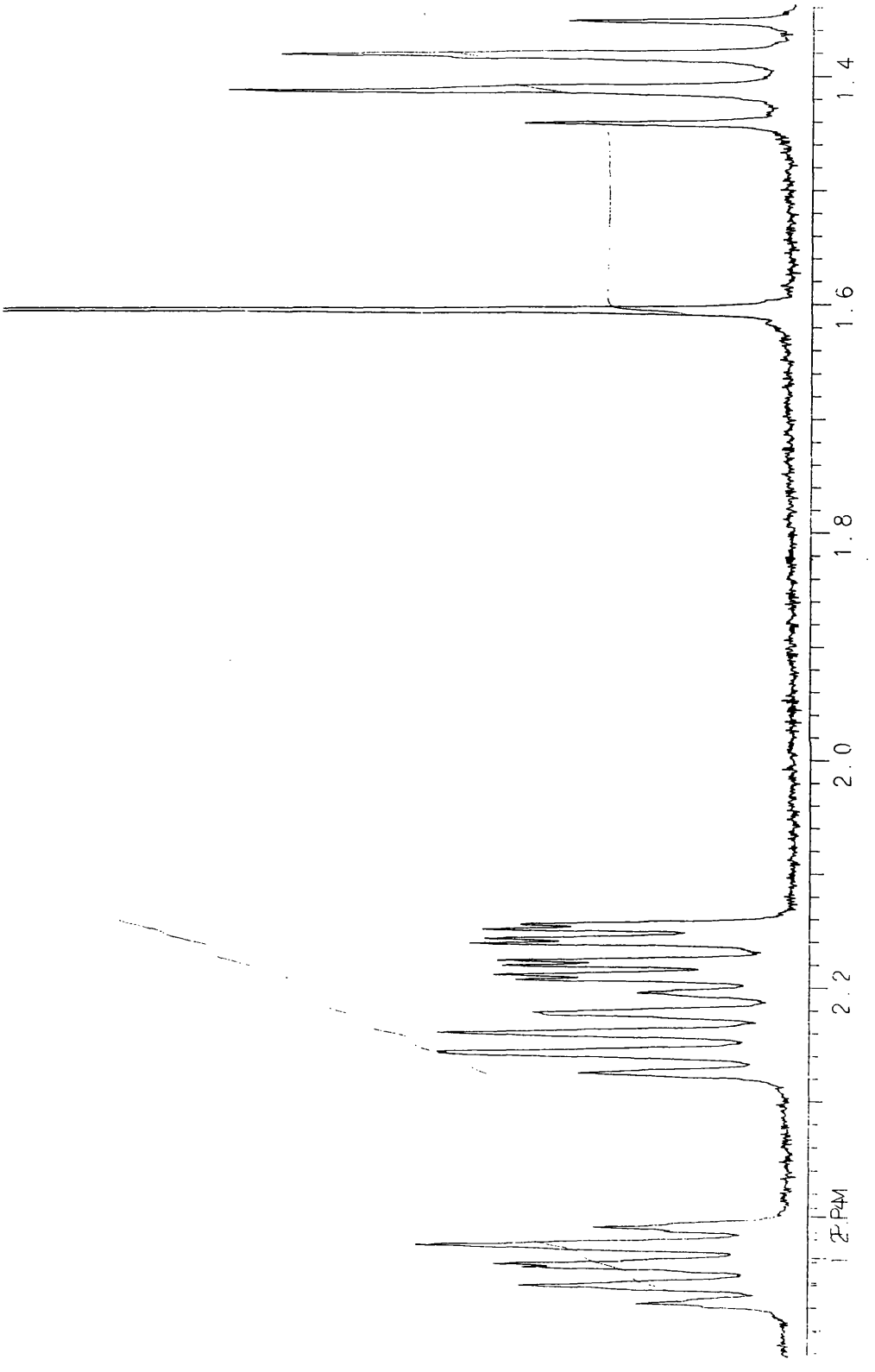


Diagram B



Spectrum 1



H-2 axial (H-2a)

As seen from the spectrum above, due to its trans diaxial orientations to H-3 and H-1, the axial proton at the C-2 position (H-2a), $\delta = 1.39$, has two large vicinal coupling constants which were found to be equal i.e. $J_{2a,3} = J_{2a,1} = 11.8$ Hz. This is in accordance with the Karplus equation[38] in which large vicinal coupling of 10-13 Hz may be identified with an approximate diaxial orientation. The geminal coupling, $J_{2a,2e}$, in this unstrained ring system is also similar resulting, in this case, in $J_{2a,2e} = J_{2a,3} = J_{2a,1} = 11.8$ Hz, and giving a multiplet the approximate form of a 1:3:3:1 quartet.

H-2 equatorial (H-2e)

On the other hand the equatorial proton at C-2 (H-2e) has again a large geminal coupling constant, $J_{2a,2e} = 11.8$ Hz, but its vicinal couplings to H-3 and H-1, $J_{2e,3}$ and $J_{2e,1}$ respectively, would be expected to be of smaller magnitudes. This can be explained in terms of its equatorial-axial orientations to H-3 and H-1, which in this chosen example, give rise to $J_{2e,3} = 1.8$ Hz and $J_{2e,1} = 3.2$ Hz, giving an approximate doublet of triplets.

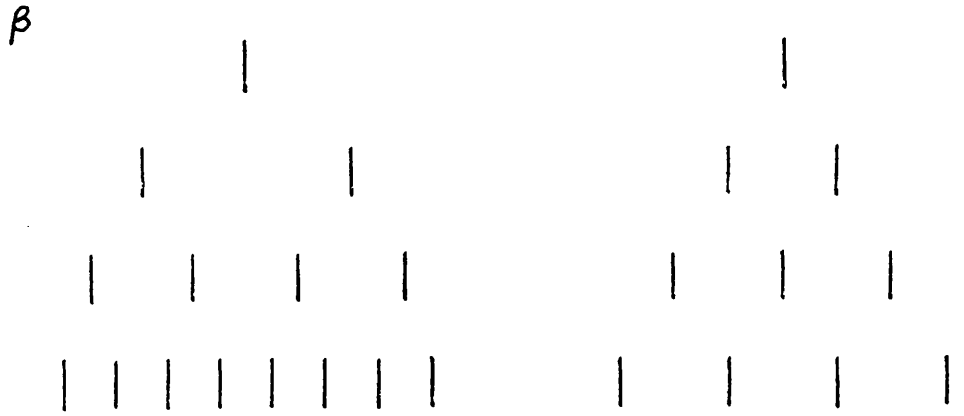
Spectral analysis of the α-anomer

Where the product exists as an α-anomer, the differences in the orientations of H-2a and H-2e to H-1 would result in a spectrum with a very different splitting pattern. For example, H-2a would then possess only one large vicinal coupling as opposed to two large vicinal couplings in the β-anomer. This arises from the diaxial orientation of H-2a to H-3, with the H-1 proton now

equatorially positioned. As a result of the axial-equatorial orientation of H-2a and H-1, a small vicinal coupling would be observed. The geminal coupling constant, $J_{2a,2e}$, would remain large and similar to the vicinal coupling constant, $J_{2a,3}$. The equatorial proton at C-2 (H-2e) would have a large geminal coupling ($J_{2a,2e}$) and two small vicinal couplings from equatorial-axial orientations to H-1 and H-3.

Splitting pattern of the α- and β-anomers

The following diagrams illustrate the splitting patterns that would be observed for the protons at C-2 (H-2a and H-2e) for both α- and β-anomers.



The table below [Table 5] summarises the J values obtained for products **(76)** to **(79)**.

Table 5

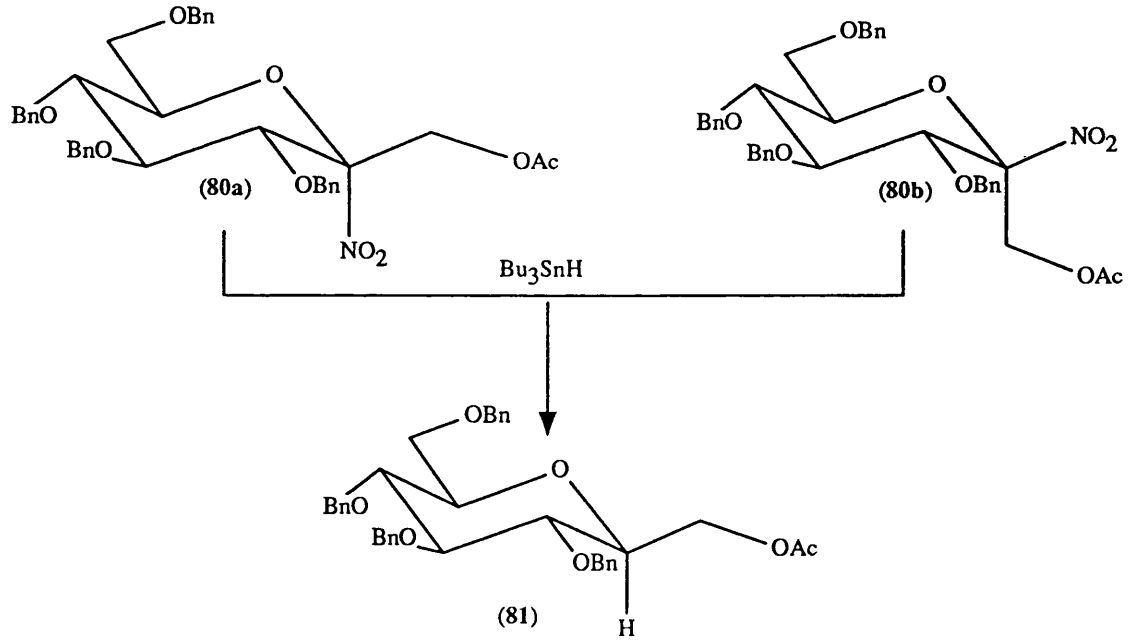
Product	H-2a	H-2e
(76)	δ 1.39 $J_{2a,2e}$ = 11.8 Hz $J_{2a,1}$ = 11.8 Hz $J_{2a,3}$ = 11.8 Hz	δ 2.18 $J_{2a,2e}$ = 11.8 Hz $J_{2e,3}$ = 1.8 Hz $J_{2e,1}$ = 3.2 Hz
(77)	δ 1.45 $J_{2a,2e}$ = 12.6 Hz $J_{2a,1}$ = 12.6 Hz $J_{2a,3}$ = 12.6 Hz	δ 2.13 $J_{2a,2e}$ = 12.6 Hz $J_{2e,3}$ = 1.7 Hz $J_{2e,1}$ = 4.94 Hz
(78)	δ1.43 $J_{2a,2e}$ = 11.2 Hz $J_{2a,1}$ = 11.2 Hz $J_{2a,3}$ = 11.2 Hz	δ2.24 $J_{2a,2e}$ = 11.2 Hz $J_{2e,3}$ = 1.1 Hz $J_{2e,1}$ = 5.0 Hz
(79)	δ 1.44 $J_{2a,2e}$ = 11.5 Hz $J_{2a,1}$ = 11.5 Hz $J_{2a,3}$ = 11.5 Hz	δ 2.13 $J_{2a,2e}$ = 11.5 Hz $J_{2e,3}$ = 1.8 Hz $J_{2e,1}$ = 3.2 Hz

As seen from the above Table, $J_{2a,1}$ values were large, between 11-13 Hz for all compounds. This could occur only if H-2a and H-1 are trans diaxial to one another. Therefore in the reductive decarboxylation step the radical was quenched from the α-face. This H-atom transfer resulted in an axially positioned H-atom, with the alkyl-substituent group adopting the equatorial position.

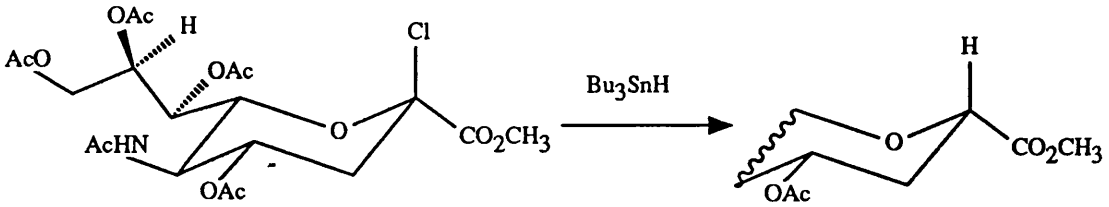
It could therefore be concluded from their ^1H nmr spectra that the products were obtained, as a result of reductive decarboxylation, with high diastereoselectivity as the β-anomers.

This is in accordance with the reduction of related compounds in the work carried out by Vasella[39] on α- and β-nitro ethers **(80a)** and **(80b)** whereby radical denitration with tributyltin hydride (Bu_3SnH) led in both cases to the β-product **(81)** [Scheme 28].

Scheme 28



Likewise Zbiral[40] demonstrated that the β-anomer (**83**) was also formed exclusively when the halide (**82**) was subjected to reduction by means of Bu_3SnH.

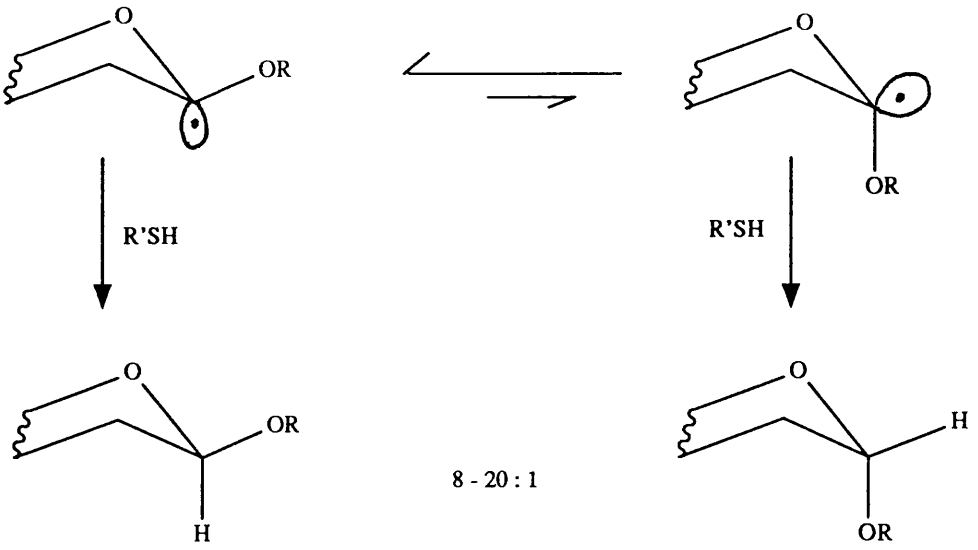


(82) (83)

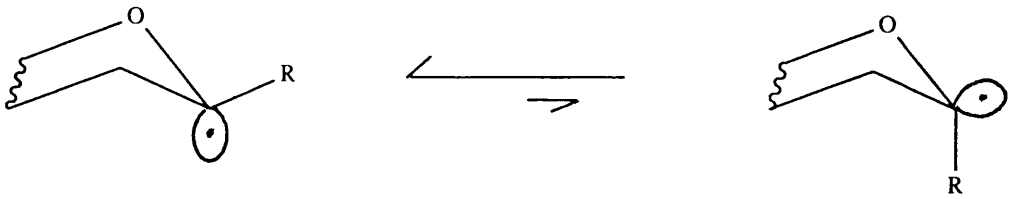
The selectivity observed is also in accordance with the *N*-bromosuccinimide mediated bromination[41] of various pyranoses and ulosonate esters in which bromine is introduced at an axial position.

2.3 Rationalisation of the diastereoselectivity observed

As indicated above, previous work from this laboratory has determined that diastereoselectivities of between 8 and 20:1 are observed for the quenching of 2-deoxy-1-alkoxyglycos-1-yl radicals by thiols at temperature between 0 °C and ambient temperature. These observations were rationalised, on the basis of literature calculations and esr measurements,[10] in terms of pyramidalised radicals with axially oriented single electrons. The formation of the α-glycoside as byproduct was interpreted in terms of a competition between the σ-radical and the alkoxyl group for the axial position antiperiplanar to a ring oxygen lone pair[5] (radical *vs* normal anomeric effect).

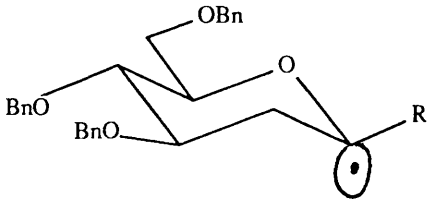


In the present investigation, greatly enhanced diastereoselectivity is observed in the radical step. This observation can be rationalised at first sight in terms of a reduced tendency of the 1-alkyl substituent vis à vis the 1-alkoxy substituent to occupy the axial position, i.e. a greater configurational stability of the intermediate radical. In accordance with this suggestion, alkyl radicals bearing a single oxygen substituent at the α-centre are known to be bent (i.e. pyramidalised) although to a lesser extent than those bearing two oxygen substituents.[42,43]



However recent esr work by the Giese/Sustmann[44] groups on closely related glycosyl radicals suggest that such radicals are essentially planar. Furthermore the radicals studied by these workers were reported to adopt a boat conformation in which the p-orbital carrying the single electron is essentially coplanar with and stabilised by the β-C-O bond. It is important to note here that the stabilisation of carbon centred radicals by β-C-O bonds is a contentious issue. Purported chemical evidence has been advanced in recent years but this is not supported by esr measurements.[44,45]

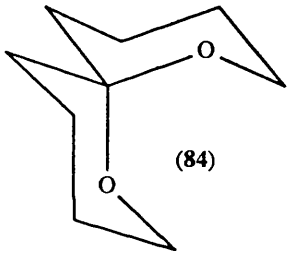
The radicals studied in this chapter differ from those scrutinised by Giese in so far as they do not possess a β-C-O bond at the C-2 position. Hence any boat conformation similar to those proposed by Giese would not benefit from stabilisation of the radical by a coplanar β-C-O bond. This being the case, the most reasonable hypothesis for the origin of the selectivity observed here is that the radical is a σ-radical which remains in the $^4C_1$ conformation favoured by glucose derivatives and is quenched from the axial direction antiperiplanar to a ring oxygen lone pair.



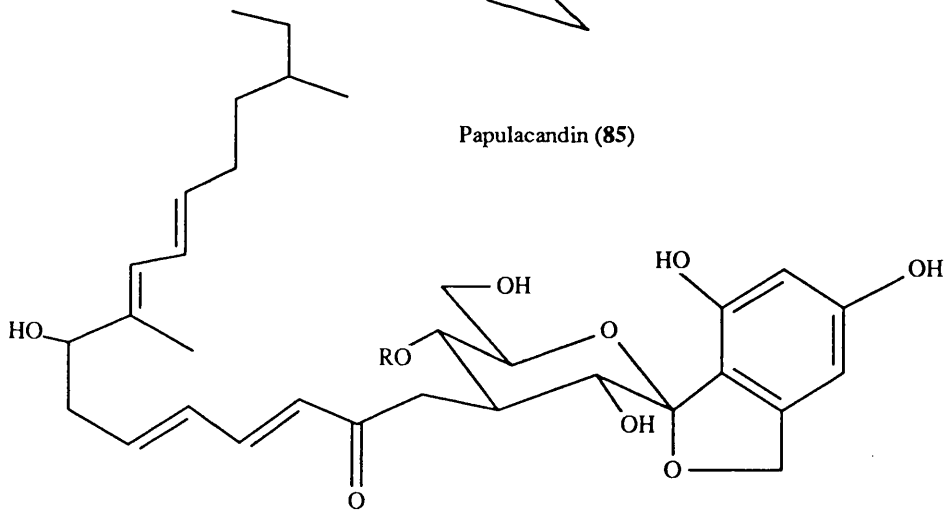
An esr spectroscopic investigation into the conformation and hybridisation (σ or π) of the intermediate radicals would evidently be of interest. To this end the recent report of Ingold on the use of *O*-acyl thiohydroxamates as radical precursors for esr spectroscopy is noted.[12]

2.4 Attempted Cyclisation

Spiroketals such as (84), derived from olive fly *Dacus oleae*, occur frequently in nature with the most widely recognised source being insect pheromones.[46] More complex spiroketals are found in *inter alia* the milbemycins and avermectins which exhibit potent antiparasitic and insecticidal properties. The spiroketal moiety is also present in some *C*-glycosides[47] such as in the Papulacandin A-D (85) antibiotics isolated from cultures of *papularia sphaerosperma* which display strong antibiotic activities against bacteria.



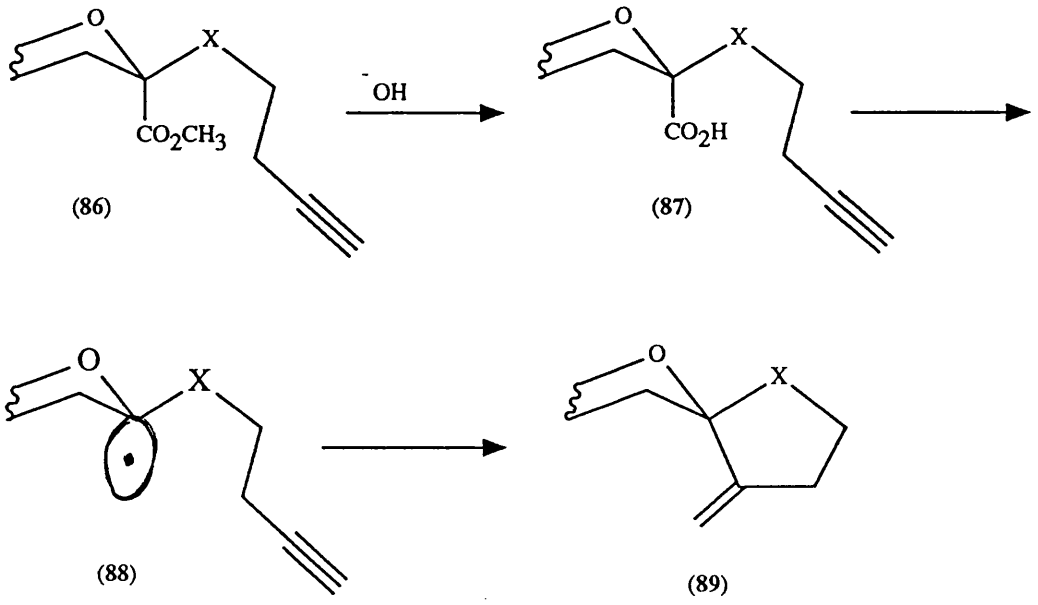
(84)



Papulacandin (85)

Elegant approaches to such carbohydrate spiroketals have recently been described by Beau[48] which involve initial C-C bond formation followed by C-O bond formation in the spirocyclisation step. Evidently, it would be interesting to investigate the possibility of cyclisation using our radical C-C bond formation methodology. The proposed synthesis involves the introduction of a substituent bearing multiple bonds at the anomeric centre. Saponification of this ester (**86**) would then give the corresponding ulosonic acid derivative (**87**). This acid on treatment with heterocyclic salt (**22**) and triethylamine should then be transformed to the *O*-acyl thiohydroxamate ester which on photolysis would generate radical (**88**). Cyclisation of this radical onto the multiple bond of the anomeric substituent group would lead to the desired spiroketal product (**89**) [Scheme 29].

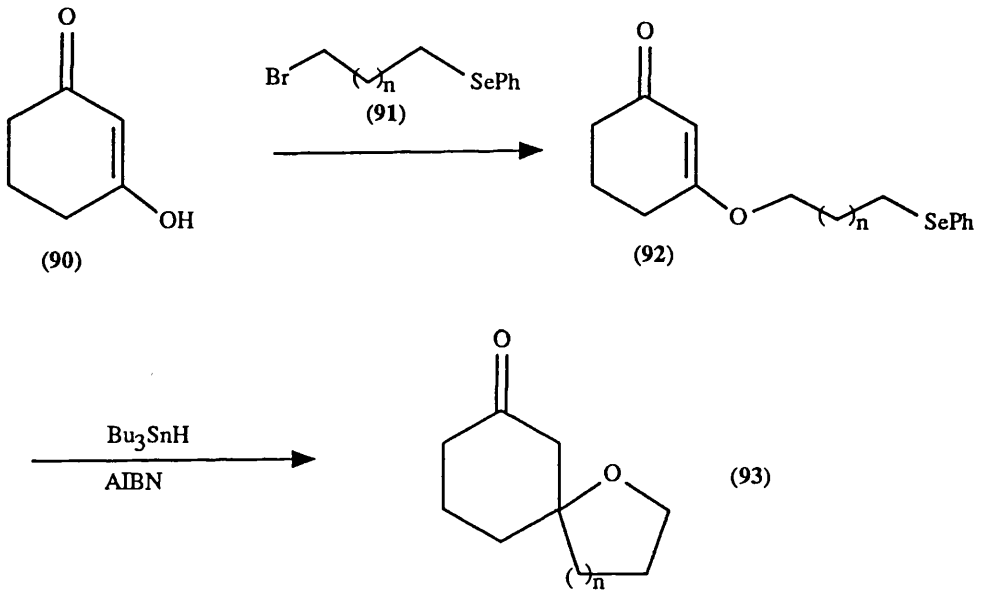
Scheme 29



The synthesis of spirosystems by means of radical reactions has not been extensively looked into. However one recent approach was that described by

Simpkins[49] who converted the commercially available β-diketone (**90**) into the intermediate phenylseleno product (**92**) in good yield by alkylation of the sodium salt of (**90**) with selenobromide (**91**). Cyclisation was achieved by slow addition of a mixture of Bu_3SnH and AIBN in benzene to a solution of (**92**) in refluxing benzene, to give (**93**) in 64% yield [Scheme 30].

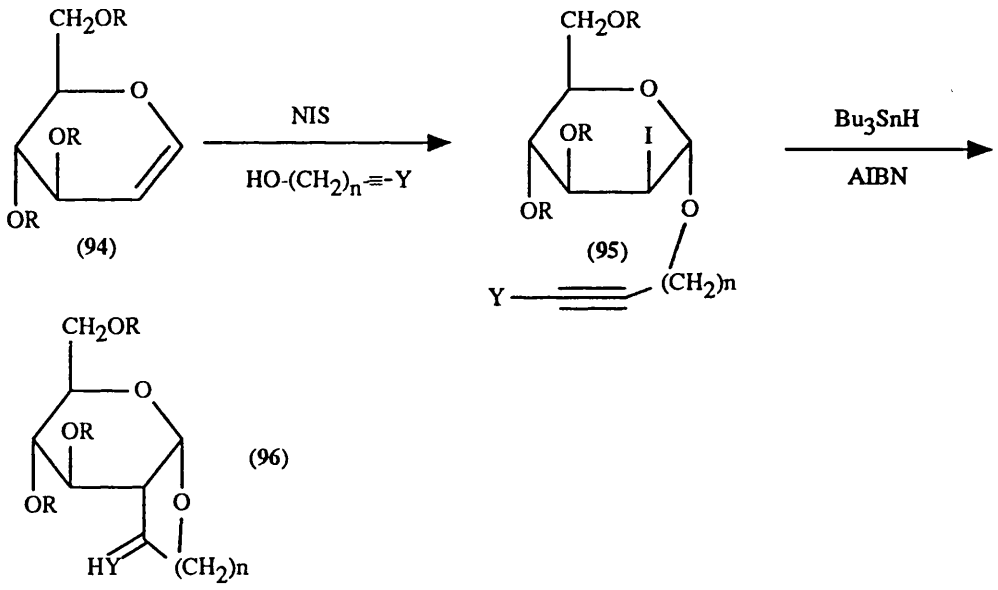
Scheme 30



Although the synthesis of spirocyclic systems of carbohydrates *via* radical cyclisation has not been well established, the use of carbohydrates as substrates for inter- and intramolecular free radical reactions to construct functionalised carbocyclic or heterocyclic systems has recently gained popularity. The use of various unsaturated α-halogenoacetals, originally developed by Stork,[50] in radical cyclisation is now an established, high yielding reaction procedure and Beau[51] has adapted this procedure to sugar templates in his synthesis of *cis*-fused

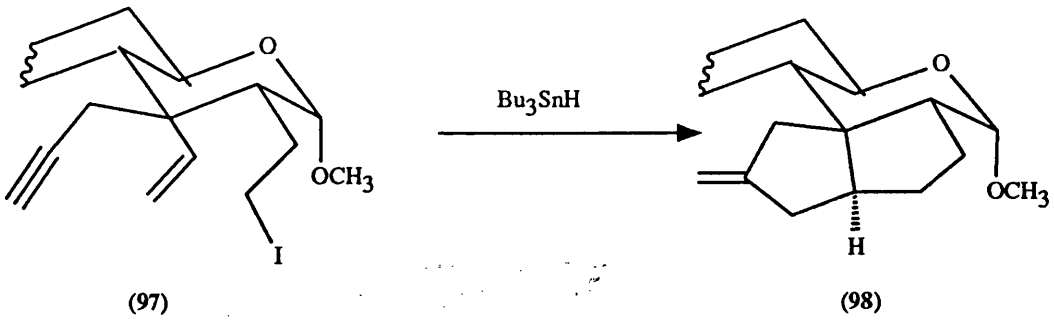
chiral bicyclic acetals. He illustrated the fact that stereocontrolled glycosidation could be achieved by reaction of simple unsaturated alcohols with glycals (**94**) and NIS giving the α-selective glycosidation leading to 2-deoxy-2-iodo-α-D-glycoside (**95**). This iodo-adduct (**95**) in refluxing benzene was treated with a solution of Bu_3SnH and AIBN in benzene over 10-15 h giving the cyclised product (**96**) [Scheme 31].

Scheme 31



Elegant work on serial radical cyclisation on sugar templates to give bis-annulated pyranosides was described by Fraiser-Reid.[52] An excellent yield of the annulated sugar (**98**) was achieved when iodide (**97**) was treated with Bu_3SnH [Scheme 32].

Scheme 32

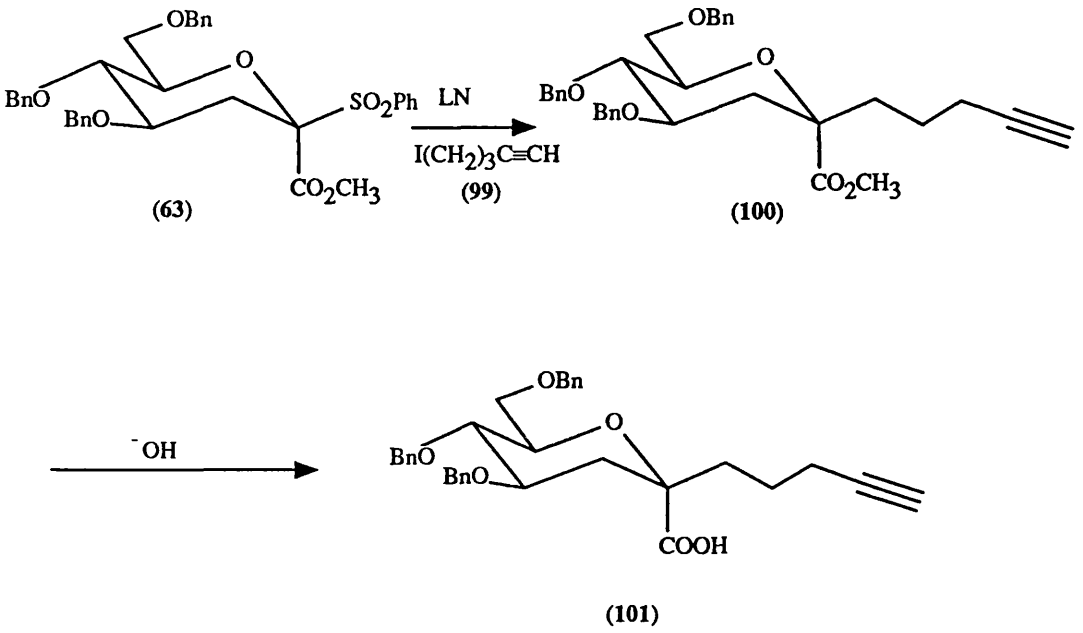


(97) (98)

2.4.1 Synthesis of ulosonic acid precursor for attempted cyclisation

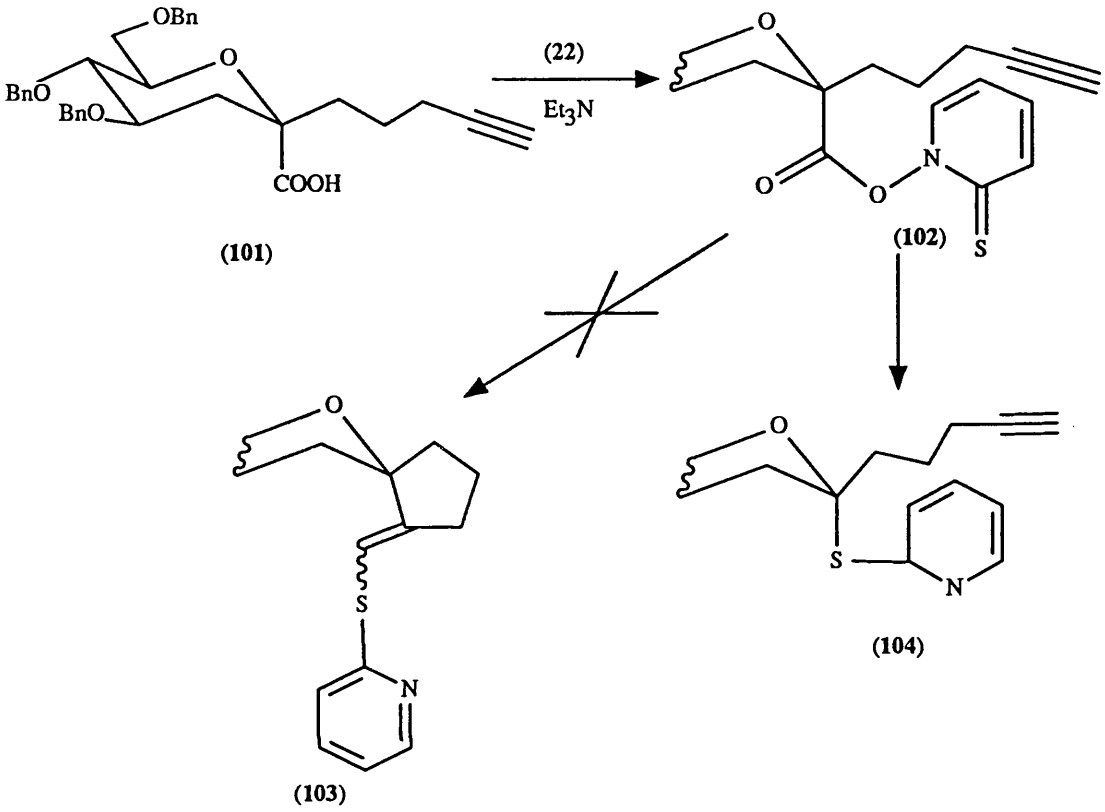
As outlined above, the approach to the synthesis of spirosystems was intended to make use of the anomeric radical generated *via* a ulosonic acid derivative. For ease of preparation a trial substrate, X = CH_2 [Scheme 29] was chosen. 5-Iodopent-1-yne (**99**), generated by Finkelstein reaction of commercially available 5-chloropent-1-yne by heating it to reflux with sodium iodide in anhydrous acetone under argon, was chosen as the electrophile for use in the desulphonylation step. In the event, reductive desulphonylation of the sulphone ester (**63**) with LN followed by quenching the anion formed with iodide (**99**) gave the product (**100**), as a single anomer, in only 26% yield. Nevertheless this ester was readily transformed into its ulosonic acid derivative by saponification with KOH giving the acid (**101**) in an excellent yield of 93% [Scheme 33].

Scheme 33



Treatment of this ulosonic acid derivative (**101**) with the heterocyclic salt (**22**) and Et_3N gave the intermediate, unisolated, *O*-acyl thiohydroxamate ester (**102**) which was subjected to photolysis at 0 °C using a 500W tungsten lamp. Work-up of the reaction mixture however did not lead to the expected cyclised product (**103**) but instead it gave complex mixture of products of which the major component was apparently sulphide (**104**) [Scheme 34].

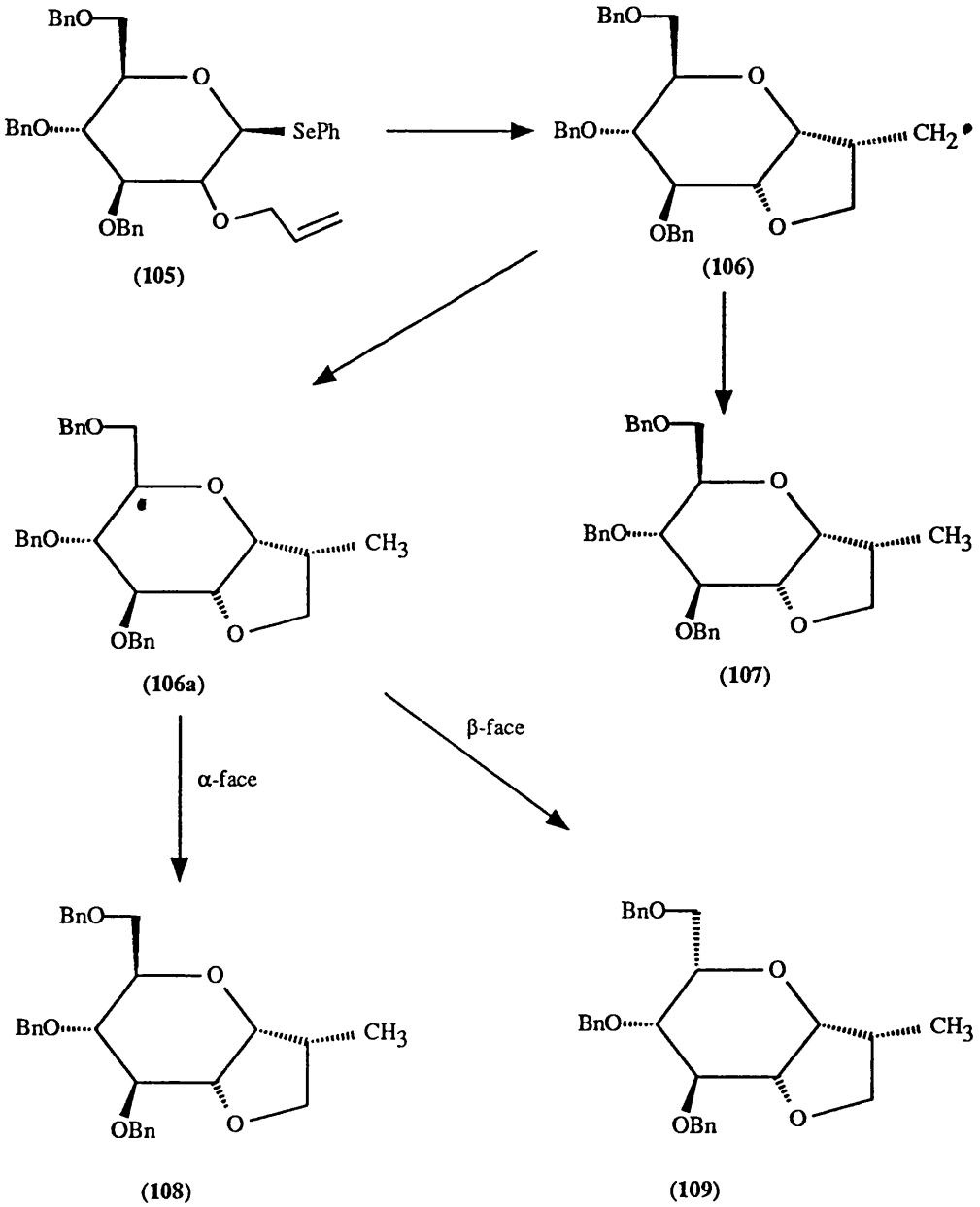
Scheme 34



This disappointing result was attributed to a relatively slow rate of cyclisation compared to the competing reaction in which the anomeric radical was quenched by the excess of *O*-acyl thiohydroxamate. At about the same time that this reaction was tried, De Mesmaeker[53] published papers on the stereoselective C-C bond formation at the anomeric centre of carbohydrates by intramolecular radical cyclisation reactions. In his paper, he highlighted the problem of 1,5-hydrogen abstraction from C-5 resulting in the scrambling of stereochemistry at this centre. Thus when phenylselenium glycoside (**105**) was treated with Bu_3SnH/AIBN in benzene heated to reflux, three cyclised products were formed,

the presence of the third unexpected product (**109**), namely the L-derivative, was rationalised in terms of an intramolecular hydrogen atom transfer from C-5 to the cyclised radical (**106**), followed by reduction of the C-5 centred radical (**106a**) by Bu_3SnH from either the β-face, resulting in product (**109**), or from the α-face giving product (**108**) [Scheme 35].

Scheme 35



Evidently a similar problem would be encountered in the system under investigation here, were it possible to overcome the inefficient cyclisation. Hence in view of this, hitherto unforseen problem, and the relatively difficult cyclisation, this particular avenue of research was abandoned.

CHAPTER 3

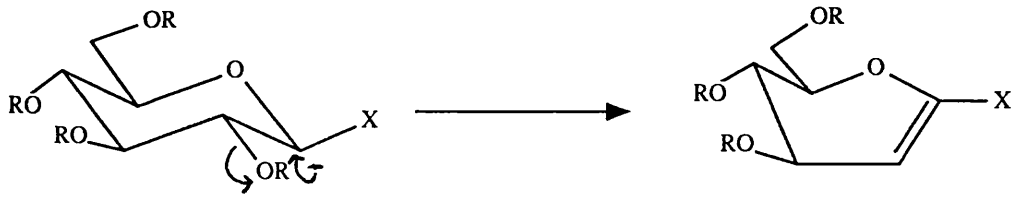
EXTENSION FROM 2-DEOXY-*C*-GLYCOSIDES

O-manno-/O-gluco-GLYCOSIDES

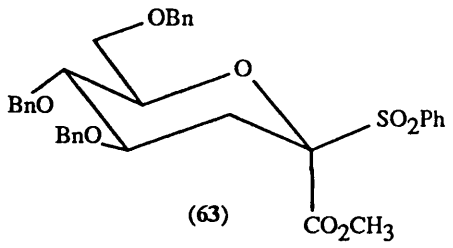
3. Extension from 2-deoxy-*C*-glycosides to *O-manno-/gluco*-glycosides

The synthesis of 2-deoxy-*O*- and 2-deoxy-*C*-glycosides *via* a free radical chain mechanism using Barton's thiohydroxamate chemistry gave excellent β-diastereoselectivity. Following these encouraging results, it was decided to extend this methodology to the synthesis of β-*O-manno*- or *gluco*-pyranosides and study the effect on the diastereoselectivity when an oxygen functionality is introduced at the C-2 position. Hence it was essential to develop an easily applicable, high yielding method of introducing an oxygen functionality at C-2 of the pyranose ring. The inclusion of an O-substituent at C-2 precludes the use of anomeric carbanions in any subsequent step owing to the possibility of elimination [Scheme 36]. Therefore the O-2 substituent must be introduced after the introduction of the 1-carbomethoxy group or otherwise a totally different strategy must be adopted.

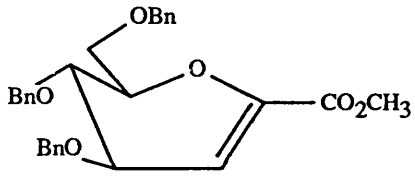
Scheme 36



Bearing in mind the facile multigram synthesis of sulphone ester (**63**) outlined in chapter 2, (**63**) was chosen as the starting material for the synthesis to be undertaken. It was envisaged that elimination of benzenesulphinic acid from sulphone ester (**63**) would provide the carbomethoxy glycal (**110**). This glycal should then undergo an appropriate addition reaction across the double bond leading to the introduction of an oxygen function at the C-2 position. In this manner the carboxyl group, which is essential in the later radical step, would then be present before introduction of the oxygen substituent, so eliminating the need for formation of an anomeric anion.



(63)

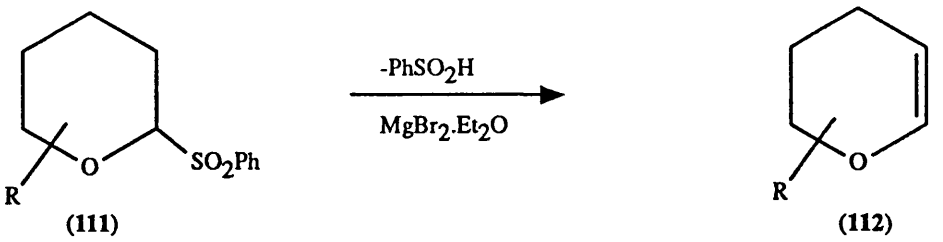


(110)

3.1. Formation of 4,5,7-tri-*O*-benzyl-1-carbomethoxy glycal (110)

Having decided on the synthetic approach, the immediate problem was to find a method of eliminating benzenesulphinic acid from the sulphone ester (**63**). Attention was turned to a report by Ley[30] whereby sulphones were displaced from 2-benzenesulphonyl cyclic ethers (**111**) using magnesium bromide etherate ($MgBr_2.Et_2O$) under ultrasonic conditions to give glycals (**112**) in 80-90% yields [Scheme 37].

Scheme 37

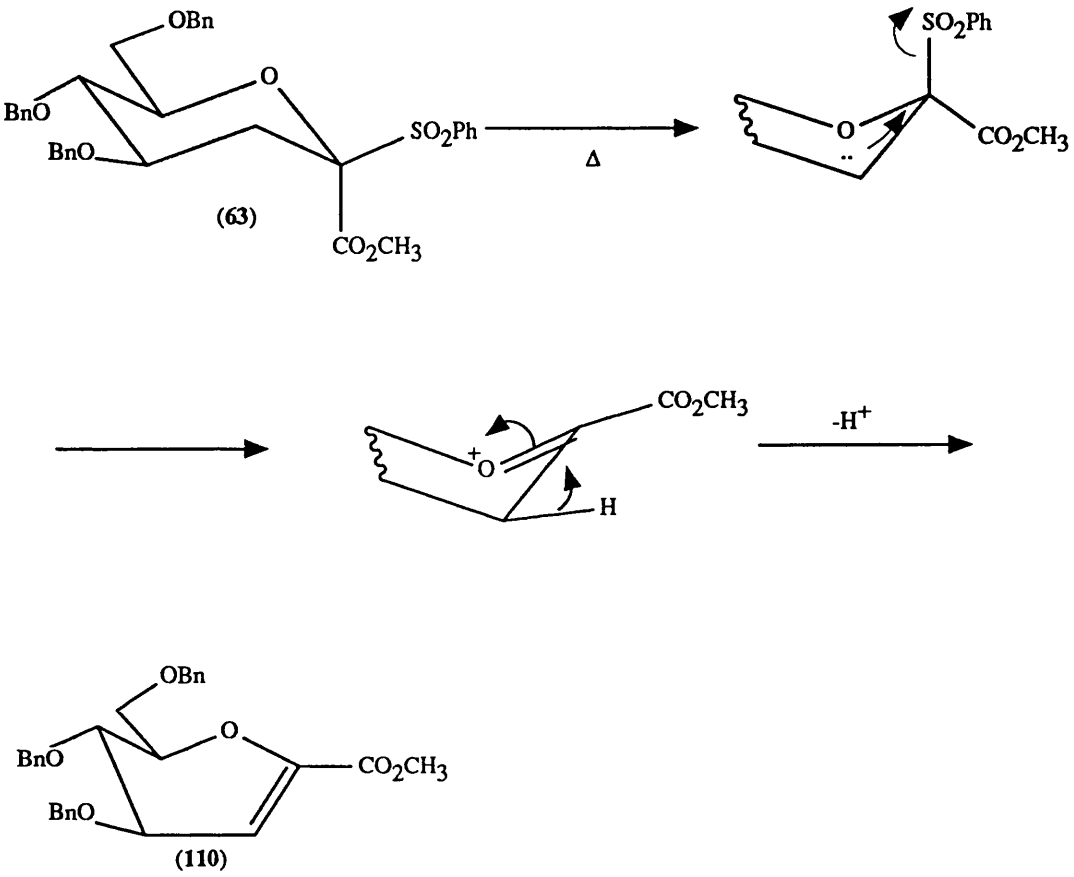


(111) (112)

Following this procedure, several attempts were made at dehydrosulphonylation of sulphone ester (**63**). Various conditions, including the use of Lewis acids ($MgBr_2.Et_2O$; $ZnCl_2$) or bases (pyridine; Et_3N; DABCO; $NaHCO_3$) in different solvents (THF; CH_2Cl_2; $CHCl_3$; C_6H_6) were employed. Ultrasonic conditions and higher temperatures were also tried. In none of these cases did the sulphone ester (**63**) undergo elimination of benzenesulphinic acid to give the glycal (**110**). The difficulties encountered in sulphone elimination step can be explained in terms of the sulphonyl leaving group occupying an equatorial site, since Ley had reported this to be a problem on related sulphone esters.

This being the case, the idea was conceived of inverting the conformation of sulphone ester (**63**) such that the equatorial sulphonyl group would adopt an axial position, anti-periplanar to a lone pair of electrons on the adjacent ring oxygen. This would facilitate the sulphone elimination and should result in the carbomethoxy glycal (**110**) being obtained [Scheme 38]. Unlike sulphones, sulphoxides do not undergo thermal *syn*-elimination with the formation of sulphenic acids. On the other hand, under various basic conditions, sulphones do undergo 1,2-elimination, giving olefins and sulphinic acids (Julia olefin synthesis).

Scheme 38



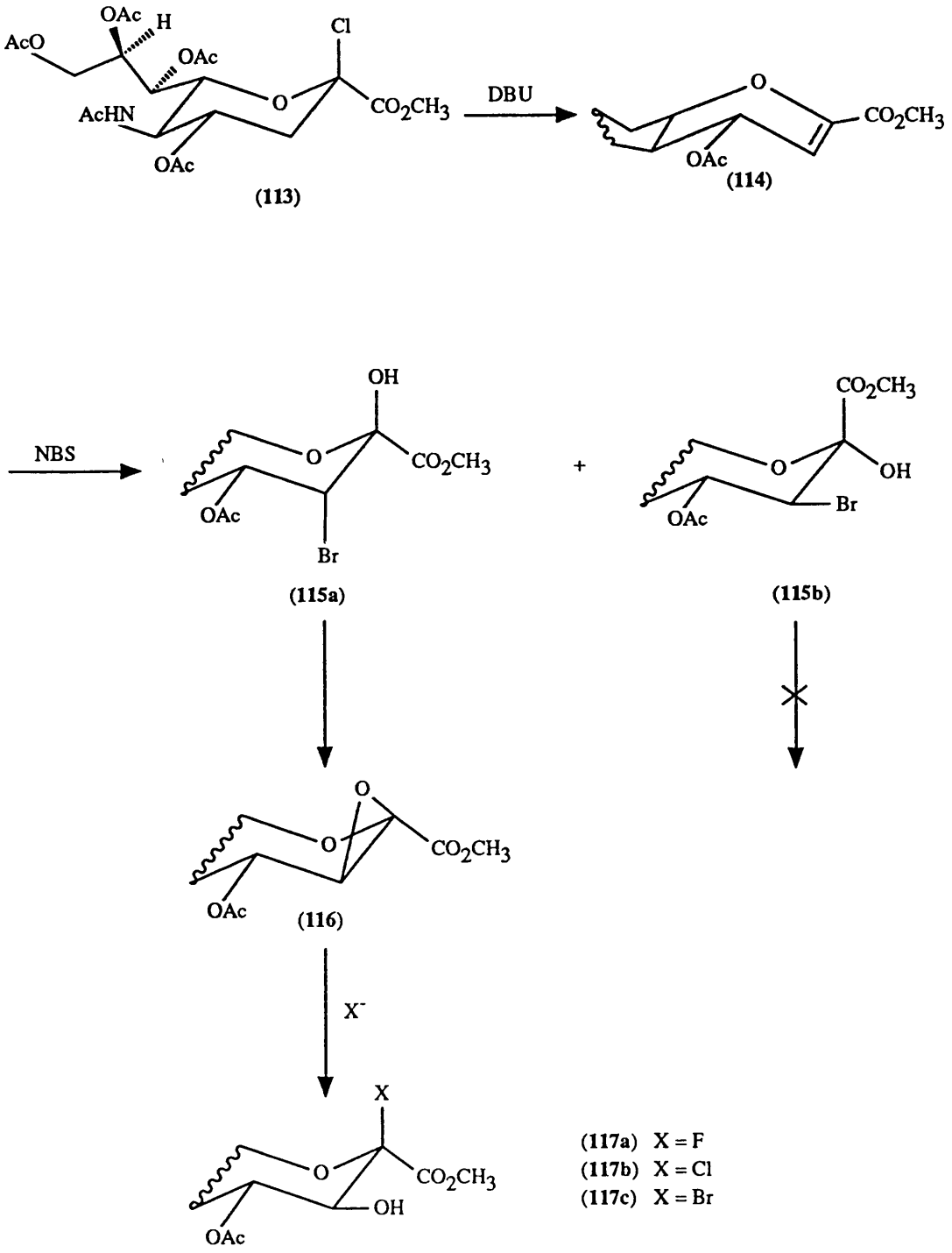
Initial attempts to pyrolyse sulphone ester (**63**) in a Kugelrohr distillation apparatus at 200 °C at 760 mmHg resulted in the decomposition of (**63**). However, a very small amount (<5% yield) of the desired product (**110**) was isolated. After various attempts to develop the method and to improve the yield, optimum conditions were obtained. The carbomethoxy glycal (**110**), previously obtained[13] only as a minor by-product from (**63**) in the course of glycosylation reactions, could now be obtained in >88% yield. The conditions involved

subjecting (**63**) to pyrolysis on 1-2 gram scale in a Kugelrohr at 200 °C at 15 mmHg in the presence of 1.2 molar equivalents of calcium oxide (CaO) for 1-2 h. The presence of CaO was found to be essential as in its absence poor yields were obtained. It probably helps to neutralise the benzenesulphinic acid formed during the course of the reaction. The product (**110**) could be crystallised from diethyl ether-petroleum (m.p. 70-71 °C), chromatographic purification not being required.

3.1.1 Introduction of an *O*-substituent at C-3

Having successfully made the glycal (**110**), the next step was to seek a method of introducing oxygen functionality across the double bond. One elegant approach reported[54] in the literature for the closely related sialic acid series involved the formation of an oxirane followed by ring opening with Lewis acids such that a nucleophilic group was introduced at the anomeric centre [Scheme 39].

Scheme 39


OAc
H
AcO
OAc
Cl
AcHN
O
CO2CH3
OAc
(113)
DBU
O
CO2CH3
OAc
(114)
NBS
OH
O
CO2CH3
OAc
Br
(115a)
+
CO2CH3
O
OH
OAc
Br
(115b)
O
O
CO2CH3
OAc
(116)
X-
X
O
CO2CH3
OH
OAc
(117a) X = F
(117b) X = Cl
(117c) X = Br

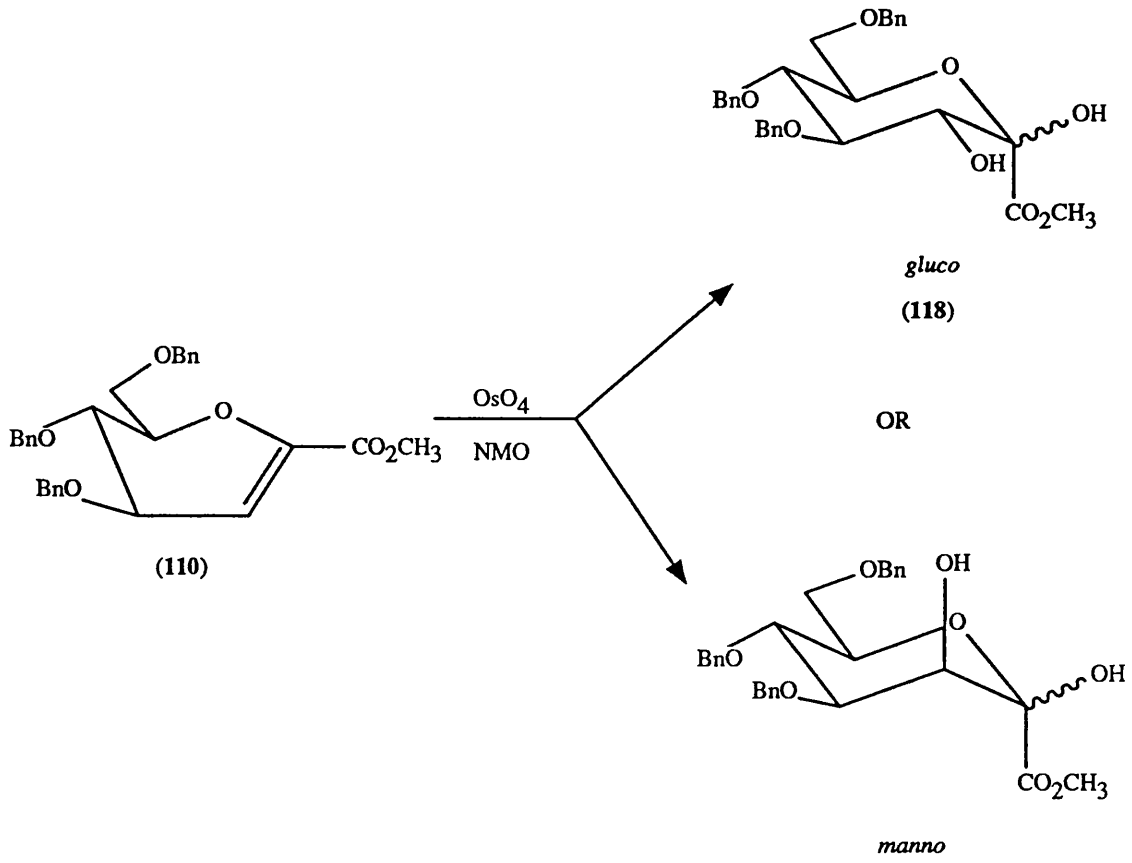
In this report, elimination of HCl from the 2-chloro derivative of the pentaacetylated neuraminic acid methyl ester (**113**) gave the corresponding tetra-*O*-acetyl-2-deoxy-2,3-dehydro-*N*-acetylneuraminic acid methyl ester (**114**). This elimination was achieved by treatment of (**113**) with 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) in benzene at room temperature followed by crystallisation of (**114**) from hexane-ethyl acetate. This product was then converted to the corresponding bromohydrins (**115a**) and (**115b**) by treatment with *N*-bromosuccinimide (NBS) in acetonitrile-water: the product ratio was found to be temperature dependent. Treatment of bromohydrin (**115a**) [the isomer (**115b**) was found to be unreactive to the conditions employed] with *N,N*-diisopropylethylamine in anhydrous acetonitrile for 4 h gave β-epoxide (**116**). This epoxide was very sensitive to Lewis acids such as boron trifluoride-ether complex ($BF_3.Et_2O$), titanium(IV) chloride ($TiCl_4$) and titanium(IV) bromide ($TiBr_4$) and when treated with these Lewis acids gave the fluoride (**117a**), chloride (**117b**) and bromide (**117c**) products respectively.

In our hands attempts at direct epoxidation of the carbomethoxy glycal (**110**) with various oxidising agents [hydrogen peroxide (H_2O_2), *t*-butyl-hydroperoxide, MMPP] failed to give any products and in all cases (**110**) was recovered unchanged. Rather than apply Goto's method of preparing bromohydrins followed by conversion into epoxides and then ring opening (a three-step synthesis leading to the *gluco*-configuration), it was decided to seek an alternative, short and simpler route to introduce a hydroxyl group at C-3 position. Hence attention was turned to dihydroxylation of the olefin bond with osmium tetroxide.

The carbomethoxy glycal (**110**) was thus subjected to *cis*-dihydroxylation[55] with a catalytic amount of osmium tetroxide (OsO_4) and *N*-methylmorpholine-*N*-oxide (NMO) as the overall oxidant. Pyridine was used to

facilitate the reaction as recommended by Criegee,[56] who observed that the rate of formation of osmium(VI) ester complexes was dramatically increased by the addition of an excess of tertiary amine. After 3 h at reflux in a THF/*t*-BuOH mixture under argon (or nitrogen), product (**118**) was obtained in >80% yield as a white crystalline solid, m.p. 97-99 °C as a single anomer, after extractive work-up and crystallisation from diethyl ether-petroleum [Scheme 40].

Scheme 40



3.1.2 Assignment of configuration of the diol (118)

Two possible configurations could arise from *cis*-dihydroxylation with OsO_4. Should the dihydroxylation take place from the β-face, the product obtained would have the *manno*-configuration. However if *cis*-dihydroxylation occurred from the α-face, the resultant product would have the *gluco*-configuration.

Kishi[57] has published an empirical rule whereby OsO_4 dihydroxylation of allylic alcohols and ethers gave preferentially the products in which the relative stereochemistry of the pre-existing hydroxyl or alkoxyl group and the adjacent newly introduced hydroxyl group is *erythro*. This stereoselectivity has been variously rationalised in terms of both steric[57] and stereoelectronic[58] effects. Brimacombe[59] has reported similar studies in the field of higher carbon sugars which support the observation. With respect to glycals, previously it had been shown that osmylation of D-glucal and its triacetate in a mixture of hydrogen peroxide and *t*-butanol followed by acetylation gave, with high selectivity, pentaacetyl-D-glucose: an observation which is in accordance with Kishi's rule. Similarly, *cis*-hydroxylation on D-galactal[60] occurred as predicted by this rule. Sharpless oxyamination[61] of (**57**) with OsO_4 and chloroamine-T provides a mixture of regioisomeric products, all of which have the *gluco*-configuration. Thus, product (**119**) would be predicted to undergo *cis*-dihydroxylation from the α-face resulting in the *gluco*-configuration (**118**).

Normally it would be possible to assign the configuration based on the coupling constants (J) of the proton at C-3. In the *manno* series, the H-3 would be in an equatorial position. Due to its equatorial-axial orientation with respect to H-4, the vicinal coupling to H-4 ($J_{3,4}$) would be expected to be small. In the case where the product has the *gluco*-configuration, H-3 would be axially placed and

the *trans* diaxial orientation with respect to H-4 would result in a large vicinal coupling of the order of 10-13 Hz. Unfortunately, the assignment of configuration from the high field ^1H nmr spectrum of (**118**) proved to be difficult owing to insufficient resolution of the H-3 signal from other ring protons and coupling to hydroxyl groups. However on the basis of subsequent correlation with known compounds, the diol (**118**) was assigned the *gluco*-configuration (***vide infra***).

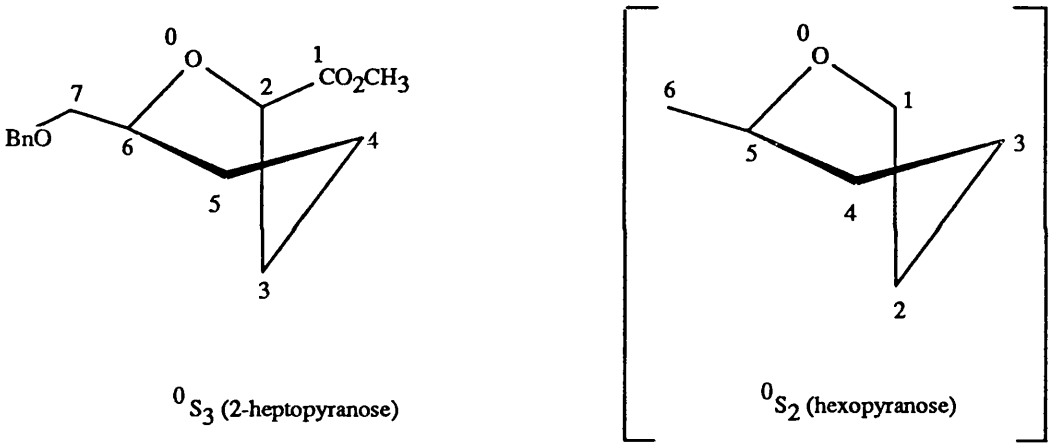
3.2 Formation of acetonide derivative (119)

Initially, in order to simplify the ^1H nmr spectrum by removal of coupling to the hydroxyl proton, means of protecting the diol were sought. Benzylation of the hydroxyl group failed (NaH, DMSO, BnCl led to destruction of products) and eventually attention was turned to the formation of an acetonide. Standard acetonylation conditions were tried. The diol (**118**) was subjected to various azeotropic reaction conditions (C_6H_6/ acetone/ camphor-10-sulphonic acid; C_6H_6/ 2,2-dimethoxypropane/ *p*-toluenesulphonic acid) and acetonation in the presence of *p*-toluenesulphonic acid. In all cases, the diol (**118**) was recovered unchanged. However when (**118**) was heated to reflux in 2,2-dimethoxypropane in the presence of *p*-toluenesulphonic acid the acetonide (**119**) was obtained in <30% yield. After various attempts to improve the yield, a successful method was developed. This involved cooling a solution of the diol (**118**) in dry toluene and 2,2-dimethoxypropane to 0 °C followed by careful bubbling of a slow stream of HCl gas into the reaction mixture for 5 min, with careful monitoring of the reaction by t.l.c.. In this manner the desired product (**119**) was obtained in 76% yield.

3.2.1 Assignment of conformation of acetonide derivative (119)

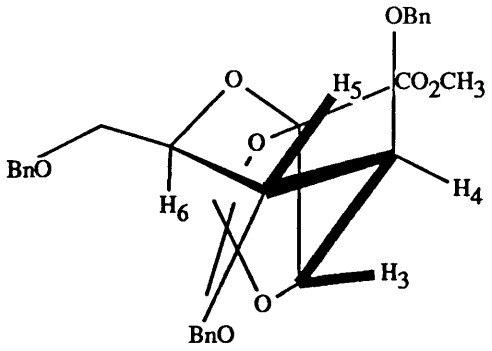
In view of the generally observed preference for acetonide formation under thermodynamic conditions to go *cis* whenever possible, the acetonide was assigned the *cis*-configuration. Careful study of the ^1H nmr spectrum of (**119**) led to the conclusion that the conformation was best interpreted[62] in terms of a twist boat conformation ($^0S_3$) [Diagram 1].

Diagram 1



This conformation is indicated by the relatively small vicinal couplings between protons 3-4 and 4-5 ($J_{3,4}$ = 1.8 Hz and $J_{4,5}$ = 1.8 Hz) together with the large vicinal coupling between protons 5-6 ($J_{5,6}$ = 9.5 Hz). Especially indicative is the presence of a four-bond W-coupling between protons 3 and 5 ($J_{3,5}$ = 1 Hz) which requires the near coplanarity of H-3 and H-5 [Diagram 2].

Diagram 2



W coupling $J_{3,5} = 1$ Hz

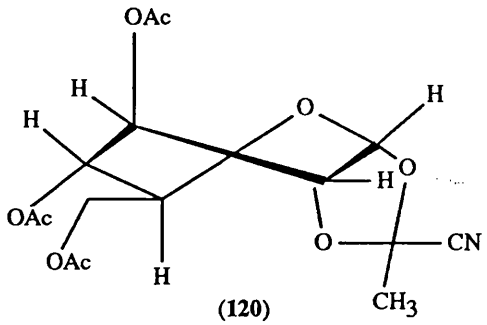
$J_{3,4} = 1.8$ Hz

$J_{4,5} = 1.8$ Hz

$J_{5,6} = 9.5$ Hz

In support of this hypothesis, the orthoester 3,4,6-tri-*O*-acetyl-1,2-*O*-(1'-cyanoethylidene)-α-D-glucopyranose **(120)** is reported[63] to exist in a twist boat conformation [Diagram 3] also on the basis of nmr spectroscopic evidence.

Diagram 3



(120)

$J_{2,3} = 2.7$ Hz

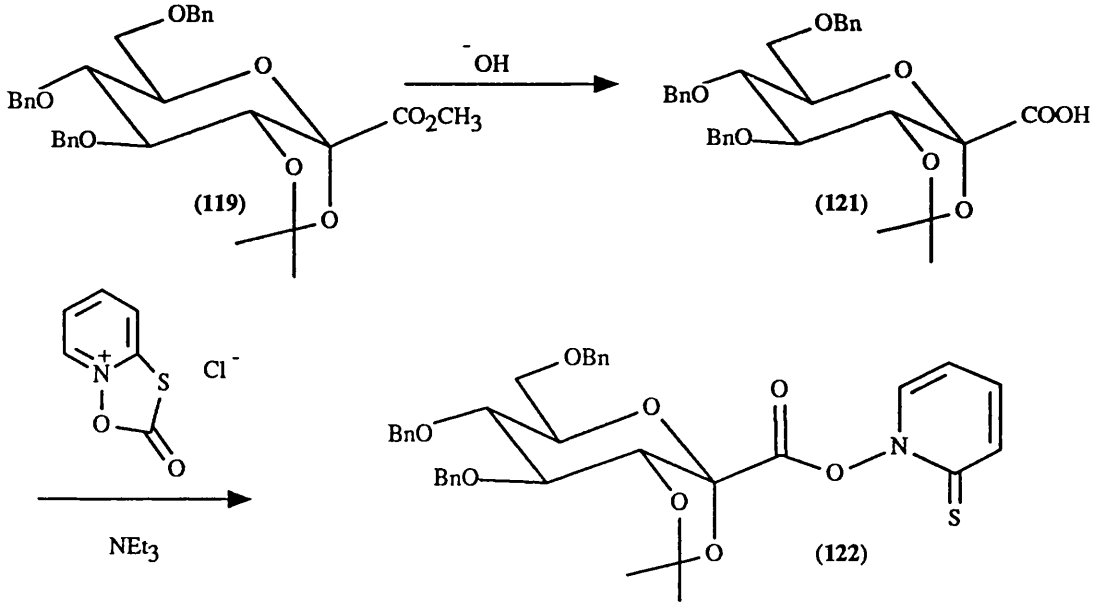
$J_{3,4} = 2.5$ Hz

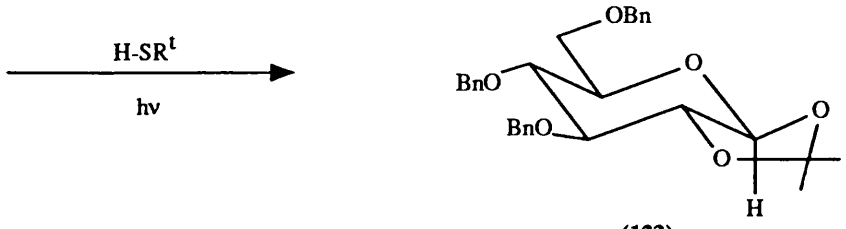
$J_{4,5} = 9.0$ Hz

3.2.2 Reductive decarboxylation *via* thiohydroxamate chemistry

On saponification with KOH the isopropylidene derivative (**119**) gave the corresponding acid (**121**) in good yield (89%). This acid (**121**) was not purified but used immediately in the following reductive decarboxylation step. Treatment of (**121**) with the heterocyclic salt (**22**) and Et_3N under argon in the dark gave the intermediate *O*-acyl thiohydroxamate ester (**122**). This ester (**122**), on treatment with 5 molar equivalents of *t*-dodecylmercaptan followed by photolysis [Scheme 41] with a 500W tungsten lamp at 0 °C, yielded a single white crystalline product in 76% yield with m.p. 55 °C and $[\alpha]_D = +39.4°$ (c = 1, $CHCl_3$).

Scheme 41





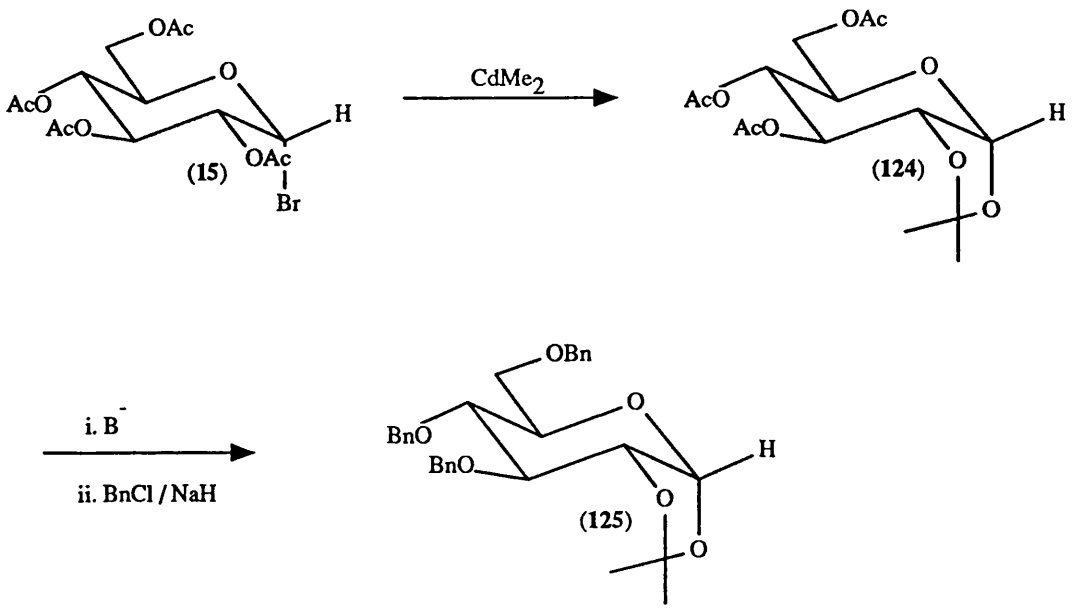
(123)

3.2.3 Assignment of configuration of (123)

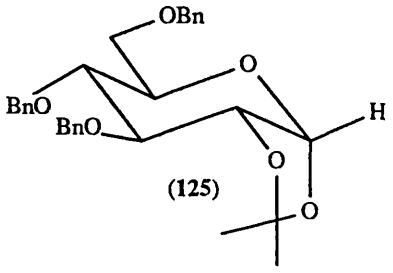
The anomeric proton was easily identified from the ^1H (400 MHz) nmr spectrum and was well separated from the other ring protons. The anomeric proton, coupled to H-2, appeared as a doublet at δ 5.65 with $J_{1,2}$ = 4.88 Hz. At first sight this small vicinal coupling was indicative of an α-*gluco*- or β-*manno*-configuration.

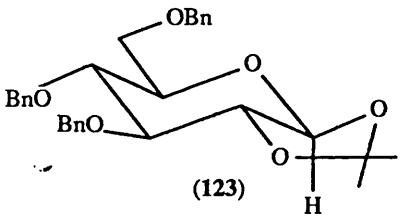
The α-*gluco*-isopropylidene derivative (**125**) has been synthesised by Boullanger.[64] In his report, 2,3:4,6-tetra-*O*-acetyl-α-bromo-*gluco*-pyranoside (**15**) was transformed into tri-*O*-acetyl-1,2-isopropylidene-D-*gluco*-pyranose (**124**) by treatment with dimethylcadmium. Saponification of (**124**) followed by benzylation gave the 3,4,6-tri-*O*-benzyl-1,2-isopropylidene-α-D-*gluco*-pyranose (**125**) in 80% yield [Scheme 42]. This isopropylidene derivative (**125**) was obtained as a white crystalline solid with m.p. 71 °C and $[\alpha]_D^{20}$ = +37.3° (c = 2.9, $CHCl_3$). Comparison of the physical data of (**123**) and (**125**) [see below] ruled out the possibility of (**123**) being the α-*gluco*-product (**125**).

Scheme 42



Physical data of (123) and (125)

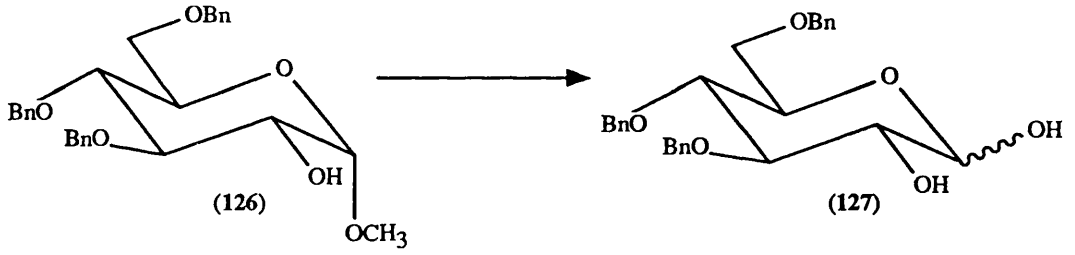




m.p. 71 °C	m.p. 55 °C
$[\alpha]_D^{20} = +37.3°$	$[\alpha]_D^{20} = +39.4°$
(c = 2.9; $CHCl_3$)	(c = 1; $CHCl_3$)
δ (H-1) 5.64	δ (H-1) 5.65
δ (H-2) 4.49	δ (H-2) 4.27
$J_{1,2} = 4.6$ Hz	$J_{1,2} = 4.88$ Hz
$J_{2,3} = 9.8$ Hz	$J_{2,3} = 3.79$ Hz

Having ruled out the possibility of the product (**123**) having the α-*gluco*-configuration, three other possibilities remained:- (**123**) could have the α- or β-*manno*-configurations or the β-*gluco*-configuration. A search through the literature revealed the known tri-*O*-benzyl-D-glucose derivative[65] (**127**) with which (**123**) might be correlated. This compound (**127**) had been prepared by heating methyl 3,4,6-tri-*O*-benzyl-α-D-glucoside (**126**) in 60% formic acid to 100 °C for 12 h followed by extractive work-up and crystallisation from ethanol as a white crystalline solid [Scheme 43] with m.p. 85-87 °C and $[\alpha]_D^{22}$ = +71° (2 min) to + 65° (24 h) (c = 1.1, 0.1% 2-pyridone in $CHCl_3$).

Scheme 43



Thus, deprotection of the acetonide (**123**) to the diol (**127**) and comparison of this product obtained with the known literature product would enable the unambiguous assignment of *manno*- or *gluco*-configuration. The deprotection of (**123**) was carried out by treatment with 2M HCl [Scheme 44]. Product (**127**), obtained as a white crystalline solid, m.p. 88-90 °C and $[\alpha]_D^{20}$ = +58° (c = 0.9, $CHCl_3$), existed as a mixture of anomers (α:β = 1:2) as determined by ^1H nmr spectroscopy. Another group has reported a closely related experiment

whereby acid hydrolysis of 3,4,6-tri-*O*-benzyl-1,2-isopropylidene-α-D-*gluco*-pyranose (**125**) gave white crystalline 3,4,6-tri-*O*-benzyl-D-*gluco*-pyranose[66] with m.p. 85-86 °C and $[\alpha]_D$ = +57.1° (c = 0.9, $CHCl_3$). The physical properties of (**127**) [see below] were very similar to those of the known *gluco*-pyranose. Unfortunately, in the ^1H (400 MHz) nmr spectrum, the signal for H-2 overlaps with other signals from the ring protons, giving insufficient resolution for the measurement of the all important coupling constant, $J_{2,3}$, to be determined.

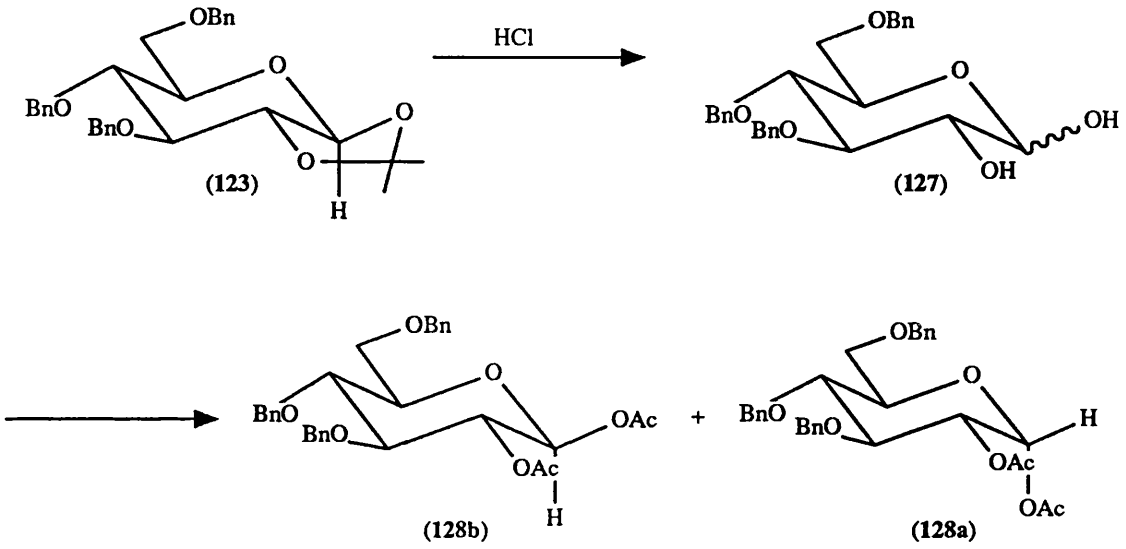
Physical data of (127) and the literature known tri-*O*-benzyl-D-glucose.

Lit. data	**(127)**
m.p. 85-86 °C	m.p. 88-90 °C
$[\alpha]_D$ = +57.1°	$[\alpha]_D$ = +58°
(c = 0.9; $CHCl_3$)	(c = 0.9; $CHCl_3$)

Although at this stage the physical constants of product (**127**) appeared to correspond to those of the *gluco*-derivative, further investigation was nevertheless still required for the unambiguous identification of configuration. The $J_{2,3}$ values would enable the assignment of configuration to be finalised. Hence the two hydroxyl groups of (**127**) were acetylated thereby resulting in the downfield shift of H-2 in the ^1H nmr spectrum and so enabling studies of $J_{2,3}$ value to be made. The acetylated product (**128**) was obtained as a mixture of anomers (α:β =

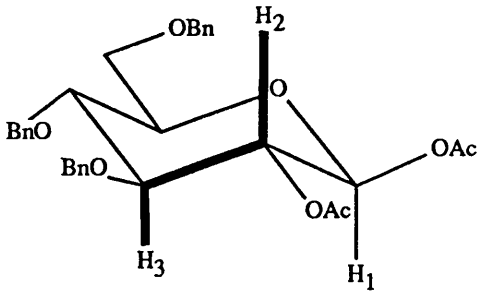
1:2) [Scheme 44].

Scheme 44



From its high field ^1H nmr spectrum, the H-2 (δ 5.1) of the β-anomer (**128b**) appeared as a double-doublet ($J_{2,1}$ = 8.23 Hz and $J_{2,3}$ = 9.4 Hz) which is indicative of the *trans* diaxial orientations of H-2 to H-1 and H-3 respectively. On the other hand, in the α-anomer (**128a**) H-2 (δ 5.03), again a double-doublet, has both a small ($J_{2,1}$ = 3.55 Hz) and a large ($J_{2,3}$ = 10 Hz) vicinal coupling. In both the anomers, $J_{2,3}$ couplings are large (9.4 Hz and 10 Hz) and this can only be attributed to the H-2 adopting an axial position with *trans* diaxial orientation to H-3. Therefore the acetate group at C-2 adopts an equatorial position corresponding to the *gluco*-configuration [Diagram 3].

Diagram 3

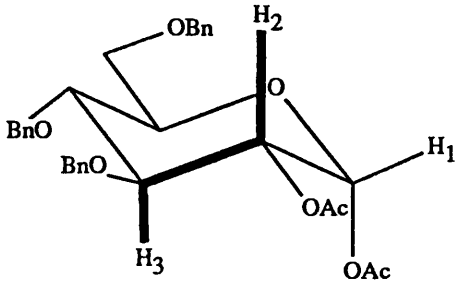


(128b)

δ 5.1 (dd)

$J_{2,1}$ = 8.23 Hz

$J_{2,3}$ = 9.4 Hz



(128a)

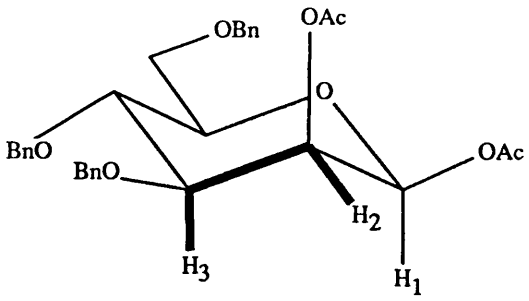
δ 5.03 (dd)

$J_{2,1}$ = 3.55 Hz

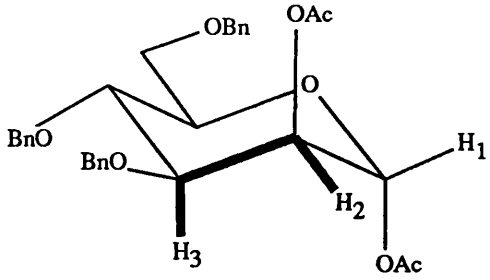
$J_{2,3}$ = 10 Hz

In the case where (**128**) would have the *manno*-configuration [Diagram 4] then $J_{2,3}$ would be of smaller magnitude for both α- and β-anomers due to the now equatorially placed H-2. It can therefore be stated categorically that osmium tetroxide dihydroxylation of the carbomethoxy glycal (**110**) takes place with very high selectivity, in accordance with Kishi's rule, to give the *gluco*-anomer.

Diagram 4



β-*manno*



α-*manno*

3.2.4 Comment

Based on the various evidence above, the isopropylidene derivative obtained on decarboxylation of (**122**) is therefore identified as the 1,2-*O*-isopropylidene-β-D-*gluco*-pyranose (**123**). This is an observation worthy of comment. Firstly, in carbohydrate chemistry and under thermodynamic equilibrating conditions isopropylidene derivatives fused to six-member rings take up preferentially the *cis*-configuration whenever possible.[67] Special conditions have to be adopted for the formation of the *trans*-isomers. Although several 2,3-*trans*-*O*-isopropylidene *gluco*-pyranose derivatives have been prepared,[68] we know of no previous examples of 1,2-β-*O*-isopropylidene-*gluco*-derivatives.

Secondly, the stereoselectivity observed in the radical reaction was extreme; the preference for axial quenching of the σ-radical therefore outweighs any preference for the formation of the more stable *cis*-acetonide.

Thirdly, the coupling constant between H-1 and H-2, $J_{1,2}$, is somewhat small in view of the *trans* diaxial nature of the two protons involved. A

significantly distorted conformation, as well as the effect of the two electronegative substituents on C-1,[69] needs to be invoked to explain this observation.

Application of the standard Karplus equation[38] [Equation 1] with the correct parameters for the dihedral angle, ϕ, between 90° and 180° for the coupling constants $J_{1,2}$, $J_{2,3}$, $J_{3,4}$ and $J_{4,5}$ for compound (**123**) leads to the dihedral angles given in the table below [Table 6; column 3].

Equation 1

$$^3J_{(H\text{-}H)} = J\cos^2\phi - 0.28$$

Clearly, given the *trans*-fused nature of the system the dihedral angle of 138° predicted for H_1-C-C-H_2 is impossibly small. However various modifications of the Karplus equation have been made with a view to taking into account the effect of electronegativity.[70, 71, 72] Vorontsova and Bochkov[71] derived a series of equations and used them to calculate dihedral angles in rigid carbohydrate orthoesters (not susceptible to conformation change on passing from solid to solution phase) for comparison with actual angles taken from X-ray crystallographic data. In particular, Equation 2, which uses the sum of the chemical shifts of the coupled spins (δ scale ppm:- parameter Y) as an indirect measure of the chemical environment and hence of the electronegativity of the substituents, was found to give good results.

Equation 2

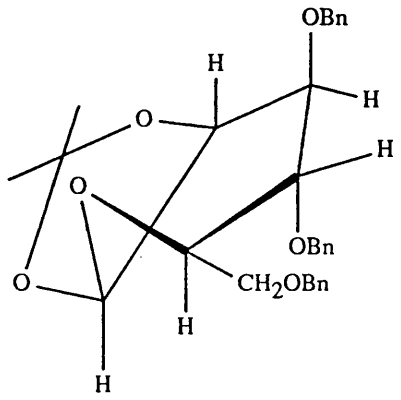
$$^3J_{(H\text{-}H)} = 0.43Y + \cos^2\phi(22.36 - 1.94Y) - 2.28$$

Application of equation 2 to the measured values of $J_{1,2}$, $J_{2,3}$ and $J_{3,4}$ [Table 6; column 4] gave a much more realistic value for dihedral angle H_1-C-C-H_2 of 164° but only changes the other dihedral angles a little.

Table 6

Spin System	Measured Coupling Constants of H-2	Calculated Φ Karplus	Bochkov
$J_{1,2}$	5	138	164
$J_{2,3}$	3.8	131	129
$J_{3,4}$	4.8	137	128
$J_{4,5}$	9.6	180	-

On this basis, we assign the *trans*-acetal (**123**) to the $^3S_1$ twist boat conformation.

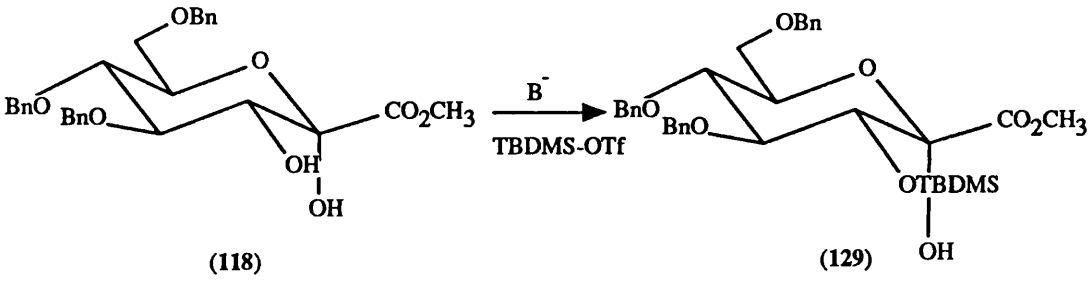


Following the encouraging observation of excellent diastereoselectivity for the isopropylidene derivative, attention was turned to the possibility of coupling the *O*-glycoside (**118**) to an alcohol (R-OH). It was hoped that by coupling (**118**) to R-OH followed by reductive decarboxylation *via* the thiohydroxamate free radical chemistry, a new entry into a highly diastereoselective synthesis of β-glucoside linkages in disaccharides (where R-OH is another sugar unit) would result.

3.3 Synthesis of glycosyl donor

In order for (**118**) to act as a glycosyl donor in coupling reactions the anomeric centre has to be activated and hence the hydroxy group at the C-2 position has to be selectively protected. The protecting group employed evidently needs to withstand the various chemical conditions of the subsequent steps. As mentioned previously, benzylation failed. Attention was turned to the use of a trialkylsilyl group as the protecting group. Silylation with *tert*-butyldimethylchlorosilane in dry dimethyl formamide (DMF) under nitrogen in the presence of imidazole heated to reflux gave very poor yield (<10%) after 3 days with the remainder being the unreacted starting material. Use of the more reactive *tert*-butyldimethylsilyl triflate[73] (TBDMS-OTf) in dichloromethane in the presence of 2,4,6-collidine under argon, however, resulted in extremely rapid reaction with the isolation of the silyl ether (**129**) in >97% yield after 5 min at room temperature [Scheme 45]. Use of excess silylating agent and longer reaction times brought about silylation of the more hindered anomeric hydroxyl group.

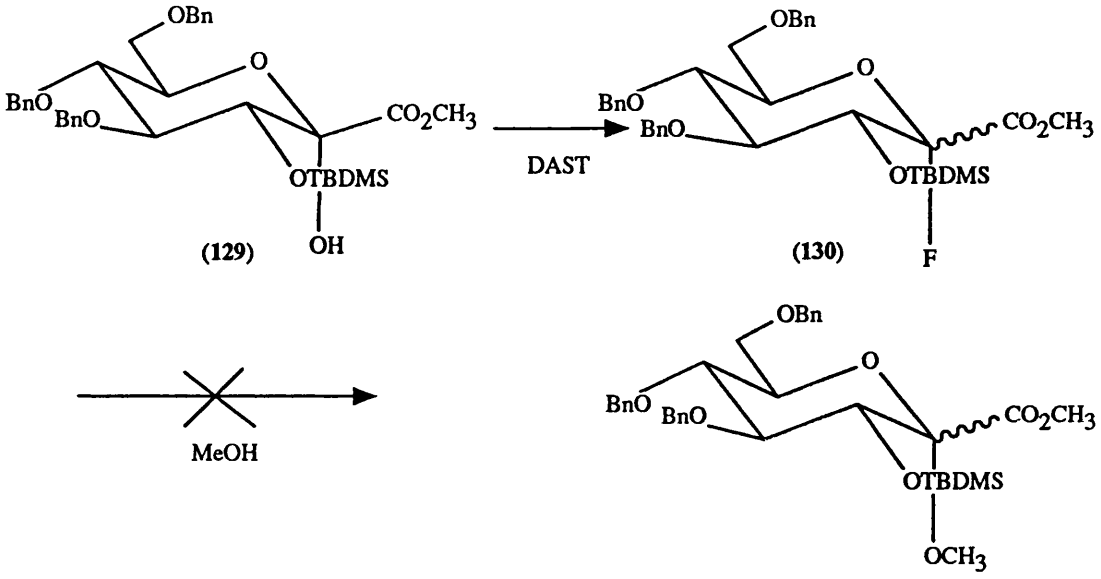
Scheme 45



(118) (129)

Having protected the OH at the C-2 position, the next step was to find a method of activating the anomeric centre. In view of recent reports on the preparation of sialic acid glycosides *via* the glycosyl fluorides,[74] activation as the fluoride was attempted. This was achieved by treatment of (**131**) with diethylaminosulphur trifluoride[75] (DAST) in dry CH_2Cl_2 at 0 °C under nitrogen. The anomeric hydroxyl group was cleanly replaced by a fluoride atom and product (**130**) was obtained as a mixture of anomers (1:3 ; β:α) in 94% yield [Scheme 46]. It is of interest that the silyl-protected hydroxyl group at C-2 was not affected by the use of DAST. Usually, the TBDMS-group is easily cleaved by fluoride (e.g. the use of tetra-n-butylammonium fluoride, TBAF, as a silyl deprotecting reagent) but under the conditions employed above, the TBDMS-group remained intact.

Scheme 46



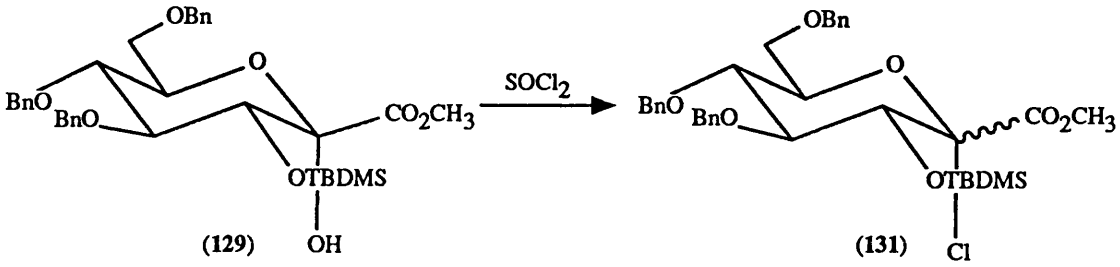
3.3.1 Coupling to R-OH (Methanol)

Unfortunately, although the glycosyl fluoride derivative (**130**) was obtained in excellent yield, the compound proved to be too stable and would not undergo coupling to an alcohol. Various reaction conditions were investigated. The use of different reagents ($SnCl_2$; $AgClO_4$; $BF_3.Et_2O$; AgCl; TBDMS-OTf; AgOTf; $MgBr_2.Et_2O$; SbF_5; $ZrCp_2Cl_2$) in different solvents and under various conditions gave in all cases the recovered fluoride (**130**). Hence, another method had to be sought. It was hoped that, by replacing the fluoride by a chloride, a less stable glycosyl chloride (**131**) would be formed which would then undergo a coupling reaction to an alcohol.

The preparation of the glycosyl chloride (**131**) was carried out by the treatment of compound (**129**) with thionyl chloride [Scheme 47]. Again, the

reaction proceeded very cleanly and rapidly and was complete within 5 min. The chloride (**131**) was obtained in 97% yield as a mixture of anomers (1:3 ; β:α).

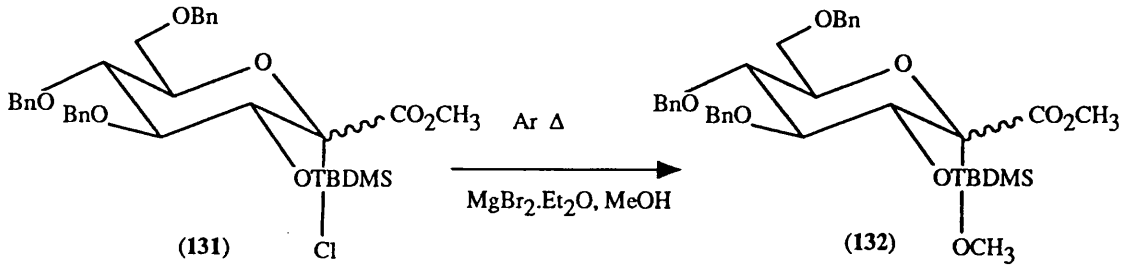
Scheme 47



(129) (131)

The glycosyl donor (**131**) was then coupled to the representative alcohol, methanol. After various attempts, optimum conditions were found in which the chloride (**131**) was heated to reflux with 5 molar equivalents of $MgBr_2.Et_2O$ in a mixture of dry 1,4-dioxan and methanol containing crushed 4Å molecular sieves under argon. The product (**132**) was obtained as separable anomers (α:β = 3.4:1) in >80% yield [Scheme 48].

Scheme 48



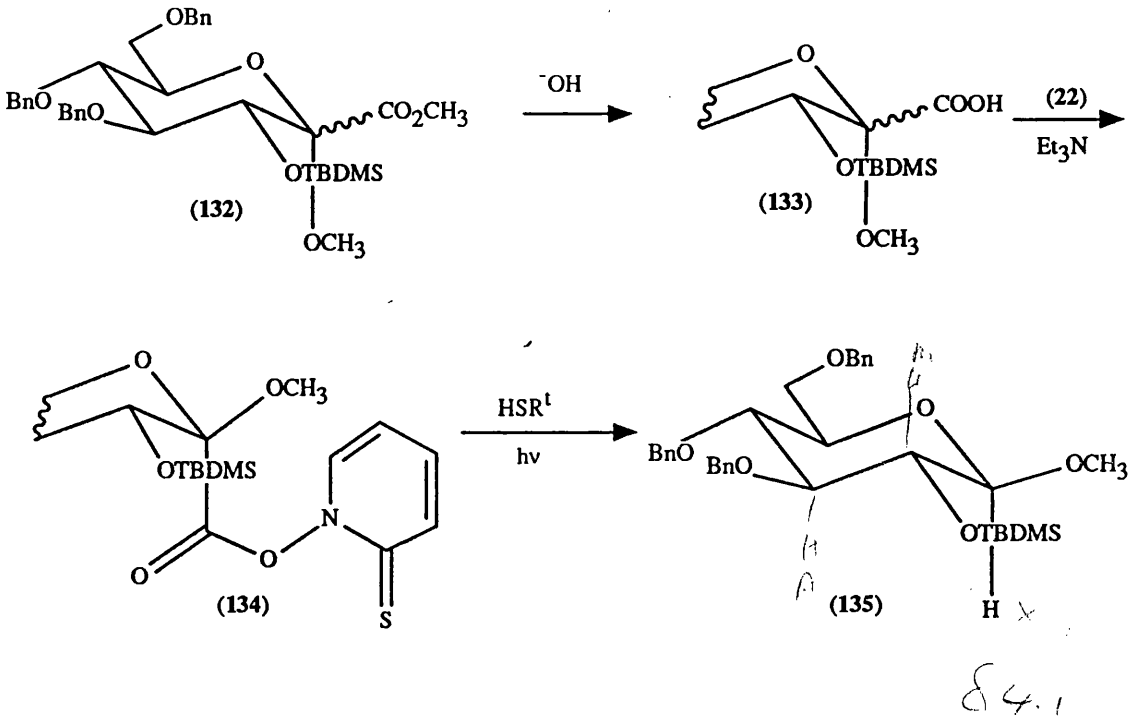
(131) (132)

The assignment of configurations of the products (**132a**) and (**132b**) was not carried out. However, based on the anomeric effect principle, the α-OCH_3 product (**132a**) would be the preferred configuration due to greater stabilisation through orbital interactions. Hence the α-OCH_3 anomer (**132a**) would be formed preferentially. On this basis, the major product would be most likely to be the α-product.

3.3.2 Reductive decarboxylation *via* thiohydroxamate chemistry

Saponification (KOH; MeOH; THF; H_2O at room temperature) of (**132a**) and (**132b**) as a mixture of anomers (4.2:1) gave the corresponding acid derivative (**133**) in 80% yield. No attempts at purification were made. The crude acid (**133**) was subjected to the reductive decarboxylation method using heterocyclic salt (**22**) to form the intermediate *O*-acyl thiohydroxamate ester (**134**). This ester was not isolated but subjected to photolysis with *t*-dodecylmercaptan at 0 °C for 1 h. Purification by column chromatography led to the isolation of product (**135**) in 60% yield as a single anomer [Scheme 49].

Scheme 49

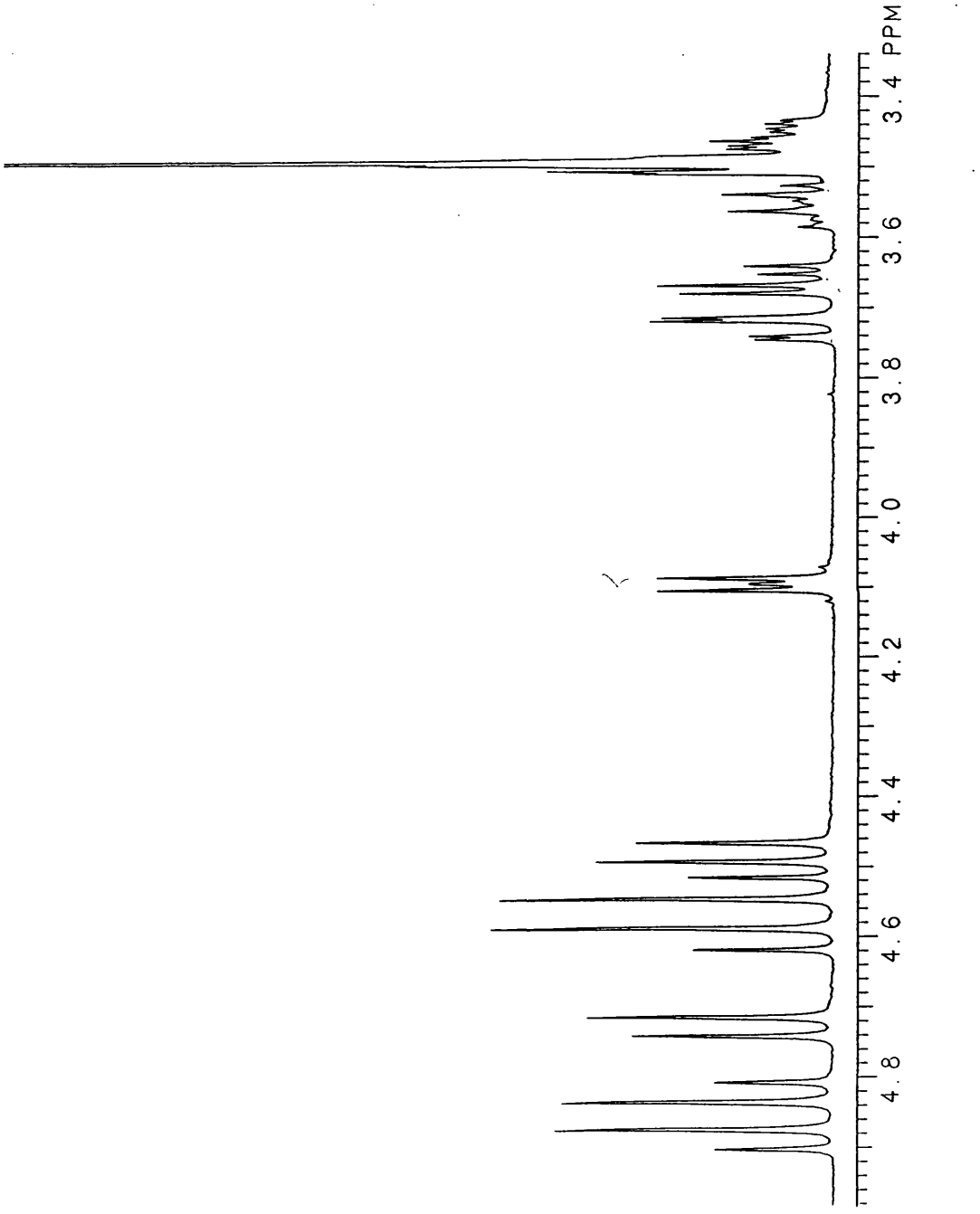


3.3.3 Assignment of configuration of (135)

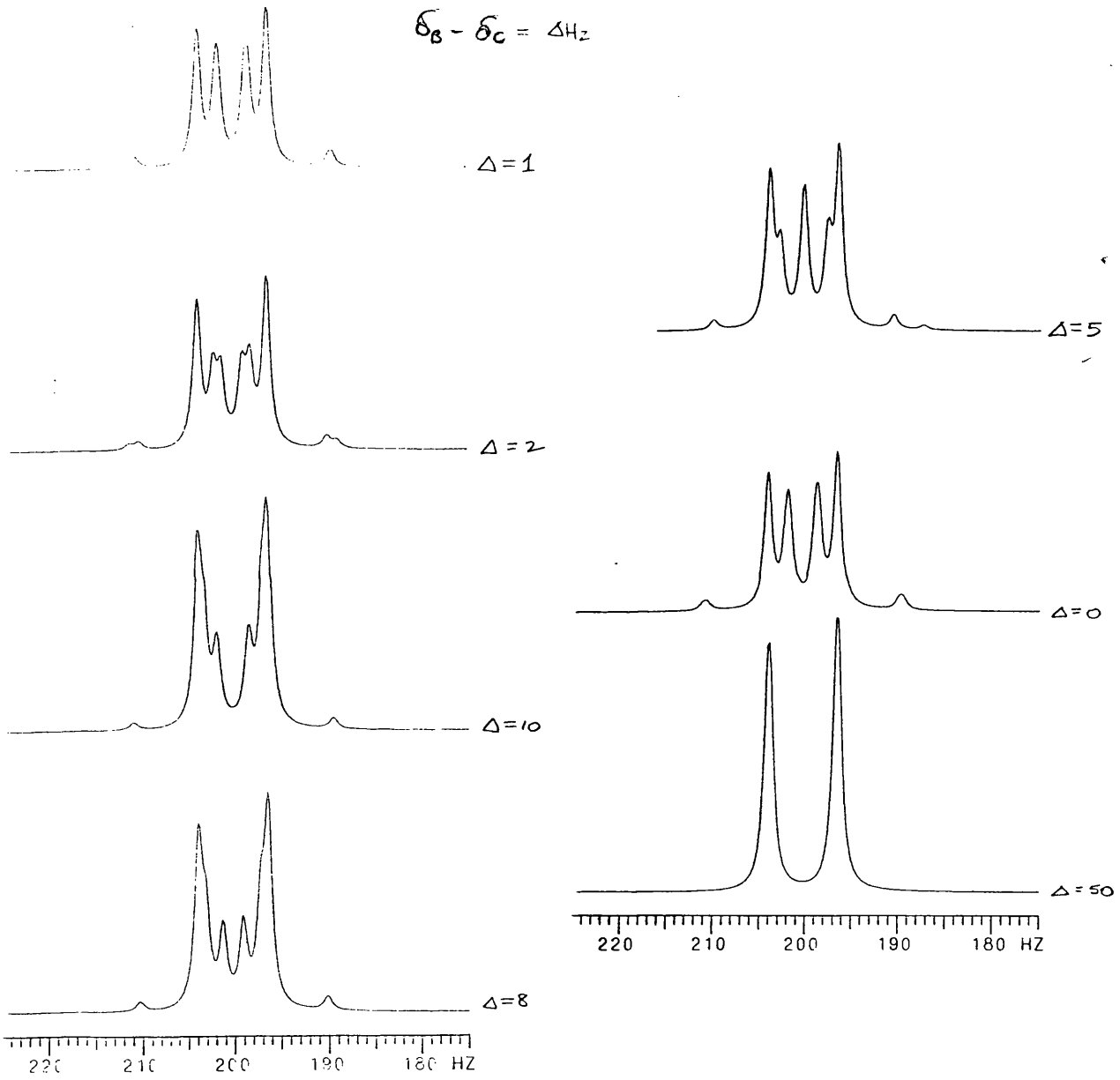
The high field nmr spectrum of (**135**) in $CDCl_3$ showed a very unusual splitting pattern for the anomeric proton at δ 4.1 ppm and this pattern was shown to vary with temperature. After consultation with Dr. G. Williams of this department, this unusual multiplet was ascribed to the phenomenon of "virtual coupling" whereby the spectrum is complicated by the very close chemical shifts of the protons at C-2 and C-3 and so first order coupling is not observed. To verify this assumption, Dr. Williams simulated, using the Varian VXR 400 instrument, the multiplicity of the anomeric proton using similar coupling constants for $J_{1,2}$, $J_{2,3}$ and $J_{3,4}$ and varying the differences in chemical shifts. As can be seen from the simulations, that derived from a chemical shift difference of 5 Hz and coupling

constants of $J_{1,2}$ = 7.5 Hz, $J_{2,3}$ = 9.0 Hz and $J_{3,4}$ = 9.0 Hz (all other J = 0 Hz) corresponds well with the experimental observations.

Observed spectrum

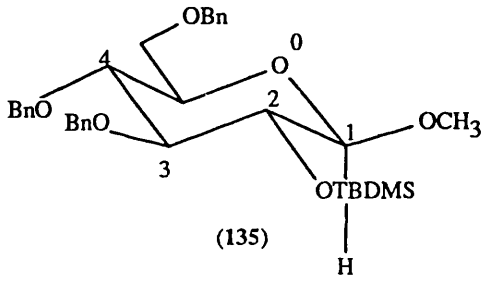


Simulated spectra



Further confirmation of the axial nature of the newly introduced proton was sought by the classical procedure of changing the nmr solvent with a view to obtaining a better dispersion of chemical shifts and so first order coupling. In d_8-toluene the anomeric proton had a chemical shift of δ 4.15 ppm and was a simple first order doublet with $J_{1,2}$ = 7.52 Hz, corresponding to a dihedral angle of approximately 180°. It can therefore be stated categorically that the product obtained from the radical reaction is the β-anomer and that it exists predominantly in the $^4C_1$ conformation [Diagram 5].

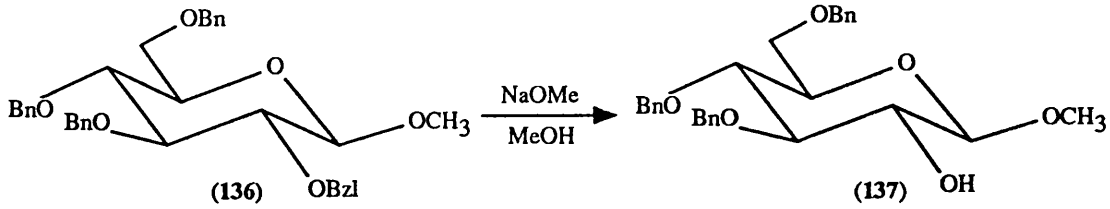
Diagram 5



(135)

As a further proof, (**135**) was correlated with the known β-methyl glucoside (**137**), prepared in the literature[76] by the saponification of methyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-glucoside (**136**) (NaOMe; MeOH) [Scheme 50], and here by desilylation of (**135**) with TBAF [Scheme 51]. As can be seen from the table below [Table 7], excellent correlation was found.

Scheme 50



Scheme 51

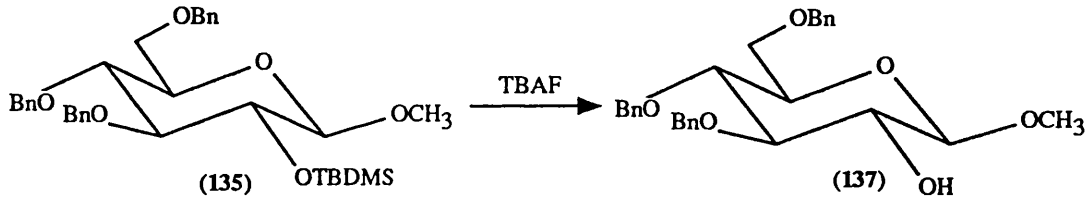


Table 7

Lit. data	Product (**137**)
m.p. 72-75 °C	m.p. 74-75 °C
$[\alpha]_D$ = -5° (c = 1, $CHCl_3$)	$[\alpha]_D$ = -5° (c = 1, $CHCl_3$)

3.3.4 Comment

The excellent diastereoselectivity observed in the reductive decarboxylation of (**134**) is again worthy of comment, particularly in the light of the work of Ritchie[13] with the closely related 2-deoxy series. The improved selectivity observed here is obviously a function of the oxygen substituent at the 2-position. A reasonable rationalisation, bearing in mind the work of Giese and Sustmann[44] (cf. *C*-glycosides, chapter 2), is that the radical intermediate inverts to a boat conformation in which the radical is periplanar to the β-C-O bond and that this is then quenched from the less hindered *exo*-face. It should be noted that the only major difference between this radical and the Giese radical is its σ- rather than π- nature.

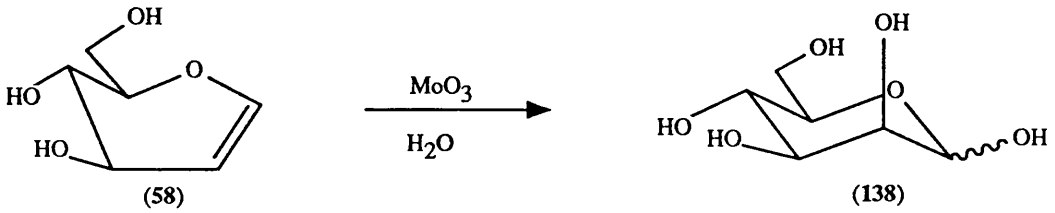
Ultimately, if it proves possible to develop a more efficient coupling reaction, this method could be used for the synthesis of pure β-glycosidic linkages.

3.4 Attempted extension to *manno*-glycosides

As observed above, the synthesis of β-*O*-*gluco*-pyranosides *via* a free radical H-atom transfer mechanism using the thiohydroxamate chemistry occurs with very high β-diastereoselectivity. It would therefore be interesting to investigate the effect on diastereoselectivity by the mere inversion of configuration at C-2, replacing the *gluco*-configuration by the *manno*-configuration.

As discussed above, *cis*-dihydroxylation of carbomethoxyglycal (**110**) with a catalytic amount of osmium tetroxide yielded the product (**118**) which has the *gluco*-configuration. The corresponding *manno*-derivative could be obtained if dihydroxylation took place from the β-face. A report[77] on *cis*-dihydroxylation of free glucal (**58**) showed that the *manno*-derivative (**138**) could be obtained exclusively with molybdenum trioxide (MoO_3) as the catalyst [Scheme 52].

Scheme 52



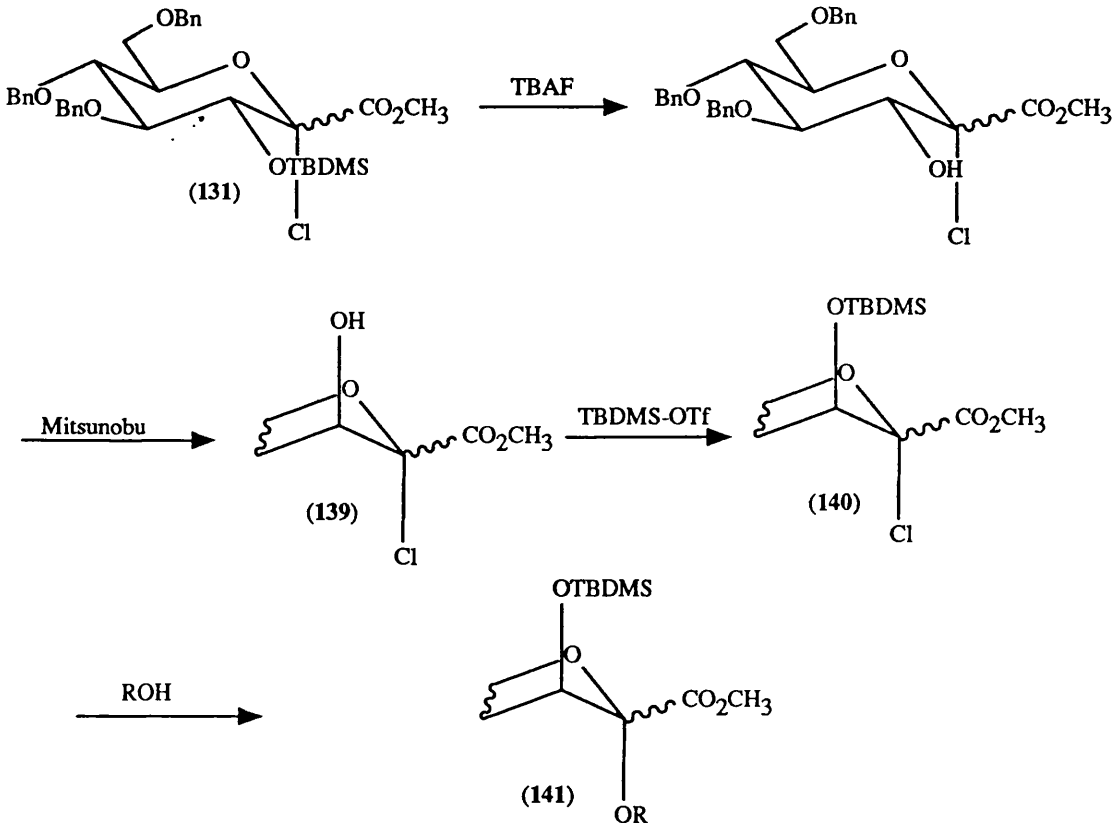
(58) (138)

However, when this method was applied to the carbomethoxyglycal (**110**) no reaction was observed. This was due, in part, to the glycal (**110**) being insoluble under the conditions employed (H_2O, room temperature) and possibly also to a need for a free OH-group to coordinate to the reagent. Various attempts were made to modify the reaction conditions but unfortunately, in all cases, (**110**)

was recovered unchanged. As a result an alternative route to the *manno* synthesis had to be sought.

One obvious approach involved the possible inversion at C-3 of the diol (**118**), generated on dihydroxylation of carbomethoxyglycal (**110**) with OsO_4, by means of the Mitsunobu[78] reaction. Attempts were therefore made to deprotect the glycosyl chloride (**131**) with a view to the subsequent application of the Mitsunobu reaction. The formate ester so formed could then be selectively cleaved to give product (**139**) and a silyl protecting group reintroduced (product (**140**)). Coupling with methanol as before and application of the decarboxylation reaction [Scheme 53] would give the desired product (**141**).

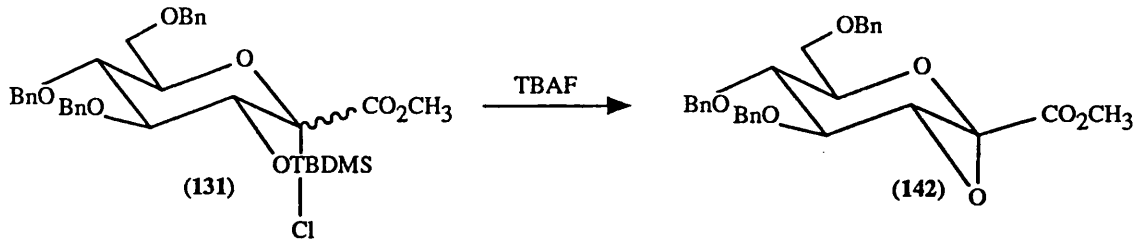
Scheme 53



3.4.1 Formation of an oxirane derivative (142)

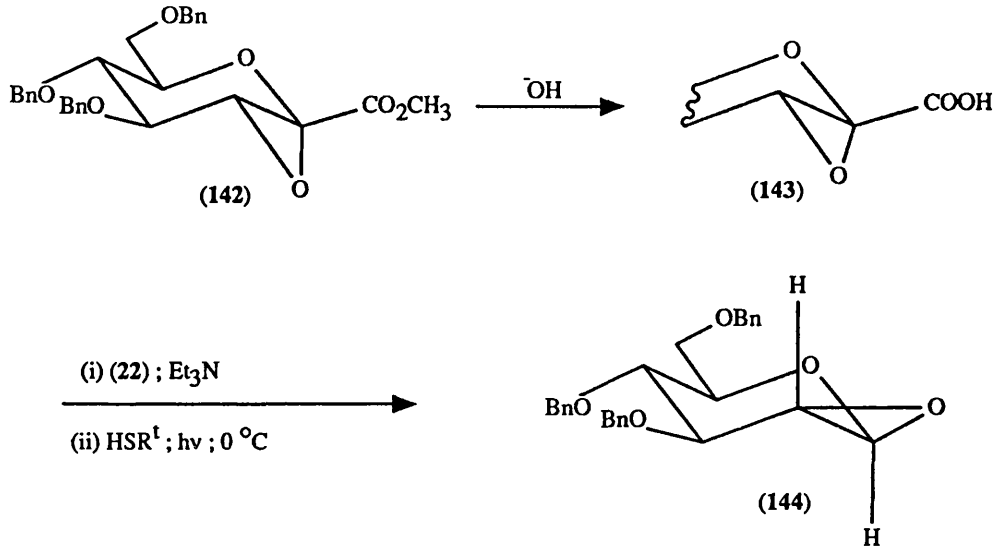
Following this scheme, the glycosyl chloride (**131**) was subjected to removal of its TBDMS-protecting group by treatment with TBAF. However, the reaction did not stop at the chlorohydrin but proceeded cleanly through to the crystalline epoxide (**142**) in 75% yield [Scheme 54].

Scheme 54



Having the epoxide (**142**) in hand, the opportunity was taken to carry out the radical chain decarboxylation reaction. The high β-diastereoselectivity, *via* the thiohydroxamate chemistry, on the isopropylidene derivative (**121**) led to a highly unusual *trans*-1,2-isopropylidene fused onto a six-membered ring (**123**). It would therefore have been interesting to observe if such a *trans*-1,2-oxirane derivative (**144**) would result from this free radical methodology [Scheme 55].

Scheme 55



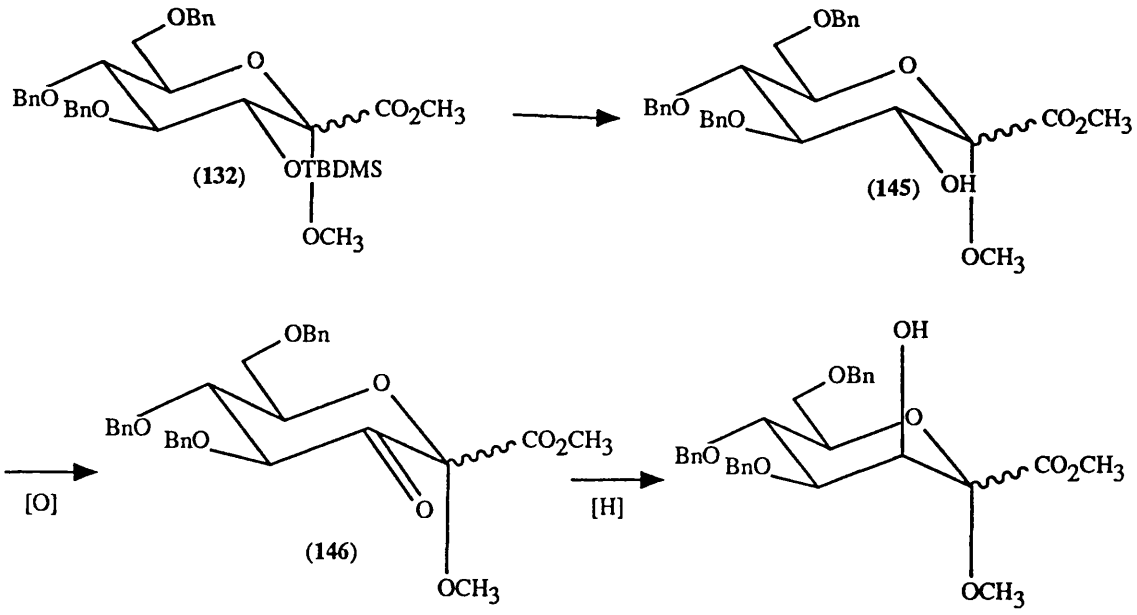
Compound **(142)** was saponified (KOH, H_2O, MeOH, THF, room temperature) to the corresponding acid **(143)** in a good yield of 92%. However, upon reductive decarboxylation of this acid a complex reaction mixture was obtained from which no epoxide (α- or β-) was isolated. Given that 1,2-anhydro-α-D-*gluco*-pyranose derivatives (the *cis*-epoxides) are relatively well known (the so-called Brigl's anhydrides[79]) this result is best interpreted in terms of the selective quenching of the radical from the α-face giving the *trans*-epoxide which then underwent rapid decomposition. The radical anomeric effect can therefore be tentatively be said to overcome the preference for the *cis*- over *trans*-bicyclo [5.1.0] heptane systems.

Returning to the problem of inversion of configuration at C-3, it was evident that, before desilylation could be applied, a less favourable leaving group had to be introduced at the anomeric centre. As the ultimate aim was to synthesise

the β-*O*-*manno*-glycosidic linkage, it was therefore decided to take advantage of the methyl glycoside (**132**) already in hand. In the event, treatment of both anomers (**132a**) and (**132b**) with TBAF in THF led cleanly to the required free secondary hydroxyl groups. However repeated attempts at the Mitsunobu inversion failed completely, probably owing to steric hinderance.

Further attempts at the inversion of configuration relied upon an oxidation-reduction sequence. Thus it was proposed that oxidation of (**145**) would provide the ketone at C-3, compound (**146**), which could be reduced by a metal-hydride reagent with the partial, if not exclusive, formation of the desired *manno*-configured alcohol [Scheme 56].

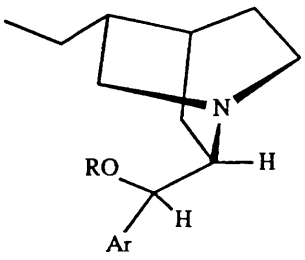
Scheme 56



Once again, however, all attempts at oxidation by the Swern

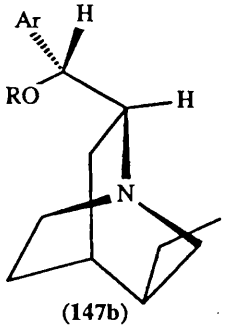
protocol,[80] with pyridinium chlorochromate[81] (PCC) or with the Ley tetrapropylammonium perruthenate[82] (TPAP)/*N*-methylmorpholine-*N*-oxide system failed completely, again probably due to steric hindrance. Unfortunately, it has therefore not been possible at the present time to prepare an appropriate precursor to test the effect of the axial C-O bond at the 2-position on the outcome of the radical reaction.

One possible avenue that it would be of interest to explore in this context is the use of Sharpless's[83] osmium-catalysed asymmetric dihydroxylation on carbomethoxyglycal (**110**), employing cinchona alkaloids such as dihydroquinine esters (**147a**) and (**147b**) as chiral ligands, the idea being that use of one of these ligands might result in a reversal of stereoselectivity as has been observed in other systems. For example, Sharpless reported that the use of ligand (**147a**) on olefin (**148**) gave diol with R-configuration while (**147b**) gave the S-diol.

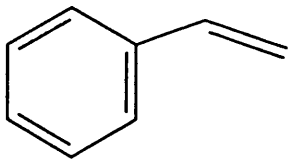


(147a)

R = *p*-chlorobenzoyl



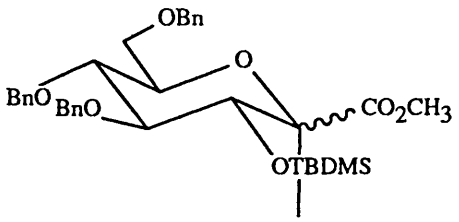
(147b)



(148)

3.5 Synthesis of β-*gluco*-*C*-glycosides

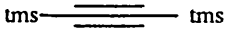
The success in synthesising highly diastereoselective β-*C*-glycosidic linkages in the 2-deoxy series prompted the investigation of the possibility of preparing such linkages in the *gluco*-series. Use of an anomeric carbanion for the introduction of the appropriate chain is not applicable here owing to the possible elimination of 2-*O*-substituent group. As a result an alternate route had to be sought, hence attention was turned to the glycosyl chloride **(131)**, already in hand.



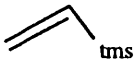
(131)

The idea was to use the anomeric centre as the electrophilic partner in the glycosidation reaction with the carbon chain being brought to the anomeric centre as the nucleophile. In this manner a whole range of electron rich molecules could be used as nucleophiles including **(149)**, **(150)**, **(151)** and **(152)** thus permitting the preparation of allyl, acetylenyl, vinyl and aryl *C*-glycosides respectively.

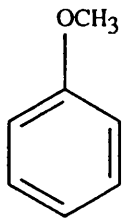
(149)



(150)



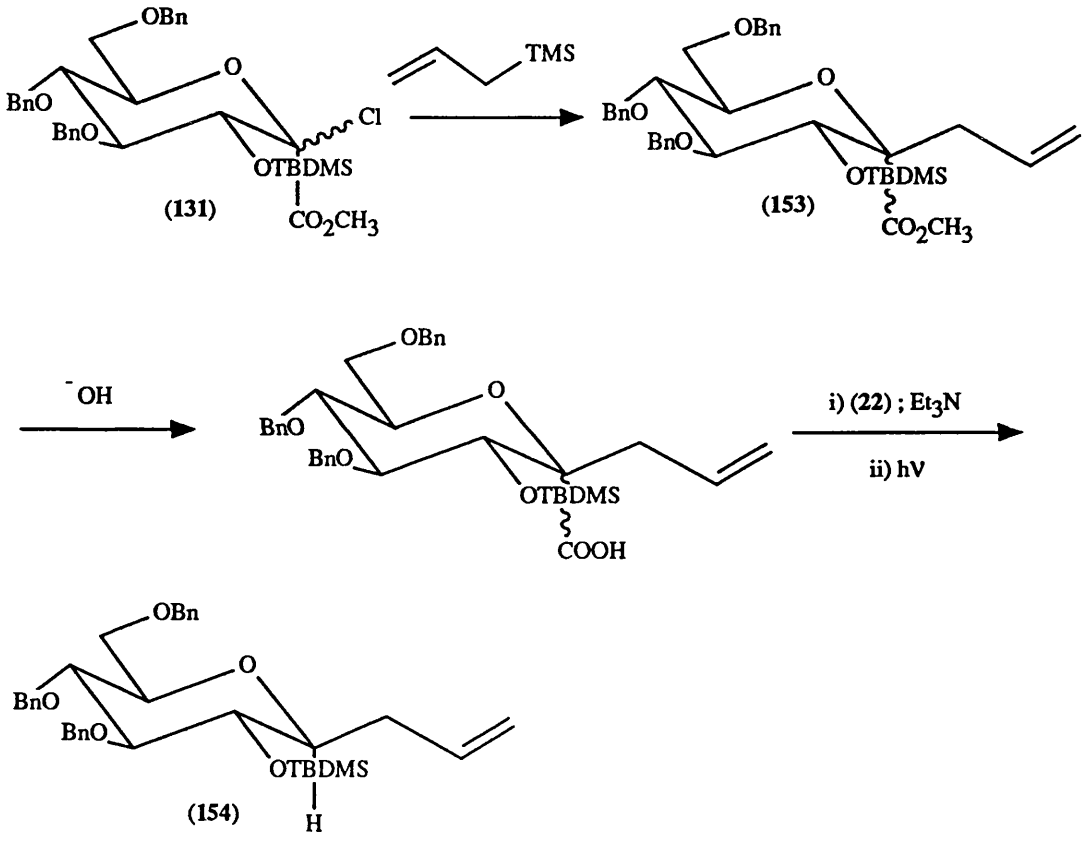
(151)



(152)

The proposed method, outlined in Scheme 57, involves introducing the carbon chain at the anomeric centre such that the product (**153**) obtained would then undergo saponification and reductive decarboxylation resulting in the β-product (**154**) [Scheme 57].

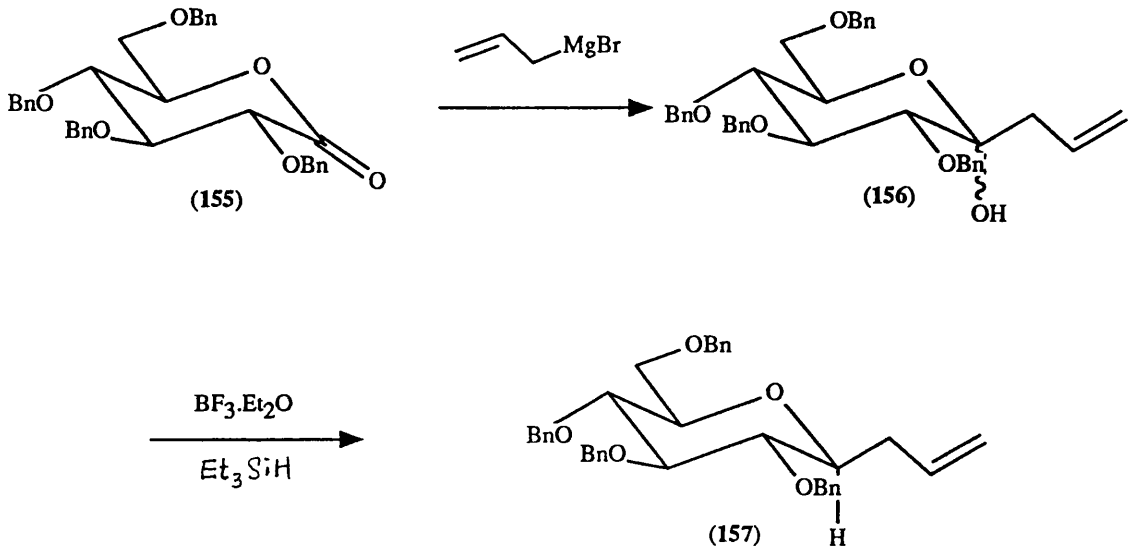
Scheme 57



This proposed method, after decarboxylation, would essentially be a radical equivalent of the Kishi method outlined in Scheme 58.

In his search for the total synthesis of palytoxin, Kishi[84] and coworkers developed a method of stereochemical control by nucleophilic addition to the pyran oxonium ion derived from readily available tetrabenzylpyranose derivatives. When 2,3,4,6-tetrabenzyl-*gluco*-pyranolactone (**155**) was treated with allylmagnesium bromide in ether, the corresponding hemiketal (**156**) was formed which on reduction with triethylsilane and boron trifluoride etherate gave the β-*C*-product (**157**) in 85% yield [Scheme 58].

Scheme 58

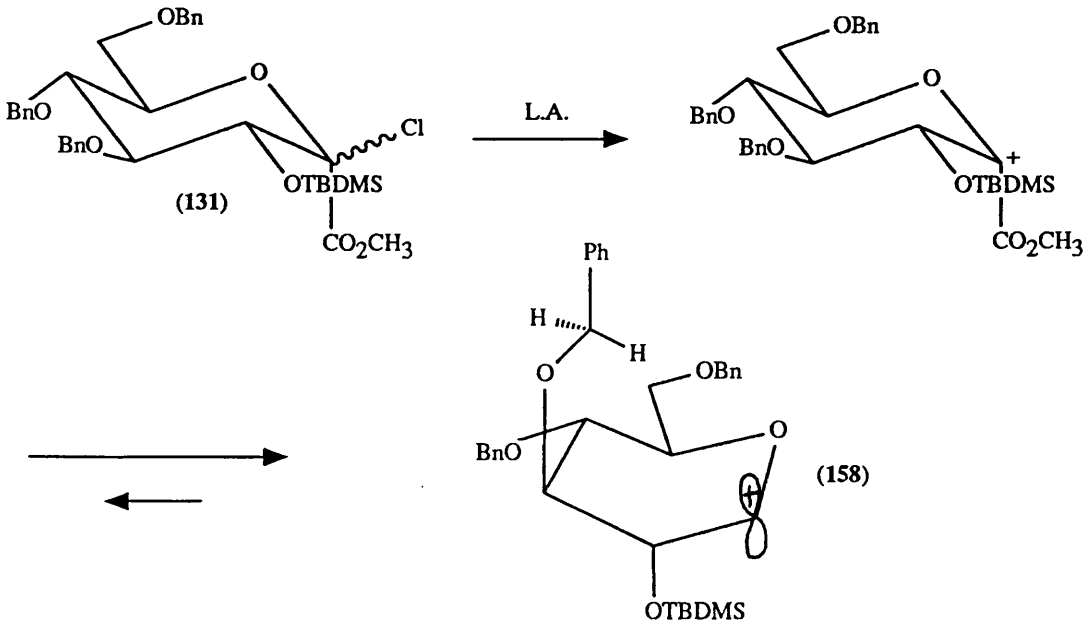


Hence the synthesis was begun by treatment of the glycosyl chloride (**131**) with allyltrimethylsilane (**149**) in the presence of a Lewis acid to activate the chloride. Under several conditions (solvents, temperatures, Lewis acids) the result obtained was always the same. An unanticipated product was formed whose ^1H nmr spectrum indicated the lost of a benzyl group; moreover the absence of

olefinic signals indicated that the nucleophile was not introduced. The mass spectrum of this product indicated a mass of 516 corresponding to loss of chloride and one benzyl group. In the infra-red spectrum, an OH stretch was observed at 3510 cm^{-1}. Based on these physical data, it is suggested that the product has the structure shown in **(160)**.

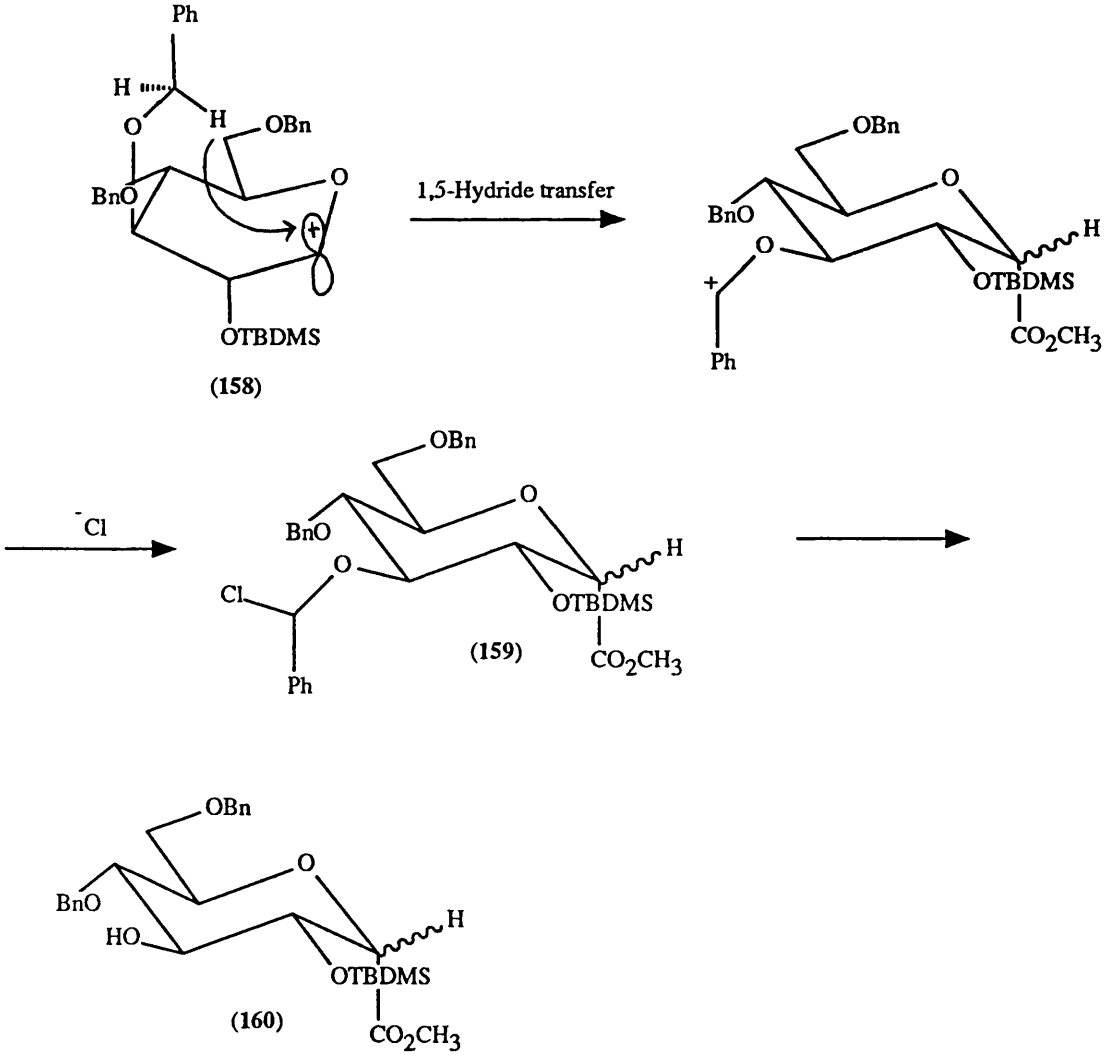
In order to explain the product observed the following mechanism is proposed. In the presence of a Lewis acid, activation of the glycosyl chloride **(131)** led to the formation of a carbocation at the anomeric centre by loss of a chloride ion. This cation derivative **(158)** adopts a boat conformation favoured by the stabilisation arising from overlapping of the vacant p-orbital with adjacent β-C-O bond and the lone pair of electrons on the ring oxygen [Diagram 6] (compare Giese's glucos-1-yl radical).

Diagram 6



As a result of this boat conformation[85] the benzyl group at C-3 position is now suitably positioned for a 1,5-hydride transfer[86] to take place. The so-formed benzyl cation probably was quenched by the chloride to give product (**159**) which is hydrolysed in the work-up (or on silica gel during column chromatography) to give benzaldehyde and the observed product (**160**) [Scheme 59].

Scheme 59



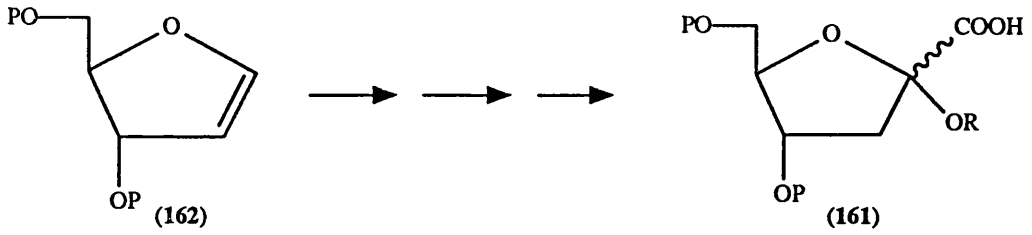
Although this system has not been investigated further, a possible solution to this problem would be the use of the TBDMS protecting group rather than benzyl groups such that no hydride transfer would then be possible.

CHAPTER 4

ATTEMPTED SYNTHESIS OF FURANOSIDES

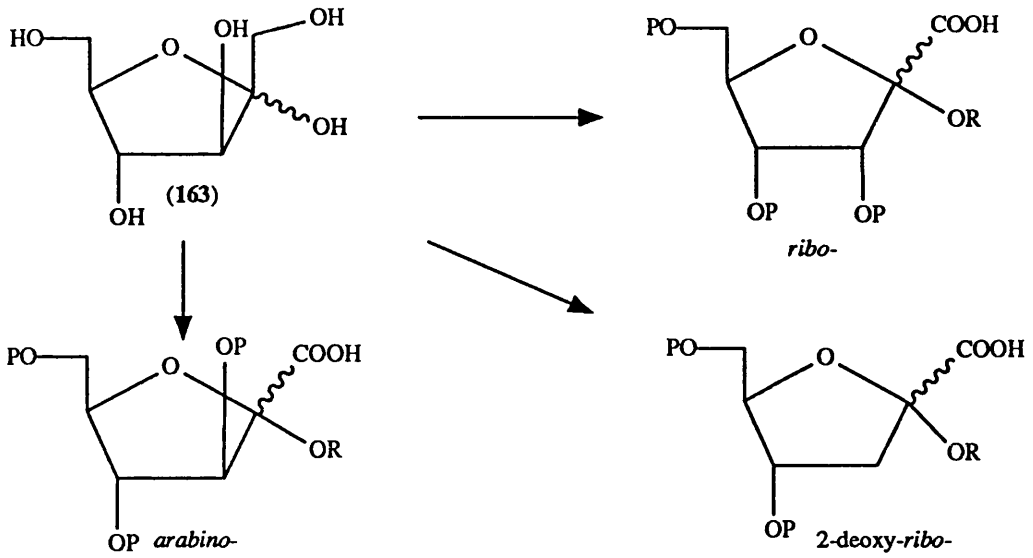
4. Attempted synthesis of furanosides

The synthesis of furanosides by the present radical methodology requires the facile preparation of 3-deoxyhexulo-2-furanosidic acids (**161**). Presumably these could be prepared from the corresponding dihydrofuran (**162**) by an analogous pathway to that employed for pyranosides. However as is apparent from this thesis, such a pathway is very convenient for the 2-deoxy series but posseses some problems for the preparation of the fully hydroxylated sugars.



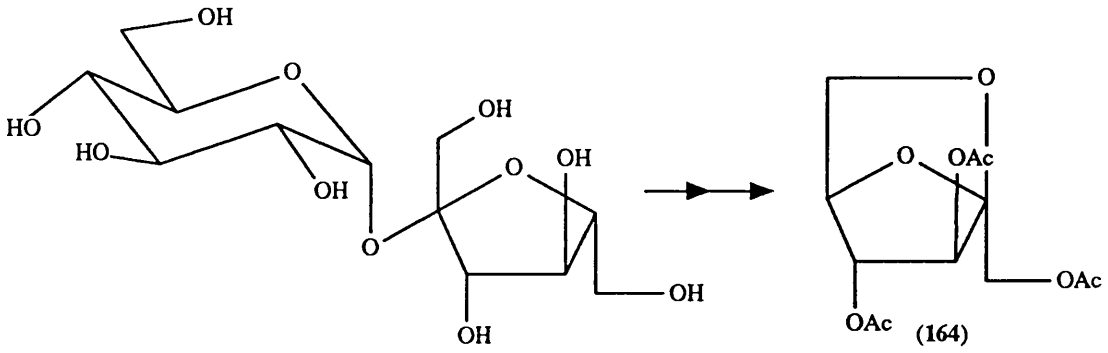
Hence alternative strategies were sought. The most attractive scheme, on paper, is the use of readily available D-*fructo*-furanose (**163**) which by selective protection and deoxygenation and/or inversion and eventually oxidation would provide the appropriate precursor to the 2-deoxy-*ribo*-, the *ribo*- and the *arabino*-series [Scheme 60].

Scheme 60

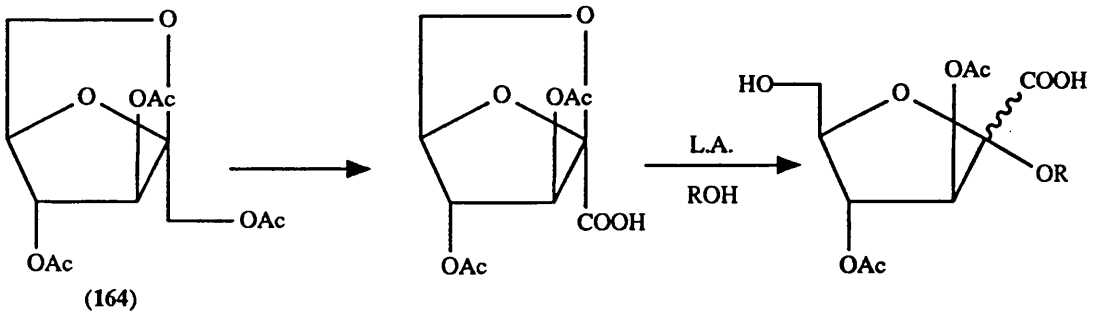


Much is known about the regioselective protection and reactions of fructose. A particularly attractive scheme would be to take advantage of the known formation of 2,6-anhydro-*fructo*-furanose derivatives on pyrolysis of extremely cheap and readily available sucrose. The procedure of Taba[87] leading to the formation of the 1,3,4-triacetate (**164**) in moderate yield is apparently the optimum [Scheme 61] at present time.

Scheme 61

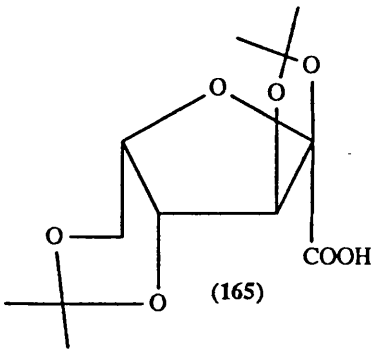


From this derivative, the primary acetate could be selectively saponified and the resultant hydroxyl group oxidised up to the requisite acid function. The labile anhydro bridge could then be activated with a Lewis acid and serve as a glycosyl donor.



(164)

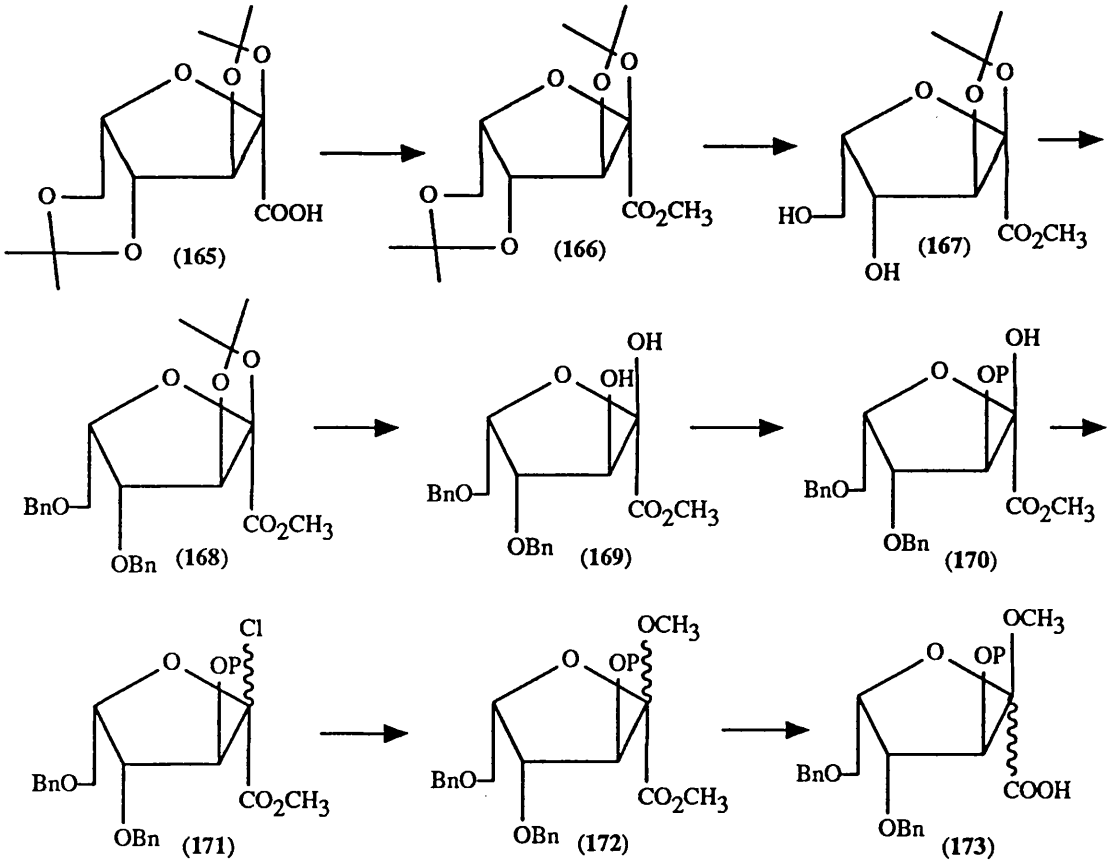
However it was deemed prudent before embarking on such a scheme to test the diastereoselectivity of the radical reaction using as substrate the readily available multi-ton industrial intermediate 2,3:4,6-diisopropylidene-2-keto-L-gulonic acid (**165**) (L-*xylo*-2-hexulofuranosidic acid). This compound is an intermediate in the industrial production of "natural" vitamin C (ascorbic acid) from D-glucose[88] and as with the approach from fructose outlined above, should provide access to the 2-deoxy-*ribo*-, *ribo*-, and *arabino*-configurations but in the L-series by suitable manipulation of protecting groups. This chapter is devoted to the study of protecting group chemistry and glycosylation reactions of (**165**).



(165)

The proposed route, outlined in Scheme 62, involves inital protection of the acid function to the corresponding ester (**166**) followed by selective cleavage of the 4,6-isopropylidene group to give the methyl 2,3-*O*-isopropylidene-L-furanosidonate (**167**). Protection as its dibenzyl ether and cleavage of the remaining 2,3-*O*-isopropylidene group should transform (**168**) into (**169**). Selective protection of the secondary hydroxyl group by treatment with TBDMS-OTf should give product (**170**) and activation to the glycosyl chloride (product (**171**)) should then enable coupling to a representative alcohol (MeOH) to give the desired product (**172**). Saponification of (**172**) should then transform it to the acid precursor (**173**) required for the thiohydroxamate chemistry.

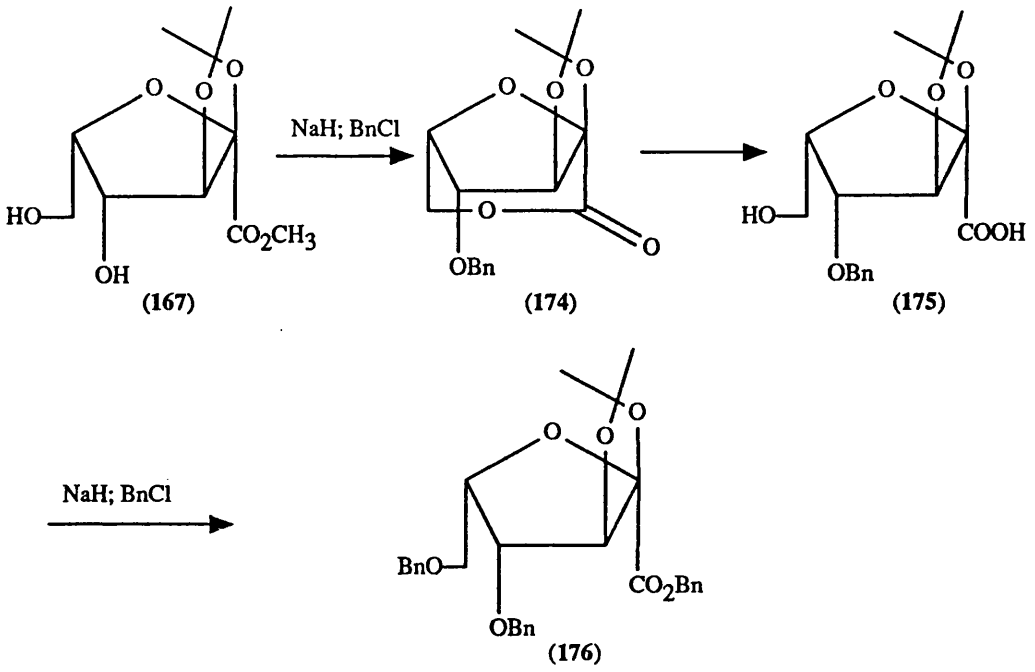
Scheme 62



In the event, the acid (**165**) was obtained by azeotroping the commercially available monohydrate in benzene in a Dean-Stark apparatus. This preparation was carried out on a 100 gram scale. When all the water had been removed, the benzene was evaporated under reduced pressure and acid (**165**) which was obtained was dissolved in dry dimethylformamide (DMF) and treated with potassium carbonate and methyl iodide in the dark. Upon work up, ester[89] (**166**) was obtained in an overall yield of 69%. Selective cleavage of 4,6-*O*-isopropylidene group was achieved by heating to reflux (**166**) in water with a catalytic (1 crystal) amount of copper(II) acetate.[90] This reaction proceeded very cleanly and product (**167**) was obtained in almost quantitative yield.

Application of a standard procedure for benzylation (NaH, DMSO, BnCl) led to a complex reaction mixture. However a product was isolated whose ^{1}H nmr spectrum indicated the presence of one benzyl group and loss of the $CO_2C\underline{H}_3$ group. The infra-red spectrum of this product indicated the presence of a carbonyl group. These observations led to the identification of the problem as one of lactonisation on alkoxide formation at C-6 [Scheme 63]. Also isolated was a very polar product whose infra-red spectrum indicated the presence of an acid group. On benzylation, this latter product led to tri-benzylated product (**176**) (by ^{1}H nmr spectroscopy). This observation could be reasonably rationalised by the lactone (**174**) being hydrolysed to product (**175**) on work-up.

Scheme 63



This unsuccessful benzylation prompted us to investigate alternative benzyl-protecting methods. Various methods[91] reported in the literature were tried (Ag_2O, BnCl, DMF; $Ni(acac)_2$, BnCl, toluene, reflux; AgOTf, BnCl) and in all cases (**167**) was recovered unchanged. As a result an alternative protecting group had to be sought. Attention was turned to the use of a silyl protecting group. Bulky silyl protecting groups (thexyldimethylsilyl; *t*-butyldiphenylsilyl) were chosen to minimise the tendency for silyl groups to undergo cleavage by acid as the next stage of the reaction involves cleaving the acetonide with acid. The mono- or/and di-silylated products were obtained easily and in good yields by standard procedures, however on attempted cleavage of the isopropylidene group by treatment with 2M HCl, desilylation was observed. Compound (**167**) was also protected as its thiocarbamate by treatment with phenylisothiocyanate in pyridine. Unfortunately, once again, on treatment with 2M HCl this thiocarbamate derivative underwent cleavage.

As seen from the above results the problem of protecting group chemistry is once again not a trivial one. The ease of protecting procedures, the choice of protecting groups as well as the ability of these groups to withstand various reaction conditions all play important parts in the synthesis of the desired β-furanosides. Both silyl- and thiocarbamate-protected compounds, whose synthesis could be easily carried out, failed to withstand subsequent reaction conditions. Eventually it was decided to return to benzylation and to modify the standard method (NaH, DMSO, BnCl) used.

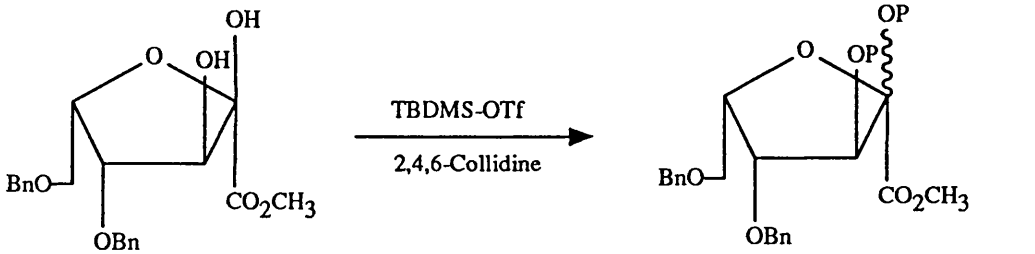
Various reaction conditions were tried (concentration of reagents, temperatures, solvent systems). Finally, a satisfactory method was developed in which product (**168**) could be obtained on a 6-7 gram scale in >70% yield. It was found that when benzylation was attempted in dry THF with a large excess (10 molar equivalents) of BnCl and temperatures varying from -78 °C to ambient temperature, no product was formed as indicated by t.l.c.. However, when anhydrous DMSO was added dropwise to this reaction mixture, the desired product could be obtained. This observation was attributed to the low solubility of the alkoxide in THF. When benzylation was carried out in DMSO, the alkoxide, being soluble in DMSO, underwent nucleophilic attack on the carbonyl function, displacing the methoxyl group, to give the compound (**174**). However when this reaction was carried out in THF, the anion formed is insoluble and does not undergo any reaction. Slow addition of DMSO then enabled the anion to dissolve and undergo rapid benzylation in the presence of large excess of BnCl.

Having now successfully obtained the desired compound (**168**) in good yield the next step was cleavage of the remaining isopropylidene group. This seemingly easy and straightforward cleavage of an acetonide proved to be a slight problem in that treatment of (**168**) with 80% acetic acid failed to give product (**169**). Treatment of (**168**) with 2M HCl required a reaction time of 3-4 days before

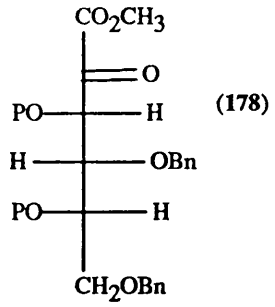
cleavage was complete. Attempts to reduce the reaction time by increasing either the temperature or the concentration of acid led to poor yields being obtained.

Having obtained the diol (**169**), the next step was to selectively protect the free hydroxyl group at C-3 position. The same methodology used for selective silyl-protection of the *gluco*-series was applied here. Thus diol (**169**) was treated with 1 molar equivalent of TBDMS-OTf in the presence of 2,4,6-collidine in dichloromethane. However the disilylated product (**177**) [Scheme 64] was obtained instead of the expected mono-silylated compound. Various attempts at mono-protection were carried out by varying the amounts of TBDMS-OTf used and by lowering the reaction temperature. In all cases, the disilylated compound (**177**) was formed leading to the somewhat unanticipated conclusion that the monosilylated diol underwent silylation more rapidly than the diol itself. Initially it was thought that (**177**) was in fact the ring opened structure (**178**) but this possibility was ruled out by the presence of signals at δ 105.89 ppm and δ 100.56 ppm in the ^{13}C nmr spectrum attributed to the anomeric carbons.

Scheme 64



(**169**) (**177**) P = TBDMS

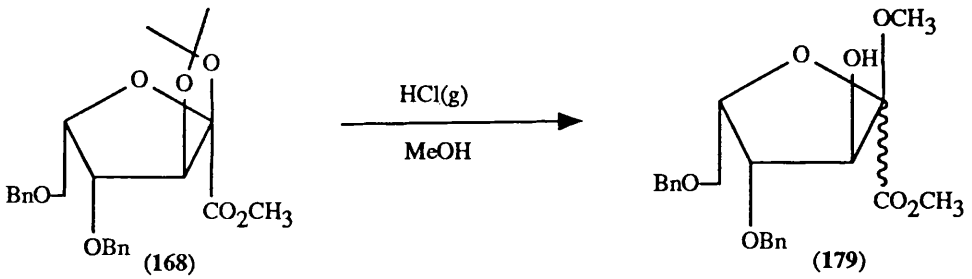


(178)

P = TBDMS

As a result, an alternative route for the synthesis of β-glycosides had to be sought. Attention was turned to the direct introduction of a methoxyl group at the anomeric position. Diol (**169**) was heated to reflux in anhydrous methanol with DOWEX 50W-H8 in the hope of forming the methyl glycoside. Unfortunately no product was obtained and diol (**169**) was recovered unchanged. Next, the isopropylidene derivative (**168**) was dissolved in anhydrous methanol under argon and a stream of HCl gas was bubbled into this reaction mixture. The idea was to cleave the isopropylidene group and introduce *in situ* the OCH_3 group at the anomeric position. After 3-4 days the desired product was obtained [Scheme 65] as two separate anomers (**179a**) and (**179b**), a minor product, with the diol (**169**) as the major product from the reaction.

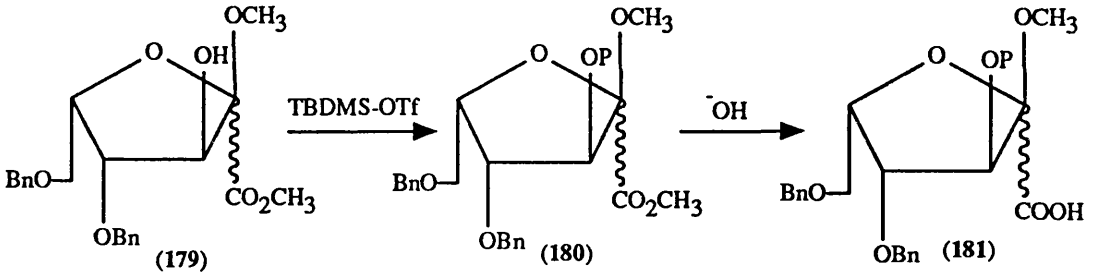
Scheme 65



(168) (179)

The major anomer was protected as its TBDMS-ether by treatment of (**179b**) with TBDMS-OTf in the presence of 2,4,6-collidine and compound (**180**) was obtained in an excellent yield of 91%. Saponification of this ester (**180**) with KOH gave the desired acid (**181**) in 85% yield [Scheme 66].

Scheme 66



After the expenditure of considerable effort on protection-deprotection, finally the thiohydroxamate chemistry could be attempted. Acid (**181**) was treated with heterocyclic salt (**22**) and triethylamine to form the intermediate *O*-acyl thiohydroxamate. This intermediate was not isolated but subjected to photolysis at 0 °C giving a polar product. After 1 h the solvent was evaporated under reduced pressure and residue chromatographed on silica gel. The ^{1}H nmr spectrum of the major product indicated the presence of the anomeric signal at δ 6.25 ppm but unfortunately the OCH_3 signal was absent. The presence of the anomeric signal indicates that the thiohydroxamate free radical chemistry was successfully accomplished. The lack of the OCH_3 signal however is indicative of hydrolysis having occurred probably on work-up or on the column (the difficulty in obtaining the methyl glycoside (**179**) may also have been due to facile hydrolysis). Seemingly glycofuranosides are more susceptible to hydrolysis than

glycopyranosides. Before further work can be carried out in this series, appropriate conditions will need to be found for the preparation and isolation of the glycosides both before and after decarboxylation. Time and lack of material has prevented the further investigation of this problem in this thesis.

CHAPTER 5

ß-TRIMETHYLSILYLETHOXYMETHYL CHLORIDE AS A CONVENIENT FORMALDEHYDE EQUIVALENT

5. β-Trimethylsilylethoxymethyl cholride (SEM-Cl) as a convenient formaldehyde equivalent

The aldol condensation[92] has long been recognised as one of the most versatile synthetic tools in organic chemistry. Its importance lies in that it provides a very rapid and efficient method for linking two smaller molecules by C-C bond formation. Furthermore the aldol products contain two functional groups: OH and HC=O enabling a number of subsequent reactions to be carried out.

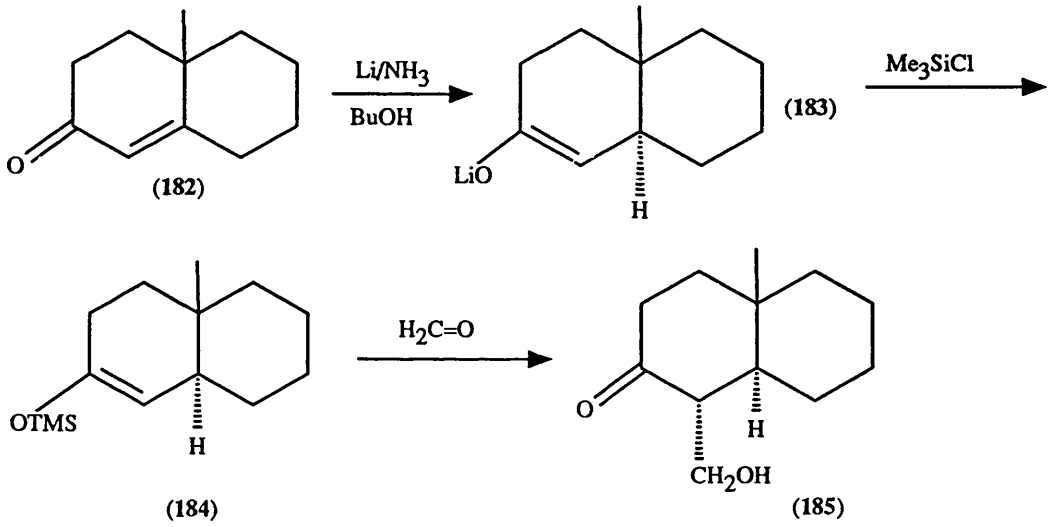
However, the classical aldol condensation type reaction is a much better reaction on paper than in the laboratory. Owing to the multitude of side reactions under classical conditions, equilibrium of all the different enolates often led to products containing di-, poly- or self-condensation products limiting the utilisation of this otherwise useful reaction.

However, the recognition of the Zimmerman-Traxler transition state hypothesis[93] and the use of kinetically generated lithium enolates enabled high yielding and excellent stereoselective aldol reactions to be achieved. Unfortunately with regard to formaldehyde as the electrophile in aldol reactions, many problems still remain owing mainly to its instability. The classically used formalin, a 37% aqueous solution of formaldehyde, is evidently not applicable to kinetic enolates. Formaldehyde can be generated as a gas by decomposition of its long-chain polymer, paraformaldehyde, however this is highly inconvenient in that the gas has to be bubbled very quickly into the reaction for in the presence of trace amounts of water, formaldehyde reverts back to the polymer.

Nevertheless the use of gaseous formaldehyde has been successfully applied by various authors as illustrated by the work of Stork,[94] who reported on the successful trapping of regiospecifically generated enolates from cyclic ketones with formaldehyde to give α-hydroxymethyl ketones. In his investigation, Stork

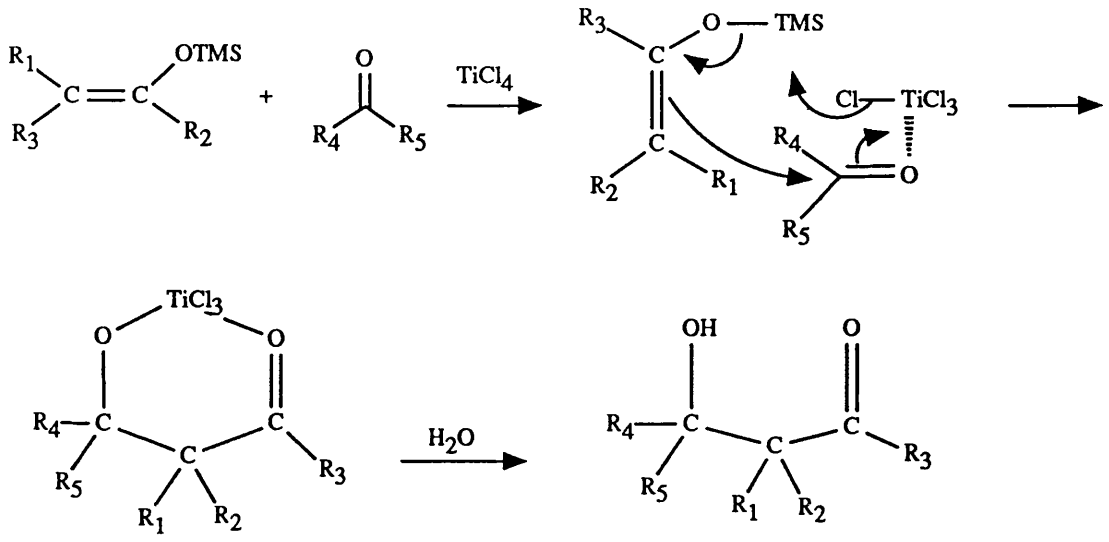
observed excellent results when the enolate ion was trapped as its trimethylsilyl ether (**184**). The lithium enolate (**183**) was obtained by reduction of enone (**182**) in the presence of *tert*-butyl alcohol with lithium in ammonia. Complete removal of ammonia followed by addition of dry THF and 2.5 molar equivalents of trimethylchlorosilane gave the silyl enol ether (**184**) in 90% yield. Regeneration of the lithium enolate with 1 equivalent of methyllithium followed by treatment with anhydrous formaldehyde gave the crystalline carbinol (**185**) in 90% yield [Scheme 67].

Scheme 67



Various attempts have been made to surmont the problems associated with the use of gaseous formaldehyde. By far the best procedure was that adopted by Mukaiyama.[95] In this variation of the Mukaiyama aldol reaction, silyl enol ethers are reacted with trioxane in the presence of titanium tetrachloride which serves both to generate *in situ* and to activate monomeric formaldehyde [Scheme 68].

Scheme 68

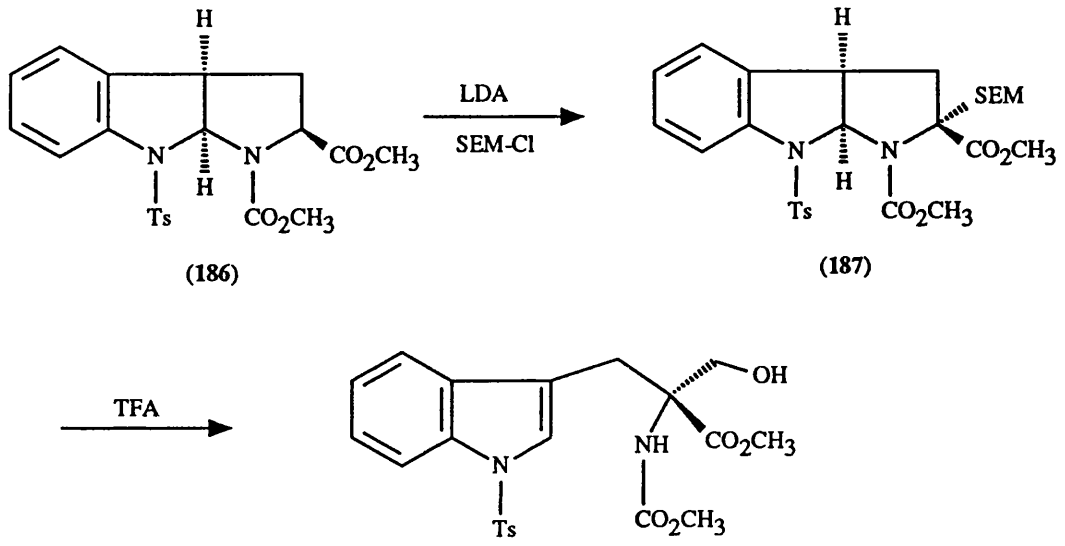


Although this method is successful it nevertheless requires the prior formation of trimethylsilyl enol ethers and the use of a Lewis acid such as $TiCl_4$.

5.1 β-Trimethylsilylethoxymethyl chloride (SEM-Cl) as a formaldehyde replacement

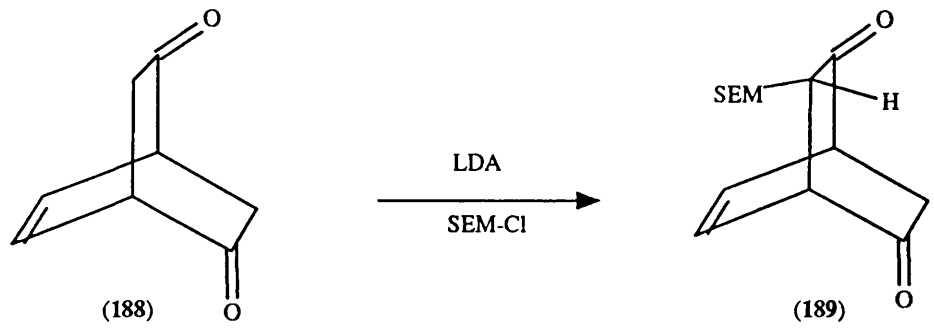
Recently the use of SEM-Cl as a convenient and efficient equivalent of formaldehyde for the trapping of ester enolates was reported. Thus in their recent investigation into the generation of "peptoids" from tryptophan, Crich and Davies[96] have shown that deprotonation of substrate (**186**) with LDA and quenching of the anion with SEM-Cl gave the SEM-derivative (**187**) in a good yield of 78%. Treatment with trifluoroacetic acid instigated cleavage of the terminal heterocyclic ring and deprotection of the β-hydroxy ester [Scheme 69].

Scheme 69



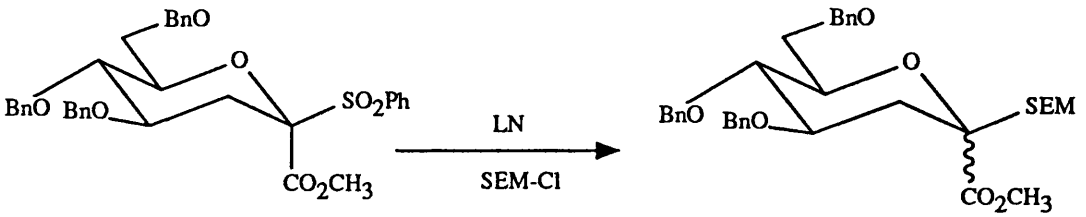
Concomitantly the Paquette[97] group reported the efficient quenching of a ketone enolate with SEM-Cl which occurred in a stereoselective manner. Thus when enolate anion (**188**) was treated with one equivalent of SEM-Cl, the product (**189**), in which the newly introduced side chain had entered from the less hindered surface *syn* to the double bond, was obtained [Scheme 70].

Scheme 70



In the course of the present investigation into the synthesis of 2-deoxy-*C*-glycosides, use was also made of SEM-Cl as an electrophile for the introduction of a one carbon unit at the anomeric position. Hence reductive desulphonylation of sulphone ester (**63**) with two molar equivalents of LN and quenching of the resultant anion with SEM-Cl gave the SEM-glycoside (**66**) in 70% yield [Scheme 71].

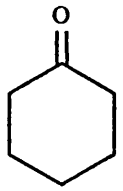
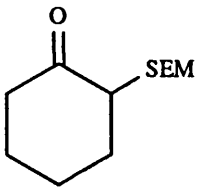
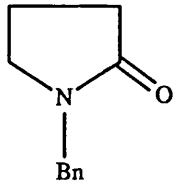
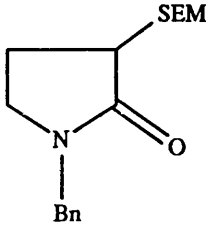
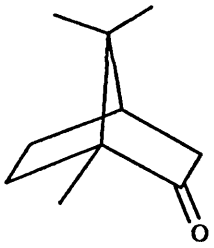
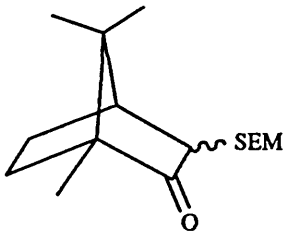
Scheme 71

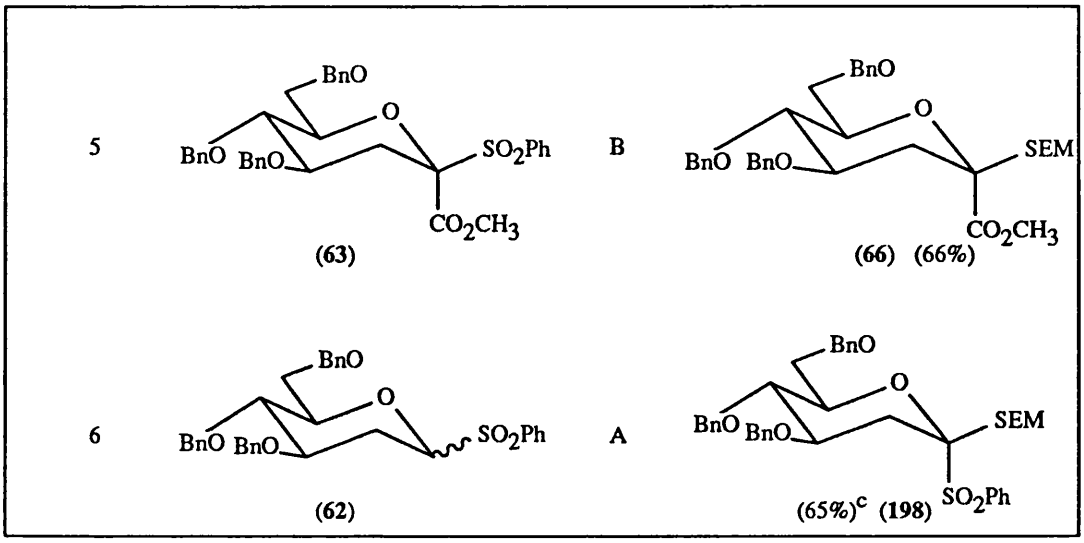


(63) (66)

The success and relative experimental facility of this reaction led us to investigate and generalise the use of SEM-Cl on various substrates. Substrates (**190**)-(**193**) were subjected to deprotonation with LDA at -78 °C in THF under an inert atmosphere. The anion formed in each case was quenched with SEM-Cl. Products were easily purified by column chromatography on silica gel using petroleum-diethyl ether mixtures as the eluant. The table below [Table 8] summarises the results obtained.

Table 8 Reaction of enolates and stabilised carbanions with SEM-Cl

Entry	Substrate	Method[a]	Product
1	 (190)	A	 (194) (76%)
2	 (191)	A	 (195) (60%)
3	 (192)	A	 (196) (57%)[b]
4	PhC≡C-H (193)	A	PhC≡C-SEM (197) (60%)



a. A: deprotonation with lithium diisopropylamide;
B: desulphonylation with lithium naphthalenide.

b. 2.5:1 endo:exo mixture of isomers.

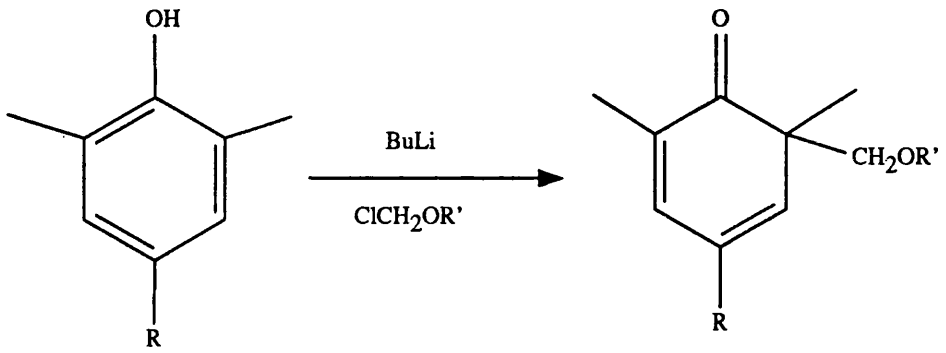
c. Decomposes rapidly on standing at room temperature.

As seen from the table this method is also applicable to the quenching of lithium salts of other stabilised carbanions as demonstrated by sulphone glycoside (**62**) and alkyne (**193**) and to the generation of lithium enolates other than by deprotonation with LDA. In the case of product (**197**), obtained by deprotonation of sulphone (**62**) with LDA and quenching the anion with SEM-Cl, rapid decomposition was observed on standing at room temperature. This was not unexpected in the light of similar observations noted by Ley in related sulphone derivatives (see Chapter 2).

In the course of this study on the general use of SEM-Cl, Topgi[98] published a related procedure in which he examined the conversion of phenols to cyclohexa-2,4-diene-1-ones [Scheme 72]. In his report lithium was used both as an efficient phenolate counter cation and due to its enhanced ability to complex with

the SEM, methoxymethyl group and (benzyloxy)methyl group, it also directs these groups to the *ortho*-position. The use of methoxymethyl chloride (MOM-Cl) in similar procedures, most notably in the classical Corey prostaglandin synthesis,[99] and of benzyloxymethyl chloride (BOM-Cl)[100] is also noteworthy.

Scheme 72



As noted from the work of Crich and Davies and from the work of Paquette, β-trimethylsilylethyl-protected aldols formed in this way may be cleaved by treatment with trifluoroacetic acid or boron trifluoride etherate ($BF_3.Et_2O$).

CONCLUSION

CONCLUSION

The reductive radical decarboxylation methodology previously developed in this laboratory for the diastereoselective synthesis of 2-deoxy-β-*O*-glycosides has been extended to encompass 2-deoxy-β-*C*-glycosides and β-glucosides. This methodology has been developed for the synthesis of the appropriately functionalised ulosonic acid derivatives. In particular, an efficient method for the elimination of phenylsulphenic acid from a phenylsulphonyl glycoside was developed. The osmium tetroxide dihydroxylation of the so-formed 1-carbomethoxyglycal procceded with very high *gluco*-selectivity. In the reductive decarboxylation step, much higher diastereoselectivities were observed than in the 2-deoxy-*O*-glycoside work and hypotheses are advanced to explain these observations.

In an attempt to extend this methodology to the synthesis of furanosides, the chemistry of 2,3:4,6-diisopropylidene-2-*keto*-L-gulonic acid has been studied resulting, most notably, in the development of a new method for the benzylation of hydroxyl esters.

β-Trimethylsilylethoxymethyl chloride (SEM-Cl) was shown to function efficiently as a formaldehyde equivalent in alodol type reactions.

EXPERIMENTAL

General Methods

Micranalysis were carried out by the microanalytical section of the Department of Chemistry at University College London.

Melting points were determined on a Kofler hot-stage microscope and are uncorrected.

Mass spectra were recorded on a VG 7070H mass spectrometer with Finnigan INCOS II data system.

^{1}H NMR spectra were recorded on a Varian XVR-400 MHz or Varian XL-200 MHz spectrometer in deuterated chloroform unless otherwise stated.

Infra-red spectra were recorded on a Perkin-Elmer 983 spectrophotometer.

1. Tetra-*O*-acetyl-α-D-*gluco*-pyranosyl Bromide (15)

To a stirred solution of ß-D-glucose pentaacetate (200 g, 0.512 mol) in glacial acetic acid (560 ml) at room temperature was added dropwise phosphorus tribromide (242.55 g, 0.896 mol). The reaction was allowed to stir overnight after which t.l.c. indicated complete consumption of starting material. The bromide **(15)** was not isolated but the reaction mixture used immediately in the following step.

2. Tri-*O*-acetyl-D-glucal (57)

To a solution of anhydrous sodium acetate (222.57 g, 2.71 mol) in water (536 ml) and glacial acetic acid (368 ml) at 0 °C was added zinc dust (203.11 g, 3.11 mol) followed by a solution of cupric sulphate pentahydrate (20.31 g, 0.08 mol) in water (74 ml). On decolourisation of the blue solution, the glycosyl bromide solution prepared above was added such that temperature remained between -10 °C and -20 °C. After 3 h, the reaction mixture was filtered through celite and the filtrate washed with acetic acid / water (1:1). Ice water was added to the filtrate and the mixture was then repeatedly extracted with chloroform. The combined extracts were washed with water, 5% $NaHCO_3$, water, saturated NaCl, dried ($CaCl_2$) and concentrated under reduced pressure. The product was isolated by crystallisation from diethyl ether-petroleum (119.2 g, 86 %), m.p. 54 °C [cf. lit.[33] m.p. 54-55 °C, 60-70 % yield].

3. D-Glucal (58)

To a solution of tri-*O*-acetyl-D-glucal (73.65 g, 0.27 mol) in dry methanol (1150 ml) at room temperature was added sodium (180 mg, 7.8 mmol). After 24 h, a stream of carbon dioxide was bubbled through the reaction mixture for 10 min before the solvent was evaporated under reduced pressure and the residue extracted with hot ethyl acetate. The combined extracts were concentrated to give the crystalline glucal (**58**) (36.19 g, 92 %), m.p. 58-59 °C [cf. lit.[33] m.p. 57-59 °C, 73 % yield].

4. 3,4,6-Tri-*O*-benzyl-D-glucal (59)

A solution of sodium hydride (24.84 g, 0.828 mol) in dry DMSO (230 ml) was stirred at room temperature. After 0.5 h into this solution was added dropwise a solution of glucal (**58**) (26.89 g, 0.184 mol) in DMSO (100 ml) keeping the temperature between 15-20 °C. This reaction mixture was stirred for a further 0.5 h after which it was treated with dropwise of benzyl chloride (74 ml, 0.644 mol) keeping the reaction mixture at room temperature. After 3 h of stirring, the reaction was complete as indicated by t.l.c.. The reaction mixture was poured onto ice-water and repeatedly extracted with diethyl ether. The combined ethereal layers were washed with water, sat. NaCl, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was crystallised from ethanol to give the title product (**59**) as a white crsytalline solid (66.4 g, 87 %), m.p. 57 °C [cf. lit.[32] m.p. 57-57.5 °C].

5. Phenylthio 2-Deoxy-3,4,6- tri-*O*-benzyl-α,ß-D-*arabino*-pyranoside (61)

A stream of hydrogen chloride gas was bubbled into a stirred solution of glycal (**59**) (10.0 g, 24 mmol) in dry toluene (30 ml) at O °C for 10 min. After a further 15 min, the solvent was evaporated under reduced pressure. The residual syrup was dissolved in dry toluene (25 ml) and treated at room temperature with thiophenol (3.7 ml, 36 mmol) followed by Hunig's base (6.3 ml, 36 mmol). When the reaction was complete, as indicated by t.l.c., it was washed with 2M KOH, 2M HCl, water, sat. NaCl, dried ($MgSO_4$) and concentrated under reduced pressure. The phenylthio-glycoside (**61**) (12.5 g, 99 %), a white crystalline solid, m.p. 57 °C [recrys. from petroleum-diethyl ether], was obtained as a mixture of anomers (α:ß = 1:5).

6. Phenyl 2-Deoxy-3,4,6-tri-*O*-benzyl-1-sulphonyl-α,ß-D-*arabino*-pyranoside (62)

A stirred solution of phenylthio-glycoside (**61**) (12.52 g, 0.024 mol) in absolute ethanol (430 ml) at room temperature was treated with magnesium salt of monoperoxyphthalic acid (12.34 g, 0.025 mol). The reaction mixture was stirred for a day after which the solvent was evaporated *in vacuo* and the residue dissolved in chloroform. The organic layer was washed with 5 % NaHCO3, water, sat. NaCl, dried ($MgSO_4$) and concentrated *in vacuo*. The product (**62**) (9.37 g, 71 %) was recrsytallised from methanol to give white crystalline solid, m.p. 102-104 °C, as a mixture of α:ß anomer in the ratio of 1:5.

7. Methyl [Phenyl 2,3-Dideoxy-4,5,7-tri-*O*-benzyl-2-sulphonyl-ß-D-*arabino*-2-heptulopyranosid]oante (63)

A stirred solution of sulphone (**62**) (4 g, 7.16 mmol) in dry THF (20 ml) at -78 °C under nitrogen was treated with 1.0M LDA (8.6 ml, 8.6 mmol). After 15 min dimethyl carbonate (0.85 ml, 10 mmol) was added dropwise and the reaction mixture maintained at -78 °C. On completion, as indicated by t.l.c., the reaction mixture was poured onto dilute NaCl solution and repeatedly extracted with diethyl ether. The combined organic layers were washed with water, sat. NaCl, dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the crude product by column chromatography on silica gel [eluant: petroleum-diethyl ether (7:3)] gave a white crystalline solid (recryst. from diethyl ether) (3.36 g, 76 %), m.p. 88 °C. $[\alpha]_D^{30}$ = +56° (c=2, $CHCl_3$) [cf. lit[13] $[\alpha]_D^{30}$ = +56° (c=2, $CHCl_3$)]. δ(400 MHz): 7.90-7.17 (20H, m, aromatic), 4.68-4.36 (7H, m, $C\underline{H}_2Ph$, H-5), 4.06-4.04 (1H, m, H-6), 3.69-3.68 (2H, m, 2 x H-7), 3.56-3.53 (1H, m, H-4), 3.40 (3H, s, $CO_2C\underline{H}_3$), 2.93-2.91 (2H, m, 2 x H-3).

General procedures for the preparation of Methyl [2-Alkyl-2,3-dideoxy-4,5,7-tri-*O*-benzyl-α,ß-D-*arabino*-2-heptulopyranosid]onates

Method I:- From Sulphone (62)

Into a solution of sulphone (**62**) (1 g, 1.79 mmol) in dry THF (5 ml) at -78 °C under nitrogen was added dropwise a solution of 1.0M LDA (2.15 ml, 2.15 mmol). After 15 min, dimethyl carbonate (0.21 ml, 2.51 mmol) was added to the reaction

mixture. When t.l.c. indicated the reaction was complete, a solution of 1.0M LN (4.48 ml, 4.48 mmol) was added to the reaction mixture at -78 °C followed by 2 mol. equivalents of the alkyl halide (3.58 mmol). The reaction mixture was allowed to warm slowly to room temperature before being poured onto water and repeatedly extracted with diethyl ether. The combined ethereal layers were washed with water, brine, dried ($MgSO_4$) and concentrated *in vacuo*. Products were isolated by column chromatography on silica gel eluting with petroleum-diethyl ether mixtures.

Method II:- From Sulphone ester (63)

A solution of sulphone ester (**63**) in dry THF at -78 °C under nitrogen was treated with 2.5 mol. equivalents of 1.0M LN followed by alkyl halide. The reaction mixture was slowly warmed to room temperature. It was then poured onto water and repeatedly extracted with diethyl ether. The combined organic layers were washed with water, brine, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography on silica gel [eluant: petroleum-diethyl ether] yielded the products.

General method for the preparation of 1.0M LN

Into a solution of naphthalene (1.28 g, 10 mmol) in dry THF (10 ml) under argon was added lithium (69 mg, 10 mmol). This reaction mixture was subjected to ultrasonic conditions at room temperature under argon for 2 h after which it was used in the reductive desulphonylation reaction as described above (see methods I and II).

8. Methyl [2-*C*-Allyl-2,3-dideoxy-4,5,7-tri-*O*-benzyl-D-*arabino*-2-heptulopyranosid]onate (64)

Sulphone (**62**) (1.0 g, 1.79 mmol) was transformed to the title compound (**64**) *via* Method I with allyl bromide (0.3 ml, 3.58 mmol) as the alkyl halide. Purification by column chromatography [eluant: petroleum-diethyl ether (17:1)] gave the title product (**64**) as a single unassigned anomer in the form of a colourless oil (0.41 g, 44 %). $[\alpha]_D^{30}$ = +42° (c=1.2, $CHCl_3$). [cf. lit.[13] $[\alpha]_D^{30}$ = +42° (c=1.2, $CHCl_3$)]. δ(400 MHz): 7.39-7.16 (15H, m, aromatic), 5.77 (1H, m, C<u>H</u>=CH_2), 5.13-5.03 (2H, m, CH=C<u>H</u>$_2$), 4.88-4.53 (6H, m, C<u>H</u>$_2$Ph), 3.76 (2H, m, <u>H</u>-4, <u>H</u>-5), 3.68 (3H, s, $CO_2C\underline{H}_3$), 3.58 (3H, m, 2 x <u>H</u>-7, <u>H</u>-6), 2.66 (1H, dd, <u>H</u>-3e, $J_{2e,2a}$ = 12 Hz, $J_{3e,4}$ = 5 Hz), 2.49 (2H, d, C<u>H</u>$_2$-CH=CH_2, J = 8 Hz), 1.54 (1H, dd, <u>H</u>-3a, $J_{3a,3e}$ = 12 Hz, $J_{3a,4}$ = 13 Hz).

9. Methyl [2-*C*-Benzyl-2,3-dideoxy-4,5,7-tri-*O*-benzyl-D-*arabino*-2-heptulopyranosid]onate (65)

Sulphone (**62**) (1.0 g, 1.79 mmol) was subjected to Method I as described above and alkylated with benzyl bromide (0.43 ml, 3.58 mmol). Purification by column chromatography on silica gel [eluant: petroleum-diethyl ether (17:1)] gave the title product (**65**) (0.51 g, 56 %) as an oil as a single unassigned anomer. $[\alpha]_D^{20}$ = +34.4° (c=1, $CHCl_3$). $\tilde{\nu}_{max}$($CHCl_3$): 1735, 1500, 1450, 1380, 1100 cm^{-1}. <u>m/z</u>: 566 (M^+), 475, 369, 351, 309, 261, 181, 91. δ(400 MHz): 7.38-7.16 (20H, m, aromatic), 4.87-4.54 (6H, m, OC<u>H</u>$_2$Ph), 3.79-3.51 (5H, m, 2 x <u>H</u>-7, <u>H</u>-4, <u>H</u>-5, <u>H</u>-6), 3.59 (3H, s,

$CO_2C\underline{H}_3$), 3.08-2.99 (2H, m, $C\underline{H}_2Ph$), 2.65 (1H, dd, $\underline{H}$-3_e, $J_{3e,4}$ = 4.1 Hz, $J_{3e,3a}$ = 7.02 Hz), 1.55 (1H, dd, $\underline{H}$-3_a, $J_{3a,4}$ = 7.02 Hz, $J_{3a,3e}$ = 7.02 Hz). (Found: C, 76.36; H, 6.69. $C_{36}H_{38}O_6$ requires: C, 76.30; H, 6.76 %).

10. Methyl [2,3-Dideoxy-4,5,7-tri-*O*-benzyl-2-*C*-trimethylsilylethoxymethyl-D-*arabino*-2-heptulopyranosid]onate (66)

The sulphone ester (**63**) (1.0 g, 1.62 mmol) was transformed to the title product (**66**) *via* Method I with SEM-Cl (0.57 ml, 3.24 mmol) as the alkyl halide. Purification by column chromatography on silica gel [eluant: petroleum-diethyl ether (17:3)] yielded the product (**66**) (0.69 g, 70 %) as an oil as a single unassigned anomer. $[\alpha]_D^{20}$ = +38.2° (c=1, $CHCl_3$). $\tilde{\nu}_{max}(CHCl_3)$: 1735, 1500, 1450, 1250, 1100 cm^{-1}. m/z: 605.2922 [$(M-H)^+$; Calc. for $C_{35}H_{46}O_7Si$: 606.3013], 548, 273, 181, 91, 73. δ(400 MHz): 7.36-7.15 (15H, m, aromatic), 4.87-4.52 (6H, m, $C\underline{H}_2Ph$), 3.77-3.75 (2H, m, 2 x $\underline{H}$-7), 3.70 (3H, s, $CO_2C\underline{H}_3$), 3.64-3.52 (7H, m, $O(C\underline{H}_2)_2$, $\underline{H}$-4, $\underline{H}$-5, $\underline{H}$-6), 2.75 (1H, dd, $\underline{H}$-3_e, $J_{3e,4}$ = 4.44 Hz, $J_{3e,3a}$ = 13 Hz), 1.57 (1H, dd, $\underline{H}$-3_a, $J_{3a,3e}$ = $J_{3a,4}$ = 13 Hz), 0.91-0.87 (2H, m, $C\underline{H}_2Si(CH_3)_3$), -0.02 (9H, s, $Si(C\underline{H}_3)_3$). (Found: C, 69.15; H, 7.68. $C_{35}H_{46}O_7Si$ requires: C, 69.28; H, 7.64 %).

11. Methyl [2,3-Dideoxy-2-methyl-4,5,7-tri-*O*-benzyl-α,ß-D-*arabino*-2-heptulopyranosid]onate (67)

The sulphone ester (**63**) (0.2 g, 0.32 mmol) was subjected to Method I as described

above and alkylated with methyl iodide (0.04 ml, 0.65 mmol). Purification by column chromatography on silica gel [eluant: petroleum-diethyl ether (4:1)] afforded the title product (**67**) as a mixture of diastereoisomers in the ratio 3:5 (80 mg, 50 %) in the form of an oil. $[\alpha]_D^{20}$ = +54° (c=1, $CHCl_3$). $\tilde{\nu}_{max}(CHCl_3)$ [Major isomer]: 2865, 1742, 1495, 1451, 1361, 1284, 1194, 1097 cm^{-1}. $\tilde{\nu}_{max}$ ($CHCl_3$) [Minor isomer]: 2865, 1728, 1497, 1361, 1285, 1195, 1097 cm^{-1}. m/z: 399 $(M-Bn)^+$, 293, 233, 91. δ(400 MHz) [Minor isomer]: 7.37-7.26 (15H, m, aromatic), 4.94-4.62 (6H, m, $C\underline{H}_2Ph$), 3.88-3.60 (3H, m, H-4, H-5, H-6), 3.72 (3H, s, $CO_2C\underline{H}_3$), 3.49-3.45 (2H, m, 2 x H-7), 2.77 (1H, dd, H-3_e, $J_{3e,4}$ = 4.7 Hz, J_{3e3a} = 13.1 Hz), 1.49 (1H, dd, H-3_a, $J_{3a,3e}$ = $J_{3a,4}$ = 13.1 Hz), 1.44 (3H, s, $C\underline{H}_3$). δ(400 MHz) [Major isomer]: 7.35-7.12 (15H, m, aromatic), 4.86-4.48 (6H, m, $C\underline{H}_2Ph$), 3.74-3.69 (2H, m, 2 x H-7), 3.68 (3H, s, $CO_2C\underline{H}_3$), 3.57-3.52 (3H, m, H-4, H-5, H-6), 2.73 (1H, dd, H-3e, $J_{3e,3a}$ = 13 Hz, $J_{3e,4}$ = 4 Hz), 1.52 (1H, dd, H-3a, $J_{3a,3e}$ = $J_{3a,4}$ = 13 Hz), 1.46 (3H, s, $C\underline{H}_3$). (Found: C, 73.42; H, 7.08. $C_{30}H_{34}O_6$ requires: C, 73.45; H, 6.99 %).

General procedure for the saponification of Methyl [2-Alkyl-2,3-dideoxy-4,5,7-tri-*O*-benzyl-D-*arabino*-2-heptulopyranosid]onates

A solution of ester in MeOH/THF was treated with a solution of KOH in water. The reaction mixture was stirred at room temperature (where necessary, the temperature was increased to facilitate the reaction) and the reaction was followed by t.l.c. On completion, the reaction mixture was diluted with CH_2Cl_2 and washed with 2M HCl. The organic layer was then washed with water, dried ($MgSO_4$) and concentrated under reduced pressure. The acid formed was characterised by infra-

red spectroscopy and was used immediately in the reductive decarboxylation reaction.

12. 2-*C*-Allyl-2,3-dideoxy-3,4,6-tri-*O*-benzyl-D-*arabino*-2-heptulpyranosidonic Acid (71)

A solution of ester (**64**) (0.26 g, 0.52 mmol) in MeOH (1 ml) was treated with a solution of KOH (0.12 g, 2 mmol) in water (0.3 ml). The reaction mixture was stirred for 3 days at 89 °C. It was worked up as described above to give the title product (**71**) (0.2 g, 77 %). $\tilde{\nu}_{max}(CHCl_3)$: 3320 (broad), 3058, 2925, 1732, 1495, 1449, 1091 cm^{-1}.

13. 2-*C*-Benzyl-2,3-dideoxy-3,4,6-tri-*O*-benzyl-D-*arabino*-2-heptulopyranosidonic Acid (72)

The benzyl ester (**65**) (0.2 g, 0.35 mmol) in MeOH (0.5 ml) and THF (0.5 ml) was treated with a solution of KOH (40 mg, 0.7 mmol) in water (0.3 ml). The reaction mixture was warmed to 50 °C and stirred at this temperature for a day. On work up, the title acid (**72**) was obtained (0.14 g, 72 %). $\tilde{\nu}_{max}(CHCl_3)$: 3200 (broad), 1732, 1500, 1450, 1100 cm^{-1}.

14. 2,3-Dideoxy-4,5,6-tri-*O*-benzyl-2-*C*-trimethylsilylethoxymethyl-D-*arabino*-2-heptulopyranosidonic Acid (73)

A solution of ester (**66**) (0.2 g, 0.33 mmol) in MeOH (0.4 ml) and THF (0.4 ml) was treated with a solution of KOH (37 mg, 0.66 mmol) in water (0.1 ml). The reaction mixture was stirred at room temperature. When t.l.c. indicated the reaction was complete, the reaction mixture was worked up as described in the general method. The title compound (**73**) was obtained (0.16 g, 82 %). $\tilde{\nu}_{max}(CHCl_3)$: 3423 (broad), 1735, 1585, 1494, 1397, 1100 cm^{-1}.

15. 2,3-Dideoxy-3,4,6-tri-*O*-benzyl-2-*C*-methyl-α,ß-D-*arabino*-2-heptulopyranosidonic Acid (74)

To a solution of ester (**67**) (0.25 g, 0.51 mmol) in MeOH (0.5 ml) and THF (1 ml) was added a solution of KOH (69 mg, 1.22 mmol) in water (0.2 ml). The reaction mixture was stirred at room temperature until t.l.c. indicated that the reaction was complete. Upon work up as described in the general method, the acid (**74**) was obtained (0.21 g, 88 %). $\tilde{\nu}_{max}(CHCl_3)$: 3500 (broad), 1728, 1500, 1450, 1370, 1100 cm^{-1}.

General method for the reductive decarboxylation of Acids with the heterocyclic salt (22)

To a stirred solution of acid in dry CH_2Cl_2 at room temperature, under argon, in the dark was added the salt (**22**). After 5 min, triethylamine was added to the reaction mixture and the reaction was followed by t.l.c. When no more acid was left (as indicated by t.l.c.), *t*-dodecylmercaptan was then added and the reaction mixture was photolysed with a 500W tungsten lamp at 0 °C for 1 h. Evaporation of the solvent followed by column chromatography of the residue gave the desired product.

16. 1-*C*-Allyl-1,2-dideoxy-3,4,6-tri-*O*-benzyl-ß-D-*arabino*-pyranose (76)

The acid (**71**) (0.2 g, 0.4 mmol) in dry CH_2Cl_2 (3 ml) was stirred with the salt (**22**) (94 mg, 0.5 mmol) and triethylamine (0.07 ml, 0.5 mmol) under the conditions described above. After 2.5 h, *t*-dodecylmercaptan (0.47 ml, 1.99 mmol) was added and the reaction mixture photolysed for 1 h at 0 °C. Purification by column chromatography on silica gel [eluant: petroleum-diethyl ether (19:1)] gave the title product (**76**) as a colourless oil in the form of a single anomer (0.13 g, 73 %). $[\alpha]_D^{20}$ = +7.6° (c=1, $CHCl_3$). $\tilde{\nu}_{max}$($CHCl_3$): 3049, 1500, 1450, 1370, 1100 cm^{-1}. m/z: 368 $(M\text{-}Bn)^+$, 181, 153, 107, 91, 41. δ(400 MHz): 7.37-7.17 (15H, m, aromatic), 5.86-5.79 (1H, m, C<u>H</u>=CH_2), 5.12-5.11 (2H, m, CH=C<u>H</u>$_2$), 5.08-4.52 (6H, m, C<u>H</u>$_2$Ph), 3.75-3.66 (2H, m, 2 x <u>H</u>-6), 3.65-3.61 (1H, m, <u>H</u>-1), 3.5-3.45 (1H, dd, <u>H</u>-4, $J_{4,3}$ = $J_{4,5}$ = 8.6 Hz), 3.42-3.41 (1H, ddd, <u>H</u>-3, $J_{3,4}$ = 8.6 Hz, $J_{3,2e}$ = 1.8 Hz, $J_{3,2a}$ = 11.8 Hz), 3.40-3.38 (1H, m, <u>H</u>-5), 2.46-2.22 (2H, m, C<u>H</u>$_2$CH=CH_2), 2.18 (1H,

ddd, H-2_e, $J_{2e,3}$ = 1.8 Hz, $J_{2e,1}$ = 3.2 Hz, $J_{2e,2a}$ = 11.8 Hz), 1.39 (1H, ddd, H-2_a, $J_{2a,3}$ = $J_{2a,1}$ = $J_{2a,2e}$ = 11.8 Hz). (Found: C, 78.37; H, 7.38. $C_{30}H_{34}O_4$ requires: C, 78.57; H, 7.47 %).

17. 1-*C*-Benzyl-1,2-dideoxy-3,4,6-tri-*O*-benzyl-ß-D-*arabino*-pyranose (77)

A solution of acid (72) (0.13 g, 0.24 mmol) in dry CH_2Cl_2 (3 ml) was stirred with the salt (22) (54 mg, 0.28 mmol) and triethylamine (0.04 ml, 0.28 mmol) under the conditions described in the general procedure above. After 2.5 h, *t*-dodecylmercaptan (0.28 ml, 1.18 mmol) was added and the reaction mixture photolysed at 0 °C for 1 h. Purification by column chromatography [eluant: petroleum-diethyl ether (9:1)] gave the title product as a single white crystalline anomer (0.11 g, 92 %) [recryst. from diethyl ether-petroleum] with m.p. 42-43 °C. $[\alpha]_D^{20}$ = +8° (c=1, $CHCl_3$). $\tilde{\nu}_{max}$($CHCl_3$): 1500, 1450, 1085 cm^{-1}. m/z: 507 $(M-H)^+$, 417, 293, 203, 181, 91. δ(400 MHz): 7.38-7.19 (20H, m, aromatic), 4.91-4.55 (6H, m, OCH_2Ph), 3.78-3.69 (2H, m, 2 x H-6), 3.63-3.57 (2H, m, H-1, H-3), 3.54-3.49 (1H, ddd, H-4, $J_{4,5}$ = $J_{4,3}$ = 9.6 Hz), 3.44-3.40 (1H, ddd, H-5, $J_{5,4}$ = 9.6 Hz, $J_{5,6m}$ = 4.6 Hz, $J_{5,6n}$ = 1.9 Hz), 3.10-2.71 (2H, m, CH_2Ph), 2.13 (1H, ddd, H-2_e, $J_{2e,2a}$ = 12.6 Hz, $J_{2e,3}$ = 1.7 Hz, $J_{2e,1}$ = 4.94 Hz), 1.45 (1H, ddd, H-2_a, $J_{2a,3}$ = $J_{2a,2e}$ = $J_{2a,1}$ = 12.6 Hz). (Found: C, 80.05; H, 7.26. $C_{34}H_{36}O_4$ requires: C, 80.28; H, 7.13 %).

18. 1,2-Dideoxy-3,4,6-tri-*O*-benzyl-1-*C*-trimethylsilylethoxymethyl-ß-D-*arabino*-pyranose (78)

A solution of acid (**73**) (0.15 g, 0.25 mmol) in dry CH_2Cl_2 (3 ml) was stirred with the salt (**22**) (58 mg, 0.3 mmol) and triethylamine (0.04 ml, 0.3 mmol) under the reaction conditions described in the general procedure. After 1 h, *t*-dodecylmercaptan (0.3 ml, 1.27 mmol) was added and the reaction mixture photolysed at 0 °C for 1 h. Purification by column chromatography [eluant: petroleum-diethyl ether (4:1)] afforded the product (**78**) as a single anomer in the form of an oil (80 mg, 58 %). $[\alpha]_D^{20}$ = +15° (c=1, $CHCl_3$). $\tilde{\nu}_{max}$($CHCl_3$):2865, 1601, 1528, 1495, 1451, 1361, 1091 cm^{-1}. m/z: 457 $(M\text{-}Bn)^+$, 447, 215, 181, 91. δ(400 MHz): 7.34-7.15 (15H, m, aromatic), 4.96-4.50 (6H, m, $C\underline{H}_2Ph$), 3.82-3.34 (9H, m, H-3, H-4, H-5, 2 x H-6, $C\underline{H}_2OC\underline{H}_2$), 2.24 (1H, ddd, H-2e, $J_{2e,2a}$ = 11.2 Hz, $J_{2e,3}$ = 1.1 Hz, $J_{2e,1}$ = 5 Hz), 1.43 (1H, ddd, H-2a, $J_{2a,2e} = J_{2a,3} = J_{2a,1}$ = 11.2 Hz), 0.94 (2H, m, $C\underline{H}_2Si(CH_3)_3$), 0.02 (9H, s, $Si(C\underline{H}_3)_3$). (Found: C, 72.03; H, 7.95. $C_{33}H_{44}O_5Si$ requires: C, 72.22; H, 8.08 %).

19. 1,2-Dideoxy-3,4,6-tri-*O*-benzyl-1-*C*-methyl-ß-D-*arabino*-pyranose (79)

A solution of acid (**74**) (0.186 g, 0.39 mmol) in dry CH_2Cl_2 (3 ml) was stirred with the salt (**22**) (93 mg, 0.49 mmol) and triethylamine (0.07 ml, 0.49 mmol) under the conditions described in the general procedure. After 1 h, *t*-dodecylmercaptan (0.46 ml, 0.2 mmol) was added and the reaction mixture photolysed at 0 °C for 1 h. Purification by column chromatography [eluant: petroleum-diethyl ether (85:15)] gave the title product (**79**) as a single anomer (94

mg, 56 %). $[\alpha]_D^{20}$ = +23° (c=1, CCl_4). $\tilde{\nu}_{max}$($CHCl_3$): 1500, 1450, 1365, 1100 cm^{-1}. m/z: 417 $(M-CH_3)^+$, 181, 169, 145, 127, 105, 107, 97, 91, 77. δ(400 MHz): 7.36-7.15 (15H, m, aromatic), 4.89-4.50 (6H, m, CH_2Ph), 3.74-3.61 (3H, m, 2 x H-6, H-3), 3.53-3.49 (1H, m, H-1), 3.49-3.44 (1H, dd, H-4, $J_{4,3} = J_{4,5}$ = 12.6 Hz), 3.43-3.41 (1H, ddd, H-5, $J_{5,4}$ = 12.6 Hz, $J_{5,6m}$ = 4.8 Hz, $J_{5,6n}$ = 1.86 Hz), 2.13 (1H, ddd, H-2_e, $J_{2e,2a}$ = 11.5 Hz, $J_{2e,1}$ = 3.2 Hz, $J_{2e,3}$ = 1.8 Hz), 1.44 (1H, ddd, H-2_a, $J_{2a,2e} = J_{2a,3} = J_{2a,1}$ = 11.5 Hz), 1.26 (1H, d, CH_3, J = 6.14 Hz). (Found: C, 77.51; H, 7.62. $C_{28}H_{32}O_4$ requires: C, 77.75; H, 7.46 %).

20. Methyl [4,5,7-tri-*O*-benzyl-3-deoxy-2-(pent-4-yn-1-yl)-D-*arabino*-2-heptulopyranosid]onate (100)

To a stirred solution of sulphone ester (**63**) (1.3 g, 2.1 mmol) in dry THF (5 ml) at -78 °C under argon was added a solution of 1.0M LN in THF (5.27 ml, 5.27 mmol) followed by 5-iodo-pent-1-yne (**99**) (0.82 g, 4.2 mmol). The reaction mixture was slowly warmed to room temperature. It was then poured onto dil. NaCl and repeatedly extracted with diethyl ether. The combined organic layers were washed with water, sat. NaCl, dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the crude product by column chromatography on silica gel [eluant: petroleum-diethyl ether (4:1)] gave the title product (**100**) (0.3 g, 26 %) in the form of an oil. $[\alpha]_D^{20}$ = +41° (c=1, $CHCl_3$). $\tilde{\nu}_{max}$ ($CHCl_3$): 1735, 1495, 1448, 1364, 1114, 1087 cm^{-1}. m/z: 451.2120 [$(M-Bn)^+$; Calc. for $C_{34}H_{38}O_6$: 542.2668], 375, 345, 267, 249, 237, 207, 91. δ(400 MHz): 7.38-7.19 (15H, m, aromatic), 4.90-4.56 (6H, m, CH_2Ph), 3.77 (1H, ddd, H-4, $J_{4,3a} = J_{4,5}$ = 11 Hz, $J_{4,3e}$ = 3 Hz), 3.75 (1H, dd, H-5,

$J_{5,4}$ = $J_{5,6}$ = 11 Hz), 3.70 (3H, s, $CO_2C\underline{H}_3$), 3.63-3.56 (3H, m, 2 x $\underline{H}$-7, $\underline{H}$-6), 2.71 (1H, dd, $\underline{H}$-3e, $J_{3e,4}$ = 3 Hz, $J_{3e,3a}$ = 11 Hz), 2.22-2.17 (2H, m, $(CH_2)_2C\underline{H}_2C{\equiv}CH$), 1.97-1.47 (6H, m, $(C\underline{H}_2)_2CH_2C{\equiv}C\underline{H}$, $\underline{H}$-3a).

21. 4,5,7-Tri-*O*-benzyl-3-deoxy-2-(pent-4-yn-1-yl)-D-*arabino*-2-heptulopyranosidonic Acid (101)

To a stirred solution of ester (**100**) (0.1 g, 0.18 mmol) in methanol (0.5 ml) was added Claisen's alkali (0.5 ml). The reaction was stirred at room temperature. When the reaction was complete, as indicated by t.l.c., it was diluted with CH_2Cl_2 and washed with 2M HCl, water, sat. NaCl, dried ($MgSO_4$) and concentrated under reduced pressure. The title compound (**101**) (90 mg, 93 %), $\tilde{\nu}_{max}$ ($CHCl_3$): 3332 (broad), 2880, 1728, 1496, 1455, 1362, 1118, 1090 cm^{-1}, was not purified but used immediately in the following reaction.

22. 1-Carbomethoxy-3,4,6-tri-*O*-benzyl-D-glucal (110)

Sulphone ester (**63**) (1.26 g, 2.04 mmol) was heated with finely ground calcium oxide (0.13 g, 2.4 mmol) in a Kugelrohr apparatus at 200 °C at 15 mmHg. When t.l.c. of an aliquot showed that the reaction was complete, it was diluted with chloroform, filtered through celite and the filtrate washed with 5% $NaHCO_3$, water, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography on silica gel [eluant: petroleum-diethyl ether (3:2)] gave the title product (**110**) as a white crystalline solid (0.86 g, 89 %) with m.p. 70-71 °C. (cf. lit.[13] m.p. 70-71 °C). $[\alpha]_D^{27}$ = +5° (c=1, MeOH). δ(400 MHz): 7.34-7.22 (15H, m, aromatic), 6.11 (1H, d, H-2, $J_{2,3}$ = 3.06 Hz), 4.29-4.27 (1H, dd, H-3, $J_{2,3}$ = 3.06 Hz, $J_{3,4}$ = 6.2 Hz), 4.20-4.17 (1H, dt, H-5, $J_{5,6}$ = 3.81 Hz, $J_{5,4}$ = 8.54 Hz), 3.96-3.92 (1H, dd, H-4, $J_{4,5}$ = 8.54 Hz, $J_{4,3}$ = 6.2 Hz), 3.85-3.84 (2H, d, 2 x H-6, $J_{6,5}$ = 3.81 Hz), 3.81 (3H, s, CO_2CH_3).

23. Methyl [4,5,7-Tri-*O*-benzyl-α-D-*gluco*-2-heptulopyranos]onate (118)

The α,ß-unsaturated ester (**110**) (1.2 g, 2.53 mmol) in THF (3 ml) and *t*-BuOH (4 ml) was treated with pyridine (0.2 ml, 2.47 mmol), *N*-methylmorpholine-*N*-oxide (0.39 g, 2.87 mmol) and water (1.3 ml). A catalytic amount of osmium tetroxide (one crystal) was added. The reaction mixture was then heated to reflux under nitrogen for 2.5 h after which it was cooled to room temperature before 20% sodium metabisulphite (10 ml) was added. The mixture was then stirred for 5 min before the *t*-BuOH was evaporated off under reduced pressure. Dilute NaCl solution

was added and the mixture repeatedly extracted with diethyl ether. The combined ethereal layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The product (**118**) was recrystallised from diethyl ether-petroleum to give a white crystalline solid (1.19 g, 92 %), m.p. 97-99 °C. $[\alpha]_D^{20}$ = +51.3° (c=1, $CHCl_3$). $\tilde{\nu}_{max}(CHCl_3)$: 3689, 3560, 3512, 1744, 1600, 1160, 1088 cm^{-1}. m/z: 418 (M-Bn)$^+$, 327, 221, 205, 181, 107, 91. δ(400 MHz): 7.38-7.16 (15H, m, aromatic), 4.88-4.49 (6H, m, CH_2Ph), 4.26 (1H, d, anomeric OH, J = 1.23 Hz), 4.06-4.03 (2H, m, H-6, H-3), 3.88 (3H, s, CO_2CH_3), 3.79-3.63 (4H, m, 2 x H-7, H-4, H-5), 2.06 (1H, d, OH, J = 8.8 Hz). (Found: C, 68.21; H, 6.15. $C_{29}H_{32}O_8$ requires: C, 68.49; H, 6.34 %).

24. Methyl [2,3-*O*-Isopropylidene-4,5,7-tri-*O*-benzyl-α-D-*gluco*-2-heptulopyranosid]onate (119)

A solution of diol (**118**) (0.2 g, 0.39 mmol) in dry toluene (6 ml) at 0 °C was treated with 2,2-dimethoxypropane (4 ml). To this mixture was bubbled a slow stream of HCl gas for 5 min. The reaction mixture was concentrated under reduced pressure and the residue chromatographed on silica gel [eluant: petroleum-diethyl ether (7:3)] to give the title product (**119**) as a colourless oil (0.16 g, 76 %). $[\alpha]_D^{20}$ = +15° (c=0.5, $CHCl_3$). $\tilde{\nu}_{max}(CHCl_3)$: 1744, 1460, 1384, 1375, 1110, 1070 cm^{-1}. m/z: 548 (M)$^+$, 492, 458, 399, 351, 181, 91. δ(400 MHz): 7.36-7.15 (15H, m, aromatic), 4.90-4.89 (1H, dd, H-3, $J_{3,4}$ = 1.8 Hz, W coupling $J_{3,5}$ = 1 Hz), 4.65-4.26 (6H, m, CH_2Ph), 4.03-3.94 (2H, m, H-4, H-6), 3.82 (3H, s, CO_2CH_3), 3.69-3.62 (3H, m, 2 x H-7, H-5, $J_{4,5}$ = 1.8 Hz, $J_{5,6}$ = 9.5 Hz), 1.59 (3H, s, CCH_3), 1.46 (3H, s, CCH_3).

(Found: C, 69.79; H, 6.51. $C_{32}H_{35}O_8$ requires: C, 70.06; H, 6.61 %).

25. 2,3-*O*-Isopropylidene-4,5,7-tri-*O*-benzyl-α-D-*gluco*-2-heptulopyranosonic Acid (121)

A solution of ester (**119**) (0.15 g, 0.27 mmol) in MeOH (0.4 ml) and THF (2.1 ml) was treated with a solution of potassium hydroxide (31 mg, 0.55 mmol) in water (0.2 ml). After stirring for 1.5 h at room temperature, the reaction mixture was diluted with CH_2Cl_2 and washed with 2M HCl, water, dried ($MgSO_4$) and concentrated under reduced pressure to give the title acid (**121**) (0.13 g, 89 %) , $\tilde{\nu}_{max}(CHCl_3)$: 3433 (broad), 1782, 1368, 1100, 1080 cm^{-1}, which was not purified further but used immediately in the next stage.

26. 1,2-*O*-Isopropylidene-3,4,6-tri-*O*-benzyl-ß-D-*gluco*-pyranose (123)

A solution of acid (**121**) (0.16 g, 0.3 mmol) in dry CH_2Cl_2 (3 ml) was stirred with the salt (**22**) (68 mg, 0.36 mmol) and triethylamine (0.05 ml, 0.36 mmol) under argon, in the dark, at room temperature for 3.5 h. *t*-Dodecylmercaptan (0.35 ml, 1.5 mmol) was then added and the mixture photolysed with a 500W tungsten lamp under argon at 0 °C for 1 h. The reaction mixture was concentrated under reduced pressure. Purification by column chromatography on silica gel [eluant: petroleum-diethyl ether (17:3)] gave the title product (123) a single white crystalline anomer (0.11 g, 75 %), m.p. 55 °C. $[\alpha]_D^{20}$ = +39.4° (c=1, $CHCl_3$). $\tilde{\nu}_{max}(CHCl_3)$: 1495, 1450,

1381, 1368, 1100 cm^{-1}. m/z: 490 $(M)^+$, 489, 475, 432, 423, 399, 341, 91. δ(400 MHz): 7.39-7.19 (15H, m, aromatic), 5.65 (1H, d, H-1, $J_{1,2}$ = 4.88 Hz), 4.74-4.41 (6H, m, CH_2Ph), 4.27 (1H, dd, H-2, $J_{2,1}$ = 4.88 Hz, $J_{2,3}$ = 3.79 Hz), 3.95-3.90 (1H, dd, H-3, $J_{3,4}$ = $J_{3,2}$ = 3.79 Hz), 3.93-3.90 (1H, m, H-5), 3.74-3.71 (1H, dd, H-4, $J_{4,3}$ = 3.79 Hz, $J_{4,5}$ = 9.6 Hz), 3.66-3.65 (2H, m, 2 x H-6), 1.54 (3H, s, $C(CH_3)_2$), 1.36 (3H, s, $C(CH_3)_2$). (Found: C, 73.34; H, 6.84. $C_{30}H_{34}O_6$ requires: C, 73.45; H, 6.99 %).

27. 3,4,6-Tri-*O*-benzyl-α,ß-D-*gluco*-pyranose (127)

A solution of (**123**) (25 mg, 5 x 10^{-5} mol) in THF (0.5 ml) was treated with 2M HCl (0.5 ml) and the reaction mixture was stirred at room temperature for a day. The reaction mixture was then neutralised with 5% $NaHCO_3$ and repeatedly extracted with ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography on silica gel [eluant: petroleum-diethyl ether (1:4)] gave the glucoside (**127**),a mixture of anomers in the ratio 1:2 (α:ß), as a white crystalline solid (17 mg, 74 %), m.p. 88-90 °C. $[\alpha]_D^{20}$ = +58° (c=0.9, $CHCl_3$). [cf. lit.[66] m.p. 85-86 °C, $[\alpha]_D$ = +57.1° (c = 0.9, $CHCl_3$)] δ(400 MHz): 7.36-7.11 (15H, m, aromatic), 5.25 (1H, dd, H-1, $J_{1,2}$ = 3.36 Hz, $J_{1,OH}$ = 2.24 Hz), 4.86-4.47 (6H, m, CH_2Ph), 4.05-4.01 (1H, m, H-5), 3.80-3.45 (5H, m, H-2, H-3, H-4, 2 x H-6), 3.31 (1H, d, OH-1 of major isomer, $J_{1,OH}$ = 3.36 Hz), 2.44 (1H, d, OH-1 of minor isomer, J = 2.24 Hz), 2.21 (1H, d, OH-2, J = 7.3 Hz).

28. Acetyl 2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-α,ß-D-*gluco*-pyranoside (128)

A solution of diol (**127**) (3 mg, 0.7 x 10^{-5} mol) in pyridine (0.5 ml) was stirred with acetic anhydride (4 mg, 4 x 10^{-5} mol) at room temperature. When the reaction was complete, as indicated by t.l.c., the solvent was evaporated under reduced pressure and the residue dried at 50 °C at 0.1 mmHg. The title product (**128**) (3.2 mg, 91 %) was obtained as a mixture of anomers in the ratio 1:2 (ß:α). δ(400 MHz): 7.33-7.11 (15H, m, aromatic), 6.27 (1H, d, H-1 of α-isomer, $J_{1,2}$ = 3.55 Hz), 5.58 (1H, d, H-1 of ß-isomer, $J_{1,2}$ = 8.23 Hz), 5.10 (1H, dd, H-2 of ß-isomer, $J_{2,1}$ = 8.23 Hz, $J_{2,3}$ = 9.4 Hz), 5.03 (1H, dd, H-2 of α-isomer, $J_{2,1}$ = 3.55 Hz, $J_{2,3}$ = 10 Hz), 4.83-4.46 (6H, m, CH_2Ph), 3.99-3.94 (1H, dd, H-4, $J_{4,3}$ = 9 Hz, $J_{4,5}$ = 10 Hz), 3.90-3.87 (1H, ddd, H-5 of ß-isomer, $J_{5,4}$ = 10 Hz, $J_{5,6a}$ = 1.74 Hz, $J_{5,6a}$ = 3.21 Hz), 3.83-3.63 (3H, m, 2 x H-6, H-3), 3.59-3.56 (1H, m, H-5 of α-isomer), 2.09 (3H, s, CH_3 of α-isomer), 2.06 (3H, s, CH_3 of ß-isomer), 1.95 (3H, s, CH_3 of α-isomer), 1.91 (3H, s, CH_3 of ß-isomer).

29. Methyl [4,5,7-Tri-*O*-benzyl-3-*O*-*t*-butyldimethylsilyl-α-D-*gluco*-2-heptulopyranos]onate (129)

A solution of diol (**118**) (0.72 g, 1.42 mmol) in dry CH_2Cl_2 (1.42 ml) was stirred at 0 °C under nitrogen. Into this solution was added 2,4,6-collidine (0.41 ml, 3.11 mmol) followed by TBDMS-triflate (0.33 ml, 1.42 mmol). After 10 min the reaction mixture was diluted with diethyl ether, washed with 2M HCl, water, brine, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column

chromatography on silica gel [eluant: petroleum-diethyl ether (3:2)] afforded the product (**129**) (0.82 g, 93 %) as a single anomer. $[\alpha]_D^{20}$ = +19.6° (c=1, $CHCl_3$). $\tilde{\nu}_{max}(CHCl_3)$: 3686, 3519, 1745, 1251, 1171, 1151, 1070 cm^{-1}. m/z: 565.2268 [(M-$^tBu)^+$; Calc. for $C_{35}H_{46}O_8Si$: 622.29616], 547, 259, 181, 91. δ(400 MHz): 7.36-6.99 (15H, m, aromatic), 5.04-4.51 (6H, m, $C\underline{H}_2Ph$), 4.13 (1H, d, H-3, $J_{3,4}$ = 7.9 Hz), 4.07-4.03 (1H, ddd, H-6, $J_{5,6}$ = 9.6 Hz, $J_{6,7m}$ = 3.8 Hz, $J_{6,7n}$ = 1.7 Hz), 3.85 (3H, s, $CO_2C\underline{H}_3$), 3.87-3.63 (3H, m, H-7n, H-4, H-5), 3.64 (1H, dd, H-7m, $J_{6,7n}$ = 1.7 Hz, $J_{7n,7m}$ = 11.14 Hz), 0.81 (9H, s, $C(C\underline{H}_3)_3$), 0.01 (3H, s, $SiC\underline{H}_3$), -0.04 (3H, s, $SiC\underline{H}_3$). (Found: C, 67.87; H, 7.43. $C_{35}H_{46}O_8Si$ requires: C, 67.50; H, 7.44 %).

30. Methyl [3-*O*-*t*-Butyldimethylsilyl-2-deoxy-2-fluoro-4,5,7-tri-*O*-benzyl-α,ß-D-*gluco*-2-heptulopyranosid]onate (130)

A solution of (**129**) (0.65 g, 1.04 mmol) in dry CH_2Cl_2 (1.04 ml) at 0 °C under nitrogen was added dropwise of DAST (0.41 ml, 3.13 mmol). After 10 min, cold water (3 ml) was added to the reaction mixture. The reaction mixture was then diluted with CH_2Cl_2, washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was column chromatographed on silica gel [eluant: petroleum-diethyl ether (9:1)] to give the product (**130**) as a mixture of isomers in the ratio 1:3 (0.61 g, 94 %). $[\alpha]_D^{26}$ = +6° (c=0.5, $CHCl_3$). $\tilde{\nu}_{max}(CHCl_3)$: 1765, 1745, 1117, 1084 cm^{-1}. m/z: 558, 543, 532, 459, 181, 91, 57. δ(400 MHz): 7.32-7.06 (15H, m, aromatic), 4.83-4.49 (6H, m, $C\underline{H}_2Ph$), 4.23-3.82 (3H, m, H-3, H-4, H-6), 3.82 (3H, s, $CO_2C\underline{H}_3$ of minor isomer), 3.80 (3H, s, $CO_2C\underline{H}_3$ of major isomer), 3.78-3.67 (3H, m, 2 x H-7, H-5), 0.82 (9H, s, $C(C\underline{H}_3)_3$ of major isomer), 0.80 (9H, s, $C(C\underline{H}_3)_3$ of minor

isomer), 0.09 (3H, s, Si(C$\underline{H}_3$)$_2$ of major isomer), 0.007 (3H, s, Si(C$\underline{H}_3$)$_2$ of major isomer), 0.002 (3H, s, Si(C$\underline{H}_3$)$_2$ of minor isomer), -0.05 (3H, s, Si(C$\underline{H}_3$)$_2$ of minor isomer). δ(376.3 MHz, ^{19}F n.m.r.)(Ref: $CFCl_3$): 25.1 (1F, d, J = 15 Hz, Major isomer), 0.03 (1F, d, J = 20.6 Hz, Minor isomer). (Found: C, 67.22; H, 7.38. $C_{35}H_{45}O_7SiF$ requires: C, 67.28; H, 7.26 %).

31. Methyl [3-*O*-*t*-Butyldimethylsilyl-2-deoxy-2-chloro-4,5,7-tri-*O*-benzyl-α,ß-D-*gluco*-2-heptulopyranosid]onate (131)

A solution of (**129**) (0.26 g, 0.42 mmol) in dry CH_2Cl_2 (2 ml) under argon at room temperature was treated with pyridine (0.03 ml, 0.42 mmol) followed by thionyl chloride (0.03 ml, 0.42 mmol). After 10 min, the reaction mixture was washed with 2M HCl, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography on silica gel [eluant: petroleum-diethyl ether (5:1)] yielded the title product (**131**) as a mixture of isomers in the ratio 1:3 (0.26 g, 97 %). $[\alpha]_D^{20}$ = +22° (c=1, $CHCl_3$). $\tilde{\nu}_{max}$($CHCl_3$): 1768, 1748, 1451, 1361, 1251, 1091 cm^{-1}. m/z: 585, 583, 547, 457, 259, 181, 105, 91. δ(400 MHz): 7.38-6.99 (15H, m, aromatic), 4.98-4.26 (7H, m, C$\underline{H}_2$Ph, $\underline{H}$-3), 4.22-4.18 (1H, m, $\underline{H}$-6 of major isomer), 4.14-4.09 (1H, m, $\underline{H}$-6 of minor isomer), 3.85-3.64 (5H, m, 2 x $\underline{H}$-7, $\underline{H}$-5, $\underline{H}$-4), 3.82 (3H, s, $CO_2C\underline{H}_3$), 0.82 (9H, s, C(C$\underline{H}_3$)$_3$ of minor isomer), 0.81 (9H, s, C(C$\underline{H}_3$)$_3$ of major isomer), 0.07 (6H, s, SiC$\underline{H}_3$ of minor isomer), 0.05 (6H, s, SiC$\underline{H}_3$ of major isomer). (Found: C, 65.69; H, 6.98; Cl, 5.71. $C_{35}H_{45}O_7ClSi$ requires C, 65.55; H, 7.07; Cl, 5.53 %).

32. Methyl [Methyl 3-*O*-*t*-Butyldimethylsilyl-4,5,7-tri-*O*-benzyl-α,ß-D-*gluco*-2-heptulopyranosid]onate (132)

To a stirred solution of the glycosyl chloride (**131**) (0.5 g, 0.78 mmol) in dry 1,4-dioxan (4 ml) were added activated 4Å molecular sieves followed by magnesium bromide etherate (1.01 g, 3.9 mmol). Anhydrous methanol (3 ml) was added and the reaction mixture was heated to reflux under argon for one day. It was then cooled to room temperature and diluted with diethyl ether, washed with water, brine, dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography [eluant: petroleum-diethyl ether (9:1)] gave the desired products (**132**) as two separate isomers in the ratio (1:3.4) (0.4 g, 80 %). $[\alpha]_D^{25}$ (Major isomer) = +27° (c=1, CCl_4). $[\alpha]_D^{25}$ (Minor isomer) = +24° (c=1, CCl_4). $\tilde{\nu}_{max}$ ($CHCl_3$) [Major isomer]: 1752, 1495, 1451, 1435, 1256, 1207, 1112, 1071, 1053 cm^{-1}. $\tilde{\nu}_{max}$ ($CHCl_3$) [Minor isomer]: 1759, 1736, 1451, 1360, 1253, 1249, 1097 cm^{-1}. m/z [Major anomer]: 579 (M-^{t}Bu)$^+$, 578, 547, 457, 277, 271, 259, 231, 207, 181, 91. m/z [Minor anomer]: 579 (M-^{t}Bu)$^+$, 578, 547, 457, 365, 349, 259, 231, 201, 181, 91. δ(400 MHz) [Major isomer]: 7.35-6.96 (15H, m, aromatic), 4.97-4.62 (6H, m, C$\underline{H}_2$Ph), 4.55-4.46 (1H, m, $\underline{H}$-6), 3.99-3.81 (3H, m, $\underline{H}$-3, $\underline{H}$-4, $\underline{H}$-5), 3.78 (3H, s, $CO_2C\underline{H}_3$), 3.76-3.66 (2H, m, 2 x $\underline{H}$-7), 3.42 (3H, s, $OC\underline{H}_3$), 0.82 (9H, s, ^{t}Bu), -0.03 (3H, s, $Si(C\underline{H}_3)_2$), -0.08 (3H, s, $Si(C\underline{H}_3)_2$). δ(400 MHz) [Minor isomer]: 7.33-7.09 (15H, m, aromatic), 4.79-4.51 (6H, m, C$\underline{H}_2$Ph), 4.27-4.24 (1H, dt, $\underline{H}$-6, $J_{6,7}$ = 2 Hz, $J_{6,5}$ = 10 Hz), 3.94-3.77 (3H, m, $\underline{H}$-3, $\underline{H}$-4, $\underline{H}$-5), 3.76 (3H, s, $CO_2C\underline{H}_3$), 3.75-3.39 (2H, m, 2 x $\underline{H}$-7), 3.37 (3H, s, $OC\underline{H}_3$), 0.81 (9H, s, ^{t}Bu), 0.06 (3H, s, $Si(C\underline{H}_3)_2$), -0.02 (3H, s, $Si(C\underline{H}_3)_2$). (Found for minor isomer: C, 67.51; H, 7.54. $C_{36}H_{48}O_8Si$ requires: C, 67.90; H, 7.60 %). (Found for major isomer: C, 67.80; H,

7.69. $C_{36}H_{48}O_8Si$ requires: C, 67.90; H, 7.60 %).

33. Methyl 3-*O*-*t*-Butyldimethylsilyl-4,5,7-tri-*O*-benzyl-α,ß-D-*gluco*-2-heptulopyranosidonic Acid (133)

A solution of ester (**132**) (0.1 g, 0.16 mmol) in MeOH (0.5 ml) was treated with a solution of KOH (26 mg, 0.47 mmol) in water (0.3 ml). After stirring at room temperature for 2 h, the reaction mixture was diluted with $CHCl_3$ and washed with 2M HCl, dried ($MgSO_4$) and concentrated under reduced pressure to give the desired acid (**133**) (96 mg, 98 %), $\tilde{\nu}_{max}(CHCl_3)$: 3400 (broad), 1796, 1776, 1727, 1360, 1258, 1080, 1048, cm-1, which was used without any further purification.

34. Methyl 2-*O*-*t*-Butyldimethylsilyl-3,4,6-tri-*O*-benzyl-ß-D-*gluco*-pyranoside (135)

A solution of acid (**133**) (90 mg, 0.15 mmol) in dry CH_2Cl_2 (1 ml) was subjected to reductive decarboxylation *via* the general procedure as described for ulosonic acid derivatives. Purification by column chromatography on silica gel [eluant: petroleum-diethyl ether (8:1)] gave the title product (**135**) as a single anomer (55 mg, 65 %). $[\alpha]_D^{20}$ = -24° (c=1, $CHCl_3$). $\tilde{\nu}_{max}$ ($CHCl_3$): 2925, 2845, 1598, 1495, 1448, 1358, 1254, 1124, 1067 cm^{-1}. m/z: 577.3000 [$(M-H)^+$; Calc. for $C_{34}H_{46}O_6Si$: 578.3063], 547, 487, 455, 277, 207, 181, 91, 73, 57. δ(400 MHz): 7.34-7.06 (15H, m, aromatic), 4.91-4.47 (6H, m, CH_2Ph), 4.11-4.09 (1H, m, H-1), 3.75-3.64 (2H, m, 2 x H-6), 3.57-3.50 (1H, m, H-5), 3.5 (3H, s, CO_2CH_3), 3.49-3.44 (3H, m, H-2, H-

3, H-4), 0.87 (9H, s, C(C$\underline{H}_3$)$_3$), 0.08 (3H, s, SiC$\underline{H}_3$), 0.04 (3H, s, SiC$\underline{H}_3$). δ(400 MHz): (d-toluene): 7.53-7.16 (15H, m, aromatic), 5.08-4.57 (6H, m, C$\underline{H}_2$Ph), 4.15 (1H, d, H-1, $J_{1,2}$ = 7.52 Hz), 3.83 (2H, d, 2 x H-6, $J_{5,6}$ = 3.27 Hz), 3.81 (1H, dd, H-2, $J_{2,1}$ = 7.5 Hz, $J_{2,3}$ = 8.05 Hz), 3.79 (1H, dd, H-4, $J_{4,3}$ = $J_{4,5}$ = 9 Hz),3.62 (1H, dd, H-3, $J_{2,3}$ = $J_{3,4}$ = 8.05 Hz), 3.52 (3H, s, OC$\underline{H}_3$), 3.48 (1H, dt, H-5, $J_{5,4}$ = 9 Hz, $J_{5,6}$ = 3.27 Hz), 1.19 (9H, s, C(C$\underline{H}_3$)$_3$), 0.39 (3H, s, Si(C$\underline{H}_3$)$_2$), 0.32 (3H, s, Si(C$\underline{H}_3$)$_2$). (Found: C, 70.34; H, 8.18. $C_{34}H_{46}O_6Si$ requires: C, 70.55; H, 8.01 %).

35. Methyl 3,4,6-Tri-*O*-benzyl-ß-D-*gluco*-pyranoside (137)

To a stirred solution of (**135**) (43 mg, 0.07 mmol) in dry THF (0.5 ml) with 4Å molecular sieves under argon at room temperature was added 1.0M TBAF in THF (0.15 ml, 0.15 mmol). The reaction mixture was stirred for a day at room temperature, poured onto water and repeatedly extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography on silica gel [eluant: petroleum-diethyl ether (3:2)] afforded the title product (**137**) as a white crystalline solid (26 mg, 74 %), m.p. 74-75 °C. $[\alpha]_D^{20}$ = -5° (c=1.1, $CHCl_3$). [cf lit.[76] m.p. 72-75 °C ; $[\alpha]_D^{20}$ = -5° (c=1.1, $CHCl_3$)]. δ(400 MHz): 7.37-7.14 (15H, m, aromatic), 4.91-4.50 (6H, m, C$\underline{H}_2$Ph), 4.17 (1H, d, H-1, $J_{1,2}$ = 7.48 Hz), 3.70 (1H, dd, H-6m, $J_{6m,6n}$ = 10.6 Hz, $J_{5,6m}$ = 4.77 Hz), 3.74 (1H, dd, H-6n, $J_{6n,6m}$ = 10.6 Hz, $J_{5,6n}$ = 2.78 Hz), 3.50-3.62 (3H, m, H-2, H-3, H-4), 2.55 (3H, s, OC$\underline{H}_3$), 3.49-3.46 (1H, ddd, H-5, $J_{5,6n}$ = 2.78 Hz, $J_{5,6m}$ = 4.77 Hz, $J_{5,4}$ = 9.3 Hz), 2.35 (1H, d, O$\underline{H}$, J = 1.69 Hz).

36. Methyl [2,3-anhydro-4,5,7-tri-*O*-benzyl-α-D-*arabino*-2-heptulopyranosid]onate (142)

A stirred solution of glycosyl chloride (**131**) (0.44 g, 0.69 mmol) in dry THF (2 ml), under argon in the presence of crusehed 4Å molecular sieves, was treated with a solution of 1.0M TBAF in THF (1.37 ml, 1.37 mmol). The reaction mixture was stirred for 4 h. It was then diluted with water and the mixture repeatedly extracted with ethyl acetate. The combined organic layers were washed with water, sat. NaCl, dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the crude product by column chromatography on silica gel [eluant: petroleun-diethyl ether (4:1)] gave the title product (**142**) (0.2 g, 60 %) as a white crystalline solid, m.p. 93-94 °C. $[\alpha]_D^{20}$ = +28° (c=1, $CHCl_3$). $\tilde{\nu}_{max}$ ($CHCl_3$): 2860, 1752, 1600, 1498, 1450, 1344, 1308, 1170, 1110 cm^{-1}. m/z: 490.2023 [(M^+); Calc. for $C_{29}H_{31}O_7$: 490.1991], 431, 400, 294, 182, 105, 91, 77, 65. δ(400 MHz): 7.36-7.15 (15H, m, aromatic), 4.82-4.55 (6H, m, CH_2Ph), 3.99 (1H, d, H-4, $J_{4,5}$ = 7.7 Hz), 3.83 (3H, s, CO_2CH_3), 3.82-3.79 (2H, m, 2 x H-7), 3.78-3.69 (2H, m, H-5, H-6), 3.55 (1H, s, H-3). (Found: C, 70.72; H, 6.05. $C_{29}H_{31}O_7$ requires: C, 79.86; H, 6.36 %).

37. Methyl 2,3-Anhydro-4,5,7-tri-*O*-benzyl-α-D-*arabino*-2-heptulopyranosidonic Acid (143)

To a stirred solution of ester (**142**) (60 mg, 0.12 mmol) in methanol (0.4 ml) and THF (1 ml) was added a solution of potassium hydroxide (21 mg, 0.37 mmol) in water (0.2 ml). After 0.5 h, it was diluted with $CHCl_3$ and washed with 2M HCl,

water, dried ($MgSO_4$) and concentrated under reduced pressure. The acid (**143**) obtained (53.5 mg, 92 %) was not purified but used immediately in the next reaction. $\tilde{\nu}_{max}$ ($CHCl_3$): 3406 (broad), 2925, 1755, 1491, 1448, 1361, 1084 cm^{-1}.

38. Methyl [Methyl-4,5,7-tri-*O*-benzyl-α-D-*gluco*-2-heptulopyranosid]onate (145a)

To a stirred solution of (**132a**) (0.27 g, 0.42 mmol) in THF (1 ml) under argon at room temperature was added crushed 4Å molecular sieves followed by 1.0M TBAF in THF (0.85 ml, 0.85 mmol). The reaction mixture was stirred for 2 h after which it was diluted with diethyl ether and filtered through celite. The filtrate was washed with water, dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel [eluant: petroleum-diethyl ether (3:2)] gave the title product (**145a**) (0.15 g, 68 %) as an oil with $[\alpha]_D^{20}$ = +59° (c=1, $CHCl_3$). $\tilde{\nu}_{max}$ ($CHCl_3$): 3559, 2952, 2865, 1748, 1601, 1495, 1448, 1358, 1268, 1071 cm^{-1}. m/z: 431.1674 [$(M-Bn)^+$; Calc. for $C_{30}H_{34}O_8$ requires 522.2253], 399, 384, 293, 275, 221, 181, 107, 91, 77. δ(400 MHz): 7.36-7.14 (15H, m, aromatic), 4.93-4.50 (6H, m, CH_2Ph), 3.83-3.78 (2H, m, H-3, H-4), 3.82 (3H, s, CO_2CH_3), 3.74-3.72 (2H, m, 2 x H-7), 3.70-3.63 (1H, ddd, H-6, $J_{6,7m}$ = 2 Hz, $J_{6,7n}$ = 4.2 Hz, $J_{6,5}$ = 10 Hz), 3.62-3.61 (1H, dd, H-5, $J_{5,6}$ = 10 Hz, $J_{5,4}$ = 8.4 Hz), 3.39 (3H, s, OCH_3), 2.41 (1H, d, OH, J = 6.45 Hz). (Found: C, 68.78; H, 6.33. $C_{30}H_{34}O_8$ requires: C, 68.95; H, 6.56 %).

39. Methyl [Methyl-4,5,7-tri-*O*-benzyl-ß-D-*gluco*-2-heptulopyranosid]onate (145b)

The ß-anomer (**132b**) (0.12 g, 0.19 mmol) in dry THF (1 ml) was subjected to the same reaction procedure as described above for its α-anomer (**132a**) by treatment of (**132b**) with 1.0M TBAF (0.38 ml, 0.38 mmol). The reaction was complete in 0.5 h as indicated by t.l.c.. It was worked up as described above. Purification by column chromatography on silica gel [eluant: petroleum-diethyl ether (1:4)] gave the title product (**145b**) (84 mg, 86 %) as an oil. $[\alpha]_D^{27}$ = +26° (c = 1, $CHCl_3$). $\tilde{\nu}_{max}$ ($CHCl_3$): 3572, 2945, 2865, 1742, 1495, 1448, 1361, 1081 cm^{-1}. m/z: 431.1658 [(M-Bn)$^+$; Calc. for $C_{30}H_{34}O_8$ requires 522.2253], 245, 221, 181, 163, 105, 91, 77. δ(400 MHz): 7.38-7.19 (15H, m, aromatic), 4.91-4.52 (6H, m, C<u>H</u>$_2$Ph), 4.10-4.06 (1H, td, <u>H</u>-6, $J_{6,7}$ = 3.55 Hz, $J_{6,5}$ = 8.54 Hz), 3.90-3.85 (2H, m, <u>H</u>-3, <u>H</u>-4, $J_{3,OH}$ == 6.75 Hz, $J_{3,4}$ = $J_{4,5}$ = 8.5 Hz), 3.83 (3H, s, $CO_2C\underline{H}_3$), 3.80-3.76 (3H, m, 2 x <u>H</u>-7, <u>H</u>-5, $J_{7,6}$ = 3.55 Hz, $J_{5,6}$ = $J_{5,4}$ = 8.5 Hz), 3.45 (3H, s, $OC\underline{H}_3$), 2.98 (1H, d, O<u>H</u>, $J_{3,OH}$ = 6.75 Hz). (Found: C, 68.45; H, 6.50. $C_{30}H_{34}O_8$ requires: C, 68.95; H, 6.56 %).

40. 2,3: 4,6-Di-*O*-isopropylidene-2-*keto*-L-gulonic Acid (165)

2,3: 4,6-Di-*O*-isopropylidene-L-gulonic acid monohydrate (100 g, 0.342 mol) in dry benzene (250 ml) was azeotroped in a Dean Stark apparatus. When all the water (6.1 ml) has been removed, the benzene was evaporated under reduced pressure. The crude title product (**165**) was not purified but used immediately in reaction 41.

41. Methyl [2,3: 4,6-Di-*O*-isopropylidene-L-*xylo*-2-hexulofuranosid]onate (166)

To a stirred solution of acid (**165**) (93.8 g, 0.342 mol) in dry DMF (300 ml) at room temperature was added potassium carbonate (70.9 g, 0.513 mol). After 10 min methyl iodide (32 ml, 0.513 mol) was added to the reaction mixture. The reaction mixture was stirred in the dark at room temperature. When the reaction was complete, as indicated by t.l.c., the mixture was poured onto water, neutralised with 2M HCl and repeatedly extracted with ethyl acetate. The combined organic layers were washed with water, sat. NaCl, dried ($MgSO_4$) and concentrated under reduced pressure. The title product (**166**) (68 g, 69 %), obtained as an oil, was not purified. δ(200 MHz): 4.80 (1H, s, H-3), 4.27 (1H, d, H-4, $J_{4,5}$ = 2.23 Hz, $J_{4,3}$ = 0 Hz), 4.14 (1H, m, H-5), 4.06 (2H, m, 2 x H-6), 3.82 (3H, s, CO_2CH_3), 1.49 (3H, s, $O_2C(CH_3)_2$), 1.39 (6H, s, $O_2C(CH_3)_2$), 1.30 (3H, s, $O_2C(CH_3)_2$).

42. Methyl 2,3-*O*-Isopropylidene-L-*xylo*-2-hexulofuranoside (167)

A solution of compound (**166**) (68 g, 0.236 mol) in water (250 ml) was heated to reflux with a catalytic amount of copper(II) sulphate (one crystal). When the reaction was complete, the solvent was evaporated under reduced pressure and the product dried at 0.1 mmHg at 20 °C. The title product (**167**) (58.4 g, 99 %) was not purified but used as crude in the following steps. δ(200 MHz): 4.69 (1H, s, H-3), 4.32 (2H, m, H-4, OH), 4.08-3.83 (3H, m, H-5, 2 x H-6), 3.81 (3H, s, CO_2CH_3), 1.99 (1H, s, OH), 1.48 (3H, s, $O_2C(CH_3)_2$), 1.37 (3H, s, $O_2C(CH_3)_2$).

43. Methyl [2,3-*O*-Isopropylidene-4,6-di-*O*-thexyldimethylsilyl-α-L-*xylo*-2-hexulofuranosid]onate and Methyl [2,3-*O*-Isopropylidene-6-*O*-thexyldimethylsilyl-α-L-*xylo*-2-hexulofuranosid]onate

To a stirred solution of thexyldimethylchlorosilane (0.46 ml, 2.32 mmol) in dry DMF (0.5 ml) under argon was added imidazole (0.32 g, 4.64 mmol) followed by a solution of diol (**167**) (0.25 g, 1.01 mmol) in dry DMF (0.5 ml). The reaction was left stirring at room temperature for a day after which it was poured onto water and repeatedly extracted with diethyl ether. The combined organic layers were washed with 2M HCl, water, brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica gel [eluant: petroleum-diethyl ether (10:1)] to afford the di-silylated product (0.2 g, 38 %) and the mono-silylated product (0.1 g, 40 %), both of which are colourless oils. $[\alpha]_D^{23}$ [di-silylated product] = +13° (c=1, $CHCl_3$). $[\alpha]_D^{20}$ [mono-silylated product] = +11° (c=1, $CHCl_3$). $\tilde{\nu}_{max}$ ($CHCl_3$) [di-

silylated product]:1746, 1463, 1377, 1127, 1091, 841, 835 cm^{-1}. $\tilde{\nu}_{max}$ ($CHCl_3$) [mono-silylated product]: 3407, 1750, 1455, 1437, 1377, 1120, 1091, 835 cm^{-1}. m/z (di-silylated product): 515 $(M-CH_3)^+$, 447, 415, 287, 205, 187, 175, 147, 133, 117, 89, 73, 59, 43. m/z (mono-silylated product): 391 $(MH)^+$, 375, 305, 247, 229, 197, 159, 117, 89, 83, 75, 59, 43. δ(400 MHz) [di-silylated product]: 4.71 (1H, s, H-3, $J_{3,4}$ = 0 Hz), 4.24-4.21 (1H, ddd, H-5, $J_{5,4}$ = 2.53 Hz, $J_{5,6m}$ = Hz, $J_{5,6n}$ = Hz), 4.16 (1H, d, H-4, $J_{4,5}$ = 2.53 Hz, $J_{4,3}$ = 0 Hz), 3.82-3.79 (2H, m, 2 x H-6), 3.75 (3H, s, CO_2CH_3), 1.63-1.54 (2H, m, 2 x $CH(CH_3)_2$), 1.51 (3H, s, $C(CH_3)_2$), 1.39 (3H, s, $C(CH_3)_2$), 0.842-0.76 (24H, m, thexyl group), 0.14-0.06 (12H, m, 2 x $Si(CH_3)_2$). δ(400 MHz) [mono-silylated product]: 4.78 (1H, s, H-3, $J_{3,4}$ = 0 Hz), 4.31 (1H, d, H-4, $J_{4,5}$ = 2.47 Hz), 4.25 (1H, m, H-5), 4.12-4.01 (3H, m, 2 x H-6, OH), 3.81 (3H, s, CO_2CH_3), 1.51 (3H, s, $C(CH_3)_2$), 1.39 (3H, s, $C(CH_3)_2$), 0.83 (13H, m, thexyl group), 0.123 (3H, s, $Si(CH_3)_2$), 0.119 (3H, s, $Si(CH_3)_2$). (Found for di-silylated product: C,58.38: H, 9.63. $C_{26}H_{52}O_7Si_2$ requires: C, 58.60: H, 9.84 %). (Found for mono-silylated product: C, 54.97: H, 8.90. $C_{18}H_{34}O_7Si$ requires: C, 55.38, H, 8.78 %).

44. Methyl [2,3-*O*-Isopropylidene-6-*O*-*tert*-butyldiphenylsilyl-α-L-*xylo*-2-hexulofuranosid]onate

To a stirred solution of *t*-butylchlorodiphenylsilane (0.8 ml, 3 mmol) in dry DMF (1 ml) under argon at room temperature was added imidazole (0.82 g, 12 mmol) followed by a solution of (**167**) (0.6 g, 2.42 mmol) in dry DMF (1 ml). The reaction mixture was stirred for a day after which it was poured onto water and

repeatedly extracted with diethyl ether. The combined ethereal layers were washed with 2M HCl, water, brine, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography on silica gel [eluant: petroleum-diethyl ether (4:1)] gave product as a white crystalline solid (0.8 g, 67 %) with m.p. 74-75 °C. $[\alpha]_D^{25}$ = -14° (c=1, $CHCl_3$). $\tilde{\nu}_{max}$ ($CHCl_3$): 3437, 1747, 1438, 1426, 1288, 1259, 1215, 1113, 1091, 1084, 823 cm^{-1}. m/z: 471 $(M\text{-}CH_3)^+$, 429, 353, 265, 241, 199, 163, 135, 91. δ(400 MHz): 7.74-7.24 (10H, m, aromatic), 4.80 (1H, s, H-3, $J_{3,4}$ = 0 Hz), 4.37-4.35 (1H, dd, H-4, $J_{4,5}$ = 2.7 Hz, $J_{4,OH}$ = 5.4 Hz, $J_{4,3}$ = 0Hz), 4.30-4.27 (1H, m, H-5), 4.13-4.02 (2H, m, 2 x H-6), 3.98 (1H, d, OH, J = 5.4 Hz), 1.56 (3H, s, $C(CH_3)_2$), 1.41 (3H, s, $C(CH_3)_2$), 1.02 (9H, s, $C(CH_3)_3$). (Found: C, 64.19; H, 6.93. $C_{26}H_{34}O_7Si$ requires: C, 64.17; H, 7.04 %).

45. Methyl [2,3-*O*-Isopropylidene-6-*O*-(*N*-phenylthiocarbamoyl)-α-L-*xylo*-2-hexulofuranosid]onate

To a stirred solution of (**167**) (0.25 g, 1.01 mmol) in dry pyridine (10 ml) under argon was added phenylisothiocyanate (1.21 ml, 10 mmol). The reaction was heated to reflux. When t.l.c. indicated no more starting material was left, the pyridine was evaporated under reduced pressure and the residue diluted with $CHCl_3$, washed with 2M HCl, water, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography on silica gel [eluant: petroleum-diethyl ether (1:1)] gave the title product (0.22 g, 67 %) as white crystalline solid, m.p. 84-86 °C. $[\alpha]_D^{23}$ = -2° (c=0.5, $CHCl_3$). $\tilde{\nu}_{max}$ ($CHCl_3$): 3546, 3406, 3379, 2985, 1745, 1595, 1525, 1511, 1441, 1378, 1111, 1091. m/z: 368 $(M\text{-}CH_3)^+$, 349, 233, 143, 135, 113, 91, 77, 71, 59, 43. δ(400

MHZ): 7.34-7.23 (5H, m, aromatic), 5.03 (1H, s, H-5), 4.73 (1H, s, H-3), 4.61 (1H, d, H-4, $J_{4,5}$ = 4.97 Hz), 4.59 (2H, m, 2 x H-6), 3.87 (3H, s, CO_2CH_3), 1.64 (bs, OH and NH), 1.39 (6H, s, $OC(CH_3)_2$). (Found: C, 53.14: H, 5.44; N, 3.54. $C_{17}H_{21}NO_7S$ requires: C, 53.25; H, 5.52; N, 3.65 %).

46 Methyl [2,3-*O*-Isopropylidene-4,6-di-*O*-benzyl-α-L-*xylo*-2-hexulofuranosid]onate (168)

To a stirred solution of 80 % sodium hydride dispersion (2.2 g, 72 mmol) in dry THF (10 ml) under argon at room temperature was added benzyl chloride (28 ml, 240 mmol). After 15 min, a solution of diol (**167**) (5.96 g, 24 mmol) in dry THF (10 ml) was added dropwise keeping the temperature at room temperature. After a furthur 20 min, dry DMSO (8 ml) was added over 0.5 h. The reaction was left stirring for a day. The reaction mixture was then poured onto water and repeatedly extracted with diethyl ether. The diethyl ether layer was washed with water, brine, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography on silica gel [eluant: petroleum-diethyl ether (4:1)] gave the product (**168**) as a colourless oil (7.2 g, 71 %). $[\alpha]_D^{20}$ = +33° (c=1, $CHCl_3$). $\tilde{\nu}_{max}$ ($CHCl_3$): 1745, 1496, 1438, 1452, 1383, 1376, 1344, 1288, 1096, 1064, 1051 cm^{-1}. m/z: 413.1589 [$(M-CH_3)^+$; Calc. for $C_{24}H_{28}O_7$ requires: 428.1835], 337, 231, 173, 159, 107, 91, 59, 43. δ(400 MHz): 6.34-7.26 (10H, m, aromatic), 5.02 (1H, s, H-3, $J_{3,4}$ = 0 Hz), 4.71-4.48 (5H, m, CH_2Ph, H-5), 4.01 (1H, d, H-4, $J_{4,3}$ = 0 Hz, $J_{4,5}$ = 3.17 Hz), 3.84-3.78 (2H, m, 2 x H-6), 3.82 (3H, s, CO_2CH_3), 1.53 (3H, s, $C(CH_3)_2$), 1.41 (3H, s, $C(CH_3)_2$). (Found: C, 66.96; H, 6.58. $C_{24}H_{28}O_7$ requires: C, 67.28; H, 6.59 %).

47. Methyl [4,6-Di-*O*-benzyl-α,ß-L-*xylo*-2-hexulofuranosid]onate (169)

A solution of (**168**) (0.1 g, 0.23 mmol) in THF (0.2 ml) was stirred with 2M HCl (0.4 ml) . When t.l.c. indicated the reaction was complete, the reaction mixture was poured onto water and repeatedly extracted with ethyl acetate. The combined organic layers were washed with 5% $NaHCO_3$ solution, water, brine, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography on silica gel [eluant: petroleum-diethyl ether (1:1)] gave the title product (**169**) as a mixture of isomers in the ratio 4:1 in the form of an oil (60 mg, 65 %). $[\alpha]_D^{20}$ = -5° (c=1, $CHCl_3$). $\tilde{\nu}_{max}$ ($CHCl_3$): 3526, 2952, 2865, 1742, 1451, 1281, 1067 cm^{-1}. m/z: 370($M-H_2O)^+$, 297, 279, 191, 181, 173, 131, 107, 91. δ(400 MHz): 7.34-7.23 (10H, m, aromatic), 4.75-4.48 (6H, m, 2 x CH_2Ph, H-3, H-4), 4.47 (1H, bs, OH of minor isomer), 4.16 (1H, dd, H-4 of minor iosmer, $J_{4,3}$ = 3.3 Hz, $J_{4,5}$ = 5.39 Hz), 4.08 (1H, m, H-5 of major isomer), 3.85-3.64 (2H, m, 2 x H-6), 3.83 (3H, s, CO_2CH_3 of minor isomer), 3.78 (3H, s, CO_2CH_3 of major isomer), 3.40 (1H, bs, OH of minor isomer), 2.80 (1H, d, OH of major isomer, J = 0.84 Hz), 1.74 (1H, bs, OH of major isomer). (Found: C, 64.59; H, 6.13. $C_{21}H_{24}O_7$ requires: C, 64.94; H, 6.23 %).

48 Methyl [2,3-Di-*O*-*tert*-butyldimethylsilyl-4,6-di-*O*-benzyl-L-*xylo*-2-hexulofuranosid]onate (177)

To a stirred solution of diol (**169**) (0.1 g, 0.26 mmol) in dry CH_2Cl_2 (0.26 ml) under argon at room temperature was added dropwise 2,4,6-collidine (0.08 ml, 0.57 mmol) followed by TBDMS-triflate (0.06 ml, 0.26 mmol). After 10 min, the

reaction mixture was diluted with CH_2Cl_2 and washed with 2M HCl and water. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography on silica gel [eluant: petroleum-diethyl ether (5:1)] gave the product (**177**) as an oil as a mixture of isomers (ratio 3:5) (82 mg, 52 %). $[\alpha]_D^{26}$ = -9° (c=1, CCl_4). $\tilde{\nu}_{max}$ ($CHCl_3$): 1751, 1494, 1458, 1451, 1435, 1360, 1250, 1216, 1189, 1127, 1094, 1059, 844 cm^{-1}. m/z: 601.3057 [$(M-CH_3)^+$; Calc. for $C_{33}H_{52}O_7Si_2$ requires: 616.3251], 560, 532, 302, 290, 278, 181, 91, 73. δ(400 MHz): 7.35-7.23 (10H, m, aromatic), 4.65-4.50 (5H, m, 2 x CH_2Ph, H-4), 4.37 (1H, m, H-5 of minor isomer), 4.32 (1H, d, H-3 of major isomer, $J_{3,4}$ = 3.67 Hz), 4.07 (1H, dd, H-4 of minor isomer, $J_{4,3}$ = $J_{4,5}$ = 6.4 Hz), 4.01 (1H, m, H-5 of major isomer), 3.87-3.60 (2H, m, 2 x H-6), 3.72 (3H, s, CO_2CH_3 of major isomer), 3.66 (3H, s, CO_2CH_3 of minor isomer), 0.84 (18H, m, $C(CH_3)_3$), 0.07 (12H, m, $Si(CH_3)_2$). (Found: C, 64.03; H, 8.77. $C_{33}H_{52}O_7Si_2$ requires: C, 64.25; H, 8.50 %).

49. Methyl [Methyl 4,6-di-*O*-benzyl-α,ß-L-*xylo*-2-hexulofuranosid]onate (179)

To a solution of compound (**168**) (0.5 g, 1.17 mmol) in dry methanol (3 ml), under argon at 0 °C, was bubbled a slow stream of HCl gas for 15 min. The reaction mixture was left stirring at room temperature for 3-4 days. The solvent was evaporated under reduced pressure and the residue purified by column chromatography on silica gel [eluant: petroleum-diethyl ether (4:1)]. The title product (**179**) was obtained (0.13 g, 29 %) as a mixture of anomers in the ratio 4.4:1 together with diol (**169**) (0.28 g, 62 %). $[\alpha]_D^{20}$ (Minor isomer) = -30° (c=2, $CHCl_3$). $[\alpha]_D^{20}$ (Major isomer) = +21° (c=1, $CHCl_3$). $\tilde{\nu}_{max}$ ($CHCl_3$) [Minor isomer]:

3546, 2945, 1745, 1495, 1451, 1264, 1094 cm^{-1}. $\tilde{\nu}_{max}$ ($CHCl_3$) [Major isomer]: 3566, 2939, 1742, 1495, 1451, 1228, 1044 cm^{-1}. δ(400 MHz) [Minor isomer]: 7.25-7.18 (10H, m, aromatic), 4.66-4.53 (4H, m, $C\underline{H}_2Ph$), 4.47-4.33 (2H, m, $\underline{H}$-5, $\underline{H}$-3), 3.98 (1H, dd, $\underline{H}$-4, $J_{4,5}$ = $J_{4,3}$ = 5.87 Hz), 3.72-3.63 (2H, m, 2 x $\underline{H}$-6), 3.68 (3H, s, $CO_2C\underline{H}_3$), 3.35 (3H, s, $OC\underline{H}_3$), 2.76 (1H, $O\underline{H}$, d, J = 7 Hz). δ(400 MHz) [Major isomer]: 7.35-7.26 (10H, m, aromatic), 4.73-4.53 (5H, m, $OC\underline{H}_2Ph$, $\underline{H}$-5), 4.42 (1H, dd, $\underline{H}$-3, $J_{3,4}$ = 4.9 Hz, $J_{3,OH}$ = 5.15 Hz), 4.10 (1H, dd, $\underline{H}$-4, $J_{4,3}$ = 4.9 Hz, $J_{4,5}$ = 2.9 Hz), 3.83 (3H, s, $CO_2C\underline{H}_3$), 3.81-3.44 (2H, m, 2 x $\underline{H}$-6), 3.32 (3H, s, $OC\underline{H}_3$), 2.56 (1H, d, $O\underline{H}$, J = 5.15 Hz). (Found [Minor isomer]: C, 65,91; H, 6.20. $C_{22}H_{26}O_7$ requires: C, 65.66; H, 6.51 %). (Found [Major isomer]: C, 65.94; H, 6.33. $C_{22}H_{26}O_7$ requires: C, 65.66; H, 6.51 %).

50. Methyl [Methyl 4,6-Di-*O*-benzyl-3-*O*-*tert*-butyldimethylsilyl-L-*xylo*-2-hexulofuranosid]onate (180)

To a stirred solution of (**179**) (80 mg, 0.2 mmol) in dry CH_2Cl_2 (1.5 ml) under argon at room temperature, was added dropwise of 2,4,6-collidine (0.06 ml, 0.44 mmol) followed by TBDMS-OTf (0.05 ml, 0.21 mmol). The reaction was complete in 10 min, as indicated by t.l.c.. It was diluted with CH_2Cl_2, washed with water, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography on silica gel [eluant: petroleum-diethyl ether (5:1)] afforded the title product (**180**) (94 mg, 91 %). $[\alpha]_D^{25}$ = +13° (c=0.5, $CHCl_3$). $\tilde{\nu}_{max}$ ($CHCl_3$): 2952, 2925, 2858, 1748, 1495, 1451, 1435, 1361, 1281, 1258, 1204, 1121, 1074, 844 cm^{-1}. m/z: 459.1798 [$(M-{}^tBu)^+$; Calc. for $C_{28}H_{40}O_7Si$: 516.2543], 427, 337, 321, 277,

199, 181, 91, 73. δ(400 MHz): 7.32-7.24 (10H, m, aromatic), 4.64-4.53 (5H, m, $C\underline{H}_2Ph$, $\underline{H}$-5), 4.36 (1H, d, $\underline{H}$-3, $J_{3,4}$ = 1.97 Hz), 3.89 (1H, dd, $\underline{H}$-4, $J_{4,3}$ = 1.97 Hz, $J_{4,5}$ = 5.09 Hz), 3.80-3.68 (2H, m, 2 x $\underline{H}$-6), 3.75 (3H, s, $CO_2C\underline{H}_3$), 3.26 (3H, s, $OC\underline{H}_3$), 0.79 (9H, s, $SiC(C\underline{H}_3)_3$), 0.01 (3H, s, $Si(C\underline{H}_3)_2$), -0.05 (3H, s, $Si(C\underline{H}_3)_2$). (Found: C, 65.20; H, 8.04. $C_{28}H_{40}O_7Si$ requires: C, 65.09; H, 7.80 %).

51. Methyl Methyl-4,6-di-*O*-benzyl-3-*O*-*tert*butyldimethylsilyl-L-*xylo*-2-hexulofuranosidonic Acid (181)

To a stirred solution of ester (**180**) (63 mg, 0.12 mmol) in methanol (0.8 ml) and THF (0.2 ml) was added a solution of potassium hydroxide (21 mg, 0.37 mmol) in water (0.2 ml). The reaction mixture was stirred at room temperature for a day. It was then diluted with CH_2Cl_2 and washed with 2M HCl, water, dried ($MgSO_4$) and concentrated under reduced pressure. The title acid (**181**) (51 mg, 85 %), $\tilde{\nu}_{max}$ ($CHCl_3$): 3419 (broad), 2925, 2858, 1775, 1732, 1665, 1605, 1495, 1461, 1451, 1361, 1338, 1258, 1124, 1064, 840 cm^{-1}, was not purified but used immediately in the reductive decarboxylation reaction.

52. 2-Trimethylsilylethoxymethyl cyclohexanone (194)

To a solution of cyclohexanone (**190**) (1.0 g, 10 mmol) in dry THF (5 ml) under argon at -78 °C was added dropwise 1.0M LDA in THF (11 ml, 11 mmol) followed by SEM-Cl (2.7 ml, 15 mmol). The reaction was followed by t.l.c. On completion, the reaction mixture was poured onto water and repeatedly extracted with diethyl ether. The combined organic layers was washed with water, sat. NaCl, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography on silica gel [eluant: petroleum-diethyl ether (9:1)] gave the title compound (**194**) in the form of an oil (0.88 g, 76 %). $\tilde{\nu}_{max}$ ($CHCl_3$): 2948, 1709, 1367, 1106, 836 cm^{-1}. m/z: 227 $(M-H)^+$; 210, 200, 185, 155, 73. δ(400 MHz): 3.77-3.30 (4H, m, $C\underline{H}_2OC\underline{H}_2$), 2.6 (1H, m, H-2), 2.41-1.38 (8H, m, ring protons), 0.92 (2H, t, $C\underline{H}_2Si(CH_3)_3$, J = 8.28 Hz), 0.01 (9H, s, $Si(C\underline{H}_3)_3$). (Found: C, 62.88; H, 10.82. $C_{12}H_{24}O_2Si$ requires: C, 63.10; H, 10.59 %).

53. Phenyl 4,5,6-Tri-*O*-benzyl-1-sulphonyl-1-*C*-trimethylsilylethoxymethyl-α-D-*arabino*-1-hexopyranose (198)

To a solution of sulphone (**62**) (0.5 g, 0.9 mmol) in dry THF (2 ml) under argon at -78 °C was added dropwise of 1.0M LDA in THF (1.07 ml, 1.07 mmol). After 15 min, dropwise of SEM-Cl (0.22 ml, 1.25 mmol) was added to the reaction mixture. When t.l.c. indicated the reaction was complete, the reaction mixture was poured onto water and repeatedly extracted with diethyl ether. The combined ethereal layers were washed with water, sat. NaCl, dried ($MgSO_4$) and concentrated

under reduced pressure. Purification by column chromatography on silica gel [eluant: petroleum-diethyl ether (1:1)] gave the product (**198**) in the form of an oil (0.4 g, 65 %). This product decomposes on standing at room temperature. δ(400 MHz): 7.33-7.17 (20H, m, aromatic), 4.89-4.49 (6H, m, C$\underline{H}_2$Ph), 4.05 (1H, m, $\underline{H}$-5), 3.99 (1H, ddd, $\underline{H}$-3, $J_{3,2a}$ = 12.63 Hz, $J_{3,2e}$ = 5.06 Hz, $J_{3,4}$ = 11 Hz), 3.97-3.47 (5H, m, C$\underline{H}_2$OC$\underline{H}_2$, $\underline{H}$-4), 3.32 (2H, m, 2 x $\underline{H}$-6), 2.19 (1H, dd, $\underline{H}$-2e, $J_{2e,3}$ = 5.06 Hz, $J_{2e,2a}$ = 12.63 Hz), 1.50 (1H, dd, $\underline{H}$-2a, $J_{2a,3}$ = $J_{2a,2e}$ = 12.63 Hz), 0.95 (2H, t, C$\underline{H}_2$Si$(CH_3)_3$, J = 8.3 Hz), -0.01 (9H, s, Si(C$\underline{H}_3$)$_3$).

54. 1-Benzyl-3-trimethylsilylethoxymethyl-2-pyrrolidone (195)

To a stirred solution of compound (**191**) (0.5 g, 2.85 mmol) in dry THF (2.5 ml) under argon at -78 °C was added dropwise of 1.0M LDA in THF (3.14 ml, 3.14 mmol) followed by SEM-Cl (0.71 ml, 3.99 mmol). When no more starting material was left, as indicated by t.l.c., the reaction mixture was poured onto water and repeatedly extracted with diethyl ether. The combined ethereal layers were washed with water, sat. NaCl, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography on silica gel [eluant: petroleum-diethyl ether (3:2)] gave the title compound (**195**) as an oil (0.52 g, 60 %). $\tilde{\nu}_{max}$ ($CHCl_3$): 3479, 2945, 1685, 1491, 1428, 1354, 1248, 1107, 857, 834 cm^{-1}. m/z: 305.1856 [(M^+); Calc. for $C_{17}H_{27}O_2NSi$ 305.1811], 277, 262, 204, 189, 91, 73. δ(200 MHz): 7.29-7.21 (5H, m, aromatic), 4.44 (2H, m, C$\underline{H}_2$Ph), 3.65 (2H, d, CHC$\underline{H}_2$OC$\underline{H}_2$, J = 4.73 Hz), 3.52 (2H, t, OC$\underline{H}_2$CH_2Si$(CH_3)_3$, J = 8 Hz), 3.22 (2H, m, 2 x $\underline{H}$-4), 2.69 (1H, m, $\underline{H}$-2), 2.02 (2H, m, 2 x $\underline{H}$-4), 0.91 (2H, t, C$\underline{H}_2$Si$(CH_3)_3$, J = 8 Hz), -0.02 (9H,

s, $Si(CH_3)_3$).

55. 3-Trimethylsilylethoxymethyl camphor (196)

To a solution of camphor (**192**) (0.2 g, 1.31 mmol) in dry THF (1 ml) under argon at -78 °C was added 1.0M LDA in THF (1.58 ml, 1.58 mmol) followed by SEM-Cl (0.33 ml, 1.84 mmol). The reaction was followed by t.l.c. On completion, the reaction mixture was poured onto water and repeatedly extracted with diethyl ether. The combined organic layers were washed with water, sat. NaCl, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography on silica gel [eluant: petroleum-diethyl ether (9:1)] gave the title compound (**196**) (0.2 g, 57 %) as a mixture of isomers in the ratio 2.5:1 (endo:exo). $\tilde{\nu}_{max}$ ($CHCl_3$): 2879, 1732, 1451, 1087, 909, 860, 840 cm^{-1}. m/z: 282.2034 [$(M)^+$; Calc. for $C_{16}H_{30}O_2Si$: 282.2015], 254, 239, 209, 196, 166, 151, 110, 95, 73, 41, 29. δ(400 MHz): 3.69-3.28 (4H, m, $C\underline{H}_2OC\underline{H}_2$), 2.77 (1H, dt, H-2 of endo isomer, J = 2 Hz, J = 3.5 Hz), 2.19 (1H, t, H-2 of exo isomer, J = 2 Hz), 2.16 (1H, s, H-3 of endo isomer, $J_{3,2}$ = 0 Hz, $J_{3,4}$ = 0 Hz), 2.11 (1H, 1H, d, H-3 of exo isomer, J = 2.2 Hz), 2.02-1.18 (4H, m, ring protons), 0.96 (3H, s, $C\underline{H}_3$ of endo isomer), 0.92 (3H, s, $C\underline{H}_3$ of exo isomer), 0.87 (3H, s, $C\underline{H}_3$ of endo isomer), 0.86 (3H, s, $C\underline{H}_3$ of exo isomer), 0.82 (3H, s, $C\underline{H}_3$ of major isomer), 0.74 (3H, s, $C\underline{H}_3$ of minor isomer), -0.02 (9H, s, $Si(C\underline{H}_3)_3$). (Found: C, 68.05; H, 10.58. $C_{16}H_{30}O_2Si$ requires: C, 68.03; H 10.70 %).

56. 1-Trimethylsilylethoxymethyl phenylacetylene (197)

To a stirred solution of phenylacetylene (**193**) (0.5 g, 4.9 mmol) in dry THF (2 ml) under argon at -78 °C was added dropwise of 1.0M LDA in THF (5.9 ml, 5.9 mmol). After 10 min, into this reaction mixture was added SEM-Cl (1.2 ml, 6.9 mmol). The reaction was followed by t.l.c. On completion, the reaction mixture was poured onto water and repeatedly extracted with diethyl ether. The combined organic layers were washed with water, sat. NaCl, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography on silica gel [eluant: petroleum-diethyl ether (3:2)] gave the title product (**197**) in the form of an oil (0.68 g, 60 %). m/z: 231.1188 [(M^+); Calc. for $C_{14}H_{20}OSi$: 232.1283], 203, 189, 159, 129, 115, 105, 73. δ(400 MHz): 7.43-7.25 (5H, m, aromatic), 4.34 (2H, s, C≡C-CH_2-O), 3.70-3.62 (2H, m, $OCH_2CH_2Si(CH_3)_3$), 0.99 (2H, m, $CH_2Si(CH_3)_3$), 0.03 (9H, s, $Si(CH_3)_3$).

REFERENCES

References

1 For recent reviews see: H. Paulsen, *Angew. Chem. Int. Ed. Engl.*, 1982, **21**, 155; R. R. Schmidt, *Angew. Chem. Int. Ed. Engl.*, 1986, **25**, 212.

2 W. A. Remers, "The Chemistry of Antitumor Antibiotics", Wiley Interscience, New York, 1979, **1**, 136; D. E. Wright, *Tetrahedron*, 1979, **35**, 1207; I. Kimura, K. Yamamoto, K. Tempaku, and M. Suzuki, *Tetrahedron Lett.*, 1987, **28**, 1917, 1921; E. Angliker, F. Barfuss, and J. Renz, *Chem. Ber.*, 1958, **41**, 479.

3 H. Drautz, H. Zähner, J. Rohr, and A. Zeeck, *J. Antibiotics*, 1986, **39**, 1657.

4 J. Golik, J. Clardy, G. Dubay, G. Groenewold, H. Kawaguchi, M. Konishi, B. Krishnan, H. Ohkuma, K. Saitoh, and T. W. Doyle, *J. Am. Chem. Soc.*, 1987, **109**, 3461; J. Golik, G. Dubay, G. Groenewold, H. Kawaguchi, M. Konishi, B. Krishnan, H. Ohkuma, K. Saitoh, and T, W. Doyle, *J. Am. Chem. Soc.*, 1987, **109**, 3462; M. D. Lee, Y. S. Dunne, M. M. Siegel, C. C. Chang, G. O. Morton, and D. B. Borders, *J. Am. Chem. Soc.*, 1987, **109**, 3464; M. D. Lee, T. S. Dunne, C. C. Chang, G. A. Ellestad. M. M. Siegal, G. O. Morton, W. J. McGahren, and D. B. Borders, *J. Am. Chem. Soc.*, 1987, **109**, 3466.

5 For discussion of stereoelectronic effects in organic chemistry and of the anomeric effect in particular, see: A. J. Kirby, "The Anomeric

Effect and Related Stereoelectronic Effects at Oxygen", Springer-Verlag, Berlin, Heidelberg, New York, 1983; P. Deslongchamps, "Stereoelectronic Effects in Organic Chemistry", Ed. J. E. Baldwin, Pergaman Press, Oxford, 1983.

6 R. Preuss and R. R. Schmidt, *Synthesis*, 1988, 694; P. Tavecchia, M. Trumtel, A. Veyrières, and P. Sinay, *Tetrahedron Lett.*, 1989. **30**, 2529, 2533; K. C. Nicolaou, T. Ladduwahetty, J. L. Randall, and A. Chucholowski, *J. Am. Chem. Soc.*, 1986, **108**, 2466.

7 J. Thiem and M. Gerken, *J. Org. Chem.*, 1985, **50**, 954; M. Perez and J. M. Beau, *Tetrahedron Lett.*, 1989, **30**, 75; Y. Ito and T. Ogawa, *Tetrahedron Lett.*, 1987, **28**, 2723; Y. Ito and T. Ogawa, *Tetrahedron Lett.*, 1988, **29**, 3987.

8 B. Giese and J. Dupuis, *Angew. Chem.*, 1983, **95**, 633; *Angew. Chem. Int. Ed. Engl.*, 1983, **22**, 622; B. Giese and J. Dupuis, *Tetrahedron Lett.*, 1984, **25**, 1349.

9 R. M. Adlington, J. E. Baldwin, A. Basak, and R. P. Kozyrod, *J. Chem. Soc., Chem. Commun.*, 1983, 944.

10 A. R. Gregory and V. Malatesta, *J. Org. Chem.*, 1980, **45**, 122; V. Malatesta, R. D. McKelvey, B. W. Babcock, and K. U. Ingold, *J. Org. Chem.*, 1979, **44**, 1872; K. Hayday and R. D. McKelvey, *J. Org. Chem.*, 1976, **41**, 2222; A. L. J. Beckwith and C. J. Easton, *J. Am. Chem. Soc.*, 1981, **103**, 615; A. L. J. Beckwith and S. Brumby, *J.*

Chem. Soc., Perkin Trans. 2, 1987, 1801.

11 D. H. R. Barton, D. Crich, and W. B. Motherwell, *Tetrahedron*, 1985, **41**, 3901; *idem, J. Chem. Soc., Chem. Commun.*, 1983, 939; for a review see: D. Crich and L. Quintero, *Chem. Rev.*, 1989, **89**, 1413.

12 K. U. Ingold, J. Lusztyk, B. Maillard, and J. C. Wlaton, *Tetrahedron Lett.*, 1988, **29**, 917.

13 D. Crich and T. J. Ritchie, *J. Chem. Soc., Chem. Commun.*, 1988, 985, 1461; *idem, Carbohydr. Res.*, 1989, **190**, C3; *idem, J. Chem. Soc., Perkin Trans. 1,* 1990, 945.

14 S. Hanessian and A. G. Pernet, *Adv. Carbohydr. Chem. Biochem.*, 1976, **33**, 111; S. Hanessian, "Total Synthesis of Natural Products: The Chiron Approach", Pergamon, Oxford, 1983.; T. D. Inch, *Tetrahedron*, 1984, **40**, 3161; J. G. Buchanan, *Prog. Chem. Org. Natl. Prod.*, 1983, **44**, 243.

15 M. Kawasaki, F. Matsuda, and S. Terashima, *Tetrahedron Lett.*, 1986, 2145 and references therein.

16 G. D. Daves and C. C. Cheng, *Prog. Med. Chem.*, 1976, **13**, 303.

17 V. Bellosta and S. Czernecki, *J. Chem. Soc., Chem. Commun.*, 1989, 199; V. Bolitt, C. Mioskowski, and J. R. Falck, *Tetrahedron Lett.*, 1989, **30**, 6027; J. S. Panek and M. A. Sparks, *J. Org. Chem.*, 1989,

54, 2038; K. Tatsuta, J. Hayakawa, and Y. Tatsuzawa, *Bull. Chem. Soc. Jpn.*, 1989, **62**, 490; J. C. Lopez and B. Fraser-Reid, *J. Am. Chem. Soc.*, 1989, **111**, 3450; M. Brakta, P. Lhoste and D. Sinou, *J. Org. Chem.*, 1989, **54**, 1890; B. Giese, T. Linker and R. Muhn, *Tetrahedron.*, 1989, **45**, 935; G. A. Kraus and M. T. Molina, *J. Org. Chem.*, 1988, **53**, 752; P. Allevi, P. Ciuffreda, D. Colombo, D. Monti, G. Speranza, and P. Manitto, *J. Chem. Soc., Perkin Trans 1*, 1989, 1281; R. Preuss and R. R. Schmidt, *Liebigs Ann. Chem.*, 1989, 429.

18 H. M. Flowers and R. W. Jeanloz, *J. Org. Chem.*, 1963, **28**, 1377; H. Paulsen, Č. Kolar, W. Stenzel, *Che. Ber.*, 1978, **111**, 2370.

19 H. Paulsen and O. Lockhoff, *Chem. Ber.*, 1981, **114**, 3102; G. M. Bebault and G. G. S. Dutton, *Carbohydr. Res.*, 1974, **37**, 309; C. Augé, C. D. Warren, and R. W. Jeanloz, *Carbohydr. Res.*, 1980, **82**, 85.

20 P. A. J. Gorin and A. S. Perlin, *Can. J. Chem.*, 1961, **39**, 2474.

21 O. Theander, *Acta Chem. Scand.*, 1958, **12**, 1883.

22 G. Ekborg, B. Lindberg, and J. Lönngren, *Acta Chem. Scand.*, 1972, **26**, 3287.

23 C. D. Warren, C. Augé, M. L. Laver, S. Suzuki, D. Power, and R. W. Jeanloz, *Carbohydr. Res.*, 1980, **82**, 71; H. B. Borén, G. Ekborg, K. Eklind, P. J. Garegg, Å. Pilotti, and C. G. Swahn, *Acta Chem. Scand.*,

1973, **27**, 2639; V. K. Srivastava and C. Schuerch, *Tetrahedron Lett.*, 1979, **35**, 3269; E. E. Lee, G. Keaveney, and P. S. O'Colla, *Carbohydr. Res.*, 1977, **59**, 268.

24 H. Mitsuya and S. Broder, *Nature*, 1987, **325**, 773; *idem*, *Proc. Natl. Acad. Sci. U.S.A.*, 1986, **83**, 1911; R. Dagani, "The Quest for Therapy" in *Chem. Eng. News*, 1987, **65**, 47.

25 H. Vorbrüggen, K. Krolikiewicz, and B. Bennua, *Chem. Ber.*, 1981, **114**, 1234.

26 For reviews of *C*-glycosides, see: U. Hacksell and G. D. Daves, *J. Prog. Med. Chem.*, 1985, **22**, 1; J. G. Buchanan, *Prog. Chem. Org. Nat. Prod.*, 1983, **44**, 243; J. Goodchild, *Top. Antibiot. Chem.*, 1982, **6**, 99.

27 M. Hori, E. Ito, T. Takita, Y. Koyama, T. Takeuchi, H. Umezawa, *J. Antibiot.*, 1964, **17A**, 96; S. Aizawa, T. Hidaka, N. Otake, H. Yonehara, K. Inose, N. Igarashi, and S. Suzuki, *Agri. Biol. Chem.*, 1965, **29**, 375.

28 N. Katagiri, K. Takashima, and T. Kato, *J. Chem. Soc., Chem. Commun.*, 1982, 664.

29 K. Ramasamy, R. K. Robins, and G. R. Revankar, *J. Chem. Soc., Chem. Commun.*, 1989, 560.

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

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

32 I. D. Blackburne, P. M. Fredericks, and R. D. Guthrie, *Aust. J. Chem.*, 1976, **29**, 381.

33 W. Roth and W. Pigman, "Methods in Carbohydrate Chemistry", 1963, **2**, 405.

34 A. P. Kozikowski and J. Lee, *J. Org. Chem.*, 1990, **55**, 863.

35 P. Brougham, M. S. Cooper, D. A. Cummerson, H. Heaney, and N. Thompson, *Synthesis*, 1987, 1015.

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

37 H. Hori, T. Nakajima, Y. Nishida, H. Ohrui, and H. Meguro, *Tetrahedron Lett.*, 1988, **29**, 6317.

38 M. Karplus, *J. Phys. Chem.*, 1959, **30**, 11; For general reading on Karplus Equation, see: D. H. Williams and I. Fleming, "Spectroscopic Methods in Organic Chemistry", McGraw-Hill, London.

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

40 W. Schmidt, R. Christian, and E. Zbiral, *Tetrahedron Lett.,* 1988, **29**, 3643.

41 R. Blattner and R. J. Ferrier, *J. Chem. Soc., Perkin Trans 1*, 1980, 1532; R. Ferrier and R. H. Furneaux, *J. Chem. Soc., Perkin Trans. 1,* 1977, 1996; L. Somsak, G. Batta, and I. Farkas, *Carbohydr. Res.,* 1983, **124**, 43.

42 A. J. Dobbs, B. C. Gilbert, and R. O. C. Norman, *J. Chem. Soc., A,* 1971, 124; H. Fischer in "Free Radicals" ed. J. K. Kochi, Wiley, New York, 1973, II, 435; L. Karplar in "Free Radicals", ed. J. K. Kochi, Wiley, New York, 1973, II, 435 and references therein.

43 For extensive lists of esr parameters including tetrahydropyranyl radicals see: "Landholt-Bornstein", Ed. A. Berndt, H. Fischer, and H. Paul, Springer-Verlag, Berlin, 1977, **9B**. 290; A. Hudson and K. D. J. Root, *Tetrahedron*, 1969, **25**, 5311; H. Zeldes and R. Livingston, *J. Chem. Phys.,* 1966, **45**, 1946; W. T. Dixon and R. O. C. Norman, *J. Chem. Soc.,* 1964, 4850; T. Shiga, A. Boukhors, and P. Douzou, *J. Phy. Chem.,* 1967, **71**, 4264.

44 H. G. Korth, R. Sustmann, J. Dupuis, and B. Giese, *J. Chem. Soc., Perkin Trans. 2,* 1986, 1453.

45 D. H. R. Barton, W. Hartwig, and W. Motherwell, *J. Chem. Soc., Chem. Commun.,* 1982, 447; D. Crich, K. A. Eustace, S. M. Fortt, and T. J. Ritchie, *Tetrahedron*, 1990, **46**, 2135 and references therein.

46 S. V. Ley, B. Lygo, H. M. Organ, and A. Wonnacott, *Tetrahedron*, 1985, **41**, 3825; For a general review, see: D. R. Kelly, *Chem. in Britain,* 1990, **26**, 124.

47 P. Traxler, W. Tosch, and O. Zak, *J. Antibiotics,* 1987, **40**, 1146 and references therein; P. Traxler, H. Fritz, H. Fuhrer, and W. J. Richter, *J. Antibiotics*, 1980, **33**, 967; T. Komori, M. Yamashita, Y. Tsurumi, and M. Kohsaka, *J. Antibiotics,* 1985, **38**, 455; T. Komori and Y. Hoh, *J. Antibiotics*, 1985, **38**, 544.

48 E. Dubois and J. M. Beau, *Tetrahedron Lett.,* 1990, **31**, 5165 and references therein.

49 D. S. Middleton, N. S. Simpkins, and N. K. Terrett, *Tetrahderon Lett.,* 1988, **29**, 1315; D. S. Middleton, N. S. Simpkins, M. J. Begley, and N. K. Terrett, *Tetrahedron*, 1990, **46**, 545.

50 G. Stork, *Bull. Chem. Soc. Jpn.,* 1988, **61**, 149.

51 C. Audin, J. M. Lancelin, and J. M. Beau, *Tetrahderon Lett.,* 1988, **29**, 3691.

52 R. Tsang and B. Fraser-Reid, *J. Am. Chem. Soc,* 1986, **108**, 2116.

53 A. De Mesmaeker, P. Hoffmann, B. Ernst, P. Hug, and T. Winkler, *Tetrahedron Lett.*, 1989, **30**, 6307, 6311.

54 K. Okamoto, T. Kondo, and T. Goto, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 631.

55 For a review on osmium tetroxide *cis*-dihydroxylation of alkenes, see: M. Schröder, *Chem. Rev.*, 1980, **80**, 187.

56 R. Criegee, *Justus Liebigs Ann. Chem.*, 1936, **522**, 75; R. Criegee, B. Marchand, and H. Wannowius, *Justus Liebigs Ann. Chem.*, 1942, **550**, 99.

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

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

59 J. S. Brimacombe and A. K. M. S. Kabir, *Carbohydr. Res.*, 1988, **179**, 21 and references therein.

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

61 K. B. Sharpless and E. Herranz, *J. Org. Chem.*, 1978, **43**, 2544; *idem*, *Org. Synth.*, 1983, **61**, 85; K. B. Sharpless, A. O. Chong, and K. Oshima, *J. Org. Chem.*, 1976, **41**, 177; K. B. Sharpless, D. W. Patrick, L. K. Truesdale, and S. A. Biller, *J. Am. Chem. Soc.*, 1975,

97, 2305.

62 J. F. Stoddart, "Stereochemistry of Carbohydrates", Wiley-Interscience, New York, 1971.

63 B. Coxon and L. D. Hall, *Tetrahedron*, 1964, **20**, 1685.

64 P, Boullanger, J. C. Martin, and G. Descotes, *J. Heterocycl. Chem.*, 1975, **12**, 91.

65 G. Ekborg, B. Linberg, and J. Lönngren, *Acta. Chem. Scand.*, 1972, **26**, 3287.

66 P. A. Gent and R. Gigg, *Carbohydr. Res.*, 1976, **49**, 325.

67 For reviews on cyclic acetals of the aldoses and aldosides, see: A. N. DE Belder, *Adv. in Carbohydr. Chem.*, 1965, **20**, 219; A. N. DE Belder, *Adv. in Carbohydr. Chem. Biochem.*, 1977, **34**, 179.

68 A. Lipták, V. A. Oláh, and J. Kerékgyártó, *Synthesis*, 1982, 421; J. S. Brimacombe, A. B. Foster, B. D. Jones, and J. J. Willard, *J. Chem. Soc., C*, 1967, 2404.

69 For general reviews on NMR in carbohydrate chemistry, see: L. D. Hall in "The Carbohydrates, Chemistry and Biochemistry", Eds. W. Pigman and D. Horton, Academic Press, New York, 1980, **1B**, 1300; T. D. Inch, *Ann. Rev. NMR. Spect.*, 1969, **2**, 35.

70 P. L. Durette and D. Horton, *Org. Mag. Res.*, 1971, **3**, 417.

71 L. G. Vorontsova and A. F. Bochkov, *Org. Mag. Res.*, 1974, **6**, 654 and references therein.

72 For a general discussion on electronegativity and the Karplus Equation, see: C. A. G. Haasnoot, F. A. A. M. de Leeuw, and C. Altona, *Tetrahedron*, 1980, **36**, 2783.

73 R. F. Stewart and L. L. Miller, *J. Am. Chem. Soc.*, 1980, **102**, 4999.

74 Y. Ito and T. Ogawa, *Tetrahedron Lett.*, 1988, **29**, 3987; S. Kusumoto, N. Kusumose, T. Kamikawa, and T. Shiba, *ibid.*, 1988, **29**, 6325; H. Kunz, H. Waldmann, and U. Klinkhammer, *Helv. Chim. Acta*, 1988, **71**, 1868.

75 W. J. Middleton, *J. Org. Chem.*, 1975, **40**, 574.

76 G. Ekborg, B. Lindberg, and J. Lönngren, *Acta. Chem. Scand.*, 1972, **26**, 3287.

77 V. Bílik and Š. Kučár, *Carbohydr. Res.*, 1970, **13**, 311.

78 For a review on the use of diethyl azodicarboxylate and triphenylphosphine in synthesis, see: O. Mitsunobu, *Synthesis*, 1981, 1.

79 P. Brigl, *Hoppe-Seyler's Z. Phyziol. Chem.*, 1921, **116**, 1; 1922, **122**, 245.

80 For a review on the use of activated dimethyl sulphoxide as useful synthetic reagent, see: A. J. Mancuso and D. Swern, *Synthesis*, 1981, 165.

81 For a review on the use of pyridium chlorochromate in organic synthesis, see: G. Piancatelli, A. Scettri, and M. D'Auria, *Synthesis*, 1982, 245.

82 W. P. Griffith, S. V. Ley, G. P. Whitcombe, and A. D. White, *J. Chem. Soc., Chem. Commun,* 1987, 1635. See also *Aldrichim. Acta,* 1988, **21**, 16.

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

84 M. D. Lewis, J. K. Cha, and Y. Kishi, *J. Am. Chem. Soc.,* 1982, **104**, 4976.

85 R. U. Lemieux, K. B. Hendriks, R. V. Stick, and K. James, *J. Am. Chem. Soc.*, 1975, **97**, 4056.

86 I. F. Watt, *Adv. Phy. Org. Chem.*, 1988, **24**, 57.

87 K. M. Taba, R. Köster, and W. V. Dahlhoff, *Synthesis,* 1983, 1036.

88 T. Reichstein, A. Grüssner, and R. Oppenauer, *Helv. Chim. Acta.,* 1933, **16**, 1019.

89 J. Kiss and W. Arnold, *Experientia,* 1980, **36**, 1138.

90 J. Kiss and H. Spiegelberg, *Helv. Chim. Acta,* 1964, **47**, 398.

91 T. W. Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons, New York, 1981.

92 H. O. House, "Modern Synthetic Reactions", Ed. R. Breslow, W. A. Benjamin, Inc., New York, 1965.

93 C. H. Heathcock in "The Aldol Addition Reaction", Asymmetric Synthesis, Ed. J. D. Morrison, Academic Press, 1984, **3**, 111.

94 G. Stork and J. d'Angelo, *J. Am. Chem. Soc.,* 1974, **96**, 7114.

95 T. Mukaiyama, K. Banno, and K. Narasaka, *J. Am. Chem. Soc.,* 1974, **96**, 7503.

96 D. Crich and J. W. Davies, *J. Chem. Soc., Chem. Commun.,* 1989, 1418.

97 L. A. Paquette, C. S. Ra, and T. W. Silvestri, *Tetrahedron,* 1989, **45**,

3099.

98 R. S. Topgi, *J. Org. Chem.*, 1989, **54**, 6125.

99 E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Am. Chem. Soc.*, 1969, **91**, 5675.

100 J. Wàgner and P. Vogel, *J. Chem. Soc., Chem. Commun.*, 1989, 1634.

APPENDIX

Tetrahedron Letters, Vol.31, No.13, pp 1897-1900, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

SYNTHESIS OF 2-DEOXY-β-C-PYRANOSIDES BY DIASTEREOSELECTIVE HYDROGEN ATOM TRANSFER

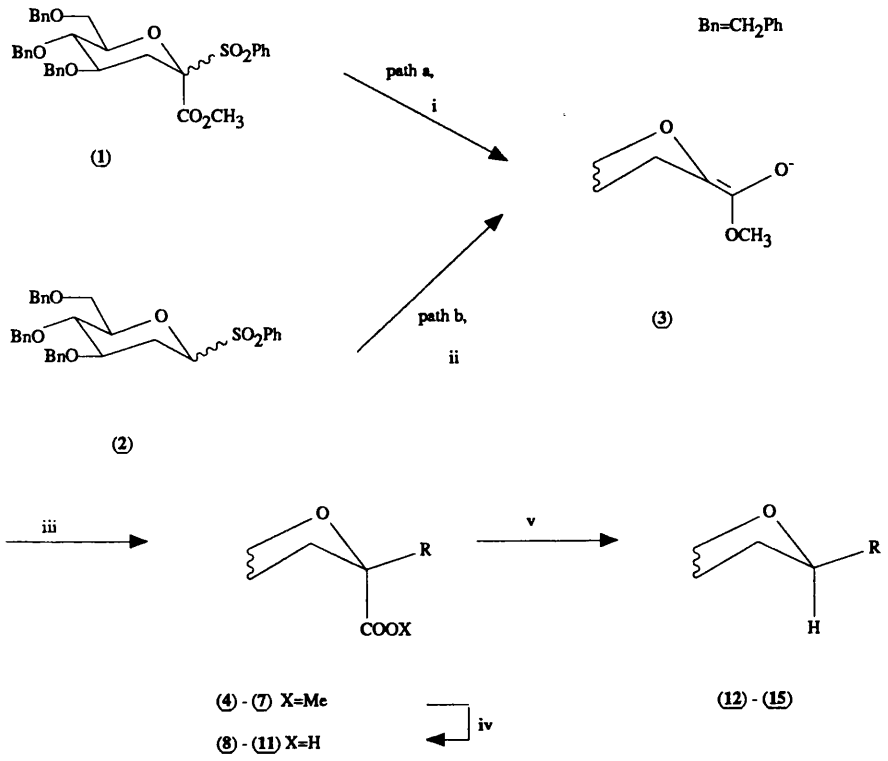
David Crich* and Linda B.L.Lim

Department of Chemistry,University College London
20 Gordon Street, London, WC1H 0AJ, UK.

Abstract: 2-Deoxy-β-C-pyranosides are synthesized by sequential treatment of methyl 3-deoxy-2-phenylsulphonyl-4,5,7-tri-O-benzyl-D-arabino-heptulosonate with lithium naphthalenide and an alkyl halide followed by saponification and reductive decarboxylation.

The synthesis of C-glycopyranosides by carbon-carbon bond formation at the anomeric centre of variously activated pyranosides has attracted much attention in recent years resulting in the description of several diverse and elegant solutions.[1] We present here an extension of our earlier work on the synthesis of 2-deoxy-β-glycosides[2] to the synthesis of 2-deoxy-β-C-glycosides in which the stereochemistry at the "anomeric" centre is determined by diastereoselective hydrogen atom transfer to a glycosyl radical.

The overall process, presented in the scheme and summarized in the table, involves formation of the key carbon-carbon bond at C-1 by alkylation of the ester enolate (**3**) with an alkyl halide.The enolate (**3**) is generated either from the 3-deoxy-2-phenylsulphonyl heptulosonate (**1**)[2] with lithium naphthalenide (LN) (path a) or in situ from the sulphone (**2**)[2] by deprotonation with lithium diisopropylamide, quenching with dimethyl carbonate and desulphonylation with lithium naphthalenide (path b). The so-formed heptulosonate C-glycosides (**4**)-(**7**) are then saponified to the corresponding acids (**8**)-(**11**) which are subject to reductive decarboxylation according to the Barton protocol[3] by reaction of their triethylammonium salts with the heterocycle (**16**) followed by tungsten photolysis of the intermediate O-acyl thiohydroxamates in the presence of a tertiary mercaptan giving ultimately the β-C-glycosides (**12**)-(**15**).



(4), (8), (12) R=$CH_2CH=CH_2$; (5), (9), (13) R=CH_2Ph ; (6), (10), (14) R=Me ;

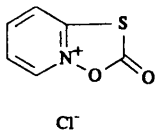
(7), (11), (15) R=$CH_2OCH_2CH_2SiMe_3$

i) LN ; ii) LDA, MeOCOOMe, LN ; iii) R-X ; iv) KOH ; v) Et_3N ;

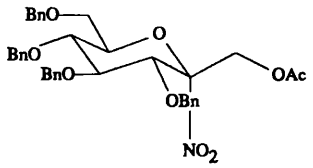
(16) R'SH, hυ

Scheme

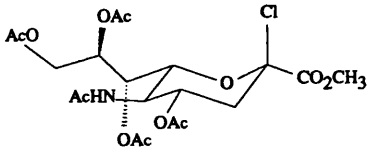
In each example the key reductive decarboxylation step was carried out at 0°C in dichloromethane and resulted in the formation of a single diastereoisomer (within the limits of n.m.r. detection), assigned as the "β-anomer". This selectivity is in accordance both with the reduction of the related compounds (17) and (18) with tin hydrides in which, it is reported, the intermediate C-1 radicals are quenched exclusively from the axial direction[4] and with the N-bromosuccinimide mediated bromination of various pyranoses and uronate and ulosonate esters in which bromine is introduced at an axial position.[5]



(16)



(17)



(18)

Table[6]

RX	Method	Ester (% Yield)	Acid (% Yield)	C-Glycosides (% Yield)
CH_2=$CHCH_2Br$	B	(4) (44)	(8) (77)	(12) (73)
$PhCH_2Br$	B	(5) (56)	(9) (72)	(13) (92)
CH_3I	A	(6) (50)	(10) (88)	(14) (56)
$Me_3SiCH_2CH_2OCH_2Cl$[7]	A	(7) (70)	(11) (82)	(15) (58)

A = path a ; B = path b

Obvious extensions to this facile, highly stereoselective, methodology include the formation of spirocyclic C-glycosides and spiroketals.

Acknowledgement: LBLL thanks the Brunei Government for a postgraduate studentship.

References

1. For some recent examples see: Bolitt,V.; Mioskowski,C.; Falck,J.R. Tetrahedron Lett, **1989**, 30, 6027; Frick,W.; Schmidt,R.R. Liebigs Ann. Chem., **1989**, 565; Tatsuta,K.; Hayakawa,J.; Tatsuta,Y. Bull. Chem. Soc. Jap., **1989**, 62,490; Preuss,R.; Schmidt,R.R.,Liebigs Ann. Chem., **1989**, 429; Cai,M.S.; Qiu,D.X. Synth. Commun., **1989**, 19, 851; Allevi,P.; Ciuffreda,P.; Colombo,D.; Monti,D.; Speranza,G.; Manitto,P. J. Chem. Soc., Perkin Trans. 1, **1989**, 1281; Brown,D.S.; Bruno,M.; Davenport,R.J.; Ley,S.V. Tetrahedron, **1989**, 45,4293; Panek,J.S.; Sparks,M.A. J. Org. Chem., **1989**,54, 2034; Motherwell,W.B.; Tozar,M.J.; Ross,B.C. J. Chem. Soc., Chem. Commun., **1989**, 1437; Bellosta,V.; Czernecki,S. J. Chem. Soc., Chem. Commun., **1989**, 199; Lopez,J.C.; Fraser-Reid,B. J. Am. Chem. Soc., **1989**, 111, 3450; Kraus,G.A.; Molina,M.T. J. Org. Chem., **1988**, 53, 752; Brakta,M.; Lhoste,P.; Sinou,D.

J. Org. Chem., **1989**, 54, 1890; Matsumoto,T.; Katsuki,M.; Jona,H.; Suzuki,K. Tetrahedron Lett., **1989**, 30, 6185; Giese,B.; Linker,T.; Muhn,R. Tetrahedron, **1989**, 45, 935; Kametani,T.; Kawamura,K.; Honda,T. J. Am. Chem. Soc., **1987**, 109, 3010; Casiraghi,G.; Cornia,M.; Rassu,G.; Zetta,L.; Fava,G.G.; Belicchi,M.F. Carbohydr. Res., **1989**, 191, 243; De Mesmaeker,A.; Hoffmann,P.; Ernst,B.; Hug,P; Winkler,T. Tetrahedron Lett., **1989**, 30, 6307.

2. Crich,D.; Ritchie,T.J. J.Chem.Soc., Chem. Commun., **1988**, 981, 1461; idem, Carbohydr. Res., **1989**, 190, C3; idem, J. Chem. Soc., Perkins Trans 1, **1990**, 0000.

3. Barton,D.H.R.; Crich,D.; Motherwell,W.B. Tetrahedron, **1985**, 41,3901; for a review see: Crich,D.; Quintero,L. Chem. Rev., **1989**, 89, 1413.

4. Baumberger,F.; Vasella,A. Helv. Chim. Acta, **1983**, 66, 2210; Schmidt,W.; Christian,R.; Zbiral,E. Tetrahedron Lett., **1988**, 29, 3643; Myrvold,S.; Reimer,L.M.; Pompliano,D.L.; Frost,J.W. J. Am. Chem. Soc., **1989**, 111, 1861.

5. Blattner,R.; Ferrier,R.J. J. Chem. Soc., Perkin Trans 1, **1980**, 1523; Ferrier,R.J.; Furneaux,R.H. J. Chem. Soc., Perkin Trans 1, **1977**, 1996; Somsak,L.; Batta,G.; Farkas,I. Carbohydr. Res., **1983**, 124, 43.

6. All new compounds gave satisfactory spectroscopic and microanalytical or high resolution mass data.

7. For the use of β-trimethylsilylethoxymethyl chloride as a formaldehyde equivalent in aldol type reactions see: Crich,D.; Davies,J.W. J. Chem. Soc., Chem. Commun., **1989**, 1418.; Crich,D.; Lim,L.B.L. Syn. Lett., **1990**, 1, 0000.

(Received in UK 7 February 1990)

SYNLETT

Accounts and
Rapid Communications in
Synthetic Organic Chemistry

1990
No. 2
February

With Compliments of the Author.

GEORG THIEME VERLAG · STUTTGART · NEW YORK

β-Trimethylsilylethoxymethyl Chloride as a Formaldehyde Equivalent in Aldol-Type Reactions

David Crich,* Linda B. L. Lim
Department of Chemistry, University College of London, 20 Gordon Street, London WC1H 0AJ, England
Received 2 January 1990

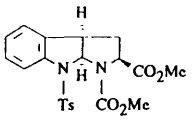
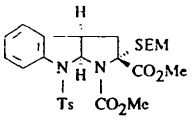
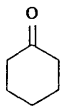
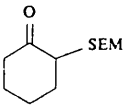
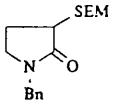
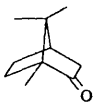
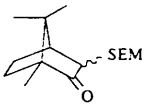
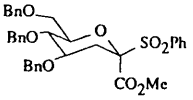
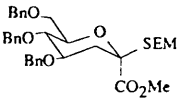
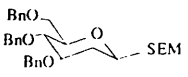
Abstract: β-Trimethylsilylethoxymethyl chloride reacts with a variety of lithium enolates and lithium salts of stabilised carbanions to give the aldol products conveniently protected as their β-trimethylsilylethyl ethers.

In the course of a recent investigation into the generation of "peptoids" from tryptophan we found β-trimethylsilylethoxymethyl chloride (SEM-Cl) to be a convenient and effective equivalent of formaldehyde for the trapping of ester enolates (Table, entry 1).[1] Paquette has also provided an example of the efficient quenching of a ketone enolate with SEM-Cl.[2] The use of benzyloxymethyl chloride in a similar context has also been described recently.[3] We report here further examples of the reaction of lithium enolates (Table, entries 2 - 5) with SEM-Cl in THF at -78 °C leading to the β-trimethylsilylethyl ethers of the products of formal aldol reaction with formaldehyde. This new use[4] of SEM-Cl presents several advantages over the more traditional aqueous formaldehyde[5] in so far as it allows controlled introduction of a single hydroxymethyl unit in a conveniently protected form. It is also vastly superior, in our hands, to gaseous formaldehyde[6] and does not require the prior formation of trimethylsilyl enol ethers as in the Mukaiyama titanium tetrachloride/trioxane method.[7]

The method is not restricted to the generation of enolates by deprotonation as illustrated by example 5 (Table) in which the enolate was accessed by reductive desulphonylation of a geminal sulphone ester[8] with two equivalents of lithium napthalenide in THF. Furthermore the method is applicable to the quenching of lithium salts of other stabilised carbanions as demonstrated by examples 6 and 7 (Table).

Finally the free hydroxy group can be revealed by treatment with tetrabutylammonium fluoride,[4] trifluoroacetic acid,[1] and boron trifluoride etherate.[2]

Table Reaction of enolates and stabilised carbanions with SEM-Cl

Entry	Substrate	Method[a]	Product[b]
1		A	 (78%)
2		A	 (76%)
3		A	 (60%)
4		A	 (57%)[c]
5		B	 (70%)
6	PhC≡CH	A	PhC≡C-SEM (60%)
7		A	 (65%)[d]

a. A: deprotonation with lithium diisopropylamide; B: desulphonylation of lithium naphthalenide.

b. All new products gave satisfactory spectroscopic and microanalytical or high resolution mass data.

c. 2.5:1 endo:exo mixture of isomers

d. Decomposes rapidly on standing at room temperature.

Acknowledgement. L.L.B.L. thanks the Brunei Government for a postgraduate studentship.

References and Notes

(1) Crich, D.; Davies, J.W. *J. Chem. Soc., Chem Commun.* **1989**, 1418.

(2) Paquette, L.A.; Ra, C.S.; Silvestri, T.W. *Tetrahedron* **1989**, *45*, 3099.

(3) Wägner, J.; Vogel, P. *J. Chem. Soc., Chem. Commun.*, **1989**, 1634.

(4) SEM-Cl has previously been used mainly for the protection of alcohols: Lipshutz, B.H.; Pegram, J.J. *Tetrahedron Lett.* **1980**, *21*, 3343 and for the combined N-protection and orthometallation of pyrroles: Edwards, M.P.; Doherty, A.M.; Ley, S.V.; Organ, H.M. *Tetrahedron* **1986**,*42*, 3723.

(5) Stetter, H. In *Houben-Weyl*, 4th ed.; Thieme: Stuttgart, 1976; Vol. 7/2b, p 1449.

(6) Stork, G.; d'Angelo, J. *J. Am. Chem. Soc.* **1974**, *96*, 7114.

(7) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503.

(8) Crich, D.; Ritchie, T.J. *J. Chem. Soc., Chem. Commun.* **1988**, 985 and references therein.

Erratum:

Janowitz, A.; Kunz, T.; Handke, G.; Reissig, H.-U. *Synlett* **1989**, 24. The following table should appear below the second reaction scheme (**3a,b** → **4a,b**):

starting material	R	solvent	product	yield (%)	*trans/cis*
3a	Me	Et_2O	**4a**	39	25:75
3a	Me	THF	**4a**	16	57:43
3b	Ph	Et_2O	**4b**	32	17:83

In Table I, R-M in entry 6 should be CH_2=CHMgBr.