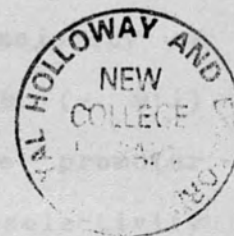THE STEREOSELECTIVE SYNTHESIS OF

ARABINOFURANOSIDES

BY

ALOYSIUS HARINDRA SIRIWARDENA

A Thesis
Presented in Candidature for the Degree of
Doctor of Philosophy in the Faculty
of Science of the University of London.

Royal Holloway and Bedford New College,
University of London,
Surrey.

November, 1986.

ProQuest Number: 10090142

ProQuest 10090142

ABSTRACT

The work presented in this thesis is concerned with the design and development of chemical methods for the stereoselective synthesis of β-L-arabinofuranosides, in particular those which constitute the oligosaccharide fragments of the plant glycoprotein extensin.

Previous methods intended for the preparation of 1,2-cis-glycofuranosides are reviewed. Relevant mechanistic and conformational studies are also discussed.

Selected glycosylation methods are examined in preliminary experiments with the model secondary alcohols — isopropanol and cholesterol. Of the methods investigated, the most successful proved to be that involving 2,3,5-tri-O-benzyl-α-L-arabino-furanosyl chloride and promoters consisting of silver or thallium cations supported on molecular sieves. Good yields (60-90%) of the β-glycosides were obtained using stoichiometric amounts of reactants, in less than 4 hours at room temperature. The majority of these glycosylations proceeded with high (~ 9:1) β-stereoselectivity. However, with one promoter (based on thallium) a reversal of stereoselectivity was observed.

The 1-0-trichloroacetimidate and 1-0-toluene-sulphonate derivatives of 2,3,5-tri-0-benzyl-L-arabinofuranose were also synthesised and studied as potential glycosylating agents.

Four new derivatives of trans-4-hydroxy-L-proline have been synthesised, characterised, and used in glycosylation reactions with 2,3,5-tri-0-benzyl-arabinofuranosyl-α-L-chloride and the molecular sieve-based promoters. The resulting β-arabino-furanosides were characterised, and each subsequently deblocked, to give the known component of extensin; 4-0-(β-L-arabinofuranosyl)-trans-oxy-L-proline.

A number of other new derivatives were made and characterised during this work. These include allyl-L-arabinofuranoside which provided an improved preparation of the known 2,3,5-tri-0-benzyl-L-arabinofuranose. An analogous synthesis of the corresponding D-ribose derivative was also achieved.

Throughout this work, extensive use has been made of ^{1}H and ^{13}C nmr spectroscopy in the identification and characterisation of the new compounds. In particular, ^{13}C nmr spectroscopy provided a very convenient means of establishing the ring sizes and anomeric configurations of the sugars.

ACKNOWLEDGEMENTS

I wish to express my sincere gratitude and thanks
to Dr. Paul Finch for the expert guidance, care and
encouragement he has given me throughout this research
work.

TO MY

I am also indebted to a number of other experts at

MOTHER AND FATHER

the University of London for generating the spectral
data. These include the nmr spectroscopists Jane

WITH LOVE.

Hawkes and Frances Gailway (King's College), Dr. G.E.
Hawkes and Dr. P. Haycock (Queen Mary College), Ron
Parkinson (Royal Holloway and Bedford New College);
the mass spectroscopists John Harper (Chelsea
College), Mr. Carter (School of Pharmacy), John Lyon
and Dr. R. Hancock (Royal Holloway and Bedford New
College).

I am also grateful to the staff and my colleagues
at the Bourne Laboratory for their help during this
work. In particular I should like to thank Drs. D.
Weigel, C. Lewis, P. Powell, H. Bolton, M. Cracknell
and L. Santing (for advice and discussion); his
Whitaker, "Bimbo" Smith and John "the glass" (for
technical assistance); Dr. F. Powell, Rima and Nadine
(for translating scientific papers); Jackie Keane (for
typing the manuscript and tolerating the many
alterations I made to the first drafts).

Finally, I thank my family and friends for their remarkable patience and understanding. I am especially indebted to Elsa without whose love and constant support this work would not have been completed.

This research was supported by the Science and Engineering Research Council.

CONTENTS

8

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1

GENERAL INTRODUCTION

1.1   Target molecules: importance and problems of

chemical synthesis.

The term "O-glycoside" encompasses a wide range of structures.   These include those of phenols and aliphatic alcohols, oligo- and polysaccharides as well as glycoproteins, proteoglycans and glycolipids.

Natural O-glycosides have been shown to perform a variety of biological functions[1-6].   A number are known   to   exhibit   important   pharmacological   and antimicrobial activities.   In fact, interest in the chemical synthesis of molecules of this type was originally generated because of their potential use as medicines.   However, crucial impetus in the chemical investigation   of   O-glycosides   has   come   as   a consequence of the realisation that several of them carry additional interesting biological information. In particular, biochemical investigations have helped establish that certain O-glycosidic structures play fundamental roles in the regulation and maintenance of living organisms.   For example, evidence exists that certain O-glycosides present in plants can profoundly influence their growth and development[7].   Discoveries

14

such as these, have further stimulated activity and interest in the chemical synthesis of O-glycosides. Synthetic studies serve to provide chemical evidence to establish the proposed structures of natural products. In addition, they could provide quantities of pure O-glycosides which can often be difficult to obtain in an unmodified form from biogenic material. If the amounts of compound required for more rigorous biochemical investigations were available, the precise molecular mechanisms by which certain processes occur within living organisms could be further clarified. It is through an appreciation of these fundamental mechanisms that biological phenomena will ultimately be understood in chemical terms.

Arabinofuranose has been identified as a constituent of a variety of plant glycosides[8]. There is also evidence that arabinose is linked to hydroxyproline in a number of plant glycoproteins and proteoglycans[9-13]. However, structural information relating to glycosides of this type is often limited due to problems associated with their isolation. For example, the O-glycosidic bond associated with arabinofuranosides is known to be a particularly acid-labile one[9]. In addition, the basic extractions which are routinely used to obtain glycopeptides from plants have on occasions been found to lead to a base-catalysed epimerisation at C-2 of the imino acid[14].

"Extensin"[15] is a glycoprotein particularly rich in L-arabinofuranose (1) and trans-4-hydroxy-L-proline (2) which has been isolated by partial alkaline[9]

1

2
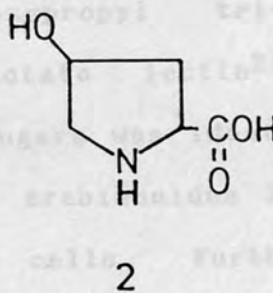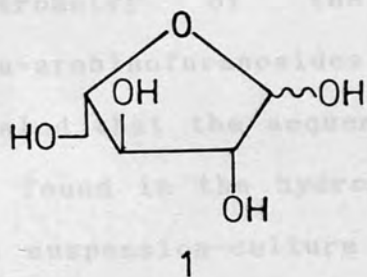
or enzymatic degradation[16] from the cell walls of a number of higher plants and algae[17,18]. This component, whose role is thought to be structural, has been the subject of several structural investigations. These have revealed that extensin is characterised by a protein backbone composed mainly of trans-4-hydroxy-L-proline to which tri-and tetra-oligo-L-arabinofuranoside chains are attached. The sequences of hydroxyprolinyl arabinosides isolated from suspension-culture tobacco cells were determined as Araf(1→2)Araf(1→2) Araf(1→4)Hyp for the trimer and Araf(1→3)[Araf(l→2)]$_2$ Araf(1→4)Hyp for the tetramer on the basis of the results of methylation analysis and periodate degra(da)tion[14,19]. The anomeric configurations were thought to be all β- from the data of optical rotation and [1]H-nmr spectroscopy[19]. However, analysis

by ^{13}C-nmr spectroscopy suggests that the non-reducing terminal arabinofuranose unit of the tetramer is joined by an α-glycosidic linkage[20].

Methylation analysis and direct-insertion mass spectrometry of the hydroxypropyl tri- and tetra-arabinofuranosides of potato lectin[21] have revealed that the sequence of sugars was identical to that found in the hydroxyproɬyl arabinosides isolated from suspension-culture tobacco cells. Furthermore, the anomeric configurations of these potato lectin glycoproteins were found on the basis of optical rotation and enzymatic evidence[21] to be the same as those determined for the plant cell wall glycoproteins.

The oligosaccharide fragments isolated from extensin or potato lectin are proposed to be those represented by structures (3) and (4). Although isolated from quite distinct sources these molecules have many structural features in common, but it is uncertain whether they have functional similarities or represent diverse group of structurally related polymers.

3

4
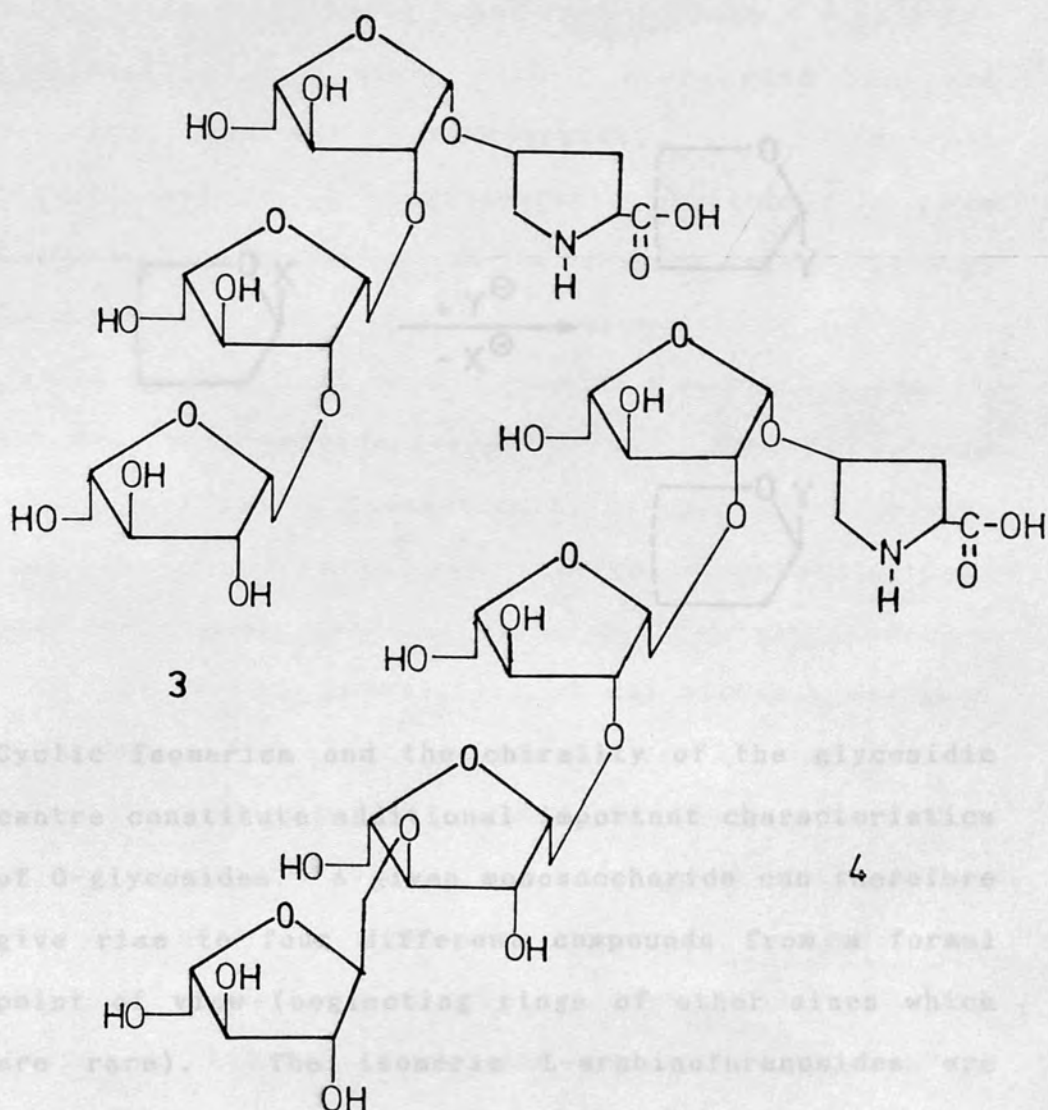
O-Glycosides may in principle be classified as acetals[22,23], in which one alkoxyl group is contained within a cyclic system and the other is exocylic. As a consequence, a major feature of the chemistry of O-glycosides is the replacement of the excocylic part of the acetal system, through a nucleophilic substitution reaction at the glycosidic centre, with retention of the cycle.

Cyclic isomerism and the chirality of the glycosidic centre constitute additional important characteristics of O-glycosides. A given monosaccharide can therefore give rise to four different compounds from a formal point of view (neglecting rings of other sizes which are rare). The isomeric L-arabinofuranosides are shown below:
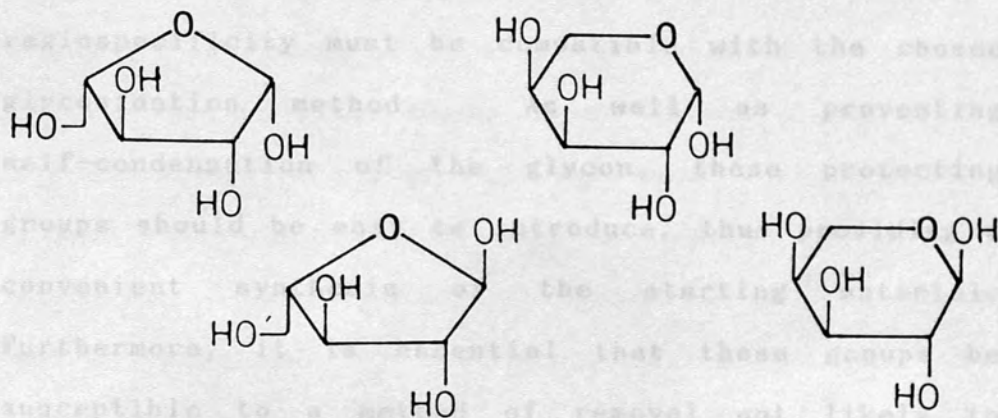
O-Glycoside synthesis is not limited to the construction of a sugar with a fixed ring size and definite anomeric configuration. A further requirement is a regiospecific building of the O-glycosidic linkage towards a particular hydroxyl function of a given aglyconic component.

The synthesis of an O-glycoside comprises a number of separate considerations[24,25]. However, these cannot be resolved independently of each other because they invariably give rise to rather contradictory practical requirements. Thus, typical glycosidation reactions involve the linking of two properly designed components. The glycon derivative has to have a fixed ring size with all its hydroxyl functions except that at the glycosidic centre suitably protected and the anomeric hydroxyl function must be activated by replacing it with an alternative leaving group. The choice of leaving group and hence the method of glycosidation determines the main conditions of the reaction. The protecting groups employed to ensure regiospecificity must be compatible with the chosen glycosidation method. As well as preventing self-condensation of the glycon, these protecting groups should be easy to introduce, thus providing a convenient synthesis of the starting material. Furthermore, it is essential that these groups be susceptible to a method of removal not likely to

cleave O-glycosidic bonds. The choice of aglycon protecting groups will be governed by similar considerations to those outlined for the protection of the glycon component.

As a consequence of these numerous requirements, a totally general synthetic method for the construction of O-glycosides has not been formulated[27,28,26]. The poor stereoselectivity of many of the methods constitutes a major problem, as the formation of anomeric mixtures represents a loss of efficiency, and their separation is usually difficult.

The stereoselective construction of O-glycosidic bonds is one of the most important objectives of carbohydrate chemistry[26]. Considerable effort has been directed towards developing glycosylating methods which can give a desired O-glycopyranoside efficiently and stereospecifically. In general, more success has been achieved in the stereoselective synthesis of 1,2-trans-O-glycopyranosides than in that of the corresponding 1,2-cis anomers[27,28,26].

The L-arabinofuranose units in extensin are linked through O-glycosidic bonds, some of which are of the 1,2-cis type. The specific problem of stereoselective O-arabinofuranoside synthesis has only rarely been addressed. Any practical synthesis of a complex arabinofuranoside would require a method for constructing these glycosidic bonds

stereoselectively.

7

+

6

5

R = C₆H₅CH₂ , Rˡ = C₆H₅CH₂CO

$R = C_6H_5CH_2$, $R^l = C_6H_5CH_2CO$
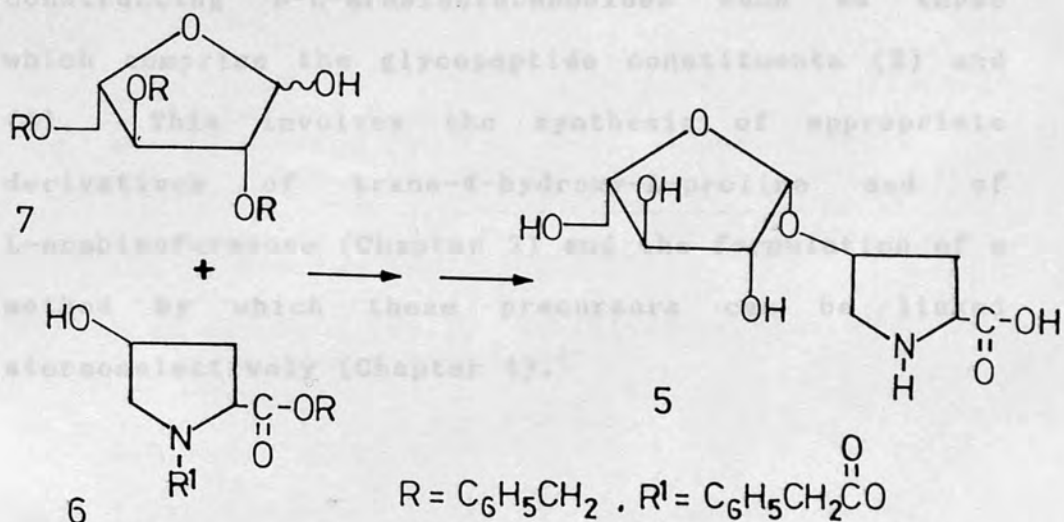
4-O-[β-L-arabinofuranosyl]-trans-oxy-L-proline

(5), a fragment of extensin, has previously been

synthesised[29] by reacting N-(benzyloxycarbonyl)-

hydroxy-L-proline benzyl ester (6) with

2,3,5-tri-O-benzyl-L-arabinofuranose (7) in the

presence of trifluoromethanesulphonic anhydride at

-15°. The required 1,2-cis-arabinofuranoside (5)was

obtained (~ 35% yield) by chromatography after

deprotection of the mixture (~ 1:1; ~ 80% yield) of α-

and β- products. It is clear that this glycosidation

method would not be satisfactory for the synthesis of

higher saccharides. The separation of mixtures of

complex α- and β- arabinofuranosides is expected to

present formidable problems and is a serious drawback

in non-stereoselective methods of this type.

A major objective of this research work has been

concerned with developing an appropriate method for

constructing β-L-arabinofuranosides such as those which comprise the glycopeptide constituents (3) and (4). This involves the synthesis of appropriate derivatives of trans-4-hydroxy-L-proline and of L-arabinofuranose (Chapter 3) and the formulation of a method by which these precursors can be linked stereoselectively (Chapter 4).

1.2   References.

1. N. Sharon and H. Lis, in "The Proteins",
   ed. H. Neurath and R.Z. Hill, Academic Press,
   Vol 5, 1-144.

2. C.C. Sweeley (ed.), Cell Surface Glycolipids,
   ACS Syumposium Ser. (1980) 128.

3. M.I. Horowitz (ed.), "The Glycoconjugates",
   Vol.4, Academic Press 1982.

4. S. Hakomori, Ann.Rev.Biochem., 50 (1981)
   733-764.

5. T. Yamakawa and Y. Nagai, Trends Biochem.Sci.,
   3 (1978) 128-131.

6. N. Sharon and H. Lis, Chem.Eng.News, 59 (1981)
   21-44.

7. P.A. Albersheim, presented at the Royal Society
   of Chemistry Carbohydrate meeting, Sheffield
   1986.

8. R.R. Selvendran and M.A. O'Neill, in
   "Encyclopedia of Plant Physiology " ed.
   F.A. Loewus and W. Tanner, Springer Verlag
   1982, Vol. 13A "Plant Carbohydrates 1".

9. D.T.A. Lamport, Nature (London),216 (1967)
   1322.

10. A.K. Allen, N.N. Desai, A. Neuberger and
    J.M. Creeth, Biochem.J., 171 (1978) 665-674.

11. D.G. Pope, Plant Physiol, 59 (1977) 894-900.

12. U.V. Mani and A.N. Radhakrishnan, Biochem.J.,
    141 (1974) 147-153.

13. D.T.A. Lamport, "Macromolecules Regulating
    Growth and Development", The 30th Symposium
    of the Society for Developmental Biology,
    113-130; K.J. Tautrydas, Planta 140 (213-220.

14. Y. Akiyama and K. Kato, Agr.Biol.Chem., 40
    (1976) 2343.

15. D.T.A. Lamport, Annu.Rev.Plant Physiol., 21
    (1970) 235.

16.   D.T.A. Lamport, Biochemistry, 8, (1969) 1155.

17.   D.T.A. Lamport, "The Biochemistry of Plants",
       Vol.3, Academic Press 1980, 501-541.

18.   B. Solheim and J. Raa (ed.), "Cell Wall
       Biochemistry", Proceeding of Symposium,
       University of Tronso, Norway (1976).

19.   Y. Akiyama, and K. Kato, Agr.Biol.Chem.,
       41 (1977) 79.

20.   Y. Akiyama, M. Mori and K. Kato, Agr.Biol.Chem.,
       44 (1980) 2487.

21.   D. Ashford, N.N. Desai, A.K. Allen, A. Neuberger,
       M.A. O'Neill, R. Selvendran, Biochem.J., 201
       (1982) 199.

22.   R.U. Lemieux, Adv.Carbohydr.Chem., 9 (1954) 1.

23.   B. Capon, Chem.Rev., 69 (1969) 407.

24.   T. Ogawa, H. Yamamoto, T. Nukada, T. Kitajima
       and M.Sugimoto, Pure and Appl.Chem., 56 (1984)
       779.

25.   C. Schuerch, Accounts of Chemical Research,
       6 (1973) 184.

26.   A.F. Bochkov and G.E. Zaikov, "Chemistry of
       the O-Glycosidic Bond: Formation and Cleavage",
       Pergamon Press, 1979.

27.   H. Paulsen, Angew.Chem.Int.Ed.Engl., 21 (1982)
       155-173.

28.   G. Wulff and G. Rohle, Angew.Chem.Int.Ed.Engl.,
       13 (1974) 157-170.

29.   A. Allerhand, K. Dill, E. Berman, J.M. Lacombe and A.
       Pavia, Carbohydr. Res., 97 (1981) 331.

CHAPTER 2

PREVIOUS STUDIES RELEVANT TO THE CHEMICAL SYNTHESIS
OF GLYCOFURANOSIDES

2.1 Methods of synthesis aimed at 1,2 cis stereoselectivity.

Previous efforts to design methods for the stereoselective synthesis of 1,2-cis-glycofuranosyl derivatives were originally initiated as a result of interest in the preparation of analogues of nucleosides and nucleotides. Although the precise details differ, several of the considerations important in the construction of 1,2-cis-glycofurano-sylamines also apply to the synthesis of 1,2-cis-glycofuranosides. The earliest of these strategies involved inverting the configuration at C-2 of a preformed 1,2-trans-glycosylamine. The synthesis of 9-β-D-arabinofuranosyladenine **(8)** from 9-β-D-xylofuranosyladenine was achieved by such a route[1]. Other examples include the inversion of the C-2 hydroxyl function of D-ribofuranosyluracil[2] and thymine[3,4] derivatives to give the corresponding 1,2-cis-arabinofuranosylamines [**(9)** and **(10)** respectively]. Although sound in principle this

particular strategy has only limited scope as a general one for obtaining 1,2-cis-glycofuranosides. Selective inversion at C-2 is not convenient for every glycoside and always involves a number of

8 X =

9 X =

10 X =
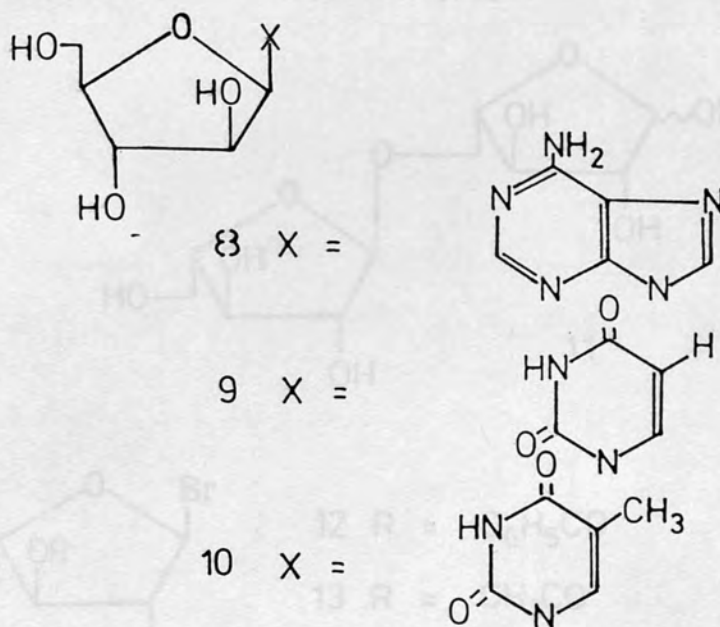
chemical steps. As a consequence, the method has only rarely been used for making 1,2-cis-glycofuranosylamines and never for 1,2-cis-glycofuranosides.

An alternative route to glycofuranosylamines employed in this early work involved the condensation of a fully protected glycofuranosyl bromide or chloride with the appropriate nucleophile. However, the use of 2,3,5-tri-O-benzoyl (12) or 2,3,5-tri-O-acetyl-L-arabinofuranosyl bromides (13) gave invariably, the corresponding

1,2-trans-glycofuranosylamines[5]. Similarly, the condensation of 2,3,5-tri-O-benzoyl-α-L-arabinofuranosyl bromide with 2,3,4-tri-O-acetyl-L-arabinose diethyl dithioacetal gave 5-O-α-L-arabinofuranosyl-L-arabinose (11)[6].

12 R = C₆H₅CO

13 R = CH₃CO

14 R = H

15 R = NO₂

R = C₆H₅CO
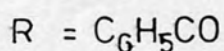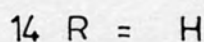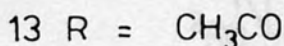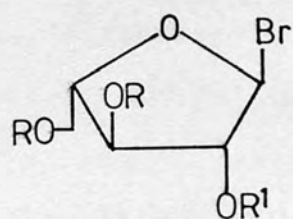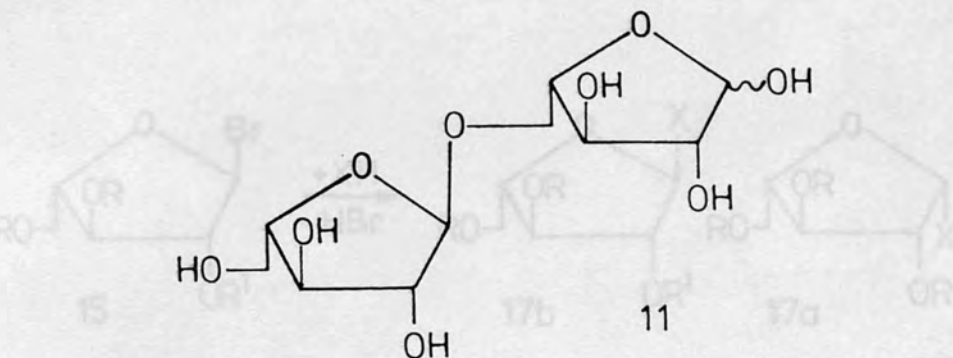
In a later study the influence of the protecting group at C-2 was shown to be important in the stereochemical outcome of the reactions of glycofuranosyl halides[7]. Thus, the reaction of various arabinofuranosyl bromide derivatives [(12), (13), (14) or (15)] with either methanol or 1,2,3,4-tetra-O-acetyl-β-D-glucopyranose (16) under catalysis by silver(1)oxide indicated that 1,2-cis-glycosides were predominantly obtained when

the group at C-2 of the glycon was not able to participate in displacement reactions at its anomeric centre. For example, the reaction of 2-O-nitro-3,5-di-O-benzoyl-α-L-arabinofuranosyl bromide **(15)** with

$R = C_6H_5CO$, $R^1 = NO_2$, $X = CH_3O$ or

$R^2 = CH_3CO$
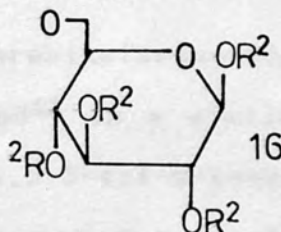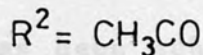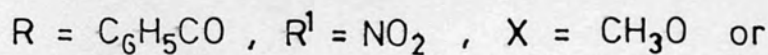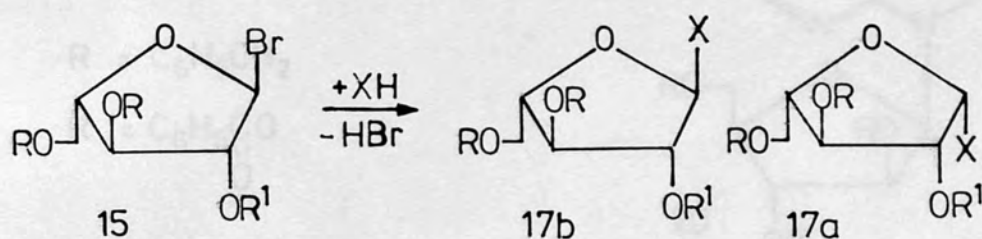
methanol or the glucose derivative **(16)** led to the formation of the corresponding 1,2-cis-arabinofuranosides **(17a)**, with only traces of the 1,2-trans anomers **(17b)**. The yields of products were not however reported.

R = C₆H₅CH₂

$R = C_6H_5CH_2$

$R = C_6H_5\overset{\overset{\textstyle O}{\|}}{C}O$
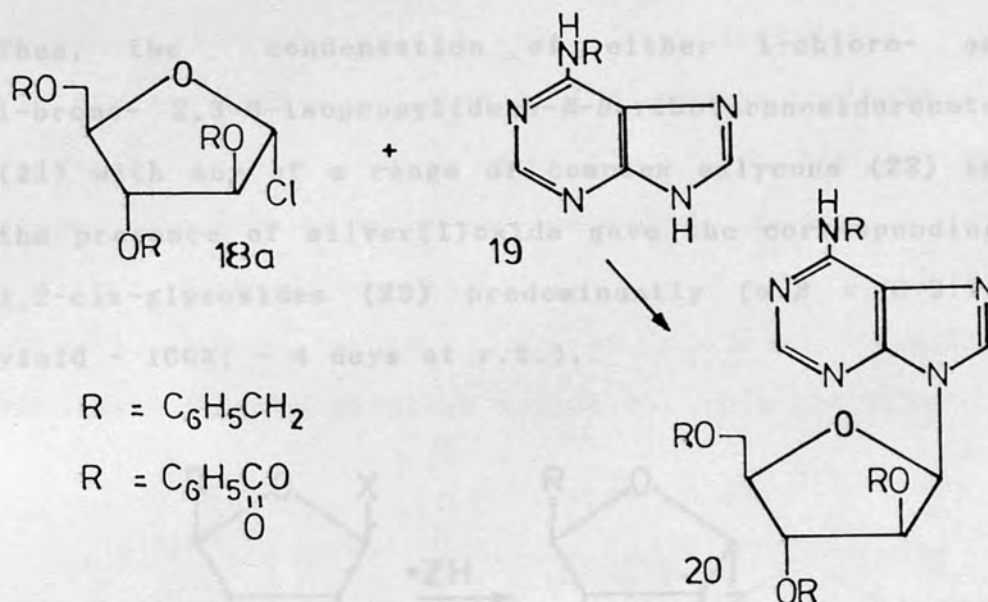
The synthesis of the 9-β-D-arabinofuranosyladenine derivative (20) has been achieved[43] in a similar way, by the reaction of 2,3,5-tri-O-benzyl-α-D-arabinofuranosyl chloride (18a) with N-benzoyladenine (19) in dichloromethane in the presence of 4A molecular sieve. A reaction time of 1 week at room temperature was needed (46% yield).

Glycosylations using electrophilic metal salt promoters have not found wide use in the synthesis of glycofuranosides[8] although the evidence suggests that considerable 1,2-cis stereoselectivity might be achieved through the use of a non-participating group at C-2 of the glycon (see discussion, Chapters 2.3 and 4.2). An isolated example where the method has been employed with some success, was in the synthesis of

several di- and tri-saccharides of D-ribofuranose[9].
Thus, the condensation of either 1-chloro- or
1-bromo- 2,3-O-isopropylidene-β-D-ribofuranosiduronate
(21) with any of a range of complex aglycons (22) in
the presence of silver(1)oxide gave the corresponding
1,2-cis-glycosides (23) predominantly ($\alpha:\beta$ = 8-9:1;
yield ~ 100%; ~ 4 days at r.t.).

$$\underset{\textbf{21}}{\begin{array}{c}R\!-\!O\!-\!X\\O\!-\!O\end{array}} \xrightarrow[-XH]{+ZH} \underset{\textbf{23}}{\begin{array}{c}R\!-\!O\\O\!-\!Z\\O\!-\!O\end{array}}$$

R = CH$_3$OC , X = Cl or Br
            ‖
            O

22 a typical component Z = $\text{...OCH}_2\text{C}_6\text{H}_5$
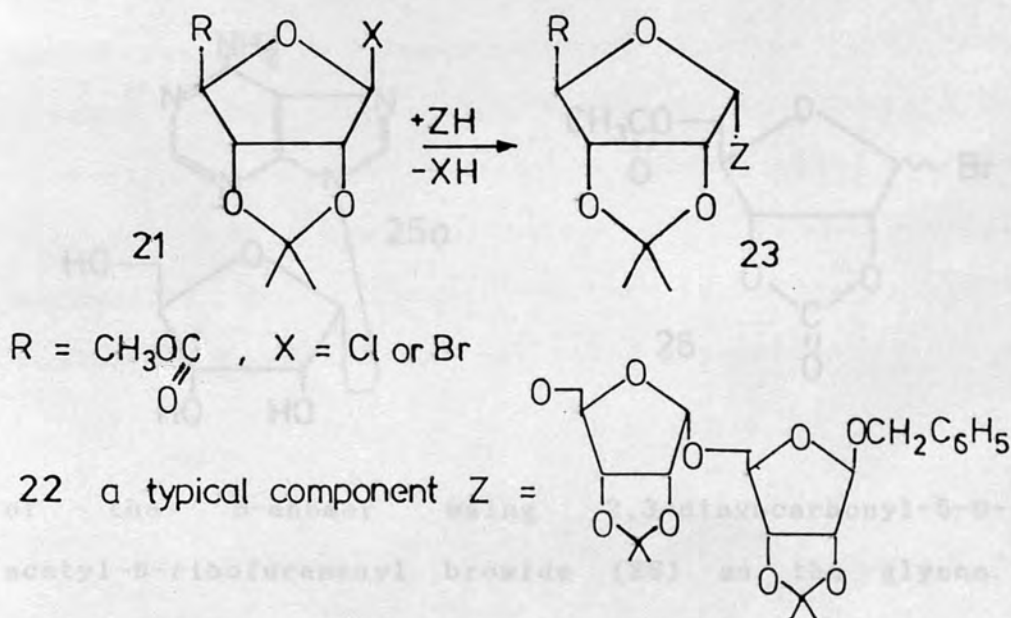
The stereochemical outcome of this reaction was
proposed to be mainly as a result of particpation by
the carboxylate group at C-5 of the glycon[10]. A
notable disadvantage of this method are the long
reaction times (~ 5 days) necessary. Furthermore,
participation from the group at C-5 of the
arabinofuranose analogue of (21) [viz. (24)] would be
expected to occur in an opposite sense to that

observed with the ribofuranose derivative **(21)** and
suggests that the method would be inappropriate for
the stereoselective synthesis of β-arabinofuranosides.

It is interesting to note that a derivative of
ribose similar to **(21)** was employed in one of the
earliest attempts to obtain a 1,2-cis-ribofuranosyl-
amine[11]. Thus, a 24% yield of 9-α-D-ribofuranosyl
adenine **(25a)** was obtained together with a 15% yield
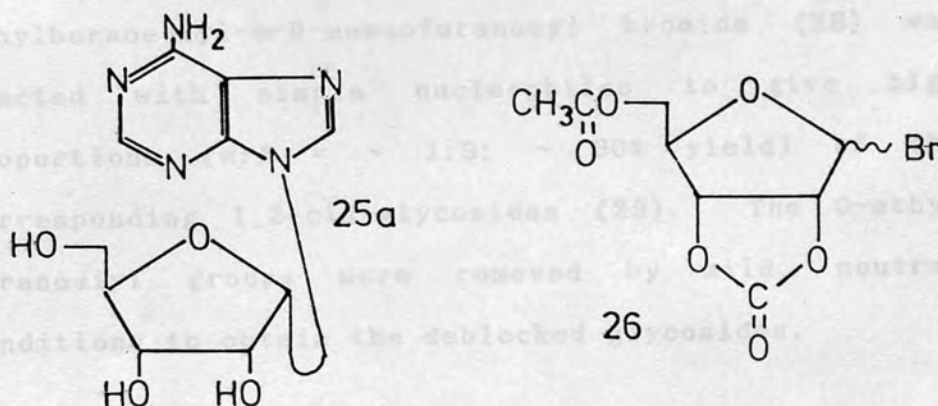
of the β-anomer using 2,3-dioxocarbonyl-5-0-
acetyl-D-ribofuranosyl bromide **(26)** as the glycon.
The absence of an acid acceptor might explain the poor
yield and steroselectivity observed in this particular
synthesis.
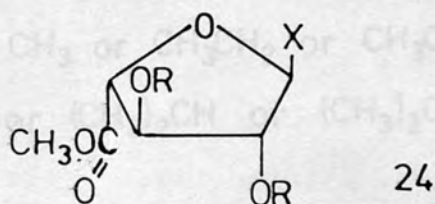
R = nonparticipating group   X = Cl or Br

Certain glycofuranosyl halides have been protected by O-ethylboron groups[12,13] in place of the more commonly used benzyl or isopropylidene groups. The high 1,2-cis stereoselectivity exhibited in substitutions at the anomeric carbon of these alternative glycons has been attributed to a directive effect of the 2,3-O-ethylboranediyl neighbouring group. In a typical reaction[13] 2,3:5,6-di-O-ethylboranediyl-α-D-mannofuranosyl bromide (28) was reacted with simple nucleophiles to give high proportions (α:β = ~ 1:9; ~ 90% yield) of the corresponding 1,2-cis-glycosides (29). The O-ethyl boranediyl groups were removed by mild, neutral conditions to obtain the deblocked glycosides.

R = C₂H₅

X = CH₃ or CH₃CH₂ or CH₃CH₂CH₂ or (CH₃)₂CH or (CH₃)₂CHCH₂
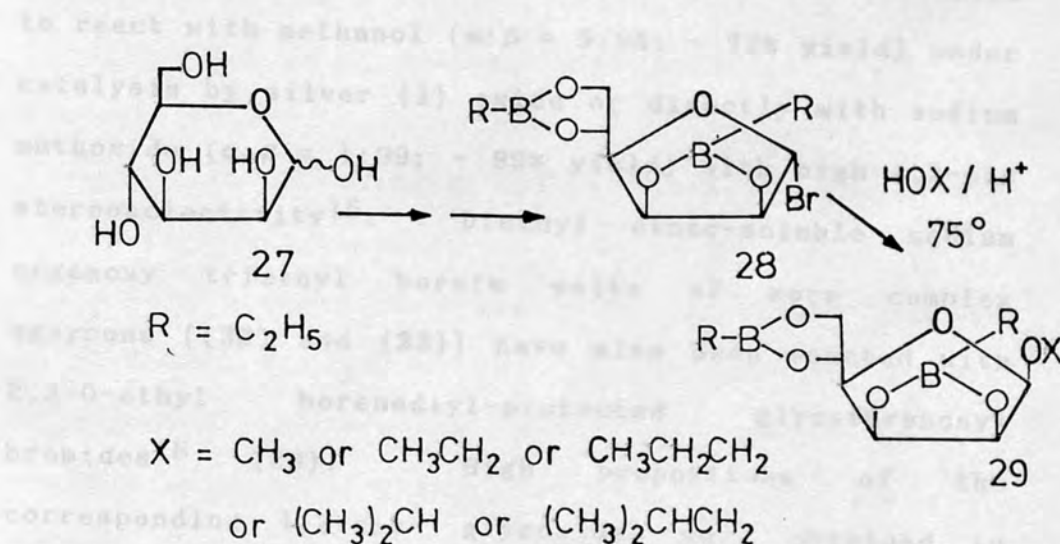
The glycosyl bromide (28) was made in high yield by the reaction of D-mannose (27) with ethylboroxine or 1,2-diethyl-1,2-bis[2,2-dimethylpropanoyloxy]-

diboroxane, followed by a reaction with phosphorous tribromide. Analogous derivatives of sugars including allo and gulo furanose [viz. **(30)** and **(31)** respectively] have also been obtained by similar
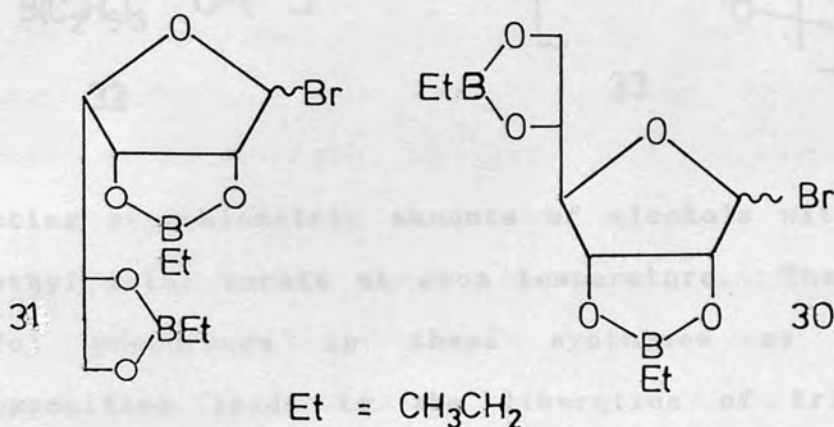
methods[12,13,14]. Glycons such as **(28)** have been shown to react with methanol ($\alpha{:}\beta$ = 5:95; ~ 72% yield) under catalysis by silver (1) oxide or directly with sodium methoxide ($\alpha{:}\beta$ = 1:99; ~ 99% yield) with high 1,2-cis stereoselectivity[15]. Diethyl ether-soluble sodium organoxy triethyl borate salts of more complex aglycons [**(32)** and **(33)**] have also been reacted with 2,3-O-ethyl boranediyl-protected glycofuranosyl bromides[16] **(28)**. High proportions of the corresponding 1,2-cis- glycosides were obtained in good yields with reaction times of ~ 4h. at ~ 0° ($\alpha{:}\beta$ = 1:99, ~ 75% yield). The crystalline aglycon salts [**(32)** and **(33)**] were obtained in quantitative yield by

32

33
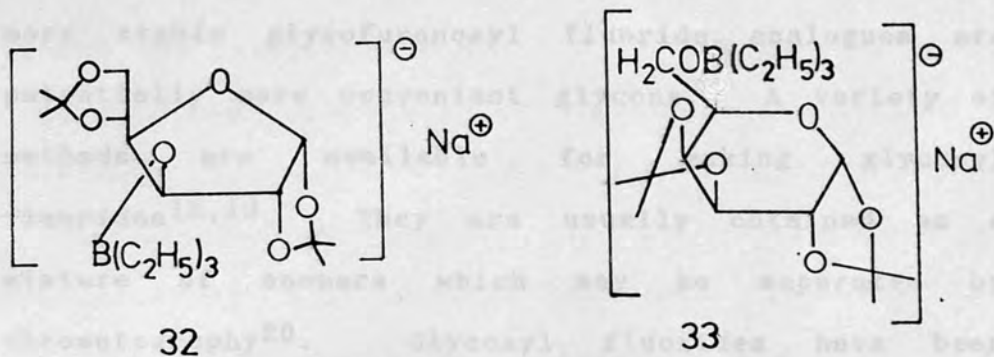
reacting stoichiometric amounts of alcohols with the triethyl metal borate at room temperature. They are useful precursors in these syntheses as their decomposition leads to the liberation of triethyl borane and nucleophilic sodium alkoxide[16]. The analogous tin organoxy triethyl borate salts have been shown to react in a similar fashion[17].

Although this method has provided a highly stereoselective route to certain 1,2-cis-glycofuranosides it is limited to syntheses with glycons capable of being protected by a 2,3-O-ethylboranediyl group. The hydroxyl functions as C-2 and C-3 of arabinofuranose are in a trans arrangement and are not suitably disposed for the synthesis of a derivative of this type. The route cannot therefore be applied to the construction of β-arabinofuranosides.

A major limitation of protected pentofuranosyl chlorides and bromides is their relative instability.

This makes them difficult to handle and store. The more stable glycofuranosyl fluoride analogues are potentially more convenient glycons. A variety of methods are available for making glycosyl fluorides[18,19]. They are usually obtained as a mixture of anomers which may be separated by chromatography[20]. Glycosyl fluorides have been reacted with alcohols to give the corresponding 1,2-cis-furanosides in high yield, when properly activated. An example is the reaction of 2,3,5-tri-O-benzyl-α-L-arabinofuranosyl fluoride **(34)** with cholestanol. In the presence of stannous

$$R = C_6H_5CH_2O , \quad Z = 3\beta - Cholestanyl$$
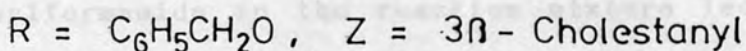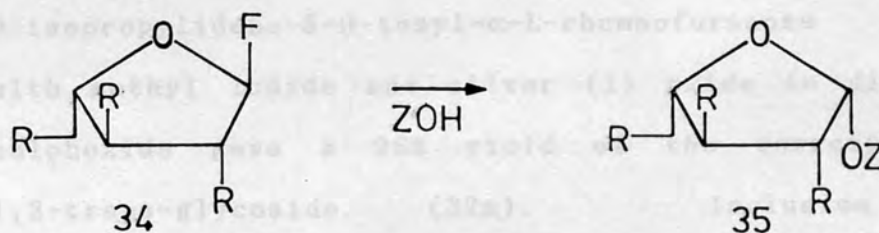
chloride and 4A molecular sieves in diethyl ether, the β-glycoside **(35)** was obtained predominantly (0°; 18h; 98%; α:β = 1:4).

A linear hexasaccharide unit has been constructed by a repetitive block synthesis using glycopyranosyl fluoride derivatives as glycons. In this particular case the glycosyl fluorides were reacted with the aglycon components in the presence of tin(II) chloride, silver perchlorate and molecular sieves in

diethyl ether at -15° to 25°. The α-glycosides were formed predominantly (α:β = ~ 9:1) and in good yield (~60-90%) even when the starting glycon constituted a mixture of anomers[21,22] (α:β = ~ 1:1)

An alternative method for the steroselective synthesis of 1,2-cis-glycofuranosides involves the reaction of protected glycofuranoses or the corresponding metalated derivatives of the free sugars, with alkylating agents. The stereochemical outcome of the reactions is found to vary dramatically with the particular reaction conditions employed[23] (see also Chapter 4.42). Thus, the reaction of 2,3-0-isopropylidene-5-0-tosyl-α-L-rhamnofuranose (36) with methyl iodide and silver (1) oxide in dimethyl sulphoxide gave a 96% yield of the corresponding 1,2-trans-glycoside (37a). Inclusion of dimethylformamide in the reaction mixture led to the predominant formation of the 1,2-cis anomer (37b). Reaction of (36) with methyl iodide and sodium hydride also gave the 1,2-cis product (37b).

In an analogous synthesis the stereochemical control possible through the use of 1-0-metalated derivatives has been exploited for the construction of more complex 0-glycosides. Thus, it was proposed that the reaction of 2,3-0-isopropylidene ribofuranose (38) with potassium tert-butoxide in tetrahydrofuran gave the 1,2-trans potassium salt (39). The readily

Ts = p-CH$_3$C$_6$H$_4$SO$_2$
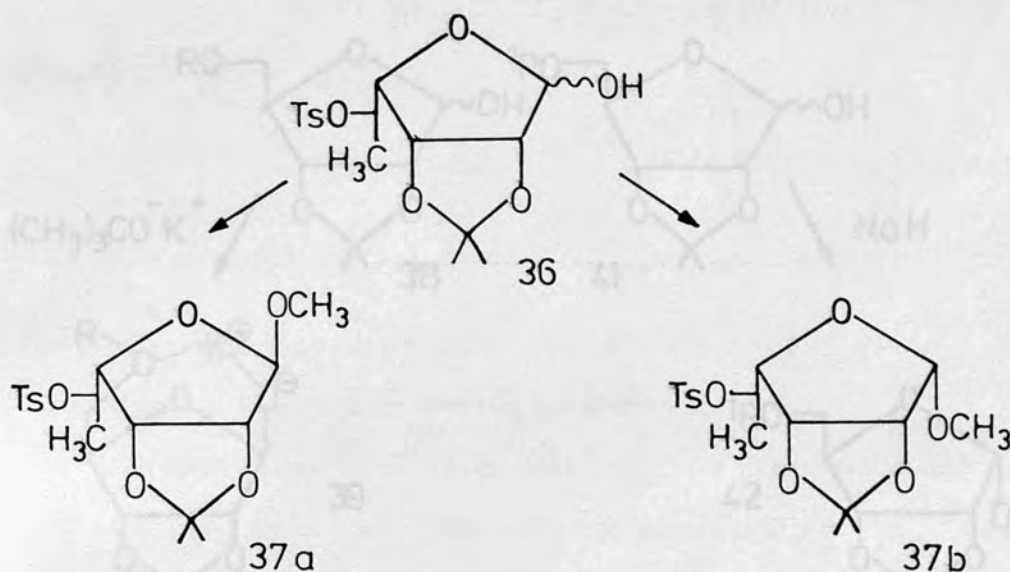
accessible trifluoromethanesulphonate derivatives (44) were found to react stereoselectively with (39) to give the 5-0-[D-ribofuranosyl]-β-D-ribofuranoside derivative (40). The alternative 1,2-cis product (43) was obtained by incorporating a bulky protecting group at C-5 of the glycon component. Thus, 5-0-tert-butyl(dimethylsilyl)-2,3-0-isopropylidene-D-ribofuranose (44) was proposed to react with sodium hydride to give the corresponding 1,2-cis sodium salt (42). This glycon was reacted with the trifluoromethanesulphonate derivative (44) to give 5-0-[D-ribofuranosyl]-α-D-ribofuranoside derivative (43) in 86% yield[24].

It should in theory be possible to obtain β-arabinofuranosides by a similar strategy. A derivative of arabinose is required with its hydroxyl
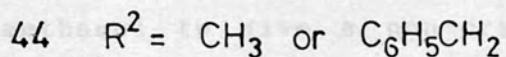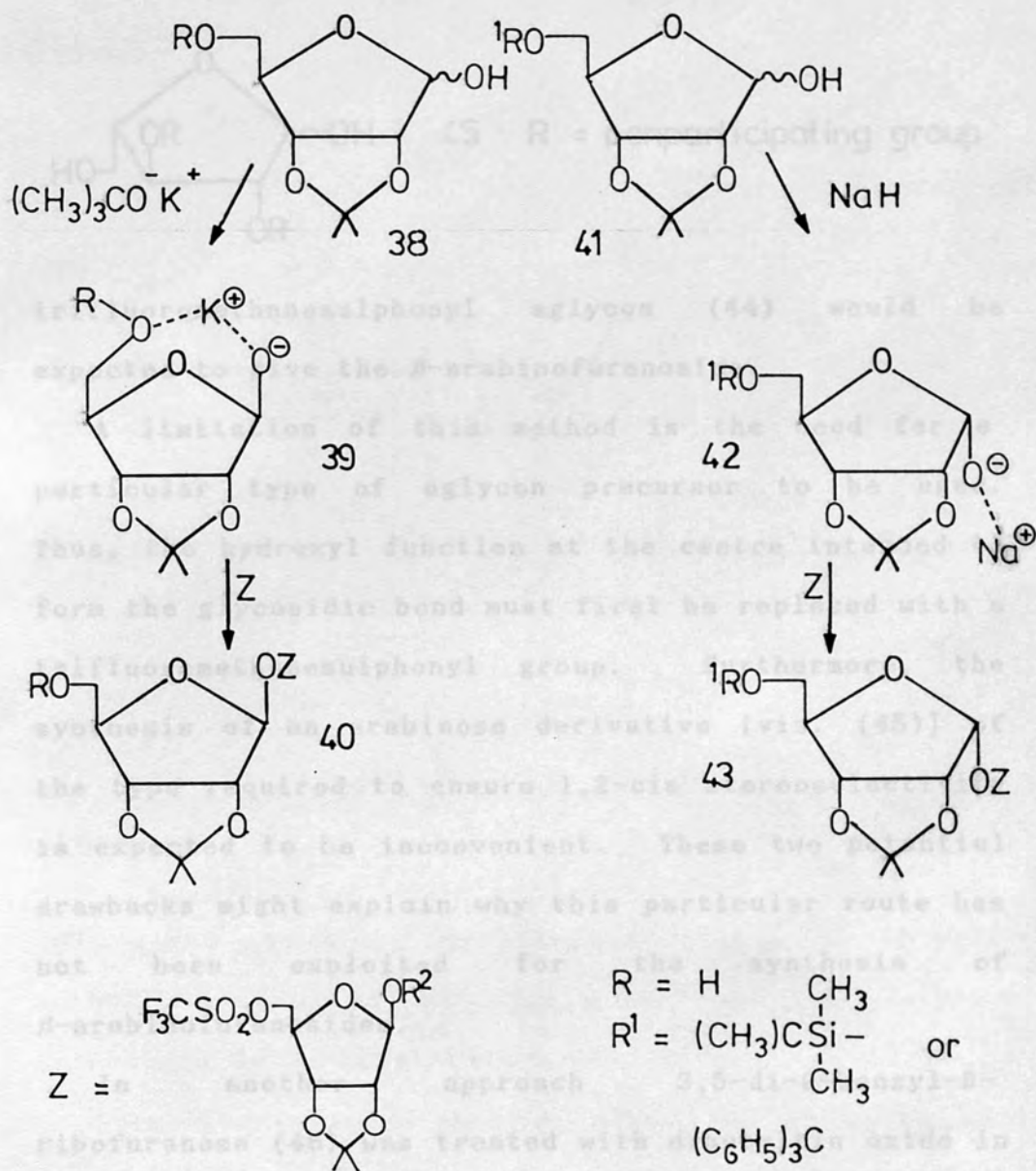
functions at C-5 and C-1 unprotected. Such a
derivative [viz. (45)] would be expected to give the
1,2-trans-O-metalated salt on reaction with potassium
tert-butoxide, if intramolecular complexation takes
place. Reaction of the glycon (45) with a

45   R = nonparticipating group
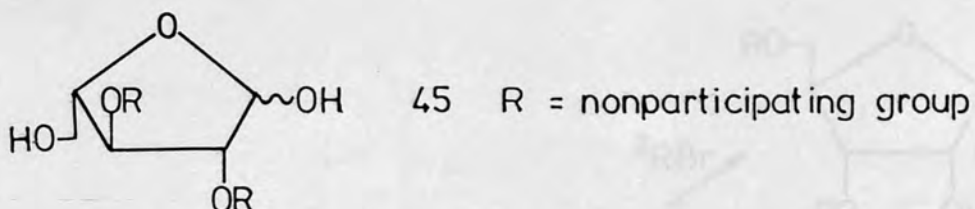
trifluoromethanesulphonyl aglycon **(44)** would be expected to give the β-arabinofuranoside.

A limitation of this method is the need for a particular type of aglycon precursor to be used. Thus, the hydroxyl function at the centre intended to form the glycosidic bond must first be replaced with a trifluoromethanesulphonyl group. Furthermore, the synthesis of an arabinose derivative [viz. **(45)**] of the type required to ensure 1,2-cis stereoselectivity is expected to be inconvenient. These two potential drawbacks might explain why this particular route has not been exploited for the synthesis of β-arabinofuranosides.

In another approach 3,5-di-O-benzyl-D-ribofuranose **(46)** was treated with dibutyltin oxide in methanol to give a non-crystalline cyclic stannylene derivative **(47)**. The reaction of **(47)** with alkyl halides such as benzyl bromide gave 1,3,5-tri-O-benzyl-α-D-ribofuranose **(48)** predominantly, with a little 2,3,5-tri-O-benzyl-D-ribofuranose **(49)**. Although a cyclic stannylene derivative of arabinofuranose [viz. **(50)**]similar to

$$R = C_6H_5CH_2 \ , \ R^1 = CH_3(CH_2)_3 \ , \ R^2 = CH_3 \ or \ C_6H_5CH_2$$
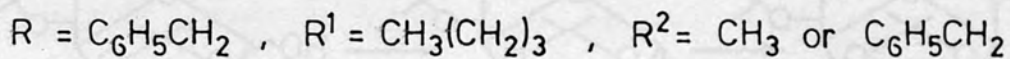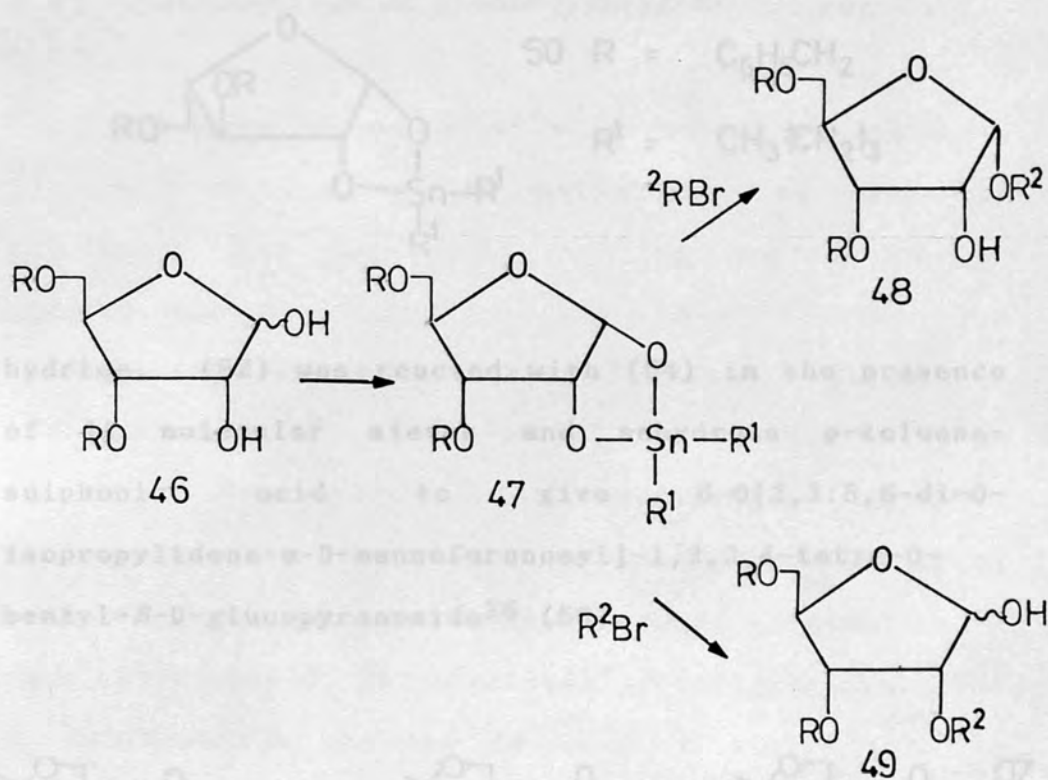
(**47**) might in theory be obtained, the scope of this method is limited by the need for the aglycon components to be alkyl halides[25].

Trichloroacetimidates have also been shown to be suitable glycons in the stereoselective synthesis of 1,2-cis-glycofuranosides. This type of glycon may be obtained by the reaction of trichloroacetonitrile with 1-O- unprotected sugar derivatives under basic catalysis. Thus 2,3:5,6 di-O-isopropylidene-D-mannofuranose (**51**) gave the 1,2-trans-trichloro-acetimidate derivative (**52**) in the presence of sodium

50 R = $C_6H_5CH_2$

R^1 = $CH_3(CH_2)_3$
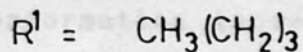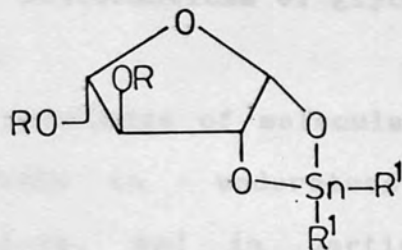
hydride. **(52)** was reacted with **(54)** in the presence of 4A molecular sieves and anhydrous p-toluene-sulphonic acid to give 6-0[2,3:5,6-di-0-isopropylidene-α-D-mannofuranosyl]-1,2,3,4-tetra-0-benzyl-β-D-glucopyranoside[26] **(53)**.

51   52   53

$O-C-CCl_3$

NH

Z =

54 R = $C_6H_5CH_2$
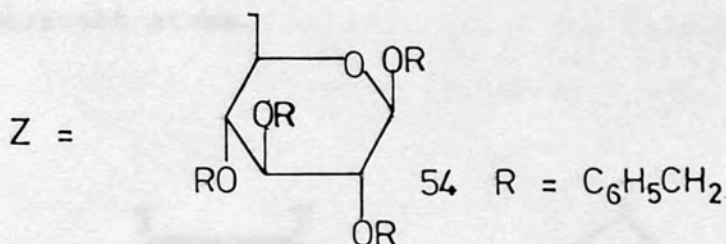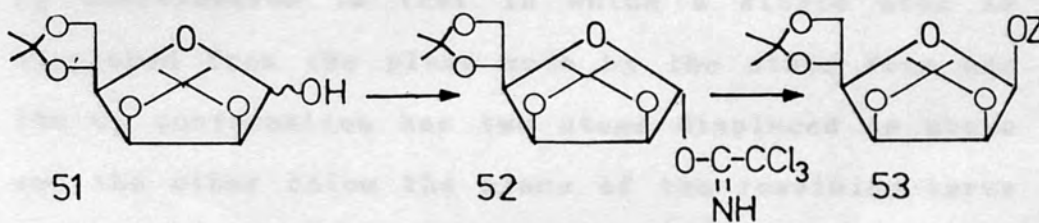
The method has not been applied to the synthesis of β-arabinofuranosides although it could in theory (see discussion, Chapter 4.3).

2.2   Conformations of glycofuranoid structures.

A knowledge of molecular conformation is required in order to understand mechanisms and rates of reactions, and in particular the application of stereoelectronic theory. In this section the conformations and stabilities of furanoid structures are considered.

It is convenient when considering furanoid conformations to confine the discussion to those puckered forms having a nominal symmetry relationship with the C_2 and C_s conformations of cyclopentane. The C_s conformation is that in which a single atom is displaced from the plane made by the other four and the C_2 conformation has two atoms displaced on above and the other below the plane of the remaining three adjacent atoms.

C_s enVelope C_2 Twist

In the furanoid sugars a more definitive designation

of conformation is required because of the specific
stereochemistry of the carbon atoms in the ring.
Several suitable methods have been proposed to
accomplish this and are currently employed[45]. This
discussion will make use of the system[46] where a
conformation with four atoms coplanar is designated V
(envelope), and that with three atoms coplanar is
designated T (twist). The atom out of plane may then
be indicated as a superscript or subscript to show
respectively displacement above or below the plane of
reference; carbon atoms are identified by a number and
the ring oxygen by "0". In principle for any furanoid
ring their exist ten possible envelope forms and ten
possible twist forms. Table 2.1 lists these twenty
furanoid conformations together with their dihedral
angles (estimated using Dreiding models). However,
there is no *a priori* reason to assume that any of
these "basic" forms represents an actual energy
minimum in any furanoid structure[45].

According to extensive x-ray crystallographic
studies[47] of low molecular weight nucleic acid
analogues the furanoid ring adopts one of two
principal puckered shapes [viz. $^2T_3$ and $^3T_2$). Both
solid-state[48] and solution[49] studies suggest that the
interconversion between the two puckered states occurs
via a pseudorotational pathway of closely related
intermediate forms rather than through a planar ring

TABLE 2.1

ESTIMATED DIHEDRAL ANGLES (DRIEDING MODELS) FOR 20

OF THE POSSIBLE CONFORMATIONS OF THE FURANOSE RING.

CONFORMATION	DIHEDRAL ANGLES (DEGREES)			
	H_1H_2	H_2X	H_2H_3	H_3H_4
V_1	170	50	30	120
$^2T_1$	180	60	50	100
^2V	170	50	50	90
$^2T_3$	170	50	60	90
V_3	150	30	50	70
$^4T_3$	140	20	50	60
^4V	120	0	30	70
$^4T_0$	100	20	20	50
V_0	90	30	0	90
$^1T_0$	70	50	20	100
^1V	70	50	30	120
$^1T_2$	60	60	50	140
V_2	70	50	50	150
$^3T_2$	70	50	60	170
^3V	90	30	50	170
$^3T_4$	100	20	50	180
V_4	120	0	30	170
$^0T_4$	140	20	20	170
^0V	150	30	0	150
$^0T_1$	170	50	30	150

X is a substituent atom at C-1.

$^0T_1$ V_1 $^2T_1$

^0V ^2V

$^0T_4$ $^2T_3$

V_4 V_3

$^3T_4$ $^4T_3$

^3V ^4V

$^3T_2$ $^4T_0$

V_2 V_0

$^1T_2$ ^1V $^1T_0$
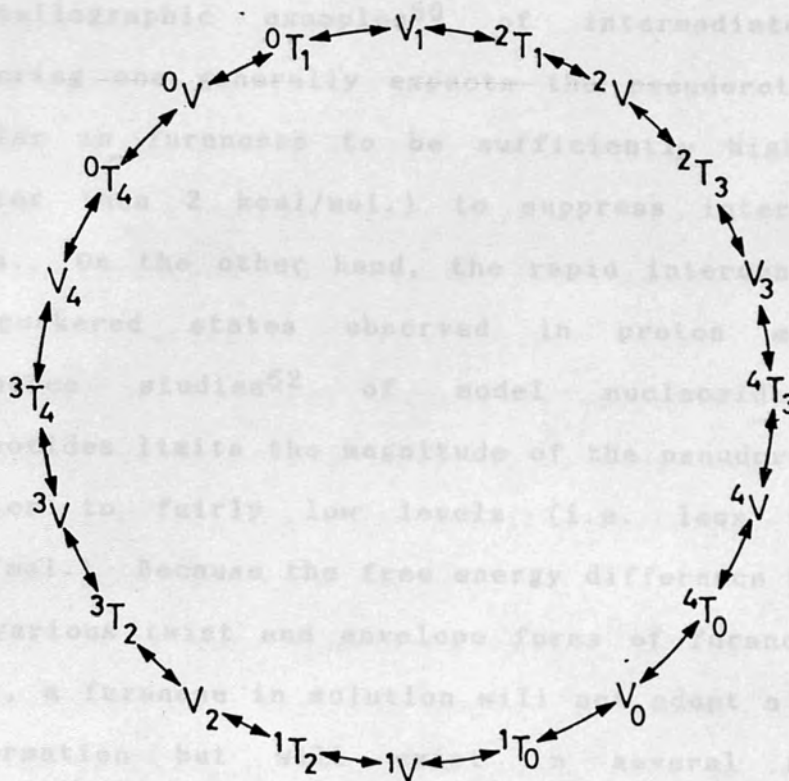
FIGURE 2.1 PSEUDOROTATIONAL ITINERARY
OF THE FURANOID RING

structure. The pucker moves continuously around the five membered system with neighbouring atoms displaced alternately above and below a mean ring plane (Figure 2.1). In contrast to the unsubstituted cyclopentane ring where the interconversion of puckered states occurs without significant energetic effects[50], the presence of endocyclic and exocyclic substituents in the pentose

moiety together with the inclusion of a ring heteroatom introduces a potential barrier that opposes free pseudorotation[45]. In view of the very few crystallographic examples[50] of intermediate ring puckering one generally expects the pseudorotational barrier in furanoses to be sufficiently high (i.e. greater than 2 kcal/mol.) to suppress intermediate forms. On the other hand, the rapid interconversion of puckered states observed in proton magnetic resonance studies[52] of model nucleosides and nucleotides limits the magnitude of the pseudorotation barrier to fairly low levels (i.e. less than 5 kcal/mol.) Because the free energy difference between the various twist and envelope forms of furanoses is small, a furanose in solution will not adopt a single conformation but will exist in several related conformations restricted to segments of the pseudorotational itenary.

The couplings between transoidal protons (located on opposite sides of the furanose ring) apparently follow a Karplus-like relationship[53,54].

$$J_{HH} = A\cos^2\phi + B\cos\phi + C$$

where ϕ is the dihedral angle between the given pair of protons and A, B and C are constants. Since ϕ is a continuous function of ring puckering, J_{HH} depends ultimately upon the phase angle of pseudorotation. Conformational analysis based on a Karplus

relationship fails to account however, for the observed couplings between cisoidal protons (located on the same side) of the furanose ring[55]. According to quantum mechanical simulations in arabinose models[55,56] there is no unique relationship between J_{HH} and ϕ in these cases. The cisoidal coupling depends in a complicated fashion upon both the chemical architecture and the conformation of the complete molecule. The procedure often used for accounting for chemical effects by either subtracting a constant value from or multiplying a specific factor with the cisoidal J_{HH} value obtained by Karplus theory can sometimes lead to errors[55].

This calls into question whether Karplus theory can be used with any confidence to account for the observed coupling constants J_{HH} even if a given sugar were to adopt a single conformation exclusively. In practice, the situation is more complicated than this, the nmr data representing a time-averaged conformation, albeit confined to a narrow segment of the pseudorotional itinerary. No single state on the pseudorotational itinerary can account for the observed three bond ^1H nmr coupling constant J_{HH}. Moreover, one could envisage a situation in which, through the operation of opposing steric and dipolar factors, two different segments of the pseudo rotational itinerary are significantly populated.

Clearly in this case, the time-averaged conformation using ^{1}H nmr data and a Karplus type relationship will bear no direct relation to those segments which are actually populated.

The conformations of various pentofuranoid derivatives, deduced using nmr coupling data are presented in Table 2.2. Since the sets of results in Table 2.2 were all obtained with different derivatives and (or) different conditions, there is no reason *a priori* to expect general agreement as to the favoured conformation associated with a given diastereomer.

There is some agreement between a number of the deductions, but in general the results show a fair degree of conformational variability for a given diastereomic furanose. It is uncertain whether these variations reflect differences in the structures of the derivatives, differences in the experimental conditions under which the results were obtained, or the inherent uncertainties associated with the conformational analysis of pentofuranoid systems using nmr data (see previous discussion).

The relative free energies of the conformers, and therefore the most likely segment of the pseudorotational itinerary that will be populated by a given furanoid sugar, might be explained and predicted to an extent by considering the various steric and electronic interactions which operate and are known

49

TABLE 2.2

CONFORMATIONS[a] OF PENTOFURANOID SUGARS:
DEDUCED FROM CONSIDERATIONS OF NMR DATA[b]

SUGAR	GLYCOSYL FLUORIDE[c]	TETRA ESTER[d]	METHYL GLYCOSIDE[e]	METHYL GLYCOSIDE[f]
α-xylo	${}^{2}V$	${}^{2}T_{3}$ ${}^{0}T_{1}$		${}^{2}T_{3}$
β-xylo	V_{2} ${}^{3}V$	${}^{3}T_{2}$ ${}^{3}V$	V_{2} ${}^{3}V$ ${}^{3}T_{2}$	${}^{3}T_{2}$
α-ribo	V_{1}	${}^{2}V$ ${}^{2}T_{1}$	${}^{2}V$ V_{3} ${}^{2}T_{3}$	${}^{0}T_{1}$
β-ribo	${}^{1}V$	${}^{3}T_{2}$	V_{2} ${}^{3}V$ ${}^{3}T_{2}$	${}^{3}T_{2}$
α-arabino	V_{0} ${}^{4}V$	${}^{0}T_{1}$	V_{3} ${}^{2}T_{3}$ ${}^{4}T_{3}$	V_{0}
β-arabino	V_{3} ${}^{4}V$	${}^{1}T_{2}$ V_{2}		${}^{3}T_{2}$
α-lyxo	V_{4}	V_{3} ${}^{4}T_{3}$		V_{3}
β-lyxo		${}^{2}T_{3}$ ${}^{3}T_{2}$		${}^{3}T_{2}$

[a] All D-series conformations.

[b] Compiled from Ref. 63.

[c] Hall et al. (Ref. 63): In $CDCl_3$; based on vicinal ${}^{1}H$-${}^{1}H$ and ${}^{19}F$-${}^{1}H$ coupling constants.

[d] Stevens and Fletcher (Ref. 63): In CD_2Cl_2; based on vicinal ${}^{1}H$-${}^{1}H$ coupling constants; protecting groups included acetyl, benzoyl and mesoyl in various combinations.

[e] Cyr and Perlin (Ref. 63): In D_2O; based on coupling by ${}^{13}C$-1 and ${}^{13}C$-2 with protons together with vicinal ${}^{1}H$-${}^{1}H$ couplings.

[f] Angyal (Ref. 63): In D_2O; based on vicinal ${}^{1}H$-${}^{1}H$ coupling constants.

to be of importance in determining the conformations of pyranoses in solution[38,40,42].

Puckering of the ring would be expected to relieve excessive torsional and van der Waals strain that would otherwise exist in a planar ring, caused by eclipsing of orbitals and substituents on adjacent ring atoms. The destabilisation generated by such eclipsing outweighs the stabilisation gained by relief of bond angle strain that would occur in a planar ring[42,45]. Contributions from differences in bond deformation strain, bond angle-bending strain and torsional strain are assumed to be negligible and only two types of nonbonded interactions are considered to play an important role in influencing the adopted conformation[42,45]. Those between ligands gauche to each other on adjacent carbon atoms (apart from those involving hydrogen atoms) and those between syn-axial ligands (other than ones between hydrogen atoms). Since 1,2-cis interactions are not favourable it may be predicted that the anomer of a furanose derivative in which groups on C-1 and C-2 are trans will be most stable. Generally speaking, this appears to be the case[59]. For example, the fructofuranosyl moiety of sucrose (a homomorph of a 1,2-cis-O-D-arabinofuranoside) adopts a $^3T_2$ (or perhaps V_2) conformation in the crystal[57,58]. However, if an anomer with hydroxyl groups trans on C-1 and C-2 also

has syn 1,3 interactions, it will be destabilised relative to the other anomer. Thus, 5-O-methyl-β-D-glucofuranose which exists predominantly in the $^3T_2$ conformation[60] has syn-1,3- interactions between O-1 and O-3 and between O-1 and O-5, but these are relieved by anomerisation to the α-anomer (1,2-cis). Indeed, at equilibrium 5-O-methyl-D-glucofuranose appears to comprise approximately equal amounts of each anomer[60]. This analysis of course, neglects the possible influence of any stereoelectronic (anomeric) effect (see below).

Another steric interaction which would be expected to play a part in determining the favoured conformation of furanosides is the orientation of the bulky sidechain at C-4. An equatorial orientation of this group would be predicted to be the most favoured.

In view of the puckering observed in glycofuranosides it may be concluded that adjacent groups with projected angles of 0° (true cis) and 120° (true trans) cannot exist. When the pyranose ring is staggered adjacent groups can in theory, adopt one of three arrangements relative to each other: equatorial-axial and equatorial-equatorial arrangements are equivalent and are those in which bonds to adjacent groups subtend an angle of 60°. The alternative axial-axial arrangement is one in which adjacent groups are 180° apart. In the furanose

52

system cisoidal or transoidal groups will each be
about 50º apart in the "axial-equatorial" arrangement.
Transoidal groups in the "axial-axial" arrangement
will be about 160º apart and closer to 75º apart in
the "equatorial-equatorial" arrangement[57]. These
arrangements are more precisely termed "quasi-axial"
and "quasi-equatorial" or sometimes "isoclinal"[42,57].
Furthermore, in the ribofuranosyl residues of
cytidylic acid[61] ($_3T^2$) and adenylic acid[62] ($_2T^3$) the
bonds to the C-2 and C-3 cis hydroxyl groups make
projected angles of 48.0º and 53.6º respectively,
while in the fructofuranosyl moiety of sucrose[57,58]
($^3T_2$ or V_2) the bonds to the C-2 and C-3 trans
hydroxyl groups make a projected angle of 78.4º.
Hence, the projected angles in the "cis-" and "trans-"
of these derivatives in the solid state are not very
different.

In the pyranose series the electronic interaction
which plays a most significant role in determining the
preferred conformation adopted by a given sugar ring
is the anomeric effect. The effect relates to the
interaction between an electronegative substituent on
the anomeric carbon atom and the ring oxygen and
appears to be most favourable when the polar bond is
gauche to one lone pair of the ring oxygen and trans
to the other[37,38].

X = electronegative atom
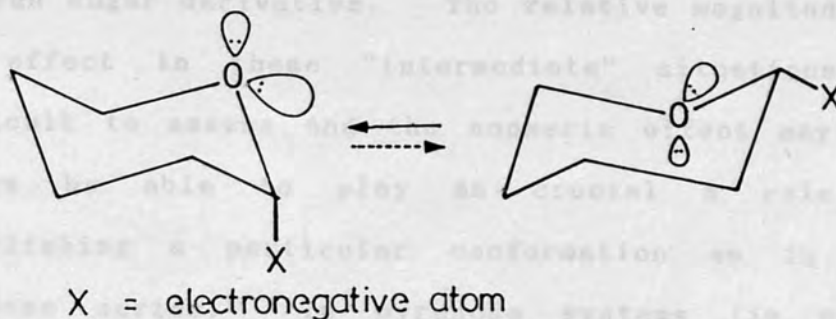
The magnitude of the effect is found to be
proportional to the electronegativity of the
substituent at C-1 and inversely proportional to the
polarity of the solvent. Various interpretations of
the origin of the effect have been proposed and its
true nature has not yet been established[37,41].
Several investigations have concluded that the effect
operates in furanose systems[63,68], but the importance
of the part it plays in determining the preferred
conformations of furanoses in solution is much less
certain than in the pyranose series.

In glycofuranoid systems there exist only two
conformers in the pseudorotational itinerary (viz. ^1V
and V_1), where a nearly correct alignment of bonds
necessary for an anomeric effect is possible. Several
conformers might be proposed in which the orientation
about the relevant C-1 to substituent bond is such
that the anomeric effect might have a less pronounced,
but perhaps significant influence on the stability of

a given sugar derivative. The relative magnitude of the effect in these "intermediate" situations is difficult to assess and the anomeric effect may not always be able to play as crucial a role in establishing a particular conformation as in the pyranose series. In pyranose systems (in chair conformations) the situation is far more clear cut; the effect operates maximally in one conformation and minimally in the other.

The majority of studies which do suggest that the anomeric effect is operational in furanose systems are all based on nmr coupling data used in conjunction with the Karplus relationship[63]. As has already been pointed out such analyses may not be strictly valid for furanose systems. The Karplus equation must be used with considerably more care when sugars bearing electronegative substituents are being studied as the dihedral angle is not the only factor which effects the coupling constant. Karplus theory[53] states that J_{HH} is a function of a combination of factors including the electronegativities of substituent atoms, and must not be used indiscriminately to relate dihedral angles with coupling constants.

Another way in which the anomeric effect is manifested is in the relative stabilities of anomers. In a furanoid (or pyranoid) system the effect will stabilise a structure in which the C-1 substituent is

TABLE 2.3

RELATIVE PROPORTIONS OF FURANOSE

ANOMERS AT EQUILIBRIUM[a]

SUGAR	α	β
XYLOSE	2	3
RIBOSE	5	17
ARABINOSE	22	7
LYXOSE	2	0
GALACTOSE	6	16
FRUCTOSE	9	31
TALOSE	20	11
ALTROSE	18	11
IDOSE	12	14

[a] Data compiled from Ref. 68, Bishop and Cooper and Ref. 47.

pseudoaxial, but in the furanoid case this can be achieved for either anomer if the ^1V and V_1 conformations are both accessible. Thus the relative proportions of two furanose anomers at equilibrium does not readily reveal the magnitude of any anomeric effect. Some results are given in Table 2.3.

The fact that certain observed furanose puckerings cannot be explained completely on the basis of these aforementioned steric and electrostatic forces alone is also true in numerous other anomalous systems which tend to adopt gauche in favour of trans rotational arrangement[64]. This so called "gauche" effect[65] is displayed by compounds with atoms such as oxygen which possess unshared n electrons. According to quantum mechanical analysis[66] the predisposition for a gauche conformation in this type of system stems from the stabilising bond-antibonding orbital interaction involving polar C-O linkages. The persistence of such affects in furanoid systems[67] presumably influences the torsions of the five membered ring and ultimately affects the potential energy of pseudorotation. Analysis currently in progress is proposed to confirm the experimental behaviour of arabinose, xylose and lyxose systems in dilute solution[69]. In all the cases considered, gauche effects appear to be a major determinant of ring puckering[69].

A comparison of Tables 2.3 and 2.4 supports the

TABLE 2.4

CONFORMATIONS[a] OF PENTOFURANOID SUGARS:
DEDUCED FROM CONSIDERATIONS OF NON-BONDED INTERACTIONS.

SUGAR	CONFORMATIONS		HYDROXYL INTERACTIONS
α-xylo	$^2T_3$	1	C_3-C_4
β-xylo	$^3T_2 \, V_3$	1	C_3-C_4
α-ribo	^3V	1	C_2-C_3
β-ribo	^2V	2	$C_1-C_2, \, C_2-C_3$
α-arabino	$^3T_2$	0	
β-arabino	V_2	1	C_1-C_2
α-lyxo	$^3T_2 \, V_3$	2	$C_2-C_3, \, C_3-C_4$
β-lyxo	$^3T_2$	3	$C_1-C_2, \, C_2-C_3, \, C_3-C_4$

[a] all D-series conformations

[b] Taken from Ref. 68, Bishop and Cooper.

prediction that in general the anomer in which groups at C-1 and C-2 are trans to each other will be favoured over the one in which these groups are cis, at least when the substituent at C-1 is a hydroxyl group. Thus, α-arabinofuranose predominates over the β-anomer at equilibrium. However, a comparison of Tables 2.2 and 2.4 shows little agreement between those conformations predicted on the basis of non-bonded interactions and those deduced on the basis of nmr data.

It appears that the various steric and polar interactions which operate in glycopyranosyl systems are much more finely balanced in glycofuranosyl systems. A change of solvent might in theory, bring about a new balance of steric and polar interactions which could lead to an alternative (perhaps quite distant) segment of the pseudorotational itinerary being favoured by a given sugar derivative.

2.3 Mechanisms of glycofuranosylation reactions.

The mechanisms of the common O-glycopyranoside
forming reactions have been studied extensively, with
the ultimate objective of creating a theoretical basis
for synthetic investigations[27]. For instance, the
clarification of some of the mechanistic features
relating to the reactions of glycopyranosyl halides
has enabled a rational synthesis of axial
O-glycopyranosides (1,2-cis configuration) to be
developed[28]. However, many aspects of O-glycosidic
bond construction remain unclear and with the
exception of this isolated example the majority of
syntheses directed at obtaining 1,2-cis-O-glycosides
(of both furanoses and pyranoses) are in essence
empirical. Only a limited amount of mechanistic
information relating specifically to O-glycofuranoside
synthesis is available but it is clear that an
appreciation of the underlying principles governing
these reactions is necessary, not only to make
technical improvements in traditional methods but also
in order to formulate and develop new and more
rational approaches to the synthesis of
1,2-cis-O-glycofuranosides.

Most of the mechanistic investigations concerned
with O-glycofuranoside synthesis, have dealt with the
solvolysis reactions of glycofuranosyl chlorides and

bromides. The earliest of these studies demonstrated that acyloxy group at C-2 of arabinofuranosyl halides participated in the nucleophilic displacement of the halogen by nucleophiles[29].

$$RO-\overset{O}{\underset{OR}{\bigvee}}\overset{R^1}{\underset{R^2}{\bigvee}}$$

55b $R^1 = H$, $R^2 = Br$

55a $R^1 = Br$, $R^2 = H$

56   $R^1 = H$, $R^2 = CH_3O$

$$R = C_6H_5\overset{\|}{\underset{O}{C}}$$
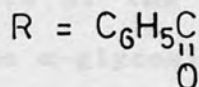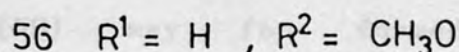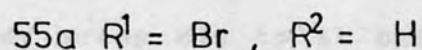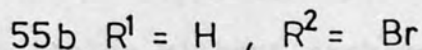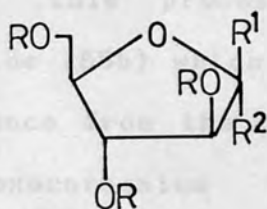
The two crystalline 2,3,5,-tri-O-benzoyl-D-arabinofuranosyl bromides, (55b) and (55a), had their anomeric configurations assigned as α- and β- respectively on the basis of their specific rotations. The rotation of the α-bromide (55b) remained constant over 2h at room temperature in methylene chloride. On solvolysis with methanol in the absence of an acid acceptor both bromides gave methyl 2,3,5-tri-O-benzoyl-α-D-arabinofuranoside (56) in high yield as the only product. Furthermore, the rates at which methanolysis of the two bromides occurred were shown in a qualitative fashion to be significantly different, that of the α-anomer being more rapid.

Anchimeric assistance by the benzyloxy group at C-2 of bromides (55a) and (55b) was proposed to

account for their product stereospecificity and different reactivities. Thus, the bromides (55a) and (55b) lead via the incipient oxocarbonium ions (57a) or (57b) respectively, to the same dioxocarbonium ion (58). This process is more difficult for the β-bromide (55b) which has to ionise without anchimeric assistance from the benzyloxy group cis to it before the dioxocarbenium ion (58) may for formed. Methanolysis of the dioxocarbonium ion (58) can lead only to the α-glycoside (56).

$$R = C_6H_5C \overset{O}{\underset{}{\|}}$$
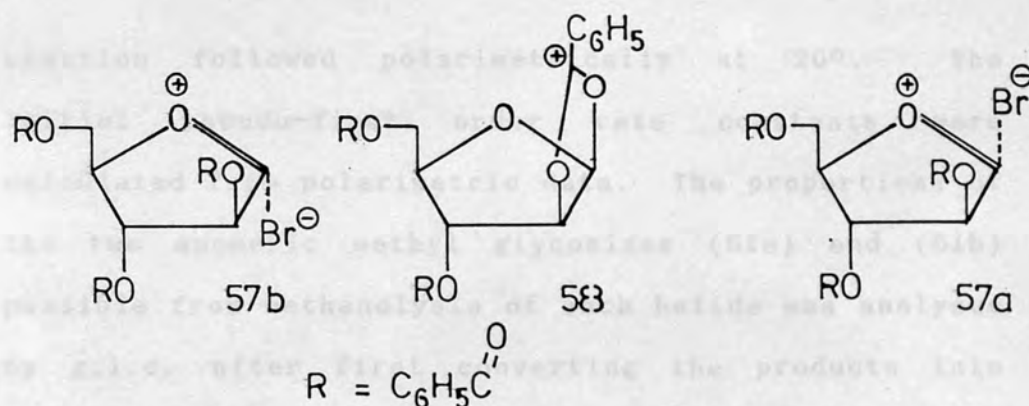
In a later study, the mechanisms which operate in the solvolyses of arabinofuransyl halides in which anchimeric assistance from the group at C-2 is not possible was investigated[30]. Each of the halides (59a), (59b) and (60) was dissolved in dichloromethane or acetonitrile, the solution was diluted with an excess of methanol and the ensuing

RO—[O, R¹, O₂NO, R², OR]

R = p-NO₂C₆H₄C(=O)

59a	R¹ = H ,	R² = Cl
59b	R¹ = Cl ,	R² = H
60	R¹ = H ,	R² = Br
61a	R¹ = H ,	R² = CH₃O
61b	R¹ = CH₃O ,	R² = H
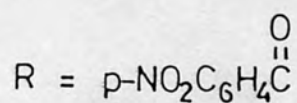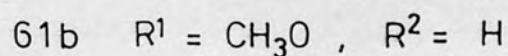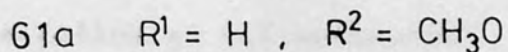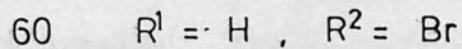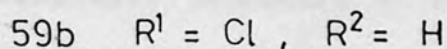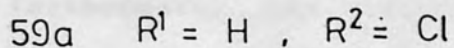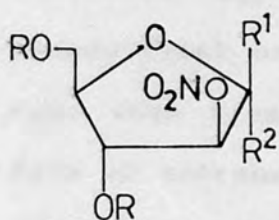
reaction followed polarimetrically at 20°. The initial pseudo-first order rate constants were calculated from polarimetric data. The proportions of the two anomeric methyl glycosides (61a) and (61b) possible from methanolysis of each halide was analysed by g.l.c. after first converting the products into alternative compounds suitable for analysis by this method. The rotation of the methyl 2-O-nitro-3,5-di-O-p-nitrobenzoyl-β-D-arabinofuranoside (61b) was shown to remain constant under the conditions of the solvolyses indicating that secondary anomerisation does not take place.

Methanolysis of the α-halides (59a) and (60) gave predominantly the inverted β-methyl glycoside (61b) with increased methanol concentration a

disproportionate increase in the rate of solvolysis resulted. Use of a polar medium acetonitrile, also increased the rate. Furthermore, the calculated pseudo-first order rate constants decreased with time save when bromide ion was deliberately added in the form of tetrabutylammonium bromide. The solvolysis of the halide was proposed to follow an S_N1 mechanism:

$$ RX \underset{k_2}{\overset{k_1}{\rightleftharpoons}} R^+ + X^- \xrightarrow[CH_3OH]{k_3} ROCH_3 + HX $$
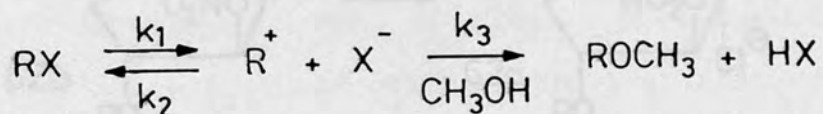
The rate constant K in the presence of an excess of methanol was expressed as:

$$ \frac{d[RX]}{dt} = \frac{-k_1[RX]}{1 + \frac{k_2[X^-]}{''k_3}} $$

$$ \text{where } ''k_3 = k_3[CH_3OH] $$

The experimental findings are compatible with an S_N1 mechanism; increasing the concentration of the halide ion progressively decreased the rate of the solvolysis. The slight decrease in the observed rate caused by the addition of bromide ion was proposed to indicate at least some external ion return. The value calculated from the rate constant data for the average

entropy of activation ($\Delta S^{\ddagger}$ -23 cal. deg.$^{-1}$mol^{-1}) was viewed to support the intermediacy of an ionic species and by its magnitude to suggest that the charge separation is substantial in the transition state which was regarded as an ion-pair (60a).

R = p-NO$_2$C$_6$H$_4\overset{\text{O}}{\overset{\|}{\text{C}}}$
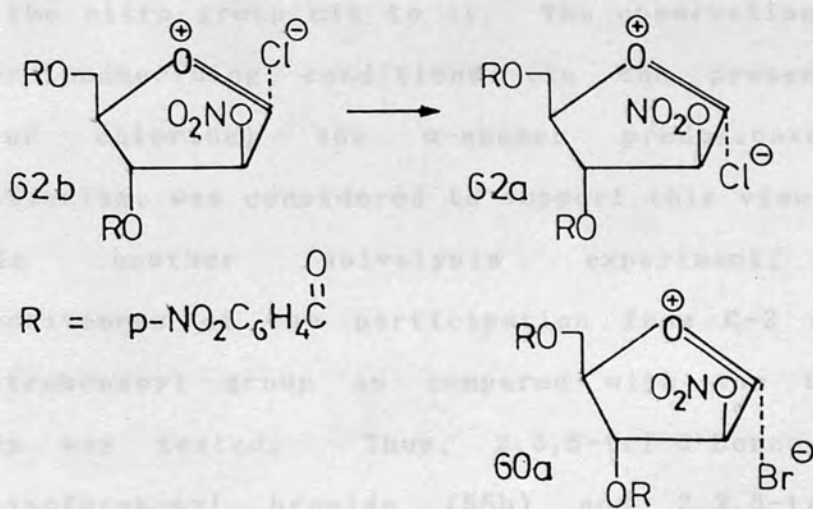
A complex mutarotation was observed on solvolysis of the β-halide (59b) in contrast to the α-halides (59a) and (60). This result was proposed to be as a consequence of the β-ion pair (62b) (formed from the β-halide) anomerising to form a proportion of the α-ion pair (62a). A substantial amount of the β-methyl glycoside was isolated and was proposed to be derived by a reaction of methanol and the α-ion pair (62a) with inversion. The nature of the rotation curve was viewed to support this mechanism. The predominant product expected from a simple reaction of

the β-halide (60) with methanol is the inverted
α-methyl glycoside (62a) and the observed result was
proposed to reflect the greater stability of the α-ion
pair (62a) compared with β-ion pair (62b). This
stability difference was proposed to be a result of
electrostatic compression between the chlorine atom
and the nitro group cis to it. The observation that,
under anomerising conditions (in the presence of
silver chloride) the α-anomer predominates at
equilibrium, was considered to support this view.

In another solvolysis experiment, the
effectiveness of the participation from C-2 of the
p-nitrobenzoyl group as compared with the benzoyl
group was tested. Thus, 2,3,5-tri-O-benzoyl-α-D-
arabinofuranosyl bromide (55b) and 2,3,5-tri-O-p-
nitrobenzoyl-α-D-arabinofuranosyl bromide (63a) were
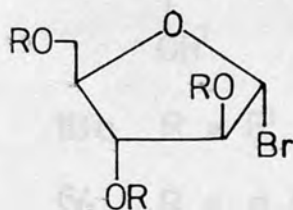
55b R = C_6H_5CO

63a R = $p\text{-}NO_2C_6H_4CO$

each reacted with an excess of methanol in
dichloromethane, and the proportions of anomeric
products determined by g.l.c. (after converting these
products into suitable derivatives). The results
showed that solvolysis of the benzoylated halide gave

predominantly the corresponding α-methyl glycoside
(α:β = 96:4) while the p-nitrobenzoylated halide
afforded a mixture containing a substantial porportion
of the corresponding β-methyl glycoside (α:β = 75:25).
This result was proposed to demonstrate the
comparative inefficiency of the p-nitrobenzoyl group
in controlling the steric course of solvolysis and was
ascribed to the greater electron attracting ability of
the p-nitrophenyl group thereby reducing the ability
of the carbonyl oxygen of the group at C-2 to take
part in an intramolecular nucleophilic attack at C-1
of an incipient oxocarbenium ion.

An analogous investigation was later conducted in
order to assess the effects of acyloxy groups at C-3

$$R^2 = C_6H_5CH_2$$

18a $\quad$ R = R^1 = $C_6H_5CH_2$

64 $\quad$ R = p-NO$_2$C$_6$H$_4$CO , R^1 = C$_6$H$_5$CH$_2$

65 $\quad$ R = R^1 = p-NO$_2$C$_6$H$_4$CO
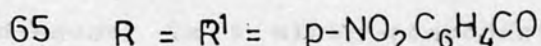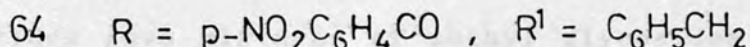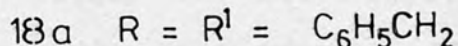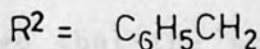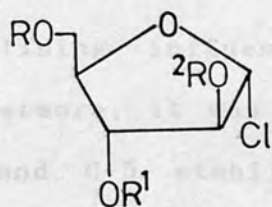
and C-5 on the properties of arabinofuranosyl
halides[31]. Each of the α-chlorides [(18a), (64) and
(65)] were reacted with an excess of methanol in
dichloromethane. The progress of the solvolysis was

followed polarimetrically at 20° and the data thus obtained used to calculate the pseudo-first-order rate constants. The proportions of anomeric glycosides formed in each of the three solvolyses was determined by g.l.c.

The relative values of the rate constants obtained suggested that the fully benzylated glycosyl halide (18a) is the most reactive : replacement of a benzyl group at C-5 by a p-nitrobenzoyl group [as in ((64)] decreased the rate of solvolysis by a factor of 8; replacement of the benzyl groups at C-3 and C-5 by p-nitrobenzoyl groups [as in (65)] decreased that rate by a factor of 106. It was proposed that electronegative protecting groups at positions other than C-2 in acylated glycofuranosyl halides exercise a stabilising influence on the carbon-halogen bond. Furthermore, it was suggested that the acyl groups at C-3 and C-5 stabilise the C-1 halogen bond by a transmission of their electron withdrawing capacity through the ring oxygen. The fact that each of the chlorides gave mixtures of methyl glycosides in which the α-anomer is a minor component (2-10%) was viewed to be consistent with the finding of the earlier kinetic study[30] in which the solvolyses of halides bearing a non-participating group at C-2 was examined and proposed to follow an S_N1 mechanism.

The data obtained from this investigation of the

glycosyl chlorides (18a), (64) and (65) was further examined[31] in order to ascertain the extent to which anchimeric assistance from acyloxy groups at C-3 of arabinofuranosyl halides effected the product stereoselectivity of these solvolytic reactions. It was suggested that if participation from an acyloxy group at C-3 did occur in (65) an intermediate of the type (67) would be formed, and the attack of nucleophiles such as methanol on this species would proceed with inversion to give the β-glycoside (68).

$$R^1 = C_6H_5CH_2 \ , \quad R = p\text{-}NO_2C_6H_4CO$$
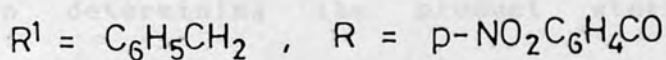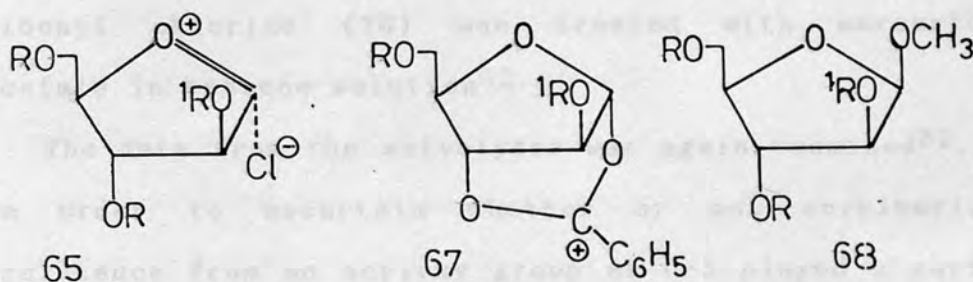
The proportion of β-glycoside (68) formed from (65) was somewhat greater than that formed from the other two halides (18a) and (64) but it was considered that this difference, although expected through anchimeric assistance from the acyloxy group at C-3 of (65), was too slight to make clear whether or not such an effect is operating. It was pointed out that anchimeric assistance from acyloxy groups at C-3 has been observed with analogous sugars. Thus

RO—⟨O⟩~Cl
70 RO   OH

69

R = C₆H₅CO
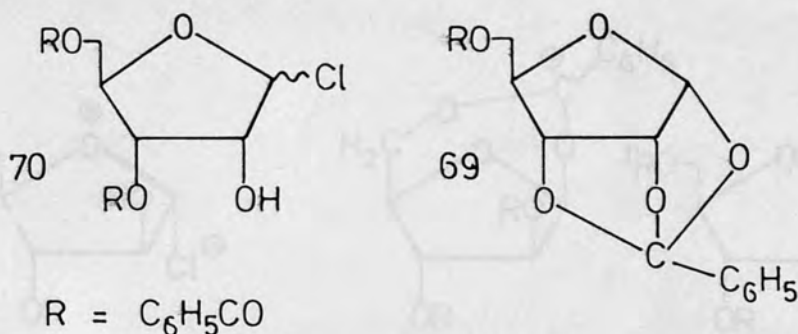
participation by an acyloxy group at C-3 was proposed
to account for the formation of 5-O-benzoyl-1,2,3-
benzylidyne-α-D-ribose **(69)** when 1,3,5-di-O-benzoyl-D-
ribosyl chloride **(70)** was treated with mercuric
acetate in benzene solution[32].

The data from the solvolyses was again examined[31],
in order to ascertain whether or not anchimeric
assistance from an acyloxy group at C-5 played a part
in determining the product stereoselectivity in
nucleophilic substitution reactions of
arabinofuranosyl halides. It was suggested that if
participation from the acyloxy group at C-5 of **(64)**
occurred it would lead to an intermediate of the type
(71) and a nucleophilic attack on this species by
methanol would proceed with inversion to give the
α-glycoside **(72)**. The anomeric proportions of methyl
glycosides formed from the halides **(18a)** and **(64)** were
found to be identical and this was proposed to support
the view that the C-5 acyloxy group does not

participate in methanolyses of this type.

64a   71   72

$R = C_6H_5CH_2$, $R^1 = p-NO_2C_6H_4CO$
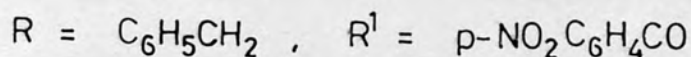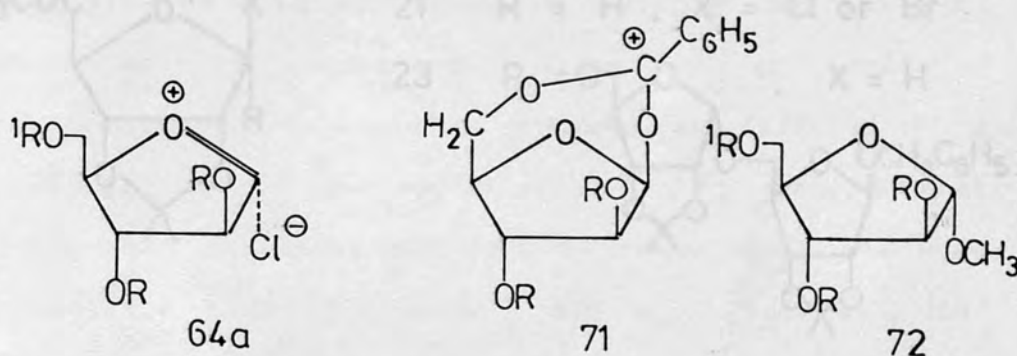
A later study[10] indicates that anchimeric assistance from certain groups at C-5 of glycofuranosyl halides is possible. Thus, the glycosidation of 1-chloro or 1-bromo-2,3-O-isopropylidene-β-D-ribofuranosiduronate (21) in the presence of silver (1) oxide gave predominantly ($\alpha:\beta$ = 8:1) the inverted α-products (23). The anomeric product ratios were found to be independent of the identity of the leaving group, the reaction temperature and the identity of the nucleophile. The intermediacy of the dioxorbornene species (73) attacked mainly from the side facing away from the carboxylate group was proposed to account for this result.

73

H₃COC structure with labels:

$21 \quad R = H , \quad X = Cl \text{ or } Br$

$23 \quad R = O \quad , \quad X = H$

$OCH_2C_6H_5$
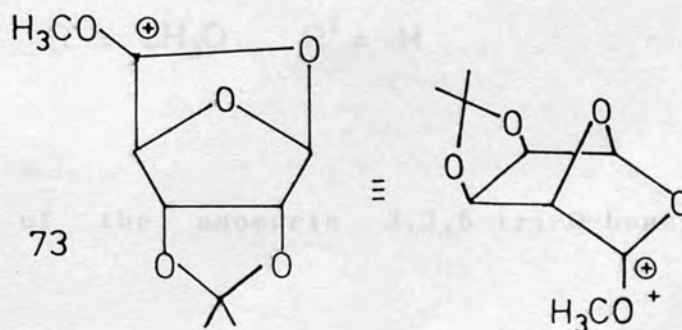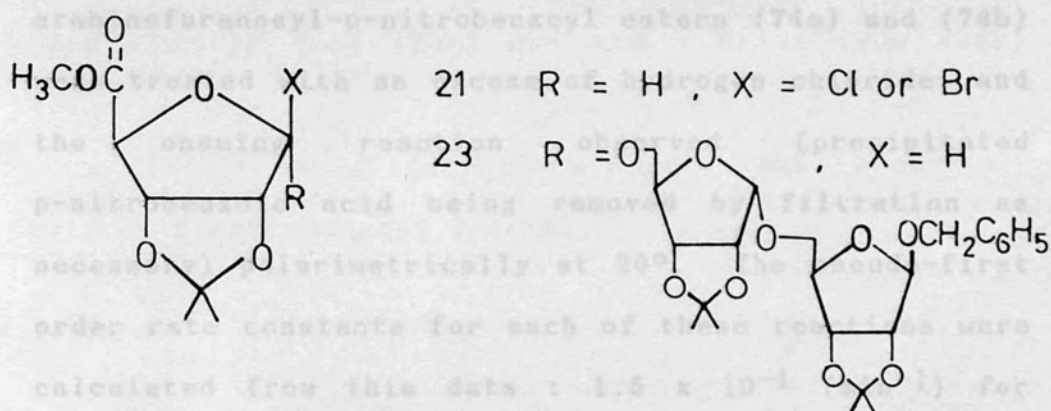
In another relevant study the mechanism of formation of certain arabinofuranosyl halides was investigated[33].

^2RO ... $R^2 = C_6H_5CH_2$

R^1

^2RO
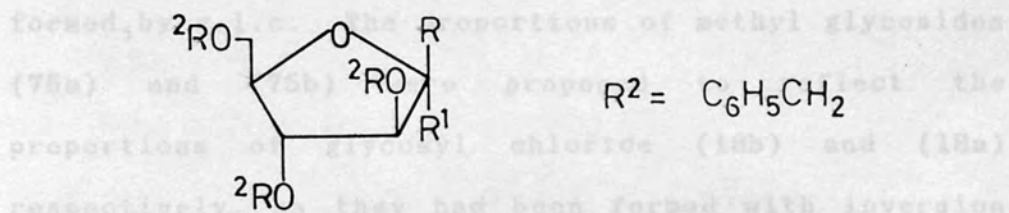
74a $R = H , \quad R^1 = p\text{-}NO_2C_6H_4CO$

74b $R = p\text{-}NO_2C_6H_4CO , \quad R^1 = H$

18a $R = H , \quad R^1 = Cl$

18b $R = Cl , \quad R^1 = H$

75a $R = H , \quad R^1 = CH_3O$

75b $R = CH_3O , \quad R^1 = H$

Thus, each of the anomeric 2,3,5-tri-O-benzyl-D-

arabinofuranosyl-p-nitrobenzoyl esters (74a) and (74b) were treated with an excess of hydrogen chloride, and the ensuing reaction observed (precipitated p-nitrobenzoic acid being removed by filtration as necessary) polarimetrically at 20°. The pseudo-first order rate constants for each of these reactions were calculated from this data : 1.5×10^{-1} (min^{-1}) for (74a) and 5×10^{-2} (min^{-1}) for (74b). The proportions of glycosyl chlorides (18a) and (18b) formed during this reaction were assayed by removing aliquots of the reaction mixture at intervals, treating them with an excess of sodium methoxide and analysing the mixtures of α- and β- methyl arabinofuranosides (75a) and (75b) formed, by g.l.c. The proportions of methyl glycosides (75a) and (75b) were proposed to reflect the proportions of glycosyl chloride (18b) and (18a) respectively, as they had been formed with inversion from the reaction of the glycosyl chlorides with sodium methoxide. The ratios of anomeric glycosyl chlorides obtained from the reactions of either p-nitrobenzoyl ester were found by this method to be very similar. This data was rationalised by proposing that the α-chloride (18a) is formed initially (from either p-nitrobenzoyl ester but at slightly different rates) and then slowly anomerises to give the β-chloride (18b), although the α-chloride remains the predominant anomer even after a long reaction period

[α:β = 75:25 from **(74a)** and α:β = 69:31 from **(74b)** after 13 days].

A similar investigation was carried out on another pair of p-nitrobenzoyl esters.

$R^2 = C_6H_5CH_2$, $R^3 = p\text{-}NO_2C_6H_4\overset{\overset{\displaystyle O}{\|}}{C}$

76a	R = H ,	$R^1 = p\text{-}NO_2C_6H_4CO_2$
76b	$R = p\text{-}NO_2C_6H_4CO_2$	$R^1 = H$
63a	R = H ,	$R^1 = Br$
63b	R = Br ,	$R^1 = H$
77a	R = H ,	$R^1 = CH_3O$
77b	$R = CH_3O$,	$R^1 = H$
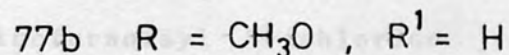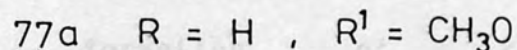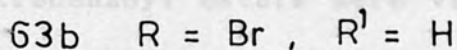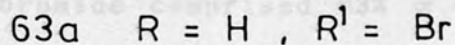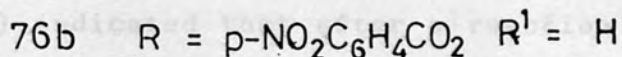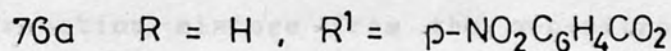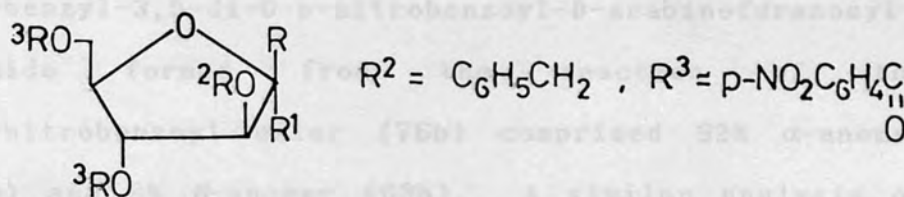
Thus, each of the anomeric 2-O-benzyl-1,3,5-tri-O-p-nitrobenzoyl-D-arabinofuranoses **(76a)** and **(76b)** were reacted with an excess of hydrogen bromide in dichloromethane and the reactions observed polarimetrically at 20°. The pseudo-first order rate constants calculated from this data were 1×10^{-1} and 3×10^{-1} (min^{-1}) for **(76a)** and **(76b)** respectively. The reaction mixture from the β anomer **(76b)** showed a rotation of 0.744° at 162 min. and 0.685° after 98

hr.; the mixture from the α anomer (76a) showed a rotation of 0.706° after 77 min. and 0.667° after 98 hr. Furthermore, analysis of the reaction mixtures by g.l.c. [after reaction with sodium methoxide to give the glycosides (77a) and (77b)] was proposed to indicate that after a reaction time of 1.45 min. the 2-O-benzyl-3,5-di-O-p-nitrobenzoyl-D-arabinofuranosyl bromide formed from the reaction of the β-p-nitrobenzoyl ester (76b) comprised 92% α-anomer (63a) and 8% β-anomer (63b). A similar analysis of the reaction mixture from the α-p-nitrobenzoyl ester (76a) indicated that after a reaction time of 18 min. the bromide comprised 83% α and 17% β. This pair of p-nitrobenzoyl esters were viewed to behave similarly to those investigated earlier. It was proposed that the formation of 2,3,5-tri-O-benzyl-α-D-arabinofuranosyl chloride (18a) from the corresponding

78   79

R = C$_6$H$_5$CH$_2$
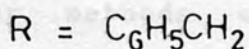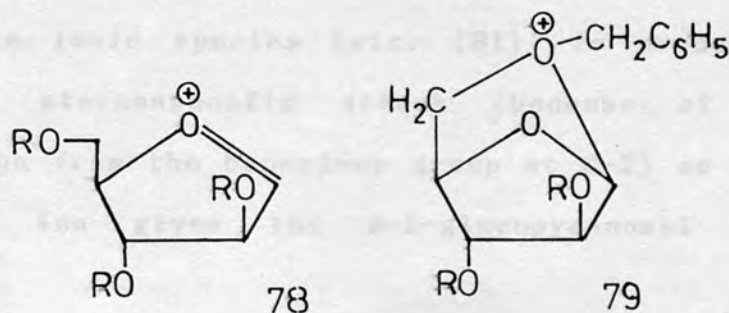
p-nitrobenzoyl esters (74a) and (74b), proceeded

through a common carbenium ion **(78)** formed by the loss of the acyl group (which precipitates as p-nitrobenzoic acid). Anchimeric participation from the benzyl group at C-5 leading to the intermediate ion **(79)** was considered in an attempt to rationalise the stereoselectivity of attack on the carbenium ion by the nucleophile. However, steric hindrance of the benzyloxy group at C-2 was viewed to be a more attractive explanation. It is interesting to note that an analogous behaviour has been observed in the D-glucopyranose series[33]. Thus, regardless of the anomeric configuration of the p-nitrobenzoate used [**(80a)** or **(80b)**], the initial product was the β-bromide **(82b)**. This anomer isomerised under the reaction conditions to give the α-bromide **(82a)**, which is the more stable anomer in the glucopyranose series (anomeric effect). The initial formation of the more reactive (β) glucopyranosyl bromide from both of the anomeric p-nitrobenzoates was proposed to suggest that a single ionic species [viz. **(81)**] is produced and that a stereospecific attack (because of steric hindrance from the benzyloxy group at C-2) on this by bromide ion gives the β-D-glucopyranosyl bromide **(82b)**.

Other methods of preparation of 2,3,5-tri-O-benzyl-arabinofuranosyl chloride lead to mixtures
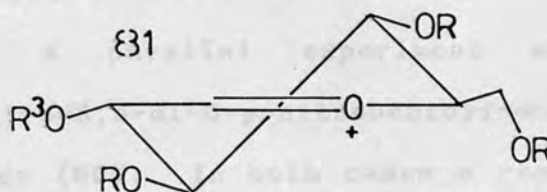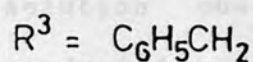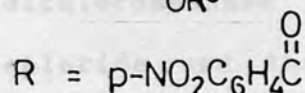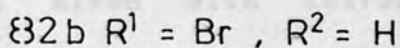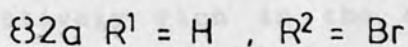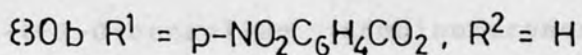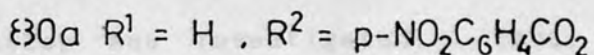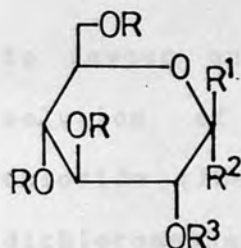
containing significant amounts of the β-anomer. Thus, reaction of 2,3,5-tri-0-benzyl-D-arabinofuranose **(83)** with hydrogen chloride[35] at room temperature or with N,N-dimethyl chloroforminium chloride[36] at -40° both gave some β-chloride **(18b)** (as measured by g.l.c. after conversion to the appropriate derivatives), in the latter case more than 50% (by ^{1}H nmr). In these two particular instances it is possible that a relatively large concentration of chloride ion is present and this may be sufficient to facilitate anomerisation of the initially formed α-anomer. Alternatively, a mixture of ion-pairs might first be formed and each attacked subsequently in a S_N2 fashion. A difference between these cases and that of the p-nitrobenzoate methods, is that the leaving groups are not removed by precipitation.

In the same study[33] the behaviour of two α-D-arabinofuranosyl halides under conditions designed

to favour anomerisation was investigated. Thus, a solution of 2,3,5-tri-O-benzyl-D- arabinofuranosyl chloride (18a) (relatively rich in the α-anomer) in dichloromethane was mixed with tetrabutylammonium chloride and the optical rotation of the resulting solution observed. A parallel experiment was conducted with 2-O-nitro-3,5-di-O-p-nitrobenzoyl-α-D-arabinofuranosyl bromide (60). In both cases a rapid levomutarotation was observed [α_{obs} ~ 1.85 → ~ 1.5 in ~ 150 min. for (18a) and ~ 2.6 → ~ 1.5 in ~ 150h for (60)] which was proposed to be consistent with the view that an appreciable proportion of β-anomer is formed when a D-arabinofuranosyl halide is permitted to attain anomeric equilibrium. This assertion seems to be at variance with an earlier result[34] obtained by the same author. Thus, prolonged treatment of 2-O-nitro 3,5-di-O-p-nitrobenzoyl-α-D-arabinofuranosyl bromide (60) in either benzene or dichloromethane with active silver chloride gave only the corresponding α-chloride (59a). This suggests that the β-chloride (59b) is formed first from the α-bromide (60) and then anomerises (implies obligatory inversion).

Certain general conclusions may be drawn from the results of these solvolysis reactions (see Figure 2.2). Nucleophilic substitution of an anionic leaving group in glycons which possess a nucleophilic substituent on C-2 invariably leads to the predominant

$R^2 = p\text{-}NO_2C_6H_4CO$

60 $R = H$, $R^1 = Br$
59b $R = Cl$, $R^1 = H$
59a $R = H$, $R^1 = Cl$

83 $R = C_6H_5CH_2$
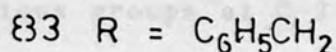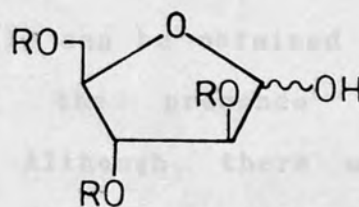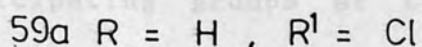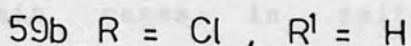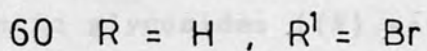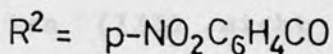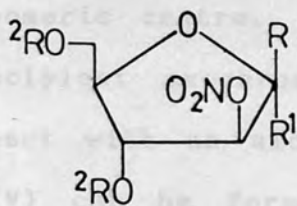
formation of 1,2-trans glycosides. This stereochemical result is found to be independent of the anomeric configuration of the starting glycosylating agent. The preponderant formation of the 1,2-trans product (VI) may be rationalised by proposing the formation of a stabilised dioxocarbenium ion (IV). This intermediate can be derived from the oxocarbenium ion (III) which is formed once the leaving group has become separated from the 1,2-trans or 1,2-cis glycons [(I) and (II) respectively]. The reactions are characterised as essentially S_N1 in which either a cis or trans group of suitable structure can act as a preassociation nucleophile. Intermediates of the type (IV) would only be expected from glycons which possess a group at C-2, nucleophilic enough to participate in reactions at the

anomeric centre. However, with certain glycons the incipient oxocarbenium ion (III) might be able to react with an alcohol before the dioxocarbenium ion (IV) can be formed. If follows that mixtures of anomeric glycosides [(V) and (VI)] can be obtained in certain cases in spite of the presence of participating groups at C-2. Although, there are examples of participation by various groups at C-3 and C-5, the main prerequisite for a 1,2-cis glycoside synthesis is the presence of a non-participating protective group at C-2 of the glycon. Thus, nucleophilic substitution of an anionic group at C-1 in 1,2-trans glycons uncomplicated by neighbouring group participation (VII) would give the 1,2-cis glycoside (IX) providing that the reaction proceeded with inversion. Furthermore, it appears that 1,2-trans glycons (VII) and the 1,2-trans ion pairs (VIII) formed from them, are more stable than their 1,2-cis counterparts [(X) and (XI) respectively] in the case of arabinofuranosyl glycons.

These observations suggest that the synthesis of a 1,2-cis glycoside from a 1,2-trans glycon should be less problematic than in an analogous synthesis of a 1,2-cis glycopyranoside from an equatorial glycopyranosyl derivative (1,2-trans glycon). However, the stereoselectivity in reactions of this type depends not only on the thermodynamic stabilities

FIGURE 2.2   SUMMARY OF MECHANISTIC STUDIES
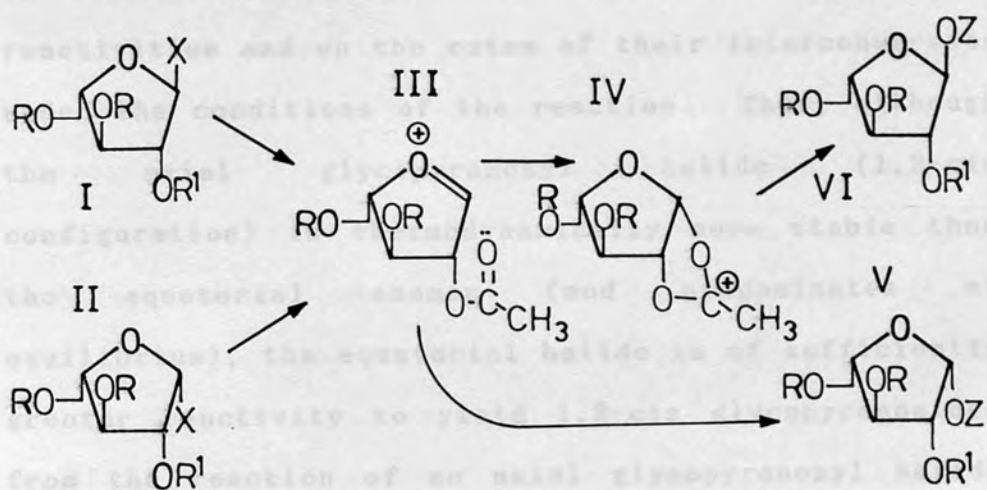
R = Protecting group , R¹ = Nucleophilic protecting group
e.g. CH_3CO or C_6H_5CO

X = Anionic leaving group e.g. $Cl^{\ominus}$ or $Br^{\ominus}$

OZ = Nucleophile e.g. alcohol
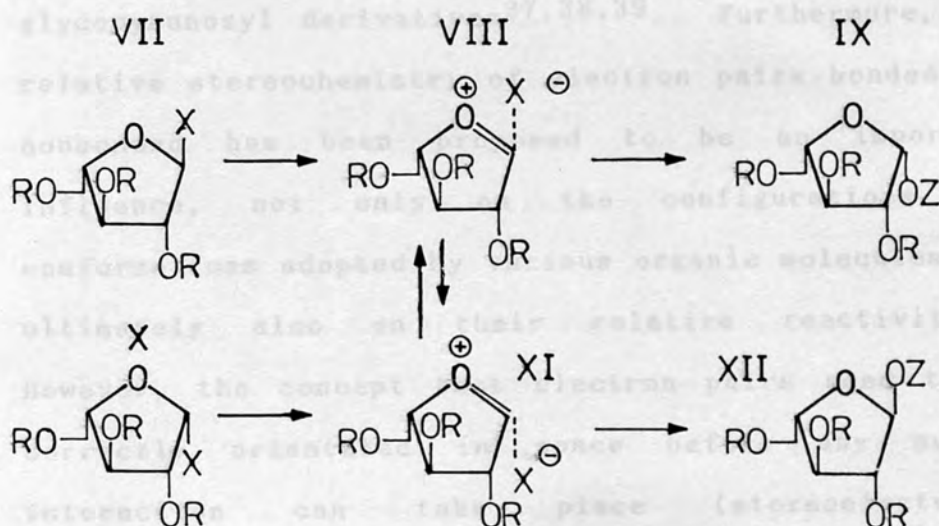
R = Nonparticipating protecting group e.g. $C_6H_5CH_2$
X = Leaving group e.g. $Cl^{\ominus}$
OZ = Nucleophile

of the anomeric glycons but also on their relative
reactivities and on the rates of their interconversion
under the conditions of the reaction. Thus, although
the axial glycopyranosyl halide (1,2-cis
configuration) is thermodynamically more stable than
the equatorial anomer (and predominates at
equilibrium), the equatorial halide is of sufficiently
greater reactivity to yield 1,2-cis glycopyranosides
from the reaction of an axial glycopyranosyl halide
(protected with non-participating groups) with an
alcohol, in the presence of tetraalkylammonium halide
in a dipolar aprotic solvent[28] (see below).

Much experimental evidence exists to support the
view that stereoelectronic effects play an important
part in determining the thermodynamic stabilities of
glycopyranosyl derivatives[37,38,39]. Furthermore, the
relative stereochemistry of electron pairs bonded and
nonbonded has been proposed to be an important
influence, not only on the configurations and
conformations adopted by various organic molecules but
ultimately also on their relative reactivities.
However, the concept that electron pairs need to be
correctly orientated in space before any mutual
interaction can take place (stereoelectronic
control)[39], and that this proper alignment of orbitals
is a necessary prerequisite to a particular transition
state being formed is a matter of some dispute,

certainly in relation to the reactions of acetals[40].

A factor which has played a significant role in the recognition of stereoelectronic effects and as a consequence in the development of the stereoelectronic theory, has been the ability to determine the shapes of organic molecules in solution. The analysis of ^{1}H nmr spectroscopic data in conjunction with Karplus-type relationships has enabled the conformations of pyranoid acetals in solution to be established with some confidence[39]. As a result of this it has been possible to identify the various steric and electronic factors which influence these systems and thereby to evaluate their relative magnitudes. The influence of stereoelectronic effects on the shapes adopted by six membered rings has proved relatively straightforward to observe because of their unique geometry. These systems usually exist in one of two chair conformations in which substituents are either axially or equatorially disposed[41].

Much less success has been achieved in establishing the shapes of the five membered ring structures in solution (see discussion Chapter 2.2) and this accounts for the particular difficulties encountered in assessing the part played by stereoelectronic effects in the chemistry of furanoid acetals. Stereoelectronic effects have in a number of instances, been implicated as influencing the

conformations adopted by certain glycofuranoid systems in solution[42]. It seems however that the steric and electronic effects that operate in establishing the preferred shapes of pyranoid acetals interact in a more complex manner in furanoid acetals. Evidence does exist in support of the view that stereoelectronic effects play an important part in the reactions of glycopyranosyl halides[28]. The "Halide ion catalysed glycosidation method" was rationalised[28] by proposing that the thermodynamic stabilities and reactivities of the axial and equatorial glycopyranosyl halides [(84a) and (84b)] was different, and that these differences were ultimately as a consequence of stereoelectronic effects. Furthermore, in this original rationalisation the concept of stereoelectronic control was invoked. Thus, it was proposed that in order for an equatorial β-glycopyranosyl halide ($^4C_1$) to react, it has first to assume a conformation in which the halide leaving group is perpendicular to a lone pair on the ring oxygen atom ($^4B^1$) which has this correct alignment of ring oxygen lone pair and leaving group in its ground state conformation.

Although this stereoelectronic control was proposed to make an important contribution to the difference in reactivity between the two glycopyranosyl halides the critical factor was

considered to be the lower energy of the resultant molecule ion pair **(85a)** relative to the corresponding intermediate arising from the α-halide **(84a)**.

$R = C_6H_5CH_2$

(84a)

(84b)
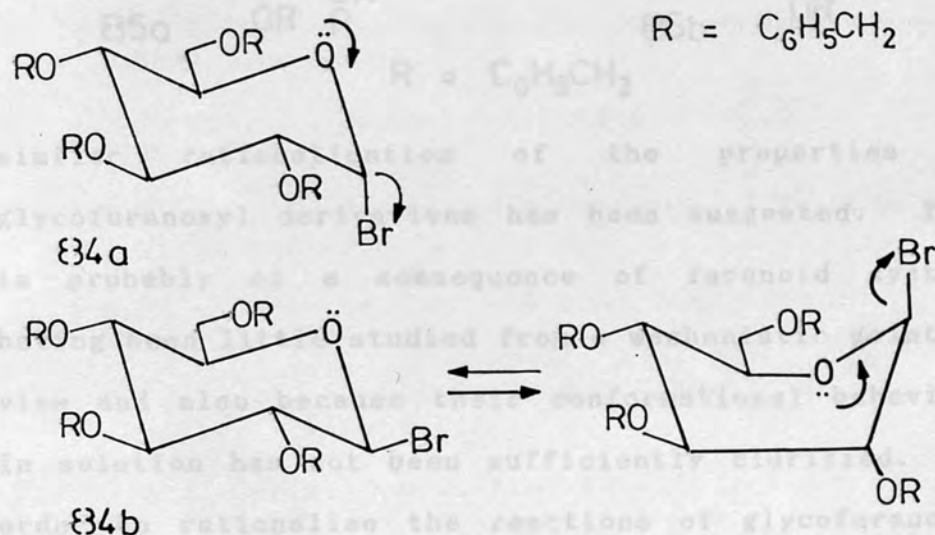
However, this assertion is not entirely convincing on steric grounds, and an alternative explanation would simply regard halide ionisation as the rate limiting step. Certainly the β-halide **(84b)** has the higher energy of the two ground states, but the relative energies of the ion pairs **(86a)** and **(86b)** are uncertain.

The appreciation of various stereoelectronic effects has been of basic importance in explaining the properties of glycopyranosyl derivatives, but no

85a   85b

R = C$_6$H$_5$CH$_2$
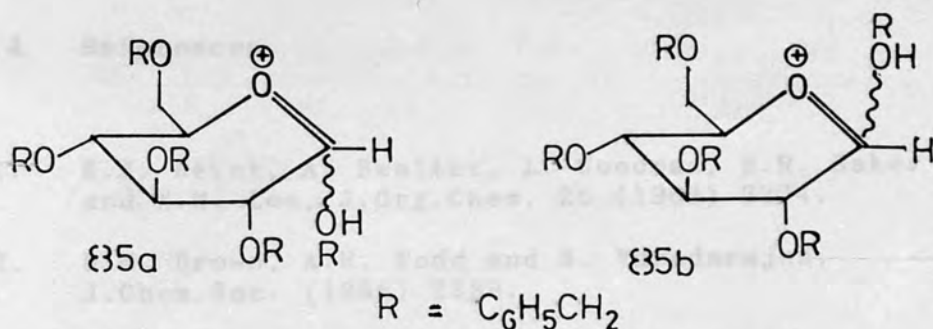
similar rationalisation of the properties of glycofuranosyl derivatives has been suggested. This is probably as a consequence of furanoid systems having been little studied from a mechanistic point of view and also because their conformational behaviour in solution has not been sufficiently clarified. In order to rationalise the reactions of glycofuranosyl halides it is important to know what factors determine the energies of the kinetically significant transition states (Curtin Hammett Principle). Additional information which might also prove useful is a more precise knowledge of the conformational behaviour of furanoid systems and the relative energies of these conformations.

86a   86b

R = C$_6$H$_5$CH$_2$
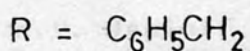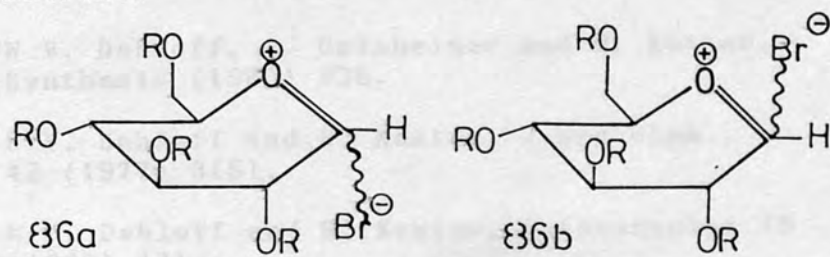
2.4 References.

1. E.J. Reist, A. Benitez, L. Goodman, B.R. Baker
    and W.W. Lee, J.Org.Chem. 25 (1962) 3274.

2. D.M. Brown, A.R. Todd and S. Varadarajan,
    J.Chem.Soc. (1956) 2388.

3. J.J. Fox, N. Young, Federation Proc. 15
    (1956) 254.

4. J.J. Fox, N. Young and A. Bendich, J.Am.Chem.
    Soc. 79 (1957) 2775.

5. R.S. Wright and H.G. Khorana, J.Am.Chem.Soc.
    80 (1958) 1994.

6. P. Andrews, L. Hough and D.B. Powell, Chem.Ind.
    (London) (1956) 658.

7. P.A.J. Gorin, Can.J.Chem. 40 (1962) 276.

8. K. Igarashi, Adv.Carbohydr.Biochem. 34
    (1977) 243.

9. R.R. Schmidt and P. Hermentin, Chem.Ber 112
    (1979) 2659.

10. R.R. Schmidt and P. Hermentin, Angew.Chem.
    Int.Ed.Eng. 16 (1977) 1.

11. R.S. Wright, G.M. Tenner and H.G. Khorana,
    J.Am.Chem.Soc. 80 (1957) 2004.

12. W.V. Dahloff and R. Koster, Synthesis (1980)
    936.

13. W.V. Dahloff, A. Geisheimer and R. Koster,
    Synthesis (1980) 935.

14. W.V. Dahloff and R. Koster, J.Org.Chem.,
    42 (1977) 3151.

15. W.V. Dahloff and R. Koster, Heterocycles 18
    (1982) 421.

16. W.V. Dahloff, A. Geisheimer, G. Schroth,
    Zeitschrift Furnaturforschung 39B(8) (1984)
    1004.

17.   W.V. Dahlhoff and K.M. Taba, Abstracts of
       the 12th International Carbohydrate Symposium,
       Utrecht, 1984, p35.

18.   W.A. Szarek, G. Grynkiewicz, B. Doboszewski
       and G.W. Hay, Chem.Lett (1984) 1751.

19.   M. Hayashi, Y. Hashimoto and R. Noyori,
       Chem.Lett. (1984) 1747.

20.   T. Mukaiyama and Y. Hashimoto, S-i Shoda,
       Chem.Lett. (1983) 935.

21.   K.C. Nicolau, R.E. Dohle, D.P. Papahatjis
       and J.L. Randall, J.Am.Chem.Soc. 106 (1983)
       4189.

22.   K.C. Nicolau, S.P. Sietz and D.P. Papahatjis,
       J.Am.Chem.Soc. 105 (1983) 2430.

23.   A.H. Haines and K.C. Symes, J.Chem.Soc. (C)
       (1971) 2331.

24.   R.R. Schmidt and M. Reichrath, Angew.Chem.
       Int.Ed.Engl. 28 (1979) 446.

25.   T.L. Su, R.S. Klein and J.J. Fox, J.Org.Chem.
       47 (1982) 1506.

26.   N.R. Fugedi, A. Liptak and P. Nanasi, Carbohydr.
       Res. C5-C8 (1982) 107.

27.   A.F. Bochkov and G.E. Zaikov, "Chemistry of the
       O-Glycosidic Bond: Formation and Cleavage"
       1979, Pergamon Press.

28.   R.U. Lemieux, K.B. Hendriks, R.V. Stick and
       K. James, J.Am.Chem.Soc., 97 (1975) 4056.

29.   R.K. Ness and H.G. Fletcher Jr., J.Am.Chem.Soc.,
       80 (1958) 2007.

30.   C.P.J. Glaudemans and H.G. Fletcher Jr.,
       J.Am.Chem.Soc., 87 (1965) 2456.

31.   C.P.J. Glaudemans and H.G. Fletcher Jr.,
       J.Am.Chem.Soc., 87 (1965) 4636.

32.   R.K. Ness and H.G. Fletcher Jr., J.Org.Chem.,
       22 (1957) 1465.

33.   C.P.J. Glaudemans and H.G. Fletcher Jr.,
       J.Org.Chem., 36 (1971) 3599.

34.   C.P.J. Glaudemans and H.G. Fletcher Jr.,
      J.Org.Chem., 29 (1964) 3286.

35.   C.P.J. Glaudemans and H.G. Fletcher Jr.,
      J.Org.Chem., 28 (1963) 3004.

36.   V. Dourtoglou and B. Gross, Carbohydr.Chem.,
      2(1) (1983) 57.

37.   A.J. Kirby, "The Anomeric Effect and Related
      Stereoelectronic Effects at Oxygen", Springer
      Verlag (1982).

38.   Anomeric Effect:Origin and Consequences, ed.
      W.A. Szarek and D. Horton (1979) Am.Chem.

39.   P. Deslongchamps, "Stereoelectronic Effects
      in Organic Chemistry", Pergamon Press
      (1983).

40.   R.U. Lemieux in "Molecular Rearrangements", ed.
      P. de Mayo, Vol. 2 (1964) 709.

41.   M.L. Sinott in "The Chemistry of Enzyme Action",
      ed. M.I. Page, Elsevier (1984) 389.

42.   J.F. Stoddart "Stereochemistry of
      Carbohydrates", Willey 1971.

43.   C.P.J. Glaudemans and H.G. Fletcher Jr.,
      J.Org.Chem., 28 (1963) 3004.

44.   J.W. Green, Adv.Carbohydr.Chem., 21 (1966) 95.

45.   B. Fuchs in "Topics in Stereochemistry", ed.
      E.L. Eliel and N.L. Allinger, Vol. 10, Wiley
      (1978) 2.

46.   L.D. Hall, Chem.Ind. (London), (1963) 950.

47.   M. Sundaralingam in "The Jerusalem Symposia
      on Quantum Chemistry and Biochemistry", Vol. 5,
      ed. E.D. Bermann and B. Pullman (1973)
      417-455.

48.   W.K. Olson and J.L. Sussman, J.Am.Chem.Soc.,
      104 (1982) 270.

49.   W.K. Olson and J.L. Sussman, J.Am.Chem.Soc.,
      104 (1982) 270. See references 10-13.

50.   D. Cremer and J.A. Pople, J.Am.Chem.Soc.,
      97 (1975) 1358.

51.   W.K. Olson and J.L. Sussman, J.Am.Chem.Soc.,
       104 (1982) 270. See references 15-21.

52.   W.K. Olson and J.L. Sussman, J.Am.Chem.Soc.,
       104 (1982) 270. See references 11-13, 22-29.

53.   M. Karplus, J.Chem.Phys., 30, (1959) 11.

54.   C. Altona, H.R. Buys, H.J. Hageman and
       E. Havinga, Tetrahedron 23 (1667) 2265-2279.

55.   A. Jaworski, I. Ekiel and D. Shugar, J.Am.
       Chem.Soc., 100 (1978) 4357.

56.   A. Jaworski and I. Ekiel, Int.J.Quantum.Chem.,
       16 (1979) 615.

57.   M. Sundaralingam, J.Am.Chem.Soc., 87 (1965)
       599.

58.   G.M. Brown and H.A. Levy, Science, 141 (1963)
       921.

59.   C.T. Bishop and A.F. Cooper, Can.J.Chem.,
       41 (1963) 2743; V. Smirnyagin and C.T. Bishop,
       Can.J.Chem., 46 (1968) 3085; B. Capon,
       G.W. Loveday and W.G. Overend, Chem.Ind., (1962)
       1537; S.J. Angyal and V.A. Pickles, Carbohydr.
       Res., 4 (1967) 269.

60.   S.J. Angyal, Angew.Chem.Int.Ed, 8 (1969) 157.

61.   M. Sundaralingam and L.H. Jensen, Abstracts,
       American Crystallographic Association,
       Bozeman, Mont., (1964) 50.

62.   J. Kraut and L.H. Jensen, Acta.Cryst., 16 (1963)
       79.

63.   S.J. Angyal, Carbohydr.Res., 77 (1979)
       37; H. Ohrui and S. Emoto, J.Org.Chem.,
       42 (1977) 1951; G.S. Ritchie, N. Cyr,
       B. Korsch, H.J. Koch and A.S. Perlin,
       Can.J.Chem. 53 (1975) 1424; J.D. Stevens
       and H.G. Fletcher Jr., J.Org.Chem., 33
       (1968) 1799; L.D. Hall, P.R. Steiner and
       C. Pedersen, Can.J.Chem., 48 (1976) 1155.

64.   W.K. Olson, J.Am.Chem.Soc., 104, (1982)
       278. See references 2, 3 and 8-14.

65.   E.L. Eliel and C.A. Giza, J.Org.Chem., 33
       (1968) 3754; S. Wolfe, Acc.Chem.Res.,
       5 (1972) 102.

90

66. T.K. Brunck and F. Weinhold, J.Am.Chem.Soc.
    101 (1979) 1700.

67. G.A. Jeffrey, J.A. Pople and L. Radom,
    Carbohydr.Res. 25 (1972) 117; 38 (1974)
    81; A. Abe, J.Am.Chem.Soc., 98 (1976)
    6477-6480; G.A. Jeffrey, J.A. Pople,
    J.S. Binkley and S.V. Vishreshwara, J.Am.Chem.
    Soc., 100 (1978) 373; G.A. Jeffrey and
    R. Taylor, J.Comput.Chem., 1 (1980) 99-109.,

68. C.T. Bishop and A.F. Cooper, Can.J.Chem., 41
    (1963) 2743.

CHAPTER 3
SYNTHESIS OF PRECURSORS

3.1 Arabinofuranose glycon precursor.

3.11 Introduction and strategy.

The D analogue of 2,3,5-tri-O-benzyl-L-arabino-furanose **(7)** has proved to be a convenient precursor in syntheses of arabinofuranosyl derivatives (see Chapter 2.3). This free sugar may be converted into a glycosylating agent by transforming its anomeric hydroxyl function into a variety of alternative "activated" functions (see Chapter 2.1). Benzylated derivatives such as **(7)** display several characteristics which make them attractive as precursors of glycons in 1,2-cis-glycoside syntheses. An essential property is the proven non-participating behaviour of benzyl ethers. In the absence of this type of group at C-2 of the glycon, the predominant products of glycosidation reactions are invariably the 1,2-trans anomers. Furthermore, the benzyl groups at C-3 and C-5 of **(7)** serve to minimise any influences (through participation) that might occur from these positions. Another important quality of benzyl ethers is their susceptibility to catalytic hydrogenolysis;

it is essential that deprotection of the newly formed
O-glycosides is achieved by methods not expected to
disrupt the labile O-glycosidic bonds.

Although the reported approach[16] for the synthesis
of the key compound (7) is in principle sound (scheme
3.1), it is found in practice to present several
problems.

SCHEME 3.1

$R = C_6H_5CH_2$
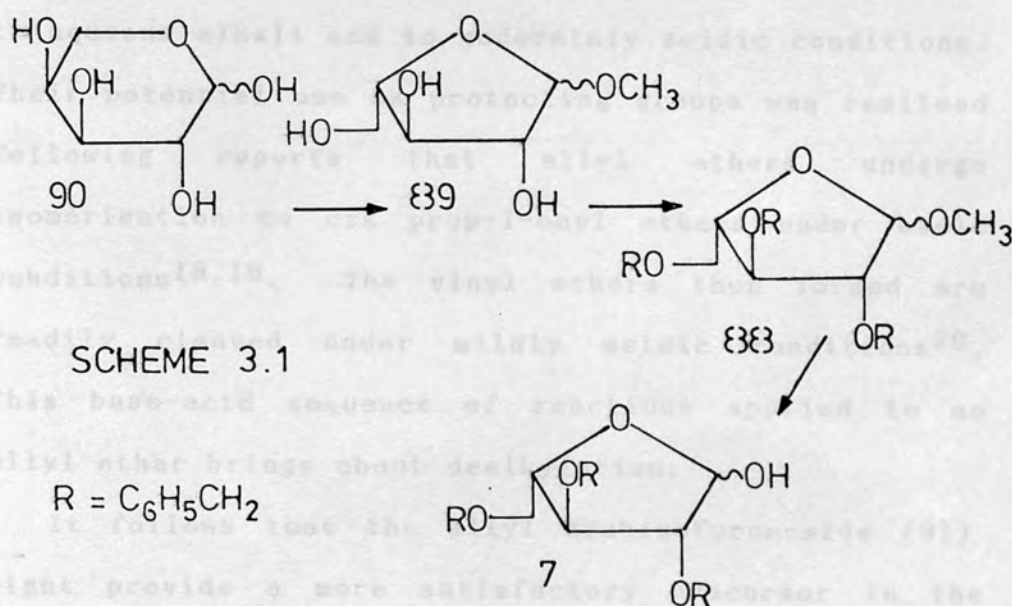
A major drawback of the original method is
encountered in its final step. The anomeric methyl
2,3,5-tri-0-benzyl-L-arabinofuranosides (88) persist
inspite of conditions expected to favour the desired
product (7). The relative lability of benzyl ethers
to acid hydrolysis imposes a limit to the severity of
the conditions which may be used to effect the

conversion of (88) to (7). It was envisaged that a significant improvement might be made to the synthesis of (7) if an alternative to the methyloxy group of (88) were available. A derivative is required bearing a group at C-1, which may be cleaved by a method not expected to cause debenzylation.

Allyl ethers have commonly been used as protecting groups since being introduced to carbohydrate chemistry[17]. They are easily prepared and are stable to aqueous alkali and to moderately acidic conditions. Their potential use as protecting groups was realised following reports that allyl ethers undergo isomerisation to cis prop-1-enyl ethers under basic conditions[18,19]. The vinyl ethers thus formed are readily cleaved under mildly acidic conditions[20]. This base-acid sequence of reactions applied to an allyl ether brings about dealkylation.

It follows that the allyl arabinofuranoside (91) might provide a more satisfactory precursor in the synthesis of (7) than the methyl arabinofuranoside (89) originally used. A similar strategy has been utilised for the preparation of benzylated glycopyranoses, and the problem of benzyl ether cleavage that may occur[21] under acidic conditions has in these cases been overcome. Thus, syntheses[22] of the 2,3,4,6-tetra-O-benzyl ethers of D-glucose and D-galactose are considerably improved by starting with

allyl, instead of methyl glycopyranosides, since

hydrolysis of the benzylated prop-l-enyl glycosides

(obtained by isomerisation of the allyl glycosides)

may be achieved under mild conditions.

A modified route to **(7)** starting from L-arabinose

is depicted in Scheme 3.2. It was envisaged that

although the synthesis of the allyl

SCHEME 3.2

$R = C_6H_5CH_2$
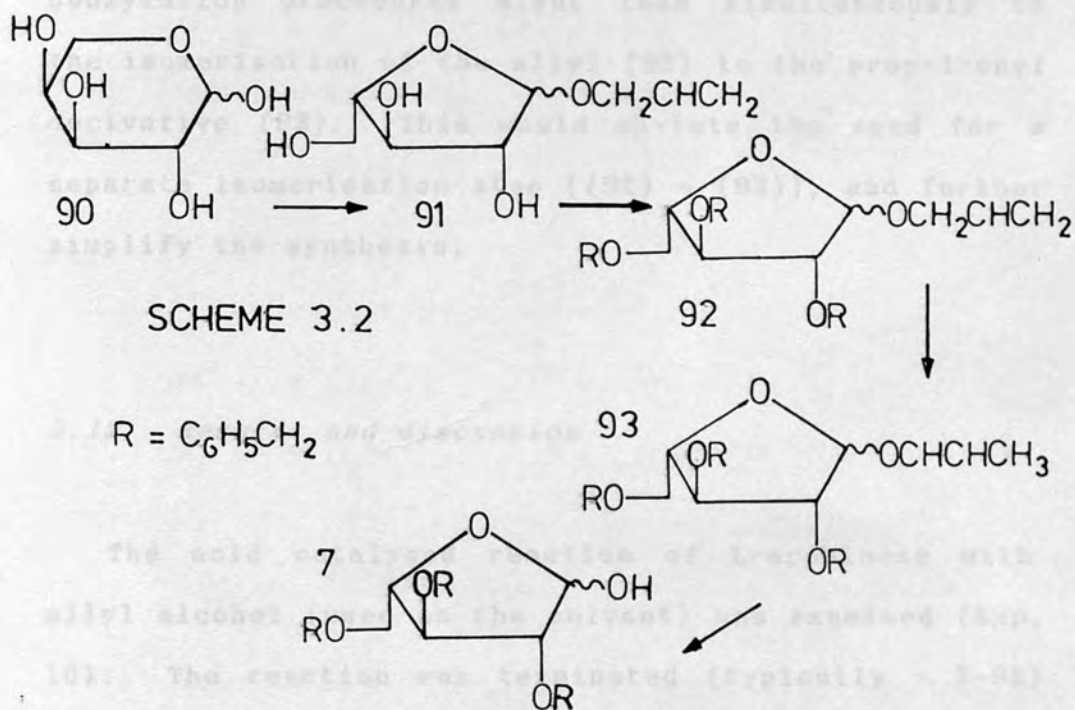
furanoside **(91)** might be problematic, it could be

achieved in a similar manner to the corresponding

methyl analogue **(89)** i.e. by an acid catalysed

reaction of arabinose **(90)** with allyl alcohol.

Removal of the acid from the equilibrium mixture at

the appropriate time would enable the "kinetic"

furanoside products **(91)** to be isolated. Alternative benzylation methods to those used in the original synthesis of **(7)** are now available[8]. It was expected that the benzylated derivative **(92)** would be more conveniently obtained from the allyl glycoside (**(91)** using these new milder methods. The possibility also exists that the basic conditions employed in these benzylation procedures might lead simultaneously to the isomerisation of the allyl **(92)** to the prop-1-enyl derivative **(93)**. This would obviate the need for a separate isomerisation step [**(92)** → **(93)**], and further simplify the synthesis.

3.12   Results and discussion

The acid catalysed reaction of L-arabinose with allyl alcohol (used as the solvent) was examined (Exp. 10). The reaction was terminated (typically ~ 7-9h) as soon as the reducing power of the reaction mixture had disappeared (Fehling's solution). This was achieved by passing the mixture through a column of anion-exchange resin which removed the acid catalyst[23]. Thus, the α- and β- allyl arabinofuranosides **(91)** were isolated as the initially formed "kinetic" products. This syrupy derivative could not be made to crystallise. Polarimetric, ^{13}C

nmr and ^{1}H nmr data indicated that the proportions of anomeric furanoside product (91) made by this method varied with each preparation.
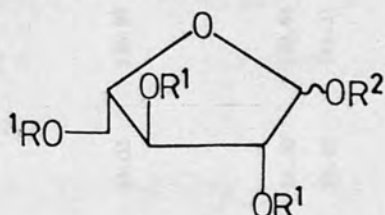
89 $R^1 = H$, $R^2 = CH_3$

91 $R^1 = H$, $R^2 = CH_2CHCH_2$

88 $R^1 = C_6H_5CH_2$, $R^2 = CH_3$

92 $R^1 = C_6H_5CH_2$, $R^2 = CH_2CHCH_2$

93 $R^1 = C_6H_5CH_2$ $R^2 = CH_3CHCH$

 7 $R^1 = C_6H_5CH_2$, $R^2 = H$

94 $R^1 = CH_3CO$, $R^2 = CH_2CHCH_2$

95 $R^1 = C_6H_5CO$, $R^2 = CH_2CHCH_2$

96 $R^1 = \begin{array}{c} CH_3 \\ | \\ (CH_3)_3CSi \\ | \\ CH_3 \end{array}$, $R^2 = CH_2CHCH_2$

It was considered prudent to establish that these allyl arabinosides were the anomeric furanosides (91), and not the pyranoside analogues, before continuing further with the proposed synthesis. ^{13}C nmr spectroscopy has been demonstrated to be of use in determining the ring sizes and anomeric configurations in the case of the four isomeric glycosides of arabinose[24], ribose, galactose and glucose[25]. This

TABLE 5.1

ASSIGNMENT OF SIGNALS[a] IN PROTON DECOUPLED ^{13}C-N.M.R. SPECTRA OF ALLYL PENTOSIDES (91), (97), (100) AND (105): DETERMINATION OF RING SIZE.

COMPOUND	Sugar Carbons					Aglyconic Carbons		
	C-1	C-2	C-3	C-4	C-5	O-CH$_2$	=CH-	=CH$_2$
Allyl α,β-L-arabinofuranoside (91)[b] (α)[d]	109.19	83.56	78.95	86.17	65.68	63.29	136.17	120.70
(β)[d]	102.88	78.95	77.39	84.55	65.29	63.29	136.24	120.74
Typical α-L-arabinofuranosides[c]	103.8±0.8	81.4±1.5	77.1±0.9	84.6±0.9	62.2±0.6			
Typical β-L-arabinofuranosides[c]	102.9±0.7	77.4±0.3	75.5±0.7	82.7±0.8	64.1±0.8			
Allyl β-L-arabinopyranoside (97)[b]	100.22	71.83	72.83	70.45	70.43	65.03	135.91	120.44
Typical α-L-arabinopyranosides[c]	104.2±2.2	72.1±0.7	74.0±0.7	69.2±0.6	66.8±0.7			
Typical β-L-arabinopyranosides[c]	100.3±2.5	69.6±1.2	70.5±0.6	70.8±0.8	64.0±0.6			
Allyl α,β-D-ribofuranoside (100)[b,e][d] (α)[d]	102.10	multiplet ~ 69.0		81.74	63.02	54.30	140.66	122.13
(β)[d]	107.82			79.92	65.60	55.99	141.31	122.65
Typical α-D-ribofuranosides[c]	103.9±0.5	71.9±0.6	70.8±1.2	84.6±1.1	62.6±0.4			
Typical β-D-ribofuranosides[c]	109.0±1.0	74.9±1.0	71.0±0.6	83.7±1.3	63.2±0.9			
Allyl α,β-D-ribopyranoside (105)[b,f] (α)[d]	100.28	multiplet ~ 70.0		67.37	65.86	32.71	155.85	120.70
(β)[d]	101.84			69.26	65.29	34.92	136.37	120.31
Typical α-D-ribopyranoside[c]	100.41	69.18	70.41	67.40	60.78			
Typical β-D-ribopyranoside[c]	105.6	72.1	69.6	69.6	65.0			

a Chemical shifts in p.p.m.; b In D$_2$O with reference to dioxan; c These values relate to data compiled from the literature and are for comparison (Ref. 25); d The resonances of the α and β isomers of these mixtures were distinguished on the basis of their different realtive intensities; e Resonances of C-2, C-3 may be interchanged; f Resonances of C-2, C-3 and C-4 may be interchanged; g Contaminated by furanose analogue: the resonances of which have not been included.

particular method enables the isomers to be distinguished on the basis of the differences between their characteristic proton decoupled ^{13}C nmr resonance patterns. Especially diagnostic is the resonance at a chemical shift of ~ 83 ppm displayed by α- and β- arabinofuranosides. All arabinopyranoside sugar resonances (except those of C-1 which occur at ~ 104 ppm and ~ 100 ppm), lie at resonances lower than a chemical shift of ~ 75 ppm. Thus, the ring size of compound (91) was established using this technique (see Table 3.1). An alternative method by which to determine the ring sizes of sugars is through the analysis of ^1H nmr spectroscopic data, and in particular through the use of NOESY and nOe difference experiments. However, data of this type is more difficult to interpret when an anomeric mixture of a sugar is being examined, as in this particular case.

The structural analysis of all new derivatives of arabinose made in this work was most conveniently achieved through the use of ^{13}C nmr data. Thus, for each compound the chemical shifts of the ^{13}C resonances in their proton decoupled ^{13}C nmr spectra were assigned by analogy[24,26,27] with those observed in the spectra of related derivatives. The analysis was further simplified through the use of ^{13}C nmr polarisation transfer experiments, which allowed the resonances of C, CH, CH_2 and CH_3 carbons to be

distinguished.

The allyl glycoside ((91) was converted (following standard methods) into the acetyl (94), benzoyl (95) and tert butyldimethylsilyl (96) analogues (Exp. 11, 12 and 13). These three new compounds all gave mass spectra and ^{13}C nmr data (Table 3.2) consistent with the structures proposed. The synthesis of the derivatives (94), (95) and (96) provided further evidence in support of the characterisation of compound (91).
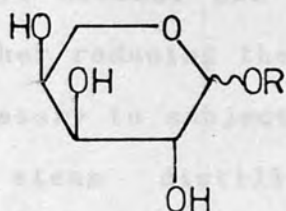
90   R = H

97   R = CH_2CHCH_2

The allyl arabinopyranoside (97) was obtained by refluxing arabinose with allyl alcohol in the presence of an acid catalyst for two hours (Exp. 14). The crystalline derivative obtained after the removal of the acid and solvent gave an elemental analysis and ^{13}C nmr data consistent with the proposed structure (97). Proton decoupled ^{13}C nmr data was particularly useful in establishing the pyranoid ring structure (see earlier discussion and Table 3.1) of compound (97).

In the original synthesis of the key compound (7),

the benzylation step i.e. the conversion of the methyl arabinoside (89) into the benzylated analogue (88) (Scheme 3.1), was achieved by heating (90) with a large excess of benzyl chloride and potassium hydroxide in either tetrahydrofuran or dioxan. Thus, the methyl arabinoside (89) was benzylated using this method to give (88) (Exp. 15.1). However, despite heating the mixture under reflux for periods of ~ 15 hours, only moderate yields of the fully benzylated derivative (88) were obtained. In addition, substantial quantities of by-products (which included benzyl alcohol and dibenzyl ether) were also formed, further reducing the efficiency of the method. It was necessary to subject this mixture to extensive periods of steam distillation to remove the various by-products, solvent and unreacted benzyl chloride that it contained.

An alternative benzylation procedure[28] was investigated with a view to improving this step of the synthesis. Thus, in a typical experiment, sodium hydride, benzyl chloride and the methyl derivative (89) were reacted in dimethyl sulphoxide (Exp. 15.2). This method proved to be considerably more convenient than that employing potassium hydroxide as a base. The yields of (88) were improved and the small amounts of by-products that formed did not warrant the use of steam distillation for their removal. The carbene

TABLE 3.2

ASSIGNMENT OF SIGNALS [a,b] IN PROTON DECOUPLED

^{13}C N.M.R. SPECTRA OF ALLYL ARABINOFURANOSIDE AND DERIVATIVES:

COMPOUNDS (91), (94), (95), (96) and (92).

COMPOUND	C-1	C-2	C-3	C-4	C-5	-OCH$_2$-	-CH=	=CH$_2$	OTHERS
Allyl α,β-L-arabinofuranoside (91)[c] (α)[e]	109.19	83.56	78.95	86.17,	65.68,	63.73	120.70	136.24	
(β)[e]	102.88	78.95	77.39	84.56	65.68				
Allyl 2,3,5-tri-O-acetyl α,β-L-arabinofuranoside (94)[c,d]	104.73 (99.27)	80.38	77.23	81.38	67.92	65.30	133.64	117.44	168.65, 170.20, 170.61 (O=C-), 20.88 (CH$_3$).
Allyl 2,3,5-tri-O-benzoyl α,β-L-arabinofuranoside (95)[c,d]	104.91	81.09	77.94	82.21	67.95	63.77	133.69	117.45	165.45, 165.82, 166.23 (O=C), ~128.3-130.2(m) (Ph).
Allyl 2,3,5-tri-O-TBDMS α,β-L-arabinofuranoside (96)[d] (α)[e]	107.71	78.62	68.79,	77.00,	65.114, [f],	62.80, [f],	134.45	116.69	~25.8(m) (CCH$_3$), ~18.0(m) (SiCH$_3$).
(β)[e]	101.22	76.91	68.18	79.19	62.80	65.14	134.54	117.02	
Allyl 2,3,5-tri-O-benzyl α,β-L-arabinofuranoside (92)[c,d] (α)[e]	106.15	84.48	81.49	89.16	70.63[f]	68.74[f]	135.07	117.71	72.71, 72.84, ~4.07 (CH$_2$ of Ph)[f], ~138.7(m) (C of Ph), ~129.0(m) (CH of Ph).
(β)[e]	100.02								

a Chemical shifts in p.p.m.; b In CDCl$_3$ with reference to Me$_4$Si; c Two anomers were clearly present in this spectrum but the minor resonances could not be measured accurately; d The resonances due to C-2 and C-5 are interchangeable; e The assignment of α and β resonances were made on the basis of the difference in their relative intensities in this spectrum; f This assignment is interchangeable.

intermediate that can be generated from dimethyl sulphoxide and sodium hydride is known to react with benzyl chloride to give stilbene[29] **(99)**. However, negligible concentrations of the methylsulphinyl carbanion are expected under the conditions that this particular benzylation experiment was conducted, and a loss in efficiency due to stilbene formation was not in fact observed.

$$H_3C-\overset{\overset{\ominus}{|}}{\underset{\overset{\parallel}{O}}{S}}-CH_2$$

98

$$C_6H_5 \underset{H}{\overset{}{C}} = \underset{C_6H_5}{\overset{H}{C}}$$
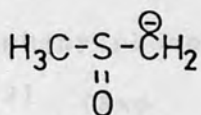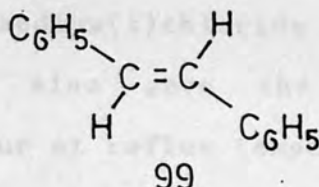
99

The success of the sodium hydride benzylation method depended on the manner in which the experiment was conducted. The benzyl chloride had to be added dropwise to the vigorously stirred and cooled polyalkoxide sodium salt; if the reaction mixture was not well stirred, or the benzyl chloride was added too quickly, the temperature of the reaction mixture increased dramatically and destroyed the carbohydrate.

Allyl arabinofuranoside **(91)** was converted (Exp. 16) by the sodium hydride-benzylation method[28] into the corresponding benzylated derivative **(92)**. A sample of this syrupy product was obtained by chromatography for analysis. The ^{1}H and ^{13}C nmr data

(Table 3.3) were as expected for this compound. The allyl derivative **(92)** was refluxed for ~ 30 min. with potassium tert-butoxide in dimethyl sulphoxide[20] to obtain the isomerised prop-1-enyl derivative **(93)** (Exp. 17.1). A sample of the syrupy product was obtained by flash chromatography for analysis. [13]C Nmr (Table 3.3) and ^{1}H nmr data indicated that the allyl derivative **(92)** had been converted into the prop-1-enyl analogue **(93)**. Treatment of **(92)** with tris(triphenylphosphine)rhodium(1)chloride in ethanol-water[30,31] (Exp. 17.2) also gave the isomerised compound **(93)** within 1 hour at reflux temperature.

The free sugar **(7)** was obtained by dilute mineral acid hydrolysis (Exp. 18) of the prop-1-enyl derivative[22] **(93)**. The product **(7)** was purified by crystallisation and had physical properties identical to those of 2,3,5-tri-O-benzyl-L-arabinofuranose **(7)** prepared via the methyl glycoside[23] **(89)**. It follows that the structures assigned to the derivatives **(91)**, **(92)** and **(93)** via which the well characterised benzylated arabinofuranose **(7)** was obtained must also be correct.

It was envisaged that the synthesis of 2,3,5-tri-O-benzyl-D-ribofuranose **(103)** might be possible using a similar strategy as that employed for the L-arabinose analogue **(7)** i.e. via the allyl ribofuranoside **(100)** rather than the methyl analogue

104

TABLE 3.3

ASSIGNMENT OF SIGNALS[a] IN PROTON DECOUPLED ^{13}C N.M.R. SPECTRA OF 2,3,5-TRI-O-BENZYL-L-ARABINOFURANOSE AND ITS PRECURSORS: COMPOUNDS (89), (88), (91), (92), (93) and (7).

COMPOUND	C-1	C-2[f]	C-3[f]	C-4[f]	C-5	CH_2 phenyl	C1 phenyl	C phenyl	Others
Methyl α,β-L-Araf (89)[c] (α)[e]	109.19	81.62	77.23	84.68	62.05				54.94 (OCH_3)
(β)[e]	103.19	77.23	75.40	82.85	63.96				
Methyl α-L-tri-O-Bn-Araf (88)[b] (α)	107.31	83.43	80.93	88.12	69.83	71.89, 72.12, 75.38	127.6- 128.4(m)	137.56- 138.11(m)	54.94 (OCH_3)
Allyl α,β-L-Araf (91)[c] (α)[e]	109.19	83.56	78.95	86.17	70.63				63.73 (OCH_2), 120.70 ($CH=CH_2$), 136.23 ($CH=CH_2$)
(β)[e]	102.88	78.95	77.39	84.55					
Allyl α,β-L-tri-O-Bn-Araf (92)[b,d] (α)	(106.13)								
(β)	100.02	84.48	81.49	89.16	70.63	72.71, 72.84, 74.07	128.4- 130.4(m)	138.38- 138.91(m)	68.74 (OCH_2), 117.71 ($CH=CH_2$), 155.07 ($CH=CH_2$)
Propenyl α,β-L-tri-O-Bn-Araf (93)[b,d] (α)	106.07	85.50	81.36	87.86	69.42	72.09, 72.15, 75.15	125.96- 130.33(m)	137.5- 138.47(m)	60.36 (CH_3), 104.27 ($CH=CH_3$), 141.84 (OCH)
α,β-L-tri-O-Bn-Araf (7)[b] (α)[c]	101.11	82.82	81.78	86.83	70.81	71.76-	127.5-	137.5-	
(β)	96.18	81.78	80.48	84.02	70.62	73.52(m)	129.8(m)	138.01(m)	

a Chemical shifts in p.p.m.; b In $CDCl_3$ with reference to Me_4Si; c In D_2O with reference to dioxan; d Two anomers were clearly present in this spectrum but the minor resonances could not be measured accurately; e The assignment of α and β resonances were made on the basis of the difference in their relative intensities in this spectrum; f The assignments of C-2, C-3 and C-4 are only tentatively distinguished from each other.

100   R = H , R^1 = CH_2CHCH_2

102   R = $C_6H_5CH_2$, R^1 = CH_2CHCH_2

103   R = $C_6H_5CH_2$, R^1 = H

101   R = $C_6H_5CH_2$,   R = CH_3
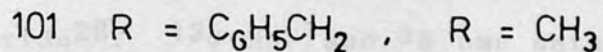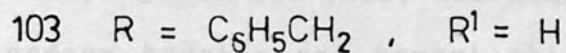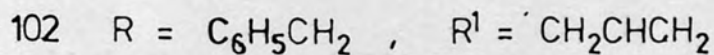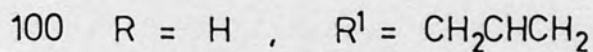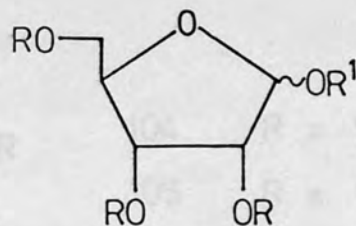
(101).   Thus, an acid catalysed reaction of D-ribose (104) with allyl alcohol (Exp. 20) gave initially the allyl ribofuranoside (100). This kinetic product was obtained in the same manner as the methyl and allyl arabinofuranosides [(89) and (91) respectively], and ^{13}C nmr was used to establish its furanoid ring structure (see previous discussion and Table 3.1). When the acid catalysed reaction of allyl alcohol and D-ribose was performed under reflux for 2 hours (Exp. 19), a product other than the ribofuranoside (100) was suggested by t.l.c. to have formed. This syrupy product was not characterised fully, but ^{13}C nmr data indicated that it was mainly a mixture of α- and β- allyl ribopyranosides (105) (see earlier discussion and Table 3.1).

106
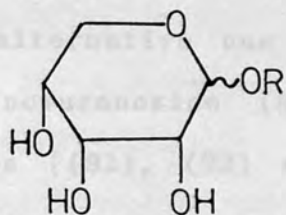
104   R = H
105   R = CH_2CHCH_2

The allyl glycoside (100) was benzylated (Exp. 21)
using sodium hydride and benzyl chloride in dimethyl
sulphoxide[28]. ^{13}C Nmr and ^{1}H nmr data of the product
of this reaction indicated that it was the benzylated
analogue (102). The allyl glycoside (102) was treated
(Exp. 22) with palladium/activated charcoal and
p-toluenesulphonic acid[32], to cleave the allyl group
and thus obtain the free ribose derivative (103). In
order to minimise debenzylation possible with
prolonged periods of treatment with acid, a tenfold
reduction of acid to that originally reported in this
method was used[33]. The syrup obtained in this way had
an optical rotation identical to that reported for
2,3,5-tri-O-benzyl-D-ribofuranose[16] (103). It follows
that the structures proposed for the new intermediates
(100) and (102) must also be correct, as they are
precursors of the known derivative (103).

Although only relatively small scale preparations
of 2,3,5-tri-O-benzyl arabinofuranose (7) were carried
out via the allyl arabinofuranoside (91), this route

(see Scheme 3.2) appears to be more convenient than the alternative one (see Scheme 3.1) via the methyl arabinofuranoside (89). None of the intermediate syrups [(91), (92) and (93)] need to be isolated in practice, as the required compound (7) could easily be purified by crystallisation at the end of the sequence of reactions.

The sodium hydride used in the benzylation of the allyl glycoside (91) was expected to promote isomerisation of the allyl to the prop-1-enyl group. However, no isomerised product (93) was obtained directly from the allyl derivative (91) under these particular experimental conditions (Exp. 16). The ineffectiveness of sodium hydride in the catalysis of this isomerisation was viewed to be related in some part to its insolubility. It was envisaged that this problem might be overcome by converting sodium hydride into the soluble sodium methylsulphinyl carbanion (106). Thus, (106) was prepared from sodium hydride and dimethyl sulphoxide[29] and cooled to room

$$H_3C - \overset{\ominus}{\underset{\overset{\parallel}{O}}{S}} - \overset{\ominus}{C}H_2 \qquad M^{\oplus}$$

106 M = Na

107 M = K
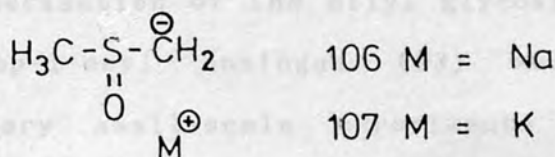
temperature. Benzylation of the allyl glycoside (91)

was conducted in the previous manner but with this alternative base (106) in place of sodium hydride (Exp. 24.1). T.l.c. analysis of the reaction mixture indicated that the allyl compound (91) had been converted to the benzylated analogue (92) within five hours. However, the examination showed no sign of any prop-1-enyl derivative (93) over a period of twenty hours. This experiment was repeated, and the temperature of the reaction medium was raised to between 60°-70° after having obtained the benzylated derivative (92) in the same medium at room temperature (Exp. 24.2). T.l.c. analysis of the reaction mixture indicated that these more vigorous conditions (over ~ 6 hours) had also failed to promote any isomerisation.

The methylsulphinyl carbanion can be generated from a number of alternative bases. Each of these reagents is reported to promote the alkylation of carbohydrates, although their relative effectiveness is in some dispute[34,35]. The possibility that the methylsulphinyl carbanion generated from potassium tert-butoxide might promote simultaneous benzylation and isomerisation of the allyl glycoside (91) to give the prop-1-enyl analogue (93) was investigated. Preliminary small-scale experiments confirmed that this transformation could be achieved under these conditions. Thus, the potassium methylsulphinyl carbanion (107) was generated from potassium tert

butoxide and dimethyl sulphoxide, and benzylation of the allyl glycoside (91) was performed employing this alternative reagent (exp. 24.3). T.l.c. analysis of the reaction mixture after five hours indicated that only the prop-1-enyl derivative (93) was present. Acid hydrolysis of the unpurified products of this reaction (Exp. 24.3) gave the known free sugar (7). It is difficult to predict how effective this benzylation-isomerisation step would be when used in the conversion of larger amounts of the allyl glycoside (91) to the prop-1-enyl analogue (93), but it appears that the synthesis of the free sugar (7) might be improved further by introducing this alternative step.

3.2   Arabinofuranose aglycon precursors.

3.21   Introduction and strategy.

A general approach through which to rationalise
the chemical synthesis of oligosaccharides is a "block
synthesis"[36]. This strategy involves joining together
composite fragments of the target molecule, rather
than sequentially linking each separate unit one at a
time.   It is possible to formulate a scheme of this
type for a synthesis of the oligosaccharide fragment
(3), and such an approach is depicted in Figure 3.1.
Thus, the four unit fragment (V) is constructed from a
pair of two unit segments (IVA) and (IVB).   These are
derived from the two unit segments IIIA and IIIB
respectively.   (IIIA) and (IIIB) are made by the
coupling of precursor (II) with precursors (IIA) and
(IIB) respectively.   Deprotection of fragment (V) will
give the target molecule (3).   Essential to the
success of this route is a stereoselective method for
making β-arabinofuranosyl linkages [steps (i), (ii)
and (v) - see Chapters 2 and 4] three of which are
present in the target molecule (3).   Another important
requirement are the three precursors (II), (IIA) and
(IIB), the first pair derived from L-arabinose and the
last one from trans-4-hydroxy-L-proline (see Chapter
3.4 for synthesis of hydroxyproline derivatives).

X = activating group

R = persistent protecting group

R¹ and R² = temporary protecting groups
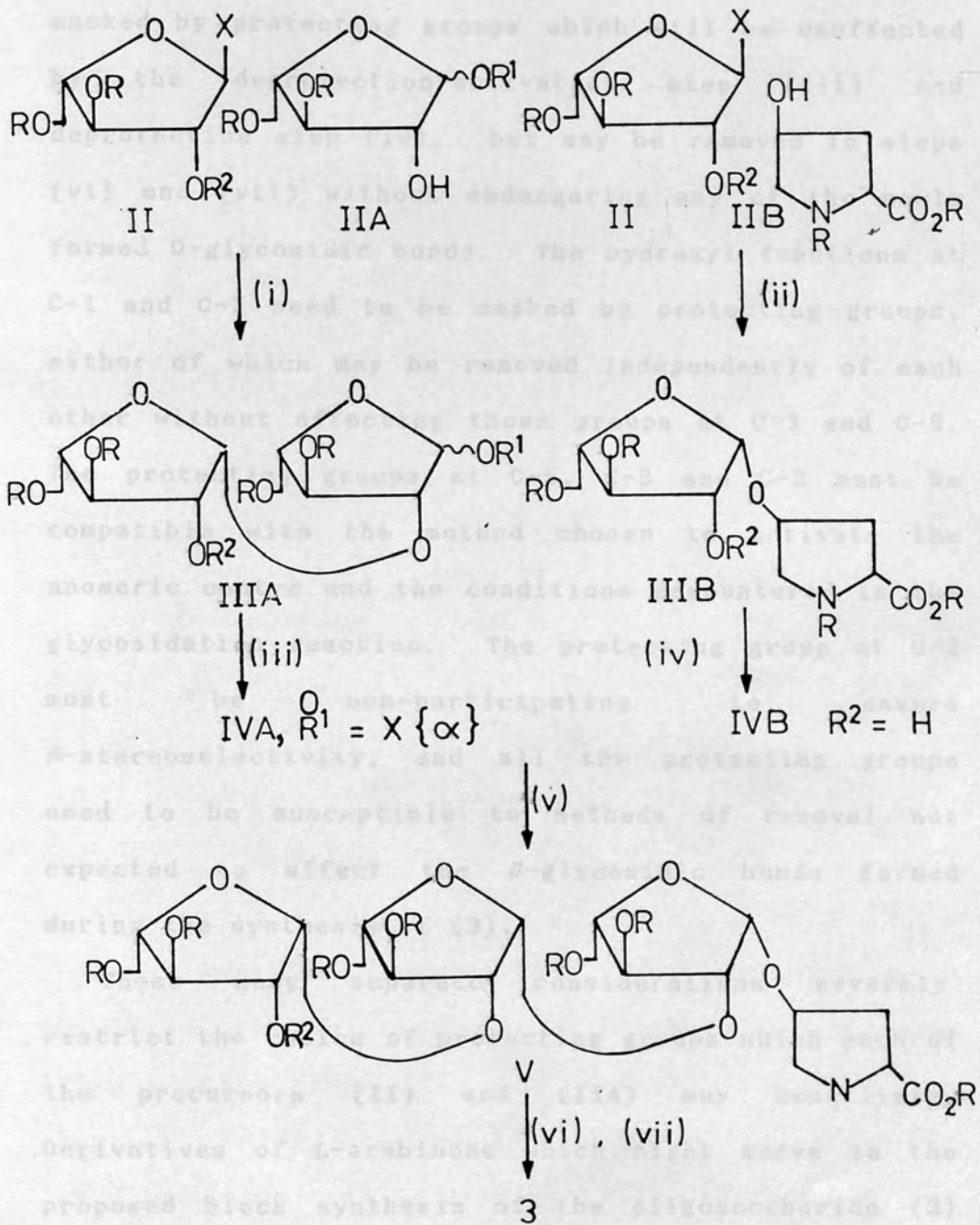
FIGURE 3.1 BLOCK SYNTHESIS

The two derivatives of L-arabinose [viz. (II) and (IIA)] must display a number of particular features. The hydroxyl functions at C-3 and C-5 need to be masked by protecting groups which will be unaffected by the deprotection-activation step (iii) and deprotection step (iv), but may be removed in steps (vi) and (vii) without endangering any of the newly formed O-glycosidic bonds. The hydroxyl functions at C-1 and C-2 need to be masked by protecting groups, either of which may be removed independently of each other without affecting those groups at C-3 and C-5. The protecting groups at C-5, C-3 and C-2 must be compatible with the method chosen to activate the anomeric centre and the conditions encountered in the glycosidation reaction. The protecting group at C-2 must be non-participating to ensure β-stereoselectivity, and all the protecting groups need to be susceptible to methods of removal not expected to affect the β-glycosidic bonds formed during the synthesis of (3).

These many separate considerations severely restrict the choice of protecting groups which each of the precursors (II) and (IIA) may constitute. Derivatives of L-arabinose which might serve in the proposed block synthesis of the oligosaccharide (3) are prop-1-enyl 3,5-O-isopropylidene-L-arabinofuranoside (108) and 3-5-O-isopropylidene-2-O-

trichloroethyl-L-arabino furanose (109). It was envisaged that these derivatives could be obtained from L-arabinose by the routes shown in Scheme 3.3.

SCHEME 3.3
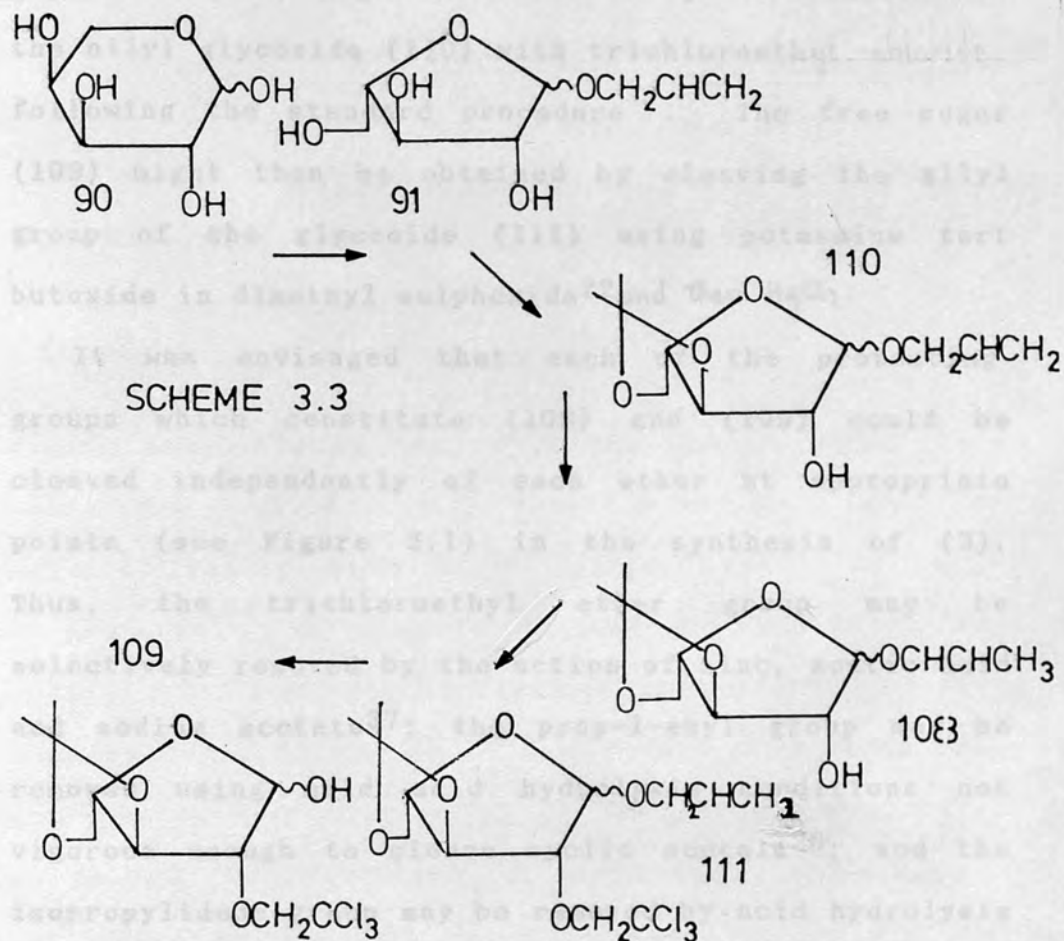
Thus, allyl-L-arabinofuranoside (91) can be made through a Fischer reaction of L-arabinose (90) and Allyl alcohol (Exp. 10). It was expected that the allyl glycoside (91) could be converted into the 3,5-0-isopropylidene derivative (110) using one of the several standard methods[8]. A base catalysed isomerisation[20] of this allyl glycoside (110) was

expected to give the prop-1-enyl analogue (108).

It was envisaged that the 2-O-trichloroethyl glycoside (111) might be obtained by the reaction of the allyl glycoside (110) with trichloroethyl chloride following the standard procedure . The free sugar (109) might then be obtained by cleaving the allyl group of the glycoside (111) using potassium tert butoxide in dimethyl sulphoxide[22] and then $HgCl_2$.

It was envisaged that each of the protecting groups which constitute (108) and (109) could be cleaved independently of each other at appropriate points (see Figure 3.1) in the synthesis of (3). Thus, the trichloroethyl ether group may be selectively removed by the action of zinc, acetic acid and sodium acetate[37]; the prop-1-enyl group may be removed using mild acid hydrolysis conditions not vigorous enough to cleave cyclic acetals[20]; and the isopropylidene group may be removed by acid hydrolysis conditions not severe enough to disrupt O-glycosidic bonds[38].

3.22   Results and discussion.

The synthesis of allyl 3,5-O-isopropylidene-L-arabinofuranoside (110) was achieved by reacting allyl-L-arabinofuranoside (91) with 2,2-dimethoxy-

propane in the presence of a trace of dry p-toluenesulphonic and (Exp 25). One advantage of this method over more traditional methods of making
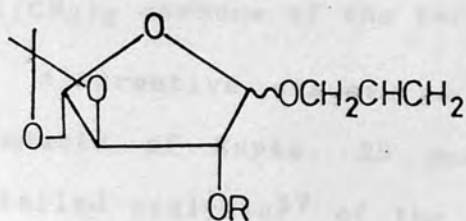
110 R = H

112 R = $(CH_3)_3CSi$ with CH_3, CH_3

cyclic acetals[8], is that problems due to adventitous water are reduced; 2,2 dimethoxypropane (used as solvent) reacts with water to give volatile, inert by-products. A sample of the product (110) was obtained for analysis by flash chromatography and gave mass spectral ^1H nmr and ^{13}C nmr data consistent with the proposed structure. Of particular diagnostic value are the resonances in the proton decoupled ^{13}C nmr spectrum of (110) at ~ 26 ppm and ~ 110 ppm corresponding respectively to the CH_3 and C carbons of the isopropylidene group.

The 2-0-tert butyldimethylsilyl analogue (112) of the isopropylidene derivative (110) was made (Exp. 26) by the standard method[8], to provide further evidence for the characterisation of (110). Mass spectral ^1H nmr and ^{13}C nmr data of a sample obtained pure by chromatography were consistent with the

proposed structure of the tert-butyldimethylsilyl derivative (112). Of particular diagnostic value are the resonances in the proton decoupled ^{13}C nmr spectrum of (112) at ~ 18 ppm corresponding to the $Si(CH_3)_2$ carbons of the tert-butyldimethylsilyl group.

Alternative structures may be proposed for the products of Expts. 25 and 26 on the basis of a detailed analysis[57] of the ^{13}C nmr chemical shifts of the acetal groups. In particular the chemical shifts of the acetal carbon atoms, and the differences between the chemical shifts of the acetal methyl carbon atoms, suggest a 1,3-dioxolane structure. This could imply that these products are pyranoid

110*   R = H

112*   R = $(CH_3)_3CSi$ with CH_3, CH_3 substituents
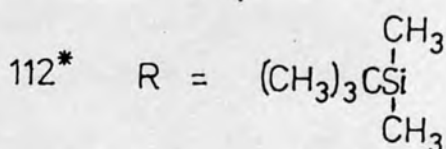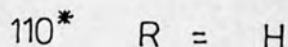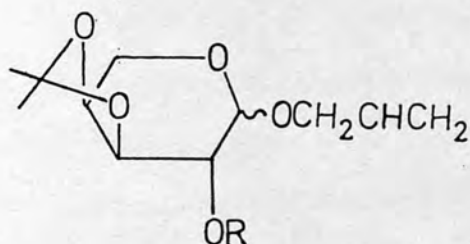
derivatives (110b*, 112b*) in which the acetal rings bridge carbon atoms 3 and 4 and which result after ring expansion under the acidic reaction conditions. On the other hand, the chemical shifts and splittings of the anomeric protons are more consistent with furanoid structures (110: δ 4.51ppm, $J_{1,2}$ 4.6Hz; δ 4.53, $J_{1,2}$ 5.4Hz; 1H, α-H1 and β-H1; 112: δ 4.70, $J_{1,2}$ 3.4Hz; 0.3H, α-H1 or β-H1). Clearly, a conclusive assignment of ring size cannot be made with the present data.

3.3   Chlorosulphonyl derivatives.

3.31   Introduction and strategy.

Glycopyranosyl chlorides bearing the chlorosulphate protecting group have been employed in several stereoselective 1,2-cis-glycoside syntheses. For example, 2,3,4-tri-O-chlorosulphonyl-β-D-xylopyranosyl chloride was reacted under modified Koenigs-Knorr conditions with 1,2,3,4-tetra-O-acetyl-β-D-mannopyranose to give, after deacylation, 6-O-[α-D-xylopyranosyl]D-mannopyranose[40]. More recently, 2,3,4-tri-O-chlorosulphonyl-β-D-L-fucopyranosyl chloride was reacted with methanol under Koenigs-Knorr conditions to give methyl 2,3,4-tri-O-chlorosulphonyl-α-L-fucopyranoside[41].

It appears that the chlorosulphonyl group does not assist anchimerically in the substitution reactions of per-O-chlorosulphonyl glycosyl chlorides. It follows that derivatives of this kind might be useful alternatives to the per-O-benzyl glycosyl halides more usually employed in synthesis of 1,2-cis-glycosides. An additional feature of the chlorosulphonyl group which makes it suitable for protecting the glycon in a glycosidation reaction is its susceptibility to removal using sodium iodide in aqueous methanol[42]. Thus, deprotection to give the corresponding hydroxyl

functions can be conveniently achieved without endangering any O-glycosidic bonds. A further practical advantage is that per-O-chlorosulphonyl glycosyl chlorides can in some cases be obtained directly in one step by the reaction of a reducing sugar with sulphuryl chloride[43]. Thus, 2,3,4-tri-O-chlorosulphonyl-β-D-xylopyranosyl chloride was obtained from D-xylose and sulphuryl chloride under the appropriate reaction conditions[44]. D-Lyxose gives 2,3,4-tri-O-chlorosulphonyl-α-D-lyxopyranosyl chloride on similar treatment[45]. In each case ^1H nmr data indicated only one anomeric product. Apparently, anomerisation does not occur to any observable extent under these reaction conditions. This allows a controlled synthesis of single anomers in these two cases.
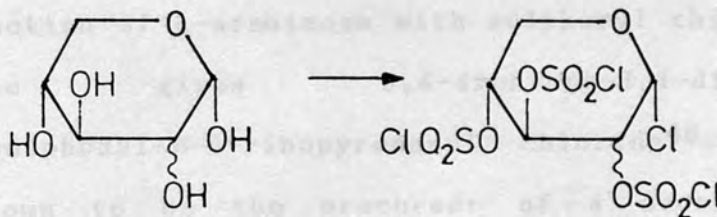
It was considered that 2,3,5-tri-O-chlorosulphonyl-α-D-arabinofuranosyl chloride (114), if it could be synthesised, might possibly provide an alternative to the corresponding per-O-benzylated

derivative (113a). Although 2,3,5-tri-0-benzyl-α-L-arabinofuranosyl chloride (113a) is an obvious precursor for the synthesis of 1,2-cis-arabinofuranosides (see chapter 2.3), the original procedure reported[16] for the synthesis of the precursor (7) of the glycon (113a) involves several steps and is relatively inefficient (see Chapter 3.1). It was envisaged that the per-0- chlorosulphonyl derivative (114) might be more convenient to synthesise than the per-0-benzyl analogue (113a).

113a   R = $C_6H_5CH_2O$

114   R = $ClSO_2O$
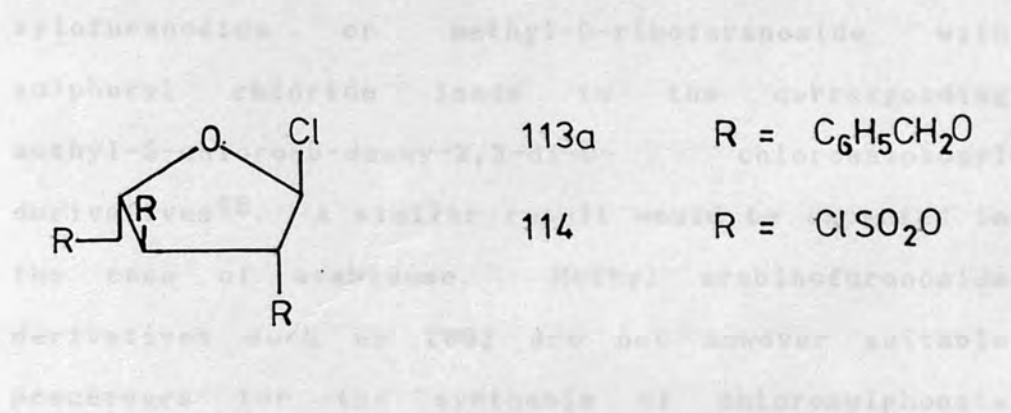
The reaction of L-arabinose with sulphuryl chloride in pyridine gives 3,4-dichloro-3,4-dideoxy-2-chlorosulphonyl-β-D-ribopyranosyl chloride[46]. This was shown to be the precursor of a second minor product formed in this reaction. Crystalline 3,4-dichloro-2,3,4-trideoxy-β-D-glycero-pent-2-enopyranosyl-3,4-dichlor-2,3,4-trideoxy-β-D-glycero pent-2-eno pyranoside was suggested to be formed by way of an intermediate pyridinium glycoside[47]. It appears that unprotected pentoses, on reaction with

sulphuryl chloride, lead preferentially to various pyranoid derivatives. It follows that the furanoid form of arabinose must be established in some way prior to any reaction with sulphuryl chloride.

The furanoid form of pentoses is commonly fixed by converting the free sugar into the corresponding methyl glycoside using a Fischer reaction and isolating the furanoside products before the thermodynamic pyranoside products are formed (see Chapter 3.1). However, reaction of methyl-D-xylofuranoside or methyl-D-ribofuranoside with sulphuryl chloride leads to the corresponding methyl-5-chloro-5-deoxy-2,3-di-0- chlorosulphonyl derivatives[48]. A similar result would be expected in the case of arabinose. Methyl arabinofuranoside derivatives such as (89) are not however suitable precursors for the synthesis of chlorosulphonate derivatives of the type (114), as the acid hydrolysis conditions required to remove the methyloxy group at C-1 of (115) would also be expected to remove the chlorosulphonyl groups at C-2 and C-3. In addition, the 5-chloro-5-deoxy group in analogue (115) would eventually have to be reconverted to a hydroxyl group, thus further reducing the attractiveness of this precursor.

116    $R = R^1 = H$, $R^2 = (C_6H_5)_3CO$

122    $R = R^1 = CH_3CO$, $R^2 = (C_6H_5)_3CO$

123    $R = R^1 = C_6H_5CO$, $R^2 = (C_6H_5)_3CO$

115    $R = ClSO_2$, $R^1 = CH_3$, $R^2 = Cl$

89    $R = R = H$, $R = CH_3$
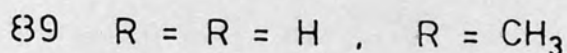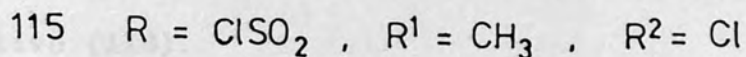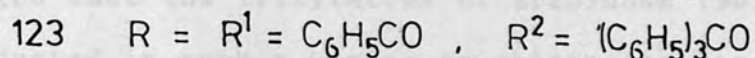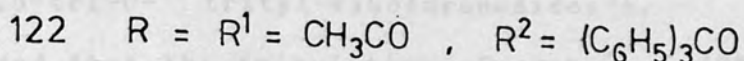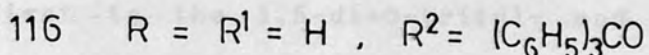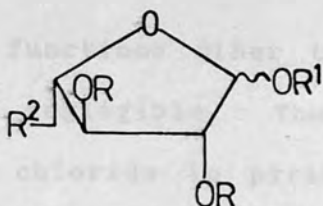
Another conceivable way of establishing the furanoid form of L-arabinose would be to take advantage of the structural difference which exists at C-5 between the two cyclical forms of pentoses; in the pyranose form of arabinose C-5 is endocyclic whereas in the furanose form it is exocyclic. Thus the furanose form of arabinose might possibly be fixed prior to a reaction with sulphuryl chloride by temporarily protecting its C-5 hydroxyl function. It was considered that this might be achieved through the use of the bulky triphenylmethyl (or "trityl") group, which reacts preferentially (for steric reasons) with primary hydroxyl functions in polyhydroxy compounds[8,49]. Vigorous conditions have in some cases led to tritylation of alternative hydroxyl functions[50], but the rate at which trityl chloride

reacts with hydroxyl functions other than at primary positions, is usually negligible. Thus, reaction of D-ribose with trityl chloride in pyridine gives the 5-O-trityl derivative[51]. More vigorous conditions lead first to the 1,5-di-O-trityl- and then to the 1,3(2),5-tri-O- trityl-ribofuranosides[52]. It was envisaged that the tritylation of arabinose (90) could be conducted in such a way as to obtain the monotrityl derivative (116).

90   116 R = $(C_6H_5)_3C$
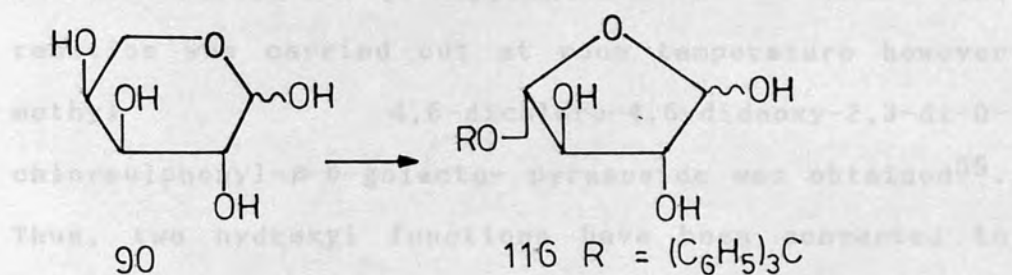
The likelihood of 5-O-trityl 2,3-di-O-chlorosulphonate arabinofuranosyl chloride being formed from the reaction of the 5-O-trityl derivative (116) with sulphuryl chloride is difficult to predict. Although the reactions of carbohydrates with sulphuryl chloride have been studied extensively[53] the investigations have been conducted almost exclusively on pyranoid derivatives. This work has helped to establish the stereochemical principles involved in the various transformations of pyranoid sugars, and

has made available a convenient and effective preparation of several useful sugar derivatives. This evidence suggests that the outcome of the treatment of 5-0-trityl-arabinofuranose (116) with sulphuryl chloride will depend crucially on the chosen reaction conditions[54]. For example, when methyl glucopyranoside (117) was treated with sulphuryl chloride and pyridine in chloroform solution at -70°, and the reaction mixture acidified at -30°, the product isolated was methyl 2,3,4,6-tetra-0-chlorosulphonyl-β-D-glucopyranoside[42]. When the reaction was carried out at room temperature however methyl 4,6-dichloro-4,6-dideoxy-2,3-di-0-chlorsulphonyl-β-D-galacto- pyranoside was obtained[55]. Thus, two hydroxyl functions have been converted to chlorosulphonyl groups, and two replaced by chlorine atoms, the ring hydroxyls being replaced with inversion of configuration.

Reaction of methyl 2,3,4,6-tetra-0-chlorosulphonyl-β-D-glucopyranoside (118) with one mole of chloride ion (pyridinium chloride or n-Bu$_4$NCl) yielded methyl 6-chloro-6-deoxy-2,3,4-tri-0-chlorosulphonyl-β-D-glucopyranoside (120). Reaction of the tetra-0 or tri-0 chlorosulphonyl glucoside derivatives [(118) and (120) respectively] with excess chloride ion gave methyl-4,6-dichloro-4,6-dideoxy-2,3-di-0-chlorosulphonyl-β-D-galactopyranoside

(119). Thus, it appears that the chlorodeoxy groups

117   R = R^1 = HO

118   R = R^1 = ClSO$_2$O

120   R = ClSO$_2$O , R^1= Cl

119

R = ClSO$_2$

156

are formed with inversion through a secondary
bimolecular displacement of certain chlorosulphonyl
groups, by chloride ions liberated during the
chlorosulphation. The primary chlorosulphonyl group
is most easily displaced, as is expected for a
nucleophilic substitution process. The fact that the
chlorosulphonyl group at C-4 is preferentially
displaced relative to those at C-3 and C-2, is
paralleled in the displacements of mesyl or tosyl
groups. It appears that replacement of anomeric
hydroxyl functions by a chloro-group occurs by way of

an intermediate 1-O-chlorosulphonyl ester, which results in an overall inversion of configuration. The displacement of 1-O-chlorosulphonyl groups is extremely facile, and only the corresponding chloro sugars have ever been isolated.

In contrast to the displacement process at carbon which occurs in these reactions, a different type of process is also possible. For example, methyl 4,6-dichloro-4,6-dideoxy-3,4-di-O-chlorosulphonyl-β-D-glucopyranoside (119) reacted with excess pyridine to give the corresponding 2,3-cyclic sulphate (156)[56]. This product is formed with retention of configuration at C-2 and C-3. Presumably one of the chlorosulphonyl groups is hydrolysed with S-O bond scission and hence with retention of configuration. The free hydroxyl group so formed then attacks the remaining chlorosulphonyl group with C-Cl bond scission to give the cyclic sulphate; the groups at C-2 and C-3 are equatorially orientated, and are favourably disposed for a cyclisation process to occur.

It was envisaged that the synthesis of 2,3-di-O-chlorosulphonyl-5-O-triphenylmethyl-α-L-arabinofuranosyl chloride (121) might be possible by the sequence of reactions depicted below. Thus, L-arabinose (90) would be converted to 5-O-trityl-L-arabinofuranose (116) in a first step and

chloride under the appropriate conditions would give the glycosyl chloride (121) in a second step.

HO — O
QH ᵔOH
90   ÖH
$\longrightarrow$
O
QH ᵔOH
RO
116 ÖH
$\searrow$
O   Cl
OR¹
RO
121   ÖR¹

$R = (C_6H_5)_3C$, $R^1 = ClSO_2$
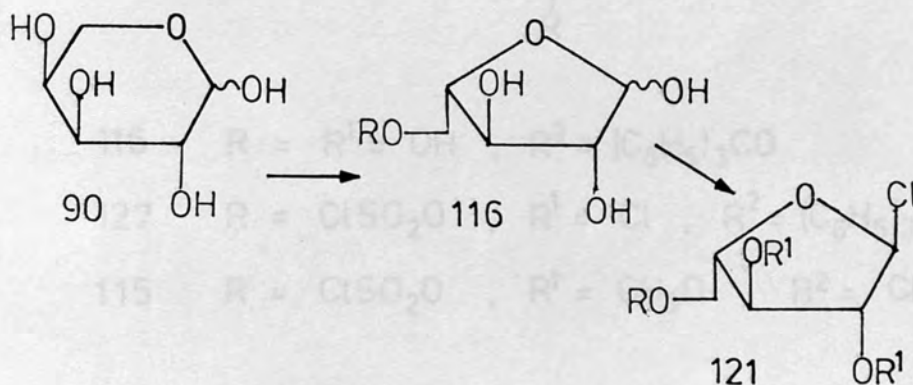
3.32   Results and discussion.

L-arabinose was treated with triphenylmethyl chloride in pyridine (Exp. 27). T.l.c. analysis of the reaction mixture indicated that all the starting sugar had disappeared within 4h at 55° to give a fast moving component. Although it was difficult to extract all traces of pyridine from the syrupy product, a portion of this syrup was purified by flash chromatography and was shown by ^{13}C nmr spectroscopy to be the expected monotrityl derivative (116).
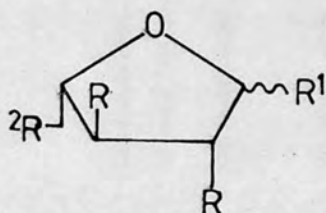
116     $R = R^1 = OH$, $R^2 = (C_6H_5)_3CO$

127     $R = ClSO_2O$, $R^1 = Cl$, $R^2 = (C_6H_5)_3CO$

115     $R = ClSO_2O$, $R^1 = CH_3O$, $R^2 = Cl$

Its furanoid ring structure was suggested by the chemical shifts of the sugar ring carbon resonances in its proton decoupled ^{13}C nmr spectrum (see Table 3.4 and earlier discussion Chapter 3.1). These all occurred at above ~ 80 ppm and are about 5 ppm downfield for those typically obtained[24,25] from the pyranoid analogues (~ 75 ppm or lower). Furthermore, a downfield shift of ~ 6 ppm of the C-5 ^{13}C nmr resonance in (116) compared with that of L-arabinofuranose (90) is indicative of O-alkylation having occurred at this carbon. The ^{13}C nmr resonances from the trityl carbons occurred at ~ 127 ppm and ~ 143 ppm, but were obscured by signals which indicated contamination by pyridine. In order to

TABLE 3.4

ASSIGNMENT OF SIGNALS[a] IN PROTON DECOUPLED ^{13}C N.M.R. SPECTRA OF 5-O-TRIPHENYLMETHYL PENTOFURANOSE AND DERIVATIVES: COMPOUNDS (116), (122), (123), (125) and (126).

COMPOUND[f]	C-1	C-2[g]	C-3[g]	C-4[g]	C-5	C-Trityl	-Cl-Phenyl	OTHERS
5-O-Tr-L-Araf (116)[c,e]	105.97	86.68 85.16	81.48	89.99	68.37	( )[d]	~132.0(m)	
5-O-Tr-1,2,3-tri -O-Ac-L-Araf (122)[b]	99.49, 95.69	75.56 74.40	80.64 77.01	83.59 81.11	62.75 64.40	143.69 143.73	127.09- 128.96(m)	169.36-169.89(m) (C,acetyl) ~20.8(m) (CH₃,acetyl)
5-O-Tr-1,2,3-tri -O-Bz-L-Araf (123)[b]	96.51	82.39	80.44	84.48	59.70	138.78, 139.36	127.04- 128.50(m)	159.91-160.11(m) (C,benzoyl)
5-O-Tr-1,2,3-tri -O-Ac-D-Ribf (125)[b,e]	98.55	76.51	70.82 74.55	86.77 80.90	63.19	~143.69	127.12- 128.68(m)	169.40-169.64(m) (C,acetyl) ~20.5(m) (CH₃,acetyl) 29.70, 130.14, 133.54
5-O-Tr-1,2,3-tri -O-Bz-D-Ribf (126)[b,e]	99.55, 95.18	77.29 75.18	71.54 72.31	84.39 81.56	65.49 63.88	143.49, 143.77	127.02- 129.9(m)	164.92-165.65(m) (C,benzoyl) 135.31, 135.55

a Chemical shifts in p.p.m.; b In CDCl₃ with reference to Me₄Si; c In DMSO-D₆ with reference to Me₄Si; d Obscured by pyridine; e Contaminated by pyridine; f Mixtures of α- and β- anomers; Tr = Triphenylmethyl, Ac = acetyl, Bz = benzoyl; g The assignments of C-2, C-3 and C-4 are only tentatively distinguished from each other.

further characterise the monotrityl derivative (116) it was separately acetylated (Exp. 28) and benzoylated (Exp. 29) by the standard methods[8] to obtain, after flash chromatography, the two fully protected ester analogues [(122) and (123) respectively]. Both these derivatives gave mass spectra ^{1}H nmr and ^{13}C nmr spectra (Table 3.4) consistent with their proposed structures.

124	R = H ,	R^1 = (C$_6$H$_5$)$_3$C
125	R = CH$_3$CO ,	R^1 = (C$_6$H$_5$)$_3$C
126	R = C$_6$H$_5$CO ,	R^1 = (C$_6$H$_5$)$_3$C
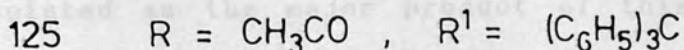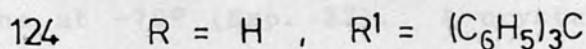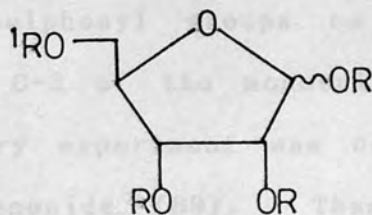
It was considered that the corresponding D-ribose analogues [(124), (125) and (126)] would provide an interesting comparison, and their synthesis was undertaken. Thus, D-ribose was treated with triphenylmethyl chloride in pyridine for 4h at ~ 50° (Exp. 30) to give the monotrityl derivative (124), which was not fully characterised. This syrup was separately acetylated (Exp. 31) and benzoylated (Exp.

32) in the standard way to obtain the corresponding fully protected ester derivatives [(125) and (126) respectively] after flash chromatography. Mass spectra and ^{13}C nmr data (Table 3.4) indicated that these two compounds were the tri-O-benzoyl (125) and tri-O-acetyl (126) analogues of 5-O-trityl-D-ribofuranose (124).

In order to establish appropriate conditions for introducing chlorosulphonyl groups on the hydroxyl groups at C-2 and C-3 of the monotrityl derivative (116), a preliminary experiment was conducted using methyl-L-arabinofuranoside (89). Thus, the methyl glycoside (89) was treated with sulphuryl chloride in pyridine at -70° (Exp. 33). A crystalline derivative was isolated as the major product of this reaction, and was shown by mass spectroscopy and ^{1}H and ^{13}C nmr spectroscopy to be methyl 5-chloro,5-deoxy-2,3-di-O-chlorosulphonyl-L-arabinofuranoside (115). Especially diagnostic was the proton decoupled ^{13}C nmr resonance at 55.91 ppm (corresponding to the C-5 sugar carbon) which was ~ 6 ppm upfield from resonance of an unprotected C-5 atom. It was not possible to design a set of conditions that gave the tri-O-chlorosulphonyl analogue of the methyl glycoside (89).

The reaction of the monotrityl derivative (116) with sulphuryl chloride was next investigated. Thus, 5-O-trityl-L-arabinofuranose (116) was reacted with

sulphuryl chloride in pyridine for 3h at -70° (Exp. 34). T.l.c. analysis of the reaction mixture indicated that after a further 15h at room temperature, all the monotrityl derivative (116) had disappeared. A simple work up of this mixture gave a syrup which only comprised two new components (of similar mobility on t.l.c.). Addition of ether to this syrup caused it to form a white solid. It was not possible however to isolate this solid product as it turned back to a syrup on filtration. Addition of ether to the syrupy filtrate gave back the white precipitate. An optical rotation and melting point of a small amount of this solid was obtained, but it proved difficult to handle the substance and consequently to make accurate measurements. ^{1}H and ^{13}C nmr data were difficult to obtain as the syrup contained traces of pyridine and was possibly also unstable. As a consequence of these problems, the product could not be characterised with certainty, but was assumed to be the required glycosyl chloride (127) and tested in a reaction with an alcohol. Thus, a portion of the syrupy product (127) was reacted with ispopropanol (used as solvent) in the presence of Ag-Z4A (Exp 35). T.l.c. analysis of the reaction mixture showed no sign of any reaction having occured within 16h at room temperature. However, when a portion of the residue of this experiment was warmed

with aqueous methanol, t.l.c. analysis indicated that a single new component was present (Exp. 35). This product was isolated by flash chromatography, but was difficult to identify on the basis of its proton decoupled ^{13}C nmr spectrum. Elemental analysis of the sample was not possible as the syrup was unstable (^{1}H nmr indicated that substantial decomposition had taken place within a few days).

3.4   Hydroxyproline derivatives.

3.41   *Introduction and strategy.*

Several studies directed at the chemical synthesis of O-glycosides comprising hydroxyamino acids have been reported, the majority of which have been concerned with linking L-serine or L-threonine to various sugar moeities[1]. A basic prerequisite in such syntheses is the temporary protection of the amino and carboxyl functions of the amino acid. The hydroxyl function in aglycons of this type remains free to react with an activated sugar component in glycosidation reactions.

2    $R = R^1 = H$.

129    $R = CH_2CH_3$, $R^1 = C_6H_5CH_2O\overset{O}{\overset{\|}{C}}$

130    $R = CH_3$, $R^1 = C_6H_5CH_2O\overset{O}{\overset{\|}{C}}$

6    $R = C_6H_5CH_2$, $R^1 = C_6H_5CH_2O\overset{O}{\overset{\|}{C}}$
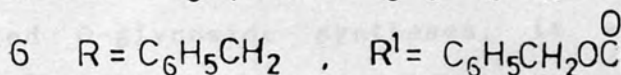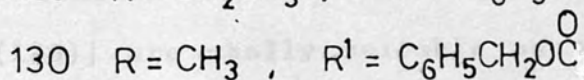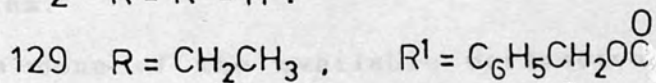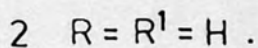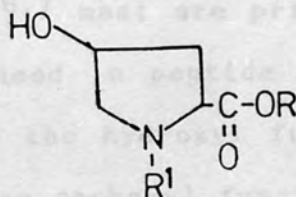
In general, benzyloxycarbonyl groups are used to protect the amino functions, and carboxyl functions are protected by esterification. Trans-4-hydroxy-L-proline (2) must be protected in an analogous fashion before it can serve as a suitable aglycon component in a typical O-glycoside synthesis.

On the occasions when (2) has been derivatised for this purpose, the imino function has been protected with an N-benzyloxycarbonyl group and the carboxyl function with an ethyl group[2] (129), a benzyl group[3,4] (6) or a methyl group[5] (130). These derivatives of hydroxy-L-proline are all syrups. Crystalline derivatives are of greater practical use, in that they are more conveniently purified, dried and handled than syrups. Although several crystalline derivatives of (2) have been prepared[6,7] most are primarily designed to meet a particular need in peptide chemistry. The majority of these have the hydroxyl function together with either the imino or carboxyl functions protected, and are therefore inappropriate for this particular problem.

As none of the available derivatives [(129), (6) and (130)] are wholly suitable as precursors for the envisaged O-glycoside syntheses, it was considered that alternative crystalline aglycons would be of some value, and their syntheses were undertaken.

It was considered that the most appropriate

protective groups would be those susceptible to a method of removal such as hydrogenolysis. Deprotection would then be possible at the end of the O-glycoside synthesis without endangering the newly formed O-glycosidic bond. Several groups of this type are available, including the benzyloxycarbonyl or p-nitro-benzyloxycarbonyl groups for the protection of the imino function, and the phenacyl or diphenylmethyl ester groups for the protection of the carboxyl function[8]. Success would depend on achieving selective reactions of the imino function and then the carboxyl function in the presence of the hydroxyl group at C-4. In addition, it is necessary to avoid making use of conditions in the preparation of these derivatives which are likely to cause epimerisation of the carboxyl function at C-2.

3.42   Results and discussion.

N-benzyloxycarbonyl hydroxy-L-proline (131) has been obtained as a crystalline derivative[9,10]. This compound is however difficult to crystallise[11], and can be more conveniently obtained pure via its cyclohexylammonium salt[12] (132). Thus, (131) was synthesised from (2) via (132) by the reported methods (Exp. 1 and 2). The physical data agreed with those

previously reported for these derivatives.

2   R = R^1 = H

131   R = H ,   R^1 = C$_6$H$_5$CH$_2$OC (=O)

132   R = C$_6$H$_{11}$NH$_3^+$,   R^1 = C$_6$H$_5$CH$_2$OC (=O)

133   R = (C$_6$H$_5$)$_2$CH ,   R^1 = C$_6$H$_5$CH$_2$OC (=O)

134   R = C$_6$H$_5$COCH$_2$,   R^1 = C$_6$H$_5$CH$_2$OC (=O)

135   R = H ,   R^1 = p-NO$_2$C$_6$H$_4$CH$_2$OC (=O)

136   R = (C$_6$H$_5$)$_2$CH ,   R^1 = p-NO$_2$C$_6$H$_4$CH$_2$OC (=O)

137   R = C$_6$H$_5$COCH$_2$,   R^1 = p-NO$_2$C$_6$H$_4$CH$_2$OC (=O)
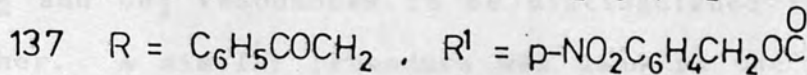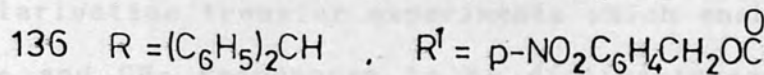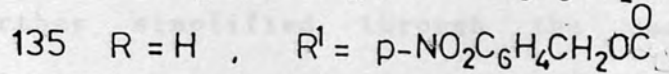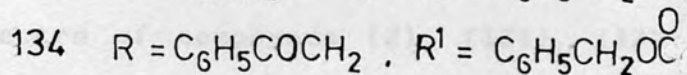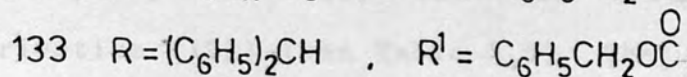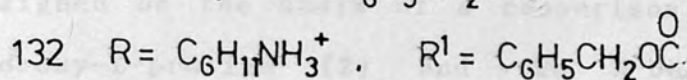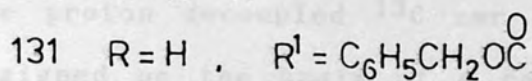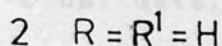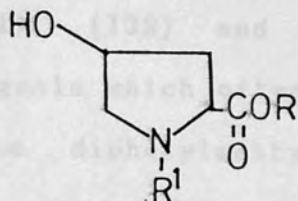
A number of alternative methods are available by which the diphenylmethyl group may be introduced[8]. The original method, involving diphenyldiazomethane was selected[13]. Thus, a solution of (131) in acetone was treated with diphenyldiazomethane (Exp. 4). The reaction mixture was worked up after 15h to give a crystalline solid in ~ 80% yield. Elemental analysis

and ^{13}C nmr data were consistent with the identity of the expected diphenylmethyl ester (133).

The 250 MHz ^{1}H nmr spectra of the imino acid derivatives (131), (132) and (133) comprise many heavily split signals which often overlap. Structural analysis of the diphenylmethyl ester (133) was therefore most conveniently achieved through the use of ^{13}C nmr data. Thus, the resonances which appear in the proton decoupled ^{13}C nmr spectrum of (133) were assigned on the basis of a comparison with those of hydroxy-L-proline (2) and the N-benzyloxycarbonyl derivative (131) (see Table 3.5) The analysis of the spectra of compounds (2), (131), (132) and (133) was further simplified through the use of ^{13}C nmr polarisation transfer experiments which enabled C, CH, CH_2 and CH_3 resonances to be distinguished from each other. A similar procedure was used in the analyses of the ^{13}C nmr spectra of other imino acid derivatives made during this work (see Table 3.5).

The proton-decoupled ^{13}C nmr spectrum of (131) showed that the majority of peaks were closely separated doublets (see Table 3.5) This feature was thought at first to indicate the presence of two isomers, possibly the cis- and trans- forms of 4-hydroxyproline (2). A base catalysed epimerisation at C-2 of the imino acid, if it had occurred during the synthesis of (131), could account for the

TABLE 3.5

ASSIGNMENT OF SIGNALS[i,j] IN PROTON DECOUPLED ^{13}C N.M.R. SPECTRA OF TRANS-4-HYDROXY-L-PROLINE AND DERIVATIVES:

COMPOUNDS (2), (132), (131), (133), (134), (135), (136) and (137)

COMPOUND	Imino Acid Carbons					Diphenylmethyl Group Carbons		
	C3	C5	C2	C4	C=O	$-O-\overset{\mid}{\underset{\mid}{C}}-H$	C	-CH (phenyl)
Hyp (2)[a]	37.43	52.87	59.79	69.96	174.08			
N-BOC-Hyp-Cyclohexylamine salt (132)[b,d]	37.92[g] 38.09	54.17 54.68	59.84 60.13	67.82 68.55	175.04 175.23			
N-BOC-Hyp (131)[b]	37.95 38.14	54.40 54.95	57.39 57.87	67.74 68.52	173.52 173.91			
N-BOC-Hyp-diphenylmethyl ester (133)[b]	37.07 37.69	54.48 54.91	57.56 58.06	67.69 68.47	170.95 171.32	76.80	140.01 140.07	~126.0- 128.0(m)[e]
N-BOC-Hyp-Phenacyl ester (134)[b]	38.01 38.50	54.38 54.80	57.36 57.76	67.65 68.42	171.64 171.97			
N-(pNO2-BOC)-Hyp (135)[b]	38.0 38.96	54.61 55.12	57.52 58.00	67.87 68.65	173.68 174.20			
N-(pNO2-BOC)-Hyp-diphenylmethyl ester (136)[b]	37.75 38.73	54.57 55.07	57.67 58.16	67.80 68.56	170.90 171.43	76.87	~140.0(m)	~123.0- 128.0(m)[f]
N-(pNO2-BOC)-Hyp-Phenacyl ester (137)[c]	38.60 39.36	54.56 55.25	57.79 58.09	69.16 69.93	171.92 172.17			

a In D$_2$O with reference to dioxan; b In DMSO-D$_6$ with reference to Me$_4$Si; c In CDCl$_3$ with reference to Me$_4$Si; d See Experiment 1 for remainder of ^{13}C nmr resonances; e This assignment is interchangeable; f This assignment is interchangeable; g Partially obscured by reference resonances (at ~39.5 ppm); h Two peaks visible, but indistinguishable; i Chemical shifts in p.p.m.; j The observed doubling of certain resonances in these spectra was shown to be as a consequence of hindered rotation about the N-O bond (see discussion, Chapter 3.4 and Table 3.6).

TABLE I Continued Overleaf.

TABLE 3.5 (Continued)

COMPOUND	N-Blocking Group Carbons					O-CH₂-	Benzyl Group Carbons		
	$-C=O$	$O-CH_2$	C	m-o-Cl (phenyl)	p-Cl or CNO_2 (phenyl)	$O-CH_2-$	$-C=O$	C	$-Cl$ (phenyl)
Hyp (2)[a]									
N-BOC-Hyp-Cyclohexylamine salt (132)[b,d]	153.91, 154.39	65.16[h]	~157.0 (m)[e]	~157.0 (m)[e]	~157.0 (m)[e]				
N-BOC-Hyp (131)[b]	153.89, 154.21	65.93	136.85, 136.72	~127.0 - 128.0(m)	128.0(m)				
N-BOC-Hyp-diphenylmethyl ester (133)[b]	170.68, 154.29	66.10[h]	136.36	~126.0 - 128.0(m)[e]	128.0(m)[e]				
N-BOC-Hyp-Phenacyl ester (134)[b]	153.69, 154.24	66.56[h,f]	136.70	~127.0 - 128.0(m)[e]	128.0(m)[e]	66.11[f]	192.42, 192.56	~127.0	~128.0(m)[e]
N-(pNO₂-BOC)-Hyp (135)[b]	153.75, 154.11	65.02[h]	144.92, 144.97[e]	~125.0 - 128.0(m)	147.04, 147.15[e]				
N-(pNO₂-BOC)-Hyp-diphenylmethyl ester (136)[b]	155.35, 154.01	65.06[h]	144.19, 144.60[e]	~125.0 - 128.0(m)[f]	146.70, 146.92[e]				
N-(pNO₂-BOC)-Hyp-Phenacyl ester (137)[c]	154.50, 154.76	65.81, 65.92	144.00[e]	~125.0 - 133.0(m)[f]	147.52[e]	66.23, 66.42	191.58, 192.13	154.19, 154.27	~125.0 - 133.0(m)[f]

formation of such a mixture. Alternatively, it was considered that the observed doublets might indicate the presence of two conformational isomers formed as a result of hindered rotation about the nitrogen carbon bond. This phenomenon is commonly observed in N-acyl derivatives, a simple example being the two methyl signals observed in the spectrum of dimethylformamide.

A ^{13}C nmr experiment was performed at an elevated temperature to confirm that the doublets observed in the proton decoupled ^{13}C nmr spectrum of (131) were due to the presence of two conformational isomers. Thus, all the doublets coalesced when the ^{13}C nmr experiment was performed at 100°, and reappeared on returning to room temperature (see Table 3.6). An alternative explanation involving slow inversion of nitrogen has also been proposed to account for this spectral feature observed in N-acyl derivatives, but is considered less likely.

It proved difficult to make the phenacyl ester (134) by the usual methods i.e. by treating a solution of (131) in ethyl acetate with triethylamine and α-bromoacetophenone under various conditions[13] (Exp. 5.1 and 5.2). A poor yield (~ 30%) of (134) was obtained, and this only after flash chromatography. Elemental analysis and ^{13}C nmr data (Table 3.5) were used to characterise this new crystalline derivative. A more convenient synthesis[14] of (134) was possible

TABLE 5.6

PROTON DECOUPLED ^{13}C N.M.R. SPECTRAL RESONANCES[a]
OF N-BOC TRANS-4-HYDROXY-L-PROLINE WITH TEMPERATURE[d]

N-Benzyloxycarbonyl trans-4-hydroxy-L-proline (151)	Imino Acid Carbons						N-Blocking Group Carbons		
	C-3	C-5	C-2	C-4	$\underset{O}{-C-O-}$	$-\overset{O}{\underset{\parallel}{C}}-$	$-O-CH_2$	$-C-$(phenyl)	$-CH-$(phenyl)
	57.95	54.50	57.39	67.74	157.52	155.89	65.93	136.85	~127.5(m)
303K	58.14	54.95	57.87	68.52	173.91	154.21			
370K	57.82	54.27	57.58	65.57	172.93	153.71	65.57	156.51	~126.5(m)
After cooling from 370 to 303K	57.92	54.47	57.56	67.71	173.48	153.86	65.92	136.80	~127.5(m)
	58.17	54.92	57.84	68.49	173.87	154.17			

a In p.p.m.; b In DMSO-D$_6$ with reference to dioxan (at 59.5 ppm); c Partially obscured by reference resonances; d To show presence of conformational isomers (due to hindered rotation about N-O bond) at room temperature.

using an alternative method which made use of
potassium fluoride. Thus, (131) was reacted with
potassium fluoride and α-bromoacetophenone in
N,N-dimethylformamide (Exp. 5.3). A crystalline
derivative was isolated in ~ 73% yield after a simple
work up of the reaction mixture. Its physical data
were identical to that previously obtained (Exp. 5.1)
for the phenacyl ester (134).

Another way of protecting the imino function of
hydroxy-L-proline is through the p-nitro-
benzyloxycarbonyl group. This N-p-nitrobenzyl-
oxycarbonyl derivative (135) has an advantage over the
alternative benzyloxycarbonyl derivative (131) in that
it can be readily crystallised[15]. Thus, compound
(135) was prepared by treating (2) with p-nitrobenz yl
chloroformate using a modified version of the
procedure previously reported for the synthesis of the
analogue (131). This alternative method (Exp. 6)
proved more convenient than that originally reported[15]
for the synthesis of compound (135), and gave it in an
improved yield (~ 90% compared with 66% obtained
previously). The physical properties of the
N-p-nitro-benzyloxycarbonyl derivative (135) thus
obtained agreed with those previously reported[15].

Treatment of a solution of the
N-p-nitrobenzyloxycarbonyl derivative ((135) in
acetone with diphenyldiazomethane gave the crystalline

143

diphenylmethyl ester **(136)** in ~ 72% yield (Exp. 7).
Elemental analysis and ^{13}C nmr data (Table 3.5) were
consistent with the proposed structure of this new
derivative. The phenacyl analogue **(137)** was made by
the reaction of **(135)** with potassium fluoride and
α-bromoacetophenone in N,N dimethylformamide[14] (Exp.
8). The new crystalline phenacyl derivative (**(137)**
was obtained in 67% yield, and was characterised using
elemental analysis and ^{13}C nmr data (Table 3.5). All
four of the new derivatives **(133)**, **(134)**, **(136)** and
(137) gave hydroxy-L-proline **(2)** (in ~ 90% yield) on
hydrogenolysis using 10% palladium on activated
charcoal in methanol-water at room temperature (Exp. 9).

3.5   References.

1.   A.F. Bochkov and G.E. Zaikov, "Chemistry of
     the O-Glycosidic Bond: Formation and Cleavage"
     Pergamon Press (1979) p 157 and references.

2.   P.D. Fiel and J.R. Vercellotti, Carbohydr.Res.
     31 (1973) 311.

3.   M.K. McNamara and B.A. Stone, Lebensm-Wiss.u.-
     Technol., 14, (1981) 182-187.

4.   A. Allerhand, K. Dill, E. Berman, J.M. Lacombe
     and A.A. Pavia, Carbohydr.Res. 97 (1981)
     331.

5.   A. Strahm, Ph.D. Thesis, Diss. ETH 6423, 1979;
     A. Strahm, Phytochemistry, 20 (1981) 1061.

6.   E. Adams, Int.J.Pept.Protein Res. 9 (1977)
     293.

7.   E. Adams, Int.J.Pept.Protein Res. 8 (1976)
     503.

8.   T.W. Greene "Protective Groups in Organic
     Synthesis", Wiley, 1981.

9.   A.A. Patchet and B. Witkop, J.Am.Chem.Soc.
     79 (1957) 185.

10. W. Grassmann and E. Wunsch,Chem.Ber. 91 (1958)
     462.

11. F.H. Carpenter and D.T. Gish, J.Am.Chem.Soc.
     74 (1952) 3818.

12. E. Baer and R.J. Stedman, Can.J.Biochem.Physiol.
     37 (1959) 583.

13. J.C. Stelakatos, A. Paganou, L. Zervas,
     J.Chem.Soc.(C) (1966) 1191.

14. J.H. Clark and J.M. Miller, Tetrahedron Lett.
     7 (1977) 599-602.

15. F.H. Carpenter and D.T. Gish, J.Am.Chem.Soc.
     74 (1952) 3818.

16. R. Barker and H.G. Fletcher Jr., J.Org.Chem.,
     26 (1961) 4605.

17.   A.H. Haines, Adv.Carbohydr.Chem.Biochem 39
        (1981) 13.

18.   I.J. Prosser, J.Am.Chem.Soc. 83 (1961) 17.

19.   C.C. Price and W.H. Snyder, J.Am.Chem.Soc.
        83 (1961) 1773.

20.   J. Cunningham, R. Gigg and C.D. Warren,
        Tetrahedron Lett. 19 (1964) 1191.

21.   C.M. McCloskey, Adv.Carbohydr.Chem. 12 (1957)
        137.

22.   J. Gigg and R. Gigg, J.Chem.Soc., C, (1966)
        82.

23.   S. Tejima and H.G. Fletcher Jr., J.Org.Chem.,
        28 (1963) 2999.

24.   R.C. Beier and P. Mundy, J.Carb.Chem. 3(2)
        (1984) 253.

25.   R.C. Beier, P. Mundy and G.A. Strobel,
        Can.J.Chem. 58 (1980) 2800.

26.   F.W. Wehrli and T. Wirthlin, "Interpretation
        of Carbon-13 NMR Spectra", Heyden, 1976.

27.   J.B. Stothers, "Carbon-13 NMR Spectroscopy",
        Academic Press, 1972.

28.   T. Iwashiga and S. Hiromichi, Chem.Pharm.Bull
        15(11) (1967) 1803.

29.   E.J. Corey and M. Chaykovsky, J.Am.Chem.Soc.
        84 (1962) 866.

30.   P.A. Gent and R. Gigg, J.Chem.Soc.Chem.Commun.
        (1974) 277.

31.   E.J. Corey and J.W. Suggs, J.Org.Chem., 38
        (1973) 3224.

32.   R. Boss and R. Scheffold, Angew.Chem.Int.Ed.,
        15 (1976) 558.

33.   R. Gigg, Personal Communication, 1985.

34.   J. Finne, T. Krusius and H. Rauvala, Carbohydr.
        Res. 80 (1980) 336.

35.   P.J. Harris, R.J. Henry, A.B. Blakeney,
        B.A. Stone, Carbohydr.Res. 127 (1984) 59.

36. T. Ogawa, H. Yamamoto, T. Nukada, T. Kitajima and M. Sugimoto, Pure and Appl.Chem., 56 (1984) 779; C. Scherch, Acc.Chem.Res., 6 (1973) 184; H. Paulsen, Angew.Chem.Int.Ed.Engl., 21 (1982) 155.

37. R.U. Lemieux and H. Driguez, J.Am.Chem.Soc., 97 (1975) 4069; M. Prystas, L. Kalvoda and F. Sorm, Collection Czechoslov.Chem.Commun, 41 (1976) 1426.

38. R.R. Schmidt and P. Hermentin, Angew.Chem. Int.Ed.Engl., 16 (1977) 48.

39. K.K. Ogilvie, S.L. Beaucage, A.L. Schifman, N.Y. Theriault and K.L. Sadana, Can.J.Chem., 56 (1978) 2768; K.K. Ogilvie, A.L. Schifman and C.L. Penney, Can.J.Chem., 57 (1979) 2230.

40. B. Coxon, H.J. Jennings and K.A. McLauchlan, Tetrahedron, 23 (1967) 2395.

41. J.R. Pougny, P. Sinay and G. Hajdukovic, Carbohydr.Res., 34 (1974) 351.

42. H.J. Jennings and J.K.N. Jones, Can.J.Chem., 41 (1963) 1151.

43. J.K.N. Jones et. al., Can.J.Chem., 40 (1962) 1408.

44. H.J. Jennings, Can.J.Chem., 46 (1968) 2799.

45. H.J. Jennings, Can.J.Chem., 47 (1969) 1157.

46. B. Coxon, Tetrahedron, 23 (1967) 2395.

47. H.J. Jennings and J.K.N. Jones, Can.J.Chem., 43 (1965) 3018.

48. B. Achmatowicz, W.A. Szarek, J.K.N. Jones and E.H. Williams, Carbohydr.Res., 36 (1974) C14-C16.

49. R.L. Whistler and M.L. Wolfrom (eds.), "Methods in Carbohydrate Chemistry", Academic Press, Vol. 2, 1962.

50. R.L. Whistler and J.N. BeMiller (eds.), "Methods in Carbohydrate Chemistry", Academic Press, Vol. 8, 1980.

51. H. Bredereck and E. Berger, Ber.Bunsenges. Phys.Chem., 73B (1940) 956.

52. H. Bredereck and W. Greiner, Chem.Ber., 86 (1953) 717.

53. E. Buncel, Chem.Rev., 70 (1970) 323.

54. H.J. Jennings, J.K.N. Jones, Can.J.Chem., 43 (1965) 2372.

55. J.K.N. Jones, *and H.J. Jennings* Can.J.Chem., 40 (1962) 1408; 41 (1963) 1151; 43 (1965) 2372; 43 (1965) 3018; A.G. Cottre , E. Buncel and J.K.N. Jones, Can.J.Chem., 44 (1966) 1483.

56. J.K.N. Jones, Can.J.Chem., 40 (1962), 1408; 41 (1963) 1151; 43 (1965) 2372.

57. J. Grant Buchanan, A.R. Edgar, D.I. Rawson, P. Shahidi, and R.H. Wightman Carbohydr. Res., 100 (1982) 75 .

CHAPTER 4
GLYCOSYLATION REACTIONS
PART A: PRELIMINARY INVESTIGATION OF SELECTED METHODS.

4.1 General introduction.

The concept of using 2,3,5-tri-O-benzyl-α-L-arabinofuranosyl chloride (113a) as the glycon in stereoselective β-L-arabinofuranoside syntheses has been demonstrated to be sound by various methanolysis studies (see Chapter 2.3).
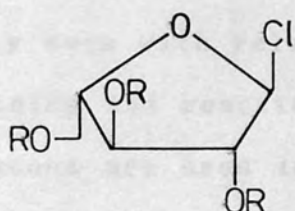
113a R = $C_6H_5CH_2$

These solvolysis reactions have proved to be useful as model systems for investigating the various characteristics of this glycosyl chloride, but they cannot necessarily serve as a general synthetic method; although there is no apparent fundamental

difference between higher and lower alcohols, their reactions with a particular glycon are found in practice to be not equivalent. For example, lower alcohols are in general relatively reactive and can be used in excess or even as the solvent in the majority of glycosidation reactions. In contrast, higher alcohols are considerably less reactive and cannot usually be used in extravagant excess. As a consequence, glycosylation of lower alcohols can be successful even with relatively unreactive glycons or by means of reversible reactions with unfavourable equilibrium constants, whereas glycosylation with higher alcohols under equivalent conditions is usually not successful.

A major shortcoming of the α-arabinofuranosyl chloride (113a) in glycosylation reactions is its low reactivity even with relatively powerful nucleophiles; useful yields and reaction rates can only be achieved when aglycons are used in large excess. Furthermore, longer reaction times and increased reaction temperatures will not necessarily lead to improvements in the efficiency of this reaction as these are also expected to promote decomposition and anomerisation of the glycosyl halide.

A variety of general approaches have been devised in order to accelerate the reactions of alcohols with glycosyl halides (see Chapter 2.1), but the majority

of these are found to be not very stereoselective.
Therefore, the investigation of a number of
alternative glycosidation methods was undertaken with
a view to finding one appropriate for the synthesis of
complex β-L-arabinofuranosides. It was proposed that
the generalities of these methods should first be
studied using the model secondary alcohols isopropanol
and cholesterol. It is difficult to predict how
effective any of these approaches might be in
practice, as the efficiency of a particular
β-arabinofuranoside synthesis depends not only on the
total yield and rate of reaction, but also on its
stereoselectivity.

4.2   Chloride activation.

4.21   *Introduction and strategy.*

Electrophilic metal salts have traditionally been
employed to promote the reactions of glycosyl bromides
and chlorides with alcohols[1]. Their primary role is
to assist in the heterolysis of the halide group, and
thus facilitate attack of the nucleophile on the
glycon[2]. Originally[3], insoluble promoters such as
Ag_2O and Ag_2CO_3 were introduced for this purpose, but
were found to form water during the reaction and

therefore not completely satisfactory. Because the use of solid desiccants such as $CaSO_4$ were found to be only marginally effective in removing this water[1], considerable attention has been paid to the use of alternative soluble promoters such as mercury(II) cyanide in nitromethane or acetonitrile[1,4]. However, although the yields of glycosides using these soluble promoters are good (typically 70-80%), the stereoselectivity is found to be rather poor (often $\alpha:\beta/ \sim 1:1$) and this usually reduces any potential advantage they might have had over insoluble promoters[1].

Recently, interest in insoluble promoters has been again revived, by the introduction of silver silicate[7,8,11] and silver zeolite promoters[5,6,8,10]. It appears that these are considerably more effective than the traditional insoluble salts, in promoting the reactions of glycopyranosyl halides with alcohols. For example[5], in a typical reaction involving supported metal promoters, a mannopyranosyl bromide (138) protected with non-participating groups was mixed with a suitably protected aglycon (139). In the presence of a zeolite supported silver promoter, the corresponding β-glycosides were formed stereoselectively ($\beta:\alpha$ = 9:1; yield $\sim$ 70%) in reaction times of between 2 and 15h at room temperature. The reactions were found to occur much

^2RO ... OR^1 ... RO ... Br ... OR^1

$R^2 = CH_3CO$, $R^1 = C_6H_5CH_2$

140   R = CH_2CHCH_2

141   R = $CH_3CCH_2CH_2C$ $\overset{\parallel}{O}$ $\overset{\parallel}{O}$

142   R = Cl_3CCO

$OCCH_3$ ... HO ... 143 ... N_3
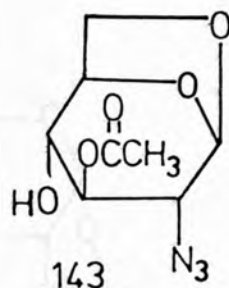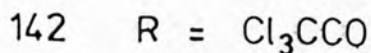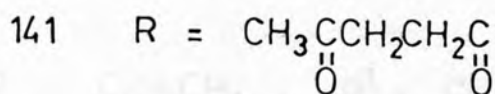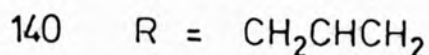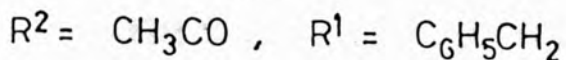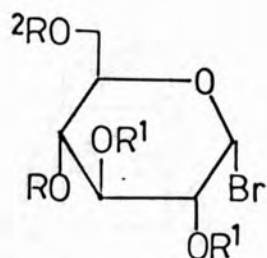
faster using the alternative silver silicate promoter, but with greatly reduced stereoselectivity ($\beta:\alpha = 1:1$; yield $\sim$ 78 %).

In another investigation[8] coupling reactions were performed in the α-D-glucopyranosyl bromide series and the α-D-mannopyranosyl bromide series with various aglycons in the presence of either silver silicate or silver zeolite promoters. For example, in a typical series of experiments the glycosyl bromides [(140), (141) and (142)] were reacted with the glycon (143) to give the corresponding anomeric glycosides. Thus, with the glycon (140) and silver zeolite – $\beta:\alpha = 1:2.2$; 59%; r.t.; 3 days; with the glycon (140) and silver silicate – $\beta:\alpha = 1:2$; 64%; -40°; 3h; with the glycon (141) and silver zeolite – $\beta:\alpha = 2:1$; 46%; r.t; 3 days; with the glycon (142) and silver silicate – $\beta:\alpha = 1.5:1$; 40%; 0°-r.t.; 16h.   The variations

138

139

$$R = C_6H_5CH_2 \ , \quad R^1 = CH_3CO$$
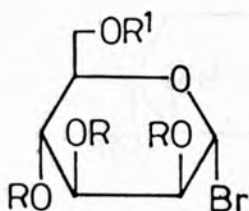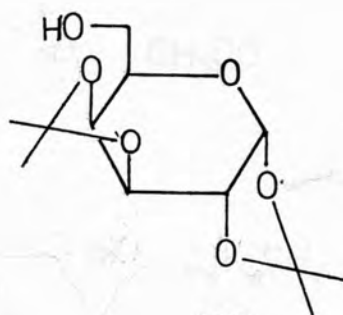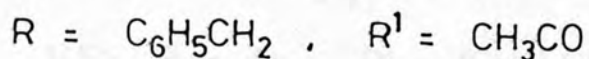
observed in these reactions and in several others conducted in this investigation were discussed in terms of the nature of the protecting groups on the glycon, the nature of the aglycon, and the identity of the insoluble promoter involved.

In another study[9] the effect of various zeolite promoters based on "soft" non-oxidising metal ions such as thallium, cobalt, or cadmium on the reactions of various glycopyranosyl bromides with alcohols was investigated. It was proposed that the use of these alternative promoters might minimise the decompostion of glycosyl halides which is often a problem when using silver salts. It was also suggested that the different coordinating abilities of Tl, Co and Cd compared with Ag might be reflected in the stereoselectivity of the glycosylation reaction. Thus, the glycon (169) which has a non-participating

$R^3 = CH_3CO$

169   $R = H$, $R^1 = Br$, $R^2 = C_6H_5CH_2$

144   $R = H$, $R^1 = Br$, $R^2 = CH_3CO$

145a $R = (CH_3)_2CHO$, $R^1 = H$, $R^2 = CH_3CO$

145b $R = H$, $R^1 = (CH_3)_2CHO$, $R^2 = C_6H_5CH_2$
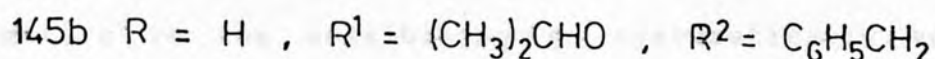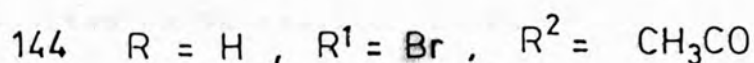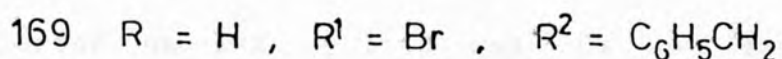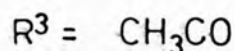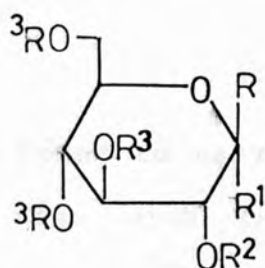
group at C-2 was reacted with isopropanol and gave the corresponding β-glycoside in the presence of thallium or silver on molecular sieve 4A ($\alpha : \beta = \sim 1:99$; 90%), whereas mixtures of anomeric glycosides were obtained when silver silicate was used as a promoter ($\alpha : \beta = 1:1$; 75%).

In the same, study glycons such as (144) bearing a participating group at C-2 were reacted with isopropanol. The expected α-product (145) was obtained exclusively in the presence of any one of a number of promoters based on Ag, Tl, Cd or Co supported on either 4A or 13X molecular sieves. Although the use of Tl, Cd or Co based promoters allowed extended reaction times to be used ($\sim$ 40h) the yields of isopropyl glycoside were in general much lower with Cd and Co promoters ($\sim$ 0-60%) than with Tl or Ag ($\sim$ 60-80%). Furthermore, the yields of product

were found to vary not only with identity of the metal but also with the nature of the zeolite support. Thus, the yield of glycoside (145a) using cobalt supported on 13X zeolite was 90% and using cobalt supported on 4A zeolite was 0%.

An attraction of zeolite-based electrophilic metal promoters over the alternative silver silicate promoters is the possibility to systematically vary features of the promoter. It follows, that the potential exists to design promoters with particular characteristics and thereby to improve or perhaps even control the stereoselectivity of a given reaction.

The molecular sieve zeolites have been defined as "aluminosilicates with a framework structure enclosing cavities occupied by large ions and water molecules, both of which have considerable freedom of movement permitting ion exchange and reversible dehydration"[12]. Zeolite minerals were discovered and named some 200 years ago, and over the past 50 years the synthesis of analogues of zeolite minerals and new variaties not found in nature has been undertaken because of their proven use in various industrial processess[13,17]. The structures of zeolites[13,17] consist of a three dimensional framework of SiO_4 and AlO_4 tetrahedra. The aluminium ion which occupies the position in the center of the tetrahedron constituting four oxygen atoms may be substituted with a silicon atom.

However, each substitution requires the presence of another suitable cation (such as Na^+, K^+, Ca^{2+}, Sr^{2+}) in order to maintain electrical neutrality. The metal ions needed for charge compensation are located at various positions in the cavities which exist in the frameworks of zeolites. The cavities are interconnected in one, two or three dimensions and have diameters which depend on the number of tetrahedra and the type of cation which constitute the particular zeolite (Table 4.1). For example, in the polyhedral structure of zeolite A the tetrahedra are arranged at the corners of a truncated octahedron
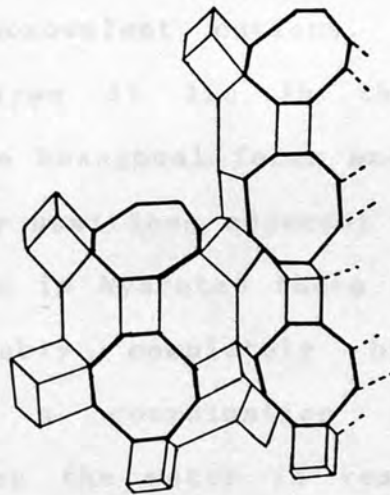
FIGURE 4.1   STRUCTURE OF ZEOLITE
TYPE A

which are themselves linked in a cubic array (Figure 4.1). This produces a central truncated cube

octahedron with an internal cavity of 11Å in diameter. Each central cavity or cage, has six apertures formed by a nearly regular ring of eight oxygen atoms with a diameter of 4.2Å. The cavities are connected in a continuous three dimensional pattern, forming a system of channels with a maximum diameter of 11Å and a minimum of 4.2Å. The truncated octahedra themselves, enclose a second set of smaller cavities (β cages) with an internal diameter of 6.6Å and are connected to the larger cavities by means of a distorted ring of six oxygen atoms with a diameter of 2.2Å. In each crystallographic unit cell of zeolite type A there are 12 AlO_4 and 12 SiO_4 tetrahedra (Table 4.1) and therefore 12 monovalent cations. Eight of these sodium ions (type I) lie in the center of the six-rings in the hexagonal faces and four sodium ions (type II) occupy positions adjacent to the eight-ring. When the zeolite is hydrated these four cations (type II) are probably completely hydrated and are surrounded by a coordination sphere of water molecules. When the water is removed, the cations possibly exist on the walls of the cavities. Monovalent cations occupy position that block part of cavities present in type A zeolites and restrict the pore size to below ~ 4Å. Although organic molecules would not be able to penetrate pores of these dimensions water molecules may readily do so. A large

TABLE 4.1

SOME PROPERTIES OF SELECTED ZEOLITES

NAME	COMPOSITION	SYMMETRY AND CELL DIMENSIONS	APERTURE SIZE $\overset{\circ}{A}$
SODALITE (natural)	$Na_8[(AlO_6)_6(SiO_2)_6]\cdot 2Cl$	CUBIC $a = 9.0\overset{\circ}{A}$	2.0
ZEOLITE A (synthetic)	$Na_{12}[(AlO_2)_{12}(SiO_2)_{12}]\cdot 27H_2O$	CUBIC $a = 12.32\overset{\circ}{A}$	4.2
ZEOLITE X (synthetic)	$Na_{86}[(AlO_2)_{86}(SiO_2)_{106}]\cdot 264H_2O$	CUBIC $a = 24.95\overset{\circ}{A}$	10
ZEOLITE Y (synthetic)	$Na_{56}[(AlO_2)_{56}(SiO_2)_{136}]\cdot 264H_2O$	CUBIC $a = 24.7\overset{\circ}{A}$	8

See Ref. 13 and 17 for fuller descriptions.

proportion of the water which is usually present in zeolites is removable by application of heat. The water molecules affect the specific positions of exchangeable cations in these zeolites but dehydration, even under stringent conditions, is not found to change the basic framework structure of zeolites.

The sodium ions normally present in type A zeolites exchange with other cations in aqueous solution. The precise nature of this cation exchange behaviour is found to depend on the particular characteristics of the zeolite type and also the cations to be exchanged. Amongst the ions which may be introduced by this treatment are those of thallium and silver, as for example in the zeolite promoters used in glycosidation reactions (see earlier discussion).

The ion exchange character of zeolites and the presence in their structures of pores with one or more discrete sizes, make them especially interesting for heterogenous catalysis. If most of the catalytic sites are confined within this pore structure and if the pores are small, the fate of reactant molecules is determined mainly by molecular dimensions and configurations. This gives rise to various shape selectivites which can be distinguished on the basis of whether the pore size limits the entrance of the

reacting molecule, the departure of the product molecule or the formation of certain transition states. However, the molecular dimensions of the glycons typically used in glycosidation reactions, make them too large to penetrate even the relatively large cavities (~ 10$\overset{o}{A}$) associated with 13X molecular sieves. It follows that any effects that zeolite-supported promoters have on these glycosidation reactions will arise through surface phenomena.

Because only limited use has been made of promoters based on electrophilic metals in glycofuranosyl syntheses[14], it is difficult to assess how effective any of them might be in promoting the stereoselective formation of β-arabinofuranosides from the arabinofuranosyl chloride (113a). Therefore, a series of experiments was undertaken in order to examine the effect of a range of silver salts and zeolite supported metal promoters on the reactions of the glycosyl chloride (113a) with the model sceondary alcohols isopropanol and cholesterol.

4.21   Results and discussion.

The reaction of the anomeric p-nitrobenzoyl esters (146) of 2,3,5-tri-O-benzyl-arabinofuranose (7) with

hydrogen chloride in dichloromethane (Exp. 37) as previously described[15], gave a syrup with an optical rotation corresponding to that reported for the α-glycosyl chloride (113a). This derivative was freshly made by this method when required for a particular experiment, and used with a minimum of exposure to moisture and light.

A preliminary experiment was conducted in order to examine the behaviour of this glycosyl chloride under solvolysis conditions. Thus, the glycosyl chloride (113a) was reacted with isopropanol (used as solvent) under nitrogen (Exp. 39). T.l.c. analysis of the reaction mixture indicated that all the starting sugar had disappeared within 14 days at room temperature.
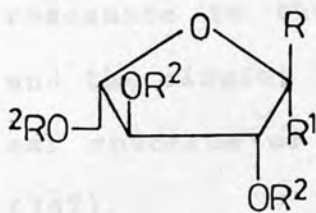
$R^2 = C_6H_5CH_2$

146b R = H , R^1 = p-$NO_2C_6H_4CO$

146a R = p-$NO_2C_6H_4CO$, R^1 = H.

113b R = H , R^1 = Cl

113a R = Cl , R^1 = H

147b R = H , R^1 = $(CH_3)_2CHO$

147a R = $(CH_3)_2CHO$, R^1 = H

148b R = H , R^1 = cholesteryl

148a R = cholesteryl , R^1 = H

Flash chromatography gave one main product, which ^{1}H and ^{13}C nmr spectroscopy indicated to be the β-isopropyl glycoside (147b). The chemical shift of 98.95 ppm observed for the C-1 resonance in the proton decoupled ^{13}C nmr spectrum (see Table 4.3 and discussion Chapter 4.51) and the splitting constant of 4Hz observed at 5.02 ppm for the H-1 resonance in the ^{1}H nmr spectrum were used to deduce its anomeric configuration. A small amount (~ 5%) of another component was also shown to be present in the original reaction mixture by t.l.c. and ^{1}H nmr spectroscopy. This could not be isolated by flash chromatography but was assumed to be the α-glycoside (147a). Especially diagnostic (see discussion Chapter 4.51) is the chemical shift of 105.04 ppm observed for the C-1 resonance in the proton decoupled ^{13}C nmr spectrum, and the singlet observed at 5.09 ppm for H-1 in the ^{1}H nmr spectrum of a mixture of the α- and β-glycosides (147).

The stereochemical outcome of this reaction suggests that the α-chloride (113a) reacts with inversion to give a predominant proportion of the β-glycoside (147b) as expected (see discussion Chapter 3.3). The minor quantity of the α-glycoside (147a) also present might indicate that the starting halide is not composed exclusively of the α-chloride (113a), or that anomerisation of either the starting

163

α-chloride (113a) or the β-product (147a) had occurred during the course of the reaction.

This experiment was repeated using stoichiometric amounts of glycosyl chloride (113a) and isopropanol (Exp. 40). T.l.c. analysis of the reaction mixture after 2 days at room temperature indicated that significant amounts of free sugar (7) were present, together with a small amount of both isopropyl glycosides (α:β = ~ 1:1) It is likely that the free sugar formed in this reaction was produced either from hydrolysis of the α-chloride ((113a) by adventitious water, or by hydrolysis of the glycoside products (147) catalysed by the hydrogen chloride by-product. This problem is expected to be accentuated when only stoichiometric amounts of isopropanol are used, as then the proportions of water and hydrogen chloride present become relatively large. This might account for the difference in yield and stereoselectivity when isopropanol was used in stoichiometric amounts rather than as the solvent (compare Exp. 39 and 40, Table 4.2).

The amount of glycon and the length of reaction time used in the solvolysis experiment (Exp. 39) would be unrealistic in any practical synthesis of β-arabinofuranosides. The effect of various silver salts on the reaction of the α-chloride (113a) with isopropanol was therefore examined, with a view to

finding a suitable promoter of this glycosidation reaction. Thus, the glycosyl chloride (113a) and an excess of isopropanol in dichloromethane were reacted under nitrogen in separate experiments (Exp. 41), with stoichiometric amounts of AgCN, CH_3CO_2Ag, $AgNO_3$, Ag_2CO_3 and Ag_2O. T.l.c. analysis of the reaction mixtures after 12h at room temperature revealed that in the majority of these reactions, only minor amounts of the glycoside products (147) were present, together with significant amounts of free sugar (7). T.l.c. also showed other minor components of intermediate mobility to be present in several of the mixtures. These by-products were not isolated by chromatography, but were considered to be partially benzylated analogues of the free sugar (7) formed through loss of benzyl groups.

In the reactions involving AgCN and CH_3CO_2Ag t.l.c. analysis of the reaction mixtures showed the presence of significant amounts (~ 25-35%) of new components (one in each case) with mobilities different from those expected for either the isopropyl glycosides (147) or the free sugar (7). Each of these two components were isolated by flash chromatography but were not characterised as they decomposed quite rapidly. A 400 MHz ^1H nmr spectrum of the CH_3CO_2Ag product was obtained and indicated that it might have been 1-0-acetate analogue of (147).

TABLE 4.2

GLYCOSIDATIONS WITH THE 2,3,5-TRI-O-BENZYL-α-L
ARABINOFURANOSYL CHLORIDE (113a) UNDER VARIOUS CONDITIONS:
SUMMARY OF RESULTS.

		ISOPROPANOL			CHOLESTEROL	
PROMOTER	TIME	EXP.	YIELD %	α:β	EXP.	YIELD % (β)
NIL(SOLVOLYSIS)	14 days	39	85	1:16		
NIL	2 days	40	30	1:1		
Ag$_2$O	12h	41.5	33	1:7		
Ag$_2$O+Z4A	12h	42.1	46	1:7		
Ag$_2$O+CaSO$_4$	12h	42.2	42	1:7		
Ag-Z4A	4h	44.1	75	1:9	45.1	79
Ag-Z13X	4h	44.2	76	1:9	45.2	70
Tl-Z4A	4h	44.3	73	1:9	45.3	68
Tl-Z13X	4h	44.4	76	1:9	45.4	64
Tl-Z4A:type II	4h	44.5	72	8:1		

Yields after isolation by chromatography; proportions of anomers by
^{1}H nmr.

Only the reaction with Ag_2O present gave synthetically useful quantities of isopropyl glycosides (147). These were isolated by flash chromatography and their structures confirmed by ^1H and ^{13}C nmr spectroscopy ($\alpha:\beta$ = ~ 1:7; yield 30-40%). The low yield obtained using Ag_2O was considered to be caused by hydrolysis of the glycosyl halide (113a) by water formed from this salt during the reaction. It was envisaged that the extent of hydrolysis in the Ag_2O-promoted reaction might be reduced by including agents which remove water. Thus, stoichiometric amounts of glycosyl chloride (113a) and Ag_2O and an excess of isopropanol were reacted in dichloromethane in the presence of either $CaSO_4$ or 4A molecular sieves (Exp. 42). However, isolation of the glycoside products from these reactions after 12h at room temperature, indicated that only minor improvements in yield had been affected by including either of these desiccants ($\alpha:\beta$ = ~ 1:7; yield 40-45%).

The effect of various zeolite supported metal promoters on the reaction of the α-chloride (113a) with isopropanol was tested with a view to further improving the efficiency of this reaction. Four types of promoter were initially selected to be examined. Each of these were prepared (Exp. 43) using the general methods previously described[5,9,16]. Two from $AgNO_3$ with 4A or 13X molecular sieves (Ag-Z4A and

Ag-Z13X respectively) and two from Tl_2CO_3 with 4A or 13X molecular sieves (Tl-Z4A and Tl-Z13X respectively).

Thus, stoichiometric amounts of the α-chloride (113a) and isopropanol in dichloromethane were reacted under nitrogen with each of these four zeolite supported promoters in separate experiments (Exp. 44). Analysis of the reaction mixtures by t.l.c. after 4h at room temperature showed that only the isopropyl glycosides (147) were present with each of the zeolite promoters. These were isolated by flash chromatography and their structures confirmed by ^{1}H and ^{13}C nmr spectroscopy (for yields and α:β ratios, see Table 4.2).

In order to further test the effectiveness of these four zeolite supported promoters on glycosylations using the α-chloride (113a), the alternative aglycon cholesterol (149) was used in
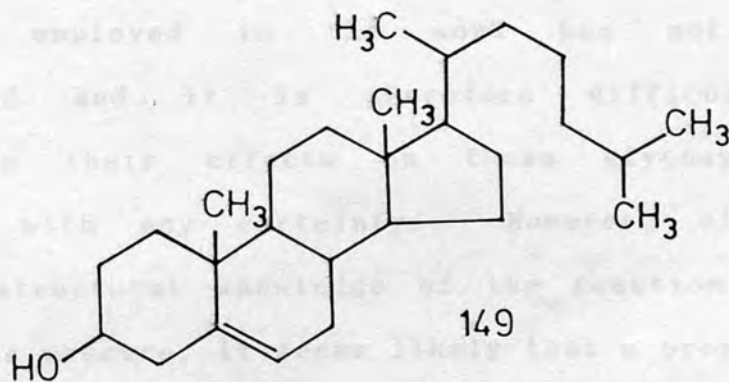
place of the less sterically hindered and more
reactive isopropanol employed in the earlier
experiments. Thus, stoichiometric amounts of the
α-chloride **(113a)** and cholesterol **(149)** in
dichloromethane were reacted under nitrogen with each
of the four zeolite supported metal promoters in
separate experiments (Exp. 45). Analysis of the
reaction mixtures by t.l.c. after 4h at room
temperature showed that one major component had formed
in each of these experiments. This was isolated by
flash chromatography and was shown by mass
spectroscopy and ^{13}C nmr spectroscopy to be the same
cholesteryl glycoside in each case (for yields see
Table 4.2). The chemical shift of 99.07 ppm
corresponding to the C-1 resonance in the proton
decoupled ^{13}C nmr spectrum of this glycoside indicated
that it was the β-anomer **(148b)** (see Table 4.3 and
discussion Chapter 4.51). The α-anomer **(148a)** could
not be observed by t.l.c.

The precise nature of the zeolite supported metal
promoters employed in the work has not been
established and it is therefore difficult to
rationalise their effects on these glycosylation
reactions with any certainty. However, although
detailed structural knowledge of the reaction sites
involved is obscure, it seems likely that a proportion
of the sodium ions originally part of the zeolite

framework have been replaced by either silver or thallium ions in these zeolite supported metal promoters. This cation exchange behaviour is known to depend upon the size and charge of the ion as well as the type of zeolite structure, and suggests that the exact nature of the reaction sites in each of the four promoters (Ag-Z4A, Ag-Z13X, Tl-Z4A and Tl-Z13X) is different. However, any differences which may exist between these four promoters is not reflected in an obvious way in the results of the experiments (see Table 4.2). In order to assess the significance of any less marked variations in these results, it would be necessary to ensure that the experiments were standardised and therefore reproducible. This is difficult to achieve in practice in reactions with heterogenous promoters; these take place at the phase border and differences between batches of a given promoter type (caused by inconsistencies in their method of production) might conceivably be the cause of slight variations which occur in these results.

An important feature of molecular sieves are the cavities enclosed within their framework structures, in which certain small ions and molecules may be trapped. Part of the success of these zeolite supported metal promoters in these glycosylation reactions is probably related to the effective way in which water and hydrogen chloride may be removed from

the reaction medium by being taken up into these pores. Furthermore, the marked improvement in the efficiency of the glycosylation reaction when silver supported on 4A molecular sieves was used (Exp. 44.1), rather than a mixture of Ag_2O together with 4A molecular sieves (Exp. 42.1), indicates that the removal of such molecules is best achieved when these cavities are intimately associated with the reaction sites as in the case of the zeolite supported metal promoters.

The fact that the products of the reaction of both isopropanol and cholesterol with the glycosyl chloride **(113a)** are formed after similar reaction times (4h) suggests that the rate determining step is the formation of a tight ion pair at the surface of the promoter, followed by a relatively fast attack of the alcohol. The role of both the silver and thallium in these promoters is likely to be to reduce the activation energy for formation of this zeolite-bound α-ion pair intermediate. Furthermore, the high β-stereoselectivity of these reactions suggests that this zeolite bound α-ion pair intermediate remains "tight" until the chloride ion is subsequently displaced from its α-face by a stereoselective attack of an alcohol on its β-face. It is also conceivable that the anionic groups present on the surface of the zeolite also contribute to the high stereoselectivity
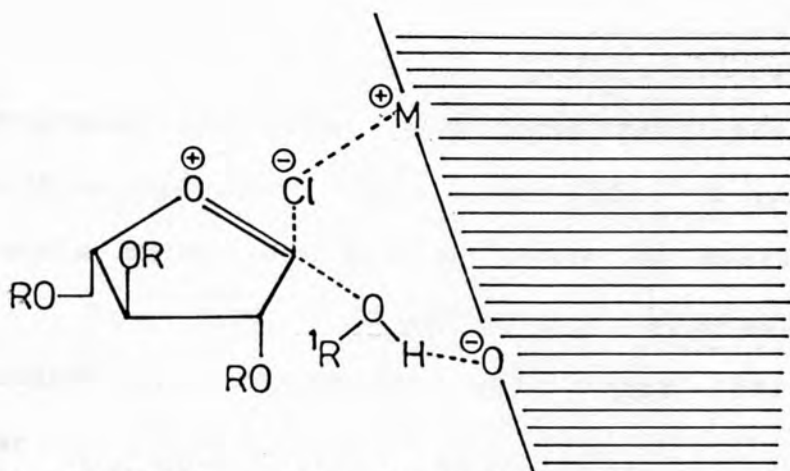
R = C₆H₅CH₂ , M = Ag or Tl

$R = C_6H_5CH_2$, M = Ag or Tl

R^1 = isopropyl or cholesteryl

and reactivity of these promoters, by interacting with the alcohol component and assisting in the deprotonation process. It follows that a highly stereoselective attack of a nucleophile on the β-face of the α-chloride would be possible through a "push-pull" mechanism[1,2,11] of this type.

A further result seems to support the view that the stereochemical outcome of this glycosylation reaction is influenced by a combination of several features of the promoter surface. Thus, stoichiometric amounts of the glycosyl chloride (113a) and isopropanol in dichloromethane were reacted under nitrogen with a promoter (Tl-Z4A; type II) which had been prepared with ~ 65% less Tl_2CO_3 than used originally (Exp. 44.5). T.l.c. analysis of the reaction mixture after 4h at room temperature showed that the only components present were the α-glycoside (147a) and a minor amount of the β-anomer (147b). The products of this reaction were isolated by flash

chromatography and their structures confirmed by ^{1}H nmr spectroscopy ($\alpha:\beta$ = 8:1; yield 72%). A number of experiments were conducted in order to clarify the reason for the surprising reversal of stereoselectivity observed with this particular promoter.

It is possible to account for the Tl-Z4A:type II result by proposing that the β-glycoside (**147b**) is formed initially (as with the other zeolite promoters), but that with this particular promoter the β-anomer (**147b**) subsequently anomerises to give the α-glycoside (**147a**). It follows that the α-glycoside (**147a**) could only be formed stereoselectively by such a process, if it were of a significantly greater thermodynamic stability than the β-anomer (**147b**). The difference in the thermodynamic stabilities of the two anomers was demonstrated in a qualitative way, by adding a trace of p-toluenesulphonic acid to a solution of the β-glycoside (**147b**) in dichloromethane (Exp. 46.1). T.l.c. analysis of the reaction mixture after 2h at room temperature indicated that the β-glycoside (**147b**) had been converted almost completely into the α-anomer (**147a**). This result is consistent with the stereoelectronic and steric considerations presented in Chapter 2.2.

An analogous experiment was performed with Tl-Z4A:type II in order to see if it promoted

anomerisation of the β-glycoside **(147b)**. It was expected that if this particular promoter has inherent acidic properties or is unable to remove the acid formed during the reaction effectively, it might behave similarly to p-toluenesulphonic acid towards the β-glycoside **(147b)**.

It is conceivable that certain of the cationic sites in the zeolite are occupied by protons. This is more likely to be the case once the promoter has been used in a glycosidation reaction; it is possible for cationic sites to be exchanged for protons liberated in these reactions thereby giving a zeolite with a number of strong acid sites[13,14,15]. Thus, a solution of β-glycoside **(147b)** in dichloromethane was stirred with either Tl-Z4A:type II (Exp. 46.2) or some promoter ("used" Tl-Z4A: type II) which had already been used to promote a glycosidation reaction (Exp. 46.3). T.l.c. analysis of the reaction mixtures indicated that even after 24h at room temperature no α-glycoside **(147a)** had been formed in either case. The negative results observed in these two experiments cannot be used to completely refute the possibility that the β-glycoside **(147b)** is being anomerised in the glycosidation reaction by the Tl-Z4A:type II. It is not certain whether either the "unused" or the "used" promoters used in these two experiments resemble the promoter present during the actual glycosidation

reaction closely enough for a valid comparison to be made.

An alternative explanation could be offered for the high α-product stereoselectivity of the glycosylation reaction in the presence of Tl-Z4A: type II by proposing that this particular promoter is able to catalyse the equilibration of the anomeric glycosyl chlorides (113). It follows that if the β-chloride (113b) is more reactive than the α-anomer (113a) and that equilibration of these chlorides can be made rapid compared with the rate at which the α-chloride (113a) reacts to give the β-glycoside (147b), the α-glycoside (147a) could be obtained as the predominant product.

Previous evidence[19] relating to the proportions of anomeric glycosyl chlorides (18) present at equilibrium in dichloromethane has been based on polarimetric data. Thus, in the presence of tetrabutylammonium chloride a solution of the α-chloride (18a) in dichloromethane was said to anomerise and give an "appreciable amount" of the β-chloride (18b) at equilibrium (see Chapter 2.3). However, analogous experiments with glycopyranosyl chlorides have indicated that if any hydrolysis of the glycosyl chloride occurs during the experiment polarimetric data can be quite misleading[55]. In order to establish whether the previous conclusions based on

polarimetric data are reliable and to further clarify the anomerisation behaviour of the α-chloride (113a) a series of experiments was conducted making use of ^{1}H nmr data rather than polarimetric data. Thus, stoichiometric amounts of a selection of salts ($ZnCl_2$, LiCl, AgCl, tetrabutylammonium bromide and tetraethylammonium chloride) and the α-chloride (113a) were mixed in deuterodichloromethane in separate experiments with a view to promoting its anomerisation (Exp. 47). The 90 MHz ^{1}H nmr spectra of samples from these experiments were recorded after reaction periods of 15 min and 4h at room temperature. In a control experiment, the ^{1}H nmr spectra of a solution of the α-chloride (113a) in deuterodichloromethane were recorded after similar reaction periods. In addition to the resonance from the anomeric proton at 6.12 ppm other resonances at δ 4.35 (1H,d,J_{23} 2.1 Hz, H-2), 3.96 (1H, dd, J_{34} 6.5 Hz, H-3) and 3.63 (2H, d, J_{45} 4.3 Hz, H-5,5') could be clearly distinguished. None of these resonances became weaker or more complex during the experiments. Furthermore, the resonance at 6.17 ppm (d, J_{12} 4Hz) assigned to the anomeric proton of the β-chloride (113a) in prevous work[24] could not be seen in any of these spectra. The results of these ^{1}Hnmr studies suggests that the β-chloride (113b) represents the minor component after equilibration of the anomers. A less likely explanation is that none

of the salts employed could promote anomerisation of the α-chloride (113a) to any appreciable extent within the 4h duration of these experiments.

A further experiment was performed in order to see if Tl-Z4A: type II might affect any anomerisation of the α-chloride (113a). Thus, the α-chloride (113a) and Tl-Z4A: type II were mixed in deuterodichloromethane and the ^{1}H nmr spectrum sample of the reaction mixture was recorded after a reaction period of 6h at room temperature (Exp. 47). No sign of the β-chloride (113b) was apparent in this spectrum.

Although a minor component of a mixture might be difficult to see by ^{1}H nmr, it was considered surprising that the "appreciable quantities" of β-chloride (113b) suggested to exist at equilibrium by the previous study[19] using polarimetry were absent in the experiments. Despite not being able to observe any β-chloride (113b) by ^{1}H nmr, it is probable that relatively small amounts of this anomer did comprise at least some of the reaction mixtures studied.

The results of these ^{1}H nmr studies also seem to indicate that only minor quantities of the β-chloride (113b) would be present at any time during the course of the glycosylation reaction. Furthermore, the result of a previous study[19] might be taken to suggest that the stereoselectivity of this glycosidation

reaction is not affected by conditions expected to promote formation of the β-chloride (113b). Thus,

RO— O R^1
RO
R^2
RO

$R = C_6H_5CH_2$

18a R^1 = H , R^2 = Cl

18b R^1 = Cl , R^2 = H

75a R^1 = H , R^2 = CH$_3$O

75b R^1 = CH$_3$O , R^2 = H
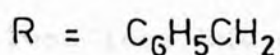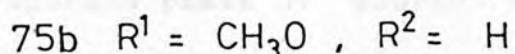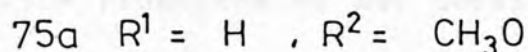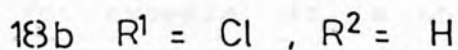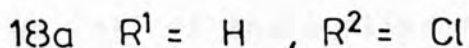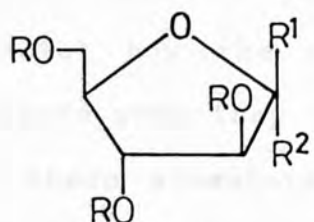
methanolysis of either the α- glycosyl chloride (18a) or the bromide analogue (60) gave the inverted β-glycoside as the predominant product, even in the presence of tetrabutylammonium bromide. If anomerisation of the α-chloride (18a) is promoted by the bromide ion added in this study, and if this anomer is less reactive than the β-chloride (18b), the stereoselectivity of these solvolysis reactions might have been expected to be altered somewhat in favour of the α-glycoside (75a) in the presence of tetrabutyl-ammonium bromide. It appears therefore that the high α-product stereoselectivity observed when using Tl-Z4A: type II to promote this glycosidation reaction, is related to some important difference between the physical characteristics of this particular promoter and those of the promoters originally used in this work.

It is reasonable to supposed that Tl-Z4A: type II

might contain significantly less thallium than does Tl-Z4A; the former is made using less than 50% of the Tl_2CO_3 used in the latter. It is not possible to predict how the properties of metal ions might be altered when they become part of the zeolite framework in these promoters. For example, it is conceivable that the thallium zeolite promoters do not constitute thallous ions but a dispersed phase of "nearly" atomic thallium metal in the cavities of the zeolite. Furthermore, it seem likely that if the sodium ions originally part of the zeolite framework have been exchanged for thallium ions in the preparation of these promoters, there will be a higher proportion of sodium in Tl-Z4A: type II than in Tl-Z4A. It is also interesting to note that the chemistry of the thallous ion bears a resemblance to those of the alkali and argentous ions[43].

The view that the relative proportions of thallium to sodium in these two thallium zeolite promoters, (Tl-Z4A and Tl-Z4A:type II) is important in determining the product stereoselectivity of glycosidations with the α-chloride (113a) seems to be supported by a previous study[20]. Thus, when a solution of the α-chloride (18a) in dichloromethane was reacted with p-nitrophenol in the presence of 4A molecular sieves, a preponderance of the α-product (150a) was obtained after 20h at room temperature (α:β

= 7:1). When this experiment was repeated, but with the aglycon introduced after an interval of 15 min, a 25% yield of the anhydro-tri-0-benzyl pentenitol (151) was isolated.

$$R = C_6H_5CH_2$$

18a	$R^1 = H$,	$R^2 = Cl$
18b	$R^1 = Cl$,	$R^2 = H$
150a	$R^1 = H$,	$R^2 = p\text{-}NO_2C_6H_4O$
150b	$R^1 = p\text{-}NO_2C_6H_4O$,	$R^2 = H$
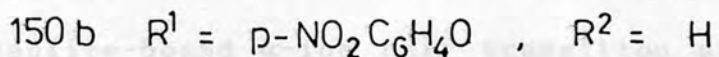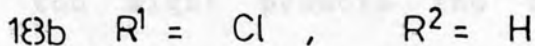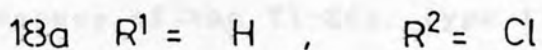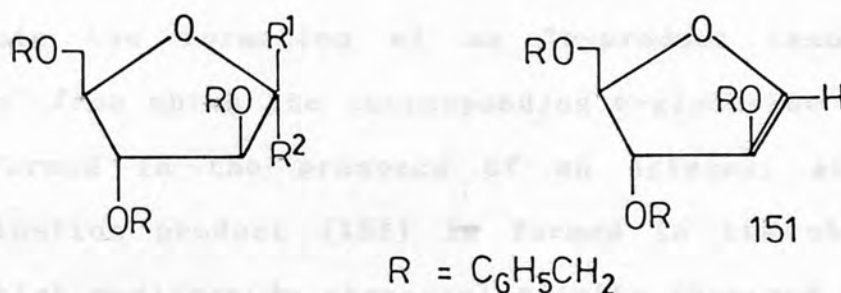
It is likely that the pentenitol (151) is formed by elimination of the components of hydrogen chloride from either anomeric glycosyl chloride (18). However, such a process would be expected to occur most easily from the β-anomer (18b); the stereoelectronic theory predicts that such eliminations proceed with greatest ease when the electron pair involved in double bond formation is orientated antiperiplanar to the leaving group bond[21]. The presence of the β-chloride (18b) is also suggested by the high proportion of α-glycoside

(150a) isolated in this study; this product is expected through an attack of the aglycon on the α-face of the β-ion pair which can be derived from the β-chloride (18b).

It appears therefore, that the sodium aluminosilicate present in these experiments serves to promote the formation of an "α-product transition state" from which the corresponding α-glycoside (150a) is formed in the presence of an aglycon, and the elimination product (151) is formed in its absence. The high α-glycoside stereoselectivity observed in the presence of the Tl-Z4A: type II promoter suggests that it too might promote the formation of a similar "α-product transition state" from the α-chloride (113a). It follows that the corresponding zeolite-bound α-ion pair transition state (from which the β-glycoside is formed), is either less reactive or less readily formed with this particular promoter.

The pore size of ~ 4Å associated with 4A molecular sieves suggests that the particular type of α-product transition state which the Tl-Z4A: type II and sodium aluminosilicate promote is located on the surface of the zeolite. One could also speculate that in these two zeolite promoters (either Tl-Z4:type II or 4A molecular sieves) the α-chloride (113a) becomes zeolite-bound as with the other four promoters (Ag-Z4A, Ag-Z13X, Tl-Z4A or Tl-Z13X) but that this

particular zeolite-bound α ion-pair intermediate is sufficiently "loose" for attack of an alcohol on its α-face. Furthermore, even if the α-product transition state has a structure approaching that of a free glycosyl cation, attack of the alcohol would still be expected to occur preferentially at the α-face [cf the formation of α-chloride **(113)** from the mixed p-nitrobenzoyl esters **(146)**], or eliminate by an E1 process.

4.3   Tosylate activation.

4.31   Introduction and strategy.

Glycopyranosyl halides have been converted into derivatives of higher reactivity by replacing the halide with a better leaving group[1]. This may be achieved through the reaction of a glycopyranosyl chloride or bromide in an inert solvent with the appropriate silver salt. Glycopyranosyl tosylate (152), triflate (153), tetrafluoroborate (154) and hexafluorophosphate (155) derivatives have all been generated in this way[22].

152	X =	$p\text{-}CH_3C_6H_4SO_2O$
154	X =	BF_4
155	X =	PF_6
153	X =	CF_3SO_2O

R = $C_6H_5CH_2$
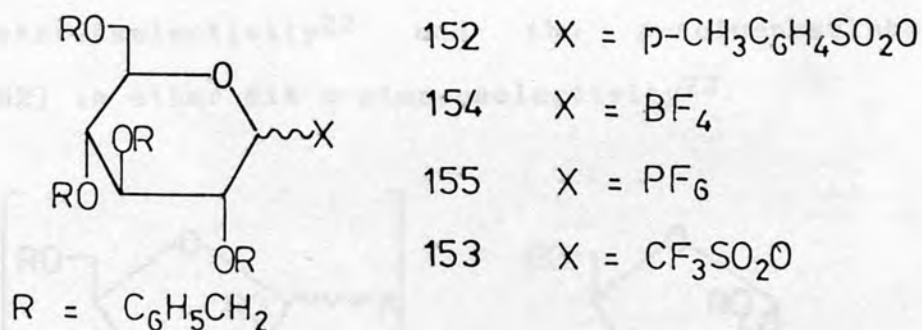
Derivatives of this type are often quite unstable and therefore not usually isolated in practice. They are instead generated *in situ* from the corresponding glycopyranosyl halides, and used immediately in glycosylation reactions. It appears that the silver ions present in homogenous solution promote the

subsequent glycosylation reactions, which have on occasion been conducted effectively at -78° [22].

Although the reactions of these alternative glycons typically give quantitative yields of glycopyranosides and proceed much faster than those of glycosyl halides, they are often not very stereoselective. The proportions of anomeric glycopyranosides formed are found to vary in a complicated fashion with the nature of the protecting groups on the glycon, and also with the precise reaction conditions. However, in some cases the reactions of these glycons have exhibited a high degree of stereoselectivity. For example, the tetrafluoroborate **(154)** in ether provided 97% β-stereoselectivity[22] and the p-toluenesulphonate **(152)** in ether 81% α-stereoselectivity[23].

164 X $= (CH_3)_2\overset{\oplus}{N}{=}CHO$

157a Y $= p{-}CH_3C_6H_4SO_2O$

R $= C_6H_5CH_2$
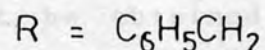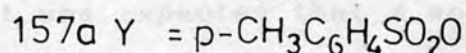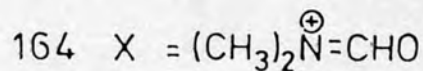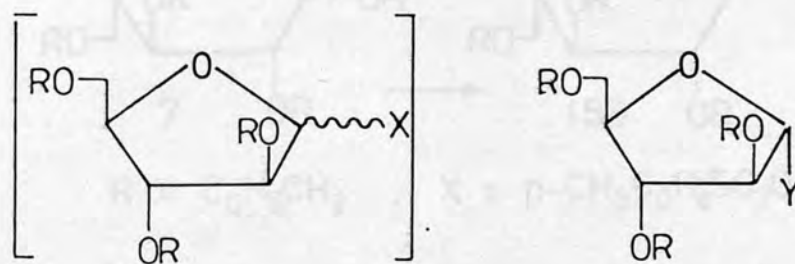
2,3,5-tri-0-benzyl-α-D-arabinofuranosyl tosylate **(157a)** has been generated[24] by the reaction of the

corresponding alkoxyiminium derivative (164) with silver p-toluenesulphonate. This compound when isolated was found by ^{1}H nmr spectroscopy to be anomerically homogenous. In practice however, the tosylate (157) was generated *in situ* and was proposed to be one of several possible glycons present in the reaction mixture (see Chapter 4.4). The synthesis of a range of D-arabinofuranosides was achieved using this reaction mixture, but usually with poor stereoselectivity. The production of anomeric mixtures of glycosides by this method may be due to the fact that the reaction medium comprised several potential glycons, only one of which might have been α-tosylate (157a).

$$R = C_6H_5CH_2 \quad , \quad X = p\text{-}CH_3C_6H_4SO_2O$$
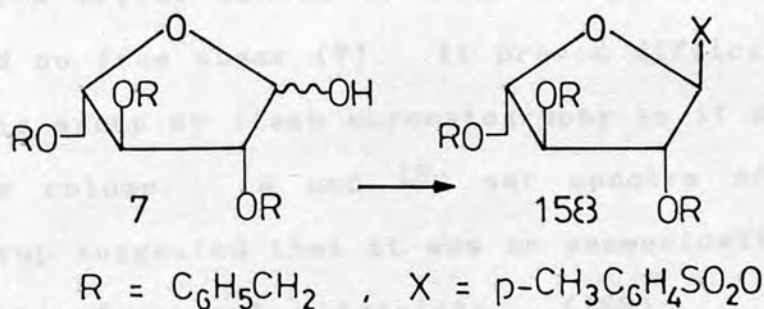
It was expected that a more stereoselective result might be obtained if the α-tosylate (157a) was the sole glycon; it might then be expected to react with an alcohol to give a predominant proportion of the inverted β-glycosides. The synthesis of the

185

α-tosylate **(158)** was undertaken with a view to examining its potential as a glycosylating agent. It was envisaged that this derivative might be most conveniently made through the reaction of the benzylated free sugar **(7)** with p-toluenesulphonyl chloride.

4.32   Results and discussion.

The benzylated free sugar **(7)** was reacted with an excess of p-toluenesulphonyl chloride in pyridine (Exp. 48).   A simple work-up of the reaction mixture after 16h at room temperature gave a crude syrup, which t.l.c. showed to comprise mainly one component and no free sugar **(7)**.   It proved difficult to purify this syrup by flash chromatography as it decomposed on the column. ^{1}H and ^{13}C nmr spectra of this crude syrup suggested that it was an anomerically homogenous arabinofuranosyl tosylate **(158)**.   Especially diagnostic were the resonances in the ^{1}H nmr spectrum at 2.3 ppm (3 protons) corresponding to the methyl protons of the tosyl group and at 7.5 – 8.5 ppm (multiplet) corresponding to the aromatic protons of the tosyl group.   The singlet at 5.3 ppm corresponding to the anomeric proton suggested that the anomeric configuration was α rather that β (in which the

anomeric proton would be expected to be a doublet).
Furthermore, there was only one resonance (at 95.8
ppm) in its proton decoupled ^{13}C nmr spectrum
corresponding to C-1.

$R = C_6H_5CH_2$

158   $R^1 = H$, $R^2 = p\text{-}CH_3C_6H_4SO_2O$

147a $R^1 = H$, $R^2 = (CH_3)_2CHO$

147b $R^1 = (CH_3)_2CHO$, $R^2 = H$

113a $R^1 = H$, $R^2 = Cl$
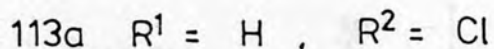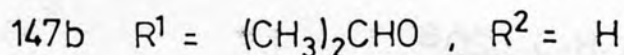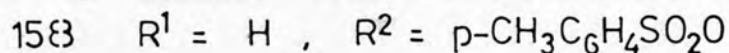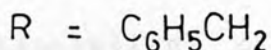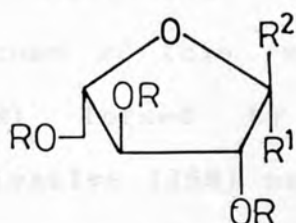
Although it was not possible to purify the syrup
and therefore to characterise it fully, the crude
product was reacted with isopropanol in order to test
its potential as a glycon. Thus, stoichiometric
amounts of the crude tosylate (158) and isopropanol
were reacted in dichloromethane (Exp. 49). T.l.c.
analysis of the reaction mixture after 6h at room
temperature indicated that the anomeric isopropyl
glycosides (147) were present in about equal
proportions ($\alpha:\beta = \sim 1:1$), together with a small
amount of the free sugar (7).

The tosylate ion is a better leaving group than

the chloride ion, and this probably accounts for the greater reactivity of the tosylate derivative (158) in comparison with the chloride analogue (113a). However, the reaction of the tosylate derivative with isopropanol is not stereoselective, and this limits its usefulness as a glycon. The stereochemical outcome of this reaction suggests that the ion pair (159) formed by dissociation of the tosylate derivative (158) may be sufficiently 'loose' to allow attack by an alcohol from the otherwise hindered α-face.

R = C₆H₅CH₂

159

$^{\ominus}OSO_2C_6H_4\ p\text{-}CH_3$
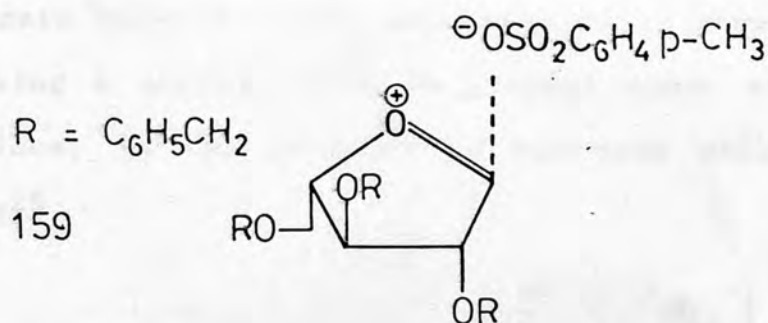
The poor stereoselectivity could also be explained by speculating that initially the β-glycoside (147a) is formed stereoselectively from the α-tosylate (158) but that it is subsequently anomerised by acid present in the reaction mixture (p-toluenesulphonic acid can be formed during the glycosylation reaction or may be a constituent of the crude tosylate syrup made use of in

this reaction).

4.4   Trichloracetimidate activation.

4.41   Introduction and strategy.

Although first discovered over a century ago, imidates have recently found wide application in carbohydrate chemistry. Three types of carbohydrate imidates may be identified on the basis of the typical chemistry they exhibit.

Imidate hydrochlorides were originally prepared by condensing a nitrile with an alcohol under anhydrous conditions, in the presence of hydrogen chloride or bromide[25].

$$R^1C{\equiv}N \ + \ R^2OH \ + \ HCl \ \longrightarrow \ \left[R^1-C \begin{array}{c} \overset{\oplus}{\diagup}NH_2 \\ \diagdown OR^2 \end{array} \right] \overset{\ominus}{Cl}$$
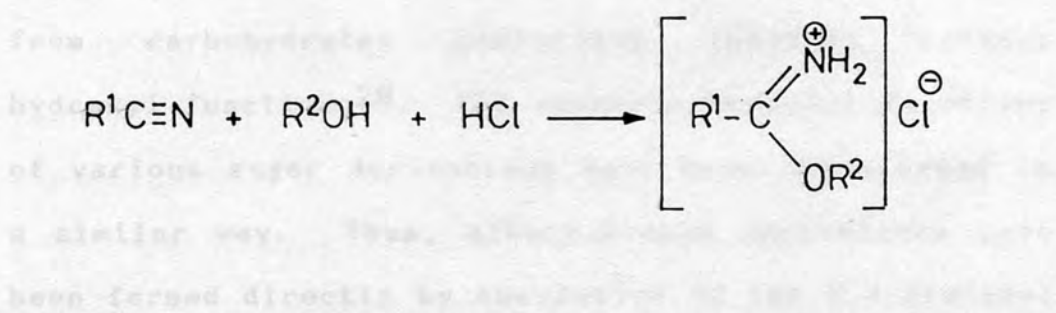
Alternatively, imidate hydrochlorides may be obtained from iminium salts. The action of phosgene on amides gives iminium salts[26].

$$(CH_3)_2NCH + COCl_2 \longrightarrow \left[\begin{array}{c} H_3C\overset{\oplus}{N}CH_3 \\ H-C \\ Cl \end{array} \right] \overset{\ominus}{Cl}$$

$$\downarrow ROH$$

$$RCl \longleftarrow \left[\begin{array}{c} H_3C\overset{\oplus}{N}CH_3 \\ H-C \\ OR \end{array} \right] \overset{\ominus}{Cl}$$
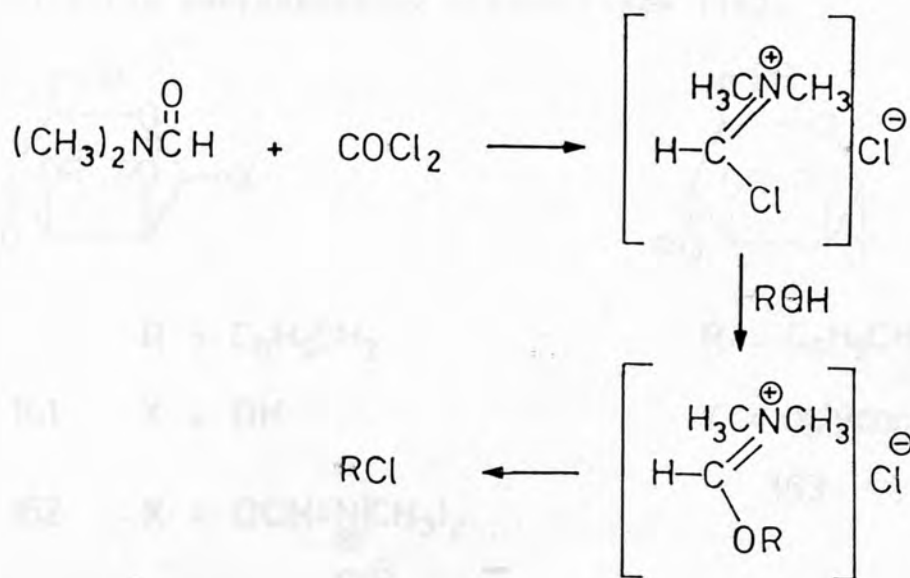
These salts react with alcohols[27] to give alkoxyiminium salts which break down to form the corresponding alkyl halides. This reaction has been exploited in the preparation of deoxy-halogeno-sugars from carbohydrates containing isolated primary hydroxyl functions[28]. The anomeric hydroxyl functions of various sugar derivatives have been transformed in a similar way. Thus, alkoxyiminium derivatives have been formed directly by the action of the N,N-dimethyl formamide/phosgene complex (160)[29]. In work with mannose (161), chemical and spectroscopic evidence for the alkoxyiminium salt (162) formed by such a reaction has been presented[30]. Species of this type were stable and anomerically pure in solution at low temperature. Furthermore they reacted with alcohols

to give the corresponding α-mannosides (163).

$R = C_6H_5CH_2$

161   X = OH

162   X = $OCH=\overset{\oplus}{N}(CH_3)_2$
        $Cl^{\ominus}$

$R = C_6H_5CH_2$

Y = aglycon

163

160 = $(CH_3)_2\overset{\oplus}{N}=CHCl, Cl^{\ominus}$
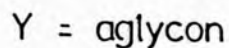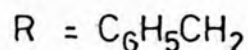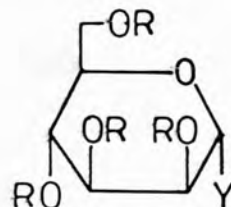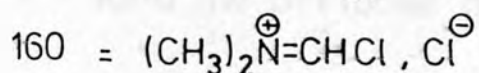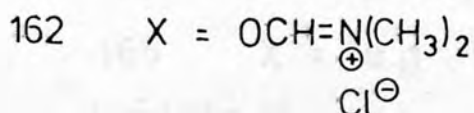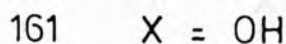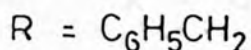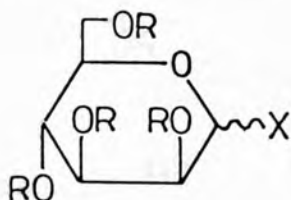
The method has also been used for the synthesis of alkoxyiminium salts of pentofuranose derivatives[24] (83). No spectroscopic evidence in support of the proposed intermediates could be obtained in this case. However, the isolation of the expected formyl ester (166) on hydrolysis of the reaction mixture was proposed to confirm the intermediacy of the corresponding alkoxyiminium salts (164). Silver p-toluenesulphonate was found to have a catalytic effect on the reaction of these activated glycons with alcohols. This observation can be explained if the O-glycosides are formed from a glycosyl tosylate (157) which could be produced via the alkoxyiminium salt (164). The O-glycoside product ratios obtained using this alkoxyiminium method were variable (60-90%) and the stereoselectivities poor (α:β = 1:8 - 10:1). This

R = $C_6H_5CH_2$

83	X = HO
164	X = $Cl^{\ominus}$ $(CH_3)_2\overset{\oplus}{N}=CHO$
18	X = Cl
157	X = $p\text{-}CH_3C_6H_4SO_2O$
165	X = e.g $(CH_3)_3CO$
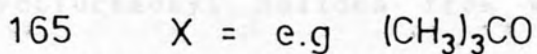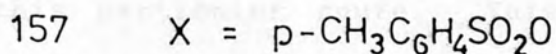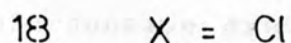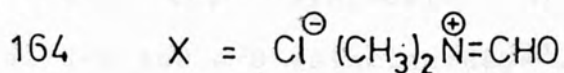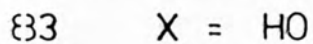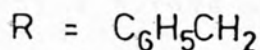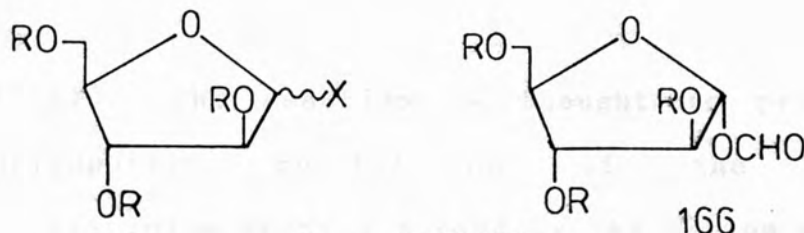
(and the D-ribose analogues)

was proposed to be as a result of a set of complex equilibria involving several species which include the alkoxyiminium salt (164), the glycosyl chloride (18) and the glycosyl tosylate (157).

Alkyl halides react with amides in the presence of silver salts to give imidates[31].
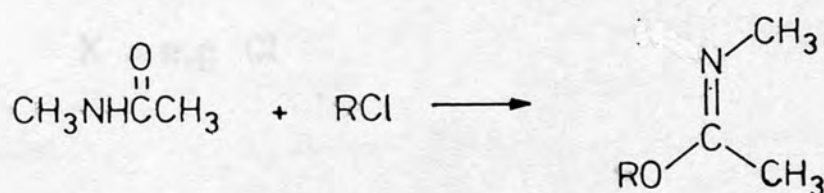
This reaction presents a further means of activating the anomeric centre of carbohydrate derivatives.

84:14). The reaction is thought to proceed by a nucleophilic substitution of the protonated alkoxyiminium species formed by the action of the acid catalyst on the glycosyl imidate. The method has been applied in the synthesis of α-D-glucosides, α-L-fucosides and α-D-galactosides[34].

Glycofuranoside syntheses have not been attempted using this particular route. This might be because the glycofuranosyl halides from which this type of imidate derivative is made, are typically reactive syrups and are therefore not ideal precursors for their synthesis.

An alternative method by which to convert alcohols to imidates is through their reaction with nitriles under catalysis by base[35].

$$X_3CC{\equiv}N \ + \ ROH \ \xrightarrow{\text{base}} \ X_3C\text{-}C{\underset{OR}{\overset{NH}{\diagdown}}}$$
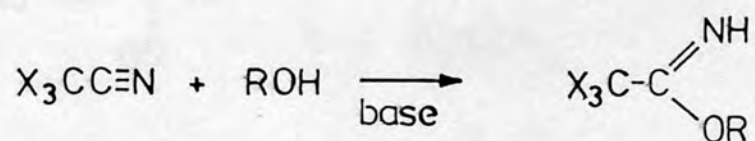
X = e.g Cl

In an early study ethanol was reacted with various nitriles in the presence of sodium ethoxide at 25° to give high conversions to imidates[36]. Furthermore, electron attracting groups in the nitrile were found to enhance their reactivity with alcohols when a basic

Imidates formed from glycosyl halides react with alcohols under catalysis by acid. This reaction proceeds efficiently and with good stereoselectivity. The synthesis of a number of O-glycopyranosides has been achieved using this procedure, including di- and tri- saccharides[32]. In a typical[32] reaction 2,3,4,6-tetra-O-benzyl-α-D-glucopyranose was converted to its α-chloro sugar (87) by a reaction with N,N dimethylchloroforminium chloride[33]. When a benzene solution of (87) was stirred at room temperature, with N-methylacetimidate, silver oxide,

87    $R^1 = H$, $R^2 = Cl$

168    $R^1 = H_3CN=CCH_3O$, $R^2 = H$

R = $C_6H_5CH_2$
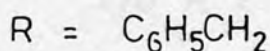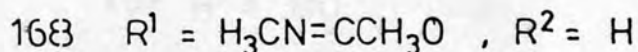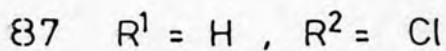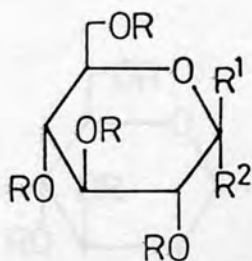
diisopropylethylamine and 4A molecular sieves the β-imidoyl derivative (168) was obtained. The stereoselectivity of this reaction has been attributed to a "push-pull" mechanism on the surface of the insoluble silver salt[32]. Reaction of (168) with an appropriate aglycon in anhydrous benzene with one equivalent of anhydrous p-toluenesulphonic acid gave the corresponding disaccharides (yield 90%; α:β =

catalyst was employed. 1-O-unsubstituted glycopyranoses (167) react with halogen-activated nitriles in the presence of base[37]. Trichloroacetonitrile was found to be more effective in this reaction that less activated nitriles such as dichloro- and chloro- acetonitrile. The imidoyl derivatives (170) obtained by this method can often be isolated as stable crystalline compounds. In addition, it is possible to obtain either the α- or β-glycosyl imidate through the choice of an appropriate basic catalyst and reaction time, thus enhancing the versatility of the method[38].

167 R^1 = HO

170 R^1 = Cl$_3$CCO
            NH

R = C$_6$H$_5$CH$_2$
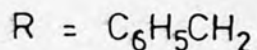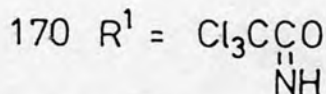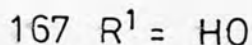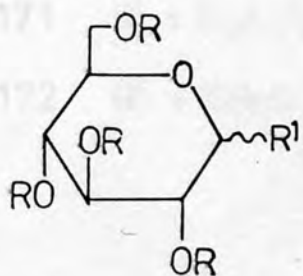
O-glycosides may be obtained by reaction of imidoyl derivatives with alcohols under acid catalysis. Protonation of the trichloracetimidoyl group converts it into a good leaving group[39] which can be displaced by nucleophilic attack of an alcohol on the anomeric carbon. O-Glycosides of opposite configuration to the starting glycosyl imidate are

usually obtained, and a number of complex glycosides and oligosaccharides have been synthesised in this way[40].

Glycofuranoside imidates have also been made by the reaction of glycofuranoses with trichloroaceto- nitrile in the presence of base. The two

171   R^1 = (C$_6$H$_5$)$_3$COCH$_2$ 54

172   R^1 = CH$_3$OC
                    ‖
                    O

R = C$_6$H$_5$CH$_2$
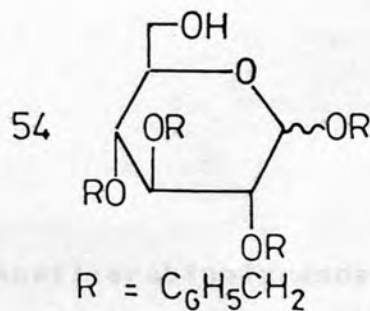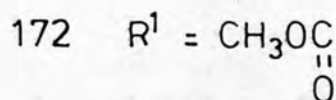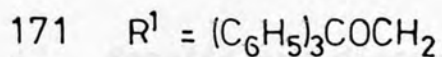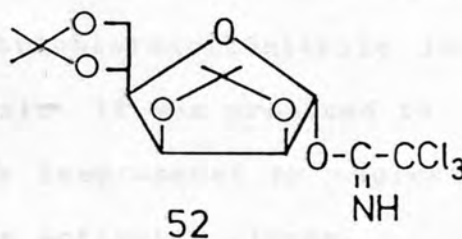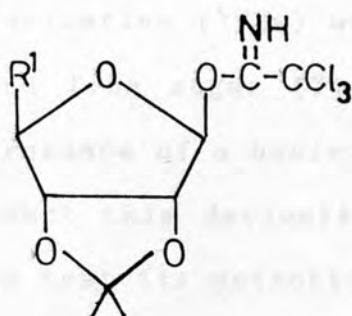
D-ribofuranosyl derivatives (171) and (172), and the D-mannofuranosyl derivative (52)[41] were all obtained as crystalline compounds. Reaction of (52) with 1,2,3,4-tetra-D-benzyl glucopyranose (54) in the presence of anhydrous p-toluenesulphonic acid and 4A molecular sieves gave the corresponding β-glycosides[42] (86% yield; 24h; room temperature).

It was envisaged that the trichloroacetimidate derivative of 2,3,5-tri-0-benzyl-L-arabinofuranose

196

7   173a
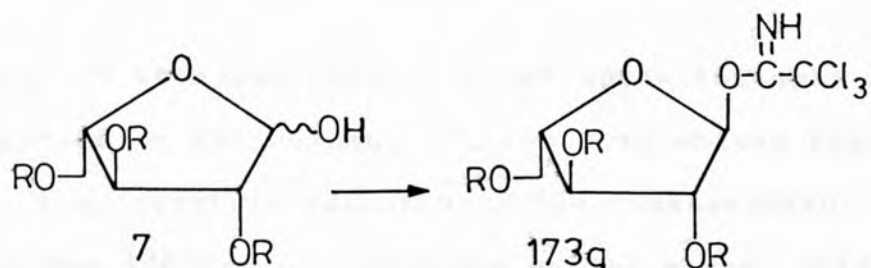
(173) might be a useful glycon for stereoselective
β-arabinofuranoside synthesis.   A synthesis of the
derivative (173a) was undertaken through a reaction of
the free sugar (7) with trichloroacetonitrile in the
presence of a basic catalyst. It was proposed to
react this derivative with isopropanol or cholesterol
to test its potential as an activated glycon.

4.42   Results and discussion.

A solution of 2,3,5-tri-0-benzyl-arabinofuranose
(7) in dichloromethane was reacted with an excess of
trichloroacetonitrile in the presence of an excess of
sodium hydride (Exp. 50.1). Although t.l.c. analysis
of the reaction mixture after 4h indicated that a
substantial amount of a new component had formed it
was not possible to monitor the progress of the
reaction accurately as there was substantial streaking
of the t.l.c. plates. The reaction was assumed to
have gone to completion after 16h at room temperature
and terminated. It was not possible to isolate the

product of this reaction by flash chromatography as it decomposed on the column. Attempts to obtain the pure product by crystallisation were also unsuccessful.

^{1}H and ^{13}C nmr spectroscopy of the syrup, obtained after simple work up of this reaction mixture, indicated that it comprised one anomerically pure arabinofuranosyl trichloroacetimidate derivative. Especially diagnostic were the two very low field resonances in the proton decoupled ^{13}C nmr spectrum at 161 ppm and 167 ppm corresponding to the trichloroimidoyl carbon atoms and also the resonance at 8.9 ppm in the ^{1}H nmr spectrum corresponding to the proton in the trichloroimidoyl group. Resonances at 6.17 ppm in the ^{1}H nmr spectrum and at 105.2 ppm in the proton decoupled ^{13}C nmr spectrum were the only signals observed in the region expected for anomeric resonances.

Although the anomeric configuration of this imidate derivate could not be deduced with certainty from ^{13}C or ^{1}H nmr data, it is expected to be the α-anomer (173a) on the basis of the mechanism proposed for the formation of the corresponding glycopyranosyl trichloroacetimidates[38]. Thus, deprotonation of the free sugars (167) would give the corresponding 1-0 metalated derivatives (174).

It is proposed[38] that in the glycopyranose case, the β-alkoxide intermediate (174b) is more

R = $C_6H_5CH_2$

M = Na or K

167b R^1 = H , R^2 = HO

167a R^1 = HO , R^2 = H

174a R^1 = $\overset{\ominus}{O}\overset{\oplus}{M}$, R^2 = H

174b R^1 = H , R^2 = $\overset{\ominus}{O}\overset{\oplus}{M}$

170b R^1 = H , R^2 = Cl_3CCO (NH)

170a R^1 = Cl_3CCO (NH) , R^2 = H
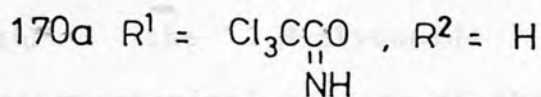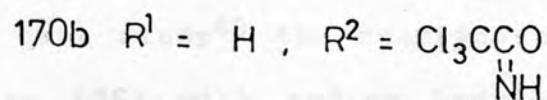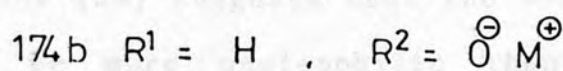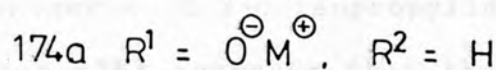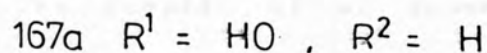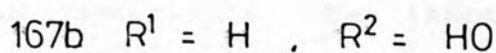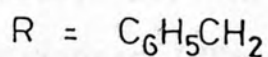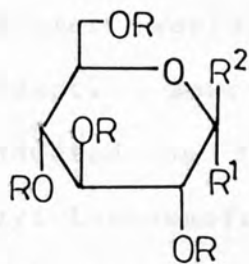
nucleophilic than the corresponding α-anomer **(174a)** because of free orbital repulsion, and gives the β-trichloroacetimidate **(170b)** initially. However this kinetic product anomerises to give the α-trichloroacetimidate **(170a)** which is stabilised by the anomeric stereoelectronic effect[21]. It has been possible to exploit the differences that exist between the various anomeric species involved, to obtain either the thermodynamic or the kinetic product.

In the arabinofuranose case, these arguments predict that the α-alkoxide anomer would be the more nucleophilic, giving rise to the α-trichloroacet-

imidate as the kinetic product. In addition, by
analogy with the arabinofuranosyl chlorides, the
α-anomer would also constitute the thermodynamic
product. However, the results of an investigation
conducted on the anomeric 2,3-0-isopropylidene-5-0-
tosyl-L-rhamnofuranoses (36) suggests that the β-sugar
(36b) may in fact be more nucleophilic than the
α-anomer (36a). In that study[40] the reaction of the
free sugar derivative (36) with sodium hydride and
methyl iodide gave the β-glycoside (37b)
preferentialy. The stereochemical outcome of this

$R = p\text{-}CH_3C_6H_4SO_2$

36a $R^1 = HO$, $R^2 = H$

36b $R^1 = H$, $R^2 = HO$

37a $R^1 = CH_3O$, $R^2 = H$

37b $R^1 = H$, $R^2 = CH_3O$

175a $R^1 = O^{\ominus}Na^{\oplus}$, $R^2 = H$

175b $R^1 = H$, $R^2 = O^{\ominus}Na^{\oplus}$
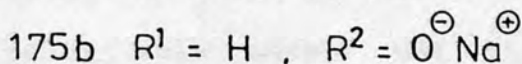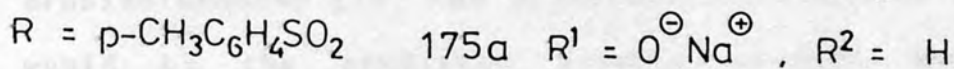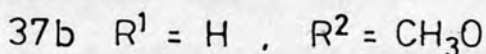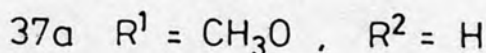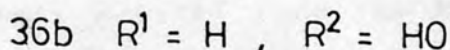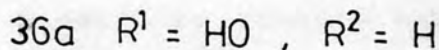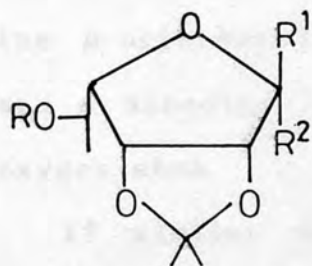
irreversible reaction was attributed to the greater
stability and nucleophilicity of the β-free sugar
(37b) over the α-anomer (37a), due to hydrogen bonding

to the C-2 oxygen atom only possible in the β-case. This reasoning was supported by the result obtained when a small quantity of dimethylformamide was included in the reaction mixture. The formation of the α-glycoside (37a) in this case was proposed to be due the greater stability of the α-free sugar (36a) over the β-anomer (36b) when intramolecular hydrogen bonding was destroyed by the addition of dimethylformamide.

The β-glycoside (37a) was also the predominant product when (36) was reacted with methyl iodide in the presence of NaH in tetrahydrofuran. This result was attributed to a stabilisation of the β-alkoxide ion (175b) by an interaction between the sodium ion, the β-orientated and negatively charged oxygen atom, and a directed lone pair orbital from the C-2 acetal oxygen atom.

If similar considerations apply in the case of arabinofuranose (7), the β-trichloroacetimidate (173b) would be the predicted kinetic product and the possibility of isolating this anomer was explored. Thus, the benzylated arabinofuranose (7) was reacted with an excess of trichloroacetonitrile in dichloromethane using K_2CO_3 rather than NaH as the basic catalyst (Exp. 50.2). It was not possible to follow the progress of the reaction accurately using t.l.c. analysis as there was substantial streaking of

the plates. However, t.l.c. did indicate that a new component, with a mobility different to that obtained using NaH as the catalyst had formed within 36h at room temperature. Efforts to isolate this product by flash chromatography proved unsuccessful as it decomposed on the column. Although ^{1}H nmr spectroscopy of the crude syrup indicated that it was predominantly the same derivative as had been obtained when using sodium hydride as catalyst two resonances (at 105.21 ppm and 91.9 ppm) in its proton decoupled ^{13}C nmr spectrum suggested the presence of a second anomer. The K_2CO_3-catalysed experiment was repeated and terminated after various reaction periods (1, 4, 16 and 30 hours) with a view to obtaining the new component suggested to be present by t.l.c (Exp. 5.3). However, ^{1}H and ^{13}C nmr spectroscopy of the syrups obtained after a simple work up of these reaction mixtures gave no valuable information as the spectra were complicated by the presence of large amounts of starting sugar (7).

Although not fully characterised it appears that an anomerically homogenous arabinofuranosyl trichloroacetimidate (173a) can be prepared by the reaction of the benzylated sugar (7) with trichloroacetonitrile under catalysis by NaH. However, the difficulties encountered in purifying this derivative suggests that it might only have

limited value as a glycon.

In spite of this, a number of experiments were
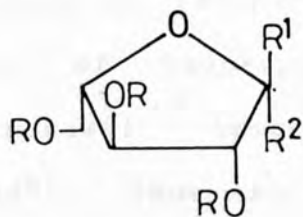
$$7 \quad R^1, R^2 = \text{H or HO}$$
$$147b \quad R^1 = H \quad R^2 = (CH_3)_2CHO$$

$$R = C_6H_5CH_2$$

carried out in order to test its potential in glycosidation reactions. Thus, the benzylated sugar (7) was reacted with trichloroacetonitrile in the presence of sodium hydride and the product filtered after 16h at room temperature and reacted with an excess of isopropanol in dichloromethane in the presence of either 4A molecular sieves, Ag-Z4A, Tl-Z4A and also in the absence of any additive (Exp. 51). T.l.c. analysis after 5h at room temperature indicated that only in the experiment with Ag-Z4A had the corresponding isopropyl glycosides (147) been formed. ^{1}H nmr spectroscopy of this reaction mixture indicated that the β-glycoside (147b) was the predominant anomer (α:β = 1:8).

The catalytic effect of the Ag-Z4A on this reaction was considered surprising as the catalysts usually employed in glycosidations with trichloracetimidates are typically acidic, such as

p-toluenesulphonic acid or boron trifluoride etherate ($BF_3.Et_2O$).

In order to confirm this phenomenon and to investigate it further, the effect of Ag-Z4A on the reaction of isopropanol with tetra-0-benzyl-α-D-glucopyranosyl trichloroacetimidate (170a) was examined[51]. Thus the trichloroacetimidate (170a) was prepared as previously described[37] and its structure (and anomeric configuration) established by ^{1}H nmr spectroscopy. Especially diagnostic were the resonances in its ^{1}H nmr spectrum at 8.5 ppm (1H,s,C=NH) and at 6.5 ppm (H,d,J_{12} 3.5Hz, H-1).

170a R^2 = Cl_3CCO , R^1 = H

176b R^2 = H , R^1 = $(CH_3)_2CHO$

R = $C_6H_5CH_2$
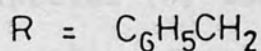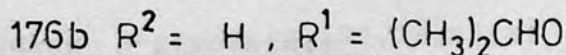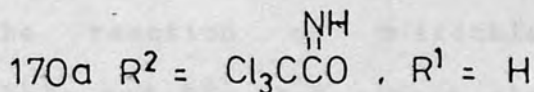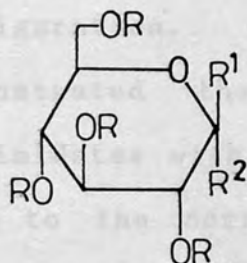
Stoichiometric amounts of this trichloro-acetimidate (170a) and isopropanol were reacted[51] in dichloromethane at room temperature under nitrogen in the presence of either $BF_3.Et_2O$, Ag-Z4A, Ag-Z4A together with crushed 4A molecular sieves, crushed 4A molecular sieves alone and as a control, with no additive. Analysis of the reaction mixtures (t.l.c.)

indicated that only in the experiments with $BF_3.Et_2O$ Ag-Z4A together with crushed 4A molecular sieves, and Ag-Z4A alone, did any glycoside products form [in reaction times of 3, 4 and 6h respectively - as indicated by the complete disappearance of starting trichloroacetimidate (170a)]. This product was isolated in each case by flash chromatography (25, 19 and 13% yield respectively). ^1H nmr spectroscopy indicated that the same product had formed in each of these experiments. The resonance at 1.2 ppm (6H, dd, OCH_3) indicated that it was an isopropyl glycoside, but it was not possible to distinguish the resonance due to H-1, and hence to confirm its anomeric configuration. However, previous work has demonstrated that the reaction of α-trichloro-acetimidates with alcohols and $BF_3.Et_2O$ almost always lead to the corresponding β-glycosides[37,38,40,41]. It was expected (by analogy with this previous work) that the reaction of the α-trichloroacetimidate (170a) with isopropanol would lead to the β-glycoside (176b) when promoted by $BF_3.Et_2O$. It follows therefore, that Ag-Z4A together with crushed 4A molecular sieves, and Ag-Z4A alone must also have promoted the same β-product.

The results of the experiments using the α-glucopyranosyl trichloroacetimidate (170a) and those using the α-arabinofuranosyl trichloroacetimidate demonstrates that AgZ-4A promotes glycosidations of trichloro -

acetimidates. It is difficult to rationalise this effect in terms of a reaction mechanism as only limited information relating to the nature of the catalylic sites in Ag-Z4A is available (see discussion Chapter 4.22). It appears however that the silver present on the surface of this particular promoter plays an important role in its catalytic effect on this reaction; crushed 4A molecular sieves or Tl-Z4A had no such observable catalytic effect.

The following mechanism may be invoked to account for the catalytic effect of the Ag-Z4A promoter on the reaction of isopropanol with the arabinofuranosyl trichloroacetimidate **(173a)**.

$$R = C_6H_5CH_2 , \quad R^1 = (CH_3)_2CH$$
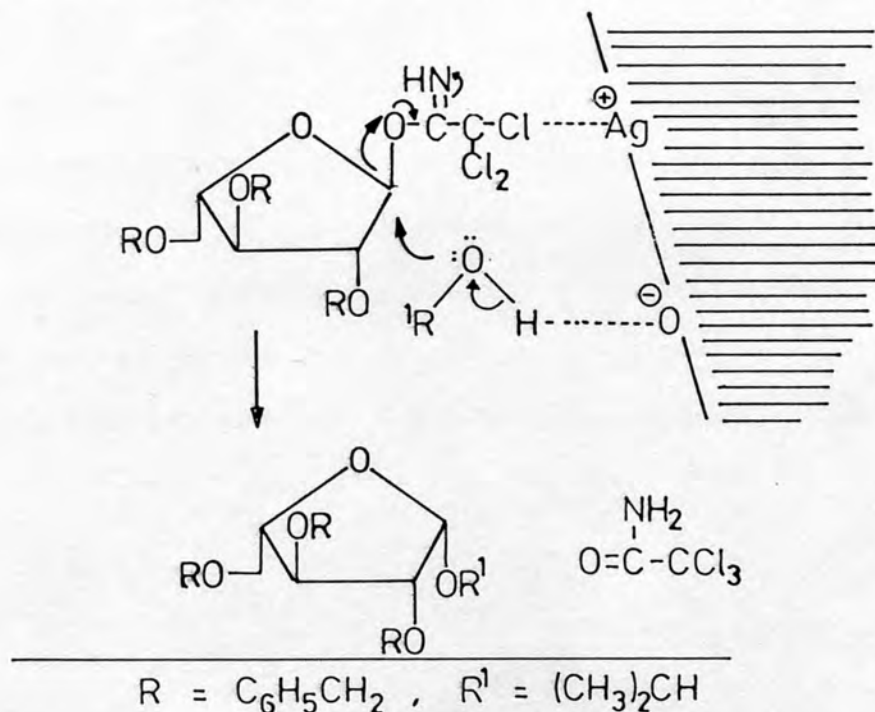
The high stereoselectivity of this reaction is consistent with the view that the trichloroacetimidate derivative forms a zeolite bound transition state, and that this is attacked on its opposite face by the alcohol. The transition state would be expected to be located on the surface of the zeolite as the trichloroacetimidate derivative is too large to penetrate its pores. The anionic sites present on the surface of the zeolite could possibly interact with the alcohol component and assist in the deprotonation process, thus further enhancing the efficiency of this reaction.

CHAPTER 4

PART B: SYNTHESIS OF TARGET ARABINOFURANOSIDES

4.5   Extensin components.

4.51   Introduction and strategy.

Of the glycosidation methods investigated in this
work the one involving 2,3,5-tri-0-benzyl-α-L-
arabinofuranosyl chloride in the presence of
zeolite-supported thallium or silver promoters has met
with particular success in reactions with isopropanol
or cholesterol (see Chapter 4.2). Having established
the general conditions under which the stereoselective
synthesis of β-L-arabinofuranosides can be achieved
using these two model aglycons, it was envisaged that
the method might be extended to glycosidations with
other complex secondary alcohols. Of particular
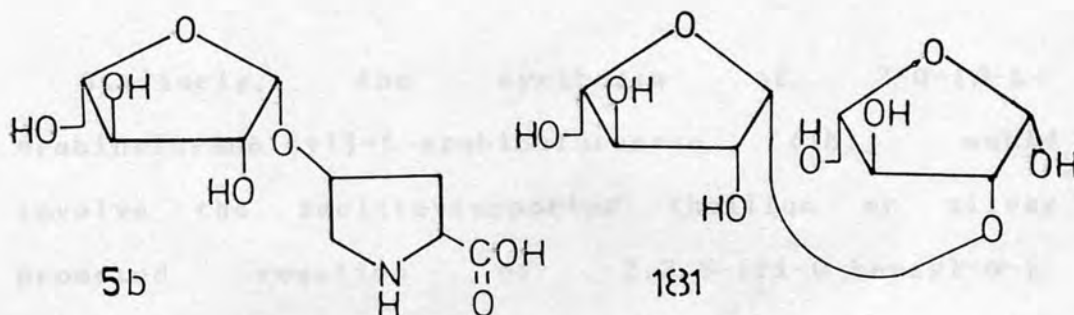
interest in this research work are the two fragments
(5b) and (181), both of which are constituents of the

plant glycoprotein extensin (see Chapter 1).

The synthesis of 4-O[β-L-arabinofuranosyl]-trans-4-oxy-L-proline **(5b)** would involve the zeolite-supported thallium or silver promoted reaction of 2,3,5-tri-O-benzyl-α-L-arabinofuranosyl chloride **(113a)** with a protected trans-4-hydroxy-L-proline derivative [**(133)**, **(134)**, **(136)** or **(137)** - see Chapter 3.4] which would give the corresponding fully protected β-derivative. Catalytic hydrogenolysis of this precursor would remove all the protecting groups and lead to the desired product.
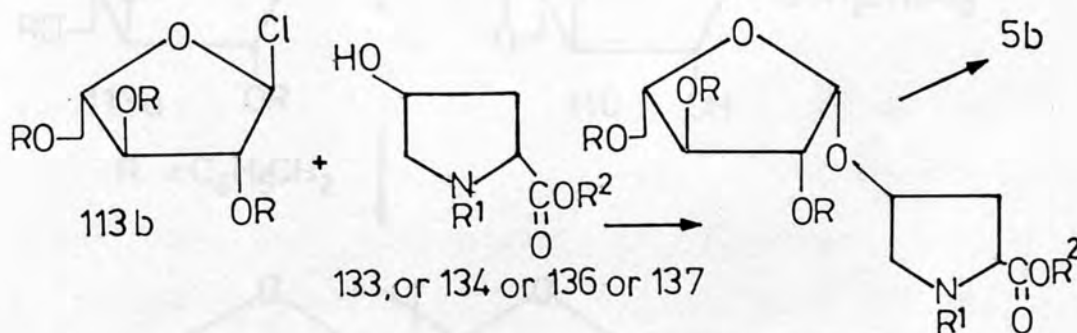
$R = C_6H_5CH_2$, see p211 for structures R^1 and R^2

Similarly, the synthesis of 2-O-[β-L-arabinofurano syl]-L-arabinofuranose **(181)** would involve the zeolite-supported thallium or silver promoted reaction of 2,3,5-tri-O-benzyl-α-L-arabinofuranosyl chloride **(113a)** with Allyl 3,5-O-isopropylidene-α and -β-L-arabinofuranosides

(110) to give the corresponding fully protected β-derivative (182). Deprotection of this compound would involve removal of the allyl group (palladium on activated charcoal with a trace of p-toluenesulphonic acid)[52], removal of the isopropylidene group (mild acid hydrolysis - conditions not expected to effect the O-glycosidic bond[53]) and finally, removal of the benzyl groups (catalytic hydrogenolysis) to give the desired product.

113a + 110

R = C₆H₅CH₂

182   181
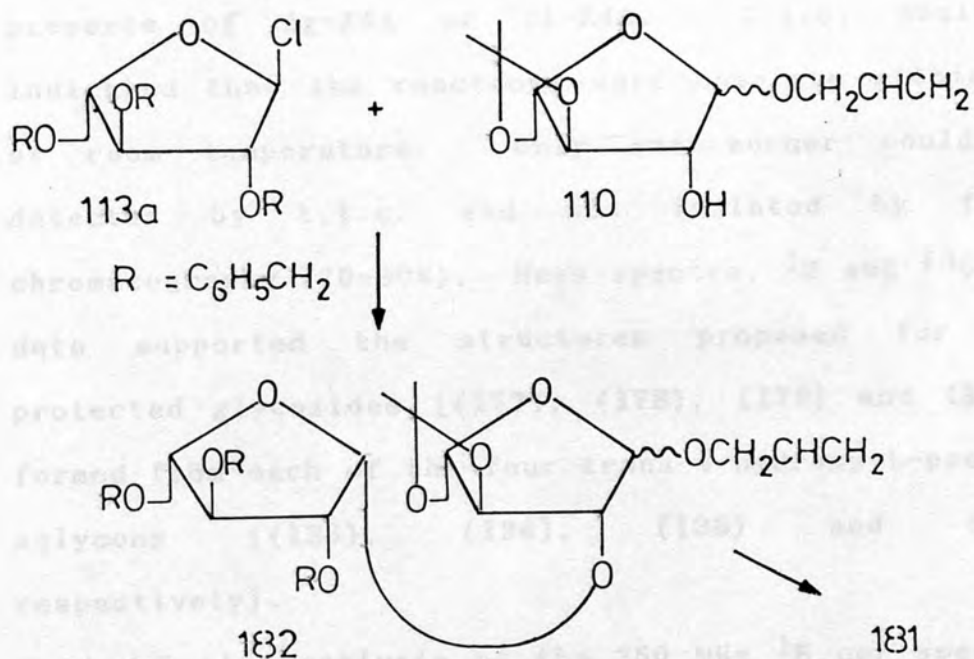
4.52   Results and discussion: arabinosyl hydroxyproline.

2,3,5-tri-O-benzyl-α-L-arabinofuranosyl chloride (113a) was reacted seperately with each of four suitably protected trans-4-hydroxy-L-proline derivatives (133), (134), (136) and (137) (Exp. 52, 53, 54 and 55). In a typical experiment, stoichiometric amounts of the glycon and an aglycon in dichloromethane were stirred under nitrogen in the presence of Ag-Z4A or Tl-Z4A. T.l.c. analysis indicated that the reactions were complete within 4h at room temperature. Only one anomer could be detected by t.l.c. and was isolated by flash chromatography (70-90%). Mass spectra, ^{1}H and ^{13}C nmr data supported the structures proposed for the protected glycosides [(177), (178), (179) and (180)] formed from each of the four trans-4-hydroxy-L-proline aglycons [(133), (134), (136) and (137) respectively].

A detailed analysis of the 250 MHz ^{1}H nmr spectra of the compounds was not undertaken; these spectra comprised many overlapping signals, many of which were heavily split and thus difficult to assign. It proved much more convenient to use ^{13}C nmr data to help establish the structures of the derivatives. The proton decoupled ^{13}C nmr spectra of these compounds

are much less complex than their ^1H nmr spectra. The
interpretation of these ^{13}C nmr spectra was further
simplified through the use of polarisation transfer
techniques (INEPT experiments), which enabled
resonances of C, CH, CH_2 and CH_3 carbons to be
distinguished.

113a

R = $C_6H_5CH_2$

133 R^1 = $(C_6H_5)_2CH$, R^2 = $C_6H_5CH_2O$

134 R^1 = $C_6H_5COCH_2$ R^2 = $C_6H_5CH_2O$

136 R^1 = $(C_6H_5)_2CH$. R^2 = $p-NO_2C_6H_4CH_2O$

137 R^1 = $C_6H_5COCH_2$. R^2 = $p-NO_2C_6H_4CH_2O$

R = $C_6H_5CH_2$

177   R = $(C_6H_5)_2CH$ R^2 = $C_6H_5CH_2O$

178   R = $C_6H_5COCH_2$ R^2 = $C_6H_5CH_2O$

179   R = $(C_6H_5)_2CH$ R^2 = $p-NO_2C_6H_4CH_2O$

180   R = $C_6H_5COCH_2$ R^2 = $p-NO_2C_6H_4CH_2O$
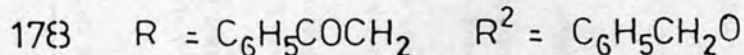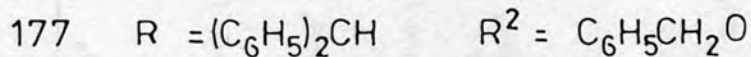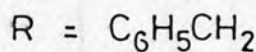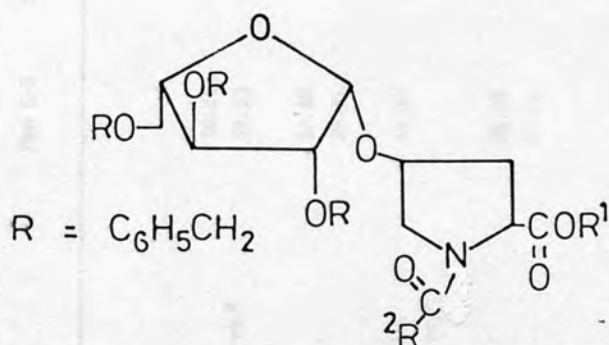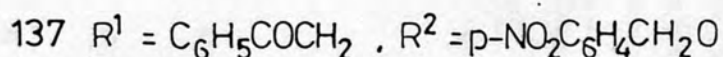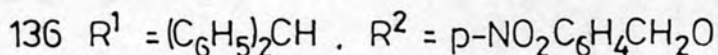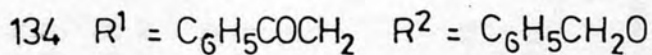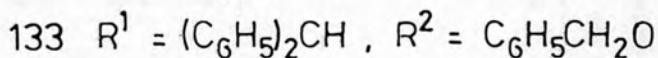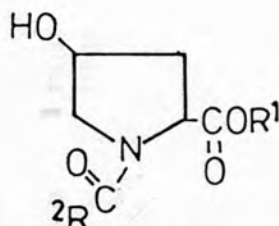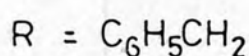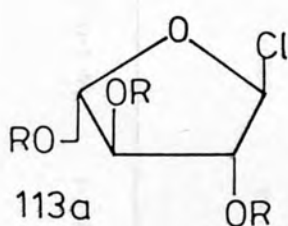
TABLE 4.3

ASSIGNMENT OF SIGNALS IN PROTON DECOUPLED ^{13}C N.M.R. SPECTRA[h,i]

OF O-GLYCOSIDES OF L-ARABINOFURANOSE:

COMPOUNDS (147b), (177), (178), (179), (180), (88a), (148b), (5b) and (5a).

COMPOUND[j]	Imino Acid Carbons					Diphenylmethyl Group Carbons		
	Hyp C-3	Hyp C-5	Hyp C-2	Hyp C-4	Hyp $(-CO_2)$	H -C-	C	-CH (phenyl)
Isopropyl β-L-A (147b)[a]								
N-BOC-4-O- β-L-A -L- Hyp diphenylmethyl ester (177)[a]	36.28 37.33	51.4	58.11 58.40	73.69 75.19	171.72	77.54 77.85	139.86[f]	~127.0 - 128.0(m)[e]
N.BOC-4-O- β-L-A -L- Hyp phenacyl ester (178)[a]	38.40 39.25	51.36	57.62 58.01	73.22 75.52	171.83			
N$_p$NO$_2$BOC-4-O- β-L-A -L- Hyp diphenylmethyl ester (179)[a]	37.37	51.61	58.16 58.40	73.21 75.43	171.42	77.47 77.89	139.58[f]	~126.0 - 128.0(m)[e]
N$_p$NO$_2$BOC-4-O- β-L-A -L- Hyp phenacyl ester (180)[a]	36.69 37.72	51.75	57.89 58.27	73.85 75.53	171.88 172.17			
Methyl α-L-A (88a)[a]								
Cholesteryl β-L-A (148b)[a]								
4-O- β-L-Araf -L-Hyp (5b)[b,c]	37.39	52.24	61.48	77.84	174.10			
4-O α-L-Araf -L-Hyp (5a)[b,c]	37.39	53.16	61.24	77.39	174.15			

a In CDCl$_3$ with reference to Me$_4$Si;   b In D$_2$O with reference to dioxan;   c See Ref. 49 ;   d See experiment 45 for remainder of ^{13}C nmr resonances;   e This assignment is interchangeable;   f This assignment is interchangeable;   g This assignment is interchangeable;   h Chemical shifts in p.p.m.;   i The observed doubling of certain resonances in these spectra was shown to be as a consequence of hindered rotation about the N-O bond (see discussion, Chap. 2 & Table 11;   j A denotes 2,3,5-tri-O-benzyl arabinofuranosyl; Hyp denotes trans-4-oxy proline.

TABLE Continued Overleaf

TABLE 4.3 (Continued)

COMPOUND[j]	N-Blocking Group Carbons					Phenacyl Group Carbons			
	-N-C-O	-O-CH2-	C	m-o-CH (phenyl)	p- -CH or -CNO2(phenyl)	-CH2	-C-O	C	-CH (phenyl)
Isopropyl β-L-A (147)[a]									
N-BOC-4-O- β-L-A -L-Hyp diphenylmethyl ester (177)[a]	154.58 154.92	67.11 67.20 [f]	136.29 156.62 [f]	~127.0 -	128.0 (m)[e]				
N-BOC-4-O- β-L-A -L-Hyp phenacyl ester (178)[a]	154.01	67.20[f]	156.61	~127.0 -	128.0 (m)[e]	67.03[f]	192.50	155.82	~127.0 - 128.0 (m)[e]
N_p NO2 BOC-4-O- β-L-A -L-Hyp diphenylmethyl ester (179)[a]	155.79	65.63	157.38[f]	~127.0 - 128.0(m)[e]	145.30				
N_p NO2 BOC-4-O- β-L-A -L-Hyp phenacyl ester (180)[a]	154.11 154.52	65.79[f]	144.05[g]	~127.0 - 128.0(m)[e]	147.59[g]	66.24 66.24[f]	191.39 191.76	~134(m)	~127.0 - 128.0(m)[e]
Methyl α-L-A (88a)[a]									
Cholesteryl β-L-A (148b)[a]									
4-O- β-L-Araf -L-Hyp (5b)[b,c]									
4-O α-L-Araf -L-Hyp (5a)[b,c]									

TABLE Continued Overleaf

TABLE 4.3 (Continued)

COMPOUND[j]	Sugar Carbons					Benzyl Group Carbons			Other Aglyconic Carbons
	Araf C-1	Araf C-2	Araf C-3	Araf C-4	Araf C-5	-CH$_2$-	C	-C1 (phenyl)	
Isopropyl β-L-A (147h)[a]	98.95	83.89	80.07	84.14		72.35, 72.41, 73.02, 73.59	~138(m)	~128.0(m)	21.56, 23.51 (CH$_3$), 69.85 (OCH)
N-BOC-4-O- β-L-A -L-Hyp diphenylmethyl ester (177)[a]	98.94 99.68	82.60	80.21	85.97		71.88, 72.37, 72.46, 75.53	~138(m)	127.0 - 128.0(m)	
N-BOC-4-O- β-L-A -L-Hyp phenacyl ester (178)[a]	98.78 99.79	82.45	80.21	83.91		72.15, 72.24, 72.56, 72.62	~138(m)	127.0 - 128.0(m)	
N$_p$NO$_2$BOC-4-O- β-L-A -L-Hyp diphenylmethyl ester (179)[a]	98.74 99.79	82.31	80.12	83.97		71.68, 72.24, 72.37, 75.21	~138(m)	126.0 - 128.0(m)	
N$_p$NO$_2$BOC-4-O- β-L-A-L-Hyp phenacyl ester (180)[a]	99.20 99.95	82.66	80.32	84.18		72.09, 72.34, 72.45, 72.57	~138(m)	127.0 - 128.0(m)	
Methyl α-L-A (88a)[a]	107.31	85.43	80.93	88.12		69.83, 71.89, 72.12, 73.38	~138(m)	~128.0(m)	54.94 (OCH$_3$)
Cholesteryl β-L-A (148b)[a]	99.07	85.62	79.97	84.03		72.28, 72.32, 72.94, 75.94	~138(m)	~128.0(m)	77.63 (C^x of Cholesterol)[d]
1-O- β-L-Araf -L-Hyp (5b)[b,c]	101.30	77.59	83.26		64.40				
1-O- α-L-Araf -L-Hyp (5a)[b,c]	107.76	82.67	77.94	85.47	62.72				

The chemical shifts of ^{13}C resonances observed in the proton decoupled ^{13}C nmr spectra of the new compounds were assigned by a systematic comparison[44] with those of related compounds. Thus, the ^{13}C nmr spectra of compounds **(147b)** and **(88a)** were assigned on the basis of a comparison with that of compound **(7)** (compare Tables 3.3 and 4.2). In the same way the ^{13}C nmr spectrum of compound **(147a)** was assigned on the basis of a comparison with those of compounds **(7)** and cholesterol (see Table 4.3 and Exp. 45). Similarly, the ^{13}C nmr spectra of compounds **(177)**, **(178)**, **(179)** and **(180)** were assigned on the basis of a comparison of the ^{13}C nmr spectrum of **(7)** and those of **(133)**, **(134)**, **(136)** and **(137)** respectively (compare Table 3.5 and 4.3). Especially diagnostic of the O-glycosidic
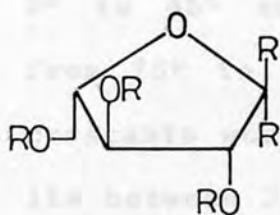
147 b R = $C_6H_5CH_2$ R = H   R = $(CH_3)_2CHO$

88a R = $C_6H_5CH_2$ R = CH_3O R = H

5b   R = R = H   R =
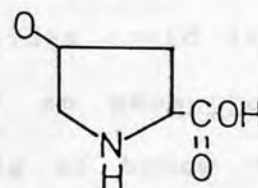
148b   R = $C_6H_5CH_2$ R = H   R = cholesteryl

bond having been formed with the imino acid derivatives, is the downfield displacement (~ 4ppm) of

the ^{13}C nmr resonances of the imino acid C-4 nuclei in the coupled compounds **(177)**, **(178)**, **(179)** and **(180)** compared with the analogous resonances in the uncoupled derivatives **(133)**, **(134)**, **(136)** and **(137)**. A similar downfield displacement is observed when cholesterol becomes O-glycosidically linked, as in the cholesteryl arabinoside **(148a)** (see Table 4.3).

A number of methods have been utilised in order to establish the anomeric configurations of sugars in solution. Assignments based on the magnitudes of the various coupling constants that can be observed in ^{1}H and ^{13}C nmr spectra have been of particular value in the configurational analysis of various sugars. For example, if in a typical furanoid sugar the dihedral angle between neighbouring cis hydrogens can vary from 0° to 45° and between neighbouring trans hydrogens from 75° to 165° [46] then the corresponding coupling constants would be expected from the Karplus curve to lie between 3.5 - 8.0 Hz and 0 - 8 Hz respectively[50]. It follows that 1,2-trans O-glycofuranosides could in theory, be recognised on the basis of an anomeric proton signal displaying a J_{12} splitting of below ~ 3.5 Hz. The splittings observed for H-1 of isopropyl 2,3,5-tri-O-benzyl-β-L-arabinofuranoside and methyl 2,3,5-tri-O-benzyl-α-L-arabinofuranoside have values of ~ 4 Hz and ~ 0 Hz respectively, and could therefore be used to assign the anomeric configurations of these

particular sugars. However, the relationships which have been established to exist between the dihedral angles and coupling constants of glycopyranoid systems are much less well defined in the case of glycofuranoid systems. Although coupling constant data has been used in the configurational analysis of furanoid systems, this information can only be used with caution. The conformational behaviour of these systems is complex making it difficult to predict the projected angles of a given conformer, and therefore the expected coupling constants, with any degree of certainly (see discussion Chapter 2.2).

Another method by which it is possible to identify the anomeric configurations of O-glycosides is through the use of proton decoupled ^{13}C nmr chemical shift data. The ^{13}C nmr chemical shift directly reflects the distribution of electrons surrounding the observed nucleus and is therefore a sensitive probe for the configurational characteristics of a molecule[44]. Furthermore, it appears that the chemical shifts of the ^{13}C nmr signals are insensitive to any conformational or population effects that might occur on O-alkylation or O-glycosidation of pentofuranoid sugars[48]. Such effects could be extremely complex as the energy barriers which exist between various conformers in furanoid systems are often very small (see discussion Chapter 2.2). O-alkylation or

O-glycosidation could conceivably alter the proportions of each conformer, or lead to steric compression which might cause distortion of the ring in one or more conformers. Either of these effects could alter the value of the spin-spin coupling between H-1 and H-2 and indicates an advantage of ^{13}C nmr chemical shift data over spin-spin coupling data in assigning the anomeric configurations of O-glycofuranosides.

The anomeric ring carbon atom in O-glycofuranosides is the most deshielded sugar carbon as a result of being connected directly to two alkylated oxygen atoms and it is therefore easy to distinguish its ^{13}C resonance from those of the other sugar atoms[47,48]. Furthermore, the 1,2-cis arrangement in β-L-arabinofuranosides introduces an important contribution for the C-1 resonance. This appears to be as a result of the greater steric compression expected in this anomer as compared with that in the 1,2-trans anomer[47,48]. The available data suggests that in deprotected O-arabinofuranosides the ^{13}C nmr chemical shift is consistently ~ 6 ppm more shielded in the β- than in the α- anomer typically ~ 102 ppm for the β- and ~ 108 ppm for the α-). Synthetic 4-O-[β-L-arabinofuranosyl]trans-4-oxy-L-proline (5b) has been distinguished from its α-anomer on the basis of their characteristic anomeric ^{13}C nmr

chemical shifts of 101.3 ppm and 107.8 ppm respectively[49]. Similarly, 6-0[β-L-arabinofuranosyl]-α,β-D-glucose and its corresponding α-anomer display anomeric ^{13}C nmr chemical shifts of 101.9 ppm and 108.9 ppm respectively, and have been assigned on the basis of this ^{13}C nmr data[47].

Another attractive feature of using the characteristic C-1 chemical shifts to identify the anomeric configuration of O-arabinofuranosides is that they are little affected by O-alkylations at other positions[43,47,48]. The effect of O-alkylation on a hydroxyl function is to displace the ^{13}C nmr resonance of the appended carbon atom downfield, whereas the resonances of the adjacent nuclei are shifted upfield to a much smaller extent. For example, the chemical shift of the C-1 nucleus in methyl α-L-arabino-furanoside remains at 108.8 ppm ± 0.8 and that of the β-L-anomer at 102.9 ppm ± 0.7 even after methylation or isopropylation at each of the hydroxyl functions at C-2, C-3 and C-5, in turn[47].

It follows from the previous discussion that the anomeric configurations of isopropyl 2,3,5-tri-0-benzyl-β-L-arabinofuranoside and methyl 2,3,5-tri-0-benzyl-α-L-arabinofuranoside can be assigned on the basis the ^{13}C nmr chemical shifts of their anomeric carbon atoms at 99.07 ppm and 107.31 ppm respectively. These assignments support those previously made for

these two compounds in this work on the basis of ^{1}H
nmr spin-spin coupling data (see Chapter 4.2). It was
also possible to assign the anomeric configurations of
each of the protected arabinofuranosides (177), (178),
(179) and (180) through the use of their
characteristic anomeric ^{13}C nmr chemical shift values
(see Table 4.3). Thus, the protected
L-arabinofuranosides of cholesterol (148b) and of the
trans-4-hydroxy proline derivatives [(177), (178),
(179) and (180)] give ^{13}C nmr chemical shifts of ~ 100
ppm for their C-1 nuclei. It follows that these are
all β-anomers by anqlogy with the ^{13}C nmr chemical
shift of ~ 100 ppm observed in the isopropyl
2,3,5-tri-0-benzyl-β-L-arabinofuranoside (147b) (see
Table 4.3). The observed doubling of certain
resonances in the spectra of the Hydroxyprolinyl
arabinosides was shown to be as a consequence of
hindered rotation about the nitrogen-oxygen bond (see
discussion Chapter 3.4 and Table 3.6)

Deprotection of the protected trans-4-hydroxy-L-
proline-L-arabinofuranosides was achieved in one step
by hydrogenolysis at slightly above atmospheric
pressure in the presence of a palladium on activated
carbon catalyst after 24 hours at room temperature
(Exp. 56). Thus, 4-0[β-L-arabinofuranosyl]-trans-4-
oxy-L-proline (5b) (85-95% yield) was obtained by this
method from each of the protected derivatives. The

product gave the reported[49] specific rotation in each case.

4.53 Results and discussion: arabinose
disaccharides.

Stoichiometric amounts of the α-chloride **(113a)** and allyl 3,5-O-isopropylidene-L- arabinofuranoside **(110)** were reacted in dichloromethane under nitrogen with either Ag-Z4A or Tl-Z4A (Exp. 57). The reaction was terminated after 4h at room temperature and the major product isolated by flash chromatography (41% yield). ^{1}H and ^{13}C nmr spectroscopy suggested that it was not composed of the allyl 3,5-O-isopropylidene derivative; the characteristic resonances expected for the allyl and isopropylidene groups were not present in these spectra (see Chapter 3.2).

The proton decoupled ^{13}C nmr spectrum of this compound comprised resonances at 138.2 (m,C,phenyl), 128.0 (m,CH,phenyl), 96.8 (C-1), 83.60, 83.28, 80.40 (C-2,C-3,C-4), 72.88, 72.32, 72.23, 71.97 (C-5; CH$_2$,phenyl). The appearance of this spectrum and the chemical shift of 96.8 (C-1), suggested that the compound might be 2,3,5-tri-O-benzyl-α-L-arabino-furanose. The ^{1}H nmr spectrum was also consistent

$R = C_6H_5CH_2$

113a $R^1 = Cl$, $R^2 = H$

183

$7\begin{cases} R^1 = H, & R^2 = HO \\ R^1 = HO, & R^2 = H \end{cases}$

$\sim OCH_2CHCH_2$

110

OH
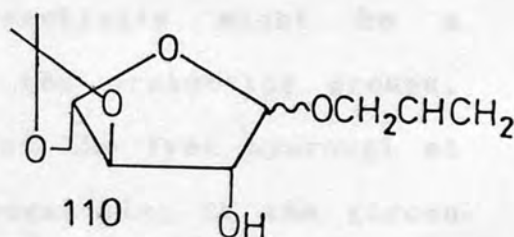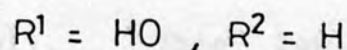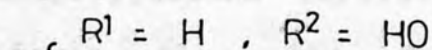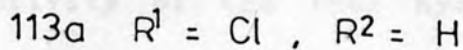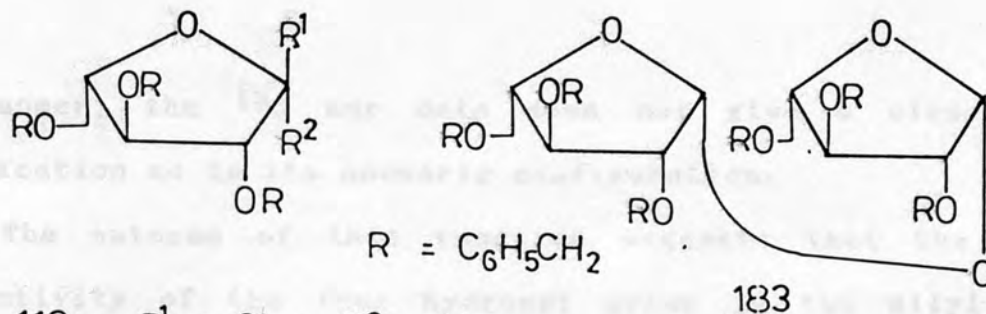
with this view. Especially diagnostic were the resonances at δ 5.42 (1H,d,J_{12} 3.47 Hz, H-1), 4.3, 4.5, 4.6 (6H,m,CH_2Ph), 4.12 (3H,m; H-2,H-3,H-4), 3.52 (2H,d,$J_{5\,5'}$ 5.3 Hz,H-5). However, its physical data do not correspond to those previously reported[54] for this sugar. Furthermore, mass spectroscopy gave its molecular weight as being 821 mass units - much higher than expected for the β-free sugar ($C_{26}H_{28}O_5$ = 420). This molecular weight is consistent with a structure comprising two molecules of 2,3,5-tri-0-benzyl-L-arabinofuranose linked together via an 0-glycosidic bond ($C_{52}H_{54}O_9$). In addition, the simplicity of the proton decoupled ^{13}C nmr spectrum and the ^{1}H nmr spectrum, suggests that it is a symmetrical molecule. However, although the resonance at δ 5.42 (1H,d,J_{12} 3.47 Hz, H-1) in the ^{1}H nmr spectrum suggests (from the magnitude of its splitting) that it is the

β-anomer, the ^{13}C nmr data does not give a clear indication as to its anomeric configuration.

The outcome of this reaction suggests that the reactivity of the free hydroxyl group in the allyl 3,5-O-isopropylidene derivative (110) is relatively low (lower than the free hydroxyl group in cholesterol). This low reactivity might be a consequence of the nature of the protecting groups, but could also be indicative of the free hydroxyl at C-2 of this glycon being inaccessible; if the glycon is mainly the β-anomer, the allyl group at C-1 and the isopropylidine group at C-3 would be expected to restrict the approach of molecules at the C-2 hydroxyl functions. As a consequence, adventitious water would compete effectively with this glycon and lead to hydrolysis of the α-chloride (113a). Attack of the β-free sugar (7) formed by this reaction on a second molecule of α-chloride would give the symmetrical β-disaccharide (183).

It was not possible despite several attempts, to obtain the desired disaccharide product (182) and the approach was not investigated further.

4.6   References.

1.   A.F. Bochkov and G.E. Zaikov, "Chemistry of
      the O-Glycosidic Bond: Formation and Cleavage",
      Pergamon Press (1979).

2.   G. Wolff and G. Rohle, Angew.Chem., 86 (1974)
      173.

3.   W. Koenigs and E. Knorr, Ber., 34 (1901) 957.

4.   B. Helferich and K. Weis, Chem.Ber., 89 (1956)
      314;   S. Hanessian and J. Banoub, Carbohydr.
      Res., 53 (1977) C13.

5.   P.J. Garegg and P.Ossowski, Acta.Chem.Scand.
      B 37 (1983) 249.

6.   P.J. Garegg, C. Henrichson, T. Norberg and
      P. Ossowski, Carbohydr.Res., 119 (1983) 95.

7.   H. Paulsen, Angew.Chem.Int.Ed., 21 (1982)
      155;   H. Paulsen and O. Lockoff, Chem.Ber.,
      114 (1981) 3102;   H. Paulsen and R. Lebuhn,
      Ann.Chem., (1983) 1047.

8.   C.A.A. van Boeckel, T. Beetz and S.F. van Aelst,
      Tetrahedron 40 (1984) 4097-4107.

9.   J.J. Krepinsky, personal communication 1984;
      J.P. Carver, J.J. Krepinsky, D.A. Schwartz,
      R.N. Shah and D.M. Whitfield, to be published.

10.   J.P. Carver, J.J. Krepinsky, R.N. Shah and
      D.M. Whitfield, submitted for publication;
      J.P. Carver, D.A. Cumming, A.A. Grey,
      J.J. Krepinsky and R.N. Shah, Can.J.Chem.,
      in press;   J.P. Carver, J.J. Krepinsky and
      D.M. Whitfield, Carbohydr.Chem., submitted
      for publication.

11.   H. Paulsen, Angew.Chem.Int.Ed., 21 (1982),
      155.

12.   J.V. Smith, Mineralogical Society of America,
      Special Paper No. 1, (1963).

13.   S.M. Csicsery, Chem.Brit., 21, (1985) 473.

14.   K. Igarashi, Adv.Carbohydr.Chem.Biochem.,
      34 (1977) 243; see chapter 2.1.

15. C.P.J. Glaudemans and H.G. Fletcher Jr.,
     J.Org.Chem., 28 (1963) 3004-3006.

16. V. Rothmund, G.Z. Kornfield, Anorg.Allg.Chem.,
     103 (1918) 129; G.Z. Kornfield, Electrochem.,
     23 (1917) 173.

17. D.W. Breck, J.Chem.Ed., 41 No. 12 (1964) 678;
     "Union Carbide Molecular Sieves for Selective
     Adsorption", B.D.H. Chemicals Ltd., Poole,
     England (third ed.)

18. R.U. Lemieux, K.B. Hendriks, R.V. Stick and
     K. James, J.Am.Chem.Soc., 97 (1975) 4056.

19. C.P.J. Glaudemans and H.G. Fletcher Jr.,
     J.Org.Chem., 36 (1971) 3599.

20. E. Zissis and C.P.J. Glaudemans, Carbohydr.Res.,
     50 (1976) 292-295.

21. A.J. Kirby, "The Anomeric Effect and Related
     Stereoelectronic Effects at Oxygen, (Reactivity
     and Structure)" Springer Verlag 1982.

22. F.J. Kronzer and C. Schuerch, Carbohydr.Res.,
     27 (1973) 379.

23. R. Eby and C. Schuerch, Carbohydr.Res., 34
     (1974) 79.

24. V. Dourtoglou and B. Gross, Carbohydr.Chem.,
     2(1) (1983) 57.

25. A. Pinner and F. Klein, Chem.Ber., 10 (1977)
     1889; A. Pinner, "Die Imidoaether und ihre
     Derivative", Oppenheim-Verlag, Berlin, 1892,
     p.1-85.

26. A. Vilsmeir and A. Haack, Chem.Ber., 76 (1927)
     133.

27. H. Eilingsfeld, M. Seefelder and H. Weidinger,
     Angew.Chem., 22 (1960) 85.

28. R. Roger, Chem.Rev., 61 (1961) 188-189;
     M.L. Schulman, Tet.Lett., (1970) 2517;
     E.M. Evans, J.Org.Chem., 33 (1968) 1074.

29. V. Dourtoglou, J.C. Zeigler and B. Gross,
     Tet.Lett., 45 (1979) 4371.

30. V. Dourtoglou, Thesis, Nancy, 1981.

31.   J. Tafel and C. Enoch, Chem.Ber., 23 (1890) 103:
        J. Tafel and C. Enoch, Chem.Ber., 23 (1890)
        1550;   G.D. Lander, J.Chem.Soc., 83 (1908) 320;
        G.D. Lander, J.Chem.Soc., 77 (1900) 729;
        G.D. Lander, J.Chem.Soc., 79 (1901) 690;
        G.D. Lander, J.Chem.Soc., 81 (1902) 591.

32.   J. Pougny and P. Sinay, Tetrahedron Lett.,
        45 (1976) 4073;   J. Pougny, J. Jacquinet,
        M. Duchet, M. Milat and P. Sinay, J.Am.Chem.
        Soc., 99 (1977) 6762;   P. Sinay, Pure Appl.
        Chem., 50 (1978) 1437.

33.   D.R. Hepburn and H.R. Hudson, Chem.Ind.,
        (1974) 664.

34.   J.R. Pougny, Nouv.J.Chim., 2 (1978) 389;
        M.A.M. Nassr, Carbohydr.Res., 77 (1979) 99;
        J.C. Jacquinet, J.Chem.Soc.Perkin.Trans.,
        1 (1979) 314;   J.C. Jacquinet, J.Chem.Soc.
        Perkin.Trans., 1 (1979) 319;   J.C. Jacquinet,
        Tetrahedron, 35 (1979) 365;   J.C. Jacquinet,
        J.Chem.Soc.Perkin.Trans., 1 (1981) 326;
        M.L. Milat, Angew.Chem.Int.Ed.Engl., 18
        (1979) 464;   M.L. Milat, Carbohydr.Res., 92
        (1981) 183;   M.L. Milat, Carbohydr.Res., 100
        (1982) 263.

35.   J.V. Nef, Ann.Chem., 287 (1895) 265;
        D.G. Neilson in "The Chemistry of Amidines and
        Imidates", ed. S. Patai, Wiley, London, (1975)
        p.385.

36.   E.K. Marshall and S.F. Acree, Am.Chem.J., 49
        (1913) 127;   E.K. Marshall, H.P. Harrison and
        S.F. Acree, Am.Chem.J., 49 (1913) 369.

37.   R.R. Schmidt and J. Michel, Angew.Chem.Int.Ed.
        Engl., 19 (1980) 731.

38.   R.R. Schmidt and J. Michel, Tetrahedron Lett.,
        25 (1984) 821;   R.R. Schmidt and M. Stumpp,
        Liebigs.Ann.Chem., (1983) 1249.

39.   F. Cramer, Chem.Ber., 92 (1959) 370;   F. Cramer,
        Chem.Ber., 94 (1961) 976.

40.   R.R. Schmidt and J. Michel, Angew.Chem., 92
        (1980) 763;   R.R. Schmidt and J. Michel ,
        Angew.Chem., 94 (1982) 77;   R.R. Schmidt and
        J. Michel., Angew.Chem., 21 (1982) 72;
        R.R. Schmidt and G. Grundler, Synthesis (1980)
        885;   R.R. Schmidt and G. Grundler, Angew.Chem.,
        94 (1982) 790;   R.R. Schmidt and G. Grundler,

Angew.Chem., 95 (1983) 805; R.R. Schmidt and
G. Grundler, Angew.Chem.Int.Ed.Engl., 21 (1982)
781; R.R. Schmidt and G. Grundler, Angew.Chem.
Int.Ed.Eng., 22 (1983) 776; R.R. Schmidt,
M. Stumpp and J. Michel, Tetrahedron Lett.,
23 (1982) 405; R.R. Schmidt and M. Hoffmann,
Tetrahedron Lett., 23 (1982) 409; R.R. Schmidt
and M. Hoffmann, Angew.Chem., 94 (1983) 417;
R.R. Schmidt and M. Hoffmann, Angew.Chem.Int.Ed.
Engl., 22 (1983) 406; P.H. Amran-Zollo, Diss.,
Univ. of Orleans 1983.

41.   R.R. Schmidt, J. Michel and M. Roos, Liebigs.
       Ann.Chem., (1984) 1343.

42.   A. Liptak, P. Fugedi and P. Nanasi,   Carbohydr.
       Res., 107 (1982) C5-C8.

43.   F.A. Cotton and G. Wilkinson, "Advanced
       Inorganic Chemistry: A Comprehensive Text",
       Wiley, 1972.

44.   J.B. Stothers, Academic Press, 1972;
       F.W. Wehrli and T. Wirthlin, "Interpretation
       of Carbon-13 NMR Spectra", Heyden, 1976.

45.   R.C. Beier and B.P. Mundy, J.Carbohydr.Res.,
       5(2) (1984) 253.

46.   R.U. Lemieux and D.R. Lineback, Ann.Rev.
       Biochem., 32 (1963) 155.

47.   P.A.J. Gorin and M. Mazurek, Carbohydr.Res.,
       48 (1976) 171.

48.   R.G.S.Ritchie, N. Cyr, B. Koch , H.J. Korsch
       and A.S. Perlin, Can.J.Chem, 53 (1975) 1424.

49.   A. Allerhand, K. Dill, E. Berman,
       J.M. Lacombe and A. Pavia, Carbohydr.Res.,
       97 (1981) 331.

50.   B. Capon, D. Thacker, Proc.Chem.Soc., (1964)
       369.

51.   C. Moss, Research work undertaken for final
       year undergraduate project, Royal Holloway
       and Bedford New College, (University of
       London) (1986).

52.   R. Boss and R. Sheffold, Angew.Chem.Int.Ed.,
       15 (1976) 558.

53.   R.R. Schmidt and M. Reichrath, Angew.Chem.Int.
       Ed., 18 (1979) 466.

54.   S. Tejima and H.G. Fletcher Jr., J.Org.Chem.,
       28 (1963) 2999.

55.   W. Korytnyk and J.A. Mills, J.Chem.Soc.
       (1959) 636.

CHAPTER 5

EXPERIMENTAL

5.1   General Experimental Techniques[18],[19]

Concentrations: were   carried   out   under   reduced
pressure   (and   usually   at   under   40º)   using   a   Buchi
rotary evaporator.

Dry apparatus: all glassware was kept at ~ 200º and
assembled   hot   under   nitrogen.   All   subsequent
manipulations   were   carried   out   with   a   positive
nitrogen pressure (nitrogen was not passed through the
reaction vessel when it was sealed so as to minimise
evaporation of reaction solvents.

Dry hydrogen chloride gas: was prepared as previously
described[18].   This   was   bubbled   into   dry
dichloromethane   to   make   the   saturated $CH_2Cl_2/HCl(g)$
reagent.

Dry   solvents: Allyl   alcohol   (distilled   on   to
activated 4A molecular sieves); chloroform (refluxed
with $CaCl_2$ and distilled); dichloromethane (distilled
from CaH_2,   immediately   before   use);   diethyl   ether
(pre-dried   over $CaCl_2$ and   then   dried   over   sodium
wire); dimethyl sulphoxide (distilled from CaH_2 under
vacuum on to activated 4A molecular sieves); methanol

(using magnesium as previously described[18]); pyridine (refluxed with and distilled from CaH_2 on to activated 4A molecular sieves); Tetrahydrofuran (refluxed with and distilled from $LiAlH_4$).

Dry solids and syrups: under vacuum (~0.5mm Hg) at room temperature for 6-24h. Molecular sieves were activated by heating in an oven at ~ 200° for ~ 36h.

Exclusion of light: experiments sensitive to light were carried out in reaction vessels that were covered with either silver foil or dark plastic sheets.

Elemental analyses: were done at the Butterworth Laboratories Limited (Teddington, Middlesex) or by the Service at Royal Holloway and Bedford New College .

Flash chromatography: was conducted following the method described by Still, Khan and Mitra[8]. The silica gel used was Kieselgel 60 (230-400 mesh ASTSM) supplied by Merck, Darmstadt, West Germany. The solvent systems employed correspond to those used in t.l.c. analysis of the compounds.

Ion exchange resin: 'Amberlite' resin IR-45 (OH), analytical grade supplied by BDH Chemicals Limited, Poole, England. This was suspended in the appropriate solvent (either methanol or allyl alcohol) for 24h before use, filtered and packed using fresh solvent.

Mass spectra: were recorded using either a VG ZAB-1F spectrometer [fast atom bombardment (f.a.b.);

thioglycerol - oxalic acid matrix; (School of Pharmacy, University of London)] a Micromass 16F spectrometer [chemical ionisation (c.i.); butane; (Chelsea College, University of London)] or a VG 12F spectrometer [c.i; methylamine; (Royal Holloway and Bedford New College, University of London)].

Melting points: were determined in capilliary tubes with a Thomas-Hoover melting point apparatus and are uncorrected.

Nuclear magnetic resonance (n.m.r.) spectra: were run either on a Joel FX90Q spectrometer [^{1}H, 89.6 MHz; ^{13}C, 22.5 MHz; (Royal Holloway and Bedford New College, University of London)] a Brucker WM-250 spectrometer [^{1}H, 250.13 MHz; ^{13}C 62.9 MHz; (King's College, University of London)] or a Brucker WH-400 spectrometer [^{1}H, 400.13 MHz; ^{13}C, 100.0 MHz; (Queen Mary College, University of London)]. The pulse sequences were constructed using the manufacturers software and all tuning and phase changes were under software control.

Optical rotations: were measured at 20-25° using either a Perkin-Elmer 141 or a Perkin-Elmer 241 polarimeter.

Sodium hydride: was obtained as a 60% dispersion in mineral oil. The mineral oil was removed by washing this dispersion several times with dry diethyl ether under nitrogen, immediately before using the reagent

for an experiment.

Thin layer chromatography (t.l.c.): was done on 'Polygram Sil G', 5 x 20 cm pre-coated plastic sheets supplied by Machery-Nagel and Company, Duren, West Germany. The solvent systems employed were Solvent A (petroleum ether, ethyl acetate; 1:3 v/v); Solvent B (petroleum ether, ethyl acetate; 3:1 v/v); Solvent C (butanol, ethanol, water; 40:19:2); Solvent D (petroleum ether, ethyl acetate; 8:1); Solvent E (ethyl acetate, ethanol, water; 5:3:2); Solvent F (ethyl acetate, petroleum ether; 1:4); Solvent G (ethyl actate, petroleum ether; 1:2); Solvent H (ethyl acetate, petroleum ether; 1:1). The plates were "developed" by spraying with a solution of sulphuric acid in ethanol (5% w/v) and heating at 100°.

5.2   Synthesis of precursors (see Chapter 3).

5.21   *Hydroxy-L proline derivatives.*

Exp.   1   N-(Benzyloxycarbonyl)-trans-4-hydroxy-L-proline cylohexylammonium salt (132).

Trans-4-hydroxy-L-proline (2) (6.65g., 50mmol) was treated with benzyl chloroformate (9.8g., 57.5mmol), and then cyclohexylamine (6.65ml., 55mmol) following the method described by Baer and Stedman[1] to give

(132) (16.2g., 89%); m.p. 190º-192º(dec.); $[\alpha]_D$ -43.2º (C,3 H_2O); [Lit.[1] m.p. 191º-192º(dec.); $[\alpha]^{25}_D$ -43.9º (C,5 H_2O)]; [1]H-nmr data (DMSO-D[6]): δ 7.31 (5H,m,Ph), 5.01 (2H,m,$\underline{CH}_2C_6H_5$), 4.23 (1H,m,H-2), 4.03 (1H,m,H;4), 3.45, 3.25 (2H,m,H-5), 2.81 (1H,broad,OH), 2.08-1.11 (m,cyclohexylamine) also at ~ 2.5 (m); ^{13}C-nmr data (DMSO-D[6]): See Table 3.5 for other resonances; δ 79.12, 48.96, 31.07, 24.70, 23.91.

Exp. 2   N-(Benzyloxycarbonyl)-trans-4-hydroxy-L-proline (131).

(132) (5.47g., 15mmol) was converted, following the method described by Baer and Stedman[1], into the syrup **(131)** (3.75, 94%); $[\alpha]$, -77.4º (C,3 $CHCl_3$); [Lit.[1] $[\alpha]^{26}_D$: -77.7º (C,3 $CHCl_3$) and[2] $[\alpha]^{20}_D$ - 72.0º (C,1 $CHCl_3$)]; ^{1}H nmr data (DMSO-D[6]): δ 7.33 (5H,m,Ph), 5.06(2H,m,$\underline{CH}_2C_6H_5$) 4.24 (1H,m,H-4), 4.03 (1H,m,H-2) ~3.35 (2H,m,H-5) 2.17, 1.94 (2H,m,H-3) also ~ 2.5(m); ^{13}C nmr data: see Table 3.5.

Exp. 3   Diphenyldiazomethane

A mercuric oxide oxidation of benzophenone hydrazone (13g., 0.066mol) using a basic catalyst following the method described by Miller[3] gave diphenyldiazomethane (11.8g., 90%); m.p. ~ 30º-33º; (Lit.[3] m.p. 29º-32º and[4] m.p. 29º-30º.

Exp. 4 N-(Benzyloxycarbonyl)-trans-4-hydroxy-L-
proline diphenylmethyl ester (133).

Diphenyldiazomethane, (2.5g., 0.0129mol) was added
in small portions (over 30 min) to a vigorously
stirred, occasionally cooled (0°, ice bath) solution
of (131) (3.1g., 0.012mol) in dry acetone (25ml). The
mixture was stirred for a further 4h at room
temperature, during which it turned from a deep violet
to a yellow colour and (131) disappeared (t.l.c.,
solvent A). The solution was concentrated to dryness
and the residue redissolved in ethyl acetate (30ml).
This mixture was filtered to removed any insoluble
material. A white solid (4.9g) was precipitated
almost immediately upon addition of dilute aqueous
sodium bicarbonate (~ 20ml) or water (20 ml) to this
filtrate. The solid was collected by filtration,
washed with water (recrystallised from ethanol) and
dried to give (133) (4.1g., 79%); m.p. 117°-119°; $[\alpha]_D$
-55.4° (C,1.25 CHCl$_3$); (Found C, 72.48; H, 5.73.
C$_{26}$H$_{25}$O$_5$N required C, 72.30; H, 5.79%; ^{1}H nmr data
(DMSO-D$_6$): δ 7.28 (15H,m,Ph), 5.08, 4.49 (4H,m; H-2;
CHC$_6$H$_5$), 4.49 (1H,m,H-4), 4.28 (1H,broad,OH) ~3.3
(2H,m,H-5), 2.25, 1.94 (2H,m,H-3); ^{3}C nmr data: see
Table 3.5.

Exp.   5   N-(Benzyloxycarbonyl)-trans-4-hydroxy-L-proline phenacyl ester **(134)**.

5.1   Method A

Triethylamine (1.5ml., 0.012mol) and bromoaceto-phenone (2.4g., 0.012mol.) were added to a solution of **(131)** (3.2g., 0.012mol.) in ethyl acetate (20ml) and the mixture stirred for 20h at room temperature.

Precipitated triethylamine hydrobromide was removed by filtration and the filtrate washed successively with water, dilute aqueous sulphuric acid, aqueous potassium hydrogen carbonate, again with water, dried ($MgSO_4$) and concentrated to give a clear syrup (4.2g).   The residue could not be made to crystallise and changed to a viscous, cloudy yellow syrup over a period of time (3 weeks).   This syrup comprised several components (t.l.c., solvent A). Fraction 1, ~0.9; $[\alpha]_D$ - 3.2º (C,2 CHCl$_3$) and fraction 3, Rf ~ 0.2; $[\alpha]_D$ - 74º (C,2 CHCl$_3$) which corresponds to starting material **(131)** were discarded.   Fraction 2 (Rf ~ 0.5) crytallised on standing (~ 1 week, room temperature) and after recrystallisation (from ethanol) gave **(134)** (1.4g., 30%); m.p. 72º-73º; $[\alpha]_D$ -77.82º (C, 1.23 CHCl$_3$); (Found: C, 65.51; H, 5.46. $C_{21}H_{21}O_6N$ requires C, 65.73; H, 5.48%); ^1H nmr data (DMSO-D$_6$): δ 7.96, 7.70, 7.56, 7.35 (10H,m,Ph), 5.53 (3H,m; $CH_2C_6H_5$ and H-2)[a] 5.19 (1H, broad) 5.07 (2H,$CH_2C_6H_5$)[a]   4.51,   4.36[b]   (2H,m,4-H)[a]   ~   3.35

(2H,m,H-5) 2,51,2.27 (2H,m,H-3)[a]. These assignments are only tentative, [b] broad; ^{13}C nmr data: see Table 3.5.

5.2 Method B

Triethylamine (1.5ml., 0.012mol) and bromoacetophenone (2.1g., 0.012mol) were added to a cold (~ 0°, ice bath) solution of (131) (3.0g., 0.012mol) in absolute ethanol (30ml). The mixture was then stirred for 5h at room temperature and for a further 10 hours in the cold (0°, ice bath). The reaction mixture comprised several minor components (t.l.c., solvent A) the major one being the starting material (131) (Rf ~ 0.2). Efforts to make (134) using this particular method were discontinued.

5.3 Method C

Potassium fluoride (1.28g., 0.022mol) and α-bromoacetophenone (1.99g., 0.01mol) were stirred together in N,N-dimethylformamide (10g) for 5 min at room temperature. (131) (3g., 0.01mol) was added and the reaction mixture stirred for ~ 1h at room temperature. When (131) had completely disappeared (t.l.c., solvent A) the reaction mixture was extracted with diethyl ether. The combined ethereal extracts were washed three times with water (to remove the DMF), dried ($MgSO_4$) and concentrated to a syrup (~ 3.6g.) which crystallised (from ethanol) to give (134) (2.8g., 73%); m.p. 71°-73°; $[\alpha]_D$ - 76.9° (C, 1.48

CHCl$_3$).

Exp. 6   N-(p-Nitrobenzyloxycarbonyl-trans-4-hydroxy-
L-proline (135).

A solution of p-nitrobenzyl chloroformate
(12.39g., 57.5mmol) in cold acetone (50ml) was added
(dropwise, over 30 min) to a cooled (0°, ice bath),
vigorously stirred solution of (2) (6.65g., 50mmol) in
water (50ml) containing potassium bicarbonate (5.0g.,
50mmol) and anhydrous potassium carbonate (17.3g.,
125mmol). The mixture was stirred for a further 4h
at 0°, during which it turned from a cloudy white to a
yellow colour. The mixture was diluted with water
(200ml.) and extracted with diethyl ether (3 x 100
ml). The aqueous solution was cooled (0°, ice bath),
brought to a pH ⩽ 2 (universal indicator paper) with
concentrated hydrochloric acid and extracted with
ethyl acetate (3 x 120ml). The combined extracts were
concentrated to a syrup (~ 14.2g) which crystallised
(on standing 1-4h, 0°) to give (after
recrystallisation from amyl acetate or ethyl acetate)
(135) (13.9g., 89%); m.p. 133°-136°; [α]$_D$ - 40.48 (C,1
CHCl$_3$); [Lit.[5] (~ 66%); m.p. 136.5°-139°; [α]$^{25}_D$ -
41.6° (C,1 N sodium hydroxide)]; ^{1}H nmr data
(DMSO-D$_6$): δ 8.22, 7.61 (4H,m,Ph), 5.22 (3H,m,CH$_2$C$_6$H$_5$
and H-2), 4.29 (2H,m,H-4), ~ 3.35 (2H,m,H-5), 2.20,
1.95 (2H,m,H-3) also at ~ 12.78; ^{13}C nmr data: see

Table 3.5.

Exp. 7   N-(p-Nitrobenzyloxycarbonyl)-trans-4-hydroxy-
L-proline diphenylmethyl ester (136).

A solution of (135) (2.33g., 0.0075mol) in dry
acetone (25ml) was treated with diphenyldiazomethane
(1.6g., 0.0085mol) as described for the preparation of
(133) which after recrystallisation (from ethanol)
gave (136) (2.6g., 72%); m.p. 160°-161°; $[\alpha]_D$ - 36.0°
(C,1.4 CHCl$_3$); (Found: C, 65.13; H, 5.11. C$_{26}$H$_{24}$O$_7$N$_2$
requires C, 65.54; H, 5.08%); ^{1}H nmr data (DMSO-D$_6$): δ
8.2, 8.0, 7.5 7.3, 6.8 (14H,m,Ph), 5.22 (3H,m; $\underline{CH}$C$_6$H$_5$
and $\underline{CH}_2$C$_6$H$_5$) 5.05 (1H,m,H-2), 4.61, 4.49 (1H,m,H-4),
4.3 (1H, broad, OH), ~3.35 (2H,m,H-5), 2.25, 1.98
(2H,m,H-3); ^{13}C nmr data: see Table 3.5.

Exp. 8   N-(p-Nitrobenzyloxycarbonyl)-trans-4-hydroxy-
L-proline phenacyl ester (137).

(135) (3.1g., 0.01mol) was treated with potassium
fluoride (1.28g., 0.022mol) and α-bromoacetophenone
(1.99g., 0.01mol) in N,N-dimethylformamide (10g) as
described for the preparation of (134), (Exp. 5.3) to
give after recrystallisation (from ethanol) (137)
(2.9g., 67.7%); m.p. 79°-82°; $[\alpha]_D$ - 68.2° (C,1
CH$_2$Cl$_2$); (Found: C, 58.95; H, 4.74. C$_{21}$H$_{20}$O$_8$N$_2$
requires C, 58.88, H, 4.71%); ^{1}H nmr data (CDCl$_3$): δ
8.22, 7.89, 6.64, 7.24, 7.28 (9H,m,Ph), 5.60

(2H,m,CH$_2$C=O), 5.25 (3H,m; H-2 and C̲H$_2$C$_6$H$_5$), 4.72 (2H,m,H-4), 3.72 (2H,m,H-5), 2.52 (2H,m,H-3) also 1.7 (broad, OH); ^{13}C nmr data: see Table 3.5.

Exp. 9   Trans-4-hydroxy-L-proline from (133) (134), (136) and (137).

In a typical experiment (133) (1.5g., 3.48mmol) in aqueous methanol (80% v/v, 25ml) was hydrogenated over a palladium (10%) on charcoal catalyst (~ 200mg). The reaction was stirred at room temperature until the starting material had disappeared (t.l.c., solvent A) and hydrogen uptake had ceased (2 - 24h). The solution was concentrated to give a residue which was rediluted with methanol and again concentrated to give a clear syrup (0.43g.) which crystallised (from ethanol) to give (2) (0.42g., 92%); m.p. 274°-275° (dec.); [α]$_D$ - 74.2^o (C,2 H$_2$O); [Lit., m.p. 273°-275° (dec.); [α]$_D$ -75.3^o (C,20 H$_2$O)]; ^{1}H nmr data (D$_2$O):δ 4.85 (OH), 4.65 (1H,m,H-4), 4.35 (1H,m,H-2), 3.48 (2H,m,H-5), 2.32 (2H,m,H-3); ^{13}C nmr data (D$_2$O): see Table 3.5.

5.22   Arabinofuranose glycon precursor

Exp. 10   Allyl-L-arabinofuranosides (91).

Concentrated sulphuric acid (0.4ml) was added

(dropwise) to a stirred, cooled (0°, ice bath) suspension of dry L-arabinose **(90)** (30g., 0.2mol), anhydrous allyl alcohol (900ml., 13.2mol) and calcium sulphate (20g). The mixture was stirred for 7-9h at room temperature and as soon as the arabinose had disappeared (Fehling's solution) it was filtered and passed through a column of IR45 (OH) resin (150ml). The resin was washed with fresh allyl alcohol (400ml) and the combined solution and washings concentrated to give **(91)** (36g., 95%); ^{13}C nmr data: see Table 3.1.

Exp. 11 Allyl 2,3,5-tri-O-acetyl-L-arabinofuranosides (94).

Acetic anhydride (0.96ml., 0.01mol) was added (dropwise, ~ 15 min) to a vigorously stirred, cooled (0°, ice bath) solution of **(91)** (0.5g., 2.63mmol) in dry pyridine (2.5ml) under nitrogen. The mixture was left stirring for one hour at 0° and for a further 24h at room temperature, poured into ice water (20ml) and extracted with dichloromethane. The organic solution was washed with cold aqueous 2N hydrochloric acid, dilute aqueous $NaHCO_3$, dried ($MgSO_4$) treated with activated carbon and concentrated. Flash chromatography of the residue gave as the first (t.l.c; solvent B, Rf ~ 0.39) fraction **(94)** (3.8g., 46%); M(mass spectrum, c.i.), 316. $C_{14}H_{20}O_8$ requires M, 316; ^1H nmr data ($CDCl_3$): δ 5.9 (1H,m,OCH$_2$C$\underline{H}$=CH$_2$),

5,38, 5.26, 5.07 (5H,m; H-1, O$\underline{CH_2}$-CH$_2$=$\underline{CH_2}$), 4.46, 4.27, (3H,m; H-2,H-3,H-4), 4.05 (2H,m,H-5), 2.12 (15H,m,3Ac); ^{13}C nmr data: see Table 3.2.

Exp. 12   Allyl 2,3,5-tri-O-benzoyl-L-arabinofuranosides (95).

A solution of (91) (0.5g., 2.63mmol) in pyridine (2.5ml) was reacted with benzoyl chloride (1.2ml., 10mmol) as described for the preparation of (94) to give after flash chromatography of the residue the first (t.l.c., solvent B) fraction (95) (0.75g., 57%); M(mass spectrum, c.i.), 534 (M + CH$_3$NH$_3^+$). C$_{29}$H$_{26}$O$_8$ requires M, 502; ^{1}H nmr data (CDCl$_3$):   8.1, 7.5 (15H,m,3Ph), 6.0, 5.2-5.6, (5H,m; H-1, O$\underline{CH_2}$-CH=$\underline{CH_2}$), 4.0-4.9 (5H, m; H-2, H-3, H-4, H-5); ^{13}C nmr data: see Table 3.2.

Exp. 13   Allyl 2,3,5-tri-O-(tert-butyldimethylsilyl)-L-arabinofuranosides (96).

tert-Butyldimethylsilyl chloride (1.39g., 9.2mmol) and imadazole (1.26g., 18.4mmol) were added to a solution of (91) (0.25g., 1.32mmol) in dry pyridine (2.6ml).   The mixture was stirred for 48h at room temperature and then concentrated.   Flash chromatography of the residue gave as the first (t.l.c., solvent D, Rf 0.65) fraction (96) (0.35g., 55.6%); M(mass spectrum, c.i.), 508 (M + CH$_3$NH$_3^+$).

$C_{26}H_{56}O_5Si$ requires M, 476; ^{1}H nmr data (CDCl$_3$): δ 5.94 (1H,m,OCH$_2$-C$\underline{H}$=CH$_2$), 5.24, (4H,m,OC$\underline{H}_2$-CH=C$\underline{H}_2$), 4.89, 4.82 (1H,m,H-1), 3.78, 4.0, 4.1 (5H, m; H-2, H-3, H-4, H-5), 0.9 (27H,m,9C-CH$_3$), 0.06 (18H,m,6 Si-CH$_3$); ^{13}C nmr data: see Table 3.2.

Exp. 14   Allyl β-L-arabinopyranoside (97).

Concentrated sulphuric acid (0.1 ml) was added to a stirred suspension of dry L-arabinose (90) (1.0g., 6.7mmol), anhydrous allyl alcohol (20ml., 0.3mol) and calcium sulphate (0.5g). The mixture was heated under reflux for 2h at 100° (water bath), filtered and when at room temperature passed through a column of IR45 (OH) resin (20ml). The resin was washed with fresh allyl alcohol (25ml) and the combined solution and washings concentrated. The residue comprised one component (t.l.c., solvent C, Rf 0.6) which was crystallised from ethanol to give (97) (1.2g., 90%); m.p. 118°-120°; [α]$_D$ + 179.4 (C,1 H$_2$O); Found: C, 50.32; H, 7.44. C$_8$H$_{14}$O$_5$ requires C, 50.51; H, 7.42; ^{13}C nmr data: see Table 3.1.

Exp. 15   Methyl 2,3,5-tri-O-benzyl-L-arabinofuranosides) (88).

15.1   Method A

A suspension of dry methyl-L-arabinofuranoside[7] (31.2g., 0.19mol), benzyl chloride (200ml., 1.7mol),

powdered potassium hydroxide (156g., 2.8mol) and calcium sulphate (30g) in dry tetrahydrofuran (400ml) was stirred (mechanical) and heated (gentle reflux) for 16-20h under nitrogen. The mixture was filtered, concentrated and steam distilled until benzyl alcohol, benzyl chloride and dibenzyl ether had been appreciably removed (t.l.c. solvent B). Flash chromatography of the residue gave a major fraction (t.l.c., solvent B, Rf ~ 0.62 and 0.56) (88) (57g., 70%). ^{1}H nmr data includes: δ 4.95 (α-H-1) and 4.72 (J_{12} 3.67 Hz, β H-1) and also 3.39 (α-OCH$_3$) and 3.31 (B-OCH$_3$).

Repeated flash chromatography of this fraction resolved the α-anomer (88a) (41.1g., 50%); $[\alpha]_D$ -43.8° (C,1 CH$_2$Cl$_2$); [Lit.[6], $[\alpha]_D^{20}$ -44.6° (C,6.0 CH$_2$Cl$_2$)]; ^{1}H nmr data: δ 7.3 (15H,m,Ph), 4.95 (1H,s,H-1) 4.6-4.4 (6H,m,C$_6$H$_5$CH$_2$), 4.22 (1H,m,H-4), 3.99 (1H,m,H-2), 3.88 (1H,m,H-3), 3.6 (2H,m,H-5), 3.39 (3H,s,CH$_3$); ^{13}C nmr data: see Table 3.3.

15.2   Method B

A solution of dry (88) (5.5g., 0.029mol) in dry dimethyl sulphoxide (15ml) was added (dropwise, ~ 30 min) to a vigourously stirred (mechanical), cooled (0°, ice bath) suspension of sodium hydride (~ 6., 0.25mol) in dimethyl sulphoxide (20ml) under nitrogen. The mixture was left stirring for ~ 1h at room

temperature during which it turned from a deep yellow to a dark red colour and became quite viscous. Benzyl chloride (13.5ml., 0.096mol.) was added (dropwise, 30 min.) to the vigorously stirred, cooled (0°, ice bath) mixture which was left for a further 3-12h at room temperature. Methanol (~ 5ml) was added to destroy the excess sodium hydride and the mixture was diluted with ice water (200ml) extracted with diethyl ether, dried (MgSO$_4$), treated with activated carbon, filtered and concentrated. Flash chromatography of the residue gave a major fraction (t.l.c., solvent B, ~ Rf 0.62 and 0.56) **(88)** (12.0g., 95%); ^{1}H nmr data: see Exp. 15.1; ^{13}C nmr data: see Exp. 15.1.

Exp. 16   Allyl 2,3,5-tri-0-benzyl-L-arabinofuran-osides **(92).**

A solution of dry **(91)** (5.5g., 0.029mol.) in dry dimethylsulphoxide (15ml) was treated with sodium hydride (~ 6g., 0.25mol) and benzyl chloride (13.5ml., 0.096mol) as described in the preparation of **(88)**, (Exp. 15.2). Flash chromatography of the residue gave a major fraction (t.l.c., solvent B, ~ Rf 0.6) **(92)** (12.6g., 94%); ^{1}H nmr data (CDCl$_3$): δ 7.2 (15H,m,3Ph), 5.8 (1H,nm,OCH$_2$CH=CH$_2$), 5.23, 5,04, 4.82, (5H,m; H-1, OCH$_2$CH=CH$_2$), 4.41 (6H,m,CH$_2$Ph), 3.4 (2H,m,H-5); ^{13}C nmr data: see Table 3.3. Repeated flash chromatography of this fraction resolved the β-anomer

(6.5g., 0.49%); $[\alpha]_D$ +50.3 (C,1 CH_2Cl_2).

Exp. 17   Prop-1-enyl 2,3,5-tri-O-benzyl-L-arabino-furanosides (93).

17.1   Method A.

A solution of dry (92) (0.5g., 1.1mmol) and potassium tert-butoxide (0.63g., 5.5mmol) in dry dimethyl sulphoxide (5ml) was stirred under nitrogen for 15-45 min at 100° (oil bath, under reflux). The mixture was allowed to cool, diluted with water extracted with diethyl ether, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue gave a major fraction (t.l.c., solvent B ~ Rf 0.77) (93) (0.44g., 87%); ^1H nmr data ($CDCl_3$): δ 7.3 (15H,m,3Ph), 6.18, (1H,dd,prop-1-enyl), 5.26 (1H,s,H-1), 4.25, (7H,m;CH_2Ph,O$\underline{CH}$=CH-CH_3), 4.3, 4.19, 4.05 (3H,m; H-2,H-3,H-4), 3.6 (2H,m,H-5), 1.59 (3H,m,OCH=CH-$\underline{CH}_3$); ^{13}C nmr data: see Table 3.3.

17.2   Method B.

A solution of (92) (0.5g., 1.1mmol), 1,4-diazobicyclo [2.2.2]octane (0.25g., 2.2mmol) and Tris(triphenylphosphine)rhodium(1)chloride (0.68g., 0.7mmol) in 10% aqueous ethanol (5ml) was heated (oil bath, reflux) and stirred for 1-3h. The mixture was diluted with water, extracted with diethyl ether, washed with acidic (pH ~ 2) aqueous sodium chloride,

dried (MgSO$_4$) and concentrated. Flash chromatography of the residue gave the major fraction (t.l.c., solvent B, ~ Rf 0.8) (93) (0.41g.,81%); ^{1}H nmr data: sdee Exp. 17.1; ^{13}C nmr data: see Exp. 17.1.

Exp. 18   2,3,5-tri-O-benzyl-β-L-arabinofuranose from (93).

A mixture of crude (93) (0.5g., ~ 1.1mmol) and 0.5N sulphuric acid (0.6ml) in acetone (6ml) was heated (reflux, oil bath) for 15-45 min. The mixture was allowed to cool, neutralised (excess Na$_2$CO$_3$), and concentrated. The residue was dissolved in dichloromethane, dried (MgSO$_4$), treated with activated charcoal and concentrated. The syrup was redissolved in cyclohexane, seeded, left for 1h at room temperature and left for a further 20h at ~ 5º to give (7) (0.41g., 89%); m.p. 88º-89º; [α[$_D$ + 6.3º (C,2 CH$_2$Cl$_2$); [Lit[7] m.p. 88º-89º; [α]$_D$^{20} + 6.5º (C,4.25 CH$_2$Cl$_2$)]; Found C, 74.43; H, 6.70.   Calc. for C$_{26}$H$_{28}$O$_5$: C, 74.26; H, 6.71; ^{1}H nmr data (CDCl$_3$): δ 7.3 (15H,m,3Ph), 5.38, 5.37, 5.34 (2H,m; H-1,OH), 4.4-4.68 (6H,m,CH$_2$Ph), 4.16, 4.1, 4.0 3.94 (3H,m; H-2,H-3,H-4), 3.56 (2H,m,H-5); ^{13}C nmr data: see Table 3.3.

Exp. 19   Allyl-D-ribopyranosides (105).

D-ribose (1.0g., 6.7mmol) anhydrous allyl alcohol

(20ml., 0.3mol) and concentrated sulphuric acid (0.1 ml) were reacted together as described for the preparation of (97). Analysis (t.l.c., solvent C) of the residue showed it to comprise one component (Rf ~ 0.7) (105) (1.1g., 86%); ^{13}C nmr data: see Table 3.1.

Exp. 20   Allyl-D-ribofuranosides (100).

Concentrated sulphuric acid (0.05ml) was added (dropwise) to a stirred, cooled (0°, ice bath) suspension of dry D-ribose (0.5g., 3.3mmol), anhydrous allyl alcohol (10ml., 0.15mol) and calcium sulphate (0.5g). The mixture was stirred for 16-22h at room temperature and as soon as the D-ribose had disappeared (Fehling's solution) it was filtered and passed through a column of IR45(OH) (10ml). The resin. was washed with fresh allyl alcohol (10ml) and the combined solution and washings concentrated to give (100) (0.6g., 96%); (t.l.c., solvent C, Rf ~ 0.5); ^{13}C nmr data: see Table 3.1.

Exp. 21   Allyl 2,3,5-tri-O-benzyl-D-ribofuranosides (102).

A solution of dry (100) (5.5g., 0.029mol.) in dry dimethyl sulphoxide (15ml) was treated with sodium hydride (~ 6g., 0.25mol) and benzyl chloride (~ 13.5ml., 0.096mol) as described for preparation of (92). Flash chromatography of the residue gave a

major ~~fraction~~ (t.l.c., solvent B, Rf 0.75) fraction
(102) (12.1g., 91%); ^{1}H nmr (CDCl$_3$): δ 7.3 (15,H,3Ph),
5.8 (1H,m,OCH$_2$-C<u>H</u>=CH$_2$), 5.25, 5.18, 5.12, 5.06 (5H,m;
H-1, OC<u>H</u>$_2$-CH=C<u>H</u>$_2$), 4.4-4.7 (6H,m,3C<u>H</u>$_2$Ph), 3.87-4.4
(3H,m;H-2,H-3,H-4), 3.55 (2H,m,H-5); ^{13}C nmr data
(CDCl$_3$): δ 134.13 (CH$_2$<u>C</u>H), 127.5-128.67 (m,Ph) 117.22
(CH=<u>C</u>H$_2$), 104.46 (C-1), 80.52, 79.81, 78.57
(C-2,C-3,C-4), 71.37, 72.33, 72.43, 73.14 (C-5;
CH$_2$Ph), 68.25 (O<u>C</u>H$_2$CH). Although the other anomer was
clearly present, its resonances could not be measured
accurately.

Exp. 22   2,3,5-tri-O-benzyl-D-ribofuranoses **(103)**.

A solution of **(102)** (1.47g., 3.2mmol) in methanol
(10ml) and water (2ml) was treated with palladium (5%)
on activated charcoal (0.1g) and p-toluenesulphonic
acid (0.01g). The mixture was heated (reflux) and
stirred for ~ 24h. After removal of the catalyst by
centrifugation, the solution was extracted with
diethyl ether, dried (MgSO$_4$) and concentrated to give
(103) (1.25g., 93%); [α]**D** +36° (C,3.25 dioxan); [Lit.[8]
[α]$_D^{20}$ +37° (C,4.0 dioxan)].

Exp. 23   Methylsulphinyl carbanion.

23.1   Using sodium hydride.

NaH(~ 0.125mol) and dry dimethyl sulphoxide (~
75ml) were reacted together (~ 70°; 4h) under nitrogen

until nitrogen evolution had ceased as previously described[9].

23.2   Using potassium tert-butoxide.

Dry potassium tert-butoxide (~ 0.125mol) and dry dimethyl sulphoxide (75ml) were reacted together (~60°; 30min) under nitrogen until a yellow solution was obtained as previously described[10].

Exp. 24   Reaction of (91) with benzyl chloride.

24.1   With sodium methylsulphinyl carbanion, method A.

A solution of dry (91) 2.9g., 0.015mol) in dry dimethyl sulphoxide (5ml) was added (dropwise, 30min) to a vigorously stirred (mechanical), cooled (0°-5°, ice bath) solution of sodium methylsulphinyl-carbanion under nitrogen.   The mixture was left stirring for ~ 1h at room temperature and then benzyl chloride (6.75ml., 0.048mol) was added (dropwise, ~ 30min) to the vigorously stirred, cooled (0° , ice bath) mixture.   Benzylation was complete within 5h at room temperature (t.l.c, solvent B).   Analysis of the reaction mixture (t.l.c., solvent B) indicated that the product was the allyl ether (92) (Rf ~ 0.6) and not the prop-1-enyl ether (93) (Rf ~ 0.8 expected).

24.2   With sodium methylsulphinyl carbanion, method B.

A solution of dry (91) (2.9g., 0.015mol) in

dimethyl sulphoxide (5ml) was reacted with sodium methylsulphinyl carbanion and benzyl chloride (6.75ml., 0.048mol) as described in Exp. 24.1. When benzylation was complete (t.l.c., solvent B) the temperature of the reaction mixture was raised to ~ 60° and left stirring for another 6h at this temperature (never above 70°). Analysis of the reaction mixture (t.l.c., solvent B) indicated that this treatment had not promoted the formation of (93).

24.3 With potassium methylsulphinyl carbanion.

A solution of dry (91) (2.9g., 0.015mol) in dry dimethyl sulphoxide (5ml) was added (dropwise, ~ 30min) to a vigorously stirred, cooled (0°-5°, ice bath) solution of potassium methylsulphinyl carbanion under nitrogen. The mixture was heated for 45 min at ~65° (not above 70°) where upon it changed from a pale yellow to a deep red brown colour. After cooling to room temperature benzyl chloride (6.75ml., 0.048mol) was added (dropwise, ~ 30min) to the vigorously stirred, cooled (occassionally; 0°, ice bath) mixture. Examination (t.l.c., solvent B) of the reaction mixture after a further 1-2h at room temperature indicated that it comprised one component (Rf ~ 0.8) which corresponded to the prop-1-enyl derivative (93). The mixture was diluted with water and extracted with diethyl ether, washed with dilute

aqueous hydrochloric acid, dried (MgSO₄) and concentrated. The residue (~ 6.0g) was diluted with IN hydrochloric acid (26ml) and acetone (220ml) and then heated (gentle reflux) for 15-30 min to give one component (t.l.c., solvent B, Rf ~ 0.27). The mixture was allowed to cool, diluted with dichloromethane, washed with a saturated aqueous $NaHCO_3$ solution, dried (MgSO₄) and concentrated. The residue was redissolved in cyclohexane, seeded, left for 1h at room temperature and then ~ 20h at +5° to give **(7)** (5.9g., 94%); m.p. 86°-87°; $[\alpha]_D$ +6.8 (C,2 CH_2Cl_2); [Lit.[7] m.p. 88°-89°, $[\alpha]_D^{25}$ +6.5 (C,4.25 CH_2Cl_2)].

5.23 L-arabinose aglycon derivatives.

Exp. 25   Allyl 3,5-O-isopropylidene-L-arabinofurano-sides **(110)**.

A solution of dry **(91)** (0.5g., 2.6mmol) in dry acetone (40ml) and 2,2-dimethoxypropane (40ml., 0.3mol) was stirred with dry p-toluenesulphonic acid (20-40mg) under nitrogen for ~ 18h at room temperature. The mixture was diluted with dichloromethane, washed with saturated aqueous $NaHCO_3$, dried (MgSO₄) and concentrated. Flash chromatography of the residue gave a major fraction (t.l.c., solvent B, Rf 0.54) **(110)** (0.26g., 43%); M (mass spectrum,

c.i.), 230. $C_{11}H_{18}O_5$ requires M,230); ^1H nmr data (CDCl$_3$): δ 5.9 (1H,m,OCH$_2$CH=CH$_2$), 5.24 (2H,m,OCH$_2$CH= CH$_2$), 4.5, 3.98-4.25, 3.45, (8H,m; OCH$_2$CH=CH$_2$,H-1,H-2,H-3,H-4,H-5,HO-2), 1.4 (6H,m,isopropylidene); ^{13}C nmr data (CDCl$_3$): δ 134.58, 134.36 (CH=CH$_2$), 117.43, 117.16 (CH=CH$_2$), 110.60, 109.70 (CH$_3$C-O), 102.79, 102.52 (C-1), 76.54-78.98 (m,C-2,C-3,C-4), 68.36, 68.85, 66.09, 66.33 (C-5,OCH$_2$-), 55.59, 54.29 (OCH$_2$-CH=CH$_2$), 24-26 (CH$_3$).

Exp. 26 Allyl 2-O-(tert-butyldimethylsilyl) 3,5-O-isopropylidene-L-arabinofuranosides (112).

A solution of dry (110) (0.5g., 2.2mmol) in dry pyridine (3.5ml) was stirred with tert-butyldimethyl-silyl chloride (1.0g., 6.6mmol) under nitrogen for ~ 48h. The mixture was diluted with dichloromethane, washed with water, dried (MgSO$_4$) and concentrated. Flash chromatography of the residue gave a first fraction (t.l.c., solvent B, Rf 0.76) (112) (0.23g., 30%); M(mass spectrum, f.a.b.), 365 (M$^+$ + Na). $C_{17}H_{30}O_5Si$ requires M, 342; ^1H nmr data (CDCl$_3$): δ 5.9 (1H,m,OCH$_2$CH=CH$_2$), 5.25 (2H,m,OCH$_2$CH-CH$_2$), 14.7, 3.6-4.3 (8H,m;(OCH$_2$CH=CH$_2$,H-1,H-2,H-3,H-4,H-05), 1.5, 1.39 (6H,m; isopropylidene), 0.9 (9H,m,3CH$_3$-C) 0.6 (6H,m,2CH$_3$-Si); ^{13}C nmr data (CDCl$_3$): δ 134.49, 134.11 (CH-CH$_2$), 117.51, 117.24 (CH=CH$_2$), 110.98, 110.19

(CH_3-$\underline{C}$-O), 101.63, 97.77 (C-1), 71.8-79.55 (C-2,C-3,C-4), 69.58, 68.50 (C-5), 59.11, 62.48 (OCH_2), 29.63 (C-Si), 27.85, 28.21 ($\underline{CH_3}$C-O), ~ 26.0 (m,$\underline{CH_3}$-C-Si), ~ 18.0 (m,CH_3-Si).

5.24   Chlorosulphonyl derivatives.

<u>Exp.   27   5-O-Triphenylmethyl-L-arabinofuranoses</u>
<u>(116)</u>.

Triphenylmethyl chloride (4g., 0.014mmol) was added to a vigorously stirred, cooled (0°, ice bath), solution of L-arabinose (1.5g., 10.0mol) in dry pyridine (18m). The mixture was heated and stirred for ~ 4h at 45°-50° until all the L-arabinose had disappeared (t.l.c., solvent C). This solution of crude **(116)** in pyridine was used in subsequent experiments. For purification, the mixture was diluted with diethyl ether, washed with cold water (~ 0°), dried ($MgSO_4$), and concentrated. Flash chromatography of the residue (which still contained a small amount of pyridine) gave a first fraction (t.l.c., solvent E) **(116)** (3.5g., 90%); ^{13}C nmr data: see Table 3.4.

Exp. 28   1,2,3-Tri-O-acetyl-5-O-triphenylmethyl-L-arabinofuranoses **(122)**.

Acetic anhydride (1.2ml., 12mmol) was reacted with a solution (6ml., ~ 3mmol) of crude **(116)** in pyridine diluted with fresh pyridine (2.5ml) as described for the preparation of **(94)**. Flash chromatography of the residue gave a fraction (t.l.c, solvent B, Rf ~ 0.39) **(122)** (0.6g., 39%); M(mass spectrum, f.a.b.), 541 (M^+ + Na). $C_{30}H_{30}O_8$ requires 518; ^1H nmr data ($CDCl_3$): δ 7.44, 7.37 (15H,m,3Ph), 6.38, 6.22 (1H,s,d; H-1), 5.58, 5.31, 5.20, 4.33, 4.18 (3H,m; H-2,H-3,H-4), 3.32 (2H,m,H-5), 2.1 (9H,m,3Ac); ^{13}C nmr data: see Table 3.4.

Exp. 29   1,2,3-Tri-O-benzoyl-5-O-triphenylmethyl-L-arabinofuranoses **(123)**.

Benzoyl chloride (1.4ml., 12mmol) was reacted with a solution (6ml., 3mmol) of crude **(116)** in pyridine diluted with fresh pyridine (2.5ml) as described for the preparation of **(94)**. Flash chromatography of the residue gave a fraction (t.l.c., solvent B, Rf ~ 0.81) **(123)** (0.5g., 24%); M(mass spectrum, f.a.b.), 727 (M^+ + Na). $C_{45}H_{36}O_8$ requires M,704; ^1H nmr data ($CDCl_3$): δ 8.04, 7.4 (30H,m,6Ph), 5.99, 5.8 (1H,s,d; H-1), 5.25, 4.55 (3H,m; H-2,H-3,H-4), 3.54 (2H,m,H-5); ^{13}C nmr data: see Table 3.4.

Exp. 30   5-O-Triphenylmethyl-D-ribofuranoses (124).

Triphenylmethylchloride   (4g.,   0.014mol)   was
reacted with D-ribose (1.5g., 10mmol) in pyridine
(18ml) as described in the preparation of (116). This
solution of crude (124) in pyridine was used in
subsequent experiments.

Exp. 31   1,2,3-Tri-O-acetyl-5-O-triphenylmethyl-D-
ribofuranoses (125).

Acetic anhydride (1.2ml.,12mmol) was reacted with
a solution (6ml., ~ 3mmol) of crude (124) in pyridine
diluted with fresh pyridine (2.5ml) as described for
the preparation of (94). Flash chromatography of the
residue gave a fraction (t.l.c., solvent B, Rf ~ 0.35)
(125) (0.45g., 29%); M(mass spectrum, f.a.b.) 518.
$C_{30}H_{30}O$ requires M,518; ^1H nmr data ($CDCl_3$): δ 7.49,
7.25 (15H,m,3Ph), 6.21 (1H,s,H-1), 4.33-5.5 (3H,m;
H-2,H-3,H-4),   3.16,   3.37   (2H,m,H-5),   2.13,   2.05
(9H,m,3Ac); ^{13}C nmr data: see Table 3.4.

Exp. 32   1,2,3-Tri-O-benzoyl-5-O-triphenylmethyl-D-
ribofuranoses (126).

Benzoyl chloride (1.4ml., 12mmol) was reacted with
a solution (~ 6ml., 3mmol) of crude (124) in pyridine
diluted with fresh pyridine (2.5ml) as described for
the preparation of (94). Flash chromatography of the
residue gave a fraction (t.l.c., solvent B, Rf ~ 0.88)

(126) (0.9g., 43%); M(mass spectrum, f.a.b.) 727 (M[+] + Na). $C_{45}H_{36}O_8$ requires M, 704; ^{13}C nmr data: see Table 3.4.

<u>Exp. 33   Methyl 2,3-di-0-chlorosulphonate-5-chloro-5-deoxy-α-L-arabinofuranoside **(115)**.</u>

Sulphuryl chloride (7.4ml., 0.09mol) was added (dropwise, ~ 30min) to a vigorously stirred, cooled (~ -78°, acetone-dry ice bath) solution of dry methyl arabinofuranoside[7] (5g., 0.03mol) in dry pyridine (20ml) and dry chloroform (50ml) under nitrogen. The mixture was left for ~ 2h at -78° and allowed to come to room temperature. When the starting sugar had disappeared (t.l.c., solvent C) the mixture was diluted with chloroform, washed with ice cold 0.5N sulphuric acid, ice cold saturated aqueous $NaHCO_3$ and water, dried ($MgSO_4$) and concentrated. The residue formed (~ 4h, ice bath) gummy crystals (t.l.c., solvent F, Rf 0.61) that were recrystallised from methanol-water to give **(115)** (8.5g., 70%); m.p. 70°-72°; [α]$_D$ -56.4° (C,2 CHCl$_3$); M(mass spectrum, c.i.) 416 (M + $CH_3NH_2^+$). $C_6H_9O_8Cl_3S_2$ requires M, 384; ^{1}H nmr data ($CDCl_3$) : δ 5.38, 5.34, 5.32, 5.29 (3H,m; H-1,H-3,H-4)[a], 4.53 (1H,m,H-2)[a] 3.79, 3.87 (2H,m,H-5), 3.45 (3H,s,CH$_3$)[a], assignments may be interchanged; ^{13}C nmr data ($CDCl_3$): δ 105.64 (C-1), 86.52 (C-2), 80.77 (C-3), 89.77 (C-4) 55.91 (C-5),

42.64 (OCH$_3$).

Exp. 34 Reaction of (116) with sulphuryl chloride.

Sulphuryl chloride (2.5ml., 30mmol) was added (dropwise, ~ 30min) to a vigorously stirred, cooled (~ -78°, acetone – dry ice bath) solution of crude (116) (18ml., 9mmol) in fresh dry pyridine (10 ml) and dry chloroform (25ml) under nitrogen. The mixture was left for 3h at -70° and then for 16h at room temperature. The mixture was diluted with dichloromethane, washed with ice cold water, ice cold saturated aqueous NaHCO$_3$ solution, dried (MgSO$_4$) and concentrated. A white solid formed on addition of diethyl ether to the residue. The solid formed a syrup on attempting to collect it by filtration. The syrup redissolved in chloroform and could be precipitated again by adding diethyl ether. A small amount of solid (~ 0.6.) was collected and dried (desiccator m.o. 87°-93° (some material chars at ~ 110°); [α]$_D$ + 10.5° (c, ~ 1 CHCl$_3$). (Difficult to obtain accurately as solid material quickly changes to syrup – not completely soluble in CHCl$_3$). The syrup comprised two main components (t.l.c., solvent B, Rf 0.77 and 0.79.)

Exp. 35 Reaction of the product of Experiment (34) with isopropanol.

A portion (0.27g.) of the residue from experiment

34, dry isopropanol (5mol., excess) and silver zeolite 13X catalyst (0.5g.) in dry dichloromethane were stirred in the dark for ~ 16h under nitrogen. The catalyst was removed by centrifugation and the supernatent concentrated. Analysis (t.l.c., solvent B) did not indicate any sign of a new component having been formed. The residue was diluted with aqueous methanol and warmed (50°, 20min.). The solution was concentrated and the residue purified by flash chromatography to give a major fraction (t.l.c., solvent B Rf 0.61) (100mg., ~ 25% of amount originally applied to column); ^{1}H nmr data (CDCl$_3$): δ 7.2 (1H,d,J$_{12}$,4.4Hz, H-1); ^{13}C nmr data (CDCl$_3$): major peaks at δ 104.99, 89.82, 86.68, 81.91 (CH; C-1,C-2,C-3,C-4), 69.72 (CH$_2$), 58.08 (CH), 42.9 (CH$_2$), 45.39 (CH$_2$), several minor peaks including ones at 128.94 (CH, Phenyl) 147.55 (C, Trityl).

5.3   Glycosylation reactions

5.31   *Preliminary investigation of selected methods.*

Exp. 36   2,3,5-Tri-O-benzyl-β-L-arabinofuranose (7).

Dry L-arabinose (30g., 0.2mol) was converted by the method previously described by Tejima and Fletcher[7] to give (7) (34g., 40%); m.p. 88°-89°; [α]$_D$

+ 6.3 (C 2, CH_2Cl_2); [Lit.[7] m.p. 88°-89°, $[\alpha]_D^{25}$ + 6.5 (C 4.25, CH_2Cl_2)]; ^1H nmr data ($CDCl_3$): δ 7.3 (15H,m,3Ph), 5.39, 5.37, 5.32 (2H,m; H-1, OH), 4.4-4.68 (6H,m,$\underline{CH}_2$Ph), 4.16, 4.1, 4.0, 3.94 (3H,m; H-2,H-3,H-4), 3.56 (2H,m,H-5); ^{13}C nmr data: see Table 3.3.

Exp. 37 1-O-(p-Nitrobenzoyl)-2,3,5-tri-O-benzyl-L-arabinofuranoses (146).

A solution of p-nitrobenzoyl chloride (1.9g., 10.2mmol) in a mixture of dry dichloromethane (10ml) and dry pyridine (3ml) was reacted with a solution of dry 2,3,5-tri-o-benzyl-β-L-arabinofuranose (7) (4g., 9.51mmol) in dry dichloromethane (15ml) as described by Barker and Fletcher[6] to give (146) (4.9g., 90%); m.p. 79°-89°; $[\alpha]_D$ +10.6 (C 4, CH_2Cl_2); [Lit.[6] m.p. 75°-92°; $[\alpha]_D^{25}$ +11 (C 6.8, CH_2Cl_2)]; ^1H nmr data ($CDCl_3$): δ 8.13 (4H,m,$pNO_2C_6H_4$), 7.3 (15H,m,3Ph), 6.53 (1H,m,H-1), 4.46-4.79 (6H,m,$\underline{CH}_2$Ph), 4.38, 4.22, 4.08 (3H,m; H-2,H-3,H-4), 3.62 (2H,m,H-5); ^{13}C nmr data ($CDCl_3$): δ 163.50, 162.55 (O-$\underline{C}$=O), 150.71, 150.52 ($\underline{C}CO_2$), 137.6 (m,benzyl,C), 131.0, 130.9 (pNO_2-C_6H_4,C), 128.0 (m,benzyl,CH), 123.4, 123.5 (pNO_2-C_6H_4,C), 101.55 95.75 (C-1), 80.58, 81.46, 83.50, 84.12, 84.43, 86.50 (C-2,C-3,C-4), 73.50, 73.47, 73.30, 72.70, 72.17, 72.13 (benzyl,CH_2), 69.73, 70.33 (C-5).

Exp.   38   2,3,5-Tri-O-benzyl-α-L-arabinofuranosyl

chloride **(113a)**.

Dry **(146)** (0.2g., 34.2mmol) was reacted with dichloromethane (3.5ml) presaturated with anhydrous hydrogen chloride gas by the method previously described for the D-enantiomorph by Glaudemans and Fletcher[11] to give **(113a)** (0.14g., 93%). A typical preparation varied from $[\alpha]_D$ -86.4 to -93.1°; [Lit. (for the α-D anomer) (i)[1] $[\alpha]_D^{20}$ +91.1 to +96° (C 1.25, CH_2Cl_2); (ii)[12] $[\alpha]_D^{20}$ +89° (C 2.66, CH_2Cl_2); (iii)[13] $[\alpha]_D^{20}$ +79.8° (C 1.3, $CHCl_3$)]; ^{1}H nmr data ($CDCl_3$): δ 7.3 (15H,m,Ph), 6.13 (1H,s,H-1) 4.4-4.6 (6H,m,$C_6H_5\underline{CH_2}$), 4.35 (1H,d,J_{23} 2.1 Hz, H-2), 3.96 (1H,dd, J_{34} 6.5Hz, H-3) and 3.63 (2H,d,J_{45} 4.3H$_2$, H-5,5[1]); ^{13}C nmr data ($CDCl_3$): δ 138.46, 138.42, 138.06 (benzyl,C), 128.19;.29.02 (m,benzyl,CH), 97.34 (C-1), 92.0, 84.22, 83.88 (C-2,C-3,C-4), 73.91, 72.81, 72.66 (benzyl,CH_2) 69.40 (C-5).

Exp. 39   Isopropyl 2,3,5-tri-O-benzyl-β-L-arabino-

furanoside **(147a)** : Solvolysis of **(113a)**.

Freshly prepared dry **(113a)** (0.14g., 0.319mmol) was stirred with dry isopropanol (10ml., 0.13mol) under nitrogen in the dark for 14 days at room temperature after which time **(113a)** was completely absent (t.l.c., solvent B). The solution was concentrated and the residue subjected to flash

chromatography to give a major fraction (t.l.c., solvent B, Rf 0.75) **(147b)** (0.12., 81.3%); $[\alpha]_D$ +68.2 (Cl, CH_2Cl_2); M(mass spectrum, f.a.b.), 485 (M^+ + Na), $C_{29}H_{34}O_5$ requires M, 462; ^1H nmr data ($CDCl_3$): δ 7.3 (15H,m,3Ph), 5.02 (1H,d,J_{12}4Hz, H-1), 4.7-4.5 (6H,m,$C_6H_5\underline{CH_2}$), 4.08 [3H,m,H-3,H-4 and $\underline{CH}(CH_3)_2$], 3.9 (1H,m,H-2), 3.55 (2H,m,H-5), 1.15 (6H,m,CH_3); ^{13}C nmr data: see Table 4.3.

A minor component (t.l.c., solvent B, Rf 0.81) could not be obtained free of the major one and comprised about 5% of the mixture. ^1H nmr spectroscopy indicated that this was the α-isopropyl glycoside **(147a)**; ^1H nmr data ($CDCl_3$) includes: δ 5.02 (d,J_{12}4Hz, β H-1) and 5.09 (s, α H-1); ^{13}C nmr data ($CDCl_3$) includes: δ 105.04 (α C-1) and 98.95 (β C-1).

Exp. 40   Reaction of **(113a)** with a stoichiometric amount of isopropanol.

A solution of freshly prepared dry **(113a)** (0.14g., 0.319mmol) in dry dichloromethane (5ml) was stirred with dry isopropanol (24μl., 0.319mmol) under nitrogen in the dark for 2 days at room temperature. Analysis (t.l.c., solvent B) of the reaction mixture showed three components: the major one corresponding to the free sugar **(7)** (Rf 0.22) and the minor ones (Rf 0.82 and 0.75) corresponding to the isomeric isopropyl glycosides **(147)**. The reaction mixture was

concentrated and the residue purified by flash chromatography to obtain the isopropyl glycosides **(147)** (~0.045g., 30%); ($\alpha:\beta$ = 1:1, by ^{1}H nmr).

Exp. 41   Reaction of **(113a)** with isopropanol in the presence of various silver salts.

41.1   With AgNO$_3$.

A solution of freshly prepared dry **(113a)** (0.14g., 0.319mmol) in dry dichloromethane (5ml) was stirred with dry AgNO$_3$ (0.054g., 0.319mmol) and dry isopropanol (27μl., 0.36mmol) under nitrogen in the dark for ~ 12h at room temperature. Analysis (t.l.c., solvent B) of the reaction mixture showed a major component (Rf 0.21) corresponding to the free sugar **(7)** and several other minor components (Rf 0.10-0.6).

41.2   With Ag$_2$CO$_3$.

The procedure followed in Experiment 41.1 was repeated but with AgNO$_3$ replaced by Ag$_2$CO$_3$ (0.088g., 0.319mmol). Analysis (t.l.c., solvent B) of the reaction mixture showed a major component (Rf 0.22) corresponding to the free sugar **(7)** and several other minor components (Rf 0.1-0.6).

41.3   With AgCN.

The procedure followed in Expertiment 41.1 was repeated but with AgNO$_3$ replaced by AgCN (0.043g., 0.319mmol). Analysis (t.l.c., solvent B) of the

reaction mixture showed a major component (Rf 0.73) and a minor component (Rf 0.23) corresponding to the free sugar (7). The reaction mixture was filtered, concentrated and immediately purified by flash chromatography to obtain the major component (Rf 0.73) (0.07g). However this component decomposed within ~ 6h to the free sugar (7) (Rf 0.24) and was not investigated further.

41.4   With CH_3CO_2Ag.

The procedure followed in Experiment$_\wedge$ was repeated but with $AgNO_3$ replaced by CH_3CO_2Ag (0.053g., 0.319mmol). Analysis (t.l.c., solvent B) of the reaction mixture showed a major component (Rf 0.5) and a minor component (Rf 0.22) corresponding to the free sugar (7). The reaction mixture was filtered, concentrated and immediately purified by flash chromatography to obtain the major component (Rf 0.5) (0.79g). ^1H nmr data included: δ 8.2 (dd?), 6.5 (s,H-1), 1.2 (m,CH_3CO_2?).

41.5   With Ag_2O.

The procedure followed in Experiment 41.1 was repeated but with $AgNO_3$ replaced by Ag_2O (0.074g., 0.319mmol). Analysis (t.l.c., solvent B) of the reaction mixture showed three components (Rf 0.81, 0.76 and 0.23). The reaction mixture was filtered, concentrated and immediately purified by flash chromatography to obtain the two fast moving

components (Rf 0.81, 0.76) which corresponded to the isopropyl glycosides **(147)** (0.049g., 33%); (α:β = 1:7, by ^{1}H nmr).

Exp. 42   Reaction of **(113a)** with isopropanol in the presence of Ag$_2$O and various solid desiccants.

42.1   With 4A molecular sieves.

A solution of freshly prepared dry **(113a)** (0.14g., 0.319mmol) in dry dichloromethane (5ml) was stirred with isopropanol (27μl., 0.360mmol), Ag$_2$O (73.9mg., 0.319mmol) and activated 4A molecular sieves (0.5g) under nitrogen in the dark.   After ~ 12h at room temperature the mixture was filtered through a bed of celite and concentrated.   Flash chromatography of the reaction mixture gave a fraction (Rf 0.82 and 0.77) which corresponded to the isopropyl glycosides **(147)** (0.069g., 46%); (α:β = ~ 1:7, by ^{1}H nmr).

42.2   With CaSO$_4$.

The procedure followed in Experiment 42.1 was repeated, but with activated 4A molecular sieves replaced by dry CaSO$_4$ (0.5g).   Flash chromatography of the reaction mixture gave a fraction (Rf 0.81 and 0.76) which corresponded to the isopropyl glycosides **(147)** (0.062g., 42%) (α:B = ~ 1:7, by ^{1}H nmr).

Exp.   43   Preparation   of   zeolite   supported   metal
promoters:

43.1   Silver 4A zeolite: (Ag-Z4A).

Powdered 4A molecular sieves (12.5g) were stirred
with AgNO$_3$ (6.25g) in water (25ml) at room temperature
for 2h in the dark. The mixture was filtered, and the
residue washed with water (3 x 25ml) then acetone (2 x
25ml) and kept at ~ 200° for 48h in the dark.   The
promoter was then stored in a dark dessicator at room
temperature and used within 5 days.

43.2   Silver 13X zeolite: (Ag-Z13X).

Powdered 13X molecular sieves (12.5g) were reacted
with AgNO$_3$ (6.25g) in water (25ml) as described for
the preparation of 4A silver zeolite promoter.

43.3   Thallium 4A zeolite: (Tl-Z4A).

Powdered 4A molecular sieves (25g) were stirred
with Tl$_2$CO$_3$ (17.25g) in water (125ml) at 40°-50° for
4h in the dark.   The mixture was filtered and the
residue washed with water (2 x 100ml) and acetone (2 x
50ml) and kept at ~ 200° for 48h in the dark.   The
promoter was then stored in a dark dessicator at room
temperature and used within ~ 5 days.

43.4   Thallium 13Z zeolite: (Tl-Z13X).

Powdered 13X molecular sieves (25g) were reacted
with Tl$_2$CO$_3$ (17.25g) in water (12 5ml) as described
for the preparation of 4A thallium zeolite.

43.5   Thallium 4A zeolite, type 2: (Tl-Z4A:typeII).

Powdered 4A molecular sieves (25g) were reacted with Tl$_2$CO$_3$ (5g) in water (125ml) as described for the preparation of 4A thallium zeolite.

43.6   "Used" thallium zeolite, type 2: ("used" Tl-Z4A:typeII).

4A thallium zeolite, type 2 (0.5g) which had been used once in a glycosidation reaction   (see Exp. 44) was washed with dichloromethane (5ml), water (5ml) and then acetone (10ml) and dried (~200°) in the dark for ~ 72h.

Exp. 44   Reaction of (113a) with isopropanol in the presence of various zeolite supported metal promoters.

44.1   With Ag-Z4A.

A solution of freshly prepared dry (113a) (0.14g., 0.319mmol) in dry dichloromethane (2.5ml) was stirred with isopropanol (24μl., 0.319mmol) and Ag-Z4A (0.4g) under nitrogen in the dark.   After ~ 4h at room temperature the mixture was centrifuged and the supernatant concentrated.   Analysis (t.l.c., solvent B) of the residue showed two components (Rf 0.81 and 0.75) which corresponded to the isopropyl glycosides (147) [(0.13g., 88%); (α:β = 1:9, by ^{1}H nmr)]. Repeated flash chromatography gave a portion of the pure β-anomer (~ 0.11g., 0.75%); [α]$_D$ +68.1 (C 1.1,

CH_2Cl_2); ^{1}H nmr data; see Experiment 39.

44.2   With Ag-Z13X.

The procedure followed in Experiment 44.1 was repeated but with Ag-Z4A replaced by Ag-Z13X (0.4g). Flash chromatography of the residue gave a fraction (t.l.c., solvent B, Rf 0.82 and 0.76) which corresponded to the isopropyl glycosides **(147)** (0.11g., 76%); (α:β = 1:9, by ^{1}H nmr).

44.3   With Tl-Z4A.

The procedure followed in Experiment 44.1 was repeated but the Ag-Z4A replaced by Tl-Z4A (0.4g.). Flash chromatography of the residue gave two components (t.l.c., solvent B, Rf 0.81 and Rf 0.75) which corresponded to the isopropyl glycosides **(147)** (0.10g., 73%); (α:β = 1:9, by ^{1}H nmr).

44.4   With Tl-Z13X.

The procedure followed in Experiment 44.1 was repeated but with Ag-Z4A replaced by Tl-Al3X (0.4g). Flash chromatography of the residue gave a fraction (t.l.c., solvent B, Rf 0.81 and 0.75) which corresponded to the isopropyl glycosides **(147)** (0.11g., 76%); (α:β = 1:9, by ^{1}H nmr).

44.5   With Tl-Z4A (type II)

A solution of freshly prepared dry **(113a)** (0.14g., 0.319mmol) in dry dichloromethane (2.5ml) was stirred with isopropanol (24μl, 0.319mmol) and Tl-Z4A:type II under nitrogen in the dark. After 4h at room

temperature the mixture was centrifuged and the supernatent concentrated. Flash chromatography of the residue gave only one fraction (t.l.c., solvent B, Rf 0.82 and 0.75) corresponding to the isopropyl glycosides (147) (0.9g., 72%) (α:β = 8:1, by ^{1}H nmr).

Exp. 45   Reaction of glycosylchloride (113a) with cholesterol in the presence of various zeolite supported promoters.

45.1   With Ag-Z4A.

A solution of freshly prepared dry (113a) (0.14g, 0.319mmol) in dry dichloromethane (2.5ml) was stirred dry with cholesterol (0.12g., 0.319mmol) and Ag-Z4A (0.4g) under nitrogen in the dark. After ~ 4h at room temperature the mixture was centrifuged and the supernatent concentrated. Flash chromatography of the residue gave only one component (t.l.c., solvent B, Rf 0.83) corresponding to the β-cholesteryl glycoside (148b) (0.199g., 79%); m.p. 51º; [α]$_D$ +49.8º (Cl, CH$_2$Cl$_2$); M(mass spectrum, f.a.b.), 811 (M$^+$ + Na) C$_{53}$H$_{72}$O$_5$ requires M,788); ^{13}C nmr data (CDCl$_3$): see Table 4.3 for glycon resonances, 11.87(a), 18.73(b), 19.39(c), 21.07(d), 22.58(e), 22.83(f), 23.84(g), 24.30(h), 28.02(i), 28.25(j), 29.72(k), 31.91(1), 35.81(m), 36.70(n), 36.21(o), 37.14(p), 39.53(q), 39.79(r), 40.34(s), 42.33(t), 50.14(u), 56.17(v), 56.77(w), 77.60(x), 121.8(y), 140.75(z).
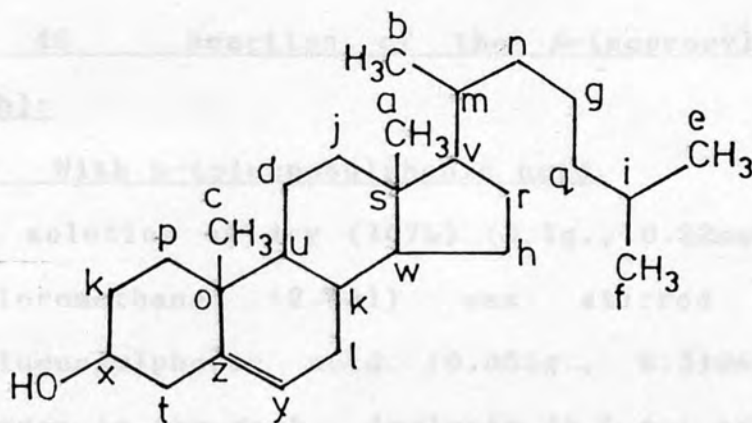
45.2   With Ag-Z13X.

The procedure followed in Experiment 45.1 was repeated but the Ag-Z4A replaced by Ag-Z13X (0.4g). Flash chromatography of the residue gave only one component (t.l.c., solvent B, Rf 0.85) which showed the same data as obtained for **(148b)** (0.176g., 70%).

45.3   With Tl-Z4A.

The procedure followed in Experiment 45.1 was repeated but with Ag-Z4A replaced by Tl-Z4A (0.4g). Flash chromatography of the residue gave only one component (t.l.c., solvent B, Rf 0.83) which showed the same data as obtained for **(148)** (0.171g., 68%).

45.4   With Tl-Z13X.

The procedure followed in Experiment 45.1 was repeated but with Ag-Z4A replaced by Tl-Z13X (0.4g). Flash chromatography of the residue gave only one component (t.l.c., solvent B, Rf 0.84) which showed the same data as obtained for **(148b)** (0.161g., 64%).

Exp. 46   Reaction of the β-isopropyl glycoside (147b):

46.1   With p-toluenesulphonic acid.

A solution of dry **(147b)** (0.1g., 0.22mmol) in dry dichloromethane (2.5ml) was stirred with dry p-toluenesulphonic acid (0.055g., 0.319mmol) under nitrogen in the dark. Analysis (t.l.c., solvent B) of the reaction mixture after ~ 2h at room temperature indicated the presence of two components. The major one (Rf 0.81) corresponding to the α-isopropyl glycoside **(147a)** and the minor one (Rf 0.75) corresponding to the β-anomer **(147b)**.

46.2   With Tl-Z4A: type II.

A solution of dry **(147b)** (0.1g., 0.22mmol) in dry dichloromethane (2.5ml) was stirred with Tl-Z4A: type II (0.4g) under nitrogen in the dark. Analysis (t.l.c., solvent B) of the reaction mixture after ~ 24h at room temperature indicated only the presence of the starting glycoside (Rf 0.76).

46.3   With "used" Tl-Z4A: type II.

The procedure followed in Experiment 46.2 was repeated, but with Tl-Z4A:type II replaced by "used" Tl-Z4A:type II (0.4g). Analysis (t.l.c., solvent B) of the reaction mixture after ~ 24h at room temperature indicated only the presence of the starting glycoside **(147b)** (Rf 0.76).

Exp. 47   Reaction of (113a) with various salts: an
attempt to obtain and see the β-anomer by ^{1}H nmr
spectroscopy.

A solution of freshly prepared dry (113a) (0.07g.,
0.16mmol) in dry deuterodichloromethane (1ml) was
mixed with dry AgCl (0.02g., 0.16mmol) under nitrogen
in the dark at room temperature. Portions (0.5ml) of
the mixture were removed (taking care not to include
any undissolved material) after ~ 15 min and again
after ~ 4h and their 90 MHz ^{1}H nmr spectra recorded
with Me$_4$Si as external standard.

The procedure was repeated replacing AgCl with
stoichiometric amounts of either ZnCl$_2$, LiCl,
tetrabutylammonium bromide, tetraethylammonium
chloride, and Tl-Z4A:type II. For a control, the
procedure was repeated without any salt being included
in the reaction mixture.

All the ^{1}H nmr spectra recorded gave similar
resonances patterns corresponding to the starting α-
chloride (113a) (see Experiment 38 for details of ^{1}H
nmr data). No sign of the β-chloride (113b) could be
observed in any of these spectra. In previous work[16]
the anomeric protons have been located at 6.11 (s,α
H-1) and at 6.17 (d,J_{1}25Hz, β H-1). However only one
anomeric proton at 6.12 (s,α H-1) could be identified
in these spectra.

Exp. 48   Reaction of 2,3,5-tri-O-benzyl-L-arabino-furanose **(7)** with p-toluenesulphonyl chloride.

p-toluenesulphonyl chloride (3.4g., 18mmol) was added in small portions (over ~ 20 min) to a vigorously stirred, cooled (ice bath, 0°) mixture of dry **(7)** (0.5g., 12mmol) and dry pyridine (6ml). The reaction mixture was allowed to come to room temperature after 5h at 0° and kept stirring under nitrogen for a further ~ 11h. Analysis (t.l.c., solvent B) of the mixture showed that the starting sugar had completely disappeared and a new component had formed (Rf 0.8). The reaction mixture was diluted with ice cold water and extracted with dichloromethane.   The dichloromethane extract was washed succesively with cold (~ 0°) aqueous hydrochloric acid IN, cold 2N $NaHCO_3$, water, dried ($MgSO_4$) and evapo rated.   The crude residue (4.5g) could not be purified by flash chromatography (decomposition to starting material occurred on column) or by crystallisation. The crude residue gave $[\alpha]_D$ -32° (C,2 $CHCl_3$); ^1H nmr data ($CDCl_3$): δ 9.25(m), 8.3(m), 7.88(d?), 7.6(dd?), 7.3(m,Ph), 5.3 (s,α,H-1), 4.7 (d,J_{12} ~ 4Hz, β, H-1), 4.58, 4.55 4.46, 4.23, 4.14, 4.01 (m,H-2,H-3,H-4 and $C_6H_5\underline{CH}_2$), 3.8 (m,H-5), 2.92 (s, broad), 2.29 (s,$\underline{CH}_3$); ^{13}C nmr data ($CDCl_3$): δ 147.08, 144.97, 142.86,141.67, 139.45, 137.87, 137.60, 137.17, 136.95, 130.13, 128.50m, 127.58, 126.61

(benzyl and tosyl CH,C), 95.83 (C-1), 83.85, 82.67, 79.47 (C-2,C-3,C-4), 74.27, 74.06, 72.97, 68.53 (benzyl CH_2,C-5), 21.67 (tosyl CH_3).

Exp. 49   Reaction of the product of experiment 48 with isopropanol.

A solution of the freshly prepared dry product of Experiment 48 [0.3g., ~ 87mmol, assuming that it is the pure tosylate derivative (158)] in dry dichloromethane (5ml) was stirred with dry isopropanol (66μl., 87mmol) under nitrogen at room temperature. Analysis (t.l.c., solvent B) of the reaction mixture after ~ 6h showed three components: A minor one (Rf 0.23) corresponding to the free sugar (7) and the major ones (over 70%) corresponding to the isopropyl glycosides (Rf 0.81 and 0.75; α:β = ~ 1:1, by ^{1}H nmr).

Exp. 50   Reaction of 2,3,5-tri-O-benzyl-L-arabino-furanose (7) with trichloroacetonitrile.
50.1   With NaH.

Trichloroacetonitrile (1ml., 9.9mmol) was added to a mixture of dry (7) (0.78g., 1.85mmol) and NaH (~ 30mg., 1.25mmol) in dry dichloromethane (10ml). The reaction mixture was stirred under nitrogen at room temperature. Analysis (t.l.c., solvent B) of the mixture after ~ 4h indicated the presence of two new components (Rf 0.78 and 0.67), together with a large

amount of starting sugar (Rf 0.24). Analysis of the same mixture after ~ 16h indicated that only one new component remained (Rf 0.67) together with a minor amount of starting sugar. It was not possible to monitor the progress of the reaction accurately by t.l.c., as substantial streaking of the plates occurred. The reaction mixture was centrifuged and the supernatent concentrated. The residue could not be purified by crystallisation or by flash chromatography [the product decomposed on the column to give only the free sugar (7)]. Spectroscopic data of the crude product (obtained after ~ 16h) includes: ^1H nmr data (CDCl$_3$): δ ~ 8.9 (1H,s,NH), ~ 6.7 (1H,s,H-1), ~ 4.9 (6H,m,3C$_6$H$_5$-C$\underline{H}_2$), ~ 4.69-4.35 (3H,m; H-2,H-3 and H-4), ~ 4.02 (2H,m,H-5); ^{13}C nmr data (CDCl$_3$): δ 171.57 (N=C), 161.77 (CCl$_3$), 138.74, 138.47, 138.09 (benzyl C), 128.3-130.51 (m,benzyl CH), 105.21 (C-1), 87.44, 84.51, 84.40 (C-2,C-3,C-4), 74.11, 72.81, 70.26 (benzyl CH$_2$).

50.2   With K$_2$CO$_3$, Method A.

Trichloroacetonitrile (1ml., 9.9mmol) was added to a mixture of dry (7) (0.78g., 1.85mmol) and dry K$_2$CO$_3$ (1g., 7.2mmol) in dry dichloromethane (10ml). The reaction mixture was stirred under nitrogen at room temperature. Analysis (t.l.c., solvent B) of the mixture after ~ 36h showed the presence of one component (Rf 0.74) together with a large amount of

starting material (Rf 0.24). It was not possible to monitor the progress of the reaction accurately by t.l.c. as substantial streaking of the plates occurred. The reaction mixture was centrifuged and the supernatent concentrated. The residue could not be purified by crystallisation or by flash chromatography [the product decomposed on the column to give only the free sugar (7)]. The crude residue showed the same ^{1}H nmr data as obtained in Experiment 50.1.

50.3   With K$_2$CO$_3$, Method B.

Trichloroacetonitrile (1ml., 9.9mol) was added to a mixture of dry (7) (0.78g., 1.85mmol) and dry K$_2$CO$_3$ (1g., 7.2mmol) in dry dichloromethane (10ml) and the reaction mixture stirred under nitrogen at room temperature. Aliquots (2.5ml) were removed (at 1, 4, 16 and 30 h), filtered through a thin bed of celite, and concentrated to give a residue. Analysis (by 90 MHz ^{1}H nmr spectroscopy) of these samples was not possible: the spectra were complicated by signals from the starting materials.

Exp. 51   Reaction of the product of experiment 50.1 with isopropanol.

51.1   With Ag-Z4A.

Trichloroacetonitrile (0.25ml., 2.48mmol) was reacted with dry (7) (0.2g., 0.46mmol) and NaH (~

20mg., 0.83mmol) in dry dichloromethane (5ml) as described in experiment 50.1. The reaction mixture was filtered (after ~ 16h) through a thin bed of celite, added to a mixture containing Ag-Z4A (0.4g) and dry isopropanol (30μl., 0.5mmol) in dry dichloromethane and stirred under nitrogen for ~ 5h at room temperature. Analysis (t.l.c., Solvent B) indicated the presence of two new components (Rf 0.81 and 0.77) corresponding to the α- and β-isopropyl glycosides (147), together with traces of another component (Rf 0.24) corresponding to the free sugar (7). The reaction mixture was centrifuged, the supernatent concentrated and the residue purified by flash chromatography to give the isopropyl glycosides (147) [0.16g., 75% based on free sugar (7)]; (α:β = 1:8, by ^{1}H nmr).

51.2   With Tl-Z4A.

The procedure followed in Experiment 51.1 was repeated but with the Ag-Z4A replaced by Tl-Z4A (0.4g). Analysis (t.l.c., solvent B) of the reaction mixture showed no sign of any isopropyl glycosides (147) during a period of 24h.

51.3   With 4A molecular sieves.

The procedure followed in Experiment 51.1 was repeated but with Ag-Z4A replaced by activated 4A molecular sieves (0.4g). Analysis (t.l.c., solvent B) of the reaction mixture showed no sign of any

isopropyl glycosides **(147)** during a period of 24h.

51.4   With no additive (control experiment).

The procedure followed in Experiment 51.1 was repeated but without any zeolite-based additive being included.   Analysis (t.l.c., solvent B) of the reaction mixture showed no sign of any isopropyl glycosides **(147)** during a period of 24h.

5.32   Synthesis of target arabinofuranosides.

Exp.   52   N-(Benzyloxycarbonyl)-4-O-(2,3,5-tri-O-benzyl-β-L-arabinofuranosyl)-trans-oxy-L-proline diphenylmethyl ester **(177)**.

52.1   With Ag-Z4A.

A solution of freshly prepared dry **(113a)** (0.14g., 0.319mmol) in dry dichloromethane (2.5ml) was added (in one batch) to a stirred mixture of Ag-Z4A (0.4g), powdered activated 4A molecular sieves (~ 0.25g) and dry **(133)** (0.138g., 0.319mmol) in dry dichloromethane under nitrogen at room temperature in an ultrasonic bath.   After ~ 3-4h, the reaction mixture was centrifuged and the supernatent concentrated. Analysis (t.l.c., solvent G) of the residue showed it to comprise mainly one component (Rf 0.47) which was purified by flash chromatography to give **(177)** (0.22g., 82%); m.p. 79°-80°; $[\alpha]_D$ +11.38° (C 1

CH_2Cl_2); M(mass spectrum, f.a.b.) 833. $C_{52}H_{51}O_9N$
requires M, 833; ^{13}C nmr data: see Table 4.3.

52.2   With Tl-Z4A.

The procedure followed in Experiment 52.1 was
repeated but with the Ag-Z4A replaced by Tl-Z4A
(0.4g.) to give after flash chromatography one
component (t.l.c., solvent G, Rf 0.47) which showed
the same data as obtained for (177) (0.18g., 71%).

Exp.   53   N-(Benzyloxycarbonyl)-4-0-(2,3,5-tri-0-
benzyl-β-L-arabinofuranosyl)-trans-oxy-L-proline
phenacyl ester (178).

53.1   With Ag-Z4A.

Freshly prepared dry (113a) (0.14g., 0.319mmol),
Ag-Z4A (0.4g) , powdered activated 4A molecular sieves
(~ 0.25g) and dry (134) (0.122g., 0.319mmol) in dry
dichloromethane were mixed as described in Experiment
52.1. Analysis (t.l.c., solvent H) of the residue
showed it to comprise mainly one component (Rf 0.71)
which was purified by flash chromatography to give
(178) (0.16g., 64%); $[\alpha]_D$ (C CH_2Cl_2);
M(mass spectrum, f.a.b.) 808 (M^+ + Na). $C_{47}H_{47}O_{10}N$
requires M, 785; ^{13}C nmr: see Table 4.3.

53.2   With Tl-Z4A.

The procedure followed in Experiment 52.1 was
repeated, but the Ag-Z4A replaced by Tl-Z4A to give

after flash chromatography one component (t.l.c., solvent H, Rf 0.71) which showed the same data as obtained for (178) (0.17g., 68%).

Exp. 54   N-(p-Nitrobenzyloxycarbonyl)-4-O-(2,3,5-tri-O-benzyl-β-L-arabinofuranosyl)-trans-oxy-L-proline diphenylmethyl ester (179).

54.1   With Ag-Z4A.

Freshly prepared dry (113a) (0.14g., 0.319mmol), Ag-Z4A (0.4g), powdered activated 4A molecular sieves (~ 0.25g) and dry (136) (0.152g., 0.319mmol) in dry dichloromethane were mixed as described in Experiment 52.1.   Analysis (t.l.c., solvent G) of the residue showed it to comprise mainly one component (Rf 0.24) which was purified by flash chromatography to give (179) (0.25g., 92%); m.p. 132°-133°; $[\alpha]_D$ -16.64 (C, 1.1 CH$_2$Cl$_2$); M(mass spectrum, f.a.b.) 901 (M$^+$ + Na). C$_{52}$H$_{50}$O$_{11}$N$_2$ requires M, 878; ^{13}C nmr data: see Table 4.2.

54.2   With Tl-Z4A.

The procedure followed in Experiment 52.1 was repeated, but with Ag-Z4A replaced by Tl-Z4A to give after flash chromatography one component (t.l.c., solvent G, Rf 0.24) which showed the same data as obtained for (179) (0.19g., 68%).

Exp. 55   N-(p-Nitrobenzyloxycarbonyl)-4-O-(2,3,5-tri-
O-benzyl-β-L-arabinofuranosyl)-trans-oxy-L-proline
phenacyl ester **(180)**.

55.1   With Ag-Z4A.

Freshly prepared dry **(113a)** (0.14g., 0.319mmol),
Ag-Z4A (0.4g), powdered activated 4A molecular sieves
(~ 0.25g) and dry **(137)** (0.13g., 0.319mmol) were mixed
as described in Experiment 52.1.   Analysis (t.l.c.,
solvent G) of the residue showed it to comprise mainly
one component (Rf 0.26) which was purified by flash
chromatography to give **(180)** (0.19g., 73%); M(mass
spectrum, f.a.b.) 853 (M$^+$ + Na). $C_{47}H_{46}O_{12}N_2$ requires
M, 830; ^{13}C nmr data: see Table 4.3.

55.2   With Tl-Z4A.

The procedure followed in Experiment 52.1 was
repeated, but with Ag-Z4A replaced by Tl-Z4A to give
after flash chromatography one component (t.l.c.,
solvent G, Rf 0.26) which showed the same data as
obtained for **(180)** (0.18g., 72%).

Exp. 56   4-O-(α-L-arabinofuranosyl)-trans-oxy-L-
proline **(5)**.

56.1   From **(177)**.

(177) (0.15g., 0.18mmol) in aqueous methanol (80%
v/v, 5ml) was hydrogenated over a palladium (10%) on
charcoal catalyst (~ 100mg) as described in Experiment
9 to give **(5)** (0.04g., 94%) [α]$_D$ +14.6^o (C 1, H_2O);

[Lit[17] $[\alpha]_D^{25}$ +14.4° (C 1.2, H_2O)].

56.2   From **(178)**.

   (178) (0.15g., 0.19mmol) in aqueous methanol (80% v/v 5ml) was hydrogenated over a palladium (10%) on charcoal catalyst (~ 100mg) as described in Experiment 9 to give **(5)** (0.05g., 96%); $[\alpha]_D$ +14.6° (C 1, H_2O).

56.3   From **(179)**.

   (179) (0.15g., 0.17mmol) in aqueous methanol (80% v/v 5ml) was hydrogenated over a palladium (10%) on charcoal catalyst (~100mg) as described in Experiment 9 to give **(5)** (0.02g., 62%) $[\alpha]_D$ + 14.7° (C 1, H_2O).

56.4   From **(180)**.

   (180) (0.15g., 0.18mmol) in aqueous methanol (80% v/v 5ml) was hydrogenated over a palladium (10%) on charcoal catalyst (~ 100mg) as described in Experiment 9 to give **(5)** (0.044g., 93%) $[\alpha]_D$ +14.6° (C 1, H_2O).

Exp. 57   Reaction of the α-glycosyl chloride **(113a)** with allyl 3,5-O-isopropylidene arabinofuranoside **(110)**.

   Freshly prepared dry **(113a)** (0.14g., 0.319mmol) Ag-Z4A (0.4g), crushed activated molecular sieves (~0.25g) and dry **(110)** (0.074g., 0.319mmol) in dry dichloromethane were mixed as described in Experiment 52.1.   Analysis (t.l.c., solvent G) of the residue showed it to comprise mainly one component (Rf 0.57), which was purified by flash chromatography to give a

first fraction corresponding to 1-O-(2,3,5-tri-O-benzyl-L-arabinofuranosyl)-2,3,5-tri-O-benzyl-β-L-arabinofuranoside (0.11g., 42%); m.p. 72° (from ethanol); $[\alpha]_D$ + 85.1 (C, 0.8 CH_2Cl_2); M(mass spectrum, f.a.b.) 844 (M^+ + Na). $C_{52}H_{53}O_9$ requires M, 821); ^1H nmr data ($CDCl_3$) : δ 7.3 (m,15H,3Ph), 5.42 (1H,d,J_{12}3.47Hz, H-1), 4.3, 4.5, 4.6 (6H,m,$\underline{CH_2}$Ph), 4.12 (3H,m;H-2,H-3,H-4), 3.52 (2H,d,J_5l_5, 5.3Hz,H-5; ^{13}C nmr data ($CDCl_3$): δ 138.19, 138.17, 138.07, 128.31, 128.07, 127.71, 127.58 ($\underline{C}_6H_5CH_2$), 96.75 (C-1), 83.60, 83.28, 80.48 (C-2,C-3 and C-4), 72.88, 72.32, 72.23, 71.96 (C-5 and $C_6H_5\underline{CH_2}$).

5.4   References.

1.   E. Baer and R.J. Stedman, Can.J. Biochem.
      Physiol, 37 (1959) 583.

2.   A.A. Patchett and B. Witkop, J.Am.Chem.Soc.,
      79 (1957) 185.

3.   J.B. Miller, J.Org.Chem., 24 (1959) 560.

4.   H. Standinger, E. Anthes and F. Pfenninger,
      Ber., 49 (1916) 1928.

5.   F.H. Carpenter and D.T. Gish, J.Am.Chem.Soc.,
      74 (1952) 3818.

6.   R. Barker and H.G. Fletcher Jr., J.Org.Chem.,
      26 (1961) 4605.

7.   S. Tejima and H.G. Fletcher Jr., J.Org.Chem.,
      28 (1963) 2999.

8.   W.C. Still, M. Khan and A. Mitra, J.Org.Chem.,
      43 (1978) 2923.

9.   E.J. Corey and M. Chaykovsky, J.Am.Chem.Soc.,
      87 (1965) 1345.

10.   P.J. Harris, R.J. Henry, A.B. Blakeney and
      B.A. Stone, Carbohydr.Res., 127 (1984) 59.

11.   C.P.J. Glaudemans and H.G. Fletcher Jr.,
      J.Am.Chem.Soc., 87 (1965) 4636.

12.   C.P.J. Glaudemans and H.G. Fletcher Jr.,
      J.Org.Chem., 36(1971) 3598.

13.   E. Zissis and C.P.J. Glaudemans, Carbohydr.
      Res., 50 (1976) 292.

14.   P.J. Garegg and P. Ossowski, Acta.Chem.Scand.,
      B37 (1983) 249.

15.   J.P. Carver, J.J. Krepinsky, D.A. Schwartz,
      R.N. Shah and D.M. Whitfield, to be published.

16.   V. Dourtoglou and B. Gross, Carbohydr.Chem.,
      2(1) (1983) 57.

17.   A. Allerhand, K. Dill, E. Berman, J.M. Lacombe
      and A. Pavia, Carbohydr.Res, 97 (1981) 331.

18.   W.D. Perrin, W.L.F. Armarego and D.W. Perrin,
       "Purification of Laboratory Chemicals",
       Pergamon Press, London, 1966.

19.   A.I. Vogel, "Practical Organic Chemistry",
       Longmans, 1948.

ERRATA

ERRATA