SYNTHESIS OF HIGHER SUGARS

A THESIS SUBMITTED FOR THE DEGREE ***OF***
DOCTOR OF PHILOSOPHY

BY

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Dedicated to
my father A. Kesavaram
and to
my mother K. Gunapushani.

CONTENTS

DECLARATION

1 hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the School of Chemistry, University of Hyderabad, Hyderabad under the supervision of Professor M. Nagarajan.

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators.

K. Narkunan.

CERTIFICATE

This is to certify that the work described in this thesis entitled **SYNTHESIS OF HIGHER SUGARS** has been carried out by Mr. K. Narkunan, under my supervision and the same has not been submitted elsewhere for any degree.

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K. Narkunan

ABBREVIATIONS

Ac	acetyl
aq	aqueous
Bn	benzyl
Bu	butyl
Bz	benzoyl
CSA	camphorsulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAH	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
Et	ethyl
h	hour(s)
HMPA	hexamethylphosphoric triamide
LAH	lithium aluminum hydride
MCPBA	*m*-chloroperbenzoic acid
Me	methyl
min	minute(s)
ml	millilitre(s)
mmol	millimole(s)
Ms	methanesulfonyl (mesyl)
NBS	N-bromosuccinimide

NMO	N-methylmorpholine N-oxide
Ph	phenyl
Pr	propyl
Py	pyridine
rt	room temperature
TBDMS	*t*-butyldimethylsilyl
TEA	triethylamine
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
TMSOTf	trimethylsilyl trifluoromethanesulfonate
Tr	trityl
Ts	*p*-toluenesulfonyl (tosyl)
W-E	Wadsworth-Emmons

ABSTRACT

This thesis deals with the synthesis of higher sugars using two methodologies, namely, 1) Wadsworth-Emmons reaction and 2) *tetra*-hydroxylation of sugar derived dienes. The thesis consists of three sections, namely, introduction, results and discussion and experimental. The results and discussion is divided into two parts. Part-I deals with preparation of sugar derived p-keto phosphonates and their use in the synthesis of higher sugars. Part-n deals with synthesis of higher sugars by *bis*-dihydroxylation of sugar dienes.

The introduction briefly presents various available methods for the synthesis of higher sugars. Different approaches, which are commonly used are discussed under six major headings, namely, 1) Wittig reaction, 2) Aldol condensation, 3) Radical reactions, 4) Nucleophilic additions, 5) (3+2) Cycloaddition and 6) Ab-initio synthesis.

Synthesis of higher sugars has been a target of interest to the organic chemist since the time of Fischer. This is due to the fact that higher sugars are, a) complex carbohydrates, which are not available in nature, b) components of some natural products like hikizimycin and tunicamycin and c) chiral, highly functionalized synthons for the preparation of macrolide antibiotics like erythromycin and streptovaricin.

Synthesis of higher sugars using **Wadsworth-Emmons** reaction.

One of the earliest methods for the synthesis of higher sugars is the **Kiliani-**Fischer **reaction,** which is used to extend the aldose chain by one carbon from the reducing end. More recently, the Wittig reaction has been used in all possible combinations. Still, due to its limitations, the need for a new methodology for this purpose was felt. The advantage of the Wadsworth-Emmons reaction over the classical Wittig reaction is well known to bear repetition.

The required p-keto phosphonates 87, **97,** 98, and 99 were obtained in quantitative yields by the acylation of lithium dimethyl methylphosphonate with the readily available methyl glycuronates or glyconate. A systematic study of the reaction of the phosphonate 87 with ***p*-anisaldehyde** in the presence of various bases like DBU, NaH, K_2CO_3, and Cs_2CO_3 showed Cs_2CO_3 to be the most suitable base for the purpose and the corresponding enone was obtained in high yield. Subsequently, phcsphonates 87, 97, 98 and 99 were condensed with various sugar aldehydes derived from aldoses at **C-1**, C-5, and **C-6** to give rise to the expected higher sugar enones, in high yields.

Similarly, to facilitate the extension of carbon chain from both ends, *C-2* symmetric ***bis*-phosphonate** 113 was prepared from **diethyl-2,3-O-isopropylidene-*L*-**tartrate **(112)** and was treated with various sugar aldehydes to provide the corresponding *C-2* symmetric ***bis*-enones** in moderate yields.

In order to highlight the synthesis of higher sugars from higher sugar enones, enone 103 was hydroxylated using osmium **tetroxide/N-methylmorpholine** N-oxide to

obtain 124 and 125 in 90% yield. While this work was in progress, Jarosz reported the preparation of 124 and 125 by the same method.

Synthesis of higher sugars using *tetra*-hydroxylation of sugar derived dienes.

Kishi, in his paper on stereochemistry of osmium tetroxide oxidation of allylic alcohol and ether systems, showed that the relative stereochemistry between the existing hydroxyl or alkoxyl group and the adjacent newly introduced hydroxyl group of the major product is *erythro* in all cases. Recently, Sharpless observed that on hydroxylation of achiral dienes and trienes, the major product has *erythro* relationship between the hydroxyl groups formed between two double bonds and selective asymmetric dihydroxylation of unsymmetrical dienes occurs at the more substituted double bond. At this stage, it was of interest to make a model in which both Kishi's and Sharpless's observations would be operative *(i.e.,* a diene attached to a chiral centre). Dienes 137 and 140 were chosen for this purpose and their advantage can be understood by analyzing the structures of all possible hydroxylated products, 151-154 and 155-158, respectively. 1) Both dienes 137 and 140 on hydroxylation provide one *meso* and one *C-2* symmetric diastereomer each, 2) one of the diastereomers obtainable from both 137 and 140 form an enantiomeric pair and 3) one of the diastereomers obtainable from 137 is identical to one of those derivable from 140. These features allow for easy and unambiguous product identification.

Dienes 137 and 140 were synthesized by the Wittig reaction of the known enals 136 and 139, respectively. Dienes 137 and 140 were hydroxylated using osmium tetroxide/N-methylmorpholine N-oxide, and the resulting hydroxylated products were converted to their peracetylated octitol mixtures 148 and 150, respectively, using

conventional protection and deprotection methods. Analysis of the mixture **148** revealed that **151-OAc**, **152-OAc** and **153-OAc** were formed in a ratio of 1.15:6.6:1. The diastereomeric peracetylated octitol mixture **150** obtained from **140** showed that **155-OAc**, **156-OAc** and **158-OAc** were present in a 1.33:1:1 ratio, respectively.

Results of the diastereoselective hydroxylation of dienes **137** and **140** indicate that the major isomer formed is the one in which both the relations between the existing hydroxyl group and the adjacent newly introduced hydroxyl group, as well as the hydroxyl groups formed between two double bonds are *erythro*. It is also interesting to note that stereo isomers **154-OAc** and **157-OAc** are not formed at all, since in them both stereochemical relationships are *threo*.

Conclusion

The above results show that the methodology developed here provides a simple and convenient procedure for the preparation of higher sugars. Higher sugars of any combination of lower constituent sugars can be synthesized easily. A study on the diastereoselectivity of complex diene hydroxylation was performed for the first time. Results of these experiments show that the major isomer formed is the one which is in accordance with Kishi's and Sharpless's observations.

INTRODUCTION

Synthetic carbohydrate chemistry is one of the fast developing disciplines in organic chemistry. The rich structural diversity of this group and the multifaceted importance of carbohydrates in biochemistry, medicinal chemistry, microbiology, technology and many other areas have long challenged synthetic chemists towards a multitude of objectives. The potential of sugars as starting points for highly efficient syntheses of non-carbohydrate targets is now well recognized by the wider chemical community. Carbohydrates also serve as excellent systems for the study of finer aspects of stereochemical influence and control of chemical transformations in multifunctional, three dimensional matrices.

The beauty of using carbohydrates as organic starting materials is due to the fact that they are inexpensive, available in bulk quantities and more interestingly, in enantiomerically pure forms. However, carbohydrates were not used by the majority of synthetic organic chemists for a long time as they were regarded as too complex, with many chiral centers and functional groups. In the recent past, this omission has been more than redressed and many scientists have realized the importance of the many latent advantages offered by carbohydrates and have taken advantage of them in numerous ways.

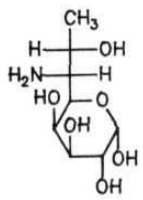
A perusal of the historical evolution of carbohydrate chemistry reveals that Fischer was the first chemist to use analytical reagents in carbohydrate chemistry in

1884,1 using which he established the relative configurations of sugars only seven years later. [2] This was one of the important milestones in the development of organic stereochemistry in general and carbohydrate chemistry in particular. Today, owing to the efforts of many dedicated carbohydrate chemists, reactions of all classes, which arc more common in modern organic chemistry, have been carried out on sugars. A collection of chemical transformations of sugars into other natural products has been expertly summarized by Hanessian.[3]

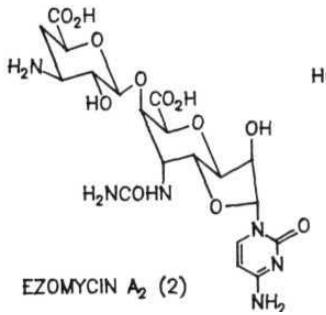
Most of the commonly occurring sugars in Nature are either pentoses or hexoses. Therefore, the simplest definition of higher carbon sugars is that they are polyhydroxy compounds possessing a chain of seven or more contiguous carbon atoms. Currently, there is an active interest in the synthesis of higher sugars as is evident from recent reviews.[4] This is because the list of natural products that contain long chain complex carbohydrates continues to grow and unlike many of the lower carbon sugars, they are less abundantly available in Nature (Figure 1). Despite the interest in the synthesis of higher sugars for over a century, [5] very few higher carbon sugars except seven carbon sugars were known till recently. On the other hand, the synthesis of these sugars in a highly stereoselective and regiocontrolled way presents a challenge to synthetic chemists.

The recent interest in the synthesis of higher carbon sugars follows from the discovery of important antibiotics containing such sugars. A few octoses have been found in plants[6] and an octitol has been observed recently in the human eye lens.[7] Lincosamine (1), an aminooctose, is a component of the antibiotic lincomycin,[8] which is a clinically used antibacterial agent. Ezoaminuroic acid is the octose nucleoside portion of ezomycins, a class of antifungal antibiotics.[9] The octosyl acids are eight carbon

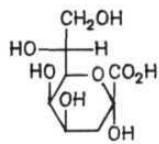
bicyclic sugars which are N-glycosidically linked to pyrimidine bases,[10] some derivatives of which are powerful phosphodiesterase inhibitors.[11] KDO (3-Deoxy-*D*-*manno*-octulosonic acid) (3) is a constituent of cell wall lipopolysaccharides of gram negative bacteria.[12] This acid is chemically bonded to the polysaccharide and lipid



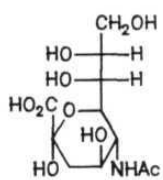
LINCOSAMINE (1)



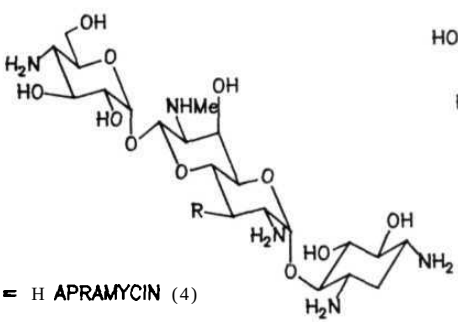
EZOMYCIN A_2 (2)



KDO (3)



Neu5Ac (6)



R = H APRAMYCIN (4)

R = OH OXYAPRAMYCIN (5)

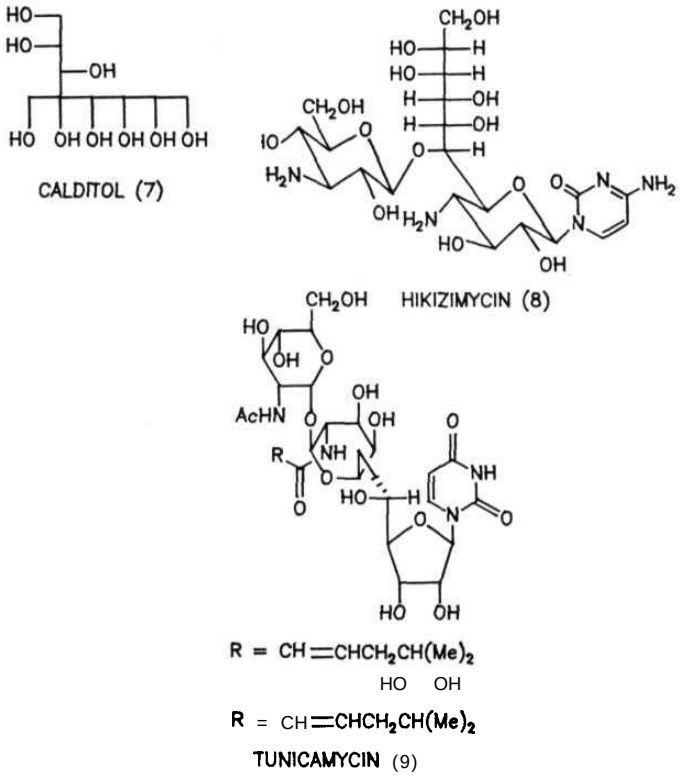


Figure 1 *Representative examples of Natural products containing higher sugar units.*

components and is responsible for the **immunospecificity** of **lipopolymers.**[13] Other important antibiotics containing the **amino-octodiose** unit are **apramycin** (4) and **oxyapramycin** (5), two broad spectrum antibiotics from the nebramycin **complex.**[14]

Among the nine carbon carbohydrates, the sialic acids, which are N- and O-acylated derivatives of neuraminic acid, are components of glycoproteins found in many types of cells.[15]

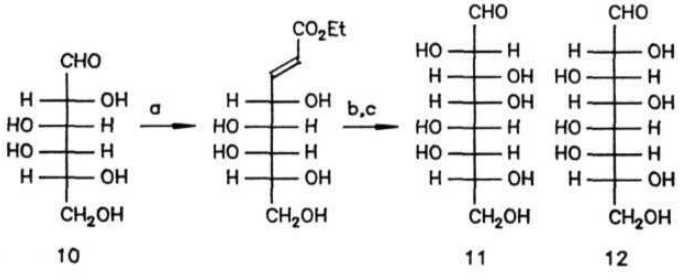
Calditol (7), a branched nonitol, has been found to be a part of the complex macrocyclic tetraether lipids isolated from the membrane of thermoacidophilic bacteria.[16] A l,2:8,9-bis(anhydro)nonitol (WF-3405), isolated from the culture of Amouroascus aureus F-3405, has been shown to exhibit antitumor activity.[17] Hikizimycin (anthelmycin) (8),[18] tunicamycin (9),[19] and sinefungin[20] are important complex nucleosidic antibiotics which contain undecose carbohydrates. Hikizimycin (8) is a powerful anthelmintic agent and has recently been shown to inhibit protein synthesis by preventing the peptide bond forming reaction. Tunicamycin (9) is a powerful glycosylation inhibitor and sinefungin has both antifungal and antiviral activity. Higher carbon sugars containing more than ten carbon atoms can be used in biological studies as non-metabolized analogues of disaccharides. Higher carbon sugars also serve as highly functionalized synthons for the preparation of complex natural products, exemplified by the macrolide antibiotics erythromycin[21] and streptovaricin.[22]

One of the earliest methods for the synthesis of higher sugars is the Kiliani-Fischer synthesis, which extends the aldose chain by one carbon from the reducing end.[23] In recent times, the cyanohydrin procedure has been augmented by other methods. These permit extension of the sugar chain by two or more carbon atoms in a single step. In the following pages, a brief account of existing methodologies available for the synthesis of higher sugars is presented. The different approaches used can be broadly classified under the following headings, depending upon the key step involved in

the homologation: (1) Wittig reaction (2) Aldol condensation (3) Radical reactions (4) Nucleophilic additions (5) (3+2) Cycloaddition (6) Ab-initio synthesis.

(1) Wittig reaction:

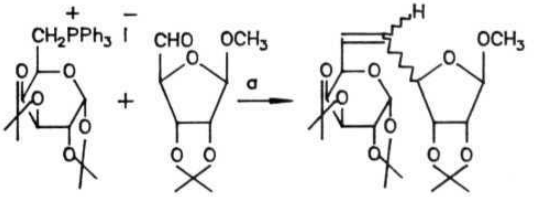
The Wittig reaction[24] has proven to be a multifaceted tool for the synthesis of higher sugars. This is because it provides many advantages over other approaches namely, (1) presence of aldehyde functionality in sugar units can be made use of for this purpose, (2) Wittig reactions in different combinations can be realized and (3) the double bond produced by the condensation reaction is, of course, amenable to suitable manipulations to incorporate additional needed or desired functionalities.



Scheme 1 *Reagents and conditions: (a)* $Ph_3P{=}CH{-}CO_2Et$, *DMF,* 90^o; *(b)* OsO_4 $HClO_3$; *(c)* H_2SO_4, *Amberlite IR-120(*H^+*),* $Na(Hg)$, $BaCO_3$.

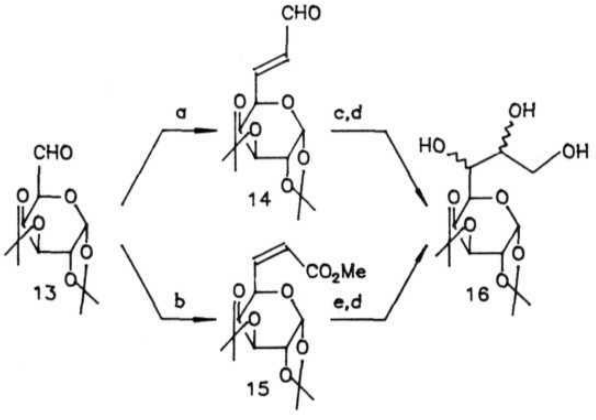
One of the classical methods of homologation of free sugars by two or three carbon atoms was pioneered by Kochetkov.[25] (Carbethoxymethylene)triphenylphosphorane was condensed with free sugars to obtain ethyl esters of a,P-unsaturated aldonic acids, which were hydroxylated and reduced to arrive at higher aldoses. This approach to higher sugars is exemplified by the synthesis of *D-threo-L-galacto-* and *D-threo-L-ido*-octoses (11) and **(12),** respectively, starting from *D*-galactose (10) (Scheme 1).

A more elegant method developed by Secrist[26] for the construction of long chain carbohydrates consists of the union of a carbohydrate derived Wittig reagent with an *aldehydo* sugar (Scheme 2). This method can be used to prepare, for example, ten to twelve carbon sugars from readily available starting materials and its potential was illustrated in a landmark synthesis of hikizimycin. But this method is limited to extending the carbon chain from the non reducing end. Additionally, this protocol yields mixtures of geometrical isomers and epimerization of the furanose derived Wittig reagent is a competing problem.



Scheme 2 *Reagents and conditions: (a) n-BuLi, THF-HMPA(2:1), -60°.*

Brimacombe developed a general method for the chain elongation of simple monosaccharides by two carbon atoms.[4c] It is based on the reaction of C-6 or C-5 sugar aldehydes with a stabilized Wittig reagent followed by hydroxylation of the double bond to result in higher homologues. Thus, for example, reaction of 1,2:3,4-di-O-isopropylidene-α-*D-galacto*-hexodialdo-1,5-pyranose (13) with (formylmethylene)triphenylphosphorane afforded the *trans*-enal **14**, while condensation with

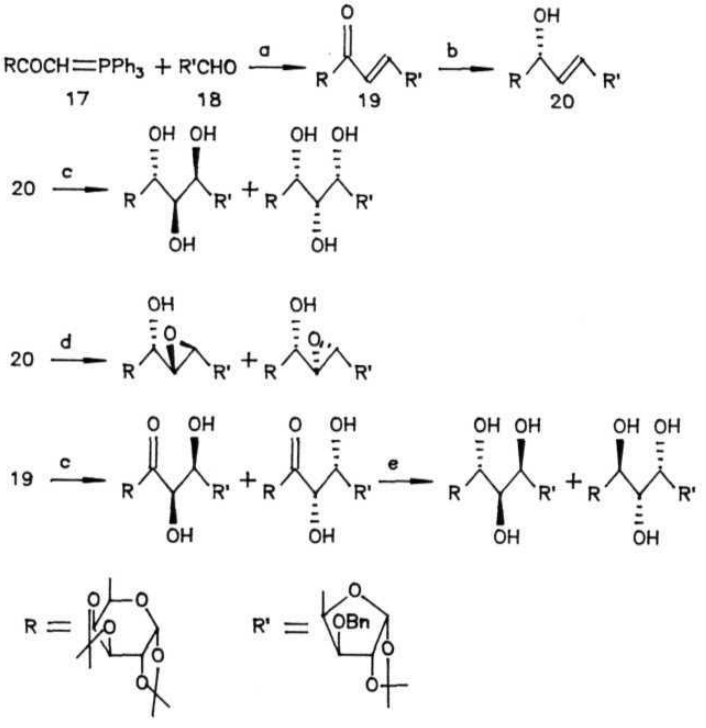


Scheme 3 *Reagents and conditions: (a) Ph_3P=CH-CHO, benzene, reflux; (b) Ph_3P=CH-CO_2Me, MeOH, 0°; (c) D1BAH, CH_2Cl_2, 0°; (d) OsO_4, NMO, acetone, H_2O; (e) LAH.*

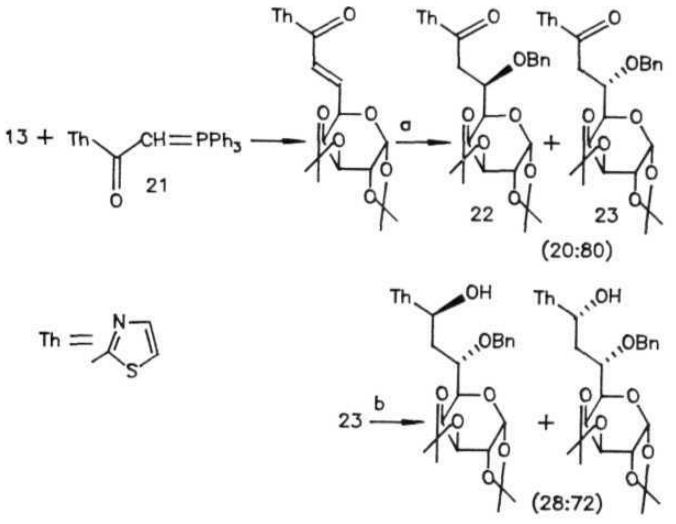
(carbmethoxymethylene)triphenylphosphorane in methanol gave the *cis*-olefinic ester 15. Both were reduced to the appropriate *E*- and *Z*-allylic alcohols. Hydroxylation of these alcohols (in accordance with Kishi's rule) or epoxidation under Sharpless's conditions followed by the opening of the oxirane ring, led to diastereomeric octoses 16 (Scheme 3). A similar methodology was adopted by Bessodes[27] for the synthesis of higher amino sugars. Regrettably, this is a lengthy and cumbersome process when complex higher carbon sugars are to be prepared, since it would require many iterative steps. The advantage is that the stereochemistry can be well controlled at each stage.

Other variations of this method involve the use of a stabilized Wittig reagent derived from carbohydrate precursors.[28] This approach, which conveniently lengthens the carbon chain from the non reducing end, was first introduced by Jarosz and co-workers. By this procedure, it is very easy to unite two sugar units in a single step to achieve higher carbon sugars of C-12 and greater lengths. In a series of papers, Jarosz has enumerated different methods for functionalizing the resulting enones, namely, (a) stereoselective reduction of the enone to an allylic alcohol[29] followed by either epoxidation[30] or hydroxylation,[28] (b) hydroxylation of the enone followed by reduction of the ketone[28] (Scheme 4).

More recently, Dondoni[31] has introduced a three carbon chain elongation of sugar aldehydes using a thiazole based stable Wittig reagent. Olefination of 1,2:3,4-di-O-isopropylidene-α-*D-galacto*-hexodialdo-1,5-pyranose (13) with triphenyl(thiazol-2-ylcarbonylmethylene)phosphorane (21) and 1,4-addition of benzyloxide anion to the resultant enone followed by unmasking of the formyl group from the thiazole ring led to 7-deoxynonodialdose epimers (Scheme 5).



Scheme 4 *Reagents and conditions: (a) toluene, reflux; (b)* $Zn(BH_4)_2$; *(c) OsOj, NMO,* *THF, t-BuOH,* H_2O; *(d) MCPBA,* CH_2Cl_2; *(e)* $NaBH_4$.

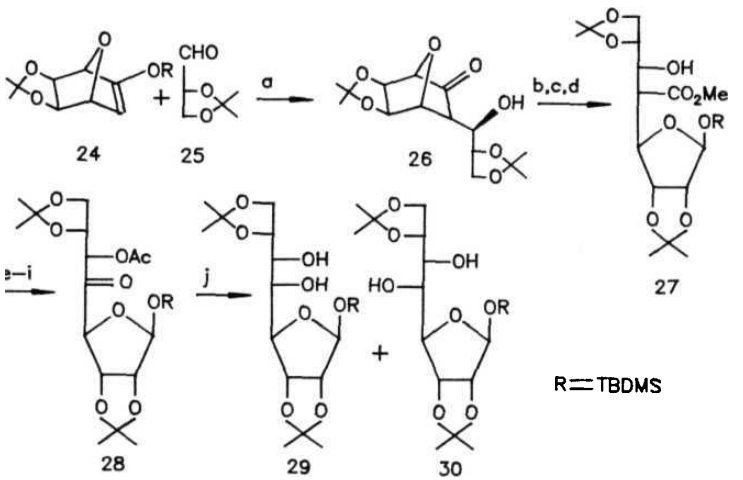


Scheme **5** *Reagents and conditions: (a) BnONa; (b) D1BAH.*

A new **stereoselective** route to 3-deoxy-2-ulosonic acids and the total syntheses of **3-deoxy-*D-arabino*-2-heptulosonic** acid (DAH), **3-deoxy-*D-glycero-D-galacto*-2-**nonulosonic acid (KDN) and **3-deoxy-*D-glycero-D-talo*-2-nonulosonic** acid **(4-*epi*-KDN)** were carried out by **Dondoni[32] using** the above strategy.

(2) Aldol Condensation:

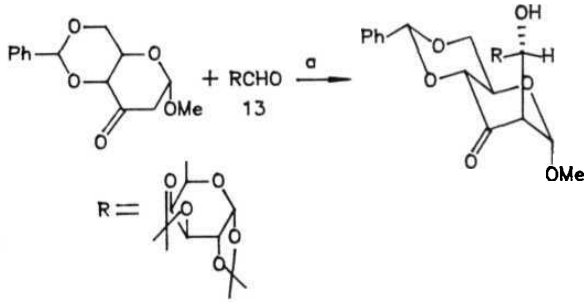
Another popular reaction which has been extensively employed in the synthesis of higher sugars is the aldol condensation. This method is particularly useful for the synthesis of branched sugars.



Scheme 6 *Reagents and conditions: (a)* $TiCl_4$, CH_2Cl_2, -78°; *(b)* MCPBA, CH_2Cl_2; *(c)* MeOH, K_2CO_3; *(d)* (t-Bu)$Me_2SiOSO_2CF_3$2,6-lutidine, CH_2Cl_2, 0°; *(e)* LAH, THF; *(f)* 2-$O_2NC_6H_4SeCN$, n-Bu_3P, THF, 50°; *(g)* Ac_2O, Py; *(h)* MCPBA, NaHCOi, CH_2Cl_2; *(i)* O_3, CH_2Cl_2, -78°; *(j)* $LiB(Et)_3H$or DIBAH.

An interesting approach to higher sugars was presented by Vogel.[33] It is based on the *cross* aldol condensation of sugar aldehydes with 7-oxanorbornan-2-one derivatives, which are readily available in both enantiomerically pure forms. For example, silyl enol ether 24 reacted with 2,3-O-isopropylidene-*D*-glyceraldehyde (25) to afford 26. Baeyer-Villiger oxidation, followed by further transformations led to an octose (Scheme 6). Fortuitously, depending upon the reducing agent used, either diastereomer could be obtained stereoselectively from 28. When Super Hydride (LiB(Et)3H) was used, the selectivity of 29 over 30 was >20:l, while, on the contrary, when DIBAH was used, a reversed selectivity of 1:11.3 was obtained. Modifications of this methodology leading to different targets were also made by Vogel.[34]

Another powerful technique involves condensation between two sugar units. This is particularly useful when branched higher sugars are required. The extent of diastereofacial preference of the condensation is dependent on whether the coupling is



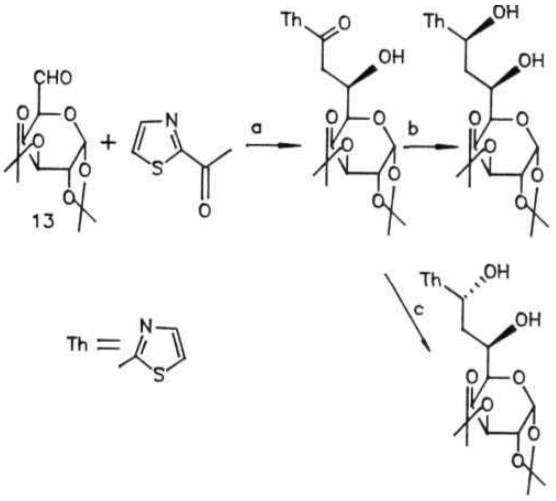
Scheme 7 *Reagents and conditions: (a)* $KN(SiMe_3)_2, ZnCl_2$.

between reactants of "matched" or "mismatched" pairs. However, if one of the faces of one partner is totally blocked, then the control elements in the other partner can be fully exploited. The generality of this principle was well studied by Fraser-Reid[35] (Scheme 7). In most instances, the condensation provides a single diastereomer exclusively. It implies that each of the aldehydes exercise their stereocontrol independently of the ketone. Similar results have also been reported by Chapleur.[36]

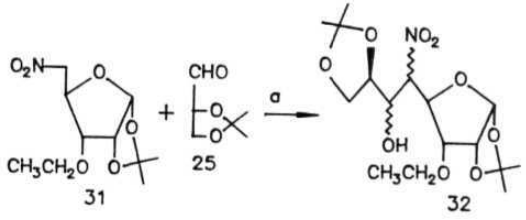
Stereocontrolled three carbon homologation of sugar aldehydes using the lithium enolate of 2-acetylthiazole was first introduced by Dondoni.[31] An attractive feature of this nucleophile is that it is a direct equivalent of pyruvaldehyde and the formyl group can be readily unmasked from the thiazole ring. This strategy provides an easy access to 7-deoxynonodialdoses starting from hexodialdoses (Scheme 8).

Potassium fluoride catalyzed Henry reaction between nitroribose derivative 31 and 2,3-O-isopropylidene-*D*-glyceraldehyde (25) afforded the adduct 32 as a mixture of diastereomers[37] (Scheme 9). The reduction of the nitro group followed by protection of the amino and hydroxyl functions is expected to furnish an intennediate for the synthesis of ezomycin.

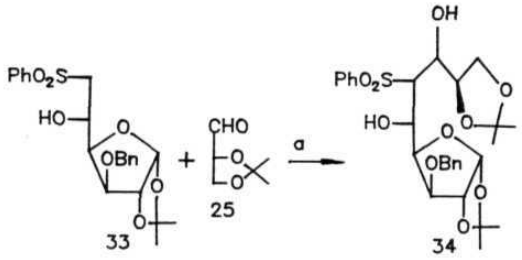
An efficient route to higher carbon sugars was developed by Kim *et al*. Conversion of sugar derived α-hydroxysulfones to their corresponding dianions and subsequent reaction with aldehydes afforded higher sugar precursors in good yields.[38] For example, sulfone 33 reacted with 2,3-O-isopropylidene-*D*-glyceraldehyde (25) to afford nonose 34 (Scheme 10).



Scheme 8 *Reagents and conditions: (a) t-BuOLi; (b) DIBAH; (c) $Me_4NBH(OAc)_3$.*



Scheme 9 *Reagents and conditions: (a) KF, n-Bu_4NI.*



Scheme 10 *Reagents and conditions: (a) n-BuLi, THF, -78°.*

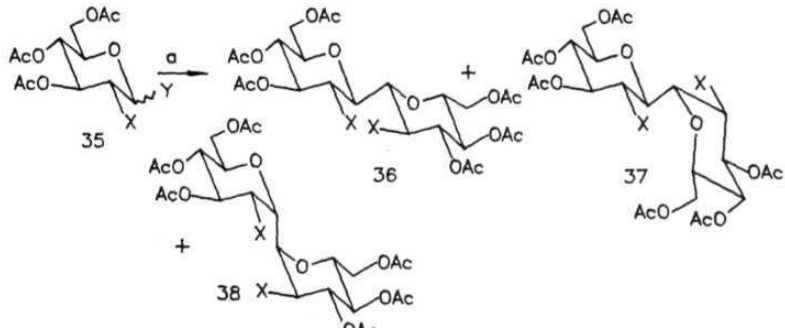
(3) Radical reaction:

Radical reactions have been comparatively less widely used for the synthesis of higher sugars. This is due to difficulties in controlling the regio- and stereochemistry of the product. Various types of carbohydrate radical reactions include additions to sugar olefins, styrene[39] and electron deficient olefins.[40]

Glycosyl bromides and selenides react with hexamethylditin to give coupling products[41] 36, 37 and 38 (Scheme 11). The reaction occurs by dimerization of glycosyl radicals.

Stereoselective synthesis of C-disaccharides based on the addition of a glycosyl radical to an *exo*-methylene δ-lactone followed by hydrogen atom abstraction was developed by Giese.[42] Thus, from *D*-glucopyranosyl bromide 39, α-methylene 8-

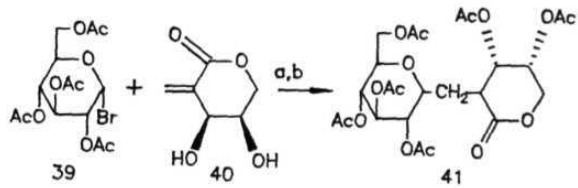
lactone 40 and tri-n-butyltin hydride, the C-disaccharide lactone 41 was obtained in 81% yield (Scheme 12).



a: X=OMe; Y=α-Br

b: X=H; Y=α-SePh

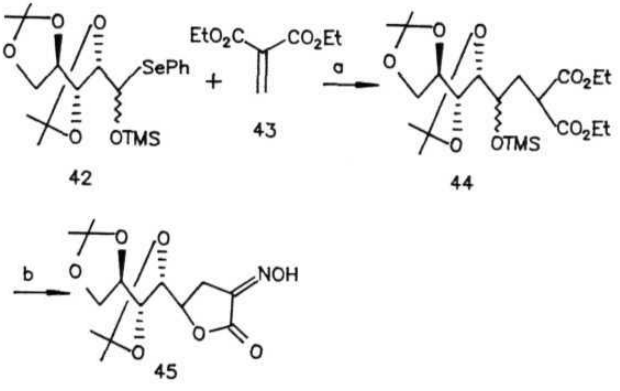
Scheme 11 *Reagents and conditions: (a) $(Me_3Sn)_2$/hν.*



a.p=10.1

Scheme 12 *Reagents and conditions: (a) n-Bu_3SnH, AIBN, 1,2-dimethoxyethane, 80°.*

A radical approach to the synthesis of KDO was used by Giese[43] (Scheme 13). Reaction of 42, the phenylselenotrimethylsilyloxy acetal of 2,3:4,5-di-0-isopropylidene-*D*-arabinose with diethyl methylenemalonate (43) in the presence of tri-n-butyltin hydride afforded 61% of octose 44. Nitrosation with isoamyl nitrite and basic cleavage using sodium ethoxide led to **45**, a precursor of KDO.

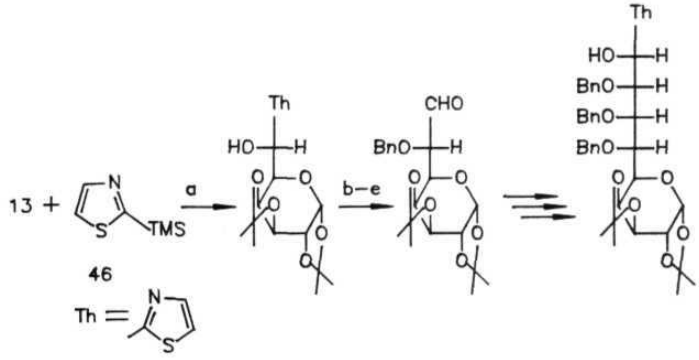


Scheme 13 *Reagents and conditions: (a) n-Bu3SnH; (b) i-amyl-ONO, NaOEt.*

(4) Nucleophilic addition:

Sugar derived carbonyl compounds have been homologated in numerous ways with a multitude of nucleophiles. One of the finer aspects of nucleophilic addition is the predictable stereochemistry of the newly formed hydroxyl group. An example of such a highly stereoselective homologation is Dondoni's iterative homologation of chiral

polyalkoxy aldehydes employing 2-(trimethylsilyl)thiazole (46) as a formyl anion equivalent[44] (Scheme 14).

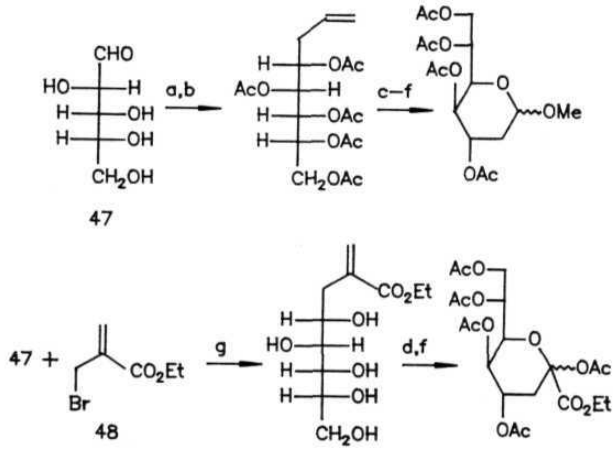


Scheme 14 *Reagents and conditions: (a) F⁻/THF, CH_2Cl_2; (b) NaH, BnBr; (c) CH_3I, CH_3CN; (d) $NaBH_4$, MeOH, -10°; (e) $HgCl_2$, CH_3CN, H_2O.*

The methodology consists of the repetitive use of a one carbon chain extension that involves two very efficient key operations, both chemically and stereochemically; (1) the *anti*-diastereoselective addition of 2-(trimethylsilyl)thiazole (46) to the chiral alkoxy aldehyde, (2) the unmasking of the formyl group from the thiazole ring in the resulting adduct.

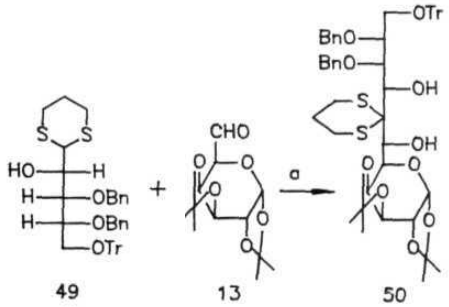
One of the elegant synthesis of higher sugars involves the tin or indium mediated allylation in aqueous media[45] (Scheme 15). This reaction can be applied to unprotected carbohydrates which makes it superior to other methods. Various 2-deoxyaldoses can be

synthesized by this protocol. Indium mediated reactions between ethyl 2-(bromomethyl)acrylate (48) and aldoses provide access to 2-keto-3-deoxyulosonic acids. These reactions are diastereoselective and the major product has a *threo* relationship between the newly generated hydroxyl group and the C-2 hydroxyl group of the starting carbohydrate. This methodology can be exploited for the preparation of a range of sugars, including heptoses, octoses and other higher sugars.



Scheme 15 *Reagents and conditions: (a) allyl bromide, Sn, EtOH, H_2O, (b) Ac_2O, Py, DMAP; (c) NaOMe, MeOH; (d) O_3, MeOH, CH_2Cl_2,-70°; (e) MeOH, H^+; (f) Ac_2O, Py; (g) In, EtOH. H_2O.*

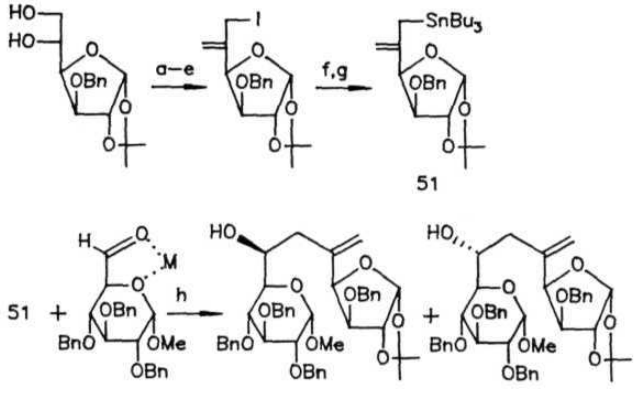
Another efficient synthesis comprises addition of the dianion of a 2-substiruted 1,3-dithiane to *aldehydo* saccharides[46] (Scheme 16). The undecose 50 is readily obtained by the condensation of dianion of 1,3-dithiane acetal of the D-arabinose derivative 49 with dialdohexose 13.



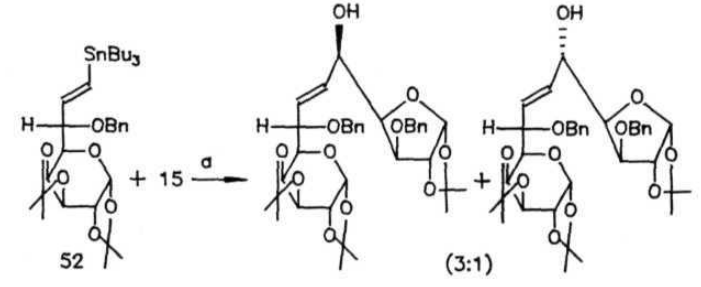
Scheme 16 *Reagents and conditions: (a) n-BuLi, THF.*

Lewis acid catalyzed addition of monosaccharide allyltin derivatives to *aldehydo* sugars has been examined by Fraser-Reid[47] (Scheme 17). The efficiency, rate and stereoselectivity of the reaction are strongly dependent on the Lewis acid catalyst used The major product is *syn* and in the most striking case, two monosaccharides have been coupled directly to give complex higher sugars.

A variation of the above procedure is addition of vinyl anion derivatives of simple monosaccharides to *aldehydo* sugars.[48] Vinyl tri-n-butylstannyl derivative 52 on



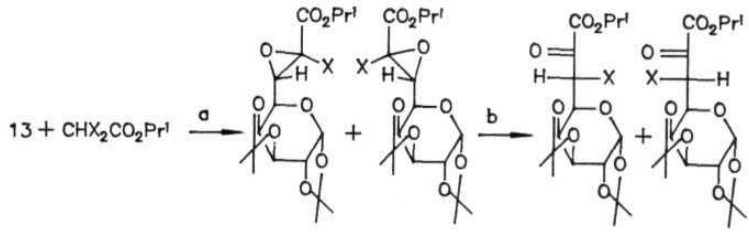
Scheme 17 *Reagents and conditions: (a) TrCl, Py, DMAP; (b) $(COCl)_2$, DMSO, Et_3N; (c) $Ph_3P{=}CH_2$, benzene, RT; (d) H^+, acetone, H_2O; (e) Ph_3P, I_2, imidazole; (f) $NaSO_2Tol$, MeOH, reflux, (g) n-BusSnH, AIBN, benzene; (h) $ZnCl_2$, CH_2Cl_2, 0°.*



Scheme 18 *Reagents and conditions: (a) n-BuLi, THF, -78°.*

treatment with n-butyllithium yielded a vinyl anion which readily added to aldehydo sugars to provide higher carbon sugars (Scheme 18).

The Darzens reaction between dialdosugar 13 and alkyl dihaloacetates afforded in high yields α-haloglycidic esters, which can easily be transformed into a-keto acid derivatives.[49] This methodology introduces a two carbon unit to a sugar moiety in high yields (Scheme 19).

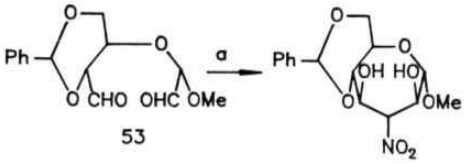


X=C1, Br, or I

Scheme 19 *Reagents and conditions: (a) i-PrOK, i-PrOH, ether; (b) MgX_2, THF.*

In addition to the above methodologies, higher sugars containing seven membered rings have also been synthesized. Synthetic routes to septanosides are very limited. One convenient device for the synthesis of septanosides is the nitromethane condensation with dialdehydes derived by periodate cleavage of a diol in a hexopyranoside ring.

Sodium **methoxide** catalyzed condensation of **nitromethane** with dialdehyde 53, obtained by periodate cleavage of methyl **4,6-O-benzylidene-α-*D*-glucopyranoside,** in the presence of KF and **dibenzo-18-crown-6** provided a single **diastereomeric** septanoside 54 exclusively[50] (Scheme 20).



53 54

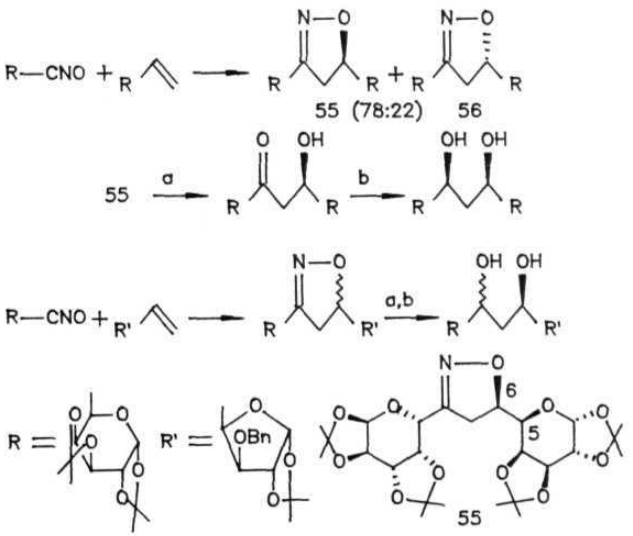
Scheme 20 *Reagents and conditions: (a) CH_3NO_2, NaOMe, KF, dibenzo-18-crown-6.*

(5) **(3+2)** Cycloadditions:

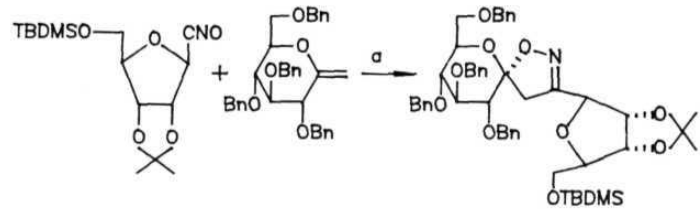
(3+2) Cycloaddition reactions of nitrones or nitrile oxides with unsaturated sugars have been used to lengthen the carbon chain in sugar units. Though nitrone or nitrile oxide cycloadditions are becoming familiar among carbohydrate chemists, their use in the synthesis of higher sugars is largely unexploited.

7-Deoxytrideca- and **6-deoxydodeca-dialdose** derivatives were prepared by cycloaddition of *D*-**galactose** derived nitrile oxide to unsaturated heptoses and hexoses followed by reductive hydrolytic cleavage of the resulting **2-isoxazolines**[51] (Scheme **21**).

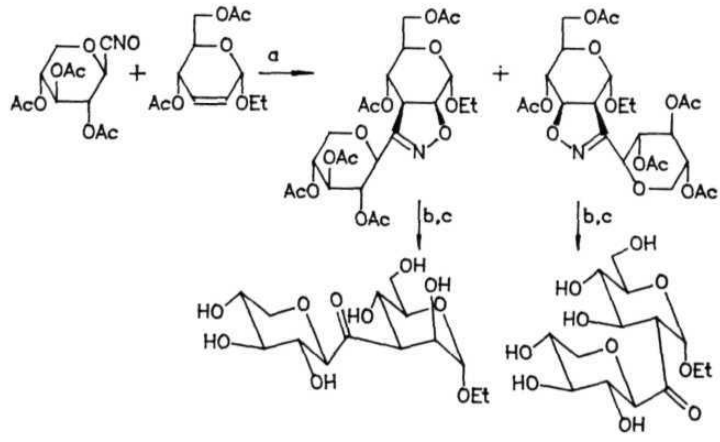
This methodology enables a convenient synthesis of higher dialdose derivatives from readily accessible sugar precursors. Interestingly, this reaction is **regiospecific** and diastereoselective in favor of adducts in which there is an *erythro* relationship between C5 and C6 and is attributed to the so called "inside alkoxy effect". Miscellaneous illustrations of the nitrile oxide cyclization are shown in schemes 22 and 23.[52]



Scheme 21 *Reagents and conditions: (a)* Pd/C, H_2, H_3BO_3, *MeOH,* H_2O; *(b)* $NaBH_4$.



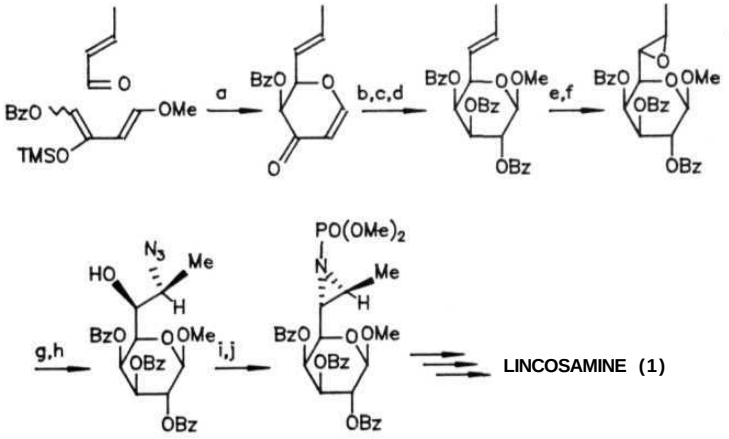
Scheme 22 *Reagents and conditions: (a) PhNCO, Et_3N.*



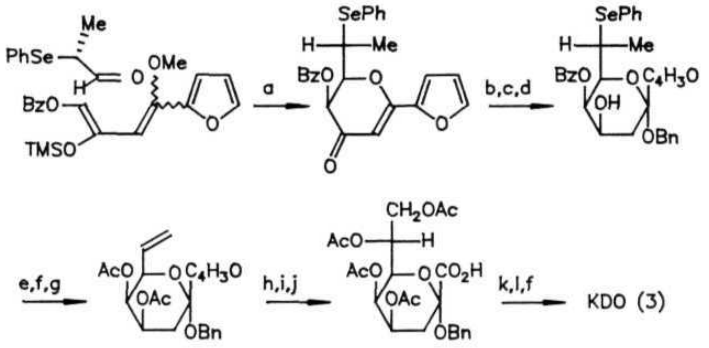
Scheme 23 *Reagents and conditions: (a) tolylene 2,6-diisocyanate, Et_3N, CH_2Cl_2; (b) KCN, MeOH: (c) Pd'C, H_2, H_3BO_3, MeOH, H_2O.*

(6) Ab-initio methods:

Danishefsky has developed an ab-initio synthesis of higher sugars based upon his Diels-Alder reaction between an aldehyde and an electron rich diene, catalyzed by Lewis acids.[53] This method is exceedingly versatile and has been applied by him for the synthesis of many biologically important molecules like lincosamine **(1)**,[54] KDO **(3)**[55] and Neu5Ac (6),56 among others. The essence of this strategy lies in the combination of suitable aldehydes with appropriate dienes and subsequent functionalization using stereoselective reactions. Representative examples of this method leading to different targets are illustrated below (Schemes 24, 25 and 26).



Scheme 24 *Reagents and conditions: (a)* $BF_3.OEt_2$, *TFA,* CH_2Cl_2, *-78°; (b)* $CeCl_3.7H_2O, NaBH_4$, *MeOH; (c)* $BzCl$, Et_3N, *0°; (d) MCPBA,* $BzCl$, $MeOH$; *(e)* NBS, $AcOH$, H_2O; *(0 DBN; (g)* $TMSN_3$, $(n\text{-butyl})_4NN_3$; *(h) TFA, MeOH; (i)* $MsCl$, Et_3N; *(j) NaH,* $(MeO)_3P$.

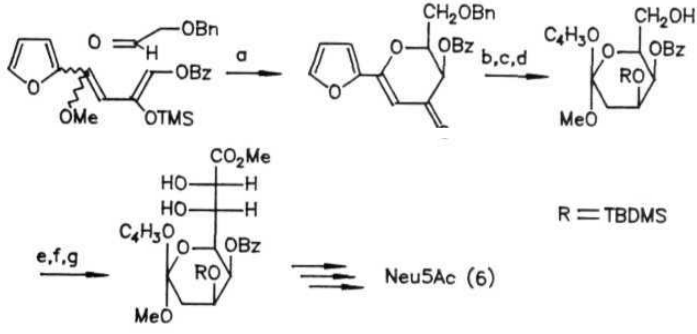


Scheme 25 *Reagents and conditions: (a)* $BF_3.OEt_2$, *TFA; (b)* $CeCl_3.7H_2O/NaBH_4$, *MeOH; (c) TMSOTf; (d) BnOH, CSA; (e)* K_2CO_3; *(f)* Ac_2O, *DMAP; (g)* H_2O_2; *(h)* OsO_4; *(i)* Ac_2O, *DMAP; 0)* RuO_2, $NaIO_4$; *(k)* CH_2N_2; *(l)* $Pd/C, H_2$, *EtOH.*

Although several methodologies are available for the synthesis of higher sugars, there is a demand for a better approach which can overcome existing drawbacks.

The ready availability of a wide variety of glyconate and glycuronate esters suggested to us that if these could be transformed to the corresponding **β-keto phosphonates,** then the Wadsworth-Emmons (W-E) reaction could be easily performed with such phosphonates, leading to higher sugars. Enones so obtained can easily be transformed to higher sugars either by oxidation followed by reduction or *vice versa,* as described earlier. This approach would have the following advantages, (i) it would be applicable to extending the sugar from both **terminii (C-1,** C-5 and C-6 from glyconate

or glycuronates), (ii) the stereochemistry can be better controlled in a W-E reaction than in a Wittig reaction and (iii) epimerization could possibly be avoided.

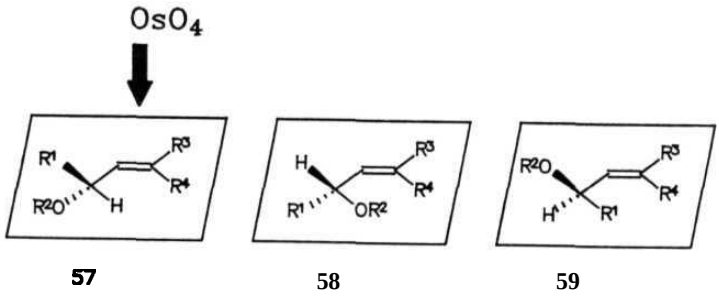


Scheme 26 *Reagents and conditions: (a) $BF_3.OEt_2$, toluene, -78°; (b) $CeCl_3.7H_2O$, $NaBH_4$, EtOH; (c) CSA, MeOH, TBDMSCl; (d) $Pd(OH)_2/C$, H_2, EtOAc-MeOH; (e) $CrO_3.Py$; (f) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$,KHMDS; (g) OsO_4.*

As seen in many of the earlier examples, hydroxylation of a double bond is a common step in the synthesis of higher sugars. It therefore occurred to us that hydroxylation of sugar derived dienes would provide a simple and direct route to higher sugars. Although the recent advancements in catalytic asymmetric dihydroxylation of olefins have reached unprecedented levels of enantioselectivity and simplicity,[57] *tetra*-hydroxylation of chiral dienes is not known in the literature. This motivated us to explore its potential for use in higher sugar synthesis, as it would simultaneously

generate several contiguous chiral centres in a single step. Dihydroxylation of olefins using osmium tetroxide is an extensively studied reaction and use of catalytic quantity of osmium tetroxide in the presence of reoxidants like NMO[58] or potassium ferricyanide[59] have made it a highly versatile process.

The empirical formulation of Kishi,[60] on the stereochemistry of osmium tetroxide oxidation of allylic alcohol systems has proved useful in predicting the stereochemistry of hydroxylated products (Figure 2). According to him, the relative stereochemistry between the existing hydroxyl or alkoxyl group and the adjacent newly introduced hydroxyl group of the major product in all cases is *erythro*. This preference can be readily explained based on the preferred conformation of sp^3-sp^2 single bond systems.



57 58 59

Figure 2.

Accordingly, among the three eclipsed conformations 57, 58 and 59 of olefins, conformation 57 is considered to be most preferred, since it is sterically least compressed. Assuming this conformational preference is reflected in the transition state,

the stereochemistry of the major product is formulated as arising from the preferential approach of osmium tetroxide to the *face* of the olefinic bond opposite to that of the existing hydroxyl or alkoxyl group. This is supported by the fact that the stereoselectivities observed for hydroxylation of ***cis*-olefins** are always higher than that for the corresponding ***trans*-olefins,** since the preference for conformation 57 over 58 and 59 is expected to be more significant for ***cis*-olefins** than for the corresponding ***trans*-**olefins.

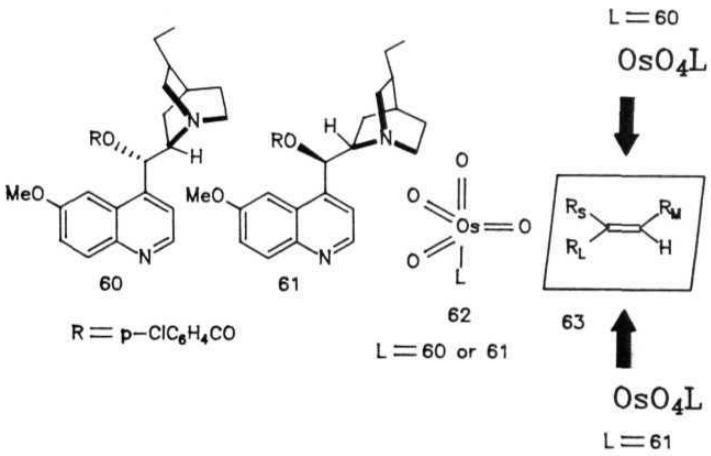
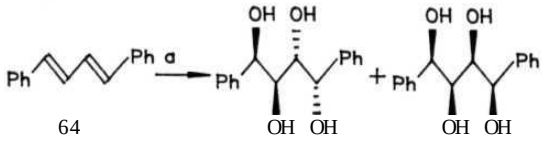


Figure 3.

More recently, Sharpless has developed a *face*-selective dihydroxylation model 63 for the catalytic asymmetric hydroxylation of prochiral olefins,[61] using either dihydroquinidine *p*-chlorobenzoate (60) or dihydroquinine *p*-chlorobenzoate (61) as the chiral ligand in the osmylating agent 62 (Figure 3). By combining both Kishi's empirical formulation and Sharpless's model, there is every likelihood of the inherent diastereofacial selectivity of the chiral allylic system 57 towards catalytic hydroxylation being enhanced in the presence of 61, whereas it would diminish with 60 as the chiral ligand in the osmylating agent 62.

Till to-date, only two reports dealing with *tetra*-hydroxylation of dienes are known. A short description of these is presented in the following paragraph.

Catalytic hydroxylation of achiral conjugated dienes and trienes was first reported by Sharpless.[62] It is found that on hydroxylation of achiral dienes and trienes, the major product has an *erythro* relationship between the hydroxyl groups formed between two double bonds. When l,4-diphenyl-l,3-butadiene (64) was treated with catalytic amount of osmium tetroxide and one equivalent of N-methylmorpholine N-oxide (NMO), tetrols

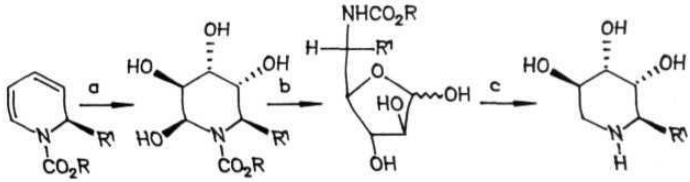


64 65 (16:1) 66

Scheme 27 *Reagents and conditions: (a) OsO_4, NMO, acetone, H_2O.*

65 and 66 were obtained in a 16:1 ratio (Scheme 27). The structure of the major diastereomer was identified to be 1,2-*syn*-2,3-*anti*-3,4-*syn* and the minor isomer was 1,2-*syn*-2,3-*syn*-3,4-*syn*.

More recently, catalytic stereoselective *tetra*-hydroxylation of 1,2-dihydropyridines has been carried out[63] (Scheme 28). 1,2-Dihydropyridines **67a** and **67b** on te/ra-hydroxylation were converted stereospecifically to the corresponding aminoarabinose and aminoaltrose derivatives 68a and 68b, respectively. In basic medium these piperidinoses equilibrated with their furanose isomers **69a** and **69b** (both a and β anomers). Hydrogenolysis of their urethane moieties led to the corresponding piperidine triols 70a and **70b.**



67 68 **69** **70**

a: R=Bn ; R'=H

b: R=Bn ; R'=Me

Scheme 28 *Reagents and conditions: (a) OsO_4, NMO, acetone, H_2O; (b) Amberlyst A-26(OH⁻); (c) Pd/C, H_2, EtOH.*

Studies on the regioselective and enantioselective asymmetric dihydroxylation of conjugated dienes have also been done.[64] Results of the regioselective experiments show that dihydroxylation preferentially occurs at 1) electron rich double bonds in case of unsymmetrical conjugated dienes, 2) highly substituted double bonds when nonconjugated dienes are used and 3) *trans*-olefins if both *cis*- and *trans*-olefins are present in a molecule.

Lack of information on the *tetra*-hydroxylation of chiral conjugated dienes prompted us to explore its utility for the synthesis of higher sugars. A study on the influence of an existing chiral centre on the product ratio will enable the prediction of diastereoselectivity in other diene systems.

The results of the investigation carried out on the application of the W-E reaction and hydroxylation of dienes for the synthesis of higher sugars are presented in the following chapter.

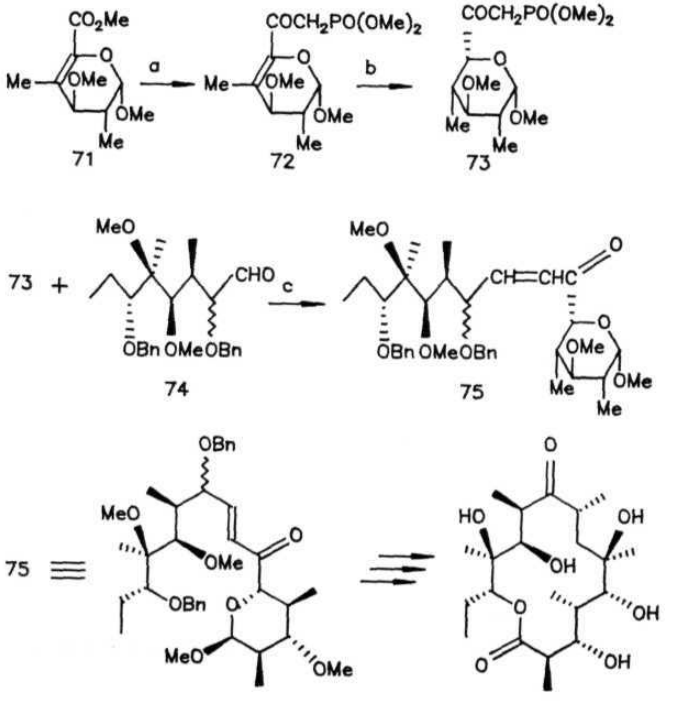
RESULTS AND DISCUSSION

PART I

Preparation of Sugar Derived P-Keto Phosphonates and Their Use in the Synthesis of Higher Sugars.

The presence of complex chiral structures in various important antibiotics and macrolides like lincomycin,[8] hikizimycin,[18] erythromycin[21] and streptomycin[22] have triggered interest among many organic chemists towards the synthesis of higher sugars. Although the thrust in this area began about a century ago,[5] general methods leading to complex higher sugars, as pointed out in the introduction, are limited. It was envisioned that the required homologation could be readily achieved by making use of the Wadsworth-Emmons (W-E) reaction, involving the combination of a P-keto phosphonate and a carbonyl compound. In the above exercise, one or both partners can be derived from sugars. A thorough search of the literature revealed that very few p-keto phosphonates derived from sugars are known. A brief summary of the existing literature on sugar derived P-keto phosphonates is presented in the following paragraphs.

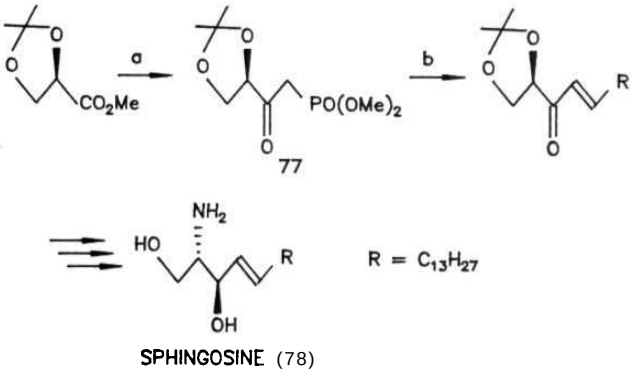
Construction of the 15-carbon chiral framework of erythronolide A (76) by combination of carbohydrate derived "chiral templates" as prefabricated segments of the target molecule using Wadsworth-Emmons reaction was pioneered by Hanessian.[65] p. Keto phosphonate 73 was obtained by acylation of ithium dimethyl methylphosphonate



Scheme 29 *Reagents and conditions: (a)* $CH_3PO(OCH_3)_2$*,n-BuLi, THF, -78°; (b)* Pd/C*,* H_2*; (c) NaH, THF.*

with the α,β-unsaturated ester 71 followed by hydrogenation. Condensation of 73 with *aldehydo* sugar derivative 74 yielded the advanced enone intermediate 75 for the target erythronolide A (76) (Scheme 29).

Formal total synthesis of *D-erythro*-C18-sphingosine (78) was carried out using a condensation between dimethyl 1,2-O-isopropylidene-*D*-glyceroyl methylphosphonate (77) and tetradecanal[66] (Scheme 30). The condensation occurred smoothly in the presence of cesium carbonate, providing the (*E*)-olefin in 85% yield.

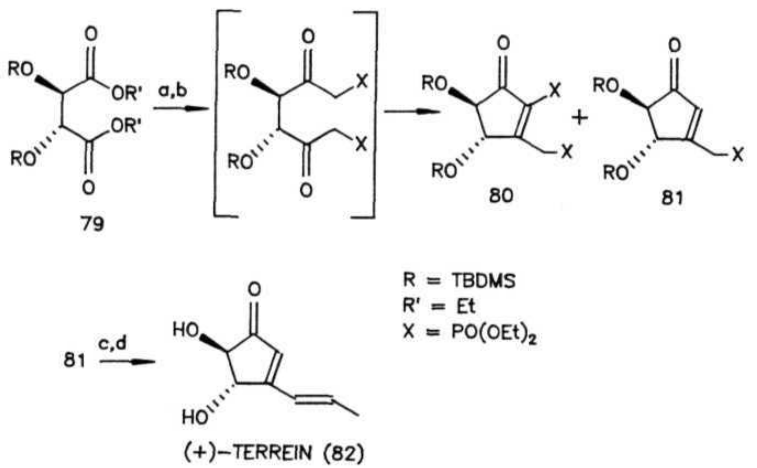


SPHINGOSINE (78)

Scheme 30 *Reagents and conditions: (a) $CH_3PO(OCH_3)_2$,n-BuLi, THF, -780; (b) Cs_2CO_3, 2-propanol, $C_{13}H_{27}CHO$.*

Recently, a total synthesis of (+)-terrein (82) from *C-2* symmetric *L*-tartaric acid was realized.[67] This synthesis involves an intramolecular W-E condensation of a *C-2*

symmetric *bis*-β-keto phosphonate (Scheme 31). Reaction of 79 with four equivalents of lithium diethyl methylphosphonate provided directly the required enone 81 and a side product 80, obtained by an intramolecular Knoevenagel condensation. Condensation of 81 with acetaldehyde followed by deprotection of the TBDMS groups gave (+)-terrein (82) in good yield.

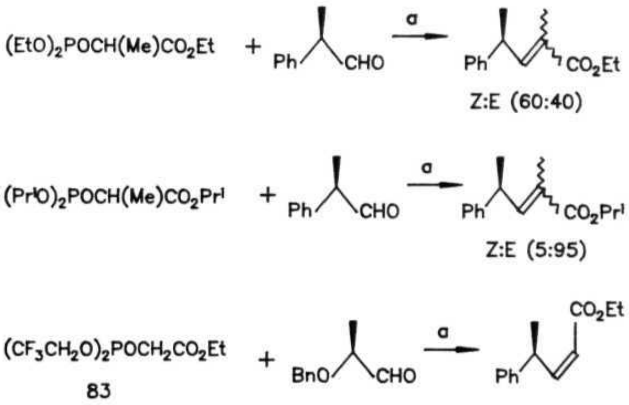


Scheme 31 *Reagents and conditions: (a) 4 equiv* $LiCH_2PO(OEt)_2$, *THF; (b) 2 equiv AcOH, 20 h, rt; (c) NaH, THF,* CH_3CHO *(monomeric), 18 h, rt; (d) 6.5 equiv* Et_4NCl, *6 equiv* $KF.2H_2O$, CH_3CN, *30 h, rt.*

These results encouraged us to elaborate upon the potentiality of the W-E reaction for use in the synthesis of higher sugars.

The W-E reaction has many advantages over the classical Wittig reaction. β-Keto phosphonates are more acidic and more nucleophilic than the corresponding phosphonium ylides. Hence, deprotonation can be effected with milder bases and the reactions are generally performed at room temperature. Increased reactivity of phosphonyl stabilized reagents permits their condensation with relatively unreactive carbonyl compounds. Additionally, the by-product of the alkenation is water soluble and the reaction conditions can be altered to yield either (*E*)- or (*Z*)-isomer.[60]

The most common application of the W-E reaction is in the synthesis of disubstituted (*E*)-alkenes. The stereoselectivity of the reaction can be maximized by increasing the size of the substituents on the phosphoryl portion. It was found that use of



Scheme 32 *Reagents and conditions: (a) t-BuOK, THF, -78°; (b) KH, THF.*

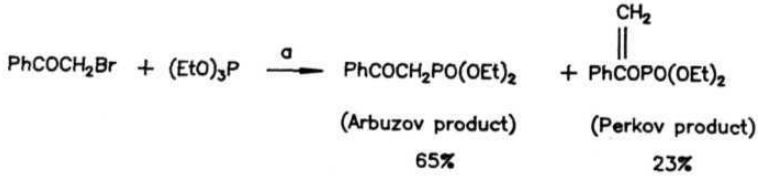
a bulky isopropyl substituent on the phosphonate as well as on the stabilizing ester increases (*E*)-selectivity steeply[68] (Scheme 32). Still and co-workers introduced a methodology that uses bis(trifluoroethyl)phosphonoesters 83 to provide a facile approach to (Z)-alkenes, when reacted with aldehydes[69] (Scheme 32). The (Z)-selectivity is presumed to occur because of rapid elimination of the p-hydroxy phosphonate before equilibration can take place. These features inspired us to make use of this methodology for our purpose.

General methods for the synthesis of p-keto phosphonates:

As P-keto phosphonates play an important role in our study towards the synthesis of higher sugars, a brief account of methods available for their synthesis is given below.

Arbuzov rearrangement:

One of the earliest methods for the synthesis of P-keto phosphonates is the Arbuzov rearrangement,[70] which makes use of an alkyl halide and a trialkyl phosphite



Scheme 33 *Reagents and conditions: (a)* $CH_3OCH_2CH_2OCH_3$, *reflux.*

(Scheme 33). Success of this reaction depends upon the nature of the halide present in the molecule. With α-haloketones, iodides give good yields of the required p-keto phosphonates. On the other hand if bromides or chlorides are used, usually a competing side product in the form of an enol phosphate due to the Perkov reaction[71] is also formed.

Acylation of lithium dialkyi methylphosphonate with carboxylic acid esters:

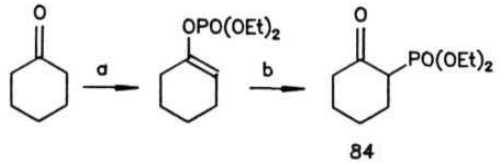
A convenient synthesis of p-keto phosphonates involves direct acylation of lithium dialkyi methylphosphonates with alkyl esters[72] (Scheme 34). This reaction is widely employed and has been applied to esters of varying complexity. It consistently provides the required P-keto phosphonates in excellent yields.

$$RCO_2R' + CH_3PO(OMe)_2 \xrightarrow{a} RCOCH_2PO(OMe)_2$$

Scheme 34 *Reagents and conditions: (a) n-BuLi, THF, -78°.*

By migration of phosphorus from oxygen to carbon:

P-Keto phosphonates are also realized by treatment of readily obtained enol phosphates with a strong base[73] (Scheme 35). This oxygen to carbon migration of phosphorus is especially suited for the synthesis of phosphonates bearing a cyclic ketone, as in the preparation of 84 from cyclohexanone. Other expedient procedures for the synthesis of p-keto phosphonates are also available in the literature.[74]



84

Scheme 35 *Reagents and conditions: (a) ClPO(OEt)2, LDA; (b) LDA.*

Acylation of lithium dialkyl **methylphosphonate** with sugar esters was selected for use in the synthesis of higher sugars, as the required sugar esters namely, glycuronates or glyconates can be easily obtained by known procedures. It is also to be noted that the synthesis of **α-iodo** ketosugars is rather difficult and none have been reported till now.

The methodology for the synthesis of higher sugars involves, in the most general sense, condensation between a sugar derived P-keto phosphonate and a sugar derived aldehyde (Figure 4).

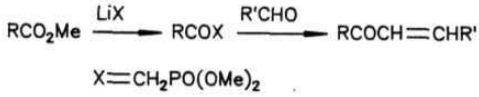
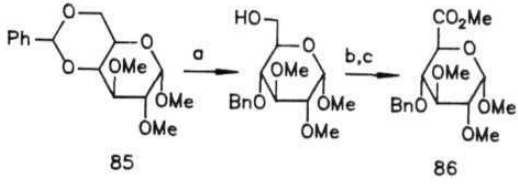


Figure 4 *General schematic representation for the synthesis of higher sugars using* ***Wadsworth-Emmons reaction****, where R and R' are sugar moieties.*

Methyl (methyl **4-O-benzyl-2,3-di-O-methyl-α-*D*-glucopyranosid)uronate** (86)[75] was chosen for initial studies to examine its conversion to the corresponding P-keto

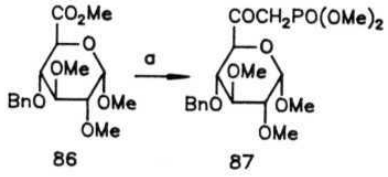
phosphonate. Glucuronate 86 was obtained from methyl **4,6-O-benzylidene-2,3-di-O-methyl-α-*D*-glucopyranoside (85)**[76] by a known sequence as shown in scheme 36.



Scheme 36 *Reagents and conditions: (a) AICI3, LAH, ether, CH_2Cl_2, 8 h; (b) CrO_3, H_2SO_4, acetone, 1 h; (c) CH_2N_2, ether.*

The required dimethyl (methyl **4-O-benzyl-2,3-di-O-methyl-α-*D*-glucopyranuronyl)methylphosphonate** (87) was obtained in quantitative yield by the acylation of lithium dimethyl methylphosphonate with 86 in THF at -78° (Scheme 37). The structure of 87 was confirmed from its spectral and analytical data. The *IR* spectrum of 87 showed the carbonyl stretching at 1720 cm^{-1}, which is 20 cm^{-1} less when compared to its parent uronate 86. Absorption at 21.8 **ppm** in the ^{31}P NMR spectrum of 87 confirmed the presence of phosphorus in 87. ^{1}H and ^{13}C NMR spectra indicated the presence of phosphorus-hydrogen and phosphorus-carbon couplings, respectively. In the ^{1}H NMR **spectrum**, apart from other signals, a pair of doublet of doublets at 3.30 and 3.20 ppm were **seen** These were attributed to diastereomeric (CH3O)- groups and **$-CH_2-$** protons attached to phosphorus. A large coupling of 22.40 Hz is due to (P-CH2) phosphorus-hydrogen coupling and a smaller coupling of **11.20** Hz is due to **(P-OCH_3)** phosphorus-hydrogen coupling. A multiplet at 54.0 and a doublet at 40.5 ppm (J = 129.0 Hz) in the

^{13}C NMR due to phosphorus-carbon couplings of (CH3O)- and $-CH_2-$ groups attached to phosphorus were seen. A peak at 199.9 ppm in the ^{13}CNMR of 87 was assigned to the carbonyl functionality. Finally, microanalytical data was in agreement with C19H29O9P.



86 87

Scheme 37 *Reagents and conditions: (a)* $CH_3P(O)(OCH_3)_2$, *n-BuLi, THF, -78°, 2 h.*

Having secured the structure of the P-keto phosphonate **87**, a systematic study of its condensation with *p*-anisaldehyde using various reagents was carried out (Table 1). Initial attempts at the condensation between 87 and *p*-anisaldehyde employing different bases such as sodium hydride,[77] potassium carbonate[78] and DBU/lithium chloride[79] were not encouraging as in most cases either the reaction did not proceed or else provided a complex mixture containing the required condensed product (as revealed by its ^1H NMR spectra). It was surprising to see the starting phosphonate 87 recovered unchanged, when sodium hydride/THF was used for olefination, for 8 h at rt. Stirring with potassium carbonate in THF at rt for 24 h also led to recovery of the starting material. Contrary to the above, when the reaction mixture was refluxed in THF with potassium carbonate for 4 h, a complex eliminated product containing no benzyl group was obtained, as indicated by its ^1H NMR spectrum. On the other hand, when the condensation was carried out in the presence of either DBU/lithium chloride or

potassium carbonate/dioxane (reflux), a mixture containing the required enone and its eliminated analog was obtained (Table 1). However, purification of the desired enone proved to be difficult.

Table 1 *Various reaction conditions attempted for the condensation of 87 with p-anisaldehyde.*

No.	Reaction conditions	Result
1.	NaH, THF, rt, 8 h.	Starting material recovered.
2.	K_2CO_3, THF, rt, 24 h.	Starting material recovered
3.	K_2CO_3, THF, reflux, 4 h.	Completely eliminated product **119**.
4.	DBU, LiCl, CH3CN, rt, 2 h.	Mixture of condensed product 88 and its eliminated derivative **119.**
5.	K_2CO_3, dioxane, reflux, 5 h.	Mixture of condensed product 88 and its eliminated derivative **119.**

As the desired enone could not be obtained in pure form from the above experiments, we looked for an alternative method for this purpose. A recent report concerning the use of cesium carbonate in 2-propanol[66] as a satisfactory base-solvent combination for the W-E reaction prompted us to explore its application to our system. Gratifyingly, reaction of 87 with *p*-anisaldehyde proceeded cleanly giving the desired enone 88 in 88% yield. The structure of 88 was readily apparent from its spectral and analytical data. The IR spectrum of 88 indicated the presence of an enone functionality ($\nu_{C=O}$ = 1660 cm^{-1}). A pair of doublets in the ^1H NMR spectrum of 88 at 7.72 and 6.85 ppm were assigned to the enone olefinic protons. The *trans* stereochemistry of the enone

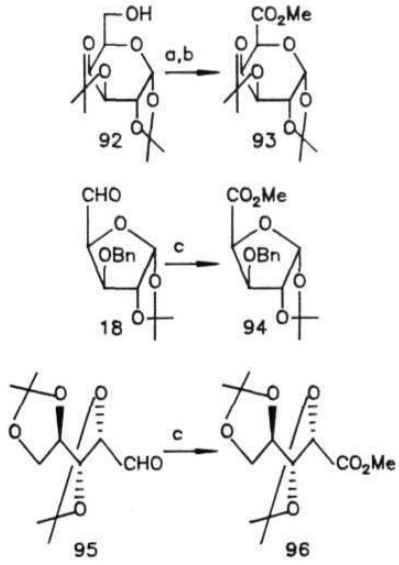
double bond in 88 was readily apparent from the coupling constant of the above doublets (about 16 Hz). Peaks at 194.1, 160.8 and 142.8 ppm in the ^{13}CNMR spectrum of 88 were assigned to the carbonyl and olefinic carbons of its enone functionality. Subsequently, the P-keto phosphonate 87 was treated with various aldehydes including 1,2:3,4-di-O-isopropylidene-α-*D-galacto*-hexodialdo-1,5-pyranose (13)[80] as shown in scheme 38. In each case, the corresponding condensation products were obtained in high yields. All these products were comprehensively characterized from their analytical and spectral data.

R'CHO	ENONE	YIELD(%)
p-Anisaldehyde	88	88
Benzaldehyde	89	85
Isobutyraldehyde	90	84
CHO		

Scheme 38 *Reagents and conditions: (a)* Cs_2CO_3, *2-propanol, 8 h.*

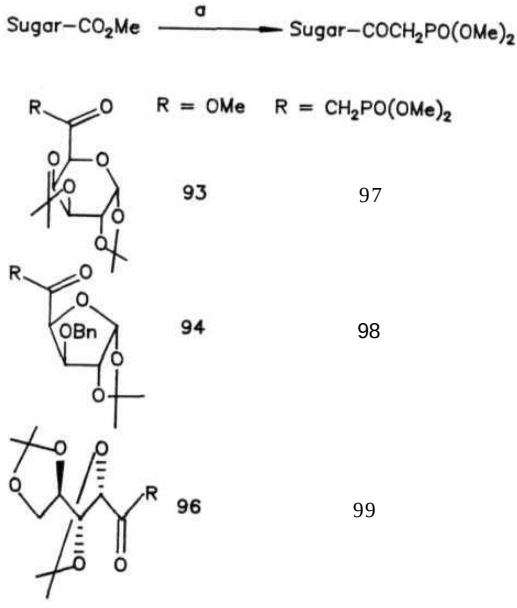
Subsequently, glycuronates 93[81] and 94 and glyconate 96[82] possessing acid groups at C-6, C-5 and C-l, respectively, were chosen for conversion to their corresponding p-keto phosphonates at C-6, C-5 and C-l, so as to establish this method

as a versatile and general one. Thus, glycuronate 93 was synthesized according to a reported procedure.[81] Methyl (3-O-benzyl-1,2-O-isopropylidene-α-*D*-xylofuranosid)-uronate (94) and methyl 2,3:4,5-di-O-isopropylidene-*D*-arabinonate (96) were prepared by bromine/methanol[83] oxidation of the corresponding aldehydes 3-O-benzyl-1,2-O-isopropylidene-α-*D*-*xylo*-pentodialdo-1,4-furanose (**18**)[84] and 2,3:4,5-di-O-isopropylidene-*aldehydo*-*D*-arabinose (95),[85] respectively (Scheme 39).

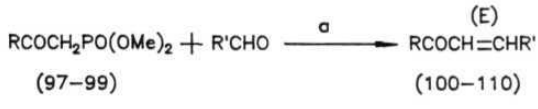


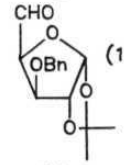
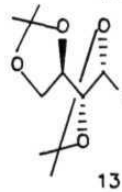
Scheme 39 *Reagents and conditions: (a) $KMnO_4$, KOH, 24 h; (b) CH_2N_2, ether; (c) Br_2, MeOH-H_2O(9:1), $NaHCO_3$, 5 h.*

The P-keto phosphonates 97, 98 and 99 were synthesized from their corresponding glycuronates 93, 94 and glyconate 96 in a manner similar to 87 and in quantitative yields (Scheme 40). The structures of 97, 98 and 99 were consistent with their spectral and analytical data. ^{31}P NMR spectra of 97, 98 and 99 showed absorptions at 22.68, 21.95 and 21.27 ppm, respectively.



Scheme 40 *Reagents and conditions: (a)* $CH_3P(O)(OCH_3)_2$*, n-BuLi, THF, -78°, 2 h.*



PHOSPHONATE	R'CHO	ENONE	YIELD(%)
97	p–Anisaldehyde	100	94
97	 (25)	101	70
97	13	102	90
97	 (18)	103	91
98	13	104	75
98	18	105	79
98	 (95)	106	76
99	13	107	70
99	25	108	76
99	18	109	91
99	95	110	65

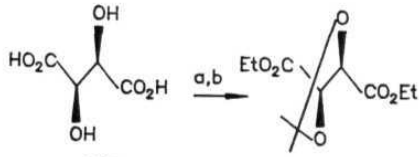
Scheme 41 *Reagents and conditions: (a)* Cs_2CO_3, *2-propanol, 8 h.*

Incidentally, in the ^{13}CNMR spectra of 97, 98 and 99, apart from phosphorus-carbon couplings with the adjacent $-CH_2-$ and $(CH_3O)-$ carbons, a long range coupling with the carbon adjacent to the carbonyl group through 3 bonds with J = 3.0 Hz was noticed. In case of 97 and 99, doublets at 200.1 (J = 5.90 Hz) and 200.8 ppm (J = 6.0 Hz) respectively, in their ^{13}C NMR spectra were attributed to phosphorus-carbonyl carbon couplings.

Encouraged by the results obtained earlier with the phosphonate 87, phosphonates 97, 98 and 99 were reacted with various aldehydes derived from aldoses at C-1, C-5 and C-6 to yield the corresponding condensed products in high yields (Scheme 41). In all cases, this reaction provides a single, geometrically pure (*E*)-isomer. The product enones **100** to **110** were fully characterized by analytical and spectral data. Of these enones, **102** and **103** have been previously reported in the literature.[28,29] The utility of such enones in the synthesis of higher sugars has been discussed by Jarosz.[28-30]

Towards further expanding the utility of this methodology for the synthesis of higher sugars, preparation of ftw-P-keto phosphonates was envisioned. This would have the following advantages: 1) extension of carbon chain from both the ends can be performed, 2) depending upon addition of the aldehyde, different condensed products can be obtained *(i.e.*. condensation with two equivalent of a single aldehyde will result in *bis*-homologation with identical groups, or on the contrary, two different aldehydes of one equivalent each will result in *bis*-homologation with different groups).

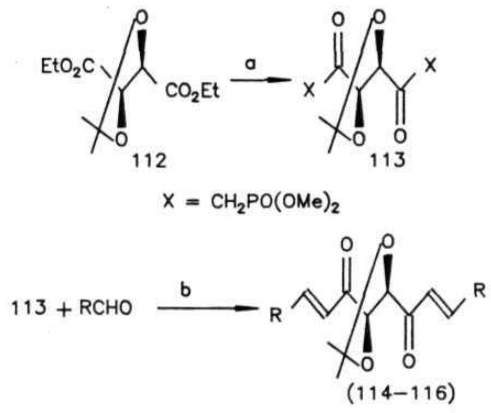
An easily available sugar dicarboxylic acid, *L*-tartaric acid **(111)** was preferred for this purpose, as the presence of *C-2* symmetry in it is an added advantage for easy product identification. Diethyl 2,3-O-isopropylidene-*L*-tartrate **(112)**[86] was prepared from *L*-tartaric acid **(111)** by esterification with ethanol, followed by isopropylidenation using acetone and copper sulfate in the presence of a catalytic quantity of sulfuric acid (Scheme 42).



111 112

Scheme 42 *Reagents and conditions: (a) ethanol, HCl, reflux, 7 h; (b) acetone, $CuSO_4$, H_2SO_4, 25 h.*

C-2 Symmetric few-phosphonate **113** was prepared from **112** by reaction with two equivalents of lithium dimethyl methylphosphonate, in THF at -78°, in quantitative yield. Once again, the structure of **113** was fully secured from its analytical and spectral data. As expected, a peak at 20.96 ppm in the ^{31}P NMR spectrum of **113** was observed, indicating the presence of a p-keto phosphonate functionality. In the ^{1}H NMR spectrum, apart from other peaks, a pair of doublets at 3.78 (J = 11.0 Hz) and 3.76 ppm (J = 11.0 Hz) and multiplet between 3.0-3.60 ppm indicated phosphorus-hydrogen couplings of the POMe and PCH_2 protons. In the ^{13}C NMR spectrum, doublets at 200.2 (J = 5.90 Hz), 81.2 (J = 2.95 Hz) and 36.7 (J = 130.90 Hz) and a multiplet at 52.9 ppm indicated



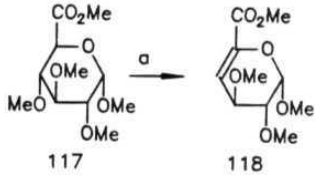
RCHO	DIENONE	YIELD(%)
13	**114**	54
18	115	44
95	116	54

Scheme 43 *Reagents and conditions: (a) $CH_3P(O)(OCH_3)_2$,n-BuLi, THF, -78°, 2 h; (b) Cs_2CO_3, 2-propanol, 8 h.*

phosphorus-carbon couplings with carbonyl, C-2, PCH_2 and POMe carbons. The *bis*-phosphonate **113** was condensed with various sugar aldehydes as shown in scheme 43. Fortuitously, condensation proceeded smoothly, providing the required *bis*-enones in moderate yields. ^1H and ^{13}C NMR spectra immediately indicated the presence of *C-2* symmetry in **114, 115** and **116.** As expected, in all cases, a single pure *(E, E)*-isomer was formed, as evidenced from their ^1H NMR spectra (olefinic coupling of 15-16 Hz).

Higher sugars containing 16 and 18 carbons can thus be easily synthesized by this method.

Our earlier observations on reactions of phosphonate 87 with various aldehydes showed formation of trace quantities of an eliminated product along with the required condensed products. A systematic survey of the literature revealed the existence of such β-elimination of a 4-alkoxy group of glycuronates in the presence of a base.[87] Methyl (methyl 2,3,4-tri-O-methyl-α-*D*-glucopyranosid)uronate (117), on refluxing with sodium methoxide readily yielded methyl (methyl 4-deoxy-2,3-di-O-methyl-β-*L*-*threo*-hex-4-eno-pyTanosid)uronate (118) (Scheme 44). A study based on E1cB mechanism has been discussed by Kovac.[88]

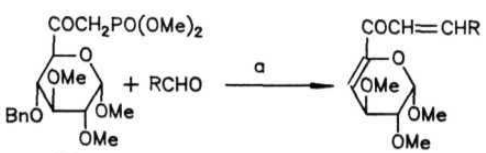


117 118

Scheme 44 *Reagents and conditions: (a) MeONa, reflux.*

With this information available, we investigated our system more carefully. On careful analysis, it was found that condensation of p-keto phosphonate 87 with *p*-anisaldehyde in presence of 3 equivalents of cesium carbonate led to complete elimination of the C-4 benzyloxy group along with W-E reaction. Characterization of **119** was done based on its spectral and analytical data ^1H NMR spectrum of **119**

indicated loss of benzyl group, as the integration in the aromatic region between 7.0-8.0 ppm was 5 protons less and also the presence of a doublet at 6.17 ppm (J = 3.06 Hz) which was assigned to C-4 proton. Four signals in the ^{13}CNMR of 119 at 162.0, 151.0, 148.0 and 145.1 ppm were attributed to the four olefinic carbons. Benzaldehyde and isobutyraldehyde were also condensed with 87 under identical conditions and the corresponding eliminated products were obtained in good yields (Scheme 45). It is interesting to note that under identical conditions, neither glucophosphonate 87 (in the absence of aldehyde) nor glucuronate 86 gave rise to such an elimination. But the enone 88, when treated with 3 equivalents of cesium carbonate in 2-propanol, led to elimination of the C-4 benzyloxy group giving the cross-conjugated dienone **119** in 80% yield. Such cross-conjugated dienones can be subjected to Nazarov type cyclizations, leading to chiral cyclopentenones.[89]

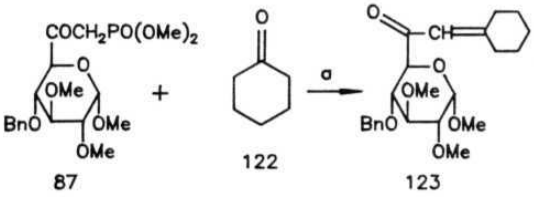


RCHO	DIENONE	YIELD(%)
p–Anisaldehyde	119	80
Benzaldehyde	120	90
Isobutyraldehyde	121	86

Scheme 45 *Reagents and conditions: (a) excess Cs_2CO_3, 2-propanol, 8 h.*

It is clear from the above experiments that elimination leading to dienone takes place in a step-wise process, namely W-E reaction first, followed by deprotonation of the C-5 proton of the W-E product. Reasons for the ready loss of C-5 proton in the condensed product, compared to the parent uronate 86 or phosphonate 87, are not clear.

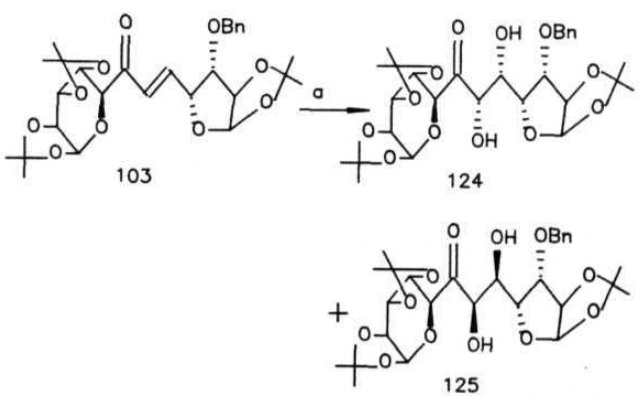
It was envisioned that condensation of sugar derived P-keto phosphonates with uloses would provide an easy access to branched sugars. P-Keto phosphonate 87 when reacted with cyclohexanone **(122)** using cesium carbonate in 2-propanol for 8 h, yielded the required condensed product **123** in 25% yield (Scheme 46). ^1H NMR spectrum immediately confirmed the structure of **123,** as the olefinic proton appeared at 6.13 ppm as a broad singlet. Absorptions at 4.85 and between 1.15 to 2.25 ppm were assigned to the anomeric and cyclohexyl protons, respectively. As attempted efforts to increase the yield of the olefination reaction were not fruitful, further experiments with ketones were not pursued.



Scheme 46 *Reagents and conditions: (a)* Cs_2CO_3*, 2-propanol, 8 h.*

After the successful execution of the W-E reaction, we turned our attention towards the synthesis of higher sugars from higher sugar enones. The strategy for functionalization of enones involved hydroxylation, followed by stereoselective reduction of the resulting dihydroxyketone.

Enone 103 was chosen as a representative example and was hydroxylated using osmium tetroxide/NMO to obtain 124 and 125 in 90% yield (Scheme 47). The diastereomers 124 and 125 were obtained in a ratio of 63:37. The stereochemistry of hydroxylation of allylic alcohols (or ethers) is controlled by the oxygen function (OR group) on the carbon a to the double bond and attack of osmium tetroxide is postulated to occur from the side opposite to the hydroxyl (alkoxyl) group.[60] Hydroxylation of enone **103** is an exceptional case, where attack of osmium tetroxide from the *face syn* to



Scheme 47 *Reagents and conditions: (a) OsO_4, NMO, acetone-H_2O (8:1), 8 h.*

the existing alkoxy linkage (ring oxygen atom) preponderated. Such an exception was also noted by Kishi, when an enone system was used as a substrate for hydroxylation.[60]

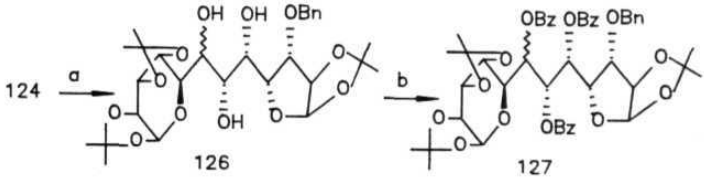
Separation of 124 and 125 was effected by chromatography. Structures of 124 and 125 were supported by their spectral and analytical data IR spectra of both 124 and 125 showed strong absorptions at 3470 and 1730 cm^{-1}, implying the presence of alcohol and keto functionalities. The 500 MHz ^1H NMR spectrum of 124 showed doublets at 6 6.00 (J = 3.77 Hz) and 5 5.65 (J - 4.88 Hz), indicative of anomeric signals of the xylofuranose and galactopyranose moieties, respectively. Correspondingly, in the 500 MHz ^1H NMR spectrum of 125, apart from other signals, doublets at 8 5.96 (J = 3.84 Hz) and δ 5.36 (J = 5.00 Hz), again due to anomeric signals of xylofuranose and galactopyranose fragments, respectively, conclusively established its structure. In the ^{13}C NMR spectrum of 124, absorptions at 207.6, 104.7 and 96.4 ppm were attributed to carbonyl and anomeric carbons. Peaks at 206.7, 104.8 and 96.2 ppm in the ^{13}CNMR of 125 were due to carbonyl and anomeric carbons.

Subsequently, a study on stereoselective reduction of keto diols 124 and 125 and structure determination of the resulting dodecito-dialdoses was undertaken. It was rationalized that by degradation of the resulting higher sugars to simpler molecules in such a way that the newly formed stereocentrcs are retained, an easy chemical correlation with compounds reported in the literature could be had and this would fix the absolute configuration of all the three newly established chiral centres. Due to the inherent nature of the hydroxylation reaction, both the hydroxyl groups come from the same *face* and the relative stereochemistry of the thus generated adjacent chiral centres has to be *syn* (*threo*

in case of *trans* double bond). This restricts the formation of diastereomers to a maximum of three, namely *D*- and *L*-arabinitol and (*meso*)-xylitol, when the newly formed centres above are excised out. Thus the stereochemistry of the osmylated products **124** and **125** and hence the structural assignments of the dodecito-dialdoses can be completed unequivocally, once the degradation products are identified. Initially, when these degradation studies were planned, the stereochemistries of the newly introduced hydroxyl groups in **124** and **125** were not known. However, as discussed later in this chapter, the structures of **124** and **125** as shown in scheme 27 are based on X-ray analysis.[28b]

A systematic study on stereoselecrive reduction of the dihydroxy ketones **124** and **125** was carried out. Reduction of **124** using sodium borohydride in THF-methanol mixture at 0°, produced a mixture of diastereomeric triols **126** (Scheme 48). The IR spectrum of the crude reduction product **126** showed absence of the carbonyl group, as the peak at 1730 cm^{-1} was missing. Attempted separation of the product mixture **126** by column chromatography was unsuccessful. 100 MHz ^1H NMR of the crude triols **126** also failed to separate the anomeric signals and therefore the diastereomeric ratio could not be obtained. It was then anticipated that separation of the anomeric signals could be effected by protecting the hydroxyl groups with a suitable electron withdrawing group such that it could also serve as a protecting group for degradation reactions. Hence, the epimeric triols **126** were benzoylated and as expected, a clear separation between the anomeric signals was revealed in the ^1H NMR spectrum. The IR spectrum of the crude tribenzoylated product **127** showed no peak in the hydroxyl region and a strong absorption at 1720 cm^{-1}, inferring complete conversion of the hydroxyl functionalities into their benzoyl derivatives. In the ^1H NMR spectrum of the crude tribenzoylated

product 127 apart from other peaks, doublets at 5.60 (J = 5.0 Hz) and 5.46 ppm (J = 5.0 Hz) were assigned to the anomeric signals of the pyranose ring of the two diastereomers formed in the sodium borohydride reduction. The epimers were present in a 1:1 ratio. An alternative reagent, which can make use of the oxygen functionalities in the sugar moieties and render the reduction highly stereoselective, was sought. Zinc borohydride has been known to coordinate with the carbonyl group and ring oxygen, in a fixed conformation in case of uronyl carbonyl reduction and the attack by hydride ion occurs from the less hindered side of the molecule.[90]



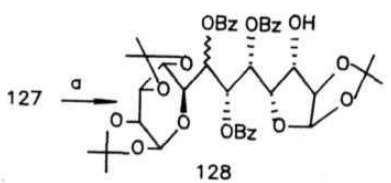
Scheme 48 *Reagents and conditions: (a) $NaBH_4$, THF-MeOH (1:1). 0°, 3 h or $Zn(BH_4)_2$, ether, 20 or 60 min; (b) BzCl, DMAP, Py, 20 h.*

Thus, the keto diol 124 was reduced with zinc borohydride in ether at 0° for 20 min. Analysis of the epimeric mixture showed an increased stereoselection of 1:2. When the same reaction was conducted at -78°, a better selectivity of 1:4 was realized However, the diastereomeric tribenzoate mixture 127 could not be separated and hence the individual components could not be identified. After failing to obtain one of the diastereomers exclusively, attention was diverted towards separation of the crude triols 126 to ascertain the absolute stereochemistry of the target higher sugars.

Table 2

No.	Reaction conditions	Diastereomeric ratio
1.	$NaBH_4$, THF-MeOH (1:1), 0°, 3 h.	1:1
2.	$Zn(BH_4)_2$, ether, 0° 20 min.	1:2
3.	$Zn(BH_4)_2$, ether, -78°, 1 h.	1:4

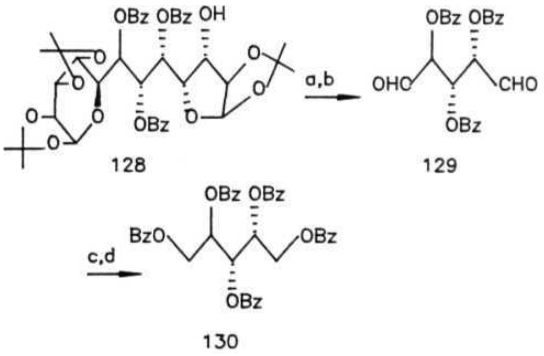
Efforts to separate the epimeric mixture of tri-O-benzoyl derivatives **127** were in vain. The degradation strategy involved catalytic reductive cleavage of the benzyl group, followed by acid hydrolysis and oxidative cleavage using sodium periodate to yield tri-O-benzoylpentodialdoses. Sodium borohydride reduction of the dialdoses followed by benzoylation would provide perbenzoylated pentitols. Since the perbenzoylated pentitols are known in the literature,[91] a ready comparison can be made with those obtained from dodecoses **124** and **125.** Hydrogenolysis of **127** with palladium/carbon in dry ethanol at 40 psi hydrogen for 6 h, produced cleanly the required debenzylated product **128** in 85% yield (Scheme 49). The IR spectrum of **128** showed an absorption at 3420 cm^{-1}, revealing the presence of a hydroxyl group. The ^1H NMR spectrum of **128** integrated for



Scheme 49 *Reagents and conditions: (a) Pd/C, H_2, ethanol, 40 psi, 6 h.*

5 protons less in the aromatic region between 7.0-8.0 ppm, inferring complete hydrogenolysis of the benzyl group in 127. Fortuitously, TLC of the crude debenzylated product separated the two diastereomers distinctly. An easy separation of the two diastereomers was then effected by column chromatography.

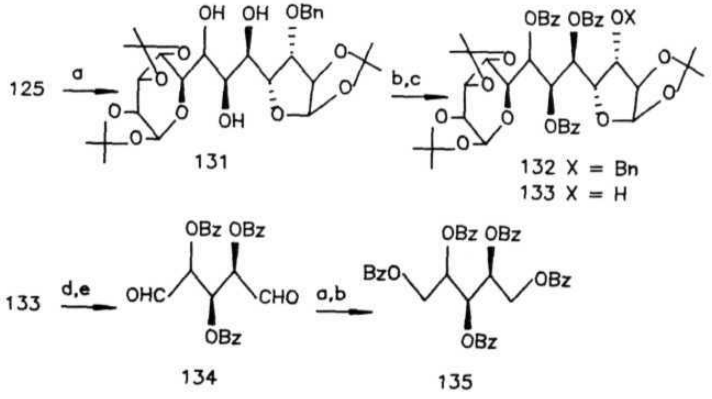
After separation, the more polar product, obtained as major product in the zinc borohydride reduction, was chosen to carry out sequential transformations to convert it to the perbenzoylated pentitol. The debenzylated product 128 was treated with TFA-water (9:1), sodium periodate, followed by sodium borohydride and then benzoylated, resulting in a complex mixture (Scheme 50). Other reagents like THF-acetic acid-water for



Scheme 50 *Reagents and conditions: (a) TFA-H_2O (9:1), 20 min; (b) $NaIO_4$, ether-H_2O (2:1), 2 h; (c) $NaBH_4$, THF-MeOH (1:1), 2 h; (d) BzCl, DMAP, Py, 18 h.*

isopropylidene group hydrolysis and horane-THF complex for reduction of dialdehyde also led to complex mixtures, from which the required perbenzoylated pentitol could not be isolated.

Subsequently, the minor isomer 125 formed in the hydroxylation reaction was reduced with sodium borohydride in THF-methanol mixture at 0° to give the corresponding triol 131. Benzoylation followed by debenzylation provided the debenzylated product 133. Spectral data of 133 were in accordance with its structure. The ^1H NMR spectrum of 133 had a doublet at 5.40 ppm (J = 5.0 Hz), due to the



Scheme 51 *Reagents and conditions: (a) $NaBH_4$, THF-MeOH (1:1), 0°, 3 h; (b) BzCl, DMA?, Py, 20 h; (c) Pd/C, H_2, ethanol, 40 psi, 6 h; (d) TFA-H_2O (9:1), 20 min; (e) $NaIO_4$, ether-H_2O (2:1), 2 h.*

anomeric signal of the pyranose ring. Sodium borohydride reduction of **125** was stereospecific, as evidenced by the ^{1}H NMR spectrum of its benzoylated derivative. Satisfied by this, transformations leading to the perbenzoylated pentitol were carried out. Debenzylated product **133** was hydrolyzed with TFA-water, then oxidatively cleaved using sodium periodate, to obtain tri-O-benzoylpentodialdose **134.** Reduction of dialdose to diol followed by benzoylation to obtain perbenzoylated pentitol was unsuccessful (Scheme **51**).

Failure to obtain the required perbenzoylated pentitols, from the corresponding dodecoses, prompted us to go for an X-ray analysis of one of the debenzylated products. At the same time, Jarosz's report on the transformation of higher sugar enones to higher sugars by the same sequence and from the same starting material appeared,[28b] wherein structures of all the derived higher sugars were ascertained by X-ray analysis. Structures of the keto diols **124** and **125** were secured by comparing their physical and spectroscopic data with that reported by Jarosz.

Conclusion:

A convenient methodology, namely the W-E reaction, for the synthesis of higher sugars has been developed. Using this, higher sugars of any length and complexity can be realized and homologation of cyclic (pyranose or furanose) or acyclic sugars can be easily performed. Synthesis of cross-conjugated enones starting from phosphonate 87 was carried out. Higher sugar synthesis by te-homologation of a *bis*-phosphonate was conceived and executed. A sequential transformation of higher sugar enones to higher sugars has been carried out Finally, this methodology provides many unique advantages

over other existing methods, namely, 1) reaction is performed under very mild conditions, 2) in all cases, it provides single pure (*E*)-isomer, so the problems due to formation of *cis*- and *trans*-isomers do not arise, 3) restrictions on homologation have been eliminated and 4) synthesis of complex higher sugars can be undertaken.

PART II

Synthesis of Higher Sugars by *Tetra*-Hydroxylation of Sugar Dienes.

In the context of our continuing interest in the synthesis of higher sugars, we were interested in *bis*-dihydroxylation of chiral sugar dienes. The unprecedented selectivity, simplicity and mild reaction conditions have made osmium tetroxide a versatile reagent for dihydroxylation reactions.[57] Though dihydroxylation has been commonly used in the synthesis of higher sugars, stereoselective *tetra*-hydroxylation of a conjugated diene leading to higher sugars has not been realized so far. This motivated us to explore its potential for use in higher sugar synthesis, as it would simultaneously generate several contiguous chiral centres.

Kishi, in his paper on stereochemistry of osmium tetroxide oxidation of allylic alcohol and ether systems, showed that the relative stereochemistry between the existing hydroxyl or alkoxyl group and the adjacent newly introduced hydroxyl group of the major product is *eryihro* in all cases.[60] Recently, Sharpless observed that on hydroxylation of achiral dienes and trienes, the major product had *eryihro* relationship between the hydroxyl groups formed between two double bonds[62] and selective

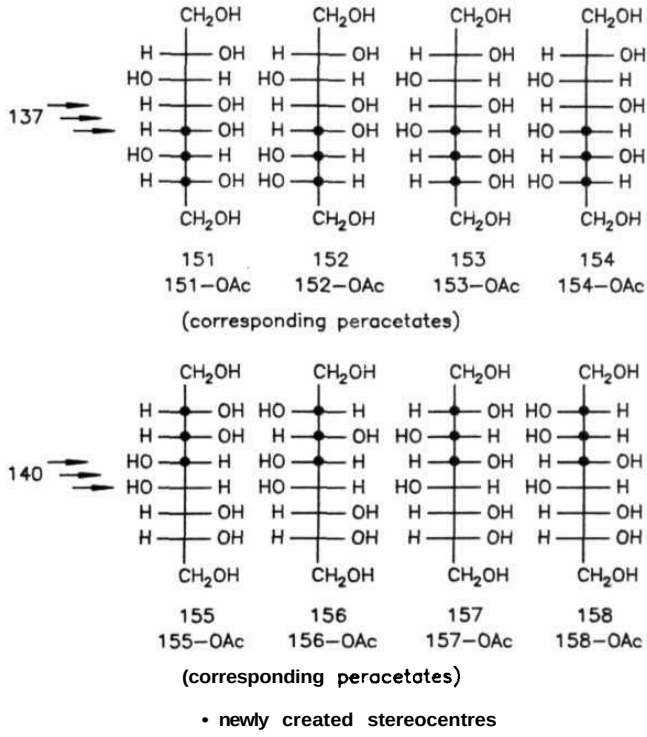
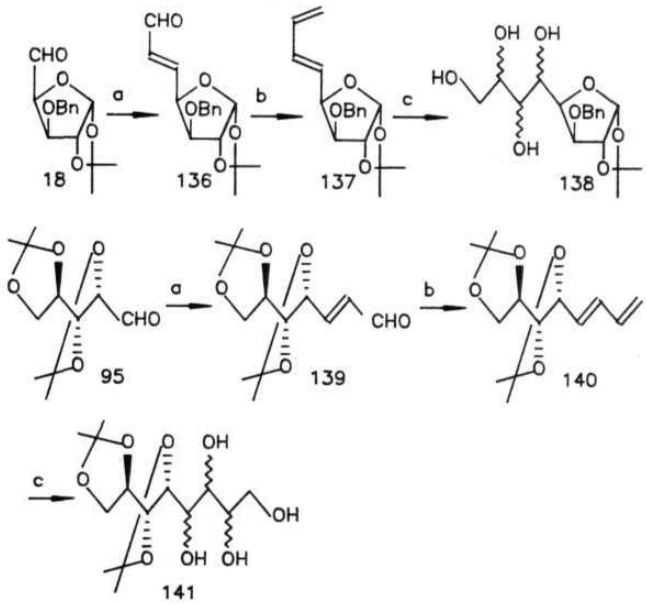


Figure 5 *Structures of all possible products obtainable from dienes 137 and 140 on hydroxylation followed by transformations as shown in the scheme 54.*

asymmetric dihydroxylation of unsymmetrical dienes occurred at the more substituted double bond.[64] We were at this stage interested in making a model in which both Kishi's and Sharpless's observations would be operative *(i.e.,* a diene attached to a chiral centre).

One of the reasons why *tetra*-hydroxylation of chiral conjugated dienes is not known could be due to the difficulties involved in separation, followed by identification of the diastereomeric products formed in the reaction. To overcome this difficulty, dienes **137** and **140** were chosen for this purpose and their advantages can be understood by analyzing the structures of all possible hydroxylated products, **151-154** and **155-158,** respectively (Figure 5). 1) Both dienes **137** and **140** on hydroxylation provide one *meso* and one *C-2* symmetric diastereomer each, 2) one of the diastereomers obtainable from both **137** and **140** form an enantiomeric pair and 3) one of the diastereomers obtainable from **137** is identical to one of those derivable from **140.** These features allow for easy and unambiguous product identification. In addition to the above, octitols **151,**[92] **155**[93] and **158**[94] are already known in the literature.

Dienes **137** and 140 were synthesized by sequential Wittig reactions of the parent aldehydes **18**[84] and **95**[85] by first refluxing with (formylmethylene)triphenylphosphorane in benzene to afford the corresponding pure *E*-enals **136**[95] and **139**[96] in good yields. Condensation of enals 136 and 139 with methylene triphenylphosphorane in THF at 0°, afforded the respective dienes **137** and **140** in 70% and 80% yields (Scheme 52). The structures of **137** and **140** were secured from their spectral and analytical data. IR Spectra of both **137** and **140** showed absorptions at 1600 cm^{-1}, assignable to olefinic C-C stretching. In the ^1H NMR spectrum of **137,** apart from other signals, a doublet at



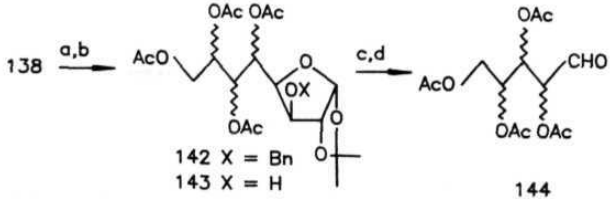
Scheme 52 *Reagents and conditions: (a) $Ph_3P{=}CH{-}CHO$, benzene, reflux, 1 h; (b) $Ph_3P{=}CH_2$, THF, 0°, 2 h; (c) OsO_4, NMO, acetone-H_2O (8:1), 8 h.*

5.89 ppm (J - 3.80 Hz) was due to the anomeric proton. Multiplets spread between 5.0-6.50 ppm in the ^1H NMR spectra of both 137 and 140 were assigned to olefinic protons. Care was taken to avoid any trace of their *cis*-isomers and epimers, so as to obtain only a maximum of four isomers from each diene on hydroxylation. Dienes 137 and 140 were

hydroxylated using osmium tetroxide and NMO in acetone-water mixture and the resulting crude tetrols were processed further as detailed below.

The task was to settle the structures of the individual diastereomers and to establish the ratio in which they were formed. It was rationalized that diastereoselectivity of the hydroxylation reaction of the *xylo* furanose derived diene 137 could be ascertained, provided the anomeric signals of the individual isomers of the crude tetrol **138** separate in the ^1H NMR spectra. As we failed to obtain the required information from ^1H NMR, an attempt to convert the crude tetrol **138** to *aldehydo*-pentoses was carried out to compare their physical data with that reported in the literature,[97] in order to settle the stereochemistry of the osmylated products.

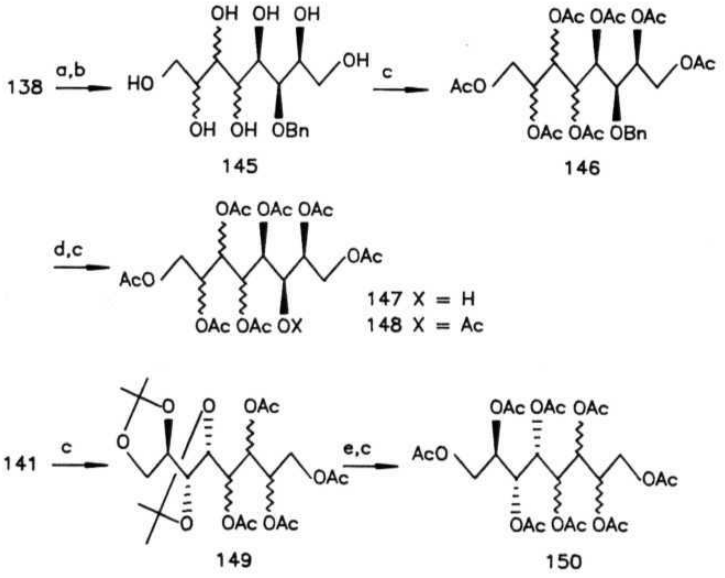
Acetylation of the crude tetrol 138 afforded the tetra-O-acetyl derivative **142,** which was debenzylated by catalytic reduction to yield **143.** The gross structure of **143** was based on its ^1H NMR spectrum. Absence of the benzyl group was apparent from its



Scheme 53 *Reagents and conditions: (a) Ac_2OPy, 100°. 3 h; (b) Pd/C, H_2, ethanol, 60 psi, 6 h; (c) TFA-H_2O(9:1), 20 min; (d) $NaIO_4$, silica gel, CH_2Cl_2, 1 h.*

^1H NMR spectrum and additionally, the anomeric protons appeared between 5.80-6.0 ppm. Peaks between 2.0-2.20 ppm were due to acetyl groups. Acidic hydrolysis of the isopropylidene group using TFA-water (9:1), followed by oxidative cleavage provided complex *aldchydo* compounds, as evidenced from the ^1H NMR spectrum of the crude mixture 144 (Scheme 53). Unfortunately, information pertaining to the structures of the individual components and their ratios could not be determined.

In the next attempt, it was planned to convert the crude tetrols to their corresponding peracetylated octitols. Acid hydrolysis of 138 followed by sodium borohydride reduction of the C-1 aldehyde provided the 3-O-benzyl-octitol derivatives 145. Acetylation of 145 yielded the peracetyl derivatives 146, the gross structures of which were ascertained from the ^1H NMR spectrum of the mixture. Signals between 7.20-7.50 and 1.90-2.20 ppm were due to the benzyl and acetyl protons, respectively. Debenzylation followed by further acetylation provided the required diastereomeric peracetylated octitols 148. The gross structures of 148 were arrived at using proton NMR. In the ^1H NMR spectrum of 148, secondary protons appeared between 5.0-5.50 ppm, primary protons between 3.80-4.40 ppm and acetyl protons between 1.90-2.20 ppm. Similarly, the crude mixture of tetrols 141 obtained from 140 was transformed to their corresponding octa-O-acetyl-octitols 150 using the sequence of reactions shown in Scheme 54. Again, proton NMR spectrum helped in assigning the gross structure of 150.



Scheme 54 *Reagents and conditions: (a) TFA-H_2O (9:1), 20 min: (b) $NaBH_4$, H_2O, 12 h; (c) Ac_2O, Py, 100°, 3 n; (d) Pd/C, H_2, ethanol, 50 psi, 6 h; (e) TFA-H_2O (9:1), 45 min*

Separation of diastereomers:

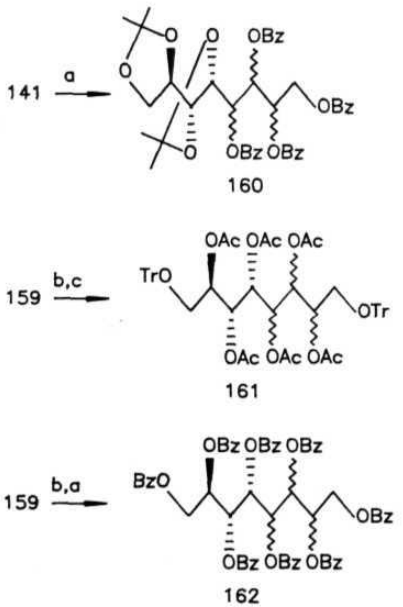
Having achieved the synthesis of **octa-O-acetyl-octitol** mixtures **148** and **150** from **their** corresponding dienes **137** and **140**, attention was next focused on the separation of diastereomers. Efforts towards the separation of diastereomers by conventional

chromatographic techniques were unsuccessful, as the octa-acetates were difficult to visualize by TLC. An examination of the literature revealed that most of the reported octa-O-acetyl octitols are crystalline in nature[98] and also due to the possible formation of symmetrical products in our systems, it was tempting to exploit their physical properties for separation. A systematic fractional crystallization of the crude octitol octa-acetates **148** and **150** was undertaken.

Partial crystallization of 148 from ethanol gave pure **151-OAc** as a colorless crystalline substance (mp 184-5°) from the unseparated 152-OAc and 153-OAc in a ratio of 1:6.6. Similarly, when the unseparated isomeric mixture containing 152-OAc and 153-OAc was partially crystallized from methanol at 0°, syrupy 152-OAc and crystalline **153-OAc** (mp 122-3°), separated in a ratio of 6.6:1. Incidentally, pure diastereomers **151-OAc**, **152-OAc** and **153-OAc** were obtained in 90% recovery, based on 148 (Figure 6). Identically, 150 on fractional crystallization afforded a 2:3 mixture of crystalline **155-OAc**[93] (mp 166-7°) and 159 (mixture containing **156-OAc** and **158-OAc**[94]) from ethanol at rt, in 95% yield, based on 150. Fractional crystallization of 159 with various solvents like methanol, *2*-propanol, aqueous ethanol and aqueous methanol was unsuccessful. Subsequently, HPLC was used to separate 156-OAc and 158-OAc.

Different aromatic derivatives of unseparaied mixtures of 141 and 159 were prepared and their HPLC analyses carried out (Scheme 55). Initial attempts were aimed towards arriving at the diastereoselectivity cum separation of the crude tetrol 141 itself, using HPLC. Tetra-O-benzoyl derivative 160 of 141 was prepared using benzoyl chloride in pyridine. Analytical HPLC separation of 160 was inadequate under reverse phase conditions. 1,8-Di-O-trityl-hexa-O-acetyl-octitol derivatives **161** of the crude

mixture containing **156-OAc** and **158-OAc** were prepared and their attempted HPLC analyses were unsuccessful due to cleavage of the trityl group under the experimental conditions. Finally, the mixture containing **156-OAc** and **158-OAc** was converted to the corresponding perbenzoates 162 in 72% yield by saponification of the acetates followed by benzoylation. The perbenzoylated **diastereomeric** mixture was separated by HPLC



Scheme 55 *Reagents and conditions: (a) BzCl, DMAP, Py, 24 h; (b) Na, MeOH, reflux, 5 min; (c) TrCl, Ac2O, Py, 5 days.*

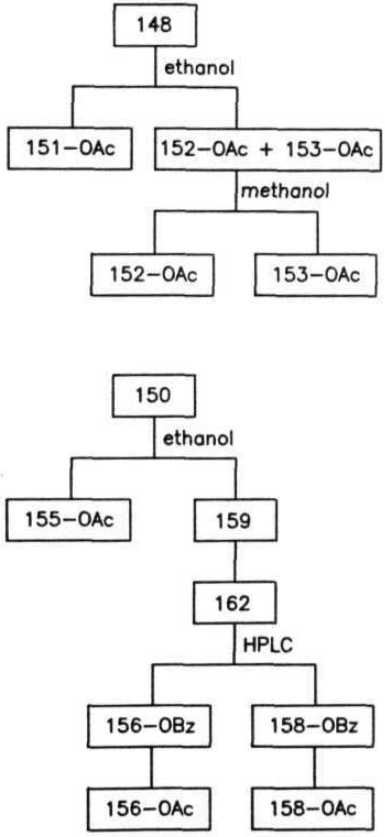


Figure 6 *Flow chart for the separation of* ***148*** *and* ***150****.* ***159*** *refers to* ***mixture*** *containing* ***156-OAc*** ***and*** ***158-OAc*** *and* ***162*** *refers to their corresponding* ***perbenzoates****.*

into two components in a 1:1 ratio with 92% recovery and were further hydrolyzed and acetylated to obtain **156-OAc (75%)** and **158-OAc** (87%). In summary, separation of the diastereomeric peracetylated octitol mixture **148** from **137** by fractional crystallization revealed that **151-OAc, 152-OAc** and **153-OAc** were formed in a ratio of 1.15:6.6:1, respectively. The diastereomeric peracetylated octitol mixture **150** obtained from **140,** by fractional crystallization and HPLC separation showed that **155-OAc, 156-OAc** and **158-OAc** were present in a 1.33:1:1 ratio, respectively (Figure 6).

Structural *identification* of diastereomers:

The structure of **151-OAc (mp** 184-5°) was confirmed by converting it into the known **(*meso*)-*threo*-*gluco*-octitol (151)**[92] **(mp** 166-9°; **lit** 166-9.5°). Further evidence for its structure comes from its ^{1}H and ^{13}C NMR spectra (it showed only half the number of signals) and finally it showed no optical rotation. The structure **152-OAc** was assigned to a syrupy material obtained from **148,** since its **enantiomer 156-OAc** (identical ^{1}H and ^{13}CNMR spectra but equal and opposite optical rotation) was obtained from **150.** Subsequently, the structure of the crystalline product obtained from **148** (one of the three diastereomers) is **153-OAc,** as evidenced from its NMR spectrum (non-symmetric). Incidentally, as **154-OAc** has *C-2* symmetry, it would show only half the number of signals in ^{1}H and ^{13}C NMR spectra when compared to **153-OAc.**

The presence of symmetry in both **155-OAc** and **158-OAc were** readily disclosed by their respective ^{1}H and ^{13}CNMR spectra. Optical rotation experiments immediately settled the structures of **(155-OAc)** and **(158-OAc)** as **(*meso*)-*erythro*-*manno*-** and *D*-***erythro*-*L*-*gulo*-octa-O-acetyl-octitol** *{C-2* symmetric), respectively. Further evidence for

their structures was forthcoming by comparing their physical data with that reported in the literature.[93,94]

In order to provide further proof for the structure of **153-OAc**, its synthesis from an entirely different starting material was undertaken. It was felt that two carbon homologation of a acyclic *aldehydo* glucose derivative would be a logical way of approaching at 153-OAc (Figure 7).

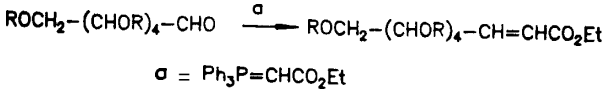
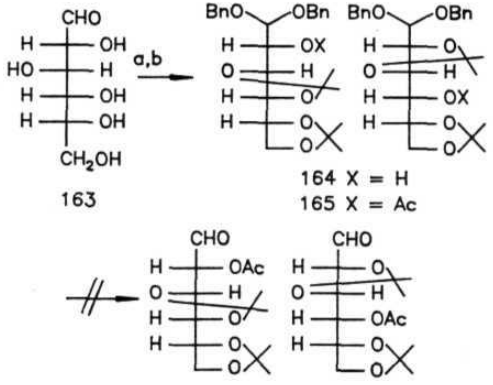


Figure 7 *Synthesis of eight carbon sugars by two carbon homologation of a six carbon sugar.*

Accordingly, a mixture of 2,3:5,6- and 3,4:5,6-di-O-isopropylidene-*aldehydo*-*D*-glucose dibenzyl acetal (164) was prepared from *D*-glucose (163) using a known procedure[99] (Scheme 56). Acetylation using acetic anhydride and pyridine yielded the corresponding 4- and 2-O-acetyl derivatives **165**. Selective deprotection of C-1 acetal by catalytic hydrogenolysis using various solvents and conditions were unsuccessful. Hydrogenolysis of 165 using 10% palladium/carbon and 60 psi hydrogen led to deprotection of C-1 acetal cum isopropylidene cleavage, whereas when the same reaction was carried out using dilute ammonia washed glassware in ethyl acetate, the starting material was unchanged even after 6 h. Different reaction conditions which were attempted are listed in table 3.



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Scheme 56 *Reagents and conditions: (a) 2,2-dibenzyloxypropane, p-TsOH, dioxane, 65°, 1.5 h; (b) Ac_2O, Py, 100°, 3 h.*

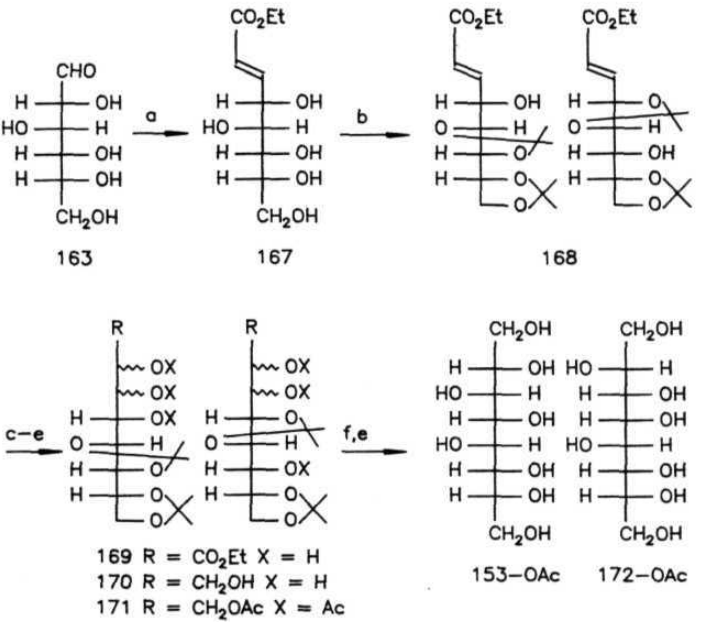
Having failed to obtain the protected *aldehydo* glucose by hydrogenolysis, an alternative method to homologate unprotected *D*-glucose itself was attempted. Ethyl (*E*)-2,3-dideoxy-*D*-*gluco*-oct-2-enonate (167)25 was prepared by the Wittig reaction of *D*-glucose with (carbethoxymethylene)triphenylphosphorane in DMF at 90°, following the procedure of Kochetkov. Protection of hydroxyl groups in 167 as isopropylidene derivatives, effected using acetone, copper sulfate and catalytic amount of sulfuric acid, provided a regioisomeric mixture of ethyl (*E*)-2,3-dideoxy-4,5:7,8- and 5,6:7,8-di-O-isopropylidene-*D*-*gluco*-oct-2-enonates (168) in 90% yield.

Table 3 *Attempted reaction conditions for the cleavage of C-1benzyl acetal in 165 using 10% Pd/C.*

No.	Reaction conditions	Result
1.	H_2, 2-propanol, 60 psi, 6 h.	Isopropylidene cleavage.
2.	H_2, 2-propanol, 60 psi, 6 h, 3 drops TEA.	Deprotection of C-1 acetal cum isopropylidene cleavage.
3.	H_2, 2-propanol, 60 psi, 6 h, 50 µl, TEA	Starting material recovered.
4.	H_2, 2-propanol, 50 psi, 6 h, ammonia washed glassware	Starting material recovered.
5.	H_2, ethyl acetate, 70 psi, 6 h, ammonia washed glassware.	Starting material recovered.
6.	H_2, ethanol, 50 psi, 6 h.	Isopropylidene cleavage.
7.	H_2, cyclohexene, reflux, 10 h.	Starting material recovered.

Hydroxylation of 168, followed by lithium aluminium hydride reduction in refluxing THF, yielded the diastereomeric tetrols **170.** Subsequent acetylation, hydrolysis of the isopropylidene groups followed by reacetylation as depicted in scheme 57 yielded the required *D-erythro-L-ido-* and *D-erythro-L-galacto*-octa-O-acetyl-octitols **(153-OAc)** and **(172-OAc)** in a 1:8 ratio.

153-OAc was separated from **172-OAc** by fractional crystallization and its spectra (^1H and ^{13}C NMR) and rotation were identical to those of **153-OAc** obtained from **137.**



Scheme 57 *Reagents and conditions: (a)* $Ph_3P{=}CH{-}CO_2Et$, *DMF, 90°, 5 h; (b) acetone,* H_2SO_4, $CuSO_4$, *25 h; (c)* OsO_4, *NMO, acetone-*H_2O *(8:1), 8 h; (d) LAH, THF, reflux, 1 h; (e)* Ac_2O, *Py, 100°, 3 h; (f) TFA-*H_2O *(9:1), 40 min.*

The structure of **172-OAc** was confirmed by hydrolysis of **172-OAc** to *D-erythro-L-galacto*-**octitol (172)** and comparison of its physical data with that reported in literature[100] (**mp** 150-1°; lit 153°).

Conclusion:

Synthesis of octitols by diastereoselective fcw-dihydroxylation of sugar derived dienes **137** and **140** were carried out using osmium tetroxide/NMO. Separation of diastereomers by fractional crystallization was performed. Results of the diastereoselective hydroxylation of dienes **137** and **140** indicate that the major isomer formed is the one in which both the relations between the existing hydroxyl group and the adjacent newly introduced hydroxyl group, as well as the hydroxyl groups formed between two double bonds are *erythro*. It is also interesting to note that stereoisomers **154-OAc** and **157-OAc** are not formed at all, since in them both the relations are *threo*. Diastereoselective synthesis of octitols starting from unprotected glucose was achieved in 7 steps.

EXPERIMENTAL

All reactions were carried out under nitrogen atmosphere unless otherwise mentioned. Reagents were transferred using standard septa-syringe techniques. All solvents were distilled from appropriate drying agents just before use. All reagents were purified by appropriate methods before use. All organic extracts were dried using anhydrous $MgSO_4$, unless otherwise mentioned.

Solvents used for chromatography were of commercial grade and were fractionally distilled before use. Hexane refers to the petroleum fraction boiling between 60-70°. Column chromatography was performed using ACME 100-200 mesh silica gel using appropriate mixtures of hexane and ethyl acetate for elution. Analytical thin layer chromatography (TLC) was performed on home made plates using ACME silica gel GF 254 grade containing 13% calcium sulfate as binder and were developed by shining ultraviolet light and/or by exposure to iodine vapours.

Melting points were determined using a Büchi 510 capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer model 1310 spectrophotometer. ^1H NMR spectra were recorded at 100, 200, 400 and 500 MHz using JEOL FX-100, Bruker ACF 200 and Bruker ACP 400 and 500 instruments. ^{13}C NMR spectra were recorded at 25, 50 and 125 MHz using the above instruments. ^{31}P NMR spectra were recorded at 40.5 and 81 MHz using JEOL FX-100 and Bruker ACF 200 instruments. All spectra were recorded using chloroform-d as solvent. Chemical shifts

are reported as 5 values in parts per million relative to tetramethylsilane (0.0 ppm) as internal standard (^{1}H & ^{13}C). 85% Aqueous H_3PO_4 (0.0 ppm) was used as an external reference for ^{31}P NMR spectra. Data are reported as follows: chemical shifts (multiplicity, coupling constants, integrated intensity). Optical rotations were measured using an Autopol-II automatic polarimeter at 25° in 1 dm cell of 1.2 ml capacity using chloroform as solvent unless mentioned otherwise. Elemental analyses were performed using a Perkin-Elmer 240C CHN analyzer. HPLC analyses were performed using LKB (2248) pumps. SuperPac pep-S 15 µm reverse phase preparative column was used for preparative separations.

A note on nomenclature and numbering used in NMR assignments for some of the compounds described in the experimental chapter.

As the products obtained in some of the experiments are complex, they have been named and numbered as described below:

Nomenclature*.

1). Compounds obtained by the condensation of a p-keto phosphonate and non-sugar aldehydes are named as derivatives of ethylene.

2). In Compounds containing two sugar moieties with an enone functionality, the parent sugar is derived from the aldehyde component of the W-E reaction and the phosphonate sugar is treated as a substituent.

Numbering used in NMR assignments:

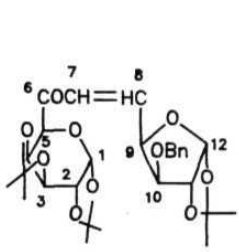
Numbering of the carbon chain in a higher sugar is done continuously using the criteria given below to determine priority.

1). When compounds contain two cyclic sugars, the anomeric carbon derived from the parent phosphonate takes priority.

2). When compounds contain one cyclic and one acyclic sugar moieties, the anomeric carbon of the cyclic sugar is given priority.

3). When compounds contain two acyclic sugar derivatives, the terminal carbon which comes from the parent phosphonate takes priority.

Representative examples are illustrated below.



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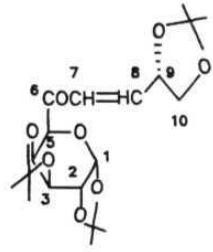
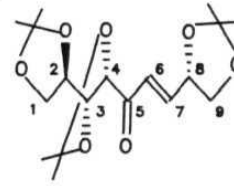


101



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Methyl (3-O-benzyl-1,2-O-isopropylidene-α-*D*-xylofuranosid)uronate (94). To a stirred mixture of 3-O-benzyl-1,2-O-isopropylidene-α-*D*-*xylo*-pentodialdo-1,4-furanose (18)[84] (557 mg, 2.0 mmol) and $NaHCO_3$ (3.36 g, 40 mmol) in a 9:1 methanol-water mixture (4 ml), a solution of Br_2 (1.60 g, 10.0 mmol) in a 9:1 methanol-water mixture (5 ml) was added dropwise.[29] After 5 h, excess Br_2 was quenched with powdered $Na_2S_2O_3$ and the contents diluted with 10 ml of water and extracted with 30 ml of ether. The ether extract was dried, evaporated and the residue purified by column

chromatography on silica gel using 10% ethyl acetate in hexane to afford 524 mg of oily 94 (85%).

IR(neat) 1750, 1730 cm^{-1}.

^1H NMR (200 MHz)

8 7.35-7.20 (m, 5H, Ph), 6.09 (d, J = 3.58 Hz, 1H, H-1), 4.83 (d, J = 3.64 Hz, 1H, H-4), 4.66 (d, J = 12.0 Hz, 1H, $PhCH_2$), 4.60 (d, J = 3.61 Hz, 1H, H-2), 4.51 (d, J = 12.0 Hz, 1H, $PhCH_2$), 4.26 (d, J = 3.68 Hz, 1H, H-3), 3.75 (s, 3H, Me), 1.47 (s, 3H, CMe_2), 131 (s, 3H, CMe_2).

^{13}C NMR (25 MHz)

168.3, 137.0, 128.4 (2C), 128.0, 127.7 (2C), 112.4, 105.7, 82.7, 81.7, 79.5, 72.2, 52.0, 26.8, 26.2 ppm.

$[\alpha]_D^{25}$ -45.0° (c 1.0).

Anal. Calcd for $C_{16}H_{20}O_6$: C, 62.32; H, 6.54. Found: C, 62.21; H, 6.58.

Methyl 2,3:4,5-di-O-isopropylidene-*D*-arabinonate (96)[82] was prepared from 2,3:4,5-di-O-isopropylidene-*aldehydo*-*D*-arabinose (95)[85] in 75% yield using the same procedure as described for 94.

Syrup; IR (neat) 1740 cm^{-1}.

^1H NMR (200 MHz)

8 4.41 (d, J= 5.50 Hz, 1H, H-2), 4.28-4.20 (m, 1H), 4.18-4.08 (m, 1H), 4.04 (d, J = 5.78 Hz, 1H), 3.95 (dd, J =3.90, 8.06 Hz, 1H, H-5), 3.74 (s, 3H, OMe), 1.41 (s, 3H, CMe_2), 1.37 (s, 6H, CMe_2), 1.30 (s, 3H, CMe_2).

^{13}C NMR (50 MHz)

171.2, 111.9, 109.8, 79.6, 77.2, 76.4, 66.6, 52.1, 27.1, 26.5, 25.9, 25.1 ppm.

$[\alpha]_D^{25}$ +23.0° (*c* 1 5, acetone), lit.[82] $[\alpha]_D^{25}$ +26.0° (c 4.92, acetone).

Preparation of β-keto phosphonates 87, 97, 98 **and** 99.

To a stirred solution of dimethyl methylphosphonate (744 mg, 6.0 mmol) in 10 ml of THF at -78°, *n*-butyllithium in hexane (5.50 mmol) was added dropwise. After 15 min, a solution of the glycuronate or glyconate (86,[75] 93,[81] 94, or 96;[82] 5.0 mmol) in 5 ml of THF was added dropwise. After warming to rt over 2 h, the reaction mixture was quenched with 12 ml of 5% aq citric acid and extracted with 50 ml of CH_2Cl_2. The CH_2Cl_2 extract was dried and evaporated to get the corresponding phosphonate (87, 97, 98 or 99) in quantitative yields. Phosphonates 87, 97, 98 and 99 can be used as such for the Wadsworth-Emmons reaction without further purification.

Dimethyl (methyl **4-O-benzyl-2,3-di-O-methyl-α-*D*-glucopyranuronyl)methylphosphonate** (87) was prepared from methyl (methyl **4-O-benzyl-2,3-di-O-methyl-α-*D*-**glucopyranosid)uronate **(86)**.[75]

Syrup; IR (neat) 1720 cm^{-1}.

^1H NMR (400 MHz)

δ 7.35-7.25 (m, 5H, Ph), 4.88 (d, *J* = 3.53 Hz, 1H, H-1), 4.82 (d, *J* = 10.70 Hz, 1H, $PhCH_2$), 4.65 (d, *J* = 10.70 Hz, 1H, $PhCH_2$), 4.33 (d, *J* = 9.82 Hz, 1H, H-5) 3.76 (d, *J* =11.30 Hz, 3H, POMe), 3.74 (d, *J* = 11.13 Hz, 3H, POMe), 3.67 (d, *J* = 9.02 Hz, 1H), 3.64 (s, 3H, Me), 3.57 (d, *J* - 9.75 Hz, 1H), 3.53 (s, 3H, Me), 3.48 (s, 3H, Me), 3.30 (dd, *J* - 14.0, 22.54 Hz, 1H, PCH_2), 3.24 (dd, *J* = 3.42, 9.52 Hz, 1H), 3.20 (dd, *J* = 14.0, 22.42 Hz, 1H, PCH_2).

^{13}C NMR (25 MHz)

199.9, 139.9, 129.6, 129.4, 129.1, 99.2, 84.7, 82.7, 79.8, 79.7, 74.9, 62.2, 60.2, 56.8, 54.0 (m), 40.5 (d, *J* = 129 Hz) ppm.

^{31}P NMR (40.5 MHz) 21.80 ppm.

$[\alpha]_D^{25}$ +98.5° (*c* 1.0).

Anal. Calcd for $C_{19}H_{29}O_9P$: C, 52.77; H, 6.76. Found: C, 52.72; H, 6.78.

Dimethyl (1,2:3,4-di-O-isopropylidene-α-*D*-galactopyranuronyl)methylphosphonate (97) was prepared from methyl (1,2:3,4-di-O-isopropylidene-α-*D*-galactopyranosid)-uronate(93).[81]

Syrup; IR (neat) 1720 cm^{-1}.

^1H NMR (200 MHz)

5 5.64 (d, *J* = 4.90 Hz, 1H, H-1), 4.64 (dd, *J* • 2.30, 7.80 Hz, 1H, H-3), 4.59 (dd, *J*= 1.90, 7.80 Hz, 1H, H-4), 4.36 (dd, *J* = 4.90, 2.30 Hz, 1H, H-2), 4.32 (d, *J*= 1.90 Hz, 1H, H-5), 3.82 (d, *J*= 11.22 Hz, 3H, POMe), 3.79 (d, *J* = 11.24 Hz, 3H, POMe), 3.64 (dd, *J* = 15.14, 20.45 Hz, 1H, PCH_2), 3.07 (dd, *J* = 15.15, 21.70 Hz, 1H, PCH_2), 1.51 (s, 3H, CMe_2), 1.42 (s, 3H, CMe_2), 133 (s, 3H, CMe_2), 1.30 (s, 3H, CMe_2).

^{13}C NMR (25 MHz)

200.1 (d, *J* = 5.90 Hz), 109.4, 108.8, 96.0, 73.2 (d, *J* = 2.95 Hz), 71.8, 70.2, 70.0, 52.0 (m), 37.1 (d, *J* = 134 Hz), 25.4 (2C), 24.4, 23.7 ppm.

^{31}P NMR (40.5 MHz) 22.68 ppm.

$[\alpha]_D^{25}$ -126.3° (*c* 0.60).

Anal. Calcd for $C_{15}H_{25}O_9P$: C, 47.37; H, 6.63. Found: C, 47.25; H, 6.60.

Dimethyl (3-O-benzyl-1,2-O-isopropylidene-α-*D*-xylofuranuronyl)methylphosphonate (98) was prepared from methyl (3-O-benzyl-1,2-O-isopropylidene-α-*D*-xylofuranosid)uronate (94).

Syrup; IR (neat) 1720 cm^{-1}.

^1H NMR (200 MHz)

δ 7.40-7.20 (m, 5H, Ph), 6.08 (d, *J* = 3.57 Hz, 1H, H-1), 4.73 (d, *J* = 3.70 Hz, 1H, H-4), 4.59 (d, *J*= 3.59 Hz, 1H, H-2), 4.58 (d, *J*= 11.70 Hz, 1H, $PhCH_2$), 4.47 (d, *J*= 11.70 Hz, 1H, $PhCH_2$), 4.29 (d, *J*= 3.72 Hz, 1H, H-3), 3.78 (d, *J* = 11.20 Hz, 3H, POMe), 3.75 (d, *J* = 11.24 Hz, 3H, POMe), 3.50 (dd, *J* = 15.30, 20.38 Hz, 1H, PCH2), 3.02 (dd, *J* = 15.40, 21.30 Hz, 1H, PCH_2), 1.47 (s, 3H, CMe_2), 132 (s, 3H, CMe_2).

^{13}C NMR (25 MHz)

200.3, 136.7, 128.7 (2C), 128.3, 127.9 (2C), 112.7, 106.1, 85.3 (d, *J* = 3.0 Hz), 83.7, 81.8, 72.5, 53.0 (m), 38.1 (d, *J* =135.30 Hz), 26.9, 26.3 ppm.

^{31}P NMR (81 MHz) 21.95ppm.

$[\alpha]_D^{25}$ -72.7° (*c* 3.10).

Anal. Calcd for $C_{18}H_{25}O_8P$: C, 53.99; H, 6.29. Found: C, 53.88; H, 6.25.

Dimethyl (2,3:4,5-di-O-isopropylidene-*D*-arabinonyl)methylphosphonate (99) was prepared from methyl 2,3:4,5-di-O-isopropylidene-*D*-arabinonate (96).[82]

Solid; mp 66-68° (hexane-chloroform).

IR(KBr) 1740 cm^{-1}.

^1H NMR (400 MHz)

δ 4.54 (d, *J* = 5.40 Hz, 1H, H-2), 4.23-4.15 (m, 2H, H-3, H-4), 4.12 (dd, *J* = 8.50, 6.18 Hz, 1H, H-5), 3.95 (dd, *J* =4.56, 8.50 Hz, 1H, H-5'), 3.81 (d, *J* = 11.30 Hz,

3H, POMe), 3.80 (d, J = 11.22 Hz, 3H, POMe), 3.46 (dd, J = 14.30, 22.43 Hz, 1H, PCH_2), 3.35 (dd, J = 14.23, 22.36 Hz, 1H, PCH_2), 1.46 (s, 3H, CMe_2), 143 (s, 3H, CMe2), 136 (s, 3H, CMe_2), 135 (s, 3H, CMe_2).

^{13}C NMR (25 MHz)

200.8 (d, J = 6.0 Hz), 111.7, 110.0, 83.1 (d, J = 3.0 Hz), 78.2, 76.6, 66.8, 53.1 (m), 37.4 (d, J = 130.75 Hz), 27.1, 26.5, 26.2, 25.2 ppm.

^{31}P NMR (81 MHz) 21.27 ppm.

$[\alpha]_D^{25}$ -2.76° (c 1.0).

Anal. Calcd for $C_{14}H_{25}O_8P$: C, 47.72; H, 7.15. Found: C, 47.65; H, 7.14.

Tetramethyl (2,3-O-isopropylidene-*L*-tartaroyl)*bis* methylphosphonate (113). To a stirred solution of dimethyl methylphosphonate (893 mg, 7.20 mmol) in 10 ml of THF at -78°, *n*-butyllithium in hexane (6.60 mmol) was added dropwise. After 15 min, a solution of diethyl 2,3-O-isopropylidene-*L*-tartrate (112)[86] (739 mg, 3.0 mmol) in 5 ml of THF was added dropwise. After warming to rt over 2 h, the reaction was quenched with 15 ml of 5% aq citric acid and extracted with 30 ml of CH_2Cl_2. The CH_2Cl_2 extract was dried and evaporated to get 113 in quantitative yield.

Syrup; IR (neat) 1720 cm^{-1}.

^1H NMR (100 MHz)

8 4.76 (s, 2H, H-2), 3.78 (d, J = 11.0 Hz, 6H, POMe), 3.76 (d, J = 11.0 Hz, 6H, POMe), 3.60-3.00 (m, 4H, PCH_2), 140 (s, 6H, CMe_2).

^{13}C NMR (25 MHz)

200.2 (d, J = 5.90 Hz), 112.9, 81.2 (d, J = 2.95 Hz), 52.9 (m), 36.7 (d, J = 130.9 Hz), 25.8 ppm.

^{31}P NMR (81 MHz) 20.96 ppm.

$[\alpha]_D^{25}$ +30.0° (c 1.0).

Anal. Calcd for $C_{13}H_{24}O_{10}P_2$: C, 38.81; H, 6.01. Found: C, 38.90; H, 5.98.

Wadsworth-Emmons condensation between β-keto phosphonate 87 and *p*-anisaldehyde.

1. With NaH/THF.

To a hexane washed NaH suspension (5 mg, 0.20 mmol) in 2 ml of THF at 0°, a solution of 87 (87 mg, 0.20 mmol) in 2 ml of THF was added dropwise and the mixture stirred at 0° for 15 min. *p*-Anisaldehyde (33 mg, 0.24 mmol) was added dropwise to the stirring reaction mixture at 0° and the contents were allowed to warm up to rt over 8 h. The reaction mixture was quenched with 3 ml of saturated aq NH_4Cl solution and extracted with 20 ml of CH_2Cl_2. The CH_2Cl_2 extract was dried and evaporated to obtain the crude material. The starting material was recovered unchanged as indicated by TLC and its ^1H NMR spectrum.

2. With K_2CO_3/THF.

To a stirred suspension of K_2CO_3 (28 mg, 0.20 mmol) in 2 ml of THF at rt, a solution of phosphonate 87 (87 mg, 0.20 mmol) in 2 ml of THF and *p*-anisaldehyde (33 mg, 0.24 mmol) were added dropwise in sequence. The reaction mixture was stirred at rt for 24 h and quenched with 1 ml of 5% aq citric acid solution and extracted with 20 ml of CH_2Cl_2 The CH_2Cl_2 extract was dried and evaporated to obtain crude material. The starting material was recovered unchanged as indicated by TLC and its ^1H NMR spectrum.

3. With K_2CO_3/THF (reflux).

To a stirred suspension of K_2CO_3 (28 mg, 0.20 mmol) in 2 ml of THF at rt, a solution of phosphonate 87 (87 mg, 0.20 mmol) in 2 ml of THF and *p*-anisaldehyde (33 mg, 0.24 mmol) were added dropwise in sequence. The reaction mixture was refluxed for 4 h and cooled. The cooled reaction mixture was quenched with 1 ml of 5% aq citric acid solution and extracted with 20 ml of CH_2Cl_2. The CH_2Cl_2 extract was dried and evaporated to obtain crude material. A complex product containing no benzyl group was obtained as revealed by its ^1H NMR spectrum.

4. With DBU/LiCl.

To a stirred suspension of LiCl (5 mg, 0.12 mmol) in 1 ml of dry acetonitrile, a solution of phosphonate 87 (44 mg, 0.10 mmol) in 1 ml of acetonitrile, DBU (16 mg, 0.10 mmol) and *p*-anisaldehyde (17 mg, 0.12 mmol) were added in sequence. After 2 h at rt, the reaction mixture was quenched with 5 ml of water and extracted with CH_2Cl_2. The CH_2Cl_2 extract was dried, evaporated and the residue purified by column chromatography on silica gel using 10% ethyl acetate in hexane. A mixture containing the required enone 88 and its benzyl group eliminated analog 119 was obtained as indicated by its ^1H NMR spectrum.

5. With K_2CO_3/dioxane.

A mixture containing phosphonate 87 (44 mg, 0.10 mmol), K_2CO_3 (14 mg, 0.10 mmol), *p*-anisaldehyde (17 mg, 0.12 mmol) and dioxane (2 ml) was refluxed for 5 h. The reaction mixture was cooled to rt, the dioxane evaporated under reduced pressure and the residue purified on a silica gel column using 10% ethyl acetate in hexane. A

mixture containing the required enone 88 and its benzyl group eliminated analog **119** was obtained as indicated by its ^1H NMR spectrum.

General procedures for **Wadsworth-Emmons** reaction with cesium carbonate:

Procedure A.

To a stirred mixture of Cs_2CO_3 (325 mg, 1.0 mmol) in 3 ml of *2*-propanol at 0°, the P-keto phosphonate (87, 97 or 99, 1.0 mmol) in 2 ml of 2-propanol was added. After 5 min, the aldehyde (1.20 mmol) in 2 ml of 2-propanol was added and the mixture allowed to warm up to rt over 8 h. It was then quenched with 3 ml of 5% aq citric acid and extracted with 30 ml of CH_2Cl_2. The CH_2Cl_2 extract was dried and evaporated to yield the crude product which was purified by column chromatography using 10% ethyl acetate in hexane.

Procedure B.

This is essentially identical to procedure A, except that the reaction time was reduced to 4 h.

Procedure C.

To a stirred mixture of Cs_2CO_3 (650 mg, 2.0 mmol) in 4 ml of 2-propanol at 0°, the bis-P-keto phosphonate **113** (402 mg, 1.0 mmol) in 3 ml of 2-propanol was added. After 5 min, the aldehyde (2.40 mmol) in 3 ml of 2-propanol was added and the contents allowed to warm up to rt over 8 h. It was then quenched with 6 ml of 5% aq citric acid and extracted with 30 ml of CH_2Cl_2 The crude product, obtained after drying and concentration, was purified by column chromatography using 10% ethyl acetate in hexane.

Procedure D.

This is identical to procedure A, except that a three fold excess of Cs_2CO_3 per mole of P-keto phosphonate 87 was used.

***(E)*-1-(4-Methoxyphenyl)-2-(methyl 4-O-benzyl-2,3-di-O-methyl-α-D-glucopyranuronyl)ethylene** (88) was obtained in 88% yield by the condensation of P-keto phosphonate 87 and *p*-anisaldehyde (Procedure A).

Syrup; IR (neat) 1680, 1660 cm^{-1}.

^1H NMR (100 MHz)

δ 7.72 (d, *J*= 15.70 Hz, 1H, H-8), 7.48 (d, *J*= 8.50 Hz, 2H, Ph), 7.22 (s, 5H, Ph), 6.90 (d, *J* = 8.50 Hz, 2H, Ph), 6.85 (d, *J* = 15.70 Hz, 1H, H-7), 4.95 (d, *J* = 4.0 Hz, 1H, H-1), 4.78 (d, *J* = 11.0 Hz, 1H, $PhCH_2$), 4.54 (d, *J* = 11.0 Hz, 1H, $PhCH_2$), 4.46 (d, *J* = 9.30 Hz, 1H, H-5), 3.88 (s, 3H, PhOMe), 3.69 (s, 3H, OMe), 3.57 (s, 3H, OMe), 3.49 (s, 3H, OMe), 3.80-3.24 (m, 3H, H-2, H-3, H-4).

^{13}C NMR (25 MHz)

194.1, 160.8, 142.8, 136.5, 129.3 (2C), 127.1 (4C), 126.5, 125.8, 120.2, 113.2, 96.8, 82.3, 80.3, 74.5, 73.8, 72.0, 60.0, 57.8, 54.4, 54.1 ppm.

$[\alpha]_D^{25}$ +107.2° (*c* 0.70).

Anal. Calcd for $C_{25}H_{30}O_7$: C, 67.85; H, 6.83. Found: C, 67.75; H, 6.80.

***(E)*-1-Phenyl-2-(methyl 4-O-benzyl-2,3-di-O-methyl-α-*D*-glucopyranuronyl)ethylene (89)** was obtained in 85% yield by the condensation of P-keto phosphonate 87 and benzaldehyde (Procedure A).

Syrup; IR (neat) 1690, 1670 cm^{-1}.

^{1}H NMR (100 MHz)

6 7.70 (d, *J* • 16.0 Hz, 1H, H-8), 7.60-7.10 (m, 10H, Ph), 6.96 (d, *J* = 16.0 Hz, 1H, H-7), 4.96 (d, *J* = 4.0 Hz, 1H, H-1), 4.77 (d, *J* = 10.0 Hz, 1H, $PhCH_2$), 4.52 (d, *J* = 10.0 Hz, 1H, $PhCH_2$), 4.48 (d, *J*= 9.0 Hz, 1H, H-5), 3.80-3.20 (m, 3H, H-2, H-3, H-4), 3.69 (s, 3H, OMe), 3.57 (s, 3H, OMe), 3.48 (s, 3H, OMe).

^{13}C NMR (25 MHz)

195.3, 144.0, 137.6, 134.3, 130.8, 128.8 (2C), 128.6 (2C), 128.3 (4C), 127.7, 123.5, 98.0, 83.5, 81.4, 79.4, 75.0, 73.1, 61.1, 59.0, 55.6 ppm.

$[\alpha]_D^{25}$ +108.8° (*c* 1.52).

Anal. Calcd for $C_{24}H_{28}O_6$: C, 69.88; H, 6.84. Found: C, 69.75; H, 6.80.

***(E)*-1-(1-Methylethyl)-2-(methyl 4-O-benzyl-2,3-di-O-methyl-α-*D*-glucopyranuronyl)ethylene** (90) was obtained in 84% yield by the condensation of P-keto phosphonate 87 and isobutyraldehyde (Procedure A).

Syrup; IR (neat) 1690, 1675, 1620 cm^{-1}.

^{1}H NMR (100 MHz)

5 7.26 (s, 5H, Ph), 6.96 (dd, *J* = 6.50, 15.70 Hz, 1H, H-8), 6.26 (dd, *J* = 1.80, 15.70 Hz, 1H, H-7), 4.88 (d, *J* = 4.0 Hz, 1H, H-l), 4.74 (d, *J* = 10.0 Hz, 1H, $PhCH_2$), 4.52 (d, *J*= 10.0 Hz, 1H, $PhCH_2$), 4.35 (d, *J* = 8.90 Hz, 1H, H-5), 3.63 (s, 3H, OMe), 3.53 (s, 3H, OMe), 3.44 (s, 3H, OMe), 3.70-3.20 (m, 3H, H-2, H-3, H-4), 2.56-2.26 (m, 1H, H-9), 1.03 (d, *J* = 6.40 Hz, 6H, CMe_2).

^{13}C NMR (25 MHz)

195.6, 155.6, 137.9, 128.1 (2C), 128.0 (2C), 127.6, 125.0, 98.0, 83.3, 81.4, 79.3, 74.7, 72.1, 61.0, 58.9, 55.5, 31.0, 20.8 (2C) ppm.

$[\alpha]_D^{25}$ +115.3° (c 1.10).

Anal. Calcd for $C_{21}H_{30}O_6$: C, 66.64; H, 7.99. Found: C, 66.58; H, 7.95.

6,7-Dideoxy-7-(methyl 4-O-benzyl-2,3-di-O-methyl-α-*D*-glucopyranuronyl)-1, 2:3,4-**di-O-isopropylidene-α-*D-galacto*-hept-6*(E)*-enopyranose** (91) was obtained in 84% yield by the condensation of β-keto phosphonate 87 and **1,2:3,4-di-O-isopropylidene-α-*D-galacto*-hexodialdo-1,5-pyranose (13)**[80] (Procedure A).

Syrup; IR (neat) 1690, 1630 cm^{-1}.

^1H NMR (100 MHz)

8 7.26 (s, 5H, **Ph),** 6.96 **(dd,** *J* = 3.60, 15.70 **Hz,** 1H, H-8), 6.64 **(dd,** *J* = **15.70, 1.80 Hz,** 1H, **H-7),** 5.56 (d, *J* = 4.90 Hz, 1H, H-13), 4.86 (d, *J*= 4.0 Hz, 1H, **H-1),** 4.66-4.16 **(m,** 7H), 3.60 (s, 3H, OMe), 3.52 (s, 3H, **OMe),** 3.44 (s, 3H, OMe), 3.66-3.16 **(m,** 3H), 1.50 (s, 3H, CMe_2), 134 (s, 6H, CMe_2), 1 30 (s, 3H, CMe_2).

^{13}C NMR (25 MHz)

215.2, 143.7, 134.1, 129.8 (2C), 128.3, 127.2 (2C), 121.8, 109.4, 108.5, 97.8, 96.2, 72.7, 70.6, 67.4, 61.0, 58.8, 56.2, 51.4, 50.7, 46.5, 35.7, 35.0, 33.1, 26.0 **(2C),** 24.1, **23.8 ppm.**

$[\alpha]_D^{25}$ +3.60 (*c* 2.60).

Anal. Calcd for $C_{29}H_{40}O_{11}$: C, 61.68; H, 7.14. Found: C, 61.56; H, **7.15.**

***(E)*-1-(4-Methoxyphenyl)-2-(1,2:3,4-di-O-isopropylidene-α-*D*-galactopyranuronyl)-**ethylene (100) was obtained in 94% yield by the condensation of P-keto phosphonate 97 **and *p*-anisaldehyde** (Procedure A).

Syrup; IR (neat) 1680, 1595 **cm^{-1}**.

^{1}H NMR (100 MHz)

8 7.70 (d, *J* - 15.90 Hz, 1H, H-8), 7.54 (d, *J* = 9.20 Hz, 2H, Ph), 7.12 (d, *J* = 15.90 Hz, 1H, H-7), 6.88 (d, *J*= 9.20 Hz, 2H, Ph), 5.70 (d, *J*= 5.0 Hz, 1H, H-1), 4.66 (d, *J*= 1.80 Hz, 1H, H-5), 4.46-4.26 (m, 3H, H-2, H-3, H-4), 3.84 (s, 3H, PhOMe), 1.52 (s, 3H, CMe_2), 144 (s, 3H, CMe_2), 1.36 (s, 3H, CMe_2), 1.32 (s, 3H, CMe_2).

^{13}C NMR (25 MHz)

196.7, 161.8, 143.7, 130.6, 127.6, 119.0, 114.4, 109.7, 109.0, 96.5, 73.4, 72.5, 70.7, 70.5, 55.3, 25.9, 24.8, 24.2 ppm.

$[\alpha]_D^{25}$ -180.5° (*c* 0.60).

Anal. Calcd for $C_{21}H_{26}O_7$: C, 64.60; H, 6.71. Found: C, 64.35; H, 7.00.

1,2-Dideoxy-1-(1,2:3,4-di-O-isopropylidene-α-*D*-galactopyranuronyl)-3,4-O-isopropylidene-*D*-*glycero*-tetr-1*(E)*-enose (101) was obtained in 70% yield by the condensation of β-keto phosphonate 97 and 2,3-O-isopropylidene-*D*-glyceraldehyde (25)101 (Procedure A).

Syrup; IR (neat) 1695, 1640 cm^{-1}.

^{1}H NMR (100 MHz)

8 6.90-6.84 (m, 2H, H-7, H-8), 5.66 (d, *J* = 4.90 Hz, 1H, H-l), 4.76-4.56 (m, 3H, H-2, H-3, H-4), 4.40-4.25 (m, 2H, H-5, H-9), 4.17 (dd, *J* - 8.0, 6.50 Hz, 1H, H-10), 3.67 (dd, *J* - 7.10, 8.0 Hz, 1H, H-10'), 1.50 (s, 3H, CMe_2), 1.41 (s, 9H, CMe_2), 1.34 (s, 3H, CMe_2), 1.30 (s, 3H, CMe_2).

^{13}C NMR (25 MHz)

196.2, 143.4, 125.0, 109.3, 108.5, 107.8, 95.0, 75.0, 73.0, 72.0, 70.2, 70.0, 68.3, 26.0, 25.5 (3C), 24.4, 23.8 ppm.

$[\alpha]_D^{25}$ -99.3° (*c* 0.73).

Anal. Calcd for $C_{19}H_{28}O_8$: C, 59.36; H, 7.34. Found: C, 59.18; H, 7.25.

6,7-Dideoxy-7-(1,2:3,4-di-O-isopropylidene-α-*D*-galactopyranuronyl)-1,2:3,4-di-O-isopropylidene-α-*D*-*galacto*-hept-6*(E)*-enopyranose (102)28 was obtained in 90% yield by the condensation of p-keto phosphonate 97 and **1,2:3,4-di-O-isopropylidene-α-*D*-*galacto*-hexodialdo-1,5-pyranose (13)**[80] (Procedure A).

Syrup; IR (neat) 1700, 1640 cm^{-1}.

^1H NMR (100 MHz)

5 6.90-6.86 (m, 2H, H-7, H-8), 5.62 (d, *J* = 4.0 Hz, 1H), 5.56 (d, *J* = 4.0 Hz, 1H), 4.68-3.66 (m, 8H), 1.50 (s, 3H, CMe_2), 1.43 (s, 3H, CMe_2), 1.36 (s, 18H, CMe_2).

^{13}C NMR (25 MHz)

195.7, 147.4, 125.1, 109.3, 109.0, 108.5, 108.3, 96.1, 73.0, 72.5, 72.0, 71.0, 70.5, 70.4, 70.1, 68.1, 67.5, 61.5, 25.5, 24.4, 24.0 ppm.

$[\alpha]_D^{25}$ -139.4° (c 1.70).

5,6-Dideoxy-6-(1,2:3,4-di-O-isopropylidene-α-*D*-galactopyranuronyl)-3-O-benzyl-1,2-O-isopropylidene-α-*D*-*xylo*-hex-5*(E)*-enofuranose (103)29 was obtained in 91% yield by the condensation of P-keto phosphonate 97 and **3-O-benzyl-1,2-O-isopropylidene-α-*D*-*xylo*-pentodialdo-1,4-furanose (18)**[84] (Procedure A).

Solid; mp 133-34° (hexane-ether).

IR (KBr) 1700, 1640 cm^{-1}.

^1H NMR (100 MHz)

8 7.30-7.20 (m, 5H, Ph), 6.96-6.90 (m, 2H, H-7, H-8), 5.96 (d, *J* = 4.0 Hz, 1H, H-12), 5.62 (d, *J* = 5.0 Hz, 1H, H-1), 4.86-4.28 (m, 9H), 3.95 (d, *J* = 4.0 Hz, 1H),

1.49 (s, 3H, CMe_2), 1.47 (s, 3H, CMe_2), 1 39 (s, 3H, CMe_2), 1.33 (s, 3H, CMe_2), 1.31 (s, 3H, CMe_2), 1.27 (s, 3H, CMe_2).

^{13}C NMR (25 MHz)

211.8, 195.8, 140.6, 137.1, 128.4, 127.9, 127.7, 126.3, 111.7, 109.6, 108.7, 104.9, 96.3, 83.0, 82.8, 79.8, 73.1, 72.1, 70.5, 70.3, 26.6, 26.0, 25.8, 24.6, 24.1 ppm.

$[\alpha]_D^{25}$ -120.0° (c 1.0); lit. $[\alpha]_D^{25}$ -127.0° (c 1.8).

6,7-Dideoxy-7-(3-O-benzyl-1,2-O-isopropylidene-α-*D*-xylofuranuronyl)-1,2:3,4-di-O-isopropylidene-α-*D*-*galacto*-hept-6*(E)*-enopyranose (104) was obtained in 75% yield by the condensation of β-keto phosphonate 98 and 1,2:3,4-di-O-isopropylidene-α-*D*-*galacto*-hexodialdo-1,5-pyranose (13)[80] (Procedure B).

Syrup; IR (neat) 1695, 1630 cm^{-1}.

^1H NMR (200 MHz)

8 7.35-7.15 (m, 5H, Ph), 6.96 (dd, *J* = 3.90, 15.72 Hz, 1H, H-7), 6.80 (dd, *J* = 1.50, 15.73 Hz, 1H, H-6), 6.08 (d, *J* = 3.60 Hz, 1H, H-1), 5.59 (d, *J* =5.0 Hz, 1H, H-12), 4.83 (d, *J* = 3.50 Hz, 1H, H-4), 4.61 (dd, *J* = 2.45, 7.76 Hz, 1H, H-10), 4.57 (d, *J* = 3.60 Hz, 1H, H-2), 4.50 (s, 2H, $PhCH_2$), 4.48-4.42 (m, 1H, H-8), 4.34 (dd, *J* = 5.0, 2.50 Hz, 1H, H-l 1), 4.32 (d, *J* = 3.46 Hz, 1H, H-3), 4.26 (dd, *J* = 2.06, 7.77 Hz, 1H, H-9), 1.49 (s, 3H), 1.46 (s, 3H), 1.40 (s, 3H), 1.35 (s, 3H), 1.33 (s, 3H), 1.30 (s, 3H), 1.26 (s, 3H).

^{13}C NMR (50 MHz)

194.9, 142.0, 137.1, 128.4 (2C), 127.8, 127.7 (2C), 126.1, 112.3, 109.7, 108.7, 105.9, 96.4, 85.1, 83.7, 82.3, 72.8, 72.7, 70.9, 70.6, 67.8, 27.0, 26.4, 26.1, 25.9, 24.9, 24.4 ppm.

$[\alpha]_D^{25}$ -100.6° (*c* 1.60).

Anal. Calcd for $C_{28}H_{36}O_{10}$: C, 63.14; H, 6.81. Found: C, 63.24; H, 6.85.

5,6-Dideoxy-6-(3-O-benzyl-1,2-O-isopropylidene-α-*D*-xylofuranuronyl)-3-O-benzyl-1,2-O-isopropylidene-α-*D-xylo*-hex-5*(E)*-enofuranose (105) was obtained in 79% yield by the condensation of P-keto phosphonate 98 and **3-O-benzyl-1,2-O-isopropylidene-α-*D-xylo*-pentodialdo-1,4-furanose (18)**[84] (Procedure B).

Syrup; IR (neat) 1690, 1625 cnr[1].

^{1}H NMR (200 MHz)

8 7.40-7.15 (m, 10H, Ph), 6.98 (dd, *J* = 4.60, 15.80 Hz, 1H, H-7), 6.83 (dd, *J* = 1.13, 15.85 Hz, 1H, H-6), 6.09 (d, *J* = 3.63 Hz, 1H, H-1), 5.99 (d, *J* = 3.71 Hz, 1H, H-l 1), 4.79 (d, *J* = 3.58 Hz, 1H, H-4), 4.80-4.75 (m, 1H, H-8), 4.62 (d, *J* = 3.96 Hz, 1H), 4.58 (d, *J*= 3.66 Hz, 1H, H-2), 4.49 (s, 2H, $PhCH_2$), 4.45 (d, *J* = 2.47 Hz, 1H), 4.38 (d, *J* = 2.45 Hz, 1H), 4.29 (d, *J* - 3.66 Hz, 1H), 3.95 (d, *J* = 3.28 Hz, 1H).

^{13}C NMR (50 MHz)

195.0, 140.3, 137.1, 136.9, 128.5 (2C), 128.4 (2C), 128.0, 127.9, 127.8 (2C), 127.7 (2C), 127.1, 112.3, 111.9, 105.9, 105.1, 85.1, 83.3, 83.1, 82.9, 82.1, 79.9, 72.2, 26.9(2C), 26.4, 26.3 ppm.

$[\alpha]_D^{25}$ -55.7° (c 1.30).

Anal. Calcd for $C_{31}H_{36}O_9$: C, 67.37; H, 6.57. Found: C, 67.45; H, 6.62.

1,2-Dideoxy-1-(3-O-benzyl-1,2-O-isopropylidene-α-*D*-xylofuranuronyl)-3,4:5,6-di-O-isopropylidene-*arabino*-hex-1*(E)*-enose (106) was obtained in 76% yield by the condensation of P-keto phosphonate 98 and **2,3:4,5-di-O-isopropylidene-*aldehydo-D*-arabinose (95)**[85] (Procedure B).

Syrup; IR (neat) 1700, 1630 cm^{-1}.

^1H NMR (200 MHz)

5 7.30-7.15 (m, 5H, Ph), 7.05 (dd, *J*= 3.90, 16.0 Hz, 1H, H-7), 6.85 (dd, *J* = 1.36, 16.0 Hz, 1H, H-6), 6.10 (d, *J* = 3.59 Hz, 1H, H-1), 4.80 (d, *J* = 3.50 Hz, 1H, H-4), 4.59 (d, *J* =3.50 Hz, 1H, H-3), 4.65-4.40 (m, 3H, $PhCH_2$, H-8), 4.32 (d, *J* =3.58 Hz, 1H, H-2), 4.09 (d, *J* = 5.78 Hz, 1H), 4.20-3.80 (m, 3H), 3.65 (t, *J* = 8.0 Hz, 1H, H-11), 1.47 (s, 3H, CMe_2), 142 (s, 3H, CMe_2), 138 (s, 3H, CMe_2), 1.36 (s, 3H, CMe_2), 1.32 (s, 6H, CMe_2).

^{13}C NMR (50 MHz)

195.8, 144.0, 137.01, 128.5 (2C), 128.0, 127.8 (2C), 125.2, 112.4, 110.3, 109.9, 105.9, 85.2, 83.8, 82.2, 81.3, 79.2, 77.1, 72.5, 67.5, 27.0 (2C), 26.8 (2C), 26.4, 25.3 ppm.

$[\alpha]_D^{25}$ -41.5° (*c* 0.80).

Anal. Calcd for $C_{27}H_{36}O_9$: C, 64.27; H, 7.19. Found: C, 63.28; H, 7.67.

6,7-Dideoxy-7-(2,3:4,5-di-O-isopropylidene-*D*-arabinonyl)-1,2:3,4-di-O-isopropylidene-α-*D*-*galacto*-hept-6*(E)*-enopyranose (107) was obtained in 70% yield by the condensation of P-keto phosphonate 99 and 1,2:3,4-di-O-isopropylidene-α-*D*-*galacto*-hexodialdo-l,5-pyranose (13)80 (Procedure A).

Solid; mp 128° (hexane).

IR(KBr) 1700,1640 cm^{-1}.

^1H NMR (400 MHz)

8 7.00 (dd, *J* = 3.96, 15.60 Hz, 1H, H-6), 6.85 (dd, *J* = 1.91, 15.65 Hz, 1H, H-7), 5.60 (d, *J* = 5.03 Hz, 1H, H-l), 4.65 (dd, *J* = 2.47, 7.77 Hz, 1H, H-3), 4.56 (d, *J* = 5.32 Hz, 1H, H-9), 4.49 (ddd, *J*= 2.0, 1.96, 3.97 Hz, 1H, H-5), 4.36 (dd, *J* =2.42,

4.99 Hz, 1H, H-2), 4.31 (dd, J = 2.16, 7.84 Hz, 1H, H-4), 4.28 (dd, J = 5.40, 7.06 Hz, 1H, H-10), 4.19 (ddd, J = 5.07, 6.32, 7.08 Hz, 1H, H-11), 4.12 (dd, J = 6.28, 8.49 Hz, 1H, H-12), 3.97 (dd, J = 4.89, 8.52 Hz, 1H, H-12'), 155 (s, 3H, CMe_2), 1.52 (s, 3H, CMe_2), 147 (s, 3H, CMe_2), 1.44 (s, 3H, CMe_2), 1.41 (s, 3H, CMe_2), 1.35 (s, 6H, CMe_2), 1.32 (s, 3H, CMe_2).

^{13}C NMR (25 MHz)

197.6, 143.6, 126.1, 112.0, 110.3, 110.1, 109.1,96.8, 83.0, 78.8, 77.5, 73.0, 71.2, 70.9, 68.1, 67.1, 27.6, 26.8, 26.7, 26.4, 26.2, 25.5, 25.1, 24.8 ppm.

$[\alpha]_D^{25}$ -65.00 (c o.6O).

Anal. Calcd for $C_{24}H_{36}O_{10}$: C, 59.49; H, 7.49. Found: C, 59.56; H, 7.54.

1,2-Dideoxy-1-(2,3:4,5-di-O-isopropylidene-*D*-arabinonyl)-3,4-O-isopropylidene-*D*-*glycero*-tetr-1*(E)*-enose (108) was obtained in 76% yield by the condensation of β-keto phosphonate 99 and 2,3-O-isopropylidene-*D*-glyceraldehyde (25)[101] (Procedure A).

Syrup; IR (neat) 1700, 1630 cm^{-1}.

^{1}H NMR (100 MHz)

8 6.91-6.78 (m, 2H, H-6, H-7), 4.67 (dt, J = 4.0, 6.60 Hz, 1H), 4.50 (d, J = 5.0 Hz, 1H), 4.31-3.81 (m, 4H), 3.65 (dd, J = 7.70 Hz, 2H), 1.43 (s, 6H), 1.39 (s, 6H), 1.32 (s, 6H).

^{13}C NMR (25 MHz)

197.4, 144.8, 125.5, 111.5, 110.2, 109.8, 82.2, 78.2, 76.4, 75.1, 68.6, 66.6, 27.0, 26.3 (2C), 26.1, 25.5, 25.0 ppm.

$[\alpha]_D^{25}$ +26.8° (c 1.0).

Anal. Calcd for $C_{18}H_{28}O_7$: C, 60.66; H, 7.92. Found: C, 60.55; H, 7.85.

5,6-Dideoxy-6-(2,3:4,5-di-O-isopropylidene-*D*-arabinonyl)-3-O-benzyl-1,2-O-isopropylidene-α-*D*-*xylo*-hex-5*(E)*-enofuranose (109) was obtained in 91% yield by the condensation of β-keto phosphonate 99 and 3-O-benzyl-1,2-O-isopropylidene-α-*D*-*xylo*-pentodialdo-1,4-furanose (18)[84] (Procedure A).

Syrup; IR (neat) 1680, 1625 cm^{-1}.

^1H NMR (100 MHz)

δ 7.32-7.16 (m, 5H, Ph), 6.96-6.88 (m, 2H, H-5, H-6), 5.94 (d, J = 4.0 Hz, 1H, H-1), 4.84-4.76 (m, 1H, H-4), 4.68-4.44 (m, 4H), 4.38-3.88 (m, 5H), 1.48 (s, 3H, CMe2), 1.44 (s, 3H, CMe_2), 1.39 (s, 3H, CMe_2), 1.32 (s, 9H, CMe_2).

^{13}C NMR (25 MHz)

197.0, 141.7, 137.1, 128.6 (2C), 128.1, 127.8 (2C), 126.5, 112.0, 111.6, 109.9, 105.0, 82.9, 82.8, 82.4, 79.9, 78.3, 76.7, 72.3, 66.8, 27.3, 26.9, 26.6, 26.4 (2C), 25.3 ppm.

$[\alpha]_D^{25}$ -10.9° (*c* 1.10).

Anal. Calcd for $C_{27}H_{36}O_9$: C, 64.27; H, 7.19. Found: C, 64.62; H, 7.19.

1,2-Dideoxy-1-(2,3:4,5-di-O-isopropylidene-*D*-arabinonyl)-3,4:5,6-di-O-isopropylidene-*D*-*arabino*-hex-1*(E)*-enose (110) was obtained in 65% yield by the condensation of p-keto phosphonate 99 and 2,3:4,5-di-O-isopropylidene-*aldehydo*-*D*-arabinose (95)[85] (Procedure A).

Solid; mp 90-91° (hexane).

IR(KBr) 1700, 1630 cm^{-1}.

^1H NMR (400 MHz)

δ 7.10 (dd, J= 4.30, 15.50 Hz, 1H, H-7), 6.86 (dd, J = 1.50, 15.60 Hz, 1H, H-6), 4.58 (ddd, J = 1.40, 4.20, 7.80 Hz, 1H, H-8), 4.53 (d, J =5.60 Hz, 1H, H-4), 4.30

(dd, J = 5.20, 6.70 Hz, 1H), 4.20 (m, 1H), 4.14-4.08 (m, 2H), 4.12 (d, J = 5.60 Hz, 1H), 3.97 (dd, J = 8.80, 4.88 Hz, 1H), 3.94 (dd, J = 3.30, 7.77 Hz, 1H), 3.68 (dd, J =7.77, 7.77 Hz,1H), 1.47 (s, 3H, CMe_2), 1.44 (s, 3H, CMe_2), 1.42 (s, 3H, CMe2), 141 (s, 3H, CMe_2), 140 (s, 3H, CMe_2), 135 (s, 9H, CMe_2).

^{13}C NMR (25 MHz)

197.3, 145.1, 125.0, 110.8, 110.0, 109.8 (2C), 82.2, 81.2, 79.3, 78.2, 77.0, 76.5, 67.5, 66.7, 27.1, 26.8, 26.6 (3C), 26.4, 25.1 (2C) ppm.

$[\alpha]_D^{25}$ +7.0° (c 1.40).

Anal. Calcd for $C_{23}H_{36}O_9$: C, 60.50; H, 7.95. Found: C, 60.35; H, 7.98.

Dienone 114 was obtained in 54% yield by the condensation of P-keto phosphonate **113** and 1,2:3,4-di-O-isopropylidene-α-*D-galacto*-hexodialdo-1,5-pyranose **(13)**[80] (Procedure C).

Solid; mp 194° (hexane-chloroform).

IR (KBr) 1690,1660 cm^{-1}.

^1H NMR (200 MHz)

δ 7.02 (dd, J = 4.15, 15.65 Hz, 2H, H-6), 6.15 (dd, J = 1.94, 15.64 Hz, 2H, H-7), 5.61 (d, J =5.01 Hz, 2H, H-1), 4.65 (dd, J = 2.46, 7.74 Hz, 2H, H-3), 4.51-4.45 (m, 2H, H-5), 4.36 (dd, J = 2.50, 5.02 Hz, 2H, H-2), 4.31 (dd, J = 2.09, 7.77 Hz, 2H, H-4), 1.52 (s, 6H, CMe_2), 143 (s, 6H, CMe_2), 1.35 (s, 6H, CMe_2), 133 (s, 6H, CMe_2).

^{13}C NMR (50 MHz)

170.9, 145.5, 121.7, 109.9, 108.9, 96.5, 72.7, 71.0, 70.6, 67.5, 26.1, 26.0, 24.9, 24.6 ppm.

$[\alpha]_D^{25}$ -128.0° (c 0.80).

Anal. Calcd for $C_{33}H_{46}O_{14}$: C, 59.45; H, 6.95. Found: C, 59.32; H, 6.90.

Dienone **115** was obtained in 44% yield by the condensation of P-keto phosphonate **113** and 3-O-benzyl-1,2-O-isopropylidene-α-*D-xylo*-pentodialdo-1,4-furanose **(18)**[84] (Procedure C).

Syrup; IR (neat) 1690, 1630 cm^{-1}.

^1H NMR (200 MHz)

δ 7.40-7.20 (m, 10H, Ph), 7.08 (dd, *J* = 4.75, 15.81 Hz, 2H, H-5), 6.82 (dd, *J*= 1.58, 15.81 Hz, 2H, H-6), 6.01 (d, *J*= 3.77 Hz, 2H, H-1), 4.88 (s, 2H, H-8), 4.88-4.80 (m, 2H, H-4), 4.65 (d, *J* = 3.92 Hz, 2H, H-2), 4.60 (d, *J* = 12.60 Hz, 2H, $PhCH_2$), 4.47 (d, *J* = 12.04 Hz, 2H, $PhCH_2$), 4.01 (d, *J*= 3.24 Hz, 2H, H-3), 1.50 (s, 6H, CMe_2), 136 (s, 6H, CMe_2), 1.33 (s, 6H, CMe_2).

^{13}C NMR (50 MHz)

196.1, 142.5, 137.2, 128.6 (2C), 128.1, 127.8 (2C), 126.6, 113.0, 112.1, 105.2, 83.4, 83.0, 81.1, 80,0, 72.4, 26.9, 26.4, 26.3 ppm.

$[\alpha]_D^{25}$ -33.0° (*c* 0.65).

Anal. Calcd for $C_{39}H_{46}O_{12}$: C, 66.27; H, 6.56. Found: C, 66.35; H, 6.58.

Dienone **116** was obtained in 54% yield by the condensation of P-keto phosphonate **113** and 2,3:4,5-di-O-isopropylidene-*aldehydo-D*-arabinose **(95)**[85] (Procedure C).

Solid; mp 120-23° (hexane).

IR(KBr) 1620,1665 cm^{-1}.

^1H NMR (200 MHz)

δ 7.12 (dd, *J* = 4.30, 15.64 Hz, 2H, H-5), 6.18 (dd, *J* = 1.67, 15.68 Hz, 2H, H-6), 4.57 (ddd, *J* = 1.69, 4.32, 7.86 Hz, 2H, H-4), 4.18-4.05 (m, 4H), 4.02-3.92 (m,

2H), 3.68 (dd, J = 7.82 Hz, 2H), 1.43 (s, 6H, CMe_2), 1.41 (s, 12H, CMe_2), 1.35 (s, 6H, CMe_2).

^{13}C NMR (50 MHz)

171.2, 147.8, 120.7, 110.6, 110.0, 81.3, 79.1, 77.1, 67.7, 27.0, 26.8, 26.7, 25.2 ppm.

$[\alpha]_D^{25}$ -6.9° (c 1.0).

Anal. Calcd for $C_{31}H_{46}O_{12}$: C, 60.97; H, 7.59. Found: C, 60.85; H, 7.55.

Cross-conjugated enone **119** was obtained in 80% yield by the condensation of β-keto phosphonate 87 and *p*-anisaldehyde (Procedure D).

Syrup; IR (neat) 1660, 1625 cm^{-1}.

^1H NMR (200 MHz)

8 7.80 (d, J = 15.80 Hz, 1H, H-8), 7.60 (d, J = 8.90 Hz, 1H, Ph), 7.25 (d, J = 15.46 HA 1H, H-7), 6.95 (d, J = 8.80 Hz, 1H, Ph), 6.17 (d, J = 3.06 Hz, 1H, H-4), 5.17 (d, J = 2.45 Hz, 1H, H-1), 4.16 (dd, J = 3.02, 7.34 Hz, 1H, H-3), 3.88 (s, 3H, PhOMe), 3.60 (s, 6H, OMe), 3.57 (d, J = 2.43 Hz, 1H, H-2), 3.54 (s, 3H, OMe).

^{13}C NMR (25 MHz)

184.8, 162.0, 151.0, 148.0, 145.1, 130.5 (2C), 127.4, 117.6, 114.4 (2C), 107.8, 99.1, 78.8, 74.6, 58.8, 56.8 (2C), 55.3 ppm.

$[\alpha]_D^{25}$ +158.1° (c 1.0).

Anal. Calcd for $C_{18}H_{22}O_6$: C, 64.65; H, 6.63. Found: C, 64.45; H, 6.62.

Cross-conjugated enone 120 was obtained in 90% yield by the condensation of p-keto phosphonate 87 and benzaldehyde (Procedure D).

Syrup; IR (neat) 1660, 1630, 1600 cm^{-1}.

^1H NMR (200 MHz)

8 7.77 (d, J = 15.50 Hz, 1H, H-8), 7.62-7.54 (m, 2H, Ph), 7.39-7.35 (m, 3H, Ph), 7.32 (d, J = 15.50 Hz, 1H, H-7), 6.14 (d, J = 3.05 Hz, 1H, H-4), 5.12 (d, J = 2.48 Hz, 1H, H-1), 4.12 (dd, J = 3.06, 7.10 Hz, 1H, H-3), 3.55 (s, 3H, OMe), 3.54 (s, 3H, OMe), 3.51 (d, J = 2.45 Hz, 1H, H-2), 3.48 (s, 3H, OMe).

^{13}C NMR (50 MHz)

184.6, 147.8, 145.0, 134.7, 130.8, 129.0 (2C), 128.6 (2C), 120.1, 108.2, 99.2, 77.9, 74.7, 58.9, 57.1, 56.9 ppm.

$[\alpha]_D^{25}$ +169.0° (c 1.0).

Anal. Calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 66.85; H, 6.59.

Cross-conjugated enone 121 was obtained in 86% yield by the condensation of β-keto phosphonate 87 and isobutyraldehyde (Procedure D).

Syrup; IR (neat) 1670, 1615 cm^{-1}.

^1H NMR (100 MHz)

8 7.05 (dd, J = 6.40, 15.50 Hz, 1H, H-8), 6.68 (dd, J = 15.50, 1.50 Hz, 1H, H-7), 6.07 (d, J = 3.40 Hz, 1H, H-4), 5.12 (d, J = 2.30 Hz, 1H, H-1), 4.12 (dd, J = 3.40, 7.20 Hz, 1H, H-3), 3.60 (s, 3H, OMe), 3.59 (s, 3H, OMe), 3.52 (s, 3H, OMe), 3.60-3.45 (m, 1H, H-2), 2.68-2.36 (m, 1H, H-9), 1.12 (d, J = 7.0 Hz, 6H, CMe_2).

^{13}C NMR (50 MHz)

185.0, 156.3, 147.6, 121.0, 108.2, 99.0, 77.8, 74.6, 58.8, 57.1, 56.8, 31.4, 21.2 (2C)ppm.

$[\alpha]_D^{25}$ +187.0° (c 0.75).

Anal. Calcd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20. Found: C, 62.15; H, 8.18.

Enone **123** was obtained in 25% yield by the condensation of p-keto phosphonate 87 and cyclohexanone **122** (Procedure A).

^{1}H NMR (100 MHz)

8 7.27 (s, 5H, Ph), 6.13 (s, 1H, H-7), 4.85 (d, *J* = 4.0 Hz, 1H, H-1), 4.73 (d, *J* = 11.0 Hz, 1H, PhCH2), 4.53 (d, *J* = 11.0 Hz, 1H, $PhCH_2$), 4.10 (d, *J* =9.0 Hz, 1H, H-5), 4.75-4.05 (m, 2H), 4.25-3.95 (m, 1H), 3.62 (s, 3H, OMe), 3.53 (s, 3H, OMe), 3.43 (s, 3H, OMe), 2.25-1.15 (m, 10H, cyclohexyl).

6C-(1,2:3,4-Di-O-isopropylidene-α-*D*-galactopyranuronyl)-3-O-benzyl-1,2-O-isopropylidene-*D*-glycero-α-*L*-ido- and **-*L*-glycero-β-*D*-gluco-hexofuranoses** (124) and **(125).**

To a solution of **103**[29] (533 mg, 1.0 mmol) in 6 ml of 8:1 acetone-water mixture, NMO.H_2O (235 mg, 2.0 mmol), followed by a solution of OsO_4 in /-BuOH (0.5 ml of *I*-BuOH containing 14 mg of OsO_4) were added and stirred under dark for 8 h. The reaction mixture was diluted with 50 ml of $CHCl_3$ and shaken vigorously with 3.2 ml of 45% aq $NaHSO_3$ solution for 20 min. The organic layer was separated, dried, evaporated and the residue purified by column chromatography on silica gel using 30% ethyl acetate in hexane to afford the less polar 124 and the more polar 125 in a ratio of 1.7:1, in an over all yield of 91% (516 mg).

Less polar **diastereomer 124.**

Amorphous solid.

IR(KBr) 3470, 1730 cm^{-1}.

^{1}H NMR (500 MHz)

8 7.35-7.29 (m, 5H, Ph), 6.00 (d, *J* = 3.77 Hz, 1H, H-12), 5.65 (d, *J* = 4.88 Hz, 1H, H-1), 4.81 (d, *J*= 6.30 Hz, 1H, H-7), 4.73 (dd, *J* = 7.77, 1.98 Hz, 1H, H-4), 4.74 (s, 1H, H-10), 4.68 (d, *J* = 11.64 Hz, 1H, $PhCH_2$), 4.64 (dd, *J*= 2.52, 7.87 Hz, 1H, H-3), 4.61 (d, *J* = 11.61 Hz, 1H, $PhCH_2$), 4.61 (d, *J* =3.82 Hz, 1H, H-11), 4.53 (d, *J*= 1.88 Hz, 1H, H-5), 4.34 (dd, *J* =2.53, 4.87 Hz, 1H, H-2), 4.28 (dd, *J* = 3.19, 6.35 Hz, 1H, H-8), 4.24 (d, *J* = 3.19 Hz, 1H, H-9), 1.50 (s, 3H, CMe_2), 1.43 (s, 3H, CMe_2), 139 (s, 3H, CMe_2), 133 (s, 6H, CMe_2), 1.30 (s, 3H, CMe_2).

^{13}C NMR (25 MHz)

207.6, 137.4, 128.4, 127.7, 111.7, 109.7, 109.0, 104.7, 96.4, 82.4, 79.1, 76.2, 72.3, 72.0, 71.7, 70.3, 68.5, 26.6, 26.1, 25.6, 24.5, 24.0 ppm.

$[\alpha]_D^{25}$ -106.0° (*c* 1.0).

Anal. Calcd for $C_{28}H_{38}O_{12}$: C, 59.35; H, 6.76. Found: C, 59.40; H, 6.80.

More polar **diastereomer 125.**

Amorphous solid.

IR(KBr) 3470,1730 cm^{-1}.

^{1}H NMR (500 MHz)

8 7.41-7.30 (m, 5H, Ph), 5.96 (d, *J* = 3.84 Hz, 1H, H-12), 5.36 (d, *J* = 5.00 Hz, 1H, H-l), 4.71 (d, *J* = 11.43 Hz, 1H, $PhCH_2$), 4.67 (d, *J*= 3.71 Hz, 1H, H-11), 4.66 (d, *J*= 1.95 Hz, 1H), 4.65 (d, *J* =2.09 Hz, 1H), 4.61 (dd, *J*= 2.13, 7.24 Hz, 1H, H-3), 4.59 (d, *J* - 3.09 Hz, 1H), 4.58 (dd, *J* - 2.45, 4.98 Hz, 1H), 4.53 (d, *J* = 11.42 Hz, 1H, $PhCH_2$), 4.37 (dd, *J* = 3.18, 7.22 Hz, 1H, H-4), 4.29 (dd, *J* =2.39, 4.97 Hz, 1H, H-2), 4.10 (d, *J* =3.19 Hz, 1H, H-5), 1.51 (s, 3H, CMe_2), 1.49 (s,

3H, CMe_2), 146 (s, 3H, CMe_2), 1.33 (s, 3H, CMe_2), 1.32 (s, 3H, CMe_2), 126 (s, 3H, CMe_2).

^{13}C NMR (25 MHz)

206.7, 137.0, 128.5, 128.1, 127.8, 111.8, 110.0, 108.8, 104.8, 96.2, 81.8, 81.2, 80.2, 77.3, 76.0, 73.0, 72.1, 71.6, 70.5, 70.2, 69.8, 26.7, 26.2, 25.8, 25.1, 24.6, 23.8 ppm.

$[\alpha]_D^{25}$ -49.0° (*c* 1.0).

Anal. Calcd for $C_{28}H_{38}O_{12}$: C, 59.35; H, 6.76. Found: C, 59.25; H, 6.72.

Reduction of 124 using $NaBH_4$ or $Zn(BH_4)_2$.

1. With $NaBH_4$.

To a solution of 124 (114 mg, 0.20 mmol) in a 1:1 THF-MeOH mixture (5 ml) at 0°, $NaBH_4$ (30 mg, 0.8 mmol) was added slowly and the reaction allowed to proceed at 0° for 3 h. The reaction mixture was diluted with 20 ml of $CHCl_3$ and washed with 7 ml of 5% aq citric acid solution. The organic layer was separated, dried and evaporated to afford 97 mg of the diastereomeric reduction products **126** in 85% yield.

Amorphous solid.

IR(neat) 3420 cm^{-1}.

^1H NMR (100 MHz)

5 7.31 (s, 5H, Ph), 5.91 (d, *J* = 4.0 Hz, 1H, H-12), 5.61-5.41 (m, 1H, H-1), 4.73-3.83 (m, 12H), 1.52 (s, 3H, CMe_2), 1.49 (s, 3H, CMe_2), 1.45 (s, 3H, CMe_2), 1.33 (s, 3H, CMe_2).

2. With $Zn(BH_4)_2$ at 0°.

To a solution of 124 (57 mg, 0.10 mmol) in ether (2 ml) at 0° , an ethereal solution of $Zn(BH_4)_2$ (0.50 mmol) was added dropwise and stirred at 0° for 20 min. The reaction mixture was quenched with 0.5 ml of saturated aq NH_4Cl solution and extracted with CH_2Cl_2. The CH_2Cl_2 extract was dried and evaporated to obtain the reduction products 126 in quantitative yield.

3. With $Zn(BH_4)_2$ at -78° .

This is identical to the above procedure, except that the reaction was conducted at -78° and stirred for 1 h.

Benzoylation of 126.

To a solution of crude 126 (obtained from $Zn(BH_4)_2$ reduction of 124) (114 mg, 0.20 mmol) in pyridine (1.5 ml) at 0°, DMAP (15 mg) was added and stirred. BzCl (0.7 ml, 6.0 mmol) was added dropwise and the reaction mixture stirred at rt for 20 h. The reaction mixture was cooled to 0° and quenched with 0.5 ml of chilled saturated aq K_2CO_3 solution and extracted with CH_2Cl_2 (20 ml). The CH_2Cl_2 extract was dried, evaporated and the residue purified by column chromatography on silica gel using 10% ethyl acetate in hexane to render 150 mg of 127 (85%).

Fluffy material.

IR (KBr) 1730 cm^{-1}.

^1H NMR (100 MHz)

δ 8.14-6.90 (m, 20H, Ph), 6.28-5.84 (m, 4H), 5.60 (d, J = 5.0 Hz, H-1), 5.46 (d, J = 5.0 Hz, H-1'), 4.74-4.00 (m, 9H), 1.55 (s, 3H, CMe_2), 143 (s, 3H, CMe_2), 1.33 (s, 3H, CMe_2), 127 (s, 3H, CMe_2), 1.17 (s, 3H, CMe_2).

Hydrogenolysis of **127.**

To a solution of 127 (132 mg, 0.15 mmol) in 5.3 ml of dry ethanol, 132 mg of Pd/C (10%) was added. The reaction mixture was shaken under 40 psi pressure of H_2 in a Parr apparatus for 6 h. The reaction mixture was filtered and washed with ethyl acetate (15 ml). The ethyl acetate extract was evaporated and the residue chromatographed on a silica gel column using 15% ethyl acetate in hexane, to afford two diastereomers of 128 in a 1:2 ratio of less and more polar products, respectively, in 85% yield (100 mg).

Less polar diastereomer.

Amorphous solid.

IR (KBr) 3440,1730 cm^{-1}.

^1H NMR (100 MHz)

8 8.14-7.14 (m, 15H, Ph), 6.29 (dd, J = 2.09, 6.25 Hz, 1H, H-7), 5.94-5.64 (m, 3H, H-6, H-8, H-12), 5.36 (d, J = 5.0 Hz, H-1), 4.64-4.42 (m, 3H), 4.30-3.94 (m, 4H), 1.46 (s, 3H, CMe2), 135 (s, 6H, CMe_2), 1.20 (s, 6H, CMe_2), 0.98 (s, 3H, CMe_2).

^{13}C NMR (25 MHz)

167.7, 165.8, 165.1, 133.7, 133.1, 132.9, 130.1, 129.9, 129.8, 129.0, 128.5, 128.4, 128.2, 111.7, 110.0, 108.6, 104.7, 96.2, 84.3, 78.5, 77.3, 73.7, 72.0, 71.1, 70.9, 70.7, 70.1, 66.9, 26.2, 26.1, 25.8, 25.7, 24.8, 24.1 ppm.

More polar diastereomer.

Solid; mp 190° (MeOH-H_2O).

IR (KBr) 3420,1725 cm^{-1}.

^1H NMR (500 MHz)

5 8.08 (d, J = 7.0 Hz, 2H, Bz), 7.92 (d, J = 7.50 Hz, 2H, Bz), 7.70 (d, J = 7.50 Hz, 2H, Bz), 7.54 (t, J = 7.75 Hz, 1H, Bz). 7.45 (t, J= 7.50 Hz, 1H, Bz), 7.42 (t, J = 7.50 Hz, 2H, Bz), 7.37 (t, J =7.75 Hz, 1H, Bz), 7.23 (t, J= 7.75 Hz, 2H, Bz), 7.13 (t, J = 7.75 Hz, 2H, Bz), 6.15 (dd, J = 2.0, 3.50 Hz, 1H, H-8), 6.00 (dd, J = 3.75, 8.25 Hz, 1H, H-7), 5.91 (dd, J =2.0, 8.50 Hz, 1H, H-6), 5.91 (d, J = 3.0 Hz, 1H, H-12), 5.60 (d, J= 5.50 Hz, 1H, H-1), 4.60 (dd, J = 7.75, 2.25 Hz, 1H, H-3), 4.50 (d, J= 3.50 Hz, 1H, H-l 1), 4.35 (dd, J =2.0, 5.0 Hz, 1H, H-9), 4.29 (dd, J = 1.75, 7.25 Hz, 1H, H-4), 4.27 (dd, J = 2.50, 5.50 Hz, 1H, H-2), 4.25 (dd, J =5.50, 2.0 Hz, 1H, H-5), 4.06 (bs, 1H, H-10), 1.58 (s, 3H, CMe_2), 1.44 (s, 3H, CMe_2), 1.33 (s, 3H, CMe_2), 122 (s, 3H, CMe_2), 1.20 (s, 3H, CMe_2), 1.16 (s, 3H, CMe_2).

^{13}C NMR (25 MHz)

167.1, 165.3, 165.0, 133.5, 132.9, 132.7, 130.1, 129.9, 129.7, 129.0, 128.3, 128.0, 111.8, 109.7, 108.8, 104.8, 96.4, 84.4, 78.6, 73.9, 71.2, 70.8, 70.5, 70.4, 69.1, 66.6, 26.4, 26.2, 25.8, 25.7, 24.7, 24.4 ppm.

Degradation of **128.**

Procedure A.

A solution of 128 (40 mg, 0.05 mmol) (more polar diastereomer of 128, mp 190°) in 2 ml of 9:1 TFA-H_2O mixture was allowed to stand at rt for 20 min. The reaction mixture was evaporated under reduced pressure with occasional addition of water. The residue was dissolved in a 2:1 ether-water mixture (30 ml) and 50 mg of $NaHCO_3$ was added and stirred. $NaIO_4$ (500 mg) was added and the mixture vigorously stirred for 2 h. The organic layer was separated, dried, evaporated and the residue reduced with $NaBH_4$ (40 mg) in a 1:1 THF-MeOH mixture (1 ml) at 0° for 2 h. The reaction mixture was

quenched with aq citric acid and extracted with 20 ml of $CHCl_3$. The $CHCl_3$ extract was dried, evaporated and the residue benzoylated using BzCl (140 mg) and pyridine (0.5 ml) in the presence of catalytic amount of DMAP for 18 h. The reaction mixture was cooled to 0° and quenched with chilled aq K_2CO_3 solution and extracted with CH_2Cl_2. The CH_2Cl_2 extract was dried, evaporated and the residue purified by column chromatography on silica gel using 10% ethyl acetate in hexane. A complex mixture was obtained, from which the required perbenzoylated pentitols could not be isolated.

Procedure B.

A solution of 128 (40 mg, 0.05 mmol) in a 1:1:1 THF-AcOH-H_2O mixture (5 ml) was refluxed for 8 h. The reaction mixture was cooled to 0°, diluted with 50 ml of ether and neutralized with 5% aq $NaHCO_3$ solution (50 ml). To the reaction mixture, NaIO4 (1 g) was added and the contents stirred vigorously for 2 h. The organic layer was separated, dried, evaporated and the residue reduced with BH_3:THF (3.50 mmol) in 2 ml of THF at 0° for 2 h. The reaction mixture was quenched with 0.2 ml of water and extracted with CH_2Cl_2. The CH_2Cl_2 extract was dried, evaporated and the residue benzoylated using BzCl (140 mg) and pyridine (0.5 ml) in the presence of catalytic amount of DMAP for 18 h. The reaction mixture was cooled to 0° and quenched with chilled aq K_2CO_3 solution and extracted with CH_2Cl_2. The CH_2Cl_2 extract was dried, evaporated and the residue purified by column chromatography on silica gel using 10% ethyl acetate in hexane. A complex benzoylated product mixture was obtained as evidenced by its ^1H NMR, from which information pertaining to its structure could not be obtained.

Reduction of 125, when carried out with $NaBH_4$ using the same procedure as described for **124,** yielded the reduction product **131** in 95% yield.

Amorphous solid.

IR(KBr) 3400 cm^{-1}.

Tribenzoyl derivative 132 was prepared from **131** in 95% yield using the same procedure as described for **127**.

Amorphous solid.

IR(KBr) 1725 cm^{-1}.

^1H NMR (500 MHz)

8 8.09 (d, *J* = 7.50 Hz, 2H, Bz), 7.99 (d, *J* = 7.31 Hz, 2H, Bz), 7.66 (d, *J* = 7.43 Hz, 2H, Bz), 7.57 (t, *J*= 7.29 Hz, 1H, Bz), 7.50-7.27 (m, 11H, Ph), 7.07 (t, *J* = 7.75 Hz, 2H, Bz), 6.16 (dd, *J* = 1.24, 8.68 Hz, 1H, H-8), 6.14 (dd, *J*= 1.26,6.11 Hz, 1H, H-7), 5.88 (d, *J* = 3.80 Hz, 1H, H-12), 5.83 (t, *J* = 6.28 Hz, 1H, H-6), 5.46 (d, *J* = 5.15 Hz, 1H, H-1), 4.86 (d, *J* = 11.80 Hz, 1H, $PhCH_2$), 4.73 (d, *J* = 11.83 Hz, 1H, $PhCH_2$), 4.56 (d, *J* = 3.80 Hz, 1H, H-l 1), 4.43 (dd, *J*= 3.59, 8.65 Hz, 1H, H-9), 4.39 (dd, *J*= 1.36, 7.77 Hz, 1H, H-4), 4.35 (d, *J* =3.56 Hz, 1H, H-10), 4.29 (dd, *J* = 2.24, 7.70 Hz, 1H, H-3), 4.25-4.15 (m, 2H, H-2, H-5), 1.41 (s, 3H, CMe2), 130 (s, 3H, CMe_2), 126 (s, 6H, CMe_2), 1.23 (s, 3H, CMe_2), 106 (s, 3H, CMe_2).

^{13}C NMR (25 MHz)

166.0, 165.4, 137.5, 133.1, 132.9, 132.2, 130.4, 130.0, 129.7, 128.5, 128.1, 127.8, 127.7, 127.3, 111.5, 109.7, 108.4, 104.9, 96.4, 82.8, 82.4, 79.4, 71.7, 71.0, 70.7, 69.8, 69.6, 66.2, 26.5, 26.2, 25.8, 25.3, 24.5, 24.4 ppm.

$[\alpha]_D^{25}$ -11.0° (*c* 1.0).

Hydrogenolysis of 132 was carried out with 10% Pd/C and H_2 using the same procedure as described for **128**, affording 133 in 87% yield.

IR, 3450, 1725 cm"'.

^{1}H NMR (100 MHz)

8 8.04-6.90 (m, 15H, Ph), 6.10-5.68 (m, 4H, H-6, H-7, H-8, H-12), 5.40 (d, *J* = 5.0 Hz, 1H, H-1), 4.50-4.10 (m, 7H), 2.76 (bs, 1H, OH), 1.38 (s, 3H, CMe_2), 124 (s, 3H, CMe2), 123 (s, 3H, CMe_2), 1.20 (s, 3H, CMe_2), 1.15 (s, 6H, CMe_2).

^{13}C NMR (25 MHz)

166.1, 165.7, 165.3, 133.3, 132.8, 132.4, 130.0, 129.7, 128.4, 128.1, 127.8, 111.4, 109.5, 108.5, 104.5, 96.2, 85.7, 79.5, 77.3, 74.9, 71.7, 71.0, 70.6, 70.3, 69.9, 66.6, 26.4, 26.0, 25.6, 25.4, 24.6, 23.9 ppm.

$[\alpha]_D^{25}$ -27.50 (c 2.55).

Degradation of 133 was carried out using procedure A as described for 128. A complex mixture was obtained, from which the required perbenzoylated pentitols could not be isolated.

***5(E)*-3-O-benzyl-1,2-O-isopropylidene-5,6,7,8-tetradeoxy-α-*D-xylo*-oct-5,7-dienofuranose (137).**

To a slurry of $Ph_3P^+CH_3I^-$ (1050 mg, 2.60 mmol) in dry THF (10 ml) at -10°, a solution of *n*-BuLi (2.40 mmol) in hexane was added dropwise and stirred at -10° for 30 min. To the stirring reaction mixture, a solution of 136[95] (609 mg, 2.0 mmol) in 10 ml of THF was added dropwise and stirred for another 2 h at 0°. The reaction mixture was

quenched with 8 ml of water and extracted with CH_2Cl_2. The CH_2Cl_2 extract was dried, evaporated and the crude product purified on a silica gel column using 10% ethyl acetate in hexane to afford 424 mg of 137 (70%).

Syrup; IR (neat) 1600 cm^{-1}.

^1H NMR (200 MHz)

6 7.30-7.20 (m, 5H, Ph), 6.45-6.20 (m, 2H, H-6, H-7), 5.89 (d, J = 3.81 Hz, 1H, H-1), 5.85-5.65 (m, 1H, H-5), 5.25-5.05 (m, 2H, H-8, H-8'), 4.59 (dd, J = 3.15, 7.45 Hz, 1H, H-4), 4.57 (d, J = 12.10 Hz, 1H, $PhCH_2$), 4.56 (d, J = 4.85 Hz, 1H, H-2), 4.46 (d, J = 12.10 Hz, 1H, $PhCH_2$), 3.80 (d, J = 3.26 Hz, 1H, H-3), 1.43 (s, 3H, CMe_2), 1.25 (s, 3H, CMe_2).

^{13}C NMR (25 MHz)

137.6, 136.3, 134.7, 128.4, 127.8, 127.6, 127.3, 118.3, 111.5, 101.8, 83.5, 83.0, 80.8, 72.1, 26.7, 26.1 ppm

$[\alpha]_D^{25}$ -74.0° (c 1.0).

Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.34. Found: C, 71.28; H, 7.32.

***3(E)*-5,6:7,8-di-O-isopropylidene-1,2,3,4-tetradeoxy-*arabino*-octa-1,3-dienose** (140) was prepared from 139[96] in 80% yield using the same procedure as described for 137.

Syrup; IR (neat) 1600 cm^{-1}.

^1H NMR (200 MHz)

6 6.50-6.20 (m, 2H, H-2, H-3), 5.72 (dd, J = 6.65, 14.15 Hz, 1H, H-4), 5.23 (d, J = 14.70 Hz, 1H, H-1), 5.12 (d, J = 8.11 Hz, 1H, H-1'), 4.40 (t, J = 7.05 Hz, 1H), 4.20-3.85 (m, 3H), 3.70 (t, J = 7.24 Hz, 1H), 1.41 (s, 6H, CMe_2), 1.39 (s, 3H, CMe_2), 1.33 (s, 3H, CMe_2).

^{13}C NMR (50 MHz)

136.2, 133.3, 130.9, 118.2, 109.7, 109.5, 81.3, 79.8, 76.7, 67.0, 27.0, 26.7, 25.3 ppm.

$[\alpha]_D^{25}$ +6.0° (*c* 1.0).

Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72. Found: C, 66.17; H, 8.75.

Hydroxylation of 137.

To a solution of **137** (605 mg, 2.0 mmol) in a 8:1 acetone-water mixture (22 ml), NMO.H_2O (1080 mg, 8.0 mmol) was added and stirred. To the stirring reaction mixture, OsO_4 (56 mg of OsO_4 in 2.2 ml of *t*-BuOH) was added dropwise and the reaction continued in the dark for 12 h. The reaction mixture was diluted with $CHCl_3$ (385 ml) and shaken vigorously with 14 ml of 45% aq $NaHSO_3$ solution for 10 min. The $CHCl_3$ layer was separated, dried and evaporated to afford 741 mg of crude tetrol **138** (90%).

Hydroxylation of **140** was carried out using the same procedure as described for **138,** to afford the crude tetrol **141** in 95% yield.

Attempted synthesis of **tetra-O-acetyl-*aldehydo*-pentose 144** from **138.**

Tetra-O-acetyl derivative 142.

To a solution of the crude product **138** (185 mg, 0.50 mmol) in pyridine (1.7 ml), acetic anhydride (1.4 ml) was added dropwise and the contents heated to 100° for 3 h. The reaction mixture was quenched with 5 ml of cold water and extracted with CH_2Cl_2. The CH_2Cl_2 extract was dried and concentrated under reduced pressure with addition of toluene (5 ml) to remove any trace of pyridine. The residue was purified on a silica gel

column using 10% ethyl acetate in hexane to afford 188 mg of 142 in 70% yield (based on crude 138).

^{1}H NMR (200 MHz)

8 7.40-7.25 (m, 5H, Ph), 5.92 (d, J = 3.80 Hz), 5.84 (d, J = 3.75 Hz), 5.70-5.40 (m, 2H), 5.20-5.00 (m, 1H), 4.70-4.50 (m, 3H), 4.30-4.00 (m, 4H), 2.13-1.91 (singlets, Ac), 1.46 (s, 3H, CMe_2), 1.30 (s, 3H, CMe_2).

Hydrogenolysis of 142.

To a solution of 142 (108 mg, 0.20 mmol) in 2.5 ml of dry ethanol, 40 mg of 10% Pd/C was added and shaken under 60 psi pressure of H_2 in a Parr apparatus for 6 h. The reaction mixture was filtered and washed with ethyl acetate (20 ml). The ethyl acetate extract was evaporated to afford 60 mg of 143 (66%).

^{1}H NMR (200 MHz)

8 6.00 (d, J = 3.80 Hz), 5.87 (d, J = 3.70 Hz), 5.60-5.05 (m, 2H), 4.90-4.75 (m, 1H), 4.65-3.90 (m), 2.15-2.01 (singlets, Ac), 1.53-1.29 (singlets, CMe_2).

Tetra-O-acetyl-*aldehydo*-pentose 144.

A solution of 143 (60 mg, 0.13 mmol) in a 9:1 TFA-H2O mixture (2.2 ml) was maintained at rt for 20 min. The reaction mixture was concentrated under reduced pressure with addition of water. The residue was dissolved in 4 ml of CH_2Cl_2 and added to a slurry of silica gel (1.60 g) in 13 ml of CH_2Cl_2 containing $NaIO_4$ (215 mg of NaIC>4 in 1.6 ml H_2O) and stirred vigorously for 1 h. The reaction mixture was filtered through a sintered crucible and washed with CH_2Cl_2. The CH_2Cl_2 extract was dried and evaporated. A complex mixture containing *aldehydo* compounds as evidenced by its ^{1}H

NMR spectrum was obtained, from which information pertaining to the structures of the individual components and their ratios could not be determined.

Synthesis of octa-O-acetyl-octitol 148 from 138.

3-O-Benzyl-octitol 145.

A solution of **138** (185 mg, 0.50 mmol) in a 9:1 TFA-H_2O mixture (2.5 ml) was stirred at rt for 20 min. The reaction mixture was concentrated under reduced pressure with addition of water. The residue was dissolved in 6 ml of H_2O and cooled to 0°. To the chilled reaction mixture, $NaBH_4$ (80 mg) was added gradually and the reaction mixture was stirred at 0° for 3 h and then overnight at rt. The reaction mixture was acidified with Amberlite IR-120 (H^+) resin (1.60 g) and filtered. The resin was thoroughly washed with water (5 ml) and the combined water extracts were concentrated under reduced pressure, with addition of methanol to remove any trace of boric acid, to furnish 150 mg of crude **145** in 90% yield.

3-0-Benzyl-l,2,4,5,6,7,8-hepta-0-acetyl-octitol 146.

To a solution of the crude mixture **145** (150 mg, 0.45 mmol) in 3 ml of pyridine, 2.5 ml of acetic anhydride was added and heated at 100° for 3 h. The reaction mixture was quenched with 10 ml of ice-cold water and extracted with CH_2Cl_2. The CH_2Cl_2 extract was dried, evaporated and the residue purified on a silica gel column using 20% ethyl acetate in hexane to afford 166 mg of **146** in 59% yield, based on crude **138.**

^1H NMR (200 MHz)

8 7.40-7.25 (m, 5H, Ph), 5.50-4.90 (m, 5H), 4.85-4.65 (m, 1H), 4.40-3.80 (m, 4H), 2.15-2.01 (singlets, Ac).

1,2,4,5,6,7,8-Hepta-O-acetyl-octitol 147.

To a solution of 146 (250 mg, 0.40 mmol) in dry ethanol (2.7 ml), 10% Pd/C (66 mg) was added and shaken under 50 psi pressure of H_2 in a Parr apparatus for 6 h. The reaction mixture was filtered and the charcoal residue washed thoroughly with ethyl acetate (15 ml). The combined extracts were concentrated to afford 193 mg of 147 (90%).

^1H NMR (200 MHz)

δ 5.60-4.95 (m, 5H), 4.50-3.60 (m, 5H), 2.15-2.03 (singlets, Ac).

Octa-O-acetyl-octitol 148.

A solution of 147 (193 mg, 0.36 mmol) in 2 ml of pyridine containing 1.5 ml of acetic anhydride was heated at 100° for 3 h. The reaction mixture was quenched with 5 ml of cold water and extracted with CH_2Cl_2. The CH_2Cl_2 extract was dried, evaporated and the residue purified on a silica gel column using 20% ethyl acetate in hexane to afford 183 mg of 148 (88%).

^1H NMR (200 MHz)

δ 5.50-4.80 (m, 6H), 4.40-3.80 (m, 4H), 2.22-1.97 (singlets, 24H, Ac).

Separation of **151-OAc, 152-OAc** and **153-OAc from** 148.

Partial crystallization of 148 from ethanol at rt, separated 151-OAc as a colorless crystalline substance (mp 184-5°) from unseparated **152-OAc** and **153-OAc** in a ratio of 1:6.6. Similarly, when the unseparated isomeric mixture containing 152-OAc and 153-OAc was partially crystallized from methanol at 0°, syrupy 152-OAc and crystalline **153-OAc** (mp 122-23°), separated out in a ratio of 6.6:1. Incidentally, pure diastereomers **151-OAc**, **152-OAc** and **153-OAc** were obtained in a 90% recovery, based

on 148. Separation of the diastereomeric peracetylated octitol mixture 148 from 137 by fractional crystallization revealed that 151-OAc, **152-OAc** and **153-OAc** were formed in a ratio of 1.15:6.6:1, respectively, on hydroxylation of 137.

(*meso*)-*Threo*-*gluco*-octa-O-acetyl-octitol (151-OAc).

Solid; mp 184-5° (ethanol).

IR(KBr) 1740 cm^{-1}.

^1H NMR (500 MHz)

δ 5.34 (d, J = 8.20 Hz, 2H, H-3, H-6), 5.25 (s, 2H, H-4, H-5), 5.11 (ddd, J = 3.0, 5.25, 8.25 Hz, 2H, H-2, H-7), 4.35 (dd, J = 3.25, 12.25 Hz, 2H, H-1, H-8), 4.13 (dd, J = 5.75, 12.25 Hz, 2H, H-1', H-8^1), 2.13 (s, 3H, Ac), 2.09 (s, 3H, Ac), 2.08 (s, 3H, Ac), 2.06 (s, 3H, Ac).

^{13}C NMR (125 MHz)

170.52, 170.04, 169.96, 169.87, 69.37, 67.88, 67.54, 61.97, 20.77 (2C), 20.71, 20.63 ppm.

Anal. Calcd for $C_{24}H_{34}O_{16}$: C, 49.82; H, 5.92. Found: C, 49.75; H, 5.90.

(*meso*)-*Threo*-*gluco*-octitol (151).[92]

To a solution of **151-OAc** (58 mg 0.10 mmol) in dry methanol (4 ml), a small piece of sodium was added and the solution refluxed on a water bath for 5 min. The crystals formed were separated from the mother liquor, washed with 2 ml of methanol and dried, affording 22 mg of 151 in 90% yield. Mp 166-69°; lit.[92] 166-69.5°.

***L*-*Erythro*-*D*-*gluco*-octa-O-acetyl-octitol** (152-OAc).

Syrup; IR (neat) 1740 cm^{-1}.

^{1}HNMR (200 MHz)

δ 5.23 (s, 1H), 5.19 (d, J = 1.62 Hz, 1H), 5.16 (s, 1H), 5.12 (s, 1H), 5.05-4.82 (m, 2H), 4.22 (dd, J = 3.63, 12.17 Hz, 1H, H-8), 4.10 (dd, J = 3.20, 12.40 Hz, 1H, H-1), 4.06 (dd, J = 5.66, 12.24 Hz, 1H, H-8'), 3.92 (dd, J = 5.10, 12.52 Hz, 1H, H-1'), 2.01 (s, 3H, Ac), 1.99 (s, 3H, Ac), 1.96 (s, 6H, Ac), 1.95 (s, 6H, Ac), 1.93 (s, 3H, Ac), 1.92 (s, 3H, Ac).

^{13}C NMR (50 MHz)

170.6, 170.5, 170.1, 169.9, 169.8, 169.7, 69.4, 68.2, 67.7, 67.4, 67.2, 62.0, 61.9, 20.7 ppm.

$[\alpha]_D^{25}$ -7.3° (c 1.0).

Anal. Calcd for $C_{24}H_{34}O_{16}$: C, 49.82; H, 5.92. Found: C, 49.75; H, 6.00.

***D-Erythro-L-ido*-octa-O-acetyl-octitol (153-OAc).**

Solid; mp 122-3° (methanol).

IR(KBr) 1740 cm^{-1}.

^{1}H NMR (200 MHz)

8 5.53 (dd, J = 3.13, 6.67 Hz, 1H), 5.43 (dd, J = 2.25, 8.34 Hz, 1H, H-5), 5.32 (dd, J = 2.18, 8.07 Hz, 1H, H-6), 5.21 (d, J = 3.35 Hz, 1H), 5.26-5.15 (m, 1H), 4.98 (ddd, J = 3.07, 5.24, 8.24 Hz, 1H, H-7), 4.31 (dd, J = 3.92, 12.23 Hz, 1H, H-8'), 4.26 (dd, J = 2.48, 12.65 Hz, 1H, H-1), 4.12 (dd, J = 4.70, 12.63 Hz, 1H, H-1'), 3.95 (dd, J = 5.69, 12.20 Hz, 1H, H-8), 2.15 (s, 6H, Ac), 2.10 (s, 3H, Ac), 2.08 (s, 6H, Ac), 2.07 (s, 3H, Ac), 2.06 (s, 3H, Ac), 2.05 (s, 3H, Ac).

^{13}C NMR (50 MHz)

170.7, 170.6, 170.1, 170.0, 169.8, 168.0, 69.6, 68.5, 68.4, 68.0, 61.6, 61.4, 20.9, 20.7, 20.5 ppm.

$[\alpha]_D^{25}$ +23.1° (*c* 0.36).

Anal. Calcd for $C_{24}H_{34}O_{16}$: C, 49.82; H, 5.92. Found: C, 49.75; H, 5.85.

Synthesis of ***octa-O-acetyl-octitol 150*** from **141.**

1,2,3,4-Tetra-O-acetyl-5,6:7,8-di-O-isopropylidene-octitol 149.

To a solution of crude **141** (161 mg, 0.50 mmol) in pyridine (4.3 ml), acetic anhydride (3.5 ml) was added and heated at 100° for 3 h. The reaction mixture was quenched with 10 ml of cold water and extracted with CH_2Cl_2. The CH_2Cl_2 extract was dried, evaporated and the residue purified on a silica gel column using 10% ethyl acetate in hexane to afford 213 mg of 149 (87%).

^1H NMR (200 MHz)

5.60-5.30 (m, 3H), 4.40-3.80 (m, 7H), 2.15-2.01 (singlets, 12H, Ac), 1.43 (s, 3H, CMe_2), 135 (s, 3H, CMe_2), 133 (s, 3H, CMe_2), 132 (s, 3H, CMe_2).

Octa-O-acetyl-octitol 150.

A solution of **149** (196 mg, 0.40 mmol) in a 9:1 TFA-H2O mixture (4.3 ml) was maintained at rt for 45 min. The reaction mixture was concentrated under reduced pressure with addition of water and dried under vacuum for 3 h. The residue was acetylated at 100° for 3 h using pyridine (4 ml) and acetic anhydride (3.4 ml). The reaction mixture was quenched with 10 ml of cold water and extracted with CH_2Cl_2. The CH_2Cl_2 extract was dried, evaporated and the residue purified on a silica gel column using 20% ethyl acetate in hexane to afford 206 mg of **150** (89%).

^1H NMR (200 MHz)

5 5.60-4.90 (m, 6H), 4.40-3.90 (m, 4H), 2.15-2.05 (singlets, 24H, Ac).

Separation of **155-OAc,**[93] **156-OAc** and 158-OAc[94] from 150.

Fractional crystallization of 150 from ethanol afforded a 2:3 mixture of crystalline **155-OAc** (mp 166-7°) and 159 (mixture containing 156-OAc and 158-OAc) in 95% yield, based on 150. Fractional crystallization of 159 using various solvents like methanol, isopropanol, aqueous ethanol and aqueous methanol was unsuccessful. Subsequently, HPLC was used to separate 156-OAc and 158-OAc.

Different aromatic derivatives of unseparated mixtures 141 and 159 were prepared and their HPLC analyses carried out. Initial attempts at the HPLC separation of 160 and 161 met with failure. HPLC separation of the perbenzoylated diastereomeric mixture 162 using 13% water in acetonitrile afforded pure **156-OBz** and **158-OBz** in a 1:1 ratio with 92% recovery. 156-OBz and 158-OBz were further hydrolyzed and acetylated to obtain **156-OAc** (75%) and **158-OAc** (87%). The diastereomeric peracetylated octitol mixture 150 obtained from 140 by fractional crystallization and HPLC separation showed that **155-OAc**, **156-OAc** and **158-OAc** were present in a 1.33:1:1 ratio, respectively.

(*meso*)-*Erythro-manno*-octa-O-acetyl-octitol (155-OAc).[93]

Solid; mp 166-7° (ethanol); lit.[93] 166-7°.

IR(KBr) 1740 cm^{-1}.

^1H NMR (200 MHz)

8 5.40 (s, 2H, H-4, H-5), 5.22 (d, J= 8.21 Hz, 2H, H-3, H-6), 4.99 (ddd, J = 2.99, 5.62, 8.12 Hz, 2H, H-2, H-7), 4.23 (dd, J - 3.03, 12.46 Hz, 2H, H-1, H-8), 4.00 (dd, J = 5.59, 12.42 Hz, 2H, H-l', H-8'), 2.09 (s, 6H, Ac), 2.08 (s, 6H, Ac), 2.06 (s, 6H, Ac), 2.04 (s, 6H, Ac).

^{13}C NMR (50 MHz)

170.6, 170.0, 169.8, 68.4, 67.6, 66.8, 61.9, 21.0, 20.8 ppm.

1,2,3,4-Tetra-O-benzoyl-5,6:7,8-di-O-isopropylidene-octitol 160.

To a solution of the crude mixture 141 (48 mg, 0.15 mmol) in pyridine (1 ml) at 0°, DMAP (5 mg) and BzCl (350 µl) were added and stirred at rt for 24 h. The reaction mixture was quenched with cold saturated K_2CO_3 solution and extracted with CH_2Cl_2. The CH_2Cl_2 extract was dried, evaporated and the residue purified on a silica gel column using 20% ethyl acetate in hexane to afford 94 mg of 160 (85%).

^1H NMR (200 MHz)

5 8.20-7.80 (m, 8H, Ph), 7.60-7.25 (m, 12H, Ph), 6.20-5.80 (m, 3H), 4.95-4.25 (m, 3H), 4.20-3.60 (m, 4H), 1.40-1.10 (singlets, 12H, CMe_2).

1,8-Di-O-trityl-2,3,4,5,6,7-hexa-O-acetyl-octitol 161.

To a solution of 159 (116 mg, 0.20 mmol) in dry methanol (6 ml), a speck of sodium was added and the contents refluxed on a water bath for 5 min. The reaction mixture was dissolved in 2 ml of water and neutralized with Amberlite IR-120 (H^+) resin. The resulting mixture was filtered and the resin was thoroughly washed with water (5 ml). The filtrate was concentrated under reduced pressure and dried in vacuum for 3 h. The residue was dissolved in pyridine (5.2 ml) and TrCl (112 mg) was added. The reaction mixture was stoppered and shaken till TrCl completely dissolved and then left at rt for 48 h. The reaction mixture was cooled to 0° and 1.3 ml of acetic anhydride was added and the contents stored at rt for 72 h. The reaction mixture was quenched with cold water (10 ml) and extracted with CH_2Cl_2. The CH_2Cl_2 extract was dried,

evaporated and the residue purified on a silica gel column using 15% ethyl acetate in hexane to afford 139 mg of 161 (71%).

^1H NMR (200 MHz)

8 7.50-7.20 (m, 30H, Ph), 5.80-4.90 (m, 6H), 3.40-2.71 (m, 4H), 2.13-1.82 (singlets, 18H, Ac).

Octa-O-benzoyl-octitol 162.

To a solution of 159 (116 mg, 0.20 mmol) in dry methanol (6 ml), a small piece of sodium was added and the solution refluxed on a water bath for 5 min. The reaction mixture was dissolved in 2 ml of water and neutralized with Amberlite IR-120 (H^+) resin. The resulting mixture was filtered and the resin was thoroughly washed with water (5 ml). The filtrate was concentrated under reduced pressure and dried in vacuum for 3 h. The residue was dissolved in 2 ml of pyridine and cooled to 0°. To the cooled reaction mixture, DMAP (20 mg) and BzCl (1 ml) were added and the contents stirred at rt for 24 h. The reaction mixture was quenched with cold aq saturated K_2CO_3 solution and extracted with CH_2Cl_2. The CH_2Cl_2 extract was dried and evaporated and the residue purified on a silica gel column using 20% ethyl acetate in hexane to afford 155 mg of 162 (72%).

^1HNMR (200 MHz)

δ 8.30-7.00 (m, 40H, Ph), 6.30-5.50 (m, 6H), 4.90-4.30 (m, 4H).

HPLC separation was performed with 13% water in acetonitrile at 9 ml/min flow rate, using a SuperPac pep-S 15 urn reverse phase preparative column. When 130 mg of **162** in 1.8 ml of acetonitrile was injected, **156-OBz** and **158-OBz** were eluted out at 26 and 30 min, respectively, in a 1:1 ratio, in an over all yield of 92%.

***D-Erythro-L-gluco*-octa-O-benzoyl-octitol** (156-OBz).

Syrup; IR (neat) 1725 cm^{-1}.

^1H NMR (200 MHz)

5 8.20-7.10 (m, 40H, Ph), 6.30-6.05 (m, 4H), 5.85-5.71 (m, 2H), 4.79 (dd, J = 3.46, 12.17 Hz, 1H), 4.75-4.62 (m, 2H), 4.44 (dd, J = 5.69, 11.96 Hz, 1H).

^{13}C NMR (50 MHz)

165.9, 165.5, 165.4, 165.1, 164.9, 133.7, 133.5, 133.4, 133.3, 133.0, 132.9, 130.2, 130.0, 129.9, 129.8, 129.5, 129.3, 129.1, 129.0, 128.9, 128.6, 128.5, 128.4, 128.3, 128.2, 70.6, 70.2, 69.6, 69.4, 69.1, 69.0, 62.6, 62.5 ppm.

$[\alpha]_D^{25}$ **-12.00 (c 1.0).**

***D-Erythro-L-gulo*-octa-O-benzoyl-octitol (158-OBz).**

Solid; mp 233-5°.

IR(KBr) 1725 cm^{-1}.

^1H NMR (200 MHz)

5 8.23 (d, J= 7.76 Hz, 4H, Ph), 7.74 (dd, J = 1.95, 7.32 Hz, 4H, Ph), 7.39 (d, ./ = 6.59 Hz, 4H, Ph), 8.15-6.85 (m, 30H, Ph), 6.16 (s, 2H, H-4, H-5), 5.70-5.55 (m, 2H, H-2, H-7), 4.80 (dd, J = 2.24, 12.60 Hz, 2H, H-1, H-8), 4.42 (dd, J = 3.33, 12.60 Hz, 2H, H-1', H-8^1).

^{13}C NMR (50 MHz)

166.3, 165.7, 165.3, 165.0, 134.0, 133.1, 130.3, 130.2, 129.7, 129.6, 129.4, 129.0, 128.7, 128.4, 128.2, 69.4, 68.6, 68.5, 62.3 ppm.

$[\alpha]_D^{25}$ -8.1° (c 0.80).

***D-Erythro-L-gluco*-octa-O-acetyl-octitol(1 56-OAc).**

To a solution of **156-OBz** (54 mg, 0.05 mmol) in a 1:1 MeOH-THF mixture (12 ml), a trace of sodium was added and the mixture refluxed on a water bath for 10 min. The reaction mixture was dissolved in 2 ml of water and neutralized with Amberlite IR-120 (H^+) resin. The resulting mixture was filtered and the resin was thoroughly washed with water (5 ml). The water extract was washed with hexane to remove the methyl benzoate formed, and the solution was concentrated under reduced pressure and dried in vacuum for 3 h. The residue was acetylated using pyridine (3 ml) and acetic anhydride (0.5 ml) at 100° for 3 h. The reaction mixture was quenched with 10 ml of cold water and extracted with CH_2Cl_2. The CH_2Cl_2 extract was dried and evaporated and the residue purified on a silica gel column using 30% ethyl acetate in hexane to afford 22 mg of **156-OAc** (75%). ^1H and ^{13}C NMR spectra of **156-OAc** were identical to **152-OAc** obtained from 148.

$[\alpha]_D^{25}$ +8.0° (*c* 1.30).

***D-Erythro-L-gulo*-octa-O-acetyl-octito(158-OAc)**[94] was prepared from **158-OBz** in 87% yield using the same procedure as described for **156-OAc**.

Solid; mp 111°; lit.[94] 110-1°.

IR(KBr) 1745 cm^{-1}.

^1HNMR (200 MHz)

5 5.45 (d, *J*= 8.95 Hz, 2H, H-3, H-6), 5.12 (s, 2H, H-4, H-5), 4.90 (ddd, *J* = 2.66, 4.20, 9.08 Hz, 2H, H-2, H-7), 4.14 (dd, *J* = 2.46, 12.52 Hz, 2H, H-1, H-8), 4.03 (dd, *J* = 4.36, 12.40 Hz, 2H, H-l', H-8'), 2.07 (s, 6H, Ac), 1.97 (s, 6H, Ac), 1.93 (s, 6H,Ac), 1.92 (s, 6H,Ac).

^{13}C NMR (50 MHz)

170.6, 169.9, 169.7, 68.3, 67.8, 67.6, 61.5, 20.7, 20.6, 20.4 ppm.

$[\alpha]_D^{25}$ +44.0° (*c* 0.50), lit. $[\alpha]_D^{25}$ +47.0° (c 0.40).

Synthesis of **153-OAc** and **172-OAc** from ethyl ***(E)*-2,3-dideoxy-*D-gluco*-oct-2-enonate** (167).

Ethyl ***(E)*-2,3-dideoxy-4,5:7,8-** and **-5,6:7,8-di-O-isopropylidene-D-*gluco*-oct-2-enonates** 168.

To 5 ml of dry acetone, a drop of H_2SO_4 (20 μl), anhydrous $CuSO_4$ (300 mg) and 167 (250 mg, 1.0 mmol) were added in sequence and stirred at rt for 25 h. The reaction mixture was filtered and the solids washed with dry acetone (10 ml). The combined washings and filtrate were made basic with 0.6 ml of ammonia solution and the resulting mixture was filtered. The filtered solution was concentrated under reduced pressure and the residue was purified on a silica gel column using 20% ethyl acetate in hexane to afford **168 in** 90% yield.

Hydroxylation of 168.

To a solution of 168 (198 mg, 0.60 mmol) in a 8:1 acetone-water mixture (3 ml), NMO.H_2O (165 mg, 1.20 mmol) was added and stirred. To the stirring reaction mixture, OsO_4 in /-BuOH (8 mg of OsO_4 in 0.3 ml of *t*-BuOH) was added dropwise and the stirring continued at rt for 8 h in the dark. The reaction mixture was diluted with $CHCl_3$ (33 ml) and shaken vigorously with 45% aq $NaHSO_3$ solution (2 ml) for 10 min. The organic layer was separated, dried and evaporated and the residue purified on a silica gel column using 40% ethyl acetate in hexane to afford **169** in 65% yield.

LAH reduction of 169.

To a solution of 169 (110 mg, 0.30 mmol) in dry THF (8 ml) at rt, LAH (50 mg) was added slowly and the mixture refluxed for 1 h. The reaction mixture was cooled and quenched with saturated Na_2SO_4 solution and filtered through a 2 cm long silica gel column packed with $CHCl_3$ and eluted with 20 ml of MeOH. The combined fractions were evaporated to dryness to yield **170** in 90% yield.

Acetylation of 170.

To a solution of 170 (80 mg, 0.25 mmol) in 1 ml of pyridine, acetic anhydride (0.8 ml) was added and heated at 100° for 3 h. The reaction mixture was quenched with 5 ml of cold water and extracted with CH_2Cl_2. The CH_2Cl_2 extract was dried and evaporated and residue purified on a silica gel column using 20% ethyl acetate in hexane to afford 171 in 71% yield.

^1H NMR (200 MHz)

δ 5.50-4.90 (m, 3H), 4.30-3.50 (m, 8H), 2.20-1.90 (singlets, 12H, Ac), 1.40-1.11 (singlets, 12H, CMe_2).

D-Erythro-L-ido- and ***-D-erythro-L-galacto-*octa-O-acetyl-octitol (153-OAc)** and (172-OAc), respectively.

A solution of 171 (74 mg, 0.15 mmol) in a 9:1 TFA-H_2O mixture (2 ml) was maintained at rt for 40 min. The reaction mixture was concentrated under reduced pressure with addition of water (5 ml) and dried under vacuum for 2 h. The resulting residue was acetylated using pyridine (1 ml) and acetic anhydride (0.7 ml) at 100° for 3 h. The reaction mixture was quenched with 5 ml of cold water and extracted with CH_2Cl_2. The CH_2Cl_2 extract was dried and concentrated under reduced pressure with

addition of toluene and the residue purified on a silica gel column using 30% ethyl acetate in hexane to afford a mixture containing **153-OAc** and 172-OAc in 85% yield. Fractional crystallization of the diastereomeric mixture using methanol at 0° afforded 153-OAc and 172-OAc in a ratio of 1:8.

***D-Erythro-L-ido*-octa-O-acetyl-octitol (153-OAc).** ^{1}H and ^{13}C NMR spectra and optical rotation of 153-OAc were identical to those of **153-OAc** obtained from 137.

***D-Erythro-L-galacto*-octa-O-acetyl-octitol (172-OAc).**

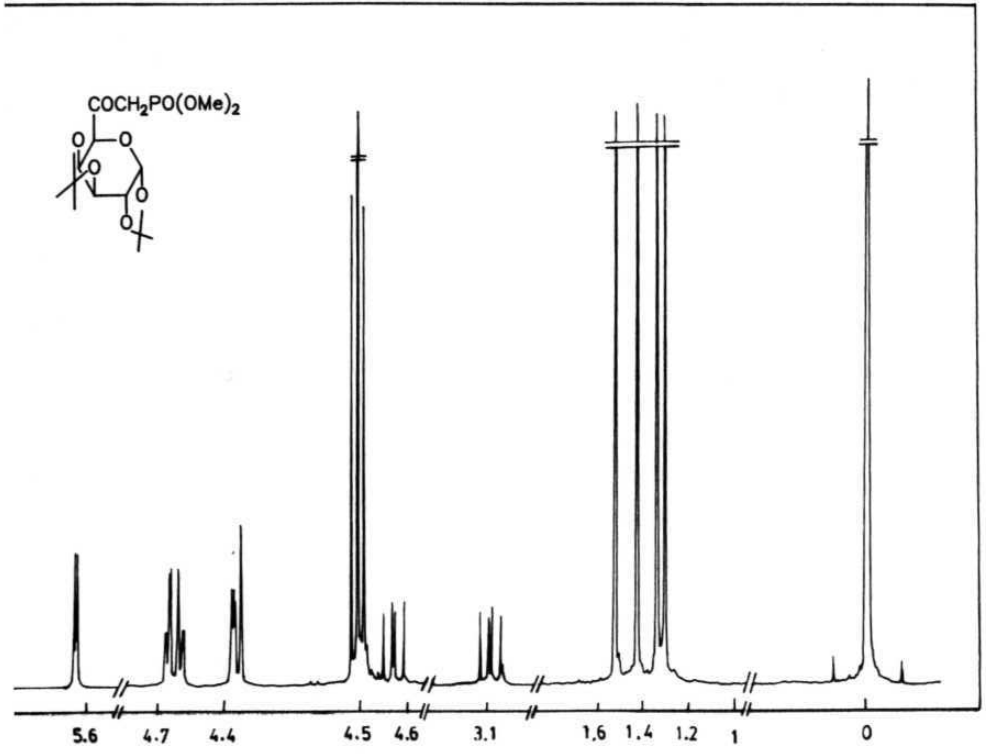
^{1}H NMR (200 MHz)

6 5.52-5.45 (m, 1H), 5.35 (s, 1H), 5.34 (d, J = 3.98 Hz, 1H), 5.26 (d, J = 2.14 Hz, 1H), 5.23-5.01 (m, 2H), 4.34 (dd, J = 12.03, 5.04 Hz, 1H, H-1), 4.27 (dd, J = 5.02, 11.54 Hz, 1H, H-8), 4.14 (dd, J = 5.48, 12.05 Hz, 1H, H-1'), 3.88 (dd, J = 6.96, 11.63 Hz, 1H, H-8'), 2.15 (s, 3H, Ac), 2.12 (s, 3H, Ac), 2.11 (s, 3H, Ac), 2.10 (s, 3H, Ac), 2.06 (s, 3H, Ac), 2.04 (s, 3H, Ac), 2.02 (s, 3H, Ac), 2.01 (s, 3H, Ac).

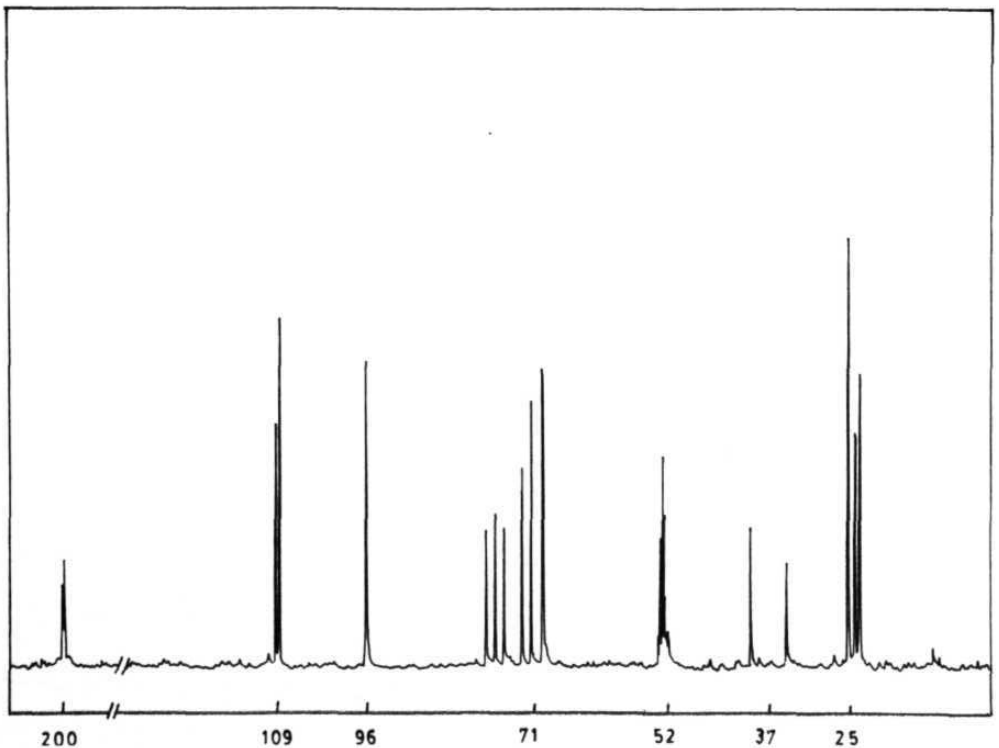
***D-Erythro-L-galacto*-octitol (172)**[100] was prepared from 172-OAc in 85% yield using the same procedure as described for 151.

Solid; mp 150-510 (ethanol-water); lit.[100] 153°.

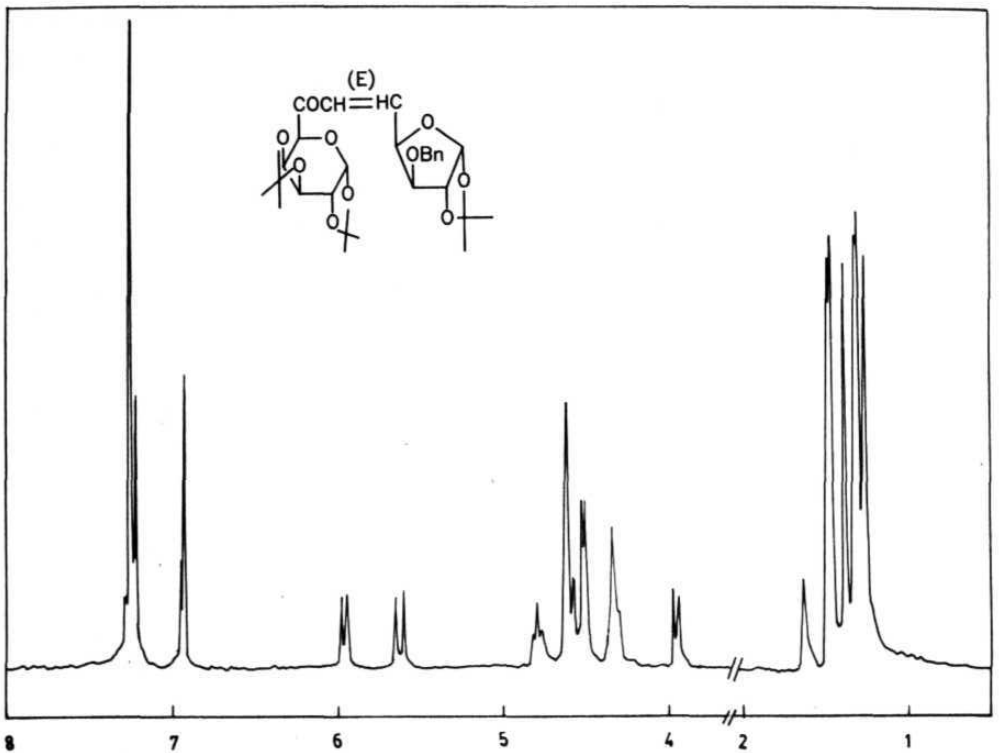
SPECTRA



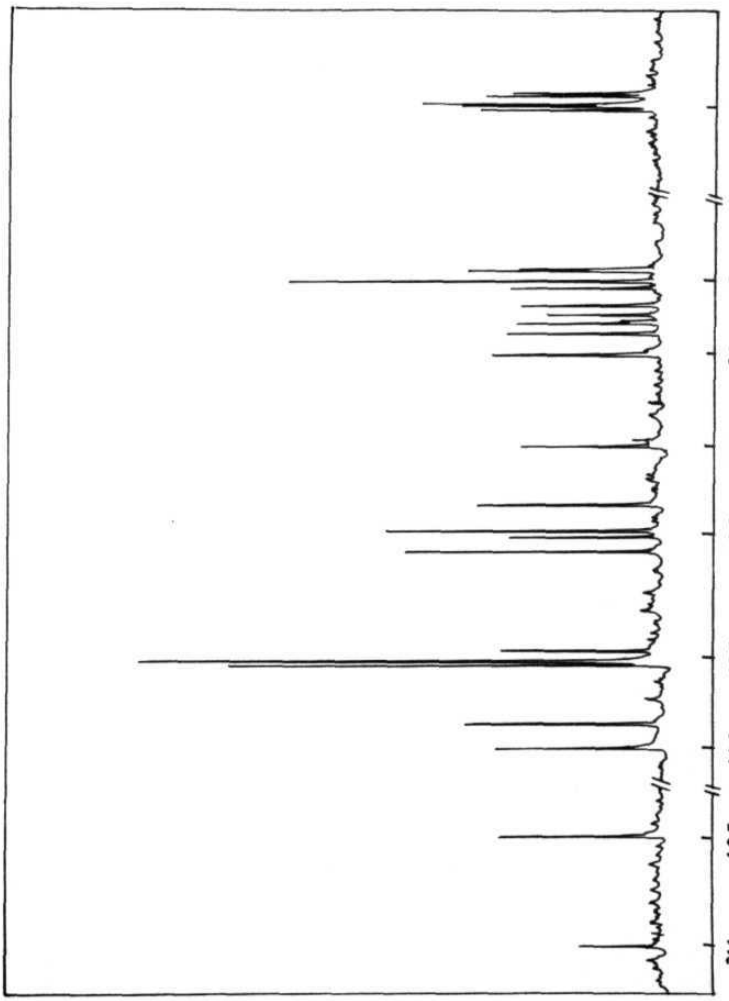
400 MHz ^{1}H NMR spectrum of 97



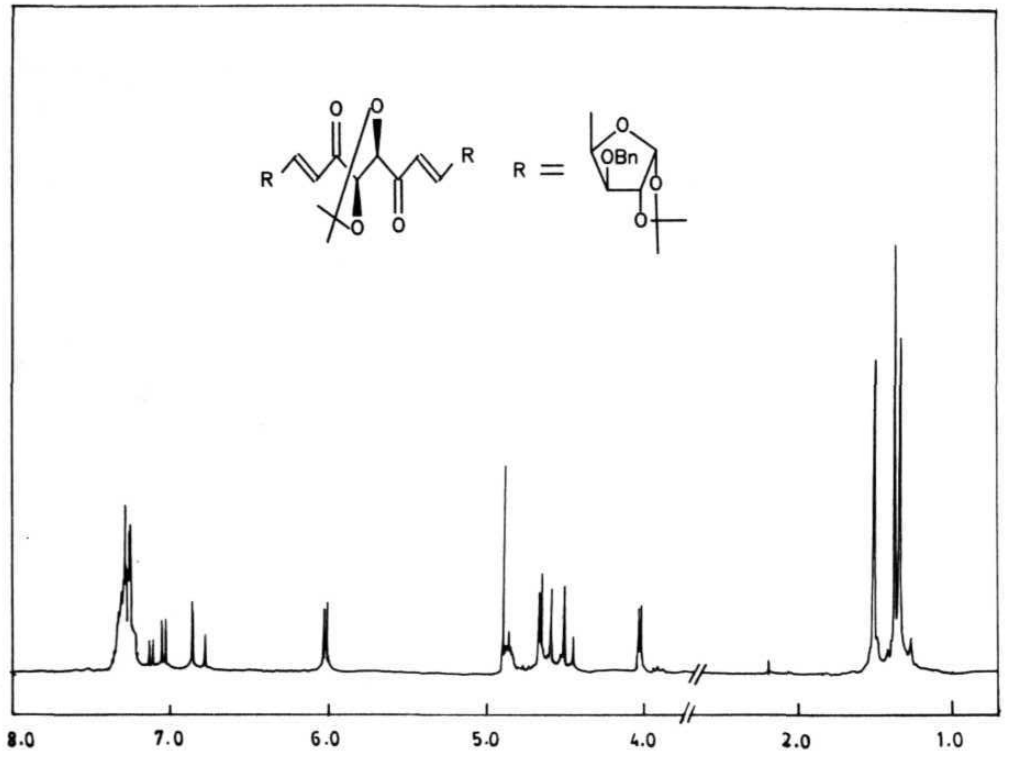
25 MHz ^{13}C NMR spectrum of 97



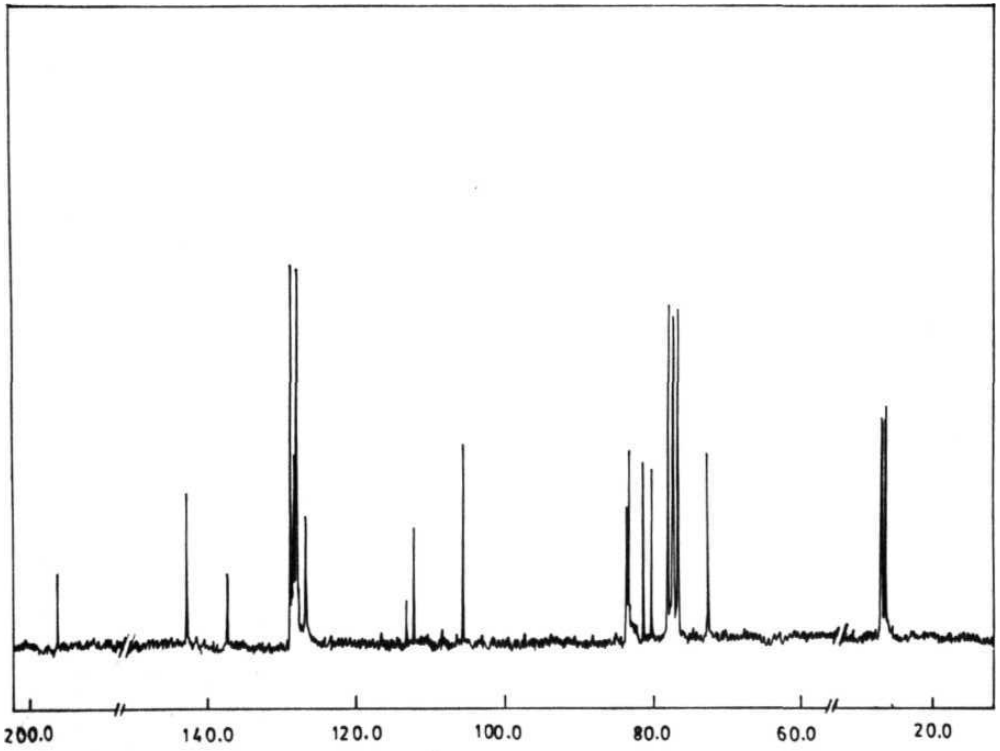
100 MHz ^{1}H NMR spectrum of **103**



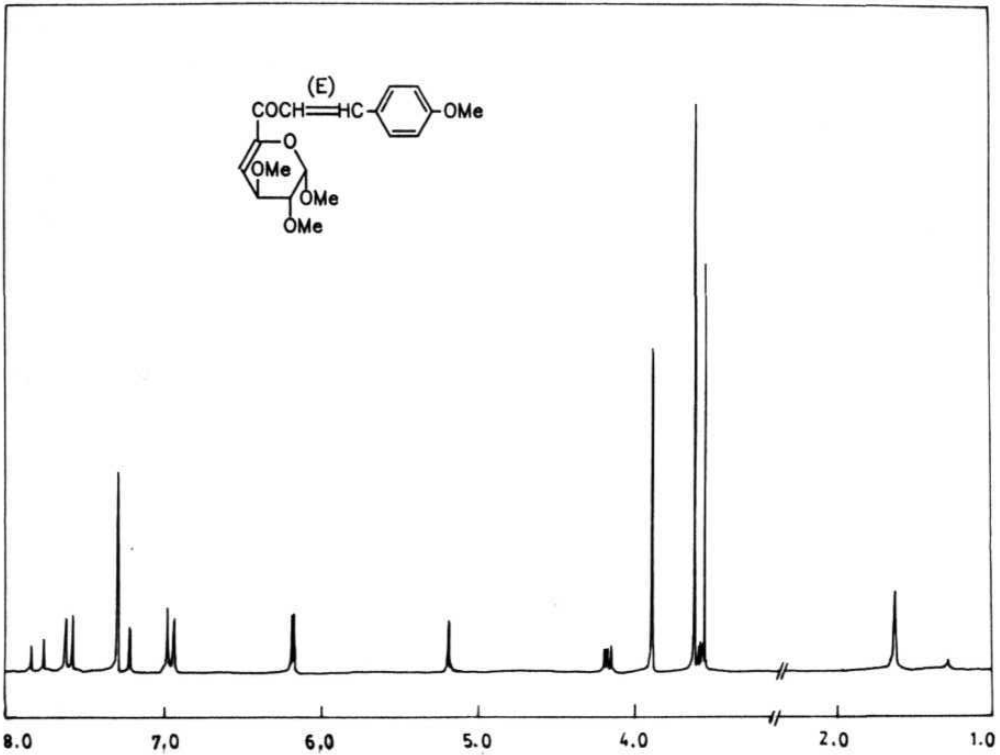
25 MHz ^{13}C NMR spectrum of **103**



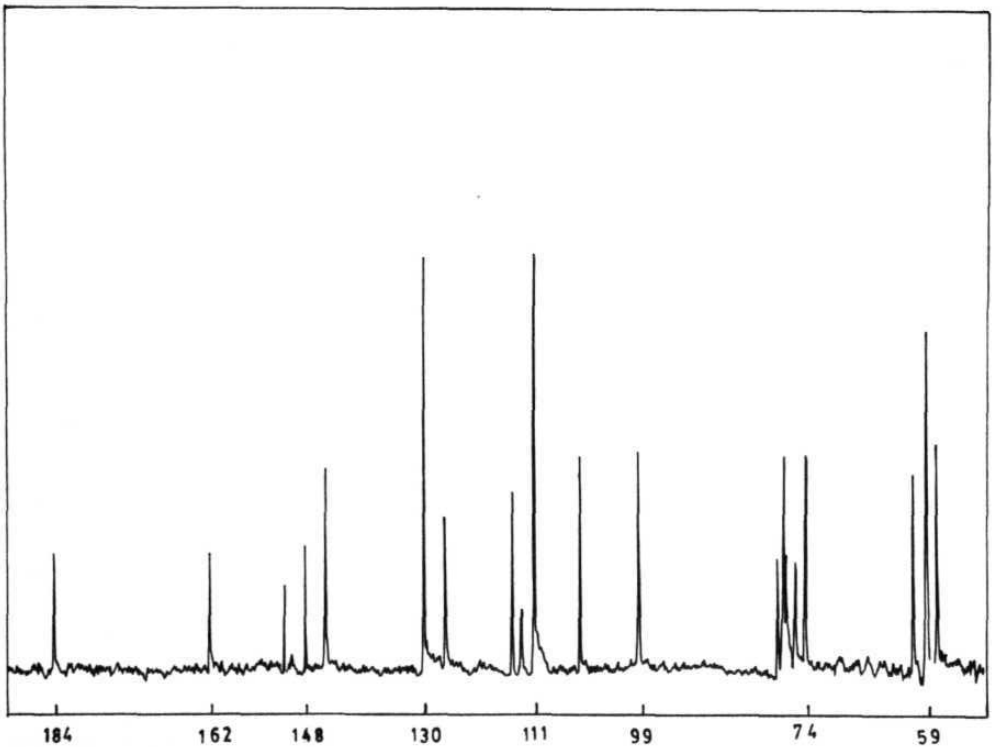
200 MHz ^{1}H NMR spectrum of **115**



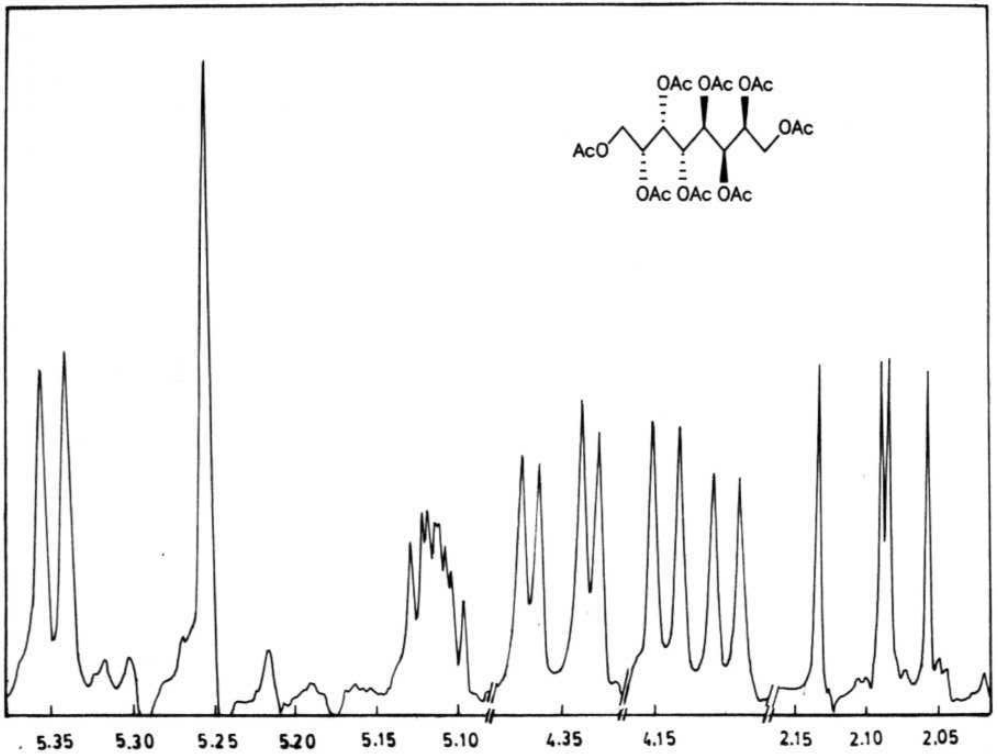
50 MHz ^{13}C NMR spectrum of **115**



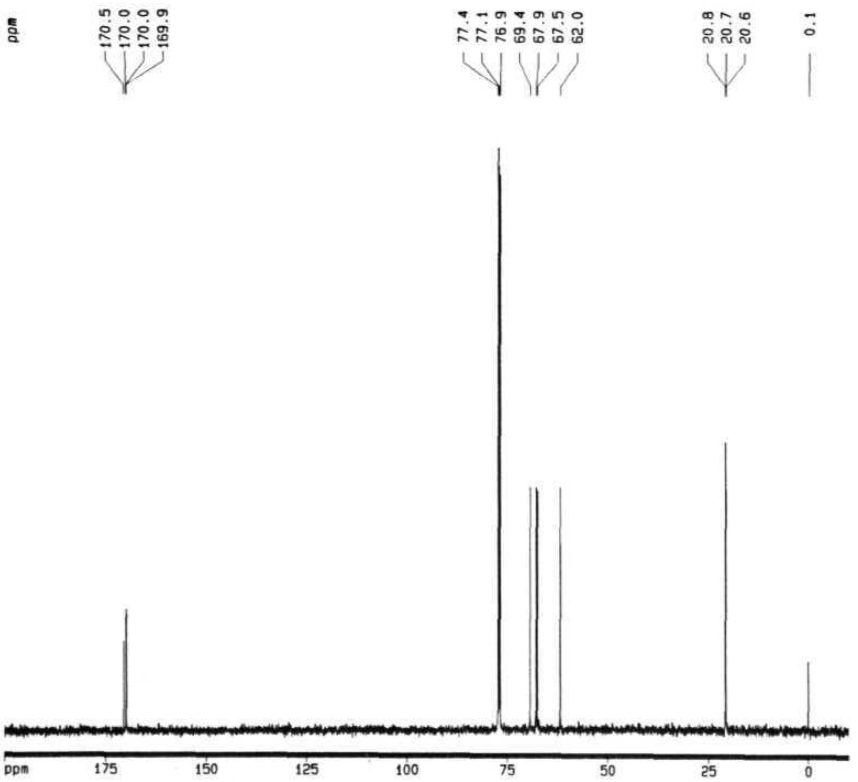
200 MHz ^{1}H NMR spectrum of **119**



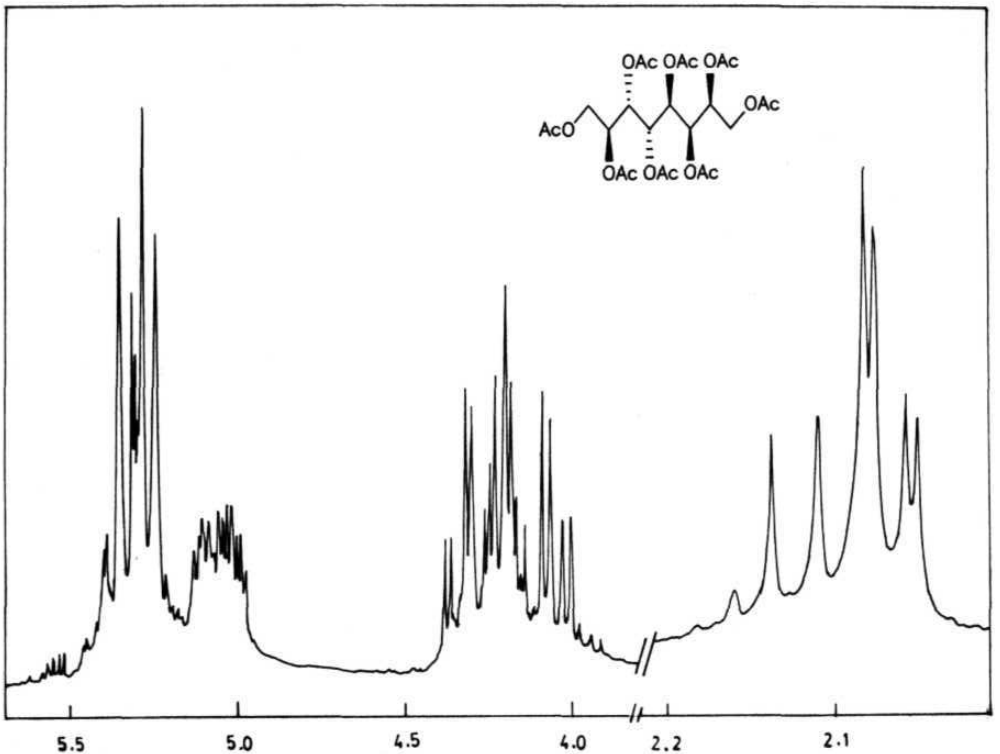
25 MHz ^{13}C NMR spectrum of **119**



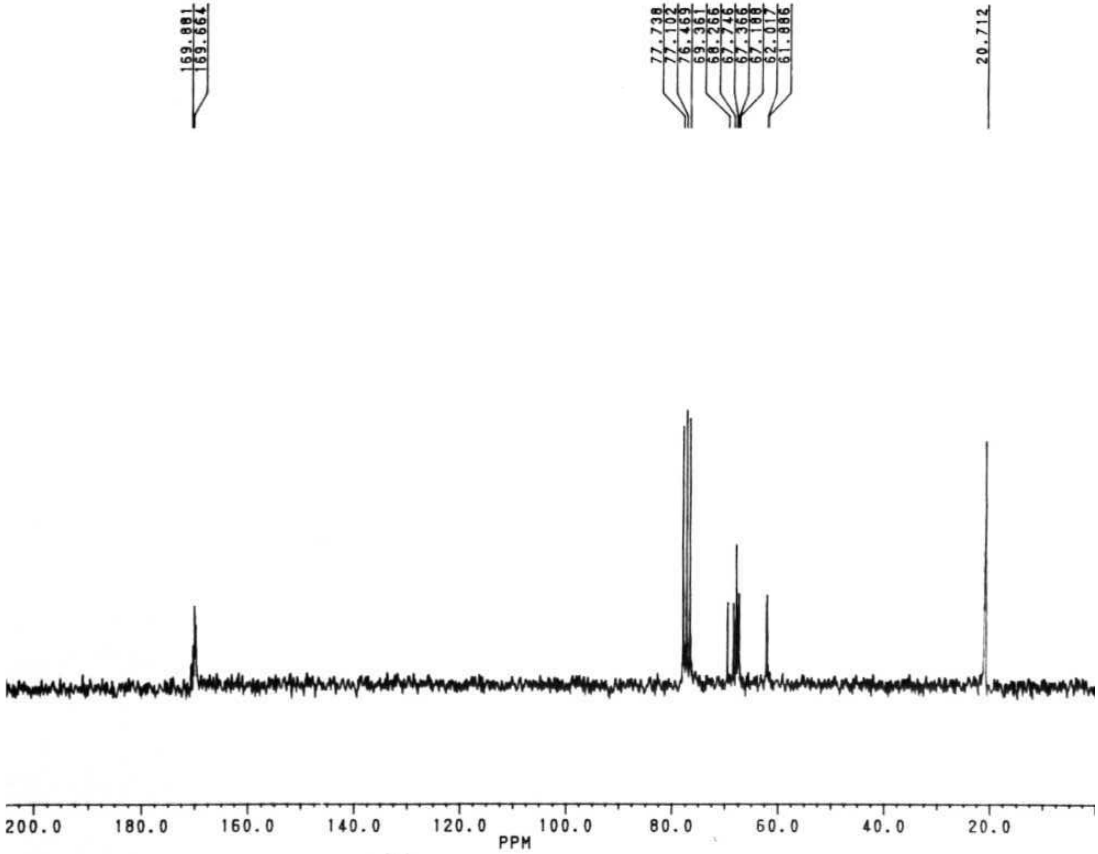
500 MHz ^{1}H NMR spectrum of **151-OAc**



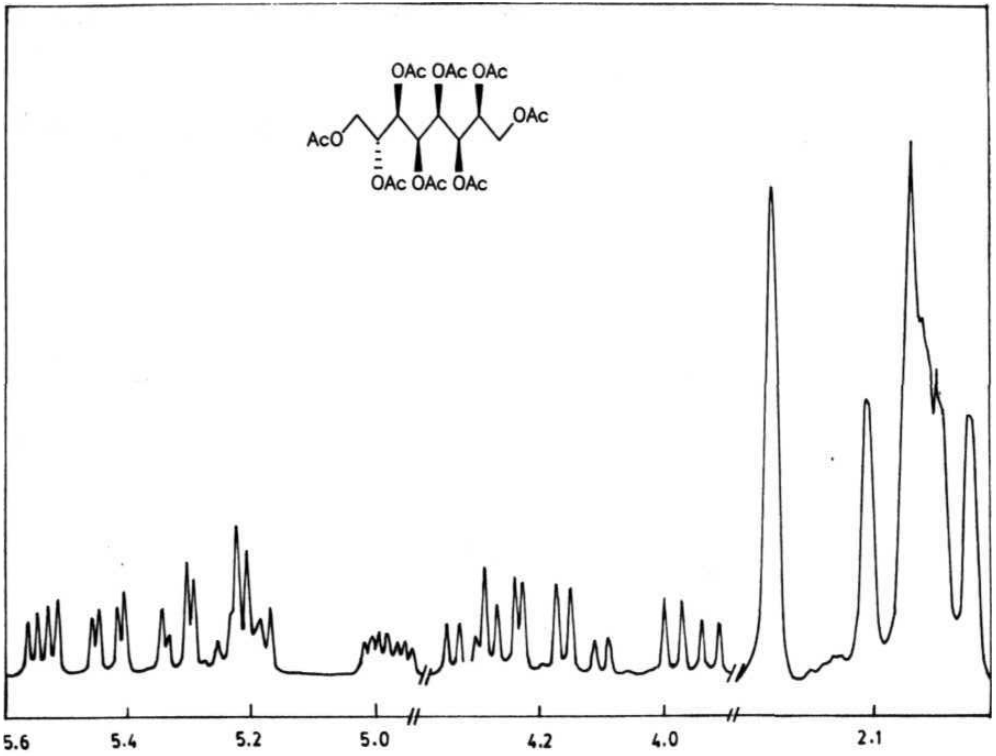
125 MHz ^{13}C NMR spectrum of **151-OAc**



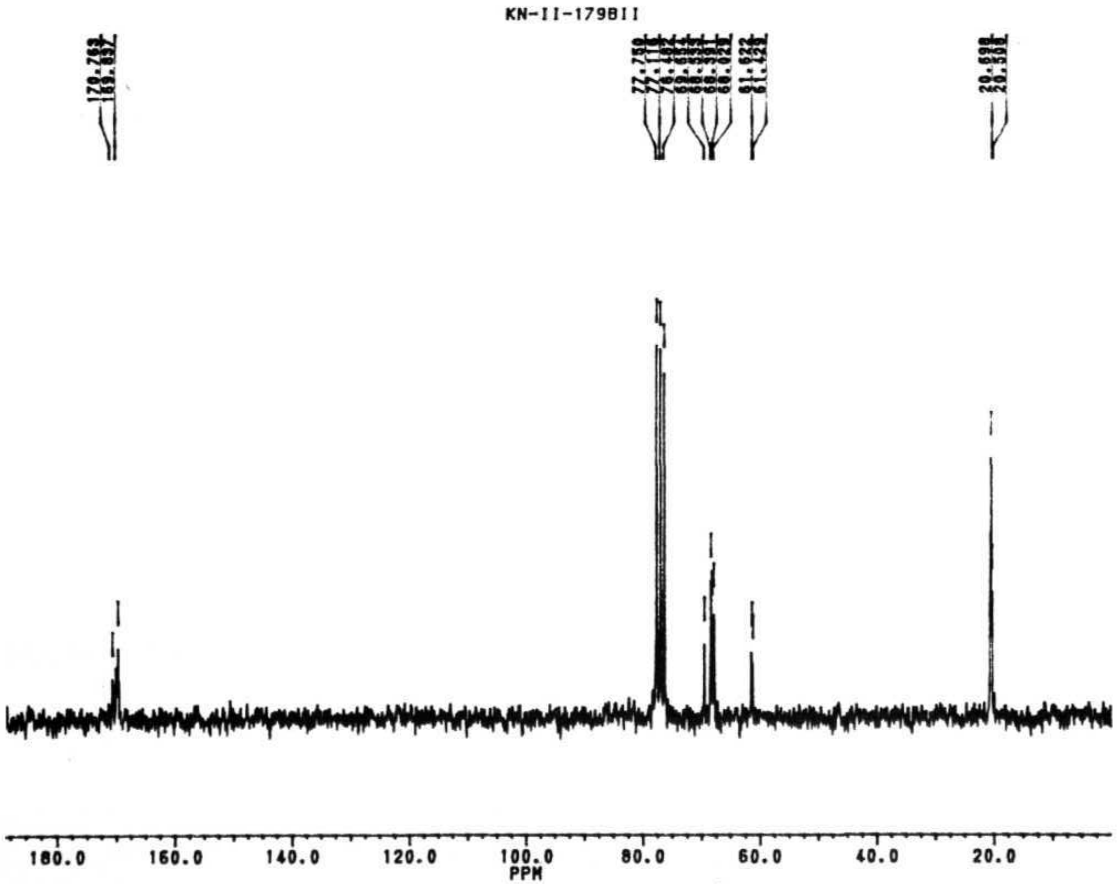
200 MHz ^{1}H NMR spectrum of **152-OAc**



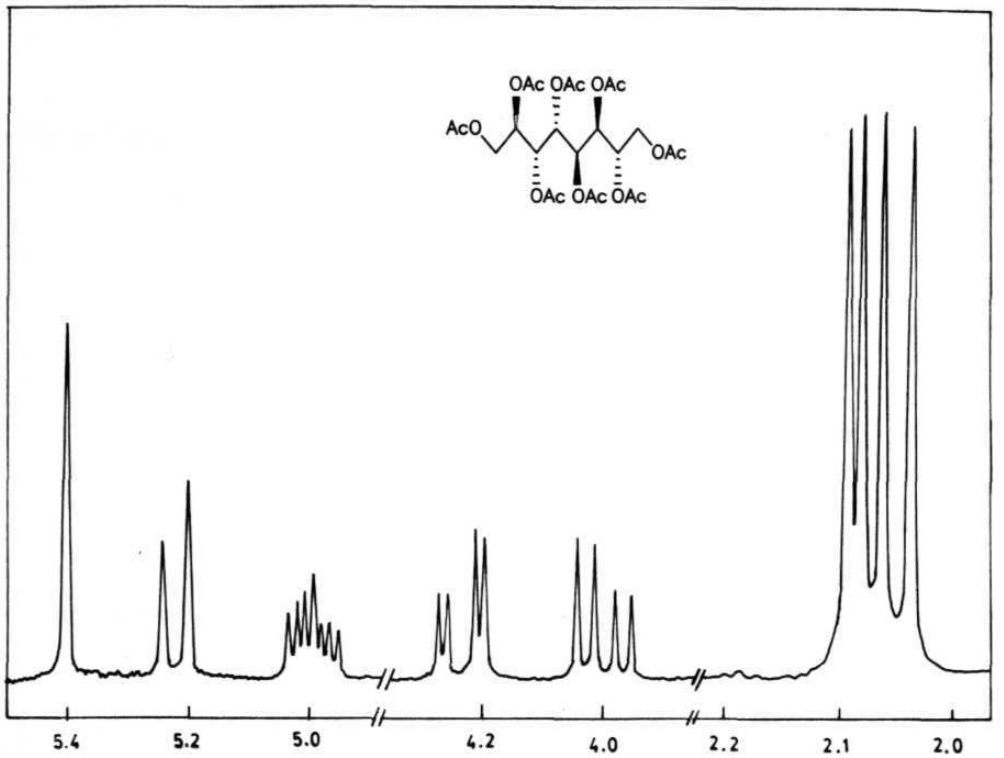
50 MHz ^{13}C NMR spectrum of **152-OAc**



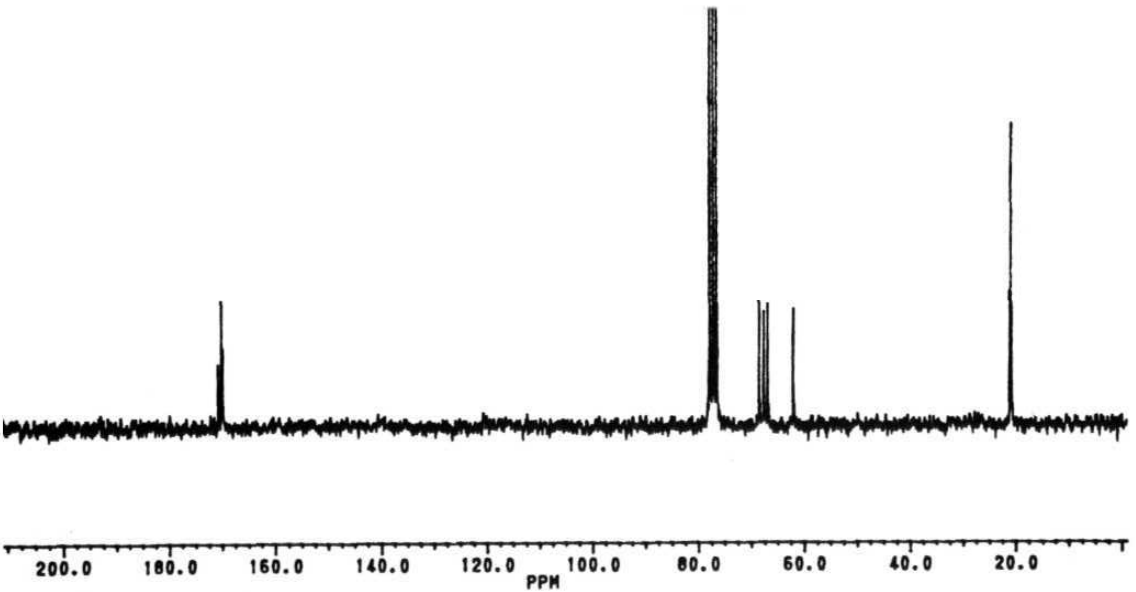
200 MHz ^{1}H NMR spectrum of **153-OAc**



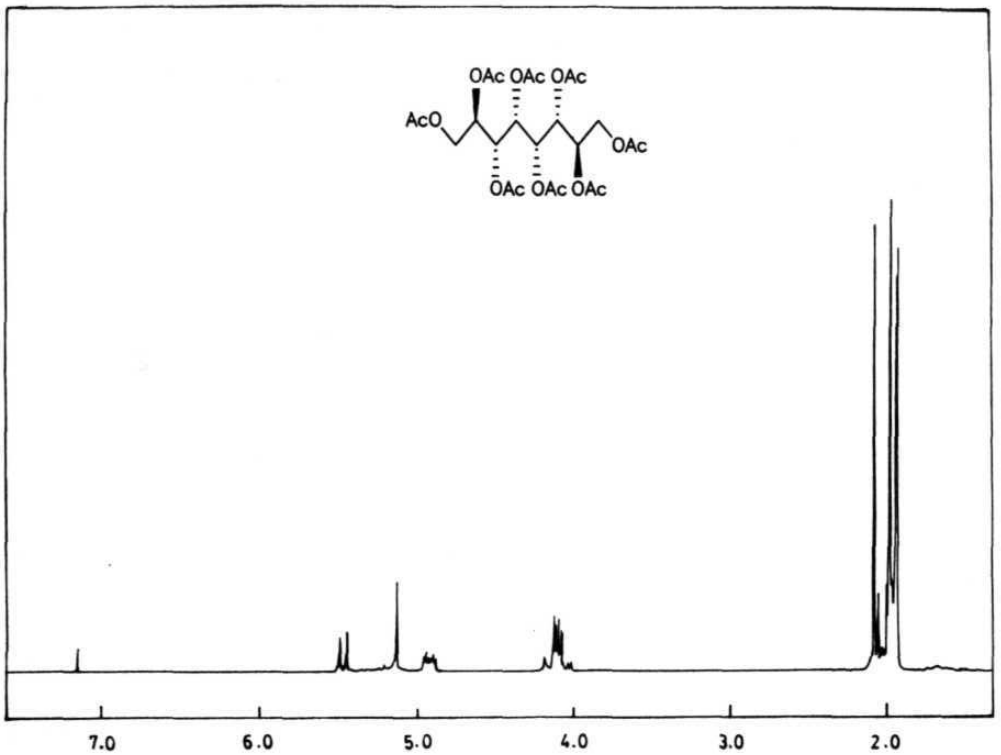
50 MHz ^{13}C NMR spectrum of **153-OAc**



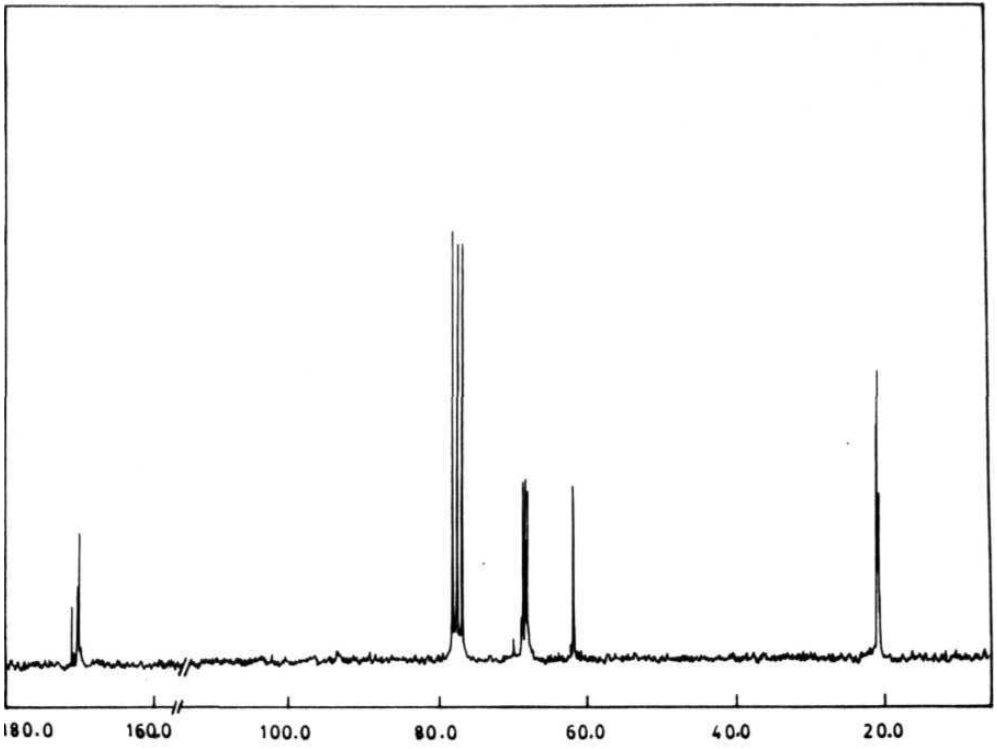
200 MHz ^{1}H NMR spectrum of **155-OAc**



50 MHz ^{13}C NMR spectrum of **155-OAc**



200 MHz ^{1}H NMR spectrum of **158-OAc**



50 MHz ^{13}C NMR spectrum of **158-OAc**

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