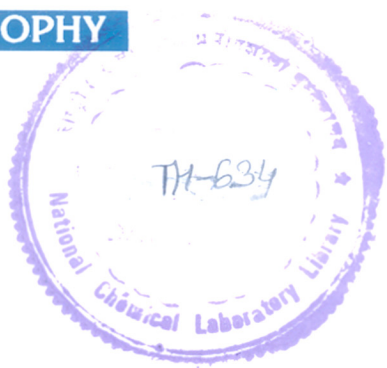
SYNTHESIS OF COMPLEX CARBOHYDRATES

THESIS

Submitted to University of Poona
for the Degree of

DOCTOR OF PHILOSOPHY

in chemistry



By

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PUNE - 411 008

1991

"Science and Peace will triumph over Ignorance and war, that nations will unite not to destroy, but to build, and that the future will belong to those who will have done most for suffering humanity"

- LOUIS PASTEUR

DEDICATED WITH LOVE AND AFFECTION

TO MY

PARENTS AND TEACHERS

DECLARATION

The research work embodied in this thesis has been carried out by me in the Division of Organic Chemistry, National Chemical Laboratory, Pune, under the supervision of **Dr Hari Babu Mereyala,** Scientist, Indian Institute of Chemical Technology, Hyderabad (formerly in NCL, Pune). The work is original and has not been submitted for any research degree of this or other Universities.

Date: 21st February, 1991

(DHAMJEWAR RAVI)

Certified that the work incorporated in the thesis "**Synthesis of Complex Carbohydrates**" submitted by **Mr Dhamjewar Ravi** was carried out by the candidate under my supervision. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

M. Hari Babu 21/2/91

(DR HARI BABU MEREYALA)
Supervisor

Date: 21st Feb' 1991

CONTENTS

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I wish to record my appreciation and thanks to **Mr G Venugopal Reddy** *and other friends for their help and pleasant company.*

My special thanks are due to **Meera**, *my wife for her unstinted co-operation extended during the work.*

Finally I thank the Director, NCL, Pune for providing facilities and CSIR, New Delhi for financial support.

(D RAVI)

GENERAL REMARKS AND EXPERIMENTAL MEMORANDA

1. All dry reactions were performed in oven dried glassware.
2. Dichloromethane was distilled from P_2O_5 and stored over 4Å molecular sieves. Diethyl ether and THF were distilled from sodium benzophenone ketyl. Petroleum ether and $CHCl_3$ were distilled over anhydrous $CaCl_2$ and P_2O_5. Pyridine was distilled and stored over KOH pellets. Toluene was distilled over sodium and stored over 4Å molecular sieves.
3. Workup procedures include drying organic extracts over anhydrous Na_2SO_4 and concentration under diminished pressure.
4. Column chromatography employed silica gel (60-120 mesh and finer than 200 mesh, Acme) unless otherwise stated.
5. Progress of the reactions was monitored by thin layer chromatography on 0.5 mm layers of silica gel-G with 13% $CaSO_4$ binder.
6. Spraying the solution of 2% phosphomolybdic acid, 1% Ce_2SO_4 $4H_2O$ in 20% aq. conc. H_2SO_4 followed by heating the plates at 130°C for visualization of spots.
7. Melting points were determined in open capillaries and are uncorrected.
8. Nuclear magnetic resonance and carbon magnetic resonance spectra were recorded in $CDCl_3$ solutions containing TMS as an internal standard on Varian J-60, Varian FT-80A, Brucker WH-90 (^{1}H-90 MHz), ^{13}C-22.3 MHz), Brucker MSL-300 (^{1}H-300 MHz, ^{13}C-75 MHz) spectrometers. Chemical shifts are expressed in downfield from TMS.

^{1}H-nmr ($CDCl_3$, TMS, δ in ppm, J in Hz)

^{13}C-nmr ($CDCl_3$, TMS, δ in ppm).

9. Optical rotations were recorded on Jasco Dip 181 digital polarimeter using sodium vapour lamp in $CHCl_3$.

ABSTRACT

The thesis "SYNTHESIS OF COMPLEX CARBOHYDRATES" has been divided into four chapters.

CHAPTER 1 : A REVIEW ON CHEMICAL SYNTHESIS OF 2-DEOXY SACCHARIDES.

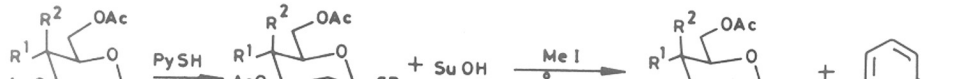
The reliazation that 2-deoxy sugars are vital components of many antibiotics and other therapeutic agents has been a source of constant research activity to synthesize them. In this chapter literature concerning the stereoselective synthesis of 2-deoxy saccharides is reviewed.

CHAPTER 2 : STEREOSELECTIVE SYNTHESIS OF α (AXIAL) LINKED 2-DEOXY SACCHARIDES BY USE OF PERACETYLATED 2-PYRIDYL 2-DEOXY-1-THIO-GLYCOSIDES AS GLYCOSYL DONORS AND METHYL IODIDE AS AN ACTIVATOR "A GENERAL GLYCOSIDATION METHODOLOGY".

A mild general method is described for the synthesis of α-linked (axial) 2-deoxy disaccharides. The easily obtainable, (from 1,2 and 3) stable 2-deoxy 2-pyridyl-1-thioglycosides (5,6 and 7 (1 mmol) (anomeric mixture α / β) on activation by methyl iodide (3% in 5 ml methylene chloride) at 50°C (molecular sieves, 4 Å) (12-36 h) (dry CH_2Cl_2) couple with equimolar amount of diverse sugar alcohols (9-13) to afford

SCHEME - 1

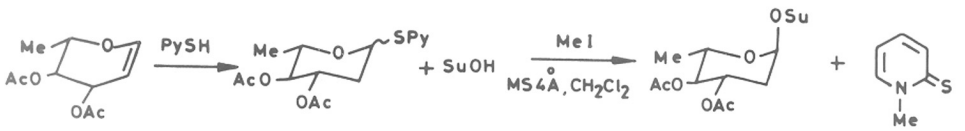
Glycosyldonors :



(1) R^1 = OAc, R^2 = H
(2) R^1 = H, R^2 = OAc

(5) R^1 = OAc, R^2 = H (α/β, 2/3)
(6) R^1 = H, R^2 = H (α/β, 2/3)

(15, 16, 18, 19, 21, 23)
α - Compounds

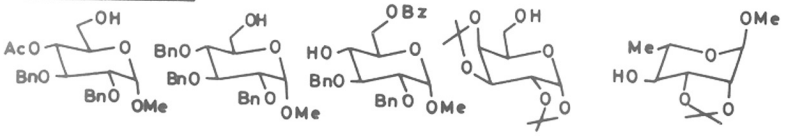


(3)

(7) (α/β, 1:1)

(17, 20, 22)
α - Compounds

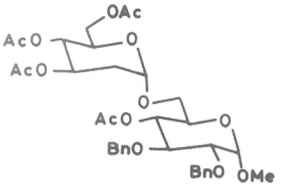
Sugaralcohols :



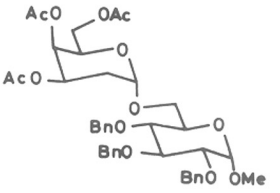
(9) (10) (11) (12) (13)

Bn = $C_6H_5CH_2$, Bz = C_6H_5CO-

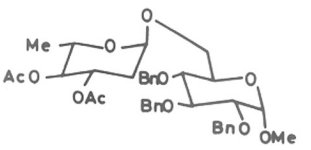
DISACCHARIDES



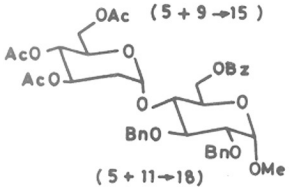
(5 + 9 → 15)



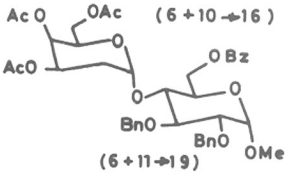
(6 + 10 → 16)



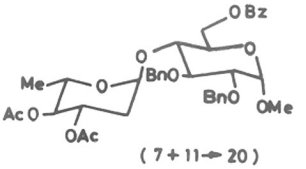
(7 + 10 → 17)



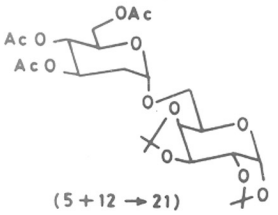
(5 + 11 → 18)



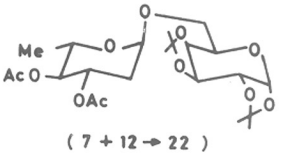
(6 + 11 → 19)



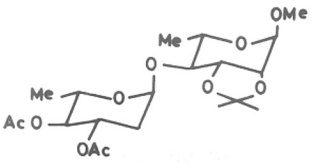
(7 + 11 → 20)



(5 + 12 → 21)



(7 + 12 → 22)



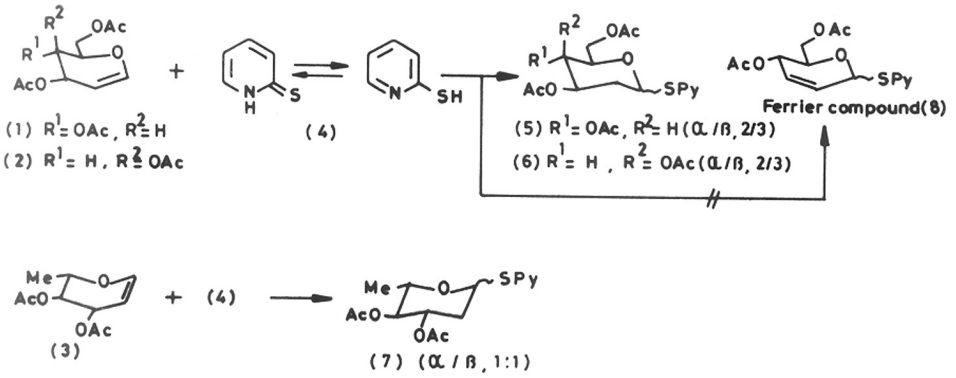
(7 + 13 → 23)

in high stereocontrol the α-linked 2-deoxy disaccharides (5+9=15, 6+10=16, 7+10=17, 5+11=18, 6+11=19, 7+11=20, 5+12=21, 7+12=22, 7+13=23) in good yield (34-88%) (SCHEME 1).

The significant achievement of this methodology as "anomeric mixture" of pyridylthioglycosyl donors (α / β 1:1) couple with sugar alcohols to give α-linked 2-deoxy disaccharides exclusively. Nine disaccharides were synthesized by this procedure giving it the status of a general methodology.

The sturdy 2-deoxy 2-pyridyl-1-thioglycosyl donors (5,6 and 7) were synthesized in good yield by 1,2-addition of 2-mercaptopyridine (4) (1 mol) on substituted glycals (1,2 and 3) (1 mol) (SCHEME 2) in CH_2Cl_2 containing catalytic amount (0.32 mol) of anhydrous p-toluenesulphonic acid. No Ferrier reaction product (8) was formed under these conditions.

SCHEME 2

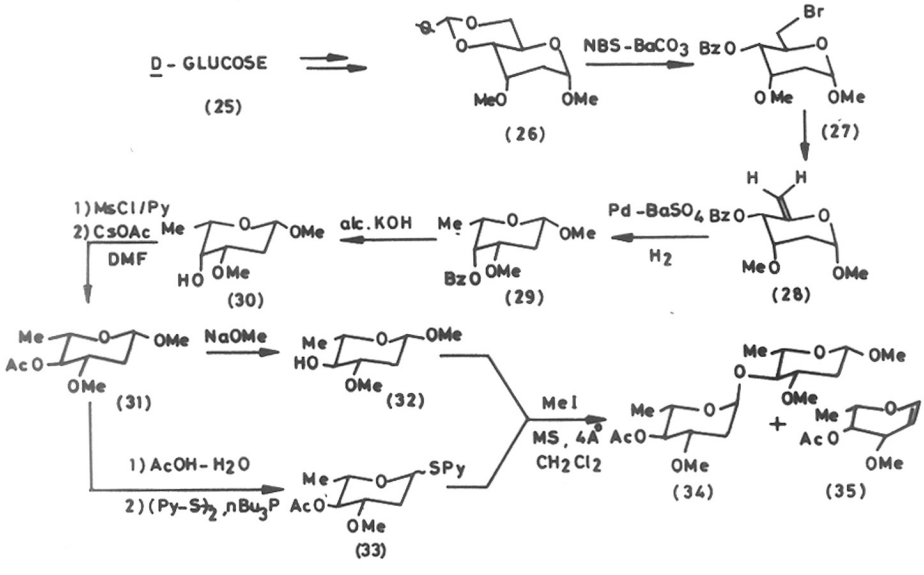


2.2 Synthesis of methyl 4-O-(4'-O-acetyl-α-L-oleandrosyl)-β-L-oleandroside (34)--"A disaccharide fragment of Avermectin" from D-glucose

A stereoselective synthesis of methyl 4-O-(4'-O-acetyl-α-L-oleandrosyl)-β-L-oleandroside derivative **34** is described starting from D-glucose. This synthesis benefits from the methyl iodide activation proce-

dure developed by us (Chapter 2) to couple pyridylthioglycosides with sugar alcohols to obtain (α)-(axial) linked deoxy saccharides.

SCHEME 3

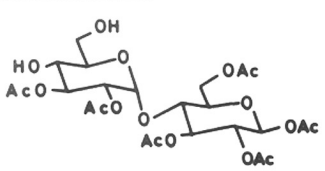


2.3 Synthesis of 2-deoxy trisaccharides by methyl iodide activation of 2-deoxy 2-pyridyl-1-thioglycosides

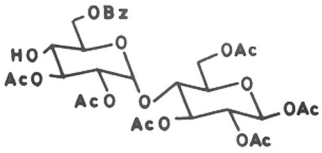
The general applicability of the methyl iodide activation procedure was also shown by the rapid synthesis of complex trisaccharides (38, 39 and 40). Thus coupling of 2-deoxy pyridylthioglycosyl donor (5) with 1,2,3,6,2',3'-hexa-O-acetyl-β-maltose (acceptor) (36) afforded the trisaccharide (38) (55%), likewise reaction of (7) with (36) and (37) afforded (39) and (40) respectively. All the trisaccharides thus obtained were characterised by ^{1}H, ^{13}C-n.m.r. and 2D-H-H spectra (Scheme 4).

SCHEME - 4

Sugar alcohols (SuOH) :

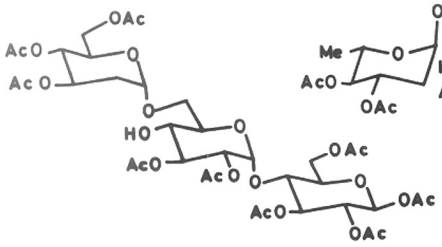


(36)

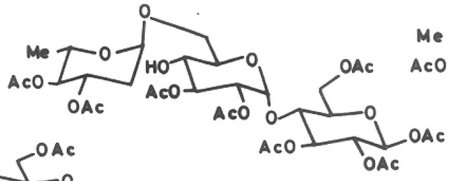


(37)

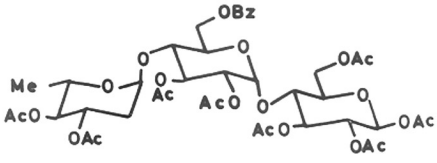
Trisaccharides :



(5 + 36 → 38)



(7+ 36 → 39)



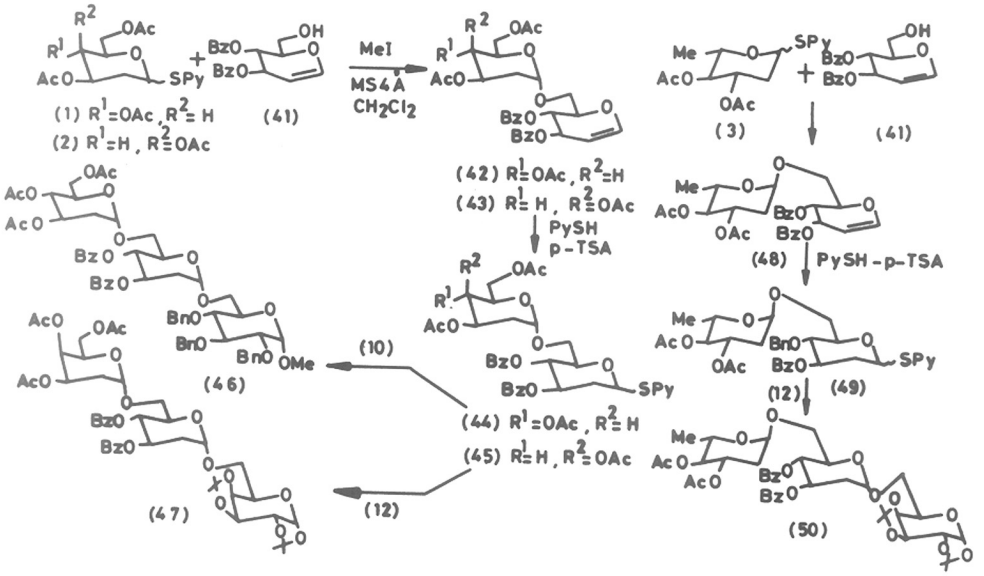
(7 + 37 → 40)

CHAPTER 3 : ITERATIVE, STEREOSELECTIVE SYNTHESIS OF α--LINKED 2-DEOXY SACCHARIDES

A new glycosidation methodology has resulted based on the 1,2-addition of 2-mercaptopyridine (**4**) on simple glycals (**1,2** and **3**) (Chapter 2) and for even greater finesse on to the sensitive saccharide glycals (**42, 43** and **48**) (for iteration) to obtain their corresponding 2-deoxy 2-pyridyl-1-thioglycosyl donors (α / β , 3/2 ratio) **44, 45** and **49** respectively. Coupling of such 2-deoxy pyridylthiolgycosides (**44, 45** and **49**) with sugar alcohols (**10** and **12**) by the proven methyl

iodide activation procedure gave the α-linked 2-deoxy saccharides 46, 47 and 50 respectively in good yield (65-85%) (Scheme 5).

SCHEME 5

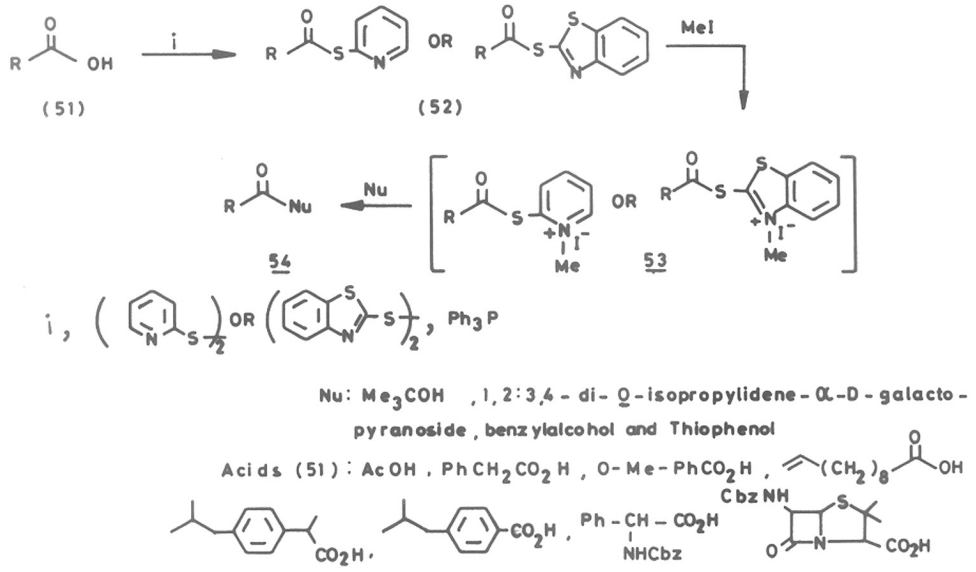


CHAPTER 4 : A NEW MILD METHOD FOR THE SYNTHESIS OF ESTERS AND BENZENETHIOL ESTERS BY ACTIVATION OF PYRIDINE-2-THIOL OR BENZENETHIAZOL-2-THIOL ESTERS BY METHYL IODIDE

The formation of an ester is one of the most well established fundamental reaction, which is widely used in organic synthesis. A mild and general one pot method is described where pyridine-2-thiol-or 2-mercaptobenzothiazol esters (52), generated in-situ, by reaction of various carboxylic acids (51) with (Py-S-S-Py or BTh-S-S-BTh/Ph_3P), (52) were activated by methyl iodide at room temperature in presence of diverse alcohols and benzenethiol to yield esters and benzenethiol

esters **54** in good yields (68-97%) (Scheme 6). Activation of thiolesters **52** with methyl iodide gives rise to a highly reactive N-methyl quaternary ammonium intermediate **53**, which subsequently undergoes a fast nucleophilic displacement to give their corresponding esters and thiol esters **54**. The mildness of this new method was demonstrated by the use of various acid and base sensitive acids to prepare their esters **54**.

SCHEME 6



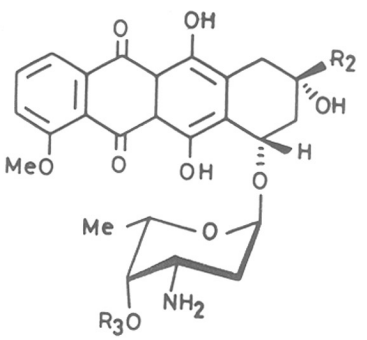
CHAPTER 1

A REVIEW ON CHEMICAL SYNTHESIS OF 2-DEOXY SACCHARIDES

1.1 Biological importance and role played by 2-deoxy saccharides

Numerous antibiotics contain carbohydrate moieties which play a crucial role in most instances by conferring the optimum biological activity on the compound[1]. Most of these sugars have unique chemical structures; the complexity and structural diversity of these sugars has encouraged many research groups to take up the challenge of synthesizing them. This has served not only to confirm many of their chemical structures but also provided sugars that are useful for the total synthesis of these antibiotics[1-5] and for studying structure-activity relationship.

Daunomycin (1)[2,3], adriamycin (2)[4] have been isolated from the cultures of Streptomyces peucetius and they possess the amino sugar L-Daunosamine. Template specific inhibition of DNA polymerase by daunomycin and its derivatives has been reported[5]. The sugar chains of the antibiotic are essential for binding in the complex[6] for biological activity. Analogs in which some of the sugar chains have been cleaved, bind weakly, with rates of dissociation of their complexation increasing as the number of sugar decreased[7]. The importance of the amino sugar residue for the binding was also emphasized by experiments in which substitution of daunosamine for N-guanidine acetyl-daunosamine or for D-glucosamine conside-



Daunomycinone

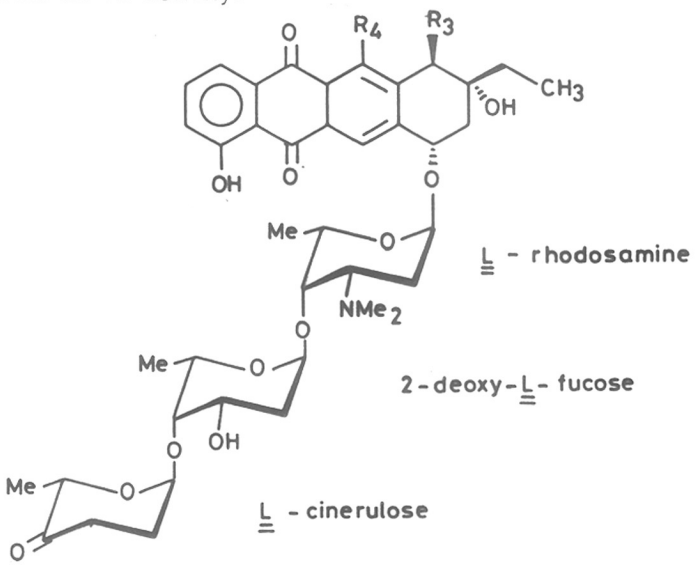
L - Daunosamine

1 Daunomycin $R_1 = CH_3$, $R_2 = COCH_3$, $R_3 = H$

2 Adriamycin $R_1 = CH_3$ $R_2 = COCH_2OH$, $R_3 = H$

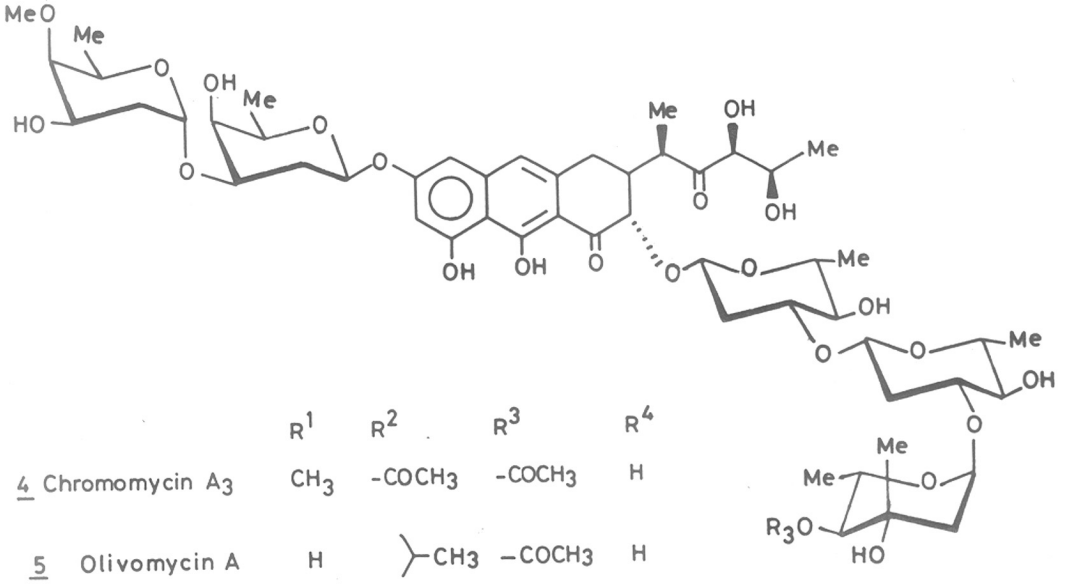
rably reduced the apparant binding constants[8]. Hence extensive studies towards the synthesis of Daunosamine have been carried out[9] with an intention to prepare various analogs.

Anthracycline antibiotic cincrubin-A(3)[10] contain a trisaccharide unit composed of L-cinerulose, 2-deoxy-L-fucose and L-rhodosamine which is essential for its activity.

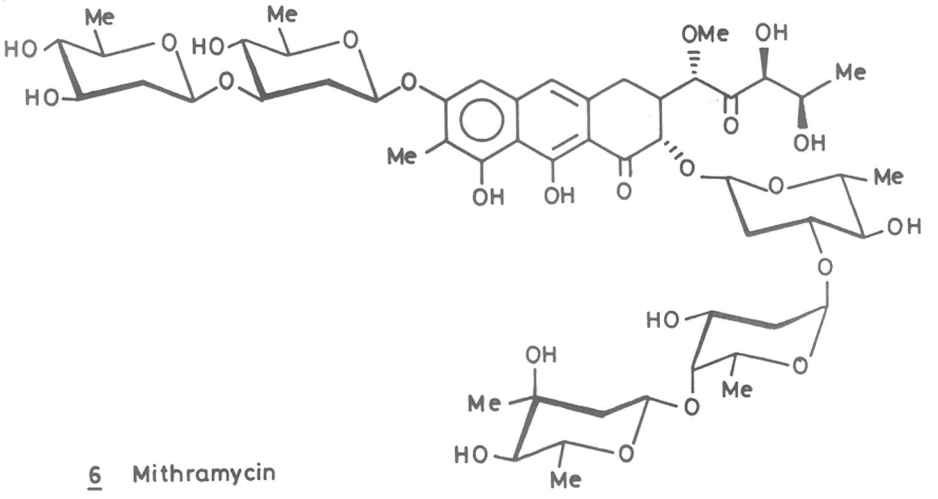


3 Cinerubin-A

Another family of anthracycline antibiotics, which contains 2-deoxy saccharides is chromomycin A_3 (4)[11], olivomycin A (5)[12] and mithramycin (6)[13] isolated from streptomyces species. They were found to be clinically effective against disseminated testicular neoplasms[14] and being used in the treatment of tonsillar tumors[15,16]. It has been observed by Behr. et al that rate of complexation of these anthracycline antibiotics with DNA is independent of the size of the sugar side chains and of the nature and base composition of the DNA[7]. The structures of the antibiotics have been confirmed by their chemical synthesis[17,18].



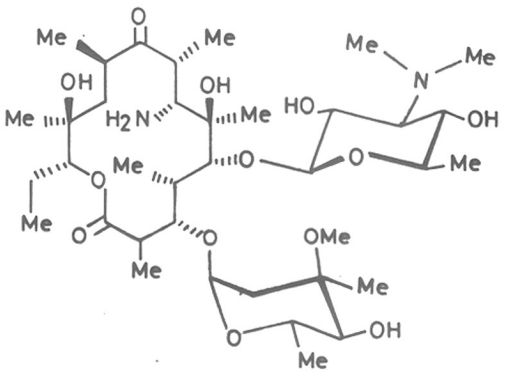
	R^1	R^2	R^3	R^4
4 Chromomycin A_3	CH_3	$-COCH_3$	$-COCH_3$	H
5 Olivomycin A	H	$\rangle-CH_3$	$-COCH_3$	H



6 Mithramycin

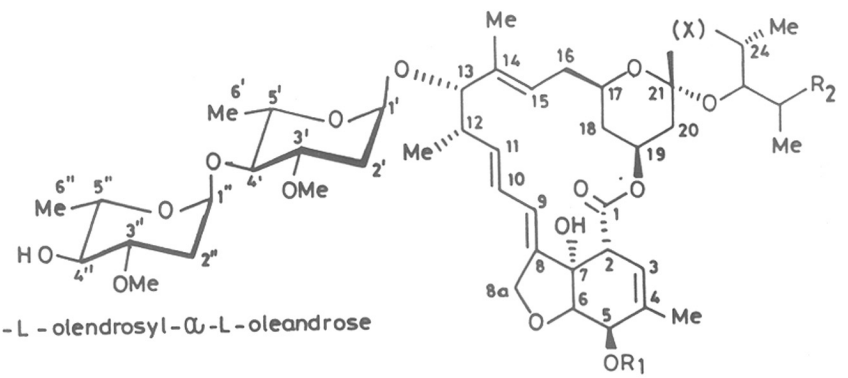
Erythromycin A (7) a 14-membered macrolide antibiotic substance produced by a strain of Streptomyces erythreus, contains D-desosamine and a neutral glycoside at C-3 which may be either L-cladinose or L-mycarose[19,20]. It has been widely used in clinical medicine to combat staphy-

lococcal, pneumonococcal, streptococcal, and mycoplasmol infections. Both the 2-deoxy sugars are necessary for optimal biological activity[21-26].



7 Erythromycin - A

In 1979, Merck Sharp and Dohme Laboratories isolated a member of the family of the macrolide antibiotics called the avermectins (8) from Streptomyces avermitilis[27-29]. 8a-8d have shown novel mode of ecto and endo parasitic activity against a broad spectrum of nematodes (worm) and arthropod parasites of animals[30]. They contain at C-13 α-L-oleandrosyl-α-L-oleandrose a 2-deoxy disaccharide fragment, which is essential for biological activity. Removal of the disaccharide brings down the acti-



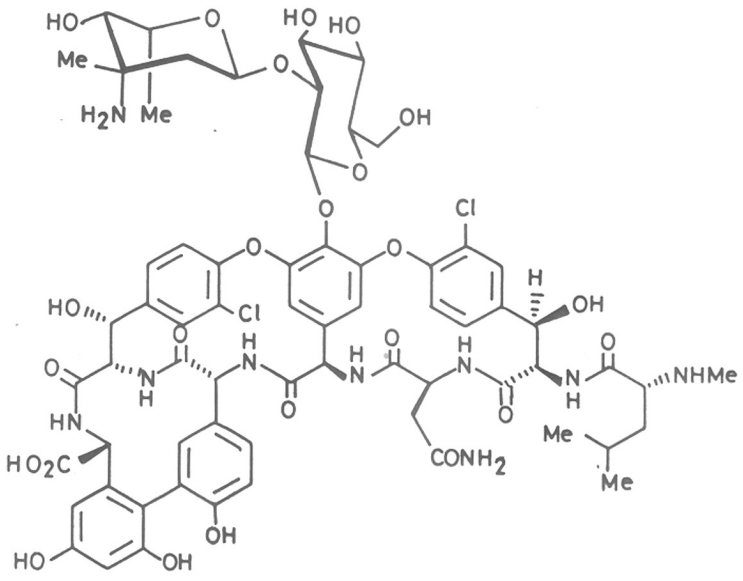
α-L-olendrosyl-α-L-oleandrose

8a $R_1 = CH_3$: Components A
8b $R_1 = H$: Components B
8c $R_2 = C_2H_5$: Components a
8d $R_2 = CH_3$: Components b

X = CH=CH– : Components 1
X = –CH(OH)–CH– : Components 2

vity of the compound considerably[31].

Vancomycin (9) a complex amphoteric glycopeptide, has been isolated from Streptomyces orientalis and is a narrow-spectrum antibiotic active against Gram-positive bacteria and some spinochelates[32-34]. Removal of one sugar unit leads to the formation of an aglucovancomycin which retains about 75% of the biological activity of the unaltered antibiotic[35].

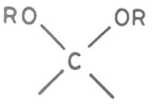


9 Vancomycin

1.2 General characteristics of O-glycosidic bond : formation and cleavage

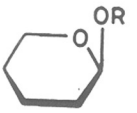
The most fundamental structrual unit of oligosaccharide chain is the O-glycosidic bond[36]. It is an example of the acetal bond 10 and has the same set of fundamental properties. O-glycosidic bond has two non-equivalent alkoxy groups attached to the glycosidic center (anomeric center). One of these groups is included in the cyclic system, where as the other is exocyclic and is much more reactive than the former (structure 11 and 12). So the typical reactions of formation and cleavage of the

O-glycosidic bond proceed by exchange of exocyclic residues of the acetal system in which the oxygen heterocycle remains unreacted.



Acetal

10



Cyclic acetal

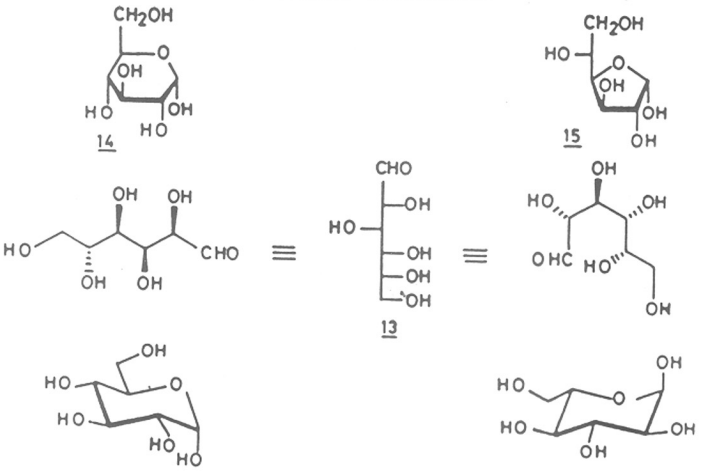
11

12

Taking D-glucose as an example it has been shown that [37] the acyclic polyhydroxy aldehyde form 13 is in equilibrium with two cyclic forms (SCHEME 1). The six membered pyranose ring 14 is favoured over the five 15 and the seven membered forms, as would be expected on conformation grounds. In the $^{4}C_{1}$ conformation, α-D-glucopyranose 16 has all its substituents equatorial except for the anomeric substituent. This form of D-glucose could be conveniently manipulated as a six membered cyclic derivative, much in the same way as a cyclohexane derivative, with allowance being made for the stereoelectronic consequences of replac-

SCHEME 1

α - D - Glucose conformations

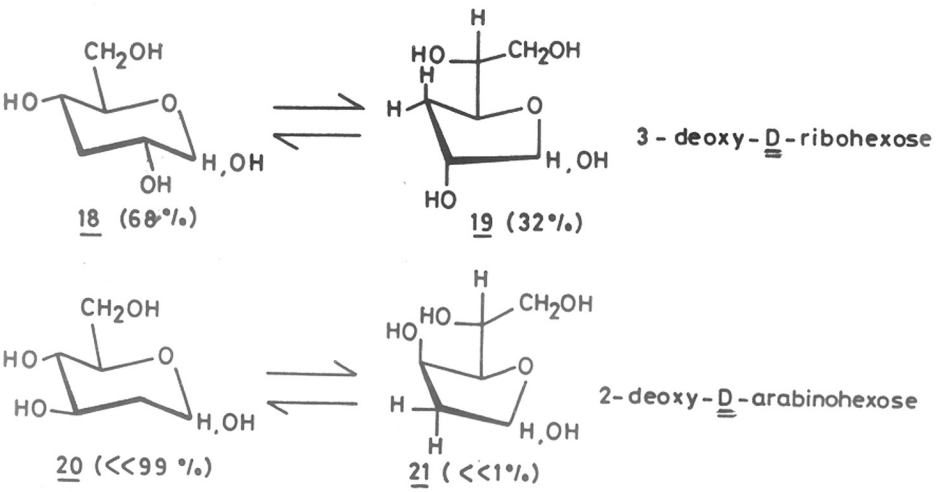


16 α-D-glucopyranose ($^{4}C_{1}$)

17 α-L-glucopyranose ($^{1}C_{4}$)

ing a ring carbon by an oxygen atom (SCHEME 1). The $^{1}C_{4}$ conformation, α-L-glucopyranose **17** also has its anomeric 1-OH in axial and all other substituents in equatorial position. The anomerization of an aldopyranose or ketopyranose may occur by a mechanism involving a cyclic intermediate, or it may proceed via an acyclic aldehydo or keto intermediate. Although the relative stabilities of the pyranoses would appear to be the determining factor in deciding the compositions of aqueous solutions of aldoses at equilibirum, it can't be denied that the relative stabilities of the furanoses may also play a minor role. The observations that 3-deoxy-D-ribohexose (18) contains 32% of furanose anomers (19) at equilibrium in aqueous solution, it would appear that a cis interaction between O-3 and C-5 is particularly unfavourable[38] (SCHEME 2). This interaction between O-2

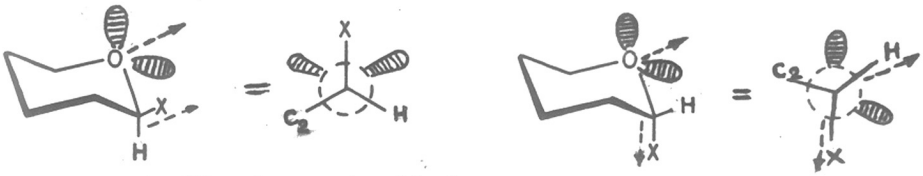
SCHEME 2



and O-3 is probably not so favourable, as indicated by the fact that no furnaose anomers (21) were detected at equilibrium in the ^{1}H-nuclear magnetic resonance spectrum of 2-deoxy-D-arabino hexose (20) in deuterium oxide[39].

1.3 The Anomeric Effect

Electronegative substituents on the anomeric carbon atom assume a higher abundance of axial positions that could be expected from the analogy with cyclohexane derivatives. This apparently anamalous situation was first discussed by Edward[40] and it has been termed the "anomeric effect" by Lemieux[41]. The anomeric effect has been interpreted in terms of polar interactions between the negative group attached to the anomeric position and non-bonded electron pair of the ring oxygen. Newman projections will reveal that an equatorially oriented electronegative substituent will be gauche to both electron lobes of the ring oxygen, where as an axially oriented substituent will be gauche to only one lobe and antiperiplanar to the other.



The Anomeric effect

Another interpretation of the anomeric effect is based on highest occupied molecular orbital, lowest unoccupied molecular oribital (HOMO-LUMO) interactions. Thus, an overlap between the HOMO of the ring oxygen (the 'p' orbital of one of its nonbonding electrons) and a suitably located LUMO (an antibonding σ^* orbital) of the anomeric carbon will increase the electron density of the group located in an antiperiplanar position relative to the oxygen HOMO. If this group is electronegative it will be stabilized, and if it is a hydrogen it will be destabilized[42-44].

Effect of substituents and solvent on Anomeric effect

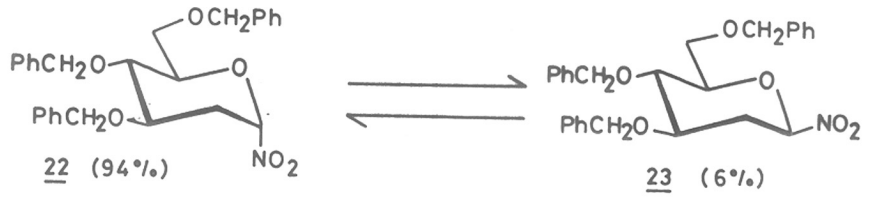
Determination of the relative representation of the axial and equatorial forms of pyranoses can be a very difficult and demanding task.

In general, the abundance of isomers at equilibrium depends mainly on the type of substituent (aglycone) on the anomeric center, other substituents on the ring, and on the nature of the solvent[128].

The character of the aglycone

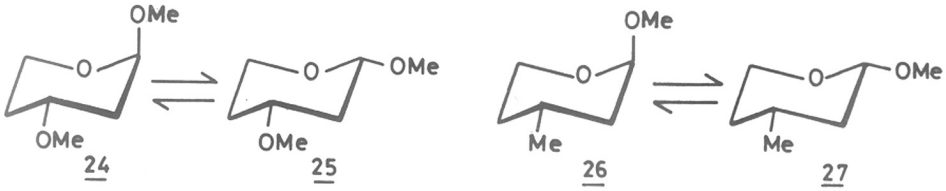
The preference for the axial position increases with the electron withdrawing character of substituent X, and is most conspicuous for the halogen and alkoxy derivatives. An increase in size of the alkoxy group diminishes the preponderance of the axial form, such that changing from a methoxyl to tert-butoxy group in 2-substituted oxane decreases the abundance of the axial form by 15%. This phenomenon was found to be caused by the entropy, rather than enthalpy term[45]. The size of a substituent does not seem to influence the equilibration. The electronegativity of 'X' by change from the ethoxy to trichloroethoxy derivative increases the population of the axial form from 80 to 95%. Similarly, in halogen derivatives of oxane, the axial forms are the sole detected species.

The preference for the axial position diminishes with less electronegative atoms linked to the anomeric center; that is F > O > N > C for the first row of the Periodic Table. For the latter two elements, N and C, the anomeric equilibrium depends on the overall polarity of the substituent. Thus, derivatives of substituted D-arabinopyranose contain 94% of the isomer **22** raising a nitro group in the axial position in equilibrium[46] and 6% of the isomer **23** having a nitro group in the equatorial position. As a rough guide it may be stated at the outset that the anomeric effect (O:X) decreases through the series where 'X' is halogen > benzyloxy > acetoxy > acetylthio > methoxyl > alkylthio > hydroxy > amino > methoxy carbonyl > 4-methylpyridinium cation.



Nature of other substituents

It is well known that the presence and configuration of a hydroxyl on C-2 of the pyranose ring markedly affects the anomeric equilibrium[39,47]. Thus, in case of D-manopyranose, the axial hydroxyl group, on C-2 increases the presence of the α-anomer (69%) relative to that for 2-deoxy-D-arabinohexopyranose (47.5%), which has no hydroxyl group on C-2. Conversely, when the hydroxyl group on C-2 is in the equatorial position as in D-glucopyranose, the portion of α-anomer decreases to 36% which is due to 2 effect operative in pentopyranoses and methylglycosides[48]. Reeves stated that any erected substituent, other than hydrogen on a pyranose ring introduced an element of instability to the ring formation[48]. The electronegativity of the substituent on C-4 also influences the anomeric equilibrium. Consequently, 2,4-dimethoxyoxane exists in methanol as an equilibrium mixture **24** ⇌ **25** containing 80% of the isomer[49] having an axial methoxyl group on C-2 (**26**) compared with 67-69 for 2-methoxy-4-methyloxane (27)[50,51].

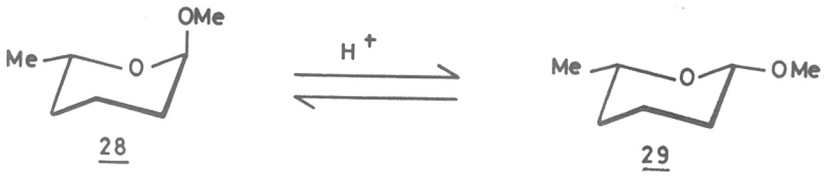


In general, the presence of several bulky substituents on the pyranose ring makes the anomeric equilibria very intricate, and even the all axial $^1C_4$ form can be observed as in β-D-xylopyranosetetraacetate (28%) or

in the corresponding tri-O-benzyl-β-D-xylopyranosylacetate[52,53] (47%).

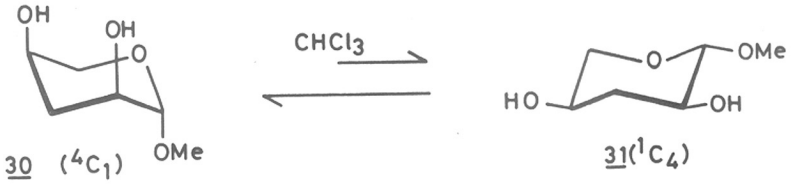
Nature of the solvent

Generally speaking, the anomeric effect, is predominant in solvent (eg. carbontetrachloride) of low dielectric constant and vice versa of solvents (eg. water) of high dielectric constant. This is exemplified by the acid catalysed equilibration of 2-methoxy-6-methyltetrahydropyran **28** ⇌ **29** which has been studied in solvents like carbontetrachloride (0.74 k.cal/mole), 1,4-dioxane (0.6 k.cal/mole), tetrahydrofuran (0.6 k.cal/mole) nitrobenzene (0.4 k.cal/mole), acetonitrile (0.35 k.cal/mole) shows that the preference for the axial methoxyl group is lessened in solvents of high dielectric constant[54]. However, the influence of the dielectric constant on the anomeric effect, and hence conformational equilibria, is often found to be incidental to other, more important solvation effects involving hydrogen bonding.



28 29

Thus, methyl 3-deoxy-β-L-erythropentopyranoside (**31**) exists predominately as the $^4C_1$ conformer **30** in solvents such as chloroform which does not form hydrogen bonds with hydrogen atoms of the hydroxyl groups. Indeed, under such circumstances, the $^4C_1$ conformer is stabilized by an intermolecular hydrogen bond involving the synaxial hydroxyl groups[54].

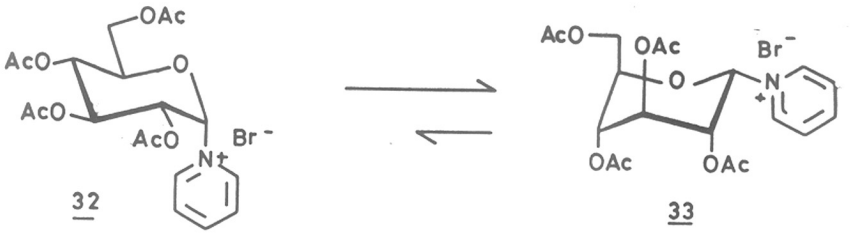


30 ($^4C_1$) 31($^1C_4$)

In summary, experimental data on the isomeric abundance at anomeric equilibrium reveal that the preference for the axial position depends on several, inter connected factors, which were classified in surveys on carbohydrate stereochemistry[55,56] and these provided a back ground for ensuing theoritical studies.

1.4 The Reverse Anomeric Effect

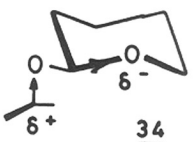
In 1910, Fischer and Raske reported the preparation of N-(tetra-O-acetyl-β-D-glucopyranosyl)-pyridinium bromide[57]. Recently Lemieux and Morgan[58] reported the preparation of the α-anomer as a syrup. Application of these synthetic methods has now yielded both the anomers for the 4-methylpyridine analogs in pure crystalline condition. The unique conformational properties of these compounds stimulated a study of related compounds[59-61].



32 33

The compounds 32 and 33 appears to have a conformation which is close to the $^{1}C_{4}$ (33) conformation where in the acetoxy groups at the 2,3 and 4-positions are in axial orientation. Such a strong distortion of the pyranose ring from the $^{4}C_{1}$-conformation, where in the substituents at the 2 to 5 positions would be in the equatorial position, must arise from powerful non-bonding interactions, arising from the 4-methylpyridinium group when in axial orientation at the anomeric center. The N-C bond length in quaternary ammonium compounds is substantially shorter

(1.48 Å) than the C-C bond (1.52 Å). It is to be noted, however, that the establishment of a positively charged atom in axial orientation at the anomeric center must be expected to meet a strongly destabilizing effect (relative to when the group is in equatorial orientation) arising from the electrostatic interaction between the C-1 to N and C-5 to O bonds, when the N and C-5 atoms are in gauche relationship. This interaction amounts to the reverse anomeric effect[62-64]. The protonation of an axial aglycone at the atom bonded to the anomeric center will cause strong destabilization of the conformation of the sugar ring relative to that where in the aglycone is in equatorial orientation. Thus, it can be speculated that for α-glucosides, the preferred point of protonation in the course of acid-catalyzed hydrolysis would be at the ring oxygen atom. On the other hand, for β-glucosides, the reverse anomeric effect would tend to lead to protonation at the oxygen of the aglycone since, in this case, protonation of the ring oxygen would have to disturb the orientation of the aglycone from the sterically and electronically most favourable position where in the first carbon of the aglycone is gauche to the ring-oxygen as depicted in structure[62] **34**.



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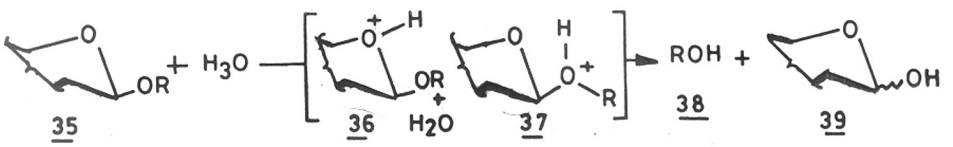
1.5 O-Glycosidic bond cleavage

Cleavage of glycosidic bond can be carried out by different methods, the most important of which is an acid-catalysed, or more generally electrophilic, solvolysis reaction. Acid-catalysed hydrolysis of O-glycosides **35** gives rise to the corresponding alcohol **38** and the reducing sugar **39** via protonated intermediates (as **36** or **37**) (SCHEME 3).

SCHEME 3



The crux of the problem is whether the reaction proceeds mainly by protonation of cyclic oxygen atom, i.e., via oxonium intermediate **36** or by protonation of the glycosidic oxygen atom, i.e., via oxonium intermediate **37**. The question was extensively disputed earlier but now seems to be finally solved atleast for typical examples of pyranosides, in favour of protonation of the glycosidic oxygen[65,66]. The basic facts are:

1) The systematically observed lower rate of hydrolysis of 1-thio-glycosides as compared with their O-analogues, attributed to the relatively lower basicity of the sulphur atom and, therefore, to the lower concentration of intermediate congugate acid under the same reaction conditions[67-70].

2) Appreciable isotope effect of glycosidic oxygen[71].

3) Preferred inversion associated with a similar acid-catalysed methanolysis of phenyl glycosides[71].

4) The fact that numerous data on the influence of the structure of glycosyl residues on relative rates of hydrolysis can be rationalized interms of the mechanism including intermediate **37** rather than that including the intermediate 36.

The oxonium ion **37** can react in two ways: with a cleavage of the glycosidic centre-oxygen or oxygen-aglycone bond.

For common O-glycosides only one direction of splitting takes place, namely that of the glycosidic centre oxygen bond. The following data support this conclusion:

1) It has been shown that hydrolysis in $H_2{}^{18}O$ proceeds with incorporation of the label into a sugar but not into aglycone[72,73].

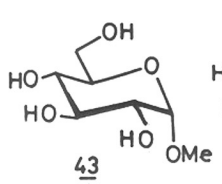
2) In the hydrolysis of oligo- or polysaccharides, as well as of other glycosides with an asymmetric centre in the aglycone, attached directly to the glycosidic oxygen, inversion of configuration or racemization in the aglycone has never been observed.[36].

3) Eliminations or rearrangements in the aglycone have also never been observed as a result of hydrolysis of the corresponding glycosides, with a few exceptions mentioned below[36].

4) The rates of hydrolysis of O-glycosides are very sensitive to steric and electronic features of the glycosyl residue and have a very low sensitivity to the same factors in the aglycone[36].

Presence of a 2-deoxy carbon in the glycoside results in appreciable acceleration of acid catalysed hydrolysis; which is illustrated by comparison of the rate of hydrolysis of three deoxy sugars **40-42** with parent glycoside **43** (hydrolysis in 2M HCl at 58°)[74].

Compound :



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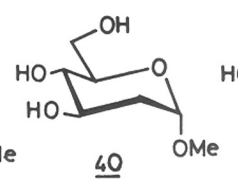

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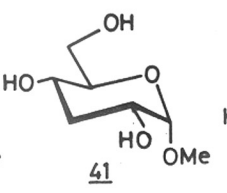

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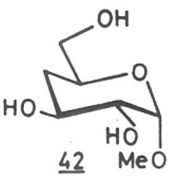


42

Relative rate :	1	2090	20	40

The enhanced acid-lability of 2-deoxy glycosides is undoubtedly due to two effects[75-82]. The removal of the hydroxyl group at C-2 would enhance the formation as well as the decomposition of the conjugate acid due to decrease of hindrance to intramolecular rotation associated with glycosyl cation formation.

1.6 SYNTHESIS OF α-2-DEOXY OLIGOSACCHARIDES : A REVIEW

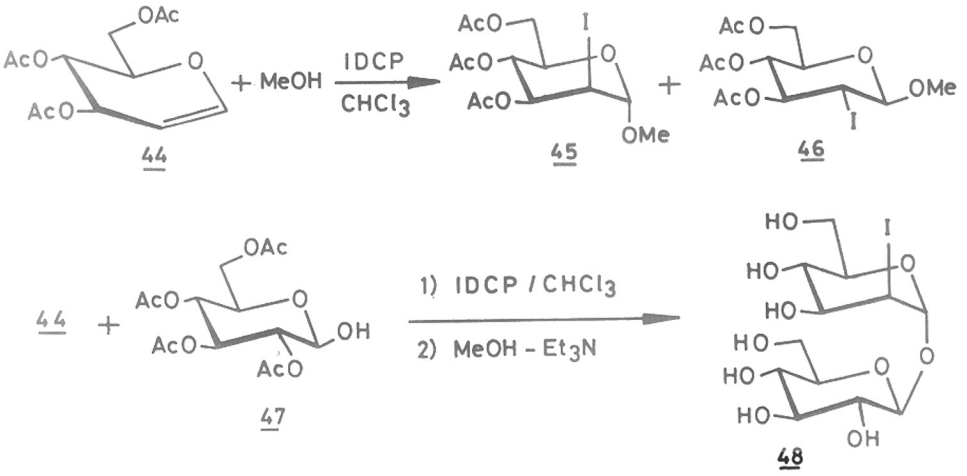
The basic concepts of glycosidation have been known for more than eighty years. Nevertheless, the stereoselective formation of a full acetal constitutes and remains one of the major challenges in carbohydrate chemistry. Within the current decade a number of attractive approaches for the glycosidation using simple alcohols and also more complex aglycones (including sugar derivatives) have been developed[83-132]. Hence, it is appropriate to review the literature regarding the synthesis of 2-deoxy saccharides. A high diastereoselectivity is desired in such synthesis and has been observed that simple transfer of a procedure worked out for certain sugar series does not necessarily apply to other isomeric series. This review centres around the stereoselective synthesis of α and β linked 2-deoxy saccharides (till November 1990).

1.6.1. Glycals as donors

Addition of halonium ion on to the glycals was observed by **Lemieux**[83]. This strategy has been further extended to the synthesis of several 2-deoxy saccharides[84]. Thus, reaction of 3,4,6-tri-O-acetyl-D-glucal (**44**)[85] with equimolar amounts of methanol and either iodonium or bromonium di-sym-collidine perchlorate complexes in chloroform gave virtually in quantitative yields of acetylated methyl 2-deoxy-2-halogeno-α -D-manno (**45**) and β-D-glucopyranosides (**46**) as anomeric mixture[84] (α /β : 82/18) (SCHEME 4). Similarly, treatment of **44** with 2,3,4,6-tetra-O-acetyl-β -D-glucose (**47**)[86] in presence of IDCP resulted in the exclusive formation of β-D-glucopyranosyl 2-deoxy-2-iodo-α -D-mannopyranoside (**48**) in 33% yield after deacetylation in methanol and triethylamine[84]. The stereoselective formation of disaccharide **48** denotes that the approach of halonium ion onto the glucal is more favoured from the β -side rather than from

the α-side, to give a cyclic, three membered halonium ion (SCHEME 4), which subsequently under goes a 1,2-trans diaxial ring opening to afford the α-glycoside **48**.

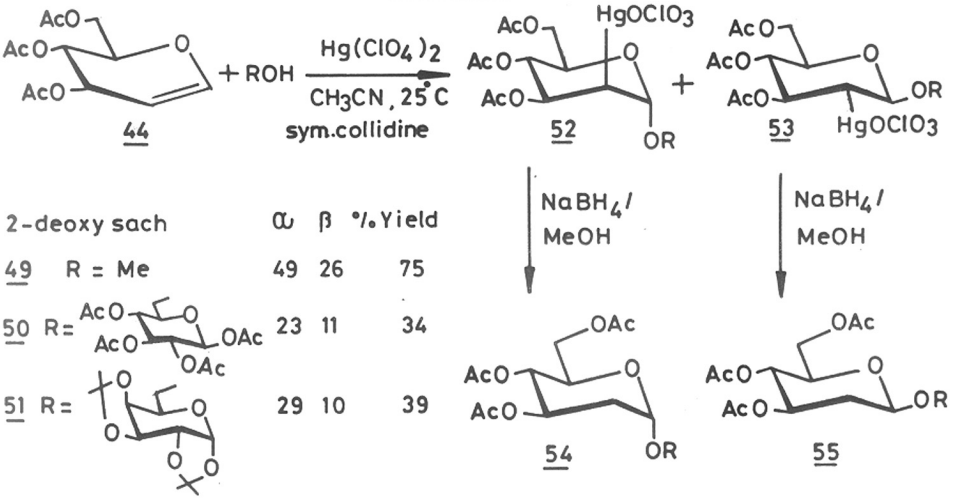
SCHEME 4



Honda et al[87-90] have developed a method of methoxymercuration of glycal **44** by using $Hg(ClO_4)_2$, followed by sodiumborohydride demercuration to afford the α and β 2-deoxy disaccharides[91] (SCHEME 5). Mercuric salts such as the bromide, chloride, cyanide, nitrate and sulfate were unreactive. Solvents suitable for methoxymercuration of **44** with $Hg(ClO_4)_2$ are limited, benzene, toluene, ether and chloroform were unsuitable because of the low solubility of the mercuric salt. N,N-dimethylformamide and dimethylsulfoxide were undesirable because of their low volatality. Acetone, nitromethane, and tetrahydrofuran were to be avoided, as they darken by interaction with mercuric salt. Pyridine retarted the reaction presumably by increasing the electron density of the mercury atom through formation of a complex. Of the various solvents examined, acetonitrile was selected as the reaction solvent. Sym-collidine was used as a base to neutralize

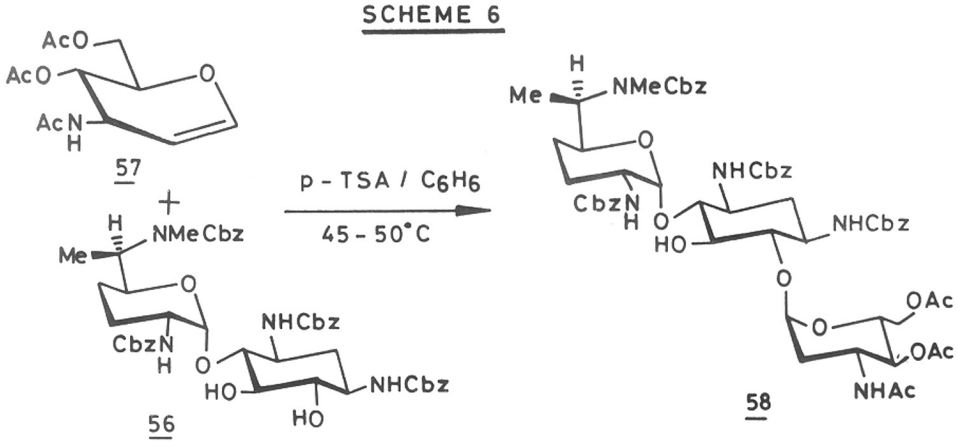
the liberated perchloric acid during the glycosidation reaction. Stronger bases were unsuitable as they caused the concurrent deacetylation and demercuration of products.

SCHEME 5



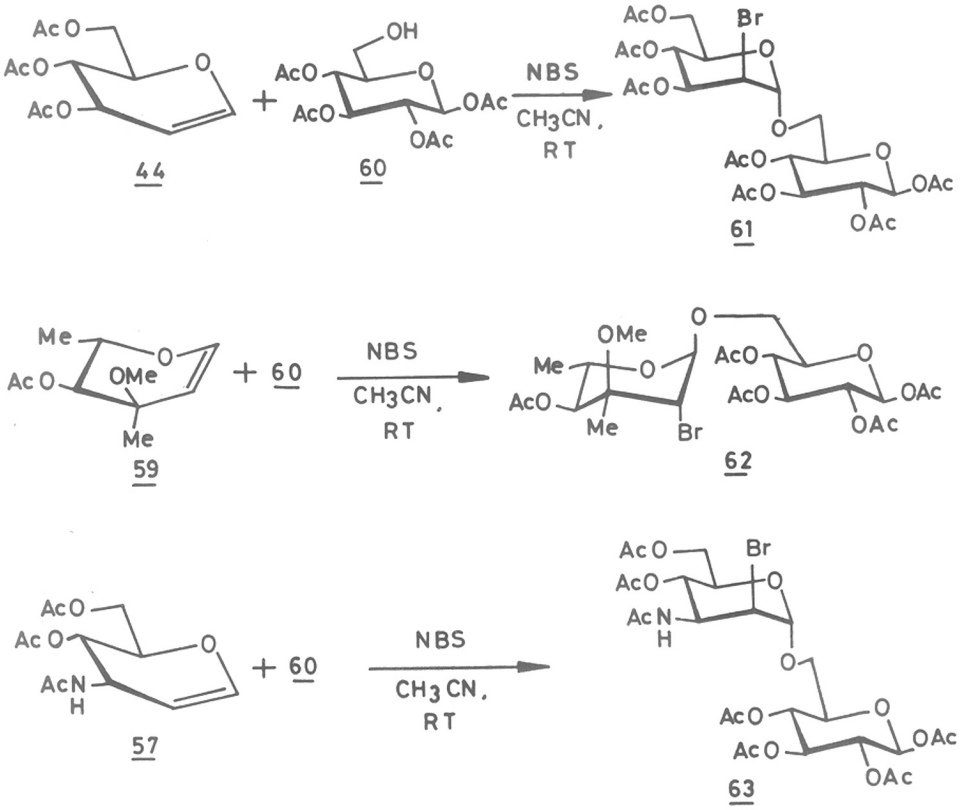
Daniels et al have used p-toluenesulfonic acid as a condensing reagent for the synthesis of a 2-deoxy saccharide[92]. Thus, acid catalyzed addition of a pseudosaccharide **56**[93] to a glycal **57** having a poor departing group at C-3 position, resulted in the regio- and stereoselective formation of a 2-deoxy-α-glycoside **58** (88% yield) (SCHEME 6).

SCHEME 6



Tatsuta et al have developed a method where N-bromosuccinimide was used as a bromonium ion source[94]. Thus, **44**, 4-O-acetyl-1,5-anhydro-2,6-dideoxy-3-C-methyl-3-O-methyl-L-ribo-hex-1-enitol (**59**)[86] and 3-acetamido-4,6-di-O-acetyl-1,5-anhydro-2,3-dideoxy-D-arabino-hex-1-enitol (**57**)[95,96] were reacted with 1.5 molar equivalents 1,2,3,4-tetra-O-acetyl-β-D-glucopyranose (**60**) in the presence of NBS in acetonitrile to obtain their corresponding (3,4,6-tri-O-acetyl-2-bromo-2-deoxy-α-D-mannohexopyranosyl)-(1→6)-O-1,2,3,4-tetra-O-acetyl-β-D-glucopyranose (**61**), (4-O-acetyl-2-bromo-2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-rhamnohexopyranosyl) (1→6)-O-1,2,3,4-tetra-O-acetyl-β-D-glucopyranose (**62**), (3-acetamido-4,6-di-O-

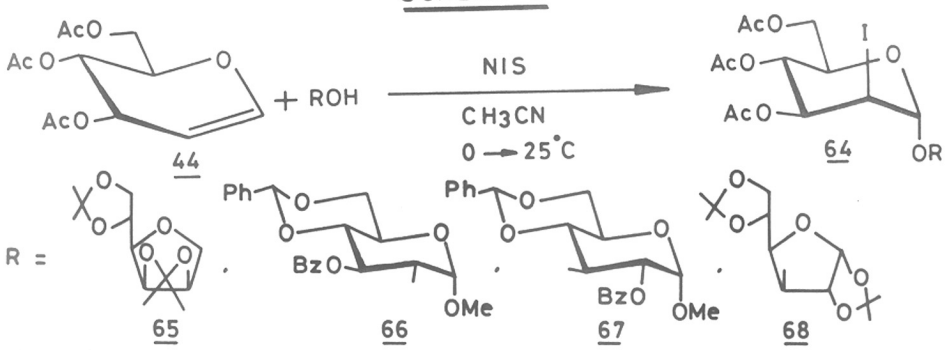
SCHEME 7



acetyl-2-bromo-2,3-dideoxy-α-D-mannohexopyranosyl) (1 → 6)-O-1,2,3,4-tetra-O-acetyl-β-D-glucopyranose (**63**) in 77-97% yields (SCHEME 7).

An attractive approach was developed by **Thiem et al** utilizing N-iodosuccinimide (NIS) as iodonium ion source for the synthesis of α-2-iodo-2-deoxy glycosides exclusively[97]. Thus, **44** on reaction with NIS in presence of equimolar amounts of several alcohols, in acetonitrile at 0°C to room temperature gave mainly α-2-iodo-2-deoxy-glycosides **64** of D-manno-series, in poor to good yields (20-82%) (SCHEME 8). This method has been used for the construction of trisaccharide unit of mithramycin of aureolic acid antibiotics[98].

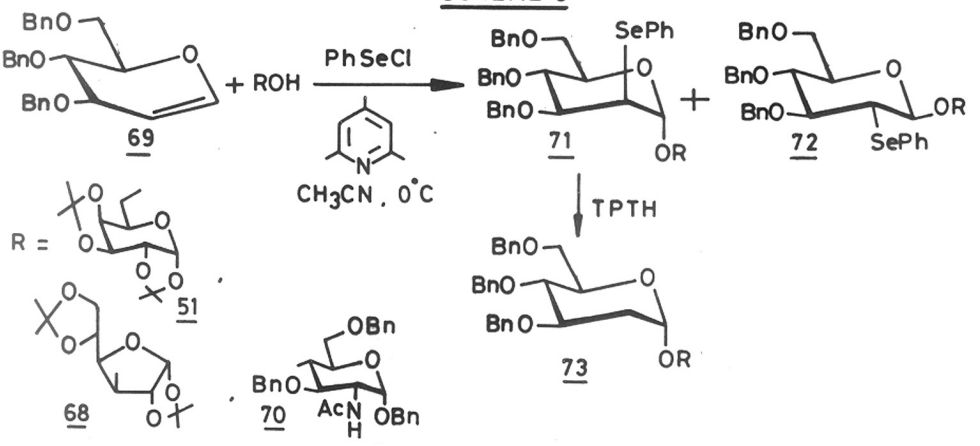
SCHEME 8



Activation of glycals with the aid of metallonium ions has also been proved to be an efficient method for the construction of 2-deoxy saccharides. **Sinay et al**[99] have developed a method in which glycal (protected as benzyl ether) was activated by pheylselenylchloride, in presence of various protected sugar alcohols to obtain 2-deoxy-2-phenylseleno glycosides[100-104]. Thus, 3,4,6-tri-O-benzyl-D-glucal (**69**)[105a] in dry acetonitrile was treated at 0°C with phenylselenylchloride, and sym-collidine in presence of various sugar alcohols, viz. 1,2:3,4-di-O-isopropylidene-α-D-galactopyranoside **51**[105b], 1,2:5,6-di-O-isopropylidene-α-D-glucofuranoside **68**[105b], benzyl 2-acetamido-3,4-di-O-benzyl-2-deoxy-α-D-glucopyranoside **68**[106]

to give their corresponding 2-deoxy-2-phenylselenodissacharides **69** in 61-80% yield, along with a small amount (6-8%) of their corresponding, β-linked saccharides **70** (SCHEME 9). The compounds **69** were reduced by triphenyltinhydride[107] to afford the corresponding α-2-deoxy disaccharides **71** in excellent yields (90-95%). The overall reaction is stereospecific as being the result of the opening of an episelenonium ion.

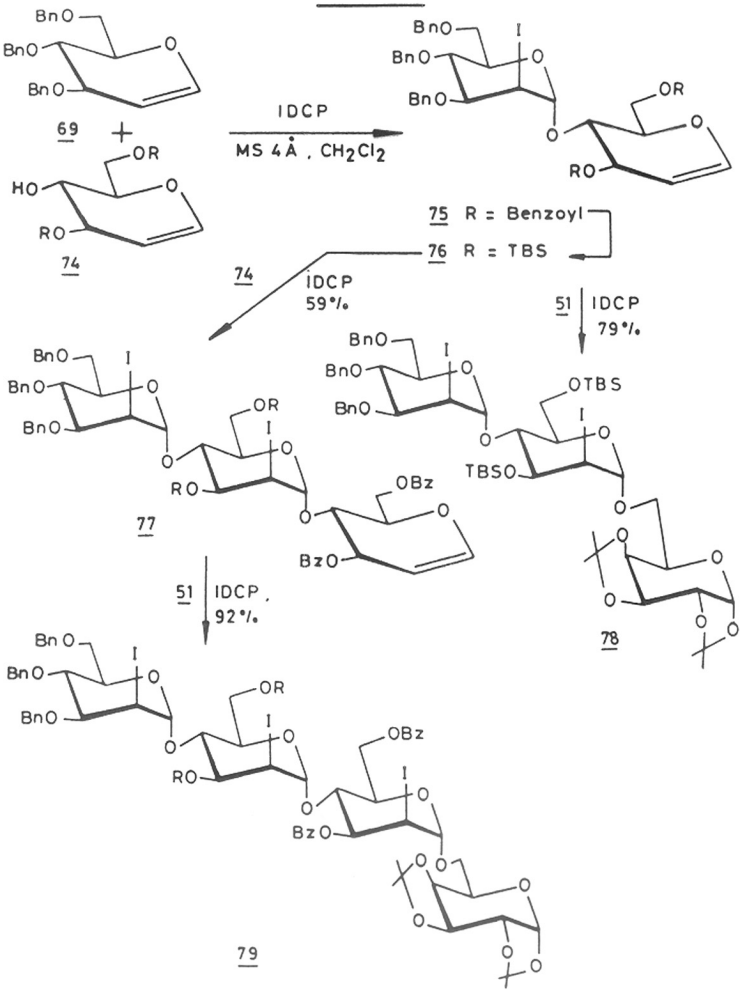
SCHEME 9



Danishefsky et al[108] have exploited iodonium di-sym-collidineperchlorate (IDCP) as a coupling reagent for the synthesis of 2-deoxy oligosaccharides in a reiterative manner. This has been demonstrated by the activation of the double bond of a glucal triether by IDCP in presence of glucals (as glycosyl acceptors) containing a hydroxy group (either at C-3 or C-4) and acyloxy groups at the other position. Thus, **69** was coupled with 3,6-di-O-benzoyl-D-glucal (**74**)[105a] in presence of IDCP, using molecular sieves 4A, and dry dichloromethane to obtain α-linked 2-iodo-2-deoxy disaccharide **75** in 58% yield (SCHEME 10). To reiterate the process with another glycal two benzoyl ester groups at **75** were replaced by di-O-t-butylsilyl ether to afford **76**. The glycal **76** is now a glycosyl donor and it is coupled with glycal **74** or a terminating sugar **51** to afford the 2-deoxy

trisaccharides (77) or (78) exclusively as α-anomers in 59 and 79% yields respectively. Coupling of 77 with 51 afforded the 2-deoxy tetrasaccharide 79 in 92% yield.

SCHEME 10

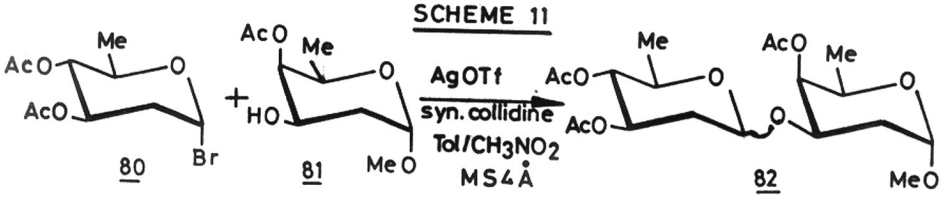


1.6.2 2-Deoxy glycosyl bromides as donors

Thiem et al have utilized 2-deoxy glycosyl bromides as glycosyl donors in the preparation of 2-deoxy glycosides[109,110]. Thus, 3,4-di-O-

acetyl-2,6-dideoxy-α-D-arabinohexopyranosylbromide (80)[110] was reacted with methyl 4-O-acetyl-2,6-dideoxy-α-D-lyxohexopyranoside (81)[111] in presence of silvertriflate, sym-collidine, molecular sieves 4A, using toluene and nitromethane mixture as reaction solvent to afford the disaccharides 82 (α/β : 2/1) in 56% yield (SCHEME 11).

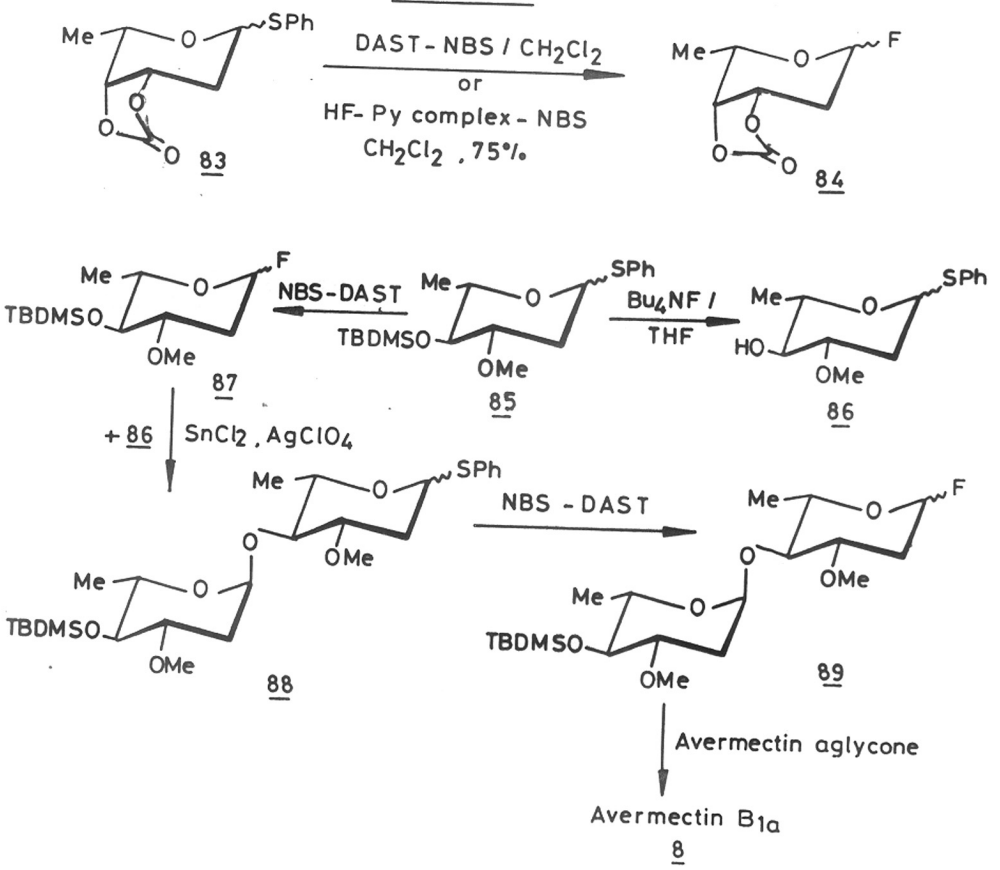
SCHEME 11



1.6.3 2-Deoxy glycosyl fluorides as donors

The use of fluorine at the anomeric center as leaving group has aroused interest in the last few years. Being a poor leaving group, fluoride leads to intermediates more stable than glycosylchlorides and bromides[112a]. **Nicolaou et al**[112b] have further extended the route to the practical synthesis of oligosaccharides from 2-deoxy pheyl-1-thioglycosides via their glycosyl fluorides[113-119]. This method involves the synthesis of 2-deoxy glycosyl fluorides from 2-deoxy phenyl-1-thioglycosides. Reaction of 2-deoxy phenyl-thiosugars derivative **83** with either diethylaminosulfurtrifluoride (DAST)-NBS or HF-pyridine complex-NBS in anhydrous dichloromethane at 0-25°C resulted in the formation of their glycosyl fluorides **84** (SCHEME 12). The usefulness of this methodology was demonstrated by the partial synthesis of Avermectin B_{1a} (**8**) by coupling the fluoro disaccharide **89** with avermectin aglycone.

SCHEME 12

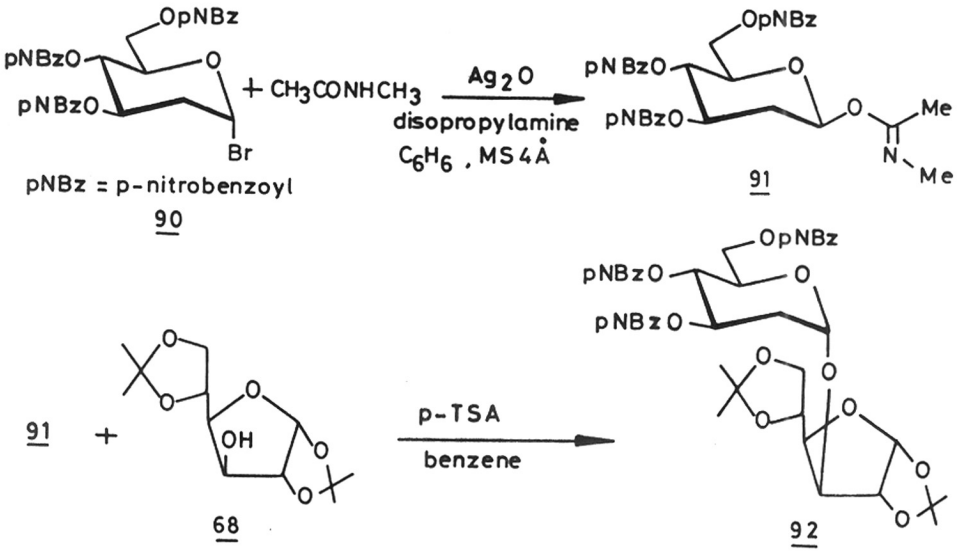


1.6.4 2-Deoxy glycosyl imidates as donors

Several 2-deoxy-α-disaccharides have been synthesized in excellent yields by using 2-deoxy glycosyl imidates as glycosyl donors by **Sinay et al**[120-122]. The donor 1-O-(N-methyl) acetamidyl-3,4,6-tri-O-p-nitrobenzoyl-2-deoxy-β-D-arabinohexopyranose **(91)**[109] was prepared (57% yield) by the reaction of 3,4,6-tri-O-p-nitrobenzoyl-2-deoxy-α-D-arabino-hexopyranosylbromide **(90)**[123,124] with N-methylacetamide, in the presence of silveroxide, diisopropyl ethylamine and powdered 4A molecular sieves and dry benzene as a reaction solvent (SCHEME 13). The acetamidate

(91) was used as such for further glycosidation step, since purification of such substances resulted in their decomposition. Glycosidation of 91 with 68 in dry benzene at room temperature in presence of p-TSA afforded the disaccharide 92 as an α-anomer in 88% yield.

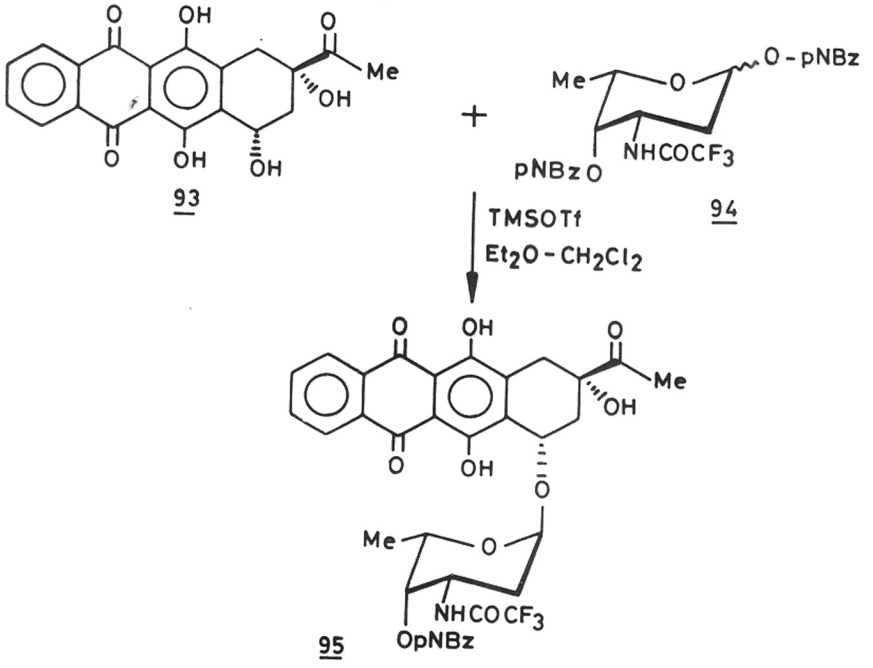
SCHEME 13



1.6.5 2-Deoxy glycosyl-p-nitrobenzoyl esters as donors

Terashima et al have developed a glycosidation method where 2-deoxy 1,4-di-O-p-nitrobenzoyl glycosides were activated with trimethylsilyltrifluoromethanesulfonate (TMSOTf) in presence of an acceptor to obtain α-linked 2-deoxy saccharides[125]. Thus, N-trifluoroacetyl-1,4-di-O-p-nitrobenzoyl-L-daunosamine **(94)**[126] on reaction with the demethoxydaunomycinone aglycone **93** in presence of TMSOTf in CH_2Cl_2-Et_2O (3:1) and molecular sieves 4Å, at -15°C afforded **95** as an α-anomer in 92% yield (SCHEME 14).

SCHEME 14

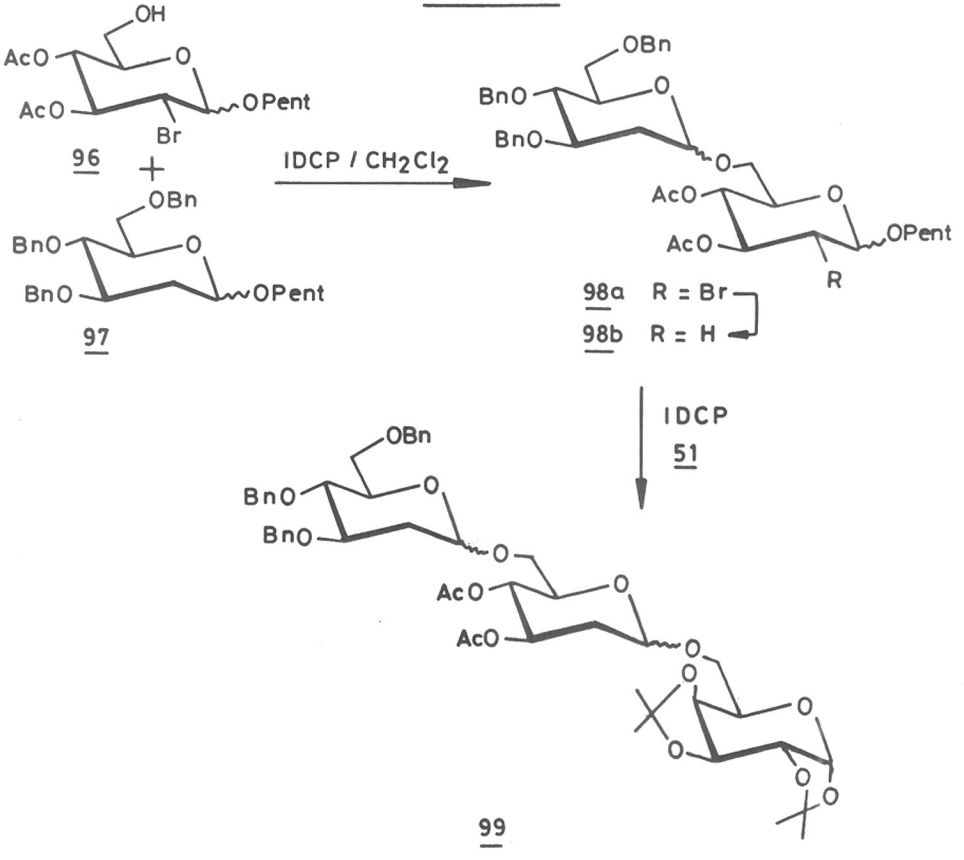


1.6.6 2-Deoxy n-pent-4-enyl-O-glycosides as donors

Recently, **Fraser-Reid et al**[127] have developed a new and simple method where 2-deoxy n-pent-4-enyl-O-glycosides "arm" or "disarm" the glycosyl donors by means of substitution at C-2 position. This result emanated from the hydrolysis of n-pent-4-enyl glycosides with various C-2 protecting groups[128], it was shown that bromine at C-2 position reacted much more slowly than the corresponding sugar with a benzyl ether at C-2 or a 2-deoxy sugar[127]. Thus, the reactivity difference was attributed to the C-2 substituent which could be considered as being "dis-armed" where as the sugars with no such substituent were "armed" toward reaction with the halonium ion. Thus, the terms "armed"/"disarmed" were coined to indicate the first observed unique reactivity phenomenon.

Thus, coupling of **96** with **97**, mediated by IDCP afforded the 2-deoxy disaccharide **98a** in 68% yield (α/β : 3/1). Radical induced debromination of **98a** then "armed" the reducing end of **98b**, allowed further coupling with **51**[105b] to obtain the 2-deoxy trisaccharide **99** in 55% yield as anomeric mixture (α/β : 4/1) (SCHEME 15).

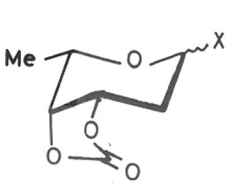
SCHEME 15

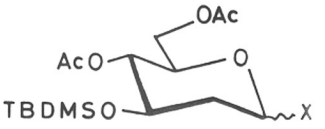


1.6.7 2-Deoxy 2-phenyl-1-thioglycosides as donors

A mild and general method for the synthesis of O-glycosides from 2-deoxy 2-phenyl-1-thioglycosides has been developed by **Nicolaou**

SCHEME 16

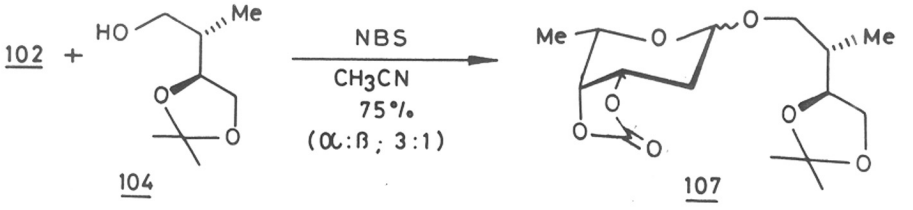


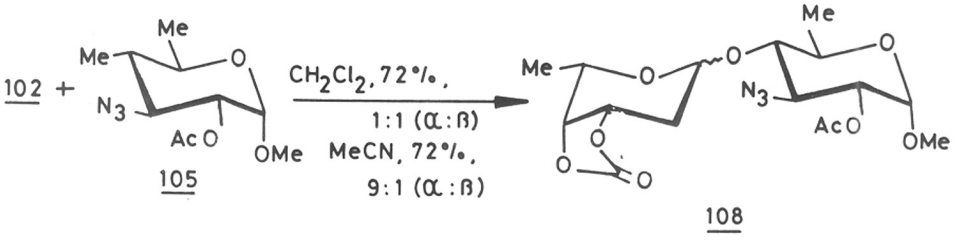


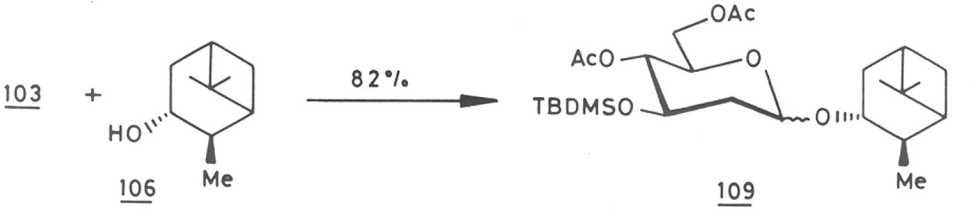
100 X = OMe, 102 X = SPh] a

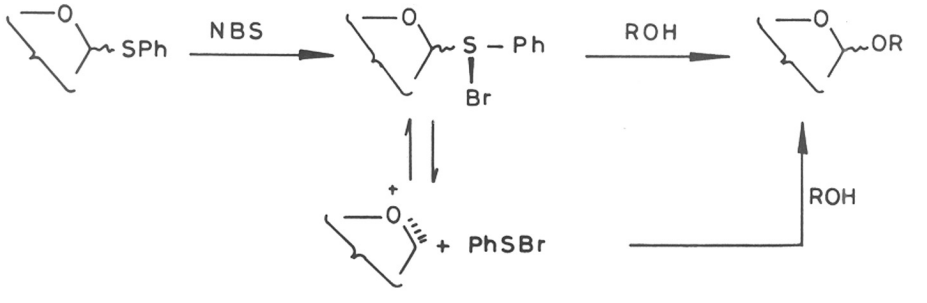
101 X = OMe, 103 X = SPh] a

a = $PhSiMe_3$, TMSOTf









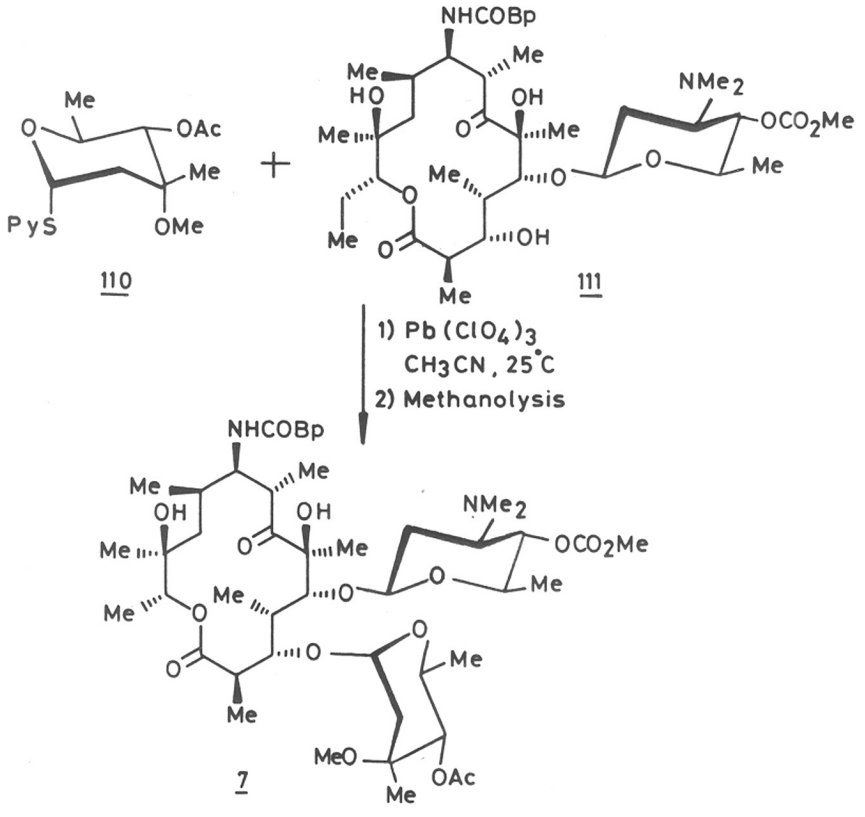
et al[129]. The 2-deoxy thioglycosides have been made by a variety of methods including the use of free carbohydrates and 1-halo derivatives and also by the procedure of Hanessian utilizing O-glycosides (trimethylsilyl)thiophenol, zinc iodide, and tetrabutyl ammonium iodide. A procedure involving reaction of methyl glycosides with $PhSSiMe_3$ in the presence of trimethylsilyltriflate (TMSOTf) was developed (SCHEME 16) for the preparation of phenylthioglycosides **102** and **103.**

2-Deoxy 2-phenyl-1-thioglycosides **102** and **103** were activated with N-bromosuccinimide (NBS) in the presence of hydroxy compounds (stoichiometric amounts) and 4Å molecular sieves in dichloromethane at 25°C to obtain O-glycosides **107-109** (α and β -anomers) in good to excellent yields (54-82%). Considerable stereocontrol can be exerted by a simple change of solvent.

1.6.8 2-Deoxy 2-pyridyl-1-thioglycosides as donors

Woodward et al have reported the use of 2-deoxy 2-pyridyl thioglycoside **110** in erythronolide synthesis for performing glycosidations[20]. The pyridylthioglycoside **110** with anhydrous $Pb(ClO_4)_2$ in the presence of aglycone component **111** in acetonitrile at 25°C, furnished after methanolysis the glycoside **7** in 55% yield (SCHEME 17). The newly introduced anomeric stereochemistry of **7** was shown to be at the desired **α**-configuration.

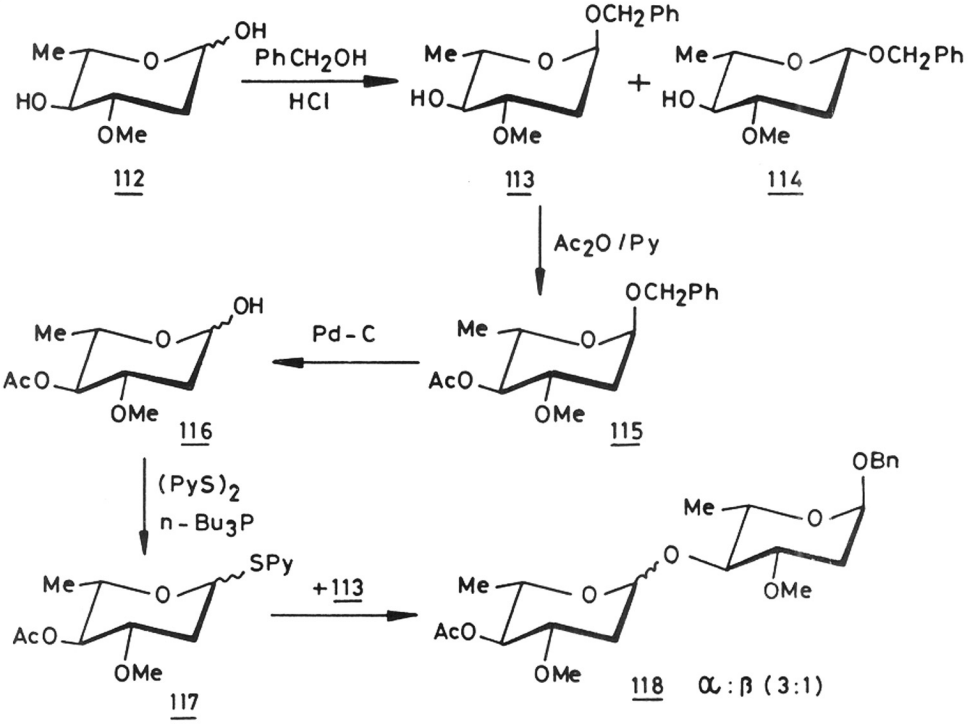
SCHEME 17



This glycosidation strategy has been further exploited for the synthesis of benzyl α-L-oleandrosyl-α-L-4-acetoxy oleandroside (118) a disaccharide component of avermectins, by **Wuts et al**[130], where oleandrose (112) was converted to its benzyl glycoside with benzylalcohol/hydrogenchloride to give a 10:1 mixture of the α- and β-glycosides 113 and 114 in 77% yield. Acetylation of the α-anomer gave a 91% yield of acetate 115 which was deprotected by hydrogenolysis to give acetates 116. Activation of the anomeric centre (SCHEME 18) was accomplished

by conversion of pyranosides **116** to the 2-deoxy 2-pyridylthioglycosides (**117**)[20] as a 1:2.4 (α / β) mixture. The coupling reaction was accomplished by reaction with $Pb(ClO_4)_2$ on the mixture of the thioglycosides **117** and benzylglycoside **113** to obtain a 59% yield of a mixture of disaccharides **118** (α /β : 3/1) with the natural isomer predominating. The poor anomeric ratio is pressumably due to the fact that oleandrose is a 2-deoxy sugar and thus lacks the electronic and steric directing effects of the C-2 substituent as is commonly observed in glycoside synthesis (SCHEME 18).

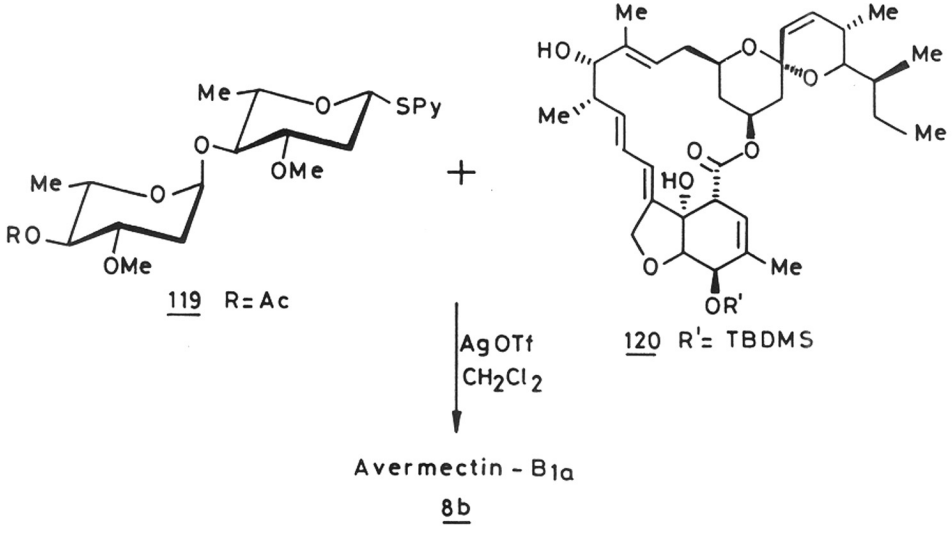
SCHEME 18



Hanessian et al have utilized 2-pyridylthiopyranoside for glycoside synthesis, its activation with various activators such as mercuric (II) nitrate, anhydrous p-TSA and NBS in the presence of various glycosyl

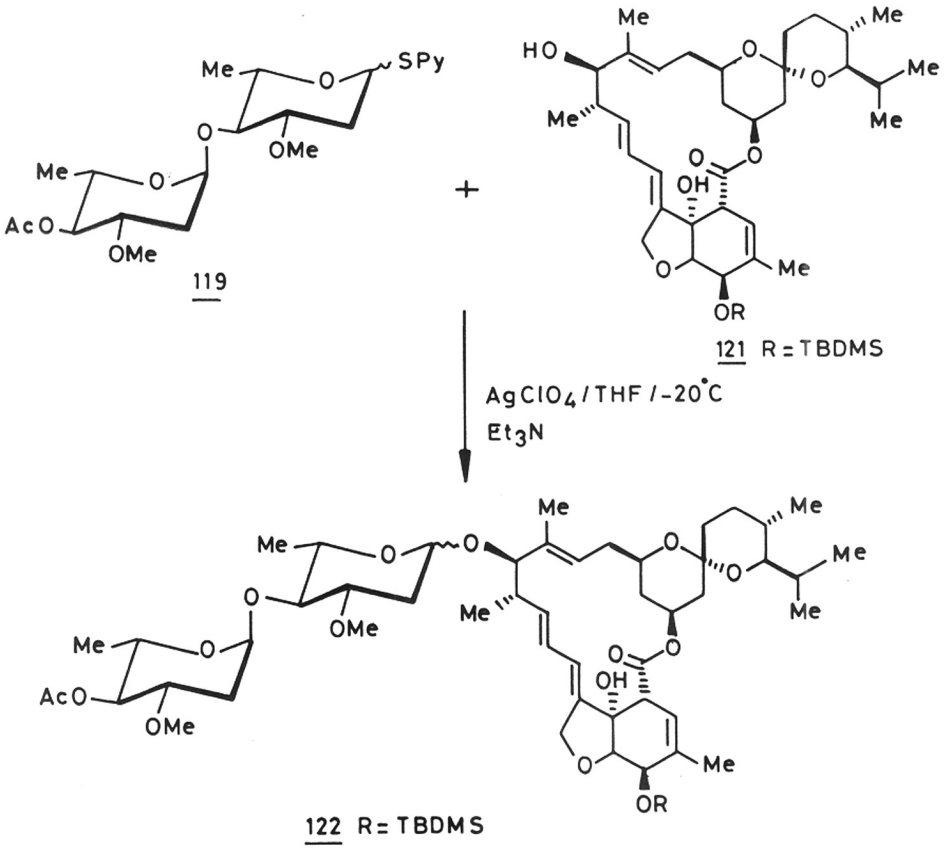
acceptors gave the glycosides[131] (α / β mixture). The glycosyl donor **119** obtained from the degradation of natural avermectin was reacted with avermectin aglycone **120** in presence of silvertriflate and dichloromethane to afford **8b** in 72% yield as a single α-anomer (SCHEME 19). However, no experimental details have been described[131].

SCHEME 19



Frei and Mereyala have synthesized various 13 β-O-glycoside derivatives of epi-avermectins[132]. Thus, 2-pyridyl-1-thio 2-deoxy glycoside **119** was reacted with glycosyl acceptor **121** in presence of silverperchlorate, at -20° resulted in the formation of mixture of glycosides **122** (SCHEME 20) in 86% yield as α/β mixture (1:1) which were separated by chromatography.

SCHEME 20



1.7 Synthesis of β-linked 2-deoxy oligosaccharides

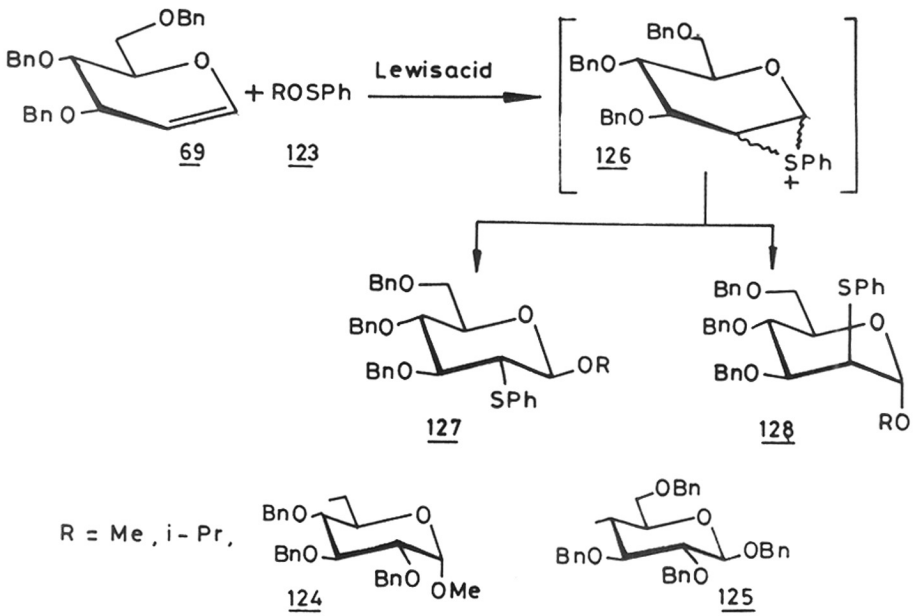
For selective formation of β-linked 2-deoxy glycosidic linkages the directing ability of the group on C-2 (PhSe,Br,Sph) has been utilized for obtaining β-selectivity[133-142]. Such groups have been cleaved after the glycosidations step by means of reduction to afford the β-2-deoxy oligosaccharides exclusively.

1.7.1 Benzyl substituted glycals as donors

A novel approach to the synthesis of 2-deoxy-β-glycosides was

developed by **Ogawa et al**[133], where a protected glycal **69** as a glycosyl donor, in presence of various sulfenate esters **123**[134] of simple alcohols and sugar alcohols **124** and **125** and Lewis acids such as TMSOTf or $BF_3.OEt_2$, or $TrBF_4$ resulted in the formation of mixture of α and β-glycosides of **D**-gluco, and **D**-manno type, with β-anomers predominating (α/β : 19/81 - 21/79) (SCHEME 21) in 33-99% yields[133].

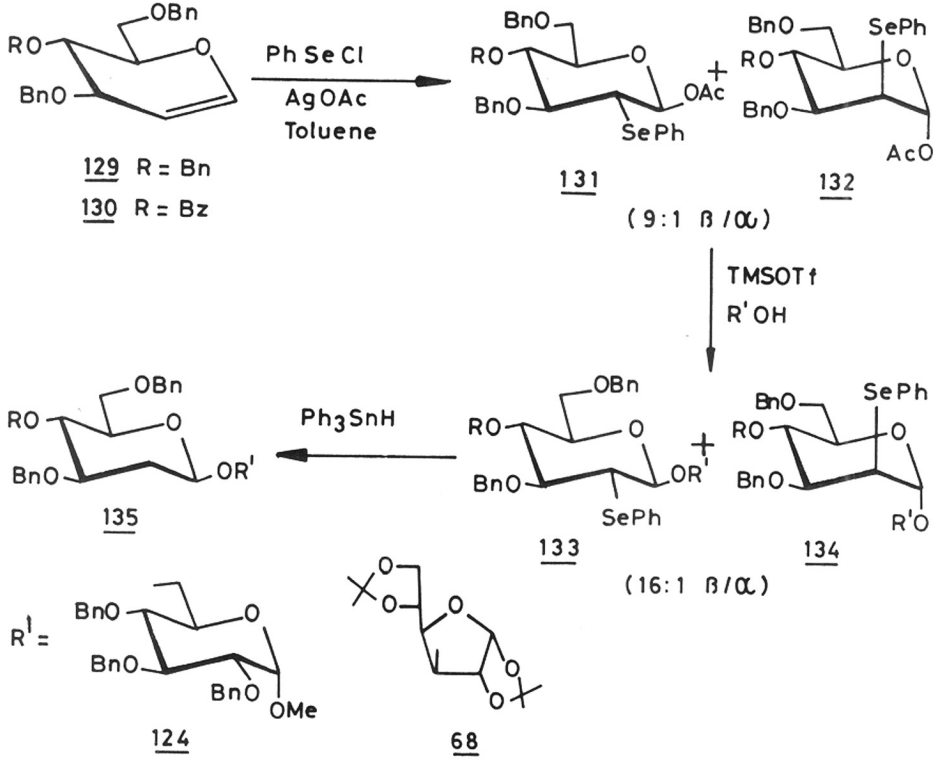
SCHEME 21



Beau et al have developed selenium based β-glycosidation method by use of benzylated glycals as donors[135]. Thus, 3,4,6-tri-O-benzyl-D-glucal (**69**) on reaction with PhSeCl followed AgOAc gave 1,2-trans acetoxy selenides **131**, **132** in a ratio of 9:1 (β / α) (81% yield). The ability of acetoxy selenides to function as glycosyl donors was tested on reaction with saccharide alcohols **124, 68** in presence of TMSOTf, molecular sieves 4Å, at 0°C to afford the β-linked disaccharide **133** (92%) and

α-linked disaccharide **134** (6%) in a ratio of 16/1 (β / α) (SCHEME 22). Reductive removal of the phenylselenyl group (Ph_3SnH) of **133** led quantitatively to the formation of 2-deoxy-β-D-disaccharides **135**. The selection of a less-polar solvent, such as dichloromethane has been found to be useful in enhancing the β-selectivity. The stereochemistry of addition of phenylselenyl group on to the glycal was strongly influenced by the nature of the glycal protecting groups, benzoylation at C-4 position favoured in α-selective reaction. The minor formation of the α-glycoside may be derived from the attack of phenyl selenyl group from β-side or from the isomerization of very sensitive phenylselenyl group.

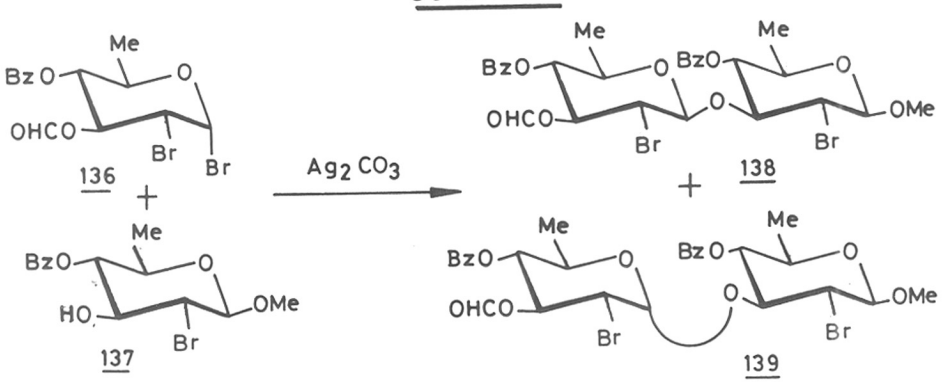
SCHEME 22



1.7.2 2-Bromo-2-deoxy glycosyl bromides as donors

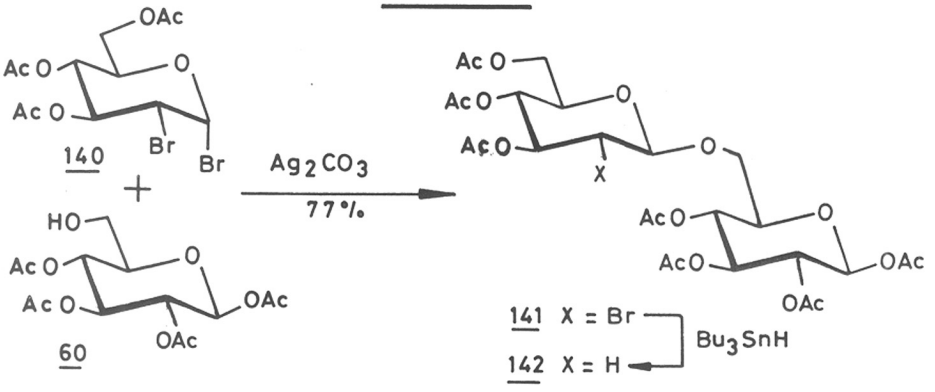
Thiem et al have reported a method where 2-bromo-2-deoxy glycosyl bromides have been used as glycosyl donors and silver carbonate as promoter[136]. Thus, the reaction of 4-O-benzoyl-3-O-formyl-2-bromo-2,6-dideoxy-glucopyranosyl bromide **(136)**[136] on reaction with methyl 4-O-benzoyl-2-bromo-2-deoxy- β -D-glucopyranoside **(137)** in presence of silver-carbonate and nitromethane-toluene mixture (1:1) and molecular sieves 4 Å gave disaccharides **138, 139** (SCHEME 23) in 61% yield. (α /β: 1/6).

SCHEME 23



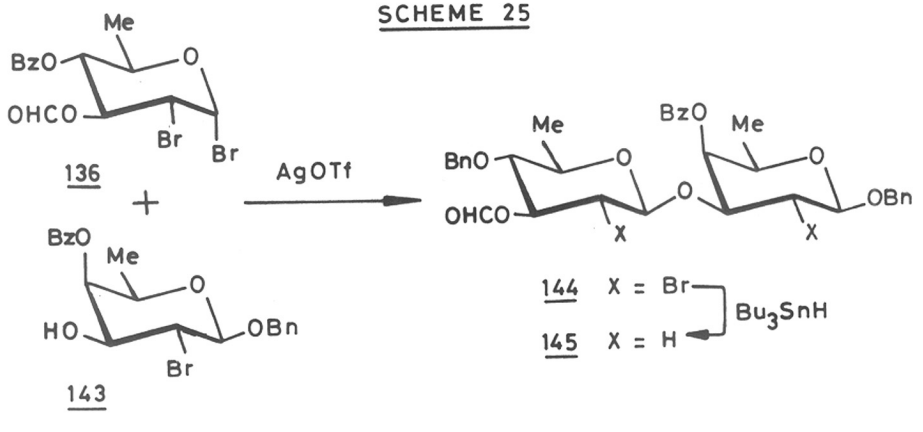
Bock et al have utilized 2-bromo-2-deoxy gluco- and mannosyl bromides as glycosyl donors for glycosidation in presence of silver silicate as an activator[137]. Thus, 3,4,6-tri-O-acetyl-2-bromo-2-deoxy-α -D-glucopyranosyl bromide **(140)**[138] with 1,2,3,4-tetra-O-acetyl-β -D-glucopyranose **(60)** gave (1 → 6) linked β-D-saccharide **141** in 37% yield. Further, 2-bromo-2-deoxy glycoside has been converted to its corresponding 2-deoxy-β-disaccharide **142** in moderate yield on treatment with tributyltinhydride (SCHEME 24).

SCHEME 24



Thiem et al[139] have further extended the use of 2-bromo-2-deoxy glycosyl bromides to the synthesis of β-glycosides related to aureolic acid antibiotics[98]. Thus, the reaction of 2-bromo-2-deoxy-glucopyranosyl bromide (**136**)[139] with galacto alcohol **143**[139] in presence of silver triflate as an activator afforded mainly the (1 → 3) β-linked disaccharide **144** (α / β : 1/3) in 56% yield. Reductive dehalogenation with tributyl-tin-hydride gave the β-linked disaccharide **145** in 76% yield (SCHEME 25).

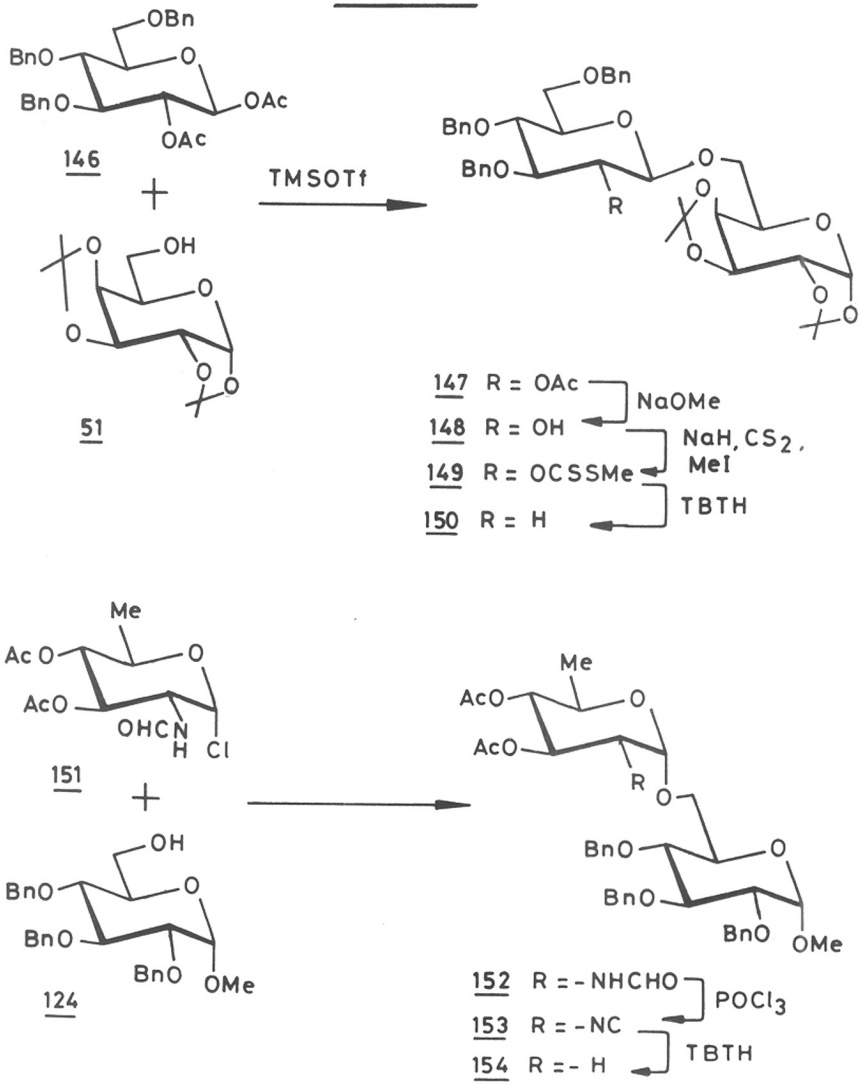
SCHEME 25



1.7.3 1,2-Trans-diacetate and 2-formamido-2-deoxy glucopyranosyl chloride as donors

Sinay et al have developed an elegant method for the synthesis of 2-deoxy β-linked disaccharides, where 1,2-trans diacetate, that have been made from their corresponding benzylated 1,2-orthoacetates, served

SCHEME 26

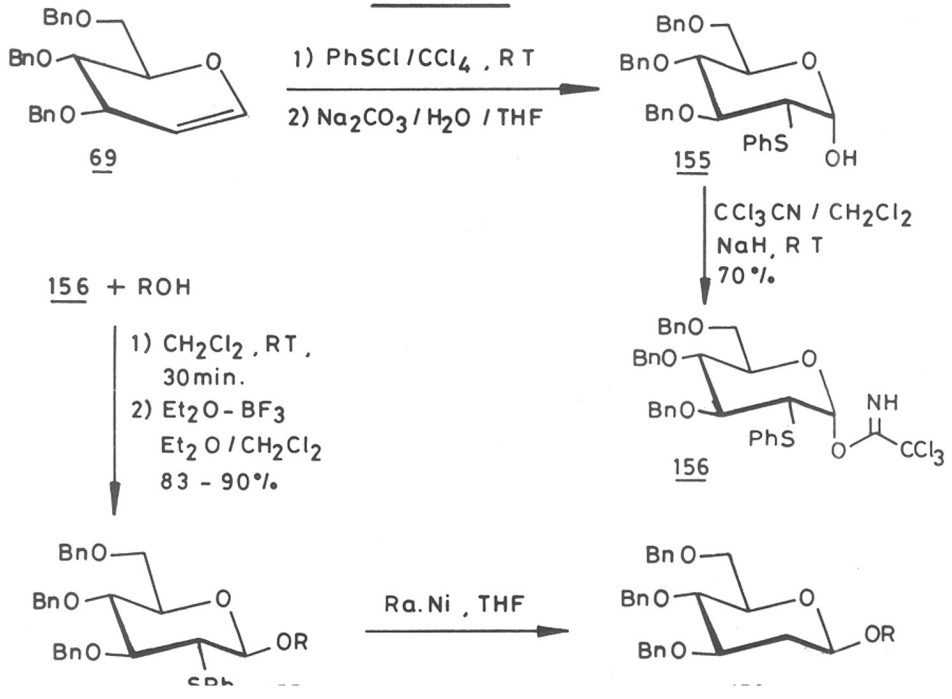


as an excellent β-glycosyl donors[140] (SCHEME 26). Thus **146** on reaction with various non-acylated glycosyl acceptors, viz. **51** in the presence of TMSOTf afforded the β-saccharide **147** (85%). Deacetylation, followed by xanthation and then radical reduction with tributyltinhydride led in high yields (100%) to the formation of 2-deoxy-β-disaccharide **150**. In another approach 3,4,6-tri-O-acetyl-2-deoxy-2-formamido-β-D-glucopyranosyl chloride (**151**)[140] on reaction with **124** in the presence of AgOTf at room temperature afforded the β-disaccharide **152** in 97% yield. The resulting disaccharide **152** was smoothly deaminated to yield the corresponding 2-deoxy-β-disaccharides **154** through intermediate isonitrile **153** by reduction.

1.7.4 O-(2-deoxy 2-phenylthio-α-D-glucopyranosyl)trichloroacetimidate as donors

A convenient synthesis of 2-deoxy-β-D-glucopyranosides was deve-

SCHEME 27

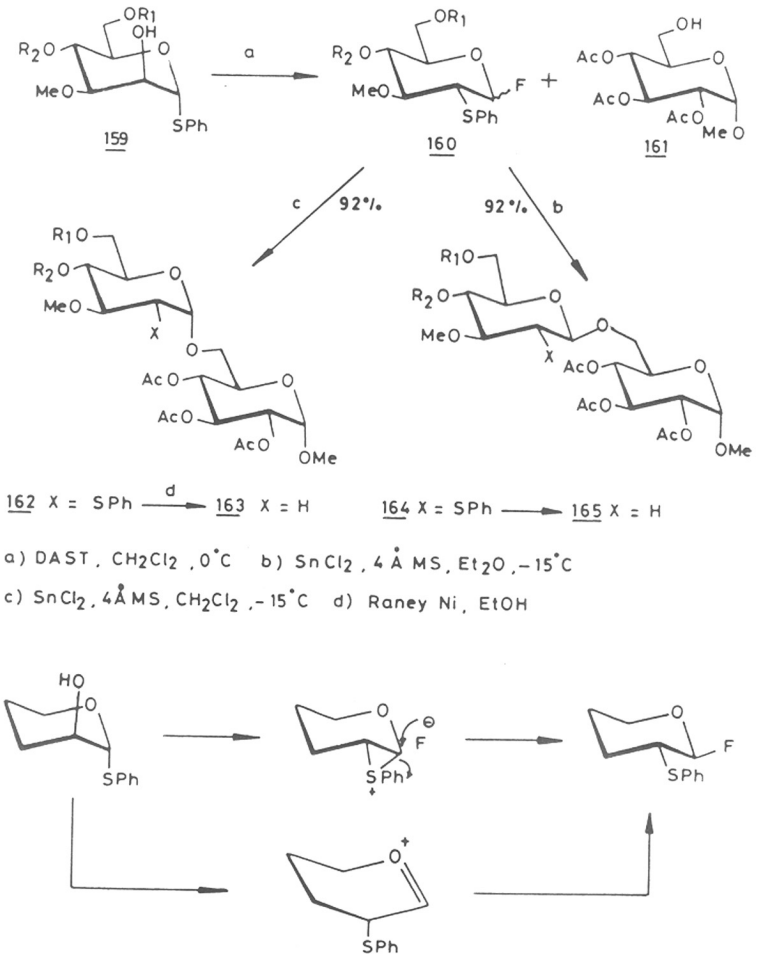


loped by **Schmidt et al**[141] where in O-(2-deoxy 2-phenylthio-α-D-glucopyranosyl)trichloroimidate (**156**) was used as a glycosyl donor. The compound **156** was prepared from the glycal **69** in 3 steps[141] (SCHEME 27). The imidate **156** is an extremely powerful glycosyl donor toward an alcohol acceptor on addition of catalytic amount of ether-borontrifluoride complex, to afford the β-glycoside **157** in 83-90% yields, which was further converted to 2-deoxy β-glycosides **158** (65-76%) by reductive desulfurisation.

1.7.5 2-Phenyl thioglycosides containing a free OH at C-2 position as donors

Stereospecific 1,2-migrations in carbohydrates were observed by **Nicolaou et al**[142], which culminated in the development of a new β -2-deoxy glycosidation methodology. This method is based on the migration of an induced group at C-1 to shift to the neighbouring position (C-2) by a "pull" from the "host" carbon initiated by the departure of a leaving group and a "push" from the ring oxygen lone pair of electrons provided the groups involved were stereoelectronically oriented in the proper fashion. This glycosidation method was achieved by (a) introduction of a phenylthio group at C-2 (b) having α- or β- directing neighbouring group and/or solvent participation and (c) desulfurization to afford the 2-deoxy -αor its β-glycoside. A three step sequence illustrates the synthesis of 2-deoxy-β-glycosides (SCHEME 28). In the presence of tin- complexing solvent or reagent the phenylthio group remains free to direct the glycosidation via a transient intermediate such as B where as in the absence of complexing medium (eg, CH_2Cl_2). The catalyst may be engaging the sulfur, thus preventing it from participating in the coupling reaction.

SCHEME 28



1.8 Biosynthesis of 2-deoxy sugars

As a component of deoxy pentose nucleic acids role in the metabolism of cell nuclei. The suggestion was forwarded by Hough and Jones[148] that deoxy pentoses may form the aldol type condensation of acetaldehyde and glyceraldehyde and essentially this would be correct. It has been demonstrated that a condensation of this type leading to the formation of a deoxypentose, since acetaldehyde reacts with 2,3-O-isopropyli-

dene-D-glyceraldehyde in the presence of pottasium carbonate to yield some 4,5-O-isopropylidene-2-deoxy-D-ribose[144,145].

Glyceraldehyde + acetaldehyde

⇅

Deoxypentosephosphate

The heat labile enzyme which catalyzes this aldol condensation, was purified eight fold from the extracts of E. Coli by combining this phosphodeoxy ribo aldolase with purified phospho riboaldolase from yeast. Racker[146,147] was able to demonstrate to long sought conversion of D-ribose into deoxy-D-ribose.

It is apparent that a triosephosphate is the common intermediate between D-ribose and 2-deoxy-D-ribose in metabolism.

CHAPTER 2

STEREOSELECTIVE SYNTHESIS OF α (AXIAL) LINKED 2-DEOXY SACCHARIDES BY USE OF PERACETYLATED 2-PYRIDYL 2-DEOXY-1-THIO-GLYCOSIDES AS GLYCOSYL DONORS AND METHYL IODIDE AS AN ACTIVATOR "A GENERAL GLYCOSIDATION METHODOLOGY"

2.1 INTRODUCTION

α-Linked 2-deoxy saccharides are of paramount importance as they are constituents of many clinically active natural products, such as Avermectins[27-31], aureolic acid antibiotics[11-13], anthracycline antibiotics[2-4]. And consequently, much effort is directed toward the efficient and stereocontrolled synthesis of such α-linked 2-deoxy saccharides.

Synthesis of α-linked saccharides in general benefit from a neighbouring non-participating group at C-2 position of the glycosyl donor for anchimeric assistance or by the operation of steric influence to direct the formation of α-linkage. Evidently the particular problems in the chemical synthesis of α-2-deoxy glycosides are the missing neighbouring group which is also associated with enhanced lability of highly unstable 2-deoxy glycosyl halides and glycals.

Although halonium ion (Br^+ or I^+) catalyzed glycosidations proved to be superior to some extent to either acid catalyzed or metal mediated glycosidations in terms of stereoselectivity and easy reducibility halogen atoms and toxicity, they too have been reported to result in the formation of considerable amount of mixtures of 2-deoxy glycosides[148-150].

This chapter delineates the development of a new glycosidation methodology to obtain α-linked deoxy disaccharides.

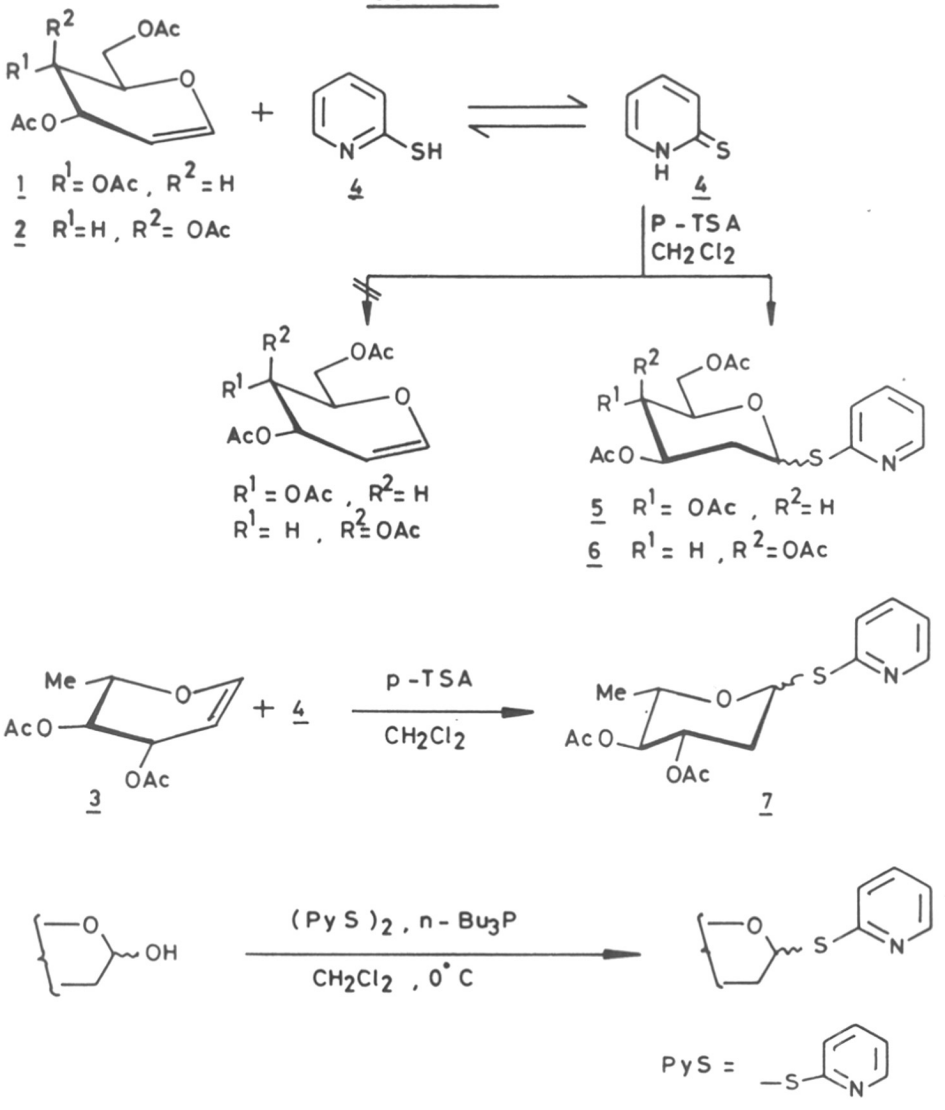
2.2 Results and Discussion

2.2.1 Preparation of 2-pyridyl 2-deoxy-1-thioglycosides (5,6 and 7) (Glycosyl donors)

2-Pyridyl 2-deoxy-1-thioglycoside donors (5,6 and 7) have been prepared either (i) by 1,2-addition of 2-mercaptopyridine to glycals in the presence of anhydrous p-TSA in dichloromethane at 50°C[151] (ii)

or by reaction of 2-deoxy glycosides with 2,2'-dipyridyl disulphide/n-tributylphosphine at 0°C in dichloromethane[20] (SCHEME 1). Either of the procedures result in the formation of α/β anomeric mixtures of 2-pyridyl 2-deoxy-1-thioglycosides (70-80% yield).

SCHEME 1



Stereoselective synthesis of α-2-deoxy saccharides still warrants more elegant methods for preparative purpose. Recent investigations in our laboratory for the synthesis of oligosaccharides revealed that 2-pyridyl-1-thioglycosides (even as anomeric mixture) on activation by methyl iodide resulted in the formation of α-linked oligosaccharides exclusively[152]. Reaction conditions such as role of activator effect of solvent and temperature have been studied earlier to give this method the status of a general methodology. Various solvents such as benzene, dichloromethane, chloroform, dimethylformamide, tetrahydrofuran have been studied and dichloromethane was found to be the appropriate solvent at an optimum temperature of 50°C. Of the several electrophilic activators such as methyl iodide, n-butyl iodide, n-butyl bromide and methyltriflate tried for glycosidation, methyl iodide was found to be the most suitable one[153]. Thus, 1 mmol of glycosyl donor was reacted with 1.1 mmol of acceptor in about 10 ml of CH_2Cl_2 (3%, MeI) at 50° (Experimental). This chapter deals with the stereoselective synthesis of α-2-deoxy saccharides from 2-pyridyl deoxy-1-thio α/β glycopyranosides using methyl iodide as an activator.

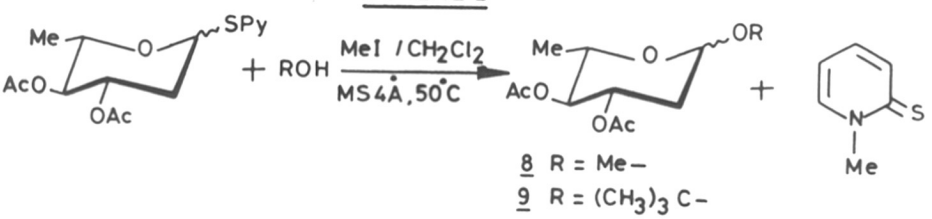
2.2.2 Synthesis of alkyl 2-deoxy glycosides

In order to study the reactivity and efficacy of the 2-pyridyl thio moiety as a good departing group, on activation by methyl iodide, glycosidation reaction of 2-pyridyl 3,4-di-O-acetyl-2,6-dideoxy α and β-L-arabinohexopyranoside (7)(α / β :1/1) with simple alcohols such as methanol and tert-butanol were studied. Thus, the reaction of 7 with equimolar amounts of anhydrous methanol in dry dichloromethane and methyl iodide (general procedure described in experimental) for 8 h afforded methyl 3,4-di-O-acetyl-2,6-dideoxy α and β-L-arabinohexopyranoside (**8**) (SCHEME 2) in 91% yield (1:1 α / β) after chromatographic purification. Compound 8 was

characterized by ^{1}H-nmr spectrum from the appearance, of two methoxy singlets at δ 3.31 and 3.42 in 1:1 ratio, and the appearance of anomeric carbons (^{13}C-nmr) at δ 99.5 and 99.9.

Similarly, when **7** was reacted with tertiary butanol (12 h), it afforded t-butyl 3,4-di-O-acetyl 2,6-dideoxy- α and β L-arabinohexopyranoside (**9**) in 85% yield (α / β 4/1/ by ^{1}H-nmr) (SCHEME 2) after chromatographic purification. ^{1}H-nmr spectrum of **9** showed two singlets at δ 1.2 and 1.21 attributed to tertiary butyl groups in a ratio of 4:1 (α/β). The ratio was further rationalized by the observation of ^{13}C-nmr, which witnessed the appearance of two doublets at δ91.00 and 93.4 (C-1 of α and β) respectively.

SCHEME 2



8 R = Me–
9 R = $(CH_3)_3$ C–

2.2.3 Synthesis of α-linked 2-deoxy disaccharides

Having established general reaction conditions for glycosidation[152,153], attention was next turned to apply this methodology for the synthesis of various 2-deoxy saccharides. Various per O-acetylated 2-pyridyl 2-deoxy-1-thio glycosides **5,6** and **7** were subjected to coupling reactions with various glycosyl acceptors such as, methyl 4-O-acetyl-3,4-di-O-benzyl- α -D-glucopyranoside (**10**)[154], methyl 6-O-benzoyl-3,4-di-O-benzyl- α-D-glucopyranoside (**11**)[155] methyl 2,3-O-isopropylidene-α-L-rhamnopyranoside (**12**)[156], methyl 2,3,4-tri-O-benzyl-α -D-glucopyranoside (**13**)[157], 1,2:3,4-di-O-isopropylidene- α-D-galactopyranoside (**14**)[158] to obtain the corresponding α -linked 2-deoxy disaccharides (5+10 → 16, 5+11 → 17, 6+13

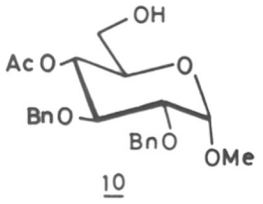
→ 19, 6+11 → 20, 7+13 → 21, 7+11 → 22, 5+14 → 18A+18B, and 7+14 → 23 A+23B) respectively. The 2-deoxy disaccharides thus obtained were characterized based on the following data.

i) ^{1}H-nmr: The newly formed O-glycosidic bond showed H-1 as a broad doublet with a coupling[84,94,97] of $J_{1,2a}$=2.5-3.6 Hz and the corresponding β-linked isomers show a double doublet with a coupling of $J_{1,2a}$=9-11 Hz and $J_{1,2e}$=0-1.5 Hz[136,140].

ii) ^{13}C-nmr: α-Linked 2-deoxy saccharides exhibit a doublet in their ^{13}C-nmr spectra for C-1' at Ca δ97-100[84,94,97]. The corresponding β-anomeric carbon appears at Ca δ102-105.[136,140].

iii) Optical rotation: α-Linked saccharides (D-configuration) exhibit high positive rotation compared to their corresponding β-anomers[97]. The β-anomers exhibit low negative rotations[140].

Glycosyl acceptors



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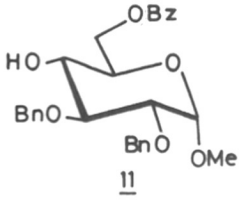

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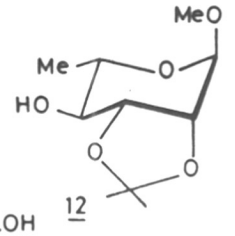

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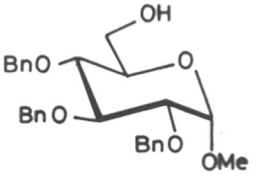

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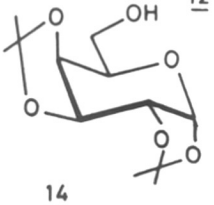


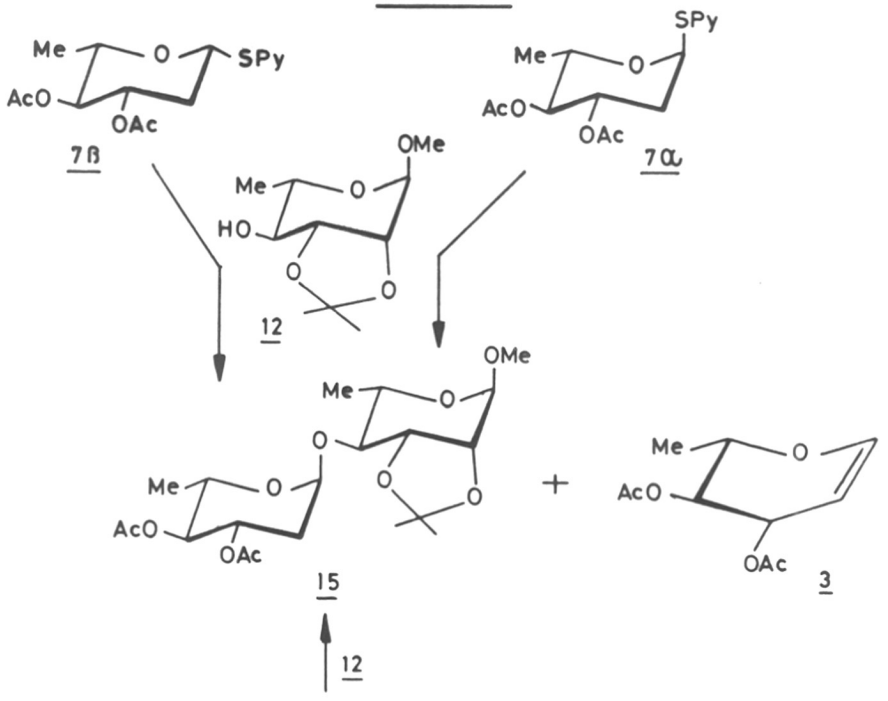
14

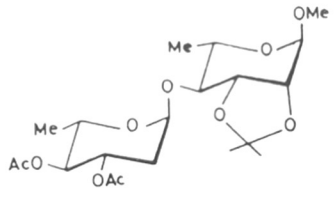
Methyl 4-O-(3,4-di-O-acetyl-2,6-dideoxy-α-L-arabinohexopyranosyl)-2,3-O-isopropylidene-α-L-rhamnopyranoside (15)

Reaction of glycosyl donor **7** (β-anomer) (Experimental,p 72) with methyl 2,3-isopropylidene-α-L-rhamnopyranoside (**12**) gave **15**. ^{1}H-nmr

spectrum (table 1 and 2) of which showed the presence of two H-6,6' methyl groups at δ1.17 ($J_{5,6}$=6.28 Hz) and 1.31 ($J_{5',6'}$=6.24 Hz) isopropylidene methyl groups as singlets at δ 1.33 and 1.54, a singlet at δ 4.85 and a broad doublet at δ 5.49 ($J_{1',2'a}$=3.15, $J_{1',2'e}$=1.0 Hz) for H-1 and H-1' respectively. The coupling constants along with the chemical shifts of H-1' confirmed the formation of α-linked disaccharide **15**. It exhibited optical rotation of $[\alpha]_D^{25}$-121° (c 1.02, $CHCl_3$) which is in agreement with the assigned α-configuration[97]. ^{13}C-nmr spectrum exhibited quartets for C-6,6' methyls at δ17.5 and 18.1 and two signals at δ95.3 and 98.3 for C-1 and C-1' respectively consistent with α-linkages[97]. Likewise, the coupling of **7** (α-anomer) with **12** under similar glycosidation conditions, resulted in the formation of α-2-deoxy disaccharide **15** in 78% yield. Similarly, coupling of α/β-anomeric mixture (1:1) of the donors **7**α/**7**β with **12** also gave **15** as single anomer.

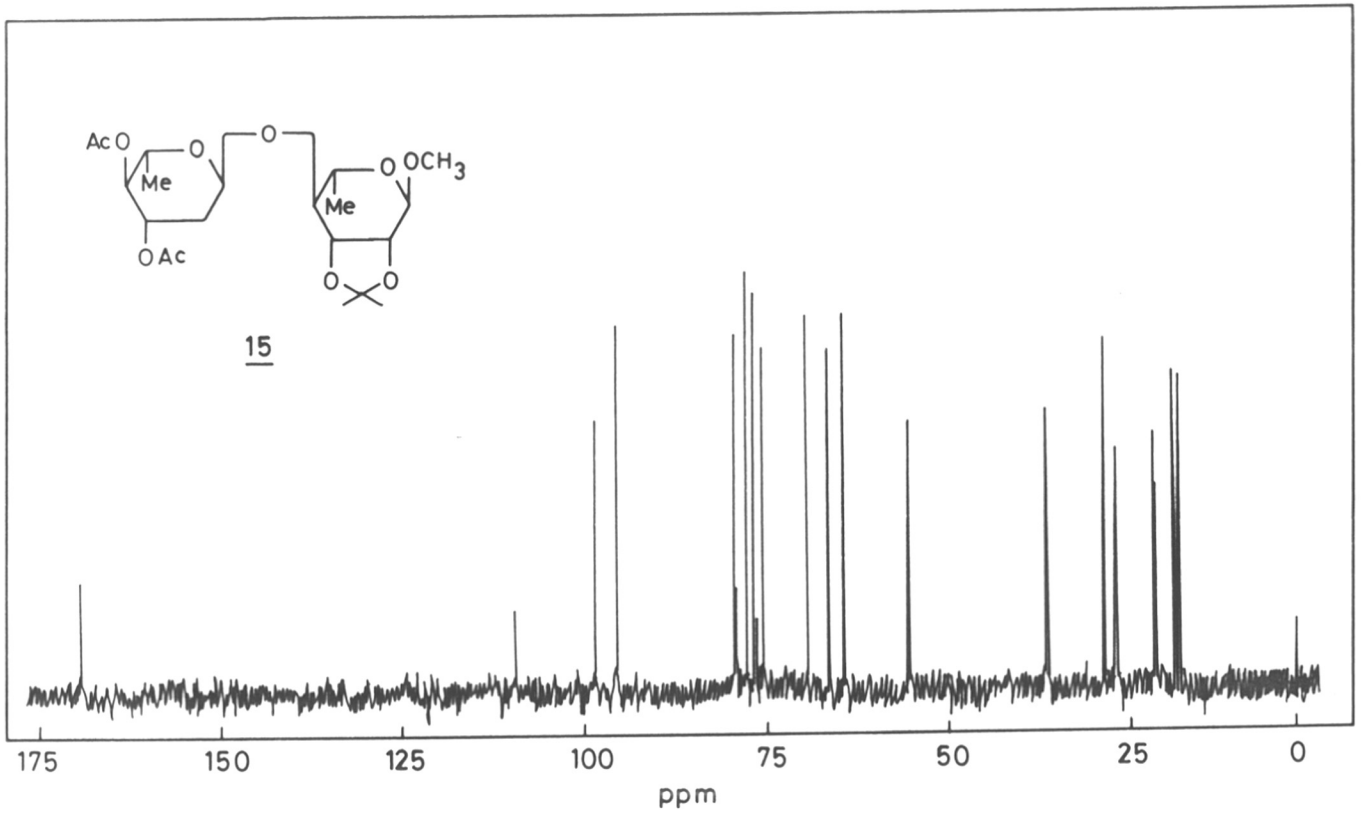
SCHEME 3





15

^1H NMR SPECTRUM OF COMPOUND 15 (300MHz, $CDCl_3$)



^{13}C – NMR SPECTRUM OF COMPOUND 15 (22.63MHz, $CDCl_3$)

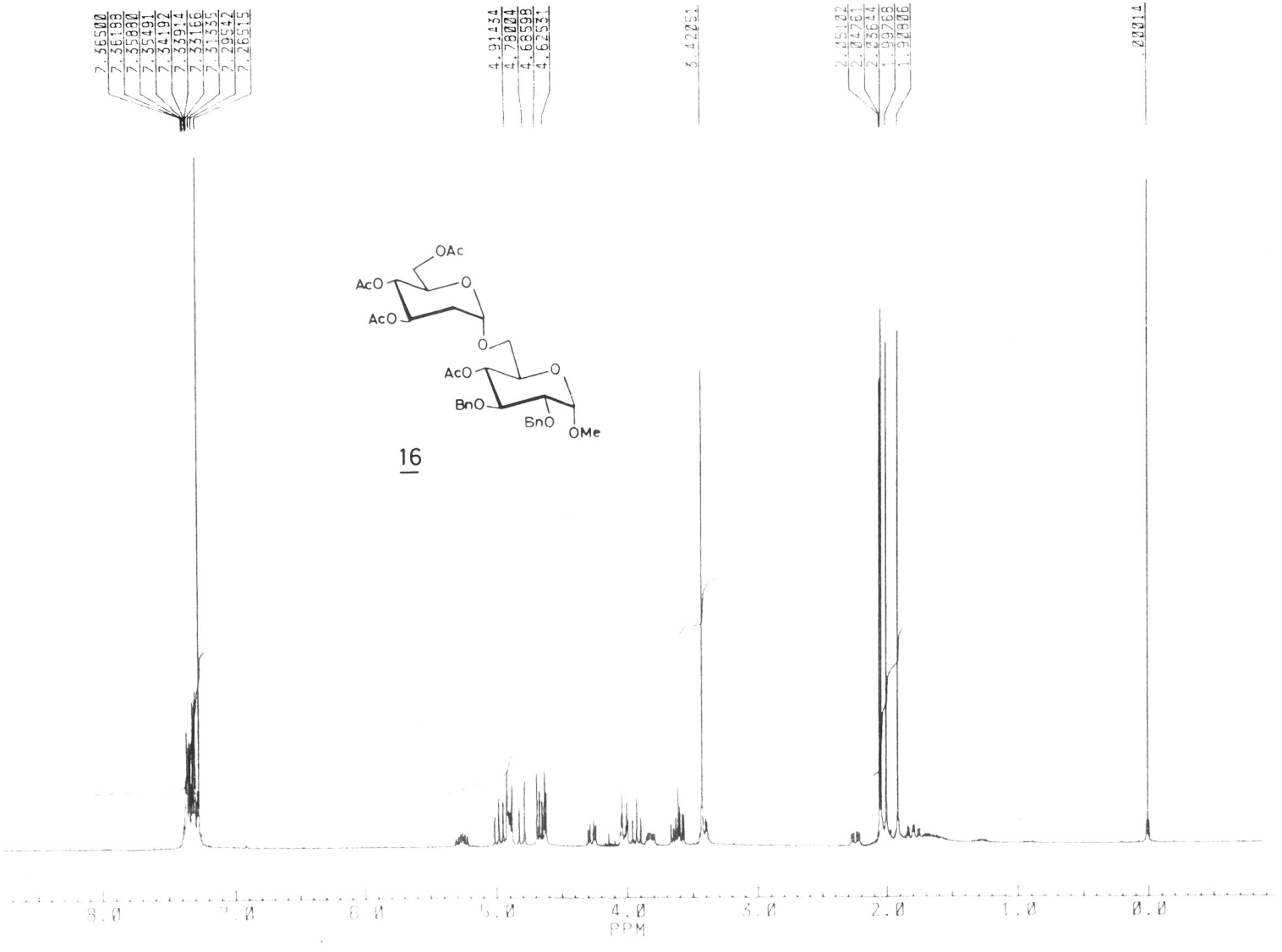
From the above experiments it is clear that "anomeric mixture of pyridyl thio glycosyl donors" lead to the stereoselective formation of α-(axial) linked 2-deoxy saccharide. Consequently anomeric mixture of 2-pyridyl 2-deoxy-1-thioglycosides as such were used for the glycosidation reactions.

Methyl 6-O-(3,4,6-tri-O-acetyl-2-deoxy-α -D-arabinohexopyranosyl)-4-O-acetyl-2,3-di-O-benzyl-α-D-glucopyranoside (16)

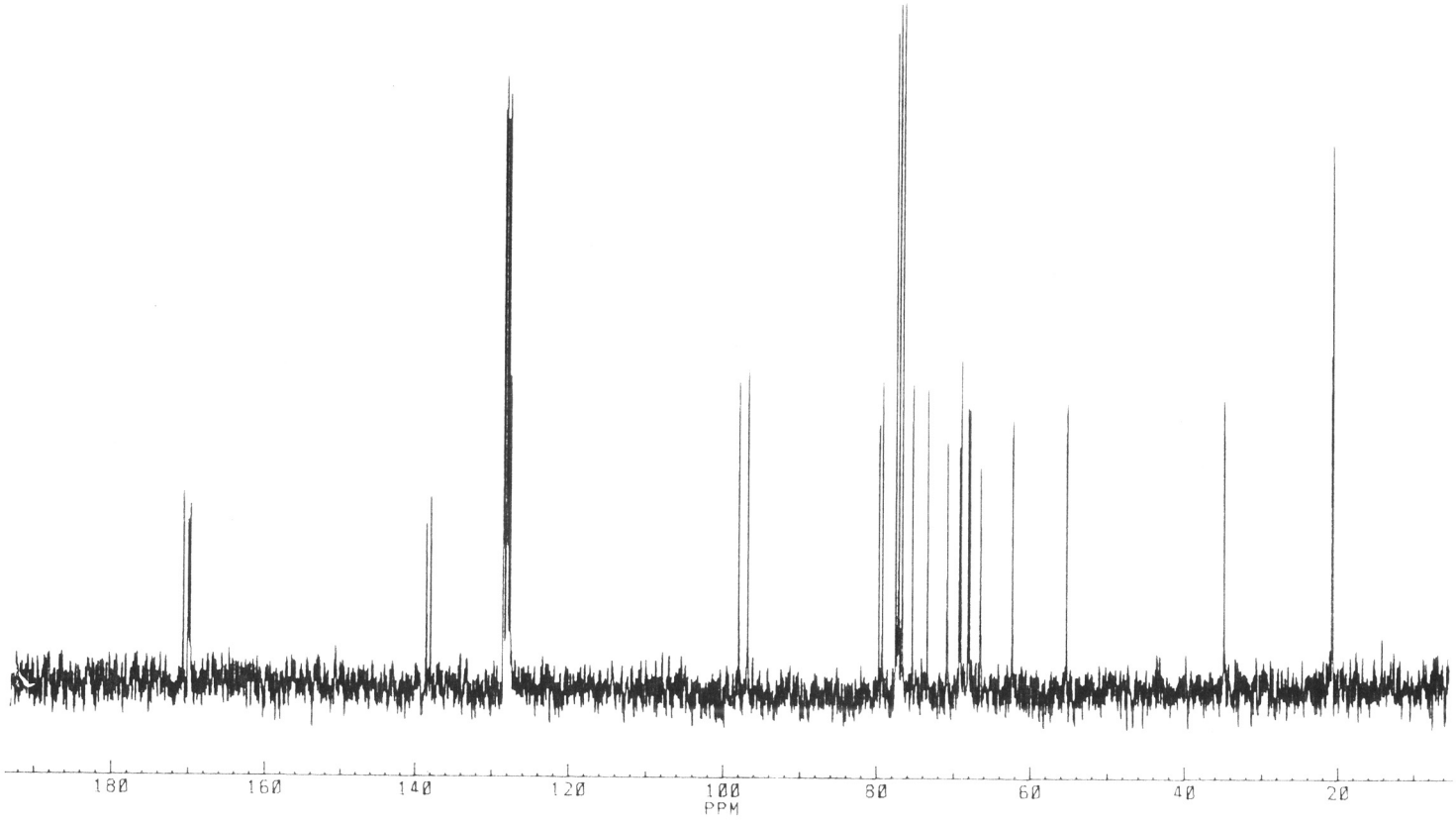
Reaction of 2-pyridyl 2-deoxy-1-thioglycosyl donor **5**[151] with methyl 4-O-acetyl-2,3-di-O-benzyl-α -D-glucopyranoside (**10**)[154] (Experimental) afforded the α-linked 2-deoxy disaccharide **16** in 53% yield as a syrup (SCHEME 4). Compound **16** was characterized by the appearance of singlets at δ 1.9, 1.99, 2.03, 2.04 (12H) (Table 1&2) for the four acetates, a ddd at δ 1.8 ($J_{1',2'a}$=3.6, $J_{2'a,3'}$=11.5, $J_{2,2'gem}$=16.7 Hz) for H-2 (axial) and at 2.25 (ddd, 1H, $J_{1',2'e}$=1.2, $J_{2'e,3'}$=5.4 Hz) for H-2 (equatorial), a singlet at δ 3.4 for the methoxyl group and by appearance of doublets between 4.5-5.0 and at δ 4.85 for H-1 and H-1' respectively. The assignment of chemical shift of δ 4.85 for H-1' which is characteristic of α-linkage is based on the 2D COSEY spectrum where H-1' at δ 4.85 shows a cross peak only with H-2' axial proton at δ2.25 and no other cross peak is observed, indicating an observable coupling with H-2'a and the coupling with H-2'b is small (Figure 1). ^{13}C-nmr spectrum showed signals at δ 96.5 and 97.7 for C-1 and C-1' are in agreement with the assigned α-linkage[97] at the newly formed interglycosidic bond. The positive optical rotation of $[\alpha]_D^{25}$ +65° (c 0.4, $CHCl_3$) was also consistent with the assigned α-configuration.

Methyl 4-O-(3,4,6-tri-O-acetyl-2-deoxy- α -D-arabinohexopyranosyl)-6-O-benzoyl-2,3-di-O-benzyl-α-D-glucopyranoside (17)

The problem of exposing secondary hydroxyls of monosaccharides



^{1}H NMR SPECTRUM OF COMPOUND 16 (300 MHz, $CDCl_3$)



^{13}C NMR SPECTRUM OF COMPOUND 16 (75 MHz, $CDCl_3$)

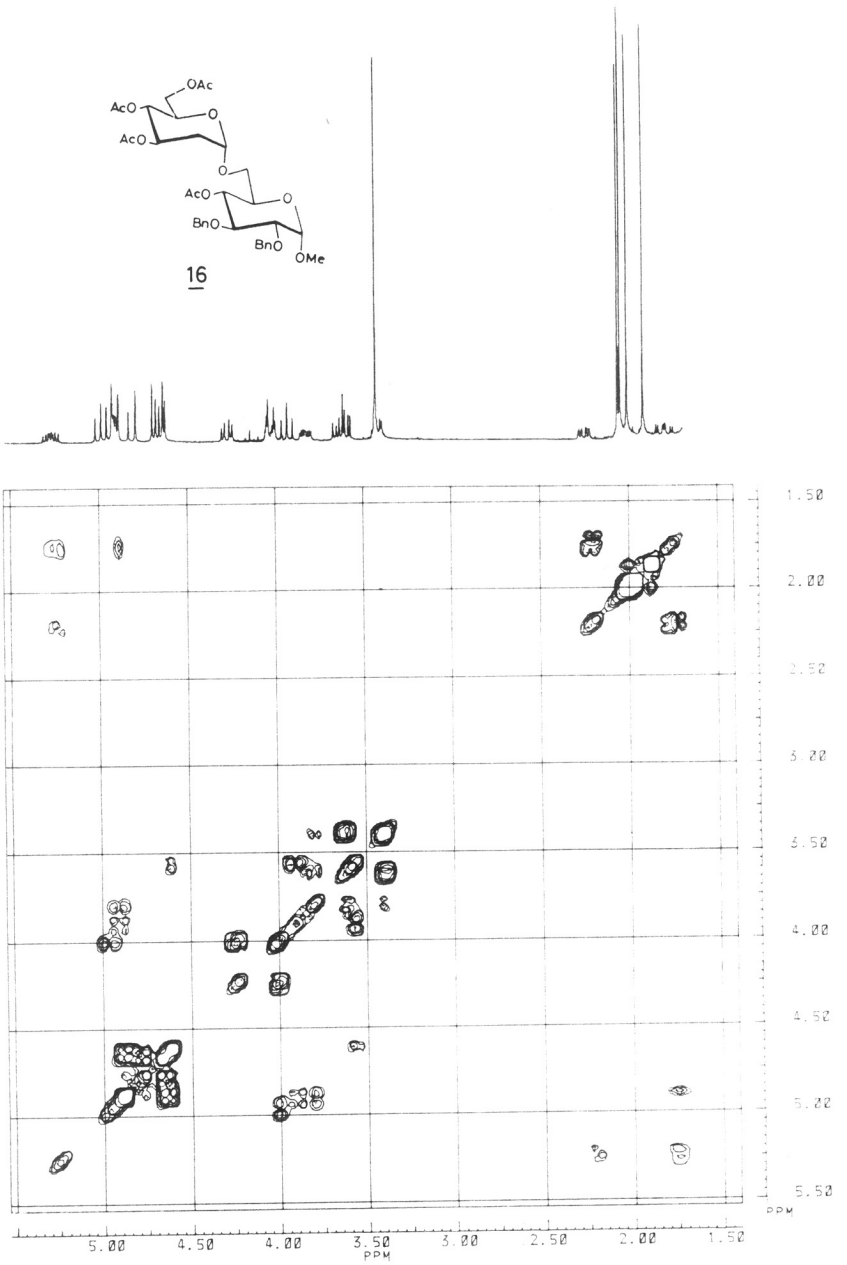
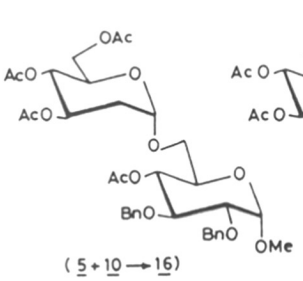
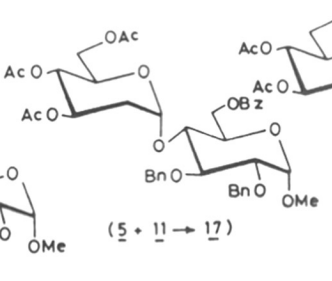


FIG. 1 2D COSEY SPECTRUM OF COMPOUND 16 (300 MHz, $CDCl_3$)

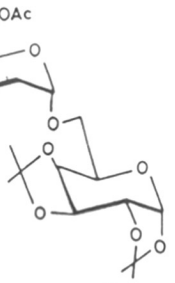
SCHEME 4



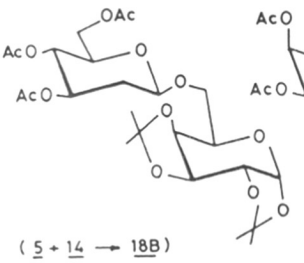
(5 + 10 → 16)



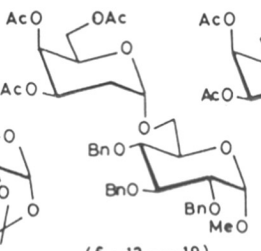
(5 + 11 → 17)



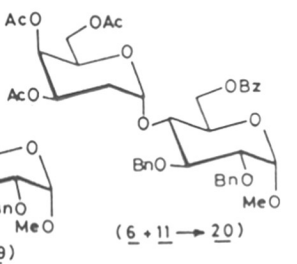
(5 + 14 → 18A)



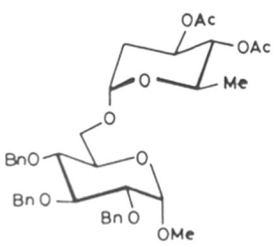
(5 + 14 → 18B)



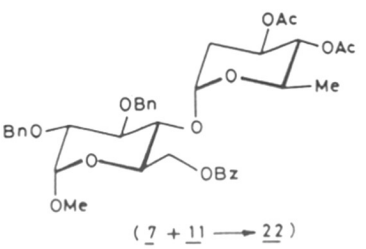
(6 + 13 → 19)



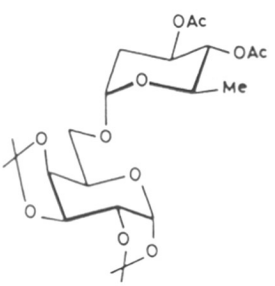
(6 + 11 → 20)



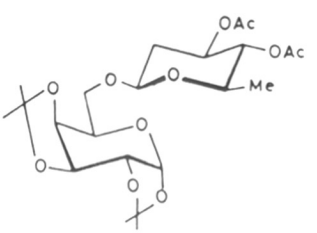
(7 + 13 → 21)



(7 + 11 → 22)



(7 + 14 → 23A)



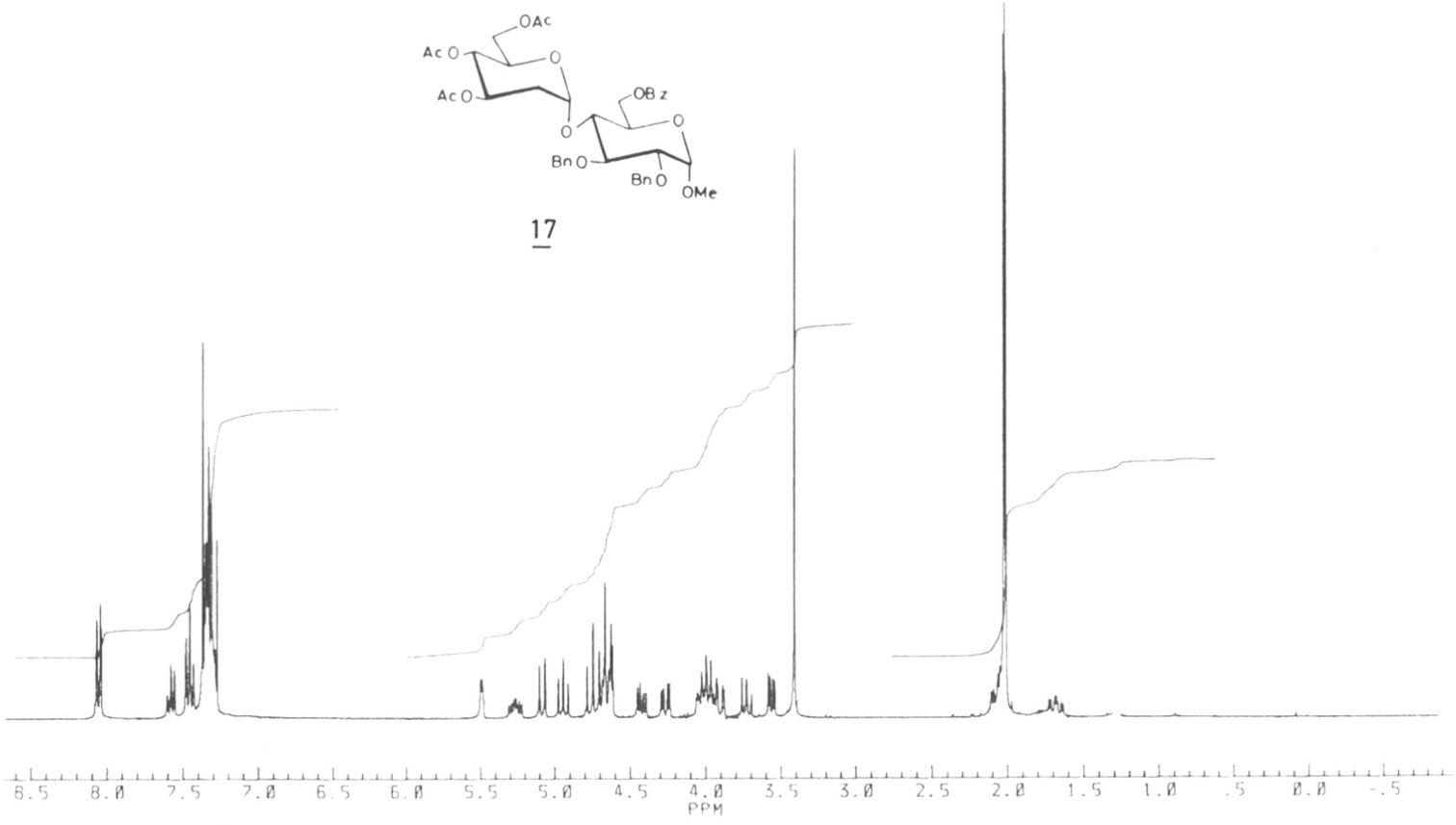
(7 + 14 → 23B)

for glycosidation is much more complicated due to relative low reactivity[159-162].

The (1 → 4) α-linked 2-deoxy disaccharide **17** was synthesized in 34% yield (syrup) by the saccharide coupling of **5**[151] with **11**[155] (SCHEME 4). The ^{1}H-nmr spectrum showed H-2 (axial) at δ 1.67 (ddd, 1H, $J_{1',2'a}$=3.9, $J_{2'a,3'}$=11.7, $J_{2',2'gem}$=16.9 Hz), H-2 (equitorial) between 1.98-2.04 (ddd, submerged) respectively of the 2-deoxy sugar unit (table 1&2). Appearance of three singlets at δ1.99, 2.00 and 2.01 respectively for three acetates and a singlet at δ 3.4 for methoxyl group has further confirmed the formation of the 2-deoxy saccharide. Appearance of a broad doublet at δ 5.48 ($J_{1',2'a}$=2.78 Hz) for H-1' has confirmed the α-configuration[97]. The chemical shift assignment for H-1' is also confirmed from 2D-COSEY correlation spectrum where the coupling to H-2'ax at δ1.67 has been observed (Figure 2). The ^{13}C-nmr spectrum of **17** showed a triplet at δ35.03 for C-2'. Appearance of a signal at δ 55.1 for methoxyl group and signals at δ 97.5 and 98.8 for C-1 (d) and C-1' (d) has confirmed the α-configuration. The positive optical rotation of $[\alpha]_D^{25}$ +60.95 (c 0.63, $CHCl_3$) is also in agreement with the assigned -configuration[97]. It has also been observed throughout that a bulky protecting group such as benzyl and benzoyl at C-6 always impeded the C-4 hydroxyl reactivity of the sugar alcohol, thus leading to lower yields of disaccharides.

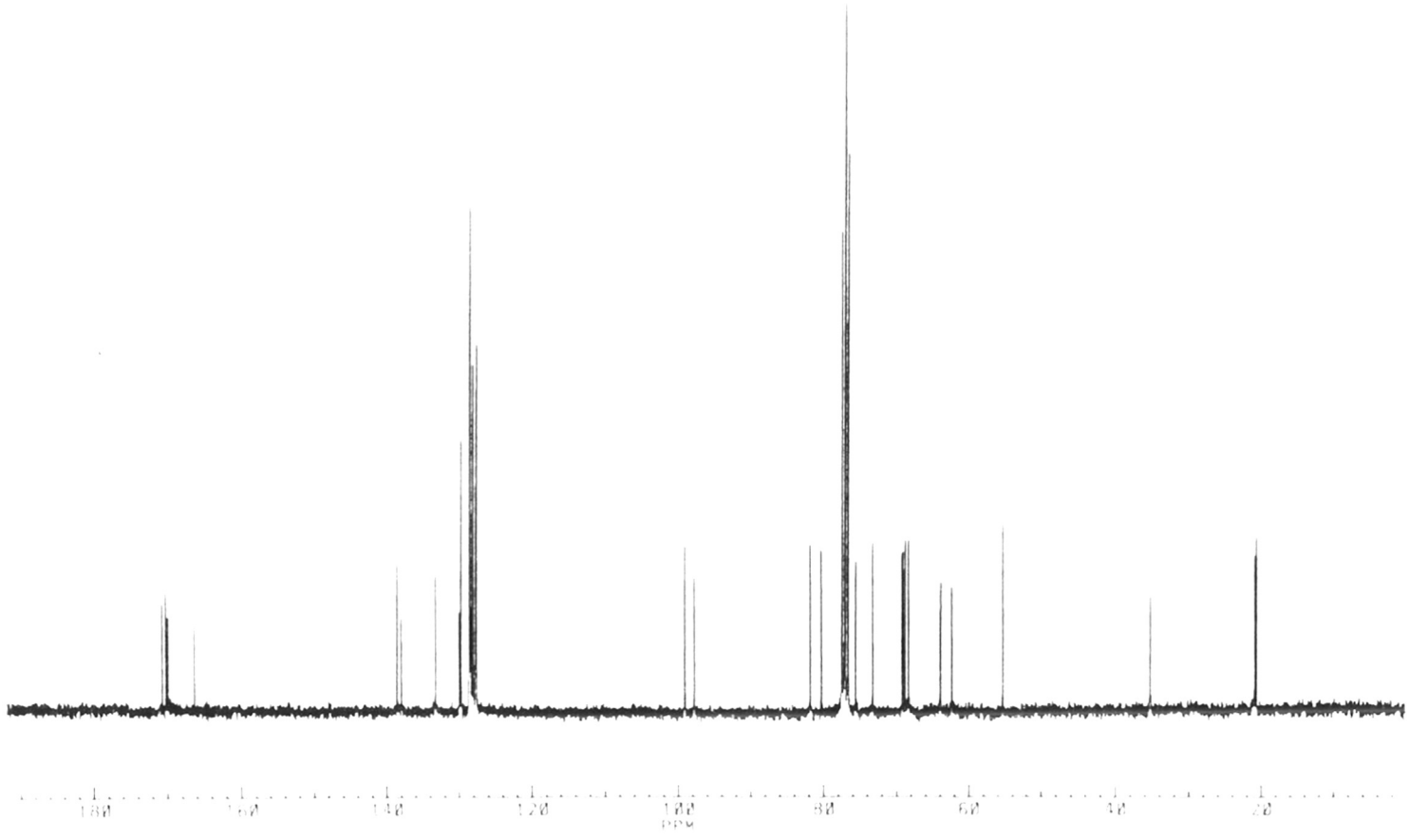
1,2:3,4-Di-O-isopropylidene-6-O-(3,4,6-tri-O-acetyl-2-deoxy- α -D-arabino-hexopyranosyl)-α-D-galactopyranoside (18)

Coupling of **5**[151] with **14**[158] (SCHEME 4) afforded 16h) the 2-deoxy disaccharide **18** primarily as α-anomer (α : β anomers, 85:15 ratio by ^{1}H-nmr) in 88% yield (syrup). Compound **18** was characterized by the appearance of singlets at δ 1.26x2, 1.62x2 (12H) (table 1&2) for the isopropyli-



17

^{1}H NMR SPECTRUM OF COMPOUND 17 (300 MHz, $CDCl_3$)



^{13}C NMR SPECTRUM OF COMPOUND 17 (75 MHz , $CDCl_3$)

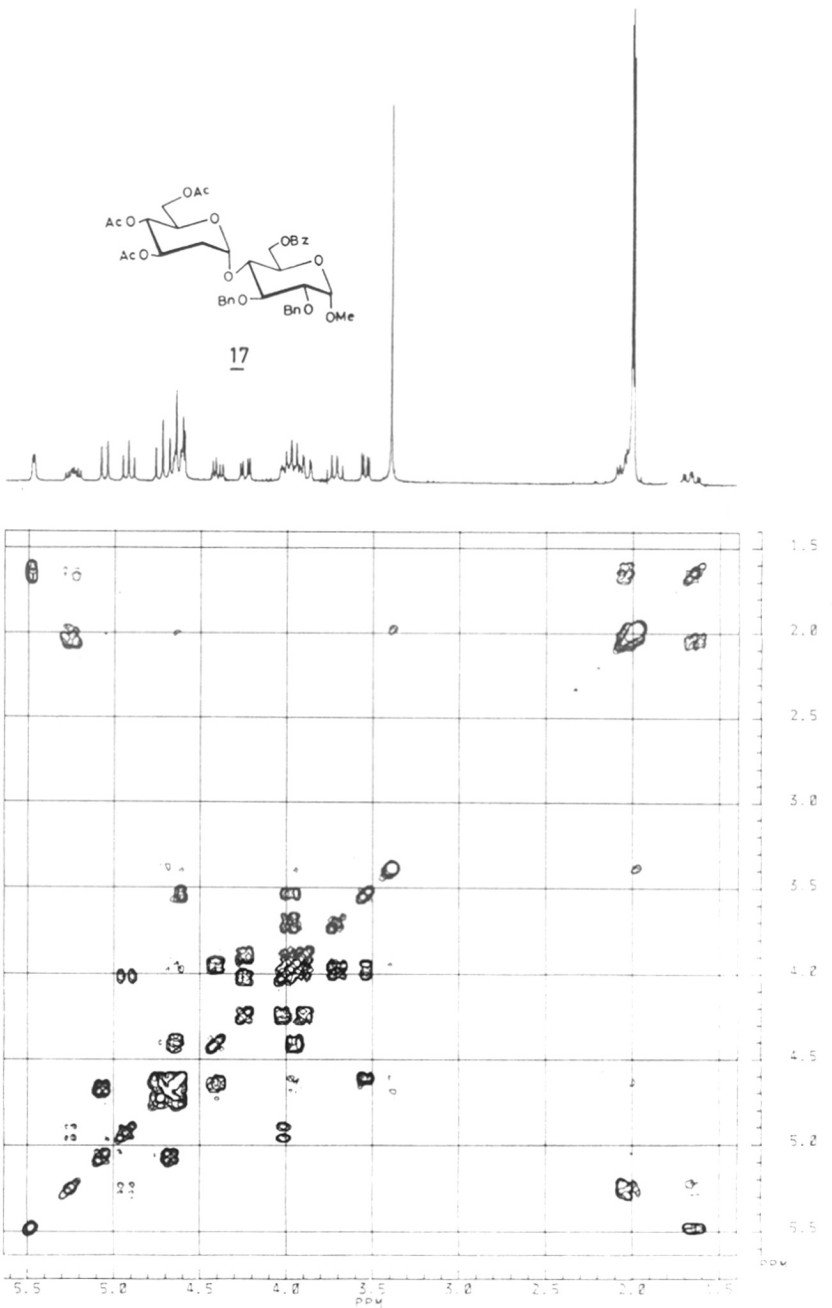


FIG. 2 2D COSEY SPECTRUM OF COMPOUND 17 (300 MHz, $CDCl_3$)

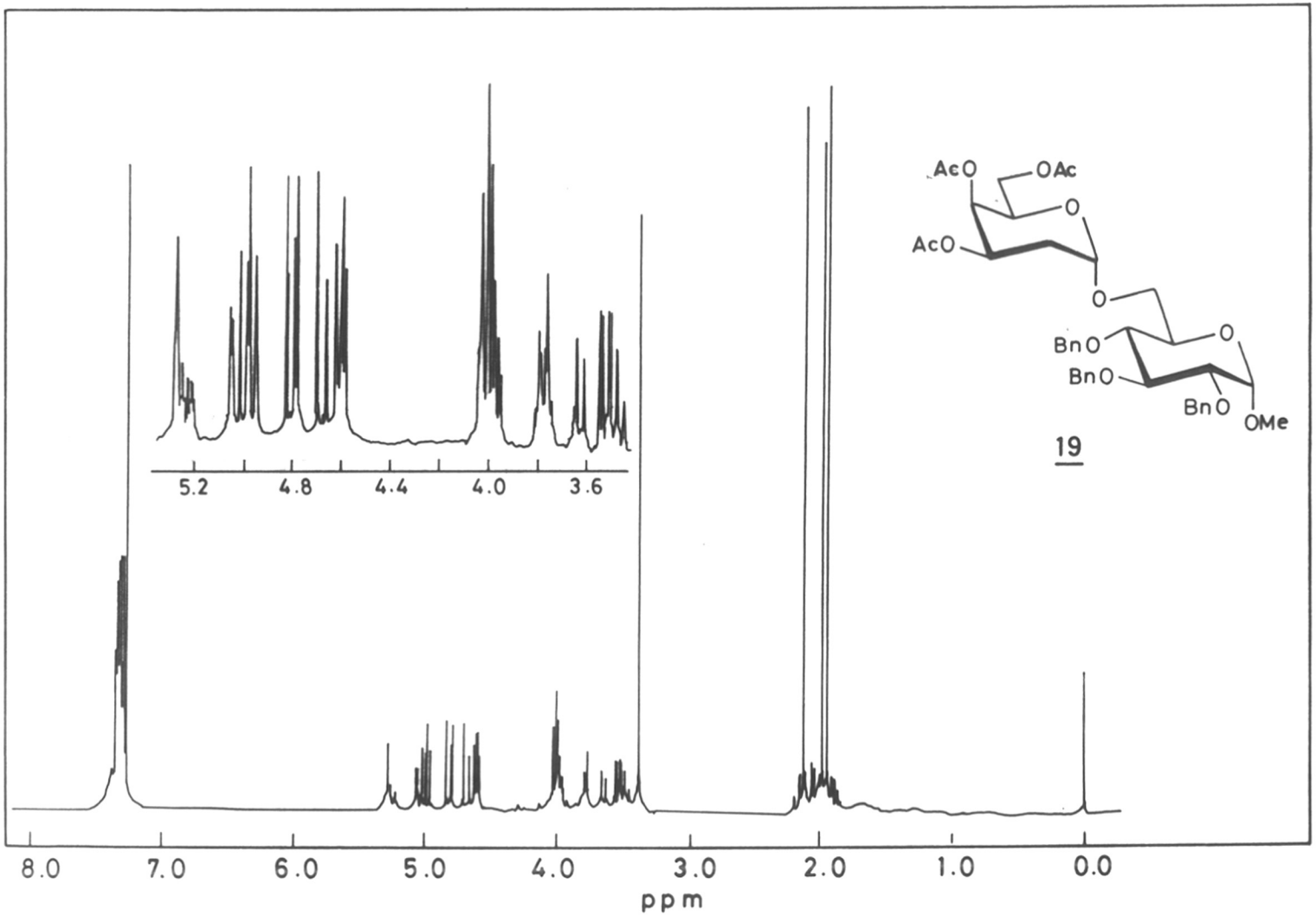
dene moiety, multiplets between δ 1.71-1.85 for H-2' (axial) and between δ 2.10-2.33 for H-2' (equatorial). H-1',1 signals appeared in the range of δ 3.33-5.5. The ^{13}C-nmr of **18** showed two doublets at δ 96.4 and 97.0 for C-1 and C-1' respectively[97]. Apperance of doublets at δ100.00 (15%) (**18B**) for C-1' is characteristic of β-linked saccharides[140]. Positive optical rotation of $[\alpha]_D^{25}$ +10.4° (c 1.0, $CHCl_3$) is also in agreement with the assigned structure.

Methyl 6-O-(3,4,6-tri-O-acetyl-2-deoxy-α -D-lyxohexopyranosyl)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (19)

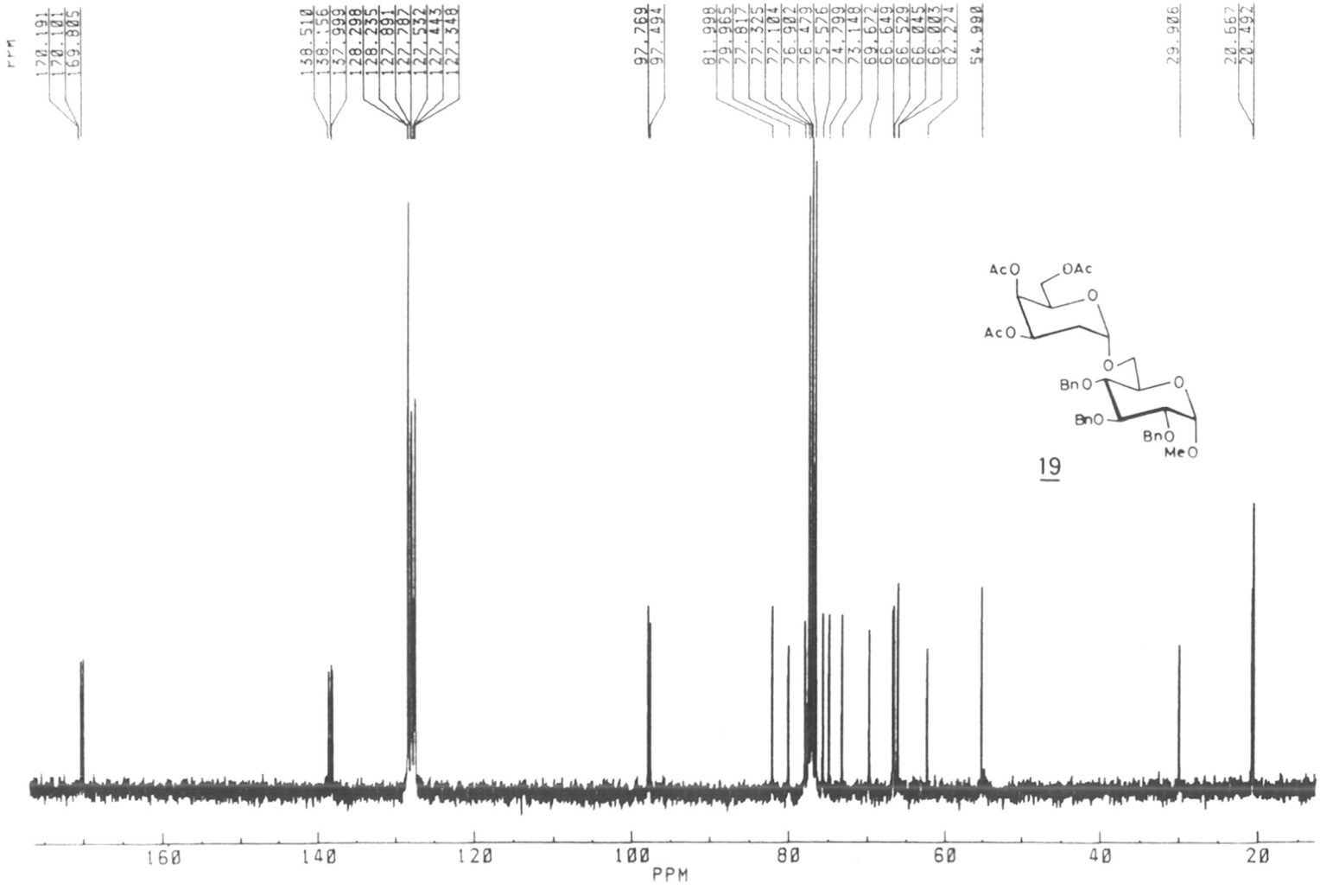
The saccharide coupling of **6**[151] with acceptor **13**[157] resulted in the isolation of a (1 → 6) α-linked 2-deoxy saccharide **19** in 71% yield as a syrup (SCHEME 4). The ^{1}H-nmr showed three singlets at δ 1.95, 1.98, 2.12. The appearance of a ddd at δ1.9 ($J_{1',2'a}$=2.8, $J_{2'a,3'}$=6.0, $J_{2',2'gem}$= 13.0), another ddd at δ2.0 (submerged) for H-2' (axial) and H-2' (equatorial) respectively of 2-deoxy sugar unit (table 1 and 2). A singlet at δ 3.4 for methoxyl group of the 2-deoxy disaccharide, a doublet between δ4.6-5.0 and at 5.05 for H-1 and H-1' respectively[97]. The assignment of chemical shift of δ5.05 for H-1' is based on the 2D COSEY correlation spectrum where it has shown cross peak with H-2'ax proton (Fig.3). The ^{13}C-nmr spectrum showed characteristic doublet signals at δ 97.4 and 97.7 for C-1 and C-1' respectively[97]. Optical rotation of $[\alpha]_D^{25}$ +86.07 (C 0.178, $CHCl_3$) was also consistent with the assigned α-configuration.

Methyl 4-O-(2,4,6-tri-O-acetyl-2-deoxy-α-D-lyxohexopyranosyl)-6-O-benzoyl-2,3-di-O-benzyl-α-D-glucopyranoside (20)

α-Linked 2-deoxy disaccharide **20** was obtained as a syrup in 45% yield from the coupling of glycosyl donor **6**[151] with the acceptor **11**[155] (SCHEME 4). The ^{1}H-nmr spectrum of **20** showed three singlets at δ 1.96,



^{1}H - NMR SPECTRUM OF COMPOUND 19 (300 MHz, $CDCl_3$)



19

^{13}C NMR SPECTRUM OF COMPOUND 19 (75 MHz, $CDCl_3$)

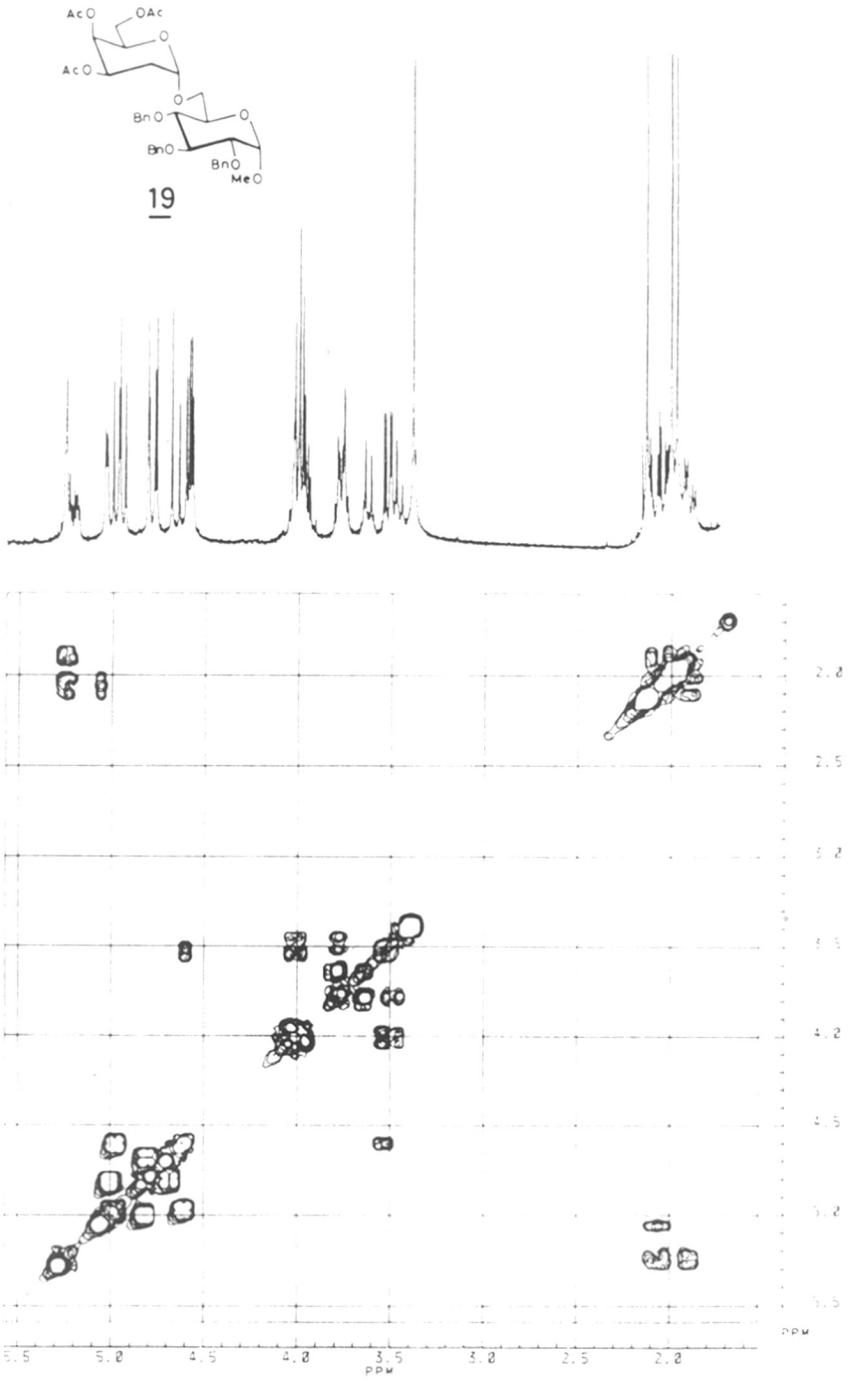
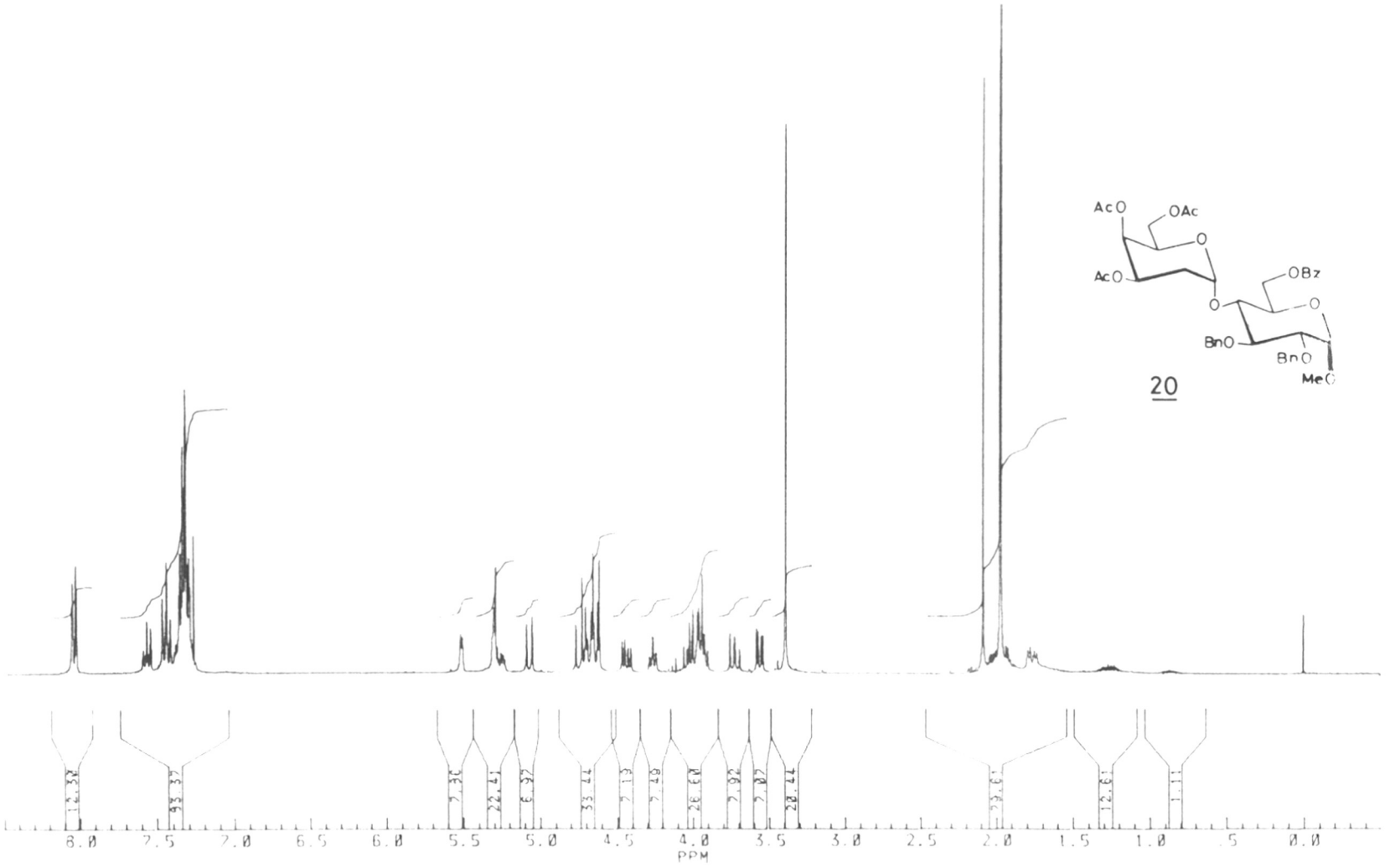
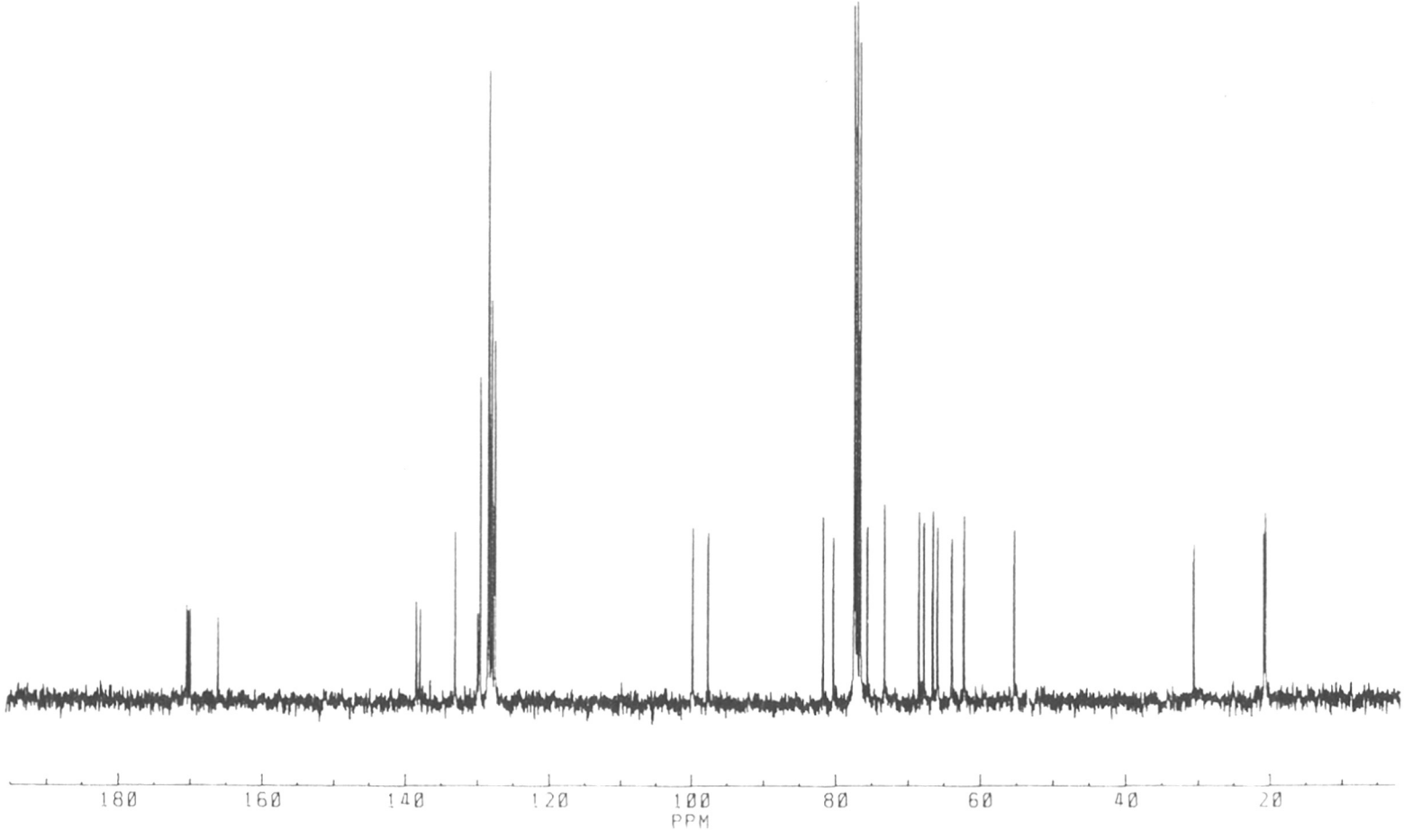


FIG. 3 2D-COSEY SPECTRUM OF COMPOUND 19



^{1}H NMR SPECTRUM OF COMPOUND 20 (300 MHz, $CDCl_3$)



^{13}C NMR SPECTRUM OF COMPOUND 20 (75 MHz, $CDCl_3$)

1.97, 2.08 (9H) for three acetates (Table 1&2). A multiplet between 1.90-2.05 for H-2' (axial) and H-2' (equatorial) of 2-deoxy sugar unit. A singlet for methoxyl group appeared at δ3.38. A broad doublet at δ5.5 ($J_{1',2'}$=3.0 Hz) for H-1', confirmed it to be an α-glycoside[97]. The ^{13}C-nmr of **20** showed two doublets at δ 97.6 and 99.7 for C-1 and C-1' respectively[97]. Further, optical rotation of $[\alpha]_D^{25}$ +75.63° (c 1.1, $CHCl_3$) confirmed the assigned αconfiguration[97].

Methyl 6-O-(3,4-di-O-acetyl-2,6-dideoxy-α -L-arabinohexopyranosyl)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (21)

The glycosyl coupling of **7**[151] with the glycosyl acceptor **13**[157] afforded in 64% yield the (1 → 6) α-linked 2-deoxy disaccharide **21** as a syrup (SCHEME 4). The ^{1}H-nmr showed a doublet at δ 1.12 ($J_{5',6'}$=6.5, H-6') for H-6' methyl group of 2-deoxy sugar, a ddd at δ 1.7 ($J_{1',2'a}$=3.6, $J_{2'a,3'}$=11.0, $J_{2',2'gem}$=13.0) and at δ 2.2 (ddd, $J_{2'e,3'}$=5.3) for H-2' (axial) and H-2' (equatorial) respectively. Methoxyl group of **21** appeared as a singlet at δ3.4 and broad doublets between δ4.5-5.1 for H-1 and H-1' respectively (table 1 and 2). The chemical shift assignment for H-1' is also confirmed from 2D-COSEY correlation spectrum where the coupling to $H\text{-}2'_{ax}$ at δ1.7 has been observed (Figure 4). The ^{13}C-nmr spectrum showed doublet signals at δ 96.9 and 97.9 for C-1 and C-1' respectively. The α-configuration of **21** has been further rationalized by the optical rotation of $[\alpha]_D^{25}$ -18.03 (c 1.02, $CHCl_3$).

Methyl 4-O-(3,4-di-O-acetyl-2,6-dideoxy- α-L-arabinohexopyranosyl)-6-O-benzoyl-2,3-di-O-benzyl-α-D-glucopyranoside (22)

Similarly, saccharide coupling of the glycosyl donor **7**[151] with the glycosyl acceptor **11**[155] afforded (32 h) exclusively the α-2-deoxy disaccharide **22** in 44% yield as a syrup (SCHEME 4). The ^{1}H-nmr of **22** showed

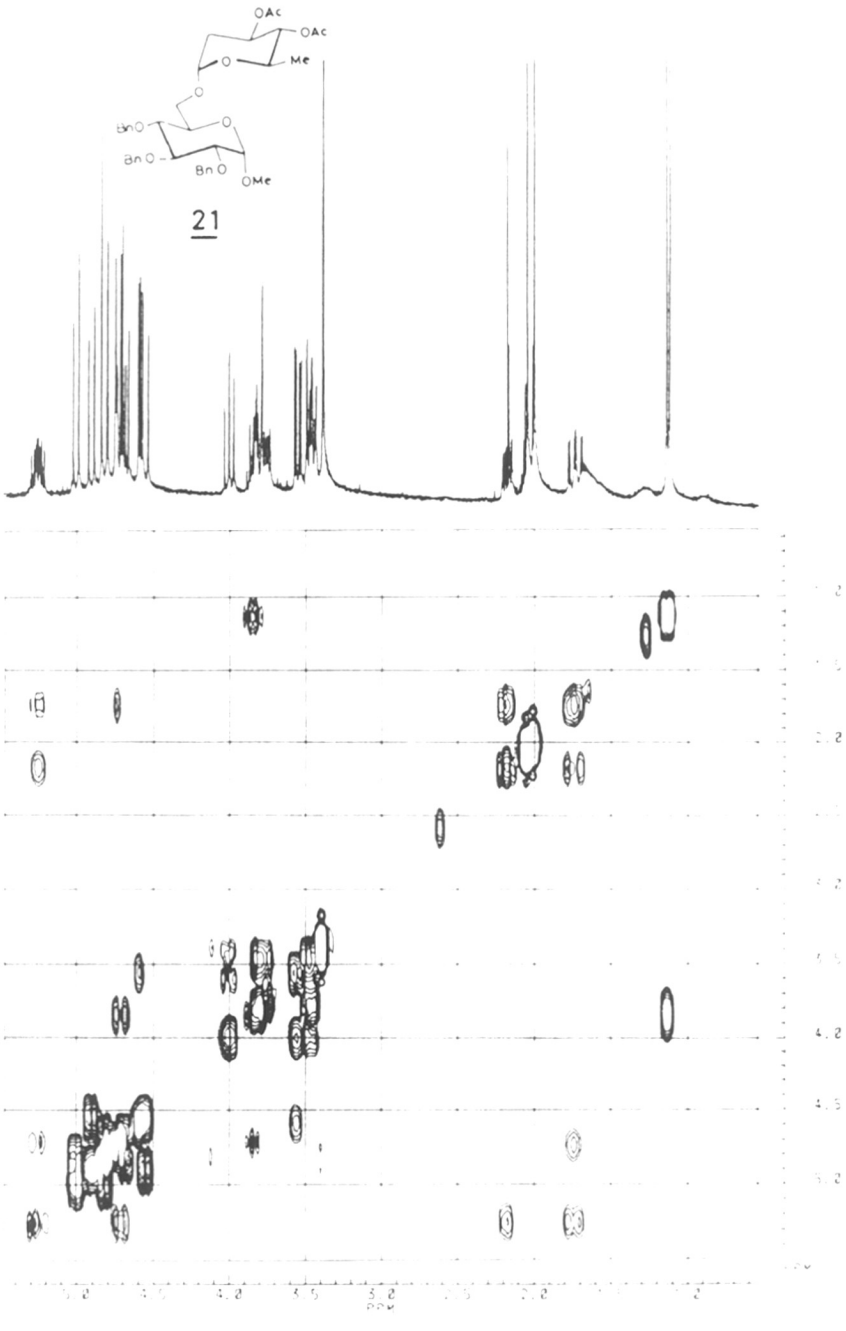
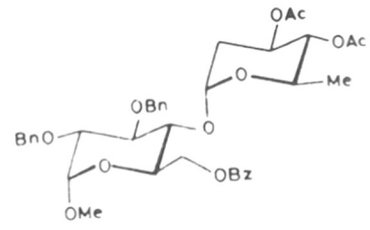
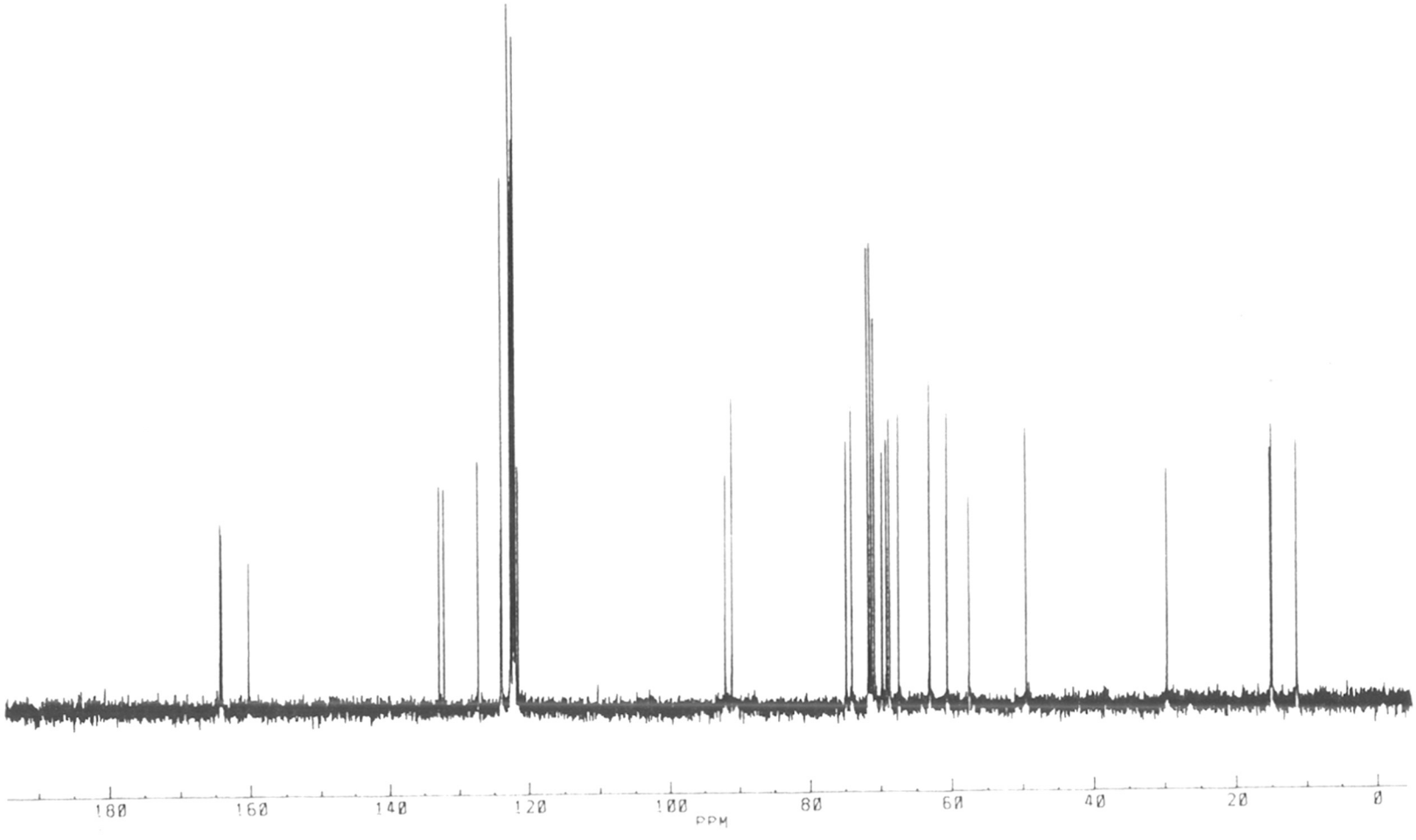


FIG. 4 2D COSEY SPECTRUM OF COMPOUND 21



22

^{1}H NMR SPECTRUM OF COMPOUND (22 (30MHz, $CDCl_3$)



^{13}C NMR SPECTRUM OF COMPOUND 22 (75 MHz , $CDCl_3$)

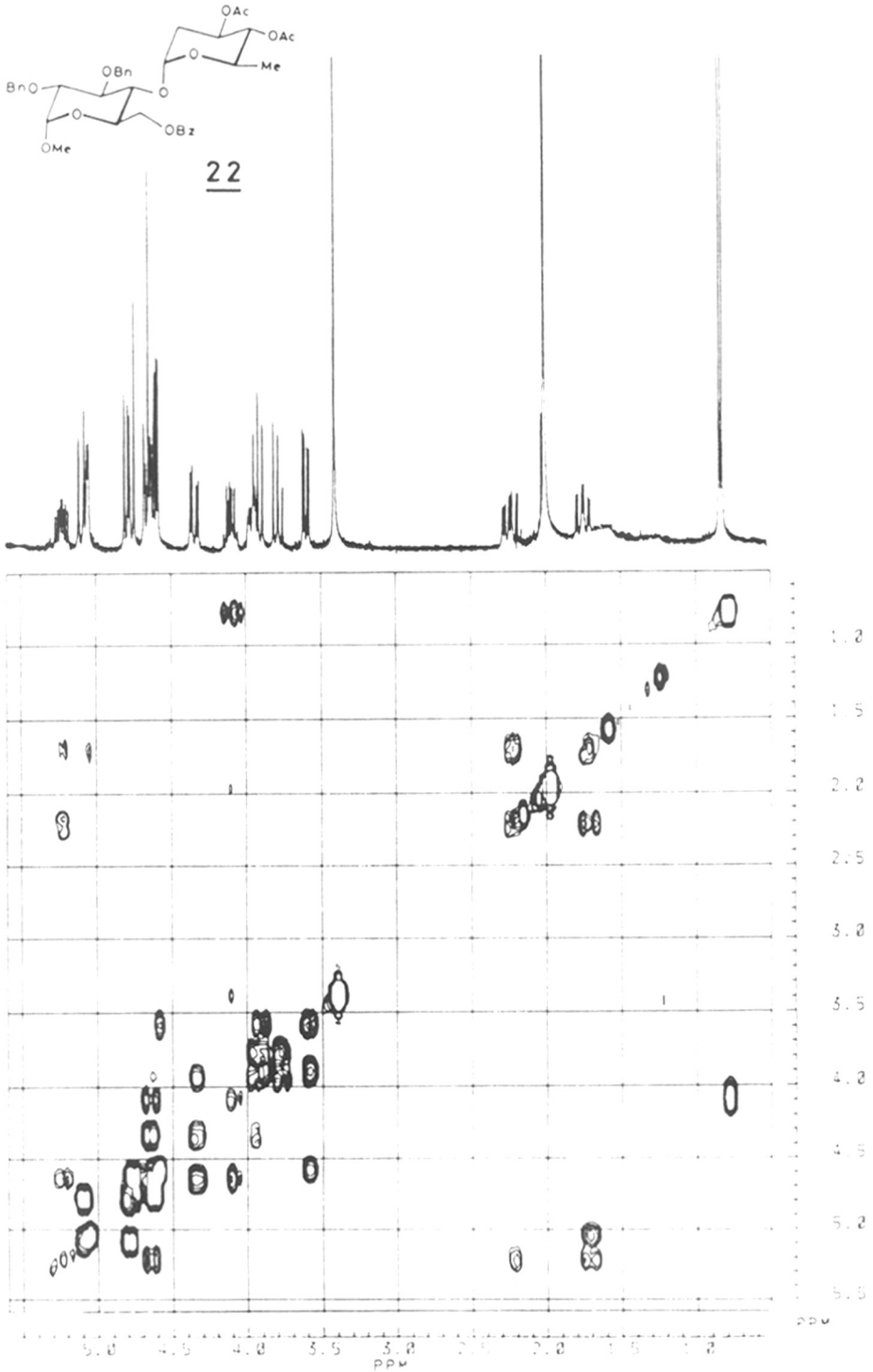
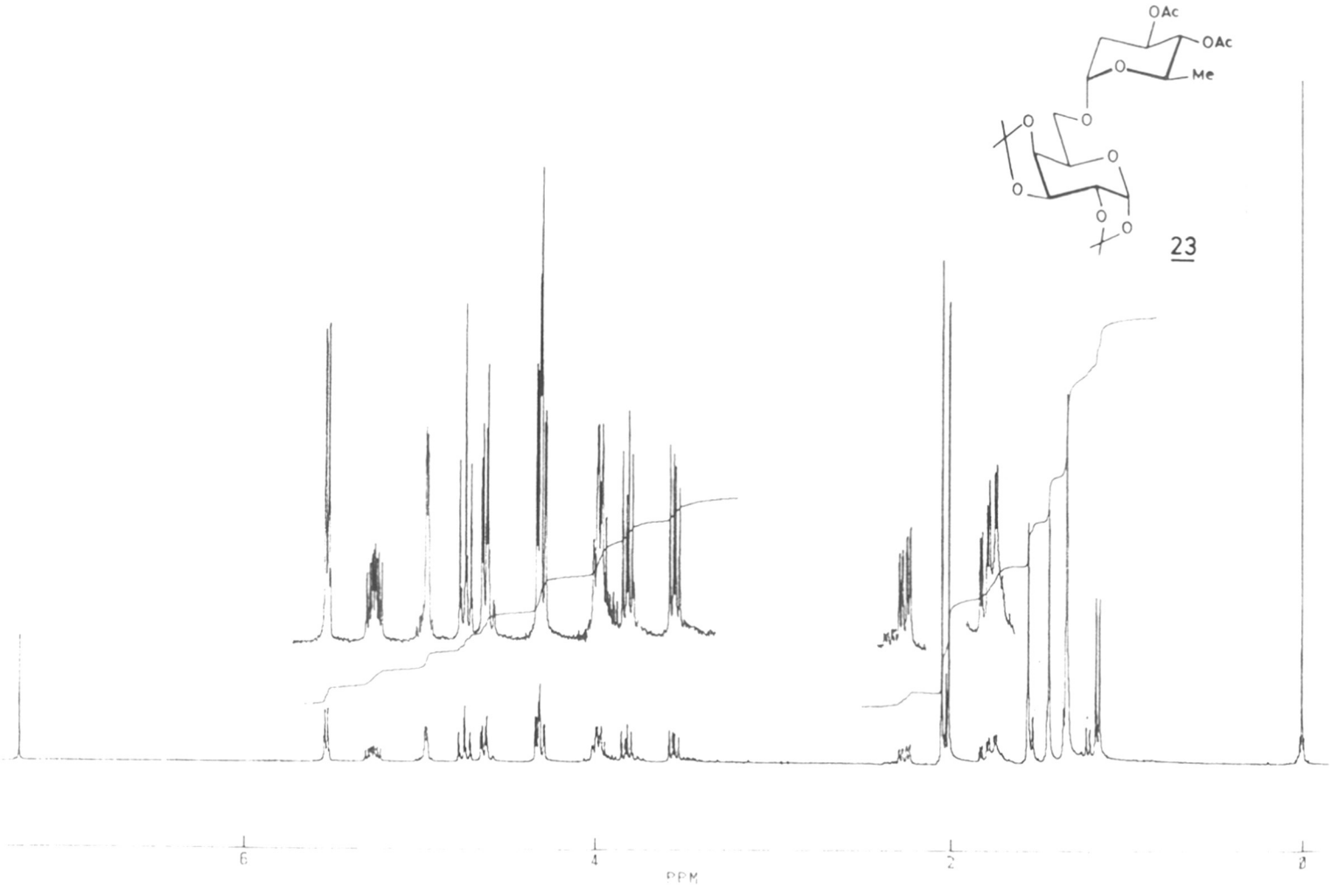


FIG. 5 2D-COSEY SPECTRUM OF COMPOUND 22

a doublet at δ 0.8 for H-6' methyl group, a ddd at δ 1.75 ($J_{1',2'a}$=3.5, $J_{2'a3'}$=-11.0, $J_{2',2'gem}$=13.07 Hz) and a ddd at 2.2 ($J_{1',2'e}$=0.94, $J_{2'e,3'}$=5.0) for H-2' (axial) and H-2' (equatorial) of 2-deoxy sugar component. Singlets at δ 2.0x2 (6H) for two acetate groups, singlet atδ3.4 for methoxyl group of **22** (table 1 and 2). Doublet between δ4.5-4.8 and a broad doublet at δ5.05 ($J_{1',2'a}$=3.5 Hz) for H-1,1' respectively[97]. Chemical shift of δ 5.05 for H-1' which is characteristic of α-linkage is assigned from the 2D COSEY correlation spectrum where it shows cross peak with H-2' axial proton (Figure 5). The ^{13}C-nmr showed a quartet at δ17.2 for C-6' methyl group, a quartet at δ 55.2 for methoxyl group and two doubelts at δ 96.8 and 97.7 for C-1, C-1' respectively, consistent with the assigned α-linkage[97]. Optical rotation of $[\alpha]_D^{25}$-28.14° (c 0.81, $CHCl_3$) is also in agreement with the assigned structure.

1,2:3,4-Di-O-isopropylidene-6-O-(3,4-di-O-acetyl-2,6-dideoxy-α-L-arabino-hexopyranosyl)-α-D-galactopyranoside (23)

Reaction of 2-pyridyl 2-deoxy-1-thioglycosyl donor **7**[151] with diacetone galactose **14**[158] afforded[23] (16h) (SCHEME 4). The 2-deoxy disaccharide **23** in 86% yield as a syrup, primarily as α-anomer (α:β-anomers, 85:15 ratio by ^{1}H-nmr). The α-configuration of the newly formed inter O-glycosidic bond is confirmed as follows. The ^{1}H-nmr of **23** showed two doublets at δ1.16 (2.55 H, $J_{5',6'}$=6.2 Hz (85%) and at 1.21 (0.45 H) (15%) for H-6' methyl group of α[97] and β-anomers[140] respectively. Singlets at δ 1.34x2, 1.44 and 1.56 (12H) (table 1&2) for the isopropylidene methyls, a broad doublet at δ4.95 and a doublet at δ5.5 ($J_{1',2'a}$=5.0 Hz) for H-1', and H-1 respectively have conformed the α-configuration. The ^{13}C-nmr showed doublets at δ96.4 and 96.90 for C-1,1' for 23A and a doublet at 100.0 (15%) for C-1' of the corresponding β-anomer[140]. Further, optical rotation



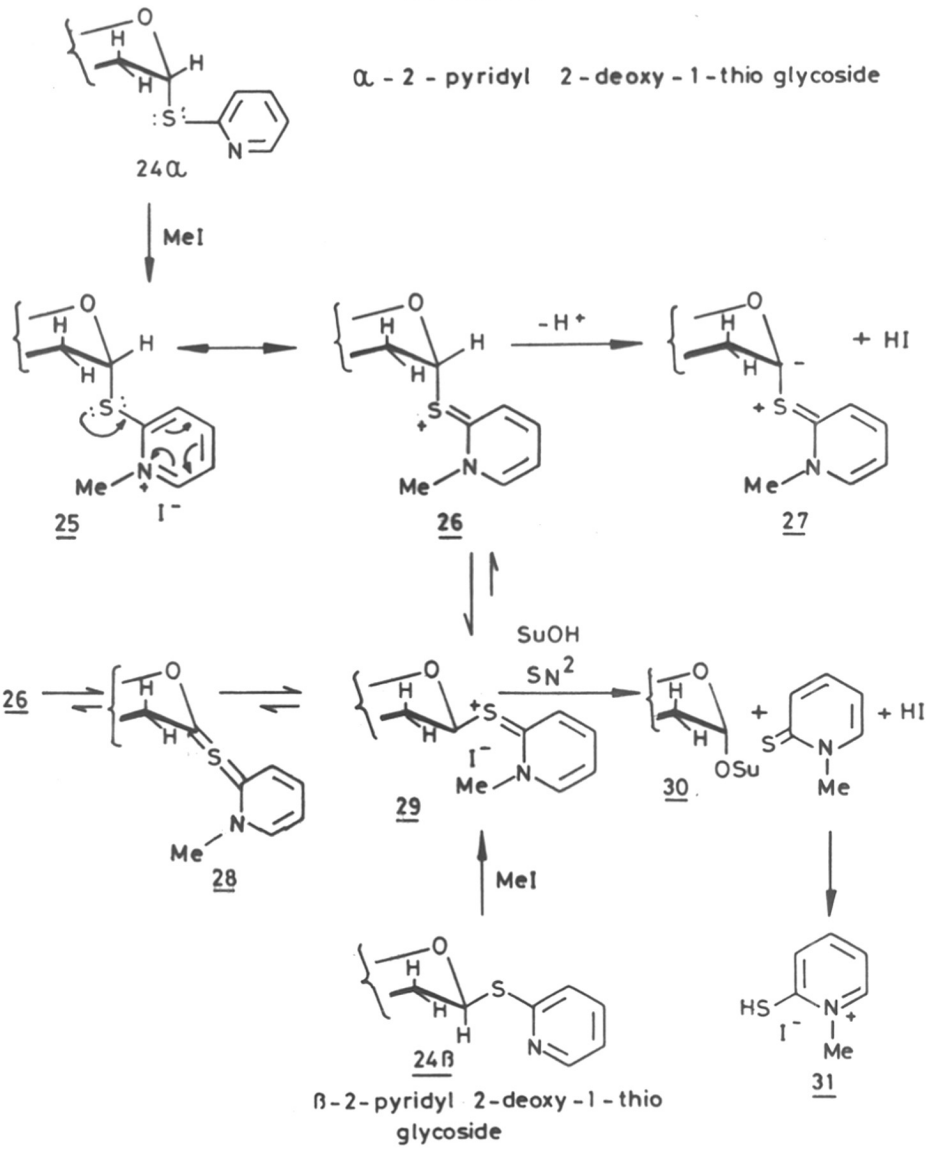
^{1}H NMR SPECTRUM OF COMPOUND 23 (300 MHz, $CDCl_3$)

of $[\alpha]_D^{25}$ -103.29° (c 1.26, $CHCl_3$) is in confirmation with the α-configuration[97].

2.3 Mechanism for α-glycosidations

First step involves N-methylation of the heterocyclic moiety of 2-pyridyl 2-deoxy-1-thioglycoside on reaction with methyl iodide leading

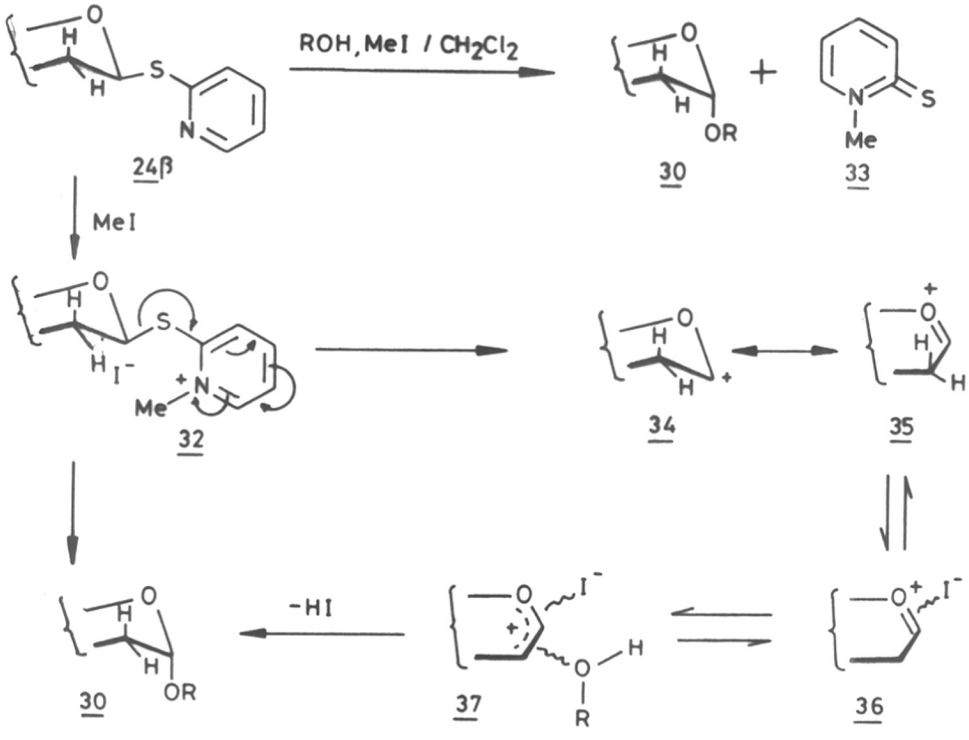
SCHEME 5



to the formation of stable N-methyl quaternary thiopyridinium salt **25.** Compound **25** is further stabilized by resonance to form the sulfenium salt **26,** which inturn loses the acidic proton at the anomeric center leading to the formation of **27,** which is further stabilized by conjugation to form **28.** Protonation of **28** leads to the β-sulfenium salt **29,** which would be stabilized due to 'reverse anomeric effect'[58,166]. Thus, equilibrium is driven from **26** to **29** ultimately. The β-sulfenium salt **29** undergoes S_N2 displacement on reaction with sugar alcohols (SuOH) leading to the stereo-selective formation of α-2-deoxy glycosides **30.** N-methyl 2-thiopyridone (**26**) which is ejected out, in turn captures the liberated HI to form the salt **31.** Thus α or β-2-pyridyl 2-deoxy-1-thioglycosides (**24α** and **24β**) lead to the formation of α-glycosides (SCHEME 5).

The study of anomerization of **24** to **29** was attempted by reaction

SCHEME 6



of 7 with MeI in nmr tube in $CDCl_3$. This reaction could not be followed due to rapid hydrolysis of 24α / 24β due to adventitious water present in the solvent.

It is also possible that the carbonium ion **34** is either captured by the alcohol leading to the formation of α-alkylglycoside **30** or that the oxocarbenium ion **35** forms an ion-pair **36** with the free iodide which in turn is displaced by an alcohol to give selectively the α-2-deoxy glycoside. **30** is also the expected thermodynamic product of the reaction (SCHEME 6).

2.4 Approaches to the Synthesis of L-oleandrose : A review

2.4.1 Introduction

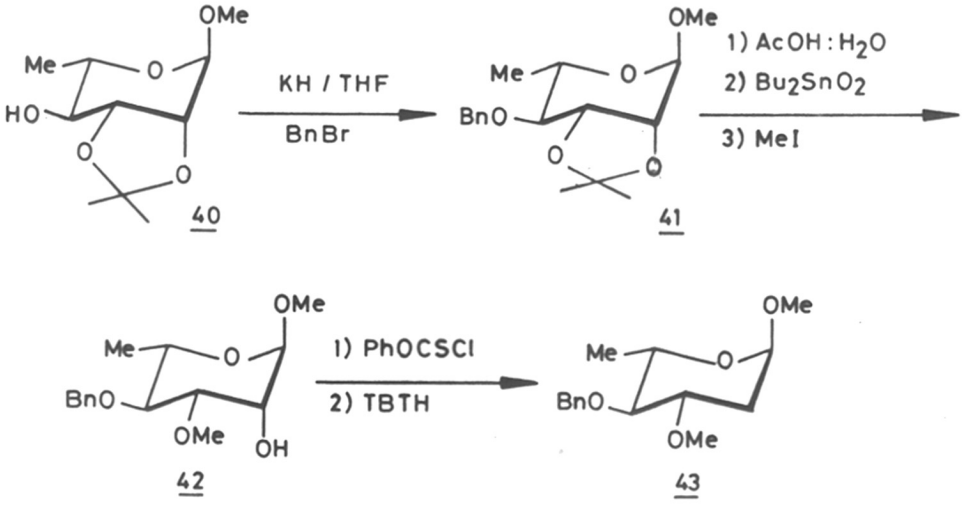
Avermectins are a group of potent broad spectrum anthelmintic agents that have been isolated from the mycelia of Streptomyces avermitilis[27-29]. They have been found to be active against helminths and arthropodes in doses as low as 10 μg/kg[167]. They are 16-membered lactones with α-L-oleandrosyl-α-L-oleandroside, a disaccharide moiety attached to C-13 position of the aglycone macrolide. Activity of avermectin was considerably reduced with the removal of saccharide units. Until recently this unusual class of disaccharides had eluded the grasp of synthetic chemists. The present review centres on the stereoselective synthesis of L-oleandrose.

2.4.1.1 Synthesis of methyl 4-O-benzyl-α-L-oleandroside

The L-oleandrose derivative, methyl 4-O-benzyl-α-L-oleandroside (**43**) was synthesized[112b] from the readily available L-rhamnose derivative, methyl 2,3-di-O-isopropylidene-α-L-rhamnoside (**40**)[168]. Benzylation of **40** afforded methyl 4-O-benzyl-2,3-O-isopropylidene-α-L-rhamnoside (**41**). Deprotection of **41** was accomplished by heating it with the 1:3 mixture

of acetic acid:water, which further on reaction with Bu_2SnO_2-MeOH at 70°C and then methyl iodide-DMF afforded methyl 4-O-benzyl-3-O-methyl--L-rhamnoside (**42**) in 78% yield (SCHEME 7). Radical induced deoxygenation at C-2 position was accomplished by converting **42** into xanthate on reaction with phenoxythiocarbonyl chloride, followed by radical reaction with n-tributyltinhydride (TBTH) to afford methyl 4-O-benzyl-α-L-oleandroside (**43**) in 90% yield.

SCHEME 7

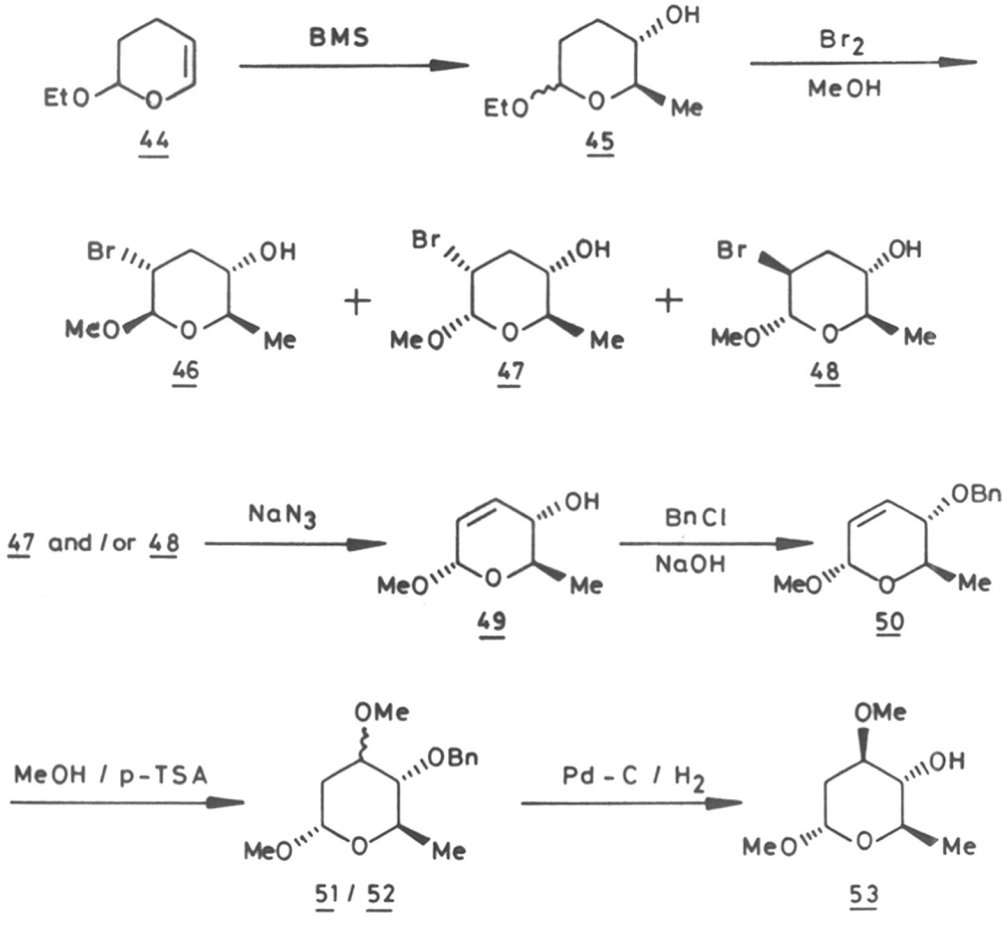


2.4.1.2 Synthesis of racemic methyl α-dl-oleandroside (53)

Methyl α-dl-oleandroside (**53**) was synthesized via the unsaturated alcohol **49** starting from ethoxytetrahydropyran (**44**), a synthetic strategy developed by **Matsumoto et al**[169]. Hydroboration and oxidation[170] of **44** afforded **45** (SCHEME 8). The alcohol **45** was treated with bromine in dry methanol containing HCl for 2 days to afford three bromocompounds (**46,47,48**). Treatment of **47** and/or **48** with sodium azide afforded an olefin **49** in 70% yield. Treatment of **49** with benzylchloride in presence of NaOH gave **50**, which was subjected to 1,2-addition[170], reaction with MeOH

in presence of p-TSA to give the addition products **51** and **52** in 65 and 21% yield respectively. Hydrogenolysis of **51** in the presence of 10% Pd-C afforded methyl α-dl-oleandroside (**53**)[171].

SCHEME 8

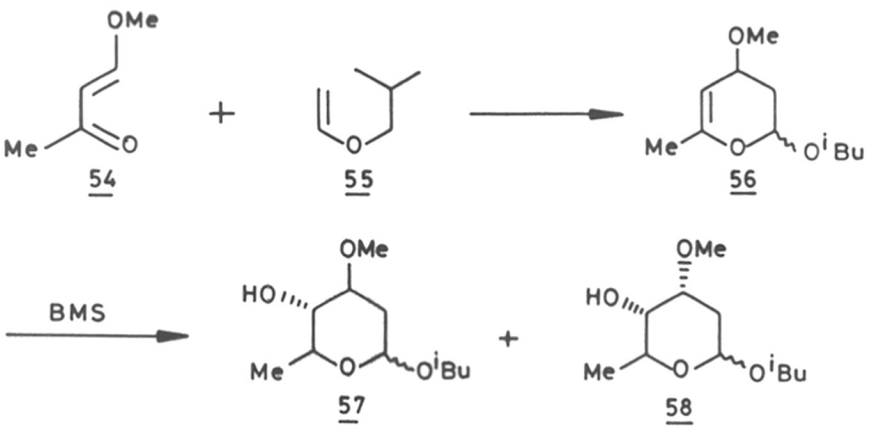


2.4.1.3 A highly diastereoselective synthesis of DL-oleandrose

Racemic oleandrose (2,6-dideoxy-3-O-methyl-DL-arabinohexose) (**57**) has been synthesized by **Berti et al**[172] 4-methoxy-3-butenone (**54**) on Diels-Alder reaction with isobutylvinyl ether (**55**) to give **56** as diastereoisomers in 55:45 ratio (SCHEME 9). Subsequent hydroboration-oxidation[173]

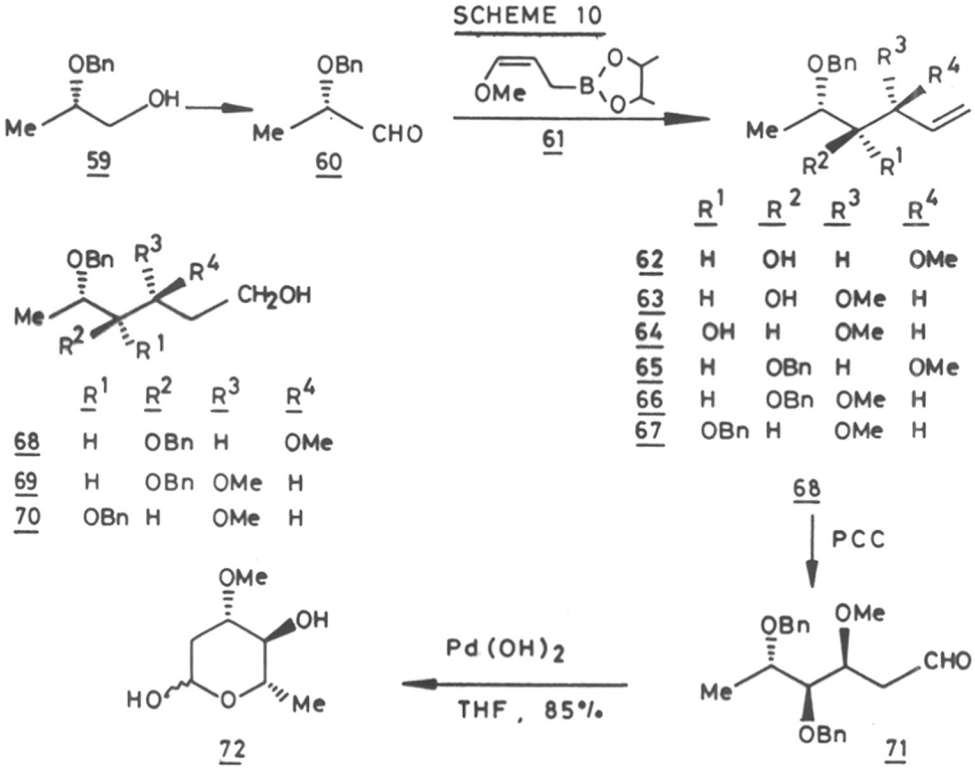
of the pure mixture of anomers with boranedimethylsulfide (BMS) gave a mixture of two of the four possible pairs of enantiomers of 2,6-dideoxy-3-O-methylhexosesisobutylglycosides, namely the isobutyl α and β-oleandrosides (α and β-57) and cymarosides (α and β-58) in 58:36:5:1 ratio.

SCHEME 9



2.4.1.4 Synthesis of L-oleandrose from a non-carbohyhdrate precursor

Racemic L-oleandrose (72) was synthesized starting from (S)-2(benzyloxy)propanol (59)[130]. Swern oxidation[174] of alcohol 53 gave in 88% yield the aldehyde 60. Three contiguous centres of oleandrose have been introduced by the reaction of aldehyde 60 with 7-methoxyallylboronate (61) (SCHEME 10) to obtain the triol derivative 62 along with two other minor isomers 63, 64 in 84% yield, in the ratio of 8.7:1.2:1.0. The triols were converted to tribenzylethers (65-67). Hydroboration of 65-67 lead to the formation of alcohols (68-70). The alcohol 68 was oxidized to aldehyde 71 in 77% yield, which was deprotected by hydrogenolysis over $Pd(OH)_2$ in THF to give racemic L-oleandrose (72) in 85% yield.



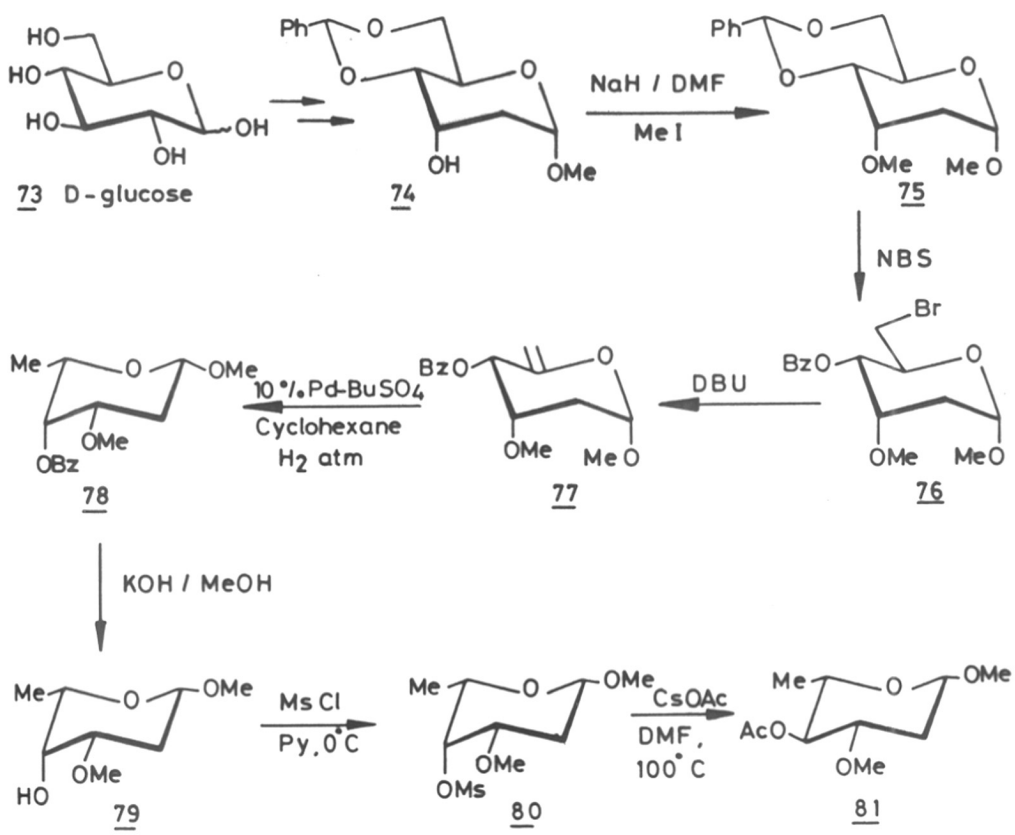
2.5 Results and Discussion:

Stereoselective synthesis methyl 4-O-(4-O-acetyl-α-L-oleandrosyl)-β-L-oleandroside (85) starting from D-glucose (73)

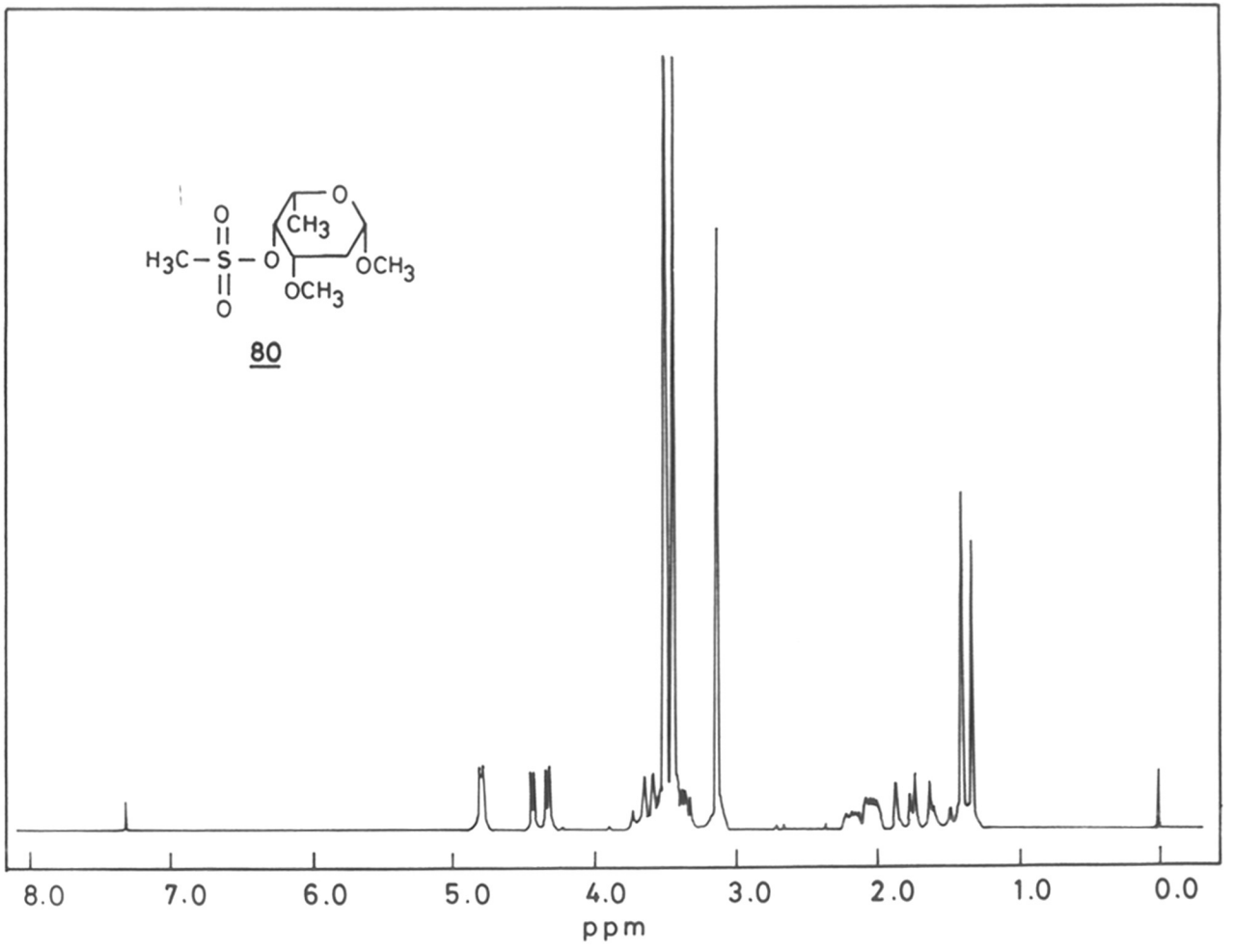
The preceeding review illustrated the various methods described for the synthesis of L-oleandrose, where in, most of the synthetic strategies either lead to racemic oleandroside[130,169,172] or make use of an expensive starting material such as L-rhamnose[112b]. We have developed a method that leads to the stereoselective synthesis of L-oleandrose from a cheap and abundantly available starting material such as D-glucose (73). 73 was converted by known sequence of reactions to methyl 4,6-O-benzylidene-2-deoxy-α-D-ribohexopyranoside (74) in 5 steps[175,176] (SCHEME 11). Methylation of 74 was accomplished by treatment with sodiumhydride and methyl

iodide in DMF[177] to afford methyl 4,6-O-benzylidene-2-deoxy-3-O-methyl-α-D-ribohexopyranoside (**75**)[178] in 85% yield, as a colorless crystalline compound, m.p. 97-99°C. The ^{1}H-nmr showed two singlets at δ 3.3 and 3.4 for anomeric methoxyl and the newly introduced methoxyl group at C-3 position. The ^{13}C-nmr showed two signals at δ 55.4 and 59.2 for anomeric methoxyl and the newly introduced methoxyl group. The 1,3-dioxalane ring opening[179] of **75** was accomplished by refluxing with N-bromosuccinimide (NBS) in carbontetrachloride to afford methyl 6-bromo-2,6-dideoxy-4-O-benzoyl-3-O-methyl- α -D-ribohexopyranoside[178] (**76**) in 80% yield as colorless crystals, m.p. 65-67°C.

SCHEME 11



The formation of compound **76** was established by the disappearance of singlet at δ 5.45 for 4,6-O-benzylidene group. The ^{13}C-nmr further showed the disappearance of a doublet at δ 102.2 for 4,6-O-benzylidene group and appearance of a singlet at δ 165.1 for benzoyl ester. Dehydrobromination of **76** was accomplished by treating with DBU in HMPA under nitrogen atmosphere at room temperature for 8 h to give methyl 4-O-benzoyl-3-O-methyl-2,6-dideoxy-α-**D**-hexo-5-enopyranoside (**77**) in 88% yield. The ^{1}H-nmr of **77** showed the presence of a double doublet at δ 4.6 for H-6,6' and disappearance of H-5 at 4.5. The ^{13}C-nmr showed a singlet at δ 152.7 characteristic signal of olefinic carbons. Stereospecific reduction of **77** in the presence of 10% Pd-$BaSO_4$ in cyclohexane under hydrogen atmosphere gave methyl 4-O-benzoyl-3-O-methyl-2,6-dideoxy-α-**L**-arabinohexopyranoside (**78**) in quantitative yield. The ^{1}H-nmr showed a doublet at δ 1.28 ($J_{5,6}$=6.8 Hz), for C-5 methyl group. Saponification of benzoyl ester **78** with 1% potassium hydroxide in dry methanol at 50°C gave methyl 2,6-dideoxy-3-O-methyl-β-**L**-arabinopyranoside (**79**) in 82% yield as a syrup. Inversion at C-4 with triphenylphosphine, diethylazodicarboxylate and benzoic and in dry tetrahydrofuran[180] (Mitsunobu reaction) met with failure. Finally, inversion was carried out successfully by converting **79** to mesitylated derivative on treatment with methanesulfonylchloride and pyridine at 0°C, to give a crystalline methyl 2,6-dideoxy-3-O-methyl-4-O-methanesulfonyl-β-**L**-arabinohexopyranoside (**80**) in 98% yield, m.p. 93°C. The ^{1}H-nmr showed the appearance of a singlet at δ3.1 for methyl sulfonyl group. Reaction of **80** with cesium acetate[181] in DMF at 100°C for 26 h gave methyl 4-O-acetyl-2,6-dideoxy-β-**L**-oleandroside (**81**) in 72% yield, as a syrup. The ^{1}H-nmr showed a doublet at δ 1.2 for C-5 methyl group,

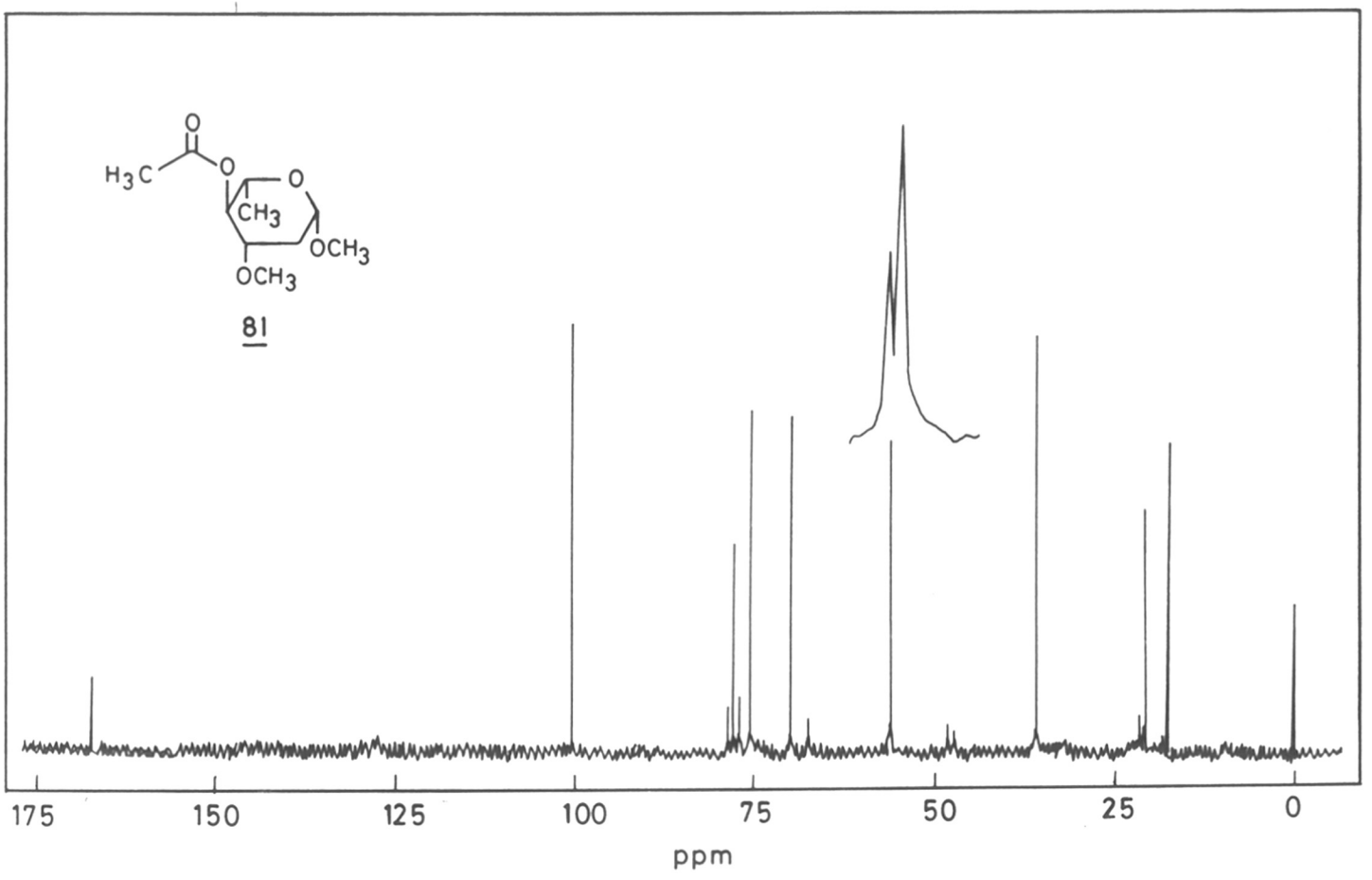


^{1}H - NMR SPECTRUM OF COMPOUND 80 (90MHz, $CDCl_3$)

a triplet at δ 4.6 ($J_{3,4}=J_{4,5}$= 10 Hz) for H-4, confirming the structure of **81**.

The intermediate **81** was used for the preparation of thiopyridyl glycosyl donor and glycosyl acceptor. Thus, **81** underwent saponification with catalytic amount of sodium methoxide in anhydrous methanol to afford methyl β-L-oleandroside (**82**) (the glycosyl acceptor) (SCHEME 12). Hydrolysis of **81** with 3:1 mixture of acetic acid:water at 60°C for 1 h afforded 4-O-acetyl-L-oleandrose (**83**) in 82% yield as a syrup, which was converted to the glycosyl donor, 2-pyridyl 4-O-acetyl-1-thio α and β-L-oleandroside (**84**) in 89% yield on treatment[20] with 2,2'-dipyridyldisulphide, and n-tributylphosphine at room temperature for 30 minutes. Compound **84** was used as such for the subsequent glycosidation step. The saccharide coupling of **82** with **84** in dry dichloromethane (containing 3% MeI), molecular sieves-4Å at 50°C (section **2.2.3**) for 20 h afforded the required disaccharide, methyl 4-O-(4-O-acetyl-α-L-oleandrosyl)-β-L-oleandroside **85** as a crystalline compound, in 78% yield, m.p. 100-101°C and a small amount (8%) of reprocessable elimination byproduct, 4-O-acetyl-3-O-methyl-L-rhamnal (**86**)[182]. The structure of **85** as an α-anomer was confirmed by the appearance of two doublets at δ 1.13 ($J_{5,6}$=6.3 Hz) and 1.3 ($J_{5',6'}$=6.1 Hz) for C-5 and C-5' methyl groups a multiplet at δ 1.44 (J=11.47, 9.78, 1.98 Hz), and 1.66 (J=11.6, 9.76, 2.8 Hz) for H-2 (axial) and H-2' (axial), a multiplet between δ 2.24-2.37 for H-2 (equatorial) and H-2' (equatorial).

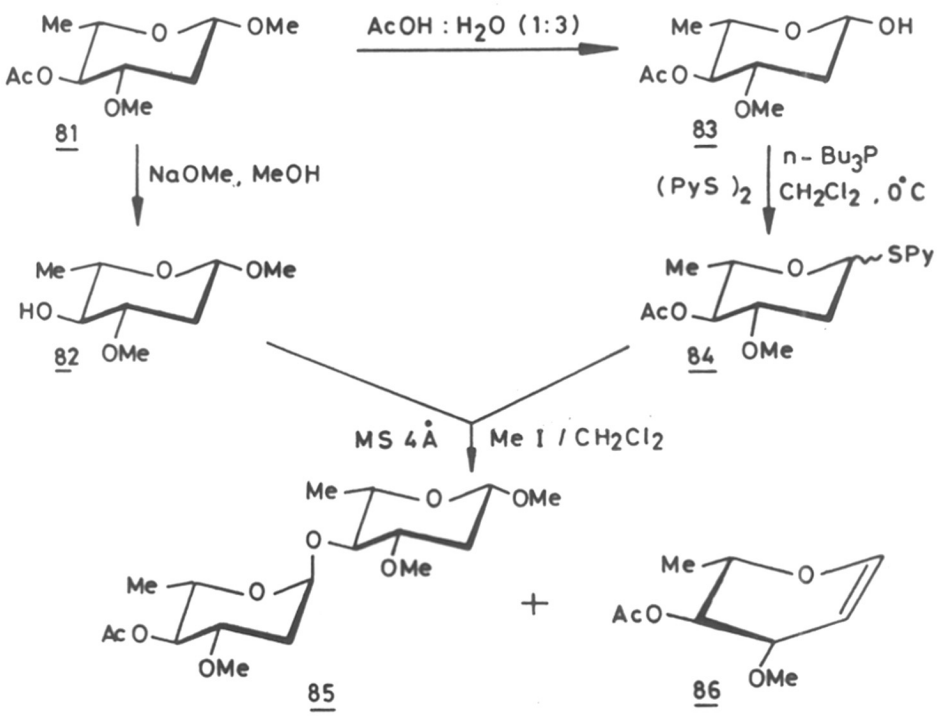
Singlets at δ 3.35x2 and 3.49 (9H) for three methoxyl groups,a double doublet at δ 4.74 and a doublet at δ 5.4 for H-1, H-1' also confirm the α-configuration. The ^{13}C-nmr showed signals at δ 17.5 and 18.6 for C-6 and C-6' methyl groups. Signals at δ 56.41 and 56.87x2 for three methoxyl



^{13}C - NMR SPECTRUM OF COMPOUND 81 (22.63MHz, $CDCl_3$)

groups, two signals at δ 98.46 and 100.8 for anomeric carbons C-1 and C-1' respectively.

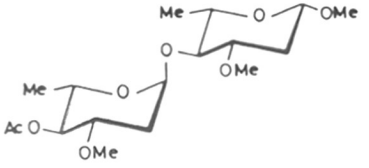
SCHEME 12



2.6 Synthesis of α -linked 2-deoxy trisaccharides

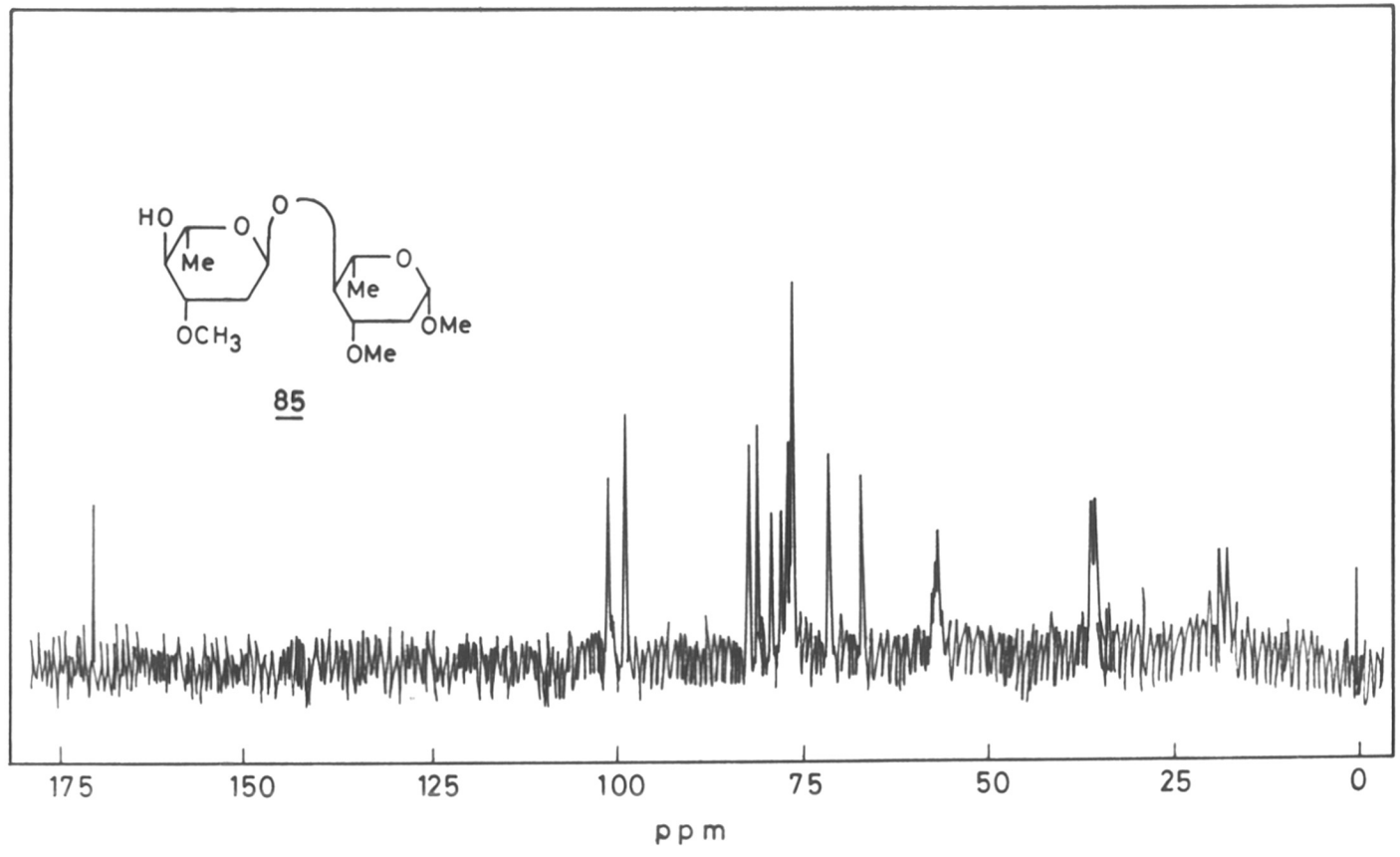
A considerable number of syntheses of 2-deoxy disaccharides[83-152] and a few syntheses of 2-deoxy trisaccharides have been described to date, specific problems appearing in such syntheses can be thus reasonably be discussed mainly at examples of trisaccharide synthesis.

Unbranched (linear)trisaccharides can generally speaking be prepared by two ways (i), by glycosidation of a monosaccharide derivative (donor) with a disaccharide glycosylating reagent (acceptor), i.e., by making the bond (a) or, (ii) alternatively by glycosidation of oligosaccharide derivative (donor) with a monosaccharide glycosy-



85

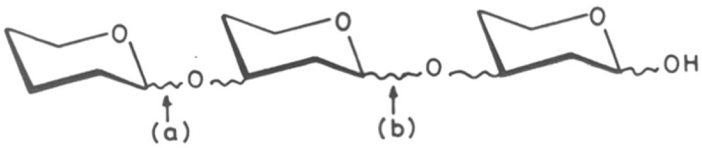
^{1}H NMR SPECTRUM OF COMPOUND 85 (300 MHz, $CDCl_3$)



85

^{13}C - NMR SPECTRUM OF COMPOUND 85 (90 MHz, $CDCl_3$)

lating reagent (acceptor), i.e., by making the glycosidic bond (b) **87**.



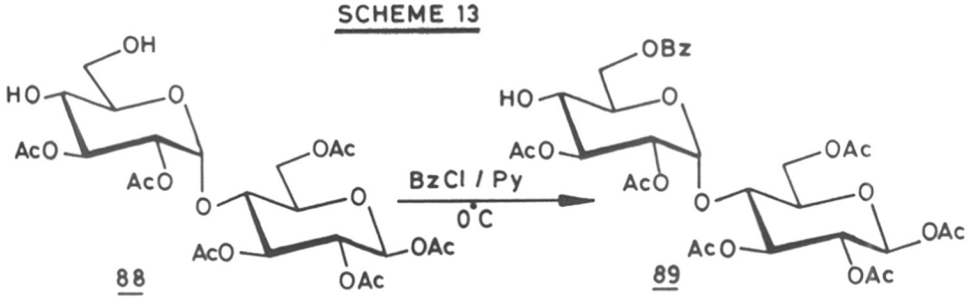
87

In continuation of our search for the synthesis of α-2-deoxy saccharides, coupling of a monosaccharide glycosyl donor with a disaccharide glycosyl acceptor was considered.

O-(3,4-di-O-acetyl-2,6-dideoxy- α-L-arabinohexopyranosyl)-(1 → 4)-(2,3-di-O-acetyl-6-O-benzoyl-α -D-glucopyranosyl)-(1 → 4)-1,2,3,6-tetra-O-acetyl-β-D-glucopyranoside (90)

The success of methyl iodide activated 2-pyridyl 2-deoxy-1-thio-methodology was demonstrated by the synthesis in good yield of the α-linked 2-deoxy trisaccharide **90** (SCHEME 14). The glycosyl acceptor, [1,2,3,6-tetra-O-acetyl-4-O-(2,3-di-O-acetyl-6-O-benzoyl-α-D-glucopyranose)] **89** was essentially synthesized by partial benzoylation[155] of 1,2,3,6-tetra-O-acetyl-4-O-(2,3-di-O-acetyl-β -D-glucopyranose) (**88**)[183] 0°C with pyridine and benzoylchloride in 80% yield (SCHEME 13). The saccharide coupling reaction of **7** with glycosyl acceptor **89** in dry dichloromethane (containing 3% methyl iodide)

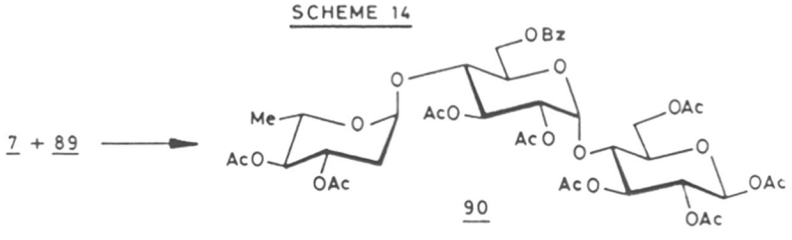
SCHEME 13



88 **89**

in presence of molecular sieves -4A at 50°C for 36 h afforded after workup and column purification, the α-2-deoxy trisaccharide **90** as a crystalline solid in 33% yield (m.p.103-105°C) primarily as α-anomer (SCHEME 14). The compound **90** has optical rotation of $[\alpha]_D^{25}$ +11.42° (c 0.98, $CHCl_3$). The formation of **90** in low yield may be attributed to the reduced reactivity of glycosyl acceptor due to the presence of bulky group at C-6 (see also page 49 for similar observation).

SCHEME 14

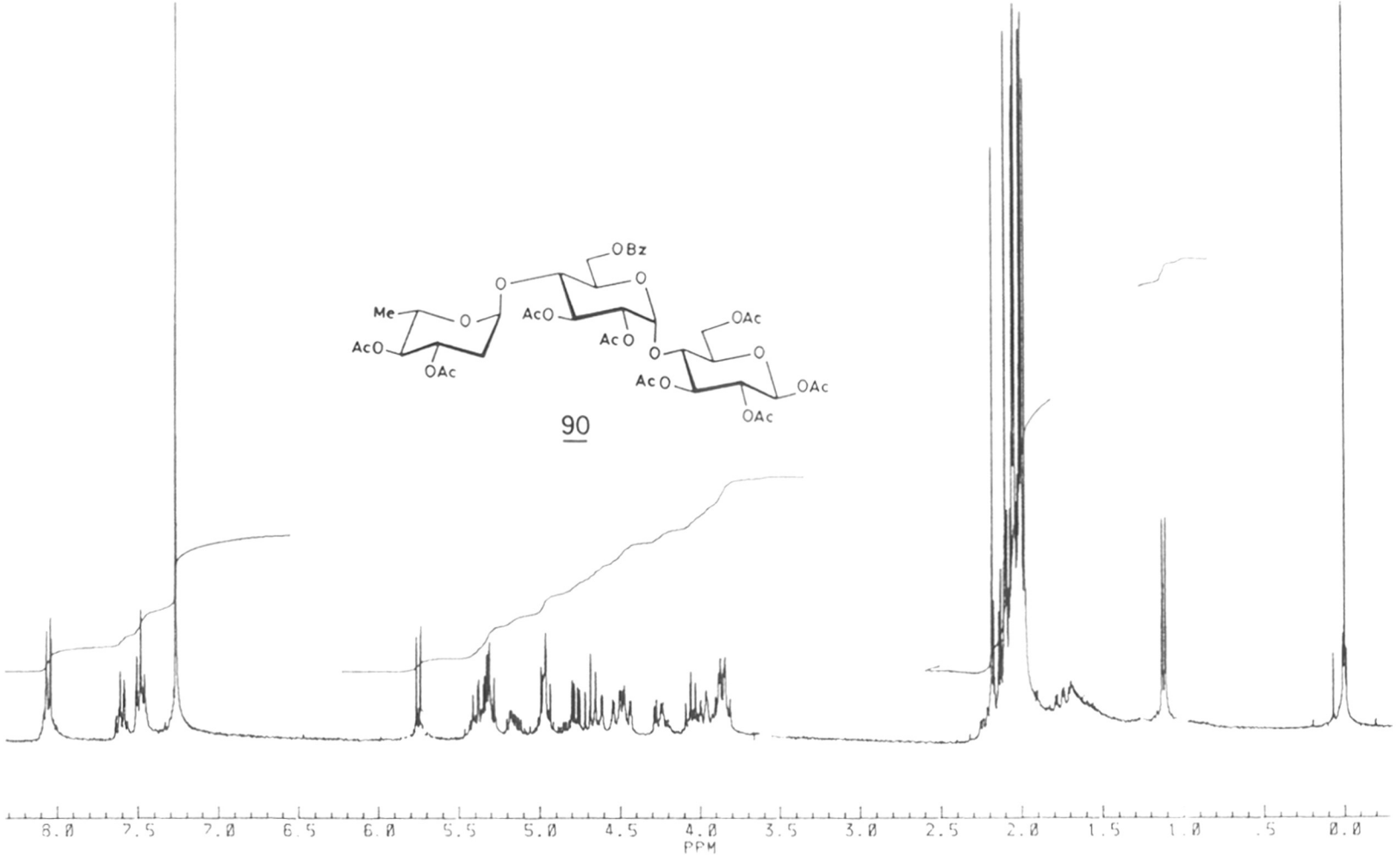


90

Compound **90** in the ^{1}H-nmr spectrum showed a doublet at δ1.1 for H-6" methyl group, eight singlets between 2.0-2.2 (24H) for 8xOAc, a multiplet at δ 1.75 for H-2" (axial) and a multiplet between 2.0-2.2 (buried under acetate signals) for H-2" (equatorial) respectively. A multiplet between δ4.9-5.5 for H-1', H-1", for other aromatic protons and doublet at δ 5.75 ($J_{1,2}$=9.2 Hz) for H-1 respectively. The ^{13}C-nmr showed a signal at δ 17.34 for C-6" methyl group a signal at δ 36.0 for C-2" of 2-deoxy sugar. The signals at δ 91.2, 95.8 and 98.5 for C-1, C-1' and C-1".

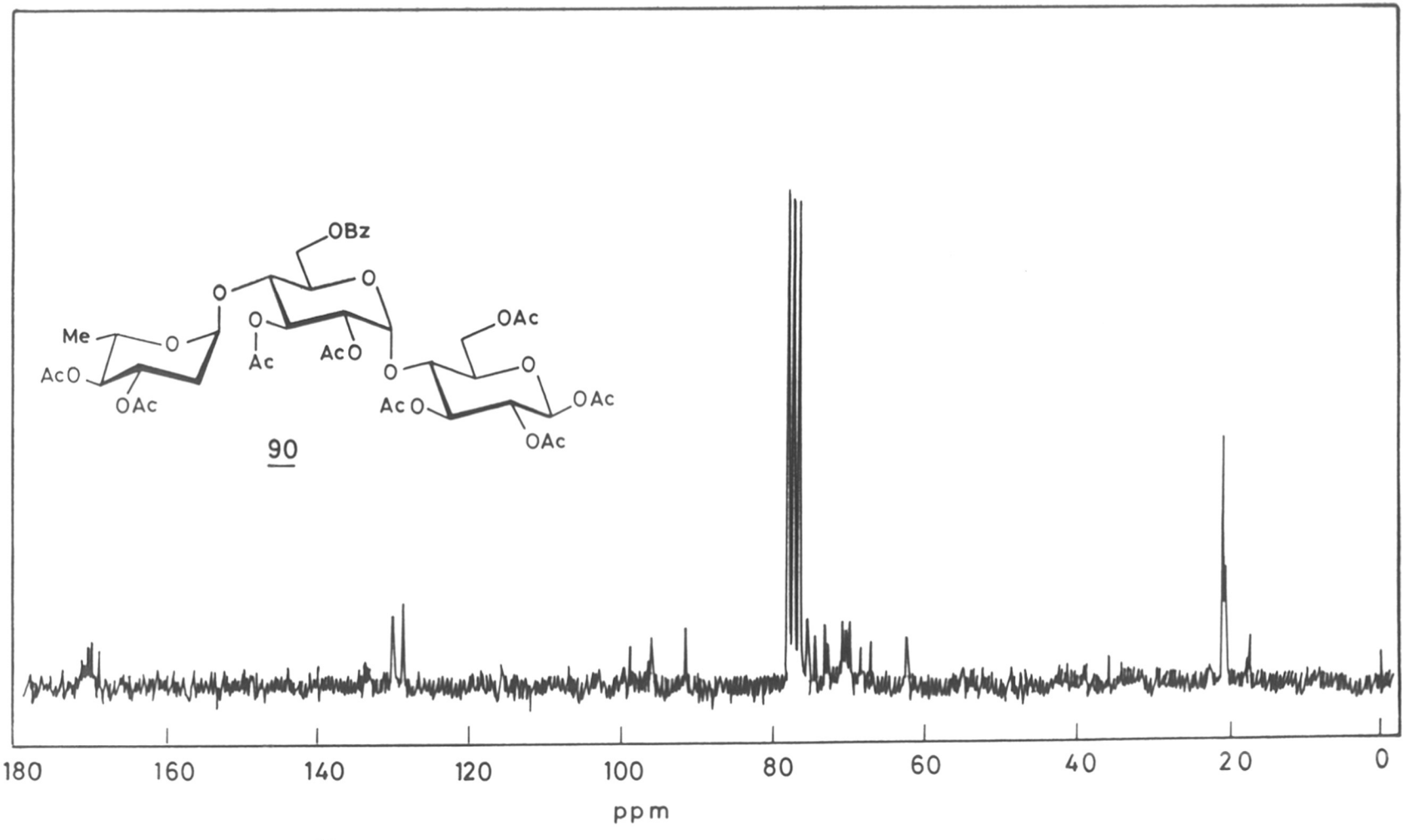
Synthesis of O-(3,4-di-O-acetyl-2,6-dideoxy-α-L-arabinohexopyranosyl)-(1 → 6)-(2,3-di-O-acetyl- α-D-glucopyranosyl-(1 → 4)-1,2,3,6-tetra-O-acetyl-β-D-glucopyranoside (91)

Regiospecific glycosidations resulted in good yields and rapidity when a diol component such as **88** was used as glycosyl acceptor



90

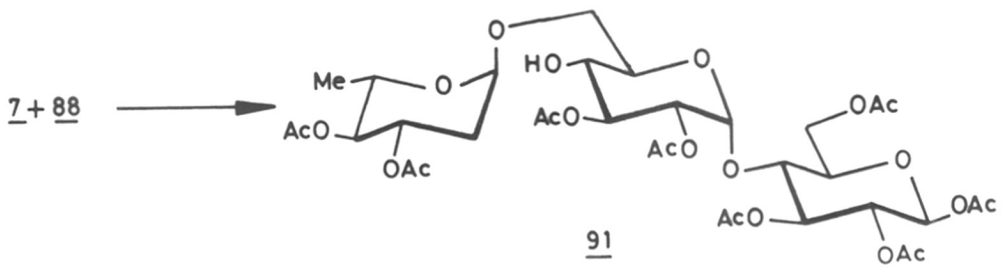
^{1}H NMR SPECTRUM OF COMPOUND 90 (300MHz, $CDCl_3$)



^{13}C - NMR SPECTRUM OF COMPOUND 90 (75 MHz, $CDCl_3$)

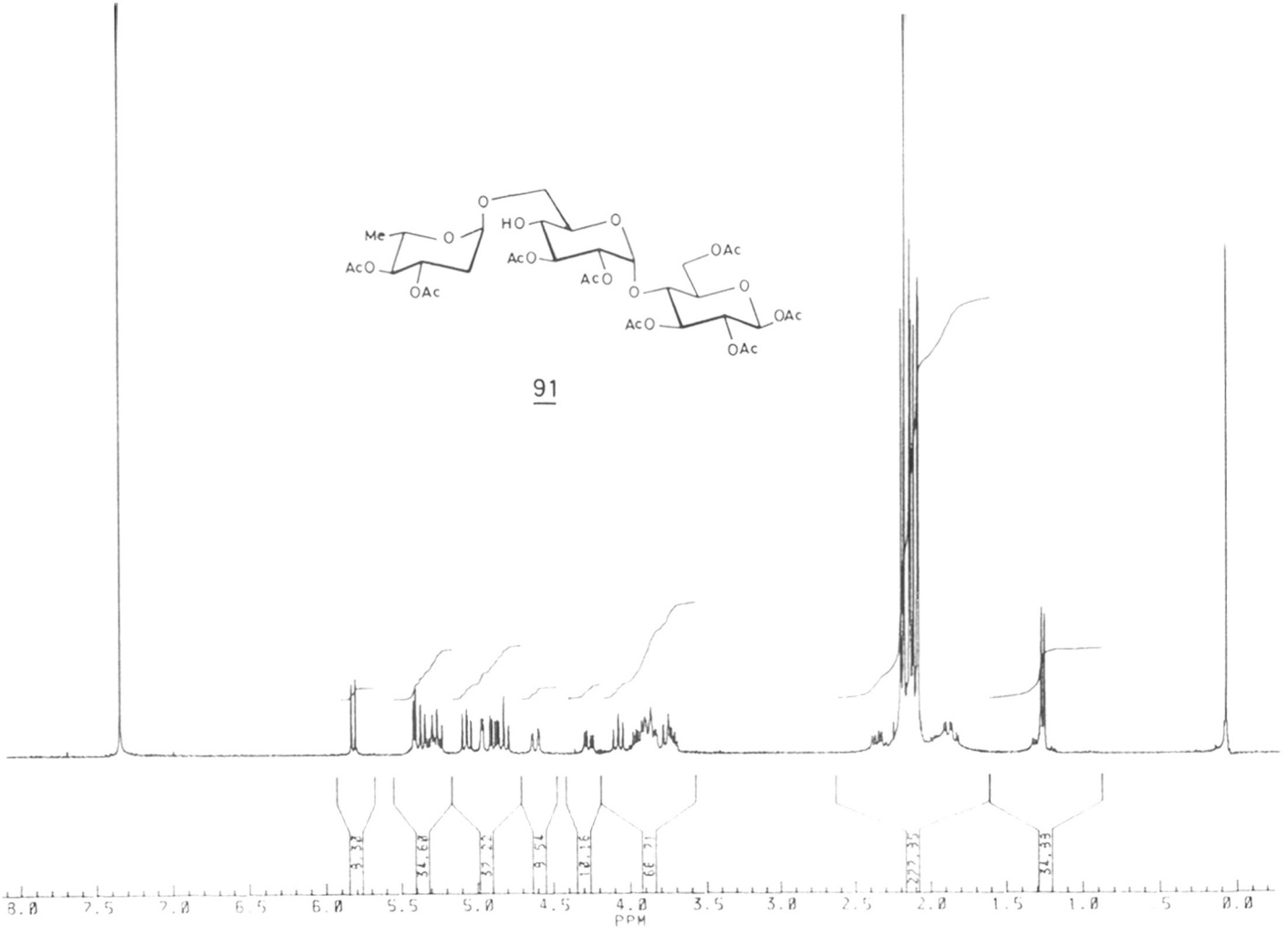
instead of **89**. Thus, the coupling reaction of **7** with **88** afforded the α-2 deoxy trisaccharide **91** as a crystalline solid m.p. 85-87°C, in 44% yield (SCHEME 15). The selective formation of (1 → 6) linked 2-deoxy trisaccharide **91** is probably due to the higher reactivity of primary hydroxyl (6-OH) over the secondary one (4-OH). The formation of **91** was established by ^{1}H and ^{13}C-nmr. The ^{1}H-nmr showed eight singlets between δ 2.1-2.2 (24 H) for 8xOAc, a doublet at δ 1.25 ($J_{5",6"}$=6.4 Hz) for H-6" methyl group. A ddd at δ 1.85 ($J_{1",2"a}$= 3.6, $J_{2"a,3"}$=11.0, $J_{2",2"gem}$=13.0 Hz) and at 2.3 ($J_{1",2"e}$=0.9, $J_{2"e,3"}$= 5.3 Hz) for H-2" (axial) and H-2" (equatorial) of 2-deoxy sugar unit respectively. A broad doublet at δ 4.9 and two doublets between 5.2-5.5 and δ 5.8 ($J_{1,2}$=8.2 Hz) for H-1", H-1' and H-1 respectively. The ^{13}C-nmr showed a signal at δ 17.2 for C-6" methyl group, a signal at δ34.7 for C-2" of 2-deoxy sugar component. Three signals at δ 91.2, 95.8 and 97.2 for C-1', C-1 and C-1" are also consistent with the assigned α-configuration[97]. The optical rotation of $[\alpha]_D^{25}$-4.82° (c 1.12, $CHCl_3$) was also in agreement with the assigned α-configuration[97].

SCHEME 15



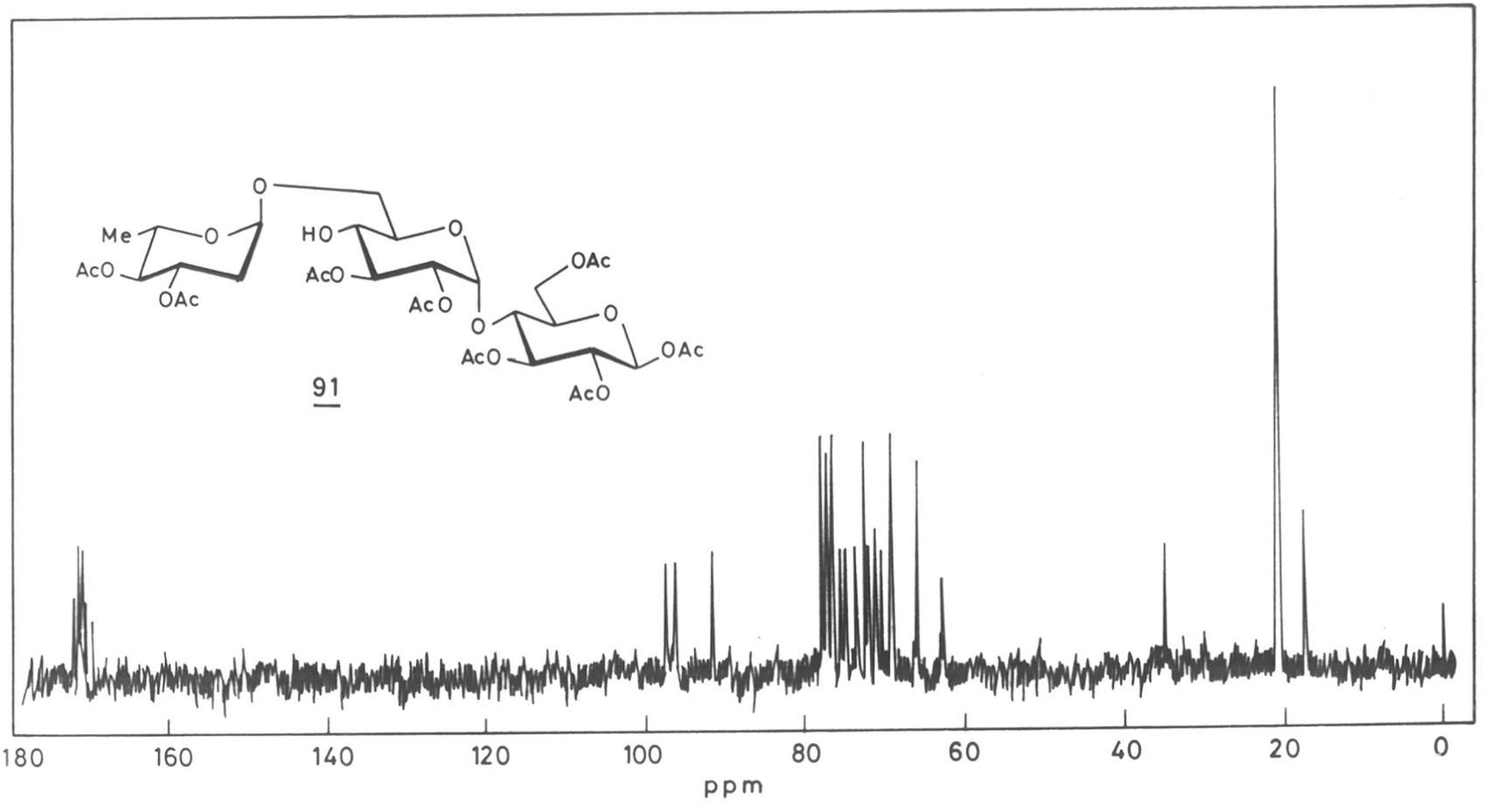
O-(3,4,6-Tri-O-acetyl-2-deoxy-α-D-arabinohexopyranosyl)-(1 → 6)-O-(2,3-di-O-acetyl-α-D-glucopyranosyl)-(1 → 4)-1,2,3,6-tetra-O-acetyl-β-D-glucopyranoside (92)

Similarly, saccharide coupling of **5** with the glycosyl acceptor



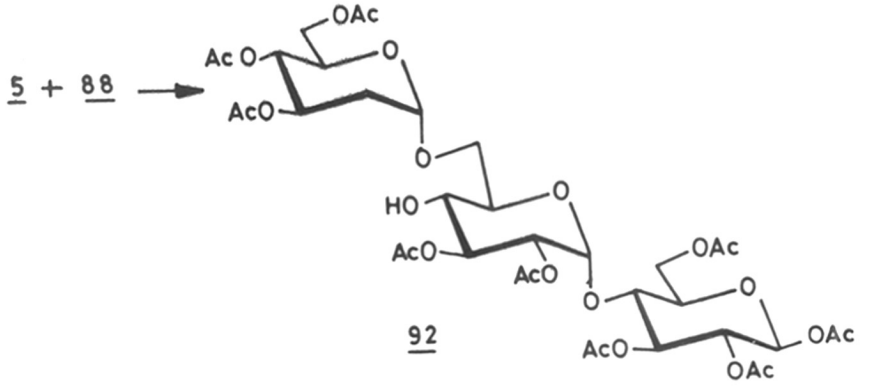
91

^{1}H NMR SPECTRUM OF COMPOUND 91 (300 MHz, $CDCl_3$)

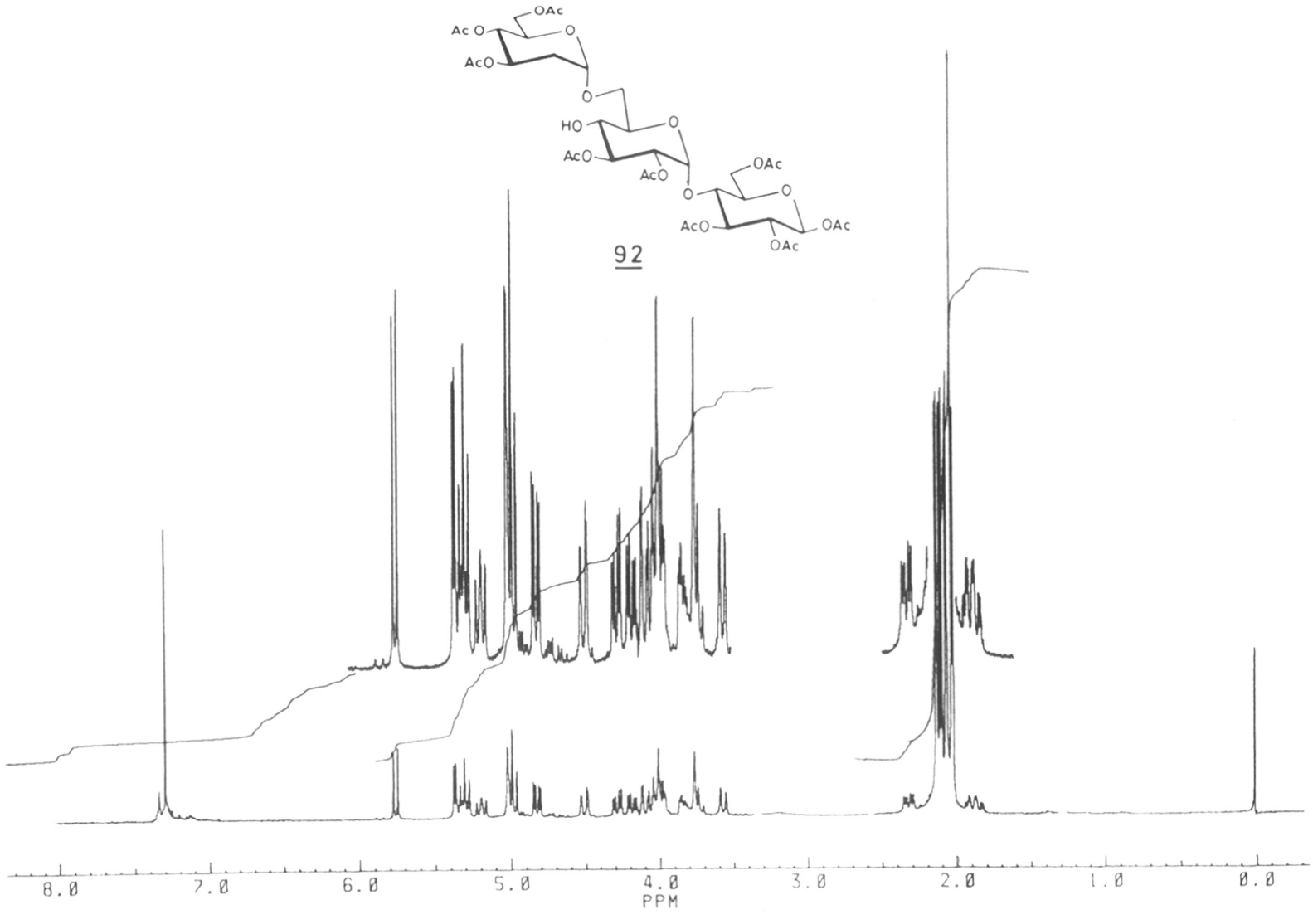


^{13}C-NMR SPECTRUM OF COMPOUND 91 (75 MHz, $CDCl_3$)

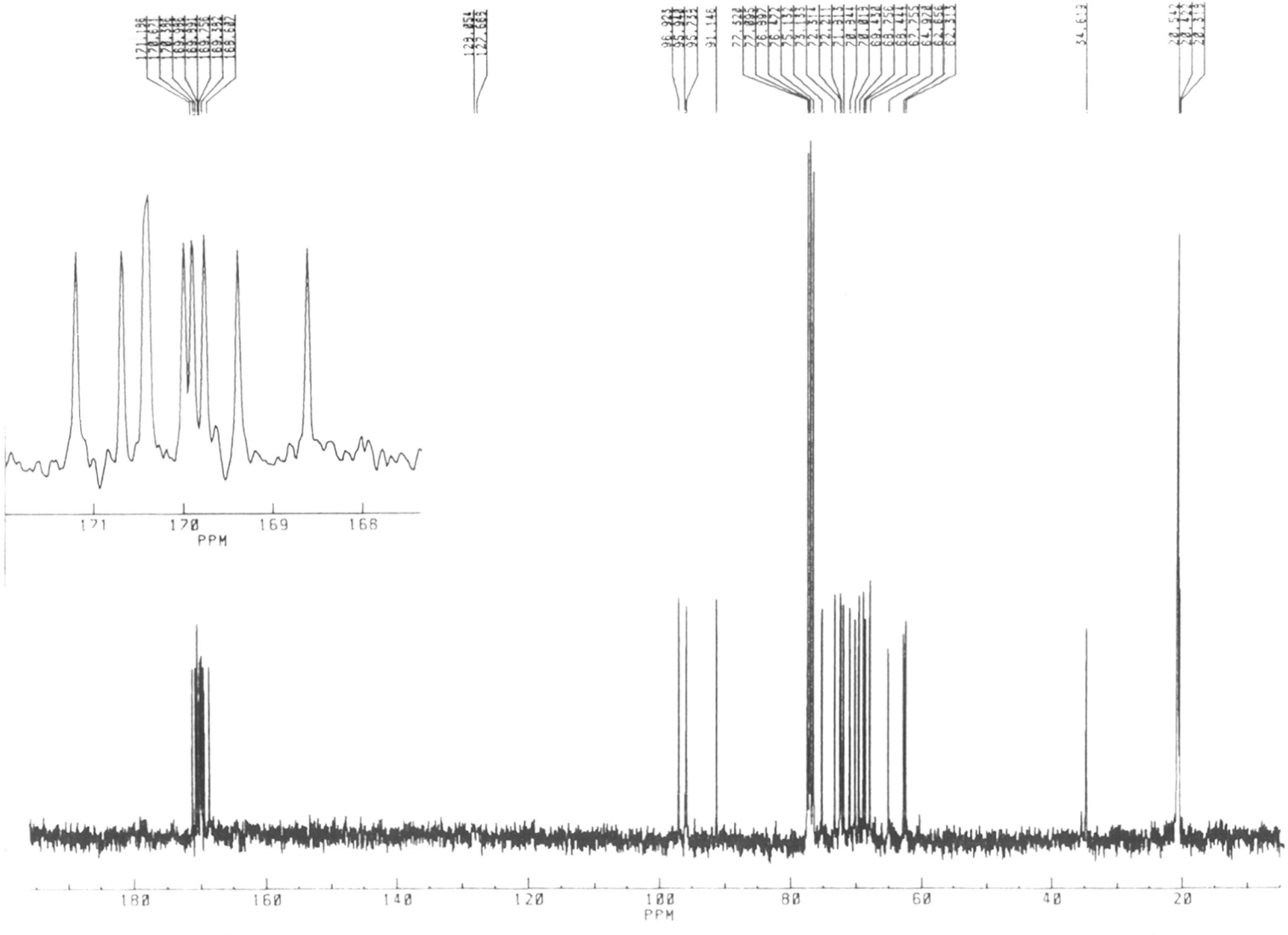
88 afforded the 2-deoxy trisaccharide **92** as an α-anomer in 49% yield (SCHEME 16). The 2-deoxy trisaccharide **92** in the ^{1}H-nmr showed a multiplet at δ 1.9 ($J_{1",2"a}$=3.6, $J_{2"a,3"}$=12.0, $J_{2",2"gem}$=15.4 Hz) and at δ 2.3 ($J_{1",2"e}$=0.42, $J_{2"e,3"}$=5.5 Hz) for H-2" (axial) and H-2" (equatorial) respectively. The apperance of nine singlets between δ2.0-2.15 (27 H) for 9xOAc, a broad doublet at δ 5.01, a doublet between 4.7-5.4 and at 5.78 ($J_{1,2}$=8.2 Hz) for H-1", H-1' and H-1 are consistent with the assigned α-configuration[97]. Chemical shift of δ5.01 for H-1' which is characteristic of α-linkage from the 2D-COSEY correlation spectrum where it shows cross peak with H-2"$_{ax}$ proton (Figure 6). The ^{13}C-nmr showed a singal at δ 34.6 for C-2" of 2-deoxy sugar unit three signals at δ 91.1, 95.7 and 96.9 for C-1', C-1 and C-1". Further optical rotation of $[\alpha]_D^{25}$ +66.27° (c 1.18, $CHCl_3$) has confirmed the assigned structure.



The excelling results described from the number of experiments shows the generality, mildness of this new method of glycosidation, the most appreciating factor being α-stereoselectivity. The generality of this method is also illustrated by considerable variation in both



^{1}H NMR SPECTRUM OF COMPOUND 92 (300 MHz , $CDCl_3$)



^{13}C NMR SPECTRUM OF COMPOUND 92 (75 MHz, CDC_3)

the 2-pyridyl 2-deoxy thioglycosides and hydroxy components. The efficiency of this coupling reaction by use of stoichiometric amounts of two main reactants makes it attractive in cases where advanced and valuable intermediates are involved. Furthermore, the extremely mild conditions and stereoselectivity should make this procedure the method of choice in the practical synthesis of complex saccharides.

Finally one of the most important features of this present methodology is the ready availability and stability of the 2-pyridyl 2-deoxy thioglycosides translating it into a highly convenient glycosidation method. This latter property of the pyridyl thioglycosides allows easy manipulations, purification and storage until activation with methyl iodide.

Table 1

Selected ^{1}H- and ^{13}C-nmr data of α-linked 2-deoxy di- and trisaccharides.

Compound No.	^{1}H-nmr, δ in ppm (J=in Hz)			^{13}C-nmr, δ ppm		
	H-1	H-1'	H-1"	C-1	C-1'	C-1"
15	4.85	5.49(3.15)	-	95.3	98.3	-
16	4.5-5.0	4.85	-	96.5	97.7	-
17	4.5	5.48(2.7)	-	97.5	98.8	-
18 (α/β:85/15)	3.33-5.42	5.5	-	96.3	97.0 100.0(β,c-1')	-
19	4.6-5.0	5.05(2.66)	-	97.4	97.7	-
20	4.6-4.8	5.5(3.0)	-	97.6	99.7	-
21	4.5 - 5.1		-	96.9	97.9	-
22	4.5-4.8	5.05(2.8)	-	96.8	97.7	-
23 (α/β:85/15)	4.95	5.5(5.0)	-	96.4	96.9 100.2(β,c-1')	-
90	5.75(9.2)	4.9 - 5.5		-	-	-
91	5.8(8.2)	5.2-5.5	4.9	95.8	91.2	97.2
92	5.78(8.2)	4.7-5.4	5.01	95.7	91.1	96.9

Table 2

Physical data of α-linked 2-deoxy disaccharides

Donor	Glycosyl Acceptor	Protected α -2-deoxy saccharide	Yield % (time, h)	Optical rotation $[\alpha]_D^{25}CHCl_3$
7	12	15	81 (18 h)	-121° (c 1.02, $CHCl_3$)
5	10	16	53 (22 h)	+65° (c 0.4, $CHCl_3$)
5	11	17	34 (30 h)	+60.95° (c 0.63, $CHCl_3$)
5	14	18	88 (18 h)	+10.4° (c 1.0, MeOH)
6	13	19	71 (34 h)	+86.07 (c 0.178, $CHCl_3$)
6	11	20	45 (24 h)	+75.63° (c 1.1, $CHCl_3$)
7	13	21	64 (29 h)	-18.03° (c 1.02, $CHCl_3$)
7	11	22	44 (32 h)	-28.14° (c 0.85, $CHCl_3$)
7	14	23	86 (16 h)	-103.29° (c 1.26, $CHCl_3$)
7	89	90	33 (36 h)	+11.42° (c 0.98, $CHCl_3$)
7	88	91	44 (25 h)	-4.82° (c 1.12, $CHCl_3$)
5	88	92	49 (31 h)	+66.27° (c 1.18, $CHCl_3$)

2.7 EXPERIMENTAL

2.7.1 Synthesis of glycosyl donors

The following glycosyl donors were made according to the literature methods and were characterized accordingly.

2-pyridyl 3,4,6-tri-O-acetyl-2-deoxy-α and β-D-arabinohexopyranoside (5)[151].

2-Pyridyl 3,4,6-tri-O-acetyl-2-deoxy-α and β-D-lyxohexopyranosiee (6)[151].

2-Pyridyl 3,4-di-O-acetyl-2,6-dideoxy-α and β-L-arabinohexopyranoside (7)[151].

2.7.2 Synthesis of glycosyl acceptors

The following glycosyl acceptors were made according to the literature methods and were characterized accordingly:

Methyl 2,3-O-isopropylidene-α-L-rhamnopyranoside (12)[156].

Methyl 4-O-acetyl-3,4-di-O-benzyl-α-D-glucopyranoside (10)[154].

Methyl 6-O-benzoyl-3,4-di-O-benzyl-α-D-glucopyranoside (11)[155].

Methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside (13)[157].

1,2:3,4-Di-O-isopropylidene-α-D-galactopyranoside (14)[158].

1,2:3,6-Tetra-O-acetyl-4-O-(2,3-di-O-acetyl- β -D-glucopyranose) (88)[183].

2.7.3 Synthesis of α-linked 2-deoxy disaccharides

Typical experimental procedure for saccharide coupling

In an oven dried round bottom flask under nitrogen was taken the peracetylated 2-pyridyl 2-deoxy thioglycoside (1.0 mmol) and molecular sieves 4 Å (300 mg, activated and powdered). Dichloromethane (10 ml) having 3% methyl iodide was added followed by the addition of glycosyl acceptor (1.1 mmol) and heated at 50°C (oil bath temperature) for 16-36

h. The progress of the reaction was done by thin layer chromatography (tlc). After completion of the reaction, it was filtered on a bed of celite, washed with dichloromethane and evaporated. The residue was purified by column chromatography to obtain the O-glycosides (33-88%). The products were characterised by ^{1}H, and ^{13}C-nmr.

Methyl 3,4-di-O-acetyl-2,6-dideoxy-α/β-L-arabinohexopyranoside (8)

2-Pyridyl 3,4-di-O-acetyl-2,6-dideoxy-1-thio α / β -L-arabinohexopyranoside **7**[151] (0.325 g, 1.0 mmol) (α /β :3/2) was reacted with dry methanol (32 μl, 1.1 mmol) in 10 ml dichlormethane having 3% methyl iodide, at 50°C for 8 h (general procedure 2.7.3) to afford compound **8** (0.224 g, 90.9%) as a syrup (α: βmixture 50:50).

^{1}H-nmr(90 MHz):(α /β :1/1): δ 3.4 (s, OMe), 3.5 (s, OMe).

^{13}C-nmr(80 MHz): δ 54.39 (q, OMe), 56.29 (q, OMe), 97.57 (d, C-1), 99.94 (d, C-1).

Analysis calcd. for $C_{11}H_{18}O_6$: C, 53.65; H, 13.66. Found: C, 53.57; H, 13.57%.

t-Butyl 3,4-di-O-acetyl-2,6-dideoxy-α/β-L-arabinohexopyranoside (9)

The reaction of the compound **7**[151] (0.325 g, 1.0 mmol) with t-butanol (74 μl, 1.1 mmol) for 12 h yielded compound **9** (0.245 g, 85%) as a syrup (α: βmixture 8:2).

^{1}H-nmr (90 MHz):(α /β :4/1): δ 1.1 (3H, d, $J_{5,6}$=6.2, H-6), 1.98, 2.05 (2s, 6H, 2xOAc), 1.21 (s, 9H, -CMe_3), 4.0 (m, 1H, H-5), 4.6 (t, 1H, $J_{3,4}=J_{4,5}$= 10.0 Hz, H-4), 5.0-5.45 (m, 2H, H-1,3).

^{13}C-nmr(22.63 MHz): δ 17.2 (q, C-6), 20.5 (2q, 2xOCOCH_3), 20.6 (q, CMe_3), 36.7 (t, C-2), 64.8, 69.2, 75.2 (3d, C-3,4,5), 90.9 (d, C-1, α -compound), 93.4 (d, C-1,β -Compound).

Analysis calcd. for $C_{14}H_{24}O_6$: C, 58.33; H, 7.79. Found: C, 58.25; H, 7.64%.

Methyl 4-O-(3,4-di-O-acetyl-2,6-dideoxy- α -L-arabinohexopyranosyl)-2,3-O-isopropylidene-α-L-rhamnopyranoside (15)

The saccharide coupling of **7**[151] (0.384 g, 1.2 mmol) with **12**[156] (0.290 g, 1.30 mmol) in dry dichloromethane (8 ml, having 3% methyl iodide) in presence of moelcular sieves 4 A (400 mg) at 50°C for 18 h, gave compound **15** (0.41 g, 81%) as a syrup, after workup and column chromatographic purification (pet. ether:ethyl acetate, 8:2).

$[\alpha]_D^{25}$ -121° (c 1.02, $CHCl_3$).

^{1}H-nmr(300 MHz): δ 1.17 (d, 3H, $J_{5,6}$=6.28, H-6), 1.31 (d, 3H, $J_{5',6'}$=6.24, H-6'), 1.33 (s, 3H, :C$\underline{Me}_2$), 1.54 (s, 3H, :CMe_2), 1.8 (ddd, 1H, $J_{1',2'a}$=3.1, $J_{2'a,3'}$=12.9, $J_{2,2'gem}$=16.6, H-2'$_{ax}$), 2.01, 2.05 (2s, 6H, 2xOCOC$\underline{H}_3$), 2.22 (ddd, 1H, $J_{2'e,3'}$=5.3, $J_{2'e1'}$=1.0, H-2'$_{eq}$), 3.38 (s, 3H, OCH_3), 3.47 (m, 1H, H-4), 3.67, 3.85 (2m, 2H, H-5,5'), 4.08 (dd, 1H, $J_{1,2}$=0.58, $J_{2,3}$=5.6, H-2), 4.16 (dd, 1H, $J_{3,4}$=7.14, H-3), 4.73 (t, 1H, $J_{3',4'}$=$J_{4',5'}$=9.63, H-4'), 4.85 (d, 1H, H-1), 5.18 (ddd, 1H, H-3'), 5.49 (brd, 1H, $J_{1',2'a}$=3.15, $J_{1',2'e}$= 1.0, H-1').

^{13}C-nmr (22.63 MHz): δ 17.5, 18.1 (2q, C-6,6'), 20.7, 20.9 (2q, 2xOCO-C$\underline{H}3$), 26.3, 27.9 (2q, :C$\underline{Me}_2$), 35.6 (t,# C-2'), 54.7 (q, OCH_3), 64.0, 66.2, 69.1, 75.0, 76.2, 77.3, 78.8 (7d, C-2,3,4,5,3',4',5'), 95.3 (d, C-1), 98.3 (d, C-1'), 109.5 (s, :C$\underline{Me}_2$), 170.1 (2s, 2xO$\underline{C}OCH_3$).

(# From DEPT measurement.)

Analysis calcd. for $C_{20}H_{32}O_{10}$: C, 55.54; H, 7.45. Found: C, 55.48; H, 7.32%.

Methyl 6-O-(3,4,6-tri-O-acetyl-2-deoxy-α -D-arabinohexopyranosyl)-4-O-acetyl-2,3-di-O-benzyl-α-D-glucopyranoside (16)

Saccharide coupling reaction of **5**[151] (0.40 g, 1.06 mmol) with sugar alcohol **10**[154] (0.48 g, 1.2 mmol) in 22 h afforded **16** (0.38 g, 58%) as

a syrup after workup and chromatographic purification (SiO_2, pet.ether: ethyl acetate; 4:1).

$[\alpha]_D^{25}$ +65° (c 0.4, $CHCl_3$).

^{1}H-nmr (300 MHz): δ1.8 (ddd, 1H, $J_{1',2'a}$=3.6, $J_{2'a,3'}$=11.5, $J_{2',2'gem}$=16.7, H-2'$_{ax}$), 1.9, 1.99, 2.03, 2.04 (4s, 12H, 4xOCOC$\underline{H}_3$), 2.25 (ddd, 1H, $J_{1',2'e}$= 1.2, $J_{2'e3'}$=5.4, H-2'$_{eq}$), 3.45 (s, 3H, OCH_3), 3.4-4.4 (m, 8H, H-2,3,5,5',6,6'), 4.5-5.0 (m, 9H, H-1,1',3',4',4,2xOC$\underline{H}_2$Ph), 4.85 (brd, 1H, H-1', submerged signal) (assigned from 2D 'H-'H spectrum), 5.25 (ddd, 1H, $J_{2'e'3'}$=5.4, $J_{2a3'}$=9.5, $J_{3',4'}$=11.4, H-3'), 7.20-7.40 (m, 10H, Ph).

^{13}C-nmr (75 MHz): δ 20.4, 20.5, 20.6 (4q, 4xOCOC$\underline{H}_3$), 34.6 (t,* C-2'), 55.1 (q, OC$\underline{H}_3$), 62.1, 66.3 (t,* PhC$\underline{H}_2$-O-), 67.7, 67.9, 68.8, 69.0, 70.6, 79.0, 79.5 (7d, C-2,3,3',4,4',5,5'), 73.2, 75.2 (2t, C-6,6'), 96.5 (d, C-1), 97.7 (d, C-1'), 127.0-139.0 (aromatic), 169.5, 169.6, 169.7, 170.4 (4s, 4xO$\underline{C}$OCH$_3$).

(* From DEPT measurement).

Analysis calcd. for $C_{35}H_{44}O_{14}$: C, 61.03; H, 6.44. Found: C, 60.96; H, 6.39%.

Methyl 4-$\underline{O}$-(3,4,6-tri-$\underline{O}$-acetyl-2-deoxy- α -D-arabinohexopyranosyl)-6-$\underline{O}$-benzoyl-2,3-di-$\underline{O}$-benzyl-α-D-glucopyranoside (17)

Saccharide coupling reaction of **5**[151] (0.42 g, 1.09 mmol) with sugar alcohol **11**[155] (0.58 g, 1.2 mmol), in 30 h, afforded **17** (0.28 g, 34%) as a syrup after workup and chromatographic purification (SiO_2, pet.ether: ethyl acetate, 9:2).

$[\alpha]_D^{25}$ +60.95° (c 0.63, $CHCl_3$).

^{1}H-nmr (300 MHz): δ 1.67 (ddd, 1H, $J_{1',2'a}$=3.9, $J_{2'_a,3'}$=11.7, $J_{2',2'gem}$=16.9, H-2'$_{ax}$), 1.9, 2.00, 2.01 (3s, 9H, 3xOCOC$\underline{H}_3$), 1.98-2.04 (1H, submerged, H-2'$_{eq}$), 3.4 (s, 3H, OMe), 3.71 (dd, 1H, $J_{3,4}$=8.8, $J_{4,5}$=9.0, H-4), 3.8 (dd, 1H, $J_{1,2}$=3.5, $J_{2,3}$=9.6, H-2), 3.85-4.1 (m, 5H, H-3,5,5',6,6'), 4.28 (dd,

1H, $J_{6,6gem}$=12.5, $J_{5,6}$=4.0, H-6/6'), 4.43 (dd, 1H, $J_{6',6'gem}$=5.5, H-6/6'), 4.5-4.8 (m, 4H, H-1, benzylic (3H), 4.92 (dd, 1H, $J_{3',4'}$=9.6, $J_{4',5'}$=9.8, H-4'), 5.05 (d, 1H, PhC$\underline{H}_2$-O-), 5.25 (ddd, 1H, $J_{2'_e,3'}$=5.1, $J_{2'_a,3'}$=9.4, $J_{3',4'}$= 11.6, H-3'), 5.48 (brd, 1H, $J_{1',2'_a}$=2.78, H-1'), 7.3-8.1 (m, 15H, aromatic).

^{13}C-nmr (75 MHz): δ 20.4, 20.5, 20.7 (3q, 3xOCOC$\underline{H}_3$), 35.03 (t, C-2'), 55.1 (q, OMe), 62.1, 63.7 (t, PhCH_2-O-, from DEPT measurement), 68.1, 68.6, 68.9, 69.0, 77.1, 80.1, 81.62 (7d, C-2,3,4,5,3',4',5'), 73.0, 75.4 (t, C-6,6'), 97.5 (d, C-1), 98.8 (d, C-1'), 127.0-139.0 (aromatic), 166.0, 169.6, 169.9, 170.4 (4s, 3xO$\underline{C}$OCH_3, O$\underline{C}$OPh).

Analysis calcd. for $C_{40}H_{46}O_{14}$: C, 63.99; H, 6.18. Found: C, 63.87; H, 6.09%.

1,2:3,4-Di-O-isopropylidene-6-O-(3,4,6-tri-O-acetyl-(2-deoxy-α -D-arabino-hexopyranosyl)-α-D-galactopyranoside (18)

Compound **5**[151] (0.401 g, 1.06 mmol) was reacted with the sugar alcohol **14**[158] (0.306 g, 1.16 mmol) in 18 h, gave the α-2-deoxy disaccharide **18** (0.49 g, 88%) after workup and column chromatographic purification (SiO_2, pet.ether:ethyl acetate: 4:1).

$[\alpha]_D^{25}$ +10.4° (c 1.0, MeOH).

^{1}H-nmr (90 MHz): (α/β : 85/15): δ 1.26x2, 1.62x2 (2s, 12H, 2x : C$\underline{Me}_2$), 1.71-1.85 (m, 1H, H-2'$_{ax}$), 1.92-2.05 (3s, 9H, 3xOCO$\underline{CH}_3$), 2.10-2.33 (m, 1H, H-2'$_{eq}$), 3.33-5.42 (m, 12H, H-1',2,3,4,5,6,6',3',4',5'), 5.5 (d, 1H, $J_{1,2}$= 5.0, H-1).

^{13}C-nmr (22.63 MHz): δ 20.5x2, 20.7 (3q, 3xOCO$\underline{CH}_3$), 24.3, 24.8, 2x25.9 (4q, 2x:C$\underline{Me}_2$), 34.9 (t, C-2'), 36.0 (t, C-2' isomer), 62.4, 66.3 (2t, C-6,6'), 68.0, 69.2, 69.6, 70.5, 70.7, 71.0 (7d, C-2,3,4,5,3',4',5'), 96.3 (d, C-1), 97.0 (d, C-1'), 100.0 (d, β C-1') (15%), 108.5, 109.3 (2s, 2x:$\underline{C}$Me$_2$), 169.8, 170.0, 170.5 (3s, 3xO$\underline{C}$OCH_3).

Analysis calcd. for $C_{24}H_{36}O_{13}$: C, 54.13; H, 6.81. Found: C, 54.07; H, 6.79%.

Methyl 6-O-(3,4,6-tri-O-acetyl-2-deoxy-α -D-lyxohexopyranosyl)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (19)

The coupling reaction of glycosyl donor **6**[151] (4.08 g, 1.06 mmol) with the glycosyl acceptor **13**[157] (0.55 g, 1.17 mmol) in 34 h gave **19** (0.56 g, 71%) as a syrup after workup and chromatographic purification (SiO_2, pet.ether:ethyl acetate; 7:3).

$[\alpha]_D^{25}$ +86.07 (c 0.178, $CHCl_3$).

^{1}H-nmr (300 MHz): δ 1.90 (ddd, 1H, $J_{1',2'_a}$=2.8, $J_{2'_a,3'}$=6.0, $J_{2',2'gem}$=13.0, H-2'$_{ax}$), 1.95, 1.98, 2.12 (3s, 9H, 3xOCO$\underline{CH_3}$), 2.0 (dd, 1H, H-2'$_{eq}$, submerged), 3.4 (s, 3H, OMe), 3.48 (t, 1H, $J_{3,4}$=$J_{4,5}$=9.48, H-4), 3.52 (dd, 1H, $J_{1,2}$=3.61, $J_{2,3}$=9.62, H-2), 3.6 (d, 1H, H-6*), 3.78 (m, 2H, H-6,6'*), 3.95-4.05 (m, 3H, H-3,5,6'*), 4.6-5.0 (m, 8H, H-1,5', 3xPh$\underline{CH_2}$-O-), 5.05 (d, 1H, H-1'), 5.21-5.3 (m, 2H, H-3',4'), 7.25-7.38 (m, 15H, aromatic). (* Assignments may be reversed).

^{13}C-nmr (75 MHz): δ 20.5, 20.6x2 (3q, 3xOCO$\underline{CH_3}$), 29.9 (t, C-2'), 54.9 (q, OMe), 62.2x2, 73.1, 74.7, 75.5 (5t*, C-6,6', 3xPh$\underline{CH_2}$-O-), 66.04, 66.5, 66.6, 69.6, 77.8, 79.9, 81.9 (7d, C-2,3,4,5,3',4',5'), 97.4 (d, C-1), 97.7 (d, C-1'), 127.0-139.0 (aromatic), 169.8, 170.1, 170.2 (3s, 3x$\underline{C}$OCH$_3$).

(* from DEPT measurement).

Analysis calcd. for $C_{40}H_{48}O_{13}$: C, 65.20; H, 5.88. Found: C, 65.11; H, 5.78%.

Methyl 4-O-(3,4,6-tri-O-acetyl-2-deoxy-α -D-lyxohexopyranosyl)-6-O-benzoyl-2,3-di-O-benzyl-α-D-glucopyranoside (20)

Saccharide coupling of **6**[151] (0.44 g, 1.06 mmol) with sugar alcohol **11**[155] (0.56 g, 1.17 mmol) in 24 h, to afford **20** (0.34 g, 45%) as a syrup,

after workup and chromatographic purification (SiO_2, benzene:ethyl acetate; 4:1).

$[\alpha]_D^{25}$ +75.63° (c 1.1, $CHCl_3$).

^{1}H-nmr (300 MHz): δ 1.90-2.05 (m, 2H, H-2'$_{ax}$2'$_{eq}$), 1.96, 1.97, 2.08 (3s, 9H, 3xOCO$\underline{CH_3}$), 3.38 (s, 3H, OMe), 3.54 (dd, 1H, $J_{1,2}$=3.5, $J_{2,3}$=9.6, H-2), 3.72 (dd, 1H, $J_{3,4}$=9.7, $J_{4,5}$=9.9, H-4), 3.9-4.05 (m, 5H, H-5,6 ,6'), 4.26 (m, 1H, H-5'), 4.42 (dd, 1H, $J_{3',4'}$=5.0, $J_{4',5'}$=12.0, H-4'), 4.6-4.8 (m, 8H, H-1,3, (3H), $PhCH_2$-$\underline{O}$-), 5.1 (d, 1H, Ph-CH_2-O-), 5.3 (ddd, $J_{2'_a,3'}$=7.5, $J_{2'_e,3'}$=3.0, $J_{3',4'}$=5.0, H-3'), 5.5 (d, 1H, $J_{1',2'_a}$=3.0, H-1'), 7.2-8.0 (m, 15H, aromatic).

^{13}C-nmr (75 MHz): δ 20.4, 20.5, 20.7 (3q, 3xOCO$\underline{CH_3}$), 30.4 (t, C-2'), 55.2 (q, OMe), 65.8, 66.4, 67.6, 68.3, 77.2, 80.2, 81.6 (7d, C-2,3,4,5,3',4',5'), 62.1, 63.8, 73.1, 75.5 (4t,* C-6,6',2xPhC$\underline{H_2}$-O), 97.6 (d, C-1), 99.7 (d, C-1'), 127.0-139.0 (aromatic), 166.0, 169.8, 170.0, 170.3 (4s, 3xO$\underline{C}$OCH$_3$, O$\underline{C}$OPh). (* from DEPT measurement.)

Analysis calcd. for $C_{40}H_{46}O_{14}$: C, 63.99; H, 6.18. Found: C, 63.87; H, 6.08%.

Methyl 6-$\underline{O}$-(3,4-di-$\underline{O}$-acetyl-2,6-dideoxy-α-L-arabinohexopyranosyl)-2,3,4-tri-$\underline{O}$-benzyl-α-D-glucopyranoside (21)

Compound **7**[151] (0.407 g, 1.25 mmol) was reacted with the sugar alcohol **13**[157] (0.641 g, 1.38 mmol) in 29 h, gave **21** (0.54 g, 64%) as a syrup, after workup and column chromatographic purification (SiO_2, benzene:ethyl acetate; 9:1).

$[\alpha]_D^{25}$ -18.03° (c 1.02, $CHCl_3$).

^{1}H-nmr (300 MHz): δ 1.12 (d, 3H, $J_{5',6'}$=6.5, H-6'), 1.7 (ddd, 1H, $J_{1',2'_a}$=3.6, $J_{2'_a,3'}$=11.0, $J_{2',2'gem}$=13.00, H-2'$_{ax}$), 2.0, 2.1 (2s, 6H, 2xOCO$\underline{CH_3}$), 2.2 (ddd, 1H, $J_{2'_e,3'}$=5.3, H-2'$_{eq}$), 3.4 (s, 3H, OMe), 3.48-3.51 (m, 3H, H-3,5,5'),

3.7-4.1 (m, 4H, H-3,4,6,6), 4.5-5.1 (m, 9H, H-1,1',4',3xOCH$_2$Ph), 5.25 (ddd, 1H, $J_{2'e,3'}$=2.0, $J_{3',4'}$=11.7, H-3'), 7.2-7.0 (m, 15H, aromatic).

^{13}C-nmr (75 MHz): δ17.8 (q, C-6'), 20.7, 20.9 (2q, 2xOCOCH$_3$), 35.2 (t, C-2'), 55.1 (q, OCH$_3$), 66.3, 73.3, 74.9, 75.6 (t,# C-6, 3xOCH$_2$Ph), 65.5, 69.0, 69.9, 74.8, 77.8, 80.2, 82.4 (7d, C-2,3,4,5,3',4',5'), 96.9 (d, C-1), 97.9 (d, C-1'), 127.0-139.0 (aromatic), 170.0, 170.6 (2s, 2xOCOCH$_3$).

(# from DEPT measurement).

Analysis calcd. for $C_{38}H_{47}O_{11}$: C, 67.14; H, 6.96. Found: C, 67.09; H, 6.87%.

Methyl 4-O-(3,4-di-O-acetyl-2,6-dideoxy- α -L-arabinohexopyranosyl)-6-O-benzoyl-2,3-di-O-benzyl-α-D-glucopyranoside (22)

Saccharide coupling of **7**[151] (0.409 g, 1.25 mmol) with sugar alcohol **11**[155] (0.66 g, 1.38 mmol) in 32 h, to afford **22** (0.23g, 44%) as a syrup, after workup and chromatographic purification (SiO_2, pet.ether:ethyl acetate; 4:1).

$[\alpha]_D^{25}$-28.14° (c 0.81, $CHCl_3$).

^{1}H-nmr(300 MHz): δ 0.8 (d, 3H, $J_{5',6'}$=6.5, H-6'), 1.75 (ddd, 1H, $J_{1',2'_a}$=3.5, $J_{2'_a,3'}$=11.0, $J_{2',2'gem}$=13.0, H-2'$_{ax}$), 2.0x2 (2s, 6H, 2xOCOCH$_3$), 2.2 (ddd, 1H, $J_{1',2'_e}$=0.94, $J_{2'_e,3'}$=5.0, H-2'$_{eq}$), 3.4 (s, 3H, OMe), 3.6 (dd, 1H, $J_{1,2}$= 3.6, $J_{2,3}$=9.4, H-2), 3.75 (dd, 1H, $J_{3,4}$=9.7, H-3), 3.8-4.35 (m, 4H, H-4,5, 5',6), 4.5-4.8 (m, 6H, H-1,6,4',6H, (3H) benzylic), 5.05 (brd, 1H, $J_{1',2'_a}$=3.5, H-1'), 5.1 (d, 1H, PhCH$_2$-O-), 5.25 (ddd, 1H, H-3'), 7.3-8.2 (m, 15H, aromatic).

^{13}C-nmr (75 MHz): 17.2 (q, C-6'), 20.6, 20.8 (2q, 2xOCOCH$_3$), 35.4 (t,# C-2'), 55.2 (q, OMe), 63.2, 73.2, 75.5 (3t;# C-6,2xPhCH$_2$O), 96.8 (d, C-1), 97.7 (d, C-1'), 127.0-138.0(aromatic), 165.9, 169.8, 170.0 (3s, 2xOCOCH$_3$,

OCOPh).

(* from DEPT measurement).

Analysis calcd. for $C_{38}H_{44}O_{12}$: C, 65.88; H, 6.4. Found: C, 65.84; H, 6.36%.

1,2:3,4-Di-O-isopropylidene-6-O-(3,4-di-O-acetyl-2,6-dideoxy- α -L-arabino-hexopyranosyl)-α-D-galactopyranoside (23)

The saccharide coupling of **7**[151] (0.407 g, 1.25 mmol) with **14**[158] (0.35 g, 1.38 mmol) in 16 h, to afford **23** (0.49 g, 86%) as a syrup, after workup and column chromatographic purification (SiO_2, pet.ether:ethyl acetate; 4:1).

$[\alpha]_D^{25}$ -103.29° (c 1.26, $CHCl_3$).

^{1}H-nmr (300 MHz) (85/15 α/β): δ 1.16 (d, 2.55 H, $J_{5',6'}$=6.2, H-6'), 1.21 (d, 0.45 H, H-6'), 1.34x2 (s, 6H, CMe_2), 1.44, 1.56 (2s, 6H, :$C\underline{Me}_2$), 1.77 (ddd, 1H, $J_{1,2'_a}$=3.2, $J_{2'_a,3'}$=9.6, $J_{2',2'gem}$=13.3, H-2'$_{ax}$), 2.0, 2.04 (2s, 6H, 2xOCO$\underline{CH}_3$), 2.24 (ddd, 1H, $J_{1,2'_e}$=1.5, $J_{2'_e,3'}$=5.00, H-2'$_{eq}$), 3.5-4.7 (m, 7H, H-2,3,4,5,5',6,6), 4.73 (t, 1H, $J_{3',4'}$=$J_{4',5'}$=9.6, H-4'), 4.95 (d, H-1'), 5.25 (ddd, 1H, H-3'), 5.5 (d, 1H, $J_{1,2}$=5.0, H-1).

^{13}C-nmr (22.63 MHz): δ 17.4 (q, C-6'), 17.6 (q, C-6' anomer, 15%), 20.7, 20.9, 24.5, 25.0, 26.1x2 (6q, 2xOCO$\underline{CH}_3$, 2x:$C\underline{Me}_2$), 35.4 (t, C-2'), 65.5 (t;* C-6), 65.7, 67.0, 69.3, 2x70.9, 71.2, 75.1 (7d, C-2,3,4,5,3',4',5'), 96.4 (d, C-1), 96.9 (d, C-1'), 100.0 (d, C-1'), 108.7, 109.3 (2s, 2x-$C\underline{Me}_2$), 170.2, 170.3 (2s, 2xO$\underline{C}$OCH$_3$).

(*from DEPT measurement).

Analysis calcd. for $C_{22}H_{34}O_{11}$: C, 55.68; H, 7.22. Found: C, 55.59; H, 7.20%.

2.7.4 Stereoselective synthesis of Methyl 4-O-(4-O-acetyl-α-L-oleandrosyl)--β-L-oleandroside (85)

Methyl 4-O-benzoyl-2,6-dideoxy-3-O-methyl-β -L-lyxohexopyranoside (78)

A solution of **77** (5.3 g, 19.06 mmol) in dry cyclohexane (75 ml) was hydrogenated in the presence of 10% palladium-on-bariumsulfate (50 mg) at atmospheric pressure. After 3 h, the theoritical amount of hydrogen has been taken up and t.l.c. (petroleum ether:ethyl acetate; 2:1) indicated that the reaction was complete (formation of slower moving spot). The catalyst was filtered off, and the filtrate was evaporated in vacuo to give **78** as a syrup, yield 5.3 g (99%).

$[\alpha]_D^{25}$ +4° (c 1.0, $CHCl_3$).

^{1}H-nmr (90 MHz): δ1.28 (d, 3H, $J_{5,6}$=6.2 Hz, C-6), 1.8-2.05 (m, 2H, H-2), 3.38, 3.57 (2s, 6H, 2xOMe), 3.3-3.7 (m, 2H, H-3,5), 4.46 (dd, 1H, $J_{1,2_e}$=4.0, $J_{1,2_a}$=10.0, H-1), 5.49 (dd, 1H, $J_{3,4}$=$J_{4,5}$=3.0, H-4).

Analysis calcd. for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.26; H, 7.20%.

Methyl 2,6-dideoxy-3-O-methyl-4-O-methanesulfonyl-β -L-lyxohexopyranoside (80)

To a solution of **79** (1.49 g, 7.82 mmol) in dry pyridine (12 ml) was added at 0°C, methanesulfonylchloride (0.72 ml, 8.72 mmol). The resulting mixture was stirred at room temperature for 1 h, and the reaction was followed by t.l.c. (petroleum ether:ethyl acetate; 4:1) which indicated a faster moving spot. The reaction mixture was diluted with dichloromethane and was washed with water (3x50 ml), 2% cold. HCl (3x25 ml), saturated $NaHCO_3$, and finally with water (2x50 ml). The organic phase was dried (anhdrous Na_2SO_4) and concentrated under diminished pressure

to give **80** (1.6 g, 80%) as colorless crystals, which was recrystallized from dichloromethane-petroleum ether, m.p. 93°, $[\ ]_D$ +9.9° (c, 0.53, $CHCl_3$). ^{1}H-nmr(90 MHz): 1.35 (d, 3H, $J_{5,6}$=6.0, C-6 Me), 1.5-2.2 (m, 2H, H-2,2'), 3.13 (s, 3H, $SO_2\underline{CH_3}$), 3.1-3.7 (2H, m, H-3,5), 3.44-3.5 (s, 6H, 2x-O$\underline{CH_3}$), 4.4 (dd, 1H, $J_{1,2_a}$=10, $J_{1,2_e}$=2, H-1), 4.8 (d, 1H, $J_{3,4}$=$J_{4,5}$=3.0, H-4).
^{13}C-nmr (22.63 MHz): δ 17.0 (q, C-6), 31.9 (t, C-2), 38.9 (q, $SO_2\underline{CH_3}$), 56.2, 56.4 (2q, 2xO$\underline{CH_3}$), 69.2, 76.8, 78.0 (d, C-3,4,5), 100.9 (d, C-1).
Analysis calcd. for $C_9H_{18}O_6S$: C, 42.50; H, 7.13. Found: C, 42.49; H, 7.15%.

Methyl 2,6-dideoxy-3-O-methyl-4-O-acetyl- β -L-arabinohexopyranoside (81)

To a solution of cesium acetate (0.99 g, 5.19 mmol) in dry DMF (5 ml) was added a solution of the mesitylated derivative **80** (1.19 m, 4.33 mmol) in dry DMF (5 ml). The reaction mixture was heated under nitrogen atmosphere at 100°C for 26 h, and completion of reaction was confirmed by t.l.c. (petroleum ether:ethyl acetate; 4:1) which showed a slower moving spot. The reaction mixture was brought to room temperature and diluted with water (250 ml) and was extracted into dichloromethane-ether (1:3). The organic phase was washed with 5% aqueous hydrochloric acid (10 ml), water and brine (10 ml), dried (anhydrous Na_2SO_4) and the solvent removed under reduced pressure to give **81** (0.61 g, 72%) after filtration on a bed of silica gel (petroleum ether:ethyl acetate; 2:1) as a syrup $[\alpha]_D^{25}$+79 (c 1.0, $CHCl_3$).
^{1}H-nmr (90 MHz): δ 1.18 (d, 3H, $J_{5,6}$=6.0, C-6), 1.7-2.15 (2H, m, H-2,2'), 2.05 (s, 3H, O$\underline{Ac}$), 3.3, 3.4 (2s, 6H, 2xOCH_3), 3.2-3.5 (m, 2H, merged signal, H-3,5), 4.3 (dd, 1H, $J_{1,2_e}$=2.0, $J_{1,2_a}$=10.0, H-1), 4.6 (t, 1H, $J_{3,4}$=$J_{4,5}$=10.0, H-4).
^{13}C-nmr (22.63 MHz): δ 17.6 (q, C-6), 20.9 (q, OCO$\underline{CH_3}$), 35.9 (t, C-2),

56.3, 56.4 (q, 2xOMe), 70.1, 75.8, 78.0 (3d, C-3,4,5), 100.7 (d, C-1), 170.1 (s, $O\underline{CO}CH_3$).

Analysis calcd. for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31. Found: C, 55.1; H, 8.25%.

2,6-Dideoxy-3-O-methyl-4-O-acetyl-α and β-L-arabinohexopyranoside (83)

A solution of **81** (1.0 g, 4.9 mmol) in acetic and water (3:1, 20 ml) was heated at 60°C for 6 h, where upon t.l.c. (petroleum ether:ethyl acetate; 2:1) showed the appearance of slower moving spot. The reaction mixture was co-evaporated with benzene under reduced pressure several times, and the resulting residue was filtered on a bed of silica gel to give **88** (0.58 g, 79%) as a syrup.

Analysis calcd. for $C_9H_{16}O_5$: C, 52.93; H, 7.90. Found.: C, 52.90; H, 7.91%.

Methyl 2,6-dideoxy-3-O-methyl-β-L-arabinohexopyranoside (82)

To a solution of **81** (2.2 g, 10.09 mmol) in anhydrous methanol (20 ml) was added 1M sodium methoxide (250 ml) and left at room tmeperature for 6 h. When t.l.c. (petroleum ether:ethyl acetate; 2:1) indicated the completion (appearance of a slower moving spot) of reaction, the reaction mixture was neutralized with amberlite resin IR 120 (H^+). The resin was filtered off, and evaporation of methanol under diminished pressure gave **82** (1.79 g, 98%) as colourless crystals which was recrystallized from ethyl acetate-petroleum ether, $[\alpha]_D^{25}$ +39.7° (c 0.5, $CHCl_3$), m.p. 69-70°C.

^{1}H-nmr(90 MHz): δ 1.3 (d, 3H, $J_{5,6}$=6.0, H-6), 2.12-2.4 (m, 2H, H-2,2'), 3.05-3.3 (m, 3H, H-3,4,5), 3.35, 3.4 (2s, 6H, 2xOMe), 4.3 (dd, 1H, $J_{1,2_e}$=2.0, $J_{1,2_a}$=10.0, H-1).

^{13}C-nmr (22.63 MHz): δ 17.4 (q, C-6), 34.7 (t, C-2), 60.0x2 (2q, 2xOMe), 70.4, 74.3, 79.4 (d, C-3,4,5), 90.0 (d, C-1).

Analysis calcd. for $C_8H_{16}O_4$: C, 54.53; H, 9.15. Found: C, 54.49; H, 9.17%.

Methyl 4-O(4'-O-acetyl-α-L-oleandrosyl)- βL-oleandroside (85)

To a dry round bottomed flask (10 ml) were added 2-pyridyl 2,6-dideoxy-3-O-methyl-4-O-acetyl-1-thio α and β-L-arabinohexopyranoside **84** (0.31 g, 1.00 mmol), methyl 2,6-dideoxy-3-O-methyl- -L-arabinohexopyranoside (**82**) (0.16 g, 1.1 mmol) and 4A° molecular sieves (0.3 g). It was dried in high vacuo at 50°C for 5 min. Then dry dichloromethane (10 ml) containing 3% MeI was added and the reaction mixture was heated to 50°C for 20 h. The reaction was followed by t.l.c. (petroleum ether:ethyl acetate; 2:1) which indicated a faster moving spot. The reaction mixture after cooling was filtered on a celite bed and washed thoroughly with dichloromethane. The filtrate was concentrated under reduced pressure to abrown residue, which was chromatograped (petroleum ether:ethyl acetate; 2:1) to afford the required disaccharide **85** (0.22 g, 78%) as colourless crystals, which was recrystallized from dichloromethane-petroleum ether to colourless needles, m.p. 100-101°C, $[\alpha]_D^{25}$-37.2° (c 1.0, $CHCl_3$). ^{1}H-nmr (300 MHz): δ 1.13 (d, 3H, $J_{5',6'}$=6.3, C-6*), 1.34 (d, 3H, $J_{5,6}$=6.1, C-6*), 1.44 (ddd, 1H, $J_{1,2a}$=9.5, $J_{2.3}$=11.0, $J_{2,2'gem}$=13.0, H-2ax**), 1.66 (ddd, 1H, $J_{1',2'}$=2.8, $J_{2',3'}$=10.8, $J_{2'a,2'e}$=13.0, H-2ax**), 2.11 (s, 3H, 4'-OAc), 2.24-2.37 (m, 2H, H-2,2'eq), 3.2 (t, 1H, $J_{3,4}$=$J_{4,5}$=9.48, H-4), 3.25-3.33 (m, 2H, H-3,3', merged), 2x3.35 (2s, 6H, 3,3' OMe), 3.49 (s, 3H, -OMe), 3.56 (dq, 1H, H-5), 3.84 (dq, 1H, $J_{4',5'}$=9.87, H-5'), 4.34 (dd, 1H, H-1), 4.66 (t, 1H, $J_{3',4'}$=$J_{4',5'}$=9.8, H-4'), 5.40 (d, 1H, H-1').

(*, ** assignments may be reversed.)

^{13}C-nmr (22.63 MHz): δ 17.5, 18.6 (2q, C-6,6'), 35.3, 35.9 (t, C-2,2'), 56.4, 56.9 (2q, 3xOMe), 66.7, 71.0, 75.8, 76.5, 80.6, 81.7 (6d, C-3,4,5,3', 4',5'), 98.46, 100.8 (2d, C-1,1'), 170.2 (s, $\underline{C}OCH_3$).

Analysis calcd. for $C_{17}H_{30}O_8$: C, 54.34; H, 8.34. Found: C, 54.29; H, 8.36%.

2.7.5 Synthesis of α-linked 2-deoxy trisaccharides

O-(3,4-Di-O-acetyl-2,6-dideoxy-α-L-arabinohexopyranosyl)-(1 → 4)-(2,3-di-O-acetyl-6-O-benzoyl-α-D-glucopyranosdyl)-(1 → 4)-1,2,3,6-tetra-O-acetyl-β-D-glucopyranoside (**90**).

Saccharide coupling of **7**[151] (0.42 g, 1.39 mmol) with sugar alcohol **89** (0.98 g, 1.41 mmol) in dry dichloromethane (8 ml, having 3% methyl iodide) in the presence of molecular sieves 4A (400 mg) at 50°C for 36 h, after workup and chromatographic purification (SiO_2, pet.ether:ethyl acetate; 1:1) afforded the α-2-deoxy trisaccharide **90** (0.37 g, 33%) as a colourless foam.

$[\alpha]_D^{25}$ +11.42° (c 0.98, $CHCl_3$); m.p.: 103-105°C.

^{1}H-nmr (300 MHz): δ 1.1 (d, 3H, H-6''), 1.75 (m, 1H, H-2''$_{eq}$), 2.0-2.2 (8s, 25H, 8xOCO$\underline{CH_3}$, H-2''$_{eq}$ buried under acetate signals), 3.8-4.3 (m, 6H, H-2,2',4,4',5,5'), 4.4-4.8 (m, 4H, H-3,3',6,6'), 4.9-5.5 (m, 6H, H-6,6',4'',3'', 1',1''), 5.75 (d, 1H, $J_{1,2}$=9.2, H-1), 7.4-8.1 (m, 5H, aromatic).

^{13}C-nmr (75 MHz): δ 17.3 (q, C-6''), 20.5x2, 20.6x2, 20.7x4 (3q, 8xOCO$\underline{CH_3}$), 36.0 (t, C-2''), 62.2, 62.3, 67.0, 68.3, 69.8, 70.3, 70.5, 70.9, 72.6, 73.0, 74.3, 75.2, 75.3 (11d, 2t, C-2,3,4,5,6,2',3',4',5',6',3'',4'',5''), 91.2 (d, C-1'), 95.8 (d, C-1), 98.6 (d, C-1''), 128.5, 129.6 (aromatic), 168.7x2, 169.5x2, 170.0x4 (8s, 8xO$\underline{CO}CH_3$, O$\underline{CO}$Ph).

Analysis calcd. for $C_{41}H_{52}O_{23}$: C, 53.94; H, 5.74. Found: C, 53.89; H, 5.71%.

O-(3,4-di-O-acetyl-2,6-dideoxy-α-L-arabinohexopyranosyl)-(1 → 6)-(2,3-di-O-acetyl-α-D-glucopyranosyl)-(1 → 4)-1,2,3,4-tetra-O-acetyl-β-D-glucopyranoside (91)

Compound **7**[151] (0.44 g, 1.36 mmol) was reacted with **88**[183] (0.89 g, 1.49 mmol) in 25 h, to give **91** (0.42 g, 44%) as a foam after workup and chromatographic purification (SiO_2, pet.ether:ethyl acetate; 1:1).

$[\alpha]_D^{25}$-4.82 (c 1.12, $CHCl_3$): m.p.:85-87°C.

^{1}H-nmr (300 MHz): δ 1.25 (d, 3H, $J_{5'',6''}$=6.4, H-6''), 1.85 (ddd, 1H, $J_{1'',2''_a}$ = 3.6, $J_{2''_a,3''}$=11.0, $J_{2'',2''_{gem}}$ =13.0, H-2''$_a$), 2.1-2.25 (8s, 24H, 8xOCOC$\underline{H}_3$), 2.3 (ddd, 1H, $J_{1'',2''_{eq}}$ =0.9, $J_{2''_e,3''}$=5.3, H-2''$_{eq}$=), 3.6-4.0 (m, 6H, H-2,2',4'*, 5,5',5''), 4.1 (dd, 1H, $J_{3,4}$=9.6, $J_{4,5}$=H-4*), 4.2-4.85 (m, 4H, H-3,3',6,6'), 4.9 (d, 1H, H-1''), 5.1 (dd, 1H, $J_{3'',4''}$=8.0, $J_{4'',5''}$=9.0, H-4''), 5.2-5.5 (m, 4H, H-1',3'',6,6'), 5.8 (d, 1H, $J_{1,2}$=8.2, H-1).

* assignment may be reversed.

^{13}C-nmr (75 MHz): δ 17.2 (q, C-6''), 20.2, 20.3, 20.5x6 (3q, 8xOCO$\underline{C}H_3$), 34.7 (t, C-2''), 62.6, 65.6x2, 68.8x2, 70.1, 70.8, 71.6, 72.2x2, 73.2, 74.5, 78.1 (13d, C-2,3,4,5,6,2',3',4',5',6',3'',4'',5''), 91.2 (d, C-1'), 95.8 (d, C-1), 97.2 (d, C-1''), 169.0, 169.8, 170.3, 170.4, 2x170.5, 170.8, 171.5 (7s, 8x O$\underline{C}OCH_3$).

Analysis calcd. for $C_{34}H_{48}O_{22}$: C, 50.49; H, 5.98. Found: C, 50.41; H, 5.87%.

$\underline{O}$-(3,4,6-tri-$\underline{O}$-acetyl-2-deoxy-α-D-arabinohexopyranosyl)-(1 → 6)-$\underline{O}$-(2,3-di-$\underline{O}$-acetyl-α-D-glucopyranosyl)-(1 → 4)-1,2,3,6-tetra-$\underline{O}$-acetyl-β-D-glucopyranoside (92)

Saccharide coupling of **5**[151] (0.4 g, 106 mmol) with glycosyl acceptor **88**[183] (0.6 g, 1.16 mmol) in 31 h, gave the α-2-deoxy trisaccharide **92** (0.44 g, 49%) as a foam after workup and column chromatographic purification (SiO_2, pet.ether:ethyl acetate; 1:2).

$[\alpha]_D^{25}$+66.27° (c 1.18, $CHCl_3$); m.p: 100-102°C.

^{1}H-nmr (300 MHz): δ1.9 (ddd, 1H, $J_{1'',2''_a}$=3.60, $J_{2''_a,3''}$=12.0, $J_{2''2''_{gem}}$=15.4, H-2''$_{ax}$), 2.0-2.15 (9s, 27H, 9xOCO$\underline{CH}_3$), 2.3 (dd, 1H, $J_{1'',2''e}$=0.42, $J_{2''e,3''}$= 5.5, H-2''$_{eq}$), 3.55-4.5 (m, 11H, H-2,2',3,3',4,4',5,5',5'',6,6), 5.01 (brd, 1H,

H-1"), 4.7-5.4 (m, 6H, H-1',3",6',6"), 5.78 (d, 1H, $J_{1,2}$=8.2, H-1).

(assignment from 2D, ^{1}H-^{1}H correlation spectrum).

^{13}C-nmr (75 MHz): 20.3x3, 20.4x3, 20.5x3 (9q, 9xOCO<u>CH_3</u>), 34.6 (t, C-2"), 62.3, 62.6, 64.9 (t,# C-6,6',6"), 67.7, 68.4, 68.7, 69.4, 70.0, 70.8, 71.8, 72.2, 72.3, 73.1, 75.1 (11d, C-2,3,4,5,2',3',4',5',3",4",5"), 91.1 (d, C-1'), 95.7 (d, C-1), 96.9 (d, C-1"), 168.6, 169.3, 169.7, 169.8, 169.9, 170.3x2, 170.67, 171.1 (9s, 9x<u>OCO</u>CH_3).

(# from DEPT measurement).

Analysis calcd. for $C_{36}H_{50}O_{24}$: C, 49.88; H, 5.89. Found: C, 49.86; H, 5.80%.

CHAPTER 3

ITERATIVE, STEREOSELECTIVE SYNTHESIS OF α-LINKED 2-DEOXY SACCHARIDES

3.1 INTRODUCTION

The chemical synthesis of α-2-deoxy oligosaccharides is still receiving much attention due to the discovery of numerous physiologically active glycosides, such as chromomycin[11], mithramycin[13], and olivomycin[12] which constitute potent cystostatic agents[184]. Therefore, much attention has been concentrated towards the stereoselective synthesis of the 2-deoxy oligosaccharide components. To achieve this target, two main problems have to be dealt with:

i) One is that of designing a protective group strategy that allows chemical reaction at the desired hydroxyl group(s) while leaving the other groups intact,

ii) and the second factor being to obtain the desired α-selectivity in as far as in fewer steps, without resorting to chromatographic separation of anomeric mixture.

Fraser-Reid and coworkers have recently developed a reiterative method for the synthesis of 2-deoxy oligosaccharide termed as "Armed-Disarmed" strategy, wherein n-pentenyl 2-deoxy α-and β-glycoside (armed glycosyl donors) couple with 2-halo-n-pentenylglycoside (disarmed acceptor) on activation by IDCP to afford the 2-deoxy disaccharides (α/ β 3:1 ratio)[127]. The disaccharide thus obtained has been used for further coupling only after it was converted to the armed 2-deoxy disaccharide by reductive dehalogenation, and was terminated finally to give a trisaccharide (α/β :4/1).

In an another approach, developed by Danishefsky and co-workers[108], glycal protected at 3,6-positions as esters acts as a glycosyl acceptor (Chapter 1, SCHEME 10). Glycal protected as tribenzyl ether acts as a donor to undergo 1,2-iodoglycosyloxylation in presence of IDCP[83] to give α 2-iodo-2-deoxy glycoside. The process was reiterated with or without protection and deprotection, with either glycals (glycosyl acceptor) to yield further a trisaccharide glycal which could be reiterated or with a terminating sugars to yield the α-2-deoxy trisaccharides. However, this operation was not successful when both glycosyl donors and glycosyl acceptors were protected as esters. This, strategy seems to be quite useful in terms of generality. This method too needs a further reduction to obtain 2-deoxy saccharide (Chapter 1, SCHEME 10).

3.2 Development of reiterative, stereoselective glycosidation methodology for the synthesis of α-linked 2-deoxy saccharides

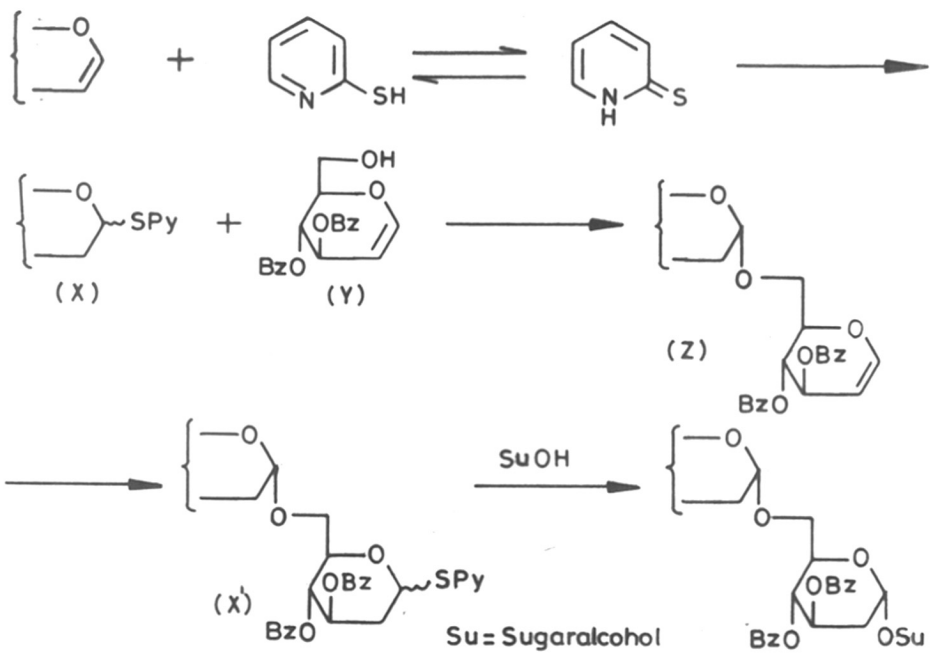
Our extensive studies[152,153] on the stereoselective formation of oligosaccharides have indicated tremendous potential for the use of 2-pyridyl-1-thioglycosides as glycosyl donors, we looked into the utility of this finding even for a reiterative glycosidation methodology. Earlier, we have also reported[151] that 2-mercaptopyridine undergoes a facile 1,2-addition on substituted D-glucal, D-galactal and L-rhamnal to give their corresponding substituted 2-pyridyl-1-thioglycosyl donors (Chapter 2, SCHEME 1).

3.2.1 STRATEGY

A reiterative glycosidation process can be realized if (i) substituted 2-deoxy 2-pyridyl-1-thio glycosyl donor (X) be coupled to glycal acceptor (Y) on activation by methyl iodide to obtain the disaccharide glycal

(α -anomer exclusively) (Z), (ii) if 2-mercaptopyridine could be added (1,2-addition) to the sensitive saccharide glycal (Z) to give 2-deoxy 2-pyridylthiosaccharide donor (X') for further coupling. In these steps the preformed glycosidic linkages and the protecting groups should remain unaffected (SCHEME 1).

SCHEME 1



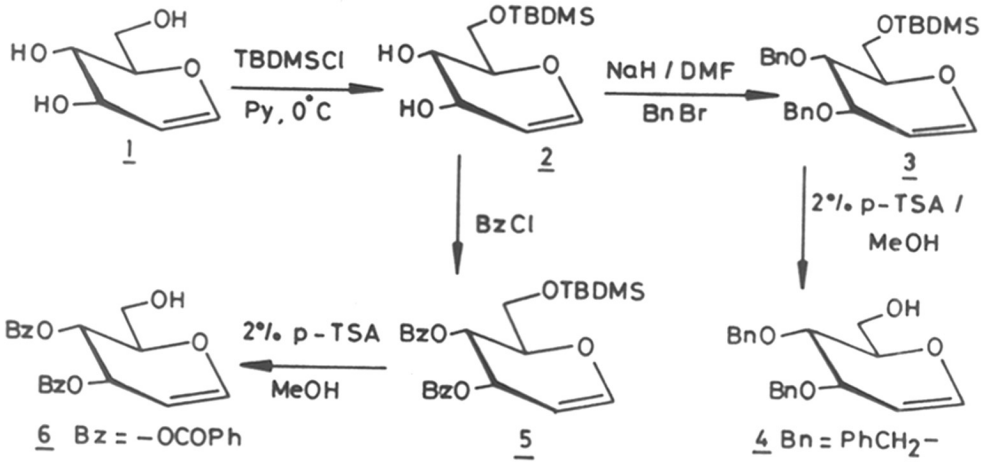
Hence 2-pyridyl 2-deoxy-1-thioglycosides (protected as esters) have been proposed as glycosyl donors, and glycals (protected as tribenzyl ethers at C-3,4 positions) as glycosyl acceptors, for iterative, stereoselective synthesis of α-linked 2-deoxy saccharides.

3.2.2 Synthesis of glycal acceptors

The glycal acceptor, 3,4-di-O-benzyl-D-glucal was prepared from D-glucal (1) in three steps in improved yields. 1 was protected at C-6 position as 6-O-t-butyldimethylsilyl-D-glucal (2)[105a] on treatment with t-butyldimethylsilylchloride/pyridine at 0°C (SCHEME 2) in 80% yield and was

then converted to its corresponding 6-O-t-butyldimethylsilyl-3,4-di-O-benzyl-D-glucal (3) on treatment with sodiumhydride and benzyl bromide in N,N'-dimethylformamide (DMF) in 92% yield. The preparation of the 3 by the method of Blackburne and coworkers using silver oxide and benzyl bromide gave 3 only in 24% yield[105a]. The deprotection of the t-butyldimethylsilyl group was accomplished by treating 3 with 2% p-TSA/ MeOH strictly at -5°C, followed by neutralization with basic ion-exchange resin, to yield 3,4-di-O-benzyl-D-glucal (4) in 78% yield (SCHEME 2).

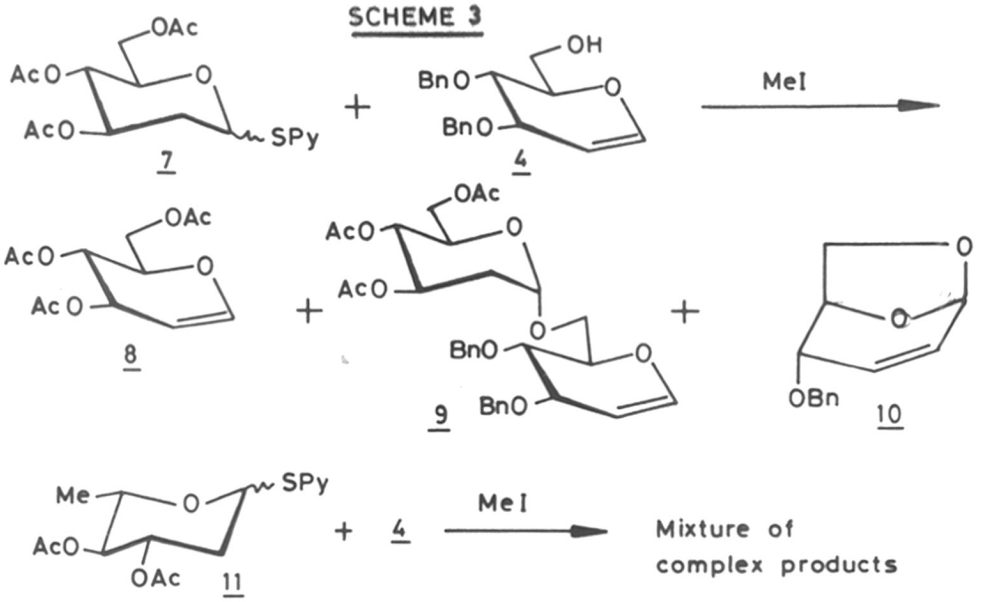
SCHEME 2



Coupling of 2-pyridyl 3,4,6-tri-O-acetyl-2-deoxy-1-thio α and β -arabinohexopyranoside (7) with 4 in dry dichloromethane containing 3% MeI, molecular sieves 4 Å (200-300 mg) at 50°C, for 18 h lead to the formation of tri-O-acetyl-D-glucal (8) (10%), α-2-deoxy disaccharide glycal (9) (12%) and 1,6-anhydro-2,3-dideoxy-4-O-benzyl-β -D-erythro-hex-2-eno-pyranose (10) (50-60%) (SCHEME 3). The disaccharide glycal 9 in its ^{1}H-nmr showed three singlets at δ 2.01, 2.02 and 2.05 for three acetate groups, a ddd at δ 1.8 ($J_{1',2'a}$=3.6, $J_{2'a,3'}$=11.6, $J_{2,2'gem}$=13.6) and at

2.25 ($J_{1,2'e}$=0.92, $J_{2'e,3'}$=5.4 Hz) for H-2'$_{ax}$,2'$_{eq}$ respectively. The appearance of a double doublet at δ6.4 ($J_{1,2}$=6.1, $J_{1,3}$=1.2 Hz) for H-1 (olefenic proton) of glycal. The disaccharide glycal **9** formation in extremely lower yield may be attributed to the faster intramolecular nucleophilic addition of the 6-hydroxyl group of the glycal **4** to give **10** which competes with the slower intermolecular glycosidation reaction. This is similar to the well known intermolecular Ferrier reaction. Similarly, when 2-pyridyl 3,4-di-O-acetyl-2,6-dideoxy-1-thio α and β-L-arabinohexopyranoside (**11**) was subjected to glycosidation with **4** under the established glycosidation reaction conditions, resulted in an inseparable mixture of products (SCHEME 3). And consequently, 3,4-di-O-benzoyl-D-glucal (**6**) was thought to be an ideal glycosyl acceptor due to the electron withdrawing ester func-

SCHEME 3

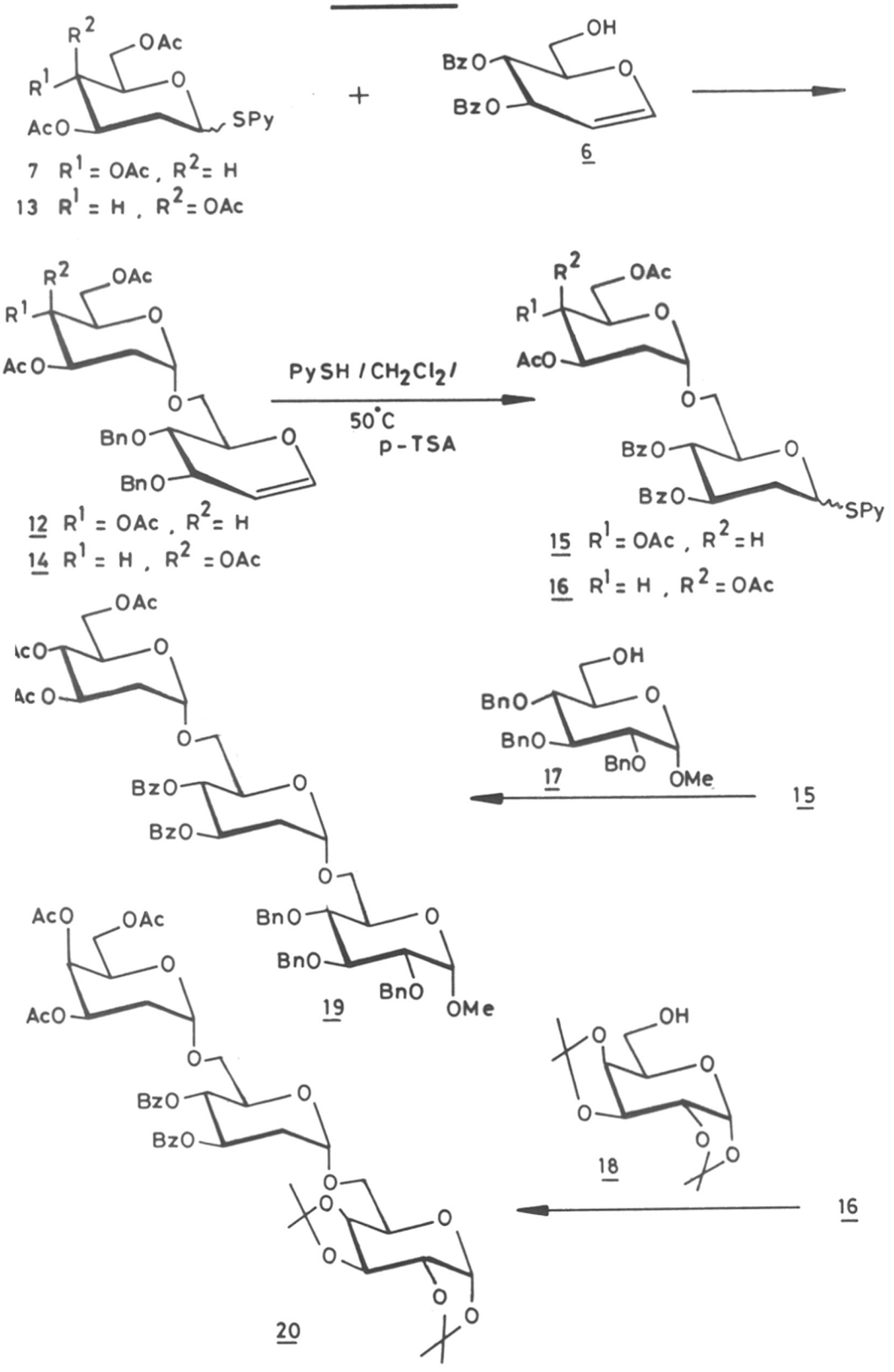


tions that make the enol ether electron deficient[108]. The 6-O-t-butyldimethylsilyl-D-glucal (**2**) on treatment with 2-mole equivalents of benzoyl chloride and pyridine gave 6-O-t-butyldimethylsilyl-3,4-di-O-benzoyl-D-

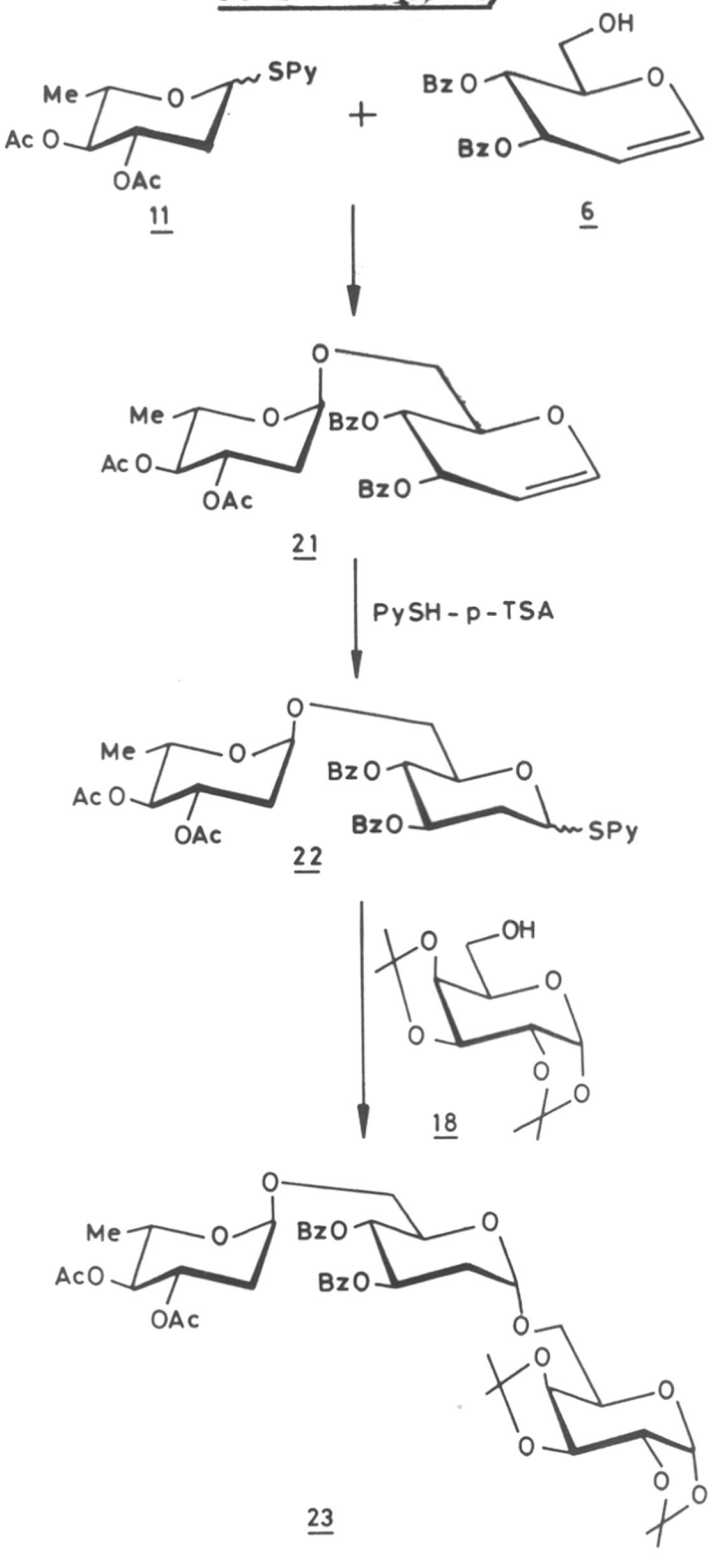
glucal (**5**) in 98% yield. Deprotection of **5** was accomplished by treating with 2% p-TSA/MeOH at -5°C for 3 h, followed by neutralization with basic ion-exchange resin to afford **6** in 68% yield. Glycosidation of **7** with equimolar amounts of **6** in dichloromethane containing 3% methyl iodide, 4 Å molecular sieves for 31 h, lead to the formation of the α -2-deoxy disaccharide glycal **12** in 53% yield as a syrup (SCHEME 4). Formation of **12** was characterised by the appearance of three acetyl groups at δ 2.0x2, 2.03 as singlets (from the donor) aromatic signals between δ 7.3-8.5 and enol ether protons H-1 and H-2 at δ 6.5 (dd, $J_{1,2}$=5.5, $J_{1,3}$=1.6 Hz) and δ 5.05 (dd, $J_{2,3}$=4.6 Hz) respectively for the acceptor. The newly formed glycosidic bond has been assigned α -linkage from the appearance of H-1' at δ 4.95 (dd, $J_{1',2'a}$=3.6, $J_{1',2'e}$=1.2 Hz), $H\text{-}2'_{ax}$ at δ 1.8 (dd, $J_{2'a,3'}$= 11.5, $J_{2,2'gem}$=16.7 Hz) and $H\text{-}2'_{eq}$ at δ 2.2 (dd, $J_{2'e,3'}$=5.4 Hz) respectively. The ^{13}C-nmr spectrum of **12** also showed characteristic signal for C-1' at δ 99.0 indicating the formation of α-linkage, C-1, C-2 of the glycal at δ 96.0 and 145.7 respectively and the C-2' (2-deoxy) signal at δ 34.6.

The sensitive disaccharide glycal **12** smoothly underwent 1,2-addition reaction with 2-mercaptopyridine in presence of catalytic amount of anhydrous p-toluenesulfonic acid in dry dichloromethane at 50°C for 20 h, according to the procedure reported by Mereyala[151] to yield cleanly 2-pyridyl 2-deoxy-1-thiodisaccharide (**15**) (α/β ;2/1) in 88% yield. There was no evidence for the formation of Ferier rearranged products. Formation of the addition compound **15** was characterised by the appearance of thiopyridyl aromatic signals between δ 7.2-8.5, anomeric signals H-1 (α -anomer) at δ 6.5 (dd, $J_{1,2_a}$=6.0, $J_{1,2_e}$=2.0 Hz), and H-1 (β-anomer)

SCHEME 4


7 R1 = OAc , R2 = H
13 R1 = H , R2 = OAc
6
PySH / CH2Cl2 /
50°C
p-TSA
12 R1 = OAc , R2 = H
14 R1 = H , R2 = OAc
15 R1 = OAc , R2 = H
16 R1 = H , R2 = OAc
17
15
19
18
16
20

SCHEME 4 (CONTD)

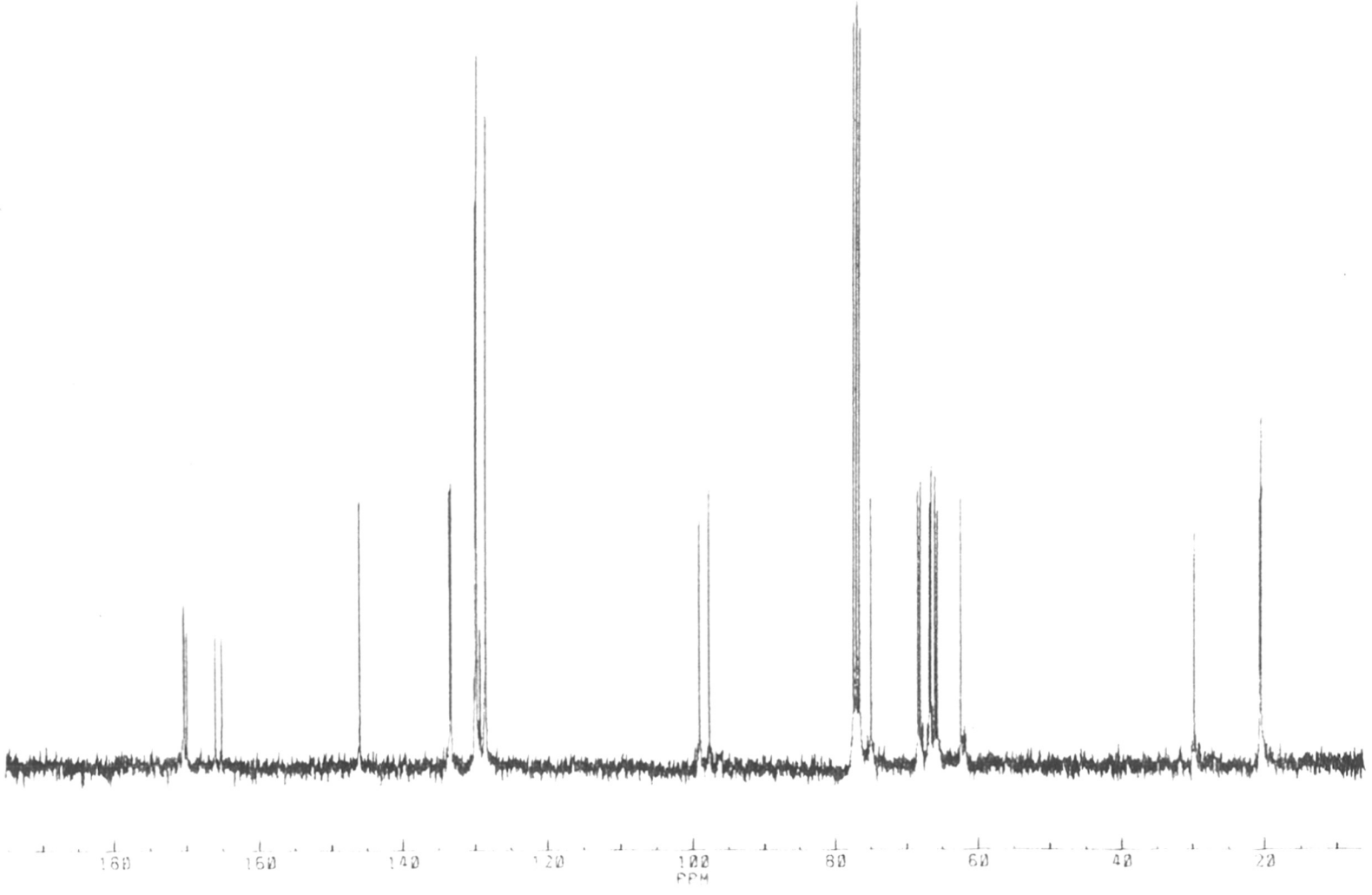


at δ5.5 (dd, $J_{1,2_a}$ =12.0, $J_{1,2_e}$ =2 Hz). To reiterate the glycosidation process, the 2-deoxy pyridyl-thioglycoside **15** was subjected to coupling reaction with methyl 2,3,4-tri-O-benzoyl-α -D-glucopyranoside (**17**) for 25 h to afford the 2-deoxy trisaccharide **19**, exclusively as an α-anomer in 64% yield as a syrup. The ^{1}H-nmr of **19** showed three singlets at δ1.95, 2.02 and 2.05 for three acetate groups, a ddd between δ1.6-1.9 for H-2'$_{ax}$ and H-2"$_{ax}$ (buried under acetate signals). A multiplet between δ2.2-2.6 due to H-2'$_{eq}$, and H-2"$_{eq}$ and a singlet at δ 3.4 due to methoxyl group of the terminating sugar. The appearance of two broad doublets between δ4.5-5.1 for the H-1" and H-1' indicate the formation of α-linkage. The ^{13}C-nmr showed signals at δ 34.5 and 34.9 due to C-2' and C-2" respectively, a signal at δ 54.9 for methoxyl group of the terminating sugar. The signals at δ 96.9, 97.25, and 97.87 for C-1,1',1" are also characteristic of α-linkages at anomeric positions.

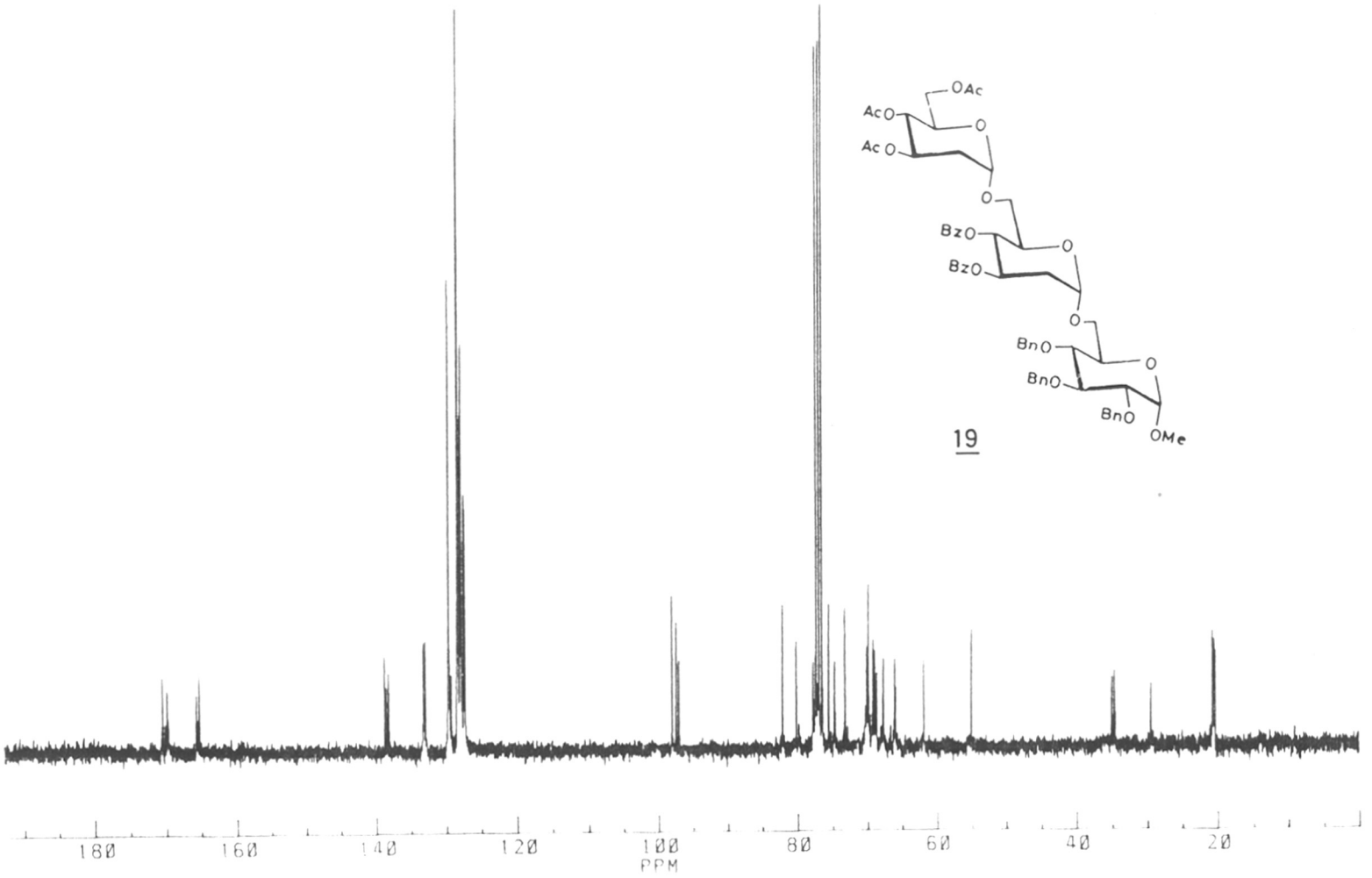
To study the efficiency of this new glycoisidation method 2-pyridyl 3,4,6-tri-O-acetyl 2-deoxy 1-thio α and β-D-lyxohexopyranoside (**13**) and 2-pyridyl 3,4-di-O-acetyl-2,6-dideoxy-α and β-L-arabinohexopyranoside (**11**) were also tried as glycosyl donors in such reactions.

Synthesis of trisaccharide (20):

Coupling of **13** with **6** for 27 h afforded the disaccharide glycal **14** in 64% yield. Formation of **14** was characterized by the appearance of three acetyl groups at δ 1.91 and 1.98x2 as singlets (from the donor), aromatic signals between δ 7.3-8.0 and enol ether protons H-1 and H-2 at δ 6.5 ($J_{1,2}$=5.5, $J_{1,3}$=1.6 Hz) and 5.0 (dd, $J_{2,3}$=4.8) respectively (from the acceptor). The newly introduced O-glycosidic bond has been assigned α-linkage from the appearance of H-1' at δ 5.65 as a broad doublet, H-2'$_{ax}$



^{1}H NMR SPECTRUM OF COMPOUND 14 (75 MHz , $CDCl_3$)

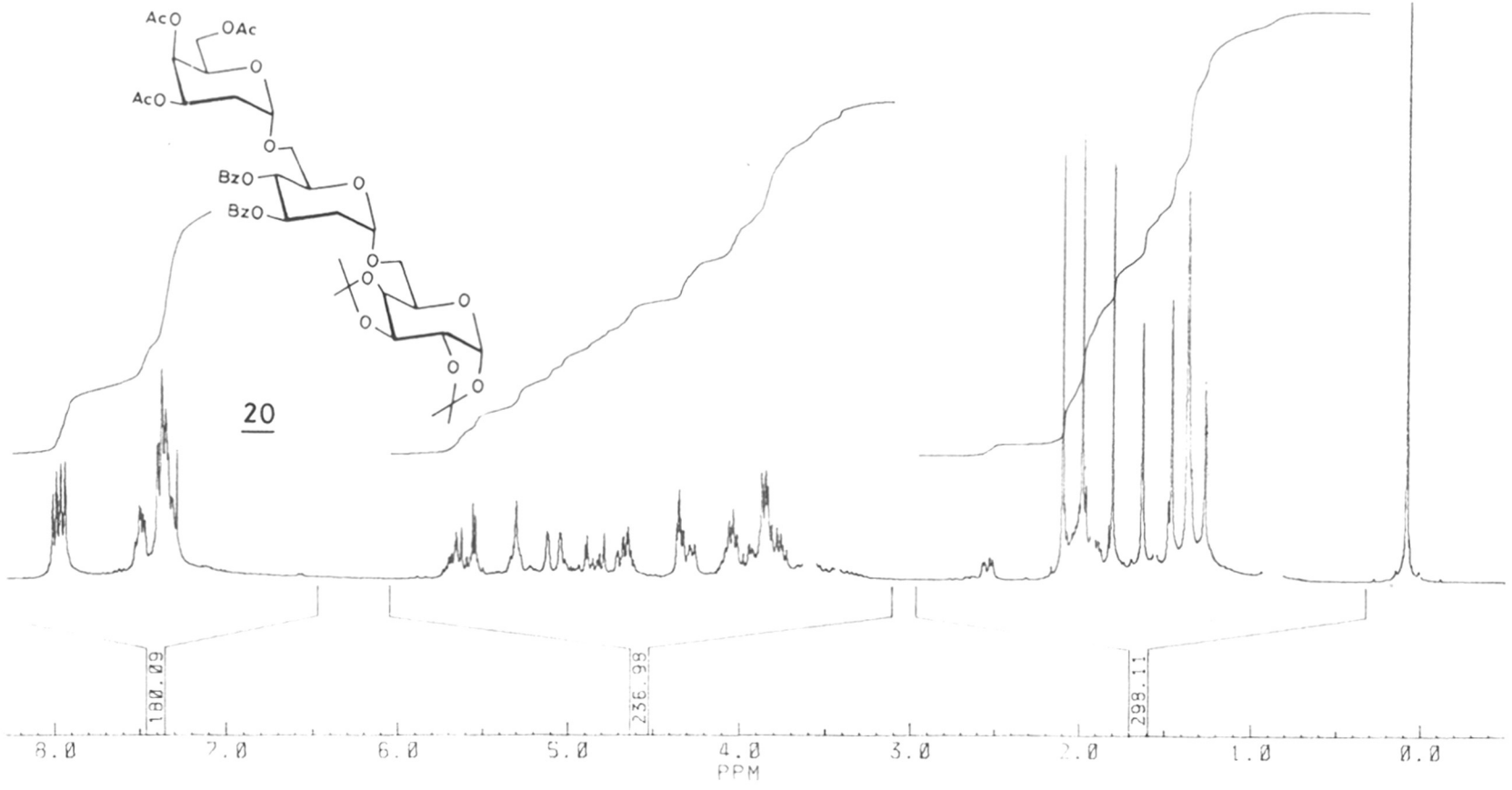


^{13}C NMR SPECTRUM OF COMPOUND 19 (75 MHz , $CDCl_3$)

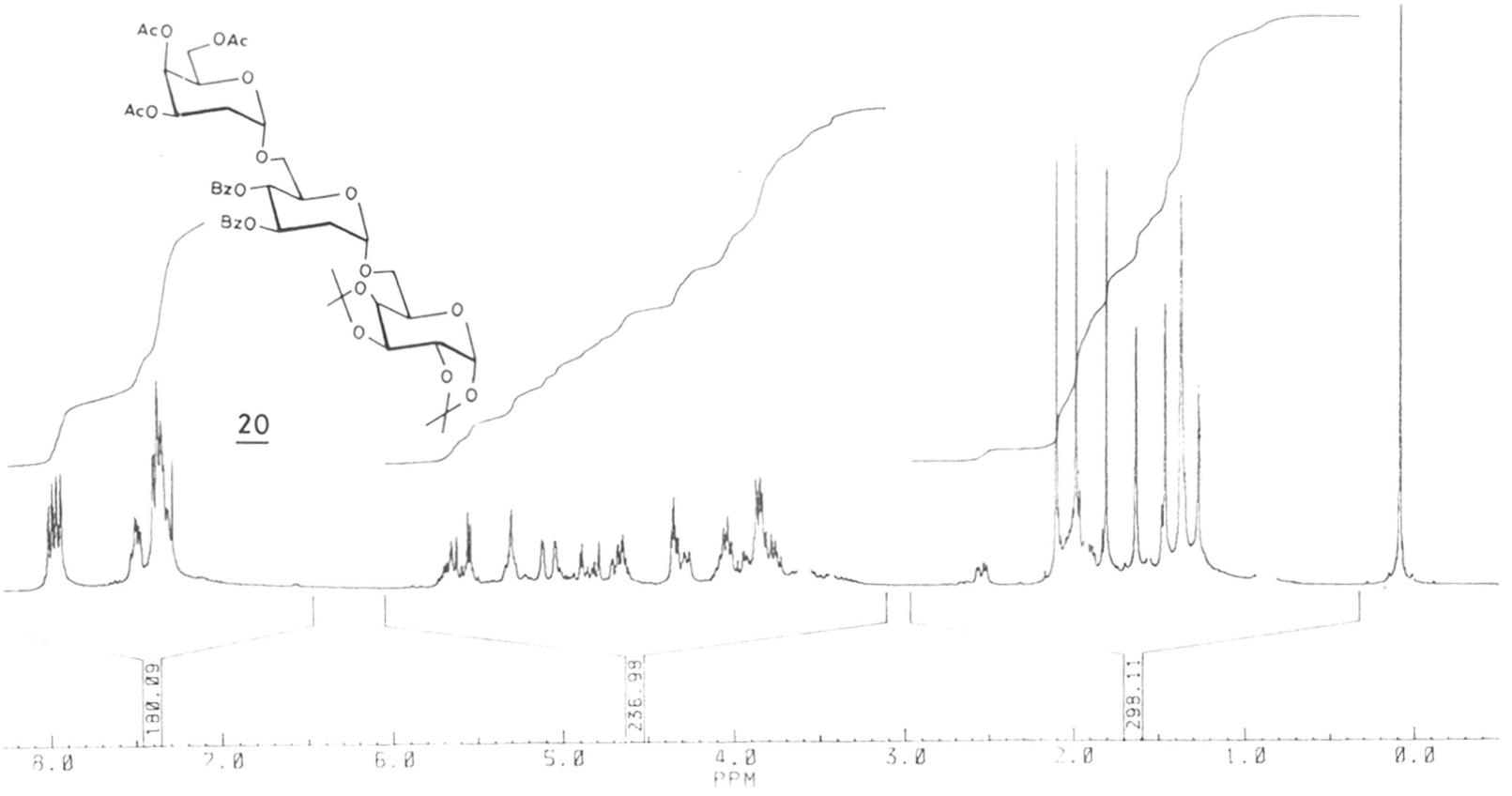
at δ 1.8 ($J_{1',2'_a}$=2.8, $J_{2'_a 3'}$=6.0, $J_{2,2'gem}$=13.0 Hz) and H-2'$_{eq}$ at δ 2.0 (buried under acetate signals). The ^{13}C-nmr spectrum of **14** also showed characteristic signal for C-1' at δ98.9 indicating the formation of α-linkage, C-1 and C-2 of the glycal at δ 145.8 and δ97.5 respectively and the C-2' (2-deoxy) signal at δ 29.7. The glycal **14** underwent a smooth 1,2-addition with 2-mercaptopyridine in presence of p-TSA at 50°C in dichloromethane for 14 h to give 2-pyridyl 2-deoxy-1-thiodisaccharide **16** in 60% yield. Formation of the addition compound **16** was characterized by the appearance of thiopyridyl aromatic signals between δ 7.1-8.5, anomeric signals H-1 (α-anomer) at δ 6.5 ($J_{1,2}$=5.37) and H-1 (β-anomer) at δ 5.5 (dd, $J_{1,2_a}$=12.0, $J_{1,2_e}$=3.0 Hz). The coupling reaction of **16** with a terminating sugar 1,2:3,4-di-O-isopropylidene-α -D-galactopyranoside **18** for 28 h, afforded the α-2-deoxy trisaccharide **20** in 62% yield. The ^{1}H-nmr of **20** showed four singlets at δ 1.25, 1.35, 1.45, 1.61 for methyls of two isopropylidene groups, three singlets at δ 1.79, 1.97 and 2.09 for three acetate groups, a ddd between δ1.8-2.0 (buried under isopropylidene signals) for H-2'$_{ax}$ and H-2"$_{ax}$. A multiplet at δ 2.0 (buried under acetate signals) and a ddd at 2.5 ($J_{2"e,3"}$= 4.97, $J_{2",2"_{gem}}$ = 13.0 Hz) for H-2'$_{eq}$ and H-2"$_{eq}$ respectively. The appearance of two broad doublets at δ 5.05 ($J_{1',2'}$=2.5 Hz) and 5.1 ($J_{1",2"}$= 2.7 Hz) for H-1 and H-1" indicate the formation of α-linkage. The ^{13}C-nmr showed signals at δ 24.3, 24.8, 25.8 and 26.0 for four methyls of two isopropylidene groups of the terminating sugar. The signals at δ 96.2, 97.1 and 97.4 for C-1,1',1" are also characteristic of α-linkages at anomeric carbons. Two signals at δ 108.4 and 109.1 are attributed to two isopropylidene carbons.

Synthesis of the trisaccharide (23)

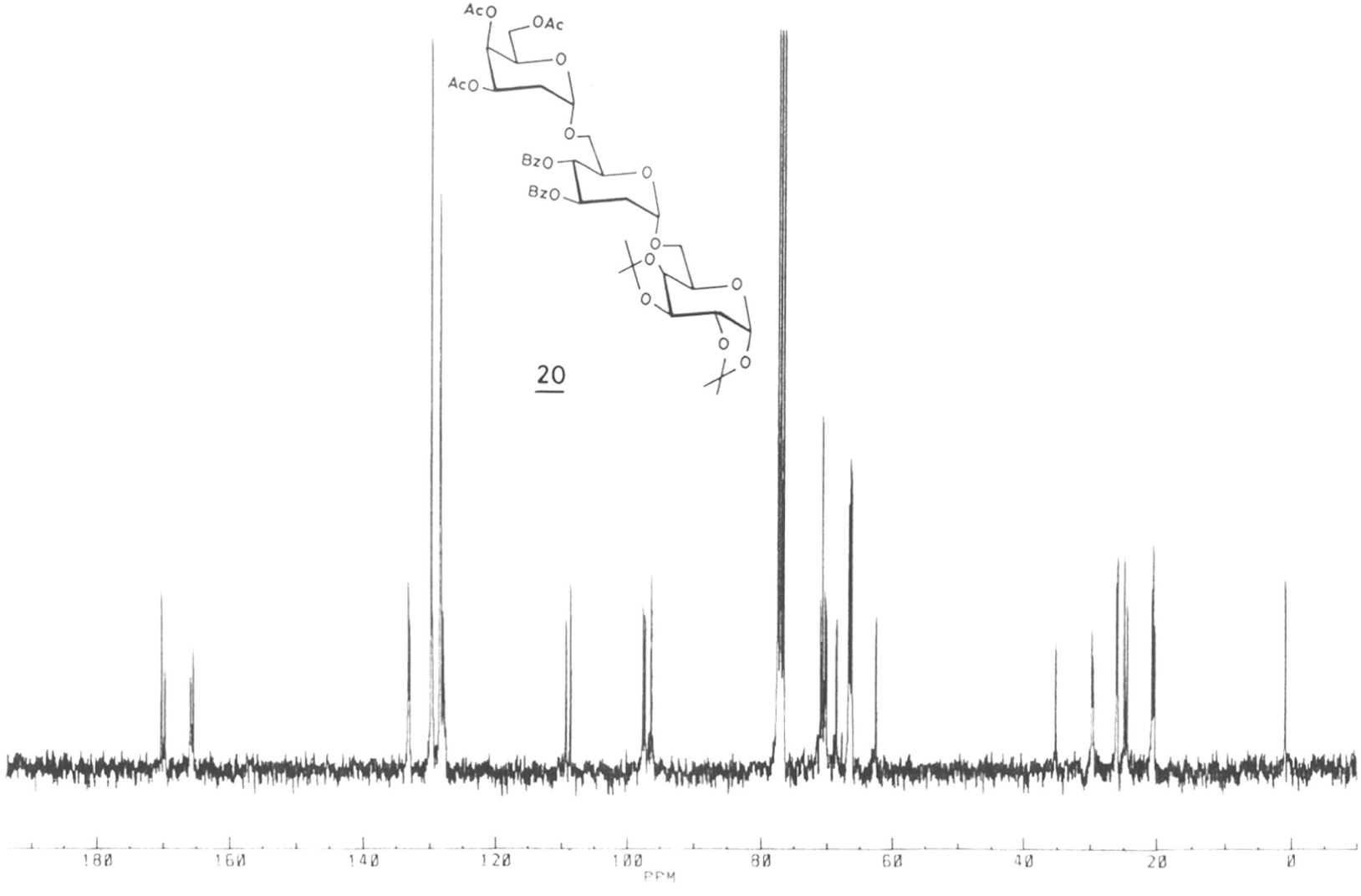
The coupling of **11** with **6** was successfully done under the establi-



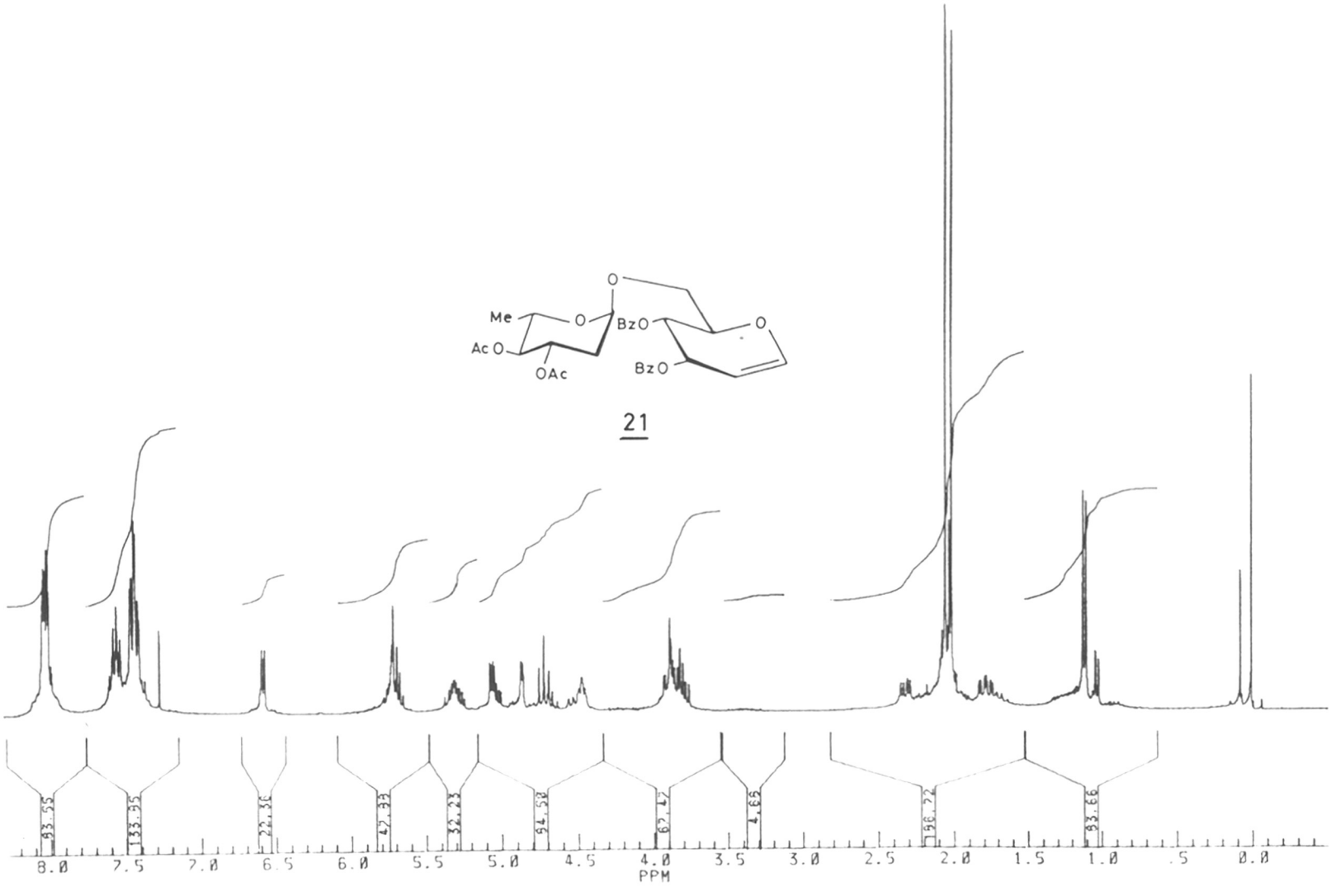
^{1}H NMR SPECTRUM OF COMPOUND 20 (300 MHz, $CDCl_3$)



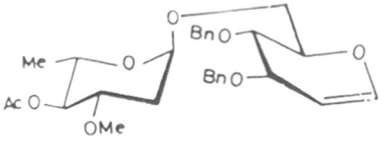
^{1}H NMR SPECTRUM OF COMPOUND 20 (300 MHz, $CDCl_3$)



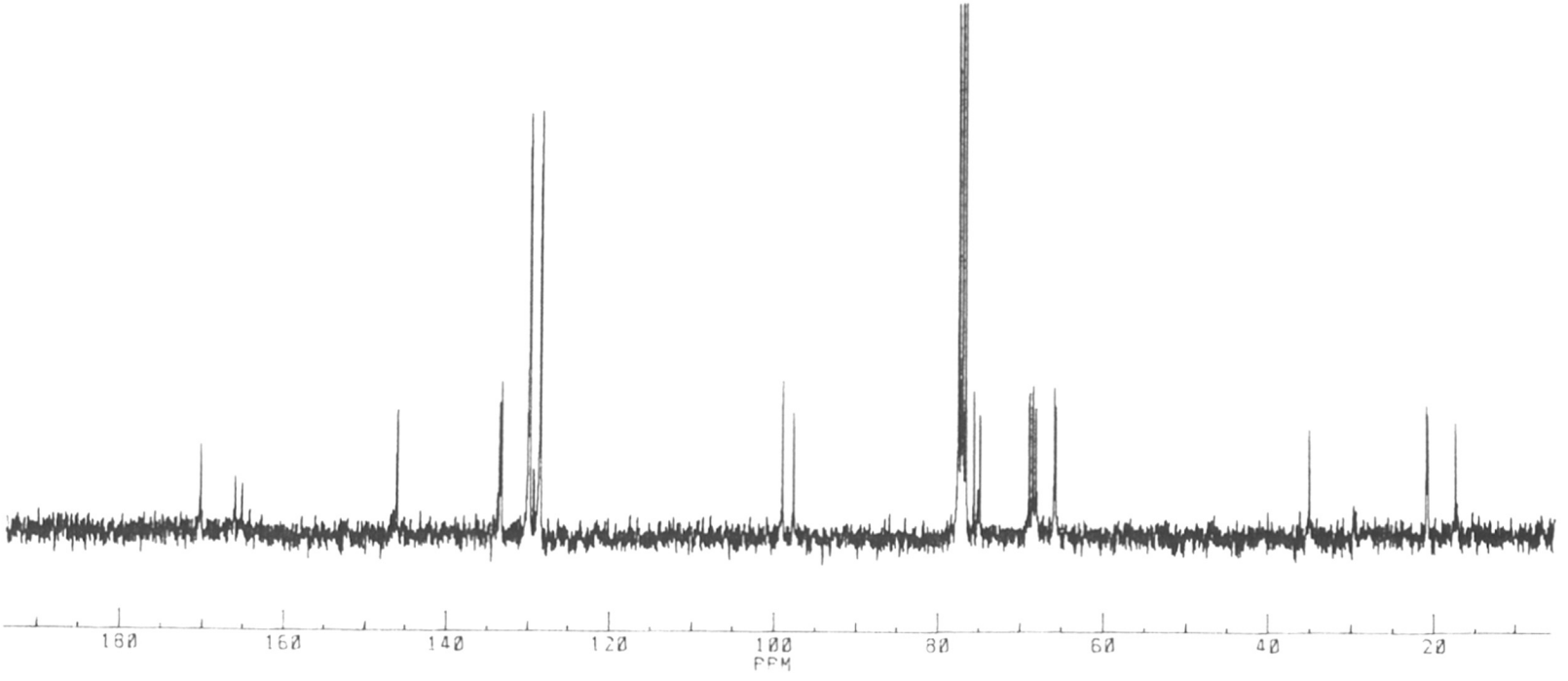
^{13}C NMR SPECTRUM OF COMPOUND 20 (75 MHz , $CDCl_3$)



^1H NMR SPECTRUM OF COMPOUND 21 (300 MHz, $CDCl_3$)

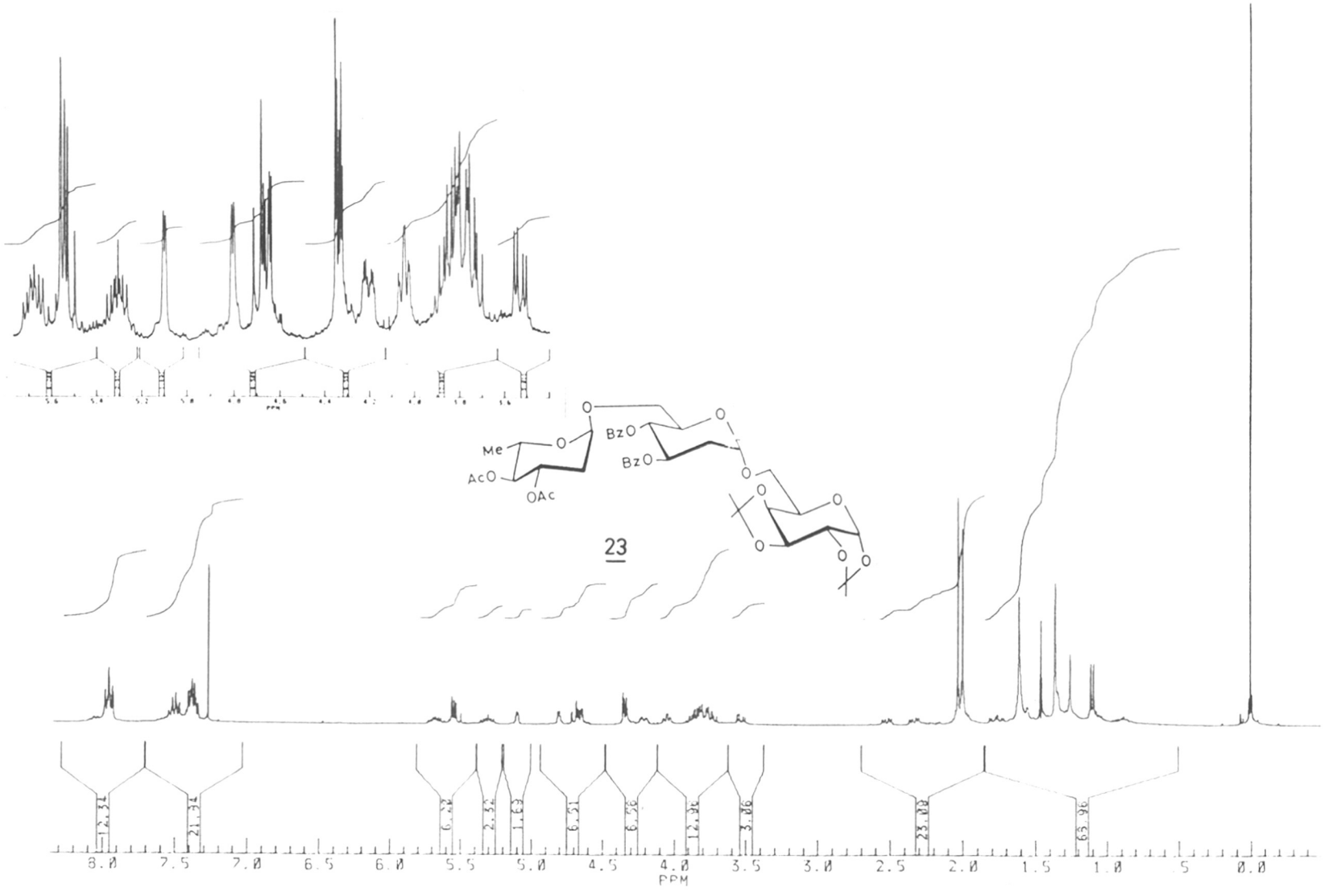


21



^{13}C NMR SPECTRUM OF COMPOUND 21 (75 MHz, $CDCl_3$)

shed glycosidation reaction conditions for 26 h, afforded the disaccharide glycal **21** (α:β;4:1) in 70% yield. Compound **21** was characterized by the appearance of a doublet at δ 1.01 ($J_{5',6'}$=6.2 Hz, 20%) and 1.1 ($J_{5',6'}$=6.2 Hz, 80%) for C-6' methyl group, and two acetyl groups at δ 2.00, 2.05 as singlets (from the donor), aromatic signals between δ 7.4-8.1 and enol ether protons H-1 and H-2 at δ 6.6 (dd, $J_{1,2}$=6.58) and 5.7 (dd, $J_{2,3}$= Hz) respectively from the acceptor. The newly introduced O-glycosidic bond has been assigned α-linkage from the appearance of H-1' at δ 4.85 as a broad doublet and a ddd atδ1.7 ($J_{1',2'a}$=3.6, $J_{2'a,3'}$=11.0, $J_{2,2'gem}$= 13.0 Hz) and at 2.35 ($J_{2'e,3'}$=5.3 Hz) for H-2'$_{ax}$ and H-2'$_{eq}$. The ^{13}C-nmr spectrum of **21** also showed characteristic signal for C-1' atδ98.78 (for α-anomer), 99.1 (for β-anomer) indicating the formation of β-linkage, C-1 and C-2 of the glycal at δ145.8 and 97.48 respectively and the C-2' (2-deoxy) signal at δ34.9. The disaccharide glycal **21** underwent a smooth and fast 1,2-addition with 2-mercaptopyridine and p-TSA at 50°C for 17 h in dichloromethane afforded the addition product 2-pyridyl 2-deoxy-1-thiodisaccharide **22** in 66% yield in α/β:3/2 ratio. Formation of the addition compound **22** was characterized by the appearance of thiopyridyl aromatic signals between δ 7.05-8.5, anomeric signals H-1 (α -anomer) at δ 6.52 ($J_{1,2_a}$ = 6.0 Hz) and H-1 (β -anomer) at δ 5.7($J_{1,2_a}$=13.2, $J_{1,2_e}$=2.0 Hz). The glycosidation process was reiterated by coupling it with a terminal sugar **18** for 24 h, to give the trisaccharide **23** exclusively as an α-anomer in 72% yield. The ^{1}H-nmr of **23** showed singlets atδ1.6x2 for methyls of two isopropylidene groups, two singlets at δ 1.99 and 2.02 for two acetate groups, a ddd at δ 1.75 ($J_{1',2'a}$=3.6, $J_{2'a,3'}$=11.67, $J_{2',2'gem}$=13.0) for H-2'$_{ax}$ and 2.0 (buried under acetate signals) for H-2''$_{ax}$, a ddd at



23

^{1}H NMR SPECTRUM OF COMPOUND 23 (300 MHz , $CDCl_3$)

δ 2.3 ($J_{2'e,3'}$=5.3) and at 2.5 ($J_{2''e,3''}$=5.3) for H-2'$_{eq}$ and H-2''$_{eq}$ respectively. The appearance of two broad doublets at δ 4.8 and 5.1 for H-1' and H-1'' indicate the formation of α-linkage. The ^{13}C-nmr showed signals at δ24.4, 24.83, 25.87, 26.05 for four methyls of two isopropylidene groups of the terminating sugar. The signals at δ 96.2, 97.0 and 97.5 for C-1,1',1'' are also characteristic of α-linkages at anomeric carbons. Two signals at δ 108.5 and 109.1 are attributed to two isopropylidene carbons.

From the above experiments the following attributes are corollary to this new glycosidation method.

i) This method does not involve any deprotection or protection or reduction steps at any stage.

ii) The very sensitive inter O-glycosidic linkages and protecting groups were unaffected.

iii) The sensitive disaccharide glycals were successfully converted to the more stable pyridyl thioglycosides, and can be used for the subsequent coupling reaction whenever needed.

iv) The stereoselectivity obtained is the unique achievement of this methodology.

v) Finally, all the pyridyl thioglycosyl donors are quite stable for storage at room temperature.

3.3 EXPERIMENTAL

6-O-Tert-butyldimethylsilyl-3,4-di-O-benzoyl-D-glucal (2)[105a]

D-Glucal 1 (2.4 g, 15.4 mmol) was dissolved in dry pyridine (20 ml) and cooled to 0°C. Tert-butyldimethylsilylchloride (2.5 g, 16.93 mmol) was then gently added to it and stirred at 0°C for 1 h when the t.l.c. (petroleum ether:ethyl acetate; 1:1) showed completion of reaction (appearance of a faster moving spot), benzoylchloride (4.1 g, 30.8 mmol) was added gradually under stirring at 0°C and was brought to room temperature (30 mint). To the reaction mixture was added water (20 ml) and extracted into diethyl ether (100 ml). The organic layer washed with cold 2% aqueous HCl (3x50 ml), aqueous $NaHCO_3$ and water dried (Na_2SO_4) and concentrated to give **2** (7.2 g, 80%) as a syrup.

$[\alpha]_D^{25}$ -94° (c 1.0, $CHCl_3$).

Analysis calcd. for $C_{26}H_{32}O_6Si$: C, 66.63; H, 6.89. Found: C, 66.61; H, 6.78%.

3,4-Di-O-benzoyl-D-glucal (6)

Compound **2** (7.2 g, 14.0 mmol) was dissolved in methanol (25 ml) and cooled to -5°C in salt-ice mixture. Then a solution of 2% p-TSA in methanol (20 ml) was added and stirred at -5°C for 3 h and the reaction was followed by t.l.c. (benzene:ethyl acetate; 8:2), which showed a slower spot. Then it was neutralized with basic ion exchange resin A-35 Tulsion (10 ml), stirred at room temperature for 15 min and filtered. Solvent was evaporated under reduced pressure to give a syrup, which was filtered on a small bed of silica gel (60-120 mesh) (pet.ether:ethyl acetate; 4:1) to give **6** (4.0 g, 74%) as a syrup.

$[\alpha]_D^{25}$ -168° (c 1.00, $CHCl_3$).

^{1}H-nmr (80 MHz): δ 3.85 (dd, 2H, $J_{1,2}$=6.3, $J_{1,3}$=1.3 Hz, H-6,6'), 4.2 (m, 1H, H-5), 5.0 (dd, 1H, $J_{3,4}$=3.2, $J_{4,5}$=4.8, H-4), 5.76-6.0 (m, 2H, H-2,3), 6.65 (dd, 1H, $J_{1,2}$=6.4, $J_{1,3}$=1.3, H-1), 7.6-8.4 (m, 10H, aromatic).

Analysis calcd. for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12. Found: C, 67.71; H, 5.09%.

O-(3',4',6'-Tri-O-acetyl-2'-deoxy- α-D-arabinohexopyranosyl)-(1 → 6)-1,5-anhydro-3,4-di-O-benzoyl-2-deoxy-D-arabinohex-1-enopyranose (12)

Saccharide coupling of **7** (0.45 g, 1.18 mmol), with glycal **6** (0.64 g, 1.78 mmol) (Section 2) in dichloromethane (8 ml, containing 3% methyl iodide), molecular sieves 4 A° (400 mg) at 50°C for 31 h, afforded the disaccharide glycal **12** (0.39 g, 53%) as a syrup, after column chromatographic purification.

$[\alpha]_D^{25}$ -14° (c 1.0, $CHCl_3$).

^{1}H-nmr (300 MHz): δ 1.8 (ddd, 1H, $J_{1',2'_a}$=3.6, $J_{2',_a3'}$=11.5, $J_{2',2'gem}$= 16.7, H-$2'_{ax}$), 2.0x2, 2.03 (3s, 9H, 3xOCO$\underline{CH_3}$), 2.2 (ddd, 1H, $J_{1',2'_e}$=1.2, $J_{2'_e3'}$=5.4, H-$2'_{eq}$), 3.6-5.4 (m, 10H, H-1',2,3,4',5,5',6,6'), 5.6-5.9 (m, 2H, H-3,4), 6.5 (dd, 1H, $J_{1,2}$=5.5, $J_{1,3}$=1.6, H-1).

^{13}C-nmr (75 MHz): δ 20.5 (3q, 3xOCO$\underline{CH_3}$), 34.6 (t,* C-2'), 62.0, 65.7, 68.0, 68.4, 68.8, 69.1, 74.9, 75.3 (8d, C-3,4,5,6,3',4',5',6'), 96.0 and 99.0 (d, C-2 and C-1'), 128.3-133.3 (aromatic), 145.7 (d, C-1), 164.9, 165.8, 169.7 (5s, 2xO$\underline{CO}$Ph, 3xO$\underline{CO}$$CH_3$):

(* from DEPT measurement).

Analysis calcd. for $C_{32}H_{34}O_{13}$: C, 61.34; H, 5.47. Found: C, 61.33; H, 5.48%.

O-(3',4',6'-Tri-O-acetyl-2'-deoxy- α -D-arabinohexopyranosyl)-(1 → 6)-2-pyridyl-3,4-di-O-benzoyl-2-deoxy-1-thio-D- α / β -arabinohexopyranoside (15)

A solution of **12** (0.230 g, 0.38 mmol) and 2-mercaptopyridine (0.06 g, 0.54 mmol) and p-TSA (0.2g, 0.11 mmol) in dry dichloromethane (3.0 ml) was heated for 20 h, when t.l.c. (pet.ether:ethyl acetate; 1:1) showed completion of reaction (26 h), it was poured into ice-cold water and extracted into dichloromethane. The organic phase was washed with 2% cold potassium hydroxide and water. Dried over Na_2SO_4 and concentrated to give **15** (0.22 g, 88%) as a syrup.

^{1}H-nmr (300 MHz): (α/β): δ 1.9, 2.05, 2.1 (3s, 9H, 3xOCO$\underline{CH_3}$), 2.2-5.7 (m, 15H, H-1',2,2,2',2',3,3',4,4',5,5',6,6,6',6'), 5.5 (dd, 1H, $J_{1,2'_e}$=2.00, $J_{1,2'_a}$=12.0, H-1, β -compound), 6.5 (dd, 1H, $J_{1,2_a}$=6, $J_{1,2_e}$=2.0, H-1, α -compound), 7.1-8.51 (m, 14H, Ph, SPy).

Analysis calcd. for $C_{37}H_{39}NO_{13}S$: C, 60.23; H, 5.33. Found: C, 60.19; H, 5.31%.

O-(3",4",6"-Tri-O-acetyl-2"-deoxy-α -D-arabinohexopyranosyl)-(1 → 6)-(3',4'-di-O-benzoyl- α-D-arabinohexopyranosyl)-(1 → 6)-methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside (19)

Saccharide coupling of **15** (0.22 g, 0.30 mmol), with the sugar alcohol **17** (0.23 g, 0.22 mmol) afforded (26 h) the α-2-deoxy trisaccharide **19** (0.2 g, 57%) as a syrup after column-chromatographic purification (pet.ether:ethyl acetate; 8:1).

$[\alpha]_D^{25}$ +58.85° (c 0.87, $CHCl_3$).

^{1}H-nmr (300 MHz): δ 1.6-1.9 (m, 2H, H-2'$_{ax}$,2"$_{ax}$), 1.95, 2.02, 2.05 (3s, 9H, 3xOCO$\underline{CH_3}$), 2.2-2.6 (m, 2H, H-2'$_{eq}$,2"$_{eq}$), 3.3-4.2 (m, 10H, H-2,5,5',5",

6,6',6''), 3.4 (s, 3H, OCH_3), 4.5-5.7 (m, 15H, H-1,1',1'',3,3',3'',4,4',4'', 3xOCH_2Ph).

^{13}C-nmr (75 MHz): δ 20.3, 20.4, 20.5 (3q, 3xOCO$\underline{CH_3}$), 34.5, 34.9 (2t, C-2',C-2''), 54.9 (q, OMe), 61.8, 68.5, 68.8 (3t, C-6,6',6''), 69.0, 69.8, 70.0, 70.2, 71.7, 73.1, 77.0, 77.7, 80.0, 81.9 (10d, C-2,3,4,5,3',4',5',3'',4'',5''), 73.2, 74.6, 75.4 (t, 3xOCH_2Ph), 96.9 (d*, C-1), 97.25 (d, C-1')*, 97.87 (d, C-1'')*, 127.0-139.0 (aromatic), 165.0, 165.2, 165.5, 169.4, 169.5 (5s, 3xO$\underline{C}OCH_3$, 2xO$\underline{C}$OPh).

(*from DEPT measurement)

(* Assignments may be reversible).

Analysis calcd. for $C_{60}H_{66}O_{19}$: C, 66.05, H, 6.09. Found: C, 66.01; H, 6.02%.

O-(3',4',6'-Tri-O-acetyl-2'-deoxy-α-D-lyxohexopyranosyl)-(1 → 6)-1,5-anhydro-3,4-di-O-benzoyl-2-deoxy-D-arabinohexo-1-enopyranose (14)

Saccharide coupling of **13** (0.401 g, 1.06 mmol) with glycal **6** (0.46 g, 1.26 mmol) afforded (27 h) the disaccharide glycal **14** (0.42 g, 64%) as a syrup, after chromatographic purification (SiO_2, pet.ether:ethyl acetate; 2:1).

$[\alpha]_D^{25}$ -72.88° (c 1.35, $CHCl_3$).

^{1}H-nmr (300 MHz): δ 1.8 (ddd, 1H, $J_{1',2'_a}$=2.8, $J_{2'_a,3'}$=6.0, $J_{2',2'_{gem}}$=13.0, H-$2'_{ax}$), 1.91, 1.98x2 (2s, 9H, 3xOCOCH_3), 2.0 (ddd, 1H, buried under acetate signal, H-$2'_{eq}$), 3.6-4.4 (m, 6H, H-5,5',6,6,6',6'), 4.8-5.0 (m, H-2,4), 5.1-5.2 (m, 2H, H-3',4'), 5.65 (m, 2H, H-3,1'), 6.5 (dd, 1H, $J_{1,2}$=5.5, $J_{1,3}$= 1.6, H-1).

^{13}C-nmr (75 MHz): δ 20.4x2, 20.6 (2q, 3xOCO$\underline{CH_3}$), 29.72 (t, C-2'), 62.3, 65.6 (2t, C-6,6'), 65.9, 66.5, 66.7, 68.0, 68.33, 74.9 (6d, C-3,4,5,3',4',5'),

97.5 and 98.9 (d, C-2, C-1'), 123.0-133.0 (aromatic), 145.8 (d, C-1), 164.9, 165.7, 169.6, 170.0, 170.1 (5s, 3xO<u>C</u>OCH$_3$, 2xO<u>C</u>OPh).

Analysis calcd. for $C_{32}H_{34}O_{13}$: C, 61.34; H, 5.47. Found: C, 61.33; H, 5.43%.

<u>O</u>-(3',4',6'-Tri-<u>O</u>-acetyl-2'-deoxy-α-D-lyxohexopyranosyl)-(1 → 6)-2-pyridyl-3,4-di-<u>O</u>-benzoyl-2-deoxy-1-thio-α / β-D-arabinohexopyranoside (16)

A solution of **14** (0.4 g, 0.04 mmol) and 2-mercaptopyridine (0.12 g, 0.96 mmol) and p-TSA (0.04 g, 0.2 mmol) in dry dichloromethane (8 ml) was heated at 50°C (14 h) when t.l.c. (pet.ether:ethyl acetate; 1:1) showed a slower moving spot and completion of reaction, it was worked up as described for compound **15**. Column chromatography of the crude residue gave **14** (0.36 g, 68%) as a syrup.

^{1}H-nmr (300 MHz) (α / β;1/1): δ 2.18x3 (3s, 9H, 3xOAc), 3.5-6.0 (m, 15H, H-1',2,2,2',2',3,3',4,4',5,5',6,6,6',6'), 5.5 (dd, 1H, $H_{1,2_a}$=12.0, $J_{1,2_e}$=3.0, H-1,β-compound), 6.54 (d, 1H, $J_{1,2_a}$=5.37, α-compound), 7.1-8.5 (m, 14H, Ph, SPy).

<u>O</u>-(3",4",6"-Tri-<u>O</u>-acetyl-2"-deoxy-α-D-lyxohexopyranosyl)-(1 → 6)(3',4'-di-<u>O</u>-benzyl-2'-deoxy-α-D-arabinohexopyranosyl)-(1 → 6)-1,2,3,4-di-<u>O</u>-isopropylidene-α-D-galactopyranoside (20)

Saccharide coupling of **16** (0.309 g, 0.4 mmol), with the sugar alcohol **18** (0.16 g, 0.6 mmol) and 4A molecular sieves (300 mg) for 28 h afforded the α-2-deoxy trisaccharide **20** (0.22 g, 62%) as a syrup, after column chromatographic purification (pet.ether:ethyl acetate; 2:1).

$[\alpha]_D^{25}$ +40° (c 1.0, $CHCl_3$).

^{1}H-nmr (300 MHz): δ 1.25x2, 1.45, 1.61 (4s, 12H, 2x:CMe_2), 1.79, 1.97, 2.09, (3s, 9H, 3xOAc), 1.8-2.0 (m, 3H, buried under acetate signals, H-2'$_{ax}$, H-2"$_{ax}$, H-2'$_{eq}$), 2.5 (dd, 1H, $J_{2"_e 3"}$=4.9, $J_{2",2"_{gem}}$=13.04, H-2"$_{eq}$), 3.5-

4.85 (m, 13H, H-1,2,3,4,5,5',5",6,6,6,6',6",6"), 5.05 (brd, 1H, $J_{1',2'}$=2.5, H-1'*), 5.1 (brd, 1H, $J_{1",2"}$=2.7, H-1"*), 5.3 (m, 2H, H-4',4"), 5.5-5.7 (m, 2H, H-3',3").

(*,** Assignments may be reversed).

^{13}C-nmr (75 MHz): δ 20.2, 20.4, 20.6 (3q, 3xOCO<u>CH$_3$</u>), 24.3, 24.8, 25.8, 26.0 (4q, 2x:C<u>Me$_2$</u>), 29.69, 35.1 (2t, C-2',C-2"), 66.1x2 (3t, C-6,6',6"), 62.5, 66.3, 68.4, 70.0, 70.1, 70.3, 70.5x2, 70.9 (10d, C'-2,3,4,5,3',4',5',3", 4",5"), 96.2, 97.1, 97.4 (3d, C-1,1',1"), 108.4, 109.1 (2s, 2x:<u>C</u>Me$_2$), 127.0-133.0 (Aromatic), 165.2, 165.6, 169.5, 170.0x2 (4s, 3xO<u>CO</u>CH$_3$, 2xOC<u>O</u>Ph). Analysis calcd. for $C_{44}H_{54}O_{19}$: C, 59.58; H, 6.13. Found: C, 59.51; H, 6.07%.

<u>O</u>-(3',4'-Di-<u>O</u>-acetyl-2',6'-dideoxy- α -L-arabinohexopyranosyl)-(1 → 6)-1,5-anhydro-3,4-di-<u>O</u>-benzoyl-2-deoxy-D-arabinohex-1-enopyranose (21)

Coupling reaction of **11** (0.404 g, 1.24 mmol) with glycal **6** (0.48 g, 1.37 mmol) for 26 h afforded the 2-deoxy disaccharide glycal **21** (0.64 g, 50%) as a syrup, after column chromatographic purification (SiO_2 pet.ether:ethyl acetate; 2:1).

$[\alpha]_D^{25}$ -167.6° (c 1.3, $CHCl_3$).

^{1}H-nmr (300 MHz):(α / β mixture), δ 1.01 (d, 0.6 H, $J_{5',6'}$=6.2, H-6'), 1.1 (d, 2.4 H, $J_{5',6'}$=6.2, H-6'), 1.7 (ddd, 1H, $J_{1',2'_a}$=3.6, $J_{2'_a,3'}$=11.0, $J_{2',2'_{gem}}$=13.0, H-2'$_{ax}$), 2.0, 2.05 (2s, 6H, 2xOCOC<u>H$_3$</u>), 2.35 (dd, 1H, $J_{2'_e,3'}$=5.3, H-2'$_{eq}$), 3.7-4.5 (m, 4H, H-5,5',6,6), 4.7 (t,1H, $J_{3',4'}$=$J_{4',5'}$=9.6, H-4'), 4.85 (d, 1H, H-1'), 5.05 (dd, 1H, $J_{2,3}$=3.3, $J_{3,4}$=6.2, H-3), 5.3 (ddd, $J_{2'_e,3'}$=11.0, $J_{2'_e,3'}$=5.3, $J_{3',4'}$=11.7, H-3'), 5.6-5.8 (m, 2H, H-2,4), 6.6 (d, 1H, $J_{1,2}$=6.58, H-1), 7.4-8.1 (m, 10H, Ph).

^{13}C-nmr (75 MHz): δ 17.31 (q, C-6'), 20.6, 20.8 (2q, 2xOCO$\underline{CH_3}$), 34.9, 65.5 (2t*, C-2',6), 65.7, 67.9, 68.3, 68.7, 74.7, 75.4 (6d, C-3,4,5,3',4',5'), 97.45, 98.78 (d,# C-2,1'), 99.1 (d, C-1'-β- 20%), 128.5-133.3 (Aromatic), 145.8 (d, C-1), 164.9, 165.8, 170x2 (3s, 2xO$\underline{C}$OCH$_3$, 2xO$\underline{C}$OPh).

(* from DEPT measurement)

(# assignment may be reversed).

Analysis calcd. for $C_{30}H_{32}O_{11}$: C, 63.37; H, 5.68. Found: C, 63.75; H, 5.62%.

$\underline{O}$-(3,4-Di-$\underline{O}$-acetyl(-2',6'-dideoxy-α-L-arabinohexopyranosyl)-(1 → 6)-2-pyridyl 3,4-di-$\underline{O}$-benzoyl-2-deoxy-1-thio-α/β-arabinohexopyranoside (22)

A solution of **21** (0.26 g, 0.44 mmol) and 2-mercaptopyridine (0.072 g, 0.68 mmol) and p-TSA (0.024 g, 0.14 mmol) in dry dichloromethane (4 ml) was heated at 50°C for 17 h, during which t.l.c. (pet.ether:ethyl acetate; 1:1) showed a slower moving spot. It was worked up as described for compound **15**. Column chromatography of the crude gave **22** (0.24 g, 78%) as a syrup.

^{1}H-nmr (300 MHz): (α/β mixture), δ 1.0 (d, 3H, $J_{5',6'}$=6.3, C-6' Me), 1.99, 2.01 (s, 6H, 2xOCOCH$_3$), 1.5-5.6 (m, 13H, H-1',2,2,2',2',3,3',4,4',5,5', 6,6), 5.7 (dd, 1H, $J_{1,2a}$=13.2, $J_{1,2e}$=2.0, H-1, β compound), 6.52 (dd, 1H, $J_{1,2_a}$=6.0, H-1,α-compound), 7.05-8.5 (m, 14H, Ph, Spy).

Analysis calcd. for $C_{35}H_{37}NO_{11}S$: C, 61.84; H, 5.49. Found: C, 61.82; H, 5.51%.

$\underline{O}$-(3",4"-Di-$\underline{O}$-acetyl-2",6"-dideoxy-α-L-arabinohexopyranosyl)-(1 → 6)-(3',4'-di-$\underline{O}$-benzoyl-2'-deoxy-α-D-arabinohexopyranosyl)(1 → 6)-1,2:3,4-di-$\underline{O}$-isopropylidine-α-D-galactopyranoside (23)

Saccharide coupling of **22** (0.28 g, 0.4 mmol), sugar alcohol **18** (0.16 g, 0.44 mmol) for 24 h, afforded the 2-deoxy trisaccharide **23** (0.21

g, 62%) as a syrup after column chromatographic purification (SiO_2 pet. ether:ethyl acetate; 2:1).

$[\alpha]_D^{25}$ -53.2° (c 1.0, $CHCl_3$).

^{1}H-nmr (300 MHz): δ1.1 (d, 3H, $J_{5'',6''}$=6.2, H-6''), 1.6x2 (s, 12H, 2x:CMe_2), 1.75 (ddd, 1H, $J_{1',2'_a}$=3.6, $J_{2'_a,3'}$=11.67, $J_{2',2'_{gem}}$=13.0, H-2'$_{ax}$), 2.0 (m,1H, buried under acetate signals, H-2''$_{ax}$), 1.99,2.02(2s, 6H, 2xOCOCH_3), 2.3 (ddd, 1H, $J_{2'_e,3'}$=5.3, H-2'$_{eq}$), 2.5 (ddd, 1H, $J_{2''_e,3''}$=5.3, H-2''$_{eq}$), 3.5-4.75 (m, 12H, H-2,3,4,4',4'',5,5',5'',6,6,6',6'), 4.8 (brd*, 1H, H-1'), 5.1 (brd*, 1H, H-1''), 5.3-5.7 (m, 3H, H-1,3',3''), 7.3-7.95 (m, 10H, aromatic).

(*, **, ***=Assignments may be reversed).

^{13}C-nmr (75 MHz): δ 17.6, 20.6, 20.8 (3q, C-6, 2xOCO<u>C</u>H_3), 24.4, 24.8, 25.8, 26.0 (4q, 2x:C(<u>C</u>H_3)$_2$), 34.8, 35.0 (2t, C-2',2''), 65.4, 66.1x2, 68.8, 69.5, 69.8, 70.5x2, 70.8, 74.9 (10d, C-2,3,4,5,3',4',5',3'',4'',5''), 96.2, 97.0, 97.5 (d, C-1,C-1' and C-1''), 108.5, 109.1 (s, 2x:<u>C</u>Me_2), 128.0-133.0 (aromatic), 165.3, 165.6, 169.9, 170.0 (4s, 2xO<u>C</u>OCH_3, 2xO<u>C</u>OPh).

Analysis calcd. for $C_{42}H_{52}O_{17}$: C, 60.86; H, 6.32. Found: C, 60.84; H, 6.29%.

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CHAPTER 4

A NEW MILD METHOD FOR THE SYNTHESIS OF ESTERS AND BENZENE-THIOL ESTERS BY ACTIVATION OF PYRIDINE-2-THIOL OR BENZENE-THIAZOL-2-THIOL ESTERS BY METHYL IODIDE

4.1 INTRODUCTION

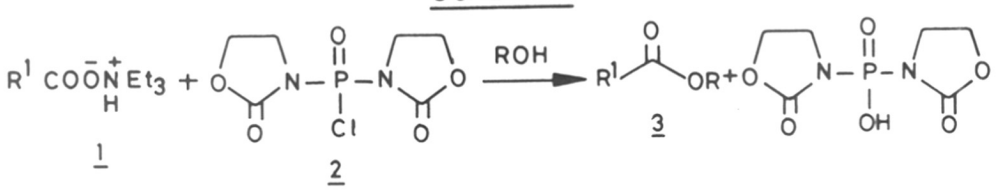
Formation of ester is one of the most well-established fundamental reaction which is widely used in organic synthesis. Although a number of useful methods have been presented to activate the carboxylic group toward facile esterification, only a few mild and efficient methods are available for the preparation of bulky esters and benzenethiol esters, specially by use of equimolar amounts of the reactants. In recent years thiol esters (2-pyridyl, alkyl and benzene) have gained importance in the synthesis of various natural products and thiophilic metal ions have been used for their activation. A great need still exists for efficient methods to prepare hindered esters in high yields under mild conditions. Our recent synthesis of complex carbohydrates indicated that pyridyl-2-thio group is a good leaving group when activated by methyl iodide, this result prompted us to extend its utility toward the synthesis of esters[1-5].

4.2 Synthesis of Esters: A Review

4.2.1 N,N'-Bis[2-oxo-3-oxazolidinylphosphorodiamide chloride as an activator

N,N'-Bis[2-oxo-3-oxazolidinyl]phosphorodiamide chloride **2** was used for the activation of carboxylic acids and subsequently for the preparation of esters and amides[6]. The activation mechanism assumed to consist of nucleophilic substituition at the phosphorous atom by the carboxylate ion **1** to give ester **3** and amide respectively (SCHEME 1).

SCHEME 1

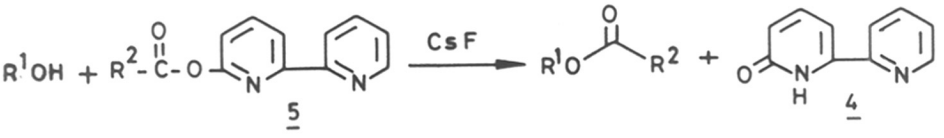


1 2 3

4.2.2 6-(2-Pyridyl)-2-pyridone as an activator

A method for selective acylation of hydroxyl groups using 6-(2-pyridyl)-2-pyridone (4) as a condensing agent, was developed by **Mukaiyama et al**[7]. The method involves, the preparation of acylating reagent **5** by the reaction of acylchlorides with 2,2'-bypyridyl-6-one **4** and triethylamine or by the treatment of carboxylic acids and **4** with 2-chloro-1-ethylpyridinium-tetrafluoroborate[8] and triethylamine. The activated ester **5** thus obtained was converted to an ester in presence of cesium fluoride in acetonitrile at room temperature (27-90% yield)[9-11] (SCHEME 2).

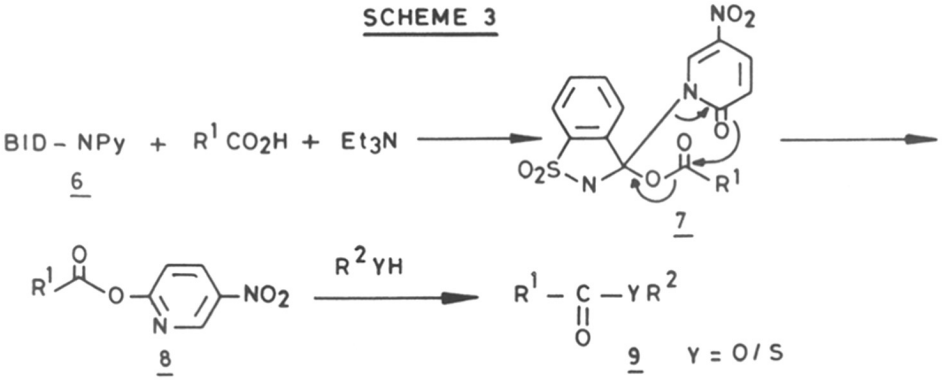
SCHEME 2



4.2.3 3-(5-Nitro-2-pyridon-1-yl)-1,2-benzoisothiazole 1,1-dioxide as an activator

An efficient method for the synthesis of esters and peptides has been developed by **Inomata et al**[12,13] using 3-(5-nitro-2-pyridon-1-yl) 1,2-benzoisothiazole 1,1-dioxide (BID-NPy) (**6**) as a condensing agent. Thus, reactions of **6** with acids and alcohols in presence of triethylamine in dichloromethane (SCHEME 3) leads to the formation of the activated

SCHEME 3

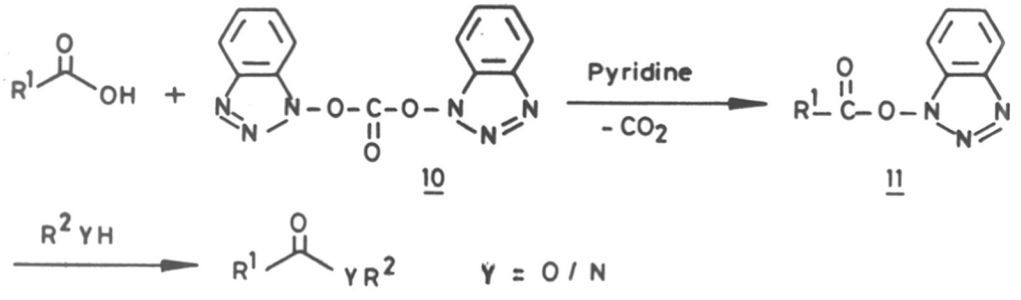


ester **8** through a cyclic transition state **7** presumably is followed by the attack of the nucleophile (R^2YH) to give the product **9.**

4.2.4 Carbonyl dibenzotriazole as an activator

Carbonyl dibenzotriazole (**10**) as a condensing agent was used by **Ueda et al**[14], for the preparation of esters, amides and dipeptides by the reaction of various nucleophiles at room temperature[14-16] (SCHEME 4).

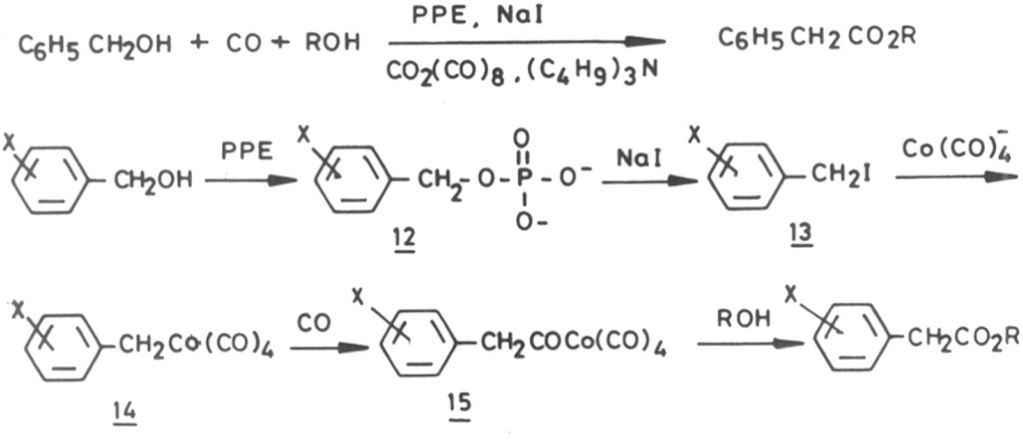
SCHEME 4



4.2.5 Ethylpolyphosphate as an activator

Benzyl alcohols were converted into the corresponding one carbon-homologated amides or esters in one pot by cobalt carbonyl catalyzed carbonylation in the presence of ethylpolyphosphate[17,18] (PPE) and sodium iodide[19] (SCHEME 5).

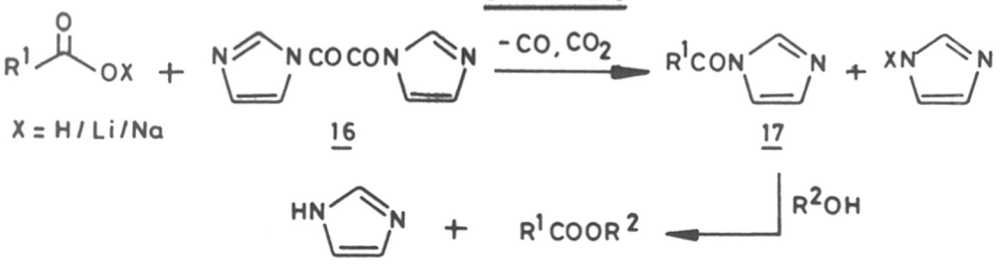
SCHEME 5



4.2.6 1,1'-Oxalyldiimidazole as an activator

Reaction of 1,1'-oxalyldiimidazole **16** and 1 equivalent of carboxylic acids or its Li, Na salt, proceeded in chloroform or dichloromethane[20] at 25-45°C to give pure 1-acylimidazoles **17**[21-23] with the removal of CO and CO_2. Then the imidazole **17** was transformed into esters upon treatment with alcohol (SCHEME 6).

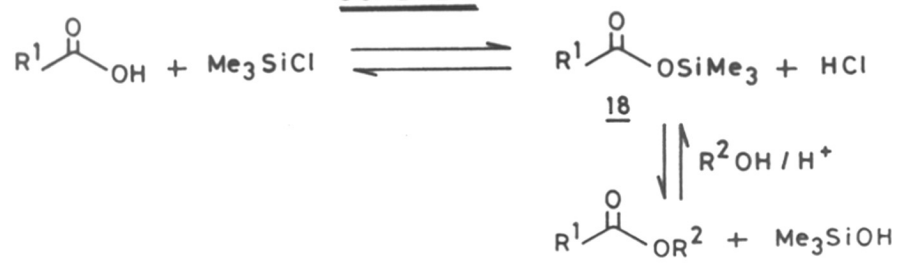
SCHEME 6



4.2.7 Trimethylsilyl chloride as an activator

Chlorotrimethylsilane was used both as acid catalyst and dehydrating agent for the preparation of carboxylic esters[24]. The carboxylic acid was first converted to the silyl ester **18**, which on displacement of the silanol with the alcohol then gave the ester (SCHEME 7).

SCHEME 7

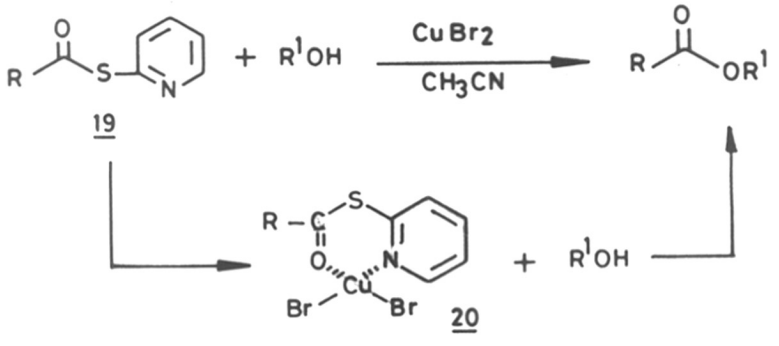


4.2.8 2-Mercaptopyridine or 2-thiopyridylchloroformate as an activator

Sterically hindered esters were prepared from S-2-pyridylthioates in good to excellent yields in presence of $CuBr_2$ in acetonitrole[25]. Carboxylic acids were converted to 2-pyridyl esters[26,27] and S-2-pyridyl thioa-

tes[28-30]. S-2-Pyridyl esters are essentially prepared in quantitative yields by two methods, (a) reaction of carboxylic acid chlorides with 2-mercaptopyridine in the presence of triethylamine, (b) or by reaction of carboxylic acids with 2-thiopyridyl chloroformate in the presence of triethylamine[31]. The activated esters **19** were then converted to their corresponding esters by reaction with alcohols by use of $CuBr_2$ in acetonitrile, at room temperature and at 80°C (SCHEME 8).

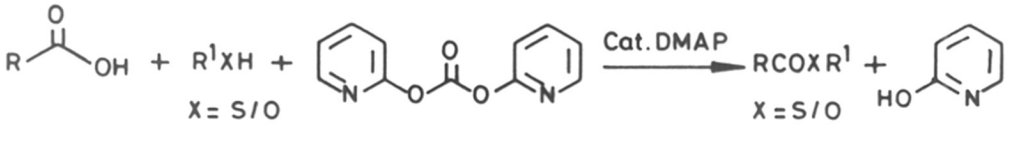
SCHEME 8



4.2.9 Di-2-pyridylcarbonate as an activator

Di-2-pyridyl carbonate (2-DPC) **21** as a coupling agent for the direct esterification of carboxylic acid was used[32-34]. This method reaches a limit in case of aromatic acids where substantial amount of 2-pyridyl esters and their corresponding anhydrides are also isolated (SCHEME 9).

SCHEME 9

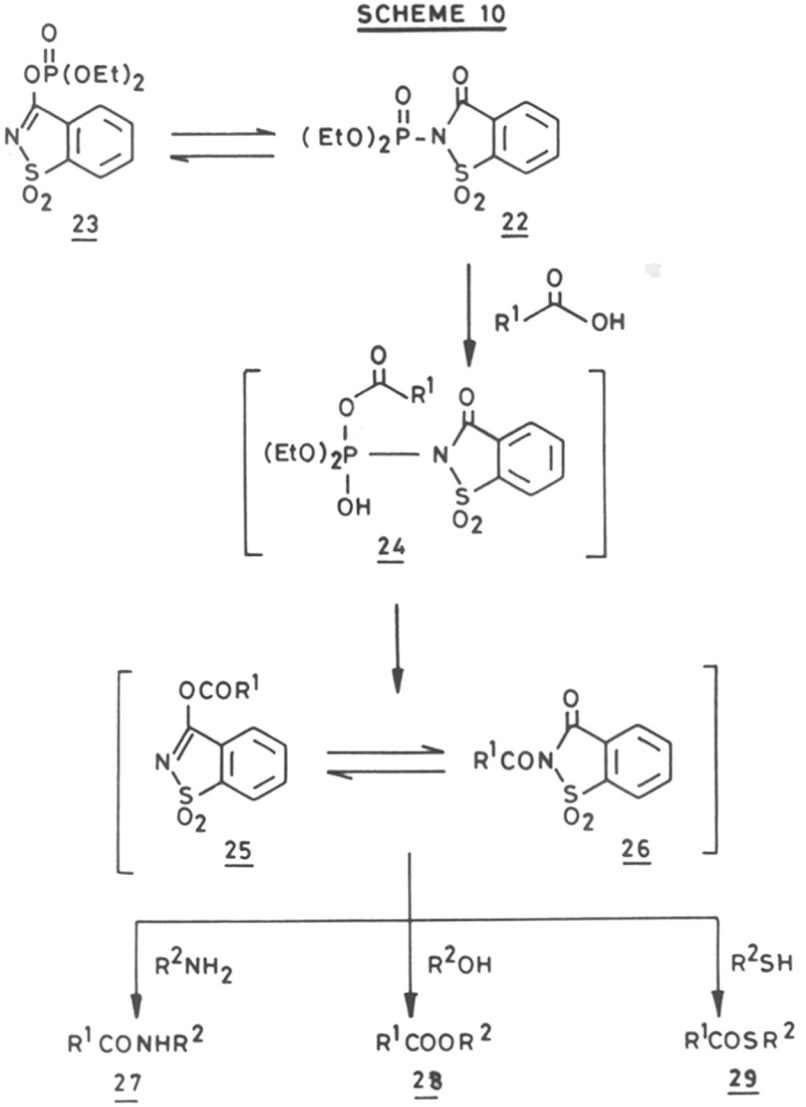


4.2.10 Diethyl 2-(3-oxo-2,3-dihydro-1,2-benzisosulfonaxolyl)phosphate as an activator

A variety of amines, active hydroxyl amines thiols and acids were converted to amides **26**, esters **27** and thioesters **28** in good yield by the

use of diethyl 2-(3-oxo-2,3-dihydro-1,2-benzisosulfonazolyl)phosphate (DEBP) (22) as an activating agent[35] on reaction with acids (SCHEME 10).

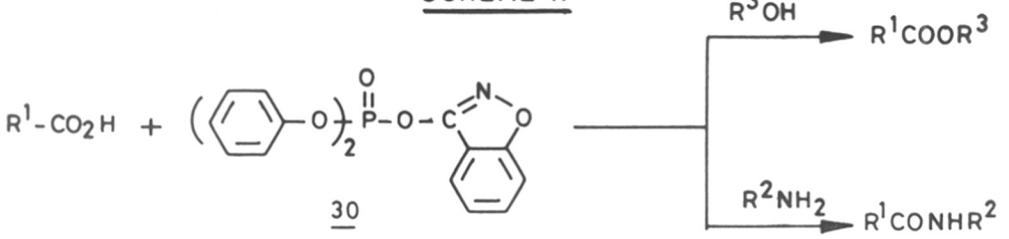
SCHEME 10



4.2.11 1,2-Benzisoxazol-3-yl-diphenylphosphate as an activator

Carboxylic acid esters and amides were prepared by the reaction of carboxylic acids with alcohols and amines in presence of 1,2-benzisoxazol-3-yl-diphenylphosphate (**30**) as an activator[36] (SCHEME 11).

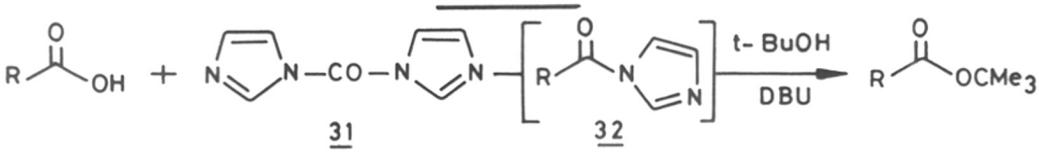
SCHEME 11



4.2.12 N,N'-Carbonyldiimidazole as an activator

Carboxylic acids were treated with N,N'-carbonyldiimidazole (**31**) to give an active N-acylimidazole **32** which was then converted to the corresponding tert-butyl ester in presence of DBU[37] (SCHEME 12).

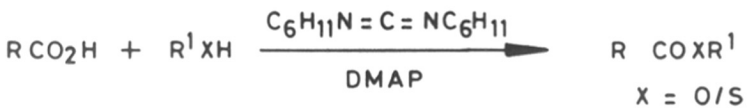
SCHEME 12



4.2.13 Dicyclohexylcarbodiimide as an activator

Dicyclohexylcarbodiimide (DCC) activated esterification of carboxylic acids with alcohols and thiols in presence of 3-10% of DMAP was developed by **Wolfgang**[38] (SCHEME 13). However, the possibility of synthesizing tert-butyl esters reaches a limit with more bulky, i.e. sterically hindered carboxylic acids.

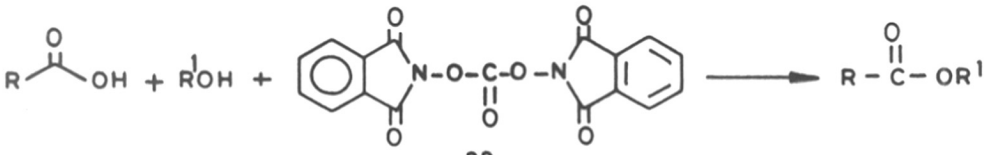
SCHEME 13



4.2.14 Diphthalimidocarbonate as an activator

Diphthalimido carbonate (DPC) (33) was considered as condensing reagent for the preparation of carboxylic esters[39,40]. DPC 33 would exhibit appreciable reactivity toward carboxyl groups (SCHEME 14).

SCHEME 14

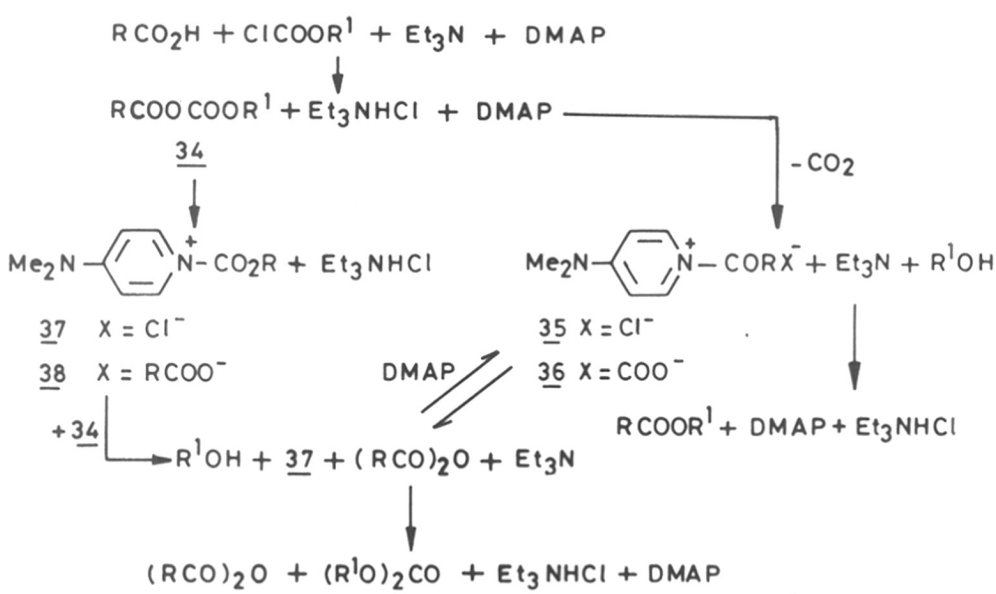


33

4.2.15 4-(Dimethylamino)pyridine as an activator

Simple aliphatic carboxylic esters were prepared in high yields by the reaction of acids with equimolar amounts of chloroformates[42] and triethylamine in the presence of a catalytic amount of 4-(dimethylamino)pyridine[41]. However, the use of alkylchloroformates led to the formation of the acid anhydride and the carbonate and byproducts[43,27b]. They have found that increasing the amount of DMAP drastically decreased the formation of acid anhydride and carbonate. The reaction mechanism has not been fully elucidated (SCHEME 15).

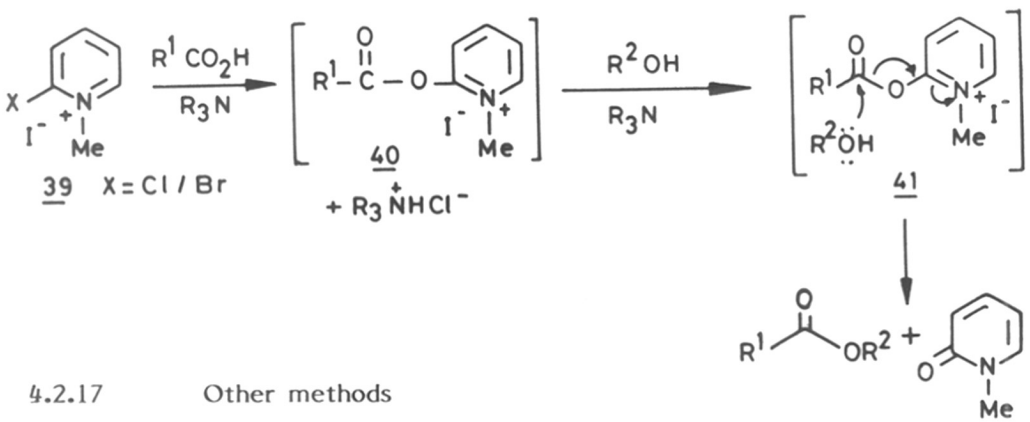
SCHEME 15



4.2.16 2-Halo-1-methylpyridinium iodide as an activator

2-Halopyridinium salts were proposed as condensing agents by **Mukaiyama** for the preparation of carboxylic esters from the reaction of equimolar amounts of free carboxylic acids and alcohols[44-46] (SCHEME 16). 2-Acyloxy-1-methylpyridinium iodide (**40**) an active acylating intermediate, was produced by nucleophilic attack of carboxylate ion on 2-chloro or 2-bromo-1-methylpyridinium iodide (**39**). The intermediate **40** on reaction with several alcohols gives rise to esters .

SCHEME 16



4.2.17 Other methods

Phosphorous pentoxide as an activator was used for the preparation of aliphatic esters, where in copper sulphate has been used as water scavenger and also as an indicator[47].

The preceeding review deliniates the various attractive methods applied for the conversion of carboxylic acids into their corresponding esters, amides, thiol esters. Among the reported esterification methods most of them are not of general applicability specially for the preparation of bulky esters and benzenethiol esters. A great need still exists for efficient method to prepare hindered esters in high yields under mild conditions.

The preparation of the most of the activated esters itself involve either acidchlorides or their corresponding lithium or sodium salts as

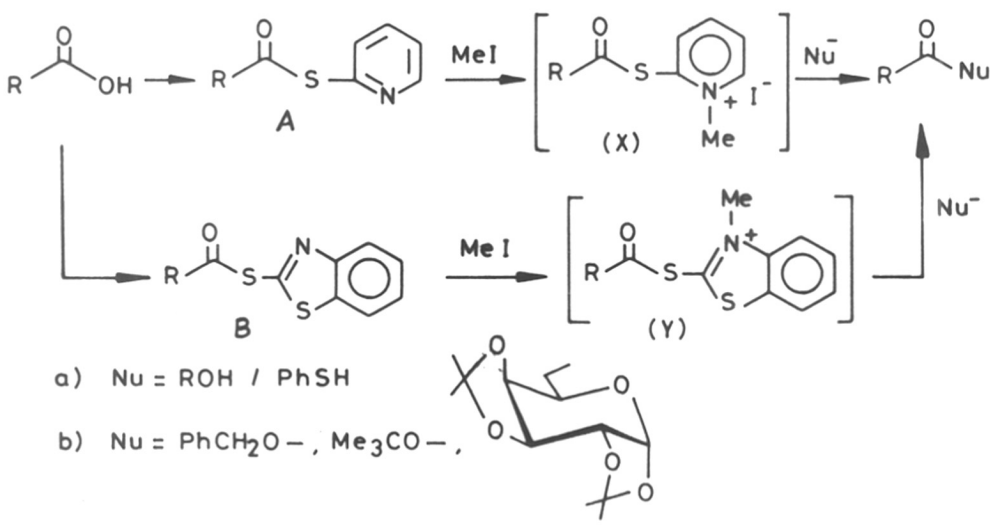
starting materials. The reagents used for the preparation of activated esters are hardly stable and can be stored for a little time under drastic conditions. The preparation of reagents involve the use of toxic reagents such as carbonylchloride. And hence, there is scope to develop new methods for the synthesis of carboxylic esters under mild conditions that will be of general applicability.

4.3. Results and Discussion

This chapter describes a new rapid and mild method for the synthesis of sterically hindered esters and benzenethiol esters. This method has originated based on our methyl iodide activation procedure developed for performing glycosidations[48].

According to this method carboxylic acids were converted to their corresponding 2-pyridyl-thio esters (X) or 2-mercaptobenzothiazolyl esters (Y), they on subsequent activation by methyl iodide underwent facile one-pot nucleophilic displacement (ROH or PhSH) to yield the corresponding esters (a) and benzene thiol esters (b) in good yield (SCHEME 17). Thus phenyl acetic acid on treatment with 2,2'-dibenzothiazolyldisulphide and benzyl alcohol in presence of methyl iodide for 2 h to obtain benzyl phenyl acetate (1) in 97% yield. The ester is characterised by the appearance

SCHEME 17



of absorption at 1735 cm^{-1} in its IR. The ^{1}H-nmr showed a singlet at δ 5.1 (2H) arising from methylene group of benzyl alcohol. To study the efficiency of this method for the preparation of bulky esters it (X) was subjected to reaction with sterically hindered nucleophile such as tert-butyl alcohol. Thus, tert-butylphenyl acetate (**2**) was obtained (4 h) at room temperature in 79% yield. The appearance of a singlet at δ 1.5 (9H) (^{1}H-nmr) was attributed to tert-butyl group. The IR spectrum showed an absorption at 1720 cm^{-1}, which was consistent with the assigned structure.

In an estirification method developed by A Benerji and coworkers[47], aliphatic acids, secondary aliphatic acids, secondary and tertiary alcohols could not esterified. But by our methodology such aromatic and secondary aliphatic esters also were obtained in good yields. Thus, O-methyl benzoic acid was esterified in presence of benzyl alcohol and tert-butyl alcohol to yield their corresponding benzyl O-methyl benzoate (**3**) (96% yield) and tert-butyl O-methyl benzoate (**4**) (75% yield). The esters were characterised from their IR spectra.

Similarly, long chain unsaturated aliphatic acids were also esterified by this method. Thus, 10-undecenoic acid was converted to its ester cleanly on reaction with benzyl alcohol and tert-butyl alcohol to yield the corresponding benzyl (**5**) tert-butyl (**6**) esters within 2 and 6 h in 85% and 68% yields respectively.

This method was then applied to the esterification of secondary aliphatic acids. S-2-Benzothiozyl-2-(4-isobutylphenyl)propionate (SCHEME 17) in presence of methyl iodide gave its corresponding benzyl ester **7** in 2.5 h in 89% yield. Similarly, the S-2 benzothiozyl-2-(4-isobutylphenyl)-propianate could be converted to its corresponding tert-butyl ester **8** in 79% yield in 3.5 h. The formation of two esters was confirmed by the

appearance of sharp bands at 1735 cm^{-1} and 1730 cm^{-1} respectively in their IR spectra.

To test the generality of this method, nucleophiles having acid sensitive groups were also subjected to esterification. S-2-Benzothiozolyl-thiobenzoate was condensed with 1,2:3,4-di-O-isopropylidene-α -D-galacto-pyranoside **3** (20 h) to obtain 6-O-benzoyl-1,2:3,4-di-O-isopropylidene-α-D-galactopyranoside (**9**) in 86% yield, $[\alpha]_D$ +54° (c 1.0, $CHCl_3$). Similarly, 6-O-acetyl-1,2:3,4-di-O-isopropylidene- α -D-galactopyranoside (**10**) was also obtained in 95% yield in 22 h, $[\alpha]_D^{25}$-44° (c 1.0, $CHCl_3$). The protecting groups were intact after esterification. Formation of compounds **9** and **10** was also confirmed by their ^{1}H-nmr spectra.

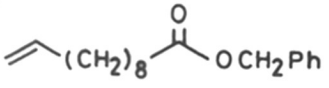
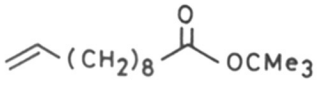
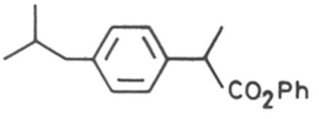
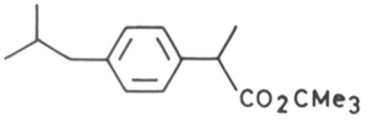
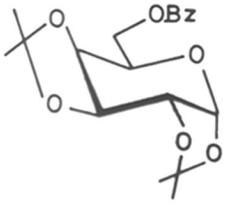
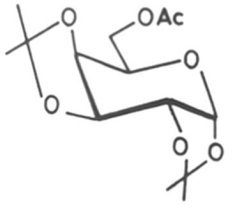
Then the attention was drawn towards the synthesis of thiol esters by use of nucleophile such as thiophenol (SCHEME 17). Thus by this methodology several thiol esters were made in good to excellent yields. Thus, O-methyl benzoic acid was conveniently converted to its corresponding S-phenyl O-methyl benzoate (**11**) in 75% yield in 11 h. The formation of thioester was confirmed by the appearance of a strong absorption at 1670 cm^{-1} in its IR spectrum which is characteristic of thio esters.

Similarly S-phenyl 10-undecenoate (**12**) and S-phenyl phenyl acetate (**13**) were obtained in 79% and 84% yields respectively and were characterised by the appearance of the strong absorptions at 1700, and 1710 cm^{-1} in their IR spectra.

Formation of thiol esters of base sensitive protected amino acids was also attempted. N-carbobenzyloxy phenylalanine was converted to thiol ester (**14**) in 24 h in 74% yield. Similarly, S-phenyl-p-isobutylbenzoate (**15**) and S-phenyl-2-(4-isobutylphenyl)-propionate (**16**) respectively were obtained 75% and 76% yields and were characterised from their IR and ^{1}H-nmr spectra.

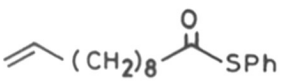
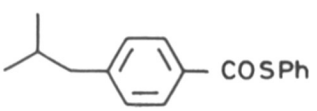
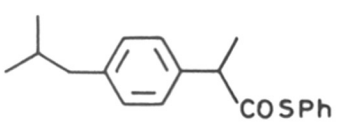
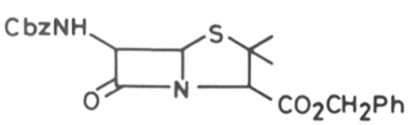
TABLE 1

ESTERIFICATION OF CARBOXYLIC ACIDS WITH NUCLEOPHILES

Entry	Ester	Time (hr)	Isolated yield
1	$PhCH_2CO_2CH_2Ph$	2	97
2	$PhCH_2CO_2CMe_3$	4	79
3	$O\text{-}Me.C_6H_4CO_2CH_2Ph$	3	96
4	$O\text{-}Me\text{-}C_6H_4CO_2CMe_3$	24	75
5		2	85
6		6	68
7		2.5	89
8		3.5	74
9		20	86
10		22	95

CONTD.

TABLE 1 CONTD.

Entry	Ester	Time (hr)	Isolated yield
11	O-Me. C_6H_4COSPh	11	75
12		3.5	79
13	$PhCH_2COSPh$	3	84
14	PhCH(NHCbz) COSPh	34	74
15		24	75
16		3	76
17		4	68

Finally, the extremely acid and base sensitive pencilline derivative was also esterified with benzyl alcohol to give **17** in 4 h in 58% yield. Its formation was confirmed by the appearance of a absorption at 1730 cm^{-1}.

During these esterification reactions, formation of alkyl aryliodides and anhydrides was not observed which are often observed during the esterification reactions.

The mechanism for the formation of esters involves electrophilic attack of methyl iodide on 'N' of S-2-pyridyl (A) or S-2-benzothiozolyl ester (B) to give a highly reactive quaternary ammonium intermediate (X/Y) which undergoes a fast nucleophilic displacement to give the required ester.

In conclusion, this new, mild and general esterification method complements the other known methods, and has advantages over the thiophilic metal ion promoted esterification in the sense that esters can be prepared by this method.

4.4 EXPERIMENTAL

Benzyl phenyl acetate (1)

A suspension of phenyl acetic acid (250 mg, 1.84 mmol) triphenylphosphine (580 mg, 2.2 mmol), 2,2'-dibenzothiazolyldisulphide (730 mg, 2.2 mmol) and 4A molecular sieves (250 mg) in dry methylene chloride (20 ml) was stirred at room tmeperature for 30 min. Then benzyl alcohol (200 mg, 1.2 mmol) and methyl iodide (1.05 mg, 7.36 mmol) in 1 ml CH_2Cl_2 were added and stirring continued at room temperature for 2 h. When the t.l.c. showed completion of reaction, solvent was removed and the residue chromatographed (SiO_2) to obtain **1** (400 mg, 97%) as a colorless liquid.

^{1}H-nmr (80 MHz): δ 3.62 (2H, s, -CO-$\underline{CH_2}$-Ph), 5.1 (2H, s,-O-$\underline{CH_2}$, Ph), 7.25 (10H, 2xPh).

^{13}C-nmr (90 MHz): δ 41.4 (t, Ph-CH_2-C=O), 66.6 (t, Ph$\underline{CH_2}$-O), 121-136 (Ph), 171.2 (s, C=O).

IR: (Neat) (cm^{-1}): 3020 (m), 1735 (s), 1490 (m), 1450 (m), 1425 (m), 1240 (m), 1150 (s), 1010 (m), 700 (m).

t-Butylphenylacetate (2)

A suspension of phenyl acetic acid (300 mg, 2.2 mmol) triphenylphosphine (690 mg, 2.64 mmol), 2,2'-dibenzothiazolyldisulphide (880 mg, 2.64 mmol) and 4A molecular sieves (300 mg) was reacted with tert-butylalcohol (162 mg, 2.2 mmol) and methyl iodide (1.05 g, 7.36 mmol) as described above. Chromatography of the residue gave **2** (151 mg, 79%).

^{1}H-nmr (90 MHz): δ 1.5 (9H, s, $(CH_3)_3$), 3.5 (2H, s, Ph$\underline{CH_2}$), 7.25-8.0 (5H, m, Ph-H).

IR (Neat): 2800 (m), 1720 (s), 1000 (s).

Benzyl O-methylbenzoate (3)

A suspension of O-methylbenzoic acid (250 mg, 1.84 mmol), triphenylphosphine (580 mg, 2.2 mmol), 2,2'-benzothiazolyldisulphide (730 mg, 2.2 mmol) and 4A molecular sieves (200 mg) was treated followed by addition of benzyl alcohol (198 mg, 1.84 mmol) and methyl iodide (1.05 g, 7.36 mmol) and worked up as described above. Column chromatography of the residue afforded **3** (400 mg, 96%) as a syrup.

^{1}H-nmr (80 MHz): δ 2.5 (s, 3H, CH_3), 5.3 (2H, s, Ph$\underline{CH_2}$-O-), 7.35-7.9 (9H, m, Ph).

^{13}C-nmr (90 MHz): δ21.83 (q, CH_3), 66.6 (t, Ph$\underline{CH_2}$-O-), 121.2-140.5 (Ph), 167.4 (s, $\underline{C}$=O).

IR (neat):

3105 (m), 2940 (m), 1720 (s), 1600 (w), 1460 (m), 1290 (s), 1255 (s), 1150 (m), 1080 (s), 740 (s), 700 (m).

tert-Butyl O-methylbenzoate (4)

A suspension of O-methylbenzoic acid (250 mg, 1.84 mmol), triphenylphosphine (580 mg, 2.2 mmol) 2,2'-benzothiazolyldisulphide (730 mg, 2.2 mmol) and 4A molecular sieves (250 mg) was treated followed by addition of tert-butylalcohol (180 mg, 1.89 mmol) and methyl iodide (1.05 g, 7.36 mmol) and worked up as described above. Column chromatography of the residue afforded **4** (265 mg, 75%) as a syrup.

^{1}H-nmr (80 MHz): δ 1.55 (9H, s, tert-butyl), 2.5 (3H, s, CH_3), 7.2 (3H, m, Ph), 7.7 (1H, m, Ph).

^{13}C-nmr (90 MHz): δ 21.35 (q, CH_3), 27.97 (q, tert-butyl), 80.5 (s, tert-butyl), 125.2-132.1 (Ph), 167.0 (s, $\underline{C}$=O).

IR: (Neat): 2960 (s), 2920 (m), 1710 (s), 1600 (w), 1470 (m), 1450 (m), 1360 (s), 1300 (s), 1265 (s), 1170 (s), 1140 (s), 1080 (s), 1050 (m), 1040 (m), 850 (m), 740 (s).

Benzyl 10-undecenoate (5)

A suspension of 10-undecenoic acid (150 mg, 0.82 mmol), triphenylphosphine (260 mg, 0.98 mmol), 2,2'-benzothiazolyldisulphide (327 mg, 0.98 mmol) and 4A molecular sieves (150 mg) was reacted followed by addition of benzyl alcohol (89 mg, 0.82 mmol) and methyl iodide (470 mg, 3.28 mmol) and worked up as described above. Column chromatography of the residue afforded **5** (200 mg, 85%) as a syrup.

^{1}H-nmr (80 MHz): δ 1.28 (12H, s, $(-CH_2-)_6$), 2.28 (2H, d, $=C-\underline{CH_2}-$), 2.8 (1H, d), 4.8 (2H, m), 5.05 (2H, s, $Ph\underline{CH_2}$), 5.5-6.0 (1H, m), 7.36 (5H, s, Ph).

IR: ($CHCl_3$): 2920 (s), 2840 (s), 1735 (s), 1635 (m), 1490 (m), 1450 (s), 1425 (s), 1375 (m), 1235 (m), 1160 (s), 990 (s), 910 (m), 755 (s), 700 (s).

t-Butyl 10-undecenoate (6)

A suspension of 10-undecenoic acid (250 mg, 1.4 mmol), triphenylphosphine (427 mg, 1.63 mmol), 2,2'-benzothiazolyl disulphide (541 mg, 1.63 mmol) and 4A molecular sieves (250 mg) was reacted, followed by addition of tert-butylalcohol (100 mg, 1.3 mmol), and methyl iodide (772 mg, 5.3 mmol) and worked up as described above. Column chromatography of the residue afforded **6** (135 mg, 68%) as a syrup.

^{1}H-nmr (80 MHz): δ 1.3 (12 H, $(CH_2)_6$), 1.45 (9H, s, tert-butyl), 1.6-2.1 [(2H, $CH_2=CH-\underline{CH_2}$), (2H,$\underline{CH_2}-C=O$)], 4.85-5.05 (2H, $\underline{CH_2}=CH-$), 5.55-6.0 (1H, m, $CH_2=\underline{CH}$).

IR($CHCl_3$): 2960 (s), 2920 (s), 2840 (s), 1730 (s), 1640 (m), 1450 (m), 1390 (m), 1370 (s), 1255 (m), 1155 (s), 1000 (w), 920 (m), 860 (w).

Benzyl 2(4-isobutylphenyl)-propionate (7)

A suspension of 2(4-isobutylphenyl)-propionic acid (150 mg, 0.728 mmol), triphenylphosphine (230 mg, 0.88 mmol), 2,2'-benzothiazolyldisul-

phide (300 mg, 0.88 mmol) and 4A molecular sieves (150 mg) was reacted, followed by addition of benzyl alcohol (80 mg, 0.728 mmol) and methyl iodide and worked up as described above. Column chromatography of the residue afforded **7** (190 mg, 89%) as a syrup.

^{1}H-nmr (80 MHz): δ 0.85 (6H, d, 2xCH_3), 1.45 (3H, d, CH_3), 5.05 (2H, s, Ph-$\underline{CH_2}$), 2.4 (2H, d, CH_2-), 3.7 (1H, m, CH), 7.1-7.2 (9H, m, Ph-H).

^{13}C-nmr (80 MHz): δ 18.27 (q, CH_3), 22.09 (q, CH_3), 29.85 (d, CH), 44.77 (t, CH_2), 44.88 (d, CH), 65.9 (t, Ph$\underline{CH_2}$-O-), 120.6 (Ph), 174.0 (s, -$\underline{C}$=O).

IR(Neat)(cm^{-1}): 2940 (s), 2850 (m), 1810 (w), 1755 (s), 1510 (m), 1460 (s), 1450 (s), 1430 (m), 1380 (m), 1240 (m), 1160 (s), 1075 (m), 1010 (m), 850 (m), 760 (s), 700 (s).

t-Butyl 2(4-isobutylphenyl)-propionate (8)

A suspension of 2(4-isobutylphenyl)-propionic acid (150 mg, 0.728 mmol), triphenylphosphine (230 mg, 0.88 mmol), 2,2'-dibenzothiazolyldisulphide (300 mg, 0.88 mmol) and molecular sieves 4A (150 mg) was reacted, followed by addition of tert-butylalcohol (54 mg, 0.72 mmol) and methyl iodide (420 mg, 2.92 mmol), and worked up as described above. Column chromatography of the resulting residue afforded **8** (144 mg, 74%), as a syrup.

^{1}H-nmr (90 MHz): δ 0.9 (6H, d, 2xCH_3), 1.4 (9H, s, tert-butyl), 1.5 (3H, d, CH_3), 1.85 (1H, m, CH), 2.4 (2H, d, CH_2), 3.55 (1H, q, CH), 7.1 (4H, m, Ph).

IR: (Neat) (cm^{-1}): 2940 (s), 1510 (m), 1455 (s), 1370 (s), 1335 (m), 1255 (s), 1150 (s), 1095 (m), 1075 (m), 1060 (m), 1025 (m), 900 (w), 855 (s), 765 (m).

6-$\underline{O}$-Benzoyl-1,2:3,4-di-$\underline{O}$-isopropylidene-α-D-galactopyranoside (9)

A suspension of benzoic acid (100 mg, 0.762 mmol), triphenylphos-

phine (240 mg, 0.914 mmol), 2,2'-dibenzothiazolyldisulphide (300 mg, 0.914 mmol) and molecular sieves 4A (100 mg) was reacted, followed by addition of 1,2:3,4-di-O-isopropylidene galactose (100 mg, 0.381 mmol) and worked up as described above. Column chromatography of the residue afforded **9** (120 mg, 86%) as a syrup, $[\alpha]_D^{25}$ +54° (c 1.00, $CHCl_3$).

^{1}H-nmr (60 MHz): δ 1.3 (12H, 4xCH_3), 4.15-4.7 (m, 9H), 5.5 (d, 1H, H-1), 7.6 (5H, m, Ph).

6-O-Acetyl-1,2:3,4-di-O-isopropylidene-α-D-galactopyranoside (10)

A suspension of acetic acid (100 mg, 1.4 mmol), triphenylphosphine (460 mg, 1.8 mmol), 2,2'-dibenzothiazolyldisulphide (600 mg, 1.8 mmol) and molecular sieves 4A (100 mg) was reacted, followed by addition of 1,2:3,4-di-isopropylidene-α-D-galactopyranoside (200 mg, 0.7 mmol) and methyl iodide and worked up as described above. Column chromatography of the resulting residue afforded **10** (172 mg, 86%) as a syrup $[\ ]_D$ -44° (c 1.0, $CHCl_3$).

^{1}H-nmr (60 MHz): δ1.3 (12H, s, 4xCH_3), 2.8 (3H, s, OAc), 3.95-4.5 (6H, m), 5.5 (1H, d, H-1).

O-Methyl phenylthiobenzoate (11)

A suspension of O-methylbenzoic acid (200 mg, 1.4 mmol), triphenylphosphine (480 mg, 1.7 mmol), 2,2'-dibenzothiazolyldisulphide (600 mg, 1.7 mmol) and molecular sieves 4A (200 mg) was reacted, followed by addition of thiphenol (160 mg, 1.4 mmol) and methyl iodide (840 mg, 5.8 mmol) and worked up as described above. Column chromatography of the resulting residue afforded **11** (248 mg, 75%) as a syrup.

^{1}H-nmr (60 MHz): δ2.4 (3H, s, CH_3), 7.4 (10H, m, Ph-H).

IR: (neat): 3030 (m), 2900 (m), 1670 (s), 1590 (m), 1575 (m), 1470 (m),

1430 (s), 1240 (s), 1140 (s), 1085 (m), 1060 (m), 1020 (m), 990 (m), 950 (s), 930 (s), 820 (s), 780 (s), 740 (s), 680 (s).

Thiophenyl 10-undecenoate (12)

A suspension of 10-undecenoic acid (250 mg, 1.35 mmol), triphenylphosphine (430 mg, 1.63 mmol), 2,2'-dibenzothiazolyldisulphide (540 mg, 1.63 mmol) and 4A molecular sieves (250 mg) was treated, followed by addition of thiphenol (148 mg, 1.35 mmol) and methyl iodide (760 mg, 5.4 mmol) and worked up as described above. Column chromatography of the residue afforded **12** (296 mg, 79%), as a syrup.

^{1}H-nmr (90 MHz): δ 1.35 (9H), 2.6 (2H, t-CO$\underline{CH_2}$), 4.9 (m, 2H, ethylenic), 5.56-6.05 (1H, m), 7.3 (5H, s, Ph).

IR: (cm^{-1}, neat): 2900 (s), 2830 (s), 1700 (s), 1630 (m), 1470 (m), 1430 (m), 1020 (m), 900 (m), 740 (s), 680 (s).

Thiophenyl phenylacetate (13)

A suspension of phenyl acetic acid (300 mg, 2.2 mmol), triphenylphosphine (680 mg, 2.6 mmol), 2,2'-dibenzothiazolyldisulphide (860 mg, 2.6 mmol) and moelcular sieves 4A (300 mg) was reacted, followed by addition of thiphenol (240 mg,. 2.2 mmol), methyl iodide (1.24 g, 8.8 mmol) and worked up as described above. Column chromatography of the resulting residue afforded **13** (210 mg, 84%), as a syrup.

^{1}H-nmr (60 MHz): δ3.8 (2H, s, CH_2), 7.3 (5H, s, Ph), 7.5 (5H, s, Ph).

IR(cm^{-1}, $CHCl_3$): 3000 (s), 2875 (s), 1710 (s), 1625 (m).

N-Carbobenzyloxythiophenylphenylalanate (14)

A suspension of N-carbobenzyloxyphenylalanine (200 mg, 0.72 mmol), triphenylphosphine (220 mg, 0.84 mmol), 2,2'-dibenzothiazolyldisulphide (280 mg, 0.84 mmol), 4A molecular sieves (200 mg) was treated, followed by addition of thiophenol (79 mg, 0.72 mmol) and methyl iodide (400 mg,

2.88 mmol) and worked up as described as above. Column chromatography of the resulting residue afforded **14** (195 mg, 74%).

^{1}H-nmr (80 MHz): δ 2.8 (1H, s, CH), 5.15 (2H, s, $\underline{OCH_2}Ph$), 7.27 (15H, m, Ph-H).

IR: (cm^{-1}, $CHCl_3$): 3320 (s), 3020 (m), 2920 (m), 1720 (s), 1680 (s), 1580 (m), 1530 (s), 1490 (s), 1450 (s), 1330 (m), 1310 (m), 1240 (s), 1150 (m), 1040 (s).

Thiophenyl (4-isobutyl)benzoate (15)

4-Isobutylbenzoic acid (200 mg, 1.00 mmol), triphenylphosphine (360 mg, 1.2 mmol), 2,2'-dibenzothiazolyldisulphide (460 mg, 1.2 mmol) and molecular sieves (200 mg) was reacted followed by addition of thiophenol (120 mg, 1.0 mmol) and methyl iodide (640 mg, 4.5 mmol) and workedup as described above. Column chromatography of the resulting residue afforded **15** (225 mg, 75%) as a syrup.

^{1}H-nmr (60 MHz): δ0.9 (6H, d, Me_2), 1.9 (1H, m, CH), 2.5 (2H, d, -CH_2Ph), 7.2 (6H, m, Ph), 7.8 (3H, m, Ph-H).

Thiophenyl 2(4-isobutylphenyl)-propionate (16)

A suspension of 2(4-isobutylphenyl)-propionic acid (300 mg, 1.4 mmol), triphenylphosphine (460 mg, 1.7 mmol), 2,2'-dibenzothiazolyldisulphide (600 mg, 1.7 mmol) and 4A molecular sieves (300 mg) was reacted, followed by addition of thiophenol (160 mg, 1.4 mmol) and methyl iodide (840 mg, 5.8 mmol) and worked up as described above. Column chromatography of the resulting residue gave **16** (330 mg, 76%) as a syrup.

^{1}H-nmr (90 MHz): δ 0.8 (6H, d, 2xCH_3), 1.5 (3H, d, CH_3), 1.8 (1H, m, CH), 3.9 (1H, q, CH), 7.06-7.25 (9H, m, Ph).

IR(cm^{-1}, neat): 2930 (s), 2840 (s), 1695 (s), 1575 (m), 1500 (m), 1470 (s), 1460 (m), 1430 (s), 1300 (m), 1160 (m), 1115 (m), 1060 (m), 990 (s), 930 (s), 840 (m), 740 (s), 680 (s).

Benzyl-6-N-carbobenzyloxyaminopencillanate (17)

A suspension of 6-N-carbobenzyloxyaminopenillanic acid (200 mg, 0.56 mmol), triphenylphosphine (180 mg, 0.7 mmol), 2,2'-dibenzothiazolyl-disulphide (230 mg, 0.7 mmol) and 4A molecular sieves (200 mg) was reacted, followed by addition of benzyl alcohol (60 mg, 0.56 mmol) and methyl iodide (320 mg, 2.2 mmol) and worked up as described above. Column chromatography of the resulting residue gave **17** (170 mg, 68%).

^{1}H-nmr (90 MHz) : δ 1.11 (s, 3H), 1.70 (s, 3H), 4.74 (s, 1H), 5.11 (1H), 5.20, 5.31 (4H, 2 x Ph$\underline{C}H_2$-O-), 6.30 (1H), 7.2-7.77 (m, 10H, Ph), 7.81 (1H).

IR ($CHCl_3$) (cm^{-1}) : 3412, 1804, 1755, 1673, 1614.

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