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Approach to the synthesis of herbicidins

Das, Kajal Kanti, Ph.D.

City University of New York, 1993

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Approach to The Synthesis
of
Herbicidins

by

Kajal Kanti Das

A dissertation submitted to the Graduate Faculty in Chemistry in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York.

1993

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This manuscript has been read and accepted for the Graduate Faculty in Chemistry in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

27th Aug. 1993
Date

Chair of Examining Committee

Sept. 21, 1993
Date

Executive Officer

Supervisory Committee

The City University of New York

ABSTRACT

Approach to The Synthesis of Herbicidins

by

Kajal Kanti Das

Advisor: Professor Vernon G. S. Box

The Herbicidins are structurally intriguing antibiotics which show remarkable biological activity. We have tried to develop a synthetic route to these antibiotics, based on the use of glucose as a chiral synthon, because the structures of these molecules can be regarded as being composed of glucose derived units.

The retrosynthetic plan called for the construction of one half of the Herbicidin molecule from a D-glucofuranosidic unit which would be converted into a suitable 6-deoxy-6-iodo-D-glucofuranoside. The other half of the Herbicidin molecule would be derived from a D-glucopyranosidic unit which would be transformed into a 3,6-anhydro-D-glucopyranoside and thence to the target synthon.

The pivalate ester was extensively used for the protection of hydroxyl groups and several interesting selective esterification reactions were encountered. The unusual migration of the pivalate group from C-2 to C-1 was also encountered during a hydrolysis of a 3,6-anhydro-D-glucopyranoside, and this reaction was of significant mechanistic interest.

The pivalate ester group was utilized in a number of synthetic intermediates, primarily because of its relatively low migratory aptitude, to its adjacent carbon atom, via the formation of highly crowded cyclic and neopentyl type intermediate. From our esterification reactions we were able to determine the relative reactivities of the hydroxyl groups of 4,6-O-anisylidene-D-glucopyranose and its derivatives.

This thesis is dedicated to my father *Late Hari Ranjan Das,* who was a mathematics teacher at the Hindu School; Calcutta, India. By his encouragement I took the initiative and was able to complete and to acquire the degree.

Acknowledgments

Endeavoring to fulfill my parent's wish in my life, I must acknowledge their guidance from my childhood to my B.Sc. (Ramkrishna Mission Boys' Home, Rahara) and M.Sc. (Calcutta University); and their encouraging me to acquire the highest degree in my life.

Professor Vernon Box's role as thesis advisor was a task well done. Indeed, his invaluable contribution to the scientific expansion of my intellect has indelibly reinforced the long standing truth that only a life that is lived for others is a life worthwhile. Ingenuity and resourcefulness are perhaps the two most important qualities that characterize this truly outstanding scientist, and the lessons learnt will certainly become a part of life's application.

The members of my thesis committee, Prof. Richard Frank, Prof. Robert Engel, and Prof. Neil Mckelvie (who replaced the late Prof. Donald L. Sloan Jr.), have not only provided practical advice, but have demonstrated confidence in my capabilities of realizing the set goals.

A sincere thank you is extended to the City College Department of Chemistry which provided the laboratory space, chemicals and financial assistance for this work. Mr. Ramsay Pal who was very helpful in the acquisition of all the mass spectra. Prof. Theodore Axenrod and his graduate students for taking ^{1}H n.m.r. spectra as well as 2D n.m.r.; Prof. Thomas Katz, of Columbia University for allowing me to take the optical rotations of some sugar compounds. Special thanks to Emeritus Professor Seymour Lieberman for providing me with an enormous quantity of laboratory equipments, as well as glassware.

Special Thanks to Hugo Schimatz not only for making scientific glassware but for lots of moral advice; Mr. Joseph La Rubio and Mr. Miguel Mieles (for supplying me valuable chemicals); Mr. Derek Quinlan (our electronic technician) for fixing electrical instruments; our departmental secretaries Ms. Joan Godette, Ms. Barbara Alexandar.

A very special thank to Mr. Curtis Rias, Director of Microcomputing and the "Faculty Resource Center", and all of it's employee namely Mr. Vernon C. Ballard, Jr.; Mr. Vernon Kellman; Mr. Marc Antony Lundy; and Ms. Jennifer Sassani for their restless help, not only allowing me to use computer, but also helping me to solve the problems related to using the computer.

A special thank to my beloved *Boudi-Rani* for "PFD".

Special thanks to the Government of U.S.A. and the American society for allowing me to pursue my higher study. Because America is only the country in the world who allows to pursue the foreigners to study *with financial support.*

Finally, but also of vital importance, was the emotional and practical support of Prof. Michael Green our Chairman, Professor Richard Pizer our Executive officer and Mrs. Cordella Stokes, our Program Assistant.

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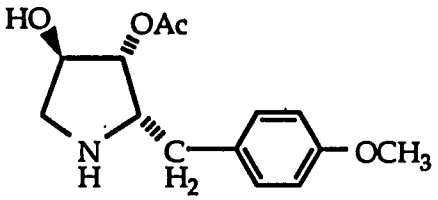
The diagrams of compounds in the chapters 1, 2 and 3-5 are numbered independently for each of these sections and not sequentially throughout the manuscript.

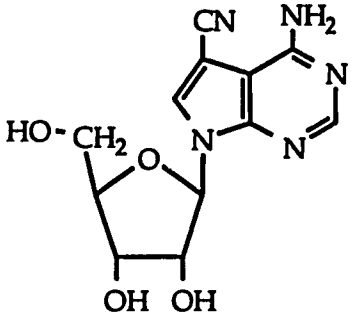
CHAPTER - 1

INTRODUCTION

Only a few antibiotics, such as the glutarimide-group antibiotics, anisomycin and toyocamycin are known to have herbicidal activity. The former group exhibits contact but non-selective killing effects and the latter inhibits germination of various plant seeds. During the course of investigations directed toward the discovery of new antibiotics with herbicidal activity, many strains of *Streptomyces* producing glutarimide antibiotics were detected.[1]



Anisomycin

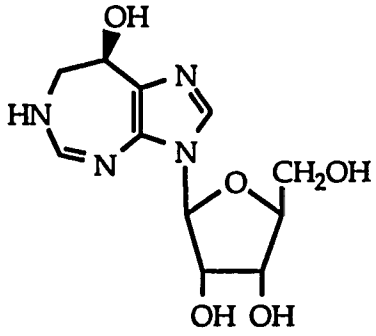


Toyocamycin

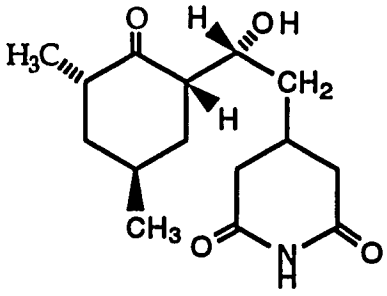
Herbicidins A (**1**) and B (**2**), two new antibiotics with selective and contact herbicidal activity, were produced by a new species of *Streptomyces* designated as *S. saganonensis*. Among tested microorganisms, the herbicidins indicated some activity against fungi *in vitro* and *Xanthomonas oryzae in vivo*. Their characteristic features were brought into relief by their selective and contact killing effect on many dicotyledonous plants, as well as their inhibitory effect on the germination process of plant seeds, such as the Chinese cabbage. A mutant of *Streptomyces saganonensis*. No. 4075, obtained by way of the N-methyl-N'-nitro-N-nitrosoguanidine (NTG) treatment, produced herbicidins F and G without herbicidins A and B. Isolation of the antibiotics were performed by adsorption on a resinous adsorbent followed by elution with aqueous methanol. It is unfortunate that herbicidins F and G do not have any inhibition activity at a concentration level of 100 μg/ml against

all strains of bacteria and the yeast fungus.[1] However herbicidins F, as well as herbicidin G, do demonstrate inhibitory activity against some fungi such as *Tricophyton rubrum, T. asteroides, T. mentagrophytes, Botrytis cinerea, Blastomyces brasiliensis.*

Herbicidins were produced through the process of submerged fermentation by *Streptomyces saganonensis.* Isolation of the antibiotics from the culture broth was performed by adsorption on Duolite S-30 column, followed by elution with aqueous acetone. The solution was concentrated under reduced pressure to dryness, and the remaining material was extracted with methanol. The methanol extract was evaporated to dryness under reduced pressure affording the crude mixture of herbicidins as a solid. Purified Herbicidins A and B were subsequently isolated by silica gel chromatography. Herbicidins F and G were obtained from a mutant of *Streptomyces saganonensis.* No. 4075, isolated by adsorption on resin followed by elution with aqueous methanol. Purification was achieved by silica gel column chromatography. Herbicidin E was produced from the same *Streptomyces saganonensis.* No. 4075, with 9-β-D-arabinofranosyl adenine and deoxycoformycin.[1]



Coformycin



Cycloheximide

It was also reported that Herbicidin A, was successfully converted into Herbicidin B, by initially incubating in a phosphate buffer solution at pH 7.0

and at 27 °C, followed by mild hydrolysis with aqueous alkali at a pH 8.5. This piece of evidence supported the fact that all Herbicidins have the same skeleton. In contrast to these known antibiotics with herbicidal activity, herbicidins A and B were shown to have contact and selective activity, especially against dicotyledonous plants. In general, *Herbicidin A has a more selective effect between rice plant and other plants than herbicidin B.*

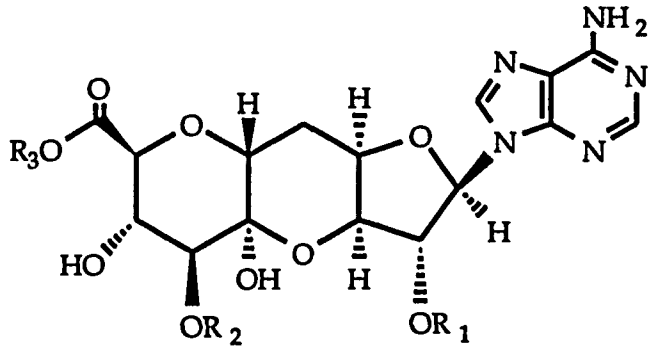
The minimal inhibitory concentrations (MIC) of herbicidins against bacteria, yeast and fungi (like *Trichophyton, Aspergillus* and *Penicillium*), were determined by conventional methods,[1] and those were found to be positive. Perhaps the most characteristic feature of herbicidins A and B were demonstrated by their selective herbicidal activity, when sprayed on the stems and leaves of plants, where they were found to be protective against bacterial leaf blight. Among monocotyledonous plants, the rice plant exhibited strong resistance to herbicidins. Other plant species such as the goose grass, as well as other monocotyledonous plants were blighted by the spraying herbicidins.

Anti microbial activities of herbicidins F and G over various micro-organisms were found to be negative. However, growth of *Trychophyton mentagrophytes* SANK 11868, was inhibited by herbicidin F at 6.25~12.5 μg/ml and herbicidin G at 100 μg/ml.

Herbicidins are found to be non toxic to humans. The toxicity was determined on mice both intravenously and through intraperitoneal dosage. No harmful effect on the killifish plant was observed after their incubation in a water bath containing 100 ppm of either A or B at room temperature for two days. Other antibiotics, such as cycloheximide (Glutarimide-group antibiotic) are known to have phytotoxic effects on various kinds of plants. The non-selective killing effect however, between mono- and dicotyledonous plants, as

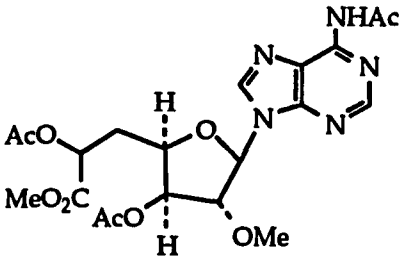
well as its toxicity, prevents its use as a weed killer. No contact herbicidal activity against plants is described for these antibiotics.

In purified form, the herbicidins are white crystalline solids. Acid hydrolysis of the herbicidins afforded adenine, thus the herbicidins must have the adenine moiety in their structures. All herbicidins forms crystalline oxime derivative when treated with hydroxylamine hydrochloride in methanol containing sodium acetate; which can easily be reconverted to herbicidins by mild acid treatment. ^{13}C NMR spectra of herbicidins indicated that there is an O-C-O quaternary carbon signal, δ, at 93.9 ppm, shifted to 155.8 in their oxime derivatives. These results indicate that the intramolecular hemiketal formation leads to ring closure.

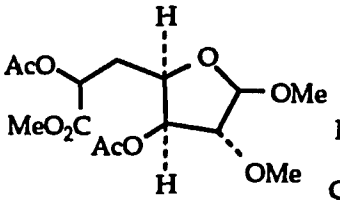


	R_1	R_2	R_3
(1) Herbicidin A	CH_3	$CO(CH_2OH)=CHCH_3$	CH_3.
(2) Herbicidin B	CH_3	H	CH_3
(3) Herbicidin E	CH_3	$COCH(CH_3)_2$	CH_3
(4) Herbicidin F	CH_3	$CO(CH_3)C=CHCH_3$	CH_3
(5) Herbicidin G	H	$CO(CH_3)C=CHCH_3$	H

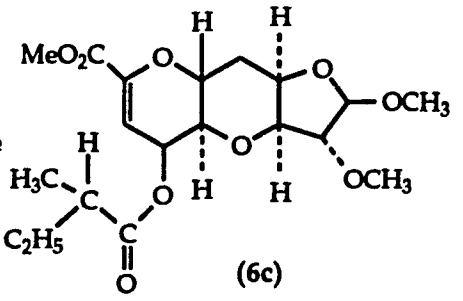
Sodium periodate oxidation of (**2B**) in aqueous acetic acid followed by acetylation provided a compound, which was characterized as (**6a**).



(6a)

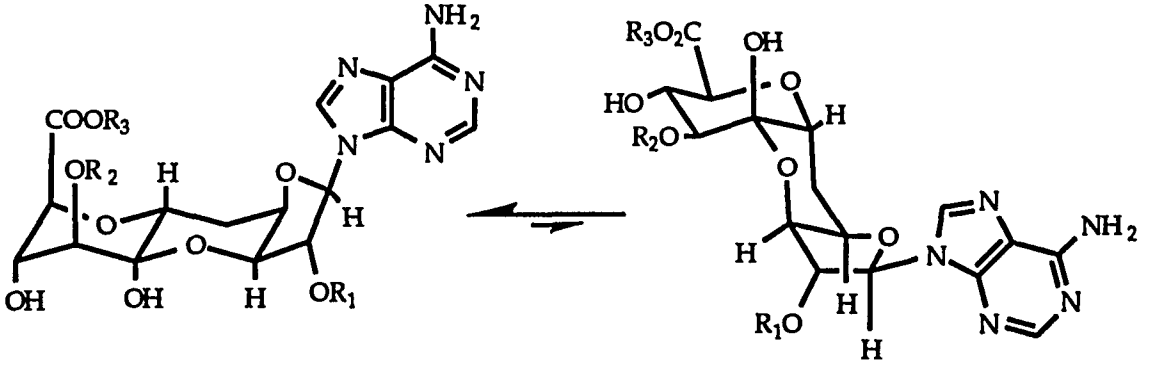


(6b)



(6c)

Methanolysis (5% HCl-MeOH) of (**6a**) gave a compound which was characterized as (**6b**). Hydrogenation (PtO_2/H_2); methanolysis followed by dehydration (elimination of H_2O) of herbicidin A (**1**); provided (**6c**).



(1a) (1b)

Other chemical degradation studies[1d] and physico-chemical evidences show that there is a glucose like as well as a xylose like unit present. The glucose C-1 is connected with the xylose unit via its C-5.

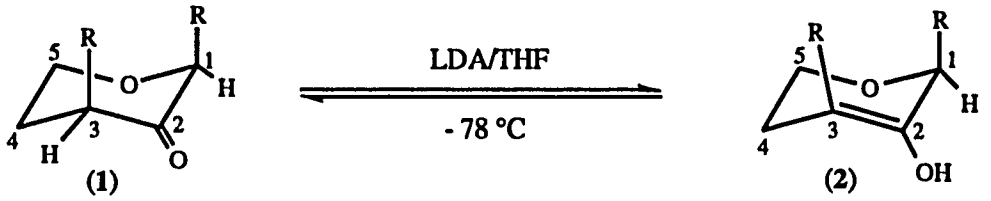
Proton magnetic resonance spectra of herbicidins were unable to indicate which conformation was present in solution, (**1a**) or (**1b**). However, the complete structure was determined by X-ray crystallography and was found to be structure (**1a**).[1]

CHAPTER - 2

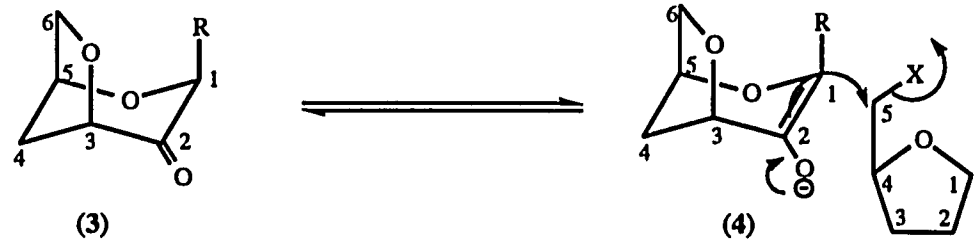
REVIEW

Synthesis and Chemistry of 3:6-anhydroglucopyranoside:[2,3]

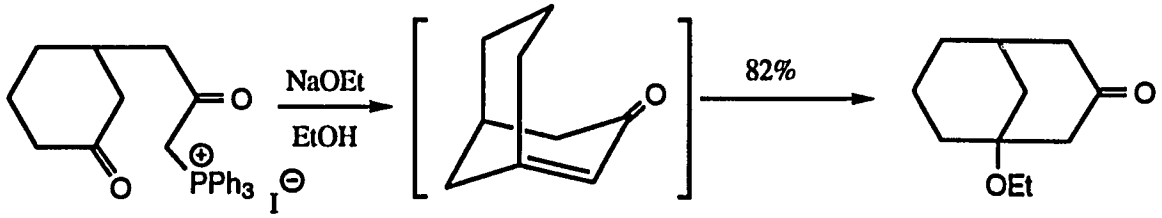
One of the known methods for the 'C-C' bond formation at C-1 of glucose (GC-1) with C-5 of xylose (XC-5) involved putting a good leaving group at 'XC-5' and making 'GC-2' a ketone, which on treatment with LDA at -78 °C, would involve enolization of only the 'GC-1' hydrogen atom. In the previous work,[2c] it was found that only the C-3 proton was involved in the enolization process with the 'GC-2' ketone group, irrespective the nature of R.



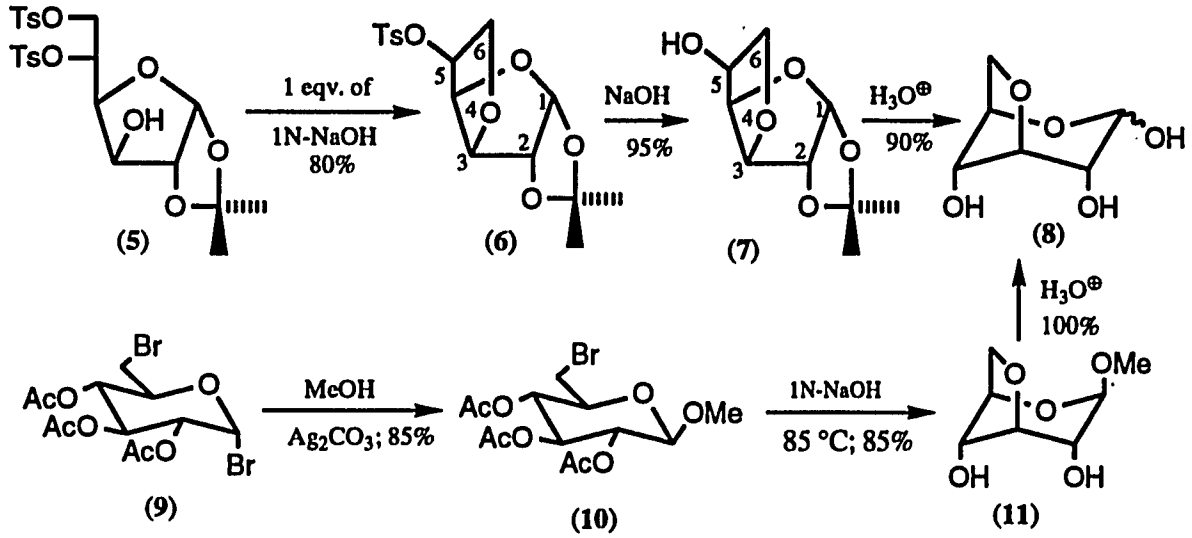
Protection of the C-3 proton from enolization (with the C-2 ketone) was thought to be achievable by making a "bridge-head" in the glucose unit, (i.e. 3-6 anhydrous sugar) which would prevent the aforesaid enolization due to "Bredt's Rule".



Of course, it is presently known that there are several bridgehead alkenes which are known as "Bredt's Rule violators".[4] For Example:

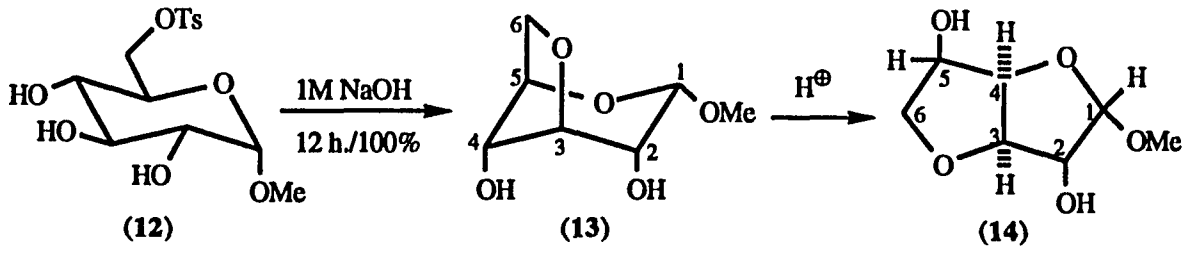


Ohle, H. *et al.* [3g] synthesised 3:6-anhydroglucopyranoside (8) following two different pathways. (a) 1,2-Isopropylidene 5,6-ditosylate (5) on treatment with 1.1 molar equivalent of sodium hydroxide provided the 1,2-isopropylidene 3,6-anhydroglucofuranose 5-tosylate (6), which on further hydrolysis with base followed by cleavage with aqueous acid provided the 3,6-anhydroglucose (8).

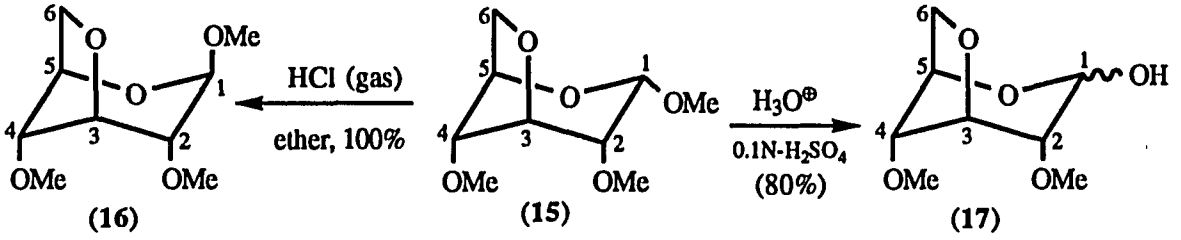


(b) 1,6-Dibromoglucopyranose triacetate (9) on treatment with anhydrous methanol in the presence of silver carbonate provided methyl 2,3,4-tri-O-acetyl-6-deoxy-6-bromo-β-D-glucopyranoside (10), which on treatment with excess alkali provided the β-methyl 3,6-anhydroglucopyranoside (11), which on prolonged hydrolysis with dilute sulfuric acid provided the 3,6-anhydroglucose (8).

Haworth *et. al.* [3c] have made the 3:6-anhydroglucopyranose (13) in which the C-1 was protected by a methyl group. A solution of 6-tosyl 1-α-methyl-glucopyranoside (12) in ethanol was treated with 1(M) sodium hydroxide at room temperature for 12 hours and 1 hour at 80 °C, and quenching the mixture with dry ice, evaporation of the solvent and

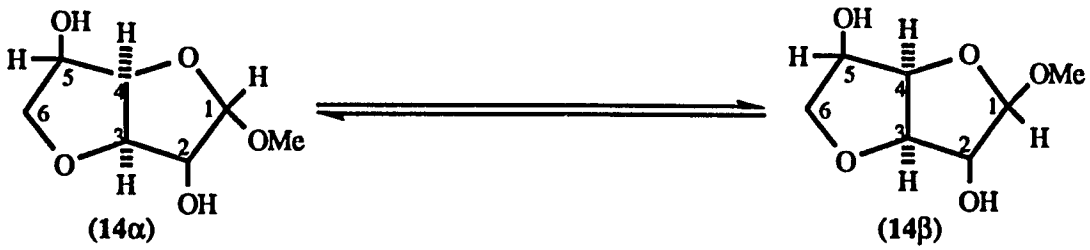


continuous extraction of the residue with boiling acetone provided the 3:6-anhydroglucopyranoside (**13**) in quantitative yield. It was found that the α- and the β- form of 3:6-anhydro-methyl-glucopyranoside were to convertable directly into the more stable 3:6-anhydro-α- and -β-methylglucofuranoside respectively; this ring change from pyranose to furanose occurred in quantitative yield. Direct transformation of 2:4-dimethyl-3:6-anhydro-α-methylglucopyranoside (**15**) into its corresponding β-pyranoside has also

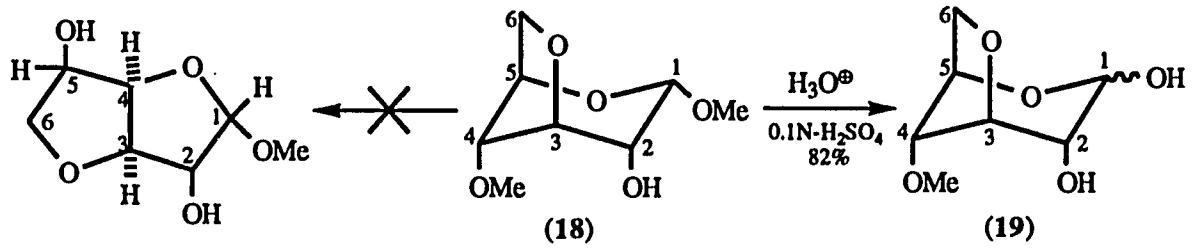


been effected, when dissolved in ethereal hydrogen chloride (for a short period of time) was completely converted into its β-isomer (**16**). On the other hand, when the same substrate (0.2 g.), was dissolved in 10 ml of 0.1N-sulfuric acid, the optical rotation $[\alpha]_D$ changed from +43° to a constant value (-20°), and the isolated final product was found to be identical to 2:4-dimethyl 3:6-anhydroglucopyranoside (**17**).

Prolonged treatment with the methanolic hydrogen chloride provided a equilibrium mixture of α- and β-methyl furanoside. This pyranoside to furanoside change *does not occur in the case of pyranosides which contain*

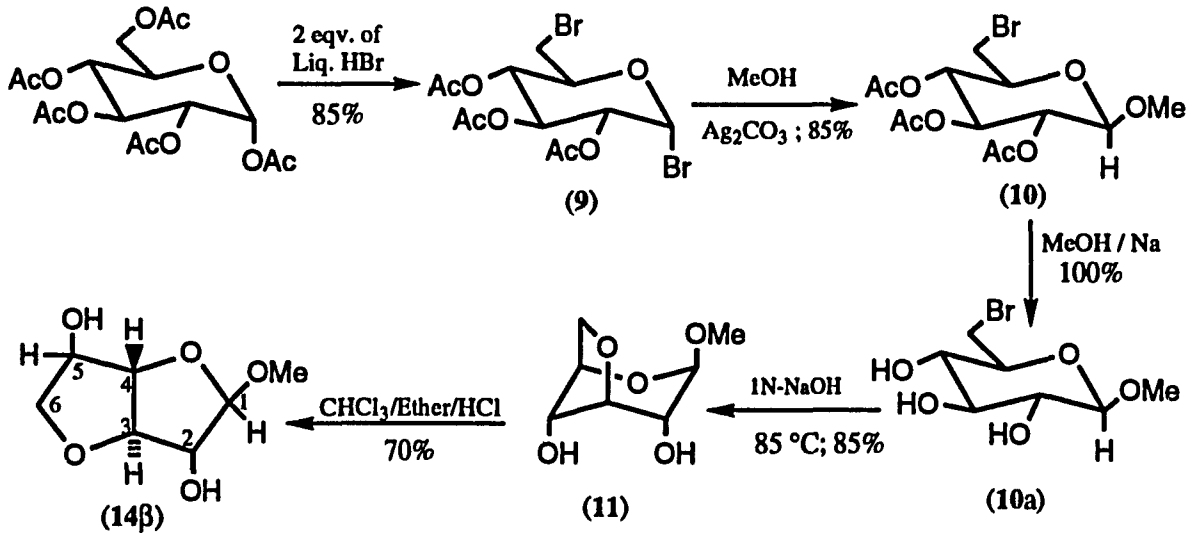


no anhydro ring and having no free hydroxyl group at C-4. Facts supporting this are that, when a methanolic solution of 4-O-methyl 3:6-anhydro-α-methyl-glucopyranoside (**18**) containing hydrogen chloride was found to be



remain unchanged. On the other hand when the same substrate (0.2 g.) was dissolved in 0.1 N-sulfuric acid (10 ml), the optical rotation $[\alpha]_D$ gradually changed from +18° to a constant value (-16°) after 3 hours and the final product was characterized as 4-O-*methyl* 3:6-*anhydro-glucose* (**19**).

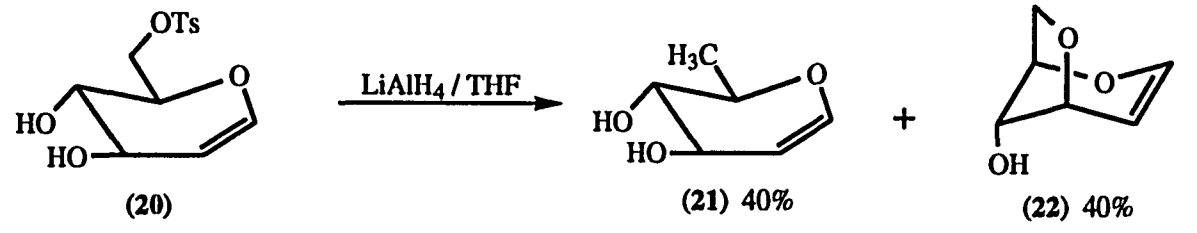
3:6-Anhydro-β-methylglucopyranoside was synthesized by the treatment of penta-acetyl glucose with 2 molar equivalents of liquid hydrogen bromide to provide 2,3,4-triaceto-1,6-dibromoglucopyranoside (**9**). The later on treatment with anhydrous methanol in the presence of silver carbonate to provide 2,3,4-triaceto-β-methylglucopyranoside-6-bromohydrin (**10**) in 85% yield. Dissolving the triaceto-bromohydrin in anhydrous methanol and treating with catalytic amount of metallic sodium for 18 hours at room temperature provided methyl-β-D-glucopyranose 6-bromohydrin (**10** a) in nearly quantitative yield. This bromohydrin after dissolving in 1(N) sodium hydroxide was heated for 2 hours at 85-90 °C.



Neutralization of the solution with dry-ice followed by evaporation of the solvent, the residue was extracted with boiling acetone. Removal of the solvent, and distillation of the residue at 160 °C/0.02 mm., provided the syrupy methyl 3:6-anhydro-β-D-glucopyranoside (**11**).

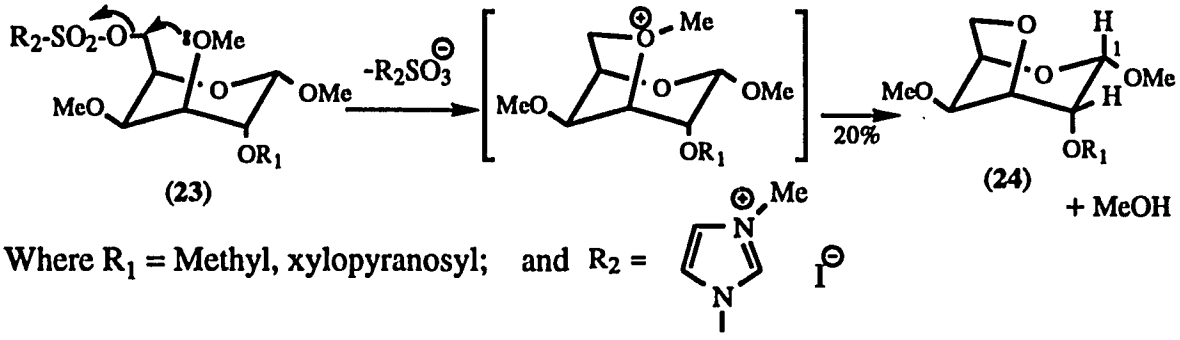
The transformation of methyl 3:6-anhydro-β-D-glucopyranoside (**11**) into its corresponding furanoside (**14** β) was performed (a) with a solution of chloroform, ether and hydrogen chloride, in 70% yield. (b) Methanolic hydrogen chloride, converts the pyranoside first into the β-furanoside and then attained an equilibrium mixture of α- and the β- form (described before) of the furanoside. Therefore, in order to isolate the β-isomer, the acid must be arrested quickly. (c) 0.1(N)-Sulfuric acid at room temperature provided the unprotected-3-6-anhydro sugar (**8**).

Fraser-Reid *et al.* [3f] reported the formation of a unsaturated



anhydro sugar; 3,6-anhydro D-glucal (W-22) as side product when the D-glucal 6-tosylate (W-20) was treated with $LiAlH_4$ in anhydrous THF.

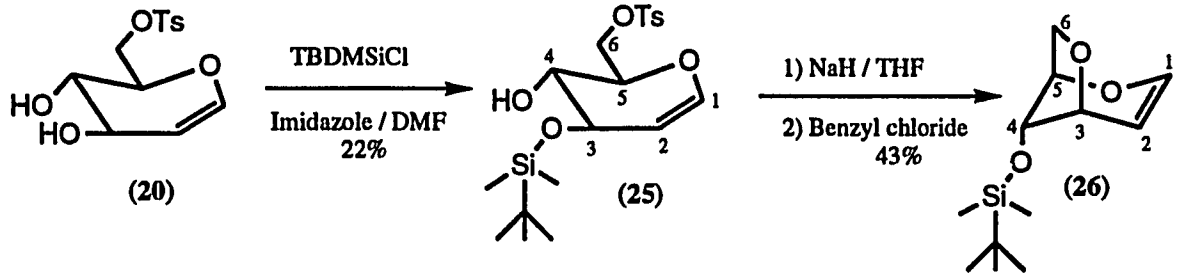
Aspinall *et al.* [3e] reported the synthesis (and the nmr δ value of H-1 as well as the $J_{1,2}$ value) of 3,6-anhydro-α-D-methylgalactopyranoside derivative



Where R_1 = Methyl, xylopyranosyl; and R_2 =

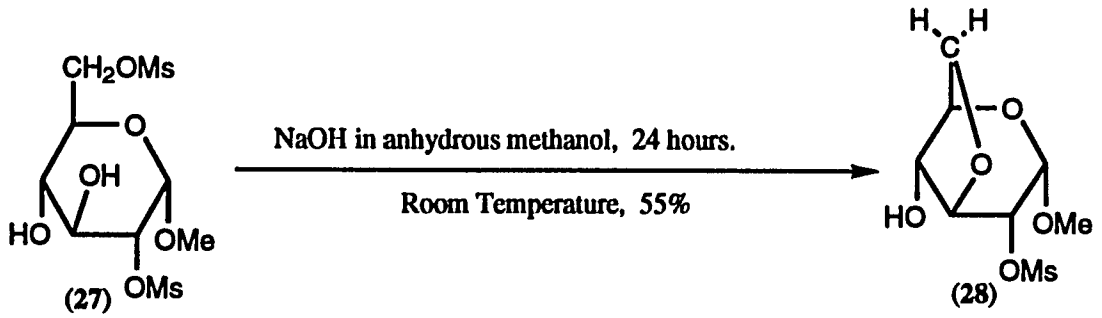
during the solvolysis of (23) with intramolecular participation and subsequent loss of 3-O-methyl or 3-O-glycosyl (24) substituent in 20% yield. In the pmr spectra the anomeric (H-1) proton resonates at a δ: 4.84 (d, $J_{1,2}$ = 2.85 Hz) which is a regular *"a-e"* coupling.

Crich *et al.* [3d] found the silyl migration of partially silylated glucal,

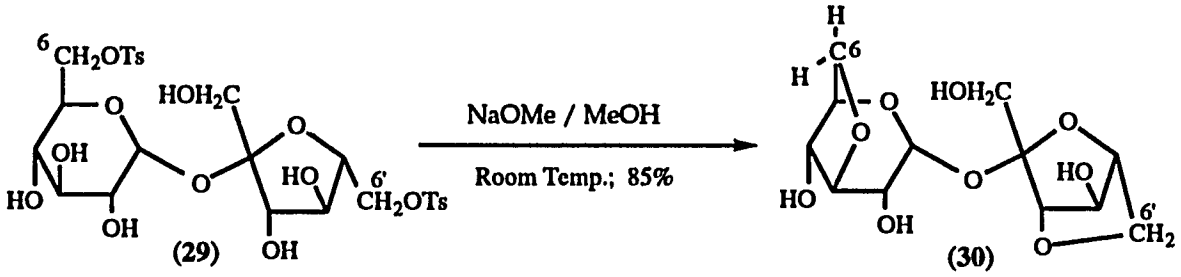


followed by formation of a 3:6 linkage (ring closure) when they attempted to benzylate in THF with benzyl chloride and sodium hydride.

Wolform *et al.* [3a] reported that the 3-6 anhydro sugar (28), can be made by converting the C-6 (OH) to a good leaving group (i.e. mesylate) and making C-3 oxygen as a nucleophile. Unfortunately the yield was low.

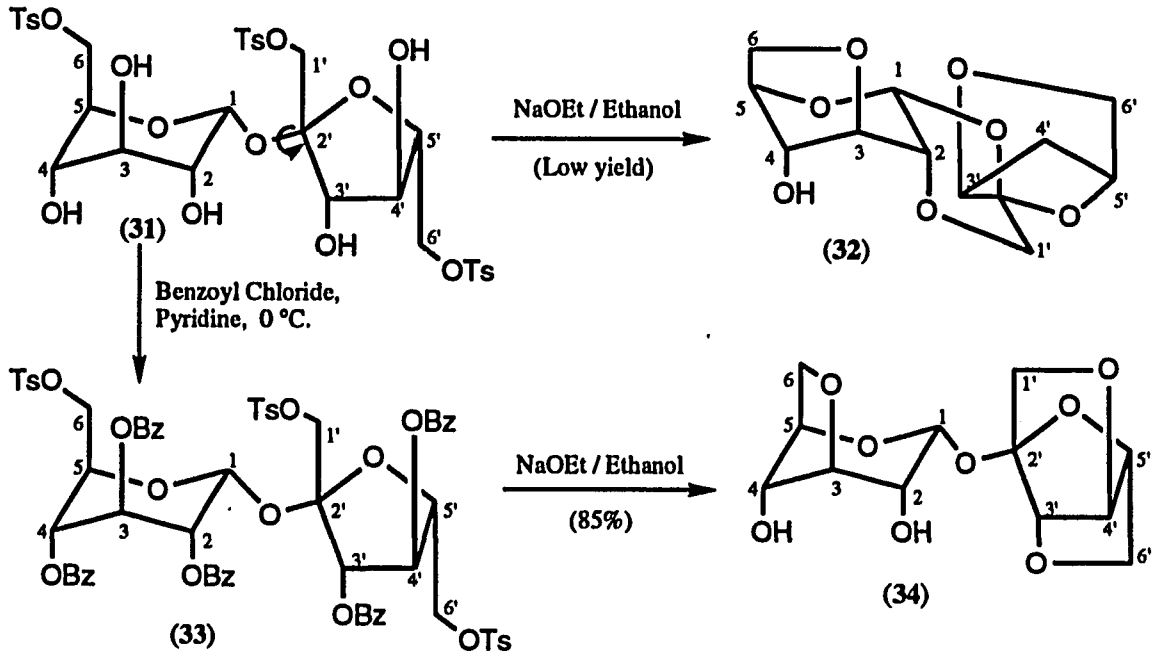


Bolton et al.[3b] reported the formation of dianhydro sugar (30) by the



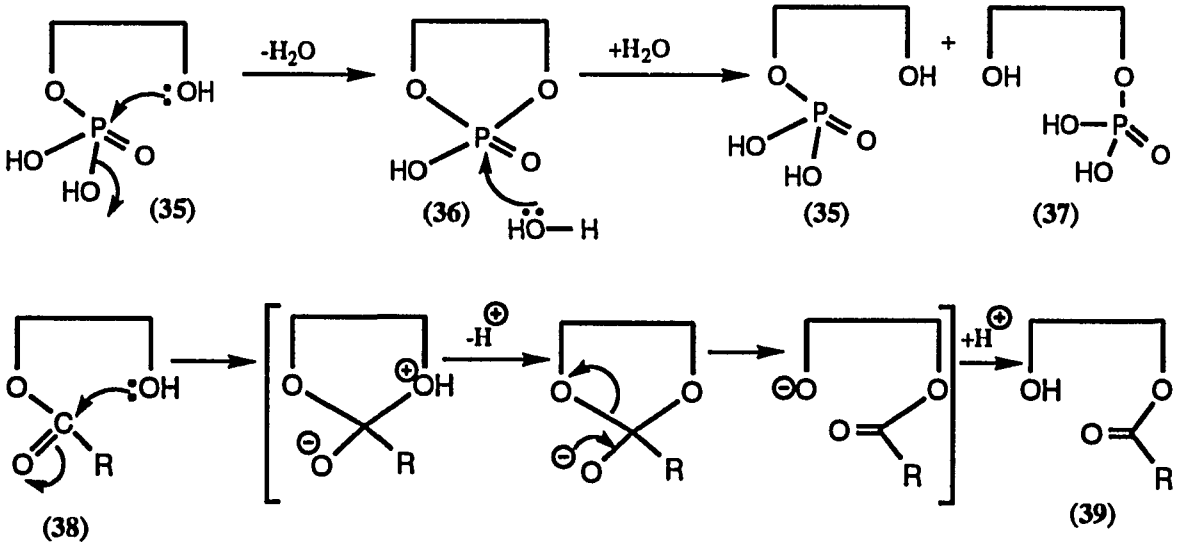
partial tosylation of sucrose to the 6,6'-di-O-tosylsucrose (29) was isolated in 18% yield. Treatment of the disulphonate with sodium methoxide in anhydrous methanol gave the expected 3,6:3',6'-dianhydrosucrose (30) as a syrup which was not oxidized by periodate. Using 6-mesylate as reactant 1-O-methylgluco-pyranose gave 3,6-anhydrous sugar.

Richardson et al.[3h] reported most interesting results. 6,1',6'-tri-O-tosylsucrose (31) on treatment with sodium ethoxide provided the 2,1':3,6:3',6'-trianhydride (32) in low yield. Where as the pentabenzoate of the tri-O-tosylate (33) provided the 3,6;1',4';3',6'-trianhydride (34) in high yield.



Selective Protection of Hydroxyl group as Ester and Migration of ester to the neighboring -OH group and strategy to prevent the migration:

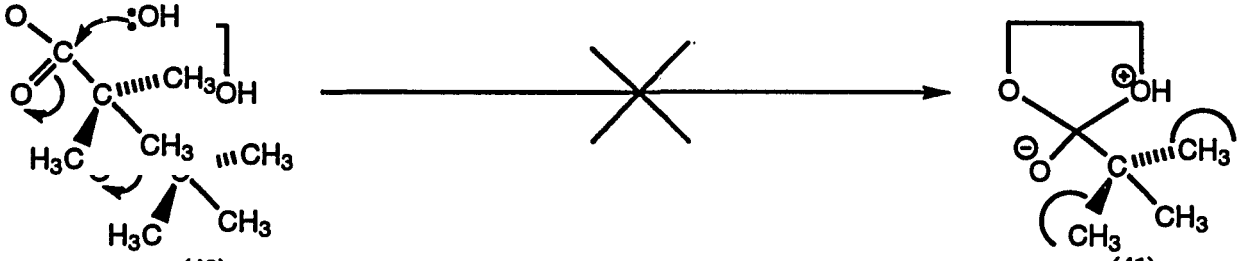
During the investigations on glycosyl esters, it was found that partially protected esters (including inorganic esters) isomerise under neutral and mildly acidic conditions.[8] The adjacent free OH behaves as a nucleophile



R = CH_3; C_2H_5; C_6H_5 etc.

towards the electrophilic ester group, first forming a cyclic (transition state) intermediate , followed by ester group migration towards the more stable (lower energy state) isomer.

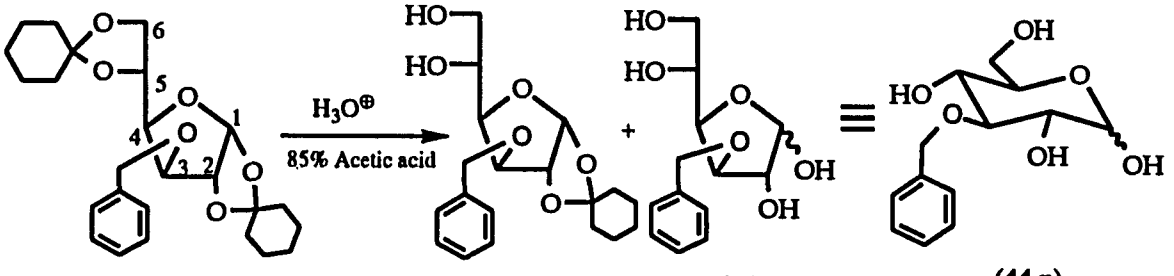
It was therefore necessary that an O-acyl protecting group be introduced that would not migrate easily and is inert towards regular reactions with esters and that can be detected by p.m.r. spectroscopy. The pivaloyl group,[9a-c] which has been utilized in the selective acylations of partially protected monosaccharides , became the choice protecting group. In order to migrate,



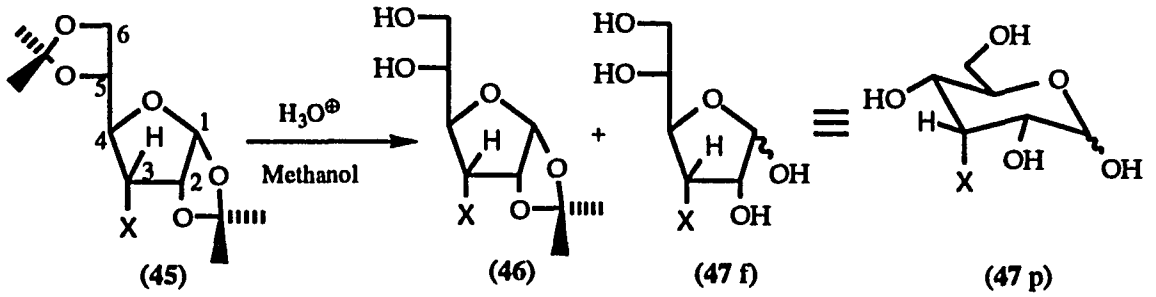
(40) (41)

an ester group must be attacked at the carbonyl carbon-atom by the neighbouring hydroxyl group to form the cyclic intermediate (**41**). In case of pivalate the attack is not favorable due to the extremely crowded neopentyl-like system. The pivaloylation reaction is also known to be highly selective.

Selective Cleavage of the 5:6 -acetal of dicyclohexyl or diacetone gluco-furanose derivative: [6a-d]



(42) (43) (44 f) (44 p)

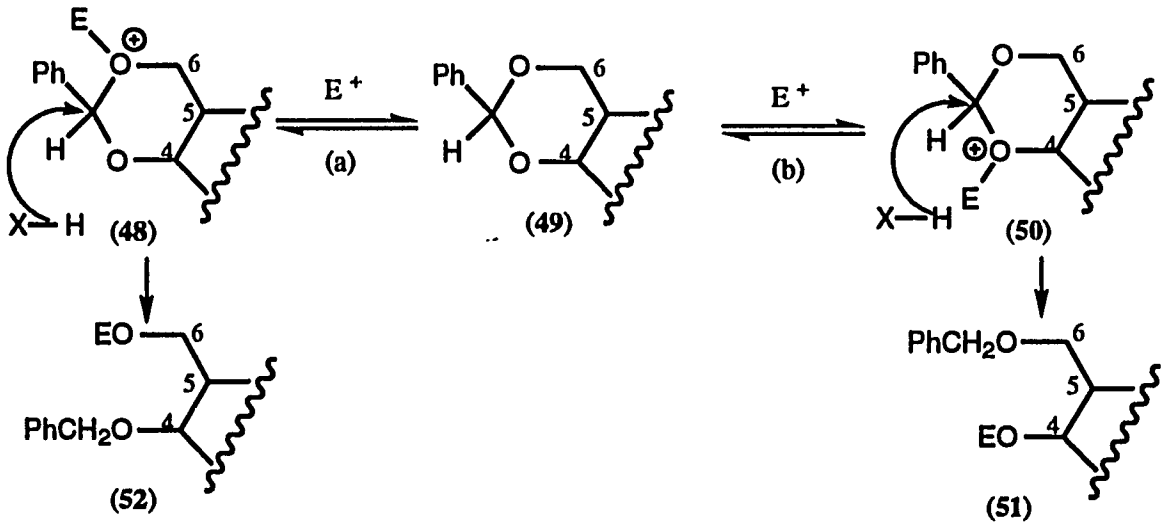


Where X = I; CH_2Br; CH_2-O-CO-C_6H_5

The 5,6-acetal group can be selectively cleaved by hydrolysis to give the 1,2-mono acetal derivative. The reaction conditions need to be *carefully* controlled to avoid extensive hydrolysis to the parent sugar. The partial hydrolysis of 3-O-benzyl-1,2:5,6-di-O-cyclohexylidene-α-D-glucofuranose (**42**) and 3-deoxy-3-substituted-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (**45**) provided a mixture of three products respectively. The unhydrolysed starting materials; 3-substituted-1,2-monoacetal, and 3-substituted glucose/allose . In every case the latter is highly soluble in water, thus, can be removed simply by a partition between water and a suitable organic solvent. Now the unreacted material and the 3-benzyl-1,2-monoacetal are in the organic solvent phase. Evaporating the solvent and column chromatographic purification, eluting first with hexane removes the diacetal completely, and then with commercial methanol to elute the pure 3-benzyl-1,2-monoacetal.

Selective Reductive-Cleavage of 4:6-benzylidene glucopyranoside derivative:[7]

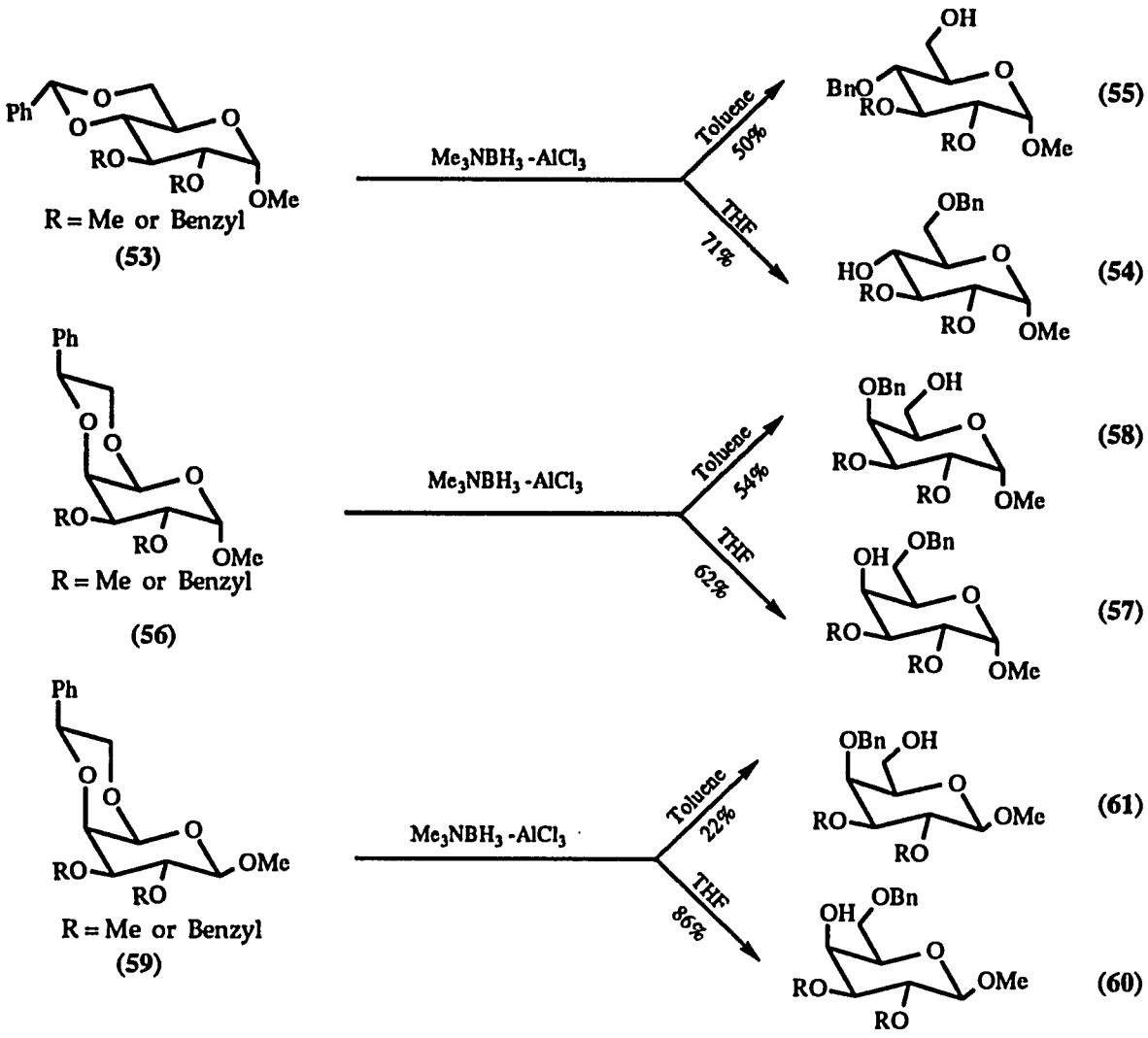
Reductive cleavage of the 4,6-O-benzylidene group of hexopyranosides using lithium aluminium hydride-aluminium chloride gives varying regioselectivity depending on the structure of the starting material. With hexopyranosides containing bulky substituents (*e.g.* benzyl) in the 3-position, however, the major product has a free 6-hydroxyl group and the benzyl group



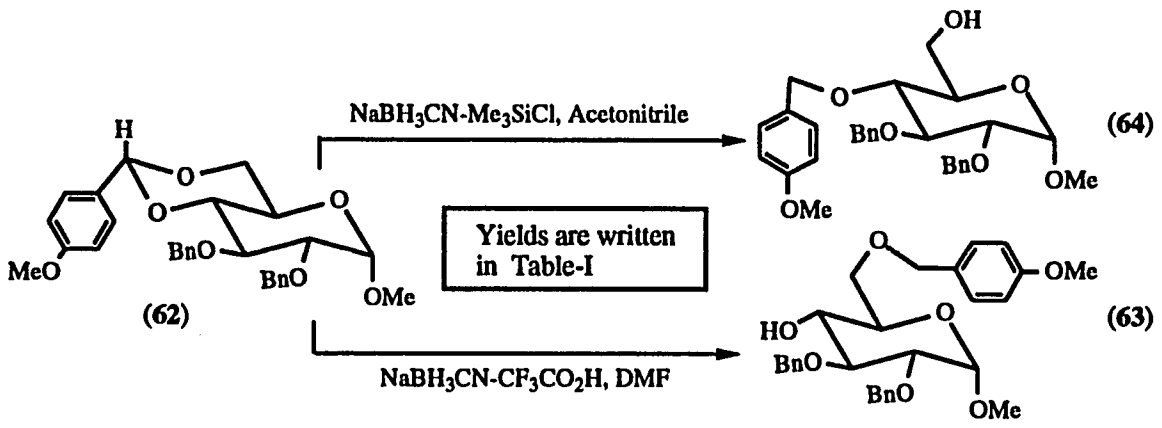
at O-4. In contrast, reductive cleavage of 4,6-O-benzylidene acetals of hexopyranosides using sodium cyanoborohydride-hydrogen chloride, results in the benzyl group in the main product occupying the O-6 position and the 4-hydroxyl-group being free.

On the other hand, with the borane trimethylamine-aluminium chloride reagent and toluene (μ=0.31D) as solvent, 4-O-benzyl ethers with the 6-OH free are obtained (in 40-50% yield). Still, with other variations such as using tetrahydrofuran (μ=1.75D) as solvent, 6-O-benzyl ethers with the 4-OH free are obtained (in 75-87% yield).

At this point there is no general reagent which will give only free hydroxy at C-6 in very high yields; (perhaps with trace amounts of the 4-hydroxy isomer).



In preference to the benzylidene substituted-glucopyranoside, 4-methoxy-benzylidene substituted-glucopyranoside on treatment with the $NaBH_3CN$-CF_3CO_2H reagent gave the desired 4-hydroxy glucopyranose derivative (63). The reversed regioselectivity, giving the compound 4-O-(4-methoxybenzyl) regio-isomer (64) was observed when trimethylsilyl chloride was used as electrophile and acetonitrile as the solvent.[7d & e]



It is to be noted that *this reagent fails to cleave the acetal if there is no methoxy group in the benzylidene.* The regioselection of this reaction has been associated with the steric bulk exerted by the substituent at O-3 giving kinetic control of the reaction, or *steric-approach control* of the electrophile. Kinetics of the reaction was extensively studied. Using analytical amounts of the reagent (Me_3SiCl-$NaBH_3CN$), results in a rather sluggish reaction. However, with 5-6 molar equivalents of the reagent, the reaction went to completion in 0.5-18 hours in 85-90% yield (the trimethylsilylated product was desilylated during workup). Choice of solvent can also control the regeoselectivity as well as the kinetics of the reaction. As methoxybenzylidene acetals are considerably more acid sensitive than benzylidene acetals, a polar solvent is necessary in order to stabilize the intermediate 4-methoxybenzylic cation formed in the reaction and avoid the unwanted hydrolysis. DMF, being a polar (μ=3.86D) and slightly basic solvent, provides good selectivity using $NaBH_3CN$-CF_3CO_2H such that *thermodynamic protonation* of O-4 by CF_3CO_2H followed by reduction gives the corresponding 6-O-(4-methoxybenzyl) ether. Stabilization of the intermediate benzylic cation by DMF is so effective that almost no hydrolysis was observed.

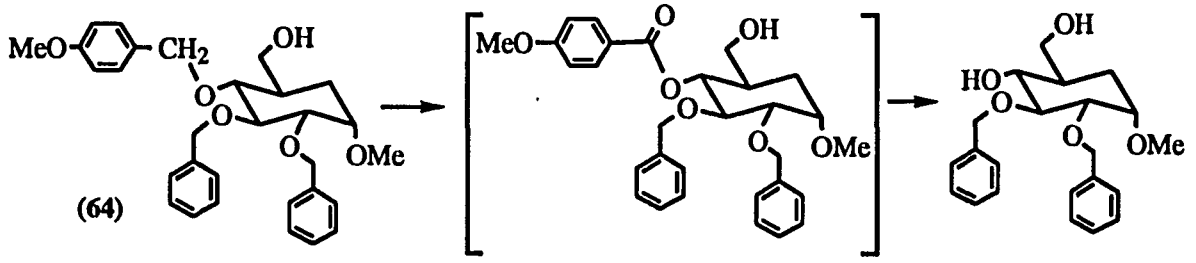
On the other hand, Trimethylsilyl chloride, proves to be a sterically more demanding electrophile than the proton (whose size is negligible), thus giving preference for activation of O-6, resulting in the formation of the corresponding 4-O-(4-methoxybenzyl) ether. This reaction failed using unsubstituted-benzylidene glucopyranoside.

SOLVENT EFFECT: Solvent choice plays a major role in this type of reaction. With acetonitrile as a solvent the regioselectivity is good, whereas with DMF a *ca* 1:1 mixture of regioisomers is obtained. The results are summarized in the following table.[7d & e]

Table-I

Starting Material	Reagent	Solvent Used	Product (63) (%)	Product (64) (%)
(62)	$NaBH_3CN$-TFA	DMF	85	3
(62)	$NaBH_3CN$-Me_3SiCl	DMF	45	45
(62)	$NaBH_3CN$-Me_3SiCl	Acetonitrile	13	76

On the other hand methoxybenzyl ether can be cleaved by cerric(IV) ammonium nitrate, even in the presence of the benzyl ether group, which remains unaffected. It undergoes via p-methoxy benzoate derivative:



Photochemical Deoxygenation of Sugars from Carbohydrate Esters:

Portella *et al.* [10d] reported the photochemical transformation of esters into paraffins. Portella *et al.* [10e] and Collins *et al.* [10f] separately reported the photochemical deoxygenation of sugars from their esters with hexamethyl phosphoric triamide (HMPT) in water under nitrogen atmosphere. Scharf *et al.* [10g] reported that esters of such sterically hindered, aliphatic carboxylic acids such as pivalic acids are more efficiently deoxygenated than regular carboxylic esters and aromatic esters.

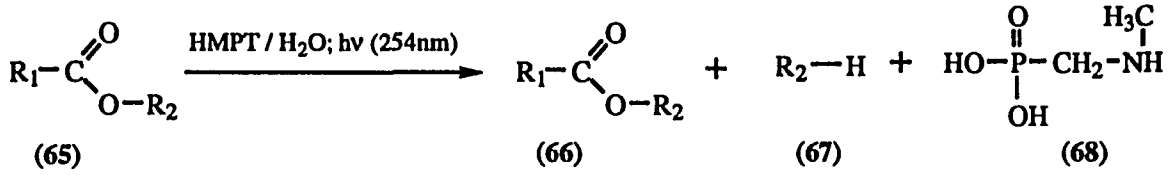
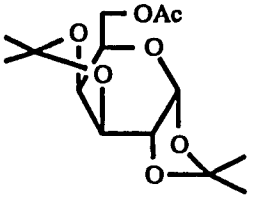
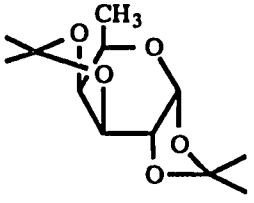
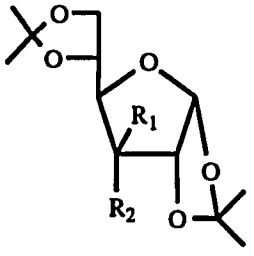
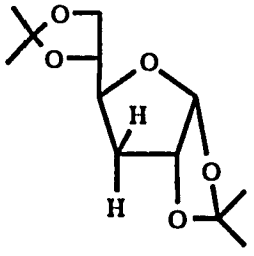
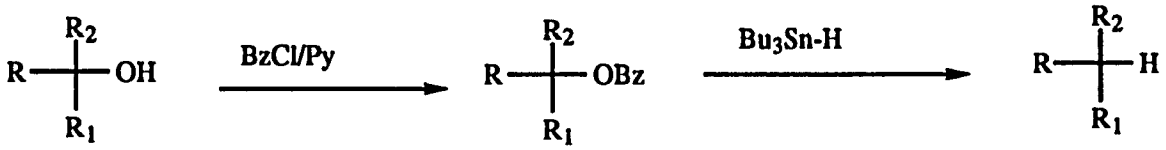


Table-II

Entry	Reactant	Product	Functional Groups	Yield	Ref.
1				85% 65%	10d & 10e 10f
2			R_1 = OAc, R_2 = H	65%	10d & 10e
3			R_1 = OAc, R2 = H	65%	10f
4			R_1 = H, R2 = OAc	65%	10f
5			R_1 = Piv, R2 = H	75%	10f

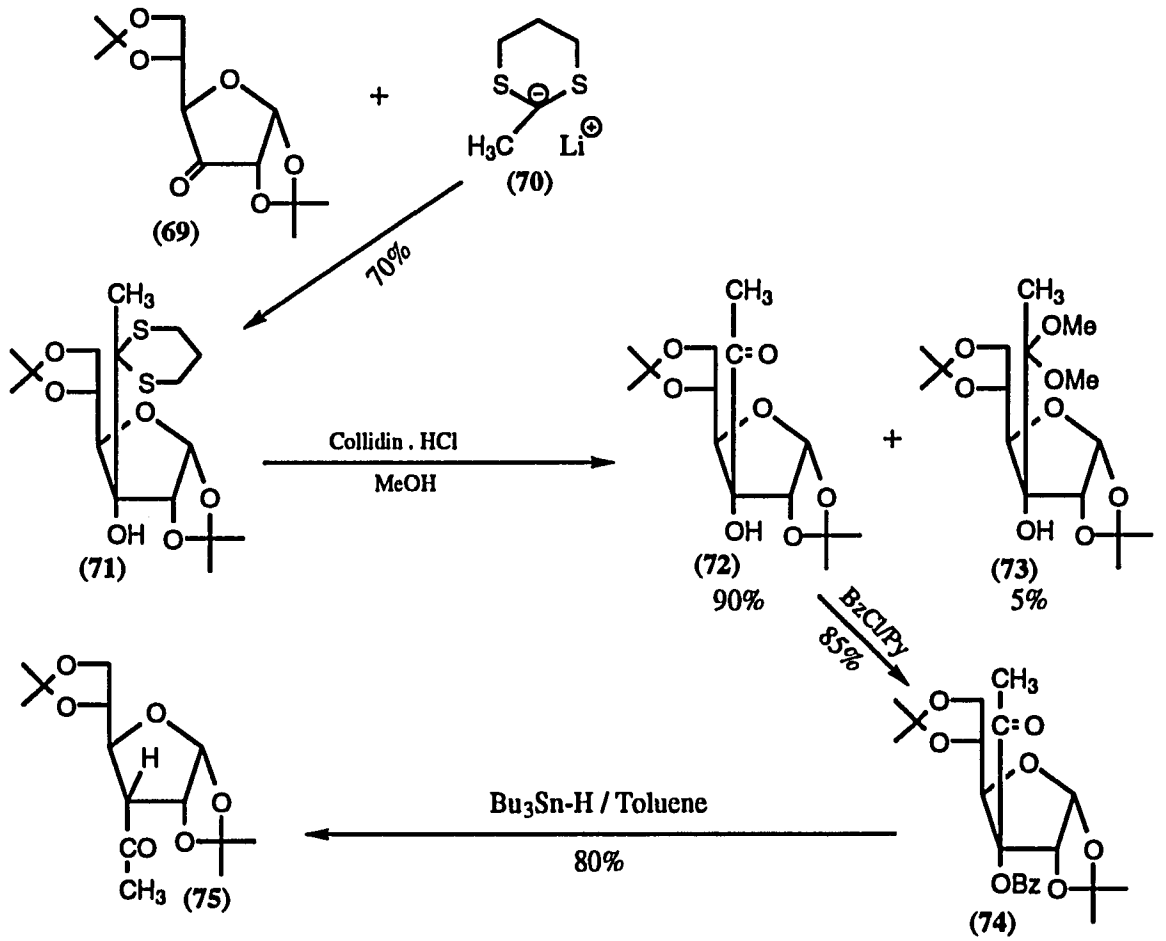
Radical deoxygenation of α-keto-O-esters:

Khoo and Lee,[10a& b] reported that alkyl esters could be converted to the corresponding alkanes by radical deoxygenation with tributyltin hydride under drastic conditions with 20 to 89% yield.



Where R = CH_3CO or C_6H_5CO

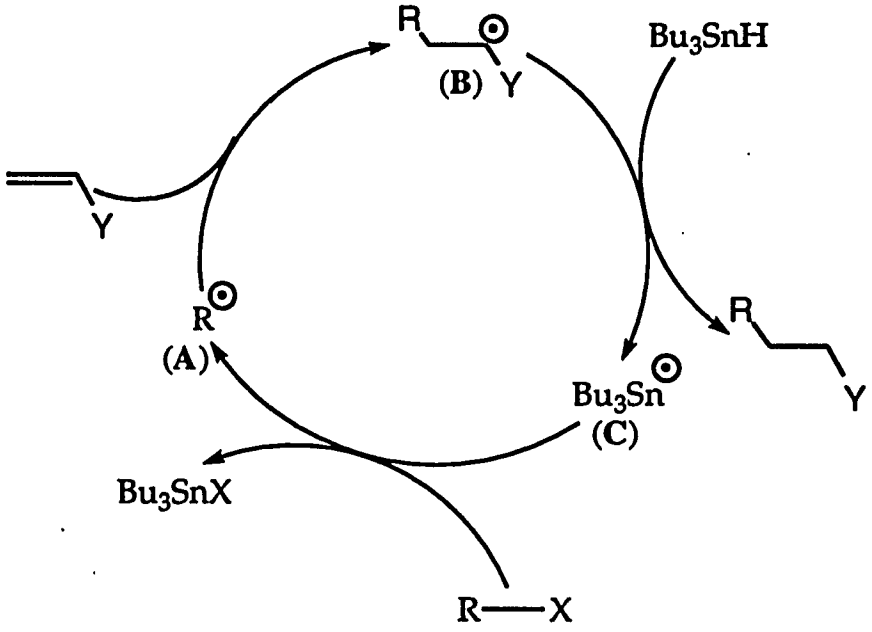
Acetyl branched-chain sugars, however, with a *tertiary* hydroxyl group at the branching point, were converted to their deoxy branched-chain-sugars with the same reagent in milder condition.[10c]



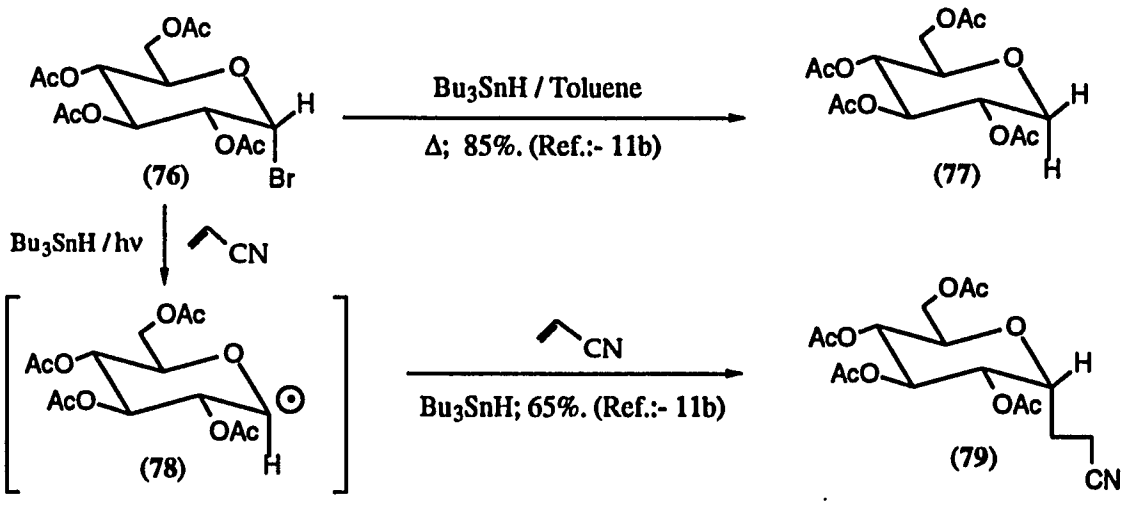
Radical "C-C coupling" with tributyltin hydride:

Alkyl halides undergo "C-C-coupling" on reaction with tri-n-butyltin hydride in the presence of electron-deficient alkanes, under anhydrous conditions and under a nitrogen atmosphere.[11]

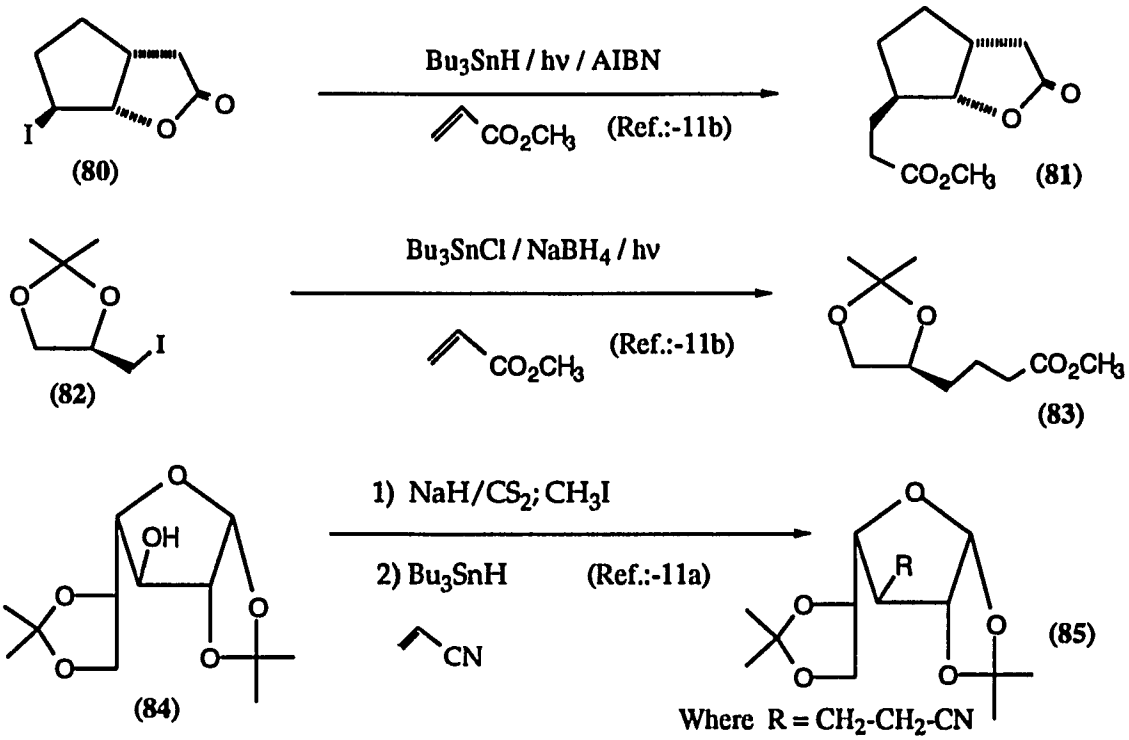
Electron deficient alkenes are generally α-β-unsaturated esters or α-β-unsaturated nitriles. In such reactions the adduct radicals must be trapped by an donor molecule subsequent to the C-C bond formation in order to prevent polymerization. It was found that the reaction could be carried out successfully using xanthates, selenides, and tertiary nitro compounds.



It is however necessary to mention that, in the case of alkyl iodides the reactions could be carried out with substoichiometric amounts of organo tin compounds because the butyl tin hydride could be regenerated *in situ* from the tin halide with $NaBH_4$. This C-C-coupling reaction could also be

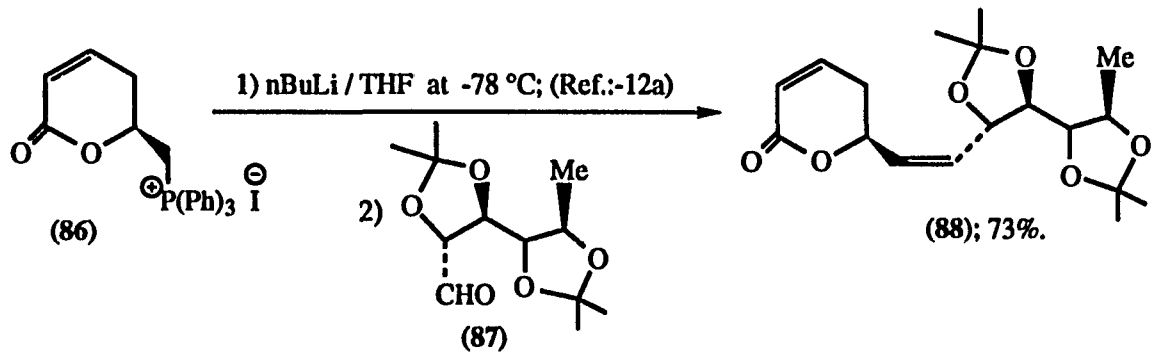


extended to thioalkylated alcohols, which is analogous to the Barton's deoxygenation reaction, in which AIBN was used as radical initiator.

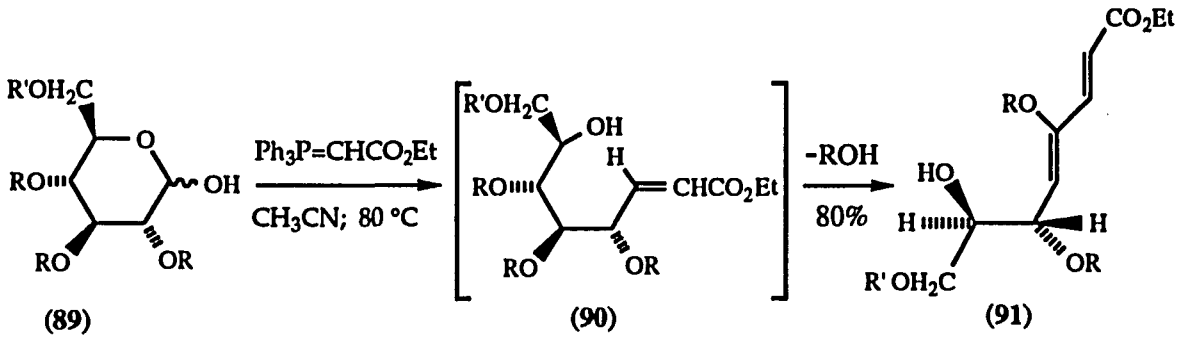


Wittig Reactions in Carbohydrate Chemistry:-

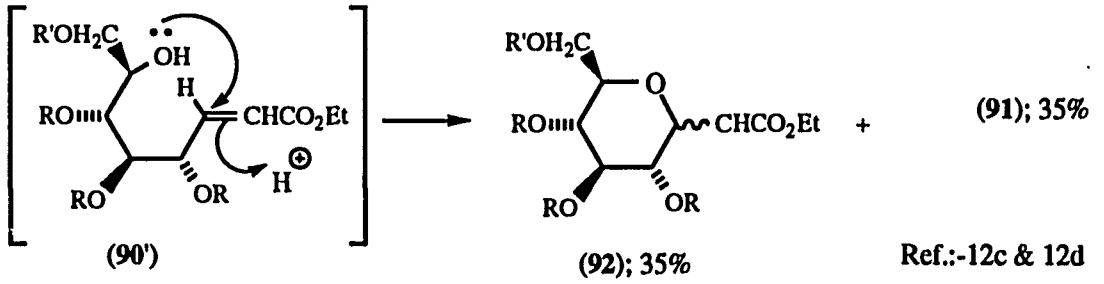
The Wittig olefination reaction became a well known procedure in carbohydrate chemistry. However, up to this time the olefination was done primarily on protected sugars, and only on just a few unprotected sugars.



Very recently, a series of Wittig olefination reactions were performed in the presence of one or more than one free hydroxyl groups,[12] resulting in the formation of different products depending on the *basicity of the ylides.*



When, R = R' = Acetate

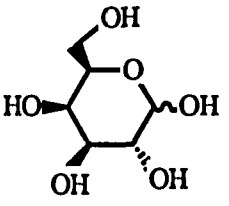
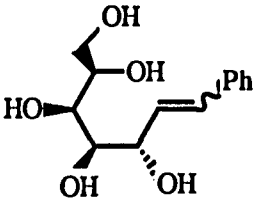
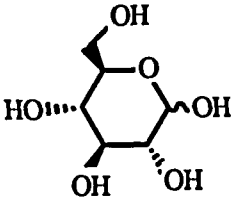
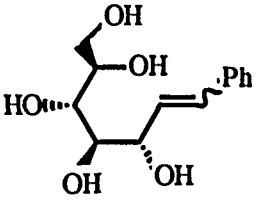
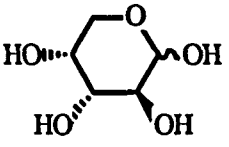
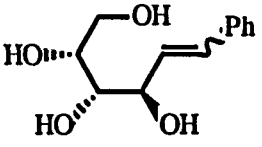
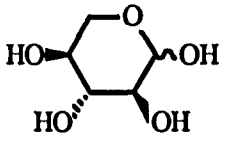
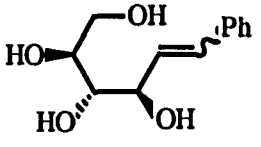


Non stabilized ylides yielded chiral glycerol derivatives, whereas resonance-stabilized ylides and semistabilized benzylidenetriphenyl-phosphoranes, formed chain elongated sugar derivatives.

The reactions of D-galactose (entry-1), D-glucose (entry-2), D-arabinose (entry-3) and L-xylose (entry-4) with benzylidenetri-phenylphosphorane in

dioxane gave the chain elongated compounds as (E)/(Z) mixtures in 66-72% yields, which are tabulated in the following table. Treatment of all the products with ozone gave the parent sugars in very good yields, and it was noteworthy that the corresponding C-2 epimeric sugars could not be detected. This observation indicated that *resonance stabilized* ylides have no direct role with respect to enolization of the C-1 oxo with the C-2 proton. As usual reaction yields moderate.

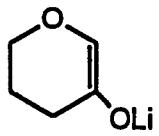
Table-III

Entry	Starting Sugar	Product	Yield (%)
1		 (93)	72
2		 (94)	70
3		 (95)	66
4		 (96)	68

Alkylation of glycosides at C-1 via the trapped enolate anion:[13a & b]

Of the variously known methods for the formation of C-glycosides at the anomeric center, only a few of these methods which have been used in approaches to herbicidins will be discussed here. Of course all of them involve either enolate anion (or its trapped form) or a suitable C-1 substituted glycosyl compounds in which the C-1 substituent group is a very good leaving group.

(i) Lithiated 3-ketotetrahydropyran and silyl enol ethers are perhaps among the more versatile reagents in this scope of synthetic organic chemistry. 3-Ketotetrahydropyran on treatment with LDA (lithium diisopropylamide) at very low temperatures gives the corresponding lithiated derivative. In a more conventional sense, the introduction of



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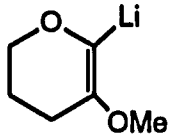
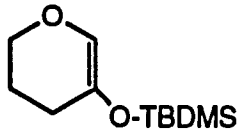


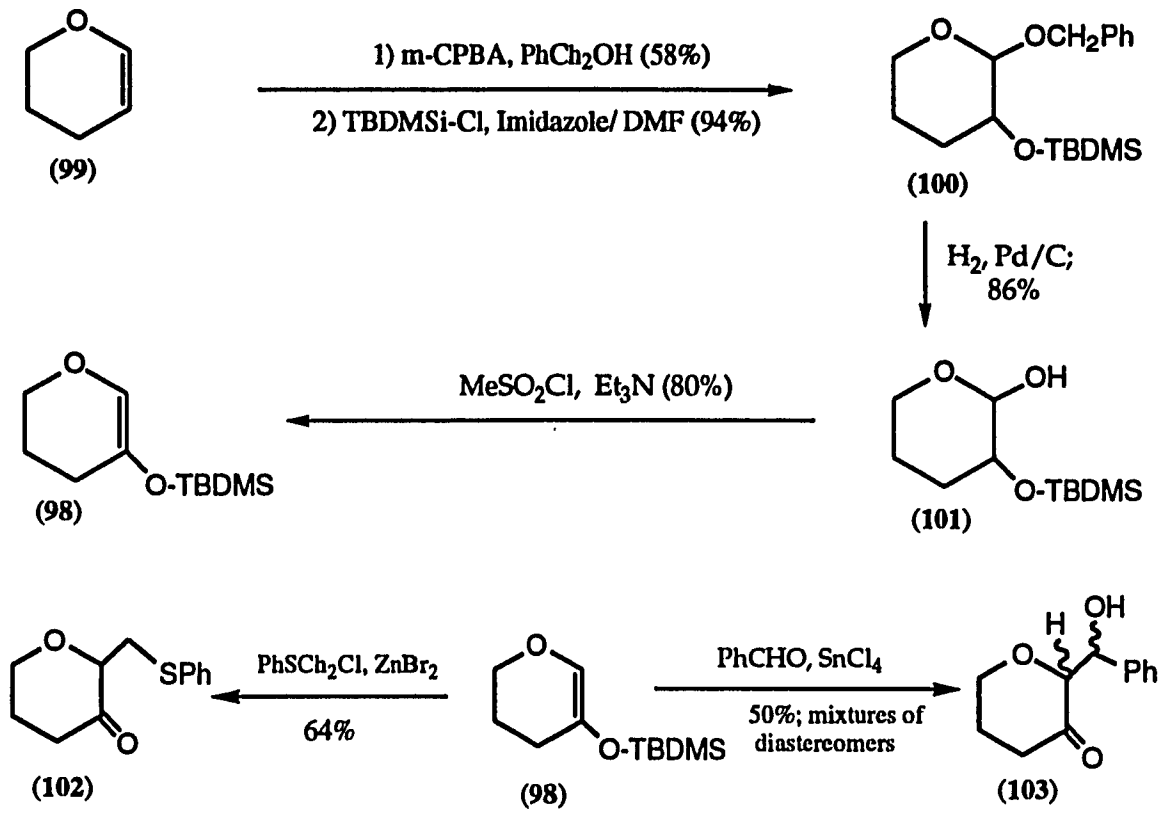
(97a)



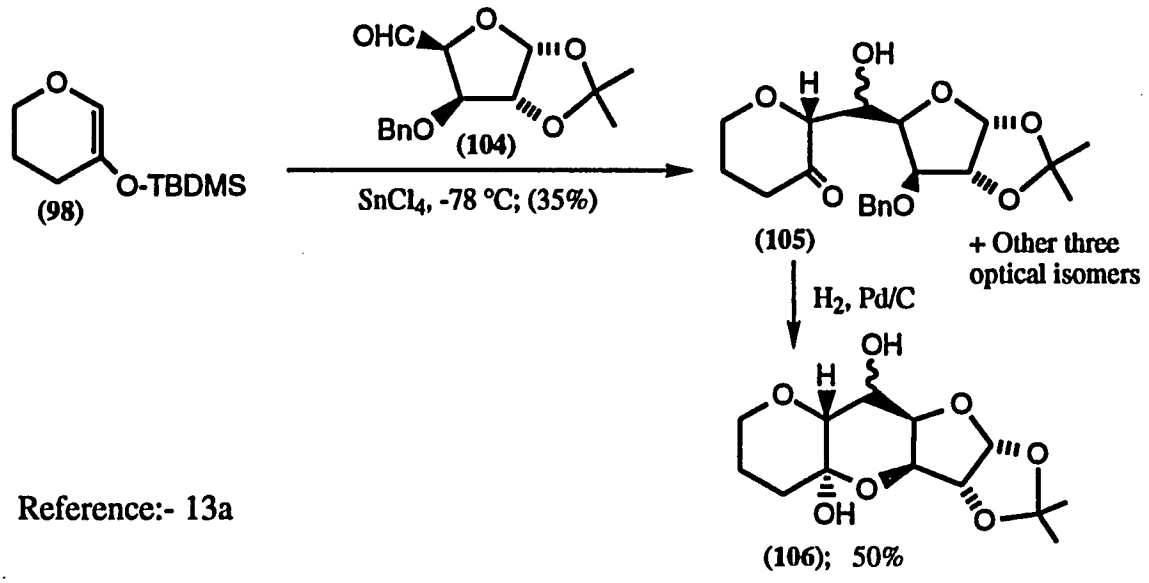
(98)

enol ethers greatly expanded the synthetic scope of enolate chemistry by introducing an electrophile to a ketone under nonequilibrating conditions. On the other hand, although the reactivity of C-2 silyl enol ethers is much lower than the lithiated analog, this method provides the most promising results.[13a] Not only these labile silyl derivatives provide access to the corresponding enolate, but they are also compatible with wide a range of "S_N1-type" electrophiles in the presence of Lewis acids. A silyl derivative of enolate (97) would be anticipated to provide significant advantage over the alkenyl lithium (97a) the scope of which is limited by the highly basic nature

of this species. The authors[13a] described the synthesis and the reactivity of the TBDMS ether (98).

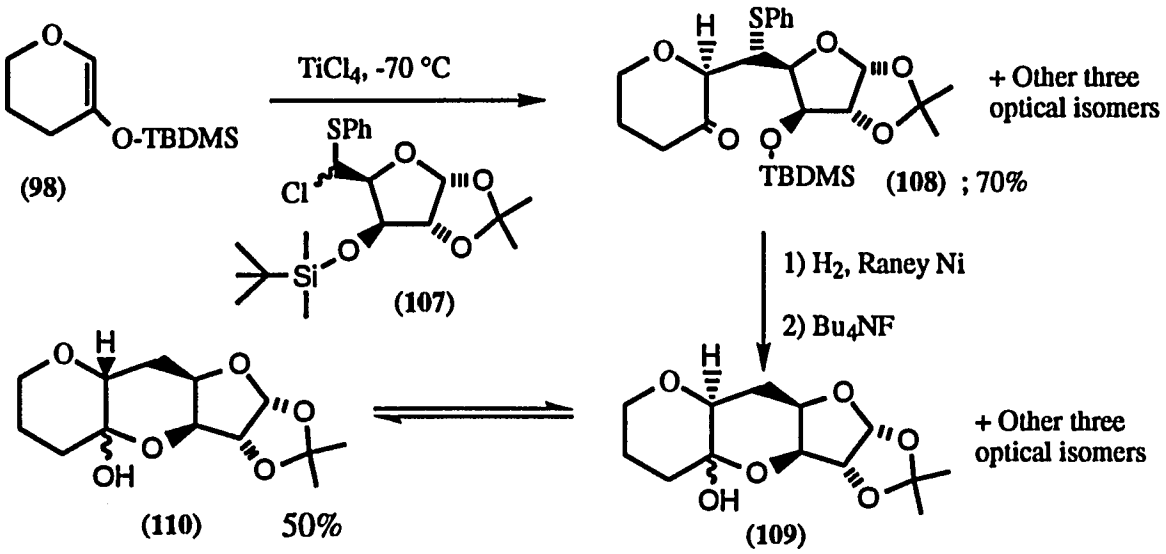


Condensation reactions of the silyl enol ether (98), using $SnCl_4$ as the Lewis acid in CH_2Cl_2 at -78 °C gave a 3:2 mixture of the two inseparable diastereomeric aldol adducts (103) in 50% yield. A similar reaction between (98) and (104) providecd a 1:1 mixture of two inseparable diastereomeric aldol adducts (105). Hydrogenolysis of this mixture gave a separable mixture of the tetracyclic hemiketals (106 a & b) in 50% yield.



Reference:- 13a

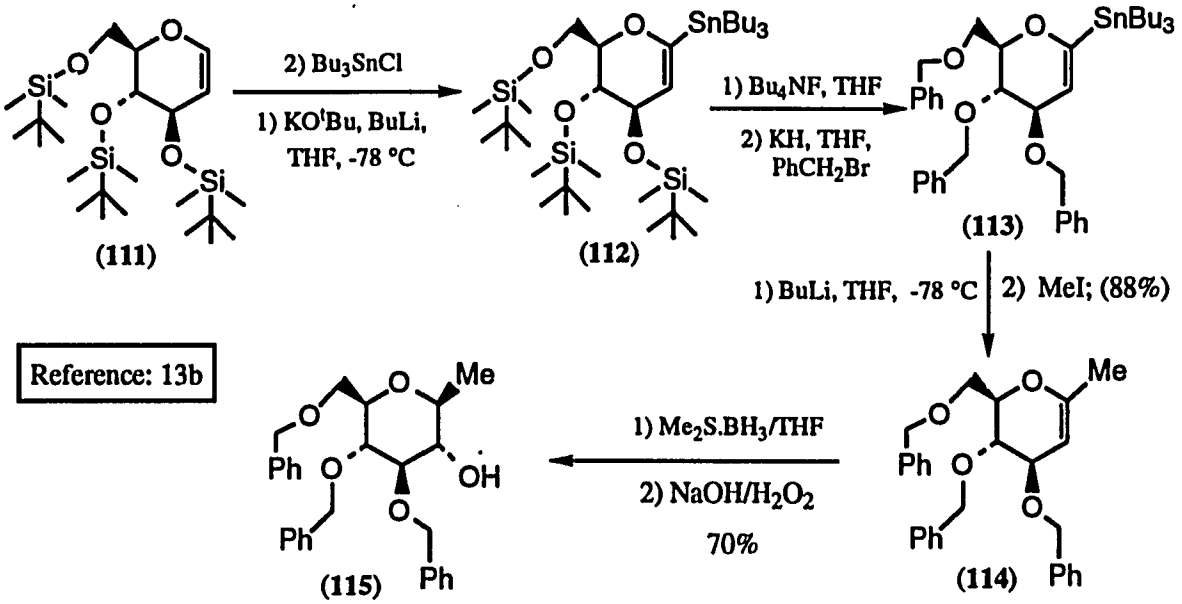
In the presence of $TiCl_4$ (CH_2Cl_2, -70 °C), α-chlorosulphide (**107**), reacted with the silyl enol ether to give a 4:1 mixture of two diastereoisomers (**108**) in 70% overall yield. The major component was easily separated and



treatment with hydrogen with the Raney nickel (as catalyst) followed by desilylation with tetrabutylammonium fluoride in tetrahydro furan to give the hemiketal (**110**) after equilibrium.

(ii) The direct formation of C-glycosides from carbohydrate precursors was achieved by the reaction of a novel 1-tributyltin derivative of D-glucal with electrophiles. Subsequent regiocontrolled introduction of a hydroxyl group at C-2 restores the full pattern of hydroxy substitution to give 1-C-substituted D-glucopyranosyl derivatives.[13b]

Optimum conditions for deprotonation and stannylation required the use of 3,4,6-tri-O-tert-butyldimethylsilyl-D-glucal (**111**), and Schlosser's base [1.8-2 mmol BuLi : 1.6 mmol ^{t}BuOK, in THF, -78 °C; 1 hour, followed by tributyltin chloride 3 mmol, -78 °C to room temperature, 2 hours]. Desilylation (Bu_4NF, THF) of the resulting adduct, and O-benzylation (KH, benzyl bromide, THF, Bu_4NI, under nitrogen atmosphere and at 25 °C), provided the 3,4,6-tri-O-benzyl-1-tributylstannyl-D-glucal (**113**) in 55% overall yield as a viscous oil.

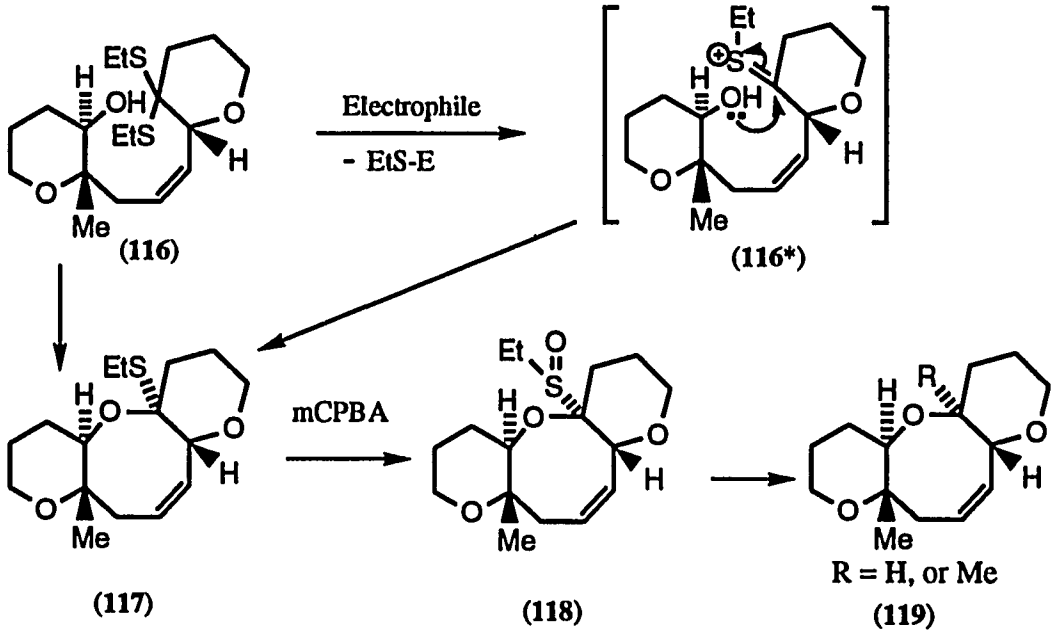


Metallation of (**113**); (BuLi, THF, -78 °C, 15 min) followed by alkylation with methyl iodide gave the corresponding 1-C-methyl derivative (**114**) in 88% yield. Hydroboration followed by oxidation ($BH_3.Me_2S$, then H_2O_2,

NaOH) gave the corresponding 1-C-methyl anhydro-D-glucitol derivative (**115**) in 70% yield.[13b]

Cyclization of Hydroxy Dithioketals:

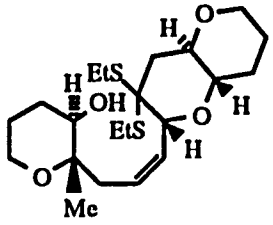
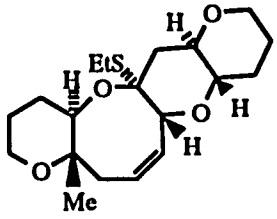
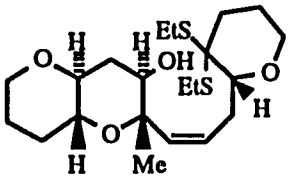
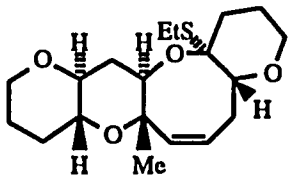
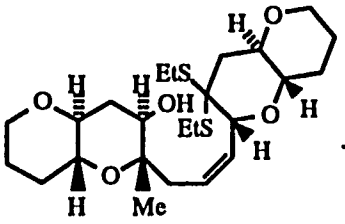
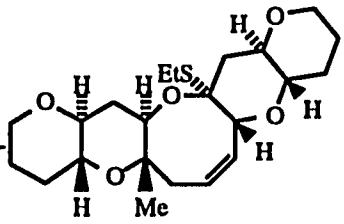
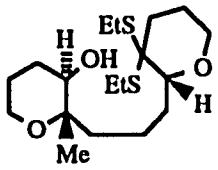
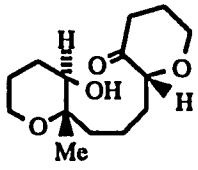
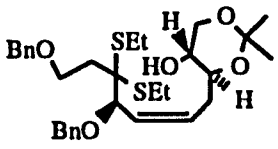
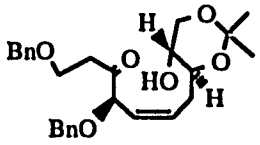
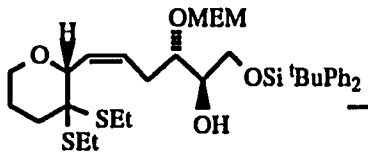
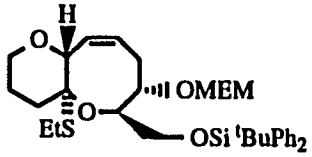
Nicolaou *et al.*[14c] developed a procedure for the construction of Oxocene (an eight membered highly strained) ring systems. For example, in a combination of nucleophile/electrophile scenario directed toward the transition state (the reaction coordinate), it was observed that the strain in the product will have a lesser effect on its activation energy. The activation of the sulfur of the dithioketal was therefore chosen as the precursor.



The attractiveness of this scheme lies in the fact that any one of the two sulfur atoms of the dithioketals will be involved in sulfonium ion formation, and the lone pair of the second sulfur atom will assist to form the sulfonium ion. The oxygen of the hydroxyl group will then be involved in the formation of the ring system. After the cyclization, the remaining sulfur group could be removed by homolytic or heterolytic "C-S" bond cleavage

leading to the desired functionality. It was also found that besides compound (**116**) other compounds also responded to this kind of reaction. Only a few of the model compounds formed "keto-intermediate" followed by cyclization. The following reactions indicate that the double bond is not essential for cyclization (entry 4 & 5). The reaction conditions are very mild.

Table-IV

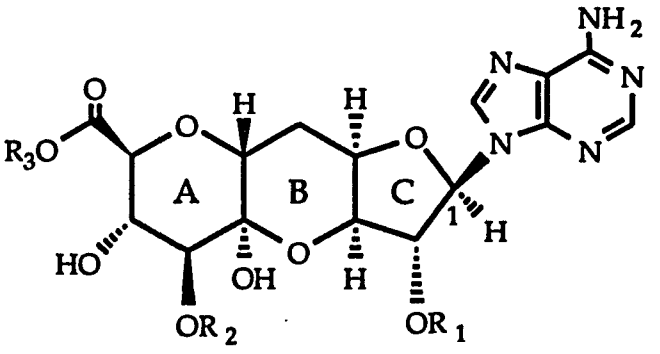
Entry	Reactants	Method	Products	Yield(%)
(1)		(B)		82
(2)		(A)		85
(3)		(A)		91
(4)		(B)		74
(5)		(A)		75
(6)		(B)		70

Method (A): 4.0 equiv of $AgClO_4$, 5.0 equiv of $NaHCO_3$, CH_3NO_2, 25 °C;
Method (B): 1.1 equiv of NCS, 1.1 equiv of $AgNO_3$, 2 equiv of 2,6-lutidine, CH_3CN, 25 °C

CHAPTER - 3

RETROSYNTHETIC SCHEMES

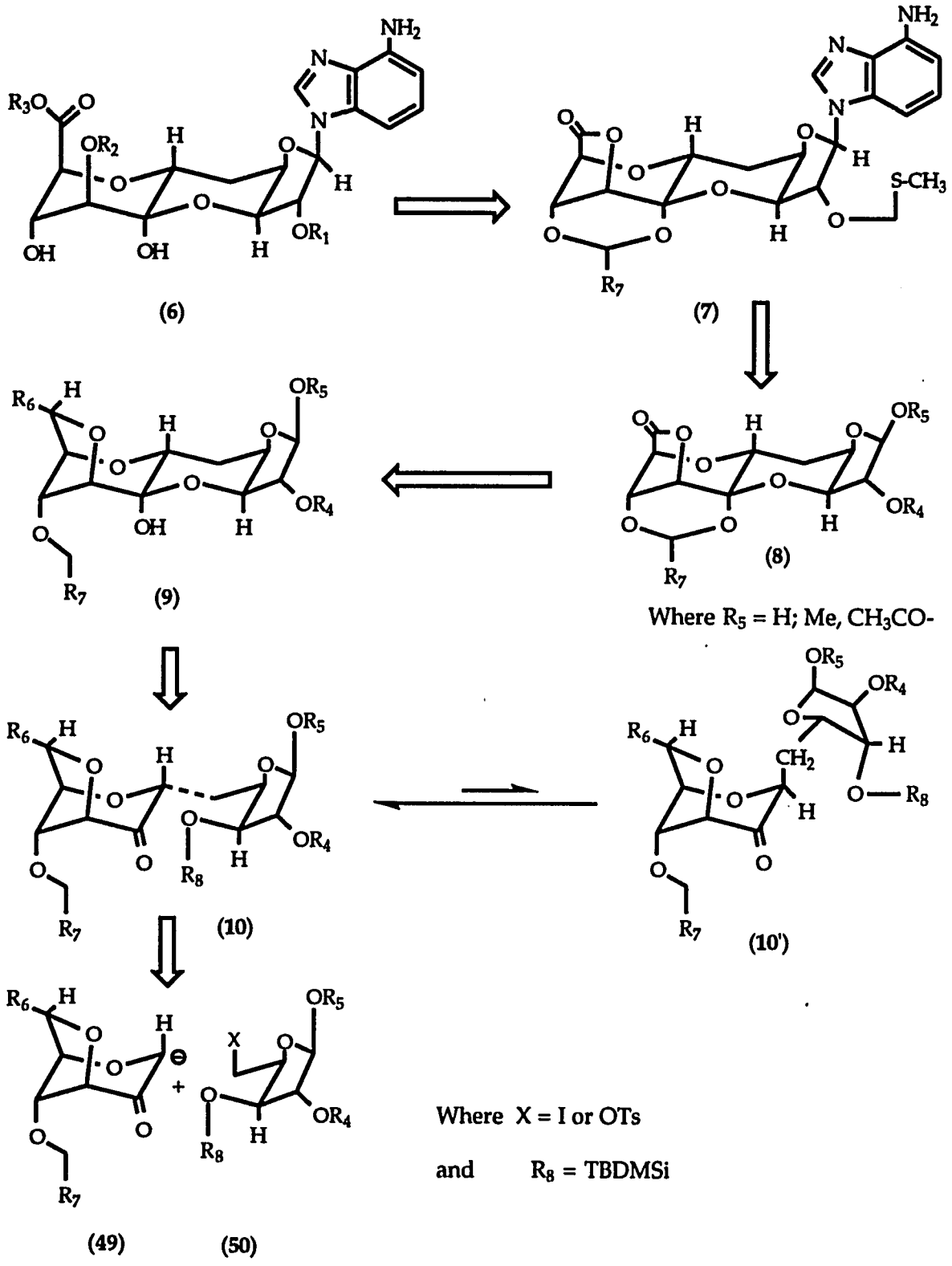
The structures of the herbicidins are shown below. Approaches to the synthesis of these compounds proceeds were developed according to the retrosynthetic schemes which follow.



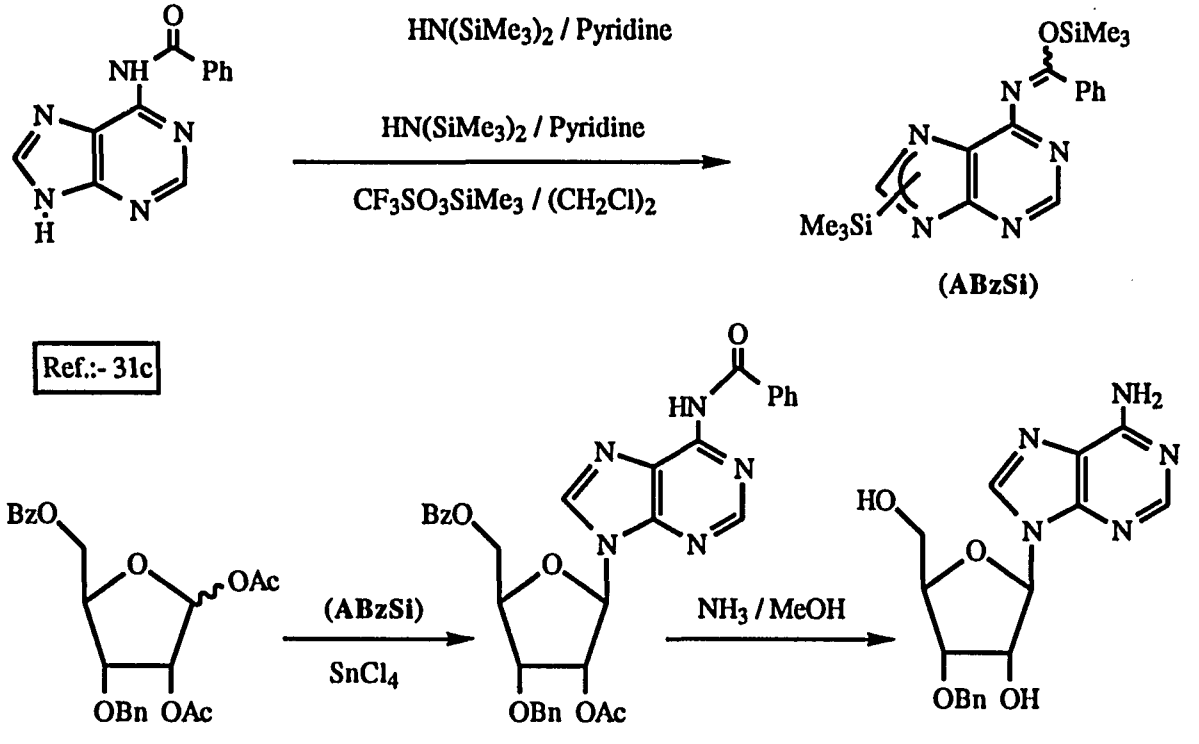
		R_1	R_2	R_3
(1)	Herbicidin A	CH_3	$CO(CH_2OH)=CHCH_3$	CH_3
(2)	Herbicidin B	CH_3	H	CH_3
(3)	Herbicidin E	CH_3	$COCH(CH_3)_2$	CH_3
(4)	Herbicidin F	CH_3	$CO(CH_3)C=CHCH_3$	CH_3
(5)	Herbicidin G	H	$CO(CH_3)C=CHCH_3$	H

Herbicidins contain three oxa-heterocyclic rings, as well as adenine nucleoside unit. Most interestingly, in ring-A, all the substituents are axial, and ring-B, seems to be a tetrahydropyran, which is connected to a five membered xylose like unit *i.e.* ring-C. The adenine unit is attached with the ring-C at its first carbon atom from its β side.

Retrosynthetic Scheme (1) :-

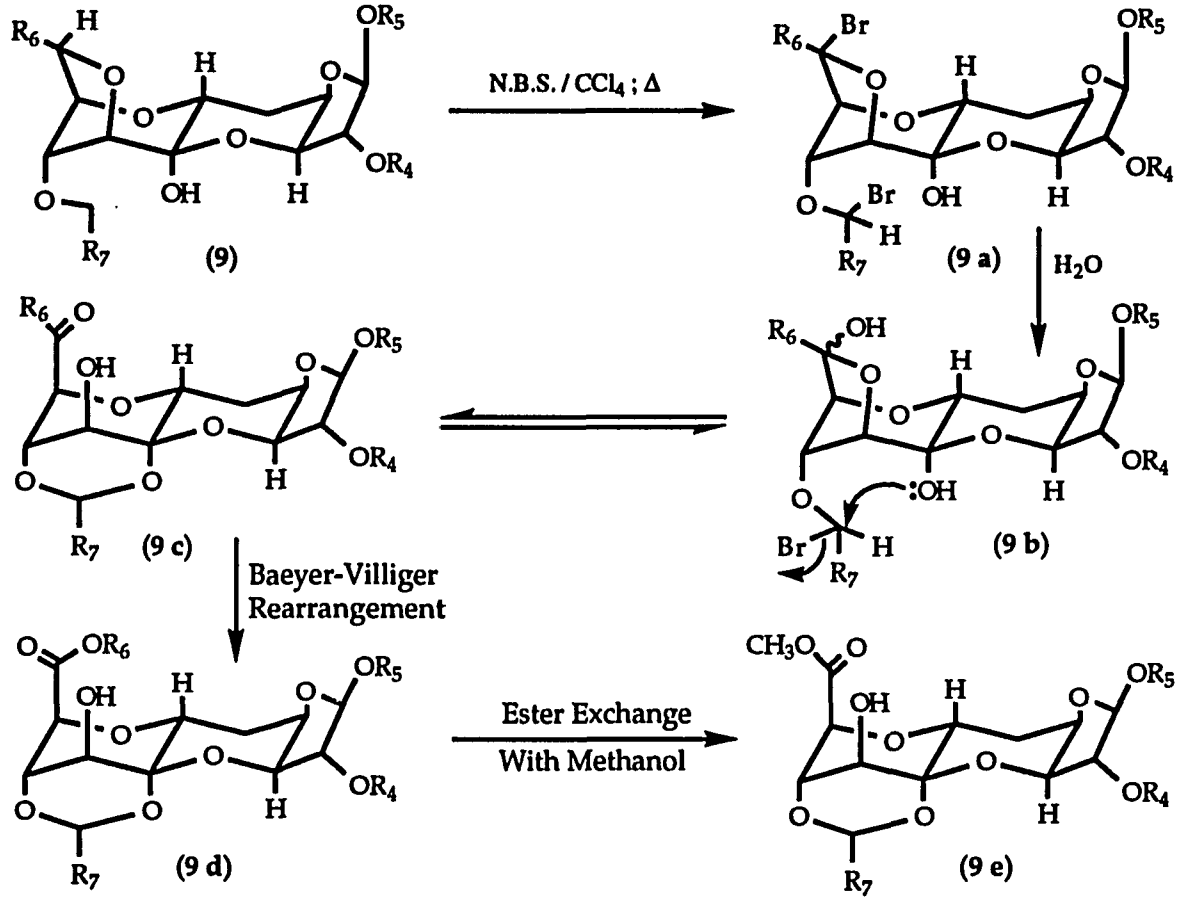


The herbicidin (6) could possibly be made from the lactone (7) by simple treatment with methanol or ethanol (i.e. ester exchange), followed by deprotection at C-2 of the xylofuranose ring. The adenine nucleoside can be put with the treatment of adenine and a iodo derivative of compound (8) treated with TMS iodide.[16] Alternatively, one of the most convenient way to attach a nucleoside on a sugar at C-1 by the reaction between the silylated amino nucleoside with protected 1-O-acetyl as well as 1-O-methyl sugars in the presence of Friedel-Crafts catalysts to provide the corresponding nucleosides, in excellent yields.[31] The reagent was prepared *in situ* at first protecting the primary amino group by benzoate followed by treatment with excess of hexamethyldisilazane (HMDS), in 1,2-dichloroethane using pyridine (as base), and trimethylsilyl trifluoromethane sulfonate (TMSOTf; CF_3SO_3-$SiMe_3$), as the Lewis acid at 40 °C.



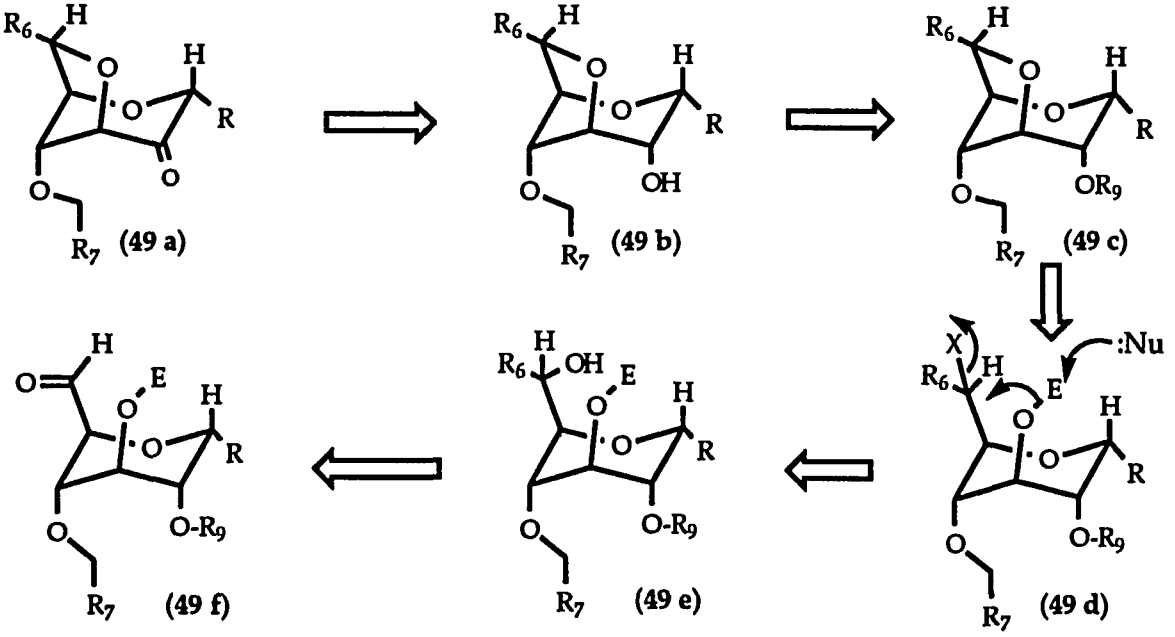
Compound (8) could be made from (9) where the O-1 of the xylose like unit is protected by R_5 and the C-6 of gluco pyranose is protected by R_6, which can be

brominated [radical bromination by N.B.S./CCl_4] and water work up to give the corresponding 6-hydroxy compound (a lactol), which could be oxidized to its corresponding ester by Baeyer-Villiger rearrangement.



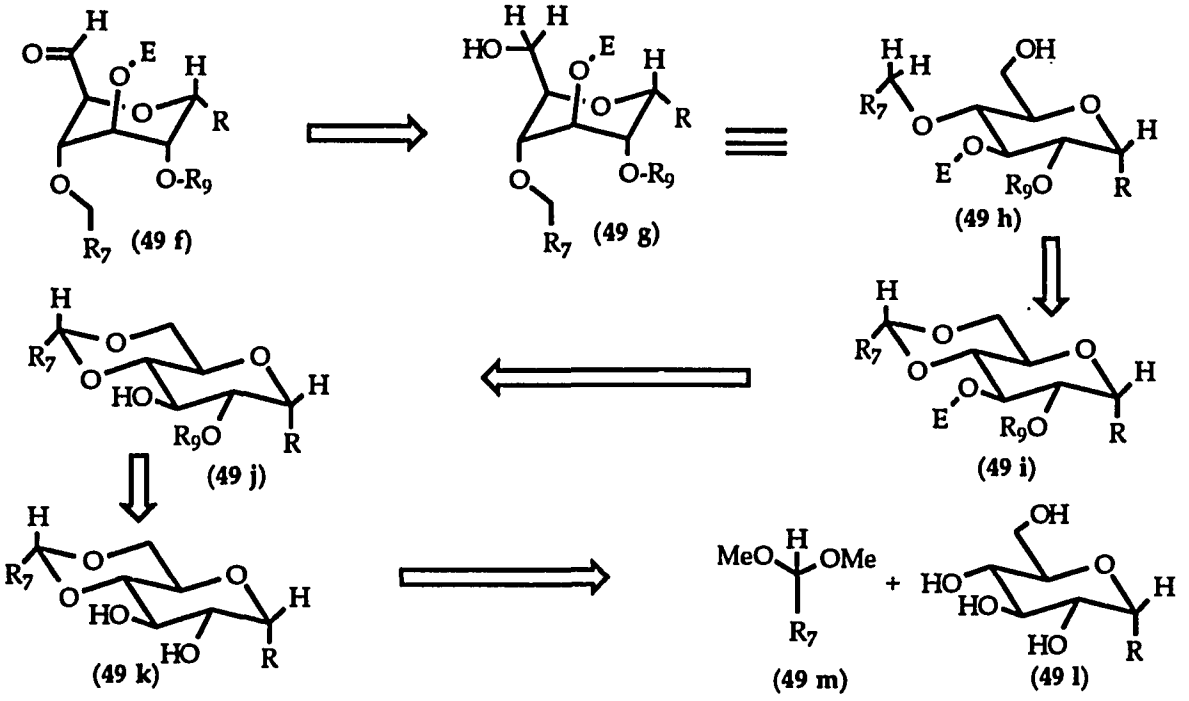
If R_5 is a benzyl and R_6 as well as R_7 is a phenyl group in compound (9), then the radical bromination of (9) with NBS (2 moles) in CCl_4 (radical bromination), followed by water work up can provide compound (8). So the best choice of R_6 is benzyl group. In order to migrate only the benzyl group we must use o- or p-methoxy benzyl group. Compound (9) could be made from compound (10) by removing the R_8 protecting group from xylose O-3 atom, which will attack the glucose C-2-oxo to form a hemiketal. So the best choice of R_8 is tert-butyldimethylsilyl group. In such case the silicon group can be replaced by hydrogen atom by simple treatment of the compound (10) with

tetrabutylammonium fluoride in THF, which will replace the silicon atom by a hydrogen followed by attacking at the C-2 oxo of the glucopyranose leading to give compound (9). Compound (10), [in which the C-1 (of glucose) and C-5 (of xylose) bond was shown by dotted one for convenience]; may be made by coupling of coupling between compound (49), which is a 3:6-anhydro sugar derivative and (50), which is a xylofuranose derivative. Compound (49) on treatment with lithium diisopropyl amide (LDA), in anhydrous THF under anhydrous nitrogen atmosphere at -79 °C, can give an C_1-C_2 enolate anion *only* between the C-2 & C-1 atoms (according to Bredt's rule, which states that double bond formation leads away from the bridge-head due to angle strain), followed by addition of (50) in the same reaction flask.



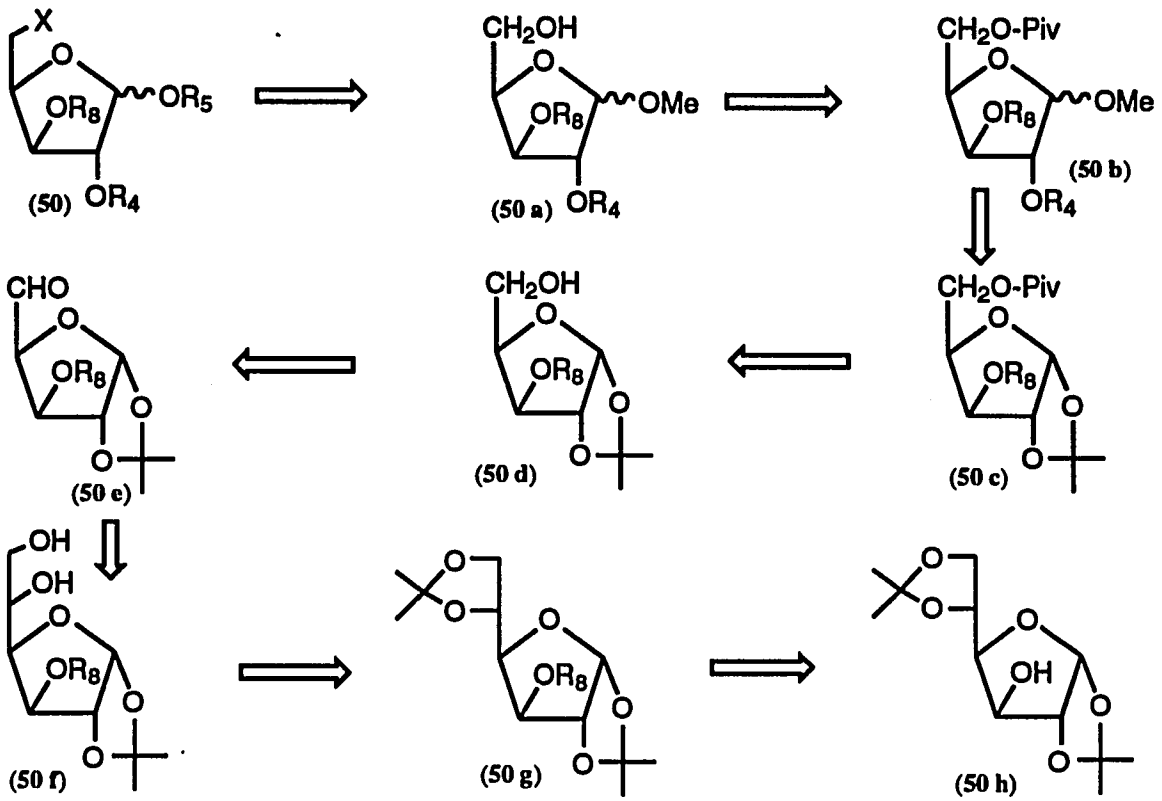
The anion (49) could be obtained from (49 a), which is a source of anion, where the group R (best choice R=H), will be replaced chemically producing the carbanion (49). Compound (49 a), which is a 2-oxo-3:6-anhydroglucopyranose could be made by oxidation from the alcohol (49 b), which could be obtained by the deprotection of the compound (49 c). The

compound (**49 c**) could be made from (**49 d**), deprotecting the O-3, by nucleophilic attack at O-3; which would attack the C-6, which contains a leaving group X (for example, a tosylate). Compound (**49 d**), the tosylate could be made from the corresponding secondary alcohol (**49 e**). Compound (**49 e**) could be made from the corresponding 6-aldehyde (**49 f**), which could be made by the Swern oxidation of the corresponding 6-alcohol (**49 h**) in which the O-2, O-3 and O-4 are protected by suitable and different protecting groups.



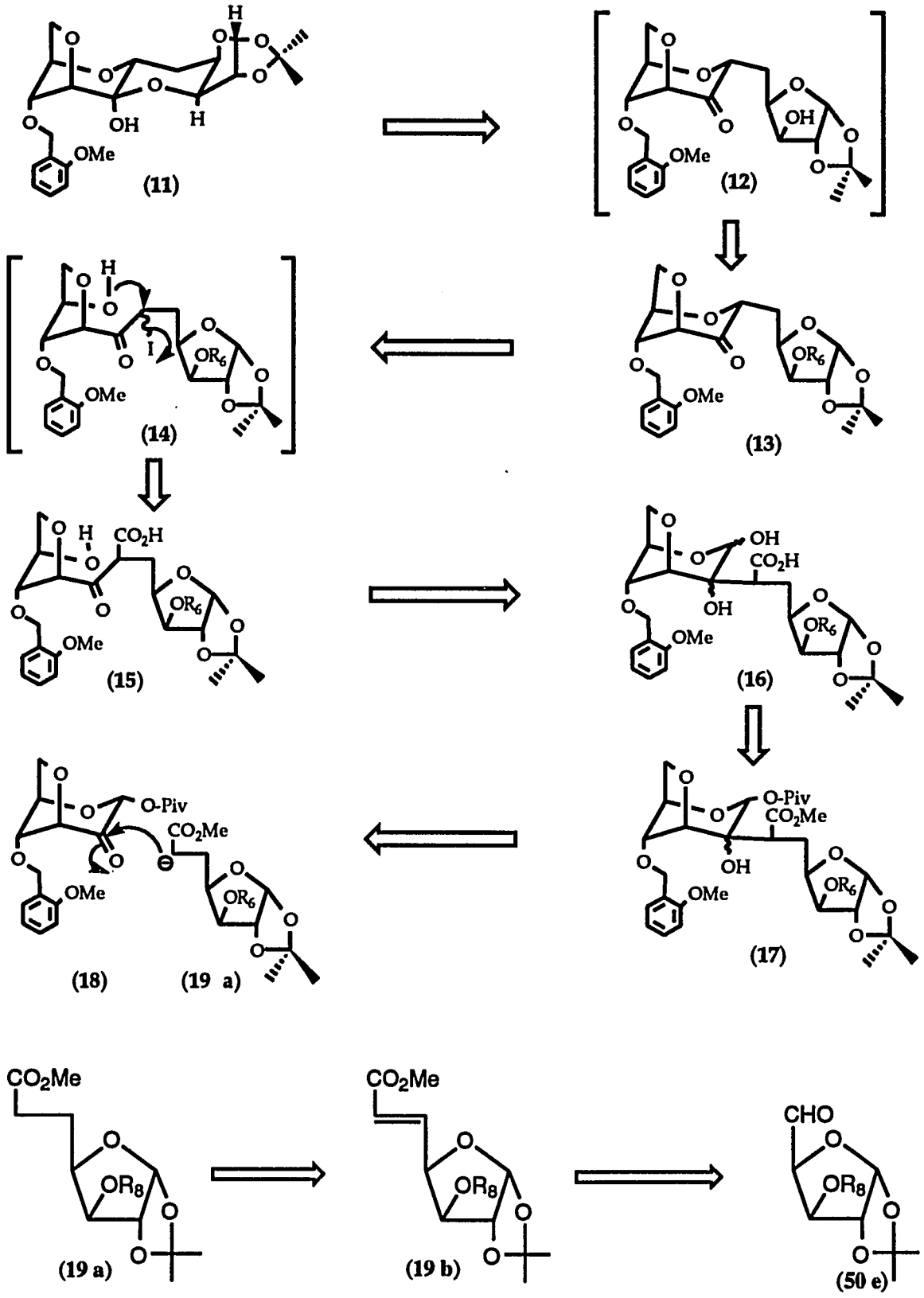
Compound (**49 h**) can be obtained by the regioselective cleavage of the benzylidene (or the substituted benzylidene glucopyranoside (**49 i**), where O-2, and O-3 are protected. The best O-3 protection is TBDMS, and R_9 is pivalate. (**49 i**) is possible to make from the diol (**49 k**), first by pivaloylation at O-2 followed by silylation the O-3 as TBDMS ether. Compound (**49 k**) can be made from the glucose or its derivative (**49 l**) and the dimethyl acetal of the aldehyde containing R_7.

Retrosynthetic Scheme of the Xylofuranose (50):-



Compound (50) could be made from the corresponding alcohol (50 a). So the best choice of X is the tosylate, and R_5 is methyl group, which could be replaced by adenine nucleoside. The alcohol (50 a) could be made from (50 b) by deprotecting (by saponification) the pivalate of the compound (50 b) at O-5. Compound could be made from compound (50 c), by methanolysis, with catalytic amount of ion exchange resin $H^{\oplus}$ form. Compound (50 c) could be made from compound (50 d), by esterification with pivaloyl chloride and pyridine at room temperature. The alcohol could be made by $NaBH_4$ reduction of the aldehyde (50 e), which could be made by periodic acid cleavage of the diol (50 f). Compound (50 g) by selective deprotection of the acetonide group. Compound (50 g) could be made from compound (50 h), which is known as diacetone glucose.

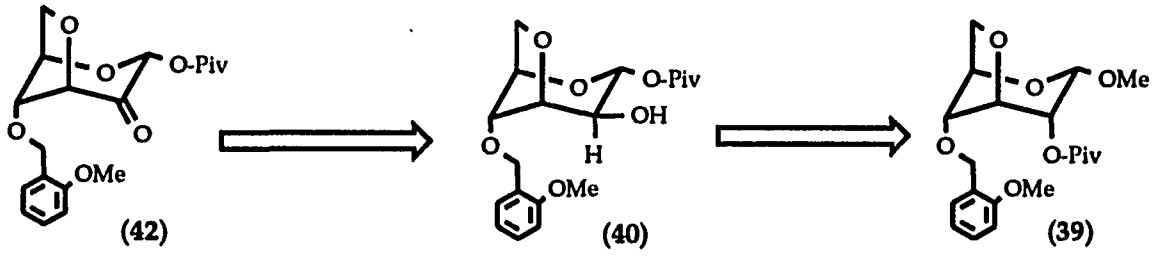
Retrosynthetic Scheme (2) :-



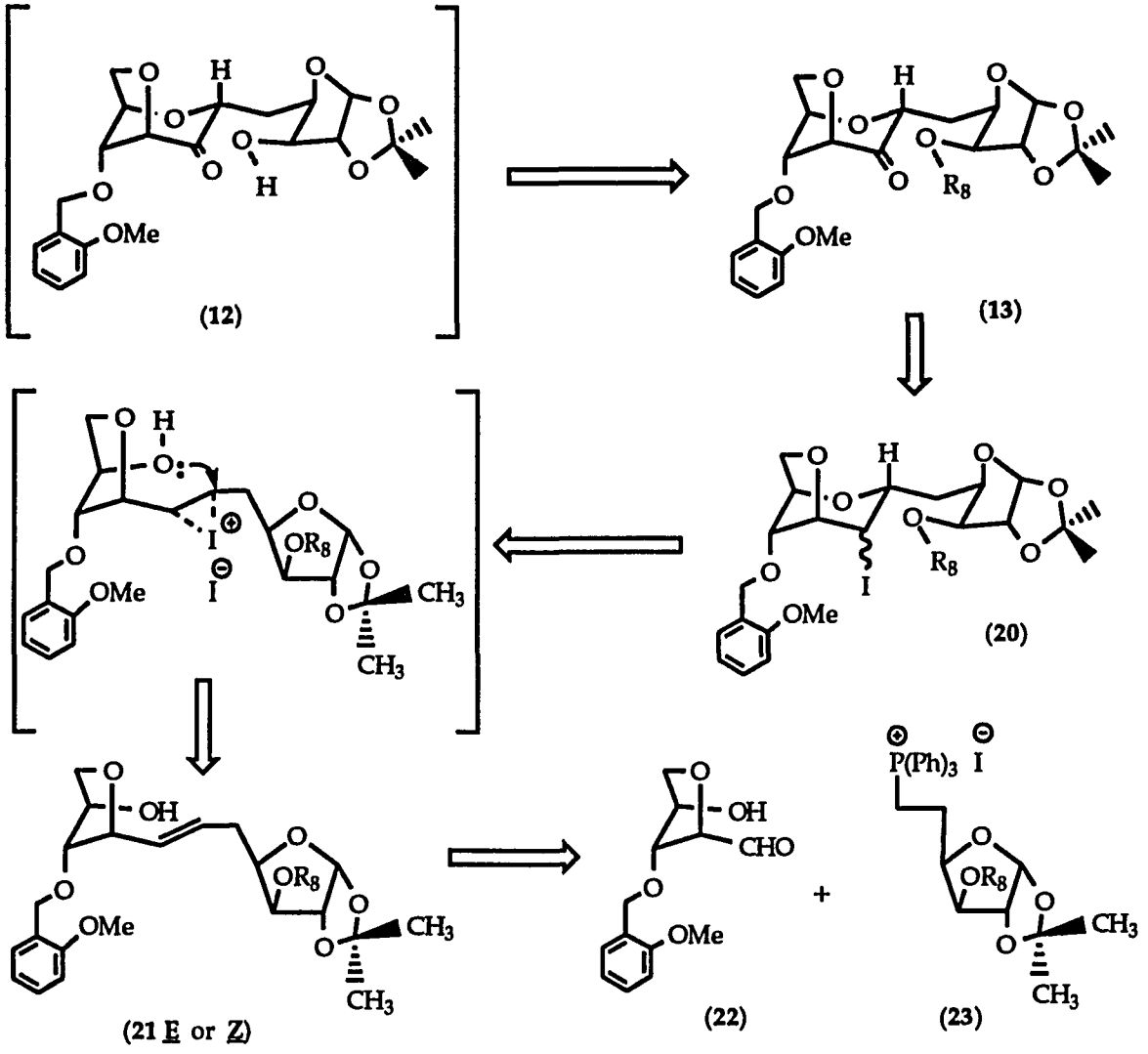
The same skeleton (**11**) can be made by the following synthetic schemes, in which the C-1 and C-2 of xylose are being protected either by isopropylidene or by cyclohexylidene unit, and xylose O-3 is being protected by TBDMS ether. Compound (**11**) could be made from compound (**13**) by *deprotection* of the silyl group. [The silyl group, which can be deprotect by the treatment of tetrabutylammonium fluoride in tetrahydrofuran solvent or boron trifluoride followed by aqueous bicarbonate treatment]. Compound (**13**) can be made from (**15**) by alkali-iodine treatment,[18] (first saponification of the ester group followed by decarboxylative iodination and immediate ring closure in the presence of base).[22] Compound (**15**) can be made by periodic acid oxidation[19] of the diol (**16**), which could be obtained by the saponification of (**17**). At this point it is to be noted that, during the saponification both the esters group will be hydrolysed. Compound (**17**) can be made by the treatment of the anion of (**19 a**). The anion of (**19 a**) can be made treating the ester with one equivalent of LDA in anhydrous THF at -79 °C,[2a] followed by the treatment with (**18**), in the same condition.[2b]

The ester (**19 a**) could be made from its corresponding α-β-unsaturated ester (**19 b**), which could be made from the aldehyde (**50 e**) by Wittig reaction.

The ketone (**18 a**) could be made by the oxidation of its corresponding alcohol (**18 b**); which could be made by acid hydrolysis of compound (**18 c**), in which the C-2 pivalate will migrate from C-2 to C-1.

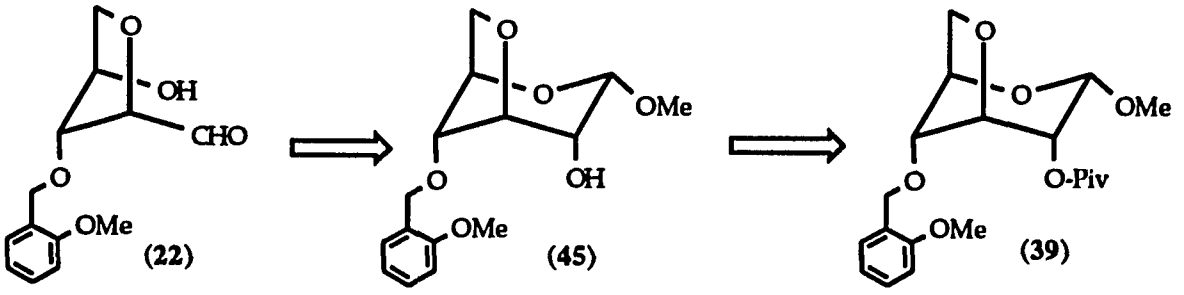


Retrosynthetic Scheme (3) :-



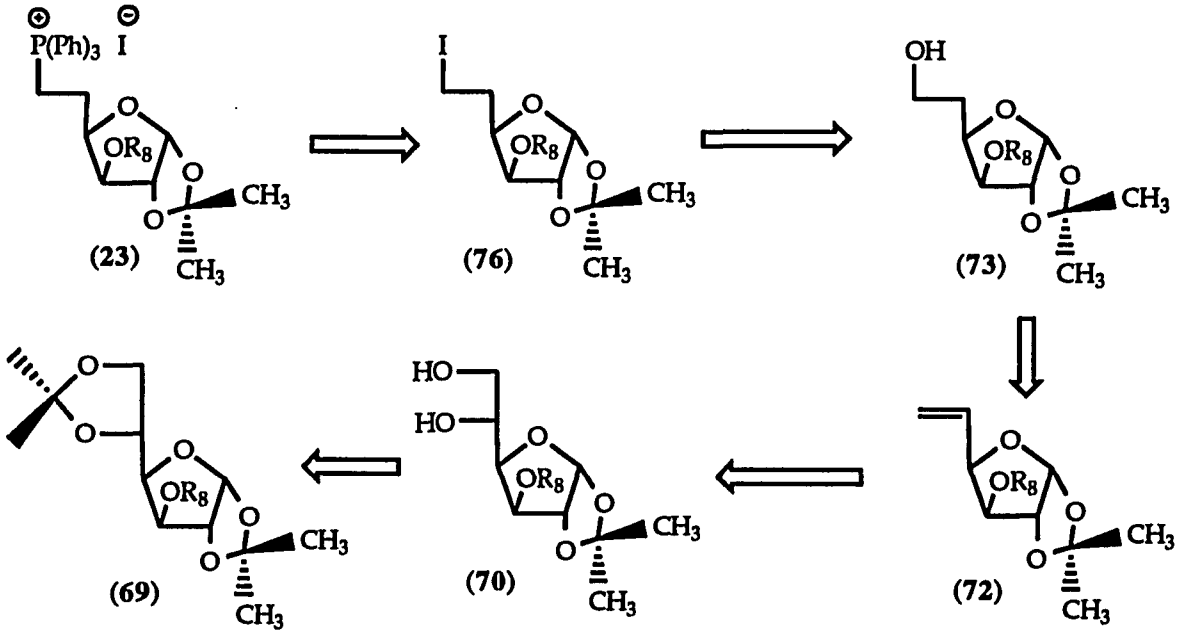
Compound (**13**) could also be made from the iodo compound (**20**), by the treatment with trimethylamine oxide in toluene in the presence of sodium bicarbonate.[21] Compound (**20**), can be made from compound (**21**) [either *E* or *Z* form] with the treatment of iodine in the presence of sodium bicarbonate in THF;[22a & b] at first an iodonium ion will be formed which will be attacked intramolecularly by the neighboring C-5 hydroxyl group. Compound (**21**) can be obtained by Wittig reaction of the ylide of the phosphonium salt of (**23**) and the aldehyde (**22**).

Retrosynthesis of the aldehyde (22):-



The aldehyde (22) could be made the by periodic acid oxidative cleavage of the 3:6-anhydro sugar (22 a), which could be made 3:6-anhydro gluco-pyranose (22 b).

Retrosynthesis of the phosphonium salt (23):-

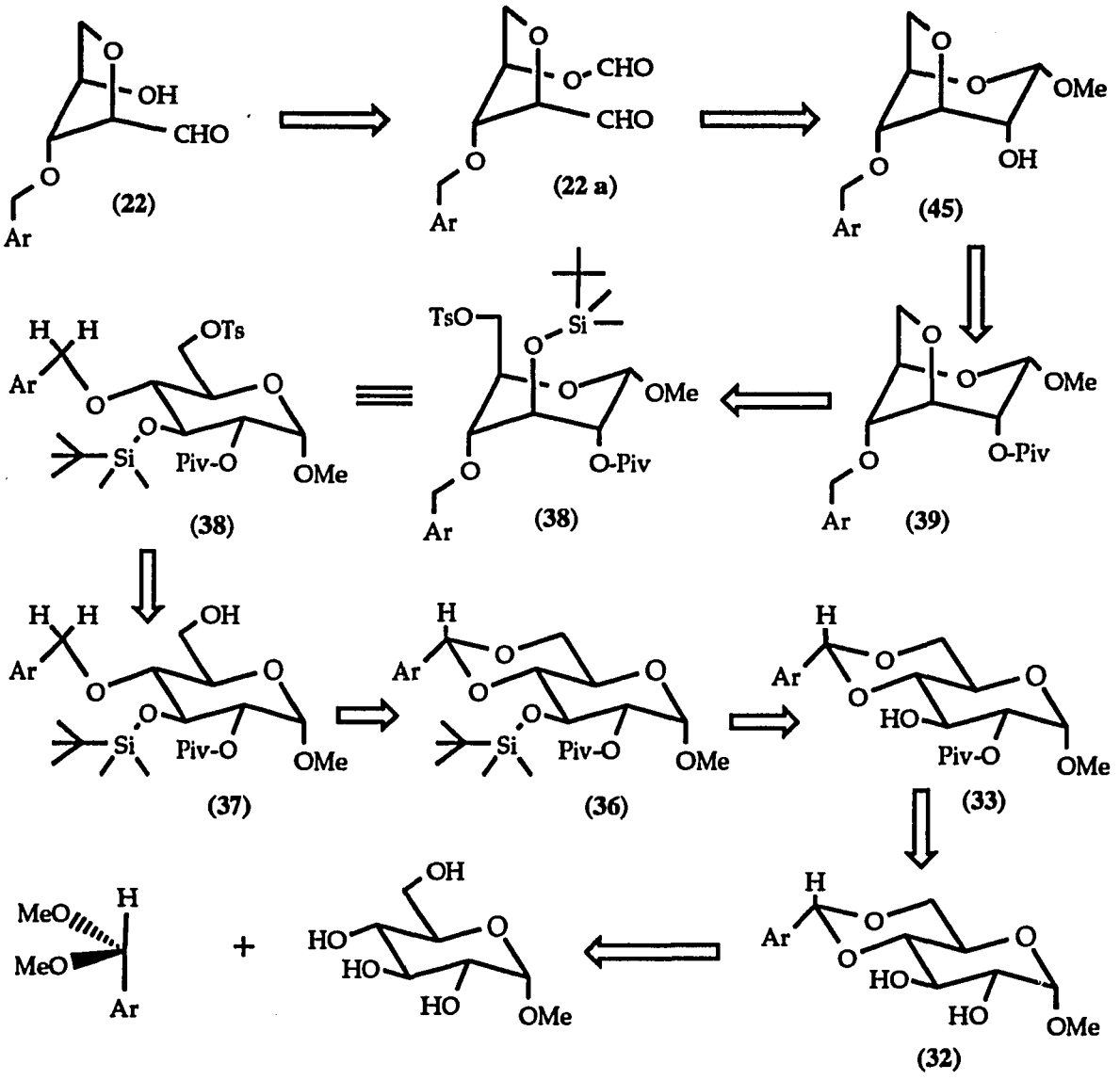


For convenience, O-3 was protected by benzyl group; *i.e.*; R_8 = Benzyl

The phosphonium salt (23) could be made by fusing the iodide (23 a) and triphenylphosphene. The iodide (23 a) can be made from its corresponding primary alcohol (23 b), which could be obtained from

compound (23 c) by the hydroboration reaction followed by the treatment with hydrogen peroxide in the presence of alkali. The olefin could be made from the diol (23 d), first by treating with methane sulfonyl chloride in pyridine, followed by the treatment with sodium iodide in 2-butanone.

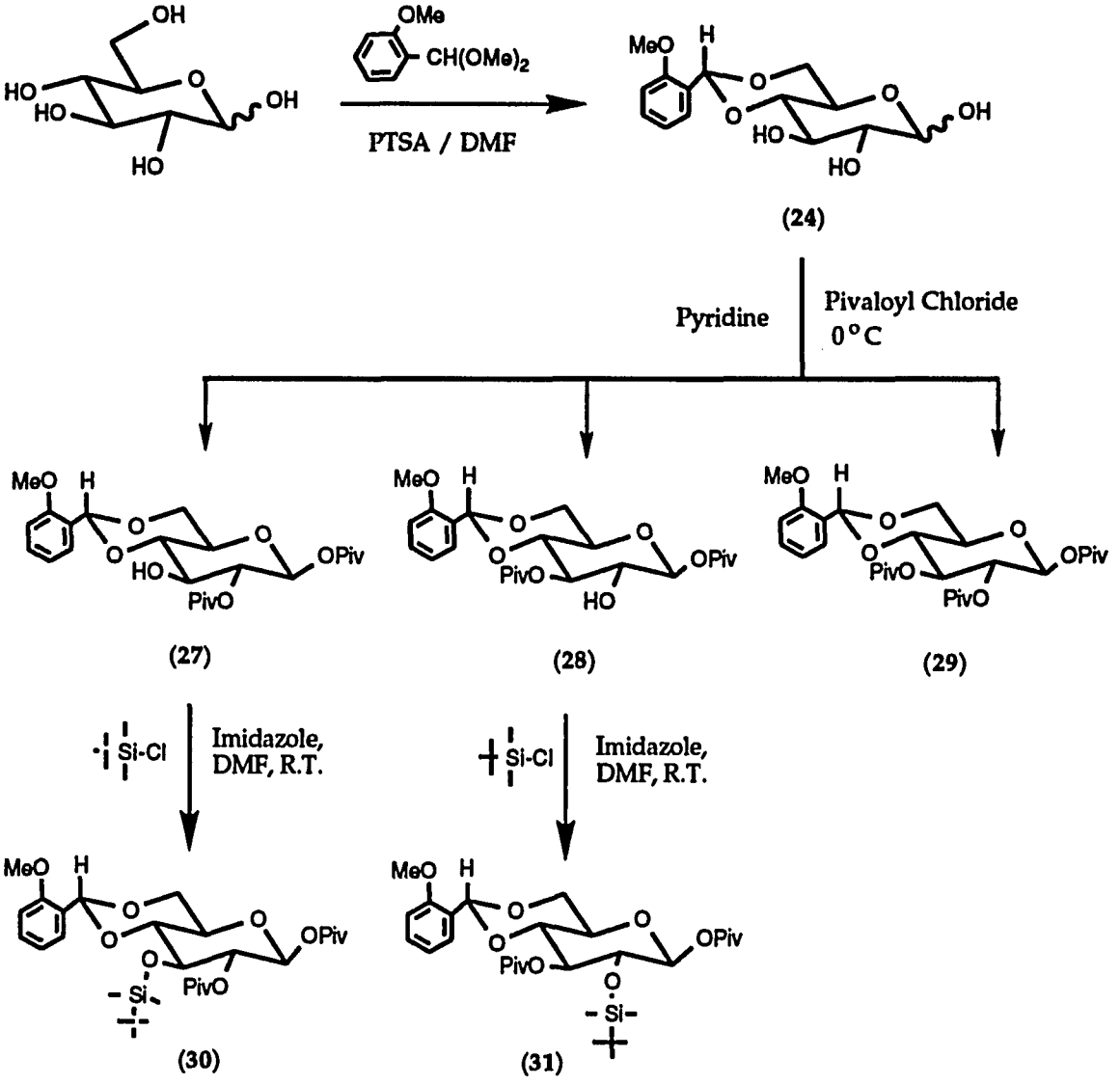
Retrosynthesis of compound (22):



CHAPTER - 4

Results and Discussions

Synthesis and Chemistry of the 3,6-anhydrosugar:-



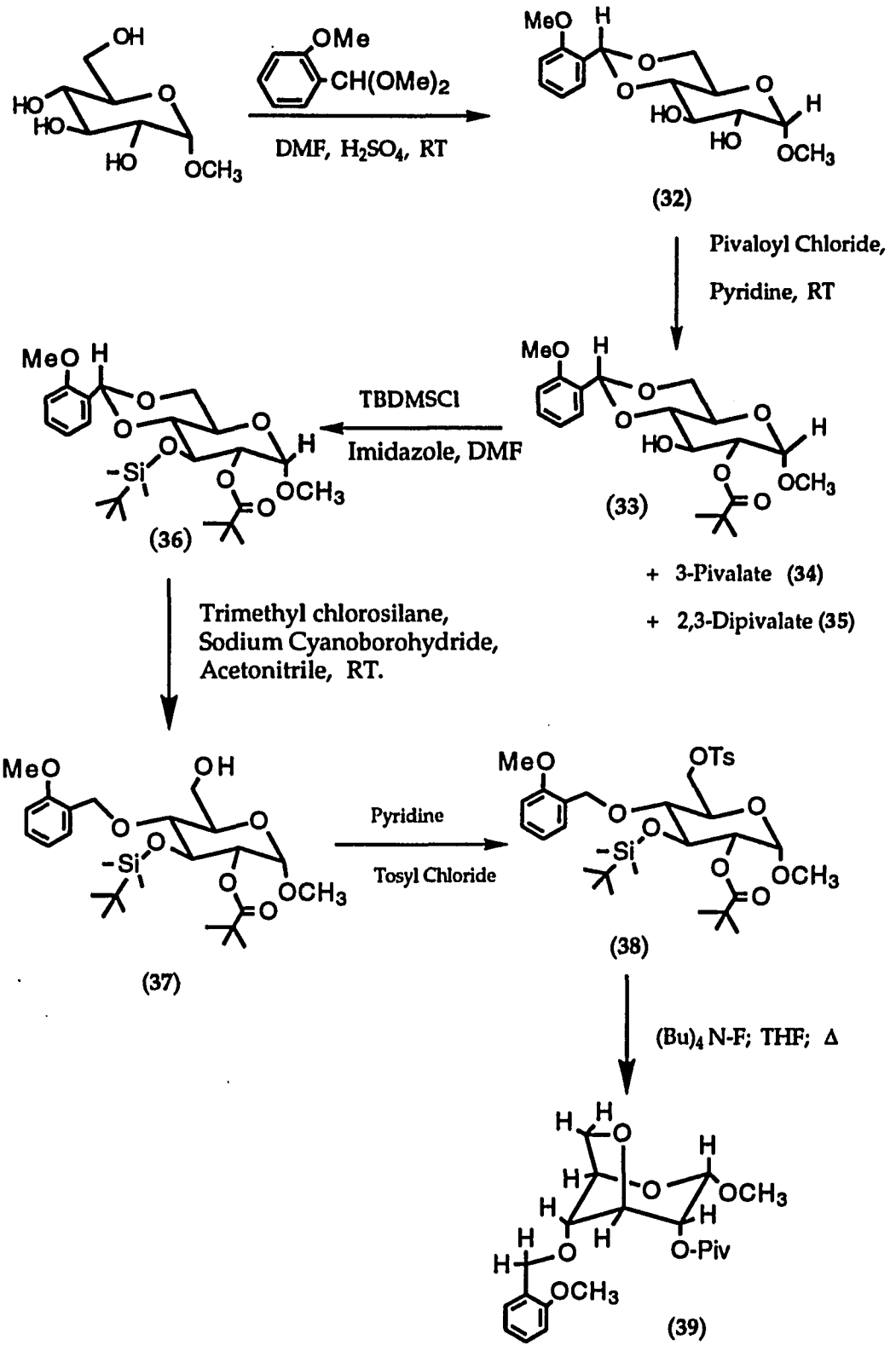
Anhydrous glucose was allowed to react with 2-methoxybenzaldehyde dimethyl acetal, in DMF, in the presence of a catalytic amount of p-toluene sulfonic acid,[6a] to give the 4,6-O-(2-methoxybenzylidene)-glucopyranoside (**24**), in 55% yield. Treatment of (**24**), with 2.2 molar equivalents of pivaloyl chloride in dry pyridine,[9] gave a mixture of pivalates. In a small scale reaction, the separation of 1,2-dipivalate (**27**), from its 1,3-isomer (**28**) was successful, however for large scale reactions the separation of the two isomers

was unsuccessful. The ^1H- N.M.R. spectrum of the mixture showed that 1,3-dipivalate was the major product. (The ratio of 1,3-dipivalate : 1,2-dipivalate was 3:2). By tert-butyldimethylsilylation of the above mentioned dipivalates, it was then possible to achieve chromatographic separation on silica gel of the two isomers, eluting with benzene only. On the other hand, when methyl-α-D-glucopyranoside was taken through the same sequence of reactions, the major product was the 2-pivalate (33), in 82% yield, which was very easy to separate from the isomeric 3-pivalate (34), 1% yield, and 2,3-dipivalate (35), 10% yield. So instead of using glucose, methyl-α-D-glucopyranoside was used as the starting material.

Methyl-α-D-glucopyranoside was allowed to react with 2-methoxy-benzaldehyde dimethyl acetal in dry DMF, in the presence of a catalytic amount of conc. sulfuric acid, and this reaction gave methyl 4,6-O-(2-methoxy-benzylidene)-α-D-glucopyranoside (32), in 80% yield.

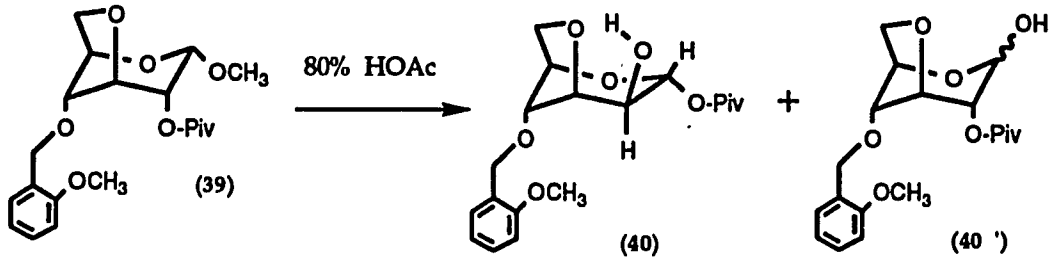
Monopivaloylation[9] of (32) in pyridine, gave the 2-pivalate ester(33), in 75-82% yield, along with very little 3-pivalate isomer (1%), and the 2,3-dipivalate (10%). After column chromatographic purification of compound (33), O-3 was protected as its silyl ether[5] (36), in 98-100% yield; by treating with TBDMSCl and imidazole in DMF as solvent.

Selective cleavage of (36) with sodium cyanoborohydride and chlorotrimethylsilane, in acetonitrile, and in the presence of *powdered* molecular sieves type 3A,[7d & e] gave compound (37) as a syrup, in 85-87% yield. Tosylation of (37) by p-toluene-sulfonylchloride in pyridine,[23] gave the corresponding tosylate (38) in 100% yield as a syrup. Treatment of (38) with tetra butylammonium fluoride in boiling THF, at the high dilution principle (to prevent polymerization), gave the 3-6 anhydrous glucose (39) in 85% yield.

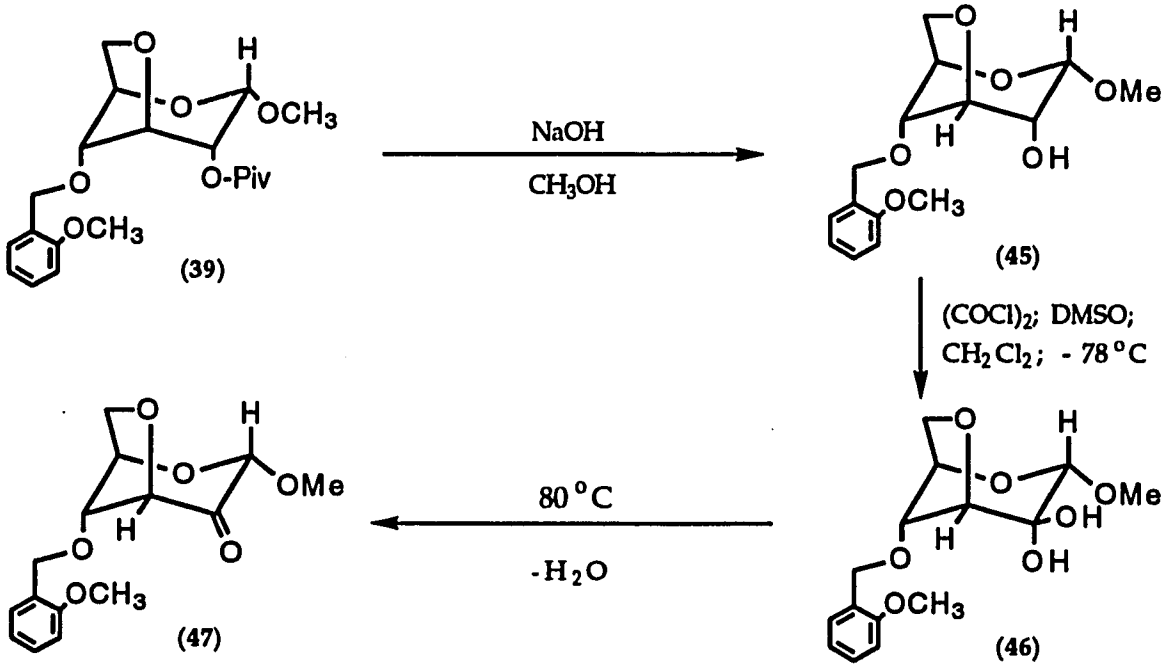


Acid hydrolysis of the ether functionality of (39) with 85% aqueous acetic acid[24] gave an unusual rearranged product (40), where the pivalate had

migrated from C-2 to C-1, with only a very small amount of (40 '). The unusual migration of the pivalate from C-2 to C-1, was proven by oxidation of compound (40) with DMSO/oxalyl chloride in anhydrous dichloromethane and at -79 °C,[25] to give the corresponding C-2 oxo derivative (42), where the anomeric proton (H-1) was found to be a singlet.



Swern oxidation of the alcohol (45), with oxalyl chloride/DMSO in dichloromethane at -78 °C gave the corresponding ketone in 88% yield, as its hydrated form (46). The dehydration was done by azeotroping the hydrate with toluene for one hour to give (47).

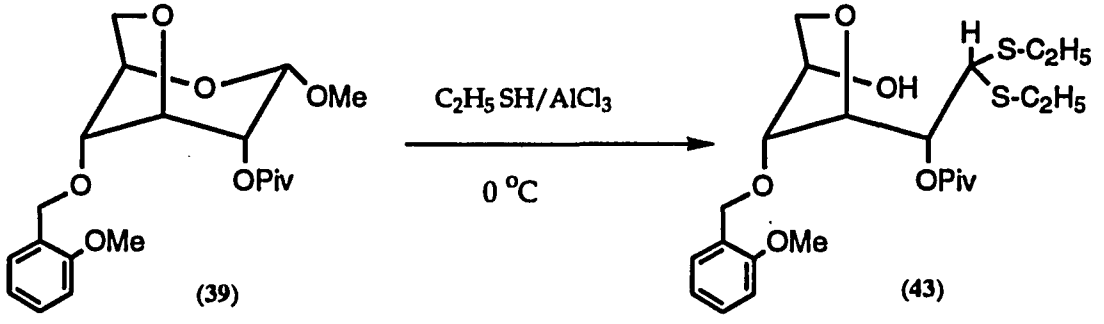


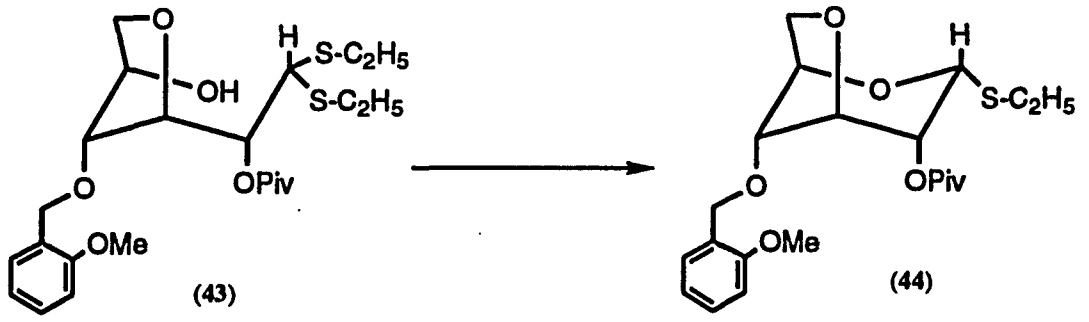
Cleavage of the pivalate group from the 3,6-anhydrous sugar (39) proved rather difficult unable even by treatment with 10 molar equivalents of sodium methoxide in methanol. It was readily hydrolyzed however, to its corresponding alcohol (45), by treatment with only two equivalents of sodium hydroxide in methanol.

Hydrolysis of the alcohol (45) with 90% acetic acid in water, to its corresponding diol and *immediate* periodic acid cleavage[19] gave compound (48), which on bicarbonate/water treatment, provided the aldehyde (22), in almost quantitative yield.

Synthesis of 3:6 anhydro glucose, 1-dithioketal:[26]

When the 3,6-anhydrous sugar (39) was treated with large excess of ethane thiol in THF at 0 °C, in the presence of anhydrous aluminium chloride, a dithioketal derivative (43) was isolated in 55% yield. One most interesting observation is that the molecular ion in the Mass Spectral data (C.I.), had only one thio-ethyl ("S-Et") group rather than two, showing the facile cleavage of the dithioketal. On the other hand the N.M.R. spectra shows the presence of dithio group at C-1, which is thought to result from the restricted rotation around the C-1 and C-2 bond.

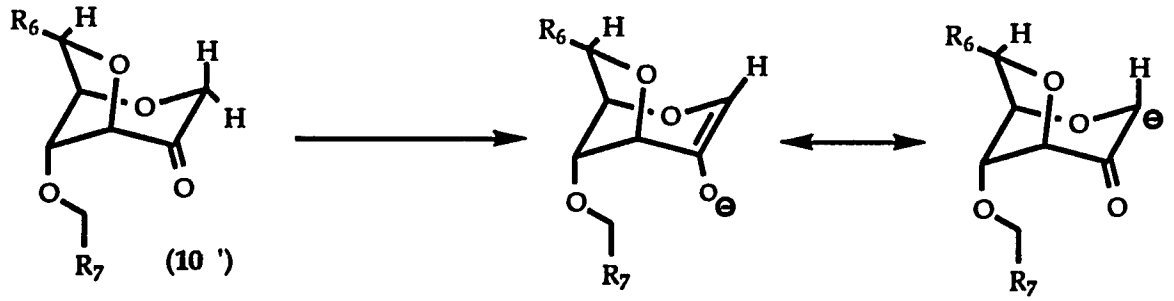




Cyclization of compound (43) to compound (44), failed when using the conventional methods.[14a & b] But when the dithioketal (43) was gently heated to reflux with benzyl bromide (resonance stabilized electrophile) for 24 hours, in dry DMF along with a little toluene, (the dithioketal is insoluble in toluene, but soluble in DMF; and to reduce the reflux temperature a little toluene was used), compound (44) was formed in 15% yield [which could be desulfured to compound (60) which is analogous to compound (10 ')], the rest of the starting material remain unreacted. Using silver nitrate in dry acetonitrile, to cyclize the compound (43) to (44), the 2-methoxy benzyl group was cleaved from the glucose unit, and the sugar molecule was found to undergo decomposition.

Synthesis of 1:5-3:6 dianhydroglucopyranose:

Deoxygenation at C-1 to make molecule (10 ') proved unsuccessful. The analogous of the 1,5-3,6-dianhydro-2-keto-sugar (10 '), [where R_6 is hydrogen and R_7 is ortho methoxy phenyl group], can be made in the same reaction

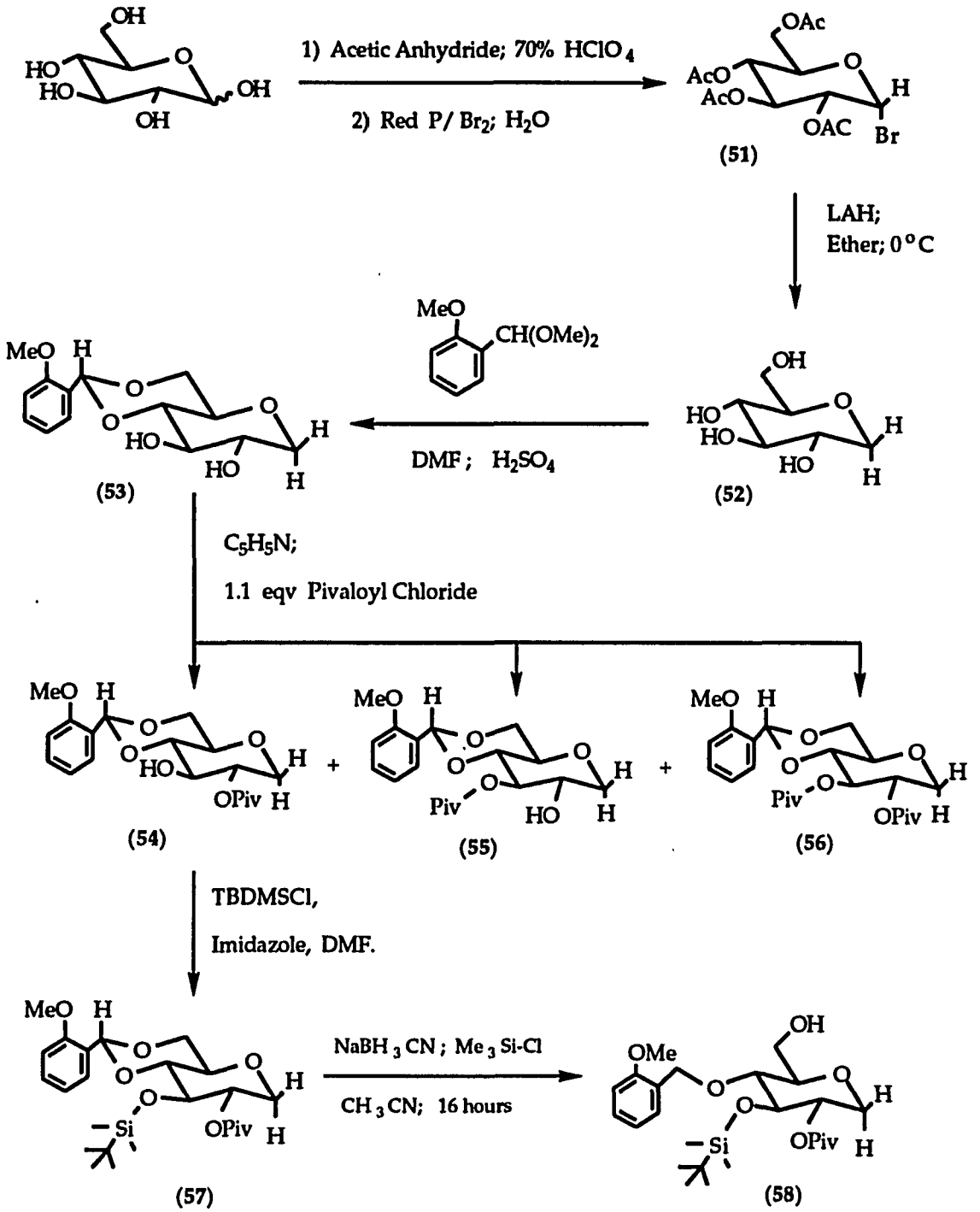


sequence by reducing the glucose derivative at the C-1-position at first to give the 1,5-anhydro glucitol. Instead of using D-glucose or methyl-α-D-glucopyranoside, 1,5-anhydro sorbitol was used, and following the same reaction sequence we were able to make the 1,5-3,6-dianhydro-2-oxo compound (**62**).

Pure anhydrous glucose was treated with acetic anhydride in the presence of 70% perchloric acid at 0 °C, to give the penta acetate, which was treated with red phosphorus/bromine followed by water (in the same reaction flask), at 0 °C, to give the 1-α-bromogluco-pyranose 2,3,4,6-tetraacetate (**51**), in 92% yield.[6a] Careful treatment of anhydrous (**51**) with lithium aluminum hydride (LAH) in anhydrous ether at 0 °C, followed by careful treatment with water (to quench the excess LAH) at 0 °C, gave 1,5-anhydro glucitol in the water layer.[27] Suction filtration of the white inorganic precipitate (Al_2O_3 /$Al(OH)_3$] from the supernatant, followed by deionization of the water layer with ion-exchange resin, followed by evaporation of water under reduced pressure gave a gum, which was crystallized from methanol providing pure crystals of the 1,5-anhydro glucitol (**52**) in 65% yield.

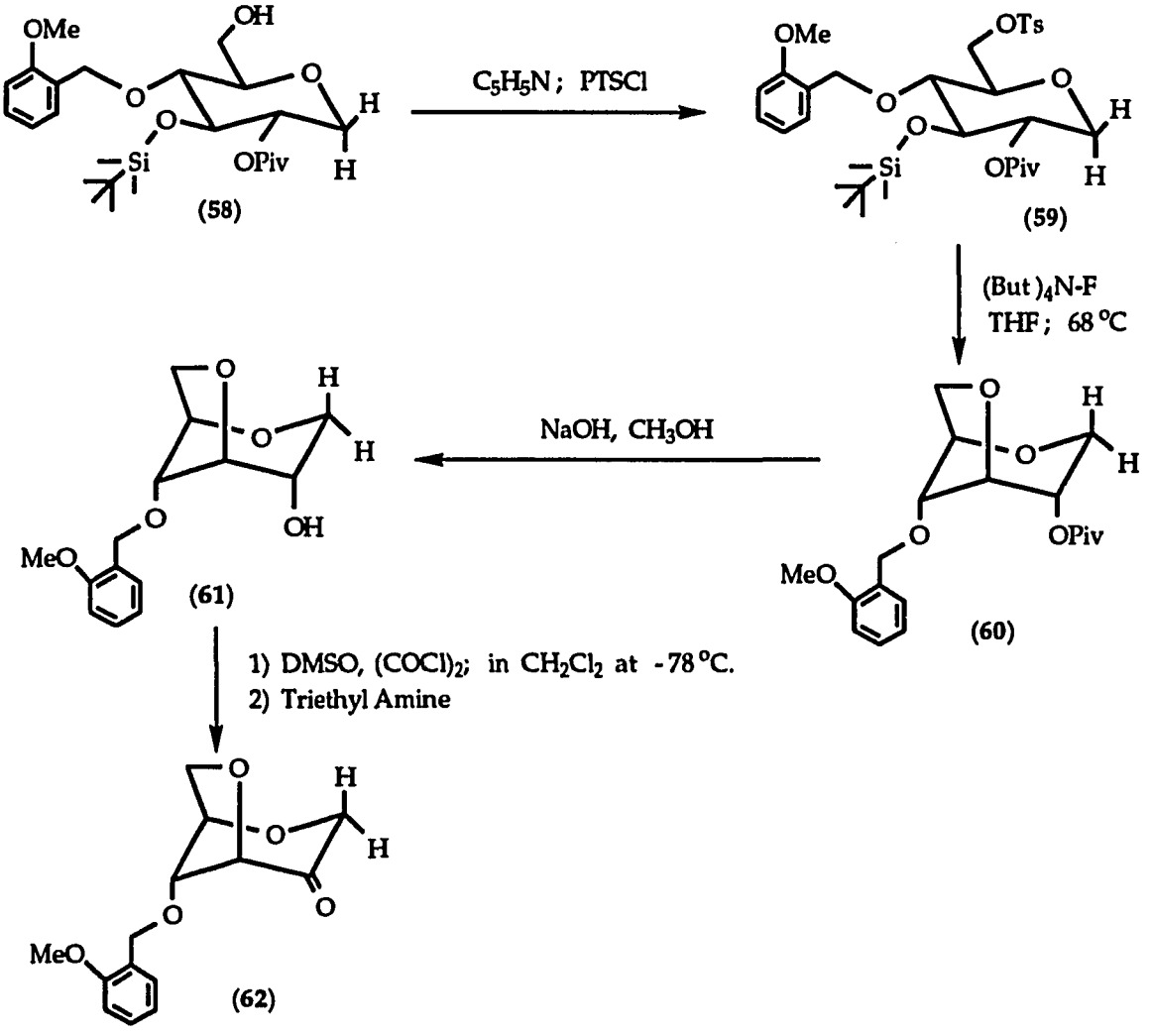
1,5-Anhydroglucitol (**52**) was treated with 2-methoxybenzaldehyde dimethyl acetal in the presence of a catalytic amount of conc. sulfuric acid in anhydrous DMF, gave 4,6-(ortho) anisilidine-1,5-anhydro- glucopyranoside (**53**) in 80% yield.

Trearment of (53) with 1.1 molar equivalents of pivaloyl chloride in pyridine at room temperature gave a mixture of the 2-pivalate (54); the 3-pivalate (55); the 2,3-dipivalate (56) and a little unreacted material. Isolation of the 2-pivalate (54) by column chromatography followed by silylation with

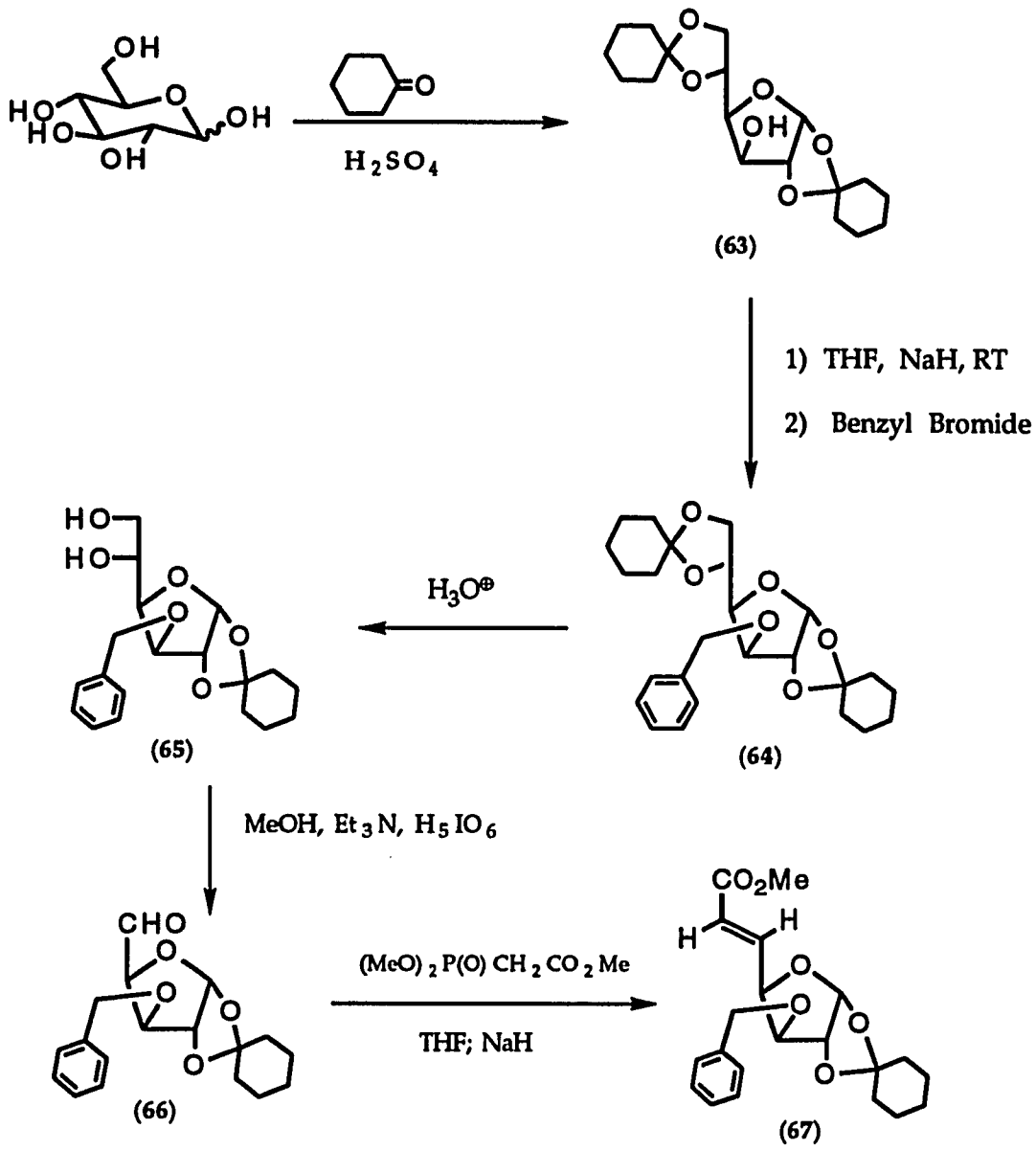


TBDMSCl (tert-butyldimethylsilyl chloride) in the presence of imidazole in dry DMF gave the corresponding silyl ether (57) in nearly quantitative yield.

Treatment of (57) with sodium cyanoborohydride in the presence of chlorotrimethylsilane (as electrophile) in acetonitrile[7e] as solvent gave the desired alcohol (58), which on treatment with tosyl chloride in the presence of pyridine gave the corresponding tosylate (59). The tosylate (59) on treatment with tetrabutyl-ammonium fluoride in boiling THF gave 1,5-3,6-dianhydro glucose (60). which on saponification followed by Swern oxidation gave compound (62), one of the target molecules, analogous to (10 ').



Synthesis of glucofuranoses

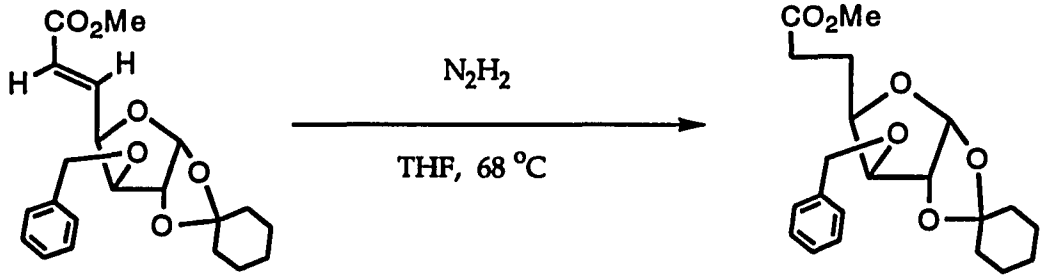


Anhydrous glucose was used to make the furanose units. Anhydrous glucose was allowed to react with a large excess of freshly distilled cyclohexanone in the presence of concentrated sulfuric acid at low temperatures, to give 1-2; 5-6, di-O-cyclohexylidene-α-D-glucofuranose (**63**) with 60% yield.[6a] Compound (**63**) was treated with sodium hydride, followed by one molar equivalent of benzyl bromide[7e] in anhydrous THF, as solvent and under a nitrogen atmosphere, gave the 3-O-benzyl ether derivative (**64**) in quantitative yield.

Several efforts for selective hydrolysis [Boiling with 85% aqueous acetic acid,[6a] treatment with I_2 in anhydrous methanol[6d]] of compound (**64**) at the 5-6 position failed. Hydrolysis with 1.6% sulfuric acid in water (v/v), in methanol-chloroform as the solvent,[6b-d] however, gave the 1-2 protected 5-6 diol (**65**) in reasonable yields (50%); along with the starting material (**64**) and 3-benzyl glucose which is highly soluble in water.

Compound (**65**) on treatment with periodic acid - triethyl amine buffer in methanol solution, provided the 5-oxo-xylofuranose derivative (**66**) in 85% yield.

Wittig reaction of the aldehyde (**66**) with trimethyl phosphonoacetate ylide[28] (which was made in situ by the treatment of the phosphonoacetate and sodium hydride) in anhydrous THF under a nitrogen atmosphere, gave the corresponding α-β-unsaturated ester derivative of xylose (**67**).



(**67**) (**19'**)

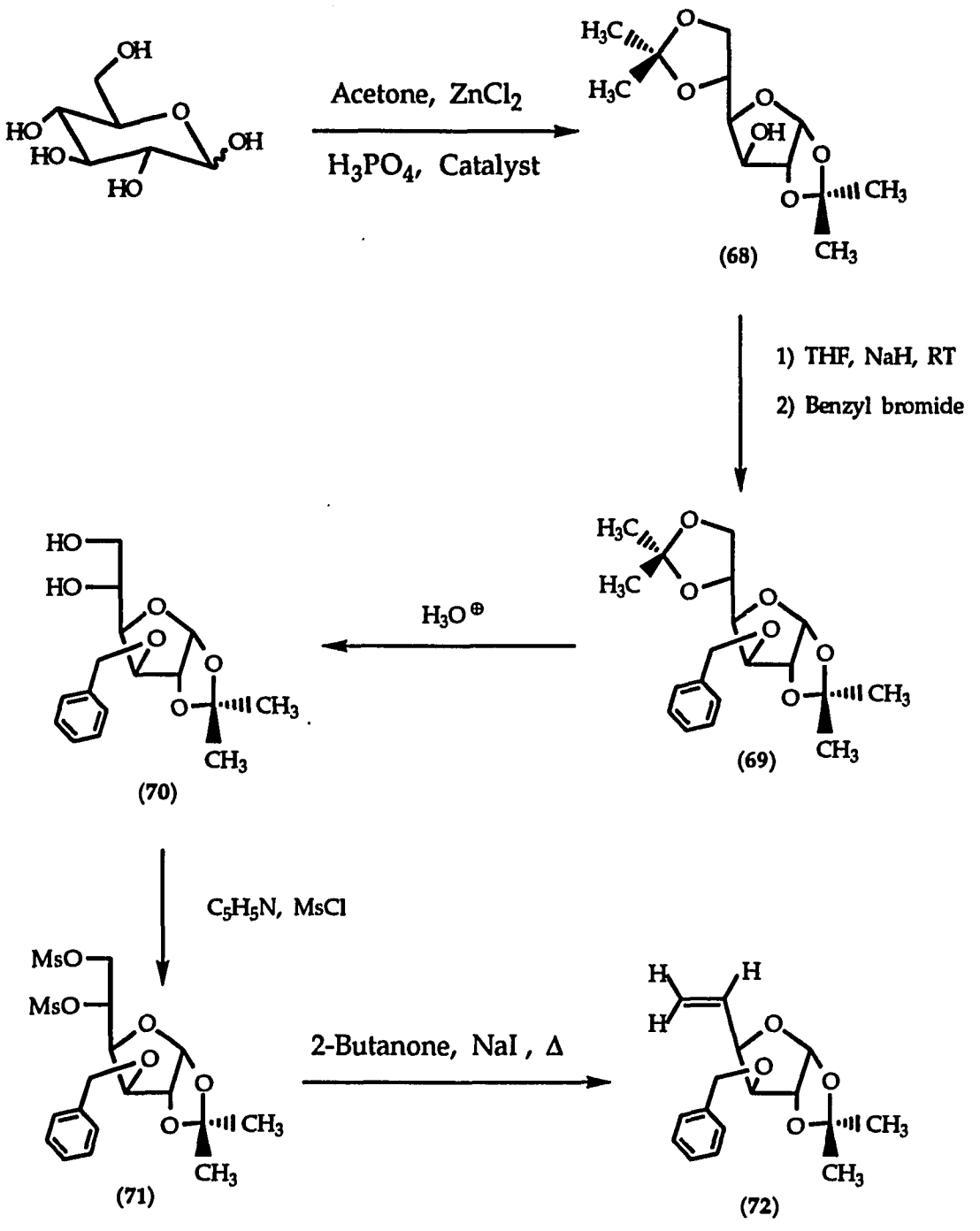
Hydrogenation of the α-β-unsaturated ester derivative with diimine (which was made in situ by the treatment of p-toluenesulfonohydrazide and aqueous sodium acetate as the base),[29] in THF at elevated temperatures gave the 6-carbomethoxy-5,6-deoxy-glucofuranose derivative (**19 '**), in nearly quantitative yield.

Anhydrous glucose was stirred magnetically in the presence of anhydrous zinc chloride in acetone, with a catalytic amount of glacial orthophosphoric acid, to give diacetone glucose (**68**) in 60-70% yield.[6a]

Benzylation at the O-3 position, first by treatment with sodium hydride in anhydrous THF (under nitrogen atmosphere at *room temperature*), followed by the addition of benzyl bromide in portions in THF, gave the benzyl ether of diacetone glucose (**69**). An ice bath was used during the addition of benzyl bromide to avoid the evaporation of solvent from the exothermic reaction.

It was observed that sodium hydride does not react with the diacetone glucose at ice cold temperatures, though the reaction is an exothermic one. On removal of the ice bath however, the reaction was observed to proceed vigorously at room temperature.

Several efforts were made for the selective hydrolysis of the benzyl ether (**69**), at the 5-6 position, including boiling with (a) 85% acetic acid;[6a] and (b) the iodine-methanol method,[6d] both of which failed. In the first case the major product was 3-benzyl glucose and in the second case the product was 1-α-O-methyl, 3-O-benzyl glucopyranoside; which is slightly soluble in water. On the contrary, hydrolysis of (**69**) with 1.6% aqueous sulfuric acid (v/v), in a methanol & chloroform mixture as the solvent, gave our desired 1-2-protected-5-6-diol (**70**), as the major product, in 50% yield. The minor product was 3-O-benzyl-α-D-glucose, which is highly soluble in water.



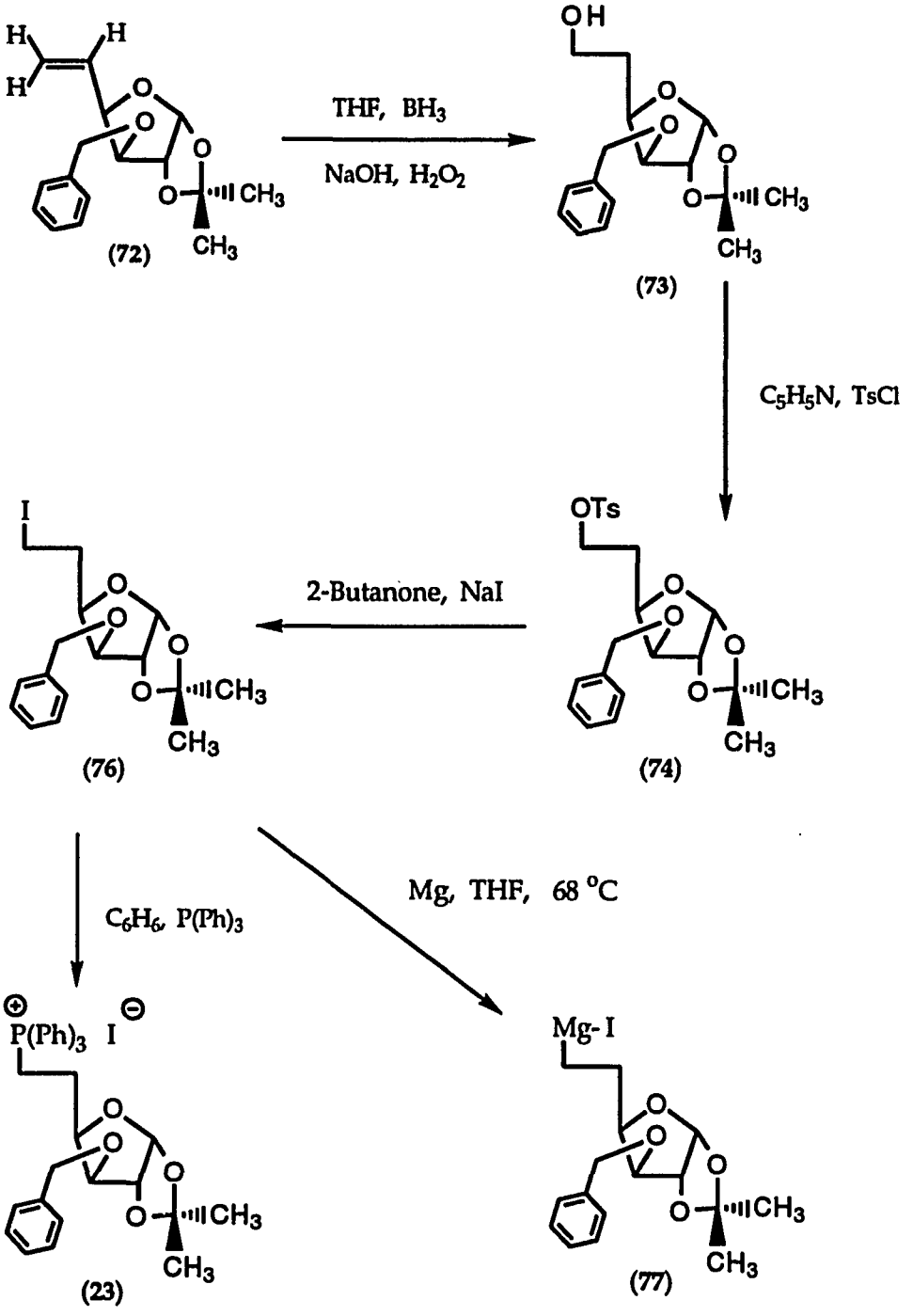
The 5,6-diol (70) was then treated with an excess of methane sulfonyl chloride (Mesyl chloride) in the presence of pyridine, in chloroform, and at ice-cold temperatures which provided the corresponding dimesylate (71), in 98% yield.

To a solution of the dimesylate (**71**) in alcohol free and anhydrous 2-butanone, a concentrated solution of anhydrous sodium iodide in anhydrous (and alcohol free) 2-butanone was added, and the mixture heated under reflux for 16 hours, to give the olefin (**72**),[6b & d] in 70% yield.

Hydroboration of the alkene (**72**), followed by treatment with hydrogen peroxide in the presence of alkali[30] provided the primary alcohol (**73**) as a gum in 60-70% yield.

The conversion of the primary alcohol (**73**) in to the corresponding iodo compound (**76**) was done via tosylate (or mesylate) formation of the alcohol , and replacement of the tosyl (or the mesyl) group by iodine, with sodium iodide in 2-butanone,[12a] which gave the highly unstable compound (**76**) in nearly 80% yield from the corresponding 6-alcohol.

The iodide (**76**), on treatment with triphenylphosphine in dry benzene provided the phosphonium salt (**23**); and on treatment with activated metallic magnesium in dry THF, at boiling temperature provided compound (**77**).

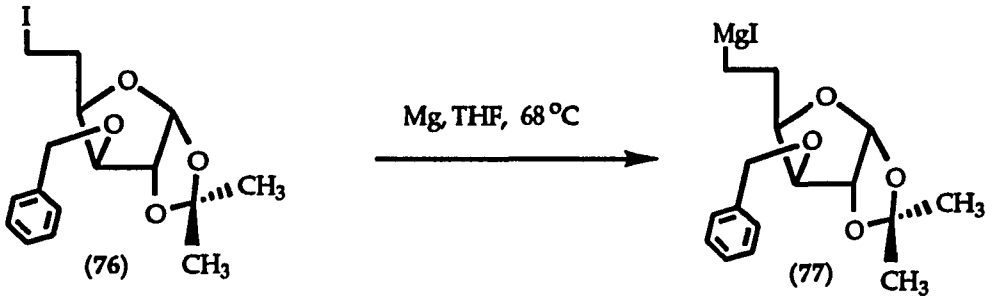

THF, BH_3
NaOH, H_2O_2
(72)
(73)
C_5H_5N, TsCl
2-Butanone, NaI
(74)
(76)
C_6H_6, $P(Ph)_3$
Mg, THF, 68 °C
(23)
(77)

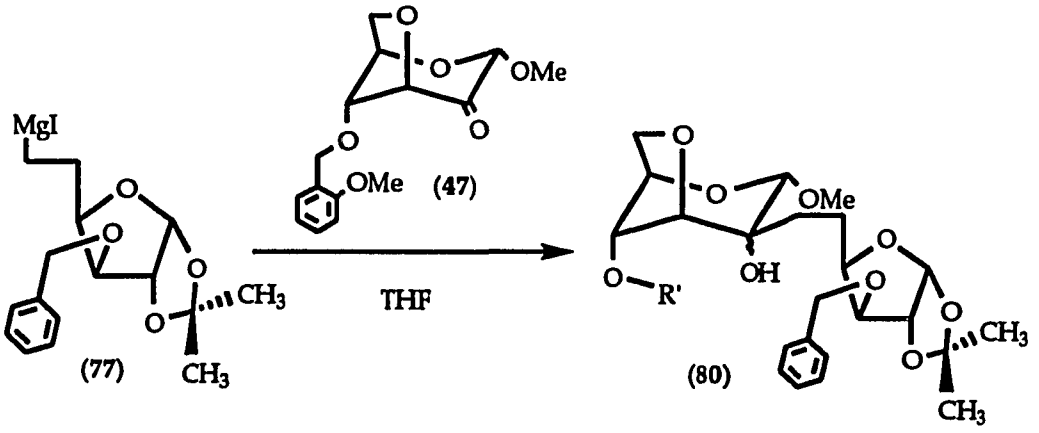
(1) GRIGNARD REACTION WITH (77) :-

(2) WITTIG REACTION WITH ALDEHYDE:-

(3) ESTER ENOLATE WITH KETONE:-

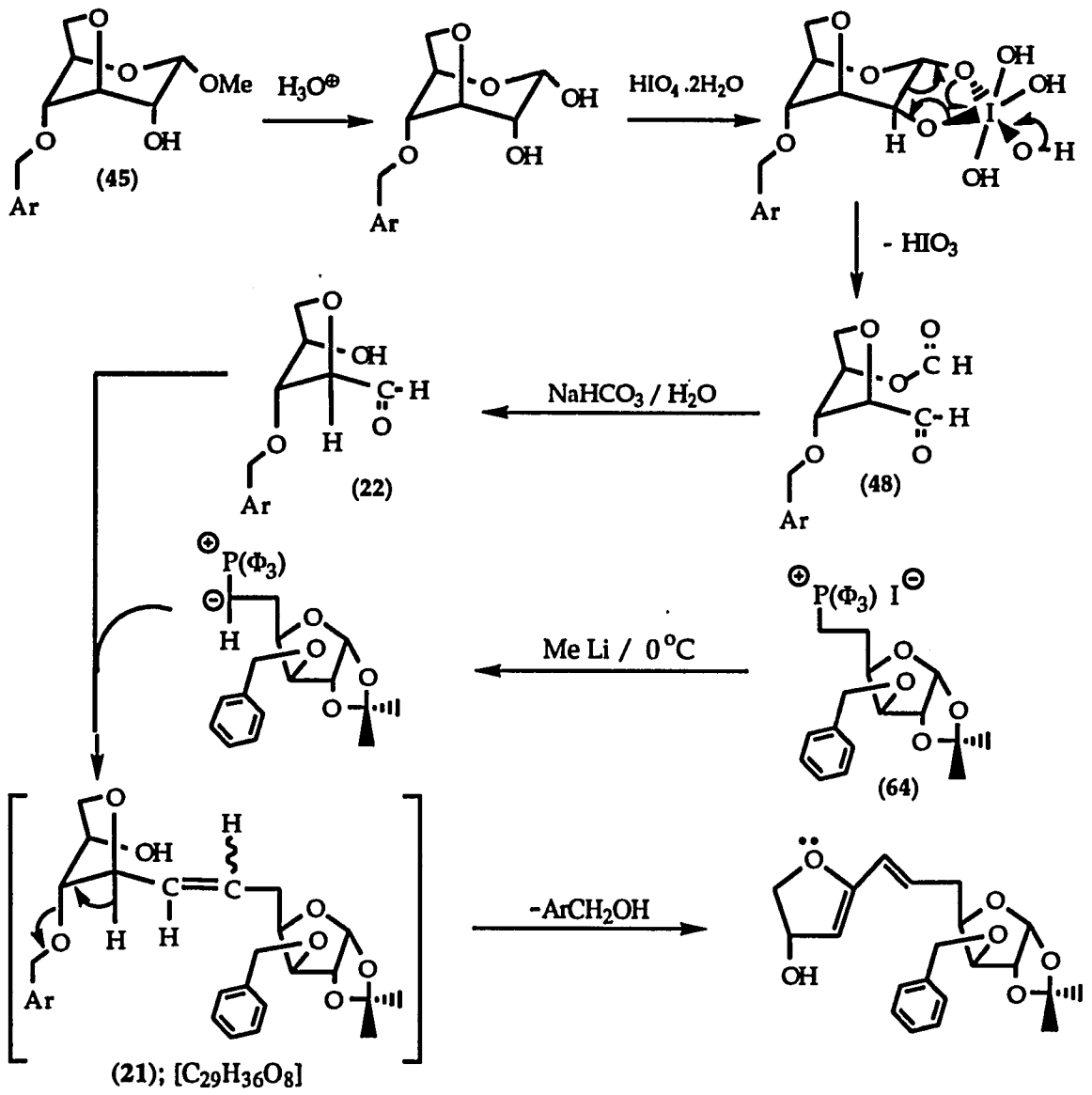
The Grignard reagent obtained by boiling the iodide (76) with activated metallic magnesium in anhydrous THF, and under nitrogen atmosphere was allowed to react with the anhydrous ketone (47) in anhydrous THF.[32] In the isolated addition product, the 2-methoxy benzyl group was found to be deprotected.

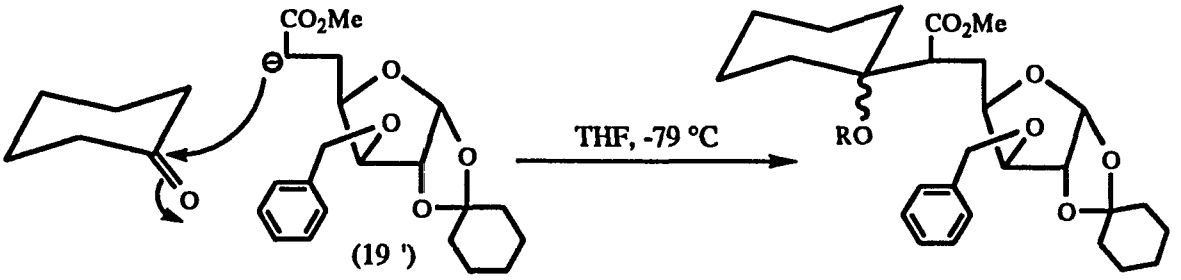




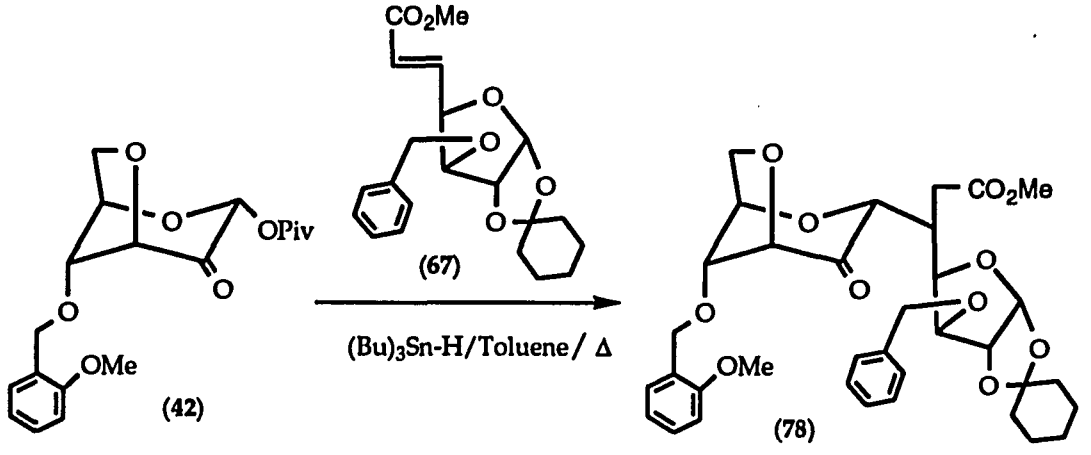
Wittig olefination of the ylide (obtained by the reaction of the phosphonium salt (23) and methyl lithium in THF at -78 °C), with the aldehyde (22), gave a compound (in which the O-3 methoxy benzyl group was deprotected) in low yield. (2-Methoxybenzyl alcohol was also isolated). Mass spectra (E. I.) indicated that there was a positive Wittig reaction. Perhaps the elimination of 2-methoxy-benzyl alcohol occurred followed by the Wittig reaction. It was also noted that in the mass spectra there was a loss of a water

molecule to aromatize the furan ring. A suggested mechanism for this reaction is shown below.





Instead of reacting the ester enolate of (**19** ') with the ketone (**42**) or (**47**) cyclohexanone was used for convenience. The ester (**19** ') was treated with one equivalent of LDA at -79 °C, followed by addition of 1.5 equivalent of freshly distilled cyclohexanone. Among the two isolated compounds the ratio of integration value in the nmr spectra between the anomeric proton and the cyclohehyl protons were examined, and none of them looks like our desired compound.

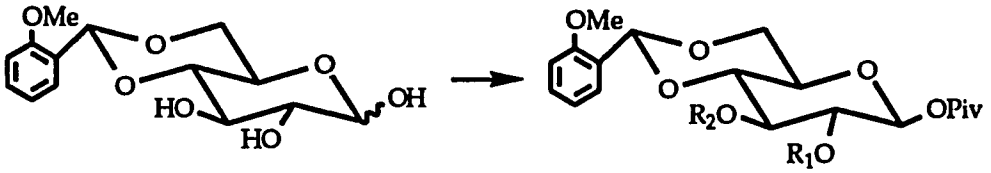


The 3,6-anhydro-2-oxo-1-pivalate (**42**) was treated with the mixture of the α-β-unsaturated ester of xylose (**67**), and tributyl tin hydride in boiling toluene under a nitrogen atmosphere with the hope of achieving a "radical C-C coupling". On every occasion the only isolated product was the starting sugar (**67**). It is noteworthy that we were unable to isolate or detect either

compound (**42**) or the reduced isomer of (**42**), where the ester at C-1 was replaced by a hydrogen atom *i.e.* compound (**62**), form this reaction. Compound (**42**) had apparently decomposed to some uncharacterizable materials.

ESTERIFICATION
of
ANISYLIDENE SUGARS

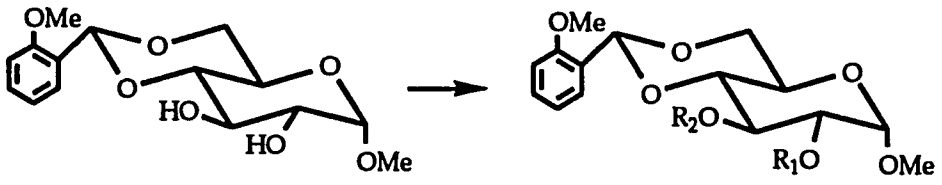
When compound (24) was allowed to pivaloylated with 1.1 eqv. of pivaloyl chloride only the compound (26) was obtained, but when compound (24) was subjected to esterification with 2.2 equivalent of pivaloyl chloride, we have never isolated any compound in which the pivalate group at C-1 was α. The isolated di- or tripivalate were always β anomers. This indicates that the OH at C-1 of structure (24 α), was not as nucleophilic as that of the anomeric structure (24 β) in esterification.



(24)

(27) : R_1 = Piv; R_2 = H.
(28) : R_2 = Piv; R_1 = H.
(29) : R_1 = R_2 = Piv.

Any molecules in conformation (24 α) must therefore have equilibriated to the conformation (24 β) , via ring opening, before the mono pivalation at O-1 occured. After completion of the monopivalate at C-1, there was a competition of O-2 and O-3 towards the dipivalation reaction, but

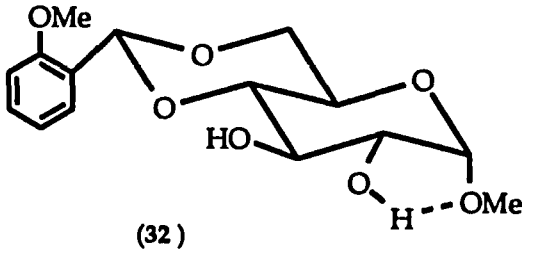


(32)

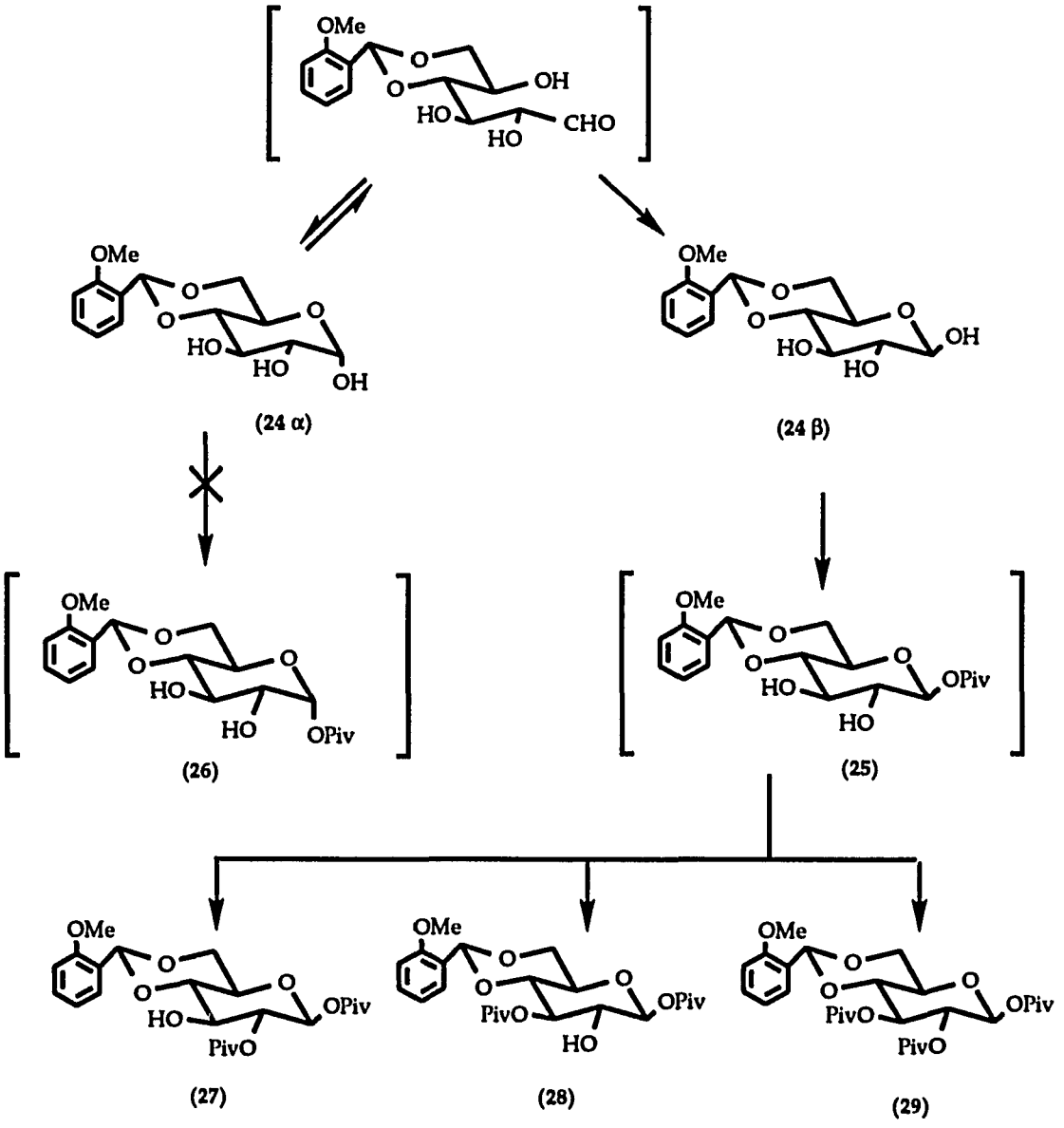
(33): R_1 = Piv; R_2 = H.
(34): R_2 = Piv; R_1 = H.
(35): R_1 = R_2 = Piv.

when compound (32) was subjected for monopivaloylation with 1.1 equivalent of pivaloyl chloride. The major product was compound (33), about

82% yield. along with 3-pivalate isomer (1%); and the dipivalate (35). This happened due to possible hydrogen bonding of C-OH with the C-1 OMe.



(32)



(24 α) (24 β) (26) (25) (27) (28) (29)

When the 1,5-Anhydro sorbitol derivative (53) was subjected for pivaloylation with 1.1 equivalent of pivaloyl chloride under similar condition, the corresponding 2-pivalate (54) and 3-pivalate (55) were obtained in 40% and 25% respectively, along with some 2,3-dipivalate (56).

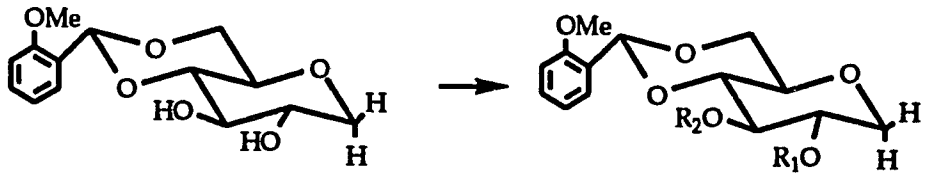
The results of the pivalation reaction were listed in the following table:-

Table-V

Starting Sugar	Equivalents of Pivaloyl Chloride added	Products			
		Starting Material Recovered	2-Pivalate	3-Pivalate	2,3-Dipivalate
(24)	2.2	38% *	(27) 20%	(28) 32%	(29) 10%
(32)	1.1	7%	(33) 82%	(34) 1%	(35) 10%
(53)	1.1	25%	(54) 40%	(55) 25%	(56) 10%

In the first entry, there is absolutely no hydrogen bonding among the C-1-β–O-pivalate and C-2-OH. As a result of fact the major product is the 1,3-isomer rather than 1,2-pivalate, similar to what is obtained in methyl β–glucopyranosides.

In the second entry, where there was an α-OMe group, which is responsible for the intramolecular hydrogen bonding. Thus causing OH-2 to be now reactive than OH-3.



(53)

(54): R_1 = Piv; R_2 = H.
(55): R_2 = Piv; R_1 = H.
(56): R_1 = R_2 = Piv.

In the third entry, there is no such effect at C-1. As a result of fact esterification rate underwent in a regular fashion at the least hindered site, thus the 2-pivalate (54) was the major product.

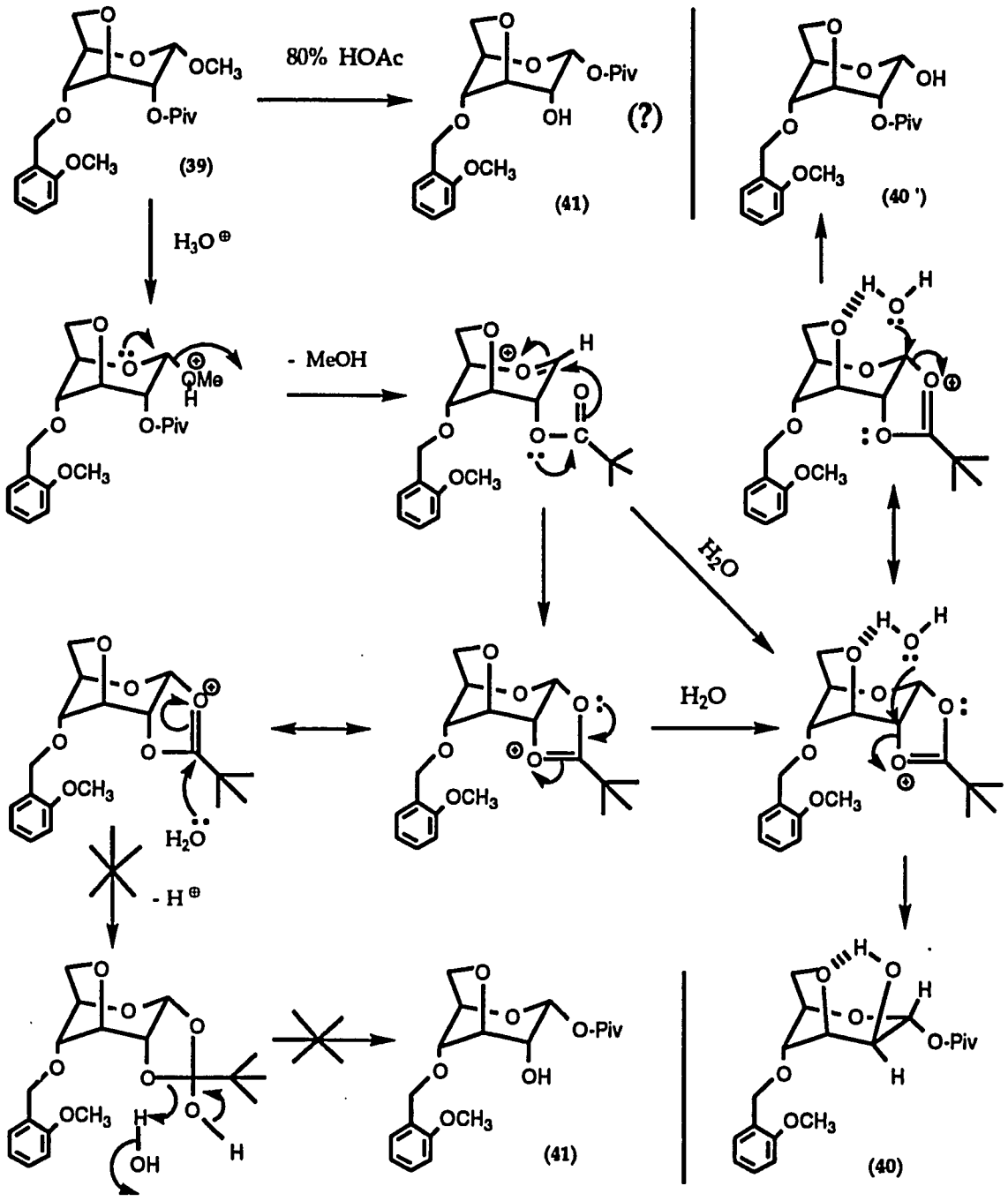
PIVALATE MIGRATION

In the previous works it was found that the O-pivalate esters do not migrate under normal or acidic conditions. Acid hydrolysis of compound (**39**) provided an unknown compound with an unusual migration of the bulky pivalate group from C-2 to C-1 was found. Facts supporting on this migration is the disappearance of the triplet of C-2 hydrogen from the down field, And on Swern oxidation of the product in which the C-1 proton became singlet. These two facts indicate that there was migration of the pivalate group.

Now question arises about the mechanism of the chemical reaction. Undoubtedly the ester has migrated via a cyclic intermediate.

The "J" value of the C-1-H (which is a doublet) clearly indicates that it is not compound (**41**), in which C-2-H are cis- (a,e); but trans- with distorted configuration in which the dihedral angle is no longer 180° as shown in the structure (**40**). In compound (**39**) the anomeric proton is a doublet having 'J' value 3.49 Hertz. If the reaction product is compound (**41**), with retention in configuration at C-2, then the anomeric proton (H-1) must be doublet with a 'J' value of 3.49 Hertz (or less). But the major hydrolyzed product we isolated the anomeric proton is also doublet having the 'J' value 5.73 Hertz. (It is however necessary to mention at this point that in cyclohexane the proton-proton trans- coupling is 7-12 Hertz). So the major product (**40**) does no longer have a regular cyclohexane (chair) structure rather than a distorted one, as shown in the following diagram which leads to reducing the dihedral angle between H(-1)-C-C-H(-2) bond. This is probably due to the formation of stable hydrogen bond between C-2 (β–OH) and β O-3 atom.

Proposed Mechanism :-



CHAPTER - 5

EXPERIMENTAL

General Procedures.

Instruments:

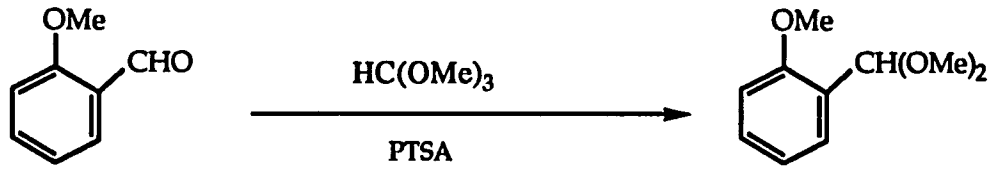
In general all reactions were carried out in flasks made of pyrex glass. Evaporations were carried out in Büchi rotavapor. Optical rotations were measured with a Perkin-Elmer model 141 polarimeter at 25 °C. The infra-red spectra were measured on a Perkin Elmer Model 247 spectrophotometer. The nmr spectra were recorded in $CDCl_3$ with tetramethylsilane as internal standard with Bruker AM 300 (both pmr and 2D) , Bruker AM 200 (pmr), and Varian-360. Mass spectra were recorded on a Finnigan Mat Mass Spectrometer, model: SSQ-70, on chemical ionization (CI) and electronic ionization (EI) only in some cases.

All chemical reactions were monitored by thin-layer chromatography carried out on freshly made, custom made plates with Merck silica gel G, with UV light and iodine chamber (where necessary). E. Merck silica gel 60; particle size 230-400 (mesh; 60 Å) was used for liquid column chromatography.

Chemicals:

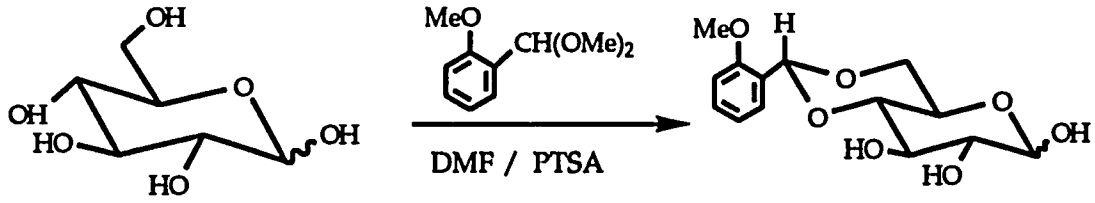
Most of the chemicals were purchased from Aldrich Chemical Co. Inc., and some chemicals were made in our laboratory. Solvents for column chromatography, supplied by Fisher Scientific, were distilled to avoid the non-volatile residual peaks in the pmr spectra. The Purified organic compounds (after column chromatographic purification); transferring into small r.b. flasks, were stored in a glass dessicator over phosphorous pentoxide and under high vacuum overnight (to remove all volatile matters perfectly) before taking the pmr spectra.

Methoxybenzaldehyde Dimethyl Acetal :-



A solution of 2-methoxy benzaldehyde (13.6 g, 0.1 mol), trimethyl orthoformate (15.9 g, 0.15 mol), anhydrous methanol (5 ml) was stirred magnetically at 0 °C. After 15 minute p-toluenesulfonic acid monohydrate (1.9 g, 0.01 mol) crystals was added and the mixture was stirred for additional 15 minutes at 0 °C. The ice-bath was then removed and the mixture was stirred for 18 hours. The volatile reaction products and excess reagents were removed using a rotary evaporator without external heating. Sodium hydrogen carbonate (5 g) was then added and the mixture was stirred for 1 hour, filtered and the solid bicarbonate was washed with 10 ml of anhydrous ether. The volatile solvent was removed at aspirator pressure and the residue was distilled at 0.1 mm of mercury pressure (b.p. 122 °C), provided the 2-methoxybenzaldehyde dimethyl acetal (17.9 g, 98%), as colourless liquid.

4,6-O-(2-Methoxybenzylidene)-glucopyranoside (24) :-

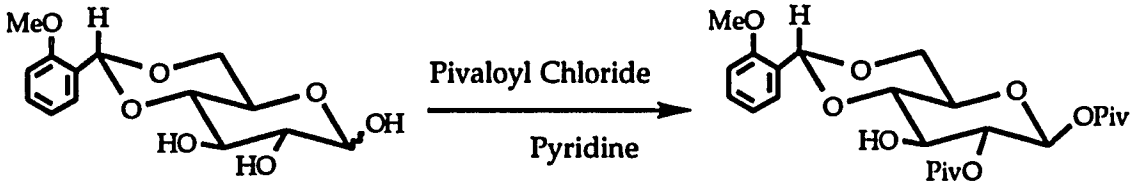


(24)

A solution of anhydrous glucose (18.0.g; 0.1 mol) in warm anhydrous DMF (100 ml), was made and then cooled to room temperature. The previously made 2-methoxy benzaldehyde dimethyl acetal was added to it,

and the mixture was stirred for 16 hours. Sodium bicarbonate (10.0 g) was then added, and the mixture was stirred for 2 hours. The residue was filtered, and the filtrate was concentrated in a rotary evaporator under high vacuum, at 65 °C. The residue was poured onto a stirred mixture of ice (25 g), saturated aqueous sodium hydrogen carbonate (50 ml). After 0.5 hour the residue was filtered off and washed successively with light petroleum and water and dried in a low temp oven and finally in a dessicator over phosphorus pentoxide for overnight to give the title compound (16.1 g, 54% yield). $[\alpha]_D$ (50mg / 5ml in methanol) 0.057°. Mass spectra calculated for $C_{14}H_{18}O_7$ (298). Found m/e = 298, C.I. 334 ($M+1+2NH_3$).

4,6-O-(2 Methoxybenzylidene)-glucopyranoside-1,2-dipivalate (27).



(24) (27)

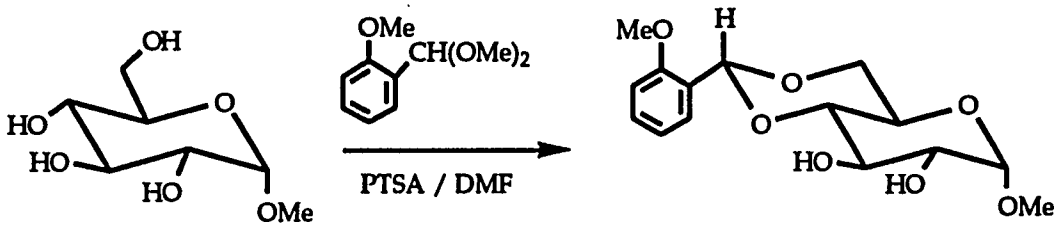
A solution of compound-(24), (10.0 g, 33.5 mmol), in freshly distilled anhydrous pyridine in a 500 ml round bottom flask was stirred magnetically in an ice-salt bath. After 30 minutes, (8.90 g, 73.8 mmol, 2.2 eqv.), of pivaloyl chloride was added dropwise, and the mixture was stirred at 0 °C for additional 3 hours. Then the ice bath was removed and the mixture was stirred for 72 hours at room temperature. Pyridine was removed at aspirator pressure and the residue was partitioned between ether and saturated aqueous bicarbonate solution (100 ml each) in a 1 litre beaker. When all the effervescence had ceased the mixture was then transferred into a separatory funnel. After removing the lower aqueous layer the ether layer was collected

after drying in a 250 ml round bottom flask, and the ether was removed using a rotary evaporator. The residue was azeotroped with toluene (100 ml x 3) and chromatographed through a silica-gel column, first eluting by hexane-ethyl acetate (10:1) to elute all the 1,2,3-tri-pivalate, and then with hexane-ethyl acetate (4:1), to give the title compound. M.P. 87-90 °C. $[\alpha]_D$ (50mg / 10ml in $CHCl_3$) -0.015°; ^1H NMR (page 132; 300 MHz); 5.87 (s, 1H, Anisylidene-H); 5.69 (d, 1H, C-1, J=8.15); 5.15 (t, 1H, C-2, J=8.15); 3.95 (t, 1H, C-3); 3.6 (bm, 2H, C-4, & C-6); 3.75 (t, 1H, C-5); 4.3 (dd, 1H, C-6); 3.82 (s, 3H, Aromatic-OCH_3); 1.18 [s, 18H, C-1 & C-2 -$C(CH_3)_3$]. Mass spectra calculated for $C_{24}H_{34}O_9$ (466.16). Found m/e = 466.2; C.I. in ammonia 467.2 (M+1), and 484.2 ($M+NH_4$).

Anisylidene Glucopyranoside 1,3-dipivalate

M.P. 76-81 °C. $[\alpha]_D$ (50mg / 10ml in $CHCl_3$) -0.013°; ^1H NMR (page 133; 300 MHz); 5.81 (s, 1H, Anisylidene-H); 5.68 (d, 1H, C-1, J=8.15); 5.1 (t, 1H, C-3, J=8.15); 3.75 (t, 1H, C-2); 3.81 (s, 3H, Aromatic-OCH_3); 1.25 & 1.18 [both singlet 2x9H, C-1 & C-3 -$C(CH_3)_3$]. Mass spectra calculated for $C_{24}H_{34}O_9$ (466.16). Found m/e = 466.2; C.I. in ammonia 467.2 (M+1), and 484.2 ($M+NH_4$).

Methyl 4,6-O-(2-Methoxybenzylidene)-α–D-glucopyranoside (32) :-



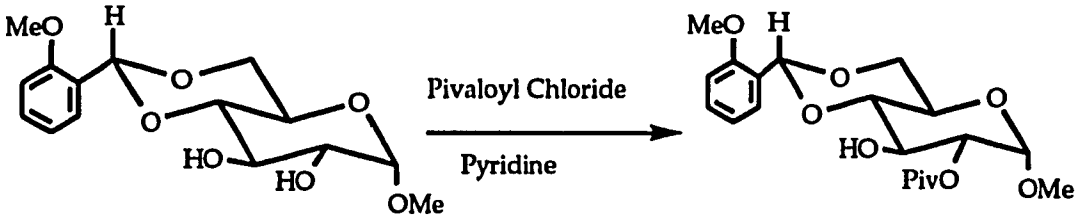
(32)

In a 500 ml round bottom flask, (19.4 g,0.1 mol) of methyl- α-D-gluco-pyranoside, methoxybenzaldehyde dimethyl acetal (0.1 mol), 200 ml of freshly

distilled anhydrous DMF were taken and the mixture was stirred magnetically until all the sugar dissolved. One drop of concentrated sulfuric acid was added to the reaction flask, and the mixture was rotated under aspirator pressure at 50 °C for 2.5 hours. The temperature was raised to 70 °C, and the aspirator was replaced by a high vacuum pump, until about 50 ml of residue left. The solution was poured on to a stirred mixture of ice (25 g), Saturated aqueous sodium bicarbonate (50 ml), and diethyl ether (50 ml, to dissolve the unreacted dimethyl acetal). After 2 hours the solid recovered by filtration was washed successively with light petroleum and water, and air dried to give (24 g, 78%) the title compound. M.P. 196-198 °C. $[\alpha]_D$ (50 mg/10ml of methanol) +0.621°.

Mass spectra calculated for $C_{15}H_{20}O_7$ (312.35). Found: m/e = 312.1; C.I. in *methane* 313.1 (M+1); and in ammonia 313 (M+1) and 330 ($M+NH_4$).

Methyl 4,6-O-(2-Methoxybenzylidene)-α-D-glucopyranoside-2-pivalate (33).

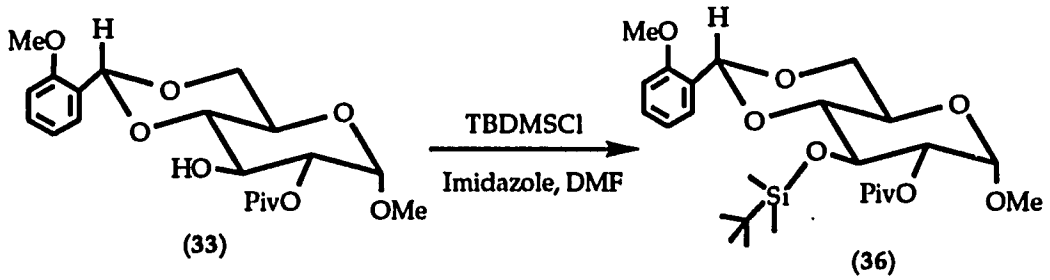


(32) (33)

In a dry 500 ml round bottom (31.2 g, 0.1 mol) of compound (32) was taken. It was dissolved in 100 ml anhydrous pyridine. The mixture was stirred in an ice bath. Pivaloyl chloride (13.3 g: 0.11 mol) was added to it dropwise, at 0 °C. After 1 hour stirring at 0 °C, the ice bath was removed and the mixture was stirred at room temperature for 36 hours. After the time period pyridine was evaporated in rotary evaporator and the residue was partitioned between

diethyl ether and saturated bicarbonate (100 ml each) taken in a 500 ml beaker very cautiously. When all the effervescence were ceased the resulting solution was transferred into a 250 ml separatory funnel. After removing the lower aqueous layer the top organic layer was washed with additional 100 ml of bicarbonate solution and finally with 100 ml water. The organic layer was taken in a 500 ml round bottom flask and the solvent was evaporated in a rotary evaporator, and the residue was azeotroped with toluene (100 ml x 3). The remaining gum was then chromatographed through a silica gel column, eluting first with hexane-ethyl acetate (10:1), to remove the dipivalate (10%) and then with the same same solvent system (4:1), to give the title compound (29.2 g, 73 - 82% yield). M.P. 106-108 °C. $[\alpha]_D$ (50mg/10ml in $CHCl_3$) +0.580°. IR ($CHCl_3$, cm^{-1}); 3400-3600 (b), 1720 (s). ^1H NMR (page 128; 300 MHz); 5.95 (s, 1H, Anisylidene-H); 4.925 (d, 1H, C-1, J=3.76); 4.74 (dd, 1H, C-2, J=3.9Hz & 9.6Hz); 4.18 (t, 1H, C-3, J=9.54Hz); 3.56 (t, 1H, C-4, J=9.23Hz); 3.8 (m, 2H, C-5 & C-6); 4.25 (dd, 1H, C-6, J=3.96 & 9.28); 3.39 [s, 3H, C(1)-OCH_3]; 3.88 [s, 3H, Aromatic-OCH_3]; 1.24 [s, 9H, C(2)-$C(CH_3)_3$]. Mass spectra calculated for $C_{20}H_{28}O_8$ (396.43). Found m/e = 396.2; C.I. in ammonia 397.2 (M+1) and 414.3 ($M+NH_4$).

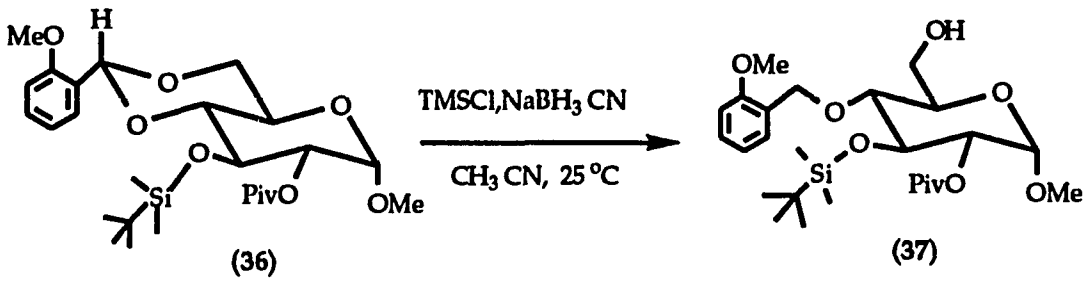
Methyl 4,6-O-(2-Methoxybenzylidene)-α-D-glucopyranoside-2-pivalate-3-tert-butyldimethylsilyl ether (36) :-



(33) (36)

In a dry 500 ml round bottom flask, (39.7 g, 0.1 mol) of compound (33), was dissolved in 200 ml of freshly distilled DMF, and 17 g (0.25 mol) of imidazole, and (19.2 g, 0.125 mol) of tert-butyldimethylchlorosilane was added to it, and the mixture was stirred for 16 hours at room temperature. After the time period, the solvent was evaporated in a rotary evaporator under high vacuum, and the residue was partitioned between water and chloroform (100 ml each). The mixture was transferred into a 250 ml separatory funnel, and the lower organic layer was removed in a 500 ml erlenmeyer flask, and the upper aqueous layer was washed with additional amount of chloroform (50 ml x 2). The combined organic layer was washed with water (100 ml), dried over $MgSO_4$ the solvent was removed in a rotary evaporator and in high vacuum dessicator to give the title compound (49.9 g: 98% yield). M.P. 79-81 °C. $[\alpha]_D$ (50mg/10ml in $CHCl_3$) +0.467°. IR ($CHCl_3$, cm^{-1}); 1720 (s). ^1H NMR (page 135; 200 MHz); 5.86 (s, 1H, Anisylidene-H); 4.87 (d, 1H, C-1, J=3.82); 4.7 (dd, 1H, C-2, J=3.82Hz & 9.2Hz); 4.18 (t, 1H, C-3, J=9.54Hz); 3.56 (t, 1H, C-4, J=9.23Hz); 3.8 (m, 2H, C-5 & C-6); 4.25 (dd, 1H, C-6, J=3.96 & 9.28); 3.34 [s, 3H, C(1)-OCH_3]; 3.8 [s, 3H, Aromatic-OCH_3]; 1.24 [s, 9H, C(2)-$C(CH_3)_3$]; 0.743 [s, 9H, C(3)-OSi-$C(CH_3)_3$]; 0.05 & -0.1 [2xs, 6H, C(3)-$OSi(CH_3)_2$]. Mass spectra calculated for $C_{26}H_{42}O_8Si$ (510.66). Found: m/e = 510.3; C.I., in ammonia 511.3 (M+1); 528.3 ($M+NH_4$).

Methyl, 2-pivaloyl, 3-tert-butyldimethylsilyl-4-O- (2-methoxy-benzyl)-α-D-glucopyranoside (37):-

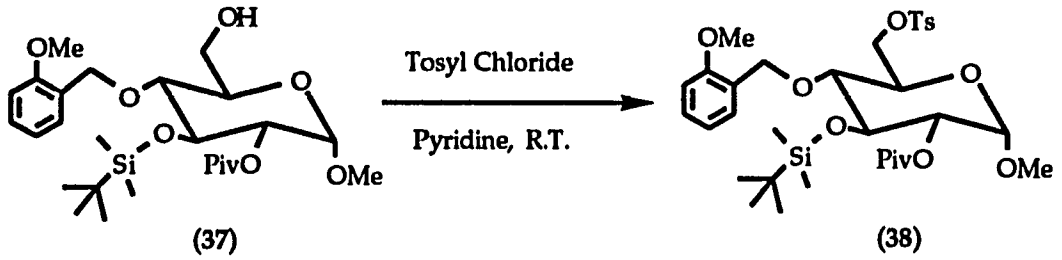


(36) (37)

A solution of compound (36); (0.51 g, 1 mmol) in anhydrous freshly distilled acetonitrile (100 ml), sodium cyanoborohydride (0.31 g, 5 mmol) and 1 g of dry powdered molecular sieves type-3A was taken in a 100 ml 3-necked round bottom flask which was cooled to 0 °C. Trimethylchlorosilane (0.6 g, 5.5 mmol) in acetonitrile (15 ml) was added to it dropwise at 0 °C with calcium chloride drying tube on the top of the addition funnel. The mixture was then stirred for 16 hours at room temperature. After the time period the reaction mixture was filtered through a bed of celite (and in absence of atmospheric moisture) and poured onto a ice-cold saturated sodium hydrogen carbonate solution, and the residue over celite bed was washed with additional 50 ml of acetonitrile. The mixture was transferred into a 500 ml round bottom flask and concentrated at reduced pressure, to remove all the acetonitrile, and the suspension of organic compound over water was repeatedly extracted with chloroform. The combined chloroform extracts was washed with saturated sodium hydrogen carbonate, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography on silica gel using first hexane-ethyl acetate (8:1), to remove any unreacted material, and the isomer of (37); and then with hexane-ethyl acetate (3:1) as eluant. Evaporation of the solvent at reduced pressure gave the

title compound (44.5 g, 78% yield) as a syrup, which solidified on long standing. M.P. 96-100 °C. $[\alpha]_D$ (50mg/10ml in $CHCl_3$) +0.561°. IR ($CHCl_3$, cm^{-1}); 3400-3600 (b), 1720 (s). ^1H NMR (page 137; 200 MHz); 4.78 (d, 1H, C-1, J=3.8Hz); 4.7 (dd, 1H, C-2); 4.9 & 4.65 (2xd, 2H, Ar-CH_2), 4.2 (t, 1H, C-3); 3.45 (t, 1H, C-4); 3.65 (bm, 3H, C-5 & C-6); 3.3 (s, 3H, C-1 O-CH_3); 3.83 (s, 3H, Aromatic-O-CH_3); 1.22 [s, 9H, C(2)-C(CH_3)$_3$]; 0.75 [s, 9H, C(3)-OSi-C(CH_3)$_3$]; 0.05 & -0.1 [2xs, 6H, C(3)-OSi(CH_3)$_2$]. Mass spectra calculated for $C_{26}H_{44}O_8Si$ (512.66). Found: m/e = 512.2; C.I. in ammonia 513.2 (M+1); 530.2 (M+NH_4).

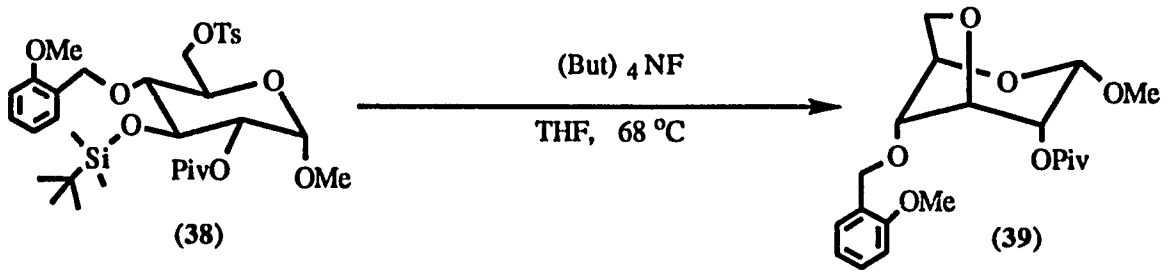
1-O-Methyl, 2-pivaloyl, 3 tert-butyl dimethyl silyl, 4-O- (2- methoxy benzyl-α-D-glucopyranoside, 6-tosylate (38) :-



(37) (38)

To a solution of compound (37); (51.66 g, 0.1 mol) in anhydrous chloroform (300 ml), pyridine (11.85 g, 0.15 mol) was added to it, and the mixture was stirred magnetically with calcium chloride drying tube, in an ice bath for 15 minutes. After this time period p-toluene sulfonyl chloride (21 g, 0.11 mol) was added to it, and the mixture was stirred at ice temperature for additional 2 hours, and then the ice bath was removed, and the mixture was stirred at room temperature for 18 hours. The resulting mixture was washed successively with 0.1 M hydrochloric acid (100 ml); 5% $NaHCO_3$ solution (100 ml); water (100 ml) and dried over magnesium sulfate and filtered. Evaporation of solvent gave the title compound (66.5 g, 100% yield) as gum. $[\alpha]_D$ (50mg / 10ml in $CHCl_3$) +0.413°. IR ($CHCl_3$, cm^{-1}).1720 (s). ^1H NMR (page 139; 300 MHz); 6.9 -7.79 (4H, Aromatic Protons); 4.7 (d, 1H C-1); 4.2 (dd, 1H, C-2); 4.17 (dd, 1H, C-3); 3.4 (m, 2H, C-4 & C-5); 4.35 (dd, 1H, C-6), 3.85 (dd, 1H, C-6); 3.9 (s, 3H, Aromatic-OCH_3); 3.3 (s, 3H, C-1 OCH_3); 2.46 (s, 3H, -pOTs); 1.29 [s, 9H, C(2)-$C(CH_3)_3$]; 0.95 [s, 9H, C(3)-OSi-$C(CH_3)_3$]; 0.05 & -0.1 [2xs, 6H, C(3)-$OSi(CH_3)_2$]. Mass spectra calculated for $C_{33}H_{50}O_{10}SSi$ (665.81). Found: m/e = 666.1; C.I. in ammonia 684.1 ($M+NH_4$)

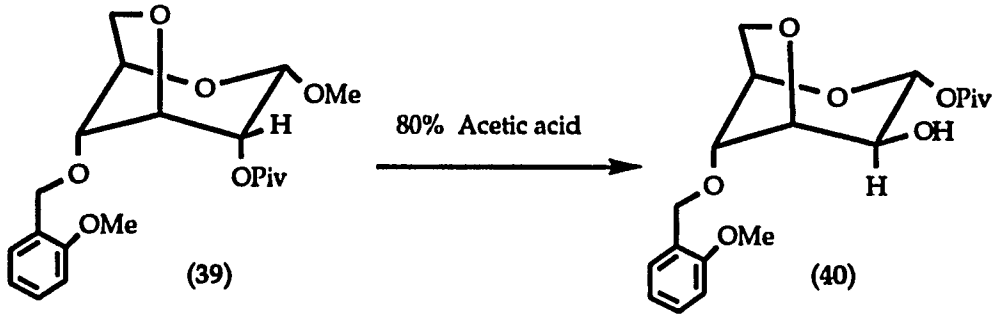
Methyl, 4-O-(2-methoxybenzyl), 3-6-anhydro-α-D-glucopyranoside, 2-pivalate (39) :-



In a dry 1-liter, 3-necked round bottom flask fitted with a 500 ml dropping funnel and a reflux condenser fitted with a $CaCl_2$ drying tube attached to it, compound (38); (13.3 g, 0.02 mol), 300 ml of dry THF was added to the flask and the solution was heated to reflux gently. Anhydrous tetrabutylammonium fluoride (7.9 g: 0.03 mol), in 300 ml of anhydrous THF was added dropwise for 3 hours, and the mixture was left in reflux condition for 18 hours. The solution was then cooled to room temperature, transferred to a one neck round bottom flask, and the solvent was evaporated in a rotary evaporator. The residual gum was partitioned between diethyl ether (200 ml) and water (100 ml). The lower aqueous layer was removed, and upper organic layer was washed with additional 2 x 50 ml of water. The ether layer was dried over magnesium sulfate. After evaporation of the organic layer, the residual gum was purified in a silica gel column, eluting by hexane-ethyl acetate (4:1) to give the title compound (6.5 g, 85% yield). $[\alpha]_D$ (50mg / 10ml in $CHCl_3$) +0.317°. IR ($CHCl_3$, cm^{-1}); 1720 (s). ^1H NMR (page 140; 300 MHz); 6.8 -7.49 (4H, Aromatic Protons); 5.11 (t, 1H, C-2); 5.01 (d, 1H, C-1, J=3.49Hz); 4.73 (dd, 2H, Ar-CH_2-); 4.45 (t, 1H, C-3, J=2.6Hz); 4.40 (t, 1H, C-4, J=4.65Hz); 4.16 (m, 2H, C-6); 3.9 (dd, 1H, C-5); 3.8 (s, 3H, Ar-OCH_3); 3.5 (s, 3H, C(1)-OCH_3); 1.22 [s, 9H, C(2)-

$C(CH_3)_3$]. Mass spectra calculated for $C_{20}H_{28}O_7$ (380). Found: m/e = 380; C.I. in ammonia 381.0 (M+1); 398.0 ($M+NH_4$).

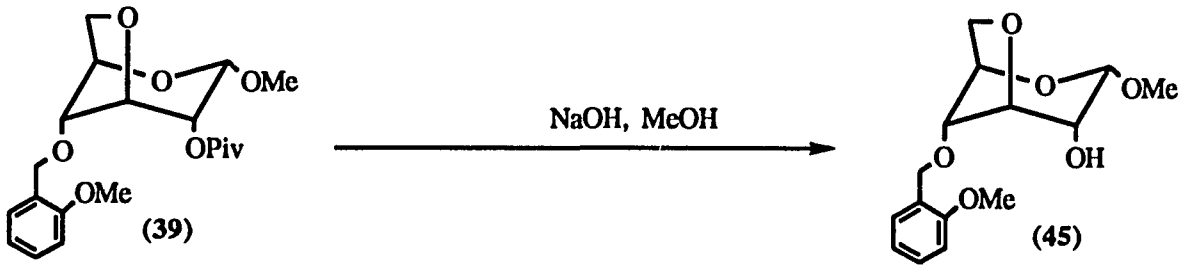
4-O-(2-Methoxybenzyl), 3-6-anhyhdro-α-D-mannopyranoside, 1-pivalate (40) :-



(39) (40)

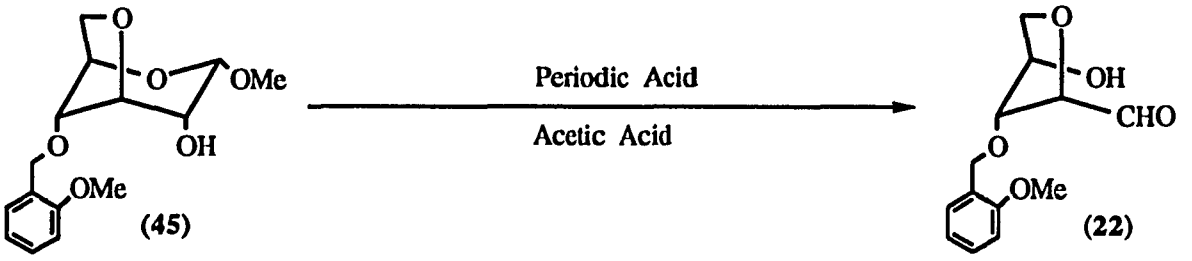
In a clear 250 ml round bottom flask 1 g (2.63 mmol), of compound (39) was dissolved in 85% acetic acid, and the mixture was stirred magnetically for over night. The solvent was removed in rotary evaporator, putting the bath temperature at 50 °C. The residue was dissolved in diethyl ether (100 ml) and washed successively with saturated sodium hydrogen carbonate (2 x 25 ml), water (25 ml), and dried over magnesium sulfate, filtered. After evaporating the solvent in a rotary evaporator the residue was purified in silica gel column, eluting with hexane-ethyl acetate (2:1), to give the title compound (70-75% yield). $[\alpha]_D$ (50mg / 10ml in $CHCl_3$) +0.425°; IR ($CHCl_3$, cm^{-1}); 3400-3600 (b), 1720 (s). ^1H NMR (page 145; 200 MHz); 6.9-7.4 (m, 4H Aromatic Protons); 5.31 (d, 1H, C-1, J=5.73 Hz); 4.57 (dd, 2H, benzyl); 4.36 (t, 1H, C-2); 4.13 (t, 1H, C-3); 3.69 (dd, 2H, C-4); 3.86 (s, Ar-OMe); 1.27 (s, 9H, ^{t}Butyl). Mass spectra calculated for $C_{19}H_{26}O_7$ (366). Found: m/e = 366.1; C.I. in ammonia 367.1 (M+1); 384.1 ($M+NH_4$)

Methyl, 4-O-(2-Methoxy benzyl), 3-6-anhydro-α-D-glucopyranoside (45) :-



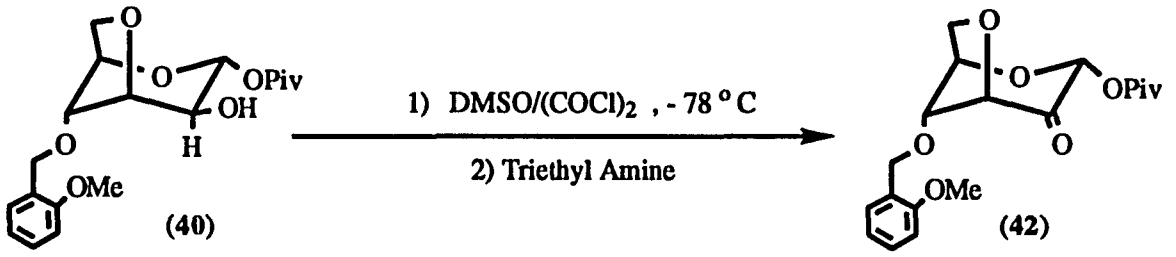
In a 250 ml round bottom flask, 1 g (2.63 mmol) of compound (39) was dissolved in 100 ml of commercial methanol, and a solution of sodium hydroxide (1 g, 25 mmol) in methanol (25 ml) was added to it. The mixture was then stirred magnetically for over night. After removal of the solvent, the residue was partitioned between water and chloroform (100 ml each). The lower organic layer was collected in a 250 ml erlenmeyer flask, and the upper aqueous layer was extracted with additional (2 x 25 ml) chloroform. The combined chloroform layer was dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure. The residue is the pure title compound (0.778 g, 100% yield). $[\alpha]_D$ (50mg/10ml in $CHCl_3$) +0.446°. ^1H NMR (page 142; 300 MHz); 4.93 (d, 1H, C-1); 4.0 (dd, 1H, C-2); 4.52 (t, 1H, C-3); 4.3 (t, 1H, C-4); 3.9 (m, 1H, C-5); 4.185 (d, 2H, C-6); 3.83 (s, 3H, Aromatic -OCH_3); 3.61 (s, 3H, C-1 OCH_3). Mass spectra calculated for $C_{15}H_{20}O_6$ (296). Found: m/e = 296; C.I. in ammonia 314 ($M+NH_4$).

Periodic acid cleavage of compound (45) :-



In a clean 200 ml round bottom flask (1 g, 3.38 mmol) of compound (**45**) was dissolved in glacial acetic acid (45 ml). Immediately an aqueous solution of periodic acid dihydrate (HIO_4. $2H_2O$); (0.847 g; 3.7 mmol) in 5 ml of water was added to it, and the mixture was stirred magnetically at room temperature for 16 hours. The solvent was removed in a rotary evaporator and the residue was partitioned between chloroform (75 ml) and water (25 ml). After removing the top aqueous layer, the organic layer was washed with saturated sodium bicarbonate (25 ml x 4); dried ($MgSO_4$) and the solvent was evaporated. The residue was purified in silica gel column, eluting with hexane-ethyl acetate (2:1) to give the aldehyde (**22**); (0.8 g, 95% yield). IR ($CHCl_3$, cm^{-1}); 3200-3600 (b), 1710 (s). ^1H NMR (page 149; 300 MHz); 7.30 (m, 4H, aromatic H); 9.66 (d, aldehyde-H, J=2.1); 4.65 (dd, 2H, Benzyl CH_2); 3.86 (s, 3H, Aromatic -OCH_3). Mass spectra calculated for $C_{13}H_{16}O_5$ (252). Found: m/e = 252; C.I. in ammonia 253 (M+1), 270 ($M+NH_4$).

4-O-(2-Methoxy benzyl), 3-6-anhydro, 2-oxo-α-D-glucopyranoside, 1-pivalate (42) :-

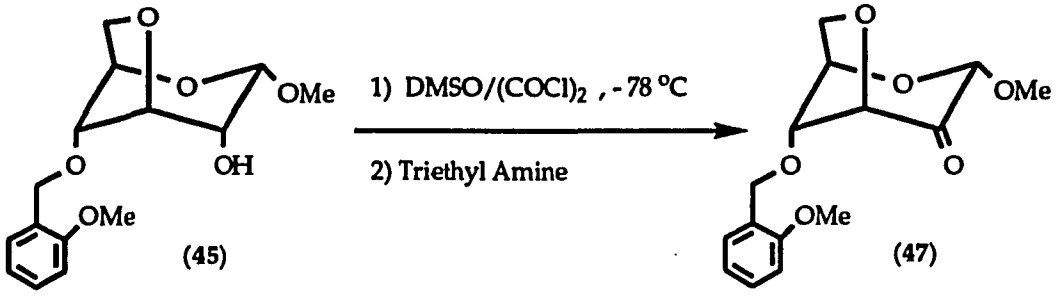


(40) (42)

Into a dry 100 ml, 3-neck round bottom flask equipped with magnetic stirrer, two dropping funnels, calcium chloride drying tube, dry dimethyl sulfoxide (1.56 g, 20 mmol) diluted with dry dichloromethane (10 ml), were added and the mixture was cooled to -78 °C with dry ice/acetone bath. Oxalyl chloride (1.4 g, 11 mmol) was taken in the dropping funnel with the help of a dry syringe and 5 ml of dry dichloromethane was added to. The oxalyl chloride solution was then added to the reaction flask at -78 °C. A vigorous gas evolution was observed. Within 2 minutes a solution of sugar (**40**); (3.66 g, 10 mmol), in dry dichloromethane (15 ml) was added rapidly to the reaction mixture, through the second dropping funnel. After 30 minutes triethyl-amine (2 g, 2.8 ml, 20 mmol) was added dropwise in the reaction flask. Stirring was continued for additional 10 minutes, and then the cooling bath was removed and the reaction mixture was allowed to warm to room temperature (25 °C). The reaction mixture was then transferred into a 125 ml separatory funnel and 20 ml of water was added to it and the mixture was shaken. Removing the lower organic layer, the upper aqueous layer was extracted with dichloromethane (15 ml). The combined organic layer was dried ($MgSO_4$), filtered, and the solvent was evaporated at reduced pressure. Azeotroping the residue with dry benzene for 30 minutes, and removal of

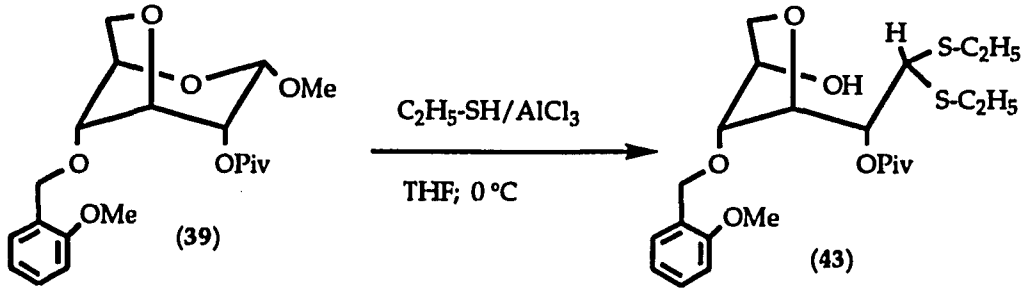
benzene at low pressure gave pure title compound (40); (3.25 g, 90% yield). $[\alpha]_D$ (50 mg/10ml in $CHCl_3$) +0.41°; ^1H NMR (page 146; 300 MHz); 6.9-7.4 (m, 4H Aromatic Protons); 5.4 (s, 1H, C-1); 4.9 (d, 1H, C-3); 4.7 (s, 2H, benzyl); 1.16 (s, 9H, ^{t}Butyl).

1-α-O-Methyl, 4-O-(2-methoxy benzyl), 2-oxo, 3,6-anhydro glucopyranside (47)



Procedure is identical for compound (15), *just above*. The starting material is compound (13), and the yield is 88%. ^1H NMR (page 144; 300 MHz); 6.9-7.4 (m, 4H Aromatic protons); 5.4 (s, 1H, C-1); 4.8 (dd, 2H, benzyl); 4.3 (d, 1H, C-3); 3.82 (s, 3H, aromatic -OMe); 3.52 (s, 3H, C-1 OMe).

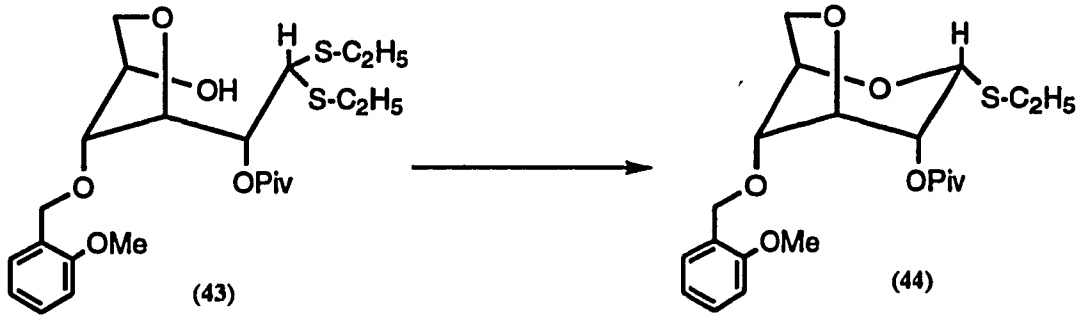
4-O-(2-methoxy benzyl), 3-6-anhydro, 1-dithioketal (43), and cyclization:-



In a proper ventilated hood a dry 100 ml 3-neck round bottom flask fitted with magnetic stirrer, dropping funnel, calcium chloride drying tube, compound (39), (3.8 g; 10 mmol) was dissolved in 15 ml dry THF, and the

flask was placed in an ice-bath. 10 ml of ethane thiol was added to it, with the help of a dry syringe. Anhydrous aluminum chloride (4.0 g, 30 mmol) in dry THF (10 ml), was added to the reaction flask dropwise, while the flask is kept in ice-bath. After 2 hours the ice-bath was removed, and the mixture was allowed to stir at room temperature for 18 hours. The entire reaction mixture was then poured onto a stirred aqueous saturated solution of sodium hydrogen carbonate. The inorganic residue was filtered from the liquid through suction, and the residue was washed with chloroform (2 x 50ml). The liquid was then transferred in to a 250 ml separatory funnel, and additional 50 ml of chloroform was added to it. The mixture was shaken well, and allowed to settle. The lower organic layer was removed in to 250 ml erlenmeyer flask, and the aqueous layer in separatory funnel was extracted with additional amount of chloroform (2 x 25ml). The organic layer was dried ($MgSO_4$), filtered into a 500 ml round bottom flask, and the solvent was evaporated in a rotary evaporator. The residual gum was purified through a silica gel column eluting by hexane-ethyl acetate (2:1) to give pure crystalline title compound (**43**) (2.6 g, 55% yield). M.P. 119-122 °C. $[\alpha]_D$ (50 mg/10 ml $CHCl_3$) +0.301°. ^1H NMR (page 147; 300 MHz); 6.8-7.3 (m, 4H Aromatic Protons); 5.45 (dd, 1H, C-2, J=5.7); 4.72 (d, 1H, C-1, J=4.66); 3.79 (s, 3H, Aromatic-OCH_3); 2.4 (m, 2H, -S-CH_2-); 2.65 (m, 2H, -S-CH_2-); 1.18 (t, 3H, CH_3 of thiol); 0.98 (t, 3H, CH_3 of thio); 1.08 [s, 9H, $C(CH_3)_3$]. Mass spectra calculated for $C_{23}H_{36}O_6S_2$ (472.2). Found m/e = 411; C.I. 411.25. (Probably due to the immediate loss of one EtSH unit from the molecular ion).

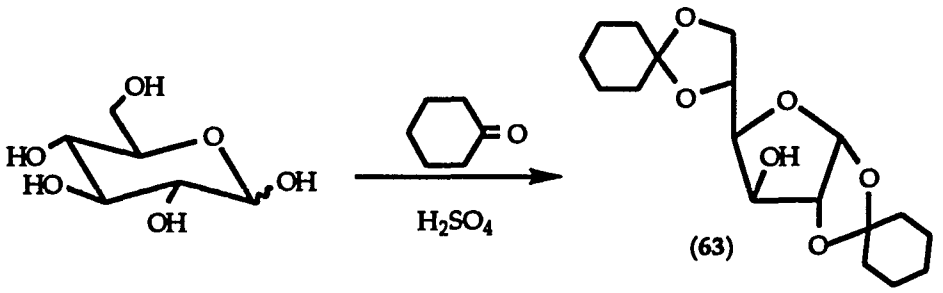
1-Thioethyl, 4-O-(2-Methoxy benzyl), 3-6-anhydro-α-D-glucopyranoside, 2-pivalate (44):



In a 100 ml round bottom flask, (1.0g; 2.1 mmol) of the dithioketal (**43**) was dissolved in 5.0 ml of anhydrous D.M.F. and 2 ml of anhydrous toluene was added to it. Benzyl bromide (0.4 g; 2.12 mmol) was added to it and the mixture was heated to reflux for 24 hours. The mixture was then cooled and the solvents were evaporated at reduced pressure using a high vacuum pump. The residue was then purified through small silica gel column eluting with hexane-ethyl acetate (4:1) to give the title compound (**44**). (0.18 g; 15% yield) as an oil. ^{1}H NMR, (page 148; 200 MHz); 6.8-7.3 (m, 4H Aromatic Protons); 5.33 (d, 1H, C-1, J=3.68); 4.89 (t, 1H, C-2, J=3.91); 4.66 (s, 2H, Ar-CH_2-); 4.45 (m, 3H, C-3 to C-5); 4.23 (d, 1H, C-6, 10.5 Hz); 3.92 (dd, 1H, C-6, J=10.6 & 2.9 Hz); 2.72 (q, 2H, C(1)-S-CH_2-); 1.3 (t, 3H, CH_3 of thio); 1.175 [s, 9H, $C(CH_3)_3$].

SYNTHESIS of the XYLOFURANOSES:-

1-2:5-6, Di-O-CYCLOHEXYLIDENE-α-D-GLUCOFURANOSE (63) [6a] :-

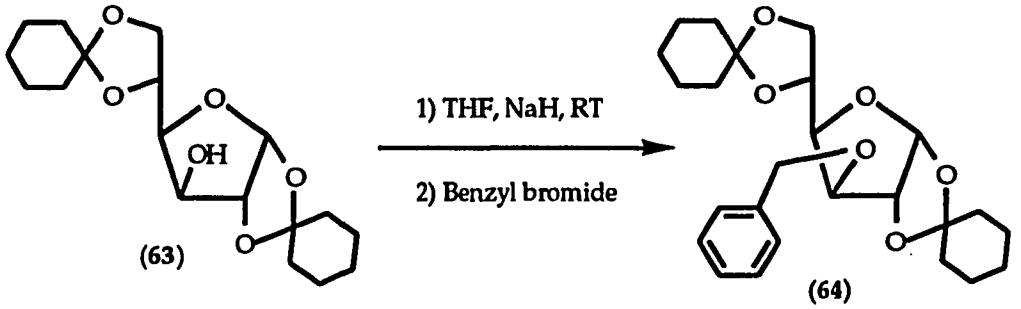


(63)

In a 3 liter round bottom flask fitted with a mechanical stirrer (at the center joint), a calcium chloride drying tube, a dropping funnel and a powder funnel. The flask was immersed in a large plastic basket filled with a mixture of ice and salt. (1.0 Kg; 1050 ml; 10 mol) of redistilled cyclohexanone to the flask and it was cooled to 0 °C. With the separatory funnel 62.5 ml of concentrated sulfuric acid was added dropwise with vigorous stirring. After 5 minutes (450 g; 2.5 mol) of anhydrous α-D-glucose was added in portions with stirring so that the reaction mixture would not rise above than 5 °C. After adding all the sugar, the mixture was stirred for additional 30 minutes in ice bath, and the external cooling bath was removed, and the reaction mixture was allowed to reach room temperature with constant stirring until the mixture becomes viscous and finally an off-white crystalline mass. Immediately the motor was disconnected from mechanical stirrer, and the glass rod of the stirrer was raised, and the stirrer was kept over the surface of the solid mass. The reaction mixture was allowed to stand at room temperature for overnight. Sodium bicarbonate (250 g), chloroform (1 L) were added to it and the mixture was stirred mechanically until all solid dissolved in the chloroform. The mechanical stirrer was then removed and upper layer was decanted into a 1 Liter round bottom flask in portions, and the solvent was removed at low pressure. The residue was dissolved in 750 ml in hot

heptane and boiled with of decolorizing carbon(15 g), filtered in hot, and cooled to -10 °C. The solid was filtered and washed with 200 ml of ice-cold heptane, and recrystallized from heptane. Yield is 552 g (65%) and its m.p. 131-132 °C.; (F.W.=340).

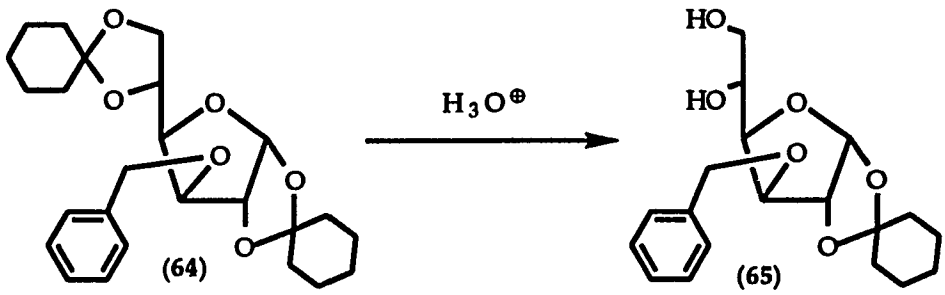
1-2:5-6, Di-O-Cyclohexylidene-3-O-benzyl-α-D-glucofuranose (64) [7e]:-



In a 1 liter round bottom flask, compound (63) (340 g; 1 mol) was dissolved in 400 ml of dry THF, 80% NaH in oil (33.5 g of; 1.1 mol) was added to it at room temperature in portions. When all the gas evaluation were being ceased the flask was kept in an ice bath for 15 minutes. Benzyl bromide (179.5 g; 1.05 mol), in 50 ml of dry THF, was added dropwise to it, and stirred for 12 hours at room temperature. After evaporating the solvent the residual gum was partitioned between diethyl ether (300 ml) and water (100 ml), and mixture was transferred into a 500 ml separatory funnel, shaken vigorously, and allowed to settle. After removing the lower aqueous layer the upper organic layer was dried ($MgSO_4$), filtered and solvent was removed at aspirator pressure, and then at high vacuum. 431 g of title compound (100%) was obtained.

Mass spectra calculated for $C_{25}H_{34}O_6$ (430). Found: m/e = 430; C.I. in ammonia 431 (M+1); 448 ($M+NH_4$).

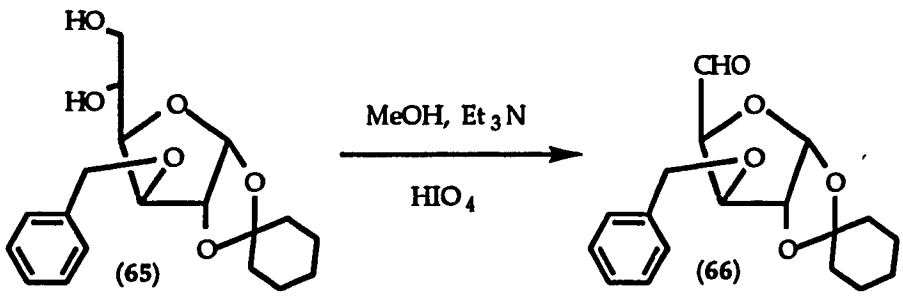
3-O-Benzyl; 1,2-O-Cyclohexylidene-α-D-glucofuranose (65) [6c]:-



In a mixture of chloroform (200 ml), 95% methanol (600 ml) and 1.6% sulfuric acid in water (200 ml), compound (64), (100 g; 0.23 mol) was dissolved, and the mixture was stirred for 24 hours. Sodium bicarbonate (10 g) was added to it and stirred for additional 30 minutes. The mixture was filtered, concentrated at aspirator pressure and the residue was taken in chloroform (100 ml). The chloroform layer was dried, and solvent was evaporated in a rotary evaporator. The residue was purified through silica-gel column, eluting first with hexane-ethyl acetate (5:1), to remove all the unreacted starting material, and then with methanol. Removal of methanol at reduced pressure gave the pure title compound (40 g; 50%).

Mass spectra calculated for $C_{19}H_{26}O_6$ (350). Found: m/e = 350.1; C.I. in ammonia 351.1 (M+1); 368.2 ($M+NH_4$).

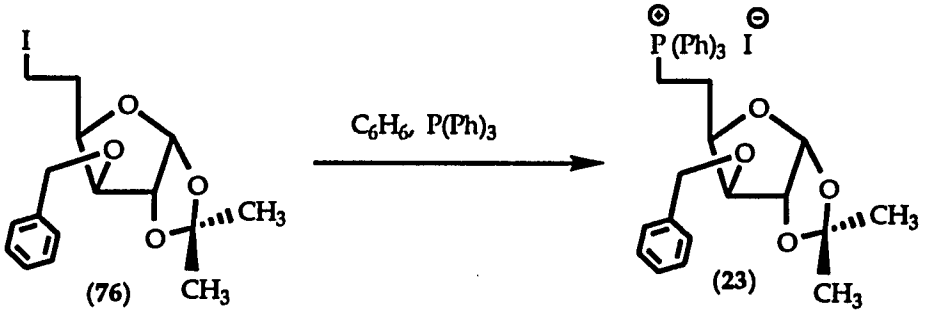
3-O-Benzyl; 1,2-O-Cyclohexylidene, 5-oxo-α-D-Xylofuranose (53) :-



Periodic acid ($HIO_4.2H_2O$), (2.508 g; 11.0 mmol) was dissolved in 75 ml of methanol, and triethylamine was added to it dropwise until the solution is just basic. Compound (65); (3.51 g, 10 mmol) in 10 ml of methanol was added to it, and the mixture was stirred for 6 hours. The solvent was evaporated and the residue was partitioned between water (25 ml) and chloroform (75 ml). The chloroform layer was separated, and the aqueous layer was extracted with additional amount of chloroform (25 ml x 2). The combined extracts was dried over magnesium sulfate, filtered and evaporated. The residue was purified through a silica-gel column eluting with hexane-ethyl acetate (4.1) gave the pure title compound (2.7 g: 85 %). ^1H NMR (page-160; 300 MHz); 9.67 (d, 1H, C-5, J=1.4); 7.3 (m, 5H, Aromatic); 6.13 (d, 1H, C-1, J=3.4); 4.64 & 4.55 (dd, 2H, benzyl); 4.58 (d, 1H, C-2, J=3.4); 4.35 (d, 1H, C-3, J=3.7); 3.5 (q, 1H, C-4); 1.58 (b, 10H, cyclohexyl).

and the residue was partioned between diethyl ether (150 ml) and water (100 ml). Transferring the contents in a 500 ml separatory funnel, the mixture was shaken vigorously, and allowed to settle. Removing the lower aqueous layer, the top organic layer was washed with 5% $Na_2S_2O_3$ solution (100 ml) immediately. Removing the lower aqueous layer, the top organic layer was dried (over $MgSO_4$), filtered, and the solvent was evaporated in a rotary evaporator. The residue was filtered through a small silica gel column, eluting with hexane-ethyl acetate (8:1), evaporation of the solvent at aspirator pressure, followed by high vacuum, gave pure (highly unstable, which slowly decomposes on standing) title compound (**76**). The yield is 24 g; 97% compared to the mesylate (**75**). $[\alpha]_D$ (50mg/5ml in $CHCl_3$) -0.151°. ^1H NMR (page 169; 300MHz); 7.31 (m, 5H, Aromatic); 5.9 (d, 1H, C-1, J=3.88); 4.7 & 4.5 (dd, 2H, benzyl); 4.61 (d, 1H, C-2, J=3.92); 3.83 (d, 1H, C-3, J=3.09); 4.3 (m, 1H, C-4); 2.08 & 2.32(m, 1H each, C-5); 3.2 (m, 2H, C-6); 1.51 & 1.32 (2 s, 3H each, the Isopropylidene). Mass spectra calculated for $C_{16}H_{21}O_4I$ (404). Found: m/e = 404.4; C.I. in ammonia 405.4 (M+1); 422.3 ($M+NH_4$).

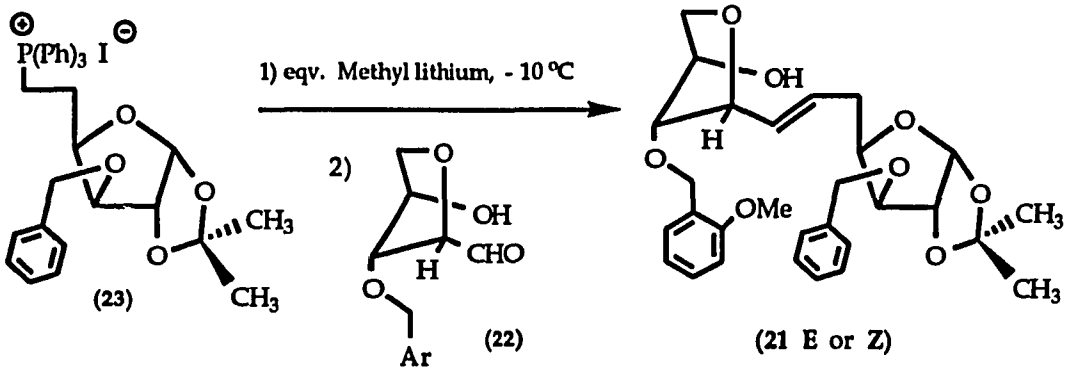
Triphenyl phosphonium salt (23), of the iodide (76) :-



The iodide (**76**), (20 g, 0.05 mol) was dissolved in anhydrous benzene (10 ml), and a solution of triphenyl phosphine (16 g, 0.06 mol) in dry benzene (20 ml) was added to it, and the mixture was heated to reflux for 18 hours. The

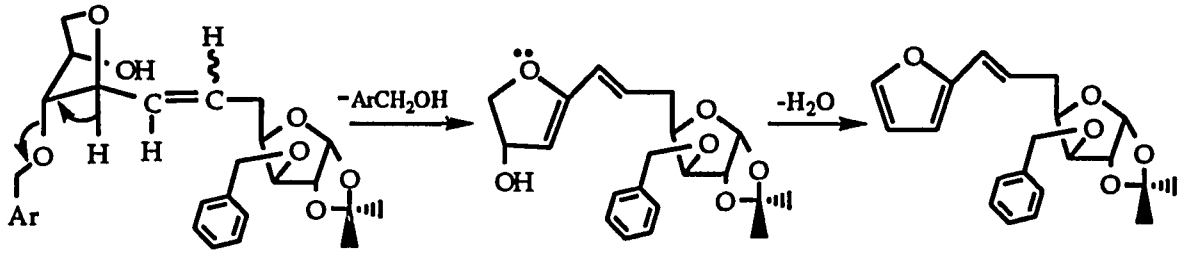
solvent was decanted, and the remaining solvent was evaporated in a rotary evaporator. The residue was purified through a silica gel column, eluting first with hexane (to remove excess triphenyl phosphine); and then with acetone (to elute the desired phosphonium salt). After removal of the solvent at aspirator pressure, pure phosphonium salt (23) was isolated as a semi-solid gum, (32 g, 98%). ^{1}H NMR (page 171; 300MHz); 7.31 (bm, 20H, Aromatic); 5.84 (d, 1H, C-1, J=3.73); 3.5 (m, 2H, C-6); 4.1 (dd, 1H, C-3); 4.6-4.7 (m, 4H, C-2, C-4, benzyl-CH_2-); 2.0 (m, 2H, C-5); 1.3 & 1.5 (2 s, 3H each, Isopropylidene). Mass spectra calculated for $C_{34}H_{36}O_4IP$ (666.3). Found: m/e = 666.0; E.I. 666.

Wittig reaction of the phosphonium salt (23), with the aldehyde (22) :-



In a dry 100 ml 3-neck flask, fitted with a rubber septum, dry nitrogen gas inlet and a 50 ml dropping funnel which was attached with a calcium chloride drying tube. 2.0 g of the phosphonium salt (23), and 20 ml of dry THF, and 5 ml dry DMSO were taken. The flask was then placed in a dry ice-acetone bath. Dry nitrogen gas was flashed through the reaction flask. With a dry glass syringe 5.1 ml of 1.7 M methyl lithium in ether was added slowly. A deep red solution was formed, and the mixture was allowed to stir magnetically at -78 °C, under nitrogen atmosphere for an hour. A solution of 0.85 g of aldehyde (22), in 5 ml of anhydrous THF was added to it, and the

mixture was allowed to stir for additional two hours at -78 °C. The dry ice bath was then removed, and the reaction mixture was left for 10 hours at room temperature. The mixture was then transferred into a 200 ml round bottom flask and the solvent was evaporated in a rotary evaporator. The residue was partitioned between chloroform (50 ml) and water (25 ml). The lower organic layer was collected in an 250 ml erlenmeyer flask and the upper aqueous layer was extracted twice with 50 ml portions of chloroform. The combined organic layer was dried ($MgSO_4$), concentrated and purified through a silica gel column eluting first with hexane-ethyl acetate (8:1), to remove all the impurities; and then with (4:1) solvent system to give the compound (50%), in which the 2-methoxy benzyl group was found to be missing.

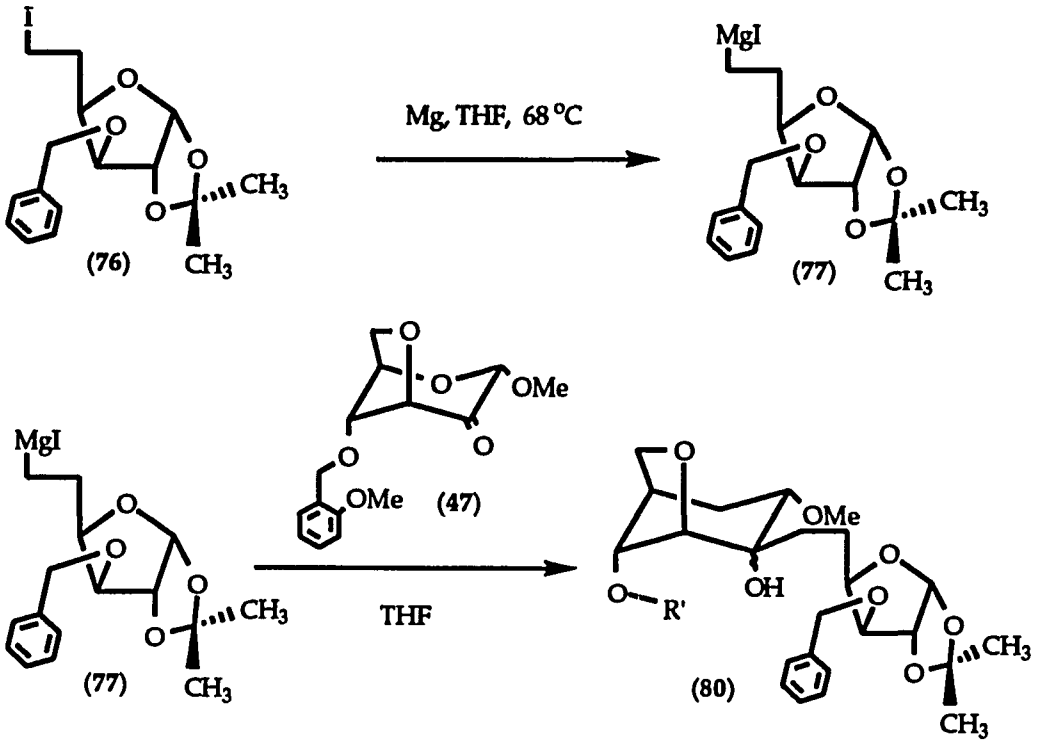


(21); $[C_{29}H_{36}O_8]$ **(21 a)**; $[C_{21}H_{26}O_6]$ **(21 b)**; $[C_{21}H_{24}O_5]$

^1H NMR (page 173; 300MHz); 7.2-7.4 (b, 5H, aromatic protons); 5.9 (d, 1H, anomeric H); 6.15-6.4 (m, 3H, olefinic protons); 3.7-4.7 and 5.2-5.7 (m, sugar protons); 2.9 and 2.4-2.7 (t, and m, 2H, xylose-C-5); 1.3 and 1.46 (two singlet, 6H, isopropylidene).

Mass spectra calculated for compound **(21)** $C_{29}H_{36}O_8$ (512), where Ar = ortho-methoxyphenyl group; **(21 a)** $C_{21}H_{26}O_6$ (374); **(21 b)** $C_{21}H_{24}O_5$ (356) Found: m/e = 356. C.I. in ammonia 374.44 ($M+NH_4$); E.I. 356.4 (100%).

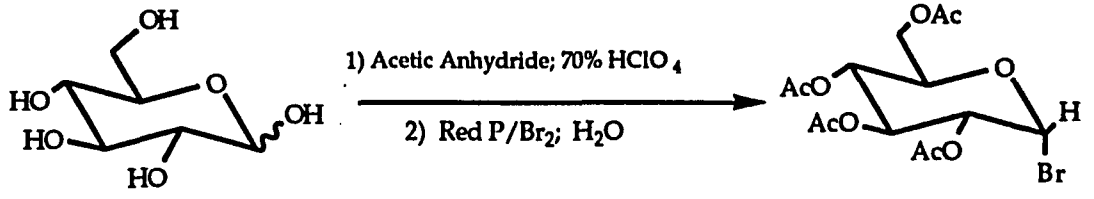
Grignard reaction between the grignard reagent (77) and the ketone (47) :-



In a 500 ml oven-dry 3-necked round bottom flask (fitted with nitrogen gas inlet tube, a dropping funnel, a reflux condenser and a calcium chloride drying tube at the top of the condenser), 10 g of metallic magnesium, 25 ml of freshly distilled anhydrous THF were taken. Dry nitrogen gas was passed through it. 10 g of dry dibromoethane was added to it (to activate the surface of metallic magnesium). A vigorous reaction was observed and the solvent started boiling. When the reaction started to cool down, 1 g of the iodide (76), in 5 ml of anhydrous THF was added to it, and the mixture was heated to reflux for an hour. 0.5 g of the ketone (47), in 5 ml of anhydrous THF was added to it through the dropping funnel and the mixture was stirred for additional 30 minutes. The mixture was then transferred into a 250 ml round bottom flask and the solvent was evaporated in a rotary evaporator. The residue was partioned between diethyl ether (100 ml) and 0.1 M acetic acid (100 ml). After transferring the mixture in to 250 ml separatory funnel, the

lower aqueous layer was removed. The upper organic layer was washed with 50 ml of 1% $NaHCO_3$ solution, 50 ml of brine, dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue was purified by a short silica gel column chromatography, eluting with hexane-ethyl acetate (2:1), to give the product where the 2-methoxybenzyl group was found to be missing, in the ^1H NMR (page 172; 300 MHz) spectra.

2,3,4,6-TETRA-O-ACETYL-α-D-GLUCOPYRANOSYL BROMIDE (51) :-

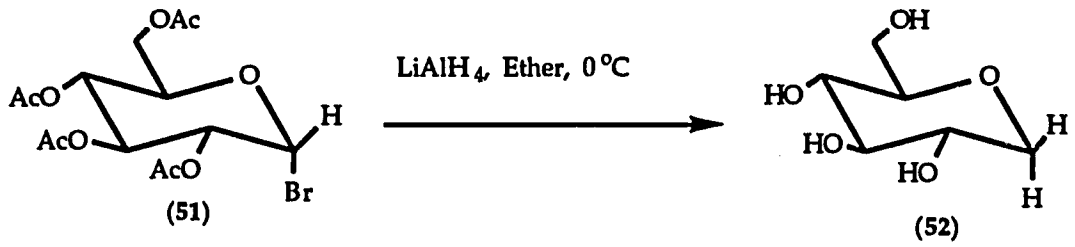


(51)

A 1-liter three-necked flask, located in the fume hood was equipped with a mechanical stirrer unit, a dropping funnel and a thermometer. The flask was immersed in an ice-salt bath supported on a laboratory jack. Acetic anhydride (432 g; 400 ml, 4.24 mol) was added to the flask, and it was cooled to 4°C. Perchloric acid (70%; 2.5 ml) was then added to it with stirring. Dry powdered α-D-glucose (100 g, 0.56 mol) was added in portions into the reaction mixture with constant stirring, to maintain the reaction temperature below 5 °C. The mixture was stirred for additional 1 hour. Red phosphorous (31 g, 1 mol) followed by bromine (181 g, 58 ml, 2.26 mol) dropwise at a rate that the temperature would not exceed than 5°C. Then water (36 ml) was added to the reaction mixture over a period of one hour, so that the temperature would not rise above than 5°C. The mixture was allowed to stir at room temperature for additional 2 hours, and then diluted with 250 ml of dichloromethane, and filtered through a large wide glass funnel having a

glass wool plug. Finally the reaction flask and the funnel were rinsed with small portions of dichloromethane. All the filtrate and the washings were transferred to a 3-liter separatory funnel and washed rapidly with two 800 ml portions of iced water. The lower methylene chloride layer from the second washing was transferred into a large beaker containing stirred saturated solution of aqueous $NaHCO_3$ solution together with some crushed ice. When the vigorous evolution of CO_2 was subsided, the mixture was transferred into a separatory funnel, and the lower methylene chloride layer was taken into a large erlenmeyer flask containing powdered activated silica gel (10 g), after 10 minutes the solution was filtered through a sintered glass funnel under reduced pressure. The solvent was removed under reduced pressure in a rotary evaporator. A syrupy mass was obtained at the bottom of the flask, which crystallized on standing. The crude product was recrystallised from ether-hexane, having m.p. 88-89°C, (215 g. 93%).

1,5 Anhydroglucitol (1,5 Anhydrosorbitol) (52):-

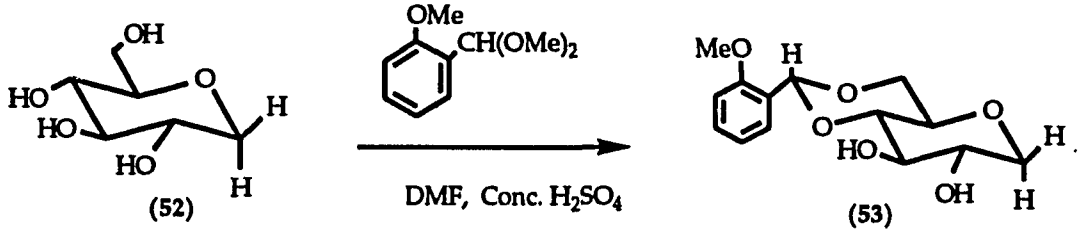


(51) (52)

A oven dry 3-litre 3-necked round bottom flask fitted with a mechanical stirrer, an one litre dropping funnel, and a reflux condenser were attached to it. Lithium aluminium hydride (60 g, 1.6 mol), one litre of anhydrous ether were charged under nitrogen atmosphere. The flask was immersed in an ice-salt bath, supported on a laboratory jack. 1-α-Bromo 2,3,4,6-tetra-O- acetoglucose (51), (205 g, 0.5 mol); dissolved in 500 ml of

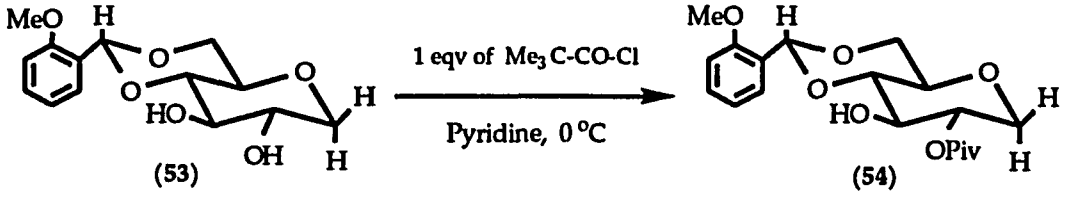
anhydrous ether was added dropwise in to the stirred ice cold slurry of LAH, through the dropping funnel over a period of 2 hours. The bath temperature was maintained below 5 °C throughout the addition. The mixture was then stirred for additional 2 hours. of water (100 ml) was added to it *very cautiously* over a period of 90 minutes, while the mixture was kept over a ice-salt bath. When the addition of water was completed, The reaction flask was disconnected from its accessories, and the contents in the flask was filtered through a buchner funnel under reduced pressure. The residue was washed with 3 x 500 ml of hot water. Dowex cation exchange resin $H^{\oplus}$ form was added slowly to the aqueous solution, until it becomes neutral. The resins were then filtered, and the water was evaporated in a rotary evaporator (making the bath-temperature 50 °C). The residual gum was dissolved in anhydrous methanol (15 ml), and transferred in to a 125 ml erlenmeyer flask, and the round bottom flask was rinsed with an additional anhydrous methanol (10 ml) and transferred into the erlenmeyer flask. The mouth of the flask was corked and the flask was stored in a freezer (at -10 °C) for 72 hours. (49.0 g. 66% yield) of 1,5-anhydro glucitol was obtained, having melting point 141°C (Literature m.p. 143 °C). Mass spectra calculated for $C_6H_{12}O_5$ (164). Found: m/e = 164; C.I. in ammonia 165 (M+1); 181.9 ($M+NH_4$).

4,6-O-(2-Methoxybenzylidene)-1,5-Anhydroglucopyranoside (53) :-



A solution of 1,5-anhydrosorbitol (52) (16.4 g, 0.1 mol), 2-methoxy-benzaldehyde dimethyl acetal (20.0 g, 0.11 mol), and one drop of conc. sulfuric acid, in 100 ml DMF, taking in a 500 ml round bottom flask, was stirred magnetically for 18 hours. Then the mixture was rotated in a rotary evaporator under reduced pressure, making the bath temperature at 50 °C, for two hours. Sodium bicarbonate (5 g) was added to it, and the mixture was stirred for additional 1 hour. The temperature was then raised to 70 °C, and the aspirator was replaced by a high vacuum pump, and the solvent was distilled off until about 50 ml remained. The solution was poured onto a stirred mixture of ice (25 g), saturated aqueous $NaHCO_3$ solution (50 ml), and 50 ml of chloroform. The entire mixture was then transferred into a separatory funnel and shaken and allowed to settle. Removing the lower organic layer, the upper aqueous layer was extracted with 50 ml of chloroform twice. The combined organic layer was dried over $MgSO_4$, filtering the residue the solvent was evaporated in a rotary evaporator. Residue is the title compound (22.5 g; 80% yield). Mass spectra calculated for $C_{14}H_{18}O_6$ (282.35). Found: m/e = 282; C.I. in ammonia 283 (M+1), 300 ($M+NH_4$).
IR ($CHCl_3$, cm^{-1}); 3150-3650 (b), 1600 (s), 1440 (s), 1500 (s).

4,6-O-(2-Methoxybenzylidene)-1,5-anhydroglucose-2-pivalate (54) :-



In a dry 200 ml round bottom flask fitted with a dropping funnel and a $CaCl_2$ drying tube, compound (53) (14.1 g, 0.05 mol) was taken, and it was dissolved in 50 ml of freshly distilled dry pyridine. The mixture was then

cooled in an ice bath. Pivaloyl chloride (6.6 g, 0.055 mol) was added to it dropwise. After 1 hour the ice bath was removed, and the mixture was allowed to stir at room temperature for 36 hours. The solvent pyridine was removed in a rotary evaporator at reduced pressure. The residue was then poured into a stirred ice cold mixture of saturated bicarbonate solution and diethyl ether (100 ml each), in a 1 litre beaker. After all the effervescence had been ceased, the contents in the beaker were transferred in to a 500 ml separatory funnel, and the lower aqueous layer was removed. The top organic layer was successively washed with water (50 ml), and brine (100 ml), then dried over $MgSO_4$, filtered the residue and the solvent was evaporated in a rotary evaporator and the residue was azeotroped with toluene (50 ml x 3). The residue was chromatographed through a silica gel column, eluting first with hexane-ethyl acetate (10:1) to elute the 2,3-dipivalate [(56), 10%)], and then with (4:1) to elute the 2-pivalate (title compound, 54; 40%); and then with (3:1) to elute the 3-pivalate [(55; 25%)]; and finally with acetone to elute unreacted (53). M.P. 124-127 °C. IR ($CHCl_3$, cm^{-1}); 3250-3650 (b), 1720 (s).1480 (s), 1490 (s), 1500 (s). ^1H NMR (page 150; 300 MHz); 6.8 - 7.60 (m, 5H, aromatic H); 5.89 (s, Anisylidene-H); 4.9 (ddd, 1H, C-2); 4.27 (dd, 1H, C-6βH); 4.03 (dd, 1H, C-1βH); 3.92 (t, 1H, C-3); 3.82 (s, 3H, Aromatic-OCH_3); 3.71 (t, 1H, C-6αH); 3.49 (t, 1H, C-4); 3.375 (m, 1H, C-5); 3.2 (t, 1H, C-1αH); 1.21 [s, 9H, C(2)-$C(CH_3)_3$]. Mass spectra calculated for $C_{19}H_{26}O_7$ (366.43). Found: m/e = 266; C.I. in ammonia 367.0 (M+1), 384 ($M+NH_4$).

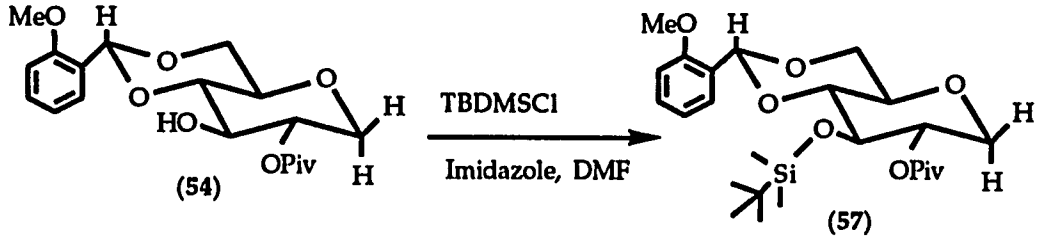
Anisylidene 1,5-Anhydro Sorbitol 3-Pivalate

^1H NMR (page 151; 300 MHz); 6.8 - 7.60 (m, 5H, aromatic H); 5.79 (s, Anisylidene-H); 4.95 (t, 1H, C-3); 4.35 (dd, 1H, C-6βH); 4.1 (dd, 1H, C-1βH); 3.8 (m, 2H, C-2 & C-6αH); 3.817 (s, 3H, Aromatic-OCH_3); 3.65 (t, 1H, C-4); 3.5 (m, 1H, C-5); 3.4 (t, 1H, C-1αH); 1.19 [s, 9H, C(2)-$C(CH_3)_3$].

Anisylidene 1,5-Anhydro Sorbitol 2-3-dipivalate

M.P. 170-173 °C. ^{1}H NMR (page 152; 300 MHz); 6.8 - 7.60 (m, 5H, aromatic protons); 5.79 (s, Anisylidene-H); 5.35 (t, 1H, C-3); 5.05 (ddd, 1H, C-2); 4.3 (dd, 1H, C-6βH); 4.1 (dd, 1H, C-1βH); 3.79 (s, 3H, Aromatic-OCH_3); 3.75 (t, 1H, C-6αH); 3.65 (t, 1H, C-4); 3.5 (m, 1H, C-5); 3.375 (t, 1H, C-1αH); 1.14 & 1.15 (2 x s, 18H, C(2) & C(3) -$C(CH_3)_3$].

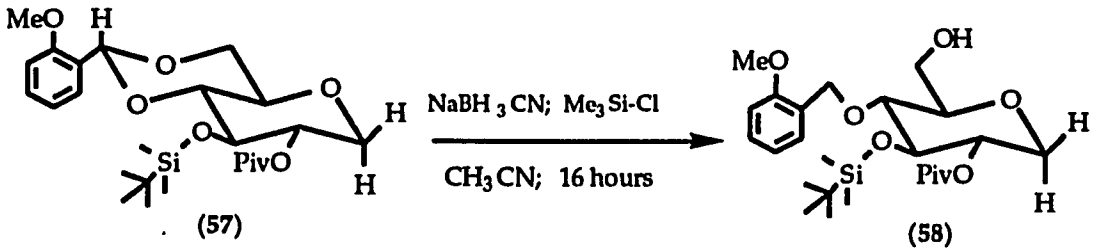
4,6-O-(2-Methoxybenzylidene)-1,5-anhydroglucose, 2-pivalate, 3-O-^{t}Butyl-dimethylsilyl ether (57) :-



In a dry 200 ml round bottom flask of compound (54) (6 g, 15 mmol) was dissolved in 50 ml of dry DMF. Anhydrous imidazole (2.6 g. 0.037 mol), and tert-butyl dimethyl chlorosilane (2.6 g, 0.018 mol) were added to it, and the mixture was stirred at room temperature for 16 hours. The solvent was evaporated in a rotary evaporator applying high vacuum, and the residue was partitioned between water and chloroform (100 ml each). The mixture was then transferred into a 500 ml separatory funnel, removing the lower organic layer the upper aqueous layer was further extracted twice with additional amount of chloroform (50 ml x 2). The combined organic solution was dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue was purified through a silica gel column, eluting with hexane-ethyl acetate (6:1). Evaporation of the solvents at reduced pressure gave (7.8 g, 100 % yield) of the title compound as gum. IR ($CHCl_3$, cm^{-1}); 1720 (s). ^{1}H NMR (page 153;

300 MHz); 6.8 - 7.60 (m, 5H, aromatic H); 5.89 (s, Anisilidene-H); 4.9 (ddd, 1H, C-2); 4.27 (dd, 1H, C-6βH); 4.03 (dd, 1H, C-1βH); 3.92 (t, 1H, C-3); 3.82 (s, 3H, Aromatic-OCH_3); 3.71 (t, 1H, C-6αH); 3.49 (t, 1H, C-4); 3.375 (m, 1H, C-5); 3.2 (t, 1H, C-1αH); 1.21 [s, 9H, C(2)-$C(CH_3)_3$]; 0.77 [s, 9H, C(3)-OSi-$C(CH_3)_3$]; 0.135 & -0.086 [2xs, 6H, C(3)-$OSi(CH_3)_2$]. Mass spectra calculated for $C_{25}H_{40}O_7Si$ (480.66). Found: m/e = 480; C.I. in ammonia 481 (M+1); 498 ($M+NH_4$).

2-Pivaloyl, 3-O-^{t}butyl dimethyl silyl, 4-(2-methoxybenzyl), 1,5-anhydro-glucopyranose (58) :-

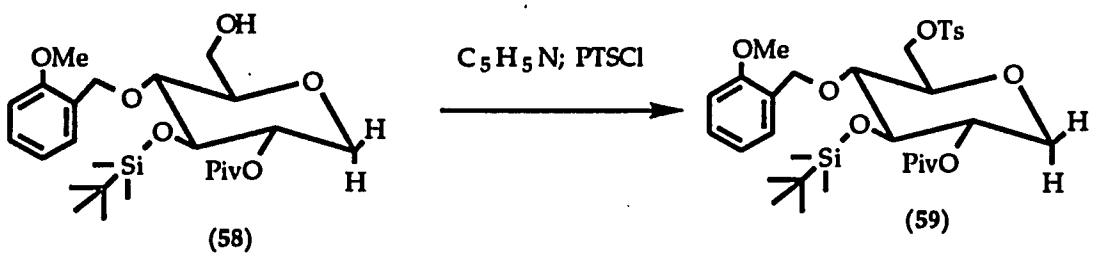


(57) (58)

In a 200 ml of 3-necked round bottom flask, attached with a 50 ml dropping funnel and a $CaCl_2$ drying tube, compound (57), (4.8 g, 10 mmol), was dissolved in 50 ml of freshly distilled anhydrous acetonitrile. 3 g of sodium cyanoborohydride (50 mmol), and 2 g of powdered molecular sieve type 3 A were stirred magnetically in a ice bath for 15 minutes. Chloro trimethyl silane (5.5 g; 55 mmol) in 10 ml of dry acetonitrile was added dropwise to it at 0 °C, and the mixture was allowed to stir at room temperature for 18 hours. The reaction mixture was then filtered through a celite pad in absence of moisture. The celite pad was washed with additional 50 ml of acetonitrile. The combined acetonitrile solution was poured on to a ice cold saturated aqueous $NaHCO_3$ solution (50 ml) with stirring taking in a 1-litre beaker. The aqueous mixture was evaporated in a rotary evaporator in order to remove the volatile solvent. The aqueous suspension was extracted

with chloroform (100 ml x 3). The combined organic solution was dried (over $MgSO_4$), filtered, and concentrated. The residue was purified through a silica gel column, eluting with hexane-ethyl acetate (3:1) to give the title compound (4.0 g, 85% yield), as a syrup. IR ($CHCl_3$, cm^{-1}); 3400-3600 (b), 1720 (s). ^1H NMR (page 154; 300 MHz); 6.8 - 7.60 (m, 5H, aromatic H); 4.85 & 4.6 (2xd, 2H, Ar-CH_2); 4.8 (m, 1H, C-2); 3.95 (dd, 1H, C-1bH); 3.85 (t, 1H, C-3); 3.80 (s, 3H, Aromatic-OCH_3); 3.7 (dd, 1H, C-6aH); 3.575 (dd, 1H, C-6bH); 3.4(t, 1H, C-4); 3.275 (m, 1H, C-5); 3.075 (t, 1H, C-1aH); 1.18 [s, 9H, C(2)-$C(CH_3)_3$]; 0.86 [s, 9H, C(3)-OSi-$C(CH_3)_3$]; 0.135 & -0.086 [2xs, 6H, C(3)-$OSi(CH_3)_2$]. Mass spectra calculated for $C_{25}H_{42}O_7Si$ (482.66). Found: m/e = 483.2; C.I. in ammonia 484.2 (M+1), 500.2 ($M+NH_4$).

2-Pivaloyl, 3-O-^{t}Butyl dimethyl silyl, 4-(2-methoxybenzyl), 1,5 -anhydro gluco-pyranose-6-tosylate (59) :-



(58) (59)

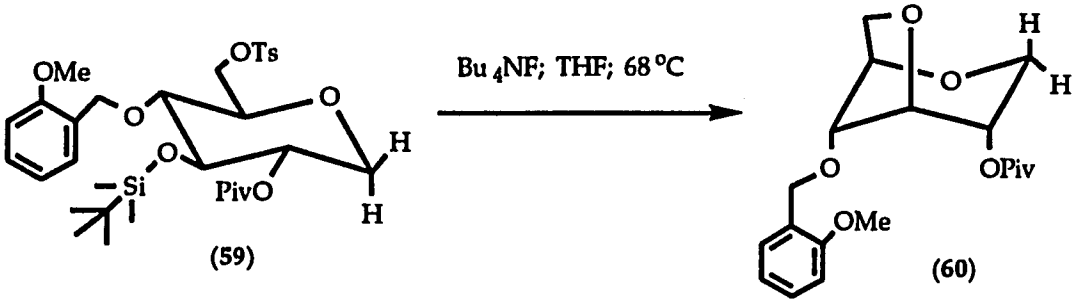
In a 100 ml round bottom flask, compound (58), (3.5 g, 7.26 mmol) was dissolved in dry chloroform (40 ml), dry pyridine (1.15 g, 14.5 mmol) was added and the mixture was stirred in an ice bath for an hour. p-toluene sulfonyl chloride (1.52 g, 8.0 mmol), was added to it, and mixture was stirred at room temperature for 18 hours. The solution was then transferred into a 250 ml separatory funnel, and washed with 25 ml of 0.1 (M) hydrochloric acid solution (1 M, 25 ml), 25% $NaHCO_3$ solution (25 ml), water (10 ml) and dried over $MgSO_4$; filtered. Evaporation of the solvent at reduced pressure gave the

title compound (4.5 g, 97% yield) as a gum. (Instead of Tosyl chloride, mesyl chloride gave the corresponding mesylate.

Physical data of the mesylate: IR ($CHCl_3$, cm^{-1}).1720 (s). ^1H NMR (page 155; 300 MHz); 6.8 - 7.60 (m, 4H, aromatic H); 4.82 & 4.6 (2xd, 2H, Ar-CH_2); 4.8 (m, 1H, C-2); 4.4 (dd, 1H, C-6βH); 4.15 (dd, 1H, C-6αH); 3.95 (dd, 1H, C-1βH); 3.85 (t, 1H, C-3); 3.83 (s, 3H, Aromatic-OCH_3); 3.457 (m, 1H, C-5); 3.35 (t, 1H, C-4); 3.1(t, 1H, C-1αH); 2.95 (s, 3H, CH_3 of Mesylate); 1.18 [s, 9H, C(2)-$C(CH_3)_3$]; 0.86 [s, 9H, C(3)-OSi-$C(CH_3)_3$]; 0.135 & -0.086 [2xs, 6H, C(3)-$OSi(CH_3)_2$].).

Mass spectra calculated for $C_{32}H_{48}O_9SSi$ (636.78). Found: m/e = 636.2; C.I. in ammonia 637.2 (M+1), 654.1 ($M+NH_4$).

2-Pivaloyl, 4-O-(2-methoxybenzyl), 1,5; 3,6-dianhydroglucose (60) :-



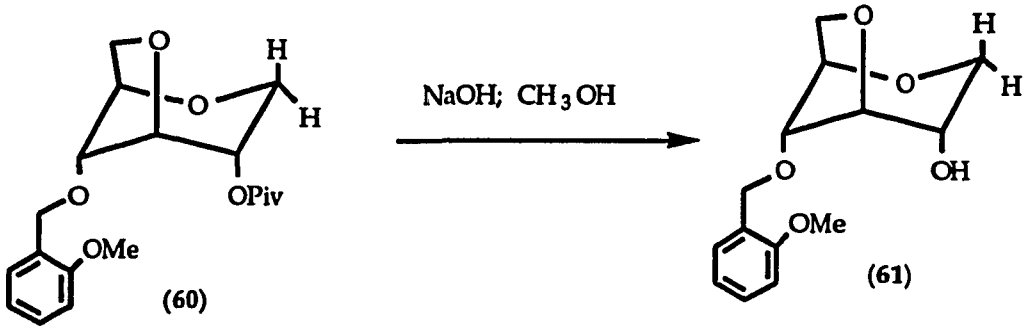
In a dry 1-litre 3-necked round bottom flask, equipped with a 500 ml dropping funnel, a reflux condenser attached with a $CaCl_2$ drying tube, compound (59), (4.45 g, 7.0 mmol); was dissolve in 500 ml of freshly distilled anhydrous THF. The solution was heated to reflux gently. Anhydrous tetrabutylammonium fluoride (3 g, 11.5 mmol), in 250 ml of anhydrous THF was added dropwise for 3 hours while the solution was under reflux condition, and the mixture was left in reflux condition for 18 hours. The solution was then cooled to room temperature, and the solvent was evaporated in a rotary evaporator under reduced pressure. The residual gum

was partitioned between diethyl ether (100 ml) and water (50 ml). The mixture was then transferred into a 250 ml separatory funnel. After removing the lower aqueous layer, the top organic layer was washed with additional amount of water (2 x 25 ml), brine (25 ml), and collected in a 250 ml erlenmeyer flask, dried over $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure. The residual gum was purified by a small silica gel column, eluting with hexane-ethyl acetate (4:1) to give the title compound (2.1 g, 85% yield).

^1H NMR (page 156; 300 MHz); 6.85, 6.93, 7.25 and 7.45 the four aromatic protons (H-1, H-3, H-2 and H-4 from the -OMe group, respectively), 4.72 m 3H (Ar-CH_2, and sugar H-2), 4.39 (t, 1H, H-4); 4.32 (t, 1H, H-3); 4.25 (dd, 1H, H-6 which is away from the C-1βH); 4.21 (d, 1H, J=12 Hz, C-1βH); 3.925 (dd, 1H, C-1αH); 3.875 (d, 1H, 15Hz, endo H-6); 3.82 (m, 1H, H-5); 3.79 (s, 3H, Aromatic -OMe); 1.156 (s, 9H, C-2 tertbutyl).

Mass spectra calculated for $C_{19}H_{26}O_6$ (350). Found: m/e = 350; C.I. in ammonia 351 (M+1), 368.0 ($M+NH_4$).

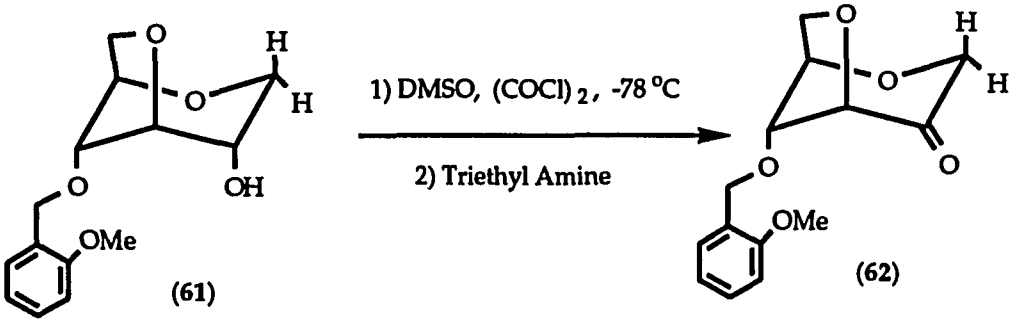
4-O-(2-Methoxybenzyl), 1,5; 3,6-Dianhydroglucose (61):-



In a 100 ml round bottom flask, 2.0 g of compound (60) was dissolved in 10 ml of methanol, and a solution of sodium hydroxide (1 g) in methanol (5 ml) was added to it. The mixture was then stirred magnetically for 18

hours. After removal of the solvent in a rotary evaporator, the residue was partitioned between water (25 ml) and chloroform (50 ml) and transferred into a 125 ml separatory funnel. After collecting the lower layer into a 250 ml erlenmeyer flask, the upper layer in the separatory funnel was extracted with additional amount of chloroform (25 ml x 2). The combined chloroform layer was dried over $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure. The residue is pure title compound (1.52 g, 100% yield). ^1H NMR (page 157; 300 MHz); 6.85, 6.93, 7.25 and 7.45 the four aromatic protons (H-1, H-3, H-2 and H-4 from the -OMe group, respectively), 4.8 (dd 3H, Ar-CH_2), 3.82 (s, 3H, aromatic -OCH_3), 3.83-4.5 (rest sugar protons). Mass spectra calculated for $C_{14}H_{18}O_5$ (266). Found: m/e = 266; C.I. in ammonia 267 (M+1), 283.9 (M+1+17).

4-O-(2-Methoxybenzyl)-2-Oxo-1,5; 3,6-Dianhydroglucose (62) :-

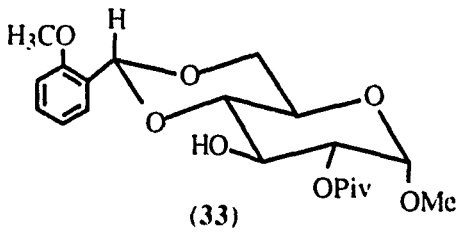


In a dry 100 ml 3-neck round bottom flask, equipped with a magnetic stirrer, 10 ml dropping funnel, a $CaCl_2$ drying tube, and containing dry dimethyl sulfoxide (1 g, 0.91 ml; 12.8 mmol), diluted with anhydrous dichloromethane (10 ml) cooled to -79 °C in a dry ice/acetone bath. Oxalyl chloride (0.8 g;0.55 ml, 6.3 mmol) was transferred to the dropping funnel with the help of a dry syringe, and 5 ml of dry dichloromethane was added into the

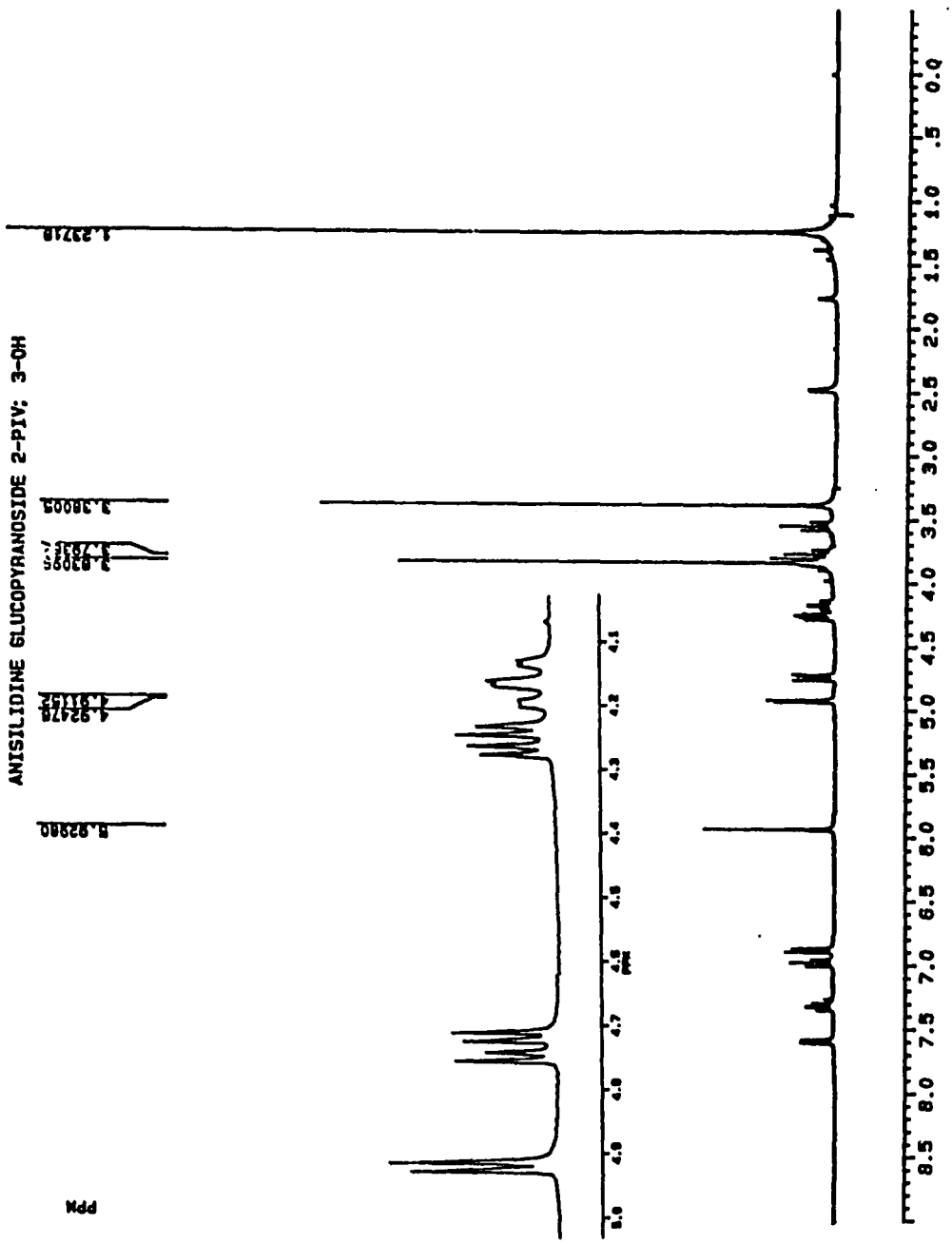
dropping funnel with the help of the same syringe. The oxalyl chloride solution was then added to the reaction flask. A vigorous gas evaluation was observed. Within 2 minutes a solution of the sugar (**61**), (1.5 g, 5.6 mmol) in anhydrous dichloromethane (10 ml) was added rapidly to the reaction mixture through the dropping funnel. After 30 minutes triethylamine (1.14 g; 1.56 ml, 11.2 mmol) was added dropwise in the reaction flask. Stirring was continued for additional 10 minutes and then the cooling bath was removed. The reaction mixture was allowed to warm to room temperature (20 minutes) and transferred into a 125 ml separatory funnel and washed with 15 ml of water. The upper aqueous layer was washed with additional amount of chloroform (25 ml x 2). The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and purified through a silica gel column eluting with hexane-ethyl acetate (3:1). Evaporation of the solvent gave the pure title compound (1.3 g. 85%).

^1H NMR (page 158; 300 MHz); 6.8 - 7.60 (m, 5H, aromatic H); 4.75 & 4.65 (2xd, 2H, Ar-CH_2); 4.55 (t, 1H, C-5); 4.45 (d, 1H, C-1H, J=16.875); 4.4 (t, 1H, C-4); 4.33 (d, 1H, C-6); 4.23 (3H, Aromatic OCH_3);4.18-4.24 (m, 3H, C-1, C-3, C-6). Mass spectra calculated for $C_{14}H_{16}O_6$ (264). Found: m/e = 264; C.I. in ammonia 265 (M+1), 281.9 (M+1+17).

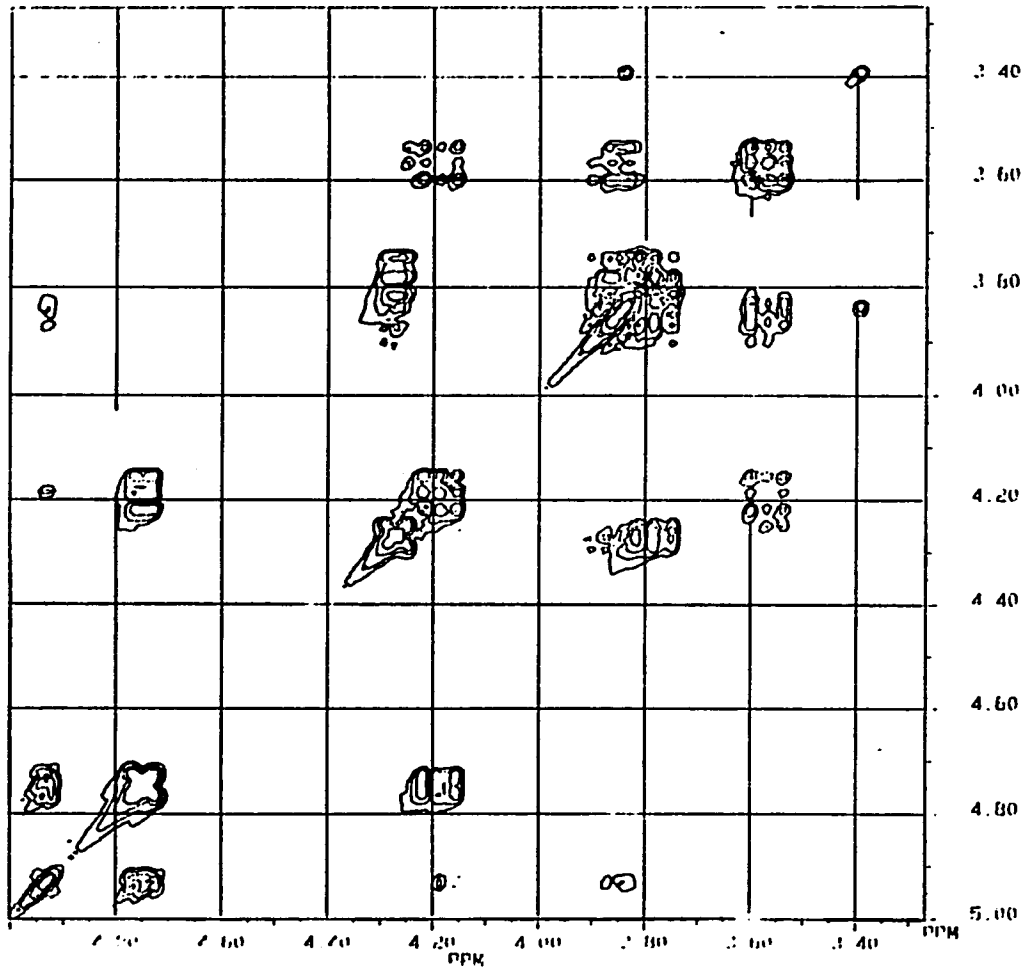
SPECTRA


H3CO
H
O
O
O
HO
OPiv
OMe

(33)


ANISILIDINE GLUCOPYRANOSIDE 2-PIV; 3-OH
PPM

METHOXY 4,6-ANISILIDENE GLUCOPYRANOSIDE 2- PIVALATE



BRUKER

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DAS SMX
AU PROG
 COSYDQF.AU
DATE 24-6-92

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SI1     256
SW2     697.350
SW1     348.675
NDO       1


WDW2      S
WDW1      S
SSB2      0
SSB1      0
MC2       M
PLIM ROW.
F1        5.001P
F2        3.268P
AND COLUMN.
F1        5.001P
F2        3.268P

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P1         8.30
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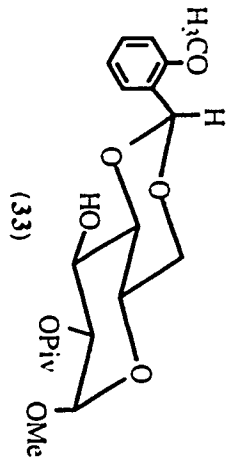

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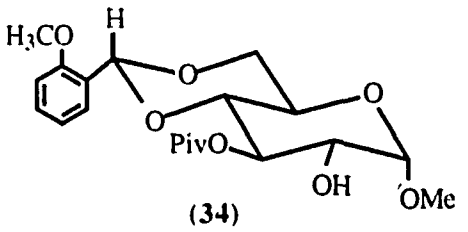
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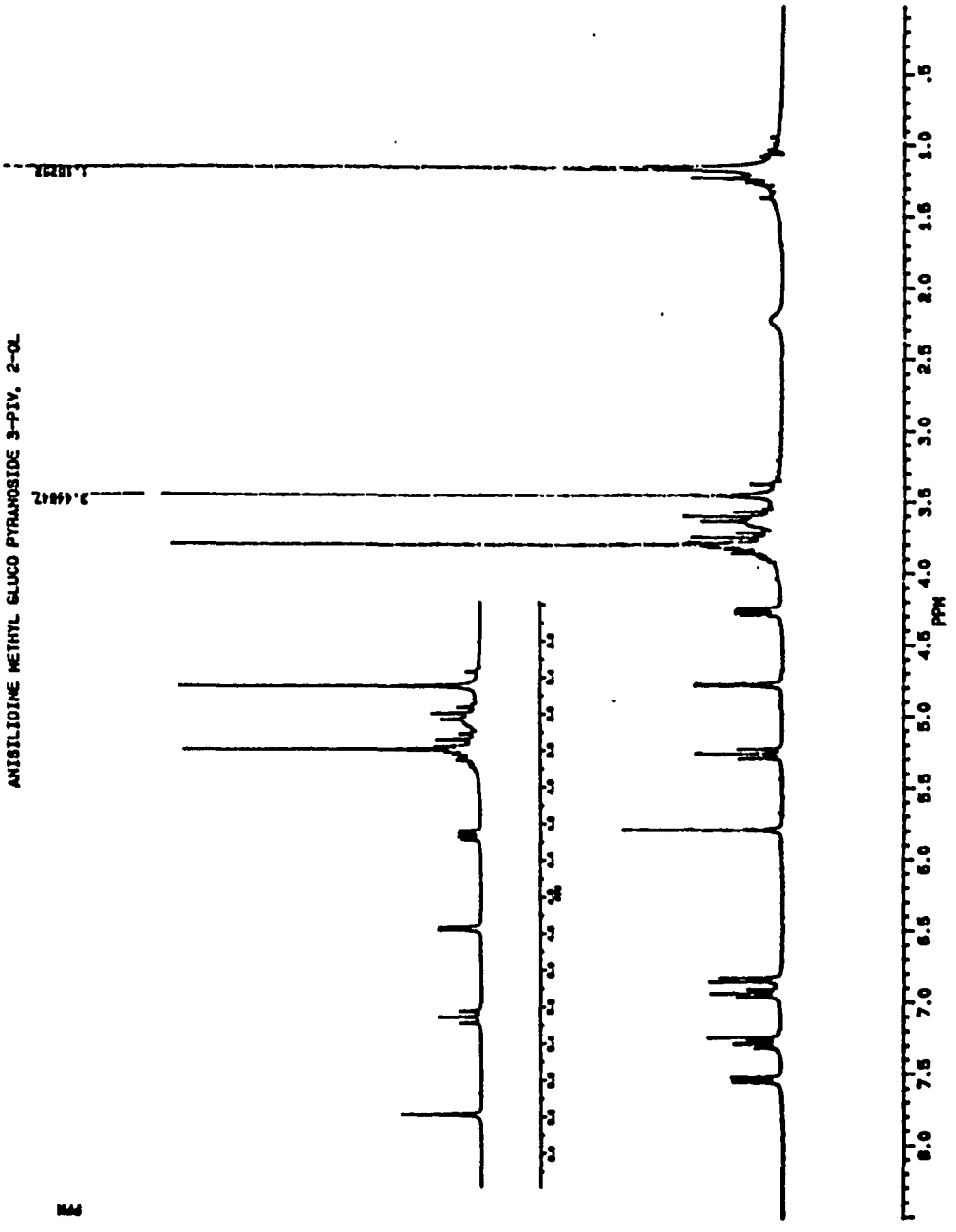
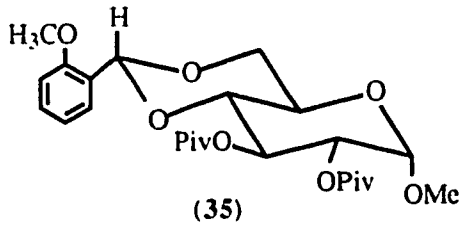
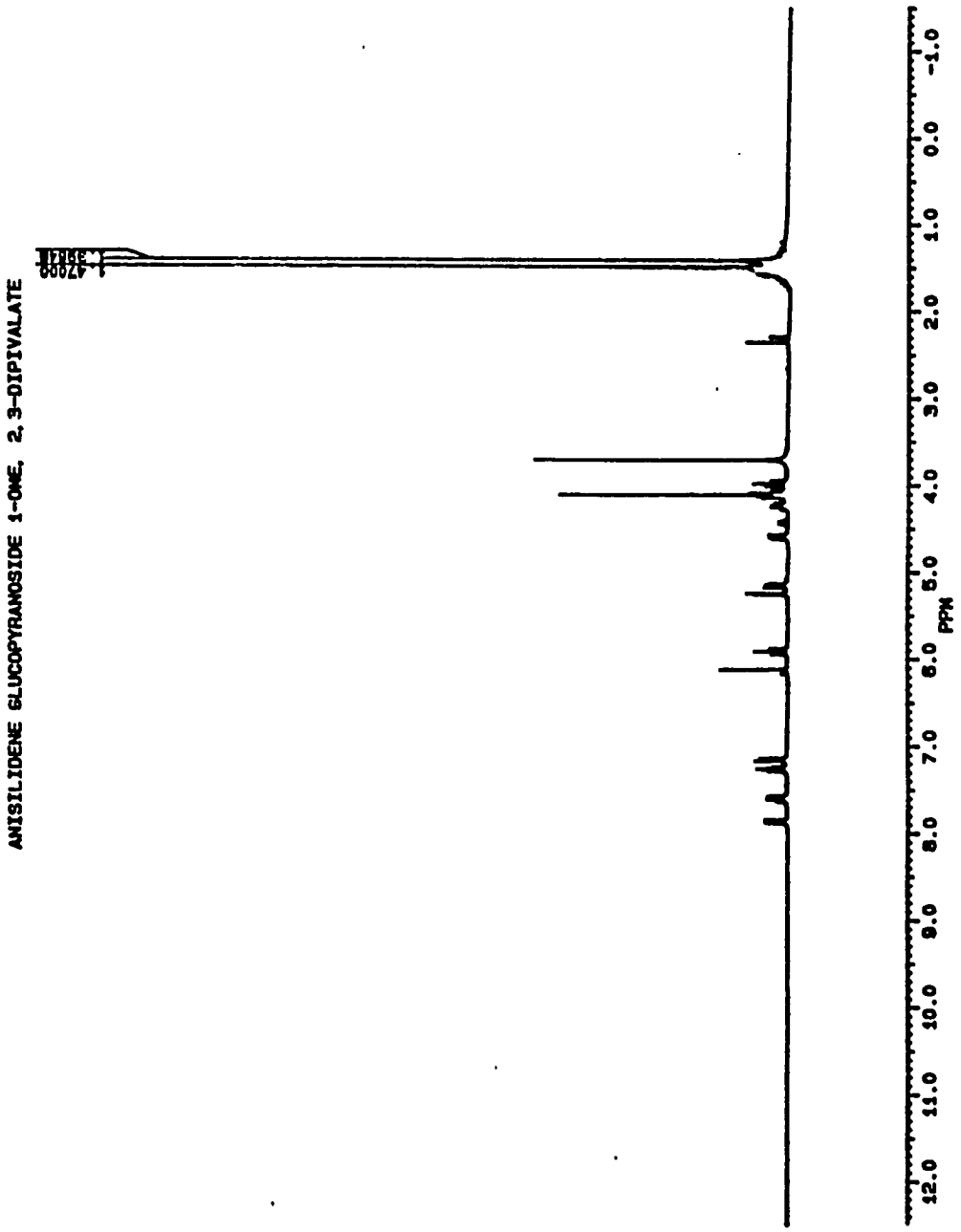
O
O
PivO
OH
OMe

(34)


ANISILIDINE METHYL GLUCO PYRANOSIDE 3-PIV, 2-OL
PPM


H3CO
H
O
O
O
PivO
OPiv
OMe

(35)


ANISILIDENE GLUCOPYRANOSIDE 1-OME, 2,3-DIPIVALATE
PPM
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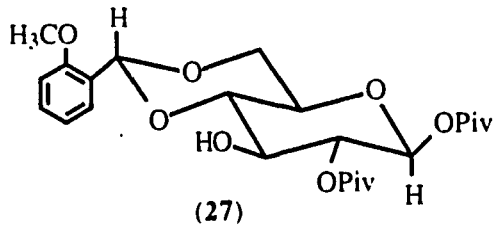
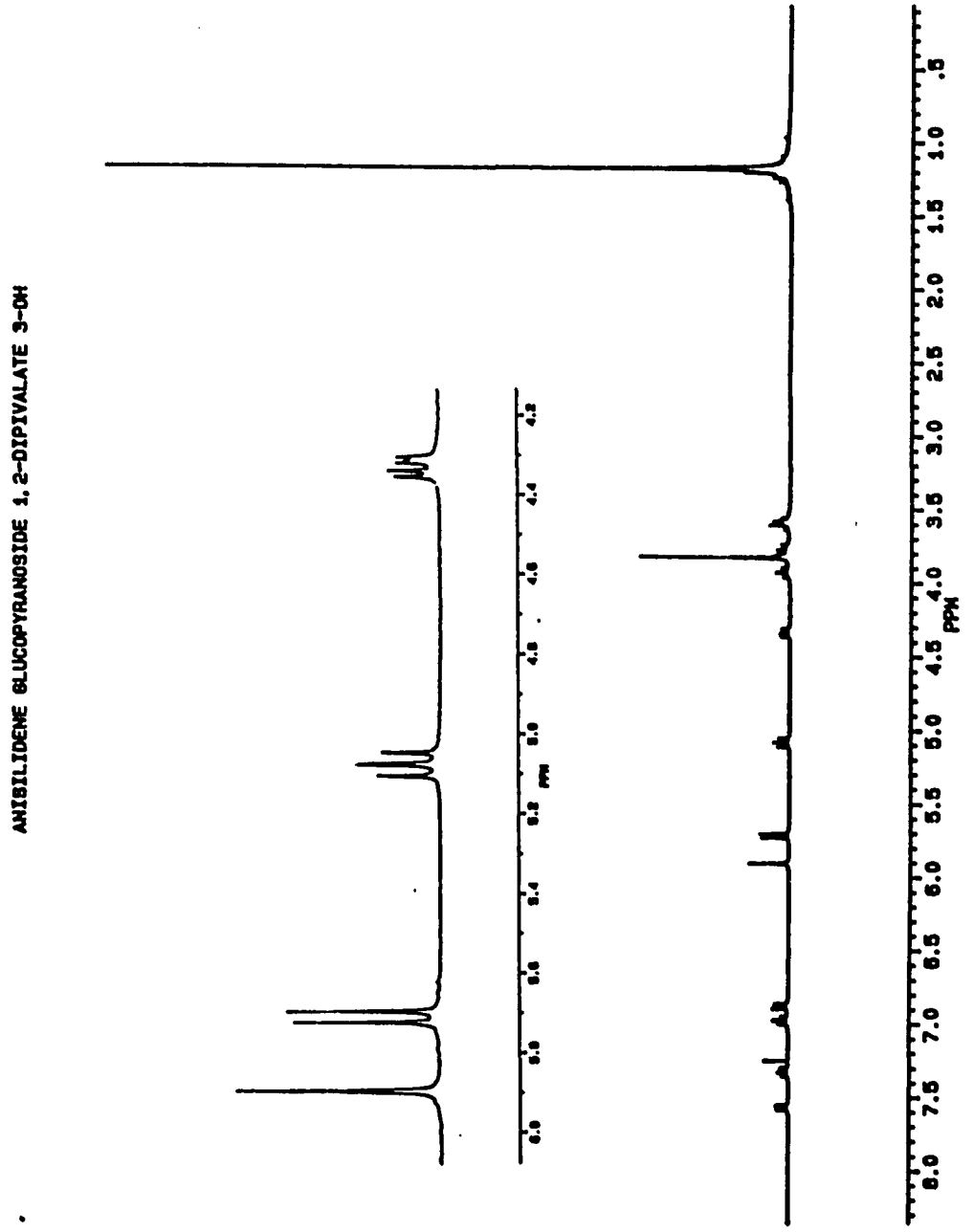
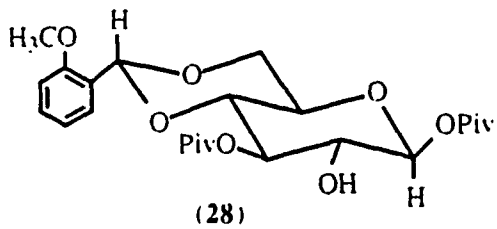
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0

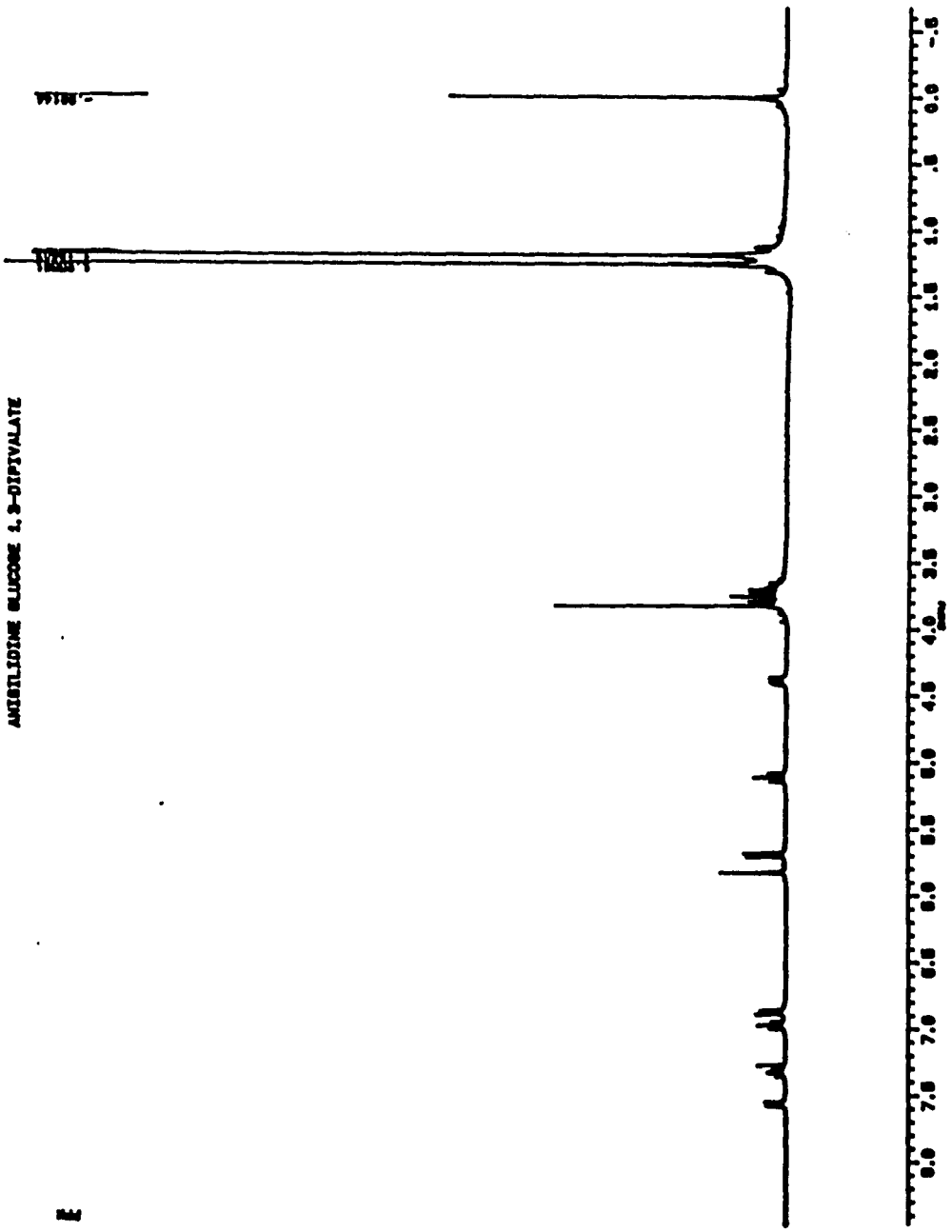

H3CO
H
O
O
O
HO
OPiv
OPiv
H

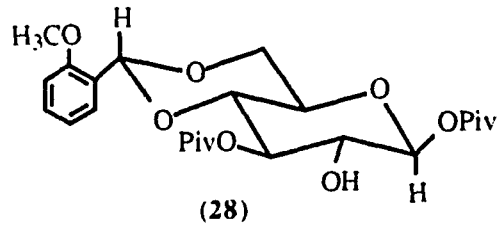
(27)


ANISILIDENE GLUCOPYRANOSIDE 1,2-DIPIVALATE 3-OH
PPM

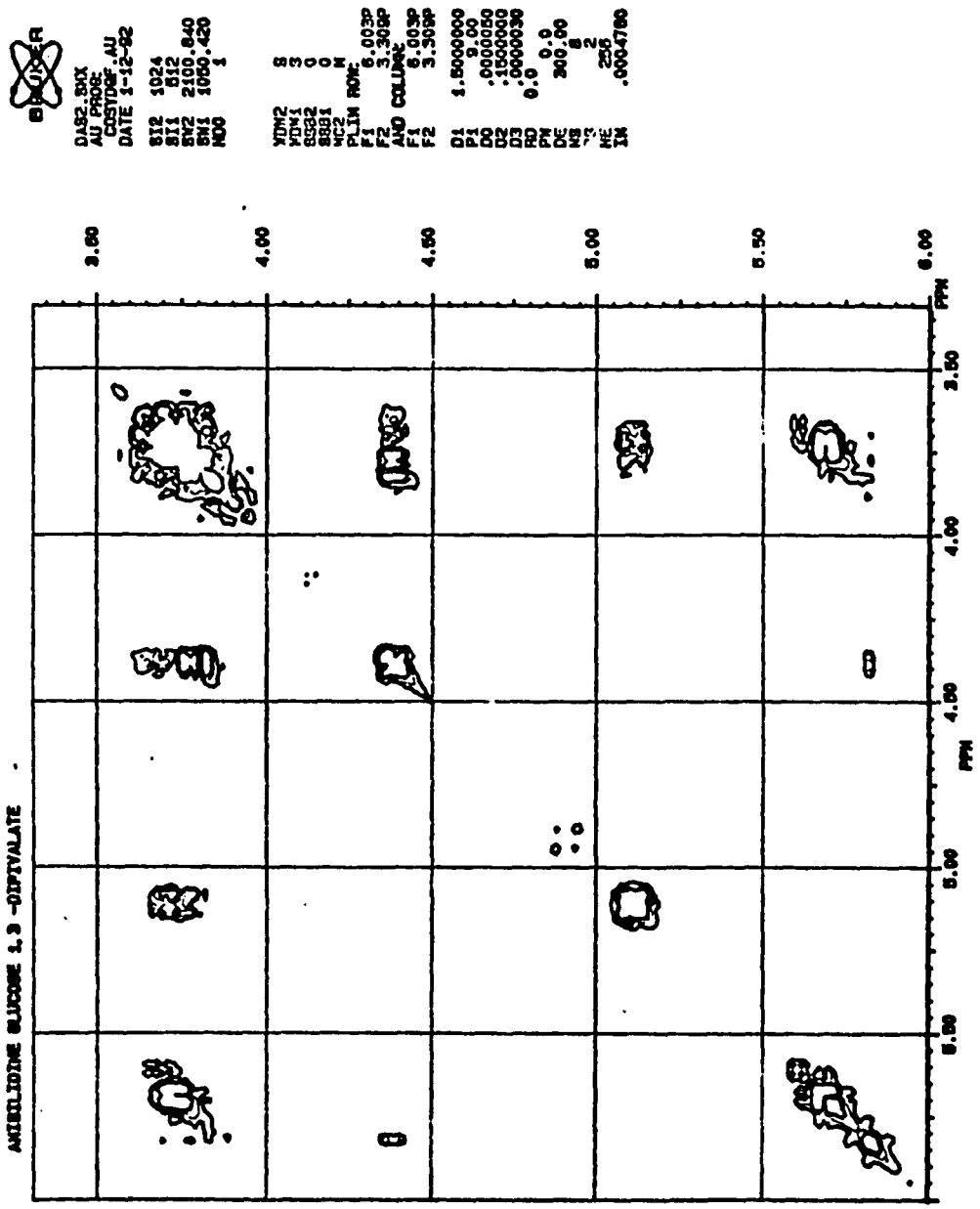


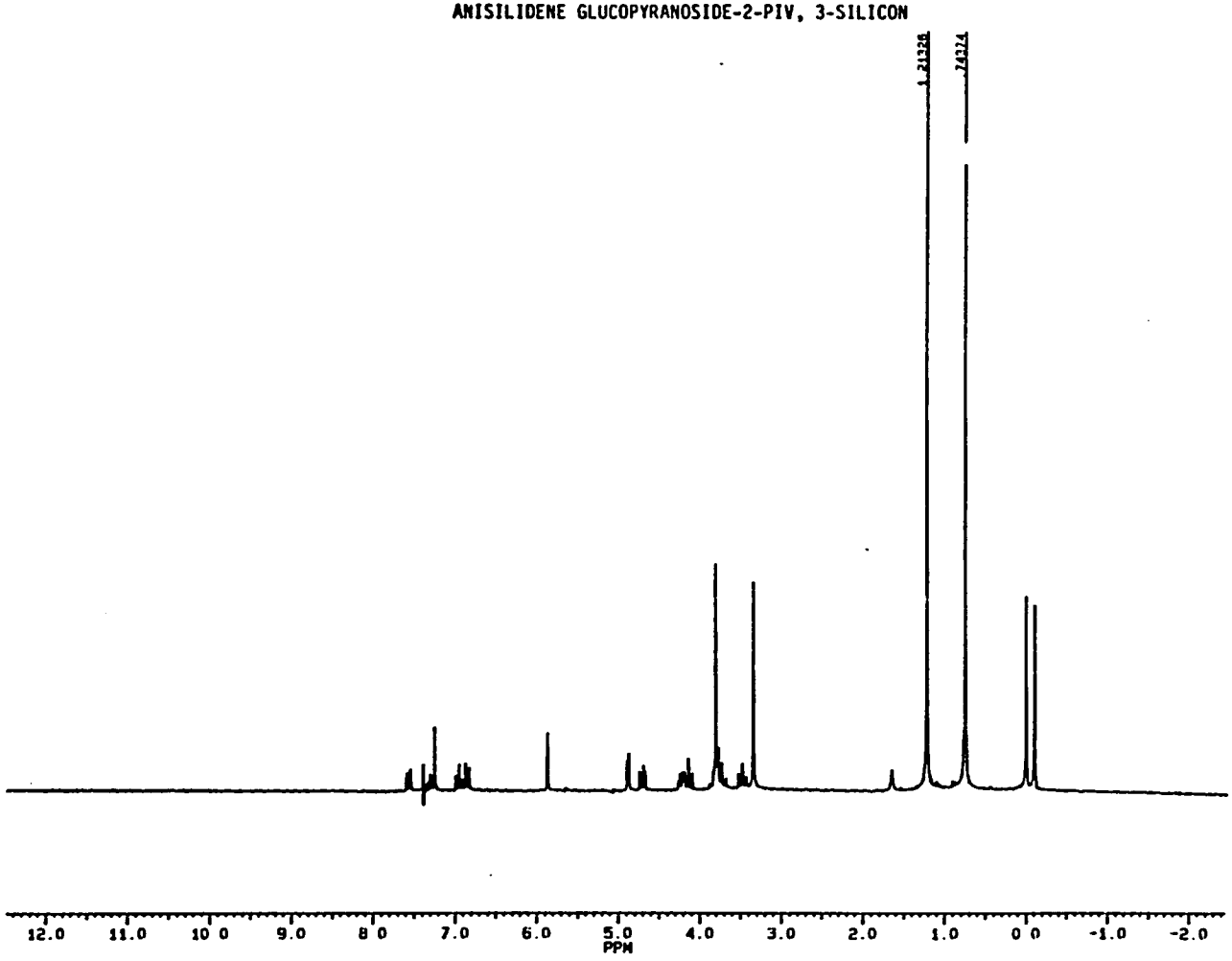
(28)

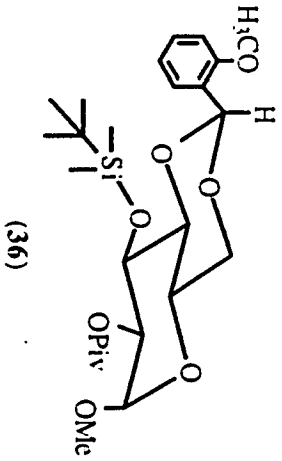



H3CO
H
O
O
O
PivO
OPiv
OH
H

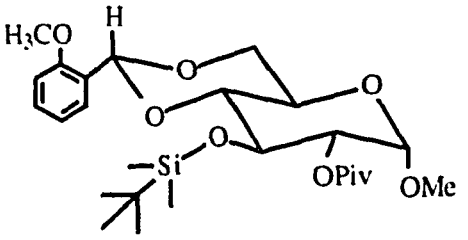
(28)


BRUKER
DAS2.5XX
AU PROG
CONTOUR.AU
DATE 1-12-92
SI2 1024
SI1 512
SW2 2100.840
SW1 1050.420
NDO 1
XDW2 8
XDW1 8
SSB2 0
SSB1 0
WC2 300
PLIM ROW 6.003P
F1 3.309P
F2 6.003P
AND COLUMN
F1 6.003P
F2 3.309P
D1 1.8000000
P1 9.00
D0 .0000050
D2 .1500000
D3 .0000030
RDO 0.0 0.0
DFC 300.00
NB 2
IN 256
.0004780
3.50
4.00
4.50
5.00
5.50
6.00
PPM
ANHEDLIDINE GLUCOSE 1,3 -DIPIVALATE

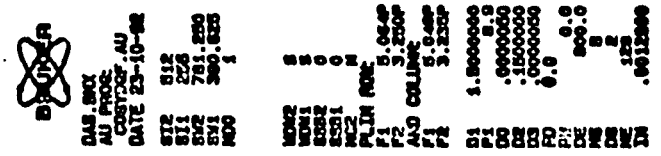

ANISILIDENE GLUCOPYRANOSIDE-2-PIV, 3-SILICON
1.21328
.74324
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
PPM
4.0
3.0
2.0
1.0
0.0
-1.0
-2.0

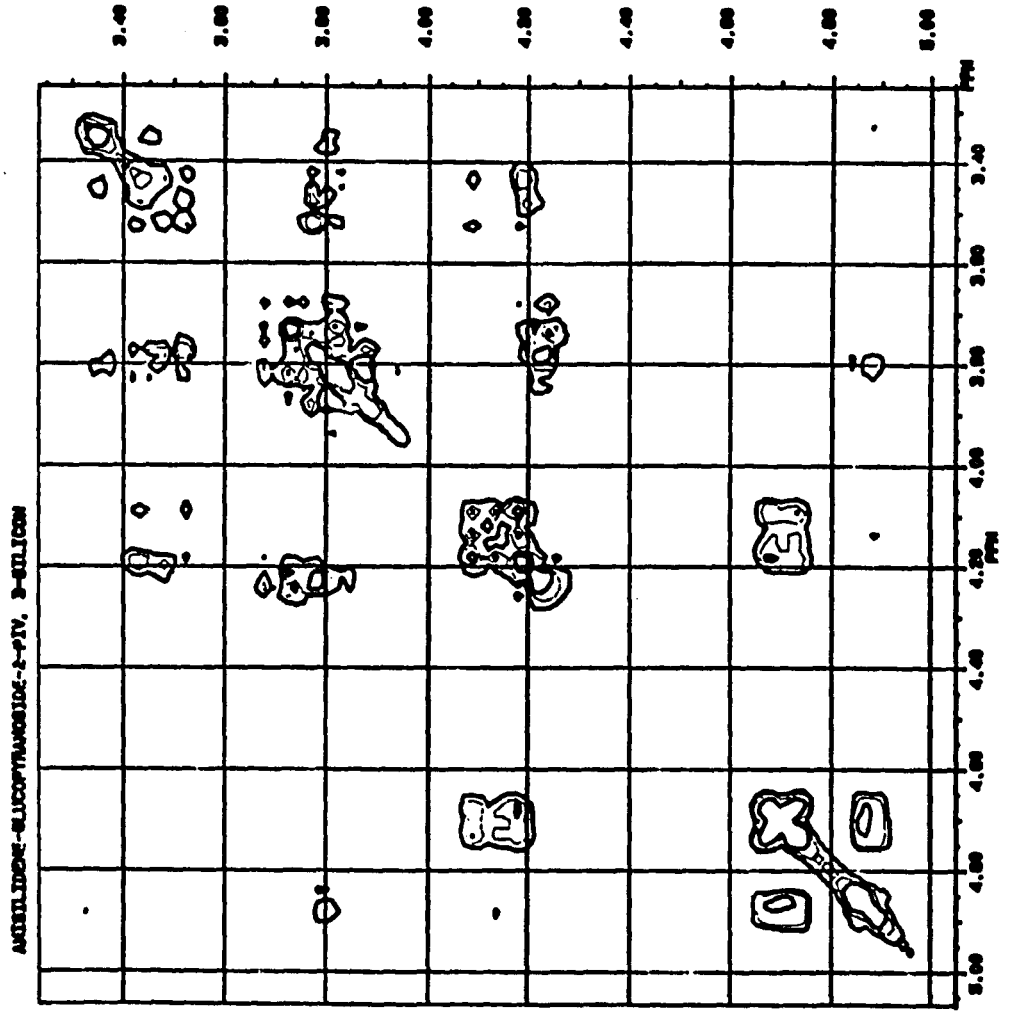

H3CO
H
Si
O
OPiv
OMe

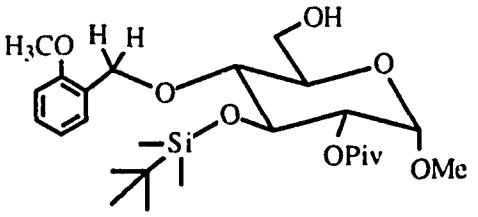
(36)



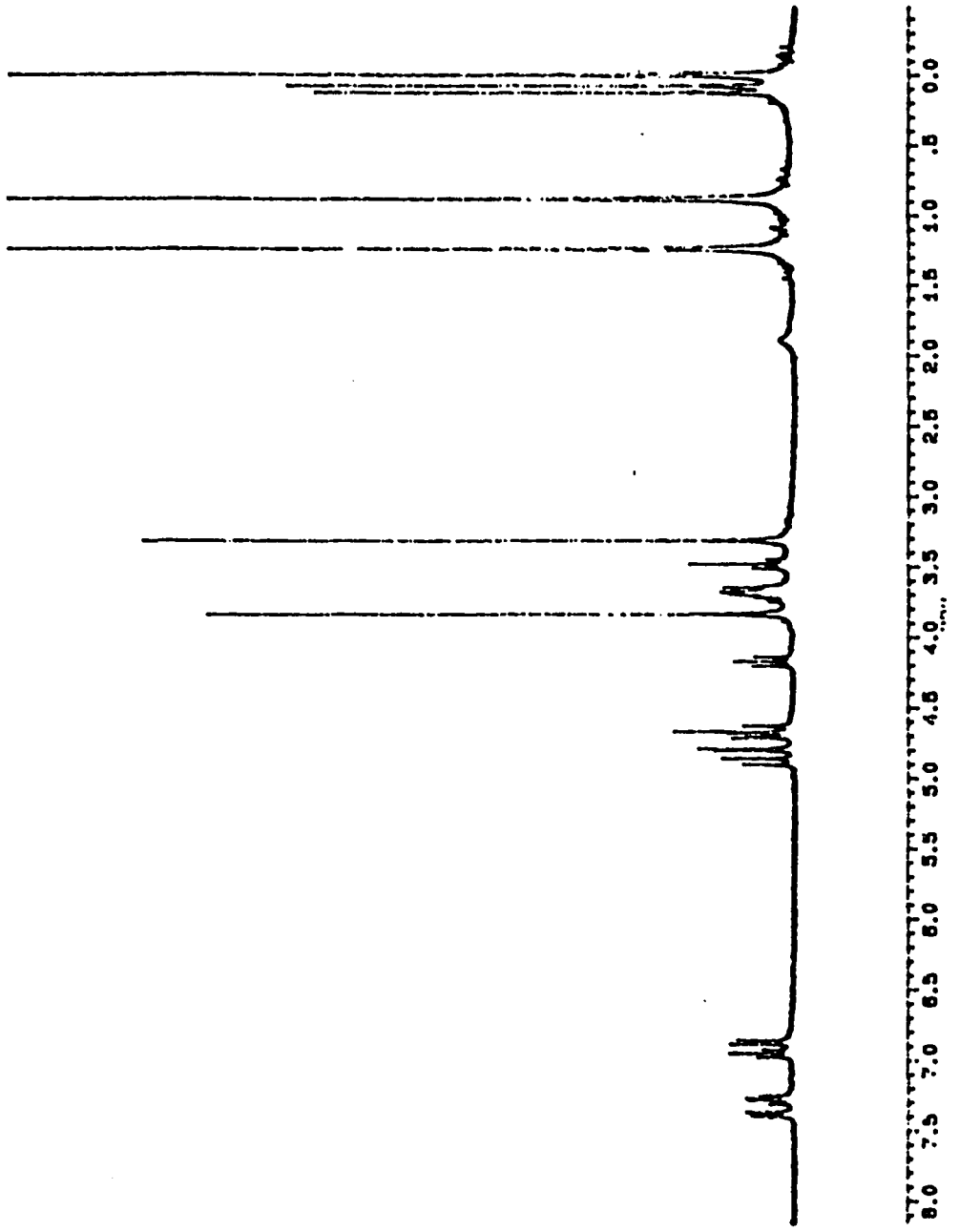
(36)

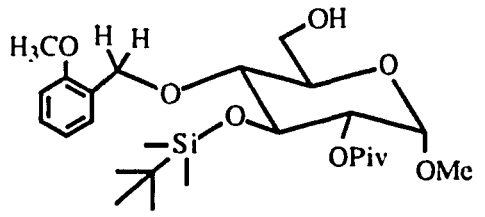




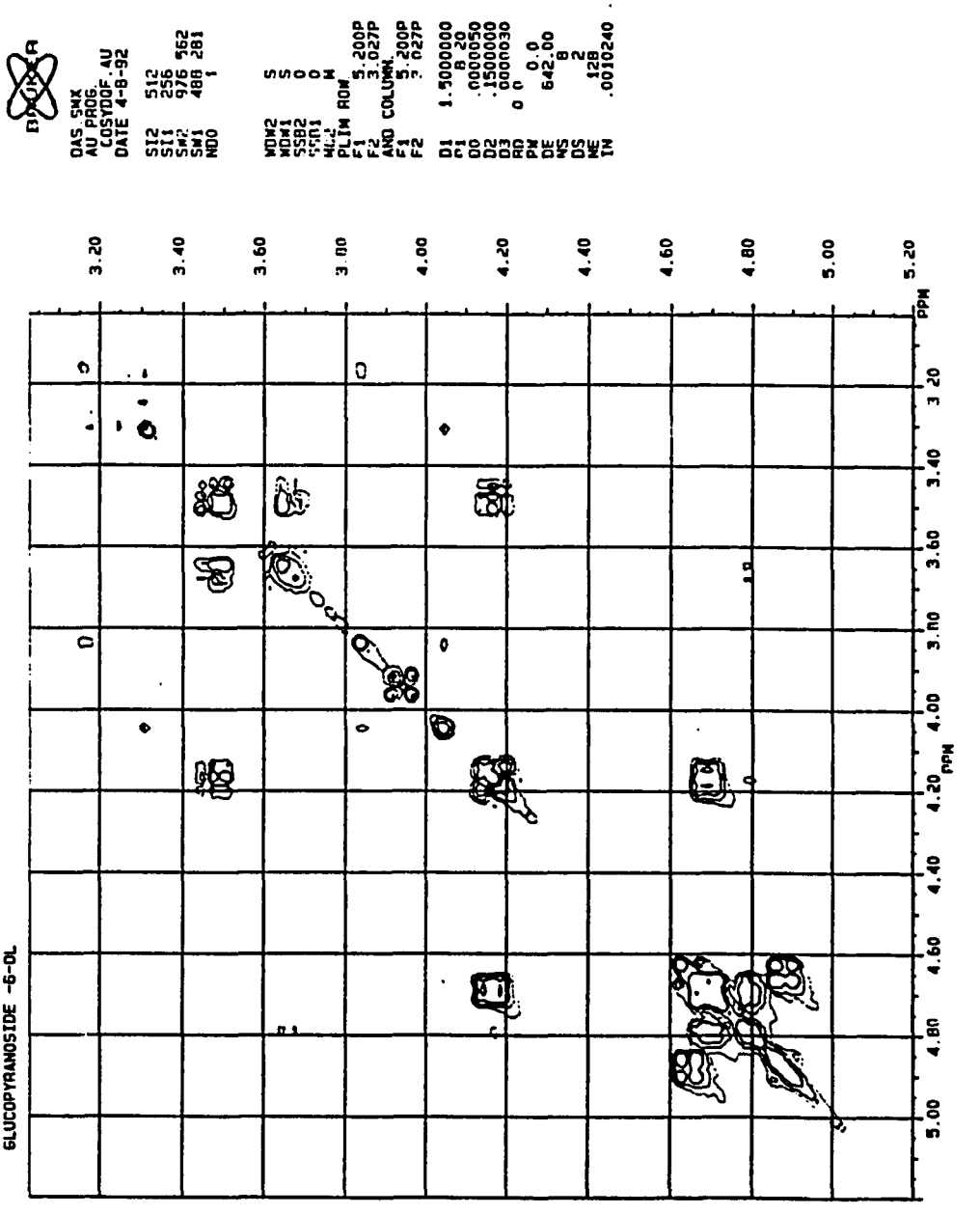

H3CO
H
H
OH
O
O
O
Si
OPiv
OMe

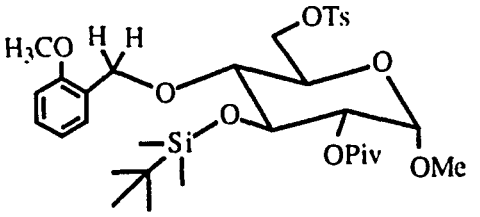
(37)


8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0

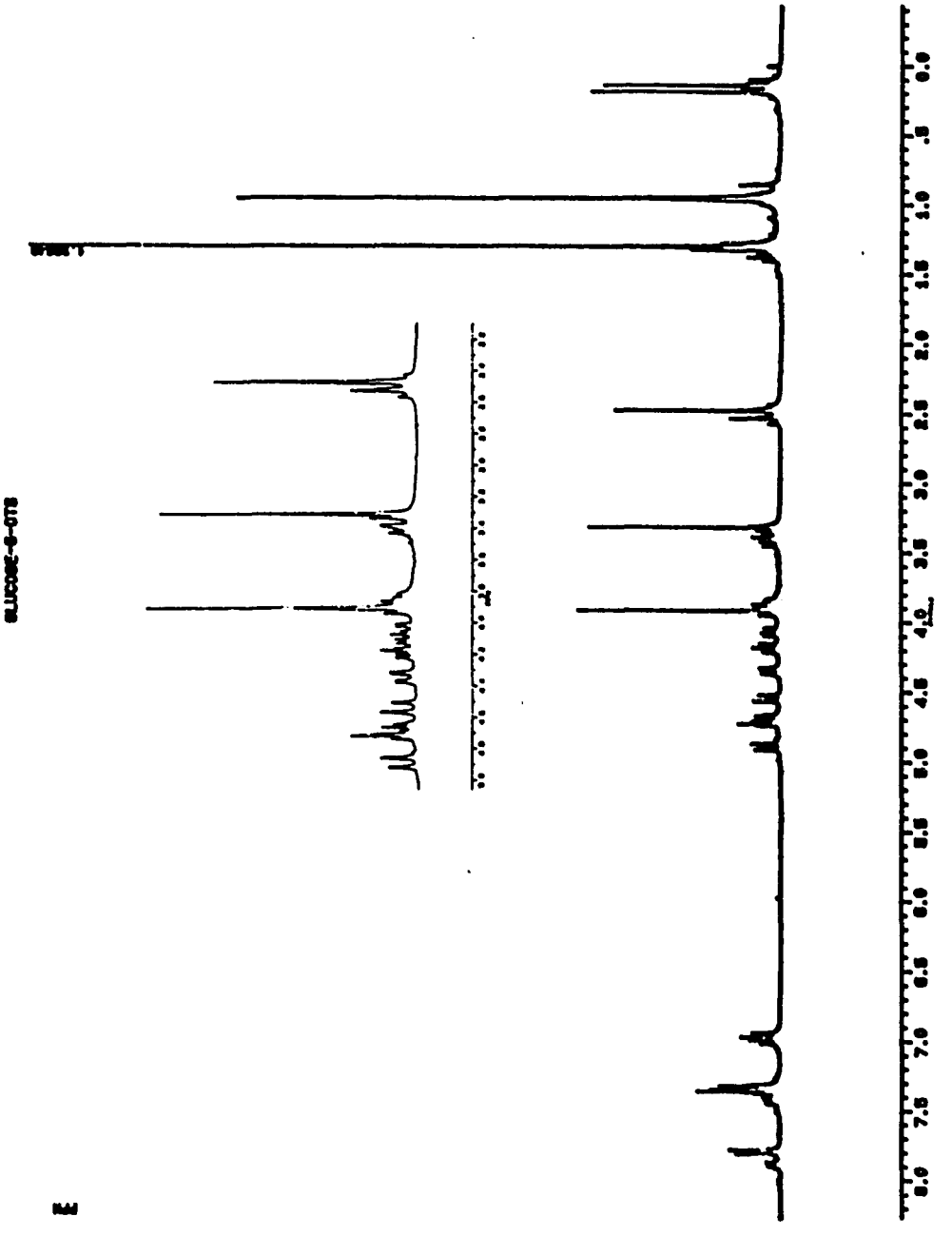

H3CO
H
H
O
OH
O
O
Si
OPiv
OMe

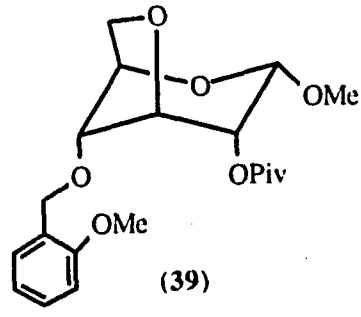
(37)


DAS SMX
AU PROG
COSYDQF.AU
DATE 4-8-92
SI2 512
SI1 256
SW2 976.562
SW1 488.281
NDO 1
MDW2 S
MDW1 S
SSB2 0
PLIM ROW
F1 5.200P
F2 3.027P
AND COLUMN
F1 5.200P
F2 3.027P
D1 1.5000000
P1 8.20
D0 .0000050
D2 .1500000
D3 .0000030
RD 0 0 0.0
PW 642.00
DE 8
NS 2
DS 128
ME .0010240
TN
3.20
3.40
3.60
3.80
4.00
4.20
4.40
4.60
4.80
5.00
5.20
PPM
GLUCOPYRANOSIDE -6-OL

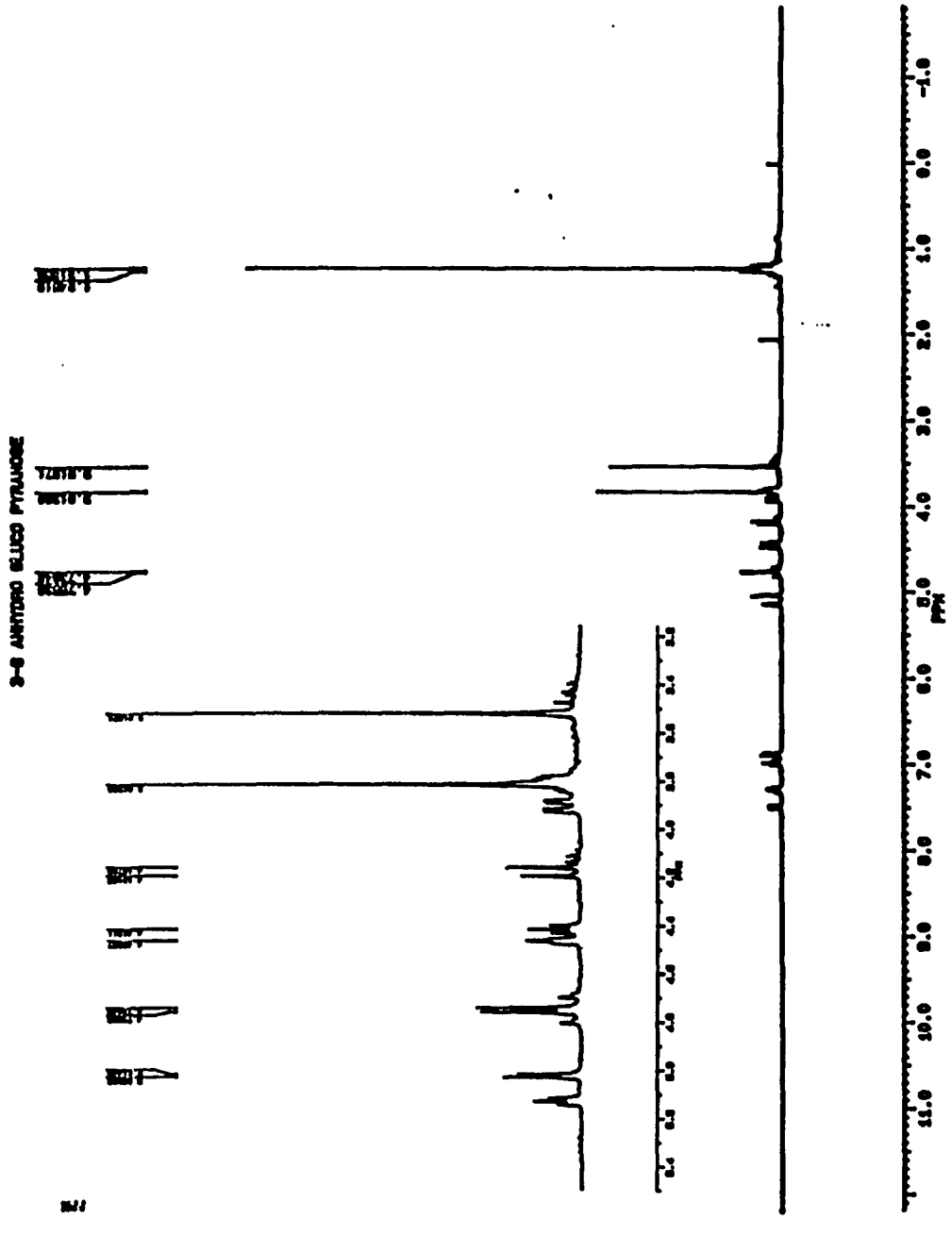


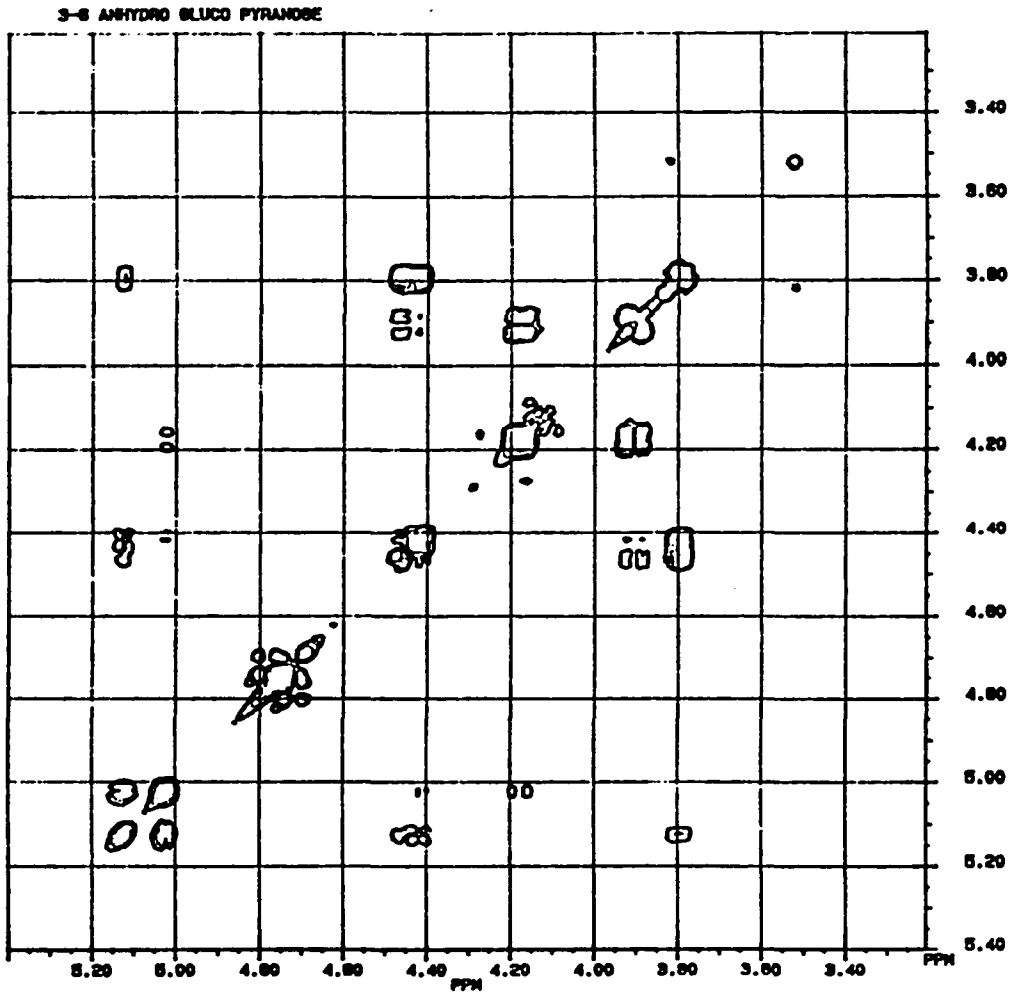
(38)





(39)

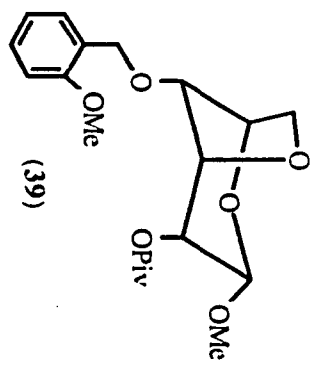




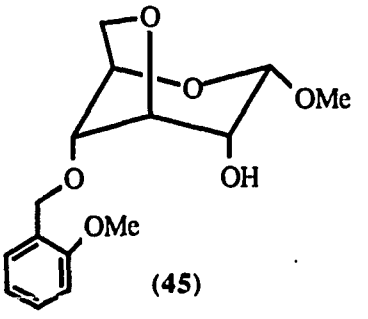
BRUKER

DAS.SMX
AU PROG:
COSYDQF.AU
DATE 9-11-92

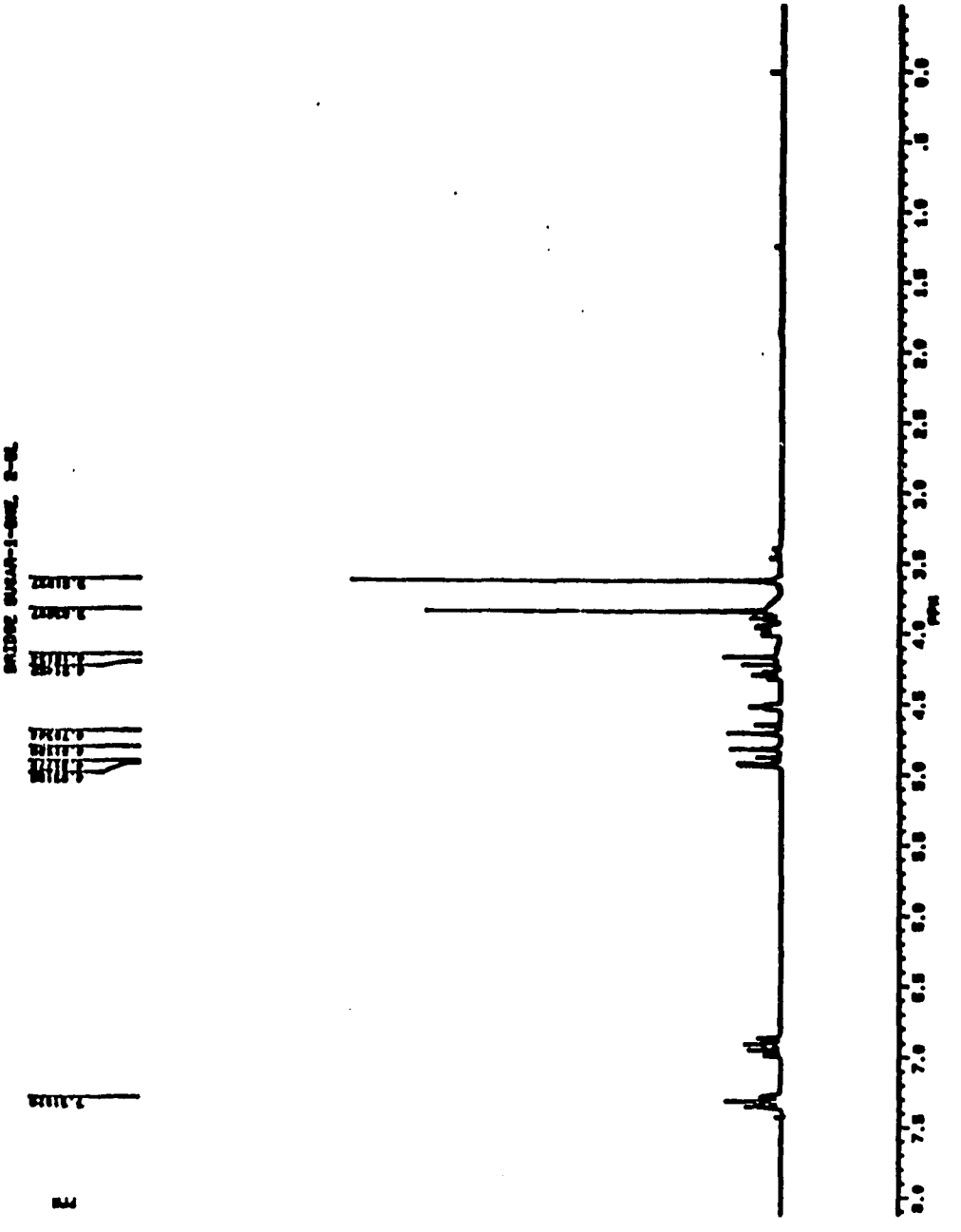
SI2	512
SI1	256
SW2	787.402
SW1	393.701
NDO	1
WDW2	S
WDW1	S
SSB2	0
SSB1	0
MC2	N
PLIN ROW:	
F1	5.400P
F2	3.206P
AND COLUMN:	
F1	5.400P
F2	3.206P
D1	1.5000000
P1	9.00
D0	.0000050
D2	.1500000
D3	.0000030
RO	0.0
PW	0.0
DE	796.00
NS	8
DS	2
NE	128
IN	.0012700

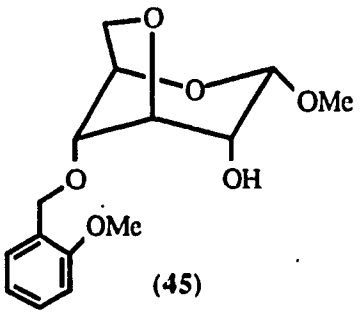


(39)

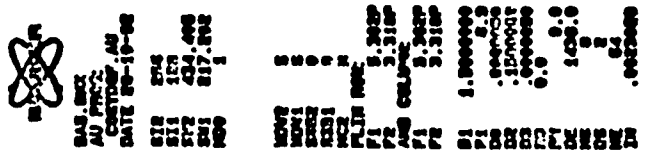


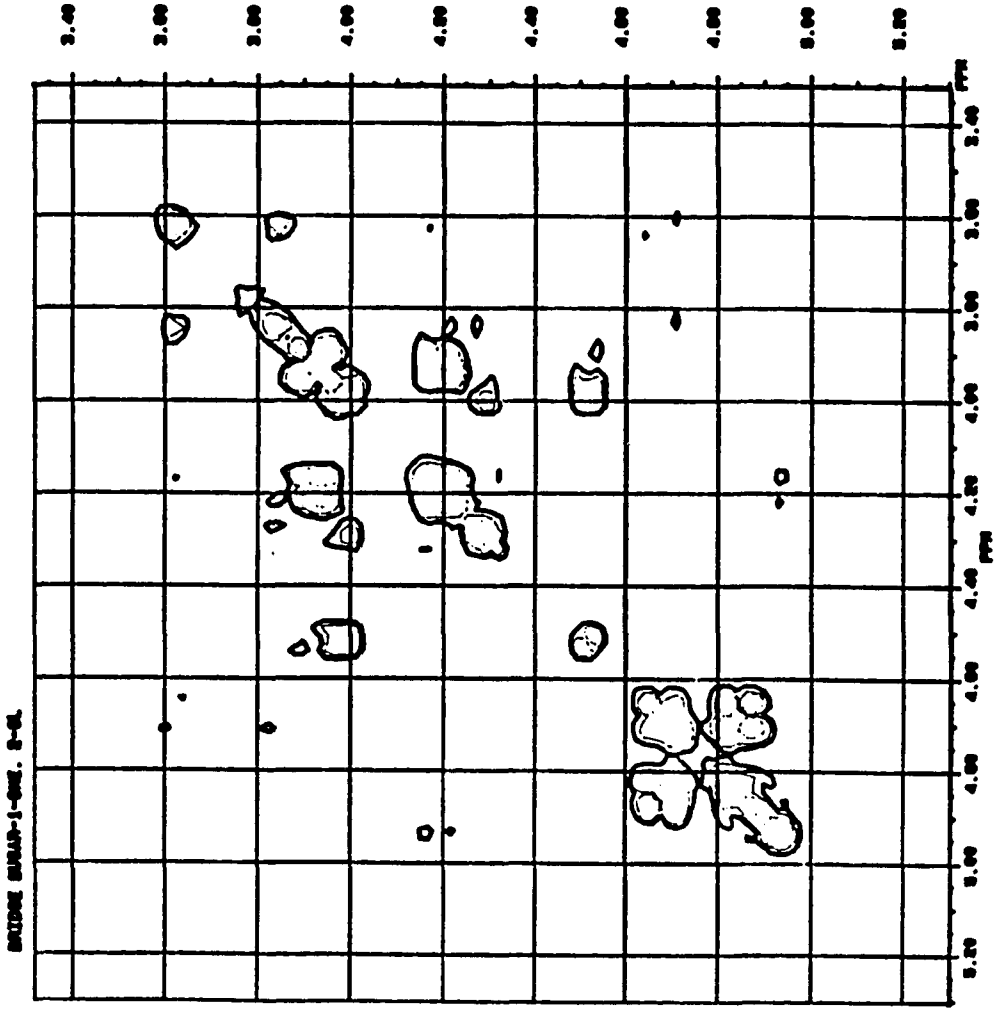
(45)

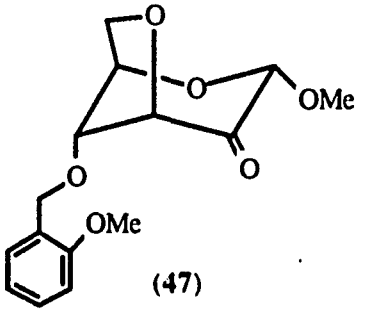




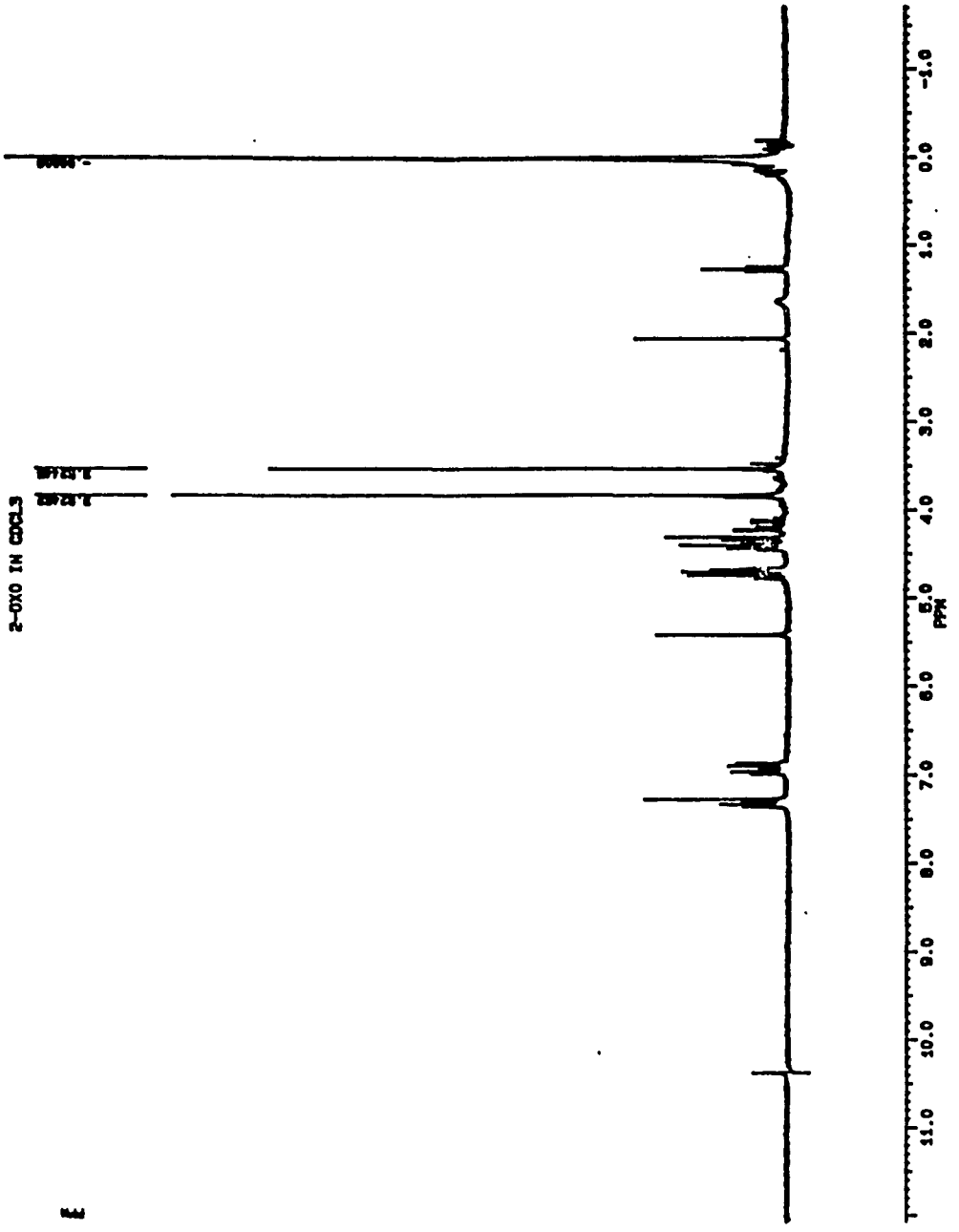
(45)

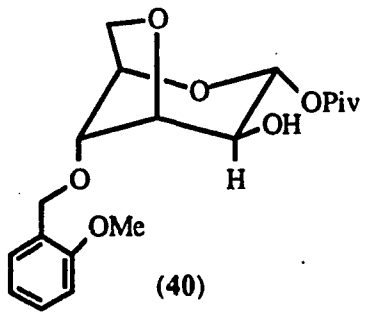




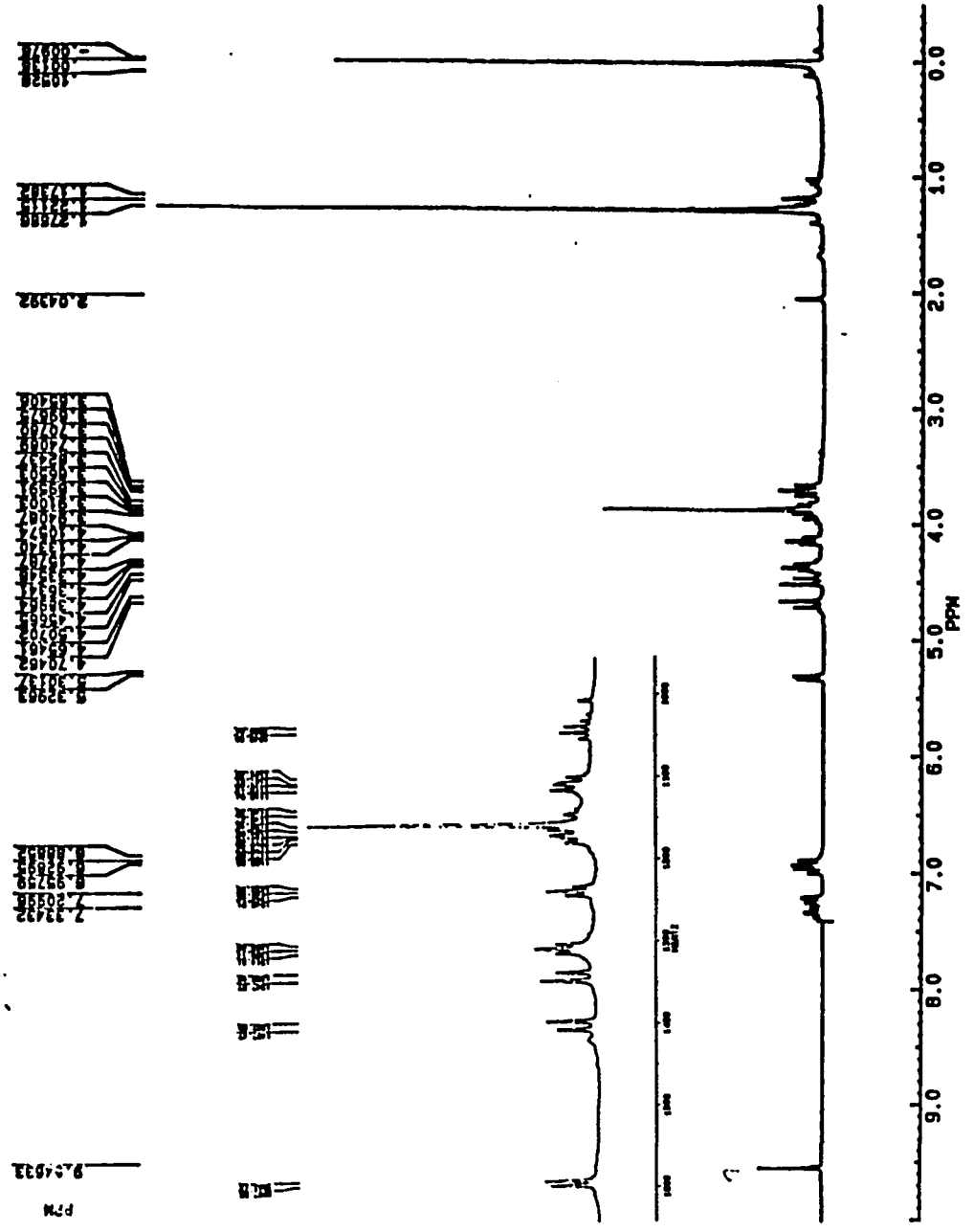


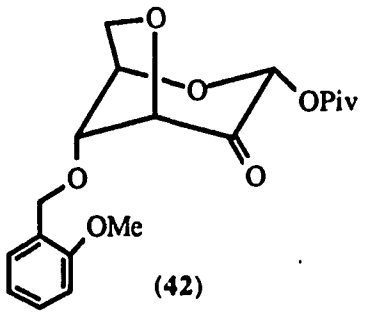
(47)



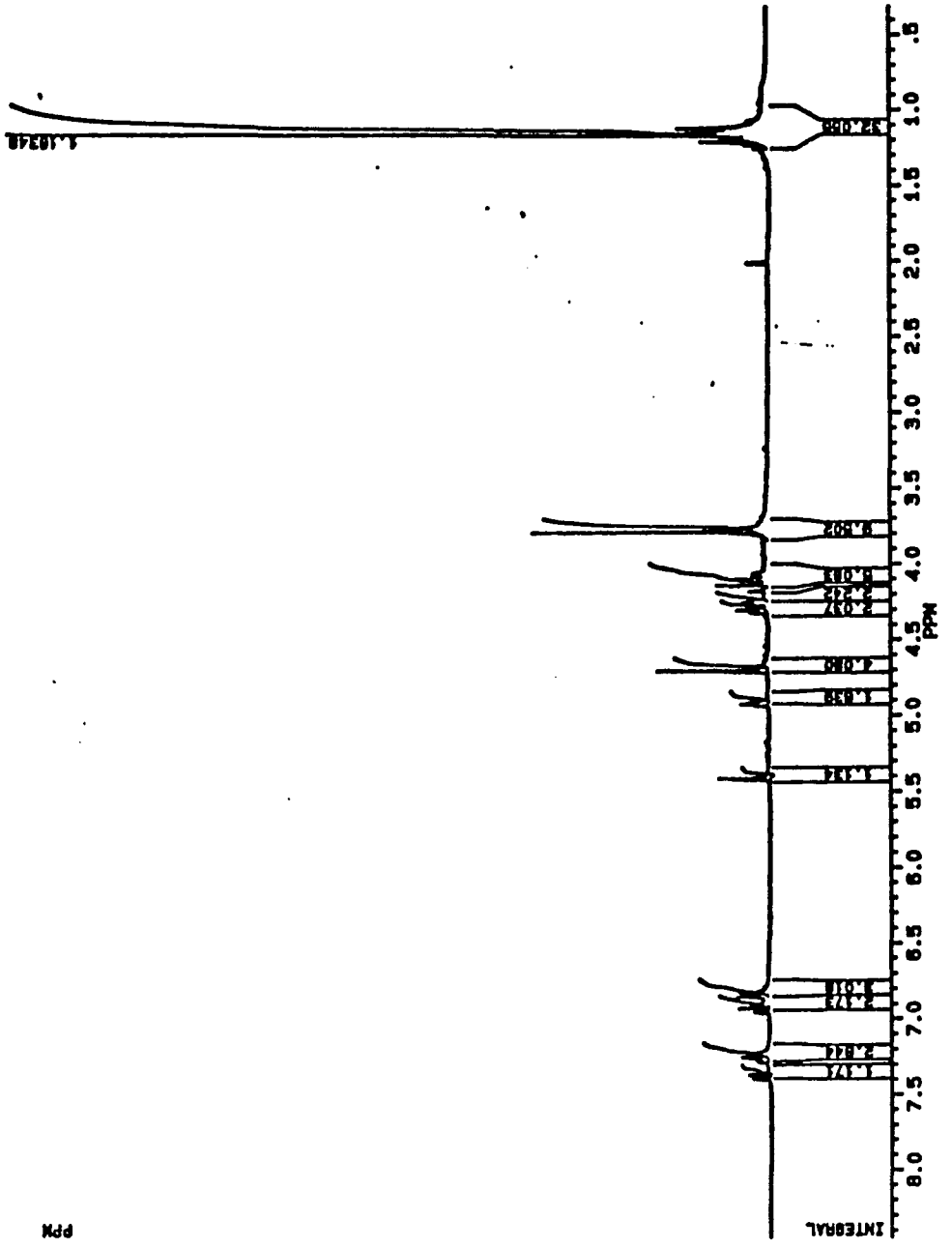


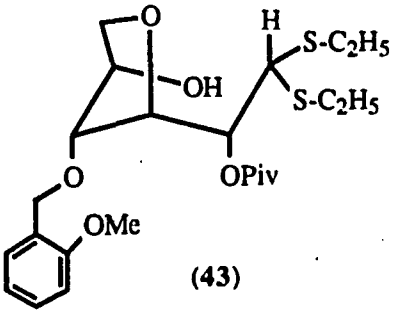
(40)



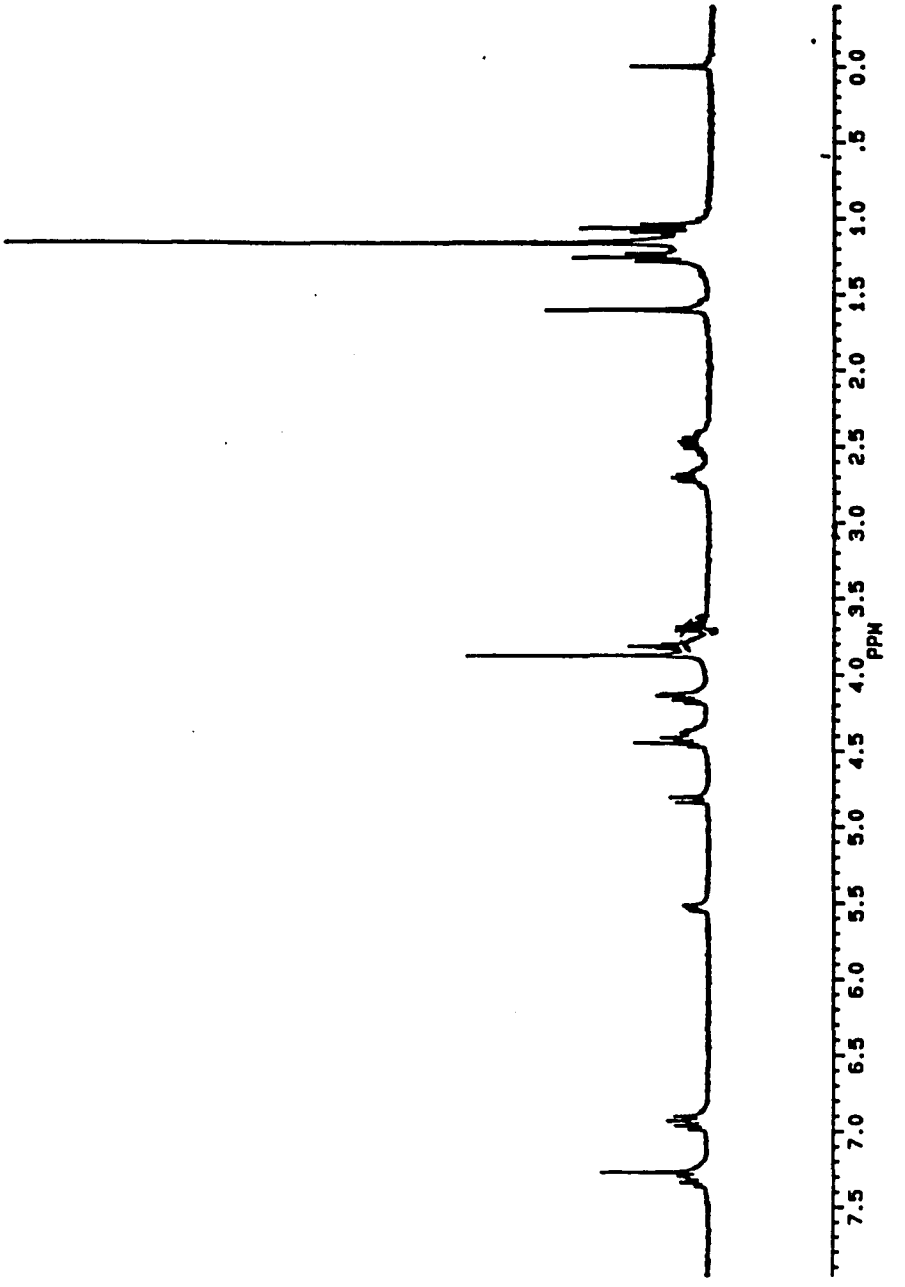


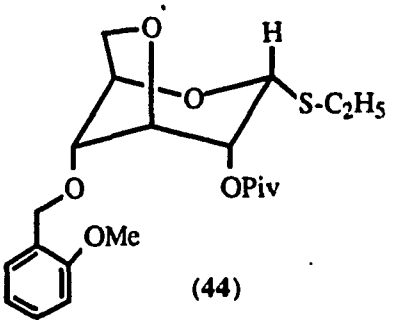
(42)



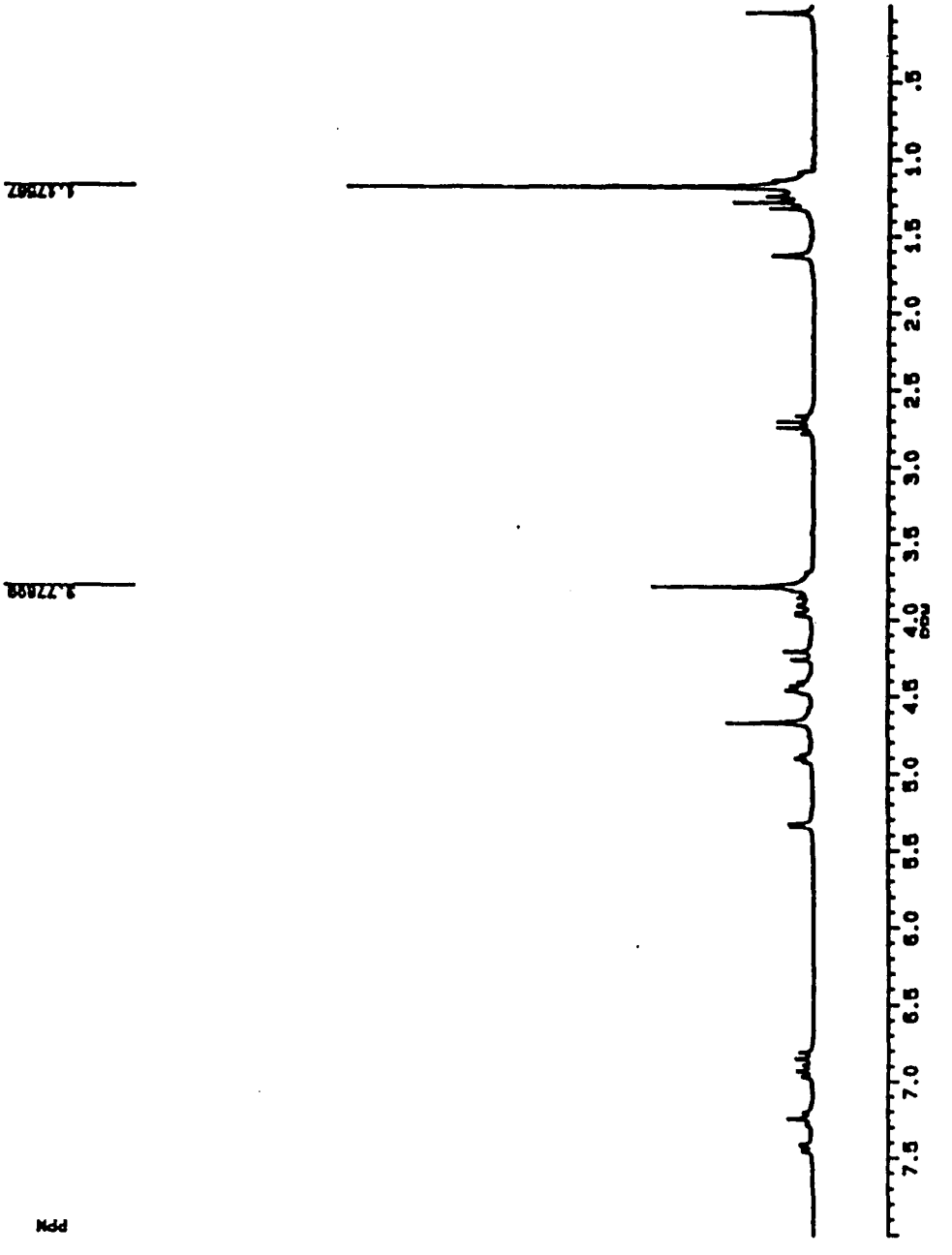

O
H
S-C2H5
OH
S-C2H5
O
OPiv
OMe

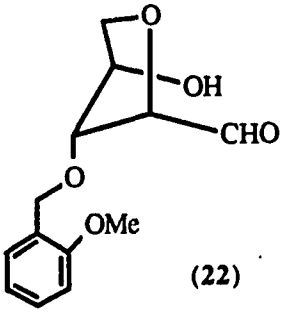
(43)


0.0
.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
PPM

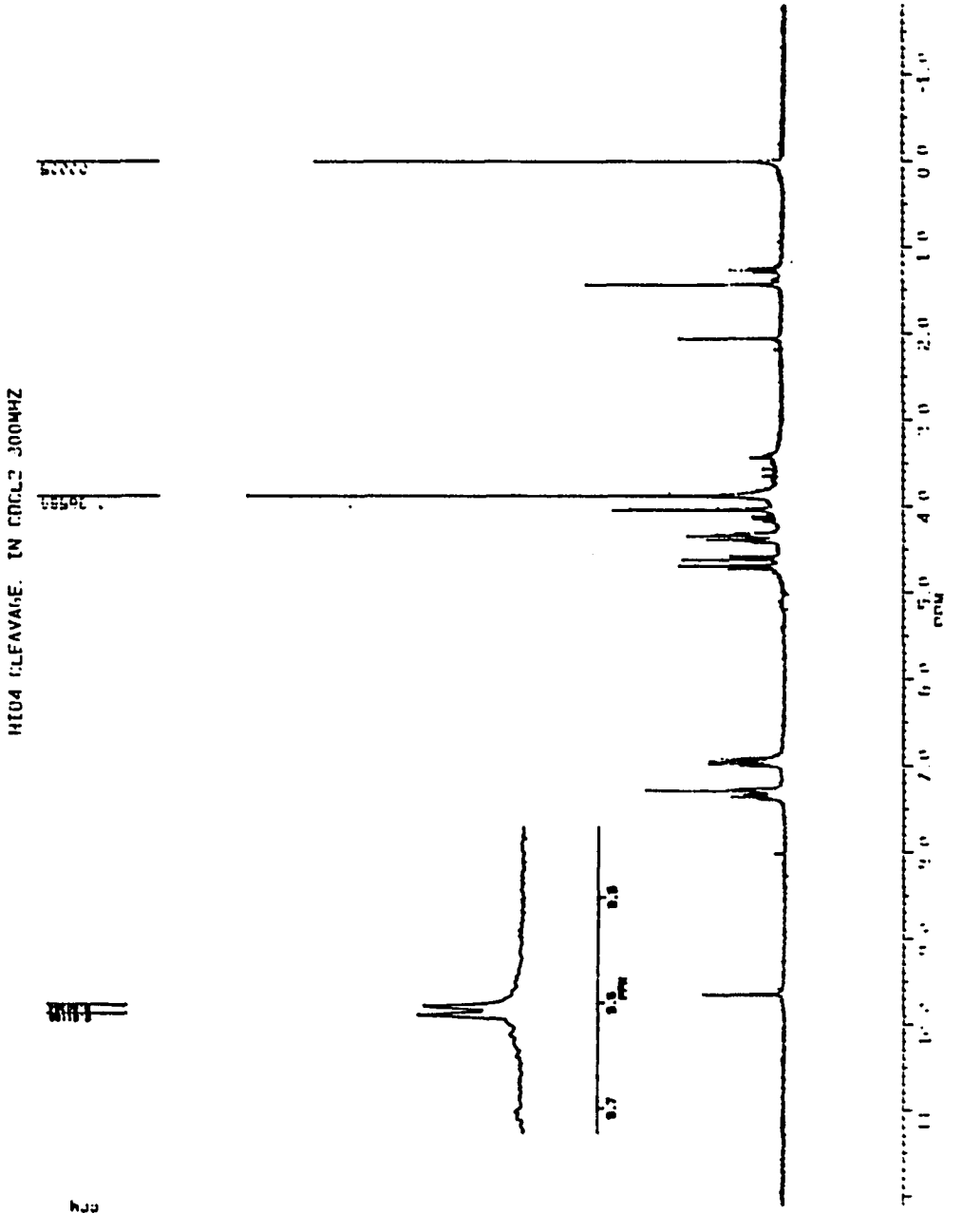

O
H
O
S-C2H5
O
OPiv
OMe

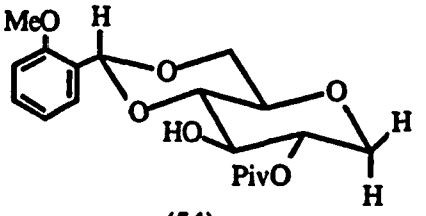
(44)


4.87867
3.77888
PPM
.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5

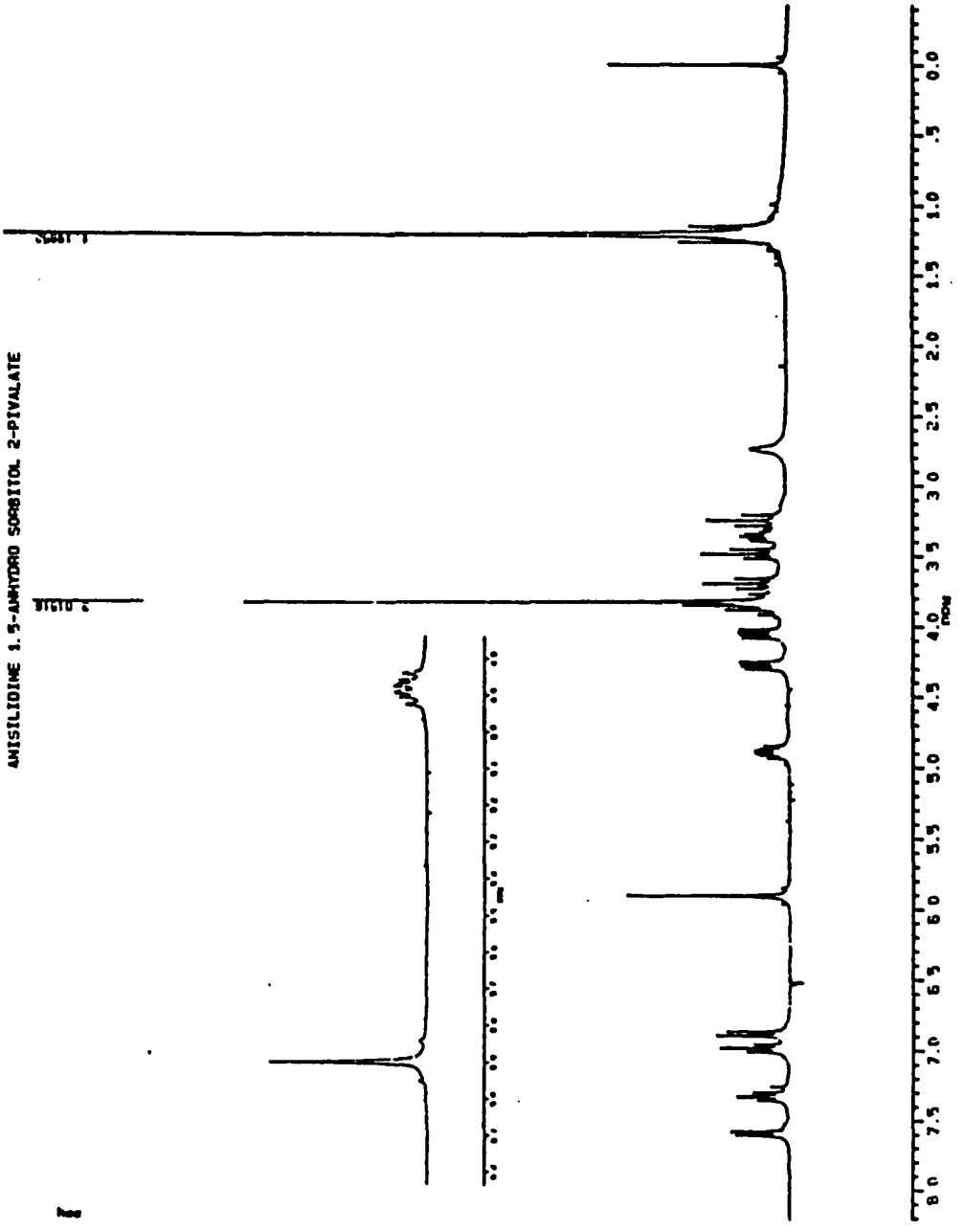


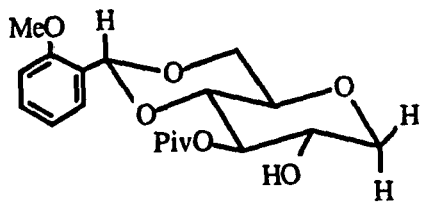
(22)



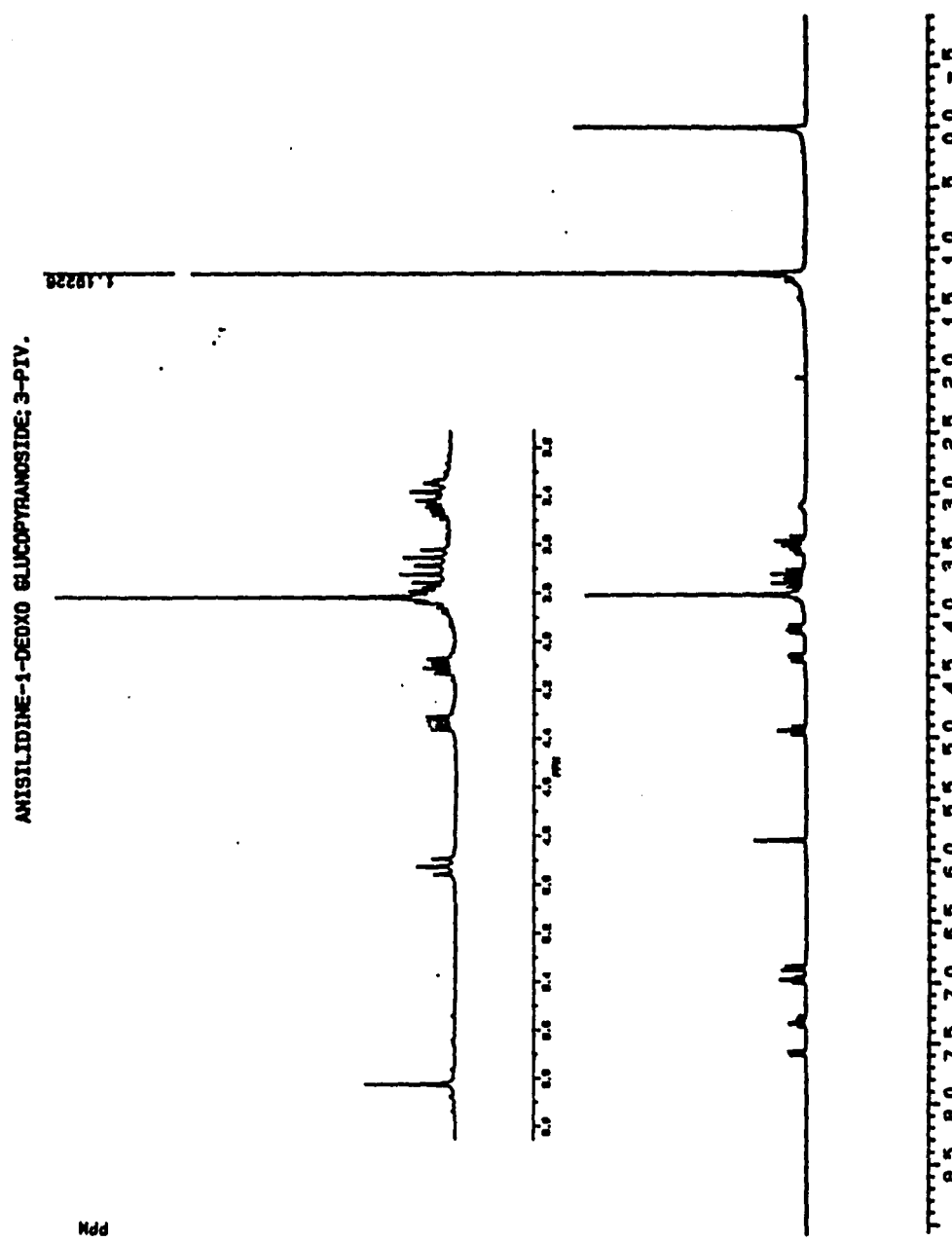

MeO
H
O
O
O
HO
H
PivO
H

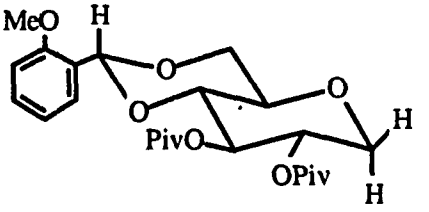
(54)


4MISILIDINE 1,5-ANHYDRO SORBITOL 2-PIVALATE
PPM

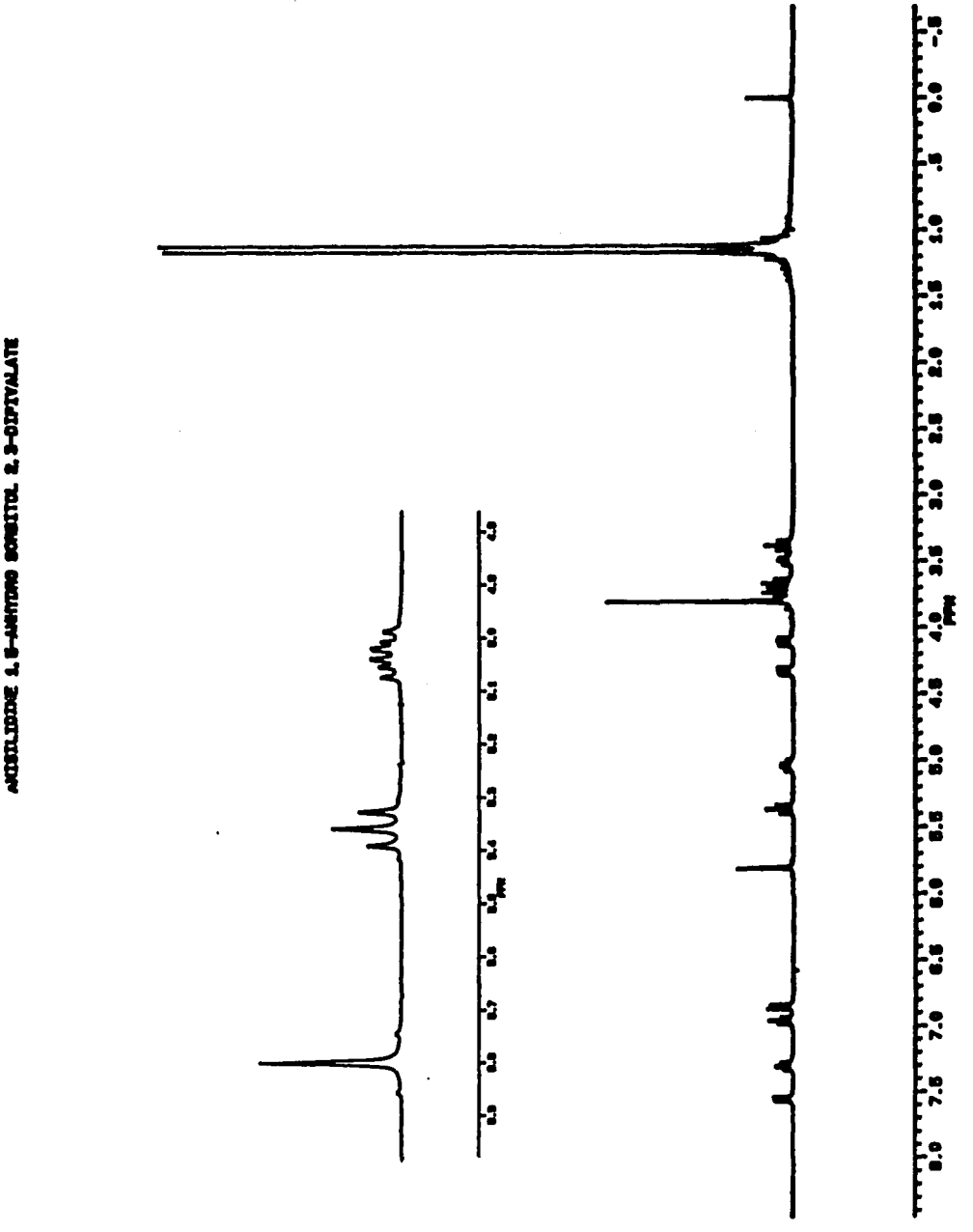

MeO
H
O
O
O
H
PivO
HO
H

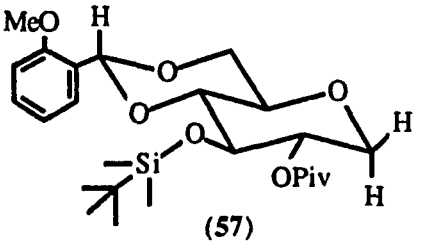
(55)


ANISILIDINE-1-DEOXO GLUCOPYRANOSIDE; 3-PIV.
PPM

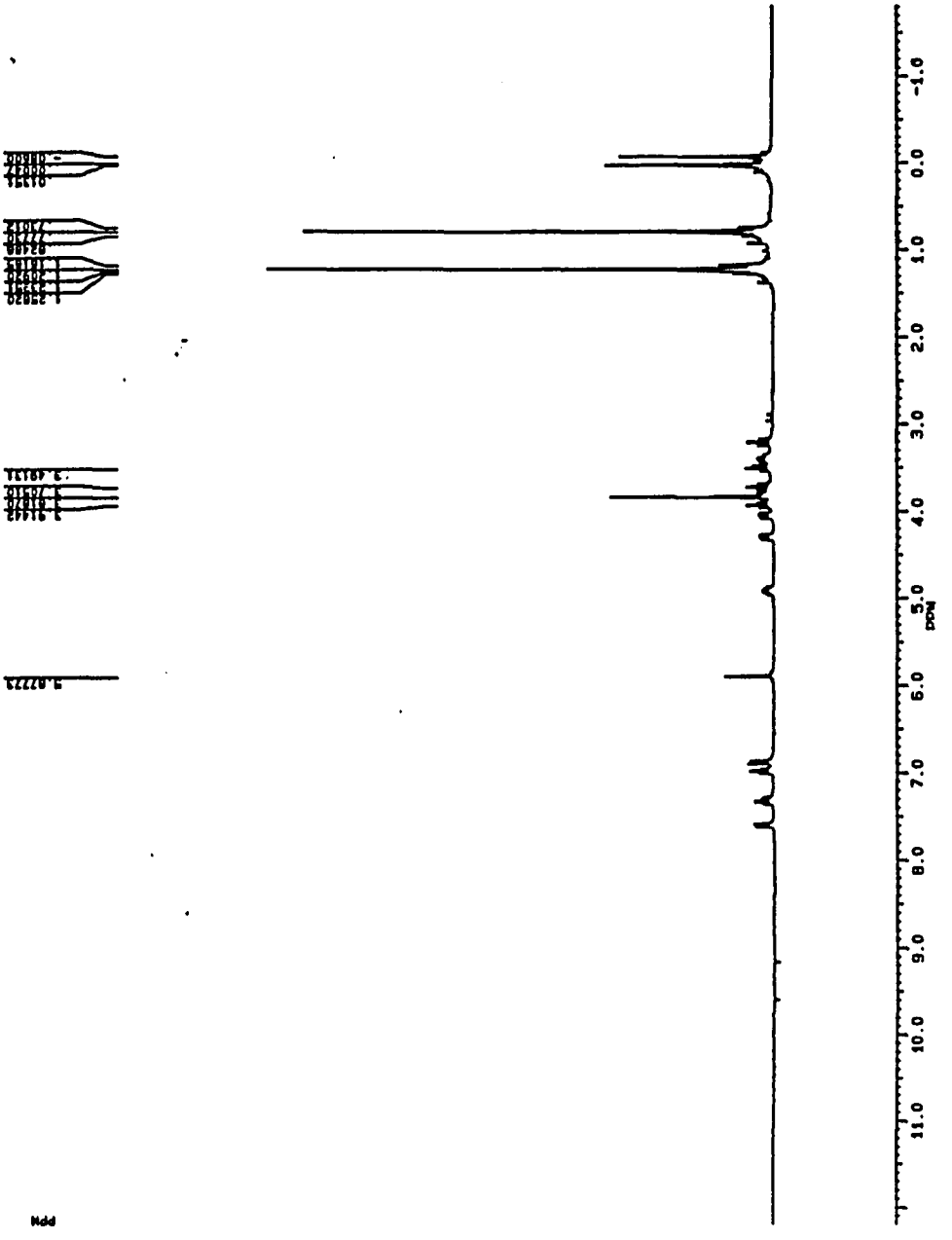


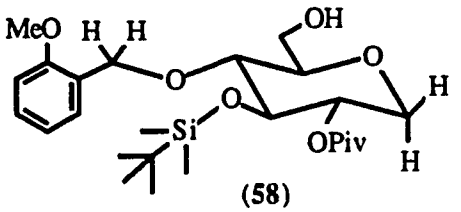
(56)



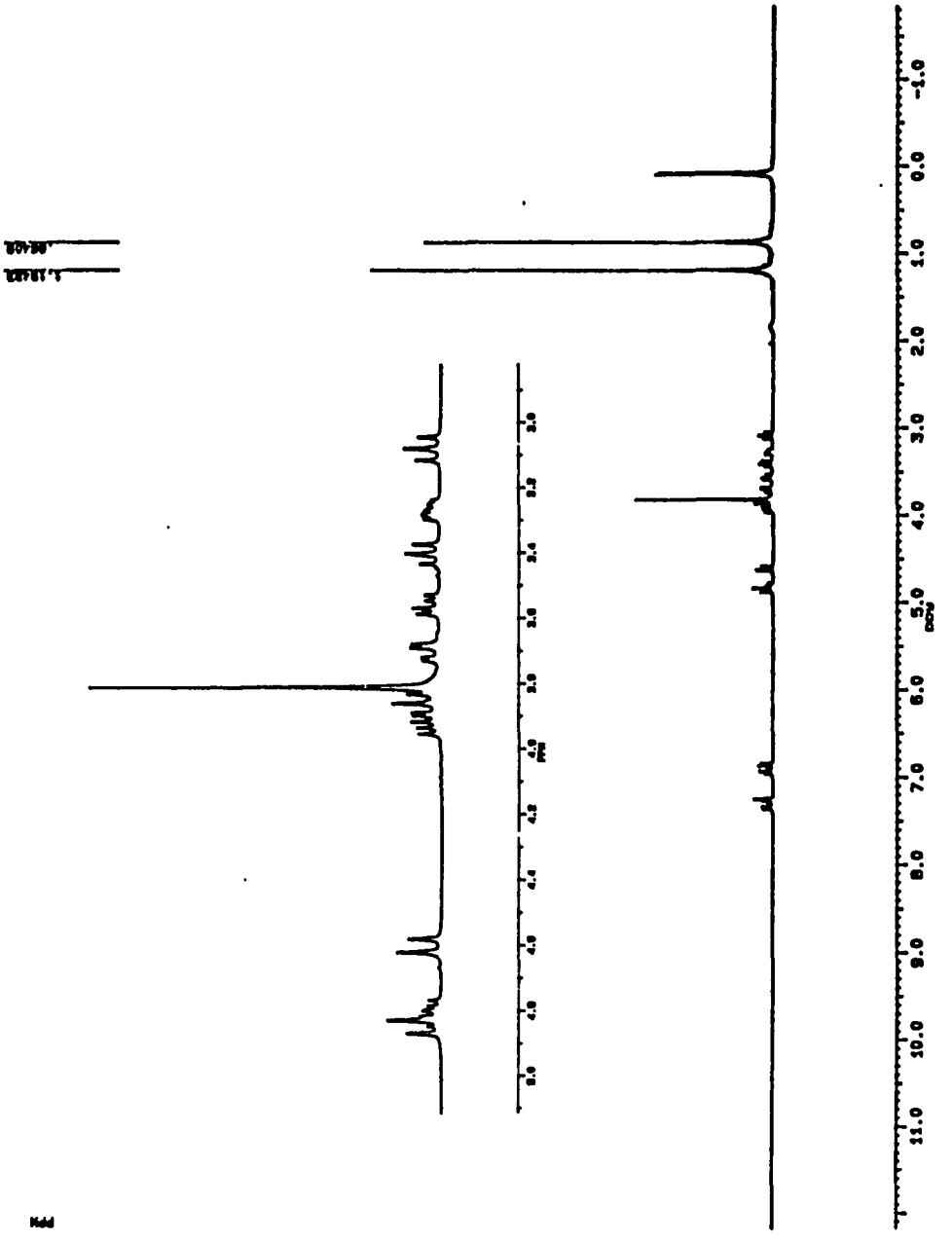


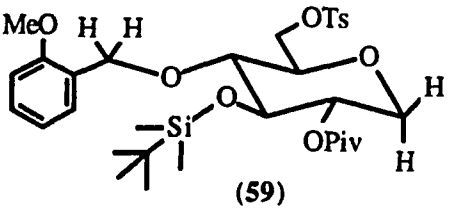
(57)



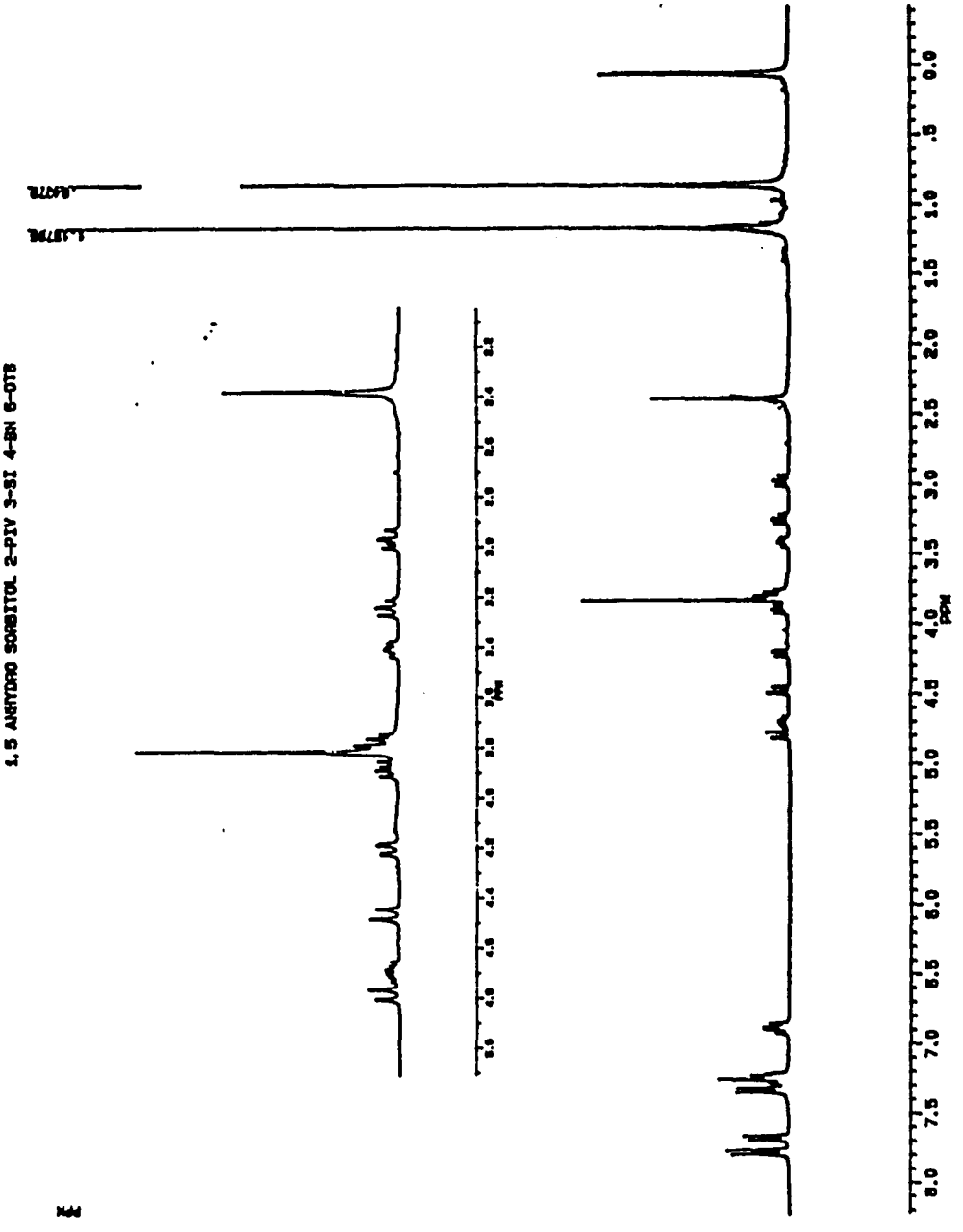


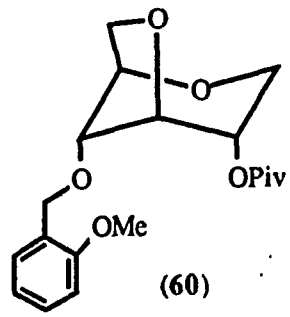
(58)



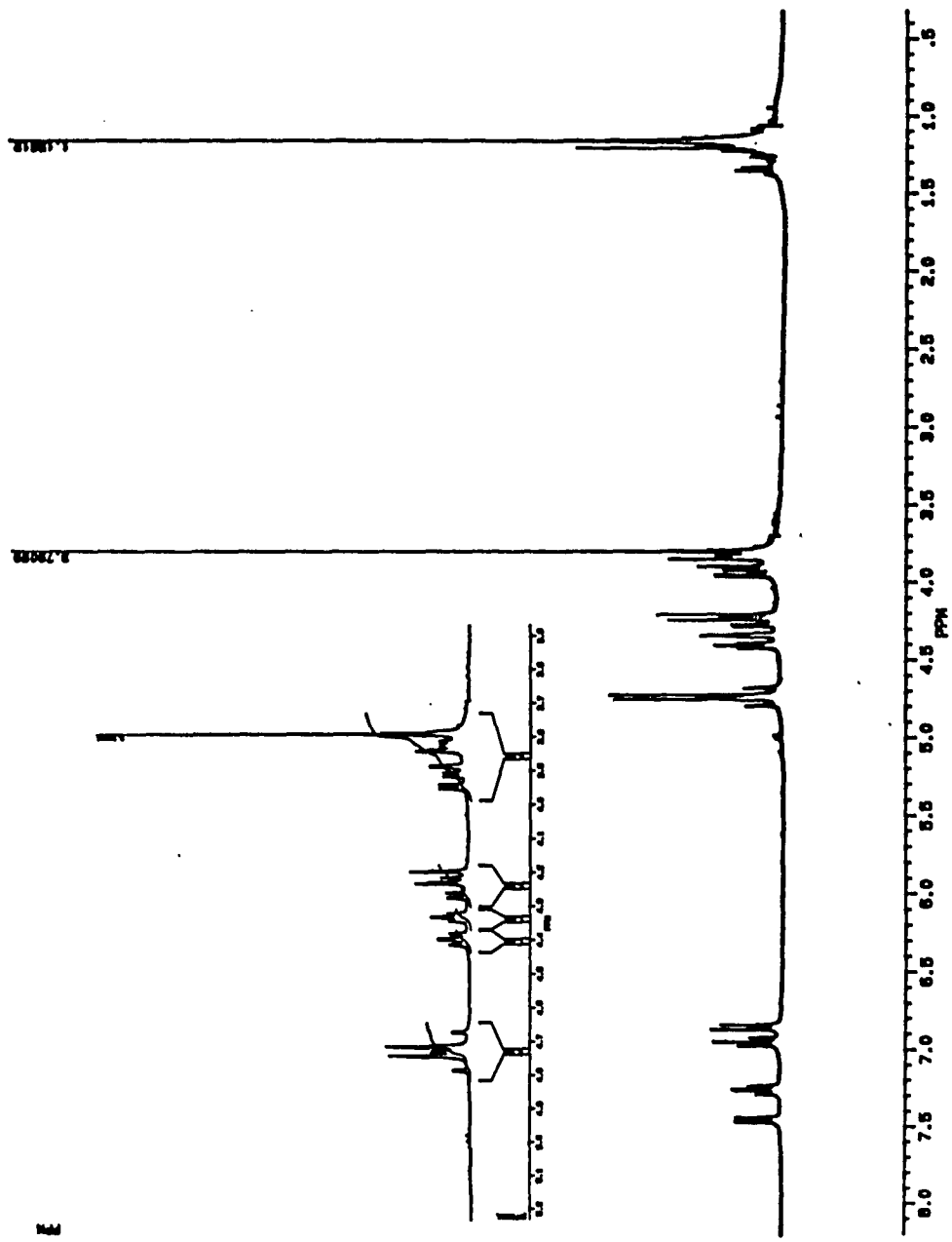

MeO
H
H
OTs
O
O
H
O
Si
OPiv
H

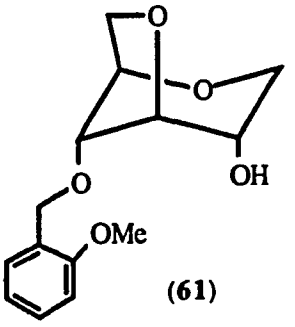
(59)


1,5 ANHYDRO SORBITOL 2-PIV 3-SI 4-BN 6-OTS
PPM

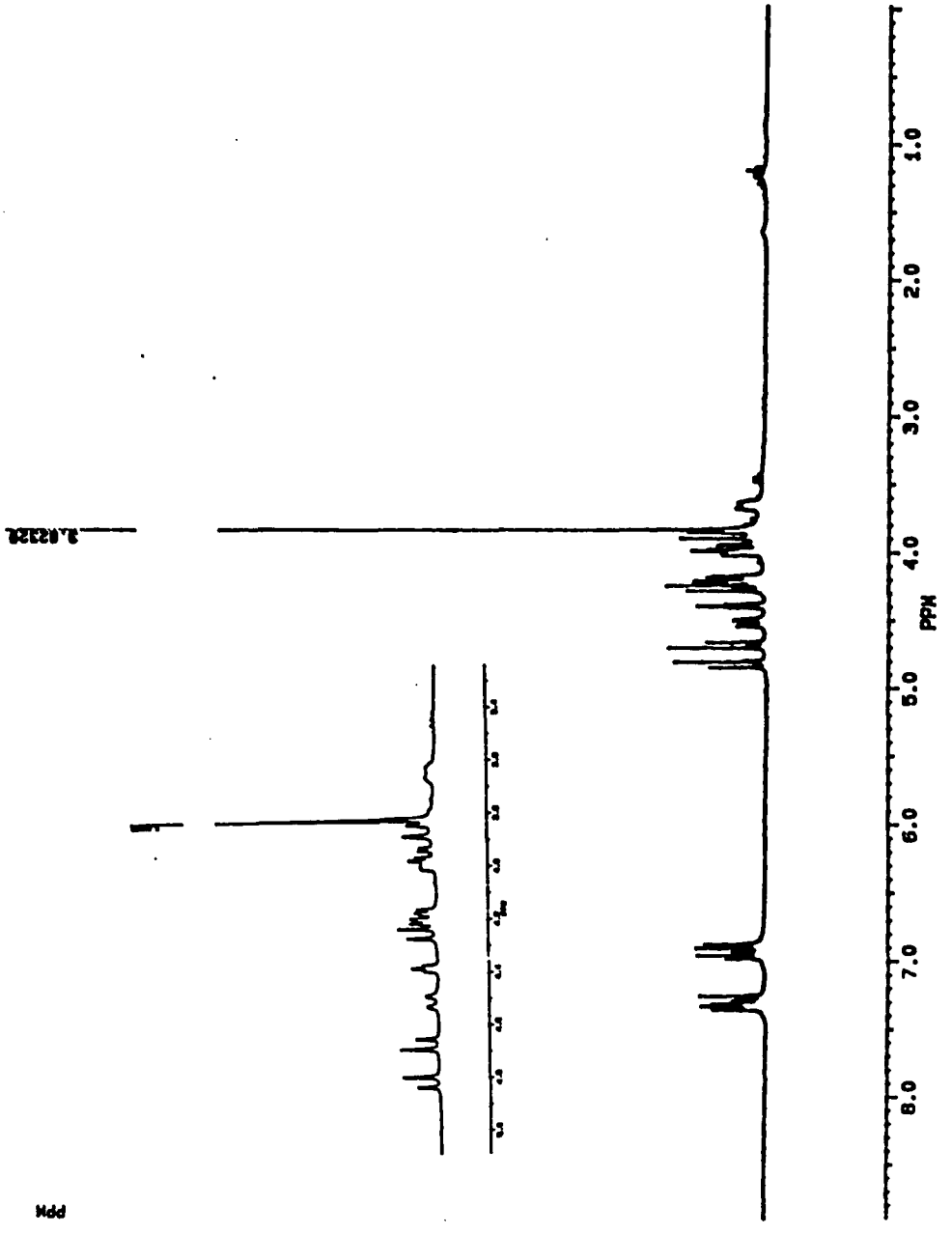


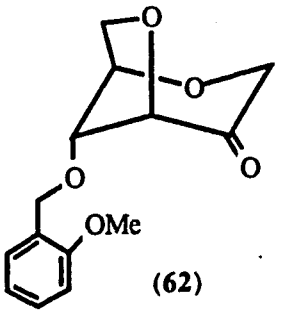
(60)



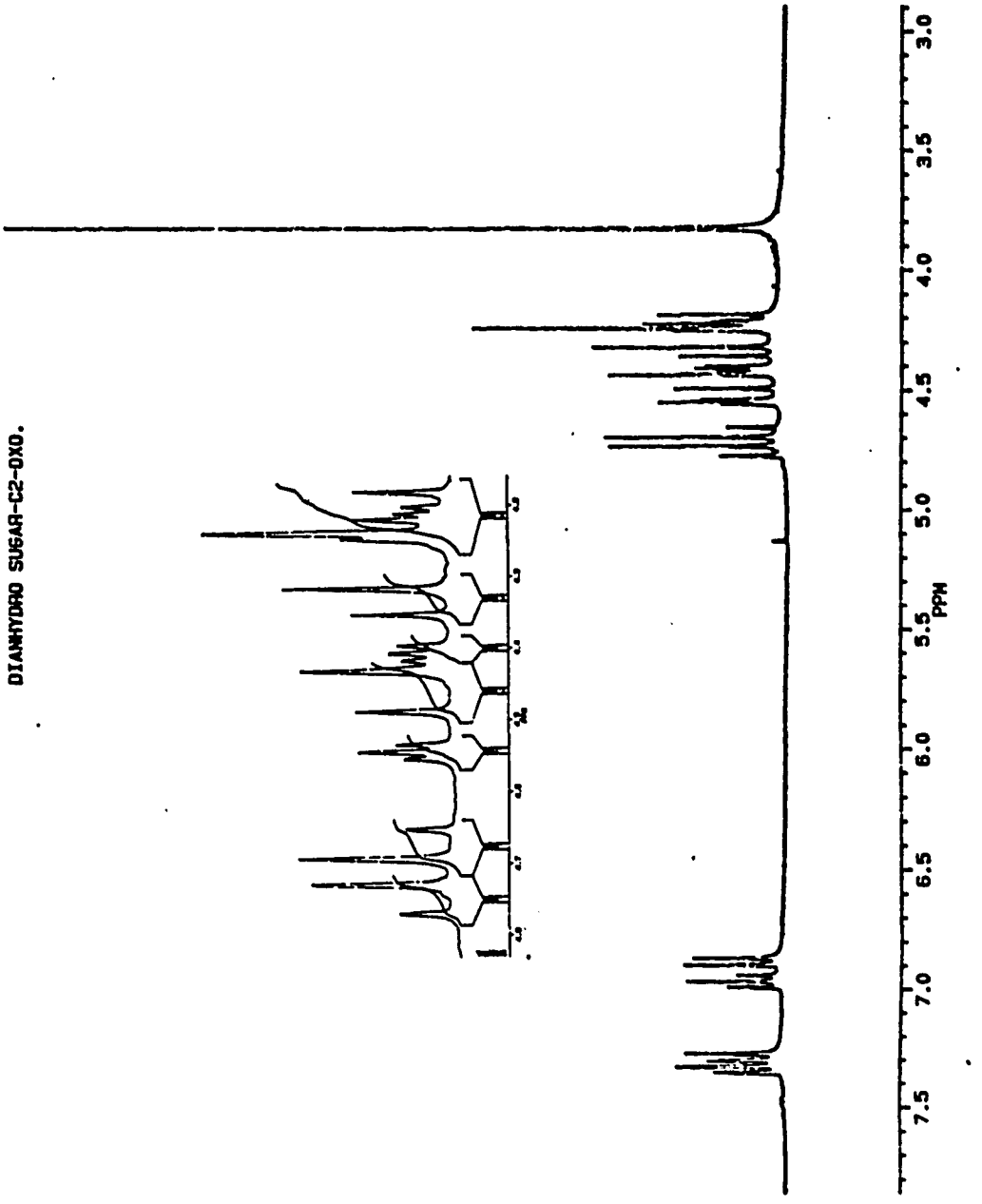


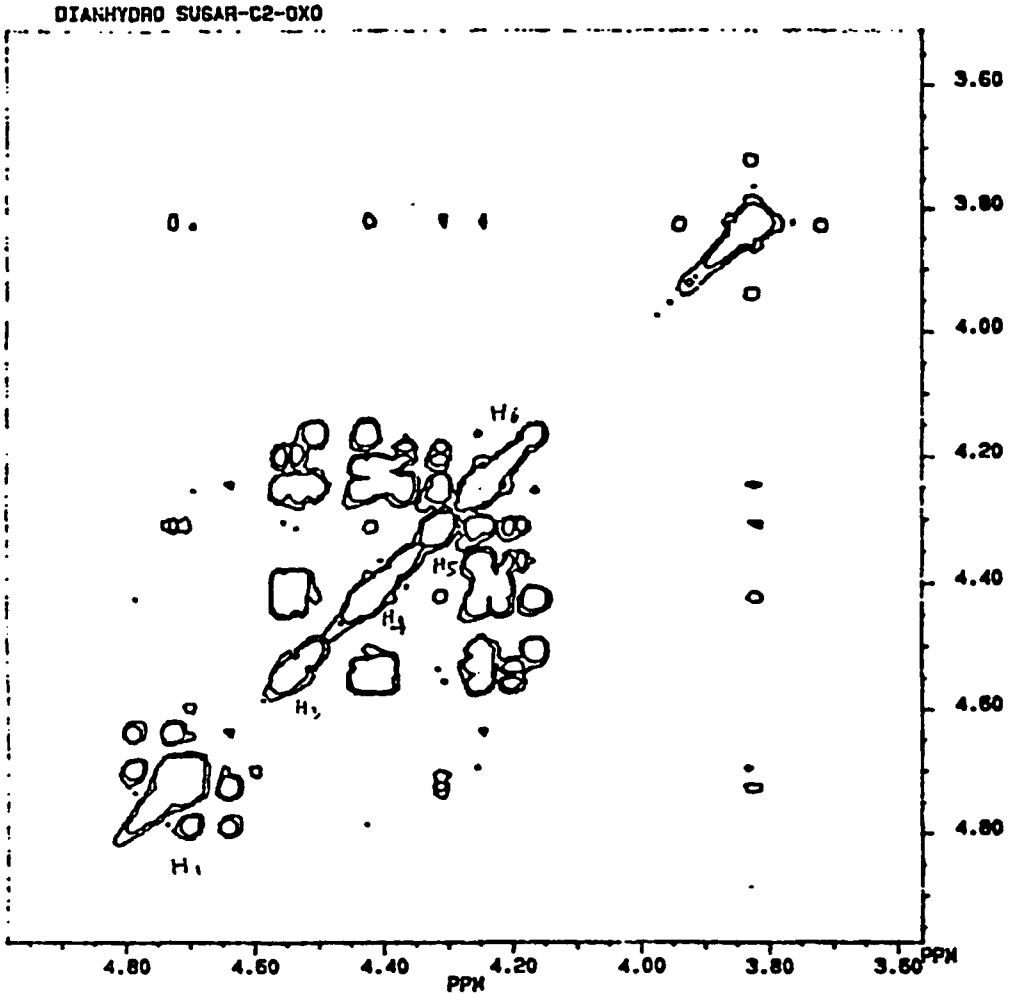
(61)





(62)





BRUKER

BM.SMX
AU PROG:
COSY.AU
DATE 1-12-89

SI2	512
SI1	256
SW2	513.347
SW1	256.674
NDO	1
WDW2	S
WDW1	S
SSB2	0
SSB1	0
MC2	M

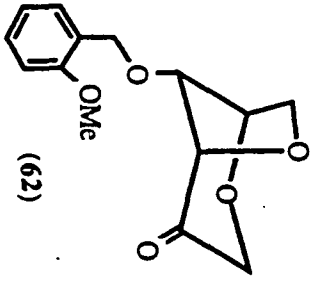
PLIN ROW:

F1	4.984P
F2	3.561P

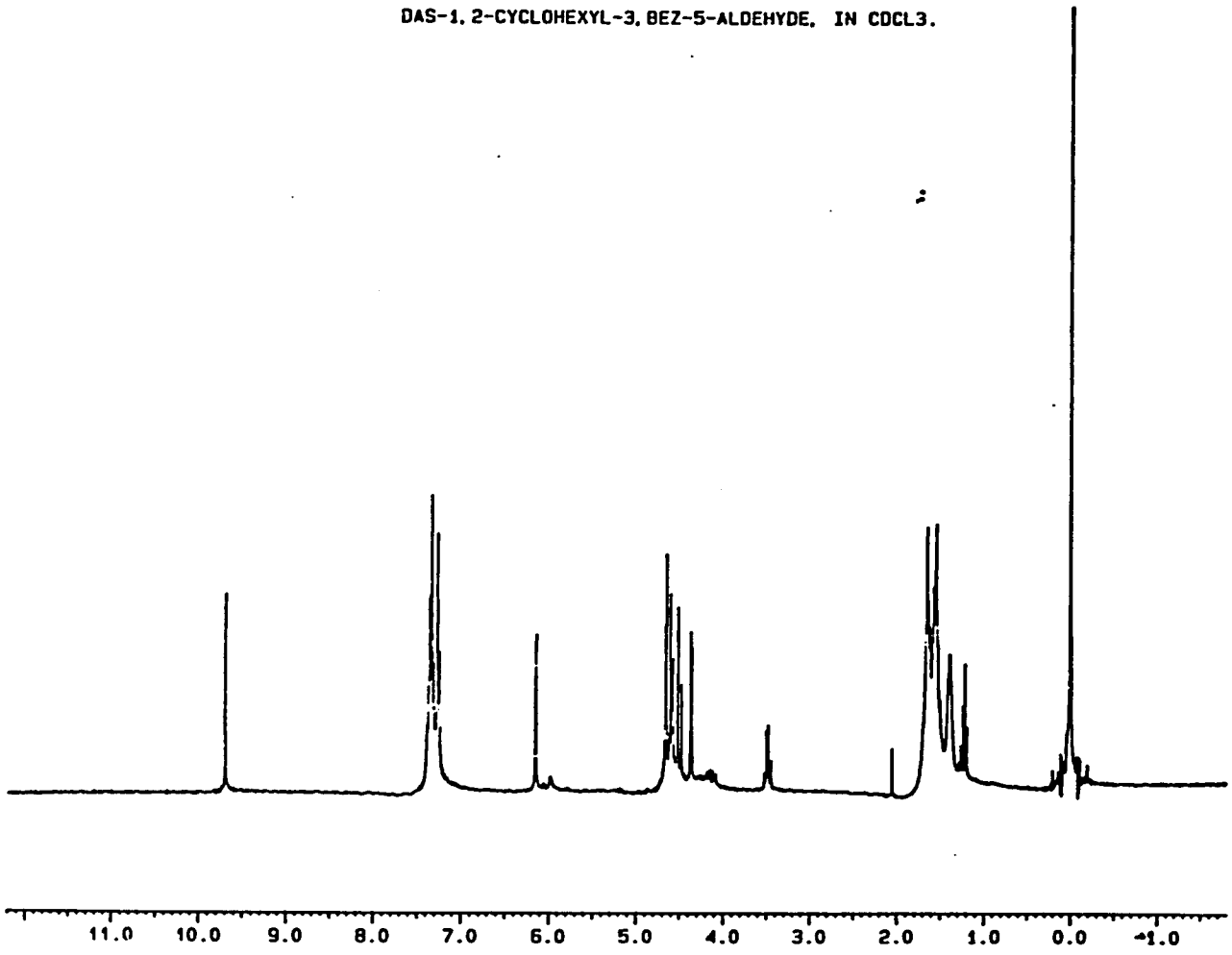
AND COLUMN:

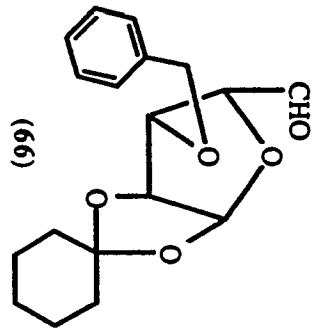
F1	4.974P
F2	3.511P

D1	2.0000000
P1	6.0
DO	.0000030
P2	3.0
RD	0.0
PW	0.0
DE	1217.0
NS	4
DS	2
NE	128
IN	.0019480

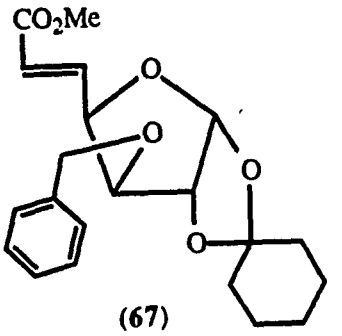


(62)

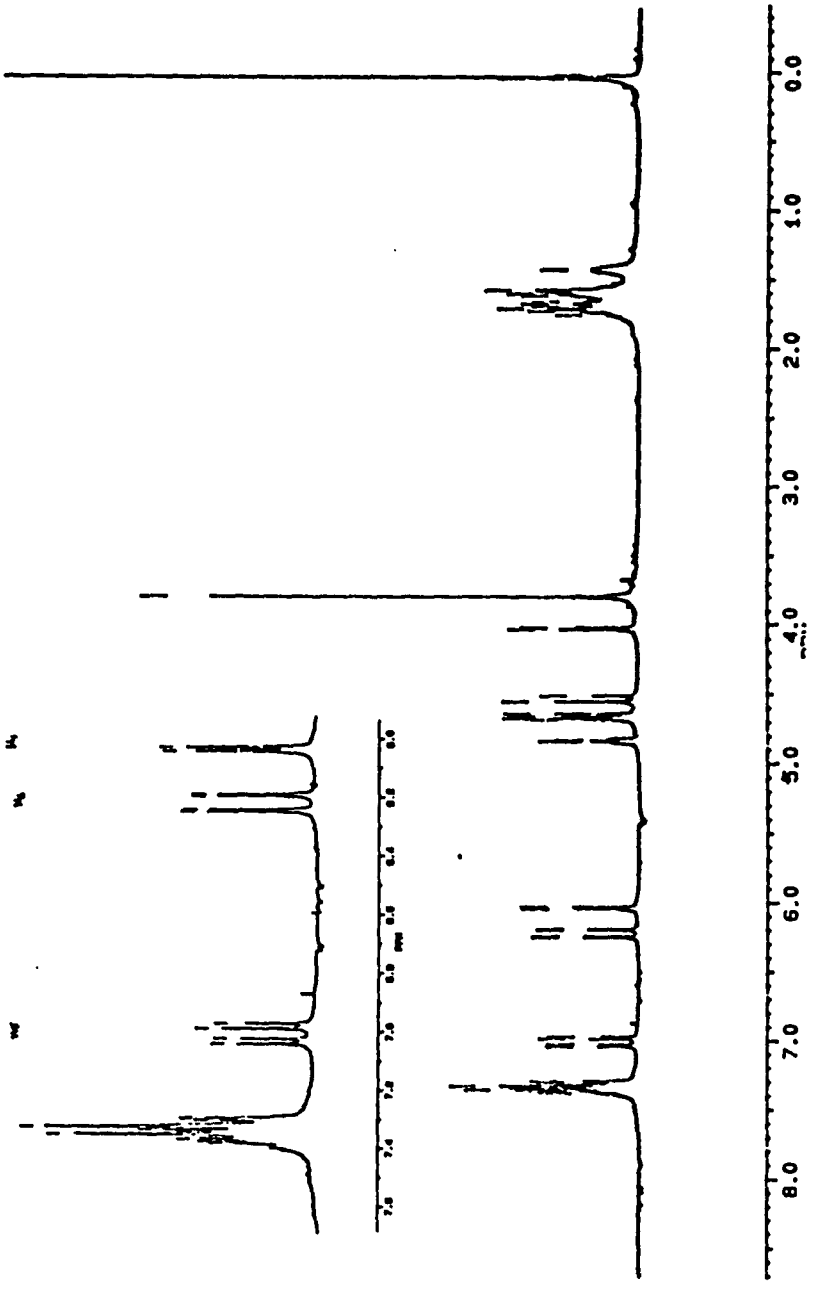

DAS-1, 2-CYCLOHEXYL-3, BEZ-5-ALDEHYDE, IN CDCL3.
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0

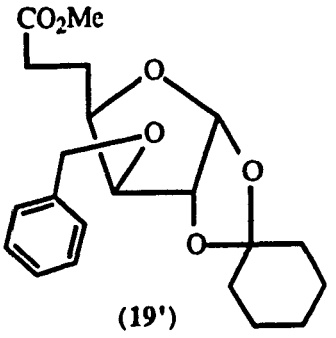

CHO
O
O
O
O

(99)

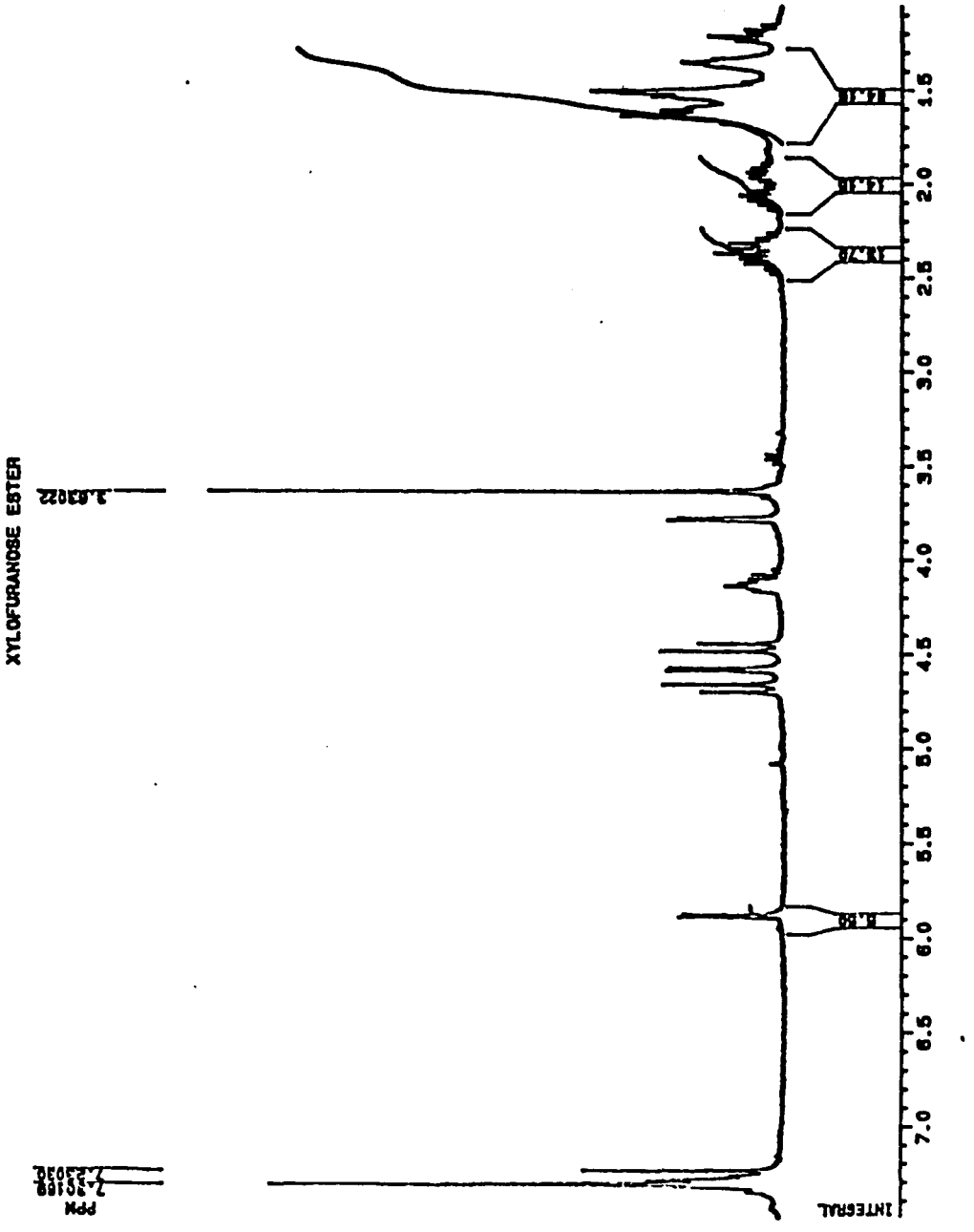


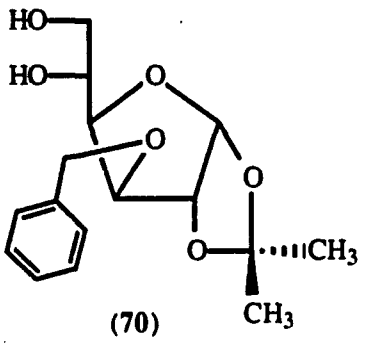
(67)



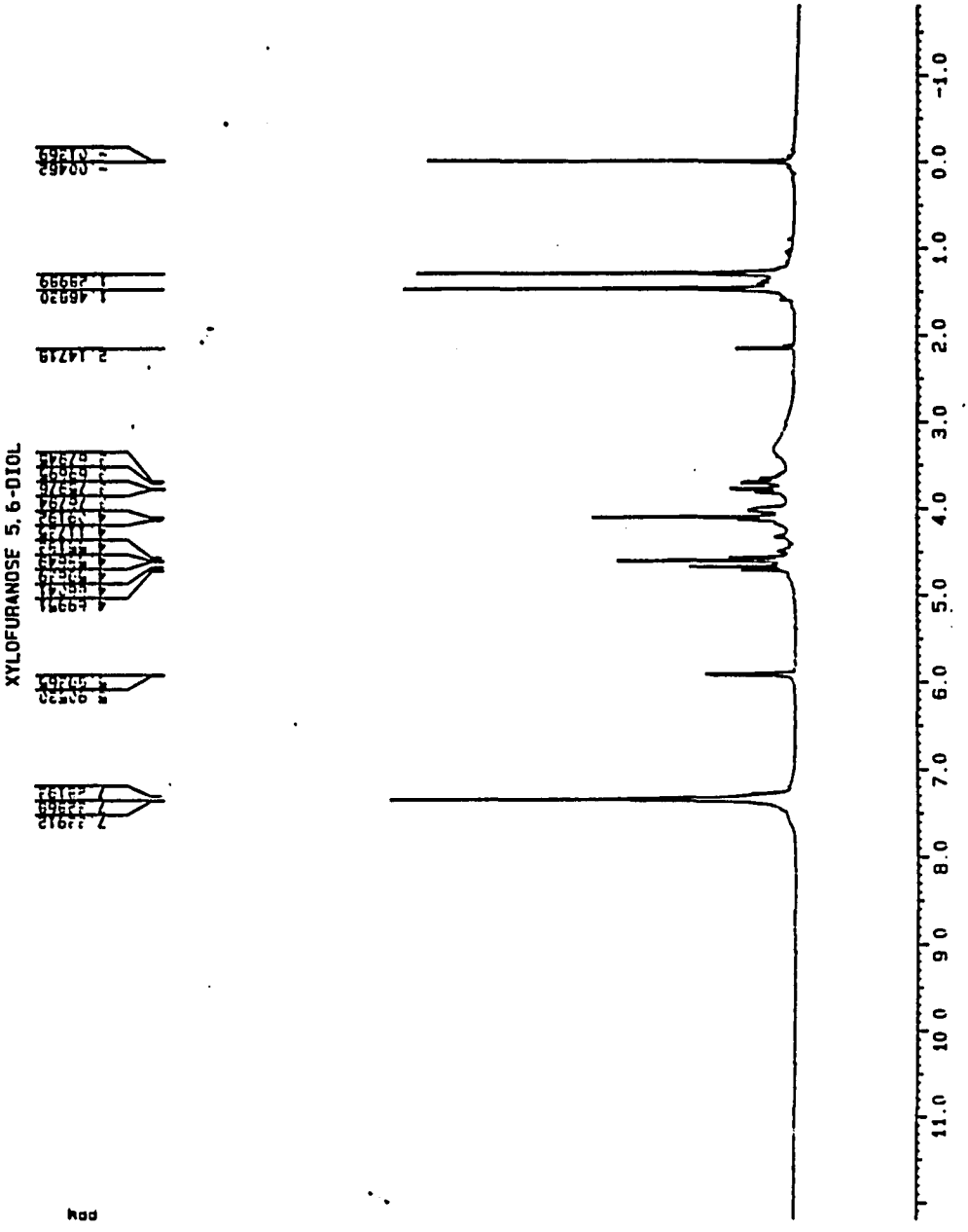

CO2Me
O
O
O
O

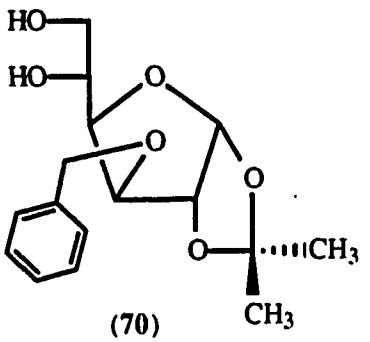
(19')


XYLOFURANOSE ESTER
PPM
INTEGRAL
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0

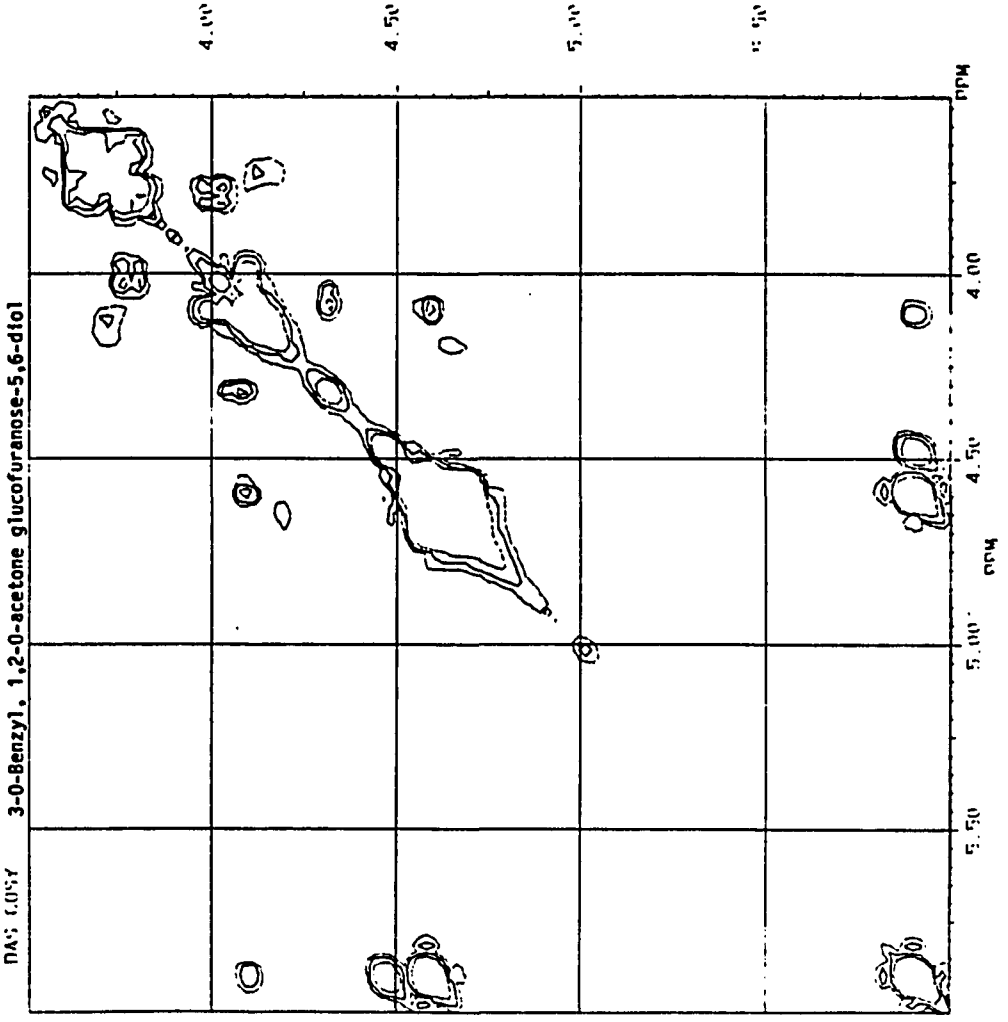

HO
HO
O
O
O
O
CH3
CH3

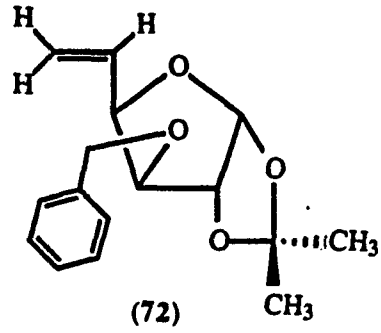
(70)


XYLOFURANOSE 5,6-DIOL
hod
-1.0
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0

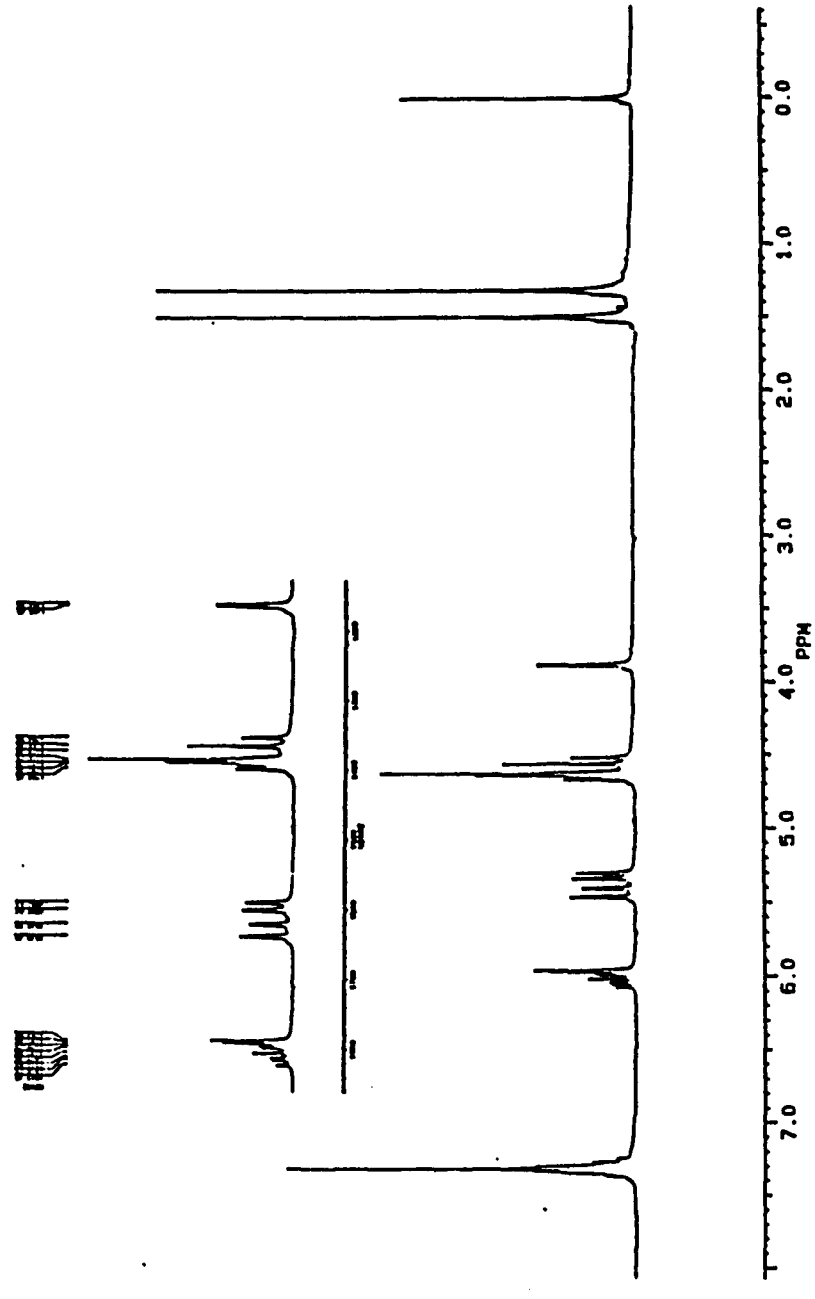

HO
HO
O
O
O
O
O
CH3
CH3

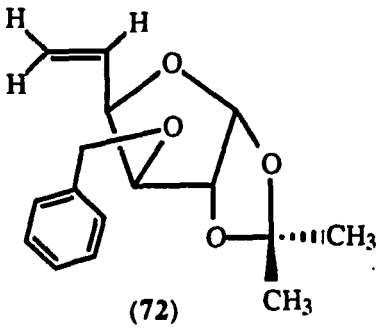
(70)


3-O-Benzyl, 1,2-O-acetone glucofuranose-5,6-diol
4.00
4.50
5.00
5.50
PPM

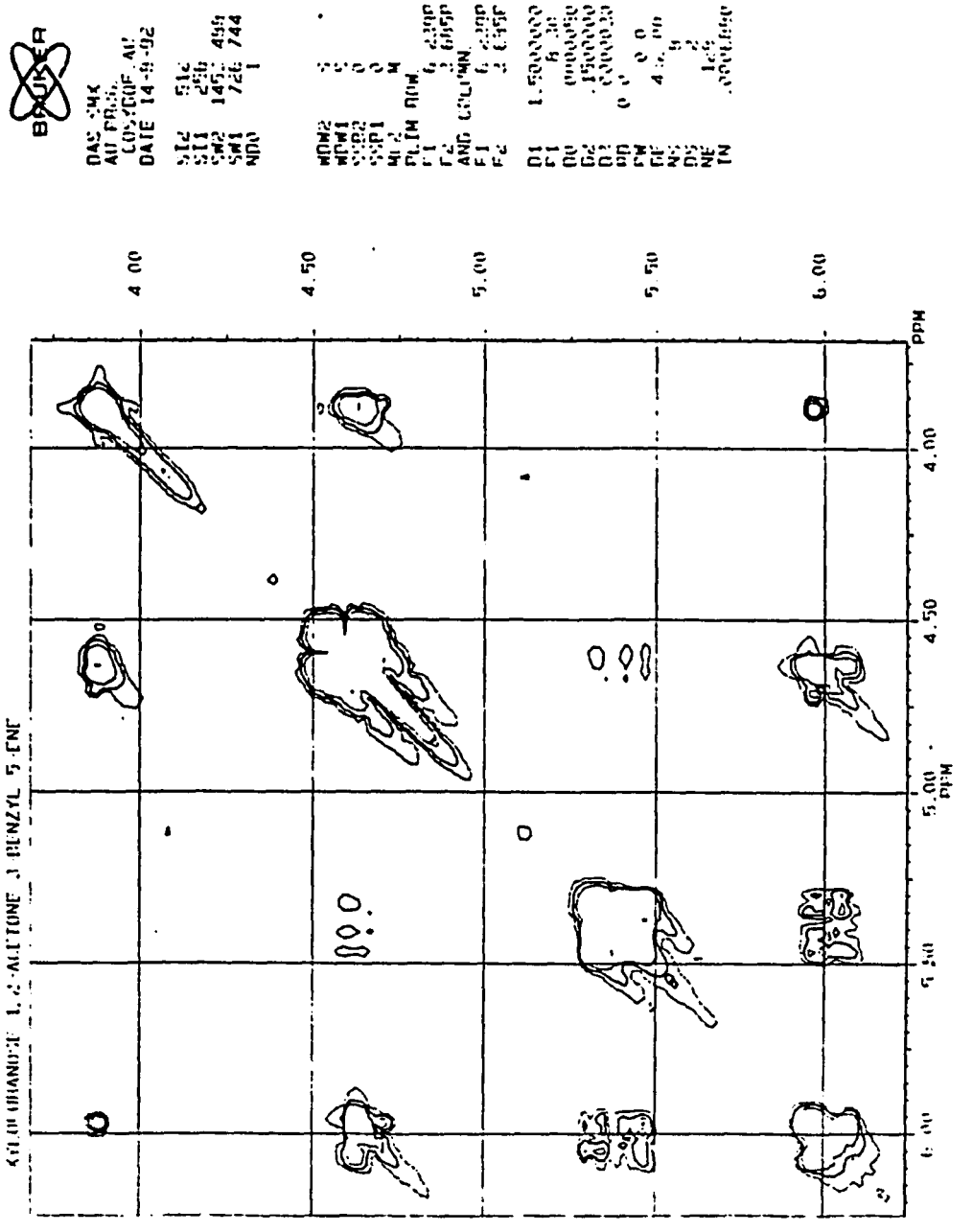


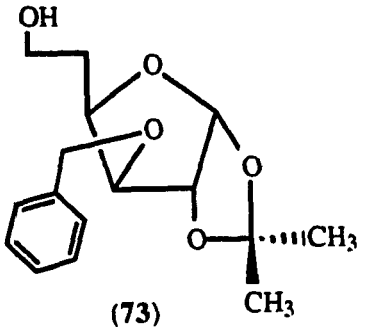
(72)



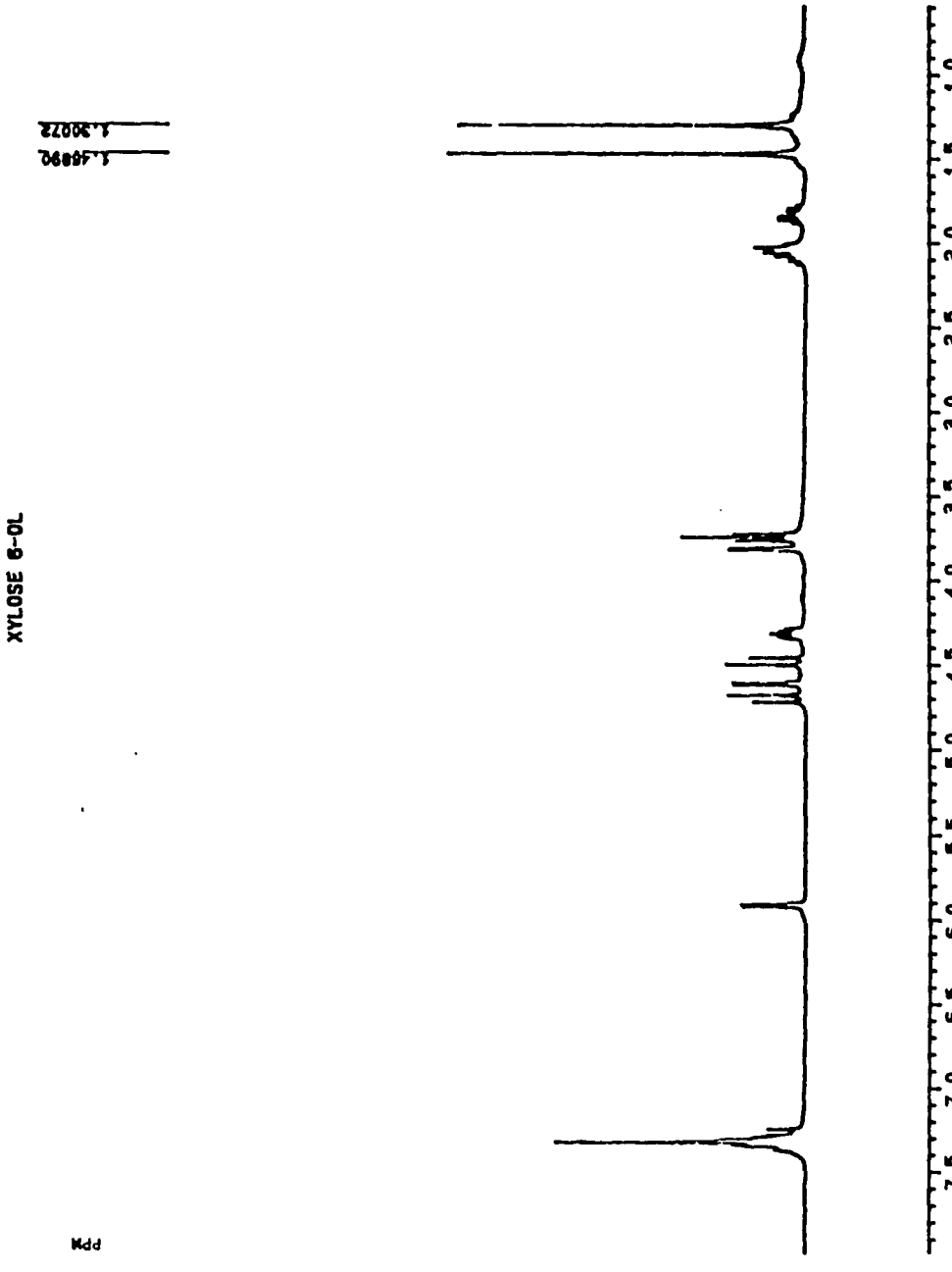


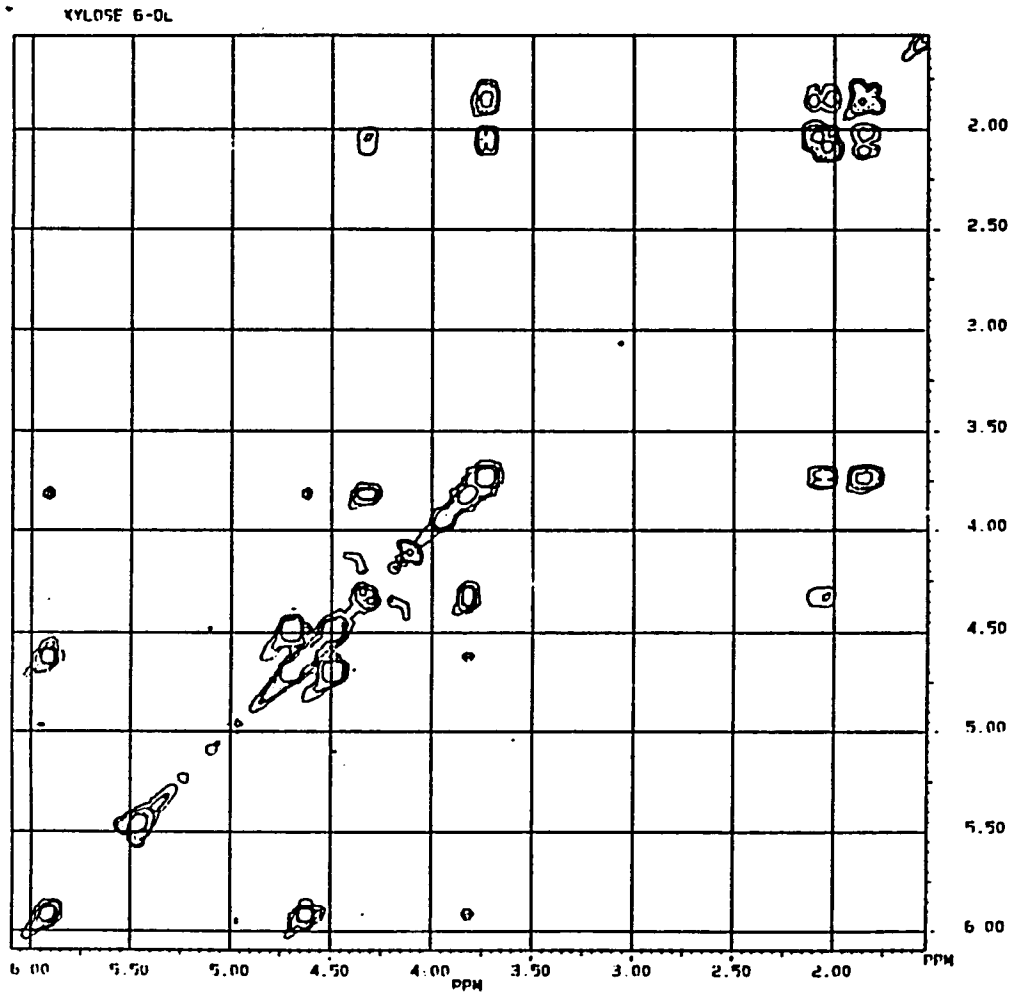
(72)



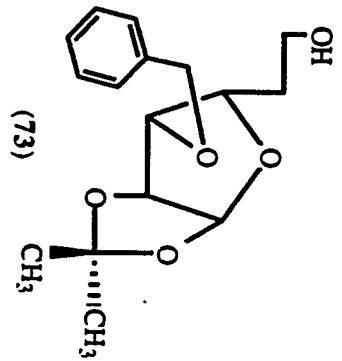

OH
O
O
O
O
CH3
CH3

(73)

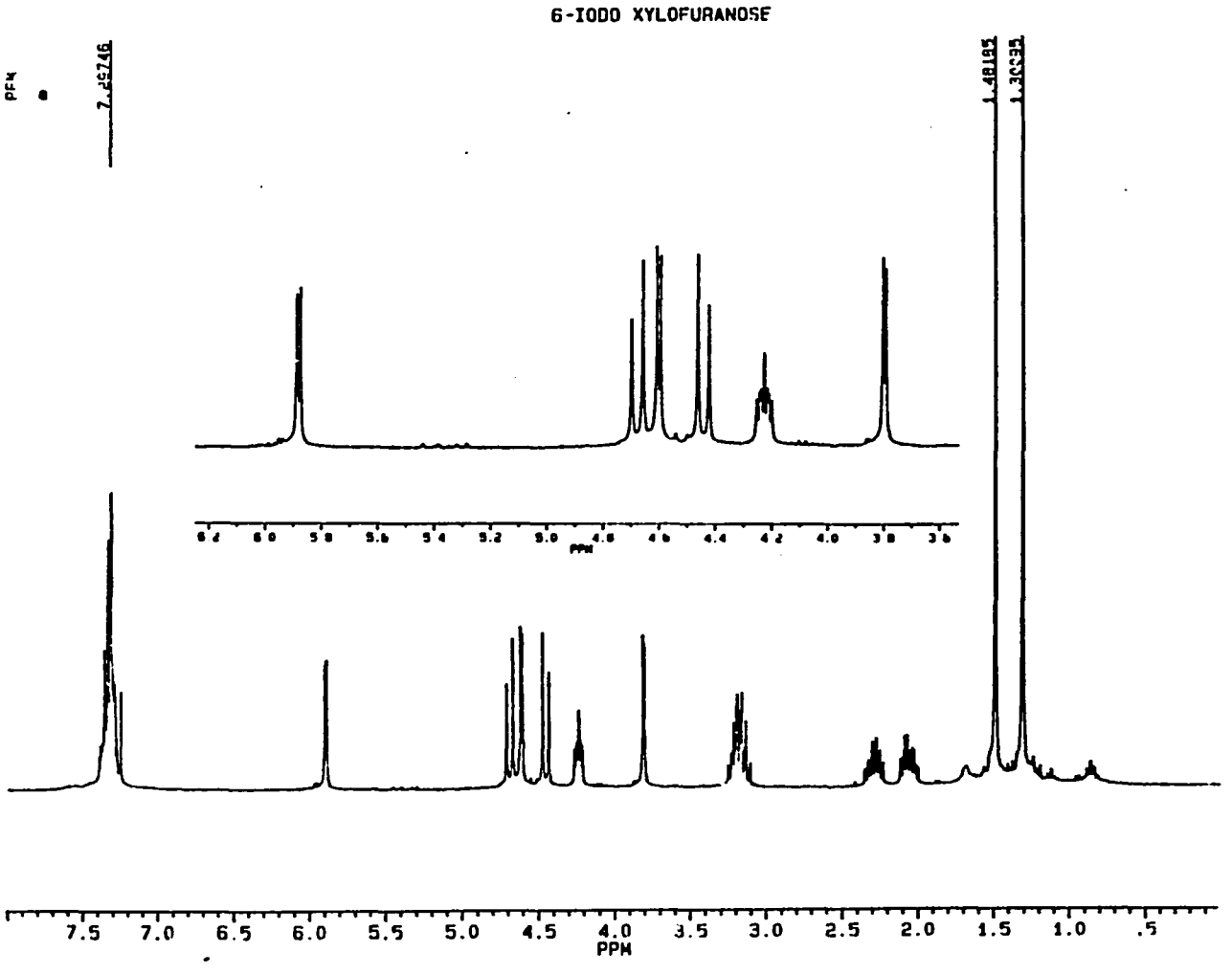

XYLOSE 6-OL
PPM
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0

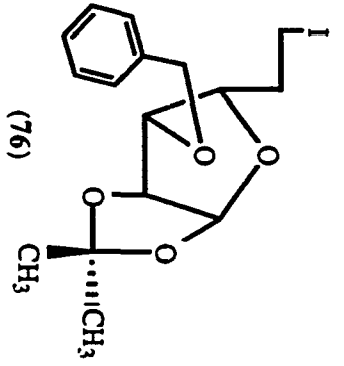


```
DAS.SMX
AU PROG.
  COSYDQF.AU
DATE 16-9-92

SI2     512
SI1     256
SW2    1779.359
SW1     889.680
NDO       1


NDW2      S
NDW1      S
SSB2      0
SSB1      0
MC2       M
PLIW 30W.
F1        6.095P
F2        1.533P
AND COLUMN.
F1        6.095P
F2        1.533P

D1     1.5000000
P1        8.30
D0      .0000050
D2      .1500000
D3      .0000030
RD      0.0
PW        0.0
DE      352.80
NS          8
DS          2
MR        128
TN      .0005620
```



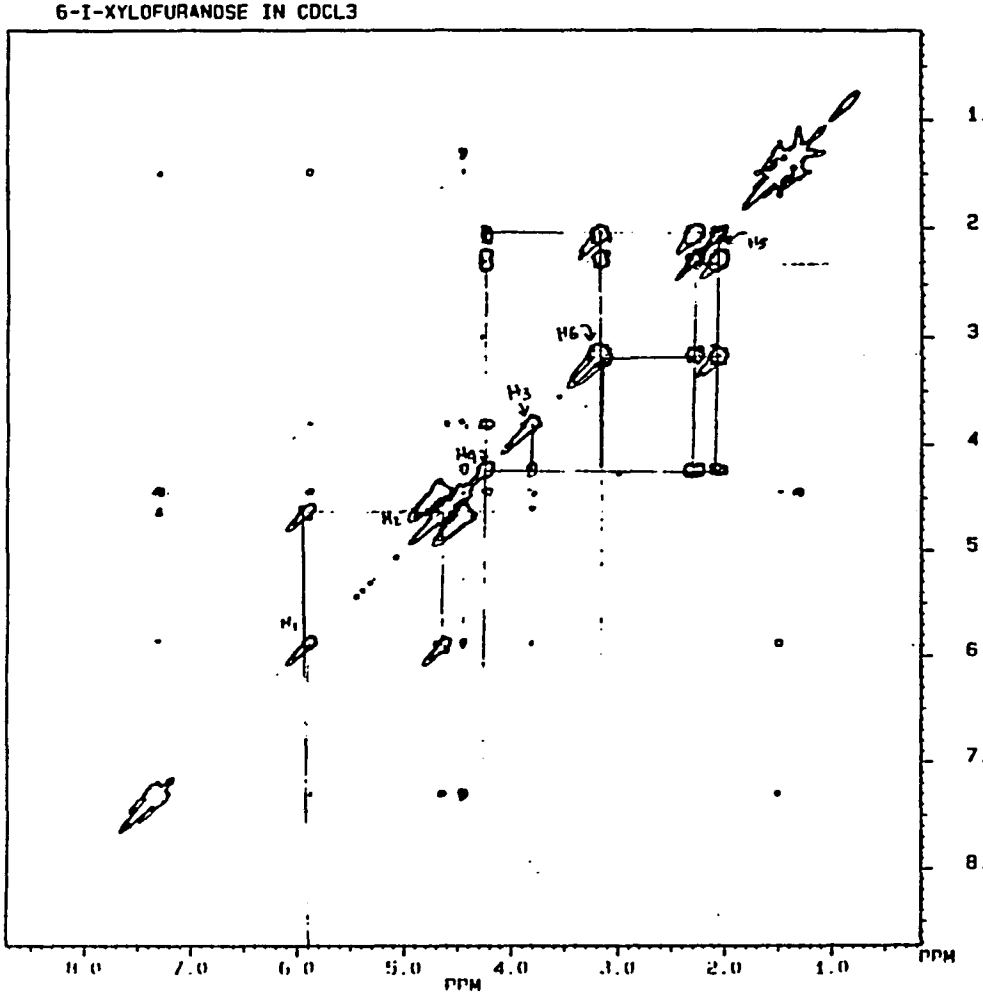
(73)


6-IODO XYLOFURANOSE
PPM
7.49746
1.48185
1.36535
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 .5
PPM


I
O
O
O
O
CH3
CH3

(76)

6-I-XYLOFURANOSE IN CDCL3

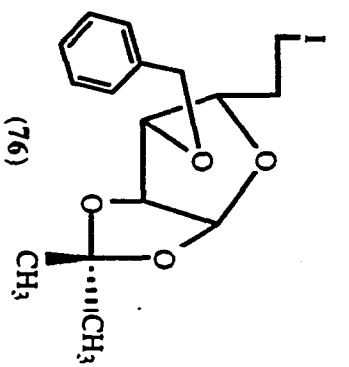


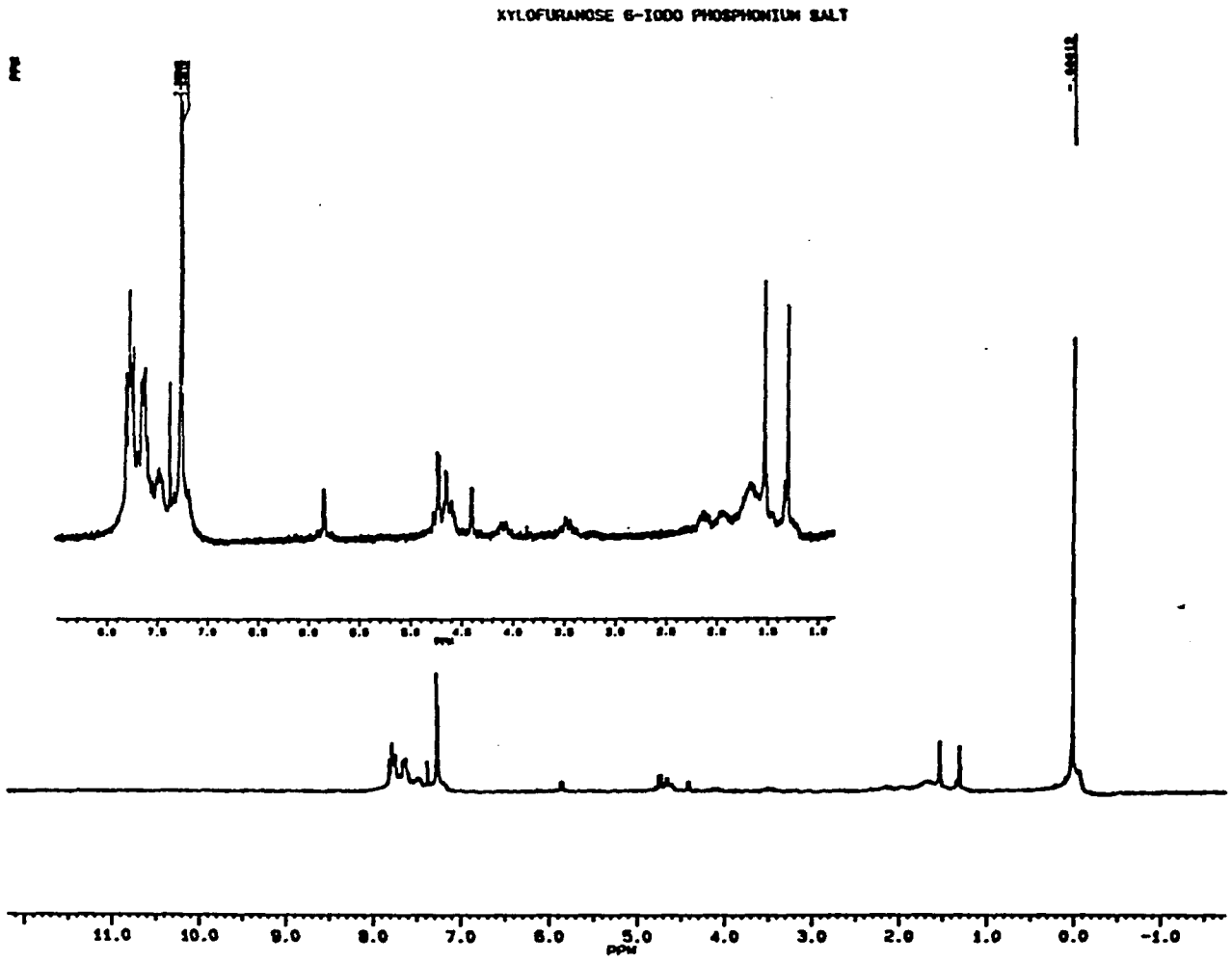
BRUKER

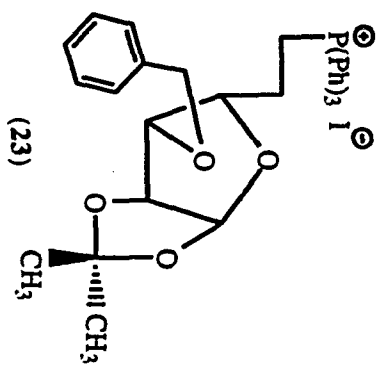
BM.SMX
AU PROG.
COSY.AU
DATE 7-9-91

SI2	1024
SI1	512
SW2	2577.320
SW1	1288.660
NDO	1
WDW2	S
WDW1	S
SSB2	0
SSB1	0
MC2	M
PLIM ROW.	
F1	8.728P
F2	.157P
AND COLUMN	
F1	8.728P
F2	.157P
D1	1.0000000
P1	25.00
DO	.0000030
P2	25.00
RD	0.0
PW	0.0
DE	245.00
NS	4
DS	2
NE	256
IN	.0003880

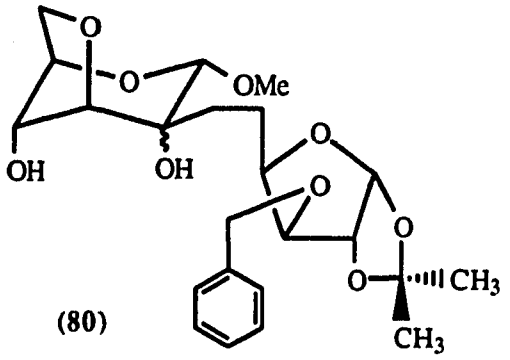
(76)



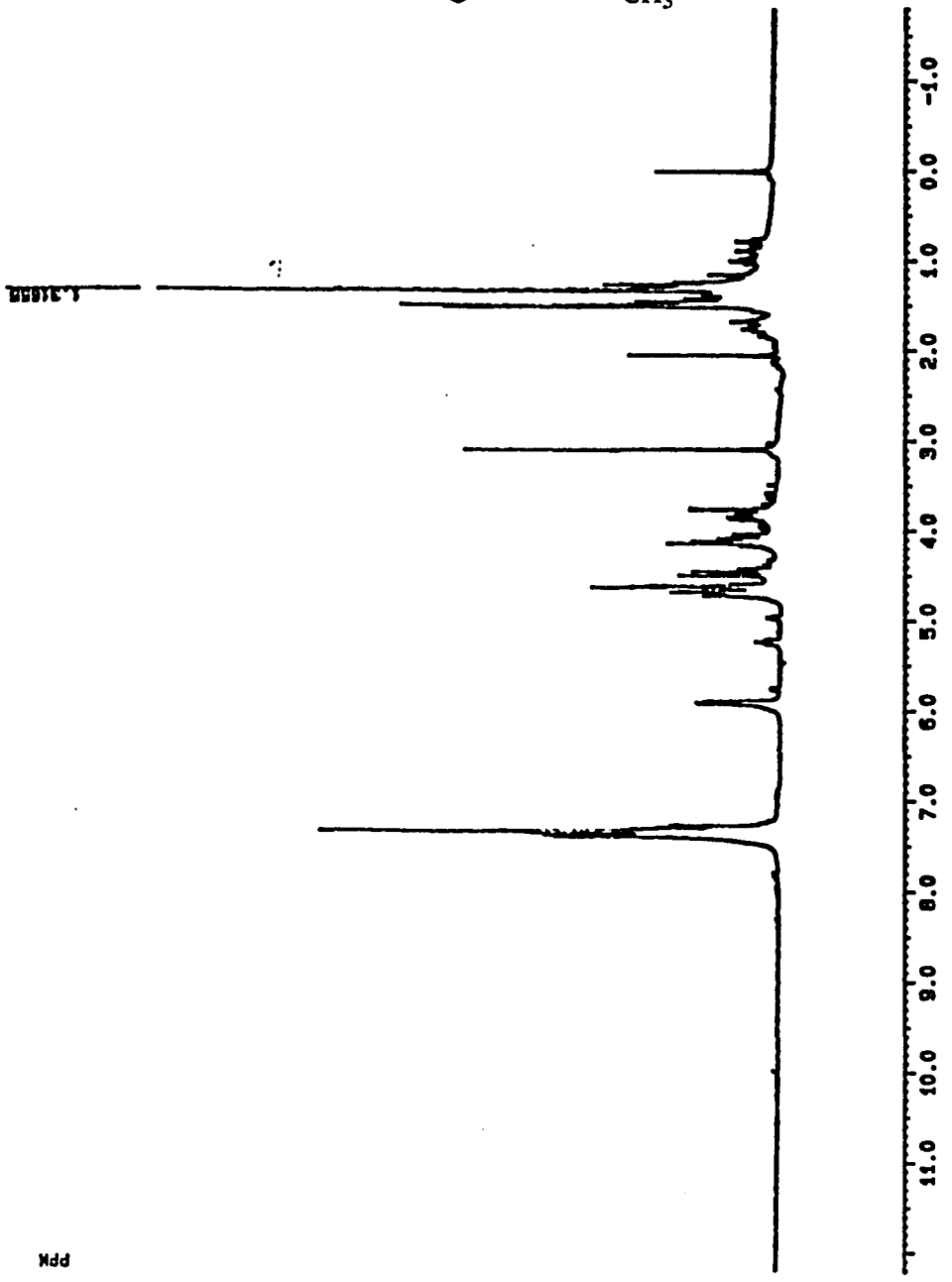

XYLOFURANOSE 6-IODO PHOSPHONIUM SALT
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0
ppm

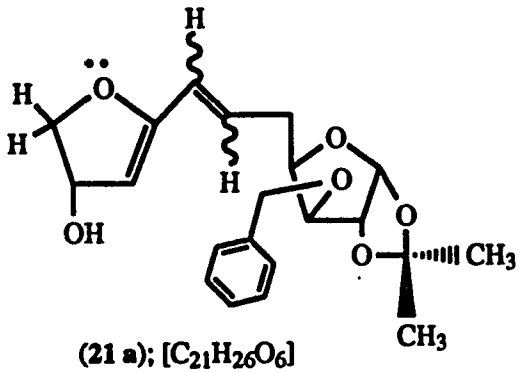

P(Ph)3 I
CH3
CH3

(23)

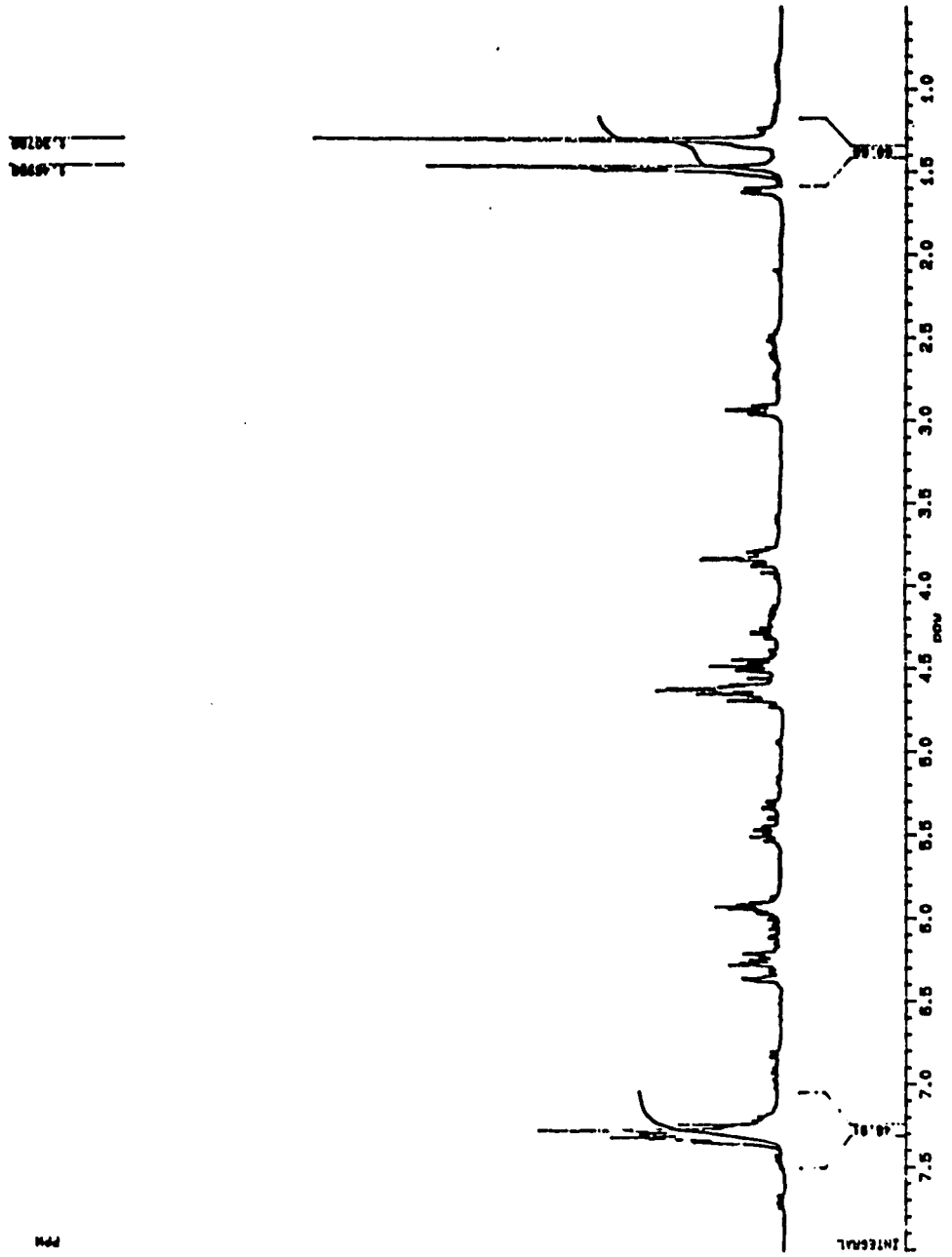

O
O
OMe
OH
OH
O
O
O
O
CH3
CH3

(80)


-1.0
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
PPM



(21 a); $[C_{21}H_{26}O_6]$



REFERENCES

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