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Chiral allylsilanes in the convergent approach to spiroketal substructures

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Chiral Allylsilanes in the Convergent Approach to Spiroketal Substructures

by

David Paul Brown

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

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.

3/1/93
Date

Chair of Examining Committee

4/27/93
Date

Executive Officer

Supervisory Committee

The City University of New York

ABSTRACT

Chiral Allylsilanes in the Convergent Approach

to

Spiroketal Substructures

by

David Paul Brown

Advisor: Professor Vernon G. S. Box

The emergence of the allylsilanes as one of the more versatile reagents in organic synthesis, has sparked new interests in their syntheses and applications. In particular, are the chiral allylsilanes whose syntheses are not only challenging, but require the use of exotic and expensive reagents. Our interests in chiral allylsilanes were kindled from our terminal objective of synthesizing spiroketal substructures having stereocenters at both of the spirocarbons.

A significant part of our investigations was therefore involved with the development of a general method for generating chiral allylsilanes from easily prepared and stable lactone precursors. The method was conceptually straightforward, involving a two-fold addition of a trimethylsilylmethylmagnesium Grignard reagent to the lactone or its derivative, followed by a thermodynamically driven Petersen-type elimination of the resulting bis(trimethylsilylmethyl) carbinol species, to give the allylsilane.

The stereoselectivity of the addition reactions of these allylsilanes with functionalized benzaldehydes were examined, by which it was clearly demonstrated that the stereo-

centers adjacent to the allylsilane moiety did influence the stereochemical outcome of these reactions. Subsequent spirocyclization of the addition compounds were also observed to be influenced by stereocenters remote from the cyclization sites.

The pivalate ester group was utilized in a number of our synthetic intermediates, primarily because of its relatively low migratory aptitude. From our esterification reactions we were able to determine the relative reactivities of the hydroxyl groups of 4,6-*O*-benzylideneglucopyranose, one of our key starting materials, towards the acylpyridinium ion. The observed differences in reactivity towards esterification was rationalized on the basis of the relative nucleophilic activation of proton acceptor sites in the molecule.

Finally, in our efforts to develop a mild, yet facile method for the pivalate ester hydrolysis, we encountered an unusual case of O(2) - O(1) ester migration. This was possible because of the high energy, and very reactive O(1) alkoxide that was formed during the cleavage process, which readily attacked the C(2) ester function in an intramolecular fashion.

This thesis is dedicated to my wife Dawn Gennivie, for her unlimited patience , and to our children Rhenne Kurt-Patrick and Davidta Ava-Dawn.

Acknowledgements

Endeavoring to fulfil God's Will in my life, I must acknowledge His ever guiding presence throughout the course of my professional advancement, which incorporated the lives of some very special persons mentioned below.

Professor Vernon Box's role as thesis advisor, was a task well done. Indeed, his invaluable contribution to the expansion of my scientific intellect has indelibly reinforced the long standing truth, that only a life that is lived for others is a life worth-while. 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, Dr. William F. Berkowitz, Dr. Richard W. Franck, and the late Dr. Donald L. Sloan Jr., have not only provided practical advice, but have demonstrated confidence in my capabilities, in terms of realizing the set goals. Dr. Franck was very instrumental in providing me with the very important reagent, chloromethyltrimethylsilane which marked the turning point of my research work. The late Dr. Sloan Jr. will be remembered, especially, as former Director of the Bridge to Graduate Studies in Science Program, in which I participated, as well as his dynamic role in my being awarded the Robert E. Marshak Distinguished Graduate Fellowship. Dr. Berkowitz's committment remained unrelenting as was reflected in his detailed editing of this thesis.

A sincere thank you is extended to the Faculty and Staff of The City College Department of Chemistry for the provided laboratory space, chemicals and financial assistance for this work. Dr. Ramsay Pal who was very helpful in the aquisition of all the mass spectra, deserves special mention.

I would especially, like to thank my wife Dawn, for her assistance in the final editing of this thesis.

Finally, but also of great significance, was the emotional and practical support of Mrs. Cordella Stokes, our Program Assistant, and Dr. Lynda L. Box, who invested the time in getting me aquainted with the research laboratory.

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CHAPTER 1

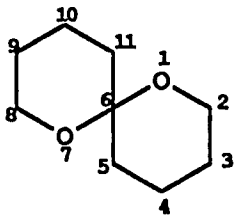
1.0.0. The Chemistry of Spiroketals

1.0.1. Introduction

Spiroketals[1] are found extensively as the substructures of naturally occuring substances from diverse sources, including insects, microbes, plants, fungi, and marine organisms. The increasing pharmacological importance of compounds containing spiroketal moieties has triggered intense interest in both their syntheses and chemical reactivities.

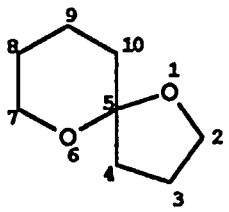
The vast majority of the chemistry in this area is focused on the spiroketal ring systems **A, B,** and **C,** presumably because most natural products fall into one of these structural categories.

A



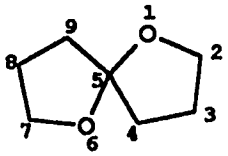
1,7-Dioxaspiro[5.5]undecane

B



1,6-Dioxaspiro[4.5]decane

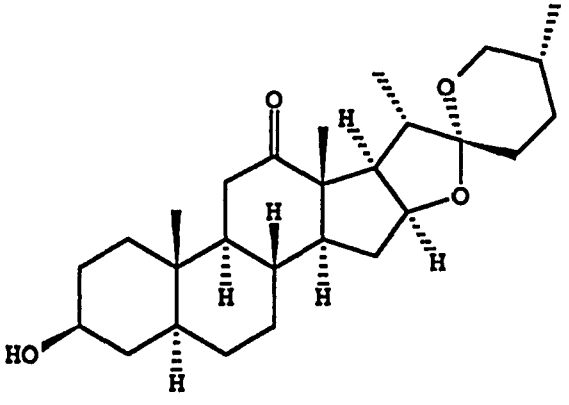
C



1,6-Dioxaspiro[4.4]nonane

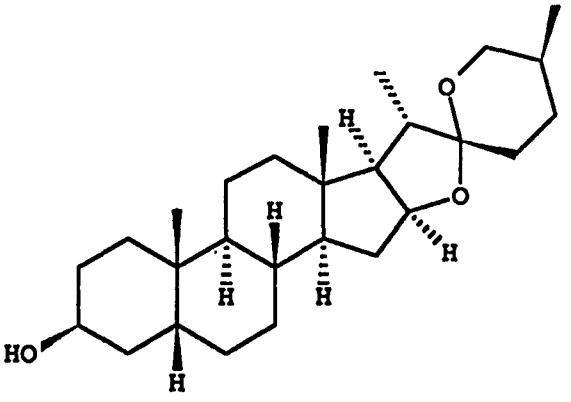
1.1.0. Naturally Occuring Spiroketals

The earliest examples of spiroketal structures in nature were originally isolated from plants found in the southwestern United States and Mexico. It has been determined that these compounds were indeed glycosides (saponins) in which the aglycone (sapogenin) consisted of a steroidal nucleus fused to the D-ring[2]. Glycosylation was usually found on the A-ring. At that time, the steroid nucleus was of more interest to synthetic chemists, and spiroketal chemistry was relatively neglected. Examples of these spiroketals are hecogenin and sarsasapogenin, named after their natural sources.



Hecogenin

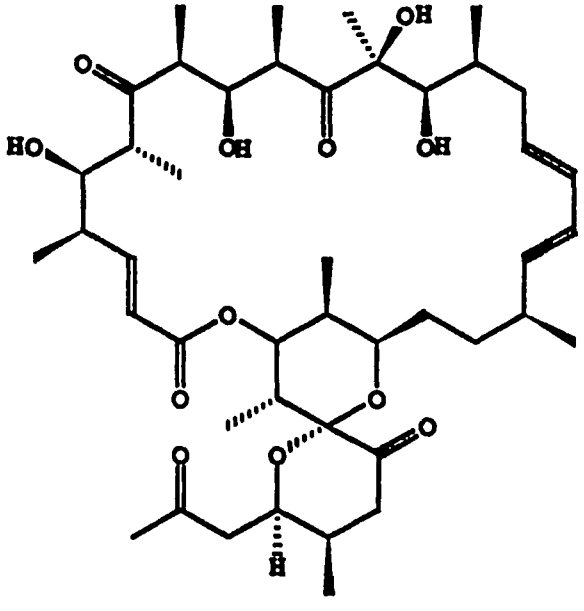
1



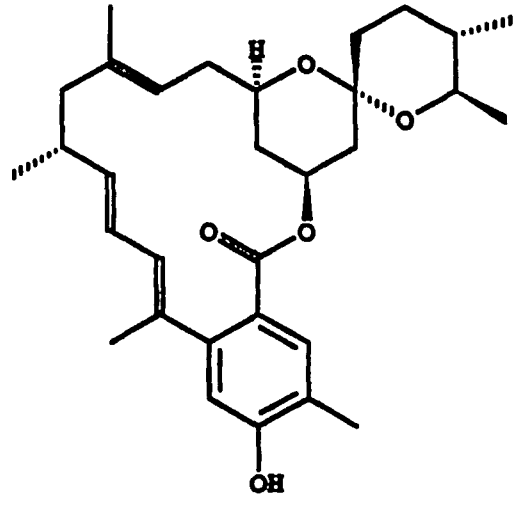
Sarsasapogenin

2

In 1958 it was demonstrated that the antibiotic oligomycin acts as a potent inhibitor of oxidative phosphorylation[3]. This inhibition is relieved by the addition of 2,4-dinitrophenol, which stimulates the usual fast rate of oxygen uptake. Oligomycin was subsequently found to be a mixture of three compounds, one of which was oligomycin B, incorporating the [5.5] ring system, 3[4].

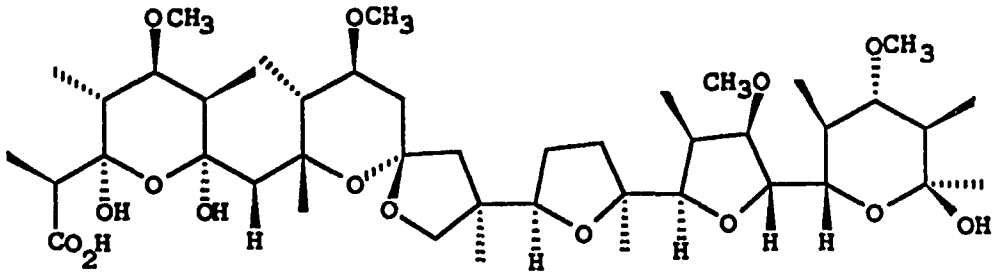


3



5

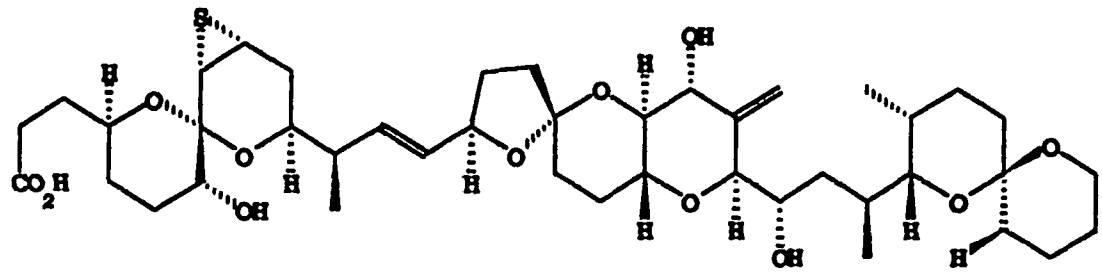
A third class of highly functionalized spiroketals are the polyketide-derived polyether antibiotics produced by filamentous branching bacteria. Of particular interest is the ionophore monensin 4, whose structural elucidation initiated the extensive and widerang-ing interest in polyethers that continues today[5].



4

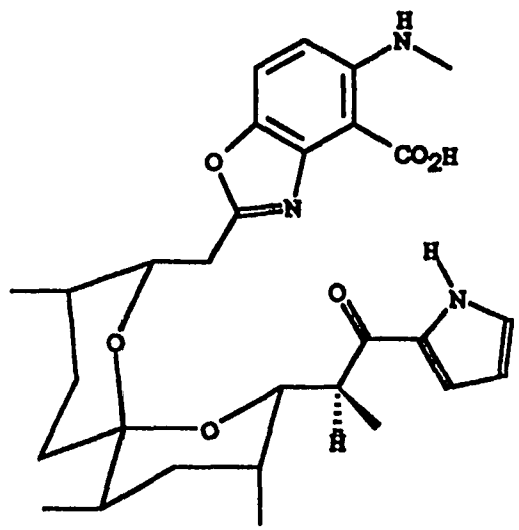
The description of the milbemycins, 5, and closely related avermectin antibiotics has generated the most activity in spiroketal synthesis. As a class, they exhibit medicinally significant insecticidal and acaricidal activity. These compounds hold enormous potential for the treatment of parasitic infections, since they also have low mammalian toxicity[6]. In particular, ivermectin or 22,23-dihydroavermectin B_1, derived from avermectin B_1 by selective hydrogenation using Wilkinson's homogeneous catalyst, has been shown to be effective in containing the transmission of *Onchocerca volvulus* microfilariae by the black fly *Simulium yahense.* The females of this species are responsible for the spread of onchocerciasis, a parasitic disease sometimes resulting in permanent blindness.

The identification of spiroketals from the marine environment is a relatively recent phenomenon. Acanthafolicin[7], 6, and okadaic acid[8] were the first polyether carboxylic acids described from these sources. These compounds are believed to be produced by symbiotic microorganisms of certain sponges, and are the causative agents of "diarrhetic shellfish poisoning".



6

An interesting class of antibiotics which includes the divalent cation ionophore A23187, calcimycin, 7, were isolated from streptomycetes[9]. These compounds possess the relatively rare ability to transport alkaline earth metal cations across cell membranes. Recent investigations have shown that calcimycin may aid sperm motility, an important factor in the fertilization process.



7

1.2.0. Conformational Aspects

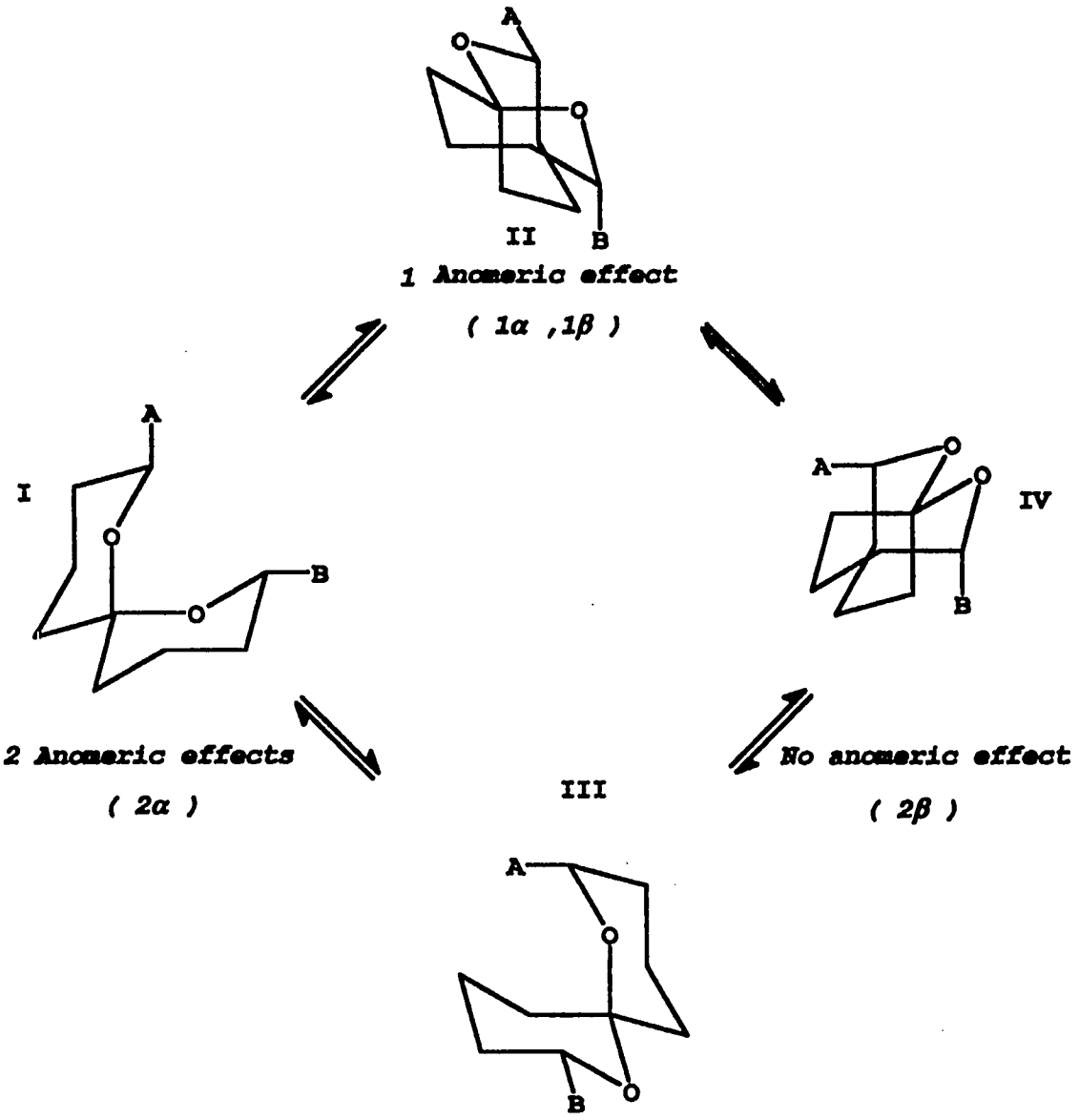
1,7-Dioxaspiro[5.5]undecanes have been studied intently and are the most easily analyzed for preferred conformations[10]. Three factors have been observed to influence conformational preferences in this system: (i) steric influences, (ii) anomeric and related effects[11], and (iii) intramolecular hydrogen bonding and other chelation effects. In cases of unsymmetrical substitution, there are four possible all-chair conformers corresponding to independent inversion of each ring. This is illustrated in scheme 1.

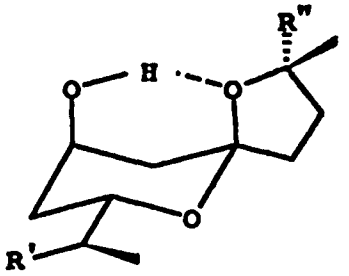
In the completely unsubstituted ring system, it has been shown[12] that conformer **I** is the most stable conformer of this ring system. This has been ascribed to maximization of a thermodynamic anomeric effect, since comformer **I** has no β-anomer configurations, which are known to be less stable than α-anomers. Indeed, this observed difference in stability is now understood to be largely accounted for by the greater *n-n* destabilizing effect in the β-anomer than that which is present in the α-anomer[11].

1.2.1. Conformations of Naturally Occuring Spiroketals

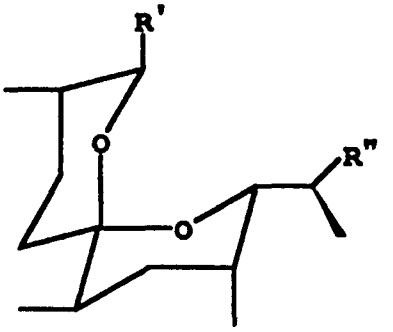
Examination of the solid state structures[13] of naturally occuring spiroketals reveals that the majority appear to reside in predictable conformations in which steric effects are minimized and anomeric effects are maximized. In the cases of spiro[5.5] systems the bis-axial arrangement, (2α), of spiro C-O bonds is commonly observed in both saturated and unsaturated ring systems. Several natural product spiroketal conformations have been redrawn in an approximate fashion from computer-generated crystal structures and are shown below. Interestingly, in the monensin-water complex **8**, as well as in various salts of monensin, both the C5 methyl and the C6 hydroxyl are axially disposed. This conformation may be stabilized by an O4-H--O6 intramolecular hydrogen bond[14].

SCHEME 1


A
O
O
II
B
1 Anomeric effect
(1α ,1β)
A
I
O
B
O
A
O
O
IV
B
2 Anomeric effects
(2α)
III
No anomeric effect
(2β)
A
O
B
O
1 Anomeric effect
(1α ,1β)

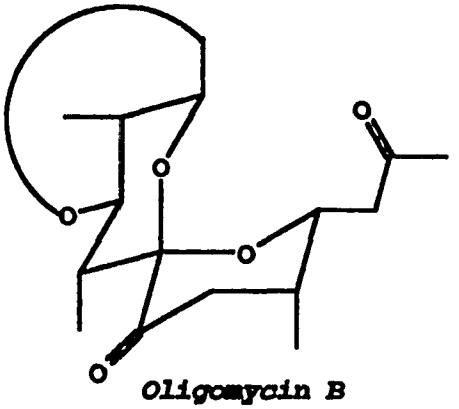


8



Calcimycin

9



Oligomycin B

10

1.3.0. Spiroketal Synthesis

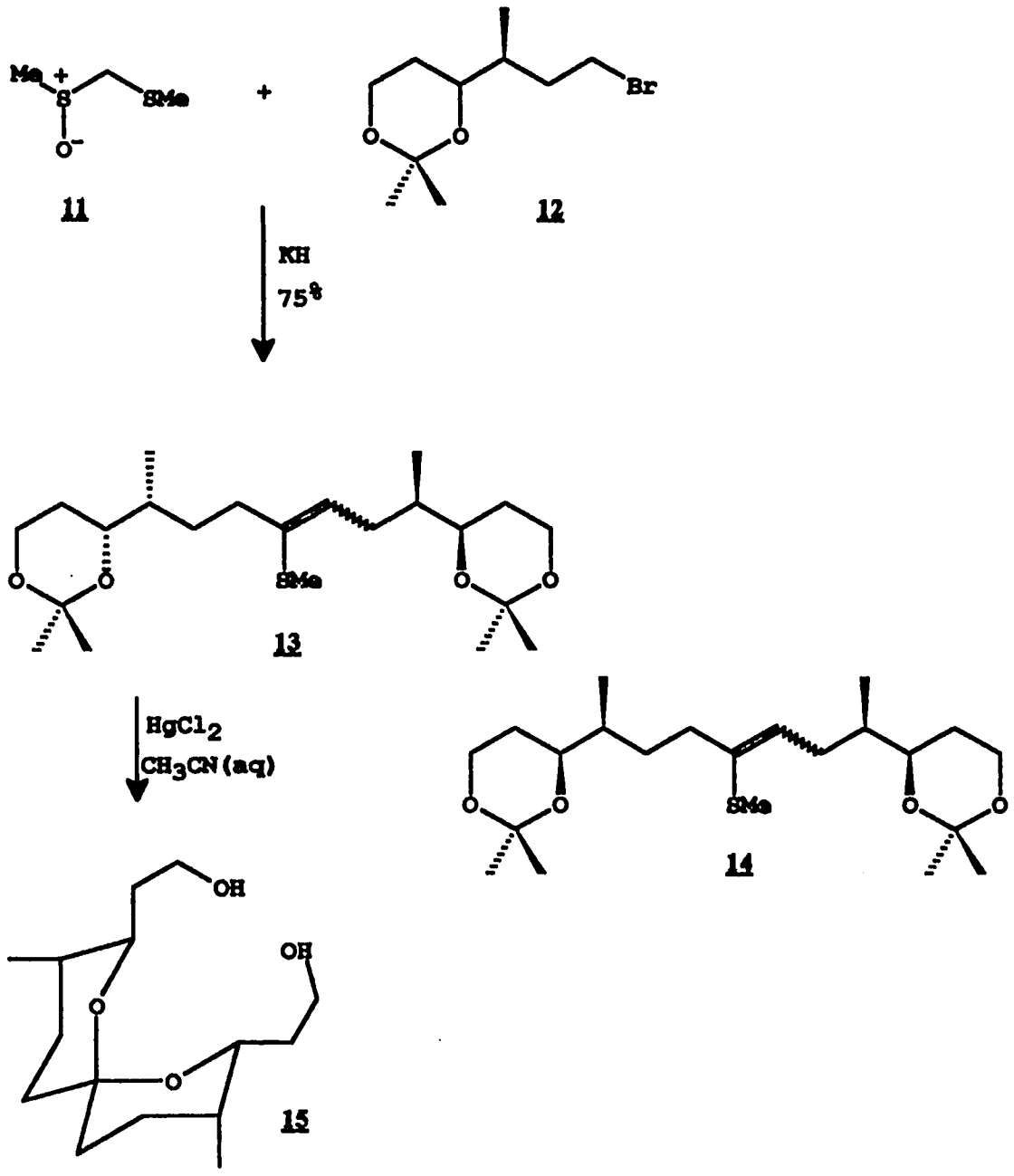
Although several strategies have evolved for spiroketal synthesis, the acid-catalyzed cyclization of a dihydroxy ketone or an equivalent thereof, is the predominant ring-forming process. Most of the early approaches took this course. Later work concentrated on devising new and more efficient methods for assembling the dihydroxy ketone precursors.

Intramolecular acid-catalyzed ketalization of dihydroxy ketones is an extremely facile process, suggesting that there is a large thermodynamic difference between dihydroxy ketones and spiroketals, much larger than in the intermolecular counterpart. This difference is a consequence of the fact that the system settles into the thermodynamic axial, axial (2α) arrangement. One need not give much thought, therefore, about the configurational outcome at the acetal center during such spirocyclization reactions.

1.3.1. Acid-Catalyzed Spiroketalizations

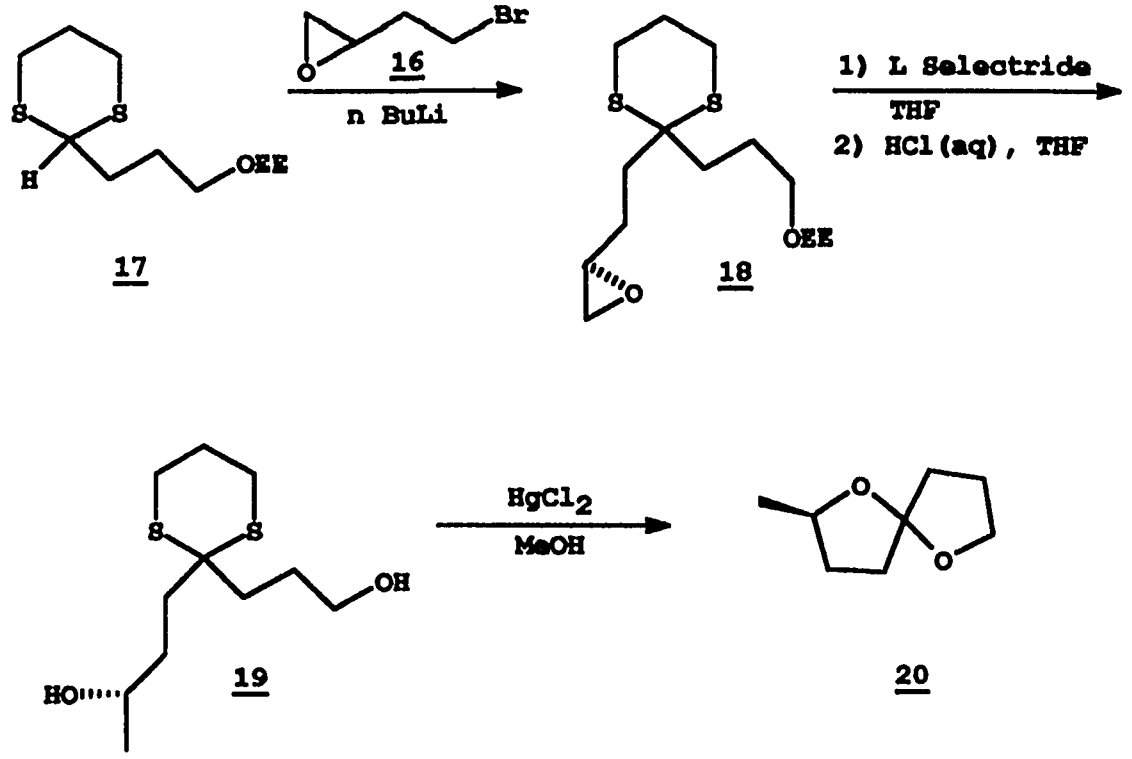
The synthetic methods in this area can be subdivided into classes based on which bond is formed to produce the precursors to cyclizations. By far the most frequently employed strategy is to use the carbonyl group (the incipient spiro carbon) as a point of attachment. Acyl anion equivalents such as 1,3-dithiane and similar substances are ideal reagents for connecting two hydroxy-alkyl fragments to a *pro*-carbonyl group that will eventually become the spiro-carbon. One of the first examples of this strategy was put forth by Evans[15], in model studies directed toward the synthesis of calcimycin.
The riveting agent 11 was alkylated with the racemic bromide 12 to give the expected mixture of isomers 13 and 14 after sulfoxide elimination, Scheme 2. Separation of 13 and hydrolysis mediated by Hg(II), led to the major spiroketal 15.

SCHEME 2



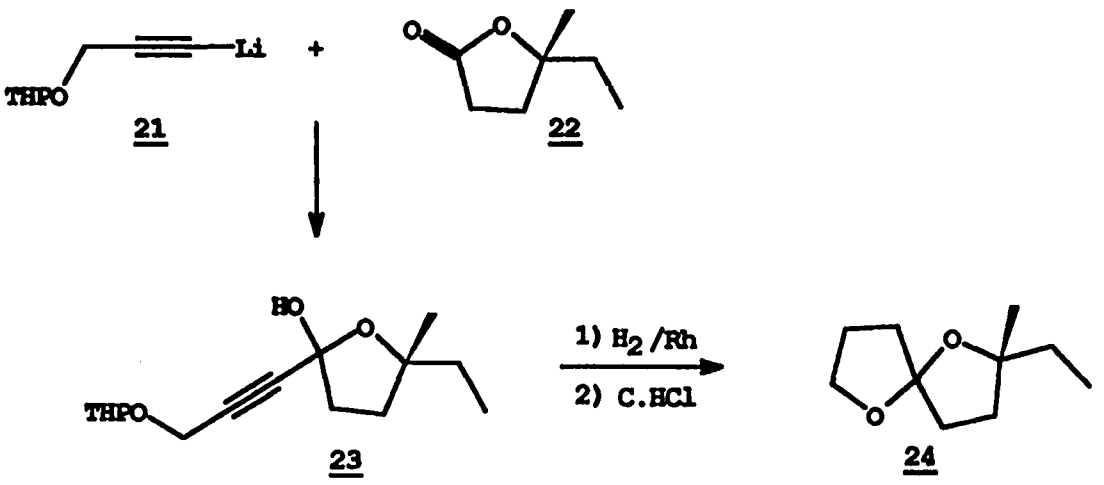
Seebach[16] used the optically pure bromo epoxide **16**, Scheme 4, available from *(S)*-(-)-malic acid, in an approach to **20**, one of four spiroketal pheromones, obtained as a 3:2 mixture of diastereomers at the spiro carbon.

SCHEME 3



A variety of nucleophiles have been added to lactone carbonyls to produce the ketone eventually destined to be the spiro-carbon[17,18]. A general sequence is exemplified in a synthesis of chalcogram **24**, involving addition of an acetylide anion to an optically pure lactone, hydrogenation of the resulting alkyne, and acid-promoted spiroketalization. In this case **24** was produced as a 2:1 mixture of E/Z isomers, Scheme 4.

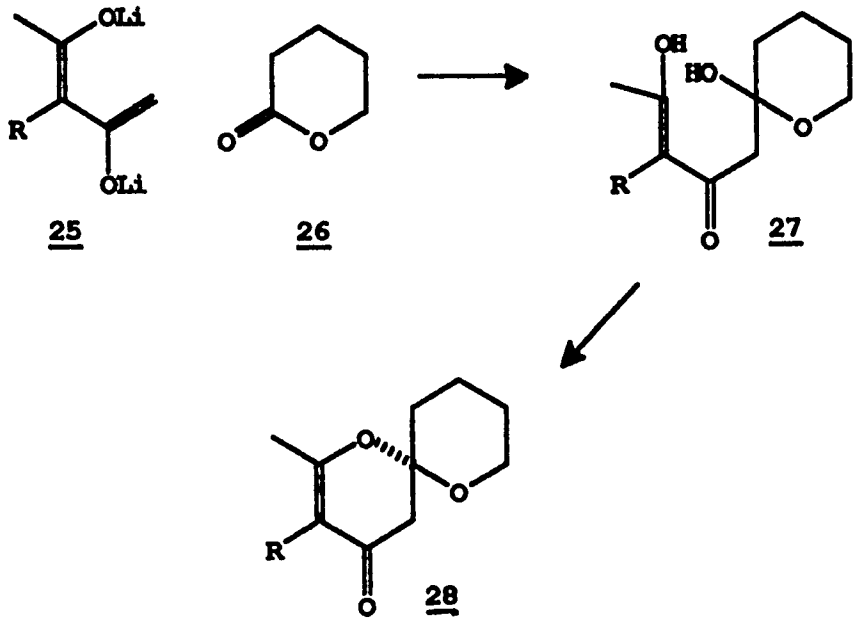
SCHEME 4

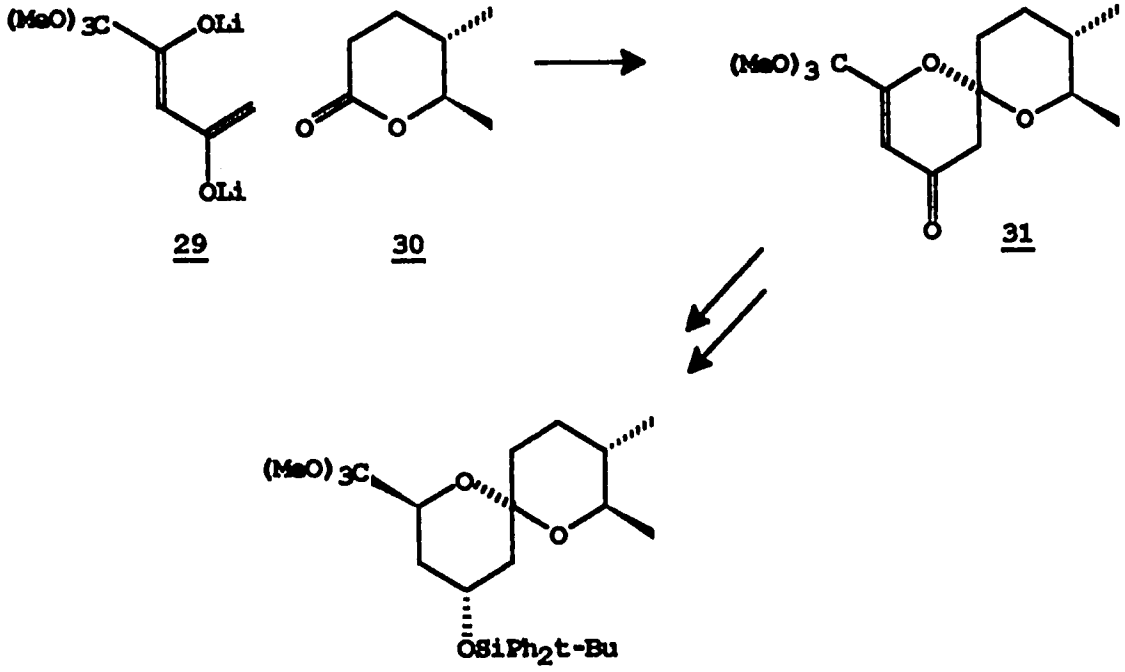


Enolate anions are convenient annelation reagents that have seen considerable success in spiroketal synthesis. Barrett developed β-diketone dianions as general reagents for the synthesis of milbemycin-avermectin spiroketals[19]. In model studies, the reaction of **25** (Scheme 5) with lactones leads to addition products that can be cyclized with acid to C2-C3 unsaturated spiroketals **28** in high yields.

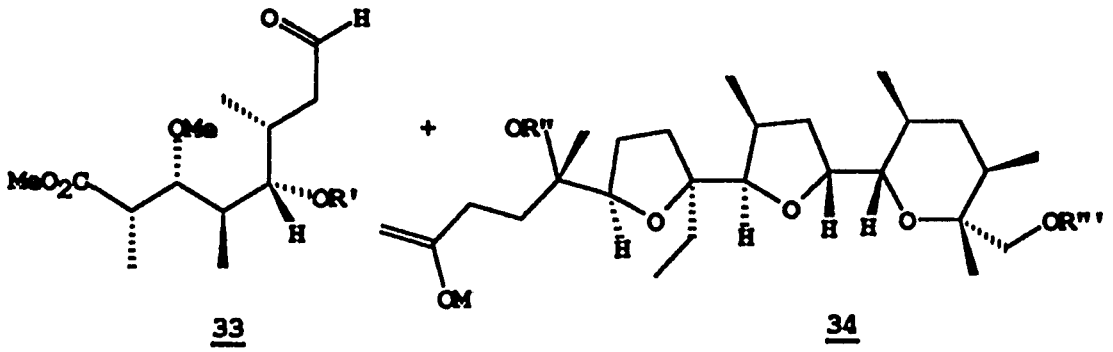
This approach was exploited in a synthesis of milbemycin β_3 by use of the carbonyl protected reagent **29** and the popular optically pure lactone **30**, providing the spiroketal **31**, which was eventually converted to **32** and thence to the natural product.

SCHEME 5

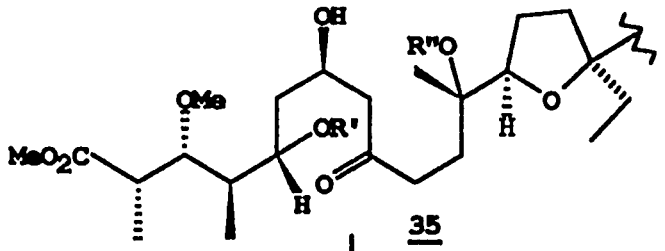

OLi
R
OLi
O
O
OH
HO
O
R
O
25
26
27
O
O
R
O
28


(MeO) 3C
OLi
OLi
O
O
(MeO) 3 C
O
O
O
29
30
31
(MeO) 3C
O
O
OSiPh2t-Bu
32

SCHEME 6



33 34



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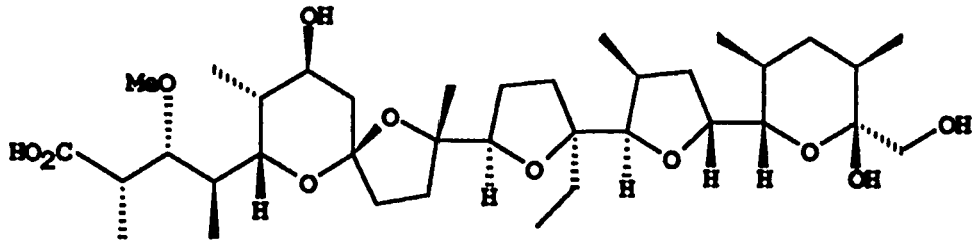
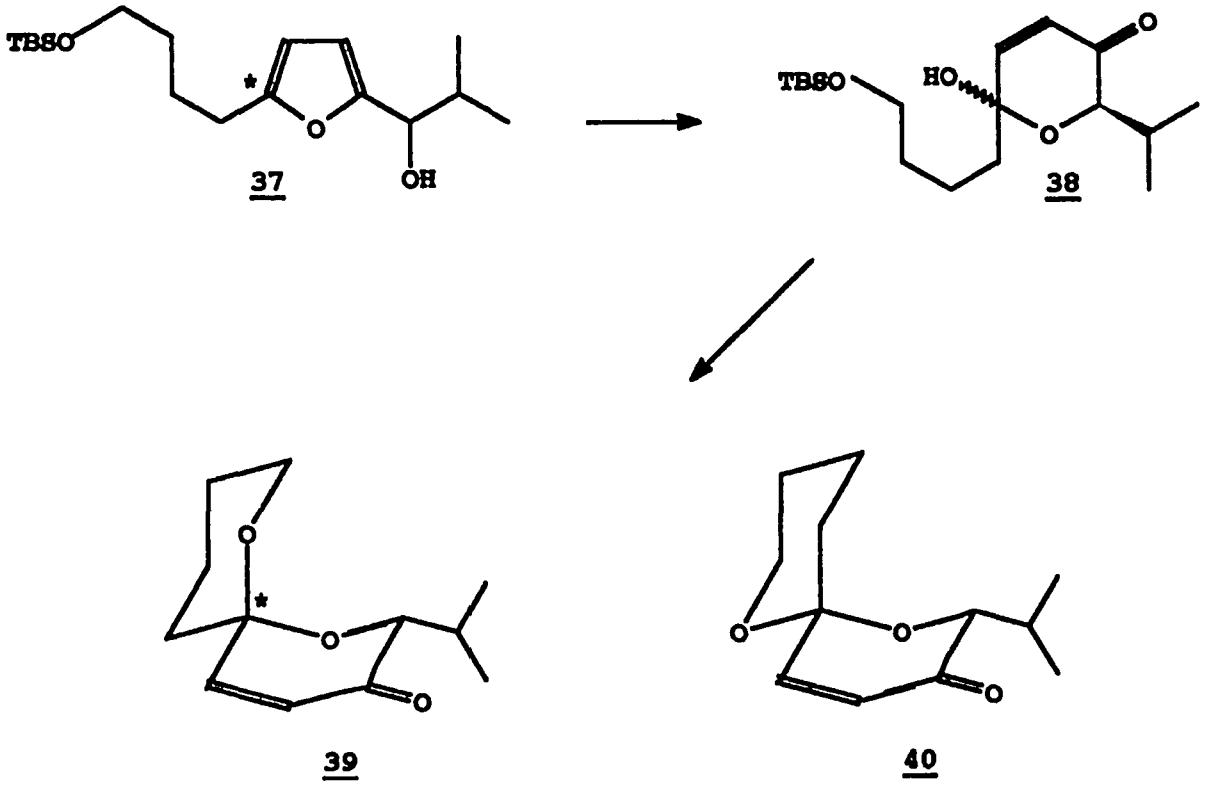


36

In a slightly different approach, Still and Kishi[20] took advantage of the developing improvements in directed aldol condensation at the time, connecting two large fragments (Scheme 6) late in their respective monensin syntheses to produce compound **35**. The dihydroxyketones generated from **35** were cyclized to form the 1,6-dioxaspiro[4.5] decane ring system of the natural product **36**. Both groups obtained a single spiroketal isomer upon ring closure corresponding to that in monensin.

The oxidation-rearrangement of 2-furyl carbinols to dihydropyranones can be effected by a number of reagents, including bromine, peracid, PCC, and others.

SCHEME 7

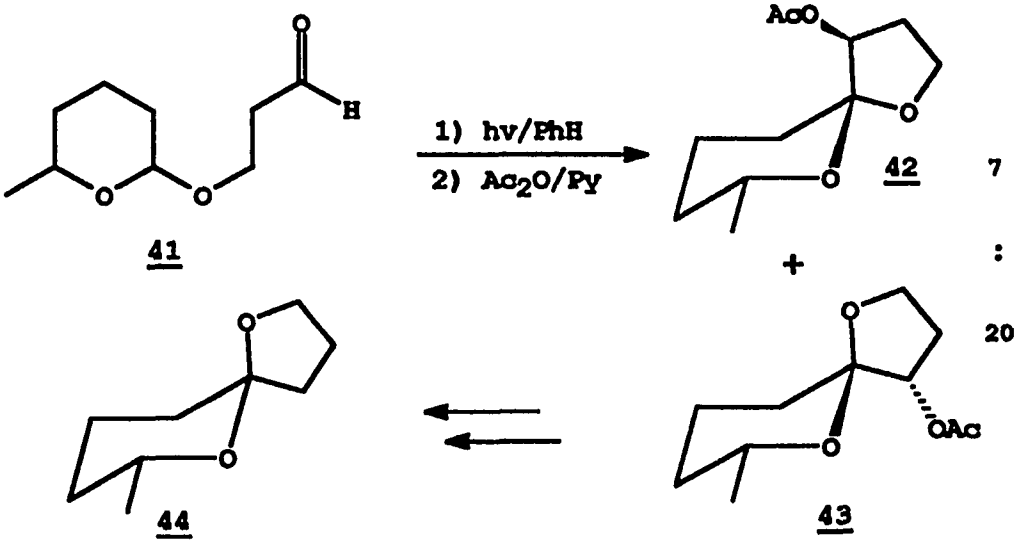


DeShong[21] effectively utilized this oxidation in spiroketal syntheses (Scheme 7). Oxidation-rearrangement of 37 with *m*-CPBA gave the hemiacetal 38. Desilylation and spirocyclization were accomplished with HF in acetonitrile to provide the thermodynamic mixture of spiroketals 39 and 40, in 91% and 5% yields respectively.

1.3.2. Processes Not Involving Internal Ketalization

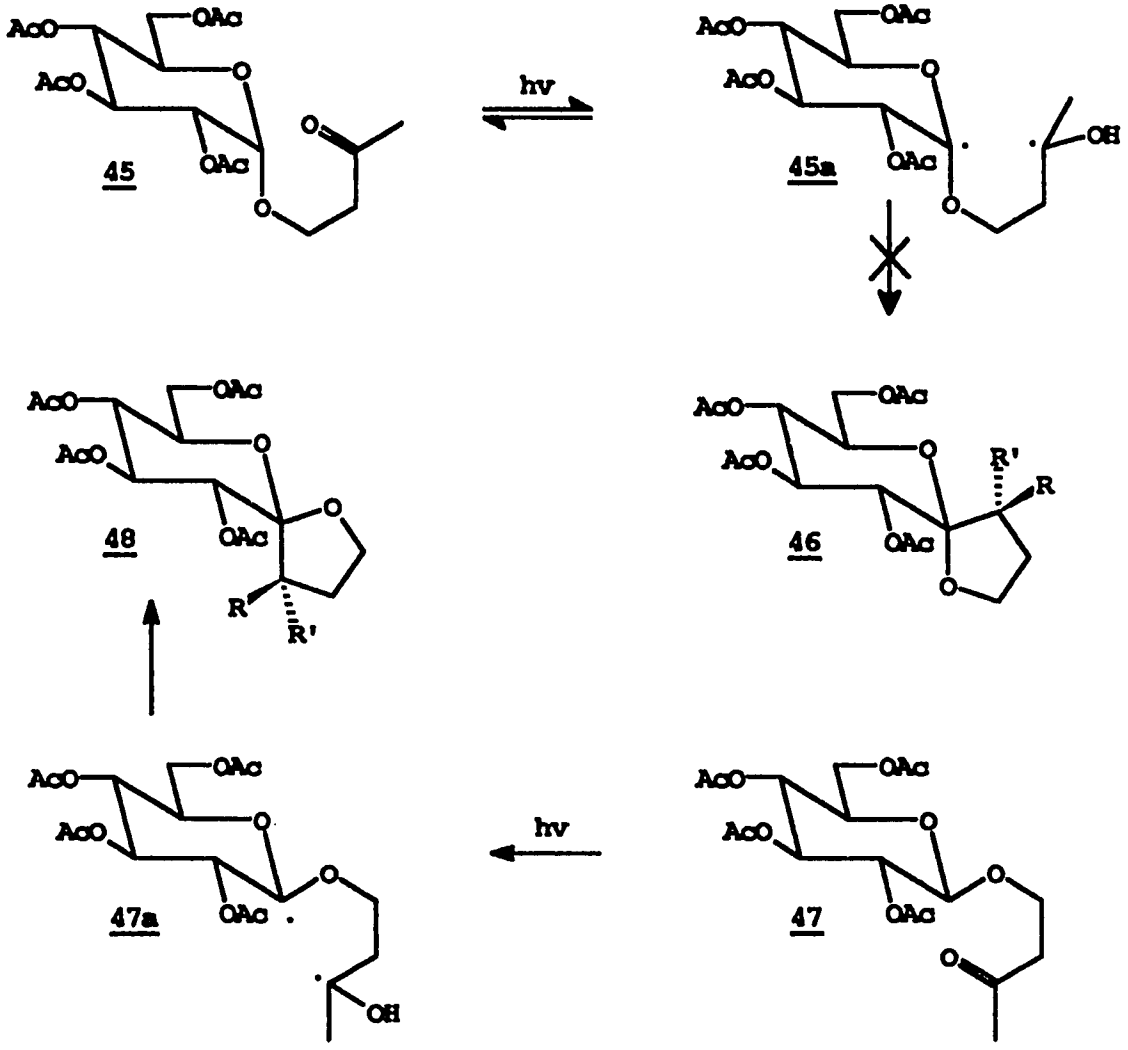
An elegant approach to spirocyclic systems via photochemical cyclization was described by Descotes[22]. Irradiation of aldehydes such as 41 (Scheme 8) in which there are no hydrogens on the atom γ to the carbonyl group, results in hydrogen atom abstraction and cyclization of the resulting biradicals to mixtures of spiroketals in moderate yield. Such a Norrish type II photochemical process represents a general route to novel 1,6-dioxaspiro[4.5]decanes which has been applied to the synthesis of the *paravespula vulgaris* pheromone 44.

SCHEME 8



Photocyclization of related sugar derivatives is highly dependent on the configuration of the anomeric center (Scheme 9) and on the nature of the substituents at C2[23]. Indeed, the photolysis of β-glucosides, β-mannosides, and α-arabinopyranosides[24] occurs rapidly with retention of configuration (46-47), while that of the α analogues (44), proceeds somewhat slowly, if at all[25]. This favored photocyclization of the β-glucosides is interpreted in terms of the greater stability of the radical formed by abstraction of the axial anomeric hydrogen atom.

SCHEME 9



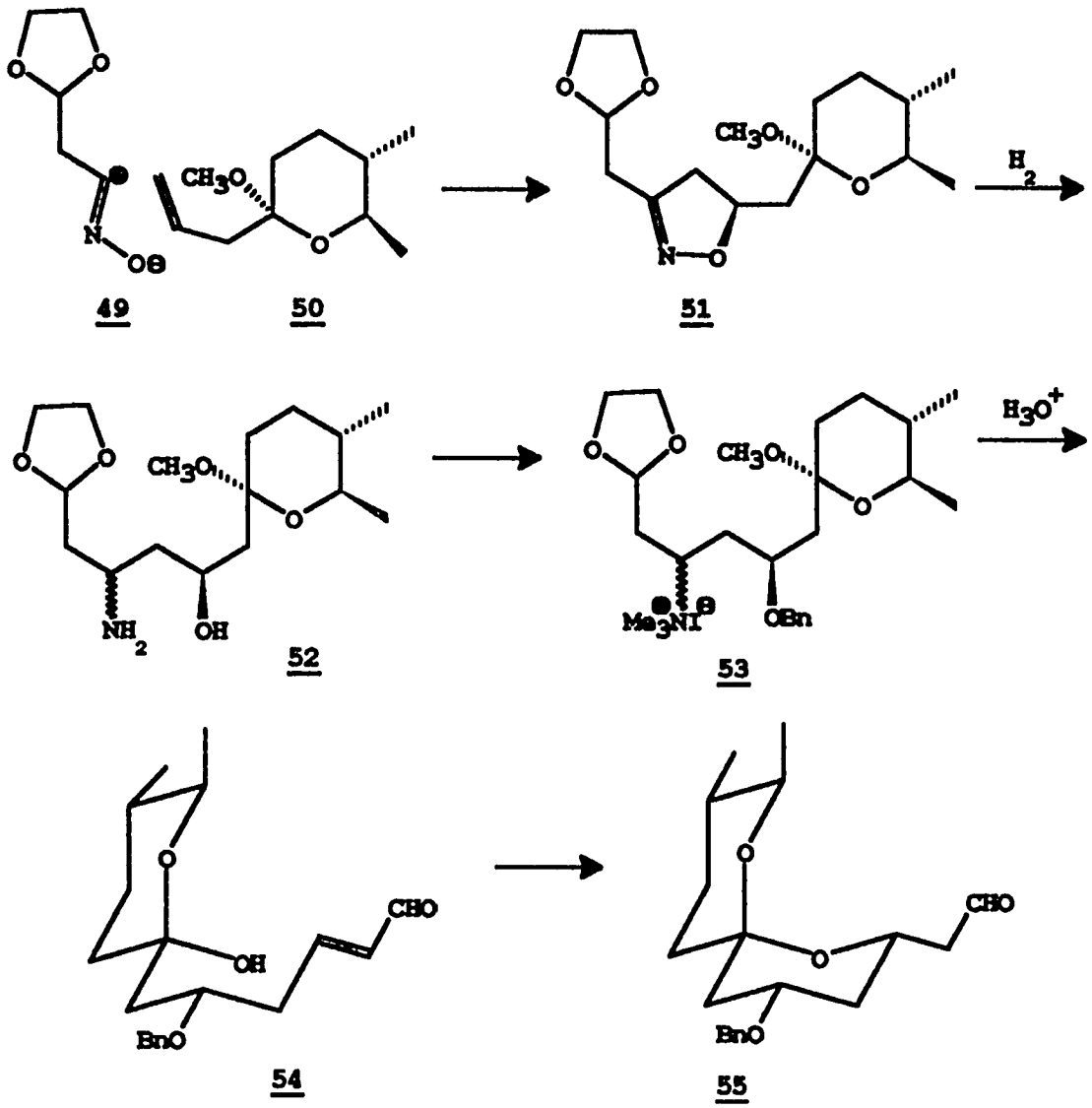
In a milbebycin β_3 synthesis reported by Smith[26], the enal precursor **54** was constructed by using the technique of 1,3-dipolar cycloaddition of a nitrile oxide to an olefin to give isoxazole **51**. Successive reduction, benzylation, and amine quaternization led to **53**. Treatment of this compound with aqueous *p*-TsOH provided the spiroketal **55**, that is thought to arise by an acid-catalyzed 1,4-addition to the conjugated enal **54**, (Scheme 10).

1.4.0. Reactions of Spiroketals

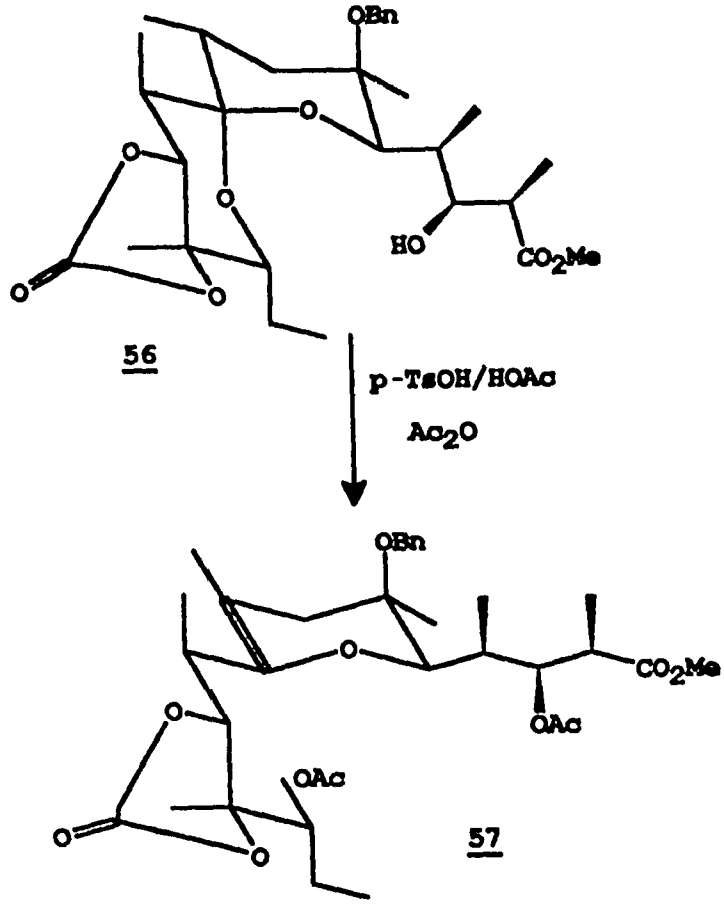
1.4.1. Conversion to Open-Chain Derivatives

The reversal of the spirocyclization reaction has been accomplished on both simple and complex derivatives. Because of the large thermodynamic difference between dihydroxy ketones and spiroketals, with the latter being favored, one must effectively trap the open chain form as a derivative of either the carbonyl group or the alcohols. Deslongchamps[27] partially opened the spiroketal **56** by treatment with *p*-TsOH in the presence of acetic anhydride to trap any intermediate alcohols. The result was the half-open dihydropyran derivative **57**, (Scheme 11).

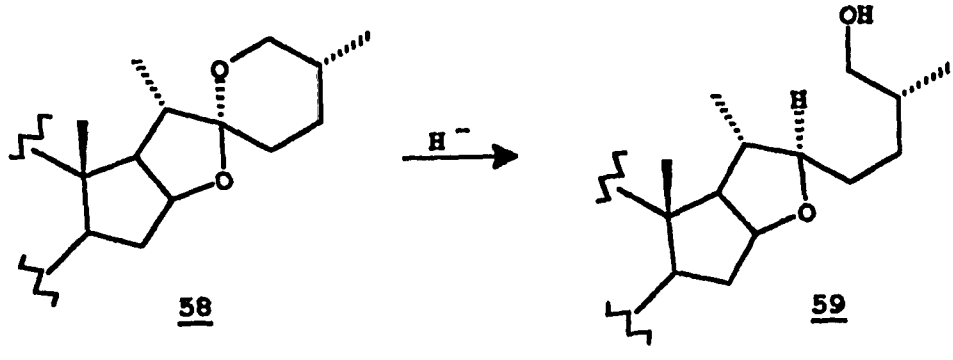
SCHEME 10



SCHEME 11



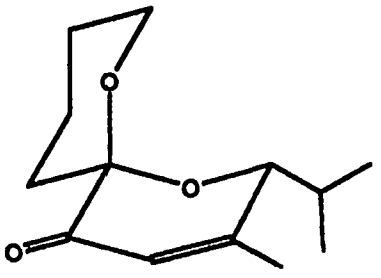
SCHEME 12



Reductive ring opening of spiroketals to monocyclic compounds can be accomplished with LAH/$ALCl_3$ in ether. This was first reported in the steroidal saponegin series and was found to give products in which only the tetrahydropyran ring had been cleaved[28], (Scheme 12).

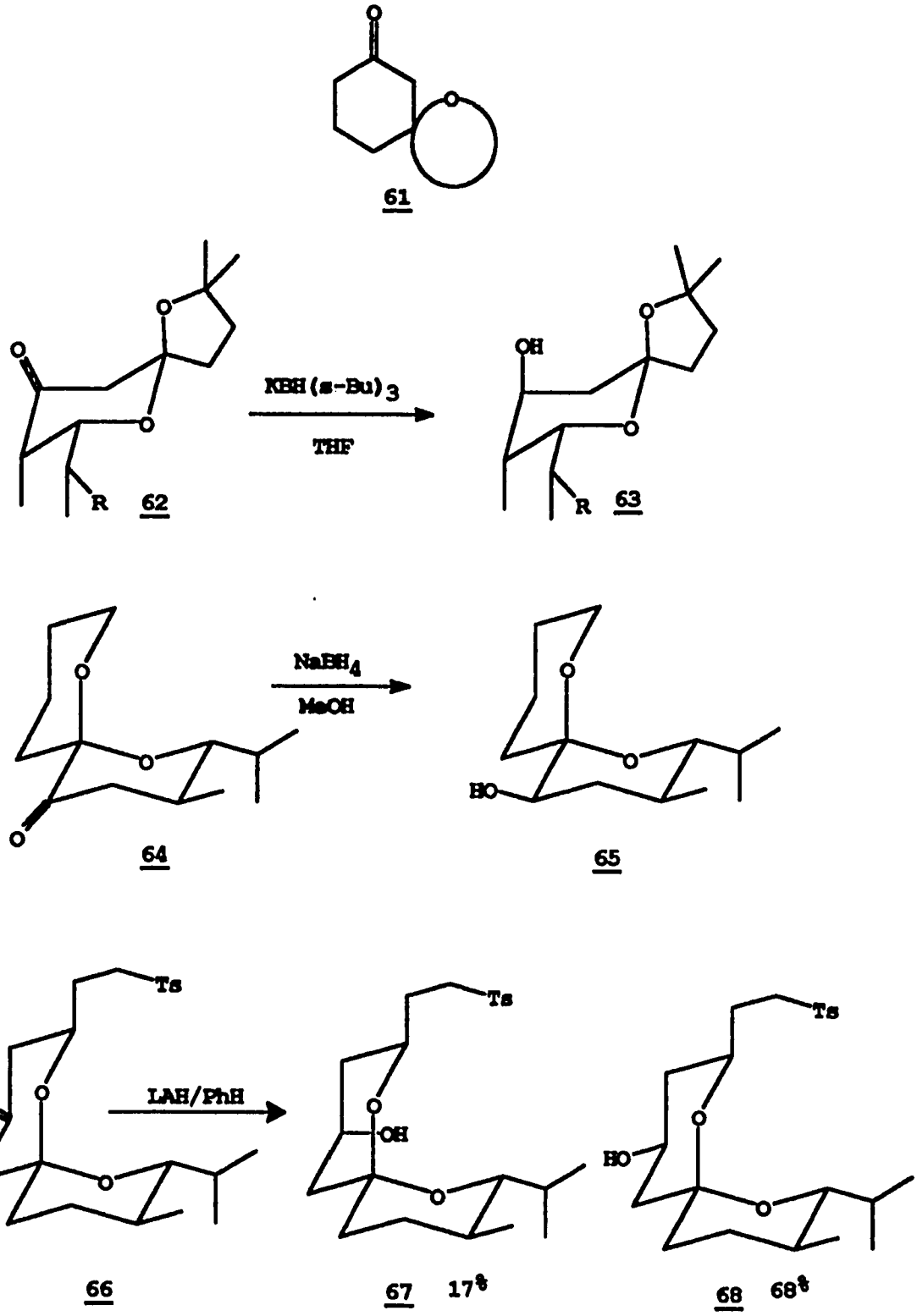
1.4.2. Reductions in Spiroketal Systems

The reduction of the tetrahydropyran-4-one derivative 60 has been studied most intently since many naturally occurring spiroketals possess hydroxyl groups at this position. The presence of the spiro center appears to impart a negligible effect on the stereoselectivity of ketone reductions. For example, bulky reducing agents that are known to produce axial alcohols with simple cyclohexanone derivatives also give predominantly axial alcohols in these systems as well[26]. In contrast, $NaBH_4$ and LAH give predominantly equatorial alcohols[21] (Scheme 13).



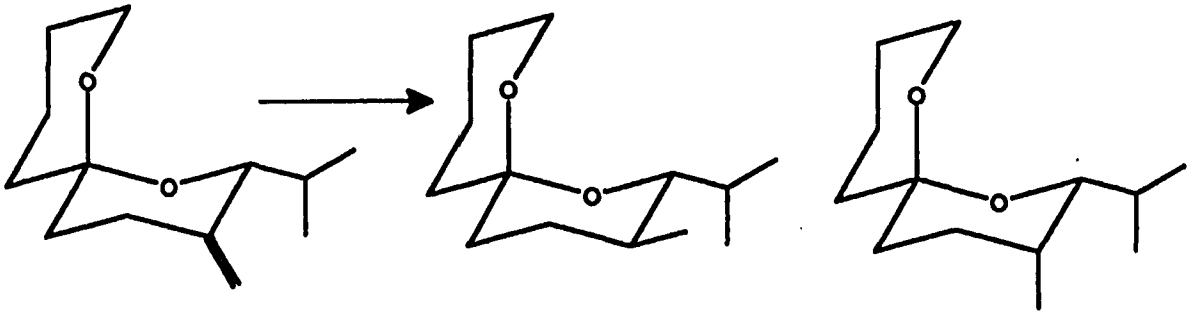
60

SCHEME 13


61
KBH(s-Bu)3
THF
OH
R
62
63
NaBH4
MeOH
HO
64
65
Ts
LAH/PhH
OH
66
67
17%
68
68%

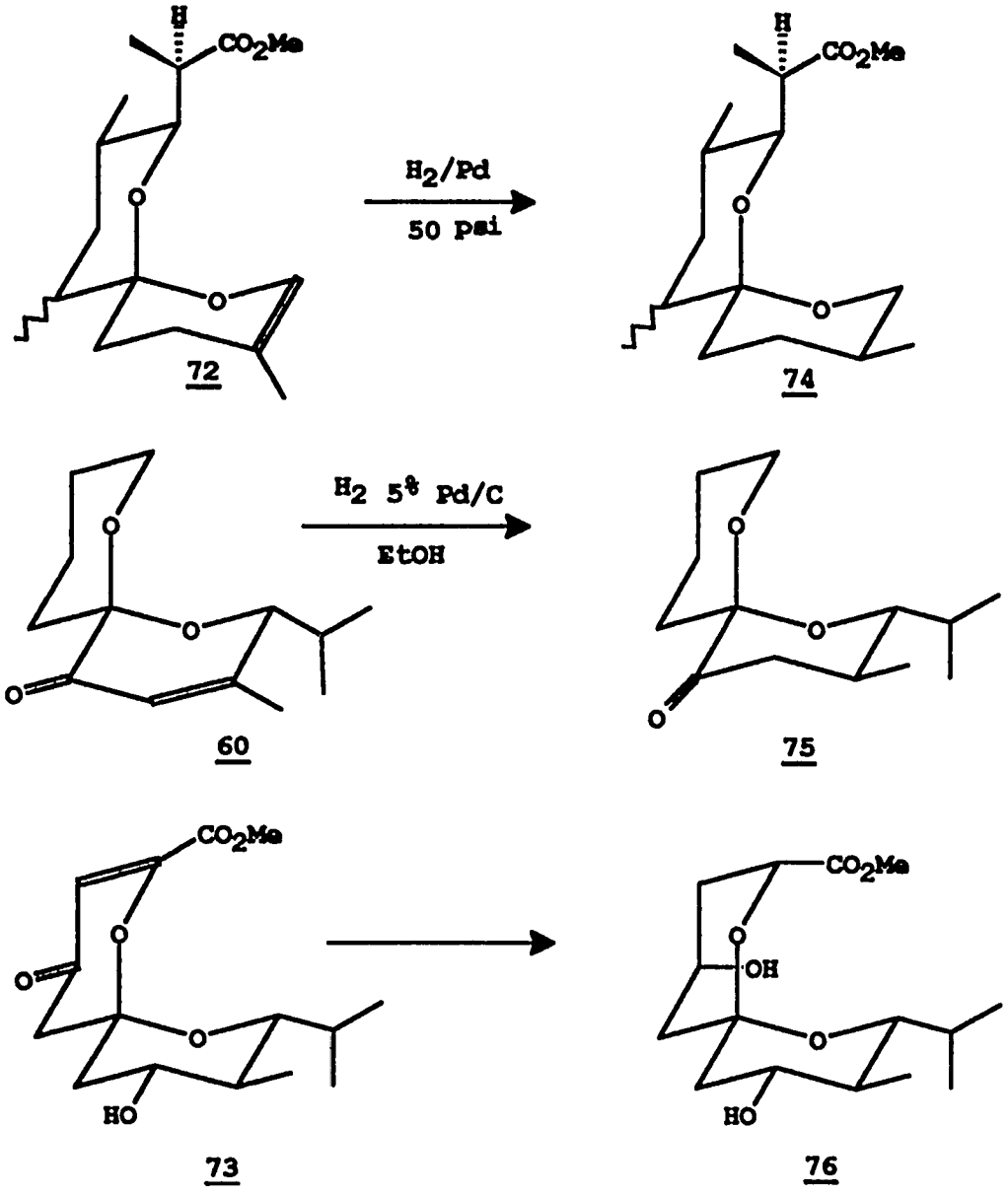
Reduction of C=C in spiroketal systems which establish relative stereochemistry have only been studied systematically in a few cases, and do not proceed with a high degree of stereoselectivity. In a study of exocyclic olefin reduction of the substrate 69, Deshong[21] found that metal-catalyzed hydrogenation gave the axial methyl isomer as the major product, whereas reduction with diimide gave a slight predominance of the equatorial methyl isomer, (Scheme 14).

SCHEME 14



69	70	71
H_2 $(Ph_3P)_3RhCl$	1.0	2.3
H_2 5% Rh/Alumina	1.0	3.0
H_2 Ra-Ni	1.0	6.6
H_2 10% Pt/Alumina	1.0	1.0
Diimide/THF	1.2	1.0
Diimide/Et_2O	1.6	1.0

SCHEME 15


H
CO2Me
O
O
72
H2/Pd
50 psi
H
CO2Me
O
O
74
O
O
O
60
H2 5% Pd/C
EtOH
O
O
O
75
CO2Me
O
O
O
HO
73
CO2Me
O
OH
O
HO
76

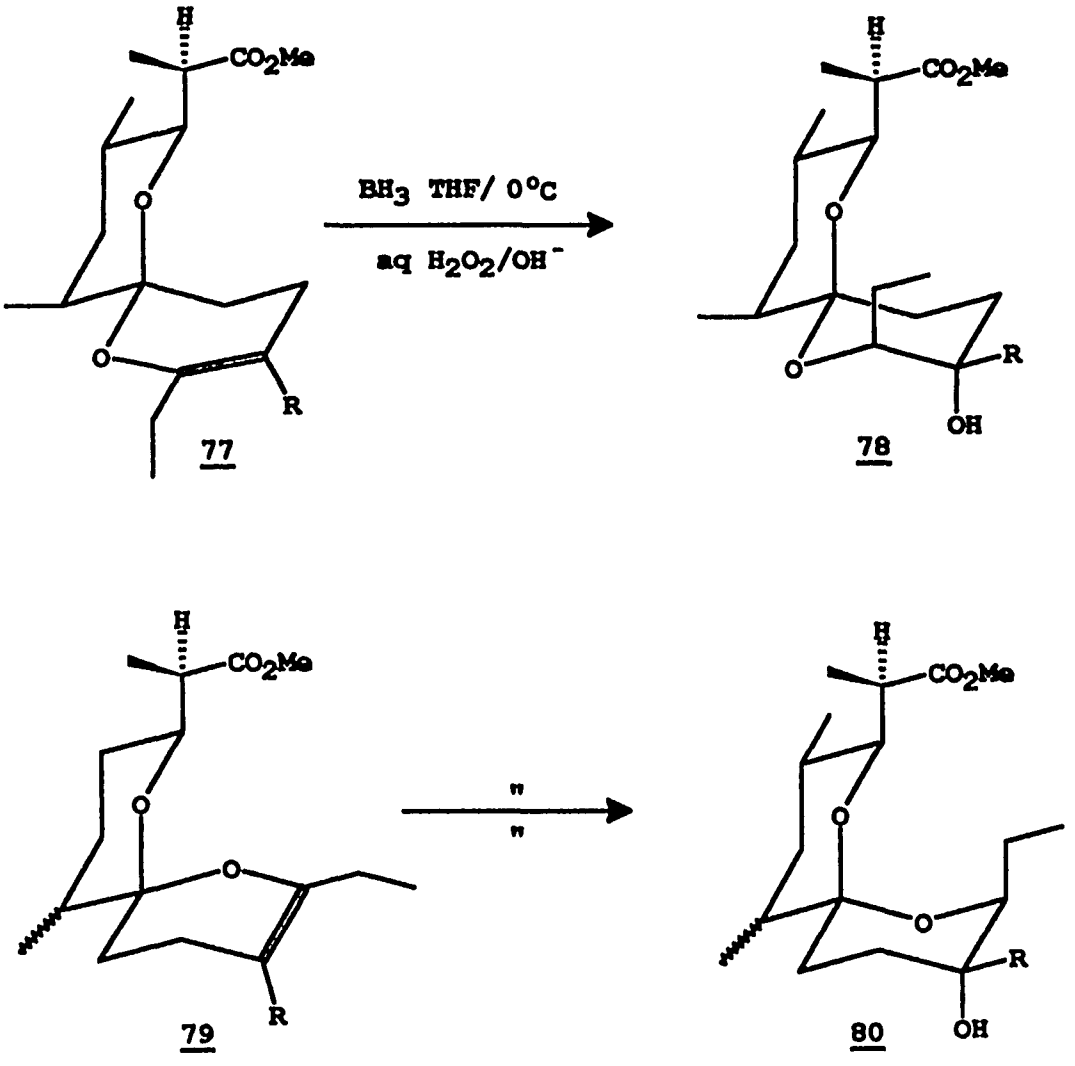
Endocyclic olefin reduction has been studied in only a few cases. Reduction of the anomerically maximized spiroketals 72, 60 and 73 (Scheme 15)[29] all proceed primarily, if not exclusively, from equivalent and least hindered faces of the olefins to provide the saturated spiroketals 74, 75 and 76. These results show that adition to endocyclic olefins in the spiro[5.5] ring system can be highly stereoselective, and tends to occur from the side of the molecule away from the axial bond at the spiro carbon.

1.4.3. Electrophilic and related Addition Reactions

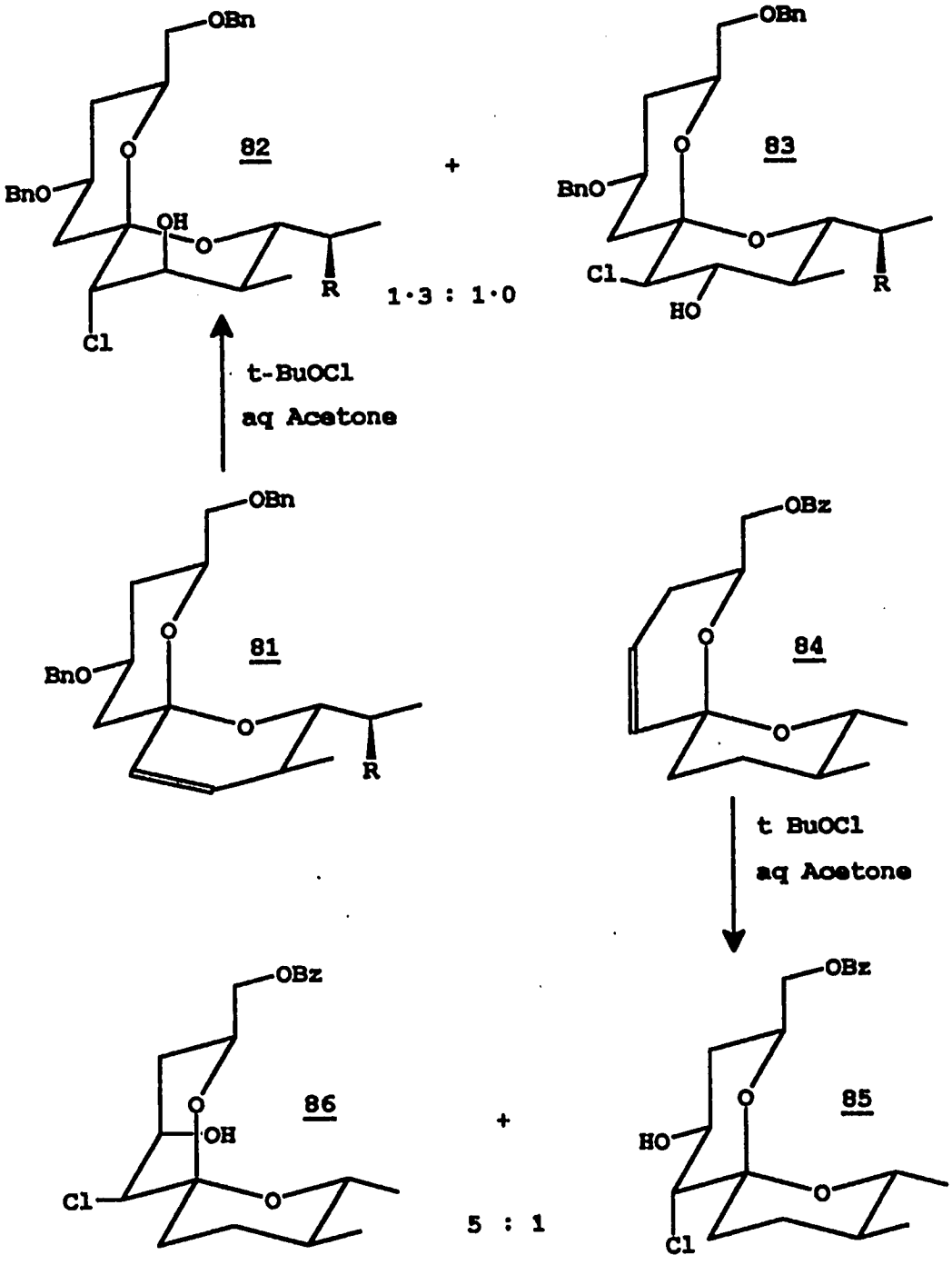
Hydroboration of endocyclic olefins tends to occur from the side of the ring away from the axial bond at the spiro carbon. Ireland repeatedly observed this phenomenon and typical cases are shown in Scheme 16[30].

Addition of electrophiles to olefins in the α,β position proceeds with decreased stereoselectivity but with high regiospecificity in the few reported examples. Electrophilic chlorohydroxylation (Scheme 17) of spiroketal 81 and 84 proceeds with variable stereoselectivity[31], but in each case only the isomers with the chlorine closest to the spiro center is observed. The rationale put forward by Williams[32], that this observed selectivity might be attributed to the inductive electron-withdrawing effect of the two oxygen atoms attached to the spiro carbon, is perhaps largely empirical. A more detailed and more plausible explanation can be had by considering the relative stabilities of the developing carbocations, and lone pair interactions. Scheme 18 depicts the possible intermediates that are formed, in which the carbon α to the quaternary (spiro) center is not easily attacked, as in a neopentyl system. In addition, lone pair interactions between the approaching nucleophile and the spiro-oxygens result repulsion of the nucleophile. Thus structure 81c would be less stable and so more reactive than structure 81b, resulting in the exclusive formation of the α-chloro compound.

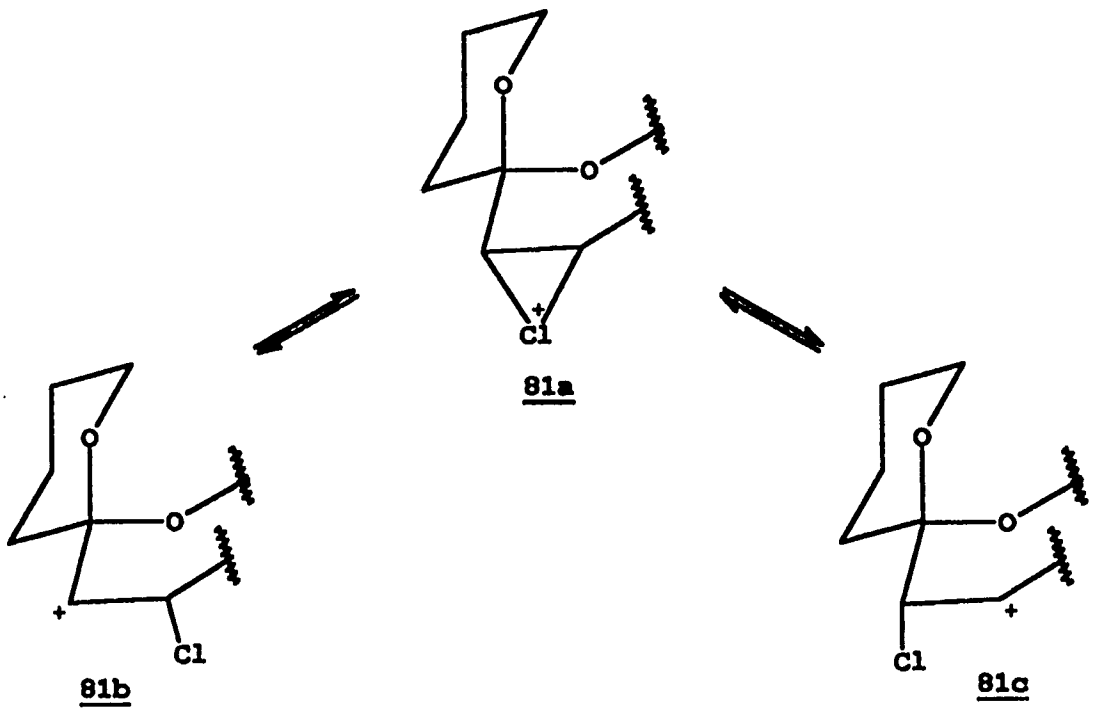
SCHEME 16


H
CO2Me
O
O
R
77
BH3 THF/ 0°C
aq H2O2/OH-
H
CO2Me
O
O
R
OH
78
H
CO2Me
O
O
R
79
n
n
H
CO2Me
O
O
R
OH
80

SCHEME 17


OBn
BnO
82
OH
O
R
Cl
+
OBn
BnO
83
O
Cl
HO
R
1·3 : 1·0
t-BuOCl
aq Acetone
OBn
BnO
81
O
R
OBz
84
O
t BuOCl
aq Acetone
OBz
86
O
OH
Cl
O
+
5 : 1
OBz
HO
85
O
O
Cl

SCHEME 18



More stable
Less reactive

Less stable
More reactive

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CHAPTER 2

2.0.0. The Chemistry of Allylsilanes

2.0.1. Introduction to Organosilicon Chemistry

Organosilicon compounds have been known since 1863 when Friedel and Crafts[1] first reported the synthesis of tetraethylsilane from diethyl-zinc and silicon tetrachloride. The first systematic studies on organosilanes were carried out by Frederick S. Kipping and his co-workers at the university of Nottingham from 1898 to 1939[2], work which the American Chemical Society has memorialized by presenting the biannual Frederick Stanley Kipping award, for " distinguished achievements in research in organosilicon chemistry". It was not until the 1940's, however, that organosilicon chemistry bloomed following the success of the silicone polymers. Today, on the industrial and commercial side of the ledger, organosilanes are found in applications ranging from solutions to synthetic problems, to healthcare products and computer chips. On the research side of the ledger, silicon compounds are being studied theoretically, investigated as synthetic reagents, and pushed even further in the quest for more knowledge of just what silicon can achieve in terms of its bonding. Silicon has the outer electronic configuration $3s^2 3p^3 3d^0$, differing from carbon in its possession of potentially low energy *d*-orbitals, which can be used to expand the valency, or to allow back-bonding. Organic compounds of silicon are normally quadri-covalent, the stereochemistry and mechanism of reactions at the silicon atom having been clearly expounded[3]. Silicon's utility in organic synthesis is largely attributed to the three main factors listed below[3b].

2.0.2. Relative Bond Strengths

From Table 1[4] below, it can be seen that, whereas silicon's bonds to oxygen and fluorine are stronger than the bonds between carbon and these elements, its bonds to carbon and hydrogen are weaker. Such characteristics give rise to a wide range of thermodynamically favorable processes.

Table 1

Some Values of Bond Energies(kJ/mol)

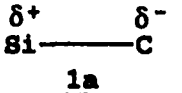
Si-F	540-570	C-F	440-465
Si-O	370-450	C-O	350-360
Si-C	230-320	C-C	347
Si-H	290-320	C-H	414

2.0.3. Vacant Low-energied *d*-Orbitals

These orbitals[5] are of suitable energy for back-bonding with a filled 2p orbital on an adjacent atom of a first-row element, enabling silicon to stabilize, for example, an adjacent carbanion. They can also be involved in substitution reactions at the silicon[3] or at an adjacent atom[6].

2.0.4. Relative Electronegativity

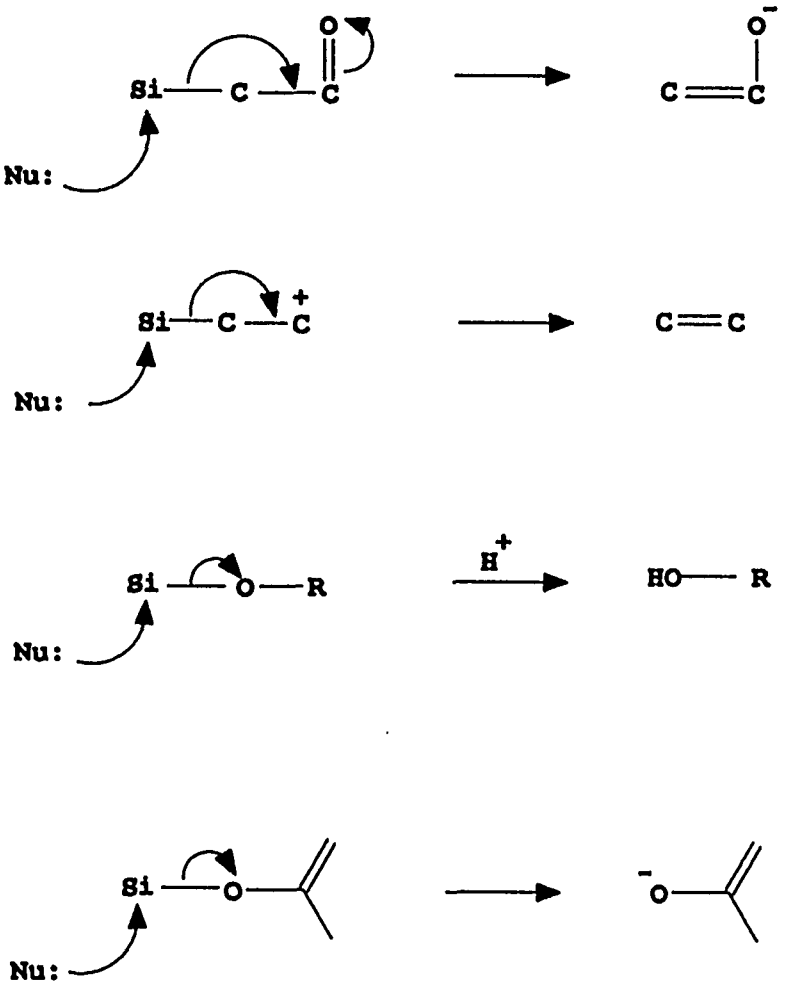
Silicon has a Pauling electronegativity of 1.90, and carbon and oxygen have values of 2.55 and 3.44 respectively, thus making silicon-carbon and silicon-oxygen bonds polarized, 1, and therefore susceptible to nucleophilic attack at silicon. This leads to bond heterolysis, especially when the carbon fragment being expelled is a good leaving group, as exemplified in Scheme 1.



1a

1b

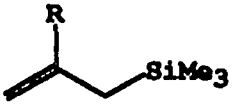
SCHEME 1



A further profound property, is the ability of a silicon-carbon bond to stabilize an adjacent carbocation 2; this phenomenon can be compared to the hyperconjugative situation in 3.

2.1.0. The Allylsilanes

Allylsilanes, 4, are exceptionally versatile organosilicon compounds with a well-established function in organic synthesis due to their undergoing, under mild conditions, highly regio- and stereocontrolled carbon-carbon bond formation. They have been widely used for the allylation of most classes of electrophiles, notably in conjugate additions (the Sakurai reaction) and in controlling polyene cyclizations[7]. Consequently, it is invaluable that general methods for their preparation be found, some of which are outlined below[7b].

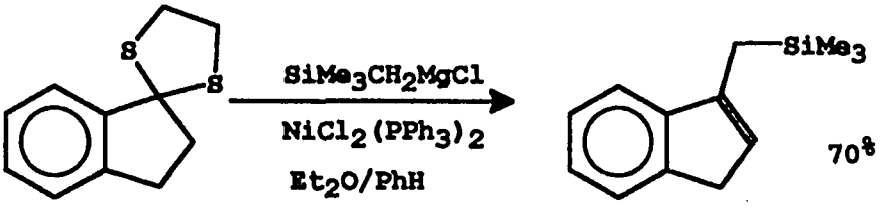


4

2.1.1. Allylsilanes from Dithioketals

Dithioketals react with Grignard reagents in the presence of a nickel catalyst to give a regioisomeric mixture of alkenes[8]. Ni and Luh considered that introduction of a

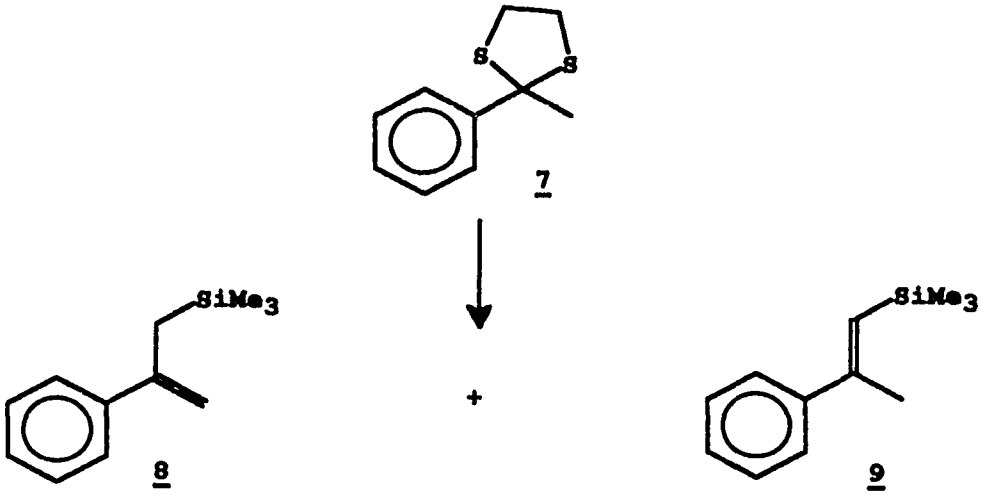
SCHEME 2



5 6

bulky trimethylsilyl group into the starting Grignard reagent would give intermediates $(RCH_2)ArC(CH_2SiMe_3)[Ni]$. In order to release the steric congestion, these intermediates did undergo regioselective elimination to yield alkenylsilanes exclusively.

SCHEME 3

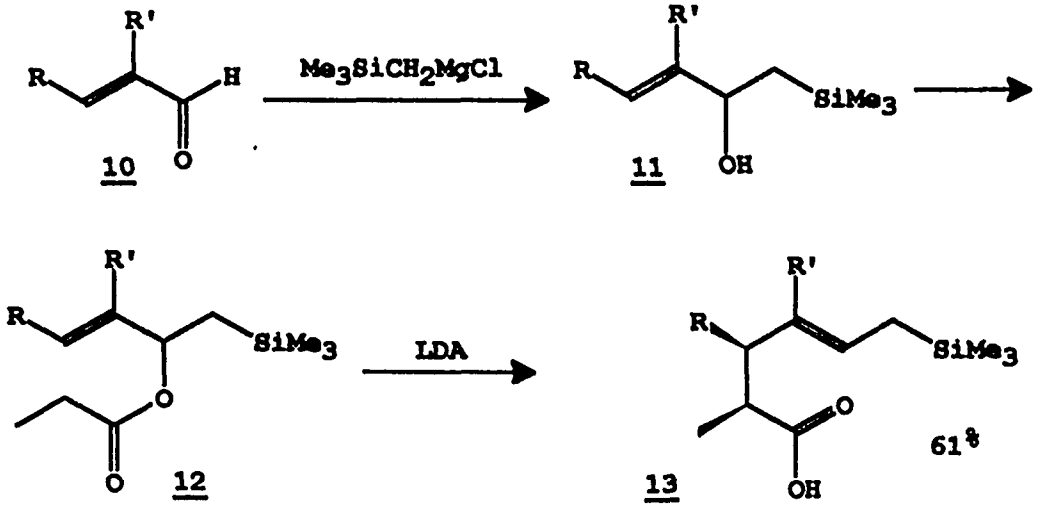


5.7 : 1.0

2.1.2. Ester-enolate Claisen Rearrangement

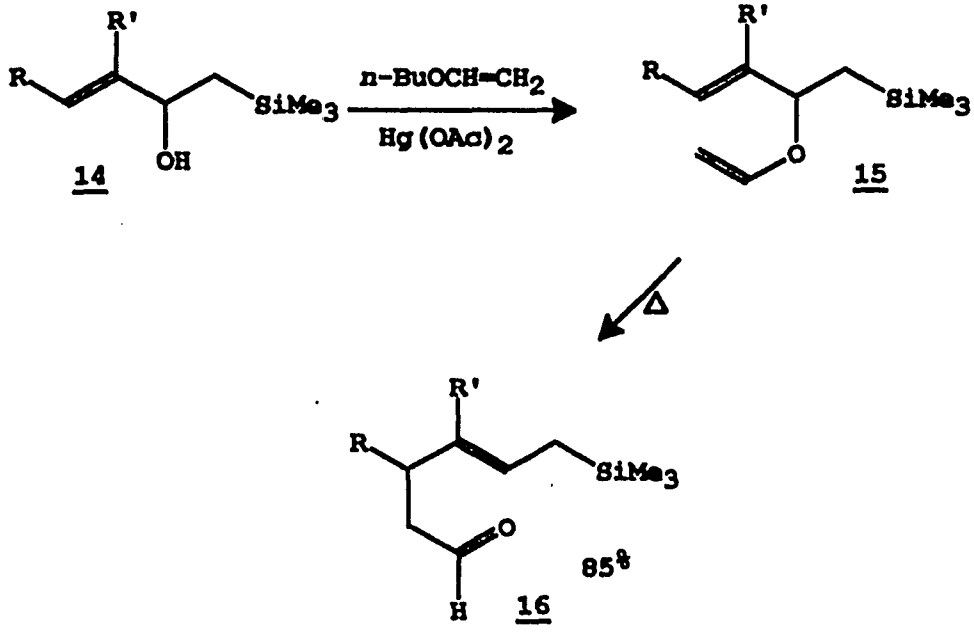
The selectivity of the Claisen rearrangement is a consequence of the highly ordered transition state, a feature it has in common with the Diels-Alder reaction.

SCHEME 4



Wilson and Price exploited this technology in the synthesis of functionalized allylsilanes[9]. Similar allylsilanes are obtained by the Claisen rearrangement of vinyl ethers[9].

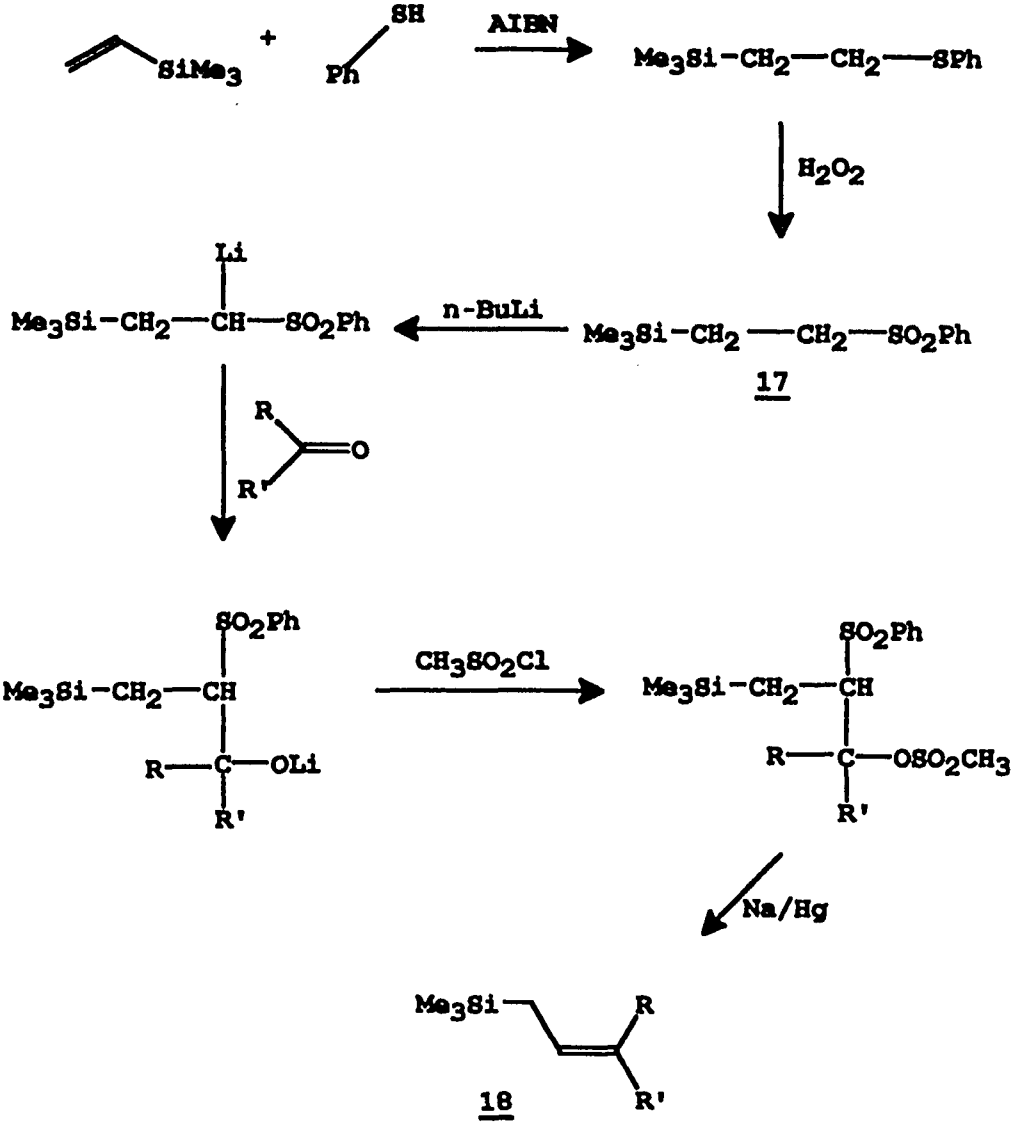
SCHEME 5



2.1.3. From 1-Benzenesulfonyl-2-trimethylsilyl ethane

The methodology developed by Shechter *et al* converted a wide variety of aldehydes and ketones to allylsilanes in excellent yields (85-95%) and on large scales[10]. The sequence for the preparation of the allylsilane 18 from 17 is summarized in the Scheme 6 below.

SCHEME 6

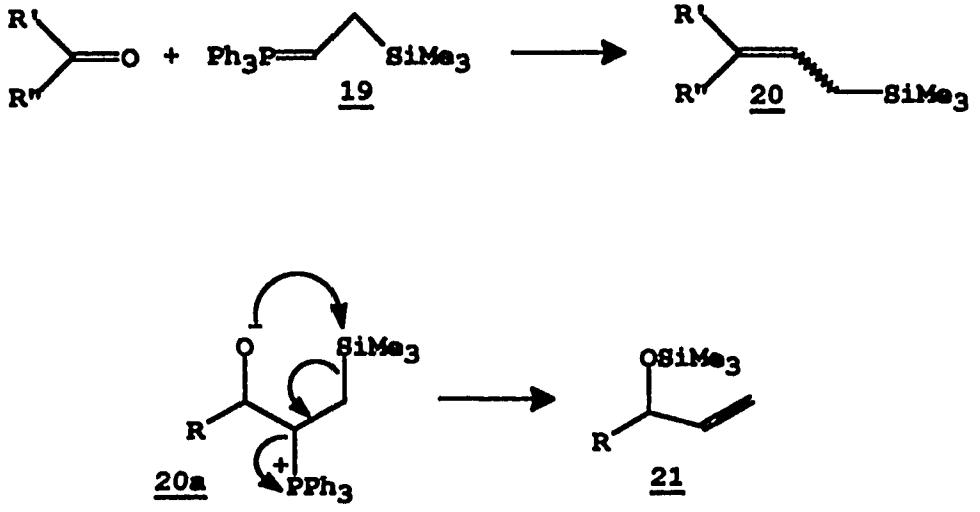


2.1.4. Wittig Route to Allylsilanes

Allylsilanes are produced when carbonyl compounds are treated with the Seyferth-Fleming ylid[11,12], 19. The method works particularly well for aldehydes and some reactive ketones, such as cyclohexanone and acetophenone, but gives poor yields with cyclopentanone and when there is an alkyl substituent on C2 in the ylide[13]. Other

shortcomings of this method include the lack of E/Z stereoselectivity of the Wittig product, the difficulty in extending this protocol to the preparation of allylsilanes with a substituent on C1, as there is no easy way to make the requisite ylides, and the formation of the silyl group rearrangement product 21 via the betaine 20a, or the corresponding pentacoordinate silicon species by eliminative 1,4(C-O) migration[14].

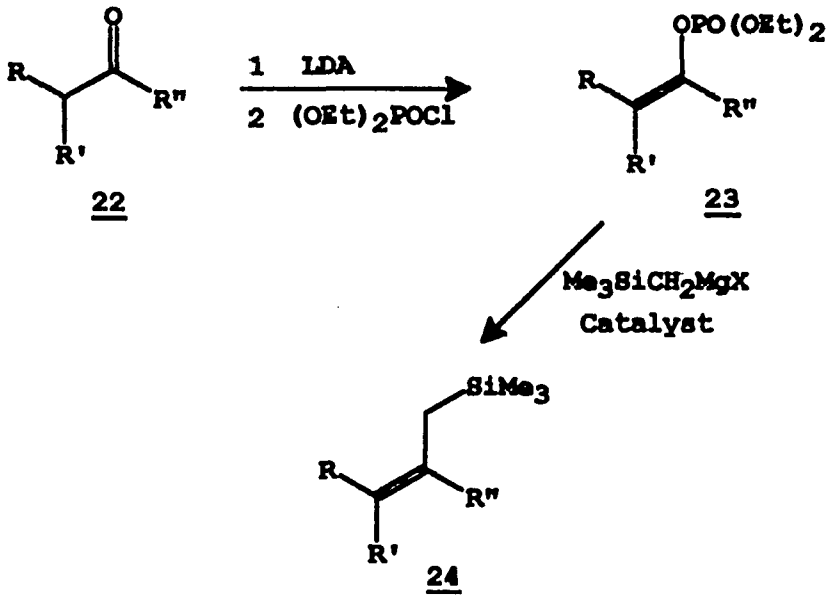
SCHEME 7



2.1.5. Transition Metal Catalyzed Cross-Coupling Reactions

A very useful procedure for the synthesis of allylsilanes involves coupling of enol silyl ethers, enol phosphates, vinyl and aryl halides as well as vinyl triflates with appropriate Grignard or related reagents in the presence of transition metal catalysts[15-18].

SCHEME 8



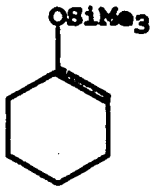
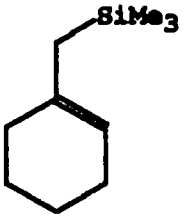
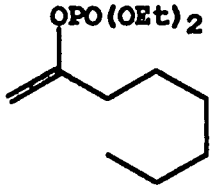
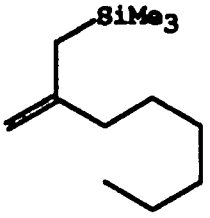
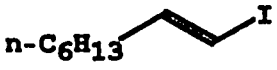
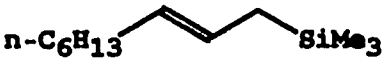
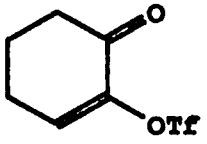
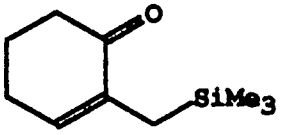
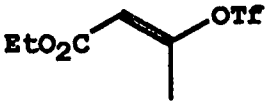
22 23 24

While the cross-coupling procedure involving enol silyl ethers and enol phosphates with trimethylsilylmethyl magnesium halide are conceptually similar and give similar yields of allylsilanes, the latter process may prove advantageous in some cases as it proceeds without isomerization of the C=C double bond, Table 2. A recent chemoselective synthesis of functionalized allylsilanes entailed Pd(0) catalyzed cross-coupling of vinyl triflates with tris(trimethylsilylmethyl)aluminum. This method is compatible with the presence of reactive functionalities such as α,β-unsaturated esters, allyl alcohols or aryl bromides in the substrate[18]. The reaction is stereospecific, (Table 2).

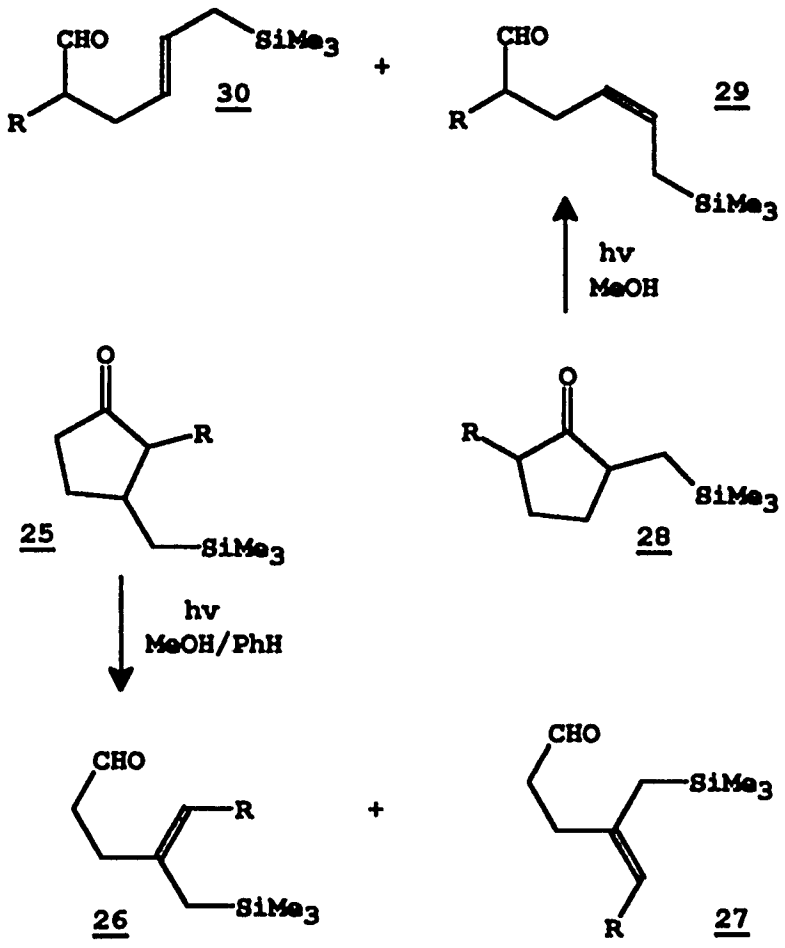
2.1.6. Photochemical Synthesis

Very recently a photochemical synthesis of allylsilane carbaldehyde has been reported[19]. Photolytic cleavage of 2-trimethylsilylmethylcycloalkanones, by Norrish type I process, gave the E-allylsilane as the main product, whilst 3-trimethylsilylmethylcycloalkanones using benzene/methanol as solvent gave the Z-allylsilane 26 as the major product.

TABLE 2

SUBSTRATE	CATALYST	ALLYLSILANE	YIELD(%)
	$Ni(acac)_2$		71
	$NiBr_2$		92
	$Ni(PPh_3)_4$		74
	$Pd(PPh_3)_4$		60
	$Pd(PPh_3)_4$		48

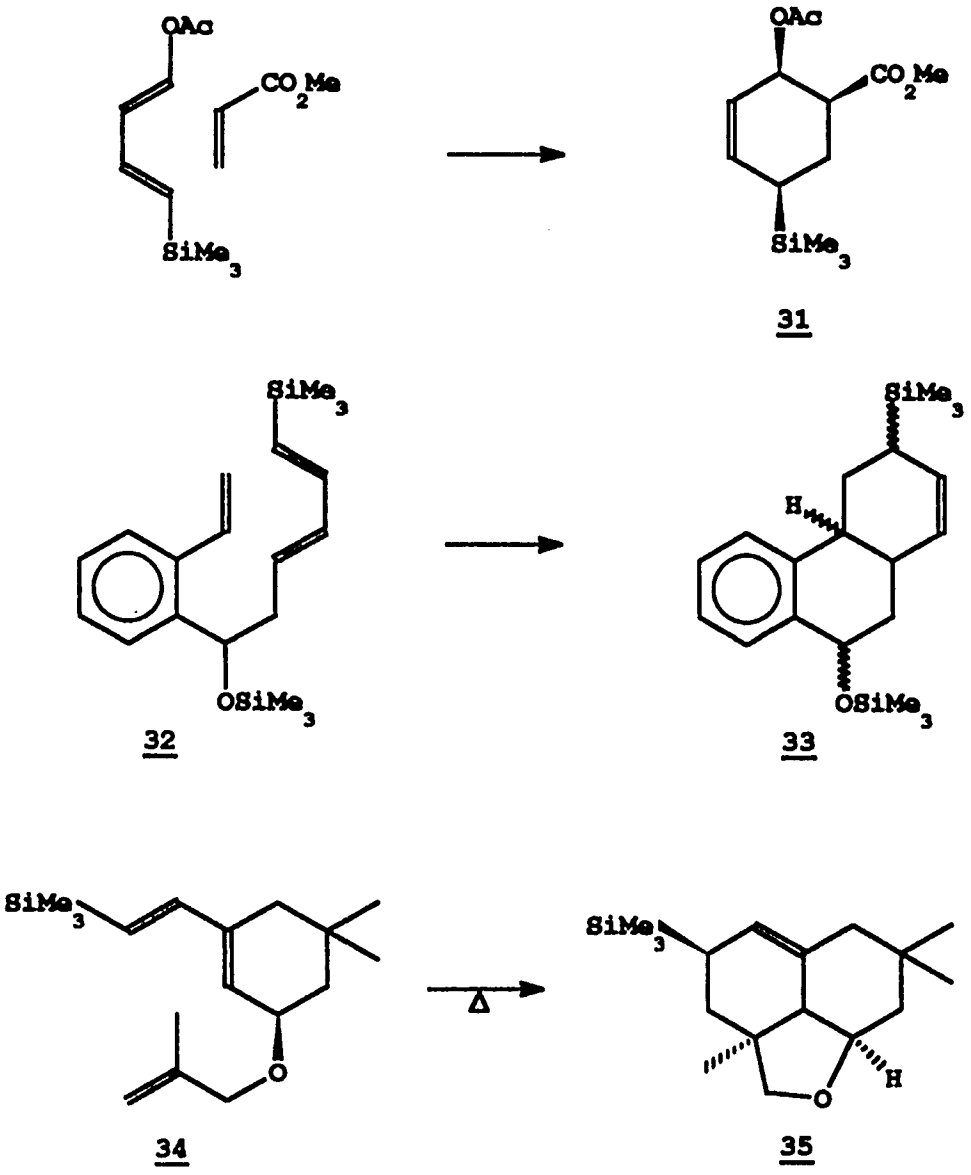
SCHEME 9



2.1.7. Diels-Alder and Ene Reactions

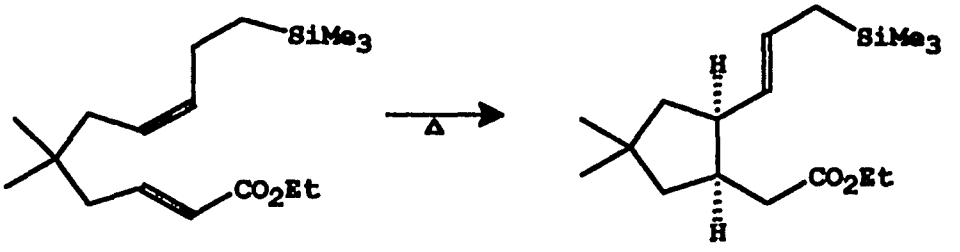
The availability of silylated 1,3-dienes has encouraged their use as synthons in Diels-Alder reactions leading to highly functionalized allylsilanes[20], Scheme 10. More complex allylsilanes are made via intramolecular Diels-Alder reactions[21,22].

SCHEME 10



A general route to *cis*-1,2-disubstituted cyclopentanoid allylsilanes hinges on the intramolecular ene reactions of activated 1,6-dienes, featuring a homoallylsilane unit as the ene donor[23], Scheme 11.

SCHEME 11

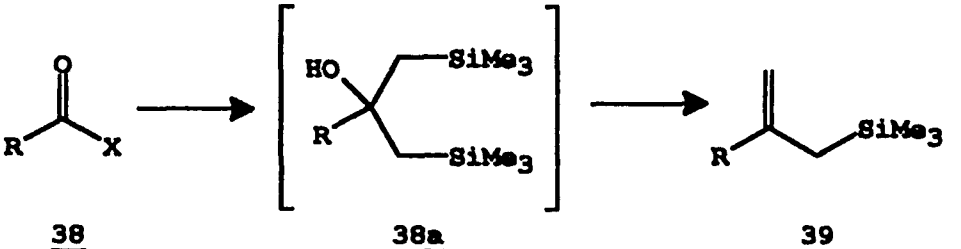


36 37

2.1.8. The Use of Organocerium Reagents

The use of carboxylic acid derivatives as functional precursors for allylsilanes has been explored. Thus a two-fold addition of trimethylsilylmethylmagnesium chloride to an ester, followed by deoxysilylation of the resulting bis(β-silyl)alcohol 38a, provides ready access to the allylsilane[24], 39.

SCHEME 12



38 38a 39

Acid chlorides and lactones are also suitable substrates for this procedure. In general, overall yields for this process are not very high, and the reaction fails completely for esters of α-branched carboxylic acids, such as methyl cyclohexanecarboxylate. A recent improvement of this procedure entails the use of trimethylcerium dichloride prepared from cerium (III) chloride and trimethylsilylmethylmagnesium chloride[25].

In our laboratory, we have been successful in improving this methodology even further, providing highly functionalized allylsilanes in excellent yields[26]. This is the subject of Chapter 4.

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CHAPTER 3

3.0.0. Research Design

3.0.1. Introduction

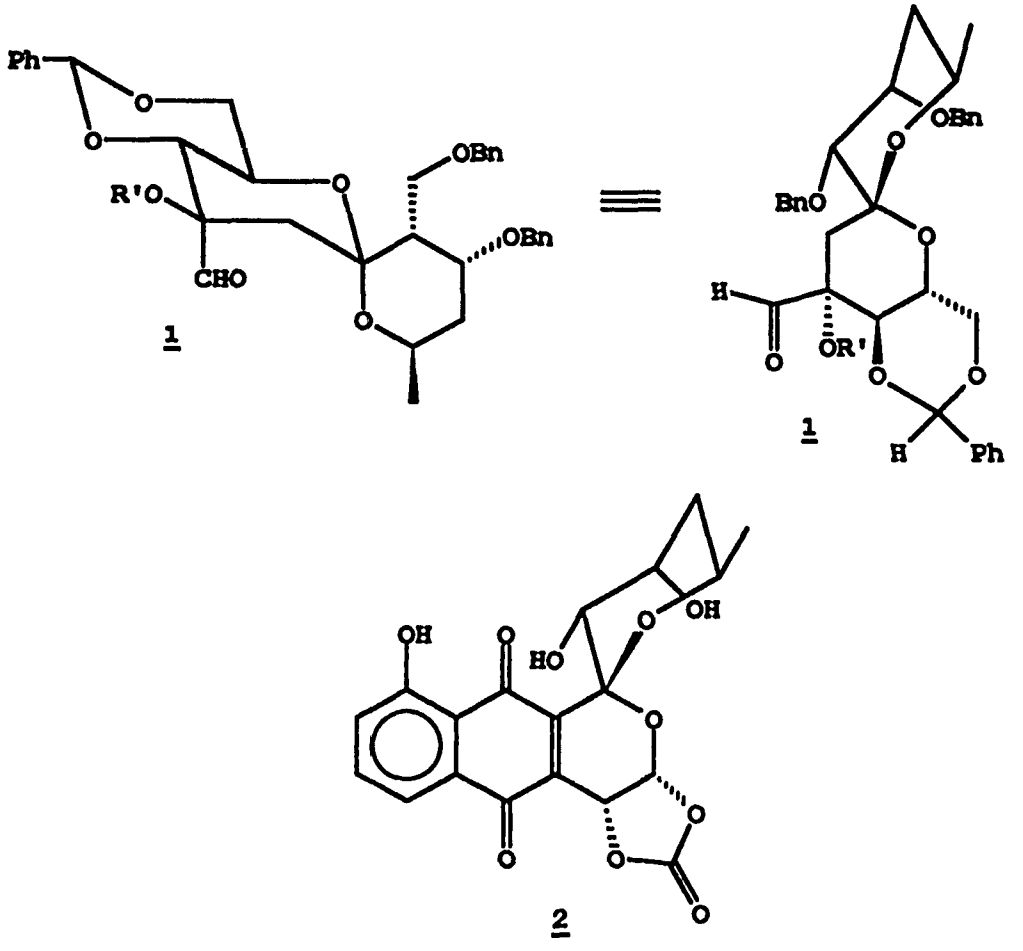
Chapter 1 gave a brief summary of the more versatile synthetic methods for approaching spiroketal substructures[1]. Of particular interest to us are spiroketal sub-units having stercocenters at both of the carbons which are directly attached to the spiro carbon.

An intriguing structural feature of spiroketals in general, is the close resemblance to two highly deoxygenated monosaccharide units fused at one common carbon, and it is on this concept that we have developed this methodology of using the monosaccharides as synthons.

3.1.0. Retrosynthetic Analysis, Purpose and Strategy

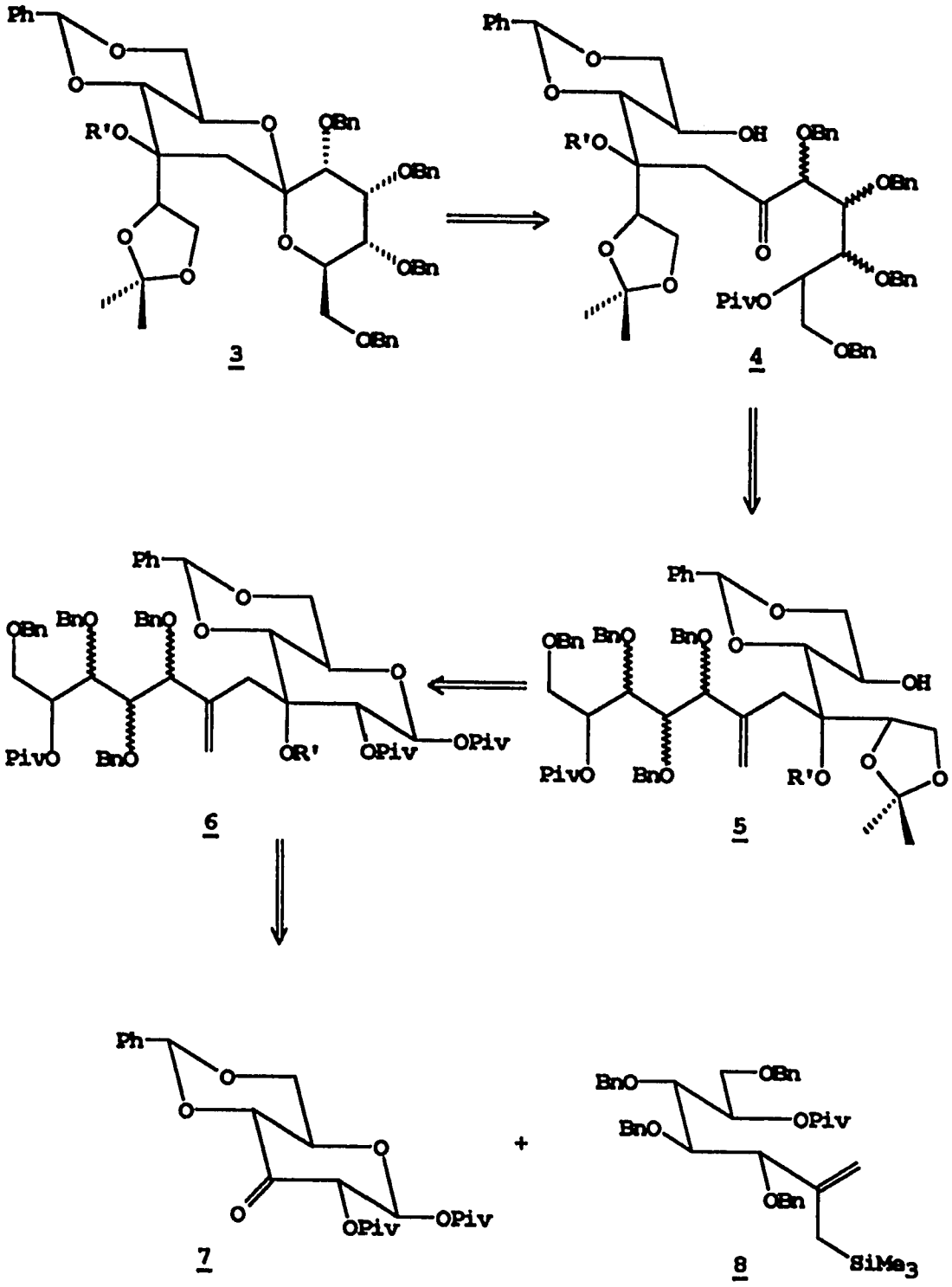
Our main objective was to develop two routes to saccharidic spiroketals; one leading to *griseusin* 2, and the other to *acanthafolicin* 9. Convergent synthetic methodology would be employed in both cases.

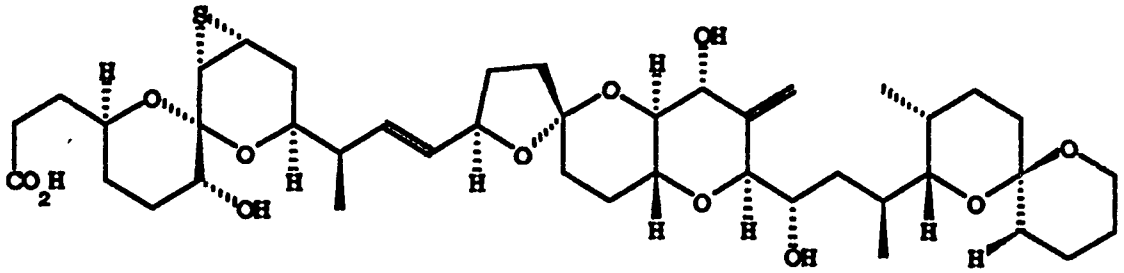
Scheme 1 depicts the retrosynthetic analysis of the *griseusin* strategy which involves the formation of one carbon-carbon bond followed by a C(3) re-organization of the resulting allyl branched-chain sugar[2] and subsequent spiro-ketalization to compound 3. The spiroketal 3 could be converted to compound 1, or taken directly into the synthesis of an analog of griseusin[3], 2.



Scheme 2 illustrates the second approach leading to the spiroketal moiety of *acanthafolicin*[4], 9. Thus, utilizing the allylsilane 8 will provide us with the spiroketal subunit 10, which contains the 1,7-dioxaspiro[5.5]undecane ring system. Similarly, the 1,7-dioxaspiro[4.5]decane ring system would be synthesized by using the allylsilane 20 in a similar sequence of reactions, Scheme 5.

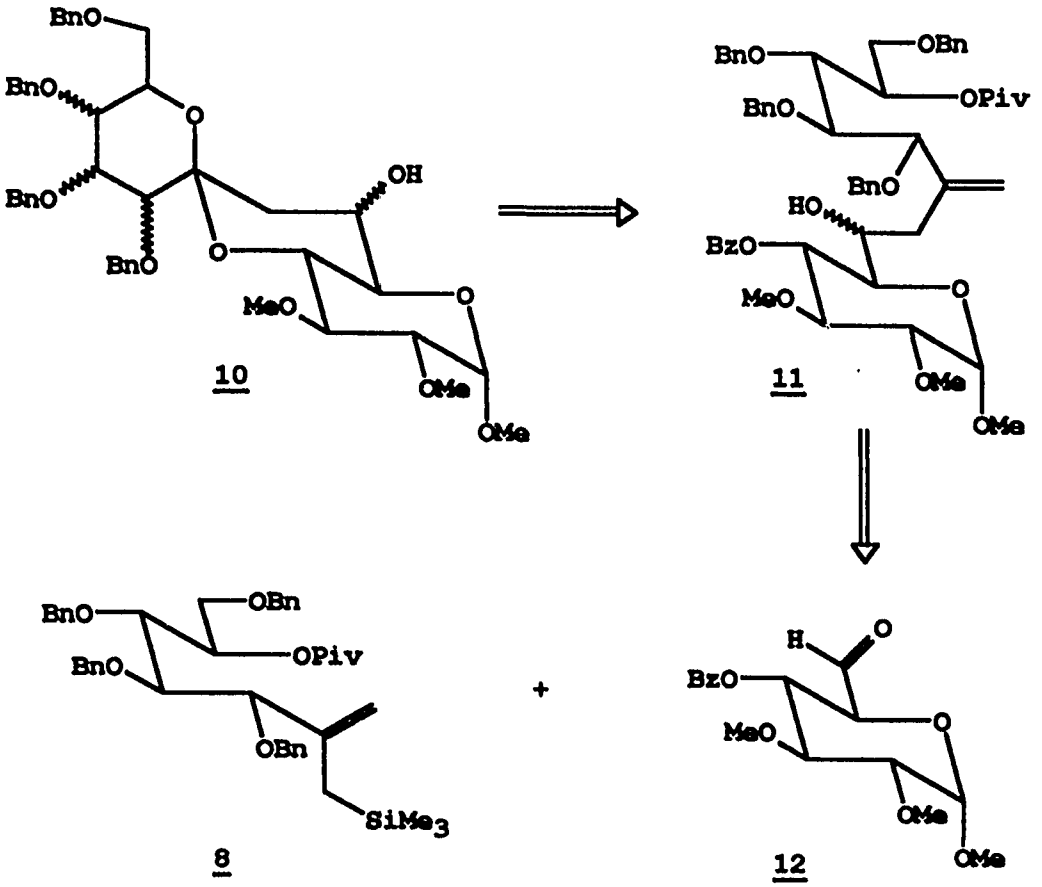
SCHEME 1


Ph
R'O
OBn
OBn
OBn
OBn
3
Ph
OH
R'O
OBn
OBn
O
PivO
OBn
OBn
4
Ph
OBn
BnO
BnO
PivO
BnO
OR'
OPiv
OPiv
6
Ph
OBn
BnO
BnO
OH
PivO
BnO
R'O
5
Ph
OPiv
OPiv
7
+
BnO
OBn
BnO
OPiv
OBn
SiMe3
8



9

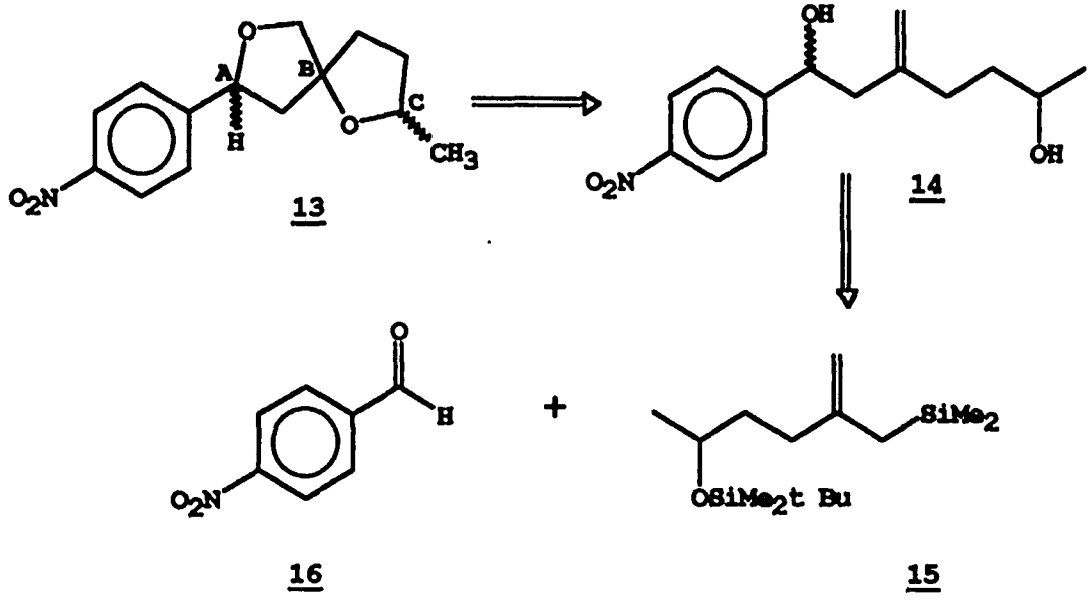
SCHEME 2


BnO
BnO
BnO
BnO
OH
O
MeO
OMe
OMe
10
OBn
OPiv
HO
BzO
11
OBn
OPiv
SiMe3
8
+
H
O
12

3.2.0. Preliminary Investigations Involving Functionalized Benzaldehydes

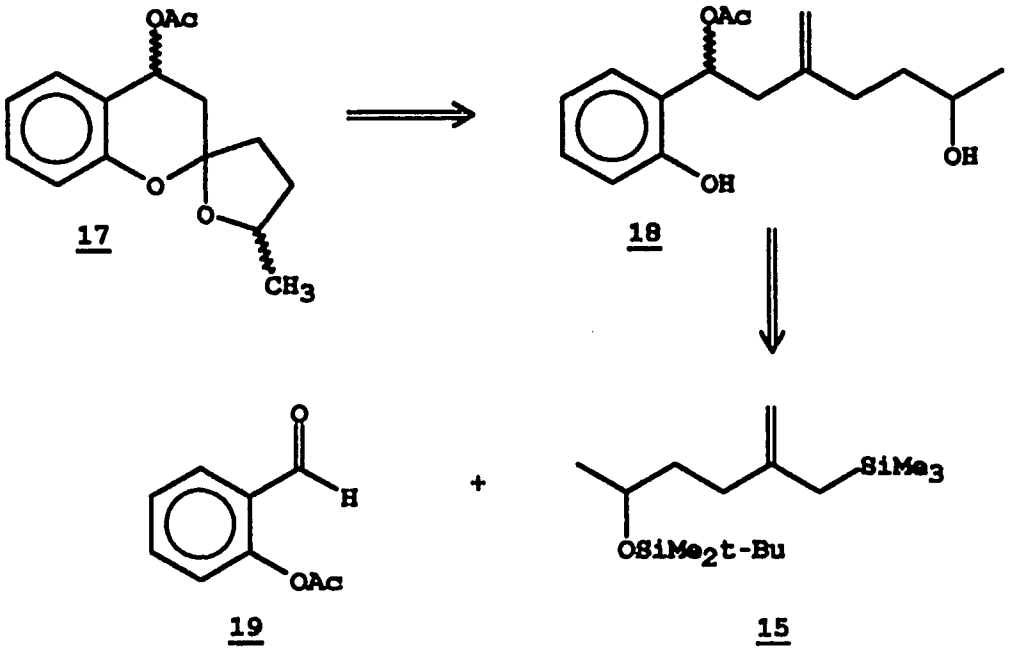
The technique of internal spiroketalization will be investigated, using simple benzaldehyde derivatives with the allylsilanes 8, 15, and 20. The proposed spiroketals and dioxaspirocompounds are exemplified in Schemes 3 and 4.

SCHEME 3



The di-oxaspirocompound 13 is particularly interesting in that we will be able to investigate the stereoselection at centers A and B with respect to C during the cyclization process. Naturally, the planar aryl group will not have any direct influence on the stereochemical outcome of the reaction. In a similar manner, we anticipate stereochemical control from C(2) at the benzylic center of compound 17 during the cyclization process, Scheme 4.

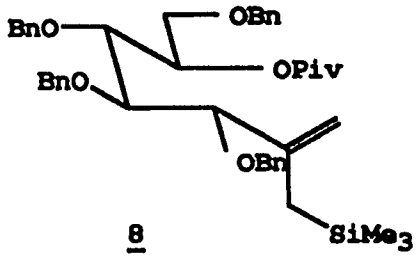
SCHEME 4



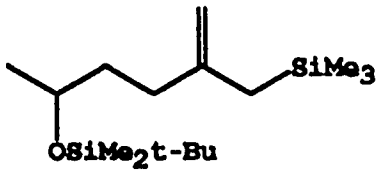
The allylsilanes **8** and **20** were chosen to provide us with preliminary stereochemical data in the reactions of chiral allylsilanes with the simple benzaldehydes. Indeed, marked differences in stereoselectivity are anticipated since the configuration at the carbon atom α to the allylsilane moiety, is reversed. It would also be interesting to see the effect of other stereocenters remote from this "active site" on the diastereoselection process.

A significant part of our investigations will thus include the development of a simple and general method for obtaining chiral allylsilanes from monosaccharides. Our initial targets will be the allylsilanes **8**, **15**, and **20** shown in Scheme 5.

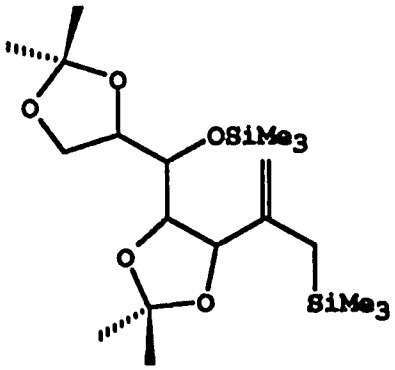
SCHEME 5



8



15



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CHAPTER 4

4.0.0. The Synthesis of Chiral Allylsilanes

4.1.0. Introduction

It was established in Chapter 2 that allylsilanes are exceptionally versatile compounds with a well-defined function in organic synthesis[1], hence general methods for their preparation are indeed invaluable. The synthesis of saccharidic allylsilanes is perhaps one of the more challenging feats in this area of chemistry. Using sugar halides as synthons for instance, in substitution reactions, is immediately ruled out since these reactions (both S_N1 and S_N2) are difficult and often lead to many products. The use of sugar lactones, on the other hand, offers a more versatile and general approach to allylsilane preparations. In addition to a minimization of the side reactions observed with sugar halides, sugar lactones are easily prepared in multigram quantities and are fairly stable.

The Grignard reagent Me_3SiCH_2MgCl has been used to convert simple, unbranched esters into allylsilanes, but the yields are only moderate and the process fails completely for more sterically conjested esters[3]. In these cases, the α-silylketone intermediate resists further addition, presumably suffering preferential enolization[4]. The use of organocerium reagents to circumvent this difficulty has been developed by two groups[2,5]. For instance, the reagent prepared from $CeCl_3$ and Me_3SiCH_2Li has been shown to be quite effective for the conversion of acid chlorides to allylsilanes, but does not react efficiently with esters[5]. Further investigations of this reaction were rewarded with the result that a mixture of $CeCl_3$ with Me_3SiCH_2MgCl, produces an improved reagent for the conversion of esters to allylsilanes[2].

4.2.0. Refining the Synthetic Methodology

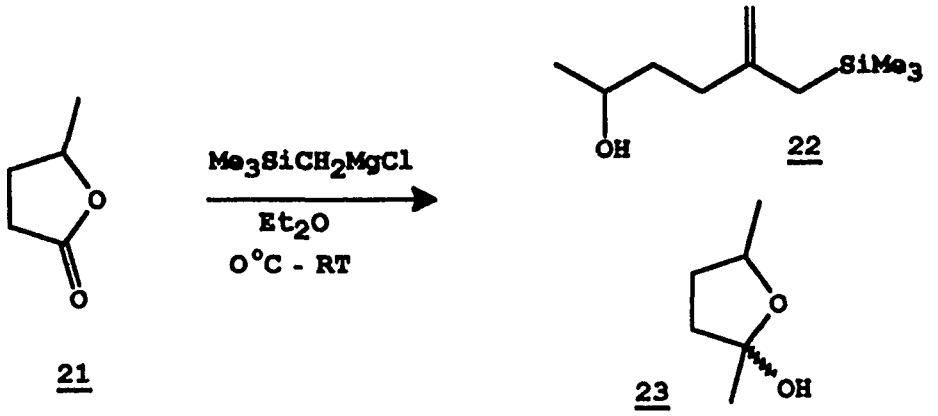
Even though the Narayanan-Bunnelle protocol[10] can be considered general, it is a procedure that is faced with some difficulty: (a) Cerium (III) chloride which is commercially available as the heptahydrate, must be completely dehydrated before being incorporated into the reaction; (b) there is a necessary full two-hour 'ageing' period that is required for best results, the implication of which is not understood; (c) the prescribed quantity of the Grignard reagent (and cerium salt) must be 25% more than stoichiometric in order to ensure complete consumption of the ester.

In light of these observations, one is left with the intriguing question addressing the mechanistic details of this reaction. Two possibilities readily come to mind; either that the proposed enolization process was being suppressed when cerium (III) chloride was added, or that the reaction was following a completely different reaction path, perhaps one involving radical species, again, through the intermediacy of the added cerium salt. On these grounds, we embarked on a thorough investigation of this reaction with the key objective of utilizing monosaccharide derivatives as synthons. This would allow us to take advantage of the natural chirality that exists within these molecules. We commenced our studies with the simple lactone γ-valerolactone, 21.

4.3.0. Allylsilane from γ-Valerolactone

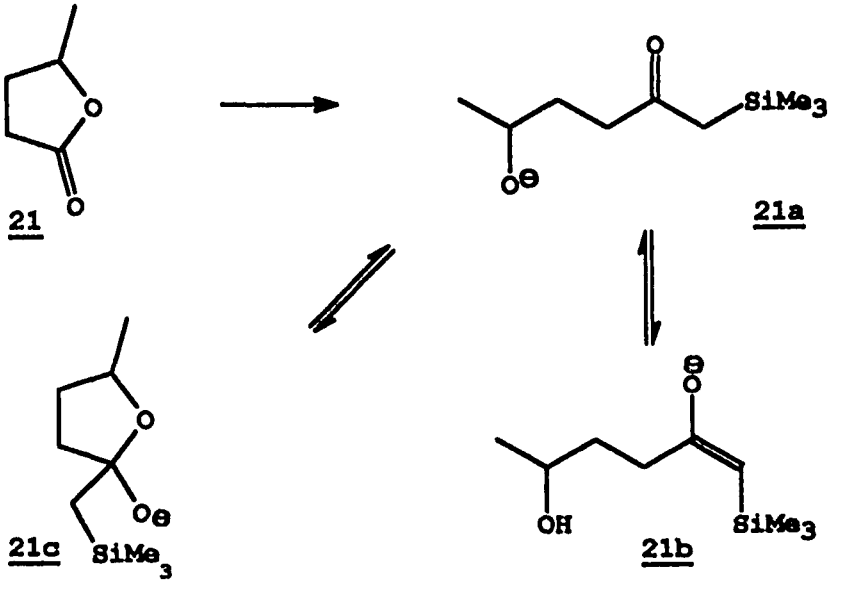
Treatment of the lactone 21 with 10 molar equivalents of the Grignard reagent (Me_3SiCH_2MgCl) in diethyl ether for up to four days gave the expected allylsilane 22, in 15% yield at best. The hemiketal 23 accounted for the major product of the reaction, (85%), Scheme 1.

SCHEME 1



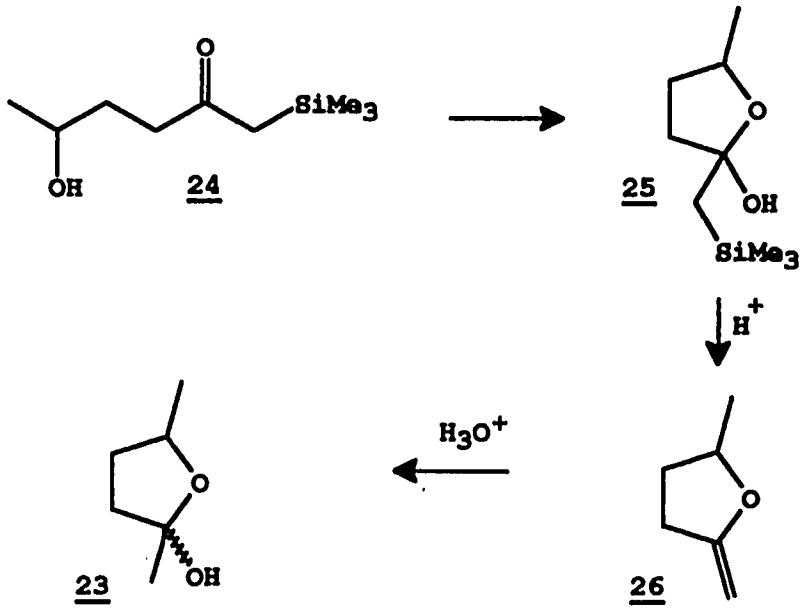
The low yield of the desired product 22 might be attributed to a competing enolization[2] of the α-silyl ketone by the secondary alkoxide generated in situ, thus defeating the second attack of the Grignard reagent, or was a consequence of lactol formation, Scheme 2.

SCHEME 2



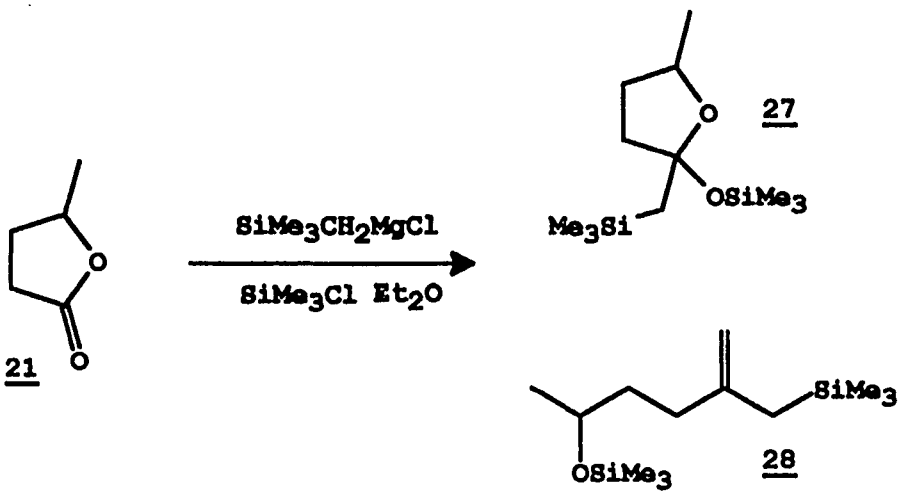
On protonation, the intermediate lactol or enolate, or both, was readily converted to the hemiketal 25 by which the major reaction product 23 was obtained on silica gel. A possible route to this conversion is shown in Scheme 3.

SCHEME 3

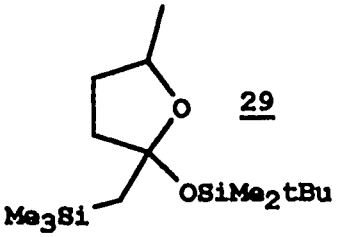


In light of these observations, we introduced a trapping agent, namely chlorotrimethylsilane, to capture the secondary alkoxide, thus preventing enolization of the ketone intermediate, or formation of the lactol, since silylation at a secondary hydroxyl function would occur faster than at a tertiary hydroxyl. The allylsilane, protected as its trimethylsilyl ether 28, was obtained; however, there was no significant improvement in the yield. Compound 27 accounted for the major product of the reaction, (80 - 87%), Scheme 4.

SCHEME 4

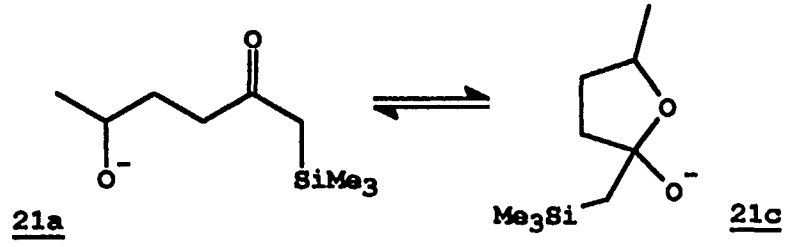


Surprisingly, with the more bulky blocking group, *tert*-butyldimethylchlorosilane, compound 29 was obtained exclusively.



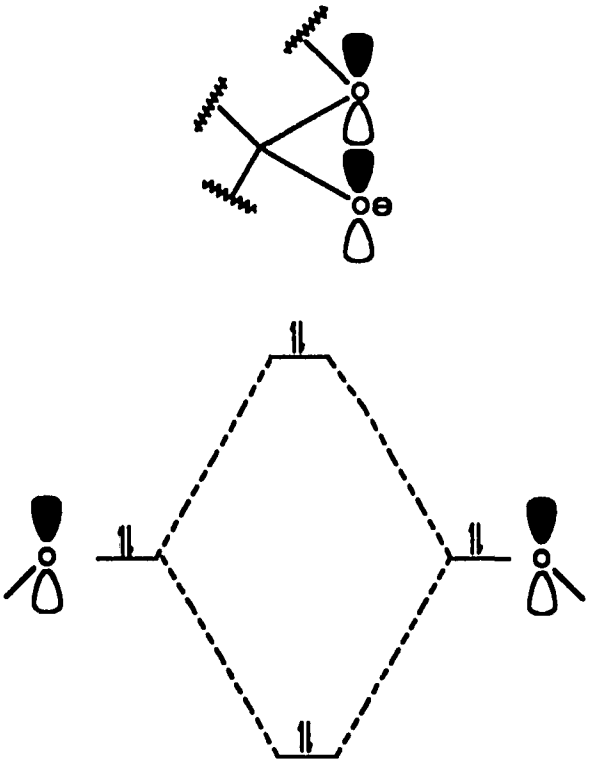
This observation is perhaps best explained by considering the equilibrium between the secondary alkoxide and the lactol, shown in Scheme 5.

SCHEME 5



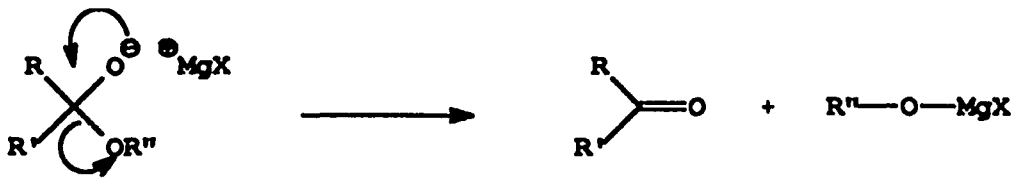
As logic dictated, the lactol **21c** would have been more stable than the secondary alkoxide **21a**, on the basis of steric and entropy factors, or there was an enhanced nucleophilicity of **21c** by the oxygen β-effect[6], Scheme 6, so making **21c** more reactive towards silylation. The fragmentation pattern shown in Scheme 7 below is known to occur fairly

SCHEME 6



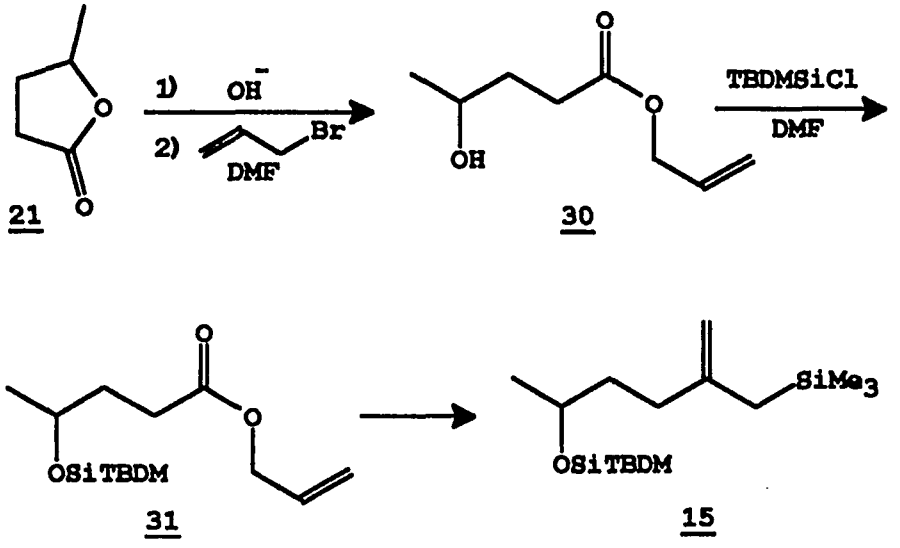
rapidly in sugar systems, suggesting a kinetic preference for the acyclic intermediate **21a** over **21c**. On these grounds, we therefore concluded that the major or exclusive formation of compounds **27** and **29** was a consequence of the enhanced nucleophilicity in the lactol **21c** by the β-effect. Indeed, if the equilibrium constant K_{eq} for the **21a** - **21c** interconversion is 0.33, and if the relative reactivity of the secondary hydroxyl function to the tertiary hydroxyl is 3:1, then it follows that the β-effect must account for at least a ten times faster reaction!

SCHEME 7



At this point we decided on a change of strategy, which was to perform the reaction on the acyclic ester derivative 31. Thus the lactone 21 was transformed into the protected allylester 31 as outlined in Scheme 8. Hydroxide saponification of 21 was followed by esterification with allyl bromide in DMF to give compound 30, which was protected as its silyl ether, through the intermediacy of imidazole in DMF at ambient temperatures.

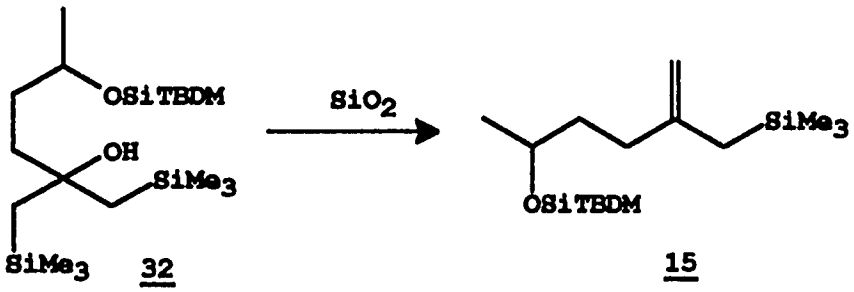
SCHEME 8



The ester 31 reacted with the title Grignard reagent in the absence of TMSiCl to give a 55% yield of the allylsilane 15. Repeating the reaction, with added TMSiCl, gave 15 along with the compound 32, in a 5:1 ratio by NMR, in 90% yield. Chromatography of this mixture on silica gel converted compound 32 into the allylsilane 15, such that 15

was obtained in an overall yield of 85%, Scheme 9. These results clearly demonstrated that enolization by the Grignard reagent was not an important factor since both the α-silylketone and the organometallic reagent were present during the reaction, and the leaving alkoxy group was quite likely trapped by the added TMSiCl.

SCHEME 9

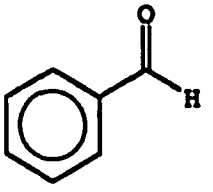
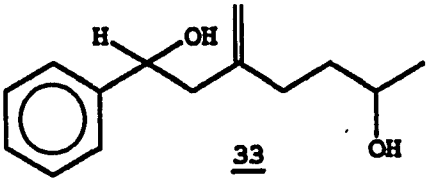
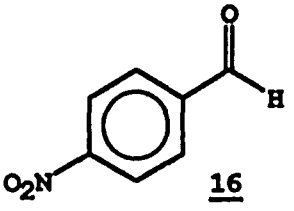
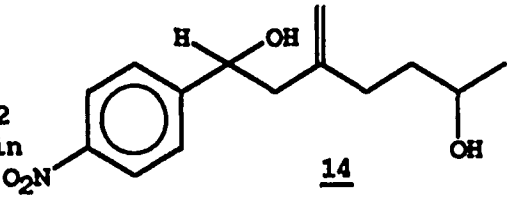
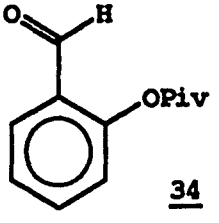
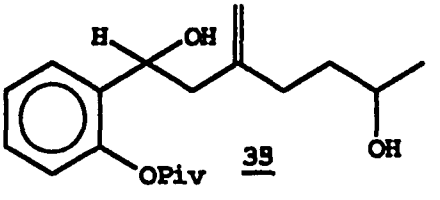
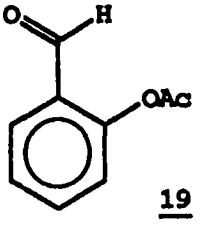
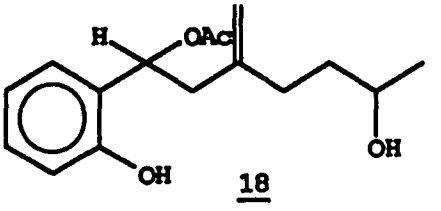


4.3.1. Synthetic Applications of 15

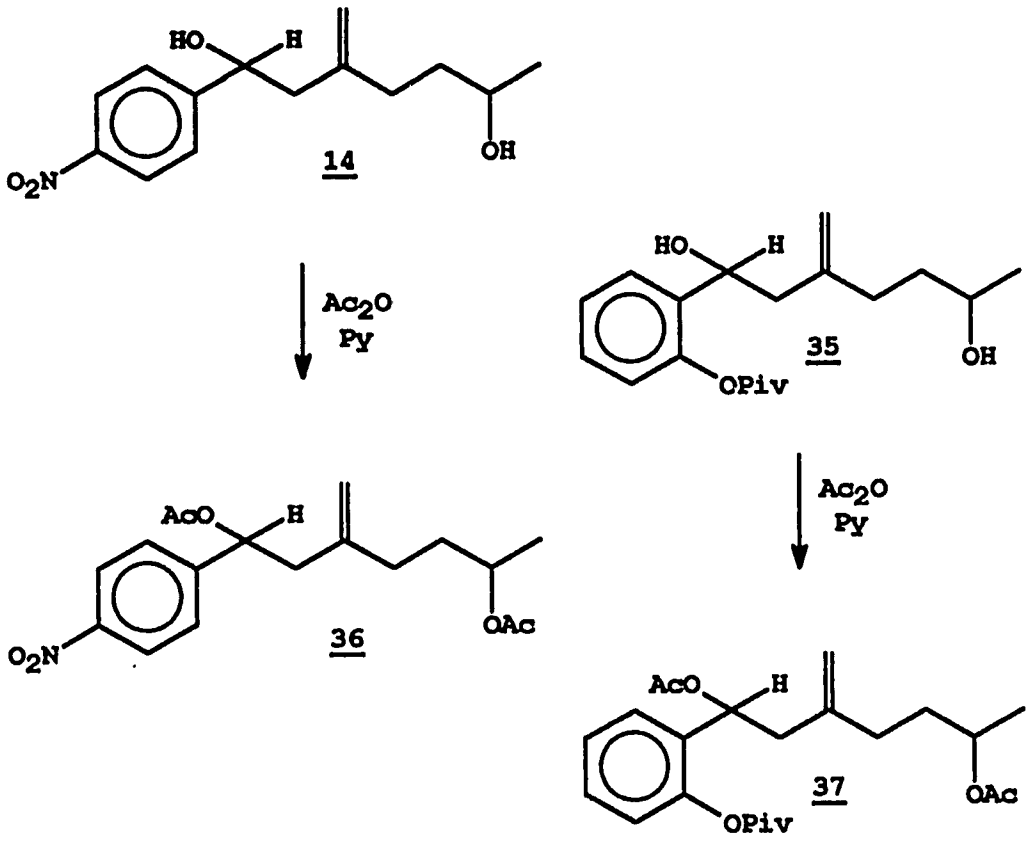
Several coupling reactions were performed using the allylsilane 15. The results are summarized in the table below. All investigations involved using 1 molar equivalent of 15 with respect to the substrate. It is noteworthy that the formation of compound 18 did occur with the expected migration of the acetyl group from the phenolic to the newly formed alcohol, during the reaction. This known phenomenon of acyl migration is indeed remarkable, and can be developed into a general procedure, utilizing ester groups with greater migratory aptitude, such as formate, for the synthesis of more elaborate spiroketal ring systems. We demonstrated the usefulness of this process in the synthesis of the spiroketal 17, which is discussed discussed below.

The coupling products 14 and 35 were further acetylated according to standard procedure providing compounds 36 and 37 respectively.

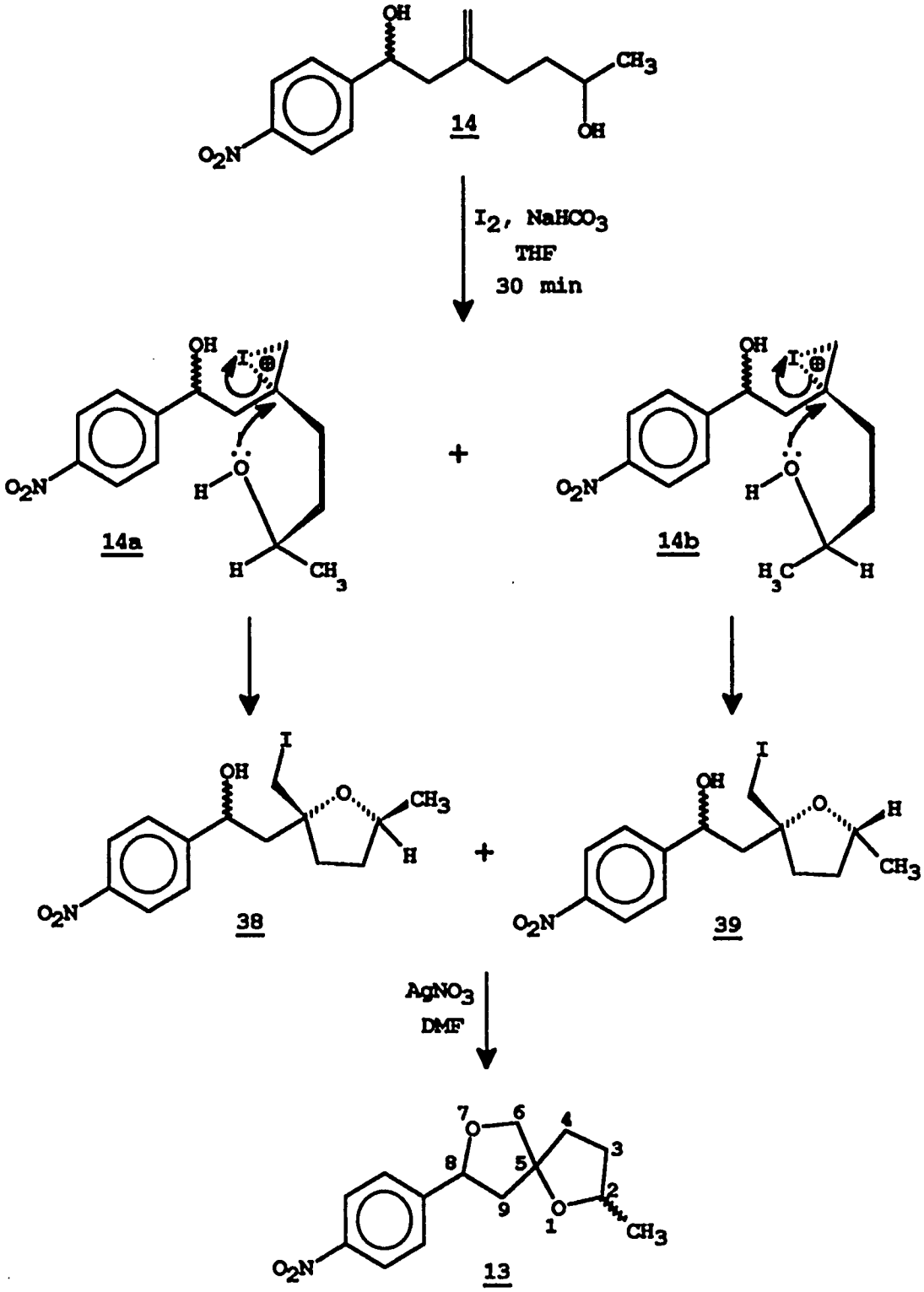
TABLE 1

SUBSTRATE	CONDITIONS	PRODUCT	YIELD(%)
	CH_3CN BF_3 OEt_2 0°C/ 1 hr	 <u>33</u>	85
 <u>16</u>	CH_3CN BF_3 OEt_2 0°C/15 min	 <u>14</u>	98
 <u>34</u>	CH_3CN BF_3 OEt_2 0°C/ 1 hr	 <u>35</u>	80
 <u>19</u>	CH_3CN BF_3 OEt_2 0°C/1hr	 <u>18</u>	85

SCHEME 10


HO
H
OH
O_2N
14
Ac_2O
Py
AcO
H
OAc
O_2N
36
HO
H
OH
OPiv
35
Ac_2O
Py
AcO
H
OAc
OPiv
37

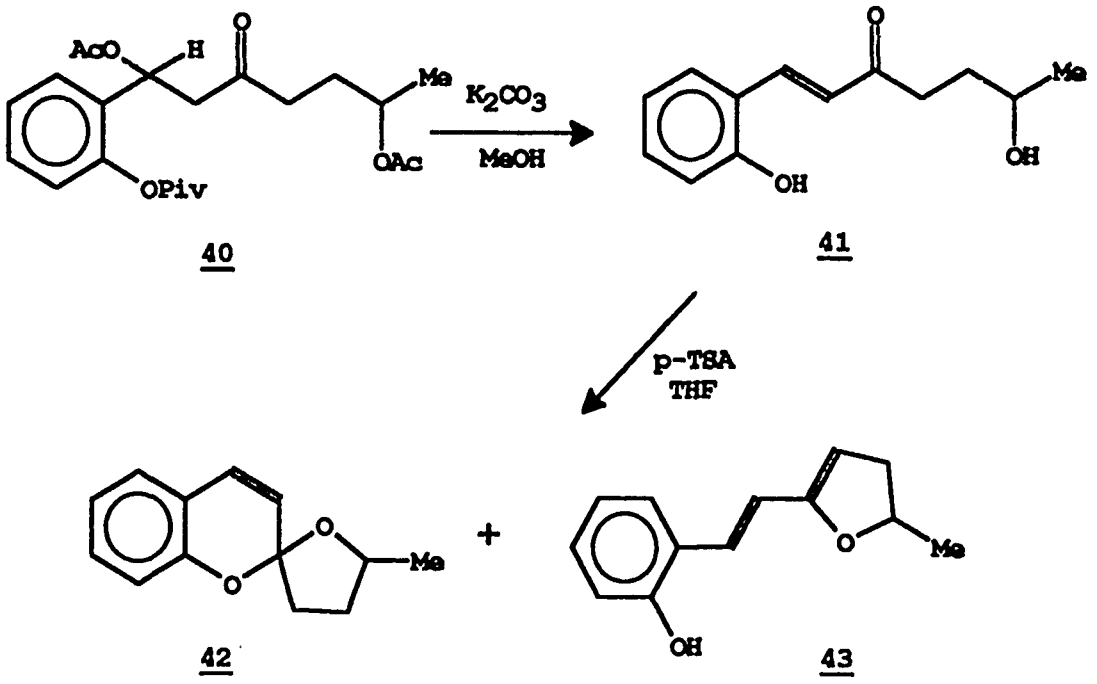
SCHEME 11


OH
CH3
O2N
14
OH
I2, NaHCO3
THF
30 min
OH
I
O2N
O
H
H
CH3
14a
+
OH
I
O2N
O
H
H3C
H
14b
OH
I
CH3
O
H
O2N
38
+
OH
I
H
O
CH3
O2N
39
AgNO3
DMF
7
6
4
3
8
5
2
9
O
1
CH3
O2N
13

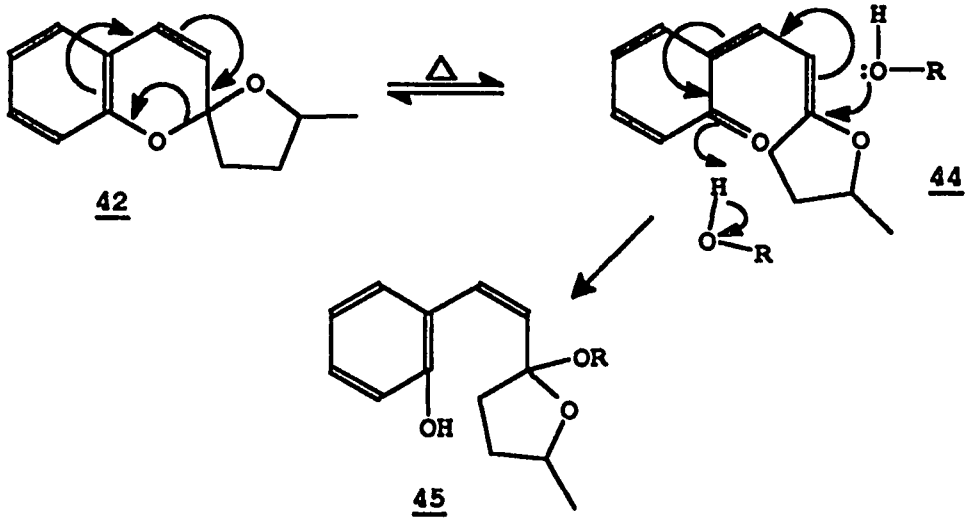
Iodoetherification of compound 14 was achieved by stirring with iodine in THF containing suspended sodium bicarbonate to give the compounds 38 and 39 quantitatively. We established that the benzylic hydroxy group was not involved in the initial cyclization, by NMR analysis of the monoacetates of 38 and 39. The expected change in the chemical shift of the benzylic hydrogen was reflected, moving from δ 4.90 to δ 5.96 ppm. High resolution proton NMR analysis of the mixture of compounds 38 and 39 also indicated that the new stereocenter had been generated in a 3:1 diastereoisomeric ratio. One must therefore conclude that this cyclization had been ifluenced by the geometry at C2. We were unable to separate these isomers, and so have not directly ascertained their stereochemical identities. Nevertheless, an indirect stereochemical assignment can be made through steric considerations of the possible transition states 14a and 14b, shown in Scheme 11. The transition state 14a has the C2 methyl group anti to the bulky *p*-nitrophenyl "Ar" group leading to the product 38. In the case of 14b, one can predict increased steric interactions due to these groups being cis to each other. It is therefore reasonable to conclude that the compound 38 would be the diastereoisomer formed in greater amounts. The mixture of 38 and 39 was converted to the 1,7-dioxaspiro[4.4]-nonane 13 in 100% yield, by reaction with silver nitrate in DMF at room temperature. As expected, 13 was obtained as a complex inseparable mixture of diastereoisomers.

The diacetate of compound 35 reacted with osmium tetroxide/sodium periodate[7] in *tert*-butanol to give the ketone 40 in 90% yield. Mild basic hydrolysis with potassium carbonate in methanol at room temperature converted 40 to the unsaturated ketone 41 in 85% yield after 5 hours. The ketone 41 was then converted to the unstable[8] but novel spiroketal 42 and the diene 43 (1:1) in about 80% yield, by treatment with *p*-TSA in tetrahydrofuran, Scheme 12. A possible route to the degradation of compound 42 is depicted in Scheme 13; a thermally induced 6 π retro-Claisen rearrangement which is followed by nucleophilic attack by solvent.

SCHEME 12

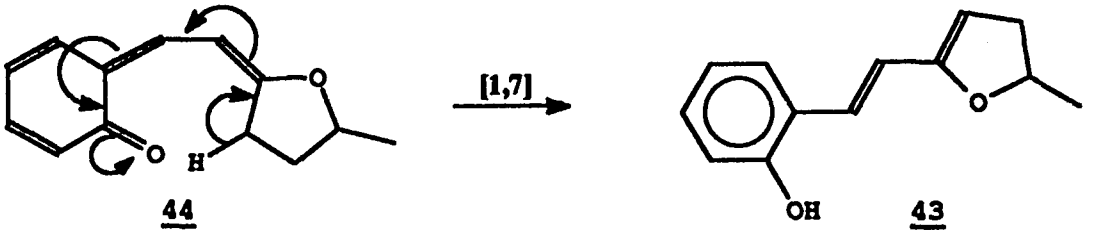


SCHEME 13



Scheme 14 shows the formation of compound **43**, via a conceivable concerted [1,7] hydride shift, such that aromaticity is also re-established.

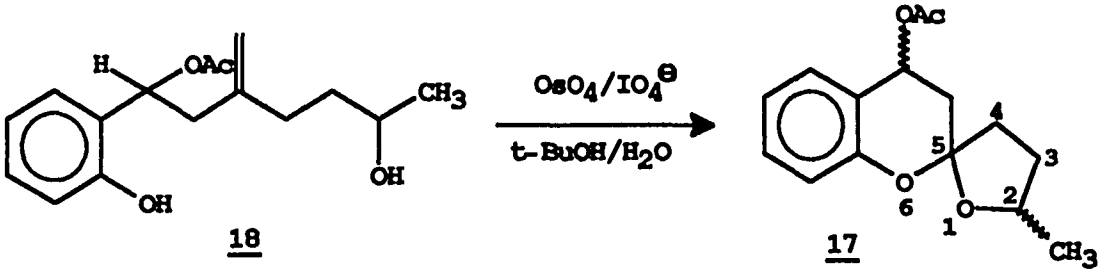
SCHEME 14



44 43

Compound 18 reacted with osmium tetroxide/sodium periodate in *tert*-butanol to give the spiroketal 17 in 90% yield. The anticipated migration of the acetyl group during the preceeding reaction had thus selectively deblocked the phenolic hydroxyl group thereby preparing this molecule for spirocyclization, Scheme 15.

SCHEME 15

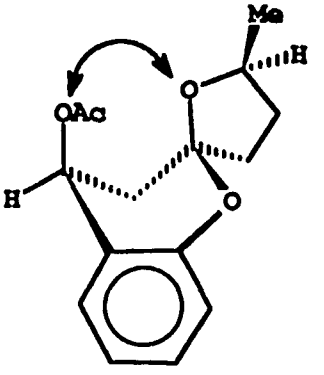


18 17

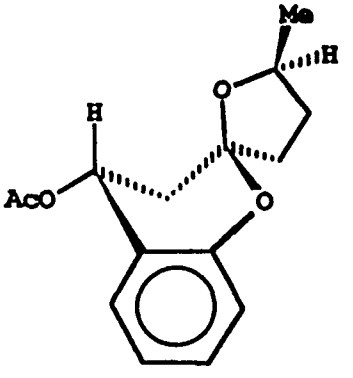
As was observed in the cases of compounds 14, 33, and 35, the new secondary hydroxyl group of compound 18, had been generated without diastereoselection, that is, a 1:1 ratio of diastereoisomers was obtained. The formation of compound 17 however, was influenced by the geometry at C(2), determined by high resolution NMR analysis of the benzylic hydrogen atom and the C(2) methyl resonance signals. Four of the expected products are shown in Scheme 16 below, however, the proton NMR spectrum revealed only two doublets for the methyl resonances.

The major diastereoisomers, δ 1.21, accounted for 62% of the mixture, while the minor diastereoisomers, δ 1.28, accounted for 38% of the mixture. Since we had anticipated four pairs of compounds, it is likely that two pairs were not formed, probably the **17a** and **17c** pairs, on stereoelectronic grounds. The remaining pairs of diastereoisomers, (**17b** , **17d**), reflect only two sets of resonance signals because of accidental coincidence.

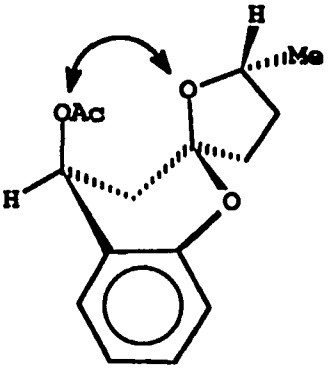
SCHEME 16



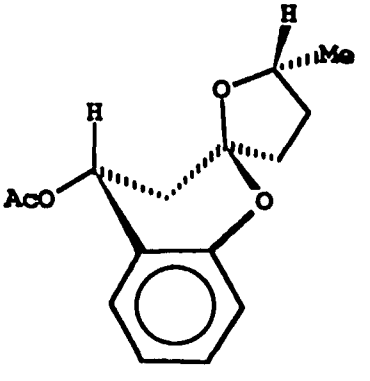
17a



17b



17c



17d

Thus our initial assertions were indeed correct, specifically that the stereochemic-

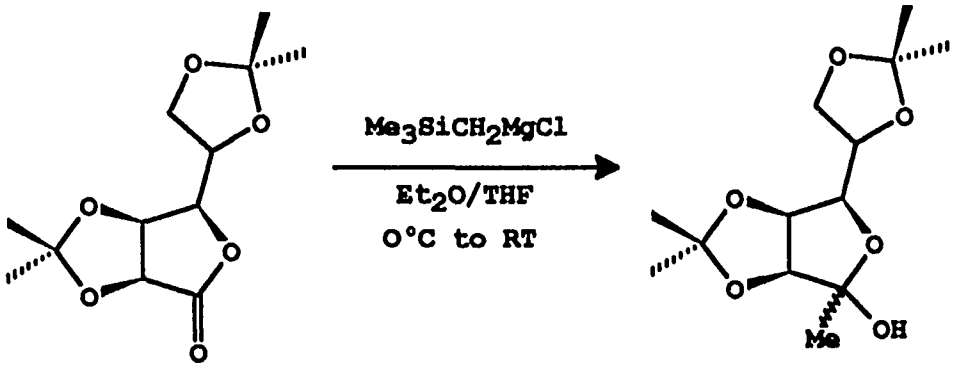
al course of these spirocyclization reactions will be influenced by other stereocenters in the molecule originating in the coupling allylsilane molecule.

With these preliminary results, we embarked on the synthesis and study of the chiral saccharidic allylsilanes discussed below.

4.4.0. Allylsilane from the Mannonolactone 46

Treating the mannonolactone 46 with four equivalents of the Grignard reagent Me_3SiCH_2MgCl in THF gave the hemiketal 47 as the exclusive product, Scheme 17.

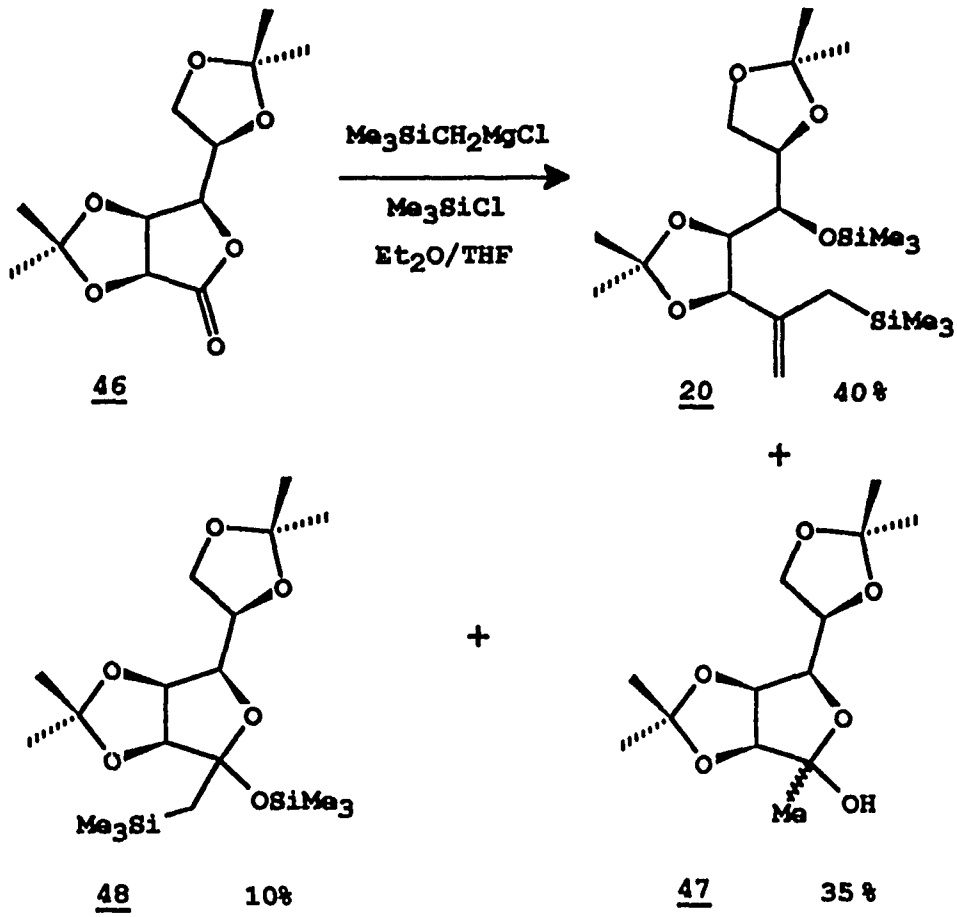
SCHEME 17



46 47

Here we again reasoned, that the reaction was stopping at the α-silylketone - hemiketal stage owing to entropy factors, and perhaps the β-effect favoring hemiketal formation. Thus the reaction was repeated with added trimethylchlorosilane. The desired allylsilane 20 was obtained in 40% yield along with the compounds 47 and 48 in 35% and 10% yields respectively. Compound 48 was clearly the hemiketal blocking product which was primarily a consequence of the aforementioned β-effect.

SCHEME 18



46 → 20 (40%) + 48 (10%) + 47 (35%)

The NMR spectrum of the crude reaction mixture had shown only traces of the compound 47, indicating that this compound had been formed from 48 during column chromatography on silica gel, by the elimination of hexamethylsiloxane and hydration of the resulting enolether. This reaction was repeated, but was quenched with allyl bromide and stirred for a further period of 18 hours (a non-aqueous work-up). No C-allylated, nor any new compounds were produced, indicating that no enolates had been formed in these reactions[9]. Thus it was clearly evident that for sugar lactones, the major limiting factor in this approach towards the synthesis of allylsilanes was lactol formation and not the suggested competing enolizations[9]. Substituting the added chlorotrimethylsilane with *tert*-

butyldimethylchlorosilane resulted in the formation of compound 47 exclusively. Steric factors in this case, outweighed the activated nucleophilicity of the hemiketal by the β-effect, resulting in the observed lack of silyl ether formation.

Our next attempt at maximizing the yield of the allylsilane was met with great improvement in the efficiency of this technique. Reactions were performed at -78°C in THF for 3 hours, using one equivalent of chlorotrimethylsilane with respect to the organometallic reagent. The targeted allylsilane 20 was obtained in an improved yield of 90%. Interestingly, when the reaction was performed under similar conditions in diethyl ether, none of the desired allylsilane was obtained, the hemiketal 47 was the only isolated product. It is therefore evident, that solvent polarity was of extreme importance for the success of this reaction. It is also noteworthy that added cerium (III) salts, or a variety of polyether chelating agents, failed to improve the process further.

Even though an improved yield of 90% was obtained for this allylsilane preparation, it would be interesting to investigate the acyclic ester approach in terms of yield and reaction conditions. Future research endeavors will address this aspect of our investigations.

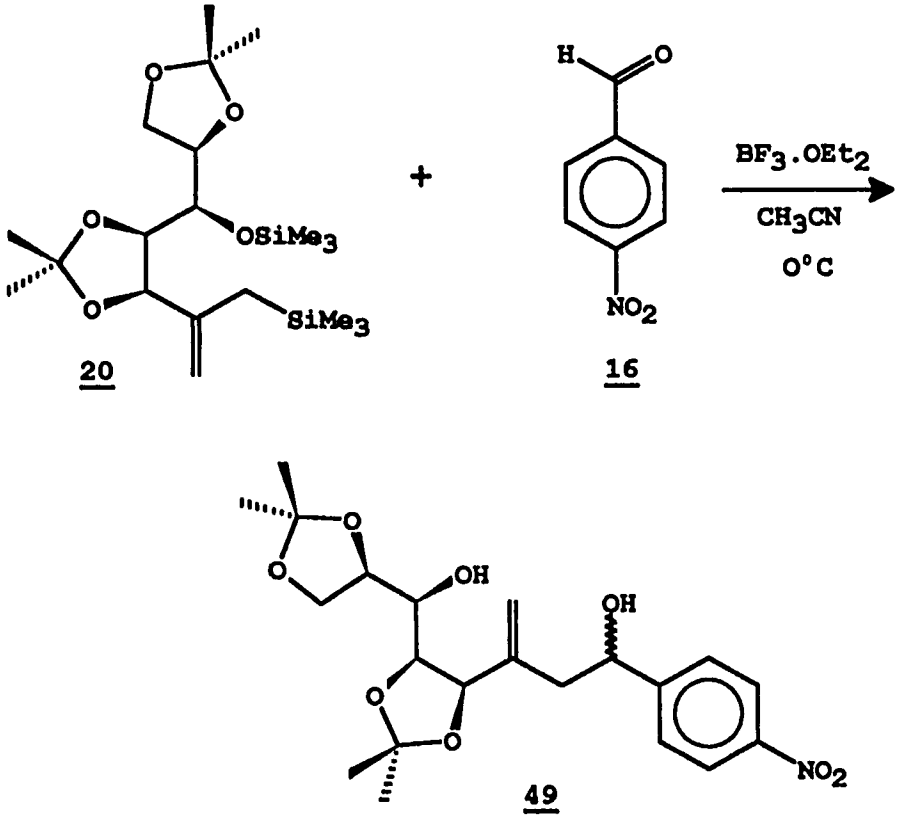
4.4.1. Synthetic Applications of Allylsilane 20

The allylsilane 20 reacted with 4-nitrobenzaldehyde, 16, to produce compound 49 as an inseparable mixture of diastereoisomers. The NMR spectrum of compound 49 had shown that the new secondary hydroxyl group was formed with a marked stereoselectivity of 9:1.

The stereochemical outcome of the above reaction ,pointed to the fact that the stereocenter at C3 in compound 20 did direct the path of this reaction. Since we were unable to separate these stereoisomers, we must resort to an indirect stereochemical assignment. Perhaps the closed transition state hypothesis first proposed by Zimmerman and Traxler[10], which is used extensively in the rationalization of the observed structure-

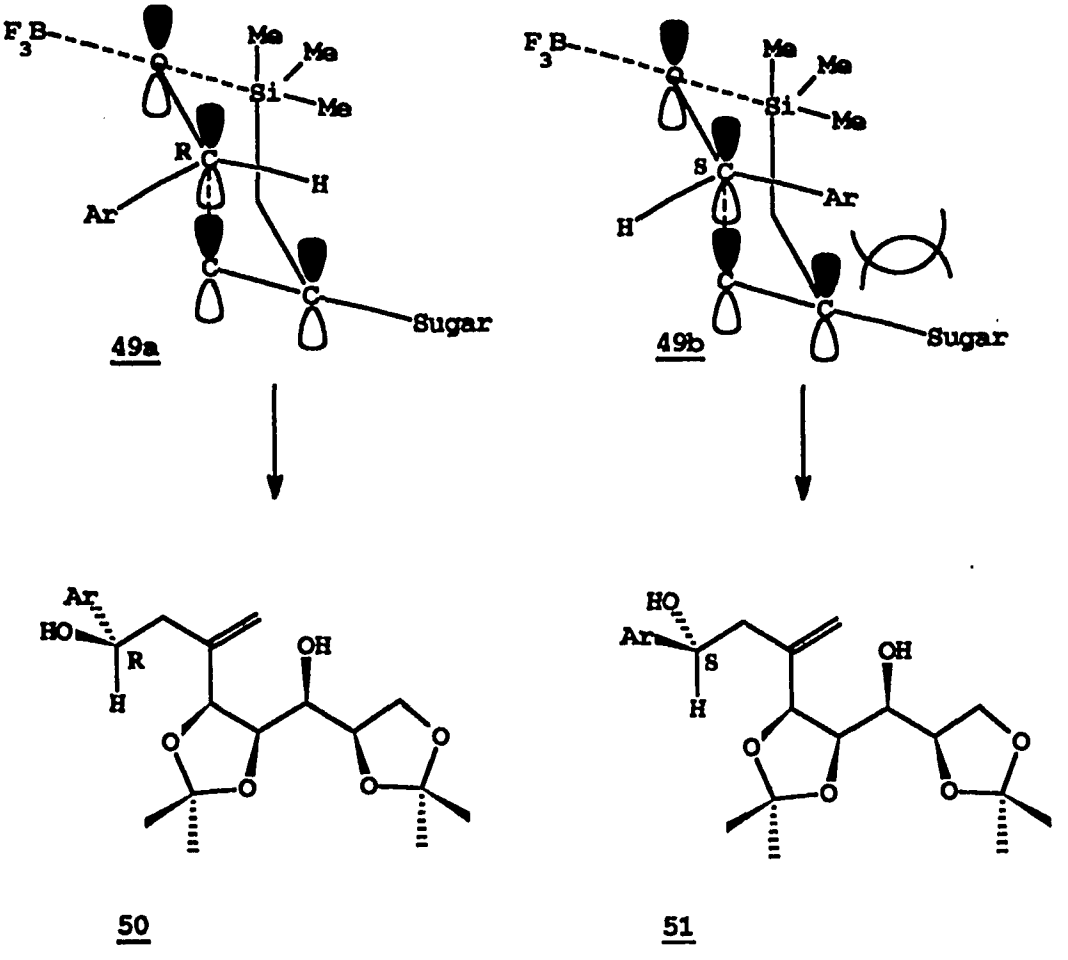
selectivity data for aldol addition reactions, would offer a plausible rationale for our results. Scheme 20 shows two proposed transition states where the dominant interactions are between the *p*-nitrophenyl and the extended carbon chain of the allylsilane. The requirement that the participating *p*-orbitals be coplanar is reflected by both transition states, however, **49b** is faced with steric congestion owing to the 1,3 diaxial-like interactions between the aryl group and the sugar framework. Thus transition state **49a** would be favored over **49b** such that **50** would be the stereoisomer formed in greater amounts.

SCHEME 19



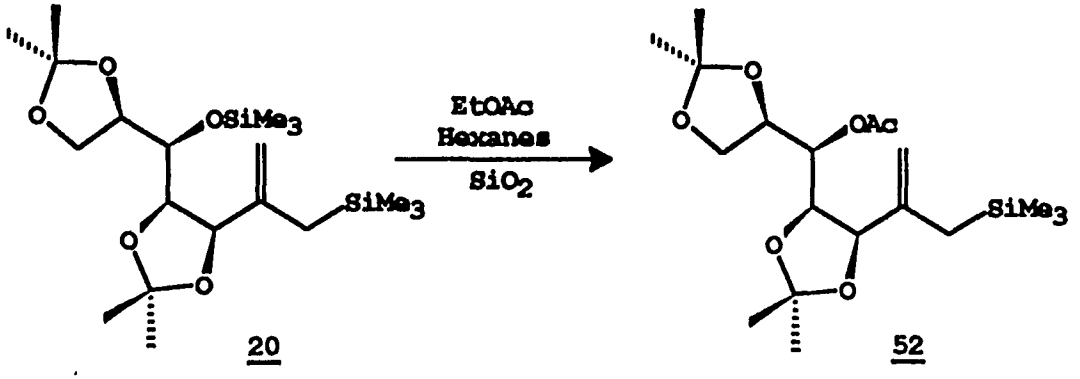
20 16 49

SCHEME 20



A particularly interesting reaction of the allylsilane **20**, was the spontaneous de-silylation - esterification that was observed when rigorous attempts at purification on silica gel were carried out. The solvent system, Hexane:Ethyl acetate ; 5:1, was used as eluent. The acetate **52** was obtained almost exclusively under these conditions.

SCHEME 21

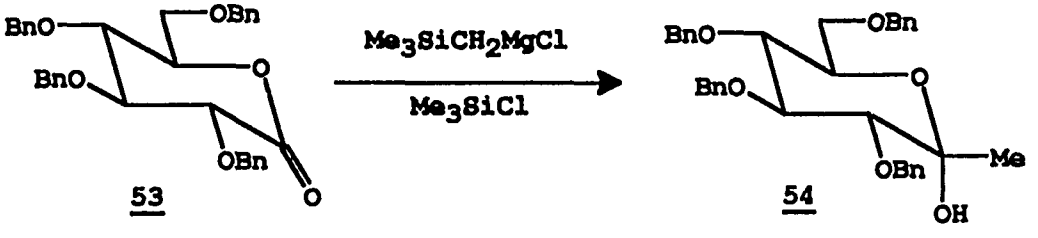


20 52

4.5.0. Allylsilane from 2,3,4,6-tetra-*O*-benzylgluconolactone, 53.

The reaction of the lactone **53** with the title Grignard reagent also gave the hemiketal, compound **54**, as the sole product, even with added chlorotrimethyl silane in THF. Hemiketal formation was clearly the hindering factor in this case, the acyclic alkoxide being discredited on entropy grounds. It was therefore evident that except for those sterically hindered lactones like **46**, the acyclic ester approach was best for the preparation of these allylsilanes.

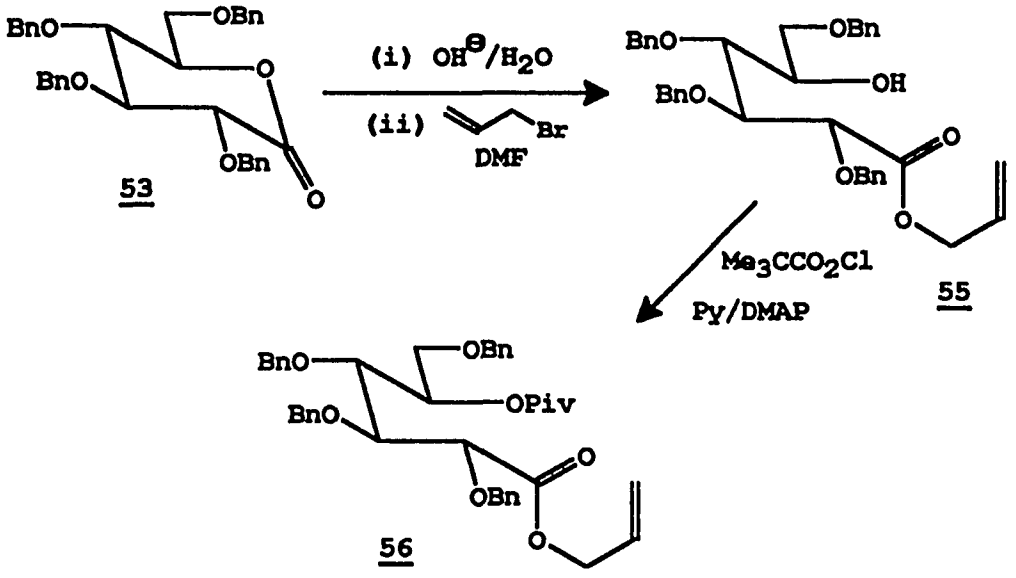
SCHEME 22



53 54

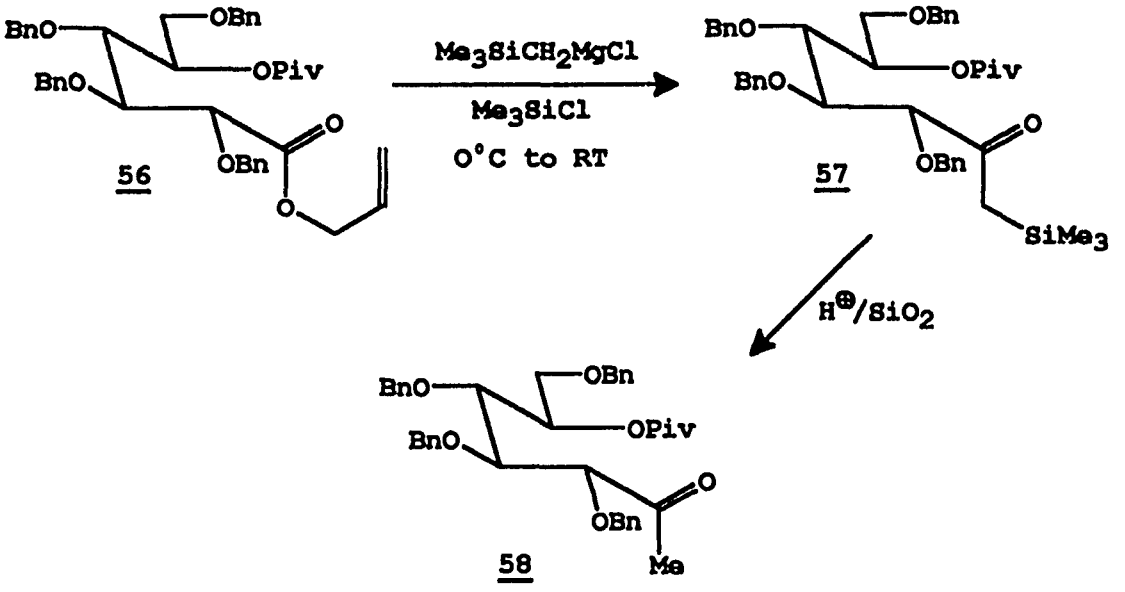
The lactone 53 was therefore converted to the ester 56 by allylating the sodium carboxylate salt to give compound 55, followed by esterification of the alcohol at room temperature to give compound 56 quantitatively, Scheme 23.

SCHEME 23



All reactions performed on the ester 56 at 0°C then room temperature, gave the α-silylketone 57 as the only product, which underwent cleavage quite readily to the methylketone 58 on silica gel. Since we were not faced with the problem of lactol formation, it was conceivable that the ketone intermediate was undergoing enolization; possibly by the Grignard reagent, or the leaving alkoxide group. We demonstrated, however, that in the case of ester 31, enolization was not important, thus casting serious doubts on this rationale.

SCHEME 24



Considering the possibility that the Grignard reagent itself might be responsible for the proposed competing enolization process, we decided to investigate the effect of added polyether chelating agents. It is known that Grignard reagents tend to form aggregates in non-polar solvents, thus we speculated that the nature of our organometallic reagent in solution might be a controlling factor. Several runs were therefore made with added 18-crown-6 or triglyme, hoping that these chelating agents would somehow facilitate the monomeric existence of the organometallic reagent in solution. All runs were accomplished with four molar equivalents of the Grignard reagent for each molar equivalent of the ester **56**. The results of these investigations are summarized in Table 2.

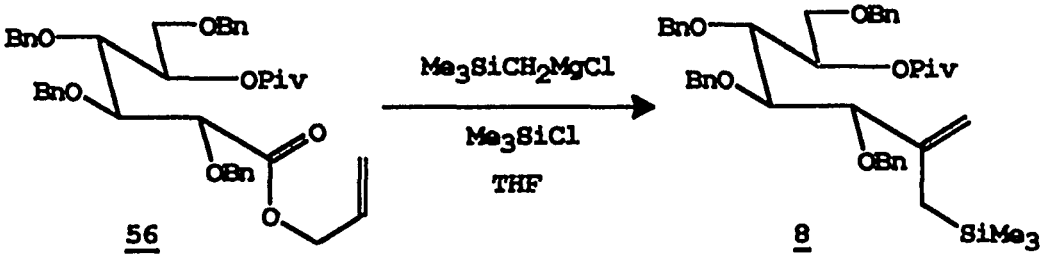
As indicated in the table below, best results were obtained when the reactions were performed in tetrahydrofuran at -78°C. The introduction of polyether chelating agents failed to improve the process further, and for all reactions it was necessary to include the four equivalents of chlorotrimethylsilane.

TABLE 2

RUN	CONDITIONS	PRODUCTS	YIELDS
1	Et_2O O^0C to RT 12 Hrs.	58	95%
2	Benzene O^0C to RT 12 Hrs.	58	95%
3	Et_2O Triglyme O^0C to RT 12 Hrs.	58	85%
4	THF Triglyme O^0C to RT 12 Hrs.	58	88%
5	THF -78^0C 3 hrs RT 12 hrs	8 58	90% 5%
6	THF Triglyme -78^0C 3 hrs RT 12 hrs	8 58	85% 12%
7	THF 18 Crown 6 -78^0C 3 hrs RT 12 hrs	8 58	25% 70%

Control reactions were performed, employing the method of Narayanan and Bunnelle[11] on the ester **56**. Not surprisingly, there was no improvement in the isolated yields of the desired allylsilane, yields were of the order 75 - 85%. It was therefore very clear from our investigations that this method is compatible with sterically congested esters and the addition of Ce(III) species is not necessary for the reaction to be successful.

SCHEME 25



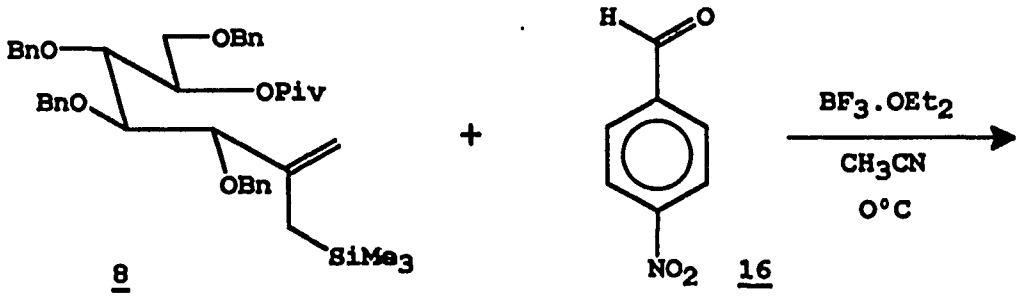
In spite of our discoveries, there still remain a number of unanswered questions regarding the mechanism of the reaction. If the enolization concept is not considered plausible, then an alternative mechanism other than the usual nucleophilic attack of the Grignard reagent, must be proposed. Perhaps one could imagine a mechanism involving radical species. In addition, it is not very clear regarding the role played by the chlorotrimethylsilane. It is logical to assume that it traps the leaving alkoxide in these acyclic ester reactions, and we have already established that it captures the secondary alkoxide in the lactone reactions. If the reaction is following a pathway involving radicals however, the role of TMSiCl might be very different. An interesting aspect of this allylsilane preparation was the apparent sensitivity of the reaction to the 'half-life' of the Grignard reagent. In support of the discoveries of Narayanan and Bunnelle, we found that the reactions worked only with freshly prepared samples of the Grignard reagent. Reactions involving compound **56** would be expected to proceed slowly because of steric factors

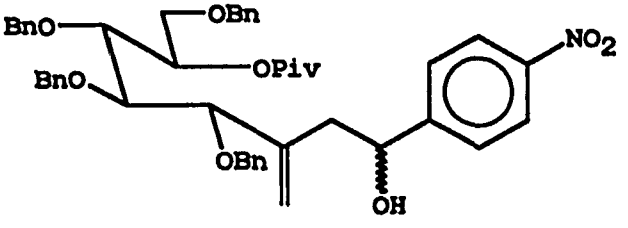
and repulsion of the nucleophile by the ether oxygens. Thus one would anticipate a competing decomposition of the Grignard reagent at elevated temperatures, which on the other hand, would be minimized at low temperature conditions where it is most stable.

4.5.1. Synthetic Applications of Allylsilane 8

The Lewis Acid catalyzed reaction of the allylsilane 8 with 4-nitrobenzaldehyde 16, also proceeded with marked stereoselectivity, producing compound 59 in 90% yield as a 7:1 mixture of diastereoisomers, inseparable by chromatography. Scheme 27 depicts

SCHEME 26



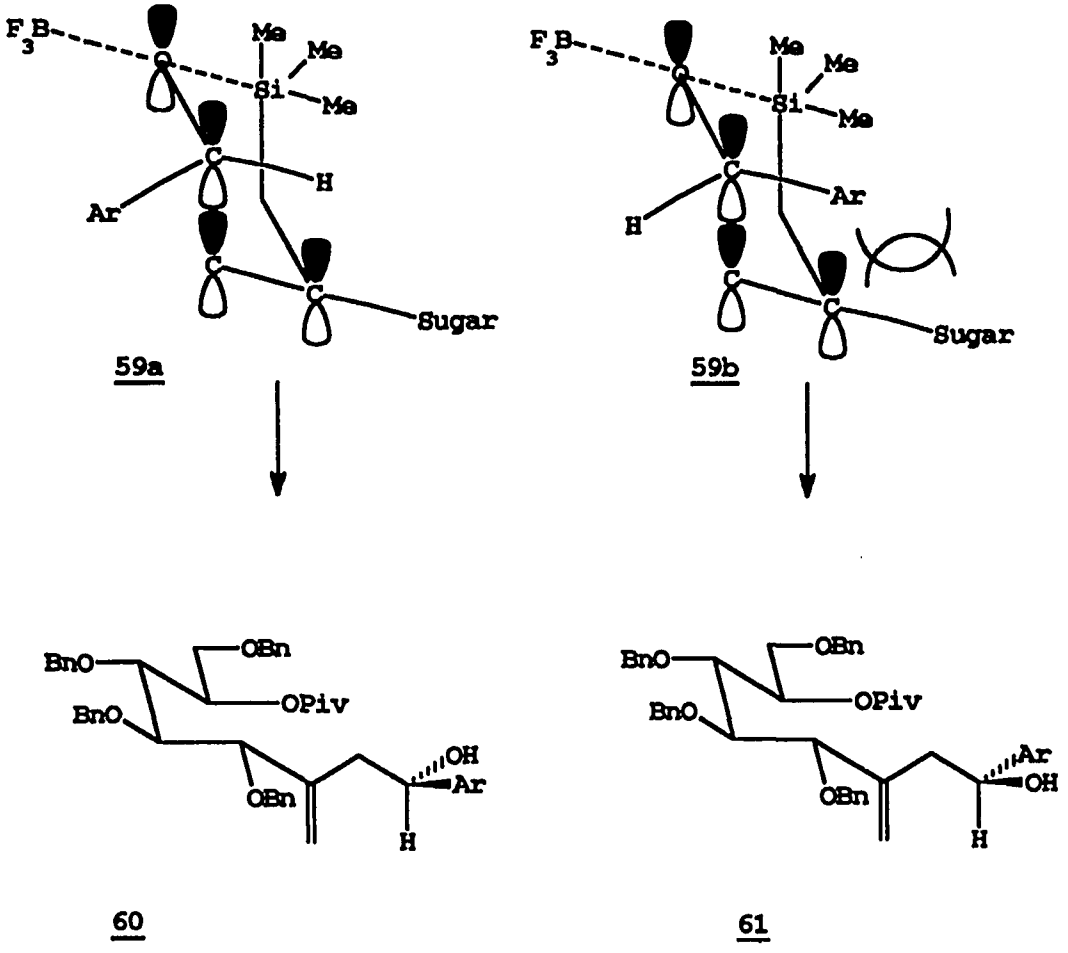


59

two proposed cyclic transition states that would allow us to make an indirect stereochemical assignment. As in the case above, the dominant interaction is between the *p*-nitrophenyl group and the extended carbon chain of the allylsilane. Thus transition state

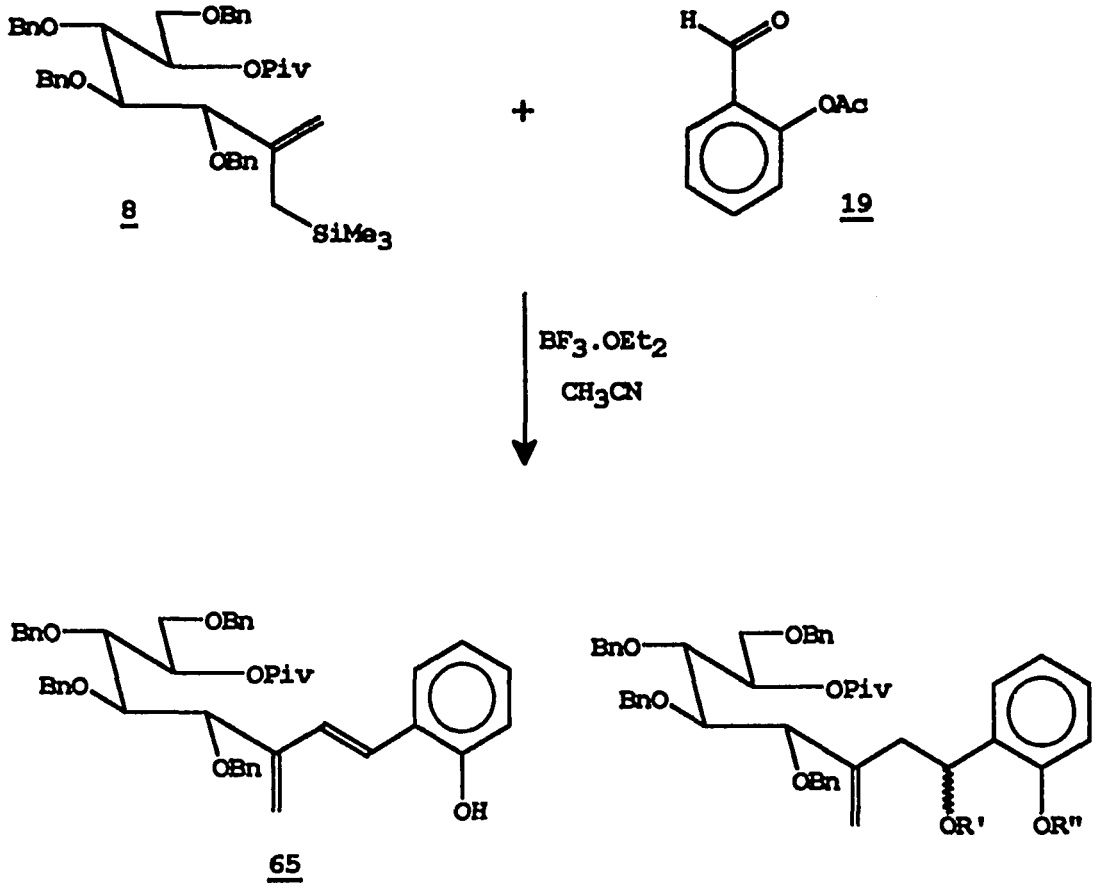
59a would be favored over 59b since steric interactions are minimized. Compound 60 would therefore be the stereoisomer formed in greater amounts.

SCHEME 27



The allylsilane 8 reacted with the acetate 19 in acetonitrile containing BF_3, to produce the diene 65 along with the compounds 62, 63, and 64, Scheme 27. Although the proton NMR spectrum for compound 65 was not conclusive, additional support for the proposed structure was obtained from mass spectral analysis, m/z 789 (M^++1) and ^{13}C NMR analysis, δ 117, 121, 123 and 133 corresponding to the olefinic carbons.

SCHEME 28



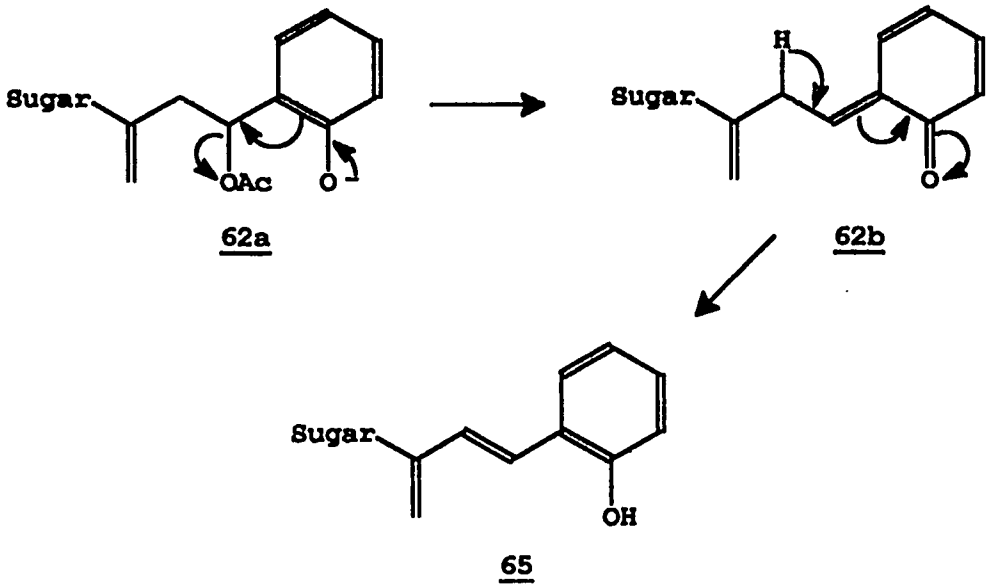
62 R' = OAc, R" = H

63 R' = H, R" = OAc

64 R' = H, R" = H

The formation of compound 65 most likely occurred during the work-up stages of the reaction. As was observed with earlier reactions, migration of the acetate to the new secondary hydroxyl group occurred. On work-up, base abstraction of the phenolic hydrogen leads to successive eliminations so forming the diene 65, Scheme 29.

SCHEME 29

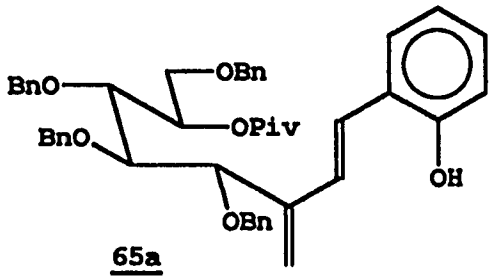


62a 62b

65

Attempts were made at minimizing this spontaneous elimination through work-up under neutral conditions at cooling temperatures. In spite of these constraints, the diene was still being formed. Thus the mixture of products, 62-64, was converted to the diene 65 by refluxing with triethylamine in THF for four hours. Compound 65 was allowed to react with acryloyl chloride, in anticipation that a Diels-Alder addition reaction would also have occured to give compound 66, Scheme 30. In support of the analytical data previously reported, the success of this reaction would provide an indirect proof for the proposed structure of compound 65. Reactions performed at room temperature in pyridine returned the starting materials. Next we tried refluxing conditions, as well as running the reactions in tetrahydrofuran with added DMAP at room temperature, and under reflux. None of these variations resulted in a successful addition, hence we opted for a more reactive dienophile, namely, maleic anhydride. As with acryloyl chloride, all attempts were met with failure, the starting materials being isolated in all cases, which included reactions at elevated temperatures. If the diene conformation was indeed *s-cis*, one must therefore conclude that either the normal *suprafacial* orientation of participating molec-

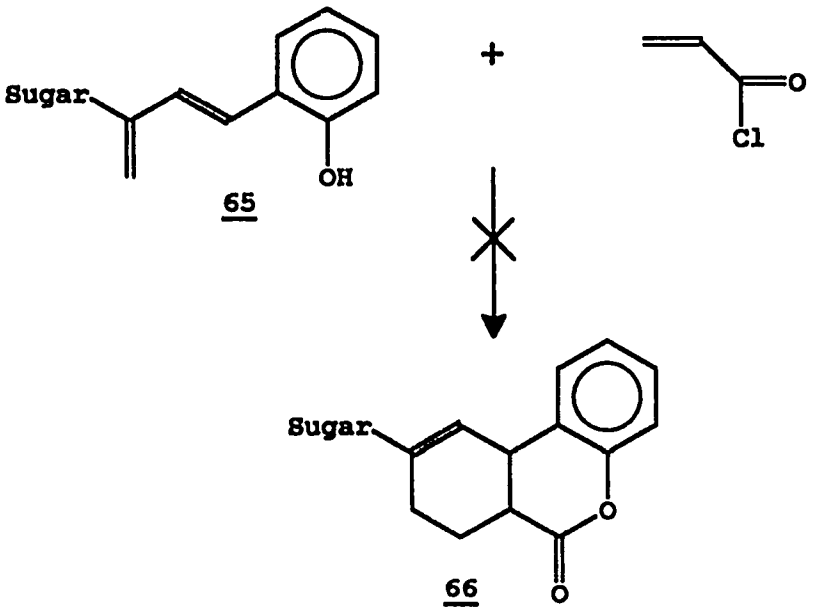
ular orbitals $[\pi 2_S + \pi 4_S]$ was not facilitated[11]. This was, perhaps, a consequence of considerable steric interactions of substituent groups, or that the diene had apparently adopted a thermodynamically more stable *s-trans* conformation, **65a**.



65a

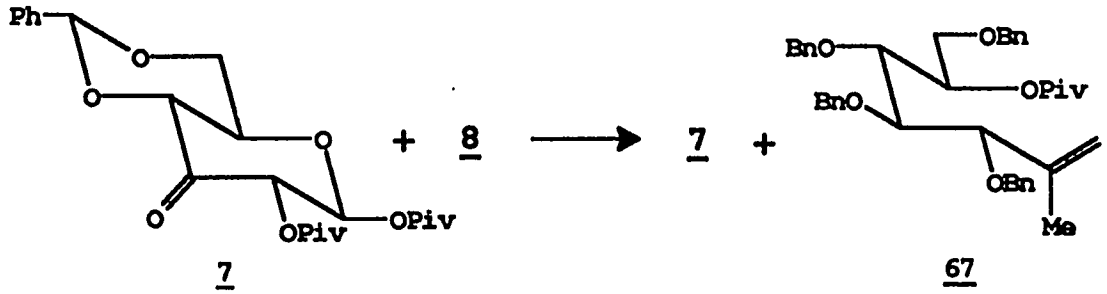
In spite of our apparent failures, this Diels-Alder reaction holds enormous potential in terms of synthetic utility, and will most certainly be the target of concentrated synthetic efforts in the future.

SCHEME 30



At this point we embarked on the pivotal bond-forming reaction of our investigations, the coupling of the allylsilane 8 with the ulose 7. Initial reactions were performed in acetonitrile with BF_3 at 0°C and subsequently at room temperature. These reactions merely resulted in protodesilylation of compound 8 to give the alkene 67. The ulose 7 was recovered unchanged, Scheme 31.

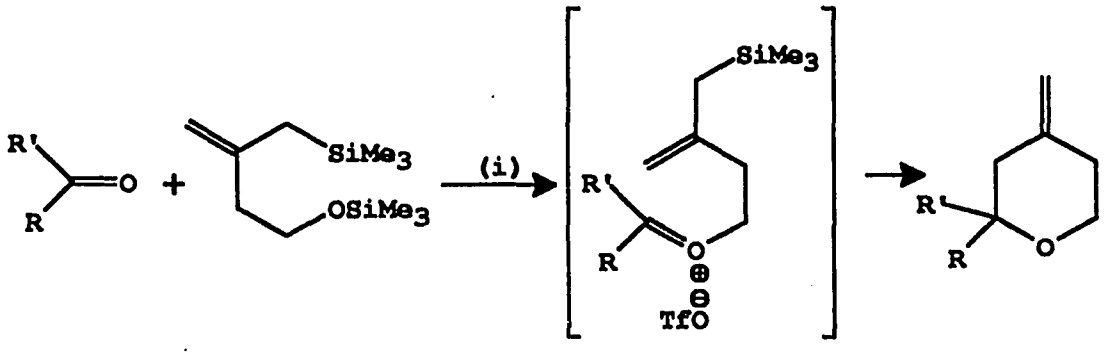
SCHEME 31



7 67

Modifications in the procedure of this reaction include fluoride catalysis, addition of 18-Crown-6 and varying the concentration of the reacting medium. As with the initial reactions, desilylation occurred in all cases to give compound 67. Disappointing though these results might have been, one should not have been too surprised. To date, there are no reported intermolecular addition reactions between highly functionalized allylsilanes and ketones. The most general reactions of this type are the intramolecular additions reported by Majetich[12] in his construction of functionalized bicyclic ring systems. The reported reactions are between allylsilanes and 3-vinylcycloalkenones. Recently, the intermolecular addition of crotylsilanes to chiral 2-*p*-tolylsulfinyl- and to 2-methoxy-2-cyclopentenones have been reported[13]. Also recently reported was the Intramolecular Silyl Modified Sakurai Reaction of Marko and Mekhalfia[14], which was used in a highly efficient synthesis of a Dacus oleae pheromone. The general form of this reaction is shown in Scheme 32.

SCHEME 32

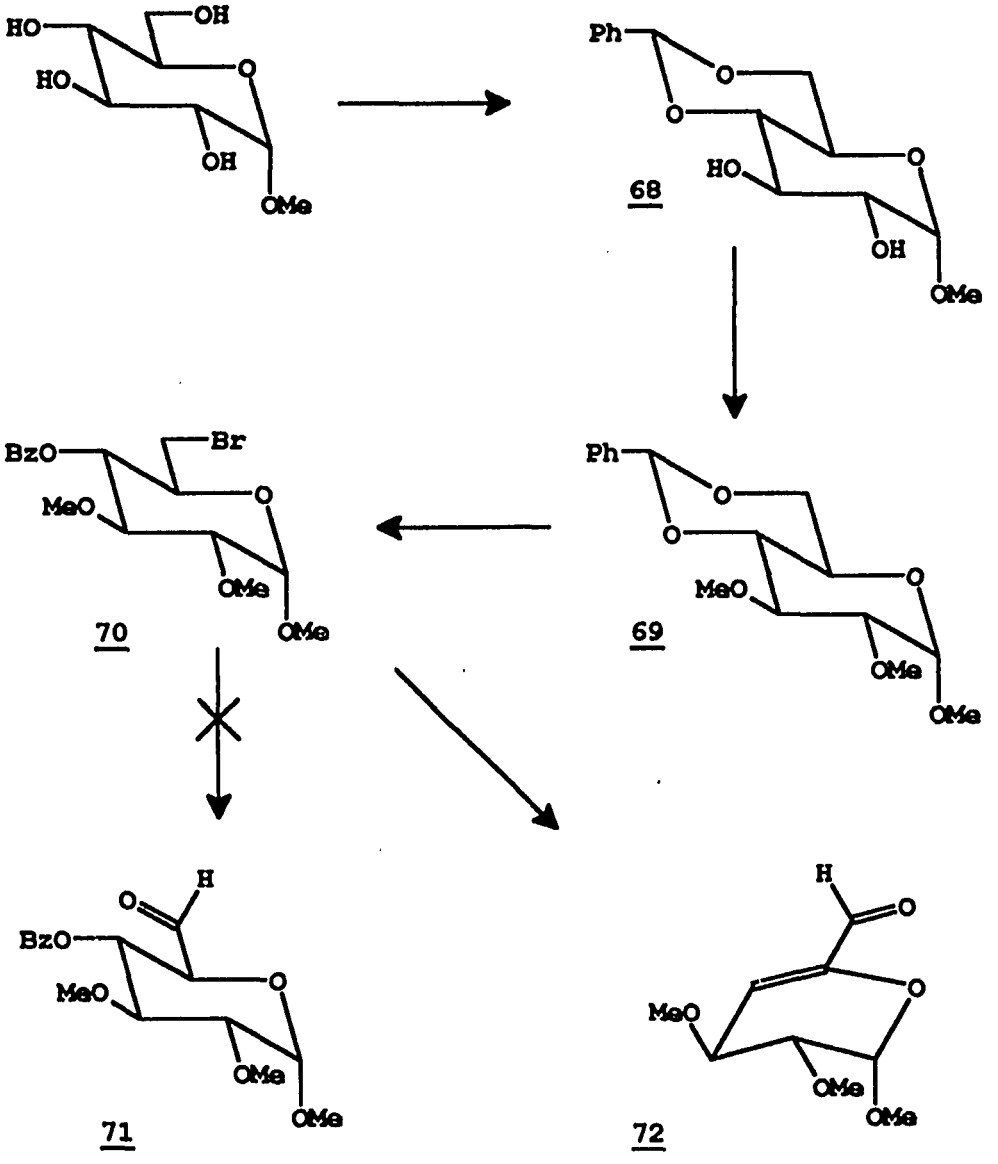


(i) = Me_3SiOTf cat/ CCl_4 / 20°C

Thus it is evident that the reactions on which we embarked have the potential for breaking new grounds in organosilicon chemistry and specifically, the chemistry of the allylsilanes.

In light of our earlier successes with the simple benzaldehyde derivatives, we next focused our attention unto sugar derivatives containing aldehyde functionalities. Indeed, numerous intermolecular allylation reactions of aldehydes have been reported[15]. Recently, Koomen and his co-workers reported the stereoselective addition reactions to the aldehyde function of some L-xylose derivatives, under the influence of Lewis Acid catalysis[16]. These and other reactions provide the established precedence for the plausibility of our alternate approach. On this basis, we attempted the synthesis of the aldehyde 71 from commercially available methyl-α-D-glucopyranoside. The sequence of reactions involved in the attempted transformation are depicted in Scheme 33.

SCHEME 33



Compound 68 was prepared according to the method of Evans[17], by the acid catalyzed acetal exchange between benzaldehyde dimethylacetal and methyl-α-D-gluco-pyranoside. Compound 68 was methylated as reported in Vogel's Text-book of Practical Organic Chemistry, page 472, 4th. Ed., providing compound 69 which was recrystallized from cyclohexane. Compound 69 was converted to 70 by irradiating a refluxing suspension in carbon tetrachloride with *N*-bromosuccinimide and calcium carbonate[18].

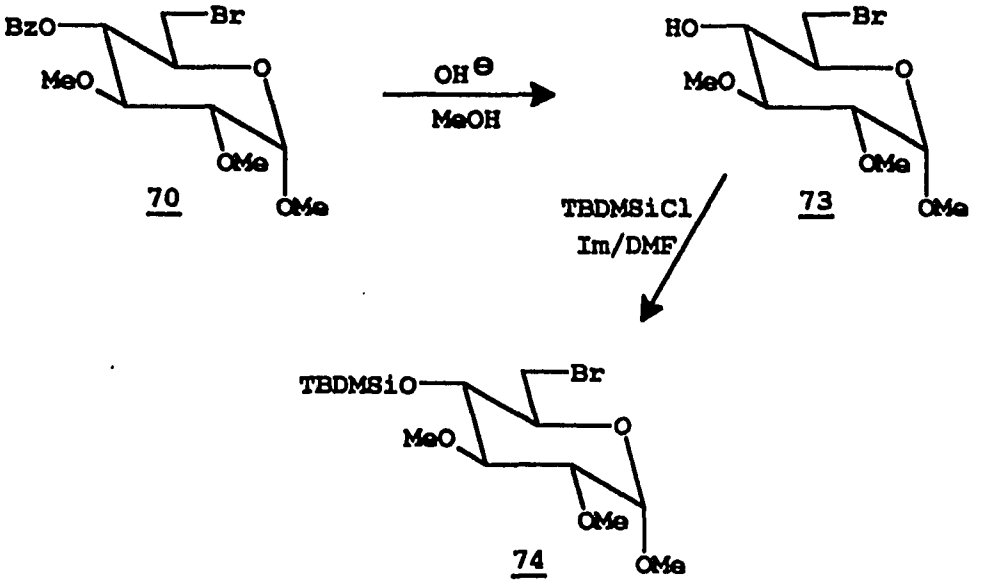
The direct oxidation of the bromide 70 to the saturated aldehyde 71 was not obtainable without insitu elimination to the unsaturated aldehyde 72. In our first attempt, compound 70 was stirred with anhydrous *N*-methylmorpholine-*N*-oxide in DMF at room temperature under a nitrogen atmosphere[19]. After a period of 12 to 18 hours, only the elimination product and the starting bromide were obtained. Next the reaction was performed at 0°C for a duration of 72 hours. There was no oxidation at this temperature, starting materials were recovered exclusively. Repeating the reaction with anhydrous trimethylamine *N*-oxide in DMF for 72 hours also resulted in a large percentage recovery of the starting material, with only trace amounts of the elimination product 72. Performing the reaction under refluxing conditions, as well as extending the reaction times failed to improve the process further. In fact, refluxing the reaction mixture resulted in considerable decomposition of the DMF. Using dry DMSO[19] and anhydrous trimethylamine *N*-oxide[20] at room temperature gave compound 72 in 84% yield. Small amounts of the starting bromide was recovered.

At this point we decided on replacing the protecting benzoate ester with one that is less conducive to elimination. Thus compound 70 was converted to compound 74 by hydroxide hydrolysis to compound 73 followed by *t*-butyldimethylsilylation, Scheme 34.

Compound 74 was stirred with anhydrous *N*-methylmorpholine *N*-oxide in DMF for 72 hours at room temperature. There was no observable oxidation under these conditions, compound 74 was recovered quantitatively. Reactions performed with trimethylamine *N*-oxide in DMF for up to 4 days at room temperature were also uneventful. Finally, oxidation was achieved when DMSO was used as solvent, however, the elimination product 72 was obtained almost exclusively. It was therefore evident that a more robust blocking group was needed, perhaps the tetrahydropyranyl ether group, that is known be even less conducive to elimination.

The reaction between the allylsilane 8 and the unsaturated aldehyde 72 in acetonitrile under Lewis Acid catalysis was also unsuccessful. All attempts which included

SCHEME 34

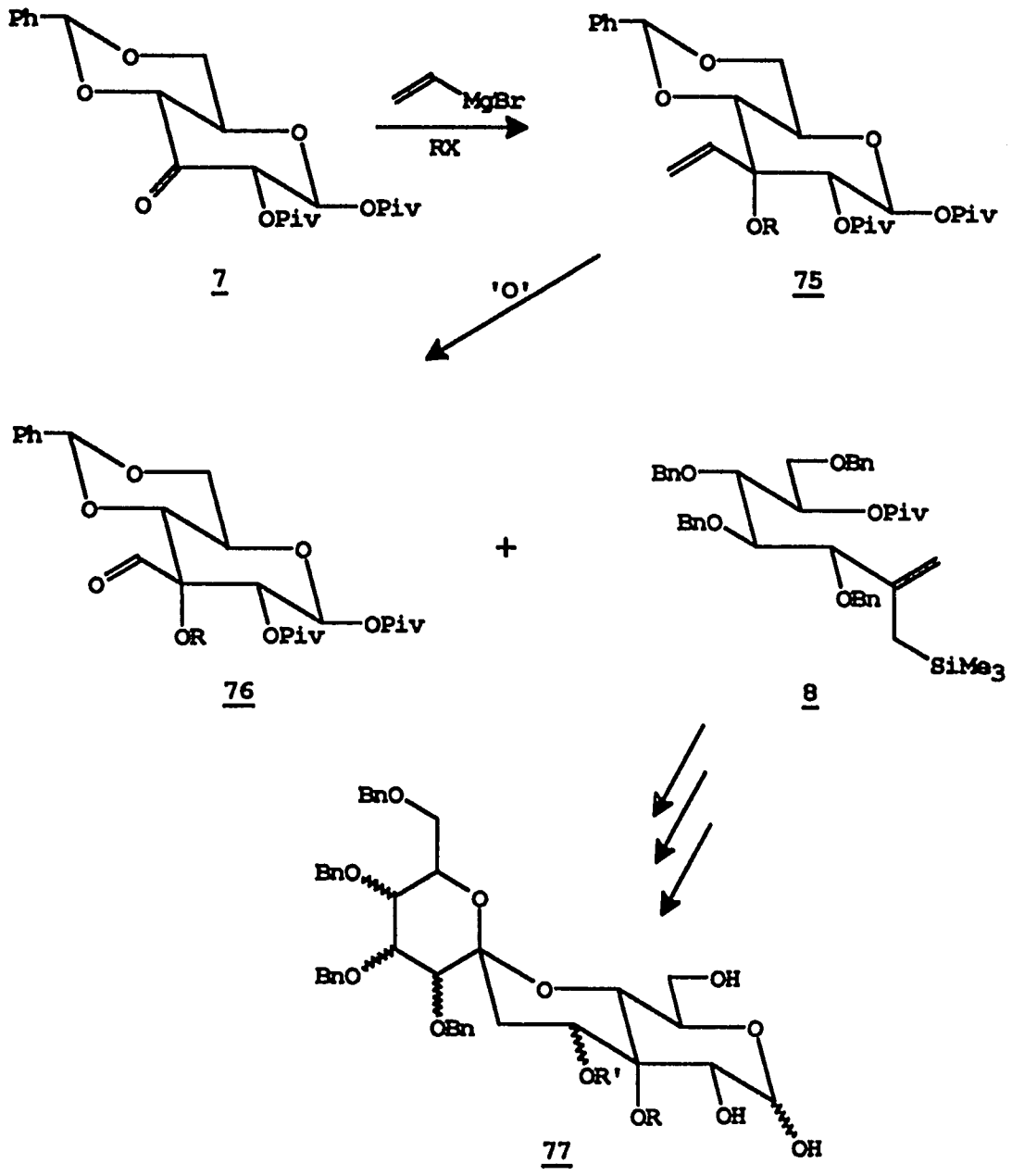


varying the reaction times and the concentration of the reaction medium, resulted in complete protodesilylation of the allylsilane to give the alkene 67, along with a 99% recovery of the aldehyde 72. This observed lack of reactivity might have been a consequence of steric hindrances leading to a negative orientation factor during intermolecular collisions.

It was clearly evident at this point that we must modify our strategy with respect to the coupling of the allylsilane with sugar derivatives. The concept of employing sugar derivatives containing aldehyde functionalities is perhaps most lucrative. Scheme 35 shows how the ulose 7 would have been converted to the aldehyde 76 which would then be coupled with the allylsilane 8 in an anticipated stereospecific fashion. This would have allowed us to prepare the [5.5] spiroketal substructure 77 which can be elaborated into a synthesis of an analog of *calcimycin.*

These are indeed novel ideas that would unquestionably break new grounds in carbohydrate chemistry and organosilicon chemistry in general. Time however was a limiting factor such that we were unable to embark on these latter modifications of our synthetic efforts.

SCHEME 35


Ph
O
O
O
O
OPiv
OPiv
MgBr
RX
7
75
OR
'O'
76
+
BnO
OBn
OPiv
SiMe3
8
77
OH
OR'
OR
OH

GENERAL EXPERIMENTAL INFORMATION

General Procedures

All moisture and/or oxygen sensitive reactions were carried out under a positive pressure of dry nitrogen in a grease free apparatus, which was flame-dried while being flushed with a steady stream of nitrogen. Sensitive liquids and solutions were transferred by syringe and introduced into reaction vessels through rubber septa. Reaction mixtures were stirred magnetically. The progress of all reactions was monitored by thin layer chromatography and/or proton NMR analysis of crude reaction mixtures. Evaporative removal of solvents was accomplished at water aspirator pressure using a Buchi rotary evaporator, removing final traces of solvent from non-volatile samples at 0.5-1.5 mm Hg with a high vacuum oil pump.

Physical Data

Infrared spectra (IR) were measured on a Perkin-Elmer 247 grating spectrophotometer. Samples were prepared as a chloroform solution in sodium chloride cells. Bands are reported in wavenumbers (cm^{-1}) calibrated with the 1601 cm^{-1} absorption of polystyrene film and are described in abbreviation: s=strong; m=medium; w=weak; br=broad. Only relevant, assignable bands are reported.

Proton nuclear magnetic resonance spectra (^1H NMR) were obtained at 200 MHz on an IBM WP/200 FT and/or at 300 MHz on an IBM NR/300 FT spectrometer. Samples were prepared as a $CDCL_3$ or CD_3COCD_3 solution. Chemical shifts are reported in parts per million (ppm; δ values) downfield from internal tetramethylsilane (TMS). Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad), integration, coupling constant, assignment.

Mass spectra (MS) were determined by either electron impact (EI) ionization

or chemical ionization (CI) using the indicated carrier gas (CH_4 or NH_3) on a Finnigan MAT SSQ 70 single focusing mass spectrometer. The protonated molecular ion (M+1) and significant adducts and fragments are reported.

Melting points were determined in open capillaries by using a Uni-melt Thomas Hoover capillary melting apparatus and are reported uncorrected.

Chromatography

Analytical thin layer chromatography (TLC) was performed on freshly coated glass plates (silica gel 60 mesh, 0.25 mm thickness, containing a 254 nm fluorescent indicator, Aldrich Chemical Company). Spots were visualized by using 254 nm ultraviolet irradiation (uv) and/or inserting the plate into a glass tank of vaporized iodine (I_2).

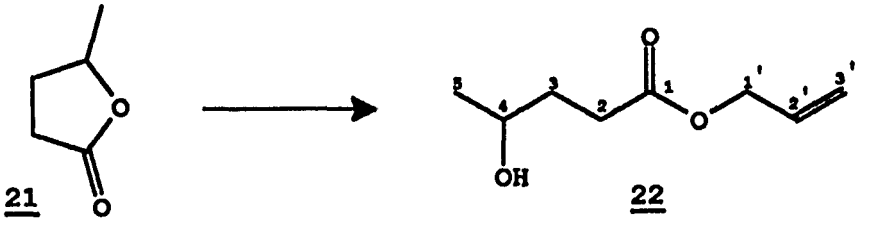
Column chromatography was performed according to standard procedure using 60 mesh silica gel from Aldrich Chemical Company.

Solvents and Reagents

Chloromethyl trimethylsilane purchased from Petrarch Systems was distilled under a positive nitrogen atmosphere at 97°C just before use. Chlorotrimethylsilane was distilled from calcium hydride under an atmosphere of dry nitrogen immediately before use. Valerolactone and phenylhydrazine were distilled under vacuum at 65°C. Benzaldehyde dimethylacetal, 2,2-dimethoxy propane, dimethyl sulfoxide and triethyleneglycol dimethylether (triglyme) were dried over 4A° molecular sieves. DMF was distilled from phosphorus pentoxide just prior to use. *tert*-Butanol and *n*-butanol were distilled from sodium under a nitrogen atmosphere just before use. Tetrahydrofuran (THF) and diethyl ether were distilled under nitrogen from sodium benzophenone ketyl. All other solvents used were purified by distillation under a nitrogen atmosphere from calcium hydride.

SPECIFIC EXPERIMENTALS

Allyl-4-hydroxyvalerate, 22.



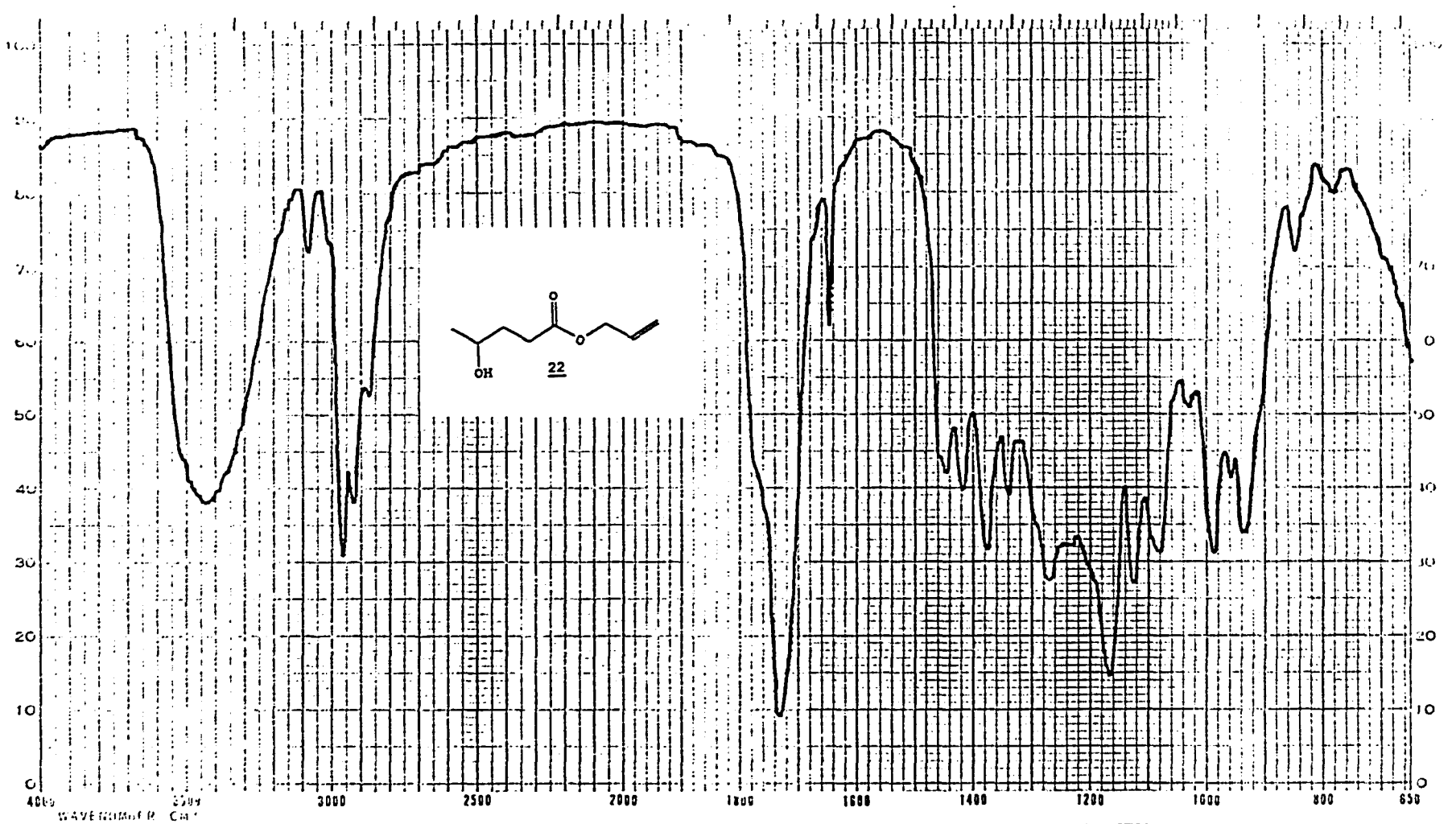
γ-valerolactone **21** (2.5 g, 25 mmol) was refluxed with a 50% aqueous potassium hydroxide (1.68 g, 30 mmol) solution for 30 minutes. The mixture was cooled to room temperature and 10 mL of dichloromethane were added with stirring. Tetrabutylammonium hydrogensulfate (2.55 g, 7.5 mmol) was then added with additional stirring for five minutes. Allyl bromide (6.05 g, 50 mmol) dissolved in 10 mL dichloromethane was later added dropwise with rapid stirring. The reaction mixture was stirred at ambient temperatures overnight after which the organic layer was separated and dried over anhydrous magnesium sulfate. Evaporation of the solvent and flash chromatography (hexanes:EtOAc ; 1:1) afforded compound **22**, (3.10 g, 78.5%).

^{1}NMR (300 MHz, $CDCl_3$, ppm): 5.85-5.98 (m, 1H) C(2')H; 5.21-5.34 (dd, 2H) C(3') H_2; 4.58 (d,2H,*J*=6.0 Hz); 3.78-3.82 (m, 1H) C(4)H; 3.08 (s, 1H) OH; 2.46-2.47 (dt, 2H) C(2)H_2; 1.72-1.80 (m, 2H) C(3)H_2; 1.19 (d, 3H,*J*=9.0Hz) C(5)H_3.

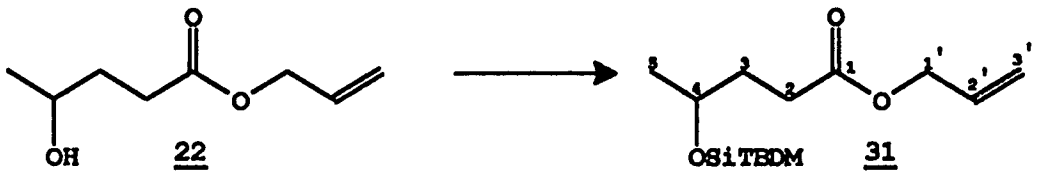
IR(neat,cm^{-1}); 3200-3600 (s) OH; 1725 (s) C=O; 1642 (w) C=C.

Mass Spectrum (EI); Calculated for $C_8H_{14}O_3$ (m/z 158.1). Observed m/z 159.1 (M^++1), 160.1 (M^++2).

PPM
0
1
2
3
4
5
6
22
HO
O
O


OH
22
3000
2500
2000
1600
1400
1200
1000
800
650

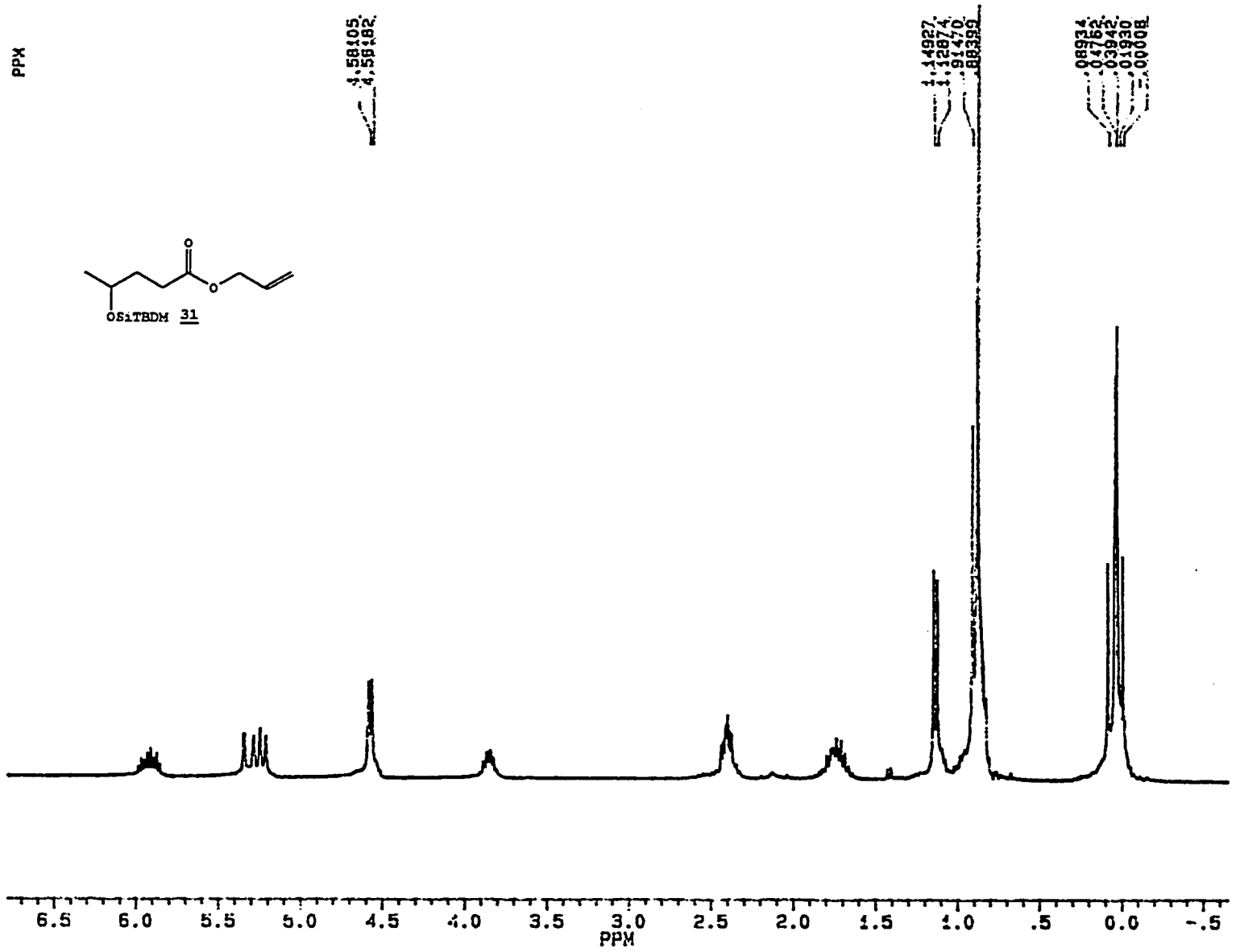
Allyl-4-(-O-tert-butyldimethylsilyl)lvalerate, 31.

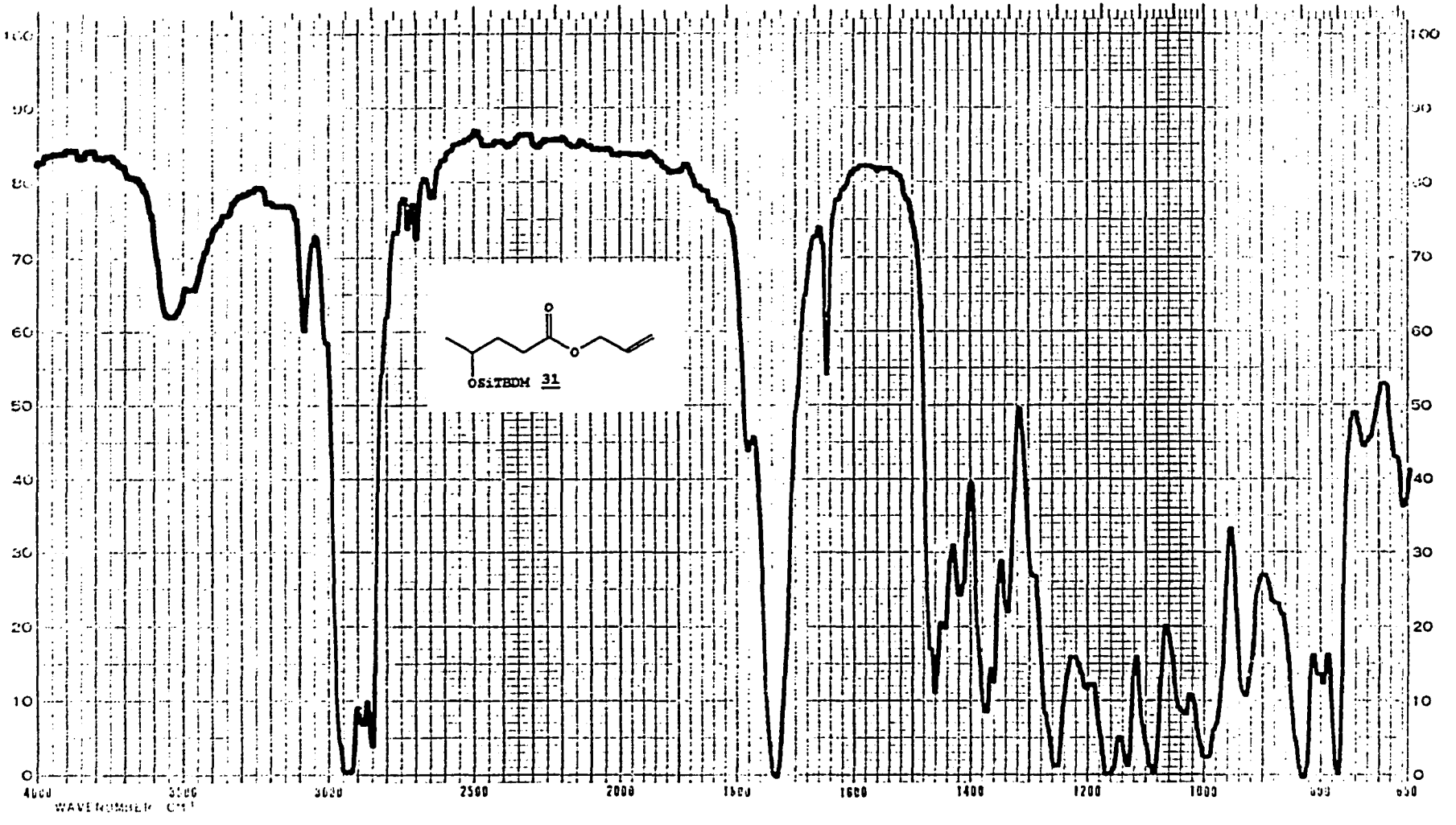


The allylester **22** (2.22 g, 14 mmol) was dissolved in 50 mL of DMF to which imidazole (1.16 g, 17 mmol) was added with stirring until dissolution was complete. *tert*-Butyldimethylchlorosilane (2.53 g, 17 mmol) was then added in one portion, into the flask equipped with a drierite guard tube, and the mixture was stirred at 35-40°C. The reaction was shown to be complete by TLC after 20 hours. Work-up consisted of pouring the reaction mixture into cold pH 7.00 aqueous buffer and extracting with diethyl ether. The organic layer was dried over anhydrous magnesium sulfate and evaporated in vacuo to give a pale yellow oil. Flash chromatography followed (Hexanes : EtOAc ; 1:1) yielding the pure product **31** (3.79 g, 98%).

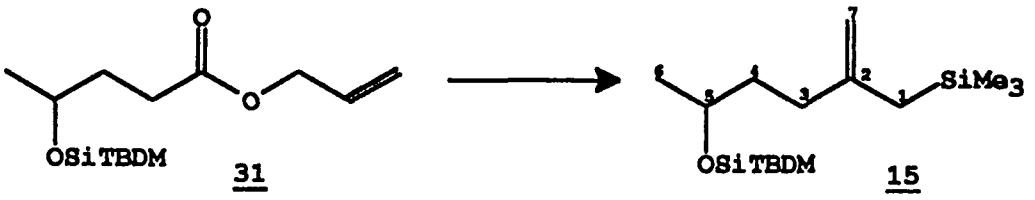
^{1}H NMR (300 MHz, $CDCl_3$, ppm): 5.85-5.98 (m, 1H) C(2')H; 5.22,5.31 (dd, 2H) C(3')H_2; 4.57 (d, 2H,*J*=6.0 Hz) C(1')H_2; 3.80-3.90 (m, 1H) C(4)H; 2.40,2.41 (dt, 2H) C(2)H_2; 1.67-1.79 (m, 2H) C(3)H_2; 1.14 (d, 3H,*J*=6.0 Hz) C(5)H_3; 0.88 (s, 9H) $(CH_3)_3CSi$, 0.04,0.05 (s, 3H; s, 3H) CH_3SiCH_3.

IR(neat, cm^{-1}); 1728 (s), 1642 (w). Mass Spectrum (CI, NH_3); Calculated for $C_{14}H_{28}O_3Si$ (m/z 272.2). Observed m/z 273.1 (M^++1), 290.1 (M^++NH_4^+).

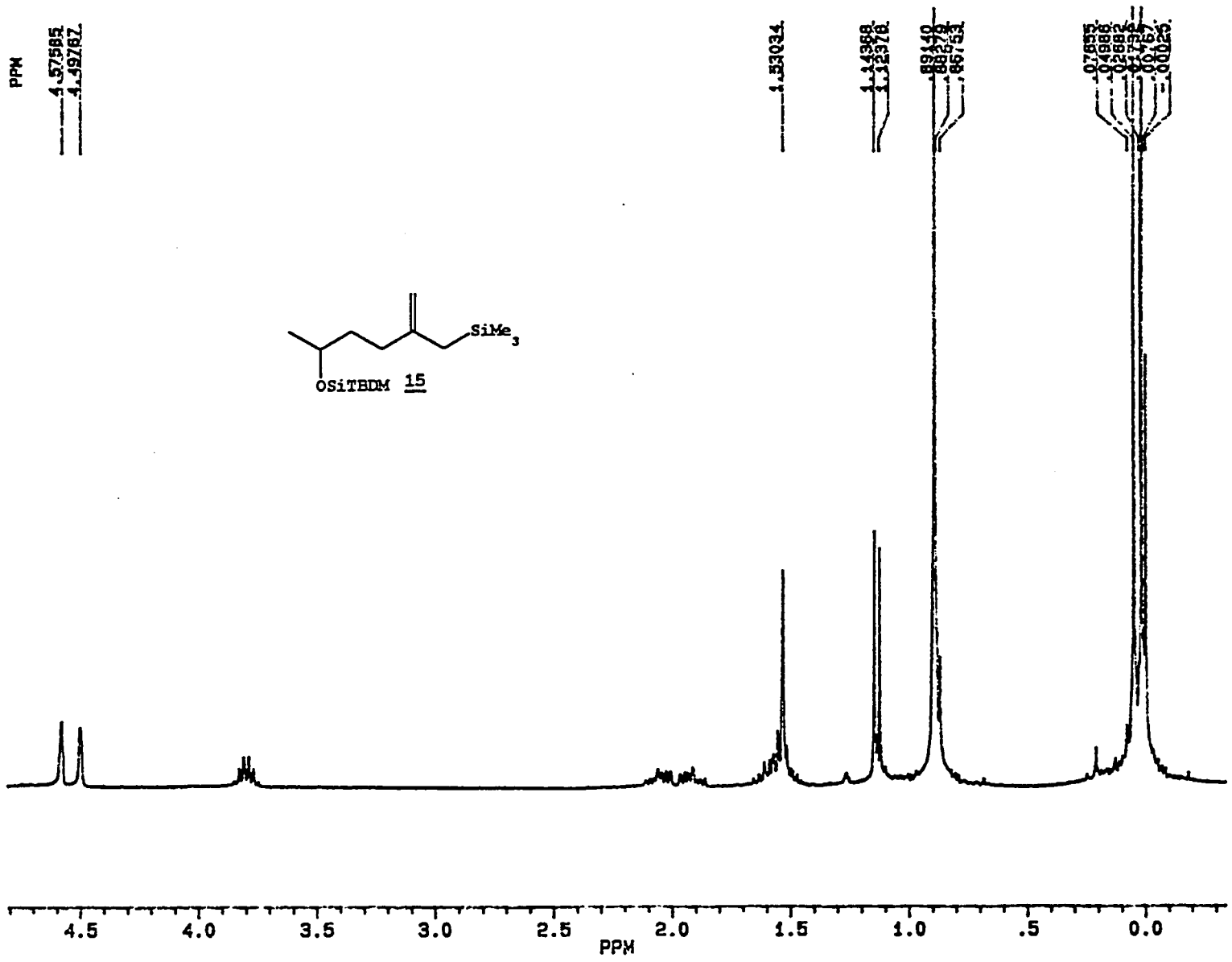

PPM
4.58105
4.58182
1.14927
1.12874
.91470
.88399
.08934
.04762
.03942
.01930
.00008
OSiTBDM 31
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
-.5
PPM


OSiTBDM 31
100
90
80
70
60
50
40
30
20
10
0
4000
3000
2500
2000
1500
1400
1200
1000
650

5-(-O-tert-Butyldimethylsilyl)-2-methylene-1-C-trimethylsilylhexane, 15.



Trimethylsilyl methylmagnesium chloride was prepared in diethyl ether according to a standard procedure and cooled to 0°C for 20 minutes. A solution of the ester **31** (4.0 g, 14.7 mmol) in dry ether (25 mL) was then added dropwise to the organometallic reagent (4 molar equivalents) with rapid stirring. When addition was complete, the ice bath was removed and stirring was continued at room temperature for 30 minutes. At this time a solution of chlorotri- methylsilane (1.76 g, 16.3 mmol) in diethylether (10 mL) was added in one portion and the reaction mixture was stirred at ambient temperatures overnight. The reaction was quenched by pouring into cold saturated aqueous ammonium chloride and extracted with hexanes. The organic layer was dried ($MgSO_4$) and concentrated to give a clear liquid, identified as the tertiary alcohol **32**. The crude product was filtered through a silica gel column using toluene as eluent, during which time the exothermic deoxysilylation process occured to give the desired allylsilane **15** in an overall 85% yield. ^1H NMR (300 MHz, $CDCl_3$, ppm): 4.49,4.57 (ds, 2H) C(7)$\underline{H}_2$; 3.76-3.82 (m, 1H) C(5)$\underline{H}$; 1.86-2.09 (m, 2H) C(3)$\underline{H}_2$; 1.52-1.70 (m, 2H) C(4)$\underline{H}_2$; 1.55 (s, 2H) C(1)$\underline{H}_2$; 1.13 (d, 3H, J=6.0 Hz) C(6)$\underline{H}_3$; 0.89 (s, 9H) $(C\underline{H}_3)_3CSi$; 0.05 (s, 6H) $C\underline{H}_3SiC\underline{H}_3$; 0.02 (s, 9H) $(C\underline{H}_3)_3SiCH_2$. IR(neat, cm^{-1}); 1630 (m), 2900 (s). Mass Spectrum (EI); Calcd. for $C_{16}H_{36}OSi_2$ (m/z 300.2). Observed m/z 300.0 (M^+).


PPM
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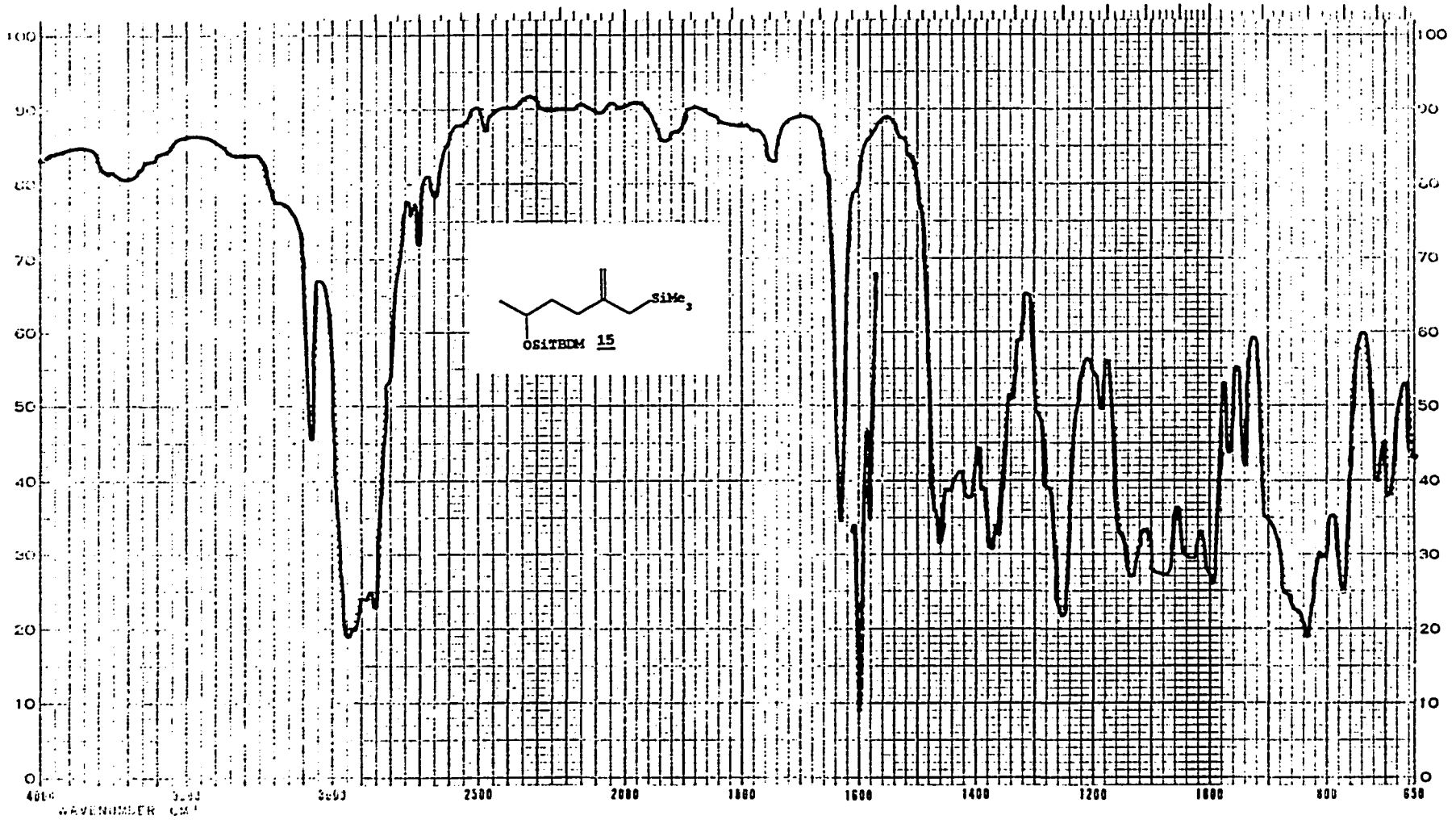
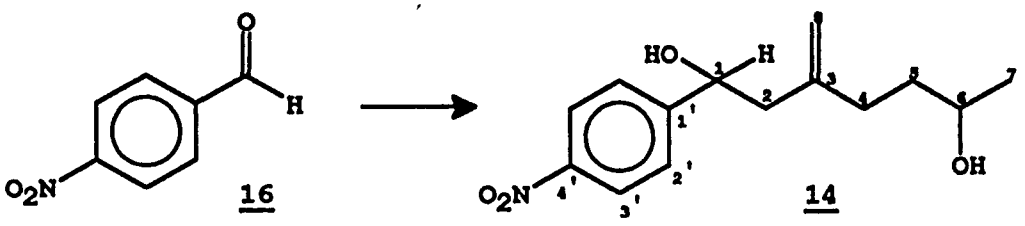
1.14368
1.13378
.88340
.88279
.86753
.07655
.04988
.02682
.01738
.00767
.00025
SiMe3
OSiTBDM 15
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM


OSiTBDM 15
SiMe3
100
90
80
70
60
50
40
30
20
10
0
2500
2000
1800
1600
1400
1200
1000
800
650
WAVENUMBER cm-1

1,6-Dihydroxy-3-methylene-1-(4-nitrophenyl)heptane, 14.



4-Nitrobenzaldehyde (0.05 g, 0.33 mmol) and the allylsilane **15** (0.1 g, 0.33 mmol) were dissolved in 5 mL of freshly purified acetonitrile and the solution was cooled to 0°C. A few drops of $BF_3.OEt_2$ solution were added and stirring was continued for 15 minutes, after which time the reaction was determined to be complete by TLC. The reaction mixture was poured into saturated aqueous sodium bicarbonate and extracted with diethyl ether, followed by drying of the organic layer and concentration in vacuo. The crude reaction product was chromatographed (toluene:EtOAc ; 1:1), so yielding the adduct **14** (0.085 g) quantitatively.

^1H NMR (300 MHz, $CDCl_3$, ppm): 8.15,8.18 (d, 2H,*J*=9.0 Hz) (C(3')$\underline{H}_2$; 7.54 (d, 2H, *J*=9.0 Hz) (C(2')$\underline{H}_2$; 4.90 (m, 1H) C(1)$\underline{H}$; 4.89,4.95 (ds, 2H) C(8)$\underline{H}_2$; 3.79-3.85 (m, 1H) C(6)$\underline{H}$; 3.21 (d, 1H) (O$\underline{H}$); 2.07-2.48 (m, 4H) C(4)$\underline{H}_2$C(5)$\underline{H}_2$; 1.58,1.63 (dd, 2H,*J*=7.0 Hz) C(2)$\underline{H}_2$; 1.19,1.21 (d, 3H,*J*=6.0 Hz) C(7)$\underline{H}_3$.

IR($CHCl_3$, cm^{-1}); 3450 (s), 1680 (w), 1380 (m).

Mass Spectrum (EI); Calculated for $C_{14}H_{19}O_4N$ (m/z 265.1). Found m/z 265.8 (M^+).

PPM
8.18160
8.15941
7.54861
7.52056
4.85054
4.88764
2.44990
2.43852
2.40833
2.37804
2.24770
2.19428
2.16851
1.62433
1.59954
1.21143
1.19130
14
OH
OH
H
O2N
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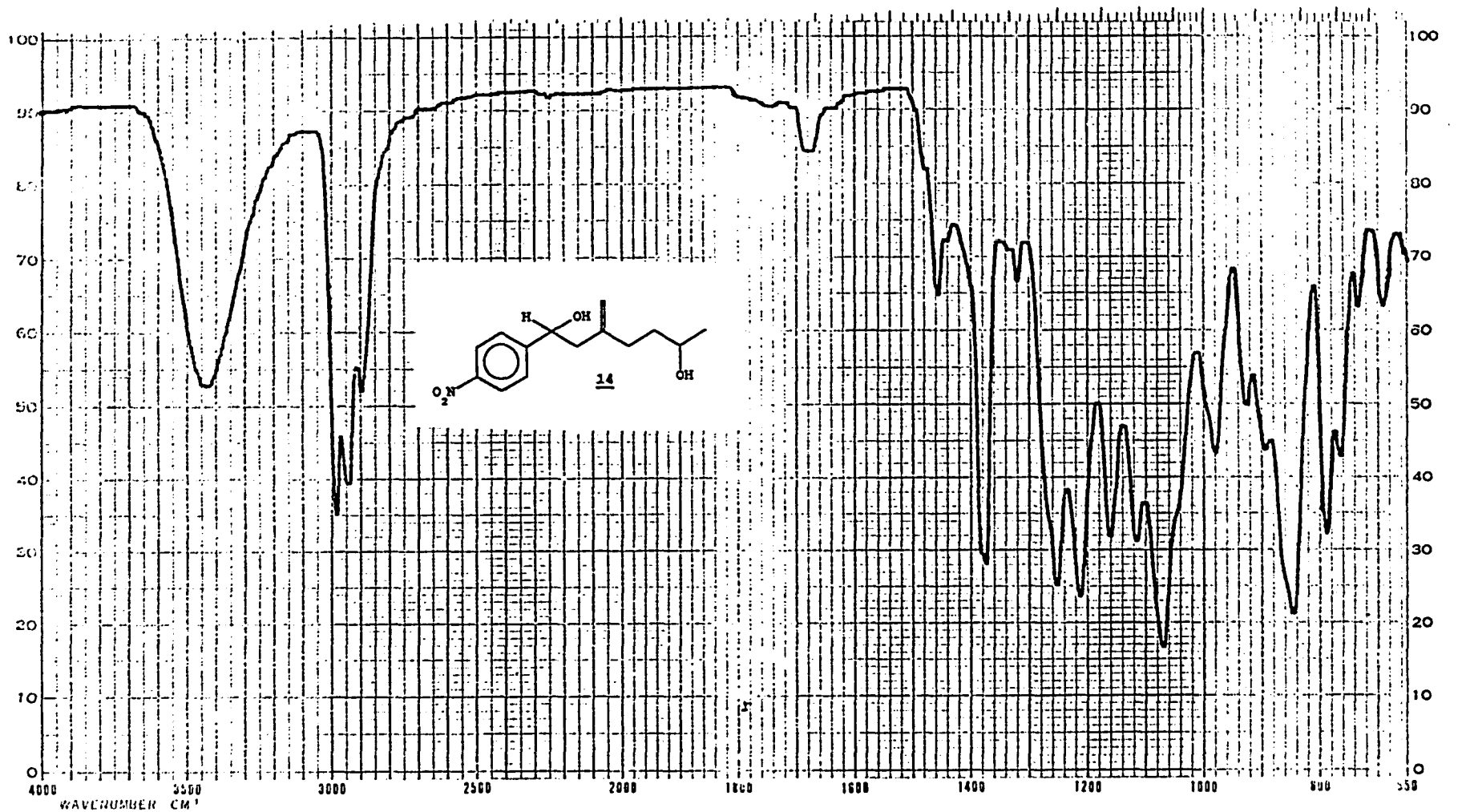
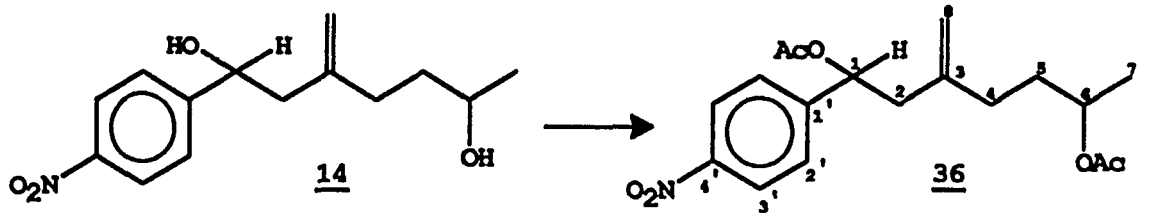
PPM


100
90
80
70
60
50
40
30
20
10
0
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
650
WAVENUMBER CM⁻¹
H
OH
OH
O2N
14

1,6-Di-O-acetyl-3-methylene-1-(4-nitrophenyl)heptane, 36.

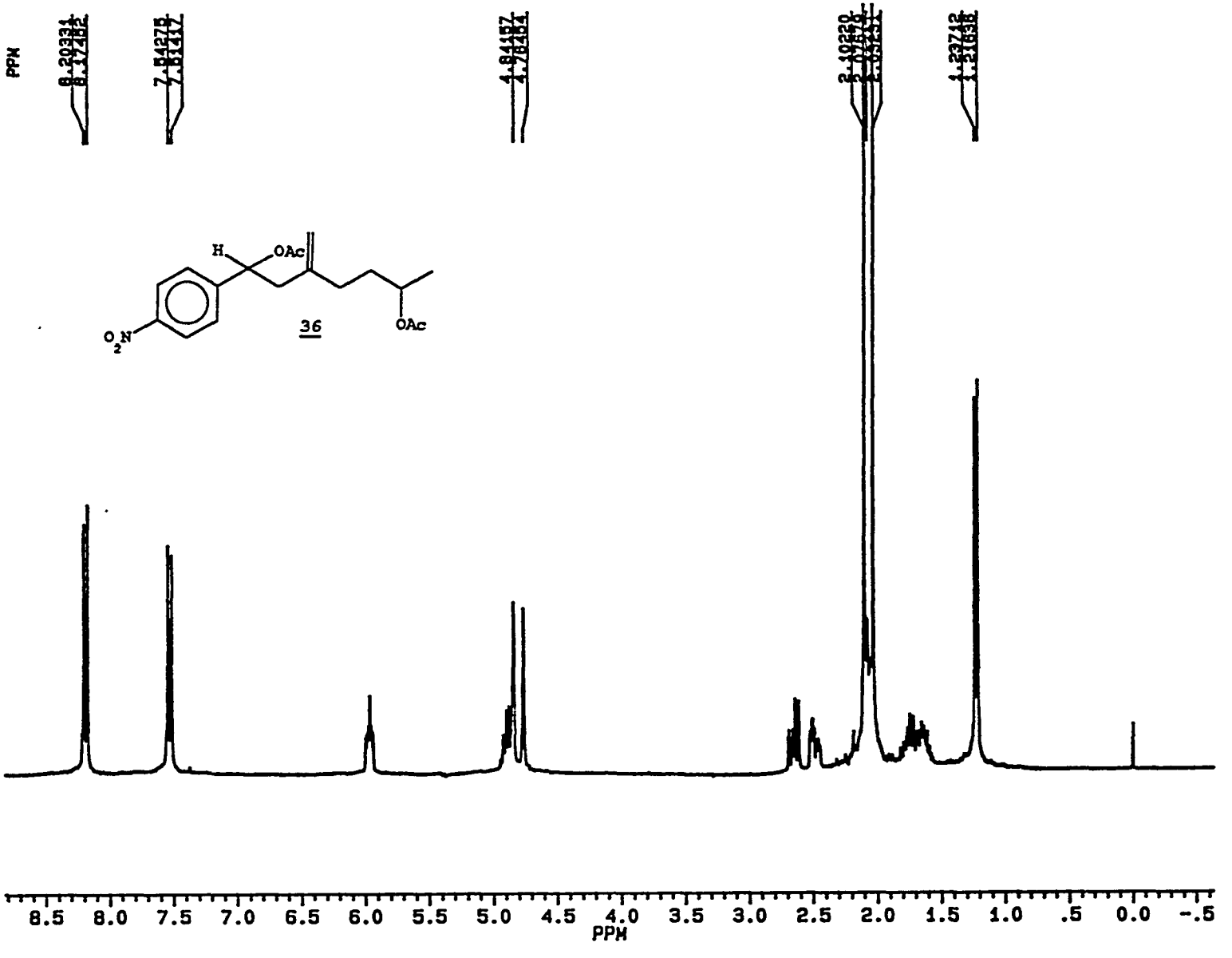


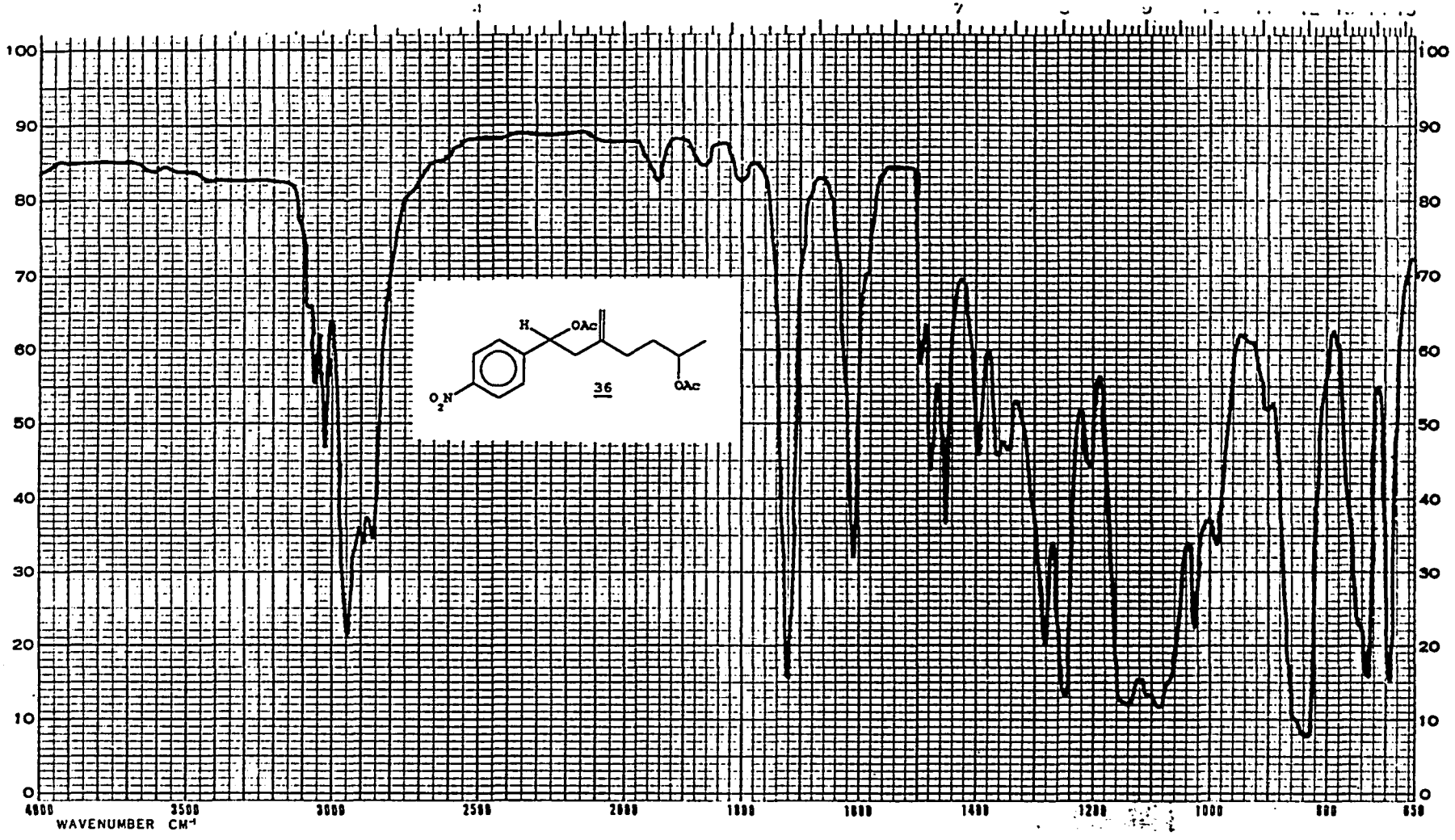
The diol **14** (0.26 g, 0.98 mmol) was dissolved in 10 mL of pyridine to which acetic anhydride (0.22 g, 2.2 mmol) was added. The reaction mixture was stirred at ambient temperatures overnight then poured into cold brine and extracted with ethyl acetate. The organic layer was dried with anhydrous magnesium sulfate. Concentration followed, removing the residual pyridine by azeotropic distillation with toluene. Chromatographic purification (Toluene:EtOAc ; 5:1) gave the compound **36** (0.33 g, 98%).

^{1}H NMR (300 MHz, $CDCl_3$, ppm): 8.19 (d, 2H, J=9.0 Hz) (C(3')$\underline{H}_2$; 7.53 (d, 2H, J=9.0 Hz) (C(2')$\underline{H}_2$; 5.93-5.99 (m, 1H) C(1)$\underline{H}$; 4.84-4.92 (m, 1H) C(6)$\underline{H}$; 4.76, 4.84 (ds, 2H) C(8)$\underline{H}_2$; 2.62,2.67 (dd, 2H, J=24 Hz) C(2)$\underline{H}_2$; 2.45,2.50 (dt, 2H) C(5) $\underline{H}_2$; 2.10 (s, 3H) C(1)H($O_2CC\underline{H}_3$); 2.03 (s, 3H) C(6)H($O_2CC\underline{H}_3$); 1.59-1.80 (m, 2H) C(4)$\underline{H}_2$; 1.22 (d, 3H, J=9.0 Hz) C(7)$\underline{H}_3$.

IR($CHCl_3$, cm^{-1}); 1720 (s), 1610 (m), 1445(m).

Mass Spectrum (EI); Calculated for $C_{18}H_{23}O_6N$ (m/z 349.4). Found m/z 349.9 (M^+), 351.0 (M^++1).


PPM
H
OAc
O2N
OAc
36
8.5 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 -.5
PPM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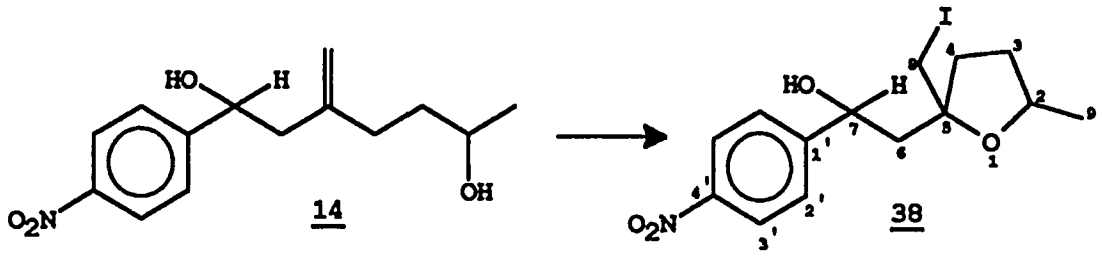
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
650
WAVENUMBER CM⁻¹
H
OAc
O₂N
OAc
36

5-(2-Hydroxy-2-(4'-nitrophenyl)ethyl)-5-iodomethyl-2-methyltetrahydro-furan, 38.



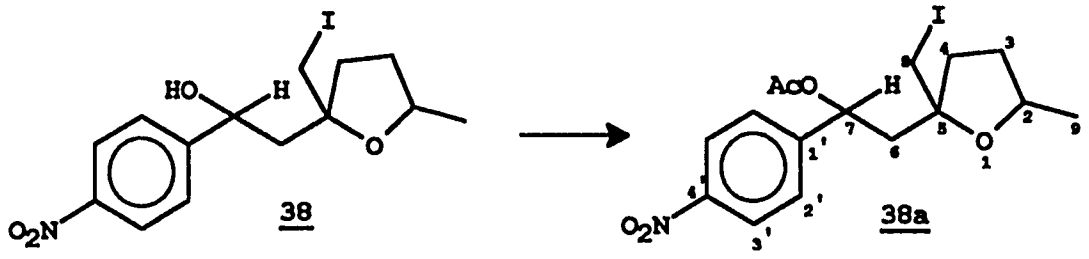
Compound **14** (0.088 g, 0.33 mmol) was dissolved in 5 mL of THF to which solid sodium bicarbonate (0.029 g, 0.35 mmol) was added with stirring. Finely divided crystals of iodine (0.086 g, 0.34 mmol) were then added with rapid stirring at room temperature. After 30 minutes, TLC indicated no further change in the reaction profile. Chromatographic purification gave the monocyclized product **38** (0.13 g, 99%) as a mixture of diastereoisomers.

^{1}H NMR(300 MHz, $CDCl_3$, ppm): 8.19 (d, 2H,*J*=9.0 Hz) (C(3')H)$_2$; 7.59 (d, 2H, *J*=9.0 Hz) (C(2')H)$_2$; 5.09 (dd, 1H,*J*=11 Hz) C(7)H; 4.73 (s, 1H) OH; 4.25-4.41 (m, 1H) C(2)H; 3.55, 3.52,3.38,3.32 (ddd, 2H) C(8)H$_2$; 2.43,2.49 (dd, 2H,*J*=18 Hz) C(6)H$_2$; 2.03-2.19 (m, 2H) C(4)H$_2$; 1.60-1.92 (m, 2H) C(3)H$_2$. IR($CHCl_3$, cm^{-1}); 3450 (m). Compound **38** was acetylated to compound **38a** and further characterized.

PPM
8.21947
8.19102
7.60655
7.58108
5.08330
4.83598
4.73405
3.53817
3.39741
2.12373
1.78532
1.67063
1.32454
1.30220
3B
HO
H
I
O
O2N
8.5
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
PPM

PPM
8.21882
8.19614
8.18949
7.60580
7.57660
3.86835
3.83429
3.39974
3.39507
2.48002
2.45461
2.12497
1.32425
1.32009
1.30413
.00002
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
PPM

5-(2-Acetyl-2-(4'-nitrophenyl)ethyl)-5-iodomethyl-2-methyltetrahydro-furan, 38a.



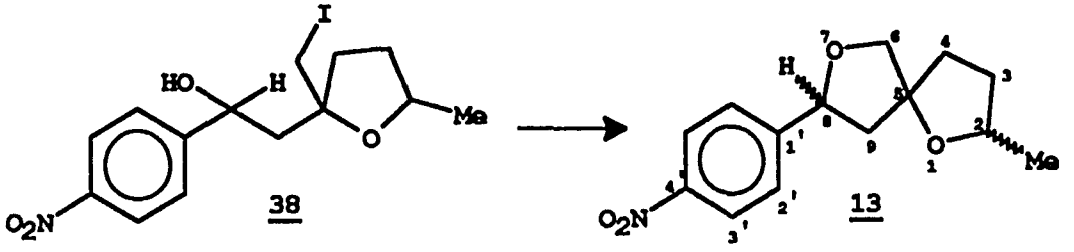
Acetylation of the compound **38** was achieved quantitatively according to the procedure given earlier. The monoacetate **38a** was obtained as a diastereoisomeric mixture, thus confirming the structure of compound **38**, that is, the tetrahydropyranyl ring was first formed.

^{1}H NMR(300 MHz, $CDCl_3$, ppm): 8.17,8.20 (d, 2H,*J*=9.0 Hz) (C(3')H)$_2$; 7.54 (dd, 2H) (C(3')H)$_2$; 5.98-6.06 (ddd, 1H) C(7)H; 4.14-4.18 (m, 1H) C(2)H; 3.18-3.41 (m, 2H) C(8)H$_2$; 2.54,2.50,2.44,2.39 (ddd, 2H) C(7)H$_2$; 2.10,2.12 (d, 3H) C(7)OAc; 1.95-2.21 (m,2H) C(4)H$_2$; 1.41-1.68 (m, 2H) C(3)H$_2$; 1.19,1.24 (d,d, 3H,*J*=6.0 Hz) C(9)H$_3$. IR($CHCl_3$, cm^{-1}); 1719 (s), 1445 (m).

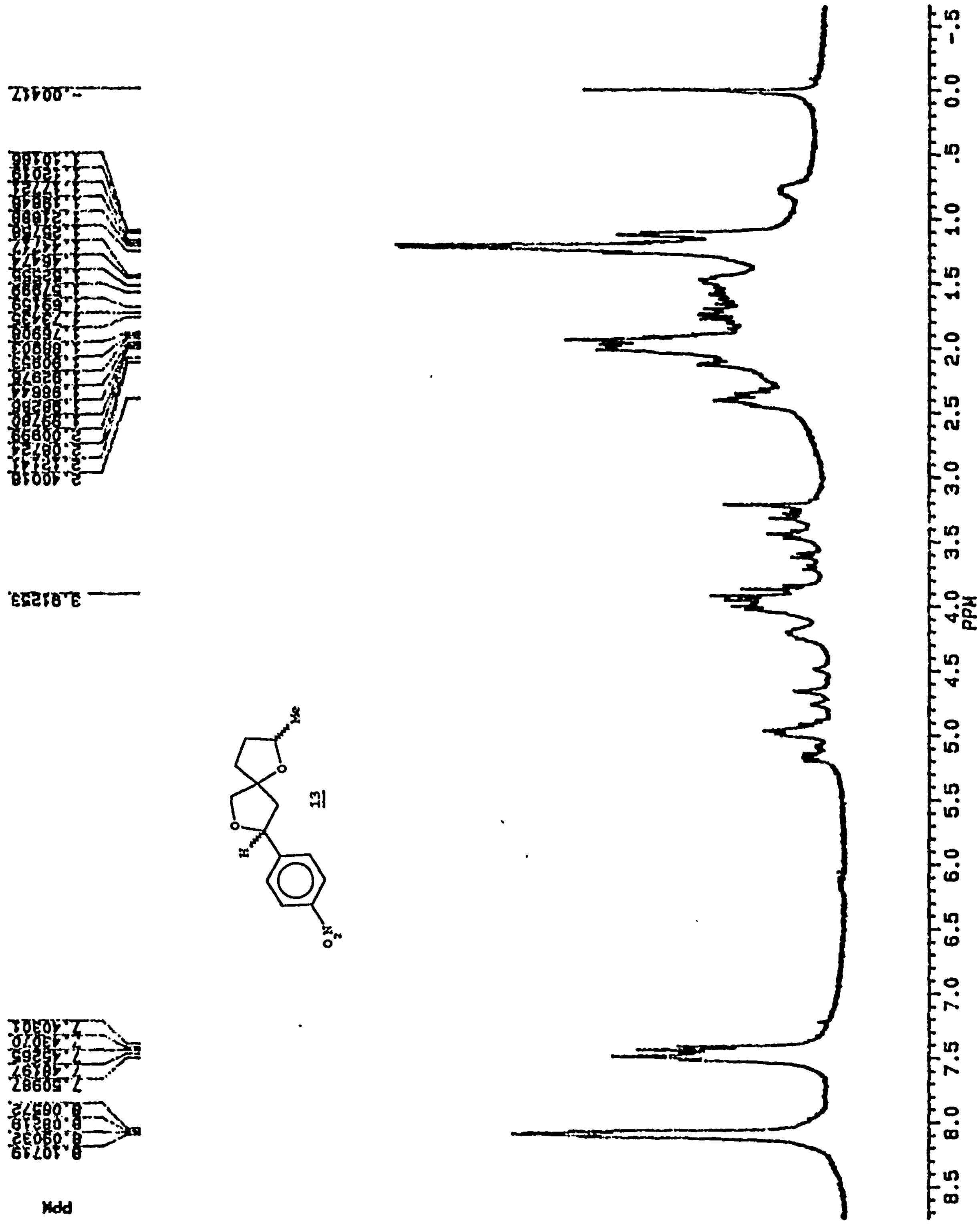
Mass Spectrum (EI); Calculated for $C_{16}H_{20}O_5NI$ (m/z 433.3). Found m/z 433.9 (M^+), 435.0 (M^++1).

PPM
8.20070
8.17305
7.84070
2.12488
2.10707
2.03057
1.25133
1.23162
1.20170
1.18162
AcO
38a
8.5 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
PPM

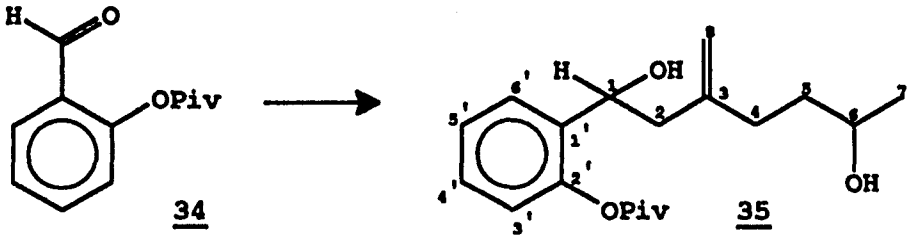
2-Methyl-8-(4-nitrophenyl)-1,7-dioxaspiro[4.4]nonane, 13.



The iodocompound **38** (0.11 g, 0.28 mmol) was dissolved in 5 mL of dry DMF to which one molar equivalent of crystalline silver nitrate was added with rapid stirring. The silver nitrate dissolved immediately, and after one minute the reaction mixture took on a cloudy appearance. After another three minutes of stirring at room temperature, a pale yellow precipitate of silver iodide was formed. The reaction was quenched by pouring into saturated aqueous sodium bisulfite, extracted with diethyl ether and dried over anhydrous $MgSO_4$. Concentration and flash chromatography afforded the compound **13** as an inseparable mixture of diastereoisomers (0.072 g, 98%).
^1H NMR(300 MHz, $CDCl_3$, ppm): 8.06-8.10 (m, 2H) $(C(3')\underline{H})_2$; 7.40-7.50 (m, 2H) $(C(2')\underline{H})_2$; 4.88-4.98 (m, 1H) C(8)H; 3.83-4.01 (m, 1H) C(2)H; 1.10-1.26 (m, 3H) $C\underline{H}_3CH$. Mass Spectrum (EI); Calculated for $C_{14}H_{17}O_4N$ (m/z 263.3).
Found 263.0 (M^+), 263.9 (M^++1).



1,6-Dihydroxy-3-methylene-1-(2-O-pivalophenyl)heptane, 35.



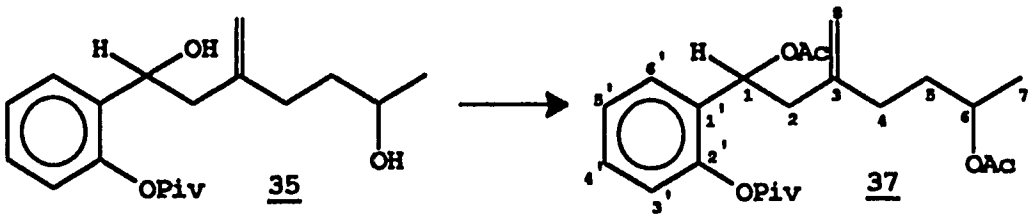
The allylsilane 15 (0.98 g, 3.27 mmol) and the protected aldehyde 34 (0.674 g, 3.27 mmol), were dissolved in 10 mL of acetonitrile and the solution was cooled to 0°C. A catalytic amount of $BF_3.OEt_2$ was added and stirring was continued at 0°C for 30 minutes. Work-up consisted of quenching with cold saturated aqueous sodium bicarbonate, and extraction with diethyl ether. Drying was achieved over $MgSO_4$ followed by concentration and chromatography (toluene:ethyl acetate; 1:1), affording the desired compound 35 (0.94 g, 90%).

^1H NMR(300 MHz, $CDCl_3$, ppm): 7.53,6.91 (d,d, 2H) C(3')HC(6')H; 7.24 (m, 2H) C(4')HC(5')H; 4.91 (dt, 1H) C(1)H; 4.86 (s, 2H) =C(8)H_2; 3.71 (m, 1H) C(6)H; 2.39 (d, 2H) C(2)H_2C= ; 2.07 (m, 2H) =CC(4)H_2; 1.52 (dd, 2H) C(5)H_2; 1.36 (s, 9H) (CH_3)$_3$C; 1.12 (d, 3H) C(7)H_3. IR($CHCl_3$, cm^{-1}); 3350 (s), 1745 (s).

Mass Spectrum (CI, NH_3); Calculated for $C_{19}H_{28}O_4$ (m/z 320.2). Found m/z 320.2 (M^+), 338.2 (M^++NH_4).

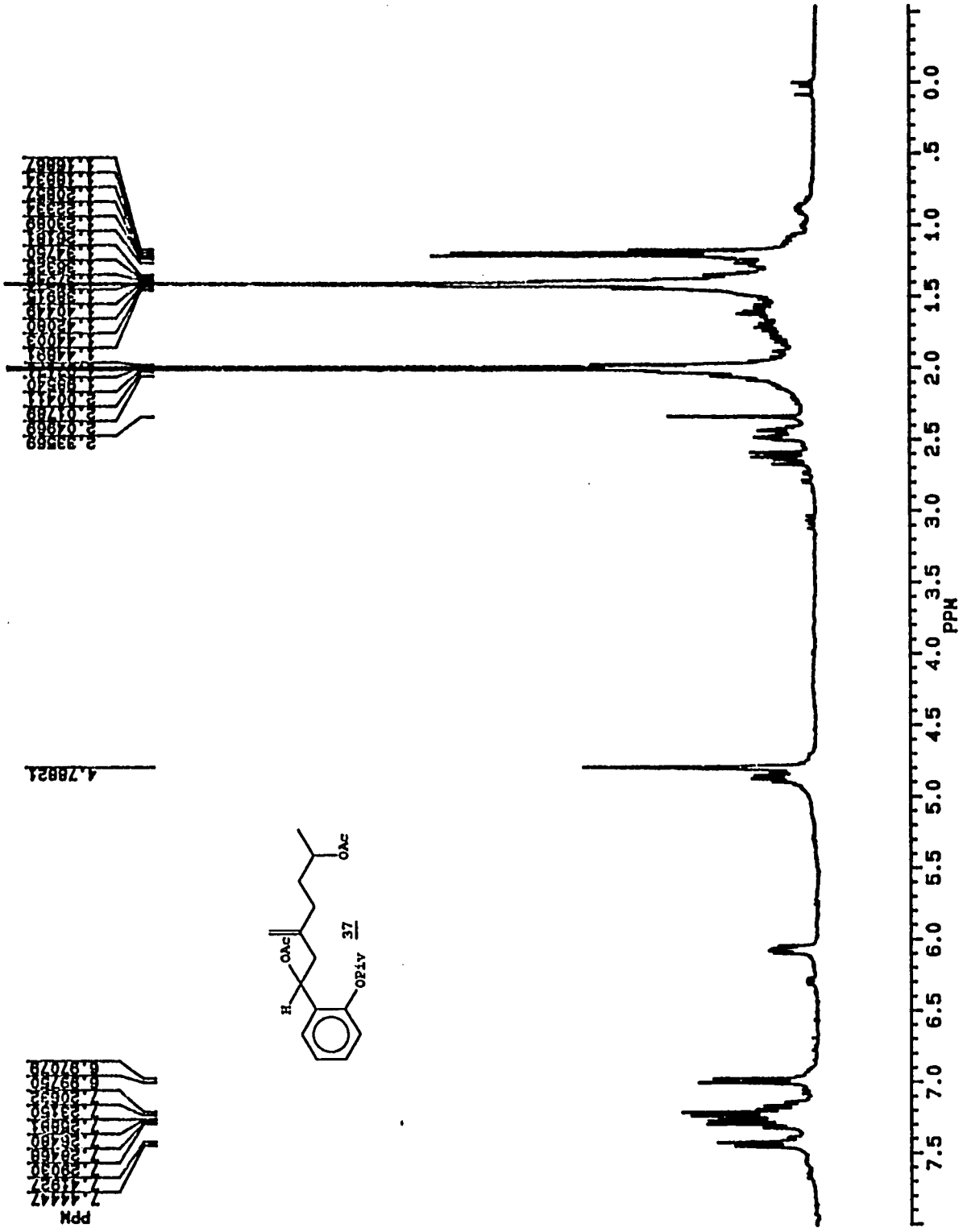
OH
OH
H
OPiv
35
PPM

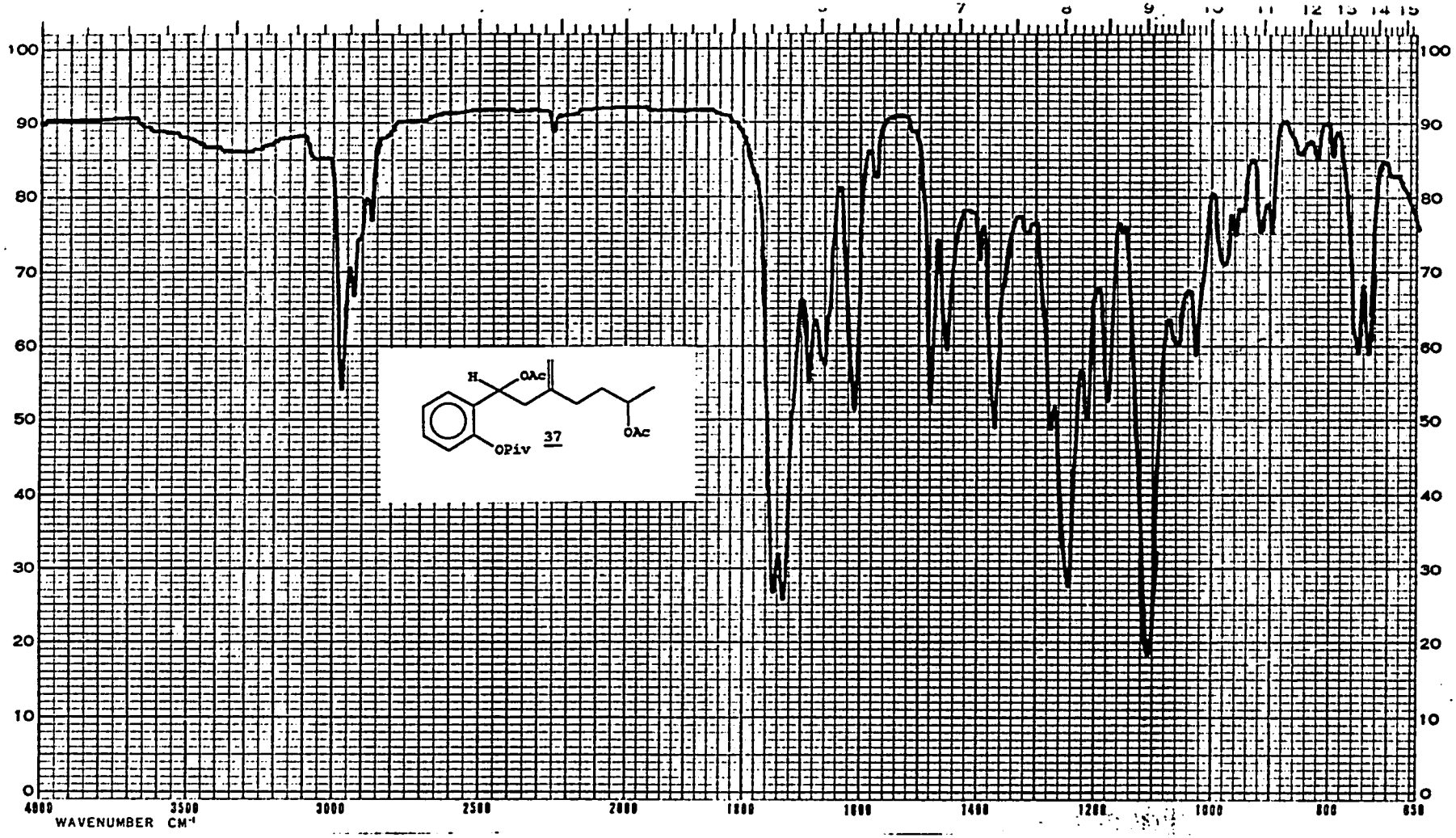
1,6-Diacetaxy-3-methylene-1-(2-O-pivalophenyl)heptane, 37.



Compound **35** was acetylated employing a standard procedure as outlined earlier, providing the desired product **37** quantitatively.

^{1}H NMR(300 MHz, $CDCl_3$, ppm): 6.97-7.44 (m, 4H) C(3',4',5',6')H; 6.05,6.07 (dt, 1H) C(1)H; 4.85 (m, 1H) C(6)H; 4.78 (s, 2H) =C(8)H_2; 2.60,2.64 (dd, 2H) C(2)H_2; 1.5-1.80 (m, 2H) =CC(4)H_2; 2.00,1.98 (ds, 6H) (CH_3CO_2)$_2$;1.39 (s, 9H) (CH_3)$_3$C; 1.19 (d, 3H) C(7)H_3. IR($CHCl_3$ cm^{-1}); 2950 (m), 1730, 1750 (s), 1610 (m). Mass Spectrum (CI, NH_3); Calculated for $C_{23}H_{32}O_6$ (m/z 404.2). Found m/z 422.3 (M^++NH_4); (EI) m/z 404.2 (M^+), 405.3 (M^++1).


OAc
OAc
H
OPiv
37
PPM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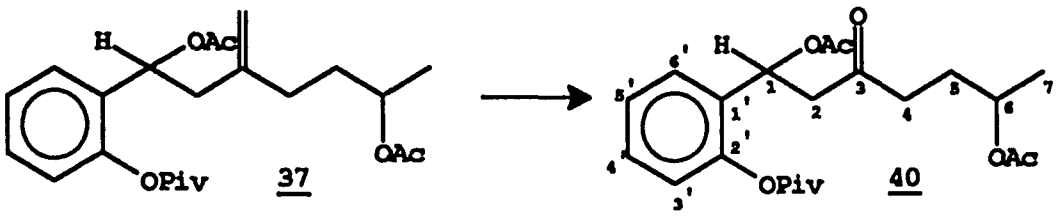
1400
1200
1000
800
650
WAVENUMBER CM⁻¹
H
OAc
OPiv
OAc
37

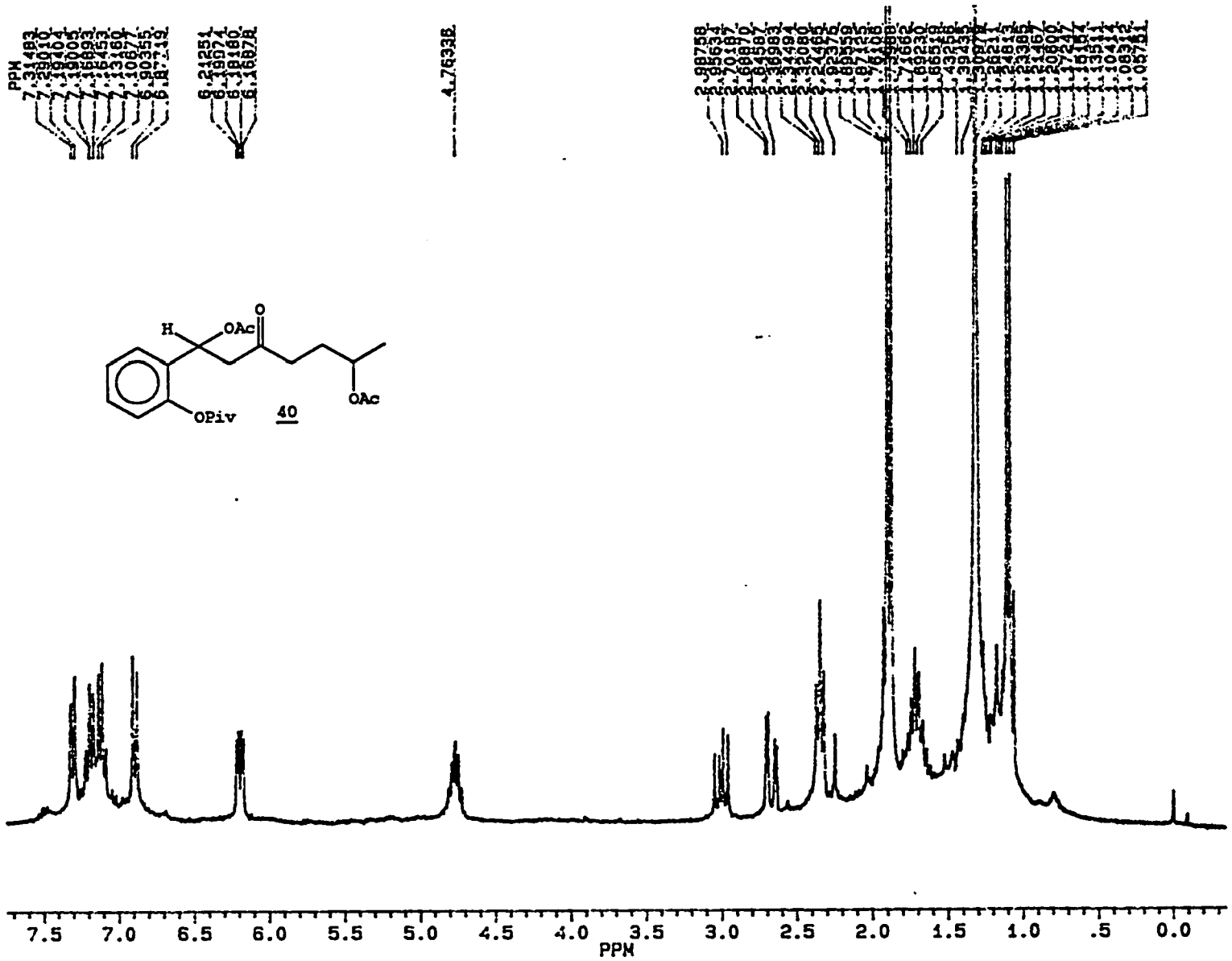
1,6-Di-O-acetyl-1-(2-O-pivalophenyl)-3-heptanone, 40.



The alkene 37 (0.28 g, 0.79 mmol) was dissolved in 10 mL absolute ethanol to which 30 mL of a solution of osmium tetroxide in *tert*-butanol (1mg/mL) and solid sodium metaperiodate (2.0 g, 9.4 mmol) were added with rapid stirring at room temperature. After three minutes of stirring, 3 mL of water were added and stirring was continued overnight after which time considerable precipitation of sodium iodate occured. Brine was added (50 mL) followed by thorough extraction (5 x 15 mL) with ethyl acetate. The organic layer was dried ($MgSO_4$) and concentrated to give the carbonyl compound 40 (0.26 g, 92%). Compound 40 was taken into the next series of reactions without further purification.

^1H NMR(300 MHz, $CDCl_3$, ppm): 6.87-7.31 (m, 4H) (aromatic C<u>H</u>); 6.17,6.20 (dd, 1H) C(1)<u>H</u>; 4.76 (m, 1H) C(6)<u>H</u>; 2.64, 2.67,2.98,2.99 (ddd, 2H) C(2)$\underline{H}_2$; 2.34 (t, 2H) C(4)$\underline{H}_2$; 1.87,1.89 (ds, 6H) $(C\underline{H}_3CO_2)_2$; 1.65-1.73 (m, 2H) C(5)$\underline{H}_2$; 1.30 (s, 9H) $(C\underline{H}_3)_3C$; 1.05,1.08 (d, 3H) C(7)$\underline{H}_3$. IR(neat, cm^{-1}); 1725 (s, br)

Mass Spectrum (CI, NH_3); Calculated for $C_{22}H_{30}O_7$ (m/z 406.2). Found m/z 424.2 (M^++NH_4); (EI) m/z 407.1 (M^++1).


H
OAc
O
OAc
OPiv
40
PPM
7.5
7.0
6.5
6.0
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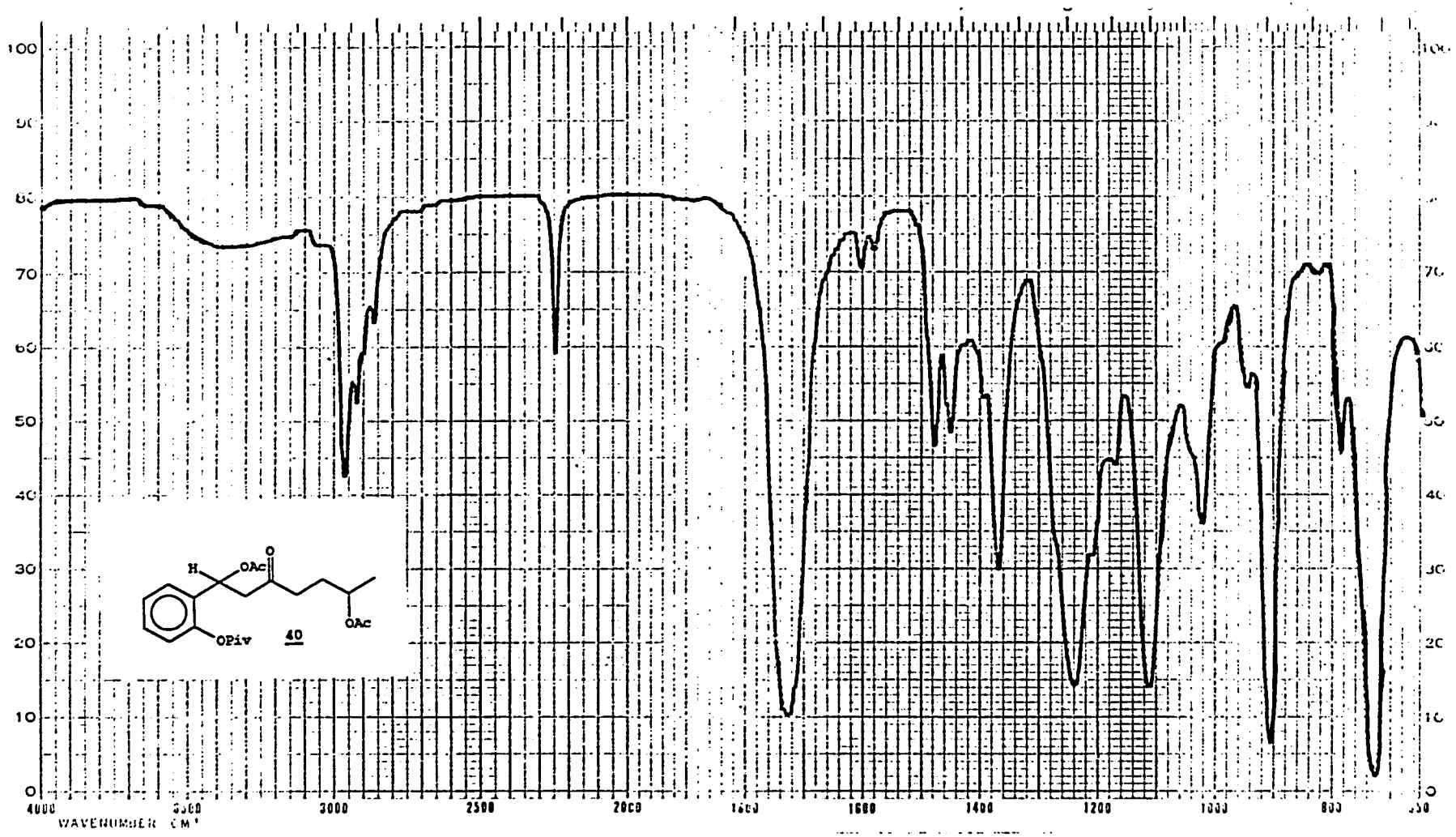
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0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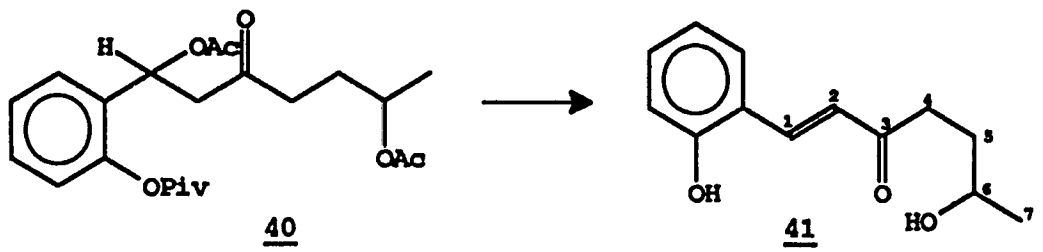
1600
1400
1200
1000
800
WAVENUMBER CM⁻¹
H
OAc
O
OAc
OPiv
40

6-Hydroxy-1-(2-hydroxyphenyl)-E-1-hepten-3-one, 41.



40 41

Compound 40 (0.15 g, 0.37 mmol) was dissolved in 10 mL methanol to which anhydrous potassium carbonate (0.051 g, 0.37 mmol) was added with stirring at room temperature. After 5 hours, TLC indicated the reaction was complete, hence was concentrated at low temperatures, brine was added and extracted with ethyl acetate. Drying of the organic extracts was achieved over $MgSO_4$, followed by concentration at reduced pressure. Flash chromatography using a 1:1 mixture of hexanes and ethyl acetate afforded the unsaturated ketone 41 (0.07 g, 85%).

^1H NMR(200 MHz, $CDCl_3$, ppm): 7.98 (d, 1H, J=16.0 Hz) ArC(1)H; 6.85 (d, 1H, J=16.0 Hz) C(2)H; 4.15 (s, 2H) OH; 3.78-3.87 (m, 1H) C(6)H; 2.84 (t, 2H) $C(4)H_2$; 1.77-1.84 (m, 2H) $C(5)H_2$; 1.23 (d, 3H) $C(7)H_3$.

IR($CHCl_3$, cm^{-1}); 3350 (s), 1710, 1700 (s), 1600 (m).

Mass Spectrum (EI); Calculated for $C_{13}H_{16}O_3$ (m/z 220.3). Found m/z 220.1 (M^+).

PPM
8.02375
7.84338
7.50588
7.38713
7.26533
7.22891
7.16832
6.89201
6.85590
6.81335
4.14633
3.84535
3.81457
2.89035
2.84348
2.80682
2.34903
1.84478
1.83342
1.82001
1.80682
1.77384
1.26819
1.24025
1.20868
.10708
.10333
.09844
.09352
.08860
.08560
.08051
OH
OH
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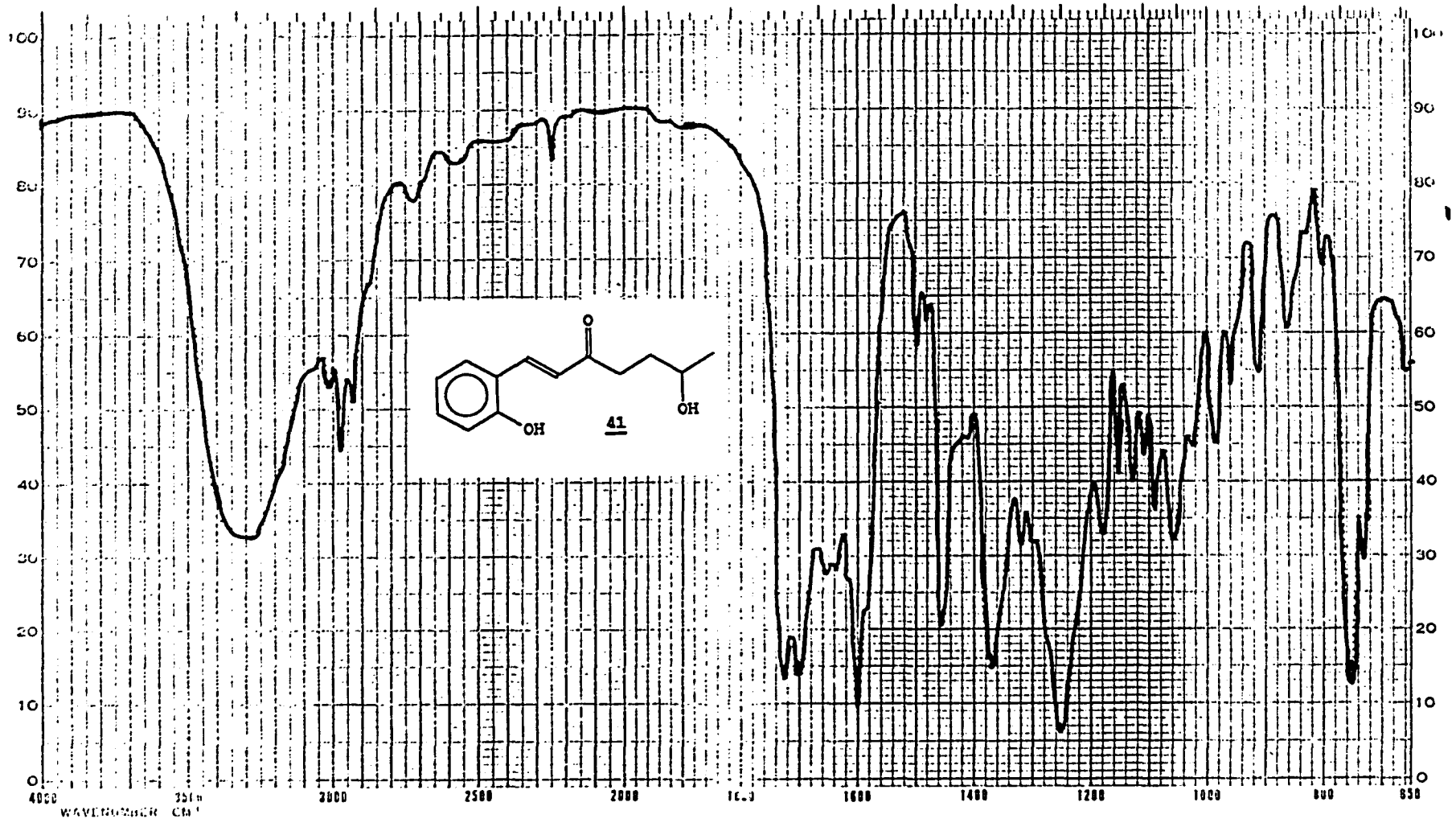
3.0
2.0
1.0
0.0
PPM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10
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4000
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2500
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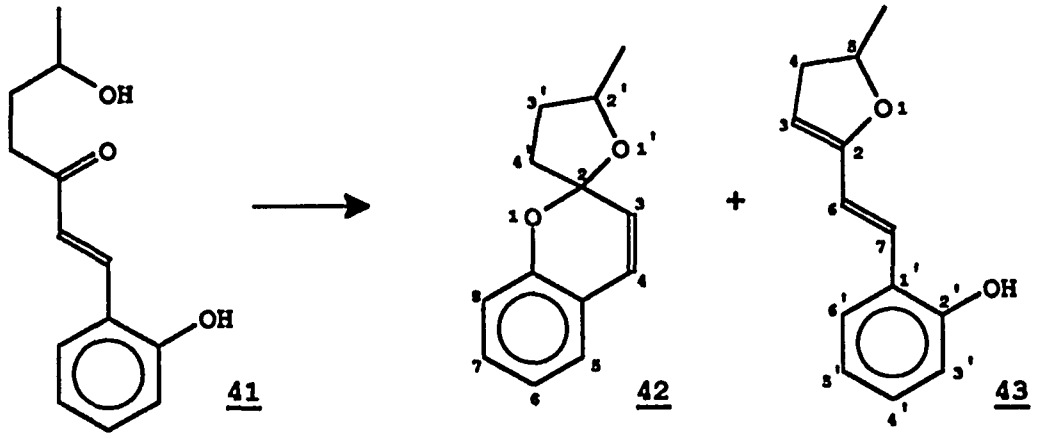
1600
1400
1200
1000
800
850
OH
OH
41

Spiro[chromene-2-tetrahydrofuran]-2'-yl, 42;

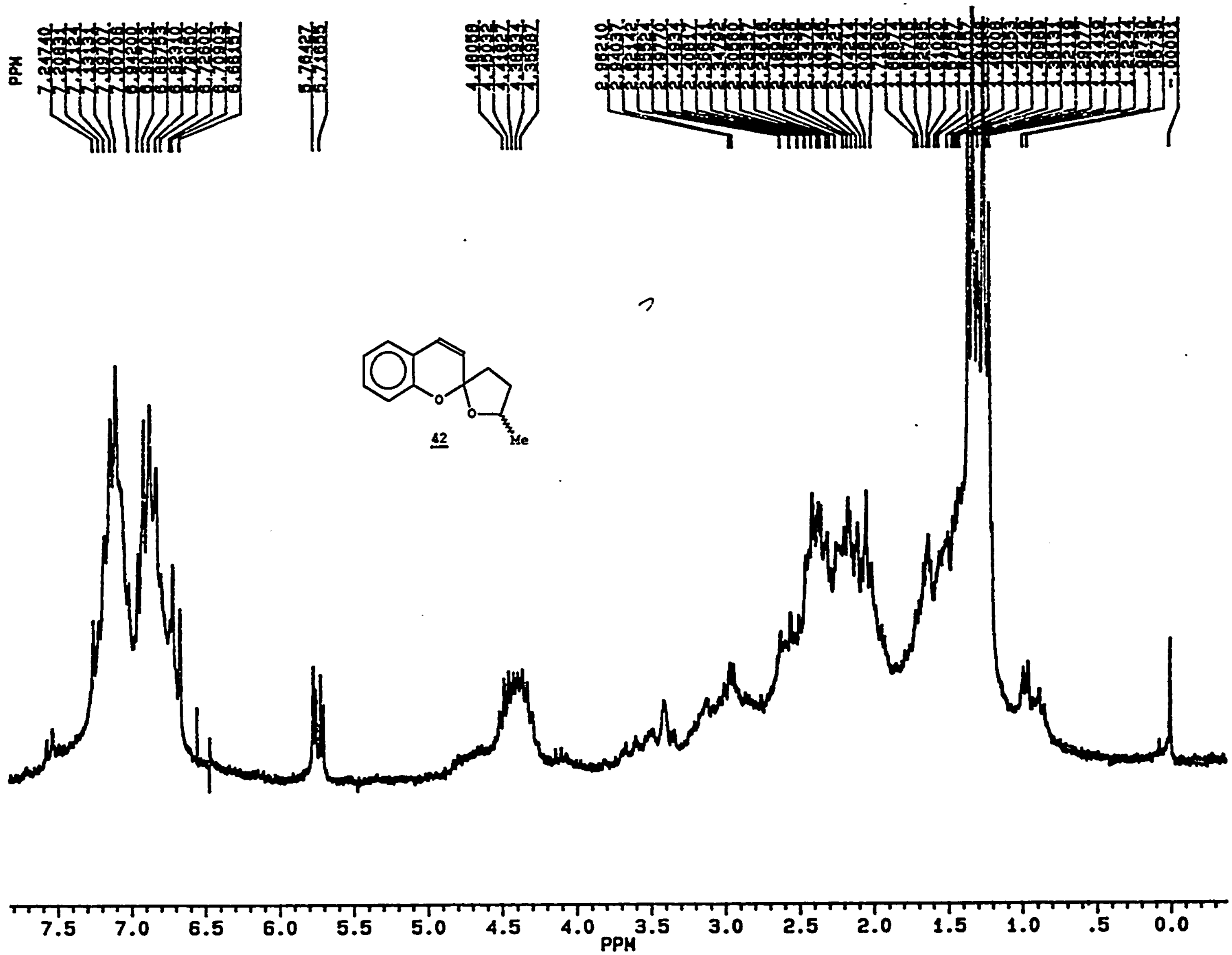
2-[2-o-Hydroxyphenyl-E-ethylene]dihydrofuran-5-yl, 43.



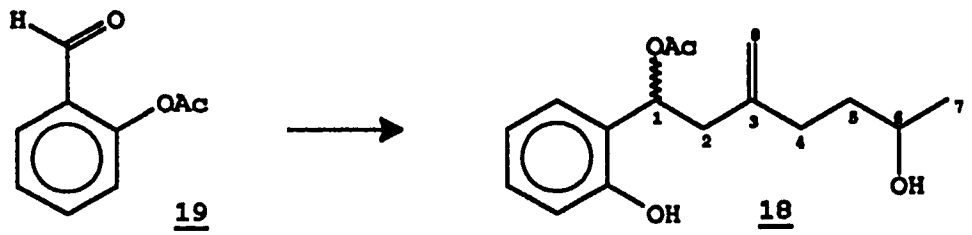
Compound **41** (0.20 g, 0.91 mmol) was dissolved in 5 mL of dry THF to which a few pellets of molecular sieves (4A°) and a small crystal of *p*-TSA (catalytic) were added with stirring. After two hours, TLC analysis revealed complete consumption of the starting material **41**, thus the reaction mixture was poured into saturated aqueous sodium bicarbonate and extracted with ethyl acetate. After drying ($MgSO_4$) and concentration, column chromatography (hexanes:ethyl acetate ; 2:1) afforded the compounds **42** and **43** in an overall yield of about 85%. The spiroketal **42** was subsequently discovered to be unstable hence was not amenable to extensive analysis.

^{1}H NMR(200 MHz, $CDCl_3$, ppm): **42**; 6.70 (dd, 1H) ArC(4)H=CH; 5.71,5.76 (dd, 1H) ArCH=C(3)H; 4.36-4.48 (m, 1H) C(2')H; 2.00-2.62 (m, 4H) C(3')H_2C(4')H_2; 1.21-1.34 (dd, 3H, *J*=6.0 Hz) CH_3C(2')H. **43**; 7.89 (d, 1H,*J*=16 Hz) ArC(7)H=CH; 6.91 (d, 1H,*J*=16 Hz) ArCH=C(6)H; 4.93-5.03 (m, 1H) CH_3C(5)H; 4.13 (t, 1H) =C(3)HCH_2; 2.75 (t, 2H) C(4)H_2; 1.28 (d, 3H) CH_3C(5)H.

IR($CHCl_3$, cm^{-1}); 3450 (s), 1600 (m), 1520 (m).


PPM
42
Me
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
PPM

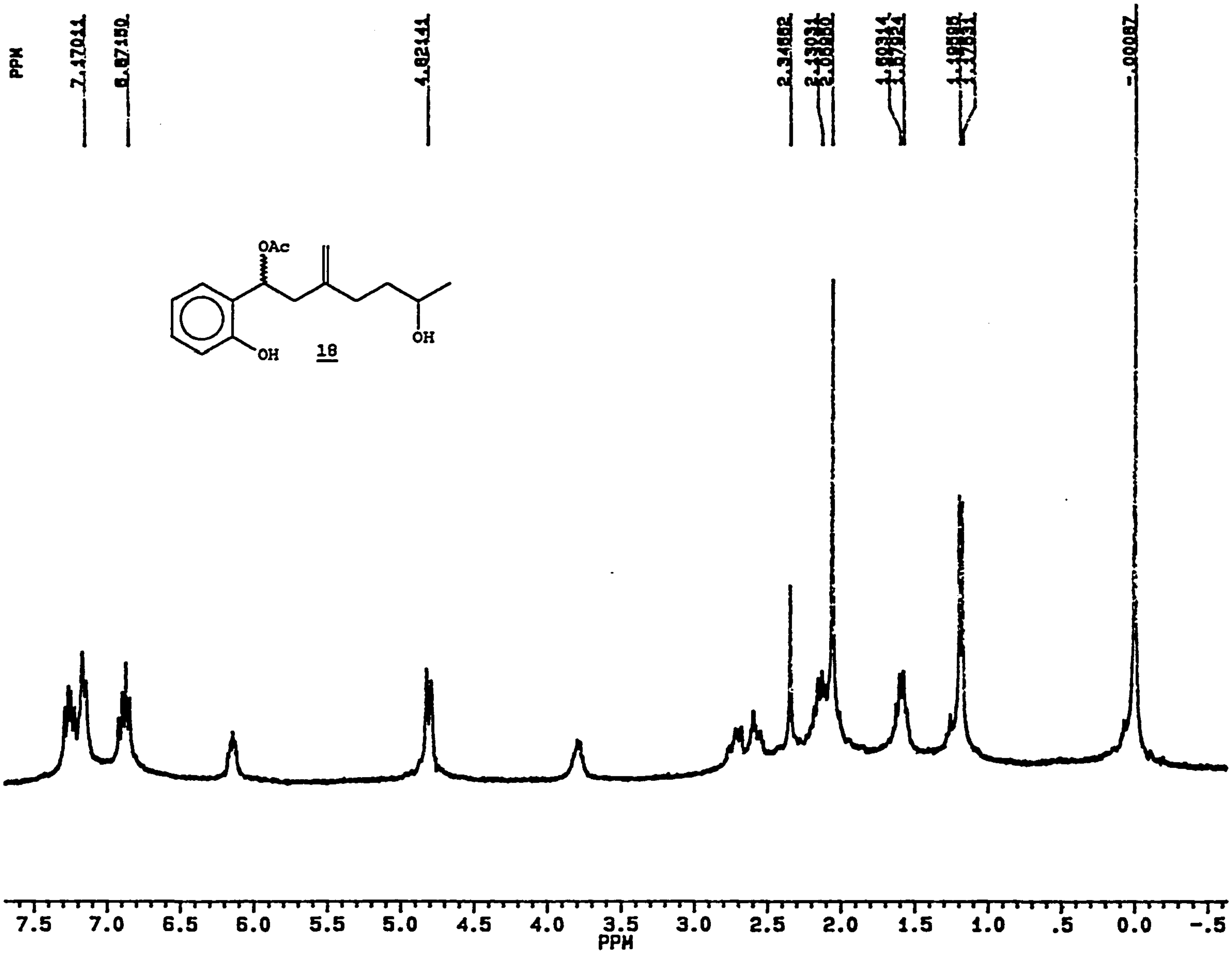
1-O-Acetyl-6-hydroxy-1-(2-hydroxyphenyl)-3-methylenoheptane, 18.



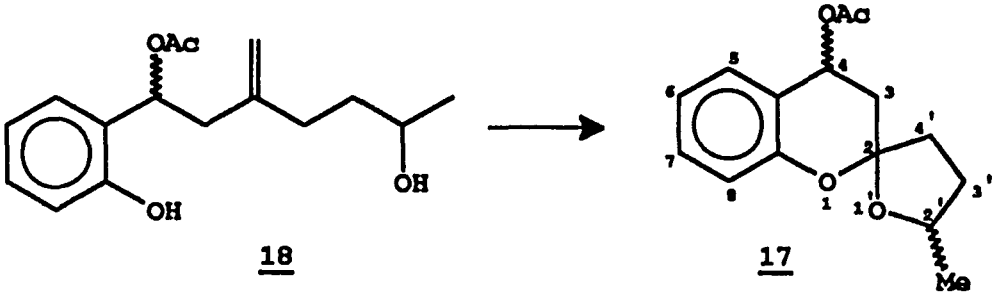
Employing the same procedure used with the pivalate **34** (page 115), compound **18** was synthesized by the BF_3 catalyzed addition of the allylsilane **15** (1.02 g, 3.43 mmol) to the acetate **19** (0.56 g, 3.43 mmol), in acetonitrile at 0°C. As anticipated, the reaction proceeded with migration of the acetate blocking group so preparing the molecule for spiroketalization. Compound **18** (0.83 g, 90%) was obtained exclusively.

^1H NMR(300 MHz, $CDCl_3$, ppm): 7.15-7.26,6.83-6.88 (m, 4H) Aromatic; 6.13-6.15 (m, 1H) C(1)H; 4.81 (d, 2H,*J*=9.0 HZ) =C(8)H_2; 3.78 (m, 1H) C(6)H; 2.56-2.72 (m, 2H) C(2)H_2; 2.34 (s, 2H) OH; 2.12-2.19 (m, 2H) C(4)H_2; 2.06 (s, 3H) CH_3C=O; 1.56-1.61 (m, 2H) C(5)H_2; 1.18 (d, 3H) C(7)H_3.

IR(neat, cm-1); 3657 (s), 1730 (s), 1633 (w).


PPM
7.17011
6.87150
4.82141
-.00087
OAc
OH
OH
18
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 -.5
PPM

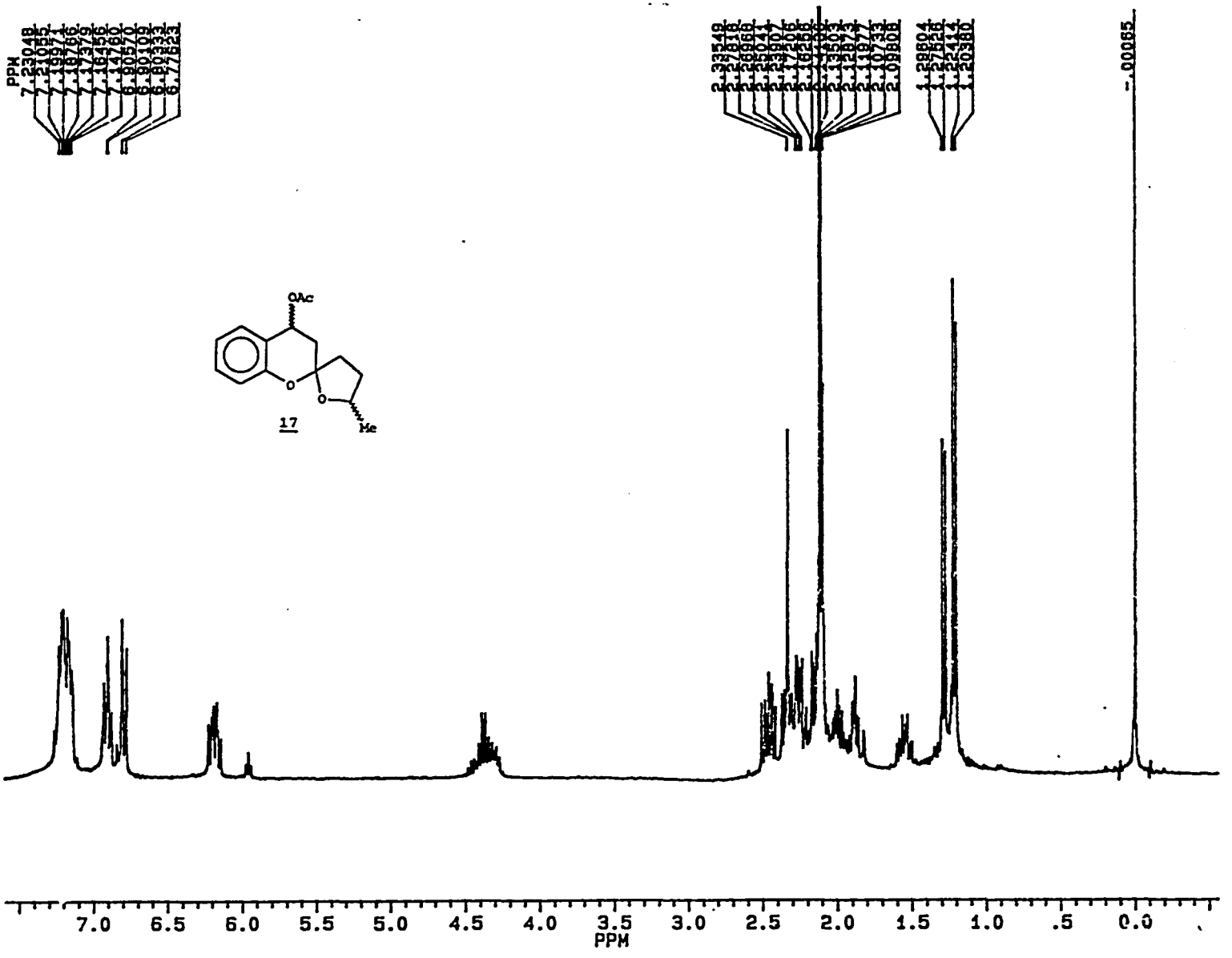
Spiro[chroman-4-acetyl-2-tetrahydrofuran]-2'-yl, 17.

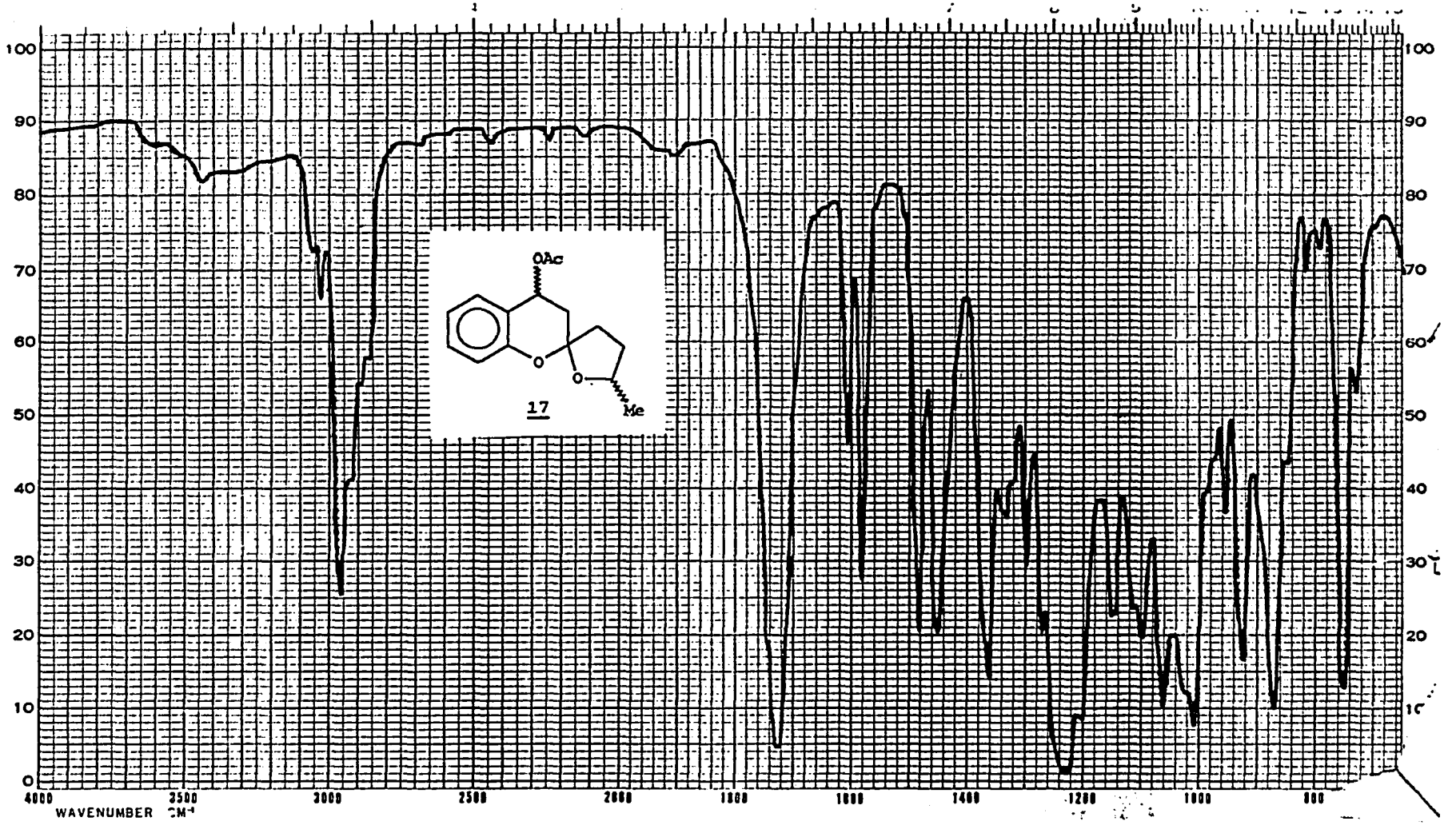


18 17

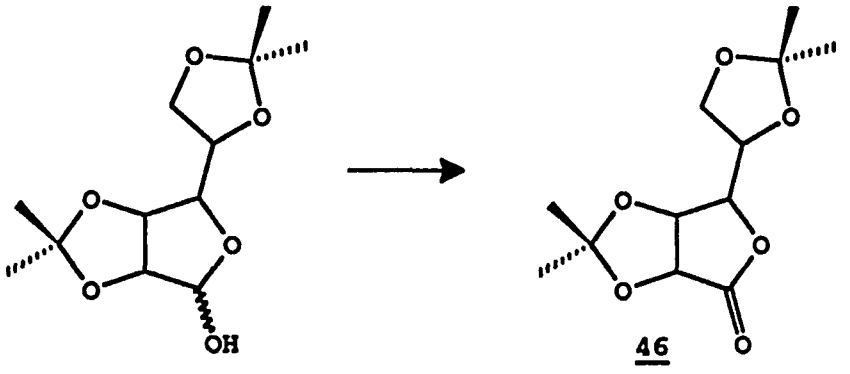
Oxidative cleavage of compound 18 (0.30 g, 1.08 mmol) was achieved according to the procedure reported earlier, using a catalytic amount of osmium tetroxide and 10 molar equivalents of sodium meta-periodate in *tert*-butanol. The spiroketal 17 was isolated as the only product (0.22 g, 90%) giving a satisfactory NMR.

^{1}H NMR(300 MHz, $CDCl_3$, ppm): 6.77-7.23 (m, 4H) Aromatics; 6.18,6.16 (dt, 1H) C(4)H; 4.26-4.47 (m, 1H) C(2')H; 2.30-2.50 (m, 2H) C(3)H_2; 2.10,2.12 (ds, 3H) CH_3C=O; 1.83-2.08 (m, 2H) C(4')H_2; 1.50-1.63 (m, 2H) C(3')H_2; 1.21 (d, 3H) CH_3CH, major isomer; 1.28 (d, 3H) CH_3CH, minor isomer. IR(neat, cm^{-1}); 1725 (s). Mass Spectrum (EI); Calculated for $C_{15}H_{18}O_4$ (m/z 262.1). Found m/z 262.1 (M^+), 263.1 (M^++1).


PPM
7.23048
7.21055
7.19971
7.18766
7.17379
7.16456
7.14760
6.90570
6.90109
6.80333
6.77823
2.33548
2.28618
2.26960
2.25041
2.23907
2.17406
2.16286
2.13503
2.12873
2.11977
2.10733
2.09902
1.28804
1.27526
1.22414
1.20380
-.00065
OAc
O
O
Me
17
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
PPM


OAc
O
O
Me
17
100
90
80
70
60
50
40
30
20
10
0
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
WAVENUMBER CM-1

2,3:5,6-Di-O-isopropylidene-D-mannono-1,4-lactone, 46.

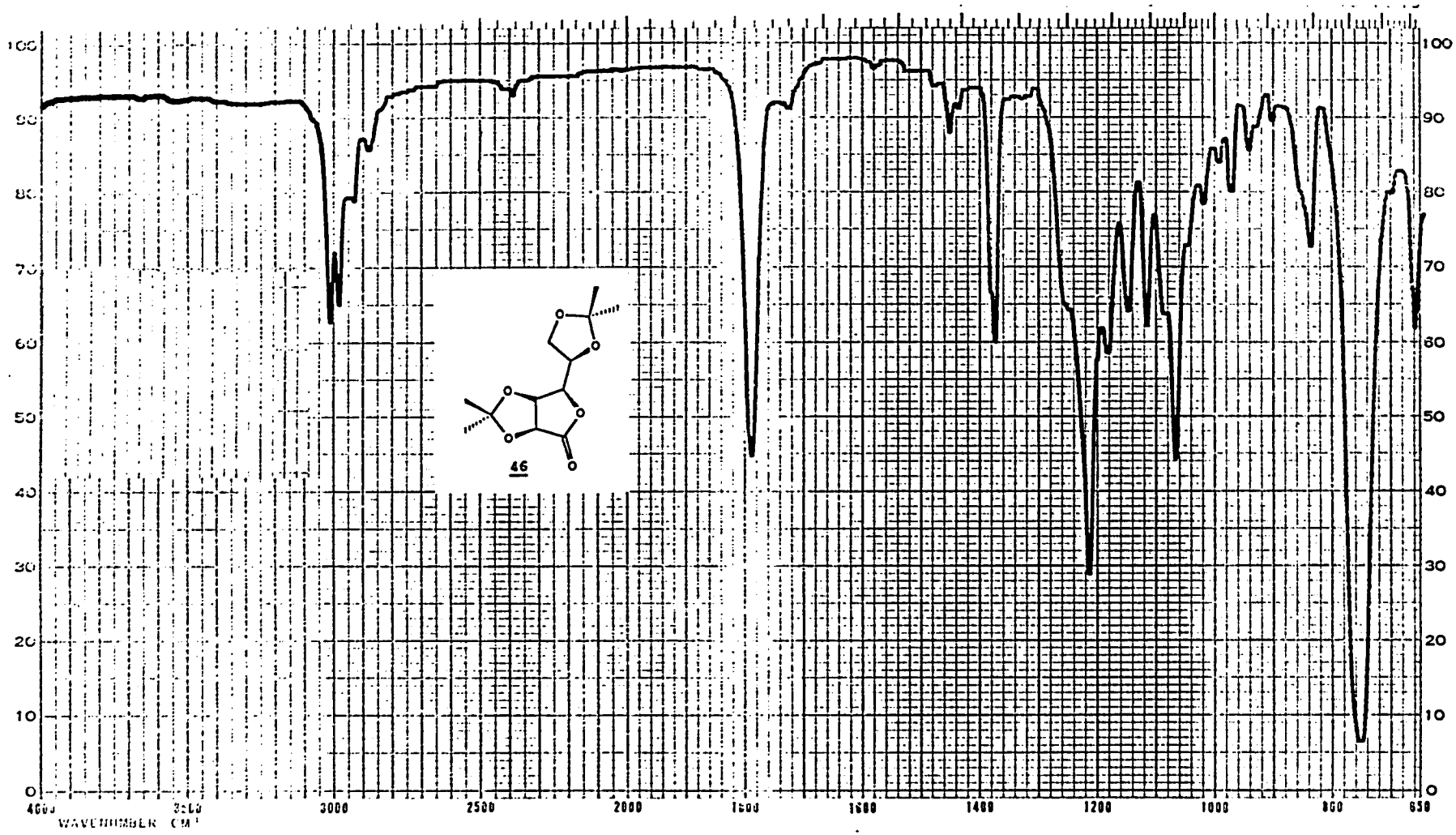


Benzene (50 mL), pyridine (2.5 mL, 30 mmol) and nicotinium dichromate (7.13 g, 15.4 mmol) were refluxed with moderate stirring using a Dean-Stark water separator until the mixture was free of water. The hemiketal (1.0 g, 3.84 mmol) was then added and stirring was continued under reflux for one hour. The reaction mixture was cooled to room temperature, diluted with toluene and suction-filtered through celite, and the residue was thoroughly washed with more toluene. The solvent was evaporated at reduced pressure, and the residual pyridine was removed by azeotropic distillation with toluene. The residue was redissolved in benzene and suction filtered through a sintered glass funnel. Evaporation of the solvent gave a white solid which was recrystal-ized (hexanes/ethyl acetate) to give the pure lactone 46 as large white needles (95%, m.p. 110-112°C).

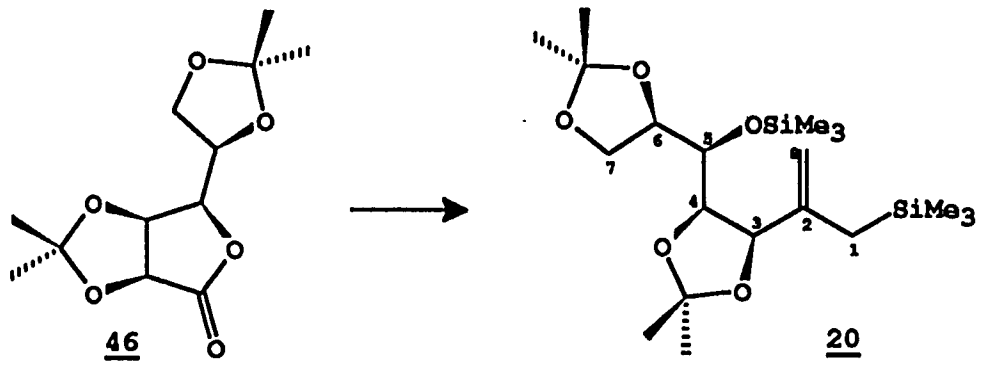
^{1}H NMR(300 MHz, $CDCl_3$, ppm): 4.83-4.91 (m, 2H); 4.35-4.49 (m, 2H); 4.03-4.19 (dd, 2H); 1.15,1.48 (ds, 6H); 1.43,1.39 (ds, 6H). IR($CHCl_3$, cm^{-1}); 1785 (s).

Mass Spectrum (EI); Calculated for $C_{12}H_{18}O_6$ (m/z 258.1). Found m/z 259.0 (M^++1).

PPM
4.85547
46
1.48473
-.00056
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM


100
90
80
70
60
50
40
30
20
10
0
3000
2500
2000
1500
1000
800
650
WAVENUMBER CM⁻¹
46

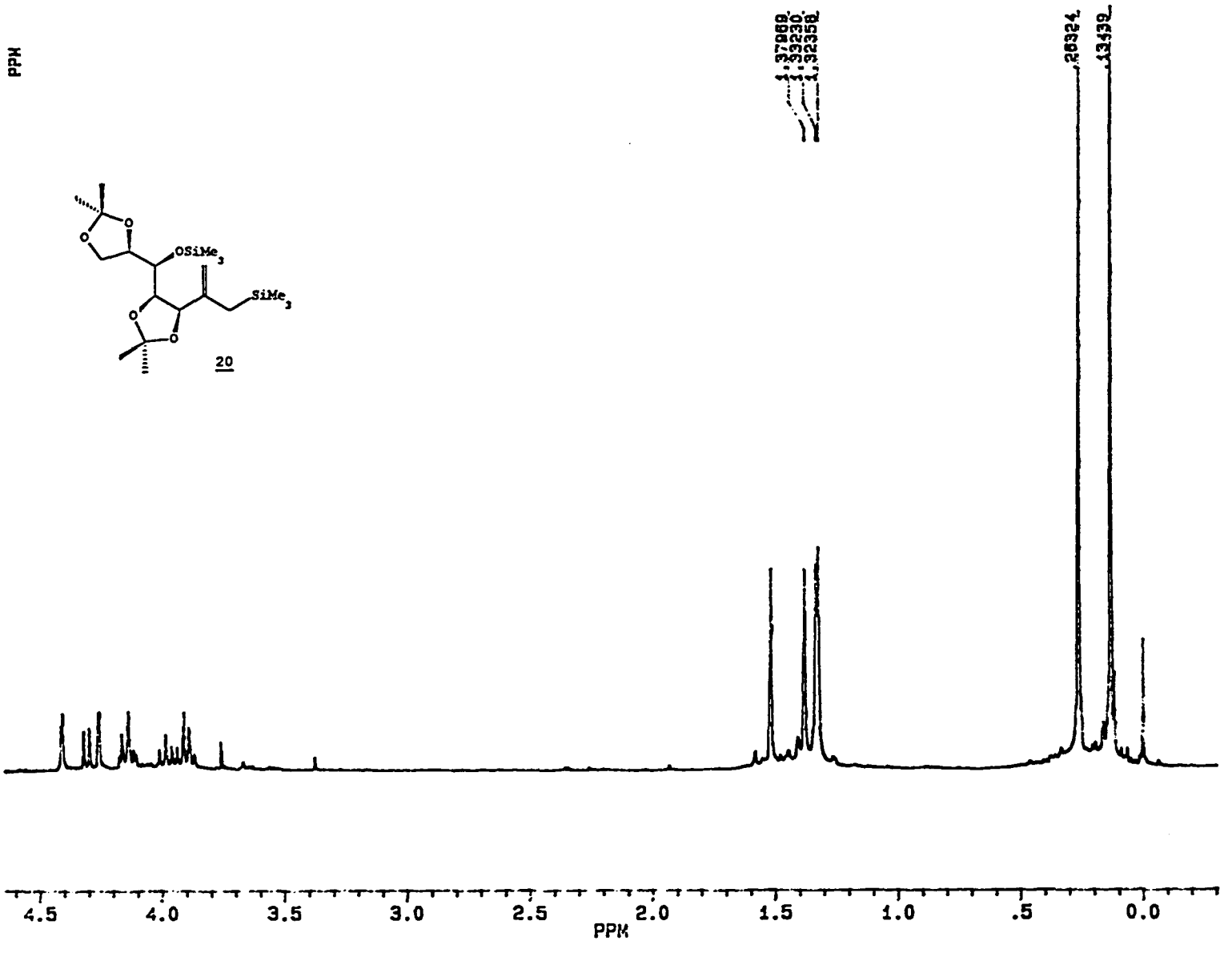
1-Deoxy-3,4:6,7-di-O-isopropylidene-1-C-trimethylsilyl-5-O-trimethylsilyl-D-manno-2-methylenoheptitol, 20.

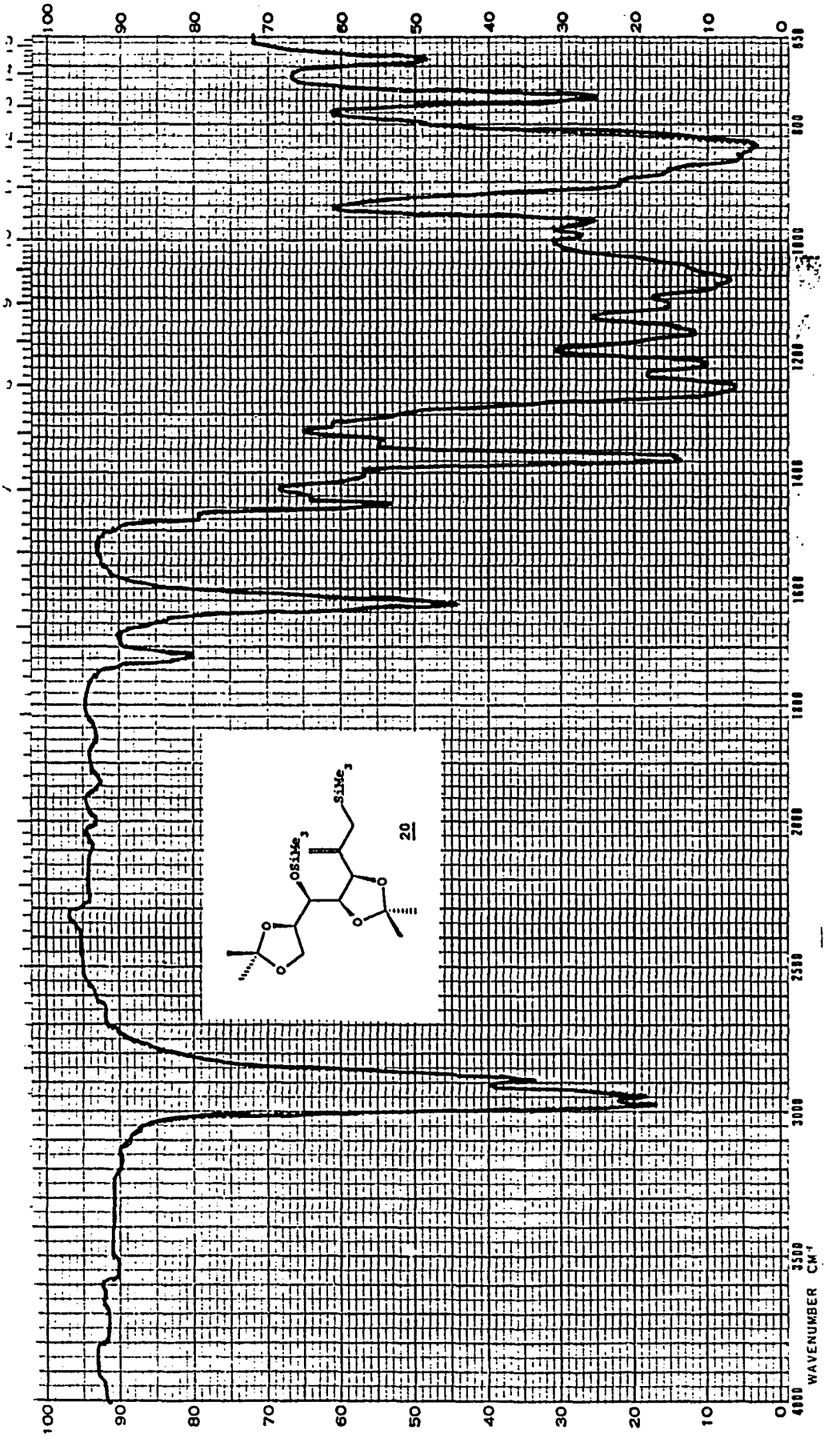


A solution of the lactone **46** (1.0 g, 3.87 mmol) and chlorotrimethylsilane (2.52 g, 23.5 mmol) dissolved in THF (20 mL), was added to a solution of trimethylsilyl methylmagnesium chloride (5 molar equivalents) in THF (80 mL) at 0°C. The cooling bath was removed and stirring was continued for 18 hours at room temperature. Work-up consisted of pouring the reaction mixture into cold saturated aqueous ammonium chloride and extracted with diethyl ether. The organic layer was concentrated at low temperatures and the crude product was chromatographed (Hexanes:EtOAc ; 5:1) so providing the desired allylsilane **20** (1.3 g, 80%) as a pale yellow oil.

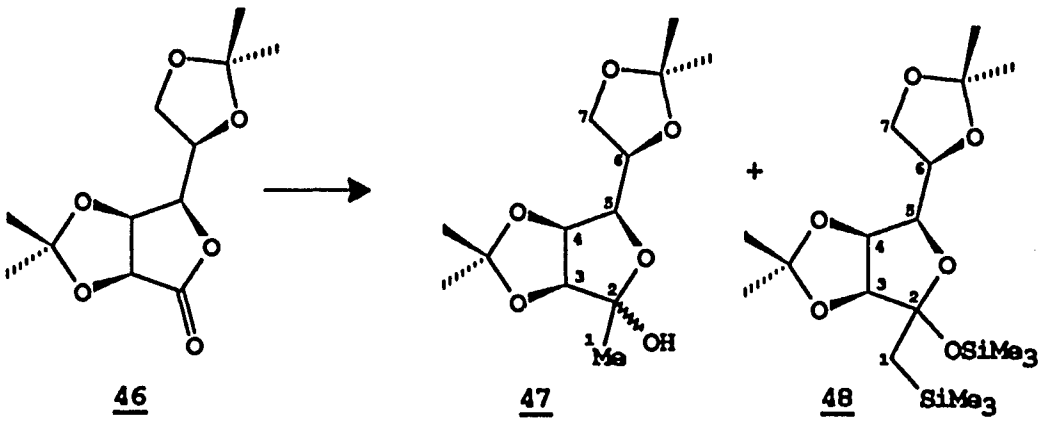
^{1}H NMR(300 MHz, $CDCl_3$ ppm): 4.41,4.25 (dd, 2H) C(8)$\underline{H}_2$; 4.30 (d, 1H) C(3)$\underline{H}$; 4.10-4.17 (m, 1H) C(5)$\underline{H}$; 3.98 (t, 1H) C(4)$\underline{H}$; 3.86-3.94 (m, 3H) C(7)$\underline{H}_2$C(6)$\underline{H}$; 1.51, 1.38 (ds, 6H) (C$\underline{H}_3$)$_2$C; 1.33,1.32 (ds, 6H) (C$\underline{H}_3$)$_2$C; 0.26 (s, 9H) OSi(C$\underline{H}_3$)$_3$; 0.13 (s, 9H) CH_2Si(C$\underline{H}_3$)$_3$. IR(neat, cm^{-1}); 1622 (m)

Mass Spectrum (EI); Calculated for $C_{20}H_{40}O_5Si_2$ (m/z 416.2). Found m/z 417.2 (M^++1).


PPM
1.37969
1.33230
1.32358
.28324
.13439
OSiMe3
SiMe3
20
4.5
4.0
3.5
3.0
2.5
2.0
PPM
1.5
1.0
.5
0.0


OSiMe3
SiMe3
20
WAVENUMBER CM-1

1-Deoxy-3,4:6,7-di-O-isopropylidene-D-manno-2-heptulofuranose, 47; Trimethylsilyl-1-deoxy-3,4:6,7-di-O-isopropylidene-1-C-trimethylsilyl-α-D-manno-2-heptulofuranoside, 48.



46 47 48

Compounds 47 and 48 were obtained from the treatment of the lactone 46 with trimethylsilyl methylmagnesium chloride (5 molar equivalents) using the same procedure reported above, but in the absence of chlorotrimethylsilane. Compound 47 was obtained as the major product after chromatography (90%).

^{1}H NMR(300 MHz, $CDCl_3$, ppm): 47; 4.84,4.81 (dd,1H) C(5)H; 4.45 (d,1H) C(3)H; 4.38 (t, 1H) C(4)H; 4.00-4.13 (m, 3H) C(7)H_2C(6)H; 2.92 (s, 1H) OH; 1.49 (s, 3H) C(1)H_3; 1.48,1.45 (ds, 6H) (CH_3)$_2$C; 1.38,1.34 (ds, 6H) (CH_3)$_2$C.

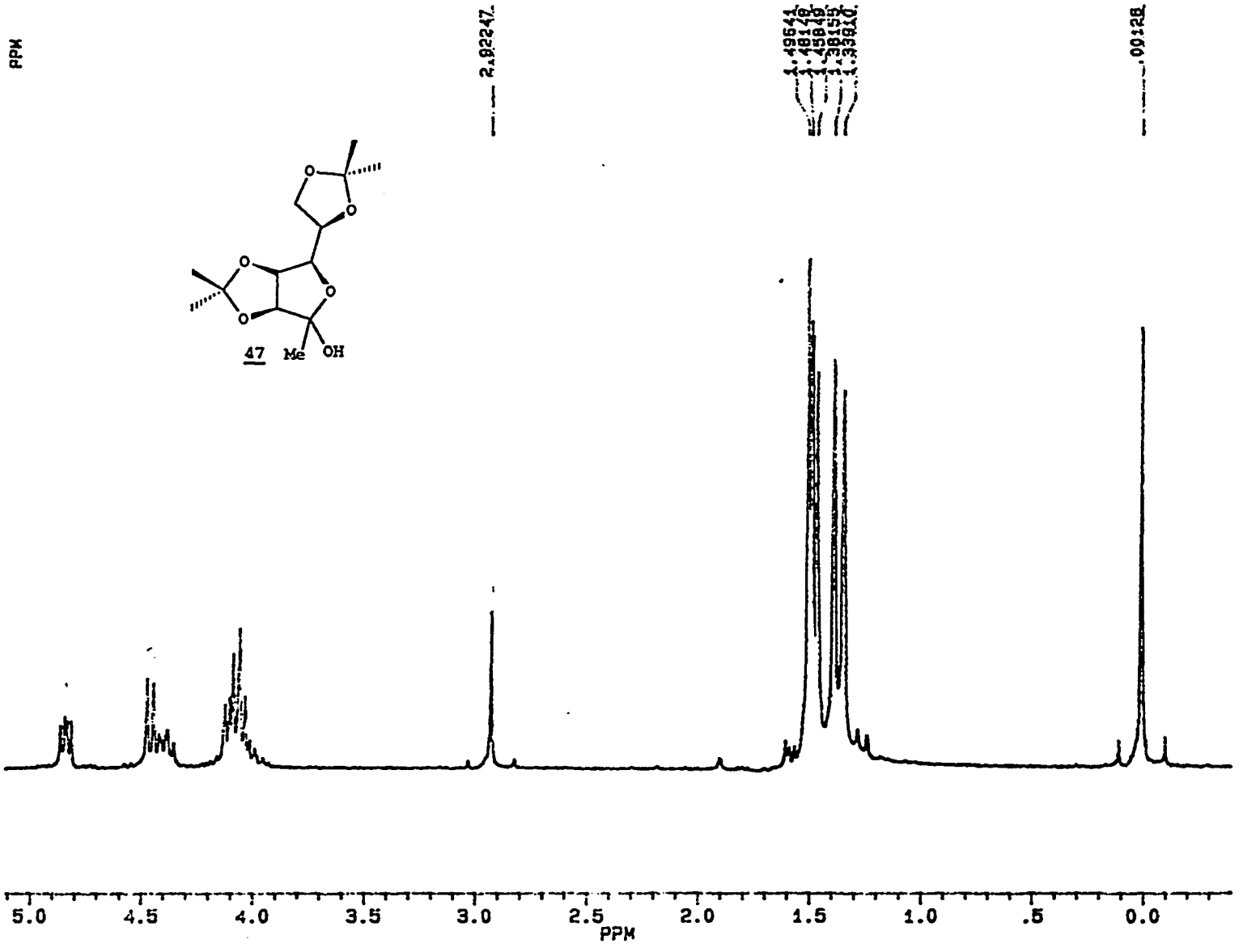
IR($CHCl_3$, cm^{-1}); 3650 (s). m.p. 99-101°C.

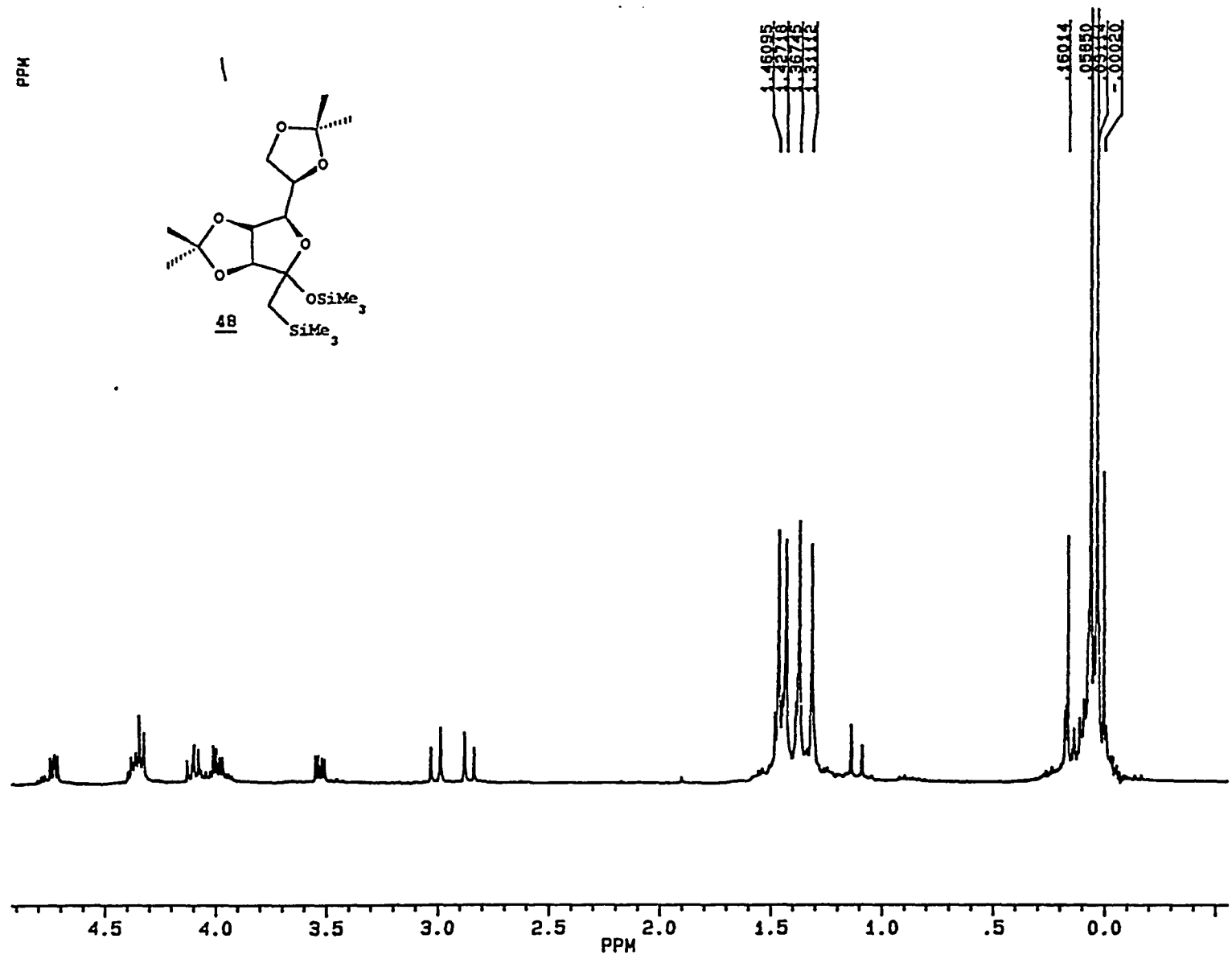
Mass Spectrum (EI); Calculated for $C_{13}H_{22}O_6$ (m/z 274.1). Found m/z 275.0 (M^++1).

48; 4.73,4.71 (dd, 1H) C(5)H; 4.33 (d, 1H) C(3)H; 4.12,4.18 (dd, 1H) C(4)H; 4.32-4.37 (m, 1H) C(6)H; 3.99,3.98 (dd, 1H) C(7)H_2; 3.54,3.51 (dd, 1H) C(7)H_2; 3.00, 2.85 (dd, 2H) SiC(1)H_2; 1.46,1.43 (ds, 6H) (CH_3)$_2$C; 1.37,1.31 (ds, 6H) (CH_3)$_2$C; 0.058 (s, 9H) (CH_3)$_3$SiCH_2; 0.031 (s, 9H) (CH_3)$_3$SiO.

IR(neat, cm^{-1}); 2950 (s).

Mass Spectrum (EI); Calculated for $C_{19}H_{38}O_6Si_2$ (m/z 418.2). Found m/z 419.2 (M^++1).


PPM
2.92247
1.49641
1.48148
1.45849
1.38155
1.33910
.09128
47 Me OH
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM


PPM
OSiMe3
SiMe3
48
1.46095
1.42718
1.36745
1.31112
.16014
.05850
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-.00020
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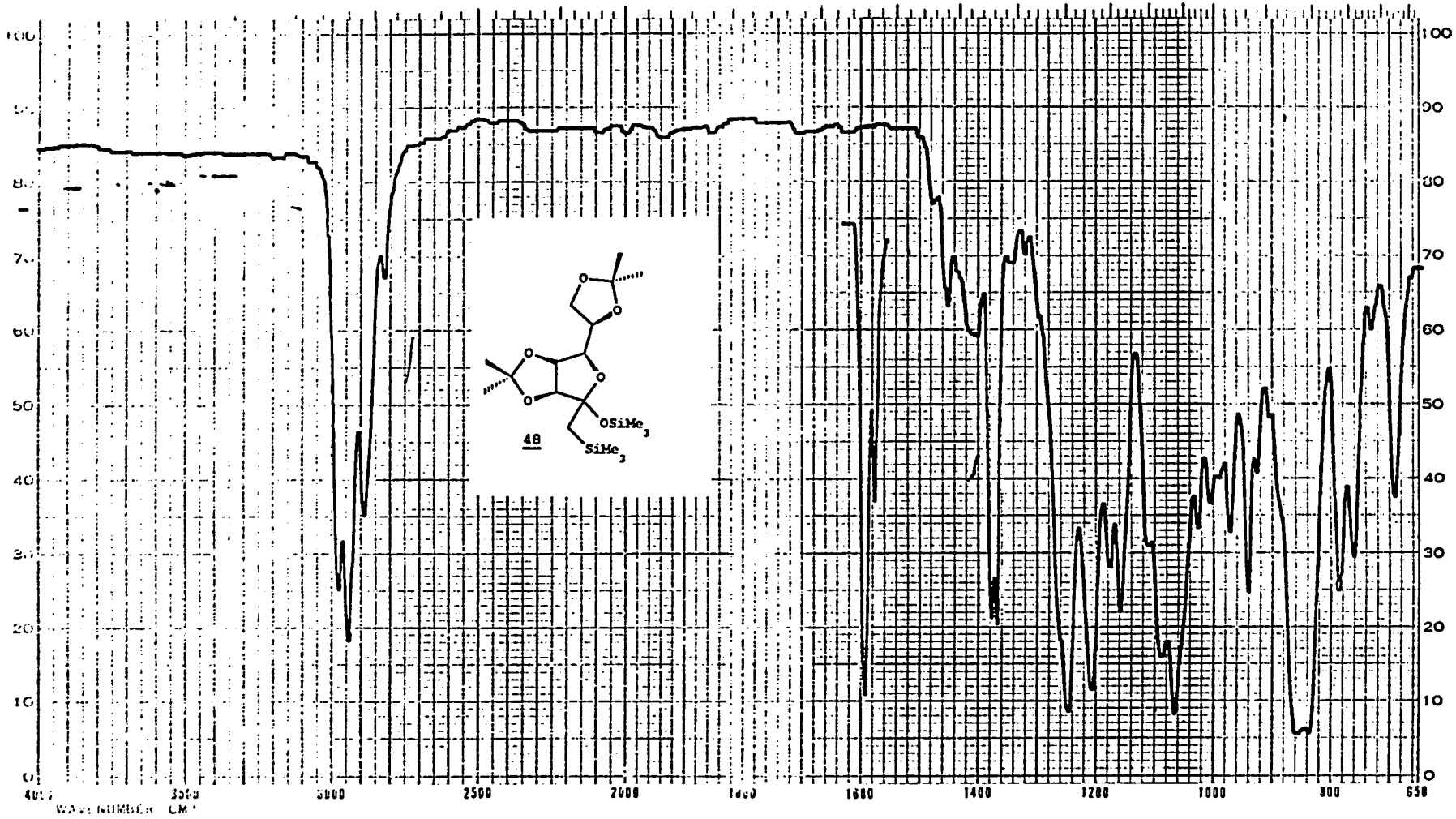
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM


100
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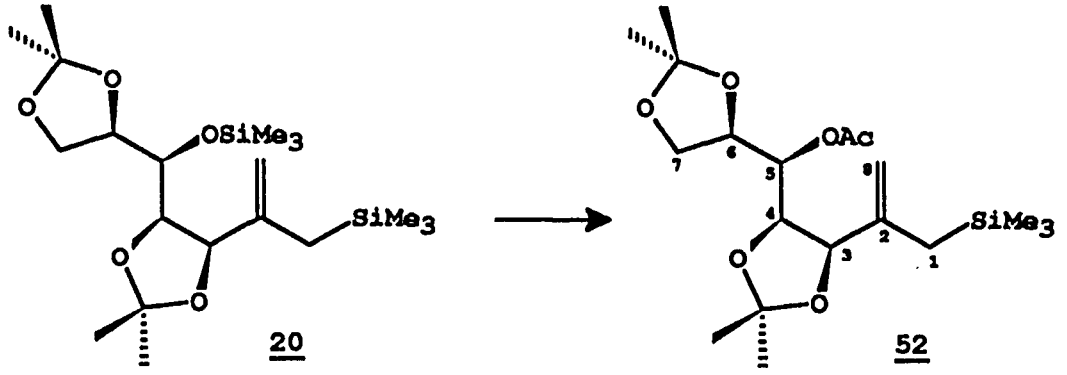
70
60
50
40
30
20
10
0
3000
2500
2000
1800
1600
1400
1200
1000
800
650
OSiMe3
SiMe3
48

5-O-Acetyl-1-deoxy-3,4:6,7-di-O-isopropylidene-1-C-trimethylsilyl-D--manno-2-methylenohepitol, 52.



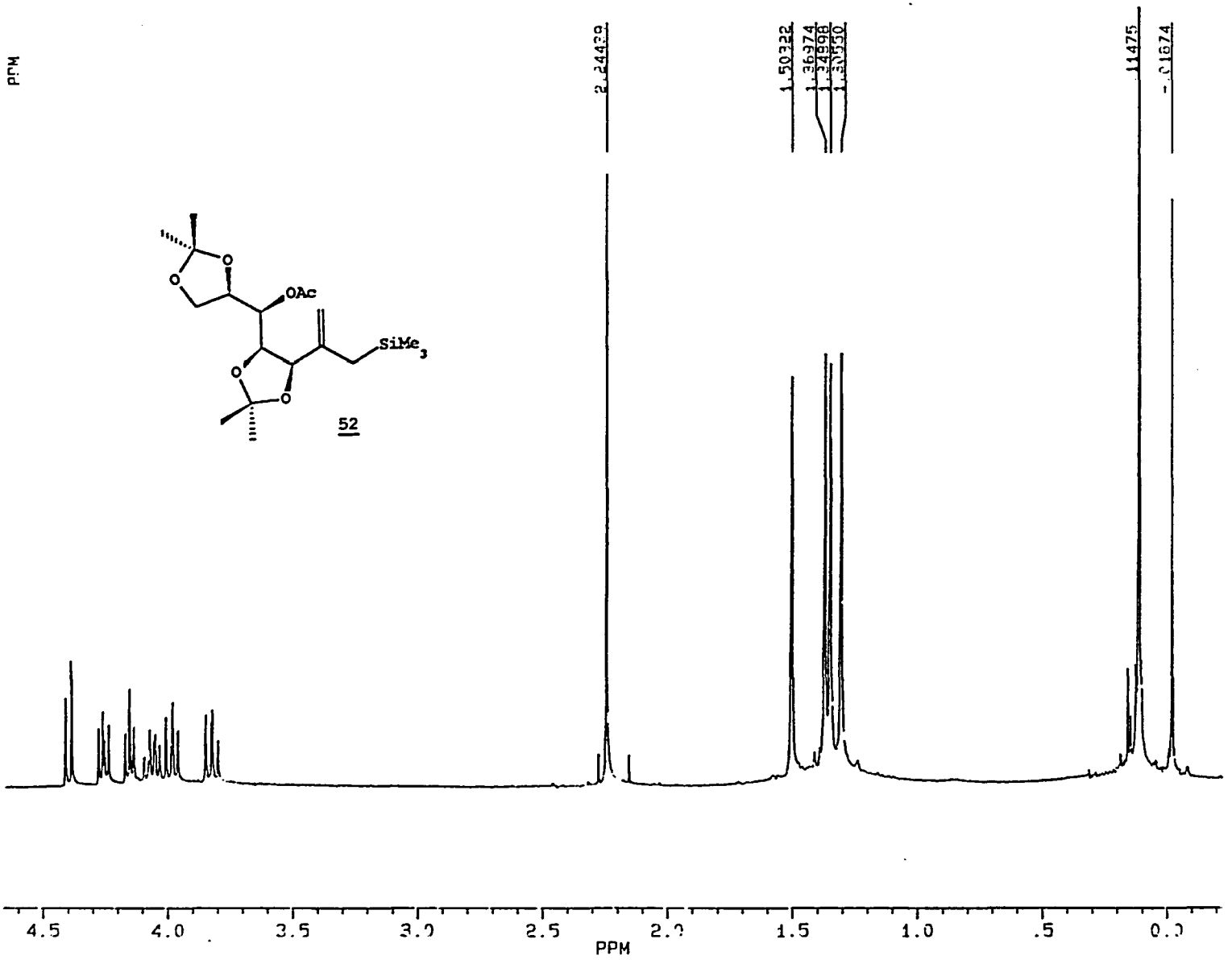
20 52

Chromatography of 1.0 g (2.40 mmol) of compound **20** on silica gel using EtOAc:hexane ; 5:1 as eluent, afforded 0.72 g (80%) of compound **52**.

^{1}H NMR(300 MHz, $CDCl_3$, ppm): 4.39 (d, 1H,*J*=7.1 Hz) =C(8)$\underline{H}_2$; 4.26 (d, 1H) C(3)$\underline{H}$; 4.24 (d, 1H,*J*=7.1 Hz) =C(8)$\underline{H}_2$; 4.15 (t, 1H) C(5)$\underline{H}$; 4.03-4.09 (m, 1H) C(6)$\underline{H}$; 3.96,3.99 (dd, 1H) C(4)$\underline{H}$; 3.83,3.80 (dd, 2H) C(7)$\underline{H}_2$; 2.24 (s, 3H) $C\underline{H}_3C$=O;1.50,1.37 (ds, 6H) $(C\underline{H}_3)_2C$;1.35,1.30 (ds, 6H) $(C\underline{H}_3)_3C$; 0.11 (s, 9H) $(C\underline{H}_3)_3Si$. IR(neat, cm^{-1}); 1718 (s), 1623 (m).

Mass Spectrum (EI); Calculated for $C_{19}H_{34}O_6Si$ (m/z 386.2).

Found m/z 387.2 (M^++1).


PPM
2.24439
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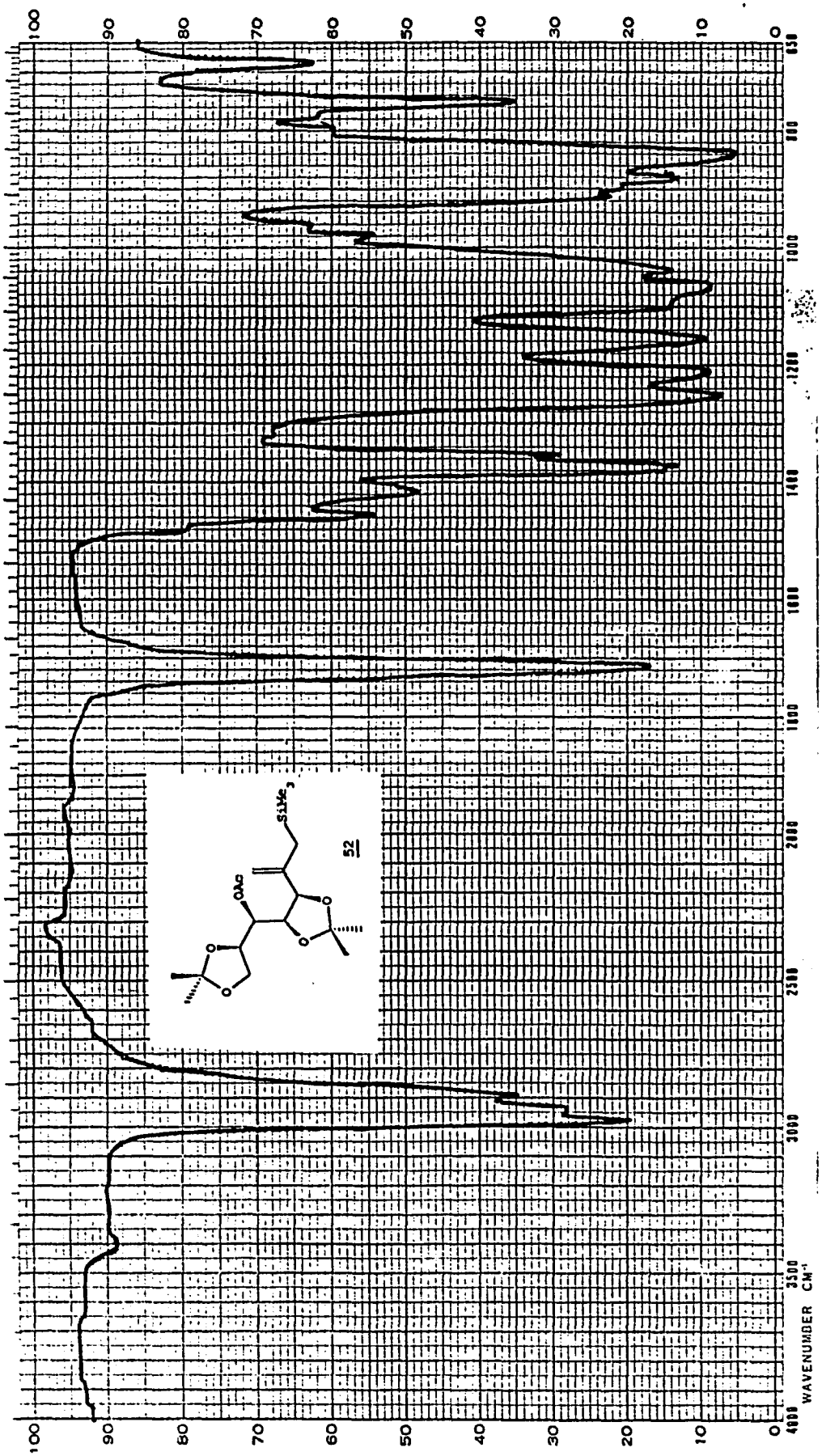
1.36974
1.34998
1.30950
.11475
-.01674
OAc
SiMe3
52
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM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90
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70
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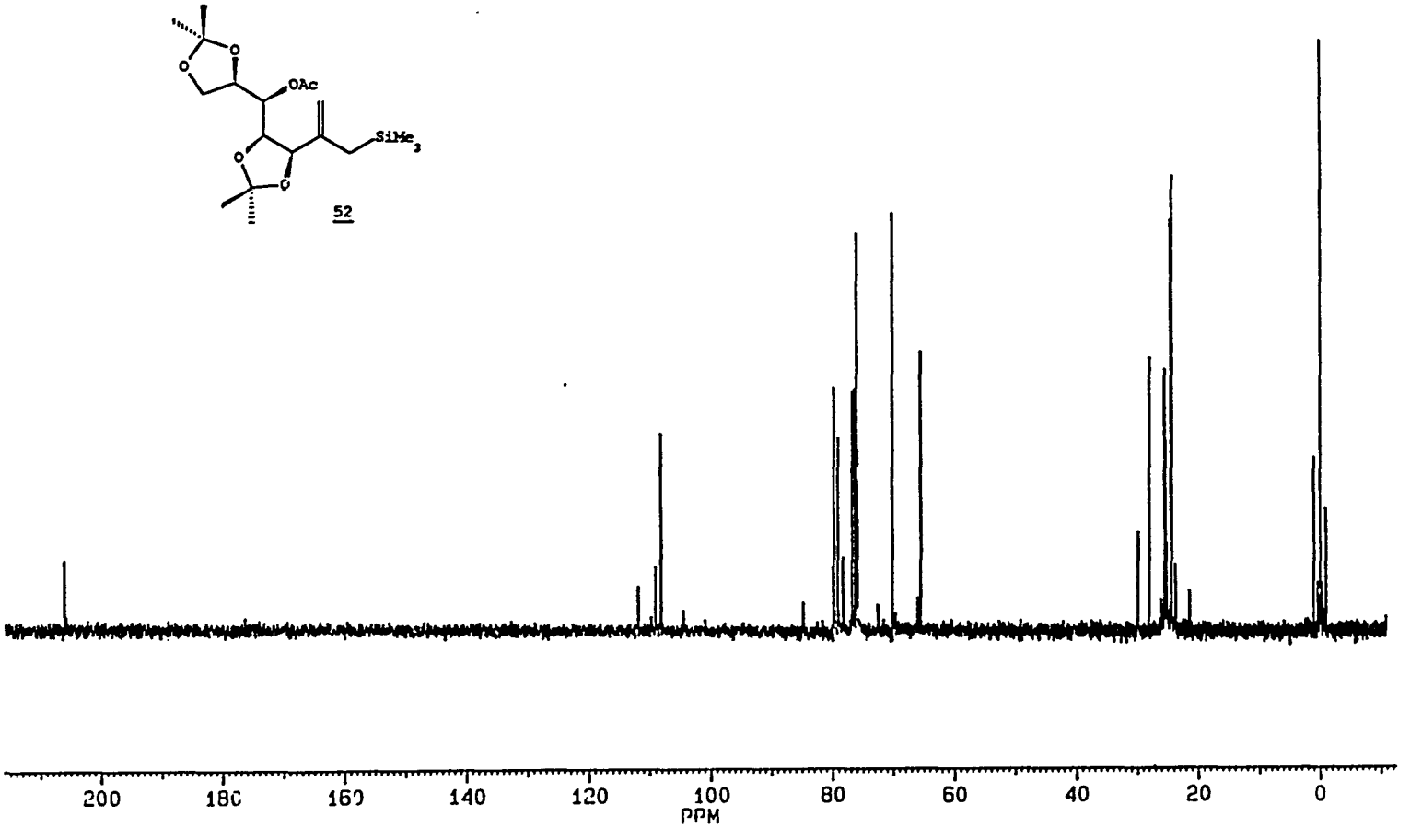
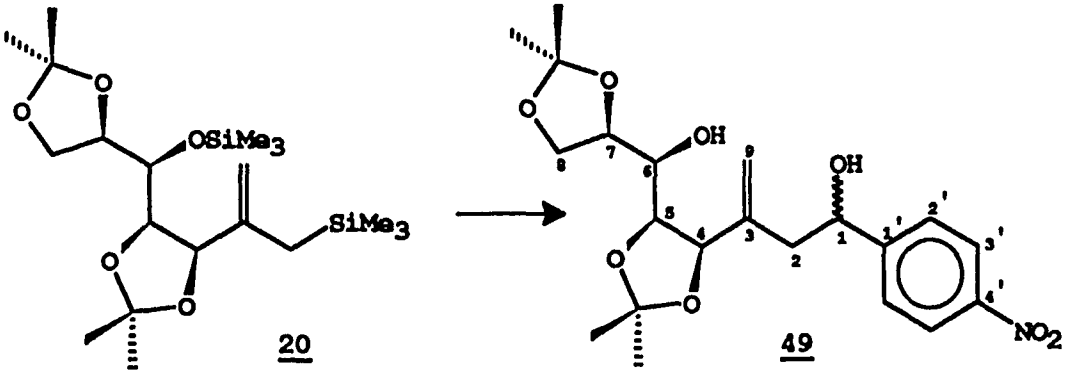
50
40
30
20
10
0
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
650
WAVENUMBER CM-1
OAc
SiMe3
O
52



52

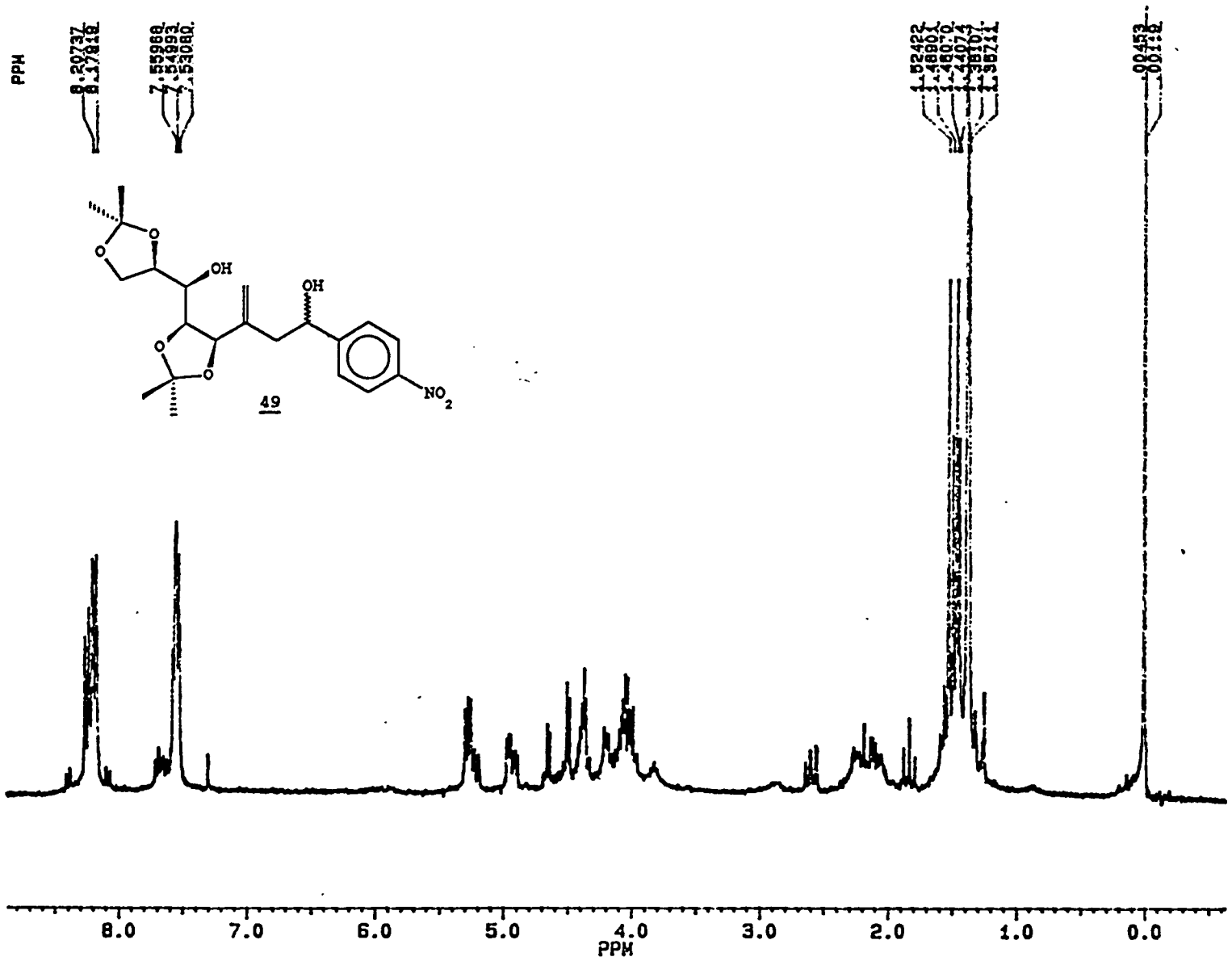
2-Deoxy-4,5:7,8-di-O-isopropylidene-3-methylene-1-(4-nitrophenyl)-manno-octitol, 49.



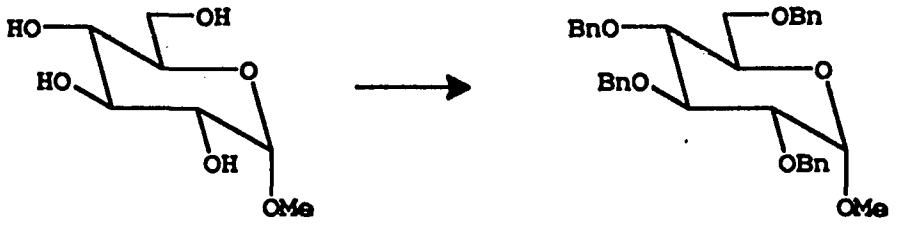
20 49

A solution of *p*-nitrobenzaldehyde (0.76 g, 1.77 mmol) and the allylsilane **20** (0.27 g, 1.77 mmol) in dry acetonitrile was cooled to 0°C and a catalytic amount of $BF_3.OEt_2$ was added with stirring and cooling for 3 minutes. The ice-water bath was removed allowing the reaction mixture to warm to room temperature with additional stirring for one hour. The reaction was quenched by pouring into cold saturated aqueous sodium bicarbonate and extracted with diethyl ether. The organic extracts were dried ($MgSO_4$) and concentrated. Chromatographic purification (hexanes:ethyl acetate ; 5:1) afforded the diol **49** (0.65 g, 88%) as an inseparable (9:1) mixture of diastereoisomers. ^1H NMR(300 MHz, $CDCl_3$, ppm): 8.17-8.26 (m, 2H) aromatic; 7.52-7.57 (m, 2H) aromatic; 5.25,5.29 (ds, 2H) C(9)$\underline{H}_2$=; 4.94,4.96 (dd, 1H) C(1)$\underline{H}$; 4.64,4.65 (dd, 2H) C(2)$\underline{H}_2$; 4.36 (t, 1H) C(6)$\underline{H}$; 4.18,4.21 (dd, 1H) C(5)$\underline{H}$; 3.97-4.09 (m, 3H) C(8)$\underline{H}_2$ C(7)$\underline{H}$; 2.01-2.23 (m, 1H) C(4)$\underline{H}$; 1.52,1.49 (ds, 6H) (C$\underline{H}_3$)$_2$C; 1.38,1.37 (ds, 6H) (C$\underline{H}_3$)$_2$C. IR($CHCl_3$, cm^{-1}); 3360 (s), 1610 (w), 1380 (m).

Mass Spectrum (EI); Calculated for $C_{21}H_{29}O_8N$ (m/z 423.2). Found m/z 423.2 (M^+).


PPM
8.29737
8.17818
7.55988
7.54993
7.53080
1.52422
1.48801
1.46070
1.44074
1.38107
1.36211
.00453
.00118
OH
OH
O
O
O
O
NO2
49
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

Methyl-2,3,4,6-tetra-O-benzyl-α-D-glucopyranoside.

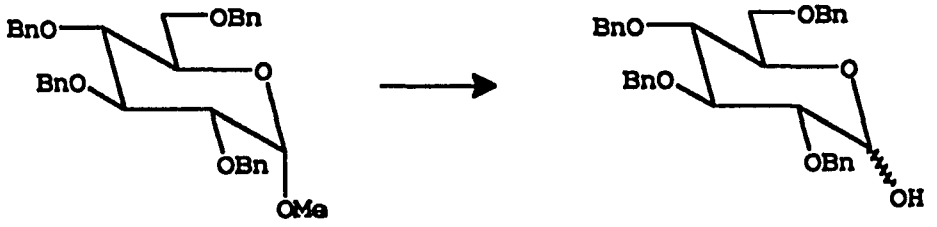


CAUTION: Although this procedure has proven to be very simple and high yielding, extreme caution must be exercised when conducting this experiment. Because of the severe fire hazard, only a technically qualified individual should attempt this reaction procedure. Large volumes of hydrogen gas are produced, hence for a 10 g reaction, a heavy 3 liter flask equipped with an Allihn condenser and a drierite guard tube should be used. It is advised that this reaction not be attempted on a scale larger than 10 grams.

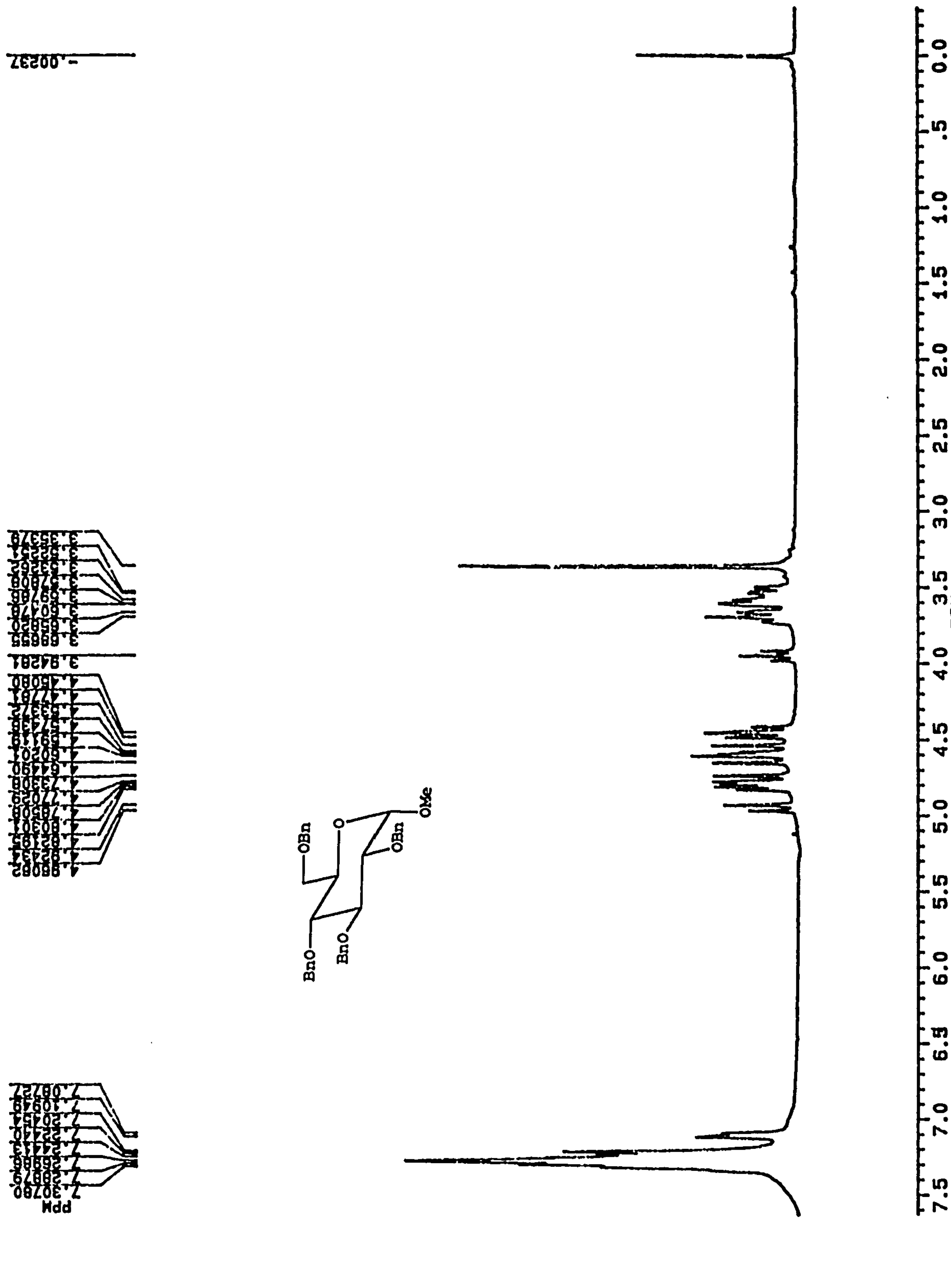
Methyl α-D-glucopyranoside (10.0 g, 51.5 mmol) and dry benzyl chloride (300 mL, dried over molecular sieves) were placed in a dry 3 L round-bottomed flask under a nitrogen atmosphere. To this mixture sodium hydride (27.7 g, 0.923 mol, 80% oil dispersion) was added. (NaH was cleaned by washing with dry hexanes through a sintered glass funnel under suction while a stream of dry nitrogen was passed through). The reaction mixture was heated at 125-130°C for three hours with stirring. Efficient stirring is highly important for the smooth running of this reaction. The reaction mixture was cooled to room temperature and diluted with 200 mL of dry toluene. The reaction mixture was suction filtered, and the solid residue was washed with dry toluene. Care must be taken at this point to avoid excessive exposure of the solid residue to the atmosphere. The filtrate was concentrated to remove the toluene, and then distilled under reduced pressure to remove the excess benzyl chloride leaving the desired product, 2,3,4,6-tetra-O-benzylated compound as a yellow oil (44 g, 96%).

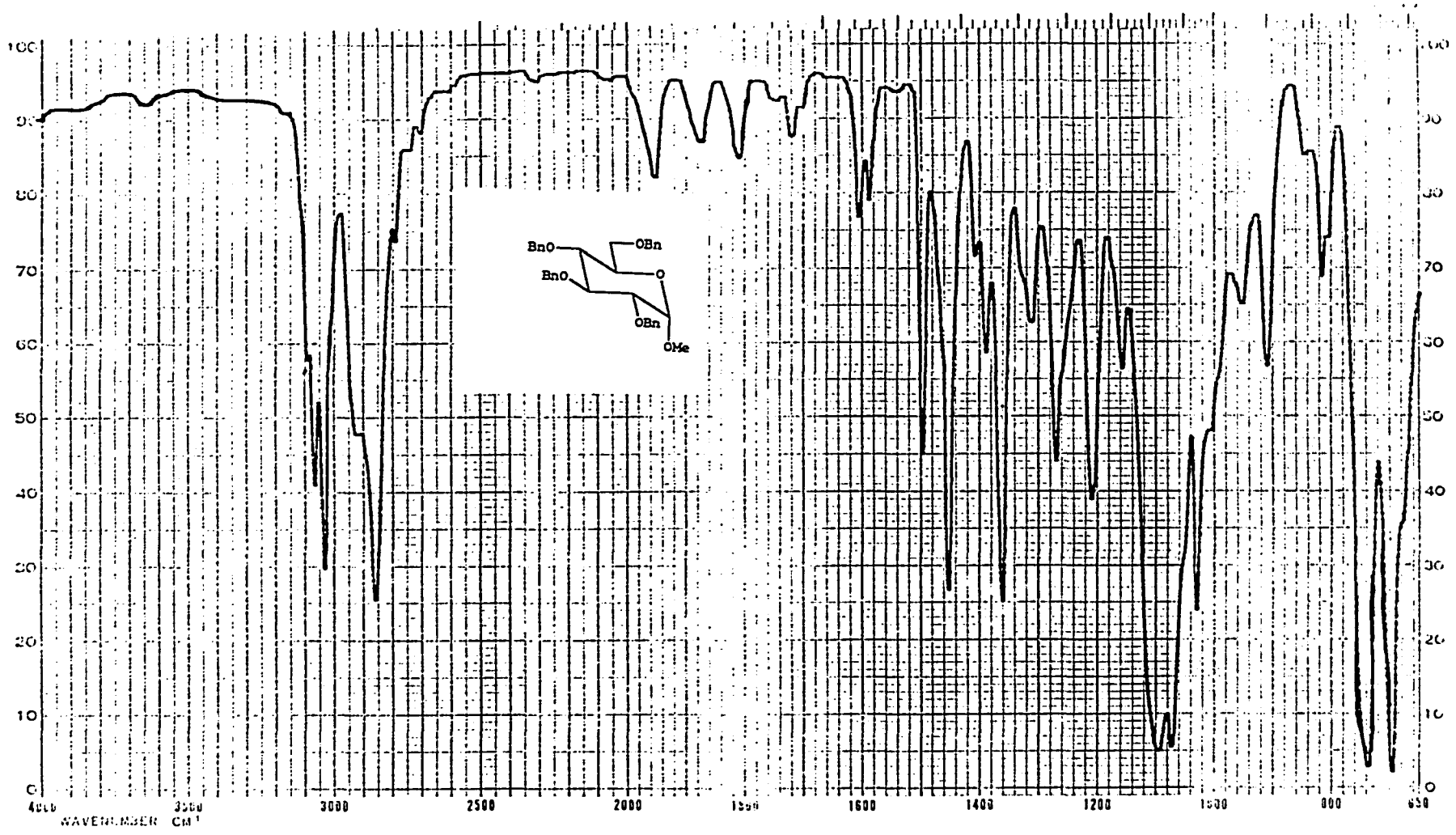
^{1}H NMR(300 MHz, $CDCl_3$, ppm): 7.08-7.31 (m, 20H) aromatic; 4.94 (d, 1H, J=12 Hz) C(1)H; 4.45-4.82 (m, 8H) CH_2(benzylic); 3.94 (t, 1H) C(2)H; 3.68 (t,1H) C(3)H; 3.52-3.60 (m, 2H) C(3)HC(4)H; 3.35 (s, 3H) CH_3O. IR(neat, cm^{-1}); 2850 (s), 2950. Mass Spectrum (EI); Calculated for $C_{35}H_{38}O_6$ (m/z 554.6). Found m/z 554.7 (M^+).

2,3,4,6-Tetra-O-benzyl-D-glucose.



The benzylated product from the above reaction was dissolved in 400 mL of 90% (v/v) aqueous acetic acid and refluxed gently for 5-6 hours. After cooling the reaction mixture to room temperature, the solvent was removed by rotary evaporation, leaving a brown solid residue. Anhydrous methanol was then added, which precipitated the cleaved product, 2,3,4,6-tetra-O-benzyl glucose, as small white needles which was suction filtered (33 g, 80%). M.p. 146-148°C, Lit. m.p. 146-149°C.
^{1}H NMR(300 MHz, $CDCl_3$, ppm): 7.08-7.28 (m, 20H) aromatic; 5.17 (t, 1H) C(1)H(OH)C(2)H; 4.42-4.91 (m, 8H) benzylic; 3.94-4.05 (m, 1H) C(2)H; 3.48-3.68 (m, 3H) C(3)HC(4)HC(5)H; 3.14 (d, 1H) OH. IR($CHCl_3$, cm^{-1}); 3460 (s).
Mass Spectrum (EI); Calculated for $C_{34}H_{36}O_6$ (m/z 540.3). Found m/z 541.3 (M^++1).


OBn
OBn
OMe
BnO
BnO
PPM

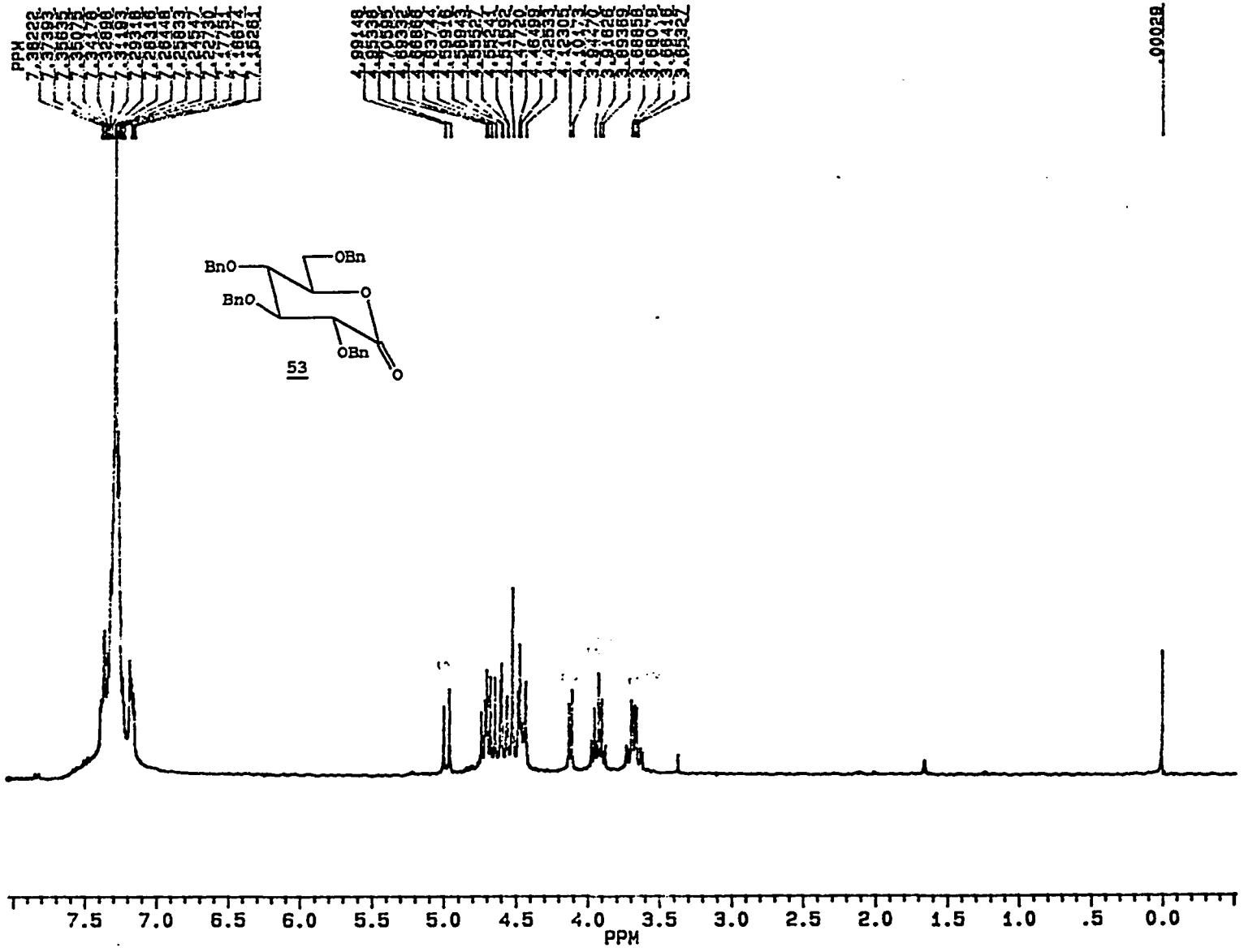

BnO
OBn
BnO
O
OBn
OMe
WAVENUMBER CM⁻¹
3000
2500
2000
1600
1400
1200
800

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
.5
0.0
PPM
BnO
BnO
OBn
OBn
O
OH
2.13533
1.48120
.01102
.00005
-.01102

2,3,4,6-Tetra-O-benzyl-D-glucono-1,5-lactone, 53.

53

A mixture of the 2,3,4,6-tetra-O-benzylglucose (3.3 g, 6.13 mmol), pyridine (5 mL), and nicotinium dichromate (10 g, 7.11 mmol) in 150 mL of benzene was refluxed with a Dean-Stark water separator for one hour. The mixture was cooled to room temperature and suction filtered through celite, and the solid residue was washed with dry toluene (5 x 100 mL). The filtrate was concentrated on the rotary evaporator, and the residual pyridine was removed by azeotropic distillation with toluene. The crude product was redissolved in benzene and filtered through a sintered glass funnel. Concentration and flash column chromatography afforded the pure lactone **53** (2.9 g, 88%). ^{1}H NMR(300 MHz, $CDCl_3$, ppm): 7.15-7.38 (m, 20H) aromatic; 4.97 (d,1H,J=11.4 Hz) C(2)H; 4.42-4.70 (m, 8H) benzylic; 4.11 (d, 1H) C(6)H; 3.94,3.89 (dt, 2H) C(3)H C(4)H; 3.65,3.69 (dd, 2H) C(5)HC(6)H. IR(neat, cm^{-1}); 1750 (s). Mass Spectrum (CI, NH_3); Calculated for $C_{34}H_{34}O_6$ (m/z 538.2). Found m/z 556.0 (M^++NH_4).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OBn
O
53
PPM
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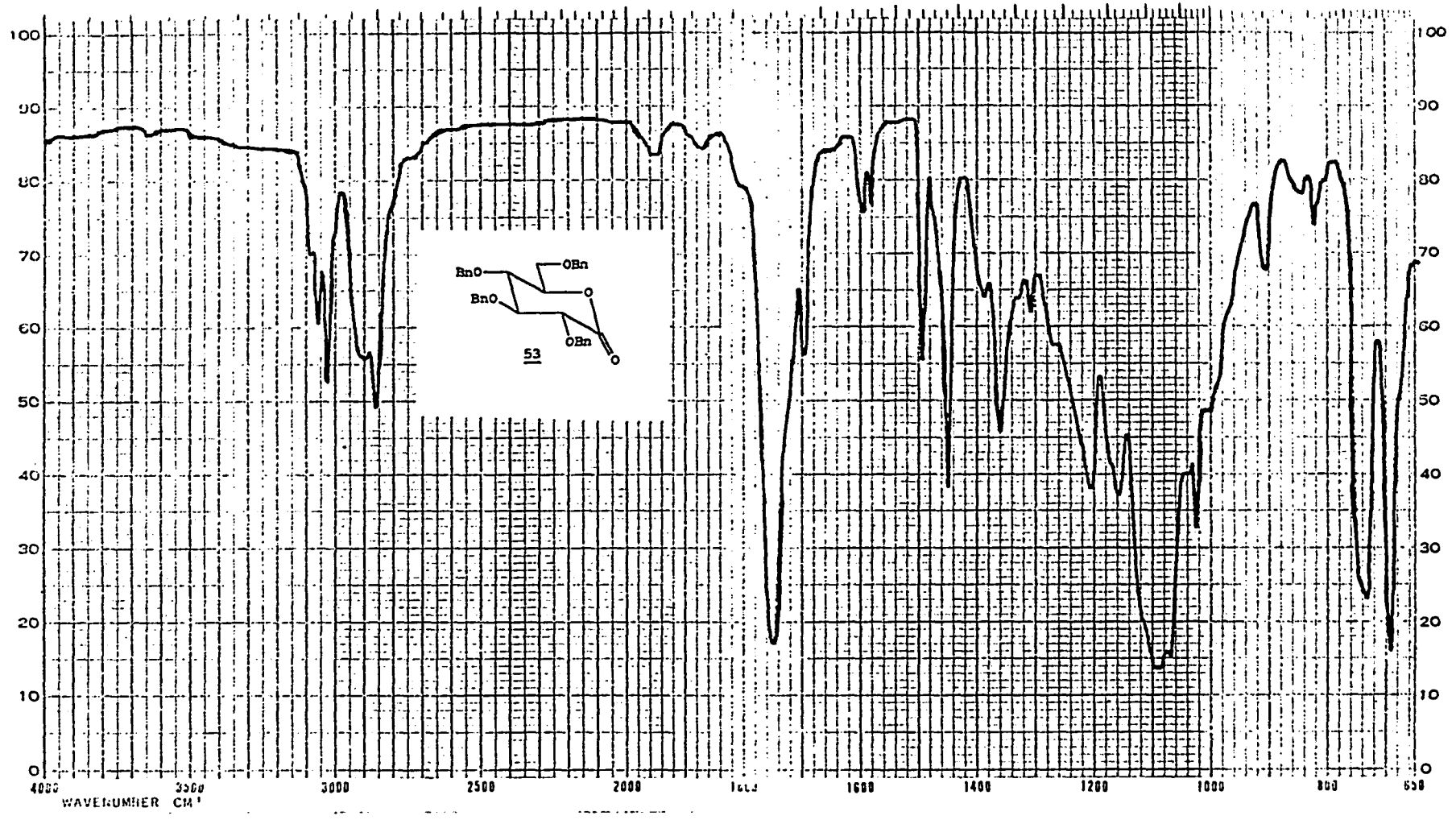
1.5
1.0
.5
0.0
PPM


BnO
OBn
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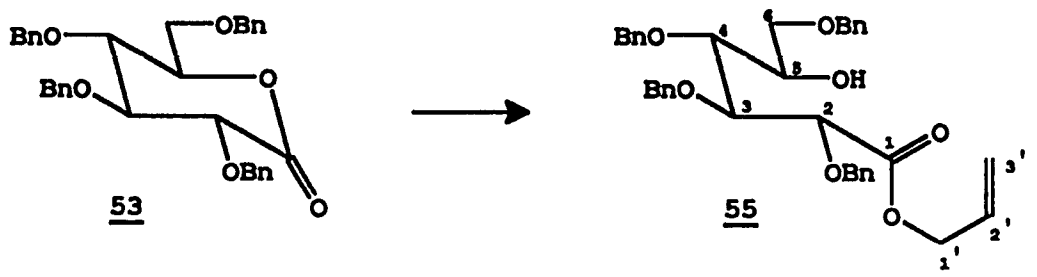
OBn
53
WAVENUMBER CM⁻¹

Allyl-2,3,4,6-tetra-O-benzyl-D-gluconate, 55.



A solution of 1.35 g (24.1 mmol) of potassium hydroxide in 50 mL of water was added to the lactone **53** (8.62 g, 16.0 mmol) and the mixture was refluxed for one hour. After cooling to room temperature, the solvent was removed by rotary evaporation, followed by a brief period of drying on the high vacuum pump. Dry DMF (100 mL) was added to dissolve the residue after which freshly purified allyl bromide (3.87 g, 32.0 mmol) was added with vigorous stirring. The mixture was stirred additionally at room temperature overnight. Work-up consisted of pouring the reaction mixture into brine (200 mL) and extracting with diethyl ether. The ethereal solution was dried over magnesium sulfate and concentrated. Chromatographic purification (hexanes:ethyl acetate ; 5:1) afforded the desired ester **55** (8.77 g, 90%), with a 5% recovery of the starting lactone **53**.

^{1}H NMR(300 MHz, $CDCl_3$, ppm): 7.17-7.36 (m, 20H) aromatic; 5.72-5.85 (m, 1H) CH_2=C(2')H; 5.23, 5.16 (dd, 2H) C(3')H_2=CH; 4.79 (d, 1H,*J*=12 Hz) C(2)HC(3)H; 4.36-4.67 (m, 8H) benzylic; 4.10 (t, 1H) C(4)H; 3.88-3.95 (m, 1H) C(5)H; 3.84,3.82 (dd, 1H) C(3)H; 3.53-3.62 (m, 2H) C(6)H_2; 2.84 (d, 2H) CHC(1')H_2; 2.32 (s, 1H) OH. IR(neat, cm^{-1}); 3500 (m), 1720 (s).

Mass Spectrum (CI, NH_3); Calculated for $C_{37}H_{40}O_7$ (m/z 596.3). Found m/z 614.0 (M^++NH_4).

PPM
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7.35587
7.33770
7.33198
7.31467
7.30625
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7.27597
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7.26391
7.24842
7.22561
7.20221
7.19373
7.17729
7.17074
7.16216
5.28212
4.81420
4.77812
4.67914
4.66000
4.61399
4.57645
4.53449
4.50265
4.49473
4.48828
4.48360
4.45045
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OBn
OBn
OH
O
O
55
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

WAVENUMBER CM-1
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3500
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2500
2000
1800
1600
1400
1200
1000
800
650
100
90
80
70
60
50
40
30
20
10
0
BnO
BnO
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OH
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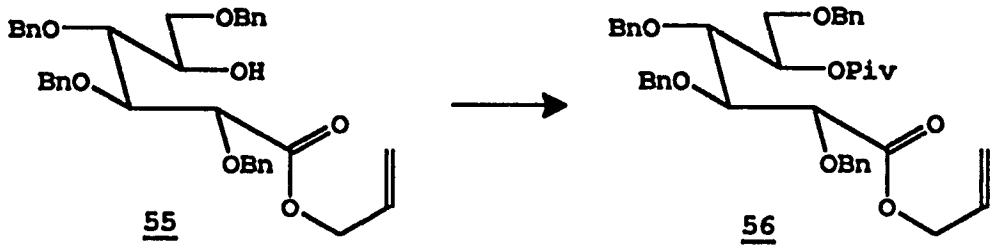
O
O
55

Allyl-2,3,4,6-tetra-O-benzyl-5-O-pivaloyl-D-gluconate, 56.

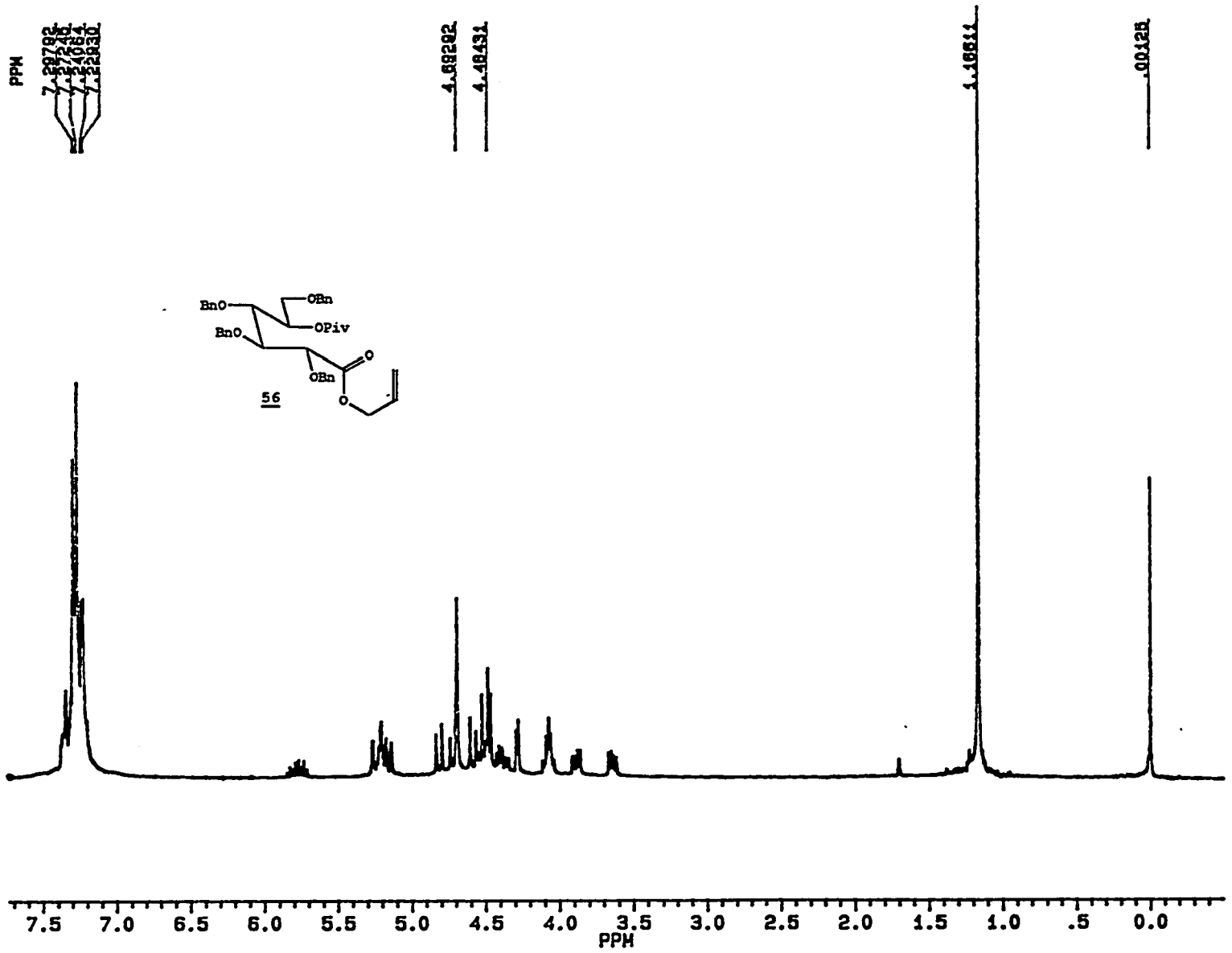


The allylester **55** (5.0 g, 8.4 mmol) was dissolved in 100 mL of dry pyridine and the resulting solution was cooled to 0°C. Freshly distilled pivaloyl chloride (1.11 g, 9.23 mmol) was added in one portion via syringe. The cooling bath was removed and stirring was continued at room temperature for 48 hours. The reaction mixture was poured into an ice/water mixture and extracted with ethyl acetate. The organic layer was dried with $MgSO_4$. The solvent was then evaporated, followed by azeotropic distillation with toluene to remove the residual pyridine. Flash chromatography on silica gel (EtOAc:hexanes 5:1) afforded the diester **56** (5.6 g, 99%).

^1H NMR(300 MHz, $CDCl_3$, ppm): 7.20-7.31 (m, 20H) aromatic; 5.71-5.84 (m, 1H) CH_2=C<u>H</u>; 5.13-5.26 (m, 3H) C(5)<u>H</u>,C<u>H</u>$_2$=; 4.81 (d, 1H,J=12 Hz) C(2)<u>H</u>; 4.34-4.42 (m, 1H) C(4)<u>H</u>; 4.46-4.73 (m, 8H) benzylic; 4.28 (d, 2H,J=6.0 Hz) =CHC<u>H</u>$_2$; 4.04-4.10 (m,1H) C(3)<u>H</u>; 3.85-3.91,3.61-3.66 (dd,dd, 2H, J_{ab}=15 Hz, $J_{5,6}$=6.0 Hz) C(6)<u>H</u>$_2$C(5)H; 1.16 (s, 9H) (C<u>H</u>$_3$)$_3$C.

IR(neat, cm^{-1}); 1750 (s), 1722 (s), 1610 (w).

Mass Spectrum (CI, NH_3); Calculated for $C_{42}H_{48}O_7$ (m/z 664.3). Found m/z 699.1 (M^++2NH_4).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OPiv
BnO
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O
O
56
7.5
7.0
6.5
6.0
5.5
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1.5
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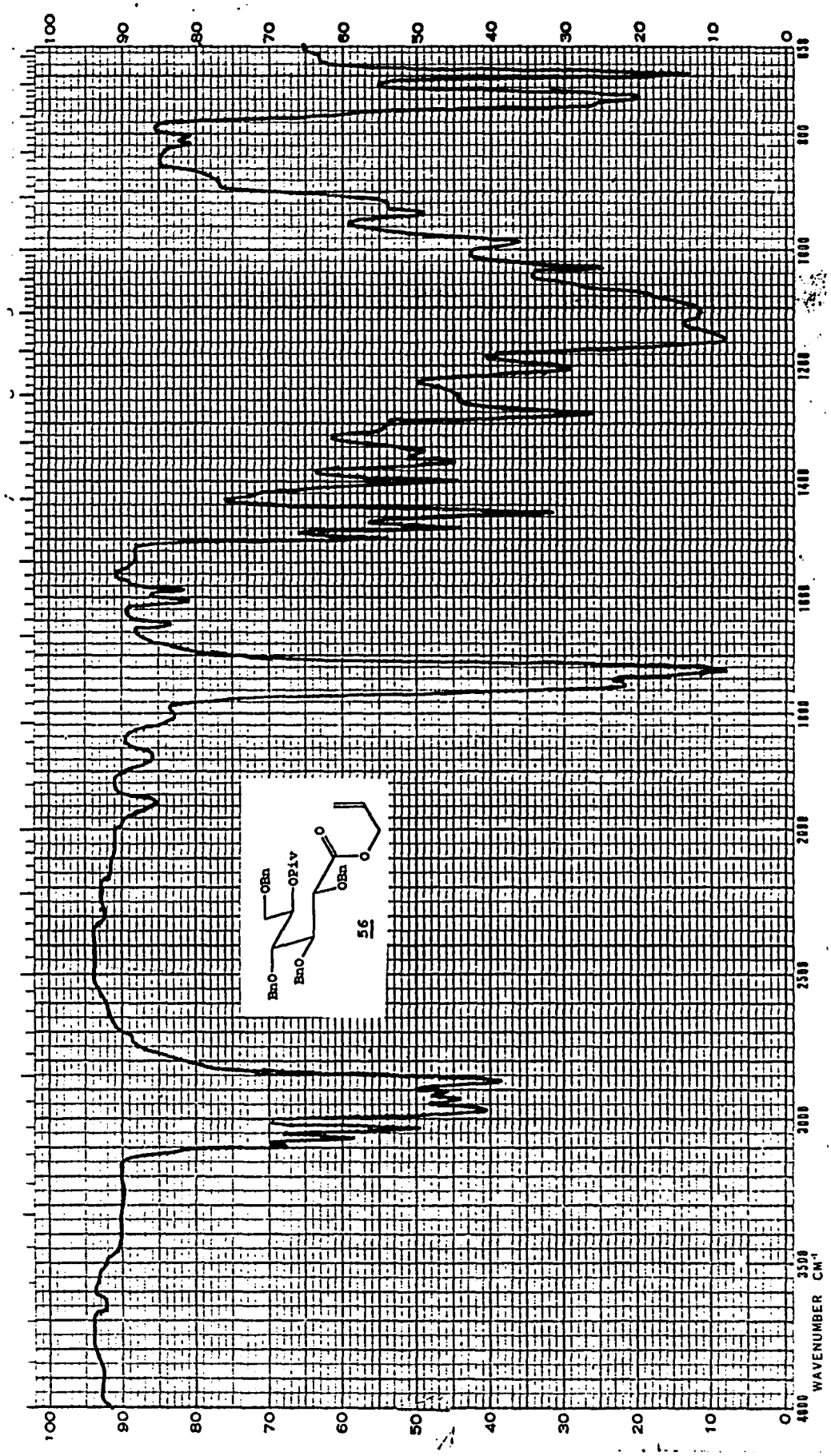
0.0
PPM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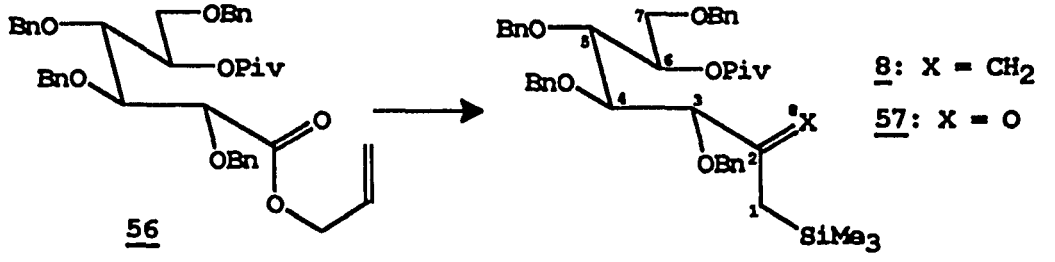
800
600
WAVENUMBER CM-1
OBn
OPiv
OBn
BnO
BnO
O
O
56

3,4,5,7-Tetra-O-benzyl-1-deoxy-2-methylene-6-O-pivaloyl-1-C-trimethylsilyl-D-glucohepitol, 8, and 3,4,5,7-tetra-O-benzyl-1-deoxy-6-O-pivaloyl--1-C-trimethylsilyl-D-gluco-2-heptulose, 57.

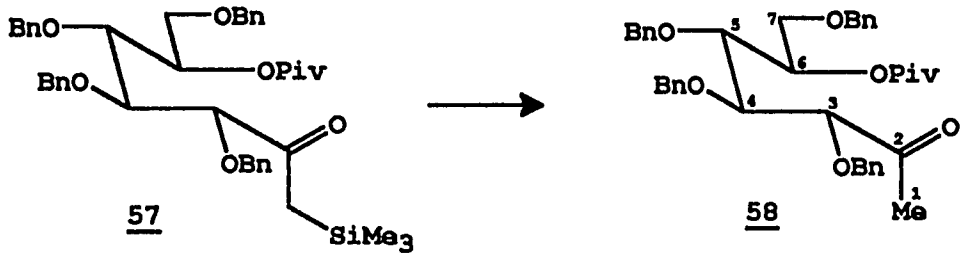


Trimethylsilyl methylmagnesium chloride (5 molar eqivalents with respect to the diester **56** was prepared according to standard procedure in THF and cooled to -78°C for 30 minutes with vigorous stirring under a positive nitrogen atmosphere. A solution of the diester **56** (3.38 g, 5.09 mmol) and chlorotrimethylsilane (3.14 mL, 5 molar equivalents) in dry THF was added dropwise during 30 minutes. Stirring was continued at -78°C for 30 minutes after which time the cooling bath was removed and the reaction mixture was allowed to warm slowly to room temperature with continued stirring overnight. Prior to work-up the reaction mixture was cooled to 0°C then quenched by stirring with cold saturated aqueous ammonium chloride, and extracted with diethyl ether. Drying of the ether layers with $MgSO_4$, concentration and chromatographic purification afforded the allylsilane **8** (3.23 g, 90%). Proton NMR analysis of the crude reaction product revealed trace amounts of the α-silylketone **57**.

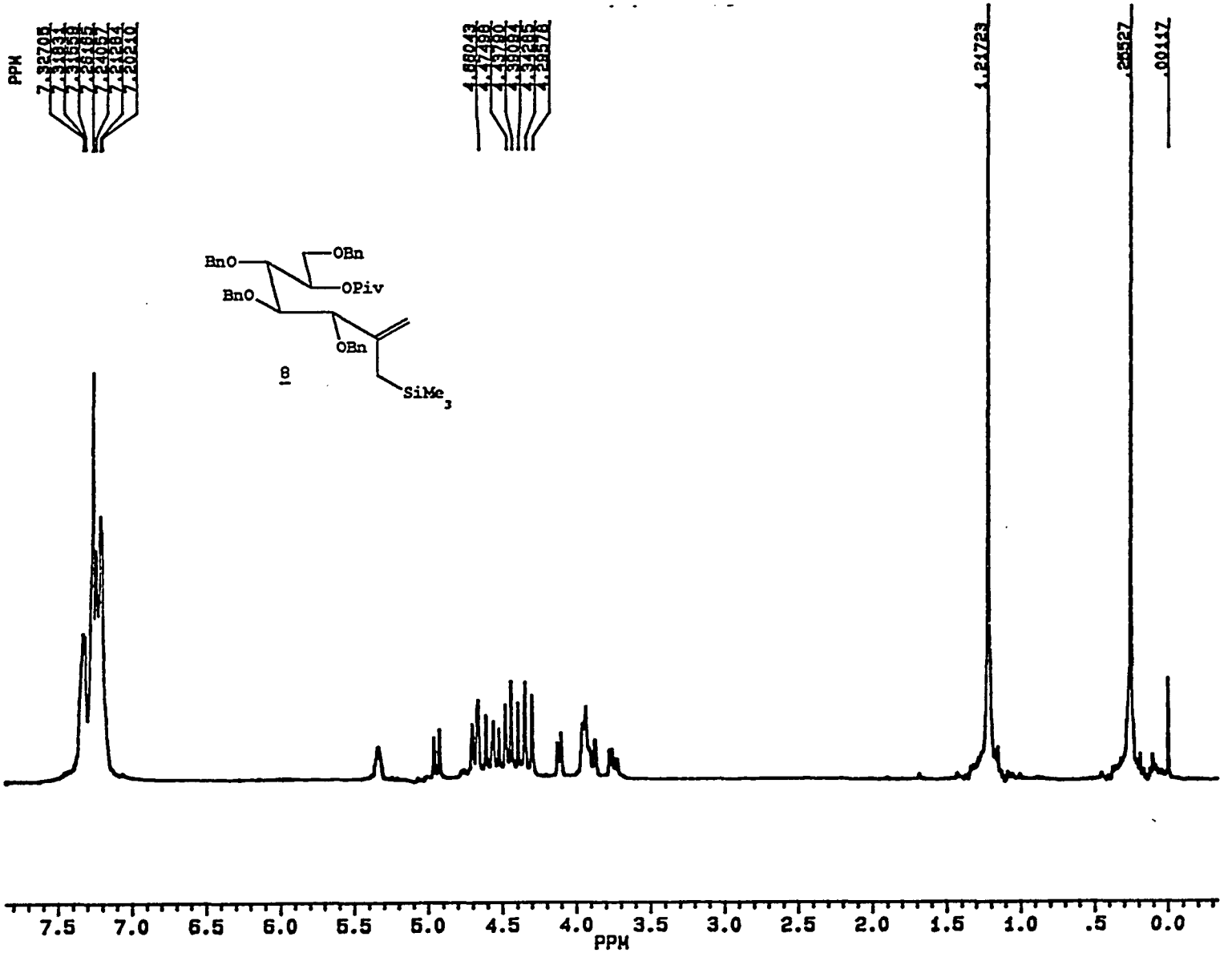
^{1}H NMR(300 MHz, $CDCl_3$, ppm): **8**; 7.20-7.33 (m, 20H) aromatic; 5.33 (m, 1H) C(6)H; 4.66, 4.47 (ds, 2H) C(8)H_2; 4.94,4.68,4.58,4.54,4.42,4.32 (d,d,d,d,d,d, 8H) benzylic; 4.11 (d, 1H,*J*=6.0 Hz) =CC(4)H; 3.87-3.96 (m, 2H) C(6)HC(5)H; 1.21 (s, 11H) $(CH_3)_3C$,$(CH_3)_3SiCH_2$; 0.25 (s, 9H) $(CH_3)_3Si$. IR(neat, cm^{-1}); 1745 (s).

Mass Spectrum (EI); Calculated for $C_{44}H_{56}O_6Si$ (m/z 708.4). Found m/z 709.3 (M^++1). 57; 7.26-7.30 (m, 20H) aromatic; 5.26 (m, 1H) C(6)H(OPiv); 3.70, 3.72 (dd, 1H, J_{ab}= 12 Hz, $J_{6,7}$=6.0 Hz); 3.91,3.93 (dd, 1H, J_{ab}=12 Hz, $J_{6,7}$=6.0 Hz) C(7)H_2; 3.99-4.03 (m, 2H) C(3)H,C(5)H; 4.42-4.71 (m, 8H) benzylic; 2.32 (d, 1H, J_{ab}=12 Hz),1.94 (d, 1H, J_{ab}=12 Hz) C(1)H_2Si; 1.19 (s, 9H) (CH_3)$_3$C; 0.01 (s, 9H) (CH_3)$_3$Si. IR(neat, cm^{-1}); 1718 (s).

3,4,5,7-Tetra-O-benzyl-1-deoxy-6-O-pivaloyl-D-gluco-2-heptulose, 58.



The conversion of compound 57 to the stable methyl ketone 58 occured spontaneously on silica gel, eluting the product quantitatively with the solvent mixture hexanes : ethyl acetate 5:1. Chromatography of 1.0 g (1.4 mmol) of 57 gave 58 (0.88 g, 99%). ^{1}H NMR(300 MHz, $CDCl_3$, ppm): 7.26-7.32 (m, 20H) aromatic; 5.20-5.24 (m, 1H) C(6)H(Opiv); 4.44-4.69 (m, 8H) benzylic; 3.95-4.03 (m, 3H) C(5)HC(4)HC(3)H; 3.91,3.88 (dd, 1H, J_{ab}=9.0 Hz $J_{6,7}$=6.0 Hz) 3.70,3.66 (dd, 1H, J_{ab}=9.0 Hz, $J_{6,7}$= 6.0 Hz) C(7)H_2; 2.01 (s, 3H) CH_3C=O; 1.19 (s, 9H) (CH_3)$_3$C. IR(neat, cm^{-1}); 1720 (s). Mass Spectrum (CI, NH_3); Calculated for $C_{40}H_{46}O_6$ (m/z 622.3). Found m/z 656.1 (M^++2NH_4).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OPiv
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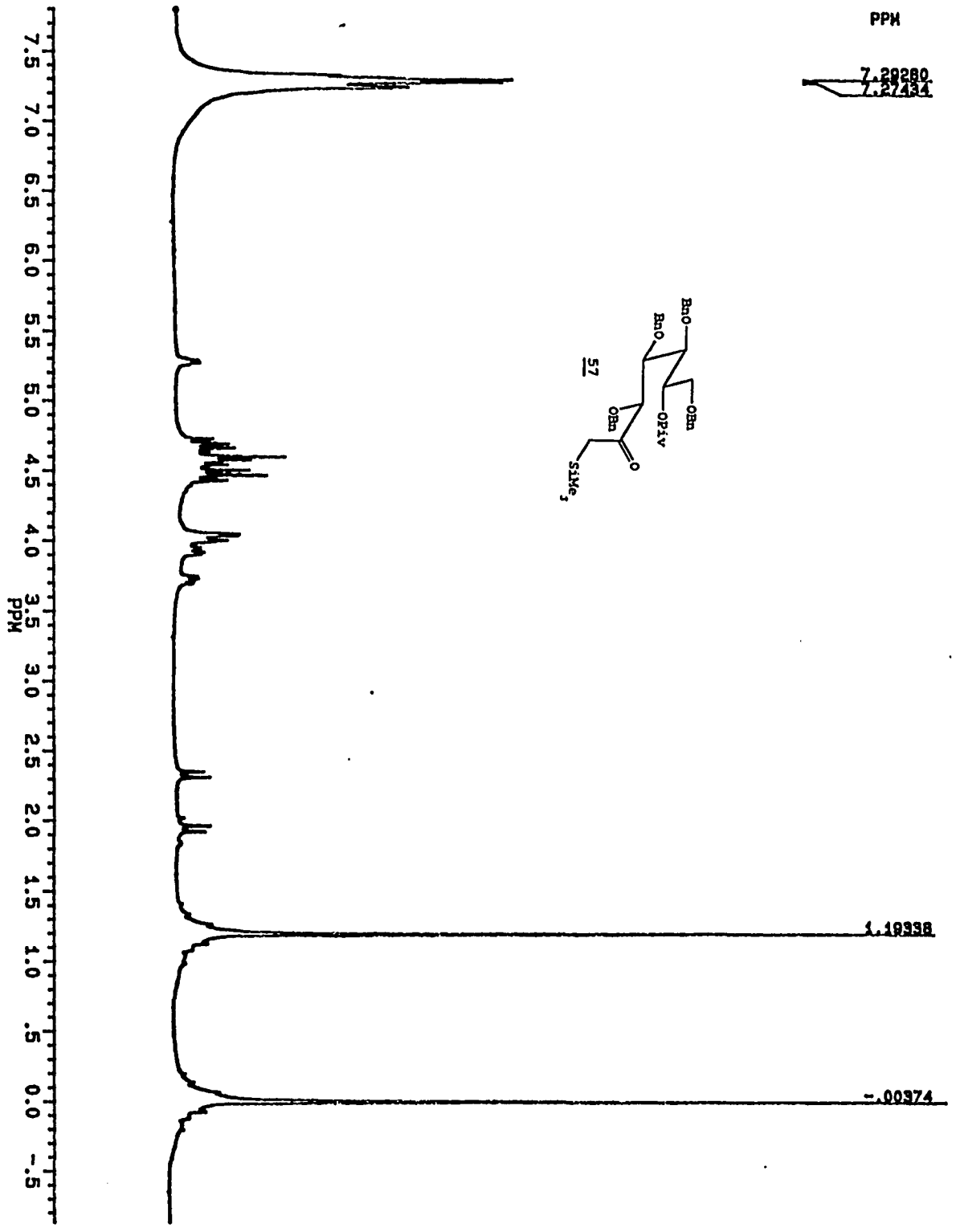
PPM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-.00974
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PPM

PPM
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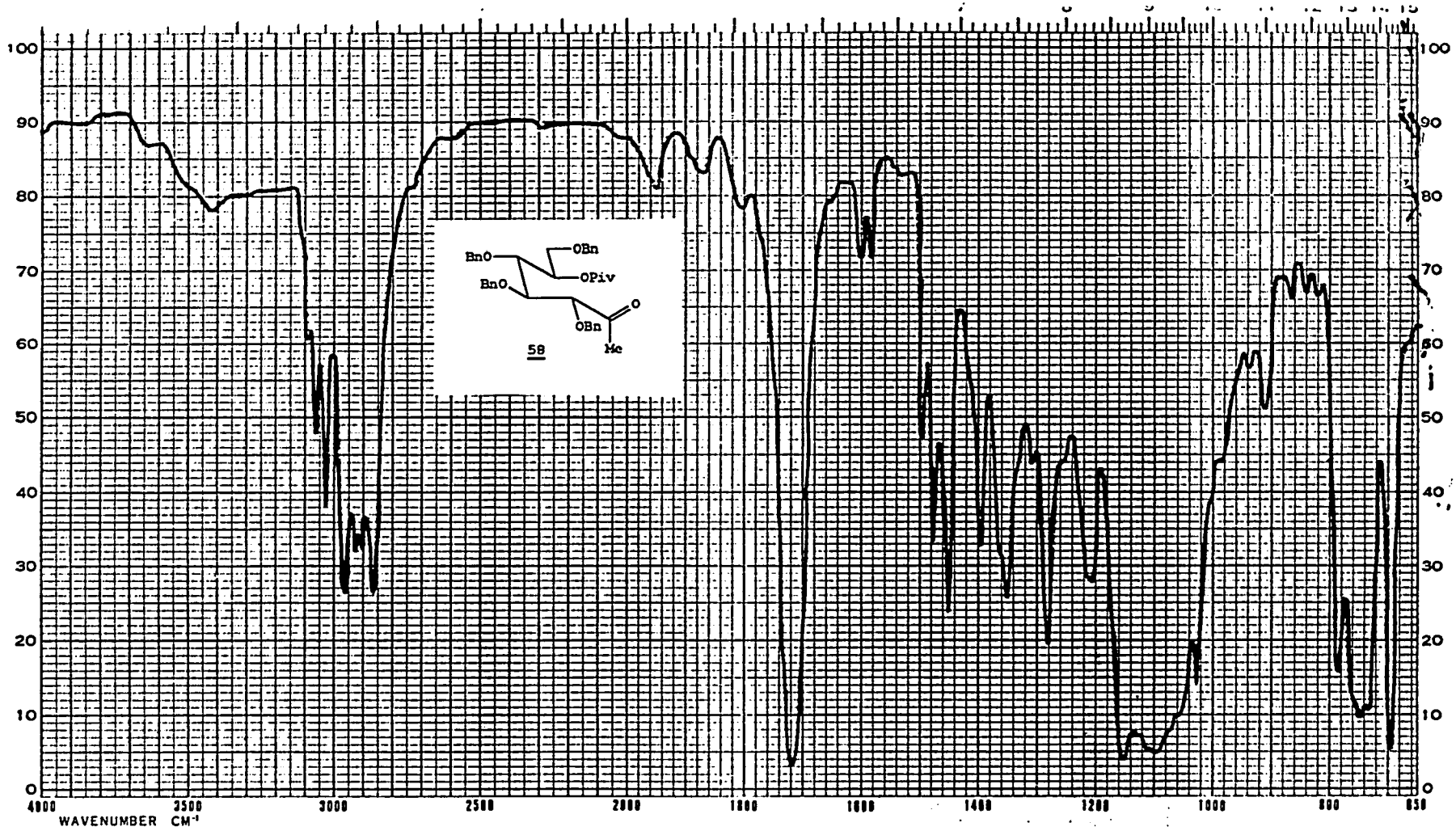
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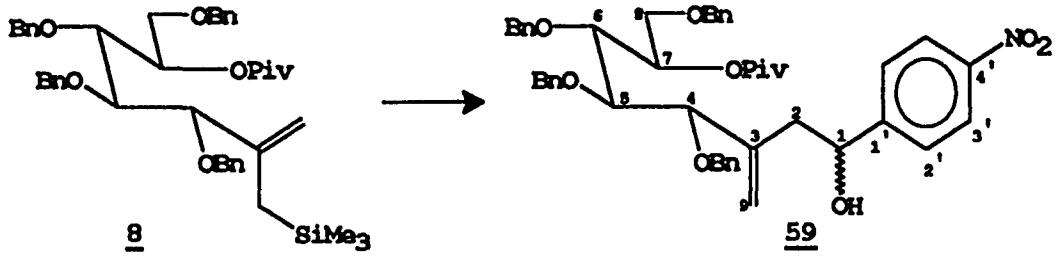
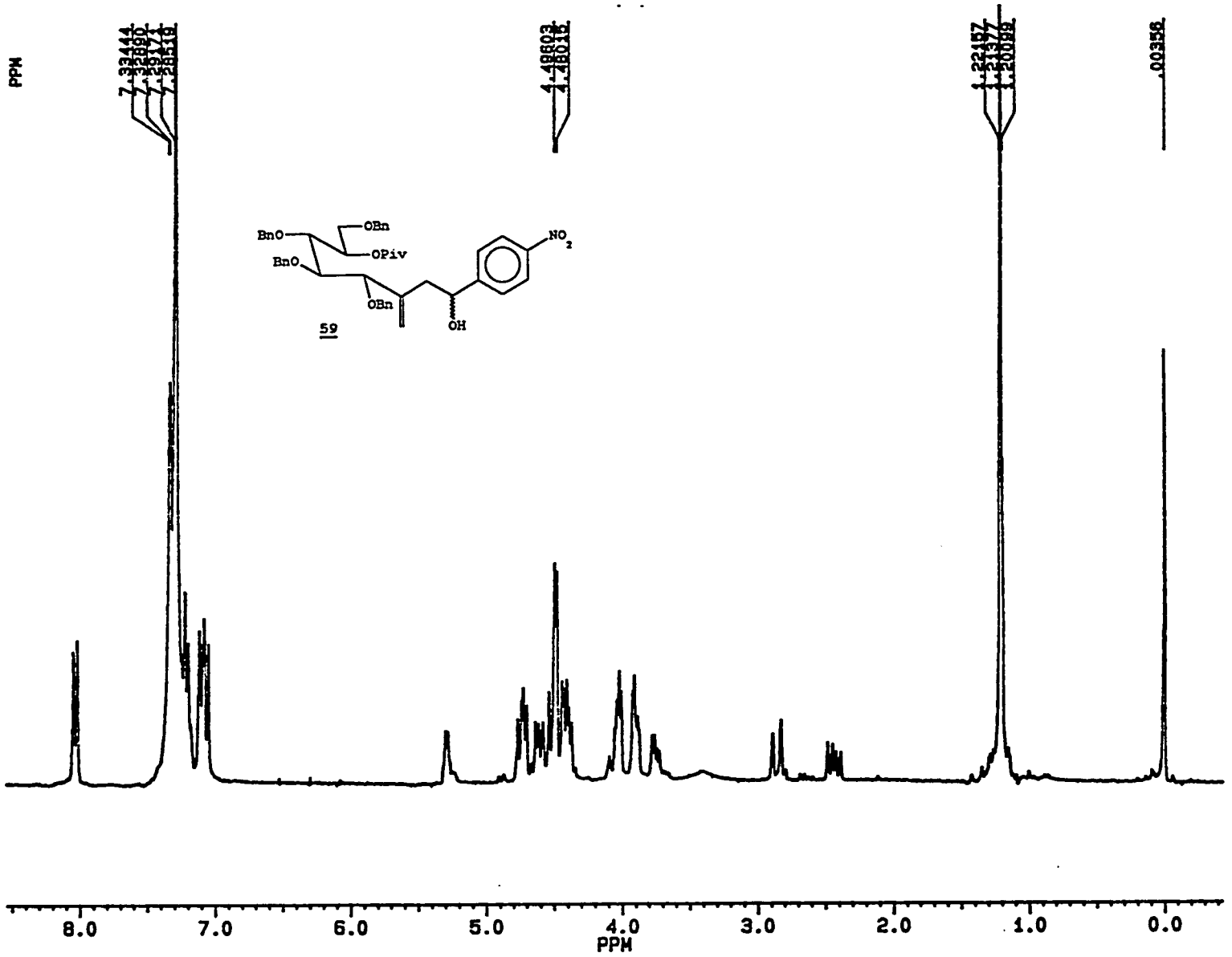
650
WAVENUMBER CM⁻¹
BnO
OBn
OPiv
BnO
OBn
O
Me
58

4,5,6,8-Tetra-O-benzyl-2-deoxy-3-methylene-1-(4-nitrophenyl)-7-O-pivaloyl-D-gluco-octitol, 59.



The allylsilane **8** (0.86 g, 1.22 mmol) and *p*-nitro-benzaldehyde (0.18 g, 1.22 mmol) were dissolved in 10 mL of freshly purified dichloromethane and the solution was cooled to 0°C with stirring. A solution of $TiCl_4$ (1.22 mmol) in dichloromethane (1.22 mL of a 1.0 M stock solution) was added via syringe and stirring was continued for 1.5 hours at 0°C. The ice bath was removed and the reaction mixture was warmed to room temperature for 15 minutes. Work-up consisted of pouring the mixture into saturated aqueous sodium bicarbonate and extracting with dichloromethane. The organic extracts were dried ($MgSO_4$) concentrated and chromatographed (hexanes:EtOAc ; 5:2) to give the compound **59** (0.85 g, 90%), as an inseparable mixture of diastereoisomers (7:1). ^1H NMR(300 MHz, $CDCl_3$, ppm): 8.01 (d, 2H,*J*=6.0 Hz) (C(3')H)$_2$; 7.04-7.33 (m, 22H) aromatic; 5.26-5.32 (m, 1H) C(7)H(OPiv); 4.39-7.80 (m, 10H) C(9)H$_2$,benzylic; 4.00-4.09 (m, 2H) C(8)H$_2$; 3.87-3.92 (m, 2H) C(6)HC(5)H; 3.76, 3.74 (dd, 1H, *J*= 9.0 Hz) =CC(4)H; 3.41 (s, 1H) OH; 2.88,2.82 (ds, br, 2H,*J*=18 Hz) =CC(2)H$_2$; 2.65, 2.62 (dd, 1H) C(1)H, minor isomer; 2.45, 2.42 (dd, 1H) C(1)H, major isomer; 1.21 (s, 9H) (CH$_3$)$_3$C. IR($CHCl_3$, cm^{-1}); 3500 (m), 1720 (s), 1604 (w).
Mass Spectrum (CI, NH_3); Calculated for $C_{48}H_{53}O_9N$ m/z 788.0). Found m/z 789 (M^++1), 806.0 (M^++NH_4).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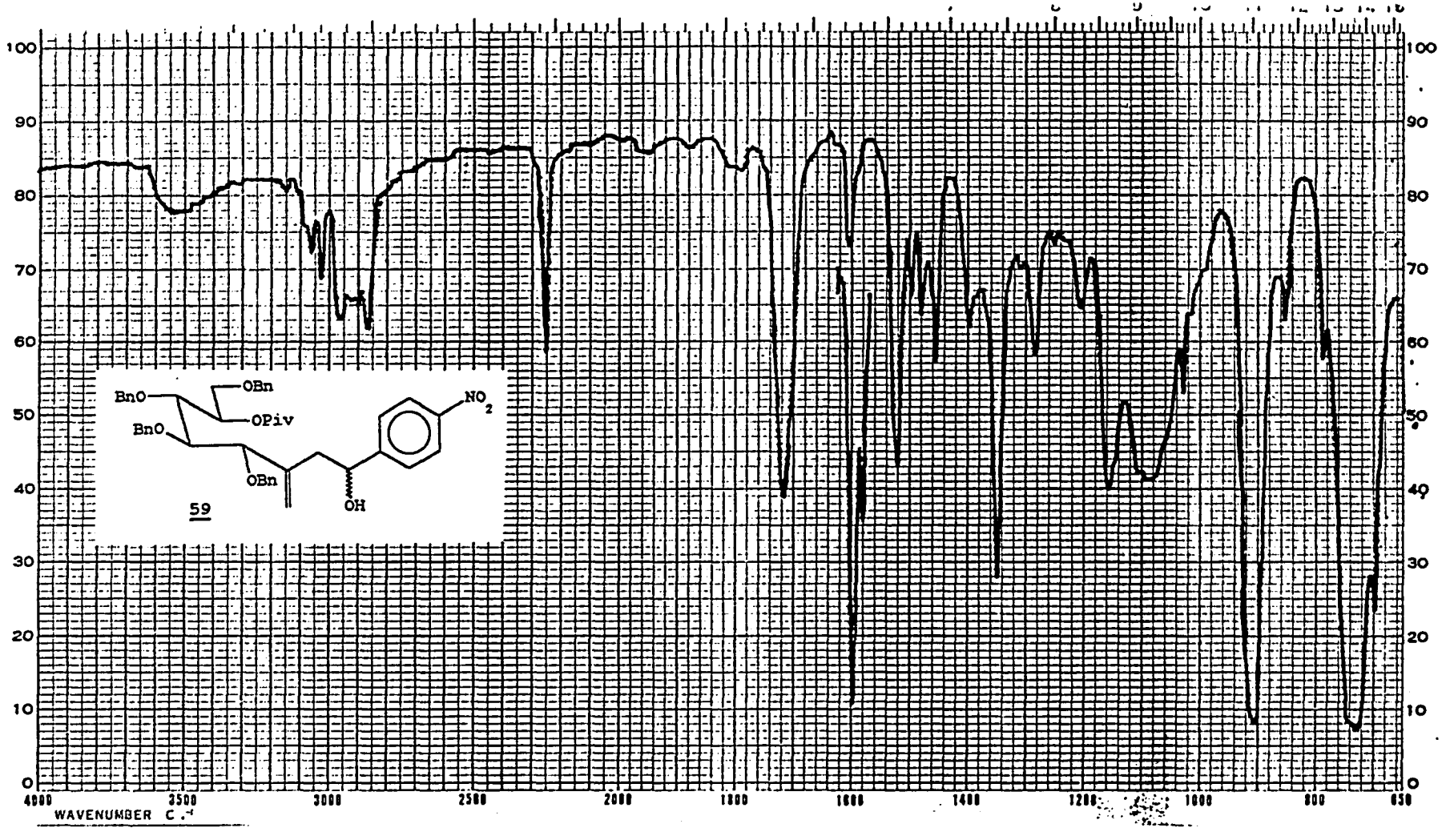
PPM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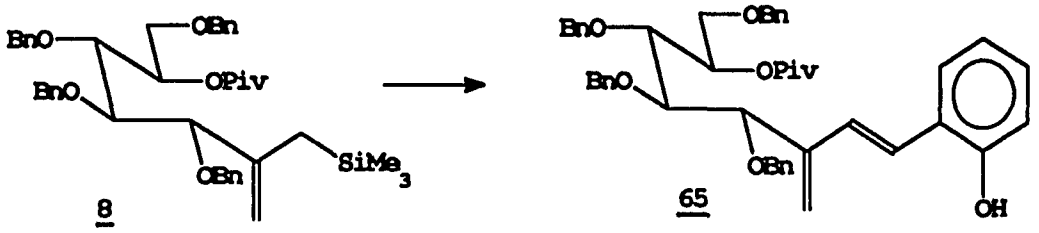
1000
800
650
WAVENUMBER C.⁻¹
BnO
OBn
OPiv
BnO
OBn
OH
NO2
59

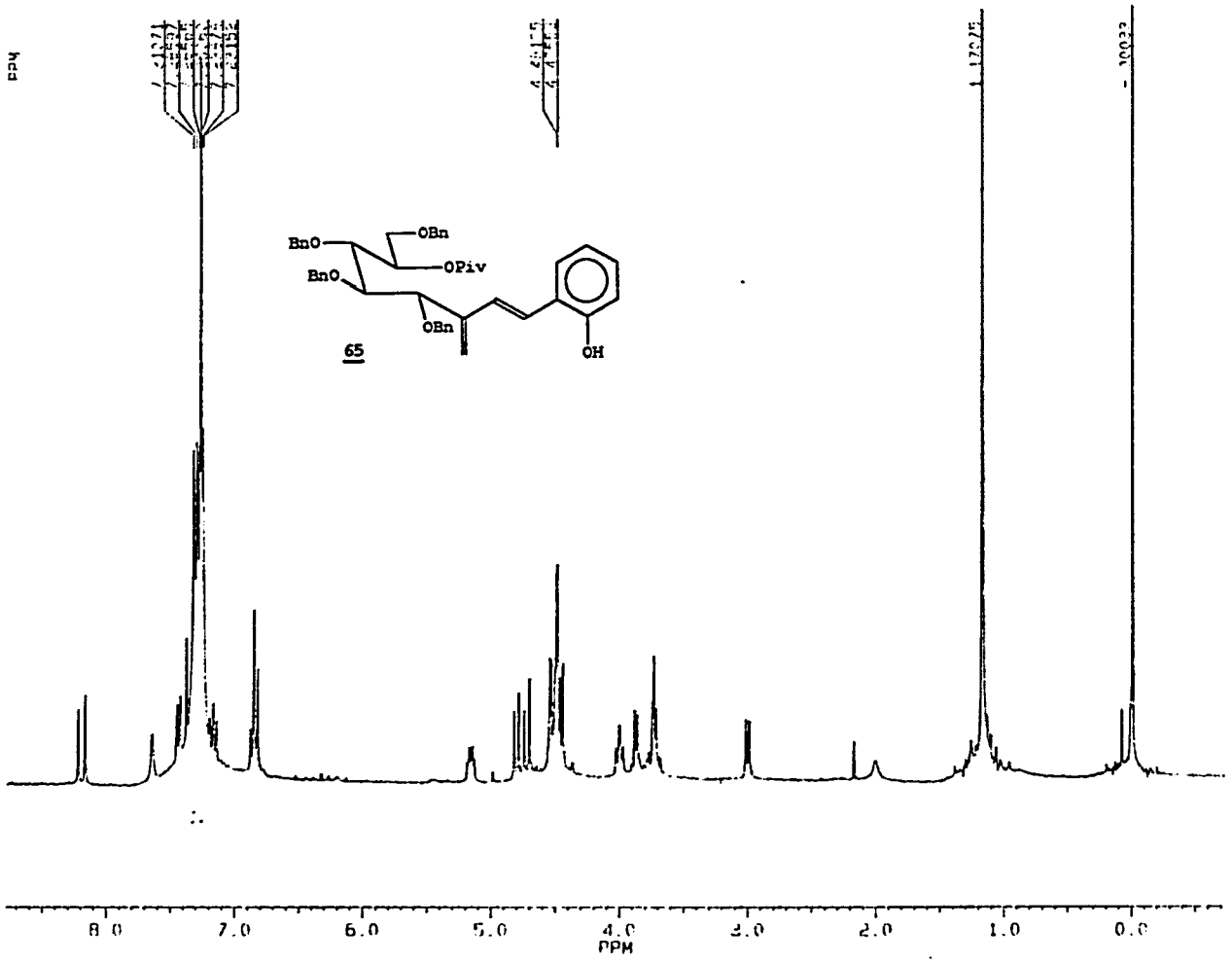
4,5,6,8-Tetra-O-benzyl-1-(1-hydroxyphenyl)-3-methylene-7-O-pivaloyl-D--gluco-1-enoctitol, 65.

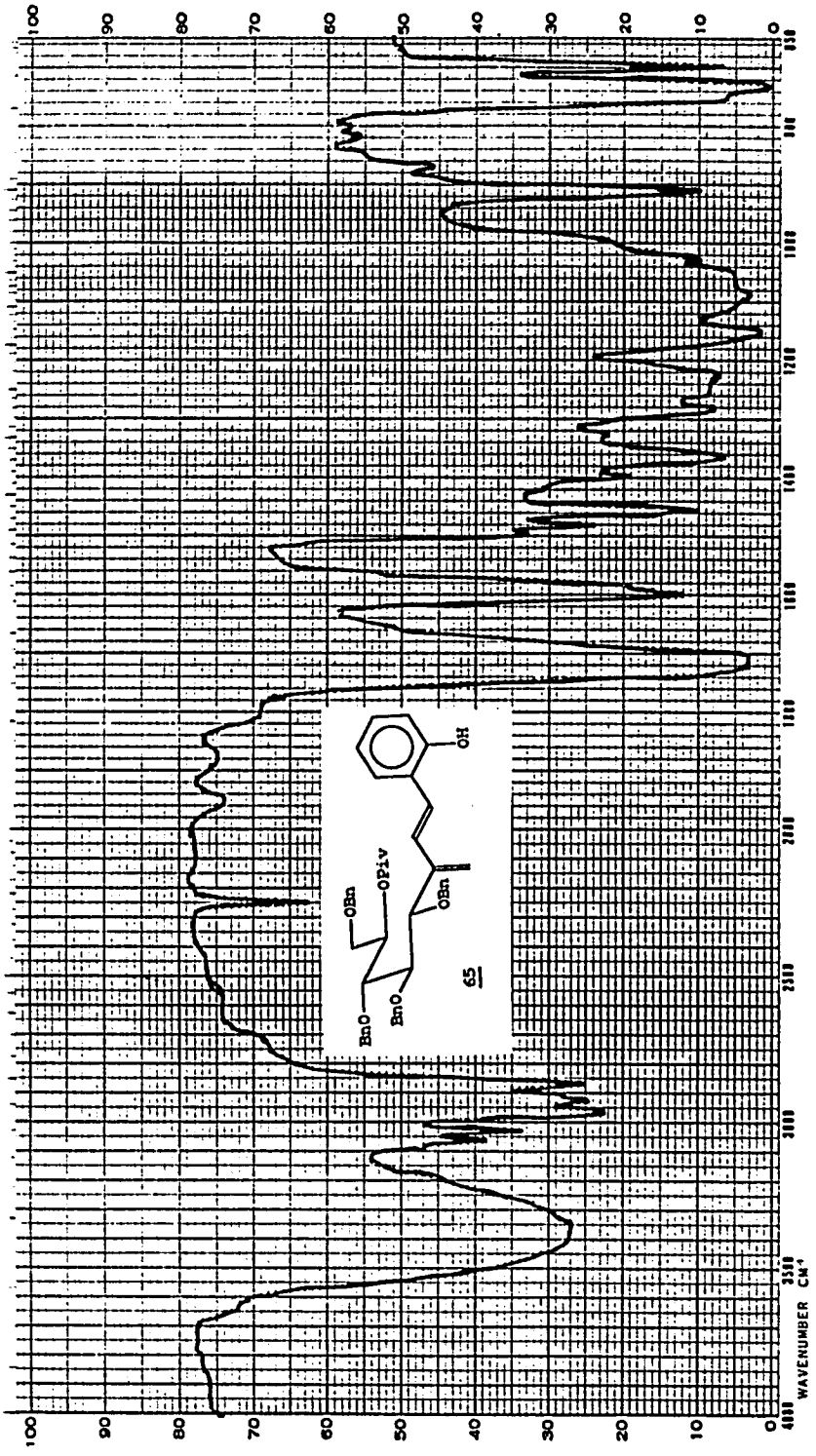


The mixture of products **62** - **65** (0.5 g), was dissolved in 20 mL of THF to which 1 mL of triethylamine was added. The reaction mixture was stirred and refluxed at 35°C for four hours, and then cooled to room temperature. Work-up consisted of washing the reaction mixture with saturated aqueous ammonium chloride, washing with water, and then brine. The organic layer was dried, concentrated, and the crude product chromatographed (EtOAc:Toluene ; 1:5) which provided the diene **65** (0.39 g) exclusively.

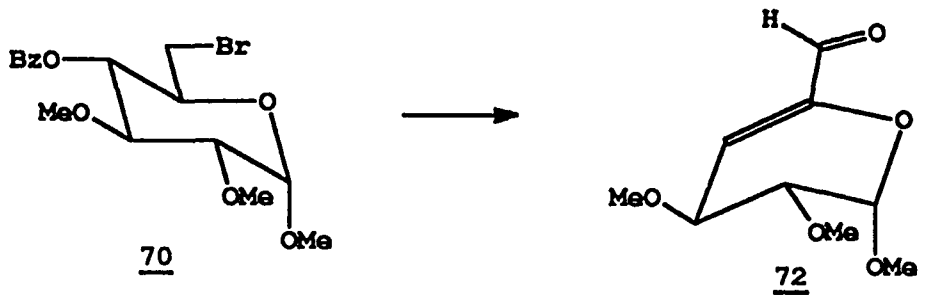
^{1}H NMR(300 MHz, $CDCl_3$, ppm): 8.18 (d, 1H); 7.13-7.43 (m, 26H); 6.85,6.83 (dd, 1H); 5.15 (m, 1H); 4.79 (d, 1H); 4.71 (d, 1H); 4.43-4.54 (m, 6H); 4.01,3.98 (dd, 2H); 3.86 (d, 1H); 3.73,3.71 (dd, 2H); 2.99 (d, 1H); 1.99 (s, 1H); 1.17 (s, 9H). ^{13}C δ 133, 129.5, 128.9, 128.7, 128.3, 128.0, 123, 121, 117, 85.5, 75.3, 73.4, 72.0, 69.6, 30.95, 30.57, 30.18, 29.79, 29.41, 29.02, 28.64, 27.34.

Mass Spectrum (EI): Calculated for $C_{52}H_{52}O_7$ (m/z 788.4). Found m/z 789 (M^++1).


BnO
OBn
OPiv
BnO
OBn
OH
65
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM


OH
OBn
OPiv
OBn
BnO
BnO
65
WAVENUMBER CM⁻¹

Methyl-α-D-gluco-4-enono-2,3-di-O-methyl-6-hexulopyranoside, 72.



To a solution of the bromide 70 (0.64 g, 1.65 mmol) in 10 mL of dimethyl sulfoxide (dried over 4A° molecular sieves), was added crystalline trimethylamine *N*-oxide (0.62 g, 8.25 mmol) under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 18 hours. Work-up consisted of pouring the reaction mixture into ice-cold brine which was extracted with diethyl ether. The organic extracts were dried over $MgSO_4$, concentrated and chromatographed (EtOAc:Hexanes ; 2:5) which provided the unsaturated aldehyde 72 (0.30 g, 90%).

^1H NMR(300 MHz, $CDCl_3$, ppm): 9.25 (s, 1H) C(6)H; 5.97 (d, 1H) C(4)H; 5.16 (d, 1H) C(1)H; 4.22,4.20 (dd, 1H) C(3)H; 3.56, 3.53, 3.52 (ts, 9H) 3 x CH_3; 3.51, 3.50 (dd, 1H) C(2)H.

Mass Spectrum (EI): Calculated for $C_9H_{14}O_5$ (m/z 202). Found m/z 202 (M^+).

72
MeO
OMe
OMe
H
O
O
ppm

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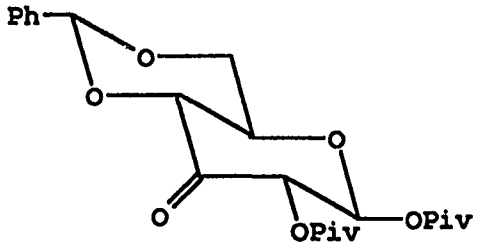
CHAPTER 5

5.0.0. The Chemistry of Glucopyranosid-3-uloses

5.1.0. Introduction

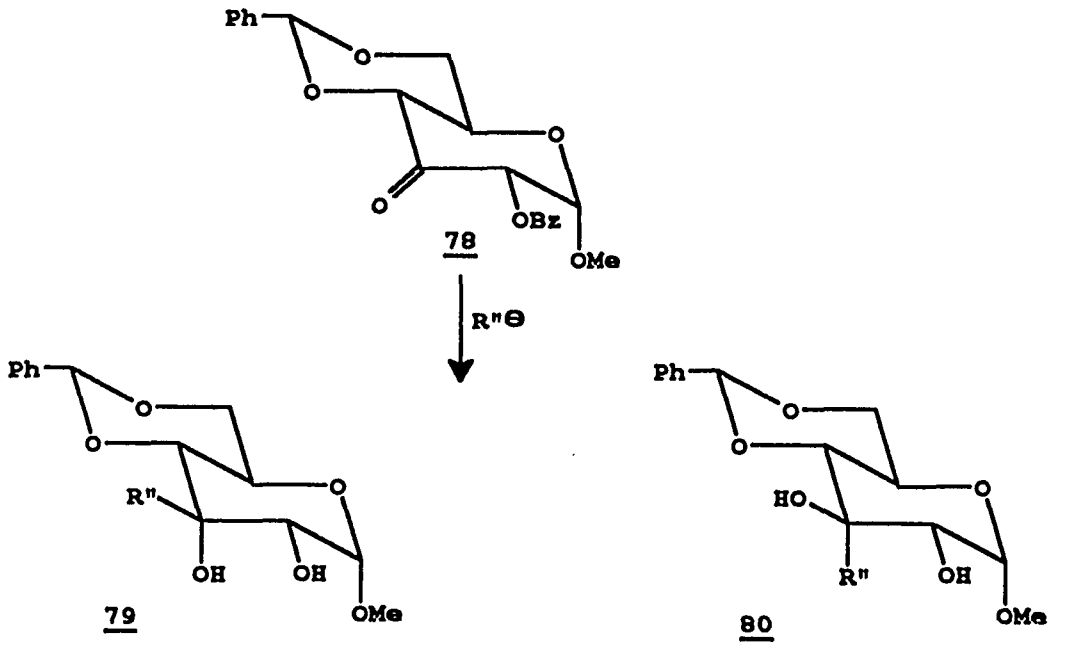
The glucopyranosid-3-ulose 7, discussed in the previous chapter, was one of the key intermediates in the convergent synthetic methodology on which we embarked. It was therefore important that the chemistry of these compounds be illuminated.



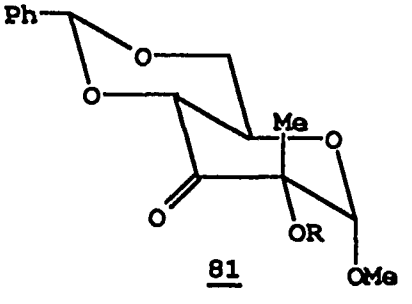
7

It has been established that the ribo-hexopyranosid-3-uloses, 78, react with Grignard reagents to give predominantly the allo-compounds, 79, and small amounts of the glucocompounds, 80, Scheme 1[1]. Specifically, the reactions of 78 were examined with allyl-, benzyl- and methylmagnesium halides, by which the allo-compounds were obtained in yields of 80%, 72% and 84% respectively[2].

SCHEME 1



It was further demonstrated that methyl 4,6-O-benzylidene-2-C-methyl-α-D-ribo-hexopyranosid-3-ulose, **81**, also gave allo-compounds as the major products from its reactions with Grignard reagents and the hydride donor reagents[3]. Thus it was evident that the axial methyl group on the adjacent carbon (C2) had little effect on the stereochemical outcome of these addition processes. Similar observations have been made in the reductions of the xylohexopyranosid-3-ulose **82**, which gave gulo-com-

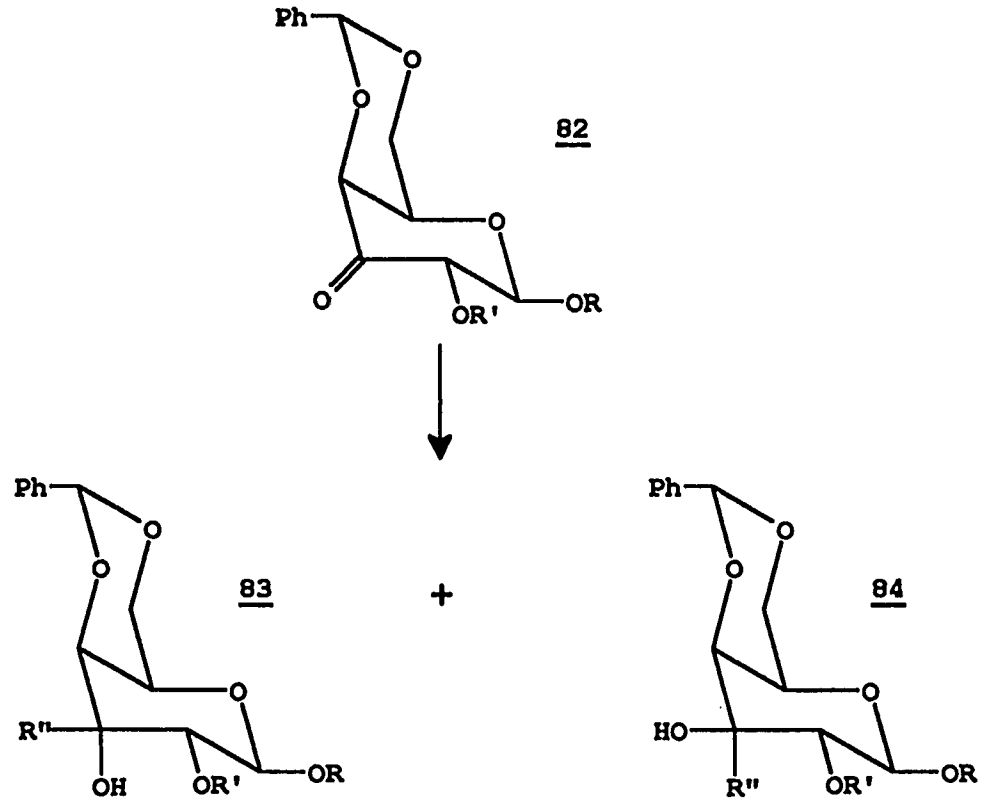


R = H

R = CH_2SCH_3

pounds, **83**, as the major products (85%), and galacto-compounds, **84**, as the minor products[4] (12%), Scheme 2.

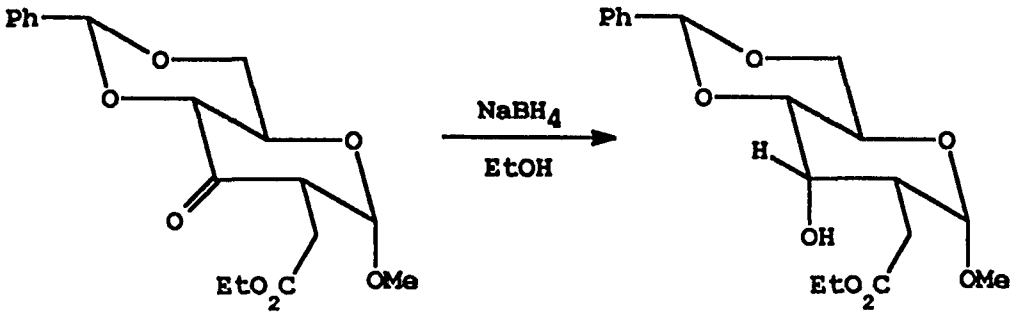
SCHEME 2



The preference for an equatorial attack by the nucleophile on the C(3) carbonyl group would thus appear to be the normal mode of reaction in these 3-uloses, independent of the C(2) **R** group when **R** is small. Such is the case when **R** is methyl, methylthiomethyl, or benzyl.

In studies directed towards the general synthesis of homochiral trisubstituted γ-butyrolactones, Wood *et. al.* observed a 95:5 stereoselectivity, in favor of the allo-product from the reduction of the 3-ulose **85** with sodium borohydride in ethanol, Scheme 3[5]. Product ratios were determined by proton NMR analysis. The expected proton-proton coupling constants for the C(3) proton ($J_{2,3}$ and $J_{3,4}$ = 3.0 Hz), were observed, consistent with the axial-equatorial-axial arrangement of protons in compound **86**.

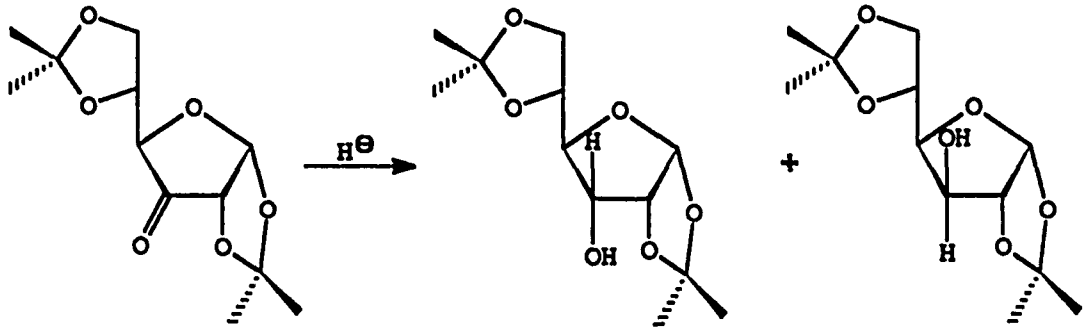
SCHEME 3



85 86 95%

In another series of reductions, Horton and his associates[6] examined the reactions of the compound 87 with several hydride donor reagents. Stereoselectivity data were determined by use of a g.l.c. system. The results of these investigations are summarized in Scheme 4 below.

SCHEME 4



87	Conditions	88	89
	$LiAlH_4/Et_2O$	97.3%	2.7%
	"Vitride"/Et_2O/PhH	98.0%	1.9%
	$NaBH_4/Et_2O$	99.0%	0.5%

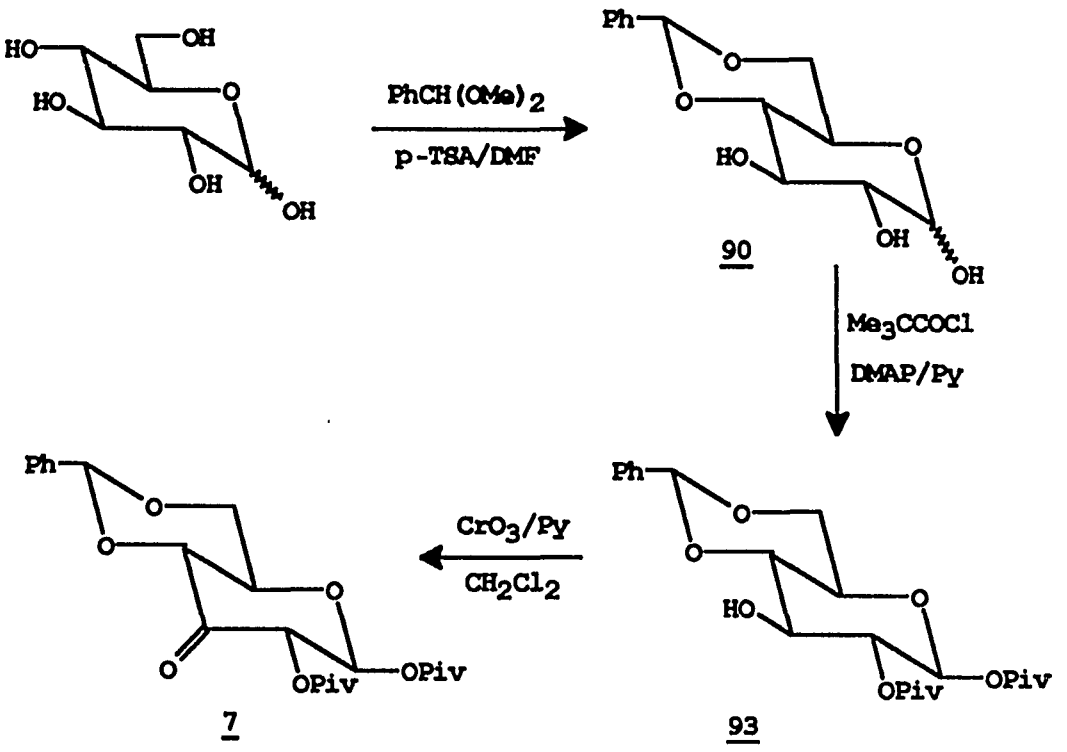
["Vitride" - Sodium bis(2-methoxyethoxy)aluminum hydride.]

As stated above, the preference for an equatorial attack by the nucleophile appears to be the normal mode of reaction with these 'uloses'. We have, however, demonstrated that for the 3-ulose 7, an axial approach of the attacking nucleophile was the dominant mode of reaction. Perhaps, the presence of the bulky, electron-withdrawing pivalate group at C(2) did influence the stereochemical outcome of these reductions. The results of these investigations are discussed below.

5.2.0. The Synthesis of the 3-ulose 7

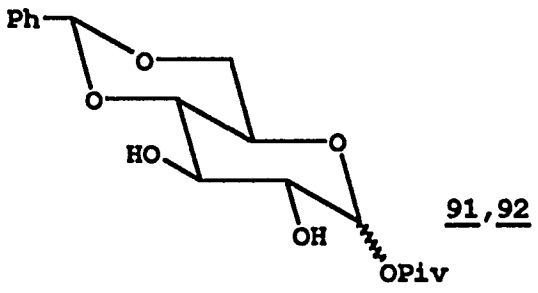
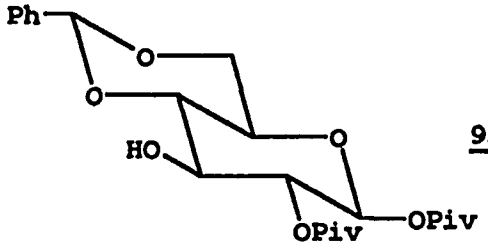
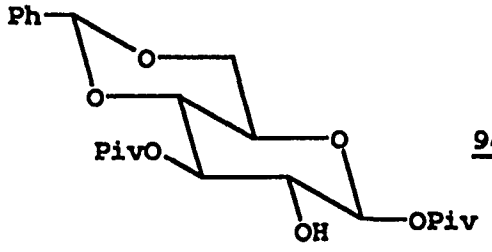
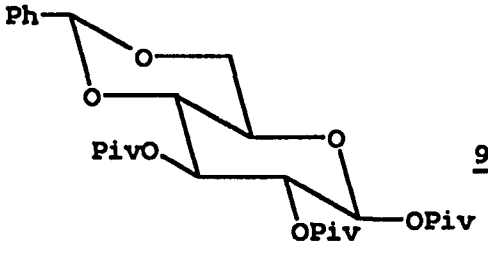
The preparation of compound 7 was achieved quite readily by the sequence of reactions shown in Scheme 5 below. 4,6-O-Benzylidene glucose, 90, was prepared by the known acetal exchange reaction between D-glucose and benzaldehyde dimethyl acetal in DMF. The esterification of compound 90 which followed confirmed the long established results regarding the relative reactivity of the different sugar hydroxyl groups. Thus compound 90 was treated with a 2.2 molar equivalent of pivaloyl chloride and a catalytic amount of DMAP (10 molar percent) in pyridine for 72 hours. A mixture of the mono-, di-, and tri-pivalates was obtained, Table 1.

SCHEME 5



The mixture of dipivalates, 93 and 94, could not be separated by column chromatography, thus we had to resort to selective crystallization from hexanes over several days, by which the 1,2 (93) was obtained in an overall yield of 38%. Equilibration studies were performed by allowing samples of the pure 1,2-dipivalate 93, and the mixture of 93 and 94, to stir in pyridine for up to seven days at room temperature. Compound 93 was recovered unaltered from the first series of reactions. Likewise, the ratio of 93:94 ; 1.8:1.0, was not at all affected in the latter case. These results confirmed our speculations that the pivalate ester group does not migrate under these conditions, hence the observed product distribution was a consequence of the different reactivities of the sugar hydroxyl groups.

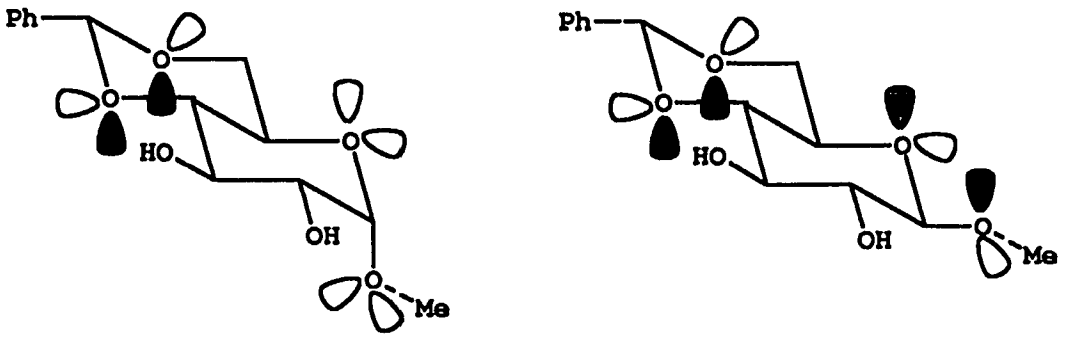
TABLE 1

Compound		Yield(%)
	91,92	20
	93	38
	94	22
	95	10

It is without question, that compound **90** was initially esterified at the anomeric center; however, in rationalizing the actual sequence of reactions, we concluded that the β-anomer was more reactive than the α-anomer. This increased reactivity has been attributed to an activated nucleophilicity of the C(1)OH group through the β-effect with O-(5). The α-anomer, on the other hand, was stabilized by the anomeric effect, which in part, was a consequence of the decreased repulsion between the lone pair orbitals of O-(5) and O-(1) hence its decreased reactivity[7]. Further analysis of the results obtained indicated an apparent failure of the α-monopivalate to undergo further esterification. No α-di, or tri-pivalates were isolated, or even detected in the NMR. This reluctance to further esterification might be a consequence of steric congestion faced by the esterifying acylpyridinium ion since the groups would be cisoid. There might also have been a minor destabilizing contribution from the β-effect. Thus multiple esterification was apparently restricted to the β-monopivalate.

Table 1 reveals that the β-1,2-dipivalate **93** was formed in greater proportions relative to the β-1,3-dipivalate **94**, 1.8:1.0, indicating a slightly greater reactivity of the C(2)OH group. Studies involving methyl 4,6-*O*-benzylidene-β-D-glucopyranoside however, revealed a slightly greater reactivity of the C(3)OH group[7]. The reverse situation was observed with the α-glucopyranoside, Scheme 6.

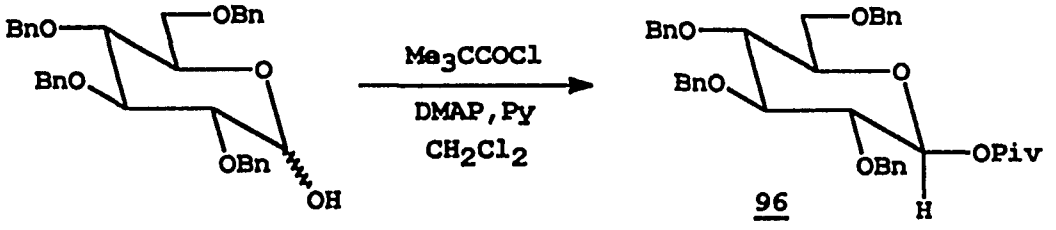
SCHEME 6



A plausible rationale for these observations involves a mechanistic proposal incorporating an acylpyridinium ion as the esterifying agent. In addition, it would appear that solvent effects are minimal, as can also be deduced from the published work of other researchers outlined below.

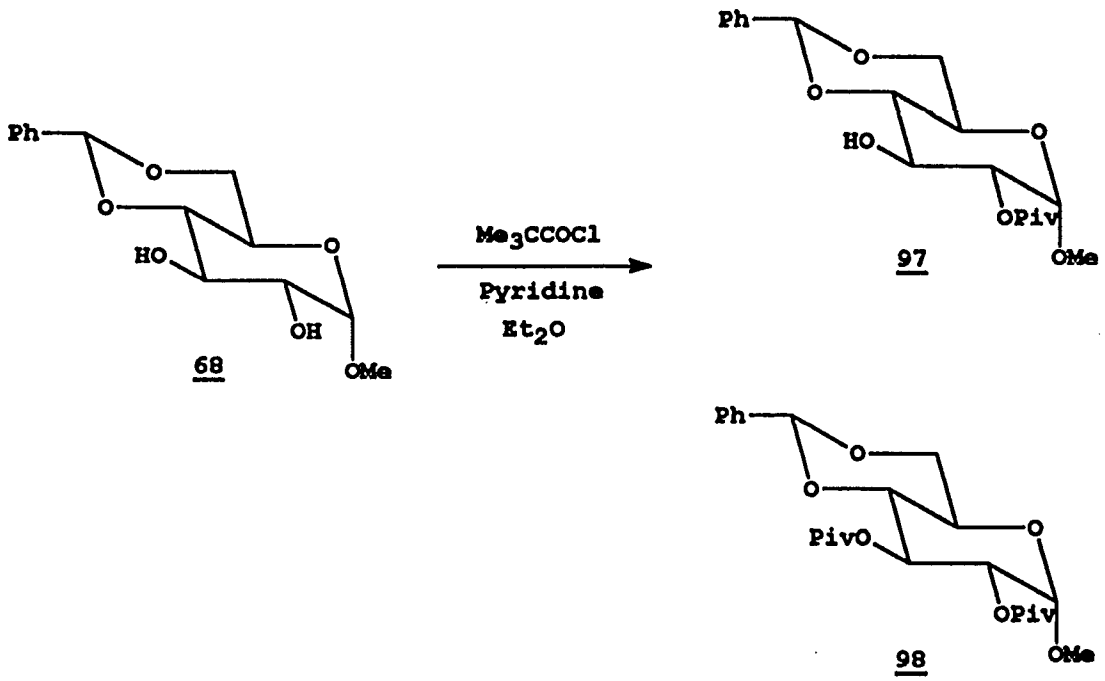
In a stereoselective synthesis of 1-*O*-pivaloyl-β-D-glucopyranuronic acid, Bols obtained the β-ester 96 (86%) exclusively from the esterification of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose with pivaloyl chloride, DMAP, and pyridine in dichloromethane, Scheme 7[8].

SCHEME 7



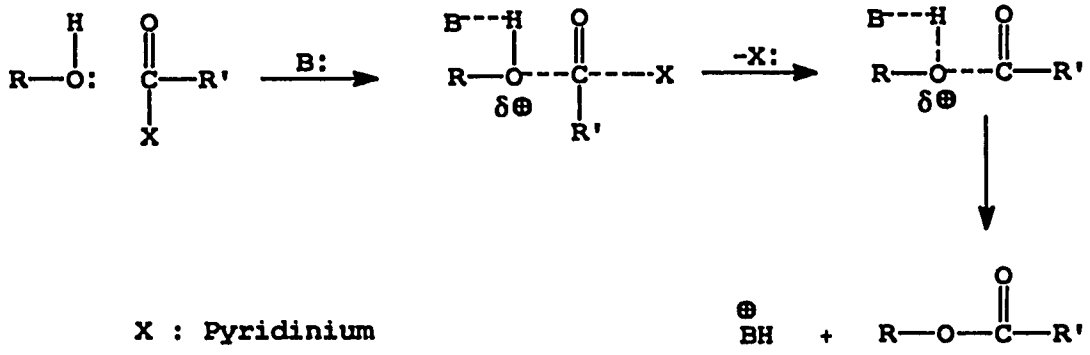
Tomic-Kulenovic treated compound 68 with 2.2 molar equivalents each of pivaloyl chloride and pyridine in diethyl ether at room temperature and obtained the monopivalate 97 (77%) after 16 hours. When the reaction time was extended to 48 hours, the di-pivalate 98 was obtained (27%) in addition to product 97, Scheme 8[9].

SCHEME 8



These discoveries provide additional support for our proposed mechanism involving an acylpyridinium ion, and a suitable proton acceptor, **B:**, as outlined in Scheme 9.

SCHEME 9

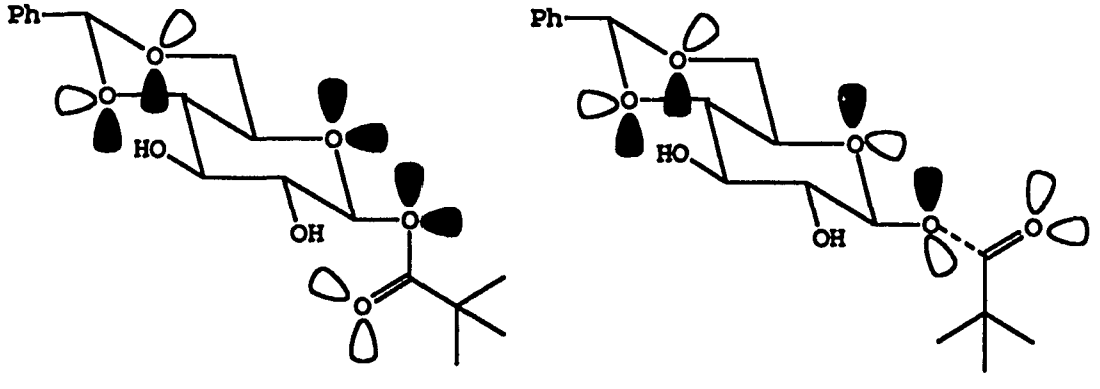


The differences in reactivity was therefore explained by considering the available proton acceptor sites for the C(2)OH and the C(3)OH of the β-anomer, namely, O-(1)

and O-(4) respectively. Thus it was postulated that site O-(4) was activated by a fixed β-effect, resulting from the coformationally-fixed benzylidene ring, while O-(1) could rotate about the C(1)-O(1) bond so varying the positions of the lone pairs and reducing the magnitude of the β-effect it experienced. The O-(4) would then be a more strongly activated proton acceptor site, capable of intramolecular hydrogen bonding, thereby accounting for the slightly greater reactivity of the C(3)OH.

As stated above, the C(2)OH group of our β-monopivalate was unquestionably more reactive than the C(3)OH, hence, if the above rationale regarding proton acceptor sites should have been adopted, then it followed that there must have been at least one other controlling factor favoring esterification at C(2). Scheme 10 shows two possible conformations of the β-monopivalate. Conformation (i) shows the carbonyl oxygen in close proximity to the C(2)OH resulting in lone pair-orbital repulsion hence an accentuated nucleophilicity of O-(2). In addition, the carbonyl oxygen can conceivably function as a proton acceptor site thereby facilitating esterification by the acylpyridinium ion.

SCHEME 10



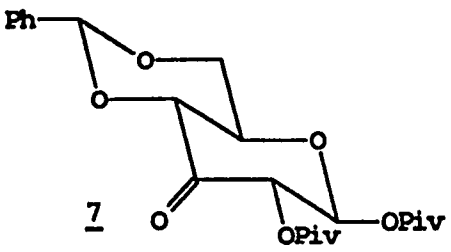
(i) (ii)

5.3.0. Hydride reduction of the 3-ulose 7.

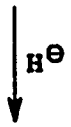
Compound 93 was oxidized to the 3-ulose 7 using Collins' reagent, in 90% yield. Compound 7 was subsequently reduced with sodium borohydride in a variety of solvents producing compounds 91, 93, 99 and 100, Scheme 11. The ratio in which products 93 and 99 were obtained, was determined by proton NMR analysis of the crude reaction mixture. The C(2)H of compound 93 appeared as a triplet at δ 5.07 ($J_{2,1}$ and $J_{2,3}$ = 9.0 Hz), reflecting the trans-diaxial arrangement of the two neighboring protons. In compound 99 however, the C(2)H appeared as the anticipated doublet of doublet at δ 4.88 and 4.86 ($J_{2,1}$= 9 Hz, and $J_{2,3}$=3 Hz) confirming the C(1)-axial-C(2)-axial-C(3) equatorial arrangement of protons. Chromatographic purification of the reaction mixture (EtOAc:hexanes ; 1:5) afforded 93 and 99 (fraction 1), compound 100 (fraction 2), and compound 91 (fraction 3). The monopivalates 91 and 100 were obtained in an approximate 1:1 ratio.

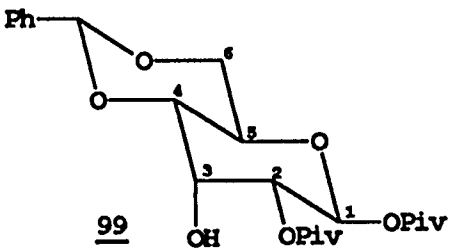
Reduction data for the different runs performed which reflect the ratio of 93:99, are depicted in Table 2 below. In spite of the fact that the tabulated results are based on the dipivalates, it is reasonable to extrapolate these data as being representative of the overall selectivity of the reactions, since the two monopivalates were isolated in roughly equal amounts.

SCHEME 11

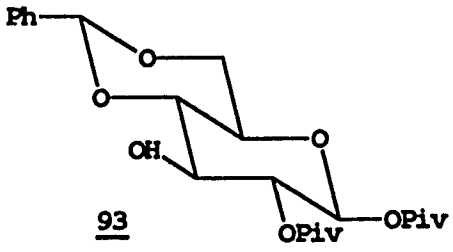


7

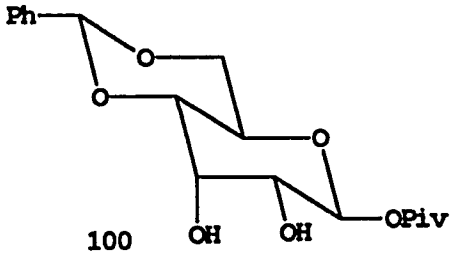




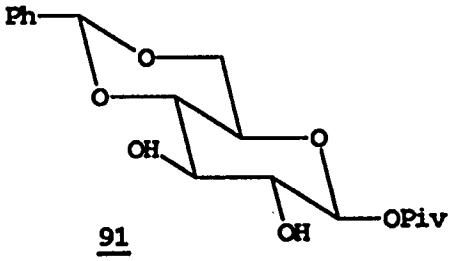
99



93



100



91

TABLE 2

Run	Solvent	Metal Salt	Product Ratio (99:93)
1	95% EtOH	None	1 : 9.0
2	Absolute Ethanol	None	1 : 1.5
3	*t*-Butanol	None	1 : 1.3
4	*n*-Butanol	None	1 : 1.0
5	*t*-Butanol	$CeCl_3.7H_2O$	1 : 1.4
6	*t*-Butanol	$CrCl_3.6H_2O$	1 : 1.3
7	*t*-Butanol	$MgBr_2$	1 : 5.0
8	*t*-Butanol	$ZnCl_2$	1 : 1.6

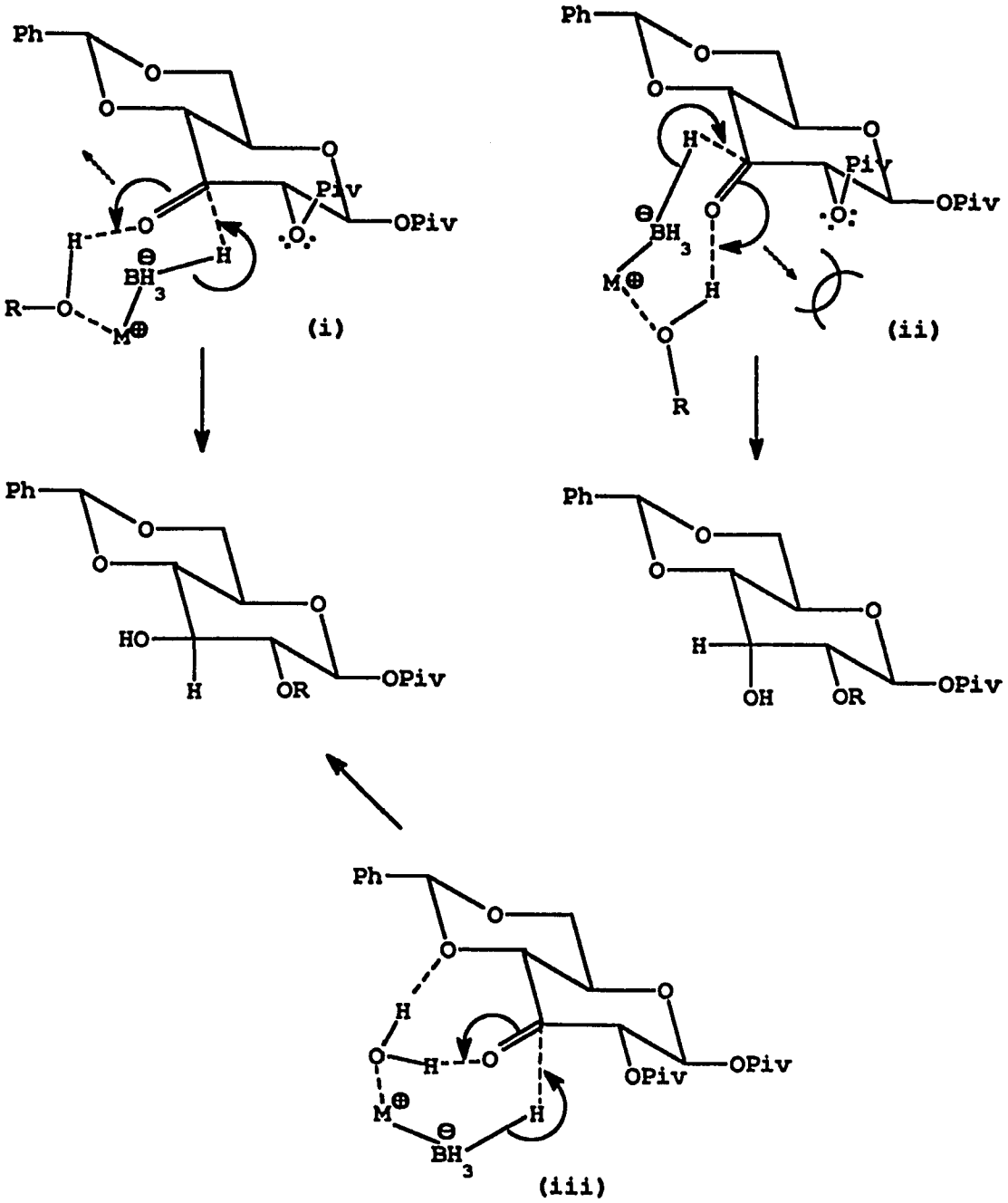
Contrary to the results reported for compounds **85** and **87**, the results of Table 2 indicates a slight preference towards an axial approach of the attacking nucleophile, such that the equatorial alcohol (the gluco product) is obtained in larger amounts. A plausible explanation for these observations is obtained by analyzing the torsional strain[10] that develops in the transition states (i) and (ii), Scheme 12. Both transition states show the C(2) pivalate group oriented above the plane of the pyranose ring, depicting the most stable arrangement for these reductions. In transition state (ii), there is a significant amount of torsional strain involving the C(2) pivalate group as the carbonyl oxygen

passes through an eclipsed conformation. Transition state (i) on the other hand, reflects no such torsional strain as the oxygen moves away from the equatorially disposed pivalate group. This proposed explanation is further supported from the fact that after chromatography, small amounts of the allo- and gluco-β-monopivalates were isolated. These products of de-esterification must have resulted from an intramolecular hydride transfer to the C(2) pivalate carbonyl group as the reactions passed through the cyclic transition states. Angyal *et al.*[11] have shown that carbohydrates form strong tridentate complexes with borate ions in solution, hence it is quite conceivable that the C(2) pivalate might have been involved in some complex formation with the intermediate -OBH_2 leading to hydride transfer and cleavage.

Attention is drawn to the fact, that there was a dramatic change in the selectivity of the reductions when the solvent was changed from aqueous ethanol (Run 1) to dry *n*-butanol (Run 4). Clearly, the nature of the solvent is important, and must therefore have been directly involved in the trasition state, Scheme 12. Thus transition state (ii) was perhaps equally populated as (i) for the *n*-butanol reactions and significantly less in the aqueous ethanol reaction. Transition state (iii) was further proposed as one that was highly populated in the aqueous ethanol reactions. This is reasonable on the grounds that water would preferentially hydrogen bond since the second hydrogen atom could have entered into such hydrogen bonding with the benzylidene oxygen as shown. This reasoning would also explain the change in selectivity between the ethanol reactions (Run 1 vs Run 2).

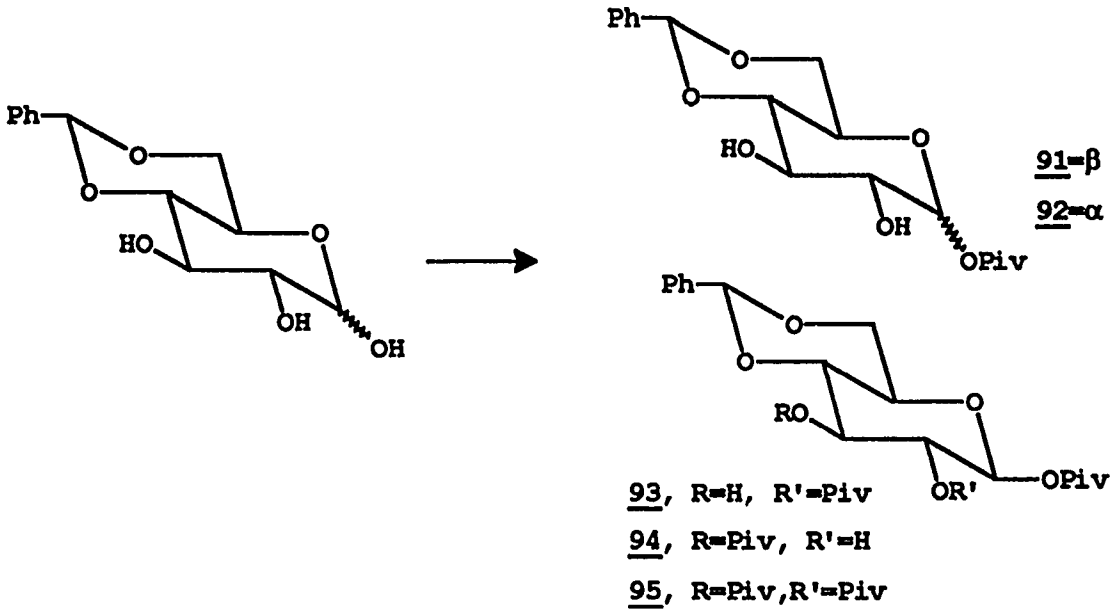
Fujii and his coworkers recently reported the effect of alkaline earth metal ions on the stereoselectivity of the reduction of α,β-epoxy ketones with sodium borohydride[12]. Calcium chloride was shown to be superior to the other metal salts investigated, with reactions being performed in methanol. It would be interesting to examine the effects of added calcium chloride on our *n*-butanol reactions.

SCHEME 12


Ph
O
O
O
Piv
OPiv
H
O
BH3
H
R
O
M⊕
(i)
Ph
O
O
H
O
Piv
OPiv
BH3
O
M⊕
H
O
R
(ii)
Ph
O
O
O
HO
H
OR
OPiv
Ph
O
O
O
H
OH
OR
OPiv
Ph
O
O
O
H
O
H
O
OPiv
OPiv
M⊕
H
BH3
(iii)

SPECIFIC EXPERIMENTALS

4,6-O-Benzylidene-1-O-pivaloyl-α-D-glucopyranoside, 92; 4,6-O-benzylidene-1-O-pivaloyl-β-D-glucopyranoside, 91; 4,6-O-benzylidene-1,2-di-O-pivaloyl-β-D-glucopyranoside, 93; 4,6-O-benzylidene-1,3-di-O-pivaloyl-β-D-glucopyranoside, 94; and 4,6-O-benzylidene-1,2,3-tri-O-pivaloyl-β-D-glucopyranoside, 95.



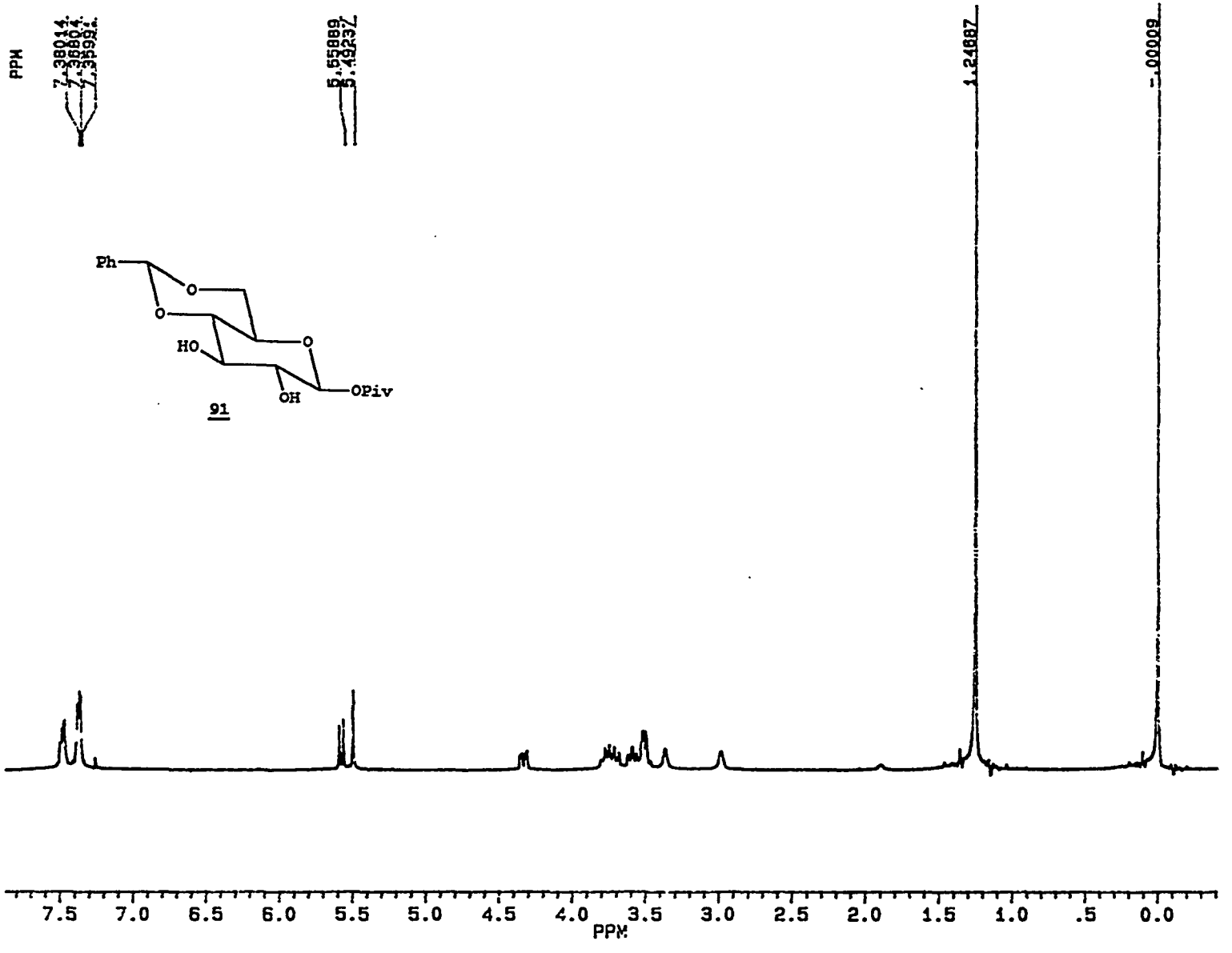
4,6-O-benzylidene glucose (10.0 g, 37.4 mmol) was dissolved in 100 mL of pyridine and the solution was cooled to 0°C. Pivaloyl chloride (9.9 g, 82.1 mmol) was then added via syringe in one portion with rapid stirring. The cooling bath was removed and stirring was continued at room temperature for a duration of 72 hours. Work-up consisted of pouring the reaction mixture into cold water and extracting with ethyl acetate, drying over $MgSO_4$, and concentrating. The residual pyridine was removed by azeotropic distillation with toluene, so providing 17.5 g of crude product.

Chromatographic purification (hexanes:acetone ; 5:1) afforded the tripivalate ester **95** (1.8 g, 10%), a mixture of the 1,2- and 1,3- dipivalates **93** and **94** (11 g, 60%), and the beta- and alpha-monopivalates **91** and **92**, (1.8:1.0 , 3.5 g), accounting for 20% of the product mixture. The dipivalate mixture could not be separated by column chromatography, hence the mixture was redissolved in an equal volume of hexanes from which the 1,2-dipivalate **93** selectively crystallized on standing over a 7-days period at room temperature. The isolated yield of compound **93** was 4.2 g (38%).

^{1}H NMR (300 MHz, $CDCl_3$, ppm): **93**; 7.35-7.50 (m, 5H) aromatic; 5.70 (d, 1H, $J_{1,2}$= 9.0 Hz) C(1)HC(2)H; 5.51 (s, 1H) benzylidene; 5.06,5.09 (dd, 1H, $J_{2,1}$=9.0 Hz) C(1)HC(2)H; 4.36,4.34 (dd, 1H,J=4 Hz) C(6)H_{eq}; 3.88 (t, 1H) C(3)H; 3.71, 3.75 (dd, 1H) C(4)HC(5)H; 3.51-3.60 (m, 2H) C(6)H_{ax}C(5)H; 2.83 (s, 1H) OH; 1.22 (s, 18H) $(CH_3)_3C$. M.p. 151-153 °C. IR ($CHCl_3$, cm^{-1});1720-1740 (s), 3474. Mass Spectrum (EI); Calculated for $C_{23}H_{32}O_8$ (m/z 436.2). Found m/z 436.2 (M^+). **95**; 7.32-7.41 (m, 5H) aromatic; 5.79 (d, 1H,$J_{1,2}$=6.0 Hz) C(1)H; 5.51 (s, 1H) benzylidene; 5.42 (t, 1H) C(2)H; 5.23,5.26 (dd, 1H) C(3)H; 4.39,4.43 (dd, 1H) C(6)H_{eq}; 3.66-3.82 (m, 3H) C(4)HC(5)HC(6)H_{ax}; 1.19,1.16,1.14 (ts, 27H) 3 x $(CH_3)_3C$. IR($CHCl_3$, cm^{-1}); 2850-3050 (s), 1720-1760 (s). M.p. 154-156°C.

Mass Spectrum (EI); Calculated for $C_{28}H_{40}O_9$ (m/z 520.3). Found m/z 520.2 (M^+), 521.2 (M^++1). **91**; 7.35-7.52 (m, 5H) aromatic; 5.57 (d, 1H,$J_{1,2}$=9.0 Hz) C(1)H; 5.49 (s, 1H) benzylidene; 4.31,4.34 (dd, 1H) C(6)H_{eq}; 3.67-3.80 (m, 2H) C(2)HC (3)H; 3.59 (t, 1H) C(4)H; 3.49-3.52 (m, 2H) C(6)H_{ax}C(5)H; 3.36,2.98 (s, 1H, s, 1H) OH; 1.25 (s, 9H) $(CH_3)_3C$. IR($CHCl_3$, cm^{-1}); 3250-3600 (s), 1720 (s).

Mass Spectrum (EI); Calculated for $C_{18}H_{24}O_7$ (m/z 352.2). Found m/z 352.1 (M^+), 353.1 (M^++1) . M.p. 171-173 °C.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5.55889
5.49237
1.24687
.00009
Ph
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O
O
HO
OH
OPiv
91
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
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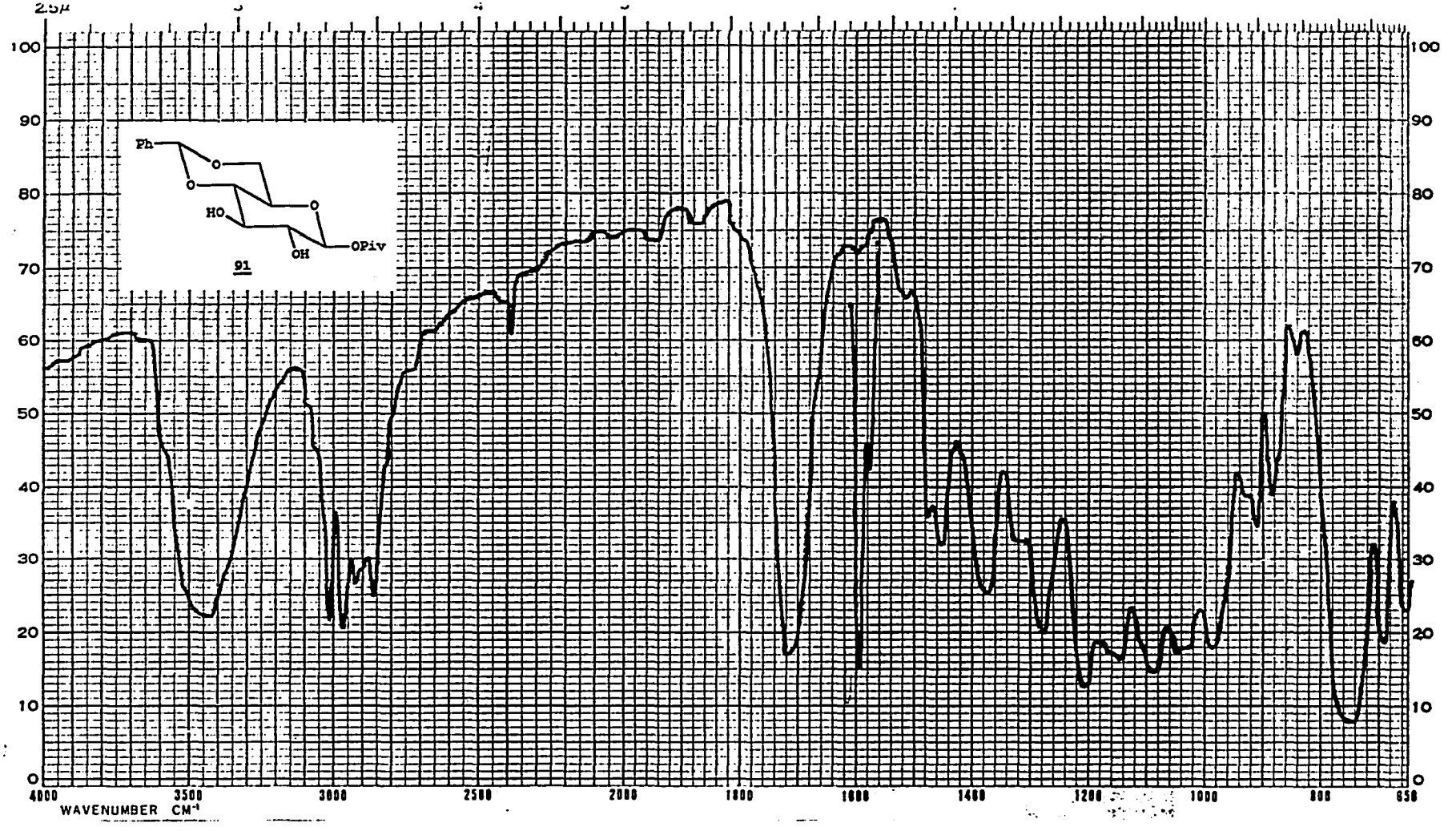
.5
0.0
PPM


2.5μ
100
90
80
70
60
50
40
30
20
10
0
Ph
O
O
O
HO
OH
OPiv
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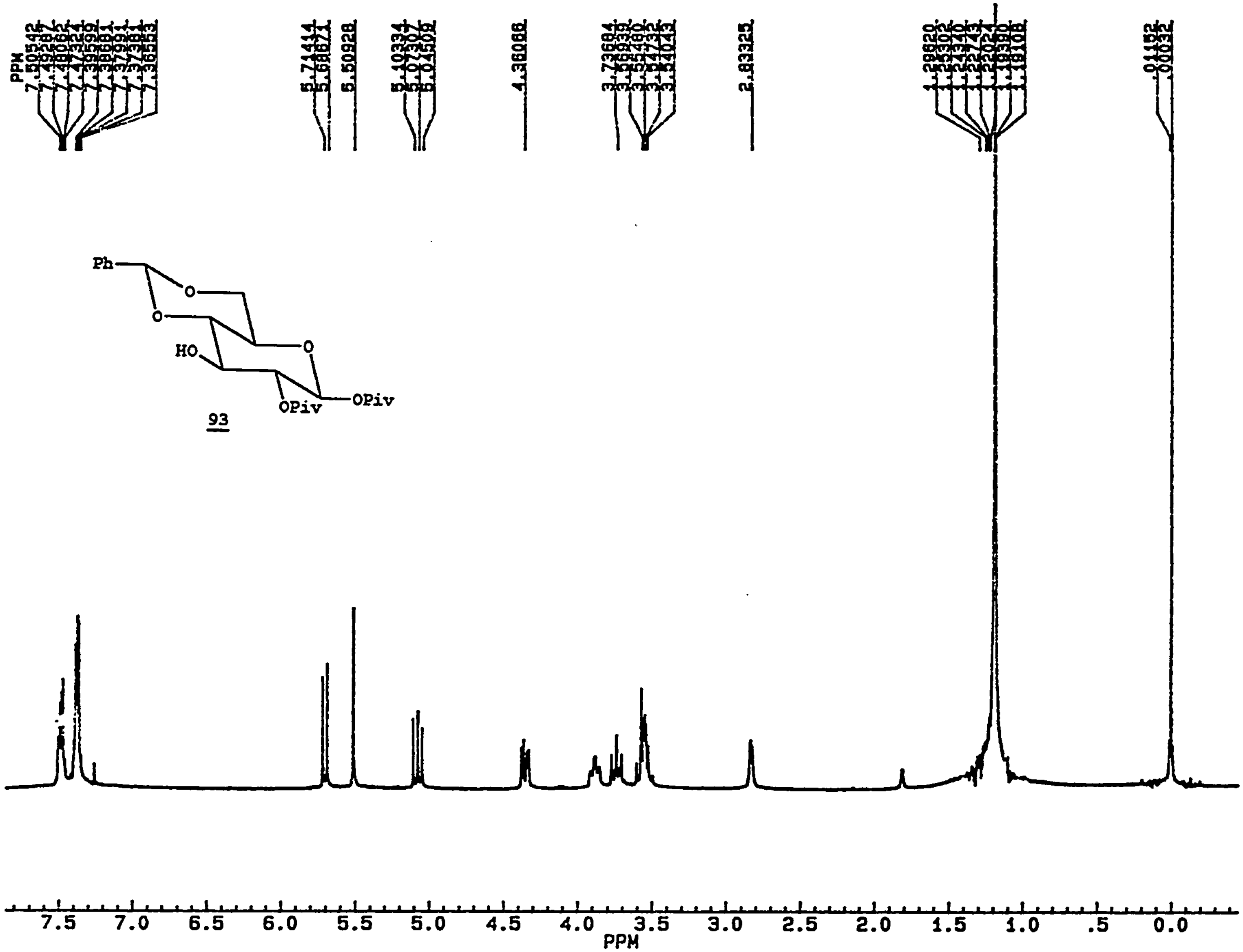
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
650
WAVENUMBER CM⁻¹


Ph
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O
HO
OPiv
OPiv
93
PPM
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7.5
7.0
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6.0
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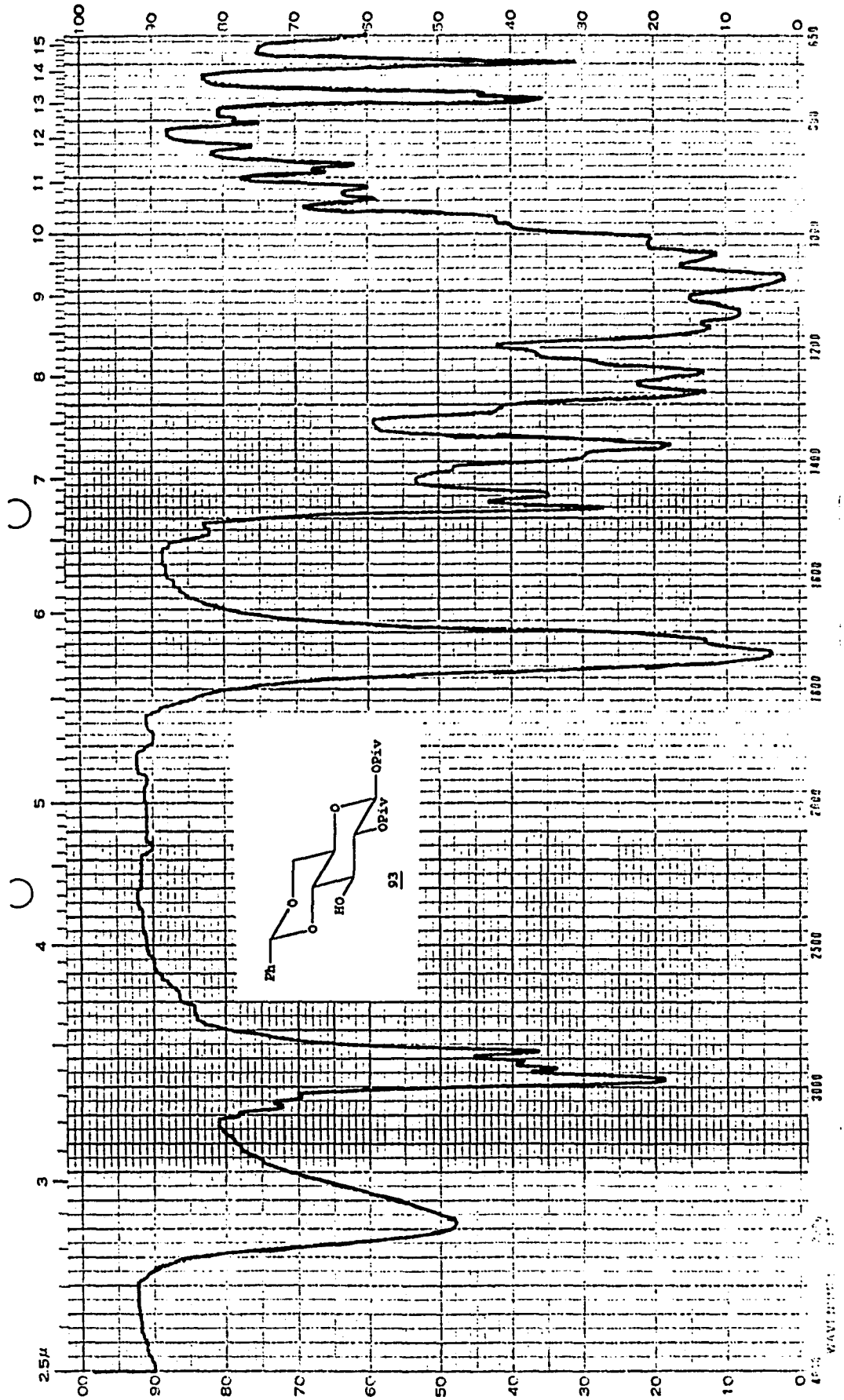
0.0
PPM


OPiv
OPiv
HO
Ph
93

PPM
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7.40524
7.37599
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7.35808
7.33698
7.32465
5.68836
5.68102
5.48866
5.47361
5.06088
3.68955
3.66618
3.64880
3.52488
3.51235
1.31385
1.30754
1.30213
1.28787
1.27408
1.24595
1.18649
1.18173
.00016
.00307
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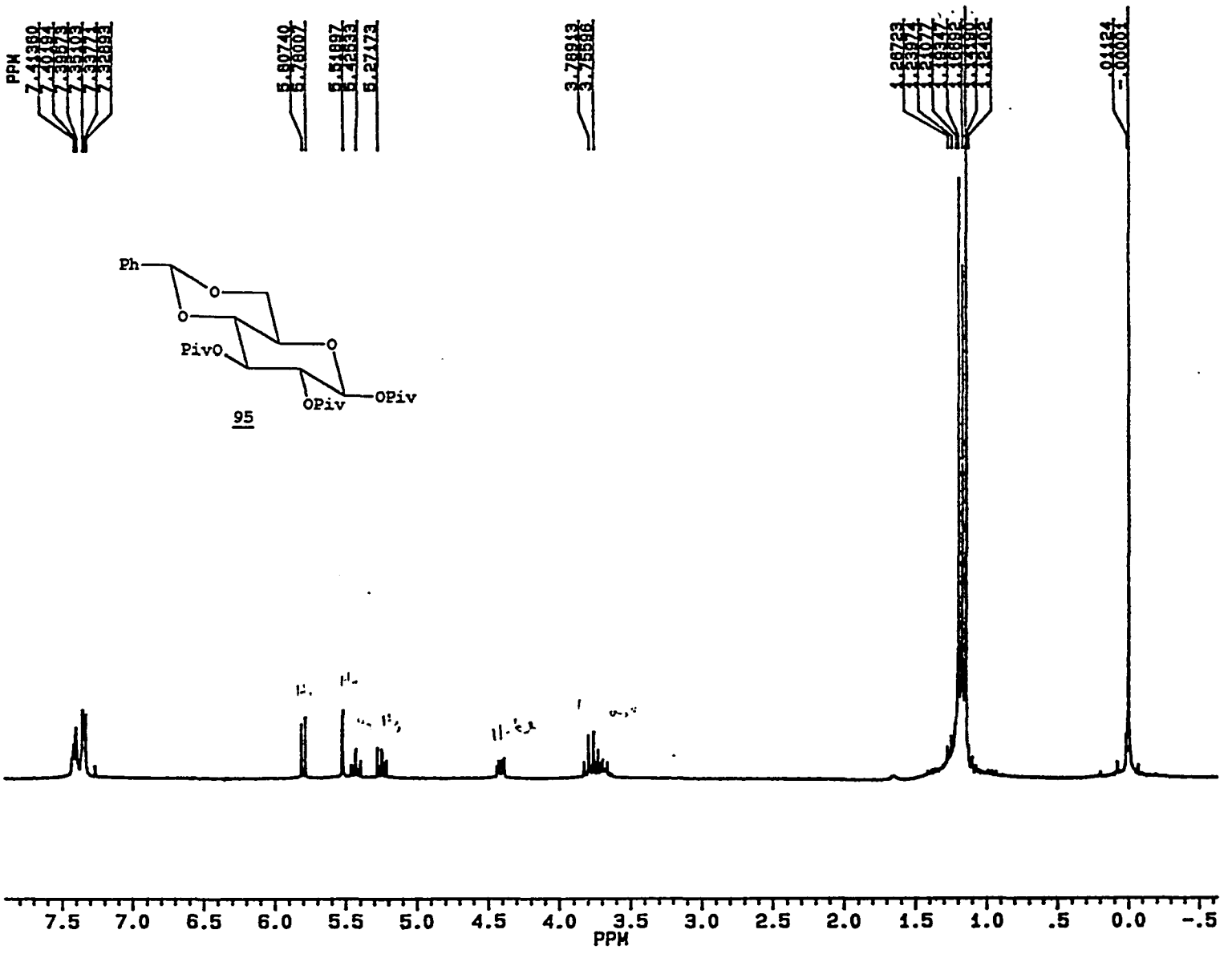
93
94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5.78007
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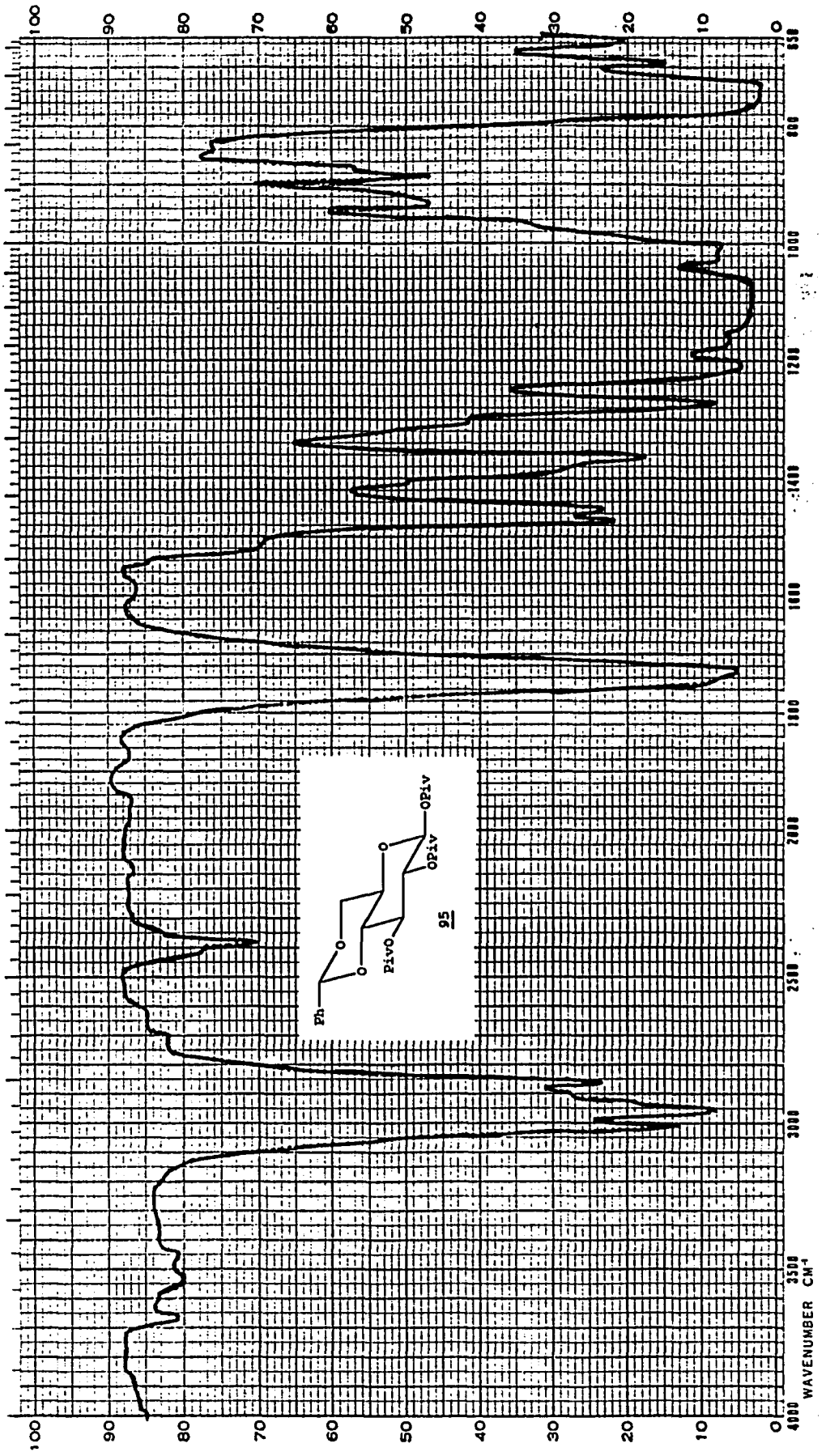
5.42833
5.27173
3.78913
3.75598
1.26723
1.23074
1.21077
1.18347
1.16885
1.13180
1.12402
.01124
-.00001
Ph
O
O
O
PivO
OPiv
OPiv
95
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
-.5
PPM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1200
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800
650
WAVENUMBER CM⁻¹
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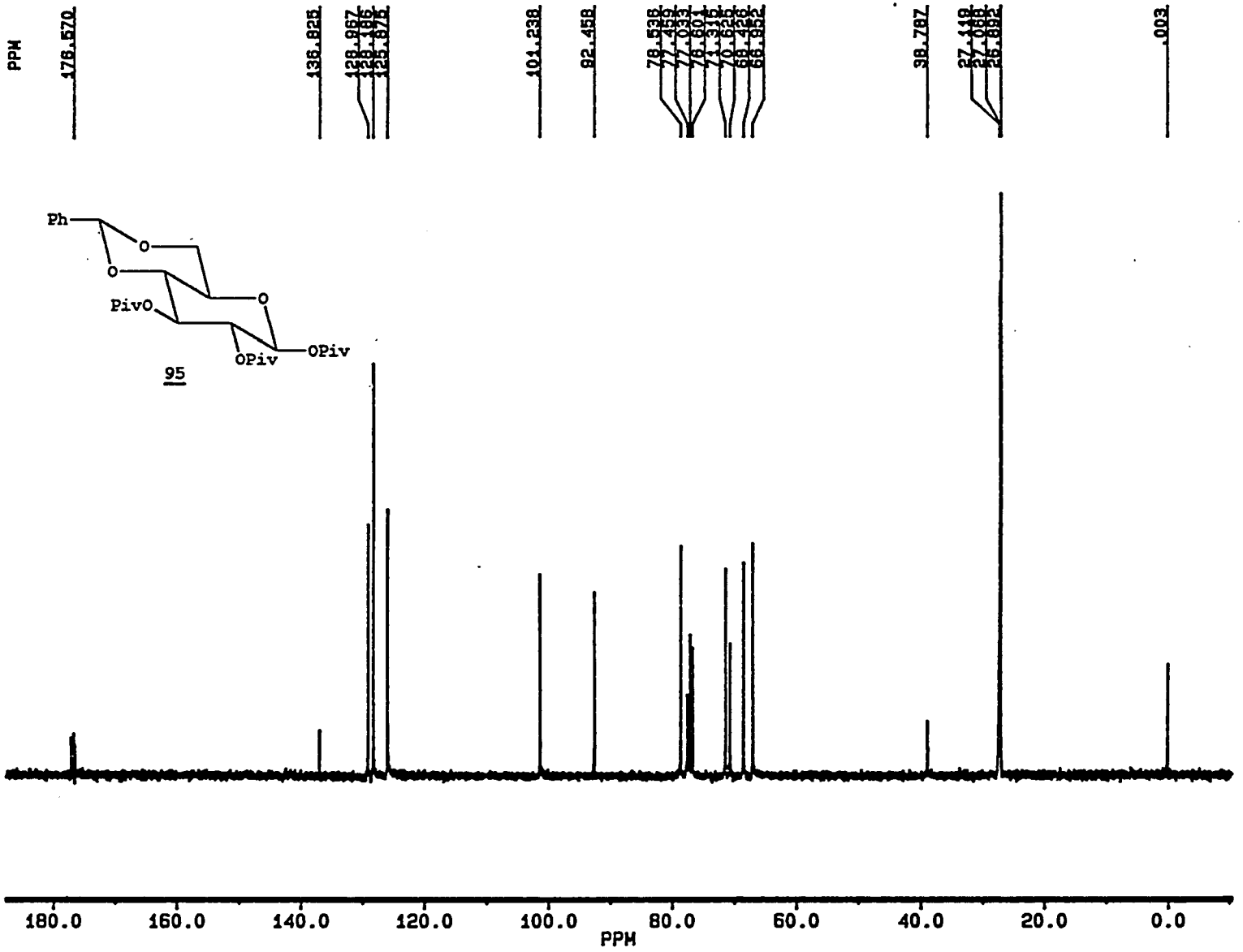
PivO
Ph
O
95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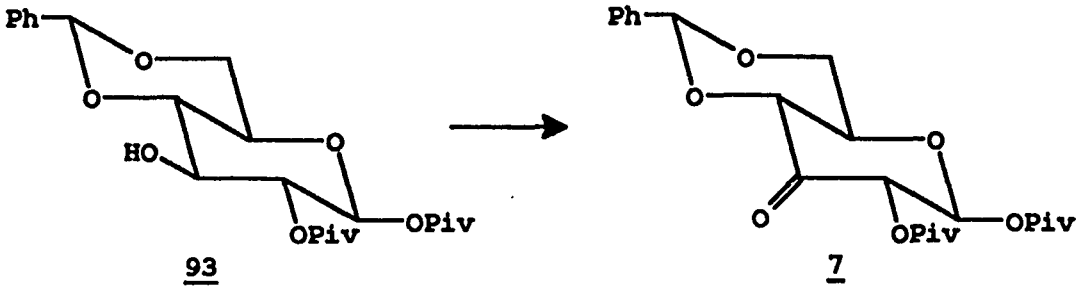
70.626
68.455
66.852
38.787
27.118
27.068
26.882
.003
Ph
O
O
O
PivO
OPiv
OPiv
95
180.0
160.0
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0.0
PPM

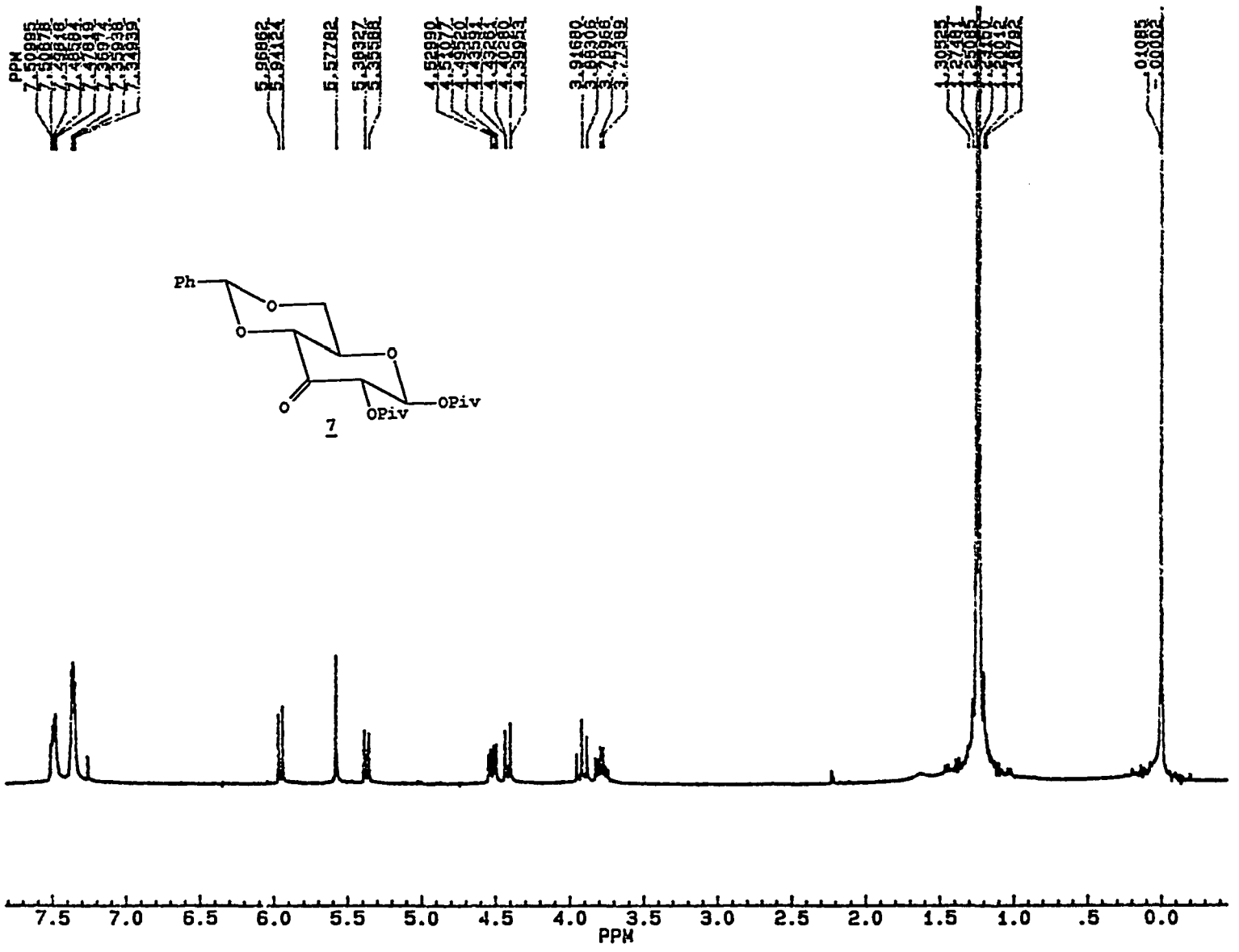
4,6-O-Benzylidene-1,2-di-O-pivaloyl-β-D-glucopyranosid-3-ulose, 7.



93 7

Compound 93 (1.00 g, 2.3 mmol) was dissolved in 20 mL of dicloromethane and added with stirring to a solution of Collin's Reagent, prepared by stirring chromic acid (1.56 g, 15.5 mmol) and pyridine (2.5 mL) in 80 mL of dichloromethane. Acetic anhydride (1.5 mL) was then added with additional stirring for 30 minutes at room temperature[13]. The excess oxidant was quenched with 10 mL of absolute ethanol, stirring for 5 minutes, followed by flash chromatography with ethyl acetate. Low temperature evaporation (30°C) of the solvent afforded the pure 3-ulose 7 (0.91 g, 90%) as a white crystalline solid. M.p. 78-80°C.

^{1}H NMR(300 MHz, $CDCl_3$, ppm): 7.34-7.51 (m, 5H) aromatic; 5.95 (d, 1H, $J_{1,2}$=6.0 Hz) C(1)H; 5.57 (s, 1H) benzylidene; 5.37 (d, 1H, $J_{2,1}$=6.0 Hz) C(2)H; 4.49,4.51 (dd, 1H) C(6)H_{eq}; 4.41 (d, 1H) C(4)H; 3.89,3.95 (dd, 1H) C(6)H_{ax}, 3.81,3.79,3.79 (ddd, 1H) C(5)H; 1.25,1.23 (ds, 18H) 2 x $(CH_3)_3C$. IR($CHCl_3$, cm^{-1}); 2850-3050 (s), 1725-1765 (s). Mass Spectrum (EI); Calculated for $C_{23}H_{30}O_8$ (m/z 434.2). Found m/z 434.1 (M^+), 435.2 (M^++1).


PPM
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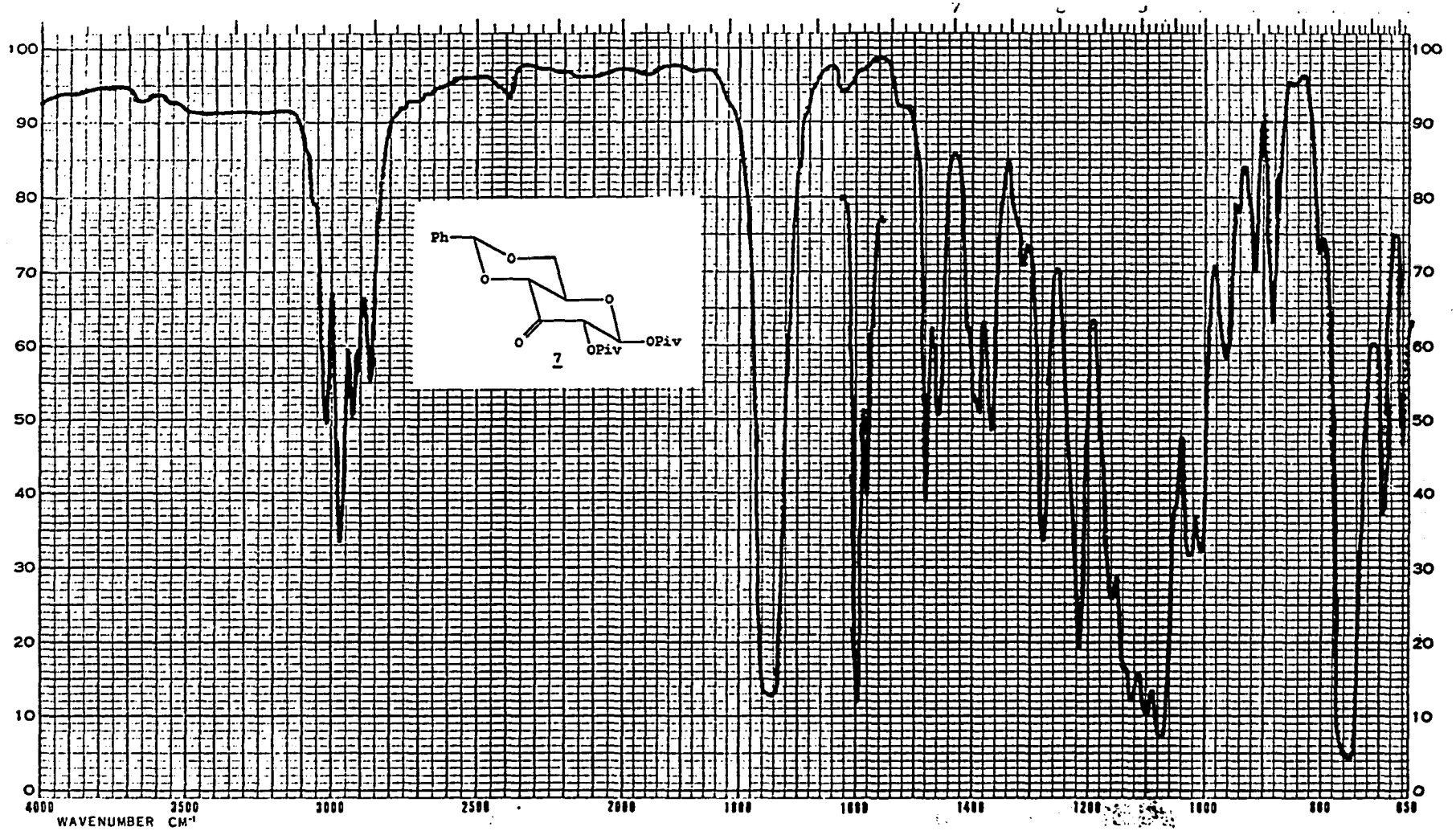
0.0
PPM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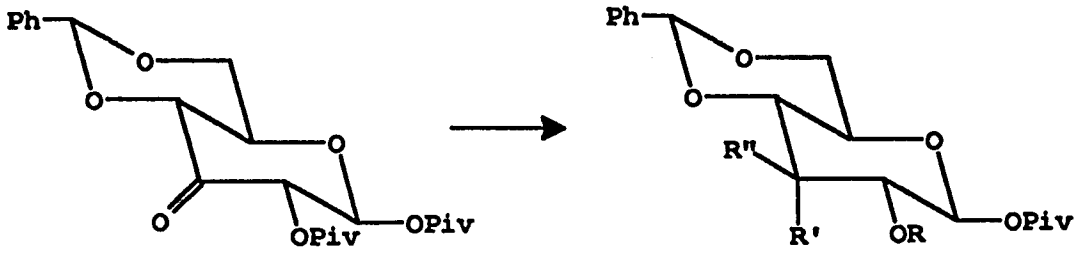
1400
1200
1000
800
650
WAVENUMBER CM-1
Ph
O
O
O
O
OPiv
OPiv
7

4,6-O-Benzylidene-1,2-di-O-pivaloyl-β-D-allopyranoside, 99; and

4,6-O-benzylidene-1-O-pivaloyl-β-D-allopyranoside, 100.



7

91: R=H,R'=H,R"=OH

93: R=Piv,R'=H,R"=OH

99: R=Piv,R'=OH,R"=H

100: R=H,R'=OH,R"=H

The 3-ulose 7 (1.66 g, 3.82 mmol) was dissolved in 20 mL of *n*-butanol to which was added sodium borohydride (0.145 g, 3.82 mmol) with stirring. The mixture was additionally stirred for one hour at room temperature. For those reactions involving metal salts as potential chelating agents, the salt was added (20 mole percent) prior to the addition of the reducing agent. The reaction was quenched by pouring into cold brine and extracted with diethyl ether. Drying was achieved over $MgSO_4$ followed by concentration and column chromatograpny (hexanes:EtOAc ; 5:1) providing 1.23 g of compounds 93 and 99 in the first fraction, 0.19 g of compound 100 in the second fraction, and 0.20 g of compound 91 in the third fraction.

^{1}H NMR (300 MHz, $CDCl_3$, ppm): 99; 7.35-7.49 (m, 5H) aromatic; 6.11 (d, 1H, $J_{1,2}$=9.0 Hz) C(1)H; 5.55 (s, 1H) benzylidene; 4.88,4.86 (dd, 1H,$J_{2,1}$=9 Hz,$J_{2,3}$=3 Hz) C(2)H; 3.61-3.75 (m, 2H) C(6)H_{eq}C(5)H; 3.44-3.56 (m, 3H) C(3)HC(4)HC(6) H_{ax}; 1.23 (s, 18H) 2 x $(CH_3)_3C$. IR($CHCl_3$, cm^{-1}); 3300-3650 (s), 2850-3015 (s), 1725 (s). 100: 7.30-7.34 (m, 5H) aromatic; 5.80 (d, 1H,$J_{1,2}$=9 Hz) C(1)H; 5.45 (s, 1H) benzylidene; 4.36,4.34 (dd, 1H) C(6)H_{eq}; 3.98-4.13 (m, 3H) C(2)HC(3)HC(4)H; 3.69 (t, 1H) C(5)H; 3.63,3.65 (dd, 1H) C(6)H_{ax}.

PPM
7.49038
7.47804
7.47086
7.38182
7.36995
7.36133
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5.70939
5.68198
5.50240
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1.24133
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6.0
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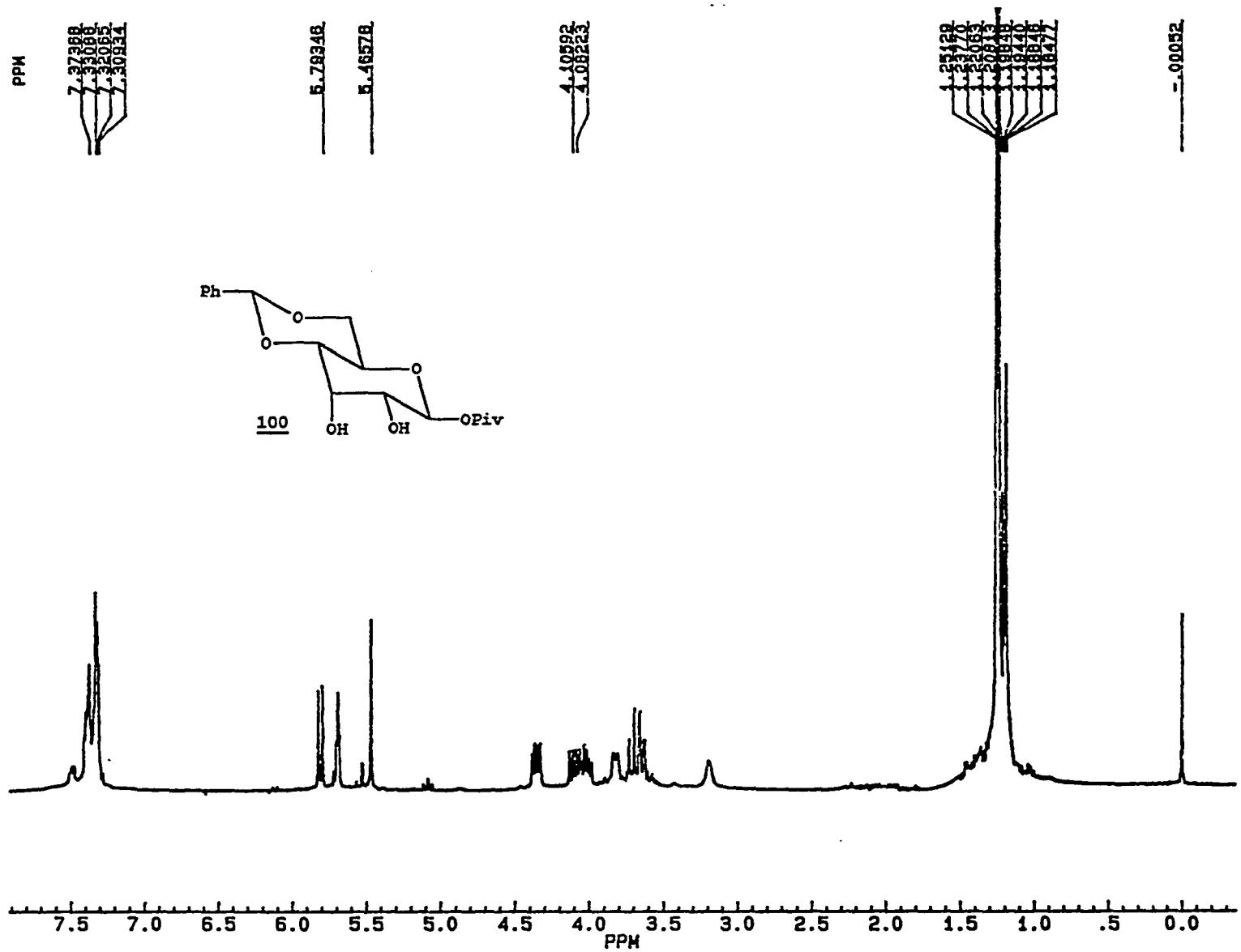
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1.20613
1.18440
1.18048
1.16477
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Ph
O
O
O
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OH
OH
OPiv
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

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2. (a) Box, V.G.S.; Box, L.L.; Roberts, E.V.E. *Carbohydr. Res.*, **1981**, *96*, 215
   (b) Box, V.G.S.; Box, L.L.; Roberts, E.V.E. *Heterocycles*, **1980**, *14*, 1269.
3. Box, V.G.S.; Box, L.L.; Roberts, E.V.E. *Carbohydr. Res.*, **1983**, *119* 85.
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11. Angyal, S.J.; Klavins, J.E.; Mills, J.A. *Aust. J. Chem.*, **1974**, *27*, 1075.
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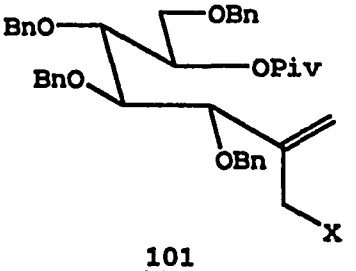
CHAPTER 6

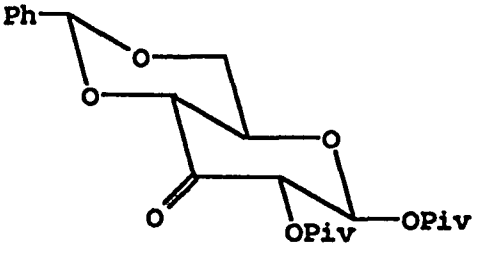
6.0.0. Nucleophilic Alternatives to the Allylsilanes.

6.1.0. Introduction

Prior to our investigations on the allylsilanes, Chapter 4, we developed an alternative approach that would have provided us with the same allyl anion equivalent to be coupled with the 3-ulose as was discussed in Chapter 5. Our objective was to synthesize the allylic halide 101, which would be subsequently converted to a Grignard reagent for coupling with the 3-ulose 7.



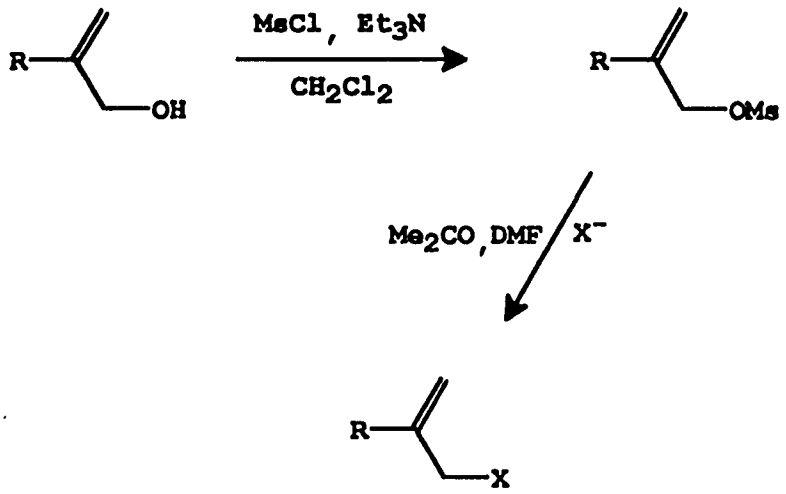
101



7

Compound 101 is easily obtainable from the allylic alcohol via the mesilate or triflate ester according to a standard procedure[1], Scheme 1.

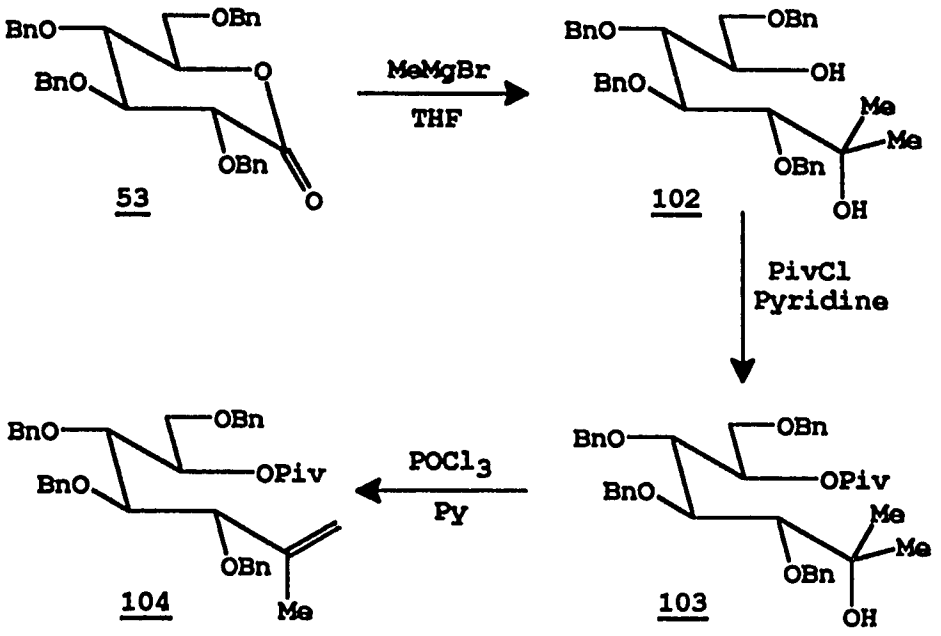
SCHEME 1



6.2.0. Synthesis of Precursor Alkene.

Scheme 2 depicts the sequence of reactions by which we synthesized the alkene **104**, the precursor molecule of the allylic halide **101**. The gluconolactone **53** was treated with an excess of methylmagnesium bromide in THF to afford the diol **102** in 97% yield. Compound **102** was quantitatively converted to the alcohol **103** through the selective esterification of the secondary hydroxyl group. Compound **103** was subsequently converted to the alkene **104** by its treatment with phosphorus oxychloride in pyridine at 0°C in 95% yield. Allylic bromination of the alkene **104** was ruled out because of the benzyl ether groups. Indeed, protecting the hydroxyl groups as methyl ethers would have been the only other suitable alternative, bearing in mind the need for easy removal.

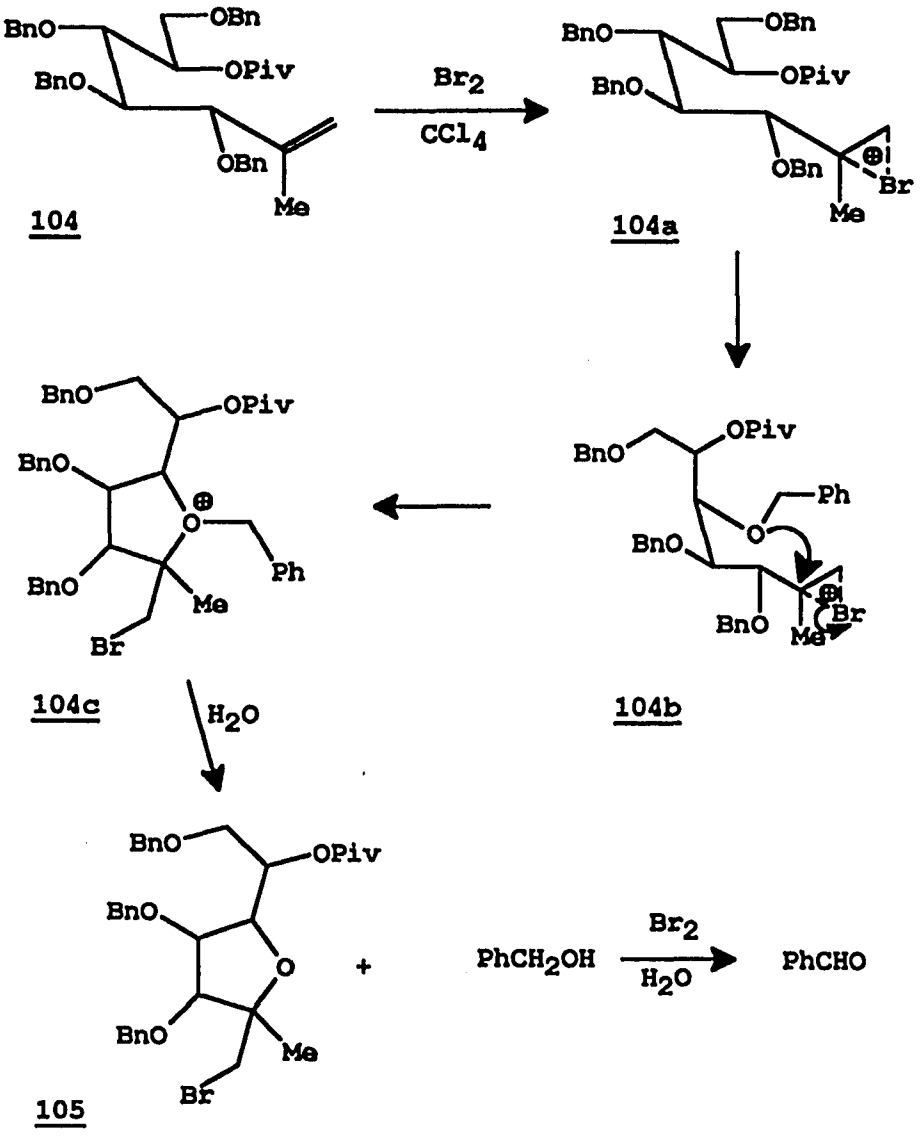
SCHEME 2



6.2.1. Halogenation-Dehydrohalogenation Reactions

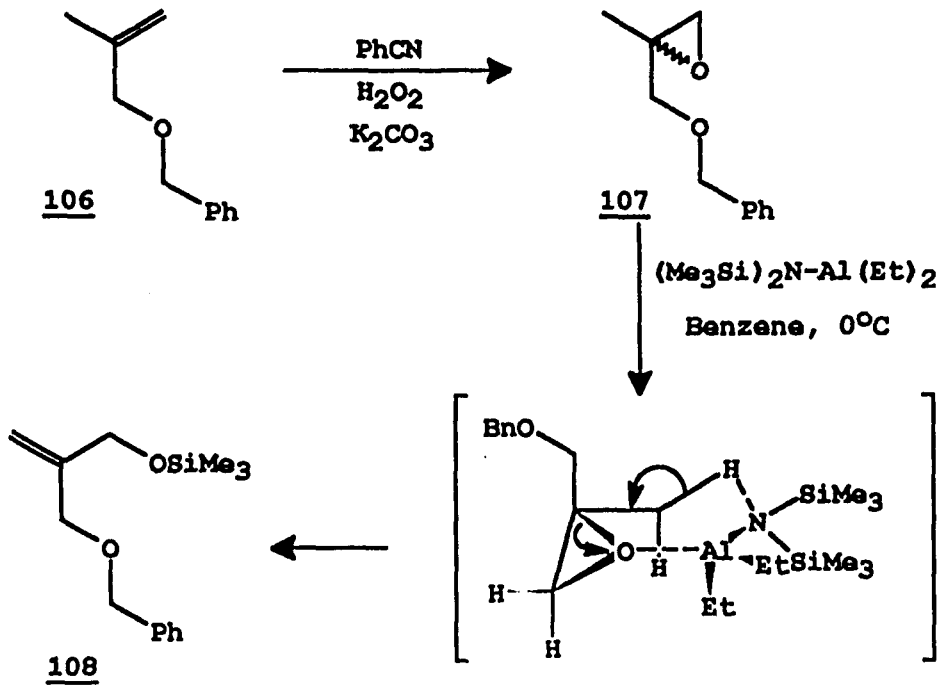
Compound **104** was treated with bromine in carbon tetrachloride at room temperature and at 0°C hoping that the vic dibromide would have been obtained. The dibromide would then be converted to the allylic bromide **101** under dehydrohalogenating conditions. This pathway proved unsuccessful in that extensive cleavage took place. Benzaldehyde, detected on all attempts, must have resulted from bromine-water oxidation (on work-up) of the cleaved benzyl alcohol. We postulated that there must have been remote participation of the C(4) benzyl oxygen during bromonium ion formation[2]. We were unable to isolate any materials suitable for structural charaterization owing to the tar-like polymeric nature of the reaction product.

SCHEME 3



The principle of epoxide isomerization[3] was adopted as an alternative approach. Model studies were performed on the alkene **106**, prepared from the benzylation of methallyl alcohol. Compound **106** was converted to the epoxide **107** using peroxybenzimidic acid, prepared in-situ[4]. Isomerization of the epoxide **107** to the allylic alcohol **108** was achieved by two methods; reaction with lithium hexamethyldisilazide in boiling ether, and at 0°C with diethylaluminum hexamethyldisilazide in ether[3a,5].

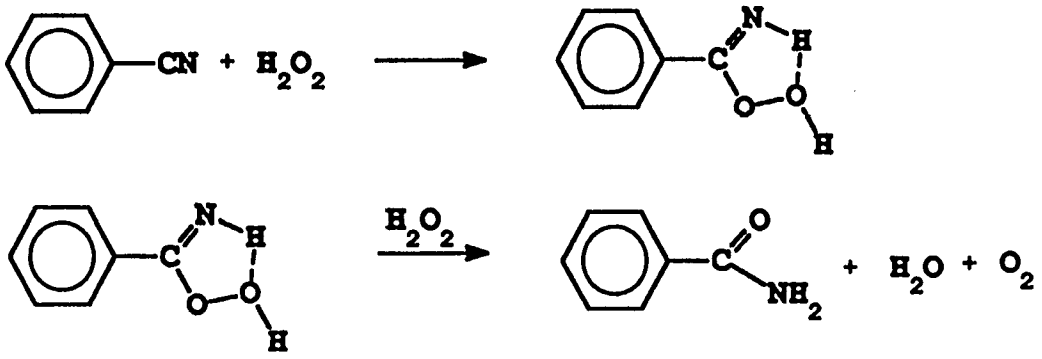
SCHEME 4



For comparative purposes, epoxide isomerization was investigated under other modified conditions. These include, the use of LDA in THF at 0°C then room temperature, the use of LDA in refluxing ether, and the use of lithium hexamethyldisilazide in diethyl ether at 0°C then room temperature. All attempts proved unsuccessful in terms of producing the desired allylic alcohol. The epoxide **107** was recovered in all cases. When LDA was used as base, extensive polymerization was observed. The most facile process for isomerization was that in which the epoxide was refluxed with lithium hexamethyldisilazide in diethyl ether, so providing the silylated allylic alcohol **108** (70%).

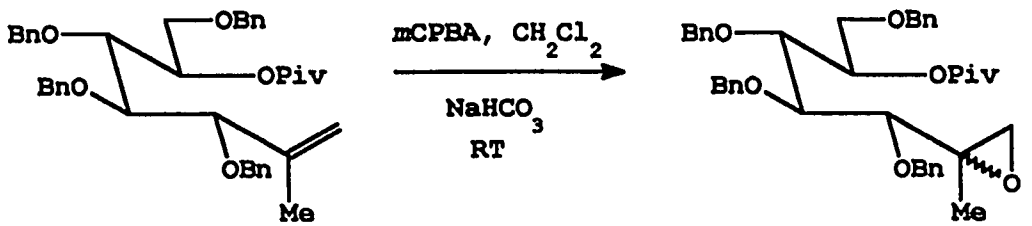
We attempted epoxidation of the alkene **104** using peroxybenzimidic acid prepared in situ. Our efforts proved futile in that the peroxibenzimidic acid intermediate merely got converted to benzamide, by its reaction with hydrogen peroxide.

SCHEME 5



Even though conditions were adjusted such that there was a favorable equilibrium between the formation of peroxybenzimidic acid and its degradation to benzamide and oxygen, there was no detectable epoxidation product with the alkene **104**. This lack of reactivity might be attributed to a rate factor by which the 'peroxy intermediate' reacted faster with hydrogen peroxide than with the alkene. Steric factors might also be significant in these reactions. Epoxide formation was subsequently achieved using *m*-CPBA in dichloromethane at room temperature. The epoxide **109** was obtained in 60% yield as a 50:50 mixture of diastereoisomers. Unfortunately, compound **109** was discovered to be unstable, decomposing to a dark polymeric residue. Scale-up efforts by this procedure also proved futile, the starting material being recovered in all instances.

SCHEME 6



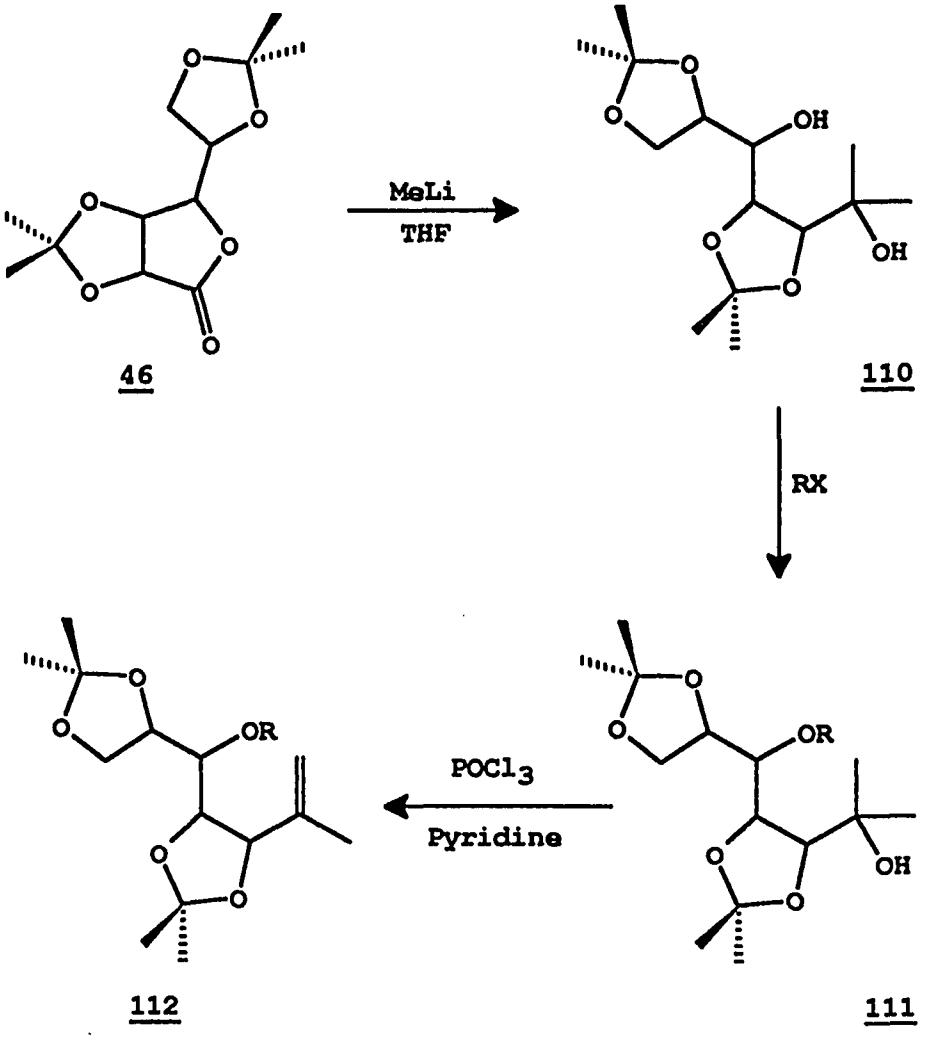
104 **109**

6.3.0. Alkene Precursor from Mannonolactone 46.

The discovered lack of stability of the epoxide 109 led us to develop a potentially more stable system in which the ether oxygens are more restricted. This was based on the assumption that the spontaneous decomposition of compound 109 was enhanced by a possible neighbouring group participation of the benzyl oxygens. We therefore proceeded with the synthesis of the alkene 112 from the readily available 2,3:5,6-di-*O*-isopropylidene-D-mannono-1,4-lactone 46.

Mannono-1,4-lactone 46 was converted to the diol 110 in 90% yield by stirring with an excess of methyl lithium in tetrahydrofuran for 48 hours at room temperature. Selective esterification of the secondary hydroxyl group with pivaloyl chloride proved to be an impossible objective under all conditions investigated. Clearly, the steric bulk of the *tert*-butyl group would be expected to interfere with the sturdy isopropylidene blocking group. Bearing in mind our terminal objectives, we chose to synthesize the methylthiomethyl ether of compound 110. The choice blocking group must be stable to base, such that if we chose to investigate to route of epoxide isomerization, we would not have been faced with a degradation problem.

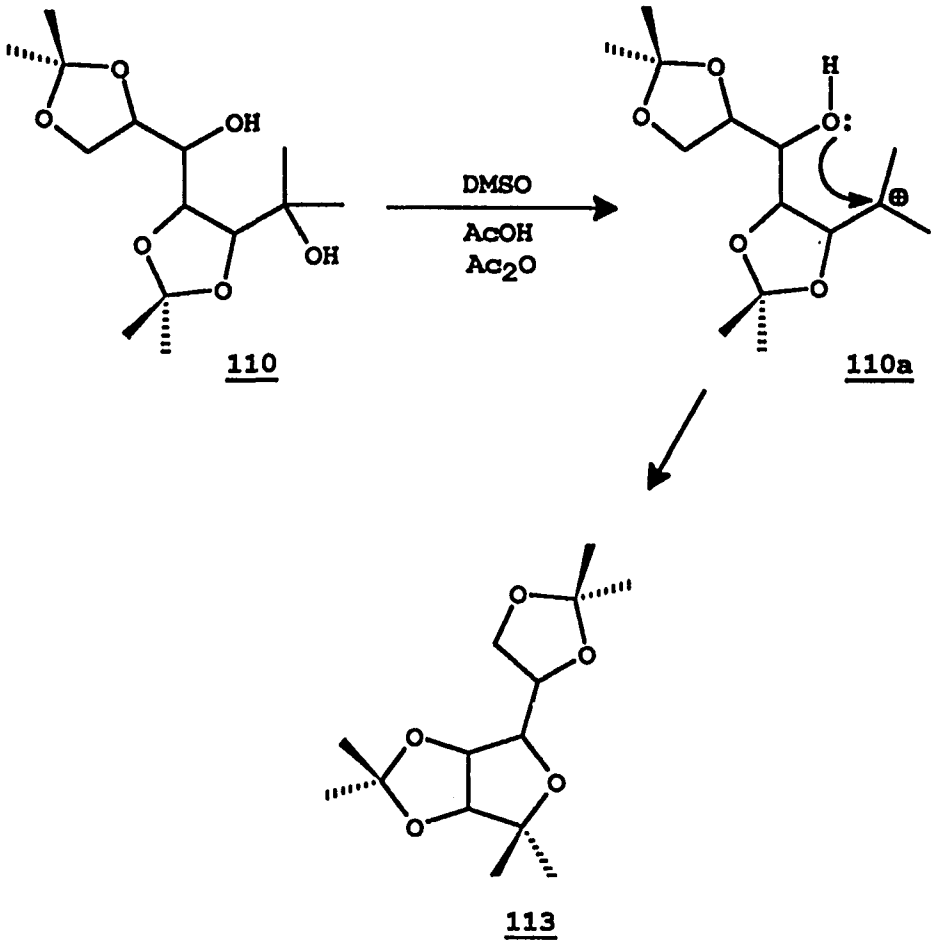
SCHEME 7



46 110 111 112

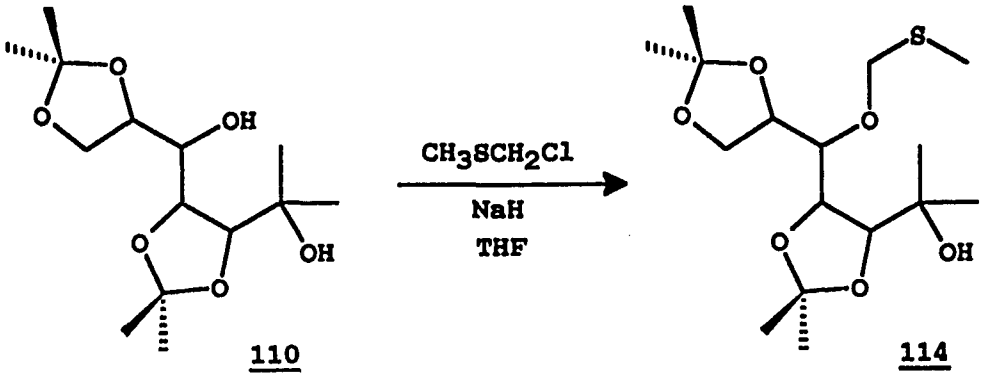
Our initial attempt at methylthiomethyl ether formation involved stirring the diol **110** with a mixture of acetic anhydride and acetic acid in dry DMSO at room temperature. Under these conditions, the ether **113** was obtained exclusively. It is conceivable that under the mildly acidic conditions, carbocation formation had occured followed by a facile intramolecular cyclization, Scheme 8.

SCHEME 8



In light of the above discoveries, we resorted to achieving ether formation under non-acidic conditions. The diol **110** was therefore treated with an equivalent of sodium hydride in THF to effect alkoxide formation, followed by addition of methylthio-methyl chloride with stirring. This method provided us with the ether **114** (87%). Compound **11** would then have been converted to the alkene **112** by its treatment with phosphorus oxychloride in pyridine.

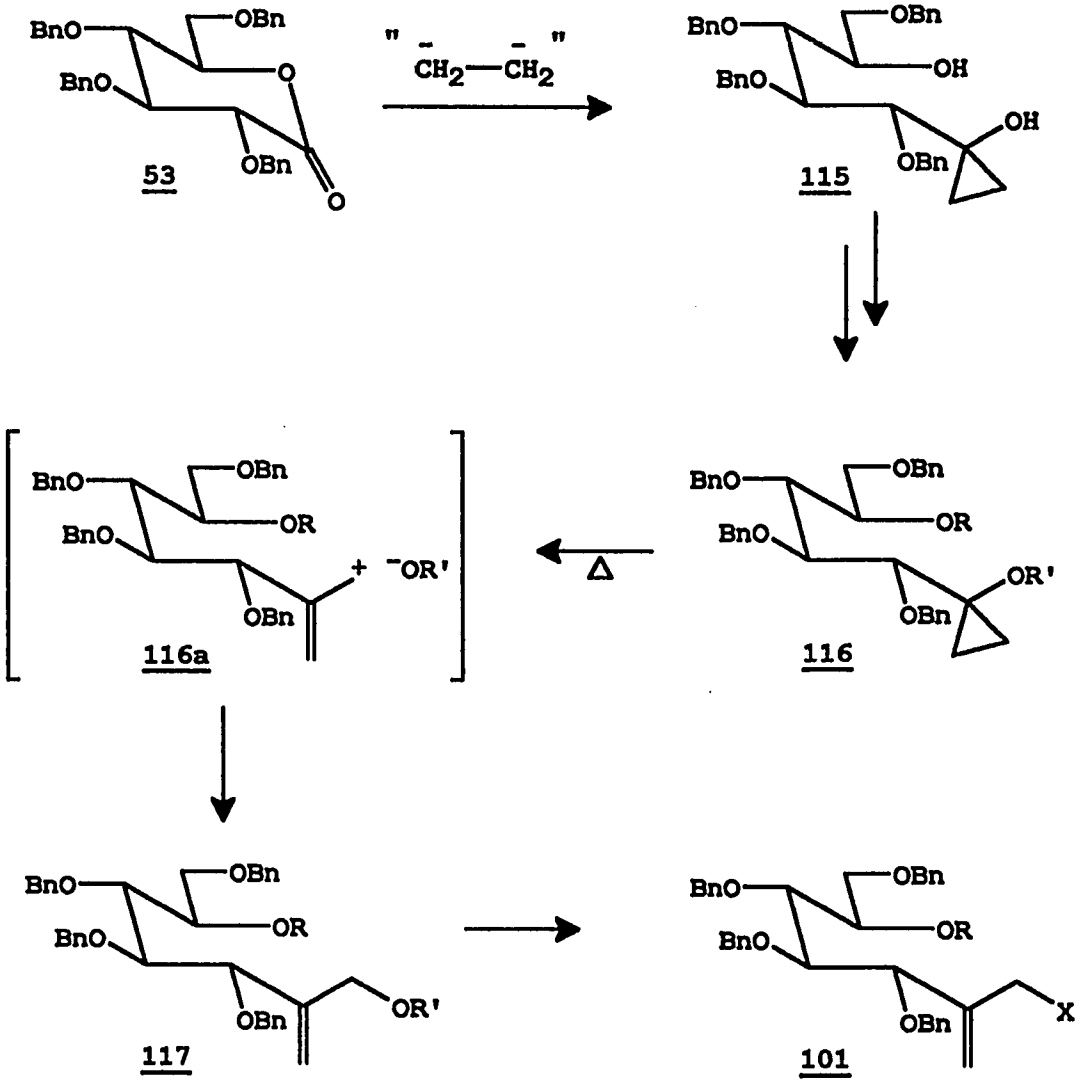
SCHEME 9



6.4.0. Butadiene Reduction Reactions

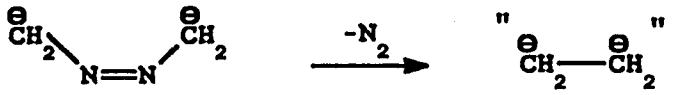
An ingenious approach towards the synthesis of the allylic halide **101**, has as its pivotal reaction, the electrocyclic ring opening of a cyclopropanol derivative. The lactone **53** would be treated with a dianion equivalent to produce the substituted cyclopropanol **115**. Protection of the two hydroxyl groups would afford compound **116** which would be isomerized to the protected allylic alcohol for subsequent coversion to the desired allylic halide.

SCHEME 10



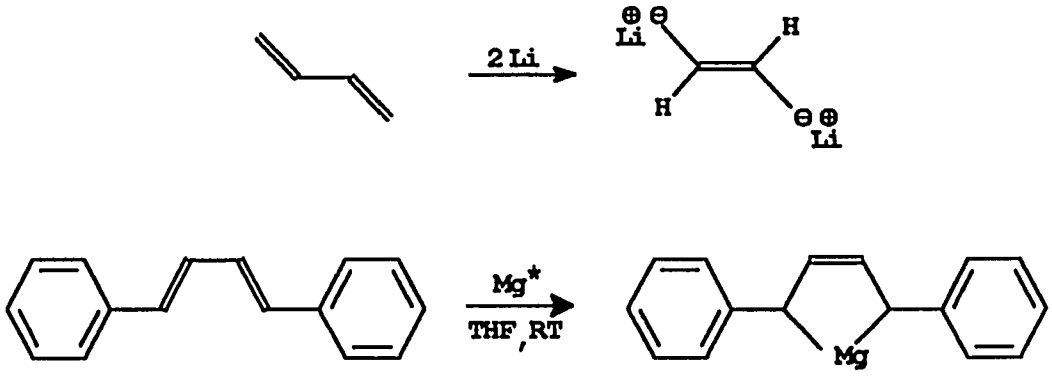
A suitable equivalent for the proposed dianion species shown in the scheme above is the azoalkane derivative shown in Scheme 11 below. Photochemical extrusion of molecular nitrogen would thus be the pivotal step to linking these intermediates.

SCHEME 11



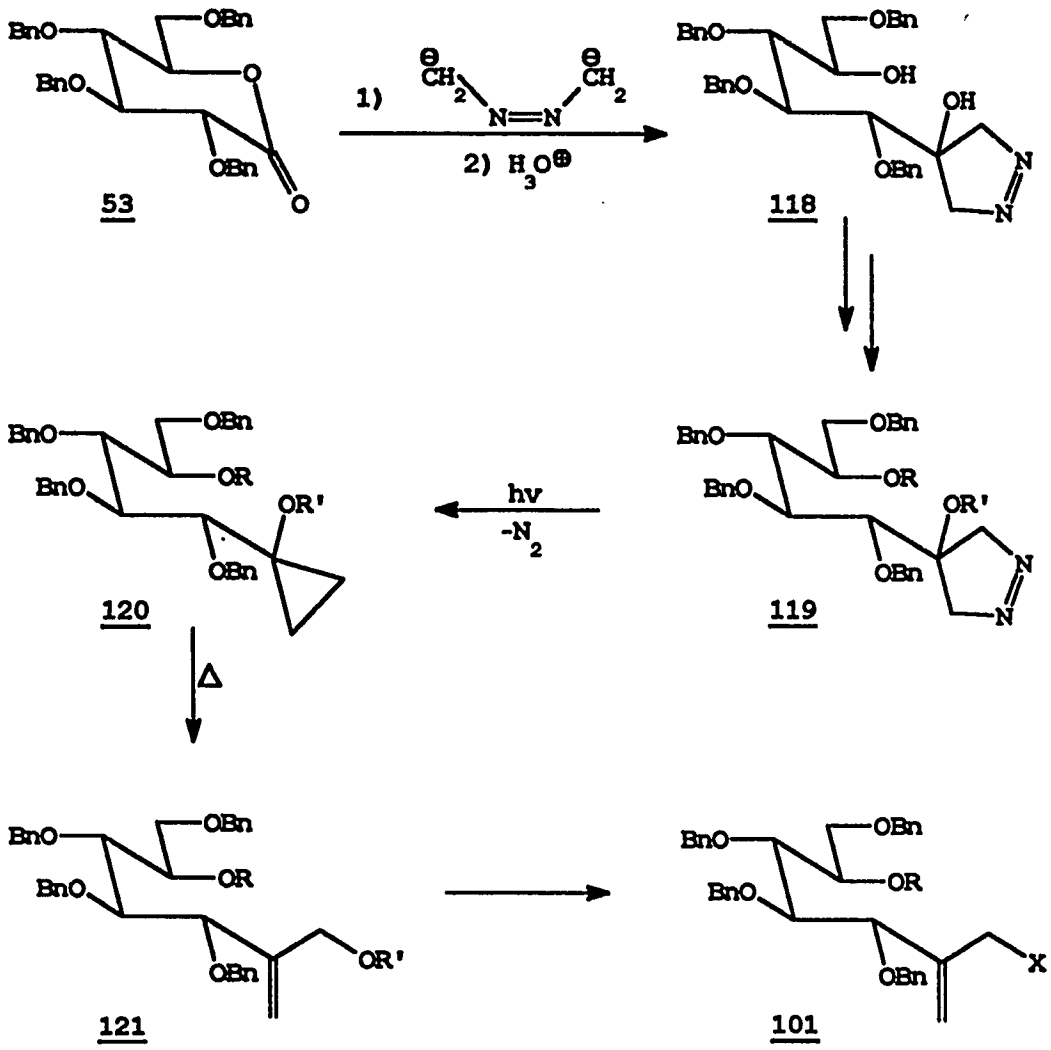
The plausibility of designing the dianion equivalent shown above was based on the known chemistry of butadiene systems. These compounds are easily converted to their dianions by dissolving metal reductions. In a recent report by Heping, substituted 1,3-dienes were shown to react with activated magnesium under mild conditions generating substituted 2-butene-1,4-diylmagnesium complexes in high yields[7]. Although these magnesium complexes were allowed to react with dihalides, we reasoned that it should be just as facile to form five-membered ring azoalkanes with lactones. The proposed

SCHEME 12



sequence of reactions involving the dianion equivalent is depicted in Scheme 13. Indeed, the technique of synthesizing functionalized cyclopropanes from azoalkanes has been highly precedented in the chemical literature[5]. A wide range of exotic organic molecules have been prepared by this technique of photochemical denitrogenation of azoalkanes.

SCHEME 13

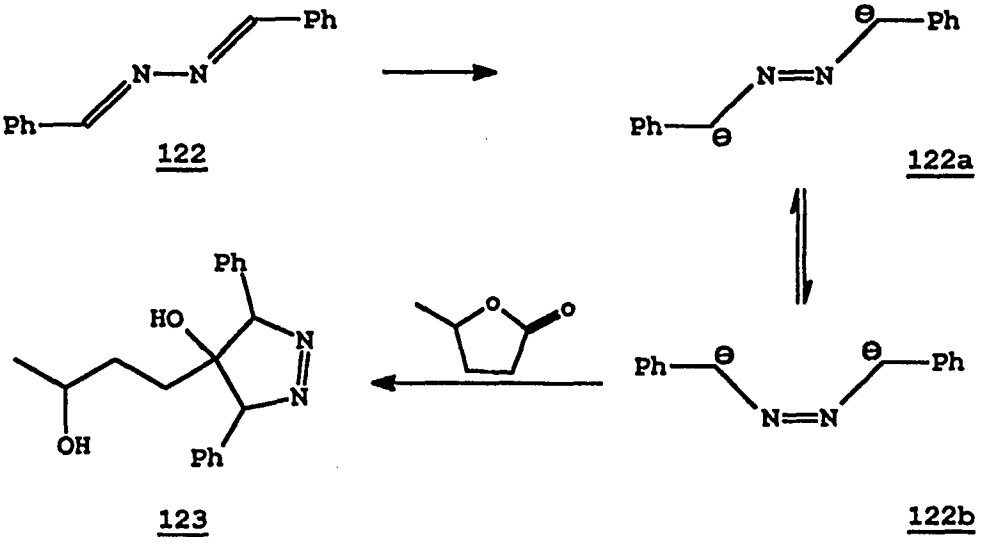


The practicality of this method lies partly in the fact that the range of activation energies for the pyrolytic extrusion of molecular nitrogen covers values as low as 15-20 kcal/mol to as high as 40-45 kcal/mol. This wide range of activation energy values translates into decomposition temperatures as low as -100°C to as high as +300°C. Many of the thermal denitrogenations are conducted in solutions of inert and thermally stable solvents. However, flash vacuum thermolysis techniques are particularly convenient and

have been used more and more frequently in recent years. Among the photochemical techniques, either direct and/or sensitized photolysis have been used. From the spectral characteristics of the *cis*-azoalkanes, which are of interest for our discussion, it is clear that the excitation process is $n_- \rightarrow \pi^*$ derived and lies in the 300-400 nm range. The singlet states of the $n_- \rightarrow \pi^*$ transition have excitation energies E_S of 70-90 kcal/mol and for the triplet states E_T is 50-60 kcal/mol. Thus, triplet sensitization can be conveniently and effectively performed with the usual carbonyl sensitizers (acetone, benzophenone, *etc.*). The quantum yields for the photoextrusion of nitrogen, depends greatly on the structure of the azoalkane, ranging from as high as unity to essentially zero. Azoalkanes for which the -N=N- bond is contained in a five membered ring photo-eliminate nitrogen efficiently, while azoalkanes whose -N=N- bond is contained in a six-memberd ring are reluctant towards photolysis.

Scheme 14 shows the sequence of reactions for model studies involving the compound 122 and valerolactone.

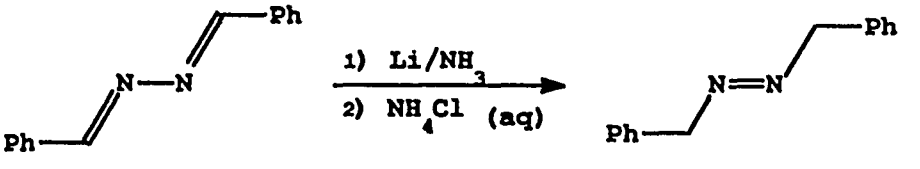
SCHEME 14



Our initial attempt at reducing compound **122** to the dianion involved the use of activated magnesium with sonication in THF. Repeated attempts with reaction times for up to three days revealed no change in the starting material. Next we tried the reaction under heterogeneous catalysis employing finely divided zinc in THF and saturated aqueous ammonium chloride. Investigations were performed at 0°C, and at room temperature. Variations including the use of zinc amalgam and aluminum amalgam in THF, also proved fruitless. The starting materials were recovered in all cases. At this point, it was apparent that a more rigorous reduction condition must be employed. We therefore opted for the technique of dissolving metal reduction.

Using 2.2 molar equivalents of lithium in THF at -78°C with added $MgBr_2$. as a complexing agent resulted in minimal reduction of the diazacompound **122**. The reaction was repeated using lithium in liquid ammonia at -78°C. Not surprisingly, reduction to the dianion was achieved, as indicated by the deep red color of the reaction medium. Quenching the reaction with saturated ammonium chloride afforded the photosensitive azoalkane **124**.

SCHEME 15

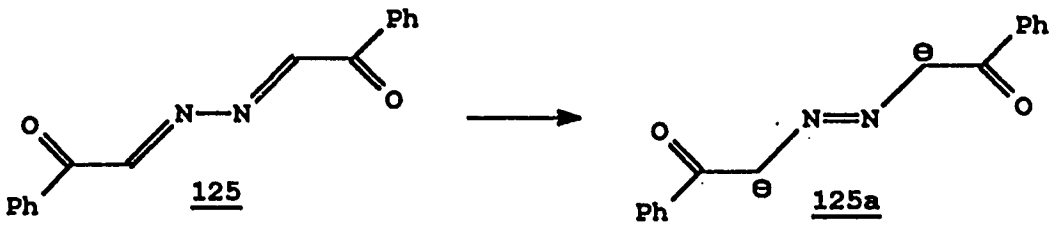


122 **124**

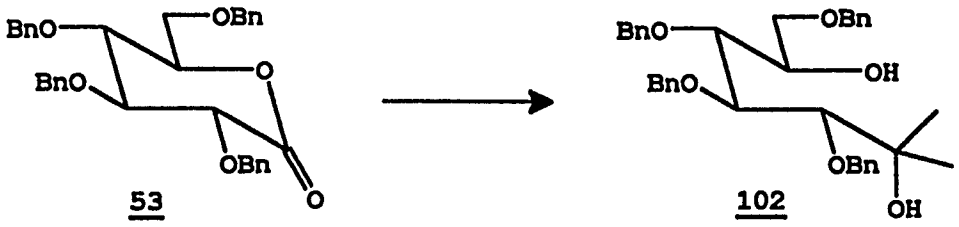
The reaction was again repeated, but with the addition of valerolactone after the formation of the dianion. On work-up, no addition product involving the lactone was ob-

served. Compound 124 and small amounts of 122 were isolated. We reasoned that this observed lack of reactivity, might have been attributed to the possibility of the dianion adopting the more stable trans arrangement. Thus further investigations were carried out incooperating $MgBr_2.OEt_2$ that hopefully would have stabilized the cis conformation. No further improvements were observed with these modifications. Our final attempts, as time permitted, involved the reaction between acetic anhydride (replacing the lactone), and the dianion. These reactions likewise, did not proceed beyond the initial reduction of compound 122.

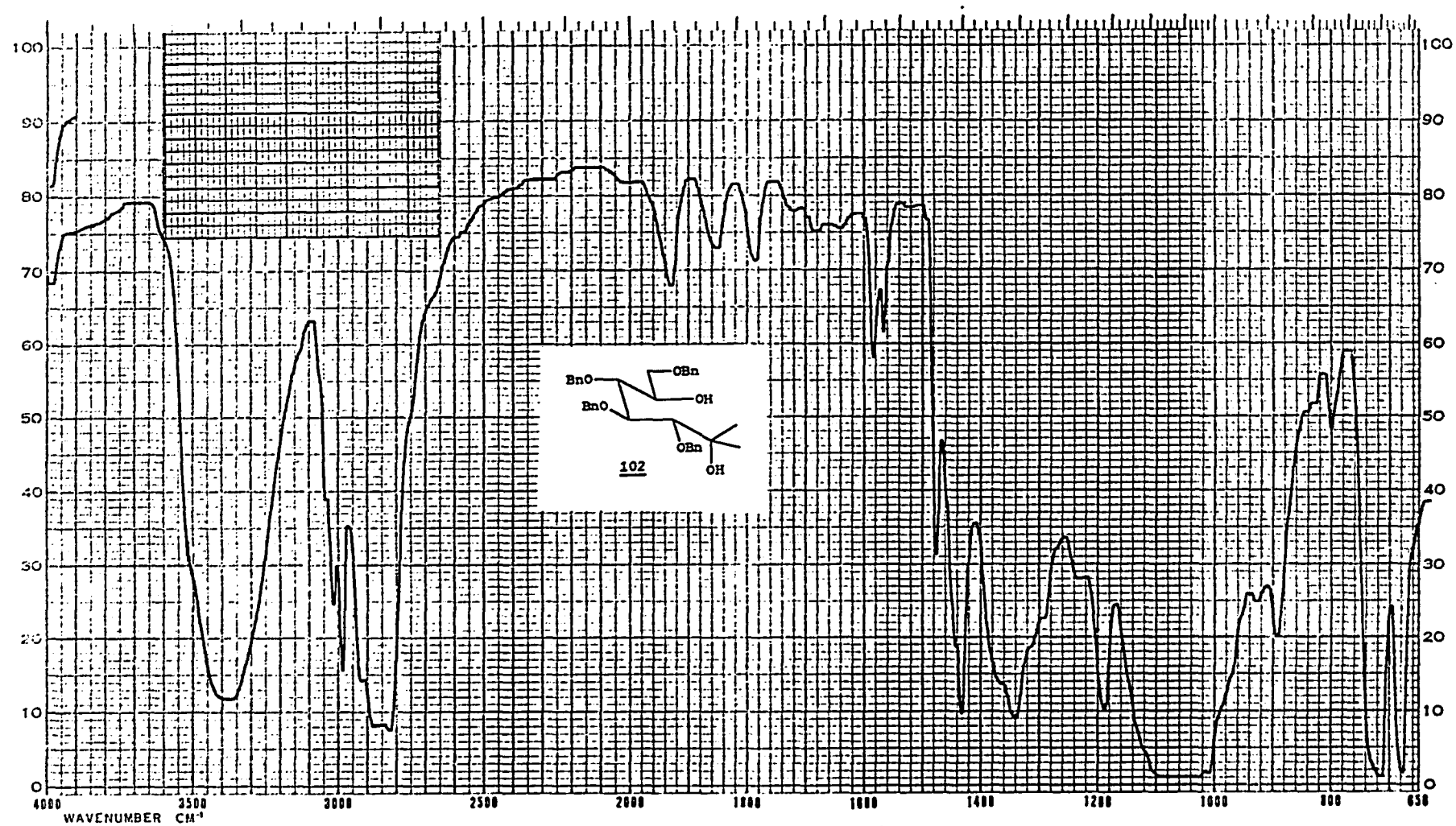
In conclusion, it is evident that further investigations are required. These should include solvent studies, temperature variations, and perhaps looking at the effects of other complexing agents so as to favor the cis arrangement of the dianion. The diazene 122 was chosen because of its availability, ease of preparation and stability. It is likely, however, that the resulting dianion was exceptionally stable, owing to charge delocalization by the phenyl rings. This would certainly have contributed to its lack of reactivity. Additional studies will therefore incorporate diazenes subtituted with groups other than phenyl. Perhaps the dianion 125a obtainable from the diazene 125, would be more reactive, since the possibilities for delocalization are significantly less.



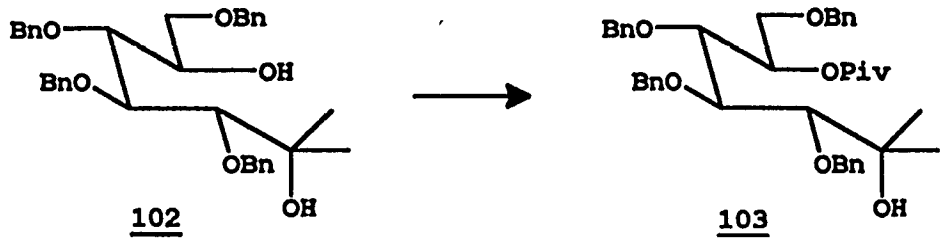
3,4,5,7-Tetra-O-benzyl-1-deoxy-2-methyl-D-glucohepitol, <u>*102*</u>.



Methylmagnesium iodide was prepared according toa standard procedure in diethyl ether from methyl iodide (4.48 g, 31.5 mmol) and magnesium turnings (4.0 g, 160 mmol), and the solution was cooled to -20°C with stirring. A solution of the lactone <u>53</u> (1.7 g, 3.15 mmol) in diethyl ether was added dropwise during 30 minutes, while maintaining the reaction temperature at -20°C. After stirring for another 30 minutes the cooling bath was removed allowing the reaction to proceed at ambient temperature overnight. The reaction was later quenched by stirring with cold dilute hydrochloric acid, and the organic products were extracted with ethyl acetate. After drying over anhydrous magnesium sulfate, the crude product was concentrated under reduced pressure and chromatographed so affording the diol <u>102</u> (1.75 g, 97.2%) as a pale yellow gum. Compound <u>102</u> was esterified to the compound <u>103</u> after IR analysis only. IR($CHCl_3$, cm^{-1}); 3200 - 3600 (s).

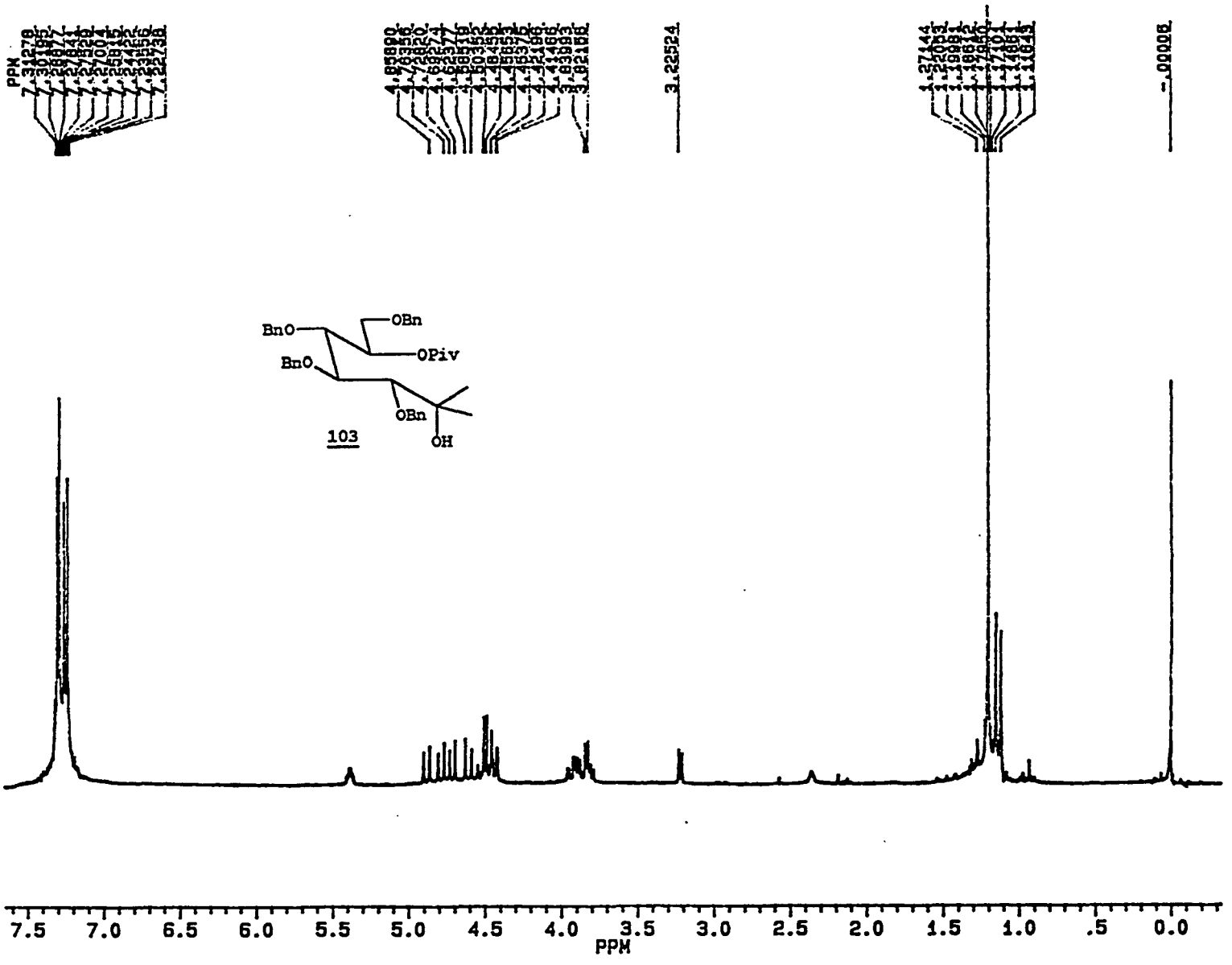

100
90
80
70
60
50
40
30
20
10
0
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
650
WAVENUMBER CM⁻¹
BnO
OBn
OH
BnO
OBn
OH
102

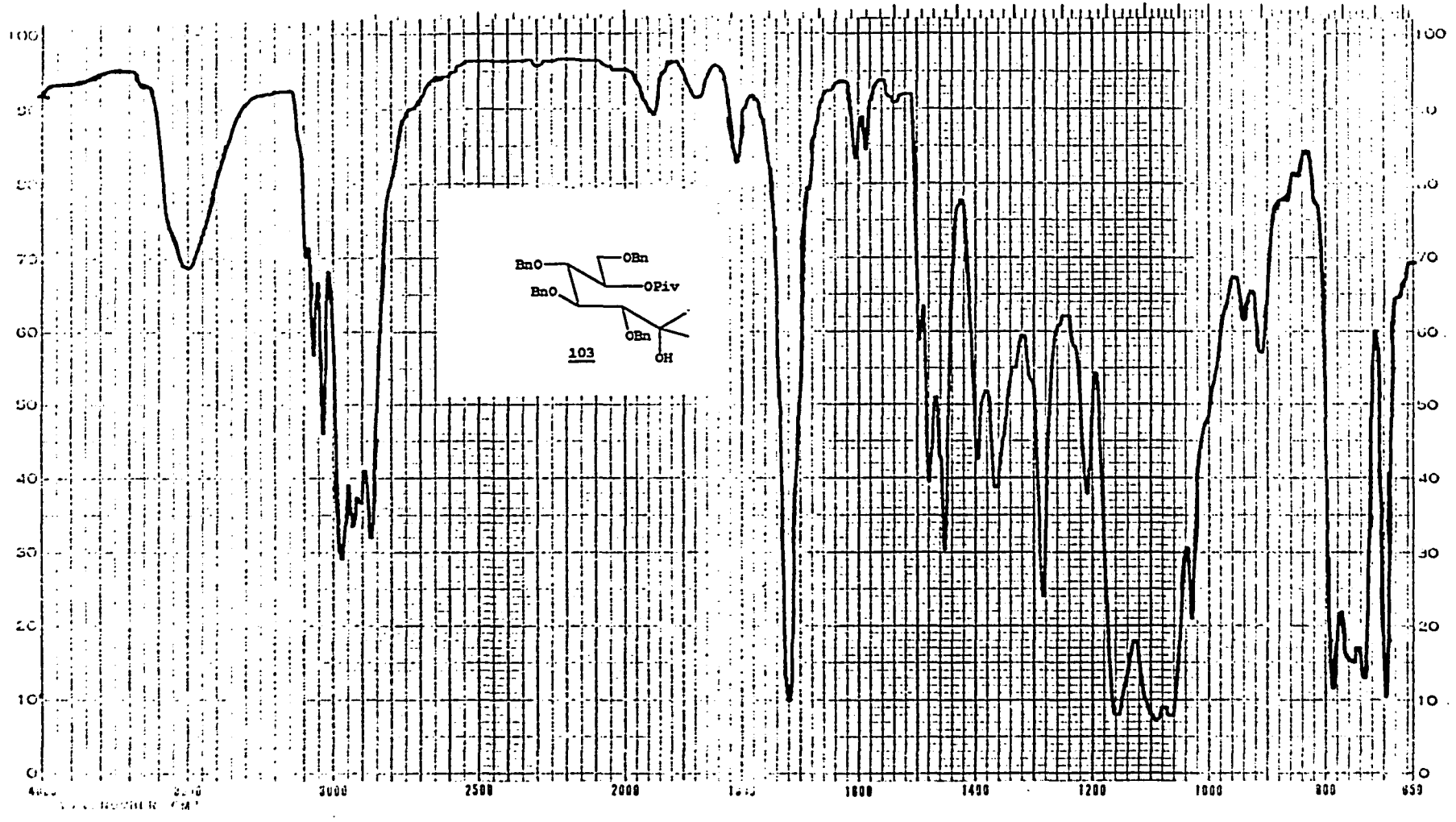
3,4,5,7-Tetra-O-benzyl-1-deoxy-2-methyl-6-O-pivaloyl-D-glucohepitol, 103.



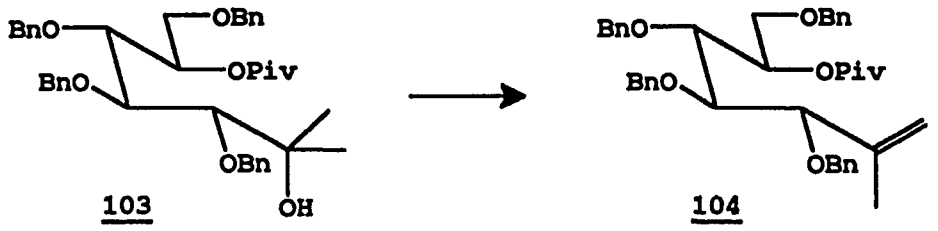
The diol **102** (1.0 g, 1.8 mmol) was dissolved in 50 mL of dry pyridine and the solution was cooled to 0°C. Pivaloyl chloride (0.28 g, 2.3 mmol) was then added via syringe with efficient stirring. The cooling bath was removed and stirring was continued at room temperature for 48 hours. Work-up followed by pouring into an ice-water mixture and extracting with ethyl acetate. After drying, the residual pyridine was removed by azeotropic distillation with toluene providing the crude product as a brown gum. Chromatographic purification (EtOAc:hexanes ; 2:5) afforded the ester **103** (1.1 g, 99%). ^{1}H NMR(300 MHz, $CDCl_3$, ppm): 7.23-7.32 (m, 20H) aromatic; 5.33-5.41 (m, 1H) C<u>H</u>(OPiv); 4.88 (d, 2H); 4.78 (d, 2H); 4.71 (d, 2H,*J*=9.0 Hz); 4.60 (d, 2H,*J*=12.0 Hz); 4.41-4.51 (m 3H); 3.78-3.95 (m, 3H);1.17 (s, 9H) (C<u>H</u>$_3$)$_3$C;1.14,1.11 (ds, 6H) 2 x C<u>H</u>$_3$. IR($CHCl_3$, cm^{-1}); 3500 (s,b), 1720 (s).

Mass Spectrum (CI, NH_3); Calculated for $C_{41}H_{50}O_7$ (m/z 655.0). Found m/z 673.0 (M^++NH_4).


BnO
OBn
BnO
OPiv
OBn
OH
103
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
PPM


BnO
OBn
OPiv
BnO
OBn
OH
103
100
90
80
70
60
50
40
30
20
10
0
3000
2500
2000
1800
1400
1200
1000
800

3,4,5,7-Tetra-O-benzyl-1-deoxy-2-methylene-6-O-pivaloyl-D-gluco-heptulose, 104.

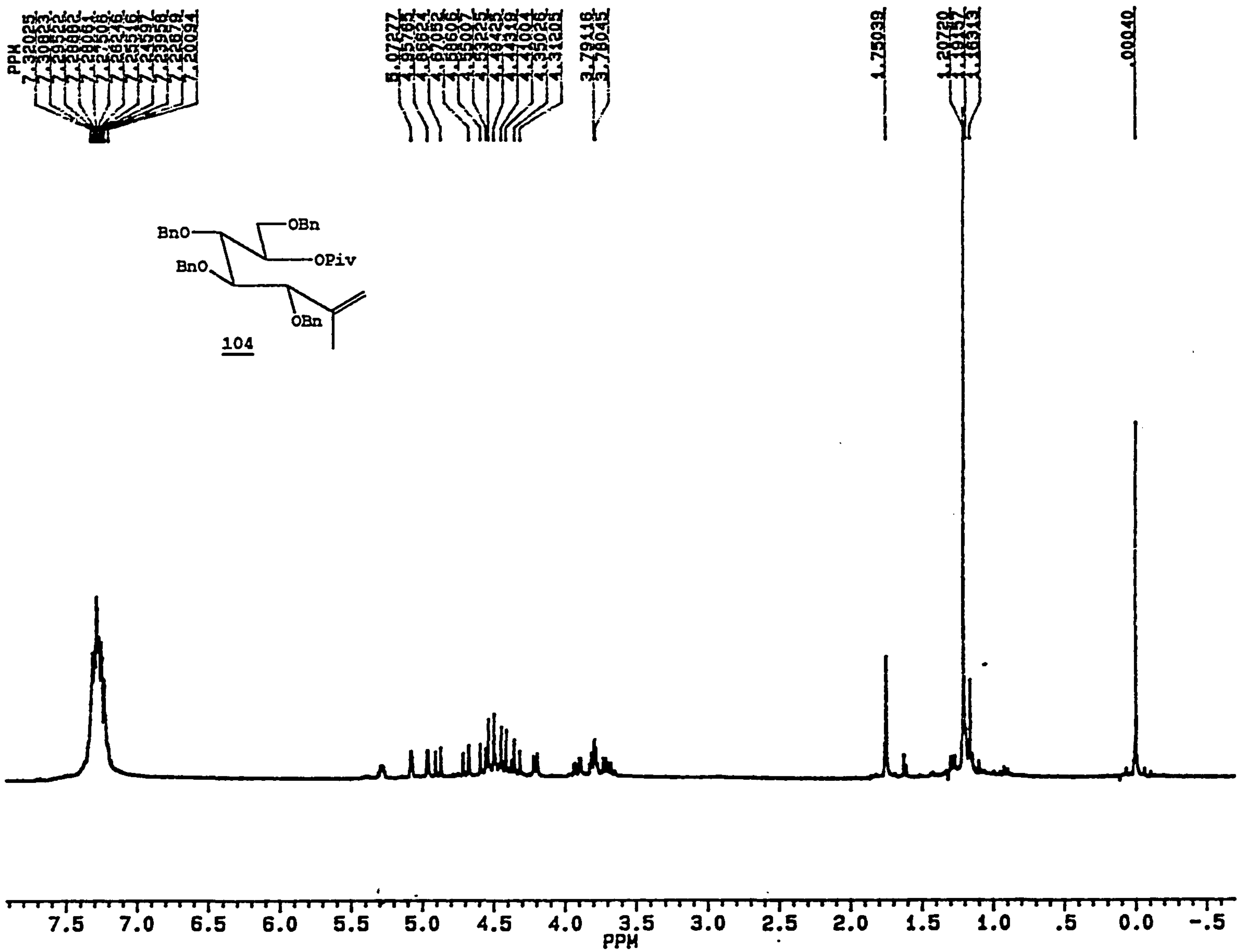


The alcohol **103** (1.51 g, 2.31 mmol) was dissolved in 50 mL of dry pyridine and cooled to 0°C. Phosphorus oxychloride (0.43 g, 2.77 mmol) was then added via syringe in one portion with rapid stirring. The cooling bath was removed allowing the reaction to proceed at room temperature for 36 hours. Work-up consisted of stirring with cold brine, extracting with ethyl acetate and drying over $MgSO_4$. After removal of the solvent, flash column chromatography (EtOAc:hexanes ; 1:5) afforded the alkene **104** (1.4 g, 95%) as a pale yellow syrup.

^{1}H NMR(300 MHz, $CDCl_3$, ppm): 7.20-7.32 (m, 20H) aromatic; 5.26-5.30 (m, 1H) C<u>H</u>(OPiv); 5.07,4.96 (ds,br, 2H) =C<u>H</u>$_2$; 4.89 (d, 1H,*J*=9.0 Hz); 4.69 (d, 1H, *J*=12 Hz); 4.57 (d, 1H,*J*=12 Hz); 4.53,4.50 (ds, 4H); 4.45,4.41 (ds, 4H); 4.33 (d, 1H,*J*=12 Hz); 4.21 (d, 1H, *J*=9.0 Hz); 3.92, 3.89 (dd, 1H,$J_{1,2}$=3.0 Hz, J_{ab}=12 Hz); 3.77-3.82 (m, 2H); 3.72 3.68 (dd, 1H, $J_{1,2}$=6.0 Hz, J_{ab}=9.0 Hz); 1.75 (s, 3H); 1.21 (s, 9H).

IR($CHCl_3$, cm^{-1}); 1723 (s), 1610 (w).

Mass Spectrum (EI); Calculated for $C_{41}H_{48}O_6$ (m/z 637). Found m/z 638.1 (M^++1).


PPM
1.75039
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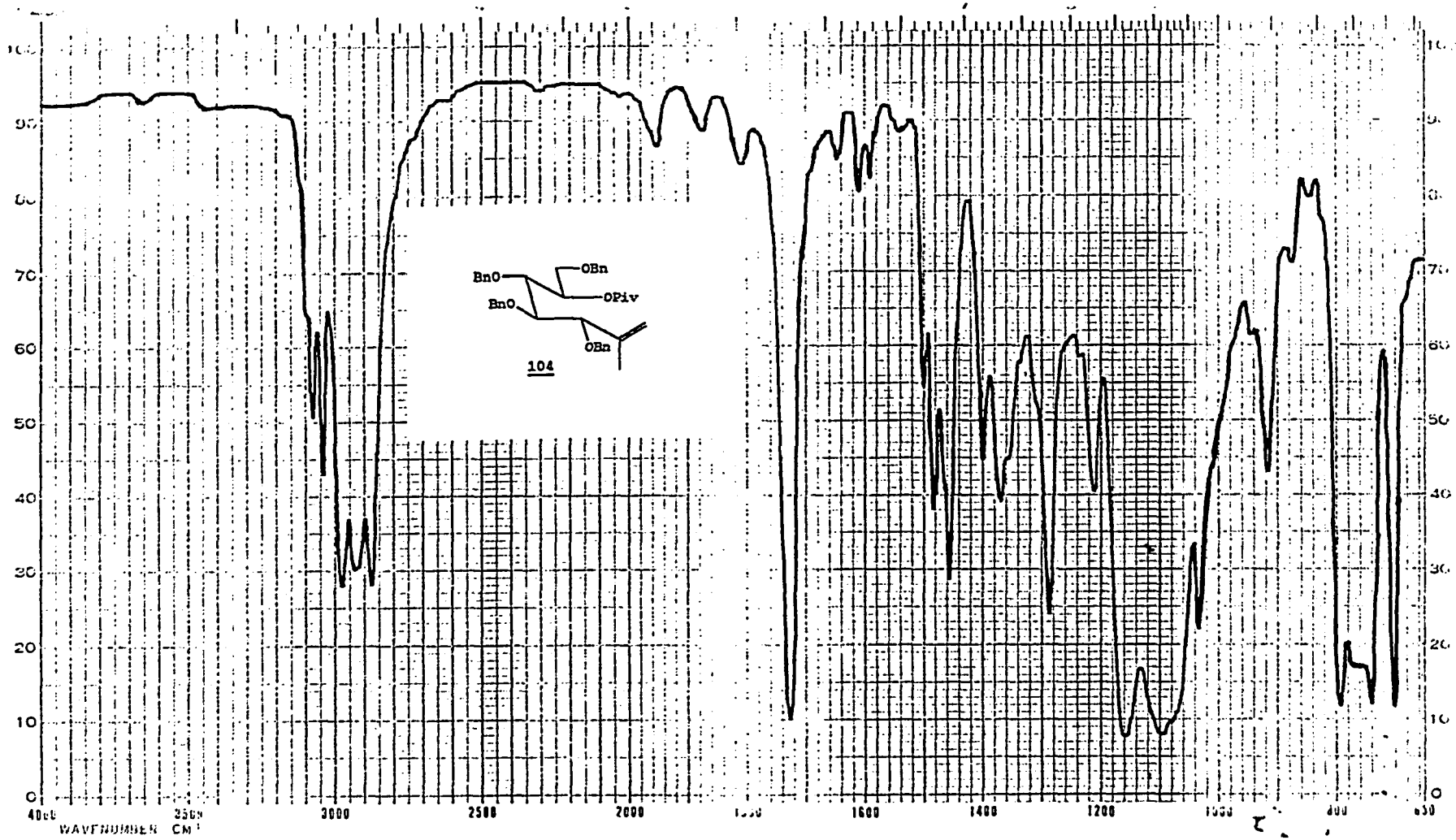
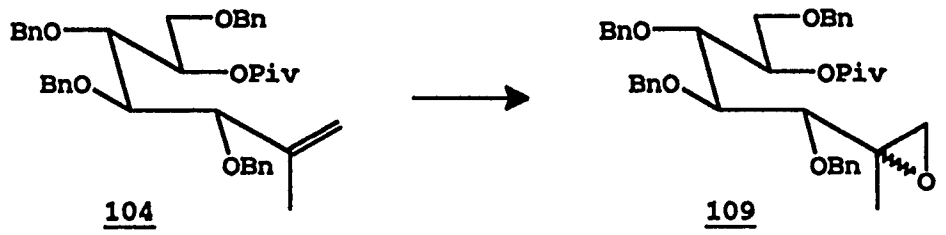
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
-.5
PPM
BnO
OBn
OPiv
BnO
OBn

104

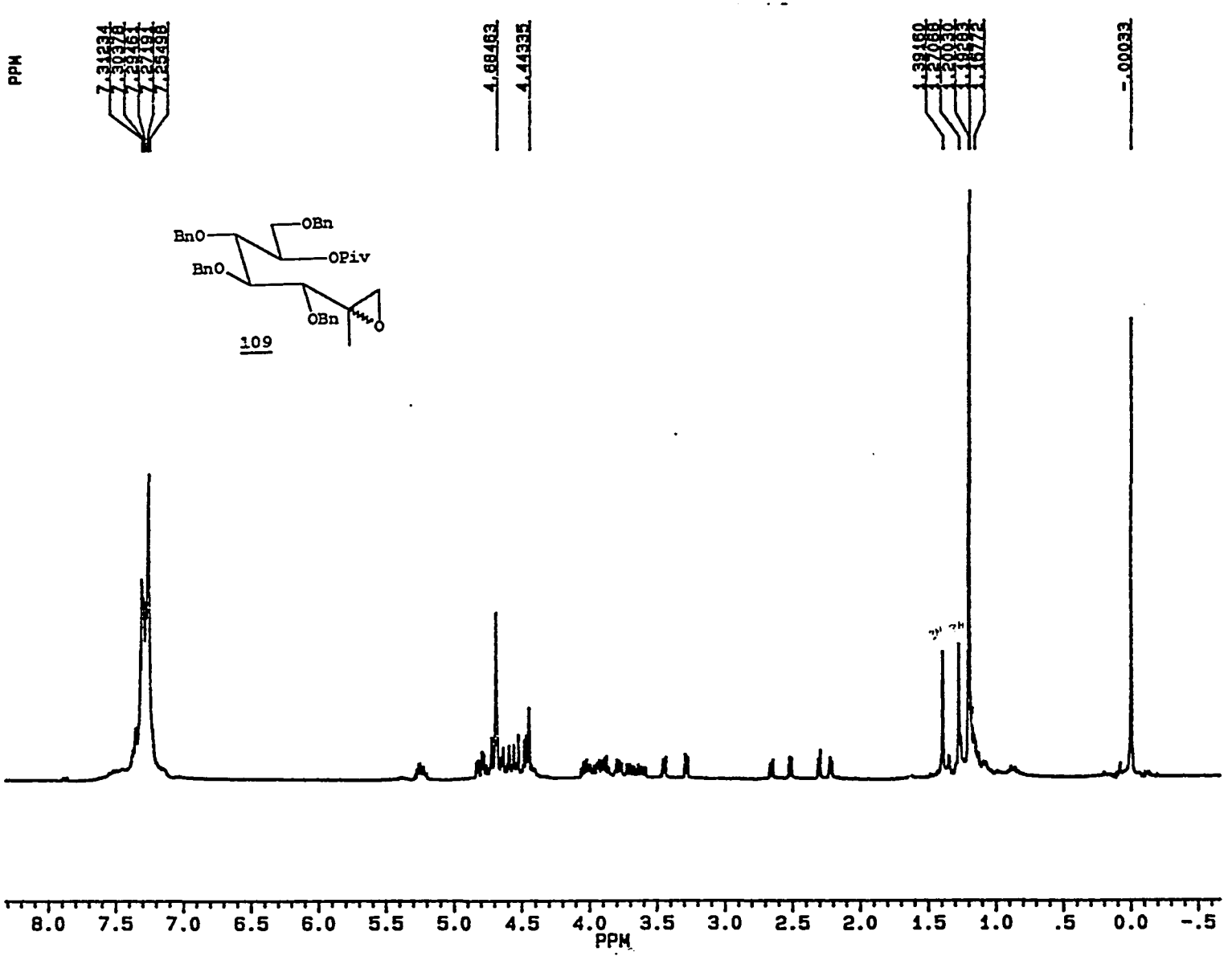

BnO
OBn
OPiv
BnO
OBn
104
WAVENUMBER CM⁻¹
3000
2500
2000
1600
1400
1200

3,4,5,7-Tetra-O-benzyl-1,2-epoxy-2-methyl-6-O-pivaloyl-D-glucoheptulose, 109.

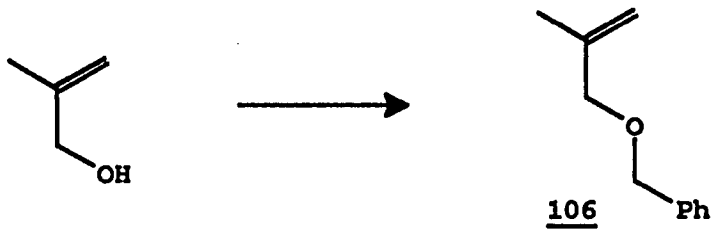


The alkene **104** (0.201 g, 0.316 mmol) was dissolved in 5.0 mL of freshly purified dichloromethane, to which was added sodium bicarbonate (0.057 g, 0.68 mmol) with stirring for five minutes. *m*-Chloroperoxybenzoic acid (0.11 g, 0.511 mmol) was then added with continued stirring at ambient temperatures for 18 hours. As preliminary analysis at this point indicated largely unconverted starting material, an aditional 0.3 g of the peracid and 0.02 g of sodium bicarbonate were added and stirring was continued for four hours. TLC analysis at this point revealed no further change in the reaction profile. Thioacetamide (0.5 g) was added with continued stirring for 30 minutes, which was followed by washing with cold water (3 x 10 mL). After drying over sodium sulfate, concentration and column chromatography nprovided the epoxide **109** as a clear syrup, in 60% yield, as a mixture of diastereoisomers.

^{1}H NMR(300 MHz, $CDCl_3$, ppm): 7.25-7.31 (m, 20H) aromatic; 5.19-5.28 (m, 1H) CH(OPiv); 4.42-4.83 (m, 8H); 3.58-4.05 (m, 4H); 3.44, 3.28 (dd, 1H,$J_{1,2}$=6.0 Hz); 2.65, 2.51 (dd, 1H,J=3.0 Hz); 2.30,2.22 (dd, 1H,J=3.0 Hz);1.39 (s, 3H);1.19 (s, 9H).


PPM
7.34234
7.30378
7.29461
7.27191
7.25498
4.68463
4.44335
1.39160
1.27086
1.20030
1.10503
1.10772
-.00033
BnO
OBn
OPiv
BnO
OBn
O
109
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
-.5
PPM

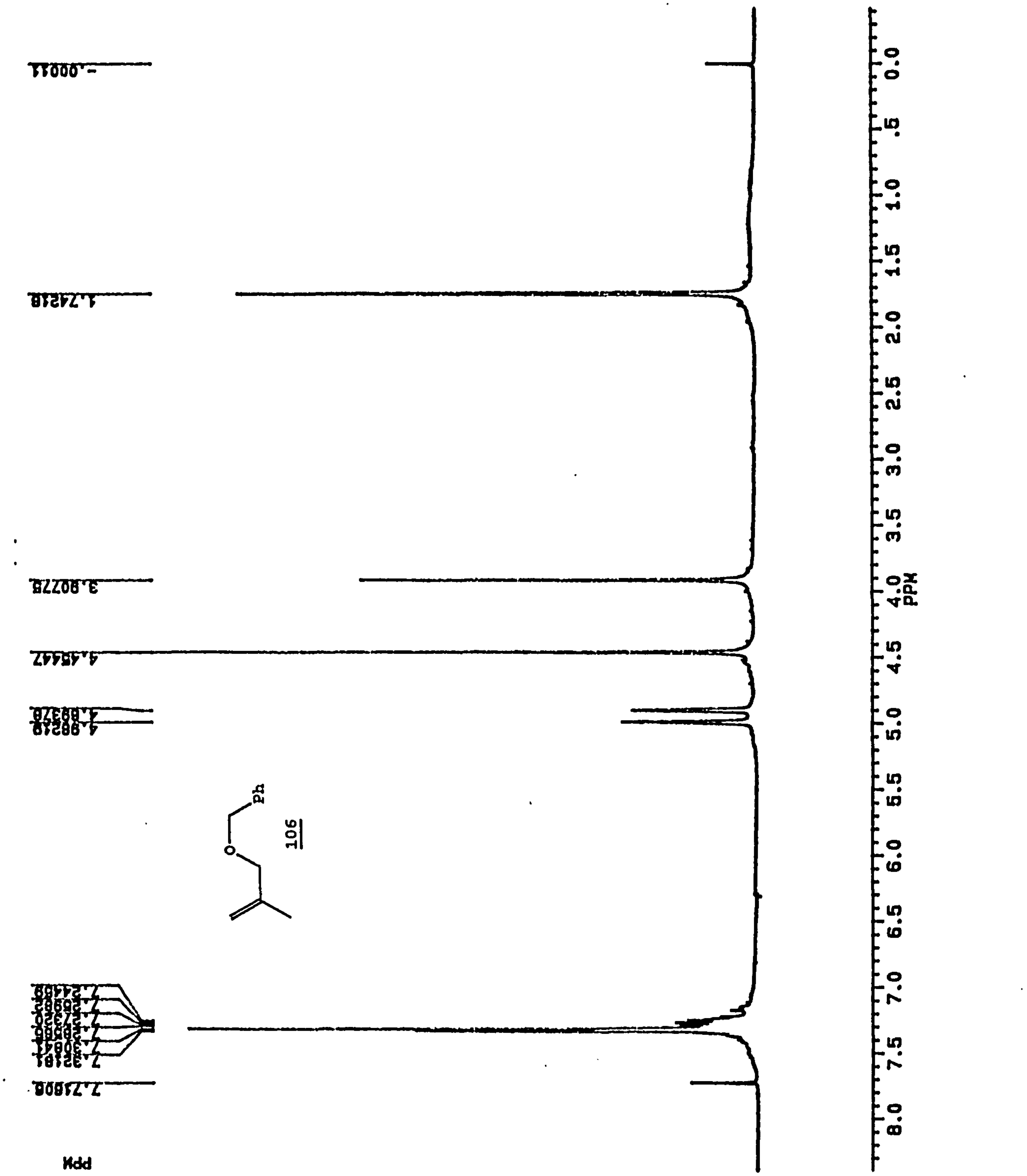
Methallyl benzyl ether, <u>106</u>.



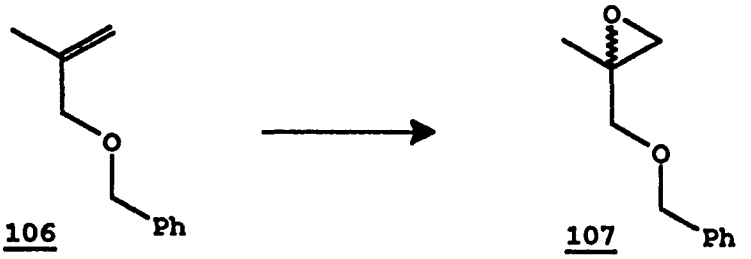
Methallyl alcohol (20.0 g, 0.277 moles) was added dropwise to a stirred mixture of sodium hydride (13.3 g, 0.555 moles) in 47.88 mL of benzyl chloride (52.67 g, 0.416 moles). When addition was complete and effervescence had ceased, the reaction mixture was suction filtered, and the excess benzyl chloride removed with the aid of the high vacuum pump. Flash column chromatography afforded the benzyl ether **<u>106</u>** (44.0 g, 99%).

^{1}H NMR(300 MHz, $CDCl_3$, ppm): 7.24-7.32 (m, 5H) aromatic; 4.98,4.89 (ds, 2H) =C<u>H</u>$_2$; 4.45 (s, 2H) C<u>H</u>$_2$, benzylic; 3.90 (s, 2H) C<u>H</u>$_2$; 1.74 (s, 3H) C<u>H</u>$_3$.

IR(Neat, cm^{-1}); 1610 (s).


O
Ph
106
PPM

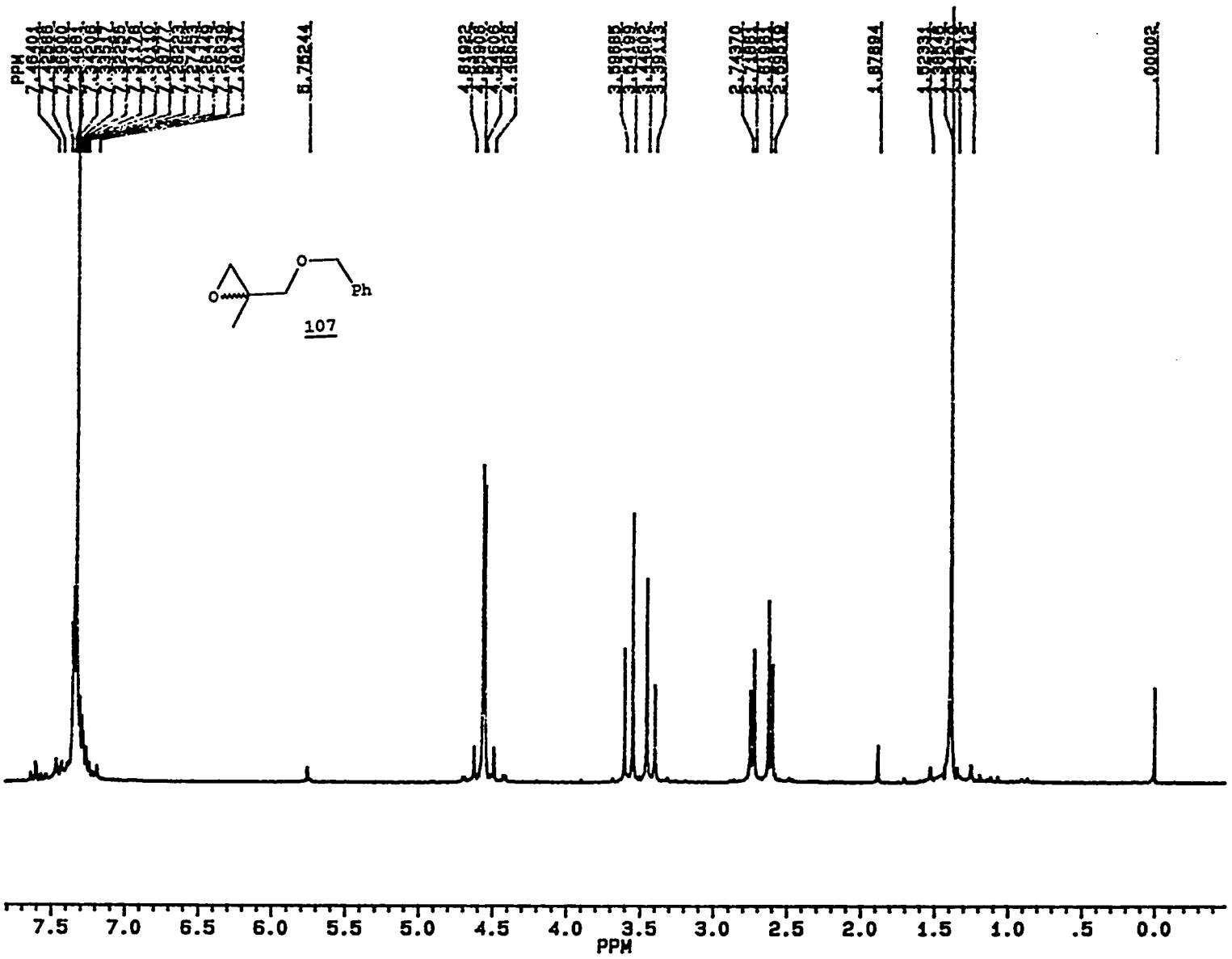
1,2-epoxy-2-methyl-propyl benzyl ether, 107.



To a stirred suspension of the alkene **106** (1.0 g, 6.17 mmol), benzonitrile (0.96 g, 9.26 mmol) and anhydrous potassium carbonate (0.154 g, 1.12 mmol) in methanol (5 mL) was added 30% aqueous hydrogen peroxide (1.75 mL) dropwise. Stirring was continued vigorously, as the progress of the reaction was followed by TLC. After stirring for one hour, an additional 0.5 mL of aqueous hydrogen peroxide was added and stirring was continued at room temperature until all of the starting material was consumed; a total reaction time of five hours. The reaction mixture was subsequently heated on a water bath at 40°C for thirty minutes, and then cooled to room temperature. Three extractions with hexanes followed, combining the organic extracts. Brine was added to the aqueous layer which was further extracted with another three portions of hexanes. Drying, concentrating and column chromatography afforded the pure epoxide **107** (0.98 g, 89%) as a clear oil.

^{1}H NMR(300 MHz, $CDCl_3$, ppm): 7.25-7.42 (m, 5H) aromatic; 4.55 (d, 2H, J=3.0 Hz) $C\underline{H}_2$, benzylic; 3.57, 3.41 (dd, 2H, J=15.0 Hz) $C\underline{H}_2$; 2.73, 2.60 (dd, 2H, J=6.0 Hz) $C\underline{H}_2$; 1.38 (s, 3H) $C\underline{H}_3$.

Mass Spectrum (EI). Calculated for $C_{11}H_{14}O_2$ (m/z 178.2). Found m/z 179.3 (M^++1).


PPM
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1.87894
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O
O
Ph
107
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7.0
6.5
6.0
5.5
5.0
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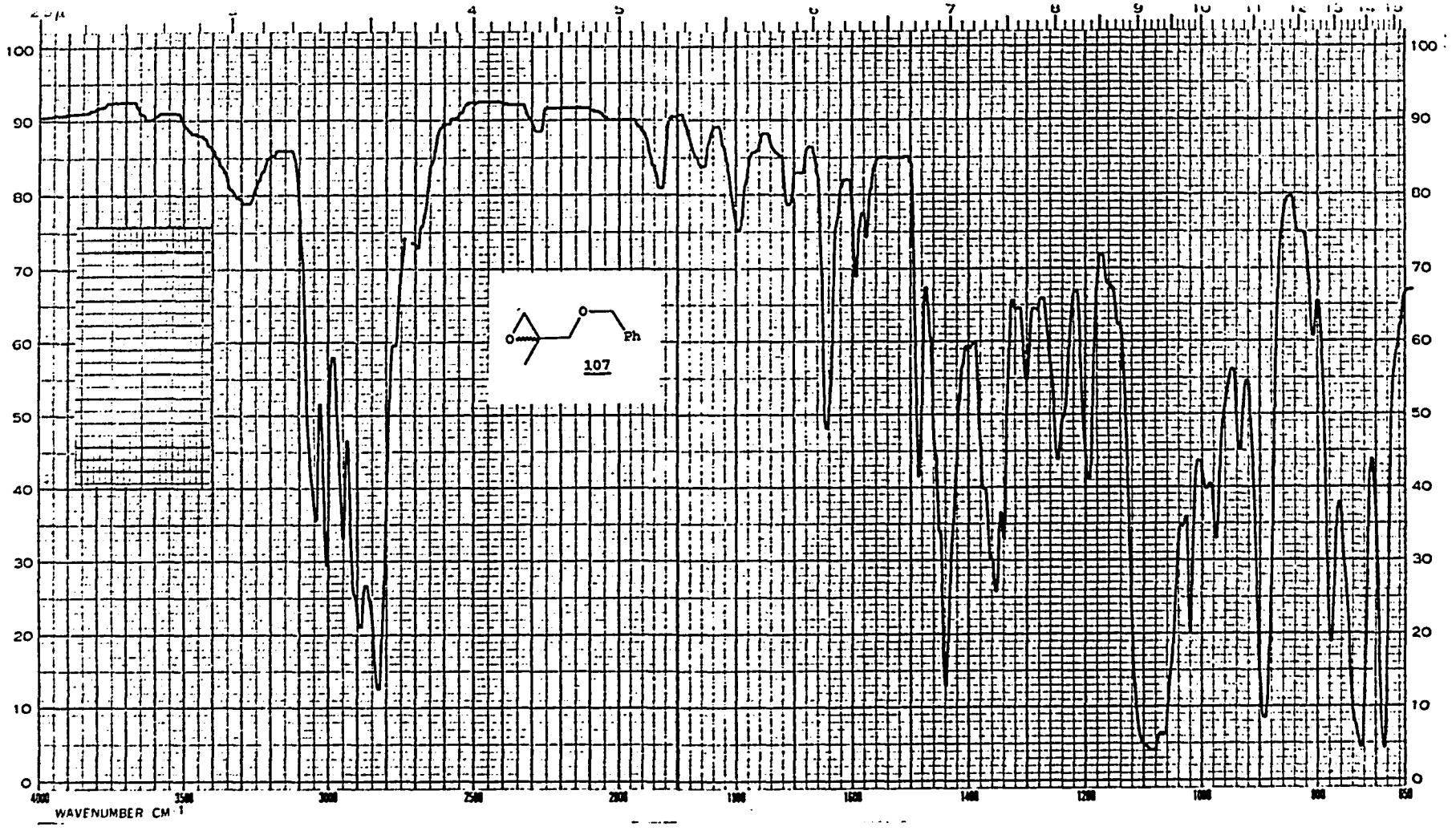
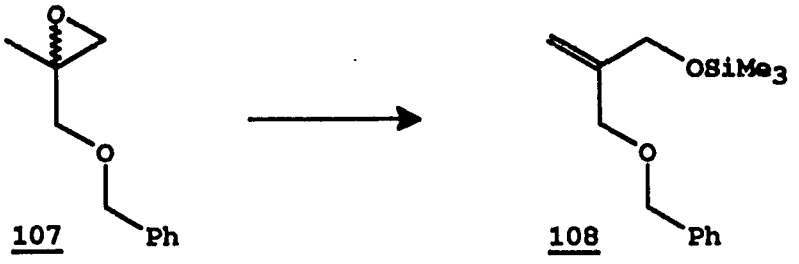
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM


WAVENUMBER CM⁻¹
Ph
107

2-Methylene-1-O-trimethylsilyl-propyl-3-benzyl ether, 108.



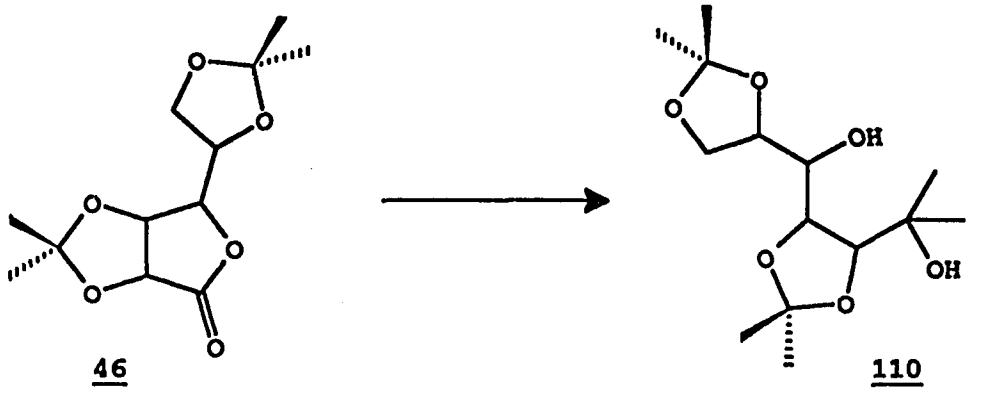
107 108

A dry 100 mL three-necked round bottomed flask, fitted with a pressure equalizing dropping funnel, air condenser and stopcock, was equipped for magnetic stirring and flushed with nitrogen while being flame dried. *n*-Butyl lithium (5.6 mL, 8.93 mmol) was added and stirring started. The flask was then immersed in an ice water bath and 2.0 mL (8.93 mmol) of hexamethyldisilazane was added dropwise over a ten minute period. The ice-bath was removed and stirring was continued for an additional ten minutes. The hexane was removed under reduced pressure while the flask was immersed in a water bath at 40-50°C and stirring continued for as long as possible. After complete evaporation of the hexanes, white crystals of lithium bis(trimethylsilyl) amide appeared. The flask was again subjected to a static nitrogen pressure and 25 mL of dry diethyl ether were added to dissolve the crystals. A solution of the epoxide **107** (0.64 g, 3.57 mmol) in dry ether was added dropwise with stirring. When addition was complete the reaction was heated under reflux at 30°C overnight under a positive nitrogen atmosphere. Work-up consisted of stirring with cold dilute hydrochloric acid and extracting with diethyl ether. Drying and concentrating was followed by flash chromatography, so affording the silylated allylic alcohol **108** in 70% yield.

Alternative Procedure For Isomerization.

Formation of lithium bis(trimethylsilyl)amide was achieved as described above. The crystals formed were dissolved in benzene, and the solution was cooled to 0°C while maintaining a positive nitrogen atmosphere. A solution of diethylaluminum chloride (22.5 mL, 22.4 mmol) in hexanes, was added slowly via syringe with efficient stirring for fifteen minutes. The epoxide **107** (2.0 g, 11.24 mmol) dissolved in 15 mL of benzene, was then added dropwise with efficient stirring. When addition was complete, stirring was continued for an additional three hours at 0°C. The addition of dilute hydrochloric acid, washing with water, drying and concentration in vacuo, provided the silylated allylic alcohol **108** in a comparable yield (70%) after chromatography.
^{1}H NMR(300 MHz, $CDCl_3$, ppm): 7.09-7.19 (m, 5H) aromatic; 4.31-4.41 (m, 2H) =C$\underline{H}_2$; 3.14, 3.06 (dd, 2H,*J*=9.0 Hz) C$\underline{H}_2$; 2.85, 2.73 (dd, 2H,*J*=15 Hz) C$\underline{H}_2$; 0.98 (s, 2H) C$\underline{H}_2$; 0.02 (s, 9H) (C$\underline{H}_3$)$_3$Si.

3,4;6,7-Di-O-isopropylidene-2-methyl-D-mannoheptitol, 110.

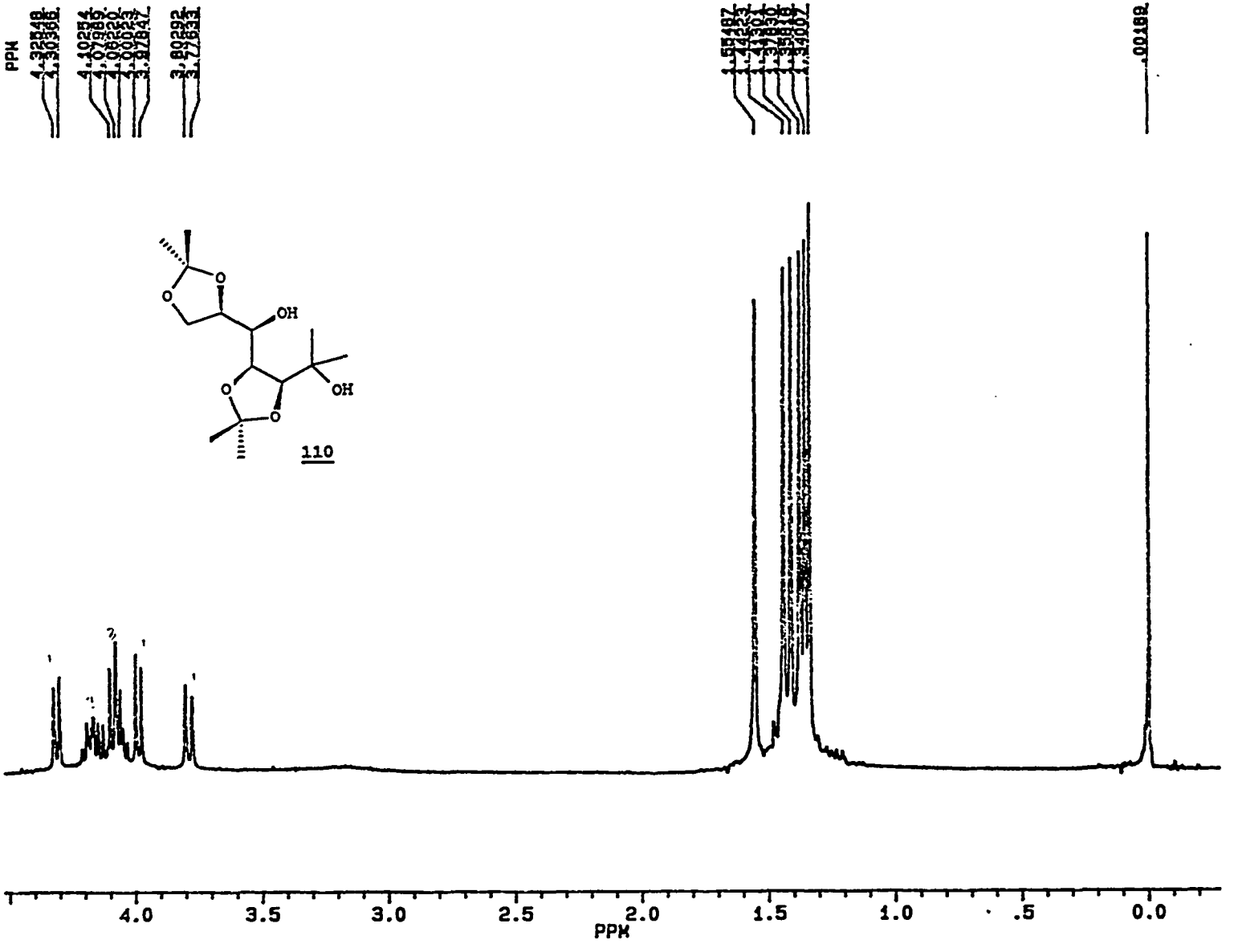


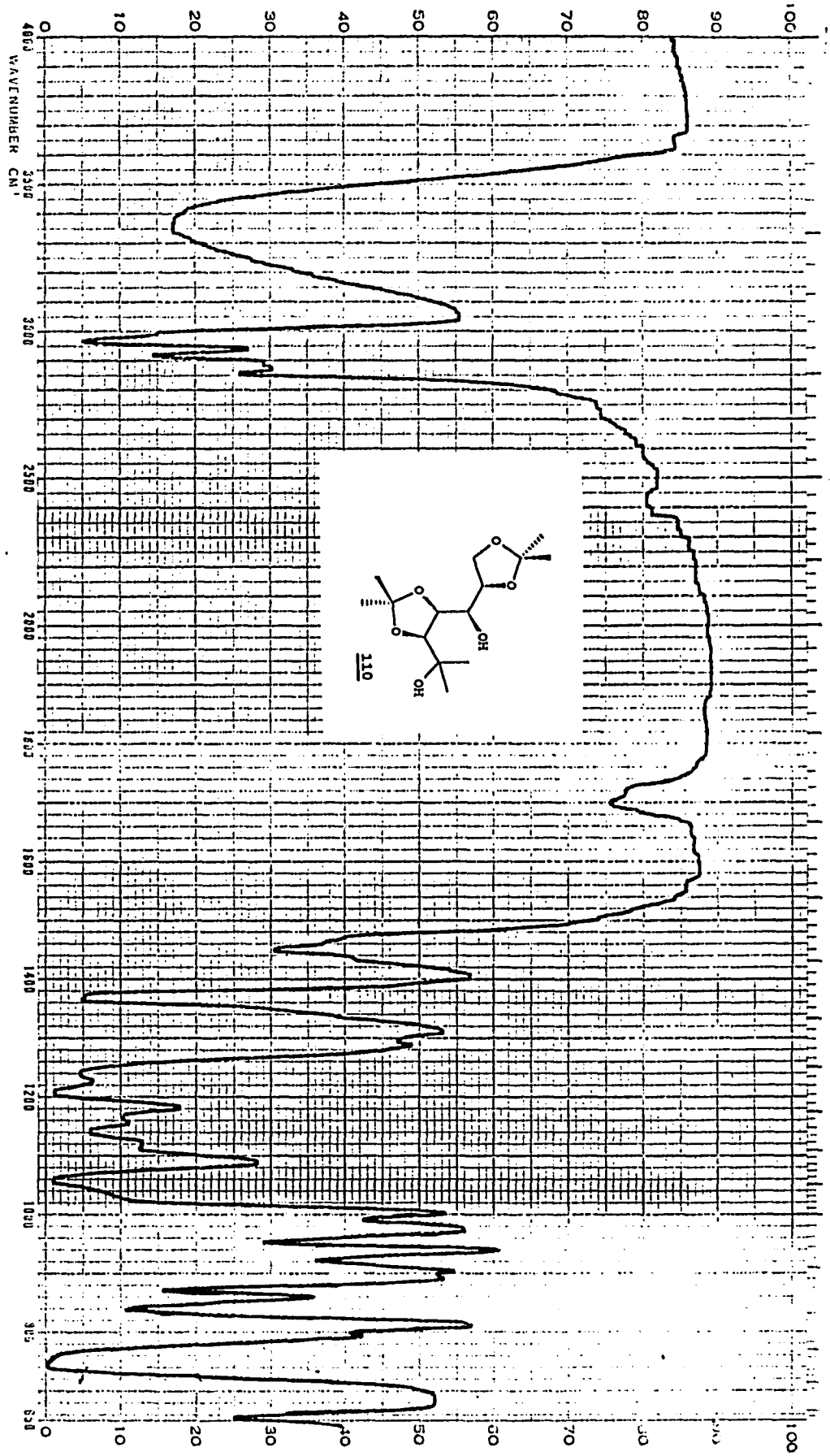
46 110

The lactone **46** (1.0 g, 3.86 mmol) dissolved in dry THF was added to an excess of a solution of methyl lithium (23.2 mmol) in diethyl ether at 0°C. The cooling bath was removed while allowing the reaction to stir at room temperature for 48 hours. Quenching was achieved by stirring with cold saturated ammonium chloride solution, and extracting with ethyl acetate. Drying ($MgSO_4$), concentration and chromatography afforded the diol **110** (1.01 g, 90%).

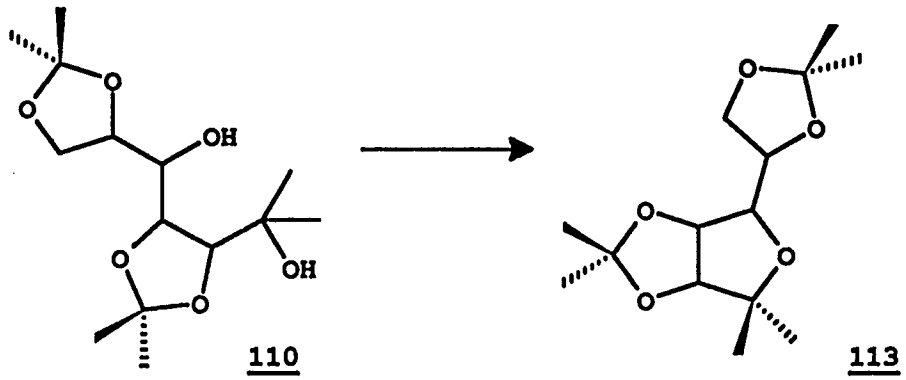
^1H NMR(300 MHz, $CDCl_3$, ppm): 4.31 (d, 1H,*J*=6.0 Hz); 4.13-4.21 (m, 2H); 4.03-4.11 (m, 3H); 3.99 (d, 1H,*J*=6.0 Hz); 3.78 (d, 1H,*J*=6.0 Hz); 1.55,1.44 (ds, 6H);1.41, 1.37 (ds, 6H); 1.35,1.34 (ds, 6H). IR($CHCl_3$, cm^{-1}); 3200-3450 (s,br).

Mass Spectrum (CI, NH_3); Calculated for $C_{14}H_{26}O_6$ (m/z 290.1). Found m/z 308.0 (M^++NH_4).


PPM
OH
OH
110
4.0
3.5
3.0
2.5
2.0
PPM
1.5
1.0
.5
0.0


WAVENUMBER CM⁻¹
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
100
90
80
70
60
50
40
30
20
10
0
OH
OH
110

1-Deoxy-3,4;6,7-di-O-isopropylidene-2-methyl-D-manno-2,5-oxolane, 113.

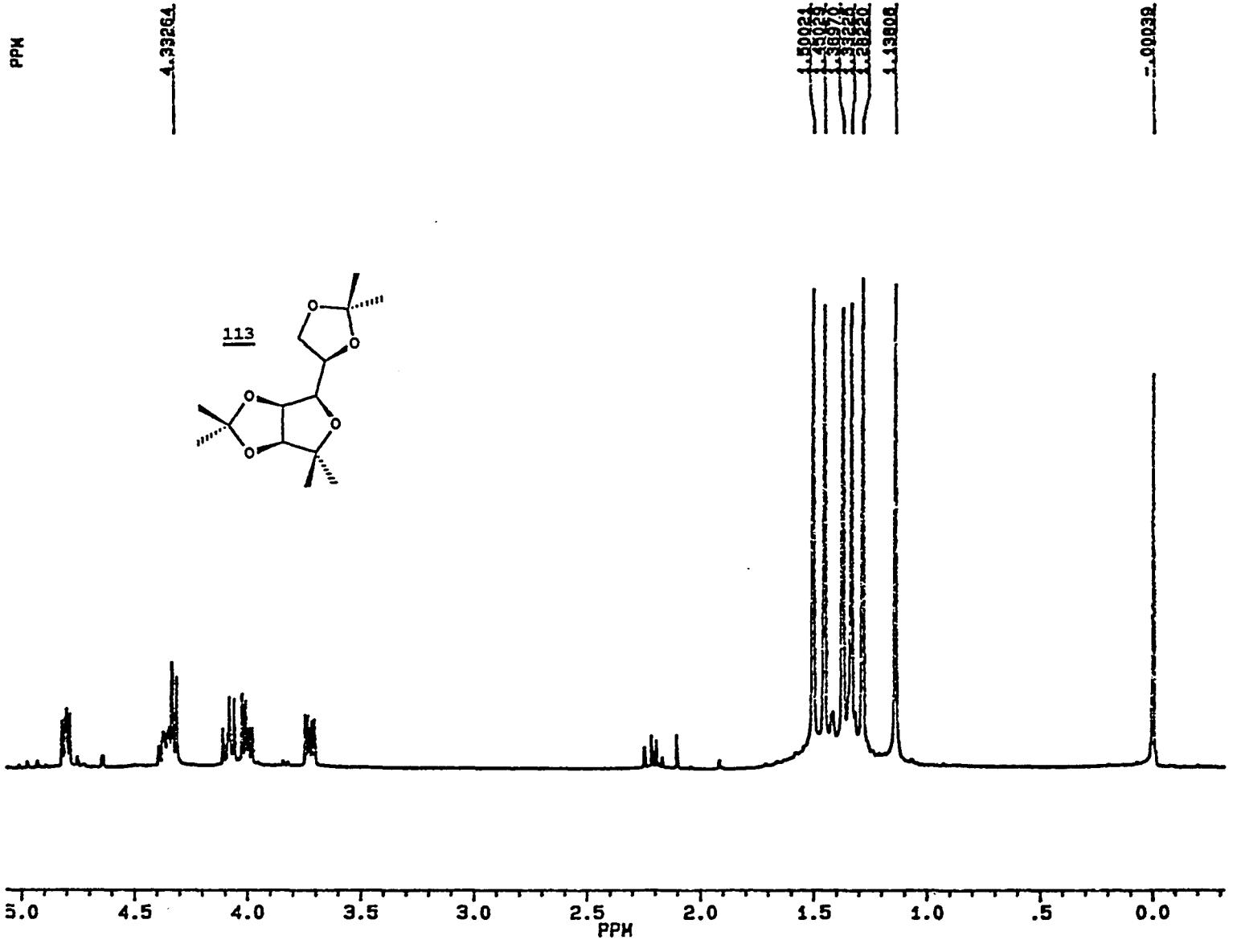


110 113

To a solution of the diol **110** (1.87 g, 6.45 mmol) in dry DMSO (20 mL) was added a mixture of 14 mL of acetic anhydride and 2.5 mL of glacial acetic acid with stirring. The reaction was allowed to stir at room temperature for 48 hours after which it was carefully poured into cold saturated aqueous sodium bicarbonate with additional stirring for one hour. Extraction with dichloromethane, washing the organic extract with dilute aqueous sodium bicarbonate and drying over anhydrous sodium sulfate, followed by concentration under reduced pressure and chromatography provided the ether **113** as the sole product (1.5 g, 85%).

^{1}H NMR(300 MHz, $CDCl_3$, ppm): 4.82, 4.80 (dd, 1H,*J*=6.0 Hz); 4.31-4.39 (m, 2H); 4.09,4.07 (dd, 1H,*J*=6.0 Hz); 4.01,3.98 (dd, 1H,*J*=6.0 Hz); 3.74, 3.71 (dd, 1H,*J*=9.0 Hz); 1.50,1.45 (ds, 6H); 1.37,1.33 (ds, 6H); 1.28,1.13 (ds, 6H).

Mass Spectrum (EI); Calculated for $C_{14}H_{24}O_5$ (m/z 272.2). Found m/z 273.0 (M^++1).


PPM
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1.45053
1.38970
1.33225
1.28220
1.13808
-.00039
113
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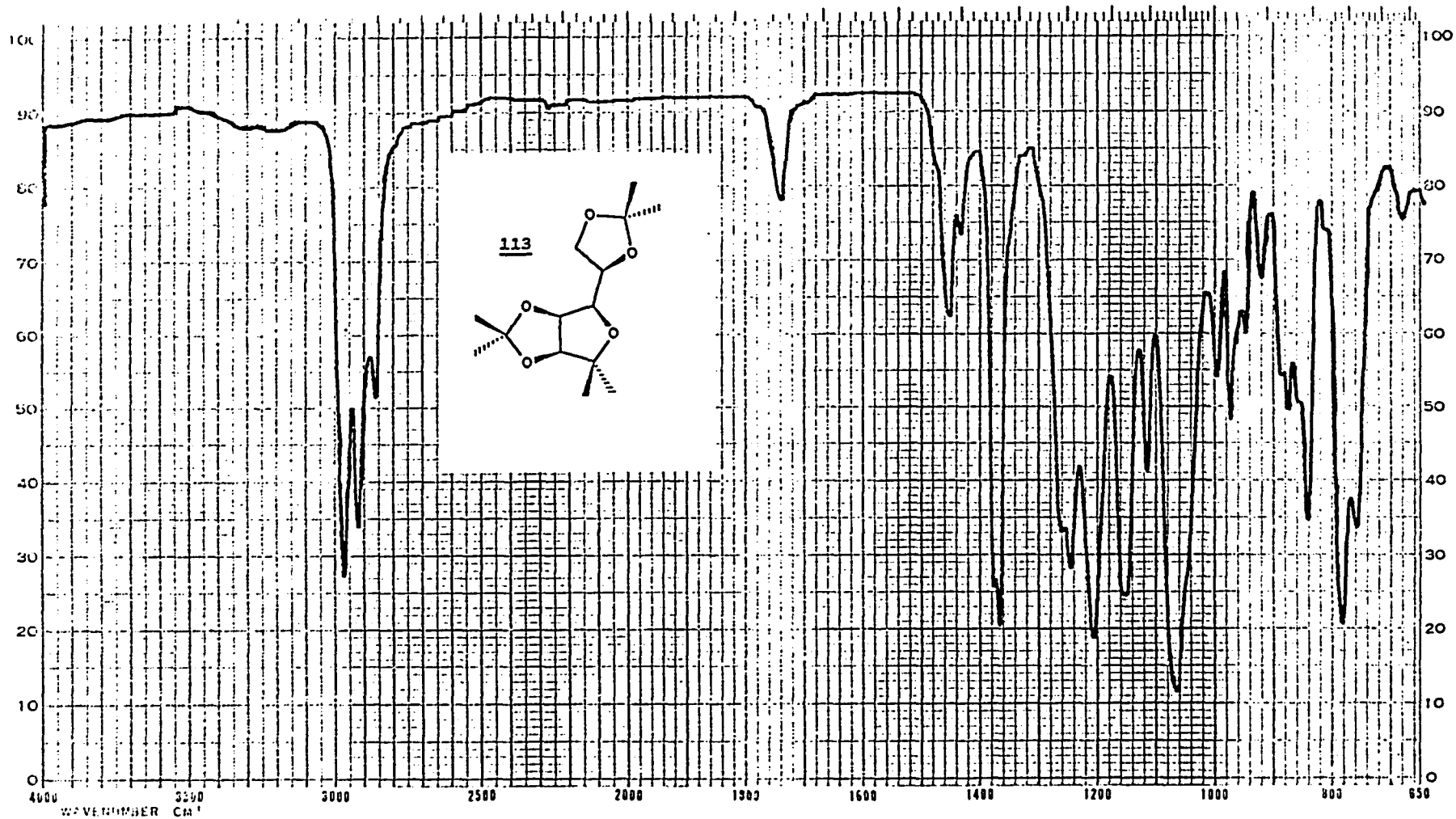
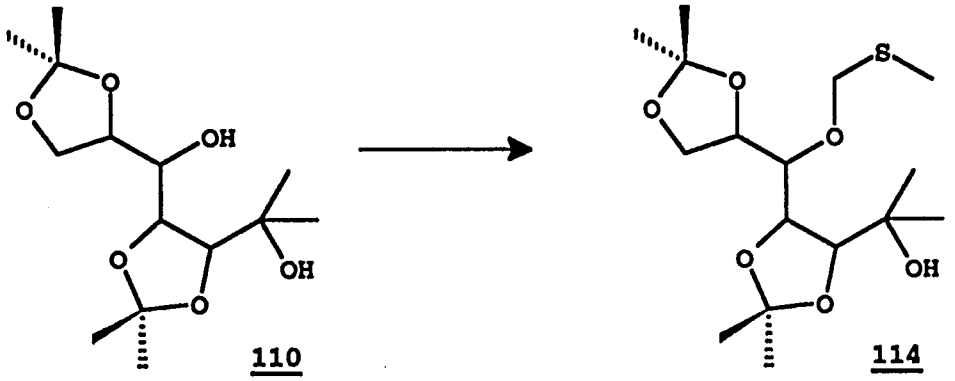
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM


113
100
90
80
70
60
50
40
30
20
10
0
4000
3500
3000
2500
2000
1500
1600
1400
1200
1000
800
650
WAVENUMBER Cm⁻¹

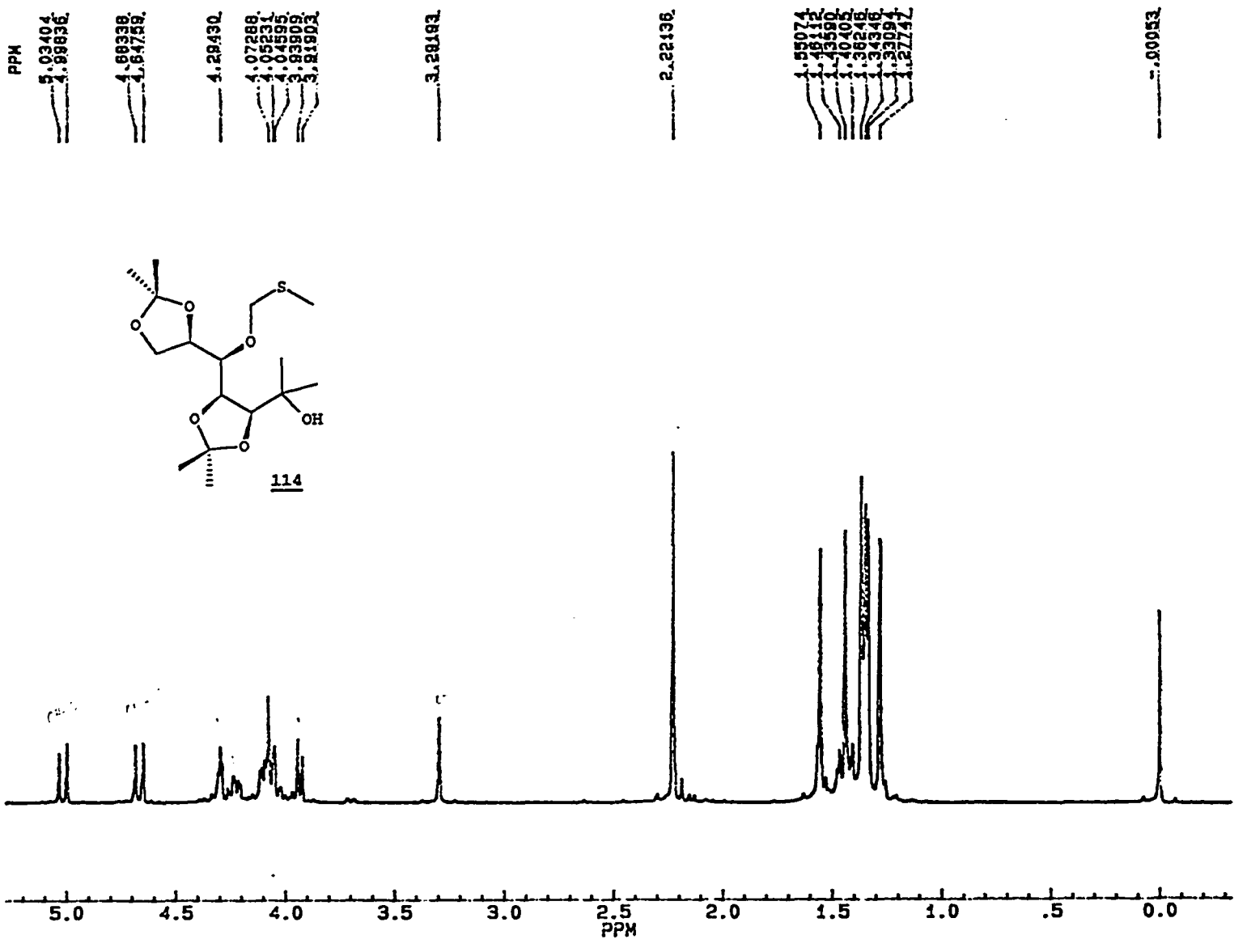
1-Deoxy-3,4;6,7-di-O-isopropylidene-2-methyl-5-O-methylthiomethyl-D-mannohepitol, 114.



110 114

To a solution of the diol **110** (0.21 g, 0.724 mmol) dissolved in THF was added sodium hydride (0.017 g, 0.73 mmol) with stirring under a positive nitrogen atmosphere. The resulting suspension was cooled to 0°C for five minutes, after which methylthiomethyl chloride (0.84 g, 0.869 mmol) was added via syringe. Stirring was continued at 0°C for 30 minutes after which time the cooling bath was removed and allowing the reaction to proceed at room temperature for 12 hours. Work-up consisted of pouring the reaction mixture into an ice-water mixture and extracting with diethyl ether. The ethereal extract was further washed with brine and dried over anhydrous potassium carbonate. Concentration and chromatographic purification afforded the ether **114** (0.22 g, 87%).

^{1}H NMR(300 MHz, $CDCl_3$, ppm): 5.02, 4.67 (dd, 2H,*J*=9.0 Hz); 4.28-4.30 (m, 1H); 4.20-4.28 (m, 1H); 4.04-4.11 (m, 3H); 3.93 (d, 1H,*J*=6.0 Hz); 3.29 (s,br, 1H); 2.22 (s, 3H); 1.55,1.46 (ds, 6H);1.40,1.36 (ds, 6H); 1.33,1.27 (ds, 6H). IR($CHCl_3$, cm^{-1}); 3500 (m). Mass Spectrum (CI, NH_3); Calculated for $C_{16}H_{30}O_6S$ (m/z 350.2). Found m/z 351.0 (M^++1), 368.0 (M^++NH_4).


PPM
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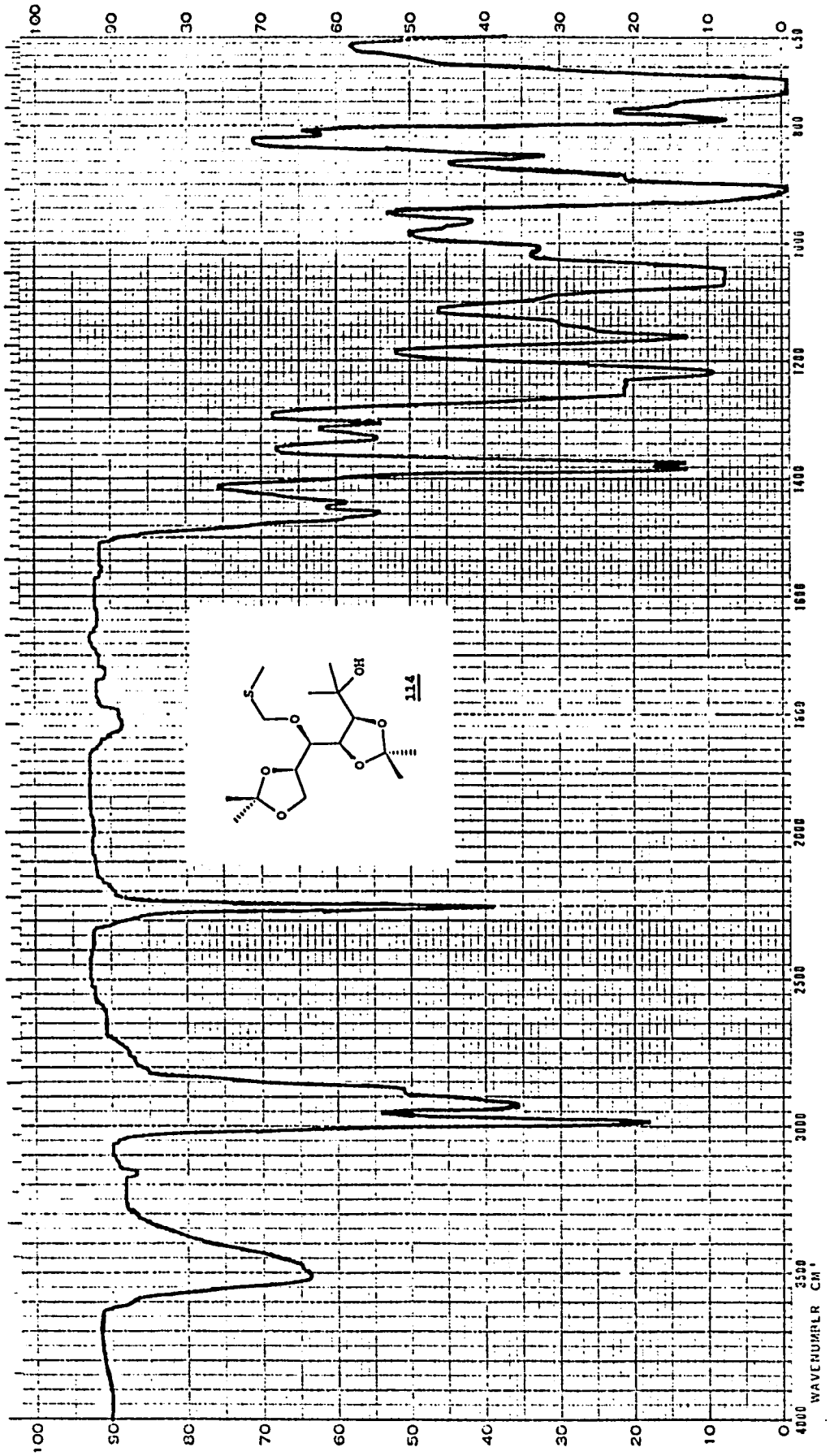
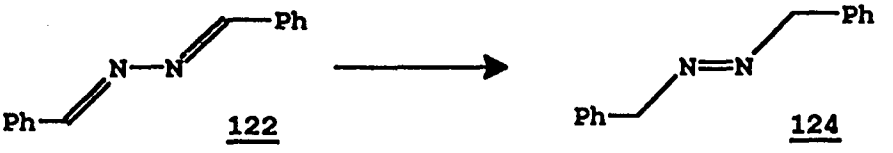
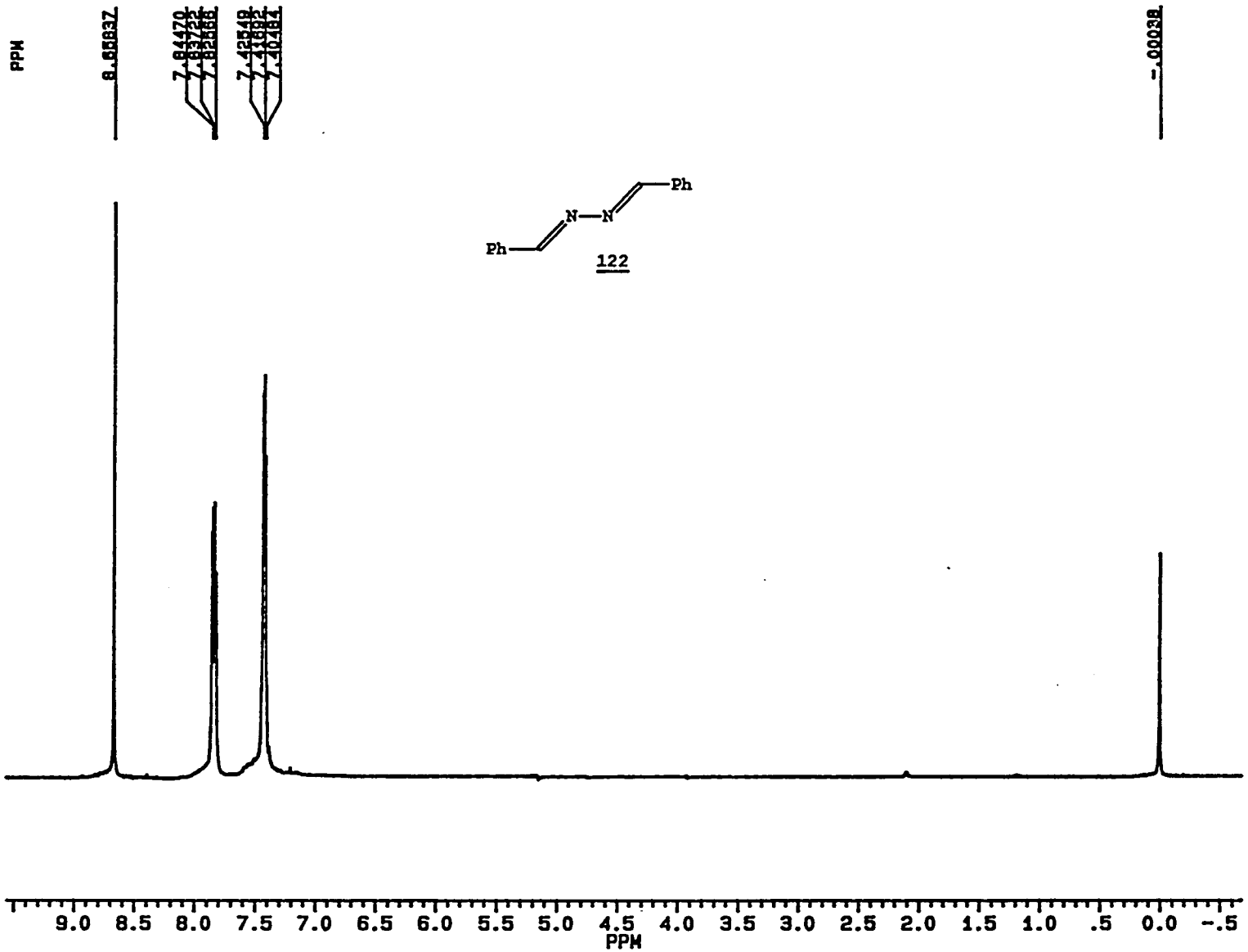
4.68338
4.64759
4.29430
4.07288
4.05231
4.04595
3.93809
3.91903
3.28193
2.22136
1.55074
1.46112
1.43590
1.40402
1.38246
1.34346
1.33094
1.27747
-.00053
OH
114
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM


114
WAVENUMBER CM'

2,3-Diaza-1,4-diphenyl-2-butene, 124.



Into a dry nitrogen flushed 100 mL three-necked flask, equipped for magnetic stirring and cooled to -78°C, was distilled 30 ml of liquid ammonia. Lithium metal (0.076 g, 11 mmol) was added as small discs while maintaining a steady stream of nitrogen. After stirring for 15 minutes, a solution of the diazene **122** (1.04 g, 4.99 mmol) in 25 mL of dry THF was slowly injected via syringe. When addition was complete, stirring was continued at -78°C for 30 minutes after which time the cooling bath was removed allowing the reaction to warm slowly to 0°C as the ammonia was simultaneously distilled off. Following the distillation of the ammonia, the reaction was quenched by rapid injection of saturated aqueous ammonium chloride. Normal workup procedure followed with extraction, drying and concentration under reduced pressure. Immediate NMR analysis of the crude product indicated the photosensitive diazacompound **124** primarily, and a trace of the starting diazene, the product of photodecomposition. ^{1}H NMR(300 MHz, $CDCl_3$, ppm):**122**; 8.65 (s, 2H); 7.81-7.84 (m, 4H); 7.40-7.42 (m, 6H); Mass Spectrum (EI); Calculated for $C_{14}H_{12}N_2$ (m/z 208.1). Found m/z 208 (M^+), 209 (M^++1). **124**; 7.12-7.52 (m, 10H); 3.78 (s, 4H).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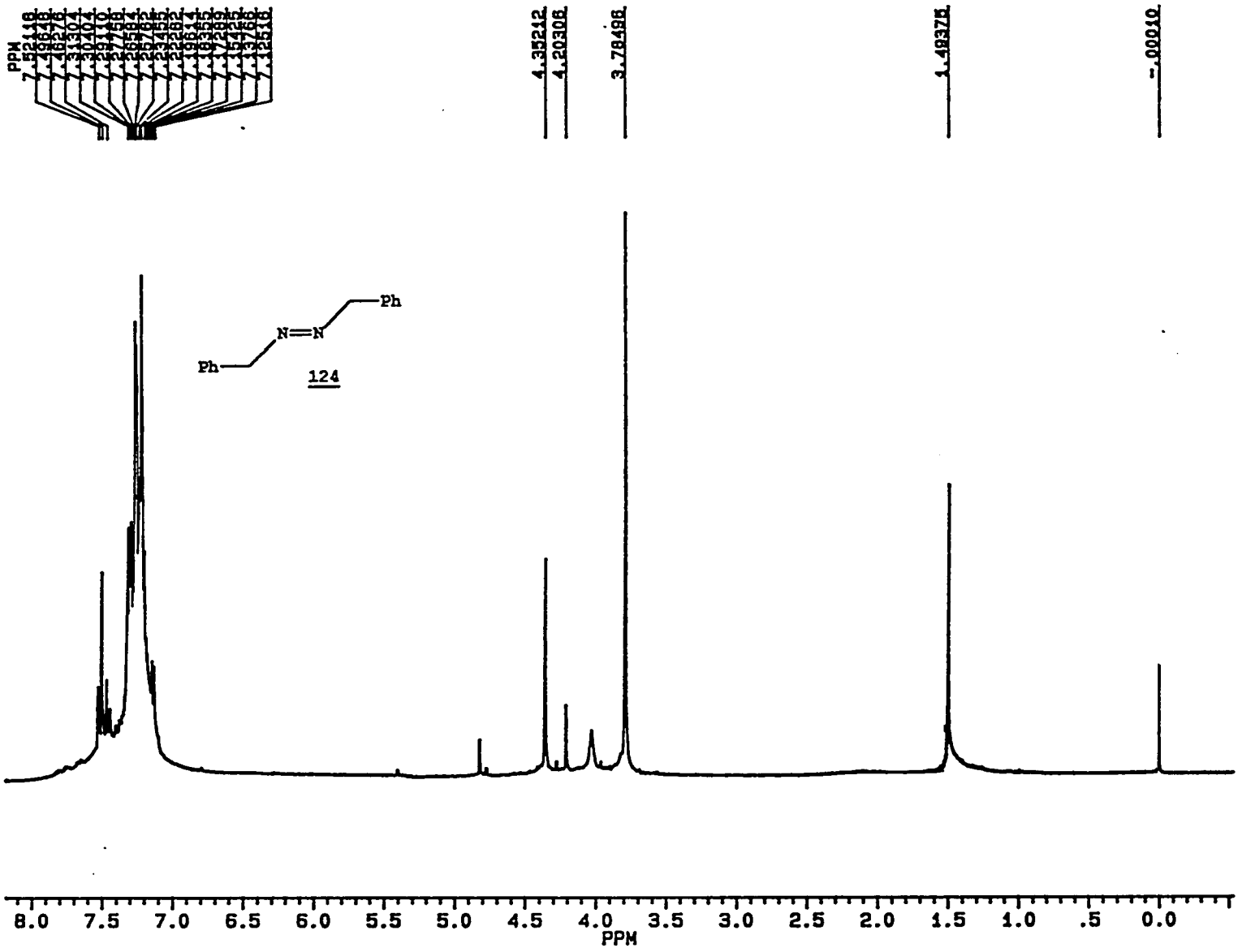
7.42549
7.41803
7.40384
-.00038
Ph
N
N
Ph
122
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 .5 0.0 -.5
PPM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7.19614
7.18365
7.17289
7.15425
7.13766
7.12510
4.35212
4.20308
3.78498
1.49375
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Ph
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Ph
124
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7.5
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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
PPM

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   (b) Stang, Hanack, Subramanian, *Synthesis*, **1982**, 85-126.
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   (b) Rickborn, B.; Thummel, R. *J. Org. Chem.*, **1969**, *34*, 3583.
   (c) Rickborn, B.; Thummel, R. *J. Org. Chem.*, **1971**, *36*, 1365.
   (d) Crandall, J. K.; Chang, L-Ho. *J. Org. Chem.*, **1967**, *32*, 532.
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   (b) Gagnieu, C. H.; Grouiller, A. V. *J. Chem. Soc., Perkins Trans. I*, **1982**, 1009.
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CHAPTER 7

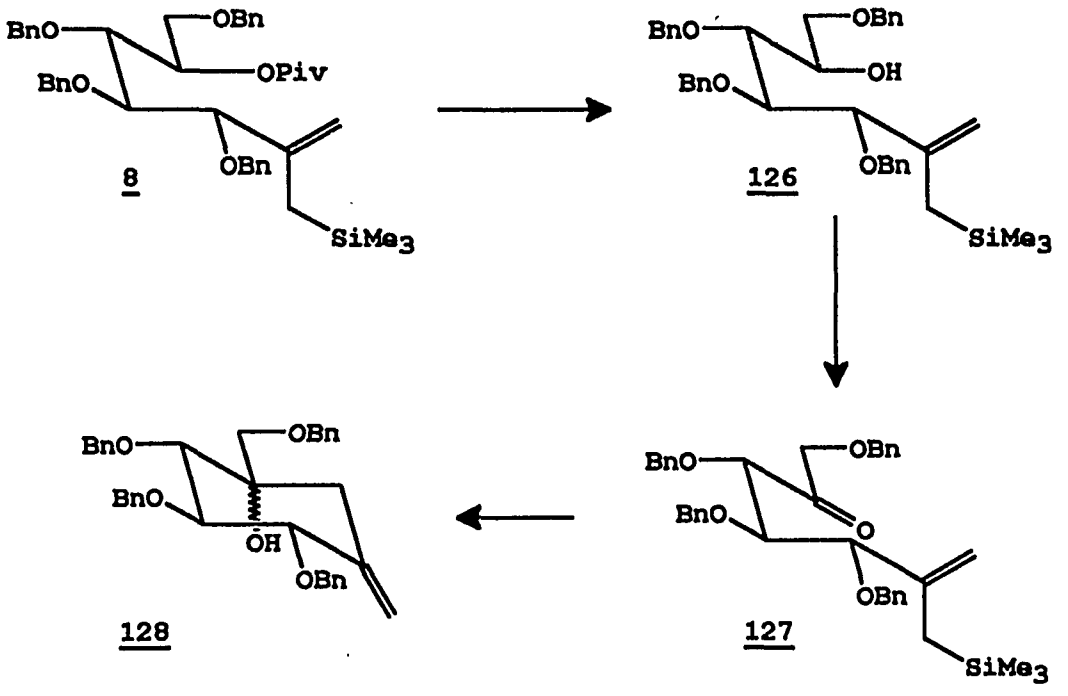
7.0.0. Selective Pivalate Hydrolysis

7.1.0. Introduction

In the early stages of our synthetic investigations, the need arose for an *O*-acyl protecting group that would not migrate readily and would be easily detectable by p.m.r. spectroscopy. These features have been reported for the pivaloyl group in selective acylations of nucleosides and partially protected D-mannitols, and in isomerization studies of 2- and 3-*O*-acyl-uridines[1]. Hough *et al.* have shown the high selectivity of pivaloyl chloride in the esterification of sucrose by which he prepared a variety of derivatives[2]. Thus the pivalate ester was utilized as the choice protecting group in a number of our synthetic intermediates. Bearing in mind the fact that this group must be easily removed at specific points in our synthesis, it was necessary for us to identify a facile, yet mild procedure for its cleavage. It was important for us to achieve this objective since we planned on extending our work on saccharidic allylsilanes into the synthesis of chiral carbocycles, Scheme 1.

Among the methods reported, the more versatile procedures include the use of hydroxide in methanol, methanolic sodium methoxide, methylamine in ether solvent[3], and hydrazine acetate[4]. Considering the reactions depicted in Scheme 1 below, it was immediately obvious that the first two methods would have been unsuitable because of the high sensitivity of our allylsilane moiety. Applying the latter reagents in addition to other hydrazine salts thus seemed to be the logical starting point for our investigations.

SCHEME 1



7.2.0. Hydrolysis of Tri-*O*-pivaloate 95.

The tripivaloate ester 95, which was obtained in multigram quantities from the esterification of 4,6-*O*-benzylidene glucopyranose, provided us with a suitable substrate for our studies. In addition to its availability, compound 95 would have allowed us to gain some interesting insights into the relative ease of hydrolysis of the triesters of these sugar derivatives. From our esterification studies, (Chapter 5), we demonstrated that the β-anomeric hydroxyl group was most reactive towards esterification by the acylpyridinium ion, and that the C(2) hydroxyl group was slightly more reactive than the C(3) hydroxyl group. The β-effect concept coupled with the idea of the C(1) pivalate acting as a proton acceptor site was adopted in rationalizing this observed selectivity[5].

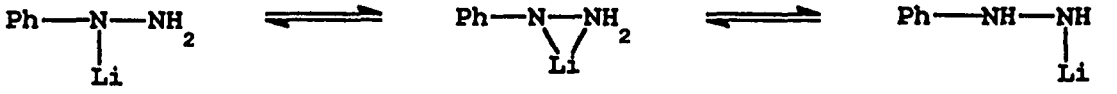
Our initial attempts at hydrolysis involved stirring compound **95** with aqueous hydrazine at room temperature. No cleavage was observed. The use of ammonia derivatives and various hydrazine salts in THF, and in *t*-butanol proved to be unsuccessful in removing the pivalate group. Stirring the substrate with anhydrous potassium carbonate suspended in methanol was also to no avail. Treating **95** with methanolic ammonia at room temperature also resulted in a 100% recovery of the starting material. At this point, we resorted to the use of phenylhydrazine in different solvents. Schumann *et al* in their syntheses of peptides, demonstrated that the phthalyl group of *N*-phthalyl derivatives of amino acids and peptides, can be removed in one step by heating in alcoholic solution with phenylhydrazine and a tertiary base[6]. In spite of the fact that these reactions were performed on *N*-phthalyl derivatives, we reasoned that similar results should be obtainable with our pivalates, being *O*-acyl derivatives.

Compound **95** was stirred with two molar equivalents of freshly distilled phenylhydrazine and one equivalent of triethylamine in 95% ethanol at room temperature for up to five days. No hydrolysis was observed. The reaction was repeated under reflux, while monitoring the course of the reaction by T.L.C. Again there was no observable hydrolysis, the starting compound was recovered with slight decomposition of the phenylhydrazine. Other investigations include performing the reaction in *t*-butanol, THF and toluene, all at room temperature and then under reflux. The starting material was recovered in all cases. It was clear that a more rigorous method of hydrolysis was needed.

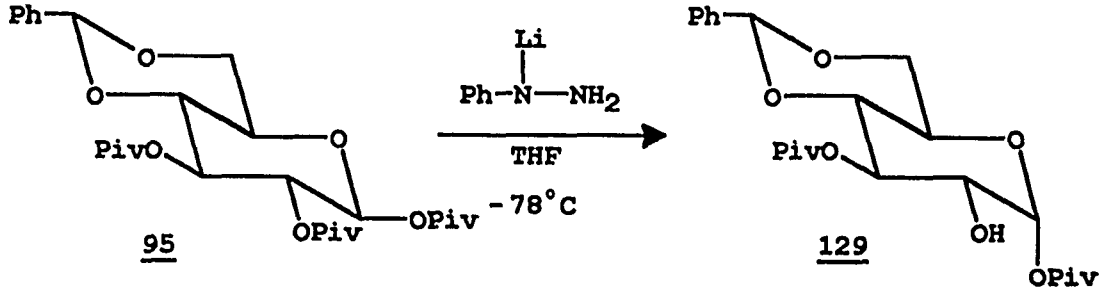
Phenylhydrazine was converted to its lithium salt by reacting with *n*-butyl lithium in THF. Lithiation was undisputably indicated by the deep red color imparted to the reaction medium. Scheme 2 shows three lithiation species that could have resulted. It was also likely that the nucleophile could have formed dimeric or even tetrameric species. Whatever was the nature of this nucleophile, we subsequently demonstrated that this was indeed a very powerful base.

A solution of the compound 95 was thus introduced which resulted in cleavage of the anomeric pivalate ester group, Scheme 3, followed by the unusual O(2) - O(1) pivalate migration.

SCHEME 2

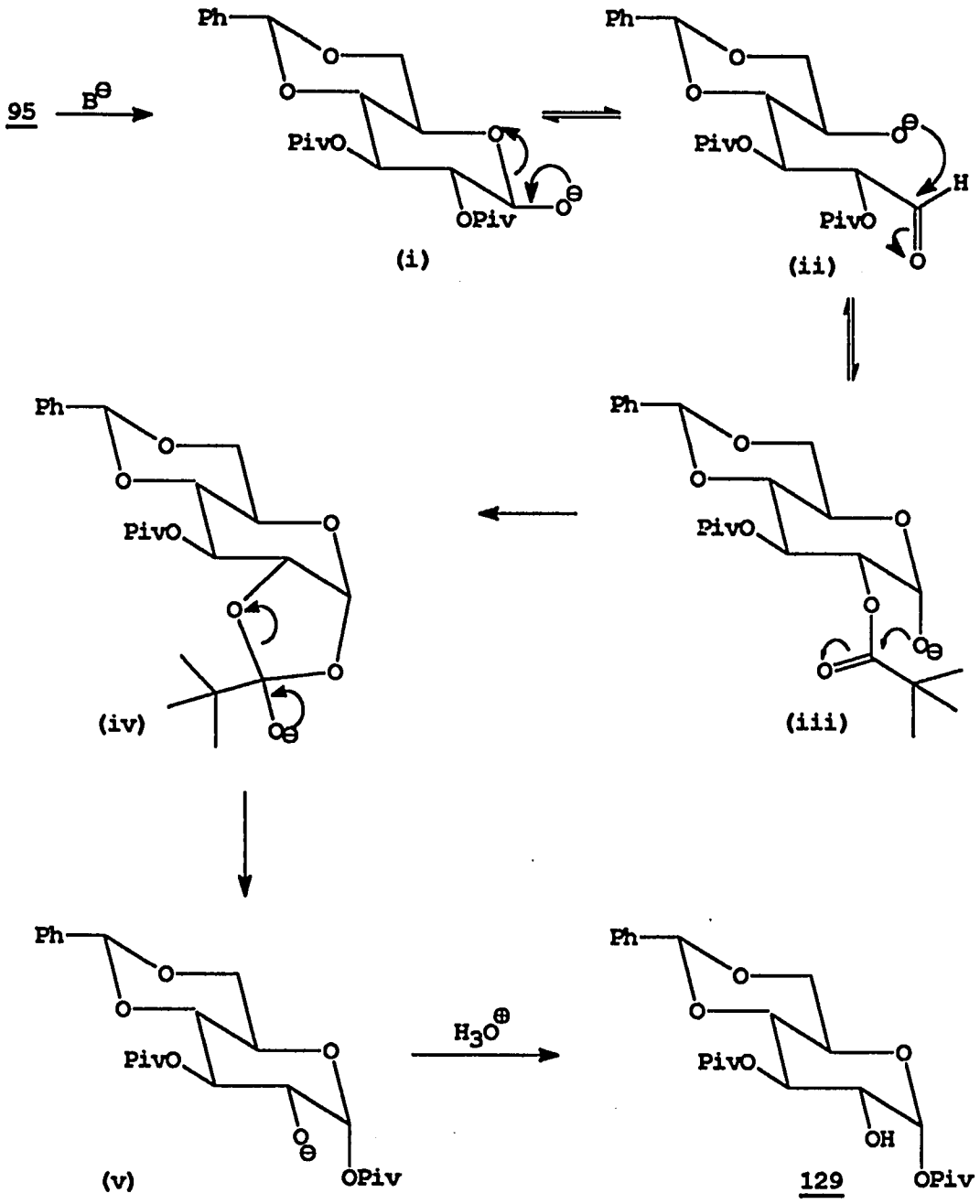


SCHEME 3



Our rationale that it was the anomeric ester group that was attacked by the nucleophile was based on the fact that we isolated the α-1,3-*O*-dipivalate 129 exclusively. Thus cleavage at C(1) must have been followed by a (2)-(1) migration of the C(2) pivalate group. Scheme 4 depicts a possible mechanism through which this observed migration might have occurred. Thus equilibration of the initially formed β-alkoxide to the more stable α-alkoxide was followed by a facile intramoleclar nucleophilic attack by this high energied intermediate. On work-up the newly formed secondary alkoxide was protonated to give the C(2) alcohol. These results unequivocally demonstrated that for the compound 95, the C(1)-ester group was most labile to basic hydrolysis.

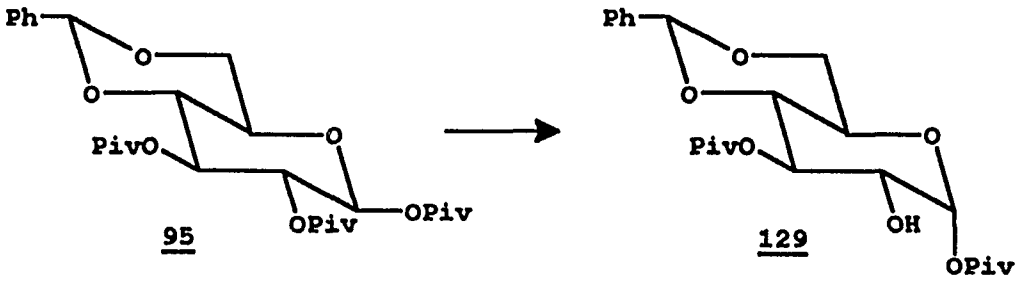
SCHEME 4



To conclude our investigations, we repeated the reaction using two molar equivalents of the base. As anticipated, a mixture of the C(3)-monopivalate, the α-1,3-dipivalate, and a small amount of the starting material **95** was obtained by NMR analysis.

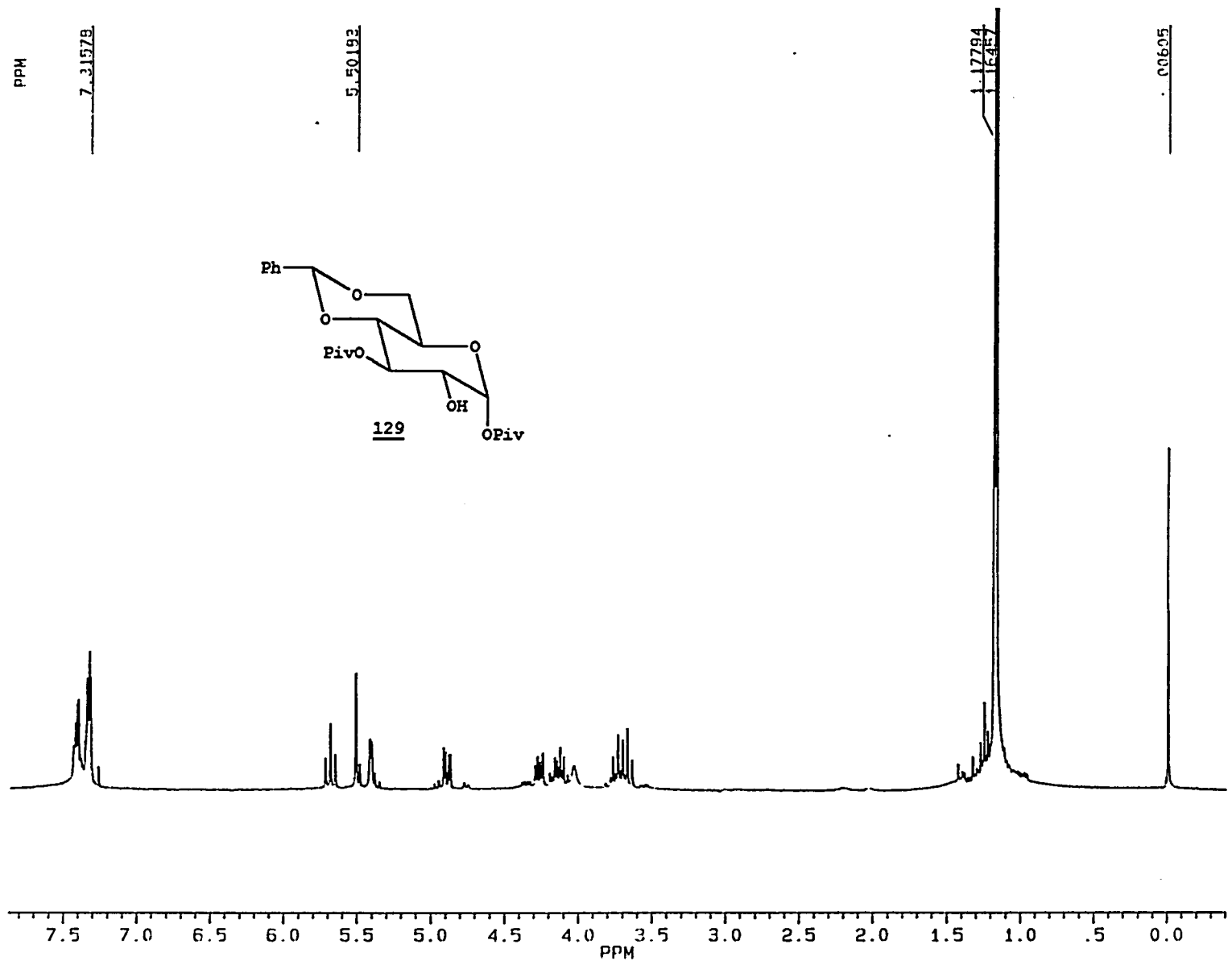
SPECIFIC EXPERIMENTALS

4,6-O-Benzylidene-1,3-di-O-pivaloyl-α-D-glucopyranoside, 129.



A solution of *n*-butyl lithium (4.22 mmol) in hexanes was cooled to 0°C, to which was added dropwise, a solution of phenylhydrazine (0.831 g, 3.84 mmol) in 10 mL of dry THF with stirring for twenty minutes under a positive pressure of dry nitrogen. The cooling bath was removed allowing the reaction mixture to warm slightly with continued stirring for thirty minutes. The reaction mixture was again cooled, to -78°C allowing for temperature equilibration. A solution of the tripivalate ester **95** (2.0 g, 3.84 mmol) in THF (20 mL) was then added dropwise with efficient stirring during five minutes. The reaction was allowed to proceed at -78°C for three hours after which time the cooling bath was removed and stirring was continued overnight at room temperature. Work-up consisted of stirring with cold saturated aqueous ammonium chloride. Extracting with ethyl acetate, drying ($MgSO_4$), concentrating and chromatographing (hexanes:EtOAc ; 5:1) afforded the α-1,3-*O*-dipivalate **129** (1.45 g, 86%). M.p. 168-170°C.

^{1}H NMR(300 MHz, $CDCl_3$, ppm): 7.30-7.45 (m, 5H); 5.67 (t,1H) C(3)H; 5.50 (s, 1H) benzylidene; 5.40 (d, 1H,$J_{1,2}$=3.0 Hz) C(1)H; 4.88, 4.86 (dd, 1H,$J_{2,1}$=3.0 Hz, $J_{2,3}$=12 Hz) C(2)H; 4.27, 4.24 (dd, 1H,J_{ab}=9.0 Hz, $J_{6,5}$=6.0 Hz) C(6)H_{eq}; 4.06-4.15 (m, 1H) C(4)H; 4.02 (s,br, 1H) OH; 3.62-3.75 (m, 2H) C(6)H_{ax} C(5)H; 1.17, 1.16 (ds, 18H) 2(CH_3)$_3$C. Mass Spectrum (EI); Calcd. for $C_{23}H_{32}O_8$ (m/z 436.2). Found m/z 437.3 (M^++1).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1.16457
.00605
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O
PivO
OH
OPiv
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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
PPM

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