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A molecular orbital study of diastereofacial selectivity in the diels alder reaction and glycosidation via glycals and aryl(bisarylthio)sulfonium salts: Effect of nucleophile and aryl substitution on face selectivity

Kaila, Neelu, Ph.D.

City University of New York, 1991

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AND

GLYCOSIDATION VIA GLYCALS AND ARYL(BISARYLTHIO)SULFONIUM SALTS: EFFECT OF NUCLEOPHILE AND ARYL SUBSTITUTION ON FACE SELECTIVITY

by

NEELU KAILA

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

1991

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

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Date

Richard V. Francke

Chairman of Examining Committee

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The City University of New York

Abstract

A MOLECULAR ORBITAL STUDY OF DIASTEREOFACIAL SELECTIVITY IN THE DIELS ALDER REACTION

AND

GLYCOSIDATION VIA GLYCALS AND ARYL(BISARYLTHIO)SULFONIUM SALTS: EFFECT OF NUCLEOPHILE AND ARYL SUBSTITUTION ON FACE SELECTIVITY

by

Neelu Kaila

Advisor: Professor Richard W. Franck

Part 1: The AM1 molecular orbital method is used to predict the face selectivity for six different Diels-Alder reactions of dienes bearing stereogenic allylic substituents. The predictions are based upon fully optimized and fully characterized transition states for each possible conformation of the 12 different transition states. The AM1 RHF method with complete geometrical optimization, is found to be adequate for predicting the face selectivities of reactions studied. Agreement with the available experimental literature is quite satisfactory. No single effect seems to dominate the predicted selectivities. They appear to result from a combination of electronic and steric interactions.

Part 2: Aryl(bisarylthio)sulfonium salts are found to be exceptionally useful reagents for glycosyl transfer of glucal to a variety of hydroxyl transfer donors. These are β selective reagents giving 2-arylthio substituted 2-deoxy-β-

glucopyranosides. The method works for both phenols and acyloins (models for aureolic acid synthesis) as well as the more common primary and secondary sugar alcohols. The substituents on the phenyl ring of the aryl(bisarylthio)sulfonium salts are varied. The face selectivity depends on the nature of the nucleophile and the thiosulfonium reagent. The p-methylphenyl{bis(p-methylphenyl)thio}sulfonium salt is the most β-selective reagent. The sulfonium salt glycosidation procedure is used for the synthesis of the 2-deoxy-1-O-{3'-(2'-deoxy-1'-O-methyl)-β-D-rhamnopyranosyl}-β-D-rhamnopyranoside, the C'-D' ring analog of aureolic acid.

This work is dedicated to

my husband and parents

for their tremendous support and encouragement throughout this work

Acknowledgements

I wish to express my deep sense of gratitude to Prof. R. W. Franck for his invaluable guidance, patience and encouragement throughout this work. I am grateful to Prof. J. J. Dannenberg for his guidance. I thank Dr. M. Blumenstein for his help in NMR experiments and Prof. Franck's group: Drs. R. B. Gupta, S. Ramesh and G. Grewal, A. Chowdhury, H. Yin, T. Nicolas, C. Soll for many helpful discussions and suggestions. Some of the compounds prepared by S. Mehboob were very helpful and I am thankful for his contribution. Finally I wish to express my gratitude to my husband Gurmit for his love, support and inspiration.

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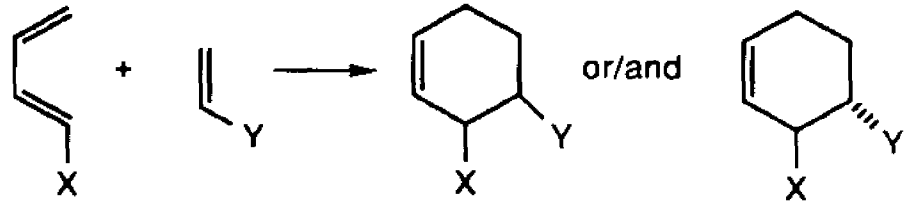
PART 1

A MOLECULAR ORBITAL STUDY OF DIASTEREOFACIAL SELECTIVITY IN THE DIELS ALDER REACTION

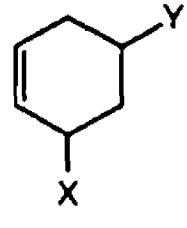
Introduction

The Diels-Alder reaction takes place between a diene and dienophile to form six membered rings with remarkably high stereo- and regioselectivity (Figure 1). This reaction has distinctive characteristics such as the formation of 3,4 disubstituted cyclohexene rather than 3,5 disubstituted cyclohexene products and in the majority of the cases formation of the more crowded *endo* adduct instead of the less encumbered *exo* product. The preeminent position held by the Diels-Alder reaction in organic synthesis can be understood from the numerous papers and reviews in recent years about the synthetic and mechanistic aspects of this reaction.[1]



Endo *Exo*

3,4 disubstituted products



3,5 disubstituted product

Figure 1. Diels-Alder reaction

The most common approach for obtaining facial selectivity in intermolecular cases is to link the diene or dienophile to a chiral auxiliary. Ideally, the auxiliary blocks one face of the diene or dienophile, a face selective cycloaddition takes place, the auxiliary is removed and one obtains an adduct enriched in one enantiomer (Figure 2A). An alternate approach is to use a chiral Lewis acid.[2]

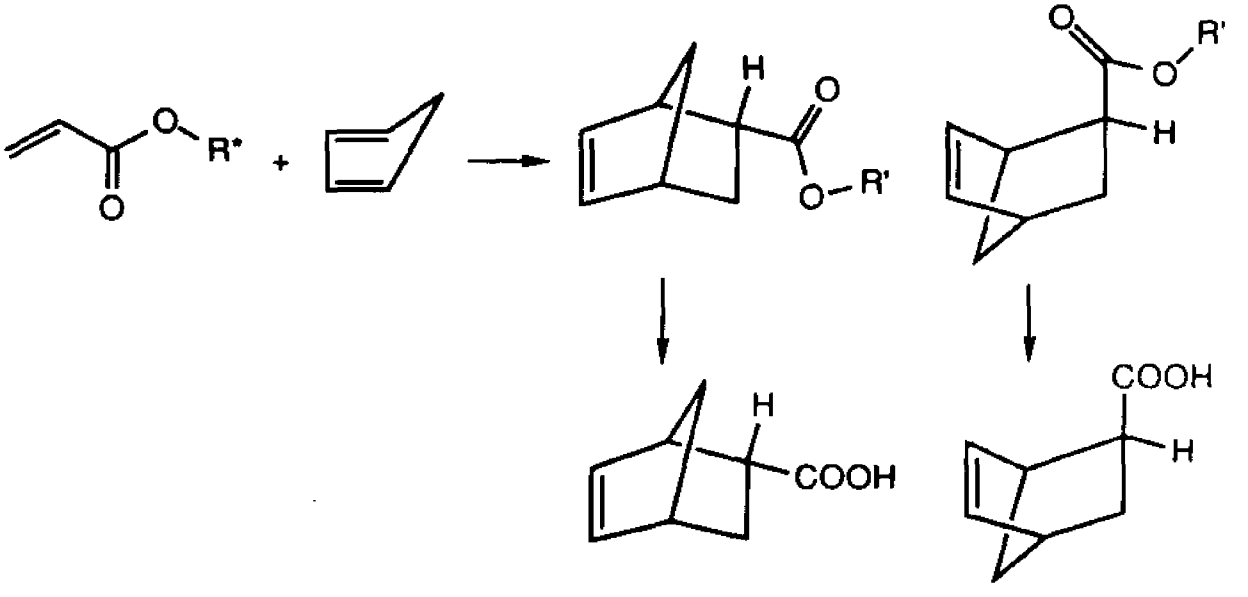


Figure 2A. Face selective cycloaddition using a chiral auxiliary

A third approach to face selectivity is to incorporate a stereogenic center within the diene or dienophile, usually at an allylic position. The product of cycloaddition are diastereomers and remain so because the stereogenic center is built into the product (Figure 2B). Usually heteroatom substitution at the allylic position exerts a pronounced effect on diastereoselectivity.[3]

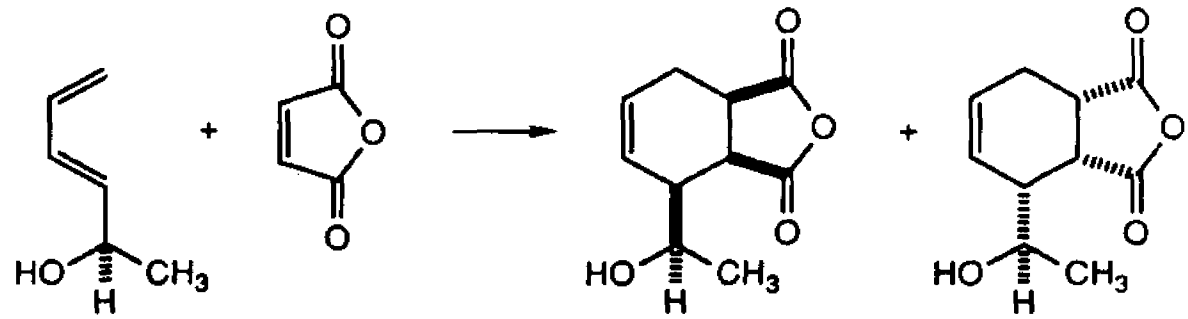
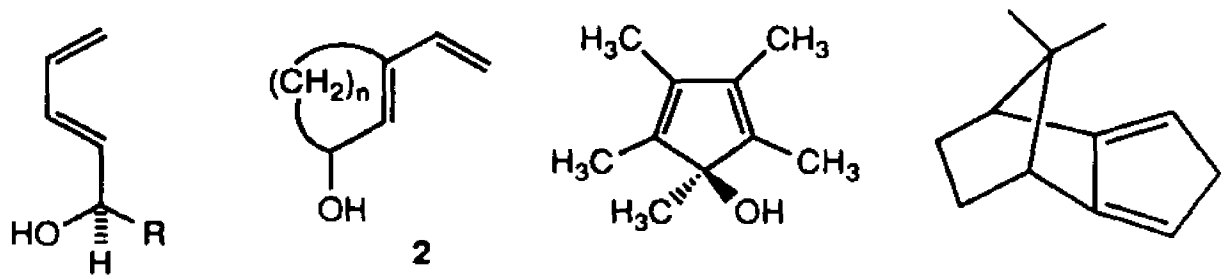


Figure 2B. Face selective cycloaddition using a chiral center within the diene

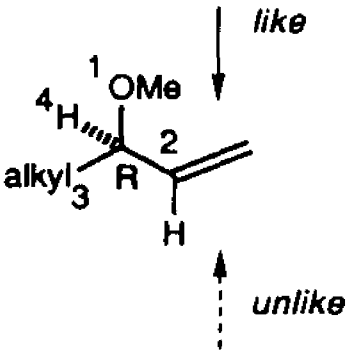
The recent interest[4] in face selectivity of the Diels-Alder reaction has focussed on three sets of experimental results for acyclic **1**,[5] semicyclic **2**[6] and cyclopentadienes **3**.[7] In addition, there have been extensive studies in the isodicyclopentadiene series **4**.[8]



1 **2** (n=2; n=3) **3** **4**

To be consistent, we define the configuration of the allylic center by always assigning the sp^2 carbon of the double bond a higher priority than the sp^3 carbon attached to the allylic center (shown in **5**). Also, in defining the facial configuration of the double bond, we always assign the priority of the allylic carbon as 1 and the vinylic carbon as 2 (shown in **6**). Thus the top face in **6** where groups are oriented clockwise is the *re* face and the alternative arrangement in the bottom face of **6** comprises the *si* face. We use the Seebach-Prelog convention[9] to describe the relative topicities of the approach

or addition to the face of an enantiomer, e.g. addition to the *si* face of the double bond with an adjacent 'R' allylic center is *unlike* (ul).



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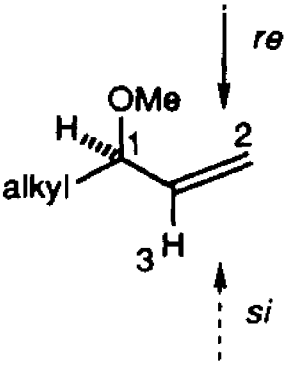
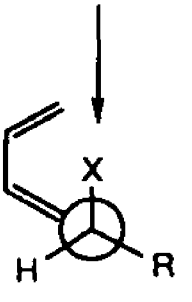


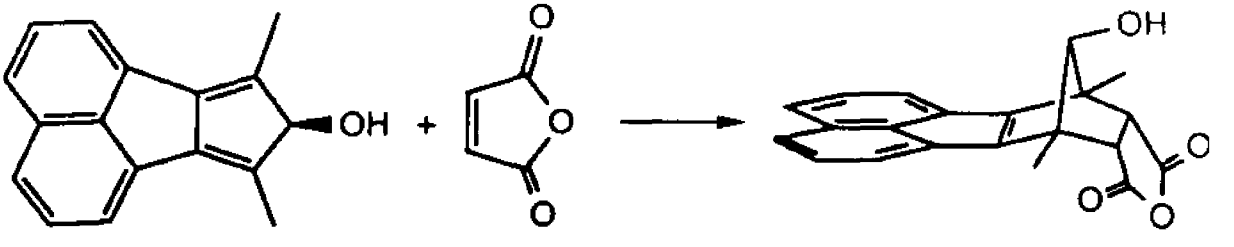
6

Three distinct methods have been used to interpret the observed face selectivities. Recently Hehre and Kahn have proposed a theory based on electrostatic attraction and repulsion of the reactants to rationalize the face selectivity in Diels-Alder reactions bearing allylic dienes and dienophiles.[10] Their theory states that, cycloadditions involving electron rich dienes and electron poor dienophiles should occur preferentially onto the diene face which is more nucleophilic and the dienophile face which exhibits greater electrophilicity. In their model, the alkyl and the hydrogen substituents of the allylic group remain somewhat in the plane of the double bond of diene or dienophile whereas the heteroatom substituted group remains perpendicular to the plane (7).



7

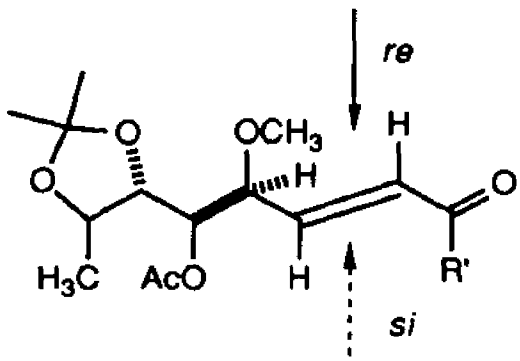
Thus, two faces of the diene or dienophile are electronically unequivalent and any attack from the top or bottom of the diene or dienophile plane (parallel to the hetero substituted group) will be controlled by the electrostatic attraction or repulsion with the hetero substituted group. For example, if the hetero atom is electron rich (O, N) then the dienophile, being electrophilic will attack the allylic diene from a face *syn* (*like*) to hetero atom due to an electrostatic attraction between the hetero atom and the dienophile. They have further suggested that if the hetero atom becomes electropositive then the dienophile will approach from the face *anti* (*unlike*) to the hetero atom due to electrostatic repulsion between the electropositive hetero atom and the dienophile. Similarly, the attack of the diene on a dienophile bearing the allylic center is also controlled by the electrostatic factor and the diene being nucleophilic in nature should show opposite facial preference. For e.g. maleic anhydride adds to a 1-hydroxycyclopenta-2,4-diene, **8**, syn to the hydroxyl group.



8

A second rationale is based on the idea that the stereogenic center has different conformations best suited to interact with the HOMO or the LUMO of the substituted reactant.[11,12] Franck's group had explained the diastereoselectivity observed in the reaction of sugar derived chiral allylic dienophile **9** with diene **10** by assuming an attack of the diene on a face opposite to allylic alkoxy

function of the chiral dienophile.[13] Thus, the allylic carbon bearing an 'R' chiral center directed diene approach from the *si* face of the dienophile.



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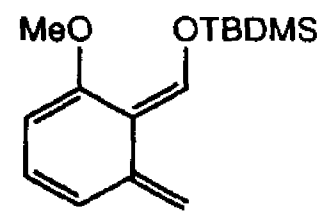

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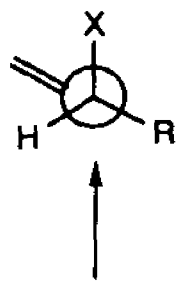
Subsequent work on intermolecular Diels-Alder reactions[14] and dipolar cycloaddition reactions[15] extended this trend for the dienophile viz. an R derived group favored *si* face attack (*unlike*) whereas an S derived group favored *re* face attack (*unlike*). Experimental results from Franck's laboratory[11] and from other workers[16] showed that the same chiral center favored opposite face selectivities in the diene and dienophile. Considering the reactivity of the diene being HOMO controlled and that of the dienophile being LUMO controlled a selection rule was proposed to rationalize the diastereoselectivity.[11] Two different rotamers of the bond connecting the allylic chiral carbon to the sp^2 carbon were considered to be responsible for the diene and dienophile selectivity. For the case of dienophile rotamer **11**, the hetero group (x) remains perpendicular to the double bond, and therefore stabilizes the LUMO of the dienophile, and increases its reactivity. The bulk of X requires that the opposite face is attacked. The HOMO of the diene was suggested to be more reactive via rotamer **12**, where the hetero atom remains orthogonal to the π system because a rotamer of type **11** would increase the stability of HOMO which would

increase the energy gap between the HOMO of the diene and the LUMO of the dienophile resulting in decrease in reactivity of the system. Thus based on a limited number of results an empirical rule had been suggested which can be stated as: the allylic center next to a diene and a dienophile will direct opposite diastereochemical outcomes in a Diels-Alder reaction. McDougal and coworkers have done experiments using dienes with substituents at 2-position to support the idea that rotamer **12** is the reactive one.[17] Recent work by Franck's group has shown that a simple theoretical argument limited to the diene conformation alone cannot explain the observed diastereoselectivity.[5a]



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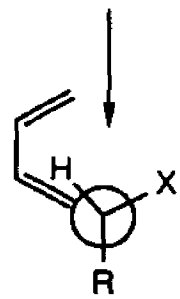
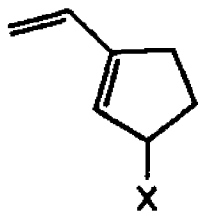
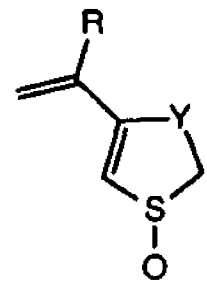


12

Overman and Hehre have studied the face selectivity in Diels-Alder reactions of semicyclic dienes **13** and **14** (type **2**, n=2) with N-phenylmaleimide(NPM) and tetracyanoethylene. In all cases but one, cycloaddition was observed preferentially from the diene face opposite to the allylic substituent. The workers suggested that in case of diene **13** (X=Me) the *endo syn* transition state (**15**, X=C, R'=CH_3) was disfavored because of simple destabilizing steric interactions between the dienophile and the allylic methyl group. For dienes with vinyl sulfinyl or allylic ether substitution they attributed the face selectivity to non bonded electrostatic interactions between the allylic hetero atom and the dienophile in the *syn* transition states.[6a]

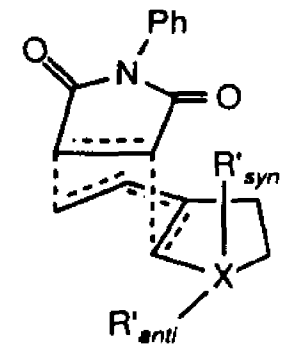


13 X = Me, OH, OMe, OtBDMS



14

R	Y
H	C
H	O
CH_3	O



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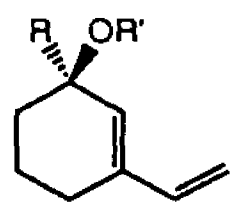


R = H, Me
R' = H, Me, TMS

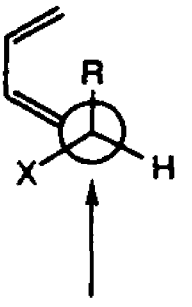
16

Franck's group has rationalized their results for dienes of type **2** (n=3) solely on steric arguments.[6b] They have studied the Diels-Alder reaction of allylically substituted vinyl cyclohexenes **16** with NPM, dimethyl acetylenedicarboxylate and N-phenyltriazolinedione. In all the examples studied the results suggested that the size of the R and OR' groups controlled the face selectivity of the Diels-Alder reaction.

Recently Cieplak, Tait and Johnson have used the concept of transition state stabilization by σ electron donation into the vacant σ* orbital associated with the incipient bond to account for axial attack of cyclohexanones[18] and *syn* approach of butadiene to 5-fluoro-admantane-2-thione.[19] In his work on cyclopentadienes, Fallis has used this version of Cieplak's theory, that is, the

cycloaddition occurs preferentially from the opposite side of the substituent which is the best electron donor so that the developing σ^* orbital can be stabilized by hyperconjugation.[7] In the isodicyclopentadiene series, the concept of orbital tilting or pyramidalization of the diene in the ground state led naturally into stabilizing one of two possible transition states because of better HOMO-LUMO overlap.[8] The idea of orbital tilting is that the σ/π interactions cause the rotation of the $p\pi$ lobes at the active centers thus controlling selectivity. A third approach is to directly calculate the transition states (TS) for the cycloaddition to both possible faces of the π system perturbed by the adjacent stereogenic center. This approach is the subject of this thesis.

There have been many calculations of the Diels-Alder transition state (discussed below); however the effect of a noncyclic stereogenic center on face selectivity has not been studied in the past. Some closely related calculations have been done by Houk and Liotta.[20,22] Houk studied the transition states for the 1,3 dipolar cycloaddition of fulminic acid to an acyclic ethylene and an adjacent chiral center using a blend of ab initio and MM2 calculations. He noted that the preferred conformation of the stereogenic center in the transition state had the hetero atom directed toward the group attached to the distal sp^2 carbon (**17**). Face selectivity was controlled by minimization of steric hinderance to approach of fulminic acid by the remaining groups of the chiral carbon.[20] Houk has also applied this approach to the isodicyclopentadiene problem.[21] Liotta applied MINDO/3 calculations of transition states to Diels-Alder reactions involving dienophiles with stereogenic centers within cyclic systems. The energies of single transition states of two diastereomeric dienophiles were compared to predict their relative reactivities.[22]



17

Dannenberg and Oliva's group[23] have used the AM1 and MNDO semiempirical molecular orbital methods to model the transition state of reaction between β-angelica lactone and cyclopentadiene. Both the methods predict the same selectivity as observed experimentally where the lactone reacts preferentially at the face opposite the methyl group (Figure 3). This reaction has been studied experimentally by Ortuno et. al.,[24] who has studied other similar Diels-Alder reactions. The same group has studied the transition state of Diels-Alder reaction between protoanemonin and butadiene also using the MNDO and AM1 methods.[25]

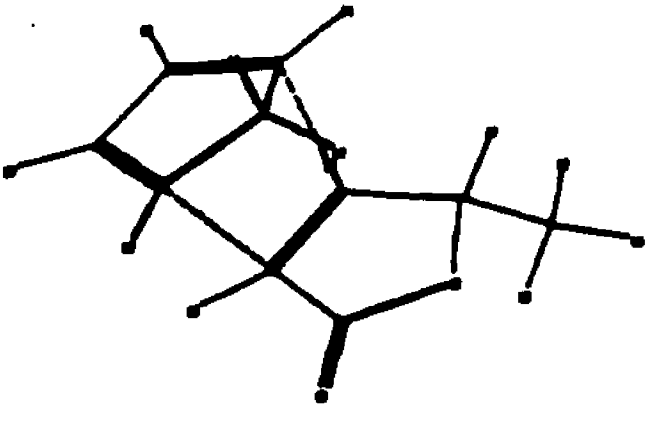


Figure 3

Transition state of Diels-Alder reaction between β-angelica lactone and cyclopentadiene.

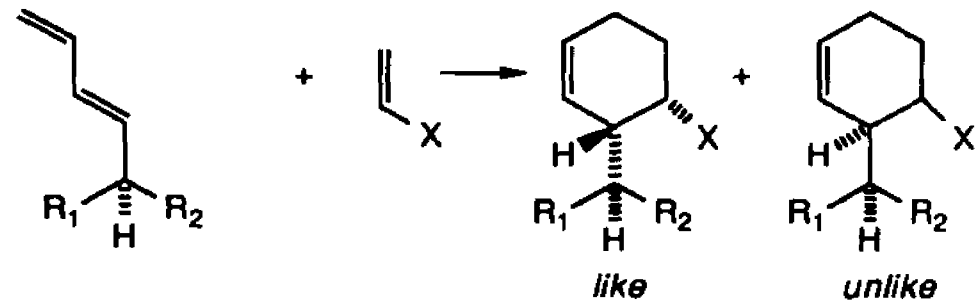
Modelling of the transition state for the Diels-Alder reaction has been one of the more controversial subjects in the field of theoretical organic chemistry. There have been many reported calculations on the archetypical reaction between ethylene and butadiene.[26] Several have predicted a symmetrical, while others an unsymmetrical, transition state. The method that we have used for this study, AM1, has been reported to predict a symmetrical transition state when RHF calculations are performed, but an extremely unsymmetrical transition state (and even a possible biradical intermediate) when the same methodology is used in a specific 3 x 3 configuration interaction (CI) procedure. In this procedure, the SCF calculation is done on the open shell biradical state, the two other states are constructed by either demoting an electron from the higher singly occupied orbital or promoting one form the lower singly occupied orbital. Dannenberg's group has found that 3 x 3 CI of this type works well for bond dissociation reactions[27] since the transition states for such reactions are usually fairly similar to the radical pairs. This procedure converges to the sum of the energies of the two independent radicals (as calculated using half electron method)[28] at large separation of the radicals. On the other hand, it has been found that 2 x 2 CI (using the RHF, doubly occupied ground state to perform the SCF calculation) is a better procedure for molecular rearrangements (such as the Cope rearrangement)[29] where there is considerable bond formation at both the bond making and bond breaking positions. In the report[30] of the 3 x 3 CI AM1 calculation of the Diels-Alder transition state (the higher or first transition state in this report), one can see that the biradical state has the least weight of the three states considered in the CI, yet it is the state for which the SCF calculation was performed. The other two states, the completely paired ground state and the paired doubly excited state, which have weighting coefficients of -

0.933 and 0.356, respectively, after CI, are likely to be inadequately described by simply demoting or promoting an electron using imperfect SCF orbitals (for comparison, the weighting coefficients for the biradical state is 0.055). We therefore believe that this calculation could lead to a misleading model of the transition state.

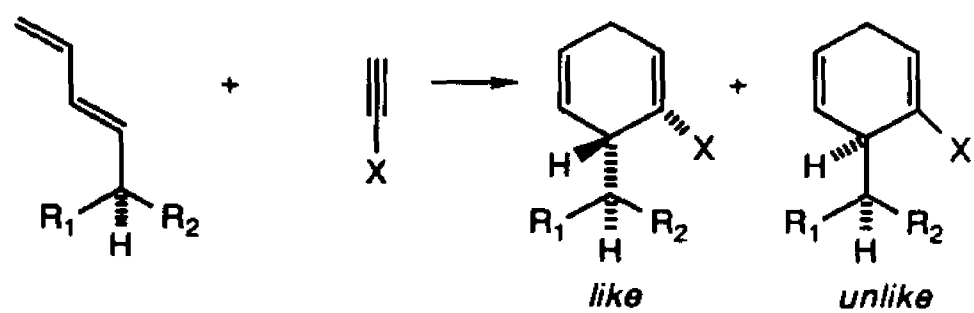
Bernardi has recently reported that a fully optimized MCSCF ab initio treatment of the reaction between butadiene and ethylene has two competing reaction channels: one synchronous and another asynchronous.[31] This is in accord with a suggestion by Dewar that both reaction paths might (in general) exist.

We, therefore, considered the RHF transition state to be a reasonable model for the calculation of the transition states for the reactions of the chiral molecules that we have considered. We have done calculations for the Diels-Alder cycloadditions of ethylene, acrolein and methyl propiolate with substituted pentadienes so that C-5 is stereogenic, $CH(OR_1)(R_2)$ (reactions **I** - **IV**, **VIII** and **IX**, Table 1).[32]

Table 1. Diels Alder Reactions Studied



18 (R_1=CH_3; R_2=OH)	+ **25** (X=H)	⟶	**28**	+	**29**	reaction I
19 (R_1=CH_3; R_2=OCH_3)	+ **25**	⟶	**30**	+	**31**	reaction II
20 (R_1=CH_3; R_2=OC_2H_5)	+ **25**	⟶	**32**	+	**33**	reaction III
21 (R_1=C_2H_5; R_2=OCH_3)	+ **25**	⟶	**34**	+	**35**	reaction IV
22 (R_1=CH_3; R_2=H)	+ **25**	⟶	**36**	+		reaction V
23 (R_1=H; R_2=OH)	+ **25**	⟶	**37**	+		reaction VI
24 (R_1=H; R_2=OCH_3)	+ **25**	⟶	**38**	+		reaction VII
19	+ **26** (X=CHO)	⟶	**39**	+	**40**	reaction VIII



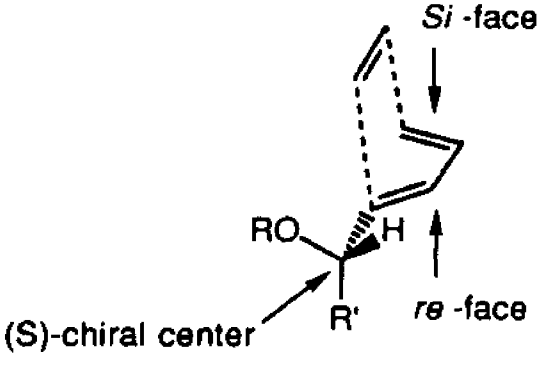
19	+ **27** (X=CO_2CH_3)	⟶	**41**	+	**42**	reaction IX

Methods

Most ab initio calculations are of the restricted Hartee-Fock (RHF) type.[33] These calculations employ a one-electron effective Hamiltonian. That is to say, the energy of each electron is calculated in the approximated field of all the others (plus the nuclei). The major obstacle to ab initio calculations for the modelling of organic systems is the difficulty of the calculations, especially with respect to the time required. The feasibility of performing such calculations decreases quickly with increasing size of the system. Semiempirical calculations[34] are therefore used to calculate the properties of large molecules. The rationale behind these calculations is to develop a physical model that can mimic an accurate MO calculation without the difficulty of performing the full calculation. In visualizing a physical model of the molecule it is immediately apparent that the inner shell electrons are not likely to play a large role in the molecular model. For this reason, the inner shell electrons are included in the "core" in semiempirical methods. Rather than calculating the energy of the electrons on the field of the nuclei, their energy in the field of the core, made up of effective nuclei containing both the nucleus and the inner shell electrons, is calculated. Among the semiempirical methods the AM1 method has been developed by Dewar et. al.[35]

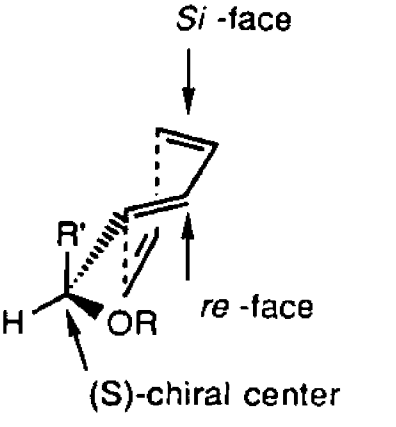
All calculations were performed using the AM1 approximation to molecular orbital theory at the RHF level. In each of the cases considered, all six possible transition states[36] {3 rotamers, each, for both the like, attack from the *si* face for 'S' chiral group (illustrated in **43**), and unlike, attack from the *re* face for 'S' chiral group (illustrated in **44**)} were individually optimized with respect to all internal degrees of freedom. All possible rotamers about the relevant bonds in

the substituent groups on the chiral center were also considered. The transition states were fully characterized by calculating the force constants, only one of which was negative in each case studied. This required a significant number of calculations as convergence to points with more than one negative force constant was quite common. In general the second negative force constant would be for a torsional mode about a bond either to or within one of the substituents on the chiral center. calculations were also performed for the reactants and products. A total of 47 individual transition states were characterized, each involving up to 84 independent internal degrees of freedom.



like -transition state

43



unlike -transition state

44

Results and Discussion

The results of the calculations are presented in Tables 2 - 4. The activation energies are close to what is expected for Diels-Alder reactions of this class. The activation enthalpy of the reaction of ethylene with butadiene has been estimated to be 27-34 kcal/mol at 298°C in the gas phase. Activation enthalpies for the reactions of our model dienes and ethylene (see Table 2) range between 25.5 and 26.3 kcal/mol.[37] The higher activation enthalpy for reaction with acrolein parallels the observation of Dewar that RHF calculations do not properly account for the effect of substituting CN groups for H on the dienophile. The gas-phase Diels-Alder reaction of butadiene and acrolein is reported to have an activation energy of 19.7 kcal/mol ($A=1.46 \times 10^9$) in the temperature range of 155-332°C.[38] We have not found appropriate quantitative gas phase activation energy data for reactions similar to reaction **IX** with an acetylenic dienophile. However, qualitative reports suggest that acetylenic dienophiles react more slowly than their ethylenic counterparts in solution.[5a,39]

Table 2. Geometric and Energetic Parameters for the Best (*like* and *unlike*) Transition States for Reactions I-IX[a]

					bond length	
reaction	product	ϕ	ΔH_{act}[b]	ΔH_f	long	short
I	28	167.4	25.50	-14.11	2.166	2.072
I	29	-38.1	25.91	-14.11	2.161	2.078
II	30	168.1	25.69	-7.69	2.154	2.071
II	31	28.0	26.30	-7.69	2.174	2.067
III	32	170.7	26.02	-13.23	2.163	2.072
III	33	175.7	26.22	-13.23	2.169	2.061
IV	34	168.7	25.66	-13.62	2.166	2.067
IV	35	22.4	26.15	-13.62	2.184	2.042
VIII	39	177.5	25.57	-40.69	2.287	1.995
VIII	40	0.8	25.98	-40.69	2.326	1.975
IX	41	182.6	33.44	-50.70	2.174	2.056
IX	42	-9.5	32.30	-50.70	2.295	1.992

[a] Long bond is always the bond to the substituted carbon of the diene.

[b] Activation Energy=Transition state energy-heat of formation of the reagents (ΔH_f).

ΔH_{act} and ΔH_f in kcal/mol, distances in A^o, angles in deg. See Figure 4D for the definition of dihedral angle ϕ.

It is apparent that AM1 successfully predicts the face selectivities for the cases studied (Table 3, assuming that the minor structural differences between the theoretical and experimental examples are insignificant). One should note that the selectivity is inverted upon changing from ethylenic to an acetylenic dienophile in both the theoretical and experimental determinations. The calculations correctly predict the predominance of *endo* product for the reactions with acrolein. The structure of the favored *endo* transition state has the carbonyl group *anti* to the double bond though the *syn* arrangement would allow for greater overlap.[40]

Table 3. Comparison of Calculated and Experimental Selectivities for Diels-Alder Reactions[a]

reaction	ΔΔHact(calculated), kcal/mol	ΔΔHact(experimental), kcal/mol
I	0.4	
II	0.6	
III	0.2	
IV	0.5	
VIII	0.4	0.9[b]
IX	-1.1	-0.6[c]

[a] $\Delta\Delta H_{act}$ is defined as *unlike - like*.
[b] reference 5a, entry 8.
[c] reference 5a, entry 18.

In the cases for reactions of substituted dienes with dienophiles ethylene and acrolein the *like* transition state is favored for each reaction studied. Furthermore, the best *like* transition state always has the OR group in the plane of the diene and extended away from the diene (we shall refer to this conformation as *anticoplanar*, see Figure 4A for definition). In this conformation, the alkyl group can point away from the dienophile, leaving the sterically less demanding hydrogen directed toward the incoming dienophile (see Figure 5A, 6A, 7A, 8A and 9A).

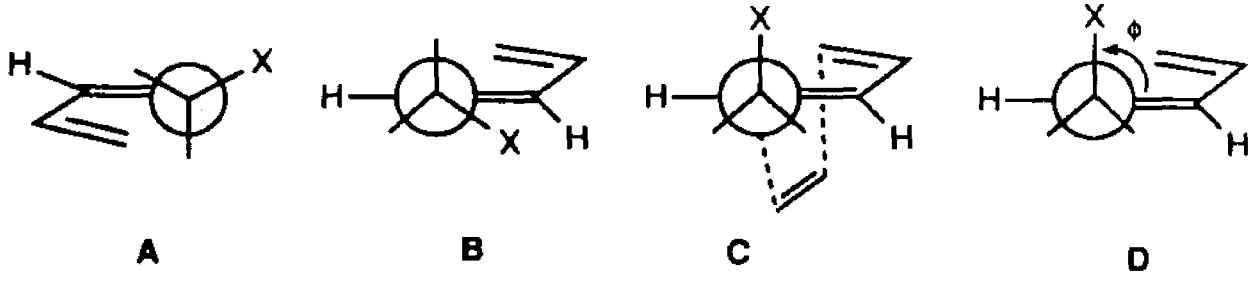


Figure 4. Conformations of the diene. In **A**, **B** and **C**, X is in the *anticoplanar*, *syncoplanar* and *away* positions respectively. The dihedral angle, ϕ, is defined as in **D**, where the positive direction is indicated by the arrow head. ϕ is positive on the *si* face and negative on the *re* face regardless of the direction of the approaching dienophile.

If the dienophile were to approach from the other face (*unlike*), the alkyl group would hinder its approach (for example, see Figure 7B) unless the chiral group changes its conformational position. In fact, the preferred transition state for

most of the *unlike* reactions has the alkoxyl group rotated by close to 180^{o} into the *syncoplanar* position (see Figure 4B). This moves the alkyl group to the opposite face of the diene, thereby allowing the dienophile to approach from the less hindered side (see figures 5B, 6B, 8B and 9B). Reaction **III** is an exception because the ethoxy is larger than the methyl group. It, therefore, prefers the less hindered, *anticoplanar* position while the alkyl group becomes positioned toward the approaching dienophile (see Figure 7B). The energy differences between the *syncoplanar* and *anticoplanar* conformations is less for *unlike* than *like* transition states since both conformations are sterically demanding only in the *unlike* (see discussion below). Significantly, the alkoxyl group prefers to be (approximately) in the plane of the diene in the favored transition states for both *like* and *unlike* reactions of all the dienes. The dienophile approaches from what is the less hindered side after this first criterion is met. Thus, the face selectivity appears to be due to a combination of steric and electronic effects.

Figure 5A. ***like*** transition state for reaction I.

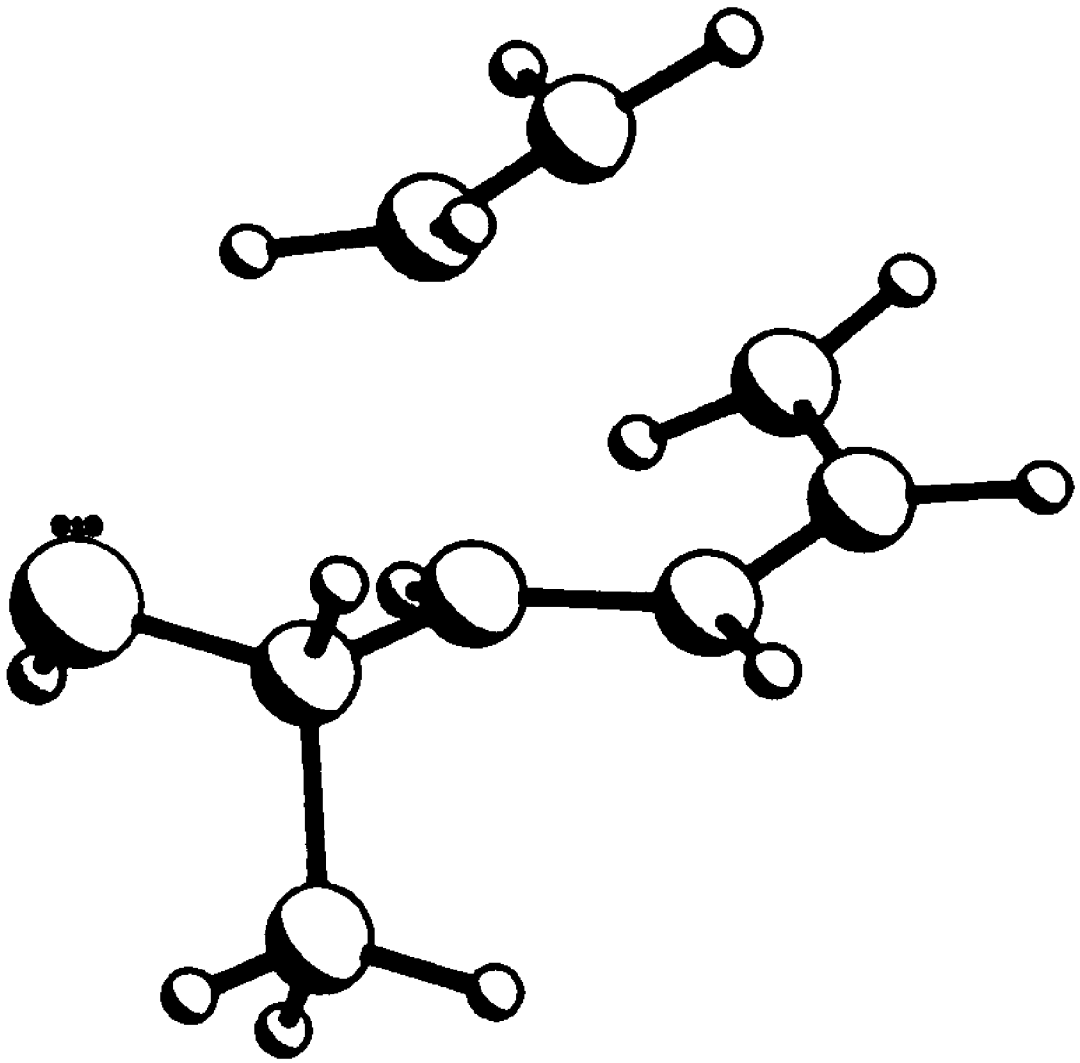


Figure 5B. *unlike* transition state for reaction I.

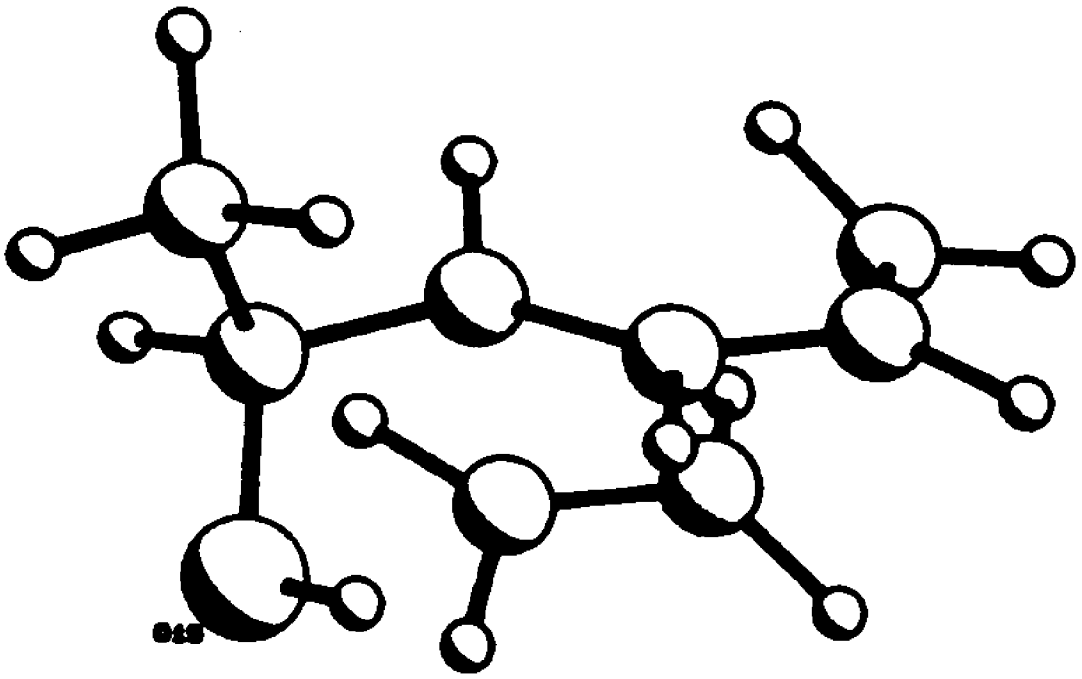


Figure 6A. ***like*** transition state for reaction II.

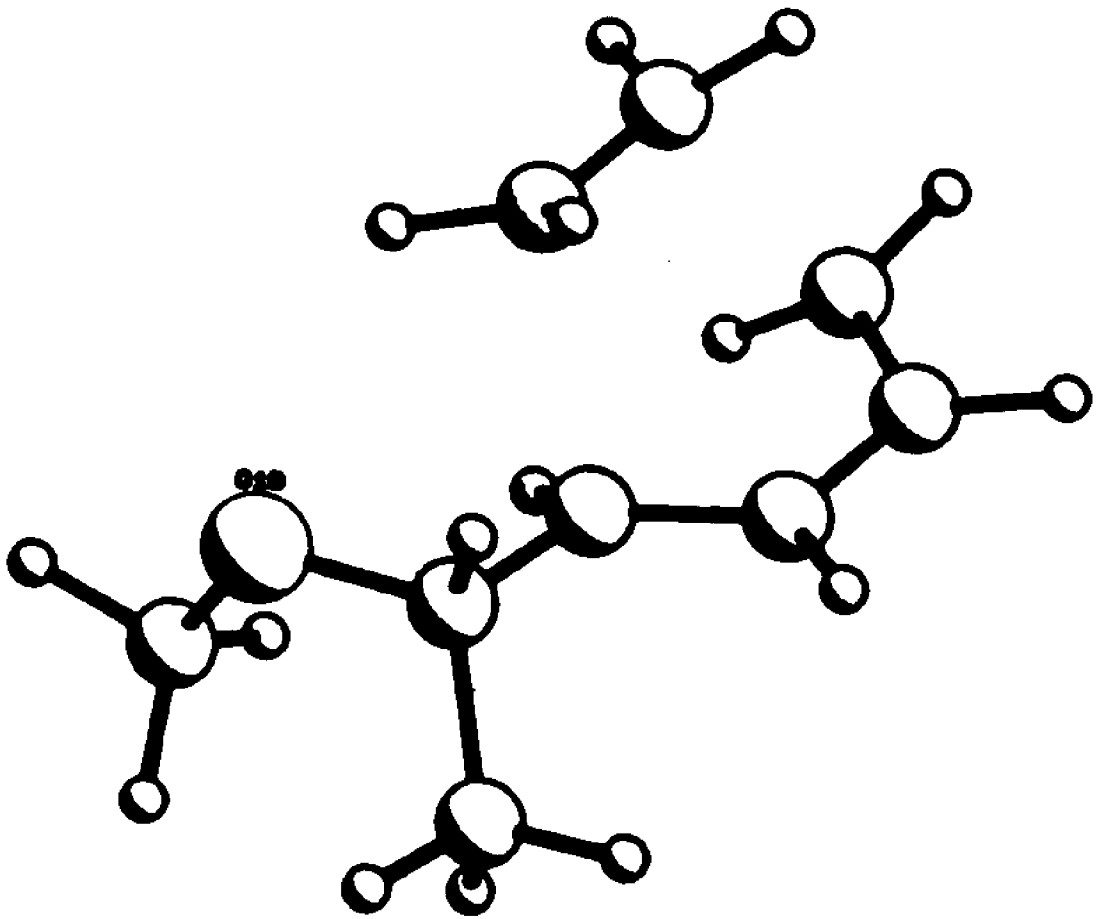


Figure 6B. ***unlike*** transition state for reaction II.

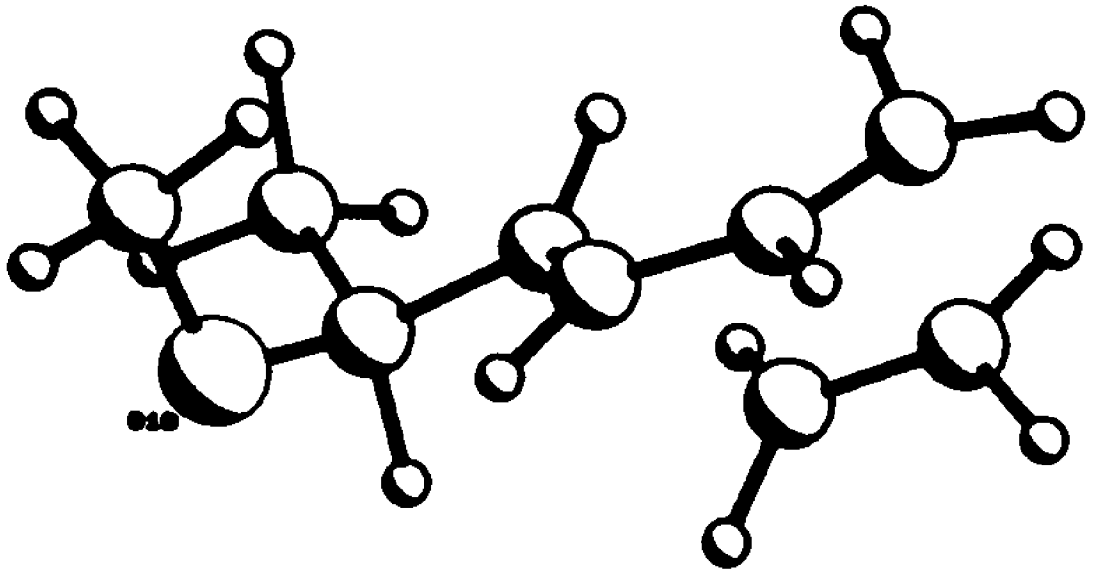


Figure 7A. ***like*** transition state for reaction **III**.

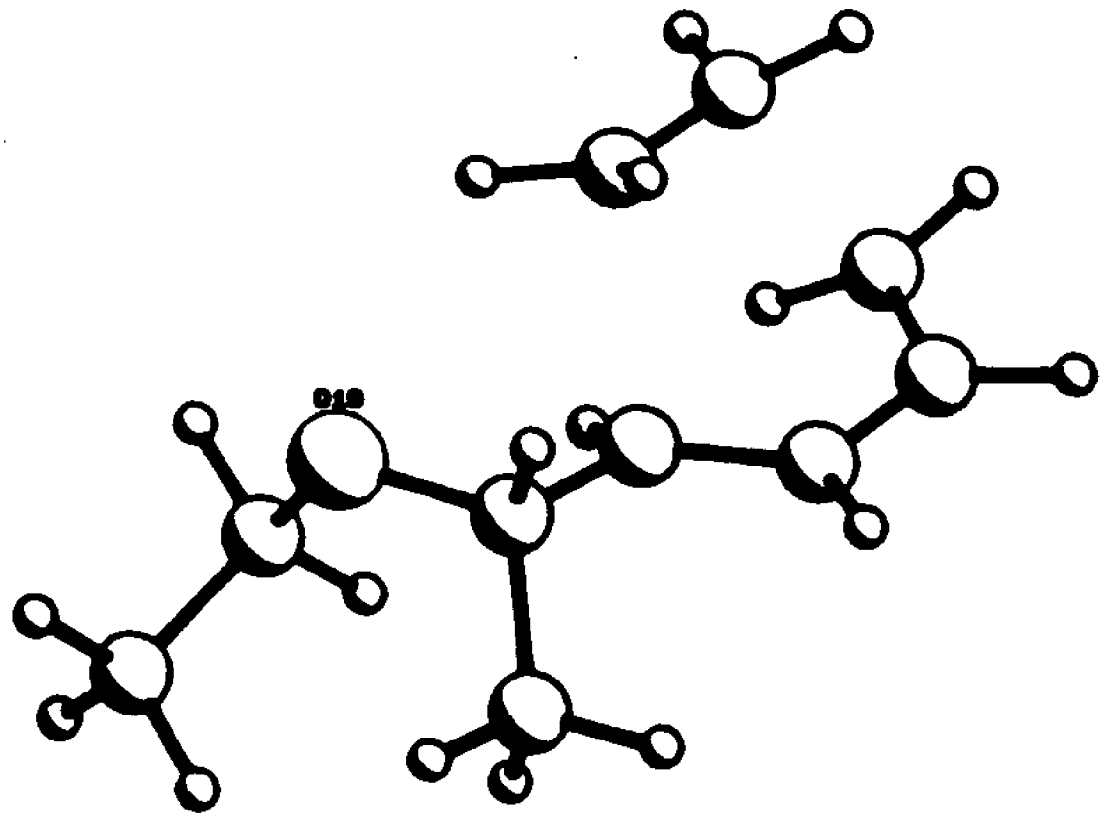


Figure 7B. *unlike* transition state for reaction III.

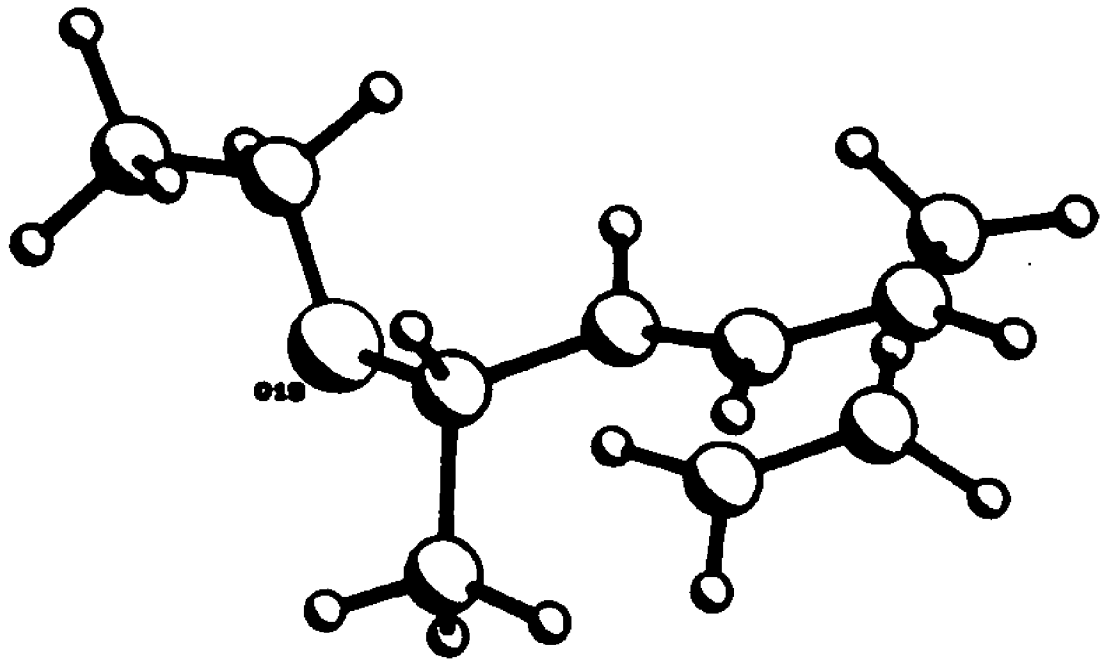


Figure 8A. ***like*** transition state for reaction IV.

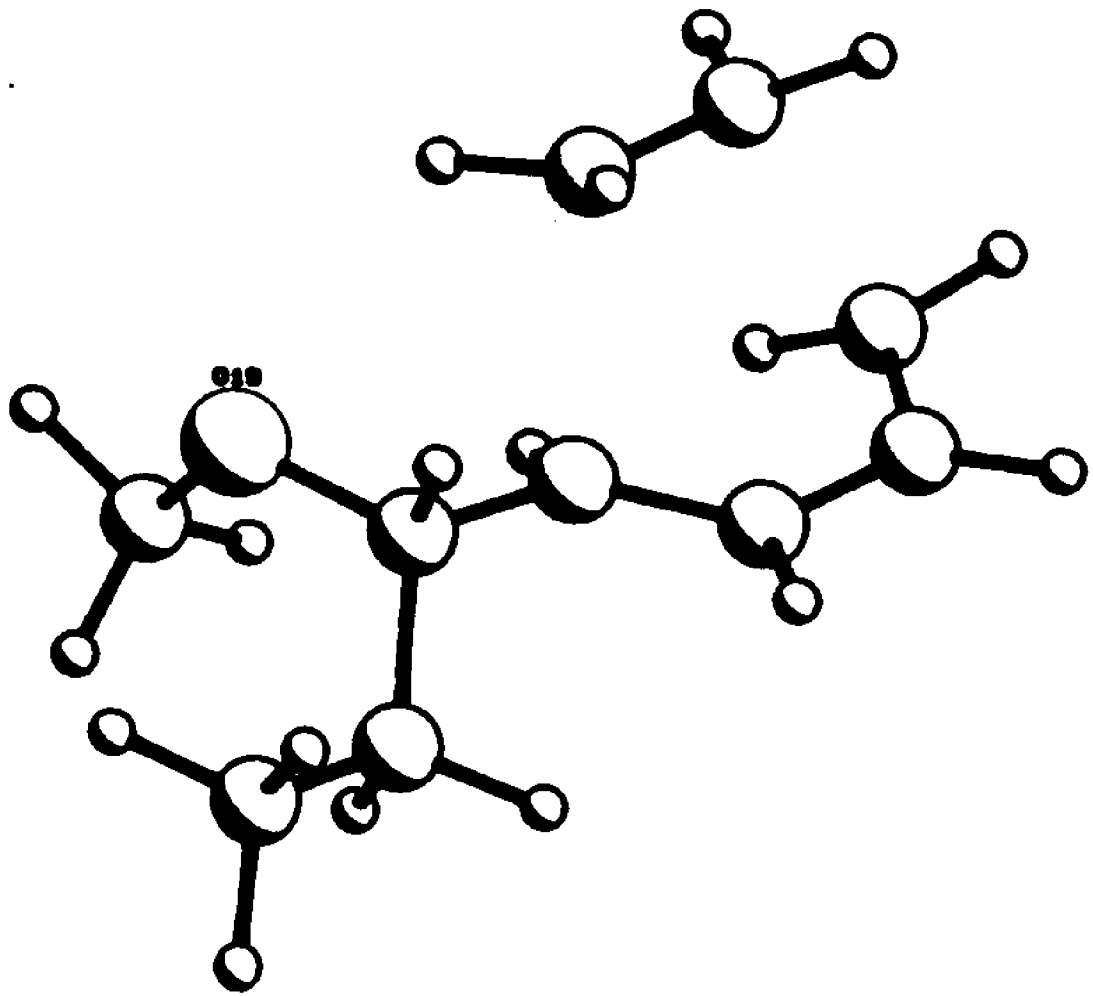


Figure 8B. *unlike* transition state for reaction IV.

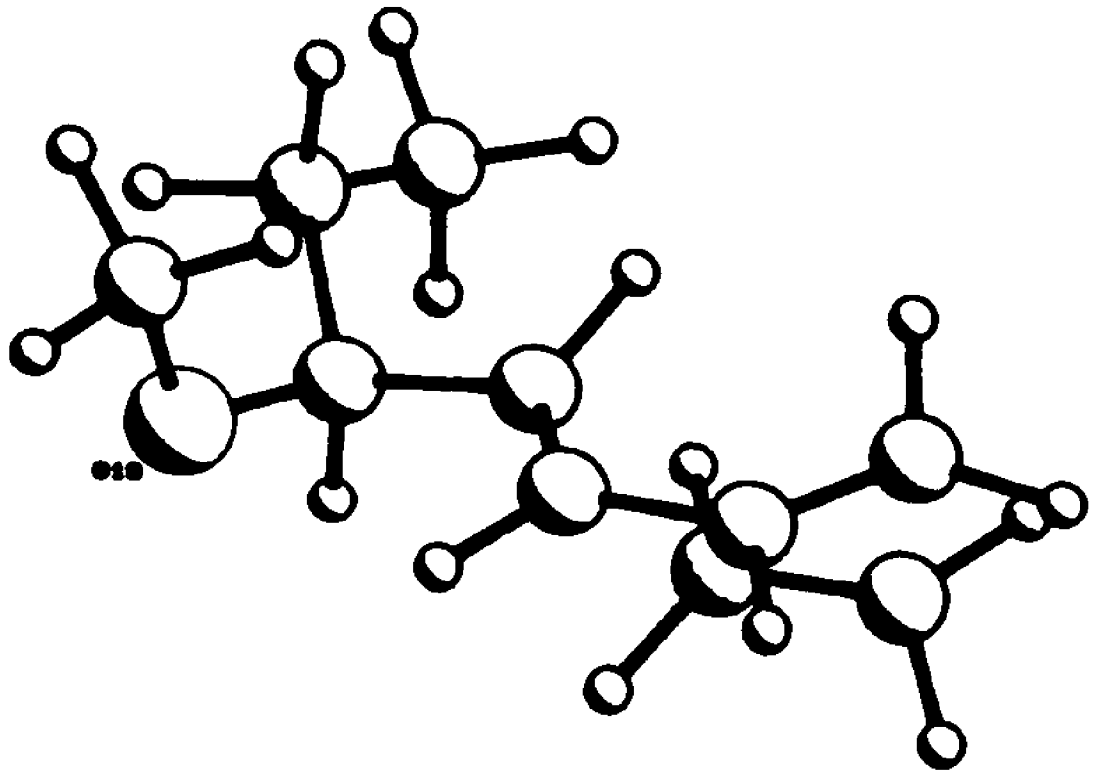


Figure 9A. ***like*** transition state for reaction VIII.

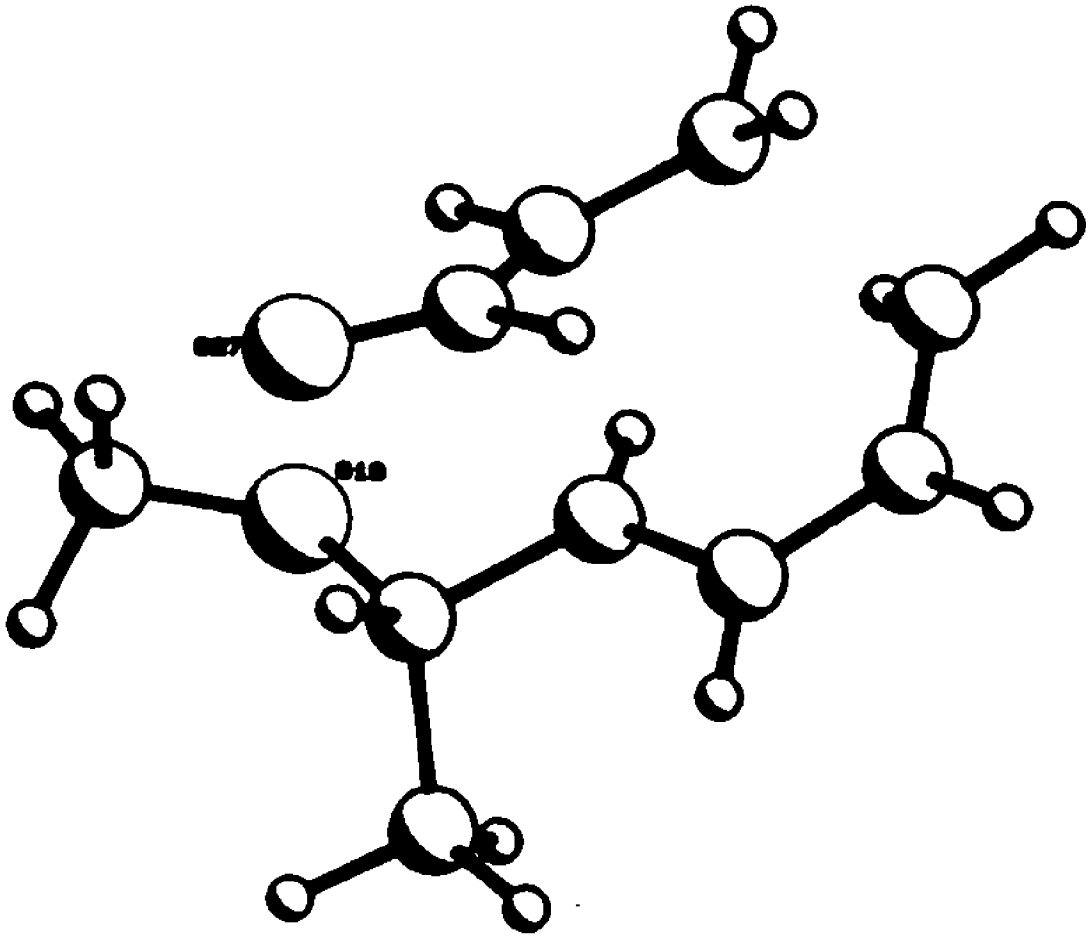
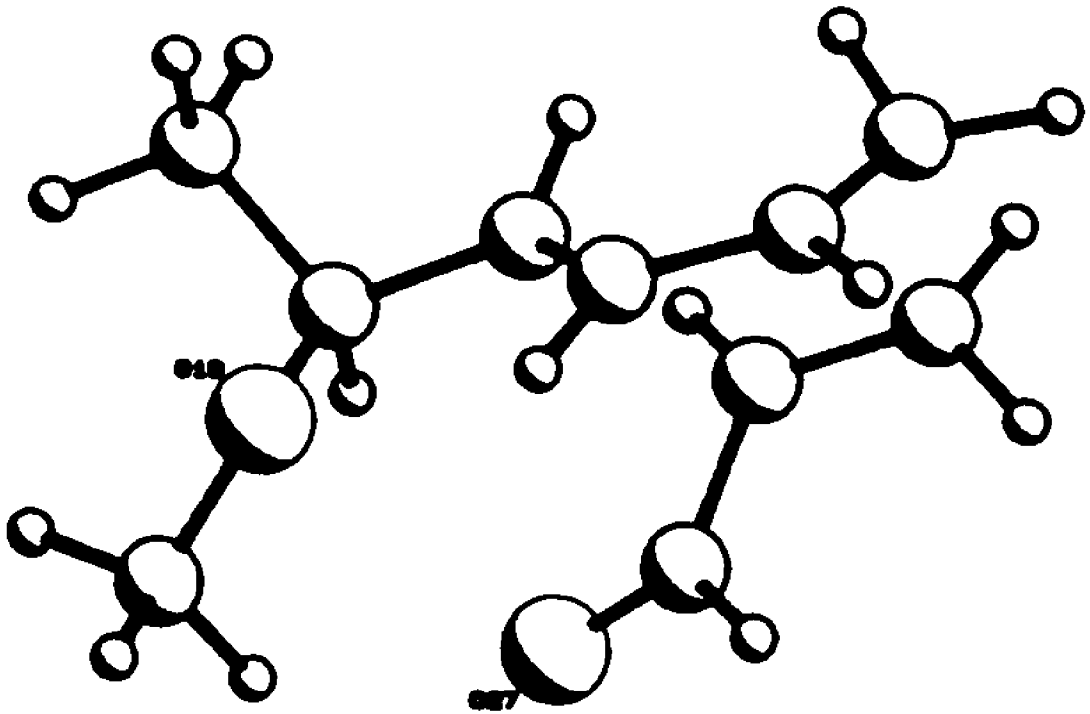


Figure 9B. *unlike* transition state for reaction VIII.



We sought in several different ways to determine the nature of whatever electronic effects might be important. First we examined the HOMO's and LUMO's in the transition states (see Table 4). As an example, variation of activation energies with HOMO and LUMO energies for reaction of 5-(S)-methoxy-1,3-hexadiene, **19**, with ethylene are shown in Figure 10. There is no apparent correlation of either MO with that of the best confirmation of the transition for each reaction (see Table 4 and Figure 10). Both the HOMO and LUMO of the best transition state are more average than extreme. Second we examined the charge densities at the oxygen and at the π positions in the diene and dienophile Again, no correlation is evident. In fact neither the charge nor π density on oxygen changes by any significant amount (see Table 4).

Table 4. Comparison of the Different Transition State Structures Characterized for Reactions **I, II, III, IV, VIII** and **IX**[a].

				bond length				charge	πdensity
reactn	prod.	ϕ	ΔHact	long	short	HOMO	LUMO	(on	oxygen)
I	**28**	167.4	25.5	2.166	2.072	-8.626	0.422	-0.325	0.079
I	**28**	38.0	26.1	2.189	2.061	-8.672	0.307	-0.324	0.081
I	**28**	234.0	26.4	2.176	2.047	-8.655	0.336	-0.329	0.081
I	**29**	-38.[illegible]	25.9	2.161	2.078	-8.673	0.408	-0.324	0.083
I	**29**	24.0	26.0	2.174	2.060	-8.663	0.347	-0.324	0.083
I	**29**	182.3	26.1	2.181	2.054	-8.659	0.324	-0.326	0.079
II	**30**	168.1	25.7	2.154	2.071	-8.574	0.516	-0.278	0.166
II	**30**	227.0	26.3	2.169	2.066	-8.669	0.377	-0.280	0.163
II	**30**	56.4	27.1	2.180	2.058	-8.434	0.543	-0.276	0.160
II	**31**	28.0	26.3	2.174	2.067	-8.648	0.378	-0.275	0.168
II	**31**	174.6	26.5	2.175	2.058	-8.519	0.465	-0.279	0.156
II	**31**	76.8	26.8	2.198	2.037	-8.612	0.295	-0.275	0.167
II	**31**	-33.4	26.9	2.165	2.071	-8.507	0.562	-0.276	0.155
II	**31**	199.0	27.0	2.166	2.069	-8.467	0.571	-0.281	0.154

Table 4.(continued) Comparison of the Different Transition State structures Characterized for Reactions **I, II, III, IV, VIII** and **IX**[a].

				bond length				charge	πdensity
reactn	prod.	ϕ	ΔHact	long	short	HOMO	LUMO	(on	oxygen)
III	**32**	170.7	25.9	2.163	2.072	-8.570	0.481	-0.280	0.172
III	**32**	211.9	26.2	2.167	2.059	-8.600	0.428	-0.284	0.161
III	**32**	57.6	26.8	2.180	2.059	-8.417	0.557	-0.277	0.164
III	**33**	175.7	26.2	2.169	2.061	-8.518	0.484	-0.281	0.162
III	**33**	-32.4	26.6	2.166	2.074	-8.499	0.574	-0.277	0.158
III	**33**	38.5	26.7	2.171	2.069	-8.675	0.367	0.279	0.173
III	**33**	203.2	27.1	2.173	2.068	-8.441	0.577	-0.285	0.153
IV	**34**	168.7	25.6	2.166	2.067	-8.548	0.481	-0.277	0.168
IV	**34**	250.5	26.3	2.169	2.060	-8.702	0.344	-0.277	0.166
IV	**34**	52.4	27.2	2.177	2.060	-8.453	0.538	-0.278	0.163
IV	**35**	22.4	26.1	2.184	2.042	-8.547	0.387	-0.276	0.166
IV	**35**	184.6	26.2	2.170	2.065	-8.515	0.494	-0.279	0.156
IV	**35**	-25.0	26.9	2.170	2.065	-8.527	0.510	-0.277	0.159
IV	**35**	96.5	27.2	2.196	2.041	-8.601	0.314	-0.278	0.157

Table 4.(continued) Comparison of the Different Transition State structures Characterized for reaction **I, II, III, IV, VIII** and **IX**[a].

				bond length				charge	πdensity
reactn	prod.	ϕ	ΔHact	long	short	HOMO	LUMO	(on	oxygen)
VIII	**39**	177.5	25.6	2.287	1.995	-8.747	-0.547	-0.286	0.151
VIII	**39**	211.6	26.4	2.289	1.995	-8.773	-0.564	-0.285	0.152
VIII	**39**	32.1	28.8	2.296	1.986	-8.624	-0.426	-0.277	0.156
VIII	**40**	0.8	25.98	2.326	1.975	-8.667	-0.610	-0.282	0.151
VIII	**40**	59.7	27.0	2.300	1.986	-8.855	-0.681	-0.269	0.167
VIII	**40**	193	29.3	2.287	1.982	-8.682	-0.547	-0.288	0.169
IX	**41**	182.6	33.4	2.174	2.056	-9.127	-0.180	-0.275	0.166
IX	**41**	256	33.8	2.171	2.061	-9.306	-0.304	-0.274	0.165
IX	**41**	80.0	37.3	2.171	2.059	-9.207	-0.207	-0.274	0.170
IX	**42**	-9.5	32.3	2.295	1.992	-8.920	-0.470	-0.280	0.157

[a] Long bond is always the bond to the substituted carbon of the diene. ΔH_{act} in kcal/mol; HOMO and LUMO in eV; Bond length in A^{o}; Charges and densities in atomic units. See Figure 4D for the definition of dihedral angle ϕ

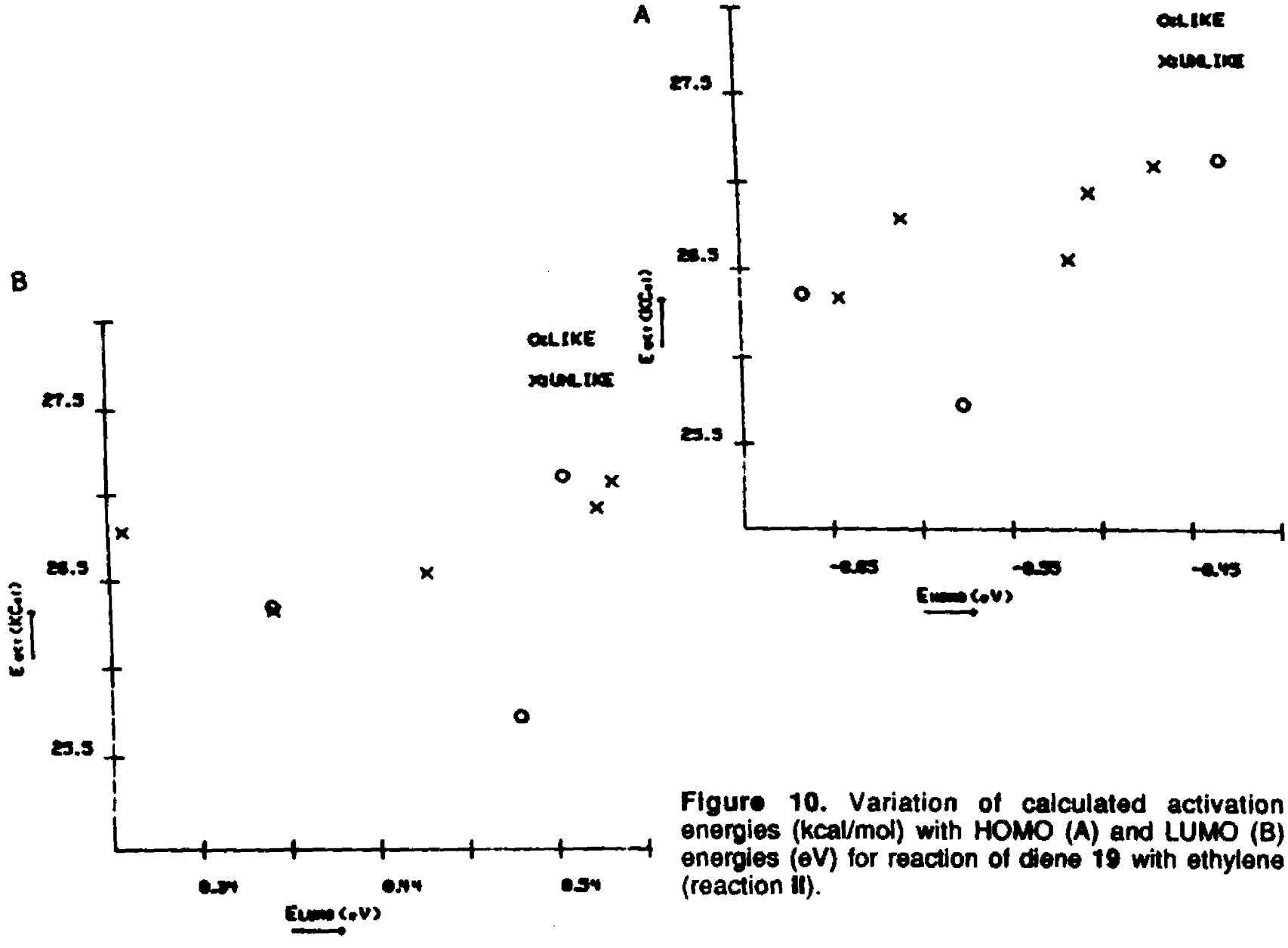


Figure 10. Variation of calculated activation energies (kcal/mol) with HOMO (A) and LUMO (B) energies (eV) for reaction of diene **19** with ethylene (reaction **II**).

We examined the selectivities for dienes **18-21**, which have alkyl and alkoxyl groups of varying bulk attached to the chiral center, in the hope of distinguishing the electronic effects (which would remain constant) from the steric effects. The selectivities of these reactions, as well as, their transition state structures, are quite similar (Figures 5-8). It should be noted that reaction **II** shows slightly more selectivity than **III** or **IV** (see below for discussion). In order to investigate whether the methyl, hydroxy or methoxy group has a natural preference for one conformational position on the chiral center, we next studied the transition states involving achiral dienes that contained only one of these groups and hydrogens on the saturated carbon. Thus, we calculated the transition state energies for the reactions of 1,3-hexadiene (**22**), 5-hydroxy-1,3-pentadiene (**23**) and 5-methoxy-1,3-pentadiene (**24**). For 1,3-hexadiene, the methyl group showed little preference between the *anticoplanar* or *away* (away from the incoming dienophile, see Figure 4C) positions, but the conformation with the methyl oriented toward the dienophile was disfavored by 0.78 kcal/mol. On the other hand, for both the hydroxy and methoxy dienes, **23** and **24**, the OR group exhibited a clear preference for the *anticoplanar* position. The *syncoplanar* position is the next best (0.34 and 1.04 kcal/mol higher with OH and OCH_3 respectively) followed by the *away* position (see Table 5).

Table 5. Activation Energies for Reactions **V**, **VI** and **VII** as a Function of the Dihedral Angle (ϕ) in Degrees (See Figure 4D for definition)

reaction	product	ϕ	ΔH_{act}(kcal/mol)
V	**36**	-97.6	25.9
V	**36**	-171.4	25.9
V	**36**	28.0	26.7
VI	**37**	179.4	25.1
VI	**37**	25.6	25.4
VI	**37**	-110.1	26.1
VI	**37**	-53.5	26.5
VII	**38**	180.5	26.1
VII	**38**	37.5	27.2
VII	**38**	-43.2	27.9

In order to minimize steric interference to the incoming alkene dienophile, the transition state should have the allylic hydrogen as the group closest to the trajectory of bond information. Thus, the alkoxyl and alkyl groups should be in either the *coplanar* or *away* positions, leaving the hydrogen oriented toward the dienophile. The calculations on the reaction of 1,3-hexadiene with ethylene have indicated that the alkyl group has no preference for either of the two acceptable positions. The determination of the transition states for the reactions

of **23** and **24** with ethylene show that OR group favors the *anticoplanar* position and strongly disfavors the *away* position, preferring the *syncoplanar* position to the latter. Only the *like* transition state can accommodate the preferences of both the alkyl and alkoxyl groups. In the *unlike* transition state, the alkoxyl group is forced to take the less favored *syncoplanar* position to avoid forcing the methyl group toward the dienophile. The preference of the OR group to be (nearly) *coplanar* with the diene seems to clearly be of electronic origin. Nevertheless, we are unable to find a simple correlation with orbital energy or electronic density that is symptomatic of the effect. The interaction is likely of too complex a nature to be effectively simplified. The preference for *anti* rather than *syn coplanar* seems to be, at least partially, of steric origin. This can be seen from the bond angles in the optimized *anticoplanar* and *syncoplanar* transition states for 5-hydroxy-1,3-pentadiene (**23**). The OCC and adjacent CCC angles increase by about 2^{o} upon going from the *anticoplanar* to the *syncoplanar* transition state (see Figure 11). The OR groups tend to be twisted slightly more out of the plane for the *unlike* than the *like* transition states, presumably to reduce the steric interaction within the reactants.

For the reaction of 5-(S)-methoxy-1,3-hexadiene, **19**, with acetylenic dienophile, **27** (reaction **IX**), *unlike* selectivity is observed. The *like* transition state, with the alkoxy *anticoplanar*, is less favored than the *unlike* due to the unfavorable steric interaction between the methoxy groups on both the diene and the dienophile. This interaction does not occur in the *unlike* transition state as the methoxy on the diene is *syncoplanar* and out of the way of the dienophile methoxy (see Figure 12). Kozikowski in ref. 12 predicted a similar transition state. Clearly, subtle interactions in the transition states can play an important role.

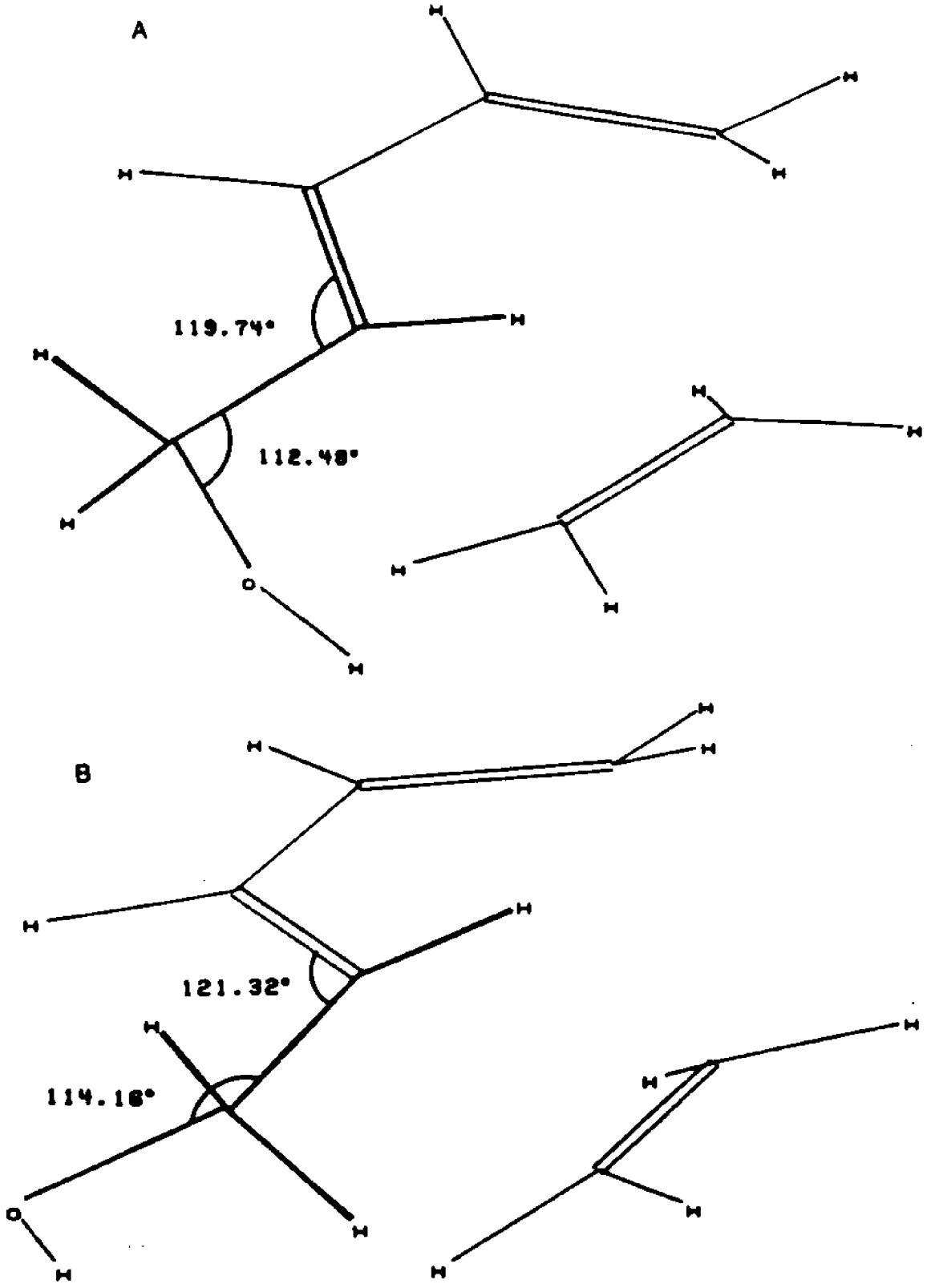


Figure 11. Transition states for reaction **VI** (A *anticoplanar*, B *syncoplanar*)

Figure 12A. ***like*** transition state for reaction **IX**.

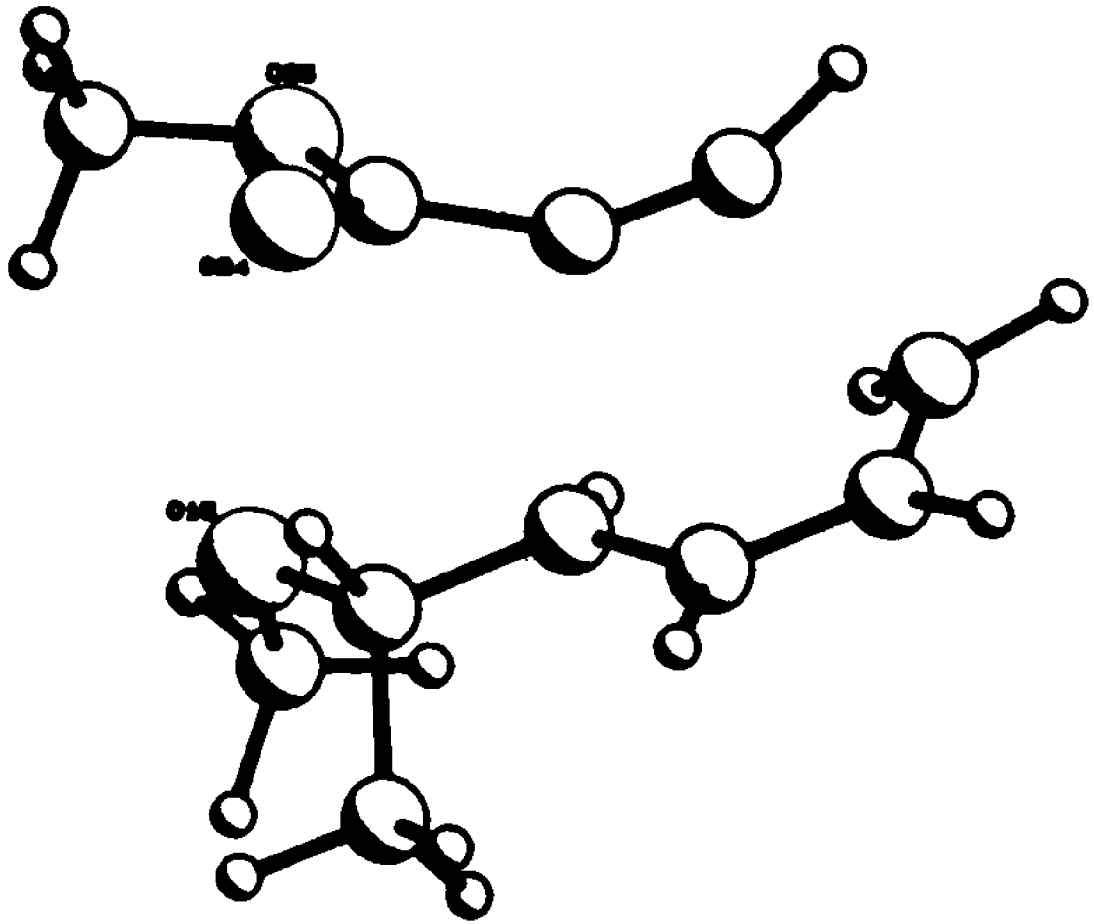
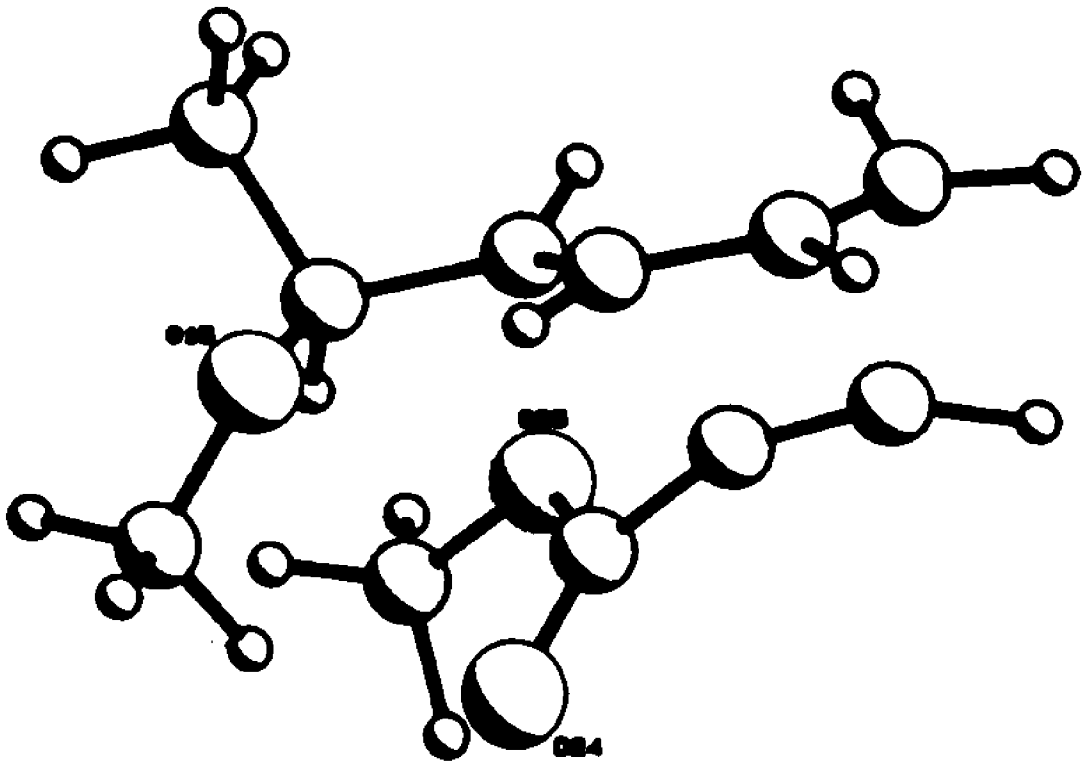


Figure 12B *unlike* transition state for reaction IX.

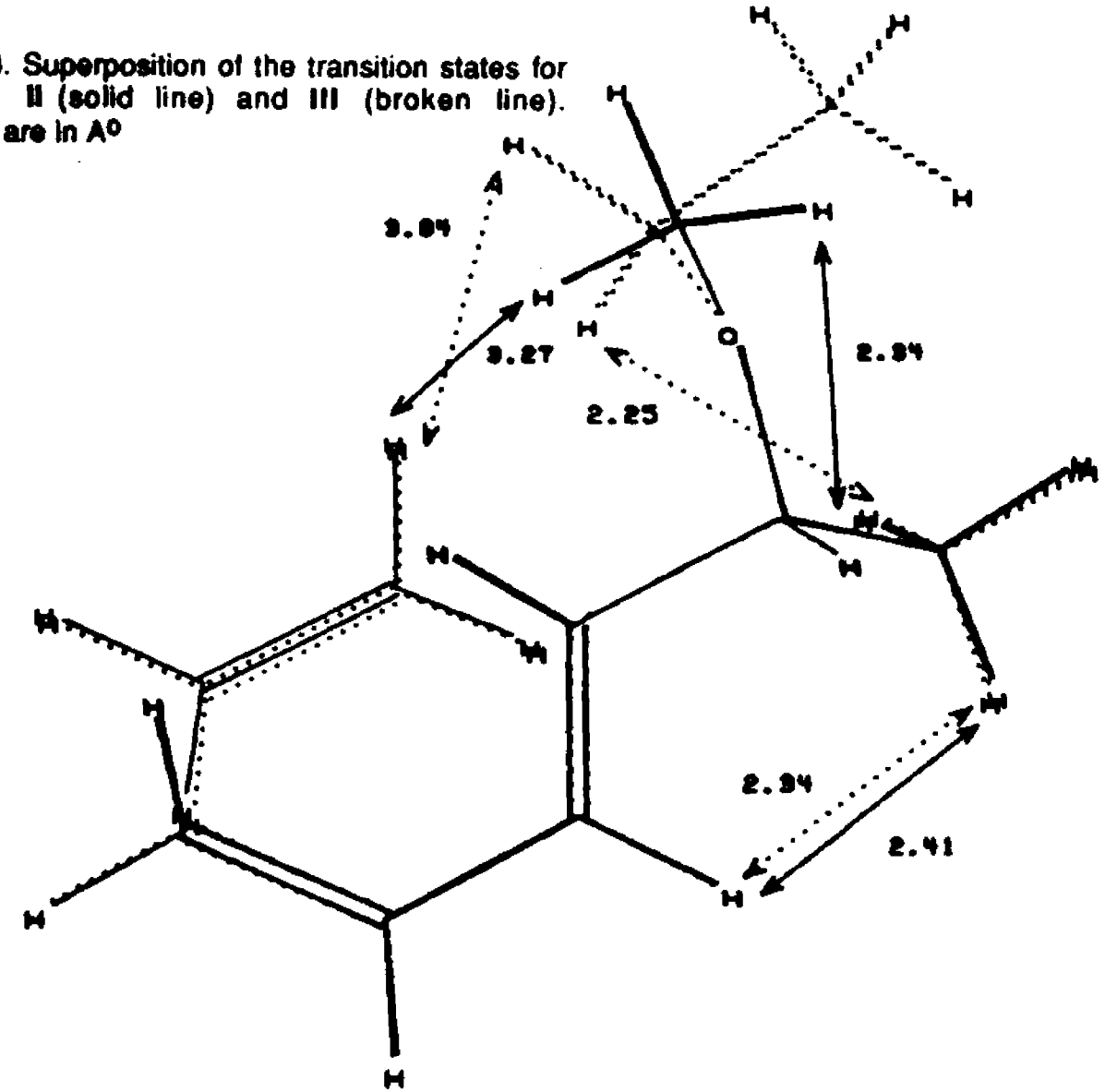


Of particular interest is the prediction that reaction of 5-(S)-methoxy-1,3-hexadiene with ethylene (reaction **II**) be considerably more selective than **III** (reaction of 5-(S)-ethoxy-1,3-hexadiene, **20**, with ethylene) and slightly more selective than **IV** (reaction of 5-(S)-methoxy-1,3-heptadiene, **21**, with ethylene). This appears to be due to the interaction between the hydrogens on the alkyl and alkoxyl groups with those on both the diene and dienophile. In reaction **II**, the diene has methyl and methoxy groups at its chiral center. In reaction **III** and **IV** the corresponding groups are methyl, ethoxy and ethyl, methoxy respectively. So, in terms of the total chain length from the end of the alkyl to end of the alkoxy groups each of the reaction **III** and **IV** has an extra carbon. Therefore in the transition state for reactions **III** and **IV**, the repulsive interactions between the hydrogens on the ends of these chains forces the transition state to assume a less favorable conformation than for **II**. The differences between the rotational conformations of the alkoxy group are particularly evident (See Figures 13 and 14). In reaction **III** repulsion between the hydrogens on the methyl and terminal carbon of ethoxy group is greater than that between the methyl and the methoxy group in reaction **II**. This added repulsion causes the ethoxy group to rotate by about 60°C in reaction **III**. Thus one of the hydrogens on the ethoxy group approaches the incoming dienophile more closely, leading to greater repulsions between the diene and the dienophile in reaction **III** (3.07A° vs 3.27 A° for reaction **II**, see Figure 13). Because of this, the bond lengths of the forming bonds are longer in the transition states for **III** than for **II** (Table 2). In addition, the hydrogens on the alkyl and allkoxyl groups as well as the hydrogens on the alkyl group and the diene, are closer in the transition state for reaction **III** than for **II**. Comparison of

the transition states for reactions **IV** and **II** leads to similar observations, except that the differences are much less (see Figure 14).

The need to completely optimize the transition states can be seen from the ranges of energies and bond lengths for the bonds being formed in the various rotamers about the C-C bond linking the chiral center to the diene (shown in Tables 2 and 4) for all of the individual transition states that have been studied. The longer bond is always that to the substituted end of the diene, as would be expected to stabilize the small amount of biradical character of the transition state. It is seen that the energy differences between the rotamers of the same transition state are of the same order of magnitude as the differences between the *like* and *unlike* transition states. Furthermore, the variation in the optimized bond lengths (2.326-2.154 A° and 1.975-2.078 A° for the long and short bonds, respectively) for all the different transition states and rotamers confirms the need for complete optimization of the transition states.

Figure 13. Superposition of the transition states for reactions II (solid line) and III (broken line). Distances are in A°



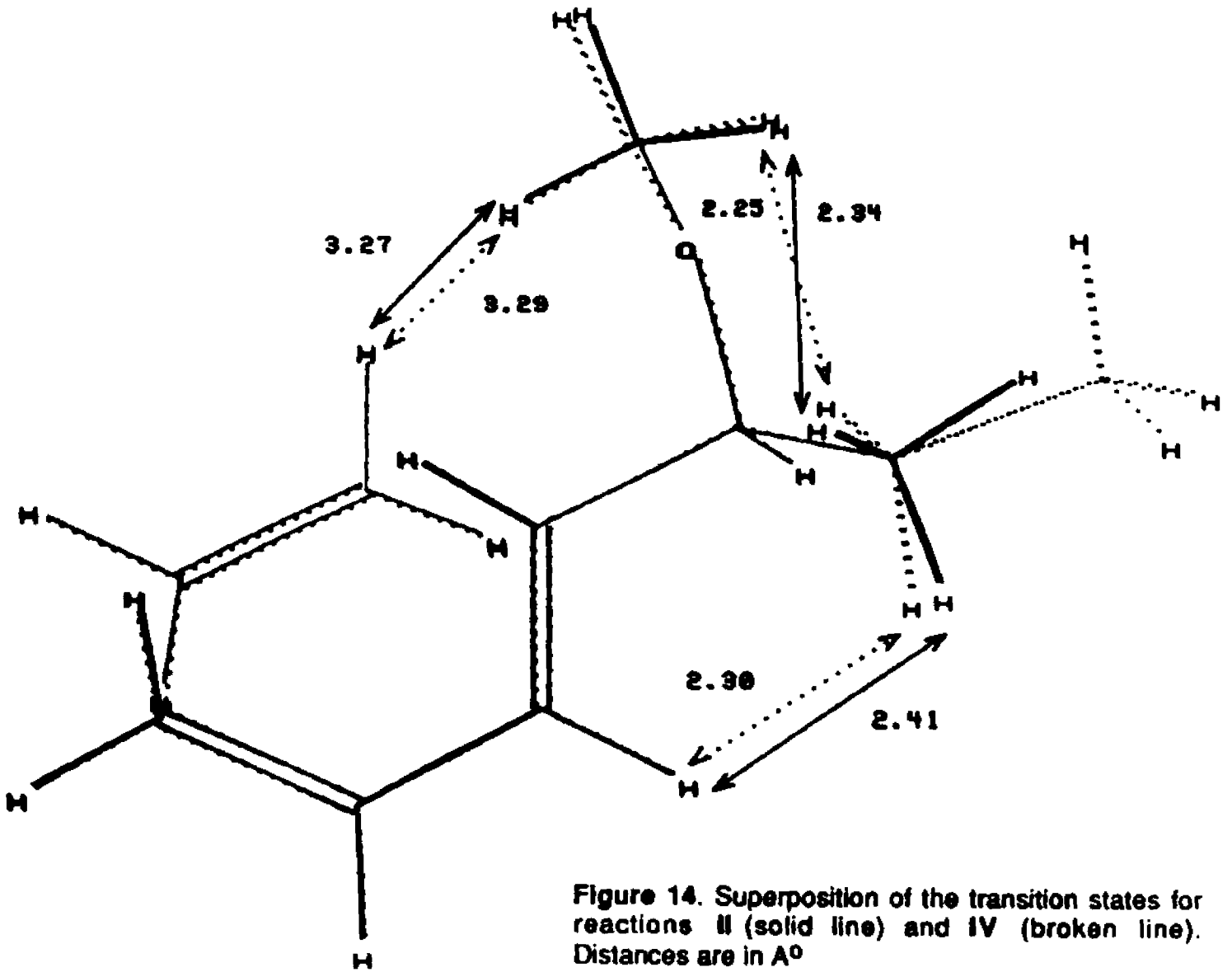


Figure 14. Superposition of the transition states for reactions II (solid line) and IV (broken line). Distances are in A°

AM1 calculations on the reagent dienes (see Table 6) indicate that the OR group prefers to be nearly in the *anticoplanar* position (ϕ~180°) with the exception of 5-(S)-hydroxy-1,3-hexadiene, **18**, for which the OR group is *syncoplanar* (ϕ~0°). In the preferred transition state of the reaction of diene **18** with ethylene (reaction **I**) the OR group is anticoplanar. Also for **IX** (reaction of diene **19** with acetylenic dienophile, **27**) the preferred transition state has the OR group syncoplanar. Thus in reactions **I** and **IX**, the conformation of the allylic groups in the starting reagents and the products do not correlate.These observations suggest that the conformation of the reagents do not always provide good indications of the eventual transition state geometries. For reactions **II**, **III**, **IV** and **VIII** the preferred transition states and dienes have the same conformations. Thus calculations on the preferred products of the specific reactions studied here suggest that four of the six cases have conformations that correlate with the reagents.

Table 6. Rotational Confirmations for Starting Dienes (in their respective s-trans Conformations)[a]

diene	ϕ	H_f
18	-14.6	-30.6
18	172.3	-30.3
18	144.7	-29.2
18	7.6	-28.9
19	151.3	-24.2
19	26.6	-23.4
19	-8.9	-22.6
19	83.4	-20.9
19	-77.6	-20.2
20	151.4	-29.7
20	-34.4	-29.6
20	-73.7	-29.6
20	-9.3	-29.3

Table 6.(continued) Rotational Confirmations for Starting dienes (in their respective s-trans Conformations)[a]

diene	ϕ	H_f
21	178.5	-30.0
21	26.9	-29.4
21	-7.5	-28.9
21	125.9	-28.7
21	-39.8	-27.7

[a] The dihedral angle (ϕ) is defined analogously to the corresponding angle in the transition states (see Figure 4D). H_f in kcal/mol; angles in deg

These observations might be due to one or more of several possibilities. First, if the transition state were early along the reaction path, it would be expected to resemble the reagents. In this case the conformation of the reagent diene would be expected to be the same as in the transition state. Second, the product might have a conformation that is related to that of the starting material in that the rotational isomer of the product can be achieved from the reagent without traversing a rotational barrier. We shall define such a situation as a conformational correlation between reagent and product. In such a case, it is likely that the transition state have a similar conformation to that of the reagent. If the preceding were untrue, the conformation would have to change along with the reaction path from reagent to transition state, and again from transition state to product. While this is not impossible, it is unlikely. Third, there may be an

energetic preference for a specific conformation in the transition state that is qualitatively different from those in the reagents and, perhaps, the products.

Therefore, in those cases where a conformational correlation between reagents and products exists, it is reasonable to suppose that the transition state has a conformation corresponding to the reagent and the product. In such cases, it may be reasonable to predict face selectivity on the basis of the conformation of the reagent dienes. The four such cases (reactions **II**, **III**, **IV** and **VIII**) studied here are in accord with this suggestion.

To the extent that is verifiable by current experiments, AM1 RHF method, with complete geometrical optimization, is adequate for predicting the face selectivities for the reactions studied. This is true despite the inability of RHF calculations to correctly predict substituent effects of the dienophile upon the activation energies. No single effect seems to dominate the predicted selectivities. Rather, they appear to result from a combination of electronic and steric interactions. The electronic effects are not clearly manifest in any simple parameter, such as HOMO/LUMO properties, charges or π densities. They seem to involve more subtle interactions that require specific calculations on each transition state. In conclusion the above data shows that predictions made by assuming that the conformations of the ground states of the reactants are reflected in the transition states are not uniformly correct. The sensitivity of the calculated activation energies to relatively small changes in molecular structure underscores the importance of complete geometrical optimization when performing calculations such as reported above.

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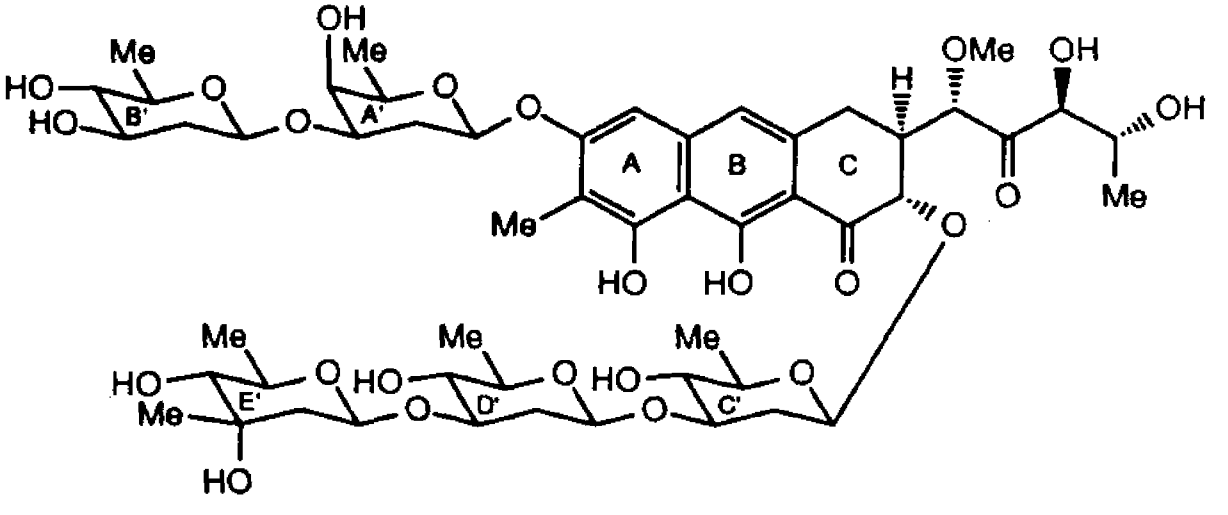
PART 2

GLYCOSIDATION VIA GLYCALS AND ARYL(BISARYLTHIO)SULFONIUM SALTS: EFFECT OF NUCLEOPHILE AND ARYL SUBSTITUTION ON FACE SELECTIVITY

Introduction

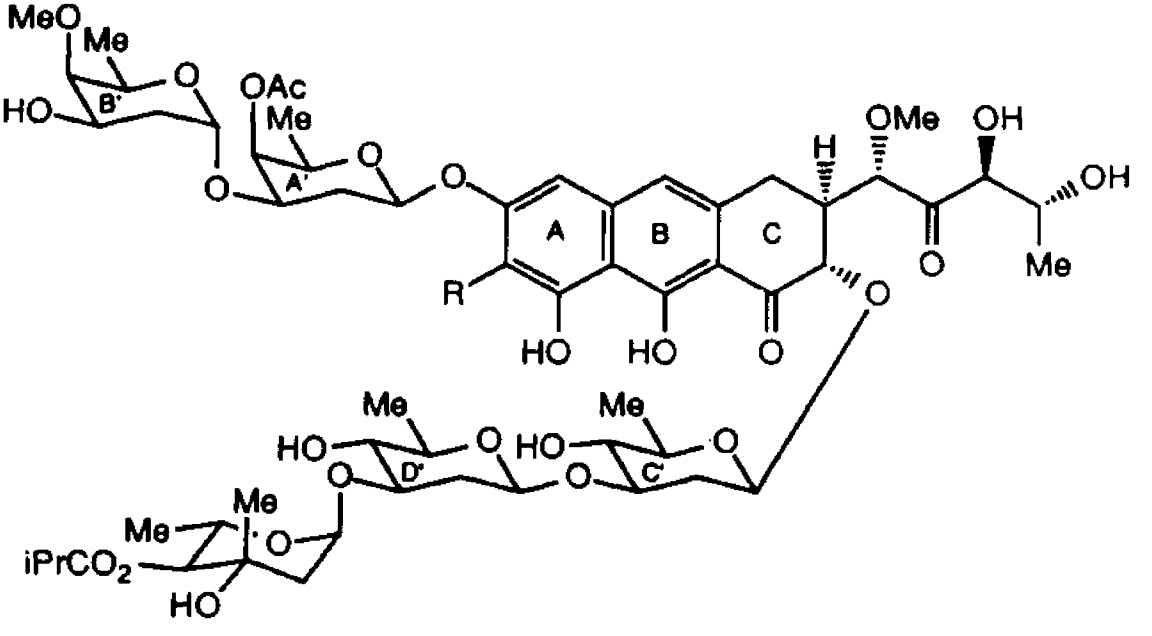
The aureolic acid group of antibiotics which include mithramycin (aureolic acid), the chromomycins, the olivomycins and related compounds have been a subject of study since their isolation in 1953. Grundy and coworkers[1] at Abbott laboratories were the first to report the isolation of aureolic acid **1**. The same compound was rediscovered later at Lepetit and then at Pfizer laboratories[1]. The compound has been found to show antitumor activity but it is not commonly used due to its high toxicity. It is marketed by Pfizer laboratories as Mithracin for use in cancer chemotherapy.



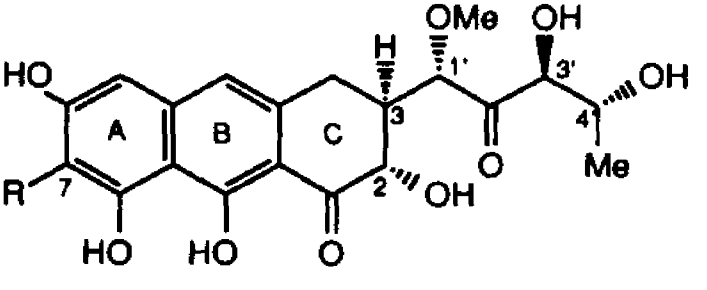
1 AUREOLIC ACID

Similar biological activity is observed in the case of chromomycins (e.g. chromomycin A_3, **2**) which were discovered in Japan[1]. Olivomycins (e.g. olivomycin A, **3**) which differ from chromomycins only in the aglycone, where the methyl at C-7 in chromomycinone **4** has been replaced by an hydrogen in olivin **5**, were discovered in Soviet Union and also show

anticancer activities[1]. Structures of the aureolic acid group are thus based upon two aglycones chromomycinone **4** and olivin **5**. The aglycones are linked at there 2- and 6- positions to chains of one, two or three sugars. Variations in the number and nature of the sugars are responsible for the differences among the individual antitumor antibiotics.



2 R = Me Chromomycins
3 R = H Olivomycins



4 R = Me Chromomycinone
5 R = H Olivin

The mode of action of these glycosylated anthracenones has been extensively studied. It is known that the drugs inhibit the action of DNA - dependent RNA polymerase. Gao and Patel[2] have done NMR(proton) studies on the nature of Chromomycin-DNA binding. The results suggest that in the minor groove a non-covalent dimer of the antibiotic binds to G.C rich sites. Therefore the synthesis of unnatural saccharide derivatives of the aglycone to test the hypothesis and perhaps make better drugs, would be useful. For this reason a total synthesis of the aureolic acids has been a topic of interest amongst several research groups. This task can be divided into three parts

A. Synthesis of the aglycone portion.

B. Synthesis of the A'-B' disaccharide and C'-D'-E' trisaccharide.

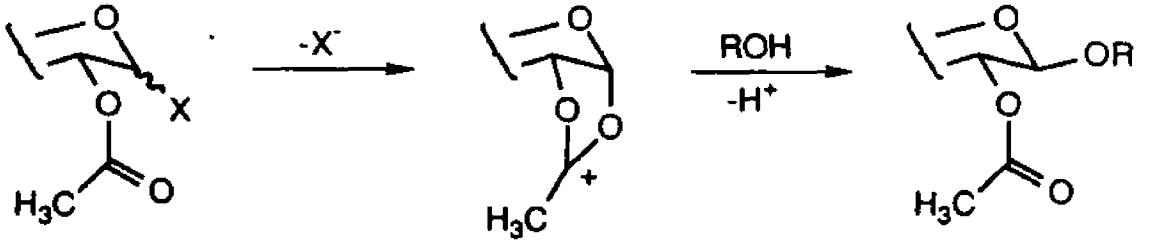
C. The final link between the saccharides and the aglycon.

There are three total syntheses of the aglycone **5** (Part A) and several syntheses of the di- and tri- saccharides (Part B).[1,3] The third and most important part, which will lead to the synthesis of semi-synthetic drugs, has not yet been accomplished. A practical 2-deoxy-β-glycosidation method needs to be developed so as to attach the sugars to the aglycone.

β-Glycosidation background

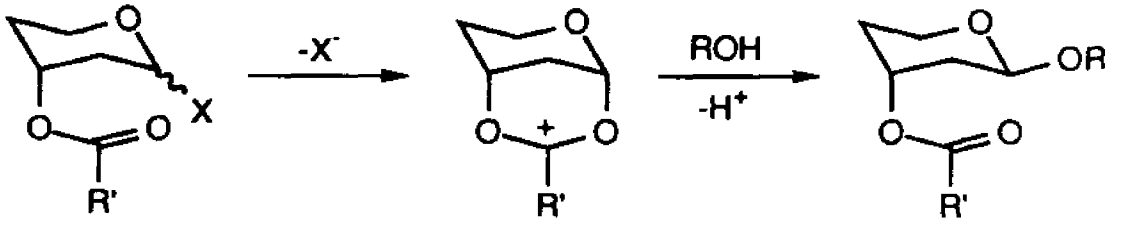
A review of the literature showed that stereoselectivity in the synthesis of β-glycosidic linkages between pyranoid ring systems is most easily achieved when a properly positioned C-2 substituent directs glycoside formation[4] (Scheme 1).

Scheme 1:



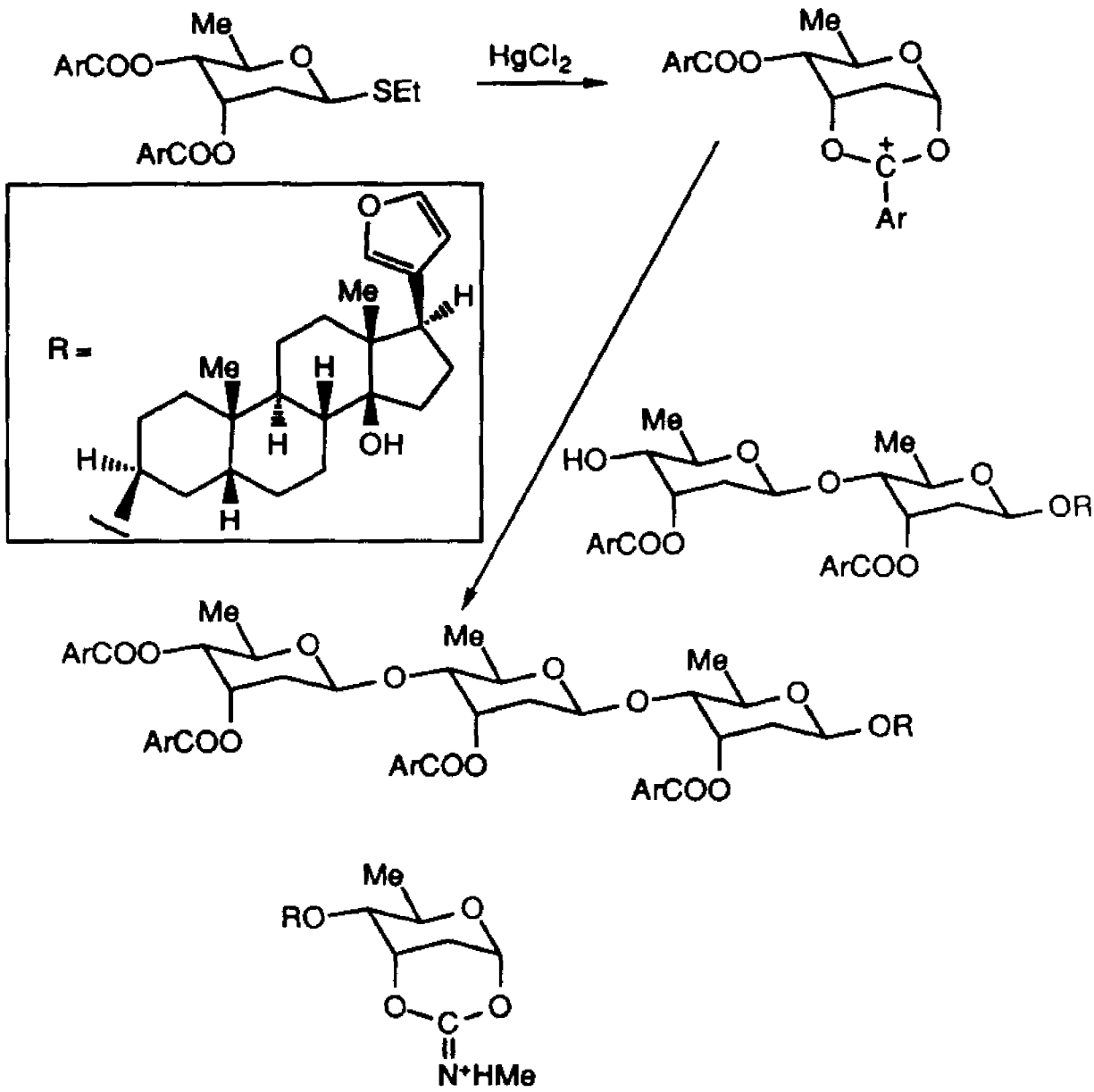
In the case of 2-deoxy glycosides where there is no functional group attached to C-2 or if the C-2 substituent does not participate in the reaction, β-glycoside formation still can be realised through other means. One of these is by participation of a group attached to another carbon atom (Scheme 2)

Scheme 2:



Wiesner and coworkers[5] have experienced success in the case of stereoselective 2-deoxy-β-glycosylation of digitoxose. They have utilized mercuric-ion catalysed cleavage of thioglycosides and a 1,3 -participation of a p-methoxybenzoyl group in a neutral medium (Scheme 3). Stereocontrol by 1,3-participation of a N-methylurethane[4] group and acetyl group[6] has also been achieved. In the former case an intermediate charged species, **6**, is believed to account for stereoselection.

Scheme 3:

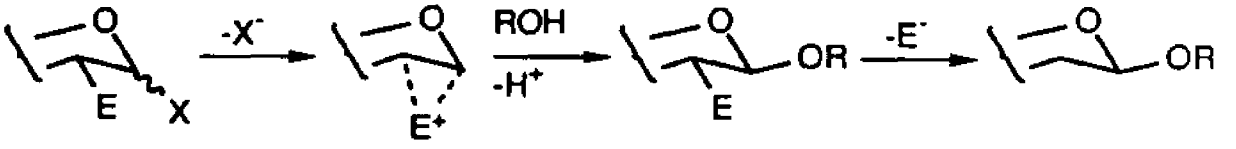


6

Binkley's group observed low stereoselectivity during the synthesis of 2,6-dideoxy disaccharides[7] using benzyloxy or p-methoxybenzyloxy group at the C-3 position. This group has also reported a procedure for obtaining 2,6-dideoxy-D-ribo-hexopyranosyl derivatives from digitoxin. These derivatives represent a convenient source of starting materials with C-3 participating groups.[8]

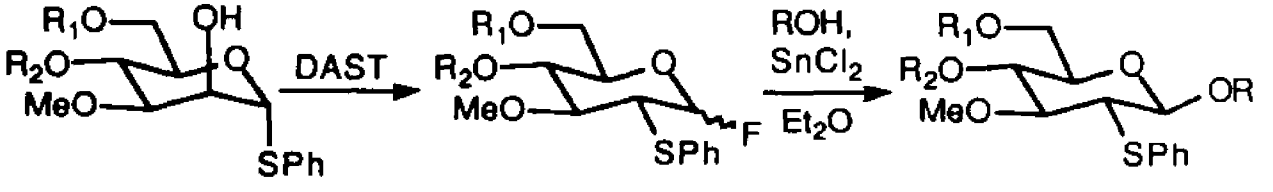
A second method is through use of a temporary participating group at C-2 which is removed after glycoside formation (Scheme 4).

Scheme 4:



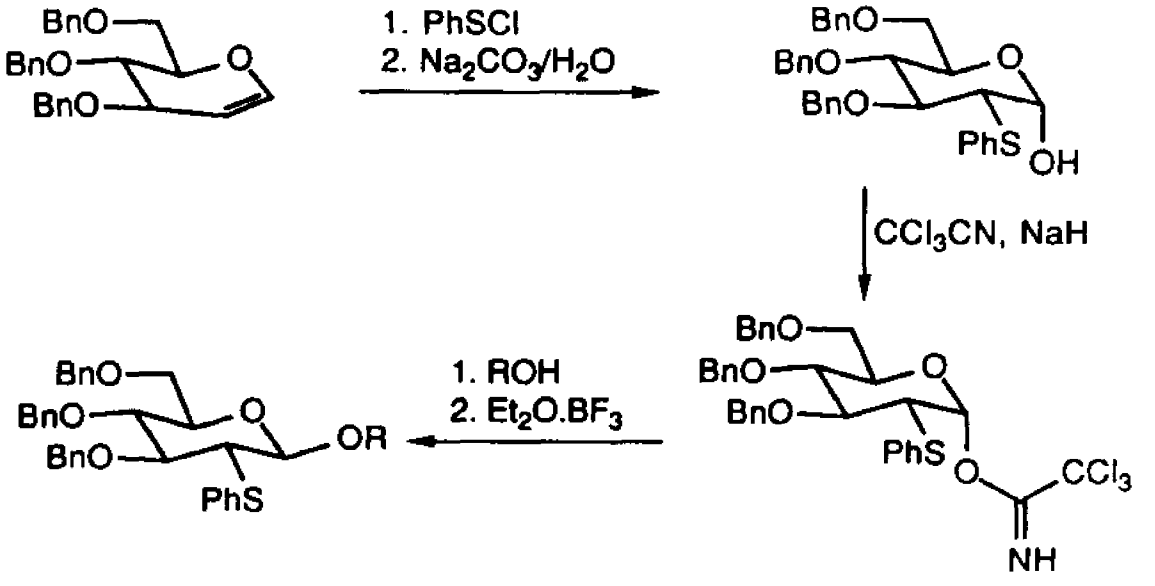
The recently introduced 2-phenylthio group as a neighboring group, generating an episulfonium ion intermediate during glycoside bond formation seems to be advantageous, because it is also readily removable by hydrogenation leaving behind the 2-deoxysugar. In the method introduced by Nicolaou et. al.[9] the required 2-deoxy-2-phenylthioglucopyranosyl fluoride was obtained from the corresponding mannopyranosyl-phenylsulfide via 1,2-migration with diethylaminosulfur trifluoride (DAST). This thioglycosyl fluoride in the presence of a tin-complexing solvent or reagent reacts with nucleophiles to give β-disaccharides as the major product (Scheme 5). The method has also been used for stereoselective glycosylation of sialic acid.[10]

Scheme 5:



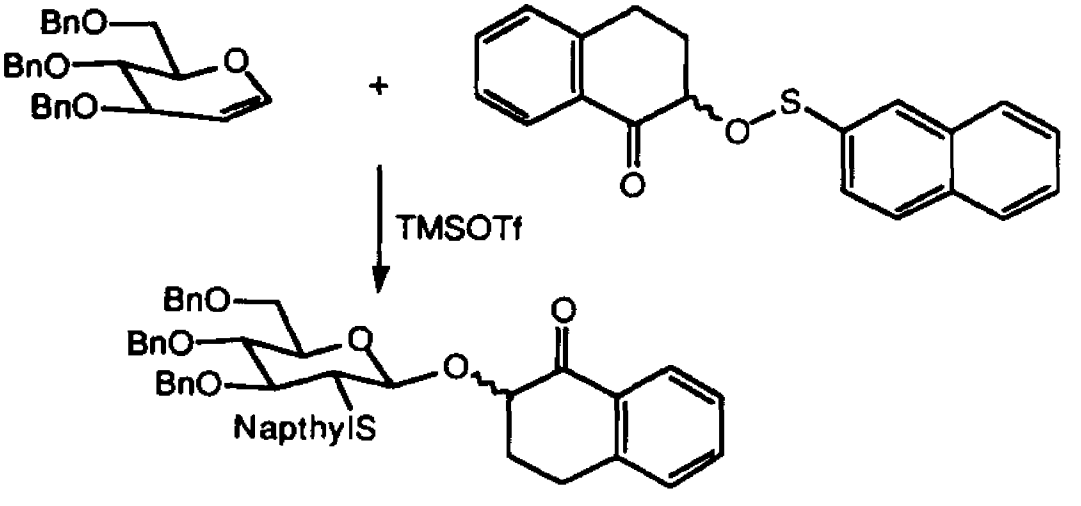
Schmidt's group synthesized O-(2-deoxy-2-phenylthio-α-D-glucopyranosyl)-trichloroacetimidate in two steps from D-glucal; the former with several alcohols gave mainly the corresponding 2-phenylthio substituted 2-deoxy-β-D-glucopyranosides (Scheme 6).[11]

Scheme 6:



A variation of this theme is the direct glycosyl transfer of glycals with sulfenate esters of the aglycone in a one-step transfer. This work was done by Ogawa's group.[12] Franck and coworkers have done the same reaction using the napthyl sulfenate ester of 2-hydroxy tetralone to synthesize the first 2-thio-β-glycoside of acyloin(Scheme 7).[13]

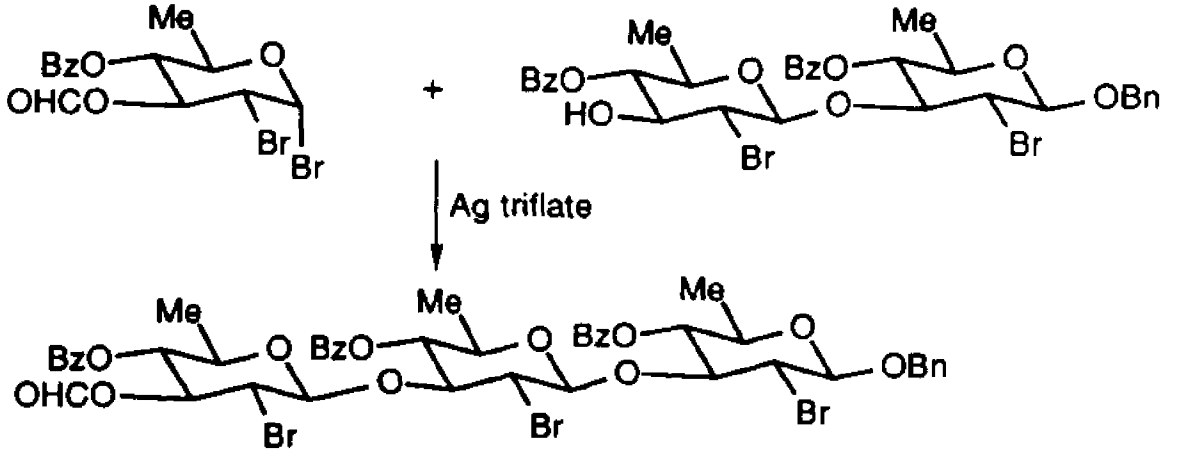
Scheme 7:



One of the common conversion sequences consists of Koenigs-Knorr reaction of 2-bromo-2-deoxy-α-D-glucopyrannosyl bromides with an alcohol in the presence of silver salts followed by replacement of the bromine attached to the C-2 with a hydrogen. Lemieux and Fraser Reid[14] in 1965 had reported such a reaction in presence of silver acetate. Binkley's group repeated this reaction and removed the bromine group at C-2 position photochemically.[15] Thiem has used the β-directing power of 2-α-bromo sugars in glycosidation and completed the preparation of the A'-B' and C'-D'-E' all β-saccharides of the aureolic acid series (Scheme 8).[16] They have also used this method for synthesis of bamflalactone acetate.[17] Silver triflate was found to be the best promoter.

Several other groups[18] have used this methodology and experimented with promoters like silver silicate, silver oxide and mercury(II)iodide.

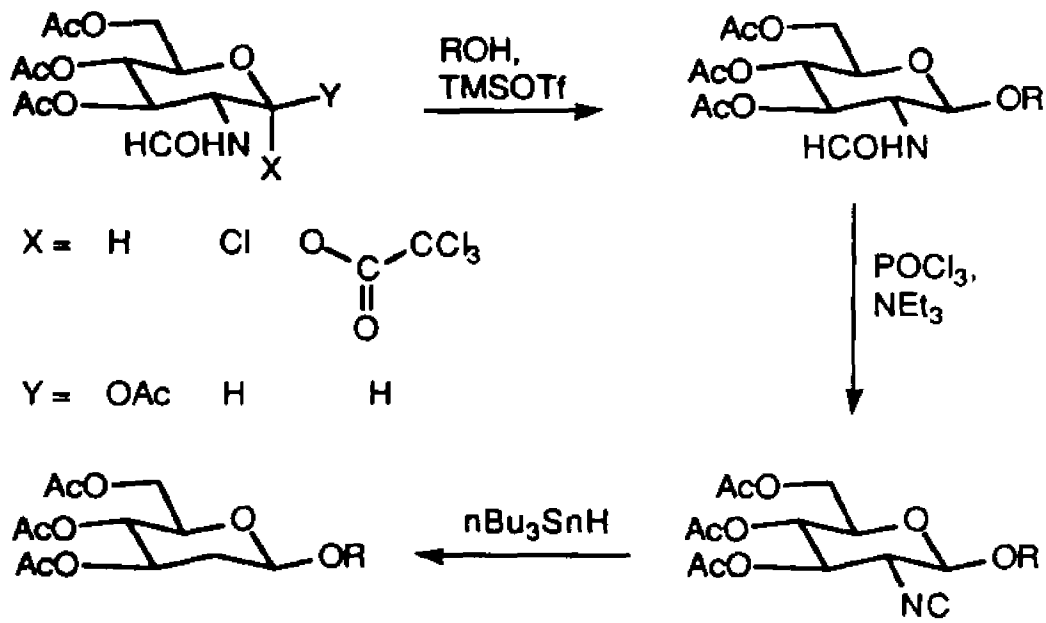
Scheme 8:



The N-iodosuccinimide method which is a slight variation of the theme, involves direct glycosylation of glycals via iodonium ion intermediates. It has been used successfully for synthesis of 2-deoxy-α-glycosides.[19] The procedure, however, works with only moderate success for β-anomers.[20]

Various derivatives of N-formyl glucosamine (β-acetate, α-chloride, α-trichloroacetamidate) have been used as glycosyl donors (Scheme 9).[21] The N-formylamino group at C-2 can easily be removed through intermediate isonitriles by radical reduction.

Scheme 9:

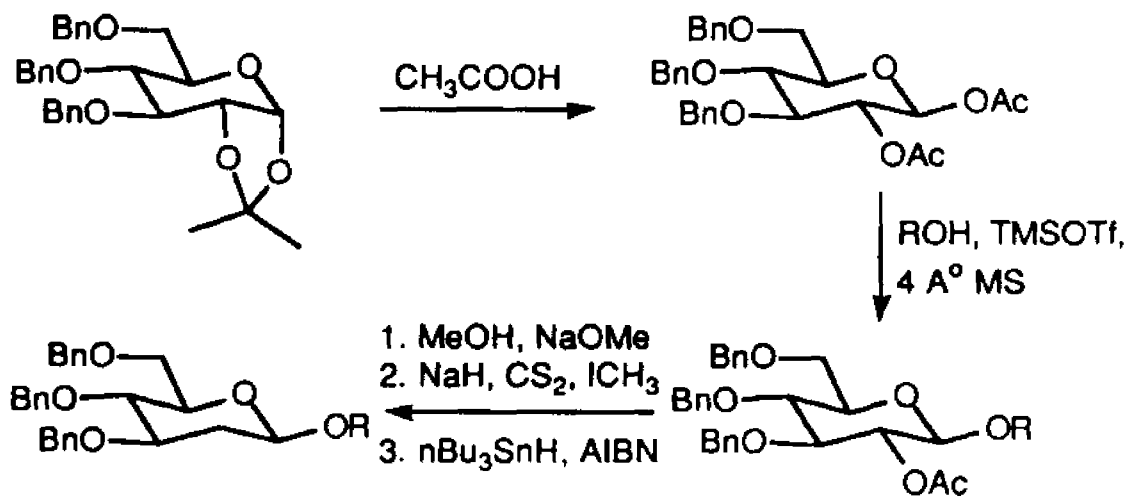


The phenylseleno group can also be used as a temporary participating group. 1,2-Trans diequatorial acetoxy-selenides, selectively prepared from glycals, react with sugar alcohols in the presence of a catalytic quantity of trimethylsilyl trifluoromethanesulfonate to give 2-deoxy-2-phenylseleno-β-pyranosides as the major products.[22] The selenide group has also been used as a stereocontrolling auxilary for selective glycosylation of sialic acid.[23]

Easily available orthoesters such as 1,2-t-butyl orthoacetyl-α-glucopyranose[24] or its 1,2-trans-di-O-acetyl[25,21b] derivative can be used as glycosyl donors. The latter give better yields and selectivities (Scheme 10). A variation in the strategy involves direct epoxidation of glycals using dimethyldioxirane, the products are

1,2-anhydro sugars. The latter on glycosylation form β-glycosidic linkages.[26] In all the above cases the acetate group at C-2 position can be removed by hydrolysis and radical deoxygenation. In a similar approach, the D-C disaccharide of Chromomycin A_3 has been synthesized by selective deoxygenation at C-2 of a natural β-linked disaccharide.[27] Kiss and coworkers[28] have used a p-tolylsulphonyl group at C-2 which is later removed using $LiAlH_4$.

Scheme 10:

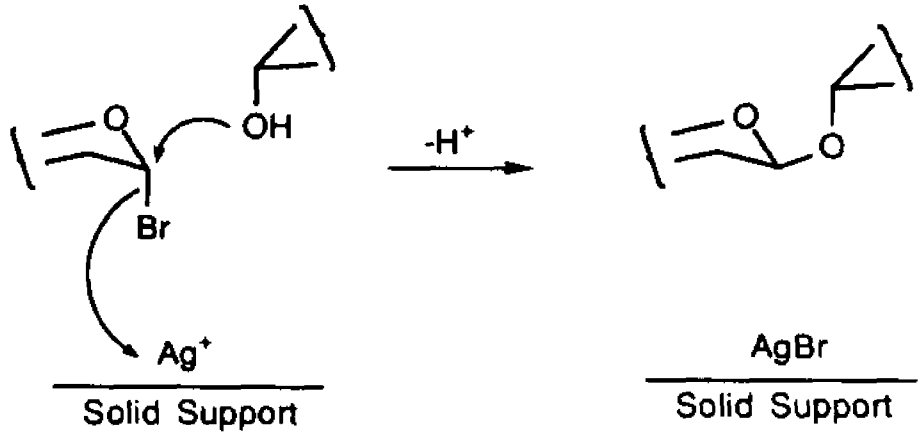


There have been reports of addition of oxymercuration of glycals. The product is a α,β mixture of 2-mercuri-2-deoxyglycosides. Reduction of the mercury compounds give the corresponding 2-deoxyglucopyranosides.[29]

A third method for β-glycoside synthesis which does not depend on group participation but rather on a combination of a 2-deoxy-α-glycosyl halide reacting with a partially protected sugar under conditions which promote reaction on the β-face of the halide (Scheme 11). In this approach selection of the reaction catalyst (an insoluble silver-ion containing salt) is critical. Silver

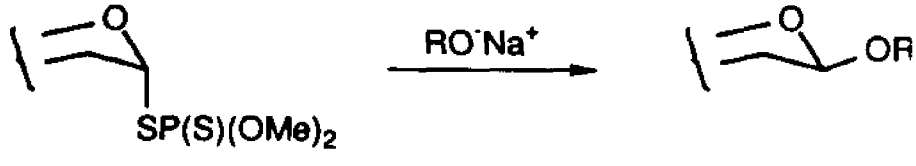
carbonate, silver silicate, silver triflate and silver zeolite have been used as promoters.[30] A mixture of mercury cyanide and mercury bromide was used for synthesis of trisaccharides containing N-acetylneuraminic acid[30d].

Scheme 11:



A novel approach involving a regio- and stereoselective addition of O,O-dimethylphosphorodithioic acid to glycals giving α-thiophosphate has been reported. The latter on reaction with sodium alcoholates give 2-deoxy-β-glycosides of simple alcohols in greater than 85% yield[31] (Scheme 12). Resin bound 2- and 4- nitrophenoxides have also been used as nucleophiles.[32]

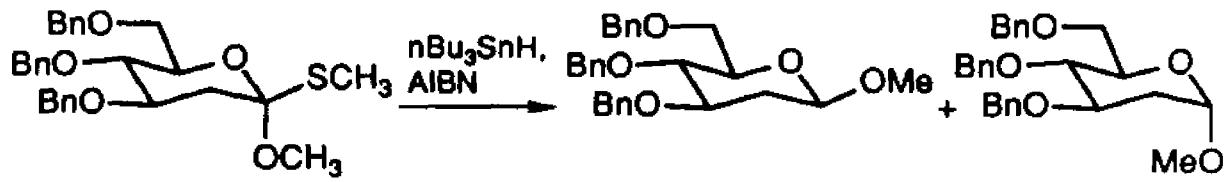
Scheme 12:



Stereoselective free-radical reactions have been used by two groups. This method relies on generating an alkoxy substituted radical at the anomeric

carbon of a sugar. Kahne's group[33] have photolytically reduced the hemithio ortho ester of 2-deoxy glucose (Scheme 13).

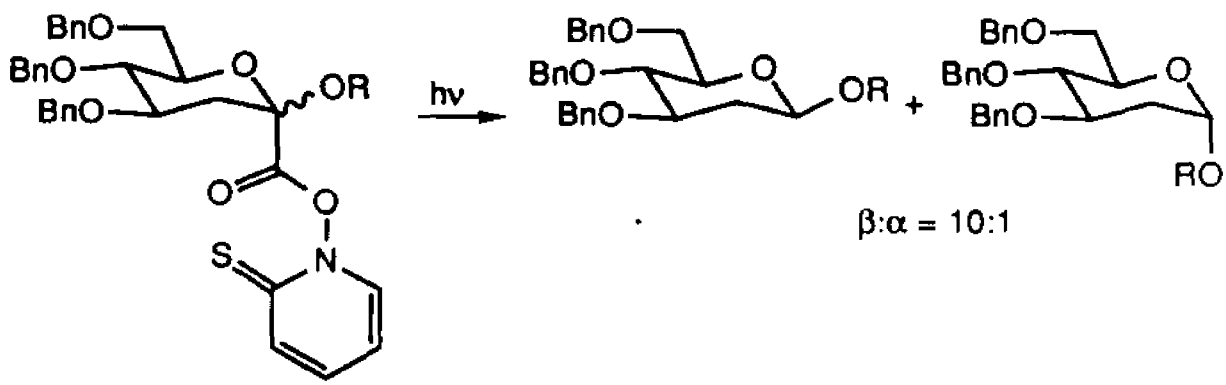
Scheme 13:



β:α = 6:1

In the case of Crich's work[34], decarboxylation of heptulosonic acid-O-glycoside by means of the derived O-acyl thiohydroxamates leads stereoselectively to 2-deoxy-β-glycosides (Scheme 14).

Scheme14:



β:α = 10:1

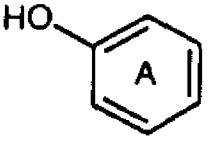
Stereoselective cyclization of acyclic precursors has been used to give β anomers predominantly. Treatment of (z)-(2R,3R,4R)-6-cyclohexyloxy-1,3,4-tribenzyloxy-5-hexen-2-ol with several kinds of organo selenium reagents, and the reduction of resulting seleno adduct with nBu_3SnH gave 2-deoxy-β-glycoside as the major product.[35] Recently several 2-deoxy steroidal glycosides were prepared via thionoester intermediates.[36]

Results and Discussion

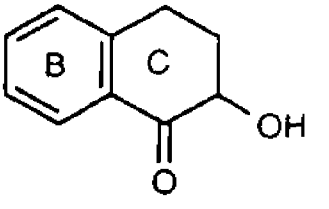
To be useful for an aureolic acid synthesis a 2-deoxy-β-glycosidation method must fulfill two important requirements.

(A) that the method work under the conditions where the acid- and base-sensitive aglycones can survive. To test this we chose phenol (**7**) as a model for ring A and acyloin (**8**) for rings B,C of the aglycone (figure **4** and **5**).

(B) Since the ultimate saccharides to be merged with aglycone must also be synthesized, the method used should not require a specialized sugar derivative as a glycosyl transfer agent.



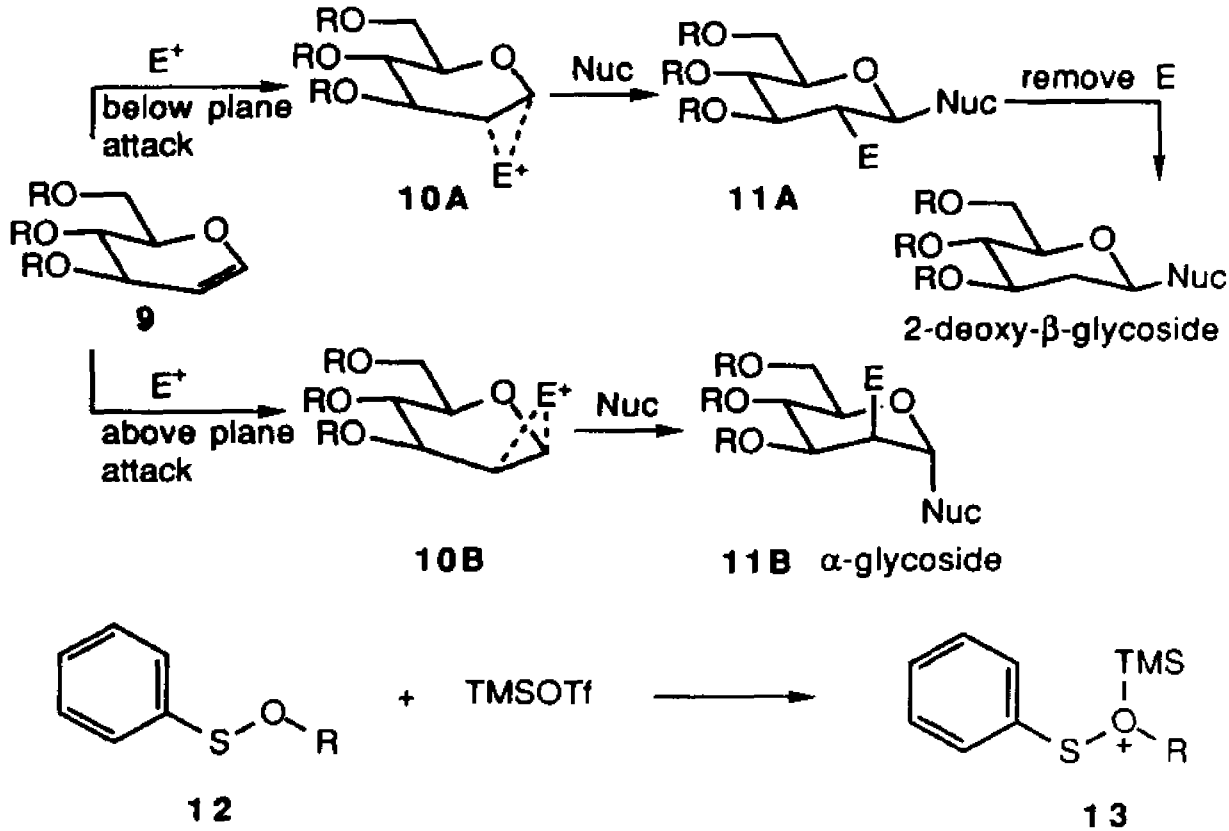
7



8

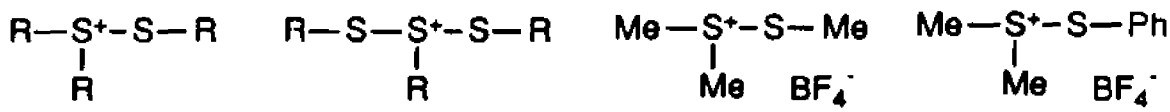
We favored schemes where simple glycals **9** were stereoselectively activated by below-plane electrophilic attack to form onium species **10A** followed by nucleophilic ring opening to form **11A** (Scheme 15). In our laboratory we first examined the Ogawa approach[12] where an aryl sulfenate ester **12** of the aglycon is preformed and then activated to a thiooxonium species **13** by trimethylsilylation. Using the above method we tried to synthesize 2-deoxy-β-glycosides of the model compounds. The model acyloin sulfenate ester was successfully synthesized and used as a glycosyl transfer agent (see page 8).[13] However, this method failed in case of phenolic aglycones since a sulfenate ester of phenol could not be prepared.

Scheme 15:



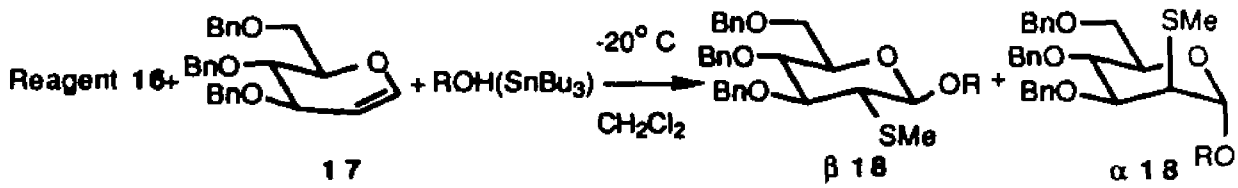
We believe that the mechanism of the Ogawa method involves an intermediate thiooxonium salt **13**, which is formed when TMS triflate reacts with the oxygen of the sulfenate ester **12**. The thiooxonium salt **13** is then attacked by the glucal to form the episulfonium salt as in Scheme 15, which is then opened by sulfenate ester to form product and a regenerated thiooxonium species. Thus, we reasoned that other reactive thioonium salts might serve to activate glucals for glycosylation.

Two types of thiasubstituted sulfenium ions, **14** and **15** are known in the literature.[37] Their synthesis and properties have been studied. In our laboratory, the commercially available methylthiosulfonium salt, **16** (type **14**) was used first. The results are shown in Table 1.[38]

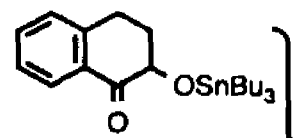
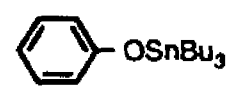


14 15 16 19

Table 1[a]: Glycosyl Transfers Using Reagent 16



17 β 18 α 18

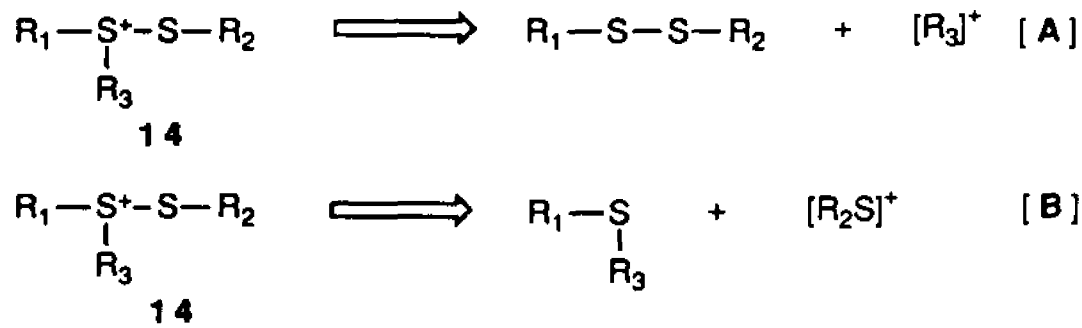
Entry	ROH($SnBu_3$)	ratio β/α	Yield %
1	MeOH	1.3/1	75
2		2.9/1	40
3		1/1	60

Models for aureolic acid

a: This work was done by S. Ramesh in our lab.

Though the salt was found to be a useful reagent for glycosyl transfer of glucal **17** to aglycones, problems arose in the desulfurization step. The final conversion of the 2-methylthio-2-deoxy-β-D-glucopyranosides β–**18** to 2-deoxy-β-glycoside was not facile. Several reagents[39] were tried for reductive removal of the methylthio group but none of them gave satisfactory results. Since the phenylthio group is relatively easy to remove we thought of using salt **19** (type **14**). The synthesis of thiasubstituted sulfonium salts **14** can be achieved by two different disconnections (Scheme 16) and both have been widely explored.

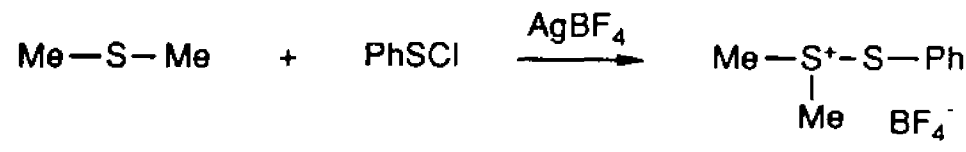
Scheme 16



14

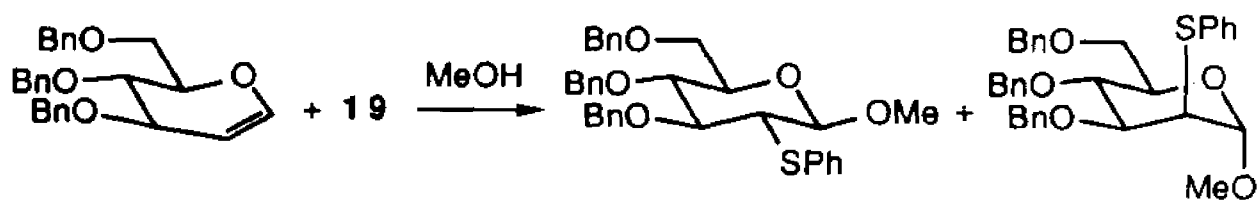
14

The disconnection of equation A corresponds to the alkylation of one sulfur atom of a disulfide, this approach has been tried only in a few cases as it suffers from severe limitations[37a]. We used the more general route reported in equation B i.e. the alkylthiolation of a sulfide. Phenylsulfenyl chloride **20**[40] was used as a sulfenylium ion 'RS$^+$' source. Reaction of dimethyl sulfide **21** with phenylsulfenyl chloride in the presence of silver tetrafluoroborate gave the dimethyl(phenylthio)sulfonium salt **19**. The reaction of methanol **22** with glucal **17** using reagent **19** afforded β and α glycosides **23** in the ratio 2/1[41] which is better than the ratio obtained when reagent **16** was used.



21 **20** **19**

Scheme 17:

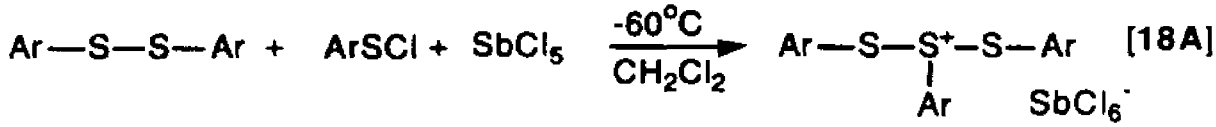


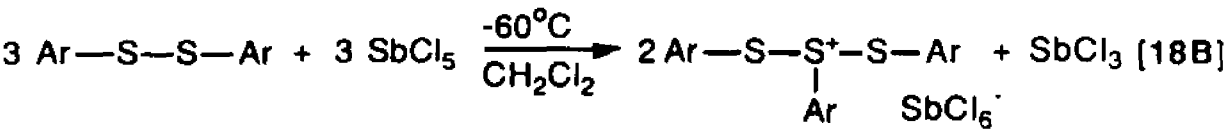
17 **β-23** **α-23**

At this time we were also looking at sulfonium salts of type **15**.

Aryl(bisarylthio)sulfonium salts **24** (type **15**) have been prepared using two general methods (A and B) Scheme 18, starting from arylsulfenyl chlorides, diaryldisulfides and antimony pentachloride[42,43] or diaryldisulfides and antimony pentachloride.[43] Use of other Lewis acids besides antimony pentachloride has been reported.[37a]

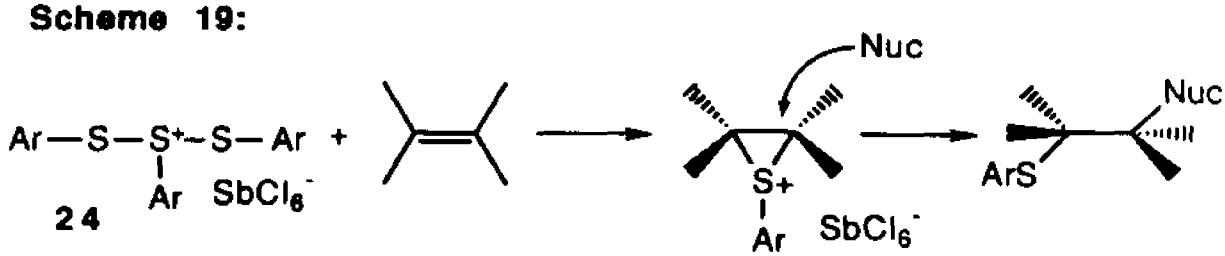
Scheme 18:





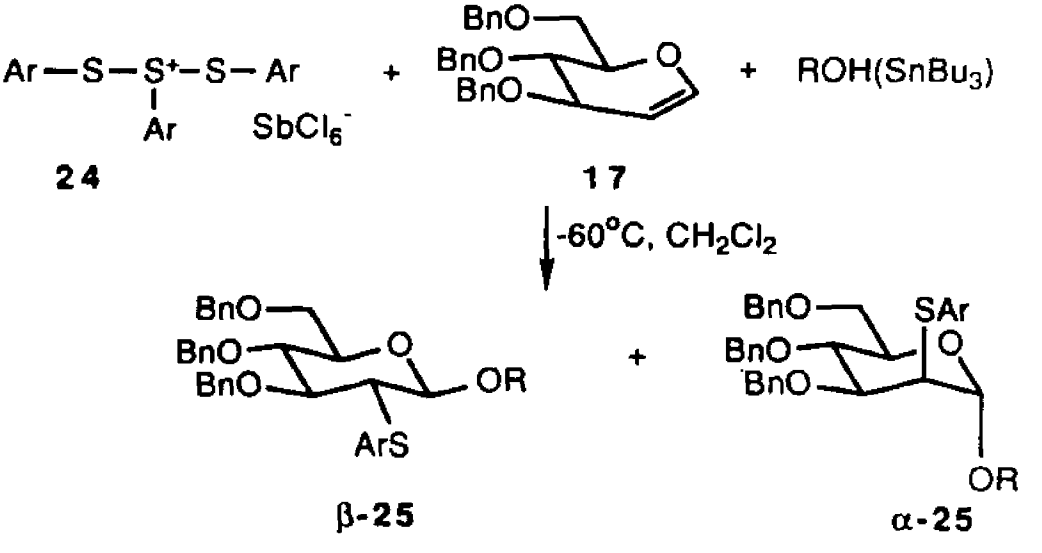
The aryl(bisarylthio)sulfonium hexachloroantimonates have been shown to activate simple alkenes toward nucleophilic addition (Scheme 19).[43,44] The intermediate 1-arylthiiranium ions (also known as the episulfonium ions) can be isolated at room temperature in some cases.[43] This use of dithiasubstituted sulfonium ions, **15** is dependent on the good leaving group properties and the weak nucleophilicity of disulfides. The thiasubstituted sulfonium ions **14**, exhibit similar reactivity. The side product in case of **14** is a sulfide molecule which is more nucleophilic than disulfides. Sulfonium ions **15** should therefore be more useful reagents for our purpose.

Scheme 19:



In our laboratory the aryl(bisarylthio)sulfonium salts **24** have in fact proven to be exceptionally useful reagents for glycosyl transfer of glycals to a variety of hydroxyl donors (aglycones)[38] Scheme 20. The results are documented in Tables 2 to 6. The reagents **24** have been found to be more β-selective compared to sulfonium salts **16** and **19**. In some cases the nucleophilicity of the aglycon hydroxyl group (ROH) must be enhanced by prior stannyl ether formation ($ROSnBu_3$).[45]

Scheme 20:

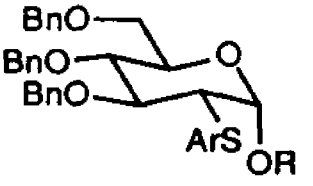


The sulfonium salts **24** were prepared using two methods (Schemes 18A and 18B).[43] In method 18A, a mixture of diaryldisulfide (1 equiv.) and arylsulfenyl chloride (1 equiv.) in dichloromethane is added dropwise with vigorous stirring to antimony pentachloride in dichloromethane (1 equiv., 1 molar soln.), at -60°C. The reaction mixture is stirred at -60°C for thirty minutes and used. In the second method, 18B, a solution of diaryldisulfide (1.5 equiv.) in dichloromethane is added dropwise with stirring to antimony pentachloride in dichloromethane (1.5 equiv., 1 molar solution) at -60°C, it is stirred for thirty

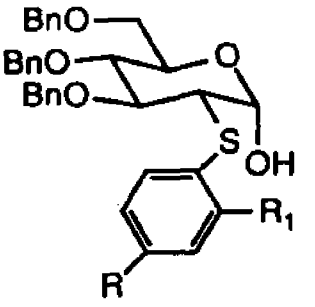
minutes at -60°C and used. The reagent prepared above can be stored at -70°C for three to four hours.

The glycosidation procedure is very simple, the reagent **24** (1.1 equiv.) at -60°C (prepared using procedure 18A or 18B) is added to a mixture of tribenzylglucal (**17**, 1 equiv.) and alcohol (2 equiv.) in dichloromethane at -60°C. The reaction is over within ten minutes and quenched with saturated sodium bicarbonate. During our search for the optimal glycosidation conditions we observed that the procedure also works well if glucal **17** is added to a mixture of alcohol and thiosulfonium salt **24** at -60°C. But, the third alternative that is addition of alcohol to a mixture of glucal **17** and reagent **24** at -60°C results in uncharacterizable products. In the latter case the glucal and thiosulfonium reagent react to give products, which do not subsequently react with the alcohol to form glycosides.

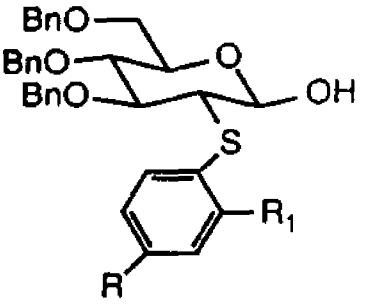
The two glycosides formed in this reaction are the 3,4,6-tri-O-benzyl-1-O-substituted-2-deoxy-2-phenylthio-β-D-glucopyranosides, β-**25** (referred to as the β-glycoside), and the 3,4,6-tri-O-benzyl-1-O-substituted-2-deoxy-2-phenylthio-α-D-mannopyranosides α-**25** (referred to as the α-glycosides). In some of the reactions we could isolate small amounts of the 3,4,6-tri-O-benzyl-1-O-substituted-2-deoxy-2-phenylthio-α-D-glucopyranosides **26** (referred to as the α'-glycosides). The 2-deoxy-β-glycosides are the major products observed in all the cases. In some of the reactions we have observed the α and β anomer of 3,4,6-tri-O-benzyl-2-deoxy-2-phenylthio-D-glucose (**27** and **28**) as the byproducts.



26



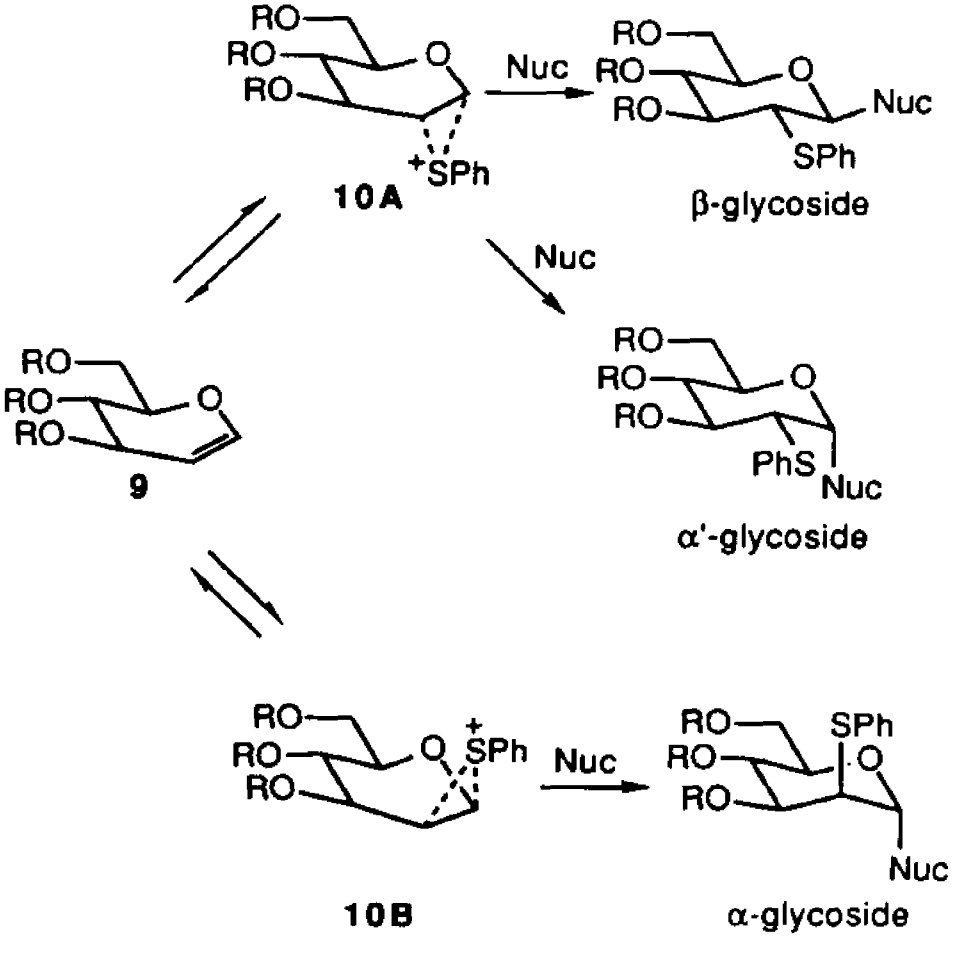
27



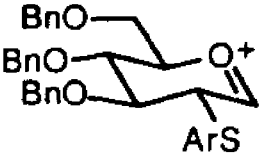
28

Formation of β and α' glycosides can be envisioned as a result of below plane electrophilic attack on glycal **9** to give intermediate onium species of type **10A** Scheme 15 (repeated below).

Scheme 15:



Nucleophilic ring opening of **10A** from the top face will give the β glycosides (β-**25**). Where as attack of nucleophile from the bottom face of 10A results in α' glycoside **26**. The latter is sterically unfavorable but favored by the anomeric effect.[46] Glycoside **26** can also be derived from axial attack of nucleophile on the oxonium species **29**. A third possibility is the epimerization of β glycoside (β-**25**) at the anomeric center, by endocyclic or exocyclic cleavage to give **26**. The top face electrophilic attack on glycal will give intermediate of type **10B**. Below plane ring opening of **10B** by a nucleophile results in α glycoside (α-**25**).



29

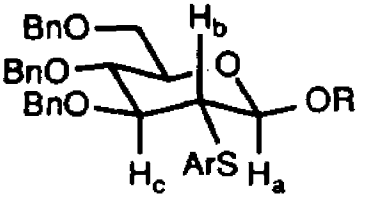
30

The formation of byproducts **27** and **28** can result from either competition of traces of water with the desired nucleophile or by hydrolysis of final products (β-**25** and/or **26**). Stereochemical outcome of the byproducts in the case where water is competing with the nucleophile can be explained in the same fashion as β (β-**25**) and α' (**26**) glycosides (discussed above). In case of final product hydrolysis, compound **28** can be formed if the thiophenyl group shows neighboring group participation during hydrolysis and directs attack of water from the top face. Byproduct **27** can result from axial attack of water i.e. when the anomeric effect dominates. Another route to obtain **27** is by anomerization of **28**. It is possible that the product hydrolysis occurs during workup of the reaction where the antimony Lewis acid (e.g. $SbCl_6^-$, $SbCl_3$) in the presence of water are hydrolyzing glycosides faster than they are being neutralized by base

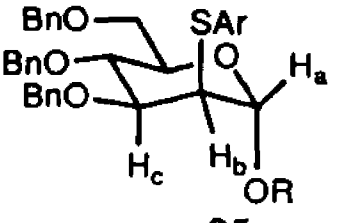
(sodium bicarbonate). To test this we tried to use an anhydrous secondary amine[47] as a quencher but could not improve the yields. We have not been able to discover an appropriate non-aqueous base to neutralize these reactions. Since our target molecules are 2-deoxy-β-glycosides, **30**, we have used WII Raney nickel in THF to desulfurize glycosides **β-25** in reasonable yields.[11]

Structure Assignment

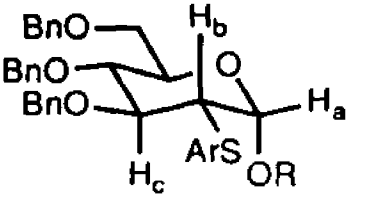
We have used proton NMR data to assign the relative stereochemistry of the isomeric glycosides. The chemical shift values of the protons of different glycosides do not vary much but coupling constant values give conclusive information and have been used for structure proof.



β-25



α-25



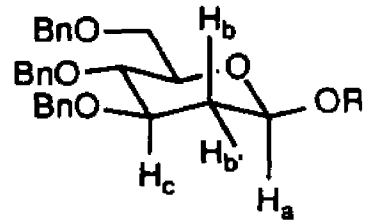
26

The glycosides **β–25** have been assigned on the basis of the proton H_b signal. This proton appears at high field compared to the other ring protons since it is attached to the thiophenyl substituted carbon C-2 and has an axial orientation. It shows a doublet of doublets with two large diaxial couplings (J = 8-12 Hz), to H_a and H_c. The peak for the H_a proton is merged with the ring protons (due to its axial orientation it comes at high field compared to H_a proton in α glycosides, see below).

The glycosides α-**25** were characterized by the proton H_a. This proton is at low field compared to the other ring protons because it is anomeric and has equatorial orientation. It appears as a doublet with small diequatorial coupling (J = 0-4 Hz) to H_b. Only in some of the cases does proton H_b appear at high field enough to be resolved from the ring protons. It shows a doublet of doublet due to two small couplings with H_a (diequatorial) and H_c (equatorial-axial, J = 0-4 Hz). For compounds where the H_b proton (because of its equatorial position it comes low field compared to the H_b proton for β glycosides) is overlapped with other protons the glycoside structure is assigned by a process of elimination or by proton NMR comparison with α glycosides of similar structure. These assignments were further comfirmed by 2D homonuclear COSY of one representative example from the β and α series where each ring proton was identified (See appendix page).

The α' glycosides, **26**, show a low field doublet for H_a. This proton appears separate from the ring protons and shows small equatorial-axial coupling with H_b. Most of the times the H_b proton signal is at high field and appears as a doublet of a doublet showing one large diaxial (with H_c) and one small equatorial-axial (with H_a) coupling.

The side products **27** and **28** are assigned on the same basis as α' and β glycosides respectively, except that no protons for the nucleophile can be seen. The signal for hydroxy proton at the anomeric center is confirmed by D_2O exchange. Homonuclear 2D NMR of one representative case in each series was taken.



30

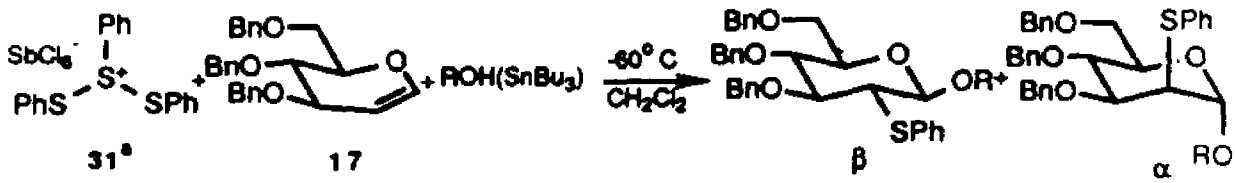
The structure assignment of 2-deoxy-β-glycosides, **30**, was done by high field C-2 protons H_b and $H_{b'}$. Due to its axial orientation H_b appears at higher field compared to $H_{b'}$. In addition proton H_b shows two large diaxial couplings (with H_a and H_c) and geminal coupling with $H_{b'}$. Whereas proton $H_{b'}$ shows two small axial-equatorial couplings (with H_a and H_c) and geminal coupling with H_b.

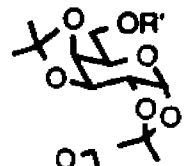
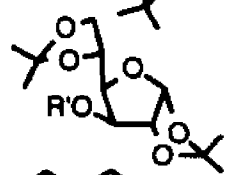
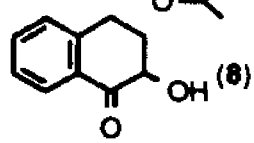
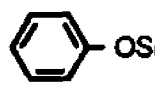
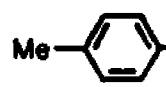
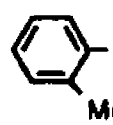
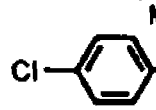
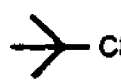
In the proton decoupled ^{13}C NMR of the glycosides the sulfur substituted C-2 carbon can be identified at higher field (chemical shift 55-60 ppm) from the other oxygen substituted ring carbons. The anomeric C-1 carbon shows a low field signal, chemical shift between 100-105 ppm.

A. Role of Nucleophile

We have used a range of nucleophiles to generalize our glycosidation method. The results of the reaction of glycal **17** with several nucleophiles in the presence of reagent **31** are documented in Table 2. The 3,4,6-tri-O-benzyl-D-glucal (**17**) used was prepared in two steps from the commercially available 3,4,6-tri-O-acetyl-D-glucal. The first step is deacetylation using basic (OH) resin. The trihydroxy glucal obtained is then benzylated.[48]

Table 2: Glycosyl Transfers Using Reagent **31**



Entry	ROH(SnBu$_3$)	ratio β/α	Yield %
1	MeOH (**22**)	3.7/1 (**23**)	83 (92[b])
2	isopropanol (**32**)	2.7/1 (**33**)	59
3	 (**34**)	5.3/1 (**35**)	70
4	 (**36**)	11.5/1 (**37**)	75
5	 (**8**)	no α isolated (**38**)	45
6	 (**39**)	4.3/1 (**40**)	64
7	 (**41**)	5.3/1 (**42**)	43
8	 (**43**)	3.7/1 (**44**)	30
9	 (**45**)	4.9/1 (**46**)	53
10	 (**49**)	5.7/1 (**50**)	60

a: Reagent **31** was prepared using procedure 18A for entries 1-6, 10 and procedure 18B for entries 7-9.
b: Reagent **31** was prepared using procedure 18B.

Reaction with methanol (**22**) resulted in β and α glycosides β-**23** and α-**23** in 3.7/1 ratio. The mixture of β-**23** and α-**23** could not be separated after repeated

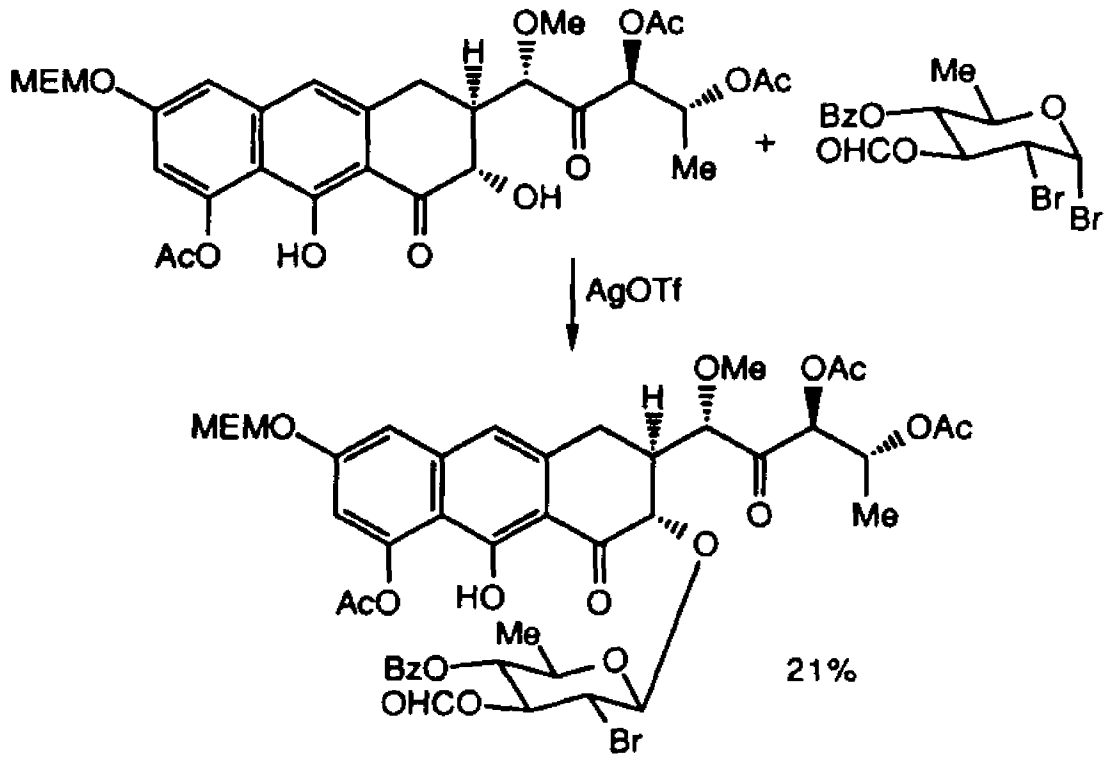
trials on HPLC. The β/α ratio was determined by the ratio of the heights of the signals for methoxy groups in the proton NMR. In few representative cases the validity of this method for determining the ratios was confirmed by running the proton NMR spectra with three different delay times (1 second, 3 second and 6 second). The β/α ratio did not change. Contrary to our expectations the reaction with isopropanol (**32**) a secondary alcohol showed lower selectivity β/α ratio is 2.7/1. The overall yield of the glycosides (β-**33** and α-**33**) was only 59%. We could isolate byproducts **27** and **28** ($R=R_1=H$) in 17% and 10% yield respectively.

Our method shows high yield and diastereoselectivity with sugars as hydroxy donors. Di-isopropylidenegalactose derivative **34** ($R'=SnBu_3$) with glycosyl donor **17** afforded anomer β-**35** as the major product (β/α=5.3/1). A small amount (4%) of the α' glycoside **26** ($Ar=C_6H_5$; R=6'-{1',2',3',4'-diisopropylidene}galactosyl) was isolated. The tin ether **34** ($R'=SnBu_3$) was prepared by refluxing the galactopyrano derivative **34** (R'=H), bis(tri-n-butyltin)oxide and molecular sieves in toluene for twelve hours[45]. The toluene was distilled off and the reaction mixture used as such for the glycosidation step. Compound **34** (R'=H) gave disaccharides **35** in lower yield.

Reaction of glucal **17** with the diacetonide of glucose derivative **36** ($R'=SnBu_3$) afforded disaccharides **37** with extraordinary high selectivity (β/α=11.5/1) and yield (75%). The α' glycoside **26** ($Ar=C_6H_5$; R=3'-{1',2',5',6'-diisopropylidene}glucosyl) could be isolated in 6% yield. The mixture of α and α' glycosides could not be separated. Their ratio was determined by proton NMR. The tin ether **36**($R'=SnBu_3$) was prepared using the same procedure as for the galactose derivative(**34**, $R'=SnBu_3$). Reaction of **36** (R'=H) with glucal **17** gave dissacharides **37** in lower yields as compared to the stannyl ether

nucleophile. Also the 5,6-acetonide was partially cleaved. In both the reactions with sugar nucleophiles byproduct **28** ($R=R_1=H$) was formed in 10-15%yield. Next we used acyloin **8**, a model for the BC ring system of aureolic acid, as the nucleophile. The product was exclusively the anomer **β-38** in 45% yield. Byproduct **28** ($R=R_1=H$) was formed in 20% yield. No other characterizable products were isolated, also, the acyloin was not recovered. We think that the reason for low yields is that our acyloin is somehow destroyed by reaction with the reagent. The only other synthesis of a 2-deoxy-β-glycoside of acyloin has been done in our laboratory with high yields using Ogawa's method[13]. Thiem's group has tried to use the NIS method with diacetyl-L-rhamnal as the glycosylating agent for the synthesis of 2-deoxy-β-glycosides of α-hydroxy tetralone. This route gives only the unnatural α-glycosides.[49] In an unpublished thesis[50] from Prof. Thiem's lab. there is described the attempted Koenigs-Knorr coupling of α-glycosyl bromide with olivin derivative to give 21% yield of the 2-bromo-2-deoxy-β-glycoside (Scheme 21).

Scheme 21:

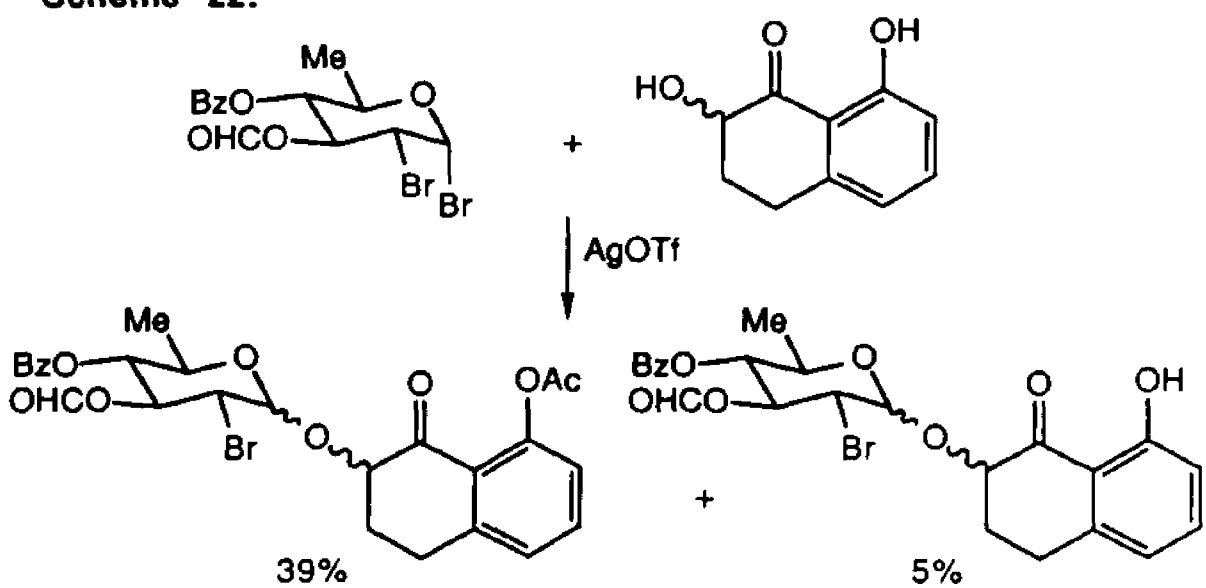


In our acyloin synthesis using the thiosulfonium reagent **31** a series of reaction conditions have been tried. We have varied reaction times and quantities of nucleophile used but no improvement in yields could be achieved. Use of the tin derivative of acyloin **8** did not give any better results. Since the acyloin used is racemic two diastereomeric glycosides **β-38** are possible. The two β diastereomers were formed in the ratio 10/1. We observe stereoselection of one enantiomer of the alcohol. That is the reaction path for one enantiomer of the alcohol to form glycoside is of significantly lower energy than the path for the other enantiomer. We do not know which enantiomer is preferred. A second possibility is that both β diastereomers are formed but equilibrate to the more stable β glycoside in the reaction conditions.

Enantiomeric discrimination in acyloin glycosides has also been seen by Thiem's group,[51] Scheme 22. They have observed the deacetylated product

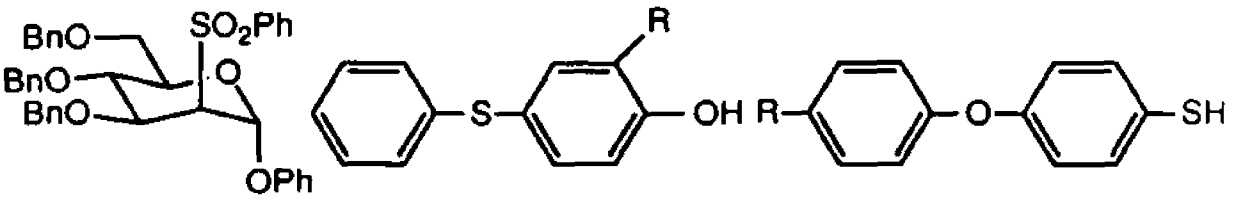
arising from only one enantiomer of acetate though only in 5% yield. During enzymic glycosylation of racemic alcohols enantiomeric stereoselectivity has been observed by Tanaka's group[52] and to a moderate extend by Satoh and coworkers.[53] We have tried to use other racemic alcohols (e.g. tetralol, α-methylbenzyl alcohol) to see if this phenomenon can be generalized and to determine what structural parameters of the racemic alcohols permit one enantiomer to be selected above the other. Our attempts have not been successful so far.

Scheme 22:



The tin ether derivatives of phenol and several substituted phenols (models for ring A of the aureolic acid antibiotics) have also been used as aglycones. We could not isolate any products when phenol **7** was used as the nucleophile. The phenyl tin ethers can be prepared by stirring a mixture of phenyl acetate and tri-n-butyltin methoxide at room temperature overnight. Phenyl tributyltin ether, **39**, on reaction with glycosyl donor **17** afforded glycosides **40** in 4.3/1 (β/α) ratio, overall yield 64%. In the proton NMR of glycoside α-**40** the H_b proton is mixed with the ring protons. We oxidized the C-

with the ring protons. We oxidized the C-2 thiophenyl group to a sulfone (α-**40A**) using m-CPBA to see if this would separate the H_b proton from the other protons. Unfortunately the NMR of the sulfone was of no help. Therefore we characterized compound α-**40** by analogy to other substituted α-phenylglycosides Byproducts **27** and **28** ($R=R_1=H$) were isolated in 16% and 8% yields respectively. We have tried this glycosylation several times in completely dry conditions to ensure that there is no water present in the reaction but the formation of **27** and **28** ($R=R_1=H$) could not be avoided. Treatment of glycoside β-**40** with the glycosidation reaction conditions gave a mixture of β-**40** and byproduct **27** ($R=R_1=H$). This would indicate that at least part of **27** ($R=R_1=H$) comes from product hydrolysis. On the other hand, when α-**40** was subjected to the glycosidation reaction conditions, it was recovered unchanged. As mentioned above we have not been able to find a solution to this problem. Triethylamine and trimethylsilyldiethylamine have been tried as the non-aqueous quenchers to avoid product hydrolysis. The best selectivity in this series was obtained with the para-methylphenyl tin ether, **41** (β/α=5.3/1). The ortho-methylphenyl tin ether **43** gives lower selectivity (β/α=3.7/1) and yield of glycosides **44**. The p-chloro substituted phenyl tin ether **45** afforded glycosides **46** (β/α=4.9/1) in 53% yield. In all the reactions with substituted phenyl tin ethers byproducts **27** and **28** ($R=R_1=H$) were obtained in 25-30% and 10-20% yields respectively. One of the side reactions observed is the electrophilic attack by PhS^+ on para position of phenol nucleophiles giving products like **47**. But in case of para substituted phenols the oxygen attacks the para position of PhS^+ to give compounds of type **48**.



α-40A 47 48

There have been other reports of the synthesis of phenyl glycosides. Kiss and coworkers[28] have used rather drastic conditions to deoxygenate the 2-position for the synthesis of 2-deoxy-β-phenylglycoside. The method by Michalaska's group[31,32] affords the 2-deoxy-β-(nitrosubstitutedphenyl)glycosides. Binkley[30f] and Crich's[34] group synthesized orthomethyl substituted phenyl glycosides as models for ring A of chromomycins (**2**).

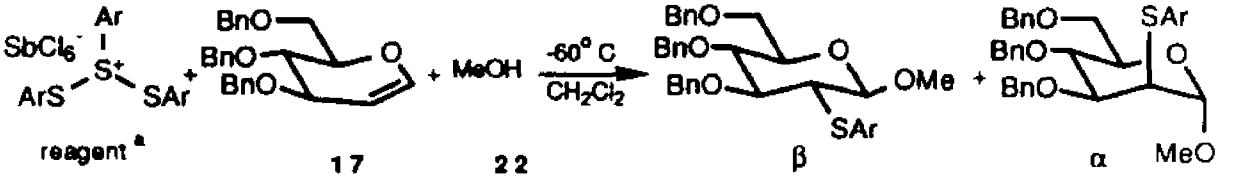
Thus, we have demonstrated that our glycosidation method can be used for stereoselective syntheses of 2-deoxy-β-glycosides. It works for both phenols and acyloins as well as the more common primary and secondary sugar alcohols. The face selectivity depends on the nature of the nucleophile.

B. Optimal thiosulfonium reagent

In our search for the BEST reagent, that is a reagent which gives high β selectivity, we varied the substituents on the phenyl ring of the aryl(bisarylthio)sulfonium reagent **24**. Tables 3 and 4 show the results. In these reactions we wanted to use a nucleophile which gave a high field signal in the proton NMR away from all the other protons of the glycoside so that the ratio of β and α glycosides formed could be determined from the mixture of the glycosides without any need for tedious separations. Neo-pentyl alcohol **49** which shows a signal around δ0.93 for nine protons seemed an ideal choice. Reaction of glucal **17** with **49** in the presence of reagent **31** afforded

glycosides **50** in β/α ratio of 5.7/1 and 60% overall yield (Table 1). The high field signal of -C(CH_3) protons for α and β glycosides **50** overlapped with each other and therefore alcohol **49** could not be used. We decided to use methanol **22** as the hydroxyl donor where the methoxyl signal for the α and β glycosides appear separately. All the sulfonium reagents used in tables 3 and 4 were prepared using procedure 18B. The required aryldisulfides were synthesized by heating the corresponding aryl thiols in DMSO at 80°C for eight hours.[54]

Table 3: Glycosyl Transfers to Methanol Using Different Reagents



Entry	Ar—		ratio β/α[a]	Yield %
1	Cl—	(51)	2.5/1 (52)	91.4
2	Me—	(53)	4.4/1 (54)	91.7
3	MeO—	(55)	2.4/1 (56)	82
4	Me, Me	(57)	4.1/1 (58)	90
5	Me	(59)	2.2/1 (61)	86.8
6		(60)	2.6/1 (62)	71.2

a: Reagents were prepared using procedure 18B.

I. Methanol as the nucleophile: At first we used the p-chlorophenyl{bis(p-chlorophenyl)thio}sulfonium reagent **51** for glycosyl transfer of glucal **17** to methanol. The glycosides **52** were formed in β:α ratio of 2.6:1 in 71% overall yield. The selectivity is lower compared to the unsubstituted phenylsulfonium reagent **31** (table 1). Since the chloro group, an electron withdrawing group, decreased the β selectivity of the reaction we tried the logical alternative of using an electron donating group. On using the p-methylphenyl{bis(p-methylphenyl)thio}sulfonium salt **53** the β/α ratio increased to 4.4/1. Glycosides **54** were formed in 92% yield. This increase in face selectivity could be due to "Less reactive reagent is more selective and vice versa". The positive charge on the p-methylphenylsulfonium salt is probably stabilized by the methyl group, which makes the reagent less reactive hence more selective. The opposite is true for an electron withdrawing group like chloro. This prompted us to try a stronger electron donating group, the methoxyl group. The p-methoxylphenyl{bis(p-methoxylphenyl)thio}sulfonium salt **55** afforded glycosides **56** in 82% total yield. But contrary to our expectations the β selectivity decreased to 2.4/1. The para methyl group is electron donating due to its inductive effect whereas the p-methoxyl group is donating through resonance effect. This difference in electron donating mechanism probably plays an important role in the reaction. Next we tried the 3,4-dimethylphenyl{bis(3,4-dimethylphenyl)thio}sulfonium reagent **57** to check if the inductive effect of the methyl group was additive. The β/α ratio (4.1/1) of the resulting glycosides **58** was almost the same as for reagent **53**.

Steric crowding around the sulfur in the sulfonium reagents lowers the β selectivity. For example the o-methylphenyl{bis(o-methyphenyl)thio}sulfonium salt **59** and the napthyl(bisnapthylthio)sulfonium salt **60** give glycosides **61** and **62** in β/α ratio of 2.2/1 and 2.6/1 respectively. In all the above cases the

ratios were determined by proton NMR. Thus the substituents on the phenyl ring of the reagent have an substantial effect on the stereochemical outcome of the glycosidation reaction. The p-methylphenylsulfonium reagent **53** has proven to be the most β selective reagent.

II. Phenyl tin ether 39 as the nucleophile: To test if the same trend in face selectivity exists in the case of other nucleophiles we studied the reaction of phenyl tributyltin ether **39** with glucal **17** in the presence of reagents **51**,**53**,**55** and **59**. The results are documented in table 4. Reaction with reagent **53** gave the highest β selectivity 5.7/1. Whereas the reagent with the electron withdrawing group, **51**, resulted in glycosides **64** in 1.7/1 β/α ratio, showing poor selectivity. The p-methoxylphenylsulfonium reagent **55** showed a decrease in ratio (β/α=2.4/1) as in the case of methanol nucleophile. Reagent **59** afforded glycosides **66** in β/α ratio of 2.6/1. In the above reactions corresponding byproducts **27** and **28** (R,R_1=Me,H; Cl,H; OMe,H; H,Me) were formed in 20-25% and 10-15% yield respectively. Para-substituted phenols of the type **67** are obtained as side products. These result from electrophilic attack of ArS^+ on **39**. Thus the effect of different reagents on stereoselectivity when **39** is the nucleophile is in the same direction but more pronounced compared to the case of methanol as nucleophile. The β/α ratio depends on the nature of the reagent used.

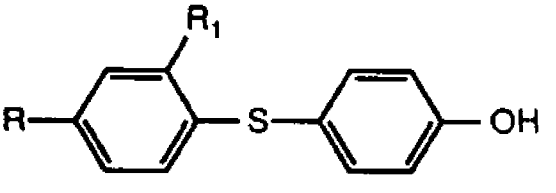


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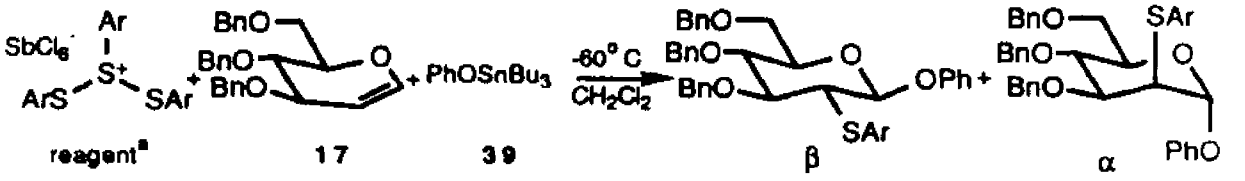
Table 4: Glycosyl Transfers to Phenol Using Different Reagents



reagent[a] 17 39 β α

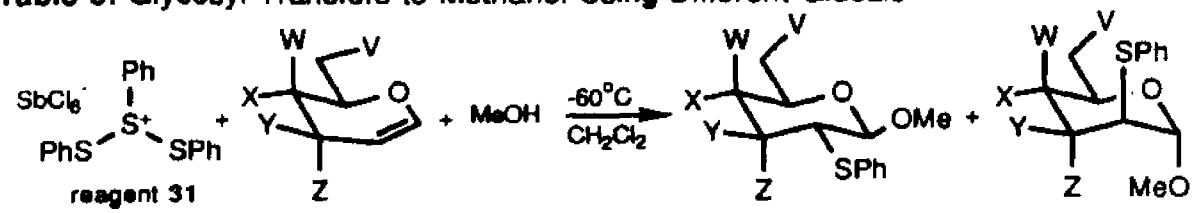
Entry	Ar—	ratio β/α	Yield %
1	Cl (51)	1.7/1 (64)	54
2	Me (53)	5.7/1 (63)	46
3	MeO (55)	2.4/1 (65)	61.7
4	Me (59)	2.6/1 (66)	47

a: Reagents were prepared using procedure 18B.

III. Role of glycal

To study the effect on stereochemistry of the glycal substrate, different glycals were examined using the phenyl(bisphenylthio)sulfonium reagent **31**. The results are given in tables 5 and 6. This work was done by G. Grewal of our lab[38].

Table 5: Glycosyl Transfers to Methanol Using Different Glucals



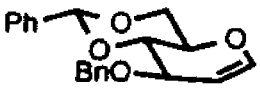
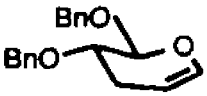
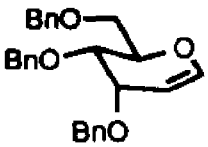
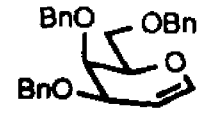
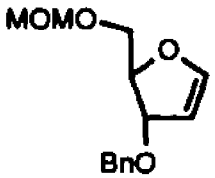
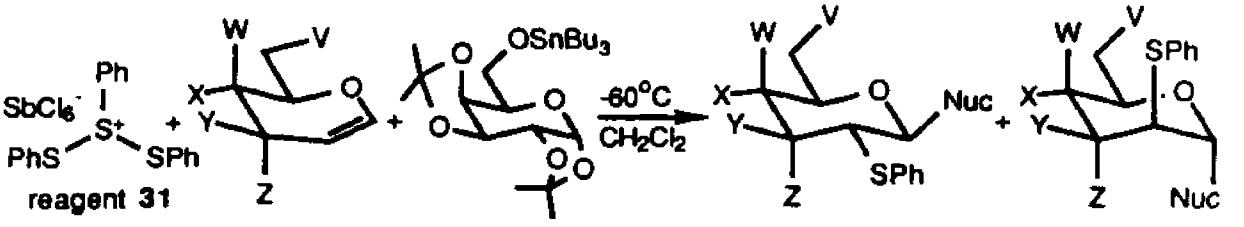
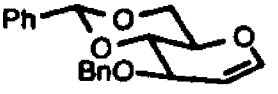
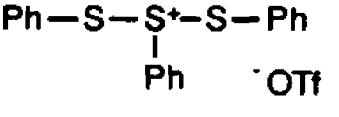
Entry	Glycal Substrate	ratio β/α	Yield %
1		3.7/1	94
2		2.7/1	86
3		2/1	76
4		2/1	62
5		2/1	80
6		1/10	80
7		12/1	92
8		2/1	90

Table 6: Glycosyl Transfers to Diisopropylidene galactose Using Different Reagents



Entry	Glycal Substrate	ratio β/α	Yield %
1		5.3/1	70
2		5.7/1	79
3		5.2/1	73
4		3.1/1	74

We have tried to use silver triflate as the Lewis acid to prepare reagents of the type **68** using procedure 18A. Glycosyl transfer of glucal **17** to methanol **22** using **68** resulted in only 25% yield of the glycosides **23**. The starting material was recovered, indicating that reagent preparation was not effective.



68

The data documented above shows that product distribution in our glycosidation procedure is a function of the nature of:

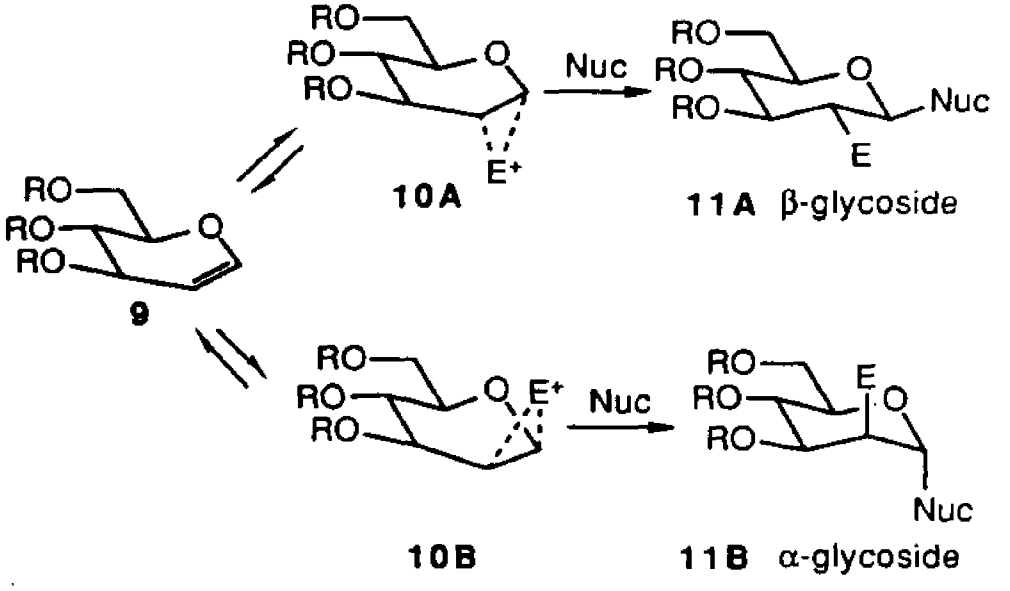
(a) Nucleophile

(b) Reagent

(c) Glycal

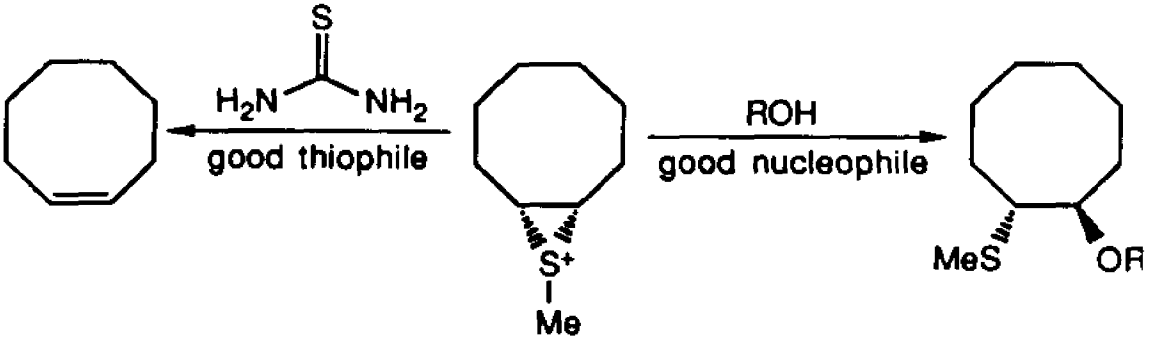
In the mechanism proposed earlier, scheme 15 (shown below), if the trapping of onium species (**10A** or **10B**) is fast, compared to their formation or reversal to glucal, then changing the alcohol nucleophilicity should have no effect on the product ratio. The use of an alcohol that is a poor nucleophile might change the rate determining step. If alcohol trapping is slow compared to equilibiration between **10A** and **10B**, then product ratios should be a function of alcohol nucleophilicity.

Scheme 15:



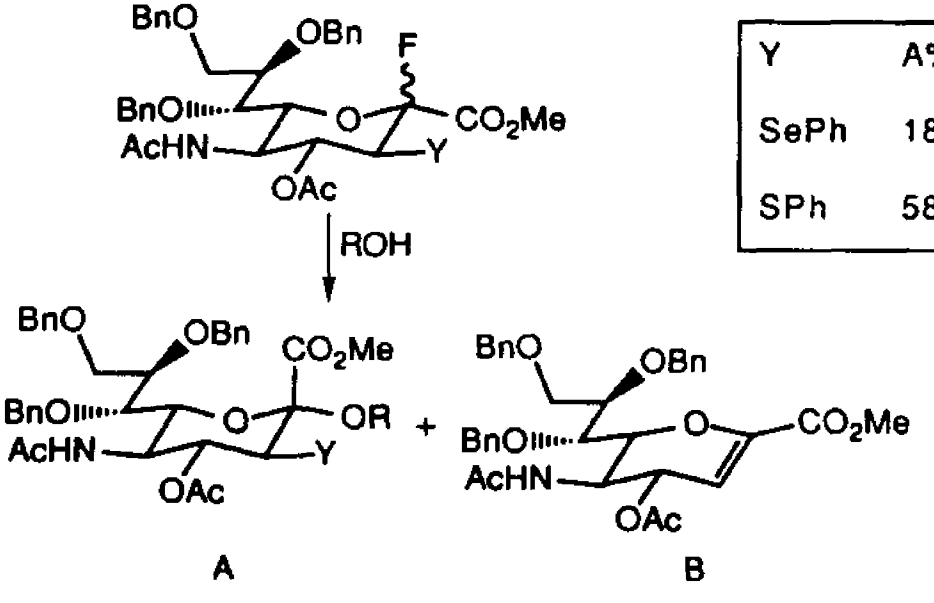
The other factor which will affect product distribution is the ease of reversibility of the initial electrophillic attack. An example of reversibility is shown in scheme 23[37a].

Scheme 23:



When the olefin is part of a sugar ring (glycal) reversibility of the electrophilic attack has been observed in case of selenium electrophiles by Ogawa and Ito[23b]. But when they replaced selenium with sulfur no products arising from the reversibility were observed (Scheme 24)

Scheme 24:

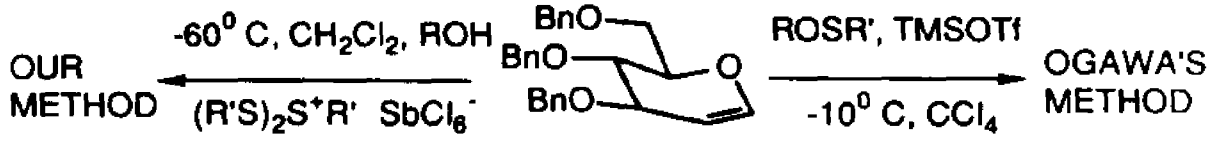


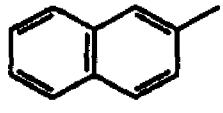
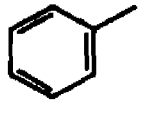
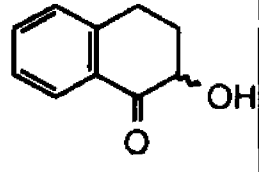
Y	A%	B%
SePh	18	69
SPh	58	0

Another possibility is that alcohols react with the sulfonium reagent to form sulfenate esters and the latter then attack the glycal as in the case of Ogawa's method.[12] To check this possibility we have compared our results with that of

Ogawa (Table 7). The stereochemical outcomes in entries 1 and 2 are not the same. The major difference is in the case of acyloin (entry 3). There is no enantioselectivity for one enantiomer of the acyloin via the Ogawa sulfenate method. In our case we observe enantiomeric discrimination of the order of 10/1. This comparison clearly indicates that the mechanism of our method of glycosidation does not involve sulfenate ester.

Table 7: Comparison of Our Results with Ogawa's Method



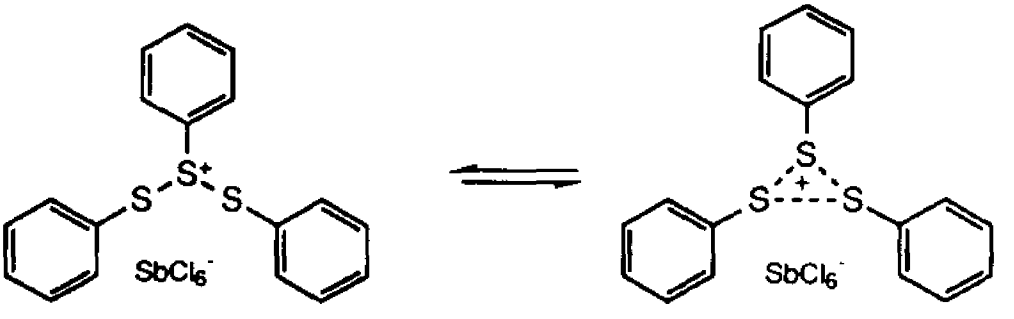
Entry	R'	R	Ratio β/α	
			OUR METHOD	OGAWA'S METHOD
1		Me	2.6/1	3.5/1
2		i Pr	2.7/1	3.8/1
3	Same as entry 1			Only β product (1/1)
4	Same as entry 2	Same as entry 3	Only β product (10/1) (enantiomeric discrimination)	

A further proof was obtained by carrying out a ^{13}C NMR experiment which was done at -60°C to mimic the reaction conditions (Table 8). The signal for the methyl carbon in methanol appears at δ49.0, in sulfenate ester, MeOSPh, at δ65.2. This signal in the mixture of reagent and methanol appears at δ59.4,

indicating that methanol is not in a free state, has not formed a sulfenate ester but is "attached" to the reagent in some way. The reagent itself shows three peaks in the ^{13}C NMR indicating that it exists in a cyclic form **69B**.[43] On addition of methanol to the reagent we observed ten peaks for the reagent indicating that the cyclic structure has been perturbed making the three phenyl rings nonequivalent. Due to the problems with our NMR instrument at low temperature we could not repeat or do any further experiments.

Table 8: Low temperature ^{13}C NMR data

	δ
$H_3\underline{C}OSPh$	65.2
$H_3\underline{C}OH$	49.0
Reagent **31** + $\underline{C}H_3OH$	59.4
Reagent **31**	124.3, 132.7, 136.7
Reagent **31** + $\underline{C}H_3OH$	124.8, 125.4, 125.7, 127.5, 129.0, 129.2, 132.7, 134.4, 135.0, 135.6

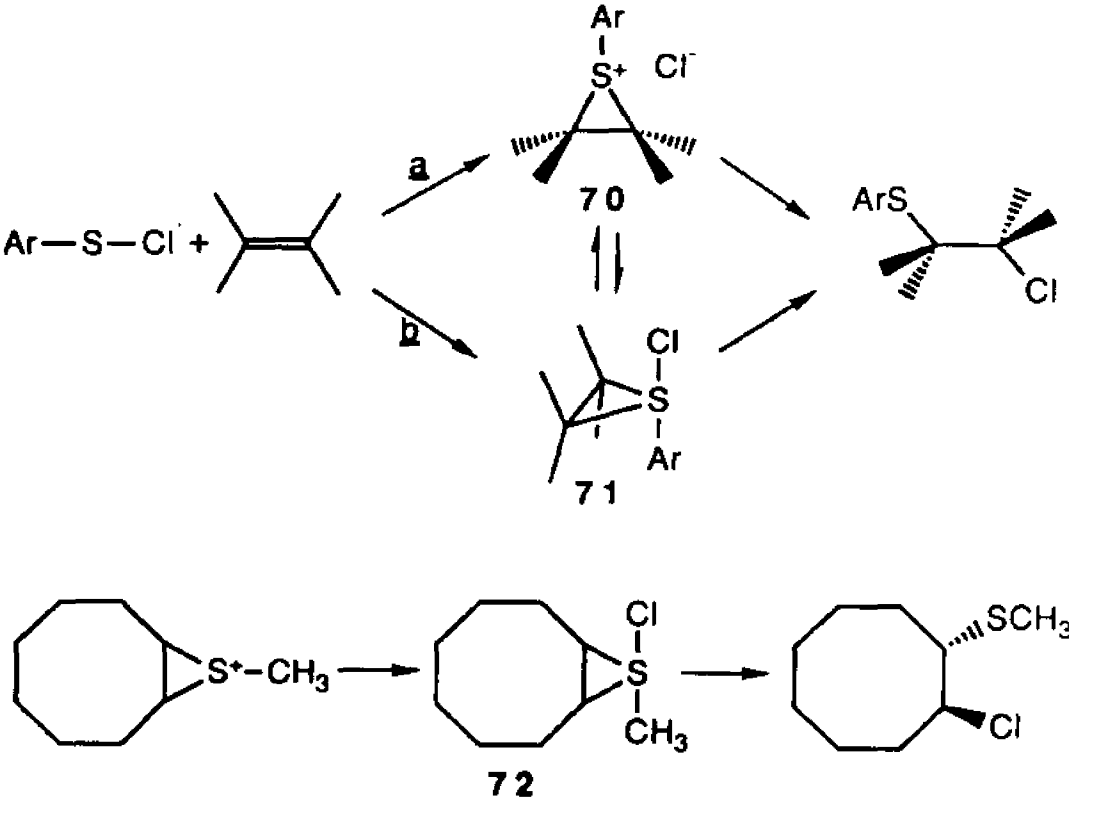


69A **69B**

In the addition of arenesulphenyl halides to alkenes to form β-haloalkyl sulfides,[55] one possible mechanism is the nucleophilic attack by olefin on the sulfur to form a episulfonium ion **70** which is ring opened by nucleophilic attack on carbon by the chloride ion (path a) similar to our scheme 15. An alternative mechanism has been proposed which involves nucleophilic attack at sulfur to form a chlorosulfurane **71** which may rearrange directly to product or ionize to

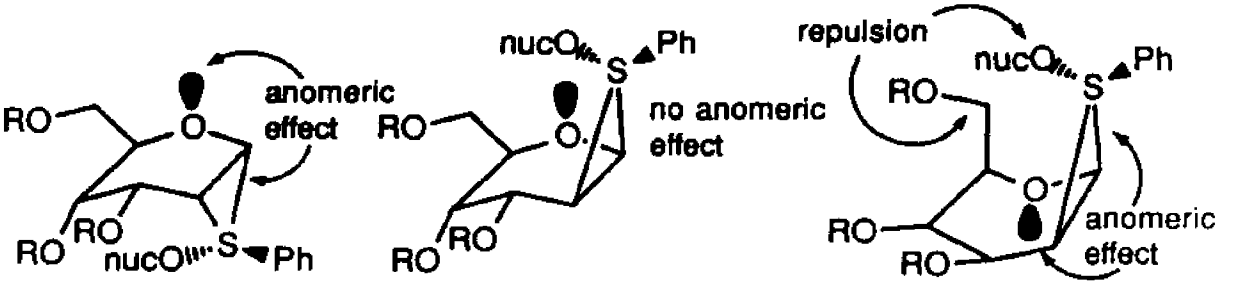
form the episulfonium ion **70** (Scheme 25). Intermediate **71** a less polar species than **70** is especially favorable in less polar solvents. Chlorosulfurane **72**, an example of intermediate **71** along path b, was observed in the reaction between the corresponding methylepisulfonium ion and a stoichiometric amount of chloride ion at -5°C by proton NMR.[56] The lesser strain in a three membered ring spanning apical-equatorial or equatorial-equatorial sites in trigonal bypyramidal sulfurane **71** compared to a tetrahedral episulfonium ion **70** also indicates preference for path b.

Scheme 25:



Our results can also be rationalized by considering sulfuranes as reaction intermediates (**73** and **74**). The bicyclic species, **73** and **74**, with the nucleophile attached at a congested site, would explain the dependence of face selectivity on nucleophile in a more satisfying way than the postulate that

isomeric onium species **10A** and **10B** are differently sensitive to the several nucleophiles attacking C-1. Thus the Dreiding models suggest that the boat form of sulfurane **73** is the stable form and benefits from an anomeric effect. One boat form of **74** has an anomeric effect but suffers from severe steric repulsions; whereas the less congested boat of **74** has no anomeric effect.



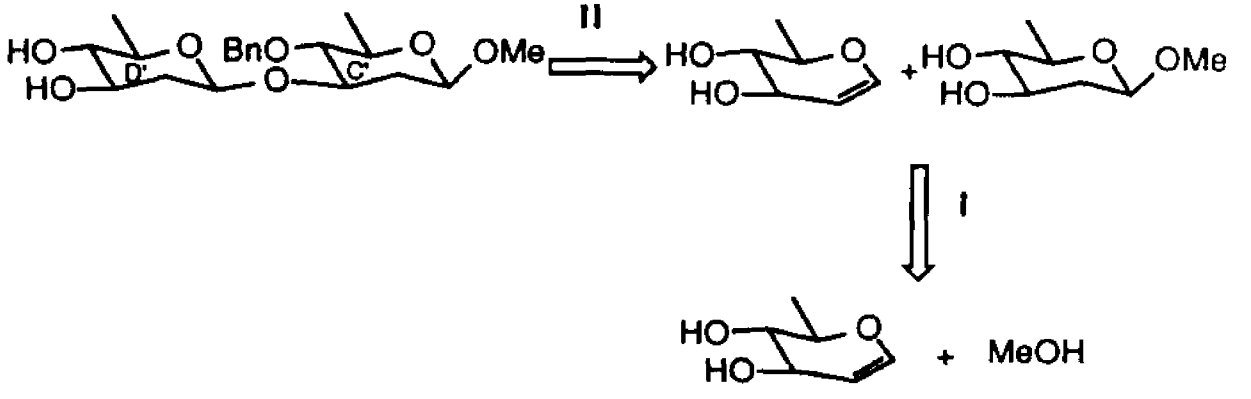
Further with racemic alcohols there would be two diastereomers possible for each of the two sulfuranes **73** and **74**. In each case one diastereomer might form (or rearrange to) product more easily than the other. This explanation, again, is more satisfying than arguing for different nucleophilicities of the enantiomeric alcohols towards C-1 of onium species **10**. Though the existence of sulfurane in our system is purely speculative (we have no experimental proof) they explain our observations in a convincing manner.

Thus the glycosyl transfer method is a straight forward one step process which does not require any specialized sugar derivatives. The reaction conditions are mild and the activating thionium reagents can be easily prepared from commercially available compounds. In conclusion we believe that the class of arylthiosulfonium salts, will be useful reagents in the field of 2-deoxy-β-glycosidation.

Synthesis of C'D' ring analog of aureolic acid

Next we have used our sulfonium salt glycosidation procedure for the synthesis of the C'-D' subunit of the trisaccharide chain of aureolic acid **1**. The retrosynthetic approach is shown in scheme 26.

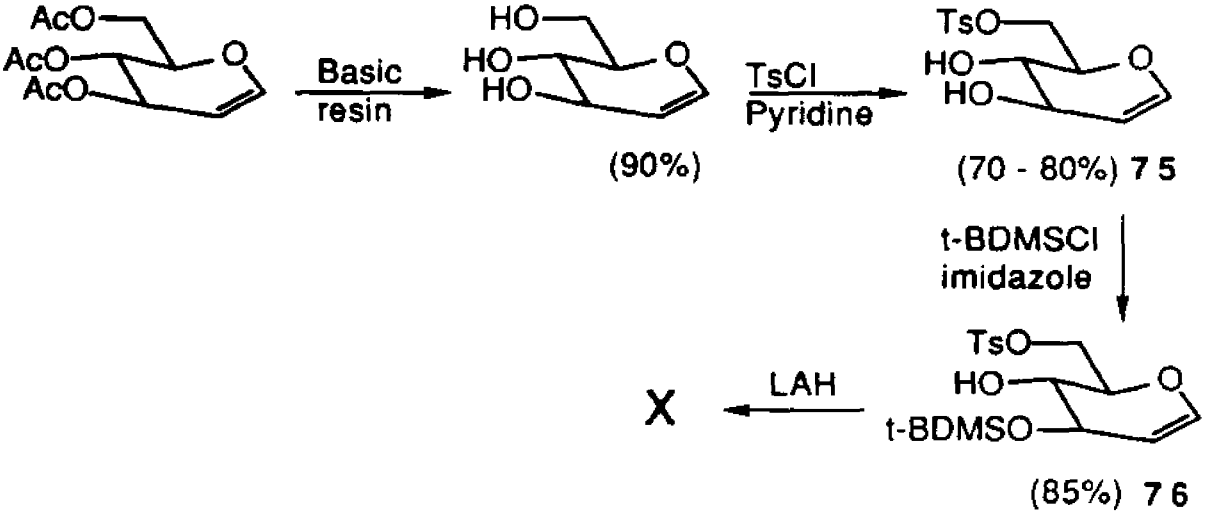
Scheme 26:



The first step is glycosidation of D-rhamnal using methanol as the nucleophile. The requirement for the rhamnal used is that the hydroxyl groups in position 3 and 4 should have different blocking groups. It is possible to protect the 3 - OH in presence of 4 since the former is allylic. The choice of blocking groups should be such that the 3 position can be deblocked without effecting the protection at 4. We decided to use substituted a silyl group at position 3 and a benzyl ether for hydroxyl group at 4. The product from the first glycosidation step, the 2-thiophenyl-2-deoxy-β-methylglycoside, on treatment with fluoride will render the 3-hydroxyl group free (leaving the 4 benzyl protection on) to be used as a nucleophile for step II glycosidation.

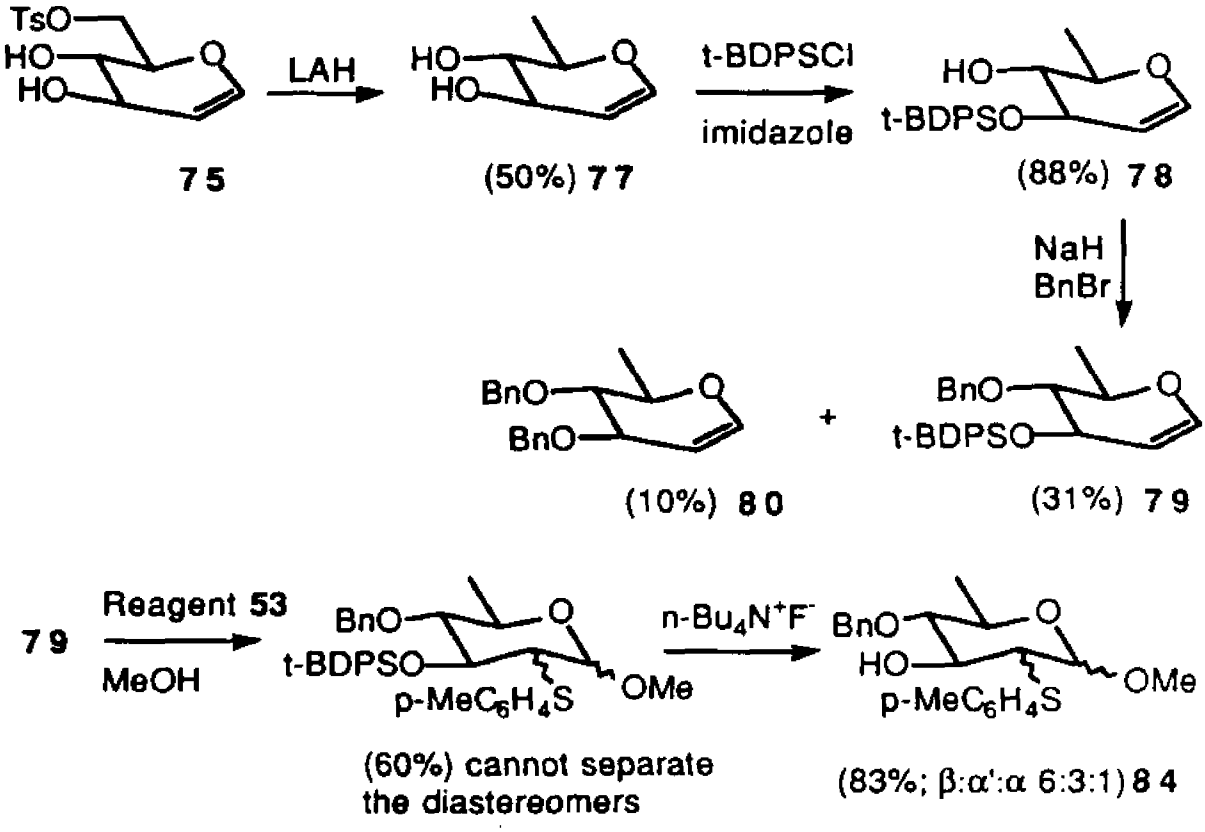
For the synthesis of protected glycal we started with commercially available 3,4,6-tri-O-acetyl-D-glucal and following standard procedure[57] converted it to tosylate **75** (Scheme 27). Compound **75** with t-butyldimethylsilyl chloride (1 equiv.) in the presence of imidazole gave the 3-protected glycal **76**.[58] The tosyl group reduction using lithium aluminium hydride (LAH) did not give satisfactory results. The starting material had disappeared after 36 hours but no characterizable products were isolated.

Scheme 27:



We decided to first reduce the tosyl group using LAH[57] and then protect the 3 position using t-butyldiphenylsilylchloride.[59] Glycal **78** thus obtained on benzylation gave the required product **79** in only 31% yield. Byproduct **80** was isolated in 10% yield. Presumably the silyl protecting group is cleaved during the reaction (Scheme 28).

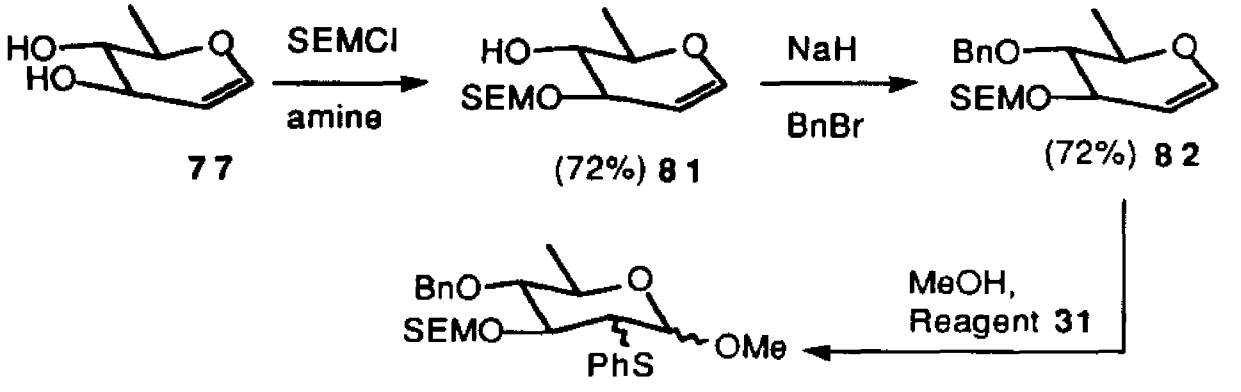
Scheme 28:



Next we decided to use the β-(trimethylsilyi)ethoxymethyl (SEM)[60] protection at the 3 position. The SEM group can be removed under the same conditions as any silyl protection (treatment with fluoride) but since a silicon-carbon bond exists in the group instead of silicon-oxygen bond, it should be less labile to benzylation conditions (used for blocking position 4). Glycal **77** on reaction with SEM chloride gave the 3-protected glycal **81**. Benzylation of **81** afforded the required glycal **82** in 72% yield. Glycosidation using the sulfonium reagent **31** and methanol resulted in glycosides **83** in β:α:α' ratio of 11.5:2:1(82% yield,Scheme 29) The reagent **31** had to be prepared using procedure 18A. When the reagent **53** prepared by procedure 18B was used during glycosyl transfer of **79** to methanol poor β selectivity was observed and glycoside α'-**84** was isolated as one of the major products (Scheme 28). We think that since the

6 position in these glycals is deoxygenated the electron density on the ring oxygen increases which facilitates the formation of α' glycosides. In procedure 18B $SbCl_3$ (a Lewis acid) is present and it can catalyze the formation of α' glycosides via anomerization of product in already susceptible 6-deoxyglycals.

Scheme 29:

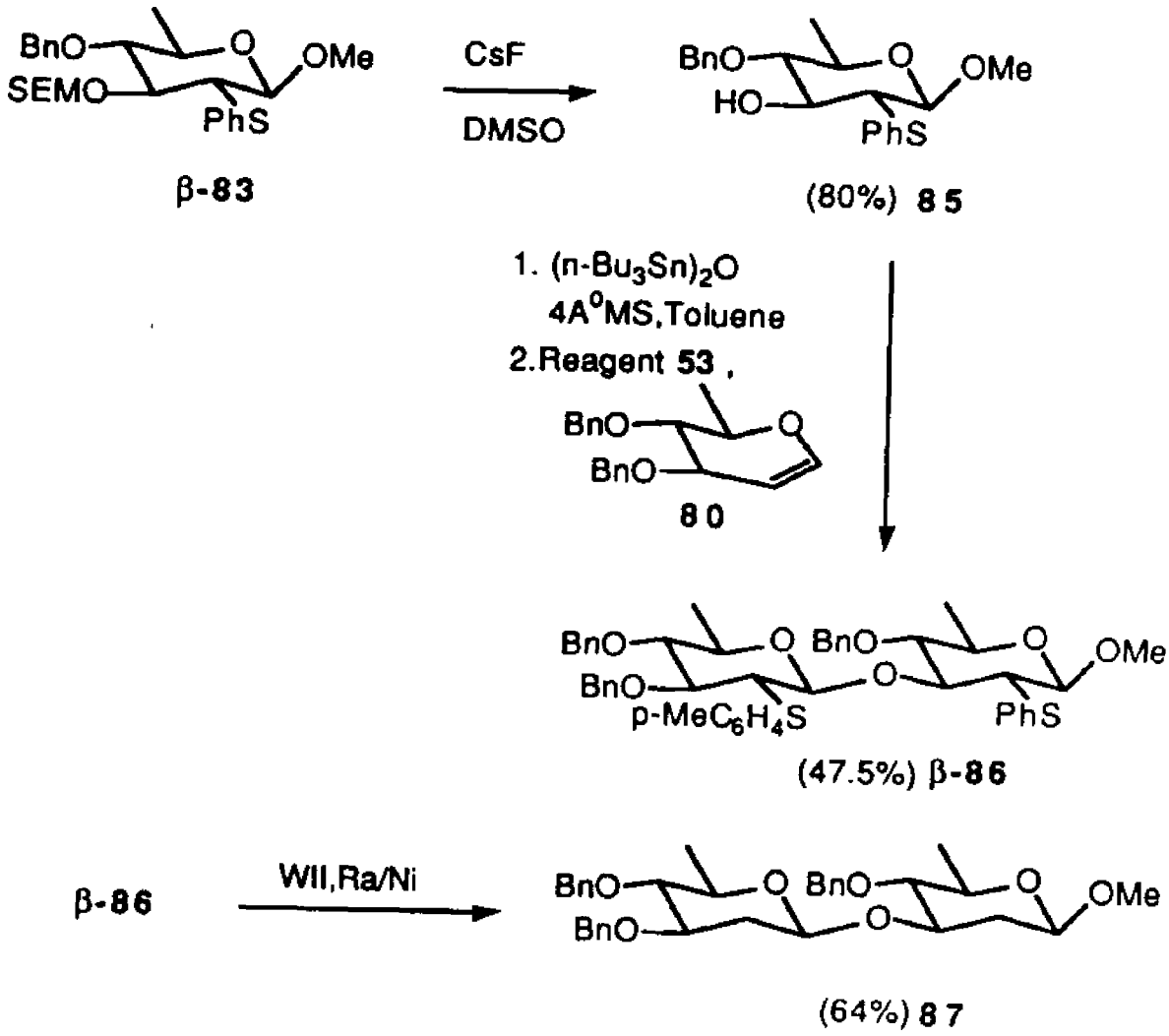


77 (72%) **81** (72%) **82**

(82%; β:α:α' 11.5:2:1) **83**

The SEM group in **β-83** was cleaved using cesium fluoride in DMSO. Tetrabutylammonium fluoride gave poor yields of **85**. Using the homonuclear 2D NMR we could assign all the protons in glycosides **84** and **85** (the signal of 3-OH group was confirmed by D_2O exchange). The tri-n-butyl tin ether of **85** was used as the aglycone for the synthesis of the disaccharide **86**. The glycosidation was done using the optimal sulfonium reagent **53** prepared by procedure 18A. Dissacharide **β-86** was obtained in 47.5% yield (Scheme 30). There are minor products, but we have not conclusively proven them to be α-**86**. Desulfurization of **β-86** using WII, Raney nickel gave the 2,2'-dideoxy-dissacharide **87** in 64%yield.

Scheme 30:


BnO
SEMO
O
OMe
PhS
β-83
CsF
DMSO
BnO
HO
O
OMe
PhS
(80%) 85
1. (n-Bu3Sn)2O
4A°MS,Toluene
2.Reagent 53 ,
BnO
BnO
O
80
BnO
BnO
p-MeC6H4S
O
BnO
O
OMe
PhS
(47.5%) β-86
β-86
WII,Ra/Ni
BnO
BnO
O
BnO
O
O
OMe
(64%) 87

EXPERIMENTAL:

General Experimental: NMR spectra were recorded on GE QE 300, JEOL FX 400 instruments with $CDCl_3$ as solvent. Elemental analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Optical rotations were determined using a Rudolph Research AUTOPOL III automatic polarimeter. Thin-layer chromatograms were done on precoated TLC sheets of silica gel 60 F_{254} (E. Merck) and short- long-wave ultraviolet light was used to visualize the spots. PLC plates were prepared by using Kieselgel 60 PF_{254} (E. Merck), and chromatotron (radial chromatography) plates were prepared by using Kieselgel 60 PF_{254} gipshaltig (E. Merck). Flash chromatography was performed with silica gel (230-400 mesh) purchased from Aldrich Chemical Co. Methanol was distilled from Mg and stored over 3 A° MS. Dry THF was obtained by distillation, under nitrogen, from sodium-benzophenon ketyl. Dichloromethane was distilled from P_2O_5. Other solvents were purified and dried by using standard procedures.

Preparation of dimethyl(phenylthio)sulfonium salt (19): To a solution of silver tetrafluoroborate (110 mg, 1 mmole) in 4 ml of acetonitrile at 0 °C dimethyl sulfide (147 µl, 2 mmole) was added. To this stirred mixture phenyl sulfenyl chloride (144.5 mg, 1 mmole)[61] was added dropwise. A white precipitate of silver chloride was formed. The supernatant liquid was syringed out and used without further purification. ^1H NMR (300 MHz, $CDCl_3$) δ 2.70 (s, 6H, 2xCH_3), 7.20-7.80 (m, 5H, Ar-*H*).

3,4,6-Tri-O-benzyl-D-glucal (17) + Methanol (22) Using Reagent 19: To a solution of the glucal (106 mg, 0.255 mmol) and the methanol (50 µl) in dry

methylene chloride at 0 °C (under argon), 1.2 ml of the reagent solution (0.30 mmol) was added by syringe technique. After the reaction was complete (about 10 min) saturated aqueous sodium bicarbonate solution (15 ml) was added and the mixture was stirred for 30 min at room temperature. The reaction mixture was extracted with dichloromethane (3X25 ml). The combined organic extracts were dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude product mixture of 3,4,6-tri-O-benzyl-2-deoxy-1-O-methyl--2-phenylthio-α-D-mannopyranoside (**α-23**) and 3,4,6-tri-O-benzyl-2-deoxy-1-O-methyl-2-phenylthio-β-D-glucopyranoside (**β-23**); β/α 2.0/1; ^{1}H NMR (300 MHz, $CDCl_3$), characteristic signals δ 3.18 (dd, *J* = 10.5, 8.8 Hz, C_2-*H* of β), 3.33 (s, OCH_3 of α), 3.53 (s, OCH_3 of β), 4.27 (d, *J* = 8.8 Hz, C_1-*H* of β).

General Procedure for preparation of Aryl tri-n-butyltin ether:

A mixture of aryl acetate (10 mmole) and tri-n-butyl tin methoxide (10 mmole) is stirred for 12 hours at room temperature. The byproduct methyl acetate is removed *in vacuo* and the product used without further purification.

Physical data: Phenyl tri-n-butyltin ether (39): oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, *J* = 7.0 Hz, 9H, $3xCH_2CH_3$), 1.30 (t, *J* = 7.4 Hz, 6H, $3xSnCH_2$), 1.34-1.45 (m, 6H, butyl group protons), 1.60-1.72 (m, 6H, butyl group protons), 6.72 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 6.80 (t, *J* = 8.4 Hz, 1H, Ar-*H*), 7.18 (t, *J* = 8.4 Hz, 2H, Ar-*H*).

para-Tolyl tri-n-butyltin ether (41): oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, *J* = 7.4 Hz, 9H, $3xCH_2CH_3$), 1.28 (t, *J* = 7.9 Hz, 6H, $3xSnCH_2$), 1.32-1.45 (m, 6H, butyl group protons), 1.59-1.71 (m, 6H, butyl group protons), 2.29 (s, 3H, CH_3), 6.62 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 6.98 (d, *J* = 8.4 Hz, 2H, Ar-*H*).

ortho-Methylphenyl tri-n-butyltin ether (43): oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, *J* = 7.2 Hz, 9H, 3xCH_2CH_3), 1.28 (t, *J* = 7.9 Hz, 6H, 3x$SnCH_2$), 1.32-1.45 (m, 6H, butyl group protons), 1.60-1.71 (m, 6H, butyl group protons), 2.20 (s, 3H, CH_3), 6.57 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 6.72 (t, *J* = 8.4 Hz, 1H, Ar-*H*), 7.02 (t, *J* = 8.4 Hz, 1H, Ar-*H*), 7.11 (d, *J* = 8.4 Hz, 1H, Ar-*H*).

para-Chlorophenyl tri-n-butyltin ether (45): oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, *J* = 7.3 Hz, 9H, 3xCH_2CH_3), 1.30 (t, *J* = 7.6 Hz, 6H, 3x$SnCH_2$), 1.32-1.45 (m, 6H, butyl group protons), 1.59-1.62 (m, 6H, butyl group protons), 6.63 (d, *J* = 8.7 Hz, 2H, Ar-*H*), 7.12 (d, *J* = 8.7 Hz, 2H, Ar-*H*).

Synthesis of t-Butyldimethylsilyl Ether of 2-Hydroxy-α-tetralone: To a solution of α-tetralone (1.47 g, 10.1 mmol) and triethylamine (2.1 ml, 15.2 mmol) in 25 ml of dry methylene chloride was added t-butyldimethylsilyltriflate (3.6 ml, 15.2 mmol). The reaction mixture was stirred at room temperature for 15 min (tlc, ethyl acetate-hexane 1:3, showed completion of the reaction). The reaction was quenched with the addition of a saturated solution of sodium bicarbonate and diluted with 100 ml of methylene chloride. The organic layer was washed with water (100 ml) and dried over anhydrous sodium sulfate. Evaporation of the solvent gave the t-butyldimethylsilyl enol ether of α-tetralone as the crude product which (with out purification) was dissolved in 30 ml of dry methylene chloride, cooled to -15 °C under nitrogen atmosphere and m-CPBA (2.18 g, 80%, 10.2 mmol) was added. The reaction mixture was stirred for 1 h at room temperature, whereupon tlc (ethyl acetate-hexane 1:9) showed incomplete reaction. A second portion of m-CPBA (1.0 g) and 20 ml of methylene chloride were added to the reaction mixture and it was stirred for one additional hour (tlc showed completion of the reaction). The reaction mixture

was diluted with 50 ml of methylene chloride and washed with saturated solution of sodium bicarbonate (2X100 ml) followed by 10% solution of sodium bisulfite (2X100 ml). The organic layer was dried over anhydrous sodium sulfate. and concentrated *in vacuo*. Radial chromatography (ethyl acetate-hexane 1:9) of the residue gave 2.05 g of t-butyldimethylsilyl ether of 2-hydroxy-α-tetralone (73% overall).

Physical data: t-butyldimethylsilyl enol ether of α-tetralone: Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.25 {s, 6H, $Si(CH_3)_2$}, 1.70 {s, 9H, $SiC(CH_3)_3$}, 2.31-2.40 (m, 2H, C_3-*H*), 2.81 (t, *J* = 7.4 Hz, 2H, C_4-*H*), 5.20-5.24 (m, 1H, C_2-*H*), 7.13-7.29 (m, 3H, Ar-*H*), 7.52 (d, *J* = 8.0 Hz, 1H, C_8-*H*).

t-Butyldimethylsilyl ether of 2-hydroxy-α-tetralone: Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.18 {s, 3H, 1/2X$Si(CH_3)_2$}, 0.25 {s, 3H, 1/2X$Si(CH_3)_2$}, 0.98 {s, 9H, $SiC(CH_3)_3$}, 2.17-2.41 (m, 2H, C_3-*H*), 3.06-3.14 (m, 2H, C_4-*H*), 4.42 (dd, *J* = 11.2, 4.9 Hz, 1H, C_2-*H*), 7.28 (d, *J* = 8.4 Hz, 1H, C_5-*H*), 7.35 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.52 (dt, *J* = 8.4, 1.0 Hz, 1H, Ar-*H*), 8.07 (dd, *J* = 8.4, 1.0 Hz, 1H, C_8-*H*).

Synthesis of 2-Hydroxy-α-tetralone (8): To a solution of the t-butyldimethylsilyl ether of 2-hydroxy-α-tetralone (0.5 g, 1.8 mmol) in dry methanol (10 ml), under a nitrogen atmosphere, Dowex-H^+ resin (0.2 g) was added. The resulting slurry was stirred for 14h at room temperature, whereupon tlc (ethyl acetate-hexane 1:2) showed completion of the reaction. The resin was filtered off and washed with methanol (15 ml). The filtrate was concentrated *in vacuo* and the residue was subjected to radial chromatography (ethyl acetate-hexane 1:4) to give 200 mg of **8** (68.5%); Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.10 (ddd, *J* = 27.9, 14.0, 5.6 Hz, 1H, C_3-*H*), 2.53-2.62 (m, 1H), 3.04-3.28 (m, 2H),

3.95 (d, J = 0.9 Hz, 1H, O*H*), 4.45 (ddd, J = 13.5, 5.6, 0.9 Hz, 1H, C_2-*H*), 7.32 (d, J = 8.4 Hz, 1H, C_5-*H*), 7.40 (t, J = 8.4 Hz, 1H, Ar-*H*), 7.57 (dt, J = 8.4, 0.9 Hz, 1H, Ar-*H*), 8.09 (d, J = 8.4 Hz, 1H, C_8-*H*).

General Procedure for Preparation of Aryl(bisarylthio)sulfonium Salt Reagent (24):

Method A (Scheme **21A**): A solution of diaryldisulfide (1 mmol) and arylsulfenyl chloride (1.1 mmol) in 3.0 ml of dry methylene chloride is added dropwise to antimony pentachloride (1.0 ml of 1M solution in CH_2Cl_2) at -60 °C (under argon). The mixture is stirred for 30 min at -60 °C to give a 0.25 M solution of **24**.

Method B (Scheme **21B**): A solution of diaryldisulfide (1.5 mmol) in 2.5 ml of dry methylene chloride is added dropwise to antimony pentachloride (1.5 ml of 1M solution in CH_2Cl_2, bought from Aldrich) at -60 °C (under argon). The mixture is stirred for 30 min at -60 °C to give a 0.25 M solution of **24**.

General Procedure for Glycosidation: To a solution of the glucal (0.255 mmol) and the nucleophile alcohol (0.51 mmol) in dry methylene chloride at -60 °C (under argon), 1.2 ml of the reagent solution (0.30 mmol) is added by syringe technique. After the reaction is complete (about 10 min) saturated aqueous sodium bicarbonate solution (15 ml) is added and the mixture is stirred for 30 min at room temperature. The reaction mixture is extracted with dichloromethane (3X25 ml). The combined organic extracts were dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude product mixture which was subjected to radial chromatography.

3,4,6-Tri-O-benzyl-D-glucal (17) + Isopropanol (32) Using Reagent 31: Glycosidation was carried out using phenyl(bisphenylthio)sulfonium salt (**31**) prepared by method **A**. Radial chromatography (ethyl acetate-hexane 1:20 to 2:1) gave 23 mg of 3,4,6-tri-O-benzyl-2-deoxy-1-O-isopropyl-2-phenylthio-α-D-mannopyranoside (**α-33**) and 64 mg of 3,4,6-tri-O-benzyl-2-deoxy-1-O-isopropyl-2-phenylthio-β-D-glucopyranoside (**β-33**); total yield 59%; β/α 2.7/1. In addition 13.2 mg (10%) of 3,4,6-tri-O-benzyl-2-deoxy-2-phenylthio-β-D-glucose (**28**, R=R_1=H) and 22.5 mg (17 %) of 3,4,6-tri-O-benzyl-2-deoxy-2-phenylthio-α-D-glucose (**27**, R=R_1=H) were also isolated.

Physical data: First fraction: **α-33:** mp 90-92 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (d, *J* = 6.1 Hz, 3H, C*H*$_3$), 1.22 (d, *J* = 6.2 Hz, 3H, C*H*$_3$), 3.70-3.93 (m, 6H, OC*H*$(CH_3)_2$, pyran ring protons), 4.27-4.33 (m, 1H, pyran ring proton), 4.61 (AB q, Δν = 19.9 Hz, J_{AB} = 11.3 Hz, 2H, PhC*H*$_2$), 4.66 (AB q, Δν = 36.2 Hz, J_{AB} = 12.1 Hz, 2H, PhC*H*$_2$), 4.72 (AB q, Δν = 100.2 Hz, J_{AB} = 10.8 Hz, 2H, PhC*H*$_2$), 5.13 (d, *J* = 1.2 Hz, 1H, C_1-*H*), 7.17-7.61 (m, 20H, Ar-*H*).

Second fraction: **β-33:** Thick oil; $[\alpha]^{25}_D$ -17.9° (c 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (d, *J* = 6.1 Hz, 3H, C*H*$_3$), 1.19 (d, *J* = 6.1 Hz, 3H, C*H*$_3$), 3.21 (dd, *J* = 8.9, 10.5 Hz, 1H, C_2-*H*), 3.44-3.74 (m, 5H, pyran ring protons), 3.96 (heptet, *J* = 6.1 Hz, 1H, OC*H*$(CH_3)_2$), 4.41 (d, *J* = 8.9 Hz, 1H, C_1-*H*), 4.51-4.62 (m, 3H, 1.5xPhC*H*$_2$), 4.81 (d, *J* = 10.9 Hz, 1H, 1/2xPhC*H*$_2$), 4.92 (AB q, Δν = 57.3 Hz, J_{AB} = 10.3 Hz, 2H, PhC*H*$_2$), 7.16-7.55 (m, 20H, Ar-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.65, 23.26, 56.73 (*C*$_2$), 69.12, 72.31, 73.37, 74.72, 74.78, 75.98, 79.31, 83.37, 102.40 (*C*$_1$), 126.35, 127.40, 127.55, 127.64, 127.78, 127.95, 128.18, 128.29, 128.39, 131.40, 136.02, 138.03, 138.23.

Third fraction: **28** (R=R_1=H): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.25 (dd, *J* = 10.7, 8.8 Hz, 1H, C_2-*H*), 3.39-3.44 (m, 1H, pyran ring proton), 3.49 (dd, *J* = 10.7, 8.6 Hz, 1H, C_3-*H*), 3.60-3.73 (m, 3H, pyran ring protons), 4.42 (d, *J* = 8.8 Hz, 1H, C_1-*H*), 4.49-4.56 (m, 2H, OH, 1/2xPhCH_2), 4.72 (AB q, Δν = 78.9 Hz, J_{AB} = 12.0 Hz, 2H, PhCH_2), 4.78 (d, *J* = 10.8 Hz, 1H, 1/2xPhCH_2), 4.89 (AB q, Δν = 58.1 Hz, J_{AB} = 10.3 Hz, 2H, PhCH_2), 7.00-7.47 (m, 20H, Ar-*H*).

Fourth fraction: **27** (R=R_1=H): mp 89-90 °C (lit.[10] mp 85.5-86 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.25-3.33 (m, 2H, C_2-*H*, O*H*), 3.50-3.63 (m, 3H, C_4-*H*, 2xC_6-*H*), 3.92 (d, *J* = 11.0, 9.0 Hz, 1H, C_3-*H*), 4.02-4.08 (m, 1H, C_5-*H*), 4.37-4.53 (m, 3H, 1.5xPhCH_2), 4.72-4.78 (m, 2H, PhCH_2), 4.92 (d, *J* = 10.2 Hz, 1H, 1/2xPhCH_2), 5.28 (t, *J* = 3.0 Hz, 1H, C_1-*H*), 7.03-7.43 (m, 20H, Ar-*H*).

3,4,6-Tri-O-benzyl-D-glucal (17) + Neopentyl alcohol (49) Using Reagent 31: Glycosidation was carried out using phenyl(bisphenylthio)sulfonium salt (**31**) prepared by method **A**. Radial chromatography (ethyl acetate-hexane 1:20 to 2:1) gave 13.8 mg of of 3,4,6-tri-O-benzyl-2-deoxy-1-O-neopentyl-2-phenylthio-α-D-mannopyranoside (α-**50**) and 79 mg of 3,4,6-tri-O-benzyl-2-deoxy-1-O-neopentyl-2-phenylthio-β-D-glucopyranoside (β-**50**); total yield 60%; β/α 5.7/1.

Physical data: First fraction: α-**50**: oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (s, 9H, 3xCH_3), 3.12 (AB q, Δν = 116.8 Hz, J_{AB} = 9.0 Hz, 2H, OCH_2C(CH_3)$_3$), 3.66-3.85 (m, 5H, pyran ring protons), 4.22 (dd, *J* = 4.7, 8.4 Hz, 1H, pyran ring proton), 4.50-4.70 (m, 4H, 2xPhCH_2), 4.67 (AB q, Δν = 110 Hz, J_{AB} = 10.8 Hz, 2H, PhCH_2), 4.90 (s, 1H, C_1-*H*), 7.13-7.45 (m, 20H, Ar-*H*).

Second fraction: **β-50:** oil; $[\alpha]^{25}_D$ -21.5° (c 0.5, $CHCl_3$);^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (s, 9H, 3xCH_3), 3.28 (dd, *J* = 8.9, 10.4 Hz, 1H, C_2-*H*), 3.32 (AB q, Δν = 150.0 Hz, J_{AB} = 8.9 Hz, 2H, $OCH_2C(CH_3)_3$), 3.40-3.73 (m, 5H, pyran ring protons), 4.31 (d, *J* = 8.9 Hz, 1H, C_1-*H*), 4.51-4.61 (m, 3H, 1.5x$PhCH_2$), 4.78 (d, *J* = 10.9 Hz, 1H, 1/2x$PhCH_2$), 4.91 (AB q, Δν = 60.9 Hz, J_{AB} = 10.3 Hz, 2H, $PhCH_2$), 7.09-7.51 (m, 20H, Ar-*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.56, 31.88, 56.30 (C_2), 68.92, 73.41, 74.82, 76.01, 79.34, 80.42, 83.30, 104.19 (C_1), 126.21, 127.48, 127.55, 127.62, 127.67, 127.82, 127.93, 128.05, 128.20, 128.26, 128.33, 128.51, 130.79, 136.16, 138.01, 138.24, 138.28. Anal. Calcd for $C_{38}H_{44}O_5S$: C, 74.48; H, 7.24; S, 5.23. Found: C, 74.39; H, 7.31; S, 5.22.

3,4,6-Tri-O-benzyl-D-glucal (17) + Phenyl tri-n-butyltin ether (39) Using Reagent 31: Glycosidation was carried out using phenyl(bisphenylthio)sulfonium salt (**31**) prepared by method **B**. Radial chromatography (ethyl acetate-hexane 1:20 to 2:1) gave 19 mg of of 3,4,6-tri-O-benzyl-2-deoxy-1-O-phenyl--2-phenylthio-α-D-mannopyranoside (α-**40**) and 82 mg of 3,4,6-tri-O-benzyl-2-deoxy-1-O-phenyl-2-phenylthio-β-D-glucopyranoside (β-**40**); total yield 64%; β/α 4.3/1. In addition 10 mg (7.3%) of 3,4,6-tri-O-benzyl-2-deoxy-2-phenylthio-β-D-glucose (**28**, R=R_1=H) and 22 mg (16 %) of 3,4,6-tri-O-benzyl-2-deoxy-2-phenylthio-α-D-glucose (**27**, R=R_1=H) were also isolated. A small amount of 4-thiophenylphenol (**47**, R=H) was obtained.

Physical data: First fraction: α-**40:** mp 88-89 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.64 (dd, *J* = 11.0, 1.7 Hz, 1H, C_6-*H*), 3.78 (dd, *J* = 11.0, 4.2 Hz, 1H, C_6-*H*), 3.89-3.91 (m, 2H, C_5-*H*, C_2-*H*), 4.00 (dd, *J* = 9.0, 9.6 Hz, 1H, C_4-*H*), 4.42-4.47 (m, 2H, C_3-*H*, 1/2x$PhCH_2$), 4.61-4.71 (m, 3H, 1.5x$PhCH_2$), 4.70 (AB q, Δν = 115.0 Hz,

J_{AB} = 10.7 Hz, 2H, PhCH_2), 5.71 (d, J = 1.5 Hz, 1H, C_1-H), 6.94-7.50 (m, 25H, Ar-H).

Second fraction: **β-40:** mp 92-93 °C; $[\alpha]^{25}_D$ -19.6° ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.51 (dd, J = 10.7, 8.6 Hz, 1H, C_2-H), 3.60-3.82 (m, 5H, pyran ring protons), 4.55 (AB q, Δν = 21.78 Hz, J_{AB} = 12.0 Hz, 2H, PhCH_2),, 4.85 (AB q, Δν = 10.0 Hz, J_{AB} = 10.0 Hz, 2H, PhCH_2), 4.86 (AB q, Δν = 145.0 Hz, J_{AB} = 10.6 Hz, 2H, PhCH_2), 4.98 (d, J = 8.4 Hz, 1H, C_1-H), 6.90 (d, J = 7.64 Hz, 2H, Ar-H), 6.99-7.24 (m, 23H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.48 (C_2), 68.74, 73.44, 74.98, 76.29, 79.07, 82.82, 101.83 (C_1), 116.66, 122.42, 126.23, 127.14, 127.52, 127.64, 127.78, 127.84, 128.07, 128.27, 128.35, 128.43, 128.73, 129.31, 132.49, 134.88, 137.86, 138.01, 138.07, 157.24. Anal. Calcd for $C_{39}H_{38}O_5S$: C, 75.70; H, 6.19; S, 5.18. Found: C, 75.61; H, 6.26; S, 5.14.

Third fraction: **47** (R=H)**:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.18 (br s, 1H, OH), 6.88 (d, J = 8.6 Hz, 2H, Ar-H), 7.18-7.31 (m, 5H, Ar-H), 7.41 (d, J = 8.6 Hz, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 116.50, 125.86, 128.31, 129.00, 135.55, 138.45, 155.89 (C_1).

Fourth fraction: **28** (R=R_1=H).

Fifth fraction: **27** (R=R_1=H).

3,4,6-Tri-O-benzyl-D-glucal (17) + para-Tolyl tri-n-butyltin ether (41) Using Reagent (31): Glycosidation was carried out using phenyl(bisphenylthio)sulfonium salt (**31**) prepared by method **B**. Radial chromatography (ethyl acetate-hexane 1:20 to 2:1) gave 11 mg of of 3,4,6-tri-O-benzyl-2-deoxy-1-O-(4'-methylphenyl)-2-phenylthio-α-D-mannopyranoside (α-**42**) and 58 mg of 3,4,6-tri-O-benzyl-2-deoxy-1-O-(4'-methylphenyl)-2-

phenylthio-β-D-glucopyranoside (β-**42**); total yield 43%; β/α 5.3/1. In addition 25 mg (18%) of 3,4,6-tri-O-benzyl-2-deoxy-2-phenylthio-β-D-glucose (**28**, R=R_1=H) and 39 mg (29%) of 3,4,6-tri-O-benzyl-2-deoxy-2-phenylthio-α-D-glucose (**27**, R=R_1=H) were also isolated. A small amount of 4-O-(p-tolyl)-thiophenol (**48**, R=CH_3) was obtained.

Physical data: First fraction: α-**42:** oil ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.27 (s, 3H, Ar-CH_3), 3.67 (dd, J = 11.1, 1.5 Hz, 1H, C_6-H), 3.80 (dd, J = 11.1, 4.1 Hz, 1H, C_6-H), 3.91-3.95 (m, 2H, C_5-H, C_2-H), 4.00 (dd, J = 9.3, 9.0 Hz, 1H, C_4-H), 4.44-4.48 (m, 2H, C_3-H, 1/2xPhCH_2), 4.62-4.72 (m, 3H, 1.5xPhCH_2), 4.73 (AB q, Δν = 111.3 Hz, J_{AB} = 10.8 Hz, 2H, PhCH_2), 6.90 (d, J = 8.6 Hz, 2H, Ar-H), 7.04 (d, J = 8.3 Hz, 2H, Ar-H),7.18-7.52 (m, 20H, Ar-H).

Second fraction: β-**42:** mp 61-63 °C; $[\alpha]^{25}_D$ -11.0° (c 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.27 (s, 3H, Ar-CH_3), 3.46 (dd, J = 10.7, 8.7 Hz, 1H, C_2-H), 3.55-3.79 (m, 5H, pyran ring protons), 4.53 (AB q, Δν = 22.1 Hz, J_{AB} = 12.0 Hz, 2H, PhCH_2),, 4.74 (AB q, Δν = 85.5 Hz, J_{AB} = 10.9 Hz, 2H, PhCH_2), 4.91 (d, J = 8.7 Hz, 1H, C_1-H), 4.91 (AB q, Δν = 67.9 Hz, J_{AB} = 10.5 Hz, 2H, PhCH_2), 6.80 (d, J = 8.5 Hz, 2H, Ar-H), 7.02 (d, J = 8.2 Hz, 2H, Ar-H), 7.19-7.57 (m, 20H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.51, 56.51 (C_2), 68.86, 73.45, 74.91, 75.02, 76.16, 79.14, 82.94, 102.23 (C_1), 116.75, 127.04, 127.45, 127.60, 127.67, 127.78, 128.00, 128.22, 128.27, 128.37, 128.67, 129.71, 131.77, 132.41, 135.02, 137.96, 138.12, 138.15, 155.25. Anal. Calcd for $C_{40}H_{40}O_5S$: C, 75.92; H, 6.37; S, 5.07. Found: C, 76.08; H, 6.21; S, 4.99.

Third fraction: **48** (R=CH_3): (contaminated with **28**, R=R_1=H) ^{1}H NMR (300 MHz, $CDCl_3$), characteristic signals δ 2.13 (s, 3H, CH_3), 6.63 (d, J = 8.2 Hz, 2H, Ar-H), 7.02 (d, J = 8.2 Hz, 2H, Ar-H).

Fourth fraction: **28** ($R=R_1=H$).

Fifth fraction: **27** ($R=R_1=H$).

3,4,6-Tri-O-benzyl-D-glucal (17) + ortho-Tolyl tri-n-butyltin ether (43) Using Reagent 31: Glycosidation was carried out using phenyl(bisphenylthio)sulfonium salt (**31**) prepared by method **B**. Radial chromatography (ethyl acetate-hexane 1:20 to 2:1) gave 10 mg of of 3,4,6-tri-O-benzyl-2-deoxy-1-O-(2'-methylphenyl)--2-phenylthio-α-D-mannopyranoside (α-**44**) and 38 mg of 3,4,6-tri-O-benzyl-2-deoxy-1-O-(2'-methylphenyl)-2-phenylthio-β-D-glucopyranoside (β-**44**); total yield 30%; β/α 3.7/1. In addition 28 mg (20.3%) of 3,4,6-tri-O-benzyl-2-deoxy-2-phenylthio-β-D-glucose (**28**, $R=R_1=H$) and 36 mg (26%) of 3,4,6-tri-O-benzyl-2-deoxy-2-phenylthio-α-D-glucose (**27**, $R=R_1=H$) were also isolated. A small amount of 2-methyl-4-thiophenylphenol (**47**, $R=CH_3$) was obtained.

Physical data: First fraction: α-**44:** thick oil; ^1H NMR (300 MHz, $CDCl_3$) δ 2.10 (s, 3H, Ar-C*H*$_3$),3.67 (dd, J = 11.0, 1.6 Hz, 1H, C_6-*H*), 3.79-3.92 (m, 3H, C_2-*H*, C_5-*H*, C_6-*H*), 4.02 (dd, J = 9.1, 9.5 Hz, 1H, C_4-*H*), 4.42-4.50 (m, 2H, C_3-*H*, 1/2xPhC*H*$_2$), 4.68-4.75 (m, 3H, 1.5xPhC*H*$_2$), 4.74 (AB q, Δν = 111.8 Hz, J_{AB} = 10.8 Hz, 2H, PhC*H*$_2$), 5.66 (d, J = 1.5 Hz, 1H, C_1-*H*), 6.89-7.51 (m, 24H, Ar-*H*). Anal. Calcd for $C_{40}H_{40}O_5S$: C, 75.92; H, 6.37; S, 5.07. Found: C, 75.65; H, 6.31; S, 5.13.

Second fraction: β-**44:** thick oil; $[\alpha]^{25}_D$ -38.7° (c 0.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 2.08 (s, 3H, Ar-C*H*$_3$), 3.57 (dd, J = 10.5, 8.7 Hz, 1H, C_2-*H*), 3.61-3.85 (m, 5H, pyran ring protons), 4.51-4.65 (m, 3H, 1.5xPhC*H*$_2$), 4.86-4.93 (m, 2H, PhC*H*$_2$), 5.01 (d, J = 8.7 Hz, 1H, C_1-*H*), 5.12 (d, J = 10.4 Hz, 1H, 1/2xPhC*H*$_2$),

6.92-7.57 (m, 24H, Ar-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.17, 56.10 (*C_2*), 68.83, 73.44, 74.86, 74.97, 76.06, 79.12, 83.29, 101.15 (*C_1*), 114.52, 122.10, 126.62, 126.80, 127.45, 127.59, 127.77, 127.91, 128.22, 128.35, 128.73, 129.02, 130.69, 131.57, 132.30, 137.93, 138.05, 138.16, 155.44.

Third fraction: **47** (R=CH_3): (contaminated with β-OH) ^{1}H NMR (300 MHz, $CDCl_3$), characteristic signals δ 2.18 (s, 3H, C*H_3*), 6.69 (d, *J* = 3.7 Hz, 1H, C_5-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) characteristic signals δ 15.53 (*C*H_3), 138.00, 138.30, 154.32 (*C_1*).

Fourth fraction: **28** (R=R_1=H).

Fifth fraction: **27** (R=R_1=H).

3,4,6-Tri-O-benzyl-D-glucal (17) + para-Chlorophenyl tri-n-butyltin ether (45) Using reagent 31: Glycosidation was carried out using phenyl(bisphenylthio)sulfonium salt (**31**) prepared by method **B**. Radial chromatography (ethyl acetate-hexane 1:20 to 2:1) gave 15 mg of of 3,4,6-tri-O-benzyl-2-deoxy-1-O-(4'-chlorophenyl)--2-phenylthio-α-D-mannopyranoside (α-**46**) and 73 mg of 3,4,6-tri-O-benzyl-2-deoxy-1-O-(4'-chlorophenyl)-2-phenylthio-β-D-glucopyranoside (β-**46**); total yield 53%; β/α 4.9/1. In addition 14 mg (10%) of 3,4,6-tri-O-benzyl-2-deoxy-2-phenylthio-β-D-glucose (**28**, R=R_1=H) and 41.5 mg (30%) of 3,4,6-tri-O-benzyl-2-deoxy-2-phenylthio-α-D-glucose (**27**, R=R_1=H) were also isolated. A small amount of 4-O-(4'-chlorophenyl)-thiophenol (**48**, R=Cl) was obtained.

Physical data: First fraction: **α-46:** oil ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.64 (dd, *J* = 11.0, 1.4 Hz, 1H, C_6-*H*), 3.78 (dd, *J* = 11.0, 4.4 Hz, 1H, C_6-*H*), 3.85-3.91 (m, 2H, C_5-*H*, C_2-*H*), 3.98 (dd, *J* = 8.9, 9.4 Hz, 1H, C_4-*H*), 4.39-4.48 (m, 2H, C_3-*H*,

1/2xPhCH_2), 4.62-4.72 (m, 3H, 1.5xPhCH_2), 4.71 (AB q, $\Delta\nu$ = 111.7 Hz, J_{AB} = 10.8 Hz, 2H, PhCH_2), 5.65 (d, J = 1.4 Hz, 1H, C_1-H), 6.92 (d, J = 8.8 Hz, 2H, Ar-H),7.17-7.52 (m, 22H, Ar-H).

Second fraction: **β-46:** mp 88-90 °C; $[\alpha]^{25}_D$ +11.2° (c 0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.49 (dd, J = 10.6, 8.8 Hz, 1H, C_2-H), 3.58-3.80 (m, 5H, pyran ring protons), 4.43-4.62 (m, 3H, 1.5xPhCH_2), 4.85-4.93 (m, 3H, C_1-H, PhCH_2), 5.08 (d, J = 10.2 Hz, 1H, 1/2xPhCH_2), 6.80 (d, J = 8.8 Hz, 2H, Ar-H), 7.15-7.55 (m, 22H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.21 (C_2), 68.70, 73.42, 74.94, 75.00, 76.20, 78.99, 82.69, 101.99 (C_1), 118.02, 127.19, 127.57, 127.72, 127.78, 127.99, 128.14, 128.24, 128.28, 128.37, 128.71, 129.17, 129.28, 132.43, 134.64, 137.79, 137.91, 137.99, 155.72. Anal. Calcd for $C_{39}H_{37}O_5SCl$: C, 71.71; H, 5.71; S, 4.91; Cl, 5.43. Found: C, 71.66; H, 5.58; S, 5.00; Cl, 5.37.

Third fraction: **48** (R=Cl); (contaminated with β-OH) ^{1}H NMR (300 MHz, $CDCl_3$), characteristic signals δ 5.45 (s, 1H), 6.77 (d, J = 7.9 Hz, 2H, Ar-H), 7.23-7.50 (m, 6H, Ar-H).

Fourth fraction: **28** (R=R_1=H).

Fifth fraction: **27** (R=R_1=H).

3,4,6-Tri-O-benzyl-D-glucal (17) + Phenyl tri-n-butyltin ether (39) Using Reagent 51: Glycosidation was carried out using p-chlorophenyl{bis(p-chlorophenyl)thio}sulfonium salt (**51**) prepared by method **B**. Radial chromatography (ethyl acetate-hexane 1:20 to 2:1) gave 33.3 mg of of 3,4,6-tri-O-benzyl-2-deoxy-1-O-phenyl--2-(4'-chlorophenyl)thio-α-D-mannopyranoside (**α-64**) and 56 mg of 3,4,6-tri-O-benzyl-2-deoxy-1-O-phenyl-2-(4'-chlorophenyl)thio-β-D-glucopyranoside (**β-64**); total yield 54%; β/α 1.7/1.

In addition 16 mg (11%) of 3,4,6-tri-O-benzyl-2-deoxy-2-(4'-chlorophenyl)thio-β-D-glucose (**28**, R=Cl; R_1=H) and 25 mg (17 %) of 3,4,6-tri-O-benzyl-2-deoxy-2-(4'-chlorophenyl)thio-α-D-glucose (**27**, R=Cl; R_1=H) were also isolated. A small amount of 4-(4'-chlorothiophenyl)phenol (**67**, R=Cl, R_1=H) was obtained.

Physical data: First fraction: **α-64:** mp 77-78 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.62 (dd, *J* = 11.1, 1.3 Hz, 1H, C_6-*H*), 3.76 (dd, *J* = 11.1, 4.0 Hz, 1H, C_6-*H*), 3.81 (dd, *J* = 4.5, 1.5 Hz, 1H, C_2-*H*), 3.85-3.90 (m, 1H, C_5-*H*), 3.98 (dd, *J* = 8.9 Hz, 1H, C_4-*H*), 4.40-4.44 (m, 2H, C_3-*H*, 1/2xPhCH_2), 4.54-4.66 (m, 3H, 1.5xPhCH_2), 4.68 (AB q, Δν = 109.8 Hz, J_{AB} = 10.8 Hz, 2H, PhCH_2), 5.66 (d, *J* = 1.5 Hz, 1H, C_1-*H*), 6.96-7.39 (m, 24H, Ar-*H*).

Second fraction: **β-64:** mp 77-79 °C; $[\alpha]^{25}_D$ ° (c , $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.43 (dd, *J* = 10.9, 8.8 Hz, 1H, C_2-*H*), 3.56-3.81 (m, 5H, pyran ring protons), 4.49-4.65 (m, 3H, 1.5xPhCH_2), 4.85 (d, *J* = 11 Hz, 1H, 1/2xPhCH_2), 4.92 (AB q, Δν = 40.8 Hz, J_{AB} = 10.4 Hz, 2H, PhCH_2), 4.96 (d, *J* = 8.8 Hz, 1H, C_1-*H*), 6.90 (d, *J* = 7.9 Hz, 2H, Ar-*H*), 7.00-7.52 (m, 22H, Ar-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.79 (*C_2*), 68.68, 73.42, 74.91, 75.03, 76.20, 79.06, 82.82, 101.75 (*C_1*), 116.63, 122.51, 127.46, 127.57, 127.75, 127.90, 128.21, 128.29, 128.35, 128.77, 129.31, 133.06, 133.19, 133.24, 133.53, 137.80, 137.96, 157.12. Anal. Calcd for $C_{39}H_{37}O_5SCl$: C, 71.71; H, 5.71; S, 4.91; Cl, 5.43. Found: C, 71.59; H, 5.67; S, 5.00; Cl, 5.60.

Third fraction: **67** (R=Cl; R_1=H): mp 67-68 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.95 (s, 1H, O*H*), 6.88 (d, *J* = 9.3 Hz, 2H, Ar-*H*), 7.11 (d, *J* = 9.3 Hz, 2H, Ar-*H*), 7.24 (d, *J* = 9.3 Hz, 2H, Ar-*H*), 7.49 (d, *J* = 9.3 Hz, 2H, Ar-*H*).

Fourth fraction: **28** (R=Cl; R_1=H): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.30 (dd, *J* = 10.2, 8.8 Hz, 1H, C_2-*H*), 3.52-3.86 (m, 5H, pyran ring protons), 4.53 (d, *J* = 8.8

Hz, 1H, C_1-*H*), 4.58-4.70 (m, 3H, OH, PhCH_2), 4.85-4.98 (m, 3H, 1.5xPhCH_2), 5.04 (d, *J* = 10.2 Hz, 1H, 1/2xPhCH_2), 6.90-7.43 (m, 19H, Ar-*H*).

Fifth fraction: **27** (R=Cl; R_1=H): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.22-3.30 (m, 2H, C_2-*H*, O*H*), 3.53-3.68 (m, 3H, C_4-*H*, 2xC_6-*H*), 3.95 (dd, *J* = 10.8, 8.8. Hz, 1H, C_3-*H*), 4.03-4.10 (m, 1H, C_5-*H*), 4.40-4.60 (m, 3H, 1.5xPhCH_2), 4.75-4.82 (m, 2H, PhCH_2), 4.90 (d, *J* = 10.2 Hz, 1H, 1/2xPhCH_2), 5.42 (t, *J* = 3.0 Hz, 1H, C_1-*H*), 6.90-7.43 (m, 19H, Ar-*H*).

3,4,6-Tri-O-benzyl-D-glucal (17) + Phenyl tri-n-butyltin ether (39) Using Reagent 53: Glycosidation was carried out using p-methylphenyl{bis(p-methylphenyl)thio}sulfonium salt (**53**) prepared by method **B**. Radial chromatography (ethyl acetate-hexane 1:20 to 2:1) gave 11 mg of of 3,4,6-tri-O-benzyl-2-deoxy-1-O-phenyl--2-(4'-methylphenyl)thio-α-D-mannopyranoside (**α-63**) and 63 mg of 3,4,6-tri-O-benzyl-2-deoxy-1-O-phenyl-2-(4'-methylphenyl)thio-β-D-glucopyranoside (**β-63**); total yield 46%; β/α 5.7/1. In addition 17 mg (12%) of 3,4,6-tri-O-benzyl-2-deoxy-2-(4'-methylphenyl)thio-β-D-glucose (**28**, R=CH_3; R_1=H) and 32 mg (22.7 %) of 3,4,6-tri-O-benzyl-2-deoxy-2-(4'-methylphenyl)thio-α-D-glucose (**27**, R=CH_3; R_1=H) were also isolated. A small amount of 4-(4'-methylthiophenyl)phenol (**67**, R=CH_3, R_1=H) was obtained.

Physical data: First fraction: **α-63:** mp 87-88 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.32 (s, 3H, Ar-CH_3), 3.67 (dd, *J* = 11.1, 1.9 Hz, 1H, C_6-*H*), 3.80 (dd, *J* = 11.1, 4.3 Hz, 1H, C_6-*H*), 3.85 (dd, *J* = 4.7, 1.5 Hz, 1H, C_2-*H*), 3.88-3.93 (m, 1H, C_5-*H*), 4.01 (dd, *J* = 9.6, 8.9 Hz, 1H, C_4-*H*), 4.43-4.48 (m, 2H, C_3-*H*, 1/2xPhCH_2), 4.62-4.74 (m, 3H, 1.5xPhCH_2), 4.73 (AB q, Δν = 113.8 Hz, J_{AB} = 10.8 Hz, 2H, PhCH_2),

5.7 (d, J = 1.5 Hz, 1H, C_1-*H*), 6.99-7.43 (m, 24H, Ar-*H*). Anal. Calcd for $C_{40}H_{40}O_5S$: C, 75.92; H, 6.37; S, 5.07. Found: C, 75.70; H, 6.48; S, 5.22.

Second fraction: **β-63:** mp 78-80 °C; $[\alpha]^{25}_D$ -9.3° (c 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35 (s, 3H, Ar-C*H*$_3$), 3.37 (dd, J = 10.6, 8.7 Hz, 1H, C_2-*H*), 3.60-3.83 (m, 5H, pyran ring protons), 4.65 (AB q, Δν = 20.5 Hz, J_{AB} = 12.0 Hz, 2H, PhC*H*$_2$),, 4.76 (AB q, Δν = 75.6 Hz, J_{AB} = 10.9 Hz, 2H, PhC*H*$_2$), 4.98 (d, J = 8.7 Hz, 1H, C_1-*H*), 5.03 (AB q, Δν = 62.4 Hz, J_{AB} = 10.4 Hz, 2H, PhC*H*$_2$), 6.96-7.48 (m, 24H, Ar-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.98, 56.66 (*C*$_2$), 68.85, 73.42, 74.89, 75.00, 76.04, 79.14, 82.82, 101.65 (*C*$_1$), 116.75, 122.35, 127.43, 127.57, 127.64, 127.74, 127.78, 127.98, 128.21, 128.27, 128.35, 129.25, 129.35, 129.47, 130.87, 133.17, 137.35, 137.94, 138.08, 138.21, 157.32.

Third fraction: **67** (R=CH_3; R_1=H): oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35 (s, 3H, C*H*$_3$), 4.82 (s, 1H, O*H*), 6.84 (d, J = 9.3 Hz, 2H, Ar-*H*), 7.12 (d, J = 8.4 Hz, 2H, Ar-*H*), 7.18 (d, J = 8.4 Hz, 2H, Ar-*H*), 7.36 (d, J = 9.3 Hz, 2H, Ar-*H*).

Fourth fraction: **28** (R=CH_3; R_1=H): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.34 (s, 3H, C*H*$_3$), 3.24 (dd, J = 10.7, 8.9 Hz, 1H, C_2-*H*), 3.43-3.51 (m, 1H, pyran ring proton), 3.56 (dd, J = 10.7, 8.8 Hz, 1H, C_3-*H*), 3.64-3.82 (m, 3H, pyran ring protons), 4.48 (d, J = 8.9 Hz, 1H, C_1-*H*), 4.57 (m, 3H, OH, PhC*H*$_2$), 4.84 (d, J = 10.7 Hz, 1H, 1/2xPhC*H*$_2$), 4.95 (d, J = 11.6 Hz, 1H, 1/2xPhC*H*$_2$), 4.98 (AB q, Δν = 58.1 Hz, J_{AB} = 10.2 Hz, 2H, PhC*H*$_2$), 7.00-7.49 (m, 19H, Ar-*H*).

Fifth fraction: **27** (R=CH_3; R_1=H): mp 93-95 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.27 (s, 3H, C*H*$_3$), 3.05 (d, J = 3.0 Hz, 1H, D_2O exchangable, O*H*), 3.28 (dd, J = 11.0, 3.0 Hz, 1H, C_2-*H*), 3.57-3.68 (m, 3H, C_4-*H*, 2xC_6-*H*), 3.93 (dd, J = 11.0, 8.9 Hz, 1H, C_3-*H*), 4.05-4.11 (m, 1H, C_5-*H*), 4.50 (AB q, Δν = 29.4 Hz, J_{AB} = 12.2 Hz, 2H, PhC*H*$_2$), 4.60 (AB q, Δν = 101.3 Hz, J_{AB} = 11.2 Hz, 2H, PhC*H*$_2$), 4.87 (AB q,

Δν = 50.0 Hz, J_{AB} = 10.3 Hz, 2H, PhCH_2), 5.29 (t, J = 3.0 Hz, 1H, C_1-*H*), 7.00-7.41 (m, 19H, Ar-*H*).

3,4,6-Tri-O-benzyl-D-glucal (17) + Phenyl tri-n-butyltin ether (39) Using Reagent 55: Glycosidation was carried out using p-methoxylphenyl{bis(p-methoxylphenyl)thio}sulfonium salt (**55**) prepared by method **B**. Radial chromatography (ethyl acetate-hexane 1:20 to 2:1) gave 30 mg of of 3,4,6-tri-O-benzyl-2-deoxy-1-O-phenyl--2-(4'-methoxylphenyl)thio-α-D-mannopyranoside (α-**65**) and 72 mg of 3,4,6-tri-O-benzyl-2-deoxy-1-O-phenyl-2-(4'-methoxylphenyl)thio-β-D-glucopyranoside (β-**65**); total yield 61.7%; β/α 2.4/1. In addition 20 mg (14%) of 3,4,6-tri-O-benzyl-2-deoxy-2-(4'-methoxylphenyl)thio-β-D-glucose (**28**, R=OCH_3; R_1=H) and 35.5 mg (24.3 %) of 3,4,6-tri-O-benzyl-2-deoxy-2-(4'-methoxylphenyl)thio-α-D-glucose (**27**, R = OCH_3; R_1 = H) were also isolated. A small amount of 4-(4'-methoxylthiophenyl)phenol (**67**, R=OCH_3, R_1=H) was obtained.

Physical data: First fraction: α-**65:** mp 72-73 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.63 (dd, J = 11.1, 1.7 Hz, 1H, C_6-*H*), 3.71-3.77 (m, 2H, C_2-*H*, C_6-*H*), 3.74 (s, 3H, Ar-OCH_3), 3.84-3.90 (m, 1H, C_5-*H*), 3.98 (dd, J = 9.0, 9.6 Hz, 1H, C_4-*H*), 4.4-4.45 (m, 2H, C_3-*H*, 1/2xPhCH_2), 4.58-4.69 (m, 3H, 1.5xPhCH_2), 4.70 (AB q, Δν = 115.1 Hz, J_{AB} = 10.8 Hz, 2H, PhCH_2), 5.65 (d, J = 1.6 Hz, 1H, C_1-*H*), 6.76 (d, J = 8.8 Hz, 2H, Ar-*H*),6.94-7.36 (m, 20H, Ar-*H*), 7.45 (d, J = 8.8 Hz, 2H, Ar-*H*).

Second fraction: β-**65:** mp 74-75 °C; $[\alpha]^{25}_D$ -9.0° (c 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.26 (dd, J = 10.6, 8.8 Hz, 1H, C_2-*H*), 3.53-3.76 (m, 5H, pyran ring protons), 3.75 (s, 3H, OCH_3), 4.45-4.59 (m, 3H, 1.5xPhCH_2), 4.82 (d, J = 10.8 Hz, 1H, 1/2xPhCH_2), 4.91 (d, J = 8.4 Hz, 1H, C_1-*H*), 4.99 (AB q, Δν = 60.3 Hz, J_{AB} = 10.4 Hz, 2H, PhCH_2), 6.75 (d, J = 8.8 Hz, 2H, Ar-*H*), 6.92-7.47 (m,

22H, Ar-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.25, 57.01, 68.80, 73.40, 74.89, 74.95, 75.94, 79.14, 82.62, 101.30 (C_1), 114.32, 116.65, 122.30, 124.53, 127.43, 127.57, 127.67, 127.76, 127.80, 126.94, 128.20, 128.31, 128.36, 129.28, 135.75, 137.90, 138.05, 138.25, 157.21, 159.58. Anal. Calcd for $C_{40}H_{40}O_6S$: C, 74.05; H, 6.21; S, 4.94. Found: C, 73.87; H, 6.19; S, 4.84.

Third fraction: **67** (R=OCH_3; R_1=H): mp 65-66 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 3.83 (s, 3H, OCH_3), 4.90 (s, 1H, O*H*), 6.80 (d, *J* = 9.3 Hz, 2H, Ar-*H*), 6.88 (d, *J* = 9.3 Hz, 2H, Ar-*H*), 7.22-7.49 (m, 4H, Ar-*H*).

Fourth fraction: **28** (R=OCH_3; R_1=H): ^1H NMR (300 MHz, $CDCl_3$) δ 3.12 (dd, *J* = 10.2, 8.8 Hz, 1H, C_2-*H*), 3.41-3.50 (m, 1H, pyran ring proton), 3.55 (dd, *J* = 10.2, 8.9 Hz, 1H, C_3-*H*), 3.67-3.88 (m, 3H, pyran ring protons), 3.80 (s, 3H, OCH_3), 4.45 (d, *J* = 8.8 Hz, 1H, C_1-*H*), 4.54-4.71 (m, 3H, OH, $PhCH_2$), 4.89-5.00 (m, 2H, $PhCH_2$), 5.01 (AB q, Δν = 74.4 Hz, J_{AB} = 10.2 Hz, 2H, $PhCH_2$), 6.73 (d, *J* = 9.3 Hz, 2H, Ar-*H*), 7.20-7.53 (m, 17H, Ar-*H*).

Fifth fraction: **27** (R=OCH_3; R_1=H): mp 84-85 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 3.27 (dd, *J* = 11.2, 3.3 Hz, 2H, C_2-*H*), 3.48 (d, *J* = 3.3 Hz, 1H, O*H*), 3.52-3.68 (m, 3H, C_4-*H*, 2xC_6-*H*), 3.81 (s, 3H, OCH_3), 4.02 (d, *J* = 11.2, 9.3 Hz, 1H, C_3-*H*), 4.13-4.21 (m, 1H, C_5-*H*), 4.50-4.68 (m, 3H, 1.5x$PhCH_2$), 4.92 (d, *J* = 9.3 Hz, 1H, 1/2x$PhCH_2$), 4.98 (AB q, Δν = 55.8 Hz, J_{AB} = 10.2 Hz, 2H, $PhCH_2$), 5.47 (t, *J* = 3.3 Hz, 1H, C_1-*H*), 6.72 (d, *J* = 9.3 Hz, 2H, Ar-*H*), 7.17-7.42 (m, 15H, Ar-*H*).

3,4,6-Tri-O-benzyl-D-glucal (17) + Phenyl tri-n-butyltin ether (39) Using Reagent 59: Glycosidation was carried out using o-methylphenyl(bis(o-methylphenyl)thio)sulfonium salt (**59**) prepared by method **B**. Radial chromatography (ethyl acetate-hexane 1:20 to 2:1) gave 21 mg of of 3,4,6-tri-O-benzyl-2-deoxy-1-O-phenyl--2-(2'-methylphenyl)thio-α-D-

mannopyranoside (α-**66**) and 55 mg of 3,4,6-tri-O-benzyl-2-deoxy-1-O-phenyl-2-(2'-methylphenyl)thio-β-D-glucopyranoside (β-**66**); total yield 47%; β/α 2.6/1. In addition 18.3 mg (13%) of 3,4,6-tri-O-benzyl-2-deoxy-2-(2'-methylphenyl)thio-β-D-glucose (**28**, R=H; $R_1 = CH_3$) and a small amount of 4-(2'-methylthiophenyl)phenol (**67**, R=H, $R_1=CH_3$) was obtained.

Physical data: First fraction: α-**66**: mp 88-89 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.50 (s, 3H, Ar-C*H*$_3$), 3.68 (dd, *J* = 11.1, 1.7 Hz, 1H, C_6-*H*), 3.83 (dd, *J* = 11.1, 4.4 Hz, 1H, C_6-*H*), 3.88-3.96 (m, 2H, C_5-*H*, C_2-*H*), 4.13 (dd, *J* = 9.2, 9.5 Hz, 1H, C_4-*H*), 4.46-4.50 (m, 2H, C_3-*H*, 1/2xPhC*H*$_2$), 4.63-4.72 (m, 3H, 1.5xPhC*H*$_2$), 4.75 (AB q, Δν = 107.1 Hz, J_{AB} = 10.7 Hz, 2H, PhC*H*$_2$), 5.66 (d, *J* = 1.4 Hz, 1H, C_1-*H*), 6.97-7.49 (m, 24H, Ar-*H*).

Second fraction: β-**66**: mp 87-89 °C; $[\alpha]^{25}_D$ -30.3° (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35 (s, 3H, C*H*$_3$), 3.52 (dd, *J* = 10.8, 8.4 Hz, 1H, C_2-*H*), 3.60-3.79 (m, 5H, pyran ring protons), 4.46-4.61 (m, 3H, 1.5 PhC*H*$_2$), 4.85 (d, *J* = 10.9 Hz, 1H, 1/2xPhC*H*$_2$), 4.96 (AB q, Δν = 57.3 Hz, J_{AB} = 10.3 Hz, 2H, PhC*H*$_2$), 5.04 (d, *J* = 8.4 Hz, 1H, C_1-*H*), 6.76 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 6.93-7.65 (m, 22H, Ar-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.93, 55.92 (*C*$_2$), 68.81, 73.43, 74.96, 75.05, 76.35, 79.11, 83.01, 102.04 (*C*$_1$), 116.35, 122.20, 126.23, 127.01, 127.46, 127.60, 127.65, 127.78, 127.96, 128.16, 128.23, 128.25, 128.37, 128.49, 129.18, 130.01, 133.01, 134.45, 137.92, 138.04, 138.07, 139.49, 157.02. Anal. Calcd for $C_{40}H_{40}O_5S$: C, 75.92; H, 6.37; S, 5.07. Found: C, 75.71; H, 6.17; S, 5.16.

Third fraction: **67** (R=H; $R_1=CH_3$): oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.46 (s, 3H, C*H*$_3$), 5.49 (s, 1H, O*H*), 6.84 (d, *J* = 8.2 Hz, 2H, Ar-*H*), 7..02-7.42 (m, 6H, Ar-*H*).

Fourth fraction: **28** (R=H; R_1=CH_3): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.24 (s, 3H, CH_3), 3.49 (dd, *J* = 10.0, 8.5 Hz, 1H, C_2-*H*), 3.58-3.90 (m, 5H, pyran ring proton), 4.58-4.71 (m, 5H, C_1-*H*, OH, 1.5xPhCH_2), 4.88-4.94 (m, 2H, PhCH_2), 5.1 (d, *J* = 10.2 Hz, 1H, 1/2xPhCH_2), 7.02-7.48 (m, 19H, Ar-*H*).

General Procedure for Glycosidation Using Methanol as the Nucleophile: To a solution of the glucal (0.255 mmol) and 50 µL of methanol in dry methylene chloride at -60 °C (under argon), 1.2 ml of the reagent solution (0.30 mmol) is added by syringe technique. After the reaction is complete (about 10 min) saturated aqueous sodium bicarbonate solution (15 ml) is added and the mixture is stirred for 30 min at room temperature. The reaction mixture is extracted with dichloromethane (3X25 ml). The combined organic extracts were dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude product mixture which was subjected to radial chromatography.

3,4,6-Tri-O-benzyl-D-glucal (17) + Methanol (22) Using Reagent 31: Glycosidation was carried out using phenyl(bisphenylthio)sulfonium salt (**31**) prepared by method **B**. Radial chromatography (ethyl acetate-hexane 1:20 to 2:1) gave 130 mg of mixture of 3,4,6-tri-O-benzyl-2-deoxy-1-O-methyl--2-phenylthio-α-D-mannopyranoside (**α-23**) and 3,4,6-tri-O-benzyl-2-deoxy-1-O-methyl-2-phenylthio-β-D-glucopyranoside (**β-23**); yield 92%; β/α 3.7/1 (β/α ratio was determined by the ratio of the heights of the signals for methoxy groups in the ^{1}H NMR). When the reagent **24** was prepared using method **A** the yield was 83%; β/α 3.7/1.

Physical data: β-23 + α-23: oil; ^{1}H NMR (300 MHz, $CDCl_3$), characteristic signals δ 3.18 (dd, *J* = 10.5, 8.8 Hz, C_2-*H* of β), 3.33 (s, OCH_3 of α), 3.53 (s, OCH_3 of β), 4.27 (d, *J* = 8.8 Hz, C_1-*H* of β); ^{13}C NMR (75 MHz, $CDCl_3$)

characteristic signals of β-**23** δ 56.21, 57.25, 68.87, 73.86, 76.25, 79.55, 83.22, 104.19 (C_1); characteristic signals of α-**23** δ 53.00, 55.07, 69.25, 71.70, 71.73, 73.80, 78.92, 101.09 (C_1). Anal. Calcd for $C_{34}H_{36}O_5S$: C, 73.35; H, 6.52; S, 5.76. Found: C, 73.36; H, 6.57; S, 5.88.

3,4,6-Tri-O-benzyl-D-glucal (17) + Methanol (22) Using Reagent 51: Glycosidation was carried out using p-chlorophenyl[bis(p-chlorophenyl)thio]sulfonium salt (**51**) prepared by method **B**. Radial chromatography (ethyl acetate-hexane 1:20 to 2:1) gave 137.6 mg of mixture of 3,4,6-tri-O-benzyl-2-deoxy-1-O-methyl--2-(4'-chlorophenyl)thio-α-D-mannopyranoside (α-**52**) and 3,4,6-tri-O-benzyl-2-deoxy-1-O-methyl-2-(4'-chlorophenyl)thio-β-D-glucopyranoside (β-**52**); yield 91.4%; β/α 2.5/1 (β/α ratio was determined by the ratio of the heights of the signals for methoxy groups in the ^{1}H NMR).

Physical data: β-**52** + α-**52:** oil; ^{1}H NMR (300 MHz, $CDCl_3$), characteristic signals δ 3.06 (dd, J = 10.6, 8.8 Hz, C_2-*H* of β), 3.27 (s, OCH_3 of α), 3.46 (s, OCH_3 of β), 4.20 (d, J = 8.8 Hz, C_1-*H* of β); ^{13}C NMR (75 MHz, $CDCl_3$) characteristic signals of β-**52** δ 56.56, 57.00, 104.20 (C_1); characteristic signals of α-**52** δ 53.34, 54.60, 100.80 (C_1).

3,4,6-Tri-O-benzyl-D-glucal (17) + Methanol (22) Using Reagent 53: Glycosidation was carried out using p-methylphenyl[bis(p-methylphenyl)thio]sulfonium salt (**53**) prepared by method **B**. Radial chromatography (ethyl acetate-hexane 1:20 to 2:1) gave 133.3 mg of mixture of 3,4,6-tri-O-benzyl-2-deoxy-1-O-methyl--2-(4'-methylphenyl)thio-α-D-mannopyranoside (α-**54**) and 3,4,6-tri-O-benzyl-2-deoxy-1-O-methyl-2-(4'-methylphenyl)thio-β-D-glucopyranoside (β-**54**); yield 91.7%; β/α 4.4/1 (β/α ratio

was determined by the ratio of the heights of the signals for methoxy groups in the ^{1}H NMR).

Physical data: **β-54 + α-54:** oil; ^{1}H NMR (300 MHz, $CDCl_3$), characteristic signals δ 3.06 (dd, J = 10.5, 8.8 Hz, C_2-*H* of β), 3.29 (s, OC*H*$_3$ of α), 3.50 (s, OC*H*$_3$ of β), 4.20 (d, J = 8.8 Hz, C_1-*H* of β); ^{13}C NMR (75 MHz, $CDCl_3$) characteristic signals of **β-54** δ 56.15, 56.85, 104.00 (*C*$_1$); characteristic signals of **α-54** δ 53.30, 54.76, 100.96 (*C*$_1$).

3,4,6-Tri-O-benzyl-D-glucal (17) + Methanol (22) Using Reagent 55: Glycosidation was carried out using p-methoxylphenyl(bis(p-methoxyphenyl)thio)sulfonium salt (**55**) prepared by method **B**. Radial chromatography (ethyl acetate-hexane 1:20 to 2:1) gave 123 mg of mixture of 3,4,6-tri-O-benzyl-2-deoxy-1-O-methyl--2-(4'-methoxylphenyl)thio-α-D-mannopyranoside (**α-56**) and 3,4,6-tri-O-benzyl-2-deoxy-1-O-methyl-2-(4'-methoxylphenyl)thio-β-D-glucopyranoside (**β-56**); yield 82%; β/α 2.4/1 (β/α ratio was determined by the ratio of the heights of the signals for methoxy groups in the ^{1}H NMR).

Physical data: **β-56 + α-56:** oil; ^{1}H NMR (300 MHz, $CDCl_3$), characteristic signals δ 2.96 (dd, J = 10.2, 9.0 Hz, C_2-*H* of β), 3.30 (s, OC*H*$_3$ of α), 3.52 (s, OC*H*$_3$ of β), 4.17 (d, J = 9.0 Hz, C_1-*H* of β); ^{13}C NMR (75 MHz, $CDCl_3$) characteristic signals of **β-56** δ 55.23, 56.46, 56.72, 68.89, 73.44, 79.36, 82.76, 103.84 (*C*$_1$); characteristic signals of **α-56** δ 54.02, 54.75, 69.30, 71.30, 71.73, 73.34, 78.96, 100.97 (*C*$_1$). Anal. Calcd for $C_{35}H_{38}O_6S$: C, 71.65; H, 6.53; S, 5.46. Found: C, 71.35; H, 6.36; S, 5.48.

3,4,6-Tri-O-benzyl-D-glucal (17) + Methanol (22) Using Reagent 57: Glycosidation was carried out using 3,4-dimethylphenyl(bis(3,4-

dimethylphenyl)lthio)sulfonium salt (**57**) prepared by method **B**. Radial chromatography (ethyl acetate-hexane 1:20 to 2:1) gave 134 mg of mixture of 3,4,6-tri-O-benzyl-2-deoxy-1-O-methyl-2-(3',4'-dimethylphenyl)thio-α-D-mannopyranoside (**α-58**) and 3,4,6-tri-O-benzyl-2-deoxy-1-O-methyl-2-(3',4'-dimethylphenyl)thio-β-D-glucopyranoside (**β-58**); yield 90%; β/α 4.1/1 (β/α ratio was determined by the ratio of the heights of the signals for methoxy groups in the ^{1}H NMR).

Physical data: β-58 + α-58: oil; ^{1}H NMR (300 MHz, $CDCl_3$), characteristic signals δ 2.17 (s, Ar-CH_3 of β), 2.20 (s, Ar-CH_3 of β), 2.20 (s, Ar-CH_3 of α), 3.05 (dd, J = 10.2, 8.9 Hz, C_2-H of β), 3.30 (s, OCH_3 of α), 3.51 (s, OCH_3 of β), 4.20 (d, J = 8.9 Hz, C_1-H of β); ^{13}C NMR (75 MHz, $CDCl_3$) characteristic signals of β-58 δ 56.15, 56.86, 68.91, 79.35, 83.11, 103.92 (C_1); characteristic signals of α-58 δ 53.34, 54.74, 69.28, 71.35, 71.69, 78.84, 101.02 (C_1). Anal. Calcd for $C_{38}H_{40}O_5S$: C, 73.94; H, 6.89; S, 5.48. Found: C, 73.82; H, 6.67; S, 5.36.

3,4,6-Tri-O-benzyl-D-glucal (17) + Methanol (22) Using Reagent 59: Glycosidation was carried out using o-methylphenyl(bis(o-methylphenyl)lthio)sulfonium salt (**59**) prepared by method **B**. Radial chromatography (ethyl acetate-hexane 1:20 to 2:1) gave 126.2 mg of mixture of 3,4,6-tri-O-benzyl-2-deoxy-1-O-methyl--2-(2'-methylphenyl)thio-α-D-mannopyranoside (**α-61**) and 3,4,6-tri-O-benzyl-2-deoxy-1-O-methyl-2-(2'-methylphenyl)thio-β-D-glucopyranoside (**β-61**); yield 86.8%; β/α 2.2/1 (β/α ratio was determined by the ratio of the heights of the signals for methoxy groups in the ^{1}H NMR).

Physical data: β-61 + α-61: oil; ^{1}H NMR (300 MHz, $CDCl_3$), characteristic signals δ 2.41 (s, Ar-CH_3 of β), 2.46 (s, Ar-CH_3 of α), 3.20 (dd, J = 10.5, 8.8 Hz,

C_2-*H* of β), 3.28 (s, OC*H*$_3$ of α), 3.42 (s, OC*H*$_3$ of β), 4.30 (d, *J* = 8.8 Hz, C_1-*H* of β); ^{13}C NMR (75 MHz, $CDCl_3$) characteristic signals of β-**61** δ 55.83, 56.90, 68.90, 76.05, 79.26, 83.46, 104.88 (*C*$_1$); characteristic signals of α-**61** δ 51.90, 54.79, 71.47, 71.77, 78.55, 78.85, 100.65 (*C*$_1$).

3,4,6-Tri-O-benzyl-D-glucal (17) + Methanol (22) Using Reagent 60: Glycosidation was carried out using napthyl(bisnapthylthio)sulfonium salt (**60**) prepared by method **B**. Radial chromatography (ethyl acetate-hexane 1:20 to 2:1) gave 110 mg of mixture of 3,4,6-tri-O-benzyl-2-deoxy-1-O-methyl--2-napthylthio-α-D-mannopyranoside (α-**62**) and 3,4,6-tri-O-benzyl-2-deoxy-1-O-methyl-2-napthylthio-β-D-glucopyranoside (β-**62**); yield 71.2%; β/α 2.6/1 (β/α ratio was determined by the ratio of the heights of the signals for methoxy groups in the ^{1}H NMR).

Physical data: β-**62** + α-**62:** oil; ^{1}H NMR (300 MHz, $CDCl_3$), characteristic signals δ 3.30 (dd, *J* = 10.5, 8.9 Hz, C_2-*H* of β), 3.32 (s, OC*H*$_3$ of α), 3.53 (s, OC*H*$_3$ of β), 4.31 (d, *J* = 8.9 Hz, C_1-*H* of β); ^{13}C NMR (75 MHz, $CDCl_3$) characteristic signals of β-**62** δ 56.16, 57.04, 68.87, 76.02, 79.32, 83.37, 104.22 (*C*$_1$); characteristic signals of α-**56** δ 52.91, 54.83, 69.21, 69.24, 71.76, 78.84, 100.97 (*C*$_1$). Anal. Calcd for $C_{38}H_{38}O_5S$: C, 75.22; H, 6.31; S, 5.28. Found: C, 74.86; H, 6.27; S, 5.28.

General Procedure for Glycosidation Using a Sugar Alcohol as the Nucleophile: To the sugar alcohol (0.51 mmol) dissolved in 14 ml of dry toluene under an argon atmosphere is added 3.0 g of activated powdered 4A° MS and bis(tri-n-butyl)tin oxide (0.255 mmole). The reaction mixture is refluxed for 12 h and thereafter toluene is distilled off. To the residue a solution of the glucal (0.255 mmol) in dry methylene chloride (3 ml) is added and the reaction

mixture is cooled to -60 °C. The reagent solution (1.2 ml, 0.30 mmol) is then added by syringe technique. After the reaction is complete (about 10 min) it is quenched with saturated aqueous sodium bicarbonate solution (15 ml) and the mixture stirred for 30 min at room temperature. The reaction mixture is filtered through celite (the celite is washed with 50 ml of methylene chloride) and the organic layer of the filtrate is dried over anhydrous Na_2SO_4. Evaporation of the solvent gives the crude product mixture which is subjected to radial chromatography.

3,4,6-Tri-O-benzyl-D-glucal (17) + 1,2,3,4-Di-O-isopropylidene-α-D-galactopyranoside (34) Using Reagent 31: Glycosidation was carried out using phenyl(bisphenylthio)sulfonium salt (**31**) prepared by method **A**. Radial chromatography (ethyl acetate-hexane 1:20 to 2:1) gave 4 mg of 3,4,6-tri-O-benzyl-2-deoxy-1-O-{6'-(1',2',3',4'-diisopropylidene)-galactopyranosyl}-2-phenylthio-α-D-glucopyranoside (**α'-35**), 22 mg of 3,4,6-tri-O-benzyl-2-deoxy-1-O-{6'-(1',2',3',4'-diisopropylidene)-galactopyranosyl}-2-phenylthio-α-D-mannopyranoside (**α-35**) and 117.8 mg of 3,4,6-tri-O-benzyl-2-deoxy-1-O-{6'-(1',2',3',4'-diisopropylidene)-galactopyranosyl}-2-phenylthio-β-D-glucopyranoside (**β-35**), total yield (**β-35**+**α-35**) 70%; β/α 5.3/1. **α'-35** was formed in 8% yield. In addition 28 mg (14%) of 3,4,6-tri-O-benzyl-2-deoxy-2-phenylthio-β-D-glucose (**28**, R=R_1=H) was also isolated.

Physical data: First fraction: **28** (R=R_1=H).

Second fraction: **α'-35:** oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 1.61 (s, 6H, 2xCH_3), 3.41 (d, J = 11.1, 3.1 Hz, 1H, C_2-H), 3.68-4.07 (m, 8H, pyran ring protons), 4.33-4.87 (m, 8H, pyran ring protons, 2.5xPhCH_2),

5.04 (d, J = 10.4 Hz 1H, 1/2xPhCH_2), 5.08 (d, J = 3.1 Hz, 1H, C_1-H), 5.57 (d, J = 5.0 Hz, 1H, C_1-H), 7.16-7.54 (m, 20H, Ar-H).

Third fraction: **α-35:** oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 6H, 2xCH_3), 1.45 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 3.64-4.02 (m, 8H, pyran ring protons), 4.18-4.40 (m, 3H, pyran ring protons), 4.50-4.68 (m, 5H, pyran ring protons, 2xPhCH_2), 4.78 (d, J = 12.6 Hz, 1H, 1/2xPhCH_2), 4.92 (d, J = 10.7 Hz, 1H, 1/2xPhCH_2), 5.17 (s, 1H, C_1-H), 5.55 (d, J = 4.7 Hz, 1H, C_1-H), 7.18-7.60 (m, 20H, Ar-H).

Fourth fraction: **β-35 :** oil; $[\alpha]^{25}_D$ -58.4° ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 1.63 (s, 3H, CH_3), 3.27 (dd, J = 10.8, 8.7 Hz, 1H, C_2-H), 3.50-3.54 (m, 1H, pyran ring proton), 3.60 (dd, J = 10.8, 10.6 Hz, 1H, C_3-H), 3.72-3.80 (m, 4H, pyran ring protons), 3.98-4.17 (m, 3H, pyran ring protons), 4.35 (dd, J = 5.0, 2.3 Hz, 1H, C_2-H), 4.52 (d, J = 8.7 Hz, 1H, C_1-H), 4.56-4.71 (m, 4H, pyran ring proton, 1.5xPhCH_2), 4.92 (d, J = 10.0 Hz, 1H, 1/2xPhCH_2), 5.00 (AB q, Δν = 72.3 Hz, J_{AB} = 10.3 Hz, 2H, PhCH_2), 5.60 (d, J = 5.0 Hz, 1H, C_1-H), 7.24-7.67 (m, 20H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.23, 24.98, 25.91, 26.18, 56.61 (*C2*), 66.64, 68.55, 68.59, 70.45, 70.55, 70.69, 73.47, 74.74, 74.88, 76.17, 79.09, 83.14, 96.27, 104.19 (*C1*), 108.95, 126.64, 127.55, 127.67, 127.75, 127.83, 128.03, 128.30, 128.39, 128.66, 132.15, 135.90, 138.02, 138.08, 138.24. Anal. Calcd for $C_{45}H_{52}O_{10}S$: C, 68.86; H, 6.68; S, 4.08. Found: C, 68.44; H, 6.87; S, 3.98.

3,4,6-Tri-O-benzyl-D-glucal (17) + 1,2,5,6-Di-O-isopropylidene-α-D-glucofuranoside (36) Using Reagent 31: Glycosidation was carried out using phenyl(bisphenylthio)sulfonium salt (**31**) prepared by method **A**. Radial chromatography (ethyl acetate-hexane 1:20 to 2:1) gave 138 mg of 3,4,6-tri-O-benzyl-2-deoxy-1-O-{3'-(1',2',5',6'-diisopropylidene)-glucopyranosyl)-2-

phenylthio-β-D-glucopyranoside (**β-37**) and 24 mg of 1:1 mixture (determ ned by NMR) of 3,4,6-tri-O-benzyl-2-deoxy-1-O-{3'-(1',2',5',6'-diisopropylidene)-glucopyranosyl}-2-phenylthio-α-D-glucopyranoside (**α'-37**) and 3,4,6-tri-O-benzyl-2-deoxy-1-O-{3'-(1',2',5',6'-diisopropylidene)-glucopyranosyl}-2-phenylthio-α-D-mannopyranoside (**α-37**), total yield (**β-37**+**α-37**) 75%; β/α 11.5/1. **α'-37** was formed in 6% yield. In addition 12 mg (9%) of 3,4,6-tri-O-benzyl-2-deoxy-2-phenylthio-β-D-glucose (**28**, R=R_1=H) was also isolated.

Physical data: First fraction: **28** (R=R_1=H).

Second fraction: **α'-37** + **α-37:** PLC of this mixture gave: Faster moving spot: oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (s, 3H, C*H*$_3$), 1.33 (s, 3H, C*H*$_3$), 1.35 (s, 3H, C*H*$_3$), 1.47 (s, 3H, C*H*$_3$), 3.63-3.92 (m, 7H, pyran ring protons), 4.03-4.12 (m, 1H, pyran ring proton), 4.18-4.34 (m, 3H, pyran ring protons), 4.50-4.68 (m, 4H, pyran ring proton,1.5xPhC*H*$_2$), 4.50-4.68 (m, 4H, pyran ring proton, 1.5xPhC*H*$_2$), 4.76 (AB q, Δν = 12 Hz, J_{AB} = 12 Hz, 2H, PhC*H*$_2$), 4.93 (d, *J* = 10.2 Hz, ^{1}H, 1/2xPhC*H*$_2$), 5.08 (s, 1H, C_1-*H*), 6.02 (d, *J* = 3.7 Hz, 1H, C_1-*H*), 7.18-7.55 (m, 20H, Ar-*H*); Slower moving spot (contaminated with faster moving spot): oil. ^{1}H NMR (300 MHz, $CDCl_3$), characteristic signals δ 1.24 (s, 3H, C*H*$_3$), 1.28 (s. 3H, C*H*$_3$), 1.41 (s, 3H, C*H*$_3$), 1.50 (s, 3H, C*H*$_3$), 5.32 (s, 1H, C_1-*H*), 5.85 (d, *J* = 3.7 Hz, 1H, C_1-*H*).

Third fraction: **β-37:** oil; $[\alpha]^{25}_D$ -34.0° ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (s, 3H, C*H*$_3$), 1.35 (s, 3H, C*H*$_3$), 1.43 (s, 3H, C*H*$_3$), 1.53 (s, 3H, C*H*$_3$), 3.24 (dd, *J* = 10.8, 8.8 Hz, 1H, C_2-*H*), 3.48-3.52 (m, 1H, pyran ring proton), 3.56 (dd, *J* = 10.8, 8.7 Hz, 1H, C_3-*H*), 3.73-3.89 (m, 5H, pyran ring protons), 4.31-4.40 (m, 3H, pyran ring protons), 4.54 (d, *J* = 8.8 Hz, 1H, C_1-*H*), 4.53-4.68 (m, 4H. pyran ring proton, 1.5xPhC*H*$_2$), 4.89 (AB q, Δν = 9.7 Hz, J_{AB} = 9.7 Hz, 2H, PhC*H*$_2$), 5.06 (d,

J = 10.4 Hz, 1H, 1/2xPhCH_2), 5.65 (d, *J* = 3.7 Hz, 1H, C_1-*H*), 7.25-7.53 (m, 20H, Ar-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.31, 26.34, 26.46, 26.85, 56.59 (*C_2*), 65.55, 68.53, 73.55, 73.60, 75.01, 76.38, 79.02, 80.26, 80.94, 82.56, 82.80, 102.69, 105.19, 108.26, 111.80, 126.94, 127.69, 127.74, 127.80, 127.92, 127.99, 128.03, 128.39, 128.42, 128.51, 128.91, 131.01, 135.65, 137.91, 138.10.

3,4,6-Tri-O-benzyl-D-glucal (17) + 2-Hydroxytetralone (8) Using Reagent 31: To a mixture of the glucal (106 mg, 0.255 mmol), 2-hydroxytetralone **8** (83 mg, 0.51 mmol) and 3.0 g of activated powdered 4A° MS in dry methylene chloride at -60 °C (under argon), 1.2 ml of the solution of phenyl(bisphenylthio)sulfonium salt, **31** (0.30 mmol) prepared using method **A** was added by syringe technique. After the reaction was complete (about 10 min) it is quenched with saturated aqueous sodium bicarbonate solution (15 ml) and the mixture stirred for 30 min at room temperature. The reaction mixture was filtered through celite (the celite was washed with 50 ml of methylene chloride) and the organic layer of the filtrate was dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude product mixture which was subjected to radial chromatography (ethyl acetate-hexane 1:20 to 2:1) to give 79 mg of 3,4,6-tri-O-benzyl-2-deoxy-1-O-{2'-(1'-tetralone)}-2-phenylthio-β-D-glucopyranosides (**β-38**); total yield 45%. The two diastereomeric β glycosides were formed in the ratio 10:1, determined by NMR of the mixture. In addition 40 mg (30%) of 3,4,6-tri-O-benzyl-2-deoxy-2-phenylthio-β-D-glucose (**28**, R=R_1=H) was also isolated.

Physical data: First fraction: **28** (R=R_1=H).

Second fraction: Minor diastereomer of **β-38** (contaminated with major diastereomer): ^{1}H NMR (300 MHz, $CDCl_3$), characteristic signals δ 3.29 (dd, *J* = 10.3, 8.9 Hz, 1H, C_2-*H*), 7.94 (d, *J* = 7.8 Hz, 1H, C_8-*H*).

Third fraction: **Major diastereomer of β-38:** colorless oil; $[\alpha]^{25}_D$ -17.6° ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.17-2.32 (m, 2H, C_3-*H*), 2.81-2.88 (m, 1H, C_4-*H*), 3.08-3.18 (m, 1H, C_4-*H*), 3.38 (dd, *J* = 10.6, 8.9 Hz, 1H, C_2-*H*), 3.49-3.78 (m, 5H, pyran ring protons), 4.38-4.41 (m, 1H, C_2-*H*), 4.51 (AB q, Δν = 24.9 Hz, J_{AB} = 12.2 Hz, 2H, PhCH_2), 4.69 (d, *J* = 8.9 Hz, 1H, C_1-*H*), 4.74 (AB q, Δν = 53.3 Hz, J_{AB} = 10.8 Hz, 2H, PhCH_2), 4.98 (AB q, Δν = 48.8 Hz, J_{AB} = 10.4 Hz, 2H, PhCH_2), 7.19-7.62 (m, 23H, Ar-*H*), 8.04 (d, *J* = 7.8 Hz, 1H, C_8-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.82, 29.01, 56.18 (*C*$_2$), 68.70, 73.56, 74.96, 75.09, 76.09, 78.95, 79.66, 83.11, 102.69 (*C*$_1$), 126.57, 126.65, 127.47, 127.59, 127.69, 127.80, 127.823, 127.99, 128.05, 128.18, 128.30, 128.33, 128.46, 128.60, 128.66, 131.35, 131.93, 133.35, 138.04, 138.25, 138.32, 143.46, 195.03., 138.20. Anal. Calcd for $C_{43}H_{42}O_6S$: C, 75.19; H, 6.16; S, 4.67. Found: C, 75.11; H, 6.06.

Preparation of Sulfone of α-40 : To a solution of of **α-40** (31 mg, 0.05 mmol) in 5 ml of dry methylene chloride was added m-CPBA (12.1 mg, 1.1 equiv.). The reaction mixture was stirred at room temperature for 30 min (tlc showed completion of the reaction), diluted with 10 ml of methylene chloride and was washed with water (20 ml), saturated sodium bicarbonate (2X20 ml) and finally with water (20 ml) again. The organic layer was dried over anhydrous sodium sulfate. Evaporation of the solvent gave 26 mg of 3,4,6-tri-O-benzyl-2-deoxy-1-O-phenyl-2-phenylsulfonyl-α-D-mannopyranoside (**α-40A**); yield 80%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.56-3.60 (m, 2H, 2xC_6-*H*), 3.80-3.90

(m, 3H, C_2-*H*, C_4-*H*, C_5-*H*), 4.27 (d, *J* = 11.2 Hz, 1H, 1/2xPhCH_2), 4.39 (d, *J* = 11.9 Hz, 1H, 1/2xPhCH_2), 4.48-4.66 (m, 5H, C_3-*H*, 2xPhCH_2), 6.25 (d, *J* = 4.2 Hz, 1H, C_1-*H*), 6.85-8.15 (m, 25H, Ar-*H*).

General Procedure for Desulfurization of 2-Deoxy-2-Phenylthio-β-Glycosides: A solution of the β-glycoside (0.1 mmol) in dry THF (3.0 ml) is added to a stirred suspension of Raney-Nickel (WII, ~ 800 mg) in 3.0 ml of THF at room temperature. The reaction is complete (monitored by tlc) in 30 min. The reaction mixture is then filtered through celite. Removal of the solvent gives a colorless residue.

Desulfurization of 3,4,6-tri-O-benzyl-2-deoxy-1-O-phenyl-2-phenylthio-β-D-glucopyranoside (β-40): Purification of the crude desulfurized product by flash chromatography on silica gel (ethyl acetate:petroleum ether 1:9) gave 36 mg of 3,4,6-tri-O-benzyl-2-deoxy-1-O-phenyl-β-D-glucopyranoside, **30** (R=C_6H_5); yield 70%; mp 51-53 °C; $[\alpha]^{25}_D$ -9.0° (c 0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.96 (dt, *J* = 12.0, 9.8 Hz, 1H, C_2-H_{ax}), 2.47 (ddd, *J* = 12.0, 4.9, 1.9 Hz, 1H, C_2-H_{eq}), 3.57-3.84 (m, 5H, pyran ring protons), 4.51-4.75 (m, 5H, 2.5xPhCH_2), 4.93 (d, *J* = 10.9 Hz, 1H, 1/2xPhCH_2), 5.08 (dd, *J* = 9.8, 1.9 Hz, 1H, C_1-*H*), 6.98-7.45 (m, 15H, Ar-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.47(C_2), 69.24, 71.50, 73.36, 74.84, 75.41, 76.45, 79.14, 97.62(C_1), 116.54, 122.18, 127.35, 127.56, 127.61, 127.84, 128.16, 128.24, 128.33, 129.27, 138.25, 157.08. Anal. Calcd for $C_{33}H_{34}O_5$: C, 77.62; H, 6.71. Found: C, 77.28; H, 6.84.

Desulfurization of 3,4,6-tri-O-benzyl-2-deoxy-1-O-{6'-(1',2',3',4'-diisopropylidene)-galactopyranosyl}-2-phenylthio-β-D-glucopyranoside (β-35): Purification of the crude desulfurized product by

flash chromatography on silica gel (ethyl acetate:petroleum ether 2:3) gave 47 mg of 3,4,6-tri-O-benzyl-2-deoxy-1-O-{6'-(1',2',3',4'-diisopropylidene)-galactopyranosyl}-β-D-glucopyranoside, **30** [R={6'-(1',2',3',4'-diisopropylidene)-galactopyranosyl}]; yield 70%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (s, 3H, C*H*$_3$), 1.38 (s, 3H, C*H*$_3$), 1.49 (s, 3H, C*H*$_3$), 1.59 (s, 3H, C*H*$_3$), 1.65-1.76 (m, 1H, C_2-*H*$_{ax}$), 2.51 (ddd, *J* = 12.5, 4.8, 1.3 Hz, 1H, C_2-*H*$_{eq}$), 3.43-3.46 (m, 1H, pyran ring proton), 3.58 (dd, *J* = 9.4, 8.6 Hz, 1H, pyran ring proton), 3.66-3.85 (m, 3H, pyran ring protons), 4.04-4.16 (m, 2H, pyran ring protons), 4.27 (dd, *J* = 8.0, 1.5 Hz, 1H, pyran ring proton), 4.36 (dd, *J* = 4.9, 2.3 Hz, 1H, C_2-*H*), 4.54-4.74 (m, 8H, pyran ring protons, 2.5xPhC*H*$_2$), 4.95 (d, *J* = 10.8 Hz, 1H, 1/2xPhC*H*$_2$), 5.60 (d, *J* = 5.0 Hz, 1H, C_1-*H*), 7.22-7.44 (m, 15H, Ar-*H*).

Preparation of 3-O-tert-Butyldiphenylsilyl-D-rhamnal (78): To a solution of D-rhamnal (**77**; 235 mg, 1.8 mmole)[57] and imidazole (306mg, 4.5 mmole) in N,N-dimethylformamide (1 ml) was added tert-butylchlorodiphenylsilane (547 mg, 2 mmol). The solution was stirred overnight and then poured into water and extracted with ethyl acetate (10 ml x 3). The organic extract was washed with water, dried (sodium sulfate) and evaporated. The oily residue was purified by flash chromatography with ethyl acetate-hexane 4:1 to give 604.5 mg of **78** (88.9%); Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 9H, SiC(C*H*$_3$)$_3$), 1.36 (d, *J* = 6.4 Hz, 3H, C*H*$_3$), 1.83 (d, *J* = 4.1 Hz, 1H, O*H*), 3.60 (ddd, *J* = 10.6, 6.5, 4.1 Hz, 1H, C_4-*H*), 3.78-3.82 (m, 1H, C_5-*H*),.4.23-4.26 (m, 1H, C_3-*H*), 4.56 (dd, *J* = 6.1, 2.4 Hz, 1H, C_2-*H*), 6.24 (dd, *J* = 6.1, 1.1 Hz, 1H, C_1-*H*), 7.32-7.48 (m, 6H, Ar-*H*), 7.68-7.73 (m, 4H, Ar-*H*).

Preparation of 4-O-Benzyl-3-O-tert-butyldiphenylsilyl-D-rhamnal (79): An 80% sodium hydride oil suspension (53 mg, 1.76 mmole) was washed with dry hexane and suspended in dry DMF/THF (3 ml 1:1 mixture). To

this suspension a solution of the glycal **78** (604 mg, 1.6 mmole) in DMF/THF (3 ml 1:1 mixture) was added dropwise with stirring at room temperature. After the addition was complete the reaction mixture was stirred for 1 hour and then tetra-n-butylammonium iodide (10 mg) and benzyl bromide (300 mg, 1.76 mmole) was added to it. After stirring for 6 h the reaction mixture was poured into water and extracted three times with ethyl acetate (10 ml). Combined organic extracts were dried over anhydrous sodium sulfate. Evaporation of the solvent gave the crude product which when subjected to radial chromatography (ethyl acetate-Hexane 1:9) yielded 235 mg (31%) of **79** and 47 mg (10%) of **80**.

Physical data: First fraction: **79:** oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (s, 9H, $SiC(CH_3)_3$), 1.41 (d, J = 6.9 Hz, 3H, CH_3), 3.50 (t, J = 6.5 Hz, 1H, ring proton), 4.01 (t, J = 6.8 Hz, 1H, ring proton),.4.40-4.45 (m, 2H), 4.65 (AB q, Δν = 62.8 Hz, J_{AB} = 11.6 Hz, 2H, $PhCH_2$), 6.17 (d, J = 9.3 Hz, 1H, C_1-*H*), 7.25-7.74 (m, 15H, Ar-*H*).

Second fraction: **80**: oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (d, J = 6.4 Hz, 3H, CH_3), 3.54 (dd, J = 8.9, 6.5 Hz, 1H, ring proton), 3.95-4.06 (m, 1H, C_5-*H*), 4.24-4.30 (m, 1H), 4.67 (AB q, Δν = 28.1 Hz, J_{AB} = 11.6 Hz, 2H, $PhCH_2$), 4.85 (AB q, Δν = 55.2 Hz, J_{AB} = 11.3 Hz, 2H, $PhCH_2$), 6.41 (dd, J = 6.1, 0.8 Hz, 1H, C_1-*H*), 7.30-7.48 (m, 10H, Ar-*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.46, 70.46, 73.94, 76.45, 79.55, 100.11, 127.55, 127.67, 127.88, 128.34, 138.32, 138.45, 144.75.

Glycal (79) + Methanol Using Reagent 53: To a solution of the glycal **79** (234 mg, 0.51 mmol) and methanol (100 µl) in 6 ml of dry methylene chloride at -60 °C (under argon), 2.2 ml of the reagent solution (0.55 mmol, prepared by method **B**) was added by syringe technique. After the reaction was complete (about 10 min) saturated aqueous sodium bicarbonate solution (30 ml) was

added and the mixture was stirred for 30 min at room temperature. The reaction mixture was extracted with dichloromethane (3X50 ml). The combined organic extracts were dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a crude product mixture which when subjected to radial chromatography (ethyl acetate-Hexane 1:9) gave 187.5 mg (60%, 0.31 mmole) of diastereomeric mixture of the methyl glycosides which (with out purification) was dissolved in 1.6 ml of dry THF and added to a solution of 243 mg (0.77 mmole) of n-Bu_4NF in 1 ml of THF. The reaction mixture was stirred at room temperature for 30 min and then poured into water and extracted three times with ethyl acetate (20 ml). Combined organic extracts were dried over anhydrous sodium sulfate. Evaporation of the solvent gave the crude product which when subjected to radial chromatography (ethyl acetate-Hexane 1:3) yielded 28.4 mg 4-O-benzyl-2-deoxy-1-O-methyl-2-(4'-methylphenyl)thio-α-D-rhamnopyranoside of α'-**84**, 56.9 mg of 4-O-benzyl-2-deoxy-1-O-methyl-2-(4'-methylphenyl)thio-β-D-rhamnopyranoside β-**84** and 9.5 mg 4-O-benzyl-2,6-dideoxy-1-O-methyl-2-(4'-methylphenyl)thio-α-D-mannopyranoside of α-**84**.; total yield 83%; β/α'/α 6/3/1.

Physical data: First fraction: α'-**84:** oil; ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (d, J = 6.0 Hz, 3H, C*H*$_3$), 2.30 (s, 3H, Ar-C*H*$_3$), 2.63 (d, J = 1.5 Hz, 1H, C_3-O*H*), 3.05 (dd, J = 10.7, 3.4 Hz, 1H, C_2-*H*), 3.10 (dd, J = 10.7, 9.4 Hz, 1H, C_4-*H*), 3.34 (s, 3H, OC*H*$_3$), 3.76 (dq, J = 9.4, 6.3 Hz, 1H, C_5-*H*), 3.97 (dt, J = 10.7, 2.2 Hz, 1H, C_3-*H*), 4.73 (d, J = 3.2 Hz, 1H, C_1-*H*), 4.79 (AB q, Δν = 70.8 Hz, J_{AB} = 11.2 Hz, 2H, PhC*H*$_2$), 7.08 (d, J = 8.0 Hz, 2H, Ar-*H*), 7.23-7.33 (m, 5H, Ar-*H*), 7.38 (d, J = 8.1 Hz, 2H, Ar-*H*).

Second fraction: β-**84** : oil; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (d, J = 6.0 Hz, 3H, C*H*$_3$), 2.29 (s, 3H, Ar-C*H*$_3$), 2.73 (dd, J = 10.8, 8.7 Hz, 1H, C_2-*H*), 3.00 (d, J = 1.5 Hz, 1H, C_3-O*H*, D_2O exchangeable), 3.10 (t, J = 8.8 Hz, 1H, C_4-*H*), 3.19-3.22 (m,

1H, C_5-*H*), 3.46 (ddd, *J* = 10.8, 8.3, 1.5 Hz, 1H, C_3-*H*), 3.48 (s, 3H, OCH_3), 4.02 (d, *J* = 8.3 Hz, 1H, C_1-*H*), 4.78 (AB q, Δν = 82.9 Hz, J_{AB} = 11.1 Hz, 2H, PhCH_2), 7.07 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 7.21-7.34 (m, 5H, Ar-*H*), 7.39 (d, *J* = 8.0 Hz, 2H, Ar-*H*).

Third fraction: **α-84 : oil**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (d, *J* = 6.2 Hz, 3H, CH_3), 2.31 (s, 3H, Ar-CH_3), 2.60 (d, *J* = 9.0 Hz, 1H, C_3-O*H*, D_2O exchangeable), 3.12 (t, *J* = 9.0 Hz, 1H, C_4-*H*), 3.28 (s, 3H, OCH_3), 3.53 (dd, *J* = 4.9, 1.3 Hz, 1H, C_2-*H*), 3.70 (dq, *J* = 9.2, 6.2 Hz, 1H, C_5-*H*), 4.26 (ddd, *J* = 9.2, 9.0, 4.9 Hz, 1H, C_3-*H*), 4.80 (AB q, Δν = 69.6 Hz, J_{AB} = 11.1 Hz, 2H, PhCH_2), 4.90 (s, 1H, C_1-*H*), 7.10 (d, *J* = 7.9 Hz, 2H, Ar-*H*), 7.24-7.39 (m, 7H, Ar-*H*).

Preparation of 3-O-β-(trimethylsilyl)ethoxymethyl-D-rhamnal (81): A solution of D-rhamnal **77** (250 mg, 1.92 mmole) in 2 ml of dichloromethane under argon was stirred overnight at room temperature with diisopropyletylamine (676 μl, 3.84 mmole) and β-(trimethylsilyl)ethoxymethyl chloride (394 μl, 2.11 mmole). The mixture was then poured into water and extracted with ethyl acetate (10 ml x 3). The organic extract was washed with water, dried (sodium sulfate) and evaporated. The oily residue was purified by flash chromatography with ethyl acetate-hexane 1:1 to give 360 mg of **81** (72%); Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02 {s, 9H, Si(CH_3)$_3$}, 0.95-1.60 (m, 2H, SiCH_2), 1.35 (d, *J* = 7.0 Hz, 1H, C_4-O*H*), 1.41 (d, *J* = 6.3 Hz, 3H, CH_3), 3.40 (ddd, *J* = 9.9, 7.0, 1.5 Hz, 1H, C_4-*H*), 3.52-3.61 (m, 1H), 3.81-3.97 (m, 3H), 4.63-4.65 (m, 1H), 4.79 (AB q, Δν = 29.1 Hz, J_{AB} = 7.4 Hz, 2H), 6.34 (dd, *J* = 6.1, 1.5 Hz, 1H, C_1-*H*).

Preparation of 4-O-Benzyl-3-O-β-(trimethylsilyl)ethoxymethyl-D-rhamnal (82): An 80% sodium hydride oil suspension (41 mg, 1.37 mmole)

was washed with dry hexane and suspended in dry DMF/THF (2 ml 1:1 mixture). To this suspension a solution of the glycal **81** (300 mg, 1.14 mmole) in DMF/THF (2 ml 1:1 mixture) was added dropwise with stirring at room temperature. After the addition was complete the reaction mixture was stirred for 1 hour and then tetra-n-butylammonium iodide (10 mg) and benzyl bromide (163 µl, 1.37 mmole) was added to it. After stirring for 6 h the reaction mixture was poured into water and extracted three times with ethyl acetate (10 ml). Combined organic extracts were dried over anhydrous sodium sulfate. Evaporation of the solvent gave the crude product which when subjected to radial chromatography (ethyl acetate-Hexane 1:9) yielded 289 mg (72%) of **82** (72%); Oil; **82:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 {s, 9H, $Si(CH_3)_3$}, 0.93 (t, J = 8.5 Hz, 2H, $SiCH_2$), 1.35 (d, J = 6.5 Hz, 3H, CH_3), 3.43 (dd, J = 8.7, 6.5 Hz, 1H, C_4-*H*), 3.58-3.71 (m, 2H, OCH_2CH_2Si), 3.94-4.00 (m, 1H, ring proton), 4.27-4.30 (m, 1H, ring proton), 4.73-4.82 (m, 3H, C_2-*H*, OCH_2O),4.76 (AB q, Δν = 45.8 Hz, J_{AB} = 11.5 Hz, 2H, $PhCH_2$), 6.33 (d, J = 6.1 Hz, 1H, C_1-*H*), 7.27-7.35 (m, 5H, Ar-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ -1.57, 17.24, 17.98, 65.24, 73.88, 74.50, 79.92, 93.97, 100.91, 127.60, 127.70, 128.27, 138.19, 144.34.

Glycal (82) + Methanol Using Reagent 31: To a solution of the glycal **82** (175 mg, 0.5 mmol) and methanol (100 µl) in 6 ml of dry methylene chloride at -60 °C (under argon), 2.2 ml of the reagent solution (0.55 mmol, prepared by method **A**) was added by syringe technique. After the reaction was complete (about 10 min) saturated aqueous sodium bicarbonate solution (30 ml) was added and the mixture was stirred for 30 min at room temperature. The reaction mixture was extracted with dichloromethane (3X50 ml). The combined organic extracts were dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a crude product mixture which when subjected to radial chromatography (ethyl

acetate-Hexane 1:9) gave 13.8 mg of 4-O-benzyl-2-deoxy-1-O-methyl-3-O-β-(trimethylsilyl)ethoxymethyl-2-phenylthio-α-D-rhamnopyranoside of **α'-83**, 27.6 mg 4-O-benzyl-2,6-dideoxy-1-O-methyl-3-O-β-(trimethylsilyl)ethoxymethyl-2-phenylthio-α-D-mannopyranoside of **α-83** and 158.6 mg of 4-O-benzyl-2-deoxy-1-O-methyl-3-O-β-(trimethylsilyl)ethoxymethyl-2-phenylthio-β-D-rhamnopyranoside **β-83**; total yield 82%; β/α/α' 11.5/2/1.

Physical data: First fraction: **α'-83:** oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.13 {s, 9H, Si(CH_3)$_3$}, 0.83-0.90 (m, 2H, SiCH_2), 1.26 (d, J = 6.3 Hz, 3H, CH_3), 3.17 (t, J = 9.0 Hz, 1H, C_4-H), 3.26 (dd, J = 11.0, 3.7 Hz, 1H, C_2-H), 3.36 (s, 3H, OCH_3), 3.52-3.61 (m, 1H, O$CH_2$$CH_2$Si), 3.50-3.82 (m, 2H, C_5-H, O$CH_2$$CH_2$Si), 3.95 (dd, J = 11.0, 9.0 Hz, 1H, C_3-H), 4.68 (d, J = 3.7 Hz, 1H, C_1-H), 4.77 (AB q, Δν = 73.1 Hz, J_{AB} = 11.1 Hz, 2H, PhCH_2), 4.96 (s, 2H, OCH_2O), 7.16-7.51 (m, 10H, Ar-H).

Second fraction: **α-83:** oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.08 {s, 9H, Si(CH_3)$_3$}, 0.82 (m, 2H, SiCH_2), 1.30 (d, J = 6.2 Hz, 3H, CH_3), 3.28 (s, 3H, OCH_3), 3.38 (t, J = 9.0 Hz, 1H, C_4-H), 3.53-3.62 (m, 1H, O$CH_2$$CH_2$Si), 3.65-3.78 (m, 3H, C_2-H, C_5-H, O$CH_2$$CH_2$Si), 4.33 (dd, J = 9.1, 4.8 Hz, 1H, C_3-H), 4.70 (s, 1H, C_1-H), 4.75 (s, 2H, OCH_2O), 4.75 (AB q, Δν = 81.2 Hz, J_{AB} = 11.1 Hz, 2H, PhCH_2), 7.18-7.49 (m, 10H, Ar-H).

Third fraction: **β-83:** oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 {s, 9H, Si(CH_3)$_3$}, 0.93-1.04 (m, 2H, SiCH_2), 1.36 (d, J = 6.0 Hz, 3H, CH_3), 3.07 (dd, J = 10.7, 8.7 Hz, 1H, C_2-H), 3.26 (t, J = 8.6 Hz, 1H, C_4-H), 3.35-3.48 (m, 1H), 3.51 (s, 3H, OCH_3), 3.61-3.73 (m, 2H), 4.03-4.10 (m, 1H), 4.18 (d, J = 8.7 Hz, 1H, C_1-H), 4.81 (AB q, Δν = 57.4 Hz, J_{AB} = 10.9 Hz, 2H), 5.09 (AB q, Δν = 33.0 Hz, J_{AB} = 6.4 Hz, 2H), 7.27-7.68 (m, 10H, Ar-H).

Preparation of 4-O-benzyl-2-deoxy-1-O-methyl-2-phenylthio-β-D-rhamnopyranoside (β-85): 382 mg of **β-83** (0.78 mmole) was dissolved in 5 ml of DMSO and added to a solution of 3.5 g of CsF (23 mmole) and 20 mg of 18-crown-6 in 6 ml of DMSO. The reaction mixture was stirred and heated to 105 °C for 12 hours and then poured into water and extracted three times with ethyl acetate (30 ml). Combined organic extracts were dried over anhydrous sodium sulfate. Evaporation of the solvent gave the crude product which when subjected to radial chromatography (ethyl acetate-Hexane 1:3) gave 225 mg of **85** (80%); Oil; $[\alpha]^{25}_{D}$ +58.9° (c 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (d, J = 6.1 Hz, 3H, CH_3), 2.79 (dd, J = 10.8, 8.8 Hz, 1H, C_2-H), 2.96 (br s, 1H, C_3-OH, D_2O exchangeable), 3.07 (t, J = 8.8 Hz, 1H, C_4-H), 3.19-3.24 (m, 1H, C_5-H), 3.43 (s, 3H, OCH_3), 3.42-3.48 (m, 1H, C_3-H), 4.02 (d, J = 8.7 Hz, 1H, C_1-H), 4.72 (AB q, $\Delta\nu$ = 80.7 Hz, J_{AB} = 11.1 Hz, 2H, PhCH_2), 7.16-7.49 (m, 10H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.83, 56.79, 57.18, 70.76, 74.12, 74.82, 83.81, 102.72, 127.71, 127.96, 128.02, 128.32, 128.84, 128.95, 133.81, 138.23.

Glycal (80) + Nucleophile 85 Using Reagent 53: To the sugar alcohol **85** (130.5 mg, 0.36 mmol) dissolved in 10 ml of dry toluene under an argon atmosphere was added 2.3 g of activated powdered 4A° MS and bis(tri-n-butyl)tin oxide (139 µl, 0.27 mmole). The reaction mixture was refluxed for 12 h and thereafter toluene was distilled off. To the residue a solution of the glycal **80** (0.18 mmol) in dry methylene chloride (2.2 ml) was added and the reaction mixture was cooled to -60 °C. 800 µl of the reagent solution (0.20 mmol, prepared by method **A**) was then added by syringe technique. After the reaction was complete (about 10 min) it was quenched with saturated aqueous sodium bicarbonate solution (15 ml) and the mixture stirred for 30 min at room temperature. The reaction mixture was filtered through celite (the celite was

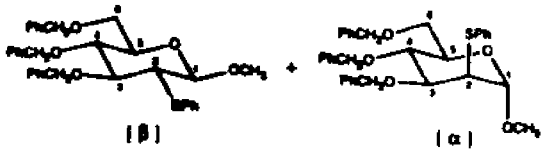
washed with 50 ml of methylene chloride) and the organic layer of the filtrate was dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude product mixture which when subjected to radial chromatography (ethyl acetate-Hexane 1:4) gave 68.5 mg of 3,4-di-O-benzyl-2-deoxy-1-O-{3'-(4'-O-benzyl-2'-deoxy-1'-O-methyl-2'-phenylthio)-β-D-rhamnopyranosyl}-2-(4''-methylphenyl)thio-β-D-rhamnopyranoside (**β-86**) (47.5%); oil ; $[\alpha]^{25}_D$ -24.0° (c 0.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.18 (d, *J* = 5.8 Hz, 3H, CH_3), 1.28 (d, *J* = 5.9 Hz, 3H, CH_3), 2.29 (s, 3H, Ar-CH_3), 2.85 (t, *J* = 8.6 Hz, 1H, C_4-*H* or C_4-*H*), 3.00-3.31 (m, 2H, C_2-*H*, C_2-*H*), 3.19-3.35 (m, 2H, pyran ring proton), 3.40 (s, 3H, OCH_3), 3.40-3.56 (m, 2H, pyran ring proton), 4.05 (dd, *J* = 10.8, 8.6 Hz, 1H, C_3-*H* or C_3-*H*), 4.08 (d, *J* = 8.4 Hz, 1H, C_1-*H* or C_1-*H*), 4.52 (AB q, Δν = 121.0 Hz, J_{AB} = 10.6 Hz, 2H, $PhCH_2$), 4.76 (AB q, Δν = 69.0 Hz, J_{AB} = 11.0 Hz, 2H, $PhCH_2$), 4.91 (AB q, Δν = 61.0 Hz, J_{AB} = 10.2 Hz, 2H, $PhCH_2$), 6.99 (d, *J* = 7.9 Hz, 2H, Ar-*H*), 7.21-7.33 (m, 20H, Ar-*H*), 7.61 (d, *J* = 7.7 Hz, 2H, Ar-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.07, 18.15, 21.08, 55.76, 56.88, 58.38, 70.64, 71.03, 75.00, 75.23, 76.32, 77.28, 82.77, 83.16, 85.34, 102.25, 103.93, 127.44, 127.63, 127.70, 127.83, 127.90, 128.17, 128.34, 128.45, 128.47, 128.71, 129.37, 132.36, 133.00, 133.11, 134.22, 136.57, 138.26, 138.40, 138.49. Anal. Calcd for $C_{47}H_{52}O_7S2$: C, 71.18; H, 6.61; S, 8.09. Found: C, 71.19; H, 6.71; S, 8.14.

Preparation of 3,4-di-O-benzyl-2-deoxy-1-O-{3'-(4'-O-benzyl-2'-deoxy-1'-O-methyl)-β-D-rhamnopyranosyl}-β-D-rhamnopyranoside (87): A solution of the **β-86** (15.8 mg, 0.02 mmol) in dry THF (1.0 ml) was added to a stirred suspension of Raney-Nickel (WII, ~ 160 mg) in 1.0 ml of THF at room temperature. The reaction was complete (monitored by tlc) in 60 min. The reaction mixture was then filtered through celite. Removal of the solvent gave a colorless residue. Purification by radial chromatography (ethyl acetate-

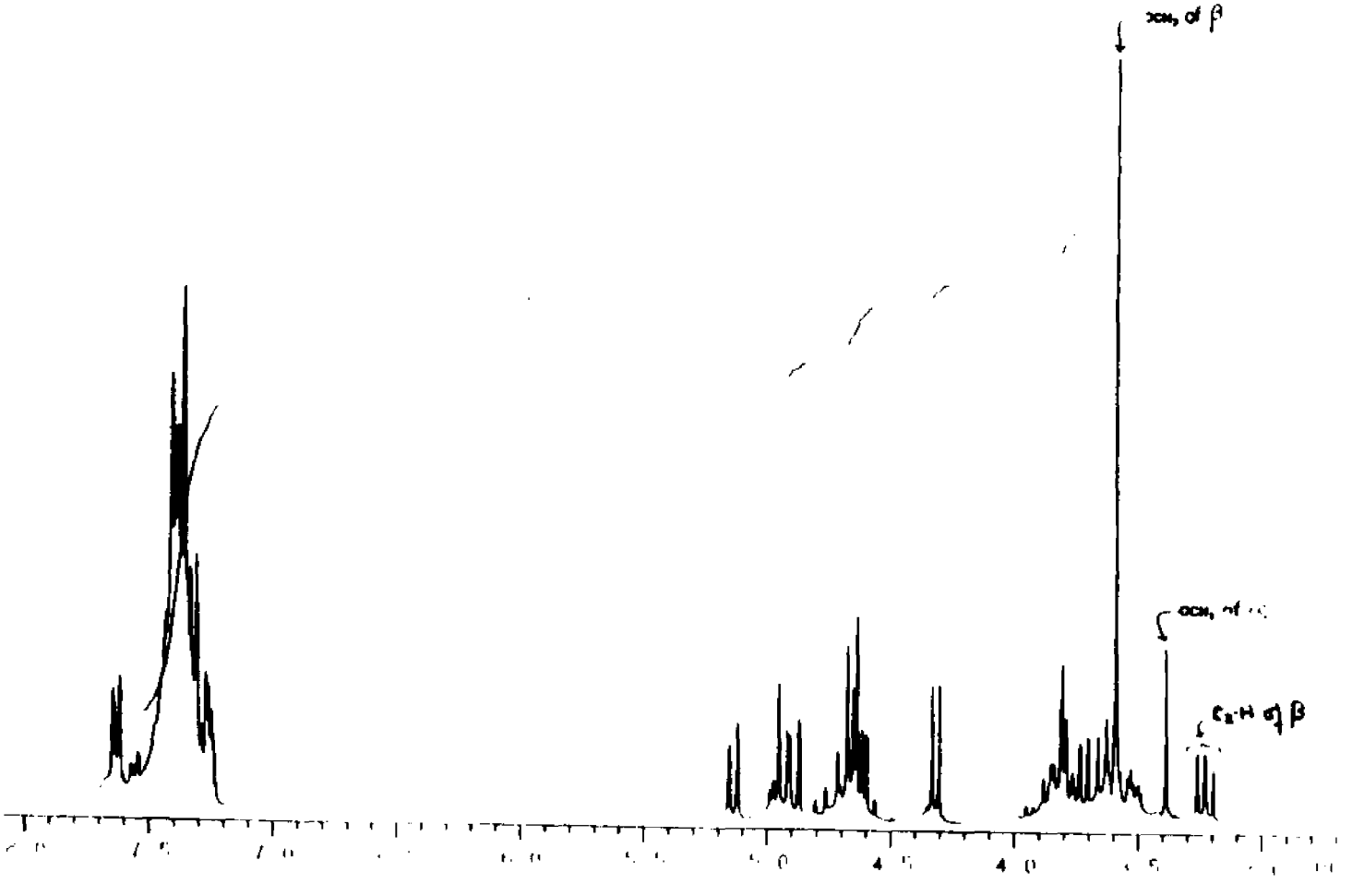
hexane 1:4) gave 11.2 mg of **87** (64%); oil; $[\alpha]^{25}_{D}$ -20.0° (c 0.06, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (d, J = 4.4 Hz, 3H, CH_3), 1.33 (d, J = 4.5 Hz, 3H, CH_3), 1.49-1.69 (m, 2H, C_2-H_{ax}, C_2'-H_{ax}), 2.21-2.34 (m, 2H, C_2-H_{eq}, C_2'-H_{eq}), 3.04 (t, J = 8.9 Hz, 1H, C_4-H or C_4'-H), 3.13 (t, J = 8.9 Hz, 1H, C_4-H or C_4'-H), 3.28-3.36 (m, 2H, C_5-H, C_5'-H), 3.47 (s, 3H, OCH_3), 3.58-3.68 (m, 1H, C_3-H or C_3'-H), 3.92-4.04 (m, 1H, C_3-H or C_3'-H), 4.32 (dd, J = 9.7, 1.3 Hz, 1H, C_1-H or C_1'-H), 4.54-4.69 ((m, 4H, C_1-H or C_1'-H, 1.5XPhCH_2), 4.80 (AB q, Δν = 86.3 Hz, J_{AB} = 10.9 Hz, 2H, PhCH_2), 5.02 (d, J = 10.5 Hz, 1H, 1/2XPhCH_2), 7.25-7.41 (m, 15H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.14, 18.19, 36.31, 37.39, 56.45, 71.16, 71.31, 74.73, 75.20, 75.79, 79.18, 82.25, 83.71, 95.73, 100.24, 127.51, 127.57, 127.64, 127.76, 128.01, 128.11, 128.32, 138.23, 138.33, 138.59.

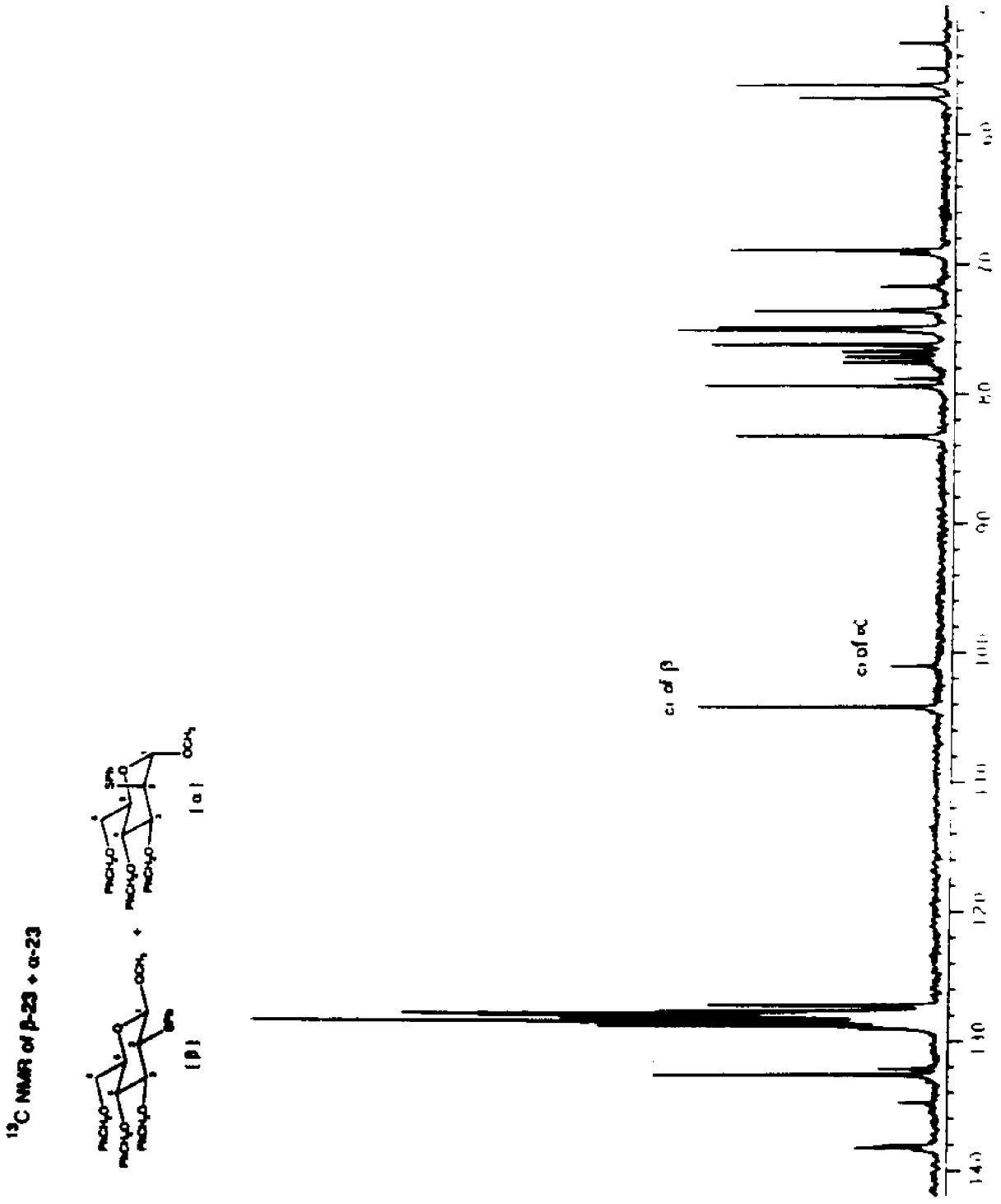
APPENDIX

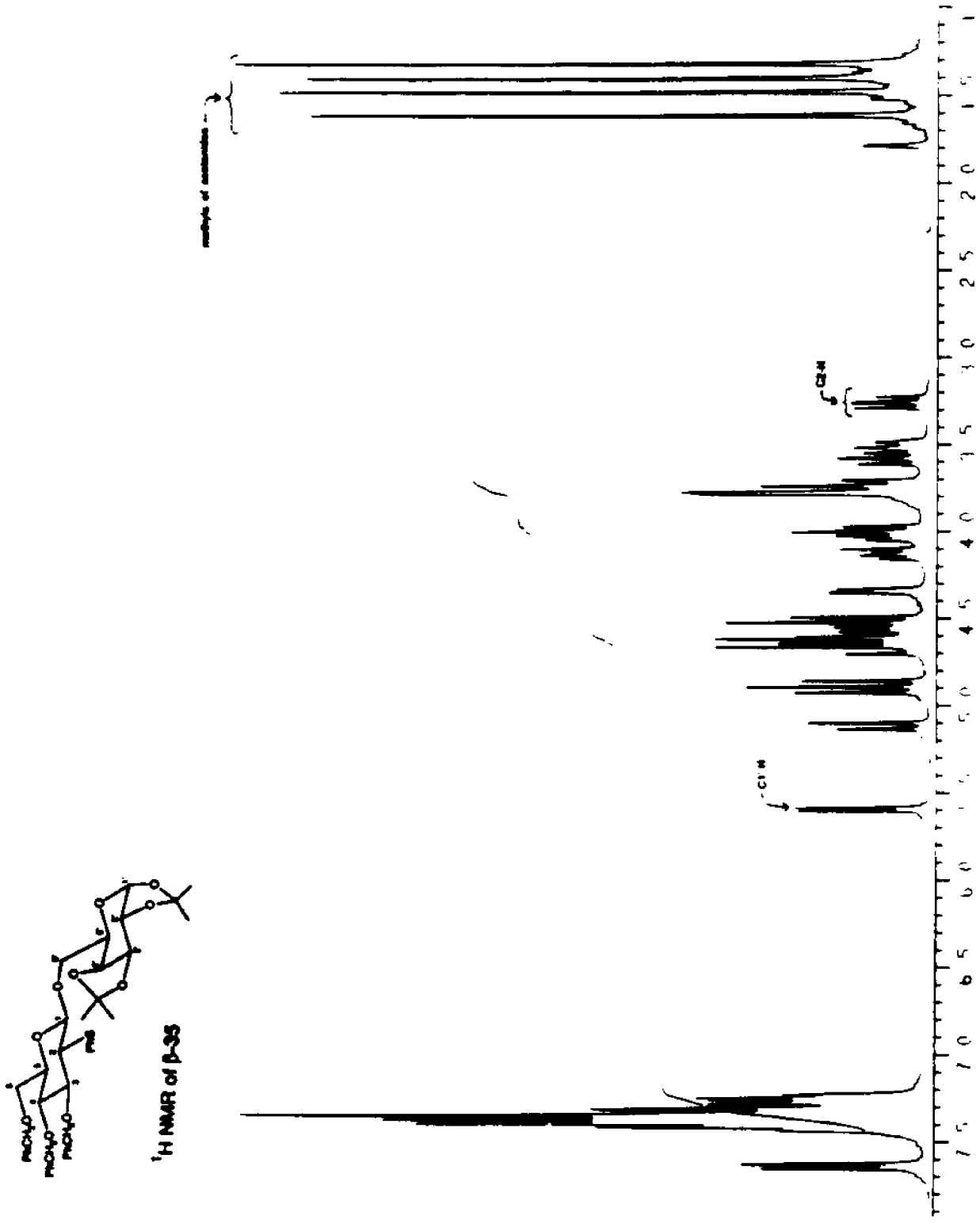
^{1}H NMR of β-23 + α-23

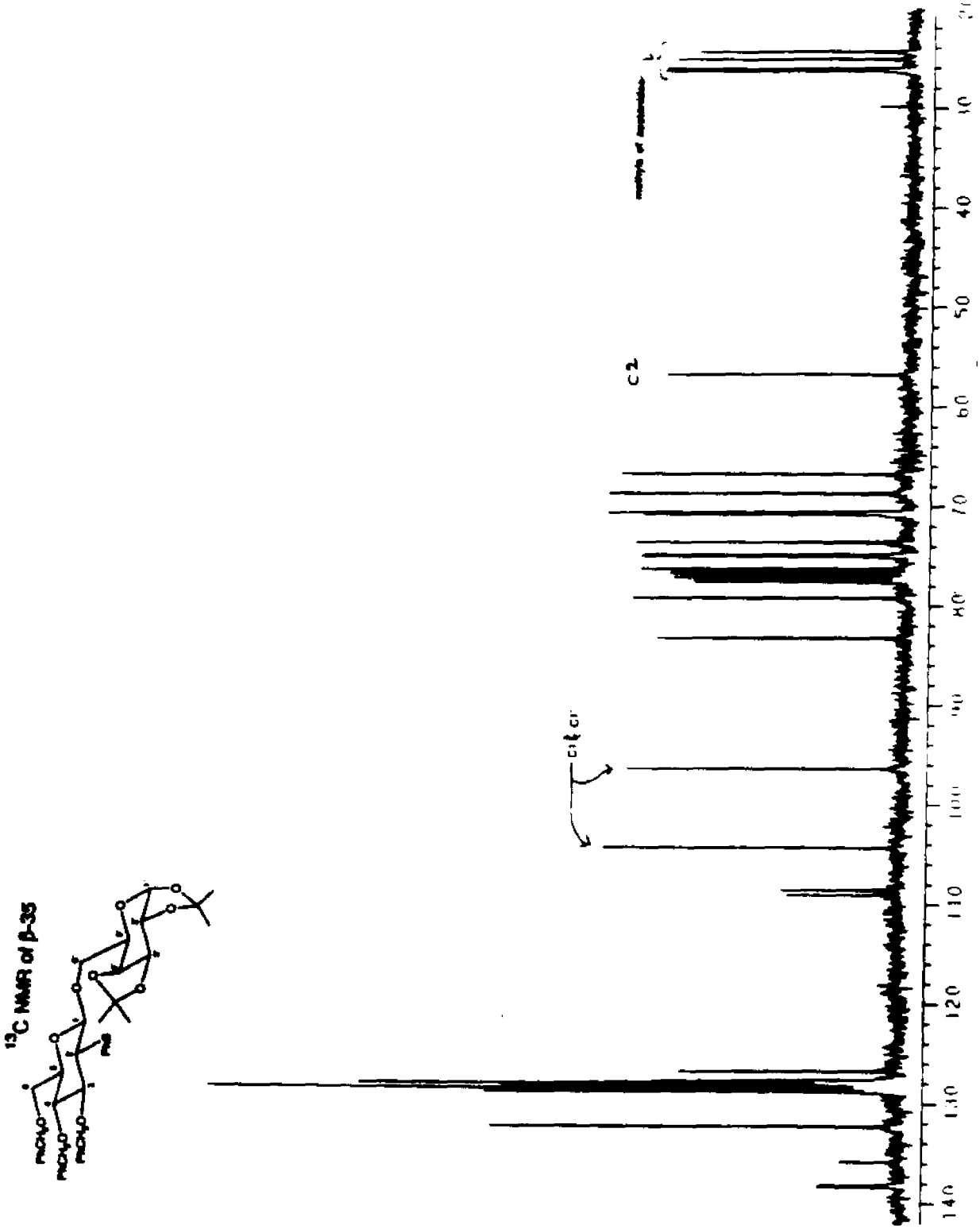


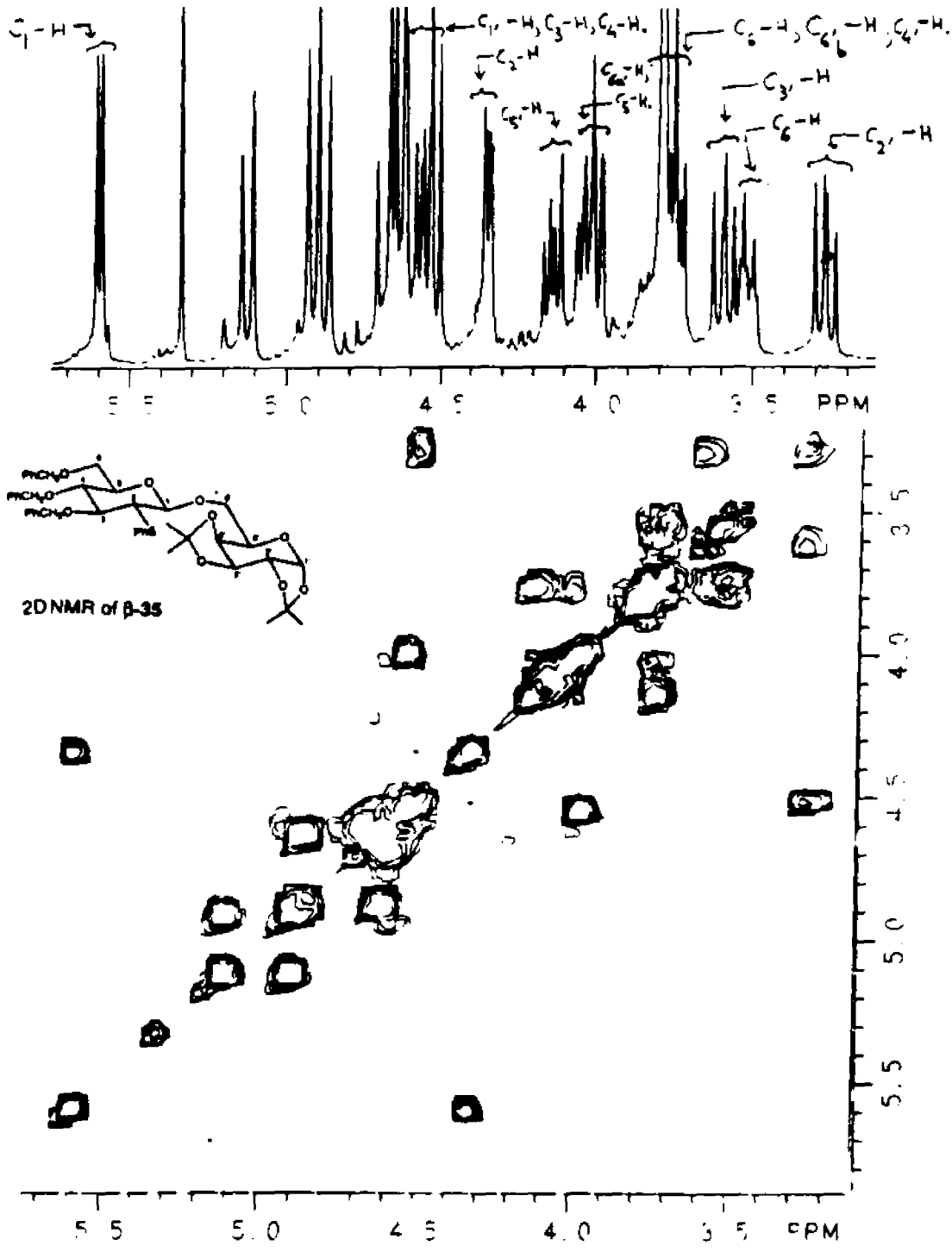
(β) (α)

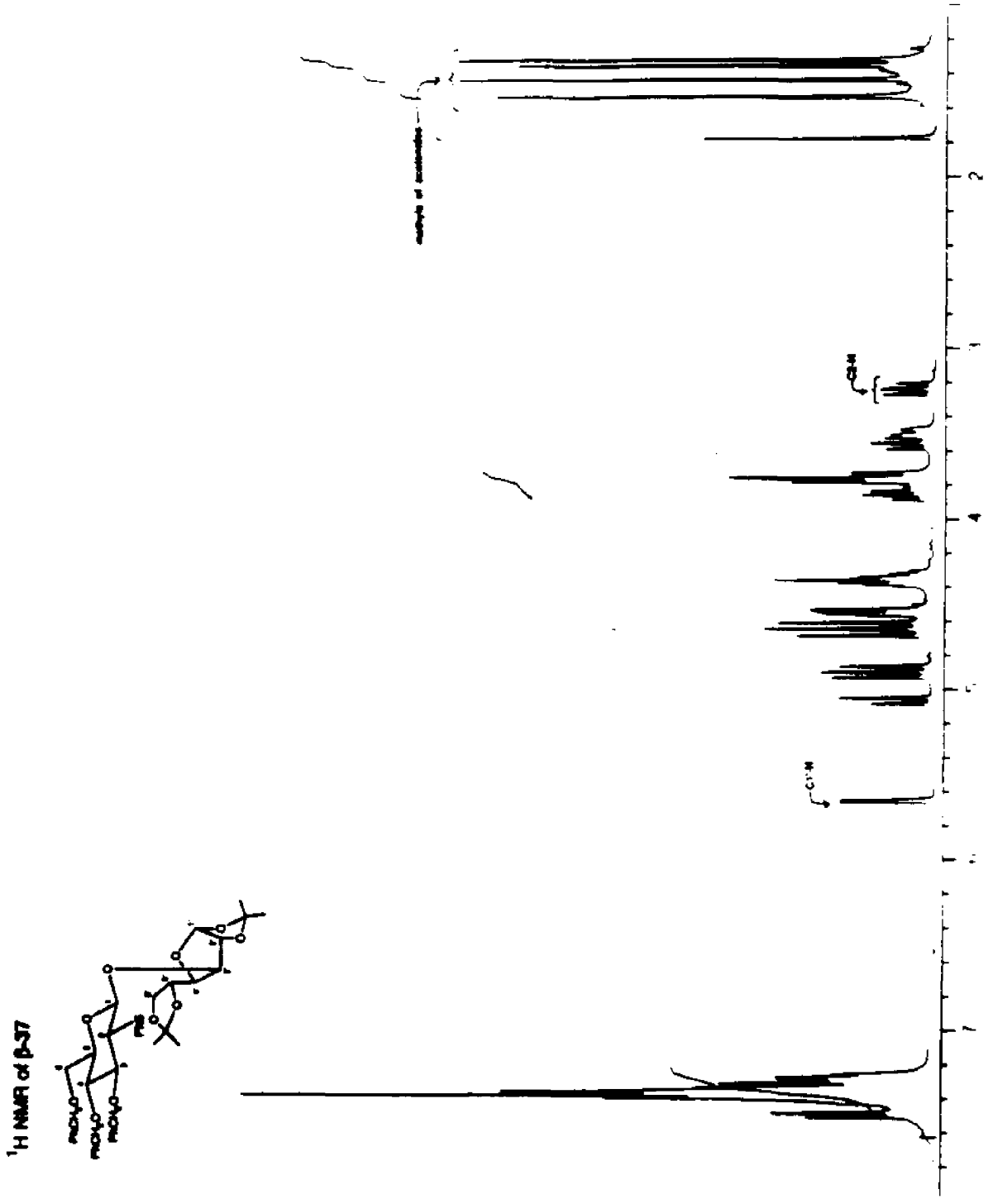


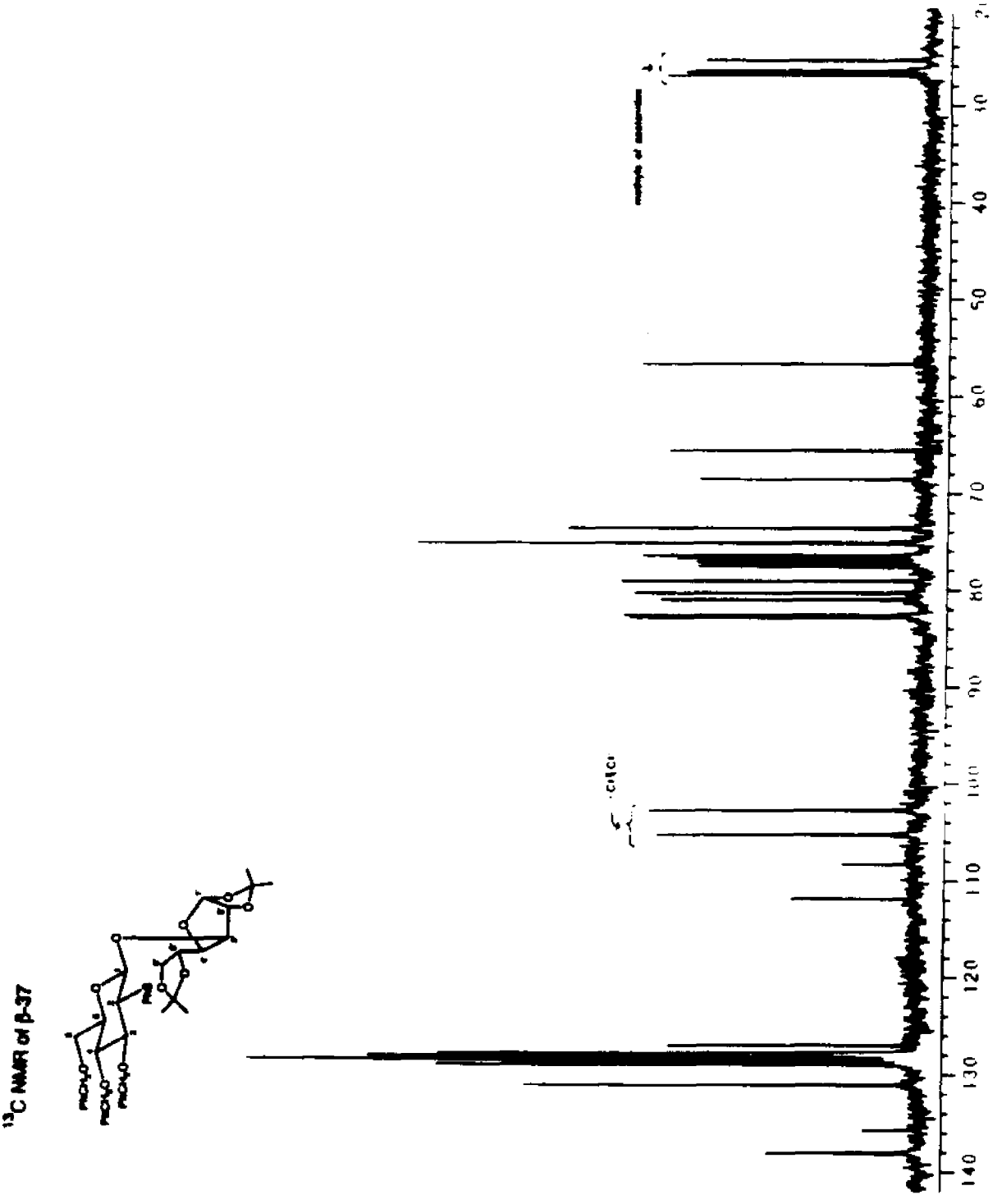

^{13}C NMR of β-23 + α-23
(β)
(α)
c1 of β
c1 of α

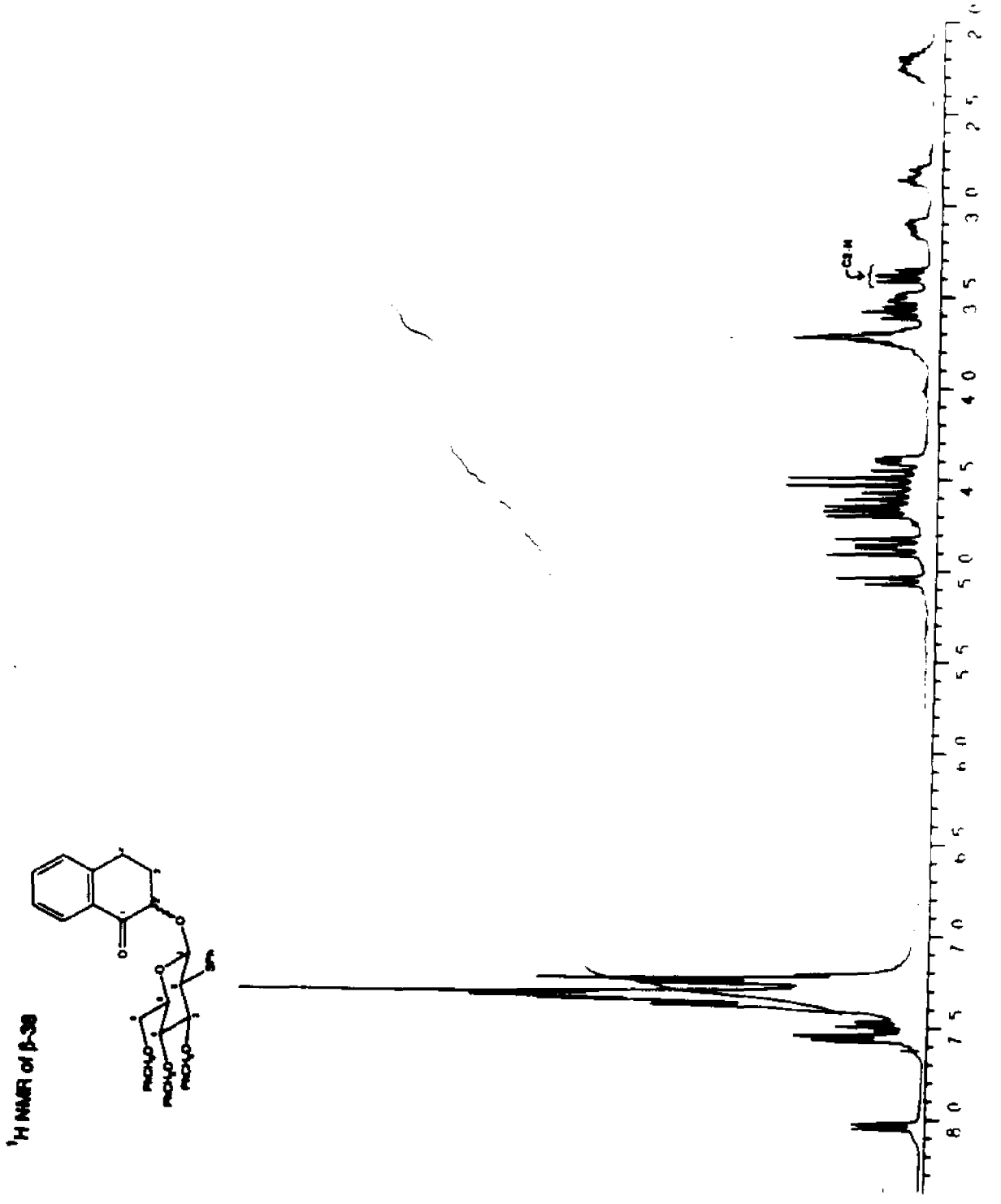

PhCH2O
PhCH2O
PhCH2O
N3
^{1}H NMR of β-35

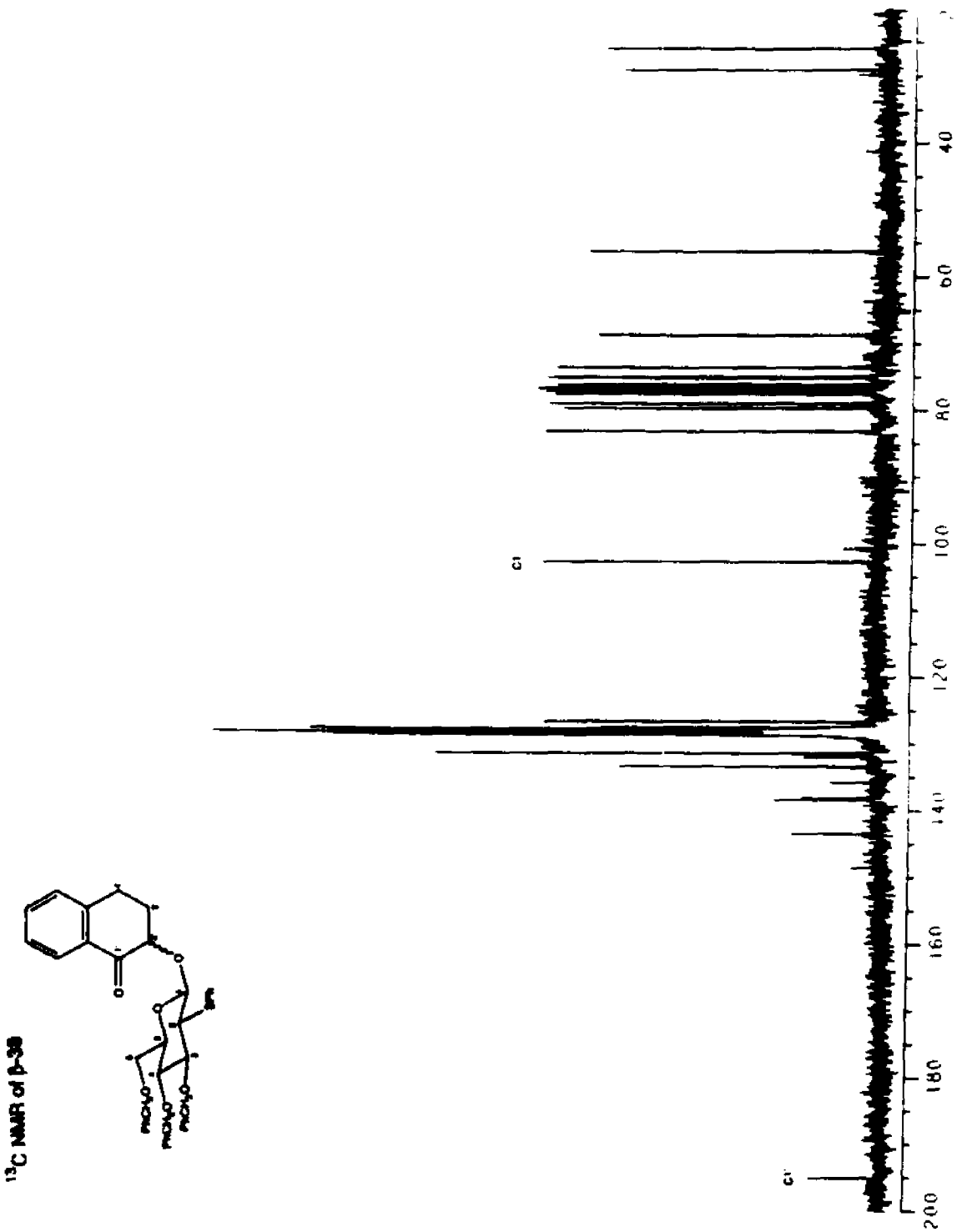

^{13}C NMR of β-35
C2
C1 & C1'
10
40
50
60
70
80
90
100
110
120
130
140

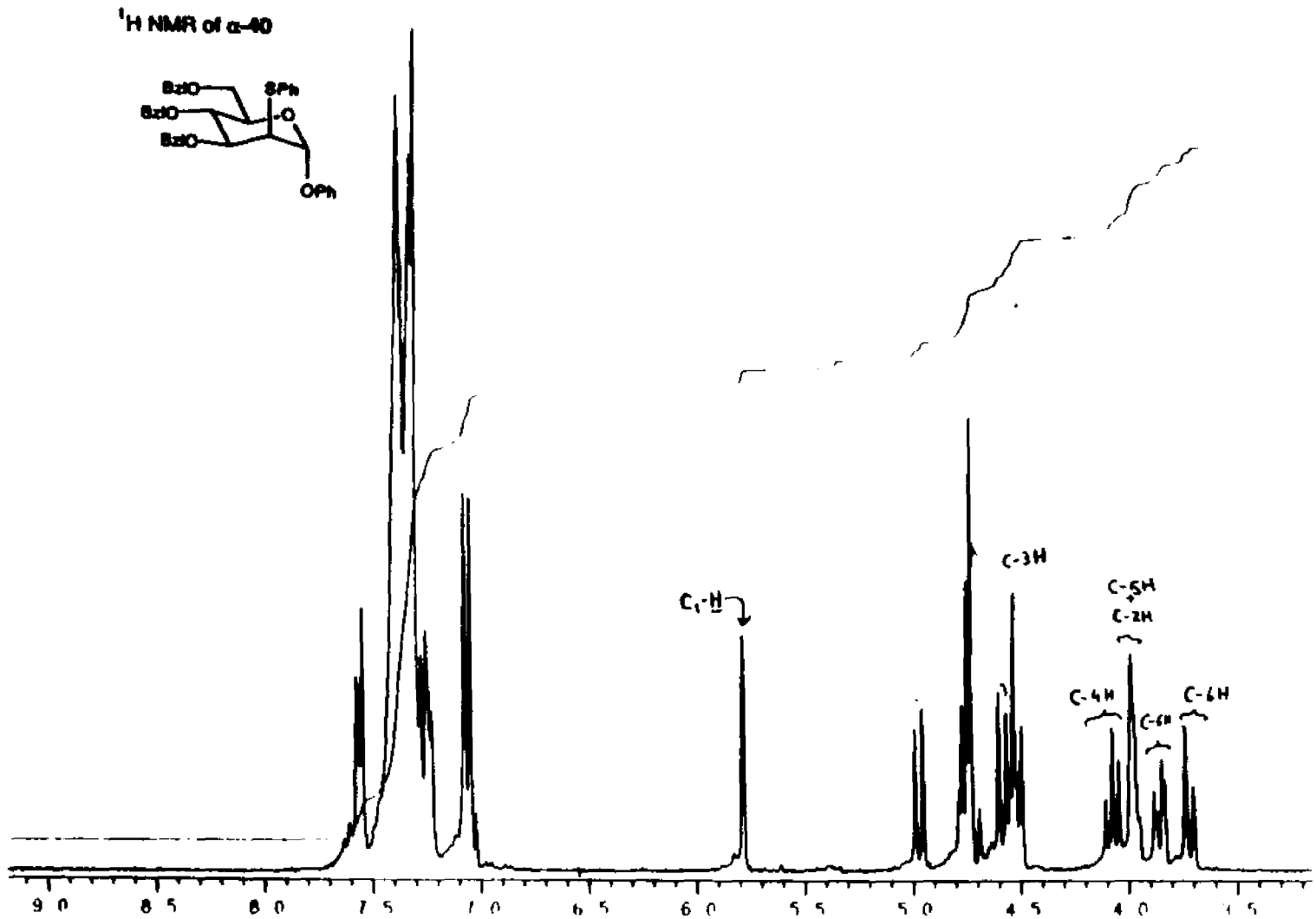

PPM
2D NMR of β-35
PPM

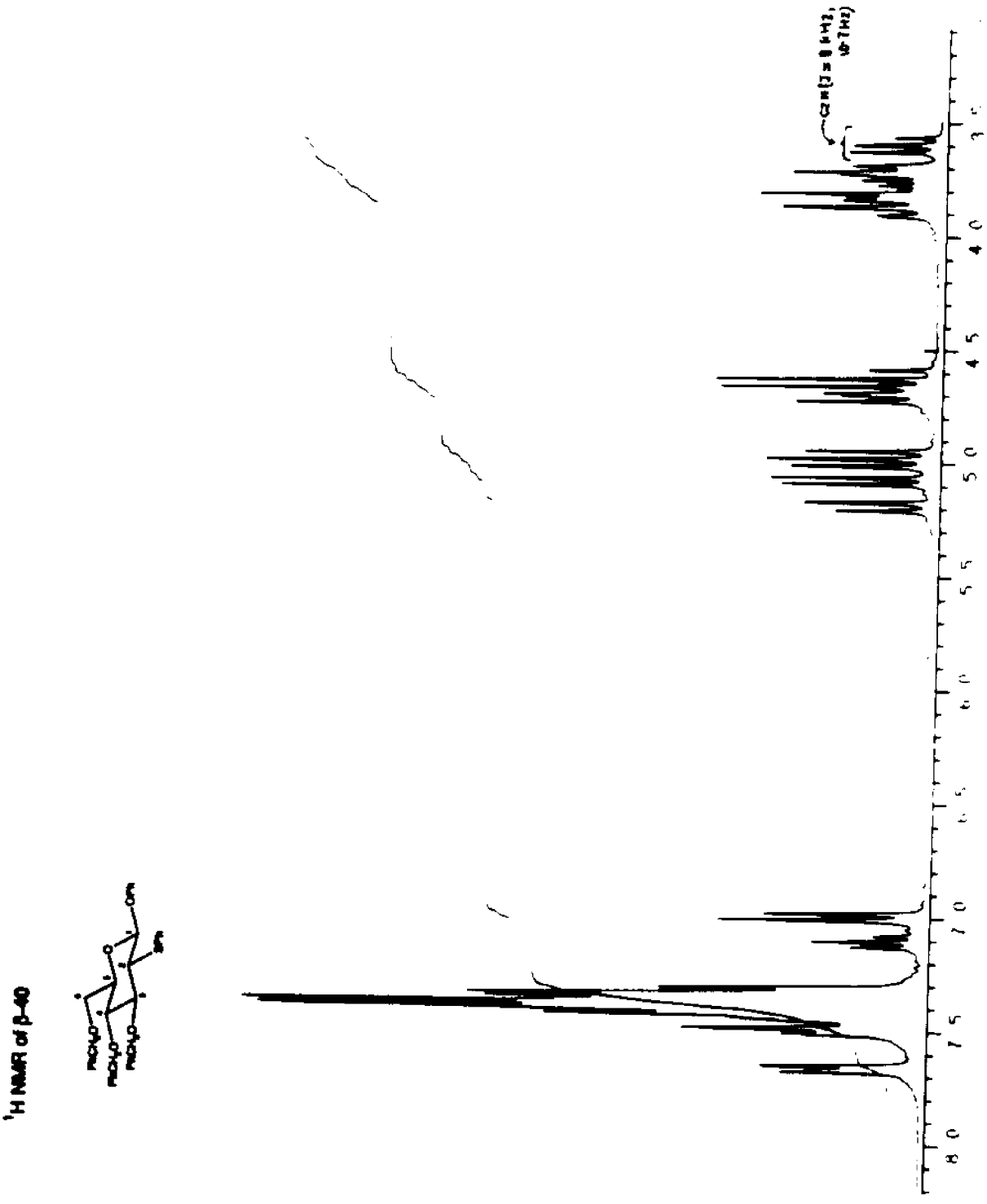

^{1}H NMR of β-37

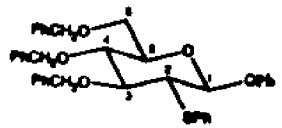

^{13}C NMR of β-37


^{1}H NMR of β-38
AcO
AcO
AcO
AcO
80
75
70
65
60
55
50
45
40
35
30
25

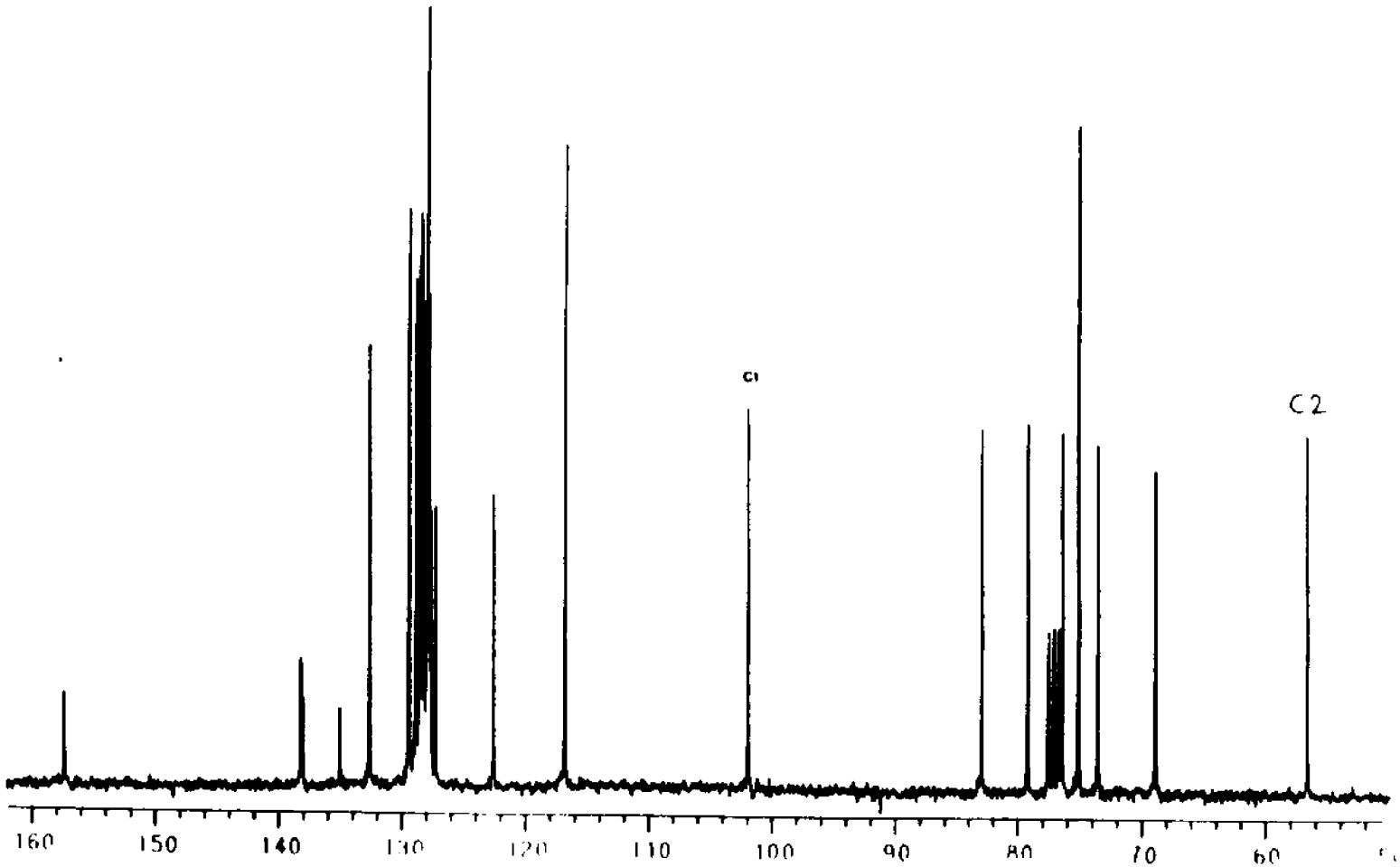

^{13}C NMR of β-38
C1
200
180
160
140
120
100
80
60
40


^{1}H NMR of α-40
BzlO
BzlO
BzlO
SPh
O
OPh
C$_1$-H
C-3H
C-5H
C-2H
C-4H
C-6H
C-6H
9 0
8 5
8 0
7 5
7 0
6 5
6 0
5 5
5 0
4 5
4 0

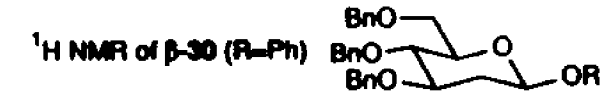

^{1}H NMR of β-40

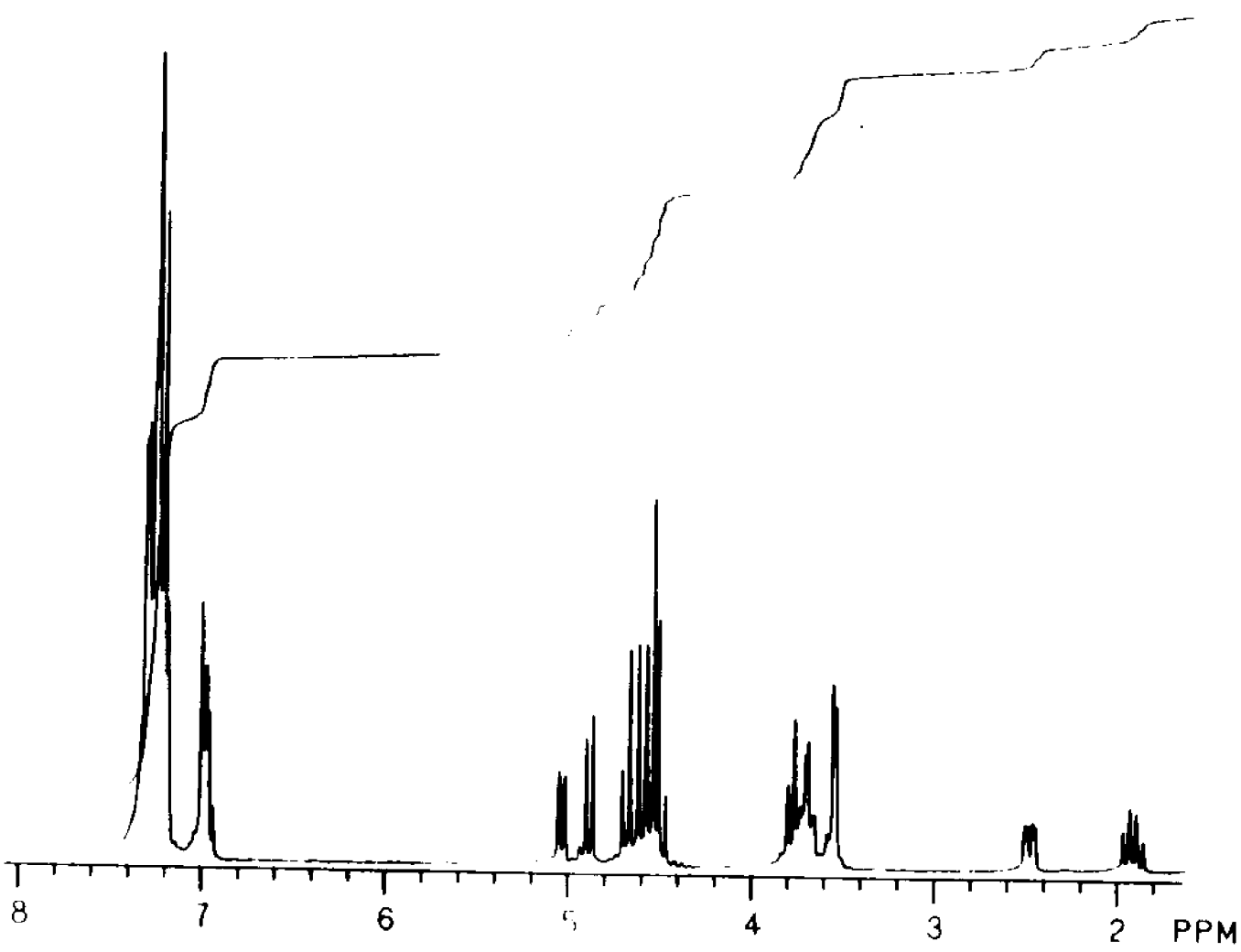


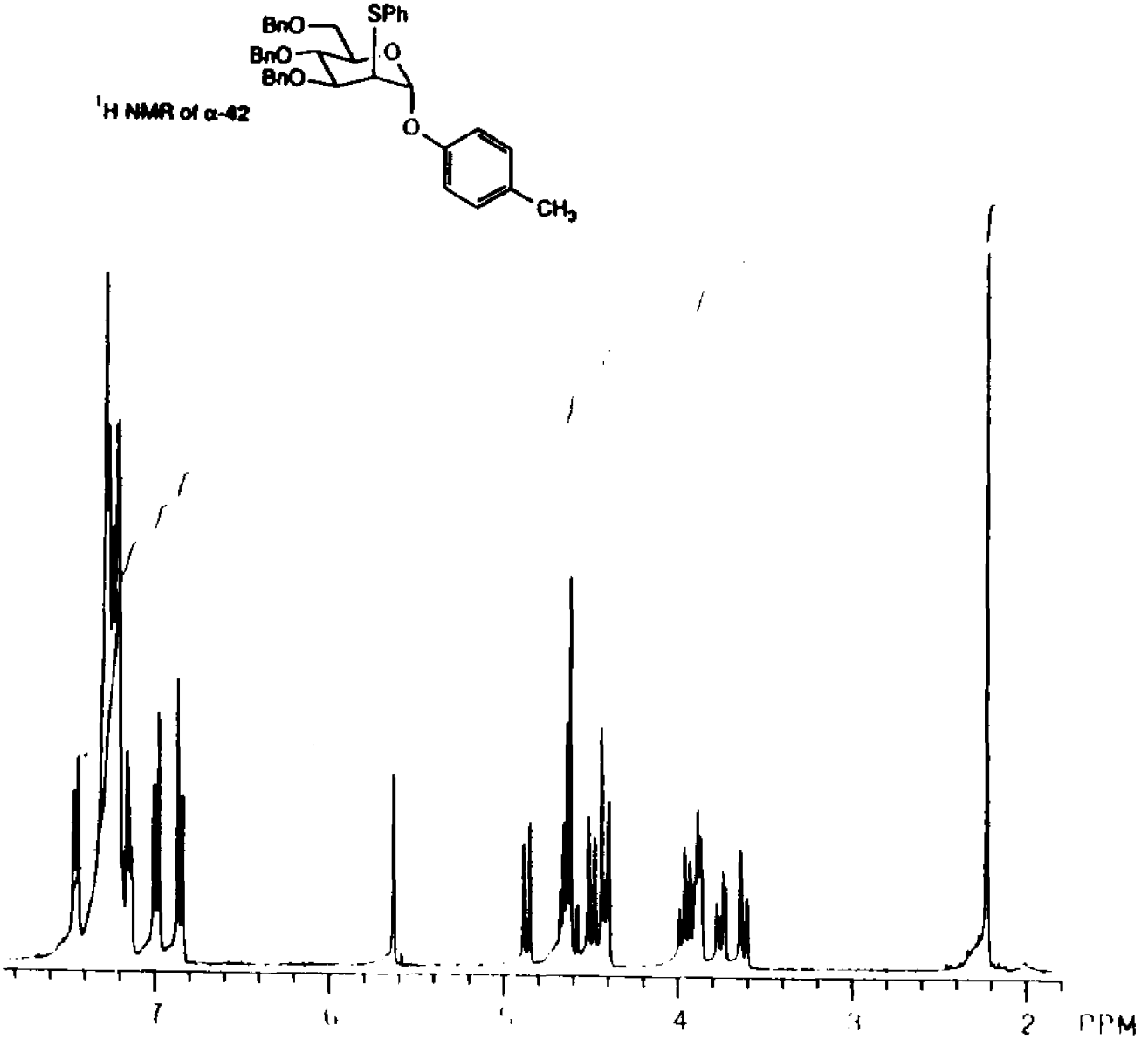
^{13}C NMR of β-40



^{1}H NMR of β-30 (R=Ph)

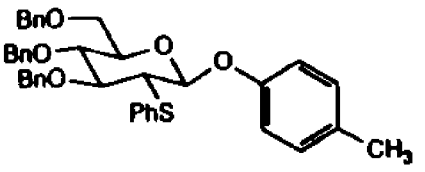


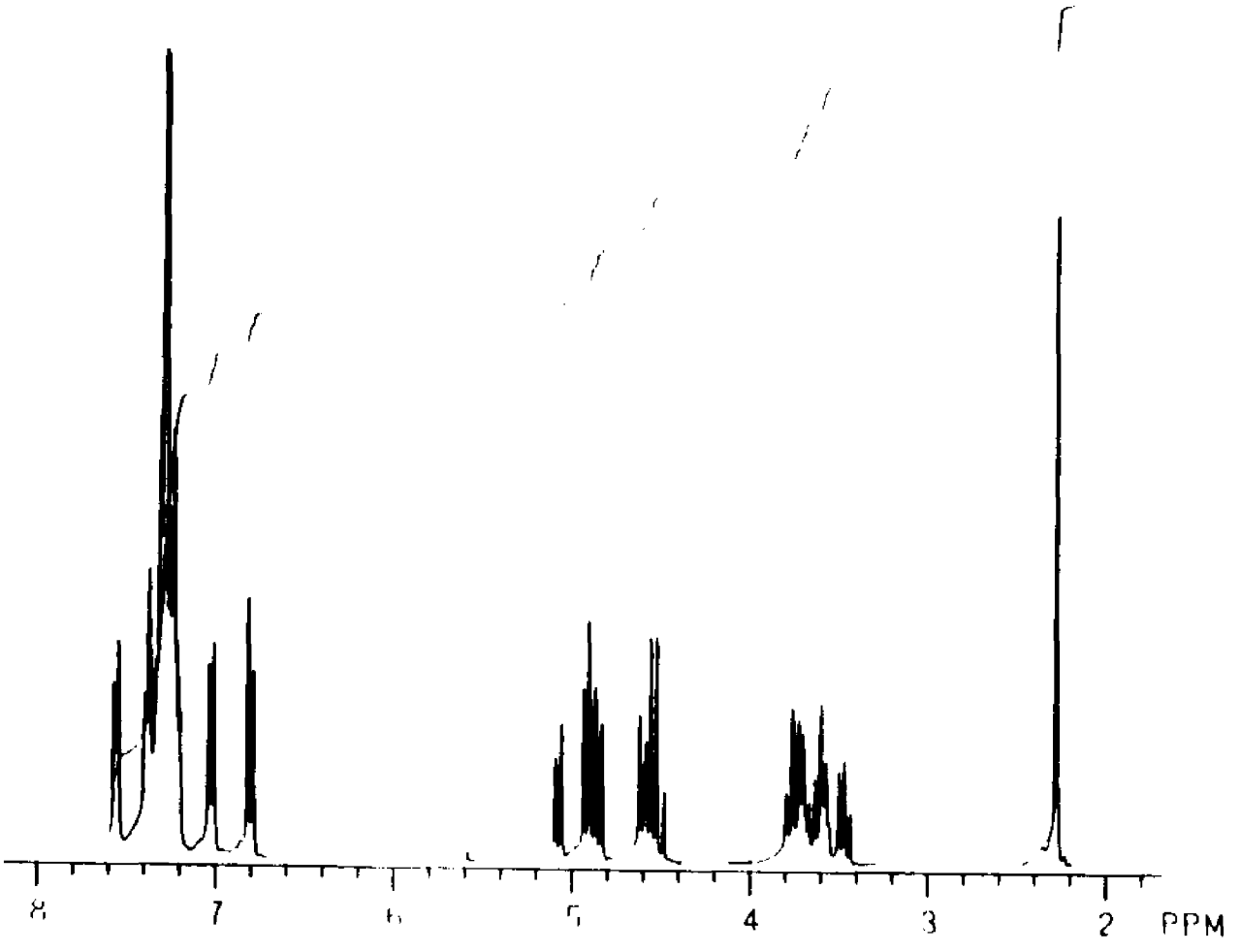




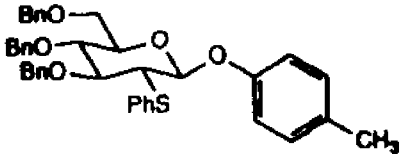
^{1}H NMR of α-42

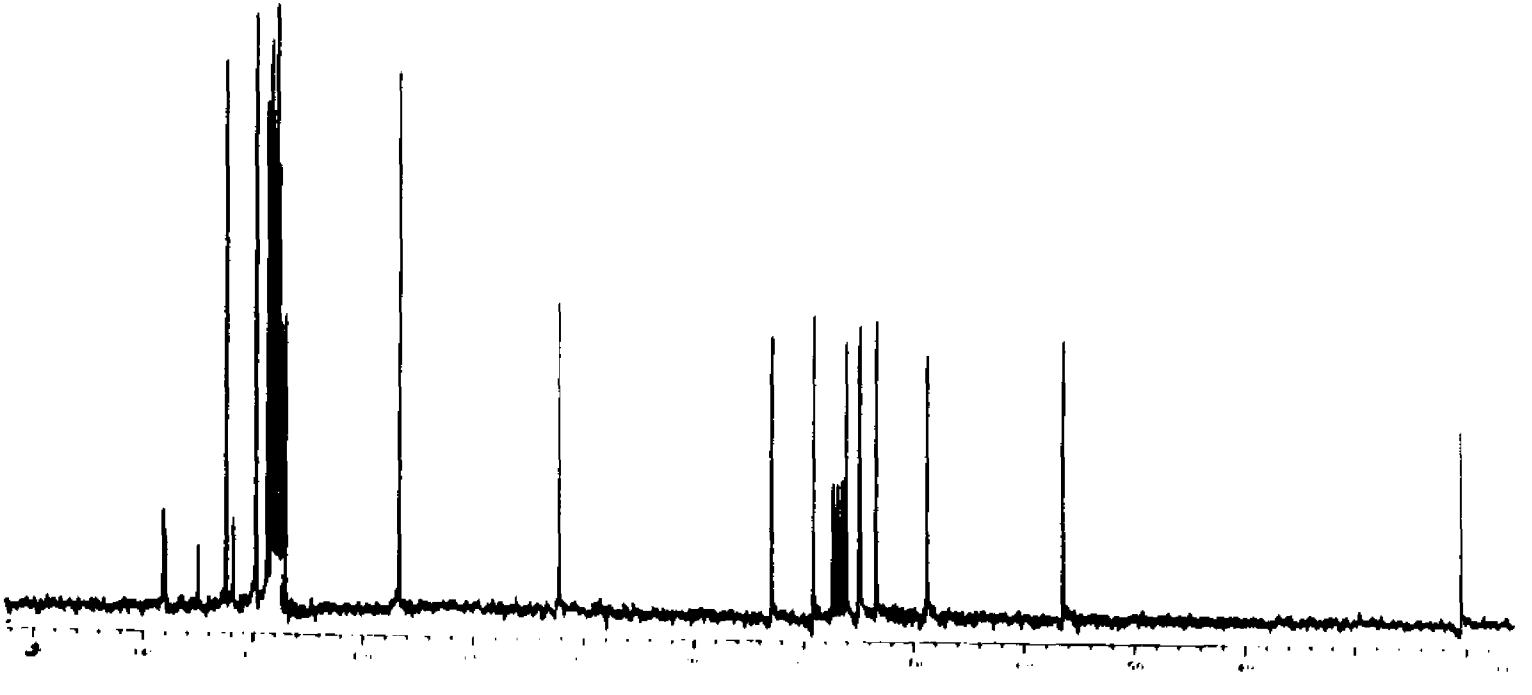
^{1}H NMR of β-42



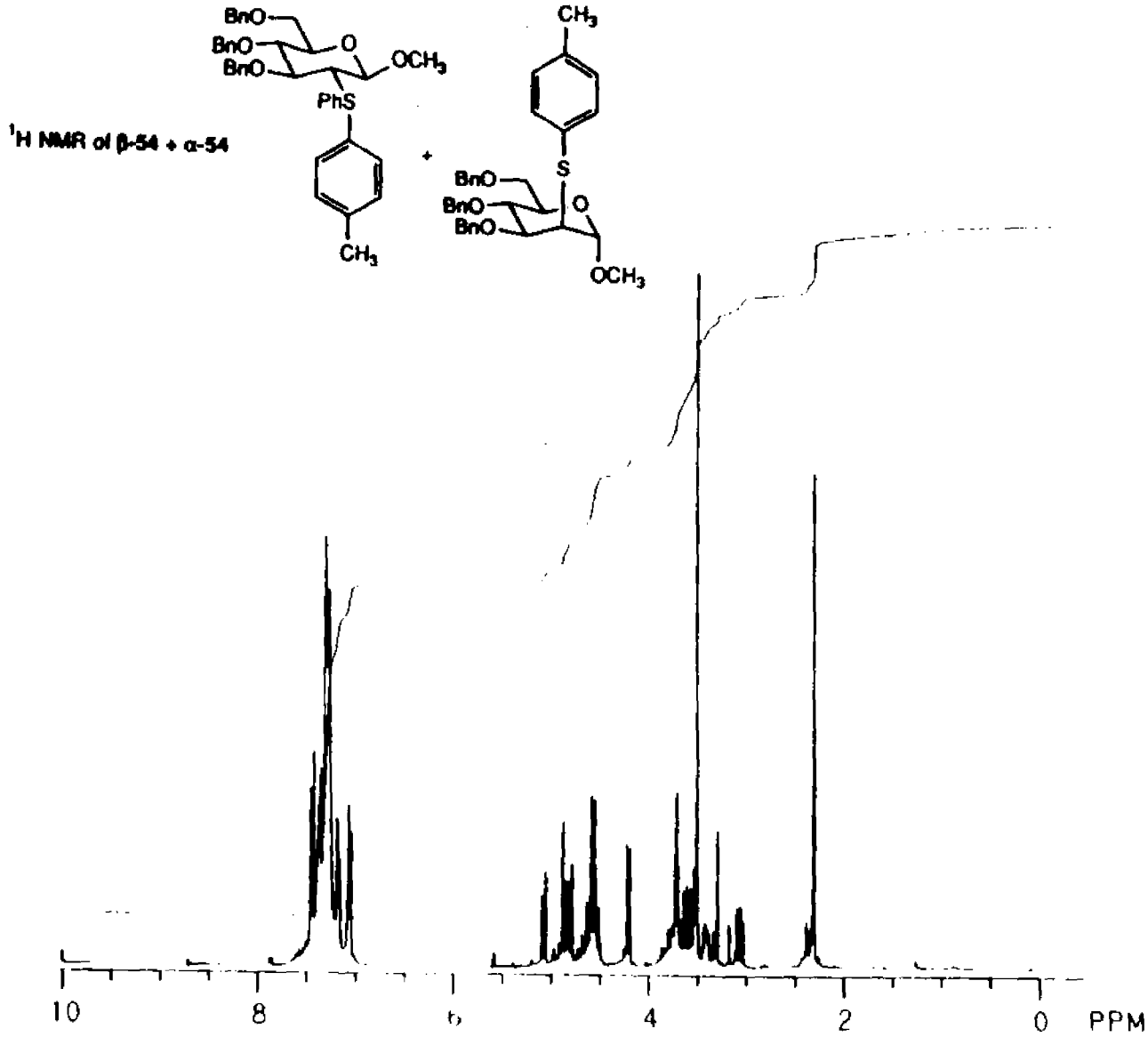


^{13}C NMR of β-42

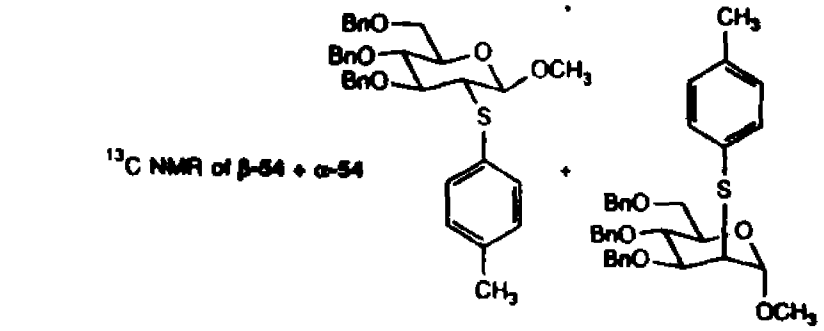


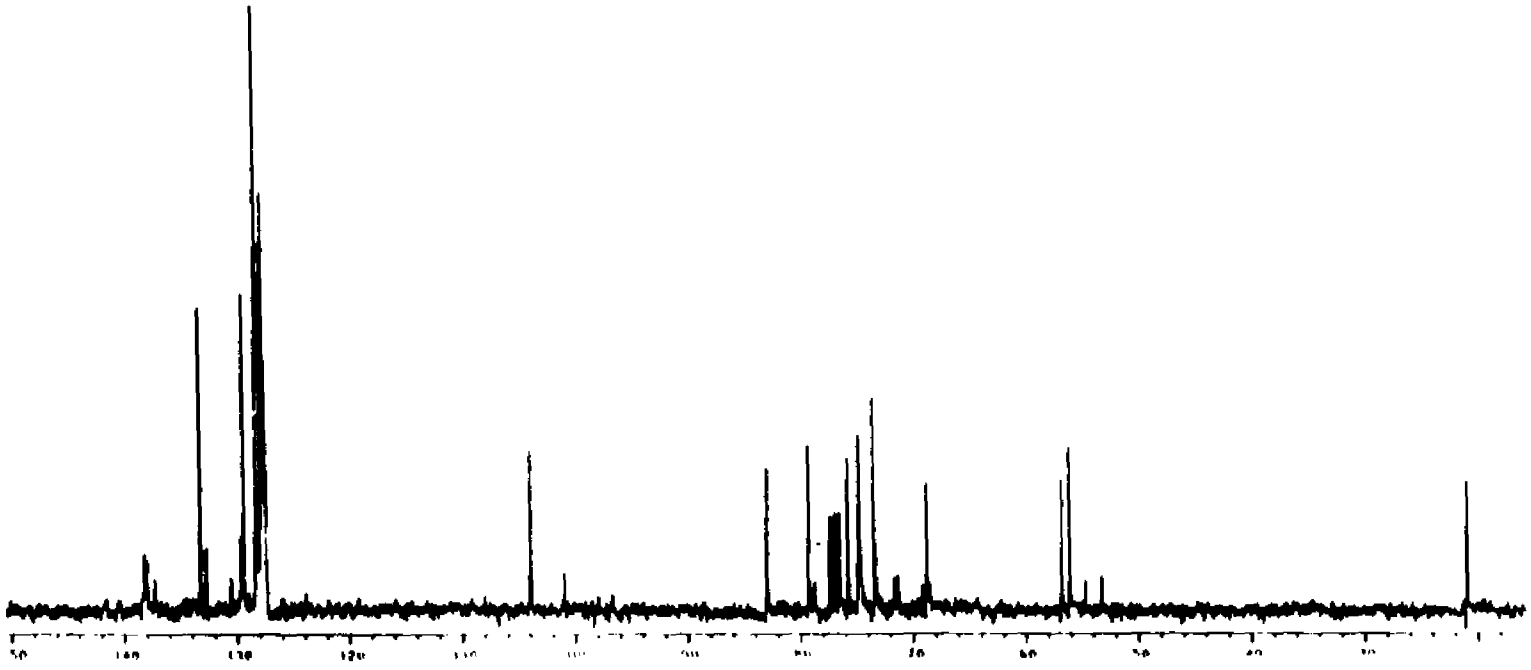


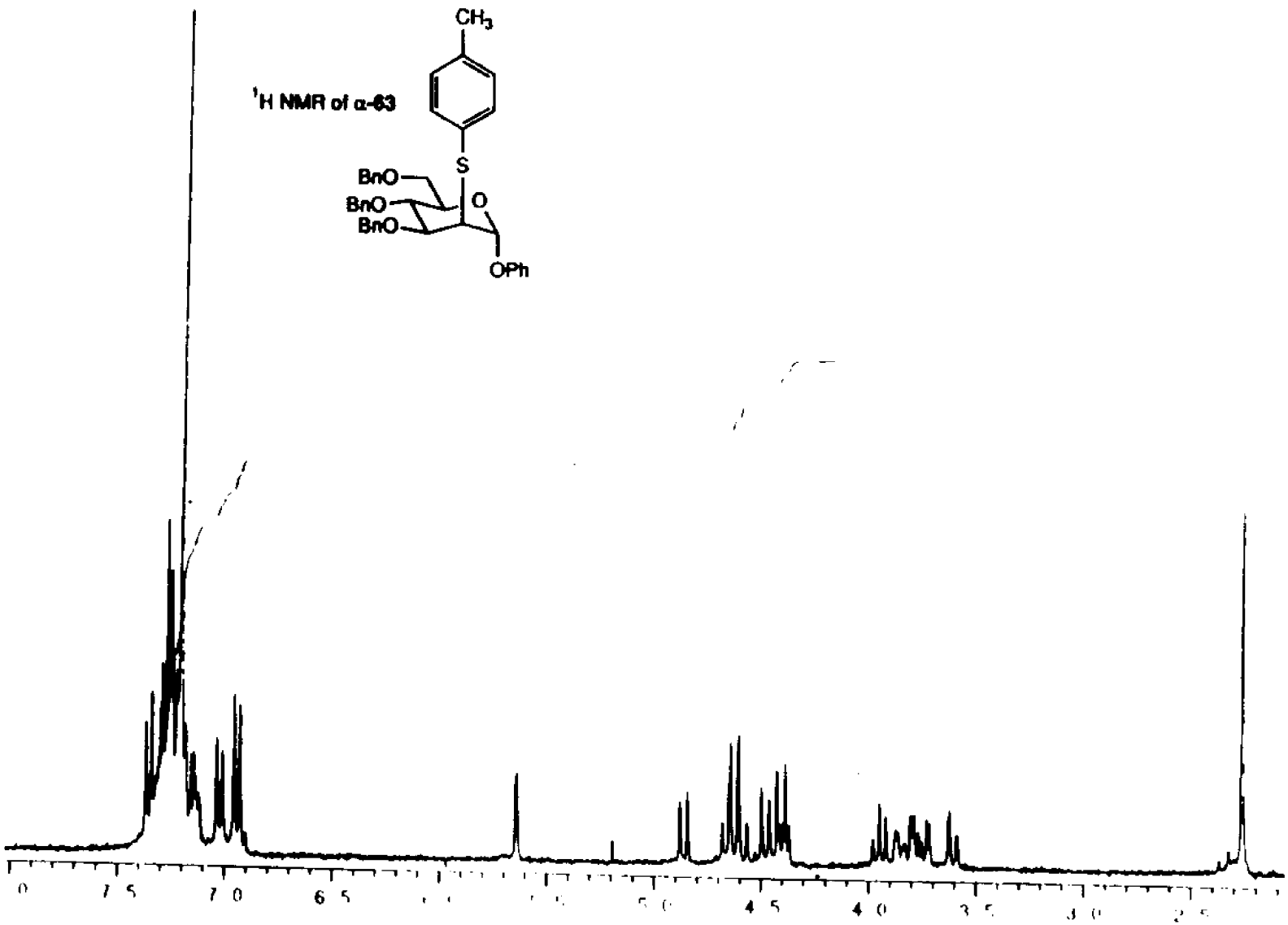
^{1}H NMR of β-54 + α-54

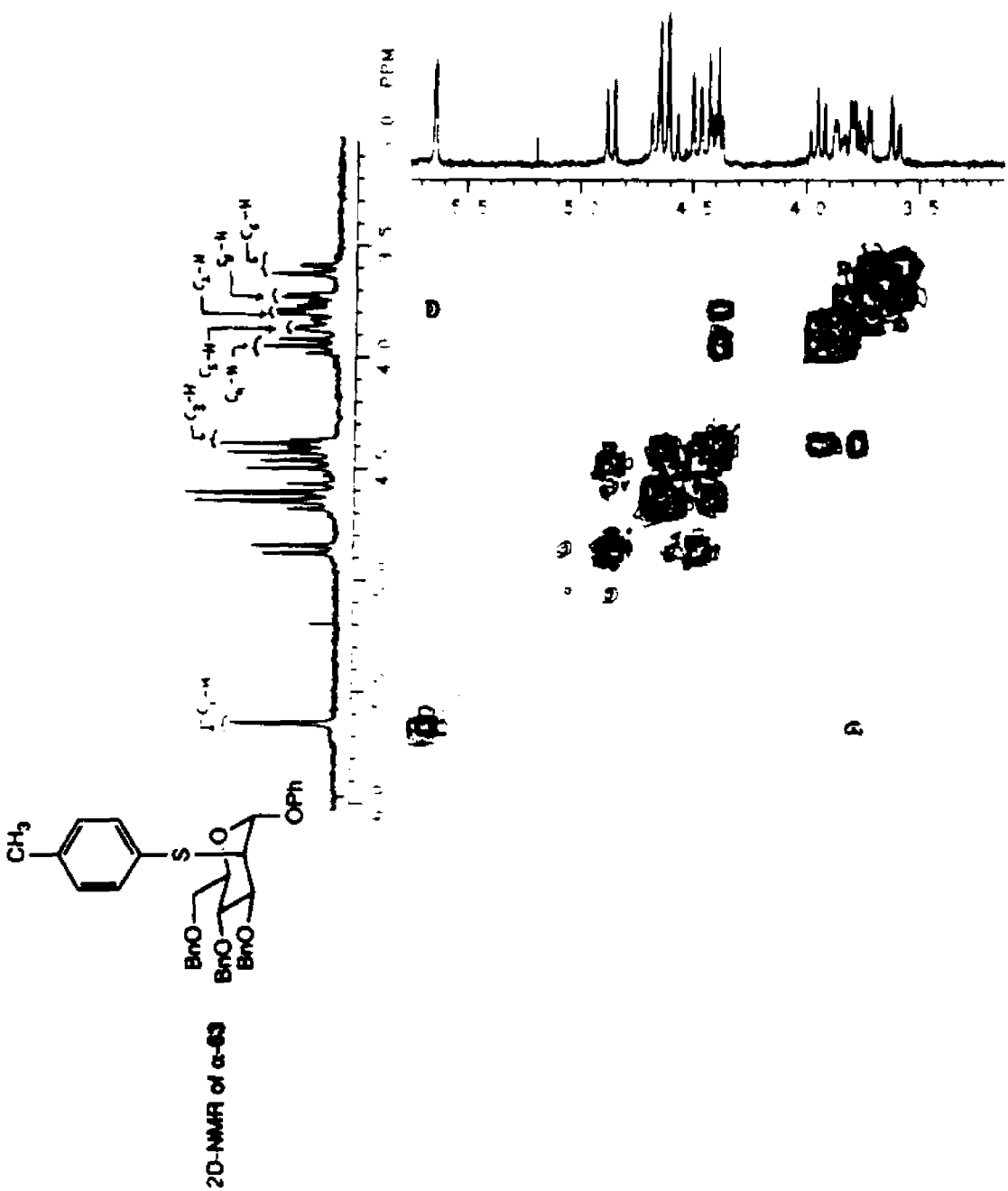


^{13}C NMR of β-54 + α-54

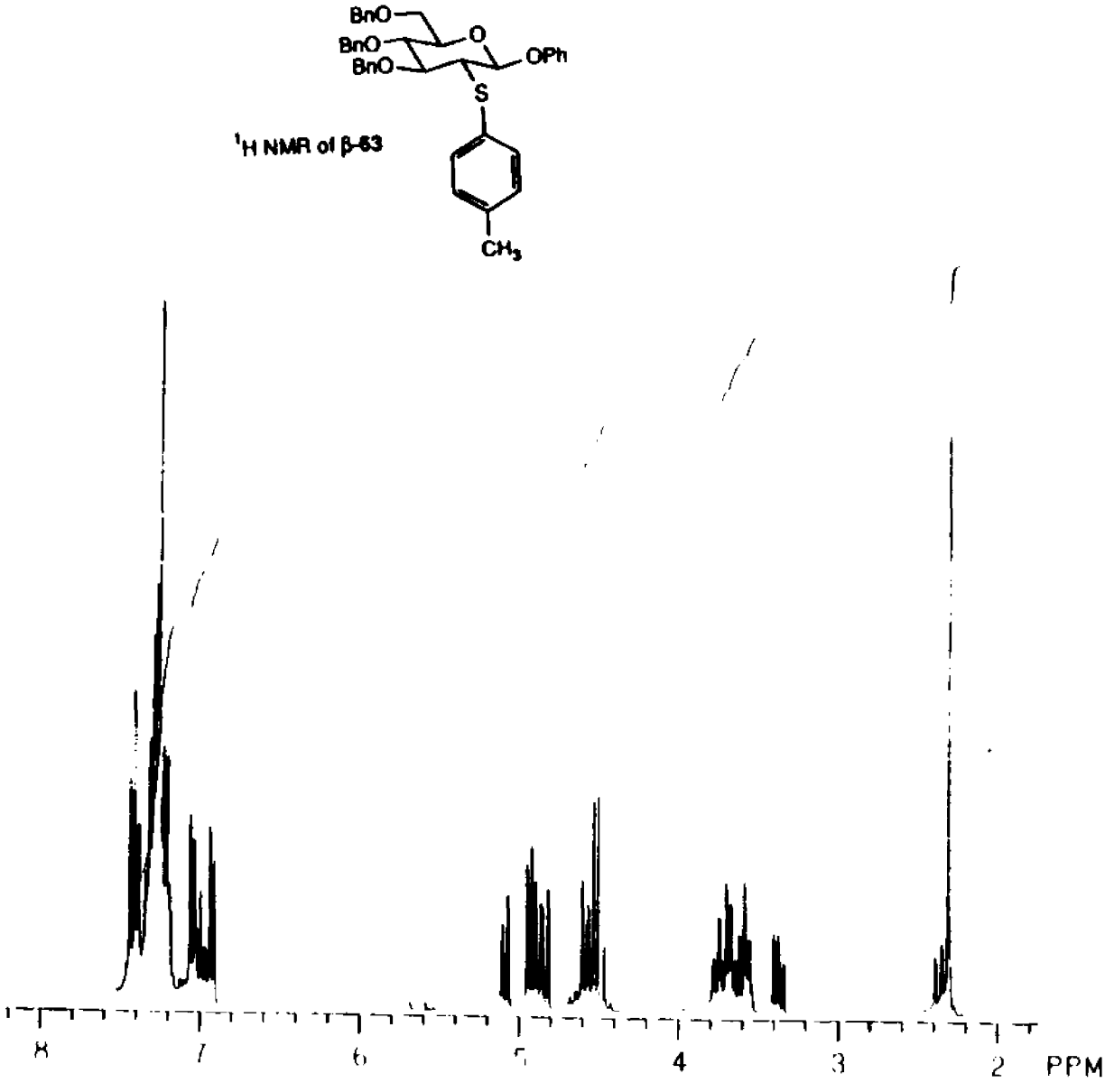




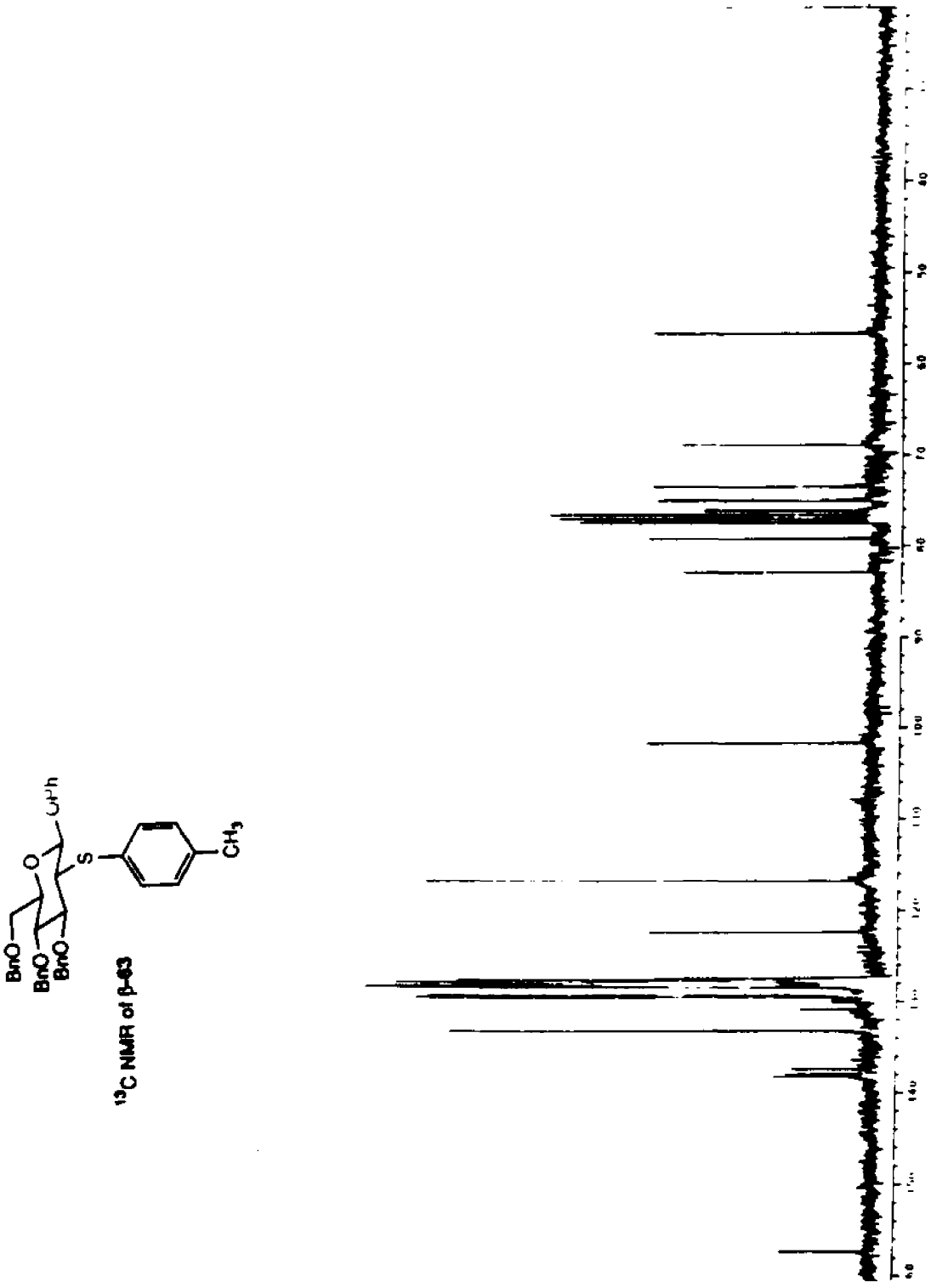

^{1}H NMR of α-63
CH3
S
BnO
BnO
BnO
O
OPh
7.5
7.0
6.5
4.5
4.0
3.5
3.0
2.5



2D-NMR of α-63

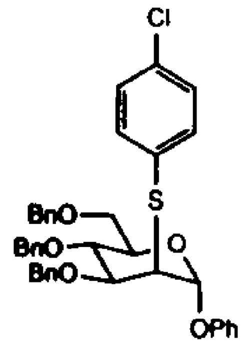


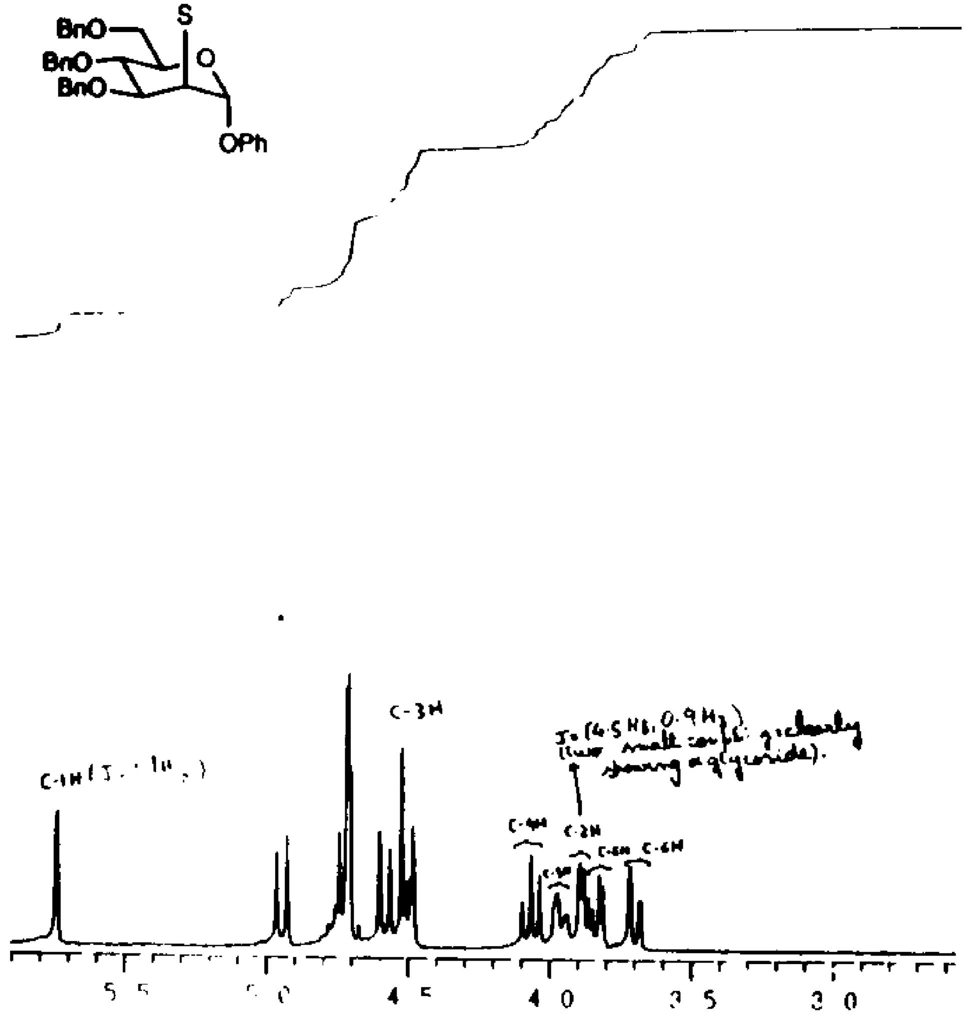
^{1}H NMR of β-63

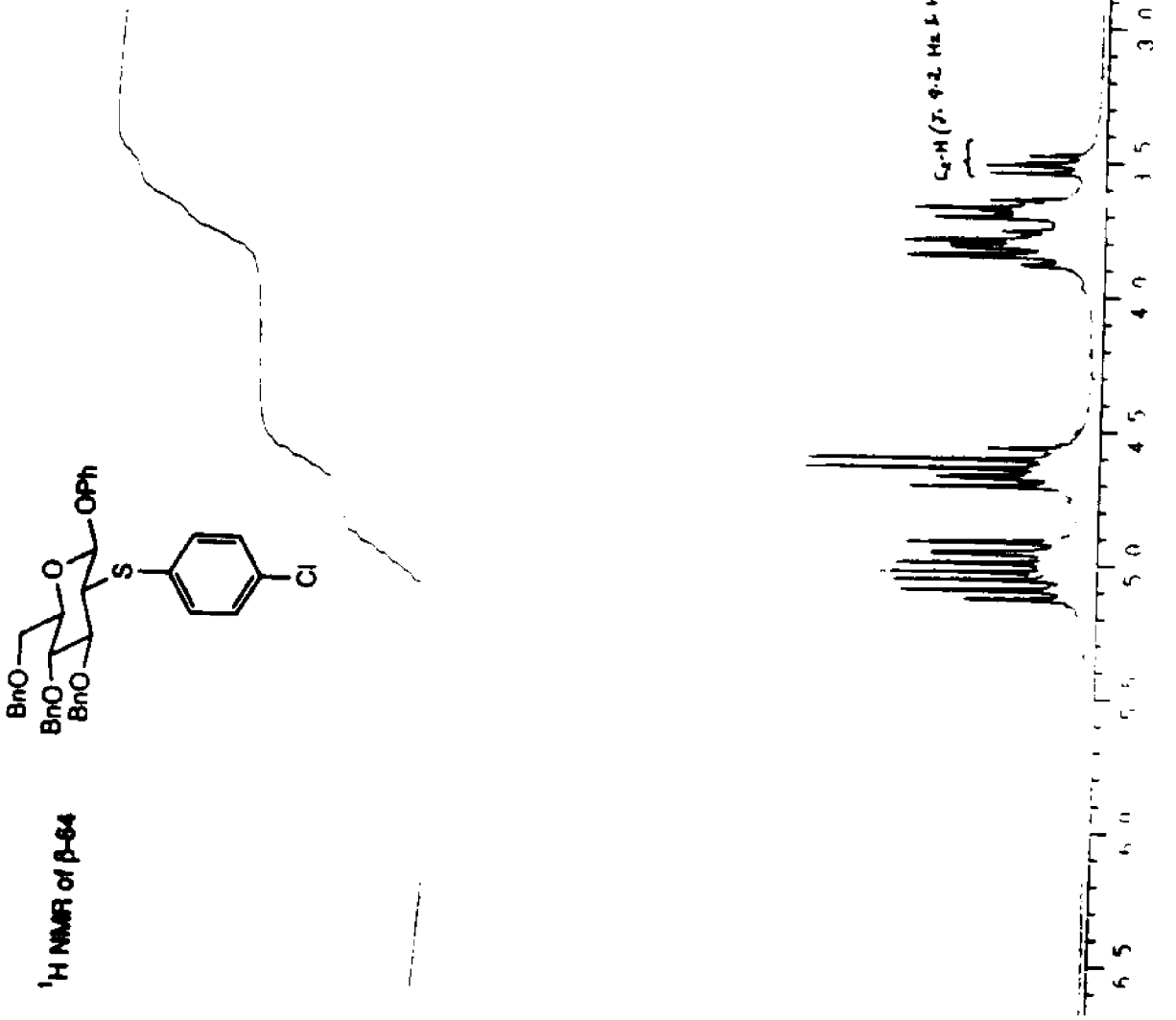


^{13}C NMR of β-63

^{1}H NMR of α-64

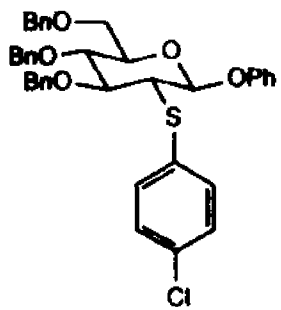


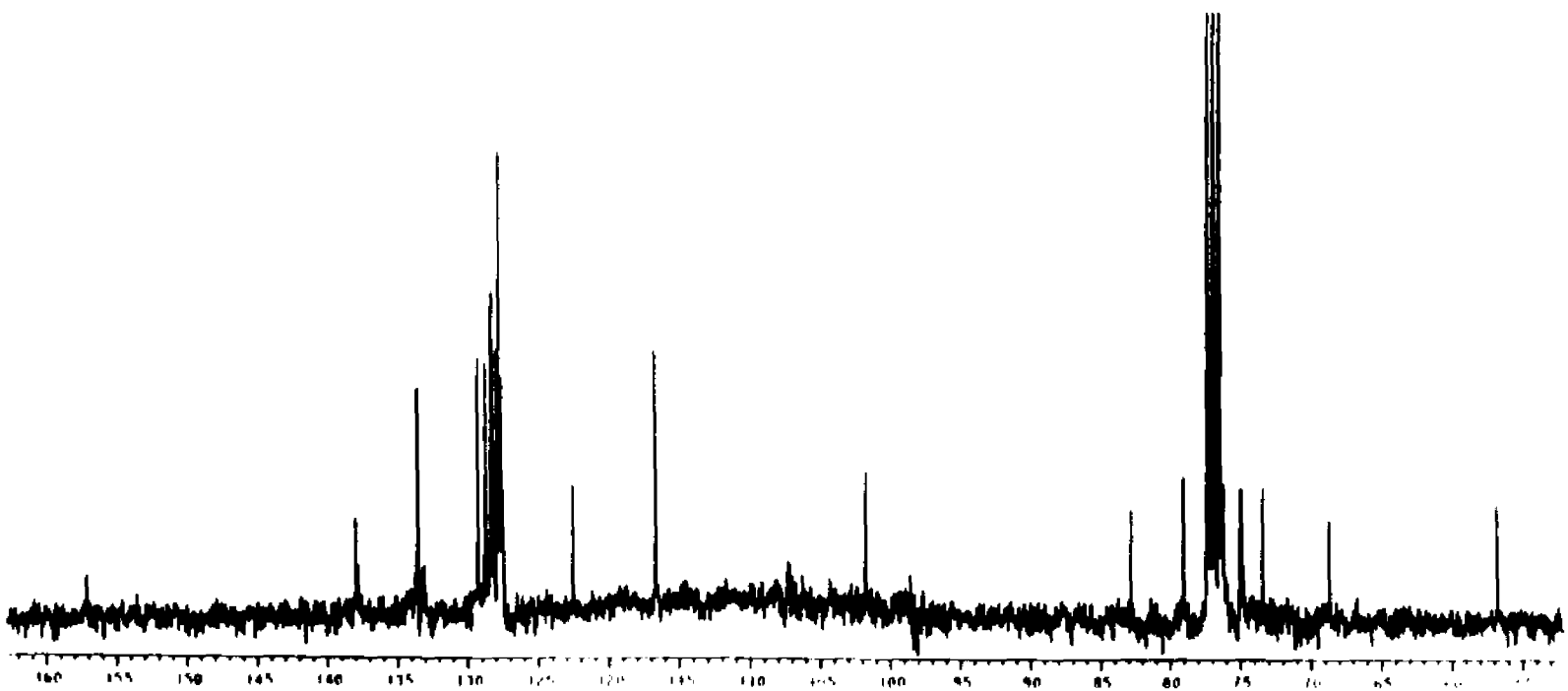


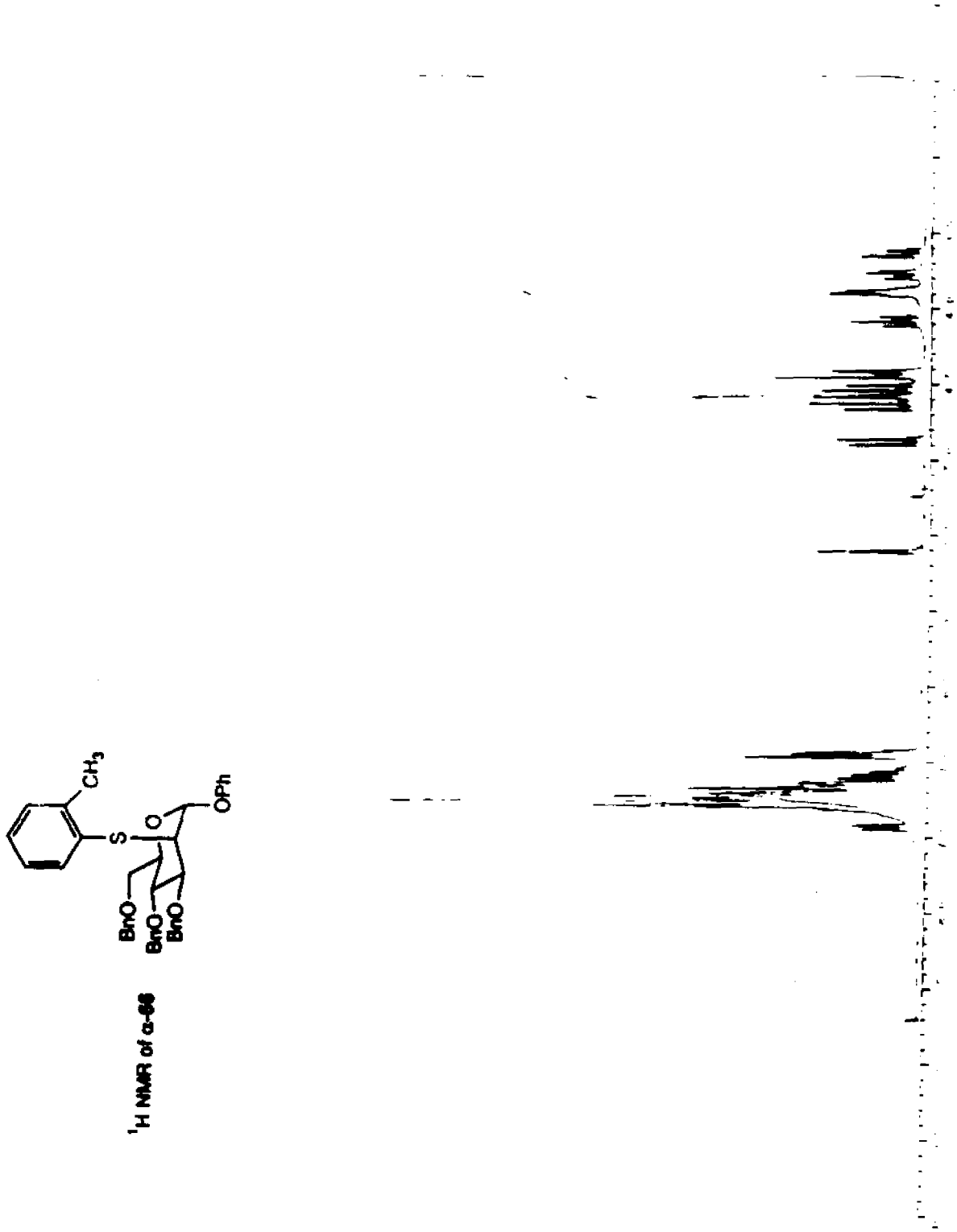


^{1}H NMR of β-64

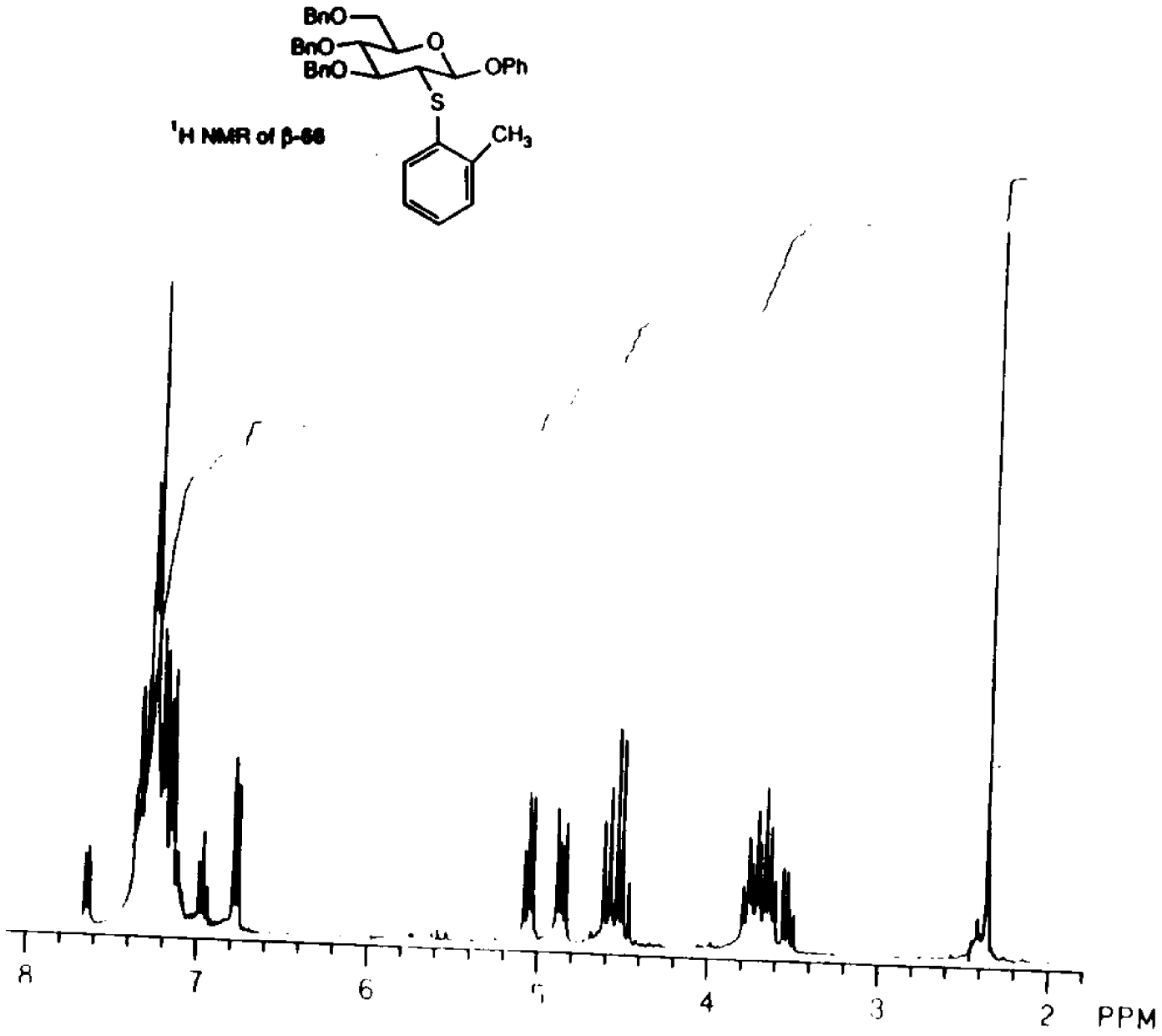
^{13}C NMR of β-64





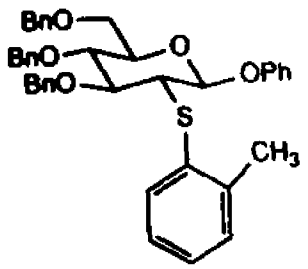


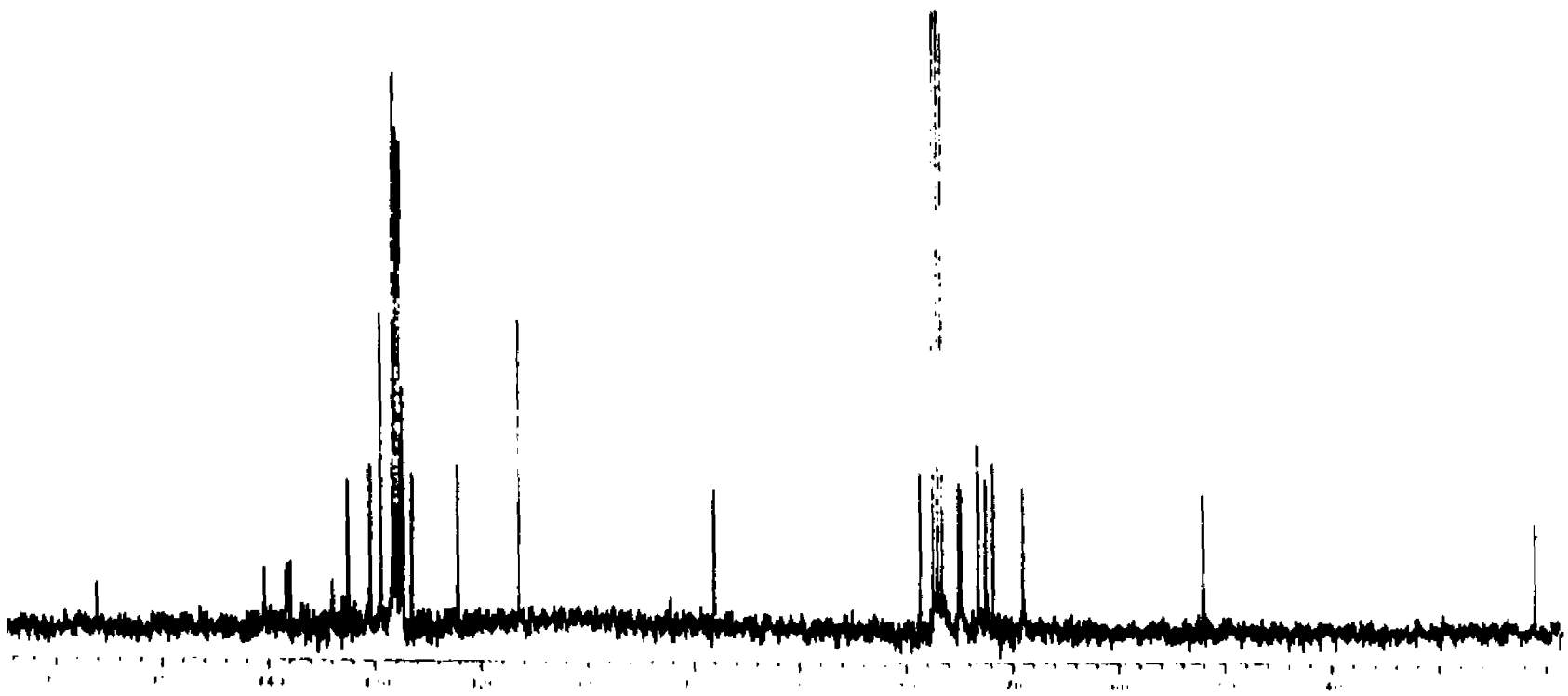
^{1}H NMR of α-68

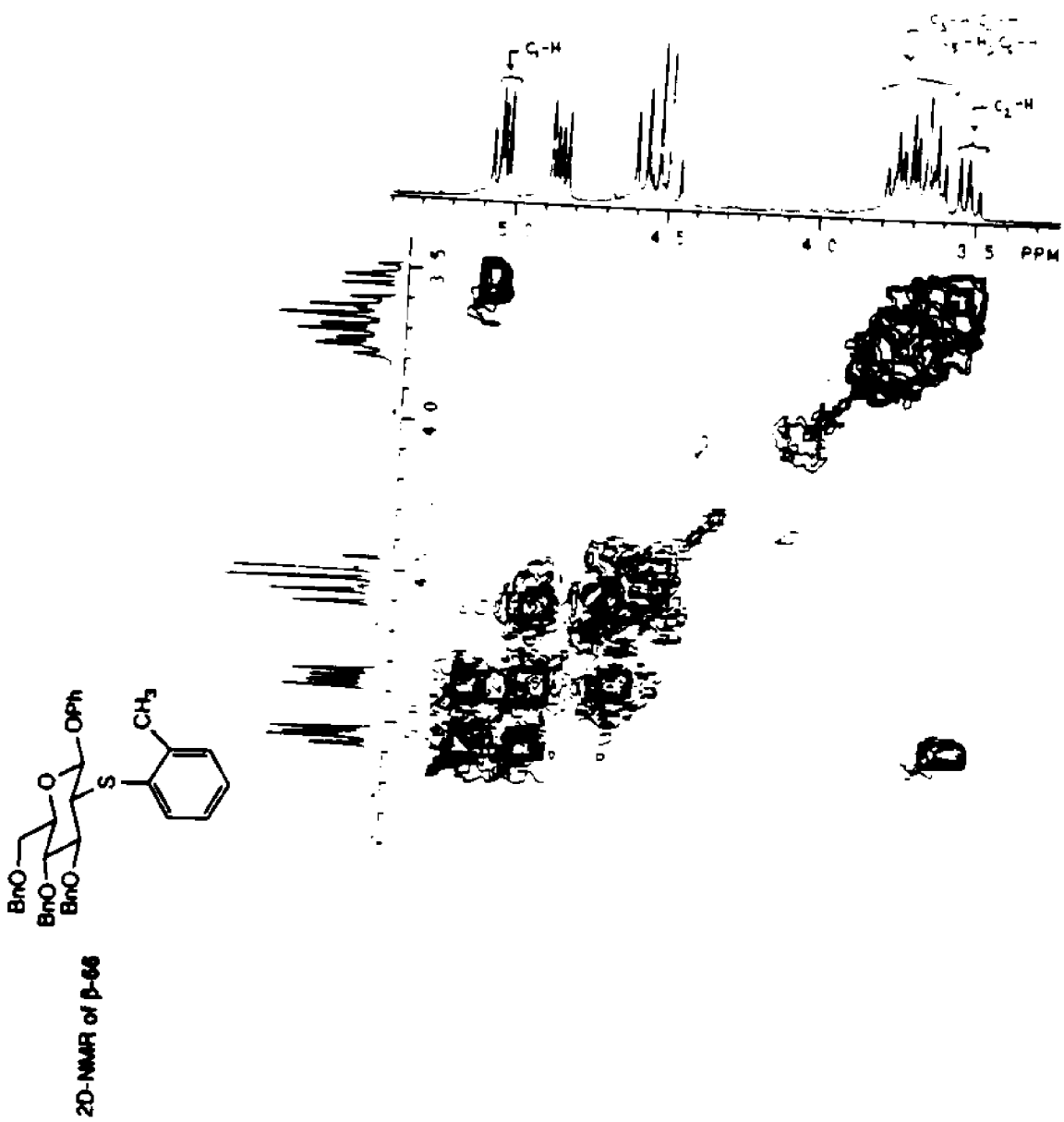


^{1}H NMR of β-66

^{13}C NMR of β-66

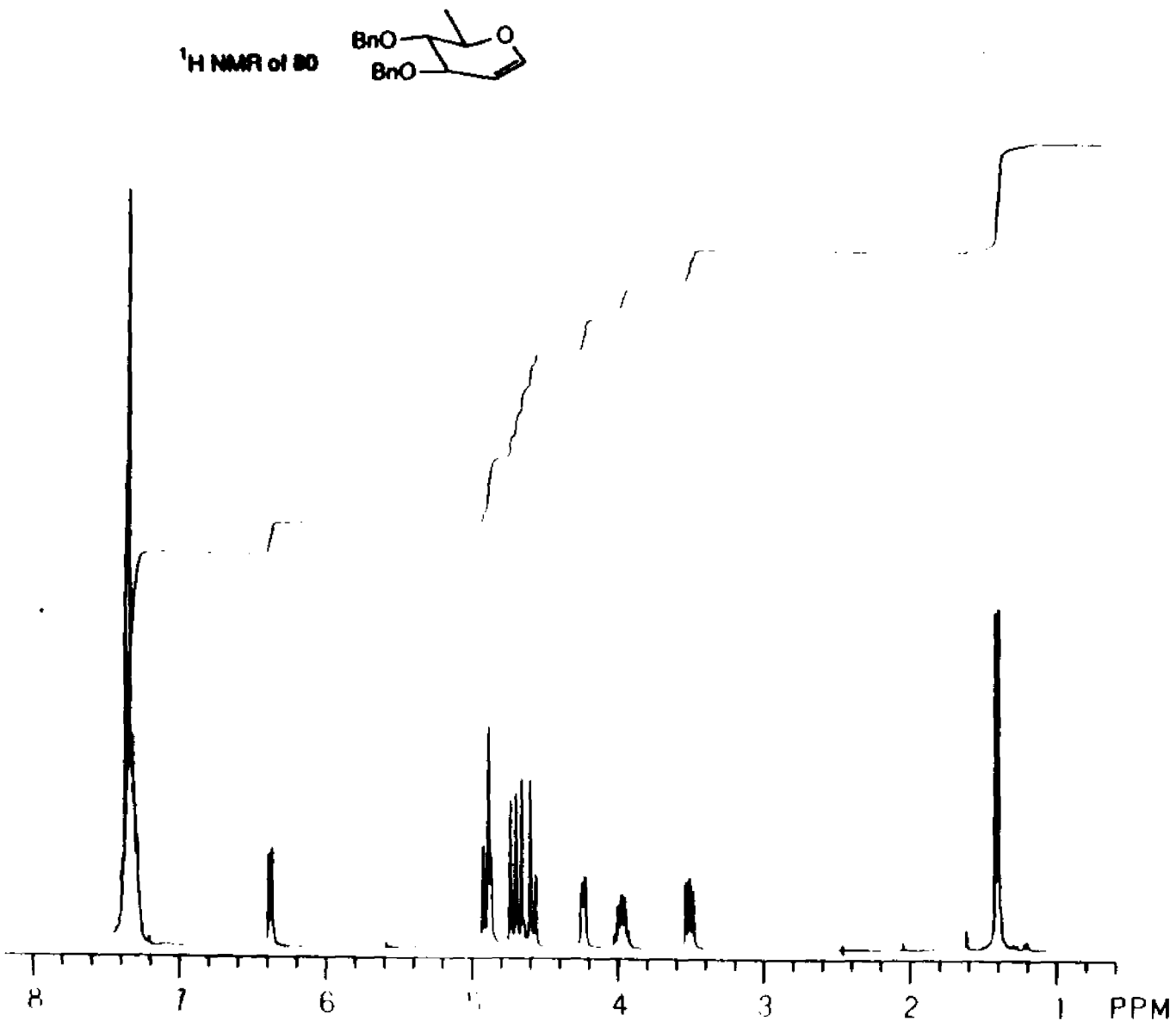




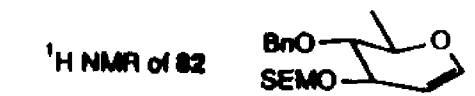


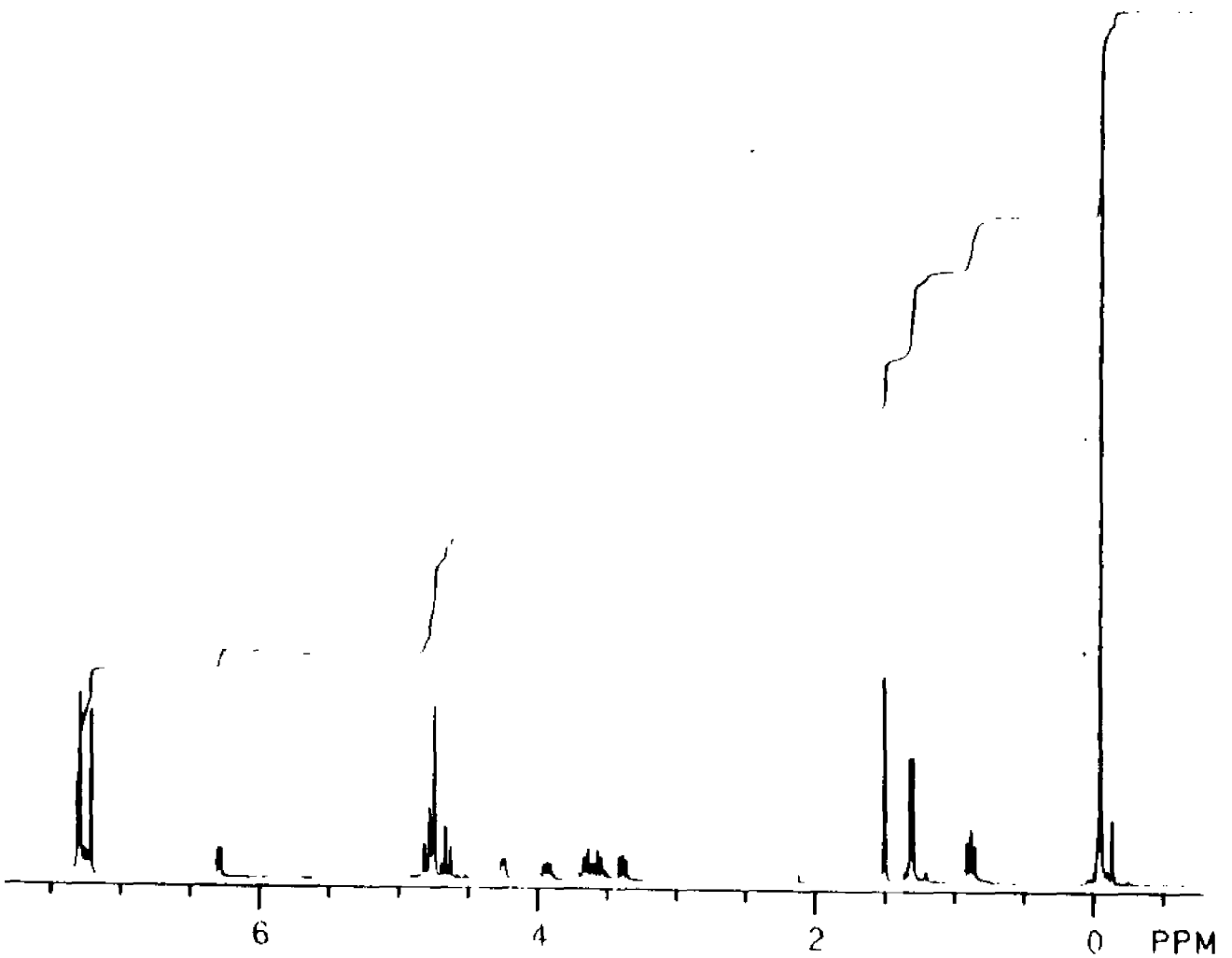
2D-NMR of β-68

^{1}H NMR of 80

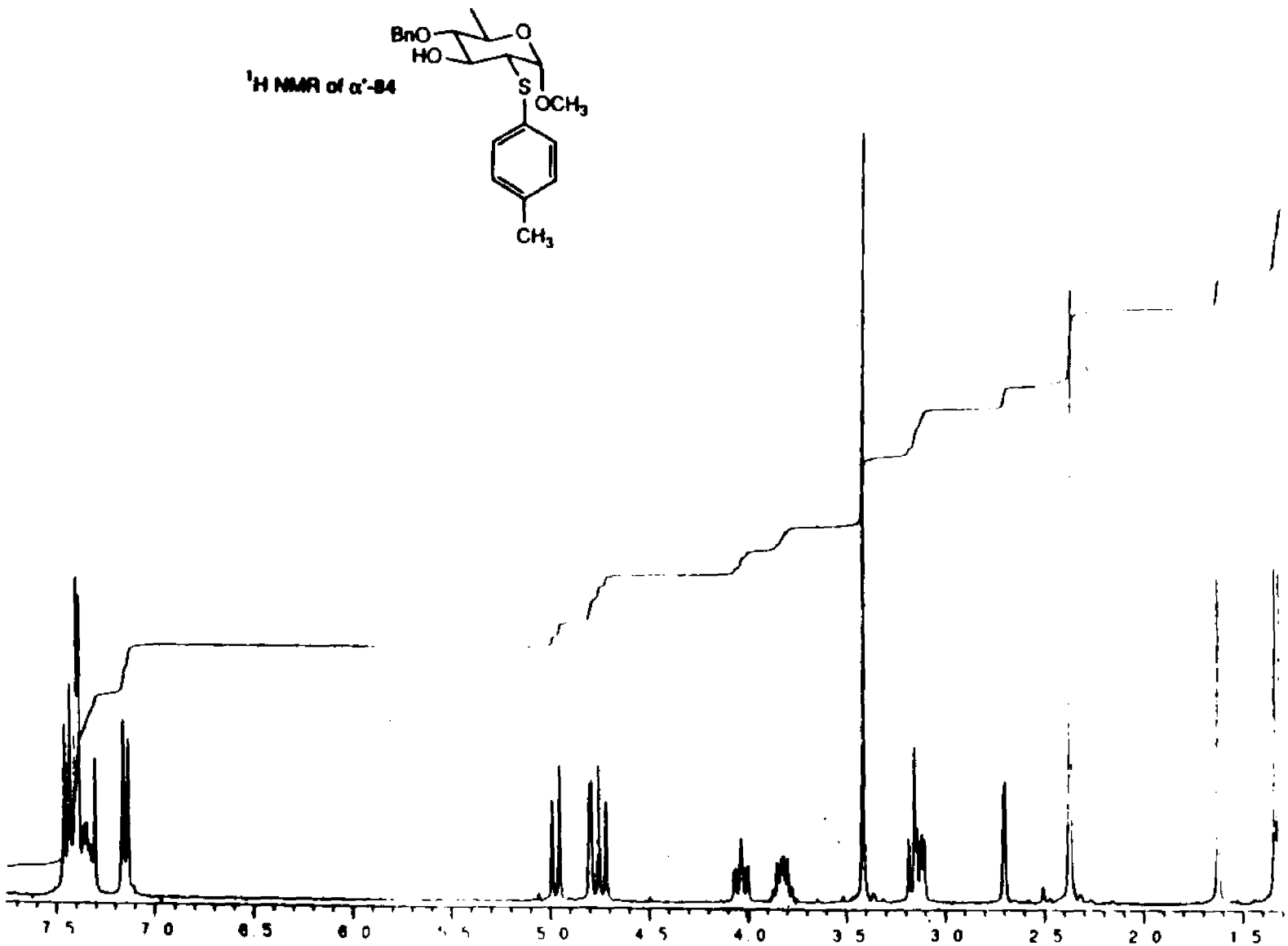


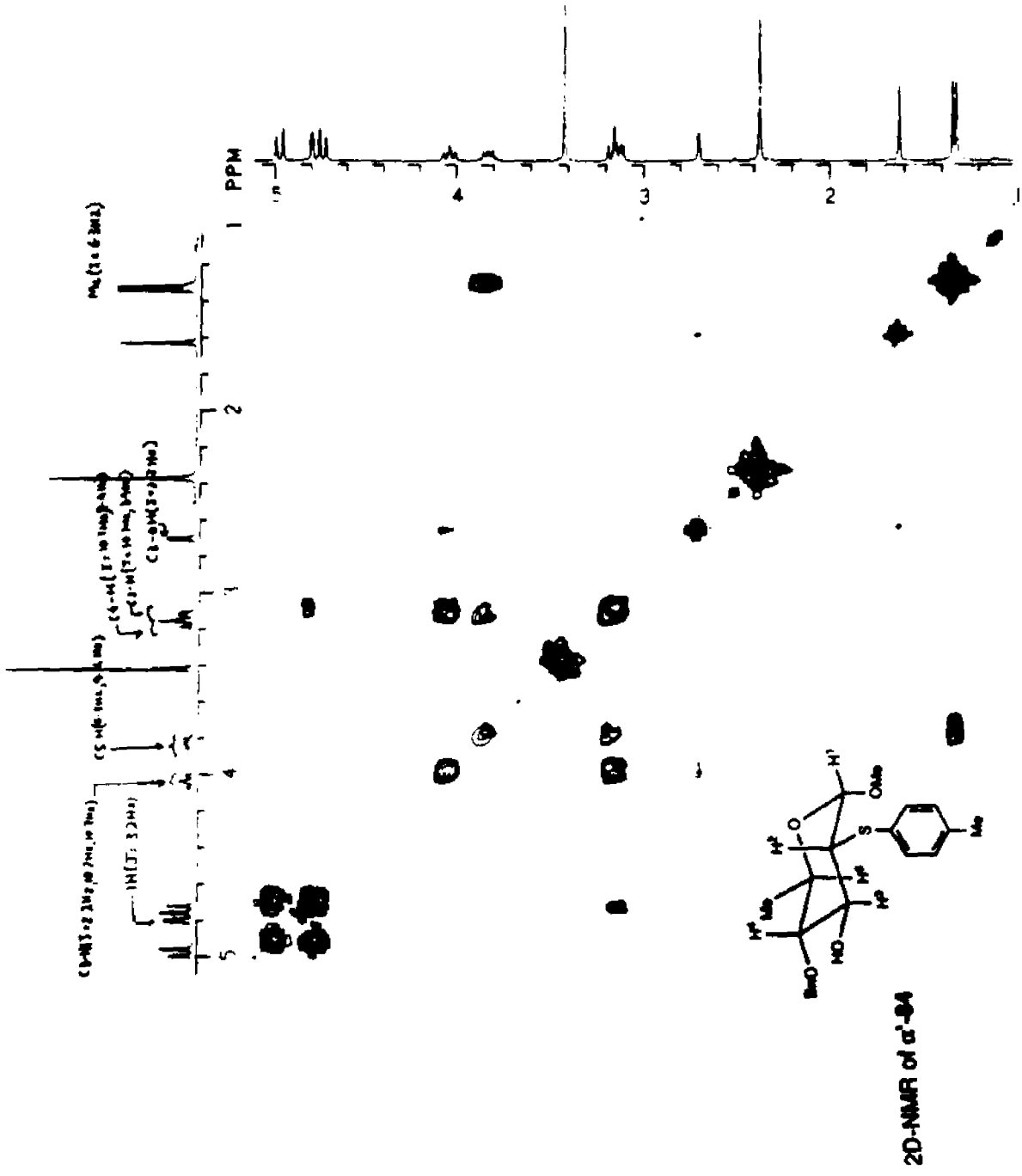
^{1}H NMR of 82



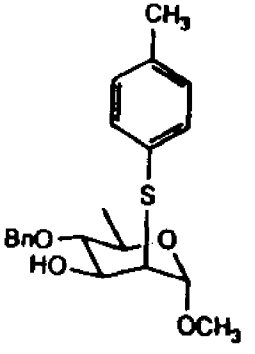


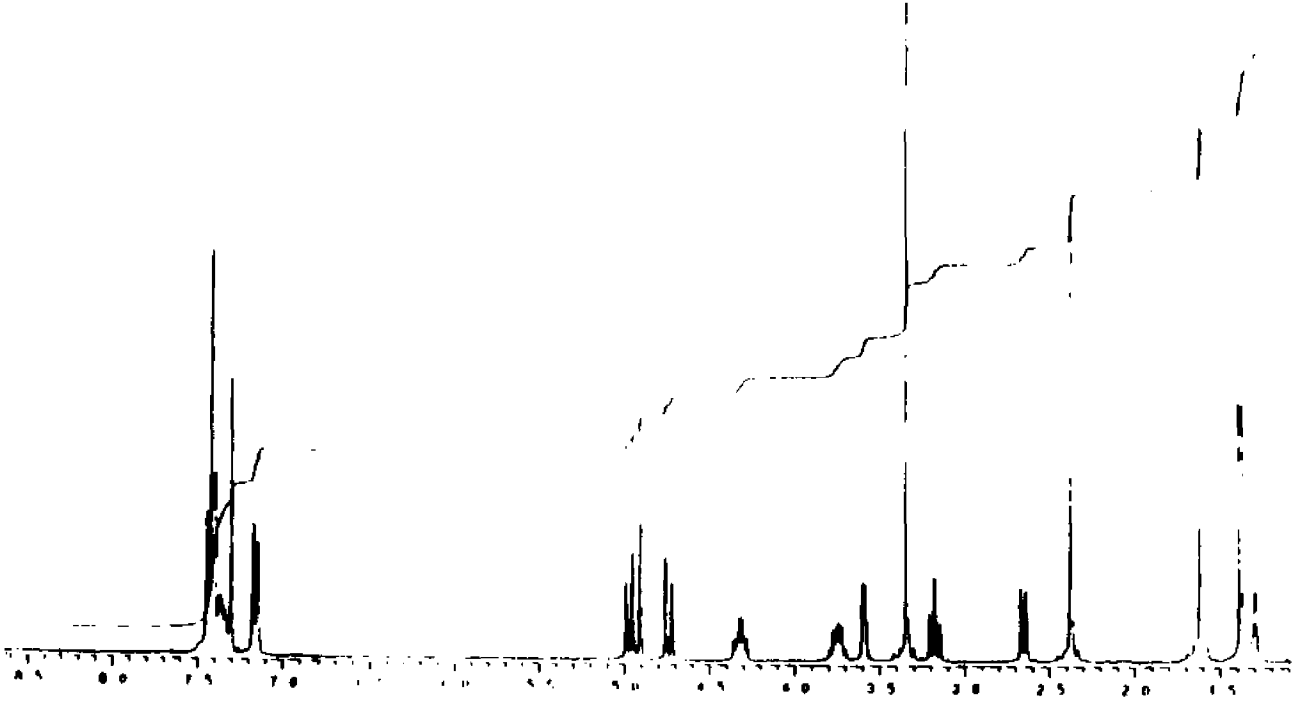
^{1}H NMR of α'-84

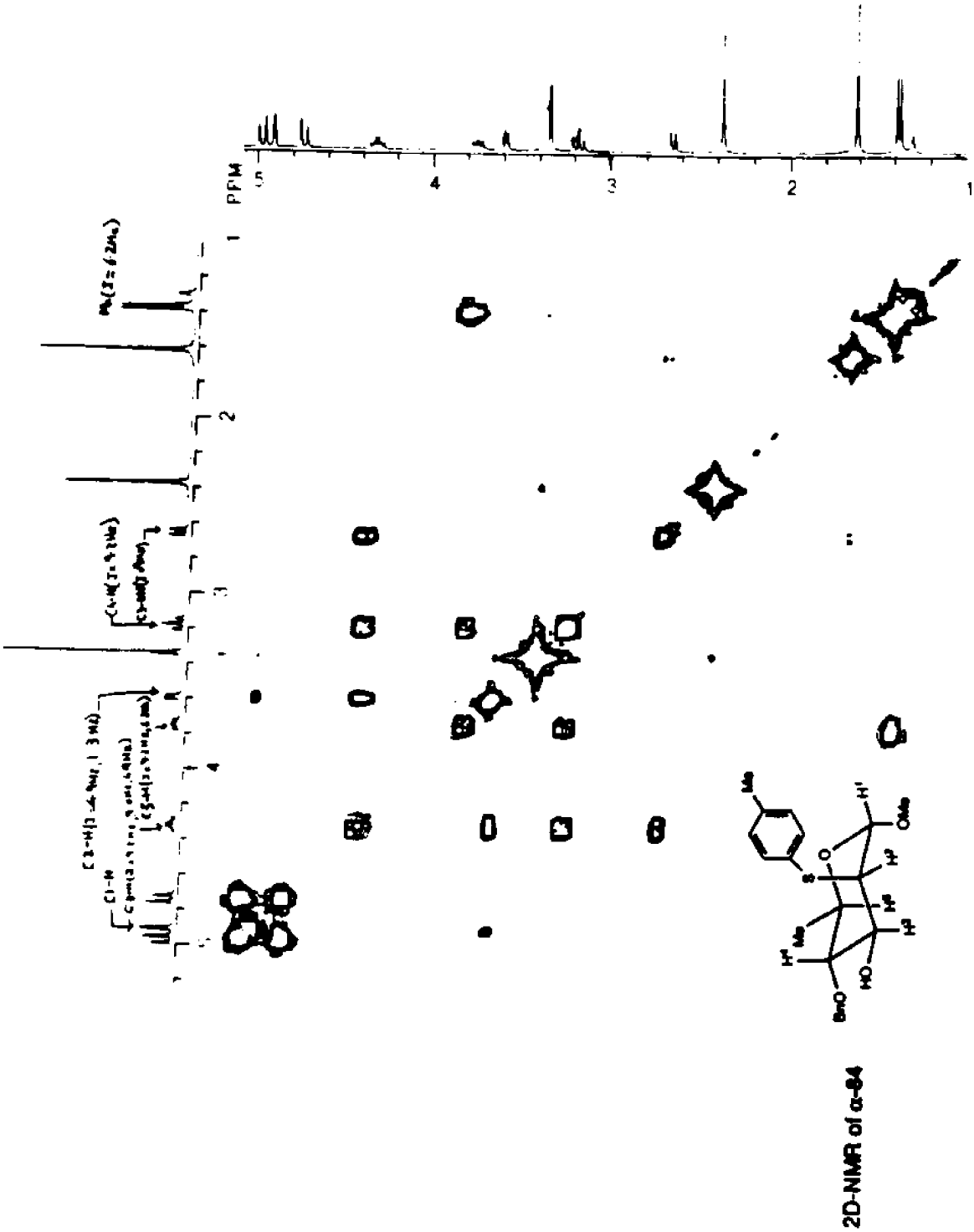



1 PPM
2D-NMR of α'-84

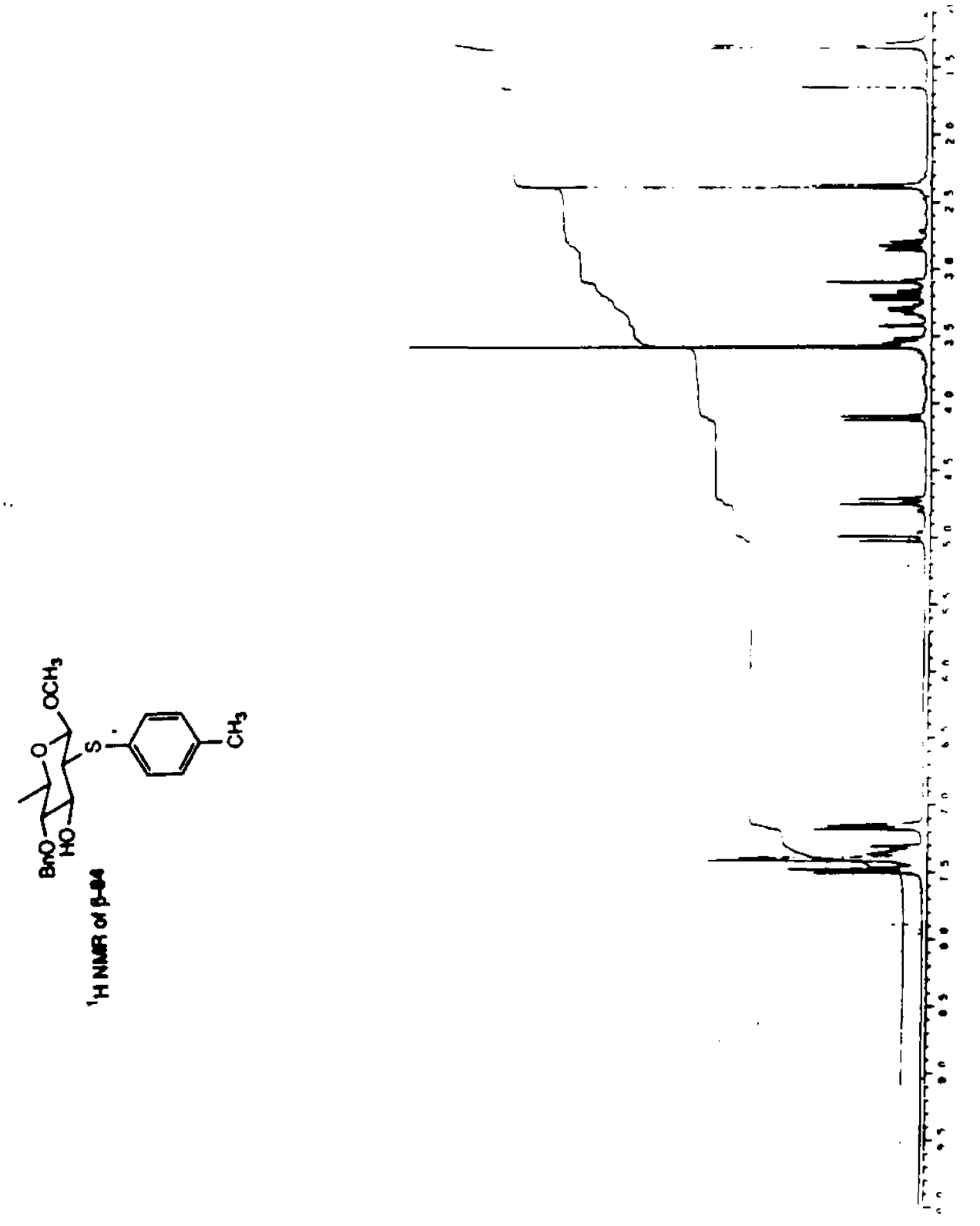
^{1}H NMR of α-84



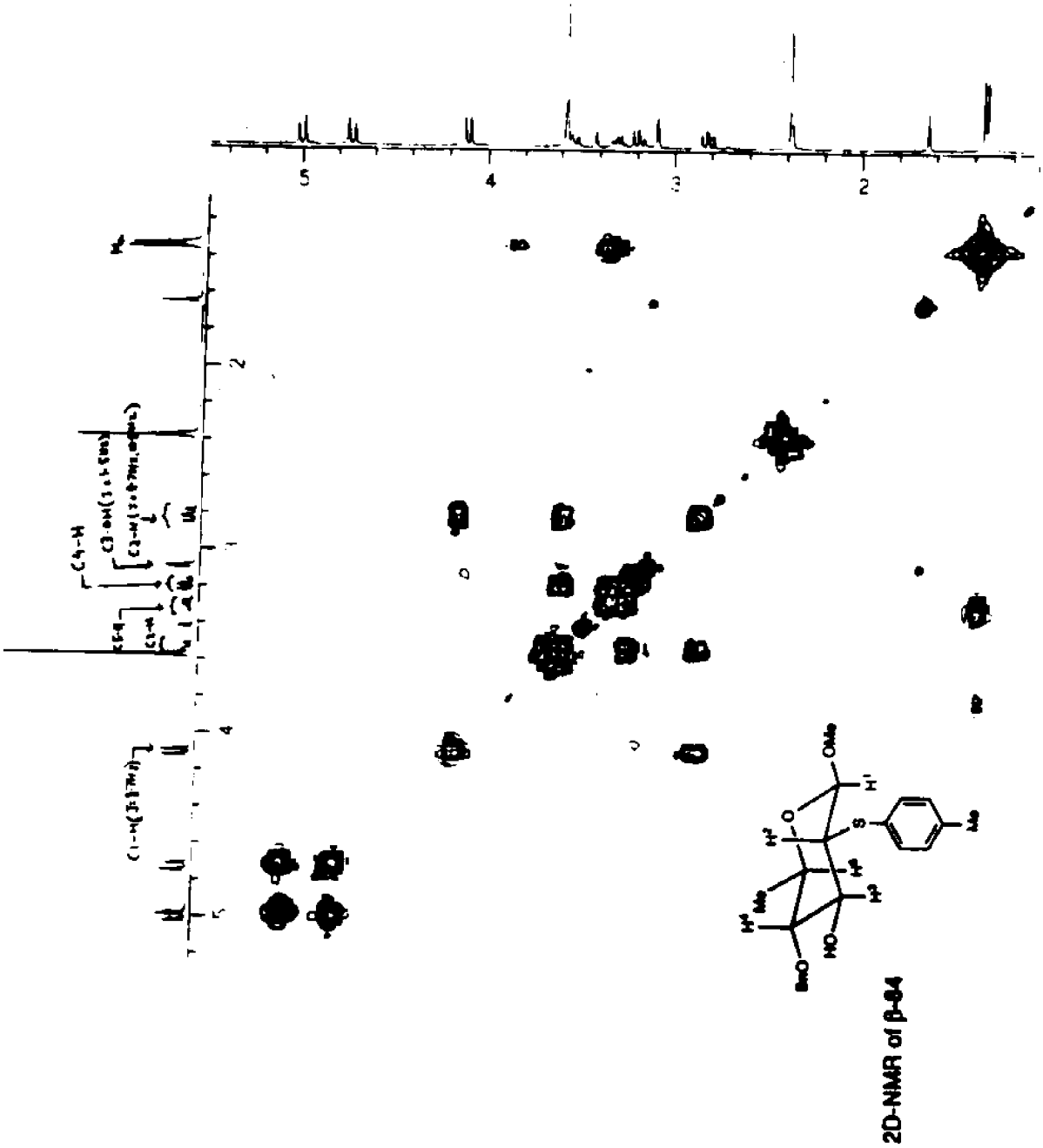




2D-NMR of α-84

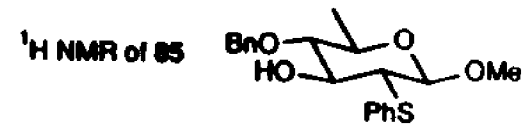


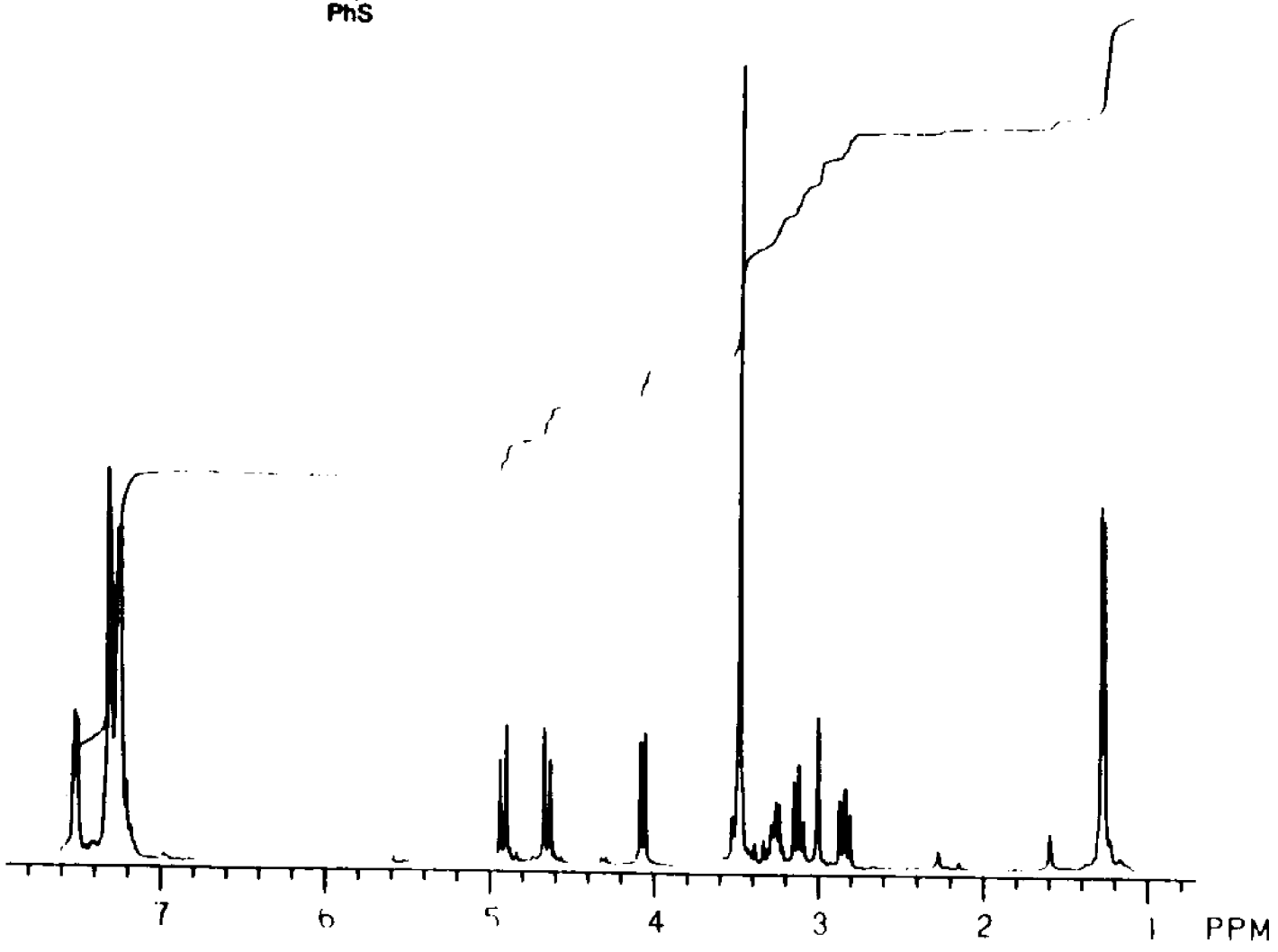
^{1}H NMR of β-84

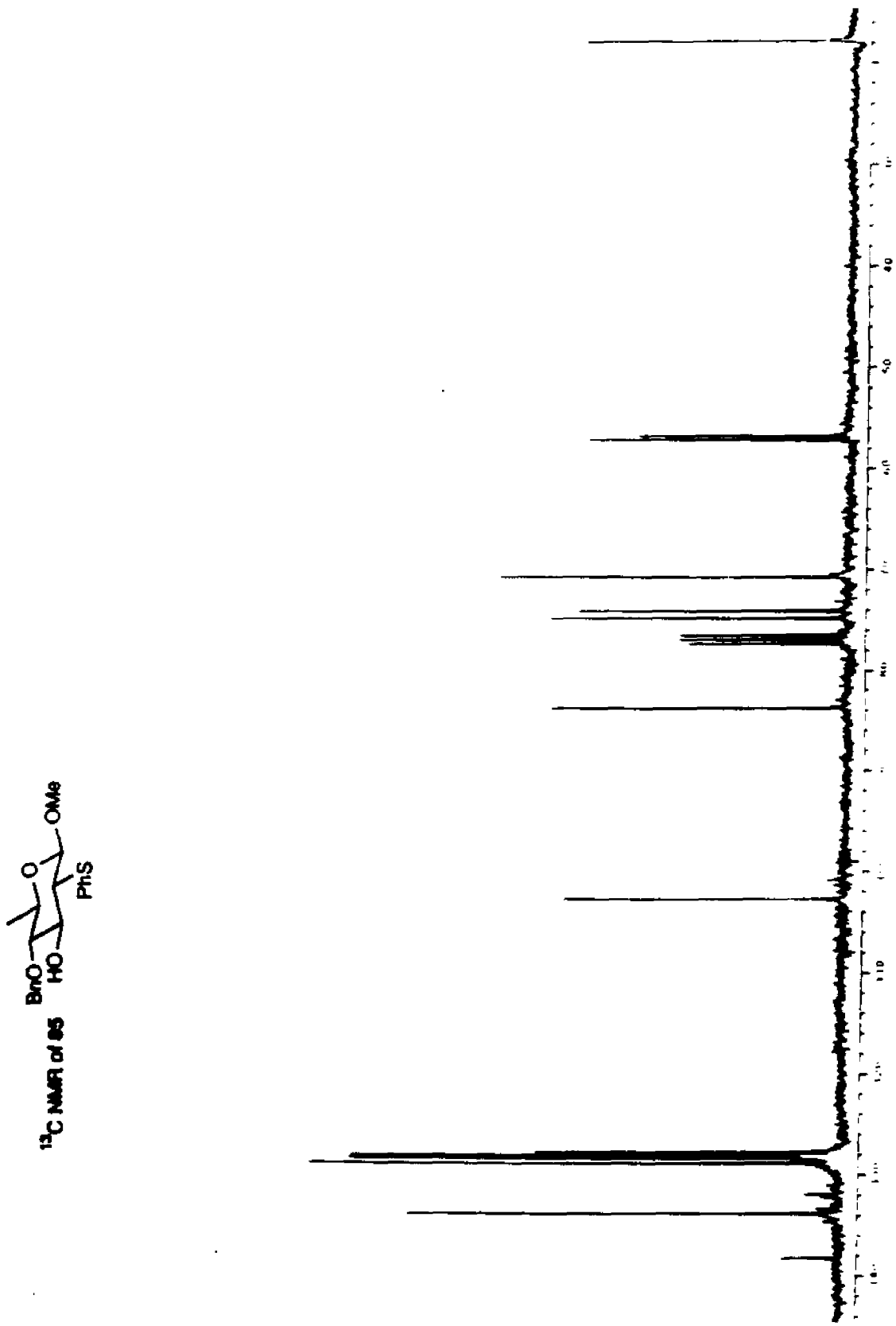


2D-NMR of β-84

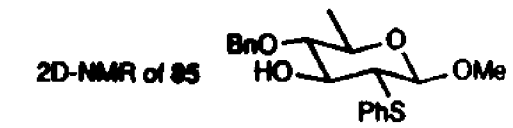
^{1}H NMR of 85

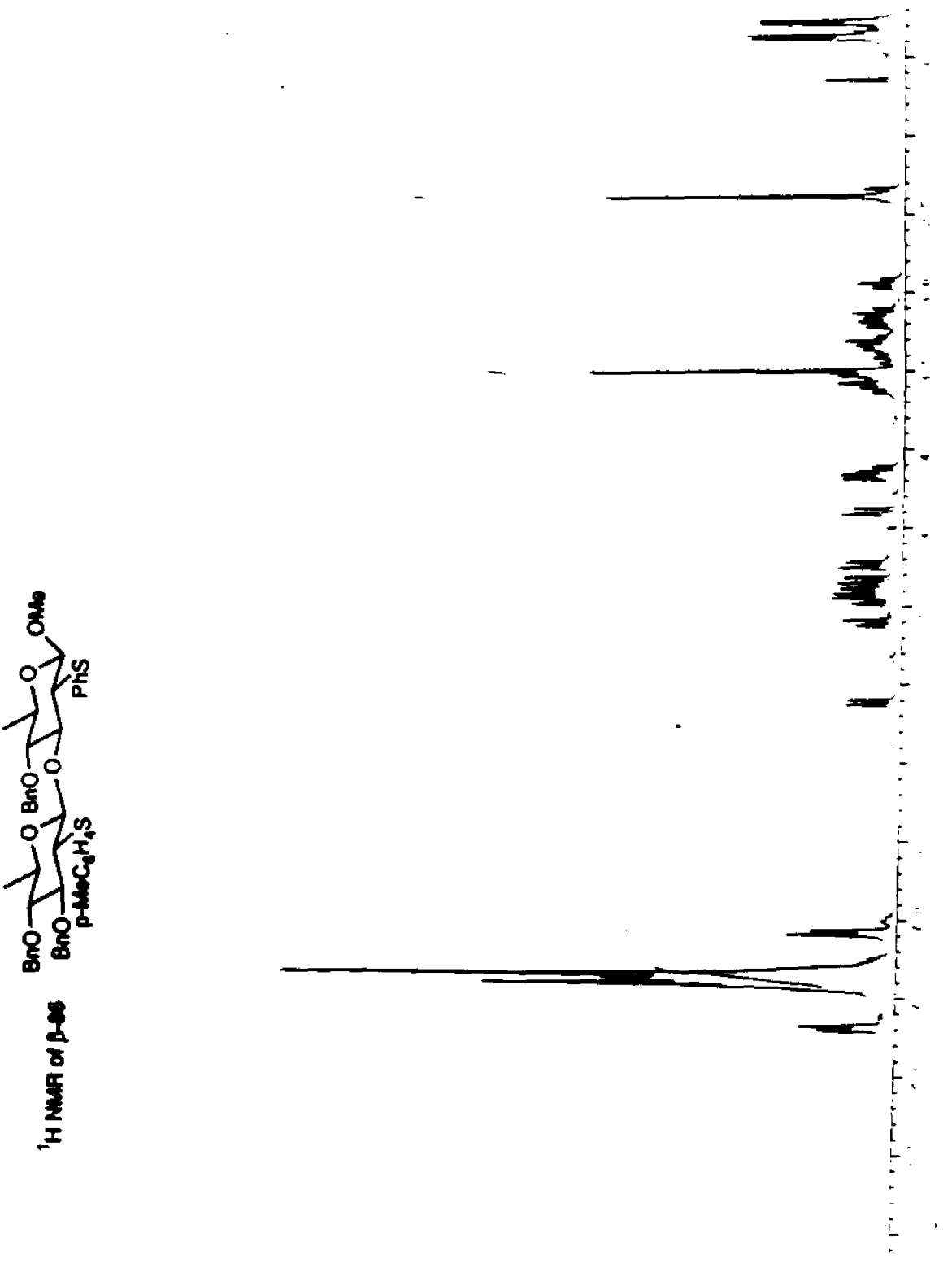


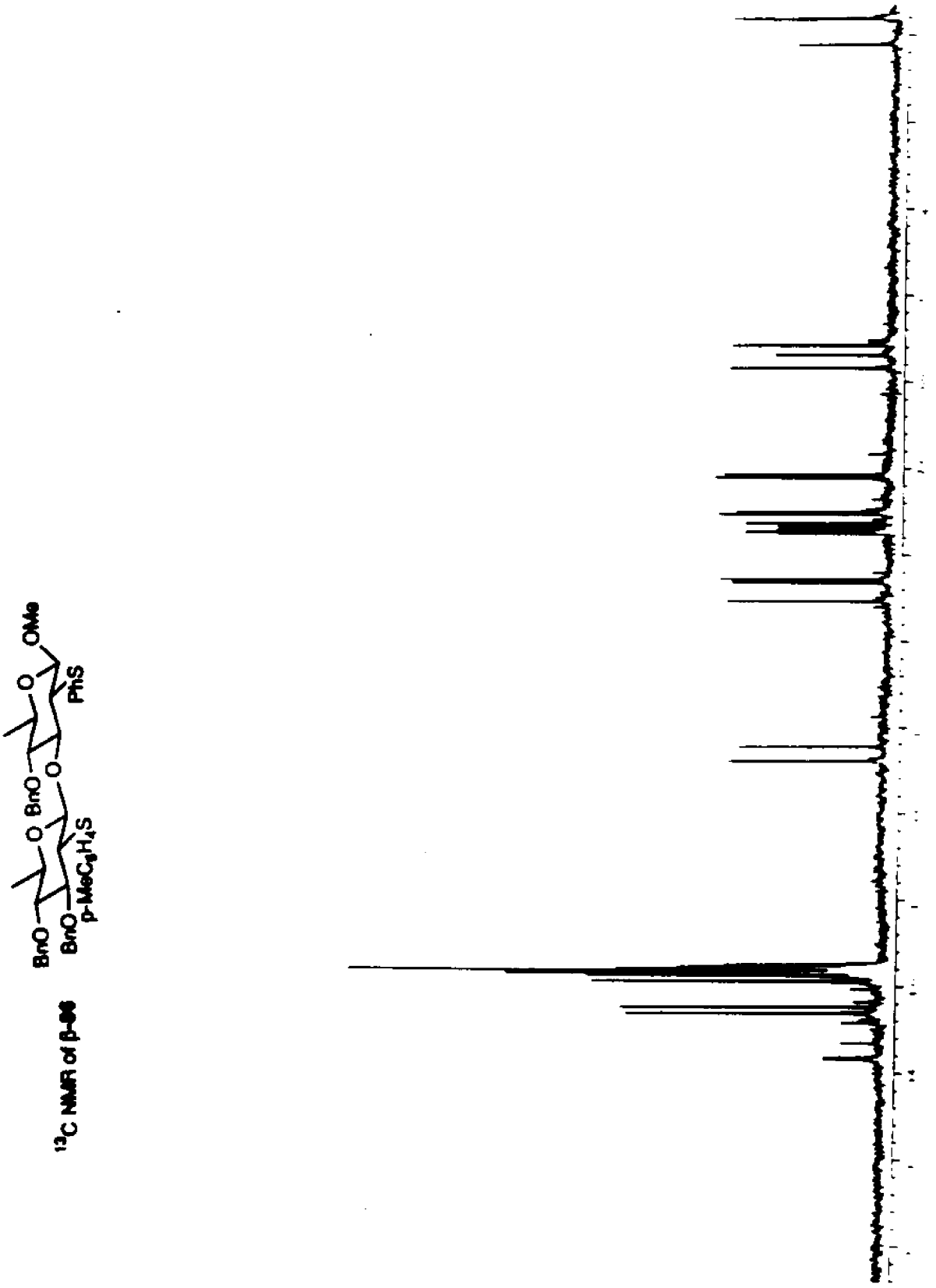


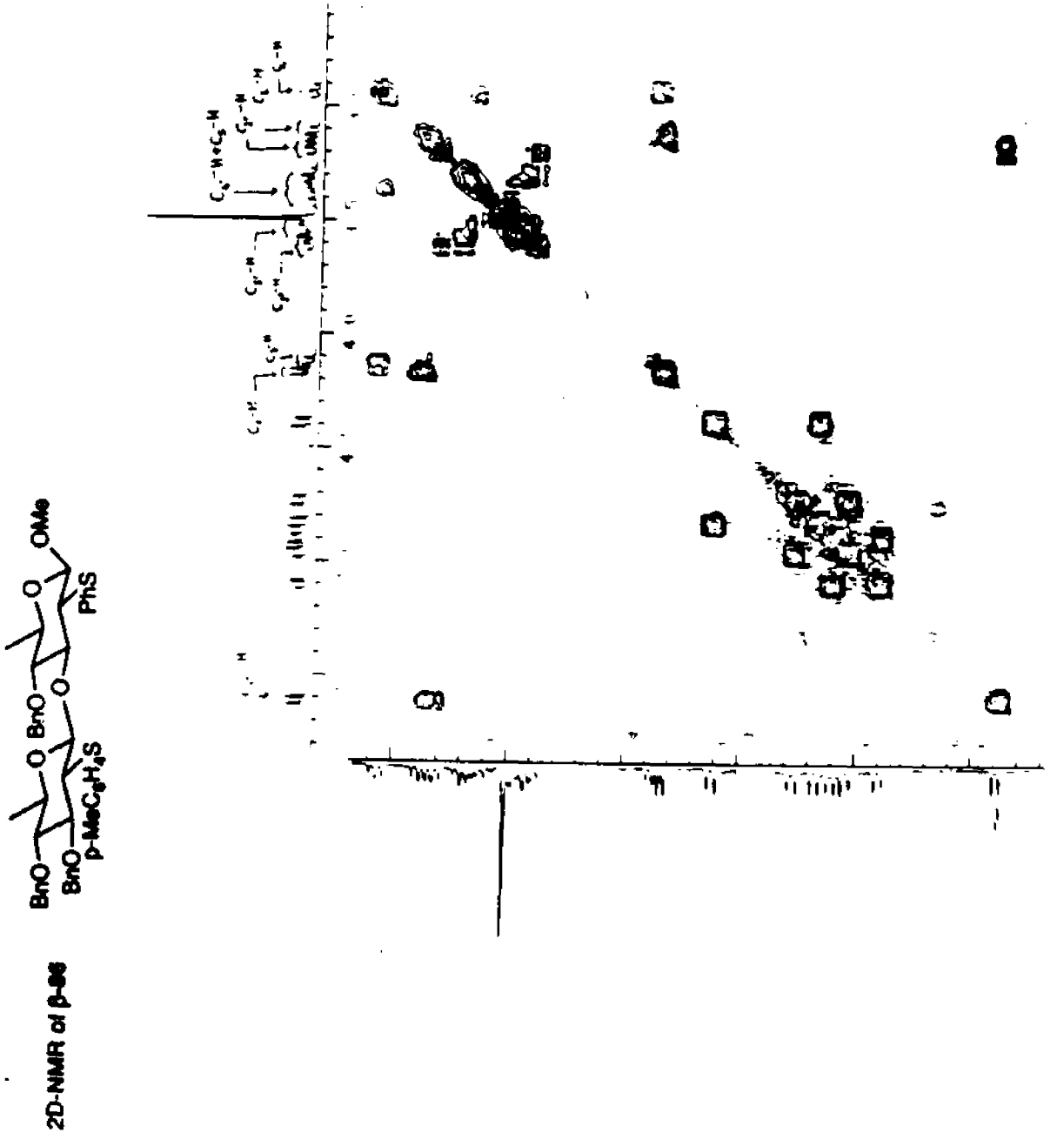

^{13}C NMR of 85
BnO
HO
O
OMe
PhS

2D-NMR of 85

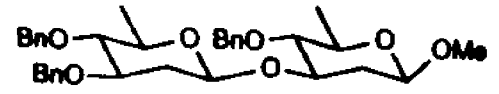


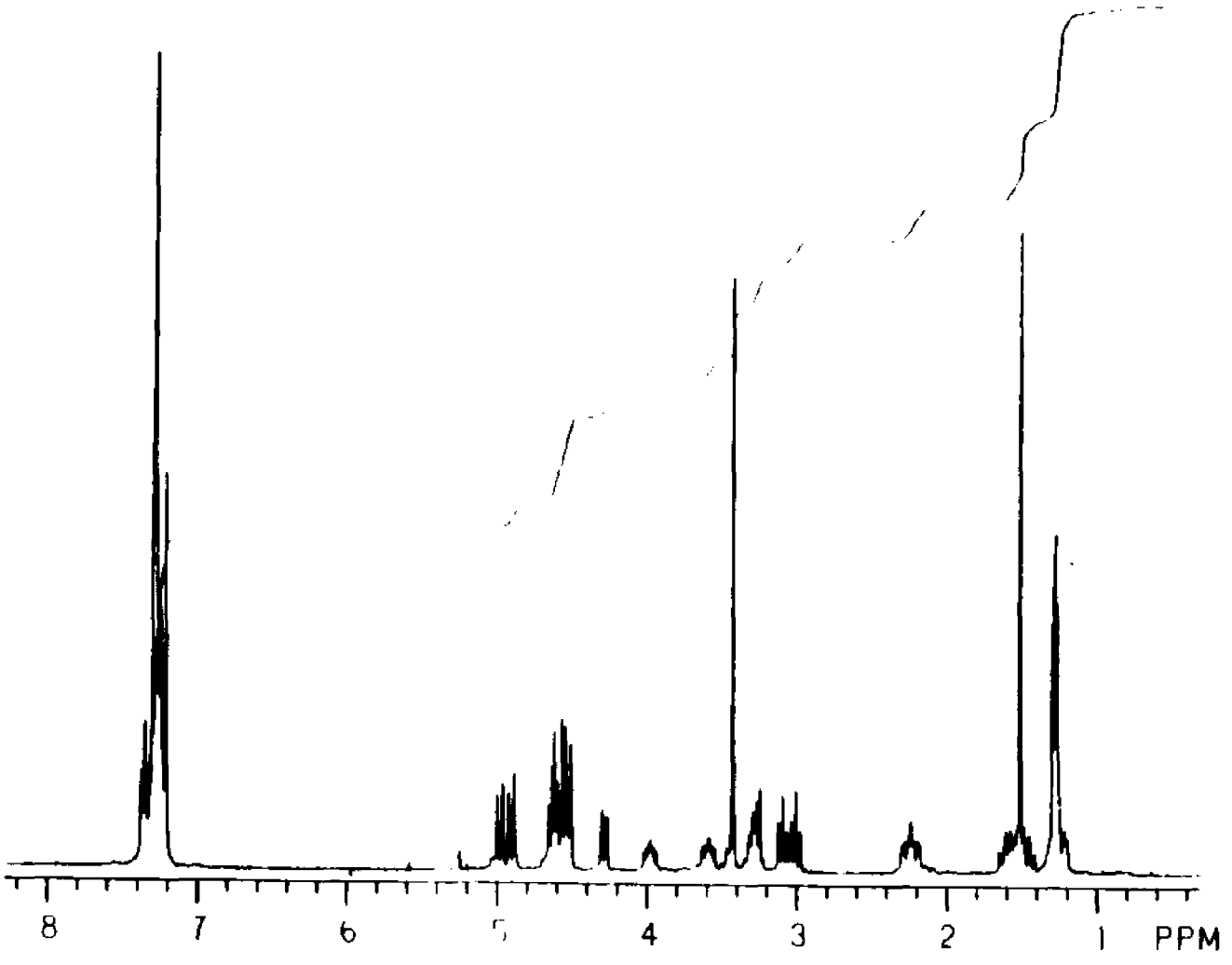

^{1}H NMR of β-86
BnO
BnO
p-MeoC$_6$H$_4$S
BnO
O
O
PhS
OMe


^{13}C NMR of β-68
BnO
BnO
p-MeC$_6$H$_4$S
O
BnO
O
O
PhS
OMe

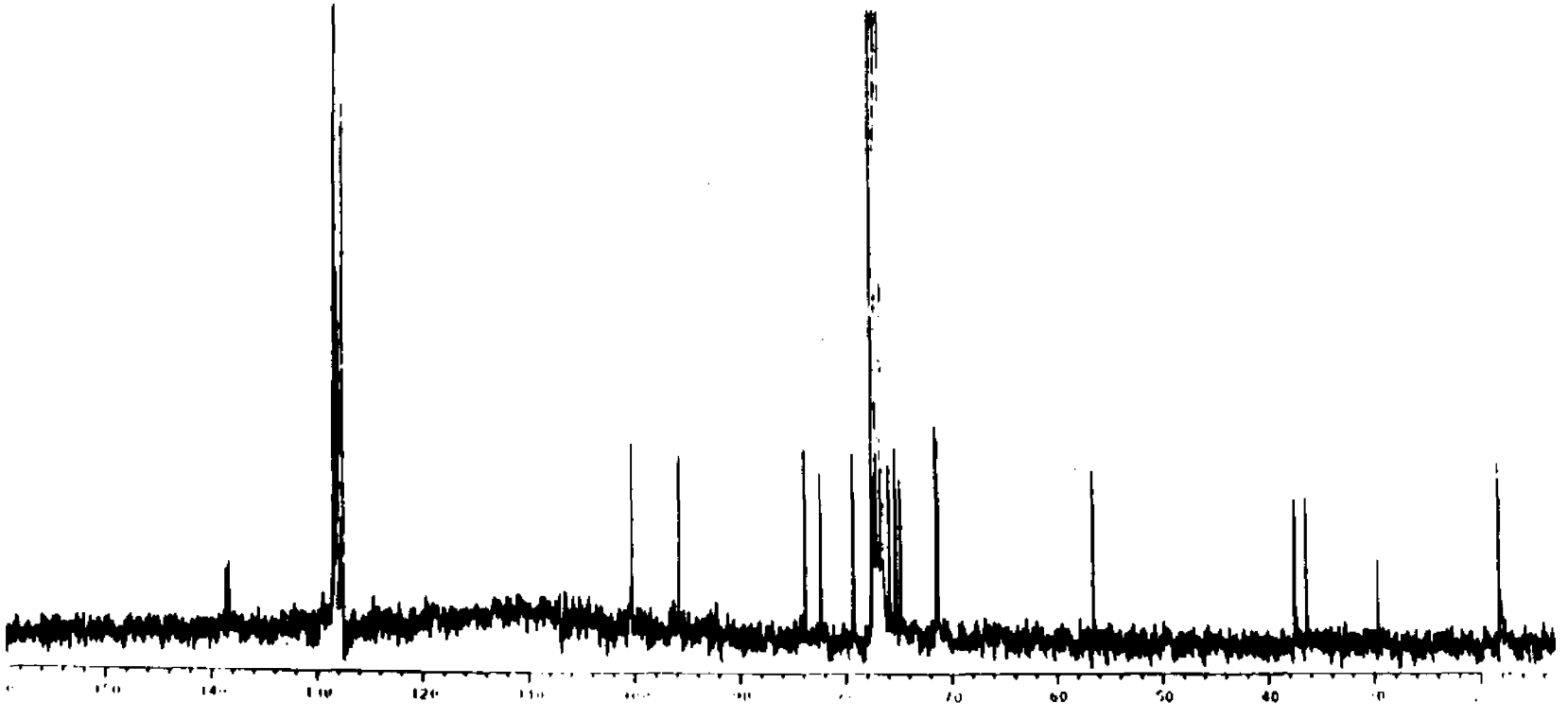

2D-NMR of β-86
BnO
BnO
BnO
p-MeC6H4S
PhS
OMe

^{1}H NMR of 87





^{13}C NMR of 87




PPM
5
4
3
2
1
2D-NMR of 87
BnO
BnO
BnO
OMe

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