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A

CYCLOADDITION FOR THE SYNTHESIS OF DISACCHARIDES

by

MARIA M. TAMAREZ

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

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THE CITY UNIVERSITY OF NEW YORK

ABSTRACT

CYCLOADDITION FOR THE SYNTHESIS OF DISACCHARIDES

By

Maria Tamarez

Adviser: Professor Richard W. Franck.

Disaccharides are active intermediates in many biological processes. Traditionally, these compounds are synthesized through the reaction of a carbohydrate precursor (glycosyl donor) and an incoming nucleophile (glycosyl acceptor) to provide a di- or oligo-saccharide. Both donors and acceptors are generally highly sensitive to the reaction conditions. For this reason, the development of optimal conditions for a particular donor and acceptor is often necessary.

Any method that can accomplish these syntheses under mild conditions will be well-received. This goal has been achieved in this project. We have developed the synthesis of disaccharides under practically neutral conditions.

The synthesis starts with the generation of a cycloadduct precursor of a disaccharide. Cycloadducts are obtained through the reaction of a chiral thiono-ketohexanolide with glycals of the allo, gluco, and galacto series. The chiral ketohexanolide was successfully obtained through enzymatic yeast reduction of the acetoacetylated Meldrum's acid. We obtained top face addition with the tribenzyl allal, and below face addition with the gluco and galacto glycals in high stereoselectivity and in reasonable isolated yield.

The C-S bond cleavage was the final stage in our cycloaddition and we developed the conditions for this desulfurization using W-2 Raney nickel. Under this standardized desulfurization procedure over-reduction and glycal elimination are avoided.

The cycloaddition between the chiral thiono-ketohexanolide and the 2-acetoxy tribenzyl glucal was also performed. Three regioisomers were isolated and fully characterized. These regioisomers are precursors of parasorboside, and two more steps, desulfurization and deprotection, could produce this natural product.

ACKNOWLEDMENTS

As I reach the end of this project, I look back and I cannot imagine how I could have ever finished it without the support of the two most important people in my life, the real heroes behind this work, my two children, Maria Eusebia and Juan Alejandro. They encouraged me to continue every moment that I was ready to quit. Whenever I doubted my potential to master the heavy work load of the Graduate School, they reminded me that I was smart and strong enough to handle it. Honestly, the only reason that I made it to the end, is the fact that I did not want to let my children down.

I am also very grateful to all the faculty members of the Graduate School that I have been fortunate to meet, especially my former mentor Dr. Valeria Balogh-Nair. She was the person that made my entrance into the Graduate School possible. She also taught me to be persistent and to persevere and for this I will never forget her.

I would like to thank my current mentor, Dr. Richard Franck, for opening the doors of his laboratory to me and for allowing me to work in this exciting project.

I would like to thank the two other members of my thesis committee David R. Mootoo and Dr. Vernon Box, and also to Dr. Klaus Grohmann, for all of their

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Finally, I would like to thank my parents, my four sisters, specially Lucia and Silvia, my brother Miguel and my sister-in-law, Dulce, for all of their encouragement during this difficult journey.

TABLE OF CONTENTS

I. INTRODUCTION.

II. RESULTS AND DISCUSSION.

A. Preliminary Studies.

B. Cycloaddition Studies with a single enantiomer of the Lactone.

IV. APPENDIX.

LIST OF TABLES

LIST OF FIGURES

I. INTRODUCTION.

A. Importance of Saccharide Synthesis.

Carbohydrate chemistry, and in particular the area related to monosaccharides and small oligosaccharides became very important in the mid-1950's, after the arrival of new synthetic and analytical methods for structure elucidation. The recognition of the importance of this class of molecules in many biological functions has generated an intense interest in developing new methods for their syntheses, both enzymatic and chemical[1,2].

B. Standard Glycosyl Transfer.

More than 90 % of all glycosylation reactions proceed through the activation of a carbohydrate precursor to become an electrophile[2,3]. This electrophile is transferred to a nucleophile to afford a glycoside. The most common ways to produce electrophiles are the modification of the anomeric center (figures 1.1 and 1.2) and the activation of a glycal, using oxygen, sulfur, selenium, halogen, proton, mercury, or nitrogen electrophiles (figure 1.3).

In the first approach, the anomeric configuration of the glycosidic bond is obtained in most cases by neighboring group participation from the C(2) substituent of the sugar, while in the latter configuration, it is regulated by the preferred facial attack of the electrophile on the particular glycal substrate[4]. The second approach, shown in figure 1.3, will provide 2-deoxy-2-*E*-(electrophile)-glycoside.

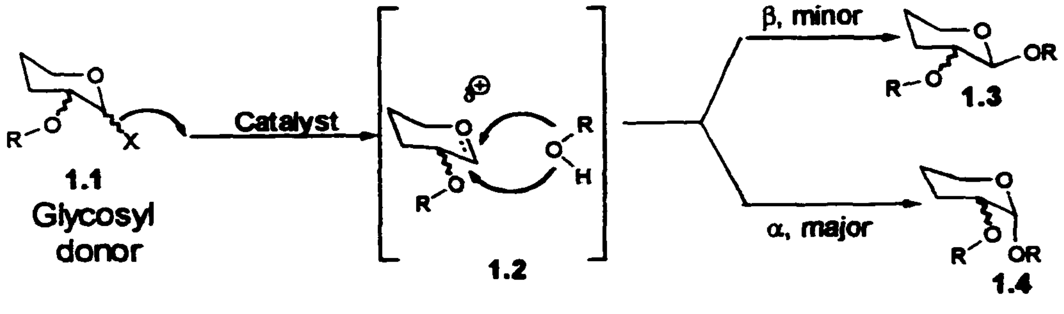


Figure 1.1 Standard Glycosyl Transfer: Non-participating Group.

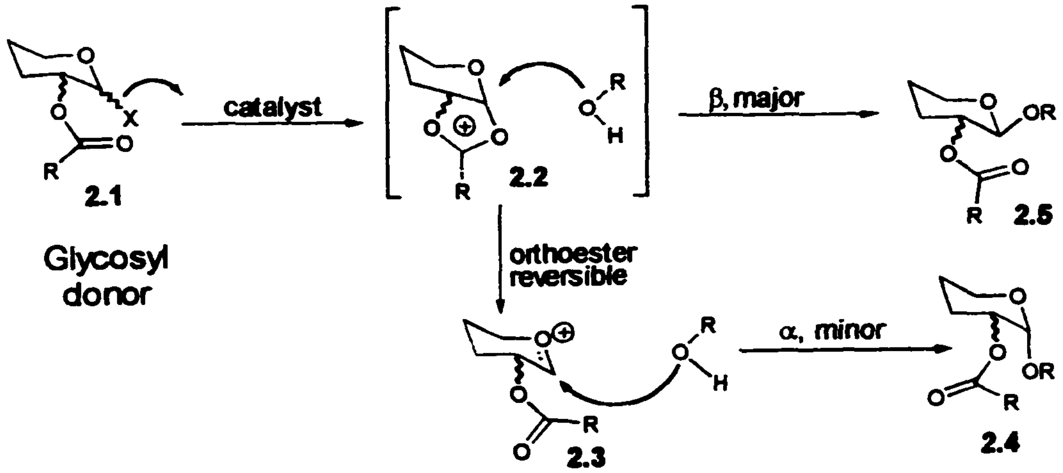


Figure 1.2 Standard Glycosyl Transfer: Participating Group.

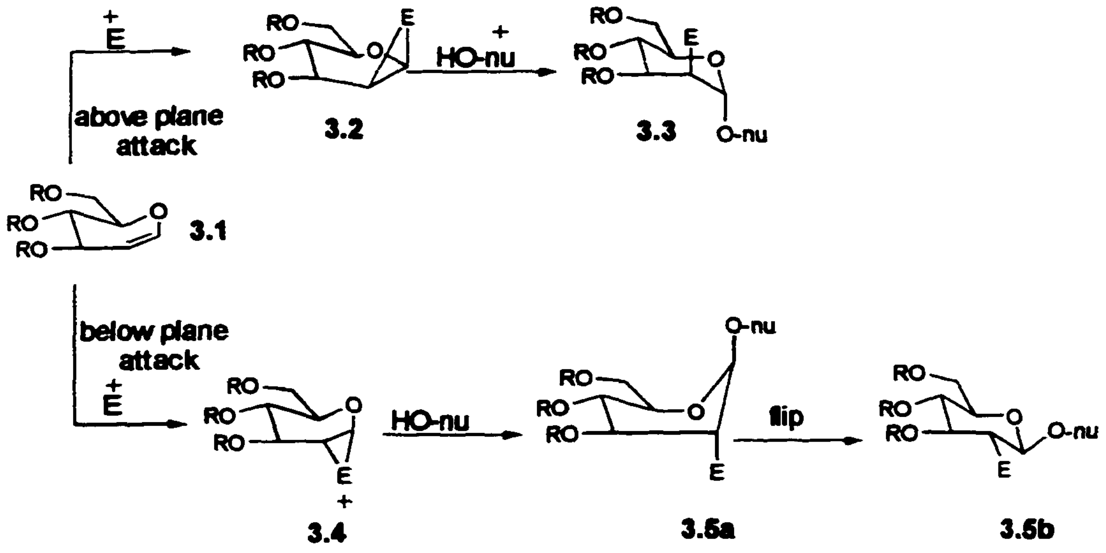


Figure 1.3 Electrophilic Attack on the Anomeric Center.

Figure 1.4 shows some of the glycosyl donors, which are similar to a number of existing methods. The most widely used donors[2] are trichloroacetimidates followed in order of decreasing use by thioglycosides, glycosyl bromides, glycosyl phosphorous derivatives, glycosyl fluorides, glycosyl chlorides, sulfoxides, 1,2-epoxides, pentenyl glycosides, anomeric acetates, seleno glycosides, xantates and reducing sugars. Anomeric diazirines are used most of the time to perform mechanistic glycosylation studies. All of these glycosyl donors have advantages and disadvantages. For example:

Trichloroacetimidate Donors. These donors can be activated with any protic or Lewis acid by coordination at the nitrogen lone pair. A possible disadvantage of

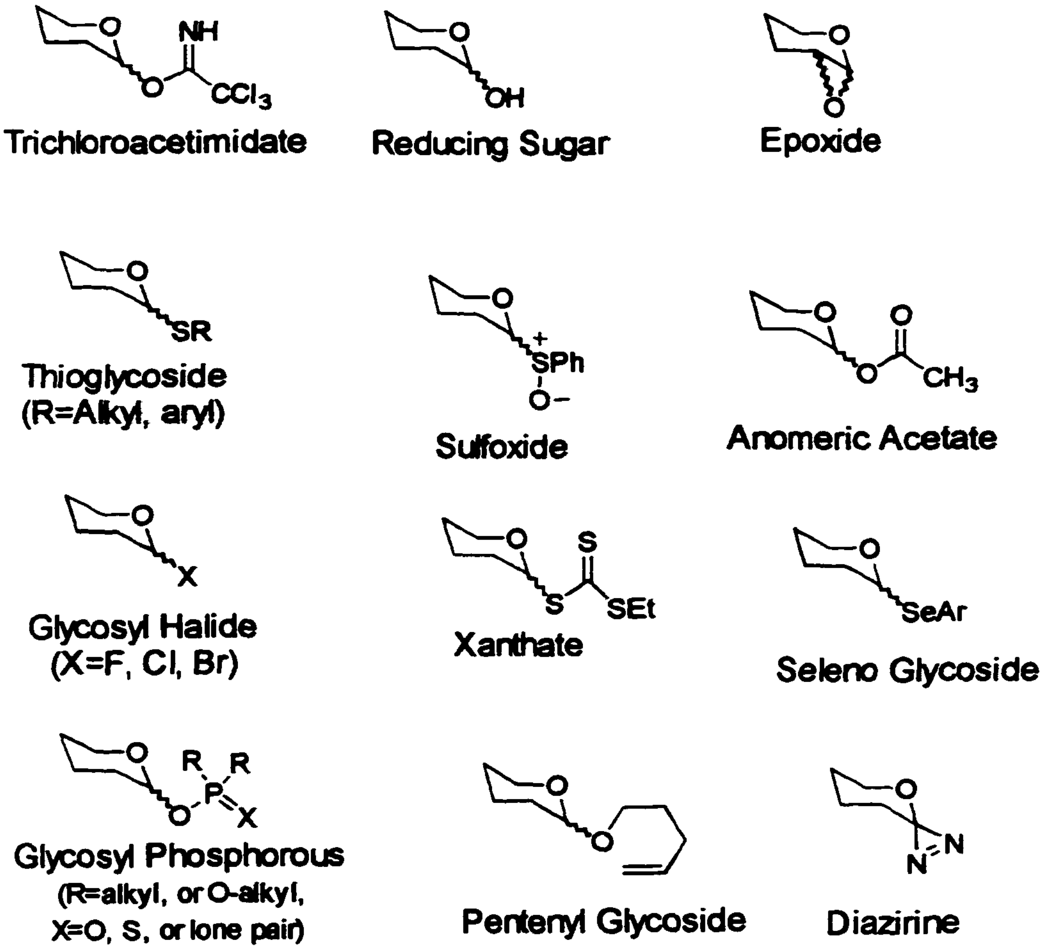


Figure 1.4 Common Glycosyl Donors.

this method is that the trichloroacetimidate is introduced as the last step of the synthesis of the donor and requires a free anomeric hydroxyl at that stage.

Thioglycoside Donors. This glycosylation procedure is very sensitive to reaction conditions and generally reaction conditions have to be optimized for each new reaction. The major advantage of thioglycosides is that the anomeric thio-functionality can be carried through all of the steps common to oligosaccharide synthesis and then the product is used as a glycosylation reagent. The down side is that the great nucleophilicity of the sulfur atom produces undesired side reactions.

Glycosyl Bromides. These classical Koenigs-Knorr donors are widely used and are very easy to prepare, but they are unstable under the reaction conditions. This results in elimination and therefore, a large excess of the donor is used which complicates the isolation of the final glycoside.

Glycosyl Fluorides. These can be generated either from reducing sugars or directly from thioglycosides. Their major advantage is that they are able to work under any reaction conditions.

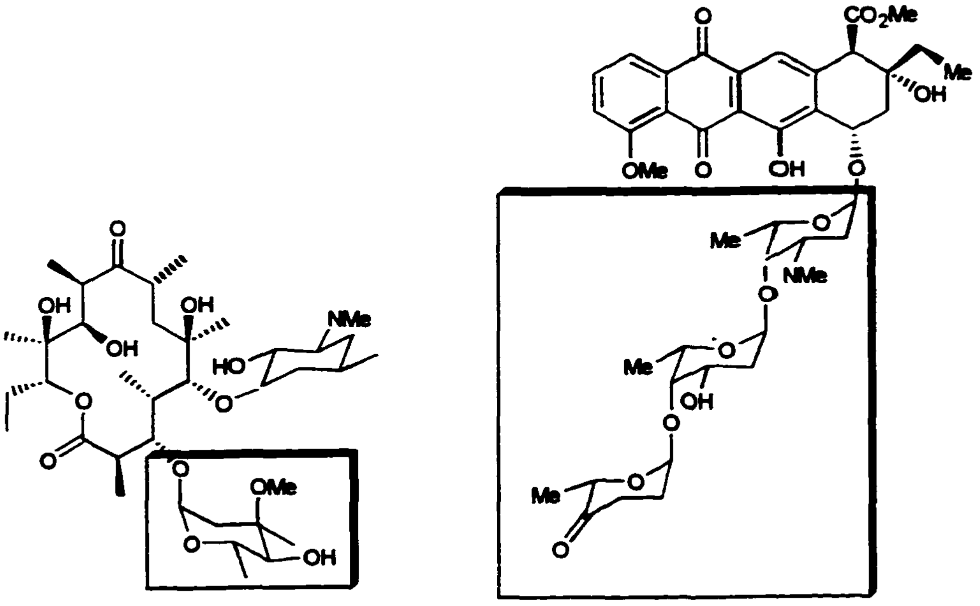
Glycosyl Chlorides. They are more stable than the bromides, and can be further purified before reaction.

Sulfoxides. The glycosylation with these donors can be performed at a very low temperature and all the reagents and products are soluble, which produces better anomeric product ratios. Unfortunately, the yield obtained is not superior to that obtained by the use of other methods and their use as glycosyl donors remains limited [2].

In general the mechanisms shown in figures 1.1 and 1.2 are very sensitive to the structure of both the glycosyl donors and acceptors. Any change in the leaving group X, under the reaction conditions, or change in the catalysts, can have dramatic effects on the yield and stereoselectivity of the glycosylation reaction[2].

C. Methods for the Synthesis of 2-Deoxy-glycosides.

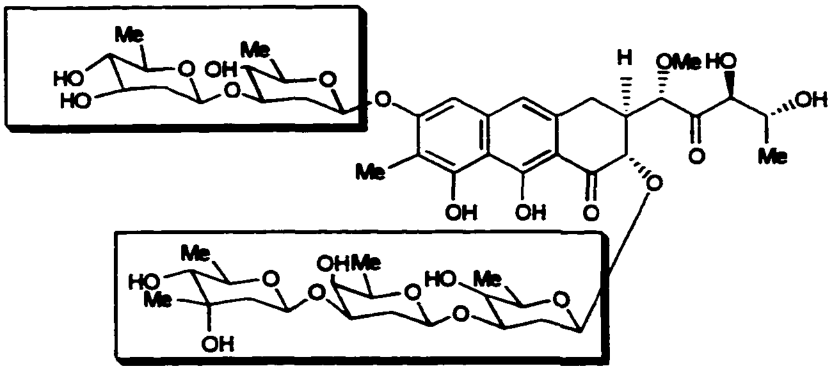
2-Deoxyglycosides are versatile synthetic intermediates. Several types of α- and β-2-deoxyglycosides are present in naturally occurring bioactive substances such as Erythromycin, Olivomycin A, Digitoxin, Aureolic acid, or more recently the enediynes antibiotics[3, 5-8], figure 1.5. All five of the glycosidic linkages of mithramycin are β.



Erythomycin A

Aclacinomycin

Figure 1.5 Natural Products with α,β-Deoxy Glycosidic Linkages.



Aureolic Acid

2-Deoxy-α-glycosides are generally prepared either by electrophilic glycosylation of hydroxyl donors with readily available glycals, or 2-deoxysugar glycosyl donors. In most of the cases, the product is easily obtained in high yield, although, the synthesis with glycals can result in 2,3-unsaturated glycosides, produced by allylic rearrangement (Ferrier reaction, figure 1.6)[9].

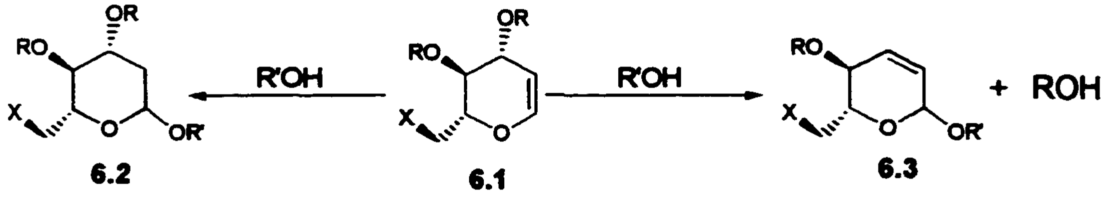


Figure 1.6 Ferrier Reaction.

While there are general methods available for the preparation of the 2-deoxy-α-glycoside, the efficient synthesis of 2-deoxy-β-glycoside has been a long-standing problem. The main problem in obtaining a highly stereocontrolled and efficient synthesis of the 2-deoxy-β-glycoside is the absence of stereodirecting anchimeric assistance from the C(2) position. To a lesser extent, the low stability of a glycosidic bond of a 2-deoxy sugar, under the normal acidic glycosylation conditions[3], can also be problematic.

Nevertheless, many different procedures have been developed for the synthesis of 2-deoxy-β-glycosides[10,11]. One of the more common approaches involves the use of a temporary participating group at C(2). For example, 2-deoxy-β-glycosides are obtained with the use of 2-bromo-2-deoxy-glycosyl bromides. When these donors are heated with silver triflate, the C(2)-bromo acts as a participating group. This substrate is subsequently removed to give a 2-deoxy product. This method and the NIS methodology were used in the syntheses of aureolic acid oligosaccharides[12]. Other temporary participating groups at the C(2) position are thiophenyl, selenophenyl and N-formyl[13-15]. One of the most successful procedures for the direct synthesis of a 2-deoxy-β-glycoside from a 2-deoxy precursor is the silver silicate mediated reaction of alcohols and 2-deoxypyranosyl bromides, but the selectivity of this method depends on the protecting groups at C(3) and C(4) of the donor and on the reactivity of the acceptor[16-18]. The anchimeric assistance of an α-p-methoxybenzoyl group at the C(3) position can also afford, in some cases, β-selectivity[19-22]. Conformationally rigid glycosyl donors, which posses a thio bridge between the C(2) and the C(6) positions, are used for the highly stereoselective syntheses of both α- and β-2-deoxy glycosides. Another highly stereoselective synthesis of 2-deoxy-β-glycosides involves the nBu_3SnH reduction of a radical generated at the anomeric position. However, yields are usually very low[23,24a]. Roush and co-workers recently developed a highly stereoselective procedure for the synthesis of aryl-2-deoxy-glycosides via the Mitsunobu reaction[25]. A versatile procedure uses the opening 1,2-anhydro sugars to provide the aryl β-glycoside with excellent selectivity and in good yield. These products are readily deoxygenated via radical chemistry to the aryl 2-deoxy-β-glycosides[24b]. The TMS-OTf promoted 1,2-trans-glycosidation reaction of phosphoroamidate donors is another procedure for the synthesis of 2-deoxy-β-glycosides[24c].

D. The Aureolic Acids and the Search for a New Glycosylation Method.

The aureolic acid group of antibiotics inhibit DNA-dependent RNA polymerase and are active against Gram-positive bacteria, DNA viruses, and certain tumors. Extensive studies have demonstrated that the sugar chains of these antibiotics are essential for binding in the complex. Since sugars play an important role in binding to DNA, modifications can be done for a better understanding of the mechanism of interaction of DNA and any developed drug[27]. The total synthesis of the aureolic acid antibiotics has been one of the goals of the Franck's laboratory since 1980. Parallel to this goal was the need to develop a more general glycosylation procedure. This goal was reached with the arylbis(arylthio)sulfonium salts as a highly stereoselective reagent for the synthesis of 2-deoxy-β-glycosides[26]. The down side of this method is the instability of the reagent above -60 °C due to the nucleophilicity of the sulfur atom. Therefore, the search for a more practical glycosylation procedure was still on going.

The key reaction in the total synthesis of crytosporin was a highly stereoselective inverse electron demand cycloaddition of an isoquinoline salt on a glycal. Notable aspects of this reaction were the high facial selectivity and the mild reaction conditions[28].

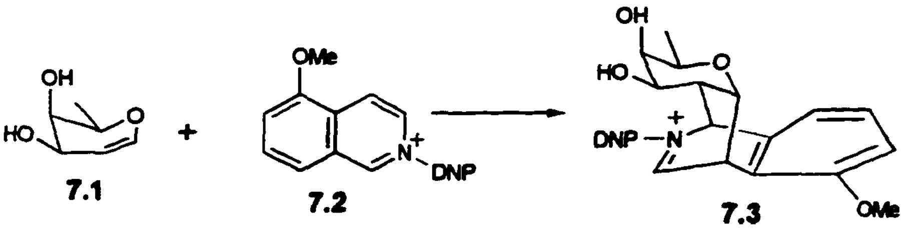


Figure 1.7 Crytosporin Key Reaction.

This reaction provided the idea of using the cycloaddition of a glycal and a heterodiene for glycosyl activation and transfer. However, the first experiment performed with the thione-oxo heterodiene 8.2 derived from a Bunte salt, and tribenzyl glucal failed, probably because self dimerization proceeded at a much faster rate than the cycloaddition [29].

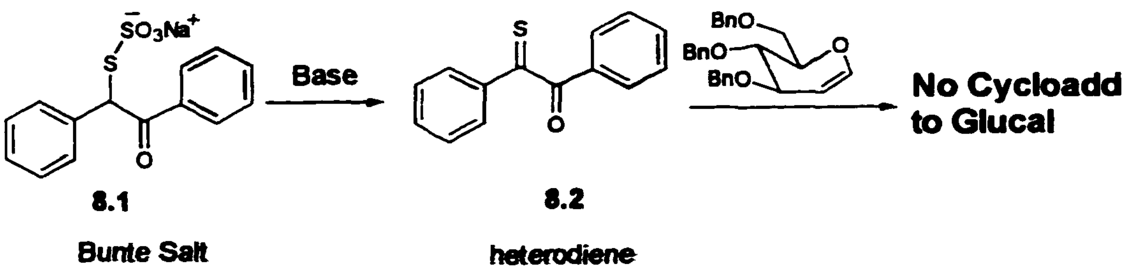


Figure 1.8 Experiment with a Bunte Salt.

A year after this failed experiment, Capozzi and co-workers published a reaction based on this same principle[30].

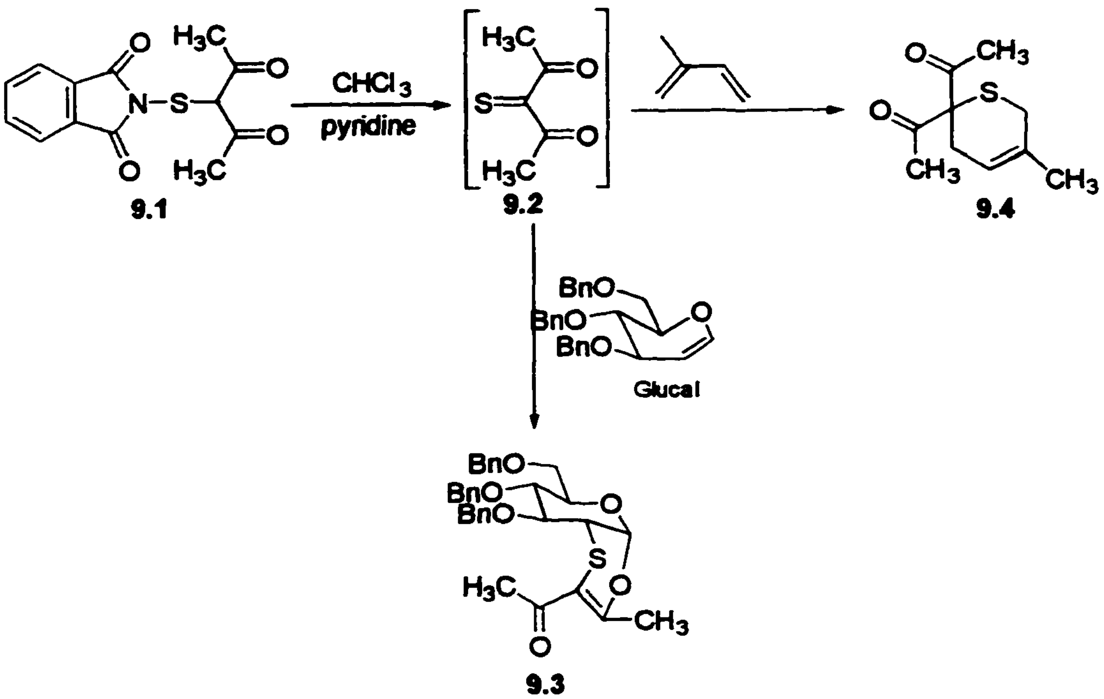


Figure 1.9 Capozzi's Successful Experiment.

In a common effort, he performed the same reaction using tribenzylglucal as the dienophile and this reaction which we have reproduced successfully [31], is the keystone in our novel glycosyl transfer method.

E. Cycloaddition for Glycosyl Transfer: General Concept.

In this general concept of glycosylation, a sugar-like dienophile, **10.1**, undergoes inverse electron demand cycloaddition with a heterodiene, **10.2**, to provide a cycloadduct, **10.3**. This cycloadduct can be further manipulated in two different pathways, *a* or *b*. Pathway *a* will afford a glycoside simply by reduction of the X-C(2) bond while *b* will afford the glycoside upon ring opening of the adduct by any nucleophile (R_1OH).

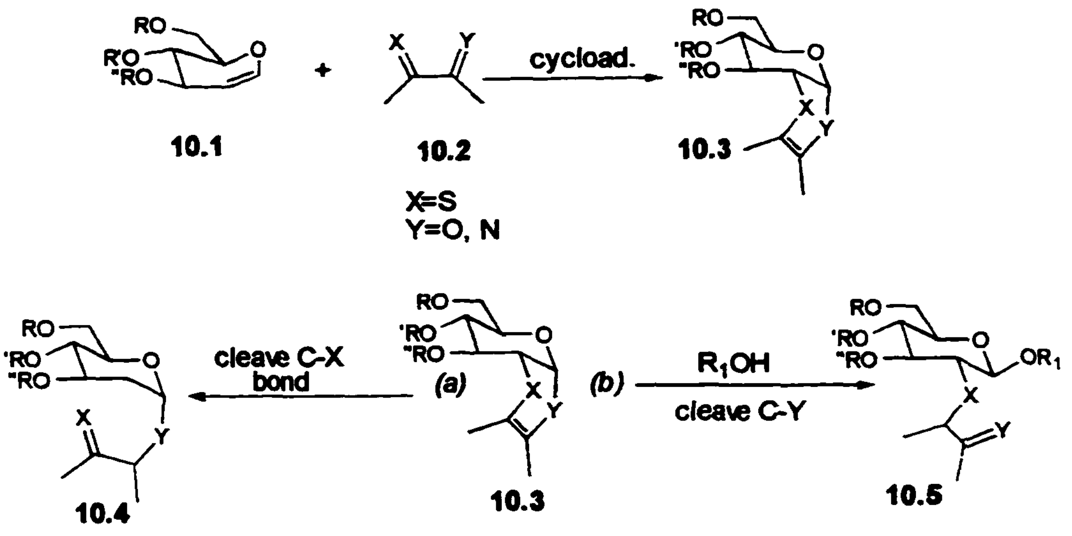


Figure 1.10 Cycloaddition for Glycosyl Transfer: General Concept.

F. Specific Aim of this Research Project.

Cycloaddition for the syntheses of disaccharides was the main goal of this research project. Preliminary cycloaddition studies between the oxothione derivatives of a cyclic and an acyclic ketone as well as a ketohexanolide and tribenzylglucal will be described. The synthesis of the chiral ketohexanolide (11.1), an important synthetic intermediate, was performed. Further cycloaddition reactions between the oxothione derivative of the chiral ketohexanolide were carried out with glycals from the allo, galacto, and gluco series. Top face addition with the allo series and below face addition with the galacto and the gluco series, were expected in high stereoselectivity following from preliminary studies.

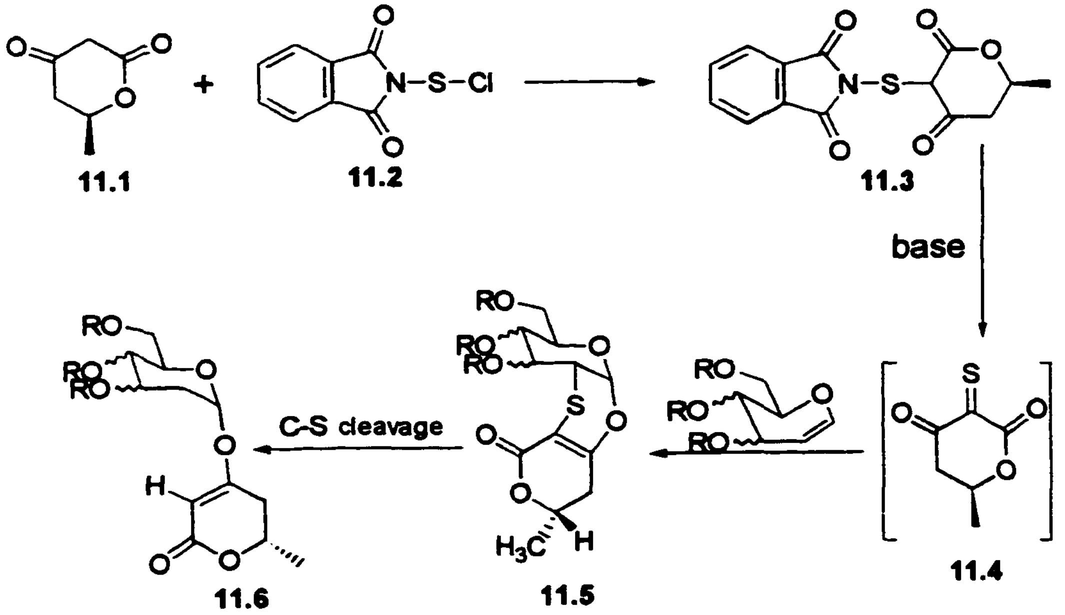


Figure 1.11 Research Goal Illustration.

Since the C-S bond cleavage is the final stage for the formation of the disaccharide, the development and optimization of the reaction conditions for C-S bond cleavage in the cycloadducts was another goal of this project.

Finally, all of these results were applied to the synthesis of the natural product, Parasorboside (figure 1.12), a disaccharide whose aglycone part is identical to the ketohexanolide **11.1**.

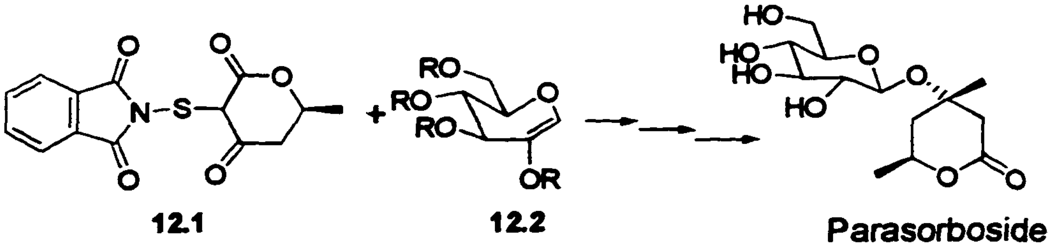


Figure 1.12 Parasorboside.

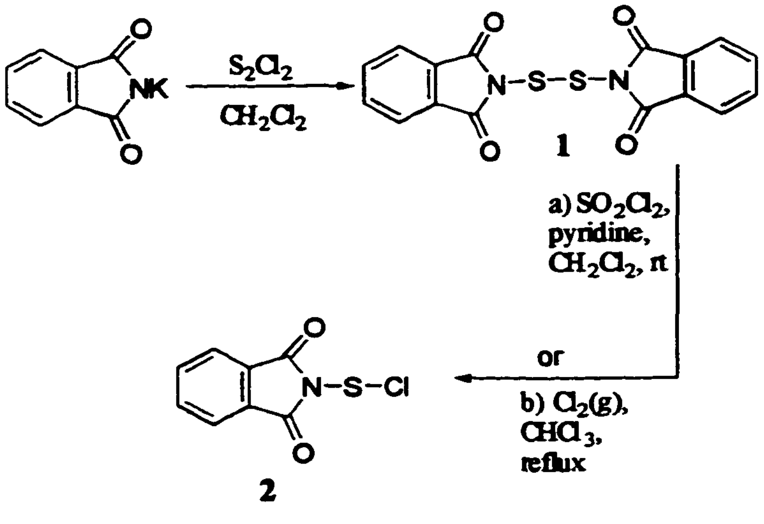
II. RESULTS AND DISCUSSION

A. Preliminary Studies.

2.1 Synthesis of Phthalimido Sulfenyl Chloride.

The phthalimido sulfenyl chloride **2** was prepared in quantitative yield in two different ways[32,33] (scheme1). The first way was through bubbling Cl_2(g) into a solution of disulfide **1**. This pathway produced the product in quantitative yield, but since Cl_2 (g) is very corrosive, it was necessary to install traps of aqueous NaOH to quench the unavoidable excess of Cl_2 coming from the reaction flask. On the other hand, the preparation using sulfuryl chloride was easier, but it had the disadvantage that the product obtained decomposed much faster upon storage at 0 °C. The product obtained through chlorine gas remained very pure even after one year. It is possible that the presence of SO_2Cl_2 used in excess, which is difficult to eliminate by rotary evaporation, promoted this faster decomposition.

Scheme 1

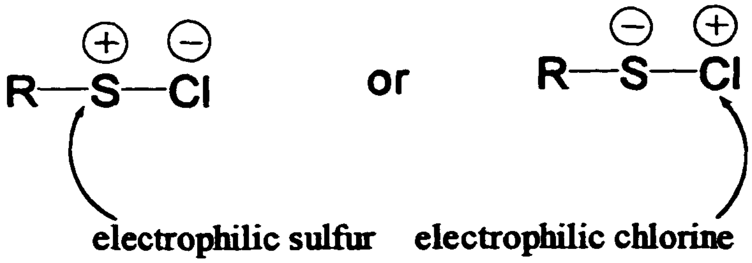


The sulfenyl chloride, 2, can be distinguished from the disulfide precursor 1 by the ^{13}C NMR. For the sulfenyl chloride, the C=O signal is at 165.59 ppm, while for the disulfide it is at 166.97 ppm (see appendix).

Once the sulfenyl chloride was available, we proceeded to the synthesis of the thioketo derivatives. We started with the commercially available 2,4-pentanedione.

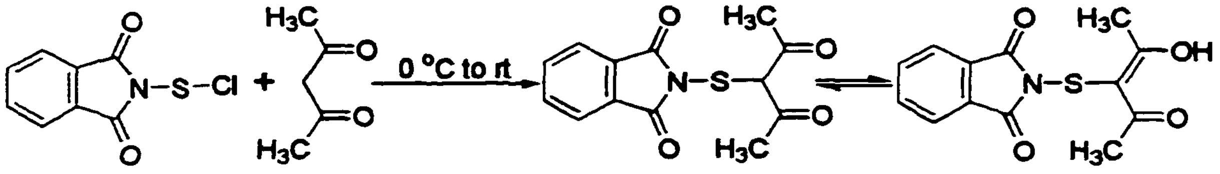
2.2 Reaction of Phthalimido Sulfenyl Chloride with 2,4-Pentanedione.

The sulfenyl chloride functional group behaves as a pseudo halogen[32], it polarizes in the same way:



In phthalimido sulfenyl chloride 2 the sulfur is highly electrophilic. It reacts with various nucleophiles (alcohol, alkene, etc.). Sulfenyl chloride reacts with 2,4-pentanedione to give the sulfino-pentanedione 3. The reaction was carried out at 0 °C, using the 2,4-pentanedione as the solvent[30] and was completed in less than 30 minutes. The yield of sulfino-pentanedione 3 was 51 % after recrystallization of the crude from $CHCl_3$: Petroleum ether.

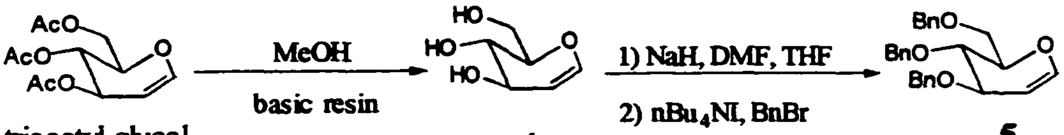
Scheme 2



2 2,4-pentanedione 3-keto 3-enol

Figure 2.1 shows the ^{1}HNMR in $CDCl_3$ of the sulfino-pentanedione **3**. The enol proton appears at 17.71 ppm, as a consequence of the hydrogen bonding with the carbonyl oxygens. Hydrogen bonding decreases the electron cloud around the enol proton and moves the absorption further downfield[34].

Scheme 3



triacetyl glucal **4** **5**

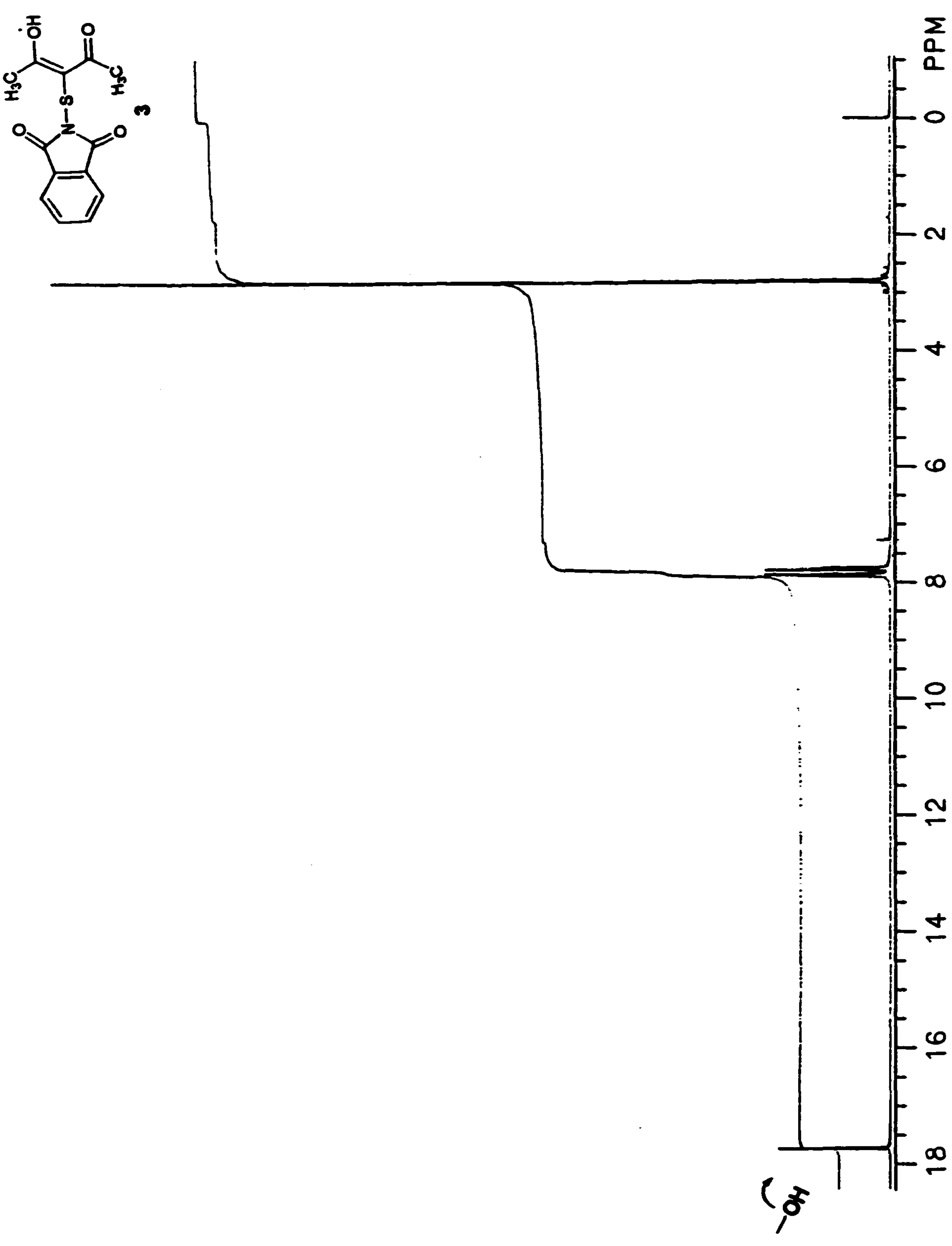
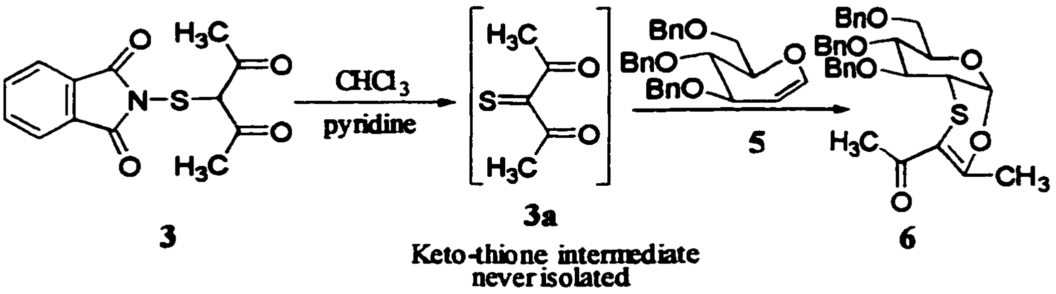


Figure 2.1 ^{1}H NMR of Sulfino-pentanedione 3.

2.3 Cycloaddition of sulfino-pentanedione 3 with tribenzylglucal.

Tribenzyl glucal **5**, synthesized according with scheme 4, was reacted with a mixture of **3** and pyridine in chloroform. The base is required for the elimination of phthalimide to form the reactive thione derivative **3a**, which has neither been isolated nor detected by ^{1}HNMR. The thione derivative **3a** is then trapped by tribenzylglucal, acting as the dienophile to afford the cycloadduct **6**[30].

Scheme 4

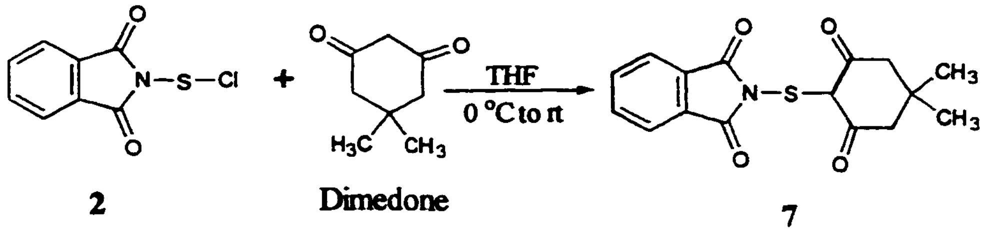


The yield of the tribenzylglucal adduct **6** after stirring for 7 days at room temperature was 94 % based on the reacted glucal. The molar relationship was ketothiono:glucal:pyridine 1:1:6. The reaction was completely stereoselective[31]. The total reaction time was decreased to 17 hours when the cycloaddition was carried out in refluxing chloroform. Longer refluxing time gave decomposition products.

2.4 Cycloaddition with Dimedone.

After the cycloaddition with the acyclic ketone, the next step was to try a cyclic one. Dimedone was chosen because of the similarity with 2,4-pentanedione. The formation of the sulfino-dimedone was much slower than the acyclic 2,4-pentanedione. Dimedone is a solid with low solubility in most solvents, which made necessary the use of a dilute solution, contrary to the 2,4-pentanedione, which is used as the solvent.

Scheme 5



The IR of sulfino-dimedone 7 in KBr is shown in figure 2.2. The carbonyl stretching band appears at 1742 cm^{-1} which is the "normal" absorption for ketones[34]. This value clearly indicates that sulfino-dimedone 7 exists mostly in the keto form. For an enolized β-diketone in which the carbonyl is conjugated with a double bond the absorption is from 1685 to 1666 cm^{-1}. The enol form was detected by the sharp band at 3204 cm^{-1}, which is characteristic of alcohols with intramolecular hydrogen bonding. The enol content of 2,4-pentanedione is 80 %. The enol form is stabilized by internal hydrogen bonding and by conjugation of the enolic double bond with the carbonyl[35]. The cyclic form of dimedone prevents the stabilization of its enol form by hydrogen bonding. This lack of enolization is probably responsible for the more slow reactivity of dimedone toward phthalimido sulfenyl chloride 2, which react by addition of the electrophilic sulfur atom to the enol double. The ^{1}HNMR, in $CDCl_3$, of sulfino-dimedone 7 shows the enol proton at 3.7 ppm. The ^{1}HNMR, in DMSO-d_6, coalesces the four aromatic protons of the phtalimide residue into a singlet (see appendix).

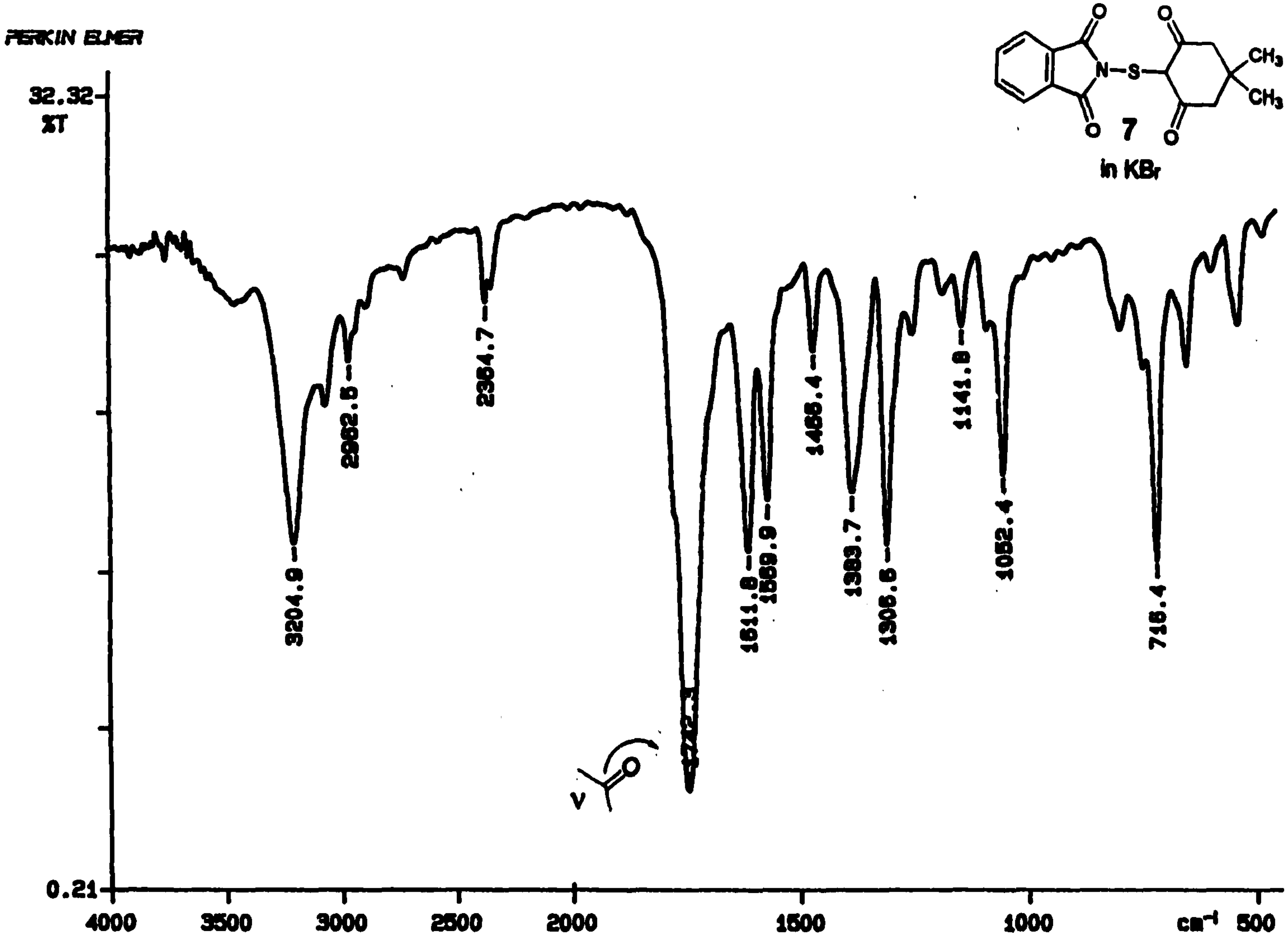
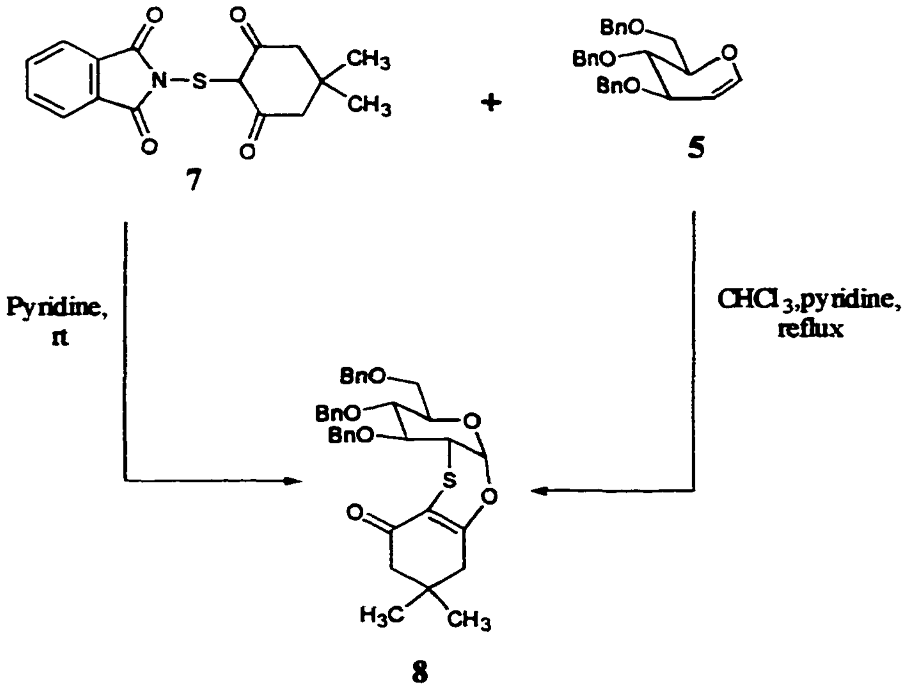


Figure 2.2 IR in KBr of Sulfino-dimedone 7.

Scheme 6



Due to the lack of solubility of the sulfino-dimedone 7 in most solvents, the cycloaddition with tribenzylglucal was run in neat pyridine at room temperature (scheme 6). In 7, the conversion of glucal to the cycloadduct 8, was less than in the pentanedione case, presumibly due to the slow rate of thiono-keto formation. The isolated yield of the product was 10-18 %. Figure 2.3 shows the most relevant signals in the ^{1}HNMR of compound 8.

In a similar way to 2,4-pentanedione, the reaction time was decreased considerably and the yield improved when the reaction was carried out in refluxing chloroform. After 3 days, the conversion of glucal to product was greater than 75 % (^{1}H NMR ratio), and the yield of the isolated cycloadduct 8 was 28 %.

A variety of reaction conditions at room temperature failed to improve the yield. These results are summarized in the following table.

Table 1

Cycloadditon with thiono-ketone derived from 7

Entry	*Thiono-ketone:glucal:base*	*Conditions:Solvent/base*	*% yield*
1	2:1:20	$CHCl_3$/pyridine	No product
2	2:1:4	THF/2,6-Lutidine	No product
3	2:1	DMSO/Lutidine/Pyridine	10.1
4	2:1:xs	Neat pyridine	18.4
5	2:1:12	$CHCl_3$/pyridine/Reflux	28.3

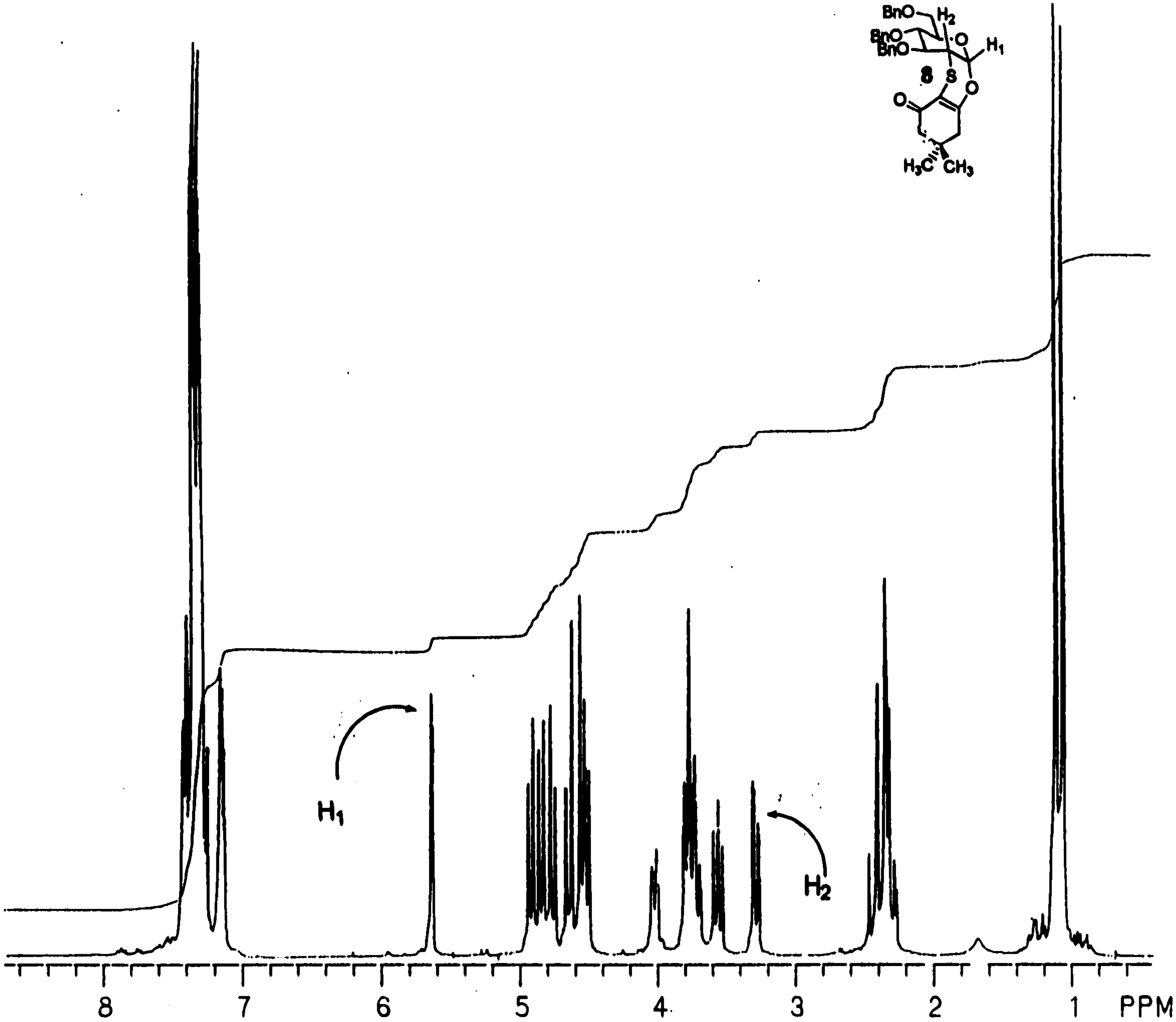
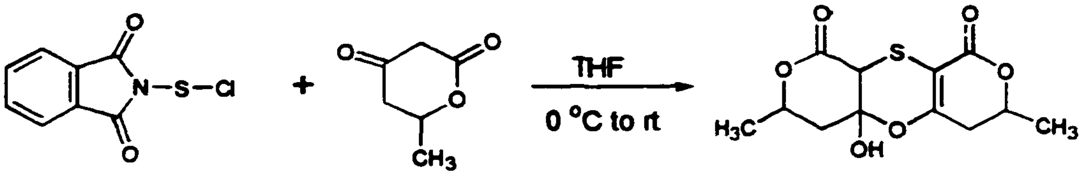


Figure 2.3 ^{1}H NMR of Dimedone-tribenzyl glucal adduct 8.

2.5 Cycloaddition with the Racemic Lactone 9.

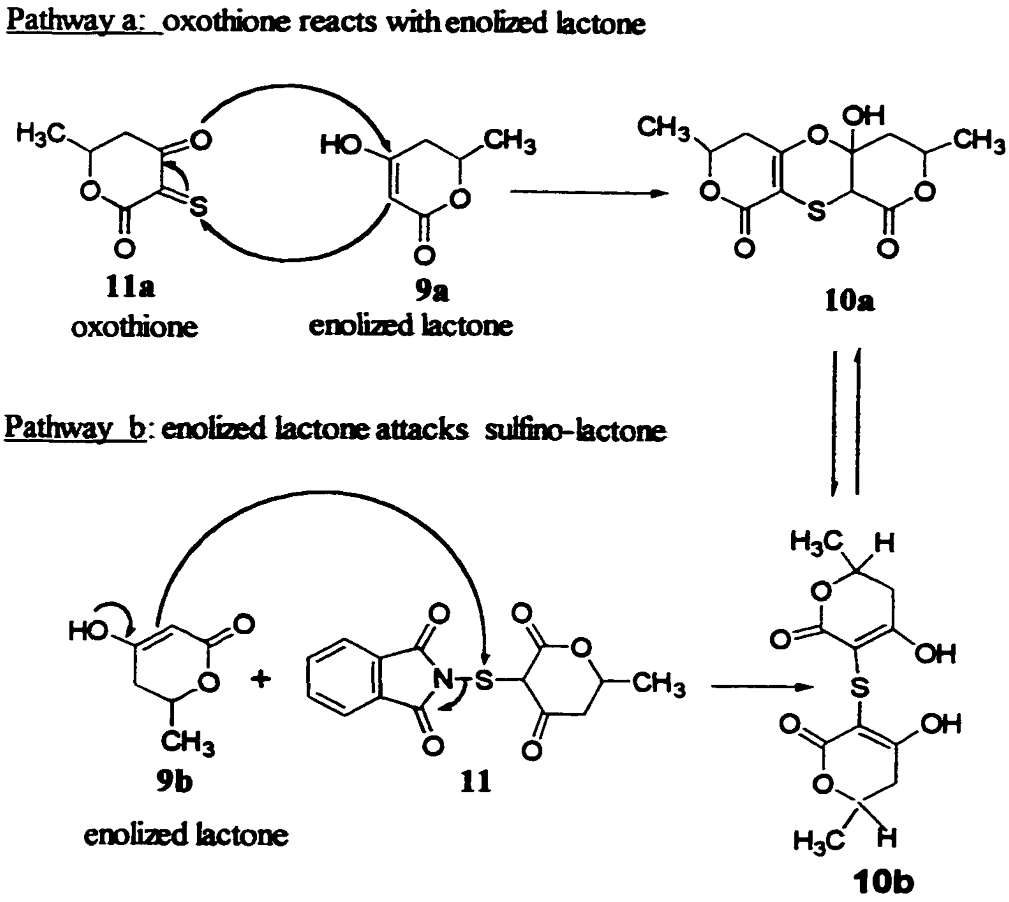
In view of these results, it looked promising to try a ketolactone, and the 5,6-dihydro-4-hydroxy-6-methyl-2H-pyran-2-one 9, available from Aldrich, was chosen. The cycloaddition started with the synthesis of the sulfino-lactone 11, from sulfenyl chloride 2 (scheme 8). At 0 °C, following the literature procedure, only the dimerized product 10 was isolated.

Scheme 7



2 **(R/S)-9** **10**

Its formation may follow the mechanistic pathway a or b in figure 2.4. The formed oxothione **11a** reacts with the enolized lactone **9a** (alkene) in a way similar to the glycal, or the enolized lactone **9b** (nucleophile) will attack the electrophilic sulfur of the sulfino-lactone **11**. The oxothione **11a** could be easily produced by the removal of a hydrogen by Cl⁻, generated when the sulfenyl chloride **2** reacts with the ketolactone **9**. The dimerized product was identified by its mass spectrum, and by its simple proton nmr (figure 2.5) which suggests a dimer such as **10b** or its ring chain isomer **10a** (figure 2.4).



Pathway a: oxothione reacts with enolized lactone

11a
oxothione

9a
enolized lactone

10a

Pathway b: enolized lactone attacks sulfino-lactone

9b
enolized lactone

11

10b

Figure 2.4 Proposed Mechanisms for the Dimerization.

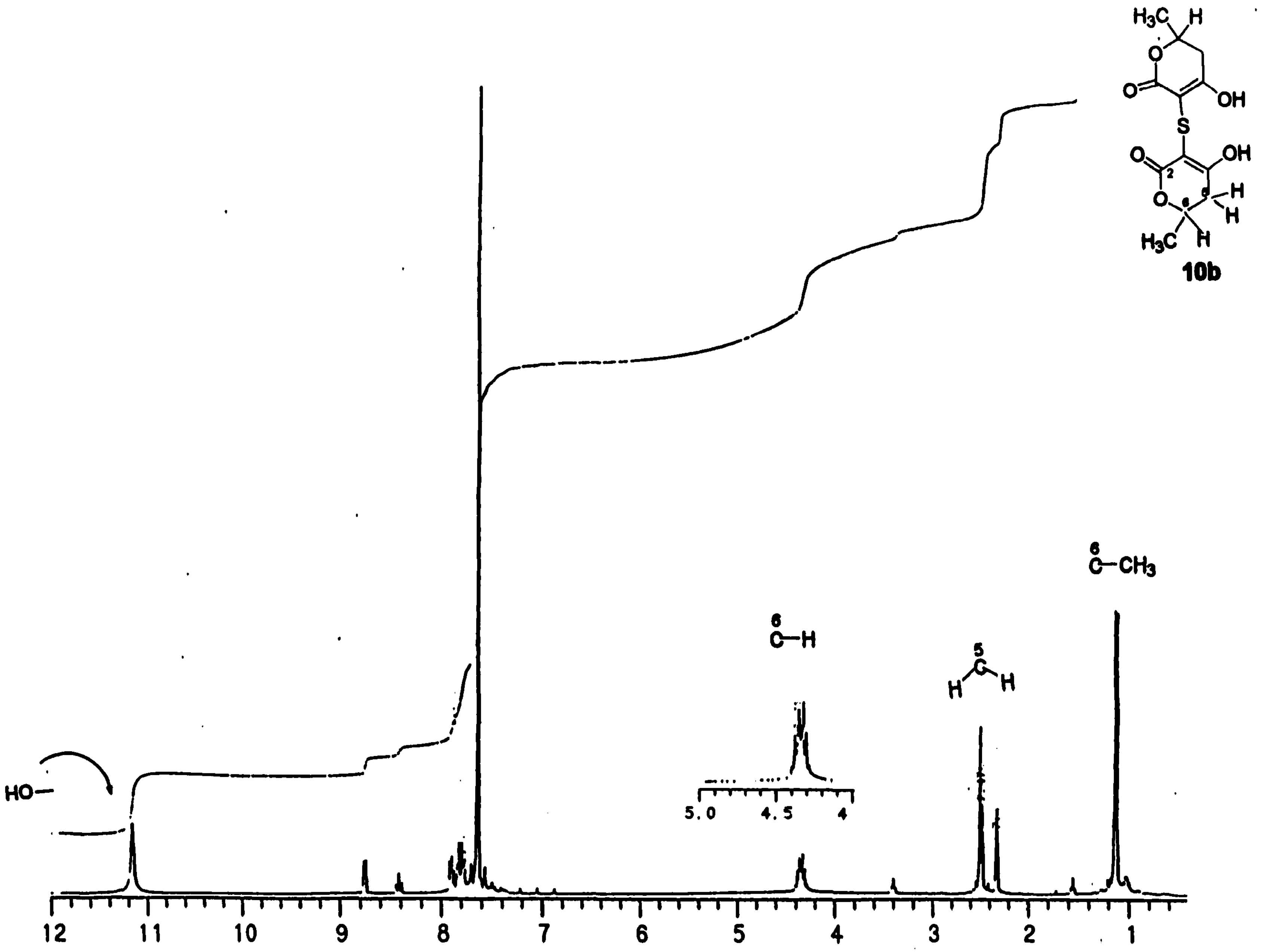
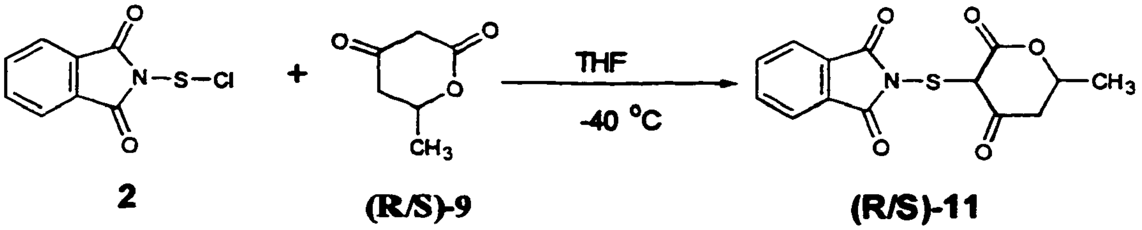


Figure 2.5 ^{1}H NMR of the Dimerized Lactone **10b**.

In order to obtain the desired product, it was necessary to modify the literature procedure. The sulfenyl chloride was dissolved in dried THF under a N_2 atmosphere using precautions to exclude air, and cooled to -40 °C. The lactone was then added dropwise to the solution, thereby keeping the concentration of the lactone low at all times, so that it could react only with the sulfenyl chloride that is in excess in solution. The crude yield was quantitative, but recrystallization decreased it to 41 %, due to decomposition of the reactive sulfino-lactone **11** during the recrystallization.

Scheme 8



The recrystallized product **11** was in the keto form while the crude product is found predominantly in the enol form. This indicates that the lactone is capable of existing in equilibrium with the keto and enol form. The keto form is the major tautomer in $CHCl_3$ or CCl_4 while the enol form is the predominant one in DMSO[36]. This tautomeric equilibrium has been detected in the ^1H NMR of **11** in $CDCl_3$.

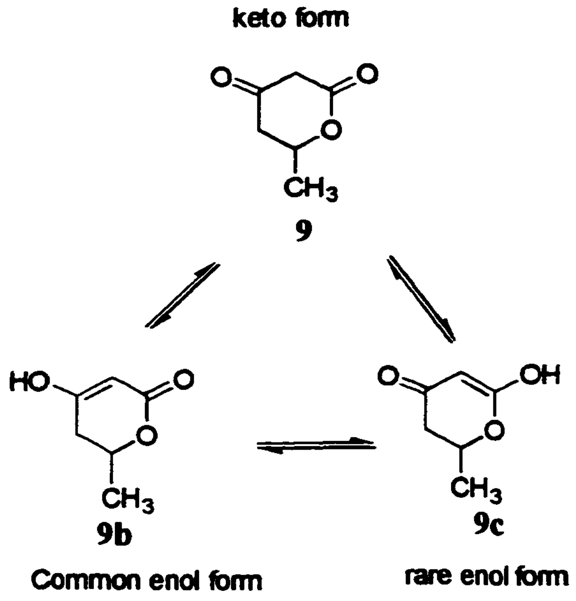
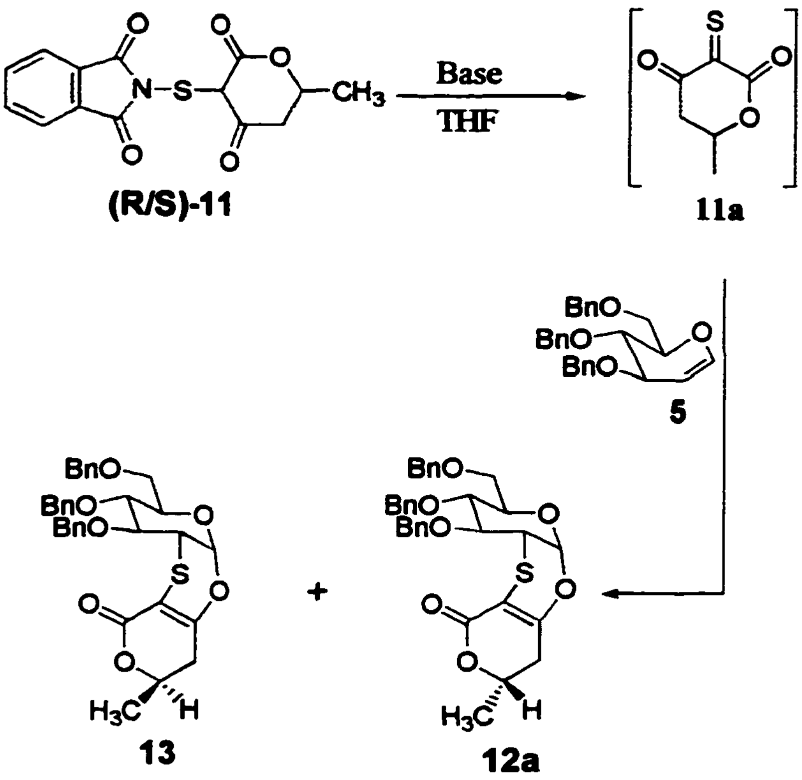


Figure 2.6 Keto-enol Tautomerization of the Lactone **9**.

The cycloaddition with the racemic sulfino-lactone, performed under the conditions specified in scheme 9, gave a 53.5 % 1:1 mixture of diastereomers (quantitative yield, based on the recovered glycal), inseparable by flash column chromatography. Further separation by silica gel preparative plate, eluting several times with 3:1 petroleum ether:ethyl acetate, provided both diastereomers **13** and **12a** as white foamy solids. This separation was later done by chromatotron plate, starting elution with 9:1 hexane:ethyl acetate and increasing to 5:1.

Figures 2.7 and 2.8 show the ^{1}H NMR of both diastereomers. The anomeric proton for compound **13** appears at 5.59 ppm with a coupling constant $J_{1,2}$ = 2.7 Hz, and for compound **12a** this signal comes more downfield at 5.72 ppm, with the coupling constant $J_{1,2} = 3$ Hz. This value is typical for an axial-equatorial coupling constant.

Scheme 9



The C(2) proton in adducts **13** and **12a** appears at 2.37 and 3.2 ppm respectively as a well-defined doublet of doublets (dd). This is due to the coupling to the axial hydrogen at C(3) ($J_{a\text{-}a}$) and the equatorial anomeric proton at C(1) ($J_{a\text{-}e}$). These values indicate a below face addition of the oxothione **11a** to the glycal **5**. Again the position of the C(2) proton is consistant with a proton attached to a carbon bearing a sulfur atom. Another signal which is characteristic of these adducts is that corresponding to the methyl group of the lactone residue. This signal appears at 1.38 ppm with a coupling constant J = 6.3 Hz.

The structure of compound **13** was further confirmed via X-ray crystallography. Figure **2.8a** shows the crystal structure of compound **13** with the sulfur atom attached to C(2) and the ketone oxygen of the lactone participating in the cycloaddition. In addition, the methyl group is in the position that corresponds to the **R**-enantiomer. Compound **12a** was later identified through the synthesis of the S-enantiomer of the chiral lactone.

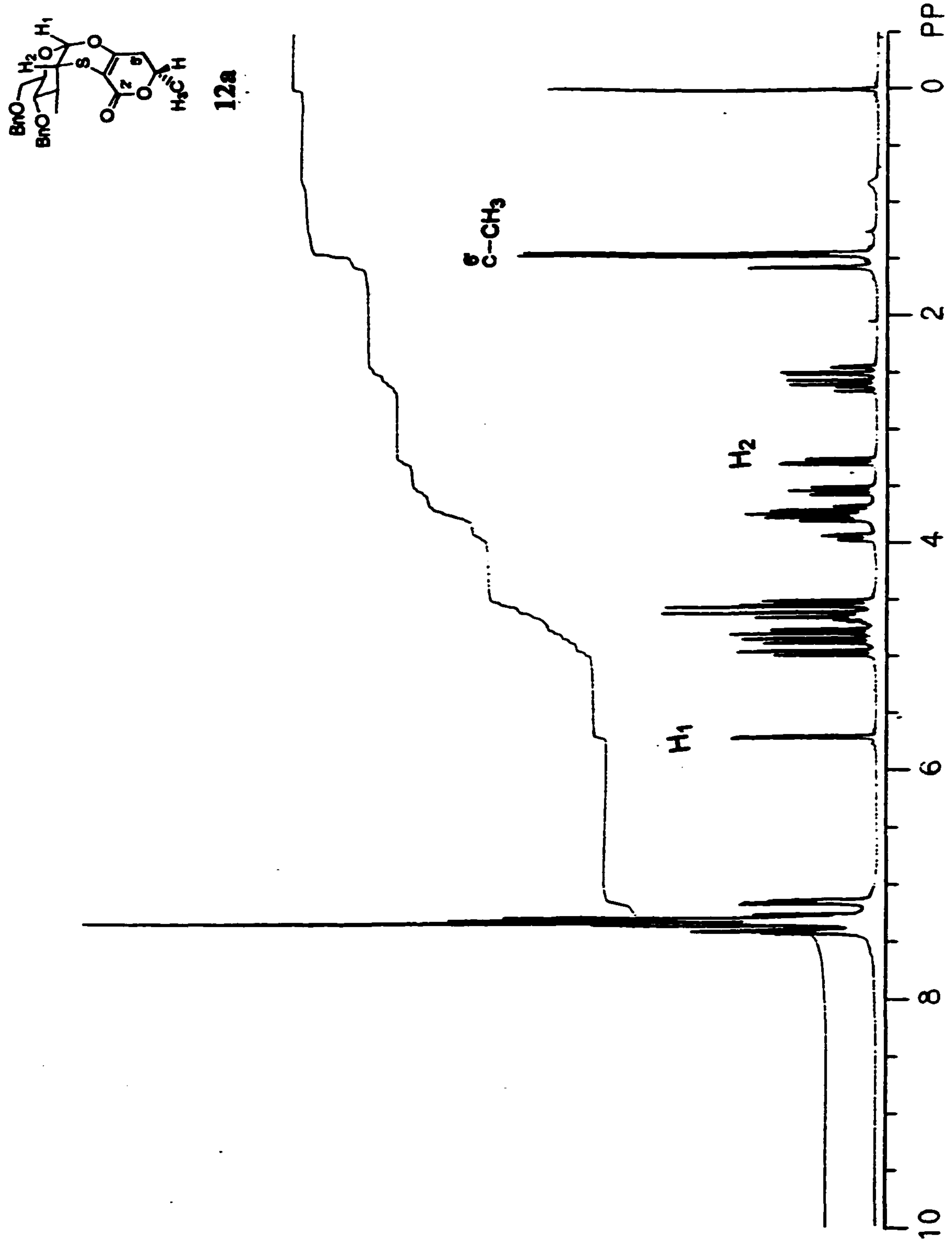


Figure 2.7 ^{1}H NMR of 12a.

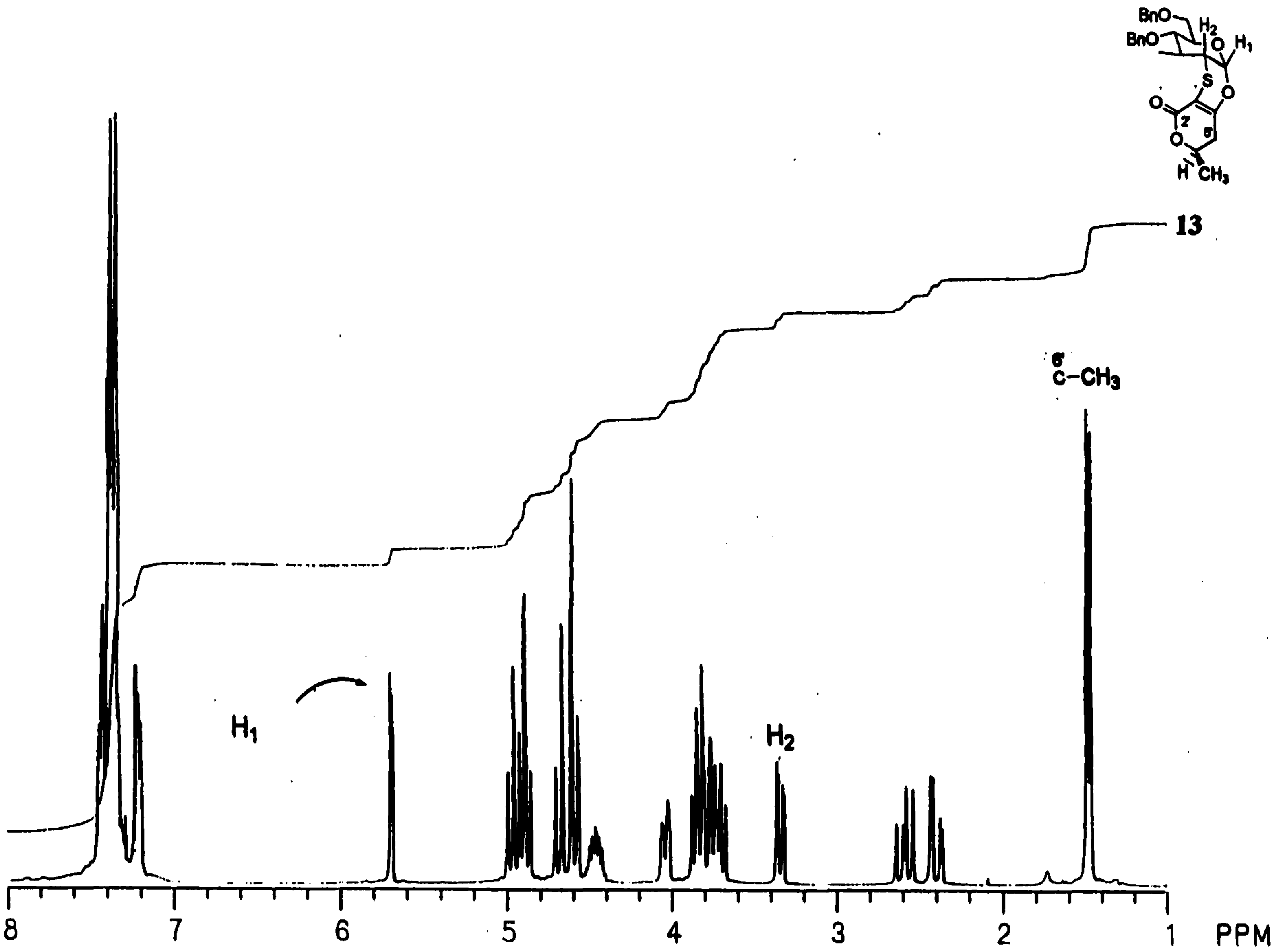


Figure 2.8 ^{1}H NMR of 13.

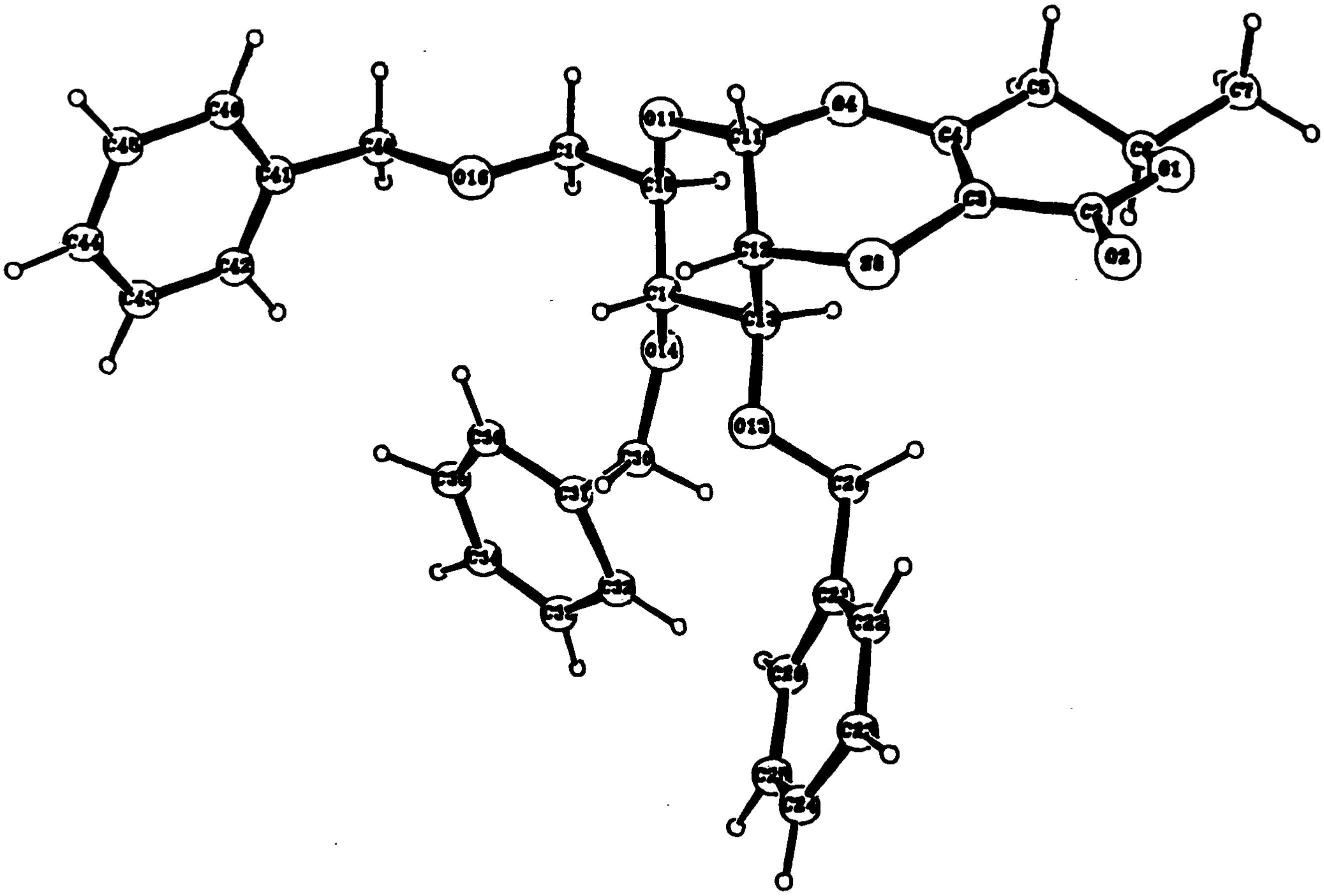


Figure 2.8a Crystal Structure of 13.

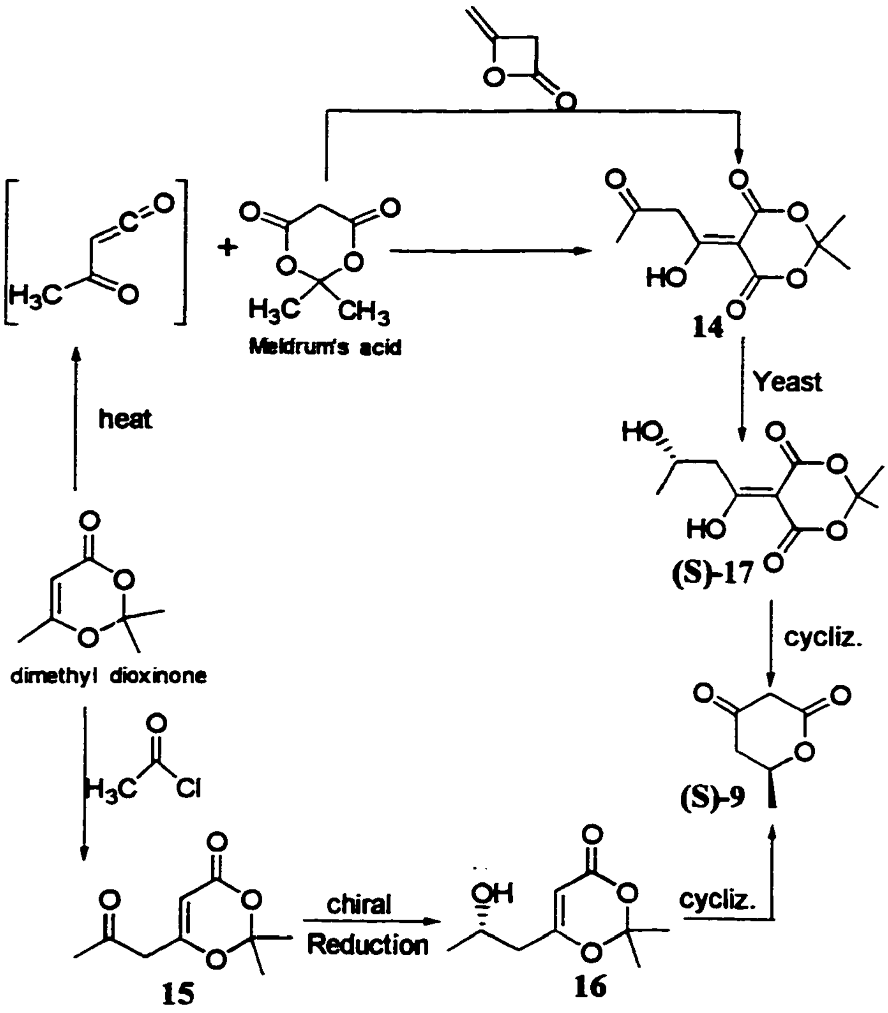
B. Cycloaddition Studies with a Single Enantiomer of the Lactone.

These preliminary experiments showed that the cycloaddition with the racemic 5,6-dihydro-4-hydroxy-6-methyl-2H-pyran-2-one was also highly stereoselective. However, the cycloaddition with the racemic lactone was not practical because of the difficult separation of the resulting diastereomers. So the next task in the project was the synthesis of a single enantiomer of the lactone.

2.6 Synthesis of the Chiral Lactone.

According to scheme 10 one of the routes to synthesize the lactone is reducing the acetoacetylated Meldrum's acid **14** with yeast, which then can produce the lactone (S)-9. The acetoacetylation of Meldrum's acid can be achieved by reacting it with diketene in the presence of triethylamine. As an alternate to the use of diketene, the acetoacetylation can be done by nucleophilic trapping of the pyrolytic product of dimethyl dioxinone.

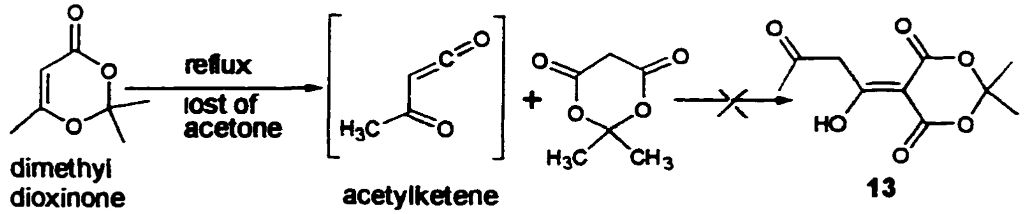
Scheme 10



2.6.1 Acetylation of Meldrum's acid via 1,3-dioxane-4-one.

Dioxinone is a commercially available liquid that is easily handled and stored. When pyrolyzed dioxinone decomposes into acetylketene and acetone[37]. The acetylketene produced in this way has been trapped via nucleophilic and cycloaddition reactions.

Scheme 11



Meldrum's acid, the acting nucleophile, was added to the refluxing solution of dioxinone in xylenes, or it was mixed with the dioxinone and then refluxed[37]. Even when the evolution of acetone was evident in both cases, neither product nor starting material was obtained, only a black charcoal residue was obtained that gave a very messy ^{1}HNMR. Since the structure of Meldrum's acid is very similar to the dioxinone, at this high temperature it may have decomposed in a manner similar to dioxinone, figure 2.9.

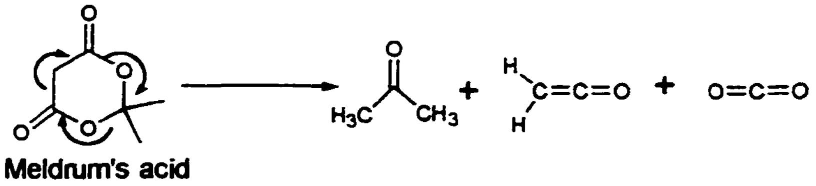
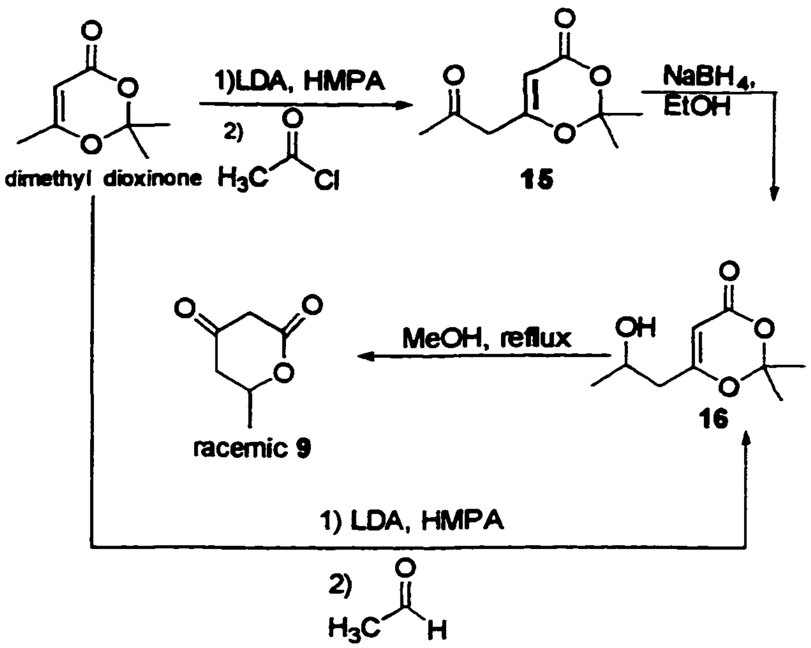


Figure 2.9 Mechanism for the Degradation of Meldrum's Acid.

2.6.2 Lactone from 1,3-dioxane-4-one.

The chiral or optically active lactone can also be obtained by ring opening of 1,3-dioxane-4-one having an external side chain with a hydroxyl group[38], such as compound 16, scheme12.

Scheme 12



In order to test the method, the racemic compound 15 was synthesized in 30 % yield from dimethyl dioxinone. The low yield in the acetylation with acetyl chloride is due to the formation of compound 16a produced in nearly 46 % yield. It was probably formed by the reaction in figure 2.10.

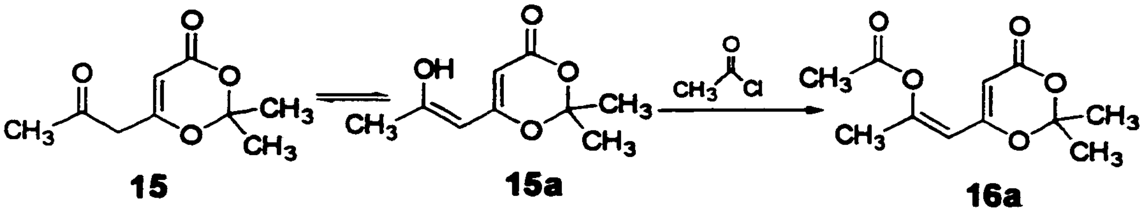


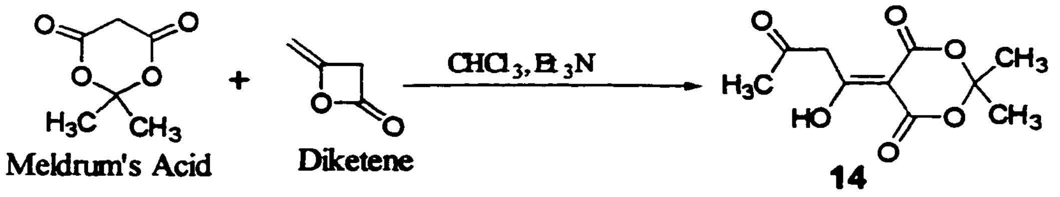
Figure 2.10 Mechanism for the Formation of **16a**.

In orden to obtain the desired alcohol directly, the anion of dimethyl dioxinone was treated with acetaldehyde. The reaction afforded the desired alcohol only in 19 % yield. With the alcohol **16** available, we proceeded with the lactonization, which was carried out in K_2CO_3/MeOH overnight[38]. This reaction gave a product which had the same R_f of the desired lactone, but whose ^{1}H NMR showed a totally different product. The acid sensitive lactone apparently did not survive the acidic work up conditions. As a result, this method was abandoned.

2.6.3 Acetylation of Meldrum's acid via diketene.

With diketene available, the acetoacetylated Meldrum's acid was synthesized according to scheme 13 in 90-94 % in multigram scale[39]. The reaction is very clean and the product can be used recrystallized or as the crude.

Scheme 13



The mechanism of this base catalyzed reaction might be visualized as the attack on the carbonyl of diketene[40] by the enolized Meldrum's acid (EMA), figure 2.11.

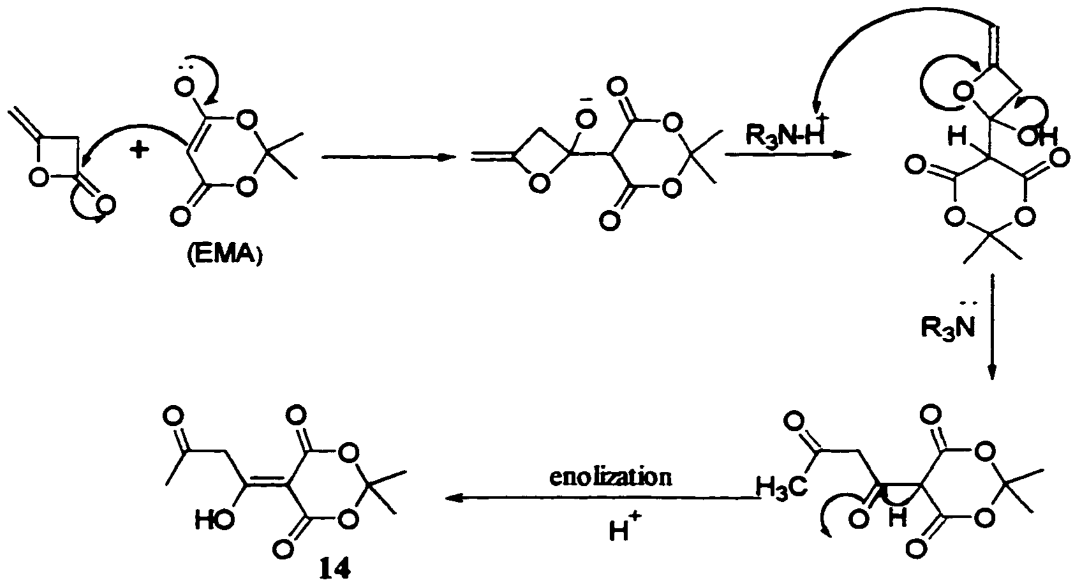


Figure 2.11 Mechanism for the Acetylation of Meldrum's Acid.

2.6.4 Yeast reduction of the acetoacetylated Meldrum's acid.

The asymmetric reduction of carbonyl compounds by baker's yeast (saccharomyces cereviceae) to obtain chiral alcohols is widely used because of the high stereoselectivity of the reduction and its simplicity[41]. When the reduction process is not completely enantioselective, the introduction of a third reagent into the reduction system, or modification of the experimental conditions are made. Some examples are the use of an organic media or an additive, change of energy source, immobilization technique, change of the pH of the medium, etc. It is possible to obtain products with high yields (80-85 %) and high optical purity (e.e. 90-99 %)[42] under optimum conditions.

The enantioselectivity[43] of the reduction depends on the difference between bulkiness of the two groups attached to the carbonyl of the prochiral molecule. In any enzyme-catalyzed process[44], the molecule presents to the incoming reagent two faces with mirror image relationship to one another: *Re* face or *Si* face.

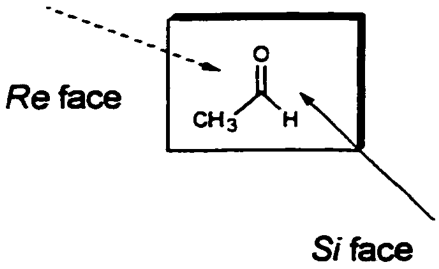
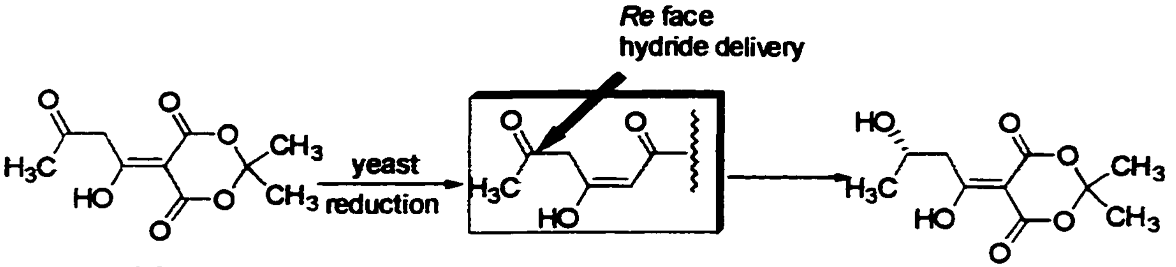


Figure 2.12 Enantiomeric Faces.

If the substituents viewed from a particular face appear clockwise in order of decreasing priority, then the face is *Re*; if counter clockwise, then it is *Si*.

In the reduction of acyclic ketones by baker's yeast (Saccharomyces cerevisiae), the stereochemical course of the reduction proceeds via hydrogen transfer to the *Re* face of the prochiral ketone. This is known as the Prelog rule[45,46].



14

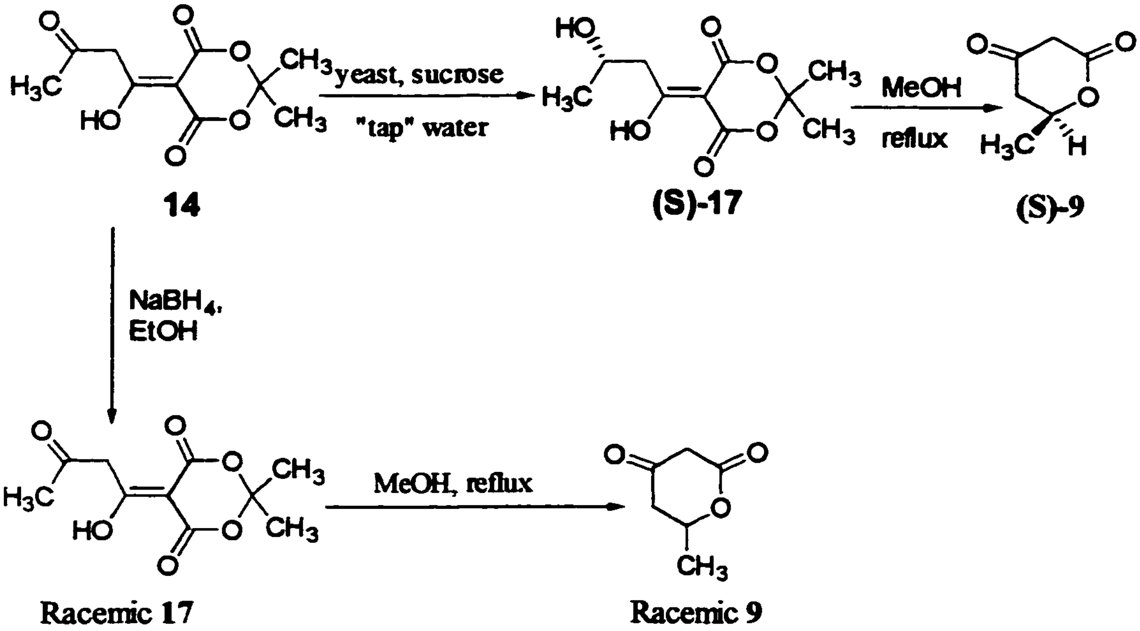
(S)-17

Figure 12.13 Yeast Reduction of Acetoacetylated Meldrum's Acid.

The acetoacetylated Meldrum's acid **14** was reduced enantioselectively with fermenting yeast to afford the corresponding alcohol **(S)-17**, scheme14, which by refluxing in methanol is converted into the desired chiral lactone in 37-50 % yield from **14**. Attempts to purify the alcohol **(S)-17** either by silica gel, florisil or neutral alumina, failed, so it was used in the lactonization step as the crude. The lactone obtained was purified by flash chromatography, or it was recrystallized from ethanol.

The overall yield depends on the extraction step where the organic material is separated from the fermentation broth. This extraction could be very difficult if most of the water is not evaporated. We found that the highest yield was obtained when the yeast-ketone mixture was shaken from 1-2 days, which allowed most of the water to evaporate and with the use of Fleischman's yeast rather than baker's yeast.

Scheme 14

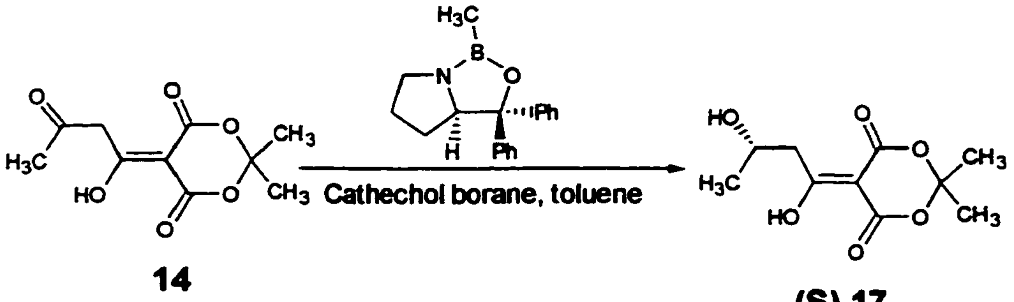


Sodium borohydride was able to reduce the acetoacetylated Meldrum's acid to the racemic alcohol, which after lactonization in refluxing MeOH gave the racemic lactone. Again, the sensitivity of the alcohol to any acidic work up, decreased the yield.

2.6.5 Reduction by chiral catalyst.

The Corey group had developed a highly enantioselective method for the reduction of ketones using the oxazaborolidine, which also had been used by the Merck group[47,48]. The enantioselective reduction of the acetoacetylated Meldrum's acid was also attempted with the oxazaborolidine as the catalyst following the literature procedure, scheme 15, but the reaction failed. The product, which seemed to be acid sensitive, apparently decomposed in the strongly acidic work up.

Scheme 15



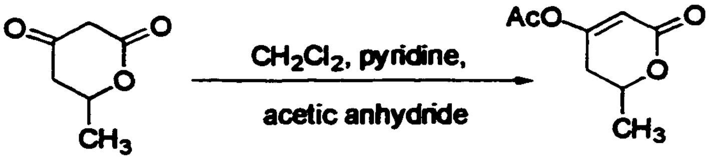
14

(S)-17
(Never Formed)

2.6.6. Lipase-catalyzed resolution.

The lipase-catalyzed esterification is another way to obtain enantiomerically pure alcohols and with this method one enantiomer of an alcohol is esterified and the other is not, leading to a resolution[49]. We followed a similar procedure for the resolution of the racemic lactone, scheme 17.

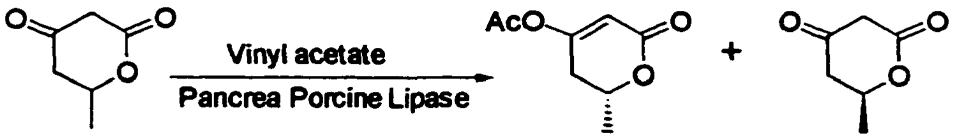
Scheme 16



(R/S)-9 **(R/S)-18**

The reaction was monitored by co-spotting the mixture on TLC with the acetylated lactone obtained in accordance with scheme 16. After 26 hours, TLC showed the acetylated product. 3 days later, the spot corresponding to the lactone disappeared and there were several other new spots. ^{1}HNMR did not show the expected products. Perhaps the long reaction time led to decomposition products.

Scheme 17



(R/S)- 9 **(R)-18** **(S)-9**

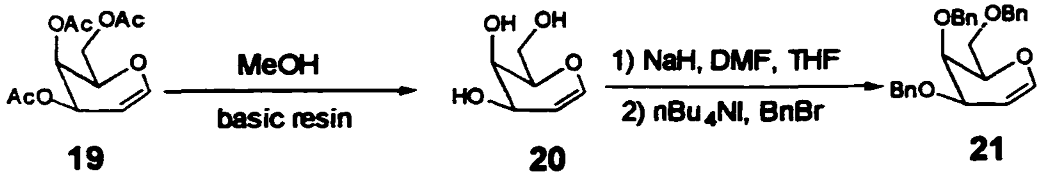
2.7 Synthesis of the Glycals.

We intended to try our cycloaddition with the acetylated and benzylated glycals from the galacto, gluco, and allo series. We used the commercially available triacetyl glucal, but all of the other glycals were synthesized following well established literature procedures. The 4,6-isopropylidene-3-hydroxyglucal 27 was also synthesized with the idea of obtaining the trihydroxy cycloadduct, that resembles natural products, which have unprotected hydroxyls group.

2.7.1 Synthesis of tribenzylgalactal.

Tribenzylgalactal 21 was easily obtained from triacetyl galactal[50], 19, in two steps in 67 % overall yield, scheme 18.

Scheme 18

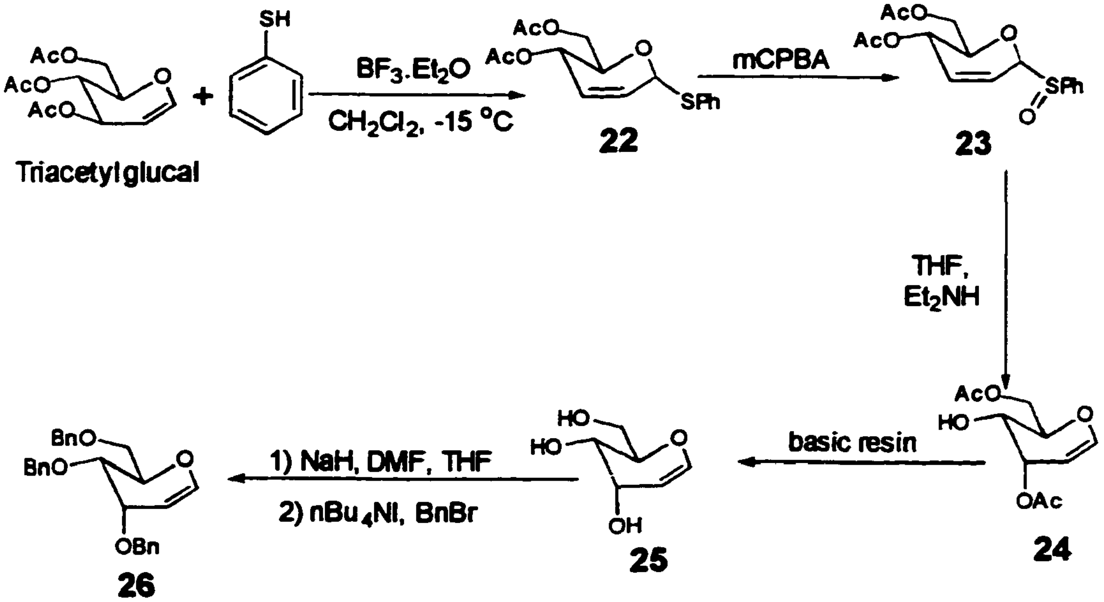


2.7.2 Synthesis of tribenzylallal.

The conversion of the commercially available triacetyl glucal to α-phenyl thioglucal[51] 22 is accomplished by treatment of the glucal with benzenethiol

($BF_3.Et_2O$) in CH_2Cl_2 at -15 °C, followed by oxidation of the α-sulfide with mCPBA to the sulfoxide **23**. Crude sulfoxide **23** is treated with Et_2NH in THF, followed by stirring the resulting crude in amberlite basic resin to give the trihydroxy allal **25**. After evaporation of the solvent to dryness, the resulting trihydroxy compound was benzylated to give tribenzylallal **26** in 40 % overall yield.

Scheme 19

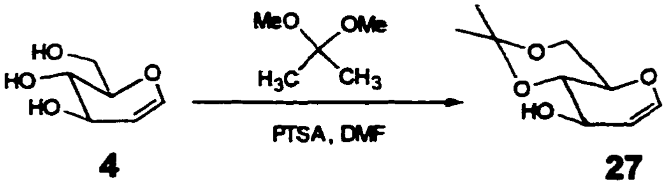


2.7.3 Synthesis of 4,6-isopropylidene-3-hydroxyglucal.

Treatment of the trihydroxy glucal **4** with 2,2-dimethoxypropane in DMF at pH 3 gave the acetonide glucal **27** in only 18 % yield. Another major product (23 %)

was obtained, which by comparison with the literature[51], was identified as the rearranged (Ferrier) product.

Scheme 20



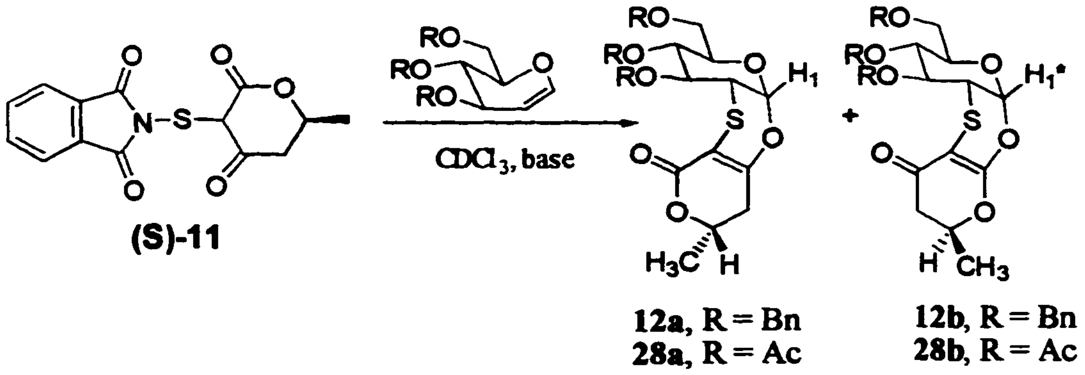
2.8 Cycloaddition with the Chiral Lactone.

The cycloaddition with chiral sulfino-lactone and the glycals from the gluco, the galacto, and the allo series were performed. Most of the cycloadditions were done first in nmr tubes in order to monitor them, and then on a preparative scale.

2.8.1 Cycloaddition in nmr tubes.

The nmr experiments were performed at room temperature using $CDCl_3$ as the solvent. The chiral sulfino-lactone **(S)-11**, prepared exactly as the racemic, was used with pyridine or 2,6-lutidine as bases.

Scheme 21



2.8.1.1.Cycloaddition with triacetyl and tribenzyl glucal.

The experiments with triacetylglucal (TAG) and tribenzylglucal (TBG) were done simultaneously using the same batch of sulfino-lactone **(S)-11**. With both glucals there were two regioisomeric adducts present as indicated by the appearance of their anomeric protons. For TBG, H_1 = 5.72 and H_1* = 5.76, and for TAG H_1 = 5.73 and H_1* = 5.8. Table 2 shows the relative conversion of each one of these regiosisomers at different times. After 1 hour in Tribenzylglucal the amount of the regiosisomer at 5.72 ppm is almost the double of the corresponding product at 5.76, while in triacetyl glucal is 1:1. In TBG the 5.76 proton disappeared after 42 hours and in TAG both protons remained up to 11 days.

Table 2

Proton NMR H_1: H_1* Anomeric Product Ratios of TAG and TBG

Glucal	*base*	*1 h*	*15 h*	*24 h*	*42 h*	*11 d*
TBG	2,6-lutidine	1.74:1	2:1	2.02:1	1:1	1:0
TAG	2,6-lutidine	1.08:1	1.3:1	1.3:1	1.3:1	1.3:3

Table 3 shows the conversion of triacetyl and tribenzyl glucal to the product. This conversion can be estimated by the comparison of its anomeric peak with the one of any of the regiososomeric products. Initially, the conversion was greater in TAG than in TBG, but after 24 hours the conversion became greater in TBG. Both glucals were consumed completely after the addition of another equivalent of the sulfino-lactone **(S)-11**.

Table 3

Proton NMR Glucal : Product Anomeric Ratios

Glucal	*Base*	*Glucal*	*15 h*	*24 h*	*11 d*	*+ 11*
TBG	2,6-lutidine	1.6:1	0.81:1	0.68:1	0.60:1	0:1
TAG	2,6-lutidine	1.52:1	0.76:1	0.76:1	0.72:1	0:1

Two more NMR reactions were done with tribenzylglucal, as indicated in table 4, using different batches of sulfino-lactone **11** with pyridine as the base. It seemed that the glucal conversion to product is faster with 1.0 equivalent of pyridine than with 1.0 equivalent of 2,6-lutidine. But while 2,6-lutidine gave only **12a** after 42 hours, in pyridine the mixture of both, **12a** and **12b**, remained after 72 hours. Table 5 shows that decreasing the molar equivalent of pyridine from 1.0 to 0.25, decreased the reactivity.

Table 4

Comparison of Bases and Reaction Rates

Base (1.0 mol equivalent)	*Anomeric Glucal:Product, 1 h*
2,6-lutidine	1.66:1
pyridine	0.67:1

Table 5

Effect of Pyridine on the Conversion of Glucal to Product

Pyridine, Mol Equiv.	*Glucal:Product, 1 h*	*Glucal:Product, 72 h*
1.0	0.81:1	0.28:1
0.25	2.3:1	0.47:1

2.8.1.2 Cycloaddition with triacetyl and tribenzyl galactal.

The reaction of tribenzylgalactal showed also two anomeric peaks corresponding to two products similar to **12a** and **12b**. Tribenzylgalactal reacts much faster than tribenzyl glucal. In 15 minutes the ratio of the unreacted glycal to product was less than 0.5. As before, 1.0 equivalent of each reagent was used in $CDCl_3$, with 2,6-lutidine as the base.

Table 6

^{1}H NMR Anomeric Product Ratios for Tribenzylgalactal

Anomeric ratios	*0.25 h*	*1.0 h*	*2.0 h*
Galactal:Product H_g:H_l	0.48:1	0.3:1	0.13:1
H_l: H_l*	2.1	2.01:1	2.03:1

2.8.1.3 Cycloaddition with tribenzyl allal.

The cycloaddition in $CDCl_3$, using 0.80 equivalent of tribenzyl allal was practically done after only 40 minutes. As in the gluco and galacto series, there were two different adducts with the anomeric proton H_1 = 5.69, H_1* = 5.82 ppm. Table 7 shows the NMR ratio between these protons.

Table 7

Proton NMR Anomeric Product Ratios for Tribenzylallal

Anomeric ratios	*5 min*	*20 min*	*30 min*	*40 min*
Allal:Product				
H_g:H_1	0.08:1	0.03:1	0.03:1	0.003:1
H_1: H_1*	2.1:1	2.4:1	2.80:1	2.80:1

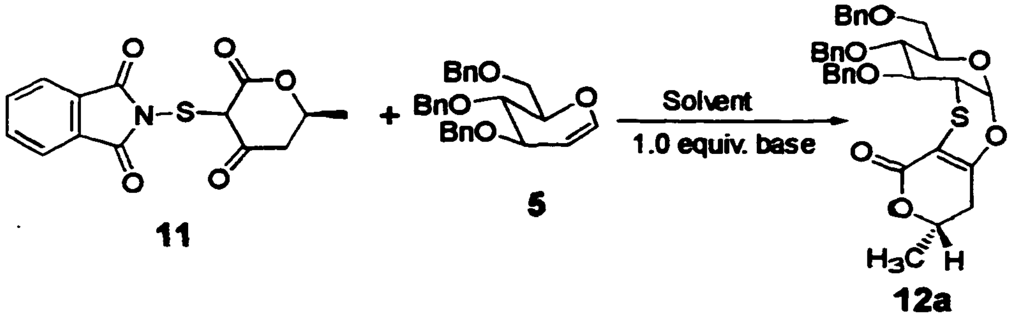
2.8.2 Preparative scale cycloadditions.

Different procedures were followed for the cycloadditions in order to improve the yields. One of them was the addition of the sulfino-lactone **(S)-11** by syringe pump (0.01 mL/min) to a stirring mixture of tribenzylglucal **5** and pyridine at room temperature. After stirring for 7 days, the conversion of glucal to product was 50 % by NMR and the yield of the isolated product contaminated with phthalimide was 26 %.

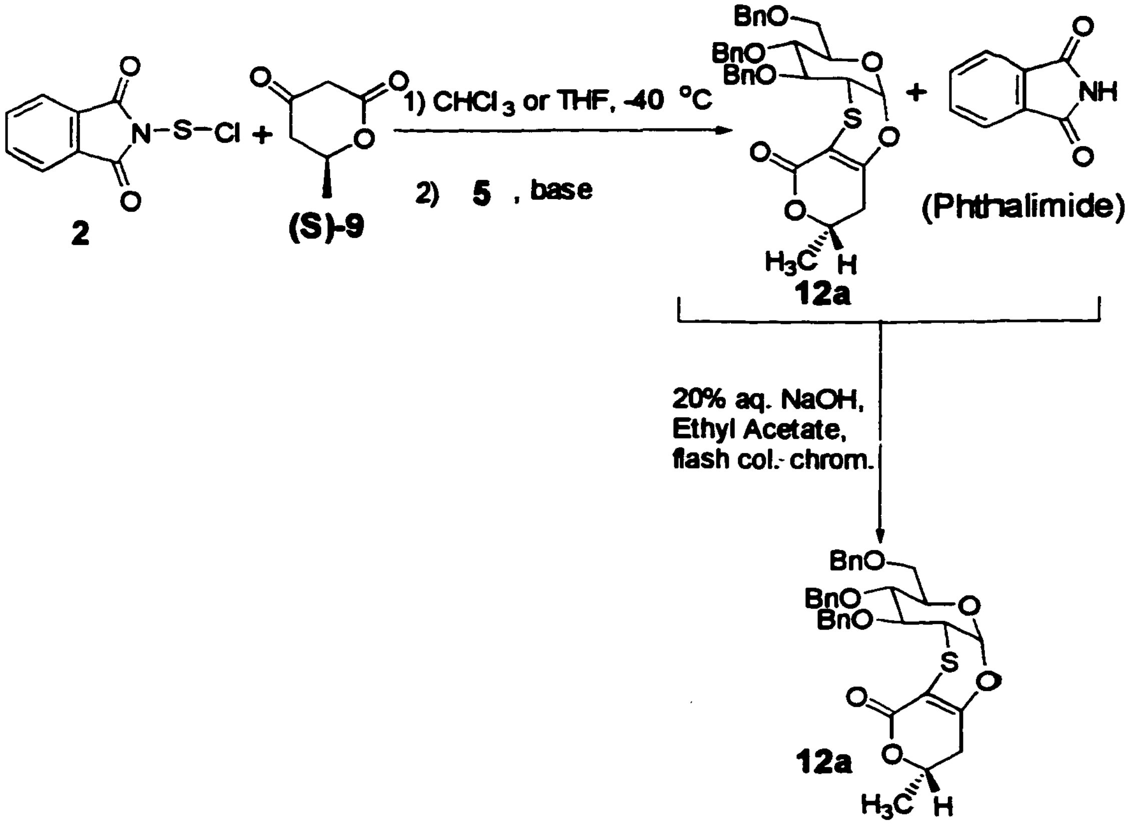
Preparative scale cycloaddition following the literature procedure were also performed with the different glycals. In the cycloaddition with tribenzylallal and tribenzylglucal, the most downfield proton corresponding to the minor adduct disappeared upon working up of the reaction mixture, while in tribenzylgalactal both regioisomers remained. Triacetyl glucal also gave two regioisomers.

In another procedure, a solution of sulfenyl chloride **2** and base in tetrahydrofuran or chloroform is cooled to -40 °C, and the enantiopure lactone **9** is added dropwise. When the lactone is consumed, the glycal is added and the reaction mixture is allowed to go to room temperature. This "one pot" cycloaddition procedure gave only one regioisomer with all of the benzylated glycals.

Scheme 22



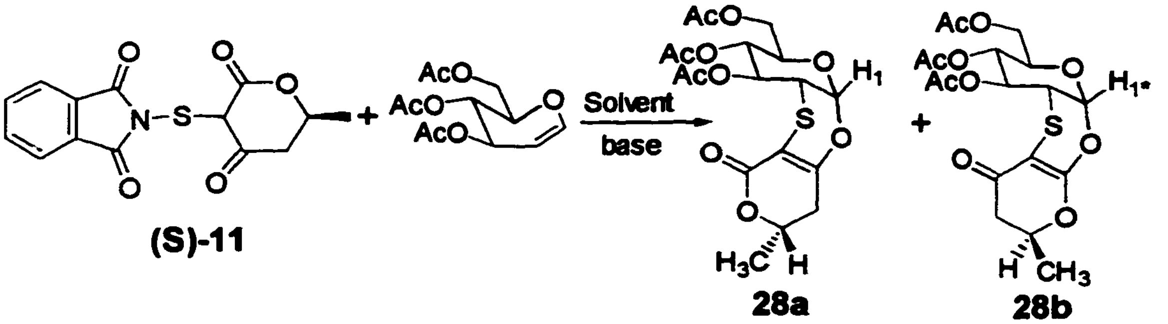
Scheme 23



2.8.3 Separation of the triacetyl glucal adducts mixture.

The cycloaddition in a preparative scale with triacetyl glucal gave a reasonable yield, 50-62 %, in 2 days but it had a complication: the cycloadducts remained as a mixture even after flash column chromatography, scheme 24.

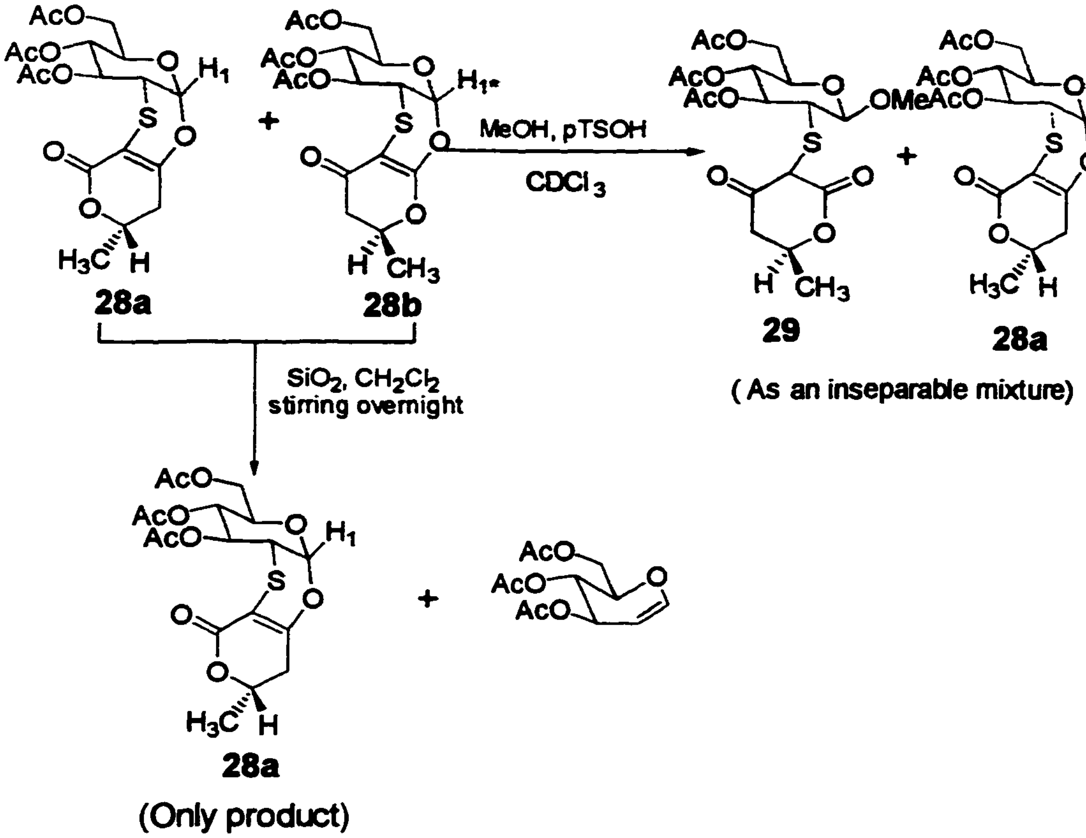
Scheme 24



In order to do the separation, this mixture was reacted with methanol in p-toluenesulfonic acid with the expectation that methanol would attack preferentially only one regioisomer. The prediction was correct: one regioisomer reacted (H_1* = 5.83 ppm). The problem was that the crude resulted in a product mixture which was difficult to purify.

It was possible to obtain one regiosomer along with some triacetyl glucal upon stirring 104 mg of a 1.2:1 mixture of **28a** and **28b**, in CH_2Cl_2, with 4 % w/w of SiO_2. After flash chromatography 75.2 g of **28a**, as a single regioisomer, was obtained. In a similar manner a mixture of tribenzylgalactal produced a single adduct by stirring on silica gel.

Scheme 25



2.8.4 Speculation for the formation of the regioisomers.

There is not a conclusive explanation for the formation of the regioisomers such as 28a and 28b. Our preliminary studies have shown the regiospecificity of the Diels-Alder reaction, with the sulfur bond (of the ketothione) always attached to the C(2) carbon of the glycal (figure 2.14). This result is in agreement with the AM1 calculations[53a] for the lumo coefficients of the ketothione 11. According to these calculations the coeffient for the sulfur atom is -0.47217, the largest absolute value, followed for the ketone oxygen that is -0.17641. The smallest value corresponded to the lactone oxygen, +0.00647.

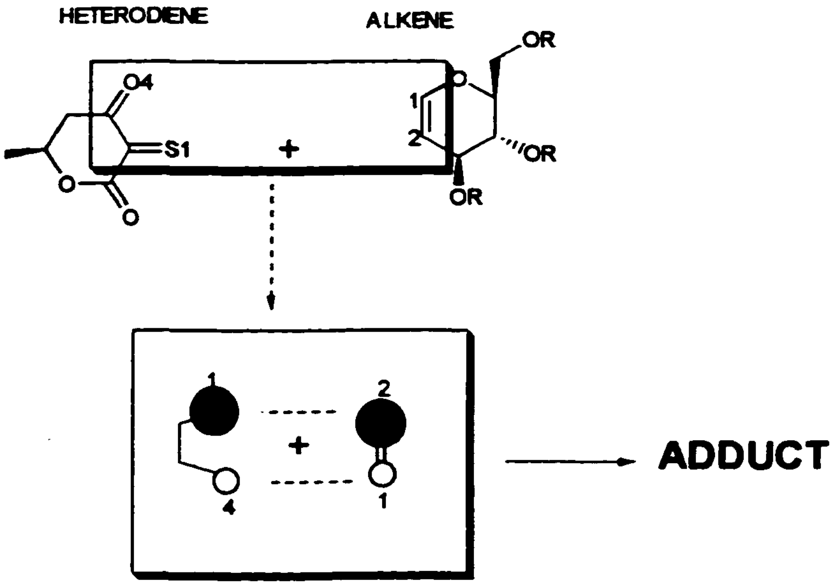
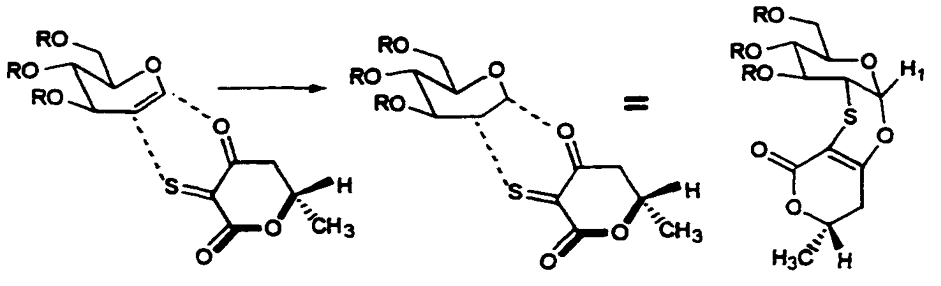


Figure 2.14 Interaction of the Coefficients in the Cycloaddition Reactions.

We can explain the formation of these apparent regoisomers, assuming that the glycal (alkene) approaches the diene (ketothione) either by path **a** to interact with the ketone oxygen, or by path **b** to interact with the lactone oxygen, as in figure 2.14.

Path a: Major cycloaddition pathway



Path b: Minor cycloaddition pathway

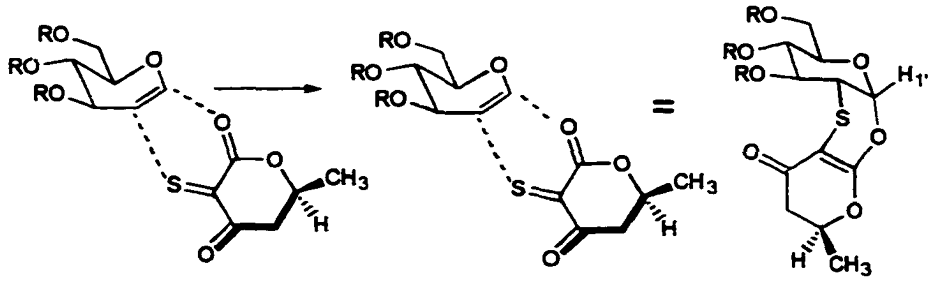


Figure 2.15 Hypothetical Formation of **12a** and **12b**.

One might be prompted to assume that path b, with the methyl group up, has more steric hindrance and therefore, it is less favored for approach by the glycal. But, the fact that cycloaddition with the racemic lactone gave a 1:1 mixture of diastereomers, ruled out this argument. One more reasonable explanation could be the stability of the resulting adducts. The regioisomer such as **28b** with the ring oxygen in the lactone next to the double bond might be more prompted to collapse or react, and this is in agreement with the fact that it disappeared upon stirring with silica gel. Under these acidic conditions, perhaps **28b** formed an oxonion ion which, upon ring opening (retro-Diels-Alder), produced the thione-lactone **11a**. This reactive intermediate reacted via cycloaddition with the glycal to give the more stable **28a** (figure 2.16). In addition, **28b** has a greater amount of reactivity with methanol in p-toluene sulfonic acid to form the β- glycoside **29**.

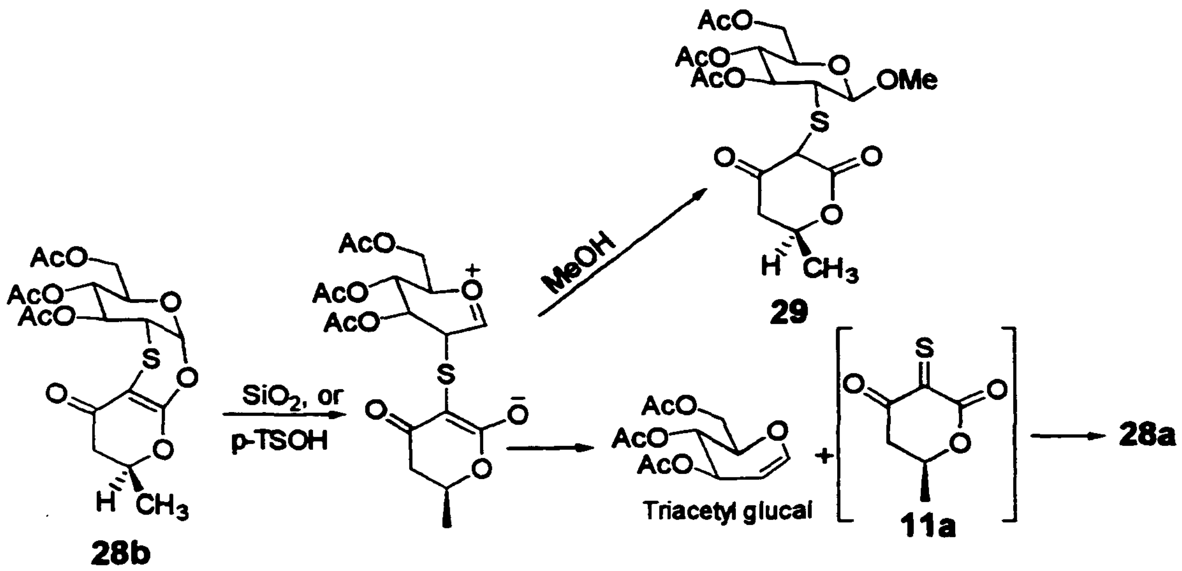


Figure 2.16 Interaction of **28b** with Methanol and Silica Gel.

2.8.5 Removal of the phthalimide.

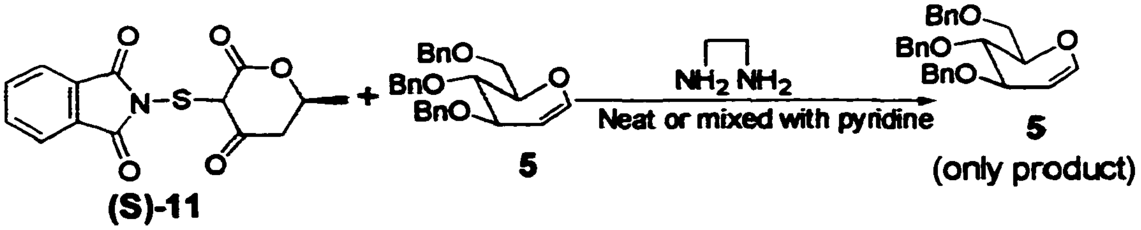
In the cycloaddition with the cyclic ketone and ketolactone, a problem arose that was not present in the cycloaddition with the acyclic 2,4-pentanedione: removal of the phthalimide. In the pentanedione-TBG adduct **6**, the phthalimide was separated efficiently by flash column chromatography because it has a lower spot with a reasonable ΔR_f. One single separation did the job. In the cyclic ketone, the removal was almost impossible in a single purification. In the acetylated adducts, it was possible to remove this side product after two purifications, but, in the benzylated adducts it was impossible, and the problem got worse from one series to the other. In the allo series, a lot of phthalimide remained even after three consecutive purifications.

In the effort to remove this group we tried to extract the resulting crude with saturated sodium bicarbonate, but it did not work. We used 10 % w/v aqueous solution of KOH to extract twice, but a lot of the product was lost because of slurry formation, and still, the removal was inefficient. We moved then to use 10 % w/v NaOH. First we extracted, no slurry was formed, but still phthalimide was present. Finally we found that total removal of the phthalimide is possible by stirring the dissolved adduct for 45 minutes with 20 % w/v aqueous NaOH. This removal always produced a loss of product with the consequent reduction of the yield.

We also removed the phthalimide by stirring the dissolved crude over basic resin. This procedure worked very well because it gave a cleaner product and avoided extraction as in NaOH, but only seemed to work well for small amounts of adduct (125-150 mg). For larger amounts of adduct, it gave a lot of impurities difficult to remove by flash chromatography and it also decreased the yield.

Recently, there was a report[53b] of the use of ethylenediamine as an efficient vehicle to remove the phthalimide. We tried it twice unsuccessfully, scheme 26.

Scheme 26



2.8.6 Solvent and face selectivity.

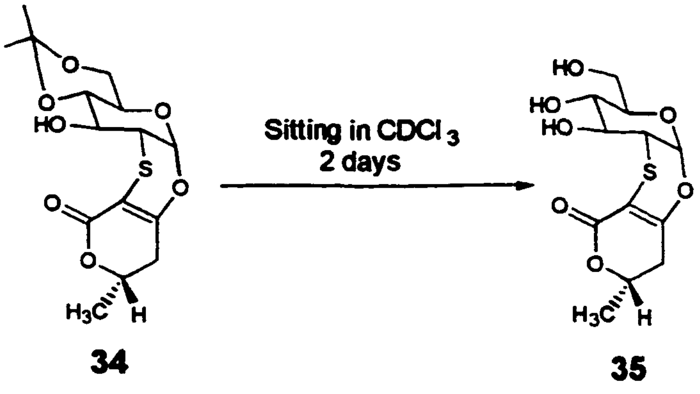
We performed a couple of cycloaddition experiments with tri-O-acetyl glucal and the chiral sulfino-lactone (S)-11, using DMSO and acetonitrile as solvents. The cycloaddition in both solvents showed an additional anomeric peak more upfield than the previous one from the regioisomer, so we assumed that it may correspond to a second, top face adduct. Since the ratio of the upfield peak was higher than the downfield peak in DMSO, the cycloaddition was run in this same solvent in a preparative scale. The yield was only 12 %, but was enough to identify both adducts, the above and below face, completely. Only one regioisomer was detected for both faces: compound **28a** for the below face and compound **30** for the above face (table 8).

2.8.7 Summary of cycloadditions.

In a preparative scale, the best procedure so far, in terms of convenience, reaction time and yield, was the "one pot" procedure. This was understandable because the sulfino-lactone **11** was used in situ, and the formation of any dimerized product was minimized, and in most of the cases, the product was isolated as a single regioisomer. The stepwise procedure was still used for the cycloadditon with triacetyl glucal, which did not react following the "one pot" procedure. Table 8 presents a summary of the isolated cycloadducts.

An interesting aspect of the cycloaddition was the generation of compound **35**, the trihydroxy adduct, upon cleavage of the acetonide moiety, after having it sit in the fridge, in $CDCl_3$, for 2 days (scheme 27).

Scheme 27



Both, the cycloadditions in NMR tubes and in a preparative scale, showed a correlation of the reactivity with the HOMO-LUMO gap of the glycal (dienophile) and the heterodiene (**11a** or **7a**, figure 2.17). The energy levels in electron volt (eV) were computed using the Spartan Program[53a] at the AM1 level. The results in table 8, show that the fastest cycloadditon is the one between the dienophile **21** and the heterodiene **11a**, which has the smallest HOMO- LUMO gap ($\Delta E = 6.83$ eV).

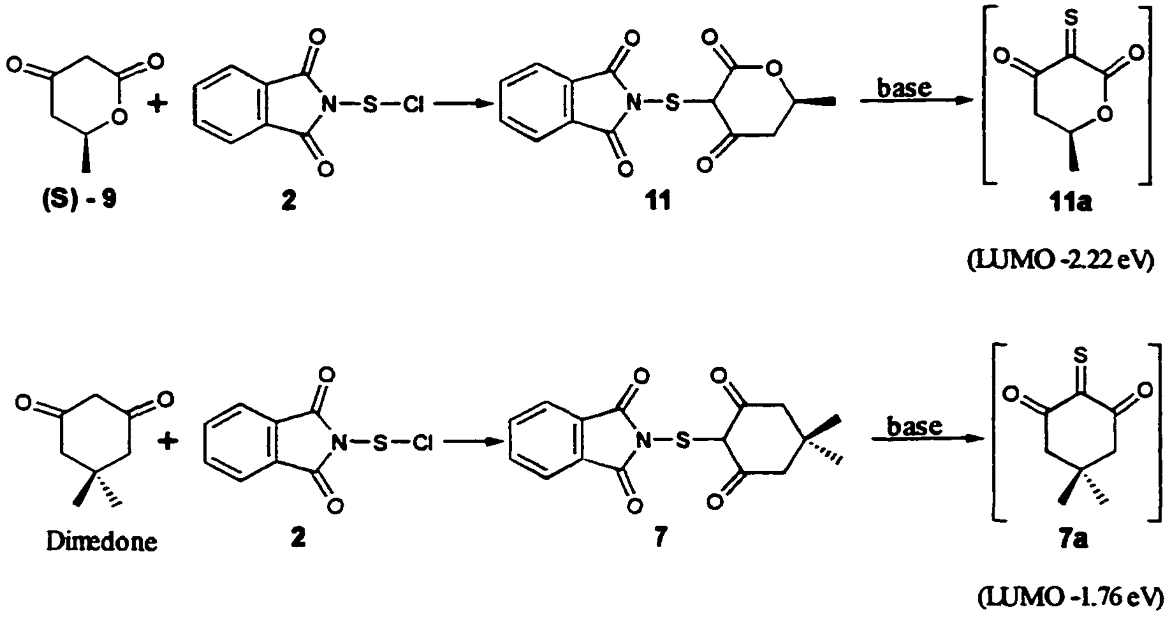


Figure 2.17 Lumo Energies of the Heterodienes Used in the Cycloadditions.

Table 8

Summary of Isolated Cycloadducts

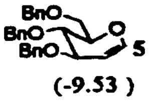
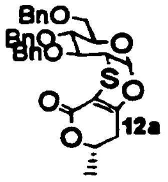
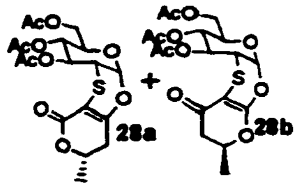
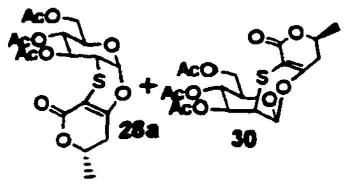
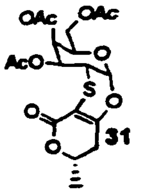
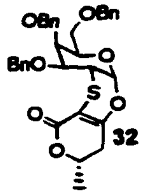
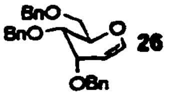
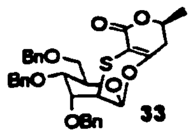
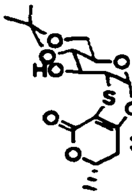
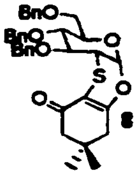
Entry	Dienophile [a]	ΔE [b] Rate	Adduct	Solvent	%Yield [c]
1	 5 (-9.53)	7.31 eV Moderate $t_{1/2}$: 15 h	 12a	$CHCl_3$	53
2	 (-9.74)	7.52 eV slow $t_{1/2}$: 48 h	 28a + 28b	$CHCl_3$	53 [d]
3	 (-9.74)	7.52 slow $t_{1/2}$: 11 d	 28a + 30	DMSO	12
4	 19	N/R Slow $t_{1/2}$: 6 d	 31	THF	40
5	 21 (-9.05)	6.83 eV fast $t_{1/2}$: 1 h	 32	$CHCl_3$	67
6	 26 (-9.50)	7.28 fast $t_{1/2}$: 2 h	 33	$CHCl_3$	91

Table 1. Continued

Entry	Dienophile [a]	ΔE [b] Rate	Adduct	Solvent	%Yield [c]
7	 **27** (-9.53)	7.31 eV slow $t_{1/2}$: 6 d	 **34**	$CHCl_3$	26
8	 **5** (-9.53)	7.77 eV slow $t_{1/2}$	 **8**	Pyridine	19

[a] Lumo energies in eV;[b] HOMO-LUMO gap; [c] Based in the isolated pure product; [d] As a 1.3:1 mixture of **28b** and **28a**.

2.9 Carbon-Sulfur Bond Cleavage.

There are not many available procedures for the successful selective reduction of the C-S bond. Most of them involve the use of three reagents: tin hydride, Nickel, and most recently samarium diodide. These reagents are prepared and used in desulfurization under many different reaction conditions. Since the C-S bond cleavage is the last step in our disaccharide syntheses, it was very important to develop the optimal reaction conditions in terms of yield and regioselectivity. A lot of time in this project was devoted to achieve this goal.

2.9.1 Desulfurization with tin hydride.

Tin hydride is a widely used desulfurization reagent and is very efficient. In most cases the best yields are obtained when the reactions are performed in aromatic

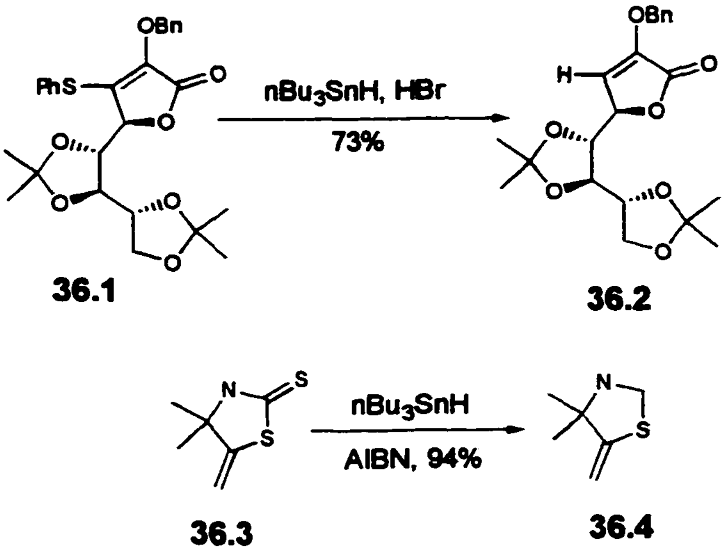


Figure 2.18 Examples of Desulfurization Reactions.

solvents such as benzene, toluene, or xylenes[54]. Under optimal conditions high yields and stereoselectivity can be achieved. Figure 2.18 shows some examples of desulfurization with nBu_3SnH.

We tried to reduce compound **12a** with tributyltin hydride. We ran the reaction under reflux with benzene, then toluene, and finally xylenes, but the cleavage did not occur, and the unreacted cycloadduct was recovered. We also tried triphenyl tin hydride under similar conditions but it also failed. In the case of the reduction of the tri-*O*-acetyl glucal adduct **28a**, some of the glycal was detected in the nmr of the crude product along with the unreacted adduct. This glycal may be produced by the mechanism shown in figure 2.19.

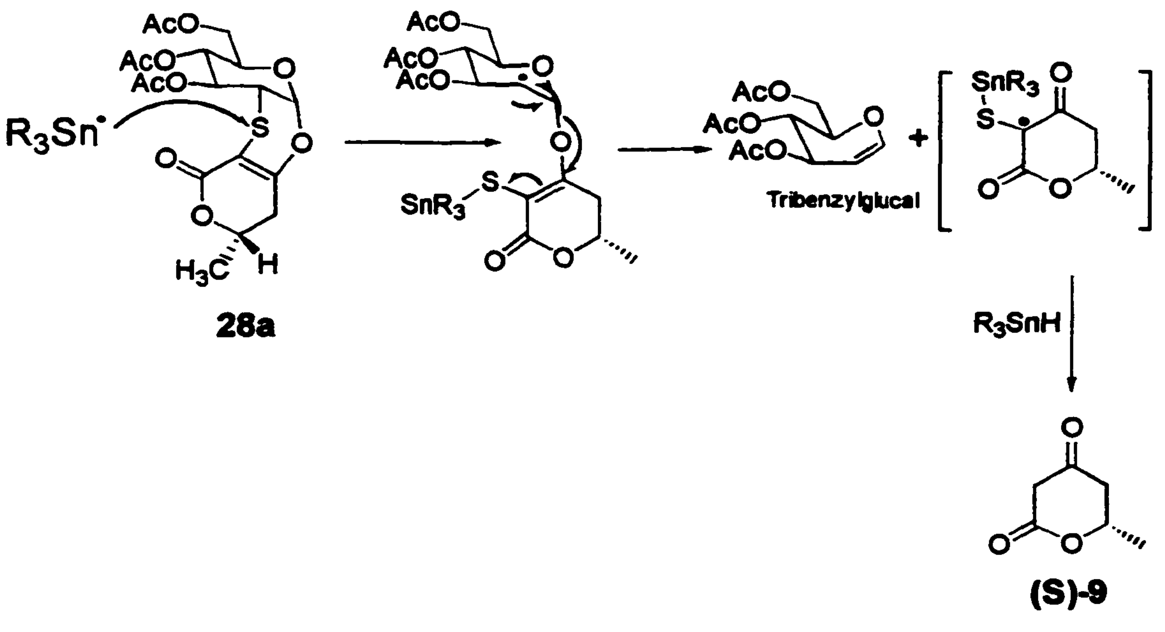


Figure 2.19 Mechanism of Desulfurization with R_3SnH.

2.9.2 Desulfurization with W-2 Raney nickel.

On treatment of the 1:1 Nickel-aluminum alloy with aqueous sodium hydroxide, the aluminum dissolves with liberation of hydrogen to provide a black sponge, called Raney nickel:

$$NiAl_2 + 6NaOH \rightarrow Ni + 2Na_3AlO_3 + 3H_2$$

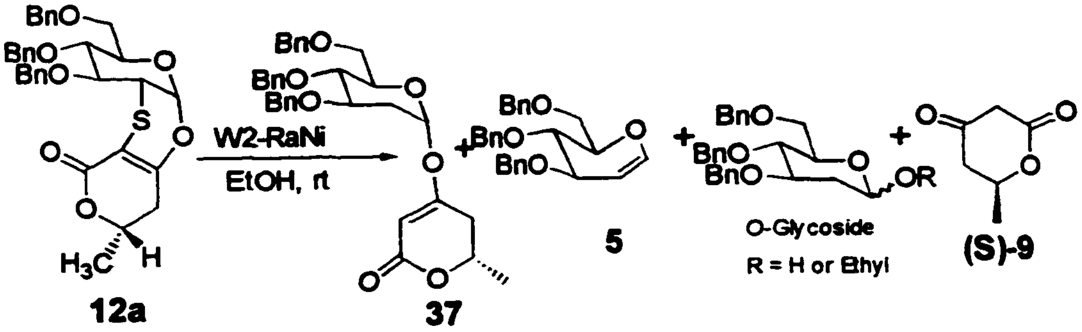
Catalysts prepared by this method are identified as W-1, W-2, W-3, etc, in which the 'W' stands for Wisconsin and the 1,2,3 stands for the chronological preparation of the nickel. Raney nickel is a very effective hydrogenation catalyst. Thiols and thioethers, both alkyl and aryl, sulfides, disulfides, sulfones, and sulfoxides are reduced with Raney nickel by replacement of the sulfur atom by atoms of hydrogen. The external application of hydrogen is not required, because an abundant quantity is adsorbed on the catalyst. The W-2 catalyst was found to contain between 170 and 460 mL of hydrogen per 4 grams.

Side reactions such as the reduction of olefinic double bonds, carbonyl, and nitro groups, which are encountered in desulfurization, can be avoided when the catalyst is deactivated, by refluxing it with acetone.

The exact mechanisms of the Raney nickel reactions are not well known, but they are probably of the free radical type[55]. It has been suggested that the reduction occurs through the interaction between the sulfur atom and the nickel metal followed by the transfer of the hydrogen absorbed on the surface of the catalyst.

W-2 Raney nickel purchased from Aldrich was used. The cycloadduct **12a** and a slurry of Raney nickel in THF were stirred at room temperature for 7 hours, but only unreacted starting material was obtained. We thought that we probably needed more drastic conditions to obtain the desulfurization. The cycloadduct was then refluxed in a Raney nickel slurry in ethanol and acetone for 1 hour. This time no starting material was recovered, but only decomposition products were obtained.

Scheme 28



The reaction was repeated at room temperature using ethanol, scheme 28. The product 37 was obtained (12 %) along with 20 % of some glycosides. These glycosides might be the result of the nucleophilic attack by the ethanol or water to the cycloadduct. In addition a minute amount of the original chiral lactone (S)-9 (0.5 mg, 5.6 %), and a lot of unidentified impurities that showed as a total of 10 spots on the TLC of the crude, were also obtained.

The ^{1}HNMR, in $CDCl_3$, of disaccharide 37 is shown in figure 2.20. The anomeric proton H_1 appears as slightly broad doublet as a result of being coupled to H_{2a}, $J_{1\text{-}2a}$ = 1.8 Hz, but only slightly coupled to H_{2e}, $J_{1\text{-}2e} \cong 0$ Hz, as is shown on the 2-D spectra. There is another downfield doublet at 5.47 ppm that corresponds to the hydrogen ($H_{3'}$) attached to the double bond of the lactone ring which has a long range allylic coupling to $H_{5'e}$, $J_{3'\text{-}5'e} = 1.5$ Hz, value within the experimental range for allylic coupling constant. This type of coupling was present on each one of the other disaccharides.

It was clear that the procedure was not convenient. It was decided that Raney nickel freshly prepared in the laboratory would give better results and that a non-polar aromatic solvent should be used. Raney nickel was prepared following the procedure from Organic Synthesis[55]. The desulfurization reaction was then run using benzene at room temperature. After 1 hour most of the starting material had disappeared. The TLC of the crude was cleaner. Only 4 spots were detected on TLC and 31 % of the product was obtained, but still a substantial amount of glucal and glucal derivatives (23 %) were obtained.

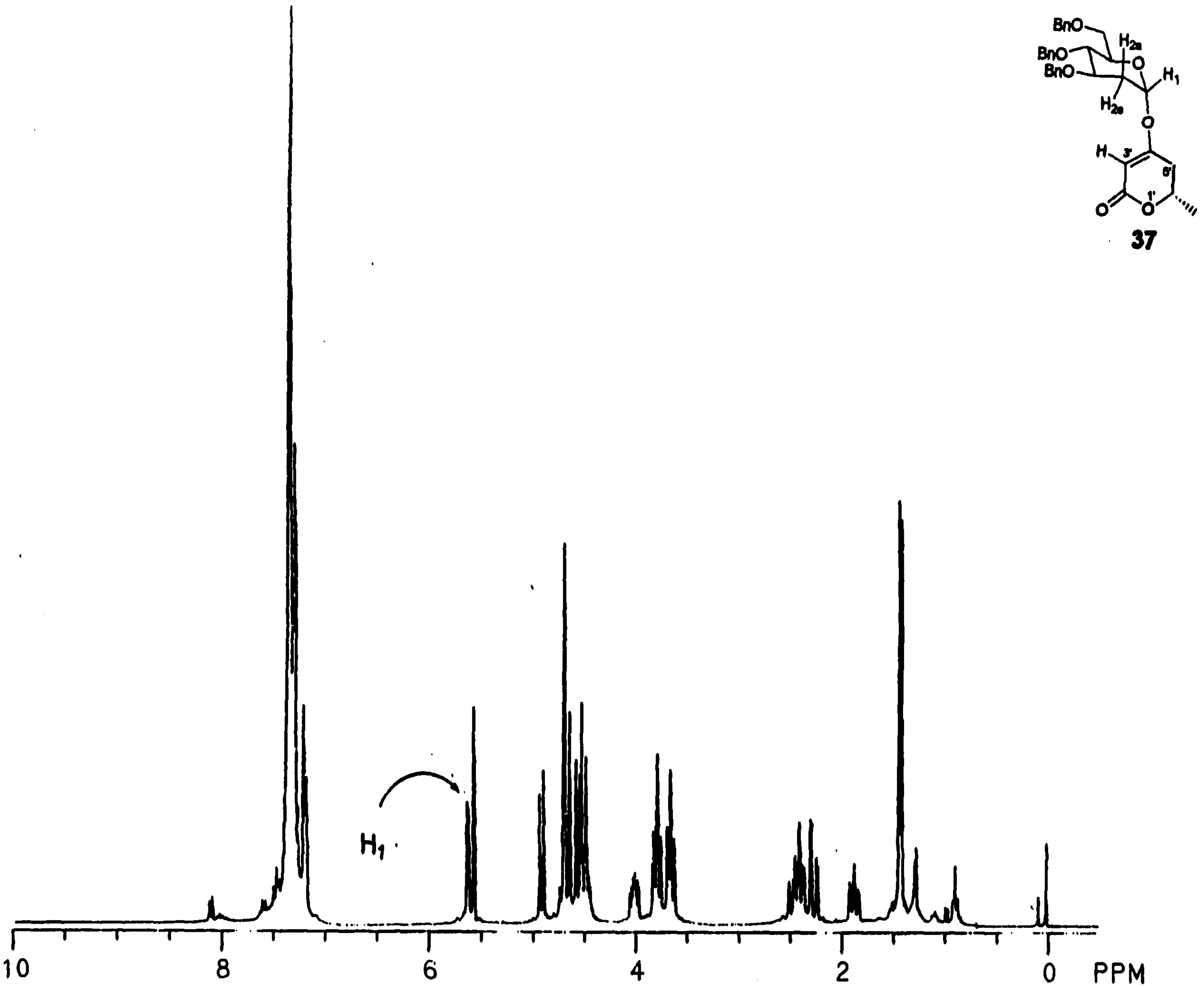
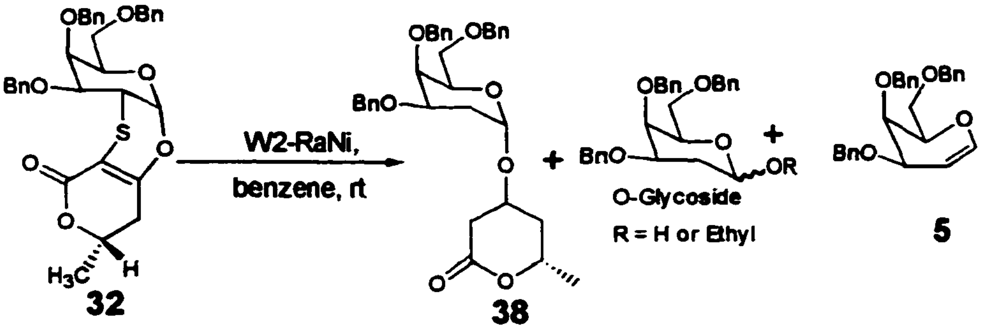


Figure 2.20 1H NMR of Disaccharide 37.

Deactivation of Raney nickel by refluxing in acetone prior to desulfurization, followed by reaction with the adduct under the same conditons, gave after stirring for 3 days, 10 % of the desired product and 25 % of the starting adduct.

Scheme 29



The desulfurization of compound **32** under the conditions specified on scheme 29 gave the overreduced product **38** in 17 % yield, along with 21 % of combined galactal derivatives.

In view of these results, we concluded that this was not the best desulfurization procedure. After several failed experiments using other glycal adducts, it was found that if the reaction was initially cooled down to 0 °C, the yield of desulfurized product would be improved, without further reduction of the double bond. Also formation of glycals and glycal derivatives was minimized. Under these new conditions yields up to 57 % have been obtained. The yield depended greatly on the activity of the Raney nickel. Highest yields were obtained when the catalyst was freshly prepared. W-2 Raney nickel remained active around five months prior to preparation.

Figure 2.21 shows the nmr spectrum of the desulfurized and reduced adduct **38**. The doublet corresponding to the vinyl proton is not longer present, and an extra multiplet appears at ≅ 4.2 ppm corresponding to C(3') proton. The carbonyl absorption frecuency in the IR spectra (appendix) increases to 1736 cm^{-1}, because it is no longer conjugated with the double bond. In the materials with carbonyl conjugated to the double bond this frequency decreases to 1707 cm^{-1}.

Table 9 presents some disaccharides obtained through the desulfurization with W-2 Raney nickel.

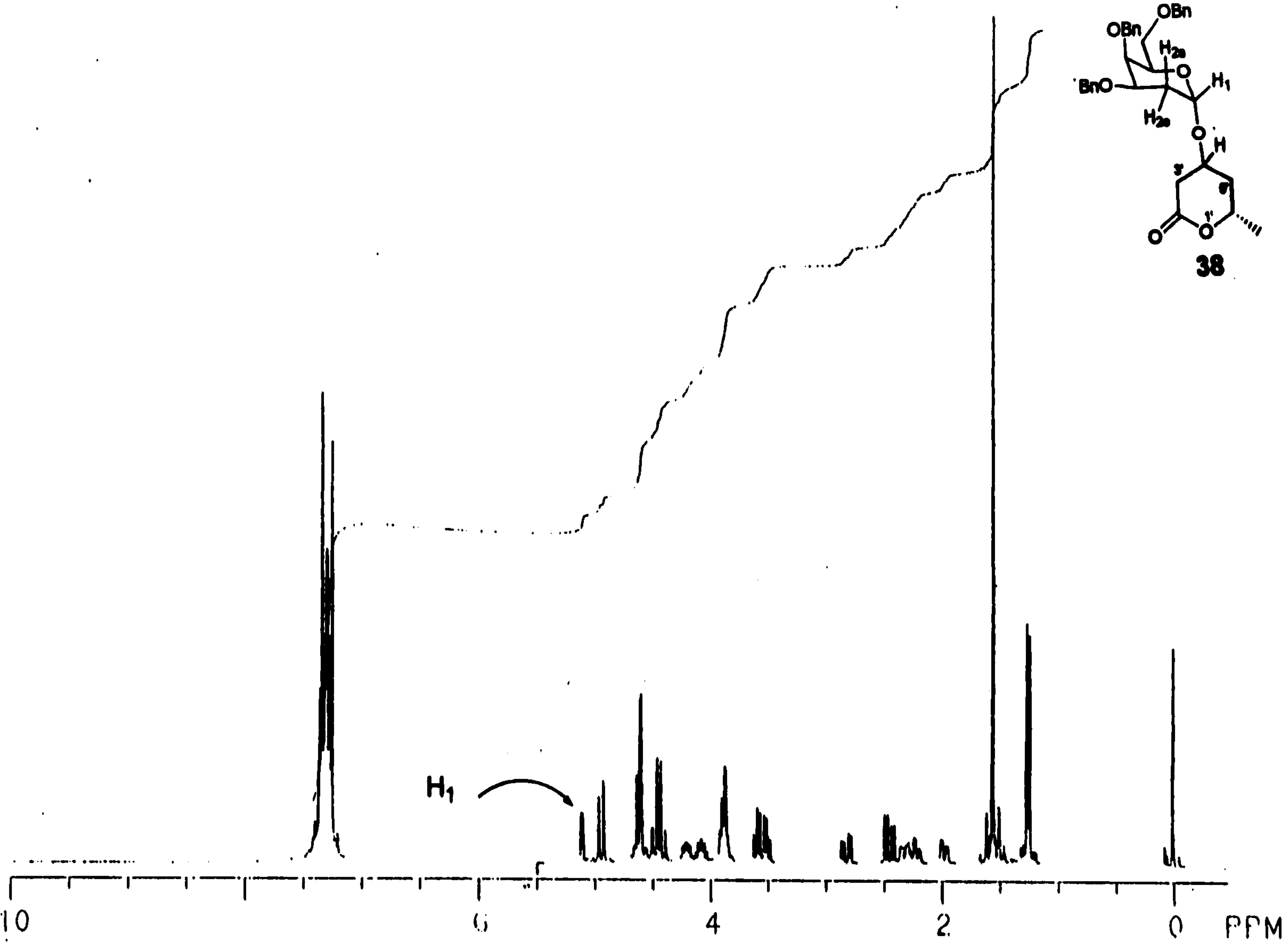
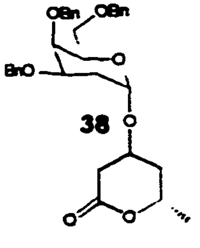
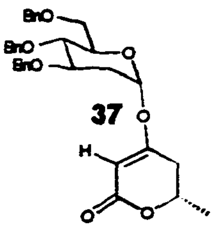
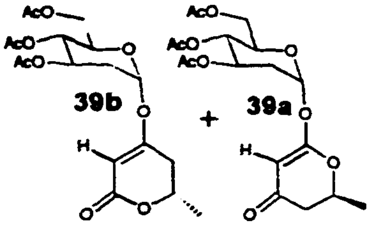
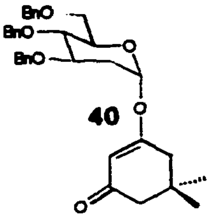
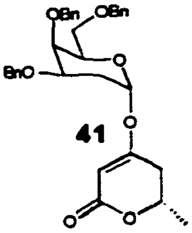


Figure 2.21 1H NMR of Disaccharide 38.

Table 9

Some Disaccharides from Raney Nickel Reactions

Entry	*Starting cycloadduct*	*Disaccharide*	*Rx Time*	*% Yield*
1	32	 **38**	45 min	17
2	12b	 **37**	2 1/2 h	57
3	28a and 28b	 **39b** + **39a**	3 h	37
4	8	 **40**	1 1/2 h	51
5	32	 **41**	3 h	31

2.9.3 Desulfurization with W-2 Raney nickel and PPh_3

Even when the reductive elimination of the glycal was minimized, the yield for the desulfurization was still low. We reasoned that probably some product was strongly adsorbed on the surface of the catalyst and was not extracted during work-up. It had been reported that in some cases the addition of PPh_3 to the reaction mixture before filtration caused desorption of the product and consequently an increment in the desulfurization yields[56]. This procedure was tested with compound **8**. After TLC indicated that the reaction was completed, the PPh_3 was added in one portion (20 mg/mg of adduct). The isolation of the product required two consecutive purifications, because of the huge amount of PPh_3 present in comparison with the product. The product was 37 % yield. This yield was less than the one obtained without this additive.

2.9.4 Desulfurization with W-2 Raney nickel and dioxane.

Another simple and efficient procedure, that had been used in the desulfurization of vinyl sulfides, is the combination of W-2 Raney nickel in dioxane at room temperature[57]. We performed that reaction, and after stirring for 1 day, the starting material along with some tribenzyl glucal was obtained.

2.9.5 Desulfurization with nickelocene.

The use of homogeneous catalysts would allow more control of the reaction conditions because these catalysts can be mixed homogeneously with the substrate to be reduced, they were expected to give better yields. In our search for a homogeneous catalyst, we tried the reaction with nickelocene and nickel boride.

The combination of Nickelocene and lithium aluminum hydride in THF has been shown to be a very efficient homogeneous catalyst for reductive hydrogenation of C-S bond, and it resembles Raney nickel in its reduction properties[58]. The catalyst is prepared by mixing an equimolar amount of nickelocene and lithium aluminum hydride in THF to form a metal hydride intermediate, which is used for desulfurization.

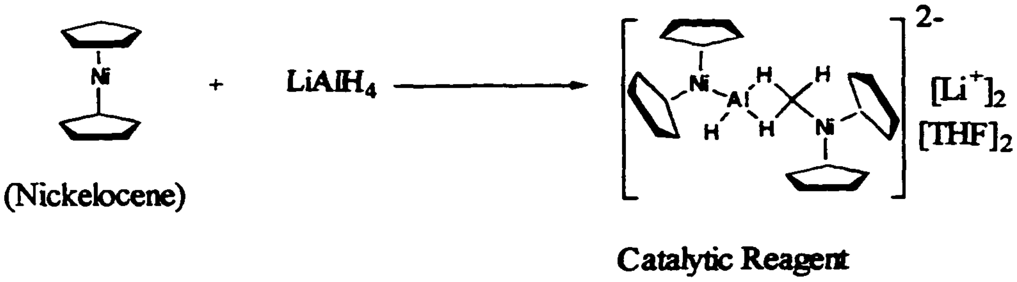
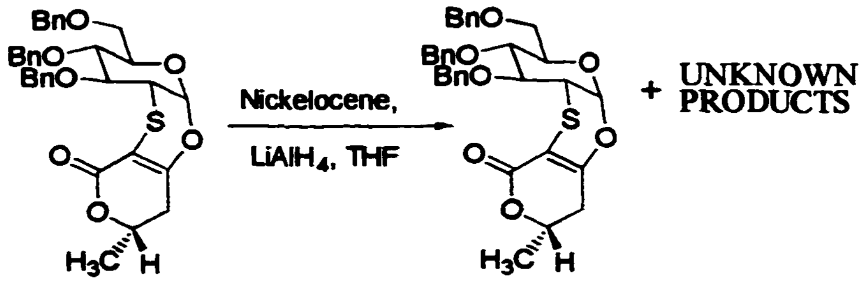


Figure 2.22 Nickelocene Complex.

The reaction using nickelocene was performed as illustrated on scheme 30. After stirring the reaction mixture for 3 days, 34 % of the starting cycloadduct was recovered along with 13 % of unidentified products, whose R_f was very similar to desired product.

Scheme 30

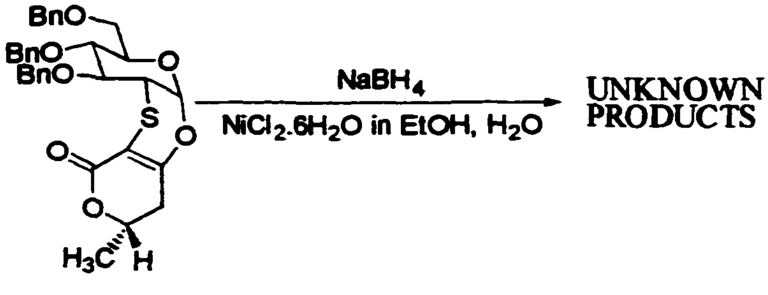


12a **12a**

2.9.6 Desulfurization with nickel boride.

Nickel Boride, Ni_2B, the black material resulting from the reaction of Sodium borohydride and nickel(II) salts, is a versatile reducing agent for many different functional groups[59]. It has significant advantages over Raney nickel as desulfurization agent because it is able to reduce the C-S bond more selectively, it is easier to prepare, it is cheaper, and since it is not pyrophoric, the exact amount to be used each time can be determined precisely. We performed the reaction as in scheme 31, but no product was obtained. No starting material was recovered and some tribenzylglucal as well as some glycal derivatives were obtained.

Scheme 31

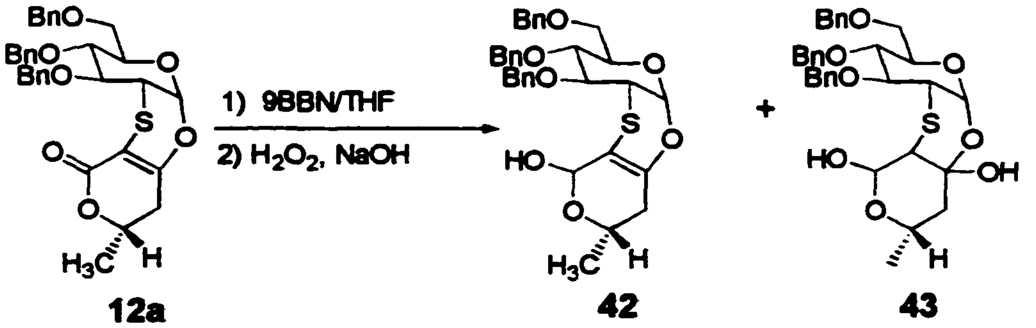


12a

2.9.7 Desulfurization of the reduced adduct.

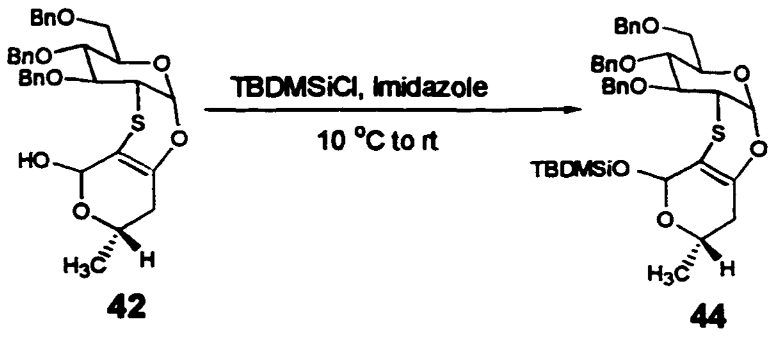
Again, with the idea of avoiding the elimination of glycals, which had been unavoidable in each one of the desulfurization reactions, we thought that if we reduce either the double bond or the carbonyl on the cycloadducts, we would be able to eliminate or decrease the reductive elimination, and therefore increase the desulfurization yield. The cycloadduct **12a** was reduced with 9-BBN. Since this reagent is more stereoselective than other borane reagents, it was expected a single reduced product would be obtained. After 20 hours of running the reaction, under the conditions specified in scheme 32, the product **42** was obtained in 21 % yield. After eluting the column with CH_2Cl_2:MeOH, 4:1 another product was obtained. The structure of this product may have corresponded to compound **43**, scheme 32, because it seemed to be a very polar compound. The 9-BBN reduction was performed twice. The yield was 21-37 % with unreacted adduct recovered up to 18 %.

Scheme 32



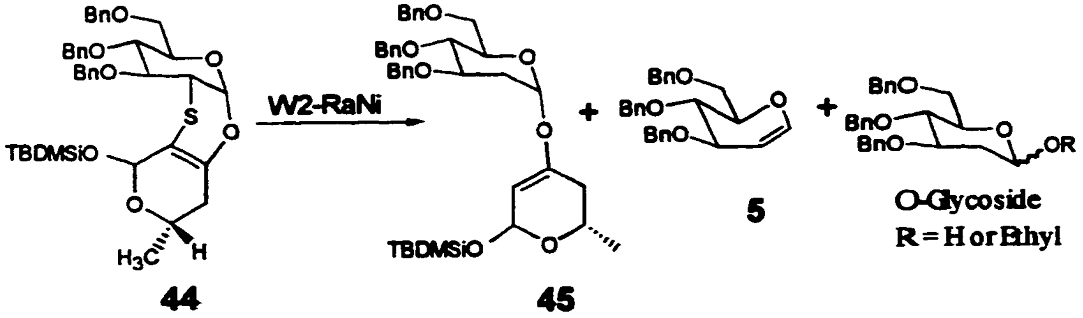
This reduced product **42** was protected as the corresponding ether by dimethyl-t-butylsilyl chloride (TBDMSCl) in DMF, scheme 33. It provided 38 % of the protected adduct.

Scheme 33



The C-S bond of this protected adduct was to be cleaved using Ph_3SnH/AIBN. After refluxing for 3 days, the starting material was recovered. This desulfurization was obtained after stirring with W-2 Raney nickel. After 20 hours, a very little amount of what seemed to be the desulfurized product, was obtained.

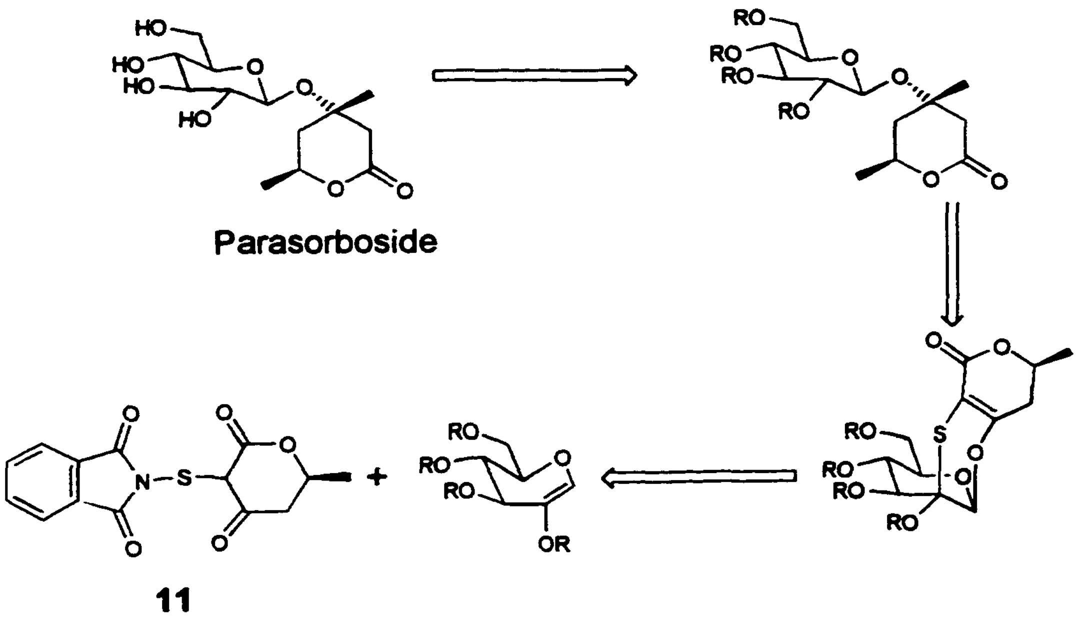
Scheme 34


BnO
BnO
BnO
S
O
O
TBDMSiO
O
H3C
H
44
W2-RaNi
BnO
BnO
BnO
O
O
TBDMSiO
O
45
+
BnO
BnO
BnO
O
5
+
BnO
BnO
BnO
O
OR
O-Glycoside
R=H or Ethyl

2.10 Synthesis of Parasorboside

Parasorboside is the glycosidic precursor of Parasorbic acid, which has antibiotic properties[60]. We can visualize its synthesis using our cycloaddition method in three steps, starting from the sulfino-lactone (S)-11 and any tetra-substituted glucal, as shown in scheme 35:

Scheme 35



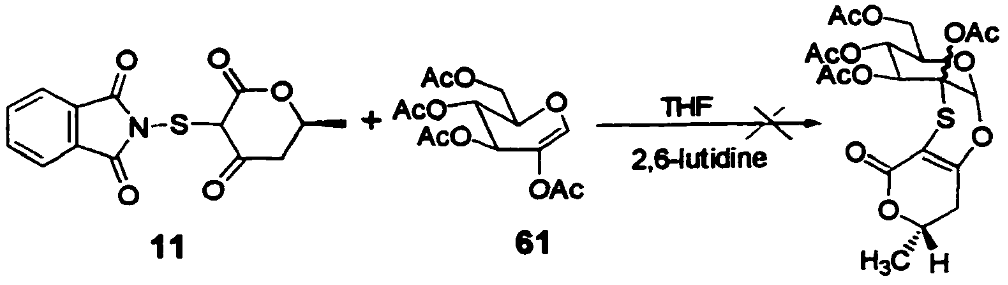
2.10.1 Cycloadditions.

We attempted the cycloaddition of this lactone with the 2-acetoxy tribenzyl glucal 49, and with tetraacetyl glucal 61. The cycloaddition with 49 was done in both NMR tube and a preparative scale.

2.10.2 Cycloaddition with tetraacetyl glucal.

The cycloaddition with tetraacetyl glucal did not give the expected cycloadduct after 10 days (scheme 36). Homo-Lumo gap studies have shown that triacetyl glucal is the least reactive glucal in the cycloaddition, so probably an extra acetoxy group slows the cycloaddition to the point that it simply does not occur.

Scheme 36

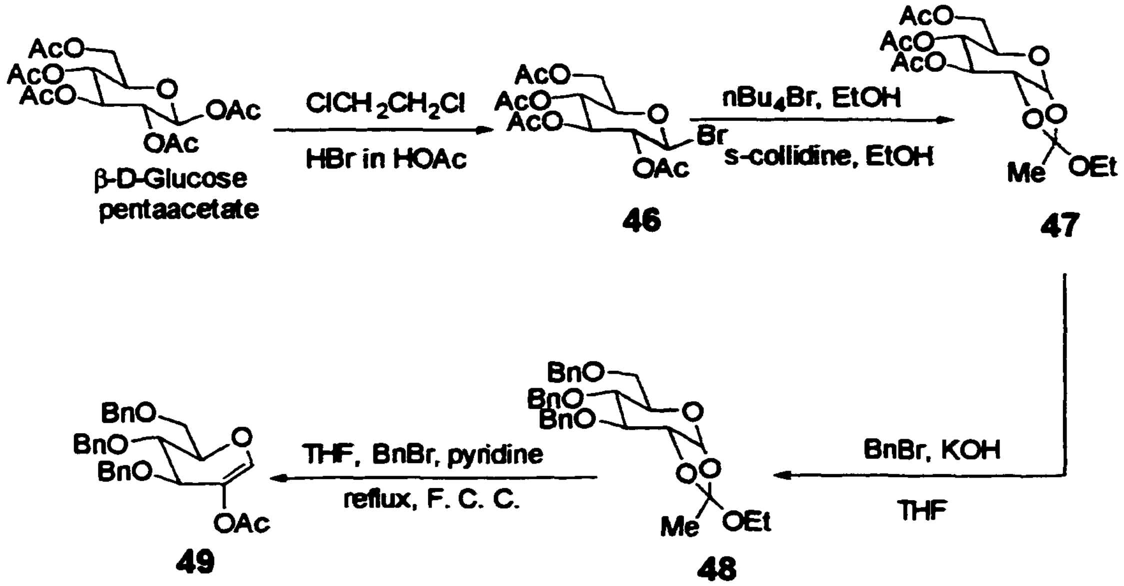


11 61 62

2.10.3 NMR Cycloaddition with the 2-acetoxy tribenzylglucal.

The 2-acetoxy tribenzyl glucal can be obtained in four steps, in 42 % overall yield (scheme37), starting from the commercially available β-D-glucose pentaacetate[61].

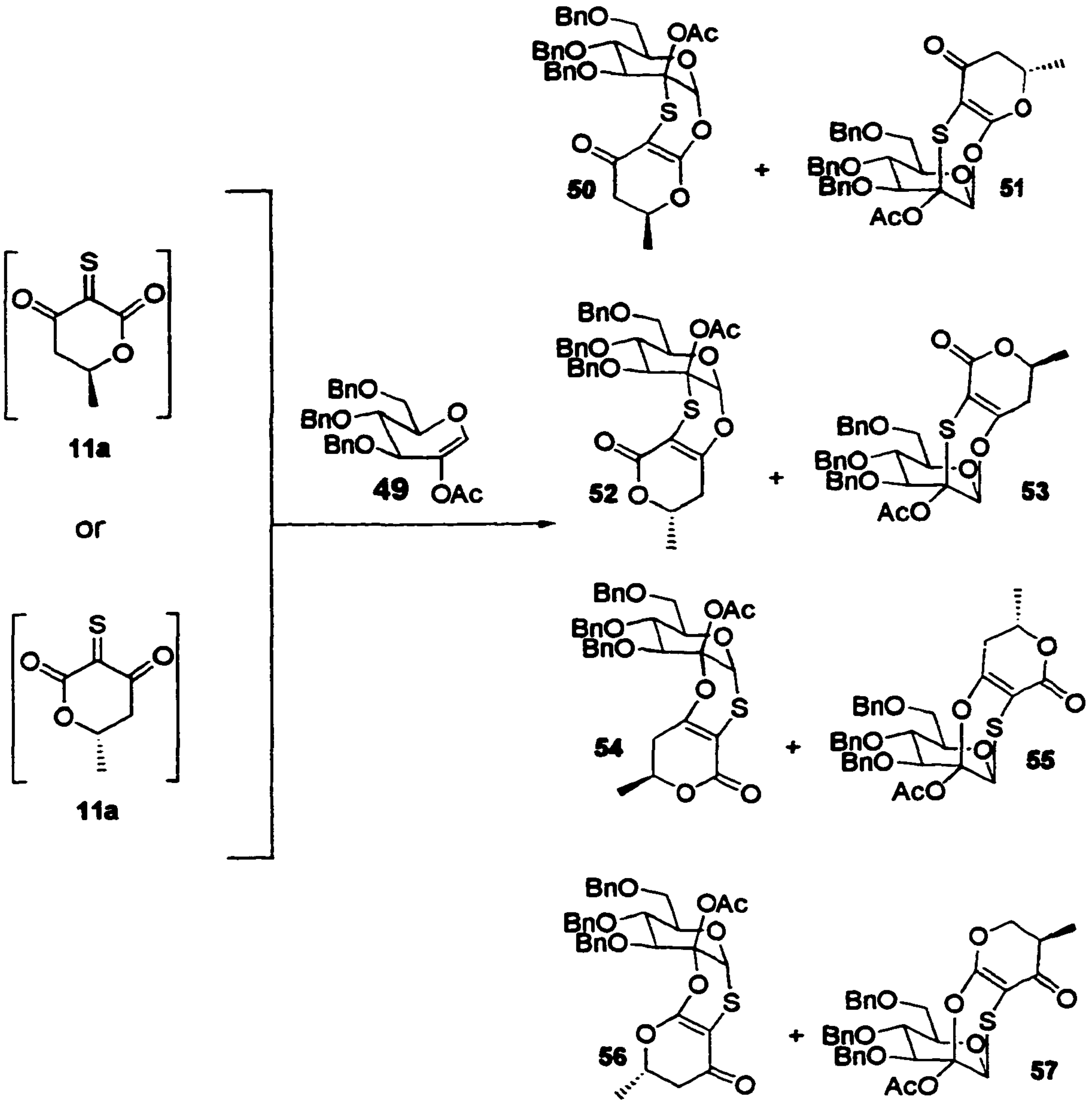
Scheme 37



The cycloaddition in an NMR tube, using $CDCl_3$ as the solvent, showed that initially there were four different peaks present corresponding to four different products: δ 5.71, 6.21, 6.28, 6.43. The initial 6.28 signal disappeared after 24 hours, while the others remained even after work up. But, which one of these is the desired precursor for the Parasorboside?

Scheme 38 shows the eight different cycloadducts that could result from the cycloaddition between the ketothione **11a** and the tetrasubstituted glucal **49**. This is due to fact that, the alkene (glucal), is now accompanied by two groups: One

Scheme 38



electron-donating group (oxygen ring), and one electron withdrawing group (the acetate). Therefore the regiospecificity of the Diels-Alder reaction, previously observed in the cycloadditions, might not be observed because the coefficients on the alkene are almost of the same size (see figure 2.14).

Looking at the ^{1}H NMR results, it is not possible to assign with certainty the structures of each one of the resulting cycloadducts. But some speculations could be made:

i) The cycloadducts such as **54**, **55**, **56**, and **57** in which the sulfur atom is attached to C(1), should have the most upfield anomeric protons.

ii) For the cycloadducts with the same regioselectivity, the corresponding anomeric proton of the top face adduct should be more upfield than the below face. For example, the anomeric proton of the cycloadduct **51** should be more upfield than the anomeric proton of the cycloadduct **50**.

iii) Based on the previous results of the cycloadditions with the other glycals and the ketothione **11a**, the least stable regioisomeric cycloadducts are **50**, **51**, **56**, **57**, in which the lactone oxygen ring is next to the double bond. Therefore, these cycloadducts are less likely to be formed.

Based on these speculations it is possible to conclude that:

a) The adduct, with the anomeric proton at 5.71 ppm, must correspond to the cycloadduct **54** or **55**.

b) The cycloadducts, with the value at 6.21 and 6.42 ppm, correspond to structures **53** and **52**, respectively. These are the above and below face adducts.

c) The initial product, with the anomeric proton at 6.28 ppm that then dissapeared, must correspond to either structures **50** or **51**. Compounds **56** and **57** probably were never formed.

Table 10

Proton NMR Ratio of Products

Solvents	*NMR Ratios of the Diastereomers, δ = 5.71 : 6.21 : 6.43*
THF	1.23 : 1.90 : 1.00
DMSO	1.43 : 1.88 : 1.00
$CHCl_3$	1.70 : 1.56 : 1.00

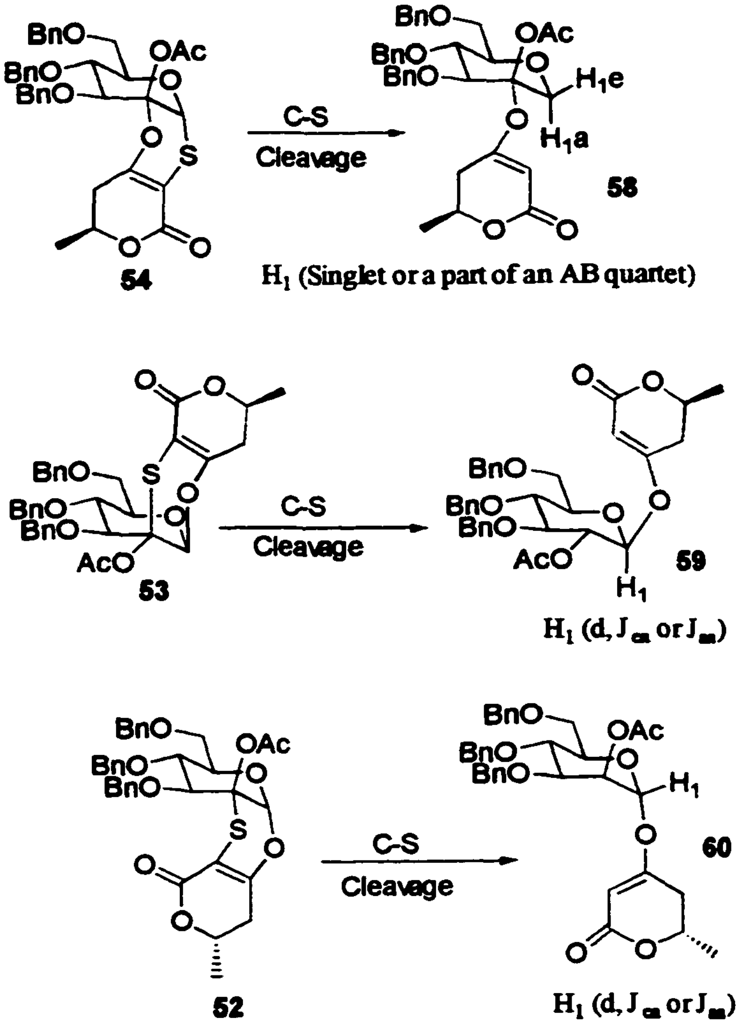
2.10.4 Preparative scale cycloadditions.

The cycloaddition in preparative scale were performed in $CHCl_3$, THF, and DMSO, using 2,6-lutidine as a base and 1.0 molar equivalent of each reagent. The ratio of the anomeric protons of each product appears in table 10. The total reaction time was 5-10 days and the combined yield after total removal of the phthalimide and flash column chromatography was 44 %. Isolation of each single regioisomer required more than one chromatography operation.

2.10.5 C-S Bond cleavage.

If we assume that the prediction for the structures of the cycloadducts are correct then, after the C-S bond cleavage, the corresponding disaccharides should be the ones shown in scheme 39. We performed several experiments in orden to cleave the C-S bond of these regiosiomers. We tried Raney nickel as well as tin hydride.

Scheme 39



2.10.5.1 C-S Bond cleavage using nBu_3SnH.

The reaction was run using a mixture of compounds **53** (H_1 = 6.21 ppm) and compound **52** (H_1 = 6.42 ppm) in nBu_3SnH/AIBN in refluxing toluene. After 20 hours, a crude residue was isolated. ^1H NMR of this residue showed a doublet at 5.4 ppm, J = 3.6 Hz, which may correspond to the expected lower face disaccharide **60**. Mass spectra showed the $M^{\cdot}$+H of the product only in 0.18 % abundance. Further attends to purify this crude residue, failed. There was no other detectable product.

Compound **53** was also treated with nBu_3SnH/AIBN. After 3 days, 1.0 mg of a product with an anomeric proton (H_1) at 4.3 ppm, J_{ae} = 1.8 Hz, was isolated. This product may correspond to compound **59**, the top face adduct in which the acetyl group at C(2) has the axial orientation.

2.10.5.2 C-S bond cleavage using W-2 Raney nickel.

Treatment of compound **53** with W-2 Raney nickel, gave a crude mixture, which after exhaustive purifications, provided tribenzylglucal **5**, 2-acetoxy tribenzylglucal **49**, and an inseparable mixture of products that looked as a single spot by TLC, but whose ^{13}C signals seemed to correspond to two different products. No further attempts to repurify this final mixture were done. If the re-purification is to be performed by chromatography or HPLC, the selection of a more appropiate solvent system should be investigated. If the separation of any of these disaccharides is successfully achieved, the tetrahydroxy parasorboside could be finally obtained by chemical or enzymatic hydrolysis of the benzyl and acetyl groups.

III. EXPERIMENTAL.

All reactions were conducted in oven-dried or flame-dried glassware under an atmosphere of dry argon or nitrogen. All solvents were purified before use; THF was distilled from sodium benzophenone ketyl; dichloromethane and chloroform were distilled from P_2O_5; triethylamine, diethylamine, DMF, and pyridine were distilled from CaH_2; and methanol was distilled from magnesium turnings. Other solvents were purified and dried using standard procedures. ^1H and ^{13}C NMR spectra were recorded on a GE QE 300 MHz instrument, in most cases using $CDCl_3$ (99.8%, 0.03 v/v TMS) as solvent. Chemical shifts are reported in δ units with coupling constants reported in Hz. TMS and residual chloroform (δ 7.26 for ^1H, δ 77.23 for ^{13}C) were used as internal references. IR spectra were recorded on a Perkin Elmer Model 1420 infrared spectrophotometer. High resolution mass spectra were performed at Urbana-Champaign University of Illinois Mass Spectrometry Laboratory and low resolution mass spectra at Hunter College Mass Spectrometry Laboratory. Optical rotations were measured on a Rudolph Autopol III polarimeter at the reported temperatures and concentrations. Melting points were measured on a Fisher-Johns stage melting point apparatus and are uncorrected. Elemental analyses were performed by Robertson Microlit Laboratories Inc., Madison, NJ and by Schwarzkopf Microanalytical Laboratory, Inc., Woodside, NY. Analytical TLC was performed with the use of plates coated with a 0.25 mm thickness of silica gel containing PF_{254} indicator (EM Science) and short-long-wave ultraviolet light was used to visualize the spots. Chromatotron Plates (radial chromatography) were prepared by using Kielesgel 60 PF_{254} (EM Science). Flash chromatography was performed as described by Still (Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* 1978, **43**, 2923-2925) with Kieselgel 60 (230-400 mesh) purchased from Aldrich and EM Science. All compounds isolated by chromatography were sufficiently pure (>95 % by NMR analysis) for use in subsequent preparative reactions.

N,N'-Dithiobis-(phthalimide (1).

A solution of sulfur monochloride (6.4 g, 49.5 mmol) in CH_2Cl_2 (3.8 mL) was added to a stirred suspension of potasium phthalimide (18.3 g, 98.9 mmol) in CH_2Cl_2 (100 mL) at 0 °C during 2 min. The white precipitate was stirred at rt for 2 1/2 h, followed by filtration and evaporation in vacuo of the solvent to give a yellow-white precipitate. Recrystallization of this crude product from chloroform afforded 11.01 g (63 %) of **1**, as large colorless needles: m.p. 229.5 °C (lit.[32] 229-230 °C); ^{1}H NMR δ 7.5-8.7 (m, 8H); ^{13}C δ 125.8, 132.6, 134.3, 166.97; IR (KBr) 1740 (ν C=O) 1466 (ν C=C) cm^{-1}.

Phthalimide-N-sulfenyl chloride (2).

Chlorine gas was bubbled for 32 h (in periods of 8 h) through a stirred refluxing solution of N,N'-dithiobis-(phthalimide) (19 g, 53.3 mmol) in chloroform (100 mL). Evaporation of the solvent in vacuo gave 14.97 g (66 %) of **2**, as bright-yellow crystals: m.p. 115-117 °C (lit.[32] 115-117 °C); ^{1}H NMR δ 7.75-8.20 (m 15 Harom.); ^{13}C NMR δ 125.08, 131.97, 135.92, 165.59, IR (KBr) 1743 (ν C=O), 1466 (ν C=C) cm^{-1}.

Phthalimide-N-sulfenyl chloride (2). Alternate Preparation.

Pyridine (0.100 g, 0.00127 mmol) and sulfuryl chloride (10.02 g, 0.074 mol) were added to an iced-cooled stirred solution of NN'-dithiobis-(phthalimide) (4.53 g, 0.0127 mol) in dried CH_2Cl_2 (100 mL) were added. The yellow colored reaction mixture was stirred for 2 d at rt and after removal of the solvent, gave 5.52g (100 %) of the title compound **2**.

2-(1-Acetyl-2-oxopropylthio)isoindoline-1,3-dione (3).

The sulfenyl chloride (3.5 g, 16.4 mmol) was added portionwise to the stirred ice-cooled pentanedione (19.68 g, 0.197 mmol) and after the addition was finished, the reaction mixture was stirred for 10 min. The cooling bath was removed and the stirring was continued at rt for an additional hour. Pentane was added and the crude precipitate formed was filtered. This crude was recrystallized from chloroform:petroleum ether to afford 2.07 g (51 %) of compound **3** as pink crystals: ^{1}H NMR δ 2.78 (s, 6H), 7.47-7.88 (m, 5H), 17.71 (s, 1H); ^{13}C NMR δ 25.44, 107.63, 123.99, 132.26, 134.79, 168.37, 201.46.

3,4,5-Trihydroxy-D-glucal (4).

Amberlite basic resin (35 g) was added to a stirred solution of triacetyl-D-glucal (10 g, 0.037 mol) in HPLC grade methanol (60 mL) and the solution was stirred for 3 h at which time TLC indicated total disappearance of the starting material. The solution was filtered to remove the resin and concentrated in vacuo to afford 4.9 g (91 %) of compound **4** as a colorless solid: m.p.54-56 °C; ^{1}H NMR (DMSO-d_6) δ 3.52-3.58 (m, 2H), 3.60-3.71 (m, 2H), 3.89-3.92 (m, 1H), 4.54-4.57 (m, 2H), 4.85 (d, J = 5.4 Hz, 1H), 5.08 (d, J = 5.4 Hz, 1H), 6.27 (dd, J = 1.5, 6.0 Hz, 1H);

^{13}C NMR (DMSO-d_6) δ 60.40, 68.44, 69.17, 79.42, 104.41, 142.88; IR (KBr): 3360 (ν OH, br), 2889 (ν CH_2), 1652 (ν C=C), 1419 (δ OH) cm^{-1}.

3,4,5-Tri-*O*-benzyl-D-glucal (5).

NaH (5.12 g, 0.128 mol) was added to a round bottom flask under N_2 and after washing with pentane (3x25 mL), THF (70 mL) and DMF (30 mL) were added. Compound 4 (4.72 g, 0.032 mol) in DMF (30 mL) was added to this stirred slurry and after the addition was completed, 10 mL of DMF were added to rinse the funnel. The resulting gray solution was stirred for 1 h and then cooled at 0 °C. To this cooled solution, tetrabutylammomonium iodide (1.18 g, 0.0032 mol) was added in one portion, followed by the addition of benzyl bromide (24.63 g, 0.144 mol) dropwise. The mixture was allowed to stir at rt overnight, after which time the TLC indicated total disappearance of the starting material. The reaction mixture was poured into saturated aqueous $NaHCO_3$. The aqueous layer was separated and extracted with chloroform (4x100 mL). The organic extracts were washed with H_2O (2x200 mL), followed by brine (2x200 mL), dried (Na_2SO_4), and concentrated in vacuo to give 17.4 g of crude. Purification by flash column chromatography eluting with hexane:ethyl acetate (4:1) afforded 12.07 g (91 %) of tribenzyl glucal 5 as a thick oil that after evaporation to dryness under vacuum became a white solid: R_f = 0.55 (3:1 hexane:ethyl acetate); m.p. 53-54°C, (lit. 57-58 °C); ^{1}H NMR δ 3.73-3.82 (m, 2H), 3.86 (dd, J = 8.4, 6 Hz, 1H), 4.03-4.08 (m, 1H), 4.19-4.22 (m, 1H), 4.53-4.66 (m, 2H), 4.81-4.88 (m, 2H), 3.82-3.73 (m, 2H), 3.86 (dd, J = 8.4, 6.0 Hz, 1H), 4.08-4.03 (m, 1H), 4.21 (ddd, J = 6.0, 2.4, 1.2 Hz, 1H), 4.54 (d, a part of an AB system, J_{AB} = 11.7 Hz, 1H), 4.63 (d, a part of an AB system, J_{AB} = 11.7 Hz, 1H), 4.65 (d, J_{AB} = 11.7 Hz, 2H), 4.83 (d, J_{AB} = 11.4 Hz, 2H), 4.87 (dd, J= 2.4, 6.5 Hz, 1H), 6.42 (dd, J = 1.2, 6.0 Hz, 1H), 7.22-7.37 (m, 15 Harom); ^{13}C NMR δ 68.73, 70.62, 73.67, 73.89, 74.61, 75.91, 100.12, 127.79, 127.88, 127.91, 128.05, 128.54, 138.20, 138.39, 138.55, 144.88; IR (Thin Film) 3030 (ν C-H), 2865 (ν CH_2), 1647 (ν C=C) cm^{-1}.

1-{(7S,8S,6R)-7,8-Bis(phenylmethoxy)-3-methyl-6-[(phenylmethoxy)methyl]-6,7,8,8a-tetrahydro-4aH,8aH--2H-pyrano[2,3-b]1,4-oxathiin-2-yl}ethan-1-one (6).

Sulfino-pentanedione 3 (1.0 g, 3.6 mmol) and tribenzylglucal 5 (1.5 g, 3.6 mmol) were dissolved in $CHCl_3$ (10 mL) with stirring and then pyridine (1.71 g, 21.6 mmol) was added by syringe, and the solution was stirred for 7 d. The reaction mixture was worked up by pouring it in $CHCl_3$ (30 mL) and washing with saturated aqueous NH_4Cl. The aqueous layer was separated and extracted with $CHCl_3$ (3x30 mL). The organic extracts were washed successively with H_2O (2x100 mL) and brine (2x100 mL), dried (Na_2SO_4), and concentrated in vacuo to give 2.32 g of a brown crude. Purification of this crude by flash column chromatography using silica gel, eluting with petroleum ether:ethyl acetate gave 0.675 g (34 %, 94 % based on the recovered glucal) of the expected cycloadduct as a white spongy powder: ^{1}H NMR δ 2.31 (s, 6H), 3.27 (dd, J = 3.0, 10.5 Hz, 1H), 3.64-3.90 (m, 3H), 3.95-4.0 (m, 2H), 4.5-4.68 (m, 4H), 4.85 (d, a part of an AB system, J_{AB} = 10.5 hz, 2H), 5.64 (d, J = 3 Hz, 1H), 7.15-7.42 (m, 15H); ^{13}C NMR δ 21.73, 30.32, 41.76, 68.22, 73.16, 73.75, 75.44, 76.58, 77.80, 78.45, 96.18, 102.08, 127.94, 128.05, 128.17, 128.60, 137.94, 138.08, 159.64, 195.33; IR (Thin Film) 2919, 2866, 1676, 1563, 1496, 1044 cm^{-1}.

1-{(7S,8S,6R)-7,8-Bis(phenylmethoxy)-3-methyl-6-[(phenylmethoxy)methyl]-6,7,8,8a-tetrahydro-4aH,8aH--2H-pyrano[2,3-b]1,4-oxathiin-2-yl}ethan-1-one (6). Alternate Procedure.

Pyridine (0.875 mL, 10.8 mmol) was added to the sulfino pentanedione 3 (0.250 g, 0.90 mmol), and to the tribenzylglucal 5 (0.750 g, 1.80 mmol) in $CHCl_3$ (10 mL). This solution was refluxed with stirring for 19 h and the cooled reaction mixture was worked up, as in the previous procedure, to provide 0.940 g of a crude residue. Purification of this residue afforded pure compound 6 (0.192 g, 39 %).

2-(4,4-Dimethyl-2,6-dioxocyclohexylthio)isoindoline-1,3-dione (7).

Sulfenyl chloride 2 (5.98 g, 0.028 mol) was added by portions to an ice-cooled stirred solution of recrystallized dimedone (3.88 g, 0.028 mol) in THF (80 mL). When the addition was finished, the solution was left stirring overnight, upon which time TLC indicated total disappearance of the starting material. Pentane (40 mL) was added to this reaction mixture. The precipitate formed was separated, and the solution concentrated in vacuo to provide a light yellow crude. Recrystallization of this crude from acetone afforded pure product 7 (6.95 g, 78 %) as white-off crystals: R_f = 0.20 (9:1 CH_2Cl_2:MeOH); m.p. 180 °C (decomposed); ^1H NMR δ 1.03 (s, 6H), 2.38 (s, 4H), 4.6 (br s, 1H), 7.71-7.83 (m, 4H); ^{13}C δ 31.78, 46.57, 77.43, 108.91, 123.83, 132.90, 134.53, 168.05, 190.43; ^{13}C NMR (DMSO-d_6) δ 27.37, 31.39, 45.64, 122.90, 132.58, 134.29, 169.20, 189.88; IR (KBr): 3204 (ν C-H), 2962 (ν CH_3), 1742 (ν C=O), 1611 (ν C=C), 1306 (δ C-CO-C) cm^{-1}; MS m/z (% rel. intensity): 291(M+2-28, 0), 275(1.6), 248(100), 147(50).

(6S,7S,8R)-6,7-Bis(phenylmethoxy)-2,2-dimethyl-8-[phenylmethoxy)methyl]-1,2,3,6,7,8,9,5a,9a-nonahydro-9-oxaphenoxathiin-4-one (8).

A solution of sulfino-dimedone 7, (100 mg, 0.32 mmol) and tribenzylglucal 5 (66.5 mg, 0.16 mmol) in pyridine (3 mL) was stirred for 7 d. The gold clear solution was treated with saturated NH_4Cl (10 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3x10 mL). The organic extracts were washed with H_2O (2x25 mL), followed by brine (1x25 mL), dried (Na_2SO_4) and concentrated in vacuo to give 0.128 g of a brownish crude solid. This crude was dissolved in CH_2Cl_2 (5 mL) and stirred with amberlite basic resin (1.25 g, 100:1 resin:crude ratio) for 1 h in order to remove the phthalimide. After removal of the resin and concentration of the solution in vacuo, 68.3 mg of a crude oil was obtained. Radial chromatography eluting with hexane:ethyl acetate (3:1) of this crude afforded 17.3 mg (19 %) of adduct **8** as a clear oil which became solid after evaporation to dryness under vacuum: $R_f = 0.34$ (3:1 hexane :ethyl acetate); m.p. 120-121 °C;

^{1}H NMR δ 1.06 (s, 3H), 1.11 (s, 3H), 2.28-2.47 (m, 4H), 3.28 (dd, J = 2.7, 10.5 Hz, 1 H), 3.56 (t, J = 10.8 Hz), 3.65-3.81 (m, 1H), 3.95-4.05 (m, 1H), 4.5-4.66 (m, 2H), 4.76 (d, J = 10.2 Hz, 2H), 4.85 (d, J = 10.5 Hz, 2H), 4.92 (d, J = 9.9 Hz, 2H), 7.13-7.40 (m, 15 Harom); ^{13}C NMR δ 27.44, 29.23, 32.36, 41.97, 43.43, 50.64, 68.17, 73.48, 73.66, 75.52, 76.53, 78.22, 78.37, 96.72, 104.03, 127.91, 128.00, 128.15, 128.32, 128.52, 128.59, 137.78, 164.04, 194.58; IR (Thin Film): 2953 (ν CH_3), 1660 (ν =C-C=O), 1601 (ν C=C), 1453 (δ CH_2) cm^{-1}; MS m/z (% rel. intensity): 604(M+18, 8.8), 587(M+1, 8), 434(100), 326(45), 180(67), 163(58), 106(26); Anal. Calc. for $C_{35}H_{38}O_6S$: C, 71.65; H, 6.53; S, 5.46. Found: C, 71.47; H, 6.55.

4a-Hydroxy-3,7-dimethyl-3,4,6,7,10a,4a-hexahydro-10aH--2H-pyrano[4,3-b]2H-pyrano[3,4-e]1,4-oxathiin-1,9-dione (10).

A stirred solution of the racemic 5,6-dihydro-4-hydroxy-6-methyl-2H-pyran-2-one (0.200 g, 1.6 mmol) in THF (6 mL) was cooled to 0 °C and sulfenyl chloride **2** (0.167 g, 0.8 mmol) was added by portions. After the addition was completed, the solution was stirred for 10 min and then allowed to reach rt. After 15 min TLC showed total disappearance of the starting material. Pentane (20 mL) was added and a precipitate was formed, which after filtration gave 0.200 g of a yellowish granular solid, identified by mass spectra and proton nmr as compound **10**: R_f= 0.11 (9:1 CH_2Cl_2:MeOH); M^+ 286; ^{1}H NMR δ 1.46 (d, J = 6.3 Hz, 6H), 2.57-2.60 (m, 4H), 4.49-4.56 (m, 2H), 11.43 (br s, 2H).

3-(1,3-Dioxoisoindolin-2-ylthio)-6-methyl-3,5,6-trihydro-2H-pyran-2,4-dione (11).

A stirred solution of sulfenyl chloride (170.8 mg, 0.8 mmol) in THF (8 mL) was cooled at –40 °C and the racemic 5,6-dihydro-4-hydroxy-6-methyl-2H-pyran-2-one (50 mg, 0.4 mmol) dissolved in 2 mL of THF was added dropwise in a period of 7 min. After 25 min all of the starting material was consumed. Pentane (10 mL) was added and a white precipitate was formed, the cooling bath was removed, and the reaction mixture was allowed to warm to rt without stirring. Filtration of this mixture provided 122 mg of a white crude solid. Recrystallization from CH_2Cl_2:Hexane afforded pure compound 11 (55.4 mg, 46 %) as colorless crystals: R_f= 0.05 (9:1 CH_2Cl_2:MeOH); ^{1}H NMR δ 1.53 (d, J = 6.3 Hz, 3H), 2.86 (dd, J = 2.36, 16 Hz, 1H), 3.04 (dd, J = 11.33, 16 Hz, 1H), 5.02-5.06 (m, 1H), 7.77-7.80 (m, 4Harom); ^{13}C NMR δ 21.12, 44.18, 72.23, 101.44, 124.67, 132.00, 135.30, 165.32, 167.94, 194.68.

(2R,3R,4R,8R)- and (8S,2R,3R,4R)- 3,4-Bis(phenylmethoxy)-8-methyl-2-[(phenylmethoxy)methyl]-2,3,4,8,9,4a-hexahydro-10aH,4aH--2H-pyrano[2,3-b]2H-pyrano[3,4-e]1,4-oxathiin-6-one (13) and (12a). General Stepwise Cycloaddition Procedure.

The racemic sulfino lactone **11** (35.5 mg, 0.116 mmol) and tribenzylglucal **5** (48.4 mg, 0.116 mmol) were dissolved in CH_2Cl_2 (1 mL), and pyridine (55.1 mg, 0.696 mmol) was added, and the solution was stirred at rt for 5 d. ^{1}H NMR of an aliquot was taken. The ratio of the anomeric protons of the product and the glucal was H_p:H_g = 1:1. The reaction was left stirring 2 more days, but the ratio glucal:product remained the same. The reaction was worked up by dissolving it in CH_2Cl_2, extracting with saturated aqueous NH_4Cl and back extracting the aqueous layer with CH_2Cl_2. The organic extracts were washed twice with brine, dried (Na_2SO_4), and concentrated in vacuo to give 95.2 mg of a crude brown solid. Purification was done by flash chromatography, eluting with Petroleum ether:ethyl acetate (3:1), and finally with pure ethyl acetate in order to remove the product, 35.6 mg (53.5 %, 100 % based in the recovered glucal), as a 1:1 mixture of diastereomers. This mixture was separated by silica gel P-plate (1000 microns 20x10 cm) eluting first with ethyl acetate then 5 times with petroleum ether:ethyl acetate 3:1. This separation afforded 2 diastereomers: **upper spot** 7.3 mg and **lower spot** 2.8 mg both as white foamy solids.

13, Upper Spot: R_f= 0.59 (1:3 ethyl acetate:hexane, eluted 5 times); m.p. 128-130 °C; ^{1}H NMR δ 1.47 (d, J = 6.3 Hz, 3H), 2.40 (dd, J = 3.6, 17.4 Hz, 1H), 2.48 (dd, J = 12.3, 17.4 Hz, 1H), 2.37 (dd, J = 2.8, 10.6 Hz, 1H), 3.67-3.85 (m, 4H), 4.04 (app d, J = 10 Hz, 1H), 4.42-4.50 (m, 1H), 4.57 (d, a part of an AB system, J_{AB}= 12 Hz, Δv =34.65 Hz, 1H), 4.59 (d, a part of an AB system, J_{AB} = 10.2 Hz, Δv = 95.55 Hz, 1H), 4.68 (d, J_{AB} = 12.3 Hz, Δv = 34.65 Hz, 1H), 4.88 (d, a part of an AB system , J_{AB} = 10.2 Hz, Δv = 29.85 Hz, 1H), 4.91 (d, a part of an AB system, J_{AB} = 9.3 Hz, Δv = 95.55 Hz, 1H), 4.97 (d, a part of an AB system, J_{AB} = 10.5 Hz, Δv = 29.85 Hz, 1H), 5.69 (d, J = 2.7 Hz, 1H), 7.20-7.50 (m, 15 Harom); ^{13}C NMR δ 20.50, 35.28, 42.92, 68.14, 72.84, 73.58, 73.77, 75.54, 76.29, 78.60, 94.67, 96.62, 128.07, 128.16, 128.41, 128.61, 128.69, 128.77, 137.60, 137.89, 159.44, 164.60; IR (Thin Film) : 2914 (v CH_2), 1703 (v C=O), 1623 (v C=C), 1495 (δ CH_2), 1453 (v_{as} C=C), 1284 (v C-O-C) cm^{-1}; MS m/z (% rel. intensity) 592(M+18, 1.79), 462(81), 434(100), 388(87), 326(37), 234(84), 108(10).

12a, Lower Spot: R_f= 0.48 (1:3 ethyl acetate:hexane, eluted 5 times); m.p. 44-47 °C; $[\alpha]_D$ = +128.8° (c = 2.56, $CHCl_3$); ^{1}H NMR δ 1.46 (d, J = 6.3 Hz, 3H), 2.48 (dd, J = 4.5, 17 Hz, 1H), 2.62 (dd, J = 10.8, 17 Hz, 1H), 3.29 (dd, J = 3, 10.8 Hz, 1H), 3.55 (dd, J = 9, 10.5 Hz, 1H), 3.68-3.82 (m, 3H), 3.96 (app dt, J = 3, 10.1 Hz, 1H), 4.52-4.69 (m, 4H), 4.79 (d, J_{AB} = 10.2 Hz, a part of an AB system, 1H), 4.98 (d, J = 10.2 Hz, a part of an AB system, 1H), 5.72 (d, J = 3 Hz, 1H), 7.15-7.44(m, 15Harom); ^{13}C NMR δ 21.7, 36.01, 43.30, 69.33, 73.20, 74.70, 74.80, 76.50, 78.40, 79.30, 95.10, 98.10, 102.40, 129.03, 129.10, 129.25, 129.59, 138.80, 138.90, 161.30, 164.85; IR (Thin Film) : 3029(v C-H), 2918 (v CH_2), 1704 (v

C=O), 1618 (ν C=C) cm^{-1} MS m/z (% rel. intensity): 592(M+18, 2.6), 434(100), 326(50), 309(25), 234(57), 146(42), 108(10), Anal. Calcd for $C_{33}H_{34}O_7S$: C, 68.97; H, 5.96; S, 5.58; Found: C, 68.96, H, 5.96; S, 5.70.

5-(1-Hydroxy-3-oxobutylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (14).

A solution of 2,2-dimethyl-1,3-dioxane-4,6-dione (7.2 g, 0.05 mol) in dried $CHCl_3$ (75 mL) was cooled to 0 °C. Distilled triethylamine (5.31 g, 0.025 mol), and then diketene (4.25 g, 0.0505 mol) were added by syringe, and the solution was left stirring overnight at rt and refluxed the next day. After refluxing for 1 h, no starting material was detected by TLC. The solution was cooled to rt and then treated with an aqueous 1N HCl solution (2x60 mL), followed by H_2O (2x60 mL) and brine (1x100 mL), dried (Na_2SO_4), and concentrated in vacuo to provide a gold oil. After rinsing this oil with petroleum ether it afforded 10.62 g (93 %) of the product **14** as clear elongated needles: R_f = 0.38 (10:1 CH_2Cl_2:MeOH); m.p. 181 °C (lit.[39] 181-182 °C); ^1H NMR δ 1.74 (s, 6H), 2.32 (s, 3H), 4.13 (s, 3H), 14.98 (s, 1H); ^{13}C NMR δ 26.96, 30.73, 50.60, 93.47, 105.66, 160.78, 170.04, 188.94, 199.72; IR (Thin Film): 1735 (ν C=O), 1669 [ν C=C(OH)-CO-enol], 1155 (νC-O) cm^{-1}.

2,2-Dimethyl-6-(2-oxopropyl)-1,3-dioxin-4-one (15).

A stirring solution of isopropylamine (2.61 g, 22 mmol) in THF (27 mL) was cooled to -10 °C and n-butyllithium (22 mmol) in THF was added dropwise. After the addition was finished the solution was cooled to –78 °C, and hexamethylphosphoric amide (7.16 g, 40 mmol) was added by syringe. After stirring for 1/2 h at this temperature, 2,2,6-trimethyl-4H-1,3-dioxin-4-one (2.84 g, 20 mmol), was added, followed by acetyl chloride (0.785 g, 10 mmol. When the addition was finished, the solution was allowed to go to rt and a 10 % aqueous HCl solution (50 mL) was added. The resulting solution was extracted with ether (4x50 mL), and the organic extracts were washed with brine (2x100 mL), dried ($MgSO_4$) and concentrated in vacuo to give 3.76 g of a red-orange crude oil, which after purification by flash column chromatography with silica gel, eluted with petroleum ether:ethyl acetate (3:1 to 1:1) gave 0.600 g of compound **15** as a clear oil: ^{1}H NMR δ 1.66 (s, 6H), 2.19 (s, 3H), 3.31 (s, 2H), 5.29 (s, 1H); ^{13}C NMR δ 25.07, 25.21, 30.33, 48.16, 96.83, 107.49, 164.66, 201.05; IR (Thin Film) : 1726 (ν C=O), 1638 (ν C=CH), 1378 (δ CH_3), 1275 (ν C-O-C) cm^{-1}; MS m/z (% rel. intensity): 185(M+1, 15), 170(10), 142(20), 86(100), 58(39), 44(78).

6-(2-Hydroxypropyl)-2,2-dimethyl-1,3-dioxin-4-one [(R/S)16].

The ketone **15** (0.590 g, 3.21 mmol) was dissolved in ethanol (16 mL), and the solution was stirred for 15 min at 0 °C. Powdered sodium borohydride (121.5 mg, 3.21 mmol) was added to this cooled solution in three portions and the mixture was stirred for 20 min. When all the starting material disappeared as indicated by TLC, a 10 % aqueous solution of HCl (20 mL) was added to neutralize the remaining reducing agent. The product was extracted with ether (3x50 mL), and the combined organic extracts washed with brine (2x100 mL), dried ($MgSO_4$), and concentrated in vacuo to give 0.4963 g (83.1 %) of compound **16** as an oil, pure enough to be used in the next step without further purification: ^{1}H NMR δ 1.27 (d, J = 6.3 Hz, 3H), 1.70 (s, 6H), 2.38 (app dd, J = 3.3, 6.15 Hz, 2H), 2.8 (br s, 1H), 4.09-4.20 (m, 1H), 5.33 (s, 1H); ^{13}C NMR δ 23.54, 24.91, 25.26, 43.26, 64.96, 94.88, 106.70, 161.61, 169.67; IR (Thin Film): 3433 (ν O-H, intermolecular hydrogen bonding), 2972 (ν CH_3), 2932 (ν CH_2), 1633 (ν C=C), 1118 (ν C-O) cm^{-1}; MS m/z (% relat. intensity): 188(M+2, 10), 146(100), 102(13).

6-(2-Hydroxypropyl)-2,2-dimethyl-1,3-dioxin-4-one (16). Via acetaldehyde.

[2,2,6-trimethyl-4H-1,3-dioxin-4-one (1.52 g, 10.7 mmol) was added dropwise to a solution of LDA (11 mmol) at −78 °C and the mixture was stirred for 1/2 h. Acetaldehyde (0.471 g, 10.7 mmol) was added dropwise while the temperature was maintained at −78 °C, and when the addition was completed, the reaction mixture was allowed to go to rt. The reaction mixture was worked up by pouring it in 25 mL of 10 % aqueous HCl and extracting with ether (3x25 mL), drying the ether extracts ($MgSO_4$), and concentrating in vacuo to give 1.69 g of an oily residue. Purification of this residue by flash column chromatography, eluting with petroleum ether:ethyl acetate (9:1 to 3:1) afforded 0.379 g (19 %) of product. This product was identical to the title compound **16**.

5-((3S)-1,3-Dihydroxybutylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione [(S)-17]. Dried Fleischman's yeast (75 g), sucrose (37.5 g), and 'tap" water (150 mL) were divided into 5 portions and placed in 5x500 mL Erlenrmayer flasks and shaken for ½ h, at which time the yeast rose and reached the opening of the flasks. Acetoacetylated Meldrum's acid **14** (1.14 g, 5 mmol), divided in five 0.228 g portions was placed in each flask and shaken for 1 d. Most of the water was evaporated. Celite (10 g) and NaCl (5 g) were placed in each flask and mixed until became a paste. This paste was extracted 6 times with CH_2Cl_2 by strong mechanical stirring, followed by decantation, starting with 150 mL of CH_2Cl_2 and the remaining 5 extractions with 100 mL. The combined organic extracts were dried ($MgSO_4$), and concentrated in vacuo to give 1.42 g (100 %) of the crude chiral alcohol **(S)-17** as a gold oil: R_f= 0.50 (CH_2Cl_2:MeOH); $[\alpha]_D$ = +41.80° (c = 0.55, EtOH), (lit[43] $[\alpha]_D$ = +50.5, c = 2.05, EtOH); ^1H NMR δ 1.3 (d, J = 6.3 Hz, 3H), 1.7 (s, 6H), 3.1 (dd, J = 3.9, 13.5 Hz, 1H), 3.3 (dd, J = 8.4, 13.5 Hz, 1H), 4.3 (m, 1H).

(S)-6-Methyl-3,5,6-trihydro-2H-pyran-2,4-dione- (9).

The enantiopure alcohol **(S)-17**, (1.91 g, 8.29 mmol) was dissolved in dried MeOH (30 mL) and stirred under reflux. After 2 1/2 h, the starting material was consumed as indicated by TLC, and the reaction mixture was cooled to rt and concentrated in vacuo to provide 1.10 g of crude. Purification of this crude by flash column chromatography using florisil and eluting with CH_2Cl_2:MeOH (20:1) afforded 0.600 g (56 %) of the enantiopure lactone **(S)-9** as a white granular solid: $R_f = 0.53$ (9:1 CH_2Cl_2:MeOH) m.p. 127-129 °C $[\alpha]^{25} = +150.74°$ (c = 2.1, EtOH), lit.[43] $[\alpha]^{29} = +153.4°$, c = 2.1 EtOH); ^{1}H NMR δ 1.53 (d, J = 6.3 Hz, 3H), 2.46 (dd, J = 11.1, 18.3 Hz, 1H), 2.73 (dd, J = 2.7, 18.3 Hz, 1H), 3.44 (d, a part of an AB system, J_{AB} = 18.9 Hz, Δv = 38.25 Hz, 1H), 3.57 (d, a part of an AB system, J_{AB} = 18.9 Hz, Δv = 38.25 Hz, 1H), 4.76-4.84 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 20.25, 34.03, 71.45, 90.58, 167.06, 172.66; IR (KBr) : 2933 (v CH_3), 1675 (v C=O), 1576 (v C=C), 1284, 1245 (v C-O), 1419 (v CH_2-CO-, active methylenes) cm^{-1}.

Racemic 6-methyl-3,5,6-trihydro-2H-pyran-2,4-dione[(R/S)-9].

The acetoacetylated Meldrum's acid, **14**, (0.5 g, 2.2 mmol) was dissolved under stirring in absolute ethanol (22 mL), and after the solution was cooled by ice-bath, $NaBH_4$ (60 mg, 1.59 mmol) was added by portions. After the starting material was consumed as indicated by TLC, the ethanol was removed by rotary evaporation. A dilute solution of 5 % v/v HCl-brine was added to this residue while cooling, and then stirred for 10 min. The reaction mixture was extracted with ethyl acetate (4x40 mL), the organic extracts dried ($MgSO_4$), and concentrated in vacuo to give 0.494 g of the racemic alcohol **(R/S)-9**, as a light-gold oily residue. This crude residue was refluxed in MeOH (15 mL), and after 1 1/2 h all of the starting material was consumed. The reflux was stopped, the reaction mixture was cooled and concentrated in vacuo to give 0.290 g of a crude. Purification of this crude by flash column chomatography using florisil, eluting with CH_2Cl_2:MeOH (20:1) gave 55.1 mg (11 %, combined two steps) of the racemic lactone **(R/S)-9**, whose ^1H NMR was identical to the commercially available lactone.

Chiral reduction of the acetoacetylated Meldrum's acid.

A three neck round bottom flask, provided with a low temperature thermometer, sealed mechanical stirrer and a septum was flame dried under vacuum and purged with argon three times. The ketone (1.0 g, 4.38 mmol), dissolved in dried THF (22 mL) was added dropwise, followed by [(S)-(-)-α,α-diphenyl-2-pyrrolidinemethanol] (111 mg, 0.438 mmol) in toluene (2.4 mL) and after the addition was finished, the gold-yellow solution was cooled down to –73 °C. Catechol borane (1.5 g, 8.76 mmol) in toluene was added dropwise to this cooled solution and the reaction was stirred at this temperature for 7 1/2 h. The reaction was quenched by the addition of H_2O at –70 °C, and after reaching rt, the white-yellowish solution was poured in ether (30 mL). The aqueous layer was separated and extracted with ether (4x30 mL). The organic extracts were washed with saturated aqueous $NaHCO_3$ (100 mL), followed by water (2x100 mL), then brine (2x100 mL), dried (Na_2SO_4), and concentrated in vacuo to give 1.121 g of a white foamy solid whose proton NMR showed neither product nor starting material.

Racemic 6-methyl-2-oxo-5,6-dihydro-2H-pyran-4-yl acetate [(R/S)-18].

The racemic lactone (100 mg, 0.78 mmol) in CH_2Cl_2 (4.0 mL) was cooled at 0 °C, and pyridine (76 mg, 0.96 mmol) was added, followed by acetic anhydride (82 mg, 0.80 mmol). The solution was stirred at rt overnight at which time TLC showed disappearance of the starting material. The reaction was poured in saturated aqueous NH_4Cl (5mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3x5 mL). The combined organic extracts were washed with 10 % aqueous $NaHCO_3$ (10 mL), followed by H_2O (2x10 mL), then brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo to give the crude product **(R/S)-18** (85.7 mg, 65 %), as a light gold oil: R_f = 0.83 (9:1 CH_2Cl_2:MeOH) ^{1}H NMR δ 1.41 (d, J = 6.3 Hz, 3H), 1.86 (s, 3H), 2.44 (dd, J = 4.2, 17.7 Hz, 1H), 2.60 (ddd, J = 2.1, 11.5, 17.6 Hz, 1H), 4.52-4.63 (m, 1H), 5.87 (d, J = 2.1 Hz, 1H); ^{13}C NMR δ 20.52, 21.43, 34.11, 72.99, 106.73, 163.91, 165.52, 167.12; IR (Thin Film) 2983, 1777, 1715, 1659, 1636, 1391, 1388, 1188, 1153 cm^{-1}; MS m/z (% rel. intensity) 170 (M+H, 1.1), 128(18), 87(17), 43(100).

Lipase Resolution of the racemic lactone.

The racemic lactone (300 mg, 2.34 mmol) was dissolved by stirring in vinyl acetate (20 mL) and after adding 300 mg of porcine pancreatic lipase (PPL, type II, from Sigma), the solution was left stirring overnight. TLC (CH_2Cl_2:MeOH 9:1) showed formation of the acetylated lactone (R_f = 0.83) as well as some unreactive lactone (R_f = 0.54) with similar intensities. The reaction was left stirring until the next day, upon which time, the TLC showed almost complete disappearance of the spot corresponding to the lactone. The acetylated lactone was still present as well as several other spots with lower R_f's. One day later the lactone had disappeared totally. The reaction mixture was filtered through a celite pad and the filtrate concentrate in vacuo to give 0.340 g of oily crude. ^{1}H NMR looked very messy. Several attempts to purify this crude failed. Leaving the reaction for such a long time probably gave polymerized products.

Trihydroxy-D-galactal (20).

Tri-*O*-acetyl galactal **19** (16.06 g, 0.059 mol) was dissolved with stirring in HPLC grade MeOH (100 mL), and amberlite basic resin (25 g) was added. After the starting material disappeared as indicated by TLC, the resin was removed by filtration and the filtrate concentrated in vacuo to give 7.3 g (84.3 %) of product **20** as a thick oil, which after evaporation to dryness, became a white solid: m.p. 79-83 °C; ^{1}H NMR (DMSO-d_6) δ 3.54-3.58 (m, 2H), 3.72 (app d, J = 6.3 Hz, 2H), 4.18 (br s, 1H), 4.36 (d, J = 3.6 Hz, 1H), 4.46 (d, J = 6.0 Hz, 1H), 4.60 (d, J = 6.6 Hz, 1H), 4.70-4.73 (m, 1H), 6.23 (d, J = 5.1 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 60.31, 63.41, 64.29, 75.51, 103.63, 143.14; IR (KBr): 3422 (ν OH), 1644 (ν C=C), 1399 (δ OH), 1150 (ν C-O-C) cm^{-1}.

Tri-*O*-benzyl-D-galactal (21).

To a round bottom flask under nitrogen was added NaH (5.12 g, 0.128 mol) and washed with pentane (4x30 mL). THF (60 mL), and DMF (30 mL) were added, then the trihydroxy galactal **20** (4.72 g, 0.032 mmol) dissolved in DMF (30 mL) was added by dropping funnel. After the addition was finished, the gray solution was stirred for 1 h at rt and then cooled at 0 °C. To this cooled solution, tetrabutylammonium iodide (1.18 g, 0.0032 mol) was added in one portion, followed by the dropwise addition of benzyl bromide (24.63 g, 0.144 mol). After stirring for 10 min, the reaction mixture was stirred at rt overnight, in which time all of the starting material was consumed. The yellowish mixture was poured in $CHCl_3$ (100 mL) and extracted with saturated aqueous NH_4Cl (100 mL). The separated aqueous layer was extracted with $CHCl_3$ (3x50 mL), and the organic extracts were washed exhaustively with water, then with brine (3x150 mL), dried (Na_2SO_4), and concentrated in vacuo to give 19.30 g of a crude gold syrup. Purification of this crude by flash column chromatography with silica gel eluting with hexane:ethyl acetate (5:1) provided 10.65 g (80 %) of tribenzylgalactal **21** as a clear oil[50], which after evaporation to dryness and storage in the freezer became an amorphous solid: R_f= 0.37 (5:1 hexane:ethyl acetate); ^1H NMR δ 3.58 (dd, J = 5.0, 12.4 Hz, 1H), 3.71 (dd, J = 7.3, 7.05 Hz, 1H), 3.86-3.88 (m, 1H), 4.09-4.13 (m, 2H), 4.34 (d, J = 12 Hz, 1H), 4.43 (d, J = 12 Hz, 1H), 4.49-4.60 (m, 2H), 4.76-4.82 (m, 2H), 6.28 (dd, J = 1.2, 6.3 Hz, 1H), 7.17-7.32 (m, 15H); ^{13}C NMR δ 68.61, 70.94, 71.06, 71.54, 73.47, 73.57, 75.87, 100.13, 127.59, 127.70, 127.83, 127.91, 128.03, 128.27, 128.48, 128.52, 138.19, 138.56, 138.69, 144.34; IR (Thin Film): 3029 (ν C-H), 2866 (ν CH_2), 1644 (ν C=C), 1349 (δ OH), 1094 (ν C-O-C) cm^{-1}.

Thiophenyl-4,6-di-*O*-acetyl-2,3-dideoxy-hex-7-enol (22).

Thiophenol (5.0 g, 45.4 mmol) was added to a solution of tri-*O*-acetyl glucal (6.186 g, 22.7 mmol) in CH_2Cl_2 (240 mL), and the solution was cooled to −17 °C. Boron trifluoride etherate (1.63 mmol, 0.231 g) was added slowly by syringe in a period of 7 min. Half an hour later, when the starting material was consumed, as indicated by TLC, the reaction mixture was poured in saturated aqueous $NaHCO_3$ (100 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3x120 mL). The organic extracts were washed with H_2O (2x100 mL), brine (200 mL), dried (Na_2SO_4), and concentrated in vacuo to give 9.52 g of a cloudy oil. Purification of this oil by silica gel, eluting with petroleum ether:ethyl acetate (9:1 to 3:1) gave 4.56 g (62.3 %) of the **α-anomer**[51] and 1.82 g (24.8 %) of the β-anomer, α:β = 2.4:1. Compound **α-anomer**: ^1H NMR δ 2.08 (s, 3H), 2.12 (s, 3H), 4.21 (dd, J = 2.4, 12 Hz, 1H), 4.24 (dd, J = 5.7, 12 Hz, 1H), 4.45-4.51 (m, 2H), 5.39 (app dd, J = 1.8, 11.4 Hz, 1H), 5.76 (d, J = 1.21 Hz, 1H), 5.88 (app d, J = 11.4 Hz, 1H), 6.1 (app dt, J = 2.1, 4.8 Hz, 1H), 7.26-7.31 (m, 3H), 7.54-7.57 (m, 2H); ^{13}C NMR δ 20.91, 21.14, 63.26, 65.34, 67.52, 83.84, 127.83, 128.72, 129.11, 131.91, 131.98, 134.99, 170.39, 170.84; IR (Thin Film) 3058, 2952, 1742, 1583, 1481, 1439, 1058 cm^{-1}.

2-Deoxy-α-phenyl sulfoxide (23).

A solution of the α-sulfide (0.490 g, 1.52 mmol) in CH_2Cl_2 (47 mL) was cooled to 0 °C and m-CPBA (0.367 g, 1.83 mmol) was added in one portion. After stirring at 0 °C for ½ h the starting material was consumed as indicated by TLC. The cloudy solution was poured in saturated aqueous $NaHCO_3$. The aqueous layer was separated and extracted with CH_2Cl_2 (3x50 mL), The organic extracts were washed with H_2O (2x100 mL) and then with brine (1x100 mL), dried (Na_2SO_4), and concentrated in vacuo to give 0.508 g (100%) of the α- sulfoxide **23** as a gold yellow oil. This crude was used in the next step without further purification. **α-sulfoxide**: ^{1}H NMR δ 2.07-2.18 (m, 6H), 4.26-4.39 (m, 4H), 5.03-5.30 (m, 2H), 6.47 (d, J = 5.7 Hz, 1H), 7.32-7.56 (m, 5Harom.); IR (Thin Film) 3058, 2955, 1746, 1643, 1370 (sulfones), 1091 and 1050 (sulfoxides) cm^{-1}.

3,6-Di-*O*-acetyl-D-allal (24).

To the α-sulfoxide **23** (0.494 g, 1.46 mmol) in THF (37 mL) freshly distilled diethylamine (0.856 g, 11.7 mmol) was added by syringe and after 5 ½ h the starting sulfoxide disappeared, as indicated by TLC. The solution was poured in ethyl acetate (60 mL) and extracted with saturated aqueous $NaHCO_3$. The aqueous layer was separated and extracted with ethyl acetate (3x100 mL). The organic extracts were washed successively with water (2x100 mL), aqueous NH_4Cl (100 mL), and brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo to give 0.526 g of a crude oil. Purification of this crude by flash column chromatography, eluting with hexane:ethyl acetate (1:1), provided 0.217 g (63 %) of diacetyl allal[51], 24, as a clear oil: ^{1}H NMR δ 2.10 (s, 3H), 2.13 (s, 3H) 2.94 (d, J = 6.6 Hz, 1H), 3.39 (dd, J= 4.5, 12.3 Hz, 1H), 3.93-3.96 (m, 1H), 4.01-4.07 (m, 1H), 4.50 (dd, J = 1.8, 12.3 Hz, 1H), 4.95 (dd ≅ t, J = 6, 5.7 Hz, 1H), 5.24 (dd, J = 3.9, 5.7 Hz, 1H), 6.50 (d, J = 6, Hz, 1H); ^{13}C NMR δ 20.95, 21.32, 63.19, 65.63, 65.88, 72.99, 97.66, 147.92, 171.41, 171.47.

Trihydroxy-D-allal (25).

3,6-Diacetoxy allal 24 (0.198 g, 0.86 mmol), in methanol (10 mL) was stirred with amberlite basic resin (0.400 g). After 1 ½ h, all of the starting material had disappeared as indicated by TLC. The resin was removed by filtration, and the solution concentrated in vacuo to give 0.104 g (83.5%) of tri-hydroxyallal as a clear oil. No other determination was done. It was used as it was in the next step.

Tri-*O*-benzyl-D-allal (26).

NaH (0.163 g, 4.16 mmol) was added in a round bottom flask with a stirring bar under nitrogen and washed with pentane (3x5 mL), then THF (3 mL) and DMF (1 mL) were added. The trihydroxy-D-allal **25** (0.103 g, 0.70 mmol) in DMF (4 mL) was added to this stirred slurry, and after stirring for 1 h at rt, it was cooled with an ice-bath. Tetrabutylammonium iodide (0.026 g, 0.070 mmol) was added followed by benzylbromide (0.539 g, 3.15 mmol). After the addition was finished, the solution was allowed to go to rt and left stirring overnight at which time all of the starting material was consumed. The solution was poured into a saturated aqueous $NaHCO_3$ solution. The aqueous layer was separated and extracted with CH_2Cl_2 (4x25 mL). The organic extracts were washed with H_2O (25 mL), brine (25 mL), dried (Na_2SO_4), and concentrated in vacuo to give 0.447 g of a gold crude oil. Purification by flash column chromatography, eluting with hexane:ethyl acetate (5:1) afforded 0.246 g (84.62 %) of the expected product **26** as a clear thick oil[51]: R_f = 0.40 (5:1 hexane:ethyl acetate); ^1H NMR δ 3.76-3.81 (m, 2H), 3.83-3.96 (m, 2H), 4.3 (dt, J = 3, 10.5 Hz, 1H), 4.43-4.72 (m, 6H), 4.88 (app t, J = 6 Hz, 1H), 6.4 (d, J = 6 Hz, 1H), 7.16-7.37 (m, 15 Harom); ^{13}C NMR δ 65.73, 69.03, 70.52, 71.42, 73.20, 73.67, 74.09, 77.43, 98.28, 127.67, 127.82, 127.97, 128.03, 128.18, 128.43, 138.07, 138.27, 138.83, 146.73; IR (Thin Film) 3029, 2866, 1642, 1492, 1453, 1228, 1116, 1027 cm^{-1}.

1,2-Dideoxy-4,6-*O*-isopropyledene-D-arabino-hex-1-enopyranose (27).

2,2-Dimethoxypropane (19.27 g, 0.185 mol) was added by syringe to the dissolved trihydroxy glucal (5.51 g, 0.038 mol), followed by p-toluenesulfonic acid (1.14 g, 6.0 mmol). The pH became 3 and the solution was left stirring for 4 h until TLC showed no change. The reaction mixture was poured in saturated $NaHCO_3$ and the aqueous layer was separated and extracted with $CHCl_3$ (3x50 mL), dried (Na_2SO_4), and concentrated in vacuo to give 3.7 g of a crude oil. Flash column chromatography, eluting with hexane:ethyl acetate (2:1) gave 1.24 g (18%) of the expected product **27** as a clear oil[52]: $R_f = 0.48$ (1:1 hexane:ethyl acetate) ^1H NMR δ 1.45 (s, 3H), 1.54 (s, 3H), 2.54 (d, J = 4.5 Hz, 1H), 3.71-3.84 (m, 3H), 3.87-3.98 (m, 1H), 4.34-4.37 (m, 1H), 4.73 (dd, J = 1.8, 6 Hz, 1H), 6.3 (dd, J = 1.8, 6.2 Hz, 1H); ^{13}C NMR δ 19.26, 22.15, 61.74, 67.19, 69.47, 73.70, 100.03, 104.09, 144.14; IR (Thin Film) 3448, 2994, 2893, 1642, 1375 cm^{-1}.

General procedure for the 'one pot' cycloaddition.

A stirring 0.1 M solution in THF or $CHCl_3$ of sulfenyl chloride was cooled to −40 °C, the enantiopure lactone in a 0.1 M solution in THF or $CHCl_3$ was added dropwise by funnel. When the lactone was consumed (as indicated by TLC) the dissolved glycal was added, and then the base. The cooling bath was removed and the reaction was allowed to warm-up to rt. When the reaction was over, the solution was poured in saturated aqueous NH_4Cl. The aqueous layer was extracted with chloroform (3x) and the organic extracts dried and evaporated in vacuo to provide a crude. In the case of the benzylated adducts, the crude was treated with a 20 % w/v aqueous NaOH solution in order to remove the phthalimide. Once the phthalimide was removed, the product was obtained through chromatographic purification.

(8S,2R,3R,4R)-3,4-Bis(phenylmethoxy)-8-methyl-2-[(phenylmethoxy)methyl]-2,3,4,8,9,4a-hexahydro-10aH,4aH--2H-pyrano[2,3-b]2H-pyrano[3,4-e]1,4-oxathiin-6-one (12a).

Following the general 'one pot' cycloaddition procedure, 0.686 g (3.21 mmol) of sulfenyl chloride in $CHCl_3$ (31 mL), was combined with 0.275 g (2.14 mmol) of the (S)-**11** lactone dissolved in 30 mL of $CHCl_3$, 0.890 g of tribenzylglucal and 0.250 μL (2.14 mmol) of 2,6-lutidine. After 15 h the reaction was worked up to give, after removal of the phthalimide, 1.17 g of a light-brown crude solid. Flash column separation with silica gel, eluting with petroleum ether:ethyl acetate (3:1), gave 0.657 g (53 %) of a single regioisomer, identical to the title compound **12a**.

((8S,2R,3R,4R)-3-Acetyloxy-2-(acetyloxymethyl)-8-methyl-6-oxo-2,3,4,8,9,4a-hexahydro-10aH,4aH--2H-pyrano[2,3-b]2H-pyrano[3,4-e]1,4-oxathiin-4-yl acetate (28a and 28b).

Following the stepwise cycloaddition procedure, a solution of 0.200 g (0.65 mmol) of thioketolactone, tri-*O*-acetyl glucal (0.177 g, 0.65 mmol) in chloroform (2.5 mL), and 2,6-lutidine (0.65 mmol, 69.7 mg) was stirred for 48 h to provide 0.354 g of a crude solid which after flash chromatography with florisil, eluting with petroleum ether:ethyl acetate (4:1 to 2:1) afforded compounds **28a** and **28b** (0.139 g, 53 %) as an inseparable mixture of two regiosomers, identified by the anomeric protons at $\delta = 5.71$, and $\delta = 5.79$ ppm in 1.3:1 NMR ratio. ^1H NMR δ 1.48-1.51 (m, 6H), 2.02-2.1 (m, 18H), 2.54-2.67 (m, 4H), 3.34-3.38 (m, 2H), 4.1-4.31 (m, 6H), 4.6-4.8 (m, 2H), 5.11-5.21 (m, 4H), 5.71 (d, J = 2.14 Hz, 1H), 5.79 (d, J = 2.52 Hz); Anal. calcd for $C_{18}H_{22}O_{10}S$: C, 50.23; H, 5.15; S, 7.45. Found: C, 50.35; H, 5.19; S, 7.44.

Selective Reaction of 28a and 28b with MeOH/p-TsOH.

The mixture of 1.3:1 **28a** and **28b** (30 mg, 0.070) mmol) in $CDCl_3$ (0.5 mL), MeOH (14.4 μL) and a small crystal of p-TsOH were placed in a vial. TLC was taken immediately and showed a new spot R_f = 0.40 (2:1 petroleum ether:ethyl acetate,) lower than the corresponding to starting mixture (R_f = 0.47). ^{1}H NMR of this solution showed that one of the anomeric peaks (at 5.79 ppm) initially present in the mixture had almost disappeared. The reaction mixture was sonicated for ½ h, and the ^{1}H NMR indicated that this anomeric peak had completely disappeared. The reaction mixture was poured in $CHCl_3$ and washed with saturated aqueous $NaHCO_3$, the organic extracts were separated, dried and concentrated in vacuo to give 33 mg of crude. TLC of this crude showed only the upper spot (R_f = 0.47,2:1 petroleum ether:ethyl acetate). It seemed that the lower spot disappeared upon work up. Flash column chromatography of this crude with florisil, eluting with petroleum ether:ethyl acetate (4:1) provided 7 mg of an inseparable mixture of the β-methoxy glycoside **29** and the cycloadduct **28a**.

Epimerization of 28a and 28b via silica gel.

A mixture of 1.2:1 **28a** and **28b** (104 mg) dissolved in CH_2Cl_2 was stirred overnight with silica gel (4.12 mg). TLC showed a substantial amount of triacetyl glucal in the reaction mixture. The reaction mixture was rinsed exhaustively with ethyl acetate. Concentration in vacuo of the filtrate gave 83.5 mg of a crude, which after flash column chromatography, afforded 75.2 mg of **28a** as a single regioisomer: m.p. 210-211 °C; ^{1}H NMR δ 1.46 (d, J = 6.6 Hz, 3H), 1.99 (s, 3H), 2.04 (s, 3H), 2.07 (s, 3H), 2.56 (dd, J = 5.1, 17 Hz, 1H), 2.66 (dd, J = 9, 17 Hz, 1H), 3.32-3.37 (m, 1H), 4.09-4.30 (m, 2H), 4.28 (dd, J = 4, 12.3 Hz, 1H), 4.62-4.69 (m, 1H), 5.06-5.14 (m, 2H), 5.70 (d, J = 2.7 Hz, 1H); ^{13}C NMR δ 20.52, 20.68, 20.62, 34.53, 40.38, 61.66, 67.66, 68.79, 70.50, 72.40, 94.48, 95.77, 158.98, 163.30, 169.55, 169.93, 170.62; IR (Thin Film): 2941 (ν CH_3), 1751 (ν C=O, $CH_3C(O)$-O), 1701 (ν C=O lactone), 1628 (ν C=C), 1375 (δ CH_3), 1222 (δ C-O) cm^{-1}.

((8S)-3,4-Diacetyloxy-8-methyl-6-oxo-2,3,4,8,9,4a-hexahydro-10aH--2H-pyrano[2,3-b]2H-pyrano[3,4-e]1,4-oxathiin-2-yl)methyl acetate [30 (above face)] and [28a below face)]

Following the stepwise cycloaddition procedure a solution of 0.879 g (2.88 mmol) of the thioketolactone, tri-*O*-acetyl glucal (0.784 g, 2.88 mmol) in DMSO (12 mL), and 2,6-lutidine (0.309 g, 2.88 mmol) was stirred for 11 d to provide 0.192 g of crude. Flash column chromatography of this crude, eluting with hexane:ethyl acetate (3:1 to 2:1), afforded 63 mg (5 %) of the below face adduct, compound **28a**: R_f= 0.4 (1:1 hexane:ethyl acetate), and 88.2 mg (7 %) of the top face adduct, compound **30**: R_f= 0.34 (1:1 hexane:ethyl acetate); m.p. 88-90 °C; ^{1}H NMR δ 1.44 (d, J = 6.3 Hz, 3H), 2.05 (s, 3H), 2.085 (s, 3H), 2.09 (s, 3H), 2.49 (dd, J = 4.5, 17.1 Hz, 1H), 2.61 (dd, J = 10.8, 17.1 Hz, 1H), 3.83-3.87 (m, 2H), 4.22-4.23 (m, 2H), 4.24-4.29 (m, 1H), 4.62-4.69 (m, 1H), 5.39 (d, J = 1.5 Hz, 1H), 5.48 (dd = t, $J_A \cong J_B$ = 9.3 Hz, 1H); ^{13}C NMR δ 20.84, 20.96, 22.85, 31.78, 34.65, 41.12, 65.30, 71.89, 72.25, 74.44, 77.43, 92.11, 96.78, 156.90, 163.88, 169.45, 170.08; IR (Thin Film): 2980 (ν CH_3), 1750 (ν C=O, -OC(O)CH_3), 1702 (ν C=O, lactone), 1203 (δ C-O) cm^{-1}; MS m/z (rel. intensity): 448(M+18, 100), 431(M+1, 11), 290(29), 230(41), 213(27); Anal. Calcd. for $C_{18}H_{22}O_{10}S$: C, 50.23; H, 5.15; S, 7.45. Found: C, 50.22; H, 5.06; S, 7.20.

(3S,8S,2R,4R)-3-acetyloxy-2-(acetyloxymetyhl)-8-methyl-6-oxo-2,3,4,8,9,4a-hexahydro-10aH,4aH--2H-pyrano[2,3-b]2H-pyrano[3,4-e]1,4-oxathiin-4-yl acetate (31).

Following the general 'one pot' cycloaddition procedure, a solution of sulfenyl chloride (0.253 g, 1.2 mmol) and the (S)-lactone (0.101 g, 0.79 mmol) in THF, was combined with tri-*O*-acetyl galactal (0.215 g, 0.79 mmol), and 2,6-lutidine (128.6 mg, 1.2 mmol). After stirring for 6 d, the reaction mixture was worked up to provide 0.452 g of a dark brown crude solid. Purification of this crude by radial chromatography, eluting with hexane:ethyl acetate (5:1 to 3:1) gave 0.136 g (40 %) of compound **29** as a clear thick oil: R_f = 0.13 (2:1 hexane:ethyl acetate); ^{1}H NMR δ 1.45 (d, J = 6.3 Hz, 3H), 2.01 (s, 3H), 2.04 (s, 3H), 2.14 (s, 3H), 2.53 (dd, J = 4.8, 17.1 Hz, 1H), 2.64 (dd, J = 9.6, 17.1 Hz, 1H), 3.61 (dd, J = 2.7, 11.7 Hz, 1H), 4.12 (d, J = 6.6 Hz, 2H), 4.38 (t, J = 6.6 Hz, 1H), 4.61-4.68 (m, 1H), 4.95 (dd, J = 3, 12 Hz, 1H), 5.40 (app d, J = 1.8 Hz, 1H), 5.75 (d, J = 2.7 Hz, 1H); ^{13}C NMR δ 20.61, 20.70 20.79, 34.64, 36.41, 61.57, 65.77, 67.20, 69.28, 72.47, 77.43, 96.42, 124.47, 135.11, 158.94, 169.93, 169.98, 170.48; MS m/z (% rel. intensity) 448(M+18, 100), 431(M+H, 50), 29(79), 230(21), 213(31), 146(19); Anal. Calcd. for $C_{18}H_{22}O_{10}S$: C, 50.23; H, 5.15; S, 7.45. Found: C, 50.06; H, 5.25.

(8S)-3,4-Bis(phenylmethoxy)-8-methyl-2-[(phenylmethoxy)methyl]-2,3,4,8,9,4a-hexahydro-10aH--2Hpyrano[2,3-b]2H-pyrano[3,4-e]1,4-oxathiin-6-one. (32).

Following the general "one pot" cycloaddition procedure, a solution of sulfenyl chloride (668.4 mg, 3.13 mmol), and the (S)-lactone (267.5 mg, 2.09 mmol) in $CHCl_3$ was combined with tri-*O*-benzylgalactal (665.6 mg, 1.6 mmol) and 2,6-lutidine (2.09 mmol, 224 mg). The reaction was stirred 17 h to provide upon work up and removal of the phthalimide, 0.658 g of a crude oily residue. Flash column purification of this crude afforded 255 mg (28 %) of compound **32** as a single regioisomer: R_f = 0.16 (3:1 petroleum ether:ethyl acetate); ^{1}H NMR δ 1.4 (d, J =

6.4 Hz, 3H), 2.4 (app d, J = 8.1 Hz, 2H), 3.40 (dd, J = 2.42, 11.12 Hz, 1H), 3.56 (app d, J = 5.6 Hz, 2H), 3.83 (dd, J = 2.83, 11.1 Hz, 1H), 3.96 (app d, J = 1.20 Hz, 1H), 4.42 (d, a part of an AB system, J_{AB} = 11.81 Hz, 1H), 4.45 (d, a part of an AB system, J_{AB} = 11.81 Hz, 1H), 4.57-4.62 (m, 2H), 4.74 (s, 2H), 4.95 (d, a part of an AB system, J_{AB} = 11.2 Hz, 1H), 5.73 (d, J = 2.79 Hz, 1H), 7.27-7.41 (m 15 Harom); ^{1}HNMR (Benzene-d_6): δ 0.84 (d, J = 6.3 Hz, 3H), 1.57 (dd, J = 4.5, 16.65 Hz, 1H), 1.76 (dd, J = 10.5, 16.65 Hz, 1H), 3.38 (dd, J = 2.7, 11.1 Hz, 1H), 3.63 (dd, J = 5.4, 9 Hz, 1H), 3.71-3.79 (m, 3H), 3.94 (app d, J = 0.9 Hz, 1H), 4.09 (t, J = 6.6 Hz, 1H), 4.24 (AB q, J_{AB} = 12 Hz, Δν/J = 2.4 Hz, 2H), 4.57 (d, a part of an AB system, J_{AB} = 11.1 Hz, Δν = 135 Hz, 1H), 4.66 (d, J = 12 Hz, 2H), 5.02 (d, a part of an AB system, J_{AB} = 11.1 Hz, Δν = 135 Hz, 1H), 5.4 (d, J = 2.7 Hz, 1H), 7.05-7.45 (m, 15 Harom); ^{13}C NMR δ 20.79, 34.98, 38.55, 68.75, 72.16, 72.58, 73.13, 73.43, 73.68, 73.90, 75.18, 77.43, 77.84, 77.89, 94.22, 97.75, 128.07, 128.19, 128.38, 128.47, 128.58, 128.70, 128.77, 137.81, 138.30, 159.93 163.98; IR (Thin film): 2931 (ν CH_3), 1703 (ν C=O), 1625 (ν C=C), 1455 (δ C-H), 1278 (δ C-O) cm^{-1}; MS m/z (rel. intensity): 592(M+1, 80), 434(100), 360(3), 309(19), 234(16), 180(47), 108(11). Anal. Calcd for $C_{33}H_{34}O_7S$: C, 68.97; H, 5.96; S, 5.58. Found: C, 69.08; H, 6.01;

8S)-3,4-Bis(phenylmethoxy)-8-methyl-2-[(phenylmethoxy)methyl]-2,3,4,8,9,4a-hexahydro-10aH--2Hpyrano[2,3-b]2H-pyrano[3,4-e]1,4-oxathiin-6-one. (32). Alternative Route.

Following the stepwise cycloaddition procedure, the chiral thioketolactone (0.1 g, 0.33 mmol), tri-*O*-benzylgalactal (109.8 mg, 0.26 mmol) dissolved in $CHCl_3$ (3.0 mL), were combined with 2,6-lutidine (35.4 mg, 0.33 mmol). After stirring for 1 h at rt the reaction mixture was worked up to give 192 mg of a crude-yellow solid, after removal of the phthalimide, which ^1H NMR showed two anomeric protons at 5.73 ppm and 5.79 ppm in a 1.41:1 ratio respectively representing two different regioisomers. The crude solid was purified by radial chromatography eluting with petroleum ether:ethyl acetate (9:1 to 5:1) to give 99 mg (67 %) of the product as a mixture of regioisomers. Only a small fraction (8.0 mg) of the regioisomer with the most upper field anomeric proton (δ = 5.73 ppm) was separated, which was identical to the title compound 32.

(2S,5aS,6R,7R,9aR)-6,7-Bis(phenylmethoxy)-2-methyl-8-[(phenylmethoxy)methyl]-1,2,3,6,7,8,9,5a,9a-nonahydro-3-oxaphenoxathiin-4-one (33).

Following the general stepwise cycloaddition procedure, the sulfino-lactone (155.8 mg, 0.51 mmol), tribenzyl allal (212.16 mg, 0.51 mmol,) in $CHCl_3$ (5.0 mL), were combined with 2,6-lutidine (54.7 mg, 0.0.51 mmol), and stirred for 1 1/2 h, upon which time, more sulfino-lactone (155.8 mg 0.51 mmol) was added. The stirring was continued for an additional 1/2 h. The reaction was worked up, and the phthalimide was removed to provide 275.2 mg of a very pure crude solid. Filtration of this crude through a short pad of silica gel, afforded compound **33** (265.2 mg, 91 %) as an off-white solid: R_f = 0.56 (3:1 hexane:ethyl acetate); ^1H NMR δ 1.39 (d, J = 6.3 Hz, 3H), 2.26 (dd, J = 4.0, 16.95 Hz, 1H), 2.45 (dd, J = 11.7, 16.95 Hz, 1H), 3.45 (dd, J = 1.5, 4.95 Hz, 1H), 3.61 (app dd, J = 3.6, 4.5 Hz, 2H), 3.74 (dd, 3.0, 4.95 Hz, 1H), 4.02 (dd, J = 3.6, 8.4 Hz, 1H), 4.29 (dt, $2J_A = J_B$, J = 4.2, 8.4 Hz, 1H), 4.36-4.50 (m, 5H), 4.6 (d, J = 12 Hz, 2H), 5.6 (d, J = 1.5 Hz, 1H), 7.13-7.34 (m, 15H); ^{13}C NMR δ 20.65, 35.11, 39.70, 69.70, 71.99, 72.25, 73.09, 73.74, 76.63, 77.02, 93.53, 97.59, 127.24, 127.94, 128.21, 128.74, 137.68, 138.25, 157.92, 164.24; IR (Thin Film): 1701 (ν C=O), 1634 (ν C=C), 1455.6 (δ CH_2), 1284 (ν C-O-C), 1113 (δ CO) cm^{-1}; MS m/z (%rel. intensity): M+18(0.6), 435(30), 434(100), 326(15), 180(58), 146(20), 91(2); Anal. Calcd. for $C_{33}H_{34}O_7S$: C, 66.87; H, 6.12; Found: C, 66.70; H, 6.55.

(6S,12S,17S,18S,1R,10R)-18-Hydroxy-6,15,15-trimetyl-5,9,11,14,16-pentaoxa-2-thiatetracyclo[8.8.0.0<3,8>.0<12,17>]octadec-3(8)-en-4-one (34).

Following the general stepwise cycloaddition procedure, the enantiopure sulfino-lactone (S)-11 (0.339 g, 1.11 mmol), and isopropylidene glucal (0.206 g, 1.11 mmol) in $CHCl_3$ (4 mL), were combined with 2,6-lutidine (18.9 mg, 1.11 mmol,), and after stirring for 6 d, the reaction was worked up to give 0.352 g of a light brown crude solid. Purification of this crude by radial chromatography, eluting with hexane:ethyl acetate (8:1 to 3:1), afforded 98.6 mg (79 % based on the reacted glucal) of compound 34: R_f = 0.12 (1:1 hexane:ethyl acetate); ^{1}H NMR δ 1.44 (s, 3H), 1.50 (d, J = 6.3 Hz, 3H), 1.55 (s, 3H), 2.50 (dd, J = 4.2, 17 Hz, 1H), 2.73 (dd, 11.1, 17 Hz, 1H), 3.2 (dd, J = 3, 10 Hz, 1H), 3.8 (d, J = 2.4 Hz, 1H), 3.65-3.93 (m, 5H), 4.11-4.68 (m, 1H), 5.7 (d, J = 3, Hz, 1H); Anal. Calcd for $C_{15}H_{20}O_7S$: C, 52.32; H, 5.85; S, 9.31. Found: C, 52.15; H, 5.80; S, 9.05.

(3S,4S,8S,2R,10aR)-3,4-Dihydroxy-2-(hydroxymethyl)-8-methyl-2,3,4,8,9,4a-hexahydro-2H-pyrano[2,3-b]2H-pyrano[3,4-e]1,4-oxathiin-6-one (35).

The isopropyledene adduct 34 was left sitting in the fridge in $CDCl_3$ inside an nmr tube for 3 d, upon which time the original clear solution became cloudy. Mass spectra showed the hydrolyzed product. Filtration of this cloudy solution afforded the trihydroxy adduct, 35, as a white powder: R_f = 0.01 (neat ethyl acetate); m.p. 212-213 °C (decomposed); ^{1}H NMR in DMSO-d_6 δ 0.47 (d, J = 6.3 Hz, 3H), 1.64 (t, J = 1.8 Hz, 2H), 1.75 (d, J = 6.9 Hz, 2H), 2.25-2.83 (m, 4H), 3.76-3.84 (m, 2H), 4.4 (d, J = 5.1 Hz, 1H), 4.63 (t, J = 2.4 Hz, 1H), 4.83 (d, J = 2.7 Hz, 1H); ^{1}H NMR in acetone-d_6: δ 1.40 (d, J = 6.3 Hz, 3H), 2.60 (dd, J = 4.8, 16.8 Hz, 1H), 2.72 (dd, J = 9.6, 16.8 Hz, 1H), 2.84 (br s, 1H), 3.13 (dd, J = 2.7, 9.9 Hz, 1H), 3.47-3.58 (m, 2H), 3.60-3.84 (m, 3H), 4.49 (br s, 1H), 4.50-4.69 (m, 1H), 4.79 (br s, 1H), 5.69 (d, J = 2.7 Hz, 1H); ^{13}C NMR DMSO-d_6: δ 20.06, 33.73, 42.32, 60.42, 69.14, 70.62, 71.86,75.49, 92.27, 96.38, 160.52, 163.49; IR (KBr) 3421 (ν O-H polymeric), 2935 (ν CH_3), 1672 (ν C=O), 1620 (ν C=C), 1289 (δ OH), 1134 (δ/ν C-O), 1061 (ν CO) cm^{-1}; MS m/z (%rel. intensity): 322(M+18, 100), 164(36), 146(88); HRMS Calcd. For $C_{12}H_{16}O_7S$ 305.0695(M+H). Found: 305.0689(M+H).

Cycloaddition in ethylediamine to remove the phthalimide.

The sulfino-dimedone 7 (2.27 g, 7.15 mmol), and tribenzylglucal (0.574 g, 1.38 mmol), dissolved in ethylediamine (30 mL), were stirred for 6 d at rt. The reaction mixture was poured in $CHCl_3$ (20 mL), and extracted with aqueous saturated ammonium chloride. The aqueous layer was separated and extracted with $CHCl_3$ (3x50 mL). The organic extracts were washed with water (2x100 mL), followed by brine (2x100 mL), dried (Na_2SO_4), and concentrated in vacuo to give 1.3 g of a greenwish oily residue. ^{1}H NMR of this residue showed only tribenzyl glucal. Reaction did not work.

Reaction of the chiral lactone (S)-9 and the Falck's catalyst.

The chiral lactone (S)-9 (0.190 g, 1.48 mmol), tribenzylglucal (0.615 g, 1.48 mmol), and triphenylphosphine-HBr (0.254 g, 0.74 mmol) were dissolved in CH_2Cl_2 (10 mL) and stirred at rt. After 15 min, TLC in hexane:ethyl acetate (1:1) showed one spot similar to the expected disaccharide product: R_f = 0.39 (1:1 hexane:ethyl acetate), which after 1 h did not show any change. An additional 0.5

equivalent of the catalyst was added and after stirring for ½ h, since the TLC did not change, the reaction was worked up by pouring it in 30 mL of saturated aqueous $NaHCO_3$. The aqueous layer was separated and extracted with CH_2Cl_2 (2x30 mL). The organic extracts were washed with brine (2x50 mL), dried (Na_2SO_4), and concentrated in vacuo to give 1.02 g of a crude solid. Purification of this crude by flash column chromatography, eluting with hexane:ethyl acetate (2:1) did not afford the starting material nor the expected product.

Desulfurization of 12a with n-Bu_3SnH.

A stirring mixture of **12a** (100 mg, 0.174 mmol), AIBN (3mg, 0.0174 mmol), and nBu_3SnH (101.4 mg, 0.348 mmol), in benzene (6 mL) was refluxed for 4 d, at which time, TLC showed only starting material. The heating was discontinued, and the benzene was removed to give a brownish solid residue. To this residue was added nBu_3SnH, AIBN, and toluene (6 mL). This mixture was refluxed for 2 d. TLC showed again only starting material. The toluene was removed, nBu_3SnH, AIBN, and xylenes (6 mL) were added to the residue and this mixture was refluxed for 2 d. TLC showed only starting material. The refluxing was stopped, the reaction mixture cooled down, and the solvente was removed to give a solid residue. Acetonitrile (5 mL) and hexane (5.0 mL) were added to this residue, and this mixture stirred vigorously for 5 min, and then transferred to a separatory funnel. The lower acetonitrile layer was separated, hexane (5.0 mL) was added, and the same procedure as before was repeated six times. The acetonitrile layer was concentrated in vacuo to provide 70 mg of unreactive **12a**.

Desulfurization of 28a and 28b with Ph_3SnH.

A stirred mixture of **28a** and **28b** (112 mg, 0.26 mmol), triphenyl tin hydride (274 mg, 0.78 mmol), and AIBN (4.3 mg, 0.026 mmol) in toluene (4 mL) was refluxed for 5 d, upon which time the TLC showed only starting material. The refluxing was stopped and reaction mixture was cooled and filtered through a celite pad. This filtrate was concentrated in vacuo to give 313 mg of an oily residue. Flash column chromatography of this residue afforded 52 mg (46 %) of unreacted **28a** and **28b**.

(6S)-4-{(2S,5S,6S,4R)-4,5-Bis(phenylmethoxy)-5-methyl-6-[(phenylmethoxy)methyl]perhydro-2H-pyran-2-yloxy}-6-methylperhydro-2H-pyran-2-one (38).

A slurry of W-2 RaNi (1/2 teaspoon, 1.5 g) in absolute ethanol was transferred to a flask provided with a stirring bar and a nitrogen inlet, and rinsed with absolute ethanol, followed by benzene until it became pH neutral. To this neutralized slurry compound **32** (31 mg, 0.054 mmol,) in benzene (2.5 mL) was added and stirred at rt. After 45 min, TLC indicated disappearance of all of the starting material. The reaction mixture was filtered through a celite pad and rinsed exhaustively with ethyl acetate. The filtrate was concentrated in vacuo to provide 20 mg of an oily residue. Flash column chromatography of this residue, eluting with petroleum ether:ethyl acetate (4:1 to 2:1), afforded 4.5 mg (16.5 %) of pure compound **38** as an oil, along with 3.4 mg of some glycal derivatives. Compound **38**: $R_f = 0.4$ (2:1 petroleum ether:ethyl acetate); ^{1}H NMR δ 1.17 (d, J = 6.3 Hz, 3H), 1.97 (dd, J = 4.8, 12.6 Hz, 1H), 2.2 (dd, J = 3.6, 12.6 Hz, 1H), 2.23-2.36 (m, 3H), 2.44 (dd, J = 7.5, 17.25 Hz, 1H), 2.83 (ddd, J = 0.9, 6.3, 17.25 Hz, 1H), 3.50 (dd, J = 5.7, 9.6 Hz, 1H), 3.6 (dd, J = 6.6, 9.6 Hz, 2H), 3.84-3.91 (m, 1H), 4.03-4.12 (m, 1H), 4.17-4.24 (m, 1H), 4.41 (d, AB quartet, J_{AB} = 11 Hz, 2H), 4.60 (d, J = 0.9 Hz, 2H), 4.61 (d, a part of an AB system, J_{AB} = 11.7 Hz, $\Delta\nu$ = 99 Hz, 1H), 4.94 (d, a part of an AB system, J_{AB} = 11.7 Hz, $\Delta\nu$ = 99 Hz, 1H), 5.1 (d, J = 3.0 Hz, 1H), 7.02-7.23 (m, 15Harom.); IR (Thin Film): 2914 (ν CH_3), 1737 (ν C=O), 1359 (δ CH_3), 1243 (ν C-O-C), 1095 (δ C-CO) cm^{-1}; MS m/z (rel. intensity): 564 (M+18, 0.6), 434(0.17), 344(0.3), 130(100), 113(27).

(6S)-4-{(4S,5S,2R,6R)-5-(Phenylmethoxy)-6-[(phenylmethoxy)methyl]-4-(phenoxymethyl)perhydro-2H-pyran-2-yloxy}-6-methyl-5,6-dihydro-2H-pyran-2-one (37). Desulfurization with W-2 Raney Nickel. General Procedure.

A slurry of W-2 RaNi (3 teaspoons, 9.0 g) in absolute ethanol was transferred to a flask provided with a stirring bar and a nitrogen inlet, and rinsed with absolute ethanol, followed by benzene until it became pH neutral. Toluene (2 mL) and benzene (2 mL) were added to this neutralized slurry and this slurry was cooled to 0 °C, followed by the addition of compound **12a** (500 mg, 0.871 mmol) in benzene (6 mL). After stirring this cooled reaction mixture for 45 min, TLC indicated disappearance of all of the starting material. The reaction mixture was filtered through a celite pad, which was rinsed exhaustively with ethyl acetate. The filtrate was concentrated in vacuo to provide 409.6 mg of an oily residue. Radial chromatography of this residue, eluting with hexane:ethyl acetate (4:1 to 1:1) afforded 270.4 mg (57 %) of the disaccharide **37** as a clear oil: $R_f = 0.33$ (1:1 hexane:ethyl acetate); ^{1}H NMR δ 1.3 (d, J = 6.3 Hz, 3H), 1.79-1.83 (m, 1H), 2.16 (dd, J = 2.83, 16.9 Hz, 1H), 2.26-2.36 (m, 2H), 3.52-3.59 (m, 2H), 3.69-3.72 (m, 2H), 3.91-3.93 (m, 1H), 4.36-4.60 (m, 5 H), 4.82 (d, J = 10.8 Hz, 1H), 7.11-7.33 (m, 15Harom); ^{13}C NMR δ 20.66, 34.56, 34.74, 68.46, 72.16, 72.35, 72.82, 73.76, 75.30, 76.85, 77.40, 94.41, 96.78, 127.78, 127.91, 128.02, 128.08, 128.59, 138.00, 138.36, 138.42, 167.35, 168.92; IR (Thin Film): 2912 (ν CH_3), 1710 (ν C=O), 1629 (ν C=CH), 1453 (ν CH_2), 1111 (ν C-CO), 833 (δ C=CH) cm^{-1}; Anal. Calcd for $C_{33}H_{36}O_7$: C, 72.78; H, 6.66. Found: C, 72.60; H, 6.78.

[6-((6S)-6-Methyl-2-oxo(5,6-dihydro-2H-pyran-4-yloxy))(2S,4S,3R,6R)-3-acetyl-4-acetyloxy-4-methylperhydro-2H-pyran-2-yl]methyl acetate (39a) and [6-((6S)-6-Methyl-4-oxo(5,6-dihydro-2H-pyran-2-yloxy))(2S,4S,3R,6R)-3-acetyl-4-acetyloxy-4-methylperhydro-2H-pyran-2-yl]methyl acetate (39b).

Following the general desulfurization procedure, a mixture of compounds **28a** and **28b** (83.5 mg, 0.19 mmol), W-2 RaNi (1 teaspoon, 3 g) in benzene (5 mL), and toluene (2 mL) were stirred for 3 h to provide 91.9 mg of an oily residue. Purification of this residue by flash column chromatography, eluting with petroleum ether:ethyl acetate (3:1 to 1:1), afforded 28.2 mg (37.7 %) of the desulfurized products **39a** and **39b** as an inseparable mixture: R_f = 0.27 (1:1 petroleum ether:ethyl acetate); ^{1}H NMR δ 1.43 (d, J = 6.3 Hz, 3H), 1.91-2.12 (m, 25H), 2.33-2.60 (m, 4H), 3.81 (app dd, J = 4.0, 5.2 Hz, 1H), 3.83-3.90 (m, 2H), 4.00 (dd, J = 2.1, 12.3 Hz, 1H), 4.20 (t, J = 1.5, 3.3 Hz, 1H), 4.27 (dd, J = 5.4, 12.3 Hz, 1H), 4.48-4.53 (m, 1H), 4.54-4.66 (m, 1H), 4.02 (t, J = 9.9 Hz, 1H), 5.24-5.36 (m, 3H), 5.38 (d, J = 1.2 Hz, 1H), 5.46 (t, J = 9.0 Hz, 1H), 5.52 (d, J = 1.5 Hz, 1H), 5.57 (d, J = 2.4 Hz, 1H); ^{13}C NMR δ 20.65, 20.81, 20.92, 21.04, 34.42, 34.59, 41.06, 62.06, 62.35, 65.25, 68.31, 68.80, 69.55, 71.83, 72.22, 72.47, 74.34, 92.04, 94.93, 95.49, 95.82, 96.66, 156.92, 168.62, 169.44, 169.80, 170.03, 170.33, 170.72; IR (Thin Film): 2929 (ν CH_3), 1746 (ν C=O), 1706 (ν C=O), 1631 (ν C=C), 1369 (δ CH_3), 1053 (ν C-CO) cm^{-1}; MS m/z (% rel. intensity), 418(M+H, 17), 431(4), 313(48), 230(19), 213(100), 146(15), 91(18); HRMS calc for $C_{18}H_{24}O_{10}$ $(M+H)^+$. Found: 401.1447

4-{(4S,5S,2R,6R)-5-(Phenylmethoxy)-6-[(phenylmethoxy)methyl]-4-(phenoxymethyl)perhydro-2H-pyran-2-ylozy}-6,6-dimethyl-5,6-dihydro-2H-pyran-2-one (40).

Following the general desulfurization procedure, compound 8 (211.5 mg, 0.36 mmol), W-2 RaNi (6 full droppers), in benzene (5 mL), and toluene (1 mL) were stirred for 1 1/2 h to provide 176.3 mg of an oily residue. Purification of this residue by radial chromatography, eluting with hexane:ethyl acetate (5:1 to 3:1) afforded 101.5 mg of compound 40 (51 %), as a clear oil: R_f = 0.5 (2:1 hexane:ethyl acetate); ^{1}H NMR δ 1.03 (s, 3H), 1.27-1.90 (m, 1H), 2.23 (app q J = 15.3, 17.4 Hz, 4H), 2.37 (app dd, J = 4.0, 13.35 Hz, 1H), 3.63 (app t, J = 9.3, 8.7 Hz, 2H), 3.74-3.82 (m, 2H), 3.83-4.04 (m, 1H), 4.48 (d, a part of an AB system, J_{AB} = 12.3 Hz, $\Delta\nu$ = 53.1 Hz, 1H), 4.55 (d, a part of an AB system, J_{AB} = 10.5 Hz, $\Delta\nu$ = 105.6 Hz, 1H), 4.66 (d, a part of an AB system, J_{AB} = 10.5 Hz, $\Delta\nu$ = 53.1 Hz, 1H), 4.69 (s, 2H, J_{AB} = 0), 4.90 (d, a part of an AB system, J_{AB} = 10.5 Hz, $\Delta\nu$ = 105.6 Hz, 1H), 5.62 (d, J = 1.8 Hz, 1H), 5.7 (s, 2H), 7.17-7.36 (m, 15 Harom); ^{13}C NMR δ 27.96, 28.86, 32.60, 34.92, 42.65, 50.85, 68.48, 72.21, 72.74, 73.79, 75.39, 77.122, 95.81, 105.01, 127.81, 127.90, 128.09, 128.19, 128.59, 138.12, 138.41, 138.57, 172.92, 199.76; IR (Thin Film): 3029 (ν C-Harom), 2956 (ν CH_3), 2867(ν CH_2), 1658 (ν C=O), 1615 (ν C=C), 1453 (δ CH_2), 1380, and 1386 (doublet, ν $C(CH_3)_2$), 1114 (ν C-CO) cm^{-1}; MS m/z (% rel. intensity):

574(M+NH_4^+, 1.36), 557(M+H, 1.1), 434(65), 326(55), 273(100), 141(71), 108(75); Anal. Calcd. for $C_{35}H_{40}O_6$: C, 75.51; H, 7.24. Found: C, 75.14; H, 7.24.

6S)-4-{(5S,6S,2R,4R)-4,5-Bis(phenylmethoxy)-5-metyl-6-[(phenylmethoxy)methyl]perhydro-2H-pyran-2-yloxy}-6-methyl-5,6-dihydro-2H-pyran-2-one (41).

Following the general desulfurization procedure, compound 32 (50 mg 0.087 mmol), W-2 RaNi (1/2 teaspoon, 1.5 g), in benzene (2 mL), and toluene (1 mL) were stirred for 3 h to provide 56 mg of an oily residue. Purification of this crude by flash column chromatography, eluting with hexane:ethyl acetate (9:1 to 5:1) afforded 14.7 mg (31 %) of compound 41: R_f = 0.39 (3:1 petroleum ether:ethyl acetate); ^{1}H NMR δ 1.42 (d, J = 6.3 Hz, 3H), 2.09 (dd, J = 4.5, 13.2 Hz, 1H), 2.25 (dd, J = 3.9, 17.4 Hz, 1H), 2.32-2.42 (m, 1H), 2.44 (ddd, J = 1.8, 11.7, 17.4 Hz, 1H), 3.50 (dd, J = 5.4, 9.15 Hz, 1H), 3.65 (app t, J = 9 Hz, 1H), 3.84 (app t, J = 6.3 Hz, 1H), 3.92 (ddd, J = 2.1, 4.5, 13.95 Hz, 1H), 3.99 (s, 1H), 4.39 (d, a part of an AB system, J_{AB} = 11.4 Hz, Δν = 19.8 Hz, 1H), 4.46 (d, a part of an AB system, J_{AB} = 11.7 Hz, Δν = 19.8 Hz, 1H), 4.46-4.58 (m, 1H), 4.61 (d, a part of an AB system, J_{AB} = 11.1 Hz, Δν = 97.65 Hz, 1H), 4.66 (s, J_{AB} = 0, 2H), 4.93 (d, a part of an AB system, J = 11.4 Hz, Δν = 97.65 Hz, 1H), 5.49 (d, J = 1.8 Hz, 1H), 5.63 (d, J = 2.7 Hz, 1H), 7.22-7.38 (m, 15Harom); ^{13}C NMR δ 20.72, 30.58, 34.67, 69.01, 70.78, 72.06, 72.30, 72.56, 73.83, 74.13, 74.75, 94.40, 97.43, 127.53, 127.91, 128.95, 128.07, 128.40, 128.53, 128.60, 128.68, 137.97, 138.31, 138.73, 167.46, 169.28; IR (Thin Film): 2870 (ν CH_3), 1706 (ν C=O), 1627 (ν C=C), 1453 (δ CH_2), 1063 (ν C-CO) cm^{-1}.

(3S,8S,2R,4R,10aR,4aR)-3,4-Bis(phenylmethoxy)-8-methyl-2-[phenylmethoxy)methyl]-2,3,4,8,9,4a-hexahydro-2H-pyrano[2,3-b]2H-pyrano[3,4-e]1,4-oxathiin-6-ol (42) and (6S,13S,3R,5R,7R,8R)-6,7-Bis(phenylmethoxy)-13-methyl-2,4,12-trioxa-5-[(phenylmethoxy)methyl]-9-thiatricyclo[8.4.0.0<3,8>]tetradecane-1,11-diol (43).

The compound **12a** (260 mg, 0.45 mmol) was cooled to 0 °C, and then a 0.5 M solution of 9-BBN (1.34 mL, 0.67 mmol) was added dropwise. The clear solution was left stirring overnight. TLC (hexane:ethyl acetate 1:1), showed a new spot (R_f = 0.36) as well as unreactive starting material. After cooling the solution, an additional 1.5 equivalent of 9-BBN was added and stirred at rt overnight. TLC showed not much change. The reaction mixture was cooled with an ice bath and 0.5 mL of H_2O_2 30 % were added followed by sodium hydroxide (3 N) and allowed to stir for 1/2 h. The white precipitate formed was diluted with 25 mL of H_2O, and the mixture extracted with ether (2x50 mL). The organic extracts washed with brine (2x50 mL), dried (Na_2SO_4), and concentrated in vacuo to give 336.2 mg of a cloudy oil. Separation by radial chromatography, eluting with hexane:ethyl acetate (5:1 to 1:2), gave 54.8 mg (21 %) of the expected product, compound **42**, as a white solid along with 40.5 mg of unreacted adduct and 72 mg of an unidentified product, compound 43, obtained after eluting the plate with $MeOH:CH_2Cl_2$ (1:4).

Compound 42 ^1H NMR δ 1.23 (d, J = 6.3 Hz, 3H), 2.23 (dd, J = 2.7, 14.4 Hz, 1H), 2.46 (dd, J = 9, 14.3 Hz, 1H), 2.90 (br s, 1H), 3.22 (dd, J = 2.7, 7.47 Hz, 1H), 3.66-4.04 (m, 7H), 4.25 (d, J = 12.9 Hz, 1H), 4.52 (d, a part of an AB system, J_{AB} = 12.9 Hz, 1H), 4.52 (d, a part of an AB system, J_{AB} = 11.7 Hz, 1H), 4.63 (d, a part of an AB system, J_{AB} = 12 Hz, 1H), 4.80 (d, a part of an AB system, J_{AB} = 4.80 Hz, 1H), 4.84 (d, a part of an AB system, J_{AB} = 5.1 Hz, 1H), 4.94 (d, a part of an AB system, J_{AB} = 10.2 Hz, 1H), 5.52 (d, J = 2.7 Hz, 1H), 7.14-7.40 (m, 15 Harom); ^{13}C NMR δ 23.90, 40.99, 43.81, 61.93, 65.44, 65.55, 73.14, 73.81, 75.37, 76.42, 78.70, 79.00, 95.42, 102.49, 128.14, 128.21, 128.31, 128.63, 128.79, 138.25, 138.40, 138.54, 146.75; IR (Thin Film): 3383 (ν O-H), 3029 (ν CH), 2925 (ν CH_3), 2867 (ν CH_2), 1641 (ν C=C), 1453 and 1359 (δ CH_3), 1118 (ν CO) cm^{-1}; MS m/z (% rel. intensity): 576(M+, 0.1), 596($M+NH_4^+$, 1.21), 587($M+NH_4^+-H_2O$, 7.5), 434(34), 236(27), 168(100), 106(34).

Compound 43 (baseline): ^1H NMR δ 1.24 (d, J = 6.3 Hz, 3H), 2.32 (dd, J = 3, 13.8 Hz, 1H), 2.49 (dd, J = 9, 13.8 Hz, 1H), 3.26 (dd, J = 2.7, 11.7 Hz, 1H), 3.36 (dd, J = 8.1, 11.55 Hz, 1H), 3.70-3.87 (m, 3H), 3.97 (app d, J = 9.9 Hz, 1H), 4.05-4.10 (m, 1H), 4.21 (d, a part of an AB system, J_{AB} = 13.5 Hz, 1H), 4.40 (d, a part of an AB system, J_{AB} = 13.2 Hz, 1H), 4.54 (d, a part of an AB system, J_{AB} = 12 Hz, 1H), 4.56 (s, J_{AB} = 0, 2H), 4.61 (d, a part of an AB system, J_{AB} = 11.4 Hz, 1H), 4.70 (d, a part of an AB system, J_{AB} = 10.8 Hz, 1H), 4.81 (d, a part of an AB system, J_{AB} = 10.8 Hz, 1H), 5.74 (d, J = 2.7 Hz, 1H), 7.14-7.41 (m, 15Harom); ^{13}C NMR δ 23.91, 41.62, 59.85, 60.23, 64.97, 68.19, 73.84, 74.22, 75.37, 75.55, 75.73, 78.66, 91.09, 91.16, 97.54, 112.06, 128.08, 128.39, 128.66, 137.17, 137.77, 137.91, 158.98; MS m/z (% rel. intensity): 594(576+NH_4^+, 0.82), 524(37), 434(100), 326(66), 196(74), 164(53), 108(14).

Desulfurization of compound 8 with RaNi and PPh_3.

Following the general desulfurization procedure, the dimedone-tribenzyl glucal cycloadduct (172.5 mg, 0.294 mmol), W-2 RaNi (1/2 teaspoon) in benzene (5 mL), and toluene (1 mL) were stirred at 0 °C. After 3 h all of the starting material was consumed. At this time the triphenylphosphine (3.46 g) was added in one portion and the slurry was stirred for 1 h. After working up the reaction, it gave 3.19 g of a white solid. Flash chromatography purification using silica gel, starting elution with hexane:ethyl acetate (3:1 to 1:1), followed by ethyl acetate:methanol (4:1) gave 112.8 mg (69 %) of the desired product contaminated with some UV inactive impurities along with 42.2 mg of tribenzylglucal plus some glycal derivatives. A second purification of this product gave 51.34 mg (36.8 %) of a very pure disaccharide, identical to the title compound **40**.

Desulfurization of 12a with Nickelocene.

Nickelocene (105 mg, 0.55 mmol), in THF (5 mL) was added by syringe to a stirred solution of lithium aluminium hydride (20.5 mg, 0.55 mmol) in THF (2 mL). The original greenish solution turned to a deep dark brown. The cycloadduct (155 mg, 0.27 mmol) in THF (1.5 mL) was added by syringe to the stirring solution. Stirring was continued for 24 h .TLC showed a spot in the reaction mixture whose R_f was identical to the expected product (R_f=0.59 2:1 petroleum ether:ethyl acetate). After stirring for 2 more days, there was no change in the TLC. The reaction mixture was quenched by adding 0.5 mL of H_2O while cooling by ice bath and stirring for 15 min. This solution was filtered through a celite pad and rinsed exhaustively with ether. The filtrate was poured in H_2O and the separated organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo to give 101.3 mg of a dark oily residue. Purification of this oily residue gave 36.1 mg of unreacted adduct along with 14.0 mg of an unknown product.

Desulfurization of 12a with $NiCl_2.6H_2O/NaBH_4$.

The cycloadduct (0.374 g, 0.652 mmol), and $NiCl_2$.6H2O (1.09 g, 4.6 mmol) were dissolved in methanol:THF (3:1, 20 mL), and cooled under stirring in an open flask. Sodium boronhydride (0.518 g, 13.7 mmol) was added portionwise. The solution turned black inmediately with evident evolution of hydrogen. After the addition was finished, the solution was stirred for an additional hour, and then filtered through a celite pad and rinsed with 150 mL of a 3:1 MeOH:THF mixture, followed by 300 mL of MeOH. The filtrate was concentrated in vacuo to give 0.628 g of a crude, whose ^{1}H NMR showed mostly the starting cycloadduct plus and additional peak at 6.40 ppm which corresponded to tribenzylglucal. Without purification, this crude was set-up to react again as above, allowing a longer reaction time. After 24 h TLC showed no starting material. The reaction was worked up as above to give 0.321 g of a dark oily crude, which TLC in hexane:ethyl acetate showed 10 different spots upon staining with cerium sulfate and heating. The ^{1}H NMR was complex. Purification of this crude gave neither product nor starting material.

{(3S,8S,2R,4R,10aR,4aR)-3,4-Bis(phenylmethoxy)-8-methyl-2-[(phenylmethoxy)methyl](2,3,4,8,9,4a-hexahydro-2H-pyrano[2,3-b]2H-pyrano[3,4-e]1,4-oxathiin-6-yloxy)}(tert-butyl)dimethylsilane (44).

A solution of dimethyl-t-butylsilyl chloride (60.74 mg, 0.403 mmol) in DMF (0.8 mL) was added dropwise to a stirred solution of the alcohol 42 (0.194 g, 0.336 mmol) in DMF (0.8 mL) at -5 ^{0}C and the solution was allowed to stir at -5 ^{0}C for 3 h. Since the TLC indicated unreacted starting material, the cooling bath was removed and the reaction mixture was left stirring overnight. The cloudy solution was poured into H_2O (0.8 mL) and concentrated in vacuo to give an oily residue. This oil was treated with 10 mL of H_2O and extracted with ether (5x20 mL). The organic extracts were washed with brine (2x100 mL), dried ($MgSO_4$), and concentrated in vacuo to give 167.0 mg of a sticky-white oily residue, which after purification by radial chromatography, eluting with hexane:ethyl acetate (4:1 to 1:1) gave 89.3 mg (38.4%) of the silylated compound 44 as a clear oil: $[\alpha]^{25}$ = +139.34° (c 0.544, $CHCl_3$), ^1H NMR δ 0.21 (S, 6H), 0.81 (S, 9H), 1.14 (d, J= 6 Hz, 3H), 2.25 (dd, J= 3.6, 14 Hz, 1H), 2.37 (dd, J = 8.1, 14.4 Hz, 1H), 3.59-3.71 (m, 4H), 3.91-3.93 (m, 2H), 4.14 (q, J = 12 Hz, 2H), 4.43 (d, J = 2.0 HZ, 1H), 4.45 (d, J = 10.8 Hz, 1H), 4.55 (d, J= 12.3 Hz, 1H), 4.72 (d, J = 9 Hz, 1H), 4.75 (d, J = 9 Hz, 1H), 4.91 (d, J = 10.5 Hz, 1H), 5.45 (d, J= 2.7 Hz, 1H), 7.07-7.3 (m, 15Harom); ^{13}C NMR δ -5.15, -5.1, -5.06, 18.55, 23.42, 26.05, 26.09, 41.50, 43.25, 62.55, 65.71, 68.45, , 73.09, 73.74, 75.32, 76.47, 78.67, 95.17, 101.44, 127.92, 127.06, 128.54, 138.04, 138.24, 138.40, 146.29, ir (thin film): 3030 (ν C-Haromatic), 2928 (ν CH_3), 2857 (ν CH_2), 1646 (ν C=C), 1455 (ν CH_3), 1361, and 1253 (δ $C(CH_3)_2$), 1073 (ν C-O-C) cm^{-1}; MS m/z (% rel. intensity): 710(M+NH4$^+$, 20), 620(3), 578(4.4), 434(97), 326(38), 294(100), 243(18), 91(4.7).

Desulfurization of compound 44 with PPh_3SnH.

A mixture of compound 44 (72 mg, 0.104 mmol), AIBN (catalytic amount), and PPh_3SnH (109.5 mg, 0.312 mmol) in toluene (3 mL), was stirred under reflux for 3 d. No product formation was detected. After working up the reaction by filtering through a celite pad and concentrating in vacuo, it provided 312.7 mg of a crude, whose after purification by radial chromatography gave 52 mg (46.4 %) of unreacted starting material.

((6S)4-{(4S,5S,2R,5R)-4,5-Bis(phenylmethoxy)-6-[(phenylmethoxy)methyl]perhydro-2H-pyran-2-yloxy}-6-methyl(5,6-dihydro-2H-pyran-2-yloxy))(tert-butyl)dimetylsilane (45).

Following the general desulfurization procedure, compound 44 (33 mg, 0.048 mmol), and W-2 RaNi (2 droppers), in benzene (2 mL), were stirred for 2 1/2 h at rt. An additional dropper of RaNi was added and after stirring for an additional 20 h, 32.3 mg of a crude oil was obtained. Purification by radial chromatography of this crude provided 5.4 mg (17 %) of an oil which by ^{1}H NMR looked like the expected product, along with 3.4 mg (17 %) of tribenzyl glucal and 2.9 mg of some unidentified glycal derivatives. ^{1}H NMR δ 0.059 (s, 6H), 0.87 (s, 9H), 1.21 (d, J = 6.3 Hz, 3H), 1.72 (ddd, J = 4.5, 9.2, 14.8 Hz, 2H), 1.89 (ddd, J = 2.7, 9.2, 14.7 Hz, 2H), 2.56-2.67 (m, 2H), 3.59-3.71 (m, 2H), 3.78 (dd, J = 3.3, 10.7 Hz, 2H), 3.9-4.04 (m, 2H), 2.54 (app t, J = 9 Hz, 1H), 4.42-4.46 (m, 1H), 4.53 (d, J = 12.3 Hz, 1H), 4.5 (d, J = 10.5 Hz, 1H), 4.63 (d, J = 12.3 Hz, 1H), 4.80 (d, J = 10.5 Hz, 1H), 4.86 (d, J = 10.2 Hz, 1H), 5.07 (d, J = 10.2 Hz, 1H), 5.12 (d, J = 2 Hz, 1H), 7.14-7.43 (m, 15Harom); ^{13}C NMR δ 18.35, 24.54, 26.05, 42.51, 42.83, 43.29, 65.16, , 68.72, 73.38, 73.83, 75.38, 76.48, 77.01, 79.25, 80.21, 84.25, 99.31, 127.80, 127.90, 127.98, 128.03, 128.17, 128.61, 128.65, 138.16, 138.31, 138.68.

Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (46).

β-D-Glucose pentacetate (3.0 g, 7.7 mmol), dissolved in distilled ethylene dichloride (3 mL) was treated with a chilled solution of glacial acetic acid (6 mL) containing 30% of hydrogen bromide. After stirring for 2 h at rt, the reaction was diluted with 30 mL of dried toluene and concentrated in vacuo (50-55 °C oil bath). The resulting gold-oily solution (5 mL), was dissolved in a mixture of ether:ethylene dichloride 3:1 (100 mL) and washed twice with an iced-cold saturated aqueous $NaHCO_3$ solution and with iced-H_2O (3x100 mL), dried (Na_2SO_4), and concentrated in vacuo to give 10 mL of a gold-yellow oil. This oil was diluted with a mixture of 50 mL of pentane and 20 mL of ether. Crystals starting forming immediately as white clear elongated prisms, which were filtered after sitting in the refrigerator for several hours to give 2.49 g (78 %) of the desired product. m.p. 88-90 °C (lit^{61} 89-90 °C); ^{1}H NMR δ 2.03 (s, 3H), 2.05 (s, 3H), 2.09 (s, 6H), 4.12 (app dd, J = 1.8, 14.1 Hz, 1H), 4.28-4.34 (m, 2H), 4.83 (dd, J = 3.9, 10.1 Hz, 1H), 5.16 (app t, J = 9.9, 9.6 Hz, 1H), 6.60 (d, J = 3.9 Hz, 1H); ^{13}C NMR δ 20.72, 20.81, 61.18, 67.43, 70.40, 70.83, 72.38, 86.78, 169.61, 161.94, 169.98, 170.64.

3,4,6-Tri-*O*-acetyl-1,2-*O*-(exo-ethoxyethylidene)-α-D-glucopyranose (47).

The tetraacetyl glucopyranosyl bromide 46 (2.05 g, 5.0 mmol) in distilled s-collidine (7 mL) was added to absolute ethanol (0.5 mL) and tetrabutylammonium bromide (0.5 g, 0.16 mmol) and the mixture was stirred under reflux (50-55 °C) for 15 h. The solution became cloudy upon the start of heating and crystals of s-collidinium bromide began to separate gradually, resulting in an almost solid reaction mixture. At the end of the refluxing period, $CHCl_3$ (15 mL) was added to the cool reaction mixture and the resulting solution was washed with 2N aqueous HCl (2x30 mL), followed by water (2x30 mL), saturated aqueous $NaHCO_3$ (30 mL), then again with water (30 mL), dried (Na_2SO_4), and concentrated in vacuo to give an oily residue which became solid after rinsing twice with absolute ethanol. Removal of the solvent in vacuo from this solid provided 1.98 g (100%) of compound **47**, pure enough to be used in the next step without further purification. m.p. 96 °C (lit^{61}. 95-96 °C); ^{1}H NMR δ 1.15 (t, J = 6.9, 7.2 Hz, 3H), 1.7 (s, 3H), 2.065 (s, 3H), 2.07 (s, 3H), 2.09 (s, 3H), 3.51 (q, J = 7.2, 6.9 Hz, 2H), 3.91-3.95 (m, 1H), 4.16-4.18 (m, 2H), 4.29 (dd, J = 3.0, 5.1 Hz, 1H), 4.88 (dd, J = 2.7, 9.5 Hz, 1H) 5.16 (dd, J = 3.0, 2.7 Hz, 1H), 5.69 (dd, J = 5.1 Hz, 1H); ^{13}C NMR δ 15.44, 20.95, 59.31, 63.27, 67.17, 68.45, 70.40, 73.32, 96.65, 97.55, 121.44, 169.31, 169.78, 170.80; IR (Thin Film): 1750.6 (ν C=O), 1368.5 (, 1219.0 1042 (ν C-O-C) cm^{-1}.

3,4,6-Tri-*O*-benzyl-1,2-*O*-(exo-ethoxyethlidene)-α-D-glucopyranose (48).

To a solution of the orthoester **47** (3.02 g, 8.0 mmol) and benzyl bromide (5.12 mmol, 3 mL) in dried THF (20 mL) was added powdered KOH, and the mixture was refluxed for 3 h with stirring. A lot of foam was developed at the beginning of the refluxing period and the solution became a thick white precipitate. After the mixture was cooled at rt, CH_2Cl_2 (60 mL) was added and the resulting solution extracted successively with water (2x60 mL), and saturated aqueous $NaHCO_3$ (60 mL). The aqueous layer was extracted with CH_2Cl_2 (2x30 mL), and the organic extracts were washed with H_2O (3x150 mL), brine (2x150), dried (Na_2SO_4), and concentrated in vacuo to give 4.36 g (100 %) of crude compound **48** as a yellowish oil. ^{1}H NMR of this crude was in good agreement with the literature reference and it was used in the following step without further purification. ^{1}H NMR δ 1.19 (t, J = 7.2, 6.9 Hz, 3H), 1.66 (s, 3H), 3.5-3.89 (m, 7H), 4.35-4.72 (m, 7H), 5.76 (d, J = 5.1 Hz, 1H), 4.16-7.42 (m, 15 Harom).

2-*O*-Acetyl-1,5-anhydro-3,4,6-tri-*O*-benzyl-D-arabino-hex-1-enitol (49).

Compound **48** (4.35 g, 8.4 mmol), bromobenzene (90 mL) and pyridine (0.6 mL) were combined and stirred under reflux (oil bath 160-170 °C) for 1 1/2 h. A lot of foam was generated inside the reaction flask. After the end of the refluxing period the solvent was removed in vacuo and the resulting brown syrup (3.72 g) was purified by flash column chromatography, eluting with petroleum ether:ethyl acetate (9:1 to 5:1) to provide 1.813 g (50 %) of compound **49** as a colorless oil which became solid after sitting in the refrigerator. ^{1}H NMR δ 2.04 (s, 3H), 3.72 (dd, J = 3.6, 10.8 Hz, 1H), 3.82 (dd, J= 5.4, 10.8 Hz, 1H), 3.97 (dd, J= 5.1, 7.1 Hz, 1H), 4.19-4.22 (m, 1H), 4.42-4.48 (m, 1H), 4.54 (app t, J = 7.2, 6.6 Hz, 2H), 4.61 (d, J = 11.7, Hz, 2H), 4.73 (d, J = 11.4 Hz, 2H), 6.61 (s, 1H), 7.21-7.35 (m, 15 Harom); ^{13}C NMR δ 24.00, 71.29, 75.67, 78.83, 80.47, 80.74, 80.89, 81.32, 131.50, 131.61, 132.16, 133.63, 141.60, 141.70, 141.90, 141.94, 142.04, 173,27. IR (Thin Film): (ν C-Haromatic), 3031.5, (ν CCH_3), 286.4, (ν C= 0), 1754.2, 1684 cm^{-1}.

(8S)-3,4-Bis(phenylmethoxy)-8-methyl-6-oxo-2-[(phenylmethoxy)methyl]-2,3,4,8,9,4a-hexahydro-10aH--2H-pyrano[2,3-b]2H-pyrano[3,4-e]1,4-oxathiin-4a-ylacetate (52 and 53) and (2S,4S,7S,3R,10aR,4aR)-3,4-bis(phenylmethoxy)-7-methyl-9-oxo-2-[(phenylmethoxy)methyl]-2,3,4,6,7,4a-hexahydro-2H-pyrano[3,2-b]2H-pyrano[3,4-e]1,4-oxathiin-4a-yl acetate (54).

Following the general "one pot" cycloaddition procedure, sulfenyl chloride (1.41 g, 6.58 mmol) in THF (35.8 mL), was combined with the chiral lactone (0.421 g, 3.29 mmol) in THF (32.9 mL), the glucal (1.56 g, 3.29 mol) in THF (10.9 mL) and 2,6-lutidine (0.762 mL, 6.58 mmol) and after stirring for 10 d at rt, the reaction was worked up to give 2.46 g of crude solid. Removal of the phthalimide from this crude using NaOH gave 1.64 g of dark brown crude syrup which ^{1}H-NMR showed three different regioisomers, represented by the anomeric protons at 5.71, 6.21 and 6.41 ppm in a ratio 1.23:1.9:1 respectively. Separation by Flash column chromatography using silica gel, eluting with hexane:ethyl acetate (2:1) gave 0.91 g of the three diastereomers (44 % combined yield), as a clear oil. This 0.91 g corresponded to 0.389 g of the anomer at 6.21 ppm, 0.149 g of the anomer at 6.42 ppm , 0.187 g of the anomer at 5.71 ppm, and 0.184 g of an inseparable mixture of the three diastereomers.

Compound 54: (H_1 at 5.71 ppm). ^{1}H NMR δ 1.37 (d, J = 6.3 Hz, 3H), 1.93 (dd, J = 11.7, 17,4 Hz, 1H), 2.15 (s, 3H), 2.3 (dd, J = 4.2, 17.4 Hz, 1H), 3.65-3.70 (m, 4H), 3.92 (d, J = 8.4 Hz, 1H), 4.40-4.55 (m, 1H), 4.46 (d, J = 12 Hz, 1H), 4.51 (d, J = 10.8 Hz, 1H), 4.63 (d, J = 12 Hz, 1H), 4.46 (d, J = 12 Hz, 1H), 4.63 (d, J = 12 Hz, 1H), 4.73 (d, J = 12 Hz, 1H), 4.99 (d, J = 10.5 Hz, 1H), 4.99 (d, J = 12.3 Hz, 1H), 5.72 (s, 1H), 7.2-7.36 (m, 15 Harom), ^{13}C NMR δ 20.62, 21.2, 30.90, 68.13, 73.43, 73.80, 75.54, 75.91, 85.84, 92.58, 104.72, 127.37, 127.91, 127.96, 128.01, 128.15, 128.26, 128.63, 128.73, 137.82, 138.09, 138.28, 161.54, 169.27; MS m/z (% relat. intensity): 650($M+NH_4^+$, 0.5), 573(M-OAc, 0.4), 492(76), 434(22), 342(14), 236(100), 168(51), 146(89), 108(21).

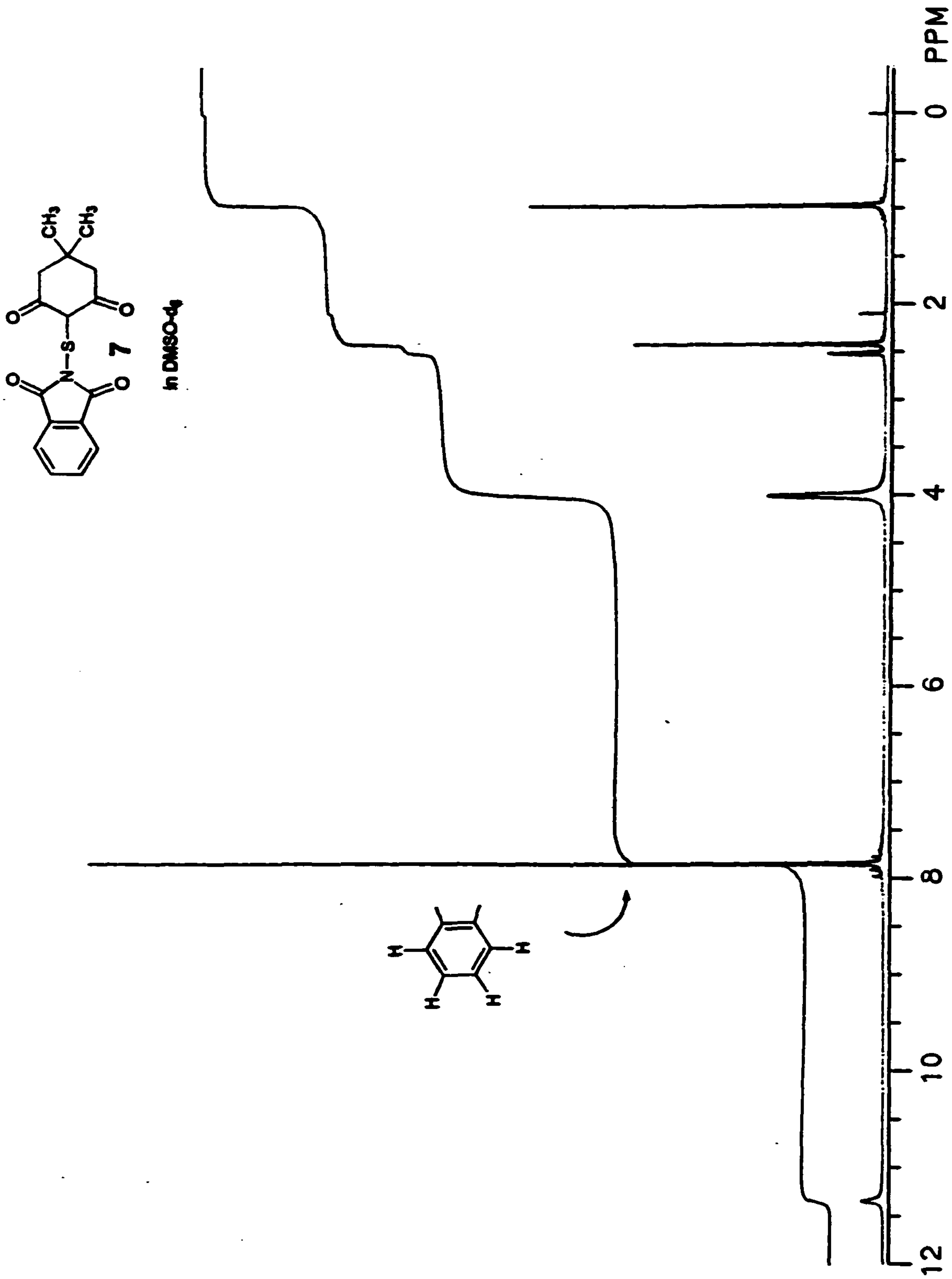
Compound 53: (H_1 at 6.21 ppm). White foamy solid; m.p. 47-49 °C; ^{1}H NMR δ 1.45 (d, J = 6.3 Hz, 3H), 2.08 (s, 3H), 2.50 (d, J = 4.8 Hz, 1H), 2.53 (d, J = 10.5 Hz, 1H), 3.72-3.81 (m, 4H), 4.03 (app d, J = 6.9 Hz, 1H), 4.50 (d, J = 12.3 Hz, 1H), 4.6 (d, J = 12 Hz, 1H), 4.6-4.67 (m, 1H), 4.78 (d, J = 10.5 Hz, 1H), 4.80 (d, 10.8 Hz, 2H), 5.1 (d, J = 10.2 Hz, 1H), 6.20 (s, 1H) 7.15-7.40 (m, 15Harom); ^{13}C NMR δ 20.75, 21.84, 34.68, 68.36, 72.65, 73.63, 74.14, 75.41, 75.95, 80.23, 82.66, 95.00, 98.00, 127.57, 127.89, 128.12, 128.54, 128.54, 128.64, 128.75, 137.61, 137.88, 138.14, 157.29, 163.11, 169.57; MS m/z (% rel. intensity):

650(M+NH4, 1), 492(100), 376(17), 162(27), 146(85), 108(8); Anal. Calcd for $C_{35}H_{36}O_9S$: C, 66.44; H, 5.73; S, 5.07; Found: C, 66.51; H, 5.87; S, 4.91. IR (thin film) 3030 (C-H, arom), 29.33 (v CH_3), 28.68 (v CH_2), 1760 (v C= 0), 17.06 (v C=O), 16.32 (v C=C) 13.86, 14.53 (δ CH_3), 10.63 (v C-O-O) cm^{-1}.

Compound 52: (H1 at 6.42 ppm):_^{1}H NMR δ 1.38 (d, J = 6.3 Hz, 3H), 2.02 (dd, J = 11.7, 17.3 Hz, 1H), 2.13 (s, 3H), 2.31 (dd, J = 3.9, 17.4 Hz, 1H), 3.63-3-76 (m, 3H), 3.95 (app dd, J = 2.1, 9.9 Hz, 1H), 4.24 (d, J = 9.3 Hz, 1H), 4.48 (d, J = 12.3 Hz, 1H), 4.53 (d, J = 10.8 Hz, 1H), 4.5-4.6 (m, 1H), 4.64 (d, J = 12.3 Hz, 1H), 4.76 (d, 12.3 Hz, 1H), 4.80 (d, J = 10.8 Hz, 1H), 4.97 (d, J = 12 Hz, 1H), 6.42 (s, 1H), 7.13-7.44 (m, 15Harom); ^{13}C NMR δ 20.62, 21.21, 31.10, 68.32, 73.57, 73.91, 74.29, 75.69, 75.79, 76.97, 77.43, 81.61, 93.39, 103.58, 127.37, 127.92, 127.99, 128.20, 128.37, 128.67, 137.89, 138.20, 138.47, 161.85, 168.96; MS m/z (% rel. intensity): 650(M+NH_4^+, 0.3), 492(8), 236(100), 168(10), 146(11), 108(5).

IV APPENDIX

1. ^{1}H NMR Spectra of Selected Compounds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S
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O
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in DMSO-d₆
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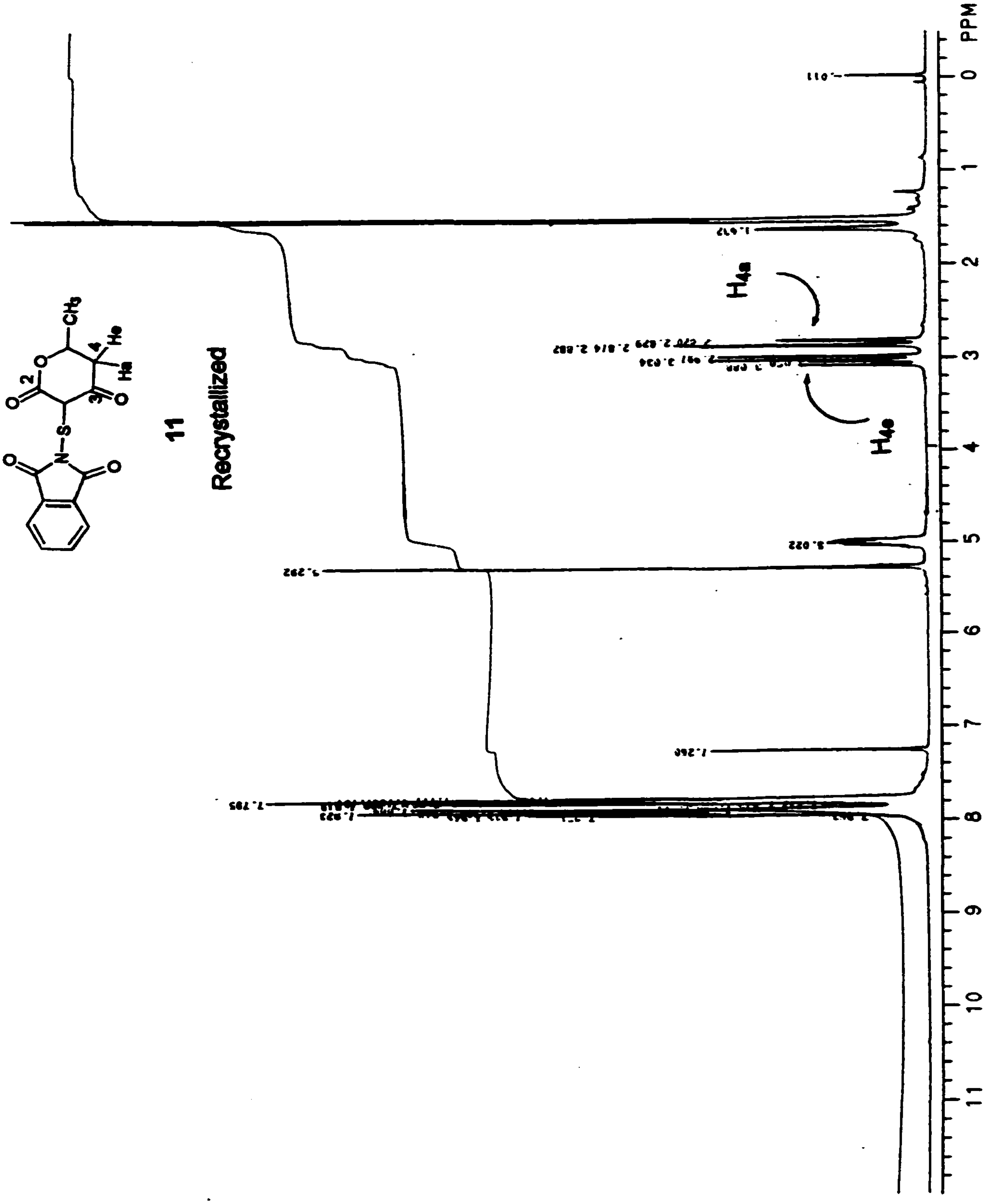
4
6
8
10
12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Ha
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5.292
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7.785
7.823
PPM
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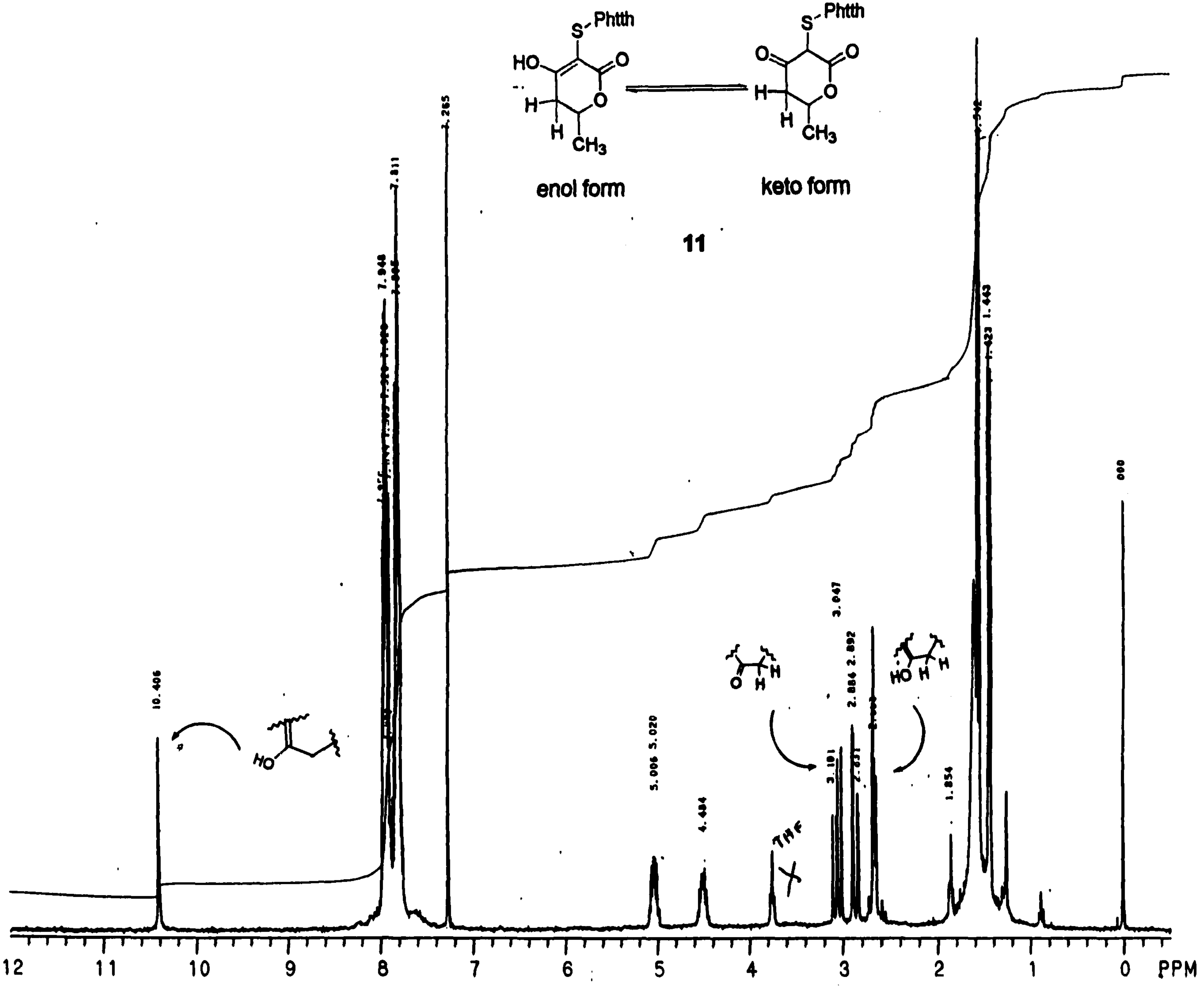
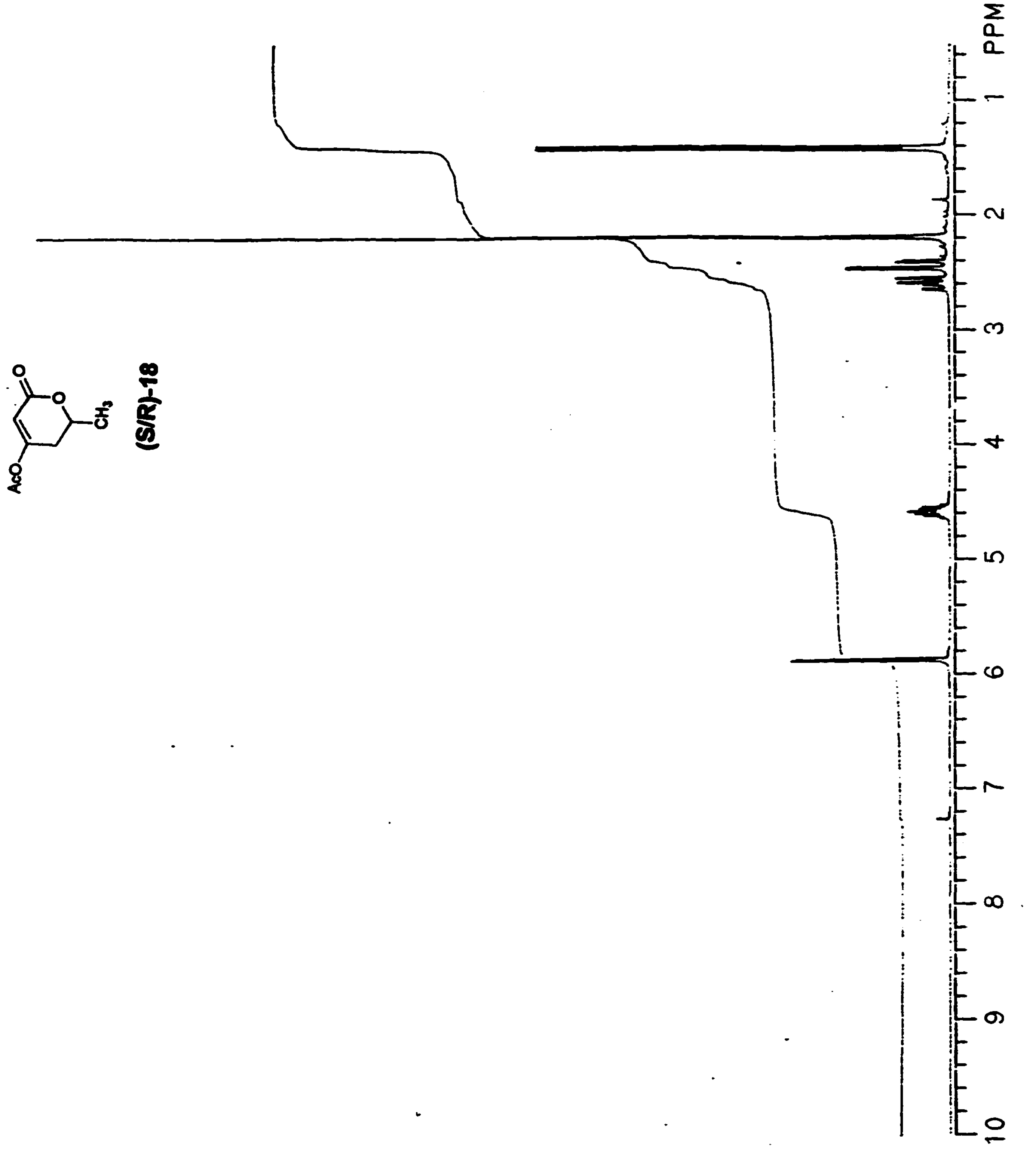
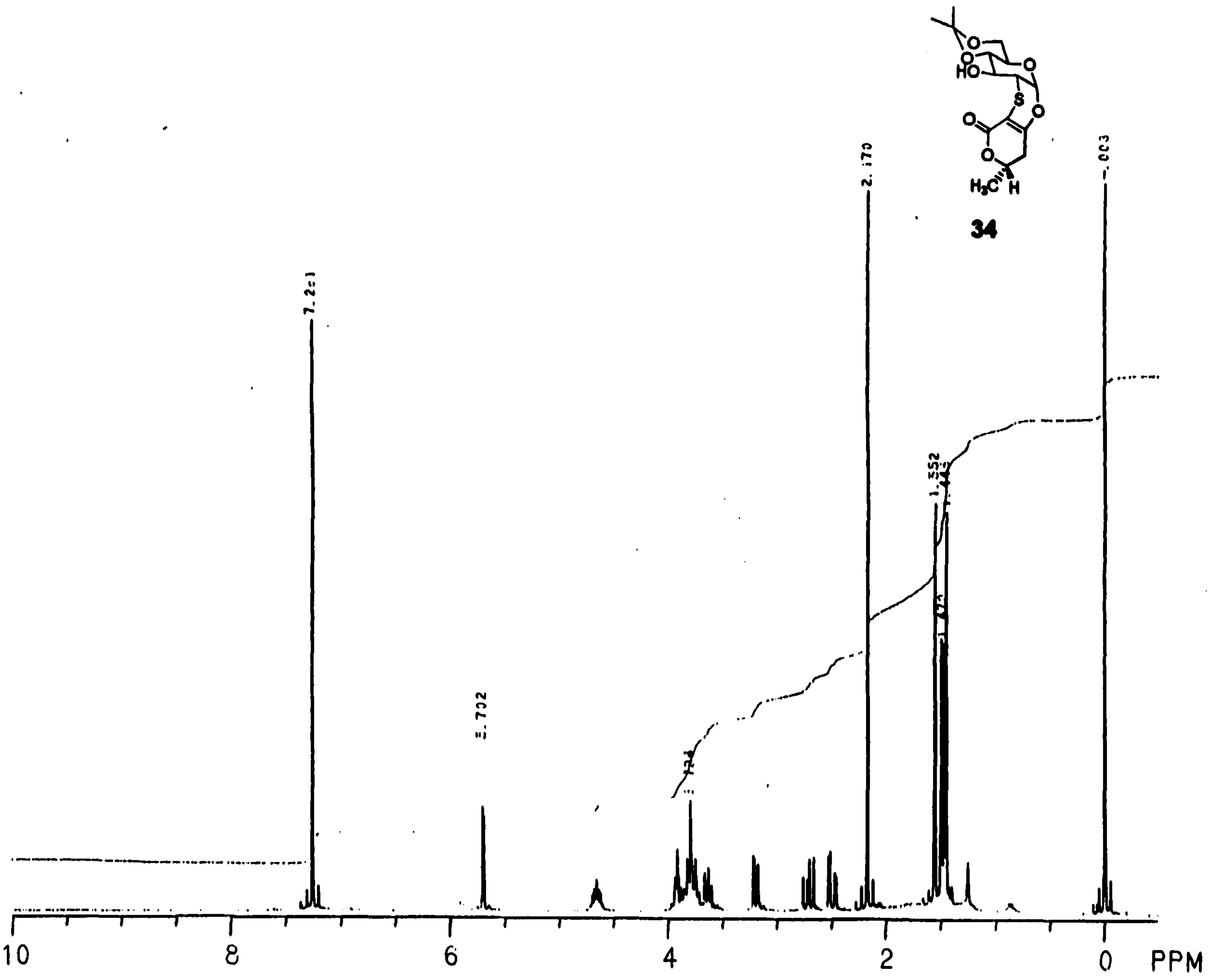
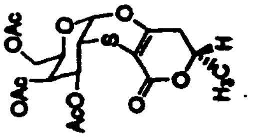
1
2
3
4
5
6
7
8
9
10
11

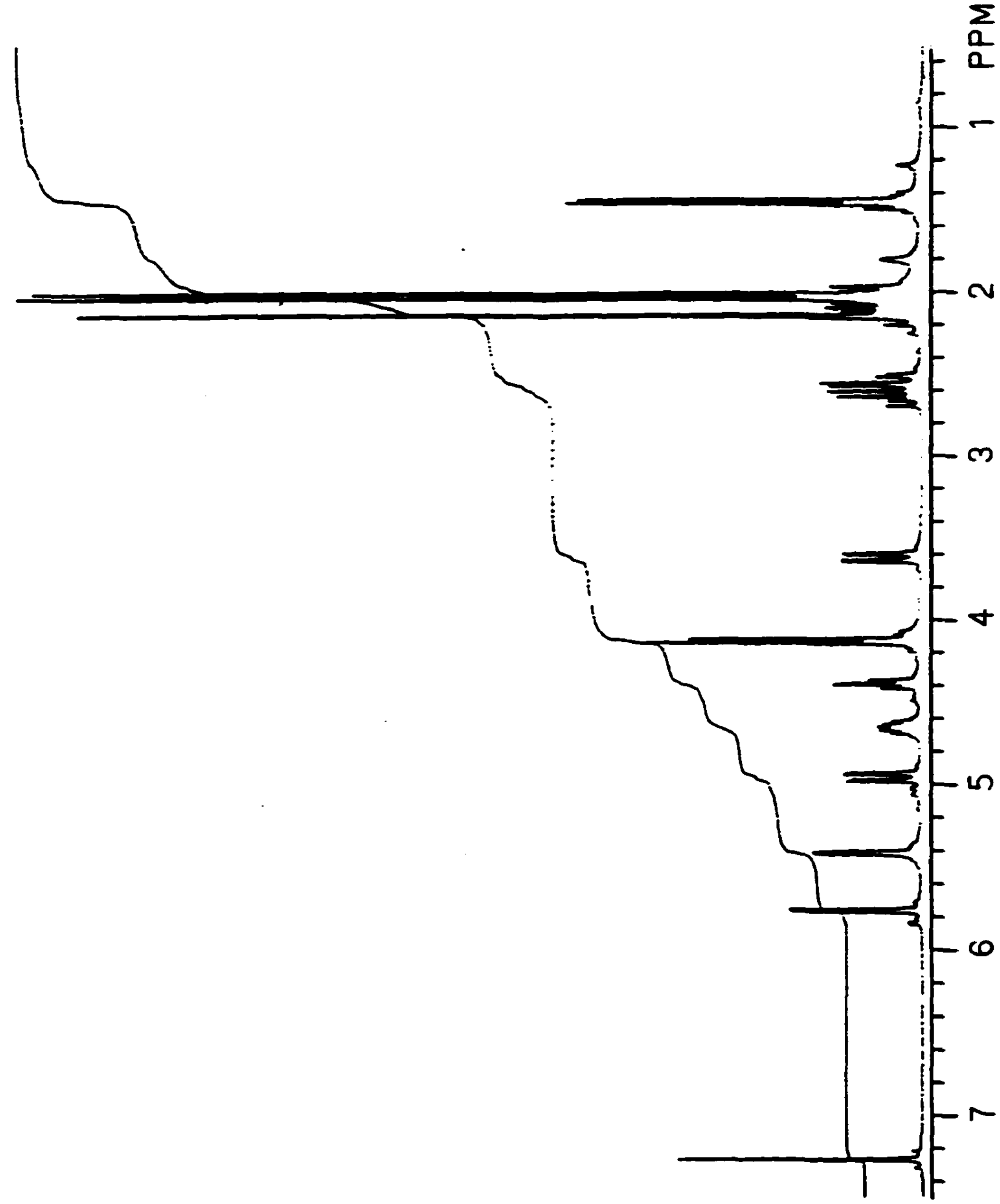

S-Phtth
HO
O
H
CH3
enol form
keto form
11
10.406
7.948
7.811
7.265
5.006 5.020
4.484
THF
3.181
3.047
2.884 2.892
1.854
1.443
1.423
000
12
11
10
9
8
7
6
5
4
3
2
1
0
PPM

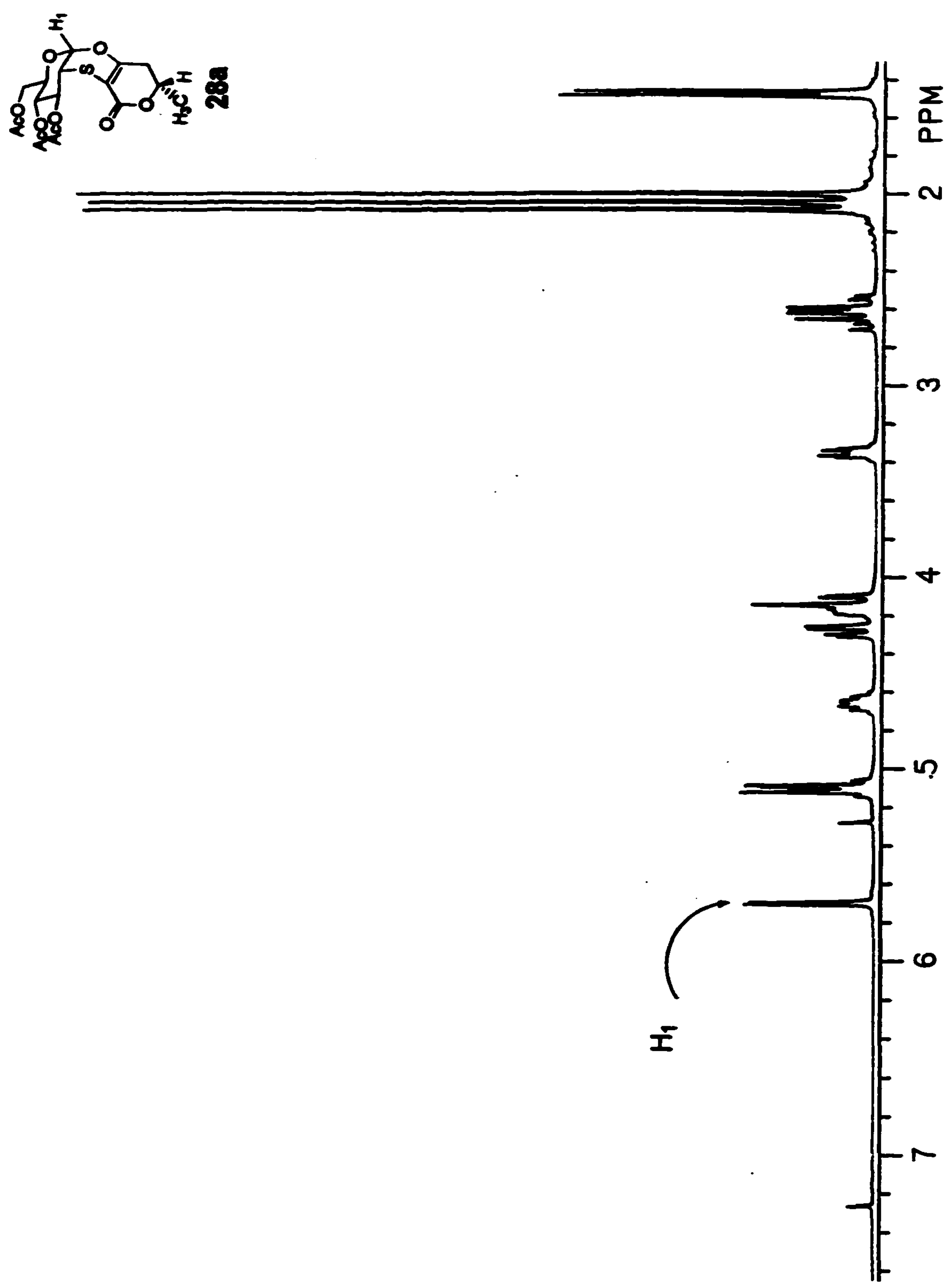

(S/R)-18

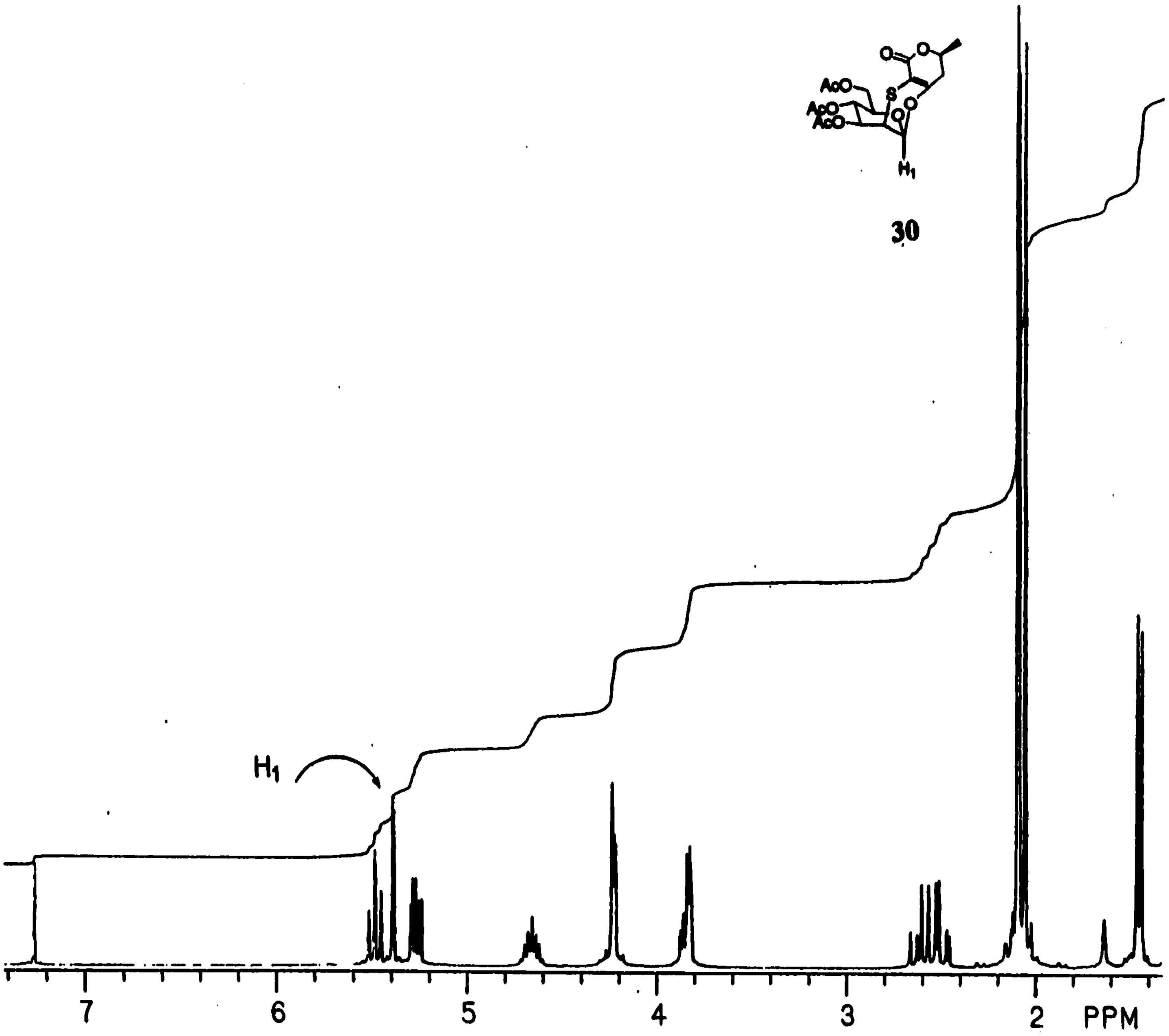

HO
O
S
H₃C
H
34
7.261
5.732
2.173
1.552
1.443
1.473
-.003
10
8
6
4
2
0
PPM



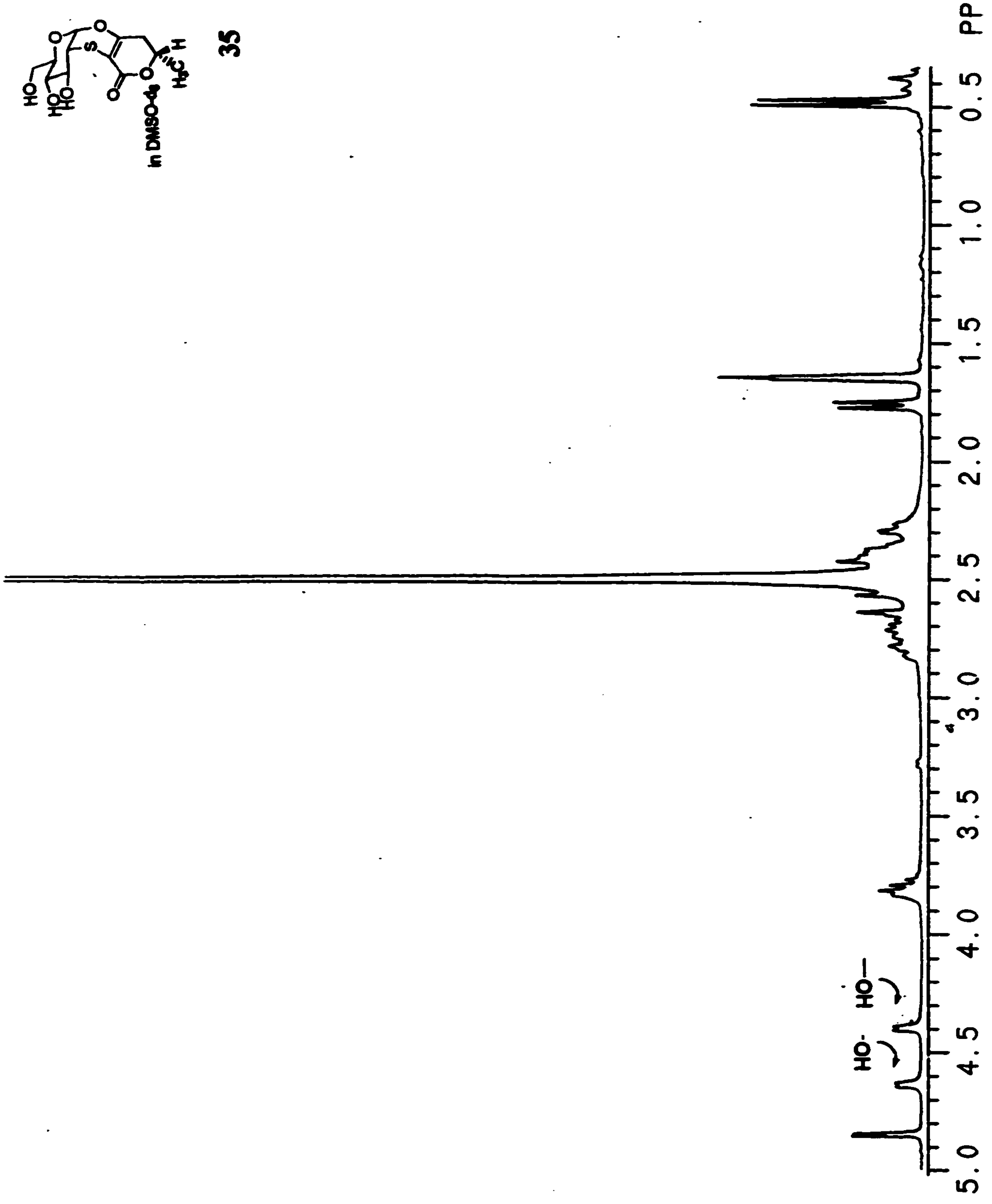
31




AcO
AcO
AcO
O
S
O
O
O
H1
H3C
H
28a
PPM
2
3
4
5
6
7
H1



30



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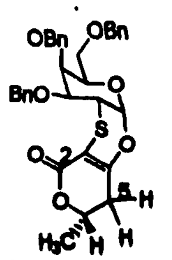
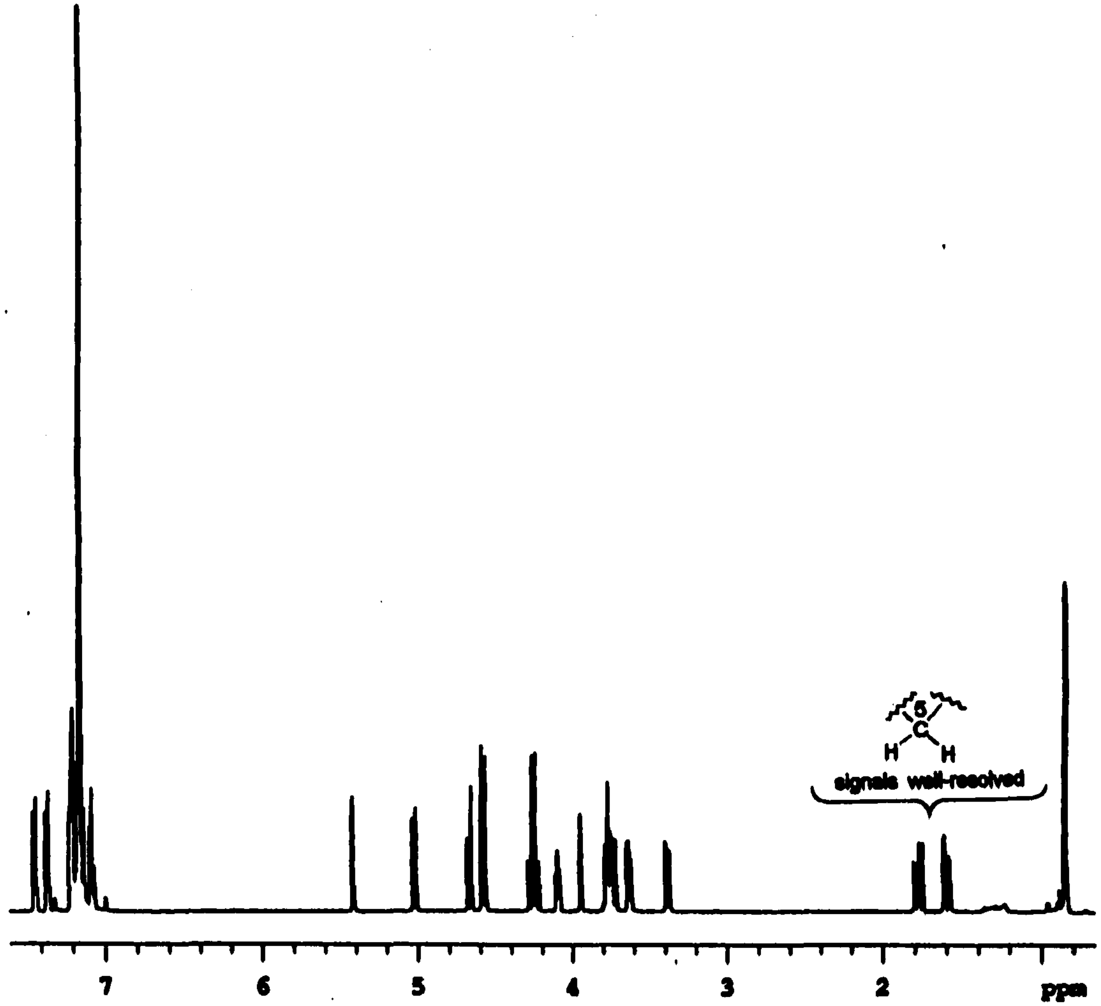
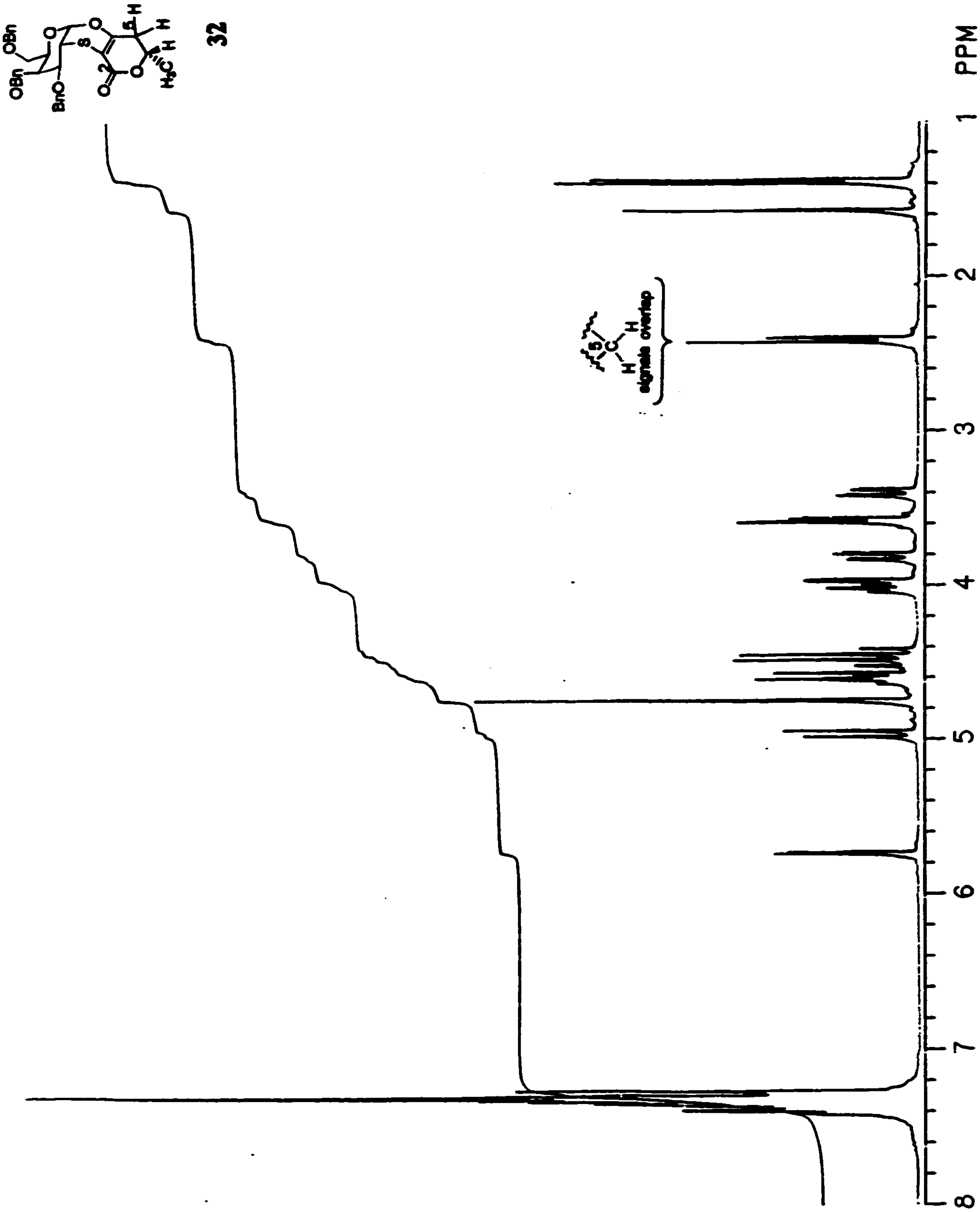


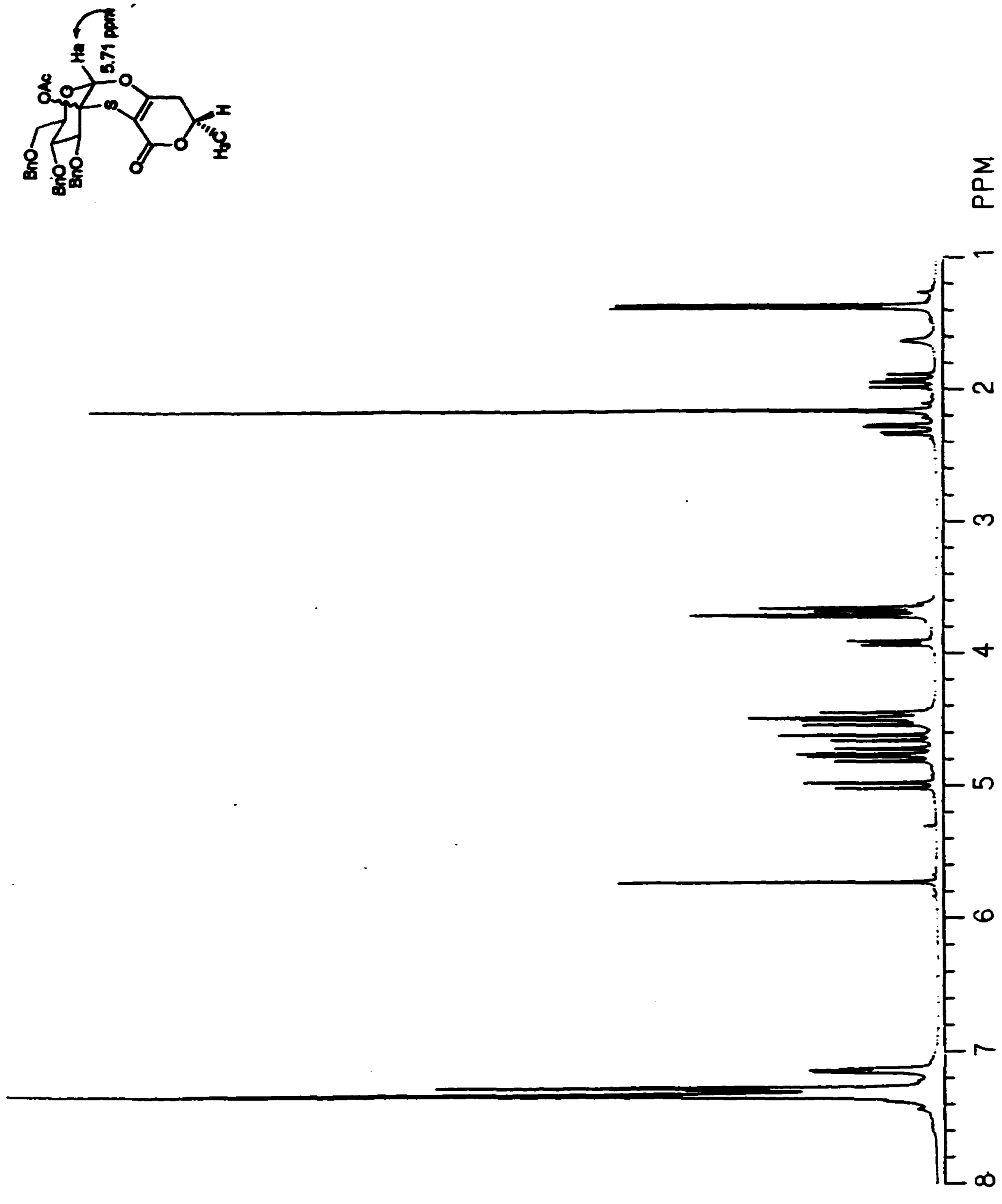
in benzene-d_6
500 MHZ

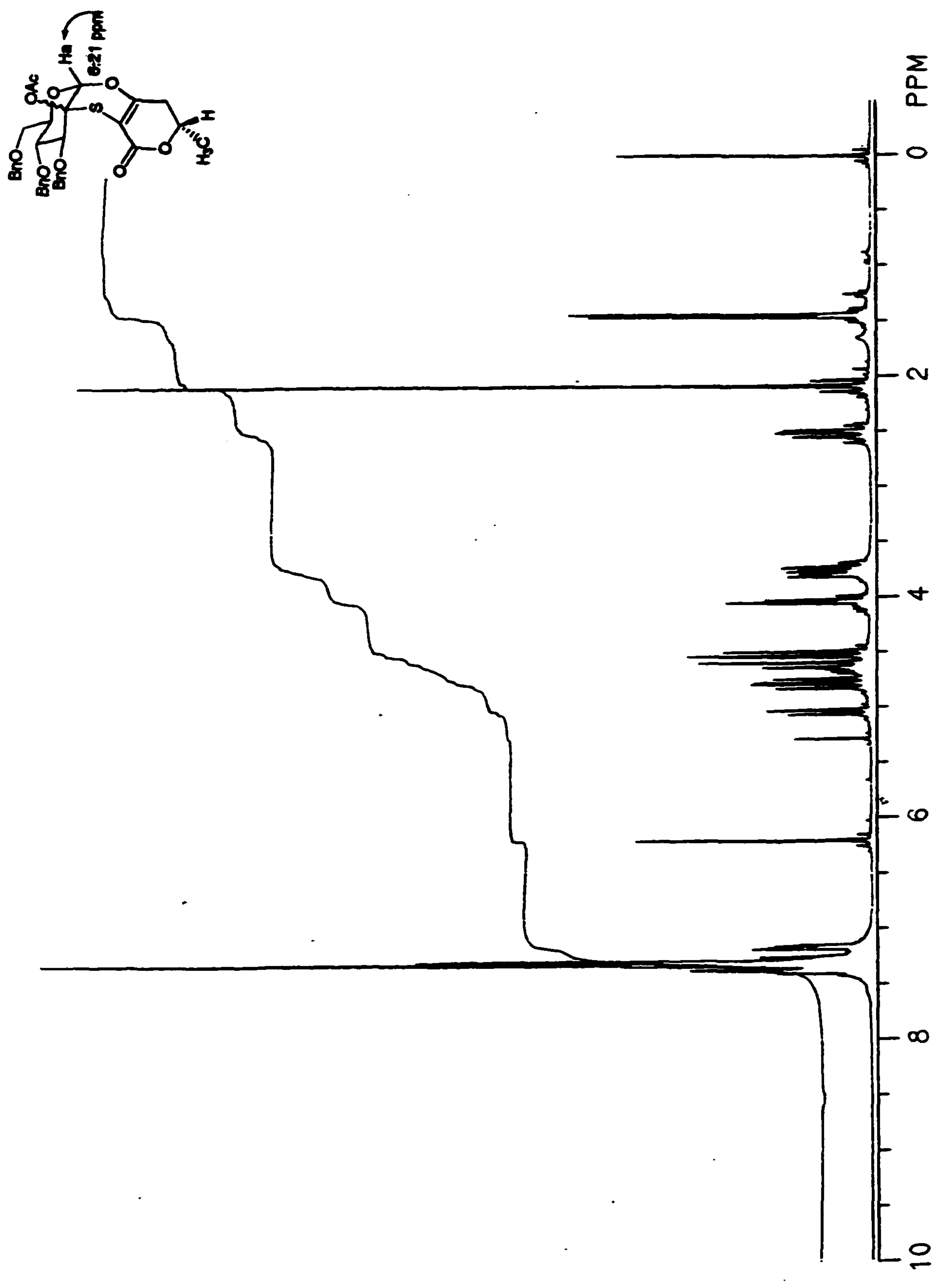
32

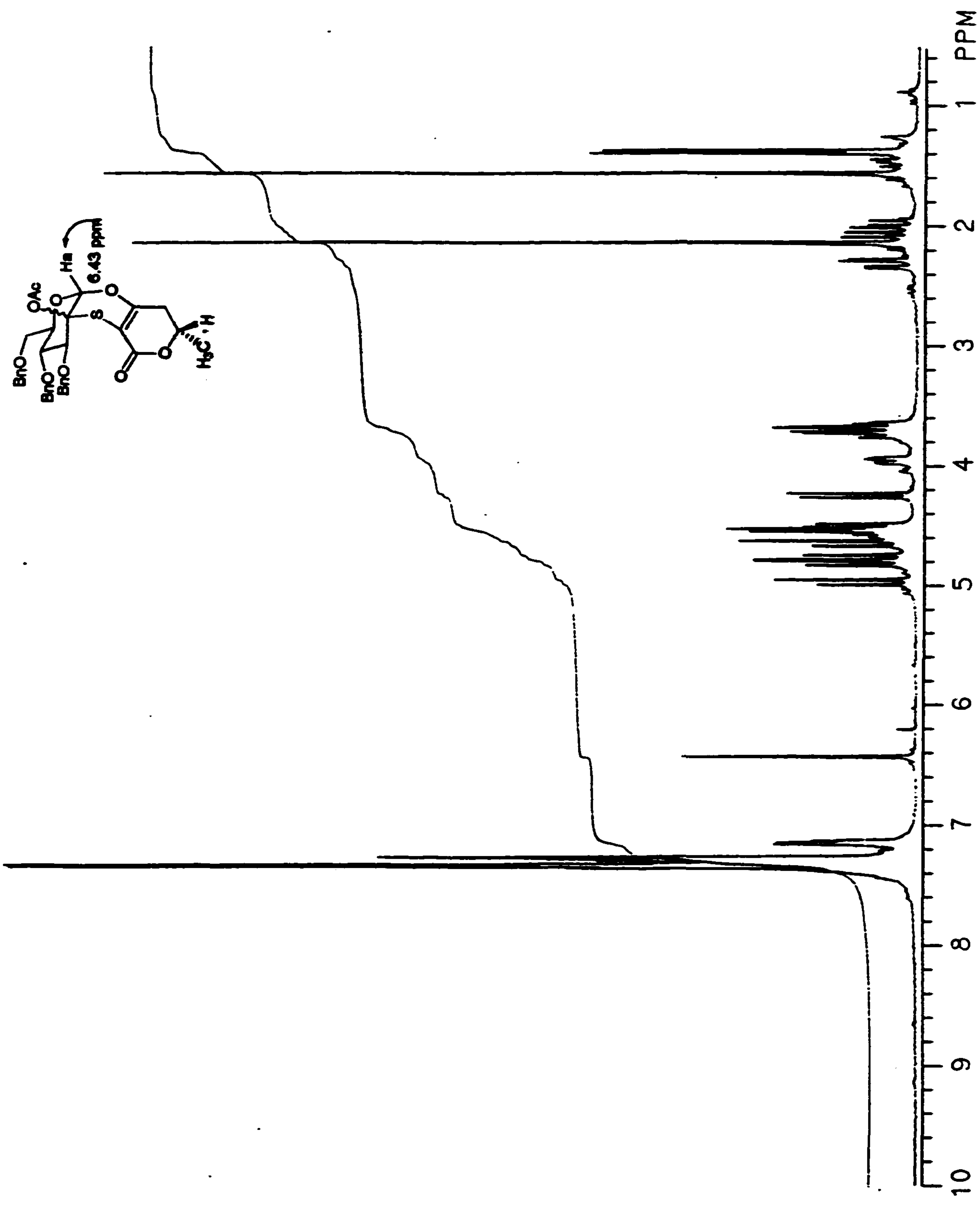


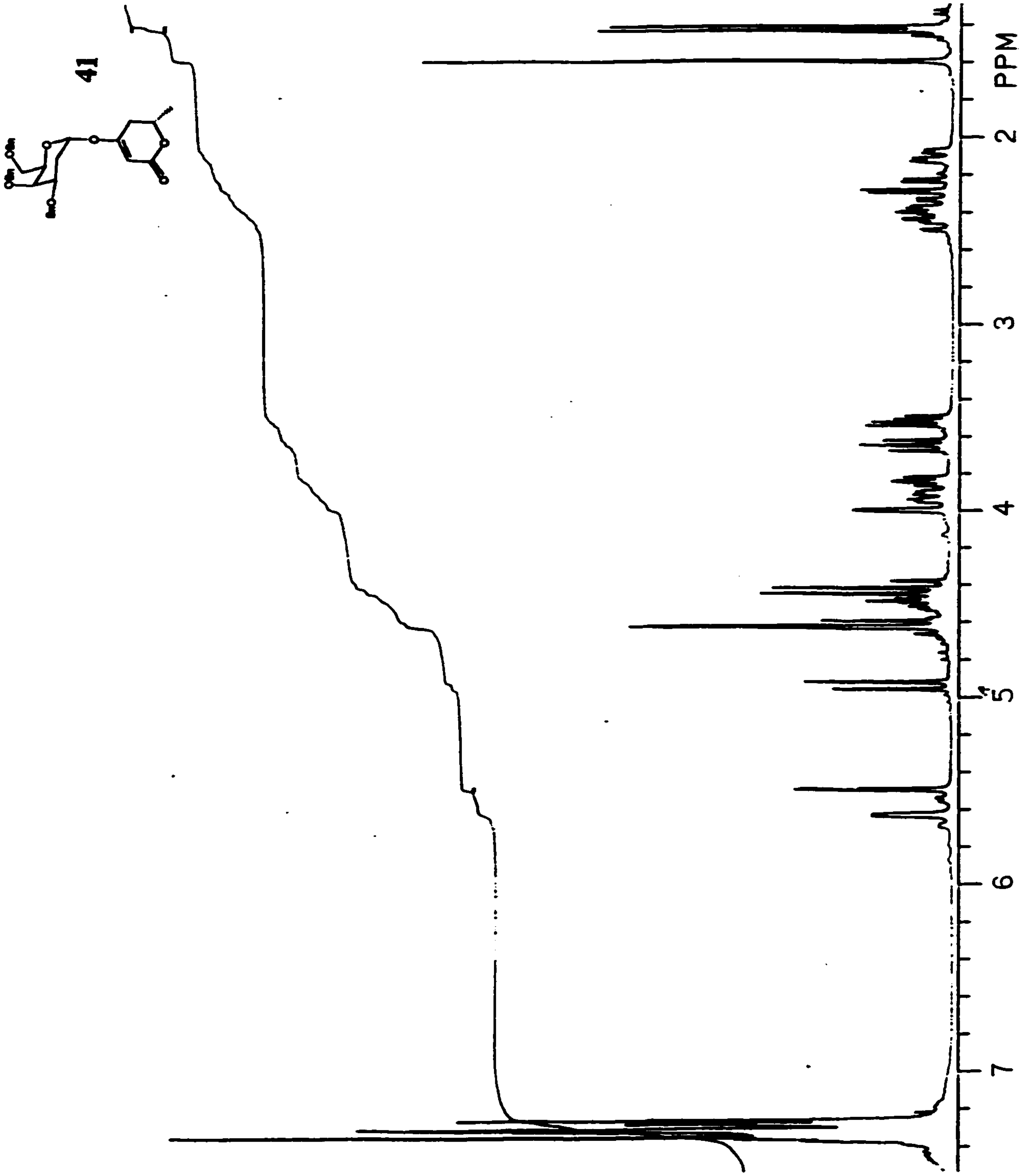

OBn
OBn
BnO
O
O
O
O
8
2
5
H
H
H
H_3C
H
C
5
H
signals overlap
PPM
1
2
3
4
5
6
7
8

32

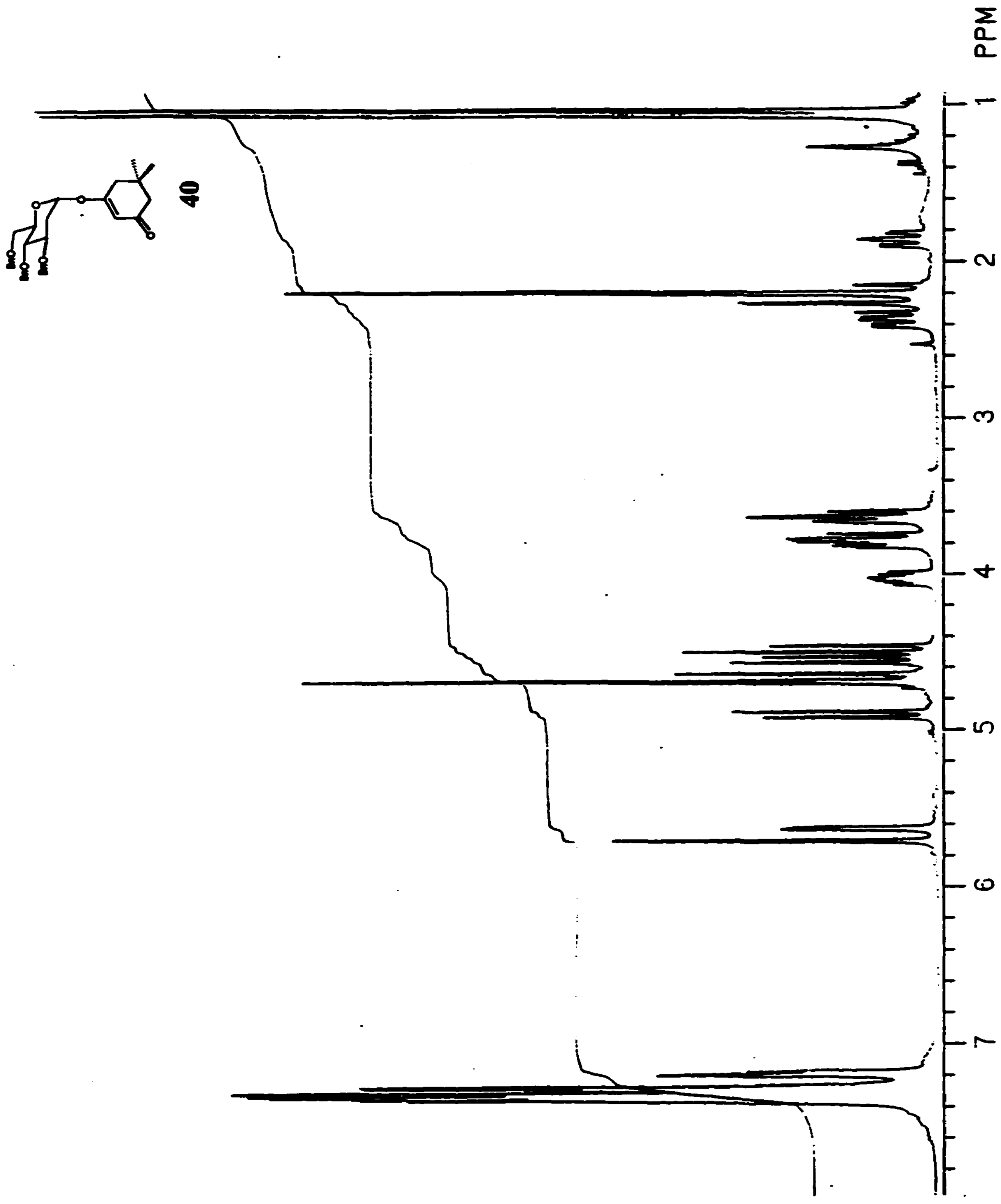

BnO
BnO
BnO
OAc
O
S
O
Ha
5.71 ppm
O
O
H_3C
H
PPM
1
2
3
4
5
6
7
8


BnO
BnO
BnO
OAc
O
S
O
O
O
Ha
6.21 ppm
H3C
H
PPM
0
2
4
6
8
10


Ha
6.43 ppm
OAc
BnO
BnO
BnO
S
O
O
O
O
H3C
H
PPM
1
2
3
4
5
6
7
8
9
10

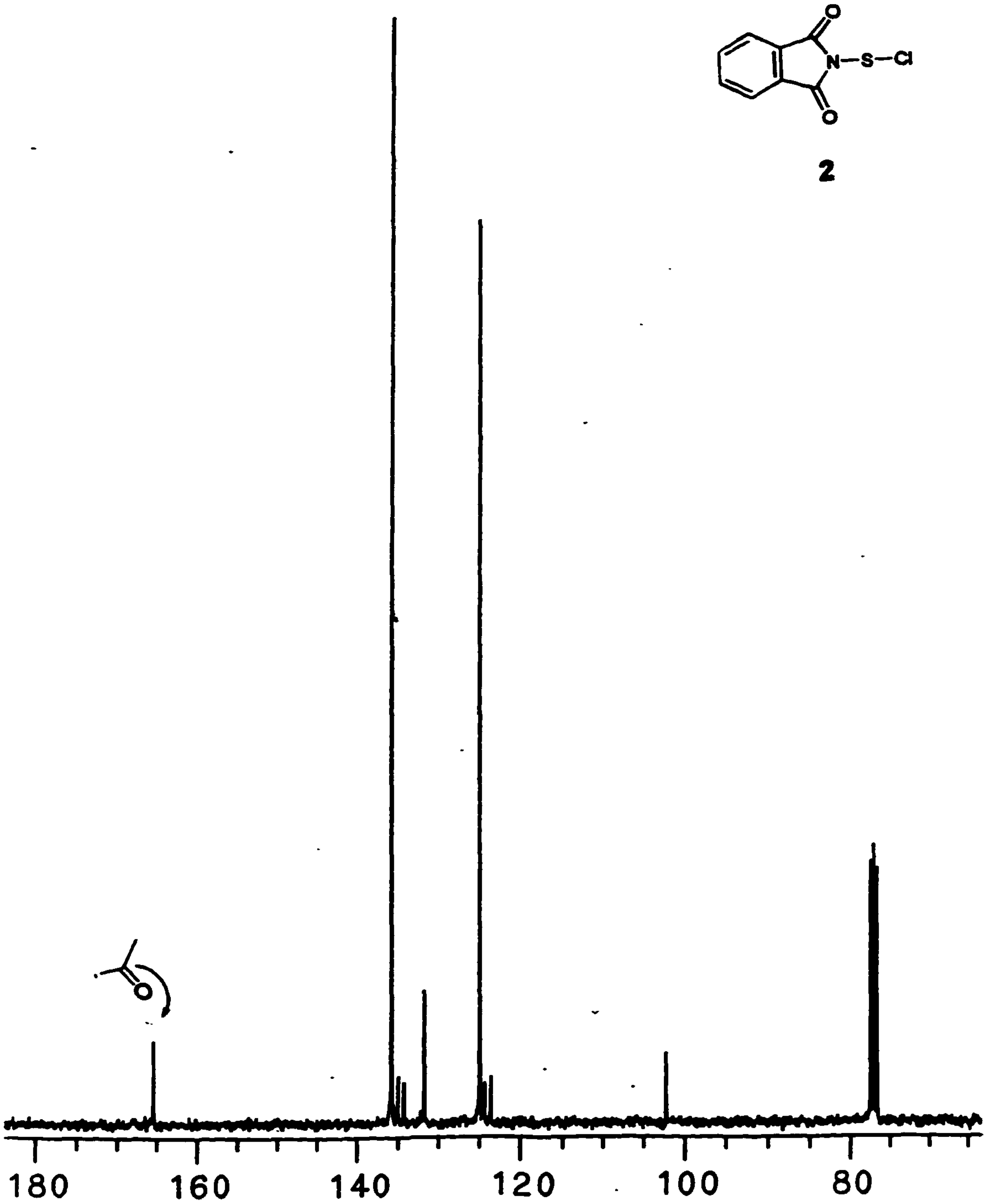


41

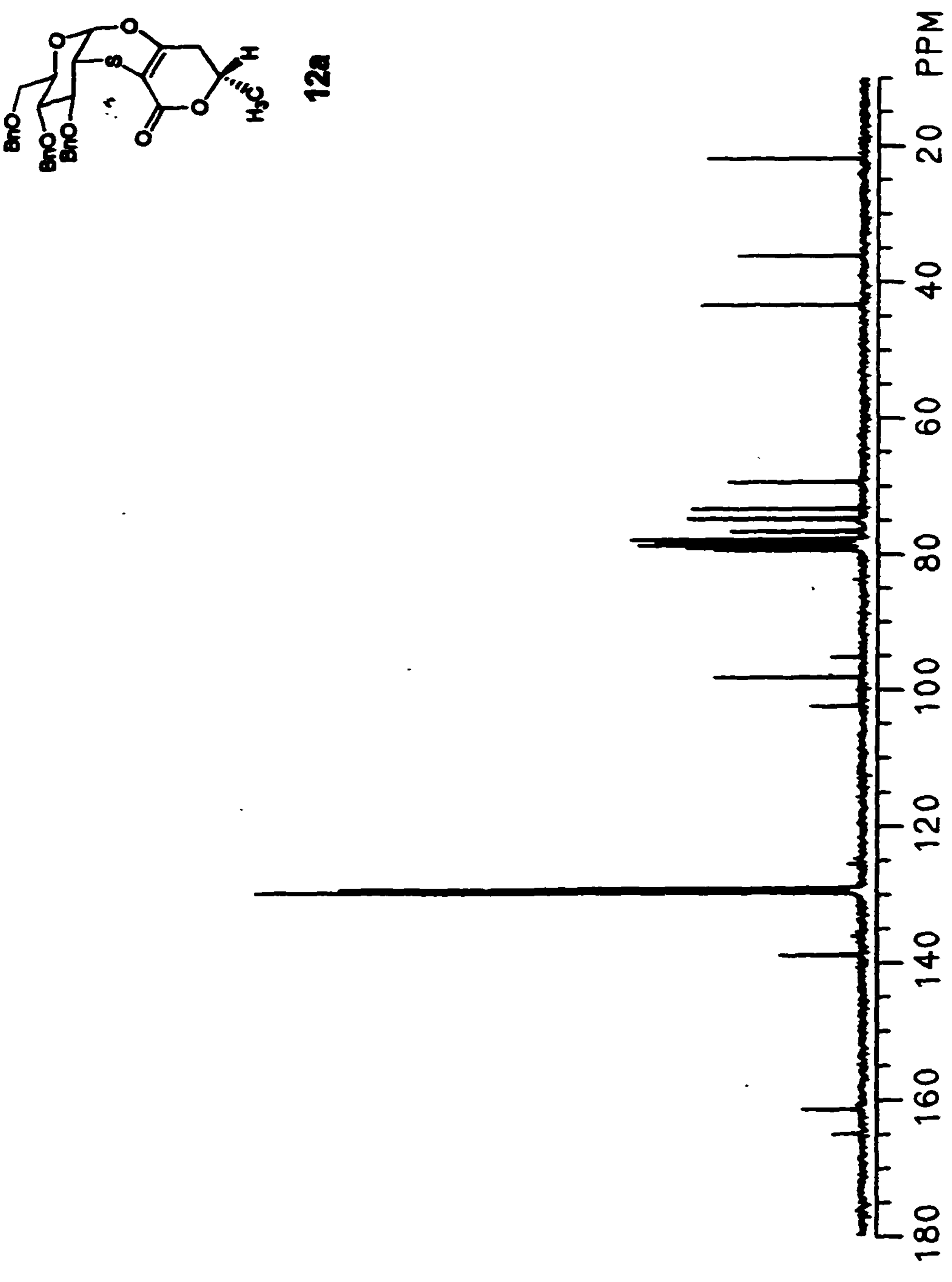


40

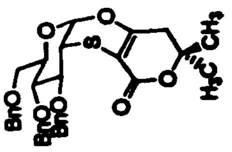
A.2. ^{13}C NMR Spectra of Selected Compounds.



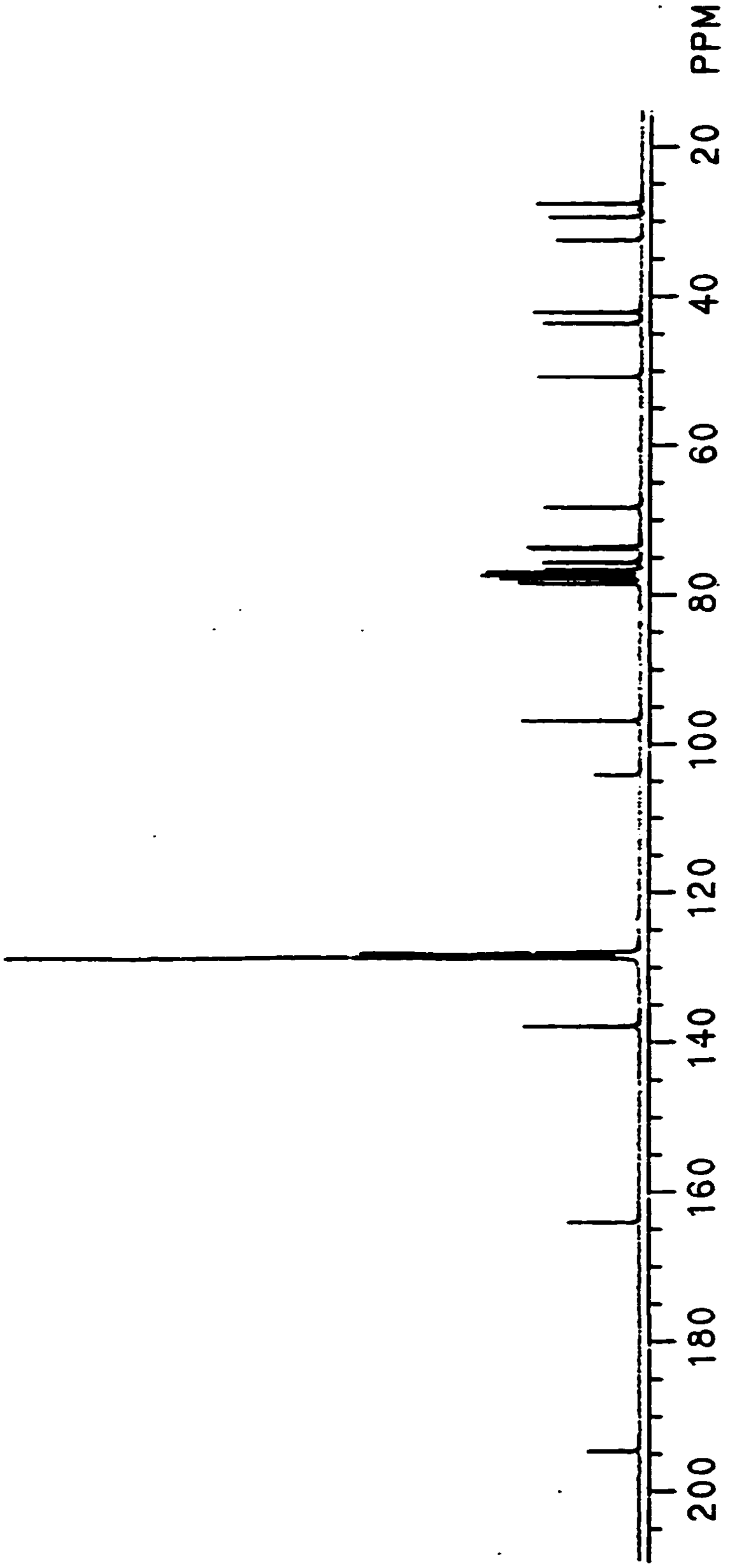
2

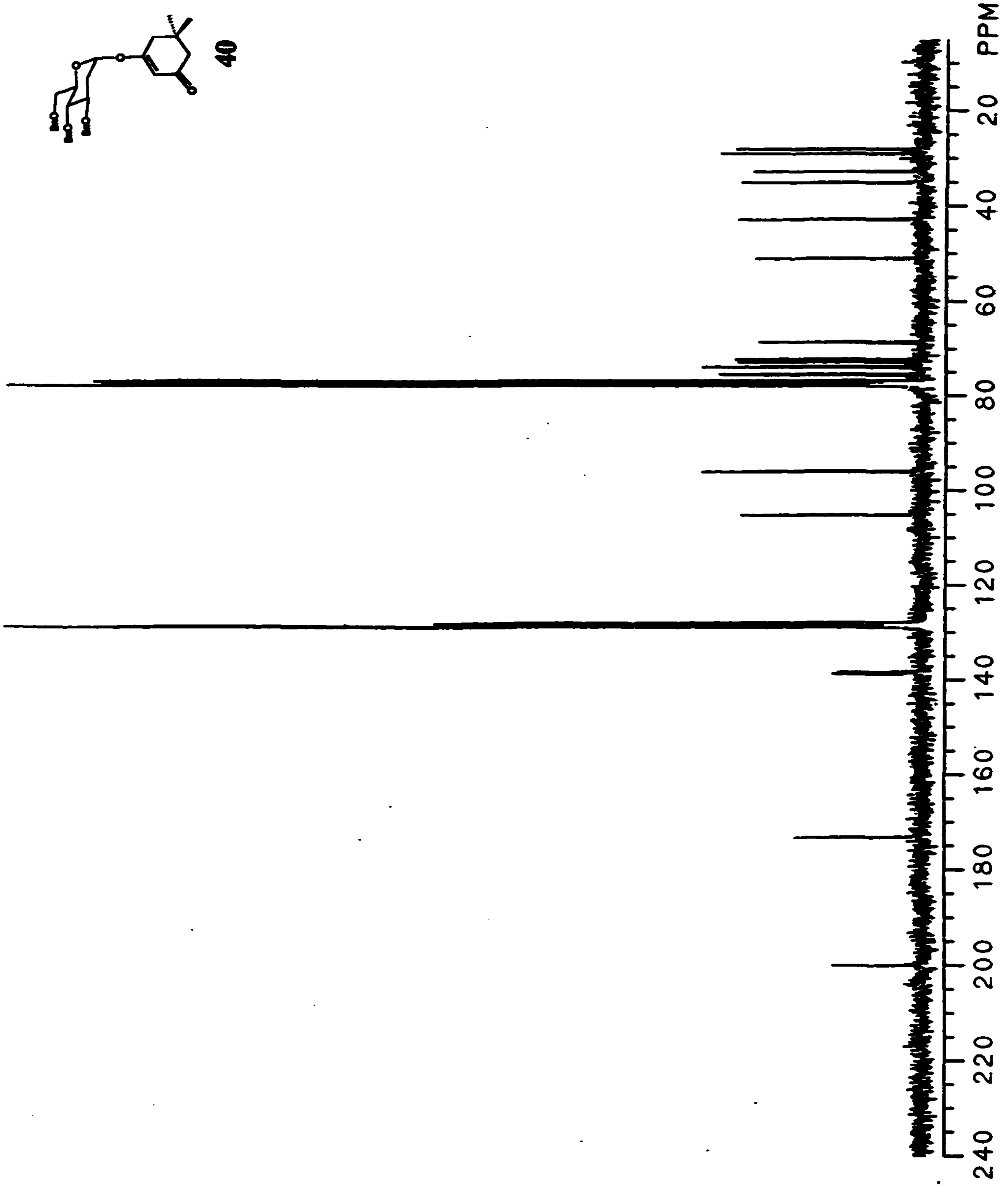


12a



13





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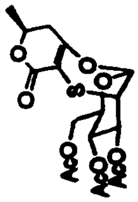

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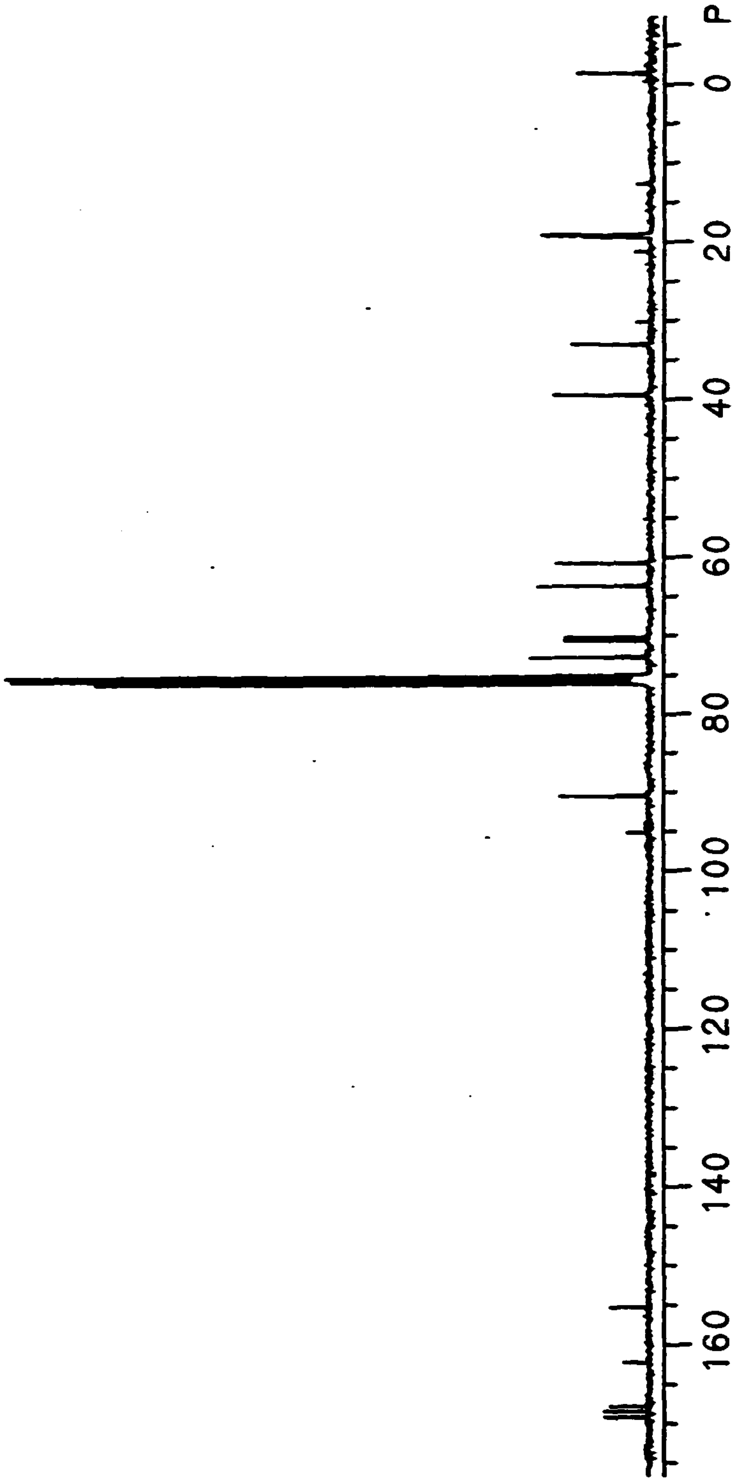
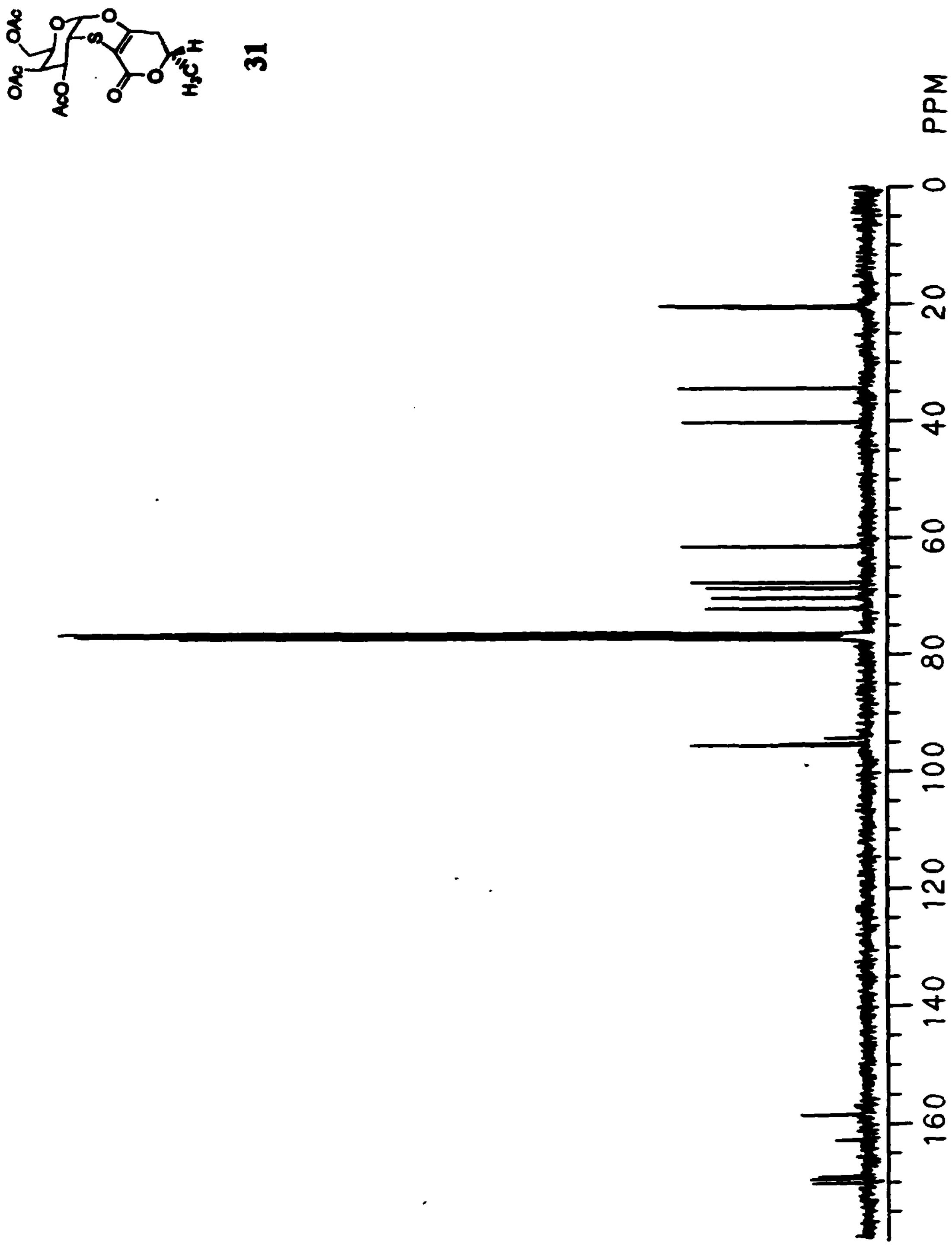
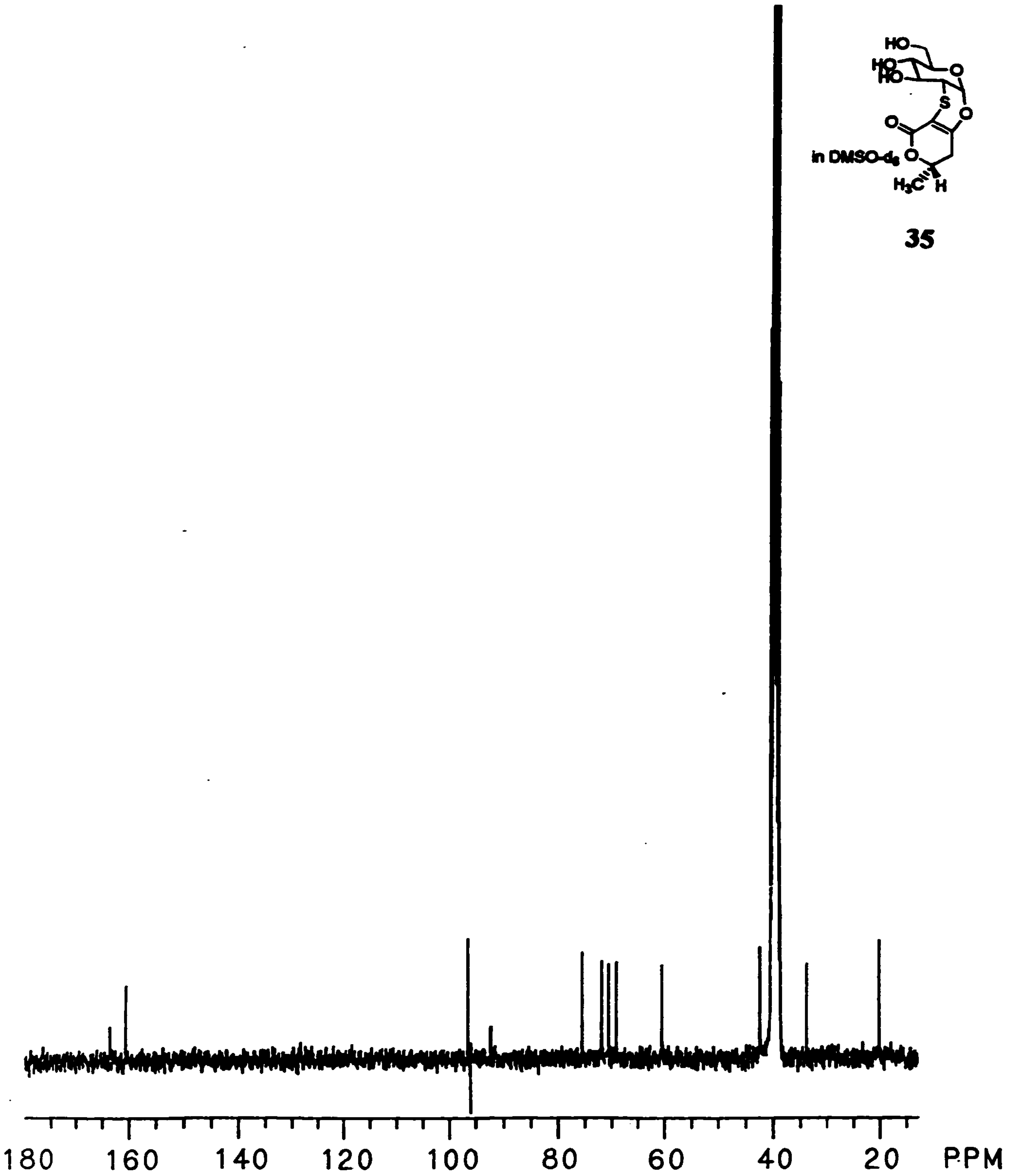
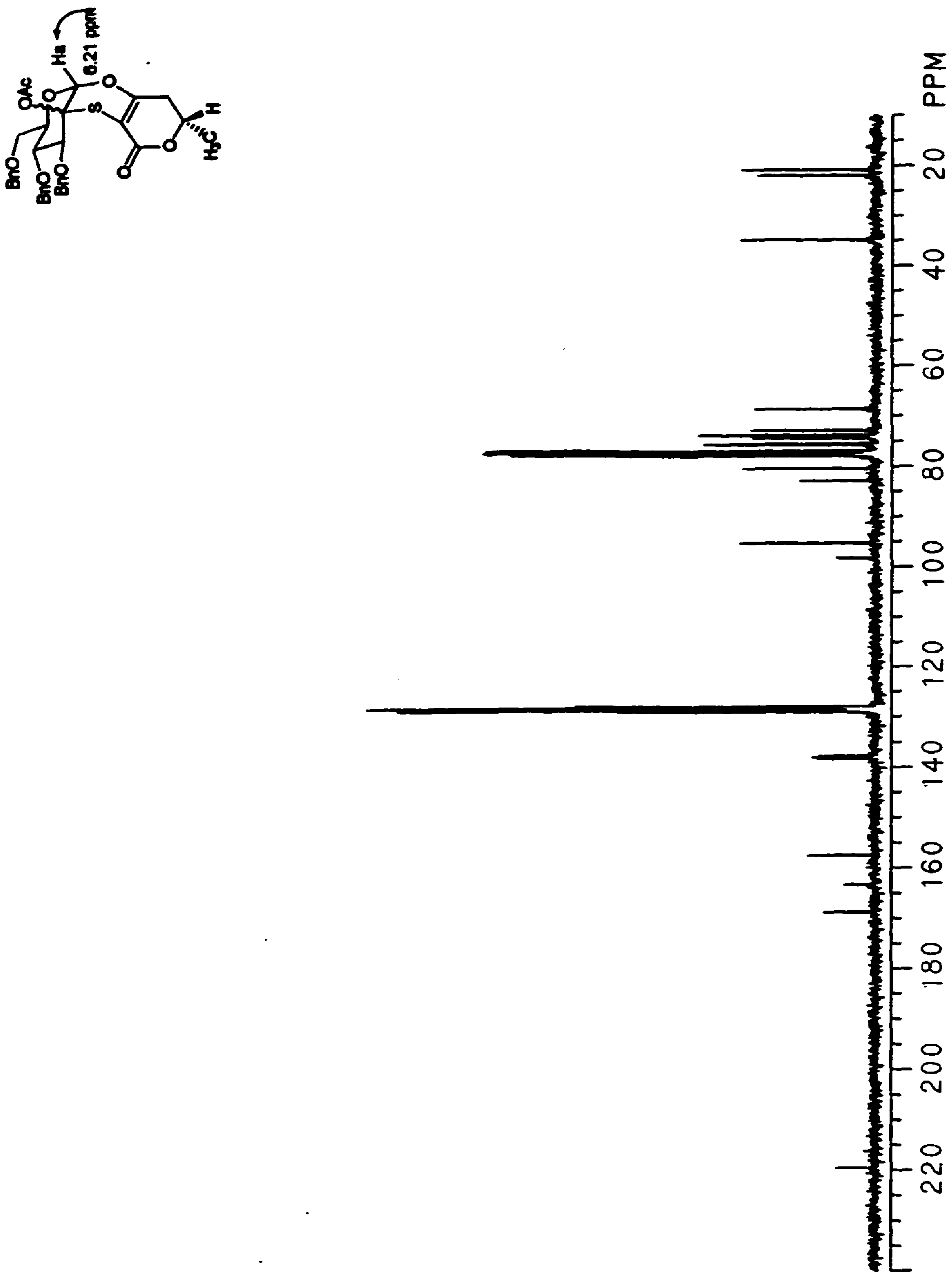


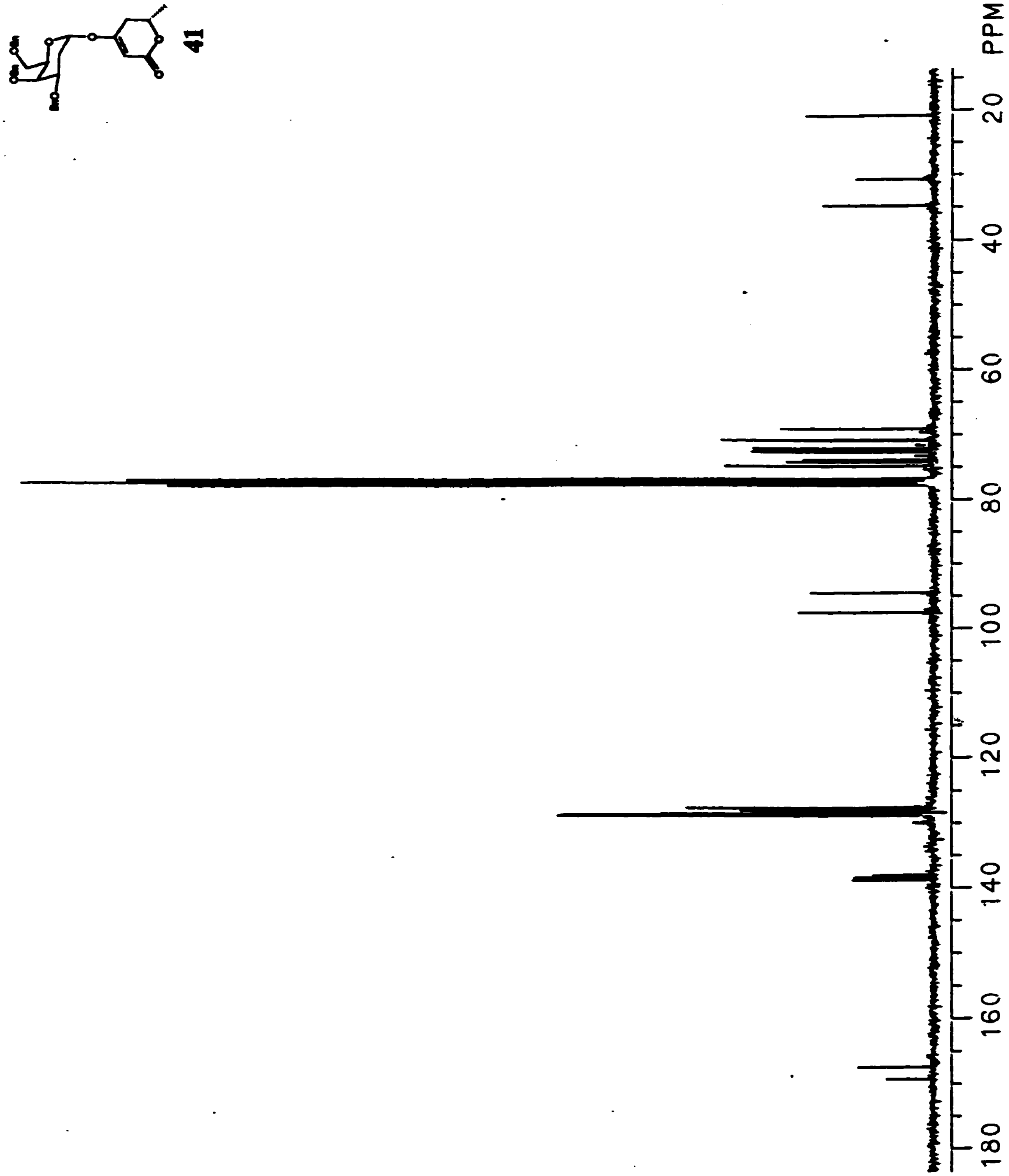


31



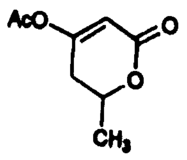
35


OAc
BnO
BnO
BnO
O
S
O
O
O
Ha
6.21 ppm
H
H_3C
PPM
20
40
60
80
100
120
140
160
180
200
220

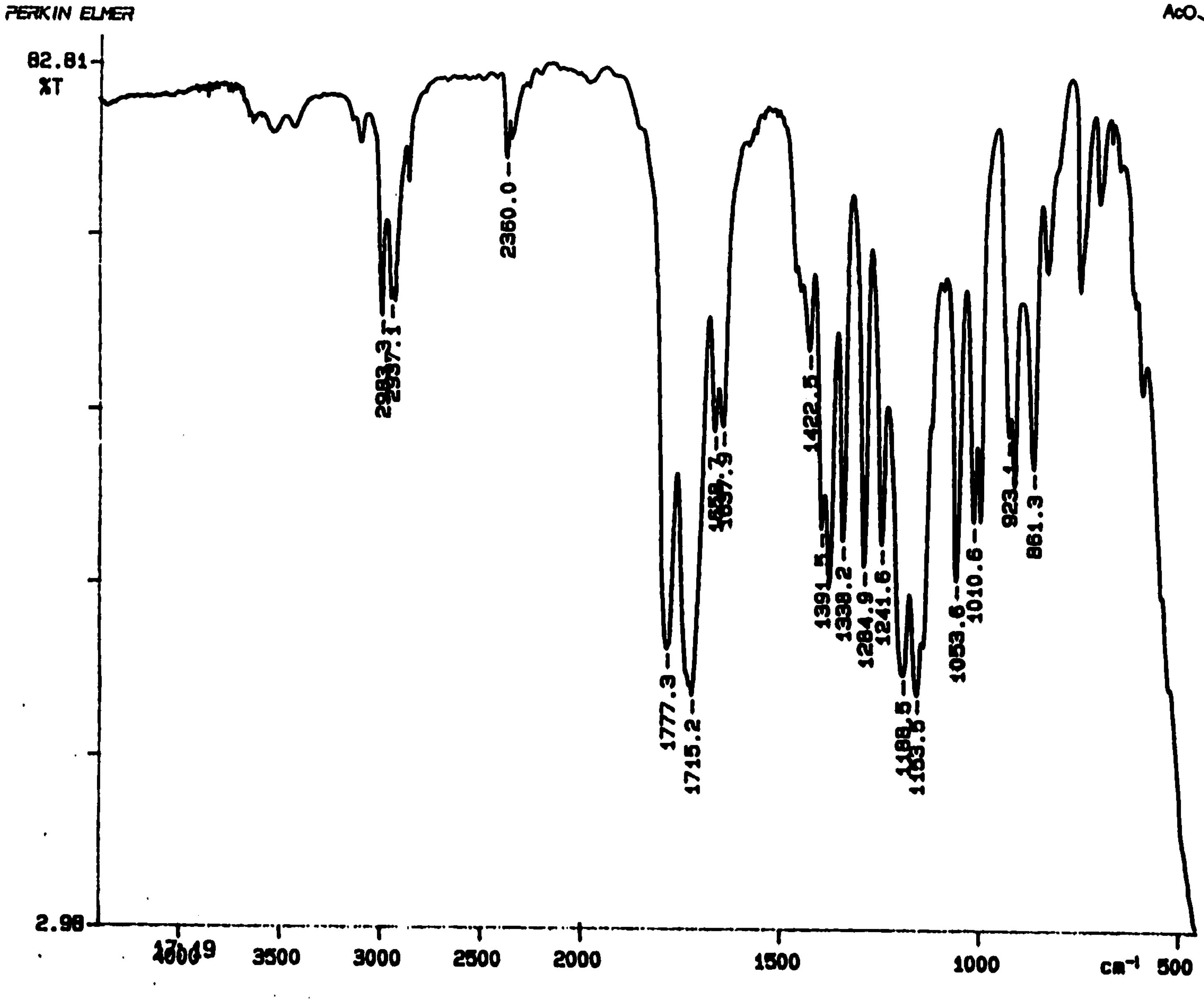


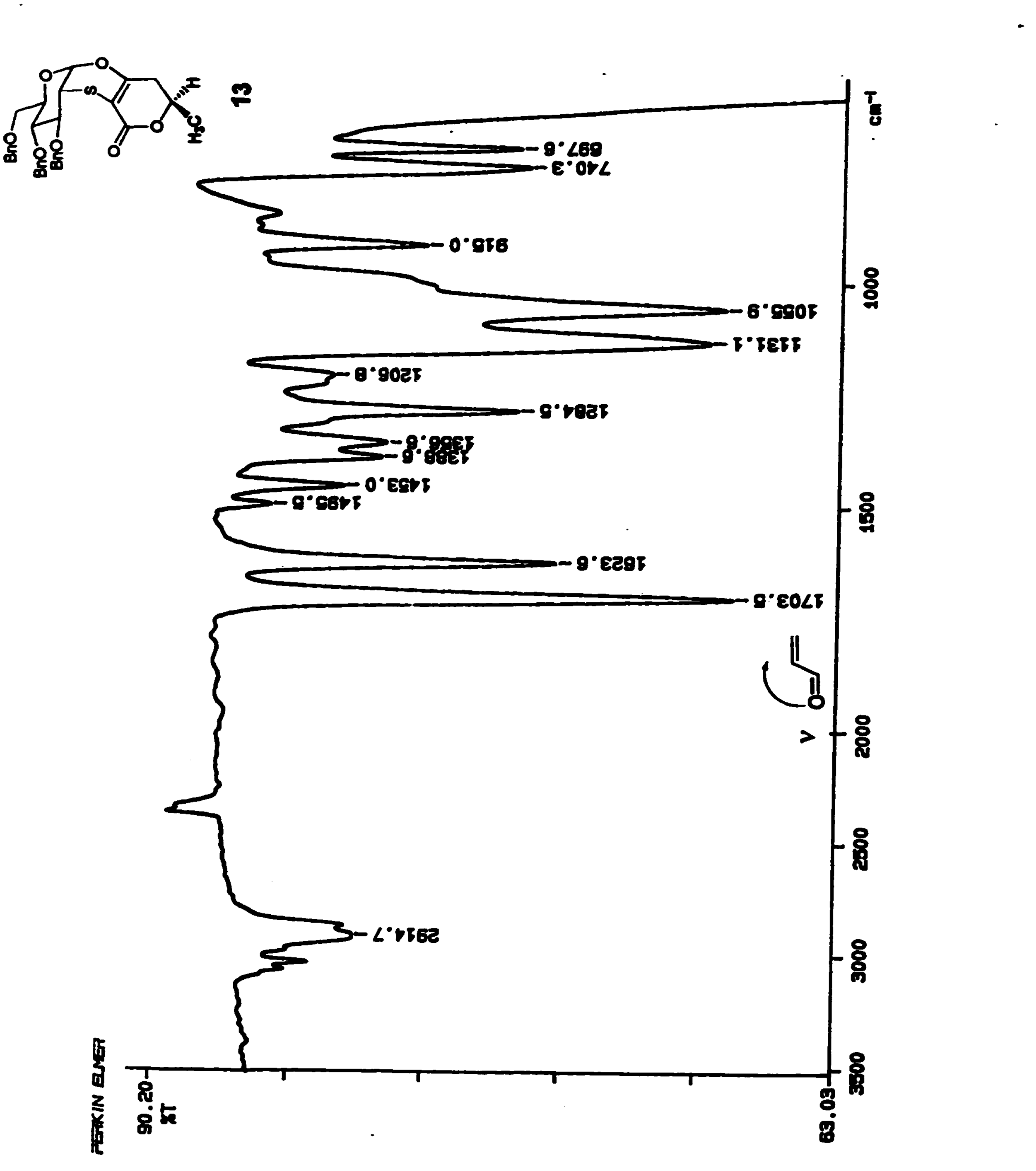
41

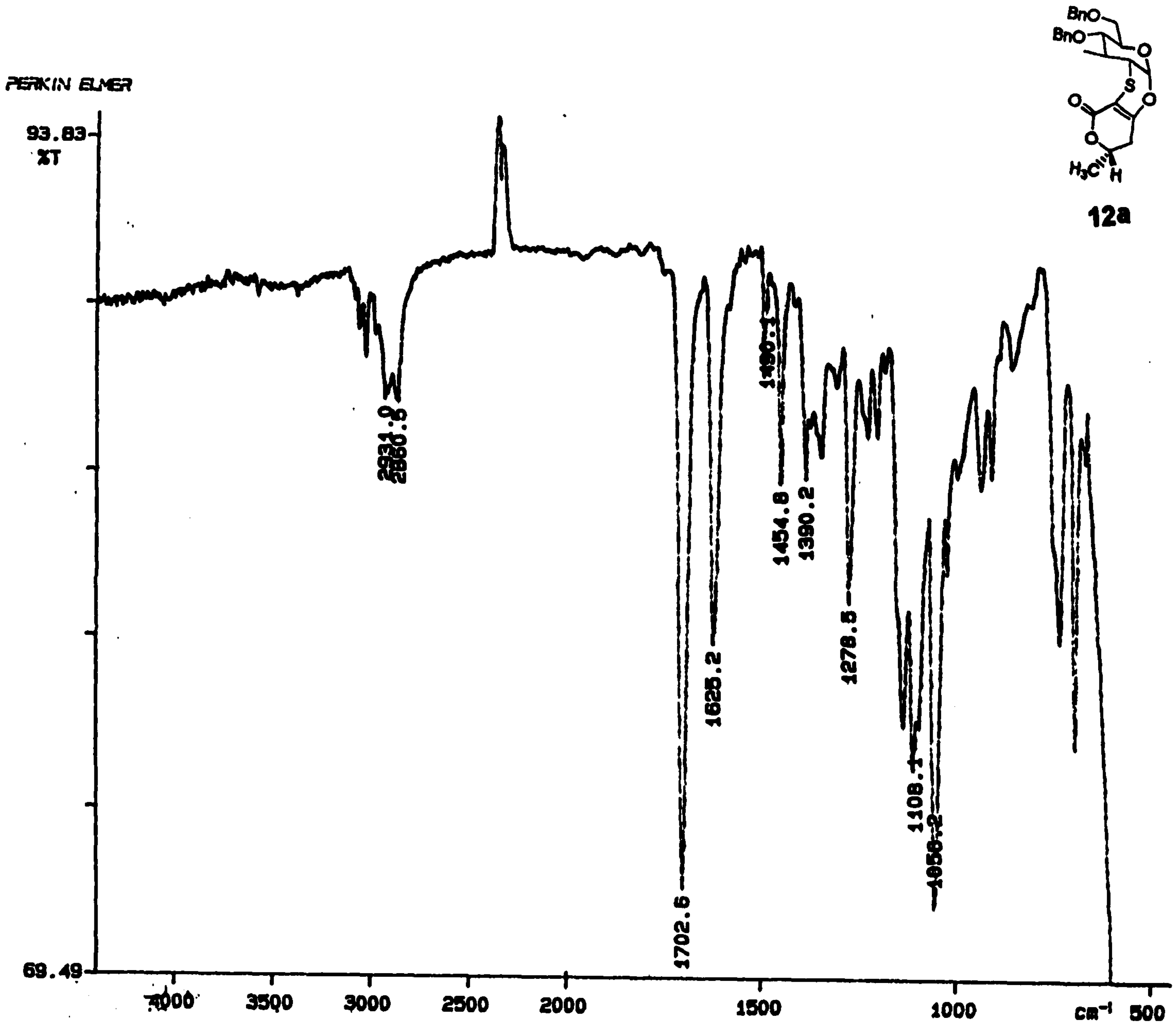
A.3. IR Spectra of Selected Compounds.



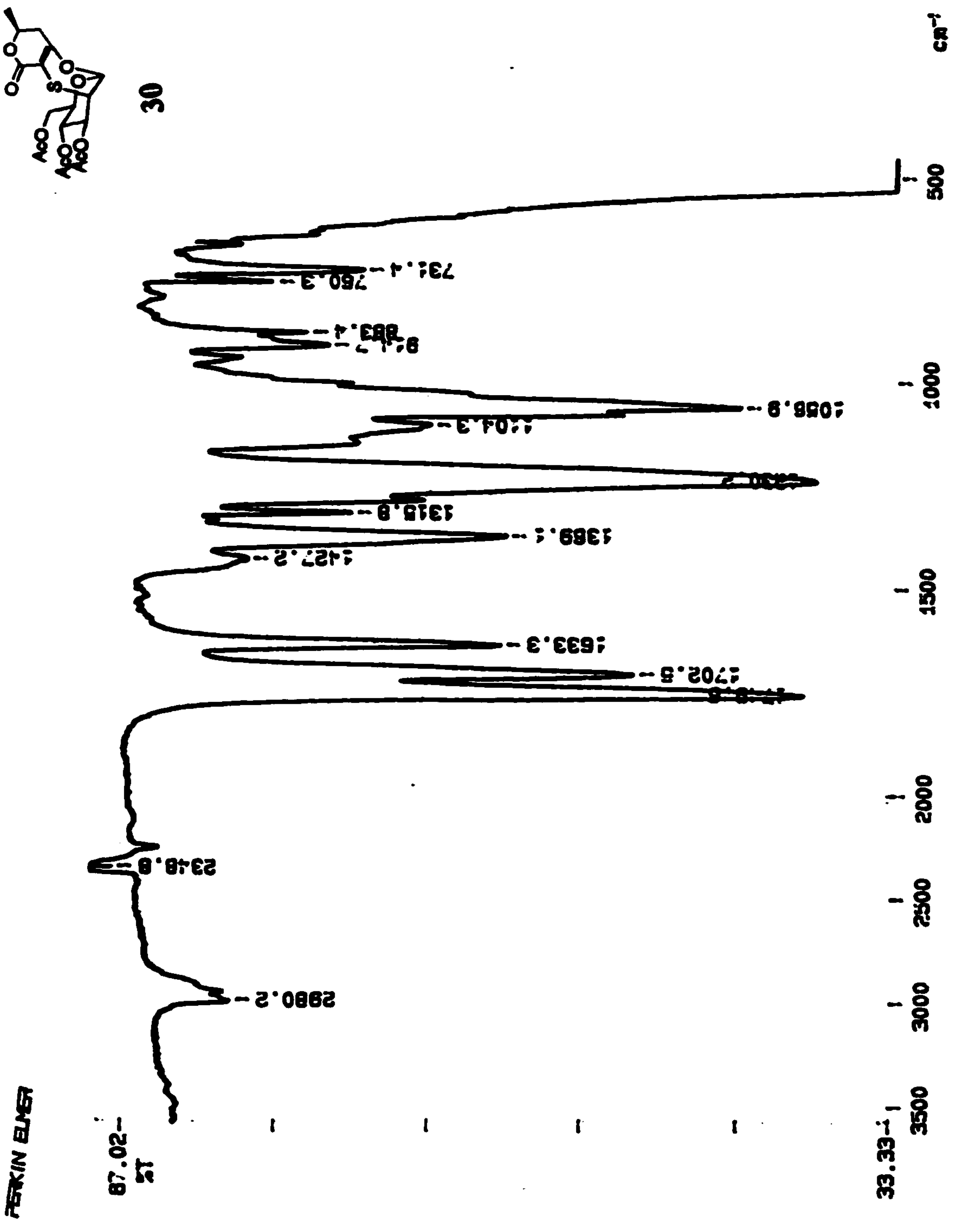
(S/R)-18


PERKIN ELMER
82.81
%T
2.98
2983.3
2937.1
2360.0
1777.3
1715.2
1658.7
1637.9
1422.5
1391.5
1338.2
1284.9
1241.6
1188.5
1153.5
1053.6
1010.6
923.4
861.3
17.49
4000
3500
3000
2500
2000
1500
1000
cm⁻¹ 500


PERKIN ELMER
90.20
%T
63.03
3500
3000
2500
2000
1500
1000
cm-1
2914.7
1703.5
1623.6
1495.5
1453.0
1398.6
1366.6
1284.5
1206.8
1131.1
1055.9
915.0
740.3
697.6
V
O
BnO
BnO
BnO
O
O
S
O
O
O
H3C
H
13

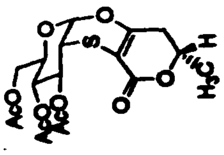

PERKIN ELMER
93.83
%T
69.49
4000
3500
3000
2500
2000
1500
1000
cm-1 500
2931.0
2860.5
1702.6
1625.2
1490.1
1454.8
1390.2
1278.5
1108.1
1056.2
BnO
BnO
O
S
O
O
O
H3C
H

12a

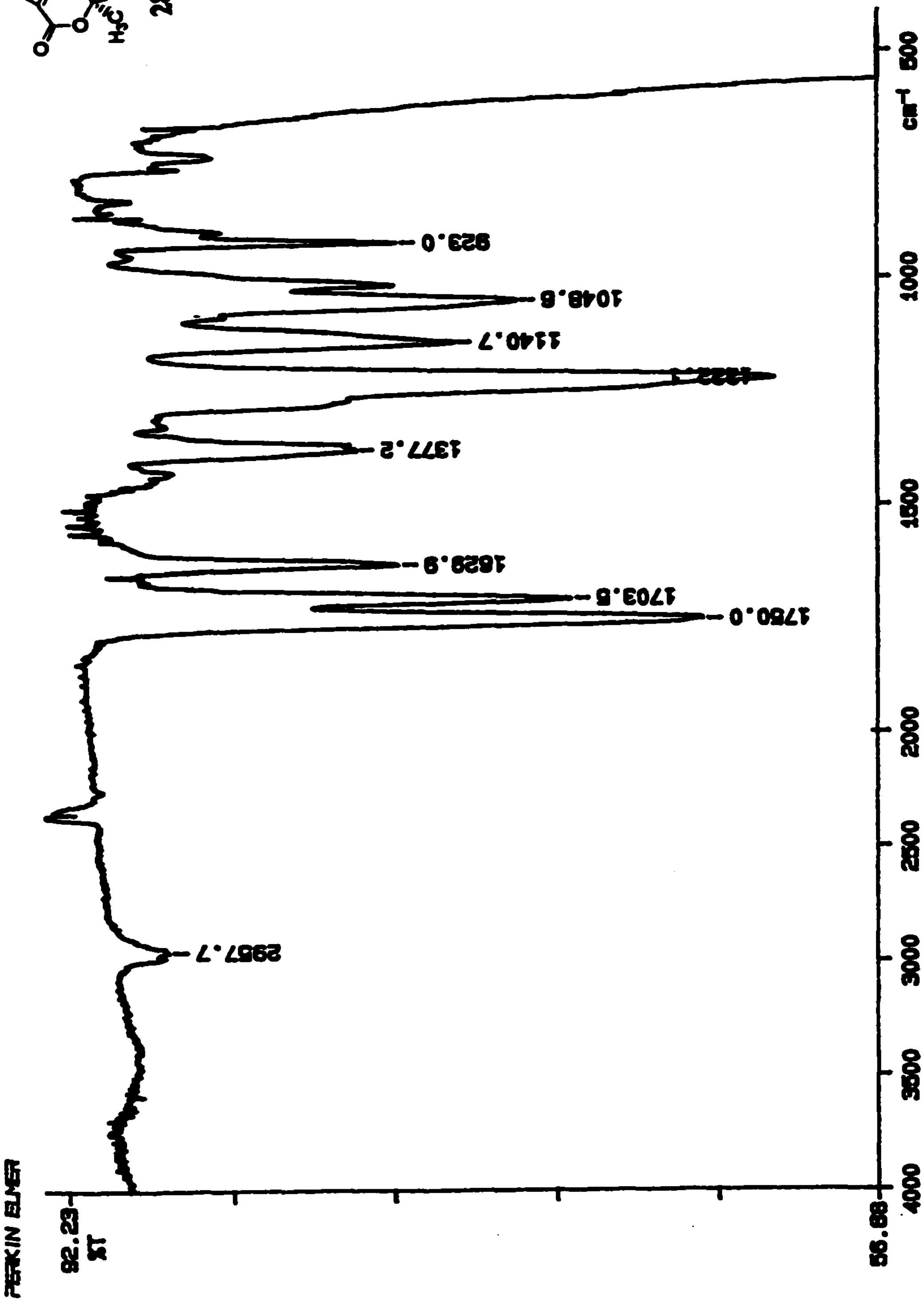


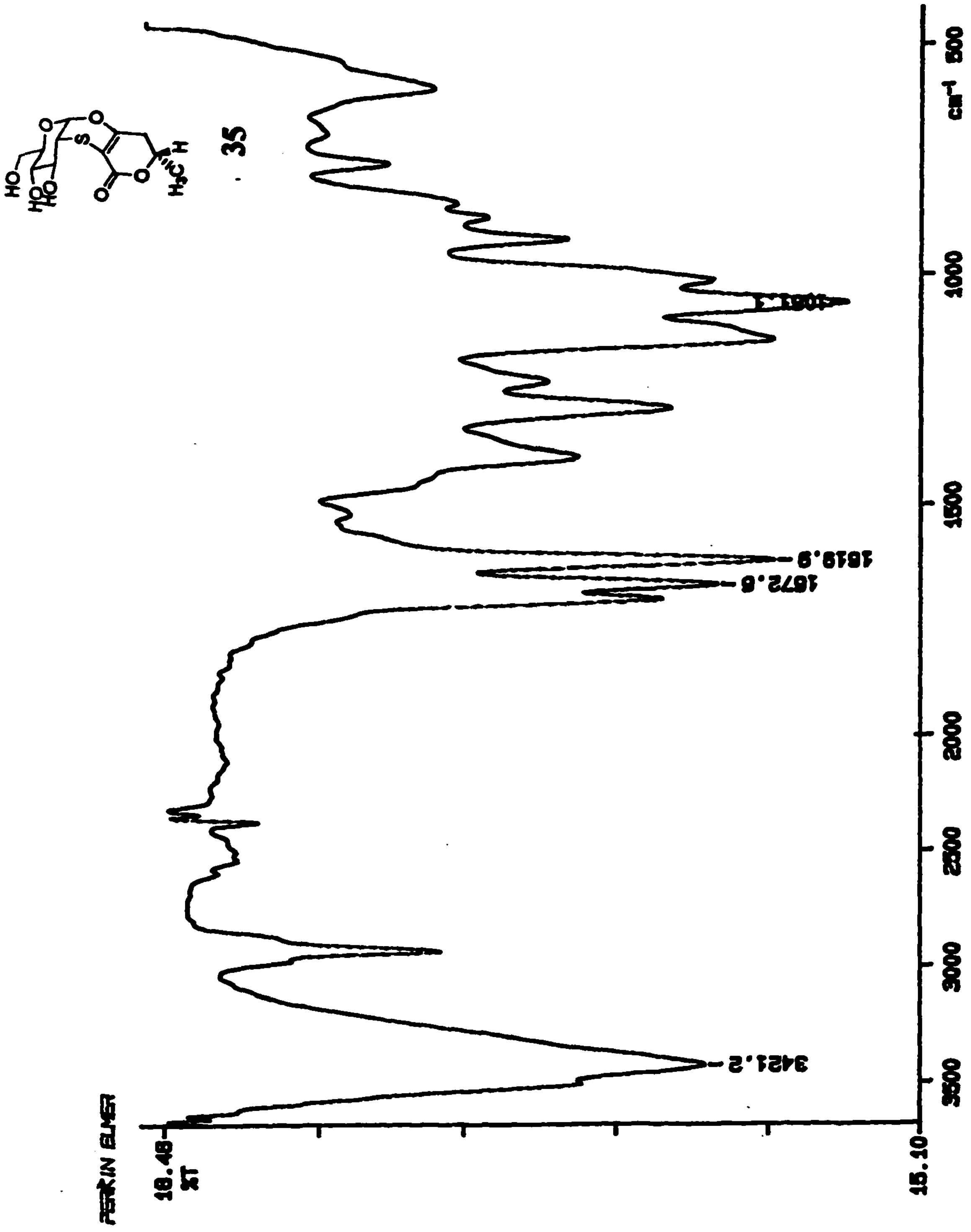
30

AcO
AcO
AcO
S
O
O
O
PERKIN ELMER
87.02
%T
33.33
3500
3000
2500
2000
1500
1000
500
cm-1
2980.2
2348.8
1702.5
1633.3
1427.2
1369.1
1318.8
1104.3
1058.9
883.4
760.3
731.4

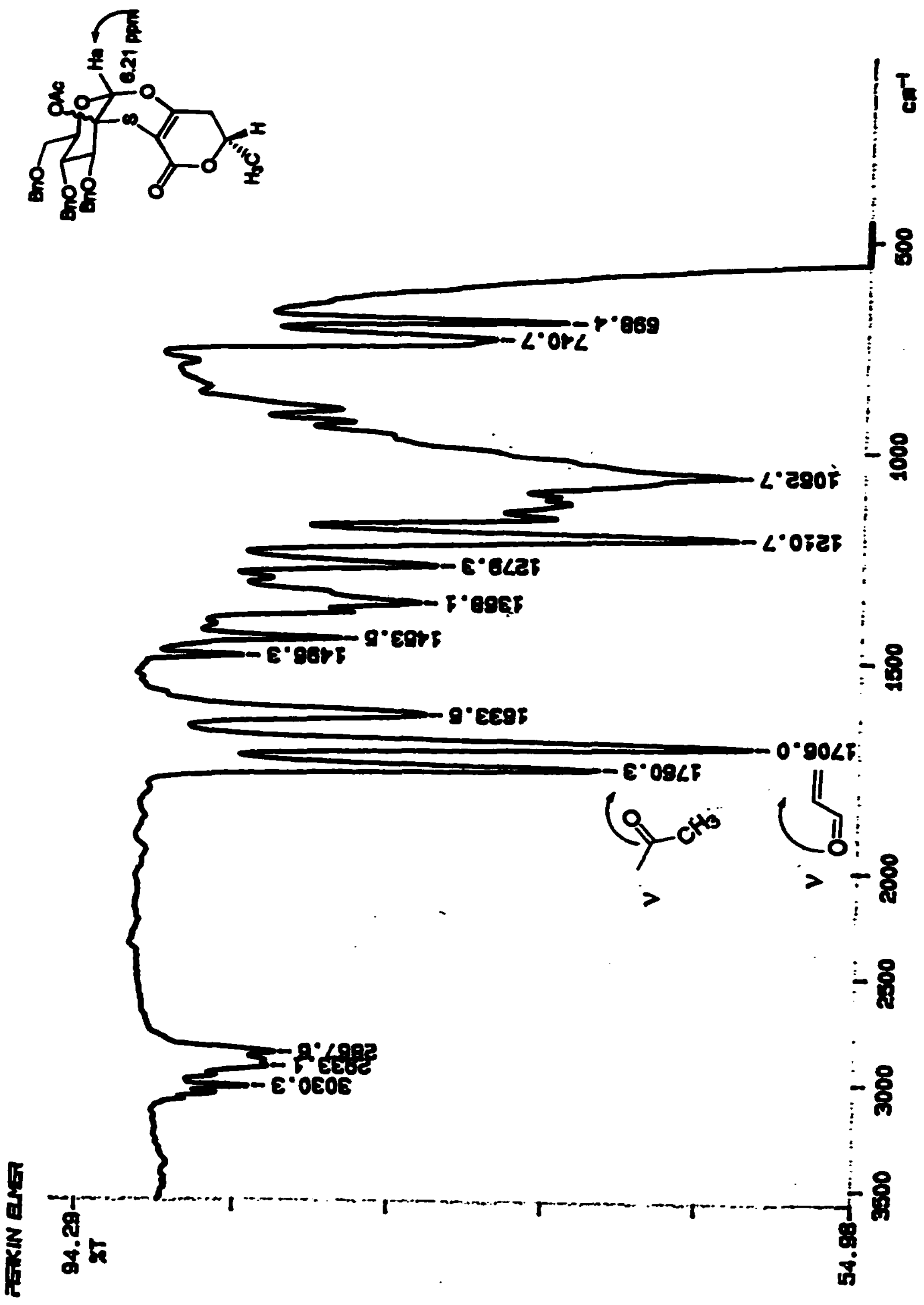


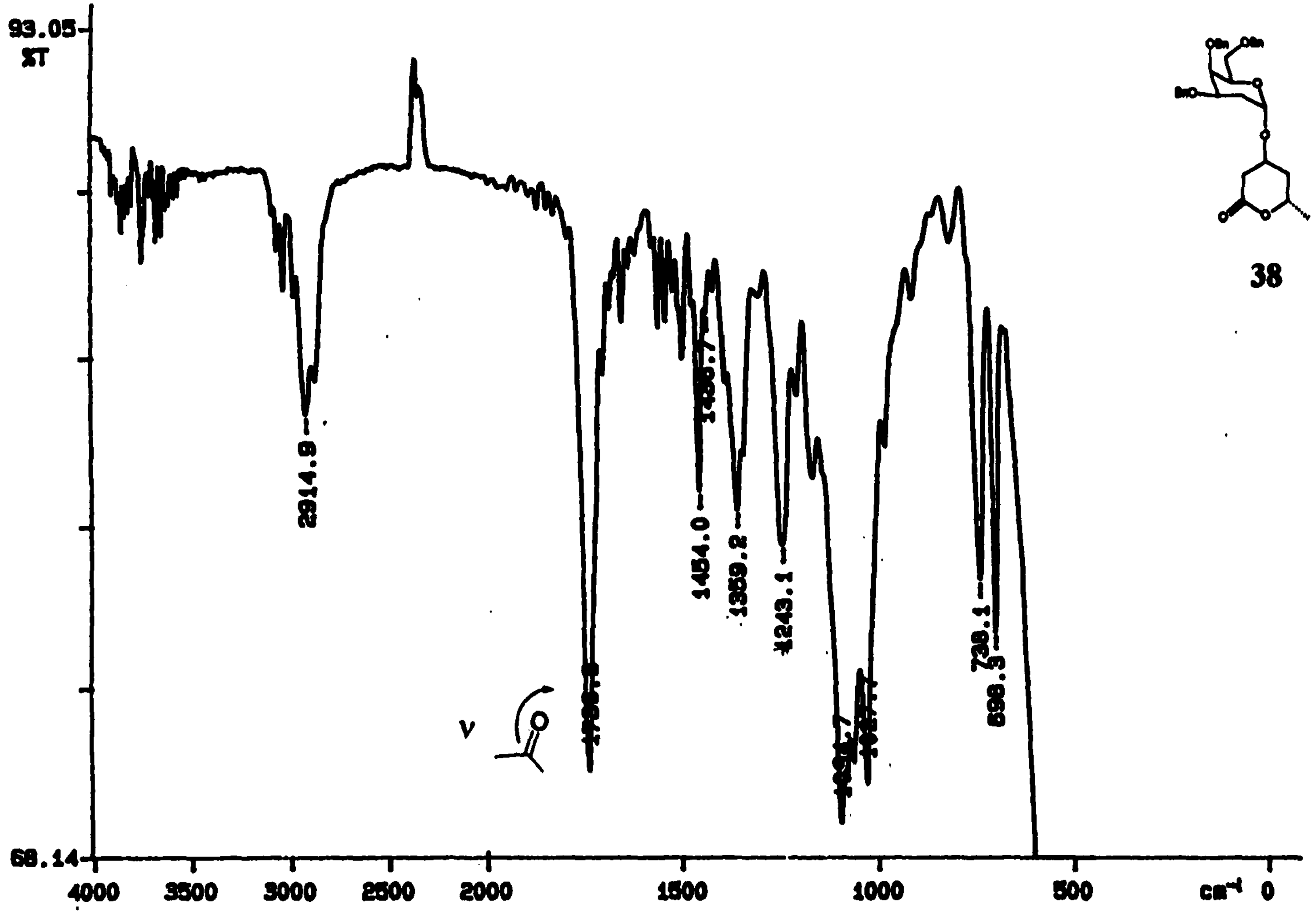
28a

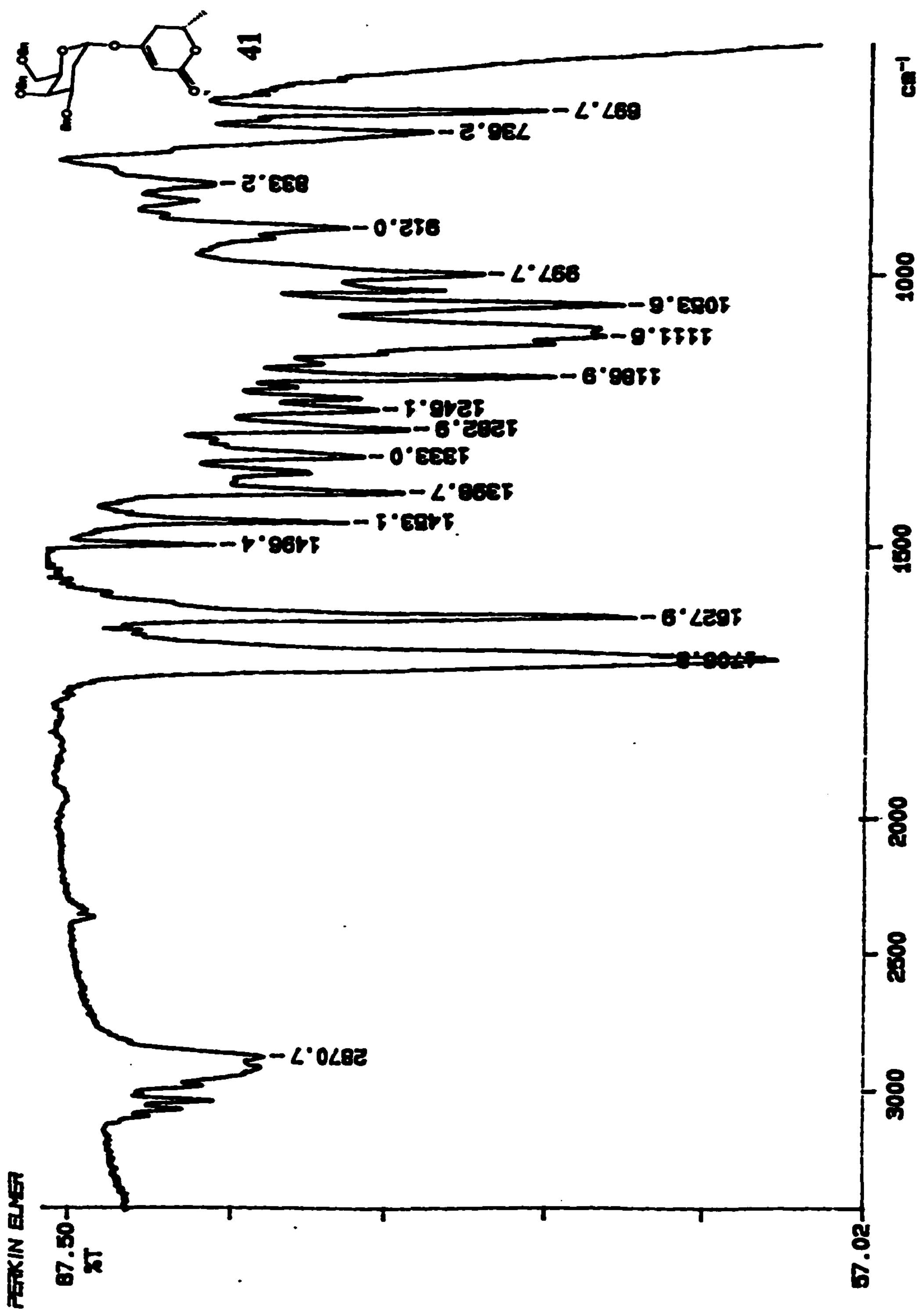

PERKIN ELMER
92.23
%T
56.68
4000
3500
3000
2500
2000
1500
1000
500
cm-1
2957.7
1750.0
1703.5
1629.9
1377.2
1222.1
1140.7
1048.6
923.0


PERKIN ELMER
18.48
%T
15.10
3421.2
1672.6
1619.9
1061.1
3500
3000
2500
2000
1500
1000
cm-1 500
HO
HO
HO
O
O
S
O
O
H3C
H

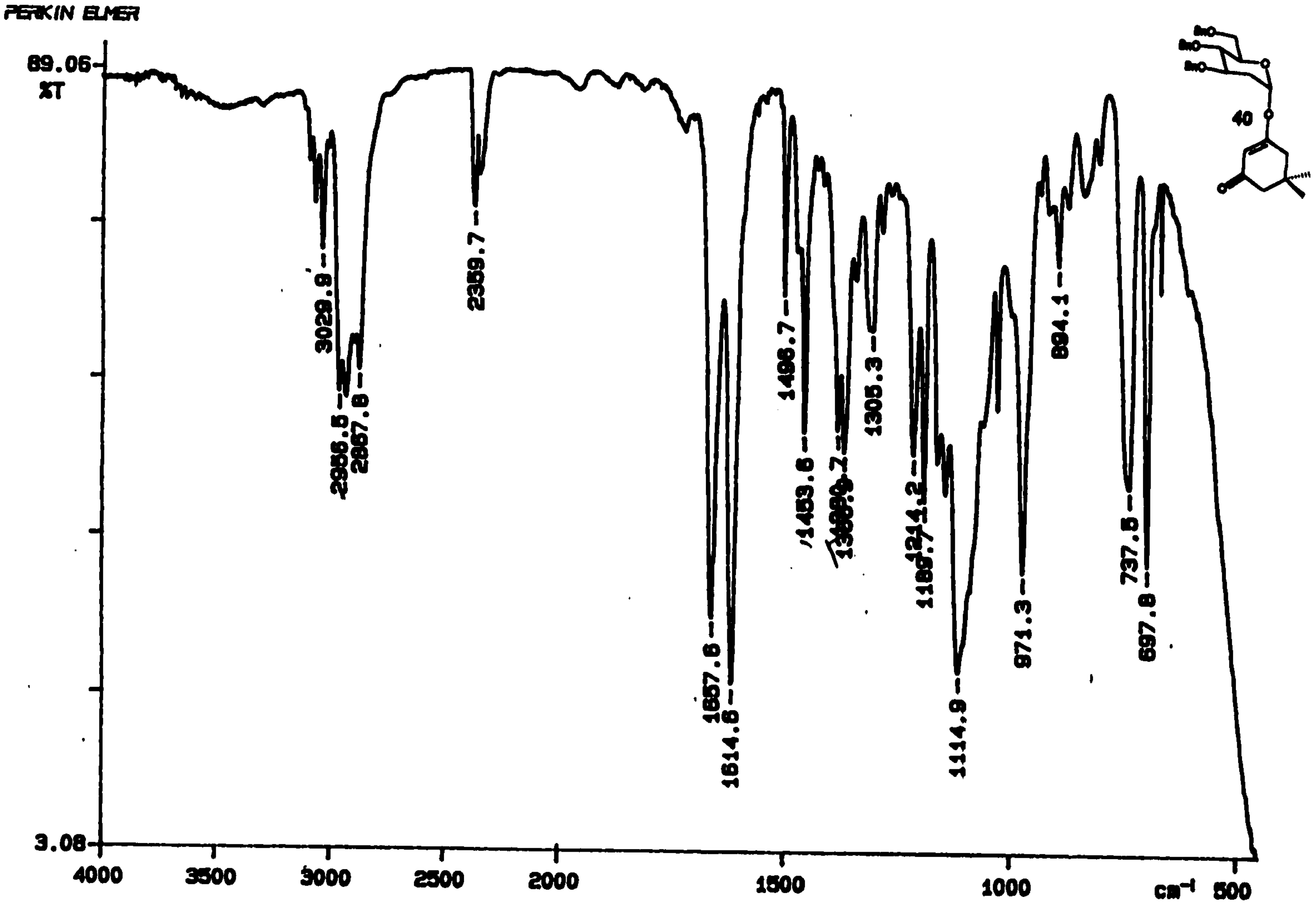
35


PERKIN ELMER
94.29
%T
54.98
3500
3000
2500
2000
1500
1000
500
cm⁻¹
3030.3
2933.1
2867.8
1760.3
1706.0
1633.8
1496.3
1453.5
1368.1
1279.3
1210.7
1062.7
740.7
698.4
BnO
OAc
Ha
6.21 ppm
S
O
H₃C
H
CH₃

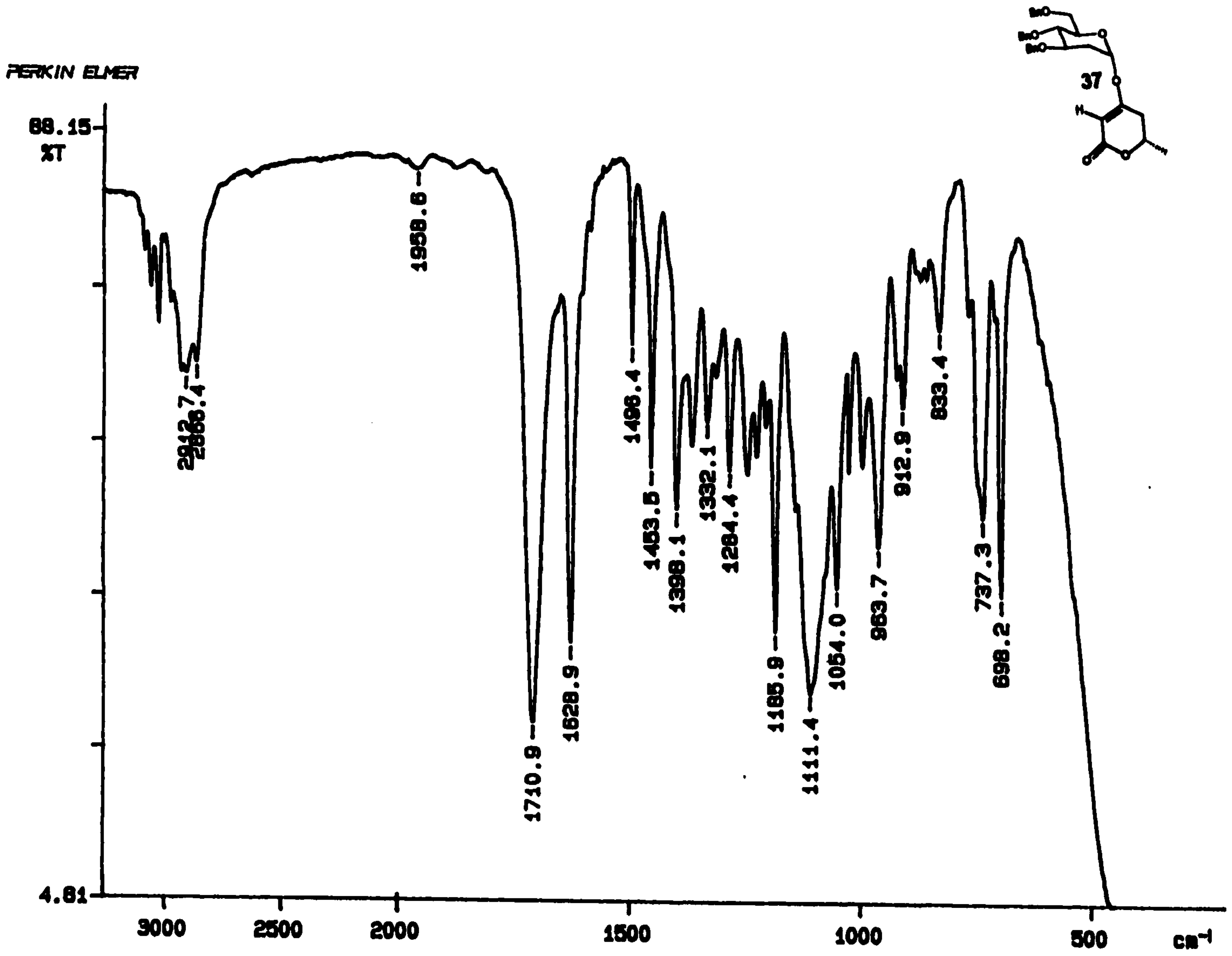

93.05
%T
68.14
4000
3500
3000
2500
2000
1500
1000
500
cm⁻¹ 0
2914.9
1454.0
1359.2
1243.1
738.1
698.3
ν
BnO
OBn
38


PERKIN ELMER
67.50
%T
57.02
3000
2500
2000
1500
1000
cm⁻¹
2870.7
1706.8
1627.9
1496.4
1453.1
1398.7
1333.0
1282.9
1246.1
1186.9
1111.6
1053.6
997.7
912.0
833.2
736.2
697.7
OBn
OBn
BnO
BnO

41


PERKIN ELMER
89.06
%T
3.08
4000
3500
3000
2500
2000
1500
1000
cm⁻¹ 500
3029.9
2956.5
2867.8
2359.7
1657.6
1614.6
1496.7
1453.6
1380.7
1366.9
1305.3
1214.2
1189.7
1114.9
971.3
894.1
737.5
697.8
BnO
BnO
BnO

40


PERKIN ELMER
88.15
%T
4.81
3000
2500
2000
1500
1000
500
cm⁻¹
2912.7
2866.4
1958.6
1710.9
1628.9
1498.4
1453.5
1398.1
1332.1
1284.4
1185.9
1111.4
1054.0
963.7
912.9
833.4
737.3
698.2
37
BnO
BnO
BnO
H

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