

1. ANIONIC ADDITIONS TO GLYCOSYL IODIDES. 2. NEUTRAL  
ADDITION OF ALCOHOLS TO GLYCOSYL IODIDES. 3. GLYCOSYL  
IODIDES IN SOLID PHASE OLIGOSACCHARIDE SYNTHESIS.

by

Michael Joseph Hadd

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A Dissertation Submitted to the Faculty of the

DEPARTMENT OF CHEMISTRY

in Partial Fulfillment of the Requirements

For the Degree of

DOCTOR OF PHILOSOPHY

in the Graduate College

THE UNIVERSITY OF ARIZONA

1998

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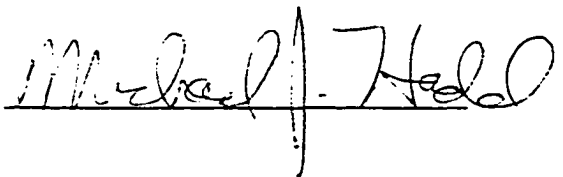
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**TABLE OF CONTENTS**

LIST OF FIGURES.....	7
ABSTRACT.....	11
CHAPTER 1. ANIONIC ADDITIONS TO GLYCOSYL IODIDES... 12	
INTRODUCTION.....	13
RESULTS AND DISCUSSION.....	20
CONCLUSION.....	36
EXPERIMENTAL SECTION.....	37
CHAPTER 2. NEUTRAL ADDITION OF ALCOHOLS TO GLYCOSYL IODIDES.....	49
INTRODUCTION.....	50
RESULTS AND DISCUSSION.....	52
CONCLUSION.....	69
EXPERIMENTAL SECTION.....	70
CHAPTER 3. GLYCOSYL IODIDES IN SOLID PHASE OLIGOSACCHARIDE SYNTHESIS.....	76
INTRODUCTION.....	77
RESULTS AND DISCUSSION.....	78
CONCLUSION.....	84
EXPERIMENTAL SECTION.....	84
APPENDIX A. <sup>1</sup> H AND <sup>13</sup> C NMR SPECTRA.....	87

APPENDIX B. SOLID PHASE IR SPECTRA.....	131
REFERENCES.....	134

## LIST OF FIGURES

Figure 1.1.	$\alpha$ and $\beta$ Glycosidic linkages.....	13
Figure 1.2.	$S_N1$ Substitution mechanism.....	14
Figure 1.3.	Explanations for the anomeric effect.....	16
Figure 1.4.	Neighboring group participation.....	17
Figure 1.5.	$S_N2$ Substitution mechanism.....	18
Figure 1.6.	Azide addition to a glycosyl chloride.....	18
Figure 1.7.	Grignard addition to glycosyl bromides.....	19
Figure 1.8.	Malonate addition to the glucosyl bromide.....	20
Figure 1.9.	Formation of glycosyl iodides from benzylated glucose.....	21
Figure 1.10.	Formation of glycosyl iodides from peracetylated glucose.....	21
Figure 1.11.	Reaction of peracetylated $\alpha$ -galactosyl iodide with alcohols.....	22
Figure 1.12.	Reaction of perivalated $\alpha$ -galactosyl iodide with allyl alcohol.....	23
Figure 1.13.	Reaction of benzyl protected $\alpha$ -glucosyl iodide with tetrabutylammonium azide.....	24
Figure 1.14.	Reaction of glycosyl iodides with methanol..	25
Figure 1.15.	<i>In situ</i> iodide catalysis.....	26
Figure 1.16.	E2 elimination of the $\alpha$ -glucosyl iodide.....	27
Figure 1.17.	Malonate addition to $\alpha$ -glycosyl iodides.....	28

Figure 1.18.	Possible <i>in situ</i> anomerization of the $\alpha$ C-glycoside.....	28
Figure 1.19.	Cyanide substitution on the glucosyl iodide...	29
Figure 1.20.	Cyanide substitution on the $\alpha$ mannosyl iodide.....	30
Figure 1.21.	Asparagine model study.....	31
Figure 1.22.	Phthalimide reaction with the glucosyl iodide.....	31
Figure 1.23.	Alkoxide reaction with the galactosyl iodide.....	32
Figure 1.24.	Sodium acetate substitution on the glucosyl iodide.....	32
Figure 1.25.	Carboxylate substitution on the glucosyl iodide.....	33
Figure 1.26.	Phenol substitution on the glucosyl iodide....	33
Figure 1.27.	C-glycoside amino acids.....	34
Figure 1.28.	Nitroacetate oxidation of the galactosyl iodide.....	34
Figure 1.29.	Mechanism of nitroacetate oxidation.....	35
Figure 1.30.	Sulphone anion reaction with the glucosyl iodide.....	36
Figure 2.1.	Sodium iodide catalysis of glucosyl chlorides.....	50
Figure 2.2.	Tetraethylammonium bromide catalysis of glycosyl bromides.....	51

Figure 2.3.	Reaction of allyl alcohol with glycosyl iodides.....	53
Figure 2.4.	Reaction of the galactosyl iodide with diacetone glucose in methylene chloride.....	54
Figure 2.5.	Formation of the galactosyl chloride.....	55
Figure 2.6.	THF reaction with the galactosyl iodide.....	56
Figure 2.7.	Reaction of glycosyl iodides in refluxing benzene.....	56
Figure 2.8.	Mannosyl iodide reaction in refluxing benzene.....	57
Figure 2.9.	Glucosyl iodide reaction with diacetone glucose in refluxing benzene.....	59
Figure 2.10.	1,6-Anhydrogalactose reaction with the fucosyl iodide.....	60
Figure 2.11.	Fucose trehalose derivative synthesis.....	61
Figure 2.12.	Formation of the $\alpha\alpha$ 1,1' linkage.....	62
Figure 2.13.	Formation of the $\alpha\beta$ 1,1' linkage <i>via</i> an $S_N2$ mechanism.....	62
Figure 2.14.	Formation of the $\alpha\beta$ 1,1' linkage <i>via</i> the $\beta$ -hydroxy anomer.....	63
Figure 2.15.	Type I $S_N2$ mechanism.....	64
Figure 2.16.	Utilization of the anti-anomeric effect to obtain $\beta$ glycosides.....	66
Figure 2.17.	Reaction of the glucosyl iodide in acetonitrile.....	66

Figure 2.18.	Possible mechanistic routes into the $\beta$ glycoside.....	67
Figure 2.19.	Galactosyl iodide reaction in acetonitrile.....	68
Figure 2.20	Reaction of the mannosyl iodide in acetonitrile.....	68
Figure 3.1.	Polystyrene support of first solid phase oligosaccharide synthesis.....	77
Figure 3.2.	Direction of solid phase oligosaccharide synthesis.....	79
Figure 3.3.	Wang resin.....	80
Figure 3.4.	Formation of the allyl glycoside.....	81
Figure 3.5.	1,6-Dimer formation.....	81
Figure 3.6.	TMSI cleavage of Wang resin.....	83
Figure 3.7.	Trityl resin support.....	83

#### List of Tables

Table 1.	Comparison of glycosyl bromides with iodides.....	60
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### Abstract

The usefulness of glycosyl iodides in carbohydrate chemistry has been demonstrated. Both anionic and neutral nucleophiles have been shown to react readily with glycosyl iodides as the glycosyl donor. High yields and stereoselectivity were obtained along with short reaction times. Anionic nucleophiles gave  $\beta$  glycosides selectively, whereas neutral nucleophiles gave  $\alpha$  glycosides in the presence of tetrabutylammonium iodide. Initial investigation of the applicability of these glycosidation conditions to solid phase oligosaccharide synthesis has been accomplished.

## CHAPTER 1

### Anionic Additions to Glycosyl Iodides



## INTRODUCTION

The glycosidic linkage is the most important bond in carbohydrate chemistry. This is the bond that covalently connects carbohydrates both to other carbohydrates in an oligosaccharide, and to amino acids in proteins and peptides through asparagine (*N*-linked) or threonine/serine (*O*-linked). Due to its presence in many biological systems, the formation of the glycosidic bond or linkage has become of primary importance for synthetic chemists working in the field of carbohydrate, and to a lesser degree protein chemistry. In developing strategies to construct the glycosidic bond, several factors are of importance: first the control of stereochemistry ( $\alpha$  vs.  $\beta$ ), second the yield of the reaction, and third the accessibility of the donor carbohydrate (Figure 1.1).

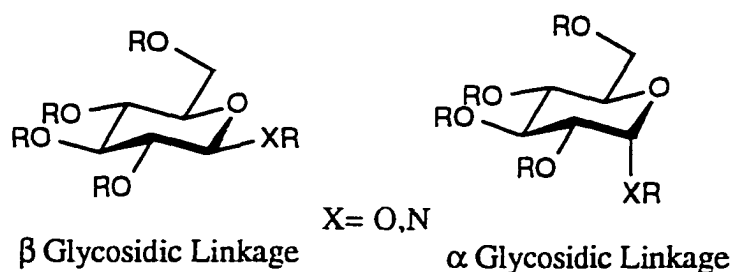


Figure 1.1.  $\alpha$  and  $\beta$  Glycosidic linkages

The formation of the glycosidic bond is in its essence a substitution reaction, where a suitable leaving group positioned at the anomeric carbon is replaced by a nucleophile. Two general types of substitution mechanisms are possible,  $S_N1$  and  $S_N2$ . The mechanism that is most widely utilized in carbohydrate chemistry is the  $S_N1$  mechanism. A typical reaction has a suitable leaving group at the anomeric center which is activated by a Lewis

acid catalyst, forming a carbocation at the anomeric center. This mechanism is favored in carbohydrate chemistry due to the participating ability of the ring oxygen, which can form an intermediate oxonium ion (Figure 1.2). Because of stabilization by oxonium ion formation, glycosidic bond construction is somewhat predisposed towards the  $S_N1$  mechanism.

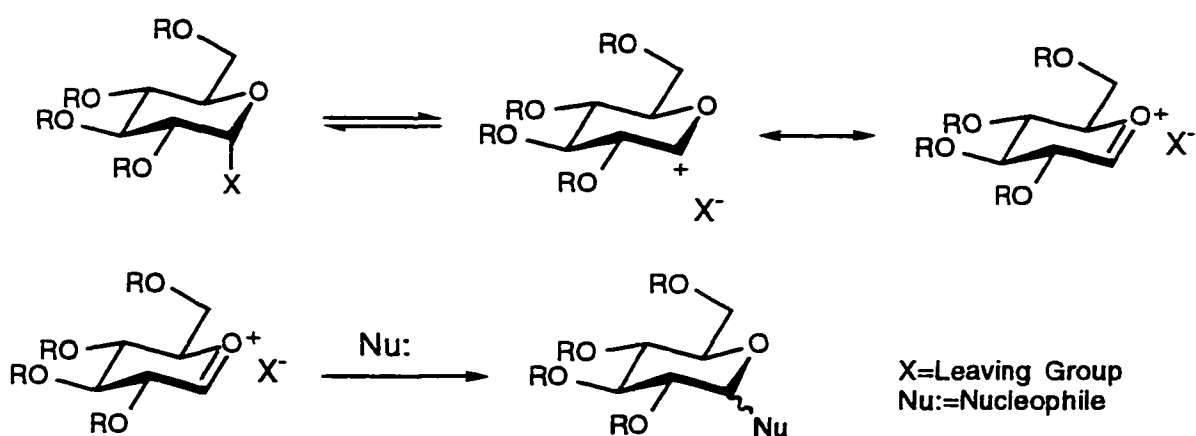


Figure 1.2.  $S_N1$  Substitution mechanism

Having a nucleophilic substitution reaction proceed through an  $S_N1$  mechanism has one major downfall: excluding other factors, it is not stereoselective since the intermediate oxonium contains an  $sp^2$  carbon at the site of substitution, leading to the possibility of a racemized product. In carbohydrate chemistry, however, “other factors” do exist that can lend specificity to the formation of either an  $\alpha$  or  $\beta$  linkage. The most widely recognized factors are the anomeric effect, and neighboring group participation.

The anomeric effect<sup>1</sup> is that an axial ( $\alpha$ ) anomer is thermodynamically more stable, in most carbohydrates, than the equatorial

( $\beta$ ) anomer when a heteroatom is present at the anomeric center. This effect has been rationalized by three different theories (Figure 1.3). The “lone pair hypothesis” states that the electronic repulsions between the lone pairs on the ring oxygen and the heteroatom on the anomeric carbon are minimized when the anomeric substituent is in the axial configuration. The orbital overlap theory states that an axially oriented heteroatom has a better  $n \rightarrow \pi^*$  overlap capacity due to the antiperiplanar orientation of a lone pair on the ring oxygen with the anomeric substituent. And finally, the dipole theory argues that an equatorial orientation of the heteroatom at the anomeric center causes an alignment of dipoles between the ring oxygen and the anomeric substituent, thus destabilizing the molecule.

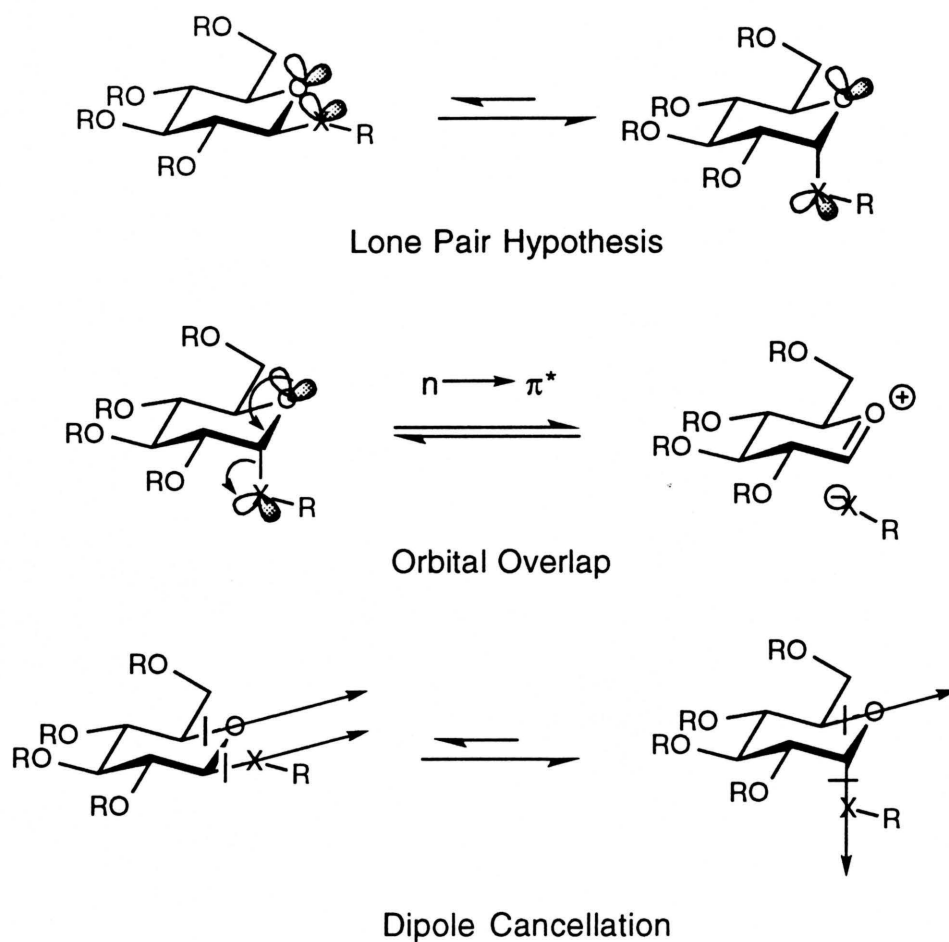


Figure 1.3. Explanations for the anomeric effect

If, however, the anomeric substituent is oriented axially then the dipoles partially cancel, leading to a more stable overall configuration. Overall these effects can combine to dictate the stereospecificity of a glycosylation reaction under reversible conditions.

Neighboring group participation<sup>2</sup> by the 2-position protecting group (usually an ester or amide; Figure 1.4) can also dictate the stereochemistry of a glycosylation reaction by blocking one face of the molecule through formation of a bicyclic dioxolenium ion, thus producing *trans* glycosidic linkages ( $\beta$  in glucose/galactose;  $\alpha$  in mannose/rhamnose). Several less

prominent factors also contribute to linkage specificity, including heterogeneous catalysts<sup>3</sup> and solvent participation.<sup>3</sup>

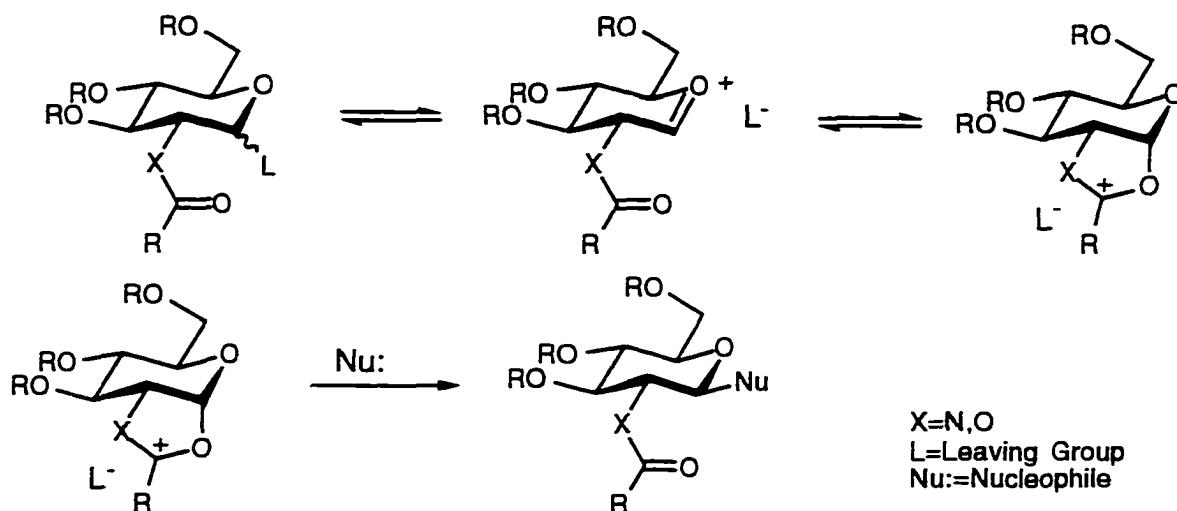


Figure 1.4. Neighboring group participation

In contrast to the  $S_N1$  mechanism, an  $S_N2$  mechanism (Figure 1.5) gives complete inversion of the original stereochemistry, leading to a stereospecific product. In order for this to be a specific approach to glycosidic bond formation, two conditions must exist: first the glycosyl donor must have a defined stereochemistry, and secondly it must be activated enough so as to react with the nucleophile of choice in an  $S_N2$  fashion.

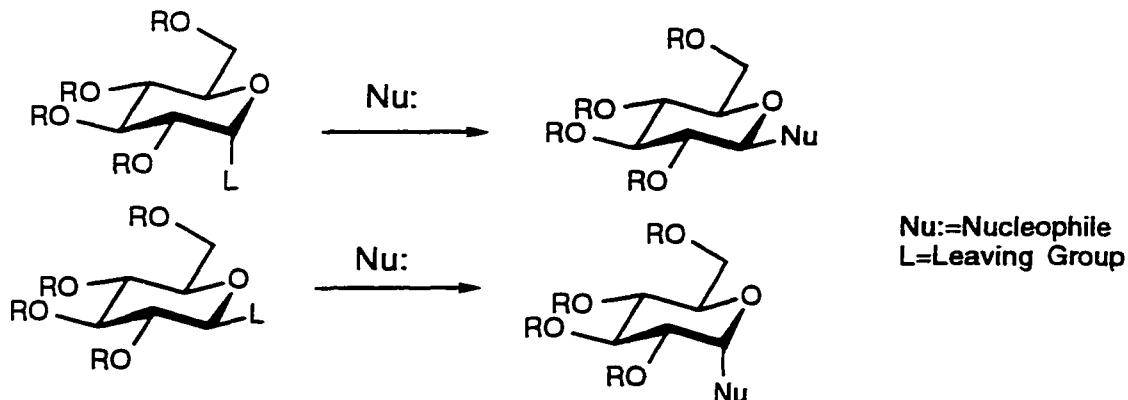


Figure 1.5.  $S_N2$  Substitution mechanism

Glycosyl chlorides and bromides are most often used in the Koenigs-Knorr method of glycosylation and undergo the aforementioned  $S_N1$  type mechanism<sup>3</sup> in the presence of a Lewis acid promoter. However, in the absence of Lewis acids, few examples of substitution reactions are known.

Some anionic additions to glycosyl chlorides or bromides have been shown with lithium azide as well as several different carbanions. Reaction of lithium azide with the glucosyl chloride of peracetylated *N*-acetylglucosamine (GlcNAc) in DMF gave a 76% yield of the  $\beta$  glycosyl azide (Figure 1.6).<sup>4</sup>

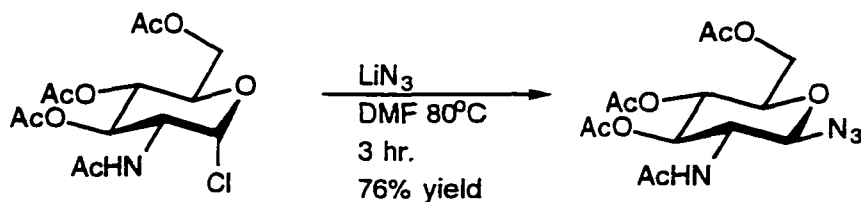


Figure 1.6. Azide addition to a glycosyl chloride

Grignard addition to glycosyl bromides has also been demonstrated. Dixit<sup>5</sup> et al. showed that vinylmagnesium bromide could react with a

glycosyl bromide to obtain the  $\beta$  C-glycoside in 85% yield (Figure 1.7). Benzymagnesium chloride was also shown to react with glycosyl bromides,<sup>6</sup> although not in a regiospecific manner.

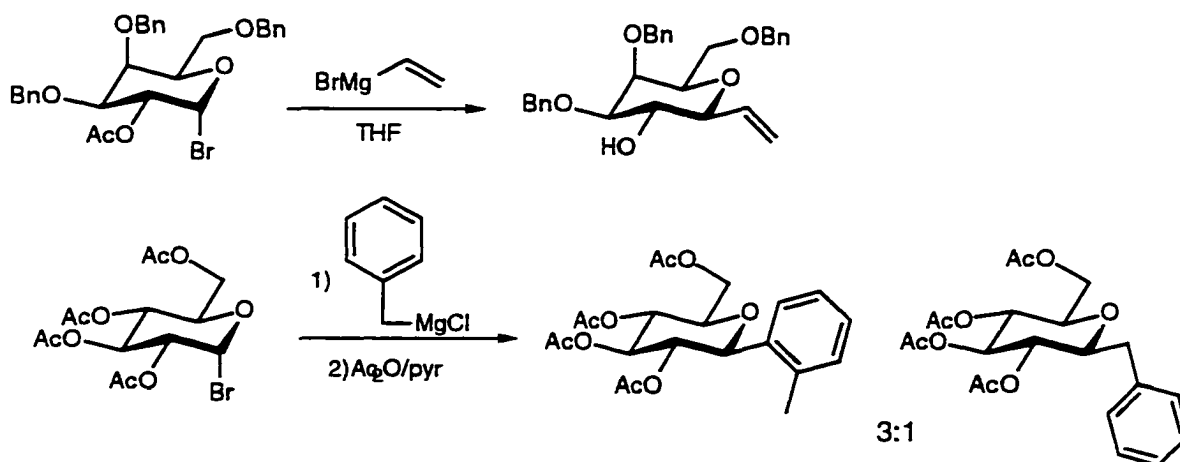


Figure 1.7. Grignard addition to glycosyl bromides

The malonate derived anion has also been shown to displace glycosyl bromides (Figure 1.8). Pernet and Hanessian<sup>7</sup> demonstrated that addition of sodium diethyl malonate to an anomeric bromide in diethyl malonate produced a 3:1  $\beta$ : $\alpha$  mixture of C-glycosides after 40 hr. It was shown that addition of tetrabutylammonium bromide reversed the anomeric selectivity of the reaction to give a 1:3  $\beta$ : $\alpha$  mixture, presumably due to *in situ* anomerization of the glycosyl bromide.

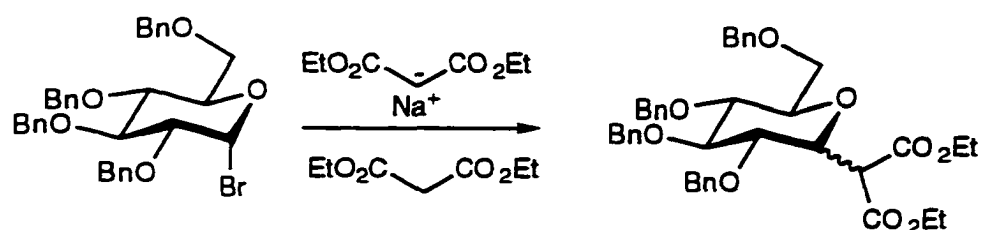


Figure 1.8. Malonate addition to the glucosyl bromide

Only these few examples are present in the literature for anionic additions to glycosyl halides. We envisioned that glycosyl iodides, which have received little attention in the literature, and have in some cases even been deemed “too reactive to be of synthetic use” might be better glycosyl donors than the glycosyl bromides or chlorides. At the time we began our research a thorough investigation of glycosyl iodides had not been reported. It seemed logical that they would be more reactive than their halogen counterparts. Indeed our research exemplifies that they are by no means of “no synthetic use”.

## RESULTS AND DISCUSSION

Our initial examination of glycosyl iodides focused on developing a clean and specific method for synthesizing glycosyl iodides from readily available protected carbohydrates. Glycosyl iodides have been synthesized by the reaction of trimethylsilyl iodide (TMSI) with various anomeric groups (OMe, OAc, OBz),<sup>8</sup> and by reaction of anomeric bromides with sodium iodide.<sup>9</sup> We found the first of these to be the method of choice since the reaction proceeds in non-polar solvents and the only by-product is trimethylsilyl acetate, which can be removed *in vacuo*. A literature



procedure<sup>10</sup> for formation of the iodides utilized anomeric acetates and reacted them in toluene at 80°C with TMSI. We found that such drastic conditions were not necessary and that reaction of peracetylated galactose proceeded cleanly at room temperature and below in dichloromethane to give the corresponding iodides in quantitative yield.<sup>11</sup> The stereochemistry of the iodides as well as their rate of formation was found to depend upon the protecting groups on the carbohydrate, and the starting configuration of the anomeric acetate.

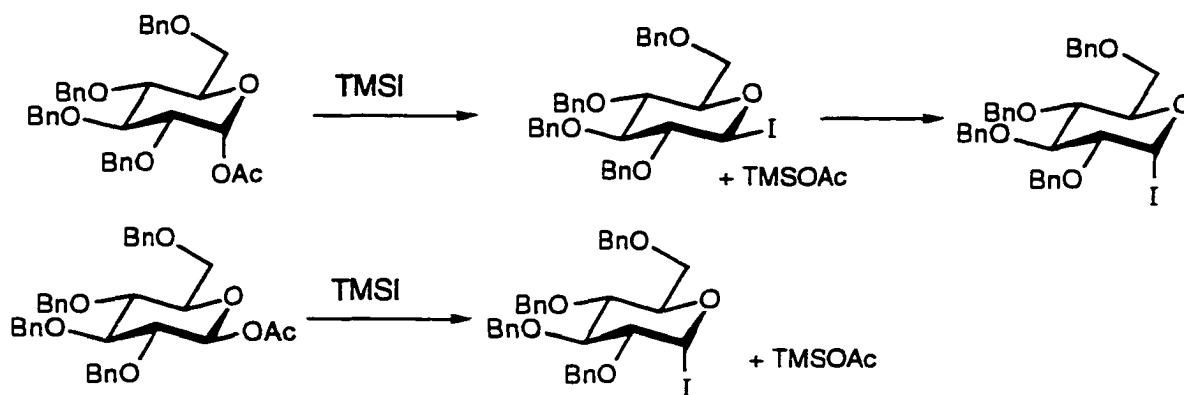


Figure 1.9. Formation of glycosyl iodides from benzylated glucose

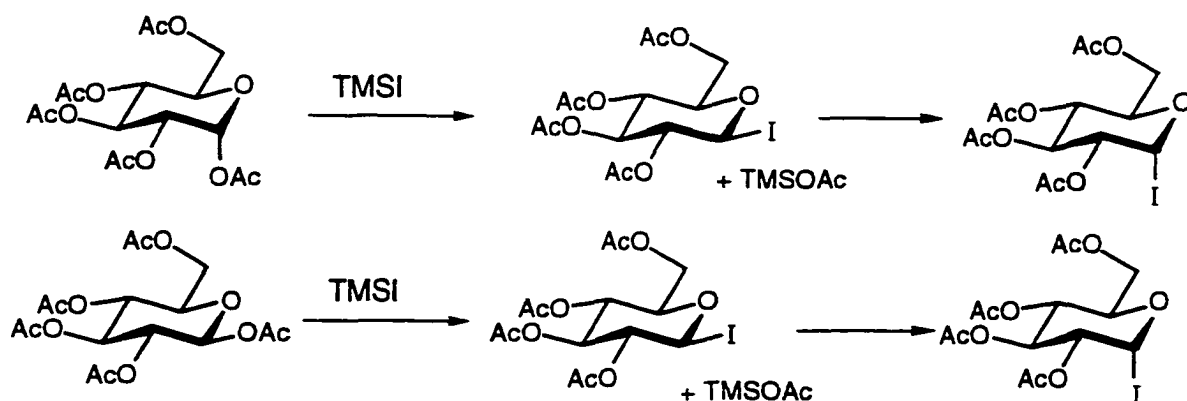


Figure 1.10. Formation of glycosyl iodides from peracetylated glucose

All of the carbohydrates tested did however equilibrate, to form the thermodynamically more stable  $\alpha$  anomeric iodide. Thus, starting from a mixture of anomeric acetates with both non-participating (Figure 1.9) and participating (Figure 1.10) protecting groups, we can synthesize specifically  $\alpha$  glycosyl iodides with no byproducts (after azeotropic evaporation of the trimethylsilyl acetate). Having accomplished this feat, our research now centered on finding a use for such easily accessible and highly reactive donors.

Our first experiments concentrated on peracetylated galactosyl iodide (Figure 1.11), which was reacted with allyl alcohol and triethylamine in acetonitrile. After refluxing for 2 hr, all of the iodide was consumed and the major product formed was the allyl orthoester, demonstrating trapping of the bicyclic dioxolenium ion. The same reaction was tried with benzyl alcohol after deletion of the base, to afford a 70% yield of the benzyl glycoside.

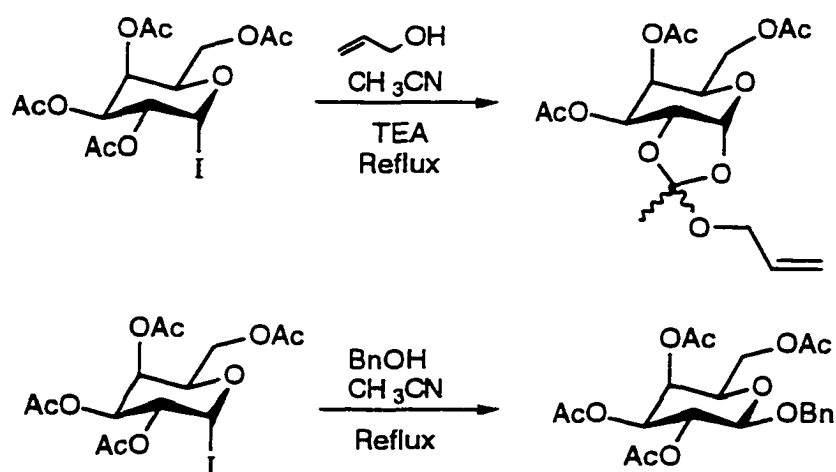


Figure 1.11. Reaction of peracetylated  $\alpha$ -galactosyl iodide with alcohols

From these two experiments several conclusions were reached. First, the peracetylated iodide under reflux conditions in acetonitrile without Lewis acid activation forms a dioxolenium ion. Second, in the presence of base, this ion may be trapped by an alcohol to give the corresponding orthoester. Last, the orthoester formed is not trapped in the absence of base, possibly because once formed it isomerizes to the more stable  $\beta$  glycoside under the acidic conditions.<sup>12</sup> Although a good yield of the benzyl glycoside was achieved, this approach could be of limited use as HI is generated *in situ* which could be hazardous to preexisting glycosidic linkages. It is noteworthy that reaction of perpivaloated galactosyl iodide with allyl alcohol and a base in acetonitrile surprisingly afforded the orthoester as well (Figure 1.12).

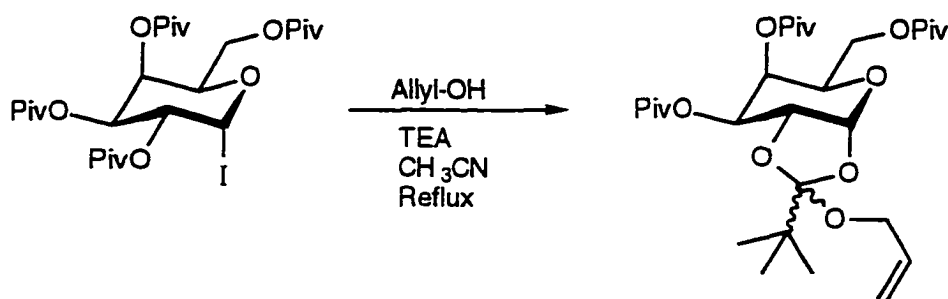


Figure 1.12. Reaction of perpivalated  $\alpha$ -galactosyl iodide with allyl alcohol

To avoid the problem of orthoester formation, we turned to benzyl protected carbohydrates where formation of the intermediate dioxolenium ion is not possible. One of the first experiments attempted (Figure 1.13) was reaction of 2,3,4,6-tetra-*O*-benzylglucosyl iodide **1.1** (formed from the corresponding acetate) with tetrabutylammonium azide, an organically soluble highly reactive nucleophile. The  $\beta$  glycosyl azide **1.2** was formed

within 5 minutes at room temperature in 92% yield with no formation of the  $\alpha$  product as evidenced by  $^1\text{H}$  NMR. This result showed that with a suitable nucleophile, the  $\alpha$  glycosyl iodides are highly activated donors and react in a stereospecific manner to produce  $\beta$  glycosides via an  $\text{S}_{\text{N}}2$  mechanism.<sup>13</sup>

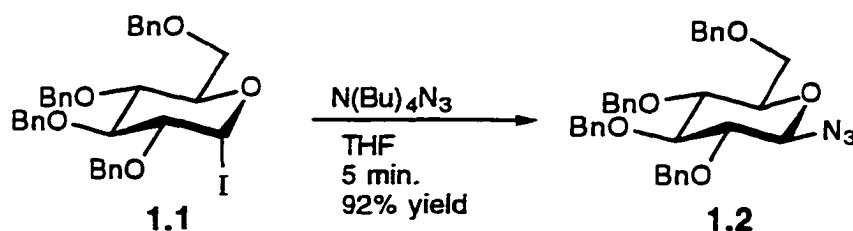


Figure 1.13. Reaction of benzyl protected  $\alpha$ -glucosyl iodide with tetrabutyl ammonium azide

A key point at this time was to define what nucleophiles were active enough to undergo this type of  $\text{S}_{\text{N}}2$  displacement. Methanol was reacted next with 1.1 and it was found that the reaction was very sluggish (45 hrs.) and led to only the  $\alpha$  product (Figure 1.14). Two conclusions were reached from this experiment: first that a neutral alcohol was not nucleophilic enough to displace the  $\alpha$  iodide, and second that over time methanol reacted with either a slowly formed intermediate oxonium or the  $\beta$  glycosyl iodide. The 2,3,4,6-tetra-*O*-benzylated galactosyl iodide 1.3 also reacted with methanol to give the methyl glycoside, but it reacted faster (23 vs. 45 hr.) and gave a mixture of anomers in a 1.2:1  $\alpha$ : $\beta$  ratio.

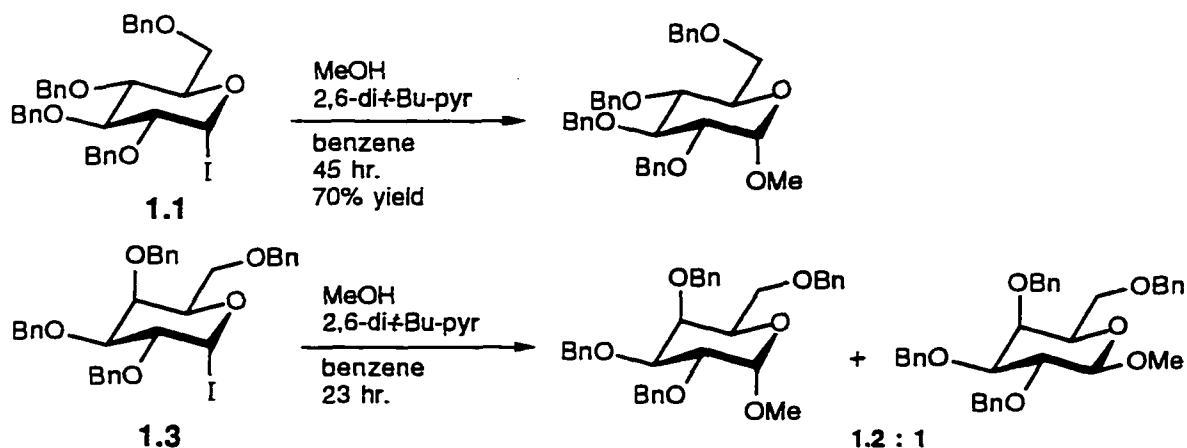


Figure 1.14. Reaction of glycosyl iodides with methanol

These results suggested that in the galactose case the  $S_N2$  reaction of the  $\alpha$  iodide was proceeding, albeit at a slow rate, and that it was in competition with either oxonium formation ( $S_N1$ ) or trapping of the  $\beta$  iodide through an  $S_N2$  mechanism. It is also possible that during the long duration of these reactions pyridinium iodide is formed which, as a byproduct, may begin to catalyze the formation of the  $\beta$  iodide *in situ* leading to an increase in the rate of  $\alpha$  glycoside formation *via*  $S_N2$  (Figure 1.15).

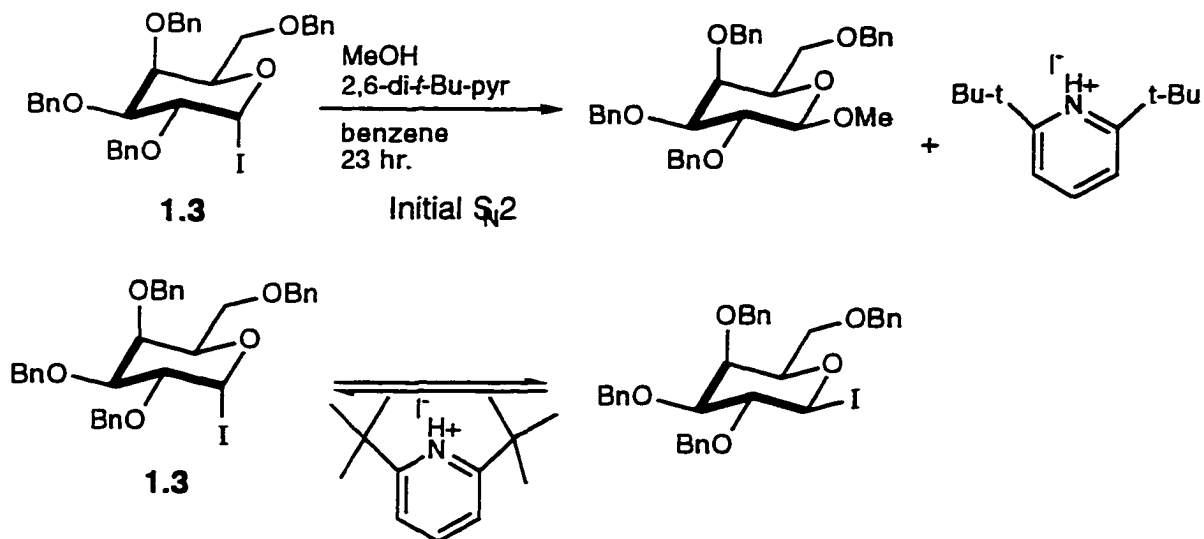


Figure 1.15. *In situ* iodide catalysis

The reactions of neutral alcohols with glycosyl iodides will be discussed in the second chapter of this manuscript where the above mentioned iodide catalysis is investigated.

At this point we began to look at various anions as potential nucleophiles. The first was the anion of acetamide which was envisioned as a model for the amide of asparagine. Reaction of the sodium anion of acetamide with **1.1** gave cleanly the eliminated glycal **1.4** (Figure 1.16). This result showed the propensity of the  $\alpha$  glycosyl iodide towards elimination, as the iodide and the C-2 proton are in a antiperiplanar orientation which facilitates an E-2 elimination.

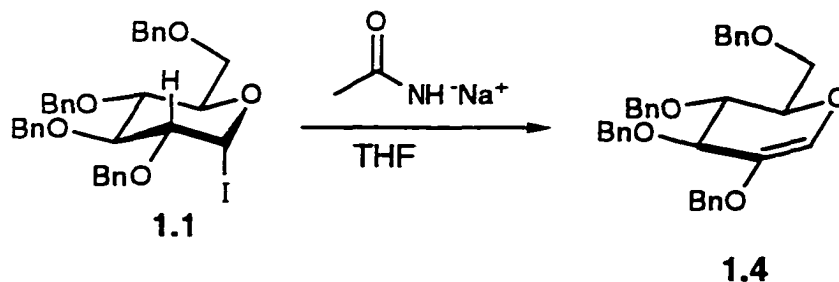


Figure 1.16. E-2 elimination of the  $\alpha$ -glucosyl iodide

We now had defined a “window of nucleophilicity” that would give us the desired stereospecific  $S_N2$  reaction with the  $\alpha$  glycosyl iodides; a nucleophile less basic than the anion of acetamide, yet more nucleophilic than methanol.

The next nucleophiles that were considered were the stabilized malonate carbanions. Sodium dimethylmalonate in the presence of 15-crown-5 was reacted with 1.1 in THF and after 5 hrs. produced a 66% yield of a 5.1:1 mixture of the  $\alpha$  and  $\beta$  C-glycosides (Figure 1.17). The same experiment was also attempted on the  $\alpha$  galactosyl iodide with the product being formed in 1 hr. in a 1:10  $\alpha$ : $\beta$  ratio and an overall yield of 58%.

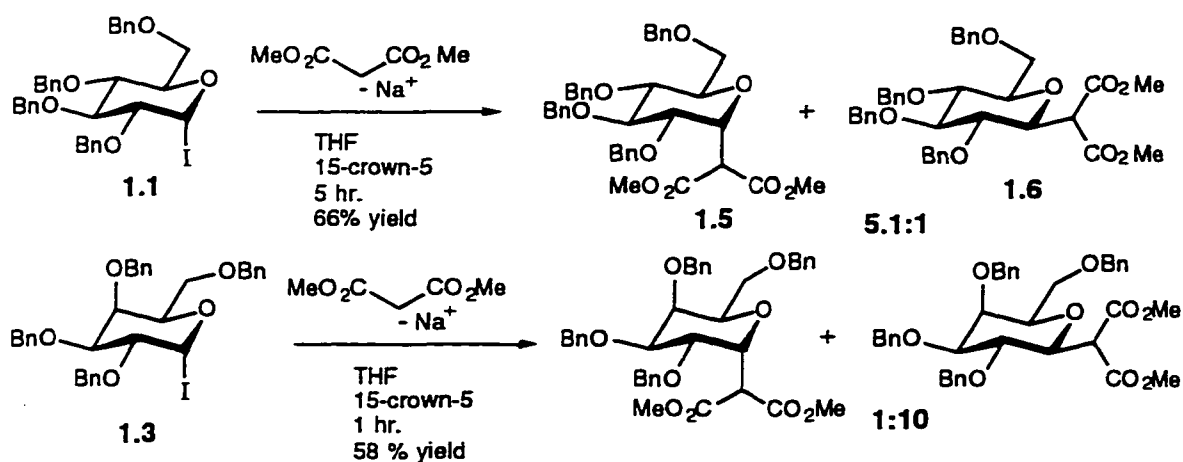


Figure 1.17. Malonate addition to  $\alpha$ -glycosyl iodides

There are several possible explanations for the stereochemistry observed in the malonate anion addition. The  $\beta$  product in both cases could be due to either S<sub>N</sub>2 reaction of the malonate anion on the  $\alpha$  glycosyl iodide, or *in situ* anomerization from the  $\alpha$  C-glycoside to the theoretically more stable  $\beta$  C-glycoside catalyzed by the basic conditions, or some mixture of both. In order to test for the possibility that the  $\alpha$  C-glycoside was undergoing *in situ* anomerization to the thermodynamically more stable  $\beta$  C-glycoside (Figure 1.18), the  $\alpha$  glycoside was resubjected to the reaction conditions to see if an equilibration towards the  $\beta$  product was observed.

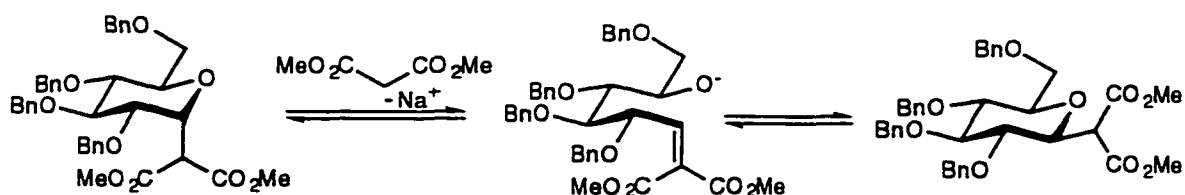


Figure 1.18. Possible *in situ* anomerization of the  $\alpha$  C-glycoside



It was shown by  $^1\text{H}$  NMR that no anomerization occurred under the reaction conditions. Therefore it was concluded that  $\beta$  product formation was derived from  $\text{S}_{\text{N}}2$  displacement of the  $\alpha$  glycosyl iodide. This conclusion is consistent with the results seen in the addition of methanol to the glycosyl iodides, i.e. the  $\alpha$  galactosyl iodide is more reactive towards  $\text{S}_{\text{N}}2$  displacement than the  $\alpha$  glucosyl iodide, and thus yields more  $\beta$  product and has an overall faster reaction rate. The  $\alpha$  products can be explained by the same mechanism as with methanol addition, that is, reaction with the  $\beta$  glycosyl iodide or with an intermediate oxonium ion occurred.

Cyanide anion addition was investigated as another means of synthesizing C-glycosides. Tetrabutylammonium cyanide was chosen as the source of cyanide as it was soluble in nonpolar organic solvents, which was in contrast to both sodium and potassium cyanide with or without the respective crown chelating agents. Reaction of **1.1** with tetrabutylammonium cyanide gave, after 10 minutes, a mixture of both the  $\beta$  C-glycoside **1.7** and the elimination product **1.4** (Figure 1.19).

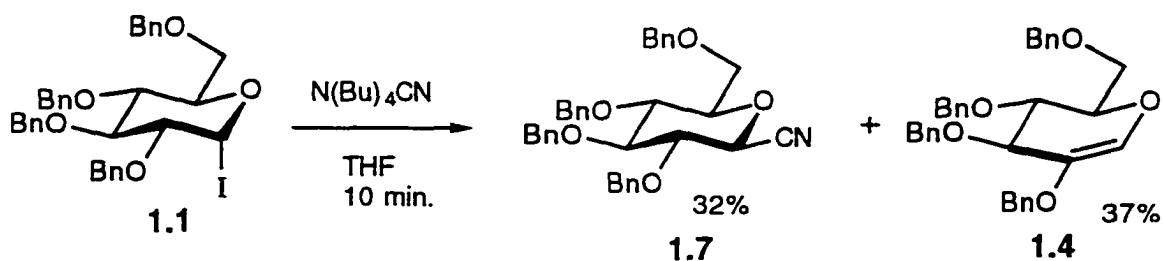


Figure 1.19. Cyanide addition to the glycosyl iodide

This is an example of the anion acting as both base, in the production of **1.4**, and as a nucleophile, in the production of **1.7**. No  $\alpha$  product was

observed and attempts to decrease the amount of elimination by decreasing the temperature or the concentration of cyanide failed. The propensity of the glucosyl iodide to undergo E-2 elimination with cyanide led us to attempt cyanide addition on the  $\alpha$  mannosyl iodide **1.8** which is incapable of undergoing E-2 elimination due to the inverted stereochemistry at the C-2 position. Indeed, reaction of tetrabutylammonium cyanide with **1.8** led to formation of the  $\beta$  C-glycoside **1.9** in a 55% yield after 2 hr. with no formation of the elimination product **1.4** (Figure 1.20). This result is also further evidence for the E-2 elimination mechanism of the glucosyl iodide and demonstrates that the mannosyl iodide is less reactive under anionic conditions than the glucosyl iodide.

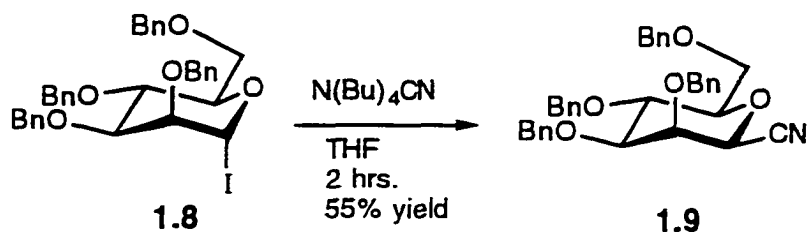


Figure 1.20. Cyanide substitution on the  $\alpha$  mannosyl iodide

The next stabilized anion that was investigated was the anion of phthalimide. This anion was chosen as a model study for the possible addition of asparagine analogs to the anomeric center to form the natural *N*-linkage found in glycopeptides (Figure 1.21).

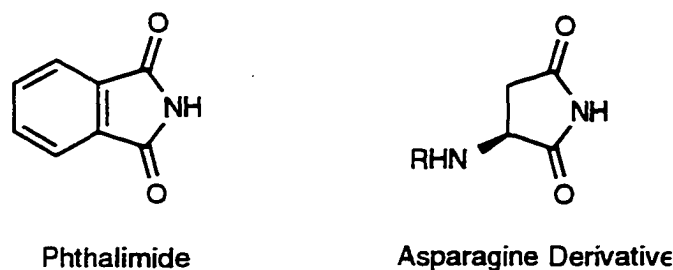


Figure 1.21. Asparagine model study

The potassium salt of phthalimide complexed with 18-crown-6 was reacted with **1.1** in THF to afford in 15 min. specifically the  $\beta$  *N*-glycoside in a 66% yield with a minor amount of elimination (Figure 1.22).

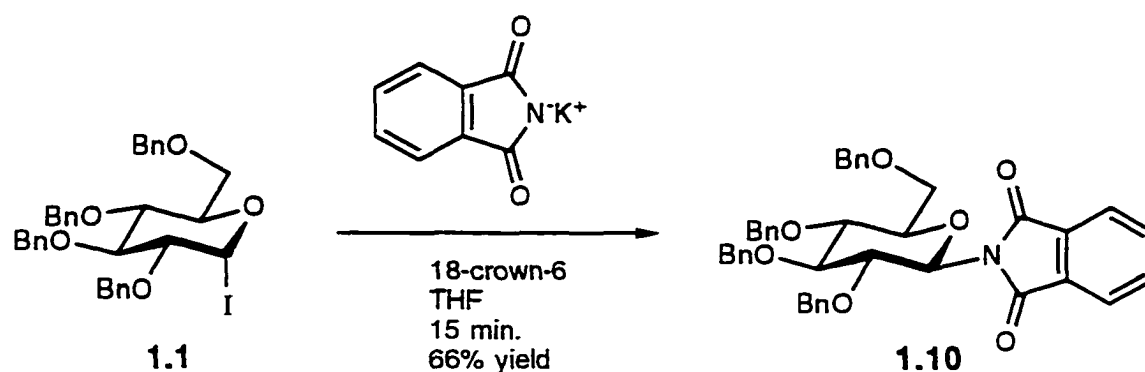


Figure 1.22. Phthalimide reaction with the glucosyl iodide

The specificity of the reaction again led us to conclude that the reaction was proceeding through an  $S_N2$  mechanism on the  $\alpha$  glucosyl iodide.

After investigating several stabilized carbanions and nitrogen anions, we turned our attention to oxygen anions. An attempt was made to determine whether or not an alkoxide would act as a potential nucleophile, or whether it would behave as a base, facilitating E-2 elimination. The sodium alkoxide of 1,2-3,4-di-isopropylidene-galactose was reacted with **1.3** in THF to quickly produce the elimination product (Figure 1.23).

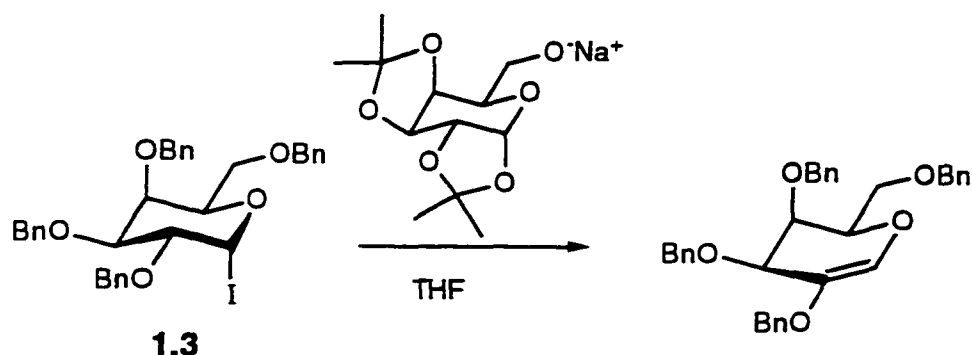


Figure 1.23. Alkoxide reaction with the galactosyl iodide

Due to this result, more-stabilized oxygen anions were chosen. Those investigated were carboxylate anions and phenolic anions. The addition of sodium acetate to **1.1** was attempted first in THF with 15-crown-5. This reaction proceeded very sluggishly (20+ hrs.) and never went to completion. However, upon addition of tetrabutylammonium hydrogen sulfate to sodium acetate in THF, the reaction was complete in 1.5 hours to give almost exclusively the  $\beta$  glucosyl acetate in 90% yield (Figure 1.24).

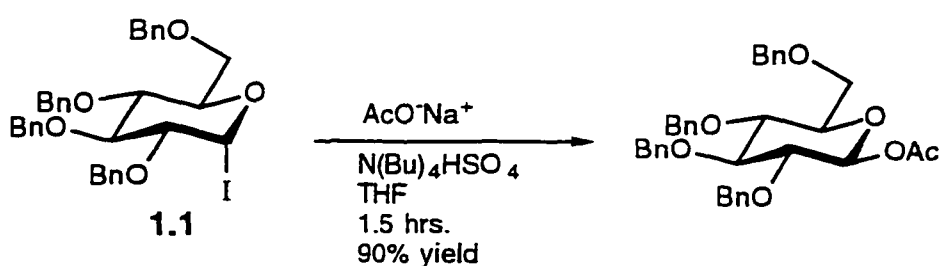


Figure 1.24. Sodium acetate substitution on the glucosyl iodide

To determine the generality of carboxylate addition, the sodium salts of pivalic and stearic acid were reacted under the same conditions to give in 20 min. the  $\beta$  glycosides **1.11** and **1.12** in >90% yield (Figure 1.25).

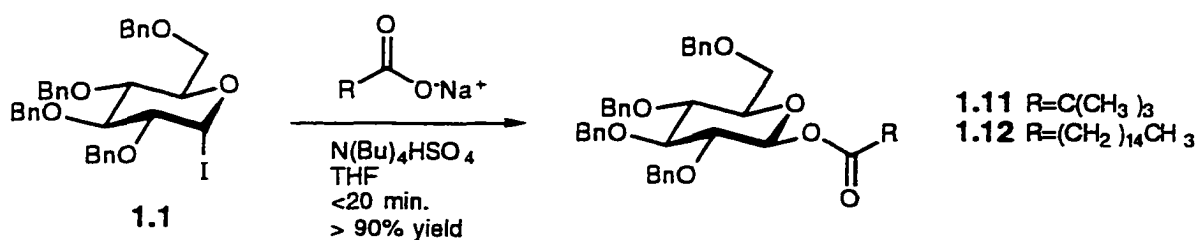


Figure 1.25. Carboxylate substitution on the glucosyl iodide

The anion of phenol was also investigated as a potential stabilized alkoxide. The sodium salt of phenol was reacted with **1.1** in THF to produce a 61% yield of specifically the  $\beta$  glycoside **1.13** in 15 min. with a minor amount of the elimination product **1.4** (Figure 1.26).

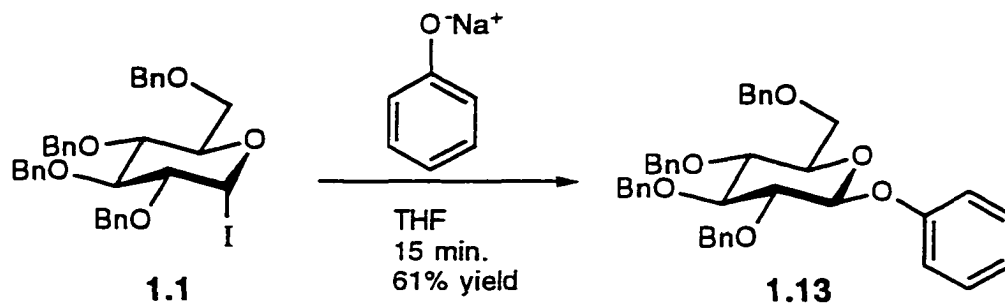


Figure 1.26. Phenol substitution on the glucosyl iodide

Another class of stabilized carbanions that was investigated was nitroacetates. We investigated these anions as possible precursors to *C*-glycoside amino acids (Figure 1.27).

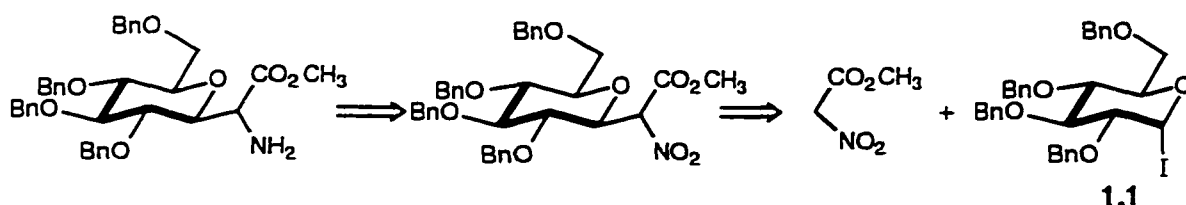


Figure 1.27. C-glycoside amino acids

Reaction of the sodium anion of methylnitroacetate in the presence of 15-crown-5 with the galactosyl iodide **1.3** in THF gave the lactone as the major product (Figure 1.28).

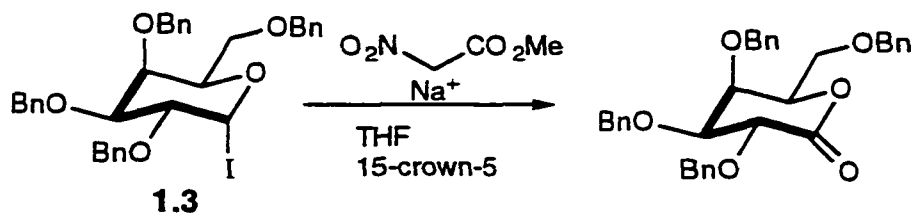


Figure 1.28. Nitroacetate oxidation of the galactosyl iodide

Instead of C-alkylation, it seems that O-alkylation was preferred followed by oxidation of the intermediate nitro compound (Figure 1.29). One example of this type of oxidation was found in the literature where benzyl bromide was shown to undergo partial oxidation to benzaldehyde by a nitroacetate anion.<sup>14</sup>

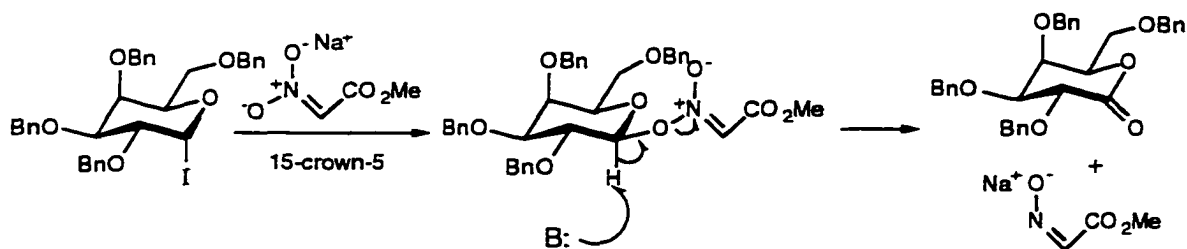


Figure 1.29. Mechanism of nitroacetate oxidation

One other class of compounds that was of interest to our group was *C*-glycoside sulphones. The first sulphone anion addition that was attempted employed the sodium anion of dimethylsulphone in the presence of 15-crown-5 (Figure 1.30). This anion proved too basic, however, as it yielded only the glycal. Our second attempt utilized a more stabilized anion where a methylene was substituted by both a sulphone and an ester. Addition of the sodium anion to the glucosyl iodide in the presence of 15-crown-5 and TBAI yielded 67% of a mixture of *C*-glycosides. The main product could be separated by HPLC and was identified as the  $\alpha$  anomer, though the stereochemistry  $\alpha$  to the sulphone was not determined. Upon decarboxylation using tetramethylammonium acetate in HMPA, the  $\beta$  *C*-glycoside sulphone was isolated in 47% yield as the only product. The reversal of the anomeric configuration during the decarboxylation is most likely due to a similar ring opening and closure as shown in Figure 1.18 for the *C*-glycoside malonates.

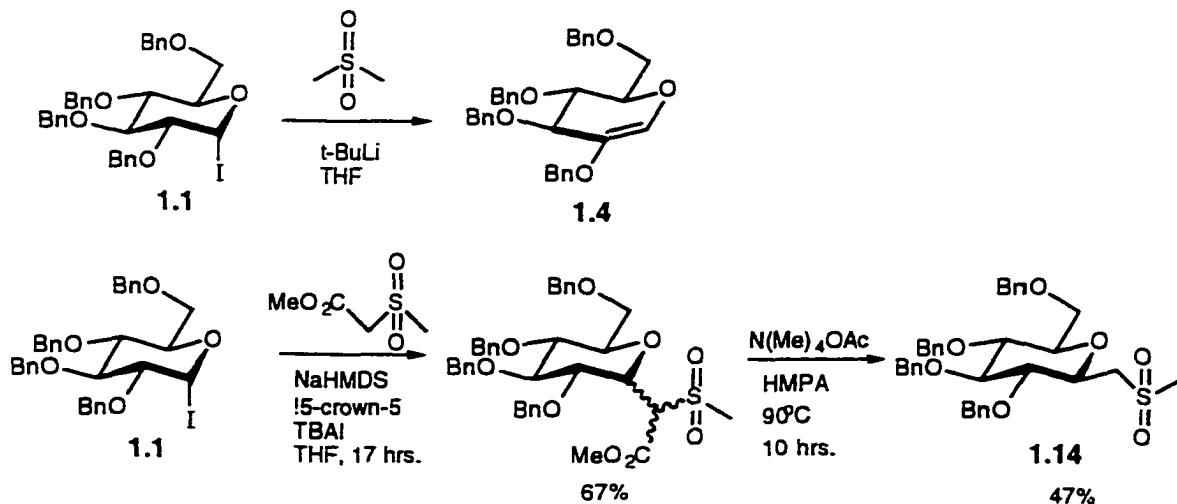


Figure 1.30. Sulphone anion reactions with the glucosyl iodide

It is noteworthy that most of the malonate-derived anions were also attempted without the use of 15-crown-5, but the reactions were slow, days vs hours, and did not go to completion.

## Conclusion

Glycosyl iodides are highly reactive substrates for S<sub>N</sub>2 displacement by stabilized anions. The reactions typically give stereoselective β glycosidic linkages in high yields with fast reaction times. A limitation of the benzyl protected glycosyl iodides is that highly basic anions cause elimination to yield glycals. Future work in this area might employ other stabilized anions, various solvent and temperature conditions, and alteration of the C-2 protecting group.



## Experimental Section

Starting materials and reagents purchased from suppliers were used without further purification. Chemicals were obtained from the following suppliers trimethylsilyl iodide (Fluka), tetra-*O*-benzylglucopyranose (Fluka), tetrabutylammonium cyanide (Aldrich), tetrabutylammonium azide,<sup>15</sup> sodium hexamethyldisilazane (Aldrich). Solvents were dried by distillation prior to use. Dichloromethane and toluene were dried over calcium hydride, and tetrahydrofuran was dried over sodium/benzophenone. Chromatography was performed using silica gel 60 (230-400 mesh ASTM). Mass spectrometry was performed by the University of Minnesota Mass Spectrometry Service and the University of Arizona Mass Spectrometry Facility.

**General procedure for acetylation of the 2,3,4,6-tetra-*O*-benzylpyranosides (10):** 3.0g (5.55 mmol) of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose was dissolved in 10 mL of CH<sub>2</sub>Cl<sub>2</sub> and cooled to 0°C; 2.24 mL (27.7 mmol) of pyridine was then added followed by 1.57 mL (22.2 mmol) of acetyl chloride. The solution was stirred for 4 hr. and then diluted in CH<sub>2</sub>Cl<sub>2</sub> and extracted twice with 2M H<sub>2</sub>SO<sub>4</sub> followed by brine and dried over sodium sulfate. The crude oil was subjected to flash column chromatography using hexanes:ethyl acetate as eluent to yield 2.9g (89%) as a clear oil, with the α anomer always as the major product (5-10:1, α:β). Characterization: 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl acetate,<sup>11</sup> 2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl acetate,<sup>17</sup> and 2,3,4,6-tetra-*O*-

benzyl-D-mannopyranosyl acetate:  $\alpha$  anomer  $^1\text{H}$  NMR (250 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  1.54 (s, 3H), 3.68-3.76 (m, 2H), 3.83 (dd, 1H,  $J = 11.1, 4.3$  Hz), 3.93-3.98 (dd, 1H,  $J = 9.5, 3.0$  Hz), 4.03-4.09 (m, 1H), 4.37-4.45 (m, 4H), 4.51-4.61 (m, 4H), 4.96 (d, 1H,  $J = 11.3$  Hz), 6.59 (d, 1H, H-1,  $J = 1.9$  Hz), 7.03 (m, 20H):  $\beta$  anomer  $^1\text{H}$  NMR (250 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  1.62 (s, 3H), 3.48 (dd, 1H,  $J = 9.3, 2.8$  Hz), 3.50 (dq, 1H,  $J = 9.5, 2.1$  Hz), 3.66-3.80 (m, 3H), 4.25 (t, 1H,  $J = 9.5$  Hz), 4.32-4.41 (m, 3H), 4.53 (apparent d, 1H,  $J = 11.4$  Hz), 4.55 (apparent d, 1H,  $J = 12.0$  Hz), 4.74-4.89 (m, 3H), 5.63 (s, 1H, H-1) 6.99-7.48 (m, 20H).

### **1-Azido-1-deoxy-2,3,4,6-tetra-*O*-benzyl- $\beta$ -D-glucopyranoside**

**(1.2):** To a solution of 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (179 mg, 0.31 mmol) in 3 mL  $\text{CH}_2\text{Cl}_2$  cooled to  $0^\circ\text{C}$  was added 48  $\mu\text{L}$  (0.39 mmol) of trimethylsilyl iodide and the reaction let sit for 30 min. The solvent was removed *in vacuo* and 2 mL of toluene was added and again removed *in vacuo*. The resulting oil was diluted in 2 mL of THF and transferred to a previously stirring solution of tetrabutylammonium azide (437 mg, 1.53 mmol) in 3 mL THF containing 3 $\text{\AA}$  molecular sieves. After 5 min TLC (3:1 hexanes:ethyl acetate) showed complete disappearance of the iodide, the solvent was removed under vacuum and the resulting oil subjected to flash column chromatography using 6:1 hexanes:ethyl acetate as the eluent to yield 160 mg (92%) of the  $\beta$  azide:  $[\alpha]_{\text{D}}^{25} + 28.4^\circ$  (19.0,  $\text{CDCl}_3$ );  $^1\text{H}$  NMR (250 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  3.16-3.25 (m, 1H), 3.30 (t, 1H,  $J = 8.7$  Hz), 3.48 (t, 1H,  $J = 9.0$  Hz), 3.55-3.61 (m, 2H), 3.68 (t, 1H,  $J = 9.2$  Hz), 4.24 (d, 1H,  $J = 8.5$  Hz, H-1), 4.32 (d, 1H,  $J$

= 12.2 Hz), 4.42 (d, 1H,  $J = 8.5$  Hz), 4.55 (d, 1H,  $J = 11.2$  Hz), 4.61 (d, 1H,  $J = 11.1$  Hz), 4.75 (d, 2H,  $J = 11.4$  Hz), 4.81-4.90 (m, 2H), 7.0-7.40 (m, 20H);  $^{13}\text{C}$  NMR (250 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  68.8, 73.7, 75.1, 75.6, 77.7, 82.1, 85.2, 90.3, 127.7, 127.8, 128.0, 128.1, 128.4, 128.5, 128.6, 128.7, 138.7, 138.8, 139.1, 139.3; HRFABMS calcd for  $\text{C}_{34}\text{H}_{35}\text{O}_5\text{N}_3$ : 565.2576. Found: 564.2539 (M-H) $^+$ .

**Dimethyl 2-(2,3,4,6-tetra-*O*-benzyl- $\alpha,\beta$ -D-glucopyranosyl) malonates (1.5/1.6):** To a solution of 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (344 mg, 0.59 mmol) in 3 mL  $\text{CH}_2\text{Cl}_2$  cooled to  $0^\circ\text{C}$  was added 93  $\mu\text{L}$  (0.65 mmol) of trimethylsilyl iodide and the reaction let sit for 30 min. The solvent was then removed *in vacuo* and 2 mL of toluene was added and again removed *in vacuo*. The resulting oil was diluted in 3 mL of THF and added to a previously stirring solution of dimethyl malonate (88  $\mu\text{L}$ , 0.77 mmol), sodium hexamethyldisilazane (650  $\mu\text{L}$  of a 1M in THF, 0.65 mmol), and 15-crown-5 (129  $\mu\text{L}$ , 0.65 mmol) in 5 mL of THF. The reaction was let stir for 5 h after which the solvent was removed *in vacuo* and the resulting oil chromatographed using 3:1 hexanes:ethyl acetate to yield 257 mg (66%) of a 5.1:1 ( $\alpha$ : $\beta$ ) mixture of anomers.  $\beta$  Anomer (1.6):  $^1\text{H}$  NMR (250 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  3.23 (s, 3H), 3.29 (s, 3H), 3.39-3.43 (m, 1H), 3.63-3.70 (m, 3H), 3.78 (t, 1H,  $J = 9.3$  Hz), 3.93 (t, 1H,  $J = 9.5$  Hz), 4.01 (d, 1H,  $J = 5.4$  Hz, CH), 4.23 (dd, 1H,  $J = 5.3, 9.8$  Hz, H-1), 4.38 (d, 1H,  $J = 12.3$  Hz), 4.54 (d, 1H,  $J = 12.0$  Hz), 4.60 (d, 1H,  $J = 11.4$  Hz), 4.72-4.82 (m, 3H), 4.87 (d, 1H,  $J = 11.3$  Hz), 5.07 (d, 1H,  $J = 11.1$  Hz), 7.04-7.36 (m, 20H);  $^{13}\text{C}$  NMR (250 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$

51.9, 54.4, 68.9, 73.4, 74.7, 74.8, 75.5, 77.6, 78.7, 79.8, 80.2, 87.7, 127.6, 127.8, 128, 128.4, 139.0, 165.4. HRFABMS calc for  $C_{39}H_{42}O_9$ : 654.2829. Found 655.2903 for  $(M+H)^+$ .  $\alpha$  Anomer(1.5):  $^1H$  NMR (250 MHz,  $C_6D_6$ )  $\delta$  3.10 (s, 3H), 3.39 (s, 3H), 3.65-3.85 (m, 6H), 4.0-4.10 (m, 1H), 4.31-4.55 (m, 7H), 4.67 (d, 1H,  $J = 11.4$  Hz), 4.76-4.83 (m, 2H), 5.30 (dd, 1H,  $J = 5.2, 10.5$  Hz, H-1), 7.05-7.32 (m, 20H);  $^{13}C$  NMR (250 MHz,  $C_6D_6$ )  $\delta$  51.9, 52.2, 52.3, 69.7, 73.3, 73.5, 73.8, 74.5, 74.7, 75.1, 78.0, 79.8, 82.0, 127.6, 128, 128.2, 128.4, 128.5, 166.6. HRFABMS calc for  $C_{39}H_{42}O_9$ : 654.2829. Found: 655.2928  $(M+H)^+$ .

**Dimethyl 2-(2,3,4,6-tetra-*O*-benzyl- $\beta$ -D-galactopyranosyl) malonate:** To a solution of 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-galactopyranoside (170 mg, 0.29 mmol) in 3 mL  $CH_2Cl_2$  cooled to 0°C was added 45  $\mu$ L (0.32 mmol) of iodotrimethylsilane and the solution let sit for 30 min. The solvent was then removed *in vacuo* and then 2 mL of THF was added and the resulting solution was transferred to an already stirring solution of dimethyl malonate (71  $\mu$ L, 0.44 mmol), sodium hexamethyldisilazane (380  $\mu$ L, 1M solution in THF, 0.38 mmol), and 15-crown-5 (75  $\mu$ L, 0.38 mmol) in 5 mL of THF. The reaction was stirred for 1 h at room temperature and then concentrated. The residue was diluted in a small amount of methylene chloride and loaded onto a silica gel column and subsequently eluted with 3:1 hexanes:ethyl acetate to yield 110 mg (58%) of a 10:1 ( $\beta$ : $\alpha$ ) mixture:  $\beta$  anomer (1.13):  $^1H$  NMR (250 MHz,  $C_6D_6$ )  $\delta$  3.16 (s, 3H), 3.30 (s, 3H), 3.43 (dd, 1H,  $J = 8.7, 2.6$  Hz), 3.54-3.72 (m, 3H), 3.83 (d, 1H,  $J = 2.6$  Hz), 4.02 (d, 1H,  $J = 5.7$  Hz), 4.20 (d, 1H,  $J =$

11.8 Hz), 4.23-4.48 (m, 6H), 4.53 (d, 1H,  $J = 11.5$  Hz), 4.62 (d, 1H,  $J = 11.3$  Hz), 4.92 (d, 1H,  $J = 11.5$  Hz), 5.09 (d, 1H,  $J = 11.3$  Hz), 7.0-7.39 (m, 20H);  $^{13}\text{C}$  NMR (250 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  51.9, 55.2, 69.0, 72.0, 73.5, 74.3, 74.8, 74.9, 77.0, 77.8, 78.0, 85.5, 127.4, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.4, 128.5, 128.6, 138.7, 138.8, 139.5, 167.3. HRFABMS calc for  $\text{C}_{39}\text{H}_{42}\text{O}_9$  : 654.2829. Found: 655.2899 ( $\text{M}+\text{H}$ ) $^+$ .

**1-Deoxy-2,3,4,6-tetra-*O*-benzyl- $\beta$ -D-glucopyranosyl cyanide (1.7):** To a solution of 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (53.9 mg, 0.093 mmol) in 1 mL  $\text{CH}_2\text{Cl}_2$  cooled to  $0^\circ\text{C}$  was added 14.5  $\mu\text{L}$  (0.10 mmol) of trimethylsilyl iodide and the reaction let sit for 30 min. The solvent was then removed *in vacuo* and 1 mL of toluene was added and again removed *in vacuo*. The resulting oil was diluted in 2 mL of THF and added to a previously stirring solution of tetrabutylammonium cyanide (124 mg, 0.46 mmol) containing 3Å molecular sieves. After 10 min, the solvent was removed *in vacuo* and the resulting material was chromatographed using 3:1 hexanes: ethyl acetate as eluent to yield 16.5 mg (32%) of the *C*-glycoside.  $^1\text{H}$  spectra matched those of the previously reported compound.<sup>18</sup>

**1-Deoxy-2,3,4,6-tetra-*O*-benzyl- $\beta$ -D-mannopyranosyl cyanide (1.9):** To a solution of 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-mannopyranoside (88 mg, 0.15 mmol) in 2 mL  $\text{CH}_2\text{Cl}_2$  cooled to  $0^\circ\text{C}$  was added 24  $\mu\text{L}$  (0.17 mmol) of trimethylsilyl iodide and the reaction let sit for 40 min. The solvent was then removed *in vacuo* and 1 mL of toluene

was added and again removed *in vacuo*. The resulting oil was diluted in 2 mL of THF and added to a previously stirring solution of tetrabutylammonium cyanide (202 mg, 0.76 mmol) in 5 mL of THF. After 2 h the solvent was removed *in vacuo* and the residue was chromatographed using 3:1 hexanes:ethyl acetate as eluent to yield 46 mg (55%) of the C-glycoside,  $[\alpha]_D^{25} -51.2^\circ$  (6.6,  $\text{CDCl}_3$ );  $^1\text{H NMR}$  (250 MHz,  $\text{CDCl}_3$ )  $\delta$  3.31-3.37 (m, 1H), 3.45 (dd, 1H,  $J = 9.3, 2.3$  Hz, H-3), 3.61-3.63 (m, 2H), 3.83 (t, 1H,  $J = 9.3$  Hz, H-4), 3.92 (d, 1H,  $J = 2.3$  Hz, H-2), 4.12 (s, 1H, H-1), 4.43-4.60 (m, 6H), 4.76 (d, 1H,  $J = 10.8$  Hz), 4.83 (d, 1H,  $J = 11.5$  Hz), 4.90 (d, 1H,  $J = 11.5$  Hz), 7.13-7.48 (m, 20H);  $^{13}\text{C NMR}$  (250 MHz,  $\text{CDCl}_3$ )  $\delta$  67.4, 68.8, 72.6, 73.6, 73.9, 74.1, 74.6, 75.3, 80.5, 82.3, 127.6, 127.8, 127.9, 128.0, 128.3, 128.4, 128.5, 137.3, 137.6, 137.8; HRFABMS calc for  $\text{C}_{35}\text{H}_{35}\text{O}_5\text{N}$ : 549.2515. Found: 550.2614 (M+H) $^+$ .

**1-Phthalimido-1-deoxy-2,3,4,6-tetra-O-benzyl- $\beta$ -D-glucopyranoside (1.10):** To a solution of 1-O-acetyl-2,3,4,6-tetra-O-benzyl-D-glucopyranoside (332 mg, 0.57 mmol) in 3 mL  $\text{CH}_2\text{Cl}_2$  cooled to  $0^\circ\text{C}$  was added 89  $\mu\text{L}$  of trimethylsilyl iodide and the reaction let sit for 30 min. The solvent was then removed *in vacuo* and 2 mL of toluene was added and removed *in vacuo*. The compound was diluted in 2 mL of THF and added to an already stirring solution of potassium phthalimide (159 mg, 0.86 mmol) and 18-crown-6 (226 mg, 0.86 mmol) in 7 mL of THF at room temperature. The reaction was complete after 15 min at which time the product was diluted in methylene chloride and washed twice with 1M KOH and once with brine and then dried over sodium sulfate to yield a

yellow oil. The resulting oil was subjected to flash column chromatography using 4:1 hexanes:ethyl acetate as eluent to yield 252 mg (66%) of the title compound:  $^1\text{H}$  NMR (250 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  3.41-3.50 (m, 1H), 3.56 (d, 1H,  $J = 10.8$  Hz), 3.63-3.75 (m, 2H), 3.90 (t, 1H,  $J = 9.5$  Hz), 4.32 (d, 1H,  $J = 12.0$  Hz), 4.50-4.67 (m, 3H), 4.80-4.90 (m, 4H), 5.03 (t, 1H,  $J = 9.2$  Hz), 5.64 (d, 1H,  $J = 9.4$  Hz, H-1), 6.76 (m, 4H), 7.08 (m, 20H);  $^{13}\text{C}$  NMR (250 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  69.1, 73.7, 74.9, 75.0, 75.5, 78.1, 78.3, 79.8, 87.0, 123.3, 127.3, 127.4, 127.6, 127.8, 127.9, 128.0, 128.2, 128.4, 128.5, 133.6, 138.9, 139.3, 167.3. HRFABMS calcd for  $\text{C}_{42}\text{H}_{39}\text{O}_7\text{N}$ : 669.2726. Found: 670.2808 ( $\text{M}+\text{H}$ ) $^+$ .

### **1-*O*-Pivaloyl-2,3,4,6-tetra-*O*-benzyl- $\beta$ -D-glucopyranoside**

**(1.11):** To a solution of 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside 263 mg (0.45 mmol) in 3 mL  $\text{CH}_2\text{Cl}_2$  cooled to  $0^\circ\text{C}$  was added 71  $\mu\text{L}$  (0.497 mmol) of trimethylsilyl iodide and the reaction let sit for 30 min. The solvent was then removed *in vacuo* followed by the addition of 2 mL of toluene which again was removed *in vacuo*. 2 mL of THF was added and the resulting solution pipetted into an already stirring solution of pivalic acid (230 mg, 2.3 mmol), tetrabutylammonium hydrogen sulfate (306 mg, 0.90 mmol), and sodium hexamethyldisilazane (1.80  $\mu\text{L}$  of a 1M solution in THF, 1.80 mmol) in 5 mL of THF. The reaction was stirred for 20 min, at which point ethyl acetate was added and the reaction mixture was washed with sodium bicarbonate (twice) and brine. The ethyl acetate layer was dried over sodium sulfate and removed *in vacuo*. The resulting oil was chromatographed using 8:1 hexanes: ethyl

acetate as eluent to yield 256 mg (90%) of the  $\beta$  glycoside with no detectable  $\alpha$  product:  $[\alpha]_D^{25} +98.9$  (7.3,  $\text{CDCl}_3$ );  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta$  1.20 (s, 9H), 3.51-3.73 (m, 6H), 4.46 (d, 1H,  $J = 12.3$  Hz), 4.52 (d, 1H,  $J = 11.0$  Hz), 4.58 (d, 1H,  $J = 12.3$  Hz), 4.68-4.86 (m, 5H), 5.57 (d, 1H,  $J = 7.9$  Hz, H-1);  $^{13}\text{C}$  NMR (250 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  27.0, 38.7, 68.6, 73.4, 74.7, 74.9, 75.4, 76.0, 77.7, 81.5, 85.1, 94.8, 127.6, 127.7, 127.9, 128.0, 128.4, 128.5, 128.6, 138.9, 139.2. HRFABMS calc for  $\text{C}_{39}\text{H}_{44}\text{O}_7$ : 624.3068. Found: 623.3013 (M-H) $^+$ .

**1-*O*-Stearyl-2,3,4,6-tetra-*O*-benzyl- $\beta$ -D-glucopyranoside (1.12):**

To a solution of 2,3,4,6-tetra-*O*-benzylglucosyl acetate 273 mg (0.46 mmol) in 3 mL methylene chloride was added 73  $\mu\text{L}$  (0.51 mmol) of trimethylsilyl iodide and the mixture let sit for 30 min at 0°C. The solvent was removed *in vacuo* and 2 mL of toluene was added and again removed *in vacuo* followed by the addition of 2 mL of THF. This solution was added to an already stirring solution of sodium stearate (a mixture with sodium palmitate) (430 mg, 1.41 mmol) and tetrabutylammonium hydrogen sulfate 397 mg (1.17 mmol) in 5 mL of THF. Immediately upon addition, TLC analysis (6:1 hexanes:ethyl acetate) showed complete disappearance of the iodide. The solvent was removed *in vacuo* after 10 min and the resulting oil purified using a 9:1 hexanes:ethyl acetate column to give a quantitative yield of a > 95:5 mixture of  $\beta$ : $\alpha$  glycosides, as a mixture of lipids.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.23-1.31 (m), 1.63 (m), 1.90-1.96 (m), 2.55-2.63 (t,  $J = 7.5$  Hz), 3.87-4.13 (m), 4.75 (d,  $J = 12$  Hz), 4.86-4.94 (m), 5.10-5.32 (m), 6.06 (d, 1H, H-1,  $J = 7.9$  Hz), 7.47-7.62 (m,



20H). HRFABMS for the stearate derivative calc for  $C_{52}H_{70}O_7$ : 806.5121. Found: 829.5035 (M+Na)<sup>+</sup>. HRFABMS for the palmitate derivative calc for  $C_{50}H_{66}O_7$ : 778.4808. Found: 801.4694 (M+Na)<sup>+</sup>. No mass peak for the corresponding acids were identified, but <sup>1</sup>H NMR integration proved difficult with the varying lipid components.

**Phenyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside (1.13):** To a solution of 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (303 mg, 0.52 mmol) in 4 mL CH<sub>2</sub>Cl<sub>2</sub> cooled to 0°C was added 81 μL (0.57 mmol) of trimethylsilyl iodide and the reaction let sit for 30 min. The solvent was removed *in vacuo* and 2 mL of toluene was added and again removed *in vacuo*. The resulting oil was diluted in 3 mL of THF and transferred into a previously stirring solution of phenol (74 mg, 0.78 mmol), sodium hexamethyldisilazane (624 μL of a 1M solution in THF, 0.63 mmol), and 15-crown-5 (124 μL, 0.63 mmol) in 5 mL THF. After 15 min, TLC (3:1 hexanes: ethyl acetate) showed complete disappearance of the iodide. The solution was diluted in ether and washed twice with 1M NaOH, once with saturated brine, and then dried over sodium sulfate. The resulting oil was purified on a column of silica gel using 6:1 hexanes:ethyl acetate as the eluent to yield 196 mg (61%) of the glycoside:  $[\alpha]_D^{25} +42.3^\circ$  (2.6, CDCl<sub>3</sub>); <sup>1</sup>H NMR (250 MHz, C<sub>6</sub>D<sub>6</sub>) δ 3.32-3.4 (m, 1H), 3.59-3.75 (m, 4H), 3.82 (dd, 1H, *J* = 7.9, 8.8 Hz, H-2), 4.31 (d, 1H, *J* = 12.3 Hz), 4.40 (d, 1H, *J* = 12.1 Hz), 4.55 (d, 1H, *J* = 11.3 Hz), 4.77-4.88 (m, 3H), 4.96 (d, 1H, *J* = 7.7 Hz, H-1), 5.00 (d, 1H, *J* = 11.4 Hz), 5.09 (d, 1H, *J* = 11.3 Hz), 6.85-7.37 (m, 25H); <sup>13</sup>C NMR (250 MHz, C<sub>6</sub>D<sub>6</sub>) δ 69.2, 73.4, 74.9, 75.0, 75.5,

75.54, 82.4, 84.9, 102.1, 117.4, 122.8, 127.6, 127.7, 127.8, 127.9, 128.0, 128.4, 128.5, 128.8, 129.6, 138.8, 139.1, 139.4, 158.1; HRFABMS calc for  $C_{40}H_{40}O_6$ : 616.2825. Found: 639.2693 ( $M+Na$ )<sup>+</sup>.

**Methyl-2,3,4,6-tetra-*O*-benzyl- $\alpha$ -D-glucopyranoside:** To a solution of 2,3,4,6-tetra-*O*-benzyl glucosyl acetate 206 mg (0.35 mmol) in 3 mL methylene chloride was added 55  $\mu$ L (0.39 mmol) of trimethylsilyl iodide and the reaction let sit for 30 min at 0°C. The solvent was removed *in vacuo* and 2 mL of benzene was added and the resulting solution added to an already stirring solution of methanol 29  $\mu$ L (0.70 mmol) and 2,6-di-*tert*-butylpyridine 172  $\mu$ L (0.87 mmol) in 5 mL of benzene and allowed to stand for 45 h. The solvent was removed *in vacuo* and the resulting oil put down a 6:1 column (hexanes:ethyl acetate) to yield 138 mg (70%) of the  $\alpha$  anomer.<sup>16</sup>

**Methyl-2,3,4,6-tetra-*O*-benzyl- $\alpha,\beta$ -D-galactopyranosides:** To a solution of 2,3,4,6-tetra-*O*-benzyl galactosyl acetate 158 mg (0.27 mmol) in 2 mL methylene chloride was added 43  $\mu$ L (0.30 mmol) of trimethylsilyl iodide and the reaction let sit for 30 min at 0°C. The solvent was removed *in vacuo* and 2 mL of benzene was added and again removed *in vacuo*. An additional 2 mL of benzene was added and the resulting solution added to an already stirring solution of methanol 22  $\mu$ L (0.54 mmol) and 2,6-di-*tert*-butylpyridine 132  $\mu$ L (0.58 mmol) in 2 mL of benzene and let sit for 42 h. The solvent was removed *in vacuo* and the

resulting oil put down a 6:1 column (hexanes:ethyl acetate) to yield 61.5 mg (41% unoptimized yield) of a 1.2:1  $\alpha$ : $\beta$  mixture.<sup>16</sup>

**1-*O*-Acetyl-2,3,4,6-tetra-*O*-benzyl- $\beta$ -D-glucopyranoside:** To a solution of 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (207 mg, 0.36 mmol) in 3 mL CH<sub>2</sub>Cl<sub>2</sub> cooled to 0°C was added 56  $\mu$ L (0.39 mmol) of trimethylsilyl iodide and the reaction let sit for 35 min. The solvent was removed *in vacuo* and 2 mL of THF was added and the resulting solution transferred into an already stirring solution of anhydrous sodium acetate (88 mg, 1.07 mmol), and tetrabutylammonium hydrogen sulfate (133 mg, 0.39 mmol) in 5 mL THF. The reaction was stirred at room temperature for 1.5 h at which point the solvent was removed *in vacuo* and the resulting oil chromatographed using 6:1 hexanes: ethyl acetate as eluent to yield 187 mg (90%) of a 7:1 mixture of  $\beta$ : $\alpha$  anomers.<sup>17</sup>

**1-Methylsulfonyl-2,6-anhydro-1-deoxy-3,4,5,7-tetra-*O*-benzyl-D-glycero-D-gulo-deptitol (1.14):** To a solution of 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (128 mg, 0.22 mmol) in 3 mL CH<sub>2</sub>Cl<sub>2</sub> cooled to 0°C was added 34  $\mu$ L (0.24 mmol) of trimethylsilyl iodide and the reaction let sit for 30 min. The solvent was then removed *in vacuo* and a previously stirred solution of methanesulfonylacetate (50 mg, 0.33 mmol), sodium hexamethyldisilazane (286  $\mu$ L of a 1 M solution in THF, 0.29 mmol), 15-crown-5 (48  $\mu$ L, 0.24 mmol), and tetrabutylammonium iodide (812 mg, 2.20 mmol) in 7 mL of THF was added. The solution was stirred at room temperature for 17 h and then purified by a 3:1

(hexanes:ethyl acetate) column to yield 99 mg (67%) mixture of the C-glycosides. 169 mg (0.25 mmol) of the C-glycoside mixture was dissolved in 2 mL of HMPA with 300 mg (2.25 mmol) of tetramethylammonium acetate and heated to 90 °C for 10 h. The reaction was then diluted with CH<sub>2</sub>Cl<sub>2</sub> and washed with 1M H<sub>2</sub>SO<sub>4</sub>, NaHSO<sub>4</sub>, and brine. The solvent was then removed and the resulting mixture was subjected to flash column chromatography using a 3:1 (hexanes:ethyl acetate) column to yield 81 mg (47%) of the title compound.<sup>18</sup>

**2,3,4,6-Tetra-O-benzyl-galacto-γ-lactone:** To a solution of 1-O-acetyl-2,3,4,6-tetra-O-benzyl-D-galactopyranoside (329 mg, 0.57 mmol) in 3 mL CH<sub>2</sub>Cl<sub>2</sub> cooled to 0°C was added (89 μL, 0.62 mmol) of trimethylsilyl iodide and the reaction let sit for 30 min. The solvent was removed *in vacuo* and 1.5 mL of toluene was added and again removed *in vacuo*. 2 mL of THF was added and the resulting solution added to a previously stirred solution of methyl nitroacetate (78 μL, 0.85 mmol), sodium hexamethyldisilazane (735 μL of a 1 M solution in THF, 0.74 mmol), and 15-crown-5 (146 μL, 0.74 mmol), in 4 mL of THF. The solution was stirred at room temperature for 1 h and then purified by a 3:1 (hexanes:ethyl acetate) column to yield 155 mg (45%) of the lactone.<sup>19</sup>

## Chapter 2

### Neutral Addition of Alcohols to Glycosyl Iodides

## INTRODUCTION

The use of glycosyl halides in the reaction with alcohols using a Lewis acid promoter is the most widely utilized method of *O*-glycoside formation. However, the use of glycosyl halides in the absence of a Lewis acid promoter has received much less attention as a method of choice for formation of the *O*-glycosidic linkage. The reason for this is the low reactivity of the glycosyl halides in the absence of a Lewis acid promoter. Kronzer and Schuerch<sup>20</sup> have shown that reaction of 2,3,4,6-tetra-*O*-benzyl- $\alpha$ -D-glucopyranosyl chloride with 10 equivalents of methanol under neutral conditions in acetonitrile does not proceed, and that the corresponding bromide takes 8 hours to react with 5 equivalents of isopropanol (Figure 2.1). They also demonstrated that with addition of an excess of sodium iodide the glucosyl chloride started to react after 10 minutes to produce selectively the  $\alpha$  methyl glycoside. The formation of the glucosyl iodide *in situ* is proposed, although the mechanism by which the iodide reacts to form the glycosidic linkage is unclear.

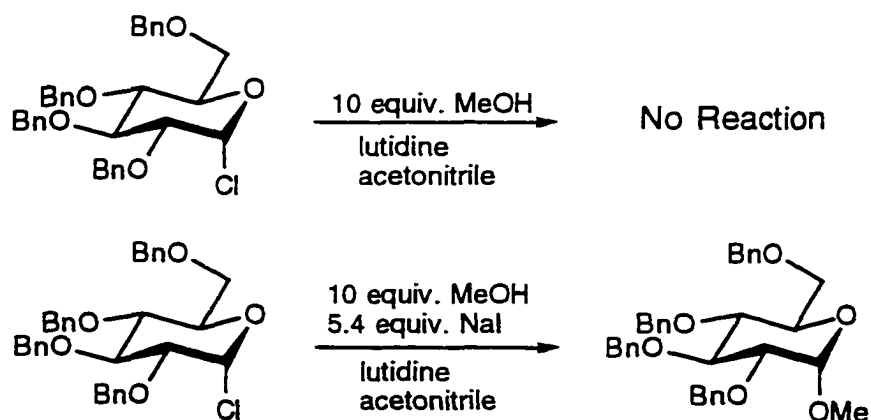


Figure 2.1. Sodium iodide catalysis of glucosyl chlorides

The reaction of glucosyl bromides under neutral conditions has also been investigated by Lemieux.<sup>16</sup> Lemieux demonstrated that the sluggish reaction rate of glycosyl bromides under neutral conditions can be greatly increased by the addition of tetraethylammonium bromide. The proposed explanation for this rate increase is *in situ* formation of the  $\beta$  glycosyl bromide which is more reactive than its  $\alpha$  counterpart (Figure 2.2). This highly reactive  $\beta$  glycosyl bromide then undergoes  $S_N2$  displacement by the acceptor alcohol to give selectively the  $\alpha$  glycoside.

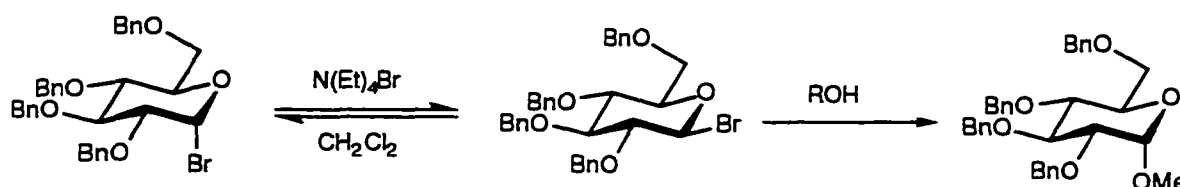


Figure 2.2. Tetraethylammonium bromide catalysis of glycosyl bromides

This method has been shown to work on both simple alcohols and on some selectively protected carbohydrates. The major drawback of this method is that activating protecting groups must be used (benzyl or isopropylidene), the typical procedure calls for a long (4 day) reaction time, and that certain 2° alcohols give low yields.<sup>21,22</sup>

Having shown in our laboratory that  $\alpha$  glycosyl iodides are easily accessible from the corresponding acetates,<sup>11</sup> we investigated the reaction of glycosyl iodides with alcohols under neutral conditions with the hope that they would be more efficient glycosyl donors than the corresponding bromides.

## RESULTS AND DISCUSSION

As was shown in Figure 1.10, the direct addition of methanol to the glycosyl iodides is very slow and does not always lead to stereospecific product formation. In keeping with the work of Lemieux,<sup>16</sup> we thought that introduction of a soluble iodide source might catalyze the reaction by formation of a more reactive  $\beta$  iodide *in situ*, leading to stereospecific  $\alpha$  glycoside formation. The  $\beta$  glycosyl iodide should be more reactive than the corresponding bromide, leading to an increase in reaction rate and possibly higher yields.

Our initial experiments focused on the formation of allyl glycosides from the corresponding  $\alpha$  iodides, using tetrabutylammonium iodide (TBAI) as the soluble iodide source and diisopropylethylamine as a hindered base (Figure 2.3). The reactions proceeded swiftly to give the  $\alpha$  allyl glycosides in good yield with high selectivity. The reactivities of the different glycosyl iodides were found to vary tremendously depending on the carbohydrate moiety. It was found that the reactivities of the various



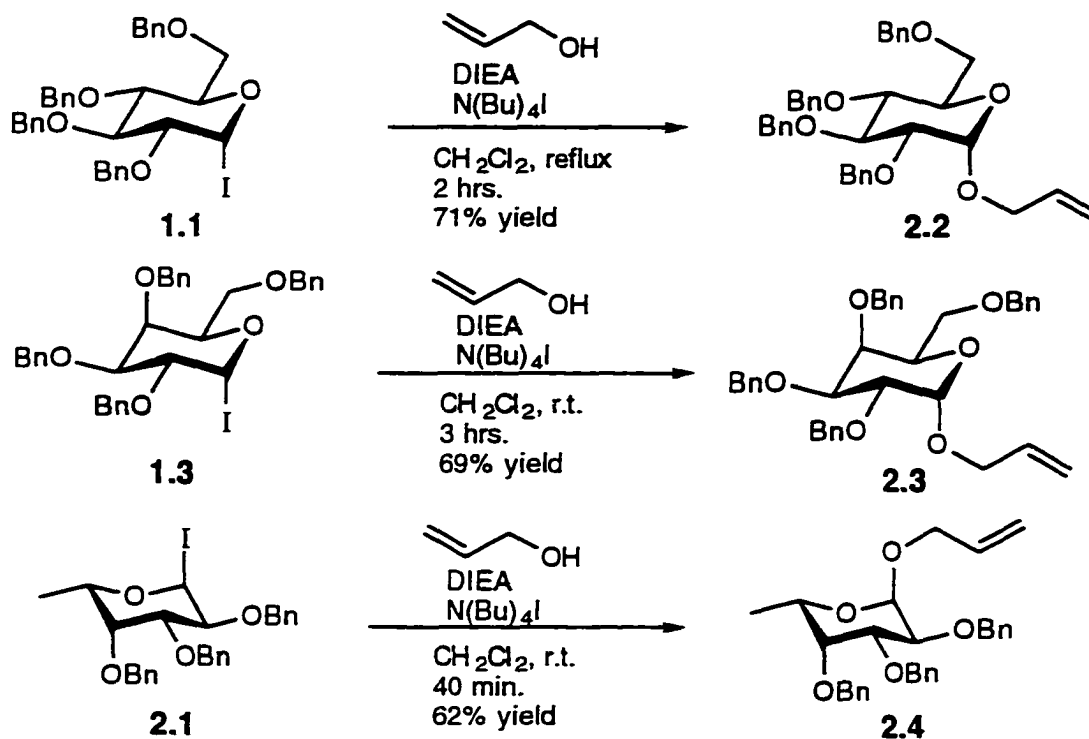


Figure 2.3. Reaction of allyl alcohol with glycosyl iodides

iodides under the TBAI catalyzed conditions were fucosyl > galactosyl > glucosyl > mannosyl.

Although allyl alcohol was shown to have reasonable reaction times with the glycosyl iodides, it was found that more pressing conditions were necessary for hindered alcohols. Diacetone glucose **2.5** was chosen as a representative 2° alcohol of moderate reactivity in order to demonstrate the applicability of this glycosidation method to common glycosyl acceptors. At first, methylene chloride was used as solvent and refluxing conditions were employed in order to facilitate the reaction. After 24 hours, reaction with the galactosyl iodide produced the  $\alpha$  glycoside in low yield (45%) along with a major byproduct (Figure 2.4). Mass spectral and  $^1\text{H}$  NMR analysis confirmed that the byproduct formed was the galactosyl chloride.

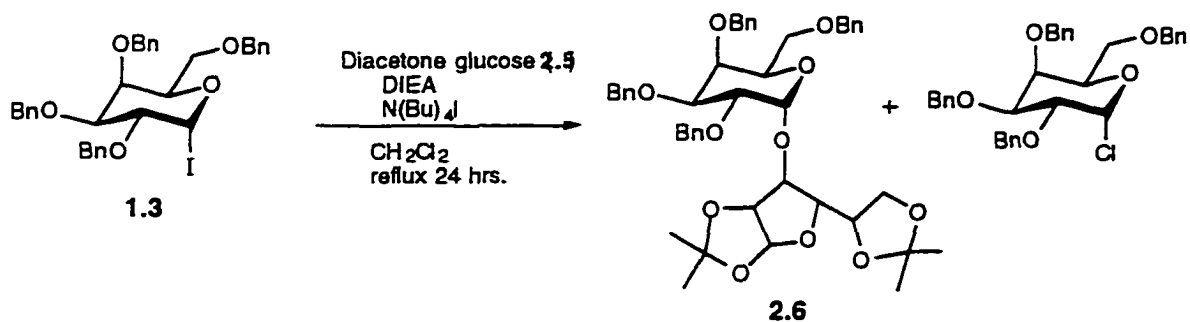


Figure 2.4. Reaction of the galactosyl iodide with diacetone glucose in methylene chloride

The formation of the galactosyl chloride can be explained by the following mechanism (Figure 2.5). First, and most important, reaction of the galactosyl iodide with diacetone glucose proceeds very slowly in refluxing methylene chloride. Due to the slow reaction time some of the TBAI begins to react with the methylene chloride (present in a large excess) to form tetrabutylammonium chloride. This soluble source of chloride ion then most probably reacts with with the  $\beta$  galactosyl iodide to give the  $\alpha$  chloride (Figure 2.5). The glycosyl chloride is slow to react under the reaction conditions and therefore effectively quenches product formation.

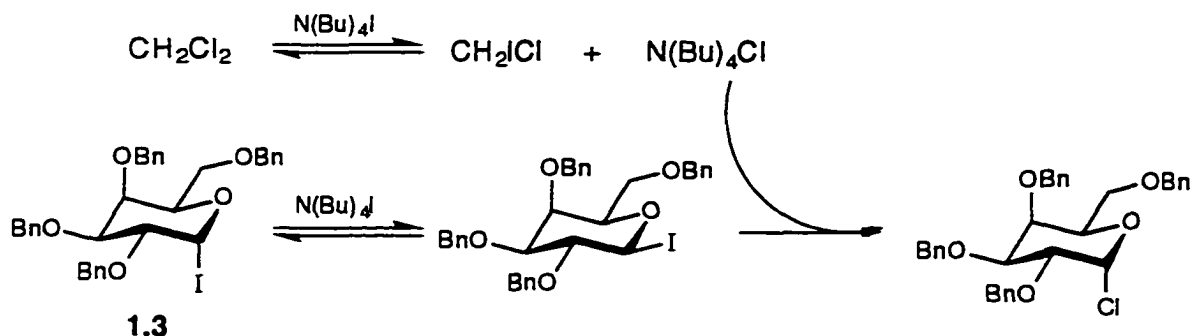


Figure 2.5. Formation of the galactosyl chloride

Due to the low reactivity of the galactosyl iodide in refluxing methylene chloride we then increased the reaction temperature by using higher boiling solvents. Dichloroethane was the first solvent that was investigated as it was similar to methylene chloride, but had a boiling point of 83°C. However, this solvent proved even more reactive with TBAI, and produced the glycosyl chloride almost exclusively in 1.5 hours. Tetrahydrofuran was tried next for its relatively higher boiling point and its ability to solubilize the TBAI. After 3 hours in refluxing THF all of the galactosyl iodide had been consumed, but again a low yield of **2.6** was obtained and a byproduct had formed. Mass spectral and  $^1\text{H}$  NMR were used to assign the byproduct's structure as a THF adduct of galactose (Figure 2.6). It seems that THF present in a large excess can react under the refluxing conditions with  $\beta$  galactosyl iodide (or the oxonium ion) to produce a THF oxonium intermediate, which then reacts with TBAI to give the iodo-THF byproduct.

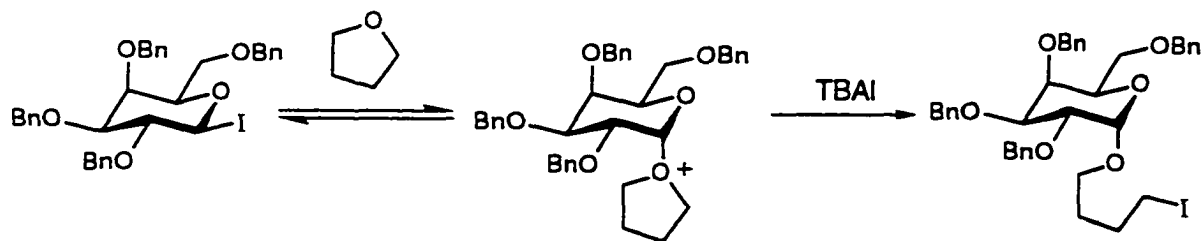


Figure 2.6. THF reaction with the galactosyl iodide

In order to avoid solvent reaction with the glycosyl iodides, benzene was then employed as solvent, even though TBAI solubility was low at room temperature.

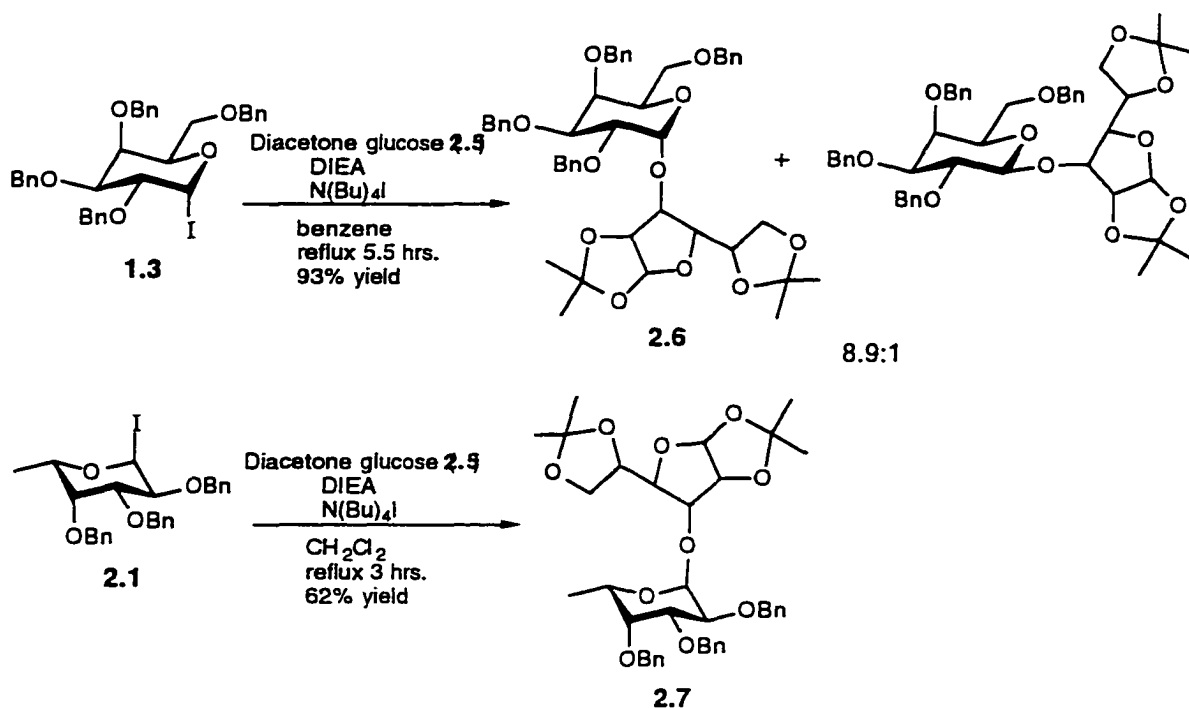


Figure 2.7. Reaction of glycosyl iodides in refluxing benzene

Reaction of **1.3** in benzene under reflux with **2.5** and TBAI proceeded smoothly in 5.5 hours to give a 93% yield of a 9:1  $\alpha$ : $\beta$  mixture along with a minor amount of the glycal (Figure 2.7). In an attempt to

increase  $\alpha$  selectivity and possibly increase the rate of reaction, the amount of TBAI was increased from 2 equivalents to 10. This increase seemed to increase the rate of glycosyl iodide disappearance, but the  $\alpha$  selectivity did not seem to change and the rate of glycal formation increased. The increase in glycal formation is most probably due to an overall increase in the polarity of the reaction medium, leading to an increase in oxonium formation and E-1 elimination. A lower temperature (40°C) was also tried in an attempt to increase  $\alpha$  selectivity, but it only slowed the overall reaction, with little or no gain in selectivity.

With these results other glycosyl iodides were then reacted with TBAI and 2.5. The fucosyl iodide 2.1 reacted in refluxing  $\text{CH}_2\text{Cl}_2$  to give a 62% yield in 3 hours of only the  $\alpha$  product (Figure 2.7). This result was in agreement with our earlier observation that the fucosyl iodide was more reactive than the galactosyl iodide. The mannosyl iodide differed from the other glycosyl iodides in that no TBAI was needed in order to give  $\alpha$  selectivity. Reaction of the mannosyl iodide with 2.5 in refluxing benzene gave in 5.5 hours a 67% yield of only the  $\alpha$  glycoside, with the glycal as a byproduct (Figure 2.8).

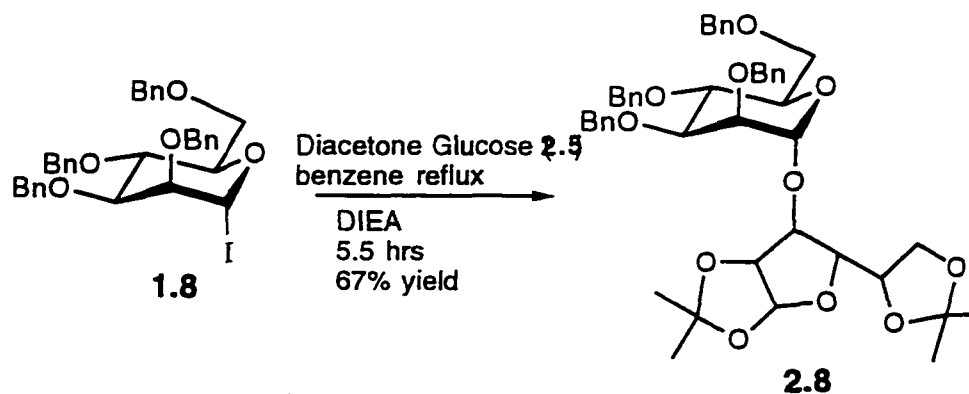


Figure 2.8. Mannosyl iodide reaction in refluxing benzene

We propose that the reaction mechanism with mannosyl iodides is an  $S_N1$  mechanism where the reactive intermediate is the mannosyl oxonium ion, which is trapped by the C-3 alcohol of diacetone glucose. Evidence for this oxonium intermediate is that the glycal is a byproduct in the reaction. In the mannose case, the only way that the glycal can be formed is through an E1 mechanism, in which the oxonium ion is the reactive intermediate. DIEA, a hindered but relatively strong base, was as in the other reactions, used to soak up the hydrogen iodide formed under the reaction conditions. In an attempt to increase the yield of the mannose glycosidation by limiting the amount of E1 elimination we decided to use a milder base. Tetramethylurea was used in the place of DIEA under the same reaction conditions, but unfortunately the amount of glycal formed was the same as with the DIEA.

The reaction of the glucosyl iodide **1.1** with **2.5**, TBAI, and DIEA (Figure 2.9, same conditions as for the galactosyl and fucosyl iodides) gave in 1.5 hours a 44% yield (based on **1.1**) of the glycal **1.4** and a 45% yield (based on **2.5**) of the  $\alpha$  glycoside **2.9**.

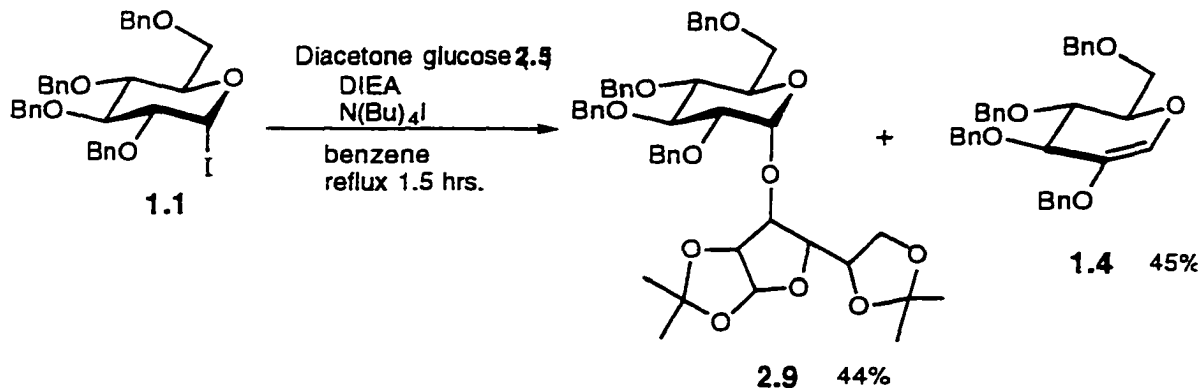


Figure 2.9. Glucosyl iodide reaction with diacetone glucose in refluxing benzene

As with the mannosyl iodide an attempt was made to limit the amount of elimination by changing to a milder base. In this case 2,6-di-*tert*-butyl-pyridine was used in place of DIEA, although again no difference was observed and the glycal was obtained as a major byproduct. It is not clear in this case whether E1 or E2 elimination is occurring.

A comparison between the reactivity of glycosyl iodides and the glycosyl bromides used by Lemieux<sup>16</sup> is shown in Table 1. Shorter reaction times, as well as improved yields are realized with the glycosyl iodides.

Donor	Acceptor	Catalyst	Time (hr)	Yield (%)
Glc-Br	2.5	N(Et) <sub>4</sub> Br	48	42
Glc-I	2.5	N(Bu) <sub>4</sub> I	1.5	44
Gal-Br	2.5	N(Et) <sub>4</sub> Br	48	62
Gal-I	2.5	N(Bu) <sub>4</sub> I	5.5	93 (9:1 α:β)
Fuc-Br	2.5	N(Et) <sub>4</sub> Br	48	47
Fuc-I	2.5	N(Bu) <sub>4</sub> I	3	62
Mann-I	2.5	none	5.5	67

All sugars are benzyl protected and products are all α unless specified

Table 1. Comparison of glycosyl bromides with iodides

In order to investigate the ability of the glycosyl iodides to react with other 2° acceptors, we chose the C-2 hydroxyl of 1,6-anhydro-3,4-isopropylidene galactose as an example of a 2° axial acceptor (Figure 2.10). Reaction of the fucosyl iodide **2.1** with the anhydrosugar and TBAI in methylene chloride at room temperature led to a 91% yield of only the α glycoside **2.10** in 5.5 hours.

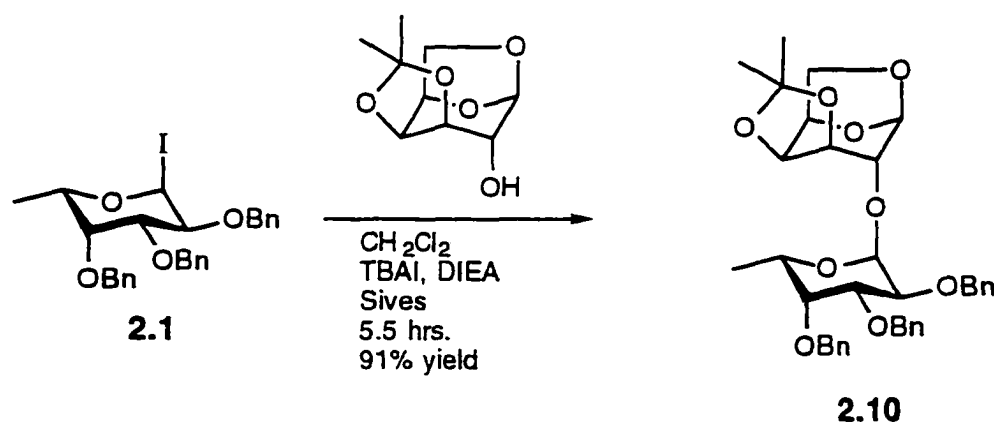


Figure 2.10. 1,6-Anhydrogalactose reaction with the fucosyl iodide



The facility with which the glycosyl iodides undergo glycoside formation led us to investigate the possibility of using them as donors in constructing the 1,1' linkage found in trehalose. The fucose derivative of trehalose has to our knowledge never been synthesized. For this reason we chose it as our synthetic target in probing the formation of the 1, 1' glycosidic linkage. Fucosyl iodide **2.1** was reacted with 2,3,4-tri-*O*-benzyl-L-fucopyranoside in refluxing benzene in the presence of 10 equivalents of TBAI and 2 equivalents of DIEA (Figure 2.11). After 1 hour the reaction gave a 90% yield of a 1.14 : 1 ratio of the  $\alpha\alpha$ : $\alpha\beta$  (**2.11** : **2.12**) trehalose derivatives.

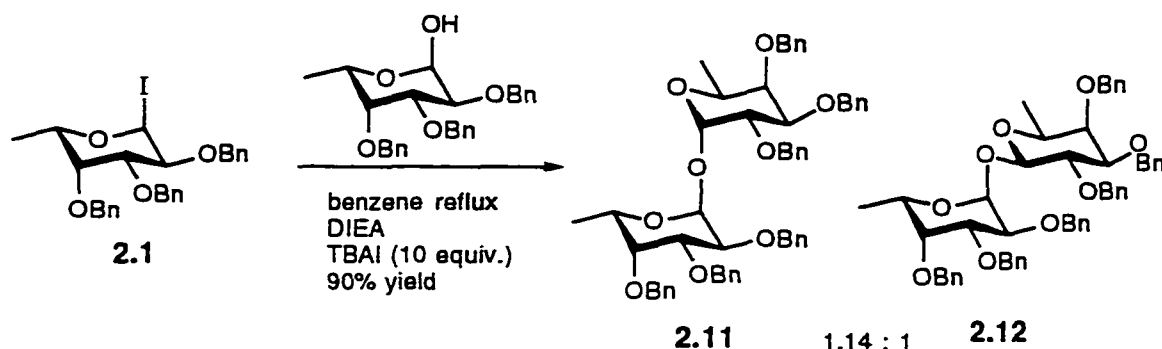


Figure 2.11. Fucose trehalose derivative synthesis

The mixture of  $\alpha\alpha$  and  $\alpha\beta$  derivatives could arise from a variety of different mechanistic scenarios. The most straightforward product to explain is the  $\alpha\alpha$  derivative. The glycosyl iodide in this reaction is expected to give the  $\alpha$  product by reaction of either the  $\beta$  glycosyl iodide or an intermediate oxonium ion. Reaction of either of these with the  $\alpha$  anomer of the acceptor would give the  $\alpha\alpha$  product (Figure 2.12). The  $\alpha\beta$  product however can be formed by having the  $\beta$  glycosidic bond arise from either the glycosyl donor, or the glycosyl acceptor. One possibility is

that the  $\alpha$  fucosyl iodide is reactive enough to allow an  $S_N2$  reaction with the  $\alpha$  anomeric hydroxyl, thus forming a  $\beta$  linkage (Figure 2.13). There are two pieces of evidence which favor this explanation: first, the fucosyl iodide is the most reactive of the glycosyl iodides and second, the C-1' hydroxyl is known to be a highly nucleophilic alcohol.<sup>23</sup>

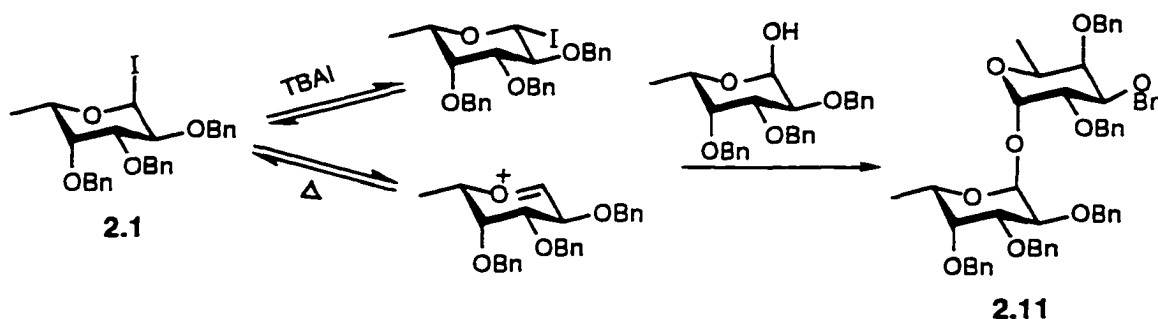


Figure 2.12. Formation of the  $\alpha\alpha$  1,1' linkage

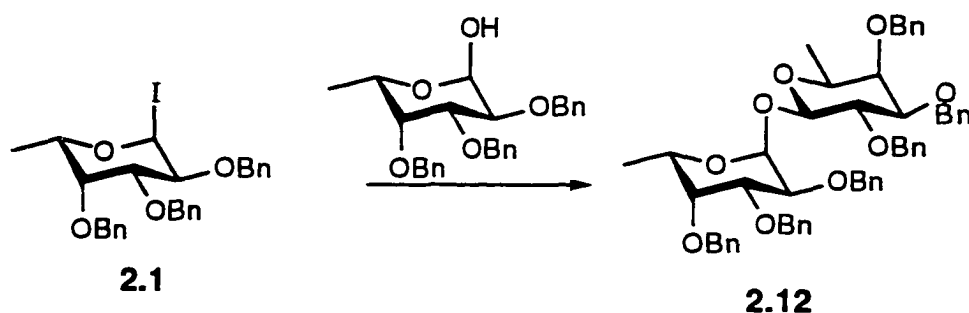


Figure 2.13. Formation of the  $\alpha\beta$  1,1' linkage *via* an  $S_N2$  mechanism

The other possibility is that the acceptor is in the  $\beta$  form when it reacts with glycosyl donor (either the oxonium ion or  $\beta$  iodide) thus forming the  $\alpha\beta$  product (Figure 2.14).

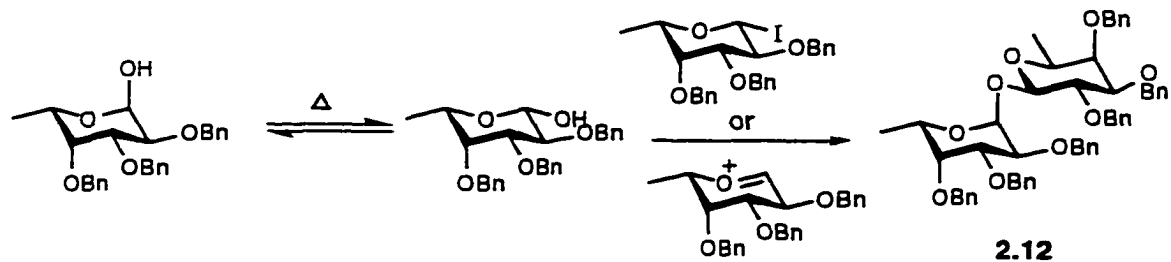


Figure 2.14. Formation of the  $\alpha\beta$  1,1' linkage *via* the  $\beta$  hydroxy anomer

In favor of this explanation, it has been demonstrated<sup>23</sup> that the  $\beta$  glycosyl alkoxide is more nucleophilic than the  $\alpha$  anomer. The alkoxide however is a different species than the neutral form present under our reaction conditions and thus a correlation between the two might not be valid.

In order to investigate these different scenarios it was thought that a  $^1\text{H}$  NMR spectrum of the acceptor in benzene would show us which anomers were present during the reaction. The  $^1\text{H}$  NMR of 2,3,4-tri-*O*-benzyl-*L*-fucopyranoside in deuterated benzene shows only the  $\alpha$  anomer. This would lend support for the  $\text{S}_{\text{N}}2$  reaction of the  $\alpha$  hydroxy anomer on the  $\alpha$  glycosyl iodide. However, the NMR was taken at room temperature in the absence of DIEA and TBAI, which might accelerate the ability of the acceptor to anomerize in such a non-polar solvent.

This reaction was also attempted using fewer equivalents of TBAI (2 vs. 10) and a lower temperature (r.t.  $\text{CH}_2\text{Cl}_2$  vs. refluxing benzene). The reaction took > 70 hours to complete but gave a 6.5 : 1  $\alpha\alpha$  :  $\alpha\beta$  ratio vs. 1.14 : 1 of the first reaction. This indicates that either less anomerization of the 1' hydroxyl occurred or that the rate of  $\text{S}_{\text{N}}2$  on the  $\alpha$  iodide is decreased. In light of all the evidence it is believed that the  $\alpha$  acceptor hydroxyl undergoes an  $\text{S}_{\text{N}}2$  reaction with the  $\alpha$  fucosyl iodide to give the

$\alpha\beta$  product, and if  $\alpha\alpha$  selectivity is desired it can be achieved by lowering the temperature and extending the reaction time.

Once it was established that we could get high  $\alpha$  selectivity in our glycosidation reactions using glycosyl iodides as the donor, we then attempted to utilize the same glycosyl iodides to specifically form the  $\beta$  linkage. In order to accomplish this task the reaction conditions were altered to favor production of the  $\beta$  glycoside. Since the glycosyl had a non-participating group at the C-2 position, the only viable mechanism that would produce a  $\beta$  linkage would be  $S_N2$  displacement of an  $\alpha$  iodide or other leaving group. This is true because either oxonium or  $\beta$  iodide reaction with a nucleophile produces the  $\alpha$  linkage. The problem that we faced was that we had shown earlier that reaction of methanol with the highly reactive galactosyl iodide in benzene was very slow, and although producing some  $\beta$  glycoside, it was not specific. Also, reaction of the glucosyl iodide with methanol did not produce any  $\beta$  glycoside. One possible reason for the sluggishness of those reactions is that the solvent used was very non-polar, thus inhibiting the type I  $S_N2$  reaction where charge is built up in the transition state (Figure 2.15). In order to facilitate the type I  $S_N2$  reaction a more polar solvent would be advantageous and might increase the rate of the reaction,<sup>24</sup> thus yielding more  $\beta$  product.

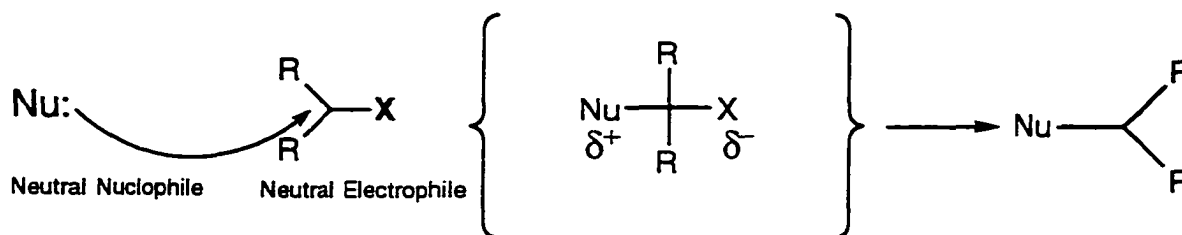


Figure 2.15. Type I  $S_N2$  mechanism

However, there is a price to be paid for the use of a more polar solvent: polar solvents also favor an  $S_N1$  mechanism by stabilizing the intermediate oxonium ion that is formed,<sup>24</sup> which would then lead to the  $\alpha$  glycoside. So in choosing a solvent to facilitate  $\beta$  glycoside formation there must be a delicate balance between facilitating the type I  $S_N2$ , and attempting not to stabilize oxonium ion formation. However, doing one without the other might not be possible.

The main reason why we can achieve  $\alpha$  selectivity in the TBAI catalyzed reactions is that the  $\beta$  iodide is a more reactive glycosyl donor than the  $\alpha$  due to the instability of the  $\beta$  iodide arising from the anomeric effect.<sup>1</sup> An idea that we explored was to take advantage of the anti-anomeric effect.<sup>25</sup> This effect arises because a positively charged substituent attached to the anomeric carbon is more stable in the  $\beta$  configuration. Therefore, a positively charged substituent at the anomeric position in the  $\alpha$  configuration should be more reactive than its  $\beta$  counterpart. If we could therefore set up an equilibrium between an  $\alpha$  and  $\beta$  positively charged moiety at the anomeric center we might be able to selectively react this with a glycosyl acceptor to form the  $\beta$  glycoside (Figure 2.16).

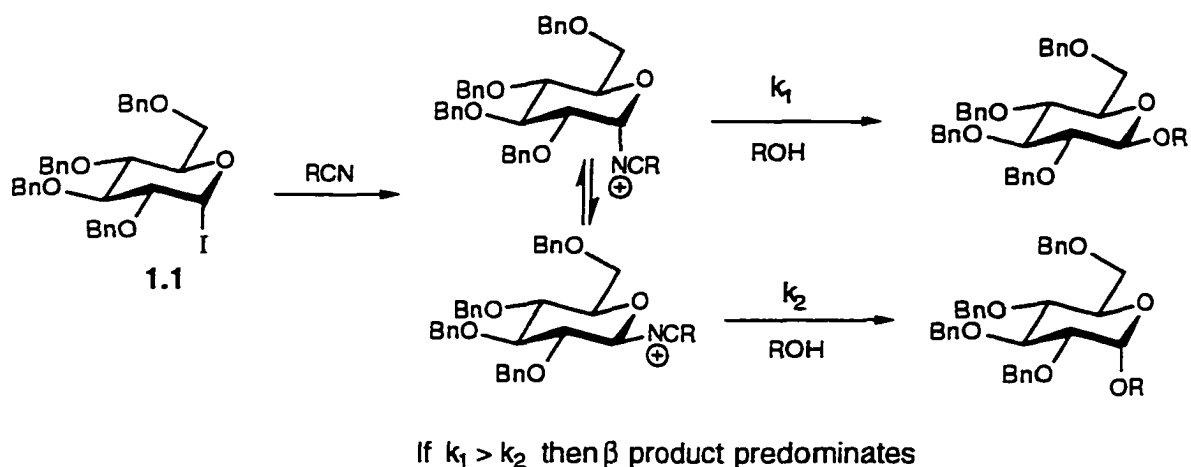


Figure 2.16. Utilization of the anti-anomeric effect to obtain  $\beta$  glycosides

Our hypothesis for setting up such an equilibrium was to utilize an  $\alpha$  nitrilium ion<sup>26</sup> that could be formed from either the  $\beta$  glycosyl iodide or the oxonium ion. To test this hypothesis the glucosyl iodide **1.1** was reacted with allyl alcohol, DIEA, and TBAI in acetonitrile (Figure 2.17). After 2 hours at room temperature a 9.8:1 ratio of  $\beta$ : $\alpha$  glycosides was obtained. In this case we had switched the selectivity from  $\alpha$  to  $\beta$ , but the cause of this selectivity was still in question.

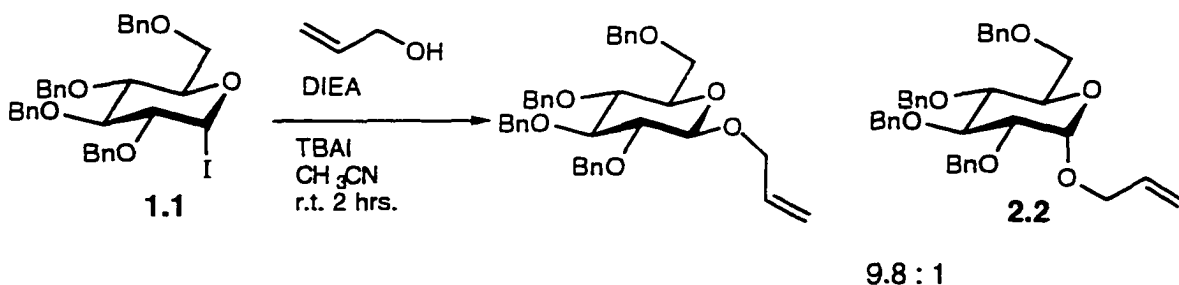


Figure 2.17. Reaction of the glucosyl iodide in acetonitrile

Two mechanisms for the  $\beta$  selectivity were probable (Figure 2.18): either the  $\alpha$  nitrilium formed and reacted with the alcohol, or due to the

increased polarity of the solvent the  $\alpha$  iodide reacted by the type I  $S_N2$  reaction mentioned earlier

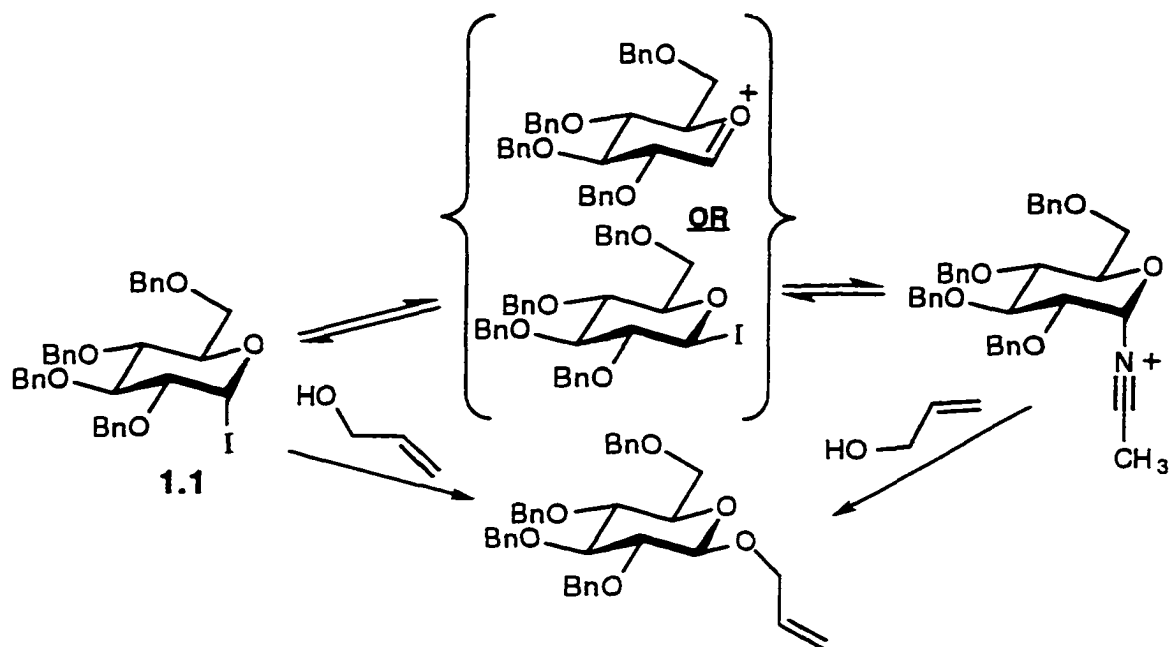


Figure 2.18. Possible mechanistic routes into the  $\beta$  glycoside

If the  $\alpha$  glucosyl iodide reacted by the type I  $S_N2$  mentioned earlier, the galactosyl iodide, shown earlier to be more reactive, might show better  $\beta$  selectivity and a faster reaction rate. However, when the galactosyl iodide **1.3** was reacted under the same conditions it yielded only the  $\alpha$  glycoside **2.3** after 45 minutes (Figure 2.19).

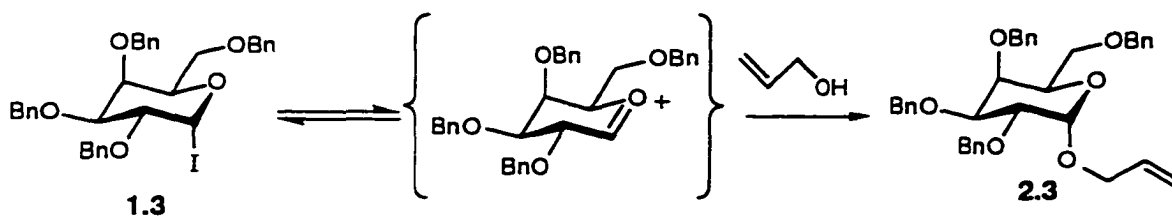
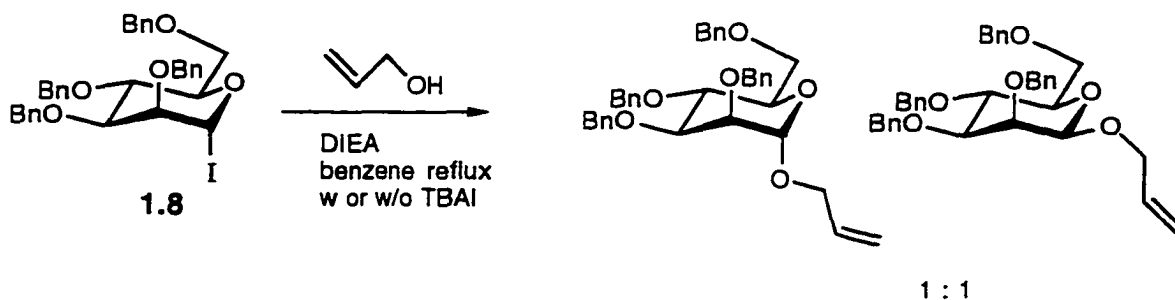


Figure 2.19. Galactosyl iodide reaction in acetonitrile

This unexpected result might be because the rate of formation of the galactosyl oxonium ion is faster than the rate of formation of the glucosyl oxonium ion, and that this galactosyl oxonium ion is then trapped by the alcohol with no nitrilium ion intermediate. Support for this theory was recently published by Deslongchamps et. al.,<sup>27</sup> who demonstrated that oxonium ions are stabilized by the presence of an axial substituent at the C-4 position of the pyranose ring, and that this stabilization is greatest if the substituent is an ether. Due to the stabilizing effect of the C-4 axial benzyl ether, the oxonium ion would be formed at a faster rate in the galactose case and due to its increased stability might exhibit selectivity for reaction with the alcohol over solvent participation by acetonitrile. Extension of these reaction conditions to the mannosyl iodide gave an approximately 1:1 ratio of  $\alpha$  and  $\beta$  anomers both in the presence and absence of TBAI (Figure 2.20).





### Figure 2.20 Reaction of the mannosyl iodide in acetonitrile

This result might be explained by an oxonium ion that is between the stability of the glucosyl and galactosyl oxonium ions, thus yielding a mixture of anomers. At this point, however, several other mechanistic explanations previously explored cannot be discounted and further research must be done to clearly demonstrate the effects of solvent and carbohydrate structure on the specificity and rate of reaction for the glycosyl iodides in polar solvents.

## CONCLUSION

The use of glycosyl iodides as effective donors in the selective synthesis of  $\alpha$  glycosidic linkages has been demonstrated. The advantages of glycosyl iodides over the corresponding bromides were shown to be the rate of reaction and the scope of glycosyl acceptors that may be employed. Initial experiments have set the stage for investigation of glycosyl iodides as donors for the construction of  $\beta$  glycosidic linkages by altering the reaction conditions while utilizing the same glycosyl iodides that have been shown to give  $\alpha$  selectivity. Future work might concentrate on expanding the variety of glycosyl acceptors used to react with the glycosyl iodides employed here.

## EXPERIMENTAL SECTION

Starting materials and reagents purchased from suppliers were used without further purification. Chemicals were obtained from the following suppliers: trimethylsilyl iodide (Fluka), tetra-*O*-benzylglucopyranose (Fluka), tetrabutylammonium cyanide (Aldrich), tetrabutylammonium azide,<sup>15</sup> sodium hexamethyldisilazane (Aldrich). Solvents were dried by distillation prior to use. Dichloromethane and toluene were dried over calcium hydride, and tetrahydrofuran was dried over sodium/benzophenone. Chromatography was performed using silica gel 60 (230-400 mesh ASTM). Mass spectrometry was performed by the University of Minnesota Mass Spectrometry Service and the University of Arizona Mass Spectrometry Facility.

**General procedure for  $\alpha$  allyl glycoside formation (2.2, 2.3, 2.4):** To a solution of the 1-*O*-acetyl-per-*O*-benzyl glycoside (0.1 mmol) in 1 mL of CH<sub>2</sub>Cl<sub>2</sub> cooled to 0°C was added trimethylsilyl iodide (0.11 mmol for glucose, fucose and 0.1 mmol for galactose). After 30 minutes the solvent was removed *in vacuo* and 1.5 mL of toluene was added and again removed *in vacuo*. 1 mL of CH<sub>2</sub>Cl<sub>2</sub> was added and the resulting solution pipetted into an already stirring solution of CH<sub>2</sub>Cl<sub>2</sub> (1 mL), allyl alcohol (0.2 mmol), DIEA (0.2 mmol) and TBAI (0.2 mmol) with molecular 4 Å sieves. The solution was then stirred for 40 minutes (fucose), 3 hours (galactose), or 2 hours reflux (glucose) and then the solvent was removed *in vacuo* and the resulting oil subjected to flash column chromatography using a 9:1 hexanes : ethyl acetate (fucose) or 6:1

(galactose, glucose) column to yield the  $\alpha$  allyl glycosides of fucose **2.4**, 62%; galactose **2.3**,<sup>28</sup> 69%; and glucose **2.2**,<sup>29</sup> 71%.  $\alpha$  allyl fucoside (**2.4**): <sup>1</sup>H NMR (250 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  1.19 (d, 3H,  $J = 6.5$  Hz), 3.32 (d, 1H,  $J = 2.7$  Hz) 3.72-3.90 (2H), 3.97-4.12 (2H), 4.23 (dd, 1H,  $J = 10.2, 3.6$  Hz), 4.28 (s, 1H), 4.42-4.61 (4H), 4.79 (d, 1H,  $J = 12.0$  Hz), 4.92 (d, 1H,  $J = 3.5$  Hz), 4.99-5.08 (2H), 5.10 (m, 1H), 5.85 (m, 1H), 7.0-7.47 (20H); <sup>13</sup>C NMR (250 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  16.9, 66.8, 68.5, 73.0, 73.4, 75.4, 77.6, 79.1, 79.4, 97.3, 116.5, 127.6, 127.7, 128.0, 128.4, 128.5, 128.6, 139.6, 139.8.

**3-O-(2,3,4,6-Tetra-O-benzyl- $\alpha$ -D-galactopyranoside)-1,2:5,6-di-O-isopropylidene- $\alpha$ -D-glucofuranose (2.6)**: To a solution of 1-O-acetyl-2,3,4,6-tetra-O-benzyl-D-galactopyranoside (140 mg, 0.24 mmol) in CH<sub>2</sub>Cl<sub>2</sub> cooled to 0°C was added trimethylsilyl iodide (34  $\mu$ L, 0.24 mmol). After 30 minutes the solvent was removed *in vacuo* and 1.5 mL of toluene was added and again removed *in vacuo*. Then 1 mL of benzene was added and the solution pipetted into an already stirring solution of diacetone glucose (48 mg, 0.18 mmol), DIEA (65  $\mu$ L, 0.37 mmol), and TBAI (137 mg, 0.37 mmol) in 1 mL of benzene with molecular 4 Å sieves. After refluxing for 5.5 hours the solvent was removed *in vacuo* and the resulting oil subjected to flash column chromatography using a 6:1 hexanes : ethyl acetate column to yield 122 mg of the  $\alpha$  anomer,<sup>30</sup> 13.7 mg of the  $\beta$  (**2.6b**) and 7 mg of the glycal (**2.6e**), for a total yield of 93% in a 9 : 1,  $\alpha$  :  $\beta$  ratio.

**3-O-(2,3,4-Tri-O-benzyl- $\alpha$ -L-fucopyranoside)-1,2:5,6-di-O-isopropylidene- $\alpha$ -D-glucofuranose (2.7)**: To a solution of 1-O-

acetyl-2,3,4-tri-*O*-benzyl-L-fucopyranoside (97 mg, 0.20 mmol) in 1 mL CH<sub>2</sub>Cl<sub>2</sub> cooled to 0°C was added trimethylsilyl iodide (29 μL, 0.20 mmol). After 20 minutes the solvent was removed *in vacuo* and 1.0 mL of toluene was added and again removed *in vacuo*. 1 mL of CH<sub>2</sub>Cl<sub>2</sub> was then added and the resulting solution pipetted into an already stirring solution of diacetone glucose (41 mg, 0.16 mmol), DIEA (55 μL, 0.31 mmol), and TBAI (116 mg, 0.31 mmol) in 1 mL of CH<sub>2</sub>Cl<sub>2</sub> with 4 Å molecular sieves. After refluxing for 3.0 hours the solvent was removed *in vacuo* and the resulting oil subjected to flash column chromatography using a 9:1 hexanes:ethyl acetate column to yield 67 mg (62%) of the α glycoside.<sup>31</sup>

**3-*O*-(2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranoside)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (2.8):** To a solution of 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-mannopyranoside (89 mg, 0.15 mmol) in 1.5 mL of CH<sub>2</sub>Cl<sub>2</sub> cooled to 0°C is added trimethylsilyl iodide (22 μL, 0.15 mmol). After 30 minutes the solvent was removed *in vacuo* and 1.5 mL of toluene was added and again removed *in vacuo*. Then 1 mL of benzene was added and the solution pipetted into an already stirring solution of diacetone glucose (31 mg, 0.18 mmol), and DIEA (40 μL, 0.24 mmol) in 1 mL of benzene with 4 Å molecular sieves. After refluxing for 5.5 hours the solvent was removed *in vacuo* and the resulting oil subjected to flash column chromatography using a 6:1 hexanes:ethyl acetate column to yield 62 mg (67%) of the α glycoside along with 24 mg of the glycal (1.4). α glycoside; <sup>1</sup>H NMR (250 MHz, C<sub>6</sub>D<sub>6</sub>) δ 1.06 (s, 1H), 1.21 (s, 3H), 1.30 (s, 1H), 1.39 (s, 3H), 3.76 (d, 2H, J = 3.6 Hz), 3.92 (t, 1H, J = 2.1 Hz), 4.03-4.14 (4H), 4.19-4.41 (9H), 4.62 (s, 2H), 4.86 (d, 1H, J = 3.6 Hz), 4.97 (d,

1H, J = 11.2 Hz), 5.40 (d, 1H, J = 1.7 Hz), 5.90 (d, 1H, J = 3.6 Hz), 7.07-7.43 (20H); <sup>13</sup>C (250 MHz, C<sub>6</sub>D<sub>6</sub>) δ 25.6, 26.2, 29.9, 67.9, 70.1, 72.2, 72.8, 73.1, 73.5, 73.7, 75.2, 75.5, 75.6, 80.3, 81.7, 84.2, 99.7, 105.8, 109.4, 127.4, 127.6, 127.7, 127.8, 128.0, 128.3, 128.4, 128.5.

**3-O-(2,3,4,6-Tetra-O-benzyl-α-D-glucopyranoside)-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (2.9):** To a solution of 1-O-acetyl-2,3,4,6-tetra-O-benzyl-D-mannopyranoside (219 mg, 0.38 mmol) in 1.5 mL of CH<sub>2</sub>Cl<sub>2</sub> cooled to 0°C was added trimethylsilyl iodide (54 μL, 0.38 mmol). After 30 minutes the solvent was removed *in vacuo* and 2.0 mL of toluene was added and again removed *in vacuo*. Then 1.5 mL of benzene was added and the solution pipetted into an already stirring solution of diacetone glucose (75 mg, 0.29 mmol), TBAI (214 mg, 0.58 mmol), and DIEA (100 μL, 0.24 mmol) in 1 mL of benzene with 4 Å molecular sieves. After refluxing for 1.5 hours the solvent was removed *in vacuo* and the resulting oil subjected to flash column chromatography using a 7:1 hexanes:ethyl acetate column to yield 102 mg (45%) of the α glycoside<sup>32</sup> along with 86 mg of the glycal (1.4).

**1,6-Anhydro-3,4-O-isopropylidene-2-O-(2,3,4-tri-O-benzyl-α-L-fucopyranoside)-D-galactopyranose (2.10):** To a solution of 1-O-acetyl-2,3,4-tri-O-benzyl-L-fucopyranoside (231 mg, 0.49 mmol) in 2 mL CH<sub>2</sub>Cl<sub>2</sub> cooled to 0°C was added trimethylsilyl iodide (74 μL, 0.52 mmol). After 10 minutes the solvent was removed *in vacuo* and 1.5 mL of toluene is added and again removed *in vacuo*. 1 mL of CH<sub>2</sub>Cl<sub>2</sub> was then added and the resulting solution added to an already stirring solution of 1,6-anhydro-

3,4-*O*-isopropylidene-D-galactopyranose (75 mg, 0.37 mmol), TBAI (344 mg, 0.93 mmol), DIEA (110  $\mu$ L, 0.63 mmol), and 4 Å molecular sieves in 1 mL of CH<sub>2</sub>Cl<sub>2</sub>. The solution was stirred for 5.5 hours before the solvent was removed *in vacuo* and the resulting oil subjected to flash column chromatography using a 3:1 hexanes:ethyl acetate column to yield 209 mg (91%) of the  $\alpha$  glycoside; <sup>1</sup>H NMR (250 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  1.08-1.12 (m, 6H), 1.37 (s, 3H), 3.30 (s, 1H), 3.42 (t, 1H, *J* = 6.1 Hz), 3.91-4.01 (m, 3H), 4.09-4.35 (m, 6H), 4.42-4.59 (m, 5H), 4.68 (d, 1H, *J* = 11.9), 4.95 (d, 1H, *J* = 6.8), 4.98 (s, 1H), 5.80 (s, 1H); <sup>13</sup>C (250 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  16.8, 24.1, 25.8, 63.3, 67.4, 69.7, 72.5, 73.2, 75.3, 75.4, 77.2, 78.6, 78.8, 79.5, 99.7, 101.1, 108.4, 127.6, 127.8, 128.0, 128.4, 128.5, 139.4.

**1-*O*-(2,3,4-Tri-*O*-benzyl- $\alpha$ -L-fucopyranoside)-2,3,4-tri-*O*-benzyl- $\alpha$ -L-fucopyranoside (2.11) and 1-*O*-(2,3,4-tri-*O*-benzyl- $\beta$ -L-fucopyranoside)-2,3,4-tri-*O*-benzyl- $\alpha$ -L-fucopyranoside (2.12)** : To a solution of 1-*O*-acetyl-2,3,4-tri-*O*-benzyl-L-fucopyranoside (100 mg, 0.21 mmol) in 1.5 mL CH<sub>2</sub>Cl<sub>2</sub> cooled to 0°C was added trimethylsilyl iodide (30  $\mu$ L, 0.21 mmol). After 20 minutes the solvent was removed *in vacuo* and 1.5 mL of toluene was added and again removed *in vacuo*. 1 mL of benzene was added and the resulting solution pipetted into an already stirring solution of 2,3,4-tri-*O*-benzyl-L-fucopyranoside (70 mg, 0.16 mmol), TBAI (600 mg, 1.62 mmol), and DIEA (56 mL, 0.32 mmol) preheated to reflux in 1 mL of benzene with 4 Å molecular sieves. The reaction was refluxed for 1 hour and then the solvent was removed *in vacuo* and the resulting oil subjected to flash column chromatography using a 7:1 hexanes:ethyl acetate column to yield 66 mg of the  $\alpha\alpha$  (2.11), 58 mg

of the  $\alpha\beta$  (2.12), and 26 mg of the glycal (2.11e). The overall yield was 90% with a 1.14 : 1,  $\alpha\alpha$  :  $\alpha\beta$  ratio of anomers.  $\alpha\alpha$  Anomer (2.11):  $^1\text{H}$  NMR (250 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  1.25 (d, 6H,  $J = 6.5$  Hz), 3.40 (d, 2H,  $J = 1.5$  Hz), 4.14 (dd, 2H,  $J = 10.2, 2.8$  Hz), 4.29 (dd, 2H,  $J = 10.1, 3.5$  Hz), 4.35 (q, 2H,  $J = 6.6$  Hz), 4.48 (d, 4H,  $J = 11.5$  Hz), 4.56 (d, 2H,  $J = 8.5$  Hz), 4.60 (d, 2H,  $J = 8.5$  Hz), 4.71 (d, 2H,  $J = 11.7$  Hz), 4.98 (d, 2H,  $J = 11.3$  Hz), 5.50 (d, 2H,  $J = 3.5$  Hz, H-1, H-1'), 7.00-7.40 (m, 20H);  $^{13}\text{C}$  (250 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  17.1, 67.2, 73.0, 73.4, 75.4, 77.2, 78.7, 79.9, 94.2, 127.6, 127.7, 128.0, 128.3, 128.4, 128.6; HRFABMS calculated for  $\text{C}_{54}\text{H}_{57}\text{O}_9$ , 849.4003, found 849.4031 (M-H).  $\alpha\beta$  Anomer (2.12):  $^1\text{H}$  NMR (250 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  1.22 (d, 3H,  $J = 6.3$  Hz), 1.30 (d, 3H,  $J = 6.3$  Hz), 3.10 (q, 1H,  $J = 7.2$  Hz), 3.18 (d, 1H,  $J = 2.8$  Hz), 3.33 (dd, 1H,  $J = 9.7, 2.6$  Hz), 3.37 (s, 1H), 4.07-4.19 (m, 2H), 4.26 (dd, 1H,  $J = 10.3, 3.3$  Hz), 4.40-4.72 (m, 10H), 4.82 (d, 1H,  $J = 11.6$  Hz), 4.99 (d, 2H,  $J = 11.4$  Hz), 5.33 (d, 1H,  $J = 11.8$  Hz), 5.39 (d, 1H,  $J = 3.5$  Hz, H-1<sup>a</sup>), 6.95-7.45 (m, 20H);  $^{13}\text{C}$  (250 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  16.8, 17.2, 67.7, 70.7, 73.1, 73.3, 74.9, 75.2, 75.3, 77.1, 77.5, 78.8, 79.7, 80.1, 82.9, 100.4, 104.2, 127.2, 127.4, 127.6, 127.9, 128, 128.4, 128.6, 139.6, 139.7; HRFABMS calculated for  $\text{C}_{54}\text{H}_{57}\text{O}_9$ , 849.4003, found 849.4031 (M-H).

## CHAPTER 3

# Glycosyl Iodides in Solid Phase Oligosaccharide Synthesis



## INTRODUCTION

Solid phase organic synthesis was initially associated with the construction of peptide bonds, but in the past few decades applications of this technique have been described across much of the spectrum of organic synthesis.<sup>33</sup> The construction of glycosidic bonds on a solid support has received attention as a possible route to complex oligosaccharides with great efficiency. Several reviews of solid phase oligosaccharide synthesis have been published and demonstrate the progress that has been achieved in this area.<sup>34,35</sup> Although glycosyl halides historically are among the most widely used glycosyl donors in solution phase synthesis, their use in solid phase synthesis has been somewhat limited.

The first report of a solid phase oligosaccharide synthesis was by C. Schuerch<sup>36</sup> in 1971 where a glycosyl bromide was used as the donor. In this report, no promoter was used and simple alcoholysis was the glycosidation method with an allylic alcohol (Figure 3.1) used as the linker to the polystyrene support.

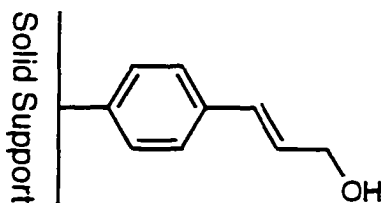


Figure 3.1. Polystyrene support of first solid phase oligosaccharide synthesis

High coupling yields were obtained in these reactions, but the reaction times were extremely slow, several days, and large excesses of the donor were needed, approximately 5 equivalents. The  $\alpha:\beta$  ratio for the coupling reaction was not determined. Other groups followed Schuerch's approach using glycosyl bromides as donors by varying the method of attachment to the solid support or using various heavy metal promoters.<sup>35</sup> However, none of the methods that utilize glycosyl halides have achieved all the desired goals of an ideal solid phase oligosaccharide synthesis: high coupling efficiency, short reaction times, high stereocontrol, efficient release from the solid support, and production of the free oligosaccharide once released (i.e. no linker).

## Results and Discussion

Our work with glycosyl iodides as donors inspired us to investigate them as potential donors for use in solid phase oligosaccharide synthesis for several reasons: 1) glycosyl iodides are readily accessible, 2) short reaction times are needed for glycosidation, 3) no heavy metal salts are needed, 4) the reaction conditions are mild and basic, 5) the reaction proceeds in benzene which has excellent resin swelling capability and 6) high anomeric selectivity is achieved.

In order to design a solid phase synthetic strategy there are several aspects that must be considered: choice of glycosidation method, direction of oligosaccharide synthesis (Figure 3.2), choice of protecting groups, and type of support (with consideration being given to both attachment and cleavage). In determining our direction of synthesis, it was thought that

addition of the preformed glycosyl iodide to an acceptor alcohol attached to the resin would achieve two goals: 1) spare the resin and any new glycosidic linkages exposure to TMSI and 2) any decomposition of the glycosyl iodide would be eliminated upon washing.

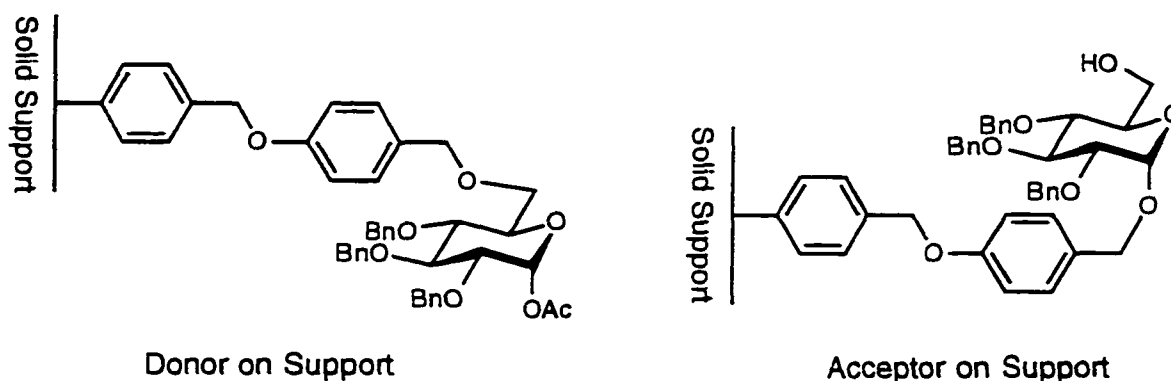


Figure 3.2. Direction of solid phase oligosaccharide synthesis

Benzyl groups were chosen as protecting for those hydroxyls not participating in further couplings, and acetyl groups as temporary protection for those hydroxyls at which future couplings would occur. The benzyl groups afford good solubility of the carbohydrate in benzene, and are stable to the reaction conditions employed throughout the synthesis. The acetyl group was chosen for its easy and quantitative removal under basic conditions, its stability toward treatment with TMSI, and because its presence or absence can be monitored by FTIR of the resin.

In choosing the solid support, we tried to find a resin that was commercially available or easily accessible, had a free primary hydroxyl for attachment, mild cleavage conditions, and upon release would yield the free carbohydrate or a suitably protected anomeric hydroxyl. The Wang

resin was initially chosen, having *p*-methoxybenzyl alcohol as its attachment to the polystyrene backbone (Figure 3.3).

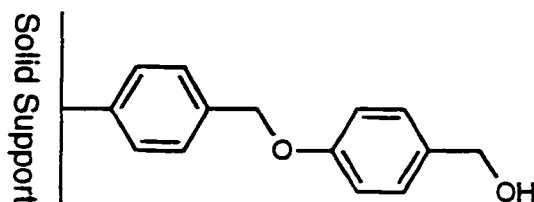


Figure 3.3. Wang resin

The Wang resin is cheap, commercially available, has a primary benzylic hydroxyl, and is in essence a *p*-methoxybenzyl protecting group. We hoped that mild conditions could be found to cleave the carbohydrate from the resin (*p*-alkoxybenzyl group) without cleaving the benzyl groups on the carbohydrate.

In order to demonstrate our ability to achieve an iterative synthesis with the glycosyl iodides, we first accomplished a solution phase synthesis of a 1,6 linked dimer of glucose. Starting from the readily available 1,6-di-*O*-acetyl-2,3,4-tri-*O*-benzylglucopyranoside (Figure 3.4),<sup>37</sup> we formed the allyl glycoside by reaction with TMSI followed by the addition of allyl alcohol and TBAI to give **3.1** in 20 minutes with a 70% yield.

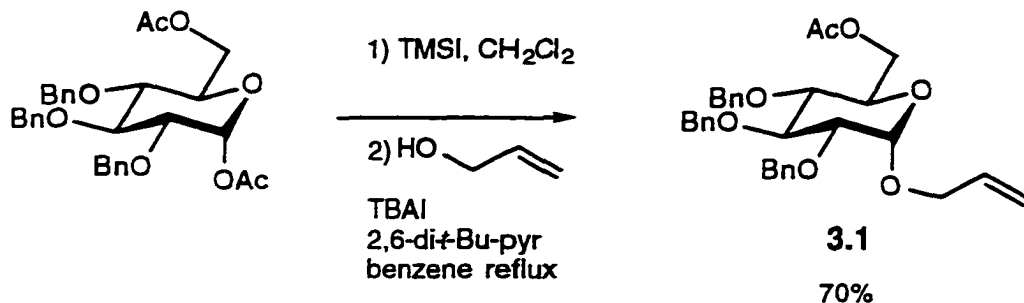


Figure 3.4. Formation of the allyl glycoside

This result was very encouraging as the limiting reagent was the glycosyl iodide which was decomposing, but when applied to solid phase the limiting reagent would be the resin hydroxyl and excess iodide would be used. The reaction time also indicated that efficient coupling to the resin might occur. After deacetylation of the C-6 acetate with *t*-butoxide/*t*-butanol in THF the resulting alcohol was reacted with the glycosyl iodide from 1,6-di-*O*-acetyl-2,3,4-tri-*O*-benzylglucopyranoside to give **3.2** in 1 hour with a 78% yield (Figure 3.5).

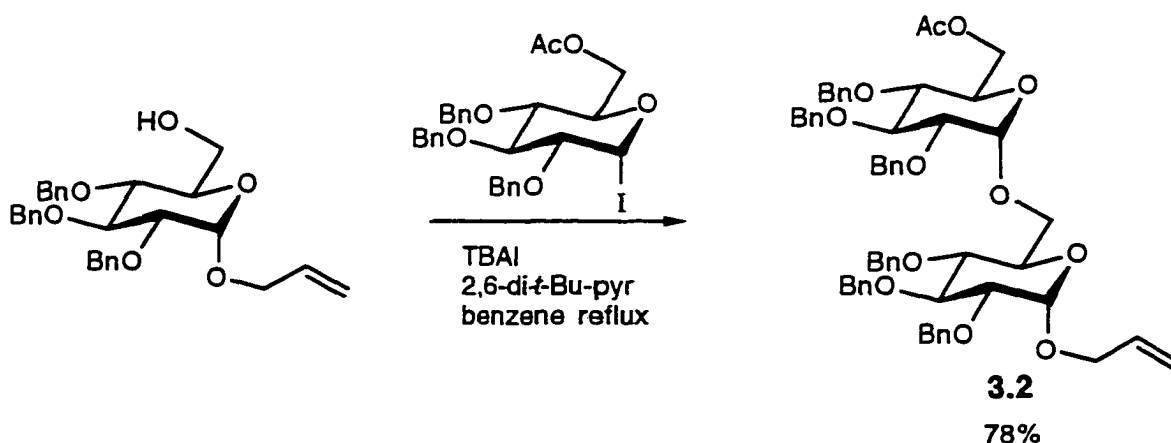


Figure 3.5. 1,6-Dimer formation

Both glycosidations were highly stereoselective as no  $\beta$  glycoside was observed in either case.

Having shown the ability to have an iterative process of glycosidation, deprotection, and glycosidation we then reacted the glycosyl iodide from 1,6-di-*O*-acetyl-2,3,4-tri-*O*-benzylglucopyranoside with the Wang resin in refluxing  $\text{CH}_2\text{Cl}_2$  for 2 hours with TBAI. An FTIR spectrum of the resin in a KBr pellet showed a carbonyl stretch that was not evident in the resin alone, indicating that some coupling had occurred. Treatment of this resin bound sugar with 0.5 M NaOMe/MeOH in THF for 2 hours followed by washing with THF:AcOH and 15-crown-5 gave the deacetylated resin as evidenced by the absence of the carbonyl stretch in an FTIR spectrum of a KBr pellet of the resin.

2,3,4,6-Tetra-*O*-benzylglucose attached to the Wang resin was then used to test possible cleavage conditions. Several cleavage conditions were attempted: DDQ,  $\text{I}_2$ , TFA, CAN, NBS,  $\text{BF}_3(\text{Et}_2\text{O})$ , TMSI; and monitored by TLC. DDQ, TFA, CAN, NBS and  $\text{BF}_3(\text{Et}_2\text{O})$  gave little or no cleavage product,  $\text{I}_2$  gave a small amount of cleavage product as the glycosyl iodide and TMSI worked well giving a large amount of the glycosyl iodide (Figure 3.6). The unexpected formation of the glycosyl iodide can be advantageous, as now this iodide may be further reacted either with another acceptor or simply quenched with water to give the free hydroxyl.

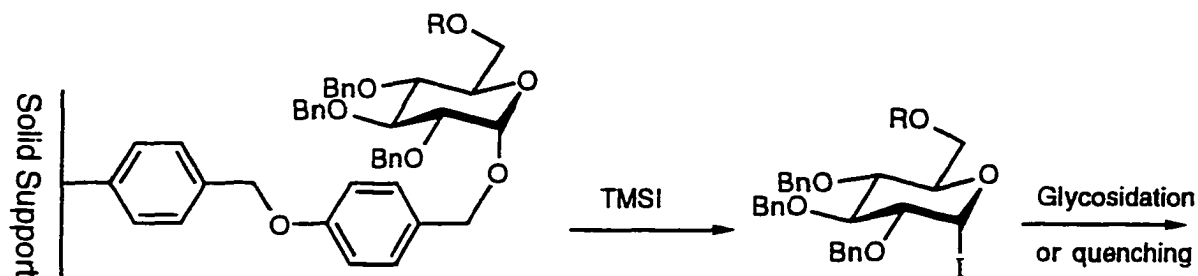


Figure 3.6. TMSI cleavage of Wang resin

The use of excess TMSI for cleavage (the use of excess is done to ensure complete reaction for most solid phase reactions) does have some disadvantages: 1) glycosidic bonds may be cleaved and 2) benzyl protecting groups might be cleaved. For these reasons we sought to develop a new resin/linker combination that exemplifies all the qualities of the Wang resin, but has milder cleavage conditions.

The trityl resin with a 1,4-benzenedimethanol linker (Figure 3.7) seemed a unique combination that might satisfy our requirements for an ideal solid support.

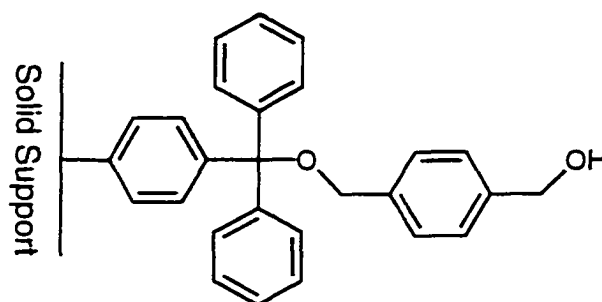


Figure 3.7. Trityl resin support

This support again has a primary benzylic hydroxyl for attachment, but the cleavage conditions are very mild (e.g. 5% TFA in  $\text{CH}_2\text{Cl}_2$ ), and

would yield a benzyl-like protecting group at the anomeric center that could be removed along with the other benzyl groups upon final deprotection. The trityl chloride resin is commercially available and reaction with commercially available 1,4-benzenedimethanol in pyridine should afford the starting resin.

## **Conclusion**

Solution phase synthesis of a 1,6 dimer of glucose has been achieved through the use of glycosyl iodides in an iterative process suitable for solid phase synthesis. Glycosyl iodides have been shown to react with Wang resin and deprotection of the acetyl group has been shown by FT-IR monitoring. TMSI was shown to cleave the carbohydrate from Wang resin with formation of a glycosyl iodide. Future work in this area will use trityl resin with a 1,4-benzenedimethanol linker to afford mild cleavage conditions, along with a highly reactive hydroxyl that is distanced from the resin core for efficient coupling.

## **Experimental Section**

Starting materials and reagents purchased from suppliers were used without further purification. Chemicals were obtained from the following suppliers: trimethylsilyl iodide (Fluka), Wang resin (NOVA Biochem), Trityl resin (NOVA Biochem), 1,4-benzenedimethanol (Aldrich). Solvents were dried by distillation prior to use. Dichloromethane and toluene were dried over calcium hydride, and tetrahydrofuran was dried over



sodium/benzophenone. Chromatography was performed using silica gel 60 (230-400 mesh ASTM). Mass spectrometry was performed by the University of Minnesota Mass Spectrometry Service and the University of Arizona Mass Spectrometry Facility.

**Allyl 6-*O*-acetyl-2,3,4-tri-*O*-benzyl- $\alpha$ -D-glucopyranoside (3.1):**

To a solution of the 1,6-di-*O*-acetyl-2,3,4-tri-*O*-benzyl- $\alpha$ -D-glucopyranoside (281 mg, 0.525 mmol) in 3 mL of CH<sub>2</sub>Cl<sub>2</sub> cooled to 0°C was added trimethylsilyl iodide (82  $\mu$ L, 0.578 mmol). After 30 minutes the solvent was removed *in vacuo* and 2.0 mL of toluene was added and again removed *in vacuo*. 1 mL of benzene was added and the resulting solution pipetted into an already stirring solution of benzene (1 mL), allyl alcohol (79  $\mu$ L, 1.15 mmol), 2,6-di-*t*-butylpyridine (174  $\mu$ L, 0.787 mmol) and TBAI (388 mg, 1.05 mmol) with molecular 4 Å sieves. The solution was then refluxed for 20 minutes and the solvent was removed *in vacuo*. The resulting oil was subjected to flash column chromatography using 6:1 hexanes:ethyl acetate to give 195 mg (70%) of the  $\alpha$  glycoside. <sup>1</sup>H NMR (250 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  1.97 (s, 3H), 3.42-3.54 (2H), 3.84 (dq, 1H, *J* = 10.0, 2.3 Hz), 3.91-4.29 (6H), 4.52 (d, 1H, *J* = 10.8), 4.60 (d, 1H, *J* = 12.1), 4.70-4.86 (5H), 4.98 (d, 1H, *J* = 10.8 Hz), 5.18 (dd, 1H, *J* = 10.3, 0.8 Hz), 5.27 (dd, 1H, *J* = 17.2, 1.3 Hz), 5.89 (m, 1H), 7.19-7.34 (15H); <sup>13</sup>C (250 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  20.7, 62.9, 68.2, 68.6, 73.0, 74.9, 75.6, 76.5, 77.0, 77.1, 77.5, 79.7, 81.9, 95.4, 118.2, 127.5, 127.8, 127.8, 127.9, 128.3, 133.4, 137.7, 138.5, 170.5.

**Allyl 6-*O*-(6-*O*-acetyl-2,3,4-tri-*O*-benzyl- $\alpha$ -D-glucopyranoside)-2,3,4-tri-*O*-benzyl- $\alpha$ -D-glucopyranoside (3.2):** To a solution of the 1,6-di-*O*-acetyl-2,3,4-tri-*O*-benzyl- $\alpha$ -D-glucopyranoside (158 mg, 0.295 mmol) in 2 mL of CH<sub>2</sub>Cl<sub>2</sub> cooled to 0°C was added trimethylsilyl iodide (46  $\mu$ L, 0.325 mmol). After 30 minutes the solvent was removed *in vacuo* and 1 mL of toluene was added and again removed *in vacuo*. 1 mL of benzene was added and the resulting solution pipetted into an already stirring solution of benzene (1 mL), allyl 2,3,4-tri-*O*-benzyl- $\alpha$ -D-glucopyranoside (96 mg, 0.196 mmol), 2,6-di-*t*-butylpyridine (108  $\mu$ L, 0.489 mmol) and TBAI (209 mg, 0.59 mmol) with molecular 4 Å sieves. The solution was refluxed for 1 hour and then the solvent was removed *in vacuo*. The resulting oil was subjected to flash column chromatography using 6:1 hexanes:ethyl acetate to give 145 mg (78%) of the  $\alpha$  glycoside. <sup>1</sup>H NMR (250 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  1.65 (s, 3H), 3.49-3.61 (3H), 3.75 (d, 1H, *J* = 11.5 Hz), 3.83-4.15 (6H), 4.23-4.61 (9H), 4.77-5.12 (10H), 5.35 (m, 1H), 5.84 (m, 1H), 7.0-7.4 (30H); <sup>13</sup>C (250 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  20.4, 63.3, 66.2, 68.4, 69.4, 71.4, 72.4, 72.9, 75.0, 75.1, 75.5, 75.6, 77.9, 78.2, 80.9, 81.0, 82.1, 82.4, 96.3, 97.1, 117.3, 127.6, 127.7, 127.8, 127.9, 128.0, 128.4, 128.5, 128.7, 134.4, 139.7.

**Trityl resin with 1,4-benzenedimethanol linker:** 500 mg of a 0.46 mmol/g trityl resin (0.23 mmol) was heated for 2 days in 10 mL of pyridene at 60 °C with 1,4-benzenedimethanol linker (800 mg, 5.75 mmol). Methanol was then added to quench the remaining active sites followed by washing with CH<sub>2</sub>Cl<sub>2</sub>.

**Appendix A**  
 **$^1\text{H}$  and  $^{13}\text{C}$  NMR Spectra**

Bruker

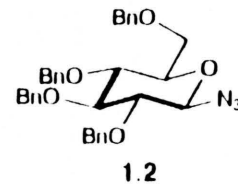
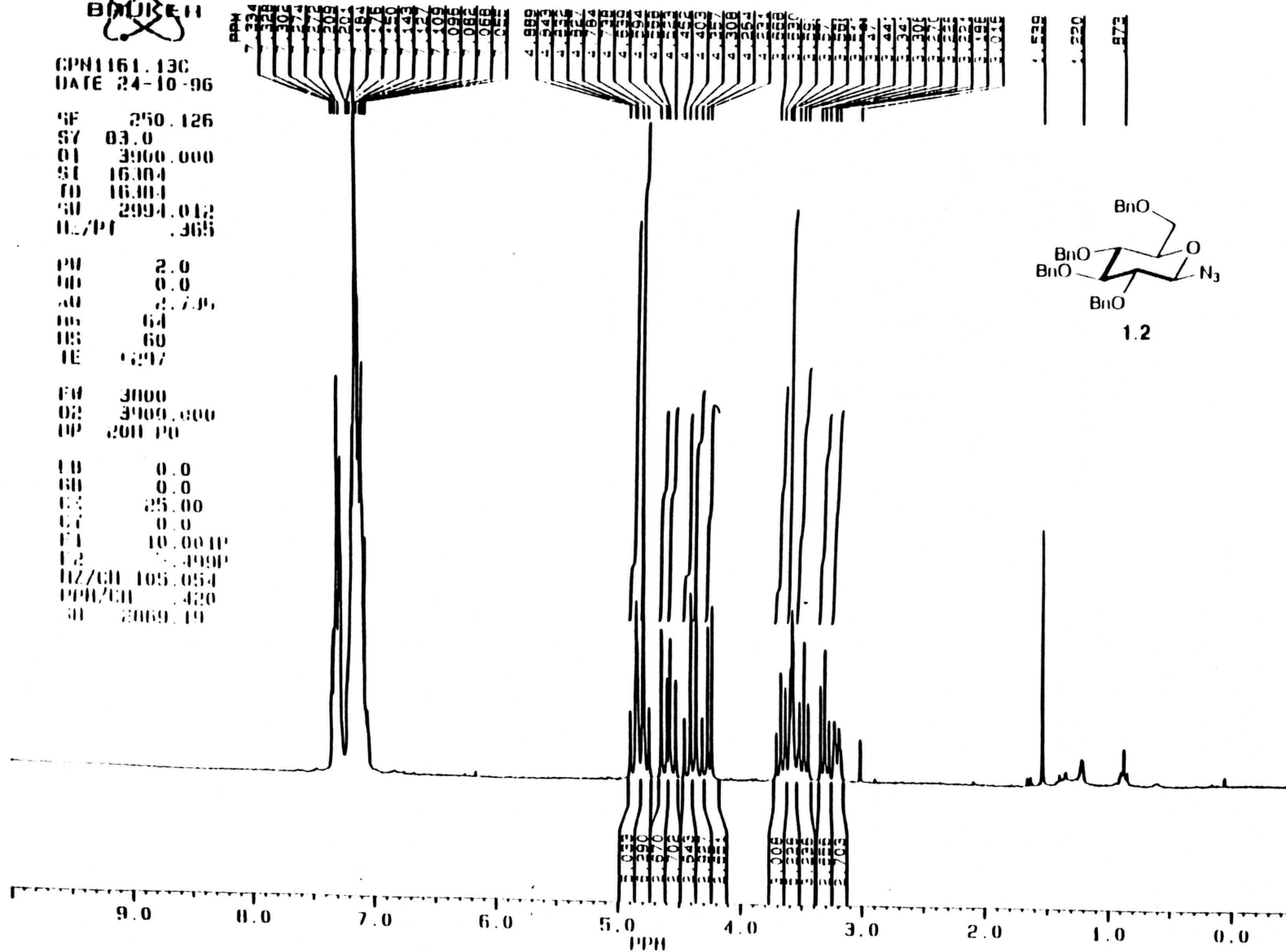
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PPM

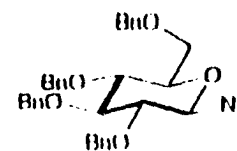
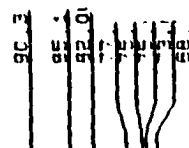
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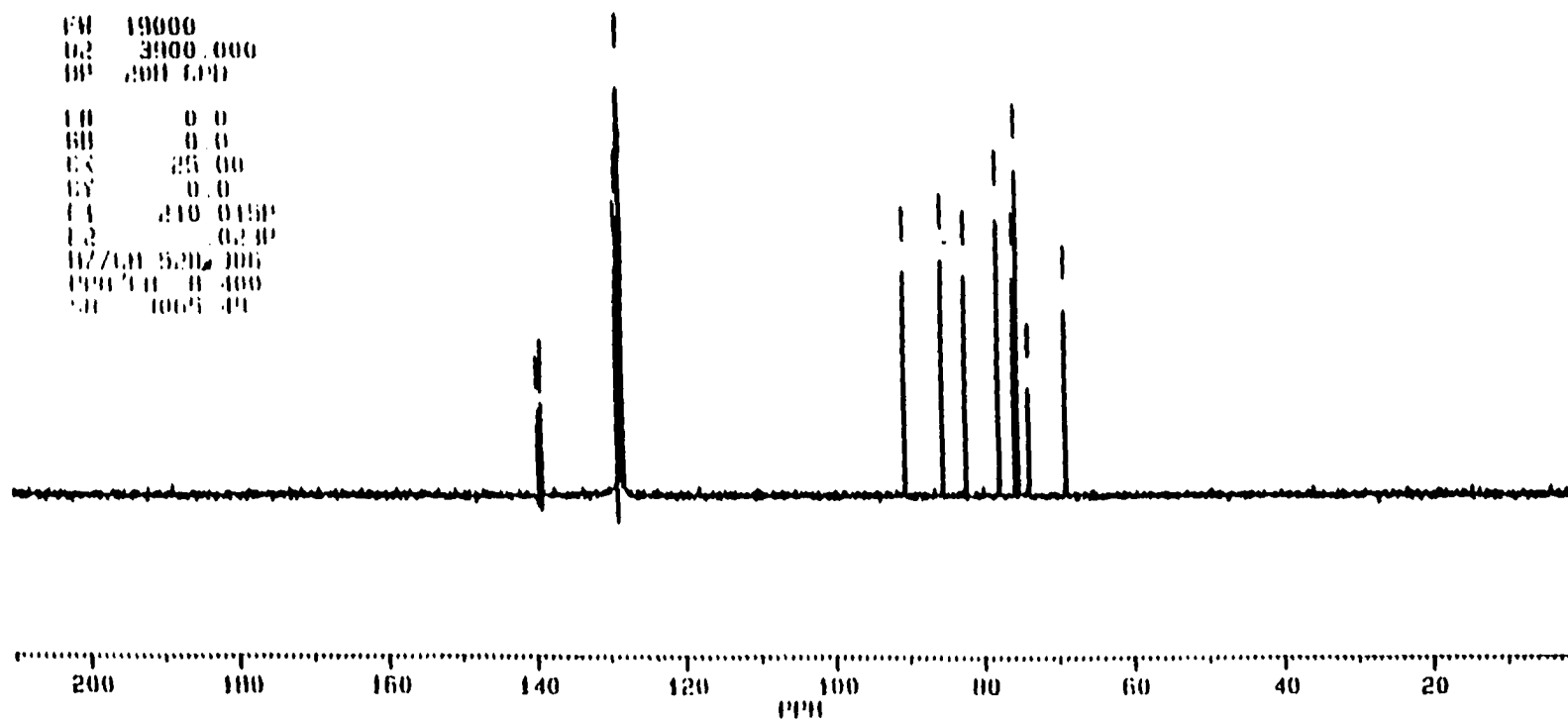
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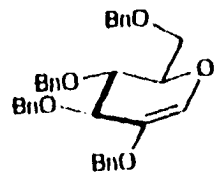
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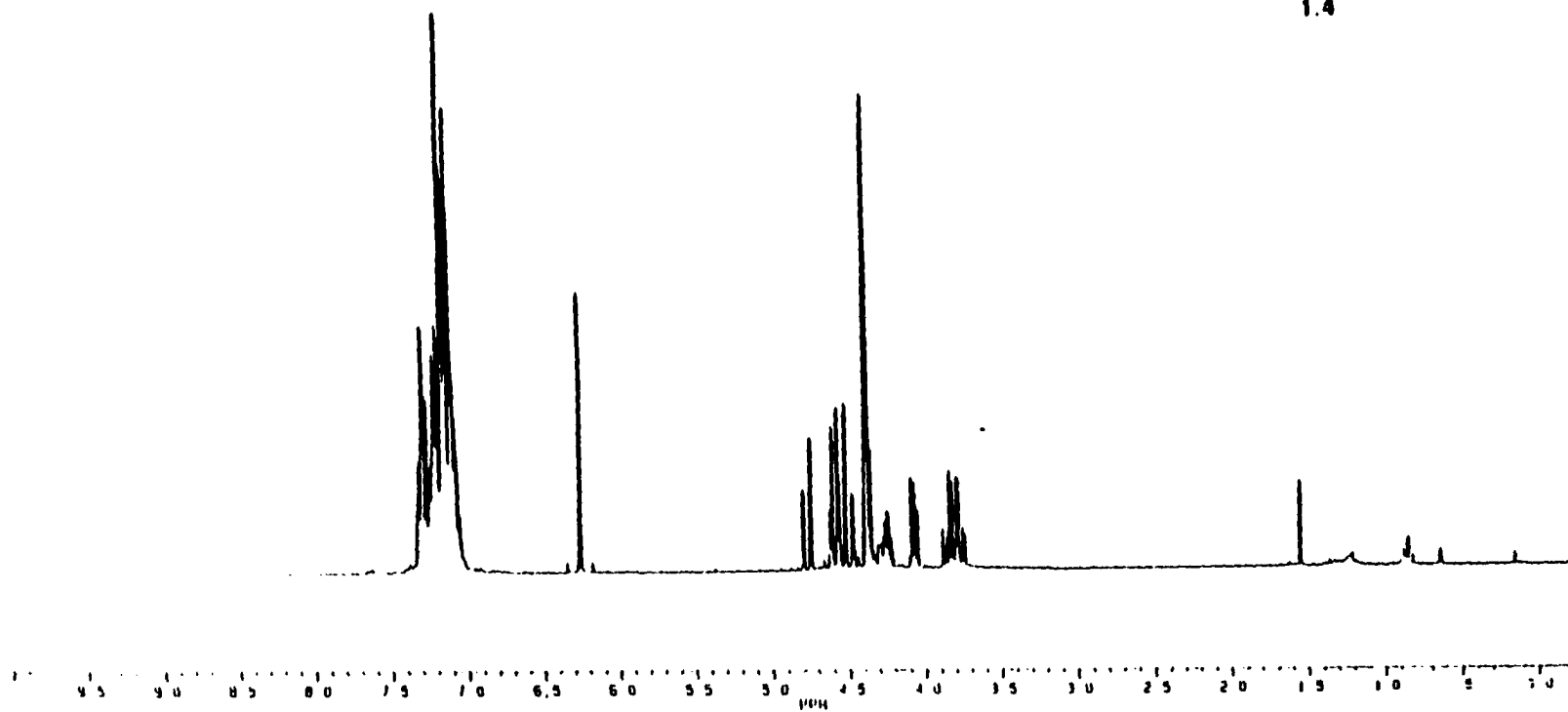


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1.4



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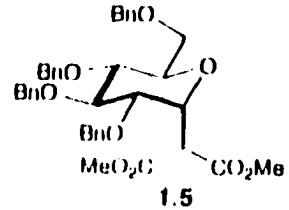
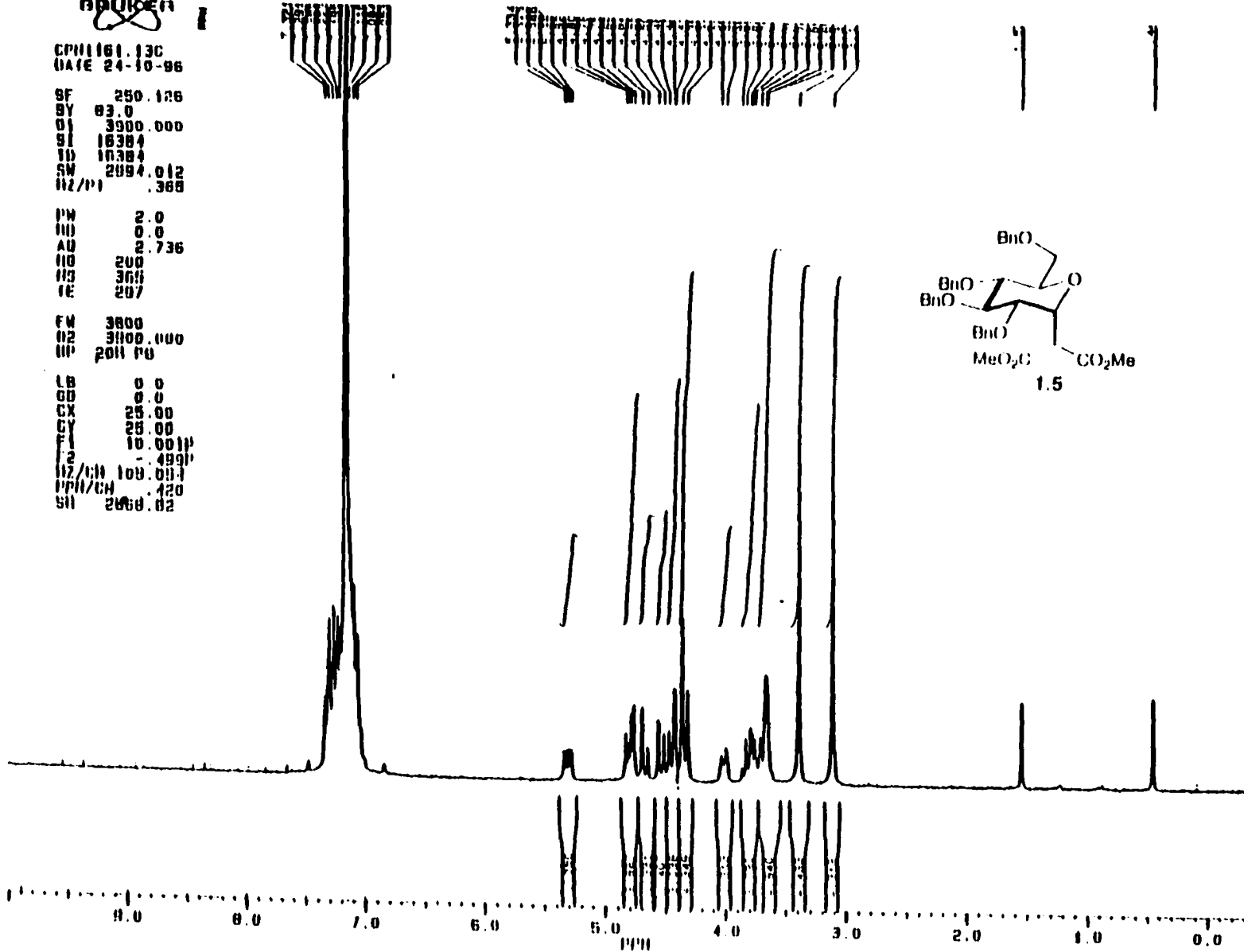
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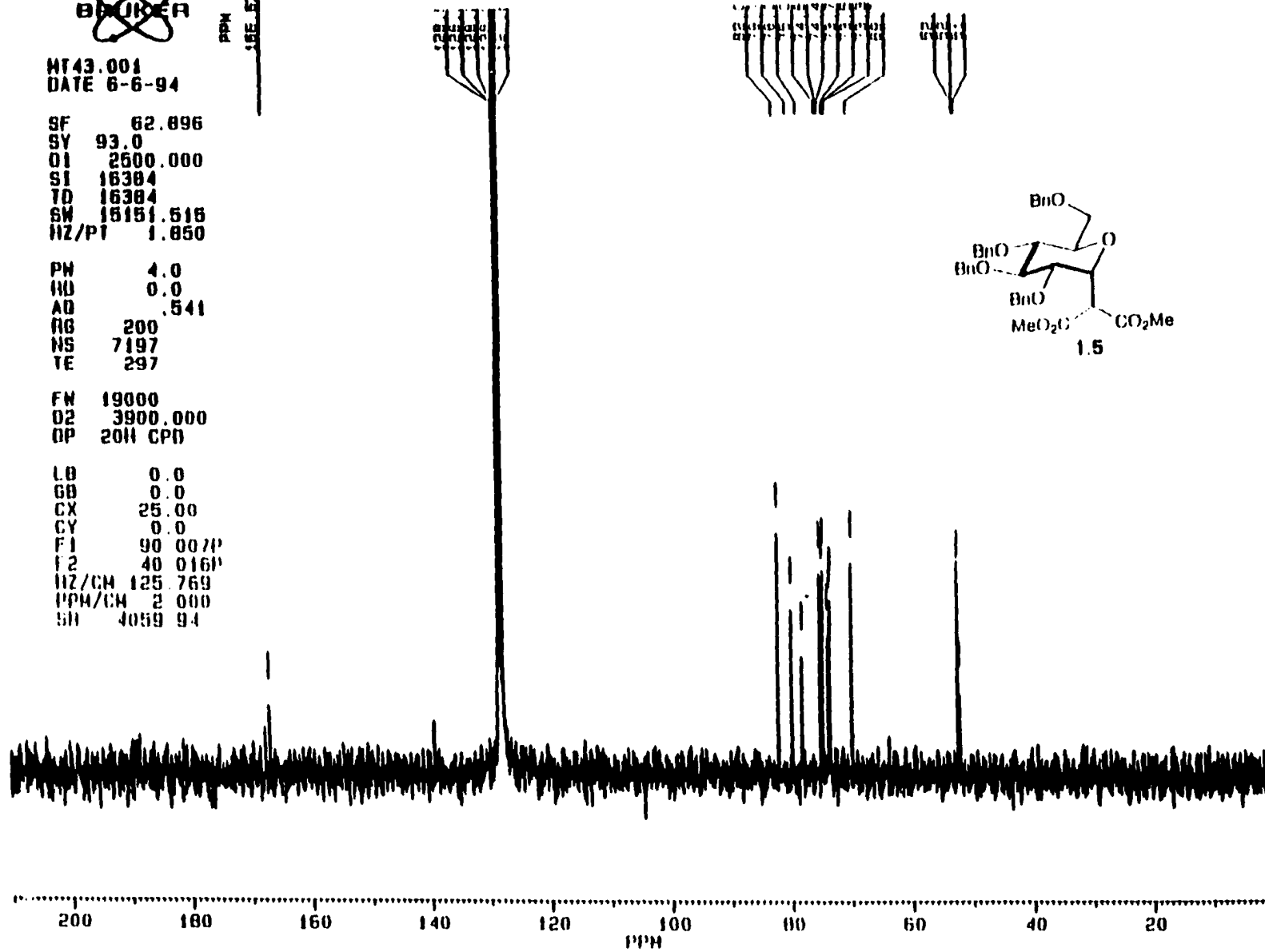
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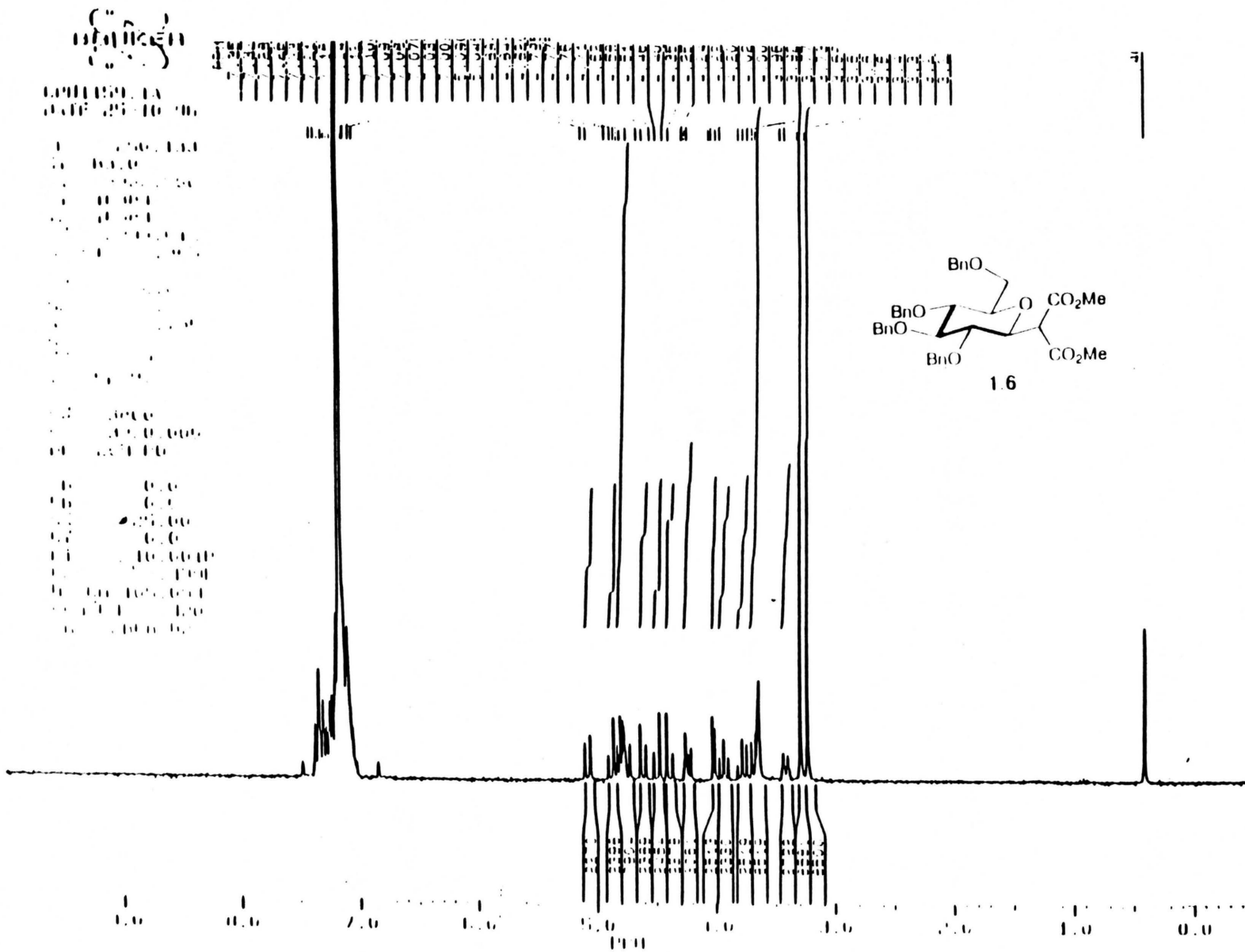
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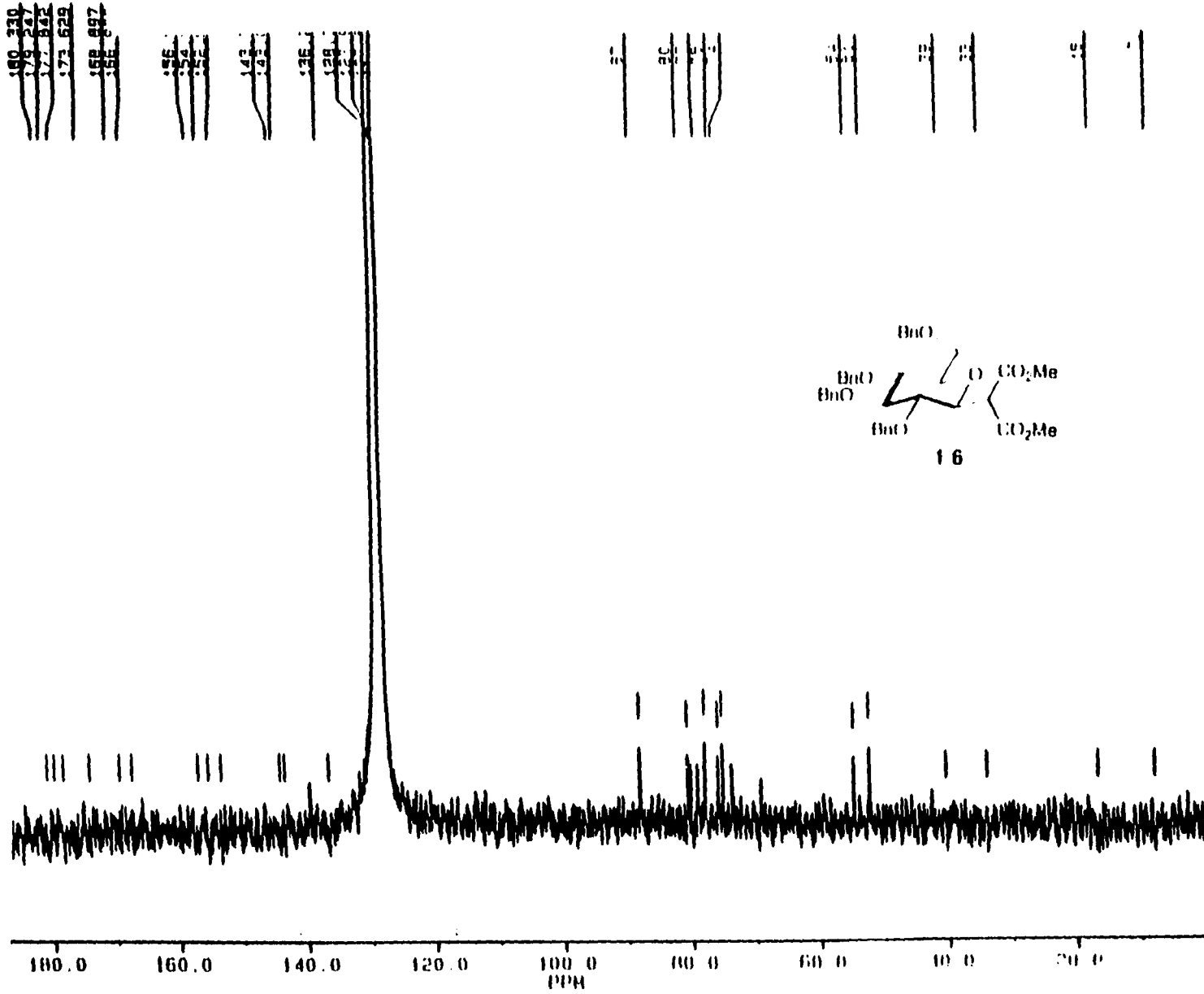
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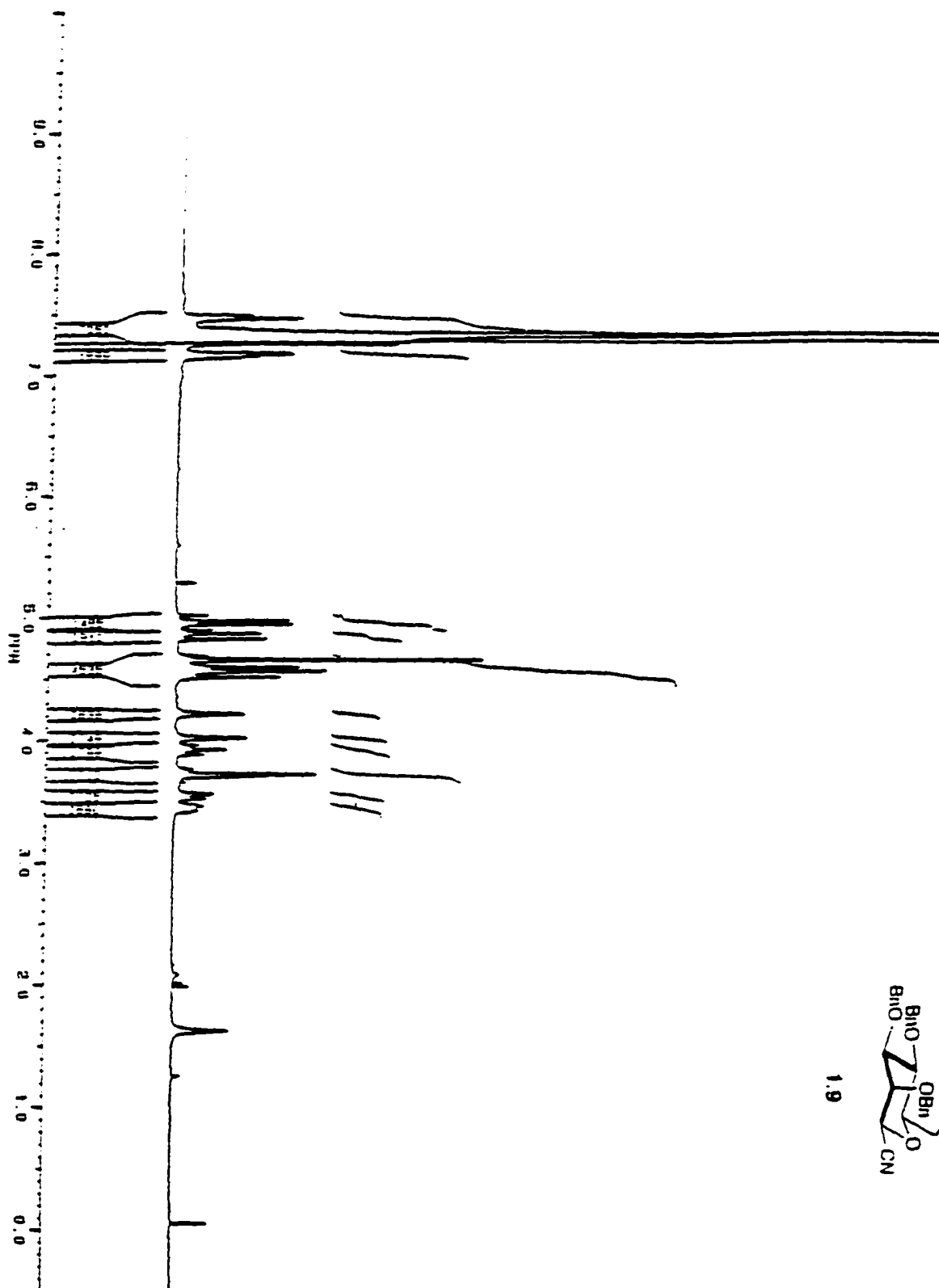
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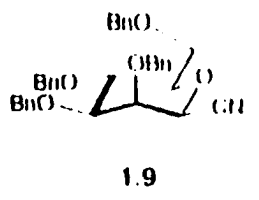
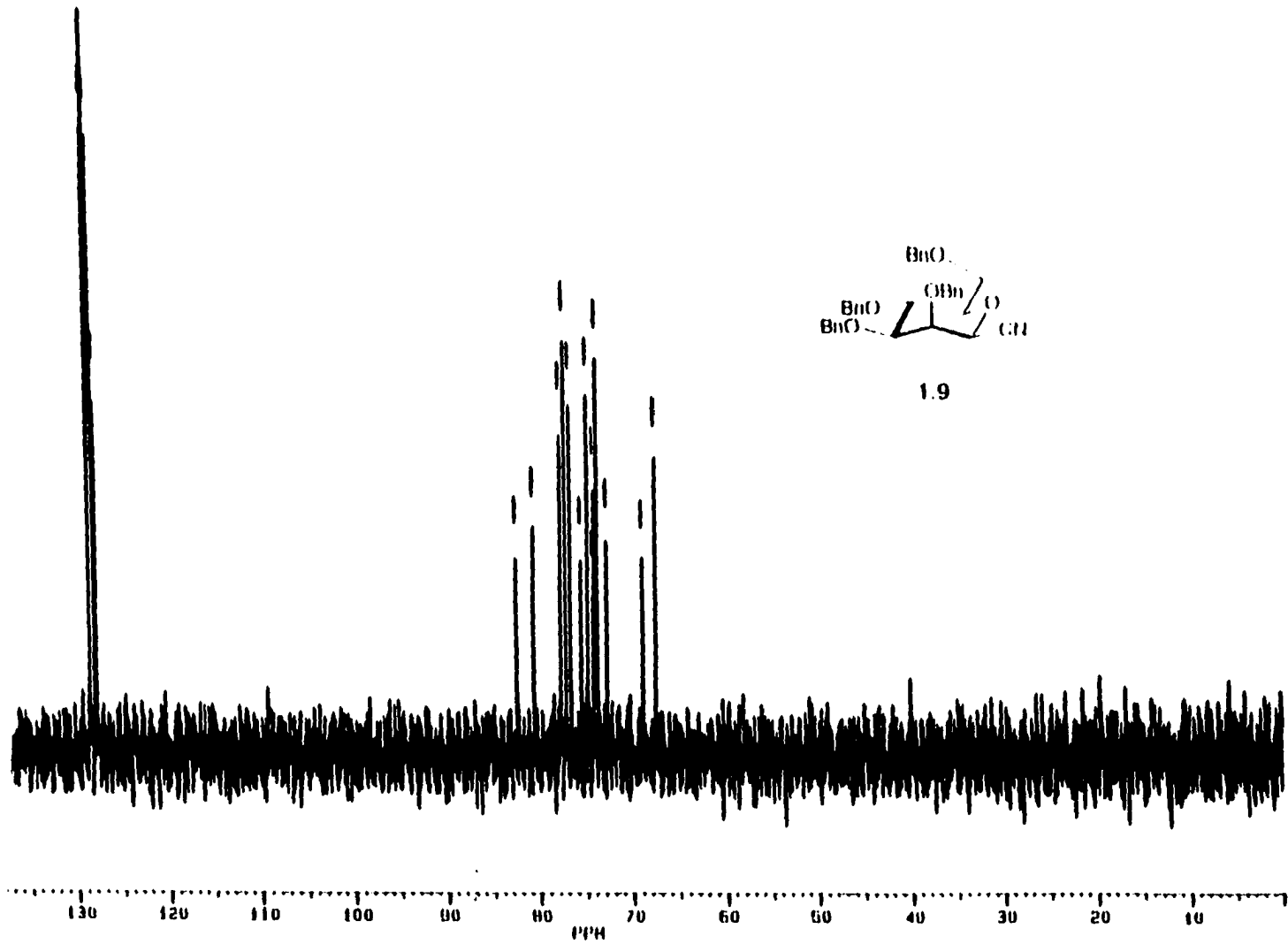


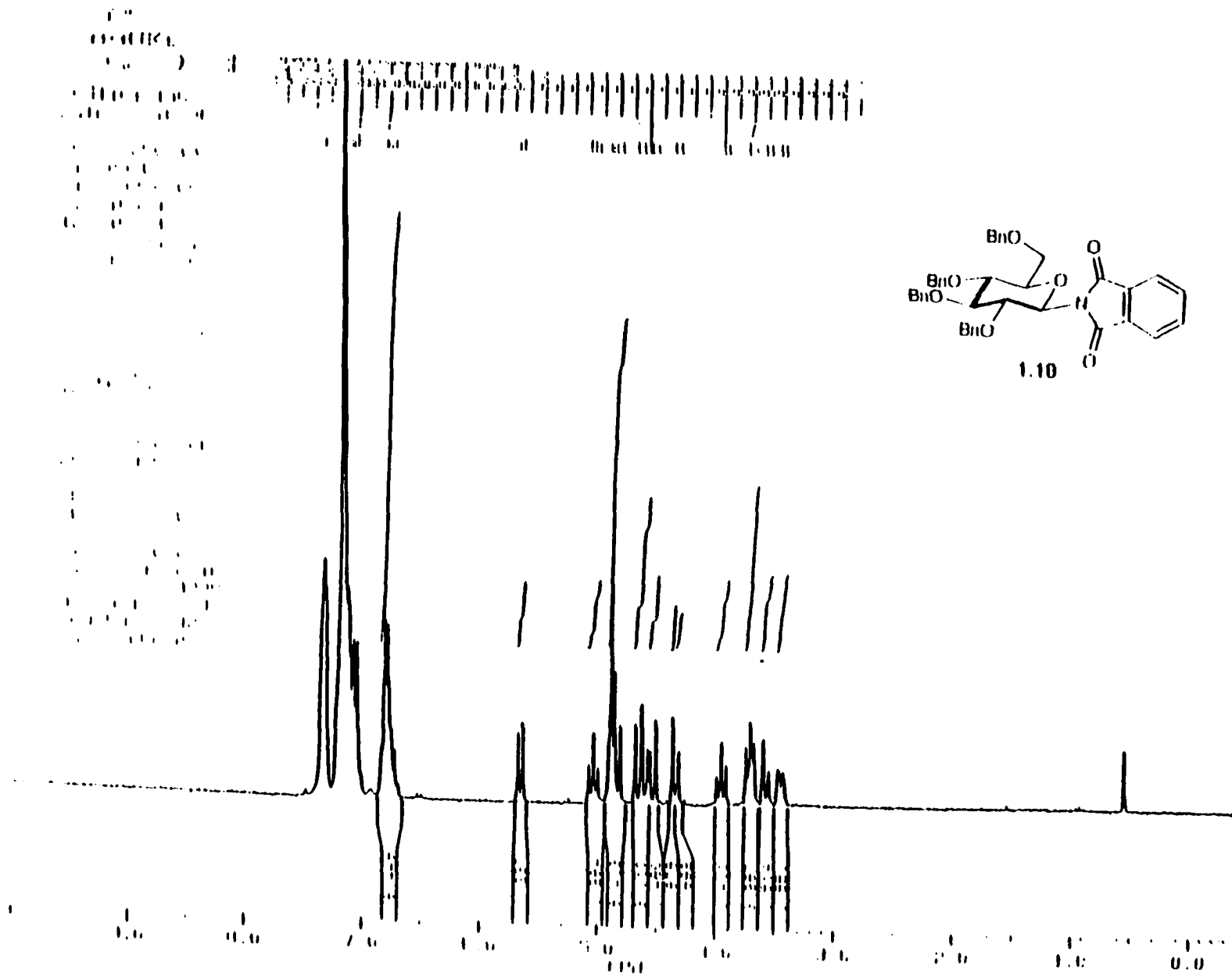


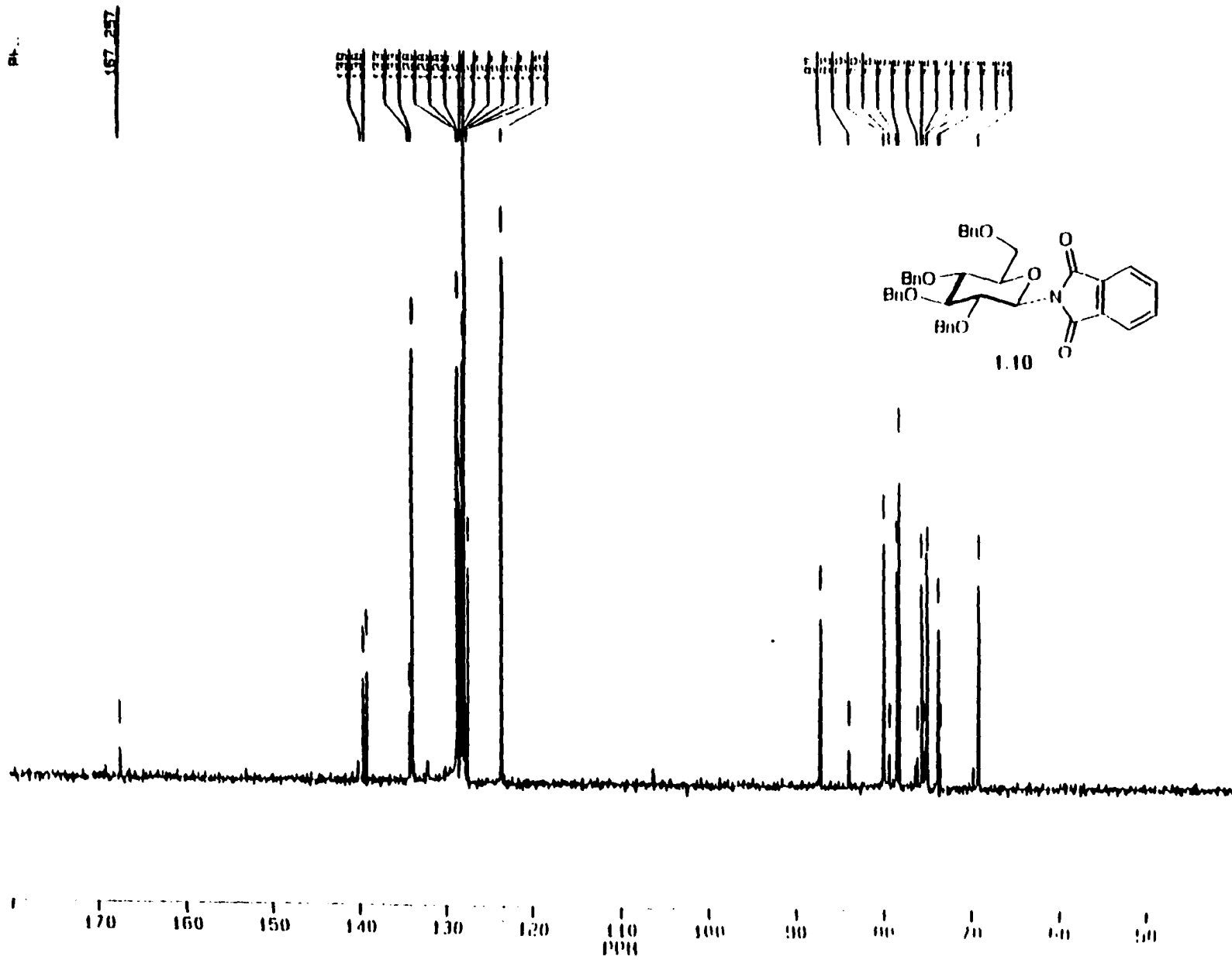


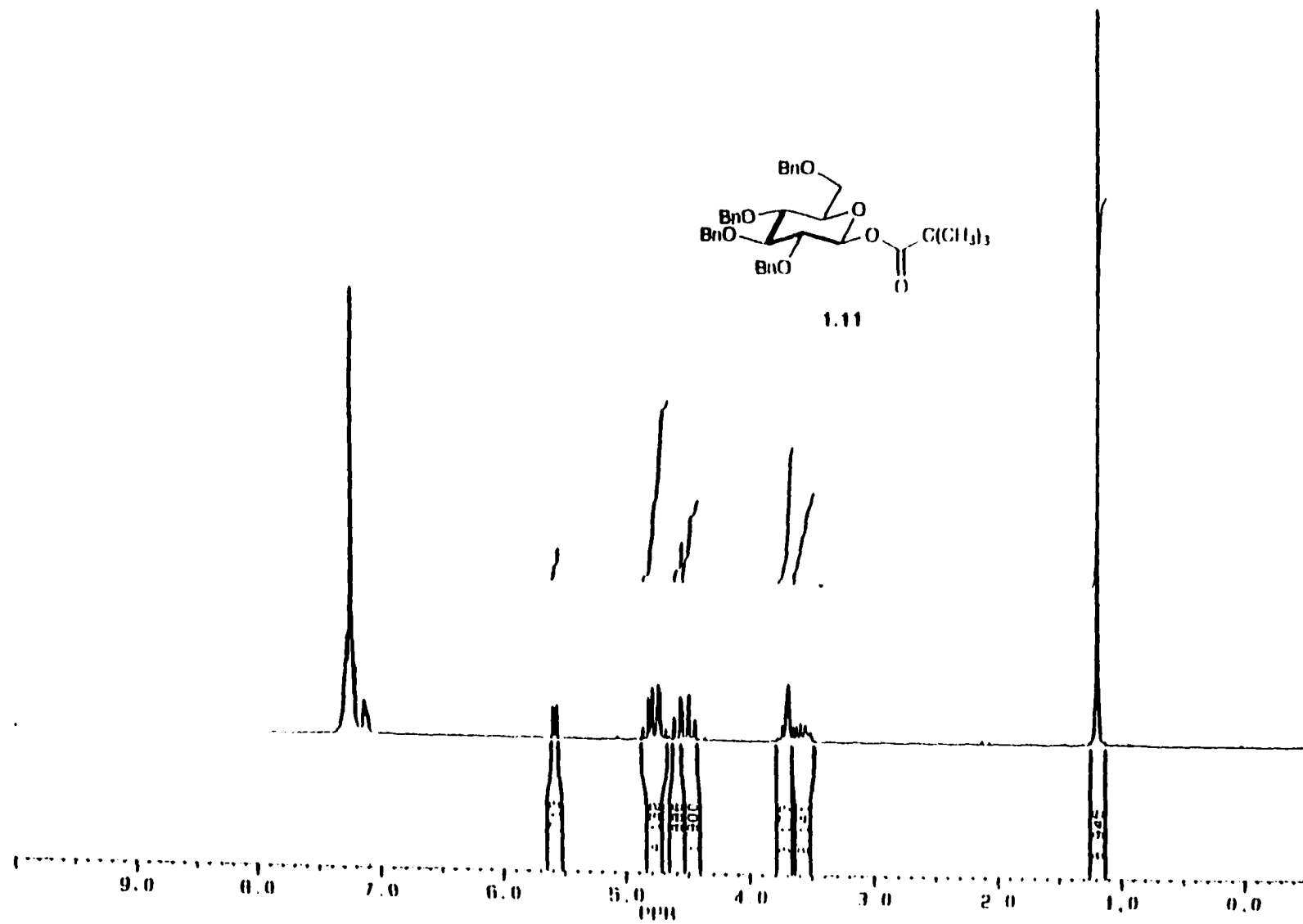


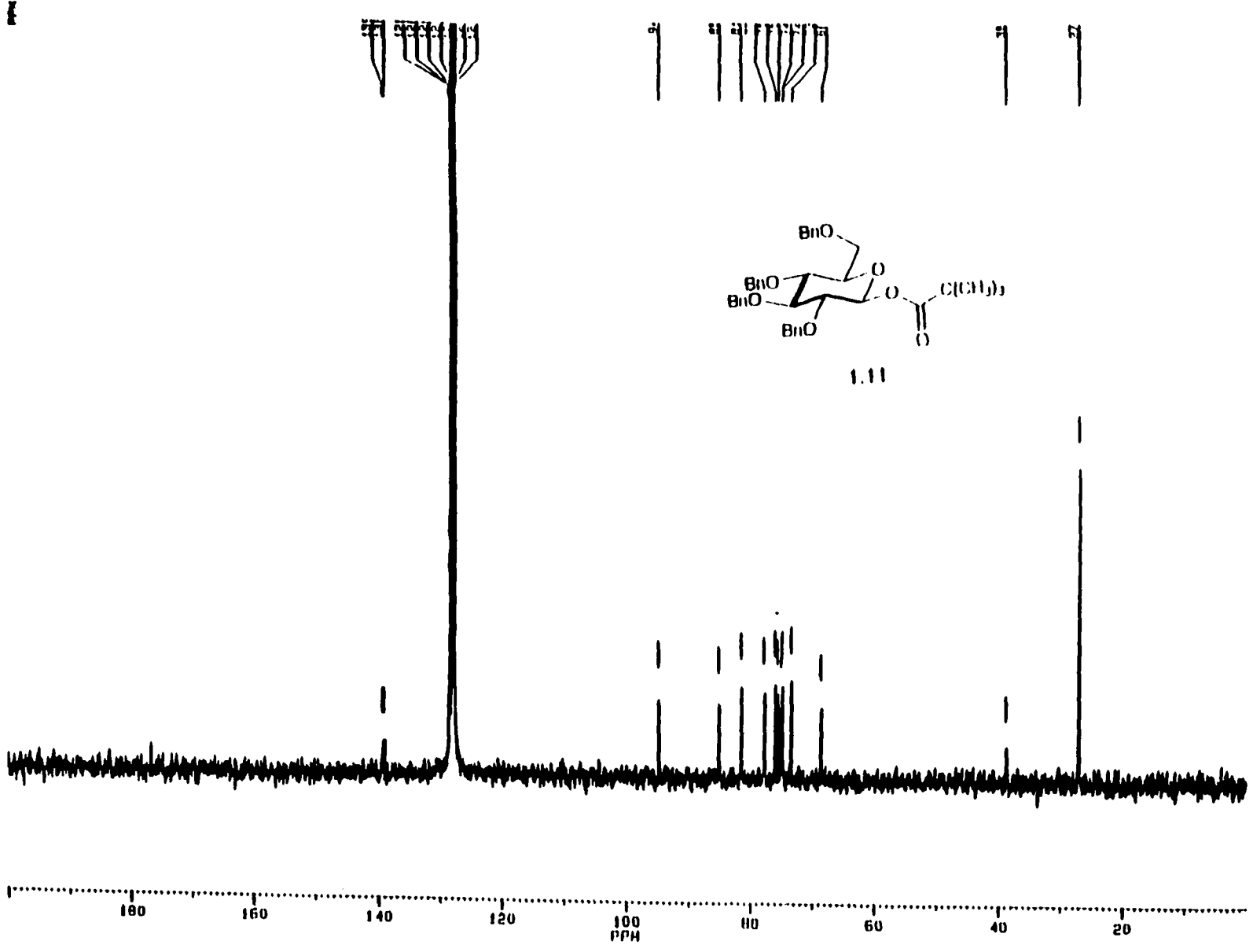




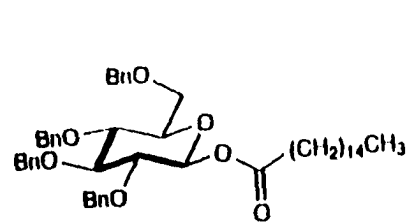




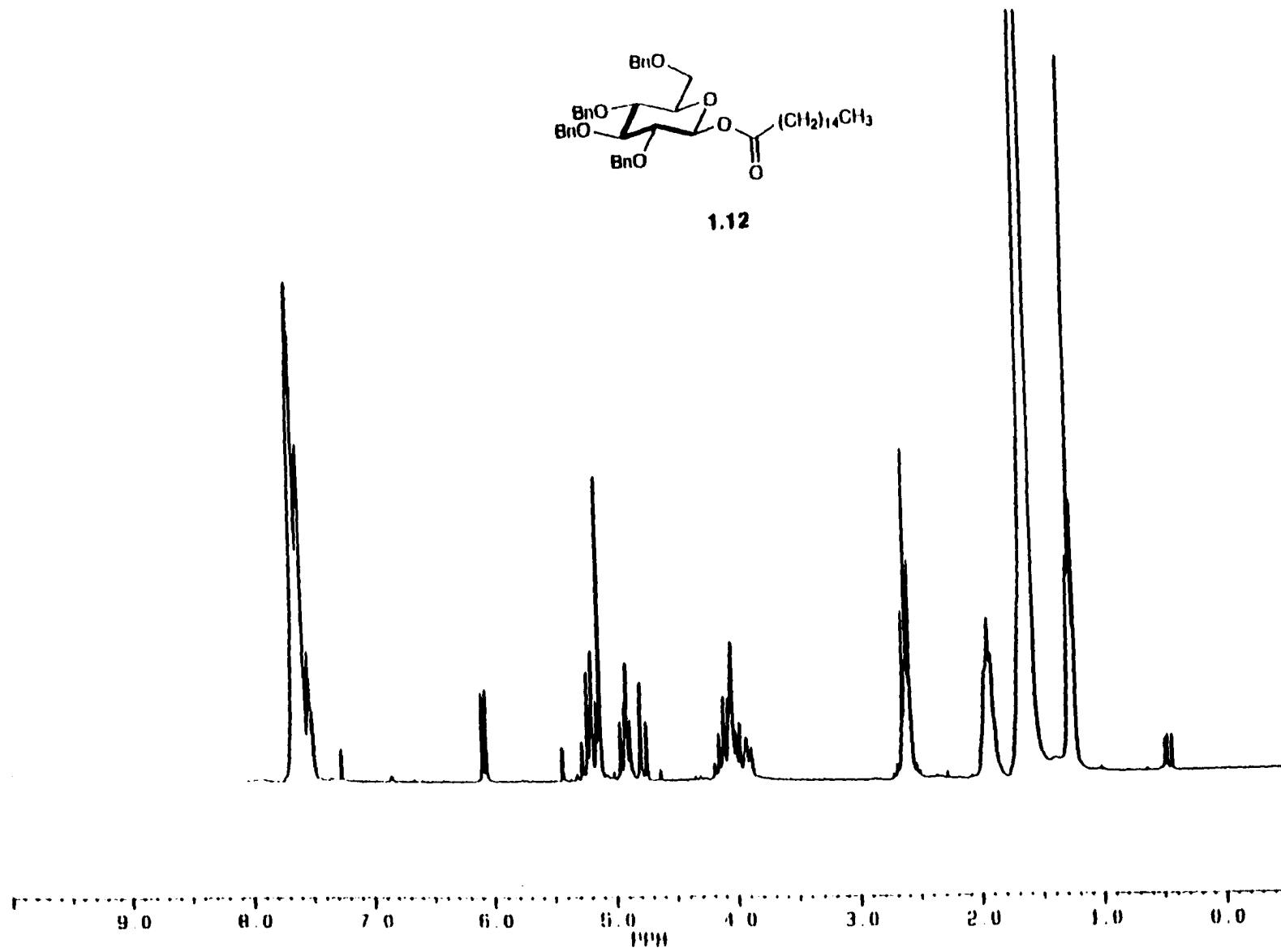


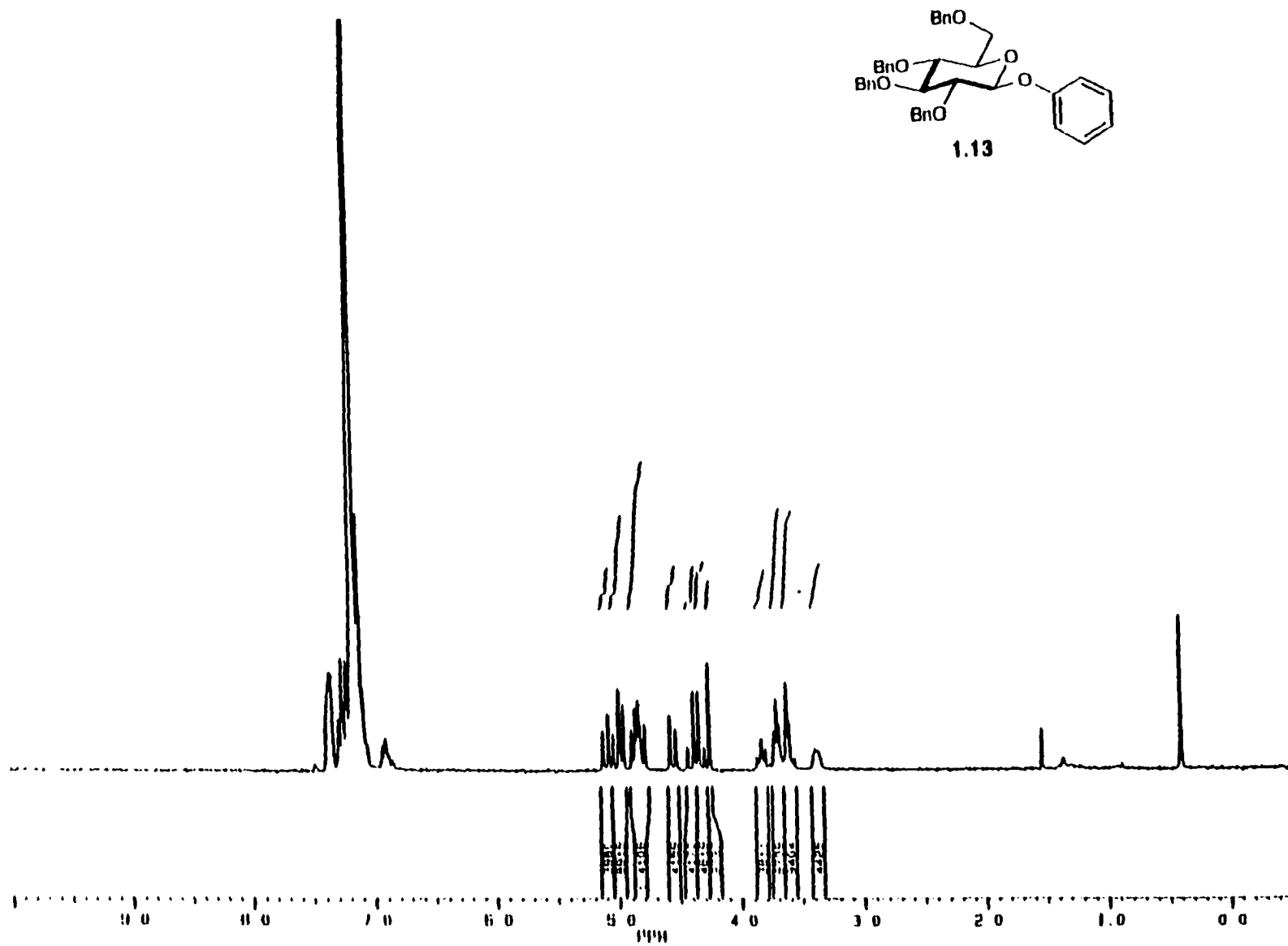


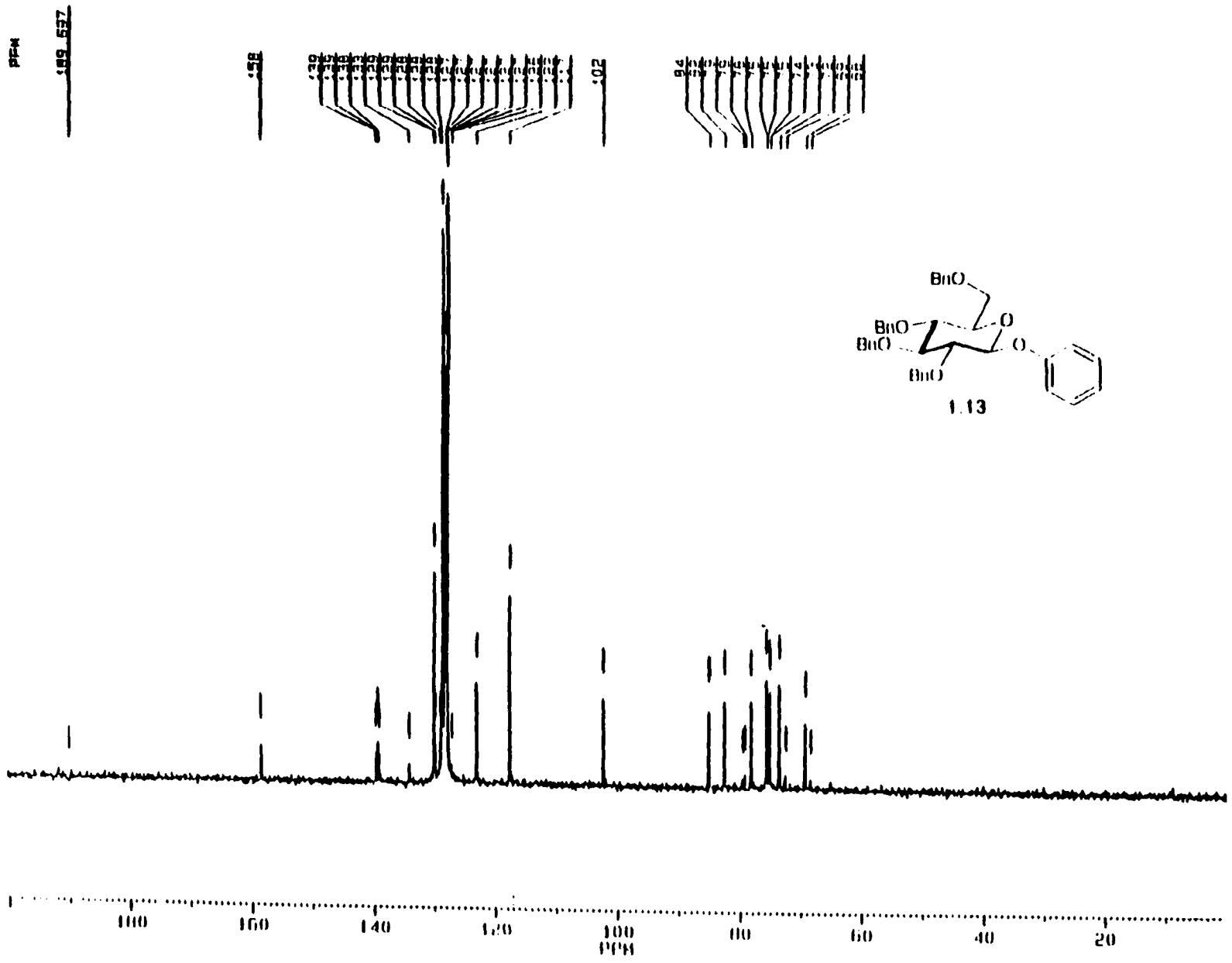


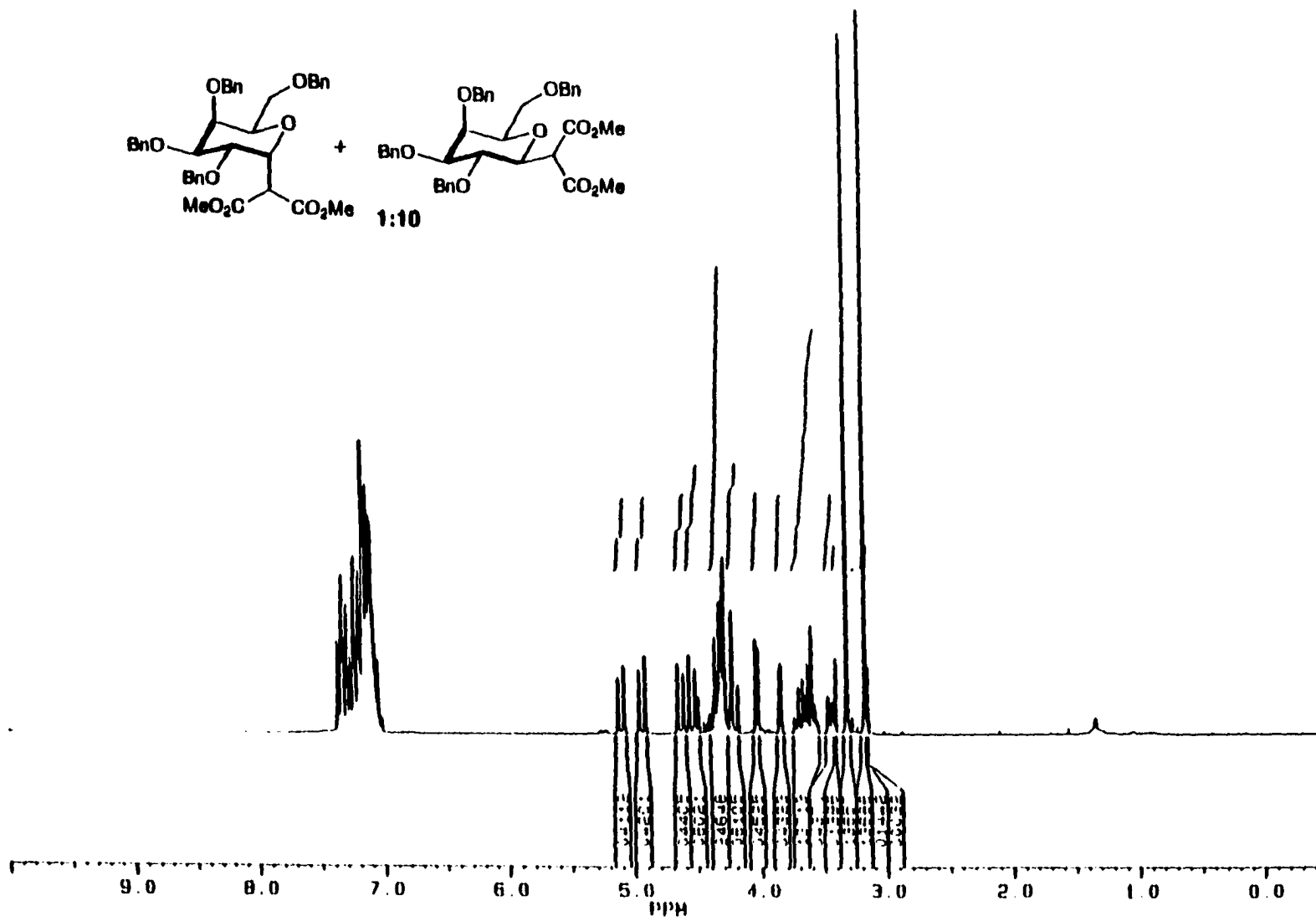


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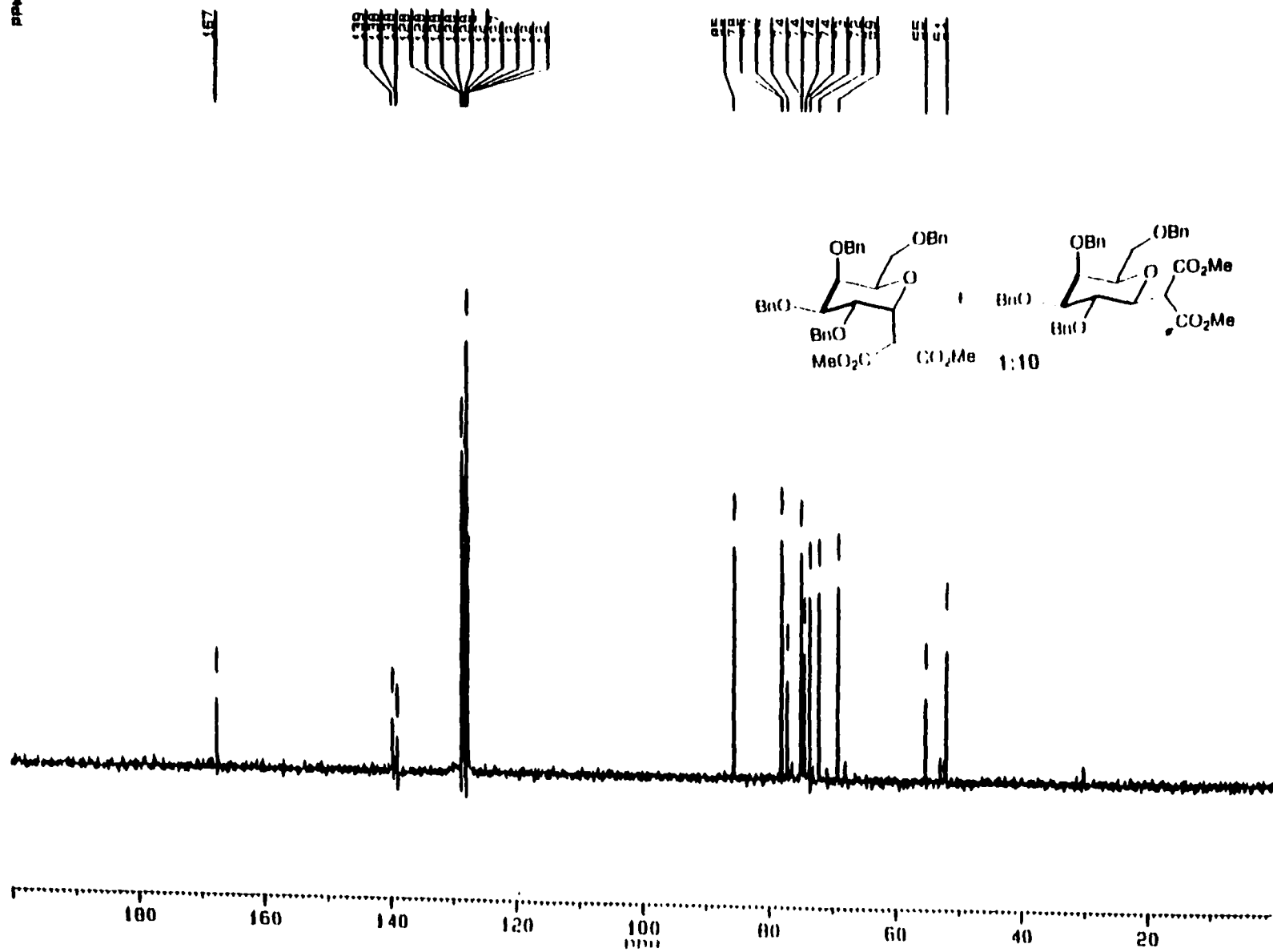


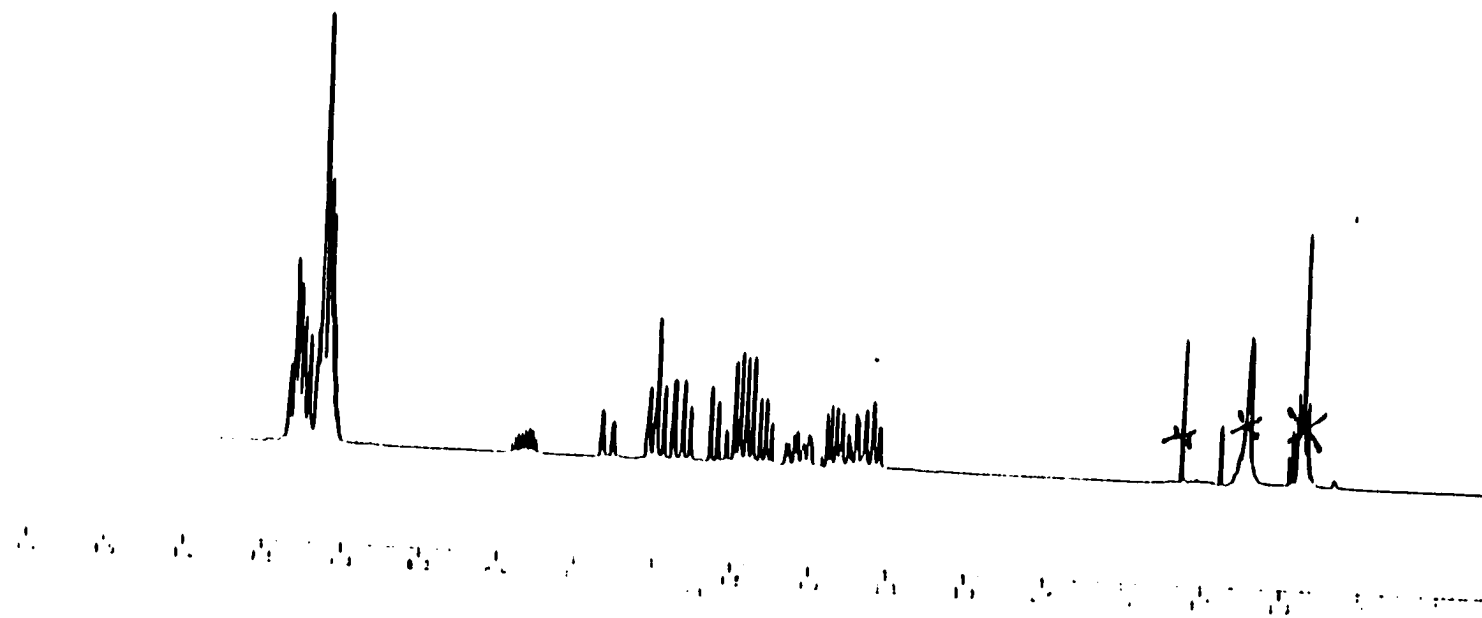
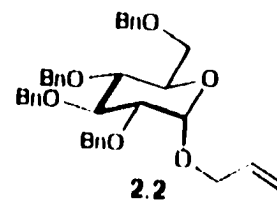


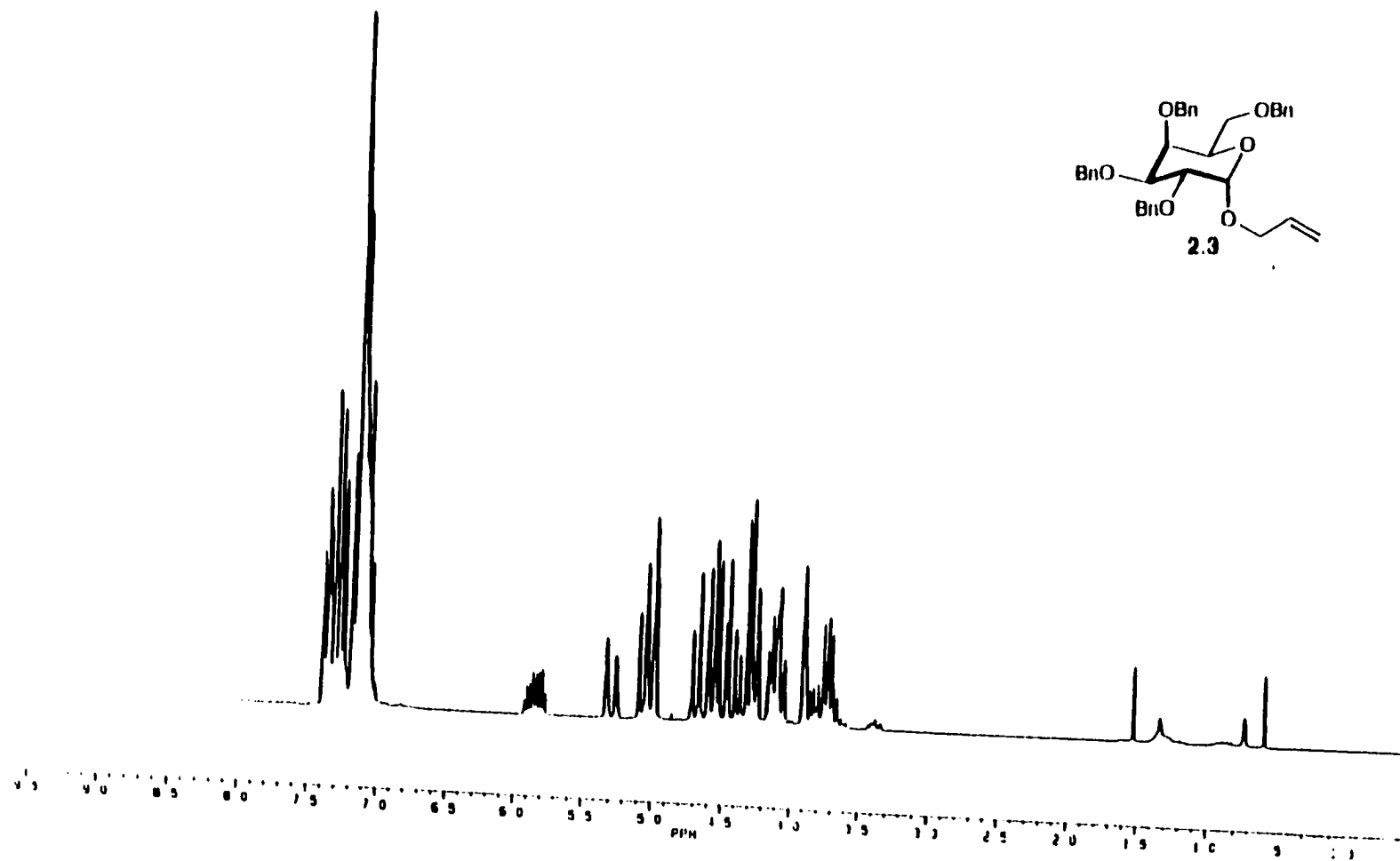


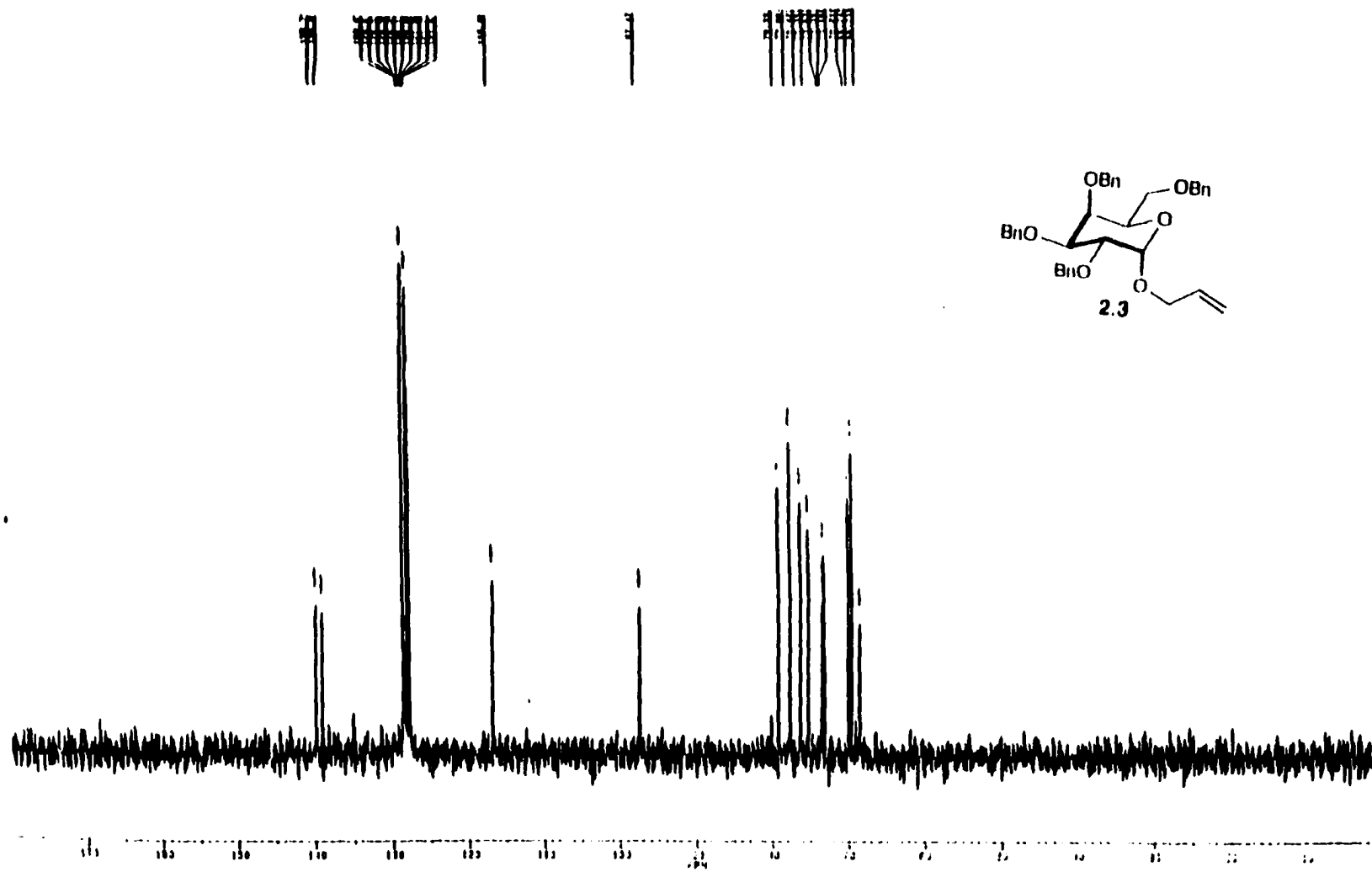


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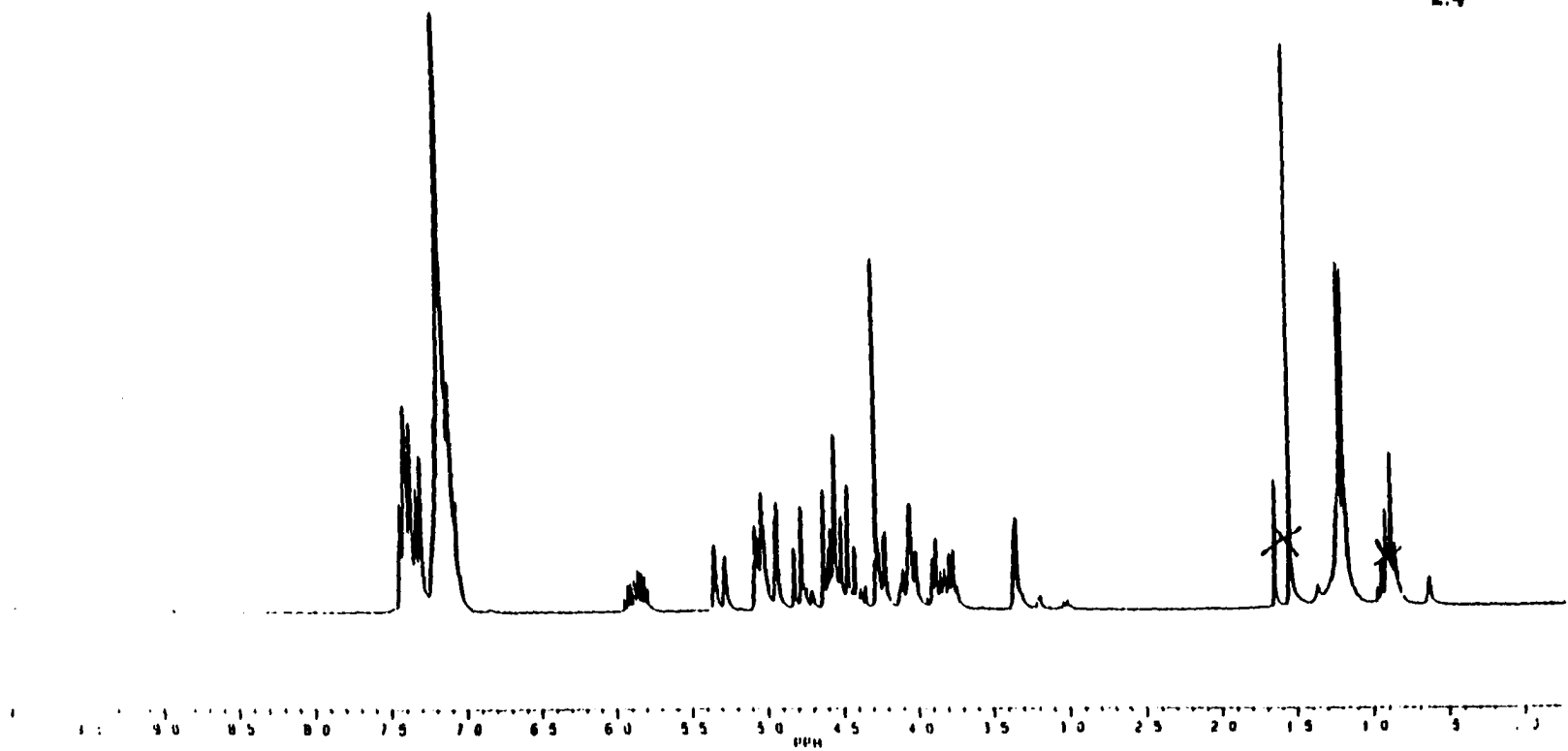
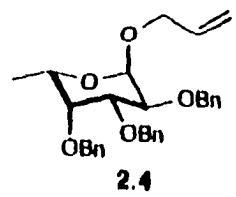


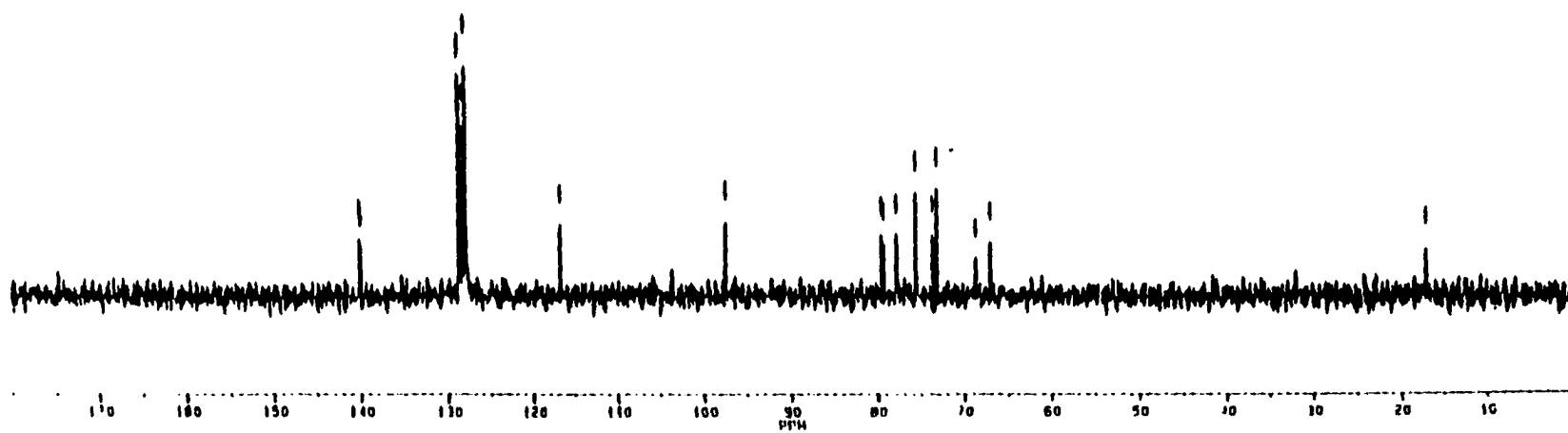
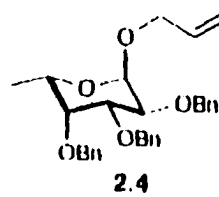


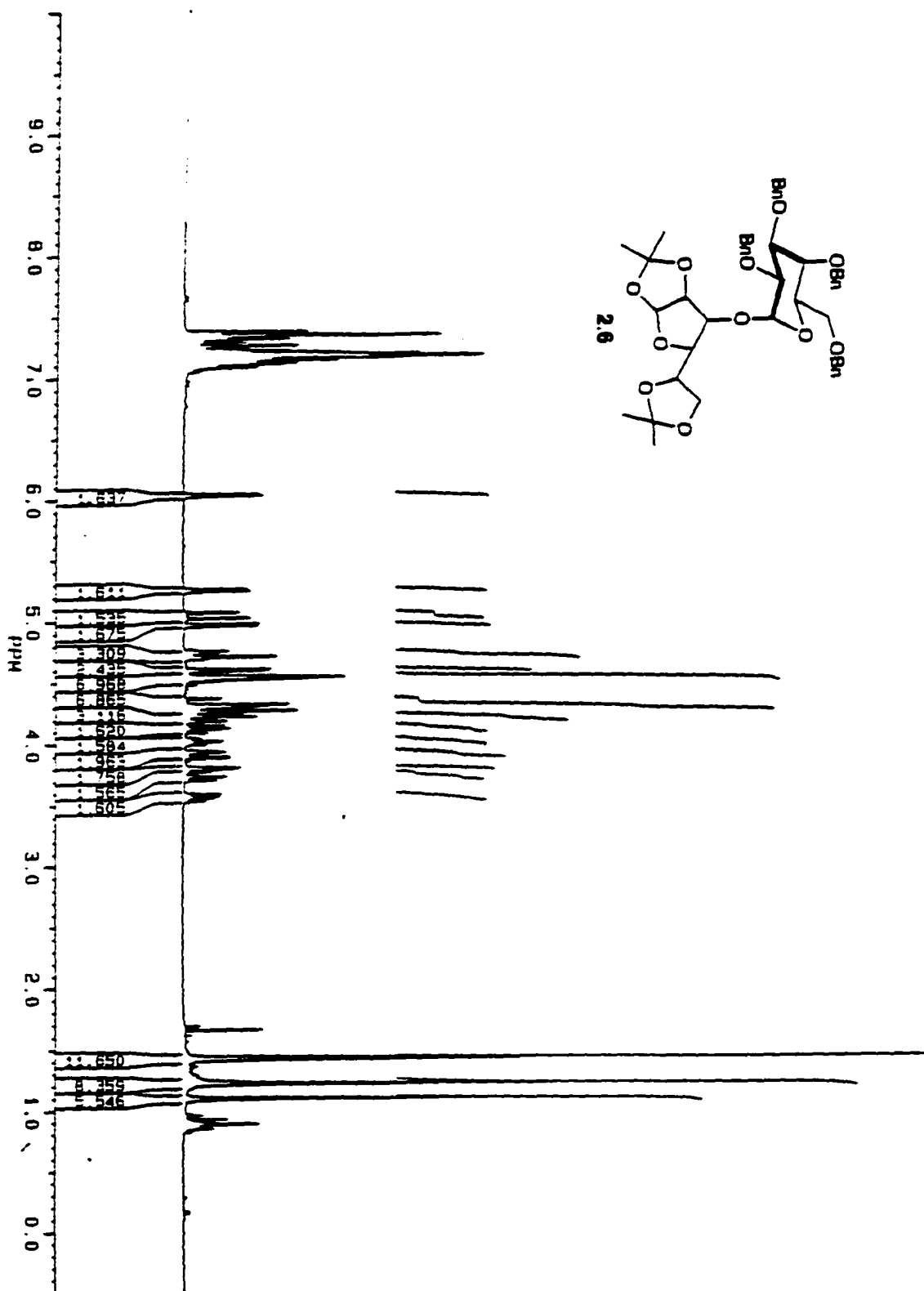


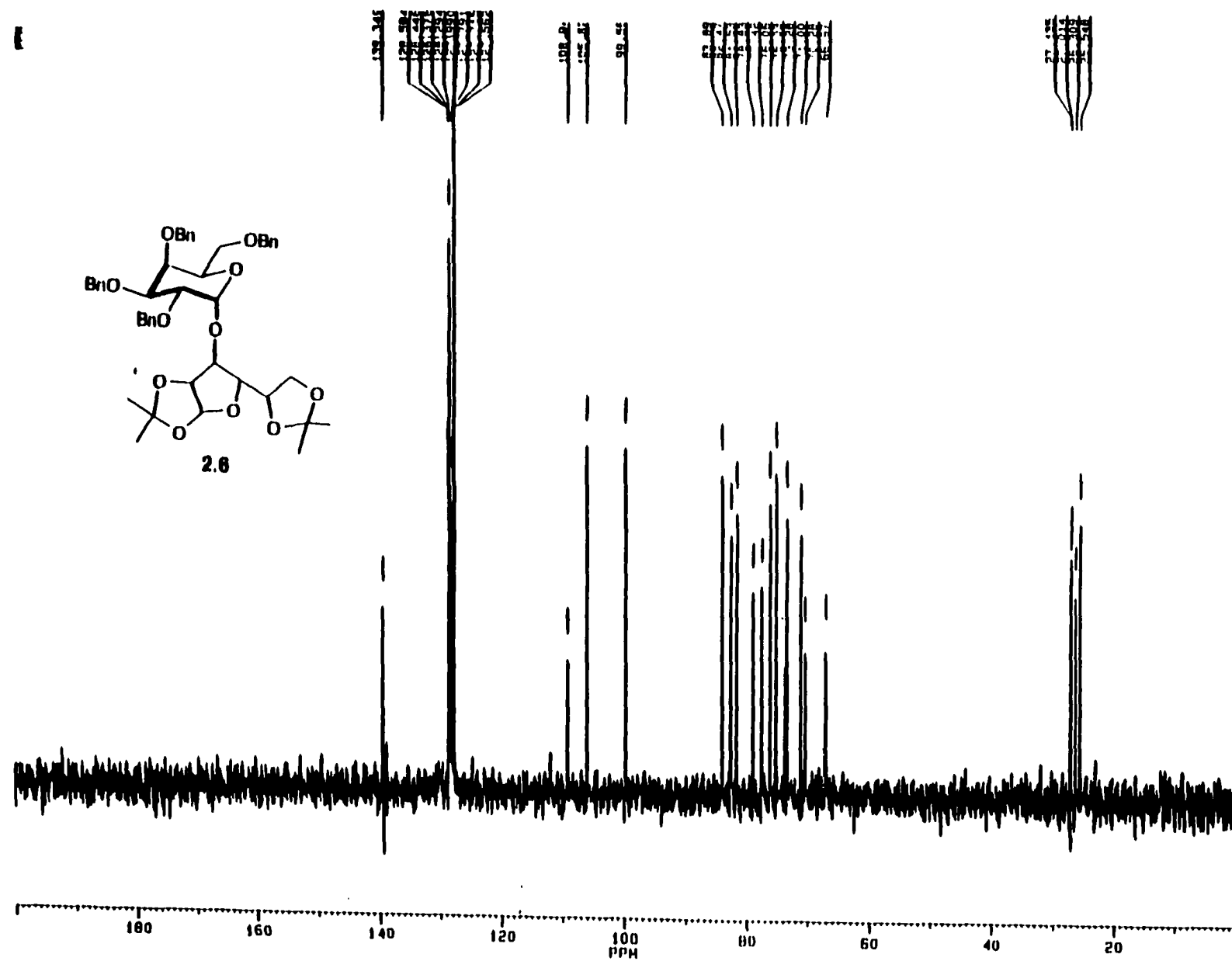


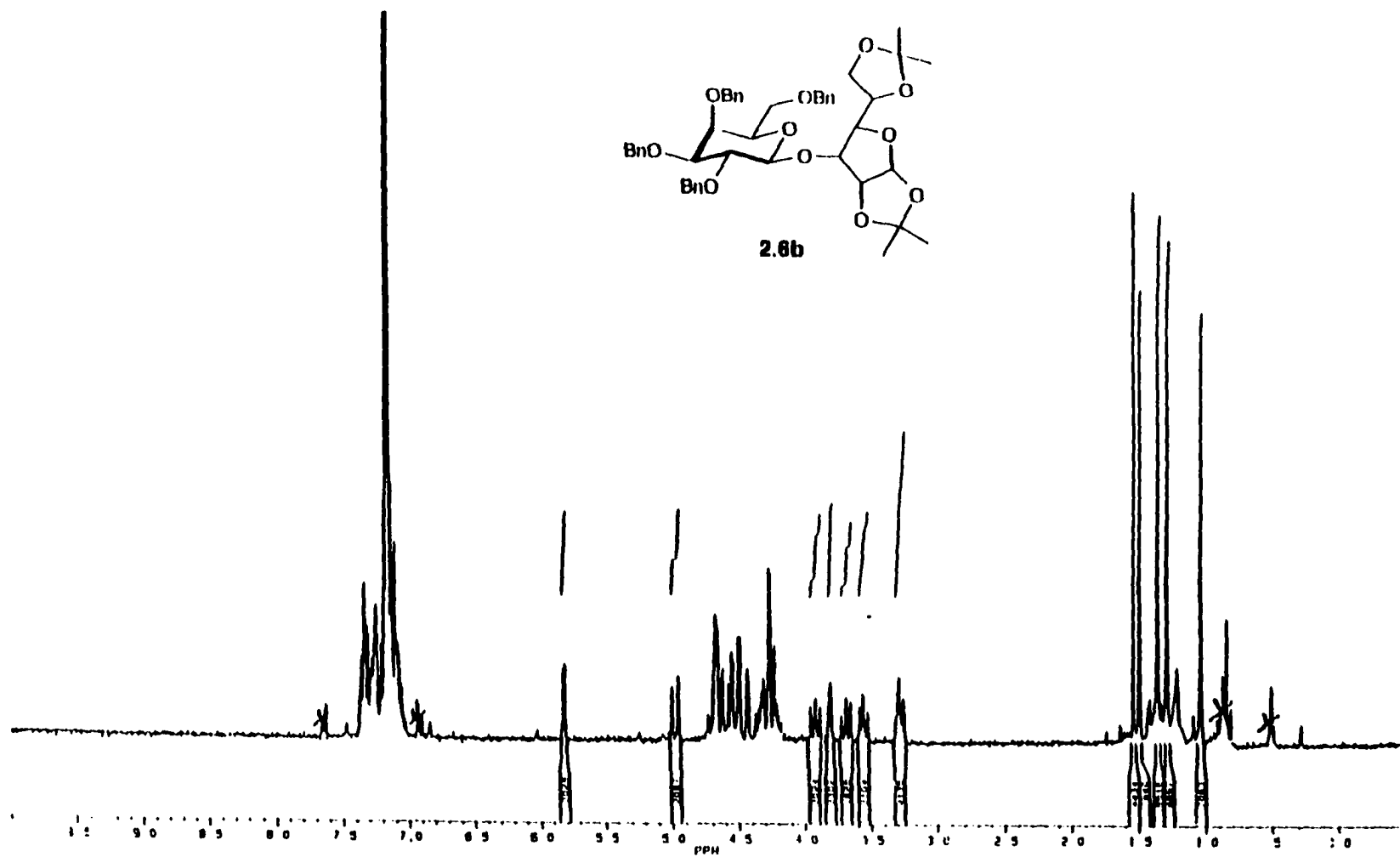


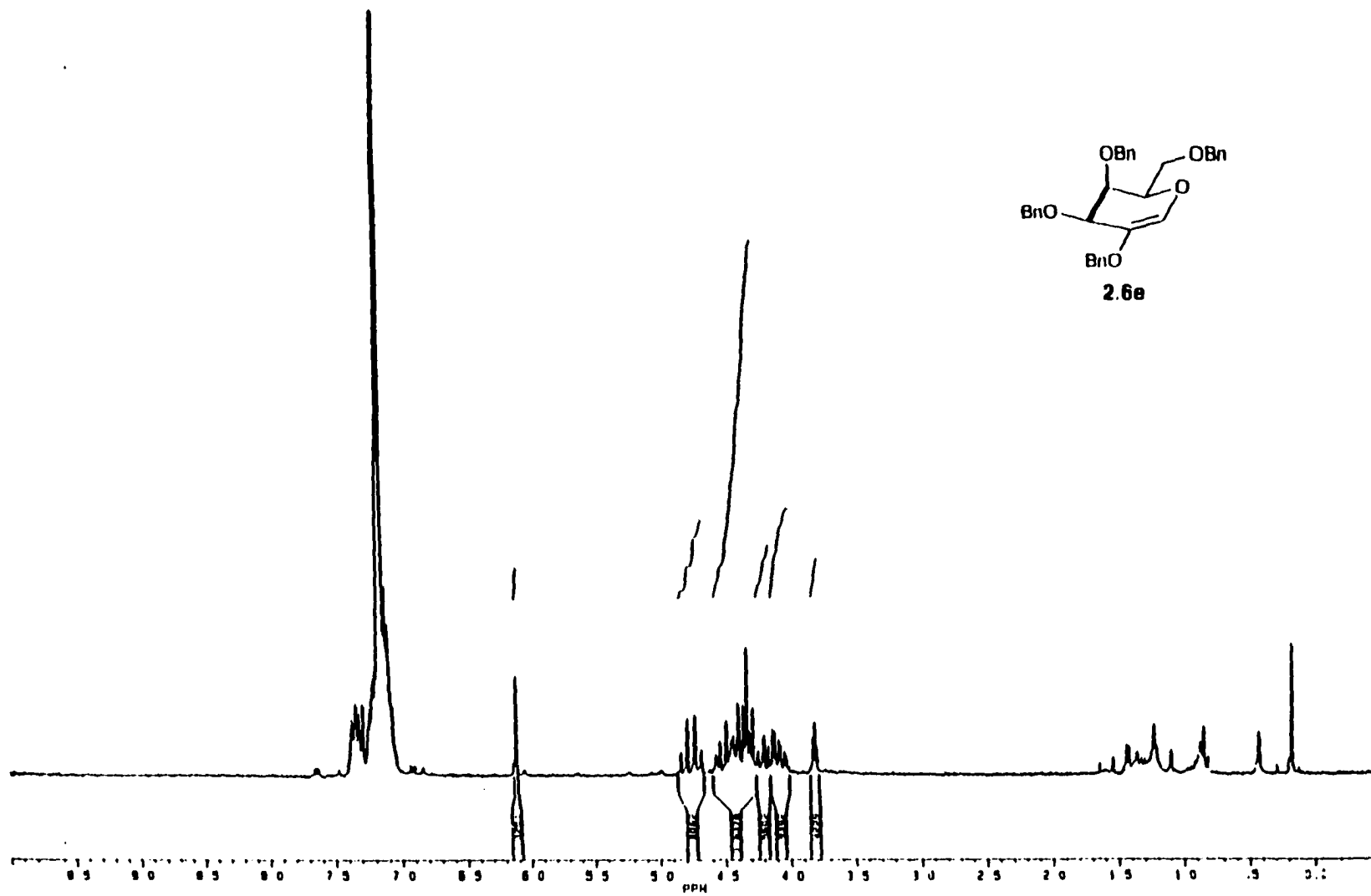


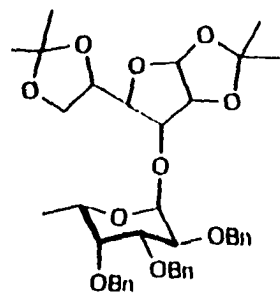




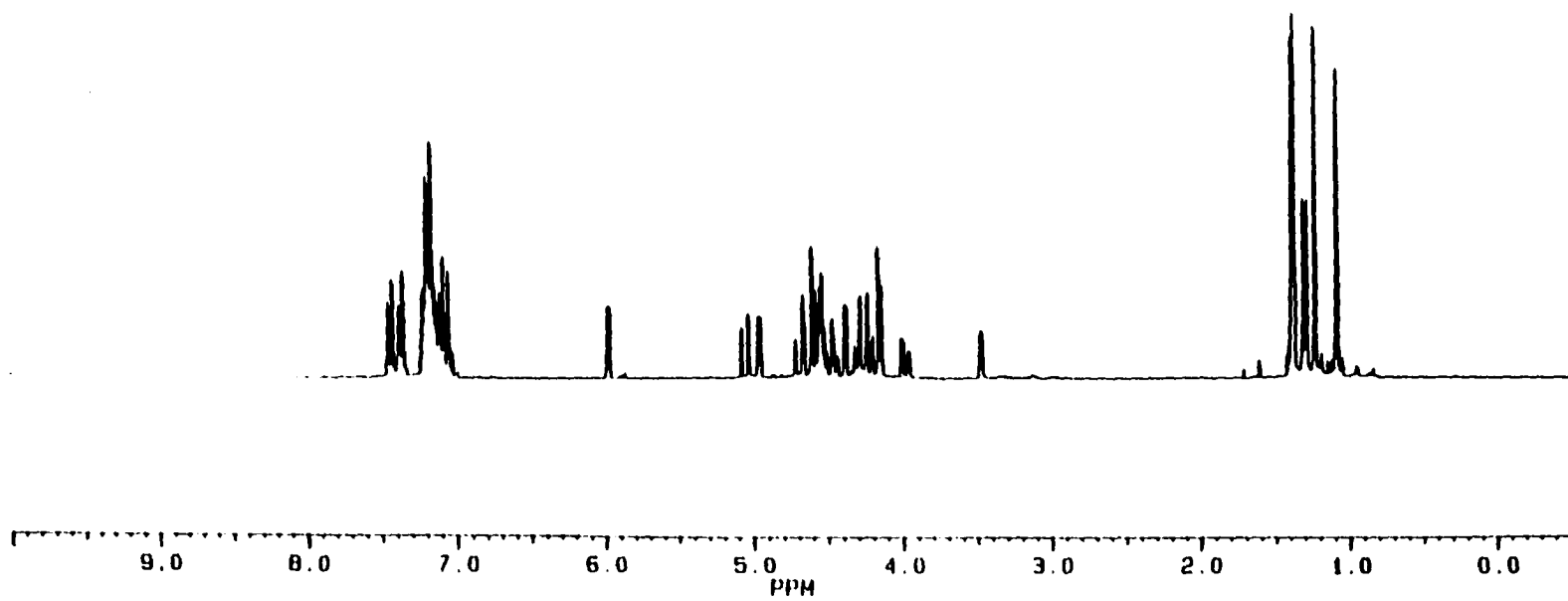


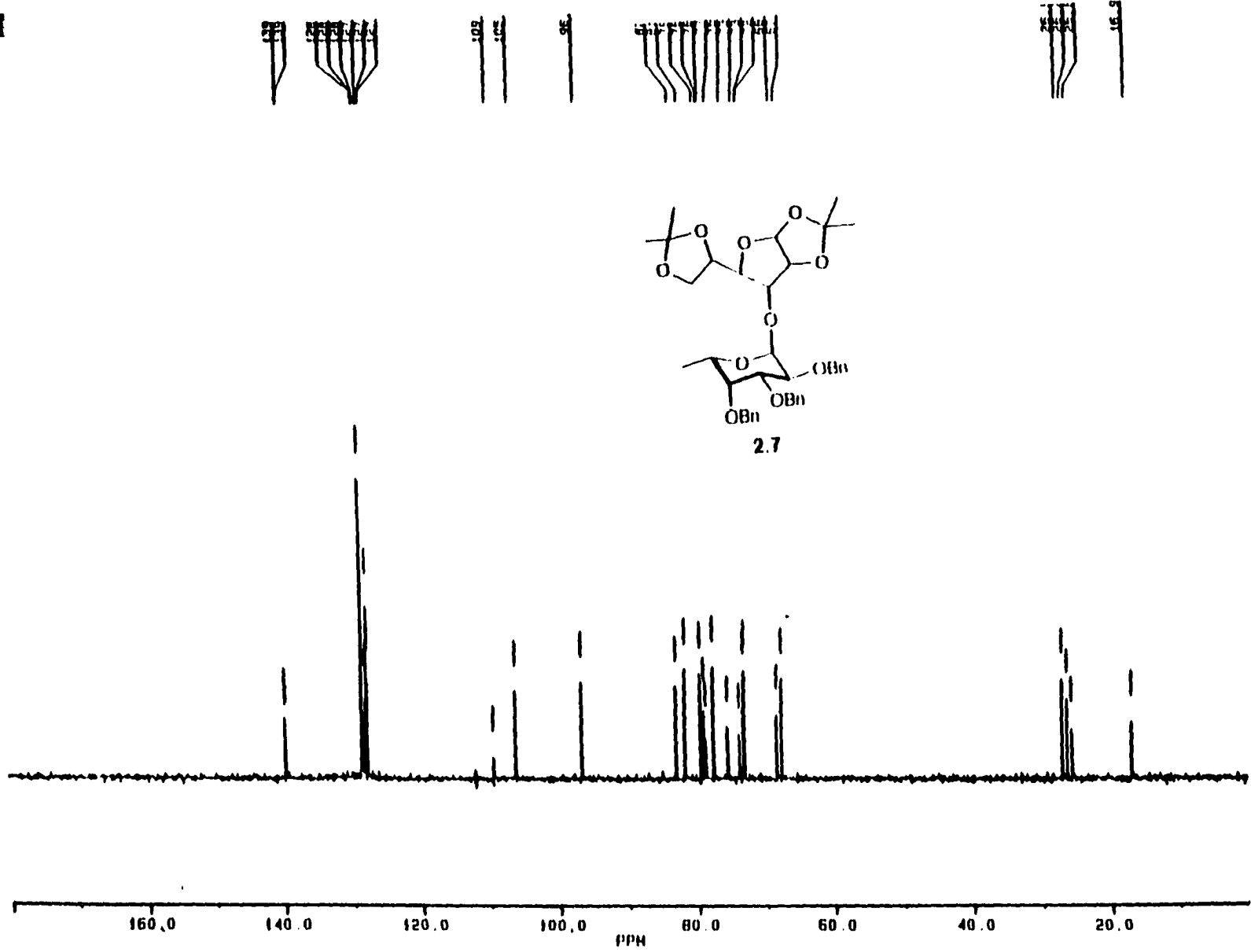




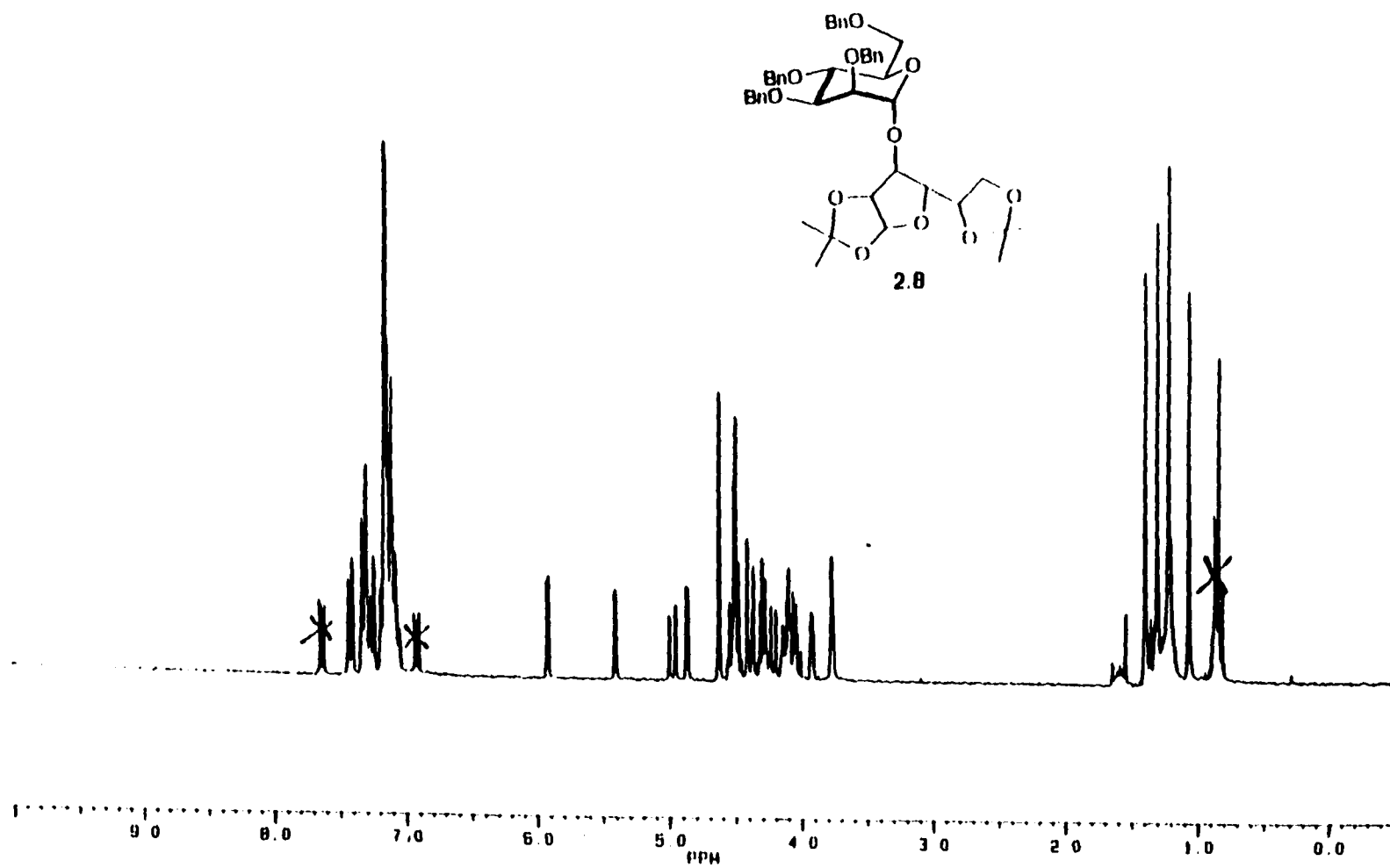


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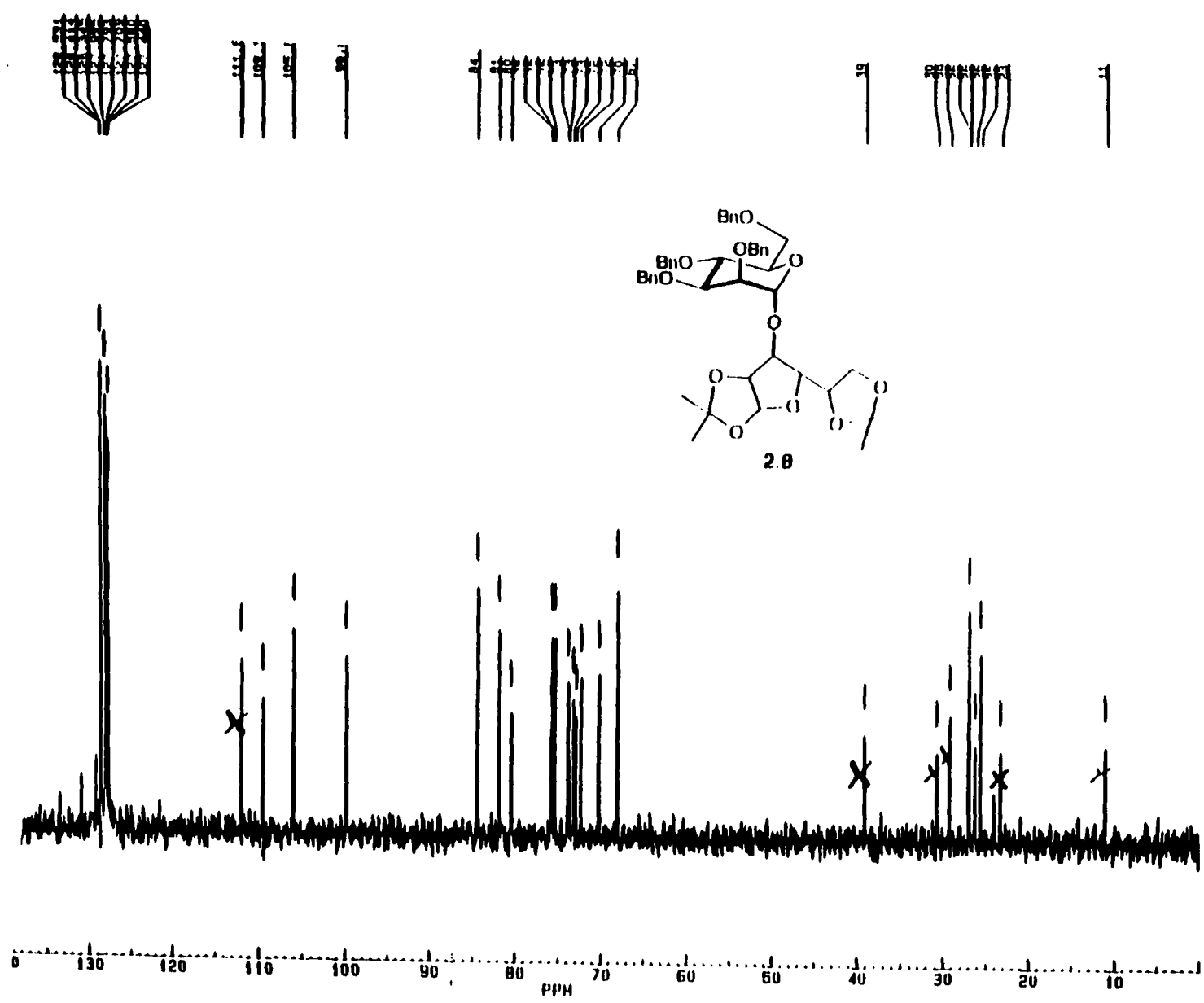


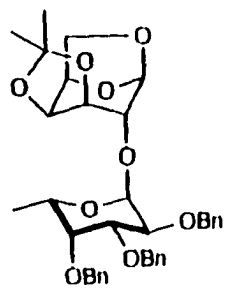




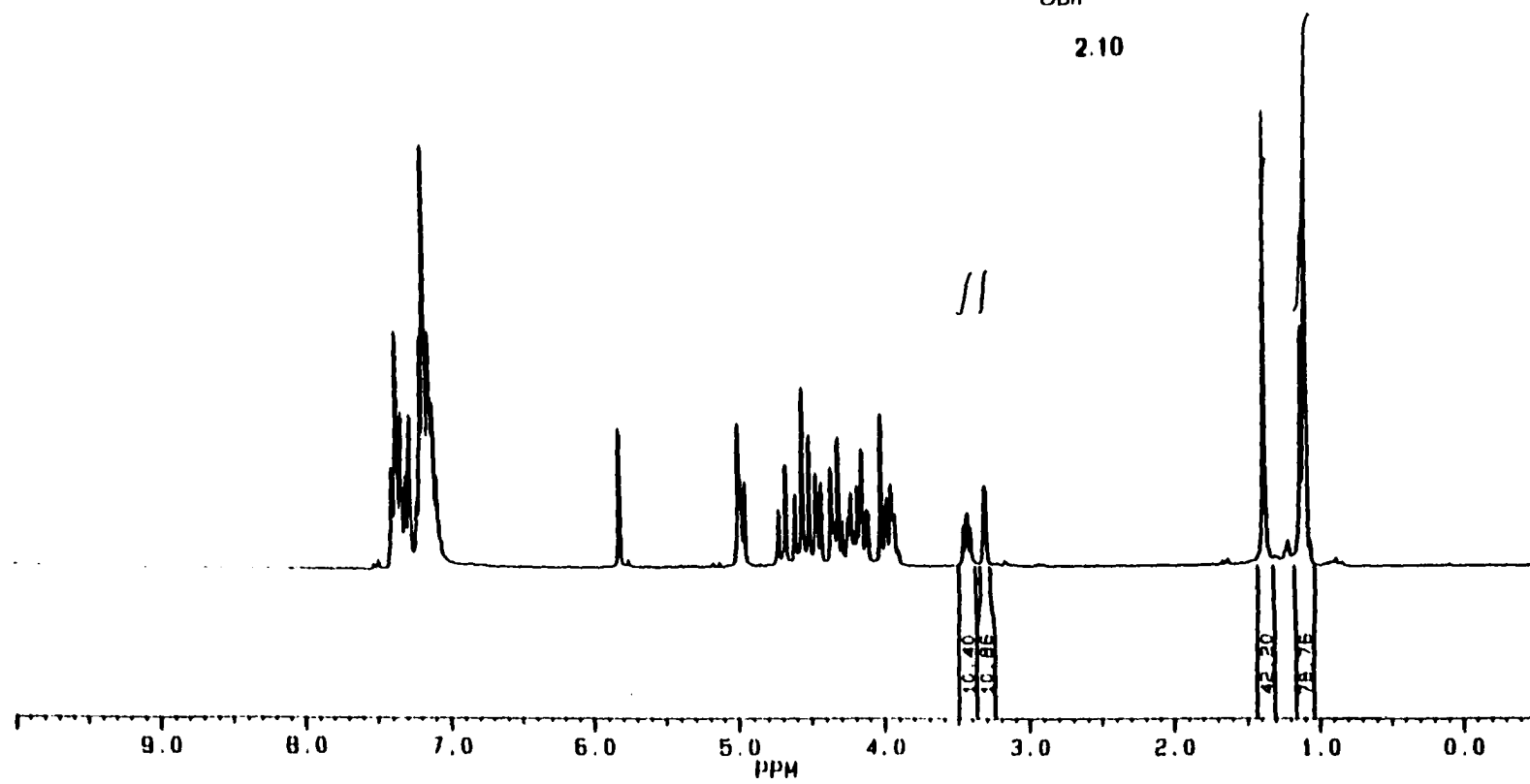


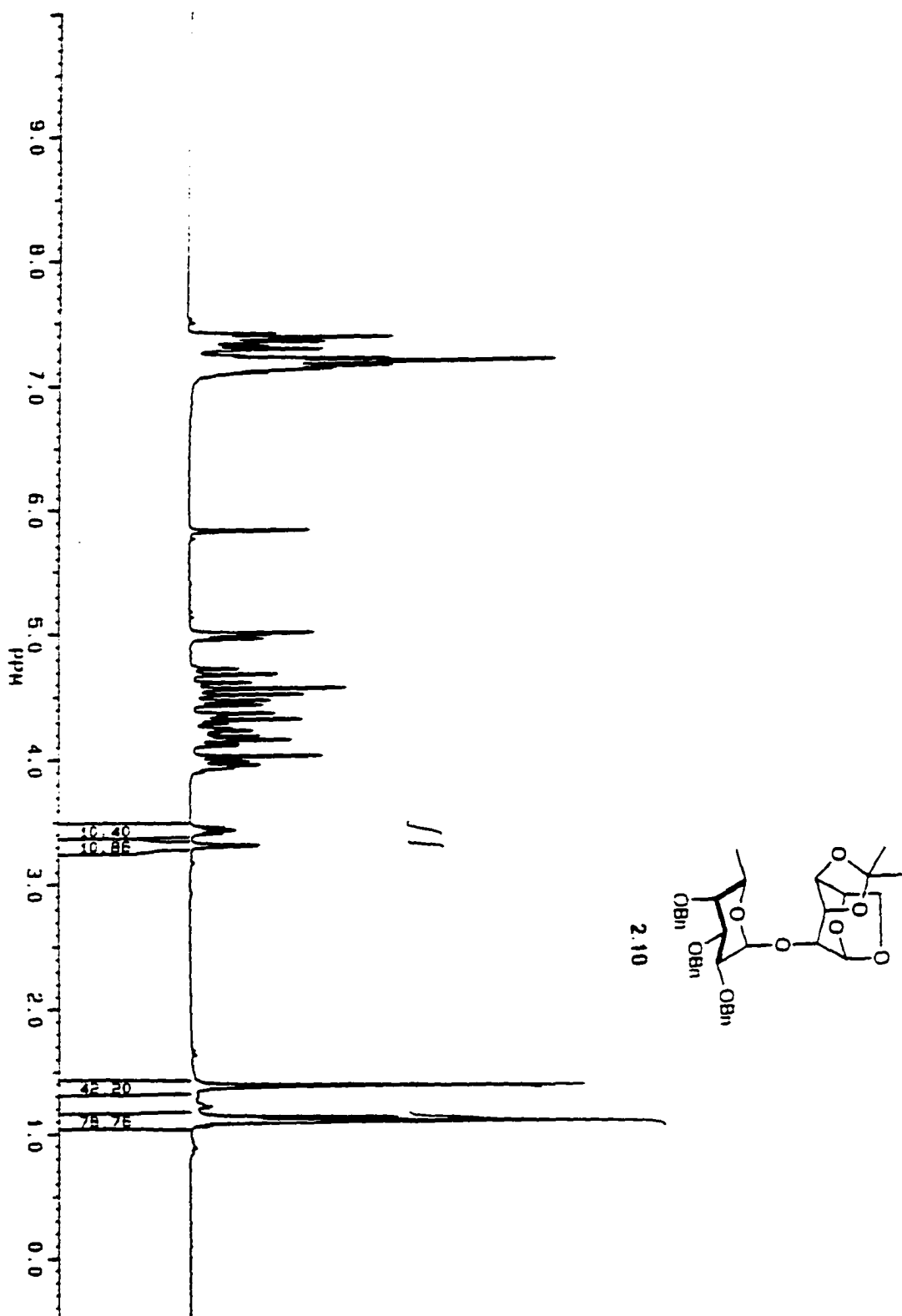
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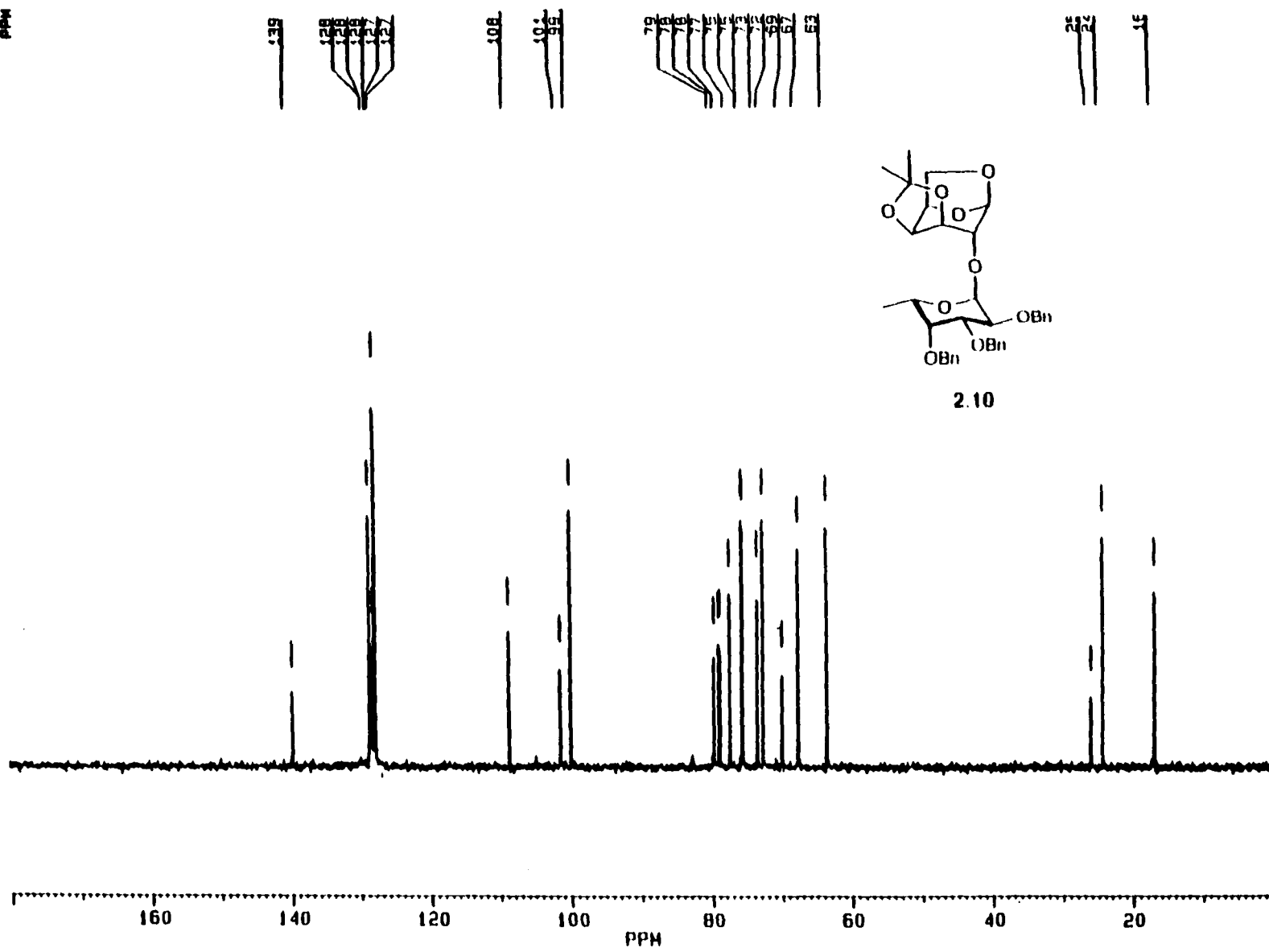


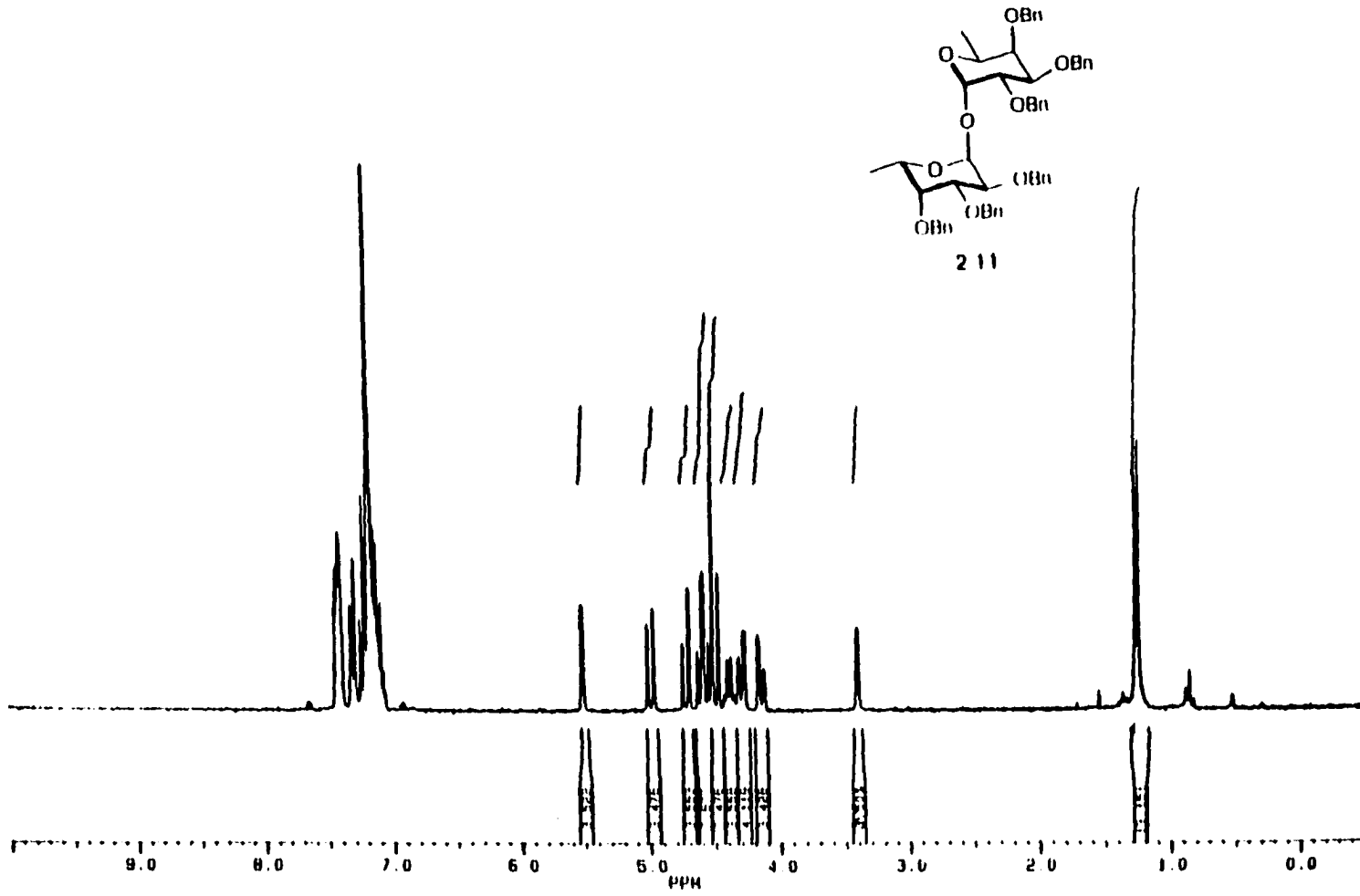
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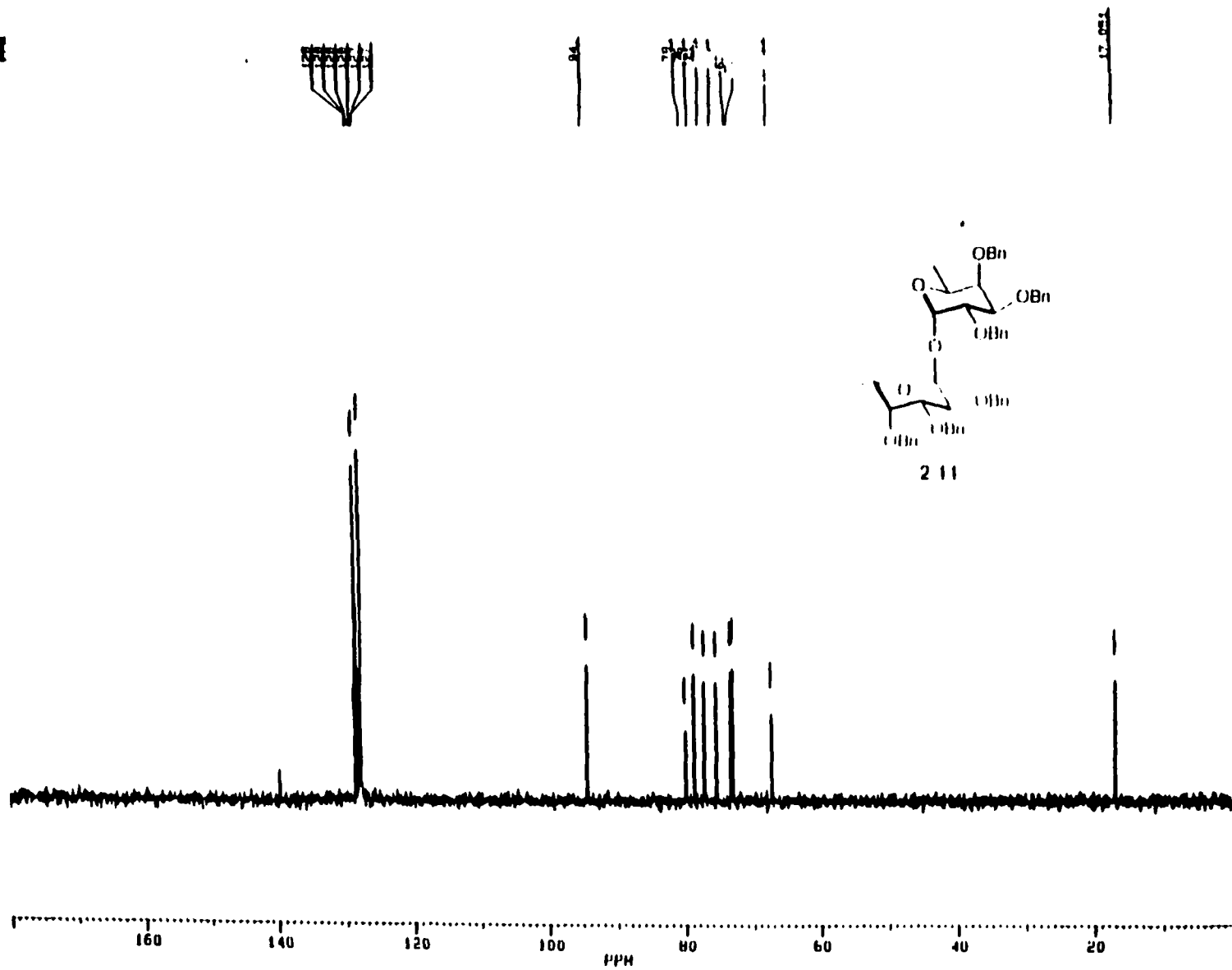


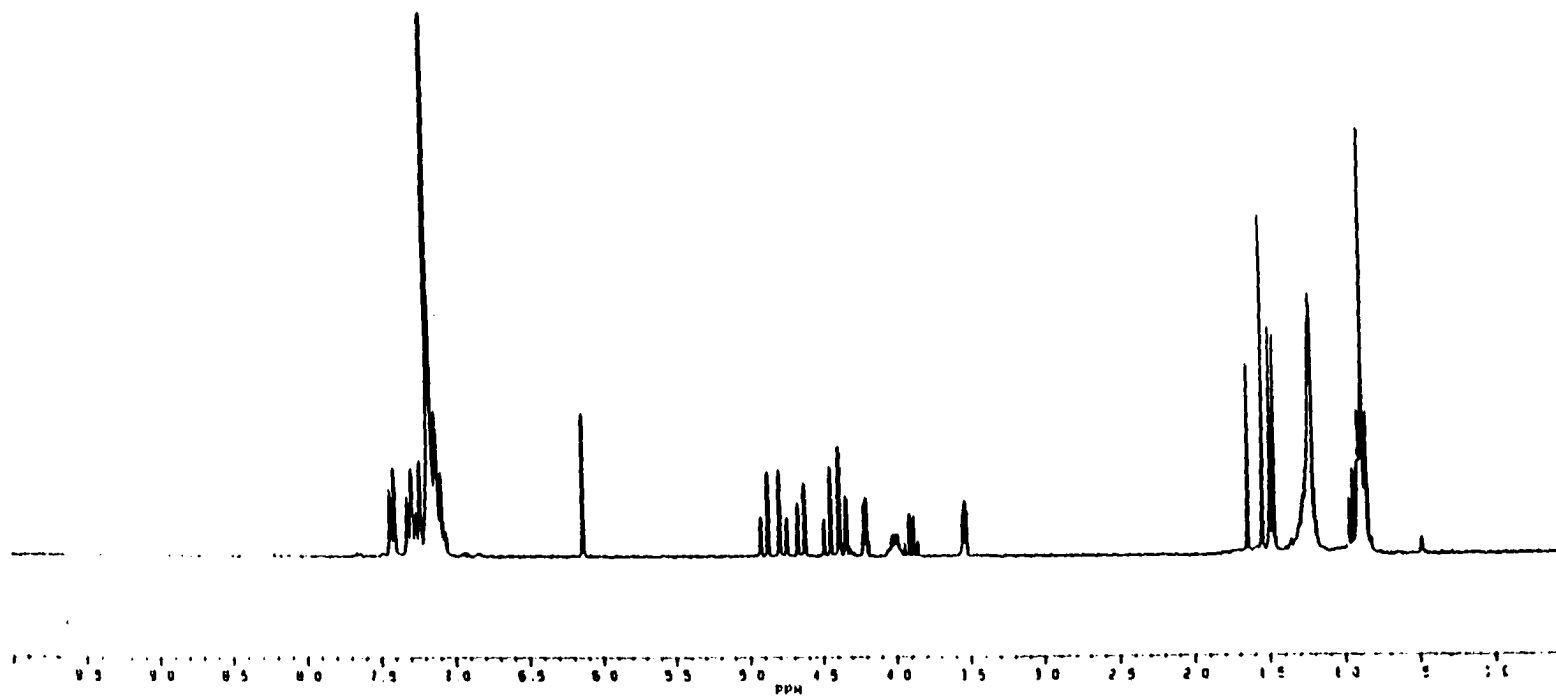
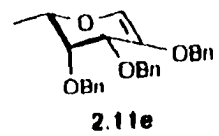


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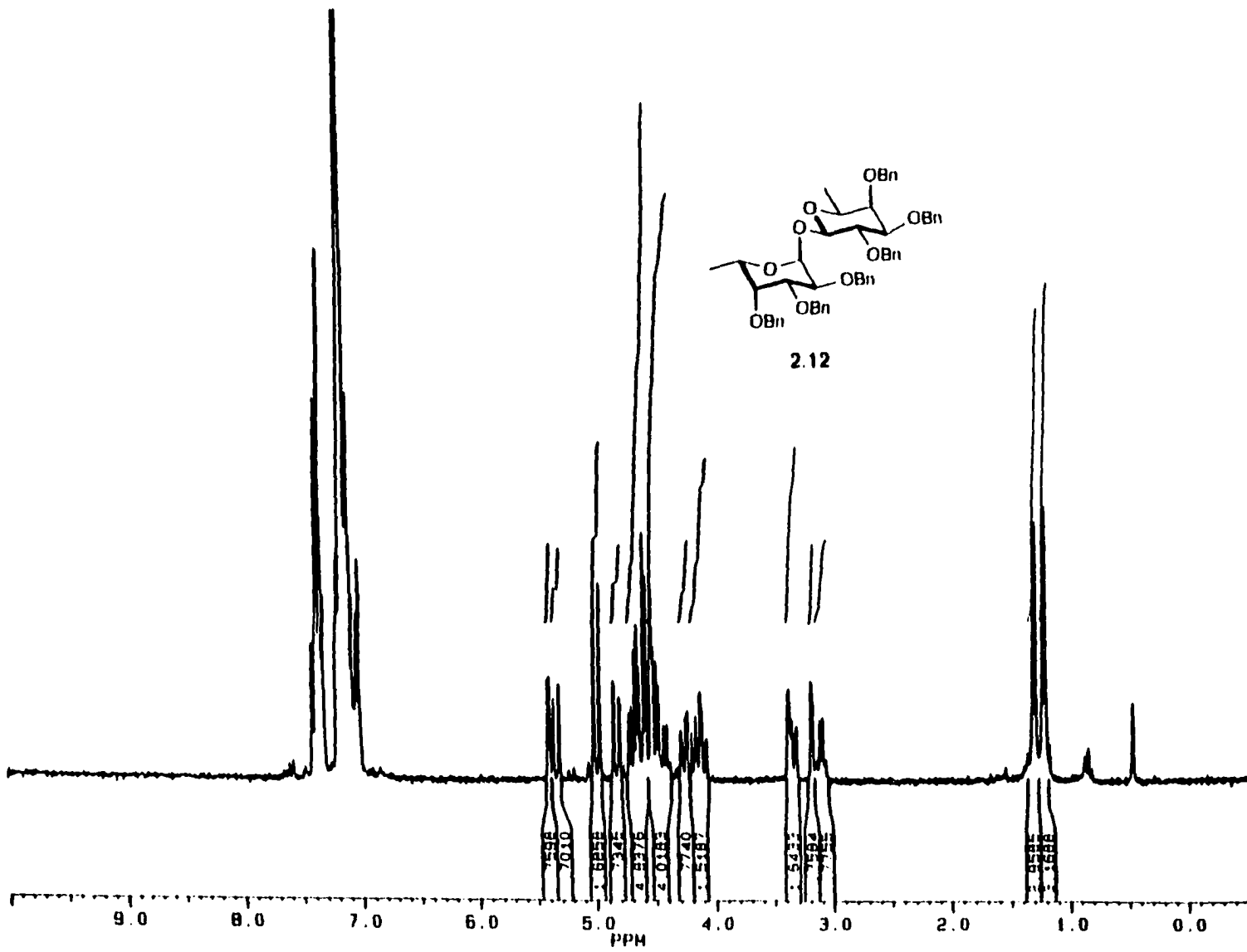


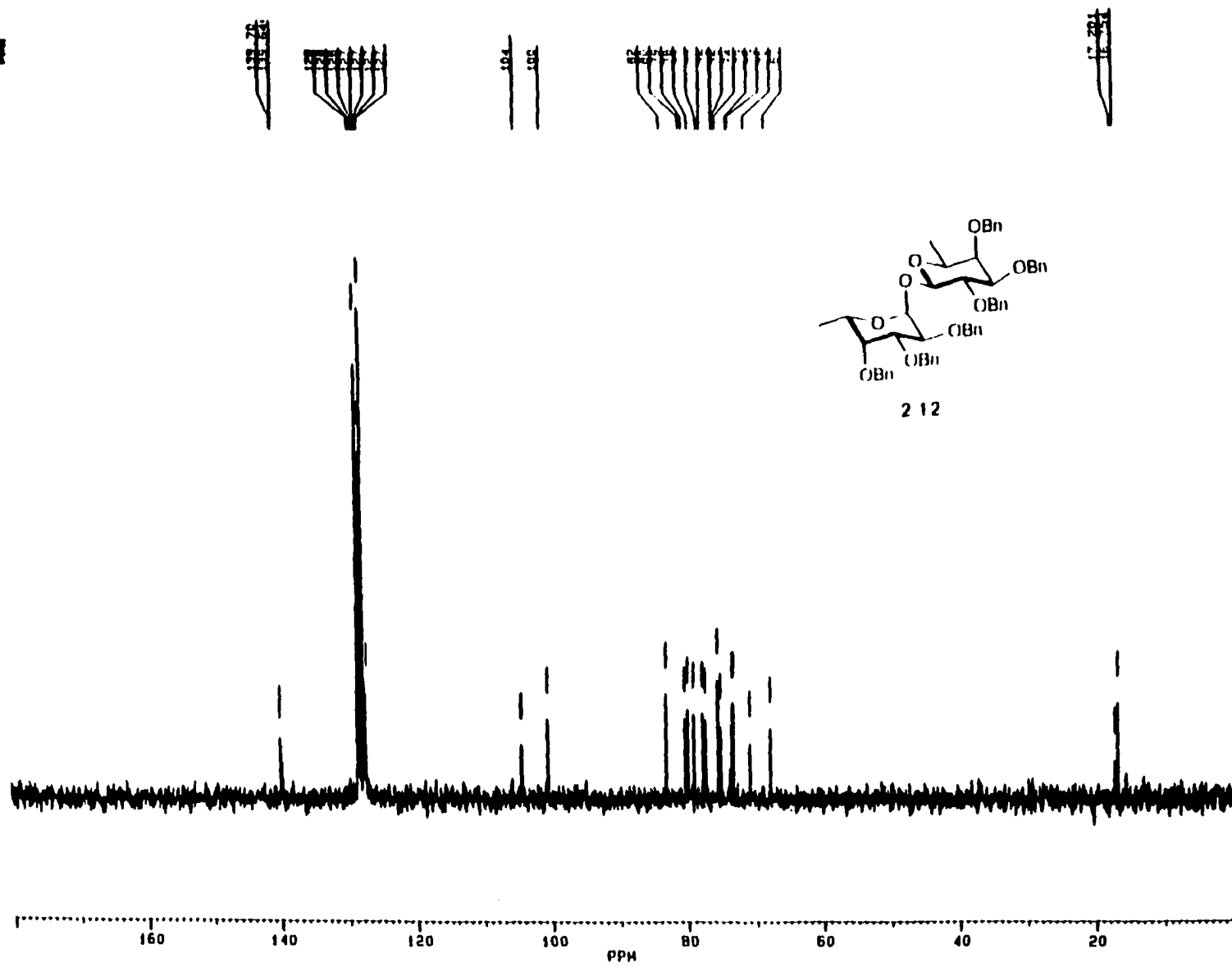


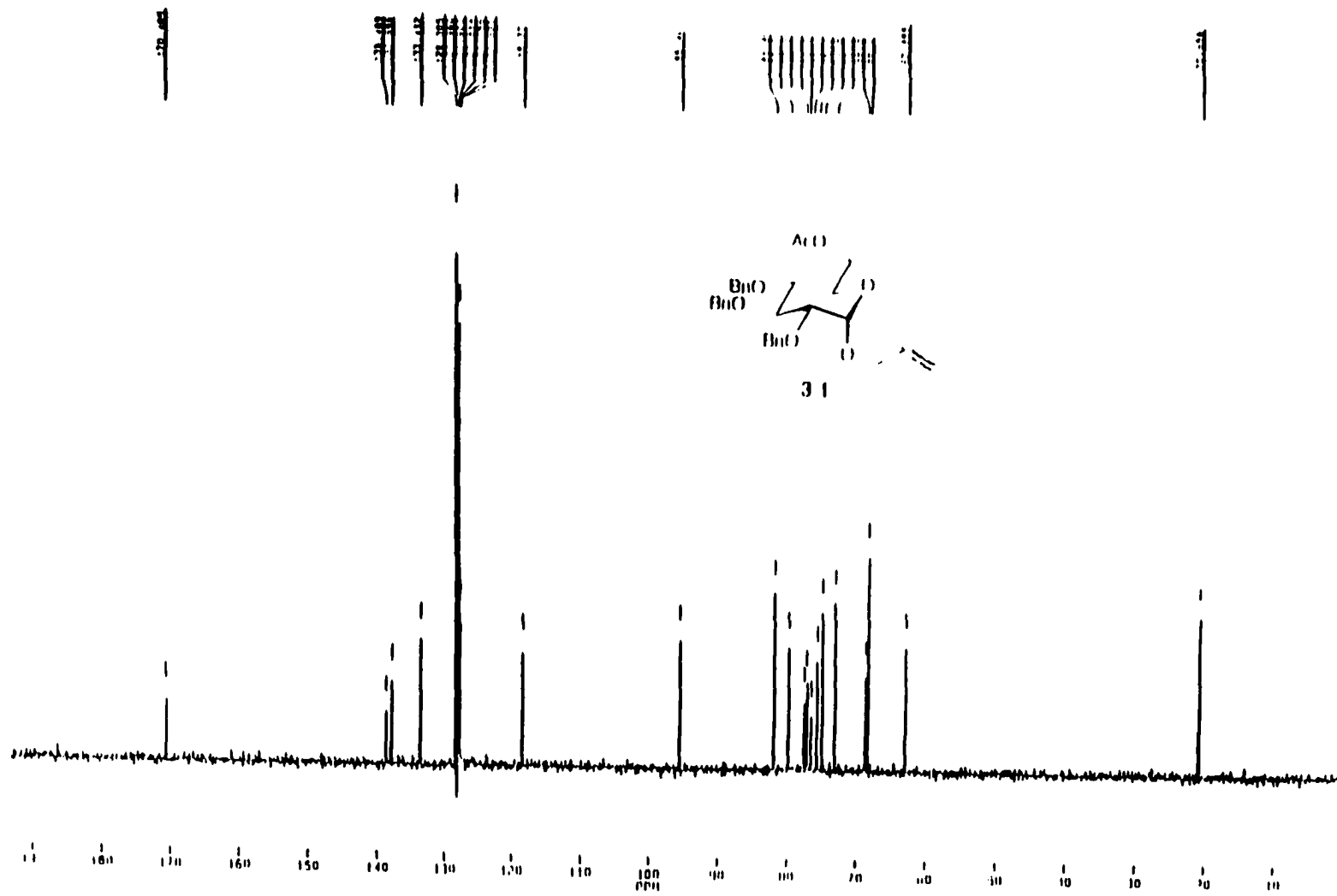


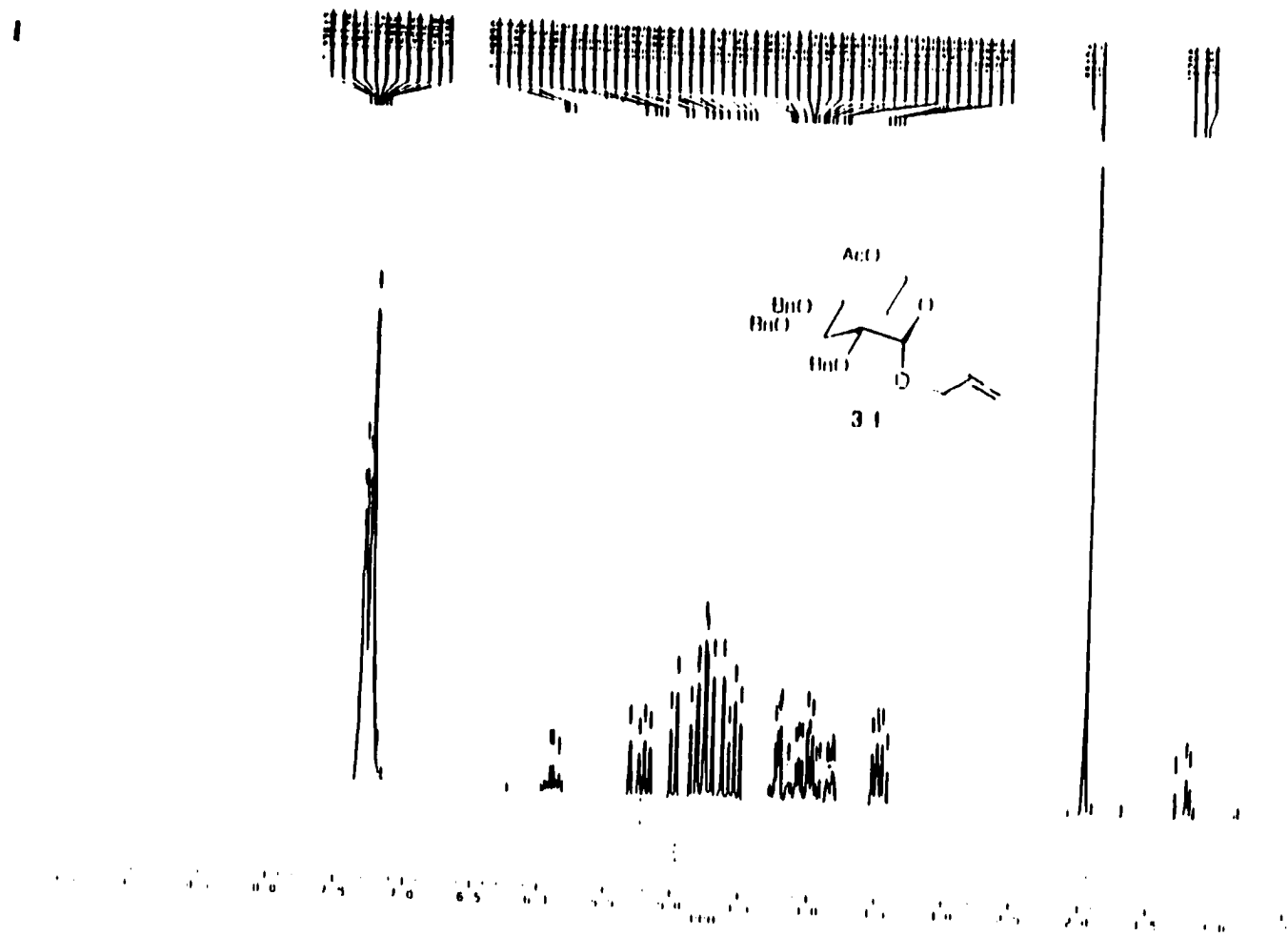


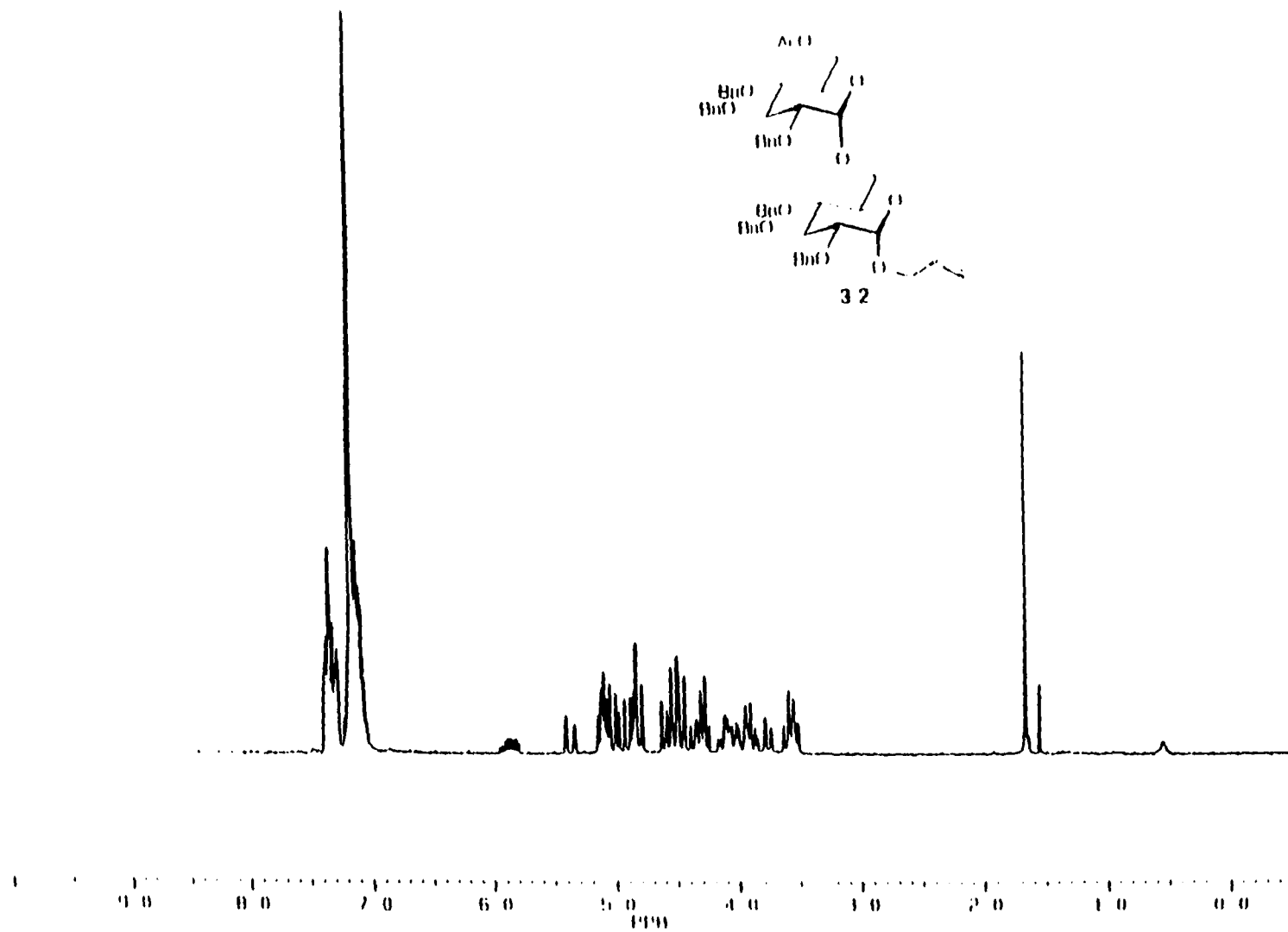




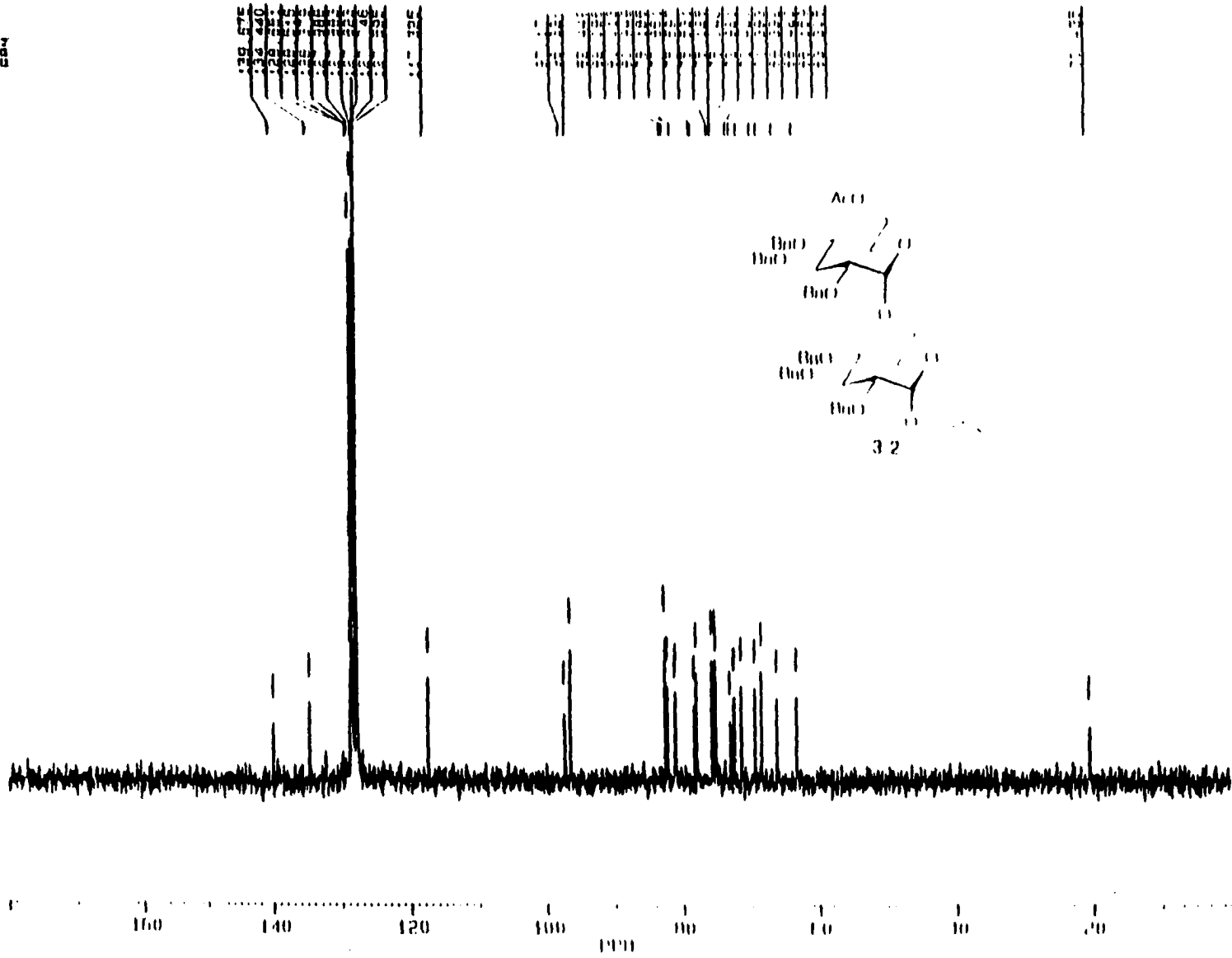




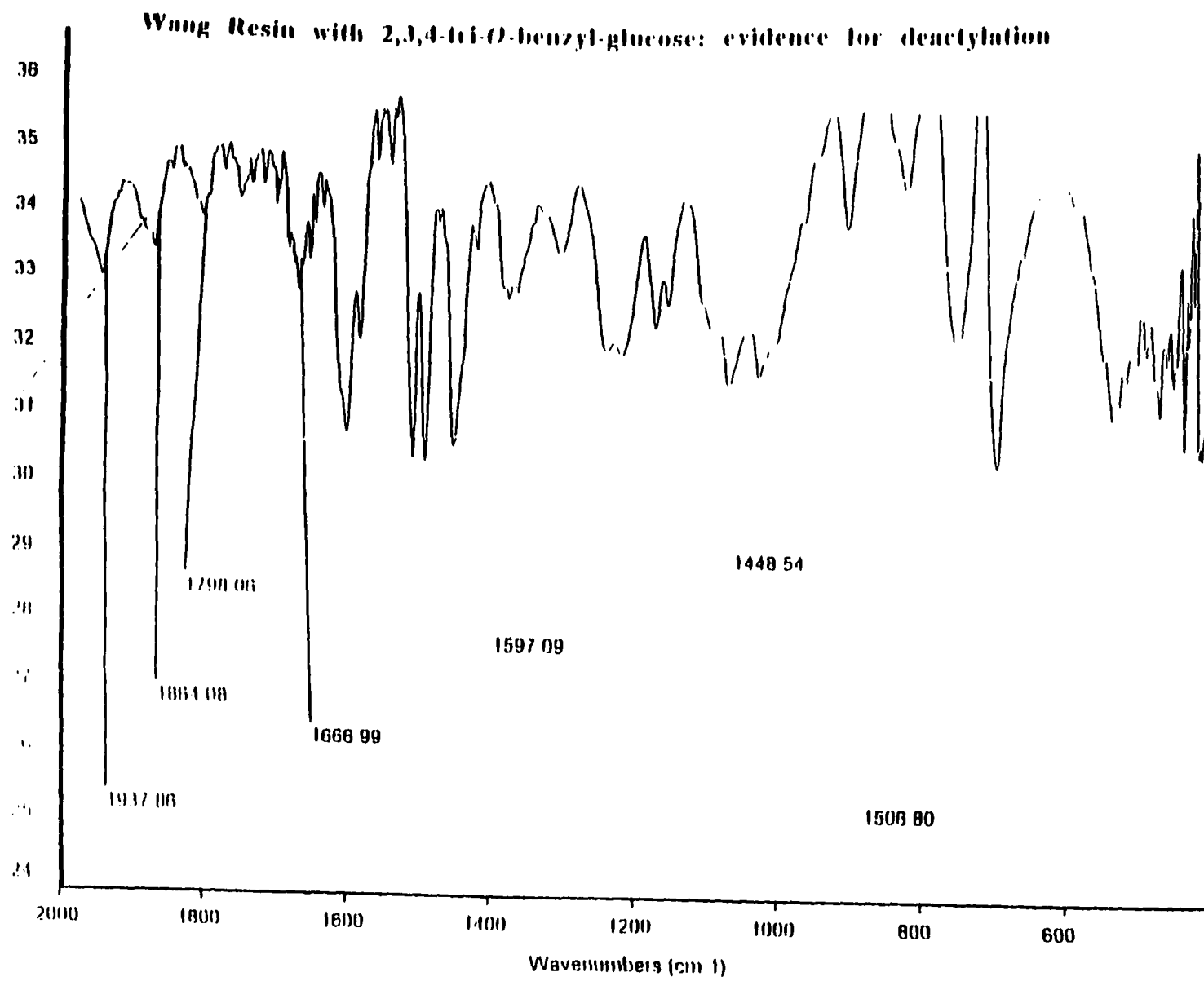




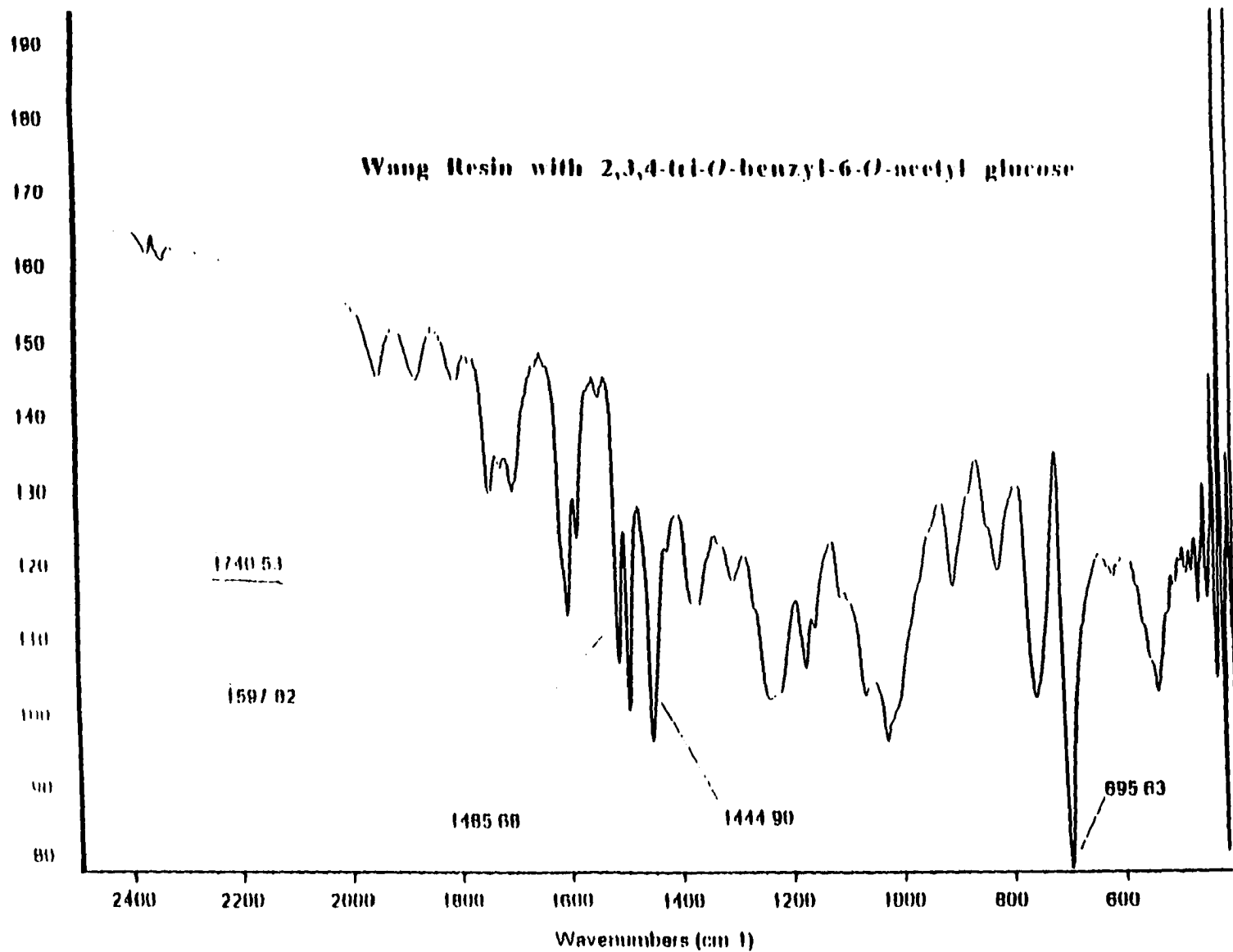
CDM



**Appendix B**  
**Solid Phase IR Spectra**







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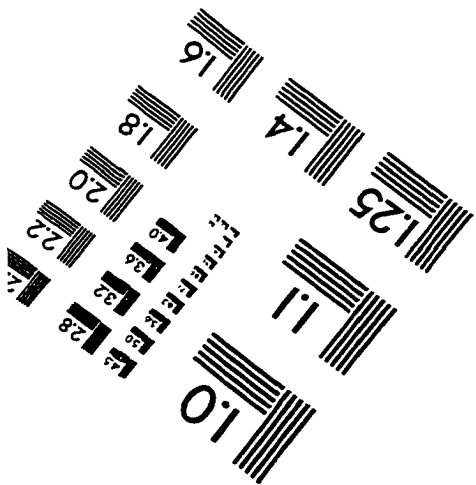
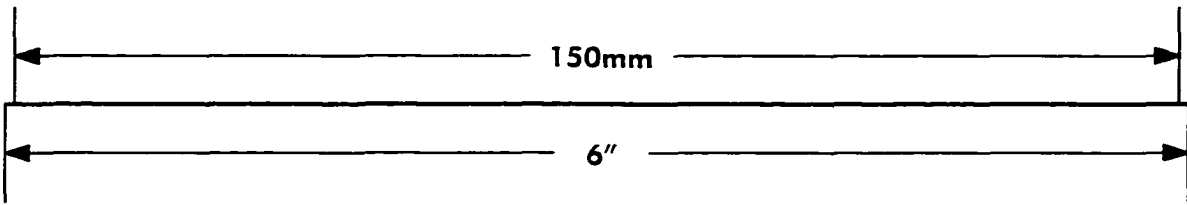
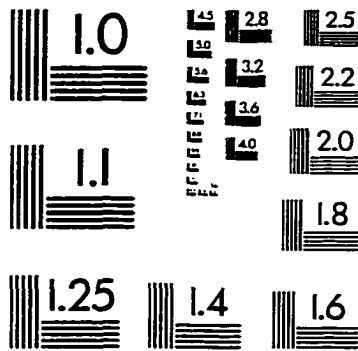
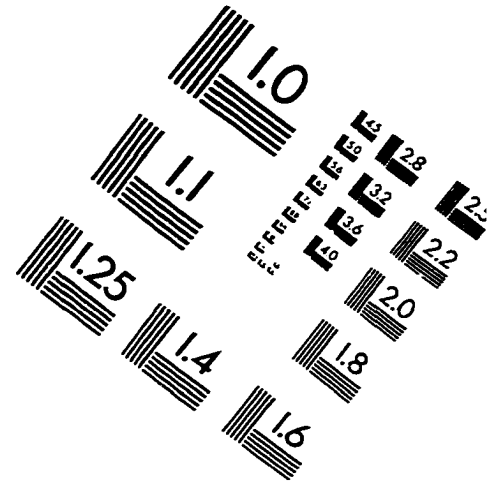
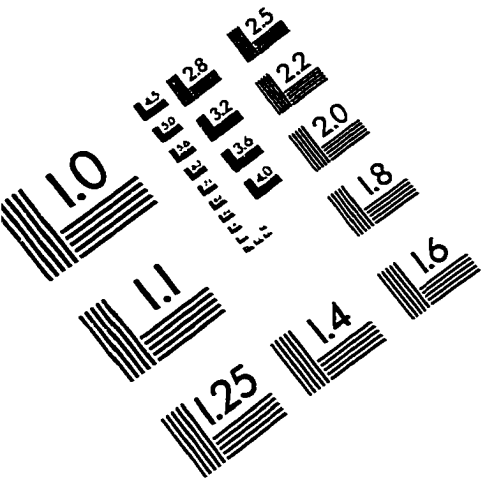
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