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APPROACHES TO THE SYNTHESIS OF IDARUBICIN-C-GLYCOSIDE

By

PETER S. BELICA

A dissertation submitted to the Graduate Faculty in Chemistry in partial fulfillment of the requirements for the degree of Doctor of Philosophy,

The City University of New York

1999

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

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THE CITY UNIVERSITY OF NEW YORK

Abstract

APPROACHES TO THE SYNTHESIS OF

IDARUBICIN-C-GLYCOSIDE

By

Peter S. Belica

Advisor: Professor Richard W. Franck

Idarubicin is an orally active anthracycline antitumor antibiotic that has entered clinical practice as a chemotherapeutic agent. Toxic side effects have been associated with the enzymatic cleavage of the idarubicin O-glycoside linkage and strategies for making an idarubicin-C-glycoside analog were explored. A new method for making C-glycosides was discovered employing a variant of the Ramberg-Bäcklund reaction. Easily prepared thioglycosides are oxidized to their sulfones, which were then subjected to standard Ramberg-Bäcklund conditions, i.e. a base plus halogenating agent. The products are exo glycals, which upon hydrogenation afford predominately the equatorial C-glycosides. The novel application was demonstrated with several sugars. The model approach to idarubicin-C-glycoside utilized daunosamine functionalized as the axial 1-hydroxymethyl compound **154** applying chemistry reported by Bednarski. The alcohol was converted, via the 1-iodomethyl C-glycoside **156,** to benzylic thioether **159** and then by oxidation to sulfone **160**. The sulfone was subjected to the Ramberg-Bäcklund conditions and hydrogenated to give an anomeric mixture of C-glycosides **162**. The anomeric integrity of the axial C-glycoside was lost during the Ramberg-Bäcklund reaction.

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Thanks are also extended to Dr. Lou Todaro for the X-ray crystal structures, to Dr. Michael Blumenstein for the 500 MHz NMR spectra, and to Professor Klaus Grohmann for his assistance when I entered the PhD. program.

I also thank my wife, Gail, and my family for their perservering moral support throughout the course of this study.

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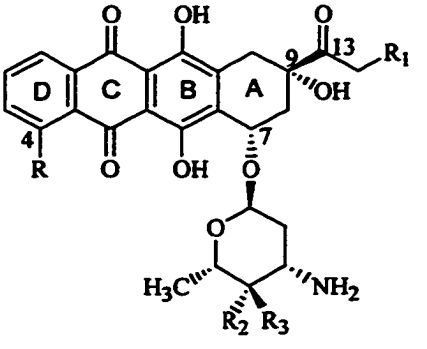
1. INTRODUCTION

In 1952, a publication[1] describing the antitumor activity of actinomycin C in animal species prompted researchers to search for other antineoplastic compounds of microbial origin. A new bacterial species, *Streptomyces peucetius,* was isolated in the early 1960s from a soil sample collected near Apulia, Italy by Farmitalia Laboratories. Fermentation and fractionation studies of the main active component yielded the potent antitumor anthracycline daunomycin.[2] Concurrent discovery of rubidomycin by Rhône-Poulenc Laboratories from *Streptomyces coeruleorubidus* and determination of its identity as daunomycin led to the coining of the name daunorubicin in recognition of the dual origin. Daunorubicin **1** is the parent of the anthracycline antibiotic family and about 2000 derivatives have been investigated, but only doxorubicin (adriamycin) **2**, epirubicin **3**, and idarubicin **4** are employed for the current clinical treatment of cancer.[3]



1 R=OCH_3, R_1=R_3=H, R_2=OH
2 R=OCH_3, R_1=R_2=OH, R_3=H
3 R=OCH_3, R_1=R_3=H, R_3=OH
4 R=R_1=R_3=H, R_2=OH

Brockmann[4] derived the name anthracycline from *anthra*quinone and tetra*cycline*, in recognition of shared properties from each class of molecules. An anthracycline is composed of an aglycone of four linearly fused six-membered rings

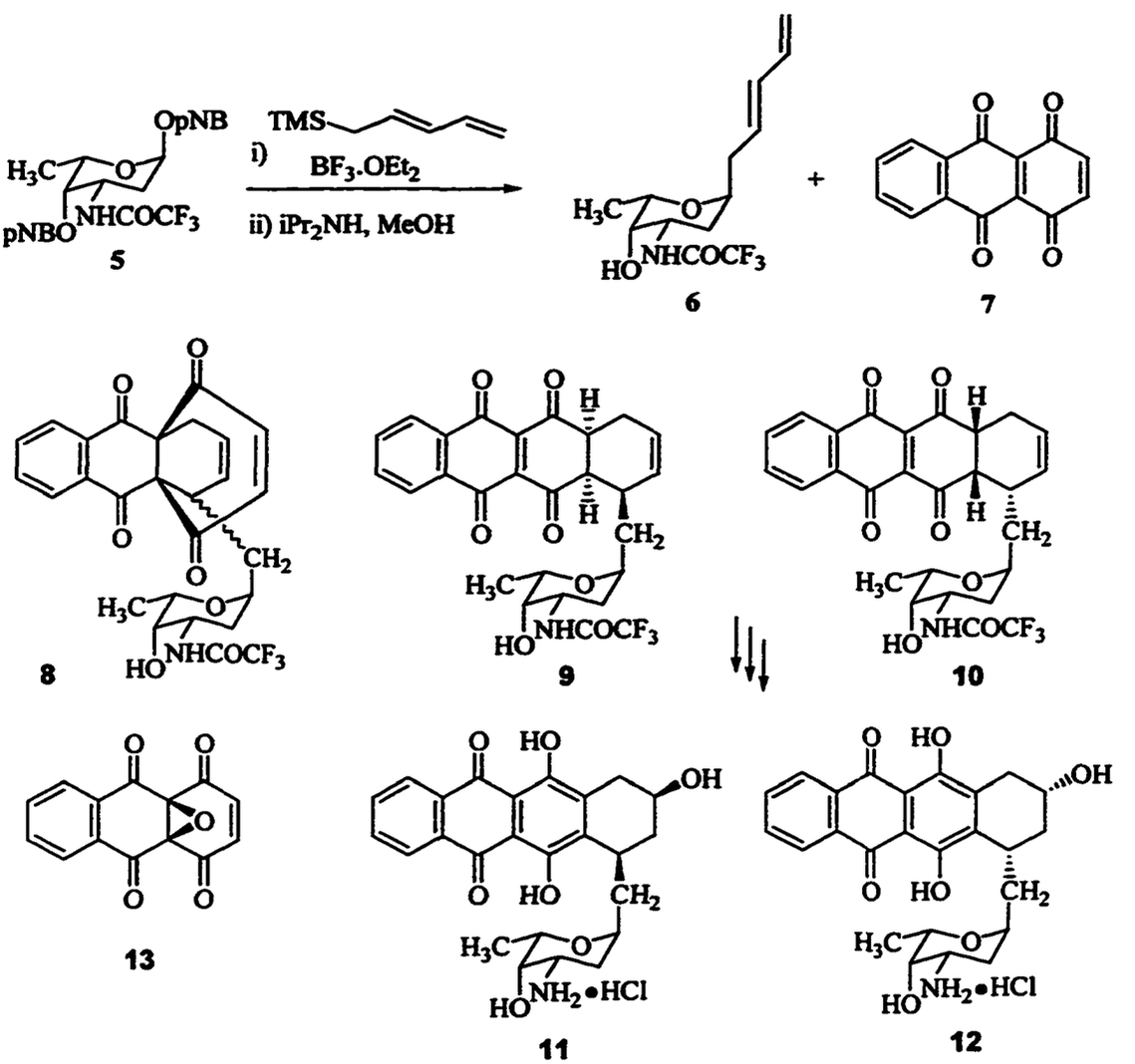
bonded with at least one sugar moiety. Cancer cell proliferation is inhibited by intercalation of the aglycone between DNA strands inhibiting DNA-processing enzymes like topoisomerase II alpha. DNA is cleaved into single or double strand breaks by this nuclear enzyme for religation in preparation for DNA replication. The DNA bound anthracycline and topoisomerase II form a ternary complex inhibiting the religation step, inducing apoptosis and cell death. Another major intracellular effect of the anthracyclines is the generation of free oxygen radicals by repetitive oxidation and reduction of the anthraquinone. Koch[5] believes that these reactive oxygen species are also responsible for antitumor activity and unwanted toxic side effects.

Idarubicin (IDA) differs from daunorubicin only by the absence of a methoxyl group at C-4, endowing the molecule with enhanced lipophilicity, thus allowing oral administration. IDA is a synthetic drug first prepared and tested in 1976.[6] The major human metabolite is idarubicinol (IOL), a 13-dihydroderivative that is unique among the anthracyclines by exhibiting activity equal to the parent compound. IDA is more bioavailable, more active, and less cardiotoxic than daunorubicin.[7] The dose limiting irreversible cardiotoxicity is a serious side effect of anthracycline therapy, prompting continued interest in molecular modification.

Anticancer drugs **1-4** suffer deactivation by hydrolytic and reductive glycosidases. Reductive cleavage of the glycosidic oxygen at C-7 is the major pathway in human metabolism,[8] and subsequent covalent binding of biological nucleophiles at position 7 is another possible cause of toxic side effects.[9] Acton[10] suggested replacement of the glycosidic oxygen by CH_2 as a means to resist metabolic deactivation. The C-glycosyl analog should also prevent alkylating activity at C-7, yet

retain the DNA binding properties necessary for antitumor activity. Acton[11] investigated the synthesis of idarubicin-C-glycoside and a method for preparing an analog was achieved as depicted in Scheme 1.1. Daunosamine **5** was reacted with (*E*)-2,4-pentadienyltrimethylsilane in the presence of $BF_3 \cdot OEt_2$ to give only the

Scheme 1.1

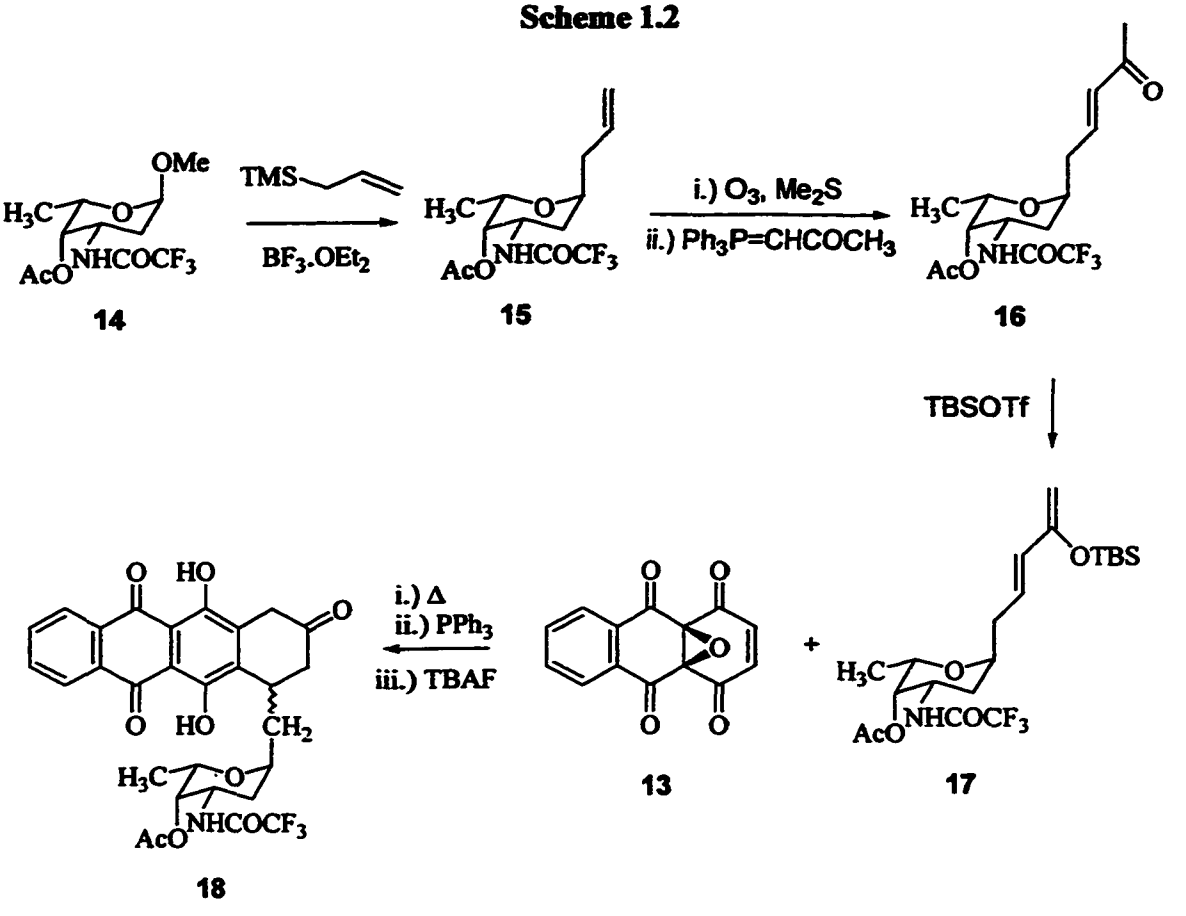


α-C-glycoside in 90% yield, which was then selectively deprotected to give **6**. The Diels-Alder reaction of compound **13** and **6** gave a diastereomeric mixture of exo-endo adducts resulting from selective facial attack on the dienophile. The diasteromeric adducts proved to be unstable. Subsequent cycloaddition of **6** with **7** gave the two

diastereomeric internal endo-adducts **8** (35%), and the external endo-adducts **9** (26%) and **10** (29%). Partial precipitation gave 75% pure **9** that was enolized with HCl/methanol and reprotected with TFAA, then crystallized to give the more stable anthracycline 8,9-olefin in 15% yield from **6**. Functionalization of the olefin with $AgOOCCF_3/I_2$ followed by treatment with methanol gave an iodohydrin that was reduced with $n\text{-}Bu_3SnH$ and light. Purification by preparative TLC and crystallization, followed by deprotection with HCl/methanol gave **11** and similarly **12**. Though the overall yields were quite low, preliminary testing of **11** and **12** showed cytotoxic effects vs L1210 cells in culture (ED_{50}'s = 4-5 μM).

Welch[12] devised an improvement of Acton's methodology, as shown in Scheme 1.2. A more complex C-glycoside diene of daunosamine was constructed prior to Diels-Alder reaction with compound **13**. Reaction of **14** with allyltrimethylsilane in the presence of TMSOTf cleanly gave the C-glycoside α-anomer **15** in 91% yield. Ozonolysis followed by treatment with Me_2S gave an aldehyde that was elaborated by Wittig reaction with $Ph_3P{=}CHCOCH_3$ to give **16** in 79% overall yield. Formation of the silyl enol-ether with TBSOTf then gave the functionalized diene **17** in 88% yield. A one pot sequence of Diels-Alder reaction with **13**, deoxygenation with PPh_3 followed by concomitant enolization-tautomerization, and finally desilylation with TBAF gave an equimolar mixture of diastereomeric ketones **18** in 27% overall yield from **13**. Unfortunately, the greatly improved overall yield was frustrated by the inability to further functionalize the 9-ketone by nucleophilic addition of an acetylide moiety. The Diels-Alder facial selectivity mimicked Acton's earlier work, but stereochemical selectivity was still an obstacle.

Scheme 1.2

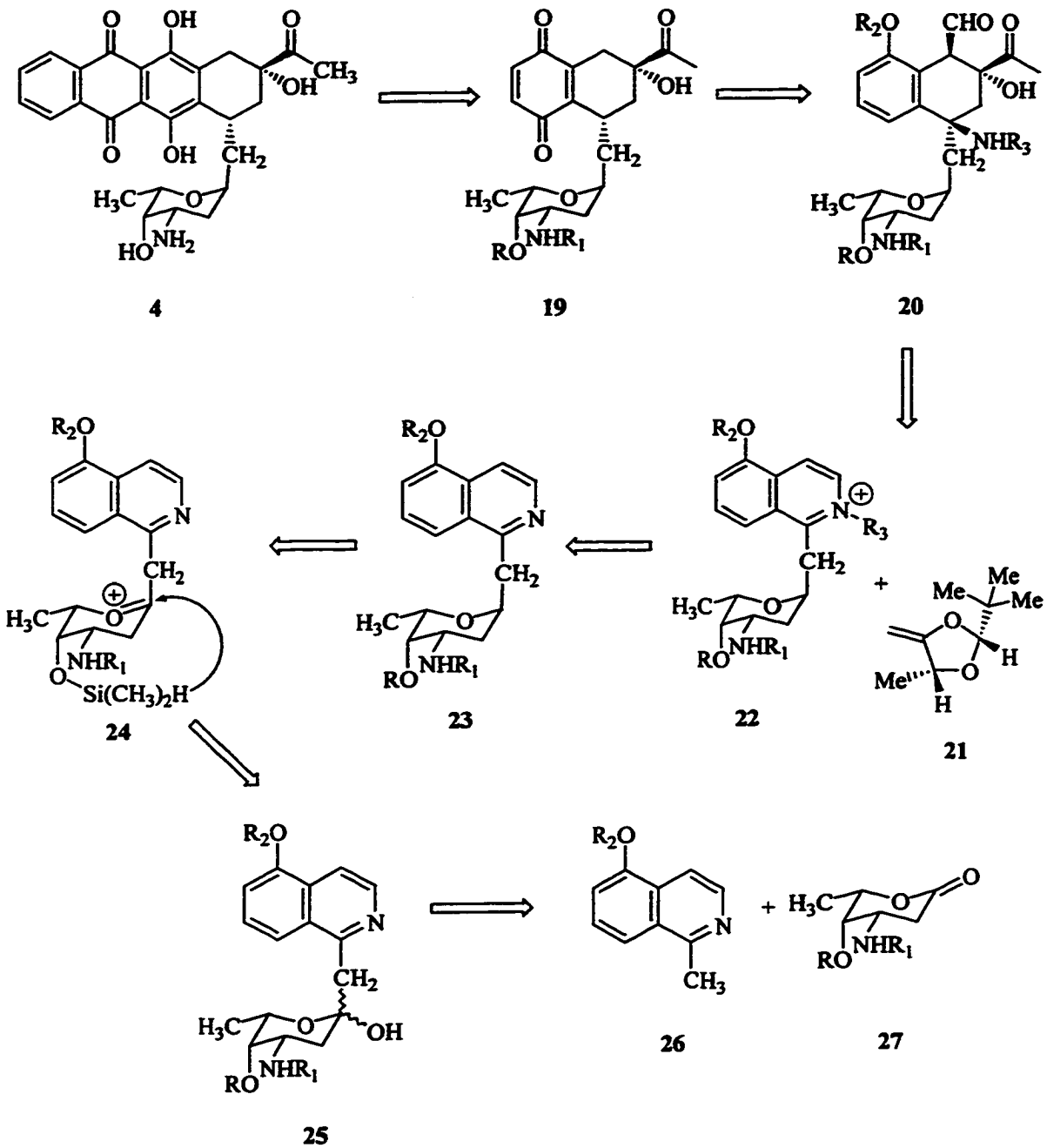


Idarubicin-C-glycoside has not yet been fully synthesized. The subject of this thesis is the investigation of alternative routes to this interesting target. Several approaches were attempted, culminating with the novel use of the Ramberg-Bäcklund reaction to make a precursor to an idarubicin-C-glycoside analog, and various C-glycosides.

2. EARLY APPROACHES

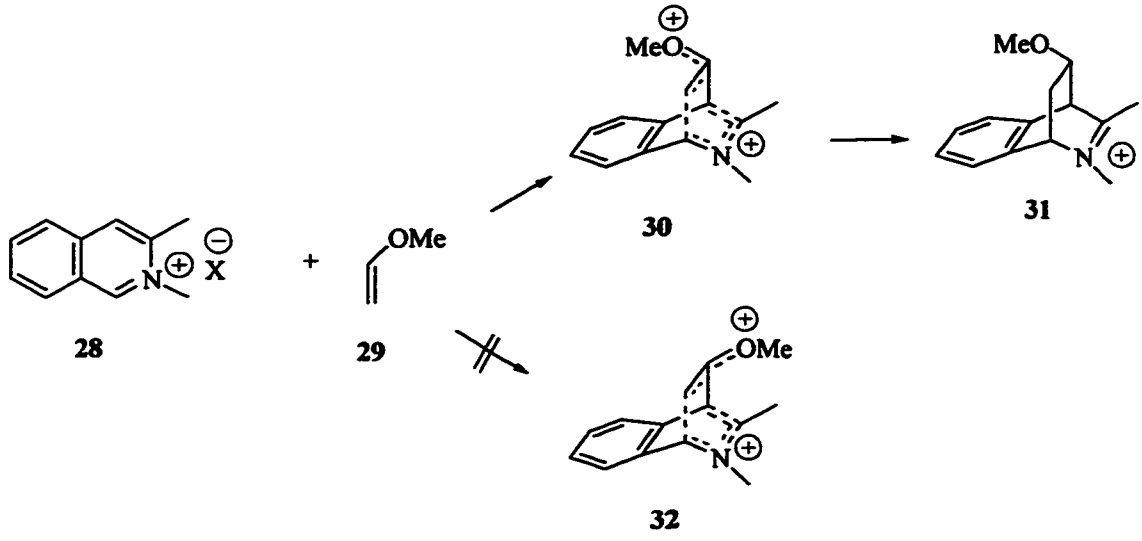
2A. Bradsher Cycloaddition

Scheme 2.1



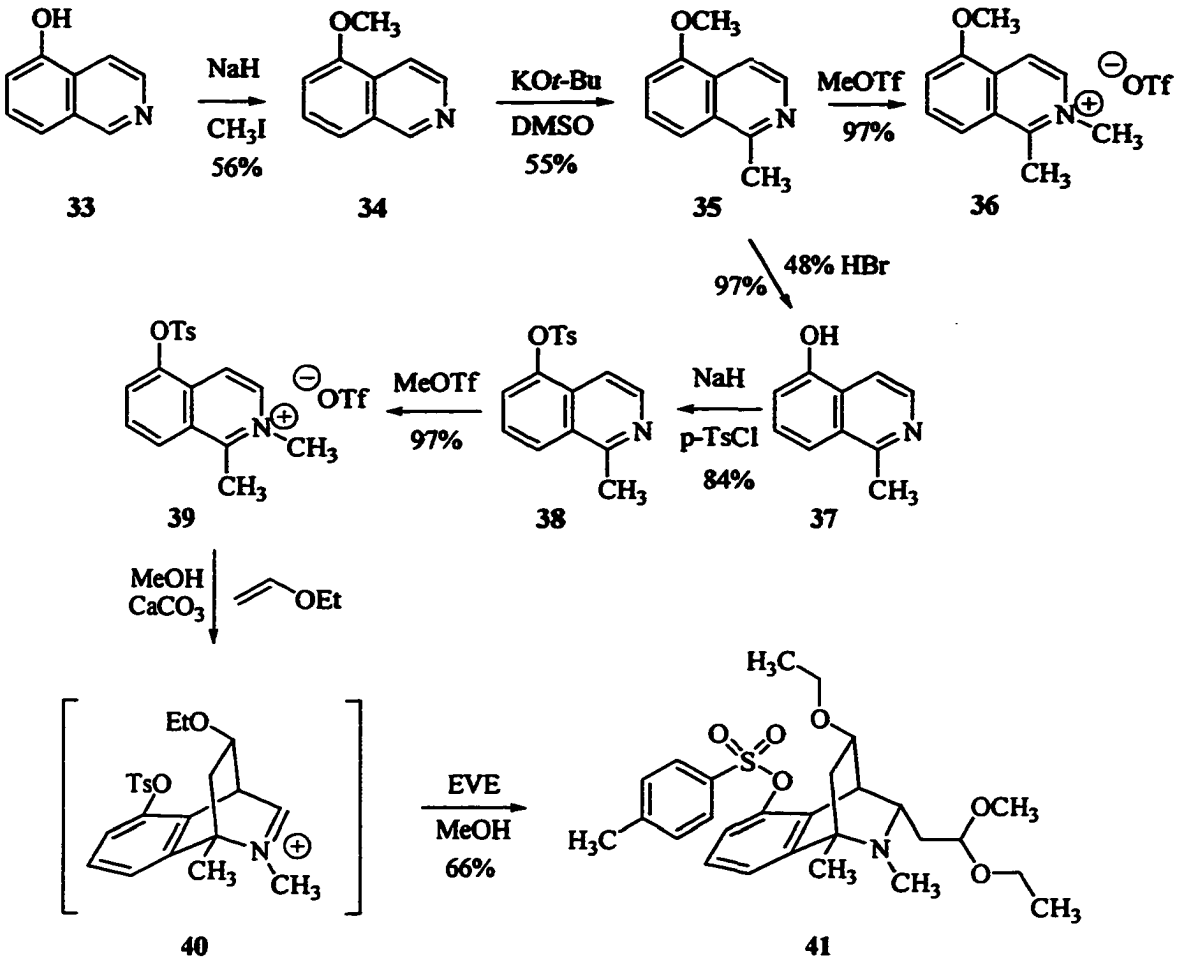
Earlier work[13] at Hunter College led to the proposal (Scheme 2.1) for a solution to the selectivity problem based on a Bradsher cycloaddition of an isoquinolinium salt **22** to a chiral dienophile **21** to give **20**. The Bradsher reaction is an inverse electron demand $4\pi + 2\pi$ Diels-Alder cycloaddition that also is referred to as a cationic polar cycloaddition. C. K. Bradsher's studies with 3-methylisoquinolinium salts[14] acting as the electron poor diene, cycloadding with electron rich dienophilic vinyl ethers and unsymmetrical alkenes,[15] demonstrated strong stereo-[16] and regioselectivity.[17] A proposed charge transfer complex (Scheme 2.2) in the transition state favors the product resulting from maximum separation of like charge.

Scheme 2.2



We obtained a result analogous to **31** by reacting excess ethyl vinyl ether with isoquinolinium salt **39** (Scheme 2.3), a readily accessible model for **22**. Commercially available 5-hydroxyisoquinoline **33** was the starting material for the isoquinolinium salt **39**. Phenolic methylation with CH_3I/NaH gave **34** in 56% yield after distillation. The simple model for **23** was obtained by 1-methylation[18] of **34** with KO*t*-Bu/DMSO to give

Scheme 2.3



35 in 55% yield after chromatography and crystallization. Quaternization proceeded readily in 97% yield with MeOTf to give **36**, after attempts with 2,4-dinitrochlorobenzene, CH_3I, and chloroacetyl chloride failed. Attempted cycloaddition of **36** with ethyl vinyl ether (EVE) was not successful, likely due to the electron donation from the 5-methoxy group. It was decided to modify the phenolic substitution with an electron withdrawing group (EWG) to decrease the HOMO-LUMO energy gap. The required phenol was obtained via deprotection of **35** with refluxing 48% HBr to give **37** in 97% yield. Benzoylation of **37** with BzCl/pyridine, followed by quaternization with MeOTf and cycloaddition with EVE possibly gave traces of a cycloadduct. A stronger EWG

was provided by tosylation of **37** with pTsCl/NaH in 84% yield. Quaternization of **38** with MeOTf gave **39** in 97% yield. Bradsher cycloaddition of **39** with a large excess of EVE in methanol gave **41** in 66% yield after chromatography. Crystals were grown from ether/hexane, and the structure of **41** was confirmed by X-ray crystallographic

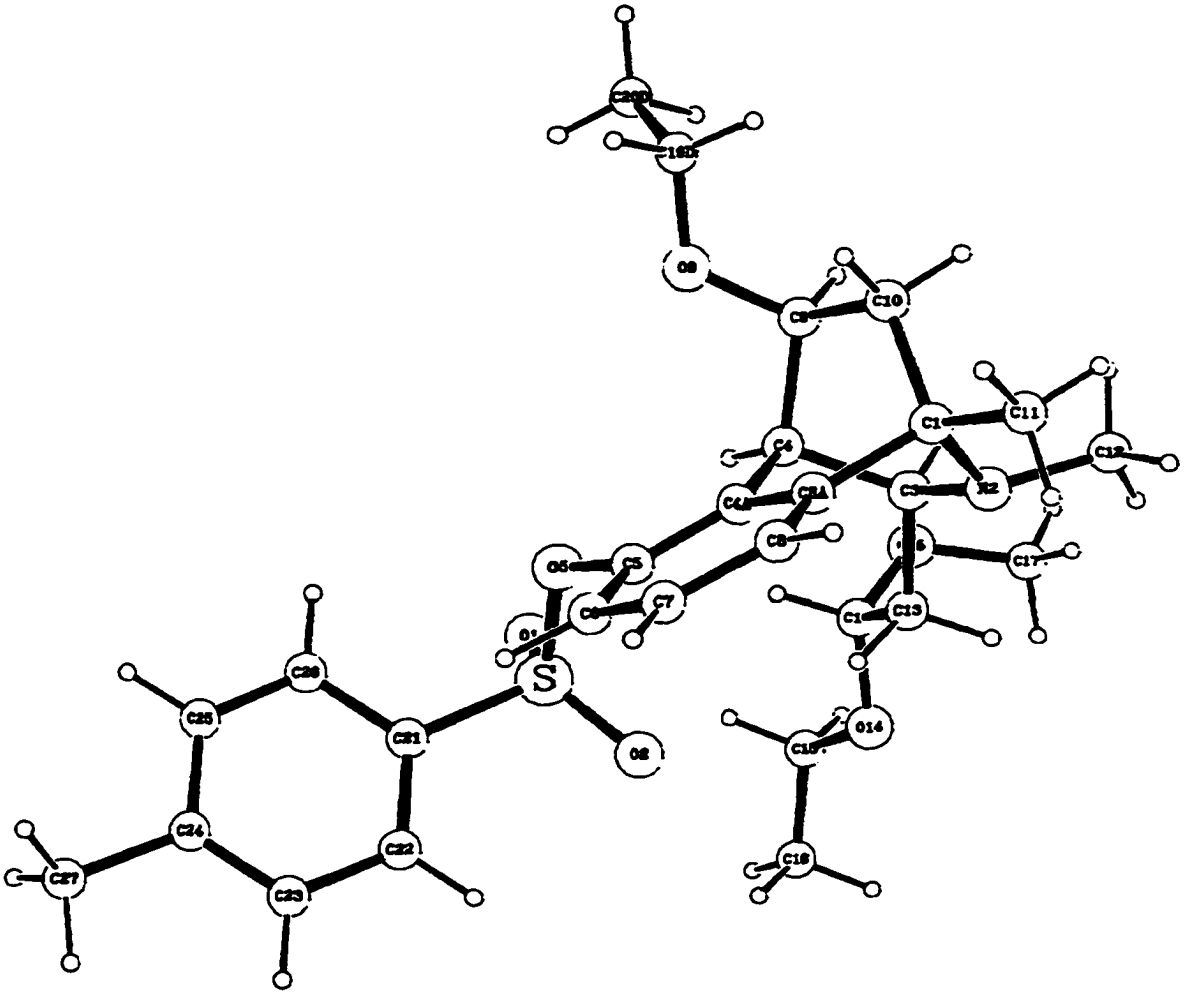
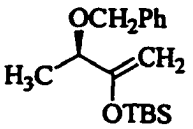


Figure 1. ORTEP drawing of the crystal structure of rac-[1α, 3β(*R**), 4α, 9*R**]-4-methylbenzenesulfonic acid 9-ethoxy-3-(2-ethoxy-2-methoxyethyl)-1, 2, 3, 4-tetrahydro-1, 2-dimethyl-1, 4-ethanoisoquinolin-5-yl ester **(41)**.

analysis (Figure 1). Apparently, the intermediate iminium cation **40** was trapped by the excess of EVE, and methanol trapped the subsequent adduct cation. The product **41**

demonstrated the power of the Bradsher cycloaddition by stereoselectively creating five chiral centers in a one-pot reaction. A quaternary chiral center was formed using an unhindered dienophile, and the exo cycloadduct was consistent with Bradsher's prediction of a product resulting from a maximum separation of like charge. The acetal side chain of **41** showed some crystallographic disorder that was attributable to the presence of some diethyl acetal (also detected in the (+)FAB MS) mixed in with the majority methylethyl acetal. Use of ethanol as a solvent would likely have provided a homogeneous acetal.



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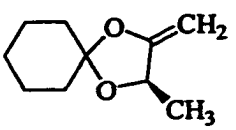

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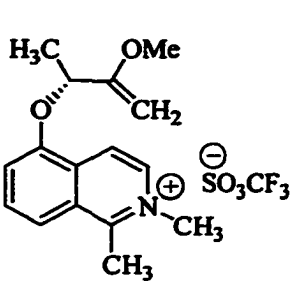

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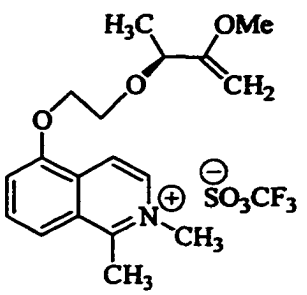
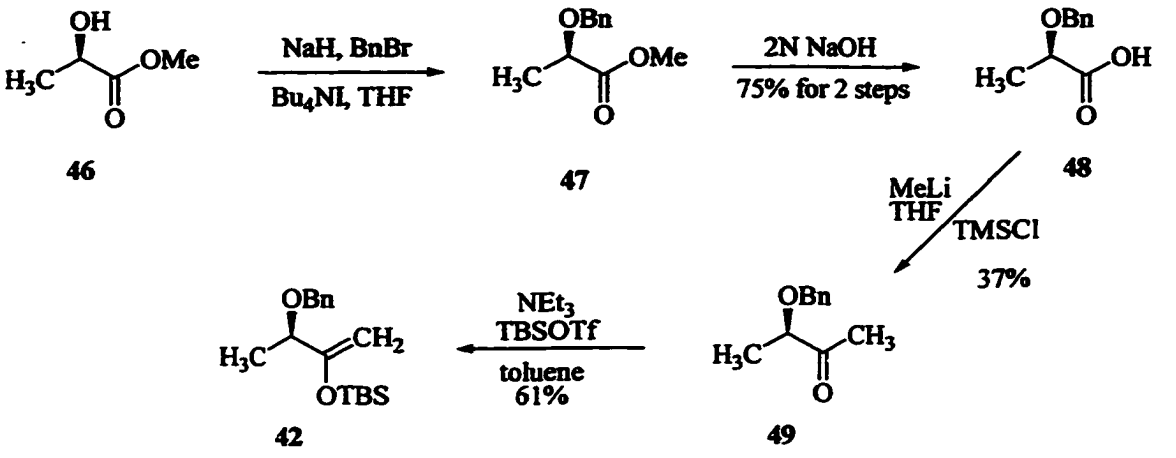


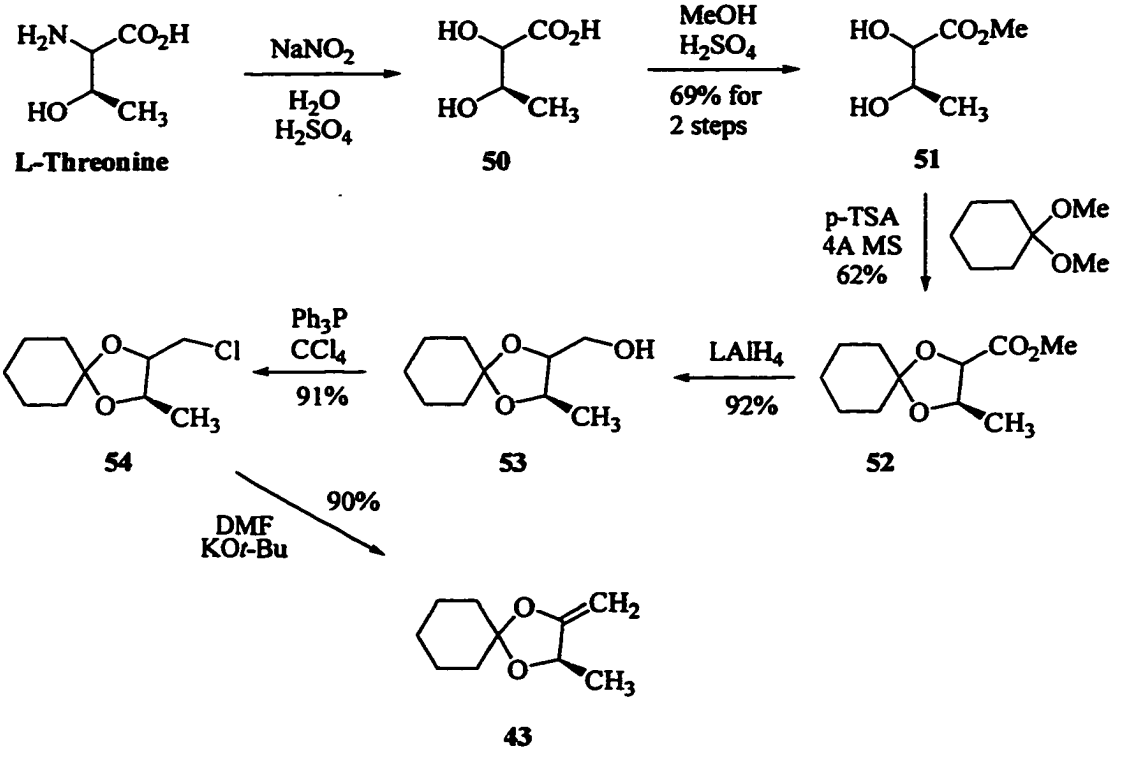
45

Unfortunately, cycloadditions of **39** with more complex chiral dienophiles **42** and **43** or with tethered **44** and **45** were unsuccessful. The overview of the preparation of compounds **42-45** is shown in Schemes 2.4-2.6.

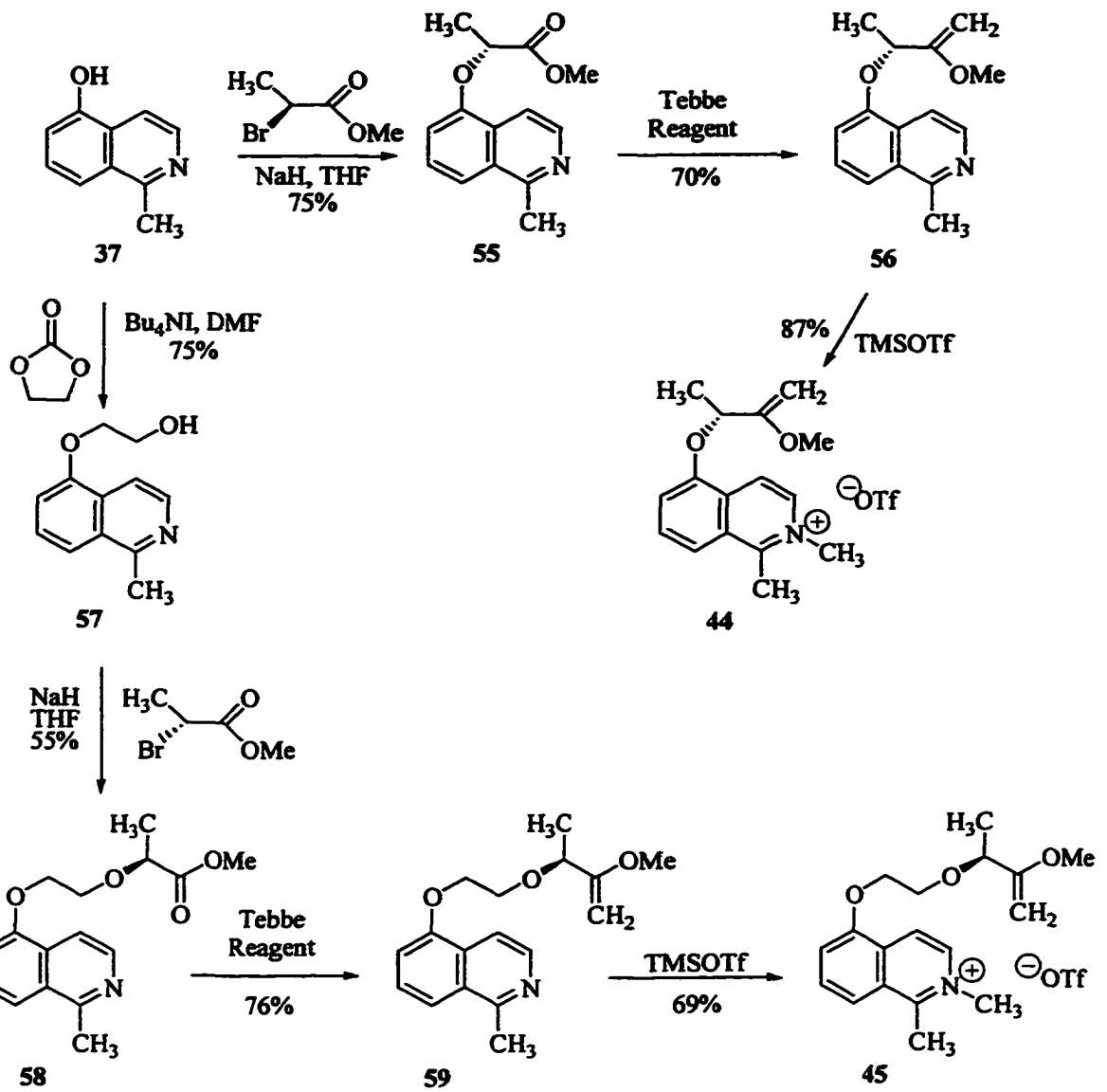
Scheme 2.4



Scheme 2.5



Scheme 2.6



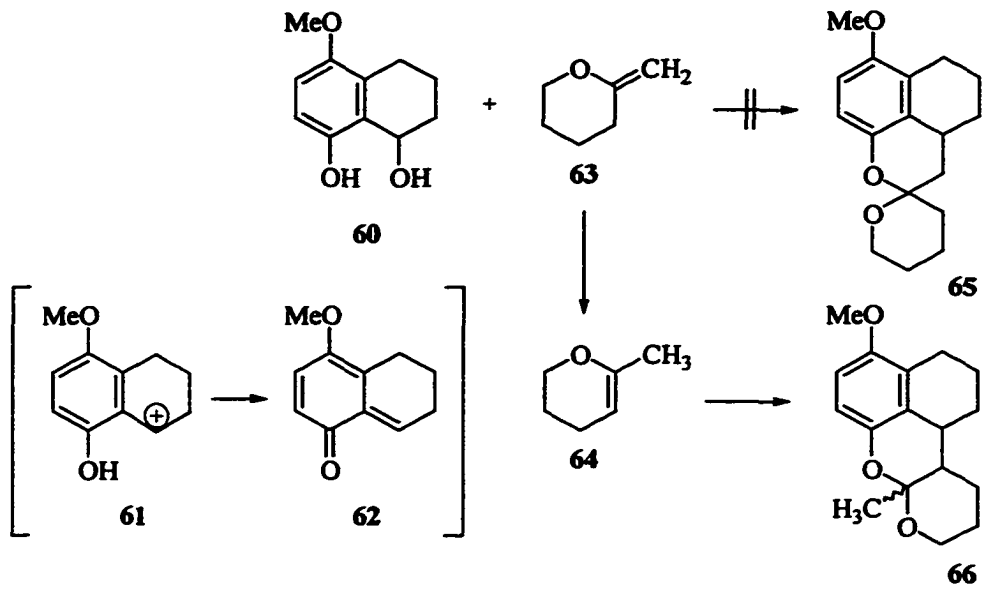
Compound **43** did form a cycloadduct with the relatively unhindered 2,4-DNP quaternary salt of isoquinoline. Thus, it was clear that the highly substituted isoquinolinium salt **22** would require a sterically unhindered dienophile, demonstrated by the lack of reactivity of the highly substituted dienophile **43** with the model 1-methylisoquinolinium salt **39**. The chiral methyl group of the dienophile was necessary

to fix the desired stereochemistry of **20**, so the Bradsher approach was reluctantly abandoned.

2B. Quinone Methide Cycloaddition

The quinone methide carbocation cyclization methodology of Angle[19] was next considered as a possibility (Scheme 2.7) for linking the aglycone and sugar. Diol **60**

Scheme 2.7

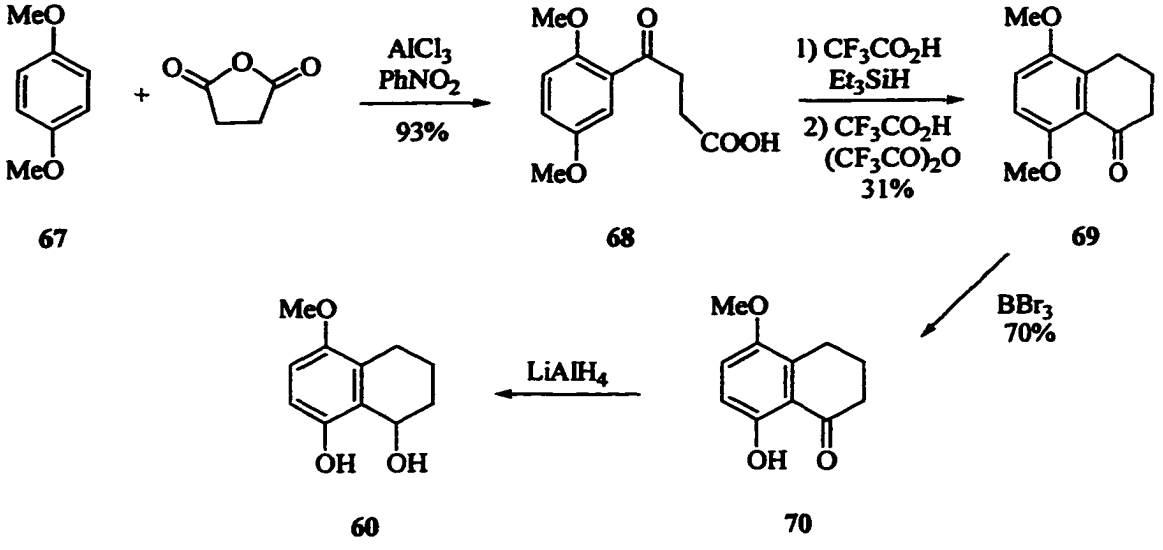


was treated with $SnCl_4$ to form carbocation **61** that presumably forms **62** and can cycloadd with model enol-ether **63**. In spite of the presence of $(CH_3O)_3SiCH_3$ as excess acid scavenger, **63** isomerized to **64** more rapidly than quinone methide formation, and **66** was formed instead of desired **65**. Three isomers of **66** were isolated, each showing six methylenes, two sp^3 methines, and a quaternary methyl other than methoxyl by ^1H and ^{13}C NMR.

Diol **60** was prepared from commercially available 1, 4-dimethoxyhydroquinone **67** in five steps as shown in Scheme 2.8. Friedel-Crafts acylation of **67** with

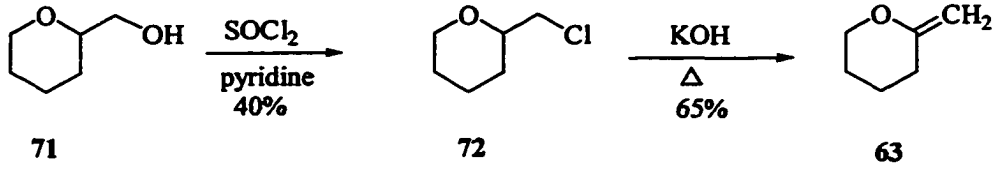
succinimide gave crystalline **68**, and the direct conversion to **69** was only achieved in low yield in contrast to the 78% yield reported by Swenton.[20] Regiospecific demethylation[21] with BBr_3 gave **70** after chromatography, and then reduction with LAH

Scheme 2.8



cleanly gave diol **60** in quantitative yield. The acid sensitive 2-methylenetetrahydropyran **63** was prepared[22] from commercially available **71** in two steps (Scheme 2.9). Successful isolation of **63** required that the distillation glassware be rinsed with a potassium hydroxide solution and oven-dried before use.

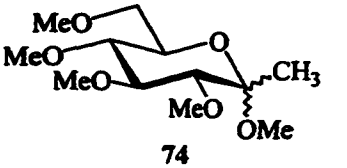
Scheme 2.9



The enol-ether of permethylated glucose **73** was more stable to the reaction conditions, but no cycloaddition was apparent with generated **62**, instead **74** was the

major isolated product. In light of the discouraging results, the quinone methide strategy was abandoned.

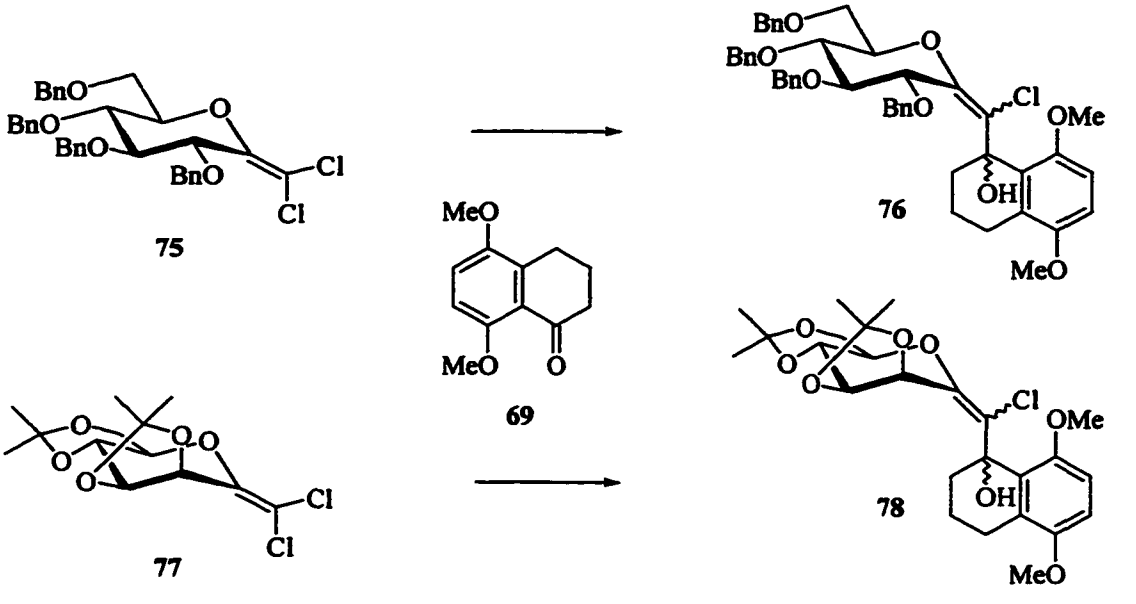
73



74

2C. Organolithium Coupling via Dichloromethylene Lactones

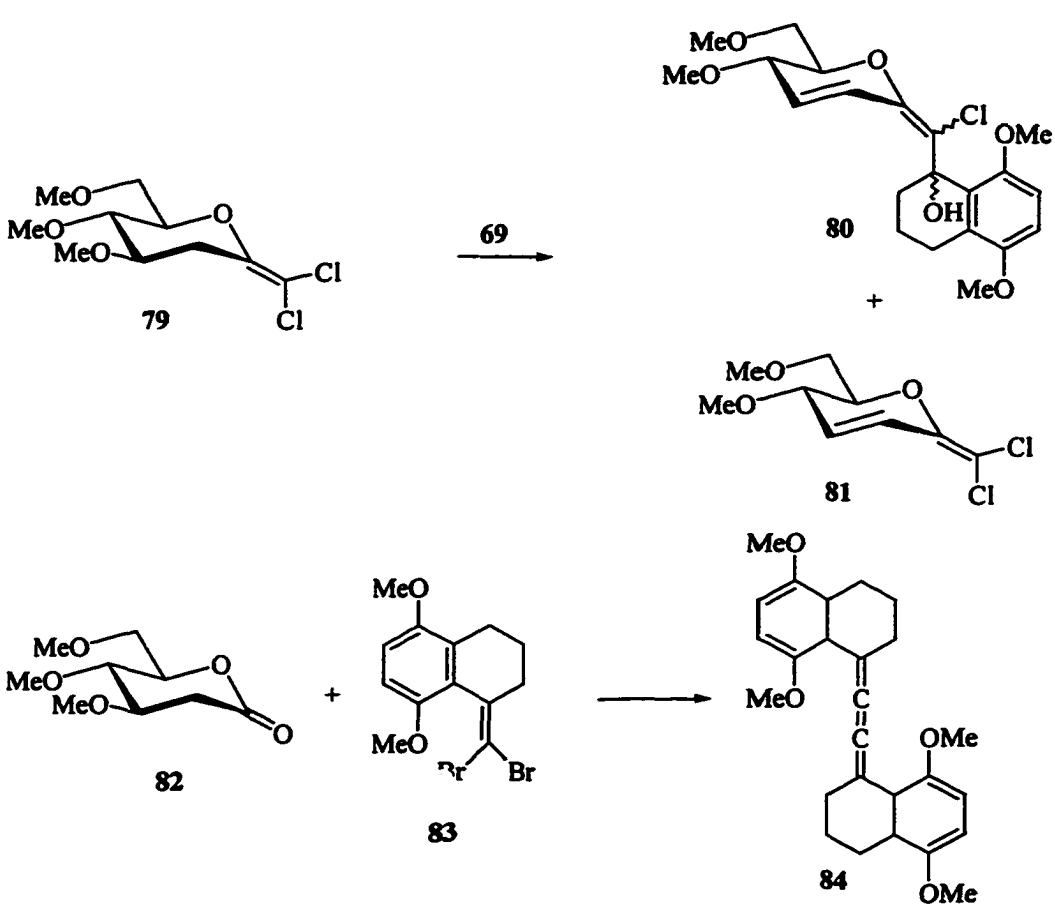
Scheme 2.10



Chapleur's methodology[23] for the dichloromethenylation of sugar lactones was applied to provide substrates for metallation and subsequent reaction with model tetralone **69** as shown in Scheme 2.10. The reaction of **75** or **77** with n-BuLi followed by the addition of **69** gave low yielding mixtures of **76** and **78** respectively. The (+)FAB MS and ^{1}H NMR spectra was consistent with the structures **76** and **78**.

Reaction of **69** with the anion from **79**, a 2-deoxy model for daunosamine, gave mostly undesired elimination products **80** and **81** in Scheme 2.11. The (+)FAB MS, ^{1}H NMR, and ^{13}C NMR spectra was consistent with the structure of **80**. The (+)FAB MS and ^{1}H NMR was also consistent with the structure of by-product **81**. Inverse addition of lactone **82** to the anion of **83** did not provide any coupled product. Instead, spectral evidence indicated that yellow crystalline **84** was curiously the likely major product. MS confirmed the molecular weight of **84**, while ^{1}H and ^{13}C NMR also provided support, but suitable crystals for a definitive crystallographic analysis could not be obtained. Since the 2-deoxy sugar was giving undesired elimination products and yields were generally low, another alternative approach was attempted.

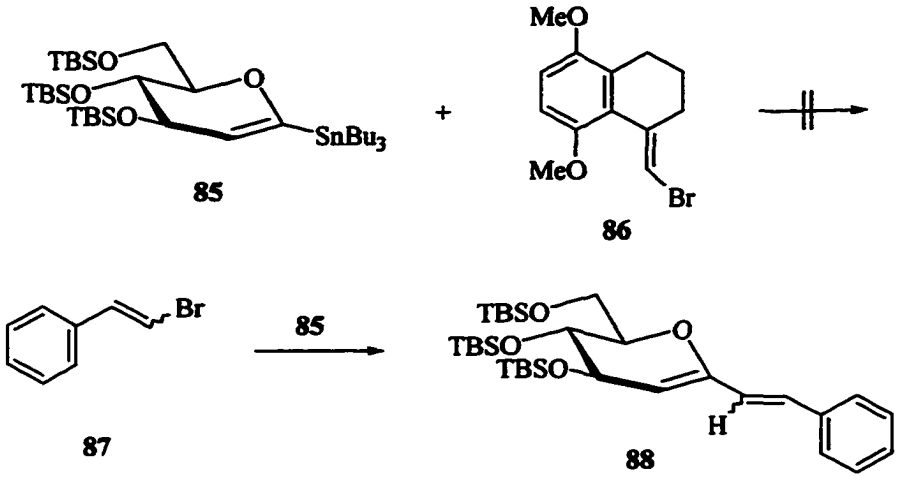
Scheme 2.11



2D. Stille Coupling

The palladium catalyzed Stille[24] coupling between a vinyl halide and a vinyl stannane was briefly explored (Scheme 2.12). Despite various combinations of substrates, catalysts, and conditions, the only coupling which showed some success was between **87** and **85**, albeit in low overall yield. Diene **88** was a 3:1 mixture of geometric isomers by ^{1}H NMR. The preparation and purification of **85** was rather difficult, and adaptation to daunosamine was not considered to be practical, so emphasis was shifted to another approach.

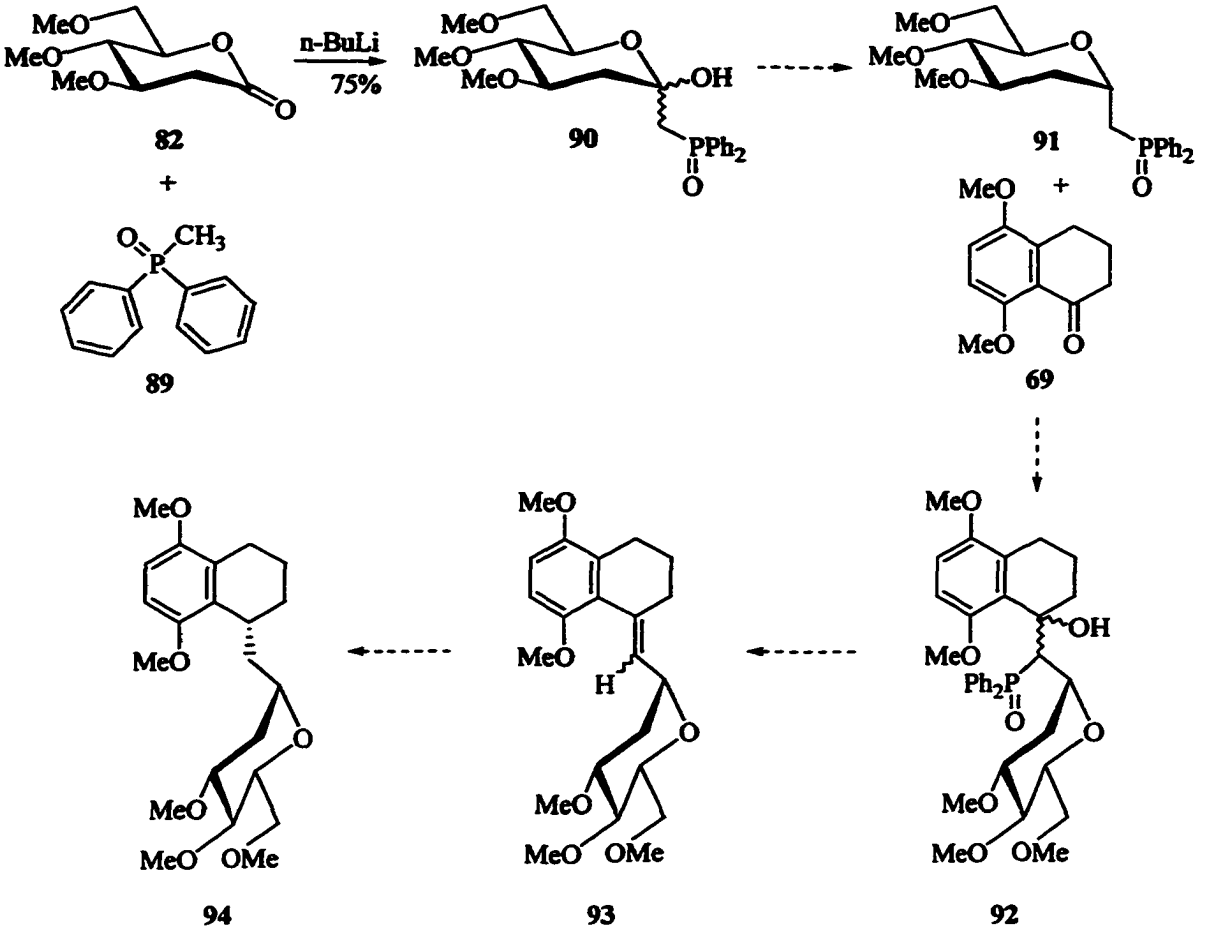
Scheme 2.12



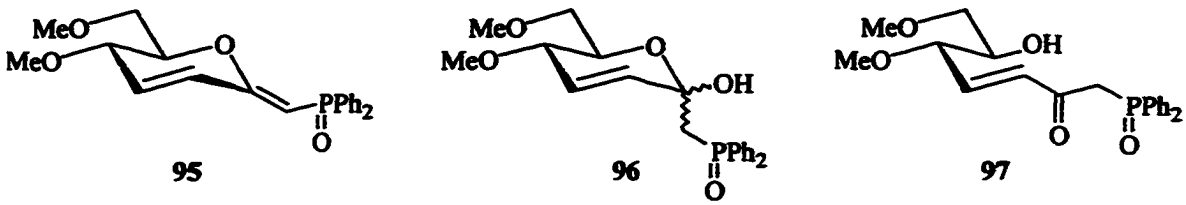
2E. Homologation with Methyldiphenylphosphine Oxide

The next approach (Scheme 2.13) was an attempt to "stitch together" the model aglycone **69** and model sugar lactone **82** using methyldiphenylphosphine oxide **89**. Warren[25] formed a stable hemi-acetal from the reaction of a non-sugar cyclic lactone with the anion of **89** generated by n-BuLi. In like fashion, hemi-acetal **90** was obtained as a single compound of undetermined stereochemistry in 75% yield and confirmed by

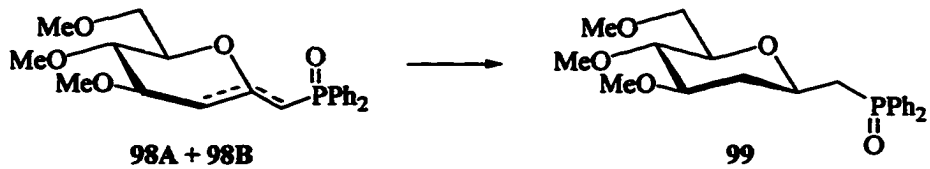
Scheme 2.13



MS, ^{1}H and ^{13}C NMR. We had planned to obtain the α-anomer **91** by varying the ionic reduction of **90** using different silyl hydrides and solvents. It was hoped that generation of the anion of **91** with n-BuLi and reaction with **69** would give **92**, which would be followed by the simultaneous elimination of the hydroxy group and phosphine oxide with NaH/DMF to give mixed alkenes **93**. Investigation to find suitable stereoselective reduction conditions of the alkenes would then have been required. All attempts to ionically reduce **90** failed, giving mostly elimination products **95**, **96**, and **97**, identified on the basis of their MS and ^{1}H NMR. However, **90** was dehydrated to give **98A** and



98B in 73% yield as a separable 86:14 endo:exo mixture of alkenes using trifluoroacetic



anhydride/NEt_3 at -72 °C. The endocyclic alkene **98A** was catalytically reduced with 10% Pd/C at 50 psi hydrogen giving β-anomer **99** in 94% yield, characterized by X-ray crystallography (Figure 2).

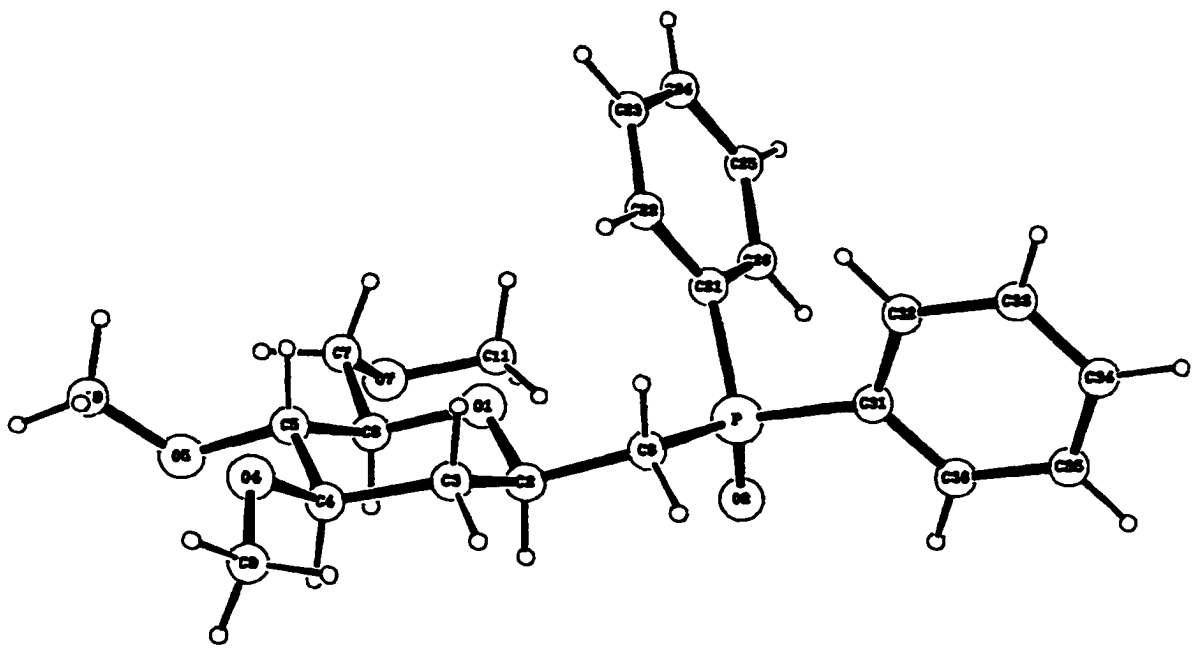
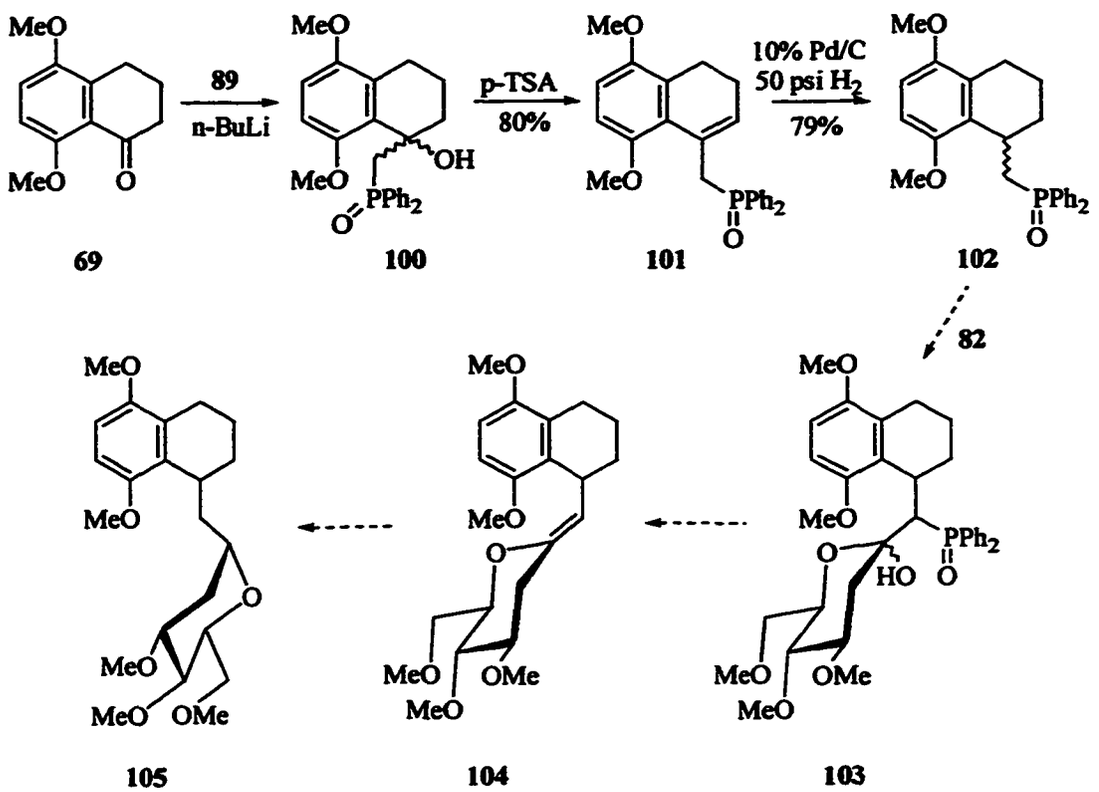


Figure 2. ORTEP drawing of the crystal structure of 2, 6-anhydro-1, 3-dideoxy-1-diphenylphosphoryl-4, 5, 7-tri-O-methyl-β-D-arabino-heptitol (**99**).

Before expending any effort exploring reductive conditions that would give the α-anomer, it was decided to test the stitching concept with the β-anomer. Thus, the

anion of **99** was generated with various bases and found to be unreactive with tetralone **69**. The bases examined were n-BuLi, LDA, KO*t*-Bu, $LiN(TMS)_2$, $NaN(TMS)_2$, $KN(TMS)_2$, and n-BuLi-TMP in the solvents THF, DMF, and THF/HMPA.

Scheme 2.14

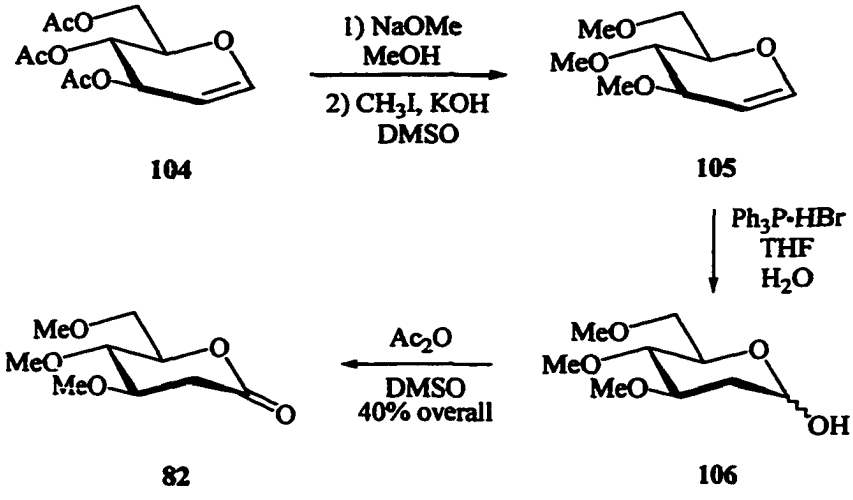


"Inverse stitching" of the pieces was then considered in Scheme 2.14. The anion of **89** added to tetralone **69** to give **100**, which readily dehydrated simply by mixing with aged chloroform and concentrating *in vacuo* to give **101** in 80% yield after chromatography. However, on a larger scale, tosic acid was needed to effect the dehydration. Catalytic reduction gave **102** in good yield, but the anion of phosphine oxide **102** was not reactive with sugar lactone **82**. This approach would have required finding stereoselective reduction conditions for **101** and **104** had the last "stitch" been successful. The MS and ^1H NMR spectra of compounds **100**, **101**, and **102** were

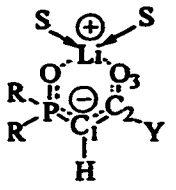
compatible with their respective structures. Compound **101** displayed a vinylic dd at 6.22 ppm, and a doublet from the exocyclic methylene at 3.98 ppm. The new methine of **102** was a multiplet at 3.47 ppm.

Crystalline lactone **82** was prepared in 40% overall yield (unoptimized) from commercially available triacetoxyglucal **104** as shown in Scheme 2.15. Hydrolysis of **104** was complete in 20 min using a 0.5 molar equivalent of NaOMe in methanol, and permethylation[26] of the crude concentrate with CH_3I/powdered KOH/DMSO gave **105** in 99% crude yield. 2-Deoxytrimethoxy glucose **106** was readily made in quantitative crude yield applying Falck's[27] methodology, and was then oxidized to a lactone with Ac_2O/DMSO to give colorless **82** after chromatography and crystallization.

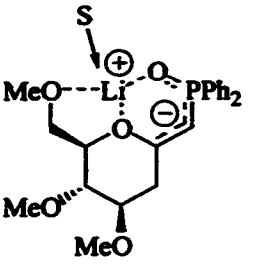
Scheme 2.15



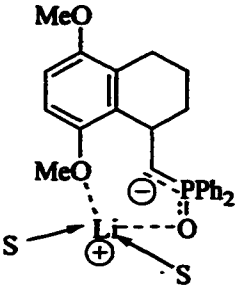
One might conclude that steric hindrance is responsible for the lack of reaction between phosphine oxides **99** and **102** with tetralone **69** and lactone **82** respectively, since the latter both react with the anion of **89**. However, lithiated carbanionic chelates[28] are known to form with phosphonates and phosphine oxides bearing 3-keto or 3-carbamoyl groups (**I-IV**). The bidentate coordination of the oxygen atoms with the



I R=EtO, Y=OMe
II R=EtO, Y=Me
III R=EtO, Y=NMe_2
IV R=Ph, Y=OMe
S=THF



Lithiated **99**



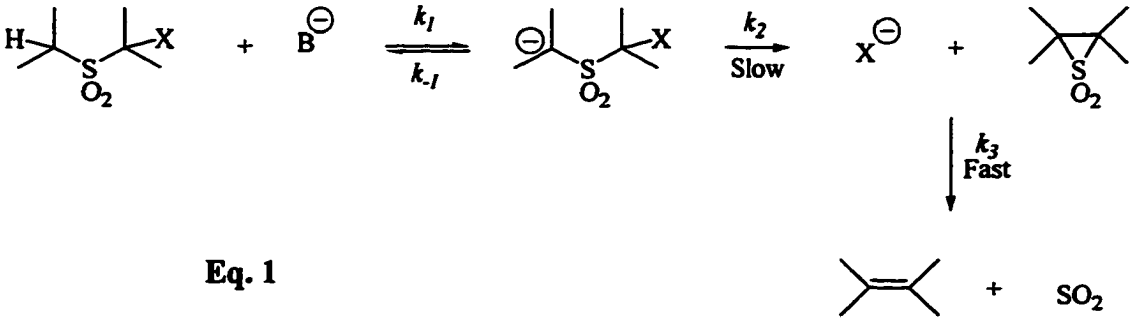
Lithiated **102**

lithium cation serves to stabilize the emergent anion. The extreme case[29] is the stable crystalline complex formed with $LiN(TMS)_2$ and **89** where no deprotonation occurs. When mixed with an alkyl-lithium, compounds **99** and **102** are likely forming lithiated carbanionic chelates with their respective proximal oxygens and form red apparent anions. Their subsequent lack of reactivity with the desired substrates is thus presumed to be due to a combination of steric hindrance and chelation stabilization, frustrating synthetic utilization.

Though the chemistry explored in the early approaches was interesting, it was not exploitable towards the IDA goal. The Ramberg-Bäcklund coupling was the final method explored and fortunately provided the means to link the sugar with an aglycone. An added bonus was the development of a new method for making C-glycosides.

3. RAMBERG-BÄCKLUND COUPLING

The Ramberg-Bäcklund (RB) rearrangement is the reaction of an α-halo sulfone with a base to give an olefin. L. Ramberg and B. Bäcklund discovered the reaction in 1940 by noting the high yield formation of 2-butene from the treatment of α-bromoethyl ethyl sulfone with an excess of aqueous sodium hydroxide.[30] Since then, it has been widely used in olefin syntheses being generally applicable and convenient. An α′ hydrogen is necessary to form the sulfone α′-anion to effect the facile intramolecular 1,3-displacement of the halide. Subsequent loss of SO_2 from the resultant thiirane 1,1-dioxide produces a double bond. Mechanistic evidence supports the intermediate episulfone formation prior to elimination of SO_2.[31a] Unlike halogen atoms α to other electron withdrawing functionalities, α-halo sulfones are unreactive in normal S_N2 reactions through a combination of polar, steric, and field effects, yet readily participate in the RB extrusion process with reactivity in the order I>Br>>Cl.[32] The reactions of α-halo sulfones in base have yielded kinetic data which support a second-order rate expression for the release of halide ion that is first-order in sulfone and first-order in hydroxide. Pre-equilibration of the α-halo sulfone and its carbanion has also been indicated. Eq. 1[31a] shows the mechanistic scheme that is considered compatible with



Eq. 1

the experimental evidence. The olefin stereochemistry is dependent on the base-solvent system used. Early reactions using aqueous hydroxide favored (*Z*)-alkene formation, but high (*E*)-stereoselectivity can be achieved with KO*t*-Bu in DMSO.

Decomposition studies with symmetrical and unsymmetrical episulfones prepared by other synthetic methods demonstrated the highly stereoselective formation of alkenes, establishing that the olefin stereochemistry was determined at the episulfone ring-closure stage. Paquette[33] (Figure 3) showed that steric requirements do exist. When R' = H, the phenanthrene formation is quantitative, but when R' = CH_3, no reaction occurs. The eclipsing methyl groups prevent coplanarity of the benzene rings prohibiting episulfone formation and intramolecular S_N2 displacement.

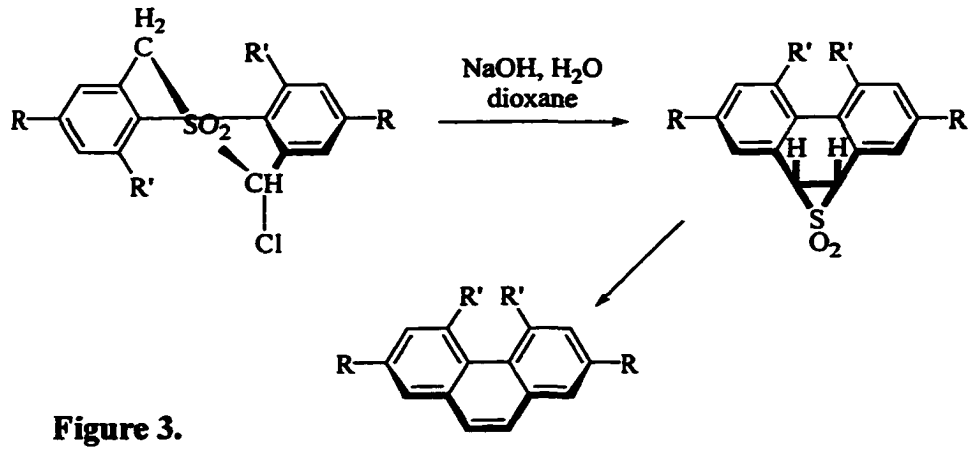


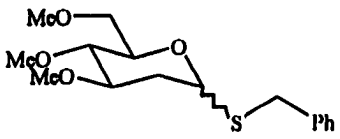
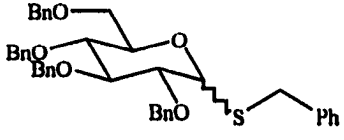
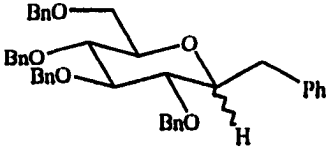
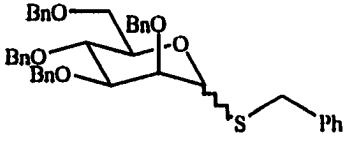
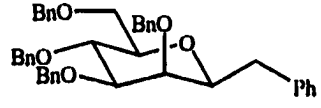
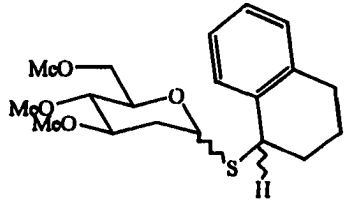
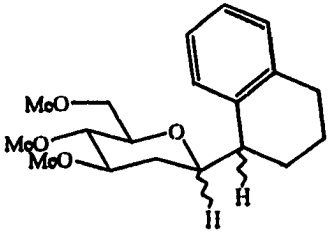
Figure 3.

α-Halo sulfones can be prepared from sulfides in a stepwise fashion by halogenation of a sulfide possessing at least one hydrogen at an α-carbon atom or by condensation of an aldehyde and mercaptan in the presence of a hydrogen halide, followed by oxidation to the sulfone. The oxidation must be kept anhydrous because of the hydrolytic susceptibility of the α-halo sulfide. α-Halo sulfones can also be prepared by halogenation of α-sulfonyl carbanions, but mixtures of α-halo isomers usually result

from unsymmetrical starting materials. Other methods include the halogenative decarboxylation of α-carboxyalkyl sulfones, the alkylation of sulfinate salts, and the cycloaddition of halosulfenes with diazo compounds.[31a,b]

Ramberg and Bäcklund's original studies with α-halo sulfones were conducted at 100 °C with 2*N* NaOH, which are obviously rather robust conditions and have undergone considerable modification since 1940. The one-pot method of Meyers[34] (KOH, CCl_4, *t*-BuOH) giving an olefin directly from the sulfone has seen widespread use, but can suffer from shortcomings that include possible multiple α-chlorination or reaction of the olefin product with concomitantly generated dichlorocarbene. These drawbacks were ameliorated by Chan[35] who devised a one-pot procedure using alumina supported potassium hydroxide in *t*-BuOH/dichloromethane with CF_2Br_2 as the halogen source to again produce olefins directly from sulfones, but largely free of the undesired by-products.

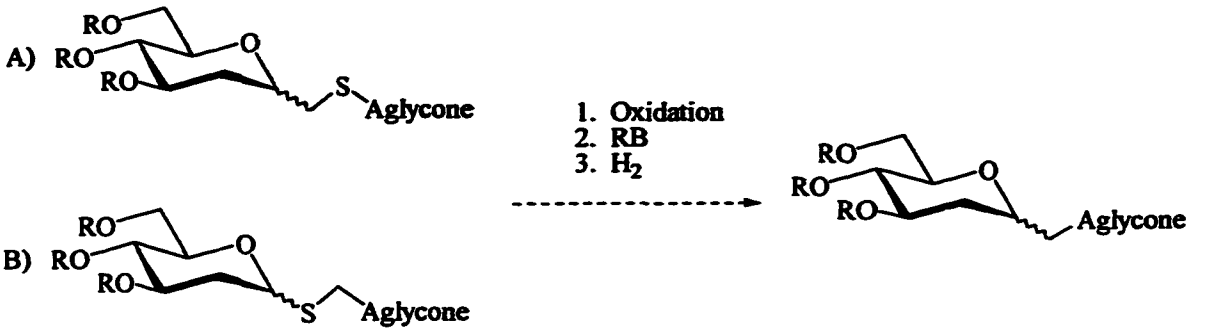
The previous early approaches related the difficulties encountered in trying to link the aglycone and sugar, so linkage via intermediacy of a sulfur tether was considered. The ease of formation of S-glycosides in both the sulfide and sulfone oxidation states is well cited.[36] Direct formation of C-glycosides from S-glycosides is not a known application of the RB reaction, although Hart had used the method to form an acyclic precursor to an aryl C-glycoside.[37] The general concept is illustrated in Scheme 3.1. The sulfide linked sugar and aglycone is oxidized to a sulfone, then subjected to the RB rearrangement and the olefin product hydrogenated. The results of the reaction sequence for several sugars are presented in the Table.

Entry	S-glycoside	Gylcosidation Method %Yield (β/α)	Sulfone Yield	Ramberg-Bäcklund Yield	Reduction Product	Yield
1		A 71 (45:55) B 77 (45/55)	95 (47:53)	78 (E:Z:endo, 76:15:9)		72.9 (100:0)
2		B 74 (45/55) C 83.6 (20:80)	95 (40/60)	85 (Z:E, 91:9)		89.3 (75:25)
3		B 78.5 (43/57)	86 (43:57)	62 (Z:E, 95:5)		63.7 (100:0)
4		B 61.7(45:55)	90 (45:55)	76 (E:Z, 55:45)		82.8 (90:10)

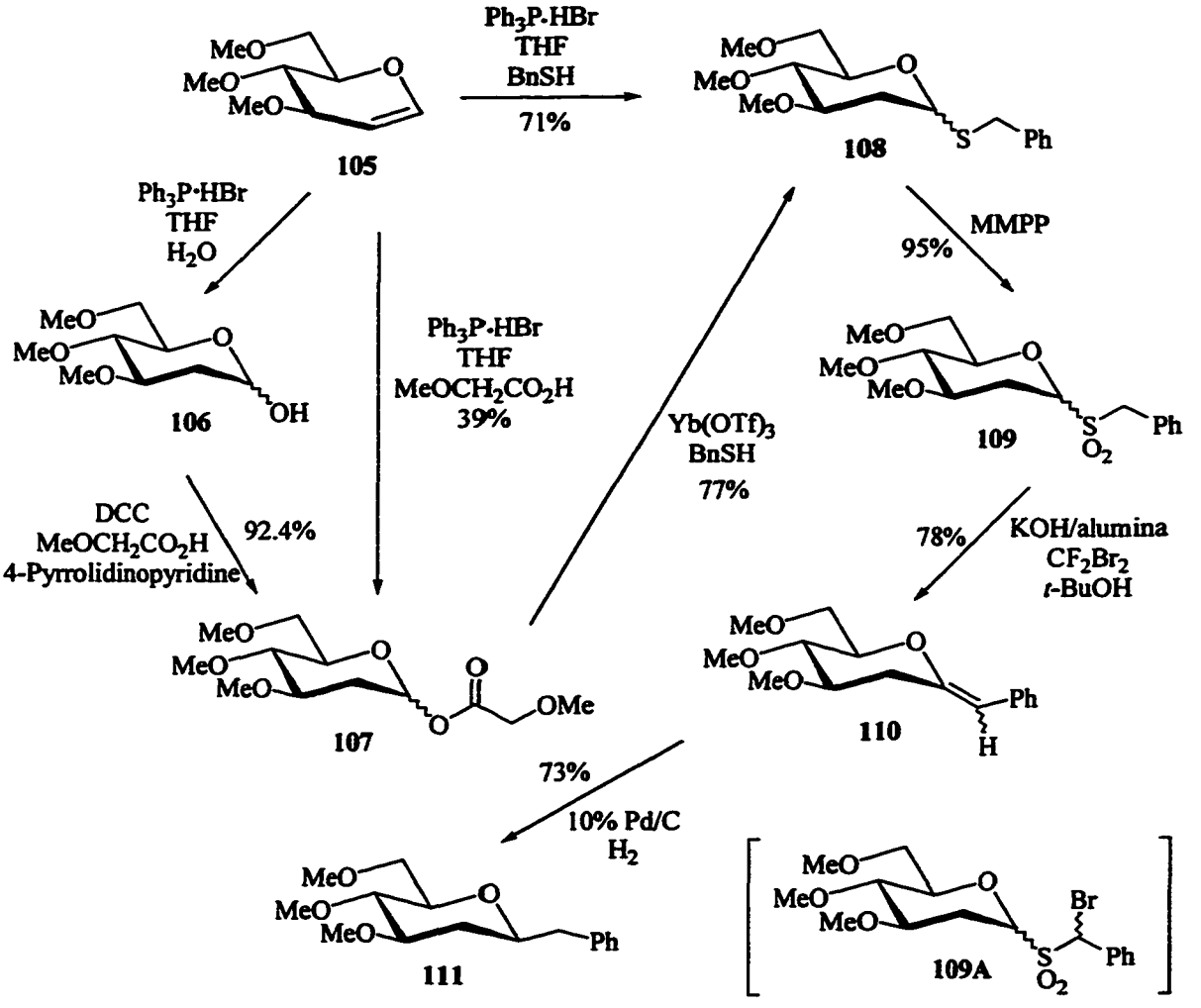
A = Falck, B = Inanaga methoxyacetic glycoside, C = Inanaga methoxyacetic acid cross-coupling

Table Results for the four-step C-glycosidation sequence using the Ramberg-Bäcklund reaction for C-C bond formation.

Scheme 3.1



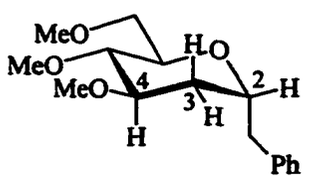
Scheme 3.2

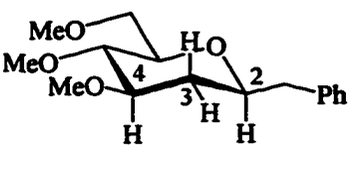


An adaptation of the Falck procedure[27] was initially used to make the thioglycoside of Entry 1 from trimethoxyglucal, but a cleaner product was obtained utilizing the Inanaga-$Yb(OTf)_3$-methoxyacetate method,[38a] as shown in Scheme 3.2. The methoxyacetyl- glycoside **107** was prepared in 92.4% overall yield applying Hassner's[39] esterification method to **106**, or in 39% yield by applying Falck's method on glycal **105**. Thioglycosidation of both samples gave a similar 44:55 β:α anomeric mixture of sulfides **108**; a result that was apparently independent of the anomeric ratio of glycoside **107**. The anomeric ratios were determined from the NMR spectra by integration of the anomeric axial proton ($H\text{-}1_a$), a doublet of doublets (dd) at 4.19 ppm (J = 1.7, 11.7 Hz), and the equatorial proton ($H\text{-}1_e$), a doublet at 5.27 ppm (J = 5.6 Hz). Oxidation of the thioacetal mixture **108** with magnesium monoperoxyphthalate (MMPP) provided the sulfones **109** in 95% yield. This product and was much easier to separate from the product obtained from the reaction of **108** with *m*-chloroperbenzoic acid. $H\text{-}1_e$ of **109** shifted upfield to 4.71 ppm (dd, J = 3.3, 7.2 Hz) and $H\text{-}1_a$ shifted to 4.02 ppm (dd, J = 1.8, 12 Hz). Bromosulfones **109A** were isolated by chromatograpy from preliminary experiments using Chan's RB methodology, and their presence was later minimized by using reagents in excess. Other classical RB conditions were unsuccessful, including Meyer's one-pot method, and the attempted stepwise formation of the halo-sulfone followed by elimination. The sulfones **109** were subjected to the one pot RB protocol of Chan[35] where a mixture with alumina-supported potassium hydroxide in *t*-BuOH/CH_2Cl_2 at 0-5 °C was treated with dibromodifluoromethane to produce the somewhat unstable olefin **110** in 78% yield. The enol-ether mixture had to be rapidly purified and reduced, or it deteriorated beyond recognition on storage. It also

degraded rapidly in deutero-chloroform, apparently giving the endocyclic olefin together with other unidentified products. The *E*, *Z* ratio was determined by integration of the vinylic protons (*E* at 6.22 ppm and *Z* at 5.48 ppm). These assignments were made by analogy with reported[40] pyran enol-ethers produced via Wittig olefination. Hydrogenation of the olefin with Pd catalysis provided equatorial C-glycoside **111** as the product (β-anomer)[41] in 73% yield.

The signal for the anomeric proton in **111** was obscured by the signals for the other ring protons. The configuration at C-1 was therefore determined from analysis of the coupling constants of the protons on C-3 (the conventions governing the nomenclature of C-glycosides transform the ring numbering[42] of **111** making the anomeric center C-2, the former C-2 becomes C-3, and so on). In C_6D_6, the two proton signals of C-3 occur at 1.77 ppm (ddd, J = 1.8, 5.1, 12.6 Hz, H-3_e) and 1.18 ppm (dt, J = 11.1, 12.9 Hz, H-3_a). In $CDCl_3$, H-3_a is an apparent quartet, but in C_6D_6, it is clearly distinguishable as a doublet of triplets. In Figure 4, the expected couplings for the protons on C-3 are listed for each C-glycoside anomer. The observed coupling constants for H_{3e} could fit either structure, but the H_{3a} couplings are only compatible





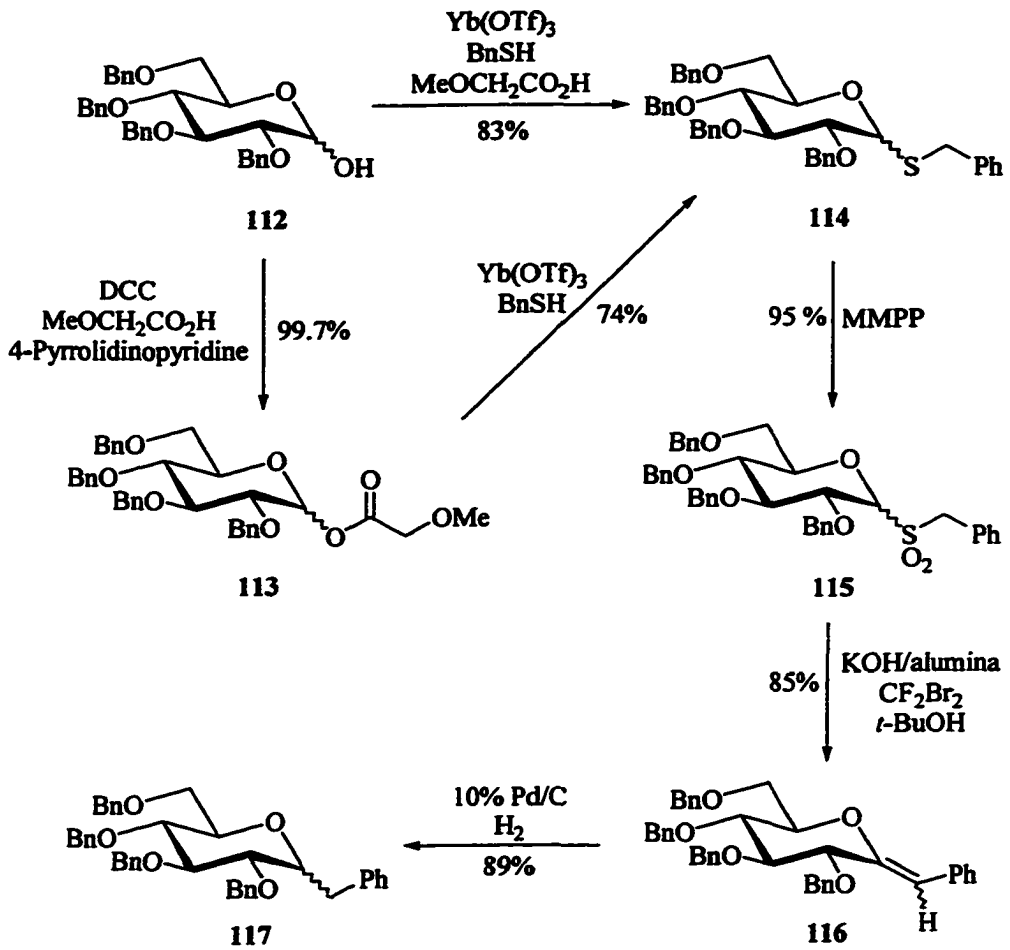
(H_{3a}-H_{2e} , H_{3a}-H_{4a} , H_{3a}-H_{3e})	H_{3a}	(H_{2a}-H_{3a} , H_{3a}-H_{4a} , H_{3a}-H_{3e})
(H_{2e}-H_{3e} , H_{4a}-H_{3e} , H_{3a}-H_{3e})	H_{3e}	(H_{2a}-H_{3e} , H_{4a}-H_{3e} , H_{3a}-H_{3e})

Figure 4. Expected Couplings for the Protons on C-3 of α, β-**111**.

with the β-anomer assuming $J_{2a3a} = J_{3a4a} = 11.1$ Hz. Vicinal coupling constants (^3J) for the chair conformation of cyclohexane are $^3J_{aa} \sim$ 7-12 Hz and $^3J_{ee} \leq {}^3J_{ae} \sim$ 2-5 Hz, and are reduced if the relevant C-C bond carries electronegative substituents.[43]

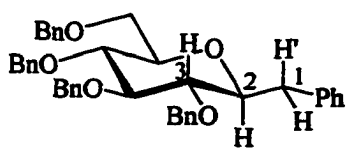
Commercially available tetrabenzylglucose **112** was the starting material for Table Entry 2, which is elaborated in Scheme 3.3. This sugar was chosen to test the scope of the Chan RB methodology to determine if β-elimination would be problematic,

Scheme 3.3



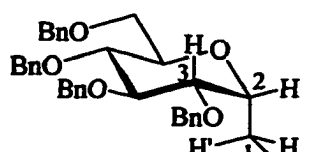
as it is with most sugars involving C-1 anions.[44] The Inanaga-Yb(OTf)$_3$-methoxyacetate method (glycosidation method **B**) gave **114** in 74% yield via **113**. Later

on, the Inanaga cross-coupling method[38] was utilized to produce **114** in 83% yield directly from **112**, giving a mixture more enriched in the α-anomer. H-1_e of **114** was a doublet at 5.22 ppm (J = 5.4 Hz) and H-1_a was a doublet at 4.23 ppm (J = 9.8 Hz). The thioglycoside mixture prepared via method B was oxidized with MMPP to give the sulfone mixture **115** in 95% yield. Quantification of the α/β ratio from the HMR spectrum was not possible because the H-1 proton of the β-glycoside was obscured by other signals. The ratio of anomers was therefore estimated from the decoupled carbon spectrum. Chan RB conditions gave **116** as a relatively stable (vis-à-vis **110**) alkene mixture (*E* at 6.50 ppm and *Z* at 5.71 ppm) with a *Z*/*E* ratio of 91:9 in an 85% chromatographed yield. The apparent absence of β-elimination of the C-2 alkoxy group suggested a more general application of the RB methodology. Catalytic hydrogenation resulted in a small amount of unwanted hydrogenolysis of the benzylic protecting groups (<10%) giving **117** as a 3:1 anomeric mixture in 89.3% yield, from which the predominant β-anomer was isolated by chromatography. The "anomeric" proton (H-2_a) signal was assigned from a 500 MHz H, H COSY NMR and appeared as a dt at 3.49 ppm (J = 2, 9 Hz). In Figure 5, the expected anomeric proton couplings are displayed. The $J_{2,3}$ = 9 Hz is indicative of the β-C-glycoside.



(H_{2a}-H_{3a} , H_{2a}-H'_1 , H_{2a}-H_1)

H_{2a}



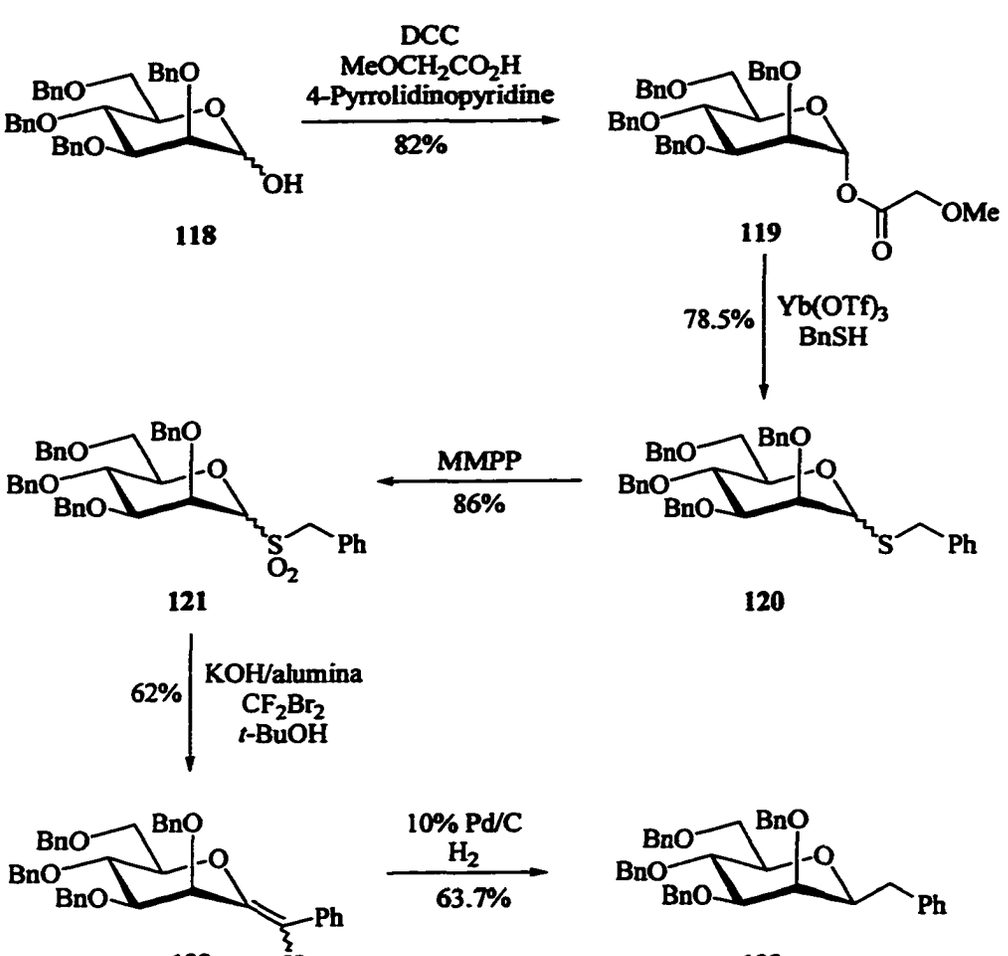
(H'_1-H_{2e} , H_{3a}-H_{2e} , H_1-H_{2e})

H_{2e}

Figure 5. Expected Couplings for the Proton on C-2 of **117**.

Commercially available tetrabenzylmannose **118** was chosen as the starting material for Table Entry 3 (Scheme 3.4), representing a very sensitive test for the β-eliminating potential of the Chan RB. Glycosidation of **118** gave **119** in 82% yield exclusively as the α-anomer (H-1_e, d, 6.31 ppm, J = 1.9 Hz), in contrast to the 4:1 α:β glycoside mixture of anomers obtained from tetrabenzylglucose. Inanaga method B gave a 57:43 β/α anomeric mixture of thioglycosides **120** (H-1_e, d, 5.29 ppm, J = 1.6 Hz

Scheme 3.4



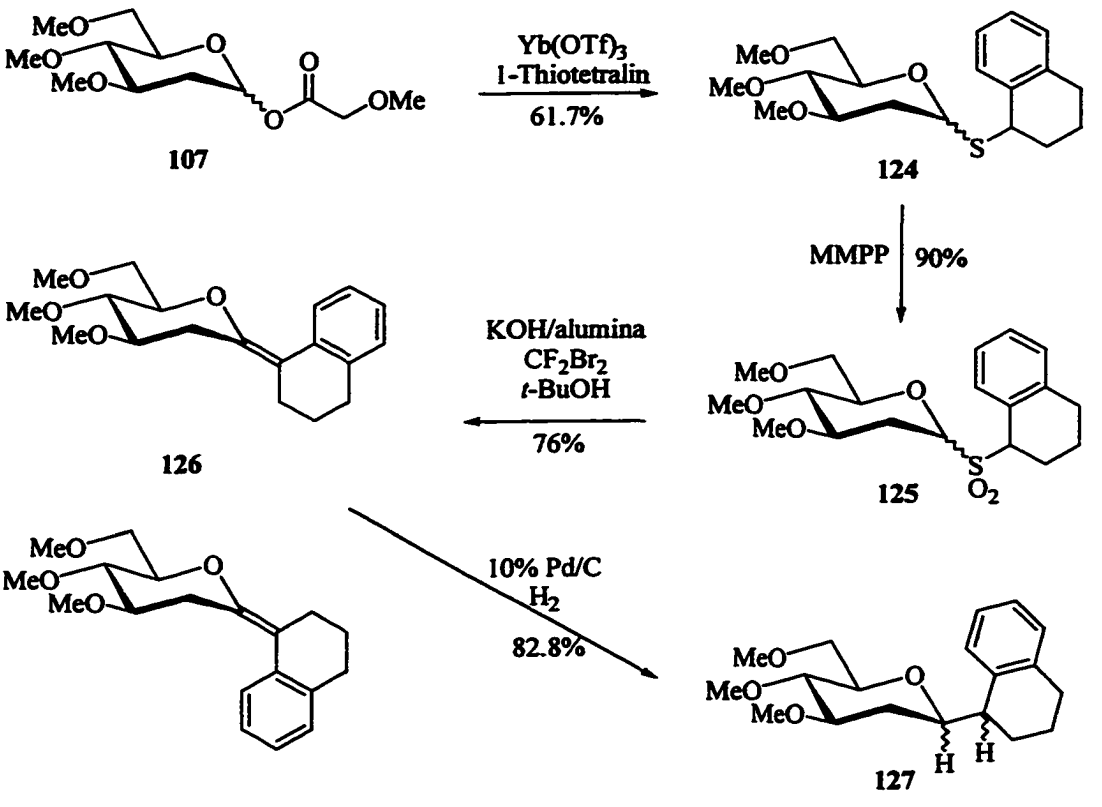
and H-1_a, s, 4.20 ppm) in 78.5% yield from **119**. Mannopyranosides in the α-form normally show a J_{H1H2} value of ~1.6 Hz and the β-form a J_{H1H2} value of ~0.6 Hz,[45] a

situation where $J_{ae} < J_{ee}$. Oxidation of **120** with MMPP gave an 86% yield of **121** (H-1_e, d, 4.74 ppm, J = 2.5 Hz and H-1_a, d, 4.23, J = 1.1 Hz) as an anomeric mixture partially separable by column chromatography. Then, the Chan RB gave **122** in 62% yield (*E* at 6.58 ppm and *Z* at 5.58 ppm). The somewhat lower yield of **122** was possibly due to some β-elimination, but no obvious β-eliminated product was observed on TLC. Catalytic reduction then gave **123** in 63.7% yield, with some yield loss due to hydrogenolysis of the benzylic protecting groups. The C-glycoside β-anomer was the only isolated product, with H-2_a appearing as a triplet at 3.54 ppm (J = 6.9 Hz), identified by H, H COSY and proton decoupling experiments. The coupling constant between the anomeric proton and H-3_e was less than 1 Hz, which is consistent with β-anomer **123**. The ^{13}C NMR data for **123** and β-**117** are also consistent with the recently reported literature data.[46]

Having demonstrated that a primary thiol works reasonably well in the RB sequence, we then showed that a secondary thiol also could be used in Table Entry 4. Treatment of commercially available 1,2,3,4-tetrahydronapthalen-1-ol with Lawesson's reagent (2,4-bis(*p*-methoxyphenyl)-1,3-dithiaphosphetane-2,4-disulfide) at reflux in toluene[47] provided 1,2,3,4-tetrahydronapthalen-1-thiol in 43.6% chromatographed yield, accompanied by considerable dehydrated starting material, but easily separable by chromatography. Scheme 3.5 outlines the synthetic transformations for the ensuing RB sequence. Inanaga method B gave **124** in 61.7% yield, with the NMR showing greatly increased complexity due to the four diastereomers now present. For example H-1_e was a doublet at 5.58 ppm, J = 5.4 Hz, H-$1'_e$ a doublet at 5.49 ppm, J = 5.7 Hz, H-1_a a dd at 4.52 ppm, J = 1.6, 11.8 Hz, and H-$1'_a$ a dd at 4.44 ppm, J = 1.8, 12 Hz. Oxidation of

124 with MMPP gave **125** in 90% yield with the complexity of the NMR again preventing an exact determination of the anomeric ratio, but appearing to slightly favor the α-anomer as seen with **109**. Chan RB gave the mixed alkenes **126** in 76% yield and the 55:45 *E/Z* ratio was estimated from the ^{13}C NMR spectrum by comparison with **110**. Catalytic reduction gave the C-glycoside **127** in 82.8% chromatographed yield as a partially separable mixture. The anomeric ratio was estimated from the weight of isolated fractions and the β-anomer (major component) was identified by similarity of its sugar ring ^{13}C NMR data with **111**.

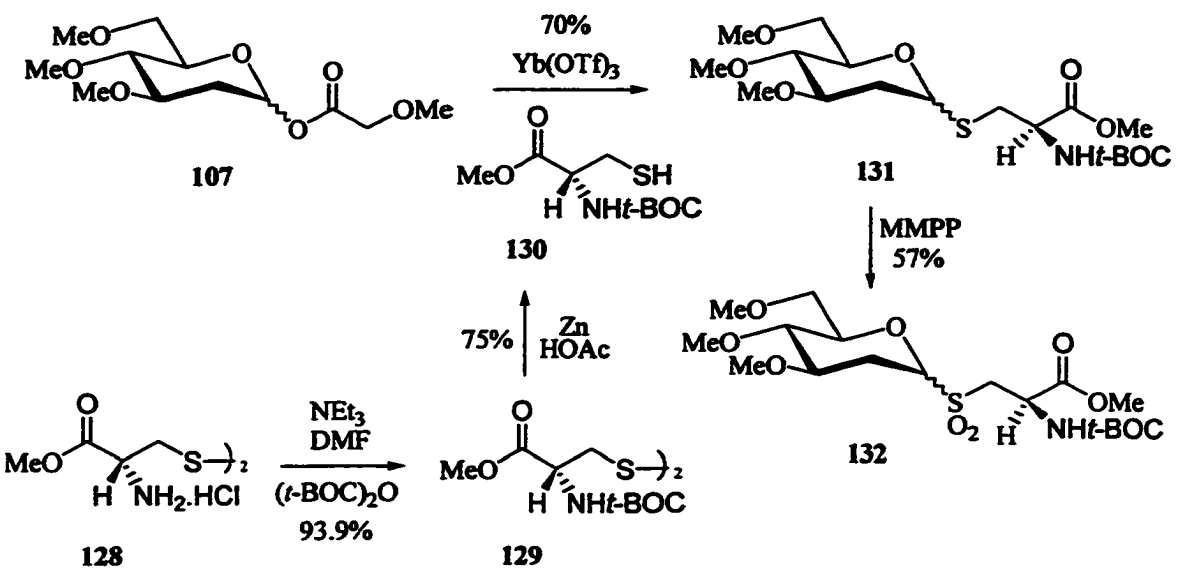
Scheme 3.5



A brief excursion to see if a C-glycopeptide could be readily made using this methodology was attempted as shown in Scheme 3.6. L-Cystine **128** was protected[48] to give **129** in 93.9% yield and then cleaved[49] in 75% yield to give L-cysteine derivative

130. Inanaga method B was then used to prepare a ~1:1 β:α anomeric mixture of thioglycosides **131** in 70% yield. H-1_e of **131** was at 5.32 ppm (d, J = 4.8 Hz) and H-1_a was a dd at 4.50 ppm (J = 1.8, 11.8 Hz). Oxidation with MMPP gave **132** in 57% yield, but the subsequent Chan RB conditions resulted in cleavage of the methyl ester and no other definite conclusions could be drawn from the ^{1}H NMR spectra of the mixture.

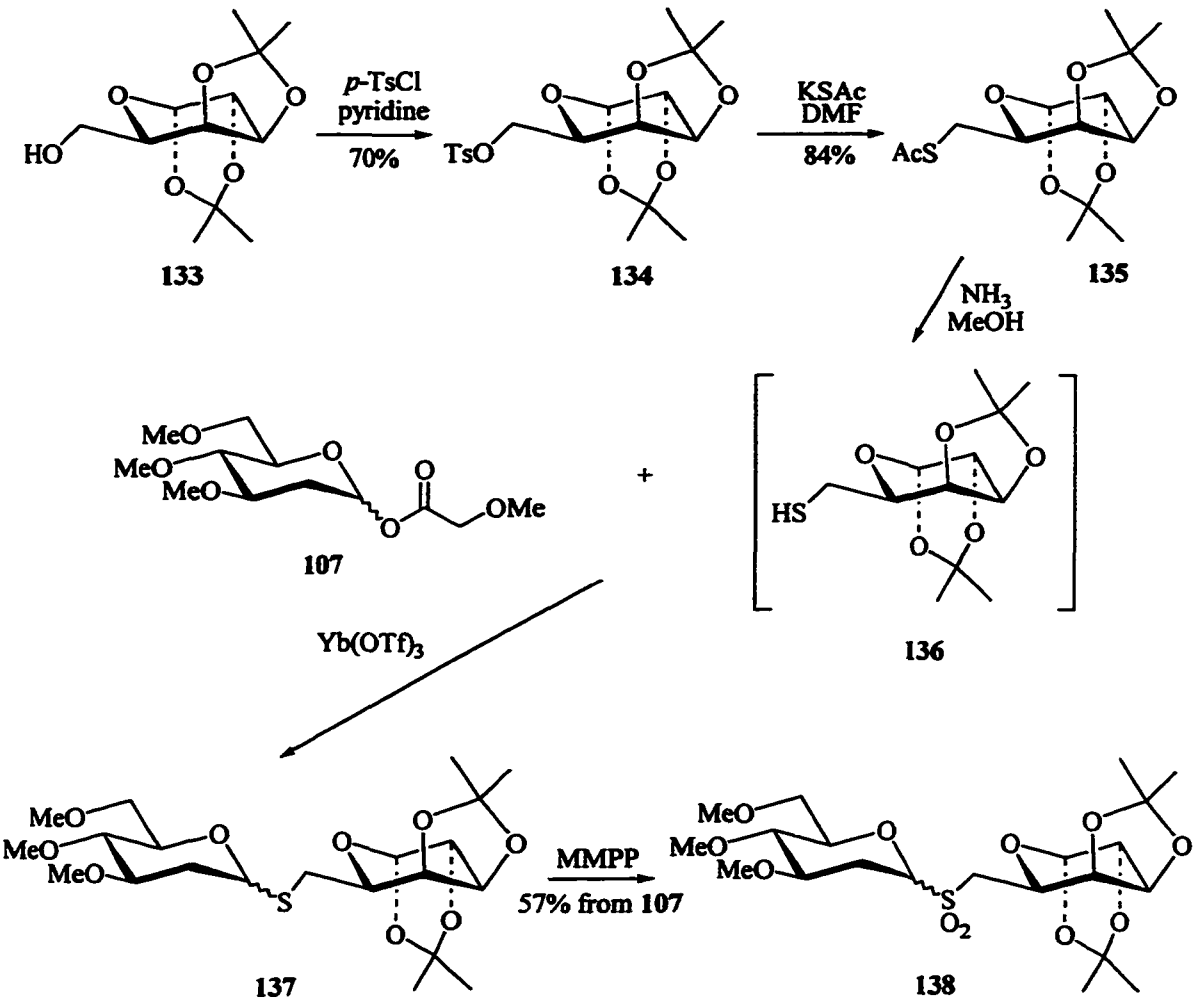
Scheme 3.6



Since a more robustly protected L-cystine was not available, we turned our attention to the more pressing question concerning applicability to making C-disaccharides. The first disaccharide attempt is outlined in Scheme 3.7 where commercially available **133** was prepared for linkage with **107** to provide the 1,6-thiodisaccharide **137**. Tosylation of **133** in pyridine provided after workup and crystallization a 70% yield of **134**. Displacement of the tosylate with KSAc in DMF at 110 °C gave **135** (-SAc singlet at 2.34 ppm) in 84% yield after chromatography. Hydrolysis of the acetate with NH_3/methanol provided **136**, which was not isolated but coupled with **107** via Inanaga method B, and subsequently oxidized with MMPP to give

138 (~1:1 anomeric mixture estimated from the ^{13}C NMR) in 57% overall yield from **107**. Chan RB conditions resulted in a mixture that by ESMS indicated a mixture of **138**, bromo-**138**, and alkene. Considerable product degradation occurred, so another 1,6-thiodisaccharide was assembled as shown in Scheme 3.8. Inanaga method B failed to couple **113** and **136**, so an alternative route was employed.

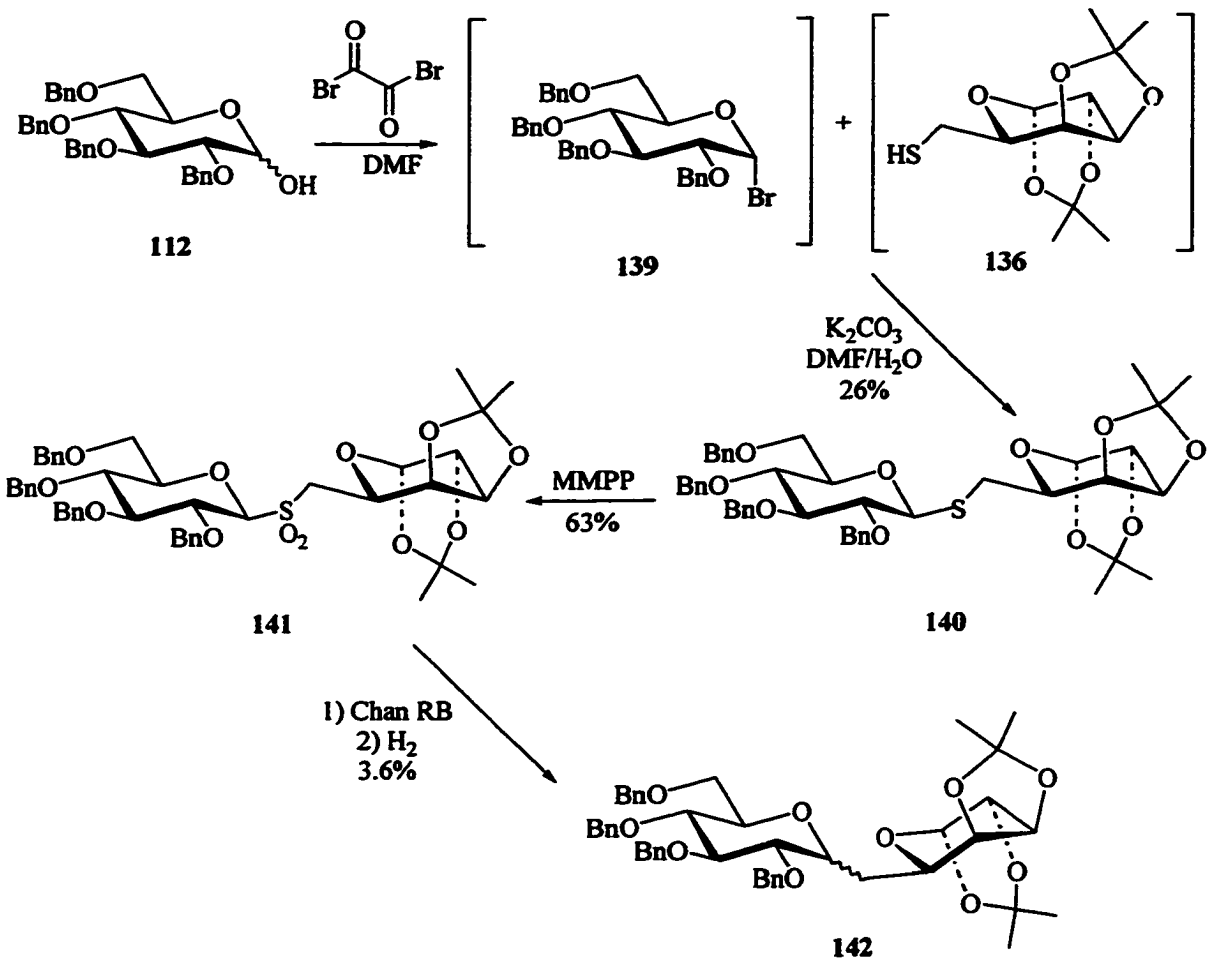
Scheme 3.7



The relatively unstable bromide **139** was prepared[50] from **112**, and after rapid work-up was coupled with freshly prepared **136**. Thiodisaccharide **140** was obtained in only 26% yield, which could probably be improved by eliminating the separate hydrolysis of

135 and relying instead on the coupling conditions[51] to directly form the desired potassium thiolate (a strategy employed in later work). The ^{1}H NMR of **140** indicated that only the β-thiodisaccharide was present from lack of a H_{1e} signal between 5 and 5.5 ppm, consistent with the S_N2 displacement of the axial bromide. Oxidation of **140** with MMPP gave **141** in 63% yield appearing as a single anomer in the ^{13}C NMR. The Chan

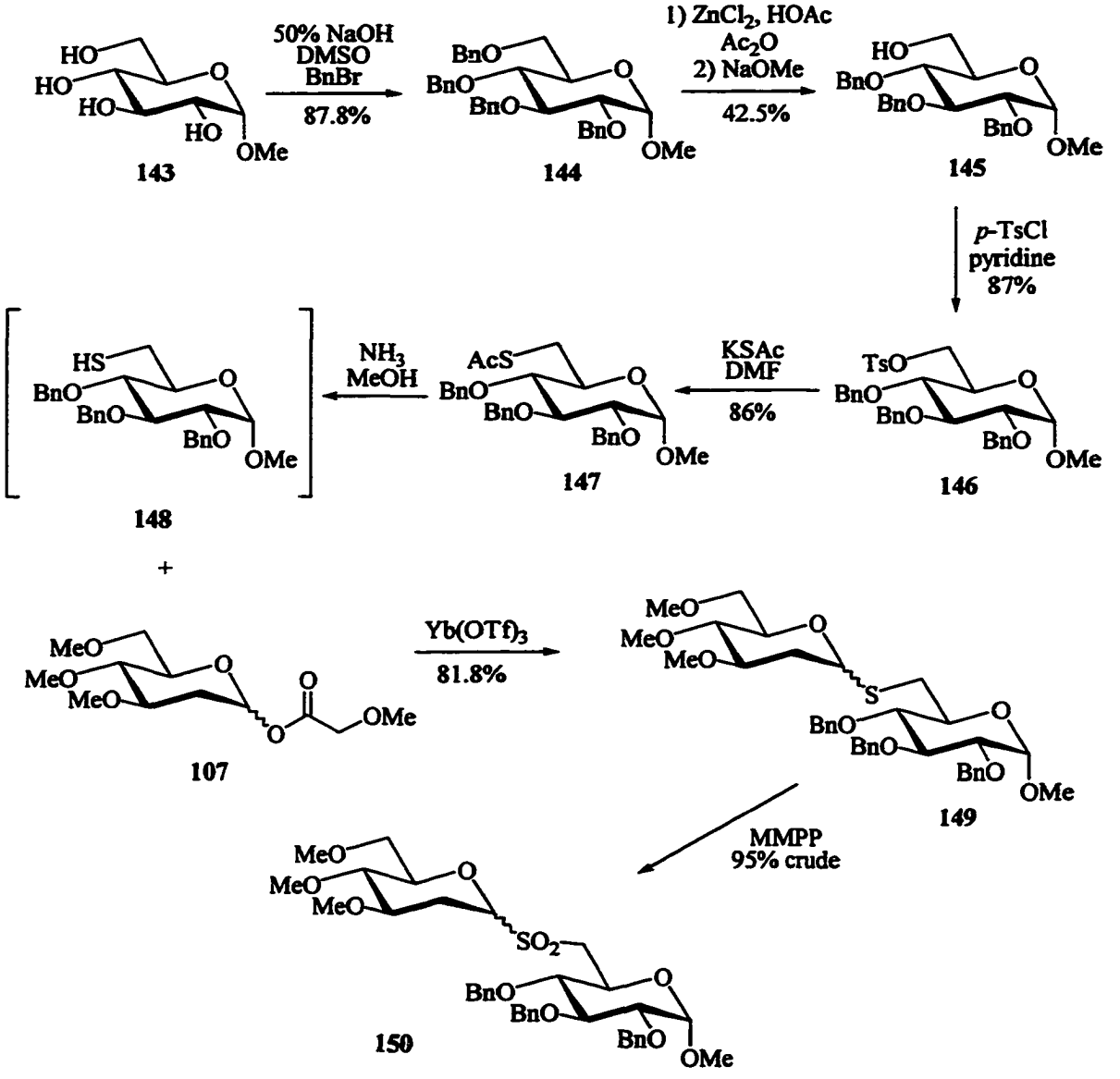
Scheme 3.8



RB conditions again gave a mixture from which the major component, bromo-**141**, was isolated as a solid. Two minor less polar components were compatible with the alkene by ESMS, and were hydrogenated to give an overall yield of 3.6% of **142** from **141**.

The major C-disaccharide, presumably a β-1,6-linkage, was cleanly separated by flash chromatography and gave an ESMS compatible with the structure shown. The overall yield leaves plenty of room for improvement, but at least the isolated C-disaccharide provided proof of concept. Degradation of product in the reaction was still a problem as evidenced by the low mass balance following chromatography. One more 1,6-thiodisaccharide was constructed as shown in Scheme 3.9. Commercially

Scheme 3.9



available **143** was perbenzylated[52] in 87.8% yield to give **144** (H_{1e}, d, 4.45 ppm, J = 2.1 Hz). Selective deprotection of the 6-OH group in 42.5% yield was somewhat disappointing giving only half of the reported yield[53] of **145** (H_{1e}, d, 4.57 ppm, J = 3.3 Hz). Routine tosylation of **145** gave **146** (H_{1e}, d, 4.52 ppm, J = 3.3 Hz) in 87% yield, followed by displacement with KSAc to give thioacetate **147** in 86% yield (-SAc singlet at 2.34 ppm). Mild hydrolysis of the thioacetate to **148** and coupling with **107** via Inanaga method B gave **149** (~1:1, α/β thioglycoside mixture by ^{13}C NMR) in 81.8% yield. Oxidation of thiodisaccharide **149** with MMPP gave **150** in 95% crude yield, sufficiently pure for the subsequent Chan RB. The Chan RB reaction mixture showed considerably less degradation, suggesting that the acetonide functionality used in the previous two disaccharide sequences had been an unlucky choice of protecting group for the sugar for this reaction. The major isolated product was α-bromosulfone-**150** as evidenced by ESMS, and the elusive alkene was not found. The C-glycopeptide and C-disaccharide side excursions failed to easily provide the desired "low hanging fruit," perhaps because the pK_a's of the protons to be removed were not as acidic as in the successful benzylic cases. Thus, experimental work was redirected towards the original focus of this thesis, the IDA-C-glycoside.

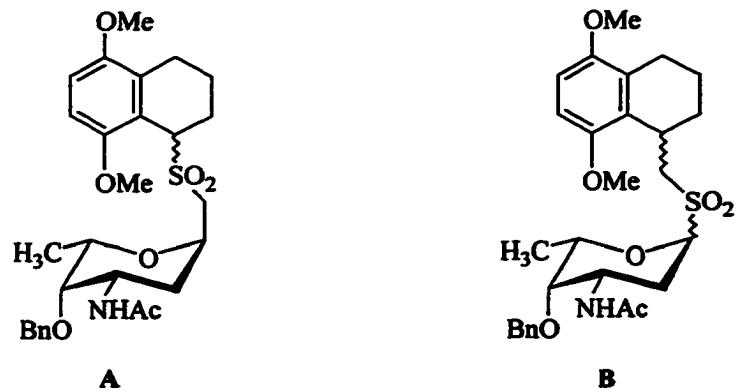
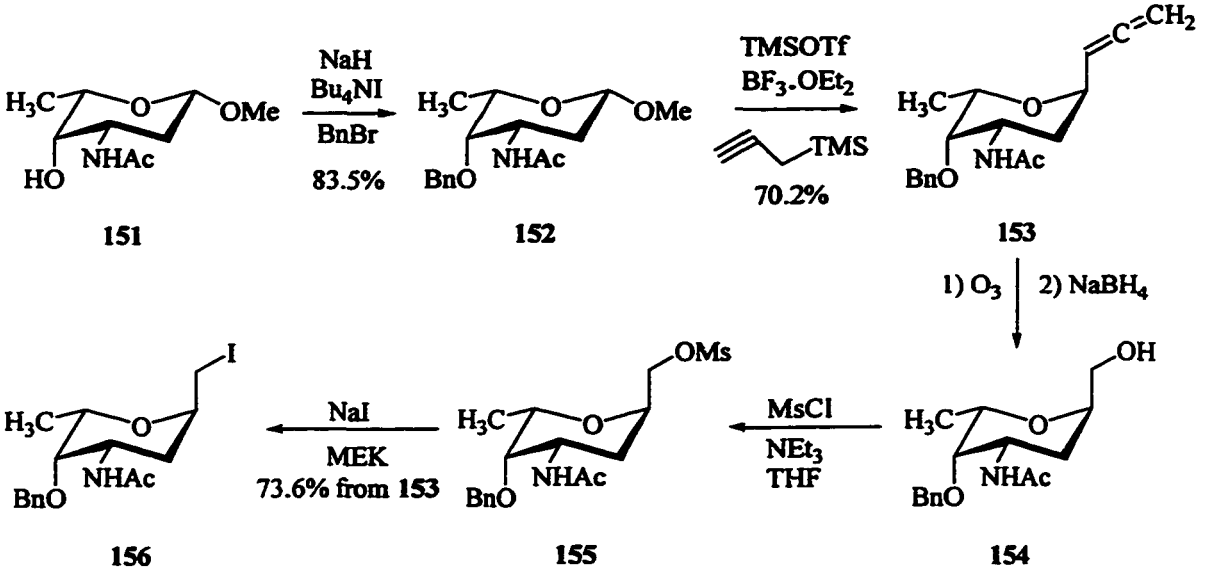


Figure 6. Potential IDA analog precursors.

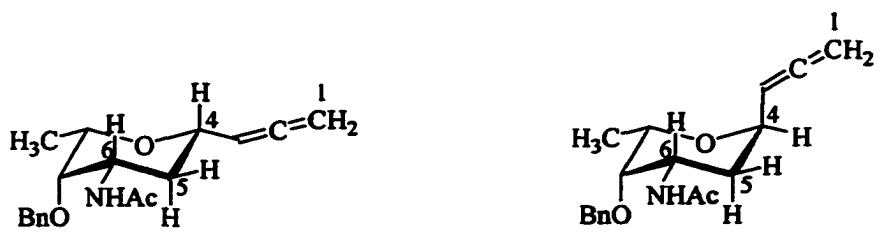
Consistent with our assumption that the Chan RB reaction would proceed smoothly if benzylic protons were involved, we chose precursor A (Figure 6) in preference to precursor B for the IDA-C-glycoside scheme. A second reason for choosing A is that the sugar (daunosamine) of IDA is an axial glycoside. When the sulfone and subsequent alkene were directly linked to the anomeric carbon, the catalytic hydrogenation step of our RB method was providing equatorial C-glycosides. Instead of studying methods to influence the geometry of the reduction of the RB product from general approach B in Scheme 3.1, general approach A was followed to prepare the IDA analog precursor detailed in Schemes 3.10-3.11. The daunosamine derivative **151** was prepared from D-mannose by the method of Horton and Weckerle.[54]

Scheme 3.10



Benzylation[55] of the C-3 alcohol gave **152** in 83.5% yield with H-1_a appearing as a dd at 4.29 ppm (J = 2.4, 11.7 Hz). The C-glycoside α-anomer **154** of daunosamine was prepared using a modification of Bednarski's methodology.[56] The reaction of TMSOTf with suitably protected glycosides in the presence of propargyl trimethylsilane

effects the preparation of C-glycosyl allenes, but these reaction conditions failed with amino sugar **152**. Earlier in this thesis, Acton's work was presented where $BF_3 \cdot OEt_2$ enabled the reaction of allyl-TMS with a daunosamine derivative. Thus, when $BF_3 \cdot OEt_2$ was used in excess with propargyl-TMS and **152**, the desired allene was obtained. A more rapid, higher yielding variation was to pre-treat the **152**/propargyl-TMS with one molar equivalent of $BF_3 \cdot OEt_2$ followed by 0.5 equivalents of TMSOTf. Allene **153** was determined to be the α-anomer by analysis of the ^1H NMR data. The observed proton signals of C-5 occur at 1.90 ppm (dt, J = 5.9, 12.7 Hz, H-5_a) and 1.71 ppm (dd, J = 4.8, 12.7 Hz, H-5_e). Assuming $J_{5a6a} = J_{5a5e}$ and $J_{4e5e} < 1$ Hz, the best fit for the expected coupling constant data (Figure 7) is for the anomeric proton to be equatorially disposed.



(H_{4a}-H_{5a}, H_{5a}-H_{6a}, H_{5a}-H_{5e})	H_{5a}	(H_{5a}-H_{6a}, H_{5a}-H_{4e}, H_{5a}-H_{5e})
(H_{4a}-H_{5e}, H_{6a}-H_{5e}, H_{5a}-H_{5e})	H_{5e}	(H_{4e}-H_{5e}, H_{6a}-H_{5e}, H_{5a}-H_{5e})

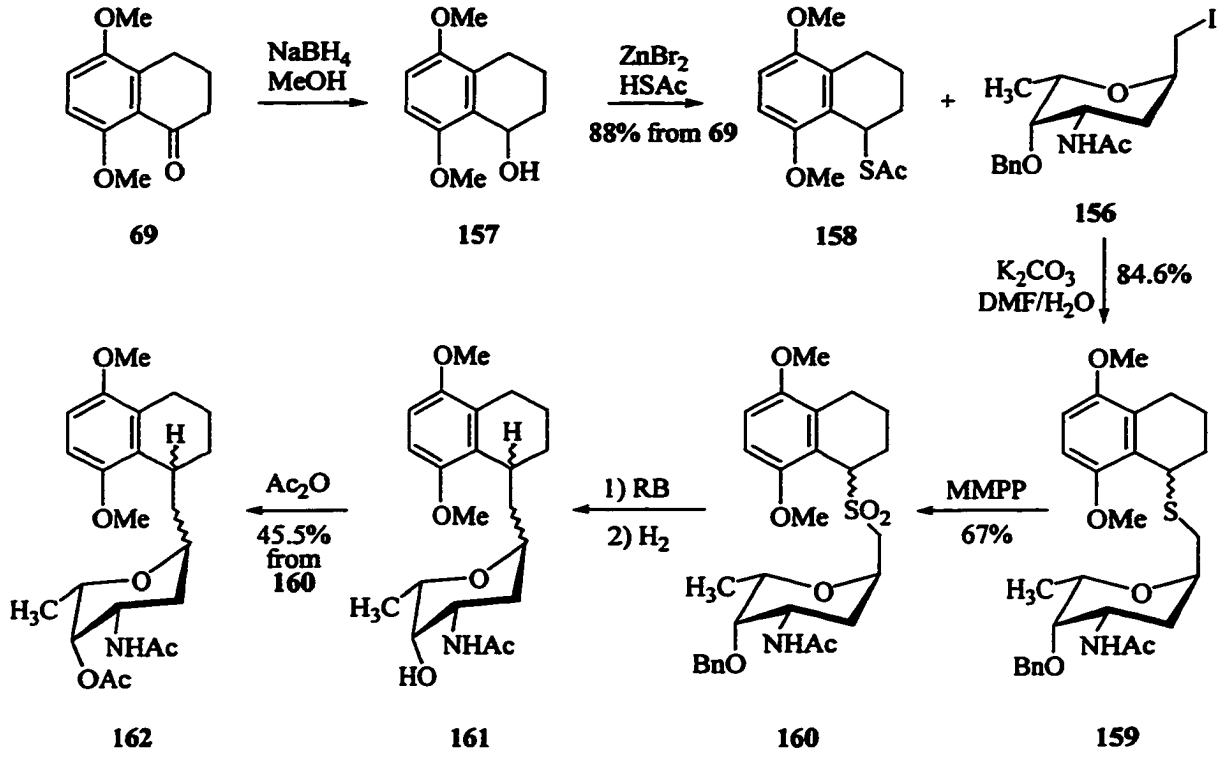
Figure 7. Expected couplings for the protons on C-5 α, β-**153**.

Ozonolysis of allene **153** and direct reduction of the cold reaction mixture with $NaBH_4$ gave **154** as a colorless foam. A purified sample of **154** was characterized by ESMS and 400 MHz ^1H NMR as still being the axial C-glycoside. Deuteration of the **154** $CDCl_3$ ^1H NMR sample shifted the anomeric proton signal from a coincident multiplet to an observable quartet at 4.01 ppm with J = 6.5 and <1 Hz. Direct conversion of alcohol **154** to a bromide via Ph_3P/CBr_4 proved to be problematic because

$Ph_3P{=}O$ co-eluted with the bromide. Mesylation of crude **154** cleanly gave the mesylate **155** (-OMs singlet at 3.10 ppm) which was then displaced with NaI giving **156** as a white solid in 73.6% overall yield from **153** after chromatography.

In Scheme 3.11, the two step preparation of the simplified IDA AB ring aglycone from tetralone **69** is illustrated. Reduction of the tetralone to the unstable tetralol **157**, followed by $ZnBr_2$[57] mediated introduction of the thioacetate gave **158** (-SAc singlet at 2.33 ppm) in an 88% yield for the two steps. Iodide **156** was efficiently

Scheme 3.11



coupled with **158** to give sulfides **159** in 84.6% yield. The K_2CO_3/DMF/H_2O mixture promoted the one-pot hydrolysis of **158** to the intermediate potassium thiolate in the presence of iodide **156** for immediate coupling, avoiding unwanted disulfide formation. Oxidation with MMPP then gave sulfones **160** in 67% yield. 500 MHz H, H COSY

spectra of each sulfone indicated that they were both α-C-glycoside anomers but were isomeric at the benzylic carbon. Both sulfone anomeric protons were found at δ 4.9, and the distinctive difference in chemical shift was for the protons at C-3, about 0.5 ppm. This difference was used as a diagnostic for the products of the Ramberg-Bäcklund reaction of these sulfones. Thus, RB of **160**, using normal Chan conditions, gave a complex mixture of alkenes whose proton NMR showed probable vinylic doublets at δ 5.32, 5.52, 5.73, and 6.45 in an approximate ratio of 7:5:1:3. Palladium-catalyzed hydrogenation gave a mixture by ESMS of alkene and **161** with the benzyl protection still intact in 76% crude yield. Resubmitting the mixture with fresh catalyst for further reduction completely reduced the alkene, but also cleaved the benzyl protecting group. ^{1}H NMR of the crude product showed a 3:1 diastereomeric mixture of β:α anomers, presumably from isomerization of the RB olefin, or from equilibration of the sulfones during the RB. A CF_2Br_2-free Chan RB control experiment demonstrated the facile α to β anomer isomerization. Crude compound **161** was acetylated with Ac_2O/pyridine to facilitate the HPLC separation of the anomers of **162**, which had a combined 45.5% overall yield from sulfones **160**. The major fraction, a 1.75:1 mixture, proved to be the pair with the identical equatorial-C-glycoside configuration but isomeric at the benzyl carbon. The configuration of the major isomer of this fraction was ultimately confirmed by X-ray crystallography with the benzylic center having the *R* configuration. Natural daunorubicin and synthetic idarubicin are α-glycosides which possess configurations at the aglycone linkage methine corresponding with ***R*-162**, but they possess the opposite (*S*) configurational notation. The key NMR chemical shift difference for this pair at C-3 was 0.17. On the other hand, the same shift

difference for the minor pair of isomers, both with axial C-glycoside configuration, was 0.63. In this alpha pair, the chemical shift (C_6D_6) of the equatorial anomeric protons was found at δ 4.2 whereas the anomeric axial proton in the structure assigned by X-ray was at 3.4 ppm, consistent with the general observation of upfield shifts of axial protons relative to their equatorial isomers.

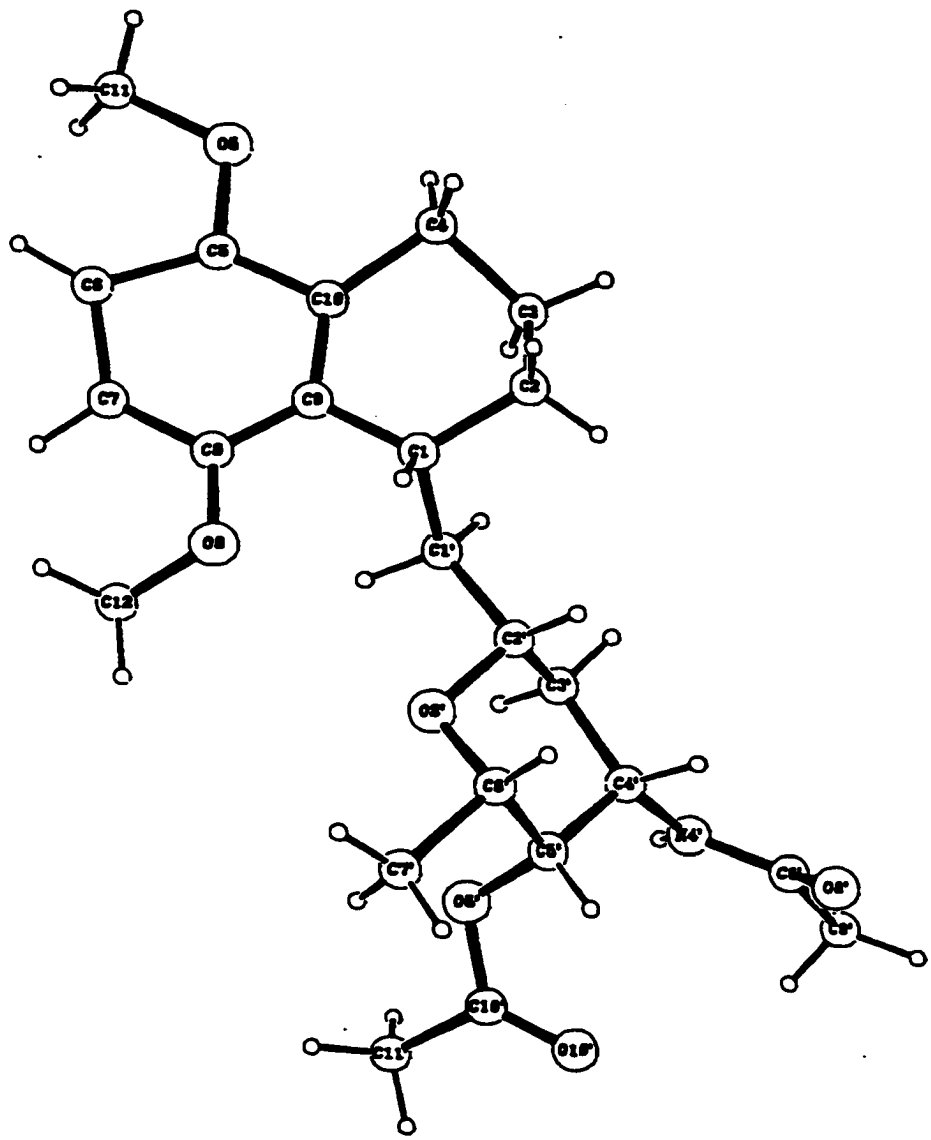
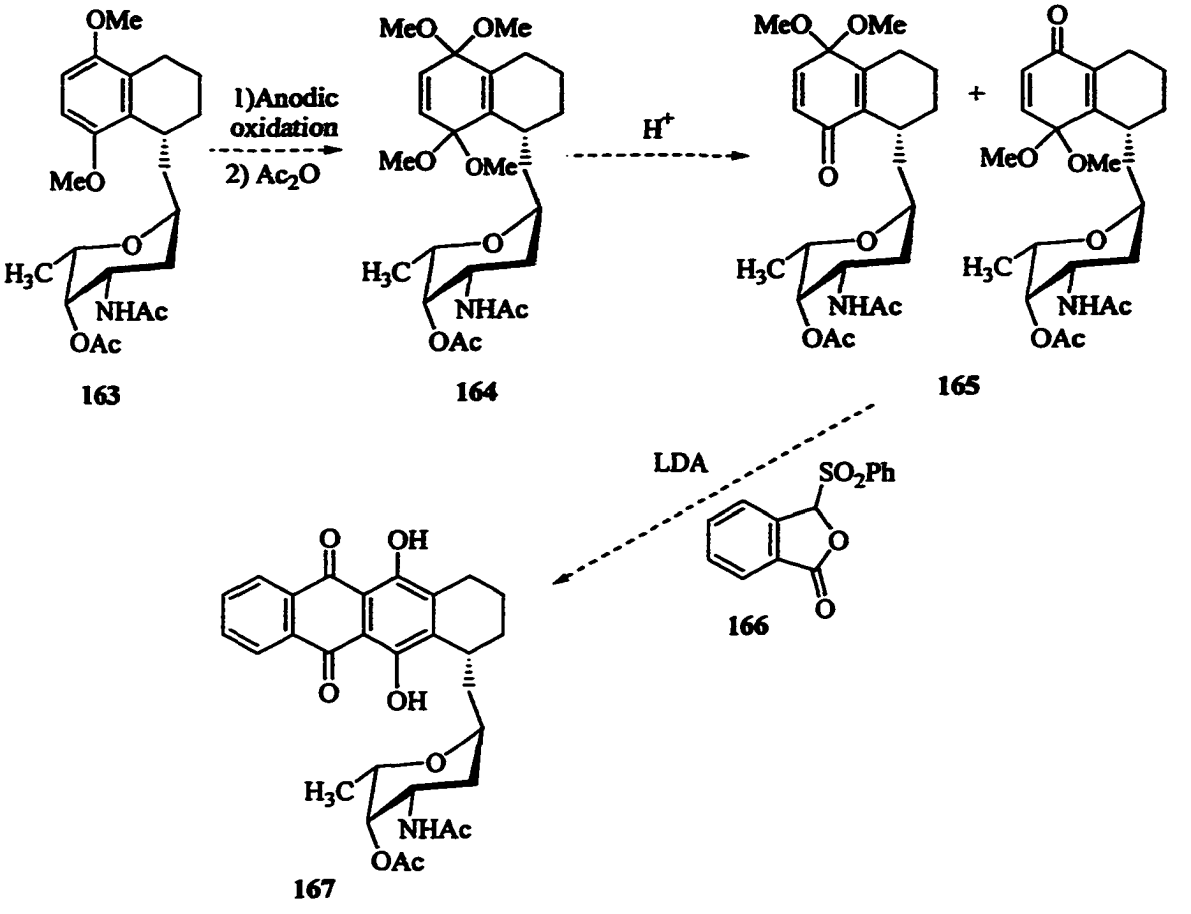
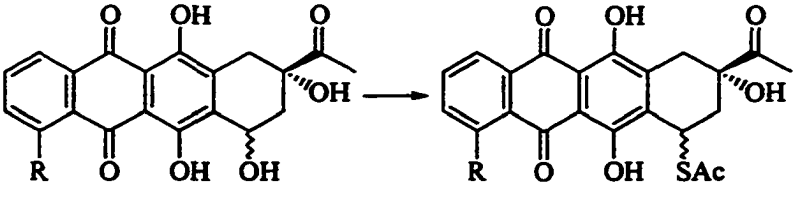


Figure 8. ORTEP drawing of the crystal structure of 4-(acetylamino)-2, 6-anhydro-1, 3, 4, 7-tetradeoxy-1-(1, 2, 3, 4-tetrahydro-5,8-dimethoxy-1*R*-naphthyl)-5-O-(phenyl-methyl)-β-L-altro-heptitol [β-(1*R*)-162].

Scheme 3.12



Scheme 3.12 shows how **163** could be elaborated using known methodology to complete the IDA-C-glycoside analog unfunctionalized at C-9. Anodic oxidation[20] in 2% KOH/methanol would give bisketal **164** after reacylation, which would then be subjected to partial hydrolysis to give mixture **165**. Subsequent reaction of monoketal mixture **165** with the anion[58] of **166** would yield **167**.



168 R=OMe
170 R=H

169 R=OMe
171 R=H

A second approach would be to use the "natural" aglycone as a partner in the RB sequence. Daunomycinone thioacetate **169** has been prepared[9] from **168** in 83% yield by refluxing in AcOH/AcSH, and the method can likely be applied to the known[59] IDA aglycone **170**. Future work to prepare the complete IDA-C-glycoside would require protection (MOM etherification or benzylation) of the hydroquinone moiety of **171** before an investigation with the Chan RB method. Aglycone **171** should couple with daunosamine iodide **156** using the K_2CO_3/DMF/H_2O method. Then oxidation with MMPP followed by the Chan RB, and catalytic hydrogenation would give IDA-C-glycoside as the N-acetamide. Time constraints prevented testing of the RB methodology on this more complex target, but perhaps other researchers may find the new C-glycoside application of the Ramberg-Bäcklund rearrangement of use.

The stereoselective reduction of the RB alkene product to obtain either stereoisomer as needed, would be a desirable addition to this C-glycoside methodology. Additionally, the low yield of C-disaccharide **142** shows that more investigation is needed before the Chan RB method can be extended to unactivated sulfones.

During the preparation of this manuscript, it was disclosed[60] that a group in England had independently discovered the use of the RB reaction to produce exo-glycals. Our disclosure[61] was submitted to the same journal (another coincidence) several weeks before the English group, but theirs was accepted several weeks before ours.

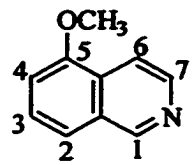
4. EXPERIMENTAL

NMR spectra were recorded on several Varian spectrometers: a 200XL (200 MHz), a Gemini 2000 (300 MHz), a 400XL (400 MHz), and a 500 MHz instrument with $CDCl_3$ as the solvent usually. Robertson Laboratory, Inc., of Madison, NJ performed the elemental analyses. Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. Optical rotations were determined using a Perkin-Elmer 241 Polarimeter, and infrared spectra were recorded on a Perkin-Elmer IR instrument.

Thin layer chromatography analyses were carried out on precoated sheets of silica gel 60 F_{254} (E. Merck) and short-wave ultraviolet light or phosphomolybdic acid spray was used to visualize the components. Flash chromatography was performed with silica gel 60 (230-400 mesh) purchased from E. M. Science. Solvents were HPLC grade for general use and anhydrous solvents were Aldrich Anhydrous grade, except for tetrahydrofuran. Dry tetrahydrofuran was obtained by distillation, under nitrogen, from sodium benzophenone ketyl. All experiments were done under an inert atmosphere of nitrogen or argon and anhydrous magnesium sulfate was used to dry all reaction extracts.

The alumina supported base was prepared by dissolving potassium hydroxide in methanol followed by mixing with 150 mesh activated neutral alumina and then concentrating under reduced pressure until solvent free.

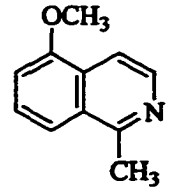
4.1 Preparation of 5-methoxyisoquinoline (34)



Sodium hydride (13.77 g, 0.344 mol, 60% in a mineral oil dispersion) was mechanically stirred with 50 mL of hexane for a few minutes and the stirring was halted. The solids were allowed to settle and the supernatant was decanted. The residual solid was stirred with 400 mL of anhydrous *N*, *N*-dimethylformamide and was cooled in a cold water bath while 5-hydroxyisoquinoline (**33**) (49.97 g, 0.344 g, 90% pure) was added portionwise. The mixture was stirred at room temperature for 30 min until hydrogen evolution had ceased, then was cooled to 15 °C prior to the dropwise addition of methyl iodide (48.83 g, 0.344 mol). The reaction temperature was maintained between 15-20 °C during the addition, then was allowed to rise to room temperature while the reaction mixture was stirred for 2 h. The reaction mixture was poured into 2 L of ice cold brine and extracted with ether (3x700 mL). The first extract had an emulsified layer that had to be filtered through Celite in order to cleanly separate the phases. The combined organic phases were washed with 2*N* sodium hydroxide solution (200 mL), brine (3x200 mL), and dried. The extracts were filtered and concentrated under reduced pressure to dryness to afford 31 g of a darkening oil. Vacuum distillation (bp 94-96 °C, 0.2 torr) of the crude oil gave 27.58 g of **34** as a very pale yellow oil (55.9% yield based on 90% pure starting material): IR ($CHCl_3$) 3034, 3011, 2964, 2939, 2913, 2842, 1631, 1586, 1495, 1464, 1428, 1394, 1376, 1321, 1277, 1251, 1177, 1113, 1068, 1034, 999, 832, 803 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.01

(s, 3H, $OC\underline{H}_3$), 6.99 (dd, 1H, J = 1.4, 7 Hz, H-6), 7.48-7.55 (m, 2H, H-7, 8), 8.00 (d, 1H, J = 5.9 Hz, H-4), 8.53 (d, 1H, J = 5.8 Hz, H-3), 9.21 (s, 1H, H-1); MS (EI^+) *m/e* 159 $[M]^+$; Anal. Calcd for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.71; H, 5.95; N, 8.36.

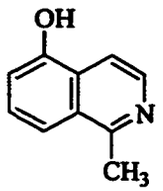
4.2 Preparation of 5-methoxy-1-methylisoquinoline (35)



Potassium *tert*-butoxide (48.59 g, 0.433 mol) was mechanically stirred with anhydrous dimethyl sulfoxide (450 mL) at 70 °C for 1 h. Then a solution of **34** (27.57 g, 0.173 mol) in 25 mL of toluene was added dropwise raising the temperature to 77 °C. Stirring of the reaction was continued at 70 °C for an additional 4 h, at which time it was cooled to 15 °C. The reaction contents were poured into ice cold brine (2 L), and extracted with ether (3x700 mL). The combined organic phases were washed with brine (3x500 mL), dried, filtered, and concentrated under reduced pressure to dryness to give 21.8 g of a dark red-brown solid. The solid was dissolved in warm toluene and flash chromatographed on silica gel (100 g) packed in hexane. The column was eluted with a gradient of 0-20% ethyl acetate:hexane to give 18 g of a slightly impure yellow solid. Recrystallization of the solid from ether/hexane gave 14.87 g of **35** as yellow-orange crystals, mp 85-87 °C. Rechromatography of the concentrated mother liquor followed by recrystallization gave an additional 1.55 g, thus affording a total of 16.42 g of **35** (55% yield): IR ($CHCl_3$) 3041, 3010, 2960, 2940, 2840, 1588, 1497, 1466, 1415,

1392, 1355, 1252, 1263, 1182, 1165, 1046, 978, 836, 806 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.95 (s, 3H, $C\underline{H}_3$), 4.01 (s, 3H, $OC\underline{H}_3$), 7.00 (d, 1H, J = 7.3 Hz, H-6), 7.50 (t, 1H, J = 8.1 Hz, H-7), 7.67 (d, 1H, J = 8.5 Hz, H-8), 7.90 (d, 1H, J = 5.9 Hz, H-4), 8.40 (d, 1H, J = 5.9 Hz, H-3); MS (EI^+) 173 $[M]^+$; Anal. Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.22; H, 6.26; N, 7.80.

4.3 Preparation of 5-hydroxy-1-methylisoquinoline (37)

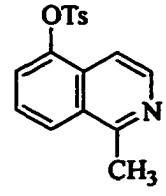


A solution of **35** (9.56 g, 0.055 mol) in 48% hydrobromic acid (100 mL) was stirred at reflux for 18 h, then concentrated under reduced pressure to dryness. A solution of 1:1 brine:water (100 mL) was added to the residue followed by the slow addition of saturated sodium bicarbonate solution (100 mL). After the addition of ethyl acetate (200 mL), the mixture was stirred for 30 min. The resultant emulsion was filtered through Celite, and the solids were washed with ethyl acetate and water. The aqueous layer was reextracted with ethyl acetate (2x200 mL) and the combined organic phases were dried and filtered.

The solids that were collected on the Celite bed were identified as being mostly the desired product by TLC (1:1 EtOAc:hexane), so they were dissolved in methanol (300 mL), and refiltered through the same Celite bed. The dissolution of solids was repeated twice, then the combined extracts were concentrated under reduced pressure to give 8.55 g of crude **37** as a dark tan solid in 97% yield: ^1H NMR (300 MHz, DMSO-

d_6) δ 2.84 (s, 3H, C<u>H</u>$_3$), 7.10 (dd, 1H, J = 0.8, 7.6 Hz, H-6), 7.46 (t, 1H, J = 8.1 Hz, H-7), 7.60 (d, 1H, J = 8.6 Hz, H-8), 7.80 (d, 1H, J = 5.9 Hz, H-4), 8.28 (d, 1H, J = 5.9 Hz, H-3), 10.47 (s, 1H, O<u>H</u>).

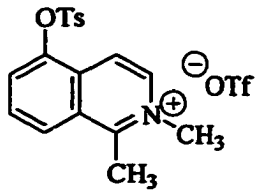
4.4 Preparation of 4-methylbenzenesulfonic acid 1-methylisoquinolin-5-yl ester (38)



A mixture of dry tetrahydrofuran (10 mL) and sodium hydride (0.2 g, 5 mmol; 60% in mineral oil dispersion) was stirred for 10 min at room temperature. To the mixture was added portionwise compound **37** (796 mg, 5 mmol) allowing the hydrogen evolution to subside between additions. The mixture was stirred at room temperature for 1 h, then a solution of *p*-toluenesulfonyl chloride (953 mg, 5 mmol) in 5 mL of dry tetrahydrofuran was added dropwise. The mixture was stirred at room temperature for 2 h, then poured into a saturated sodium bicarbonate solution (30 mL) and extracted with ethyl acetate (100 mL). The organic phase was dried, filtered, and concentrated under reduced pressure to give 1.6 g of a mixture of oil and solid. Treatment of the mixture with dichloromethane (30 mL) followed by filtration of the insoluble solid (83 mg) [identified as recovered **37** by TLC (10:90 MeOH:CH_2Cl_2)] gave a filtrate which was applied to a column of silica gel (15 g) packed in dichloromethane. Elution with dichloromethane gave the pure tosylate **38** (1.32 g, 84.2% yield) as a yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.41 (s, 3H, Ar_{tosyl}-C<u>H</u>$_3$), 2.93 (s, 3H, C<u>H</u>$_3$), [7.27, 7.73

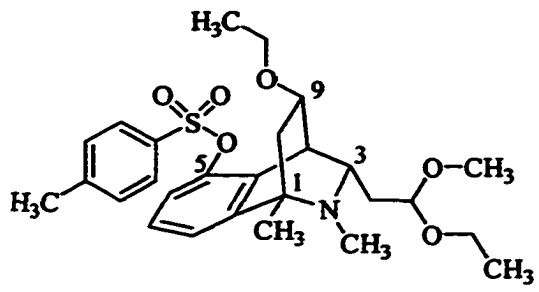
(AB_q, 4H, J = 8.1 Hz, Ar_{tosyl})], 7.44-7.51 (m, 3H, Ar), 8.02 (d, 1H, J = 6 Hz, H-4), 8.29 (d, 1H, J = 6 Hz, H-3).

4.5 Preparation of 4-methylbenzenesulfonic acid 1,2-dimethylisoquinolinium-5-yl ester trifluoromethanesulfonate (39)



A solution of tosylate **38** (1.18 g, 3.77 mmol) in anhydrous ether (50 mL) was treated with methyl trifluoromethanesulfonate (0.43 mL, 3.77 mmol) with stirring at room temperature for 30 min. The reaction solution became heterogeneous with the formation of a gummy precipitate. The mixture was concentrated under reduced pressure to dryness, then taken up in dichloromethane and again concentrated to give **39** as a hydroscopic white foam (1.74 g, 97% yield): ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.46 (s, 3H, Ar_{tosyl}-C<u>H</u>$_3$), 3.27 (s, 3H, C<u>H</u>$_3$), 4.47 (s, 3H, N-C<u>H</u>$_3$), [7.37, 7.76 (AB_q, 4H, Ar_{tosyl})], 7.81-7.99 (m, 2H, Ar), 8.01 (d, 1H, J = 7.2 Hz, Ar), 8.40 (t, 2H, J = 7 Hz, H-3,4).

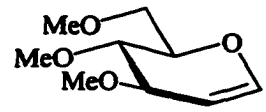
4.6 Preparation of rac-[1α, 3β(*R**), 4α, 9*R**]-4-methylbenzenesulfonic acid 9-ethoxy-3-(2-ethoxy-2-methoxyethyl)-1, 2, 3, 4-tetrahydro-1, 2-dimethyl-1, 4-ethanoisoquinolin-5-yl ester (41)



A mixture of isoquinolinium salt **39** (279 mg, 0.56 mmol), anhydrous methanol, calcium carbonate (300 mg, 3 mmol), and ethyl vinyl ether (EVE) (0.5 mL, 5.2 mmol) was stirred at room temperature for 24 h. TLC analysis (10:90 MeOH:CH_2Cl_2) of the reaction mixture showed no apparent change, so more EVE (2 mL, 20.9 mmol) was added, and stirring was continued for another 24 h. The presence of a small amount of a less polar component was evident, so more EVE (4 mL, 41.8 mmol) was added and stirring was continued for an additional 24 h. After a total of three days of stirring, the reaction contents were filtered through a Celite pad. The collected solids were washed with methanol and the filtrate was concentrated under reduced pressure to dryness. Preparative TLC of the residue yielded 28 mg of recovered **39** and 211 mg of the slightly impure product, **41**. Further purification by flash chromatography on silica gel (10 g) packed in dichloromethane and elution with 1% methanol:dichloromethane gave pure **41** (100 mg) and 75 mg of additional slightly impure product, for a total of 180 mg of **41** (66% yield, based on recovered **39**). Crystals of **41** suitable for X-ray diffraction analysis were grown from ether:hexane. IR ($CHCl_3$) 2979, 2876, 2795, 1470, 1376, 1179, 1130, 1094, 1068, 922, 816, 558 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.01-1.05 (m, 1H), 1.07 (t, 3H, J = 6.9 Hz, $OCH_2\underline{CH_3}$), 1.21 (t, 3H, J = 7.0 Hz, $OCH_2\underline{CH_3}$), 1.35-

1.55 (m, 2H), 1.50 (s, 3H, CCH_3), 2.31 (s, 3H, NCH_3), 2.38 (t, 1H), 2.46 (s, 3H, $ArCH_3$), 2.55 (dd, 1H), 3.30 (s, 3H, OCH_3), 3.30-3.40 (m, 1H), 3.46-3.53 (m, 1H), 3.61-3.76 (m, 2H), 3.77 (s, 1H), 3.83-3.89 (m, 1H), 4.61 (t, 1H, CH_{acetal}), 6.69-7.74 (m, 1H, Ar), 7.09 (s, 1H, Ar), 7.10 (d, 1H, J = 2.5 Hz, Ar), [7.36, 7.37 (AB_q, 4H, J = 8.1 Hz, Ar_{tosyl})]; ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.38 (q), 20.26 (q), 21.75 (q), 34.99 (t), 36.14 (q), 36.58 (d), 38.22 (t), 52.25 (q), 55.25 (s), 59.50 (d), 61.74 (t), 63.65 (t), 75.89 (d), 101.42 (d), 118.19 (d), 118.42 (d), 126.91 (d), 128.37 (d), 129.92 (d), 130.17 (s), 133.96 (s), 145.20 (s), 147.78 (s), 148.32 (s); MS(+) FAB *m/e* 504 $[M + H]^+$; Anal. Calcd for $C_{27}H_{37}NO_6S$: C, 64.39; H, 7.40; N, 2.78; S, 6.37. Found: C, 64.13; H, 7.71; N, 2.75; S, 6.27.

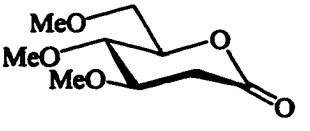
4.7 Preparation of tri-O-methyl-D-glucal (105)



A solution of tri-O-acetyl-D-glucal (**104**) (Aldrich, 27.2 g, 0.1 mol) in methanol (200 mL) was treated with 12 mL of a solution of 25% sodium methoxide in methanol and stirred at room temperature for 15 min. The solution was concentrated under reduced pressure to dryness and the residue was dissolved in methanol (200 mL). The solution was again concentrated under reduced pressure to dryness to give 20 g of the deprotected glycal as a white foam. The foam was dissolved in anhydrous dimethyl sulfoxide (500 mL) and mechanically stirred during the addition of powdered 85% potassium hydroxide (72 g, 1.09 mol). The addition of base to the deprotected glycal resulted in a mild exotherm to 27 °C over a period of 15 min. The reaction mixture was

cooled to 18 °C and methyl iodide was added dropwise (90 mL, 1.45 mol) while the temperature of the reaction was maintained below 25 °C. The mixture was stirred at room temperature for 1.5 h, then poured into ice cold brine (1.5 L) and extracted with dichloromethane (3x500 mL). The combined organic extracts were washed with brine (3x500 mL), dried, and filtered, then concentrated under reduced pressure to give 23 g of a pink oil. NMR analysis of the crude oil showed the presence of **105** and some residual DMSO. The oil was taken up in ethyl acetate (200 mL) and washed with brine (2x50 mL). The organic phase was dried and filtered, then concentrated under reduced pressure to give crude **105** as a light orange oil (18.2 g, 96.7% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.41 (s, 3H, $OC\underline{H}_3$), 3.42 (s, 3H, $OC\underline{H}_3$), 3.46 (dd, 1H, J = 2.3, 8.3 Hz), 3.54 (s, 3H, $OC\underline{H}_3$), 3.61-3.73 (m, 2H), 3.88 (ddd, 1H), 3.95 (ddd, 1H), 4.83 (dd, 1H, J = 2.9, 6.1 Hz, H-2), 6.39 (dd, 1H, J = 1.4, 6.1 Hz, H-1).

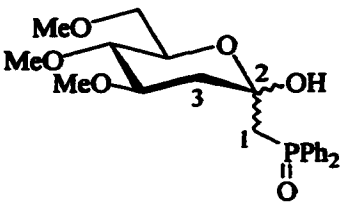
4.8 Preparation of 2-deoxy-3,4,6-tri-O-methyl-D-arabino-hexanoic acid-lactone (82)



A solution of crude glycal **105** (18.2 g, 96.7 mmol) in anhydrous tetrahydrofuran (190 mL) was stirred with triphenylphosphonium hydrobromide (1.66 g, 4.8 mmol) until most of the salt had dissolved. Water (2.61 mL, 145 mmol) was added to the reaction mixture and stirring was continued for 1.5 h at which time TLC analysis (30% EtOAc:hexane) showed the absence of **105**. The reaction was quenched by the addition of a saturated sodium bicarbonate solution (10 mL) and stirred for about five min. The

reaction mixture was concentrated under reduced pressure to near dryness and the residue was partitioned between ethyl acetate (200 mL) and brine (50 mL). The organic phase was dried, filtered, and concentrated under reduced pressure to dryness to give 20.35 g of overweight crude **106** as a pale yellow solid. Dry dimethyl sulfoxide (225 mL) was added to the solid followed by acetic anhydride (183 mL) and the mixture was stirred at room temperature for 72 h. The reaction was concentrated under reduced pressure to give 40 g of a yellow oil that was taken up in ethyl acetate (200 mL) and washed with brine (3x50 mL). The organic phase was dried, filtered, and concentrated under reduced pressure to give 20 g of a dark yellow oil. The crude oil was dissolved in toluene and flash chromatographed on silica gel (150 g) packed in hexane. Elution with 20%, then 40% ethyl acetate:hexane gave 11.2 g of a yellow oil that was still contaminated by the presence of unoxidized material, **106**. The yellow oil crystallized from isopropyl ether (25 mL) to give pure lactone **82** as a colorless crystalline solid, mp 32-33 °C (8.12 g, 41% yield): IR ($CHCl_3$) 3024, 2997, 2935, 2898, 2832, 1757,1458, 1369, 1344, 1238, 1196, 1106, 1070, 1045, 974, 816 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.69-2.83 (m, 2H), 3.40 (s, 3H, $OC\underline{H}_3$), 3.42 (s, 3H, $OC\underline{H}_3$), 3.48 (s, 3H, $OC\underline{H}_3$), 3.51 (dd, 1H, J = 3.9, 7.6 Hz), 3.66 (d, 2H, J = 3.9 Hz), 3.70 (q, 1H, J = 4.4 Hz), 4.18 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.81 (t), 56.32 (q), 57.80 (q), 58.99 (q), 71.12 (t), 76.24 (d), 76.57 (d), 78.54 (d), 169.24 (s, C-1).

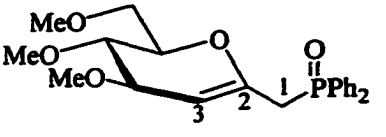
4.9 Preparation of anomeric mixture of 2, 6-anhydro-1, 3-dideoxy-1-diphenylphosphoryl-2-hydroxy-4, 5, 7-tri-O-methyl-D-arabino-heptitol (90)

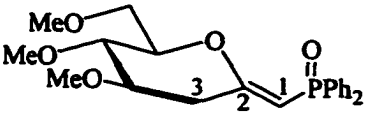


A magnetically stirred solution of methyldiphenylphosphine oxide **89** (8.65 g, 40 mmol) in anhydrous 1,2-dimethoxyethane (100 mL) was cooled to -15 °C by immersion in a dry ice/acetone bath. A 2.5M solution of *n*-butyllithium in hexane (16.4 mL, 41 mmol) was then slowly injected into the reaction while maintaining the internal temperature between -10 and -15 °C. The cooling bath was replaced by an ice/water bath when the addition was complete, and the reaction was stirred for 1 h at 0-5 °C. The ice/water bath was replaced with a dry ice/acetone bath and the reaction mixture was cooled to -65 °C. A solution of lactone **82** (4.08 g, 20 mmol) in anhydrous tetrahydrofuran (40 mL) was added dropwise to the reaction mixture while maintaining the internal temperature between -60 and –65 °C. Cooling was maintained for an additional 1 h, then the reaction mixture was allowed to warm slowly to 10 °C. The reaction was quenched by the rapid addition of a saturated ammonium chloride solution (50 mL) and stirred for five min. The mixture was extracted with ethyl acetate (2 x 200 mL) and the organic phase was dried, filtered, and concentrated under reduced pressure to dryness to give 14 g of a yellow oil. The oil was dissolved in a small amount of toluene and flash chromatographed on silica gel (140 g) packed in toluene. Elution with 50% ethyl acetate:toluene gave 7 g of a pale yellow oil that crystallized from ether/hexane to give 5.63 g of **90** as a colorless crystalline solid, mp 101-104 °C. The

filtrate was concentrated under reduced pressure to dryness to give 0.65 g of additional **90** as a white solid (total 6.28 g, 74.5% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (dt, 1H, J = 2.6, 12.4 Hz), 2.33 (dd, 1H, J = 4.7, 12.4 Hz), 2.62-2.78 (m, 2H), 2.97 (dd, 1H), 3.05 (s, 3H, $OC\underline{H}_3$), 3.15 (t, 1H, J = 9.4 Hz) 3.42 (s, 3H, $OC\underline{H}_3$), 3.44-3.48 (m, 1H, partially coincident), 3.48 (s, 3H, $OC\underline{H}_3$), 3.64-3.69 (m, 1H), 3.76 (d, 1H, J = 9.4 Hz), 6.58 (d, 1H, 2.6 Hz, O$\underline{H}$), 7.46-7.54 (m, 6H, Ar$\underline{H}$), 7.63- 7.68 (m, 2H, Ar$\underline{H}$), 7.82 (dd, 2H, J = 6.8, 12 Hz, Ar$\underline{H}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.15 (t), 39.53 (t), 41.98 (t), 42.15(t), 57.53(q), 58.77 (q), 60.22 (q), 70.88 (t), 71.38 (d), 78.77 (d), 79.62 (d), 97.92 (s), 98.05 (s), 128.06 (d), 128.33 (d), 128.67 (d), 128.90 (d), 130.12 (d), 130.28 (d), 131.16 (d), 131.36 (d), 132.03 (d), 133.10 (s), 133.95 (s), 135.12 (s); LR (+)LSIMS *m/e* 421 $[M + H]^+$.

4.10 Preparation of 2, 6-anhydro-1, 3-dideoxy-1-diphenylphosphoryl-4, 5, 7-tri-O-methyl-D-arabino-hept-2-enitol (98A) and 2, 6-anhydro-1, 3-dideoxy-1-diphenylphosphoryl-4, 5, 7-tri-O-methyl-D-arabino-hept-1-enitol (98B)

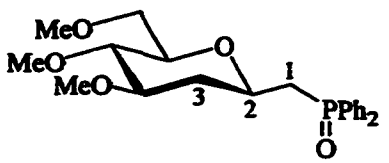




A solution of **90** (7.5 g, 17.84 mmol) in anhydrous tetrahydrofuran (100 mL) and triethylamine (14.3 mL, 102.6 mmol) was charged with activated 4 Å molecular sieves (14 g) and stirred for 10 min. The mixture was cooled to -75 °C and trifluoroacetic anhydride (3.85 mL, 27.26 mmol) was slowly injected into the reaction while the internal temperature was maintained between -72 and -75 °C. The reaction

mixture was stirred at -75 °C for an additional 2 h, then quenched by the addition of saturated sodium bicarbonate solution (10 mL). The reaction mixture was allowed to warm to room temperature and then filtered through a Celite pad to remove insoluble solids. The filtrate was concentrated under reduced pressure to near dryness and the residue was partitioned between ethyl acetate (150 mL) and brine (50 mL). The organic phase was dried, filtered, and concentrated under reduced pressure to give 10 g of an oil. The oil was dissolved in a small amount of toluene and flash chromatographed on silica gel (100 g) packed in hexane. Elution with 50% ethyl acetate:hexane gave 1.9 g of recovered **90**. Further elution with ethyl acetate, followed by 5% then 10% methanol:ethyl acetate, successively gave 4.28 g of endocyclic alkene **98A** and 0.97 g of exocyclic alkene **98B** as colorless oils [73.1% yield (97.9% yield based on recovered **90**)]. Endocyclic alkene **98A**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.11-3.46 (coincident m, 6H), 3.27 (s, 3H, OC$\underline{H}_3$), 3.29 (s, 3H, OC$\underline{H}_3$), 3.45 (s, 3H, OC$\underline{H}_3$), 4.91 (dd, 1H, =C$\underline{H}$-, H-3), 7.38-7.55 (m, 6H, Ar$\underline{H}$), 7.72-7.84 (m, 4H, Ar$\underline{H}$); Exocyclic alkene: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.43 (dd, 1H), 2.72 (dd, 1H), 2.91 (d, 1H), 3.08 (s, 3H, OC$\underline{H}_3$), 3.1-3.45 (coincident m, 3H), 3.39 (s, 6H, 2 x OC$\underline{H}_3$), 5.13 (d, 1H, =C$\underline{H}$-, H-1), 7.29-7.98 (m, 6H, Ar$\underline{H}$), 7.66-7.81 (m, 4H, Ar$\underline{H}$).

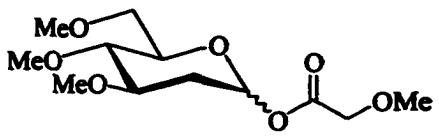
4.11 Preparation of 2, 6-anhydro-1, 3-dideoxy-1-diphenylphosphoryl-4, 5, 7-tri-O-methyl-β-D-arabino-heptitol (99)



A solution of endocyclic alkene **98** (4.28g, 10.64 mmol) in methanol (100 mL) was treated with hydrogen (50 psi) in the presence of 10% palladium-on-carbon (2 g) and stirred at room temperature for 8 h. The reaction mixture was filtered through Celite and the filtered solids were washed well with methanol. The colorless filtrate was concentrated under reduced pressure to dryness to a give 4.05 g of a thick oil. The glass-like oil was slurried with dichloromethane (100 mL) and a small amount of fine particulates were removed by filtration through a Celite pad. The filtrate was again concentrated under reduced pressure to dryness to give 4 g of **99** as a glass-like oil (93.1% yield). The oil was crystallized from isopropyl ether to give 3 g of a white solid, that was recrystallized from ethyl acetate to give crystals (mp 107-108 °C) that were submitted for X-ray analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (q, 1H, J = 12 Hz, H-3_a), 2.26 (dd, 1H, J = 5.1, 12.8 Hz, H-3_e), 2.43 (dt, 1H, J = 6, 14.5 Hz, H-1'), 2.80 (ddd, 1H, H-1), 3.04-3.11 (m, 2H), 3.20-3.24 (m, 2H), 3.27 (s, 3H, $OC\underline{H}_3$), 3.35 (s, 3H, $OC\underline{H}_3$), 3.44 (dd, 1H, J = 3, 10.7 Hz), 3.48 (s, 3H, $OC\underline{H}_3$), 3.85 (m, 1H, H-2), 7.46-7.53 (m, 6H, Ar$\underline{H}$), 7.72-7.80 (m, 4H, Ar$\underline{H}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.69 (t), 36.63 (t), 37.28 (t), 37.37 (t), 56.66 (q), 58.91 (q), 60.22 (q), 70.06 (d), 71.05 (t), 78.15 (d), 78.99 (d), 81.75 (d), 128.09 (d), 128.25 (d), 128.34 (d), 128.45 (d), 130.25 (d), 130.38

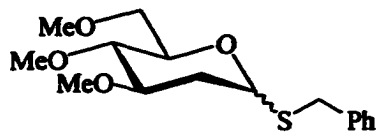
(d), 130.73 (d), 130.86 (d), 131.34 (d), 131.38 (d), 131.54 (d), 131.58 (d), 131.91 (s), 132.85 (s), 133.24 (s), 134.18 (s); LR (+) LSIMS *m/e* 405 $[M + H]^+$.

4.12 Preparation of methoxyacetyl-2-deoxy-3, 4, 6-tri-O-methyl-α, β-D-arabino-hexopyranoside (107)



A solution of methoxyacetic acid (0.98 g, 10.9 mmol), dicyclohexylcarbodiimide (DCC, 2.23 g, 10.8 mmol) and anhydrous ether (80 mL) was stirred at room temperature for 15 min. Crude **106** (2.06 g, 10 mmol) was added to the solution followed by 4-pyrrolidinopyridine (138 mg, 0.93 mmol) and stirring was continued at room temperature for 18 h. The precipitated dicyclohexylurea (DCU) was separated by filtration, washed with ether, and discarded. The filtrate was washed with brine, dried, and concentrated under reduced pressure to dryness to give 3.08 g of a yellow oil. The oil was dissolved in a small amount of toluene and flash chromatographed on silica gel (30 g) packed in hexane. Elution with a gradient of 20-30% ethyl acetate:hexane gave glycoside **107** as a pale yellow oil (2.57 g, 92.4% yield) as an 88:12 α:β mixture of anomers: ^{1}H NMR (300MHz, $CDCl_3$) δ 1.72 (ddd, 1H), 2.28 (ddd, 1H), 3.21-3.72 (coincident m, 5H), 3.40 (s, 3H, $OC\underline{H}_3$), 3.45 (s, 3H, $OC\underline{H}_3$), 3.46 (s, 3H, $OC\underline{H}_3$), 3.56 (s, 3H, $OC\underline{H}_3$), 4.04 (s, 1.8H, $C(O)C\underline{H}_2OCH_3$), 4.06 (s, 0.2H, $C(O)C\underline{H}_2OCH_3$), 5.77 (dd, 0.1H, H-$1_a$), 6.33 (dd, 0.9H, H-$1_e$).

4.13 Preparation of phenylmethyl-2-deoxy-3, 4, 6-tri-O-methyl-1-thio-α, β-D-arabino-hexopyranoside (108)



Method A:

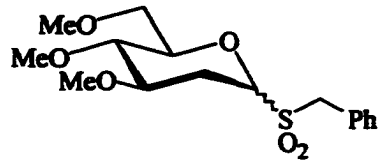
A solution of glycal **105** (1.264 g, 6.72 mmol), benzyl mercaptan (2.38 mL, 20.16 mmol), and triphenylphosphine hydrobromide (115 mg, 0.34 mmol) in anhydrous dichloromethane (20 mL) was stirred at room temperature for 20 h. The reaction was quenched by the addition of a saturated sodium bicarbonate solution (10 mL) and stirred for 10 min. The phases were separated, and toluene (20 mL) was added to the organic phase prior to its concentration under reduced pressure to dryness to give 4 g of a colorless oil. The oil was dissolved in a small amount of toluene and flash chromatographed on silica gel (23 g) packed in hexane. Elution with 5%, then 10% ethyl acetate:hexane gave thioglycoside **108** as a colorless oil (1.49 g, 71% yield) as a 45:55 β:α mixture of anomers.

Method B:

A 0.005M solution of ytterbium (III) trifluoromethanesulfonate (6 mL, 0.03 mmol) in anhydrous acetonitrile was added to a solution of glycoside **107** (1.39 g, 5 mmol) and benzyl mercaptan (621 mg, 5 mmol) in anhydrous acetonitrile (40 mL). The solution was stirred at reflux for 15 min and TLC analysis (1:1 EtOAc:hexane) showed the absence of glycoside **107**. The reaction was allowed to cool to room temperature and was quenched by the addition of a saturated sodium bicarbonate solution (20 mL). The mixture was stirred for 5 min and then diluted with the addition of ethyl acetate

(200 mL). Solid sodium chloride was added to saturate the aqueous phase and the organic phase was separated, dried, filtered, and concentrated under reduced pressure to dryness to give 1.7 g of a colorless oil. The oil was dissolved in a small amount of toluene and flash chromatographed on silica gel (25 g) packed in hexane. Elution with a gradient of 5-25% ethyl acetate:hexane gave thioglycoside **108** as a colorless oil (1.2 g, 77% yield) as a 55:45 α:β mixture of anomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.57 (bq, 0.5H, J = 11.7 Hz), 1.86 (ddd, 0.7H, J = 5.9, 11.5, 13.6 Hz), 2.13-2.23 (m, 1.2H), 3.10-3.24 (m, 3H), [3.37, 3.40, 3.42, 3.44, 3.52, 3.53 (singlets, 9H total, $OC\underline{H}_3$), 3.37-3.77 (coincident m, 6H), 3.94-4.00 (m, 1H), 4.19 (dd, 0.45H, J = 1.7, 11.7 Hz, H-1_a), 5.27 (bd, 0.55H, J = 5.6 Hz, H-1_e), 7.21-7.32 (m, 5H, Ar$\underline{H}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 33.52 (t), 33.74 (t), 34.10 (t), 34.83 (t), 56.12 (q), 56.44 (q), 58.50 (q), 58.61 (q), 59.69 (q), 59.83 (q), 70.27 (d), 70.64 (t), 71.30 (t), 76.88 (d), 78.27 (d), 78.56 (d), 78.72 (d), 78.93 (d), 79.47 (d), 81.70 (d), 126.37 (d), 126.45 (d), 127.89 (d), 127.94 (d), 128.48 (d), 128.60 (d), 137.47 (s), 137.71 (s); (+) ESMS *m/e* 313 $[M + H]^+$, 330 $[M + NH_4]^+$.

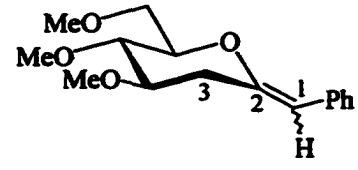
4.14 Preparation of (1*R*, *S*)-2-deoxy-3, 4, 6-tri-O-methyl-1-(phenylmethane-sulfonyl)-1, 5-anhydro-D-arabino-hexopyranoside (109)



A solution of thioglycoside **108** (1.2 g, 3.84 mmol) in ethanol (20 mL) was diluted with water (20 mL) followed by the addition of magnesium monoperoxyphthalate (MMPP) (3.8 g, 7.68 mmol). A mild exothermic reaction ensued resulting in a clear solution that was stirred at room temperature overnight. The reaction was concentrated under reduced pressure to remove most of the ethanol and the residue was then diluted with a saturated sodium bicarbonate solution (25 mL). Solid sodium chloride was added to fully saturate the aqueous phase prior to extraction with ethyl acetate (200 mL). The organic phase was dried, filtered, and concentrated under reduced pressure to dryness to give 1.37 g of sulfone **109** as a colorless oil (overweight from EtOAc, but ~95% yield) as a 47:53 β:α mixture of anomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.72 (bq, 0.53H, J = 12.3 Hz), 1.84 (ddd, 0.47H, J = 7.2, 9.9, 14.9 Hz), 2.41 (ddd, 0.47H, J = 1.8, 5.1, 12.6 Hz), 2.68 (ddd, 0.53H, J = 3.3, 4.8, 14.8 Hz), 3.03 (dd, 0.53H, J = 8.7, 9.6 Hz), 3.18 (dd, 0.53, J = 7.5, 9.6 Hz), 3.21-3.34 (m, 1H), [3.38, 3.44, 3.46, 3.47, 3.51, 3,53 (singlets, 9H total, $OC\underline{H}_3$), 3.61-3.74 (m, 2H), 3.84 (ddd, 0.5H, J = 2.4, 7.2, 9.6 Hz), 4.02 (dd, 0.5H, J = 1.8, 12 Hz), 4.18 (d, 0.5H, J = 1.5 Hz), 4.31 (ddd, 0.5H, J = 3.3, 3.4, 9.3 Hz), 4.54 (d, 0.5H, J = 13.8 Hz), 4.60 (d, 0.5H, 14.1 Hz), 4.71 (dd, 0.5H, J = 3.3, 7.2 Hz), 7.35-7.50 (m, 5H, $Ar\underline{H}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.27 (t), 25.59 (t), 55.30 (t), 55.41 (t), 56.42 (q), 57.02 (q), 58.76 (q), 58.92 (q), 59.30

(q), 60.44 (q), 71.03 (t), 71.48 (t), 74.27 (d), 76.65 (d), 78.20 (d), 78.71 (d), 79.03 (d), 80.86 (d), 83.27 (d), 83.52 (d), 127.47 (s), 127.62 (s), 128.55 (d), 128.61 (d), 128.70 (d), 130.71 (d), 130.75 (d); (+) ESMS *m/e* 345 $[M + H]^+$, 362 $[M + NH_4]^+$.

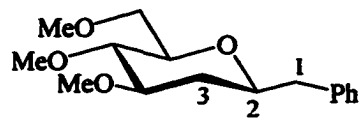
4.15 Preparation of 2, 6-anhydro-1, 3-dideoxy-4, 5, 7-tri-O-methyl-1-phenyl-D-arabino-hept-1-enitol (110)



A solution of sulfone **109** (1.37 g, ~3.65 mmol) in *tert*-butanol (10 mL) and dichloromethane (10 mL) was cooled to 5 °C and mixed with alumina supported potassium hydroxide (10 g, ~40% KOH, ~60 mmol). A chilled addition funnel was then used for the rapid dropwise addition of dibromodifluoromethane (5 mL, ~55 mmol) to the reaction mixture. Stirring was continued at 5 °C for 30 min at which time TLC analysis (1:1 EtOAc:hexane) showed no starting sulfone, a considerable amount of intermediate bromosulfones, and alkene product. Additional alumina supported potassium hydroxide (5 g, ~30 mmol) was added to the reaction and the cooling bath was removed. After stirring the reaction mixture at room temperature for 1 h, TLC analysis showed mostly the desired alkene product. The reaction was diluted with dichloromethane and filtered through a pad of Celite. The solids were washed well with dichloromethane and the filtrate was concentrated under reduced pressure to dryness to give 1.8 g of a cloudy pale yellow oil. The oil was dissolved in a small amount of toluene and flash chromatographed on silica gel (19 g) that had been washed with ethyl acetate followed by hexane. The sensitivity of the product to acid had been determined

from previous experiments and the column pre-wash was a method successfully used to prevent decomposition of such substrates during purification. Elution of the column with 5% ethyl acetate:hexane gave alkenes **110** as a colorless oil (0.79 g, 77.8% yield), as a 76:15:9 *E*:*Z*:endo mixture of alkenes. The product is unstable and the ^{1}H NMR spectrum in $CDCl_3$ had to be taken immediately after sample preparation. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03-1.75 (m, 0.5H), 2.26-2.40 (m, 0.5H), 2.78 (dd, 0.2H), 3.15 (dd, 0.8H), [3.39, 3.46, 3.55 (singlets, 9H total, $OC\underline{H}_3$)], 3.3-3.75 (m, 5H), 4.6 (d, 0.09H, H-3_{endo}), 5.48 (s, 0.15H, H-1_Z), 6.22 (s, 0.76H, H-1_E), 7.16-7.33 (m, 5H, Ar$\underline{H}$); *E* isomer ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.96 (t), 56.75 (q), 58.94 (q), 59.40 (q), 71.36 (t), 78.37 (d), 78.89 (d), 79.84 (d), 111.3 (d), 127.86 (d), 128.04 (d), 135.92 (s), 150.96 (s); (+) ESMS *m/e* 279 $[M + H]^+$, 296 $[M + NH_4]^+$.

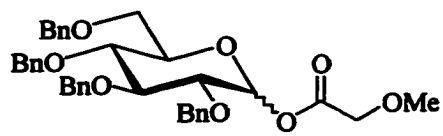
4.16 Preparation of 2, 6-anhydro-1, 3-dideoxy-1-phenyl-4, 5, 7-tri-O-methyl-β-D-arabino-heptitol (111)



A solution of mixed alkenes **110** (0.94 g, 3.38 mmol) in ethyl acetate (50 mL) was mixed with 10% palladium on charcoal (500 mg) and hydrogenated at atmospheric pressure overnight. The reaction mixture was filtered through a Celite pad and the solids were washed with ethyl acetate. The filtrate was concentrated under reduced pressure to dryness to give 0.95 g of a colorless oil. The oil was dissolved in a small amount of toluene and flash chromatographed on silica gel (18 g) packed in hexane. Elution with a gradient of 5-15% ethyl acetate:hexane gave β-C-glycoside **111** as a

colorless oil (0.69 g, 72.9% yield): $[\alpha]^{28}_D$ -0.01 (c = 1.80, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (dt, 1H, *J* = 11.3, 12.6 Hz, H-3_a), 2.07 (ddd, 1H, *J* = 1.6, 4.9, 12.8 Hz, H-3_e), 2.71 (dd, 1H, *J* = 7.6, 13.5 Hz, H-1'), 3.08-3.16 (m, 2H), 3.20-3.32 (m, 2H), [3.40, 3.46, 3.57 (singlets, 9H total, $OC\underline{H}_3$)], 3.51-3.69 (m, 3H), 7.22-7.34 (m, 5H, Ar$\underline{H}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.18 (t, C-3), 41.82 (t, C-1), 56.66 (q), 59.04 (q), 60.12 (q), 71.71 (t, C-7), 76.32 (d), 78.52 (d), 79.86 (d), 82.23 (d), 126.14 (d), 128.14 (d), 129.26 (d), 138.03 (s); (+) ESMS *m/e* 281 $[M + H]^+$, 303 $[M + Na]^+$; Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.23; H, 8.46.

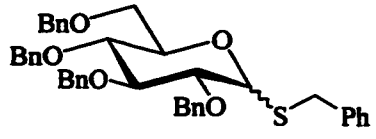
4.17 Preparation of methoxyacetyl-2, 3, 4, 6-tetrakis-O-(phenylmethyl)-α, β-D-glucopyranoside (113)



A mixture of methoxyacetic acid (0.99 g, 11 mmol), ether (50 mL), DCC (2.27 g, 11 mmol), tetrabenzylglucose **112** (Pfanstiehl, 5.4 g, 10 mmol), anhydrous tetrahydrofuran (20 mL), and 4-pyrrolidinopyridine (149 mg, 1 mmol) was stirred at room temperature overnight. The reaction mixture was then filtered to remove precipitated DCU and the solids were washed with ether (~100 mL). The filtrate was washed with water (50 mL), 5% acetic acid:water (2 x 50 mL), and 1:1 brine:saturated sodium bicarbonate solution (2 x 50 mL). The organic phase was dried, filtered, and the filtrate was concentrated under reduced pressure to dryness to give 6.79 g of a thick pale yellow oil. The oil was dissolved in a small amount of toluene and flash

chromatographed on silica gel (60 g) packed in hexane. Elution with 10% ethyl acetate:hexane gave glycoside **113** as a pale yellow oil (6.1 g, 99.7% yield) as a 6:1 α:β anomeric mixture: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.42 (s, 0.43H, $OC\underline{H}_3$ of β-glycoside), 3.44 (s, 2.57H, $OC\underline{H}_3$ of α-glycoside), 3.61-3.77 (m, 5H), 3.84-3.94 (m, 2H), 4.01-4.15 (m, 2H), 4.47-4.96 (m, 8H, $ArC\underline{H}_2$), 5.69 (d, 0.14H, J = 8 Hz, H-1_a), 6.46 (d, 0.86H, J = 3.3 Hz, H-1_e), 7.06-7.18 (m, 5H, $Ar\underline{H}$).

4.18 Preparation of phenylmethyl-2, 3, 4, 6-tetrakis-O-(phenylmethyl)-1-thio-α, β-D-glucopyranoside (114)



Method B:

A 0.005M solution of ytterbium (III) trifluoromethanesulfonate (2.5 mL, 0.0125 mmol) in anhydrous acetonitrile was added to a solution of glycoside **113** (1.28 g, 2.09 mmol) and benzyl mercaptan (0.246 mL, 2.09 mmol) in anhydrous acetonitrile (20 mL). The solution was stirred at 60-65 °C for 2 h, and TLC analysis (30% EtOAc:hexane) appeared to indicate that the reaction was incomplete. An additional portion of $Yb(OTf)_3$ solution (2.5 mL, 0.0125 mmol) was added to the reaction and the solution was stirred at room temperature overnight. TLC analysis showed little change from the previous day, and the reaction was quenched by the addition of a saturated solution of sodium bicarbonate (25 mL). The mixture was extracted with ethyl acetate (150 mL) and the organic phase was dried, filtered, and the filtrate was concentrated under

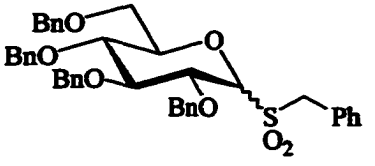
reduced pressure to dryness to give 1.59 g of an oil. The oil was dissolved in a small amount of toluene and flash chromatographed on silica gel (22 g) packed in hexane. Elution with a gradient of 2-6% ethyl acetate:hexane gave thioglycoside **114** as a colorless oil (1 g, 74% yield) as a 55:45 α:β anomeric mixture. The oil slowly solidified on refrigeration. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.35-3.89 (m, 7H), 4.01 (1/2 AB_q, 0.45H, J = 13.2 Hz), 4.14-4.20 (m, 0.55H), 4.23 (d, 0.45H, J = 9.8 Hz, H-1_a), 4.39-4.92 (m, 8H, 4 x Ar$\underline{CH_2}$), 5.22 (d, 0.55H, J = 5.4 Hz, H-1_e), 7.15- 7.40 (m, 25H, Ar$\underline{H}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 33.01 (t), 33.94 (t), 68.16 (t), 68.79 (t), 70.51 (d), 71.54 (t), 73.20 (t), 74.83 (t), 75.14 (t), 75.51 (t), 77.17 (d), 77.72 (d), 78.66 (d), 78.72 (d), 81.41 (d), 81.88 (d), 82.56 (d), 82.84 (d), 86.39 (d), 126.85 (d), 126.96 (d), 127.50 (d), 127.55 (d), 127.60 (d), 127.62 (d), 127.73 (d), 127.80 (d), 127.84 (d), 127.92 (d), 128.25 (d), 128.29 (d), 128.37 (d), 129.07 (d), 137.49 (s), 137.77 (s), 137.89 (s), 138.00 (s), 138.06 (s), 138.15 (s), 138.34 (s), 138.56 (s); (+) ESMS *m/e* 664 $[M + NH_4]^+$.

Method C

A solution of tetrabenzylglucose **112** (Pfanstiehl, 1.57 g, 2.9 mmol), benzyl mercaptan (433 mg, 3.48 mmol), methoxyacetic acid (0.023 mL, 0.3 mmol), and anhydrous acetonitrile (125 mL) was mixed with solid $Yb(OTf)_3$ (179 mg, 0.29 mmol) and refluxed for 3 h in a Soxhlet apparatus containing a thimble of powdered 4 Å molecular sieves (~10 g). The mixture was cooled to room temperature and the reaction was quenched with the addition of a saturated solution of sodium bicarbonate (40 mL). The mixture was diluted with ethyl acetate (100 mL) and the organic phase was dried, filtered, and the filtrate was concentrated under reduced pressure to dryness to give 2.6 g of a yellow oil. The oil was dissolved in a small amount of toluene and flash

chromatographed on silica gel (36 g) packed in hexane. Elution with a gradient of 2-6% ethyl acetate:hexane gave thioglycoside **114** as a colorless oil (1.57 g, 83.6% yield) as a 4:1 α:β anomeric mixture.

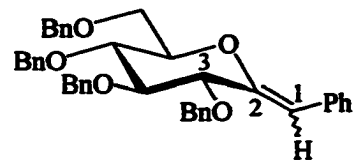
4.19 Preparation of phenylmethyl-2, 3, 4, 6-tetrakis-O-(phenylmethyl)-1-sulfonyl-α, β-D-glucopyranoside (115)



A solution of thioglycoside **114** (1 g, 1.54 mmol), tetrahydrofuran (20 mL), ethanol (15 mL), and water (15 mL) was mixed with MMPP (1.53 g, 2.02 mmol) and stirred at room temperature overnight. TLC analysis (30% EtOAc:hexane) showed mostly the mixed anomeric sulfones as overlapping spots along with the presence of a small amount of more polar components (possible sulfoxide intermediates). The reaction was diluted with a solution of saturated sodium bicarbonate (15 mL) and concentrated under reduced pressure to near dryness. The residue was partitioned between a solution of saturated sodium bicarbonate (25 mL) and ethyl acetate (150 mL). The organic phase was dried, filtered, and the filtrate was concentrated under reduced pressure to give crude sulfones **115** as a colorless oil (1 g, 95% yield, pure by TLC and NMR). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.49-3.78 (m, 4H), 4.02-4.17 (m, 3H), 4.44-4.98 (m, 9.55H), 4.73 (d, 0.45H, J = 3.0 Hz, probable H-1_e), 7.12- 7.51 (m, 25H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.84 (t), 57.93 (t), 68.65 (t), 68.74 (t), 73.22 (t), 73.63 (t), 74.31 (t), 74.90 (d), 74.91 (t), 75.16 (t), 75.27 (t), 75.66 (t), 76.57 (d), 76.90 (d), 77.84 (d),

79.21 (d), 80.34 (d), 85.56 (d), 85.80 (d), 86.39 (d), 127.36 (d), 127.52 (d), 127.67 (d), 127.76 (d), 127.93 (d), 128.29 (d), 128.38 (d), 128.63 (d), 128.73 (d), 131.00 (d), 131.07 (d), 137.10 (s), 137.23 (s), 137.46 (s), 137.59 (s), 137.66 (s), 137.84 (s), 138.01 (s), 138.16 (s); (+) ESMS *m/e* 701 $[M + Na]^+$.

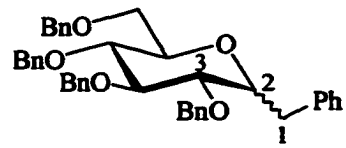
4.20 Preparation of 2, 6-anhydro-1-deoxy-1-phenyl-3, 4, 5, 7-tetrakis-O-(phenylmethyl)-D-gluco-hept-1-enitol (116)



A solution of crude sulfones **115** (1 g, 1.47 mmol) in *tert*-butanol (5 mL) and dichloromethane (5 mL) was cooled to 5 °C and mixed with alumina supported potassium hydroxide (4 g, ~24 mmol). Dibromodifluoromethane (1.25 mL, ~14 mmol) was added to the reaction in one portion and stirring was continued for 1 h. TLC analysis (30% EtOAc:hexane) showed the reaction to be incomplete and an additional portion of alumina supported potassium hydroxide (3 g, ~18 mmol) and dibromodifluoromethane (1.25 mL, ~14 mmol) were added to the reaction mixture. The reaction mixture was stirred at 5 °C for another 1 h and TLC analysis showed mostly alkene product along with a minor amount of intermediates. The reaction mixture was diluted with dichloromethane and filtered through a pad of Celite. The solids were washed well with dichloromethane and the filtrate was concentrated under reduced pressure to dryness. The residue was partitioned between brine (20 mL) and ethyl acetate (100 mL), and the organic phase was dried, filtered, and the filtrate was

concentrated under reduced pressure to dryness to give 1.1 g of a colorless oil. The oil was dissolved in a small amount of toluene and flash chromatographed on silica gel (18 g) packed in hexane. Elution with 5% ethyl acetate:hexane gave alkene **116** as a colorless oil (0.77 g, 85% yield) as a 91:9 *Z*:*E* mixture: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78-3.92 (m, 4H), 4.05 (d, 1H, J = 4.5 Hz), 4.11-4.15 (m, 1H), 4.52-4.83 (m, 8H, ArC$\underline{H}_2$), 5.74 (s, 0.91H, H-7$_Z$), 6.50 (s, 0.09H, H-7$_E$), 7.14-7.42 (m, 23H, Ar$\underline{H}$), 7.71 (d, 2H, Ar$\underline{H}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 69.00 (t), 71.60 (t), 73.34 (t), 73.92 (t), 76.76 (d), 77.74 (d), 79.11 (d), 84.43 (d), 109.46 (d), 126.38 (d), 127.62 (d), 127.71 (d), 127.87 (d), 127.90 (d), 127.94 (d), 128.06 (d), 128.20 (d), 128.36 (d), 128.39 (d), 128.43 (d), 128.51 (d), 128.74 (d), 129.23 (d), 135.15 (s), 137.87 (s), 138.14 (s), 138.17 (s), 149.05 (s); (+) ESMS *m/e* 635 $[M + Na]^+$.

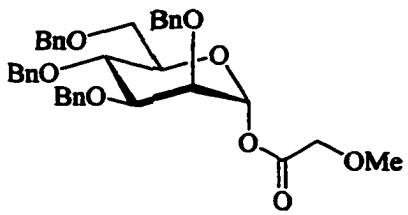
4.21 Preparation of 2, 6-anhydro-1-deoxy-1-phenyl-3, 4, 5, 7-tetrakis-O-(phenylmethyl)-α, β-D-gluco-heptitol (117)



A solution of alkene **116** (0.77 g, 1.26 mmol) in ethyl acetate (100 mL) was mixed with 10% palladium on carbon (400 mg) and hydrogenated at atmospheric pressure at room temperature overnight. The reaction mixture was filtered through a Celite pad and the solids were washed with ethyl acetate. The filtrate was concentrated under reduced pressure to dryness to give 0.8 g of an oil. The oil was dissolved in a small amount of toluene and flash chromatographed on silica gel (18 g) packed in

hexane. Elution with 5% ethyl acetate:hexane gave C-glycoside **117** as a colorless oil (0.69 g, 89.3% yield) as a 3:1 β:α mixture of anomers. Some pure β-anomer (0.24 g of the total) was isolated from a few early fractions and solidified on refrigeration. β-anomer: $[\alpha]^{27}_{D}$ -0.63 (c = 1.58, EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.73 (dd, 1H, *J* = 8.8, 14.2 Hz, H-1'), 3.15 (dd, 1H, *J* = 1.8, 14.2 Hz, H-1), 3.33-3.36 (m, 2H, H-3, 4), 3.49 (dt, 1H, *J* = 2, 9 Hz, H-2), 3.62-3.74 (m, 4H, H-5, 6, 7, 7'), [4.50, 4.57 (AB_q, 2H, *J* = 12.5 Hz, $ArC\underline{H}_2$)], [4.60, 4.82; 4.88, 4.93; 4.67, 4.94 ($3AB_q$, 6H, *J* = 11.3 Hz, $ArC\underline{H}_2$)], 7.19- 7.36 (m, 25H, Ar$\underline{H}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.70 (t), 68.77 (t), 73.24 (t), 74.85 (t), 75.03 (t), 75.45 (t), 78.50 (d), 78.85 (d), 79.91 (d), 81.61 (d), 87.32 (d), 126.11 (d), 127.47 (d), 127.64 (d), 127.69 (d), 127.83 (d), 127.90 (d), 128.07 (d), 128.29 (d), 128.40 (d), 128.45 (d), 128.48 (d), 129.03 (d), 129.64 (d), 138.17 (s), 138.21 (s), 138.37 (s), 138.57 (s), 138.82 (s); (+) ESMS *m/e* 637 $[M + Na]^+$; Anal. Calcd for $C_{41}H_{42}O_5$: C, 80.10; H, 6.89. Found: C, 79.20; H, 6.98.

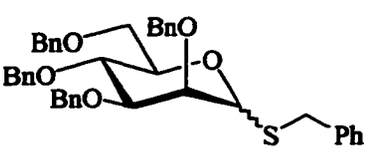
4.22 Preparation of methoxyacetyl-2, 3, 4, 6-tetrakis-O-(phenylmethyl)-α-D-mannopyranoside (119)



A mixture of commercial tetrabenzylmannose **118** (2 g, 3.77 mmol), ether (30 mL), DCC (0.841 g, 4.08 mmol), methoxyacetic acid (0.37 g, 4.1 mmol), and 4-pyrrolidinopyridine (52 mg, 0.35 mmol) was stirred at room temperature overnight.

The precipitated DCU was removed by filtration and washed with ether (100 mL). The filtrate was washed successively with water (25 mL) and brine (25 mL), and the organic phase was dried, filtered, and concentrated under reduced pressure to give 2.6 g of a yellow oil. The oil was dissolved in a small amount of toluene and flash chromatographed on silica gel (20 g) packed in hexane. Elution with a gradient of 5-10% ethyl acetate:hexane gave glycoside **119** as a nearly colorless oil (1.89 g, 82 % yield), predominately the α-anomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.40 (s, 3H, $OC\underline{H}_3$), 3.68-4.00 (m, 7H), 4.08 (t, 1H, J = 9.8 Hz), 4.51-4.87 (m, 8H, 4 x $ArC\underline{H}_2$), 6.31 (d, 1H, J = 1.9 Hz, H-1_e), 7.18- 7.42 (m, 20 H, $Ar\underline{H}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 59.17 (q), 68.58 (t), 69.20 (t), 71.88 (t), 72.31 (t), 73.17 (d), 73.27 (t), 73.93 (d), 74.45 (d), 75.07 (t), 78.64 (d), 92.24 (d), 127.46 (d), 127.64 (d), 127.74 (d), 127.95 (d), 128.23(d), 128.29 (d), 128.32 (d), 137.59 (s), 137.96 (s), 138.10 (s), 168.46 (s); (+) ESMS *m/e* 630 $[M + NH_4]^+$.

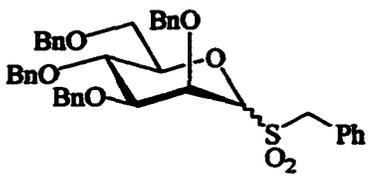
4.23 Preparation of phenylmethyl-2, 3, 4, 6-tetrakis -O-(phenylmethyl)-1-thio-α,β-D-mannopyranoside (120)



A solution of glycoside **119** (1.81 g, 2.95 mmol), anhydrous acetonitrile (30 mL) and benzyl mercaptan (0.348 mL, 2.95 mmol) was treated with a solution of 0.005M $Yb(OTf)_3$ in CH_3CN (6 mL, 0.03 mmol) and stirred at room temperature overnight. TLC analysis (30% EtOAc:hexane) showed the complete consumption of glycoside **119**

and the reaction was quenched by the addition of a solution of saturated sodium bicarbonate (25 mL). The reaction mixture was extracted with ethyl acetate (150 mL) and the organic phase was dried, filtered, and the filtrate was concentrated under reduced pressure to dryness to give 2.2 g of a cloudy oil. The oil was dissolved in a small amount of toluene and flash chomatographed on silica gel (22 g) packed in hexane. Elution with a gradient of 2-6% ethyl acetate:hexane gave thioglycoside **120** as a colorless oil (1.5 g, 78.5% yield) as a 43:57 β:α anomeric mixture: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.38-3.50 (m, 1H), 3.62-4.05 (m, 6.5H), 4.08-4.14 (m, 0.5H), 4.2 (s, 0.43H). 4.48-4.70 (m, 6H), 4.79-4.92 (m, 2H), 5.29 (d, 0.43H, J = 1.6 Hz, H-1_e), 7.15-7.45 (m, 25H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.35 (t), 34.50 (t), 68.91 (t), 69.68 (t), 71.54 (t), 71.78 (t), 71.97 (t), 72.17 (d), 73.17 (t), 73.27 (t), 74.60 (t), 74.78 (d), 74.86 (d), 74.98 (t), 75.05 (t), 75.66 (d), 75.93 (d), 79.88 (d), 80.30 (d), 80.63 (d), 81.39 (d), 84.39 (d), 127.02 (d), 127.38 (d), 127.42 (d), 127.51 (d), 127.57 (d), 127.60 (d), 127.67 (d), 127.72 (d), 127.86 (d), 127.89 (d), 128.00 (d), 128.09 (d), 128.24 (d), 128.29 (d), 128.35 (d), 128.47 (d), 129.01 (d), 129.19 (d), 137.70 (s), 137.79 (s), 138.04 (s), 138.14 (s), 138.23 (s), 138.34 (s), 138.47 (s); (+) ESMS *m/e* 647 $[M + H]^+$, 664 $[M + NH_4]^+$.

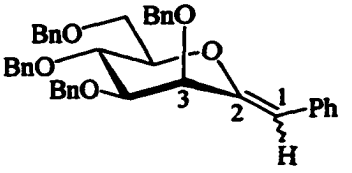
4.24 Preparation of phenylmethyl-2, 3, 4, 6-tetrakis -O-(phenylmethyl)-1-sulfonyl-α,β-D-mannopyranoside (121)



A solution of thioglycoside **120** (1.83 g, 2.83 mmol) in ethanol (10 mL), tetrahydrofuran (20 mL), and water (10 mL) was treated with MMPP (2.8 g, 5.66 mmol) and stirred at 55-60 °C for 3 h. The reaction was concentrated under reduced pressure to near dryness and the residue was partitioned between a solution of saturated sodium bicarbonate (25 mL) and ethyl acetate (100 mL). The organic phase was dried, filtered, and concentrated under reduced pressure to give 2.05 g of an oil. The oil was dissolved in a small amount of toluene and flash chromatographed on silica gel (21 g) packed in hexane. Elution with a gradient of 5-50% ethyl acetate:hexane separated the 45:55 β:α anomeric mixture of sulfones **121** as colorless oils. The chromatography yielded 0.84 g of pure α-anomer, 0.1 g of a mixture, and 0.71 g of pure β-anomer in respective order (1.65 g total, 85.9% yield). ^{1}H NMR (300 MHz, $CDCl_3$) β-anomer: δ 3.51-3.56 (m, 1H), 3.56 (dd, 1H, J = 2.8, 9.5 Hz), 3.79-3.88 (m, 2H), 4.13 (t, 1H, J = 9.5 Hz), 4.16 (d, 1H, J = 13.7 Hz), 4.23 (d, 1H, J = 1.1 Hz, H-1_a), 4.49-4.92 (m, 9H, Ar$\underline{CH_2}$), 5.10 (1/2 AB_q, 1H, J = 10.6 Hz, Ar$\underline{CH_2}$), 7.19-7.37 (m, 23H, Ar$\underline{H}$), 7.45-7.50 (m, 2H, Ar$\underline{H}$); α-anomer: δ 3.62-3.70 (m, 2H), 3.86 (dd, 1H, J = 8, 9.5 Hz), 4.13 (dd, 1H, J = 3.3, 8.2 Hz), 4.16 (d, 1H, 14.2 Hz), 4.37 (t, 1H, J = 3 Hz), 4.42-4.65 (m, 9H), 4.74 (d, 1H, J = 2.5 Hz, H-1_e), 4.77 (1/2 AB_q, 1H, J = 10.8 Hz, Ar$\underline{CH_2}$), 7.14-7.18 (m, 2H, Ar$\underline{H}$), 7.22-7.42 (m, 23 H, Ar$\underline{H}$); ^{13}C NMR (75 MHz, $CDCl_3$) anomeric mixture:

δ 56.43 (t), 56.87 (t), 68.70 (t), 69.24 (t), 70.76 (d), 72.26 (t), 72.55 (t), 72.97 (t), 73.12 (t), 73.16 (d), 73.23 (t), 73.82 (d), 74.17 (t), 75.11 (t), 75.31 (t), 75.89 (d), 78.96 (d), 80.70 (d), 83.29 (d), 86.84 (d), 90.10 (d), 126.61 (d), 127.44 (d), 127.51 (d), 127.56 (d), 127.64 (d), 127.70 (d), 127.79 (d), 127.91 (d), 128.10 (d), 128.20 (d), 128.24 (d), 128.29 (d), 128.36 (d), 128.49 (d), 128.67 (d), 128.74 (d), 128.86 (d), 130.96 (d), 131.30 (d), 137.14 (s), 137.86 (s), 137.90 (s), 137.96 (s), 138.02 (s), 138.08 (s), 138.22 (s); (+) ESMS *m/e* 701 $[M + Na]^+$.

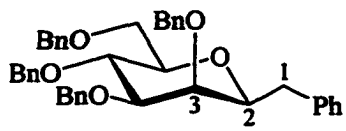
4.25 Preparation of 2, 6-anhydro-1-deoxy-1-phenyl-3, 4, 5, 7-tetrakis-O-(phenylmethyl)-D-manno-hept-1-enitol (122)



A solution of sulfone **121** (1.3 g, 1.92 mmol) in *tert*-butanol (10 mL) and dichloromethane (10 mL) was cooled to 5 °C and mixed with alumina supported potassium hydroxide (8 g, ~48 mmol). Dibromodifluoromethane (2.5 mL, ~28 mmol) was added dropwise over five seconds and the reaction mixture was stirred at 5 °C. After 5 min, TLC analysis (30% EtOAc:hexane) showed mostly alkene product with some intermediate bromosulfone and some presumably unreacted α-sulfone. Stirring of the reaction mixture at 5 °C was continued for an additional 1 h and TLC analysis showed only a trace of unreacted intermediates. The reaction mixture was diluted with dichloromethane and filtered through a pad of Celite. The solids were washed well with dichloromethane and the filtrate was concentrated under reduced pressure to dryness to

give 1.6 g of an oil. The oil was slurried in a small amount of toluene and flash chromatographed on silica gel (15 g) packed in hexane. Elution with 5% ethyl acetate:hexane gave alkene **122** as a colorless oil (730 mg, 61.5% yield) as a 95:5 *Z:E* alkene mixture: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.74 (dd, 1H, J = 3.2, 9.2 Hz), 3.78-3.83 (ddd, 1H), 3.86-3.96 (m, 2H), 4.16 (d, 1H, J = 3 Hz, H-3), 4.24 (t, 1H, J = 9 Hz), 4.47-4.74 (m, 6H, $ArC\underline{H}_2$), 4.81 (1/2 AB_q, 1H, J = 12.9 Hz, $ArC\underline{H}_2$), 5.00 (1/2 AB_q, 1H, J = 11.1 Hz, $ArC\underline{H}_2$), 5.58 (s, 0.95H, H-1_Z), 6.58 (s, 0.05H, H-1_E), 7.18-7.46 (m, 23H, $Ar\underline{H}$), 7.72 (d, 2H, J = 7.3 Hz, $Ar\underline{H}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 69.02 (t), 69.68 (t), 71.28 (t), 73.16 (t), 74.13 (d), 74.89 (d), 74.98 (t), 79.63 (d), 81.70 (d), 114.86 (d), 127.06 (d), 127.47 (d), 127.62 (d), 127.72 (d), 127.87 (d), 128.12 (d), 128.32 (d), 128.90 (d), 129.00 (d), 134.46 (s), 138.06 (s), 138.12 (s), 138.34 (s), 138.40 (s), 148.49 (s); (+) ESMS *m/e* 635 $[M + Na]^+$.

4.26 Preparation of 2, 6-anhydro-1-deoxy-1-phenyl-3, 4, 5, 7-tetrakis-O-(phenylmethyl)-D-glycero-β-D-manno-heptitol (123)

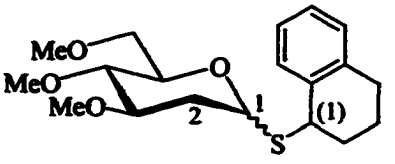


A solution of alkene **122** (720 mg, 1.175 mmol) in ethyl acetate (75 mL) was mixed with 10% palladium on carbon (500 mg) and hydrogenated at atmospheric pressure at room temperature overnight. The reaction mixture was filtered through a Celite pad and the solids were washed well with ethyl acetate. The filtrate was concentrated under reduced pressure to dryness to give 0.72 g of an oil. TLC analysis

(30% EtOAc:hexane) of the crude oil showed the presence of some more polar material that was later determined to be partially deprotected product. The crude oil was dissolved in a small amount of toluene and flash chromatographed on silica gel (22 g) packed in hexane. Elution with a gradient of 5-25% ethyl acetate:hexane gave C-glycoside **123** as a colorless oil (460 mg, 63.7% yield) and 110 mg of partially deprotected **123**. A separate experiment utilizing the pure β-sulfone of **121** was subjected to the Ramberg-Bäcklund reaction and the crude alkene **122** residue was directly hydrogenated to give C-glycoside **123** in two steps and 66% overall yield after chromatography. $[\alpha]^{27}_{D}$ -18.1 (c = 1.31, EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.80 (dd, 1H, *J* = 6.8, 13.8 Hz, H-1'), 3.08 (dd, 1H, *J* = 6.8, 13.8 Hz, H-1), 3.46 (ddd, 1H, H-6), 3.54 (t, 1H, *J* = 6.8 Hz, H-2), 3.59 (dd, 1H, *J* = 2.5, 9.5 Hz, H-4), 3.69-3.72 (m, 2H, H-3, 7'), 3.80 (dd, 1H, *J* = 2.0, 11.0 Hz, H-7), 3.94 (t, 1H, *J* = 9.8 Hz, H-5), 4.52-4.74 (m, 6H, ArC<u>H</u>$_2$), 4.86 (1/2 AB_q, 1H, *J* = 11.0 Hz, ArC<u>H</u>$_2$), 5.10 (1/2 AB_q, 1H, *J* = 11.5 Hz, ArC<u>H</u>$_2$), 7.12-7.48 (m, 25H, Ar<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.52 (t), 69.65 (t), 72.34 (t), 73.31 (t), 74.03 (t), 74.62 (d), 75.06 (t), 75.30 (d), 79.50 (d), 79.81 (d), 85.55 (d), 126.24 (d), 127.38 (d), 127.45 (d), 127.58 (d), 127.84 (d), 127.89 (d), 128.03 (d), 128.23 (d), 128.26 (d), 128.29 (d), 128.34 (d), 128.38 (d), 129.36 (d), 138.34 (s), 138.55 (s), 138.96 (s); (+) ESMS *m/e* 637 $[M + Na]^+$; Anal. Calcd for $C_{41}H_{42}O_5$: C, 80.10; H, 6.89. Found: C, 79.48; H, 6.86.

Partially debenzylated **123** mixture: (+) ESMS *m/e* 542 $[M + NH_4]^+$.

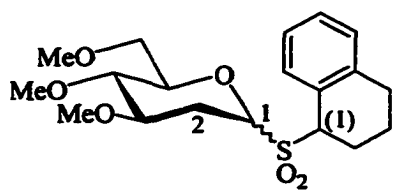
4.27 Preparation of (1, 2, 3, 4-tetrahydro-1-naphthyl)-2-deoxy-3, 4, 6-tri-O-methyl-1-thio-α, β-D-arabino-hexopyranoside (124)



A 0.005M solution of ytterbium (III) trifluoromethanesulfonate (6 mL, 0.03 mmol) in anhydrous acetonitrile was added to a solution of glycoside **107** (1.37 g, 4.92 mmol) and 1-thiotetralin (809 mg, 4.92 mmol) in anhydrous acetonitrile (40 mL). The solution was stirred at room temperature for 2 h and TLC analysis (1:1 EtOAc:hexane) showed the complete consumption of glycoside **107**. The reaction was quenched by the addition of a saturated sodium bicarbonate solution (10 mL) and was concentrated under reduced pressure to remove the acetonitrile. The residue was partitioned between ethyl acetate (125 mL) and a solution of saturated sodium bicarbonate (15 mL). Solid sodium chloride was added to saturate the aqueous phase and the organic phase was separated, dried, filtered, and concentrated under reduced pressure to dryness to give 1.9 g of a colorless oil. The oil was dissolved in a small amount of toluene and flash chromatographed on silica gel (22 g) packed in hexane. Elution with a gradient of 5-10% ethyl acetate:hexane gave thioglycoside **124** as a colorless oil (1.07 g, 61.7% yield) as an estimated 45:55 β:α anomeric mixture. The H-1_e protons at δ 5.49 and 5.58 integrated for a total of 0.45H (similar to thioglycoside **108**). One diastereomer of H-1_a at δ 4.52 was clearly discernable and integrated for 0.23H, while the other was coincident with other signals. The estimate assumes a similar total ratio of anomers as exhibited by thioglycoside **108**. A separate experiment using freshly prepared

ytterbium(III) triflate solution and recently prepared glycoside **107** gave a 91% yield of thioglycoside **124**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52-1.65 (m, 0.51H), 1.78-2.32 (m, 5.52H), 2.66-2.82 (m, 2H), 3.05-3.77 (m, 13.72H, including 12 coincident $OC\underline{H}_3$ singlets at 2 x 3.39, 3.40, 3.42, 3.43, 2 x 3.44, 3.45, 3.53, 2 x 3.54, 3.56), 4.00-4.05 (m, 0.26H), 4.21-4.25 (m, 0.73H), 4.40-4.47 (m, 0.76H), 4.52 (dd, 0.23H, J = 1.6, 11.8 Hz, probable H-1_a), 5.49 (d, 0.22H, J = 5.7 Hz, probable H-1_e), 5.58 (d, 0.23H, J = 5.4 Hz, probable H-$1'_e$), 7.03-7.47 (m, 4H, Ar$\underline{H}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.46 (t), 18.64 (t), 18.76 (t), 28.22 (t), 28.41 (t), 28.63 (t), 28.88 (t), 29.18 (t), 29.48 (t), 29.57 (t), 34.65 (t), 35.40 (t), 35.62 (t), 42.17 (d), 42.50 (d), 43.67 (d), 45.23 (d), 56.73 (q), 57.05 (q), 59.05 (q), 59.21 (q), 60.34 (q), 60.45 (q), 70.84 (d), 71.07 (t), 71.20 (t), 71.82 (t), 71.88 (t), 78.42 (d), 78.74 (d), 78.83 (d), 79.15 (d), 79.20 (d), 79.45 (d), 79.88 (d), 79.99 (d), 80.10 (d), 82.05 (d), 82.34 (d), 125.28 (d), 125.52 (d), 125.69 (d), 126.66 (d), 126.89 (d), 126.96 (d), 128.97 (d), 129.06 (d), 129.34 (d), 129.46 (d), 129.80 (d), 129.87 (d), 130.45 (d), 130.76 (d), 135.76 (s), 136.00 (s), 136.42 (s), 136.66 (s), 136.89 (s), 137.47 (s); (+) ESMS *m/e* 364 $[M + H]^+$, 375 $[M + Na]^+$.

4.28 Preparation of (1, 2, 3, 4-tetrahydro-1-naphthyl)-2-deoxy-3, 4, 6-tri-O-methyl-1-sulfonyl-α, β-D-arabino-hexopyranoside (125)

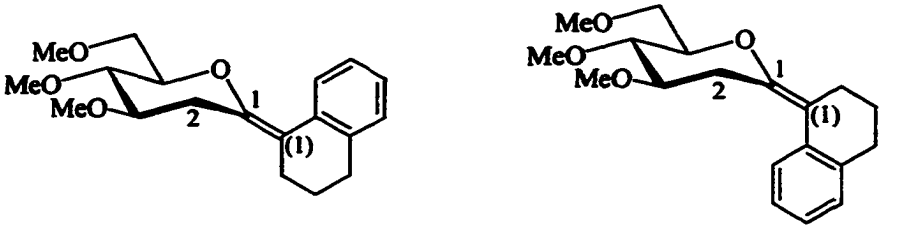


A solution of thioglycoside **124** (1.07 g, 3.04 mmol) in ethanol (10 mL), tetrahydrofuran (10 mL), and water (10 mL) was mixed with MMPP (3 g, 6.06 mmol)

and stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure to near dryness, and the residue was partitioned between a saturated solution of sodium bicarbonate (30 mL) and ethyl acetate (100 mL). The organic phase was dried, filtered, and concentrated under reduced pressure to dryness to give **125** as a colorless oil (1.05 g, 89.7% yield) that was pure by TLC analysis (1:1 EtOAc:hexane) but contained some ethyl acetate by ^{1}H NMR analysis. The oil was a diastereomeric mixture that appeared as three slightly overlapping components by TLC analysis, and was separated by flash chromatography in a separate experiment. Each of the two more polar components was a single diastereomer from ^{1}H NMR analysis, and the least polar component was a mixture of two diastereomers. The anomeric ratio of the crude collective diastereomeric mixture was assumed to be the same as estimated for thioglycoside **124**. The ^{1}H NMR spectra was a collection of coincident signals, preventing an exact determination of the anomeric ratio. ^{1}H NMR (300 MHz, $CDCl_3$) of collective mixture: δ 1.64-2.53 (m, 4.7H), 2.64-3.75 (m, 16.6H, including 12 coincident $OC\underline{H}_3$ singlets at 3.38, 3.39, 2 x 3.42, 3.43, 3.44, 3.45, 3.46, 2 x 3.51, 3.52, 3.55), 3.85-3.94 (m, 0.65H), 4.22-4.45 (m, 1.12H), 4.63-4.80 (m, 1.06H), 4.98-5.12 (m, 0.53H), 7.15-7.62 (m, 4H, Ar$\underline{H}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.56 (t), 18.64 (t), 18.73 (t), 20.42 (t), 21.08 (t), 23.43 (t), 23.68 (t), 24.40 (t), 24.50 (t), 25.56 (t), 26.27 (t), 27.48 (t), 27.64 (t), 28.21 (t), 56.25 (q), 56.30 (q), 56.76 (q), 56.84 (q), 57.27 (d), 57.58 (d), 58.56 (q), 58.56 (d), 58.68 (q), 58.76 (q), 58.97 (q), 59.15 (q), 59.72 (d), 60.22 (q), 60.27 (q), 70.64 (t), 70.86 (t), 71.04 (t), 71.35 (t), 74.14 (d), 76.44 (d), 76.56 (d), 77.86 (d), 77.93 (d), 78.43 (d), 78.64 (d), 78.80 (d), 79.17 (d), 80.80 (d), 80.85 (d), 82.06 (d), 82.42 (d), 83.09 (d), 84.28 (d), 124.95 (d), 124.99 (d), 125.22 (d), 125.32 (d), 125.57

(d), 125.70 (d), 127.76 (d), 127.84 (d), 127.97 (d), 128.04 (d), 128.16 (d), 128.33 (d), 129.06 (d), 129.36 (d), 129.82 (d), 130.04 (d), 131.31 (d), 131.61 (d), 139.34 (s), 139.63 (s), 139.73 (s), 139.98 (s); (+) ESMS *m/e* 402 $[M + NH_4]^+$, 407 $[M + Na]^+$.

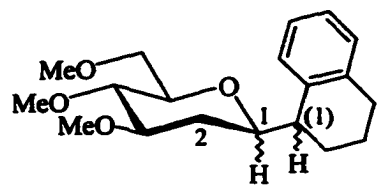
4.29 Preparation of 1, 5-anhydro-2-deoxy-3, 4, 6-tri-O-methyl-1-(*E*, *Z*)-[3, 4-dihydro-1(2H)-naphthalenylidyl]-D-arabino-hexitol (126)



A solution of crude sulfone **125** (1.05 g, 2.73 mmol) in *tert*-butanol (10 mL) and dichloromethane (10 mL) was cooled to 5 °C and mixed with alumina supported potassium hydroxide (8 g, ~48 mmol). Dibromodifluoromethane (2 mL, ~22 mmol) was added to the reaction in one portion and stirring was continued at 5 °C for 2 h. TLC analysis (1:1, EtOAc:hexane) showed the reaction to be incomplete and an additional portion of alumina supported potassium hydroxide (3 g, ~18 mmol) followed by dibromodifluoromethane (1 mL, ~11 mmol) was added to the reaction mixture. The reaction mixture was stirred at room temperature overnight and TLC analysis showed mostly alkene product along with a trace amount of intermediates. The reaction mixture was diluted with dichloromethane and filtered through a pad of Celite. The solids were washed well with dichloromethane and the filtrate was concentrated under reduced pressure to dryness to a yellow residue. The residue was dissolved in a small amount of toluene and flash chromatographed on silica gel (18 g) packed in hexane. Elution with 5% ethyl acetate:hexane gave the somewhat unstable alkene **126** as a colorless oil (0.66

g, 76% yield) estimated as a 45:55 *Z:E* mixture: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.56-2.73 (m, 7H), 2.82-3.76 (m, 15H, including 6 coincident $OC\underline{H}_3$ singlets at 3.38, 3.42, 3.48, 3.50 3.55, 3.56), 7.02-7.30 (m, 3.5H, Ar<u>H</u>), 7.98-8.00 (d, 0.5H, Ar<u>H</u>); The ^{13}C NMR (75 MHz, $CDCl_3$) sample degraded while the data was being collected. The estimated alkene ratio came from a comparison of the C-1 signals at δ 144.65 and 144.40; crude alkene (+) ESMS *m/e* 381 $[M + H + Na + K]^+$.

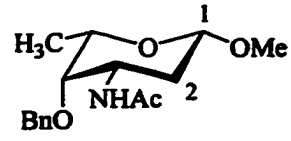
4.30 Preparation of 1, 5-anhydro-2-deoxy-3, 4, 6-tri-O-methyl-1-[1, 2, 3, 4-tetrahydro-1-naphthyl]-α, β-D-arabino-hexitol (127)



A solution of alkene **126** (0.66 g, 2.08 mmol) in ethyl acetate (50 mL) was mixed with 10% palladium on carbon (300 mg) and hydrogenated at atmospheric pressure at room temperature overnight. The reaction mixture was filtered through a Celite pad and the solids were washed with ethyl acetate. The filtrate was concentrated under reduced pressure to dryness to give 680 mg of a colorless oil. The crude oil was dissolved in a small amount of toluene and flash chromatographed on silica gel (21 g) packed in hexane. Elution with a gradient of 5% ethyl acetate:hexane gave C-glycoside **127** as a colorless oil (550 mg total, 82.8% yield) estimated to be a 9:1 β:α anomeric mixture of diastereomers. Early fractions from the chromatography gave 20 mg of a (probable) mixture of α-anomeric diastereomers, 300 mg of mixed anomers (mostly β), and 230 mg of all β-anomer as a pair of diastereomers. All β-anomer: ^{1}H NMR (300

MHz, $CDCl_3$) δ 1.35 (pentuplet, 1H, J = 12.3 Hz), 1.64-2.18 (m, 5H), 2.64-2.84 (m, 2H), 2.92-3.31 (m, 4H), 3.38-3.73 (m, 11H including 6 coincident singlets at 3.38, 2 x 3.40, 3.43, 2 x 3.54), 7.05-7.34 (m, 4H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.27 (t), 20.84 (t), 23.84 (t), 24.30 (t), 28.86 (t), 29.64 (t), 31.48 (t), 33.73 (t), 41.09 (d), 42.56 (d), 56.87 (q), 59.18 (q), 59.26 (q), 60.21 (q), 71.86 (t), 72.00 (t), 77.66 (d), 78.84 (d), 78.91 (d), 79.03 (d), 80.07 (d), 80.16 (d), 82.88 (d), 125.05 (d), 125.33 (d), 125.73 (d), 126.09 (d), 128.92 (d), 129.04 (d), 130.10 (d), 136.91 (s), 137.32 (s), 137.74 (s), 137.86 (s); (+) ESMS *m/e* 321 $[M + H]^+$, 338 $[M + NH_4]^+$.

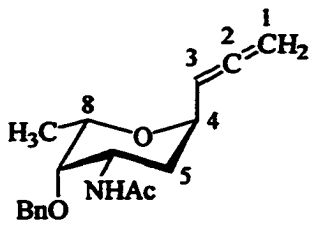
4.31 Preparation of methyl-3-(acetylamino)-2, 3, 6-trideoxy-4-O-(phenylmethyl)-β-L-lyxo-hexopyranoside (152)



A solution of glycoside **151** (4.06 g, 20 mmol) in anhydrous *N,N*-dimethylformamide (50 mL) was cooled to 5 °C with stirring, resulting in a heterogeneous mixture. Sodium hydride (1.6 g, 40 mmol, 60% in a mineral oil dispersion) was added to the mixture and stirring was continued at 5 °C until the hydrogen evolution had ceased. Tetrabutylammonium iodide (0.74 g, 2 mmol) was added to the cloudy reaction mixture followed by the dropwise addition of benzyl bromide (4.77 mL, 40.1 mmol), and the reaction was stirred at room temperature overnight. The reaction was quenched by the addition of methanol (15 mL) and the mixture was stirred at room temperature for 2 h. The reaction mixture was poured into water (300 mL) and extracted with ethyl acetate (2 x 300 mL). The organic phase was

washed with an aqueous 10% sodium sulfite solution (100 mL), brine (3 x 100 mL), dried, filtered, and the filtrate was concentrated under reduced pressure to dryness to give 9 g of a solid. The solid was slurried with ether (150 mL) which was then diluted with hexane (150 mL). The solids were collected by filtration, washed with hexane, and dried under reduced pressure overnight to give 4.48 g of glycoside **152** as a white solid. The filtrate was concentrated under reduced pressure to dryness to give 5 g of a residue. The residue was dissolved in dichloromethane and flash chromatographed on silica gel (40 g) packed in dichloromethane. Elution with dichloromethane followed by 40% ethyl acetate:dichloromethane separated most of the less polar impurities. Final elution with ethyl acetate provided additional glycoside **152** as a white solid (0.42 g, 83.5% total yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (d, 3H, J = 6.6 Hz, $C\underline{H}_3$), 1.49-1.57 (m, 1H, H-2_a), 1.55 (s, 3H, NC(O)$C\underline{H}_3$), 1.69 (ddd, 1H, J = 2.1, 4.5, 12.2 Hz, H-2_e), 3.30 (d, 1H, J = 3 Hz, H-4), 3.40 (s, 3H, $OC\underline{H}_3$), 3.48 (q, 1H, J = 6.6 Hz, H-5), 3.94 (m, 1H, H-3), 4.29 (dd, 1H, J = 2.1, 9.6 Hz, H-1), [4.32, 4.79 (AB_q, 2H, J = 12.2 Hz, $ArC\underline{H}_2$)], 5.63 (bd, 1H, J = 8.7 Hz, N$\underline{H}$), 7.20- 7.35 (m, 5H, Ar$\underline{H}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.82 (q), 22.49 (q), 32.09 (t), 47.48 (d), 55.92 (q), 71.36 (d), 75.61 (t), 76.89 (d), 100.84 (d), 127.86 (d), 128.06 (d), 128.50 (d), 138.31 (s), 169.20 (s).

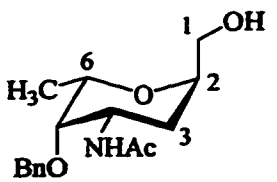
4.32 Preparation of 6-(acetylamino)-4, 8-anhydro-1, 2, 3, 5, 6, 9-hexadeoxy-1, 2, 2, 3-tetradehydro-7-O-(phenylmethyl)-α-L-altro-nonitol (153)



A solution of glycoside **152** (4.59 g, 15.6 mmol) in anhydrous acetonitrile (125 mL) was cooled to 5 °C and mixed with propargyltrimethylsilane (2.56 mL, 17.2 mmol) followed by boron trifluoride etherate (1.92 mL, 15.6 mmol) and trimethylsilyltrifluoromethane sulfonate (1.51 mL, 7.8 mmol). The solution was stirred at 5 °C for 30 min, and then allowed to stir at room temperature for 1 h. TLC analysis (EtOAc) showed the complete consumption of glycoside **152**. The reaction was quenched by the addition of a solution of saturated sodium bicarbonate (50 mL) and then brine (50 mL). The mixture was extracted with ethyl acetate (2 x 100 mL), the organic phase was dried, filtered, and concentrated under reduced pressure to dryness to give 6.2 g of an off-white solid. The solid was slurried with dichloromethane and the mixture was flash chromatographed on silica gel (50 g) packed in dichloromethane. Elution with a gradient of 5-20% ethyl acetate:dichloromethane gave allene **153** as a white solid (3.31 g, 70.2% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (d, 3H, J = 6.6 Hz, C$\underline{H}_3$), 1.60 (s, 3H, NC(O)C$\underline{H}_3$), 1.71 (dd, 1H, J = 4.6, 12.7 Hz, H-5$_e$), 1.90 (dt, 1H, J = 5.6, 12.7 Hz, H-5$_a$), 3.44 (d, 1H, J = 2.7 Hz, H-7), 3.88 (q, 1H, J = 6.6 Hz, H-8), 4.21-4.24 (m, 1H, H-6), [4.38, 4.93 (AB$_q$, 2H, J = 12.3 Hz, ArC$\underline{H}_2$)], 4.70-4.73 (m, 1H, probable H-4), 4.82-4.96 (m, 2H excluding 1/2 AB$_q$ at 4.93), 5.20-5.26 (m, 2H), 7.34-7.41 (m, 5H, Ar$\underline{H}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.39 (q), 22.63 (q), 27.74 (t), 44.72 (d), 68.25 (d), 69.72

(d), 75.71 (t), 77.28 (t), 78.29 (d), 90.55 (d), 127.96 (d), 128.15 (d), 128.59 (d), 138.37 (s), 169.10 (s, NC(O)CH_3), 207.47 (s, C-2); (+) ESMS *m/e* 302 $[M + H]^+$, 324 $[M + H + Na]^+$.

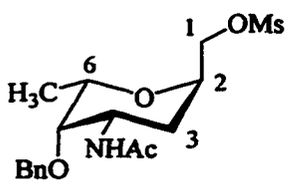
4.33 Preparation of 4-(acetylamino)-2, 6-anhydro-3, 4, 7-trideoxy-5-O-(phenyl-methyl)-α-L-altro-heptitol (154)



A colorless solution of allene **153** (3.21 g, 10.65 mmol) in dichloromethane (90 mL) and methanol (30 mL) was cooled to -70 °C and saturated with ozone from a Wellsbach ozone generator for 30 min until the solution retained a bluish color. The excess ozone was removed from the reaction mixture with a gradual flow of compressed air until the solution was again colorless. Sodium borohydride (500 mg, 13.2 mmol) was added to the -70 °C solution in one portion, and the mixture was allowed to warm to room temperature with stirring. The mixture was stirred at room temperature for 1 h and then quenched by the addition of a saturated aqueous solution of ammonium chloride (50 mL). The mixture was stirred for 10 min and extracted with dichloromethane (2 x 100 mL). The combined organic phase was dried, filtered, and concentrated under reduced pressure to dryness to give 3.2 g of crude **154** as a colorless crystalline foam used directly for the preparation of mesylate **155**. Alcohol **154** was partially purified in a previous experiment by chromatography on silica gel using a gradient of 0-100% ethyl acetate:dichloromethane followed by 5% methanol:ethyl acetate. The slightly impure product crystallized from methyl acetate/hexane to give

pure alcohol **154** as a white solid in 68.9% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (d, 3H, J = 6.8 Hz, C<u>H</u>$_3$), 1.52 (dd, 1H, J = 4.3, 12.8 Hz, H-3$_e$), 1.62 (s, 3H, NC(O)C<u>H</u>$_3$), 1.94 (dt, 1H, J = 6, 12.8 Hz, H-3$_a$), 2.09 (dd, 1H, J = 2.6, 8.5 Hz, O<u>H</u>), 3.48-3.53 (m, 2H, H-1', 5), 3.85 (q, 1H, J = 6.8 Hz, H-6), 3.93 (dt, 1H, J = 2.6, 12 Hz, H-1), 4.08-4.12 (m, 2H, H-2, 4), [4.38, 4.92 (AB$_q$, 2H, J = 12.8 Hz, ArC<u>H</u>$_2$)], 5.28 (bd, 1H, 7.7 Hz, N<u>H</u>), 7.33-7.43 (m, 5H, Ar<u>H</u>). Deuteration of this sample with CD_3OD fortuitously separated the signals for H-2 and H-4 allowing for the measurement of J = <1 and 6.5 Hz for the H-2 quartet. ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.35 (q), 22.54 (q), 25.80 (t), 44.96 (d), 60.70 (t), 68.09 (d), 72.44 (d), 75.46 (t), 77.67 (d), 128.01 (d), 128.15 (d), 128.60 (d), 138.18 (s), 169.63 (s, NC(O)CH_3) ; (+) ESMS *m/e* 294 $[M + H]^+$.

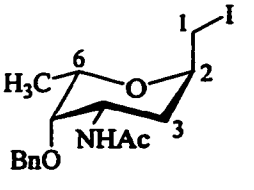
4.34 Preparation of 4-(acetylamino)-2, 6-anhydro-1-O-(methanesulfonyl)-3, 4, 7-trideoxy-5-O-(phenylmethyl)-α-L-altro-heptitol (155)



A solution of alcohol **154** (3.2 g, 10.9 mmol) in anhydrous tetrahydrofuran (100 mL) was cooled to 5 °C, treated with triethylamine (1.96 mL, 14 mmol), and then methanesulfonyl chloride (1 mL, 12.9 mmol) was added dropwise using a syringe. The solution was stirred at 5 °C for 30 min and TLC analysis (EtOAc) showed the complete consumption of alcohol **154**. The reaction was quenched by the addition of a saturated aqueous solution of ammonium chloride (50 mL) and extracted with ethyl acetate (100 mL). The organic phase was dried, filtered, and concentrated under reduced pressure to

dryness to give 4.75 g of crude mesylate **155** as an overweight colorless glassy oil. This material was used directly for the preparation of iodide **156**. A separate experiment utilizing pure alcohol **154** gave mesylate **156** in quantitative yield as a colorless foam that was homogeneous by TLC analysis (10% MeOH:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (d, 3H, J = 6.6 Hz, $C\underline{H}_3$), 1.56 (dd, 1H, J = 3.2, 12.9 Hz, H-3_e), 1.61 (s, 3H, NC(O)$C\underline{H}_3$), 1.98 (dt, 1H, J = 6.6, 12.9 Hz, H-3_a), 3.10 (s, 3H, $SO_2C\underline{H}_3$), 3.47 (s, 1H, probable H-5), 3.92 (q, 1H, J = 6.3 Hz, H-6), 4.07 (m, 1H), 4.14 (dd, 1H, J = 4.2, 11.1 Hz), 4.23-4.33 (m, 1H), [4.38, 4.76 (AB_q, 2H, J = 12.2 Hz, $ArC\underline{H}_2$), 4.62 (dd, 1H, J = 8.5, 11.1 Hz), 5.33 (bd, 1H, J = 8.1 Hz, N$\underline{H}$), 7.32-7.43 (m, 5H, Ar$\underline{H}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.50 (q), 22.76 (q), 26.19 (t), 37.88 (q), 45.30 (d), 68.30 (t), 68.95 (d), 69.94 (d), 75.62 (t), 77.38 (d), 128.32 (d), 128.85 (d), 138.14 (s), 169.93 (s, N$\underline{C}$(O)CH_3); (+) ESMS ***m/e*** 372 $[M + H]^+$.

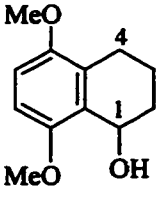
4.35 Preparation of 4-(acetylamino)-2, 6-anhydro-1-iodo-1, 3, 4, 7-tetradeoxy-5-O-(phenylmethyl)-α-L-altro-heptitol (156)



A solution of crude mesylate **155** (4.75 g, 10.9 mmol) in methyl ethyl ketone (75 mL) was mixed with sodium iodide (8 g, 53.4 mmol) and stirred at reflux overnight. TLC analysis (EtOAc) showed only a trace of possible starting mesylate **155** and the reaction mixture was concentrated under reduced pressure to dryness. The residue was partitioned between ethyl acetate (100 mL) and water (100 mL). The aqueous phase was re-extracted with ethyl acetate (100 mL) and the combined organic phase was

washed with an aqueous 10% sodium thiosulfate solution (100 mL) followed by brine (50 mL). The organic phase was dried, filtered, and concentrated under reduced pressure to give 4.1 g of an off-white solid. The crude iodide was dissolved in a small amount of dichloromethane and flash chromatographed on silica gel (40 g) packed in dichloromethane. Elution with 5% ethyl acetate:dichloromethane followed by 40% ethyl acetate:dichloromethane gave iodide **156** as a white solid (3.26 g, 73.6% overall yield from allene **153**); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (d, 3H, J = 6.6 Hz, C$\underline{H}_3$), 1.64 (s, 3H, NC(O)C$\underline{H}_3$), 1.81 (ddd, 1H, J = 1.6, 4.2, 13.3 Hz, H-3$_e$), 1.97 (dt, 1H, J = 6.3, 13.2 Hz, H-3$_a$), 3.34 (dd, 1H, J = 7, 10.4 Hz, H-1'), 3.46-3.52 (m, 2H, H-1, 5), 3.76 (dq, 1H, J = 1.2, 6.6 Hz, H-6), 4.08-4.21 (m, 2H, H-2, 4), [4.38, 4.90 (AB$_q$, 2H, J = 12.1 Hz, ArC$\underline{H}_2$), 5.30 (bd, 1H, J = 8.4 Hz, N$\underline{H}$), 7.33-7.42 (m, 5H, Ar$\underline{H}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.89 (t, C-1), 17.62 (q), 23.06 (q), 27.90 (t), 44.52 (d), 67.75 (d), 72.45 (d), 75.72 (t), 77.71 (d), 128.22 (d), 128.78 (d), 138.27 (s), 169.36 (s, N$\underline{C}$(O)CH_3); (+) ESMS *m/e* 404 $[M + H]^+$.

4.36 Preparation of 1, 2, 3, 4-tetrahydro-5, 8-dimethoxy-1-naphthalenol (157)



A solution of tetralone **69** (3.09 g, 15 mmol) in methanol (75 mL) was cooled to 5 °C and mixed with sodium borohydride (567 mg, 15 mmol). The cooling bath was removed after 5 min when the vigorous evolution of hydrogen had subsided. The solution was stirred at room temperature for 2 h and then concentrated under reduced

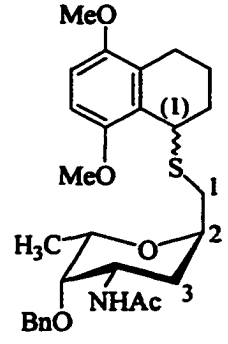
pressure to dryness. The residue was partitioned between ethyl acetate (100 mL) and a saturated aqueous solution of ammonium chloride (50 mL). The aqueous phase was re-extracted with ethyl acetate (100 mL), and the combined organic phase was washed with brine (50 mL). The organic phase was dried, filtered, and concentrated under reduced pressure to dryness to give 3.19 g of crude unstable tetralol **157** as a pale yellow oil. The crude oil was used directly in the preparation of thioacetate **158**. Crude **157**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.68-2.05 (m, 4H), 2.41-2.54 (m, 1H), 2.76 (t, 0.6H), 3.02 (t, 0.4H), 3.14 (bs, 1H, OH), 3.78 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 5.02 (t, 1H, J = 4.4 Hz, H-1), 6.7 (m, 2H, ArH); (+) ESMS *m/e* 208 $[M]^+$.

4.37 Preparation of 1, 2, 3, 4-tetrahydro-5, 8-dimethoxy-1-naphthalenethiol acetate (158)

A solution of crude tetralol **157** (3.19 g, 15 mmol) in anhydrous dichloromethane (90 mL) was cooled to 5 °C and mixed with thioacetic acid (1.24 mL, 18 mmol) followed by zinc bromide (1.69 g, 7.5 mmol). The mixture was stirred at 5 °C for 5 min and then at room temperature for 15 min. TLC analysis (30% EtOAc:hexane) showed the complete consumption of tetralol **157** and the reaction was quenched by the addition of a saturated aqueous solution of sodium bicarbonate (40 mL). The mixture was diluted with a saturated aqueous solution of ammonium chloride (40 mL) and extracted with dichloromethane (2 x 100 mL). The combined

organic phase was dried, filtered, and concentrated under reduced pressure to dryness to give 4.05 g of a yellow oil. The oil was dissolved in a small amount of toluene and flash chromatographed on silica gel (49 g) packed in hexane. Elution with 5% dichloromethane:hexane separated a less polar impurity. Continued elution with dichloromethane gave thioacetate **157** as a colorless oil (3.52 g, 88% overall yield from tetralone **69**) that slowly solidified at room temperature; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.8-2.09 (m, 4H), 2.32 (s, 3H, SC(O)C$\underline{H}_3$), 2.37-2.48 (m, 1H), 2.84-2.92 (m, 1H), 3.77 (s, 6H, 2 x OC$\underline{H}_3$), 5.10-5.12 (m, 1H, H-1), [6.64, 6.69 (AB_q, 2H, J = 9 Hz, Ar$\underline{H}$)]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.97 (t), 22.51 (t), 29.01 (t), 30.03 (q), 38.07 (d), 55.22 (q), 55.62 (q), 107.31 (d), 108.36 (d), 124.39 (s), 127.68 (s), 150.98 (s), 151.06 (s), 195.28 (s, S$\underline{C}$(O)CH_3).

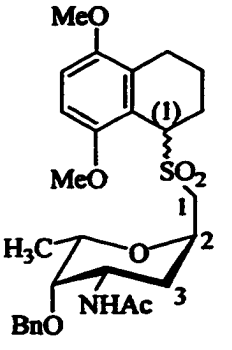
4.38 Preparation of 4-(acetylamino)-2, 6-anhydro-1, 3, 4, 7-tetradeoxy-1-(1, 2, 3, 4-tetrahydro-5, 8-dimethoxy-1-naphthalenethiol)-5-O-(phenylmethyl)-α-L-altro-heptitol (159)



A solution of iodide **156** (3.26 g, 8.08 mmol) in *N*, *N*-dimethylformamide (40 mL) was mixed with thioacetate **158** (2.58 g, 9.7 mmol), water (40 mL), and potassium carbonate (3.68 g, 26.6 mmol). The mixture was stirred at 80-85 °C overnight and TLC analysis (EtOAc) showed possibly a trace amount of unreacted iodide **156** remaining.

The reaction mixture was cooled to room temperature and diluted with brine (150 mL). The mixture was extracted with ethyl acetate (3 x 100 mL) and the combined organic extracts were washed with brine (3 x 50 mL). The organic phase was dried, filtered, and concentrated under reduced pressure to dryness to give 6.5 g of a yellow oil. The crude oil was dissolved in a small amount of dichloromethane and flash chromatographed on silica gel (60 g). Elution with a gradient of 0-30% ethyl acetate:dichloromethane gave sulfide **159** as a slightly impure colorless thick oil (4.1 g, 84.6% yield) as a presumed 1:1 mixture of diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (d, 3H, J = 6.4 Hz, C$\underline{H}_3$), 1.63 (s, 3H, NC(O)C$\underline{H}_3$), 1.75-2.25 (m, 6H), 2.30-2.50 (m, 1H), 2.78-3.00 (m, 3H), 3.08 (dd, 0.73 H, J = 6.8, 13 Hz), 3.48 (bs, 1H), 3.74 (s, 3H, OC$\underline{H}_3$), 3.81 (s, 3H, OC$\underline{H}_3$), 3.74-3.82 (m, 1H, coincident with the singlets at 3.74 and 3.81), 4.05-4.35 (m, 3H), [4.39, 4.88 (AB_q, 2H, J = 12 Hz, $ArCH_2$)], 5.34 (bd, 1H, J = 8.4 Hz, N$\underline{H}$), 6.63 (s, 2H, Ar$\underline{H}_{naphthyl}$), 7.30-7.42 (m, 5H, Ar$\underline{H}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ major diastereomeric mixture 17.15 (t), 17.75 (q), 22.66 (t), 23.04 (q), 28.01 (t), 28.77 (t), 33.83 (t), 39.64 (d), 44.99 (d), 55.52 (q), 55.88 (q), 67.94 (d), 72.58 (d), 75.78 (t), 78.07 (d), 107.41 (d), 108.06 (d), 126.72 (s), 127.39 (s), 128.27 (d), 128.74 (d), 138.48 (s), 150.94 (s), 151.20 (s), 169.31 (s); (+) ESMS *m/e* 500 $[M + H]^+$.

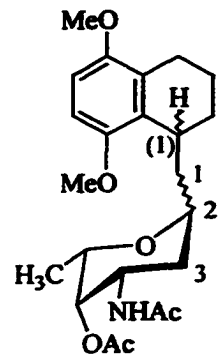
4.39 Preparation of 4-(acetylamino)-2, 6-anhydro-1, 3, 4, 7-tetradeoxy-1-(1, 2, 3, 4-tetrahydro-5, 8-dimethoxy-1-naphthalenesulfonyl)-5-O-(phenylmethyl)-α-L-altro-heptitol (160)



A solution of sulfide **159** (4.1 g, 8.2 mmol) in tetrahydrofuran (60 mL) and water (40 mL) was cooled to 15 °C and mixed with MMPP (8.93 g, 18.05 mmol). The mixture was stirred at room temperature overnight and TLC analysis (EtOAc) showed the complete oxidation of sulfide **159**. The solution was concentrated under reduced pressure to remove the tetrahydrofuran and diluted with a saturated solution of sodium bicarbonate (50 mL). The aqueous mixture was extracted with ethyl acetate (2 x 125 mL) and the combined organic extracts were dried, filtered, and concentrated under reduced pressure to dryness to give 4 g of a dark yellow residue. The residue was dissolved in a small amount of dichloromethane and flash chromatographed on silica gel (40 g) packed in dichloromethane. Elution with a gradient of 5-40% ethyl acetate:dichloromethane gave sulfone **160** as a colorless foam (2.92 g, 67% yield). Samples of both diastereomers of sulfone **160** were isolated from the flash chromatography. ^{1}H NMR (500 MHz, C_6D_6) Less polar isomer: δ 1.10 (d, 3H, J = 6.4 Hz, C$\underline{H}_3$), 1.36 (s, 3H, NC(O)C$\underline{H}_3$), 1.41-1.58 (m, 4H), 1.96 (dt, 1H, J = 5.7, 12.8 Hz, H-3$_a$), 2.50-2.56 (m, 1H), 2.69-2.76 (m, 1H), 2.79 (bd, 1H, J = 14.4 Hz), 3.04-3.08 (m, 2H), 3.12 (ddd, 1H, J = 3.6, 6.9, 17.8 Hz), 3.31 (s, 3H, OC$\underline{H}_3$), 3.37 (q, 1H, J = 6.4 Hz,

H-6), 3.51 (s, 3H, OC$\underline{H}_3$), 3.54 (dd, 1H, J = 7.4, 14.1 Hz, H-1), [4.04, 4.44 (AB_q, 2H, J = 12 Hz, ArC$\underline{H}_2$)], 4.09-4.13 (m, 1H, H-4), 4.68 (d, 1H, J = 4.6 Hz, H-(1)), 4.81 (d, 1H, J = 7.8 Hz, N$\underline{H}$), 4.91 (q, 1H, J = 6.1 Hz, H-2), 6.43 (dd, 2H, J = 9, 12.4 Hz, Ar$\underline{H}_{naphthyl}$)], 7.04-7.15 (m, 5H, Ar$\underline{H}$). More polar isomer δ 1.17 (d, 3H, J = 6.6 Hz, C$\underline{H}_3$), 1.31-1.49 (m, 2H), 1.36 (s, 3H, NC(O)C$\underline{H}_3$), 1.62-1.66 (m, 1H), 1.90 (dt, 1H, J = 5.7, 12.8 Hz, H-3_a), 2.43-2.49 (m, 1H), 2.58-2.65 (m, 1H), 2.88 (bd, 1H, J = 16.1 Hz), 3.01-3.10 (m, 2H), 3.31 (s, 3H, OC$\underline{H}_3$), 3.31-3.36 (m, 1H), 3.53 (s, 3H, OC$\underline{H}_3$), 3.60 (q, 1H, J = 6.3 Hz, H-6), 3.66 (dd, 1H, J = 7.2, 14 Hz, H-1), 4.11-4.16 (m, 1H, H-4), [4.15, 4.45 (AB_q, 2H, J = 11.8 Hz, ArC$\underline{H}_2$)], 4.75 (bs, 2H, N$\underline{H}$, H-(1)), 4.85-4.87 (m, 1H, H-2), 6.44 (dd, 2H, J = 8.9, 14 Hz, Ar$\underline{H}_{naphthyl}$)], 7.06-7.20 (m, 5H, Ar$\underline{H}$); ^{13}C NMR (75 MHz, $CDCl_3$) diastereomeric mixture δ 17.48 (q), 17.57 (q), 17.89 (t), 18.24 (t), 21.65 (t), 21.88 (t), 22.03 (t), 22.69 (t), 22.97 (q), 29.46 (t), 45.04 (d), 45.28 (d), 54.04 (t), 55.24 (t), 55.48 (q), 55.53 (q), 55.57 (q), 55.60 (q), 57.88 (d), 58.06 (d), 66.57 (d), 67.16 (d), 68.77 (d), 75.57 (t), 75.68 (t), 77.14 (d), 77.41 (d), 107.21 (d), 107.40 (d), 109.92 (d), 110.18 (d), 118.63 (s), 119.09 (s), 128.13 (d), 128.16 (d), 128.26 (d), 128.30 (d), 128.71 (d), 128.74 (d), 129.52 (s), 129.97 (s), 138.23 (s), 138.28 (s), 150.68 (s), 150.78 (s), 151.55 (s), 169.55 (s, N$\underline{C}$(O)CH_3), 169.64 (s, N$\underline{C}$(O)CH_3); (+) ESMS *m/e* 532 $[M + H]^+$.

4.40 Preparation of 4-(acetylamino)-2, 6-anhydro-1, 3, 4, 7-tetradeoxy-1-(1, 2, 3, 4-tetrahydro-5, 8-dimethoxy-1-naphthyl)-5-O-(phenylmethyl)-α, β-L-altro-heptitol (162)



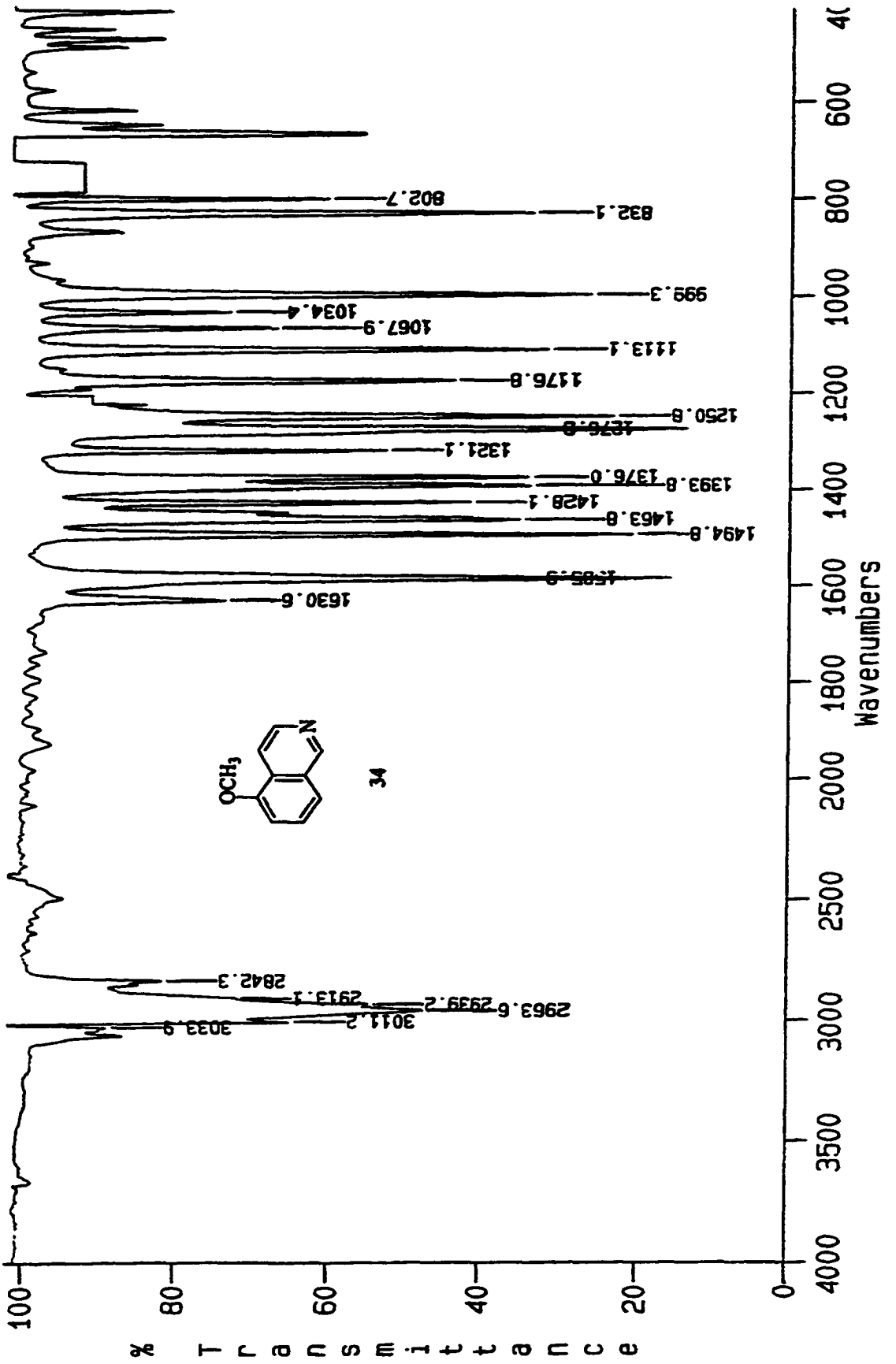
A solution of sulfone **160** (1.49 g, 2.8 mmol) in dichloromethane (15 mL) and *tert*-butanol (15 mL) was cooled to 5 °C and mixed with alumina supported potassium hydroxide (10 g, ~40%KOH, ~60 mmol). Dibromodifluoromethane (3 mL, ~33 mmol) was added dropwise to the yellowish mixture at 5 °C and the cooling was maintained for 10 min. The cooling bath was removed and the mixture was stirred at room temperature for 1.5 h. TLC analysis (EtOAc) showed only a trace amount of sulfone **160** and the reaction mixture was filtered through Celite. The solids were washed with ethyl acetate and the filtrate was concentrated under reduced pressure to dryness. The residue was partitioned between brine (50 mL) and ethyl acetate (200 mL), and the organic phase was dried, filtered, and concentrated under reduced pressure to dryness to give 1.31 g of a yellow foam. A 300 MHz ^{1}H NMR spectrum of the crude alkene mixture showed a complex mixture with probable vinylic doublets at δ 5.32, 5.52, 5.73, and 6.45 in an approximate ratio of 7:5:1:3. The crude alkene was dissolved in toluene (100 mL) and hydrogenated overnight at atmospheric pressure after adding 10% palladium on carbon (650 mg). The reaction mixture was filtered through a Celite pad and the catalyst was

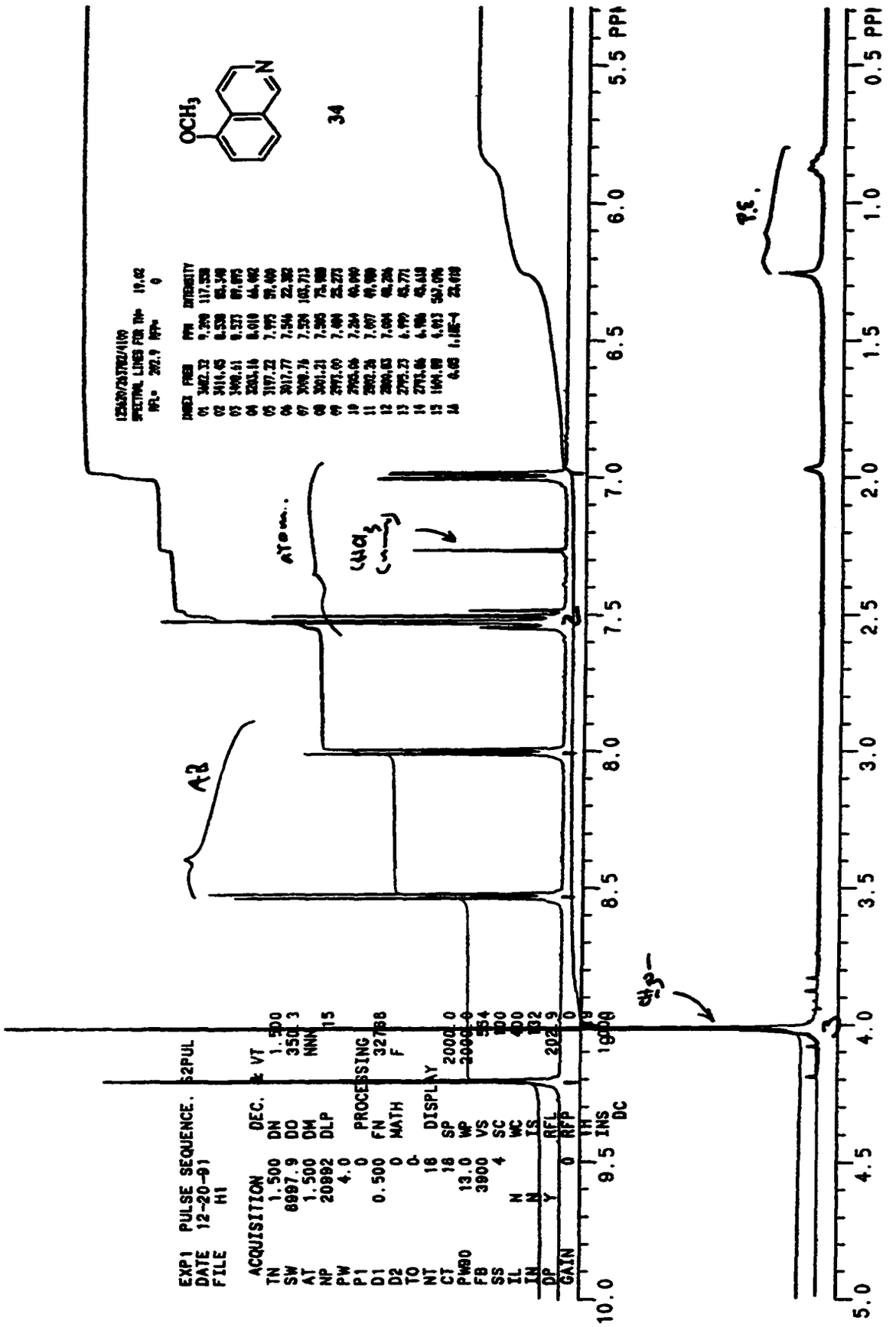
washed well with ethyl acetate. TLC analysis (EtOAc) of the filtrate showed only a trace of more polar, debenzylated material. The filtrate was concentrated under reduced pressure to dryness to give 1.3 g of a white foam. The foam was dissolved in a small amount of dichloromethane and flash chromatographed on silica gel (25 g). Elution with a gradient of 0-20% ethyl acetate:dichloromethane yielded 1 g of a colorless foam that was a mixture of alkene (vinylic doublet δ 5.52) and reduced benzylated product from analysis of the (+) ESMS (*m/e* alkene 466 [M + H^+] and product 468 [M + H^+]). The foam represented an approximate Ramberg-Bäcklund yield of 76% from the sulfone **160**. A solution of the purified foam mixture (1 g) in toluene (100 mL) was mixed with fresh 10% palladium on carbon (700 mg) and again hydrogenated at room temperature overnight. The reaction mixture was filtered through a Celite pad and the solids were washed well with ethyl acetate. TLC analysis (EtOAc) of the filtrate indicated that complete hydrogenolysis of the benzyl protecting group had occurred. The filtrate was concentrated under reduced pressure to dryness to give 1 g of **161** as a colorless foam. The ^{1}H NMR spectrum of this foam no longer showed any alkene doublet and also confirmed that debenzylation had occurred. In order to facilitate attempted separation of the diastereomeric mixture, a solution of 161 (1 g) in dichloromethane (10 mL) was treated with anhydrous pyridine (10 mL), acetic anhydride (1.5 mL), and 4-dimethylaminopyridine (100 mg). The solution was stirred at room temperature for 1 h and TLC analysis (EtOAc) showed that the acylation was complete. The solution was concentrated under reduced pressure to dryness and the residue was dissolved in ethyl acetate (150 mL). The ethyl acetate extract was washed successively with 1*N* HCl (25 mL), brine (25 mL), and a solution of saturated sodium

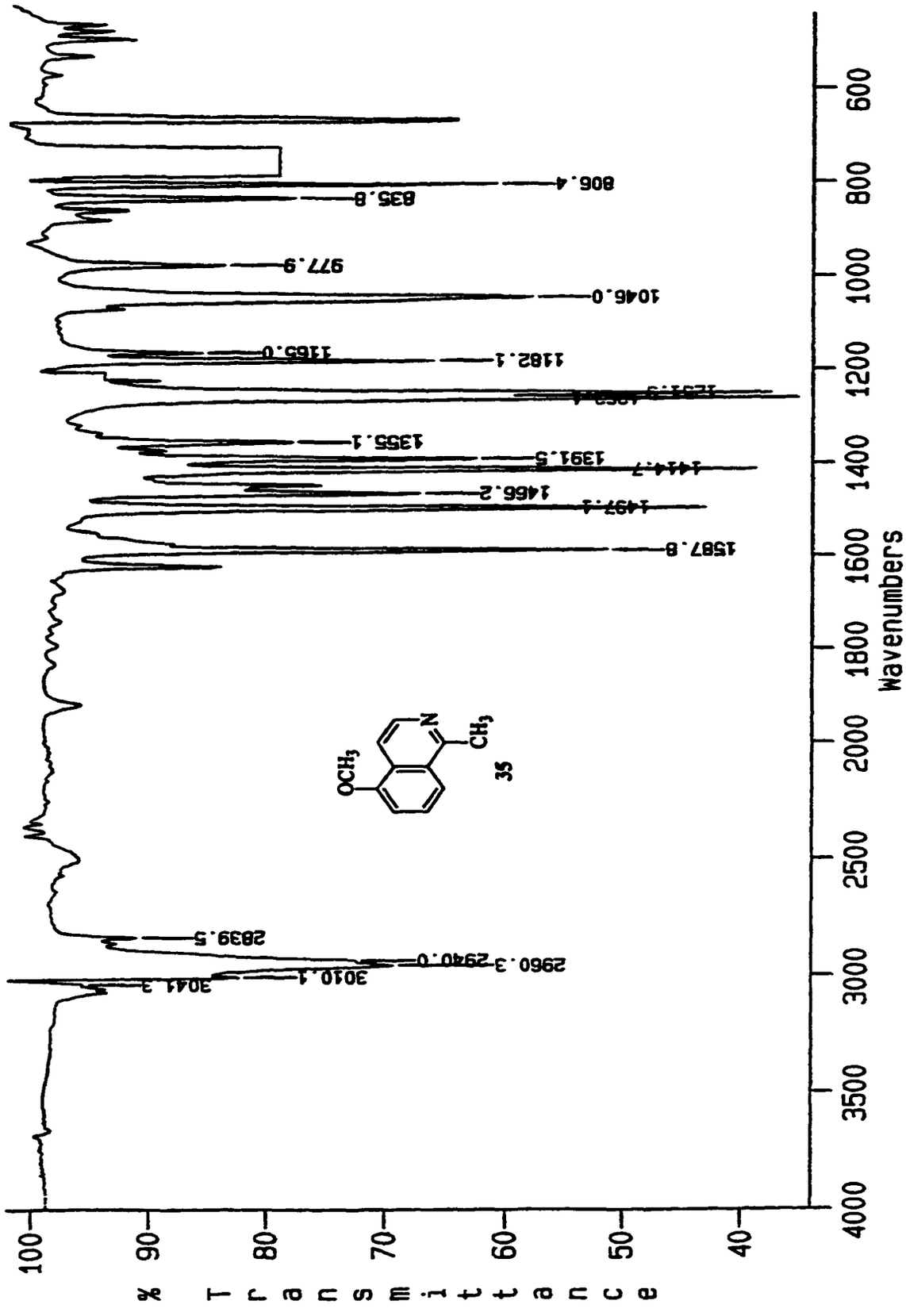
bicarbonate (25 mL). The organic phase was dried, filtered, and concentrated under reduced pressure to dryness to give 1 g of a colorless foam. The foam was dissolved in a small amount of dichloromethane and separated by preparative HPLC on a Waters Prep 500 using two porosil silica (15-20 μ) columns. Elution with 5% isopropanol:dichloromethane gave acetate **162** as two colorless foams, 400 mg of a less polar foam and 135 mg of a more polar foam. The total of 535 mg of acetate **162** represented a 45.5% overall yield from sulfone **160**. The ^{1}H NMR spectrum of the less polar foam indicated a 1.75:1 mixture of isomers, and the more polar foam indicated a 2:1 different isomeric mixture. The less polar foam was recrystallized twice from isopropanol to give 160 mg of colorless crystals as the major isomer, mp 207-208 °C. Crystals were grown from benzene for X-ray analysis showing that the major isomer was a β-C-glycoside with an *S* configuration at the benzylic methine carbon-(1). $[\alpha]^{25}_{D}$ -56.4 (c = 1.04, CH_3CN); ^{1}H NMR (500 MHz, C_6D_6) δ 1.05 (d, 3H, *J* = 6.4 Hz, $C\underline{H}_3$), 1.36 (q, 1H, *J* = 12.2 Hz), 1.52 (s, 3H, NC(O)$C\underline{H}_3$), 1.55-1.65 (m, 2.5H), 1.67 (s, 3H, OC(O)$C\underline{H}_3$), 1.67-1.80 (m, 2.5H), 2.05 (d, 1H, *J* = 11 Hz), 2.24 (ddd, 1H, *J* = 5.2, 8.4, 13.7 Hz), 2.72 (ddd, 1H), 3.06-3.10 (m, 2H), 3.37-3.55 (m, 1H, H-2), 3.41 (s, 3H, $OC\underline{H}_3$), 3.44 (s, 3H, $OC\underline{H}_3$), 3.64 (m, 1H, H-(1)), 4.25 (m, 1H, H-4), 4.84 (d, 1H, *J* = 7.8 Hz, N$\underline{H}$), 5.08 (d, 1H, *J* = 2.4 Hz, H-5), 6.45 (s, 2H, $Ar\underline{H}_{naphthyl}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.82 (t), 17.41 (q), 20.97 (q), 22.85 (t), 23.20 (q), 26.82 (t), 27.66 (d), 32.60 (t), 40.86 (d), 48.53 (d), 55.42 (q), 71.26 (d), 73.41 (d), 75.09 (d), 106.76 (d), 106.86 (d), 126.67 (s), 131.48 (s), 150.99 (s), 151.40 (s), 169.52 (s), 171.00 (s); (+) ESMS *m/e* 420 $[M + H]^{+}$; Anal. Calcd for $C_{23}H_{33}NO_6$: C, 65.85; H, 7.93; N, 3.34 Found: C, 65.85; H, 7.84; N, 3.27.

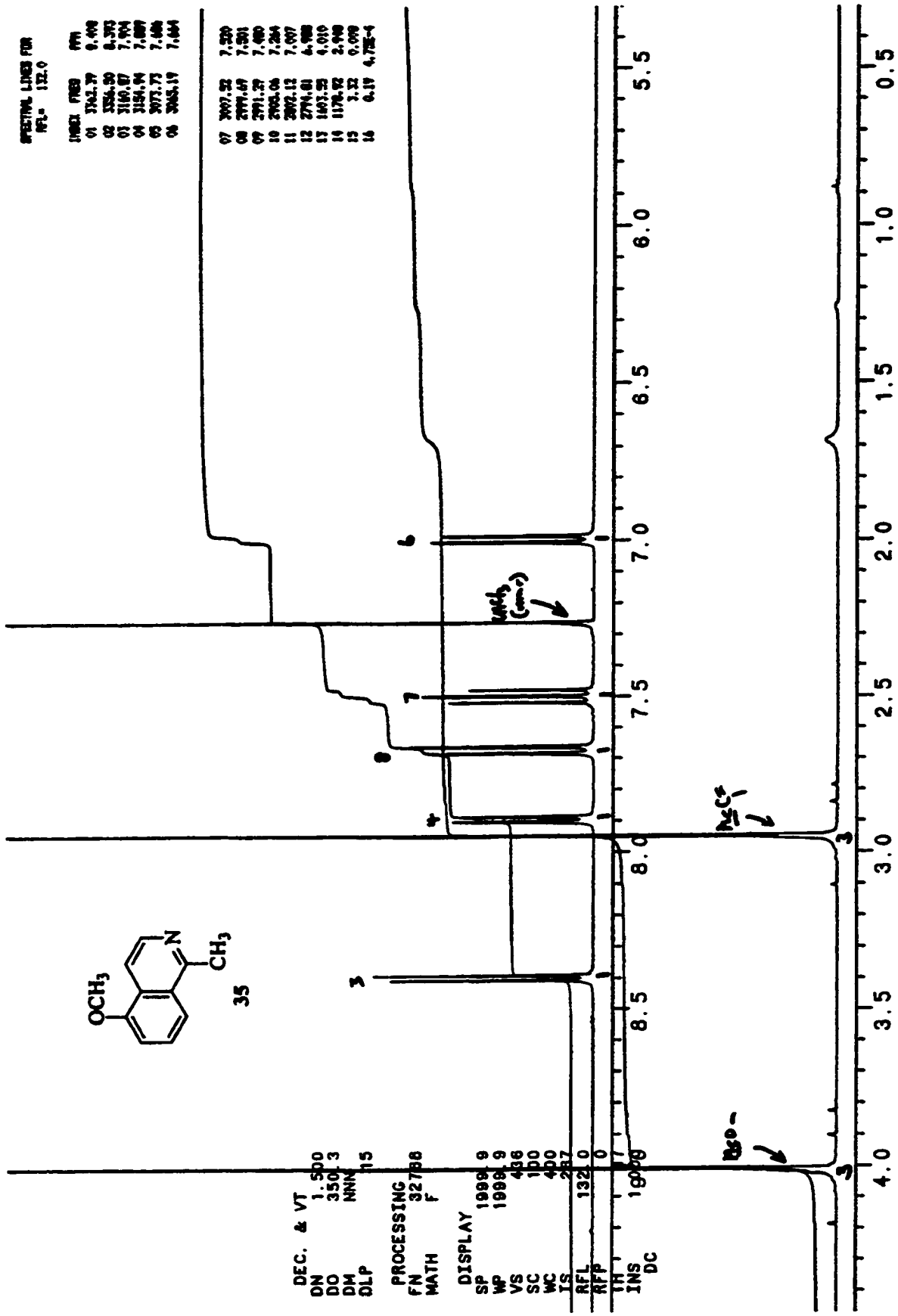
The more polar α-anomer mixture (~2:1) differing in configuration at the benzylic methine: ^{1}H NMR (500 MHz, C_6D_6) δ 1.01 (d, 1H, J = 6.4 Hz, C$\underline{H}_3$), 1.12 (ddd, 1H, J = 3.7, 11.5, 14.8 Hz), 1.24 (d, 2H, J = 6.4 Hz, C$\underline{H}_3$), 1.26-1.69 (m, 4H, coincident with NC(O)C$\underline{H}_3$ singlets at 1.51 (2H) and 1.55 (1H), 7H total), 1.77 (s, 1H, OC(O)C$\underline{H}_3$), 1.79 (s, 2H, OC(O)C$\underline{H}_3$), 1.79-1.91 (m, 2H), 2.16-2.21 (m, 0.3H), 2.40-2.46 (m, 0.7H), 2.52-2.64 (m, 1H), 3.04-3.11 (m, 1H), 3.34 (s, 2H, OC$\underline{H}_3$), 3.37-3.46 (m, 1H), 3.44 (s, 1H, OC$\underline{H}_3$), 3.46 (s, 2H, OC$\underline{H}_3$), 3.75 (s,1H, OC$\underline{H}_3$), 4.19-4.23 (m, 1H, H-2), 4.26 (q, 1H, J = 6.3 Hz, H-6), 4.52-4.58 (m, 0.7H, H-4), 4.62-4.4.70 (m, 0.3H, H-4), 4.80 (d, 0.3H, J = 8 Hz, N$\underline{H}$), 4.82 (d, 0.7H, J = 7.8 Hz, N$\underline{H}$), 5.20 (d, 0.3H, J = 2.4 Hz, H-5), 5.35 (d, 0.7H, J = 2.2 Hz, H-5), 6.47 (d, 2H, J = 1.2 Hz, Ar$\underline{H}_{naphthyl}$).

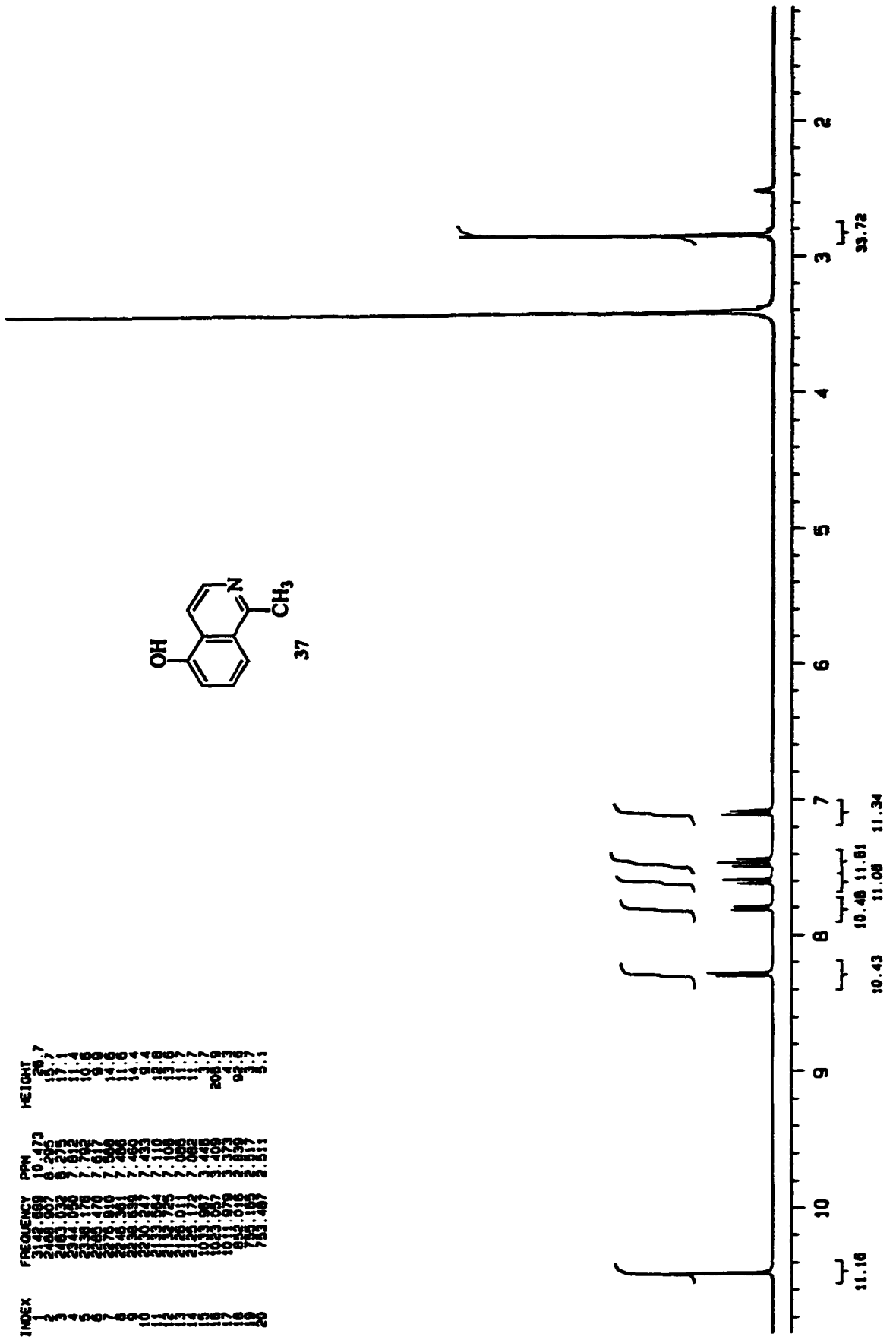
5. APPENDIX

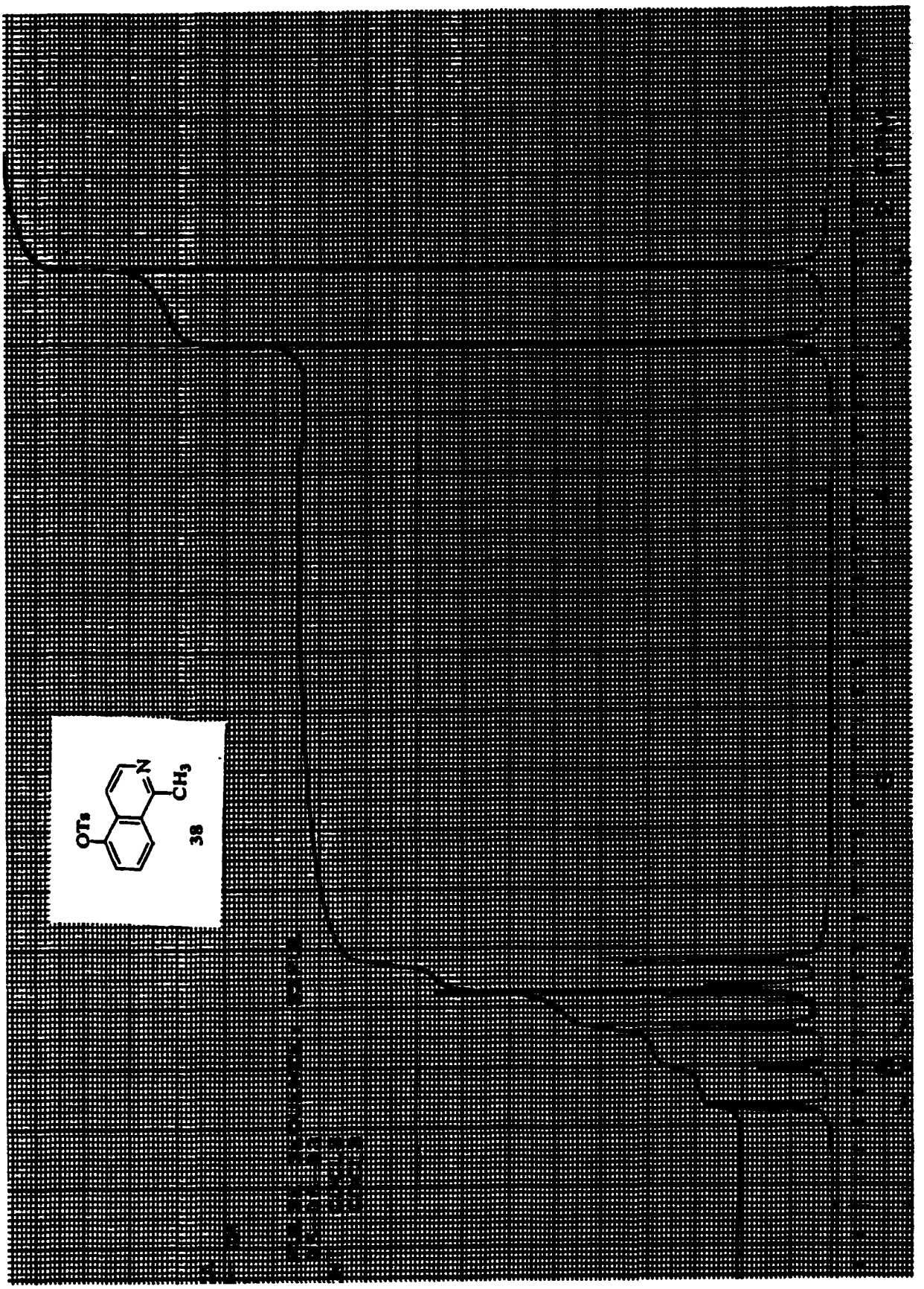


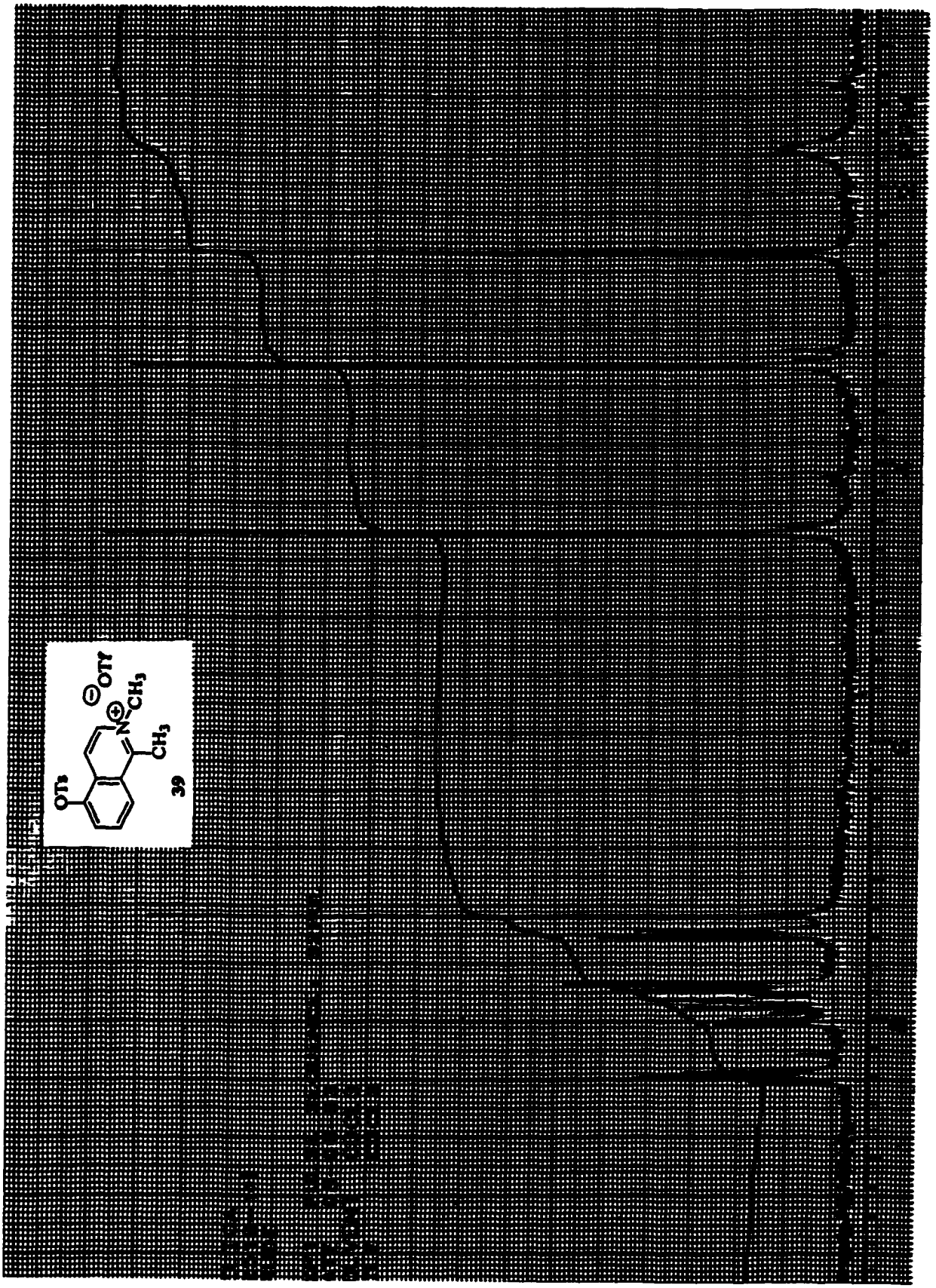


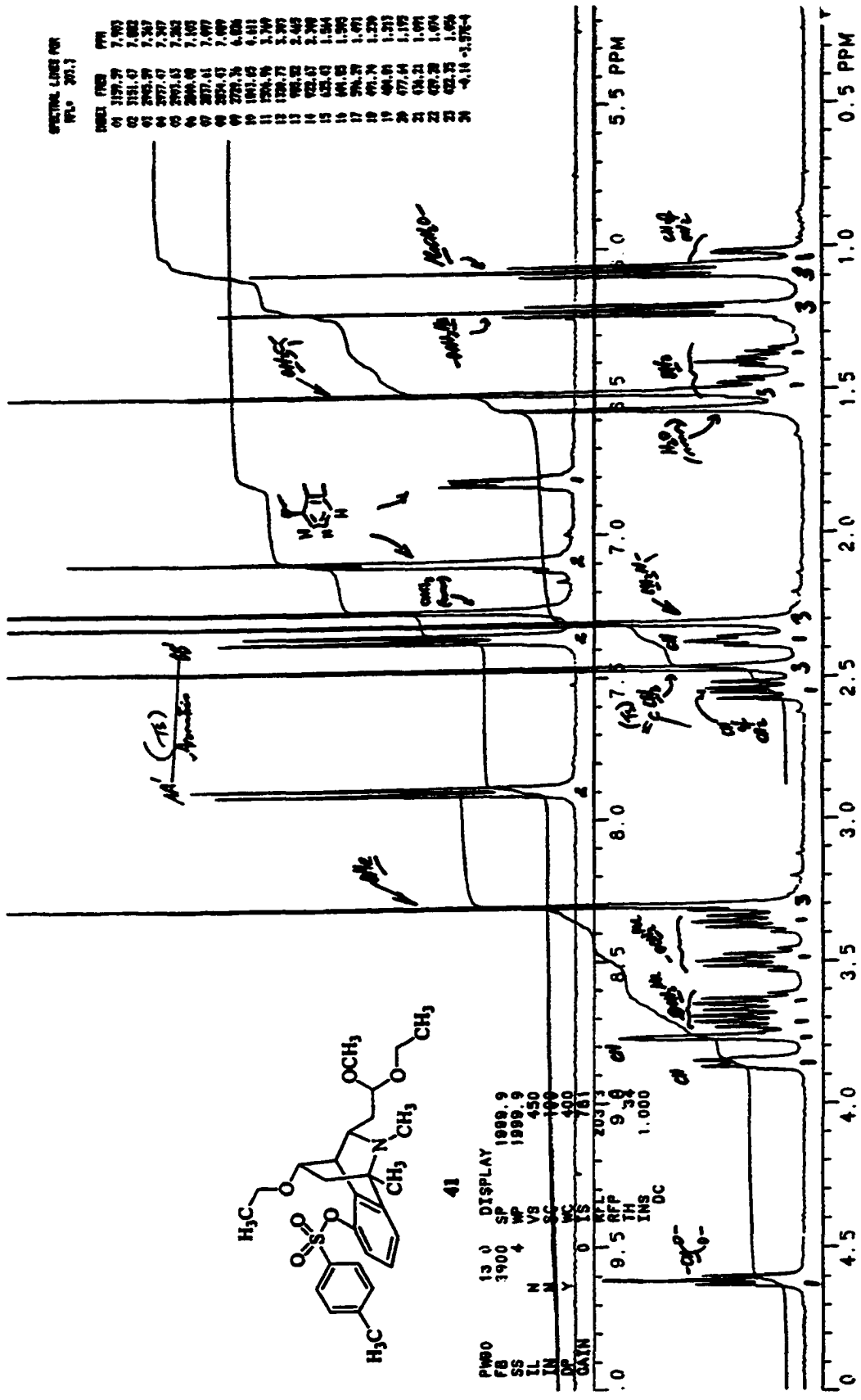












2251-104

XL-300 13C OBSERVE
SPECTRAL LINES FOR TI= 14.49
RFL= 162.5 RFP= 0

INDEX	FREQ	PPM	INTENSITY
01	7461.9	148.321	17.958
02	7434.8	147.782	20.657
03	7305.1	145.204	19.341
04	6739.4	133.960	16.897
05	6548.8	130.173	18.334
06	6536.4	129.925	158.246
07	6523.2	129.663	16.570
08	6470.4	128.615	23.128
09	6458.0	128.367	172.115
10	6444.8	128.105	19.805
11	6384.9	126.914	78.653
12	5957.5	118.419	77.398
13	5945.9	118.189	76.056
14	5102.4	101.421	79.291
15	3913.8	77.796	36.134
16	3881.6	77.156	39.938
17	3849.2	76.511	37.620
18	3817.9	75.888	70.589
19	3202.3	63.654	72.878
20	3106.3	61.745	62.920
21	2993.5	59.502	71.373
22	2779.5	55.249	33.509
23	2628.6	52.249	46.226
24	1922.9	38.223	54.159
25	1840.1	36.577	67.251
26	1818.1	36.140	66.441
27	1760.3	34.989	63.197
28	1094.2	21.749	45.328
29	1019.4	20.264	57.298
30	774.0	15.384	75.543

41

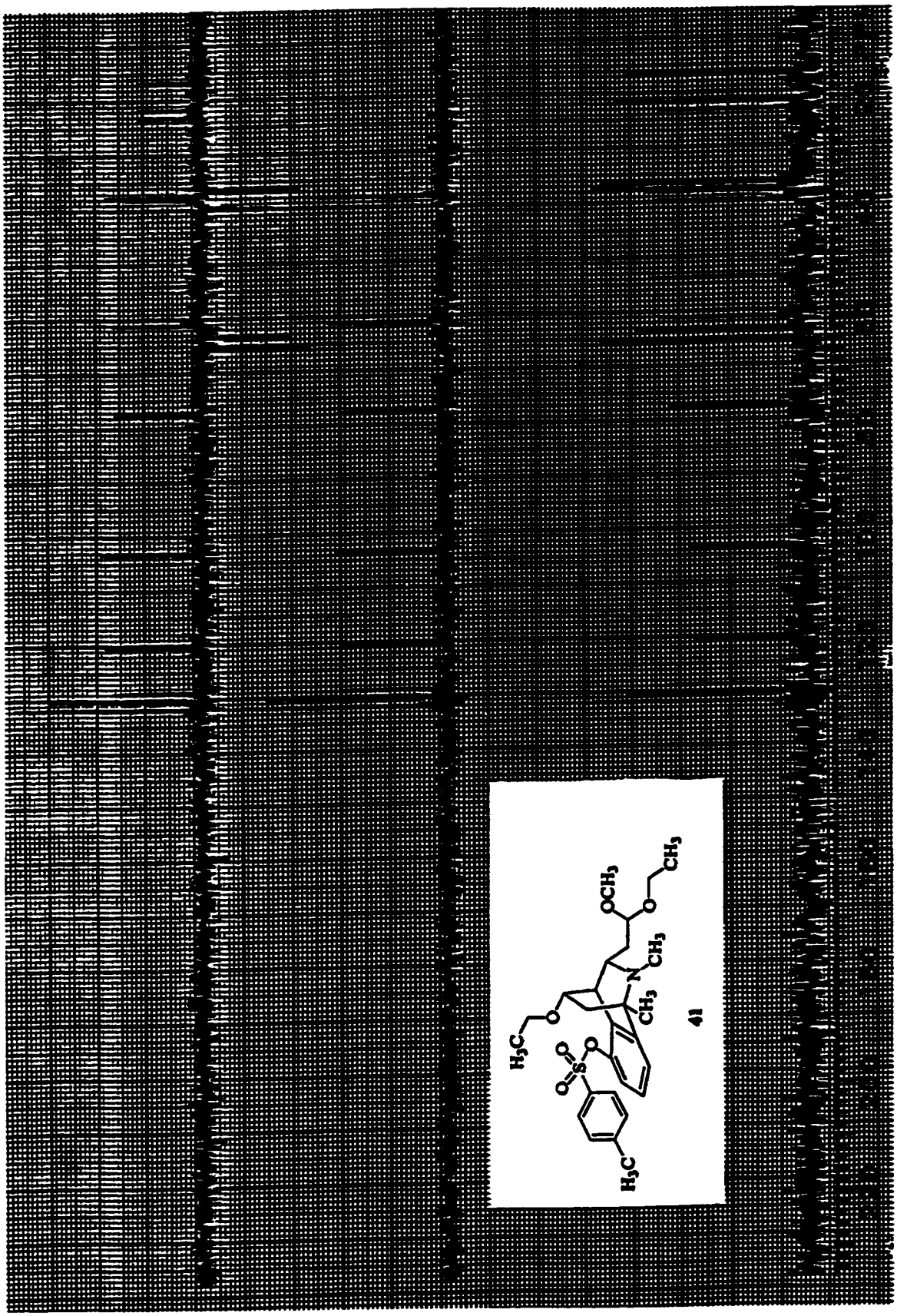


Table. X-ray Data for (41) at 295 K

Formula	$C_{27}H_{37}NO_6S$
Formula weight	503.66
Crystal size (mm)	0.08 x 0.08 x 0.48
Crystal system	monoclinic
Space group	C2/c
a (Å)	19.507(1)
b (Å)	8.129(1)
c (Å)	34.547(2)
β (°)	93.803(4)
V (Å^3)	5466.3(18)
Z	8
d_{calc} (g cm^{-3})	1.224
μ(Cu $K\alpha$) (cm^{-1})	13.39
Absorption correction	numerical
min transmission (%)	82.00
max transmission (%)	92.23
Maximum θ(°)	60
Unique reflections	4049
Observed reflections [$I > 3.0\sigma(I)$]	1806
Number of variables	343
R	0.050
R_w	0.058
$(\Delta\rho)_{max}$ (e Å^{-3})	0.15
$(\Delta\rho)_{min}$ (e Å^{-3})	-0.16

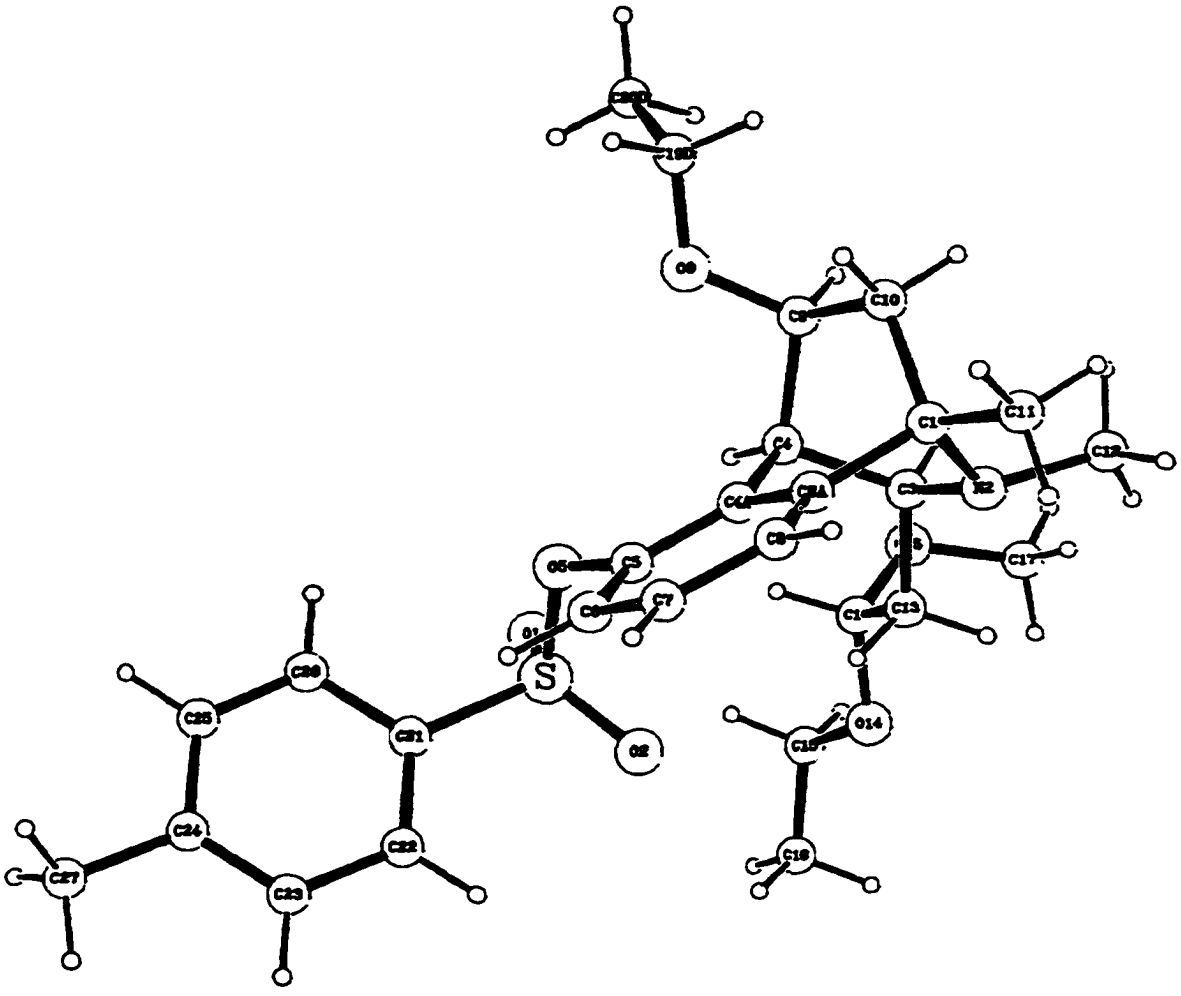


Figure 1. ORTEP drawing of the crystal structure of rac-[1α, 3β(*R**), 4α, 9*R**]-4-methylbenzenesulfonic acid 9-ethoxy-3-(2-ethoxy-2-methoxyethyl)-1, 2, 3, 4-tetrahydro-1, 2-dimethyl-1, 4-ethanoisoquinolin-5-yl ester **(41)**.

Table III. Bond Angles (°) for (41)

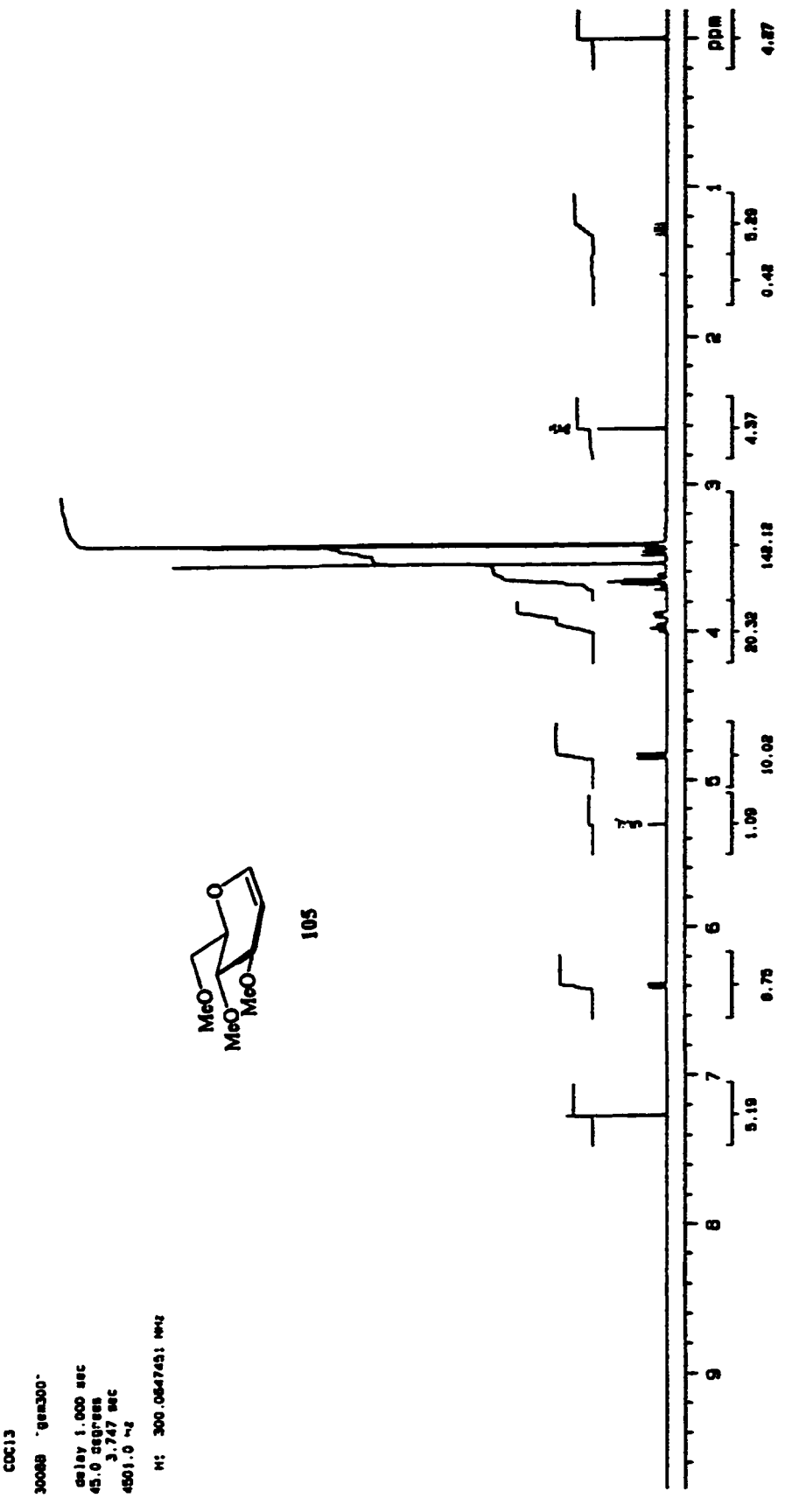
Atom 1	Atom 2	Atom 3	Angle	Atom 1	Atom 2	Atom 3	Angle
O1	S	O2	121.8(3)	C4A	C5	C6	122.3(5)
O1	S	O5	103.2(2)	C5	C6	C7	118.7(5)
O1	S	C21	109.8(2)	C6	C7	C8	120.7(5)
O2	S	O5	108.9(2)	C7	C8	C8A	119.3(5)
O2	S	C21	108.9(2)	C1	C8A	C4A	113.1(4)
O5	S	C21	102.4(2)	C1	C8A	C8	127.2(4)
S	O5	C5	121.2(3)	C4A	C8A	C8	119.7(4)
C9	O9	C19	106.2(5)	O9	C9	C4	107.9(4)
C14	O14	C15	112.5(4)	O9	C9	C10	113.5(4)
C14	O15	C17	116.0(4)	C4	C9	C10	109.6(4)
C1	N2	C3	112.4(3)	C1	C10	C9	110.2(4)
C1	N2	C12	115.8(4)	C3	C13	C14	115.5(4)
C3	N2	C12	109.6(4)	O14	C14	O15	110.4(3)
N2	C1	C8A	104.9(3)	O14	C14	C13	106.7(4)
N2	C1	C10	110.5(4)	O15	C14	C13	114.4(4)
N2	C1	C11	110.0(4)	O14	C15	C16	110.8(5)
C8A	C1	C10	105.9(4)				
C8A	C1	C11	113.4(4)				
C10	C1	C11	111.8(4)	S	C21	C22	121.3(4)
N2	C3	C4	110.3(3)	S	C21	C26	117.8(3)
N2	C3	C13	109.1(3)	C22	C21	C26	120.8(4)
C4	C3	C13	113.4(4)	C21	C22	C23	119.6(5)
C3	C4	C4A	108.4(3)	C22	C23	C24	121.1(5)
C3	C4	C9	106.0(3)	C23	C24	C25	118.8(5)
C4A	C4	C9	107.1(3)	C23	C24	C27	122.2(5)
C4	C4A	C5	126.9(4)	C25	C24	C27	119.0(5)
C4	C4A	C8A	113.9(4)	C24	C25	C26	121.1(5)
C5	C4A	C8A	119.2(4)	C21	C26	C25	118.6(4)
O5	C5	C4A	117.3(4)	C9	O9	C19	119.6(5)
O5	C5	C6	120.2(4)	O9	C19	C20	106.0(7)

Standard deviations are in parentheses.

Table II. Bond Distances (Å) for (41)

Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance
S	O1	1.453(4)	C4A	C5	1.367(6)
S	O2	1.415(4)	C4A	C8A	1.386(6)
S	O5	1.590(4)	C5	C6	1.365(8)
S	C21	1.757(5)	C6	C7	1.370(8)
O5	C5	1.422(6)	C7	C8	1.396(8)
O9	C9	1.420(6)	C8	C8A	1.384(7)
O9	C19	1.565(9)	C9	C10	1.535(7)
O14	C14	1.414(5)	C13	C14	1.487(7)
O14	C15	1.416(7)	C15	C16	1.41(1)
O15	C14	1.429(6)			
O15	C17	1.391(8)	C19	C20	1.44(2)
N2	C1	1.490(6)	C21	C22	1.380(6)
N2	C3	1.469(6)	C21	C26	1.385(7)
N2	C12	1.473(6)	C22	C23	1.368(8)
C1	C8A	1.515(7)	C23	C24	1.364(8)
C1	C10	1.550(6)	C24	C25	1.400(7)
C1	C11	1.518(7)	C24	C27	1.511(9)
C3	C4	1.544(6)	C25	C26	1.369(7)
C3	C13	1.539(6)			
C4	C4A	1.494(6)			
C4	C9	1.537(6)			

Standard deviations are in parentheses.



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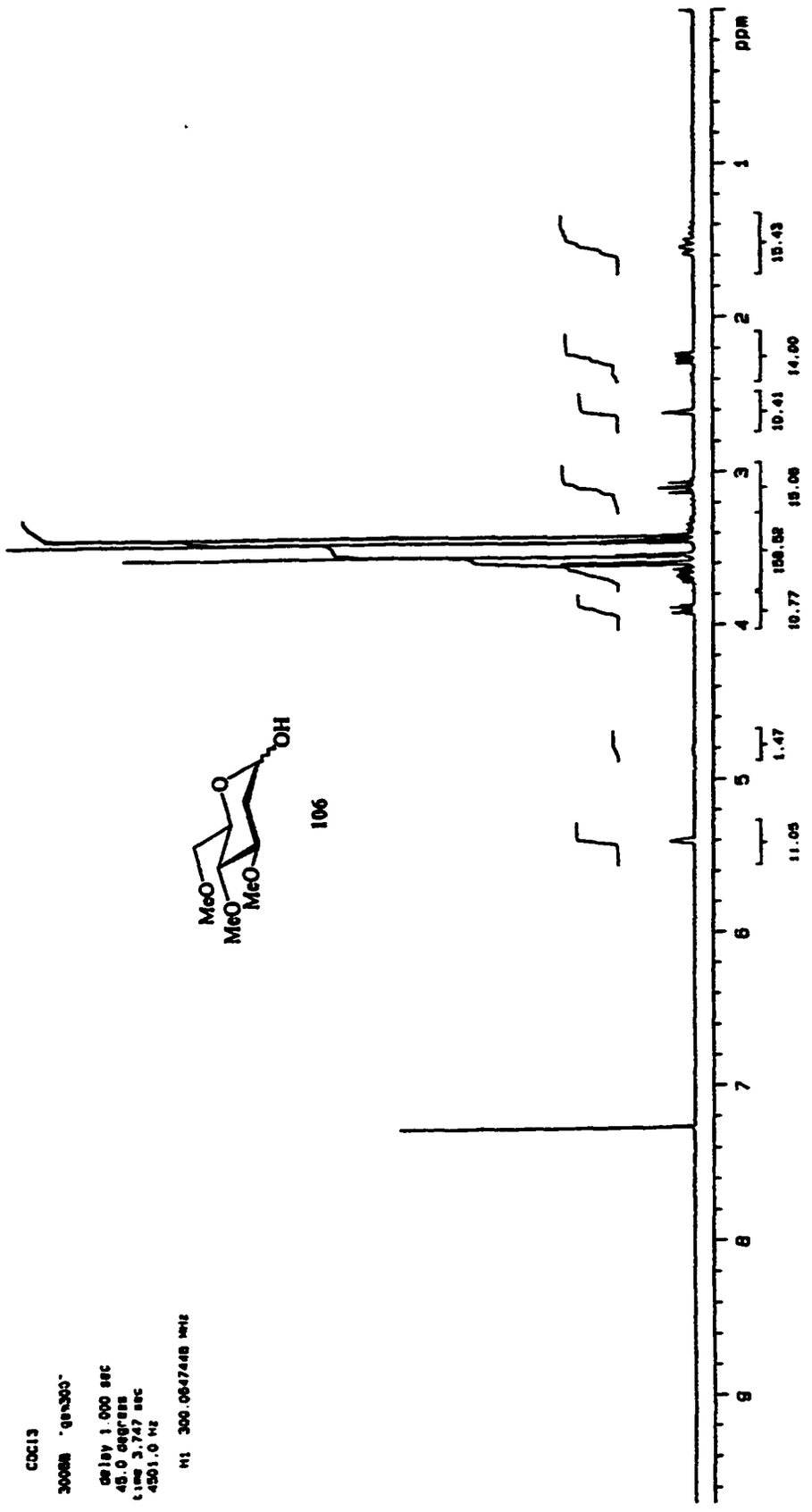

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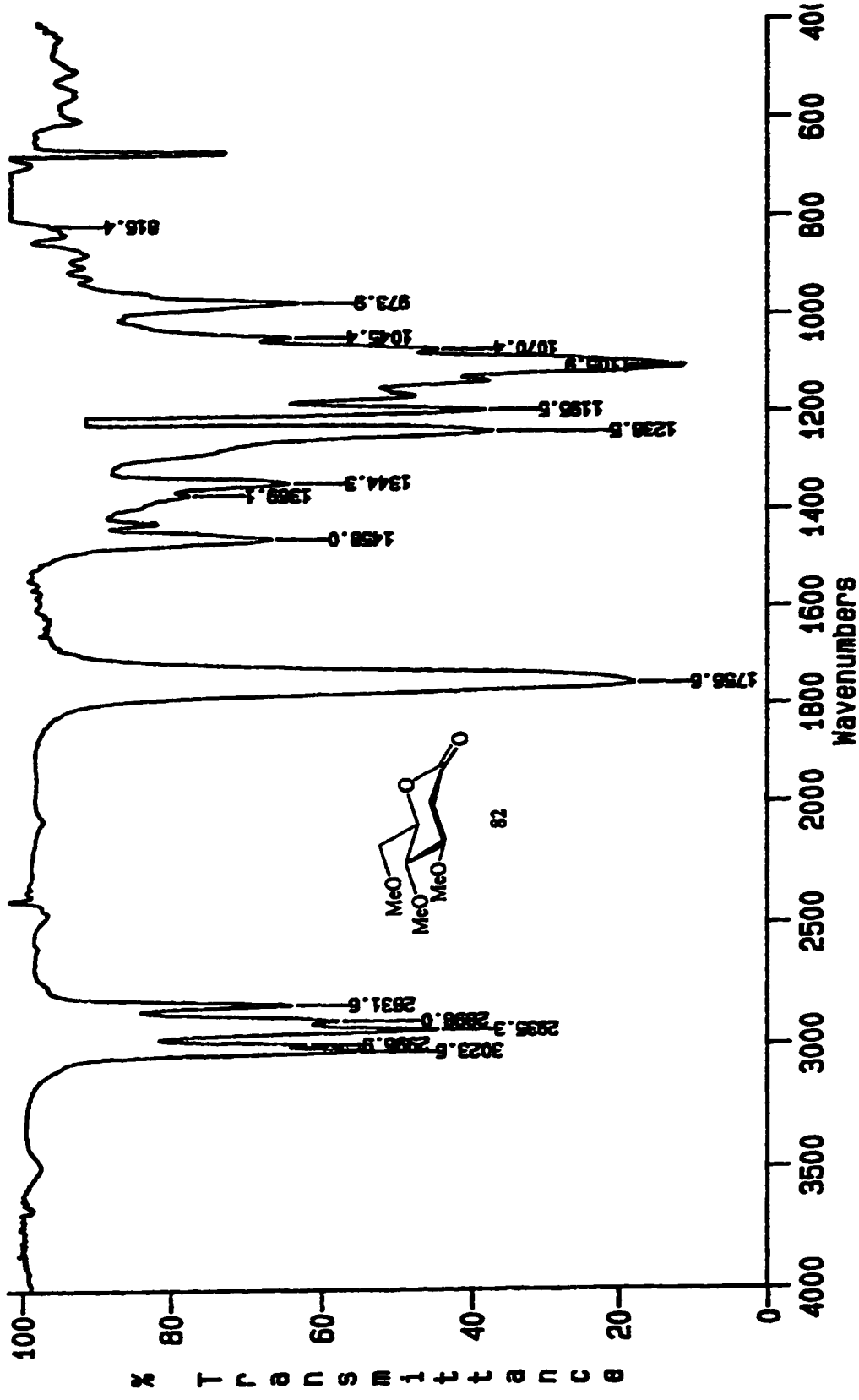
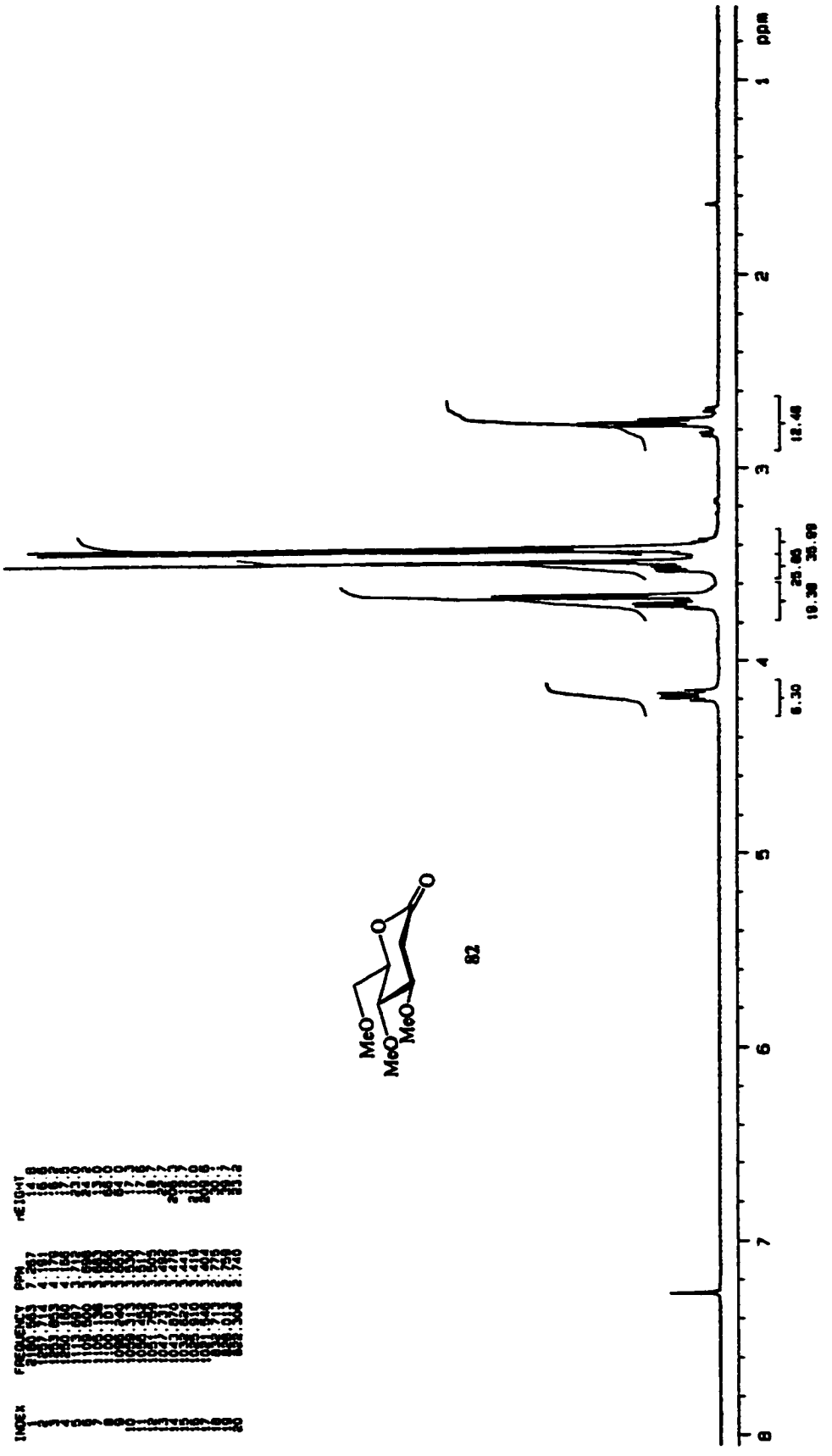
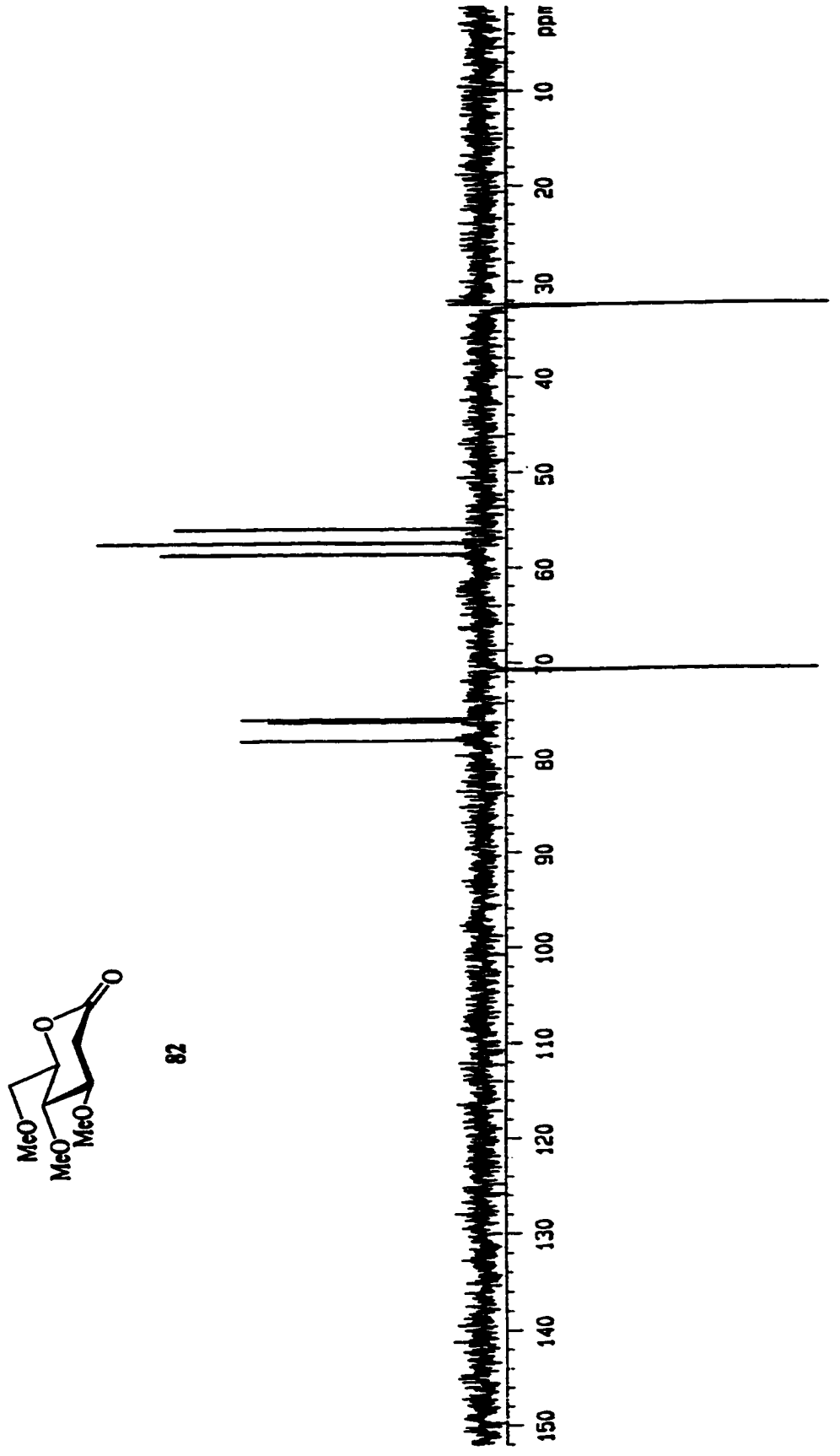
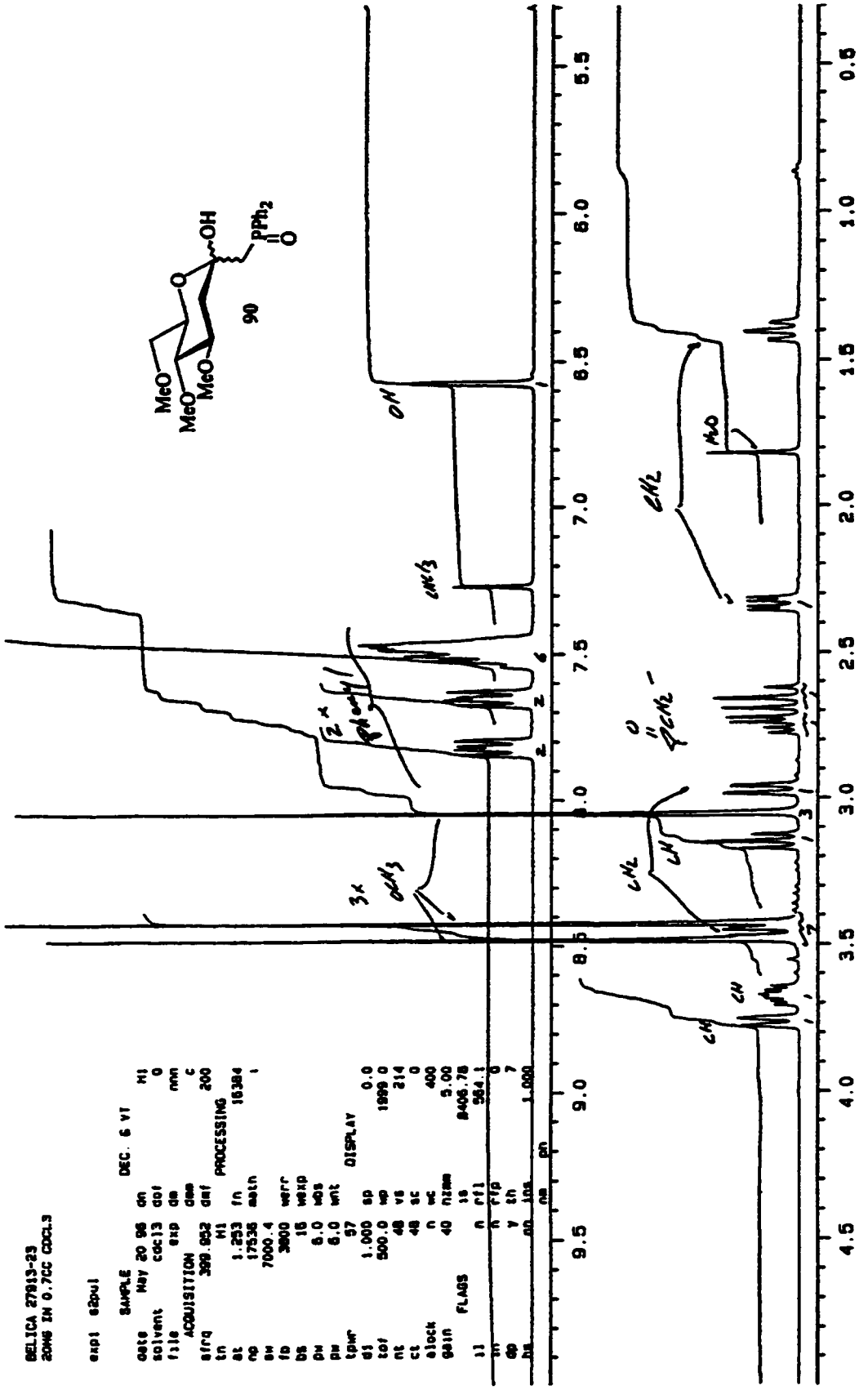
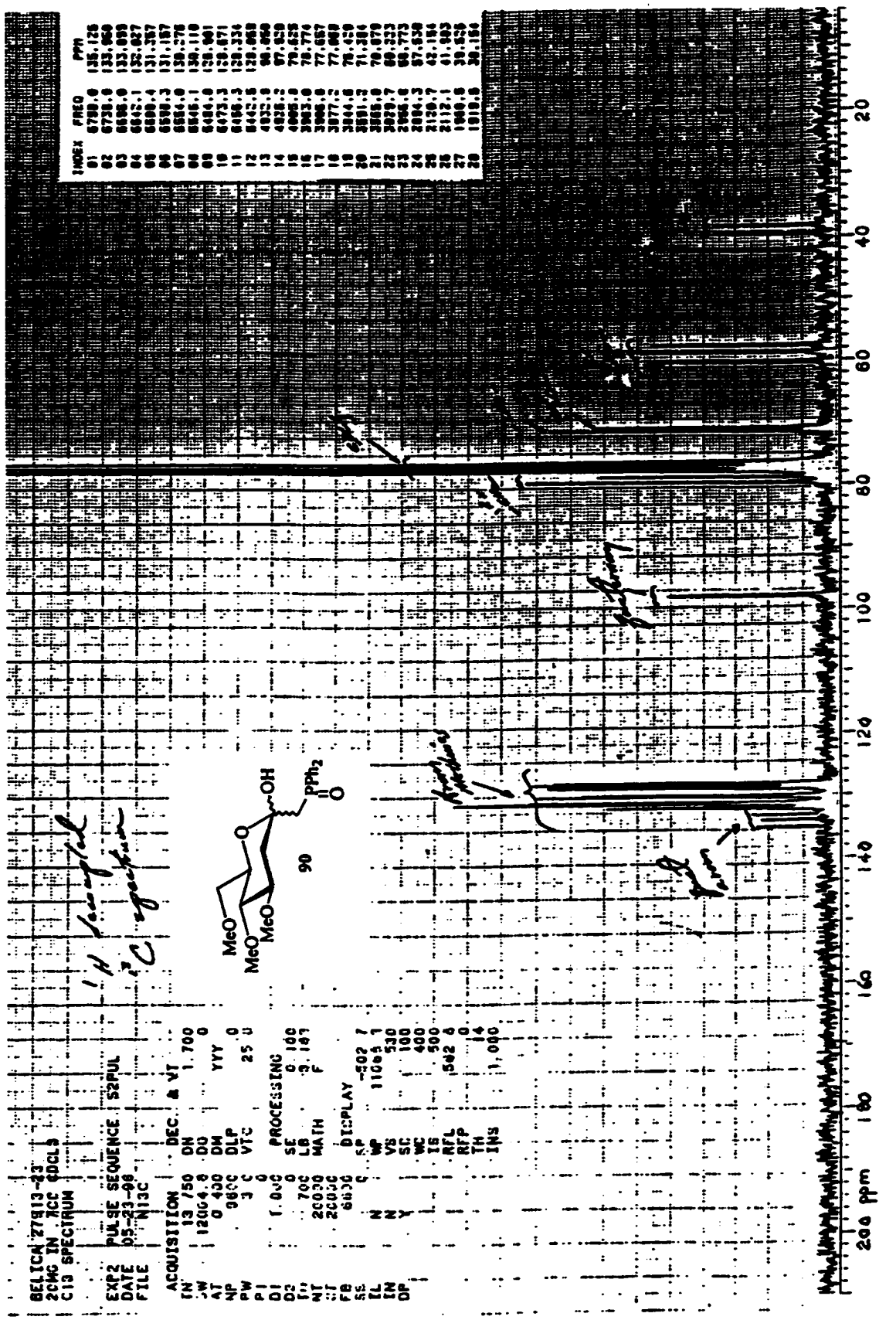
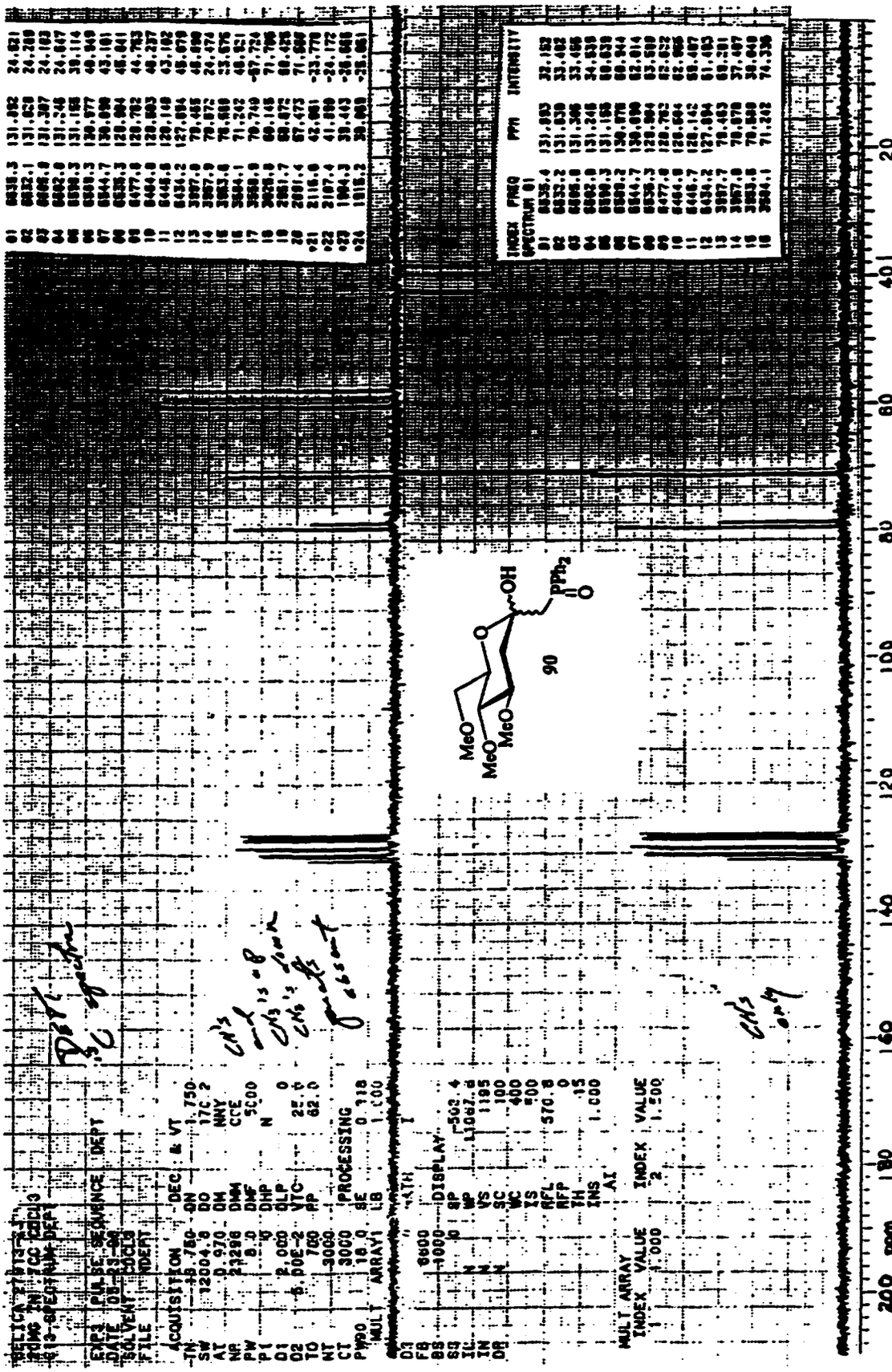


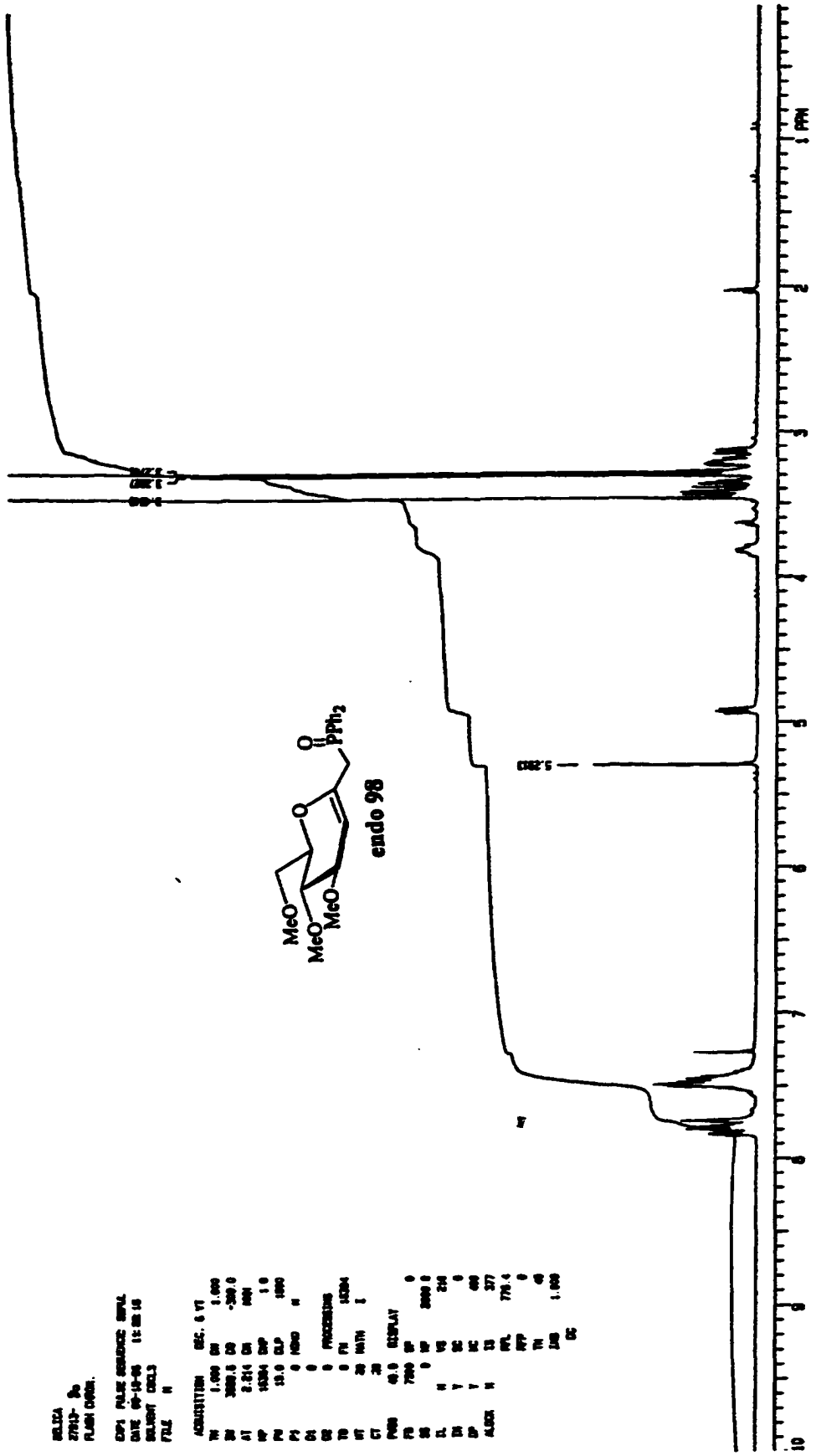


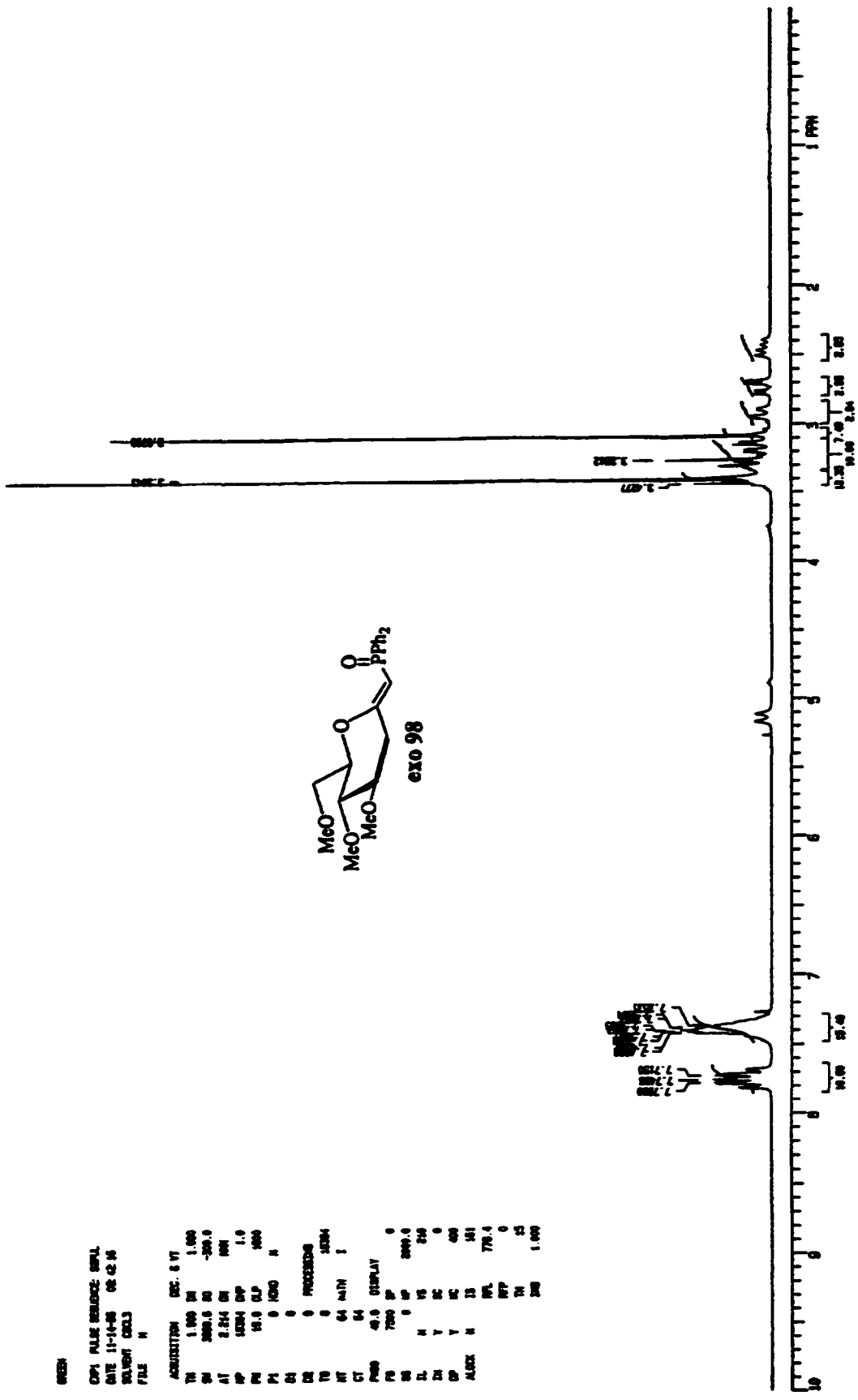


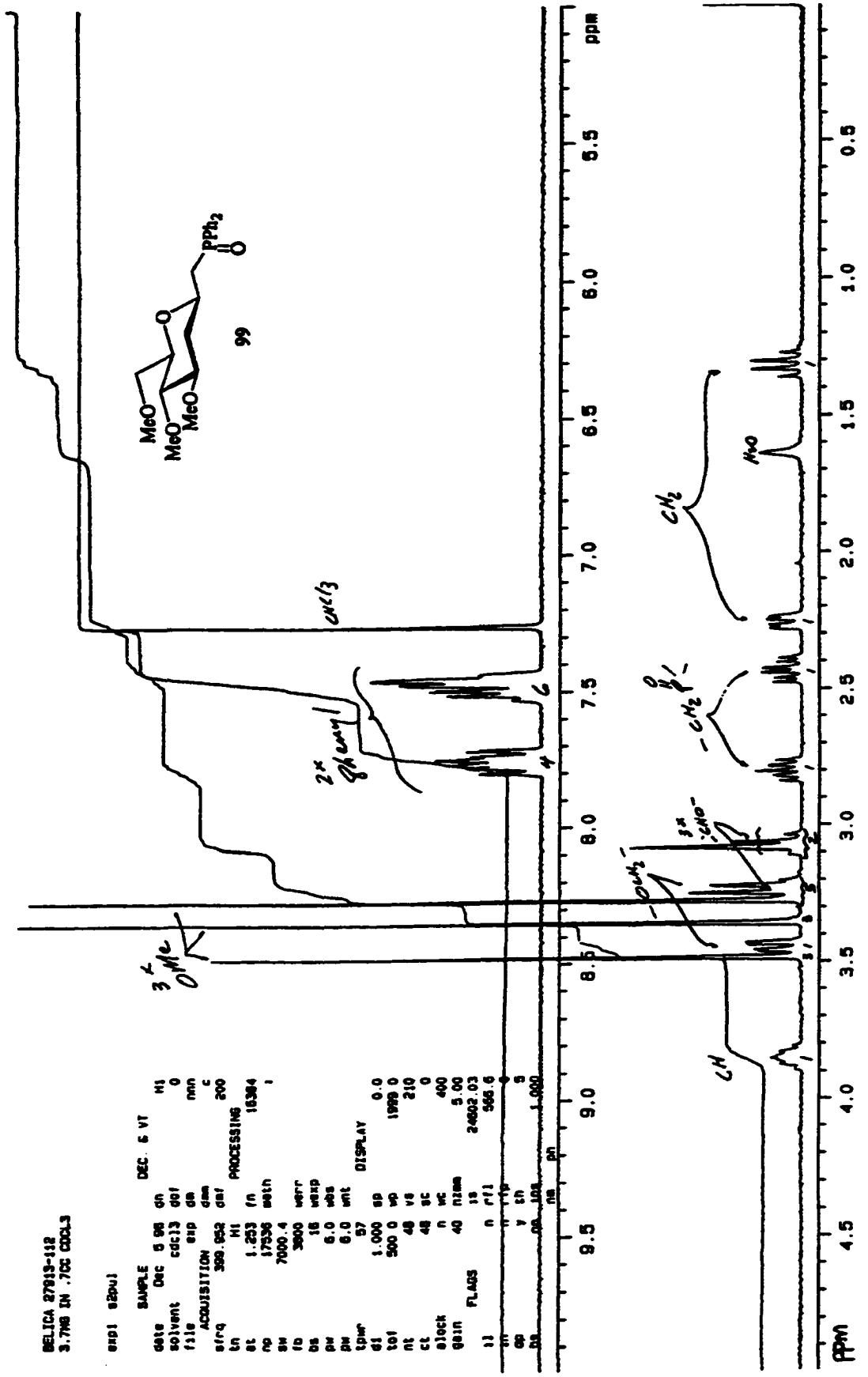


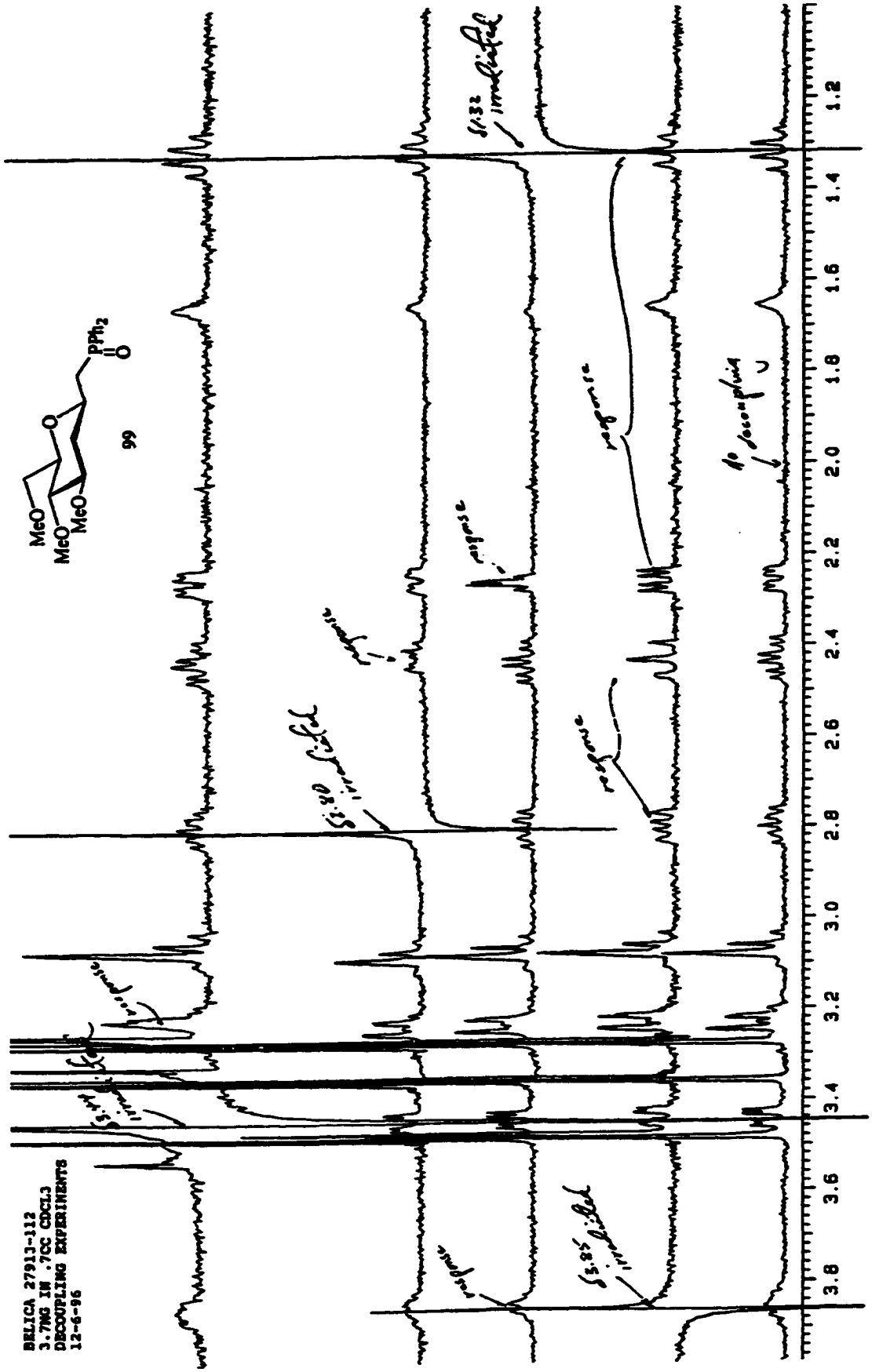


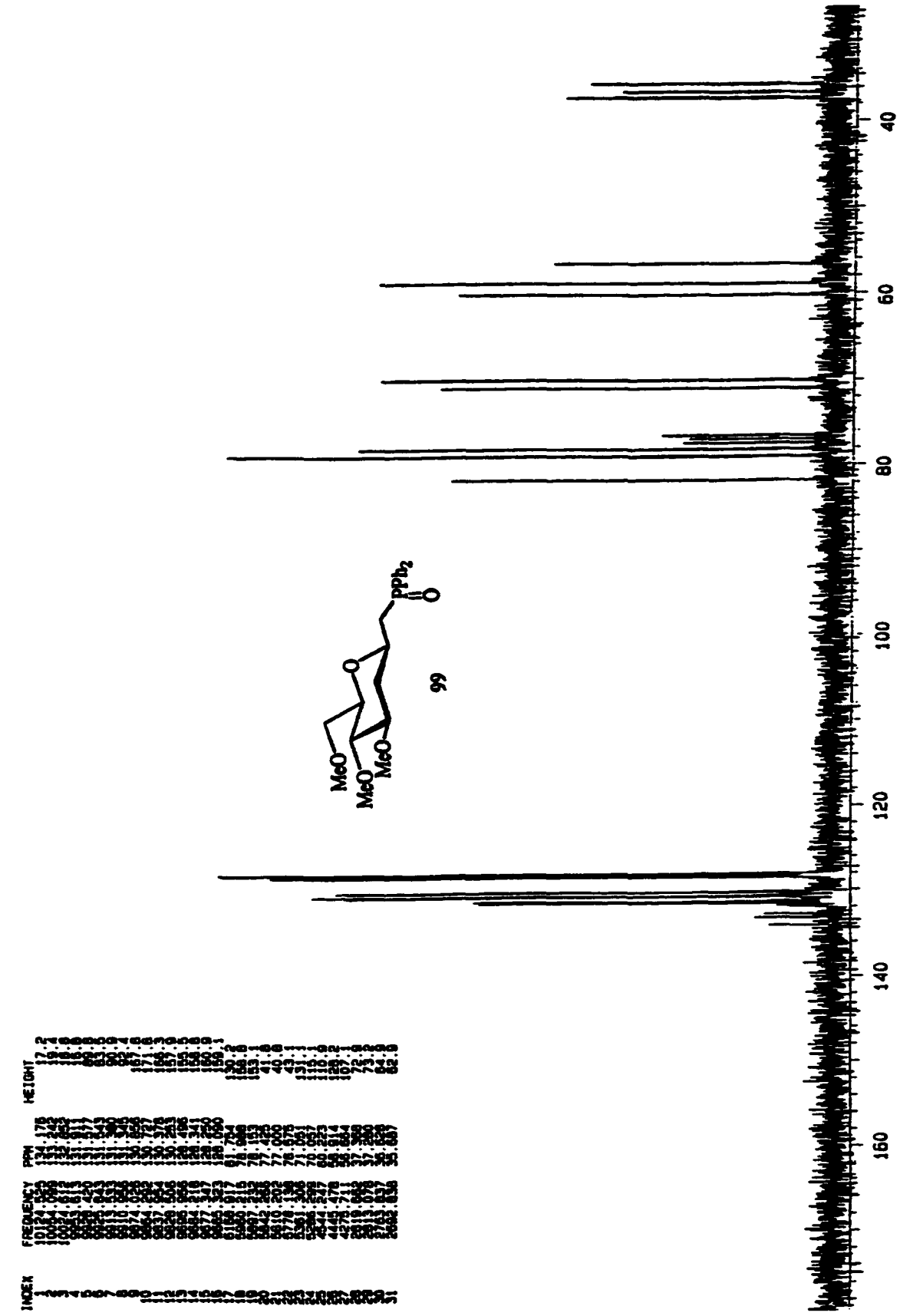












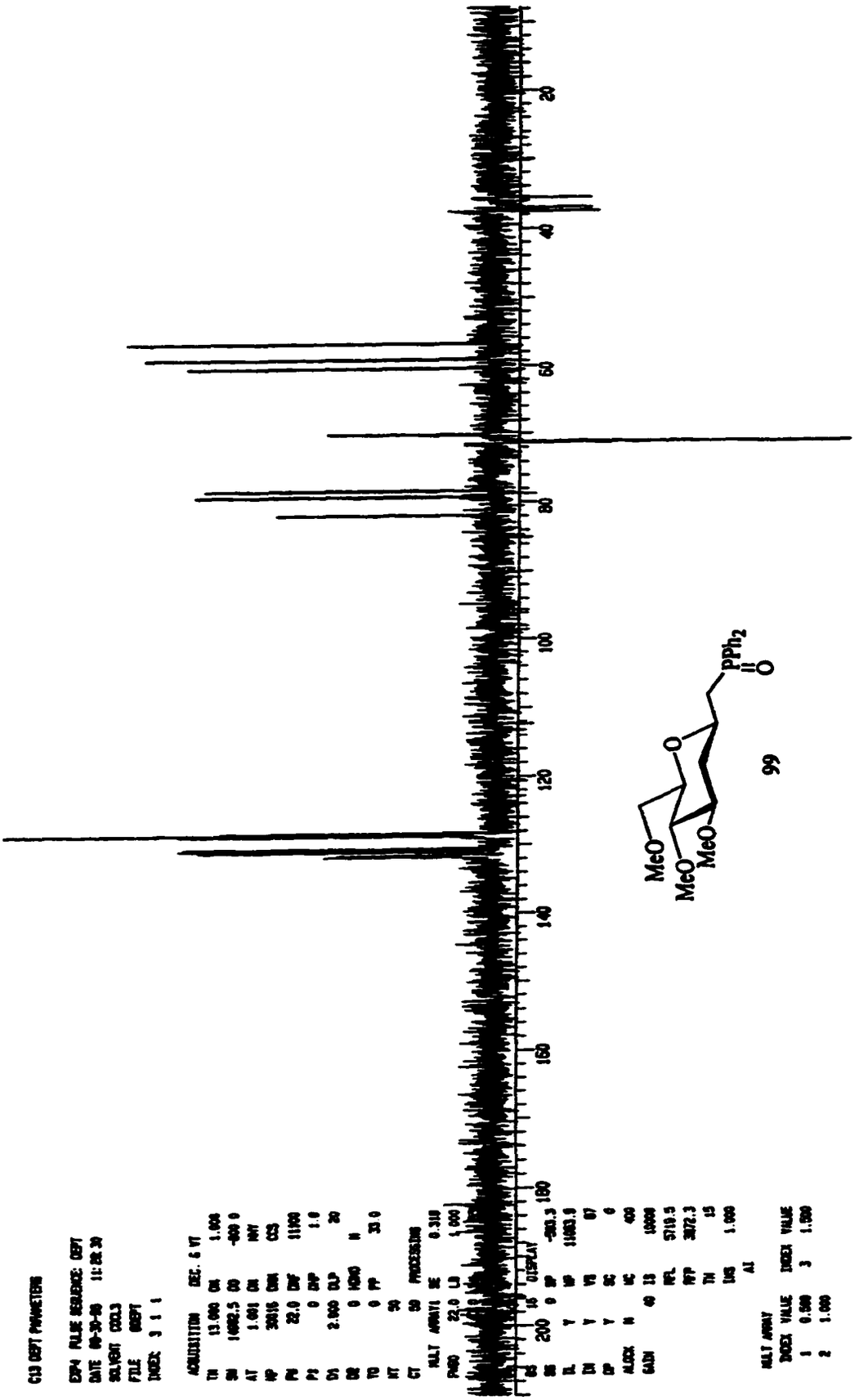


Table. X-ray Data for (99) at 295 K

Formula	$C_{22}H_{29}O_5P$
Formula weight	404.45
Crystal size (mm)	0.23 x 0.28 x 0.84
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a (Å)	5.723(2)
b (Å)	14.965(2)
c (Å)	24.960(4)
V (Å^3)	2137.6(9)
Z	4
d_{calc} (g cm^{-3})	1.257
μ(Cu $K\alpha$) (cm^{-1})	13.68
Absorption correction	numerical
min transmission (%)	51.41
max transmission (%)	75.42
Maximum θ(°)	75
Unique reflections	2548
Observed reflections [$I > 3.0\sigma(I)$]	1893
Number of variables	253
R	0.0575
R_w	0.0696
R (antipode)	0.0626
R_w (antipode)	0.0758
$(\Delta\rho)_{max}$ (e Å^{-3})	0.48
$(\Delta\rho)_{min}$ (e Å^{-3})	-0.44

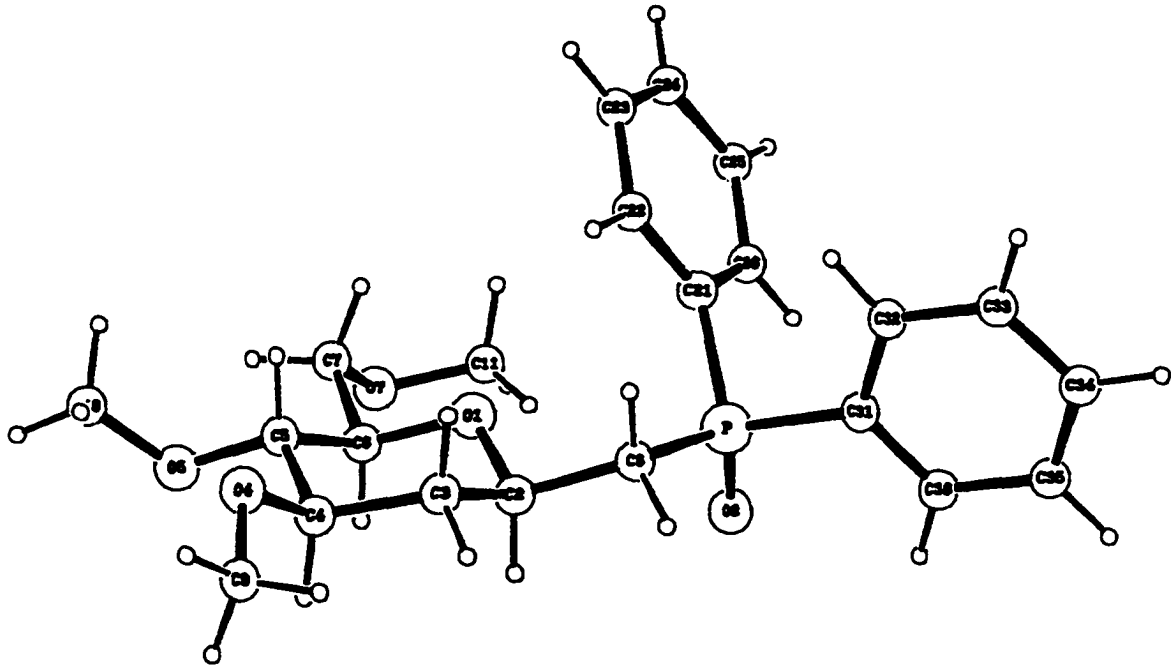


Figure 2. ORTEP drawing of the crystal structure of 2, 6-anhydro-1, 3-dideoxy-1-diphenylphosphoryl-4, 5, 7-tri-O-methyl-β-D-arabino-heptitol (99).

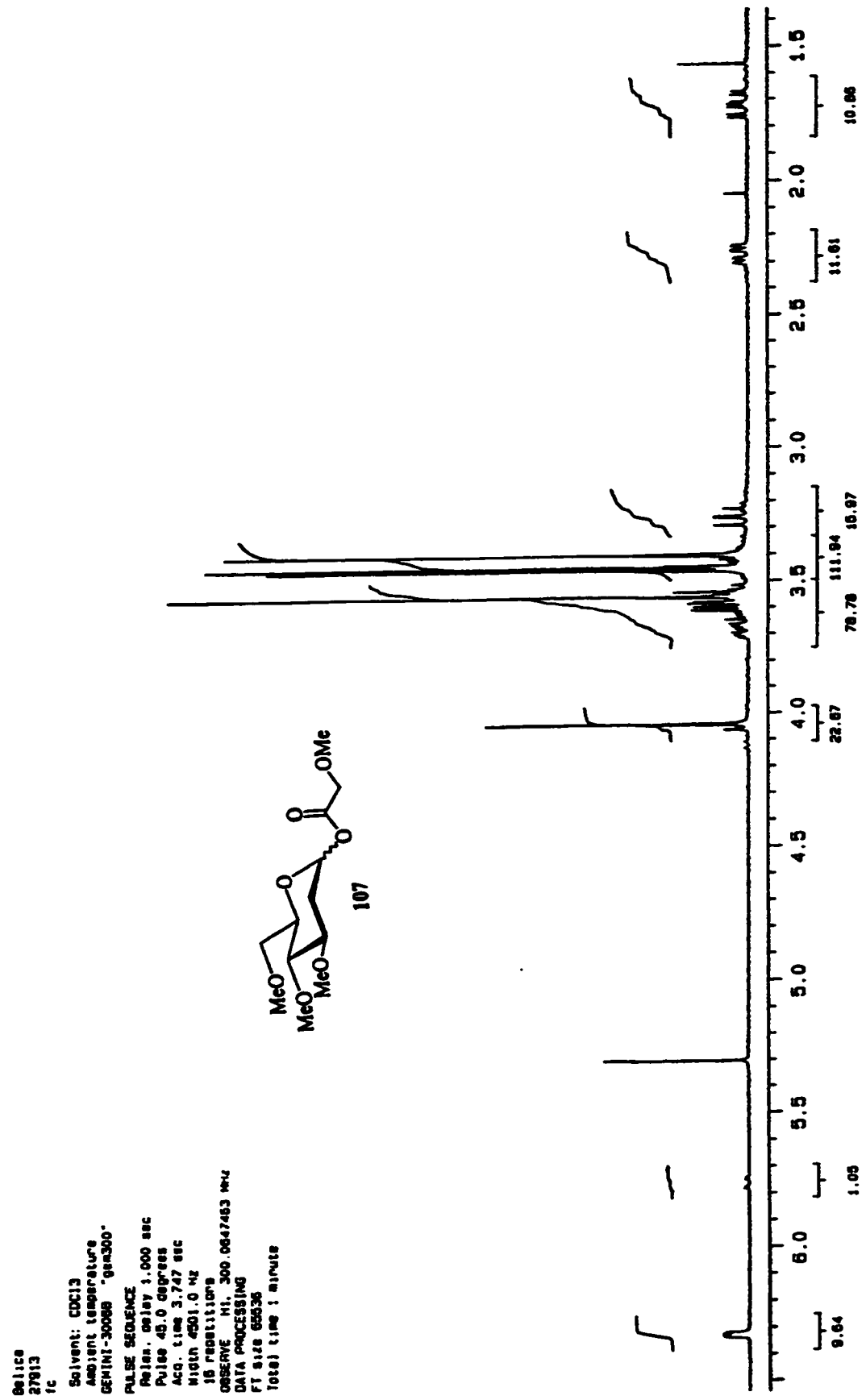
Table II. Bond Distances (Å) for (99)

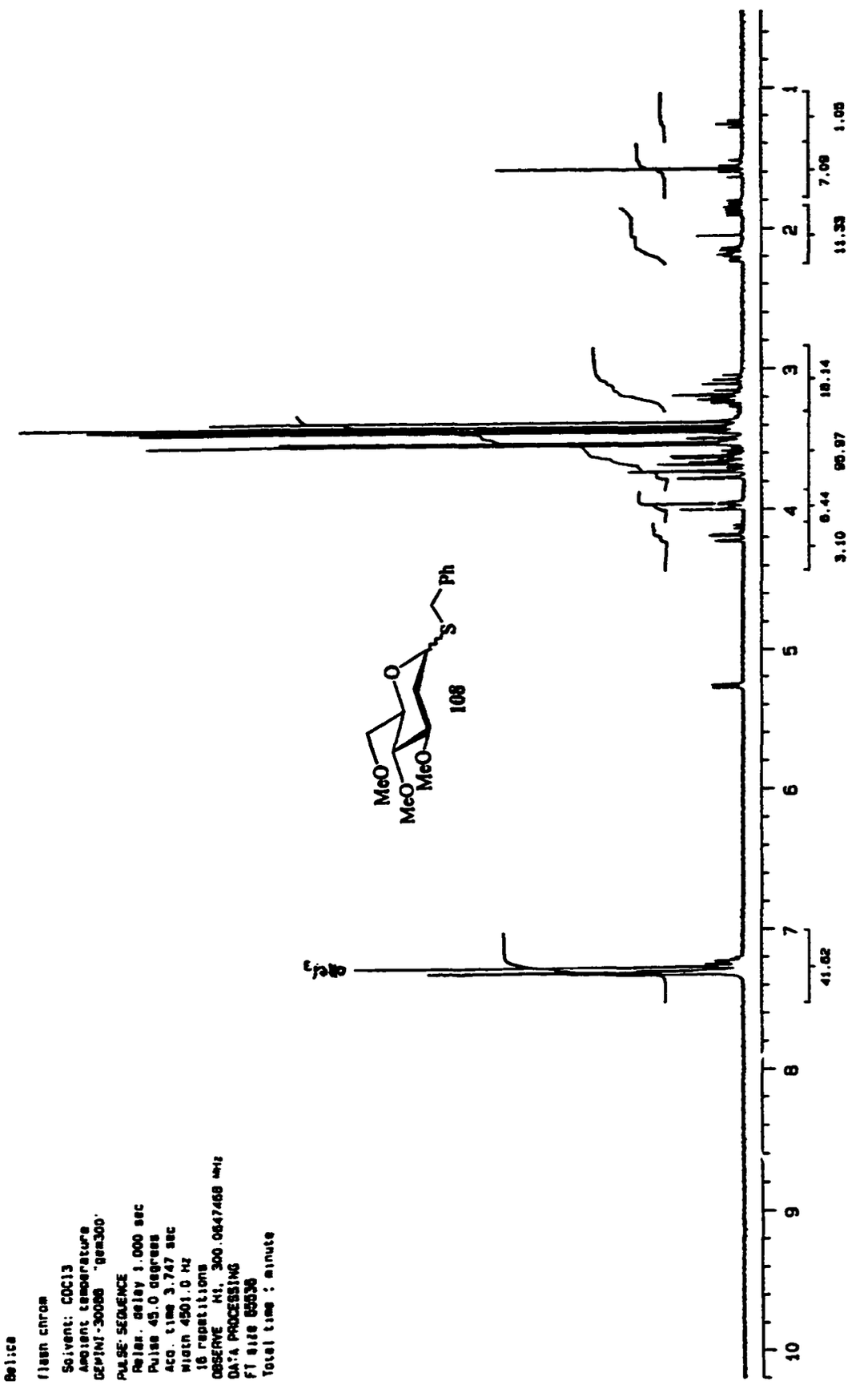
Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance
P	O2	1.472(4)	C4	C5	1.510(6)
P	C8	1.786(5)	C5	C6	1.535(7)
P	C21	1.806(5)	C6	C7	1.529(7)
P	C31	1.809(5)	C21	C22	1.390(7)
O1	C2	1.437(5)	C21	C26	1.377(7)
O1	C6	1.435(5)	C22	C23	1.395(7)
O4	C4	1.444(7)	C23	C24	1.391(8)
O4	C9	1.394(7)	C24	C25	1.383(9)
O5	C5	1.429(5)	C25	C26	1.380(7)
O5	C10	1.383(9)	C31	C32	1.390(9)
O7	C7	1.423(7)	C31	C36	1.362(9)
O7	C11	1.398(6)	C32	C33	1.385(8)
C2	C3	1.523(7)	C33	C34	1.35(1)
C2	C8	1.532(6)	C34	C35	1.37(1)
C3	C4	1.527(6)	C35	C36	1.40(1)

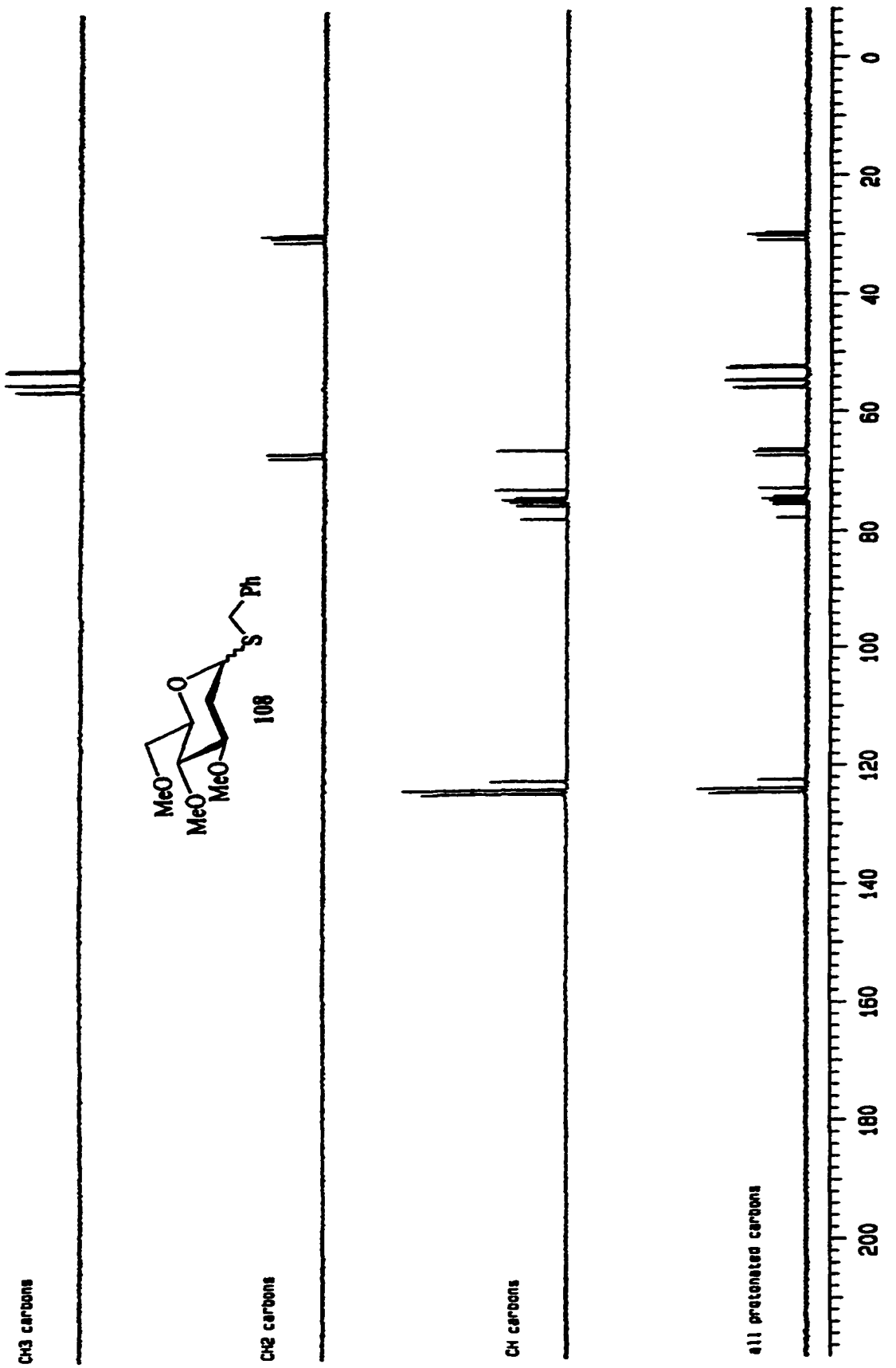
Table III. Bond Angles (°) for (99)

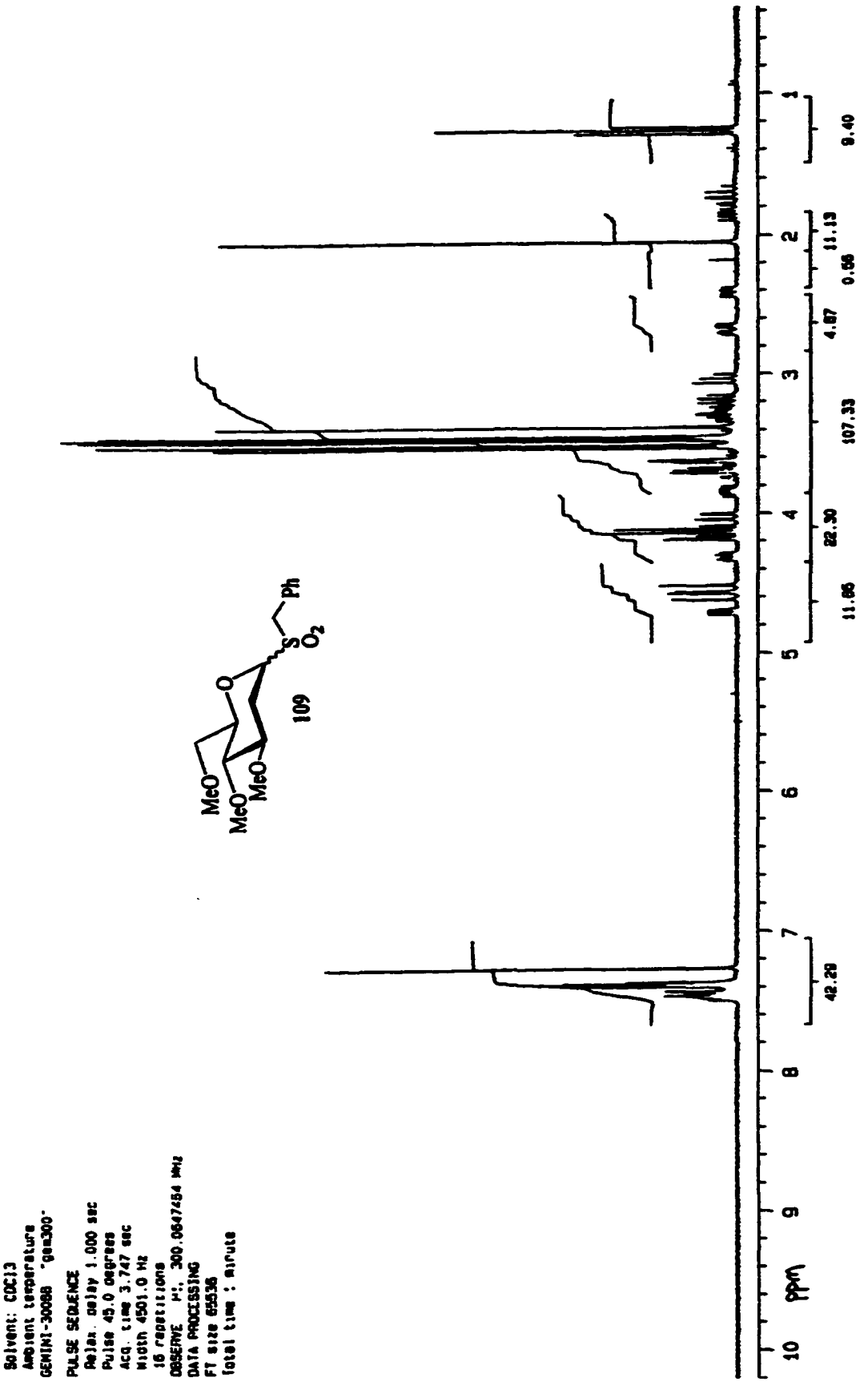
Atom 1	Atom 2	Atom 3	Angle	Atom 1	Atom 2	Atom 3	Angle
O2	P	C8	116.2(2)	O1	C6	C7	107.7(4)
O2	P	C21	112.6(2)	C5	C6	C7	110.3(4)
O2	P	C31	111.0(2)	O7	C7	C6	113.0(4)
C8	P	C21	109.7(2)	P	C8	C2	117.7(3)
C8	P	C31	103.4(2)	P	C21	C22	124.2(4)
C21	P	C31	102.7(2)	P	C21	C26	116.6(4)
C2	O1	C6	112.1(3)	C22	C21	C26	119.1(4)
C4	O4	C9	113.8(5)	C21	C22	C23	119.7(5)
C5	O5	C10	115.0(4)	C22	C23	C24	120.3(5)
C7	O7	C11	115.0(4)	C23	C24	C25	119.6(5)
O1	C2	C3	109.8(4)	C24	C25	C26	119.7(5)
O1	C2	C8	108.7(3)	C21	C26	C25	121.6(5)
C3	C2	C8	108.7(4)	P	C31	C32	122.6(4)
C2	C3	C4	110.6(4)	P	C31	C36	119.0(5)
O4	C4	C3	109.4(4)	C32	C31	C36	118.4(5)
O4	C4	C5	106.2(4)	C31	C32	C33	120.2(6)
C3	C4	C5	111.2(4)	C32	C33	C34	121.3(7)
O5	C5	C4	109.8(3)	C33	C34	C35	119.2(6)
O5	C5	C6	107.6(4)	C34	C35	C36	119.9(7)
C4	C5	C6	110.0(4)	C31	C36	C35	120.9(7)
O1	C6	C5	109.2(4)				

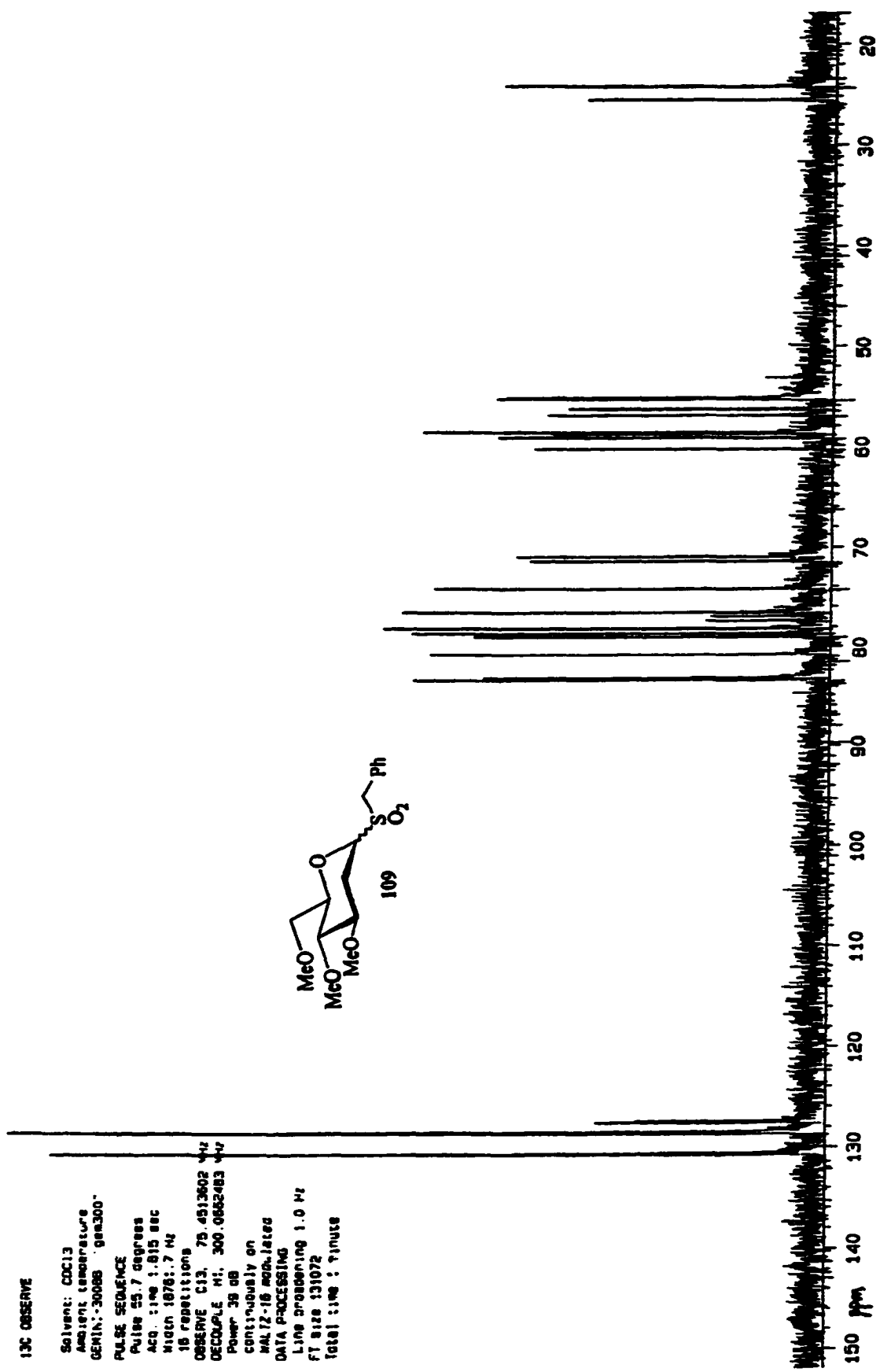
Standard deviations are in parentheses.

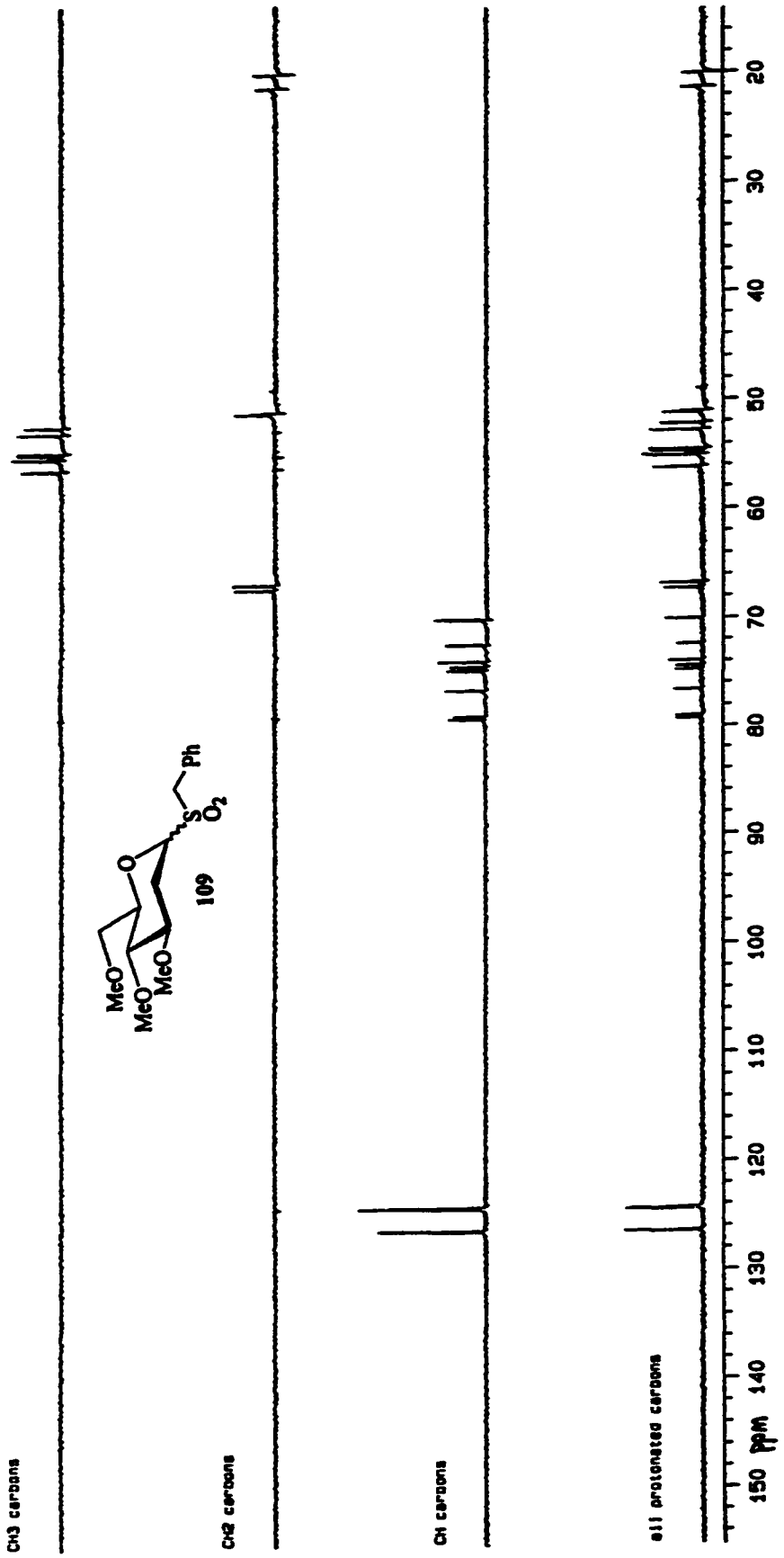


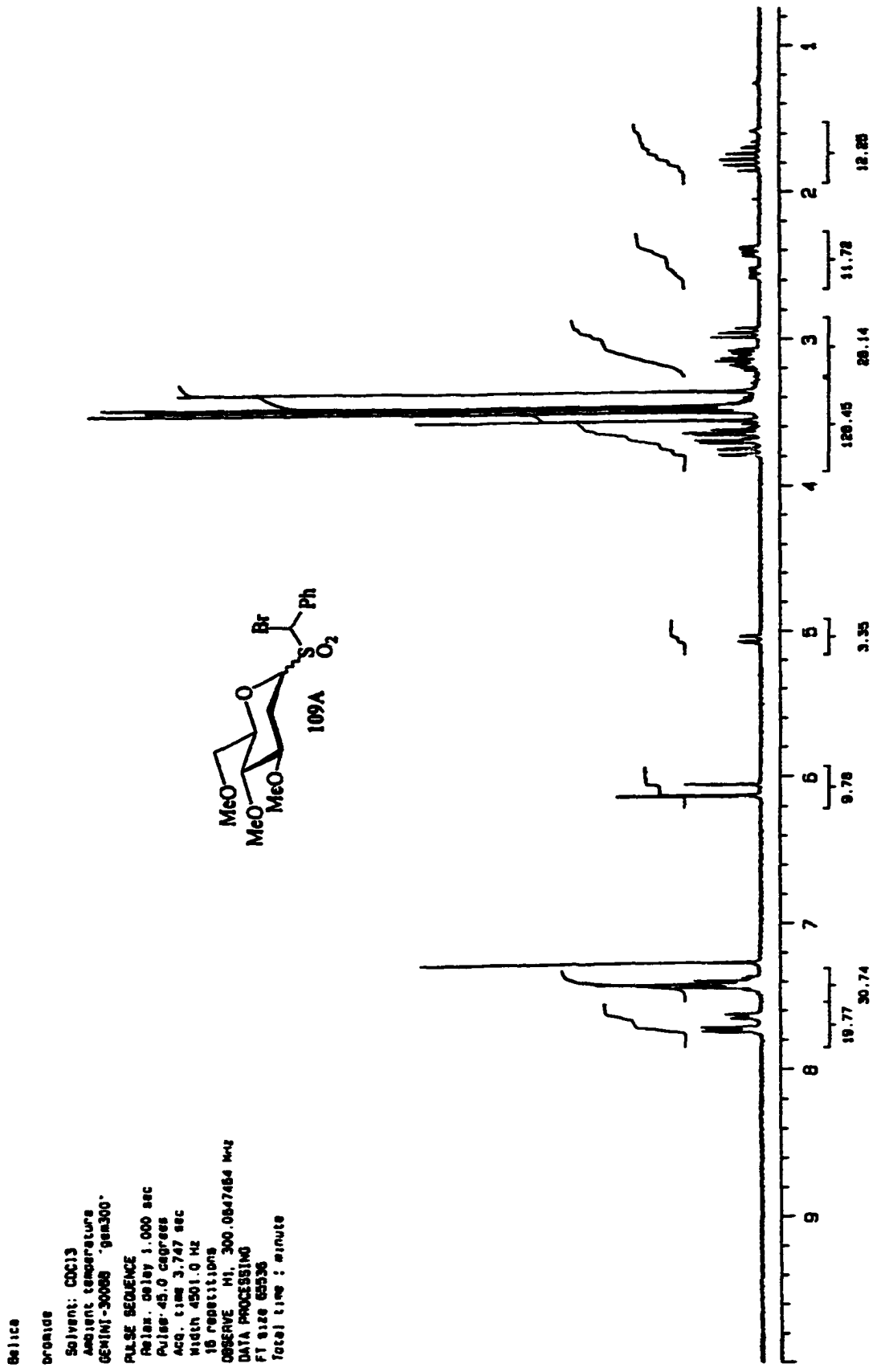


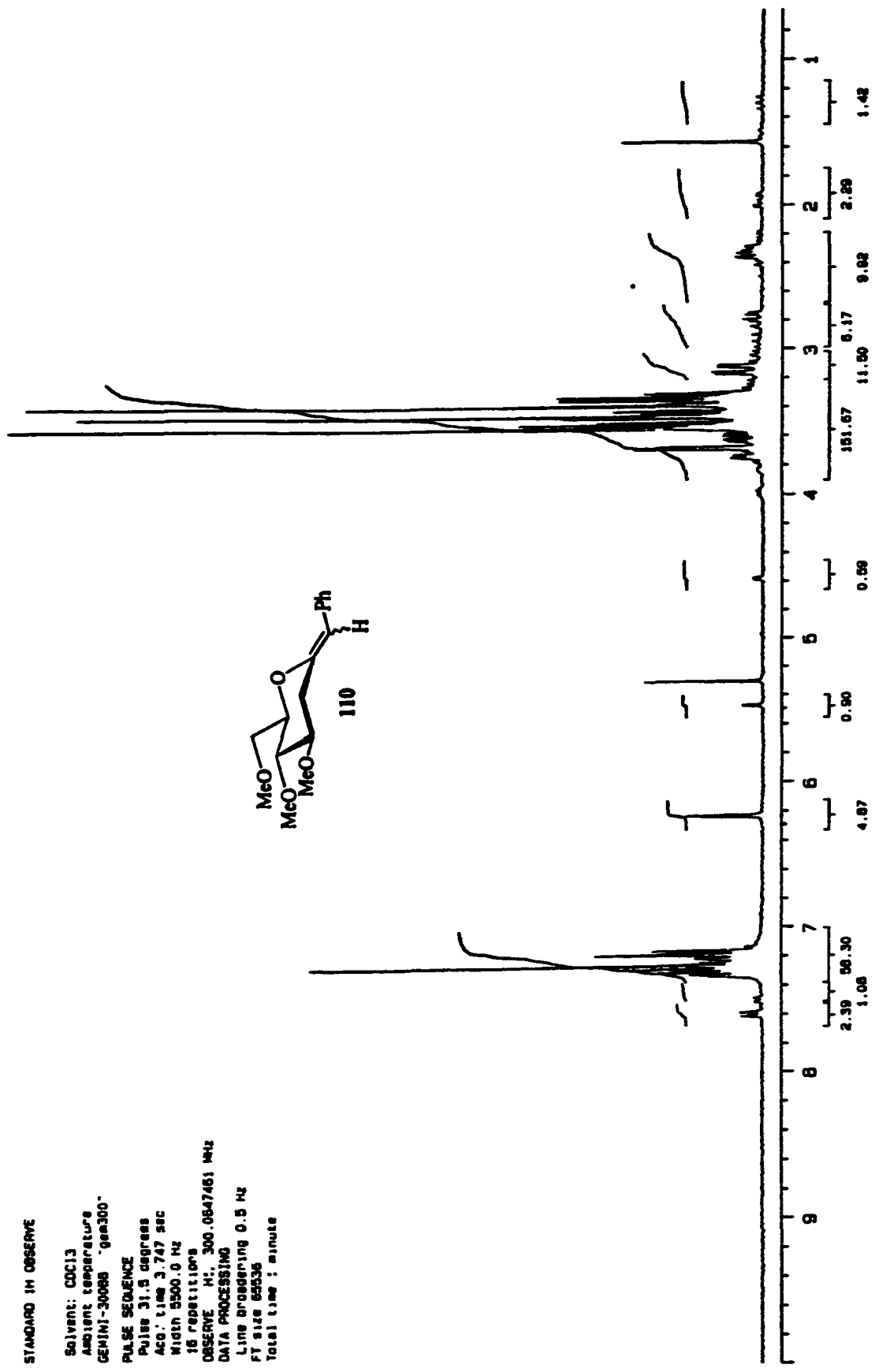


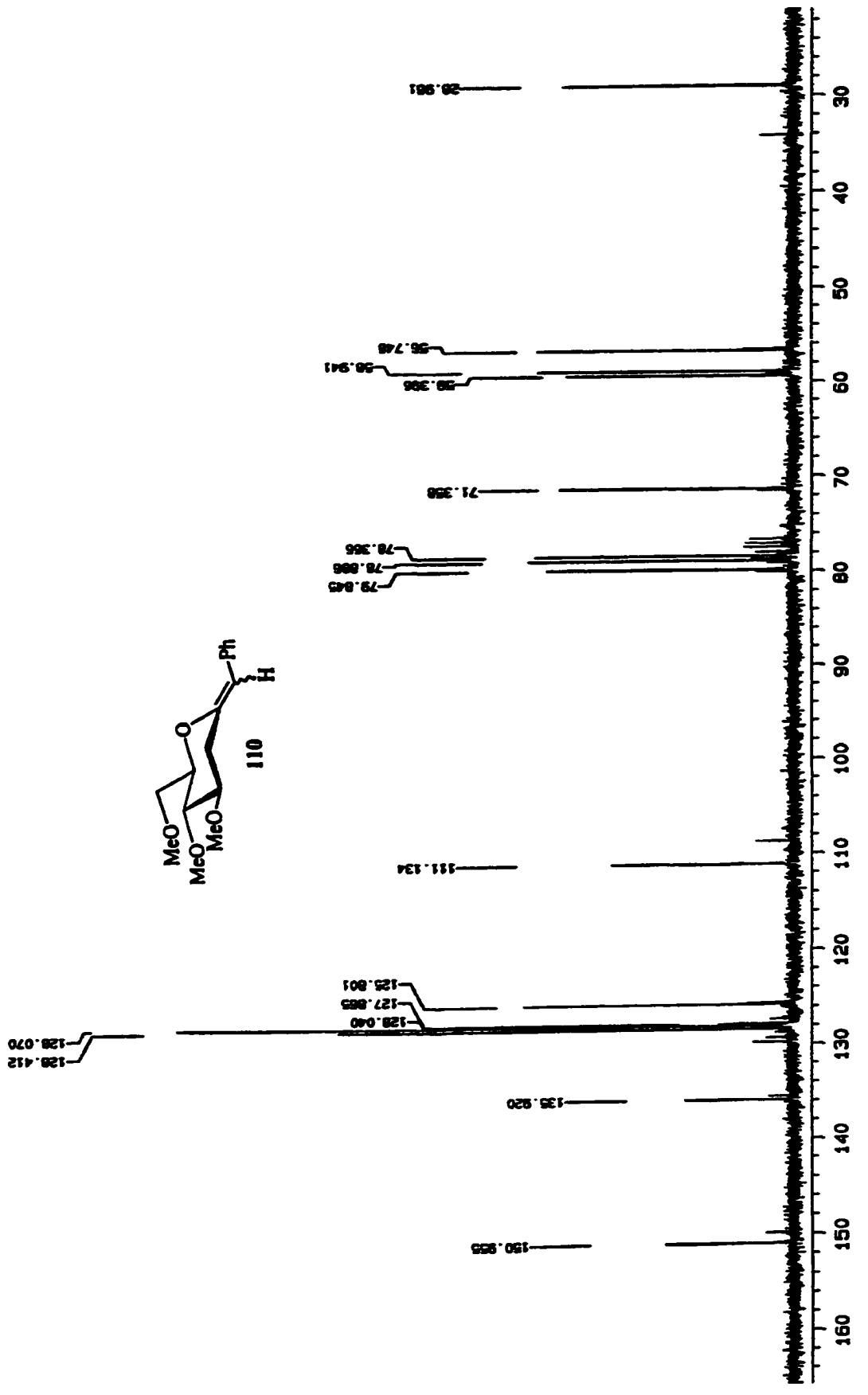


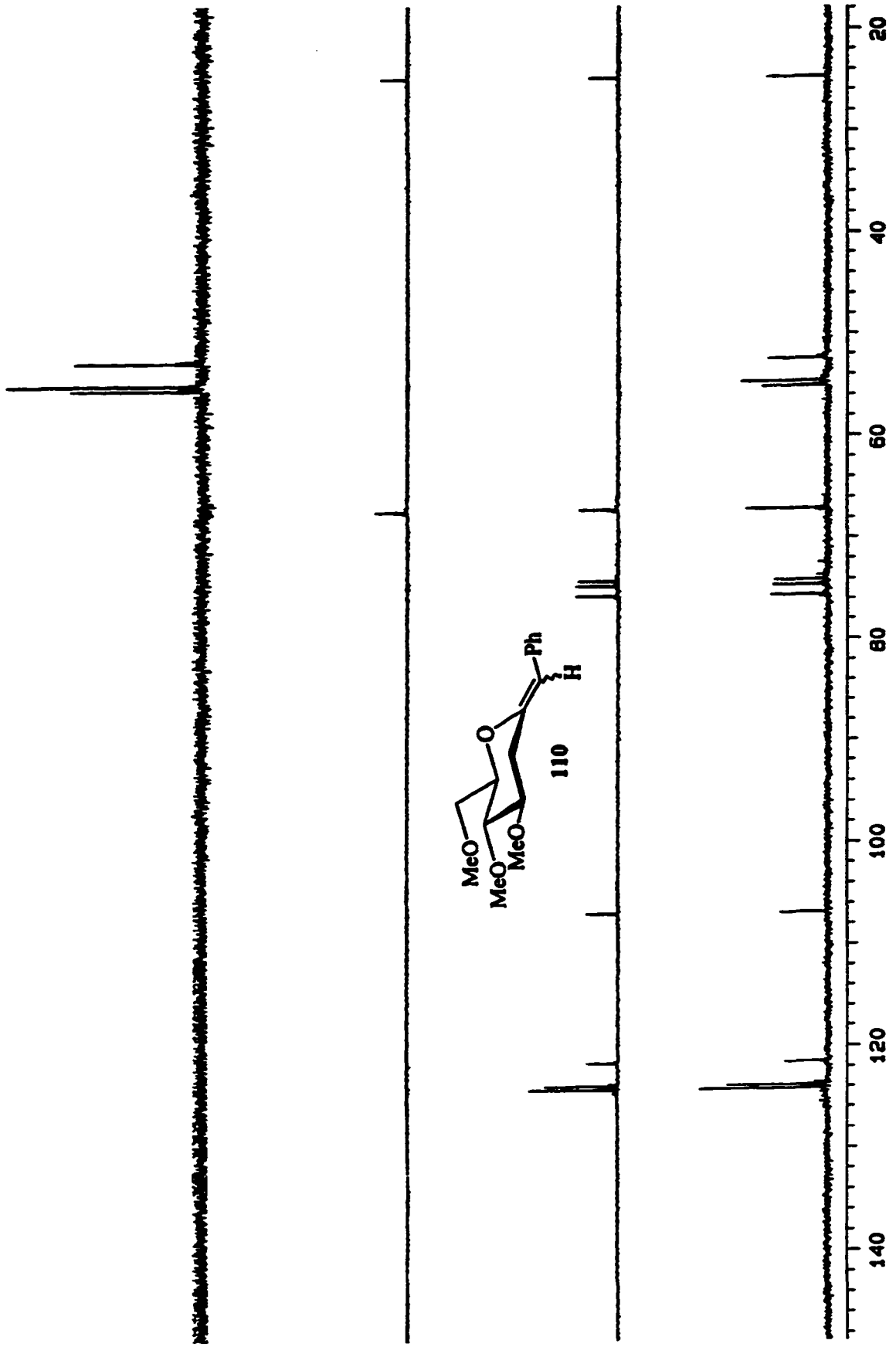


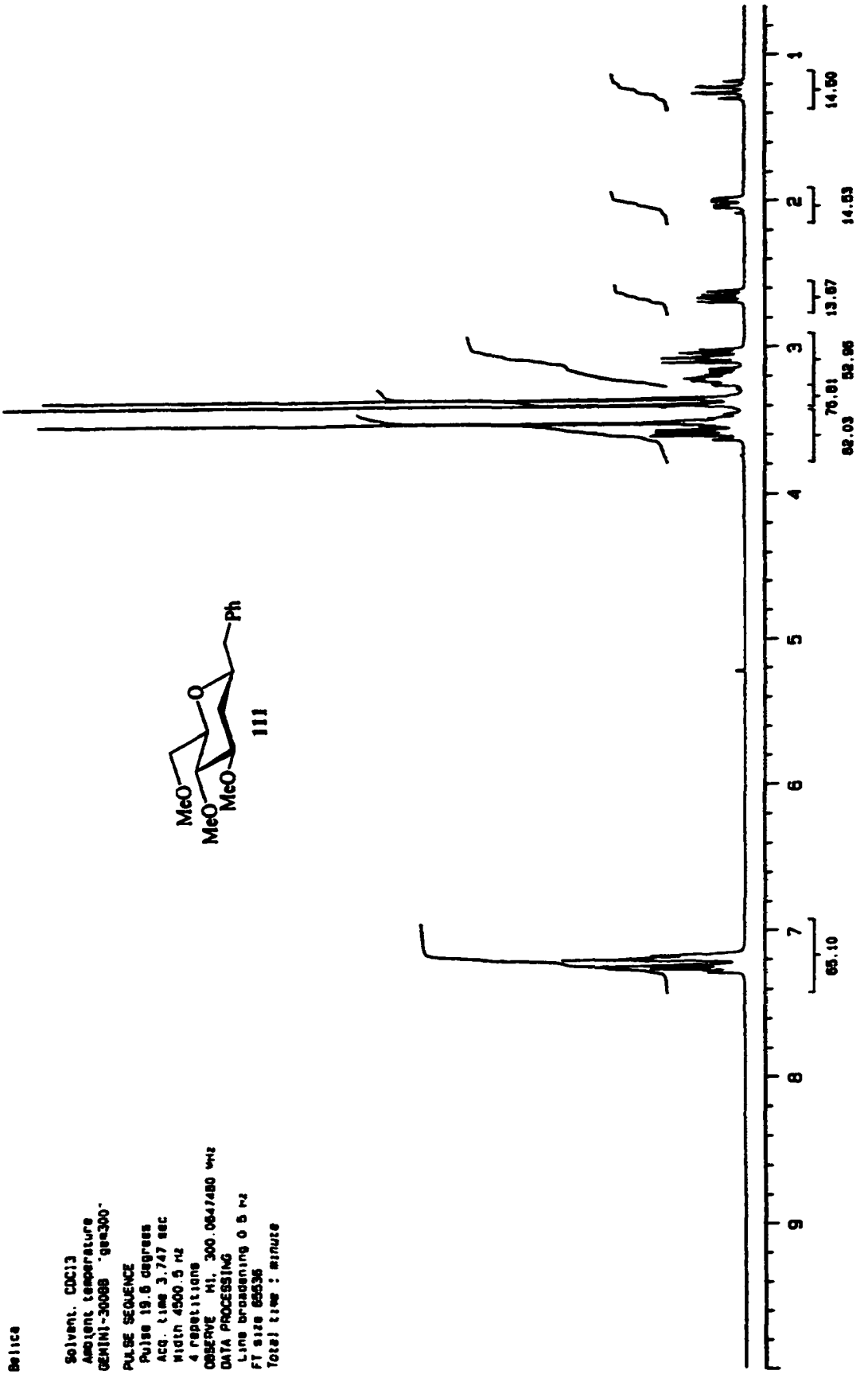


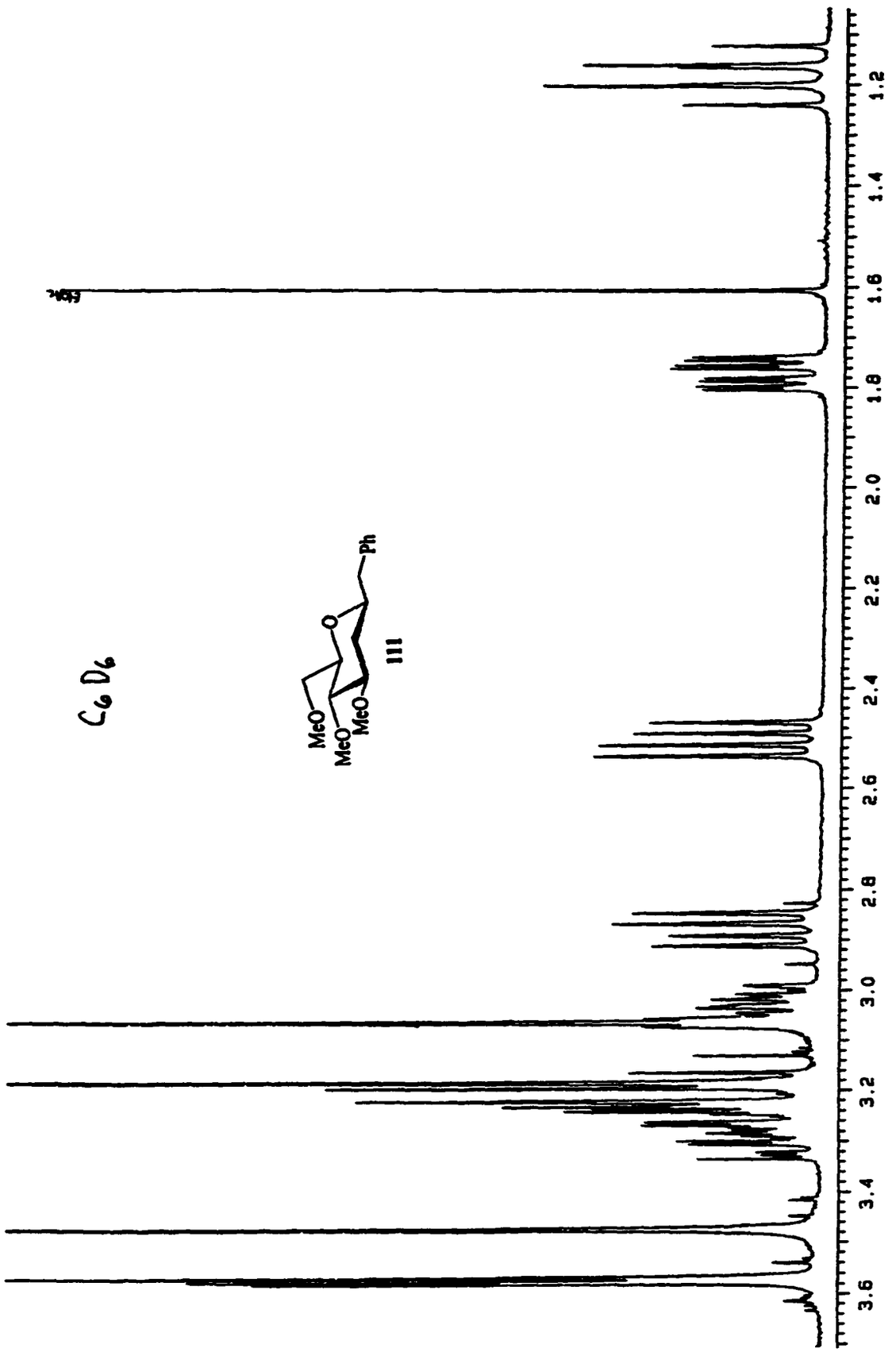


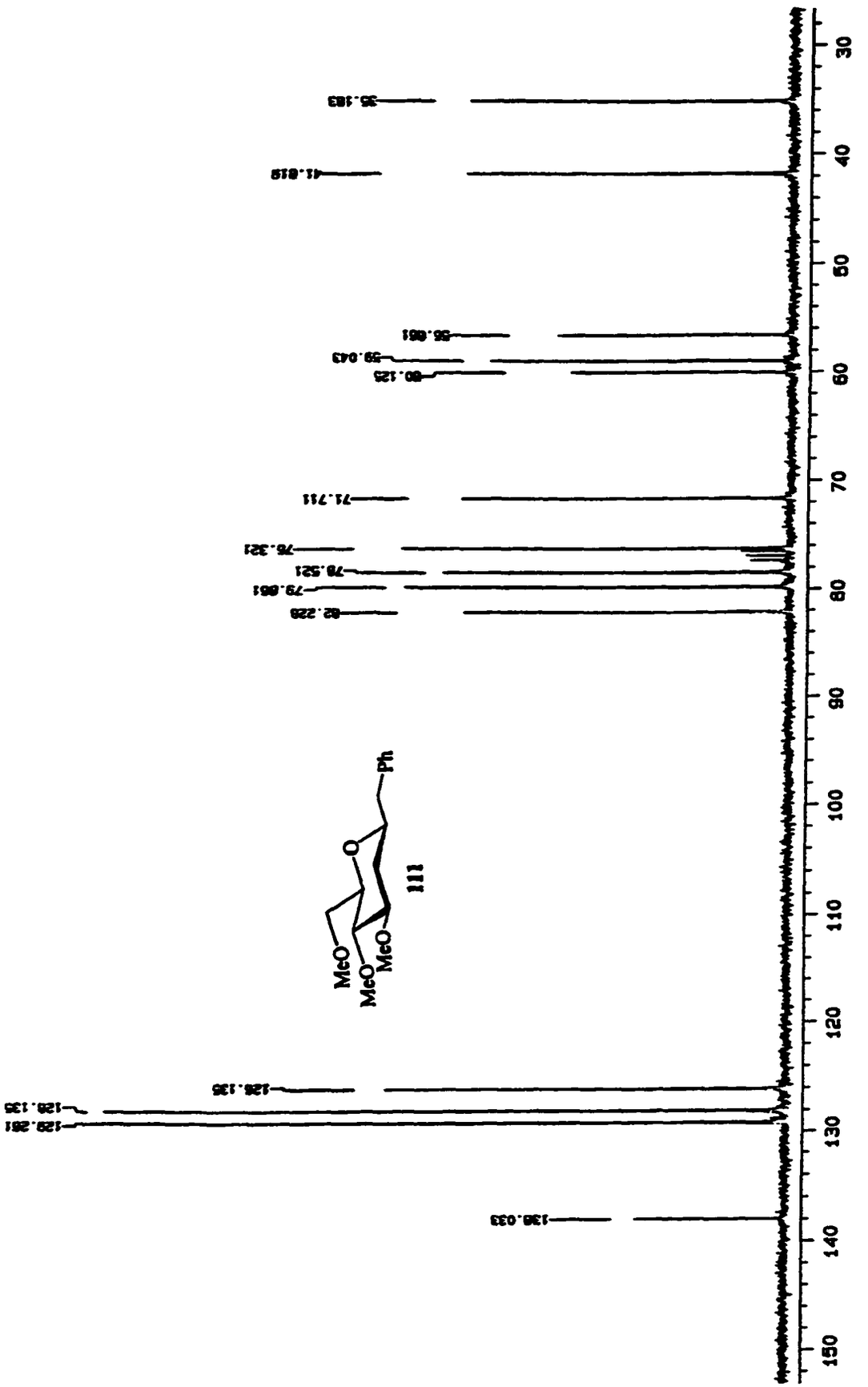


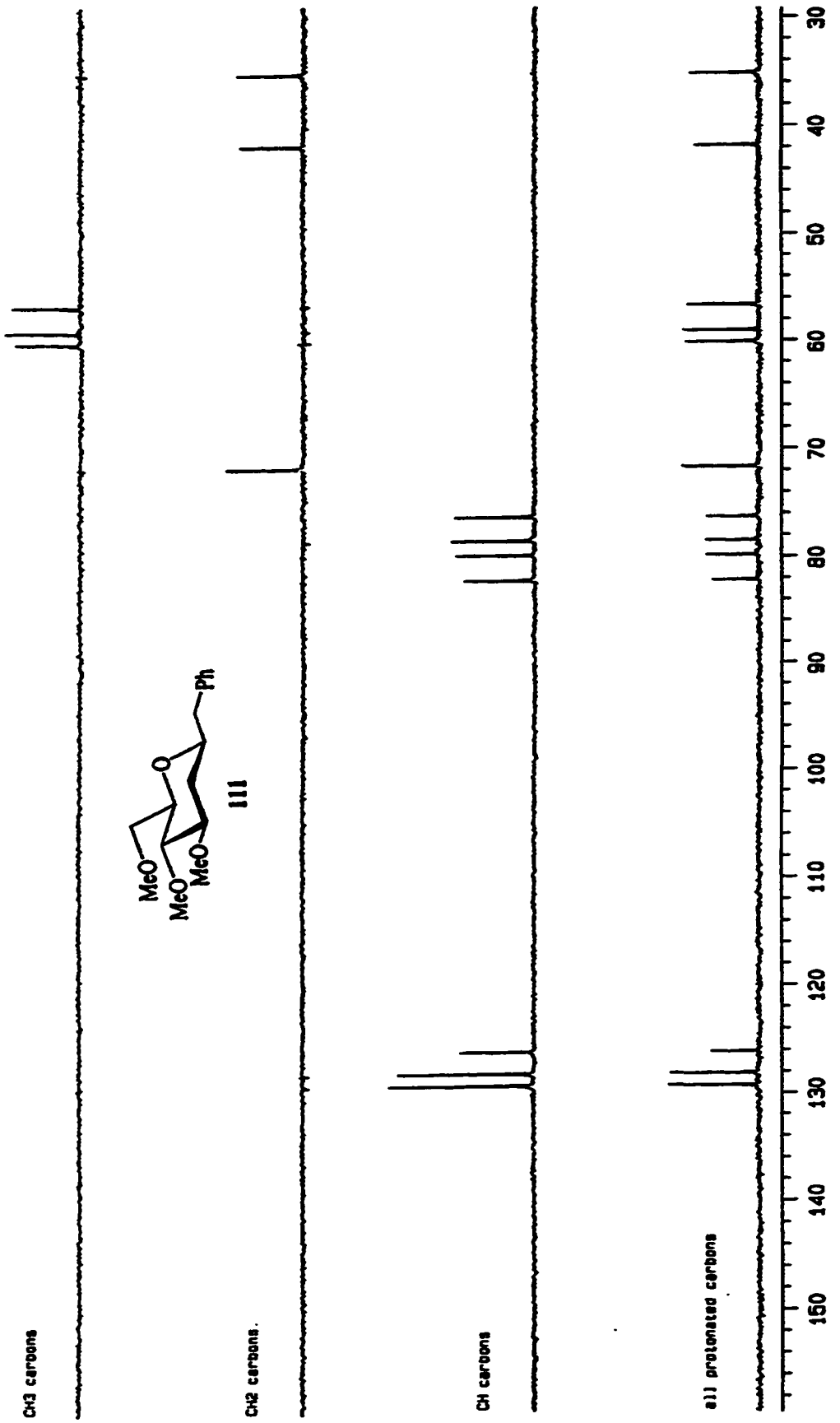


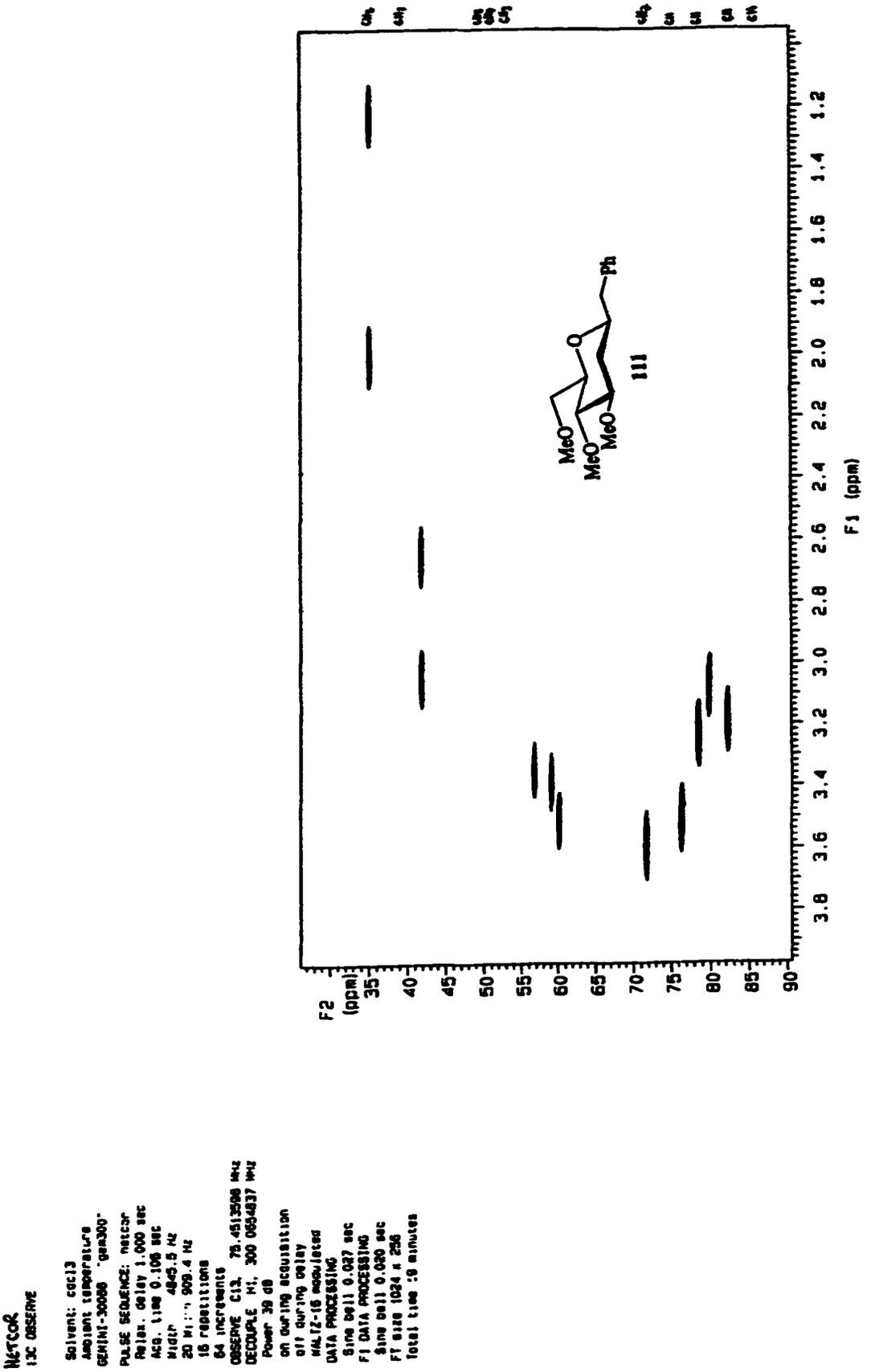






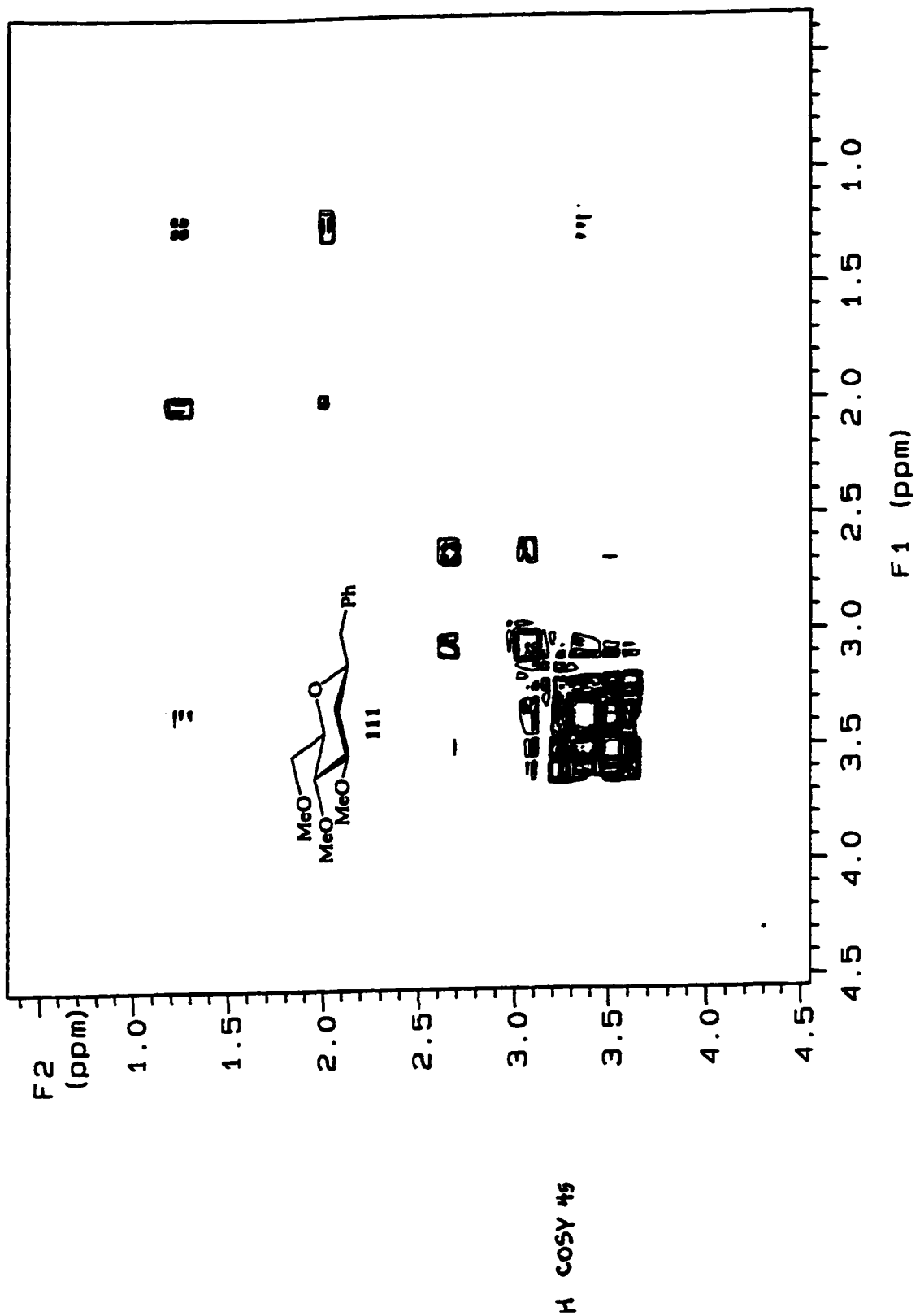


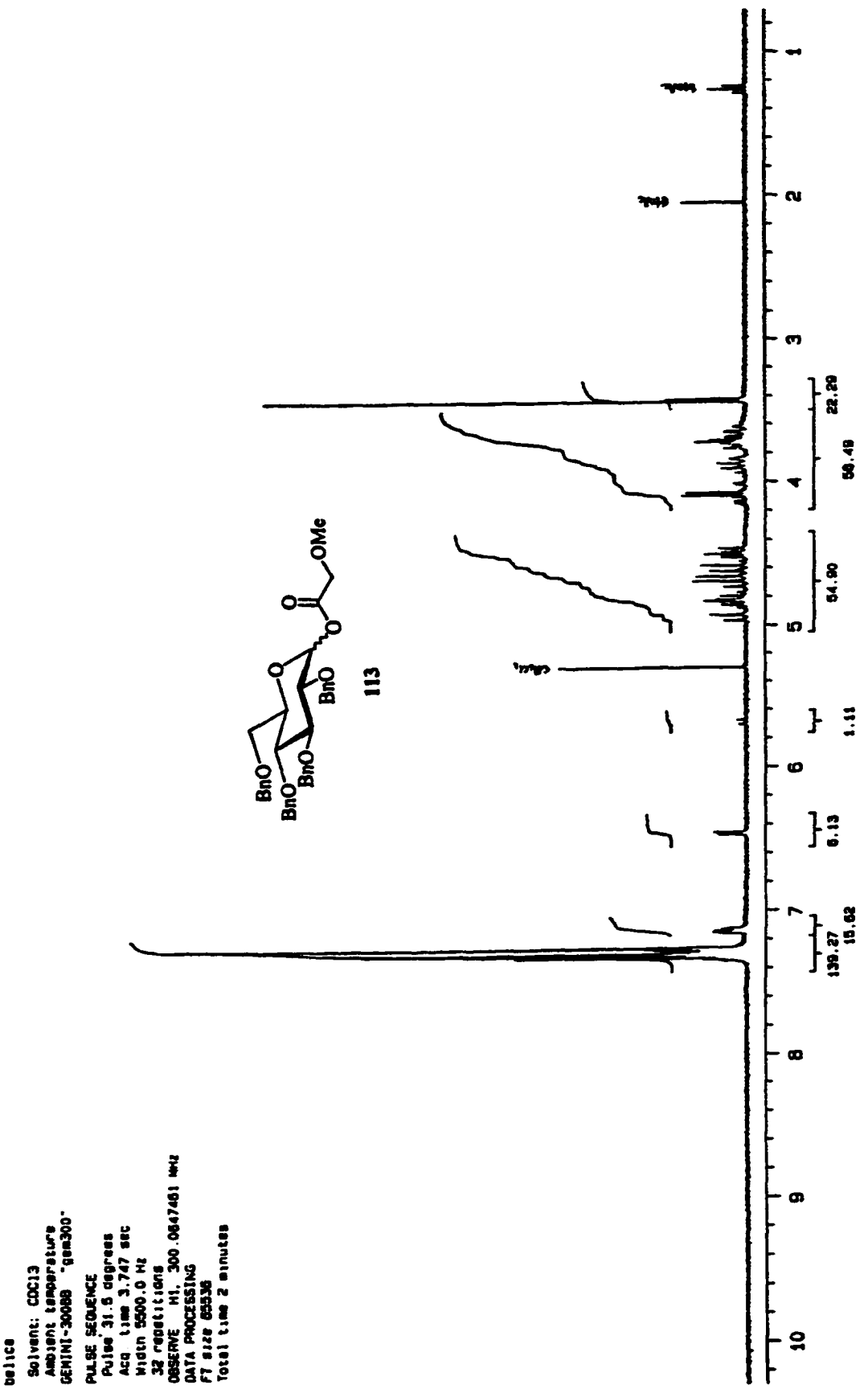


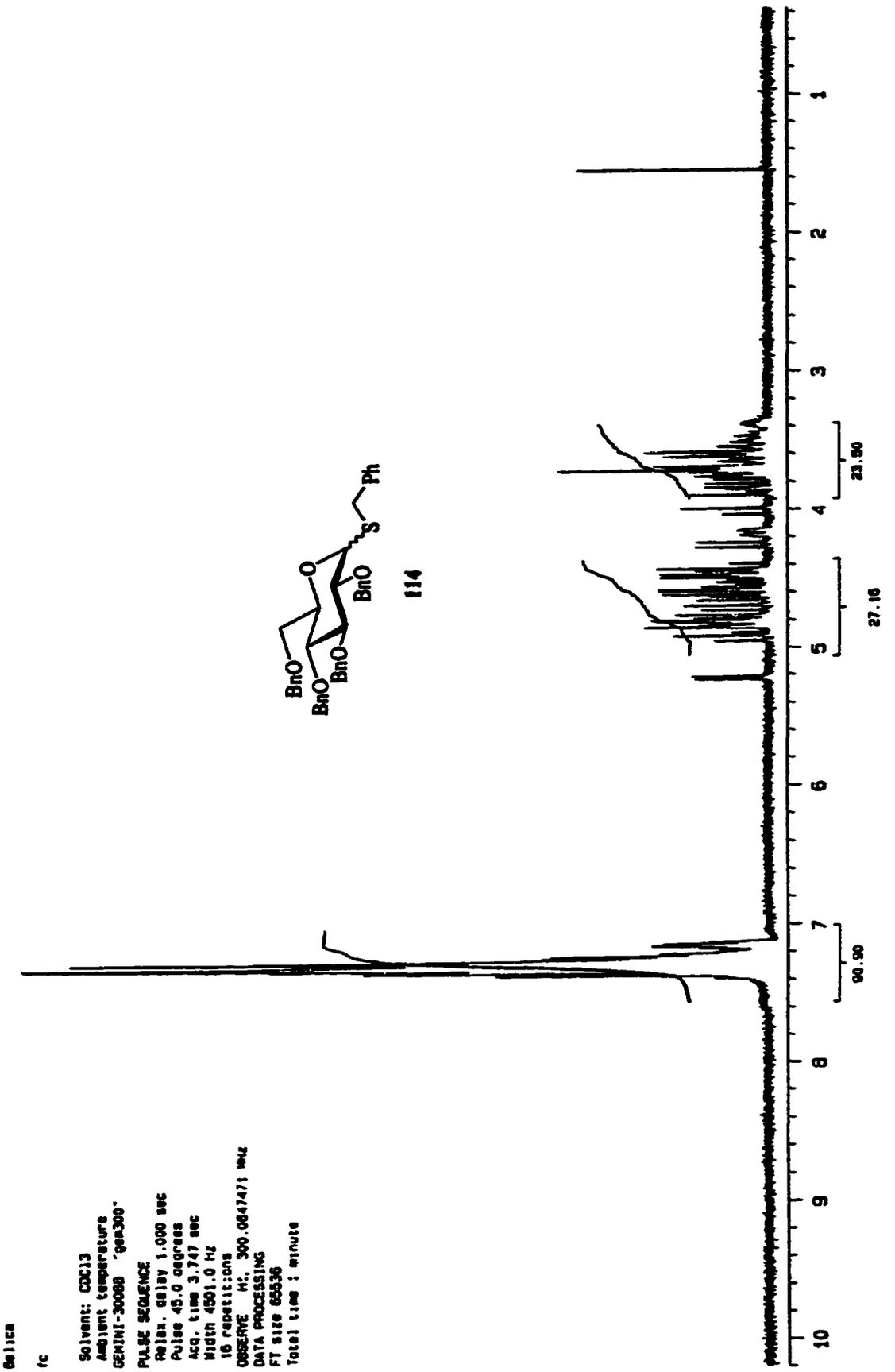


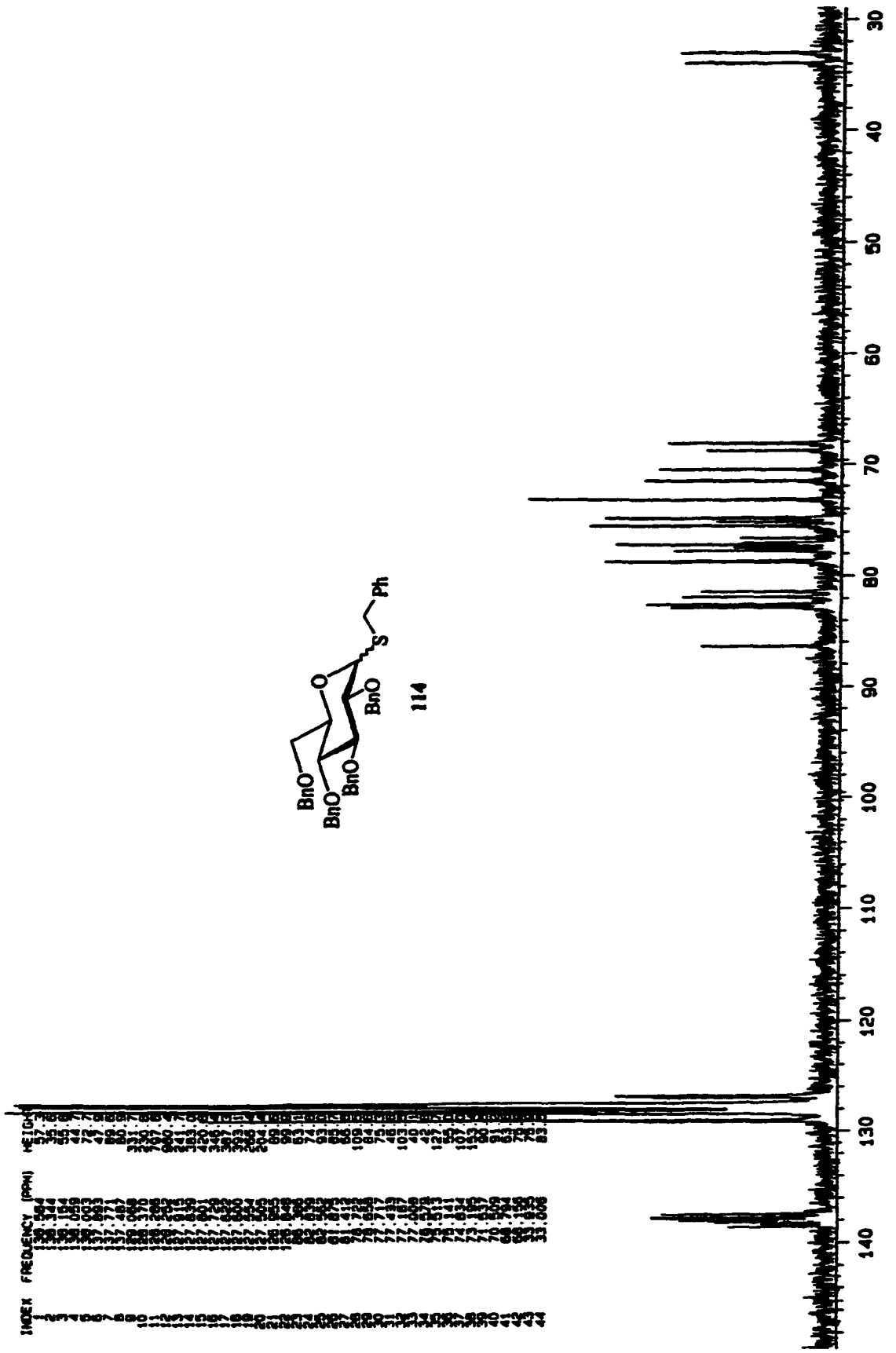
Nercor
13C OBSERVE

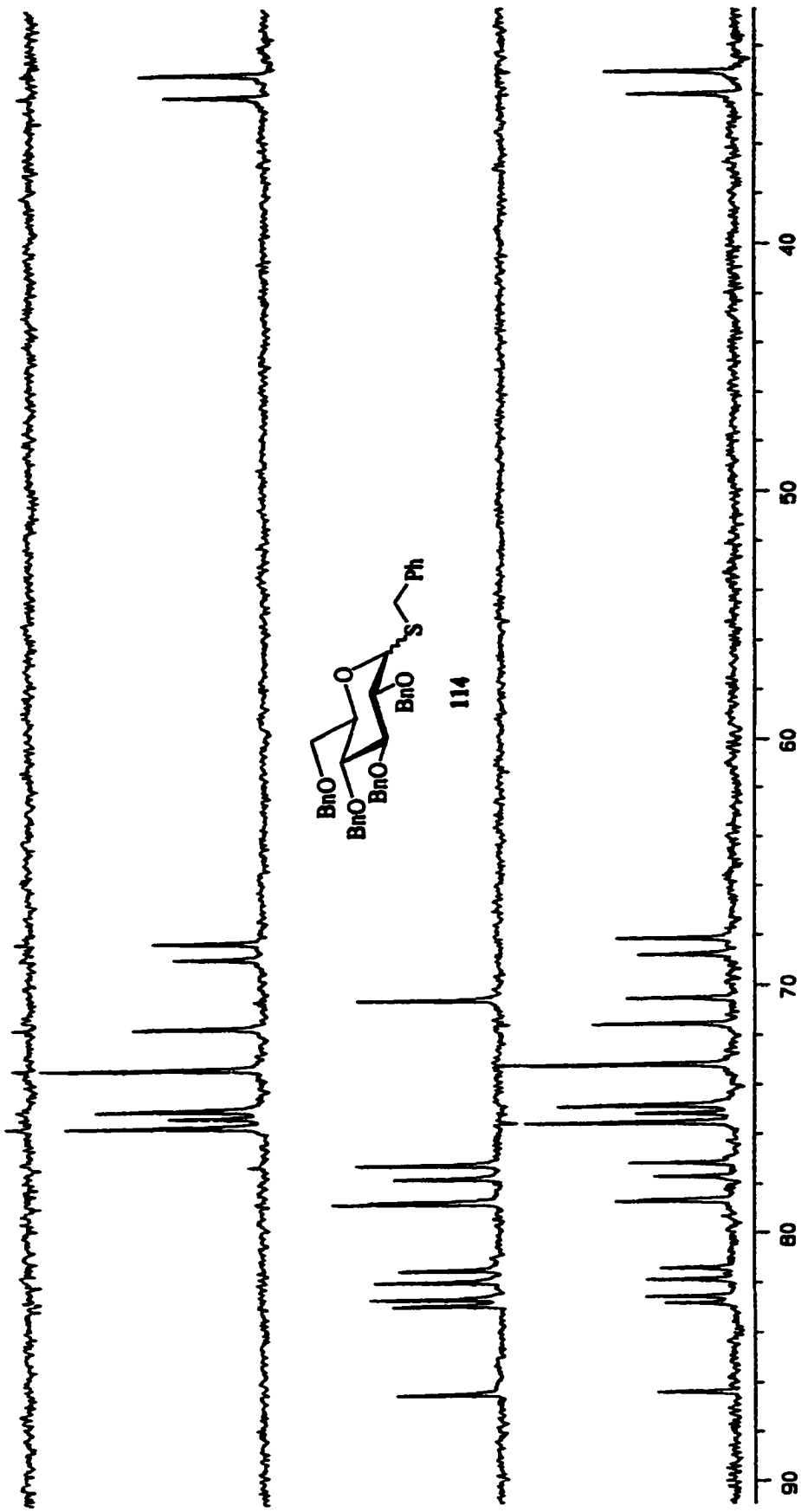
Solvent: cdcl3
Ambient temperature
GEMINI-300BB "gem300"
PULSE SEQUENCE: nercor
Relax. delay 1.000 sec
Acq. time 0.106 sec
Width 4845.5 Hz
20 Hz
16 repetitions
64 increments
OBSERVE C13, 75.4513598 MHz
DECOUPLE H1, 300.0664837 MHz
Power 39 dB
on during acquisition
off during delay
WALTZ-16 modulated
DATA PROCESSING
Sine bell 0.027 sec
F1 DATA PROCESSING
Sine bell 0.020 sec
FT size 1024 x 256
Total time 19 minutes

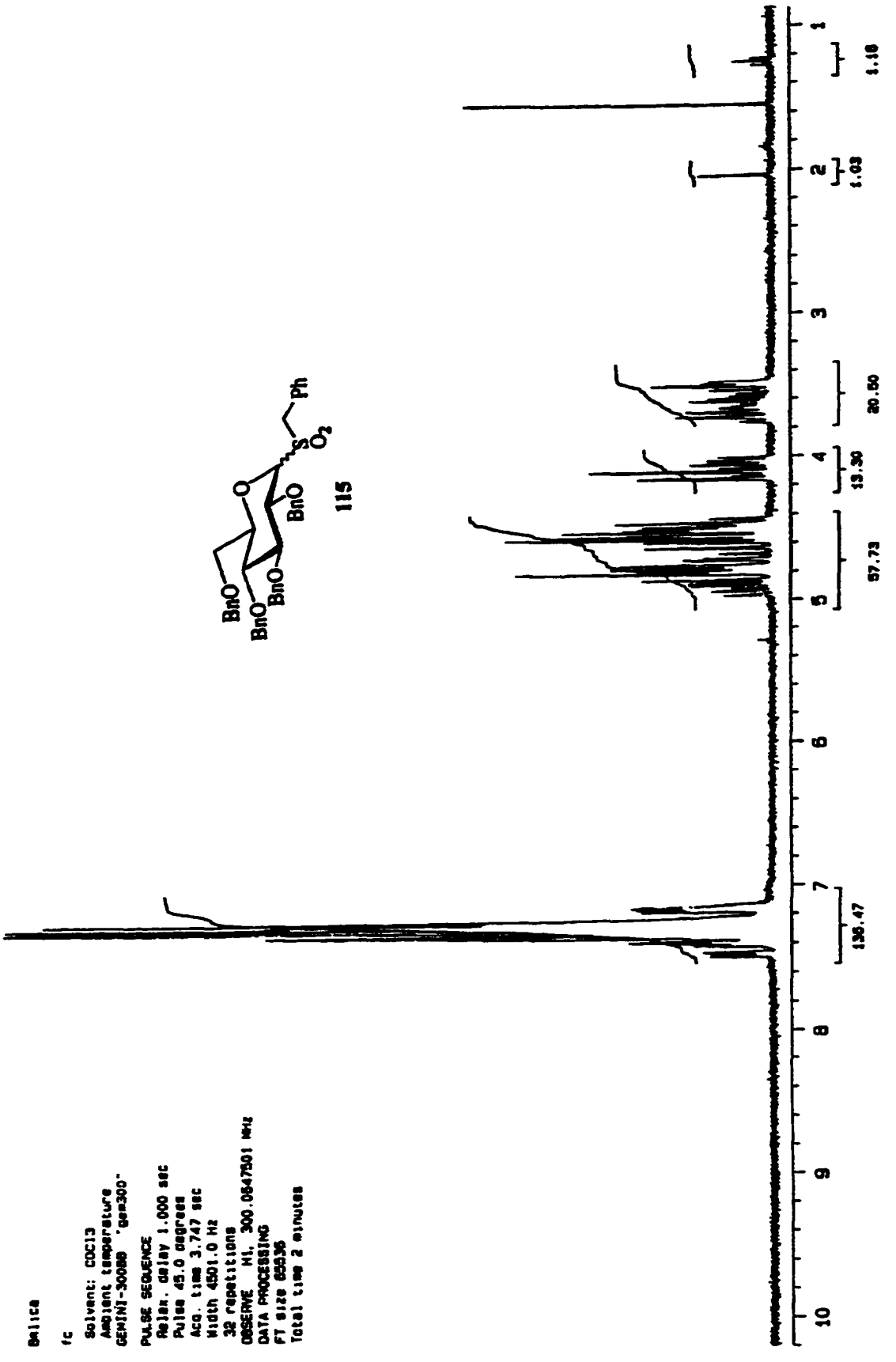


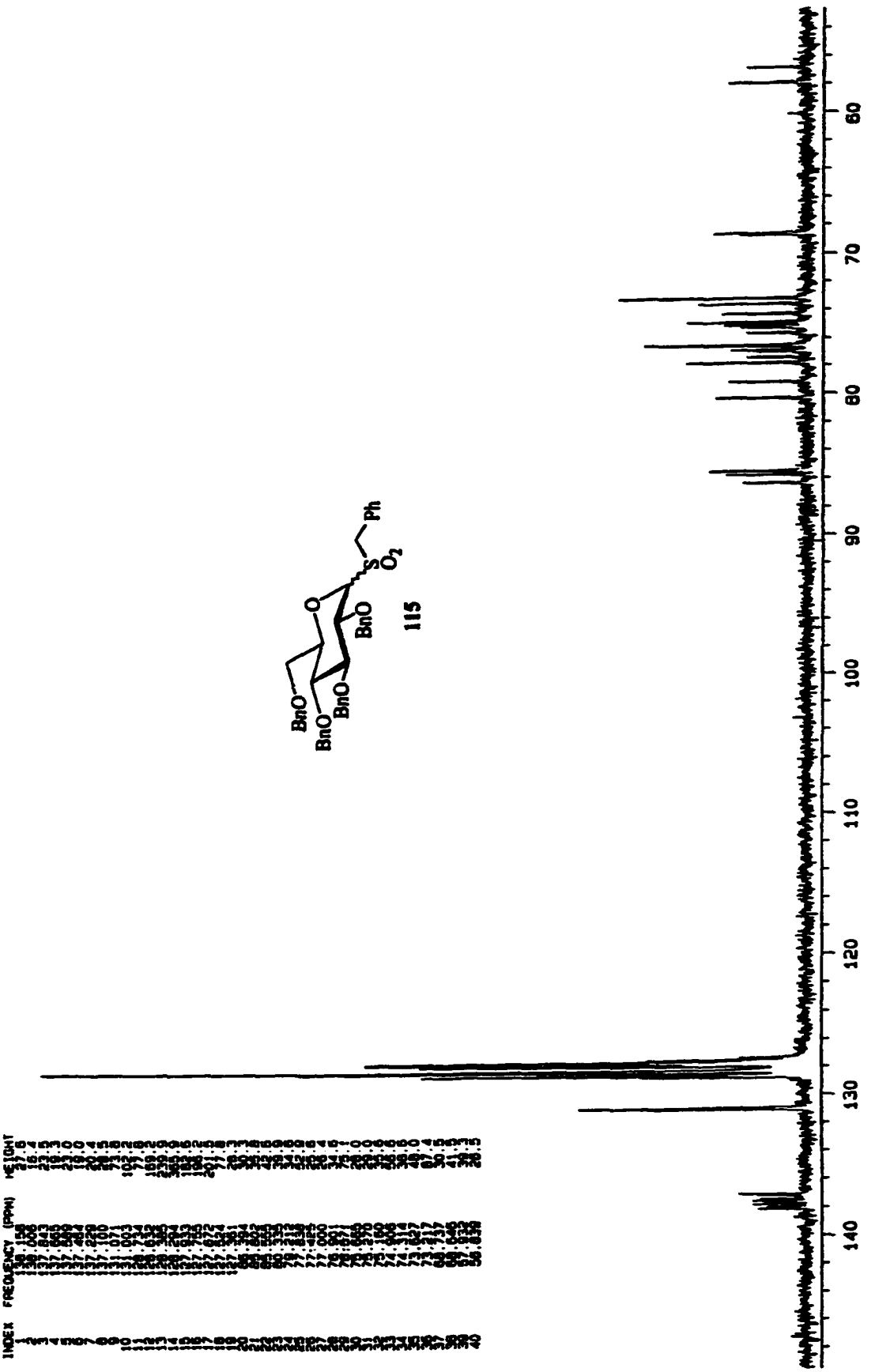


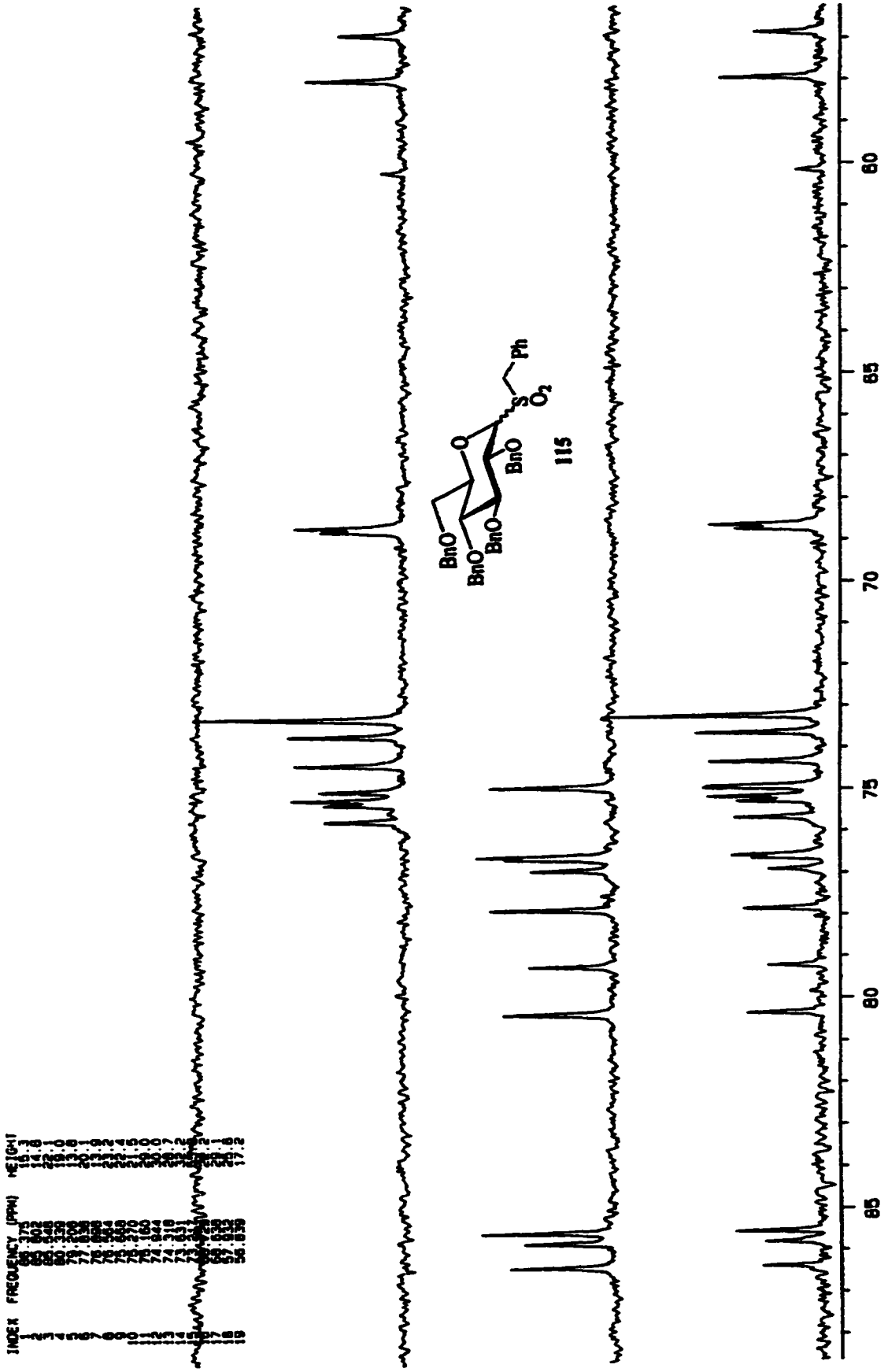


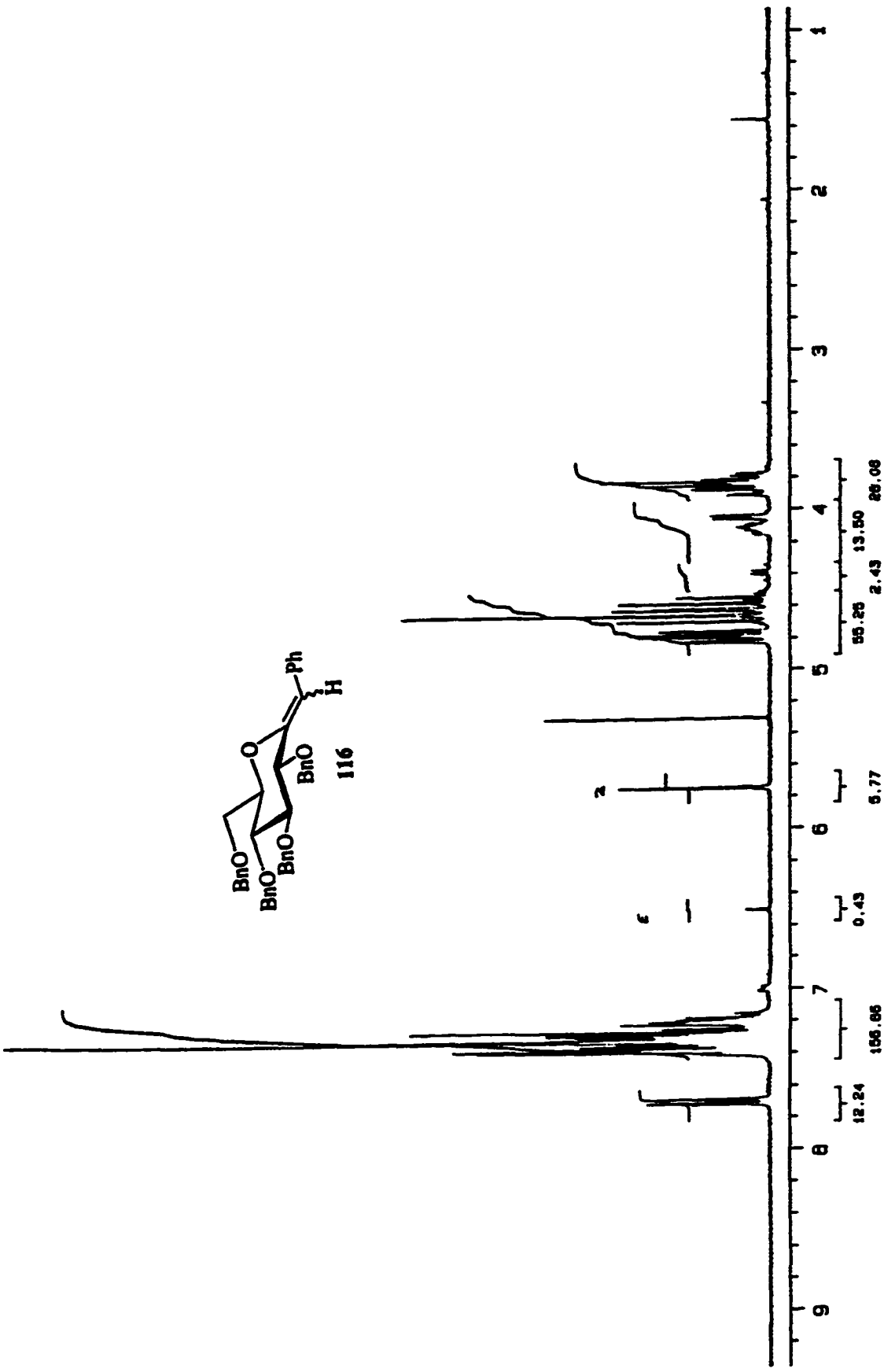


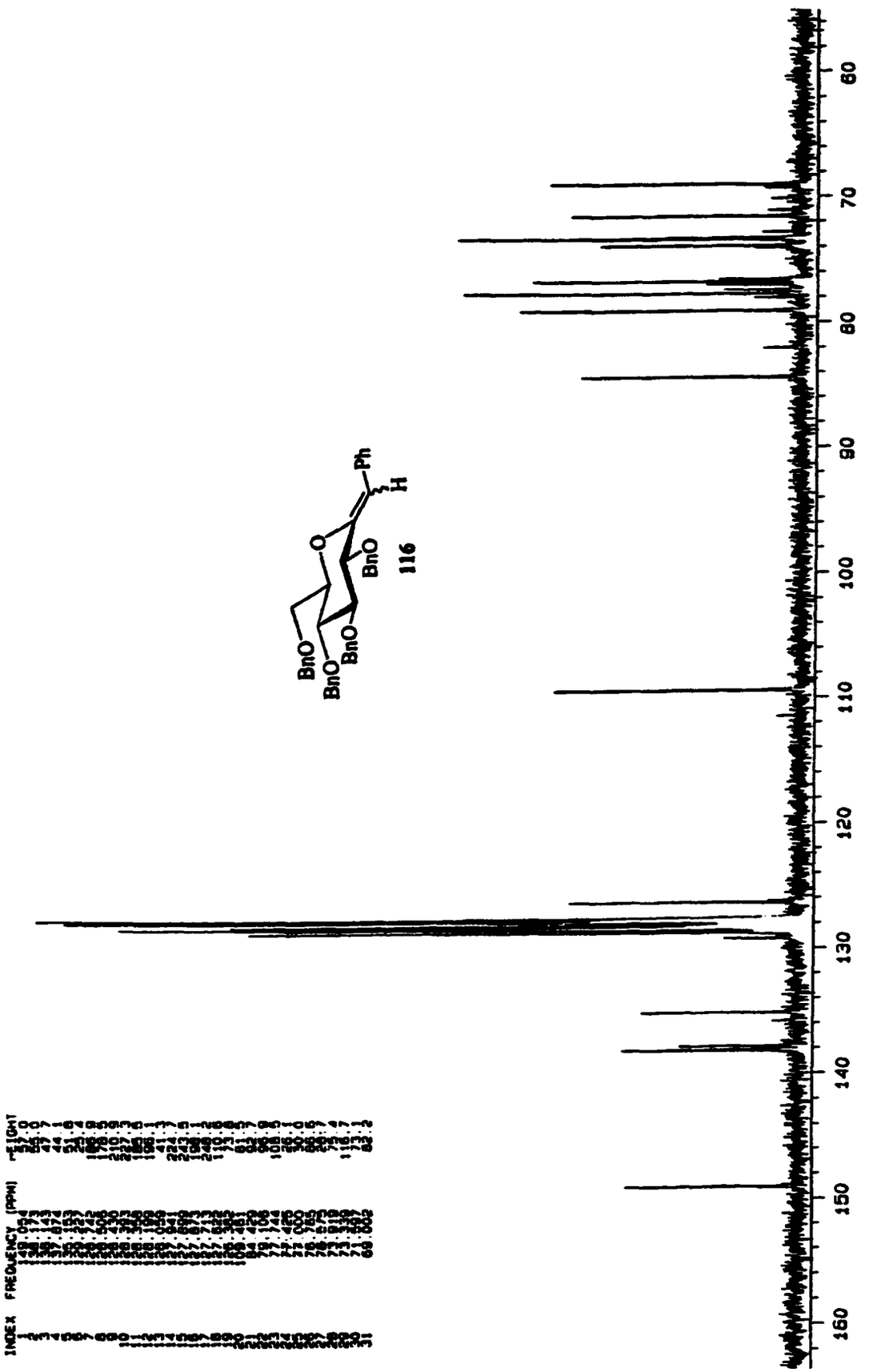


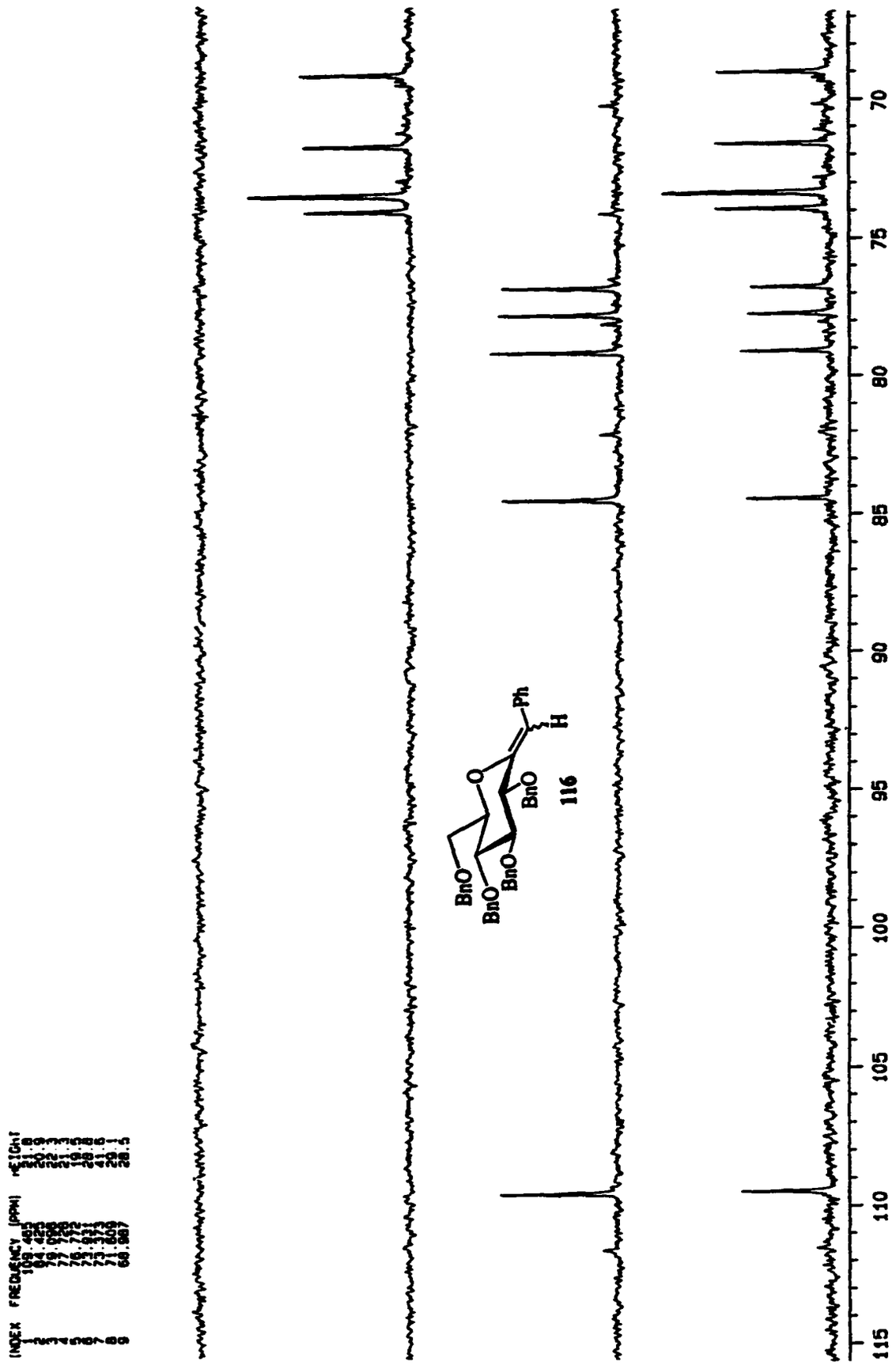


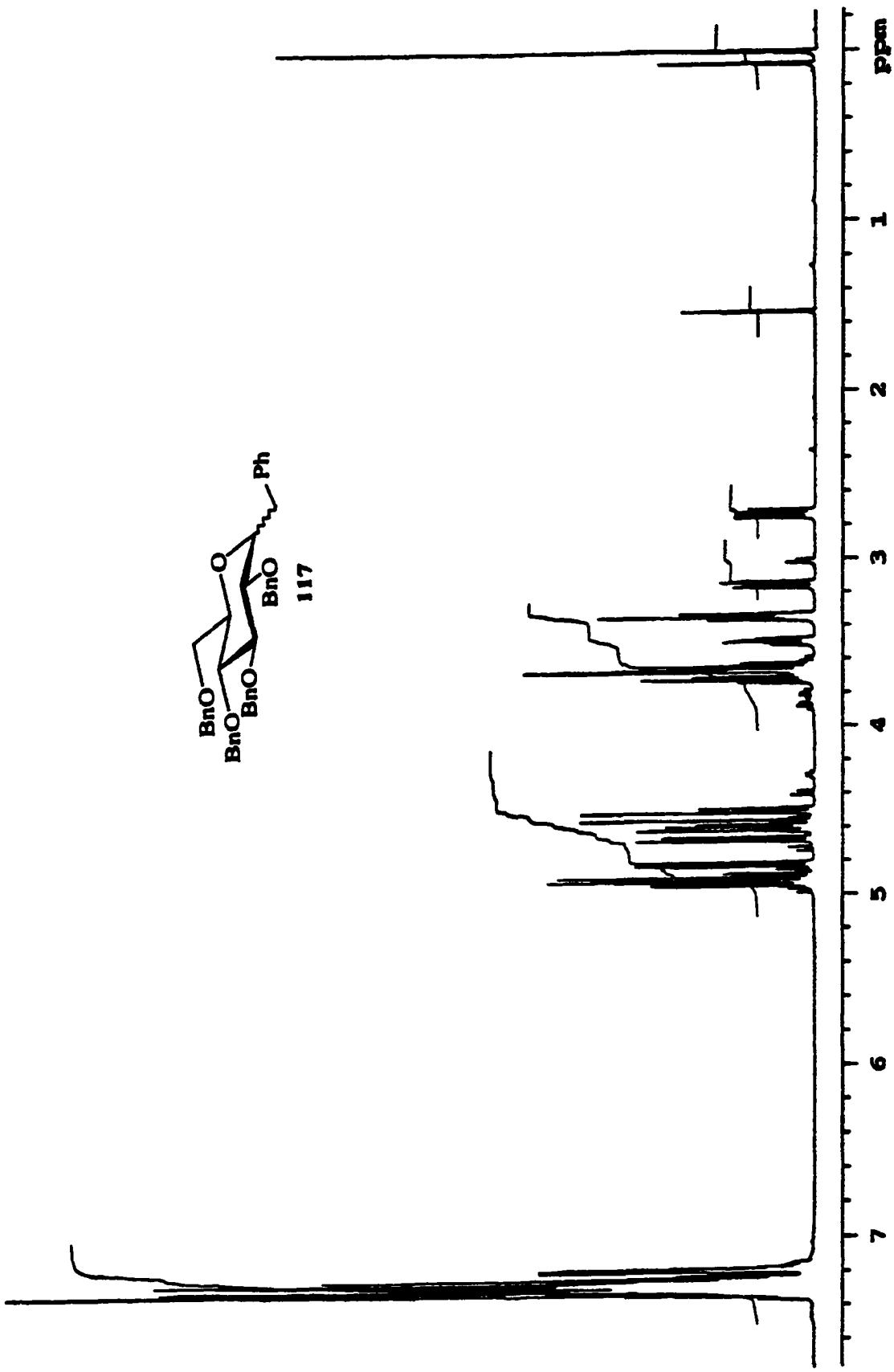


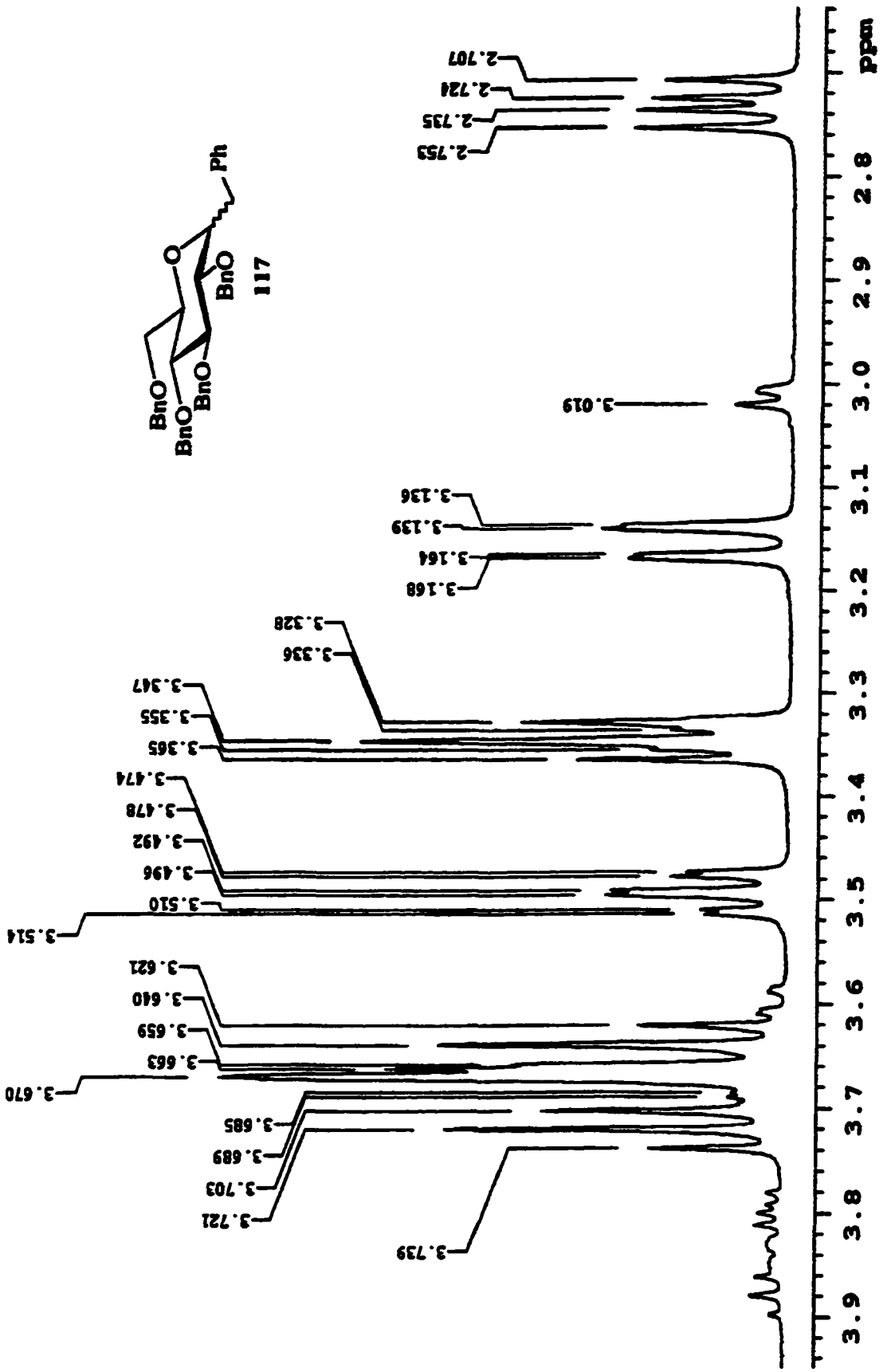


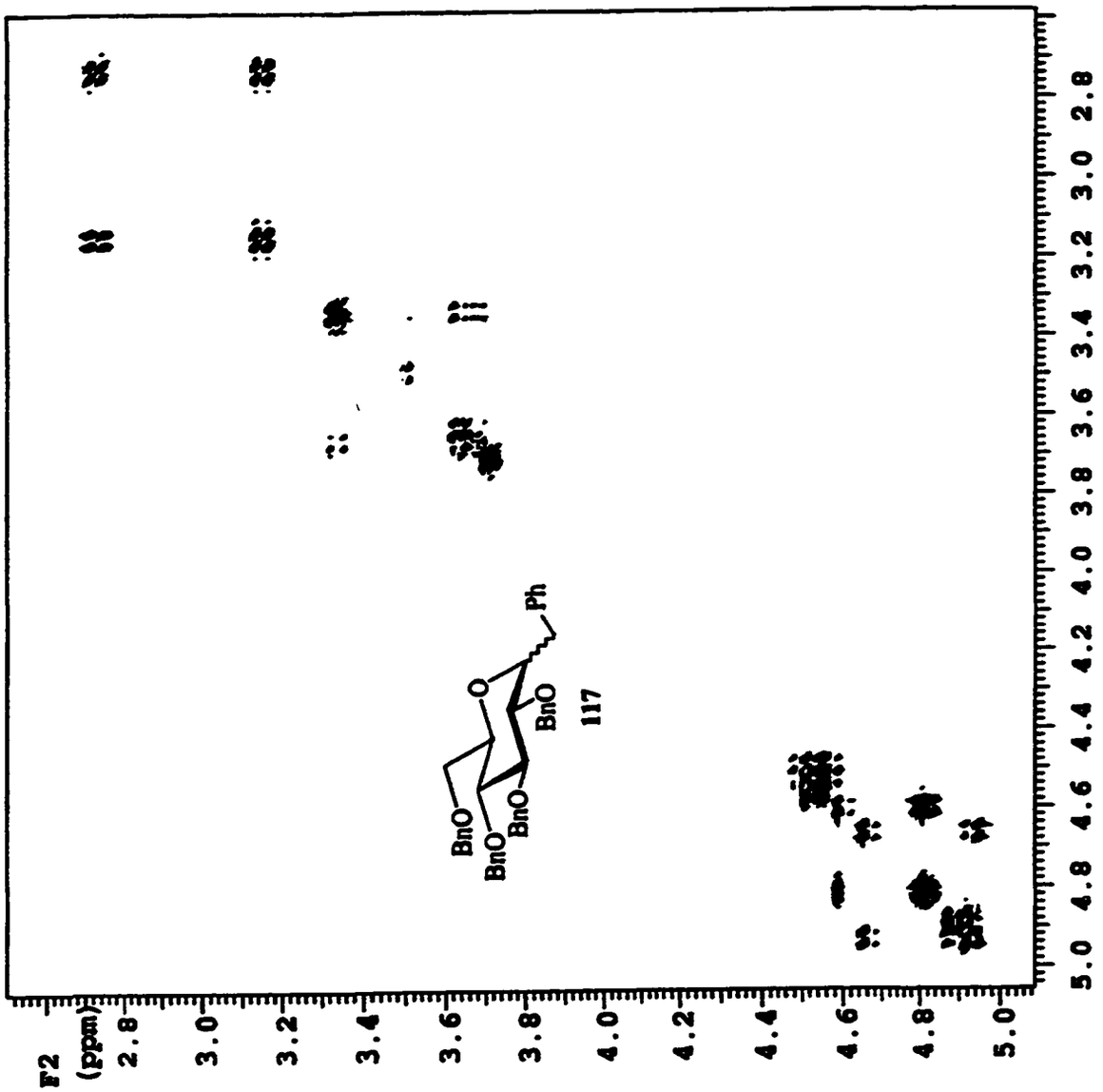


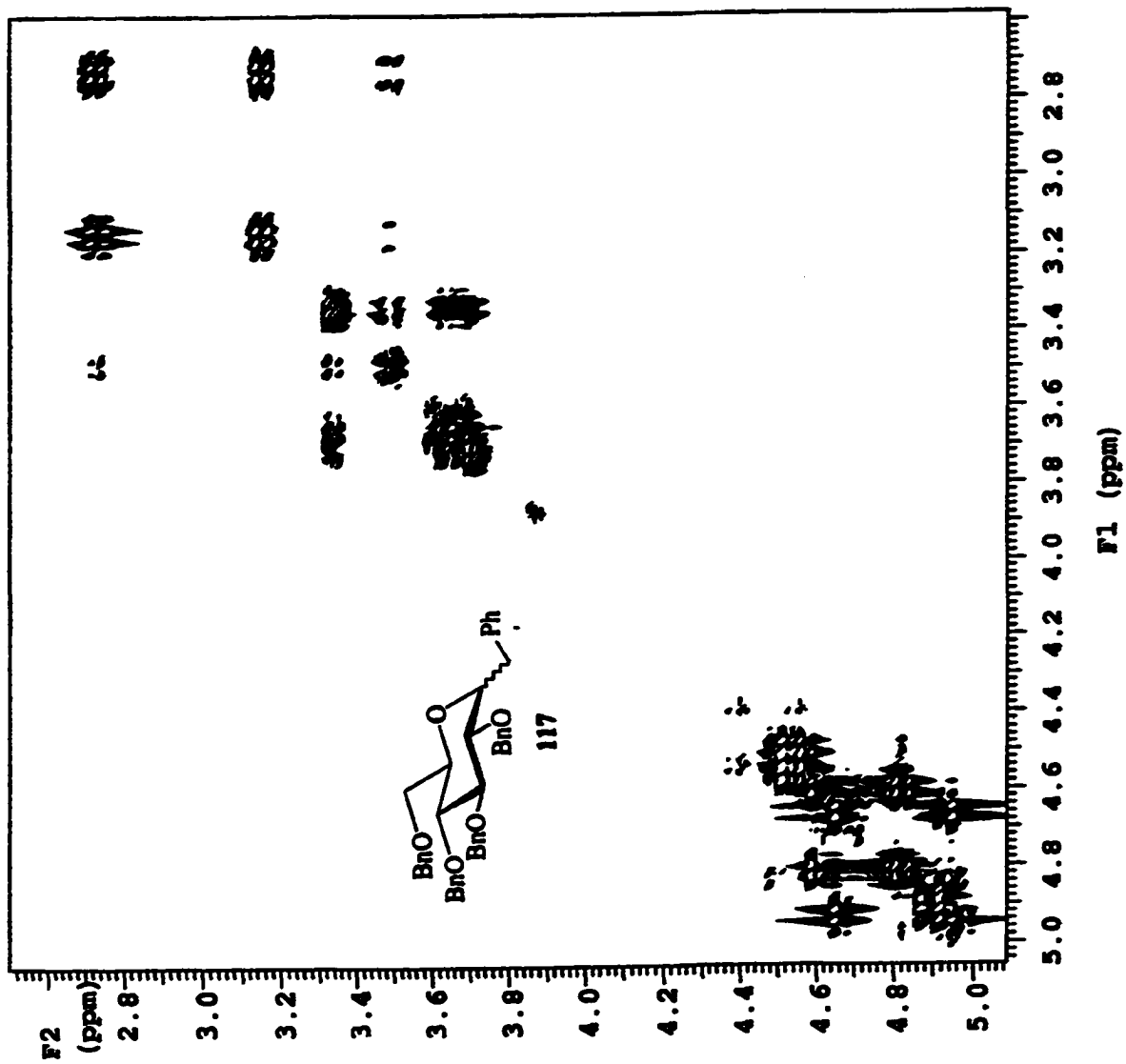


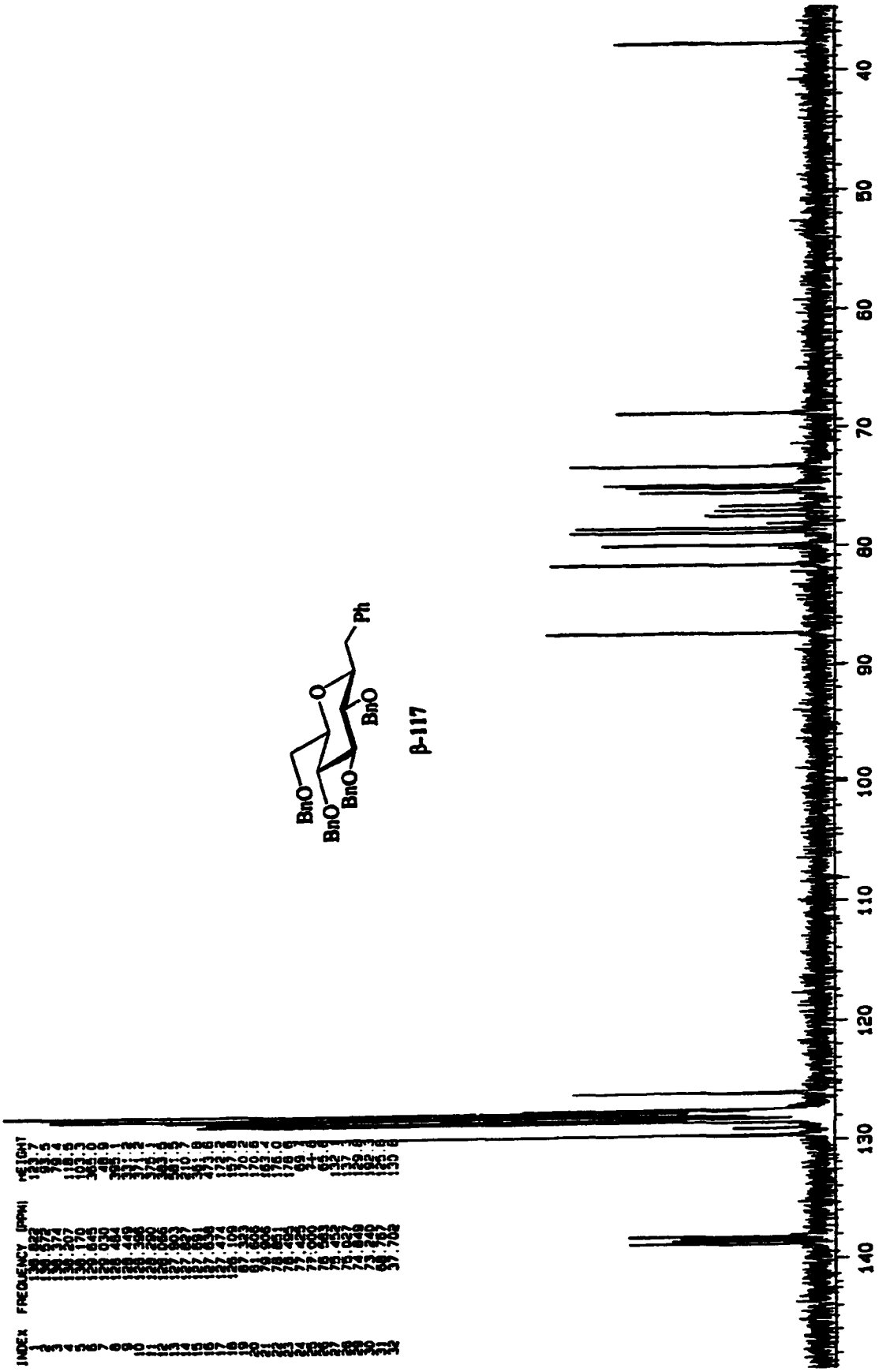


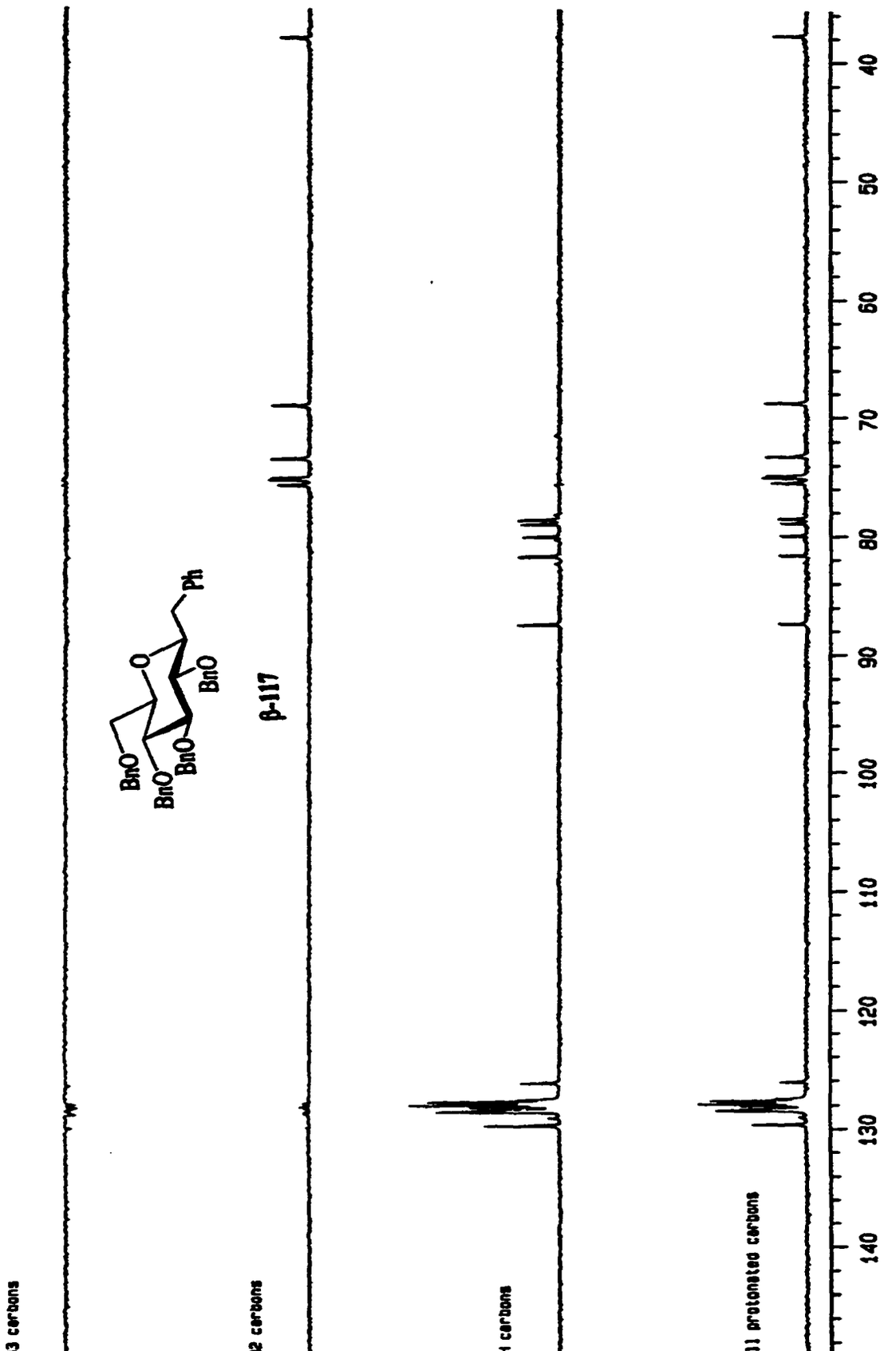


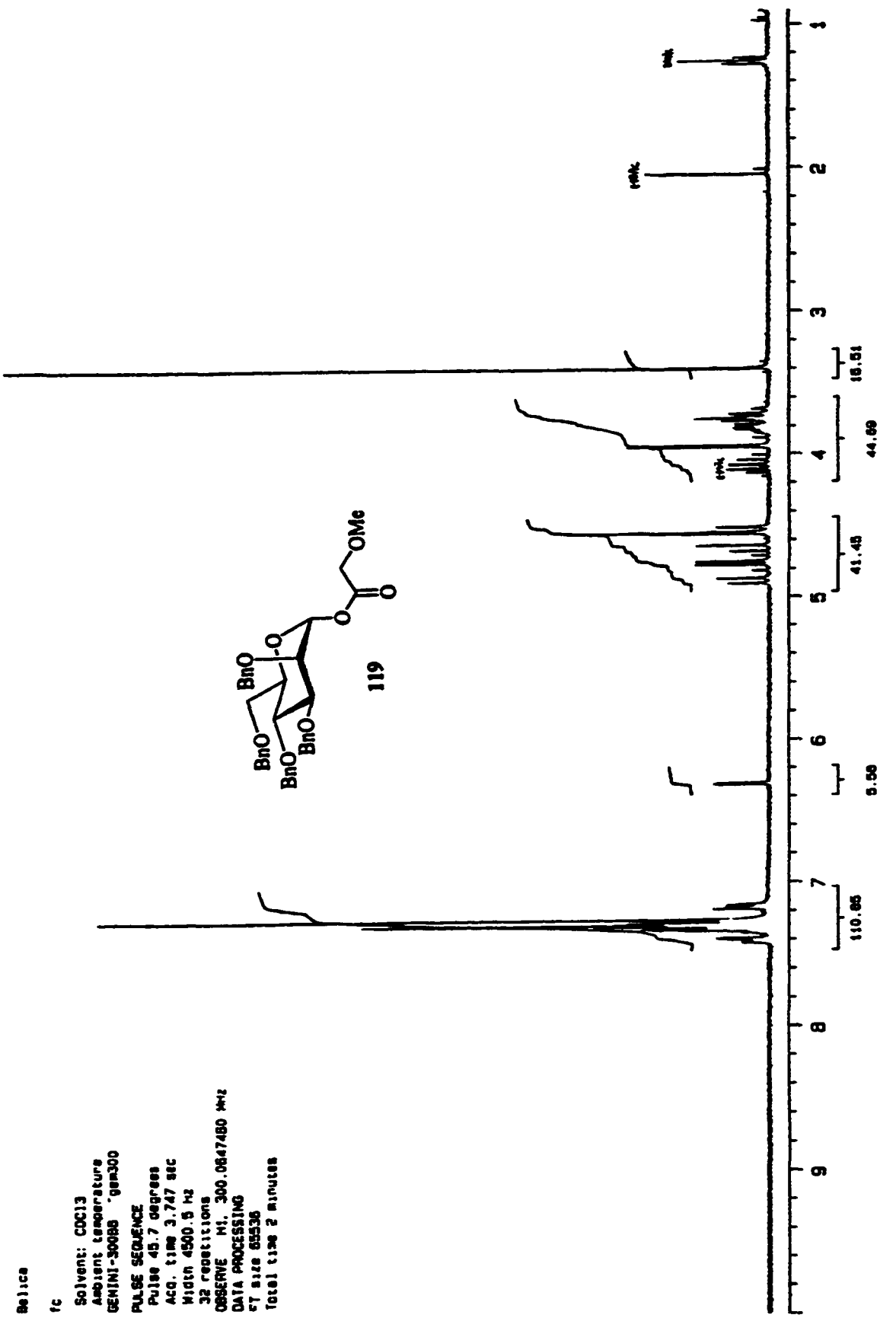


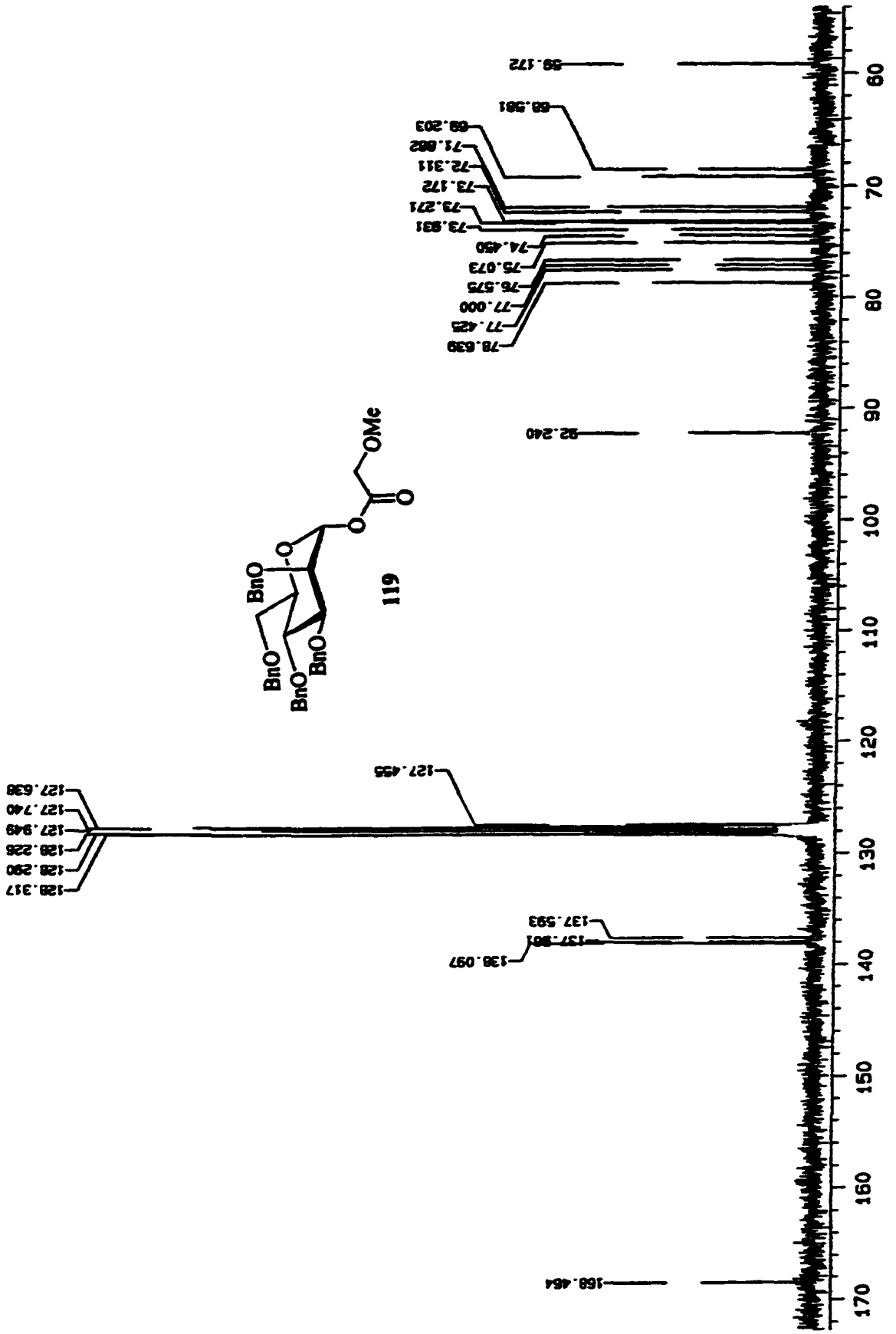


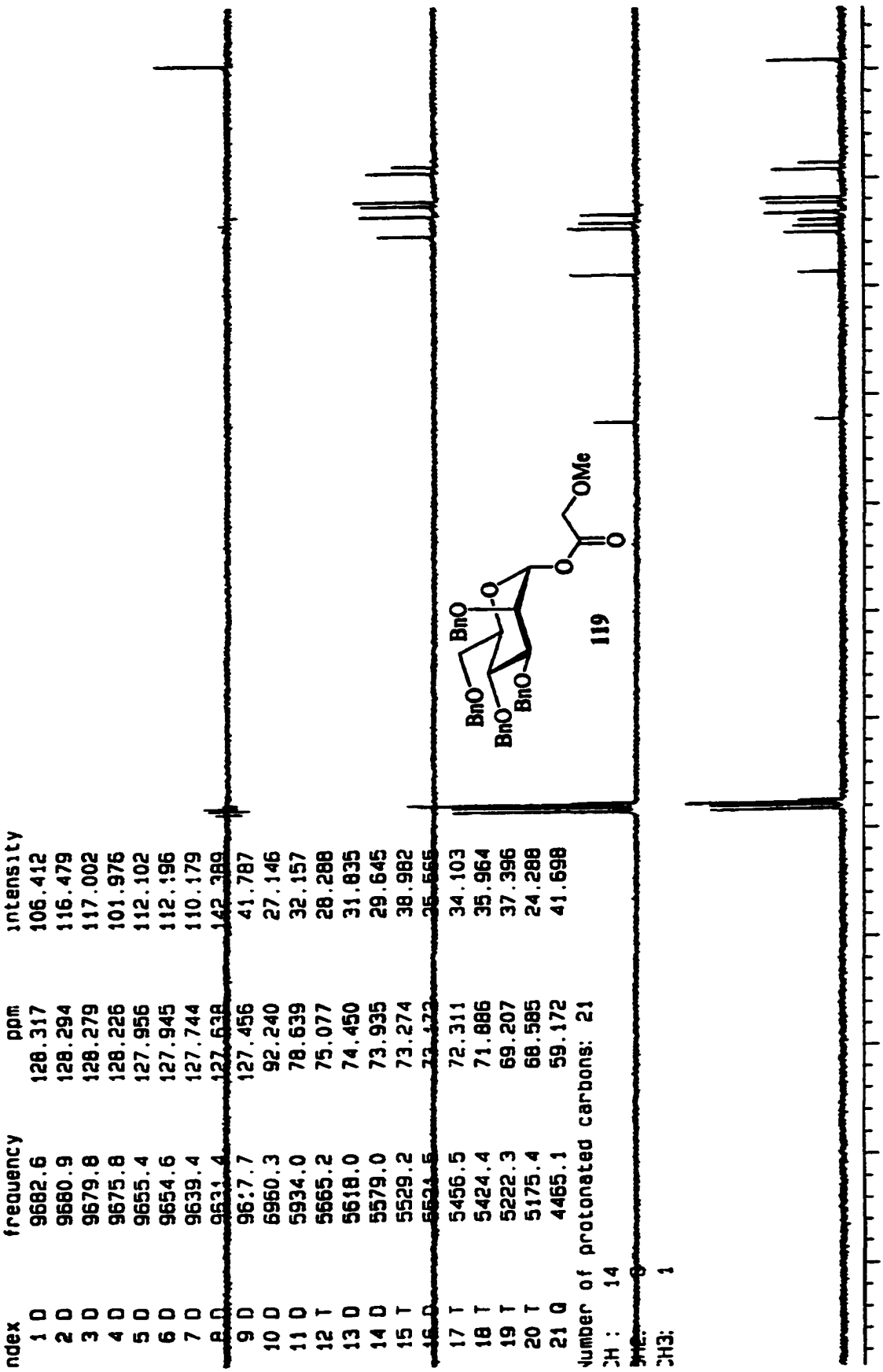


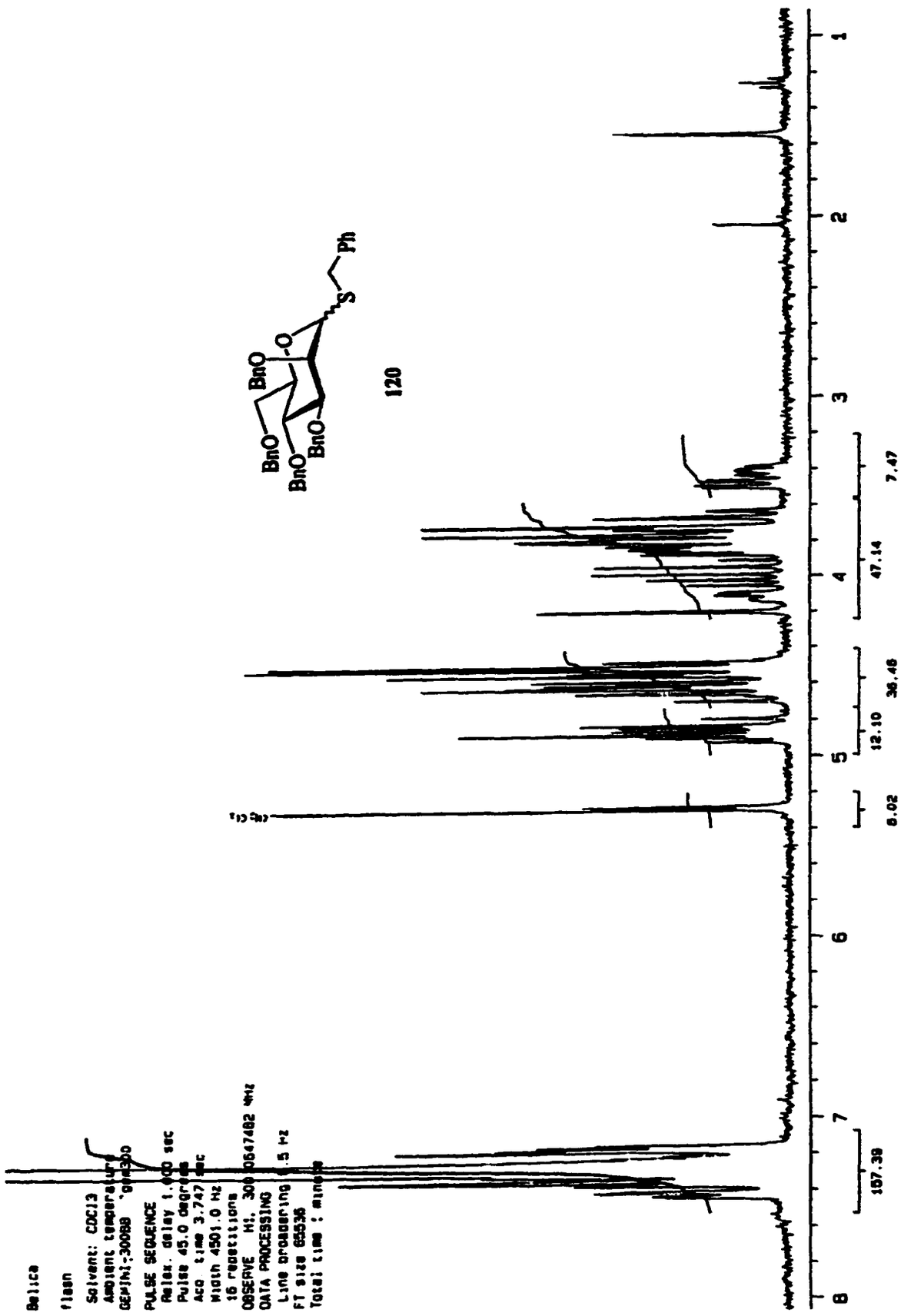


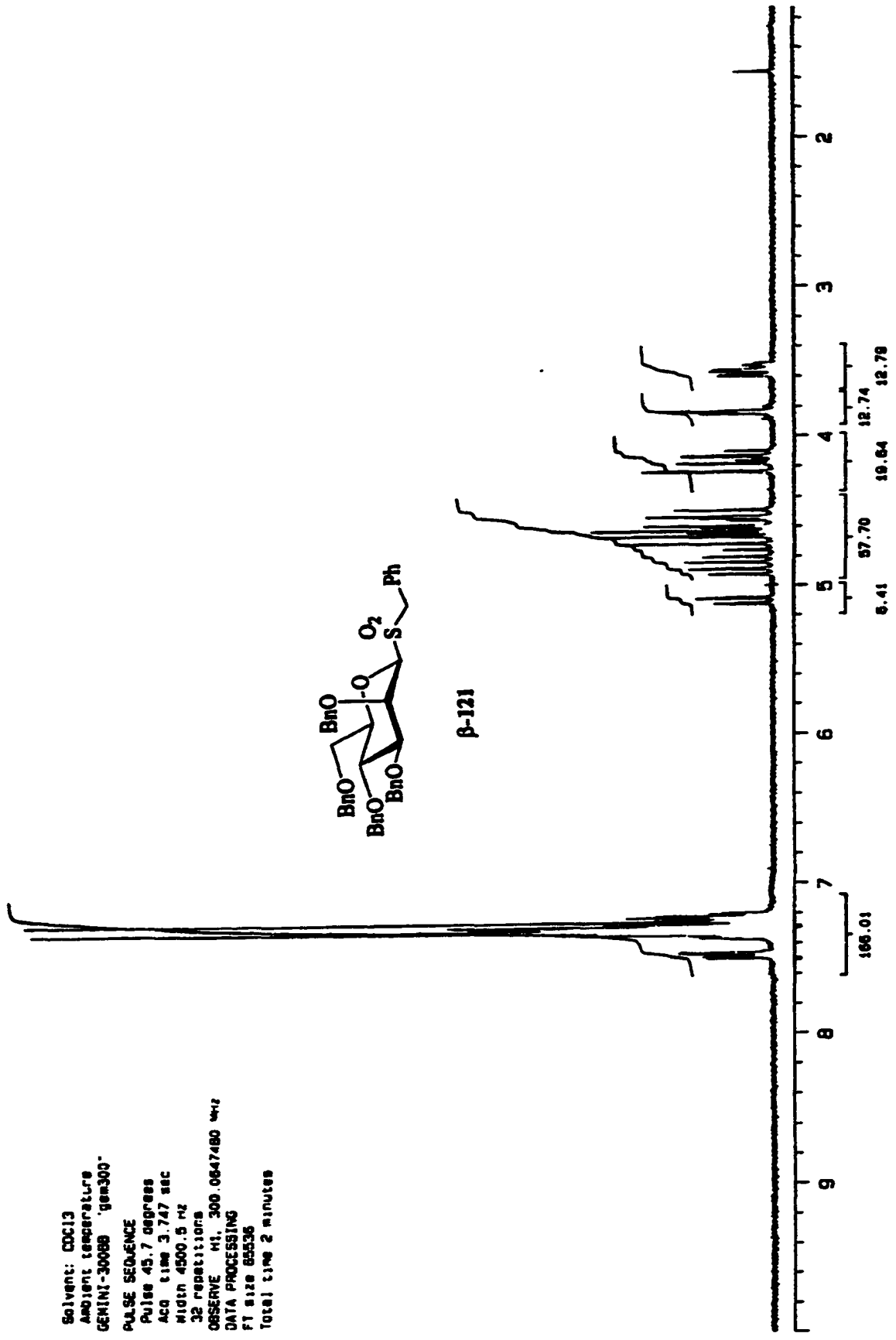


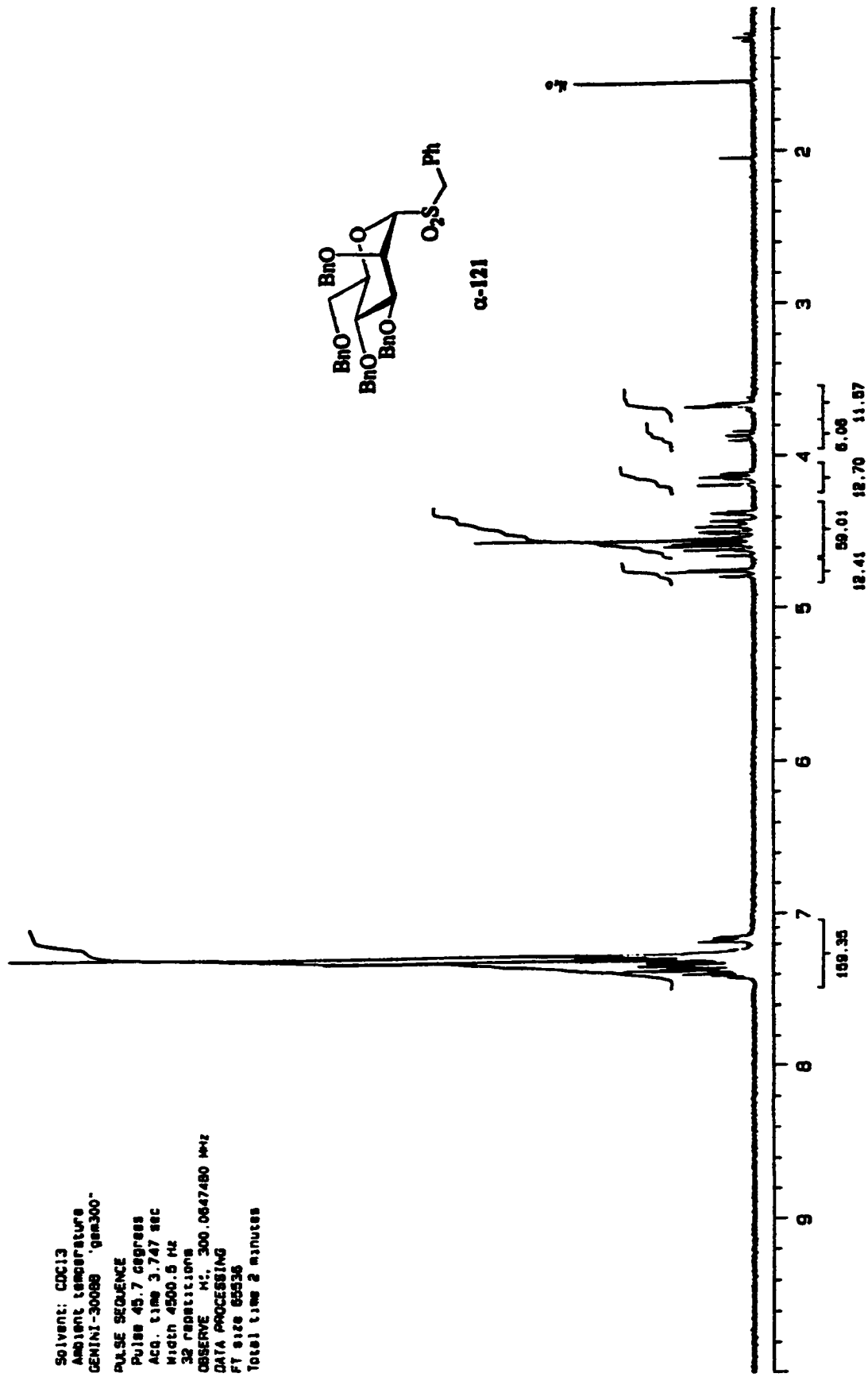


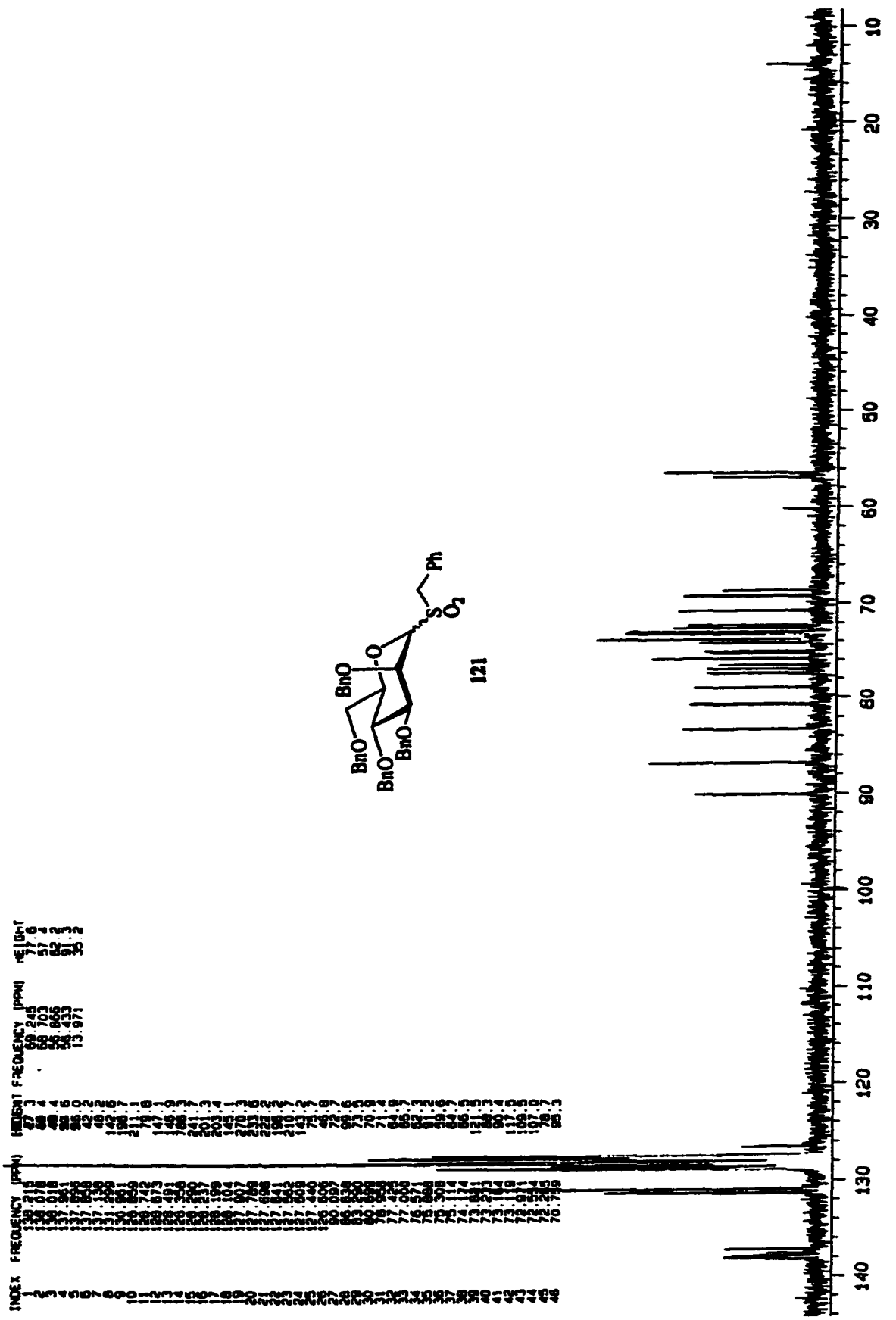


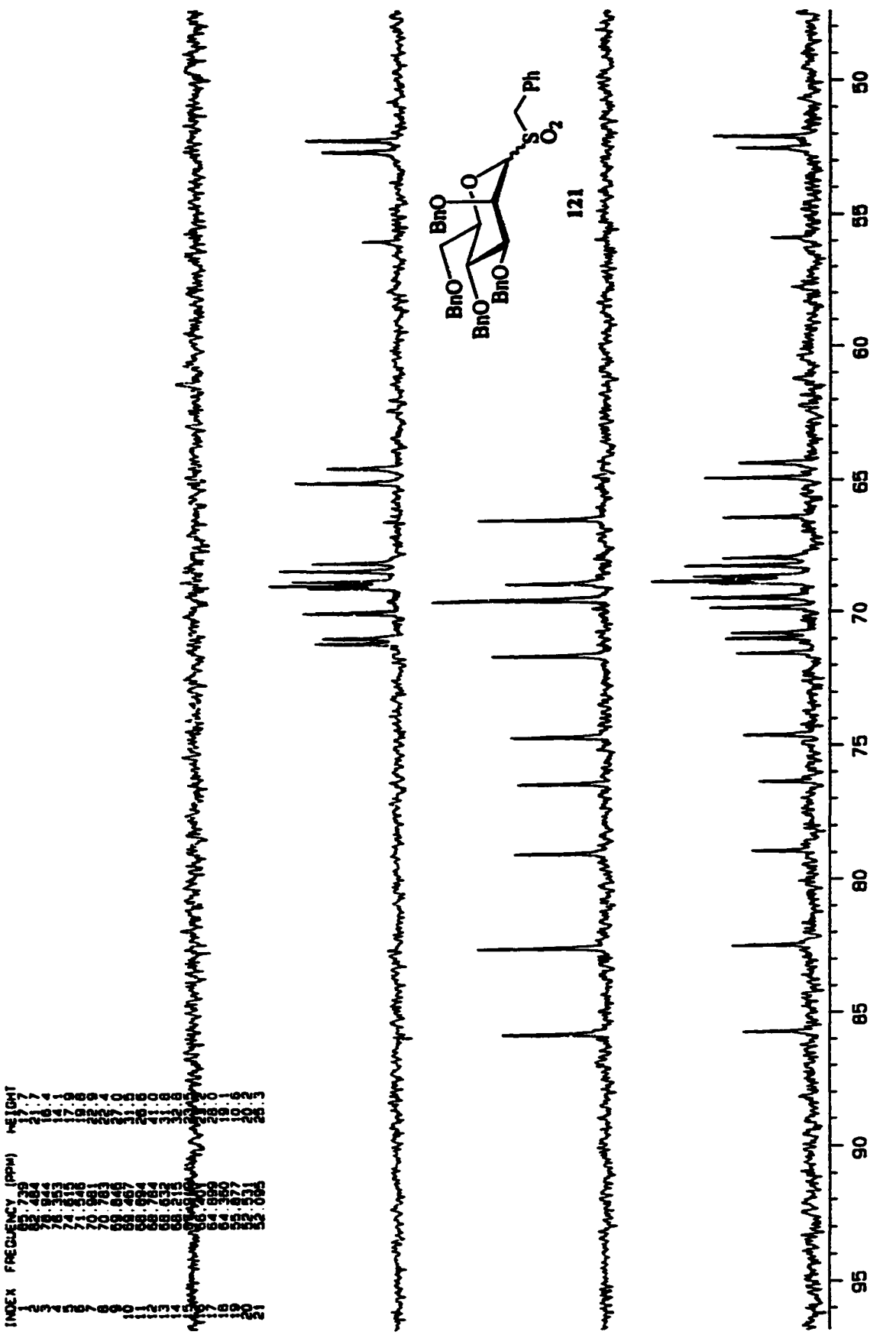


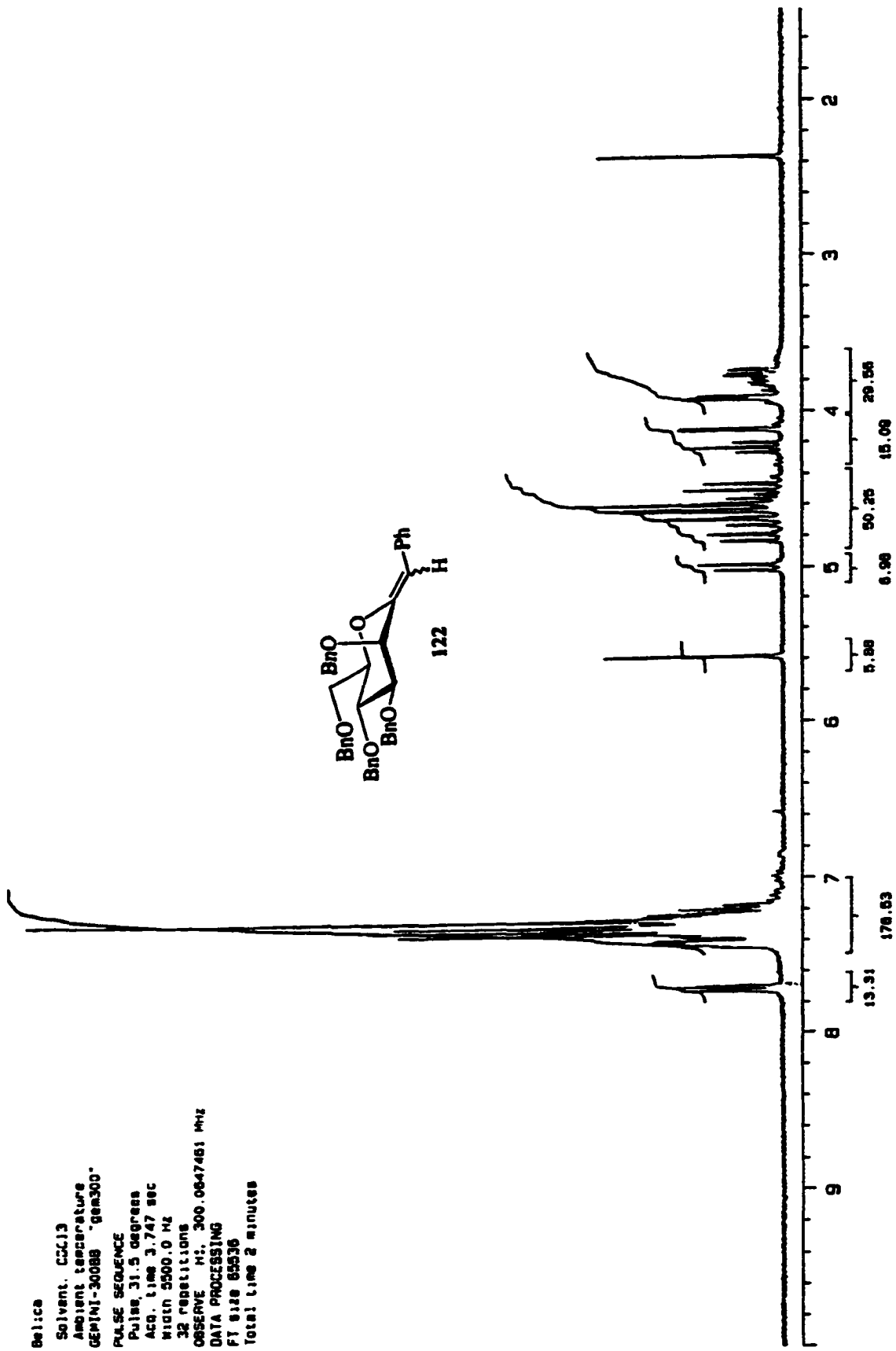


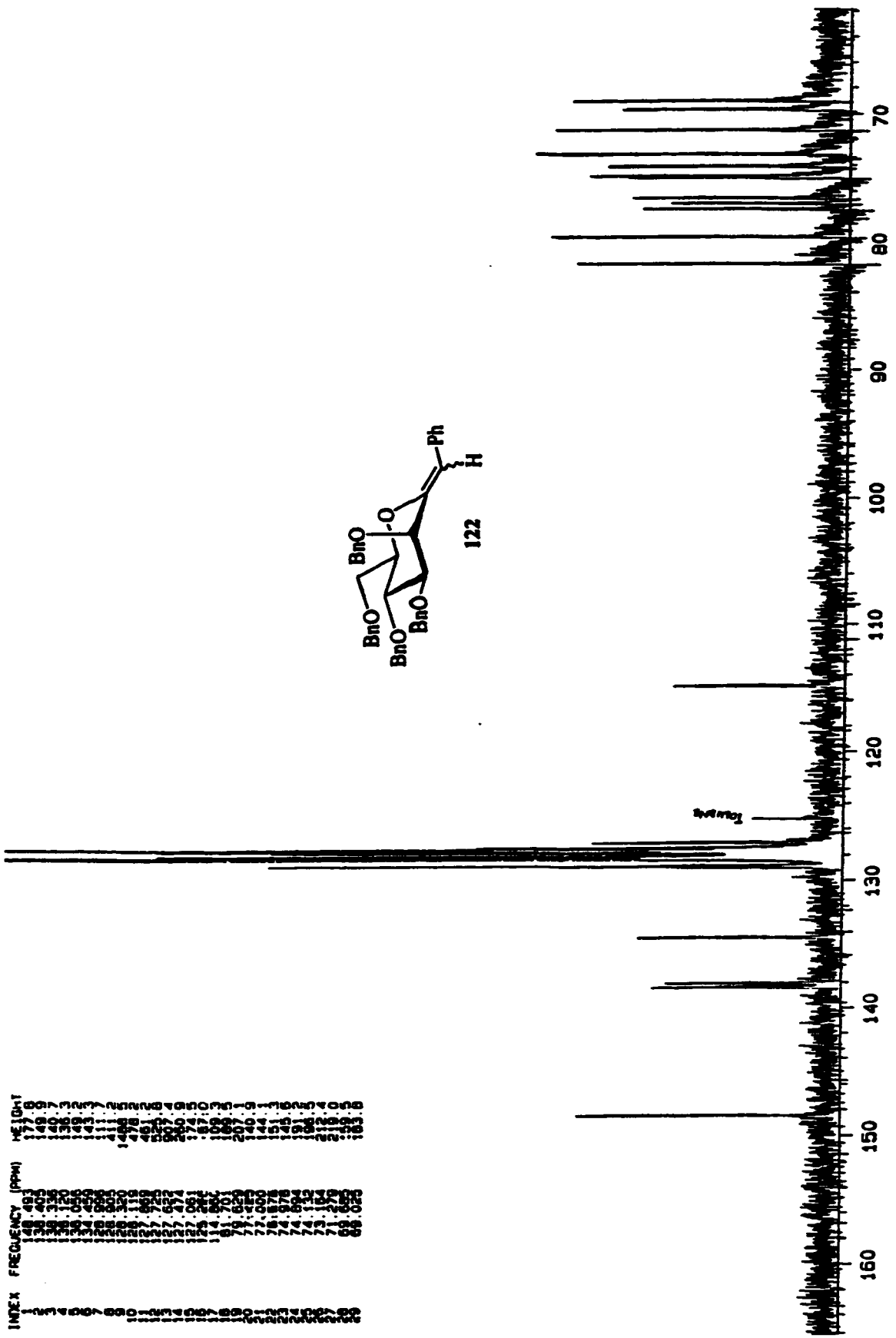


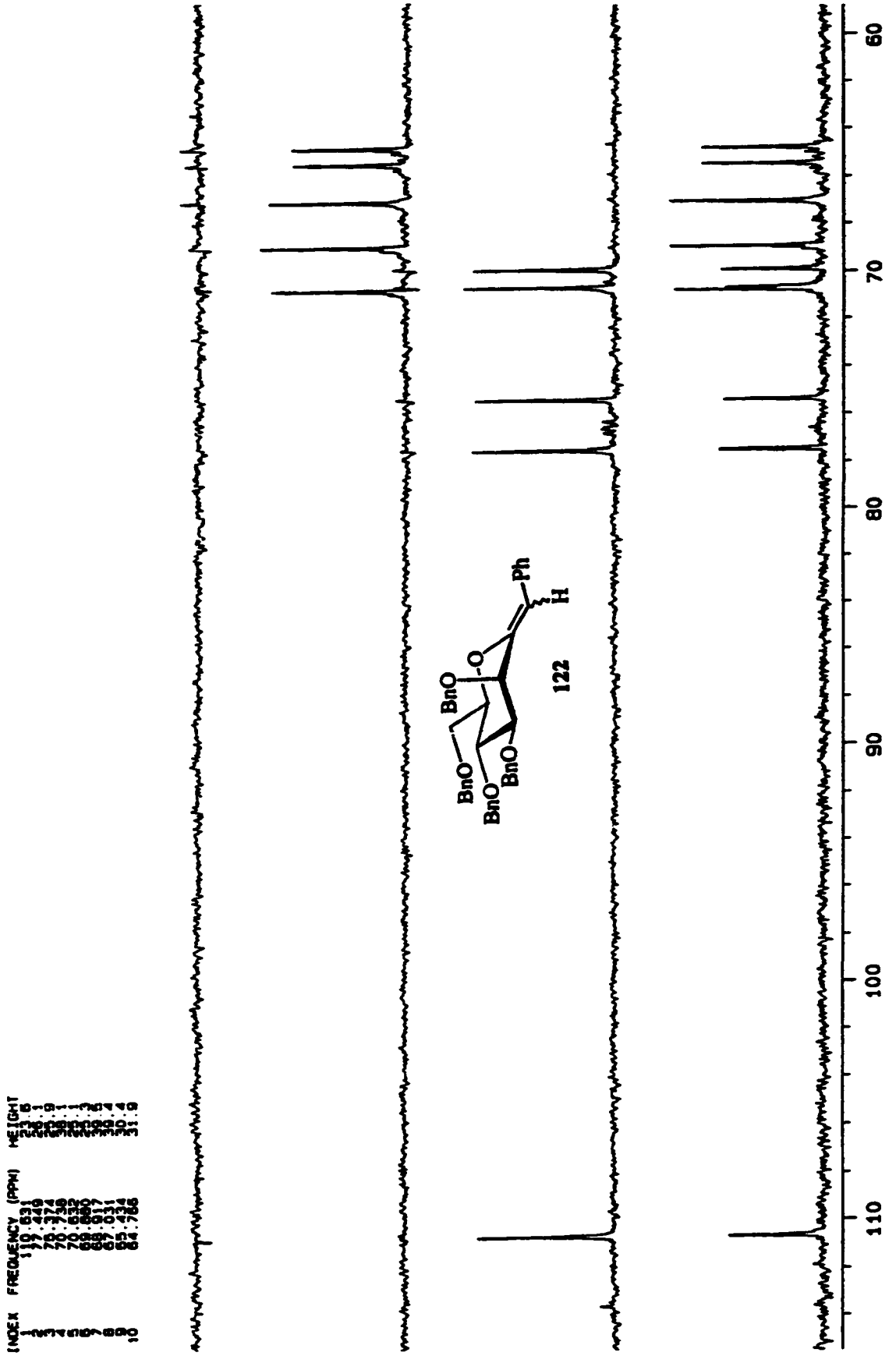


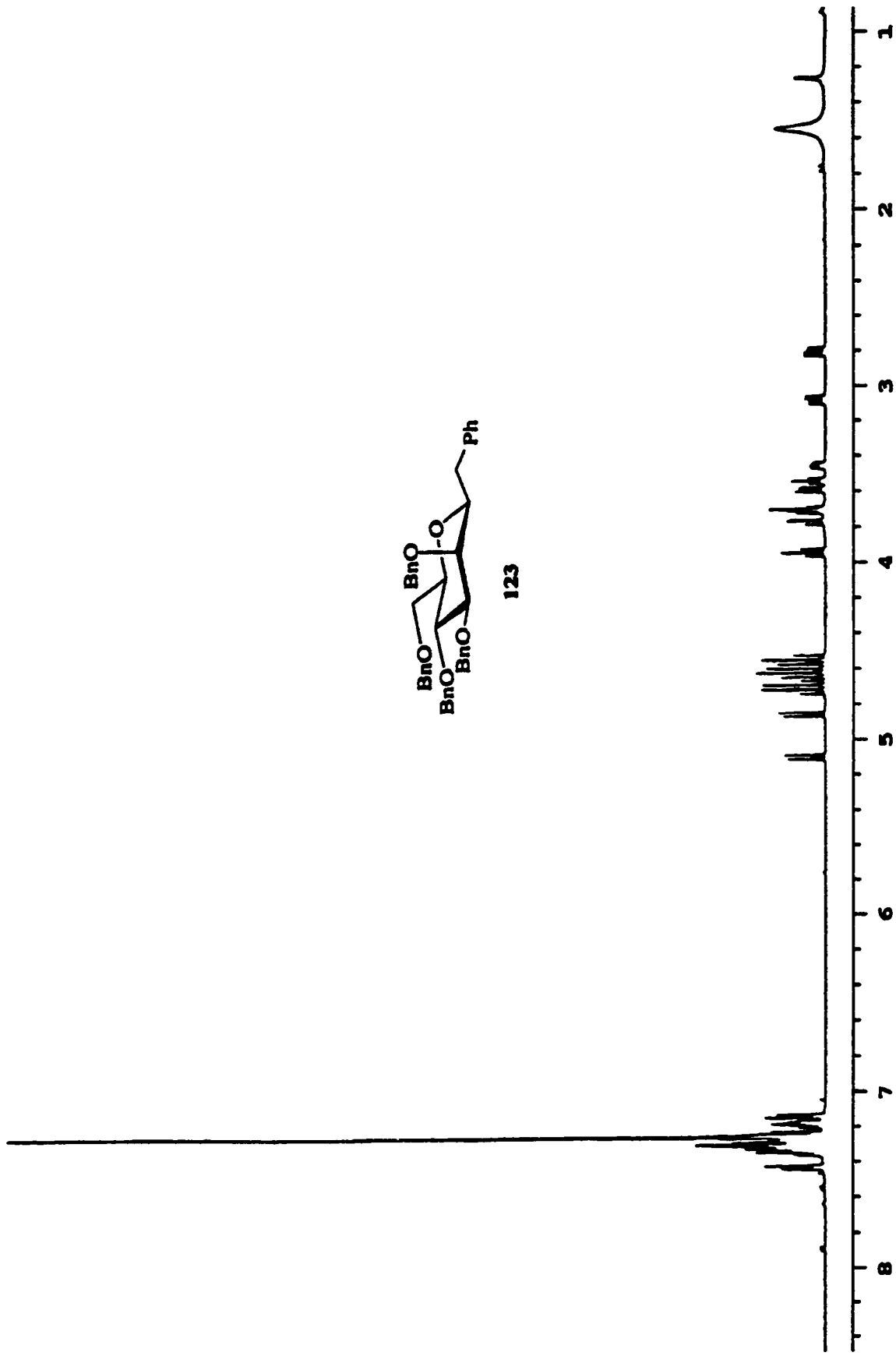


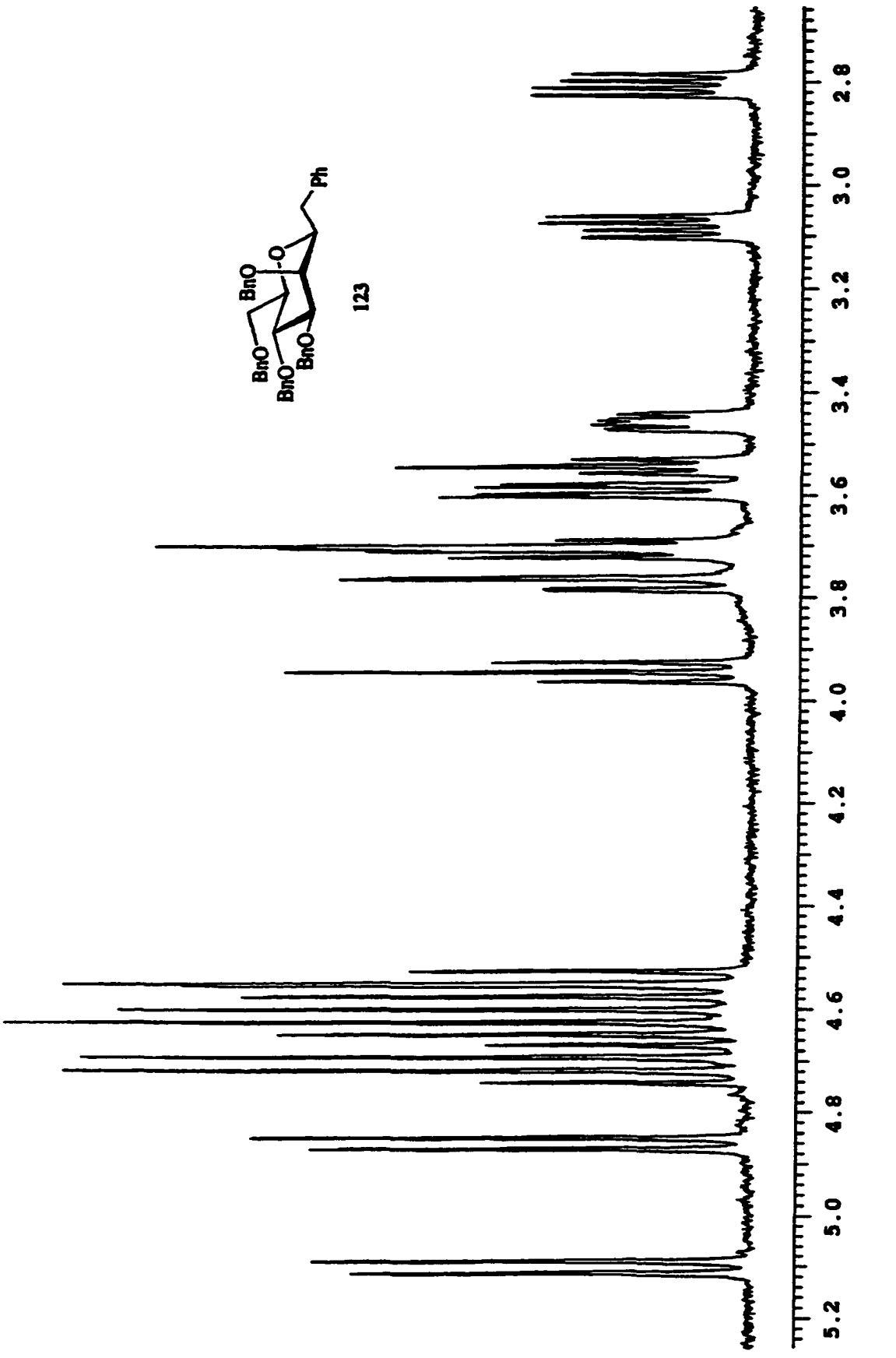


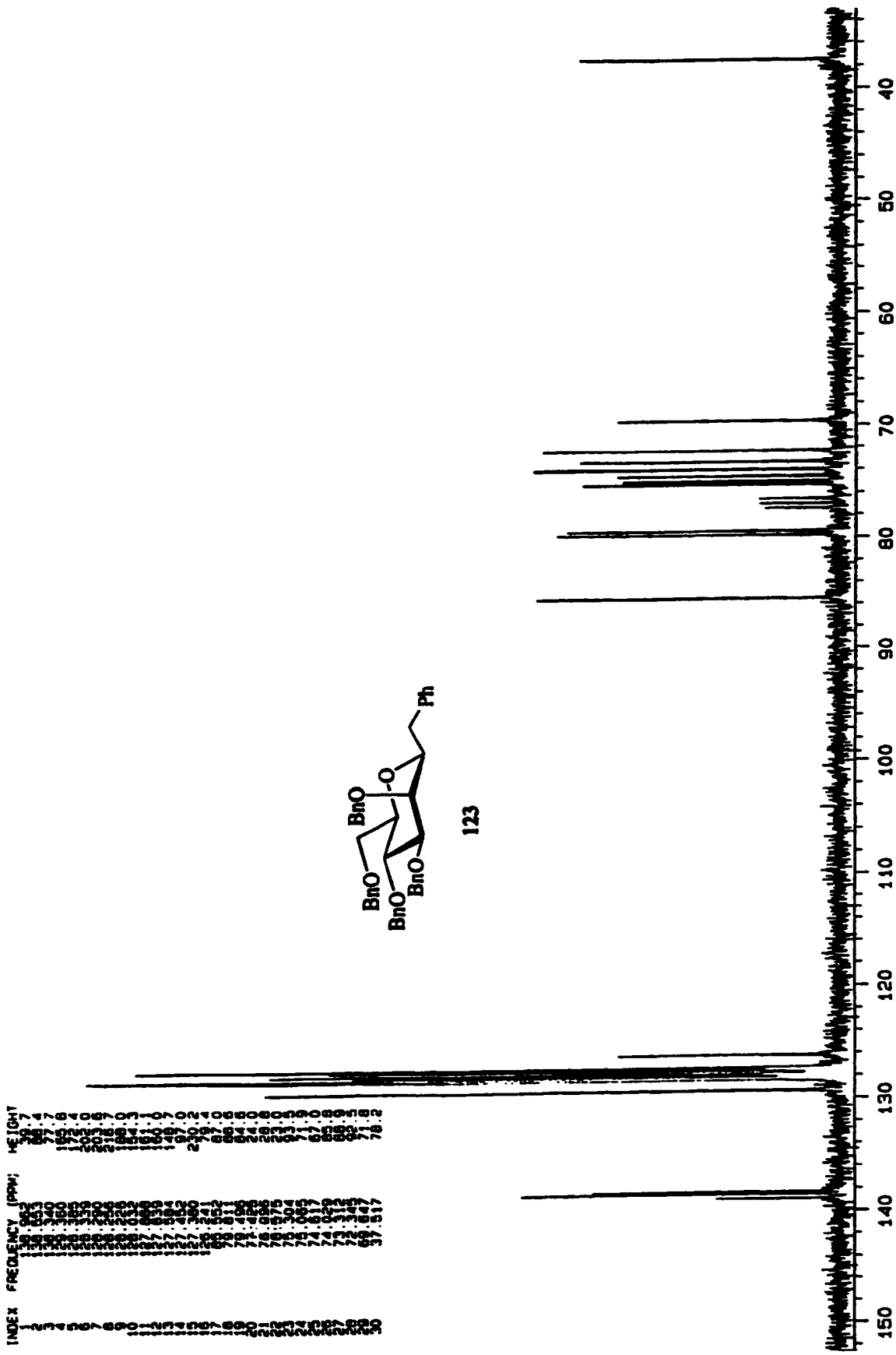












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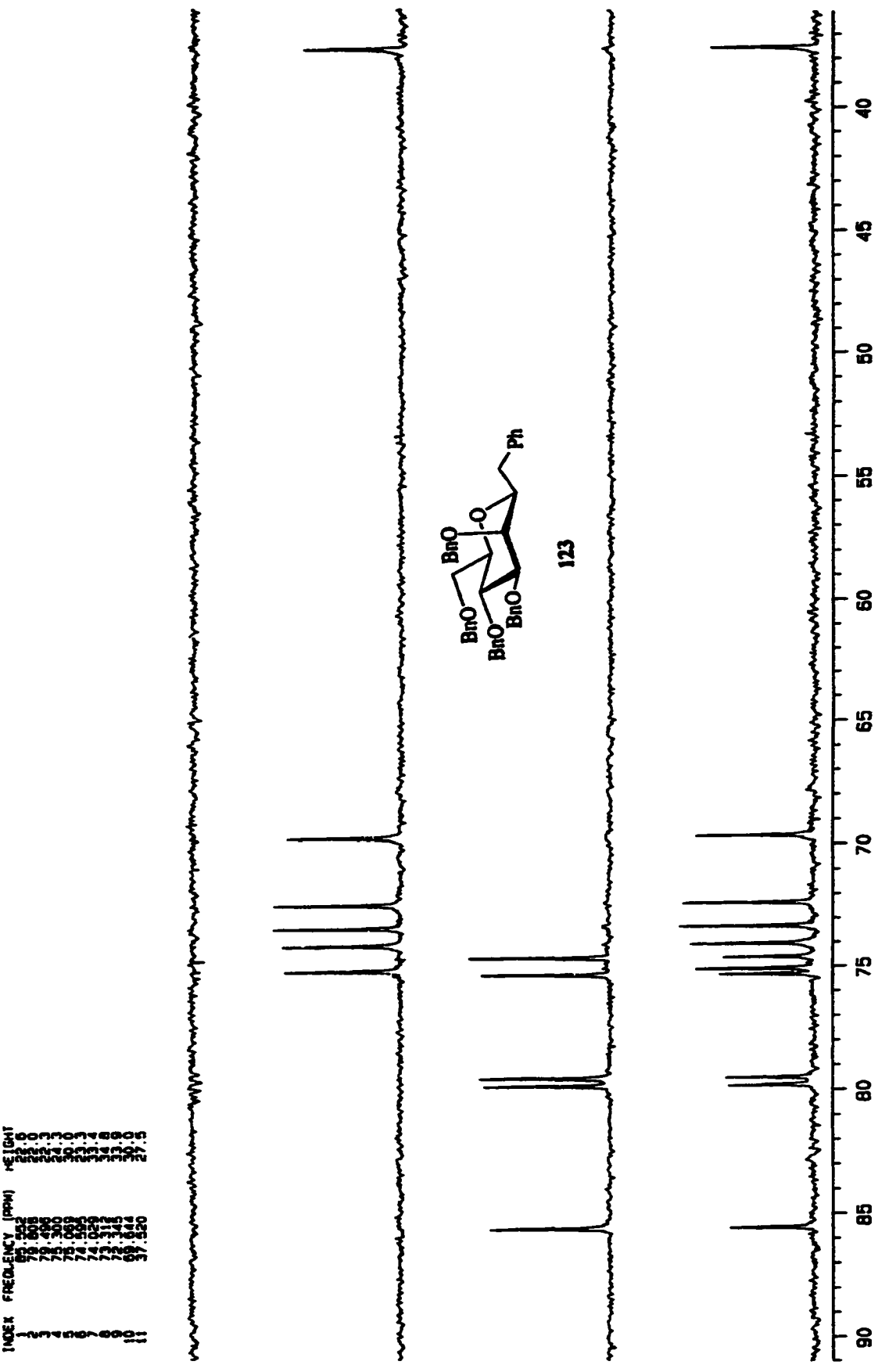

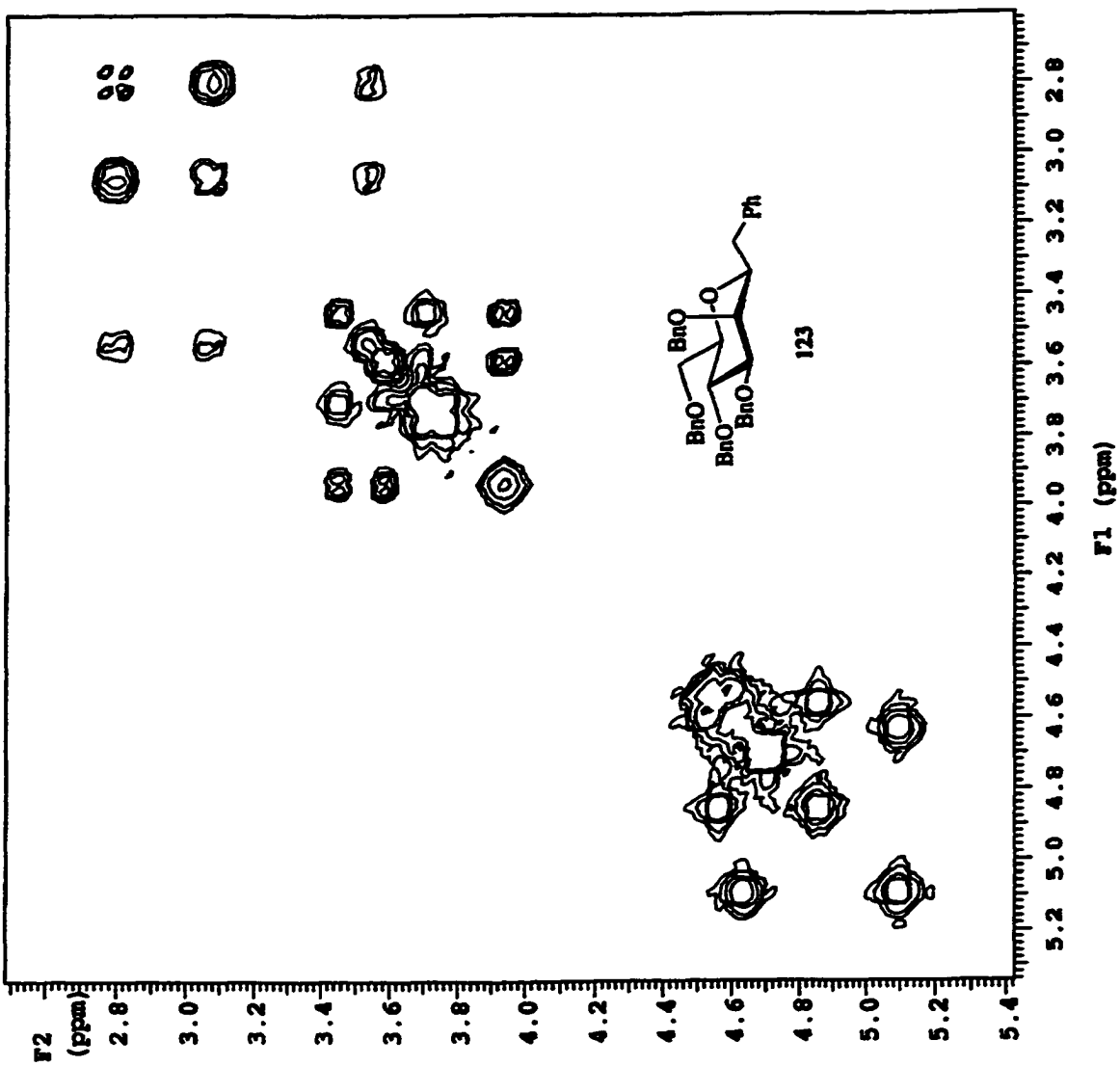

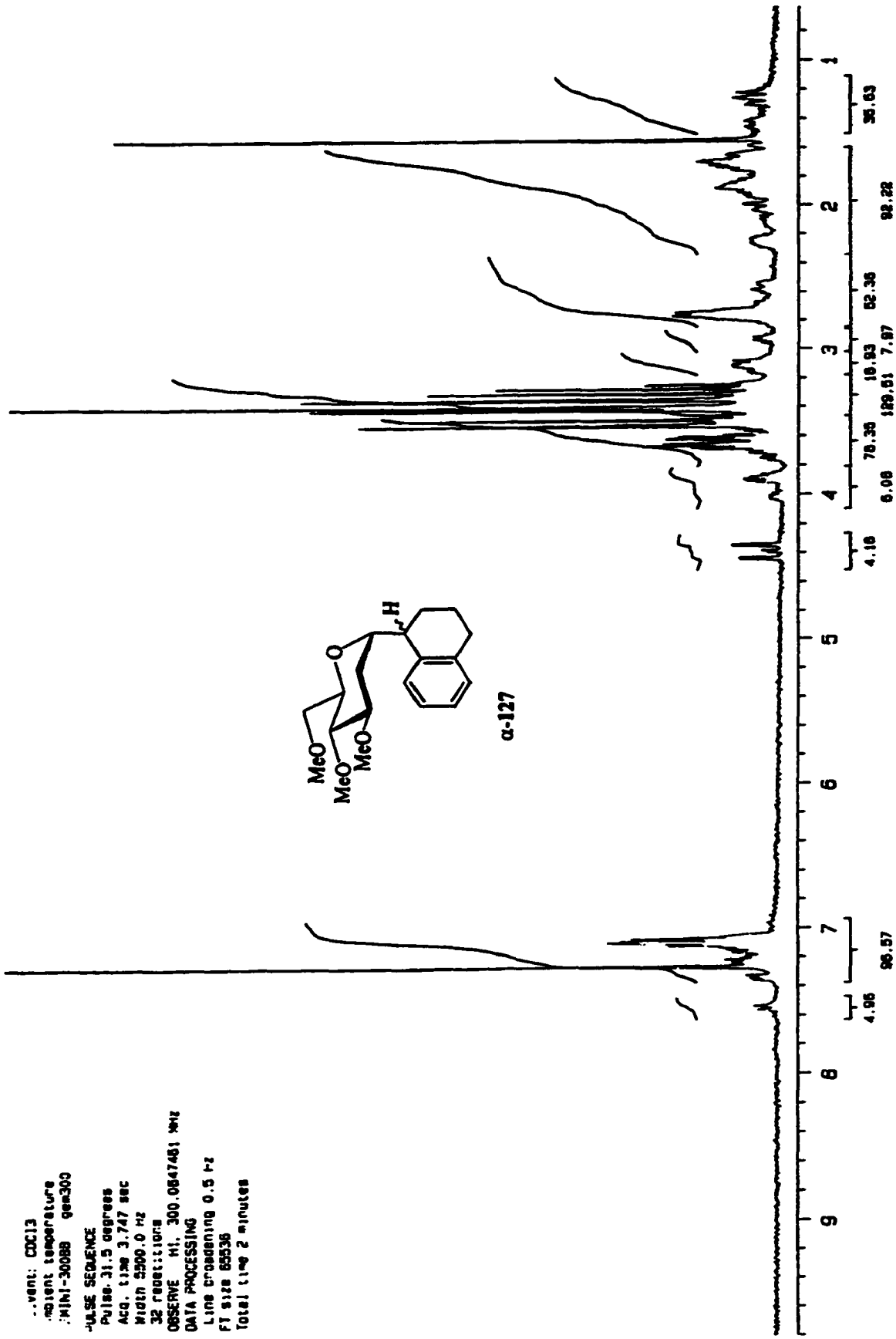

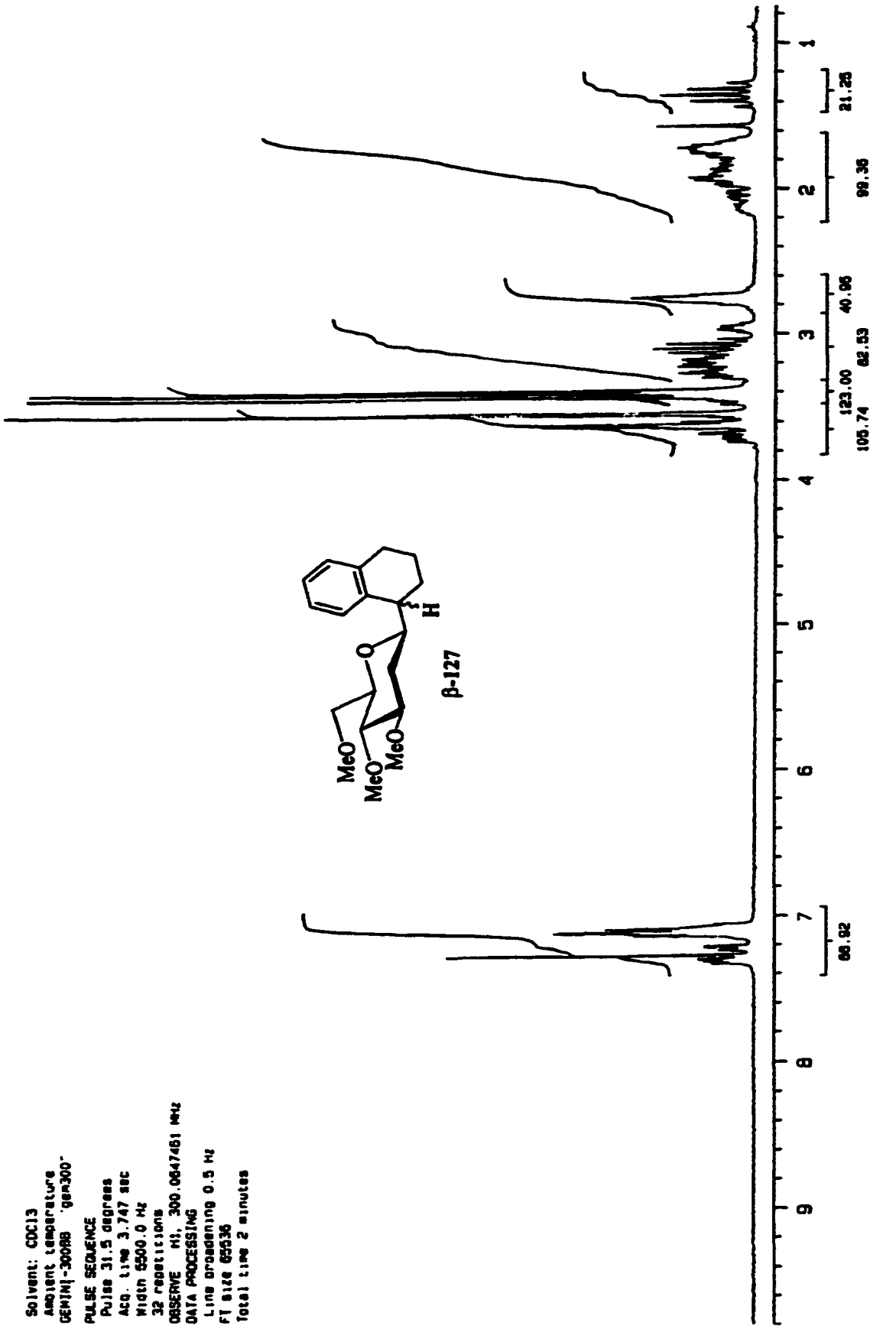

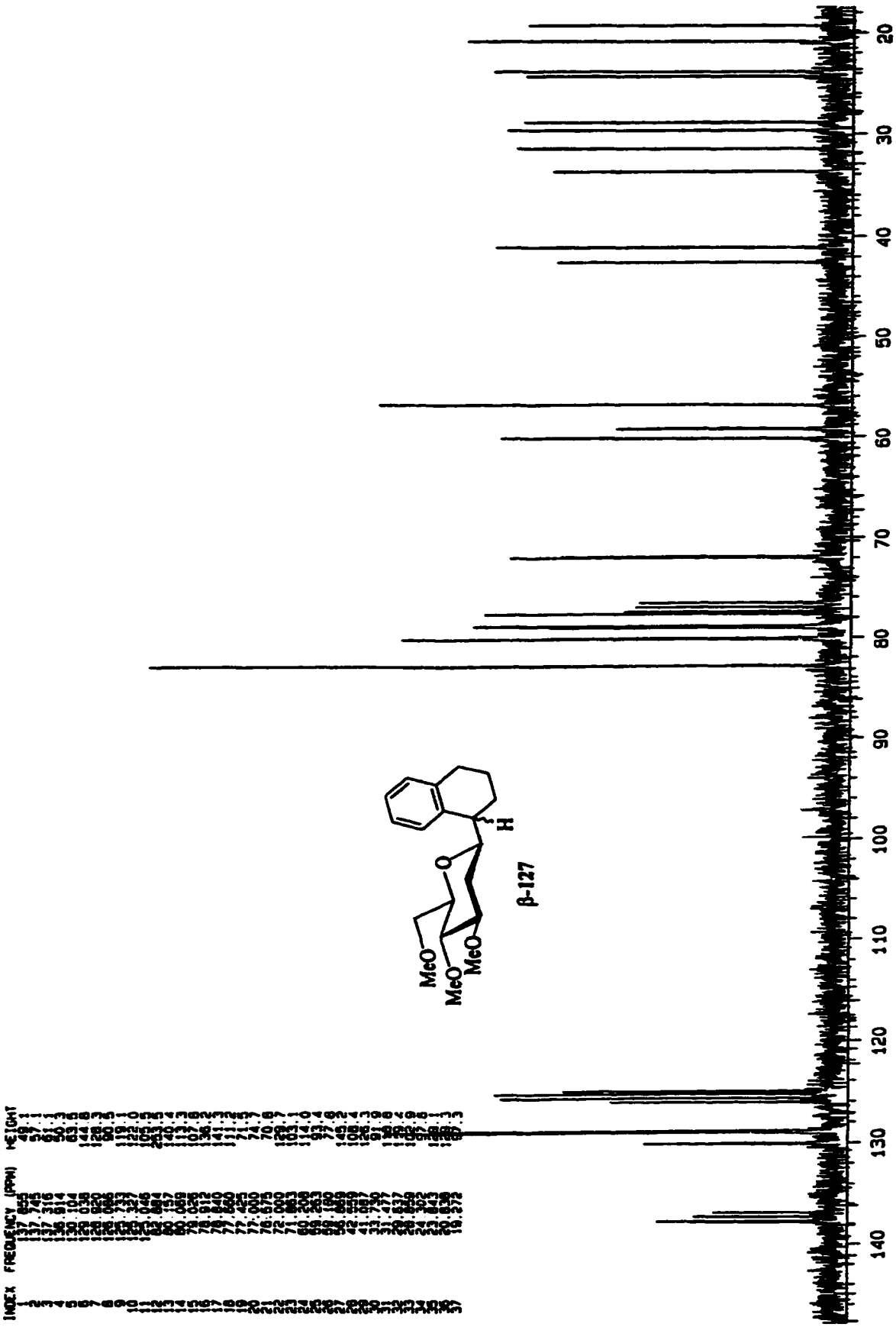

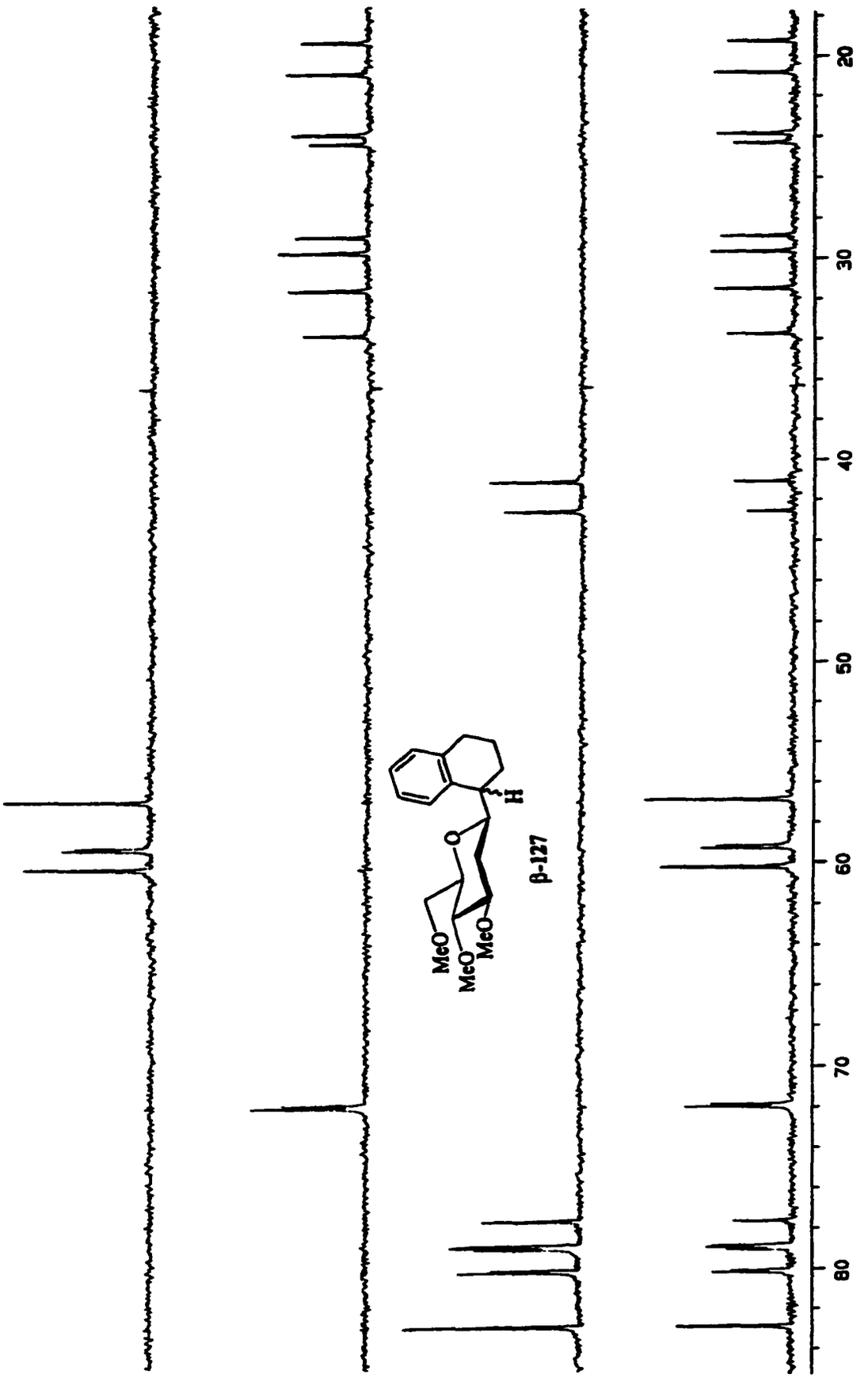

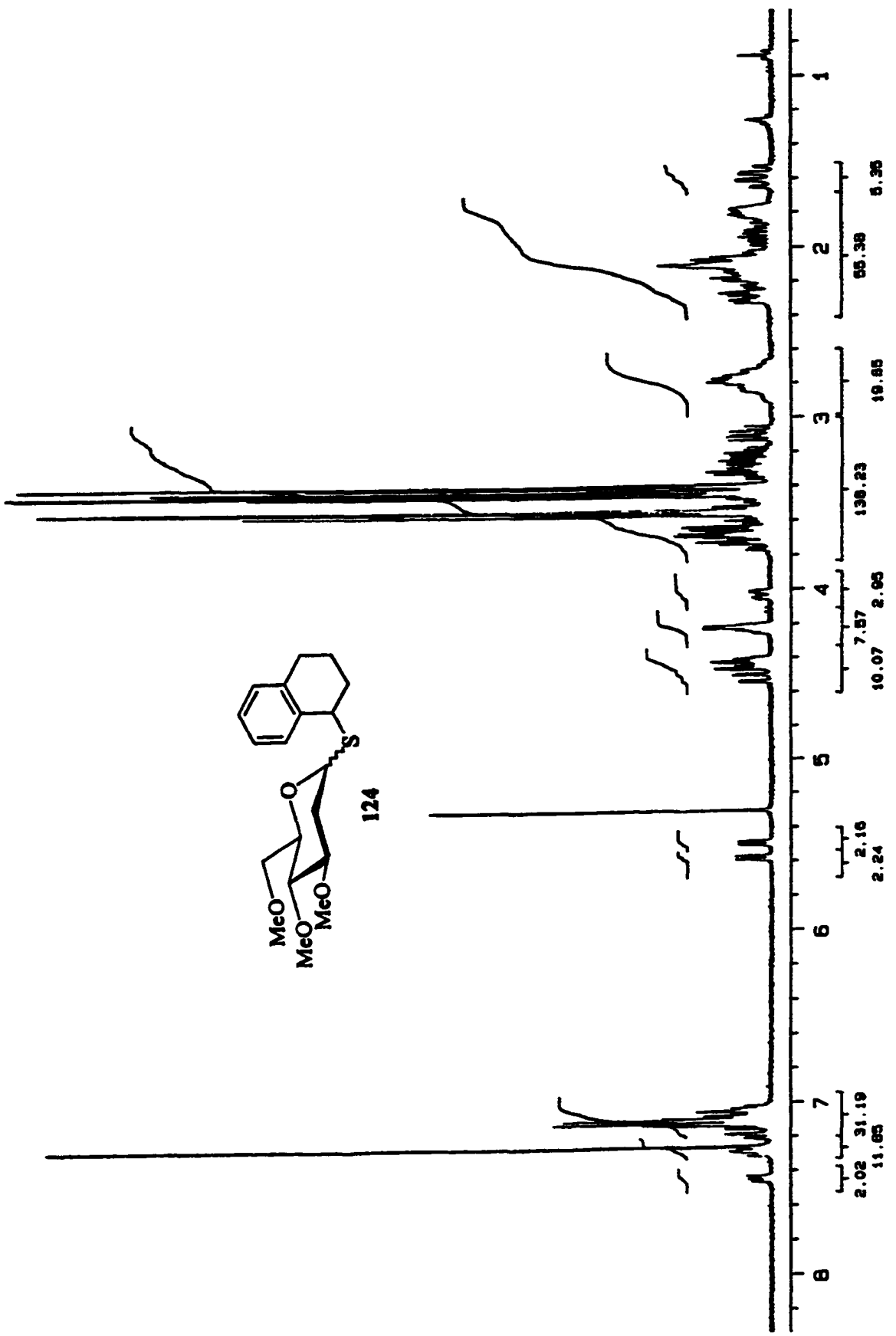

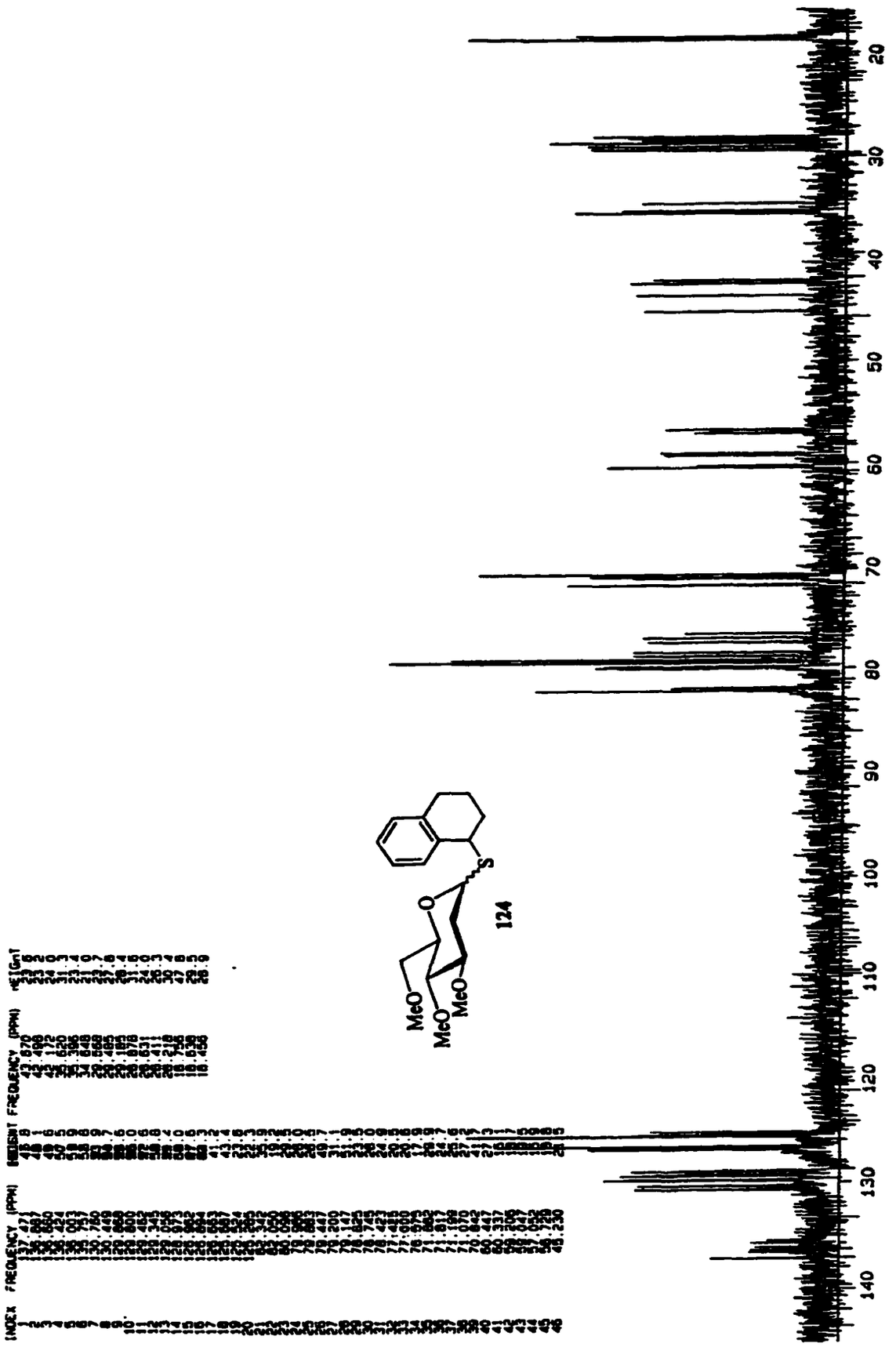

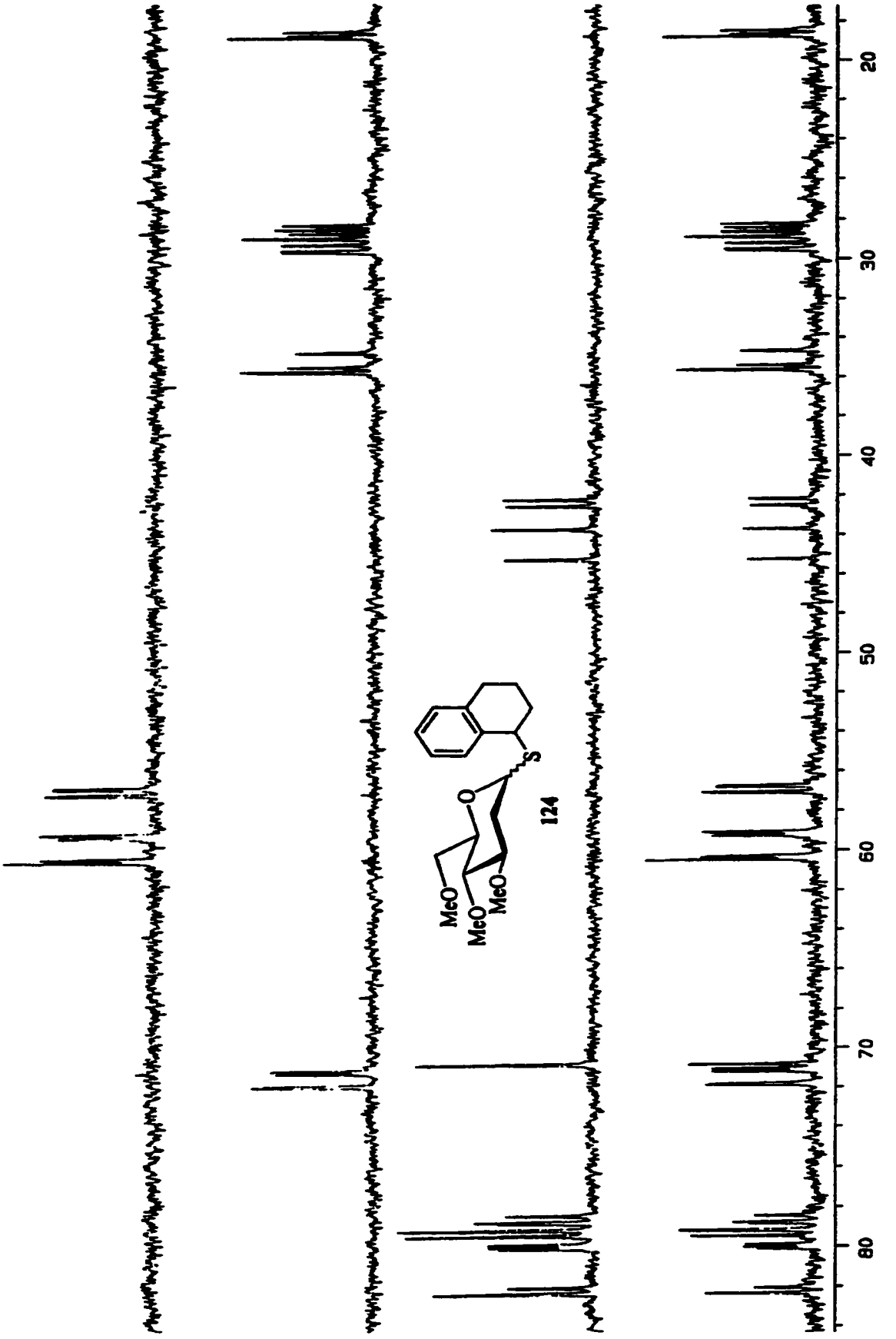

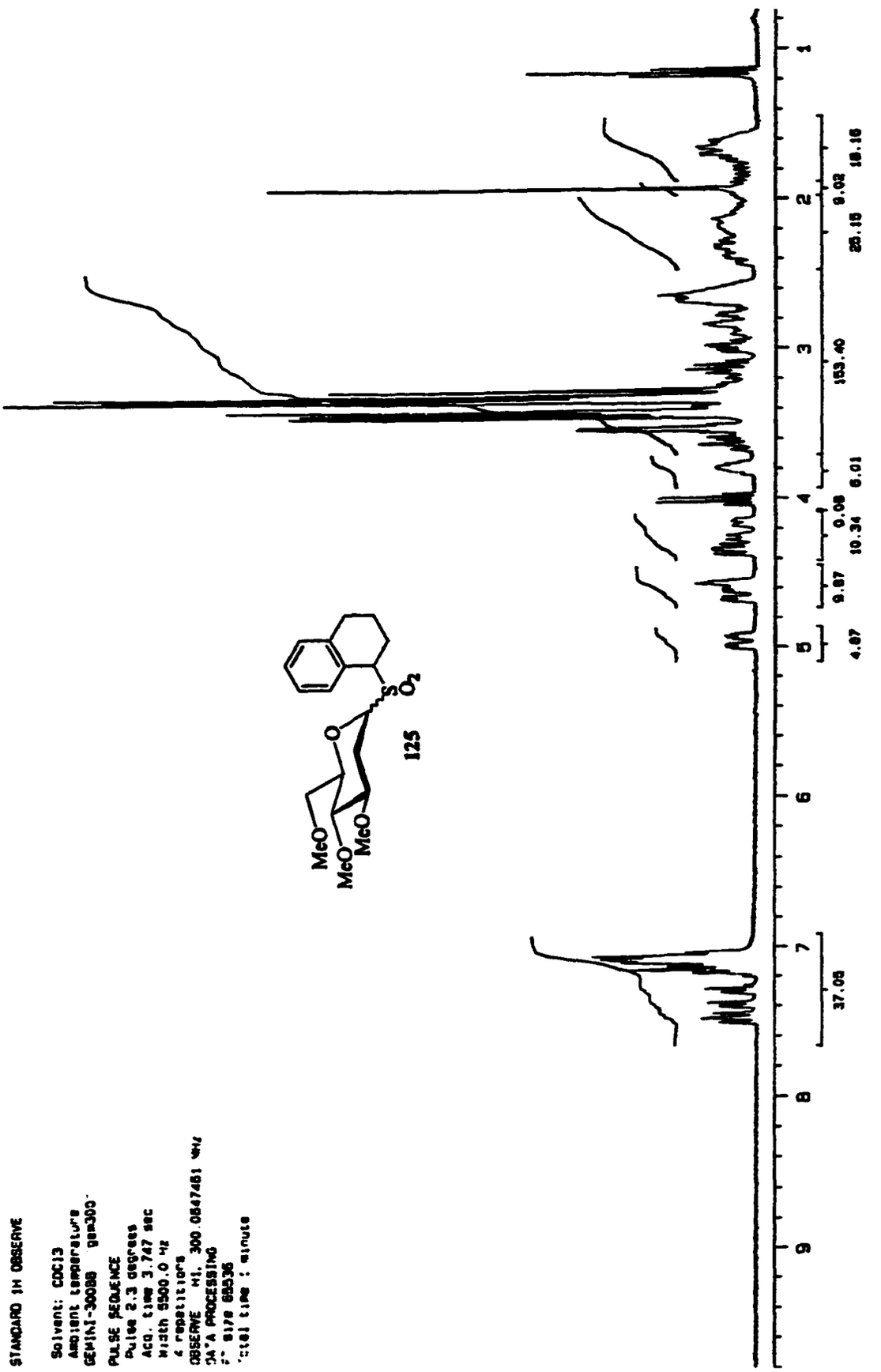

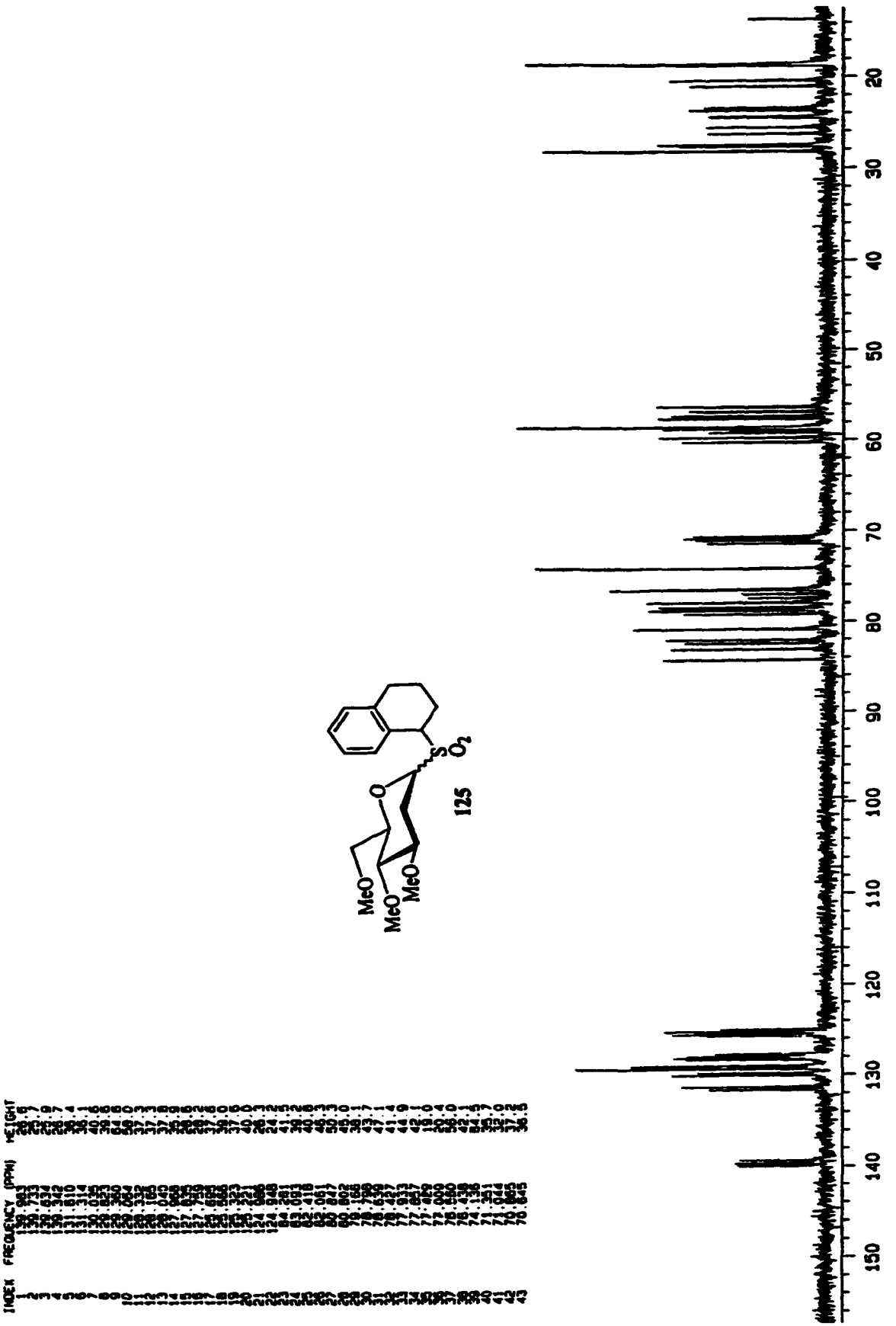

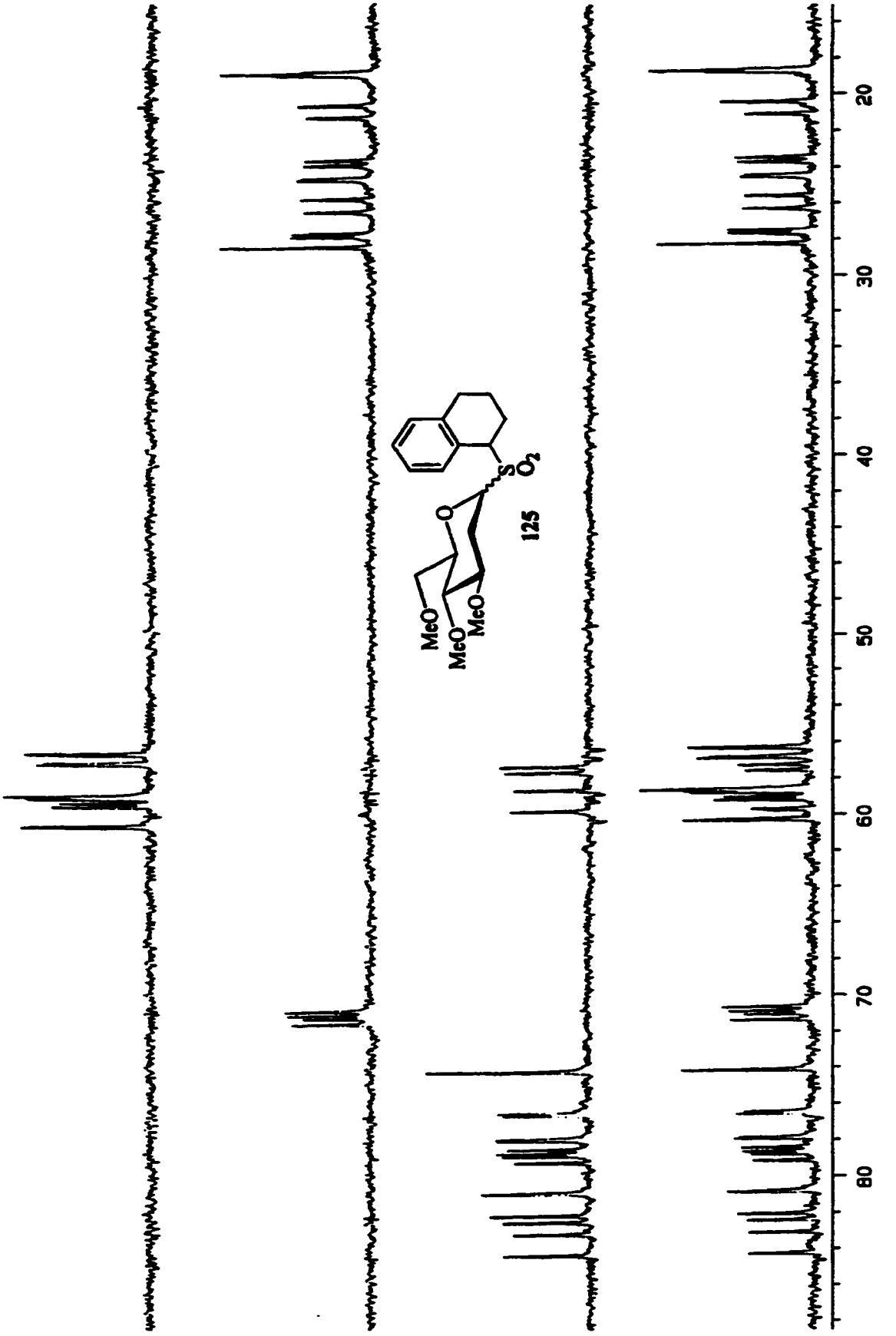

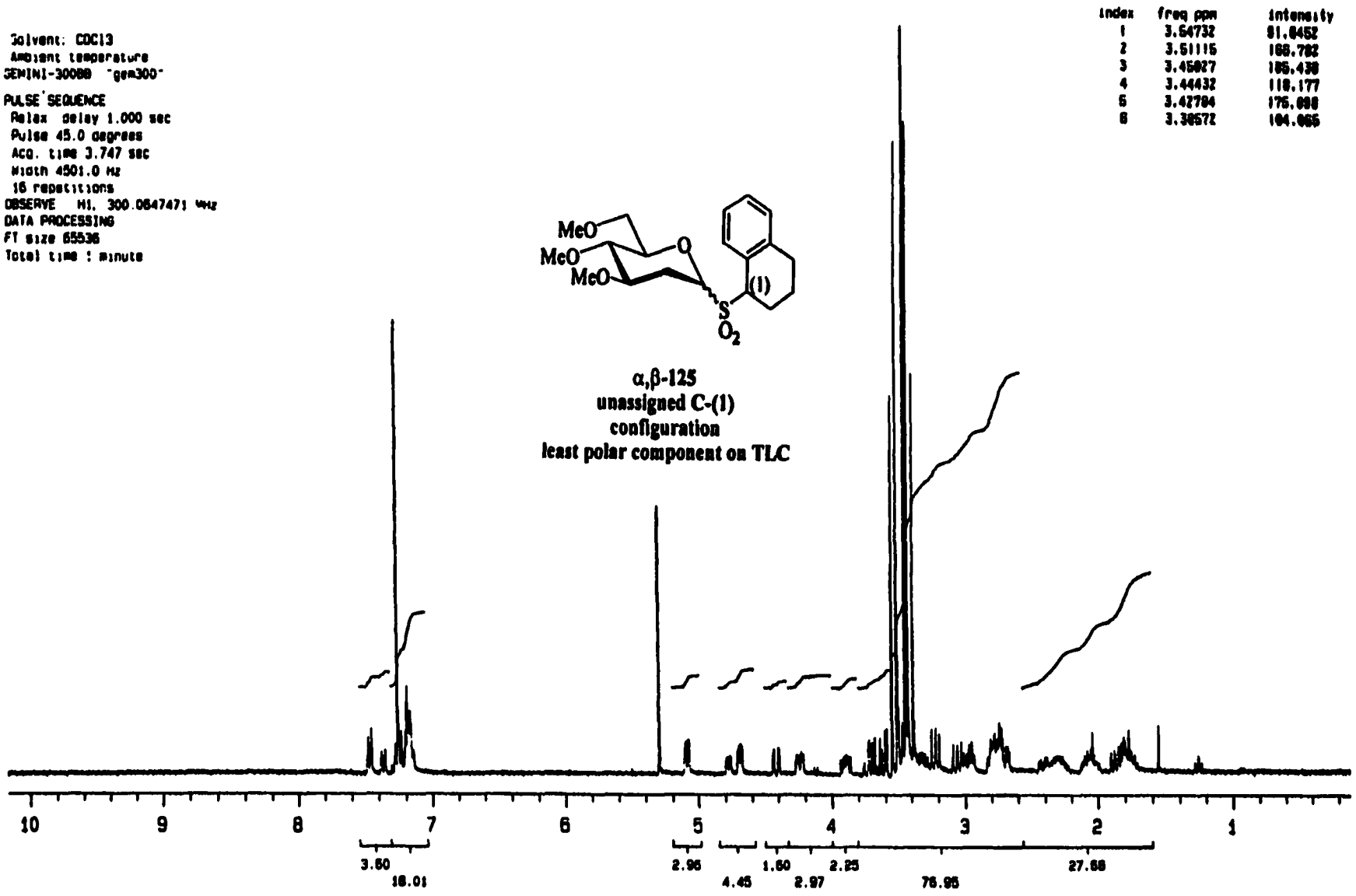

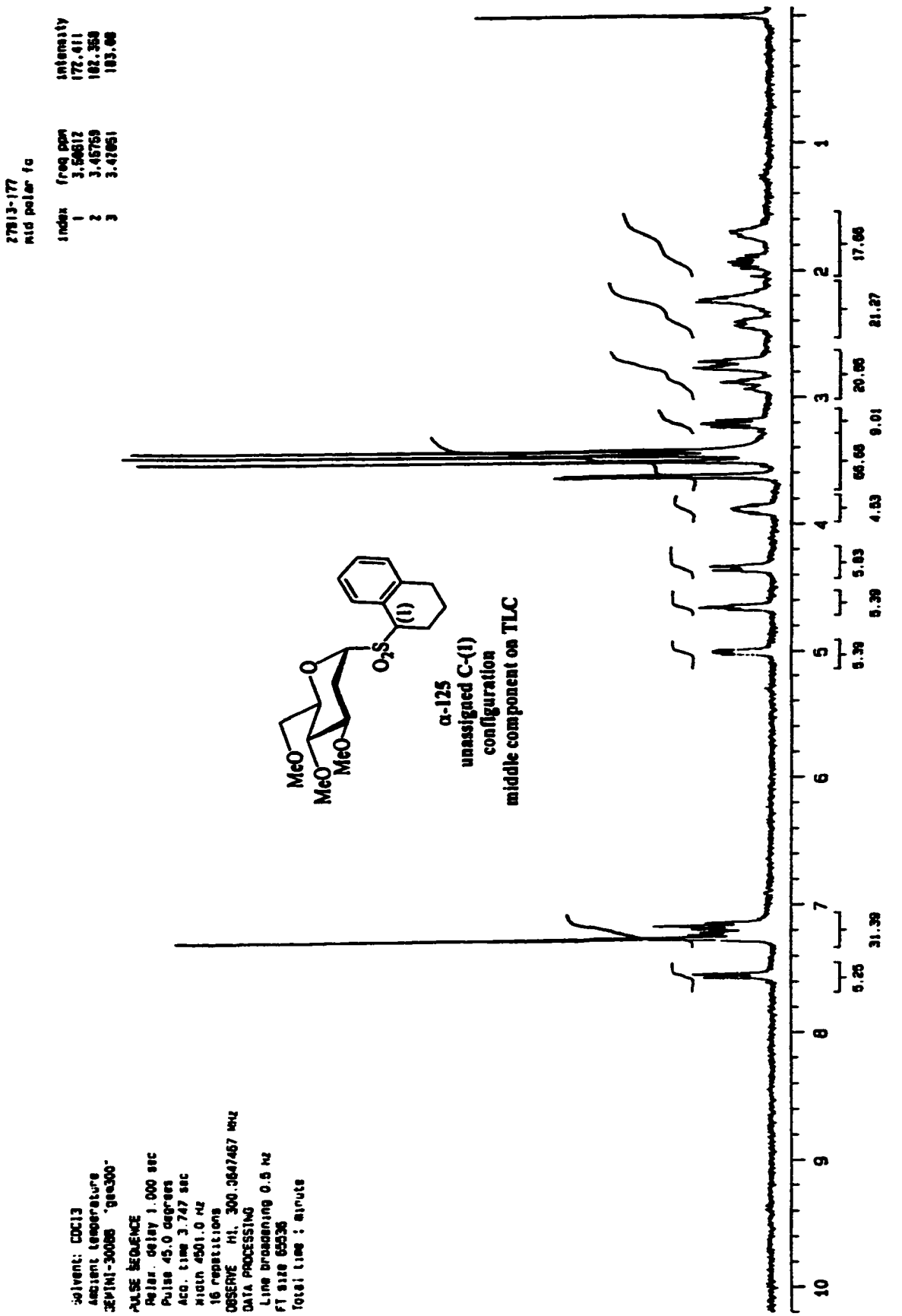

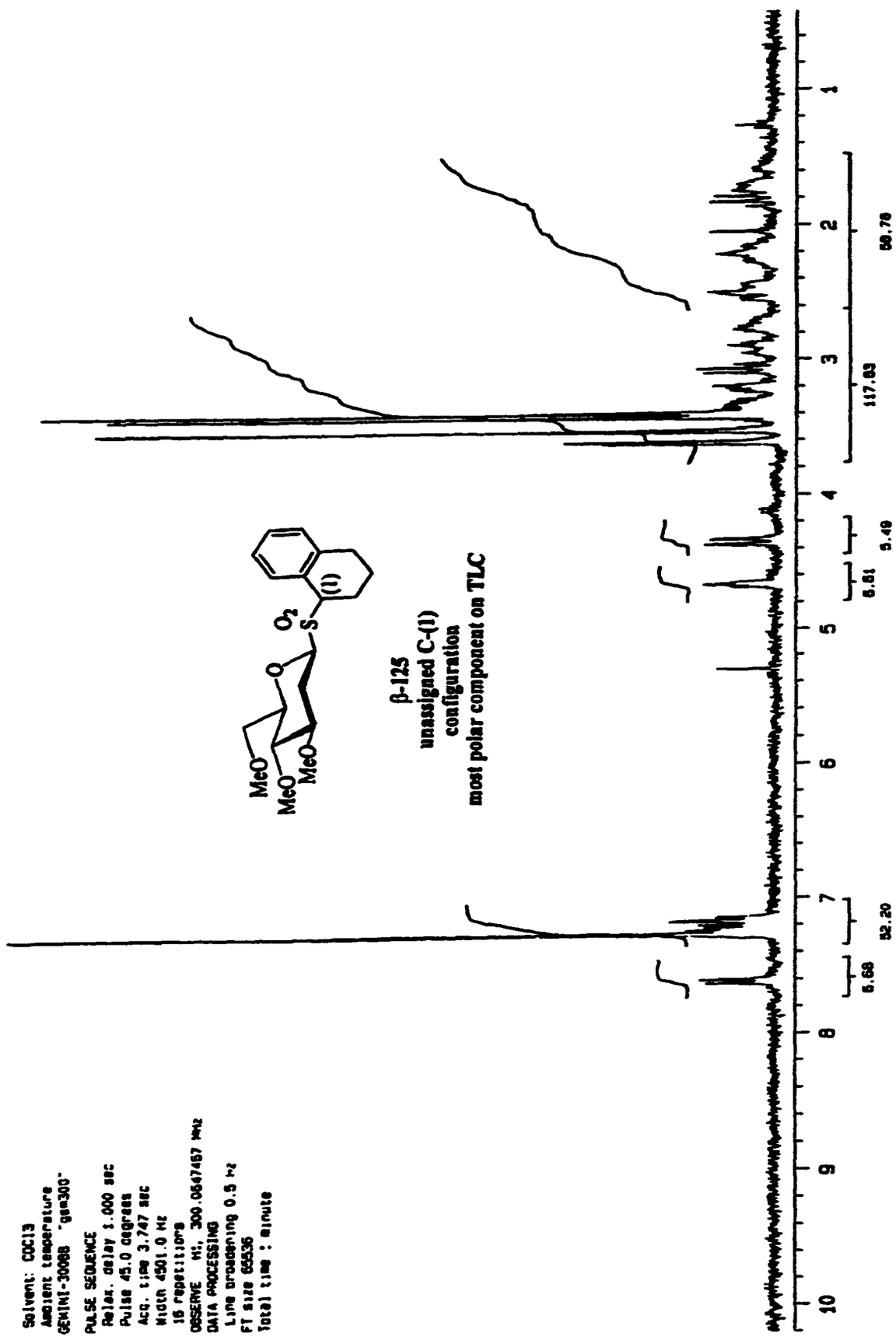

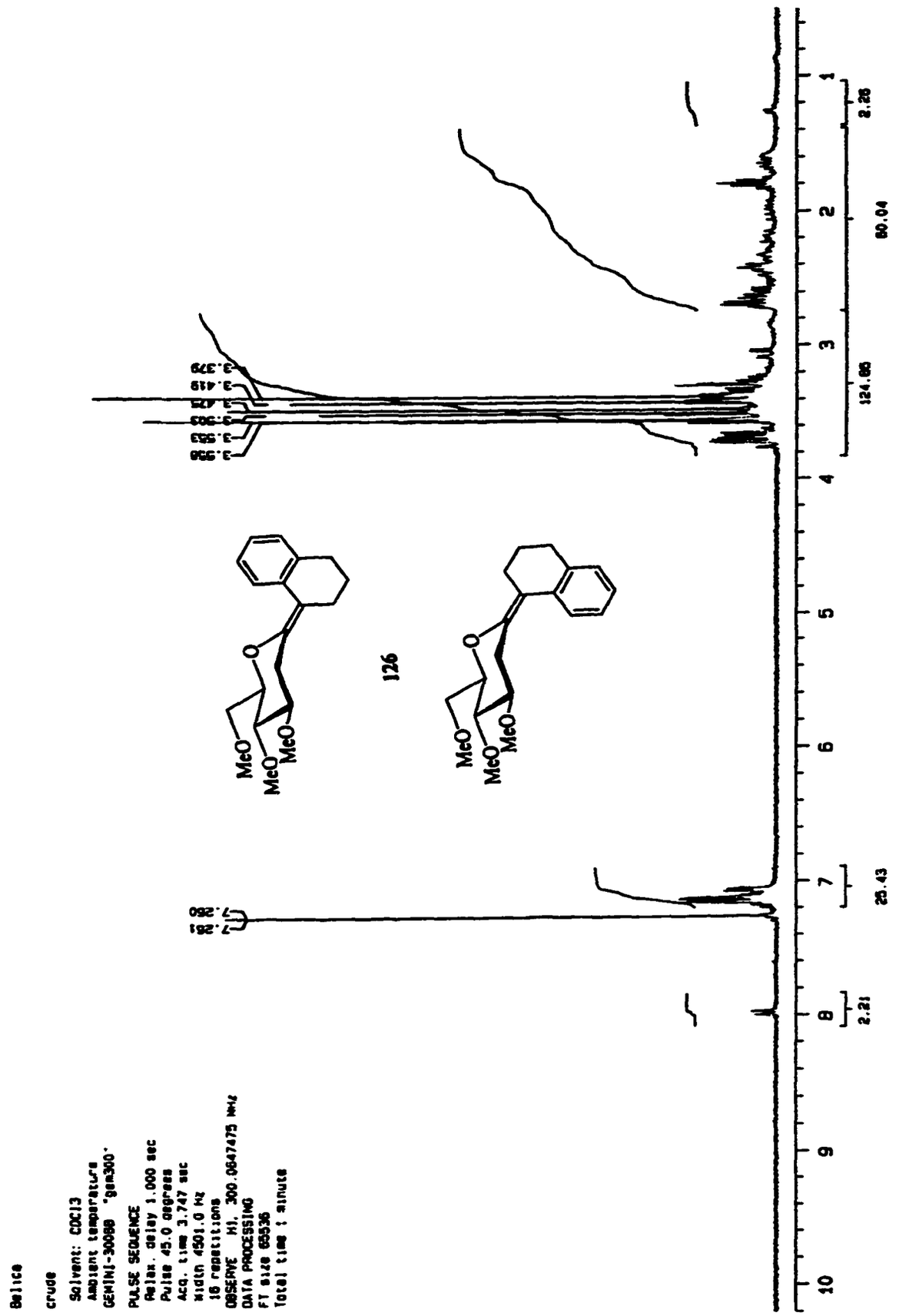

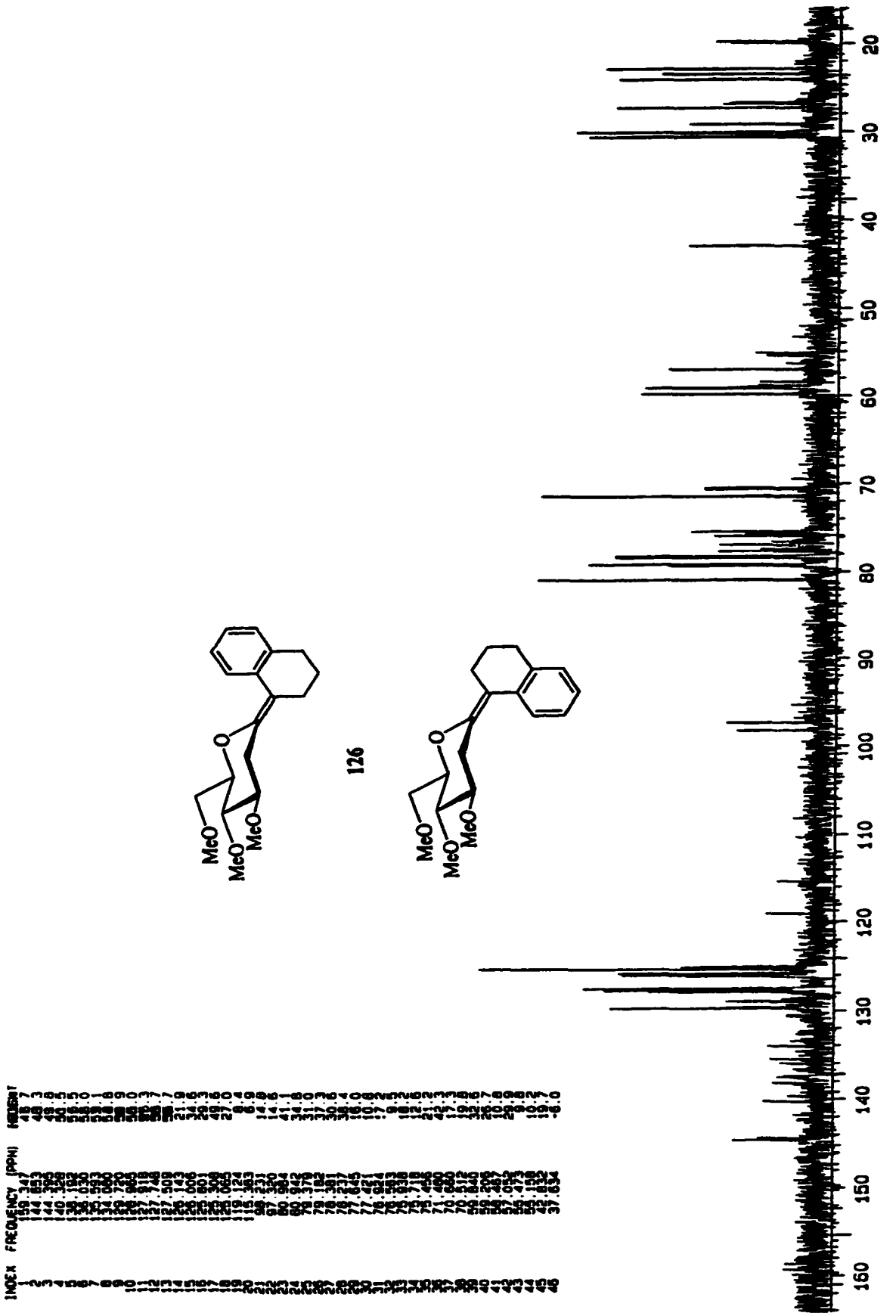

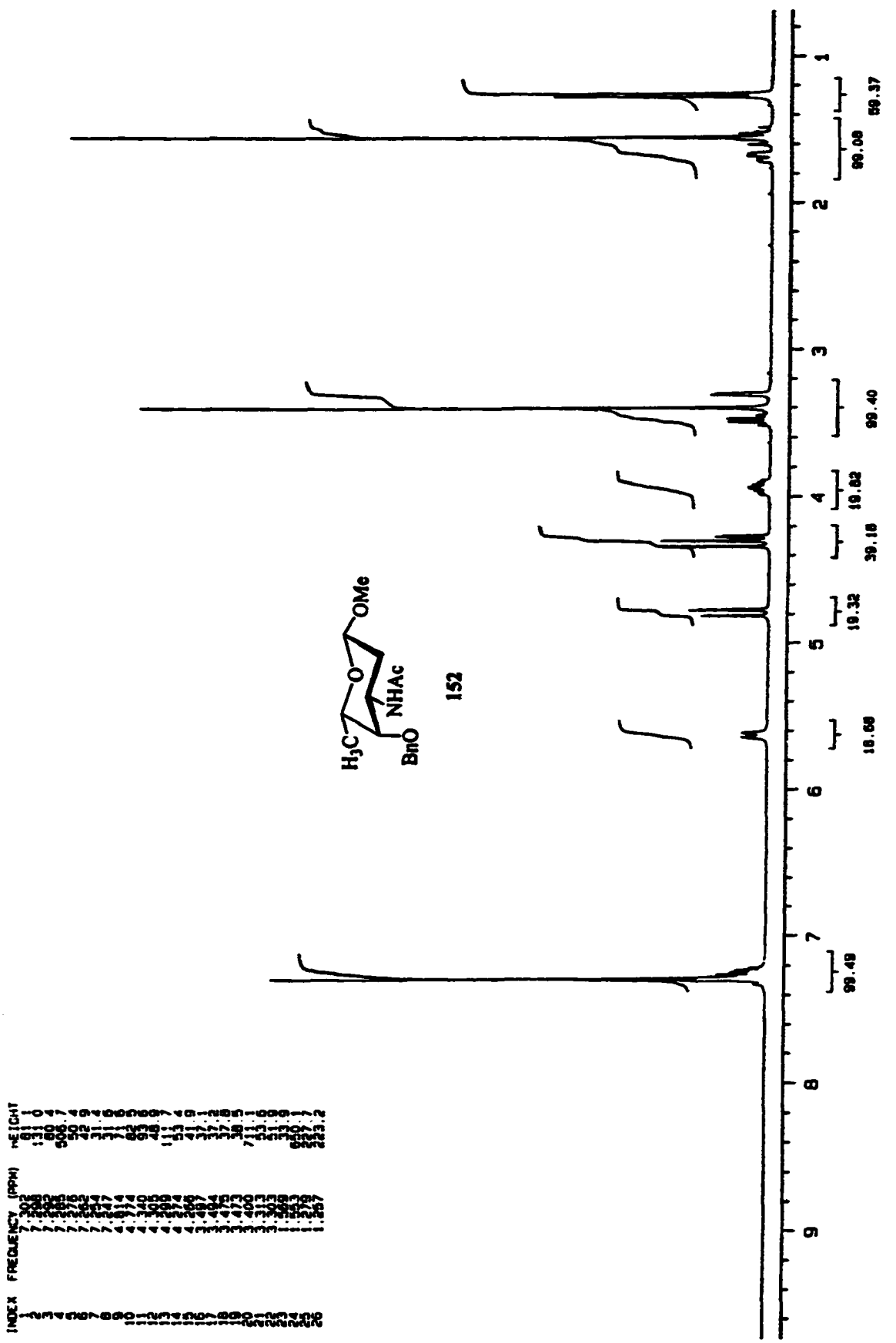

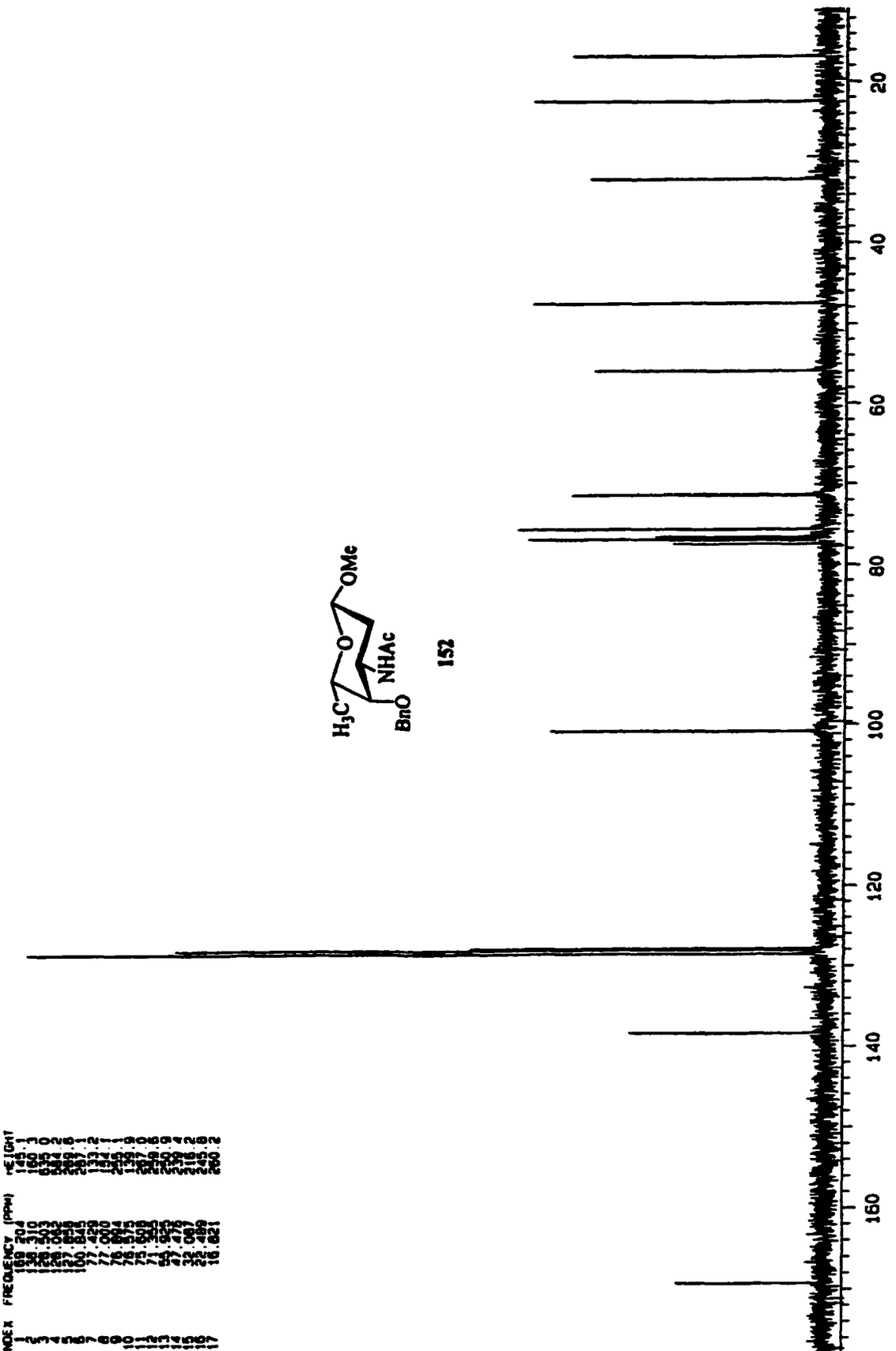

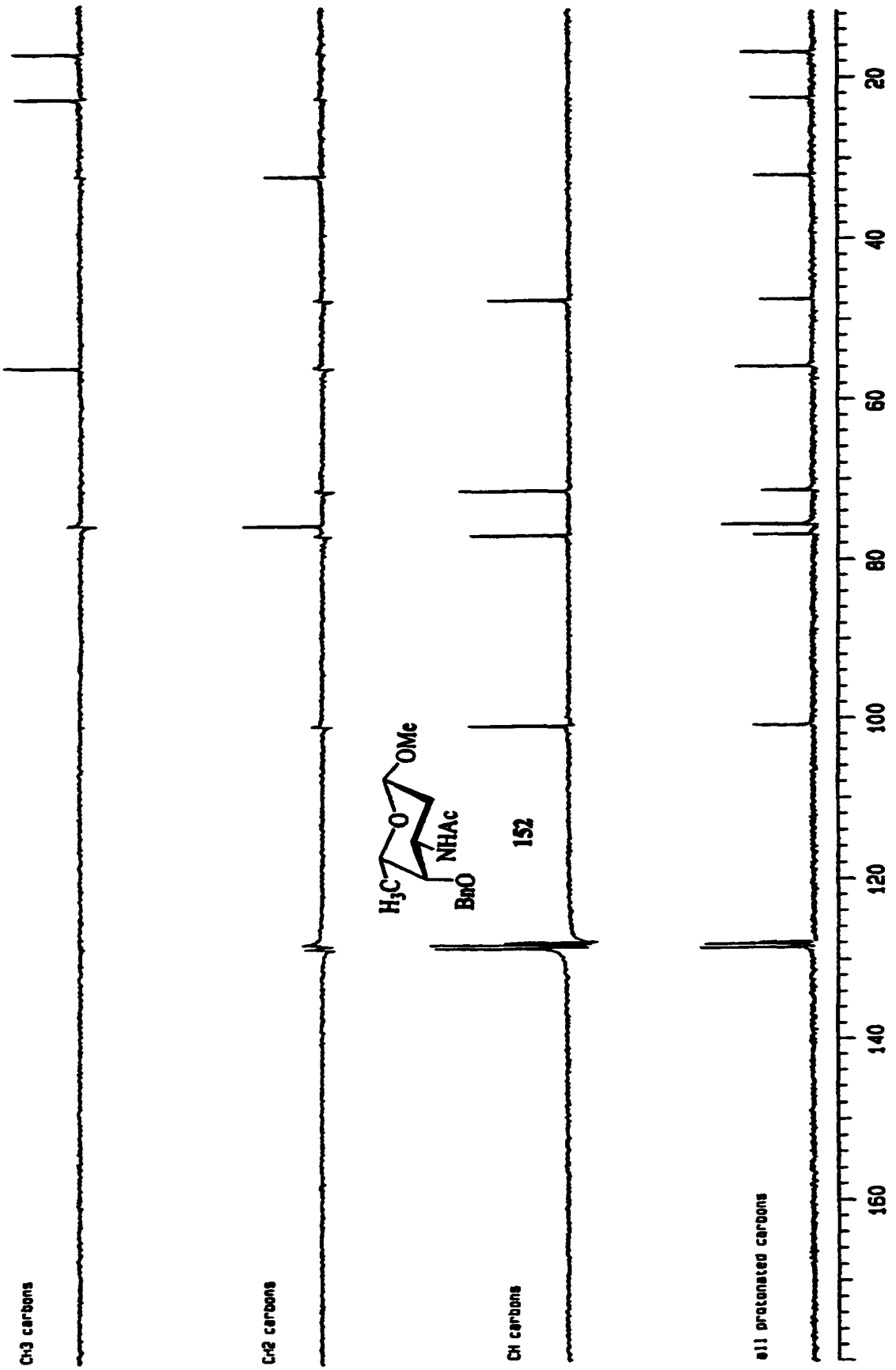

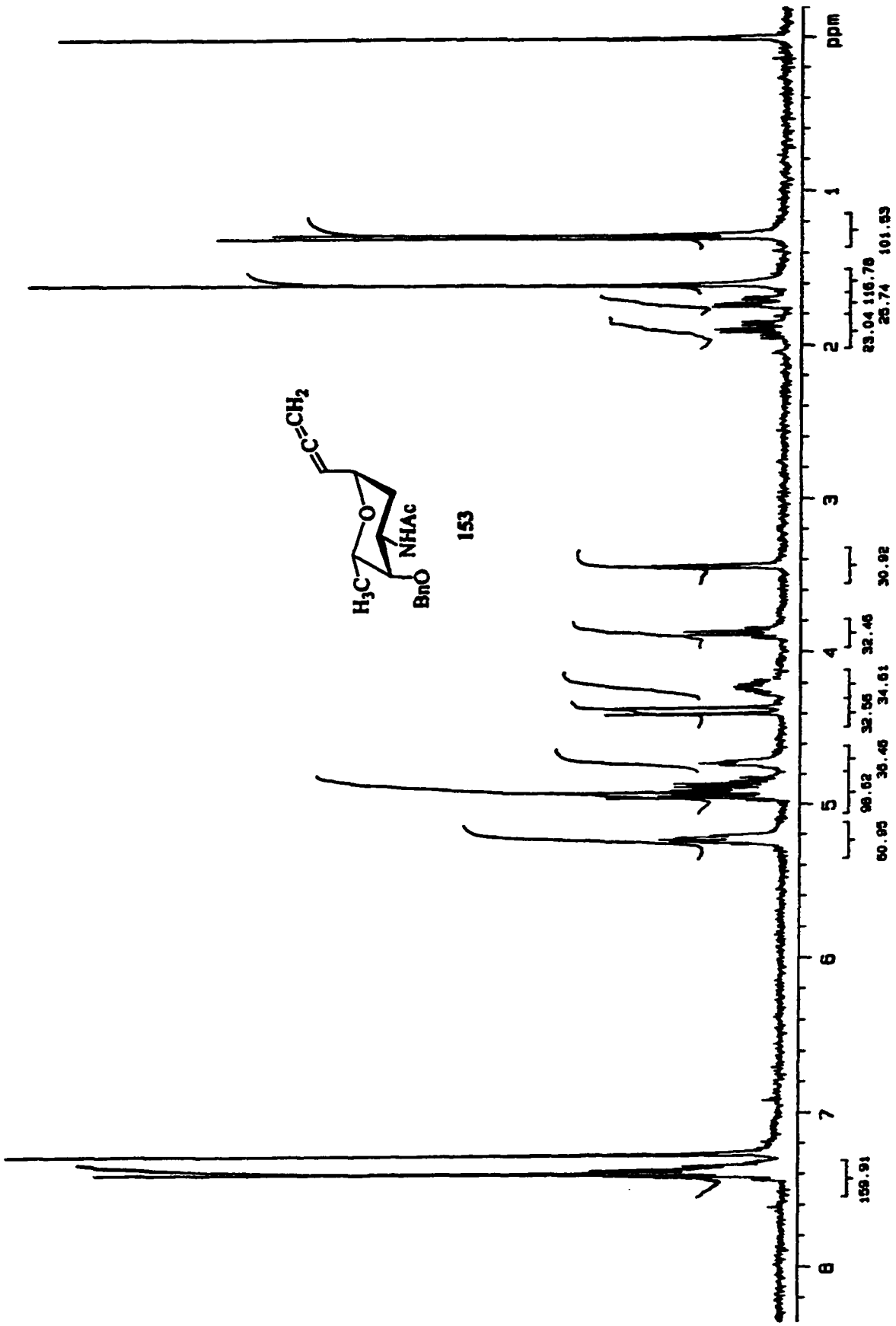

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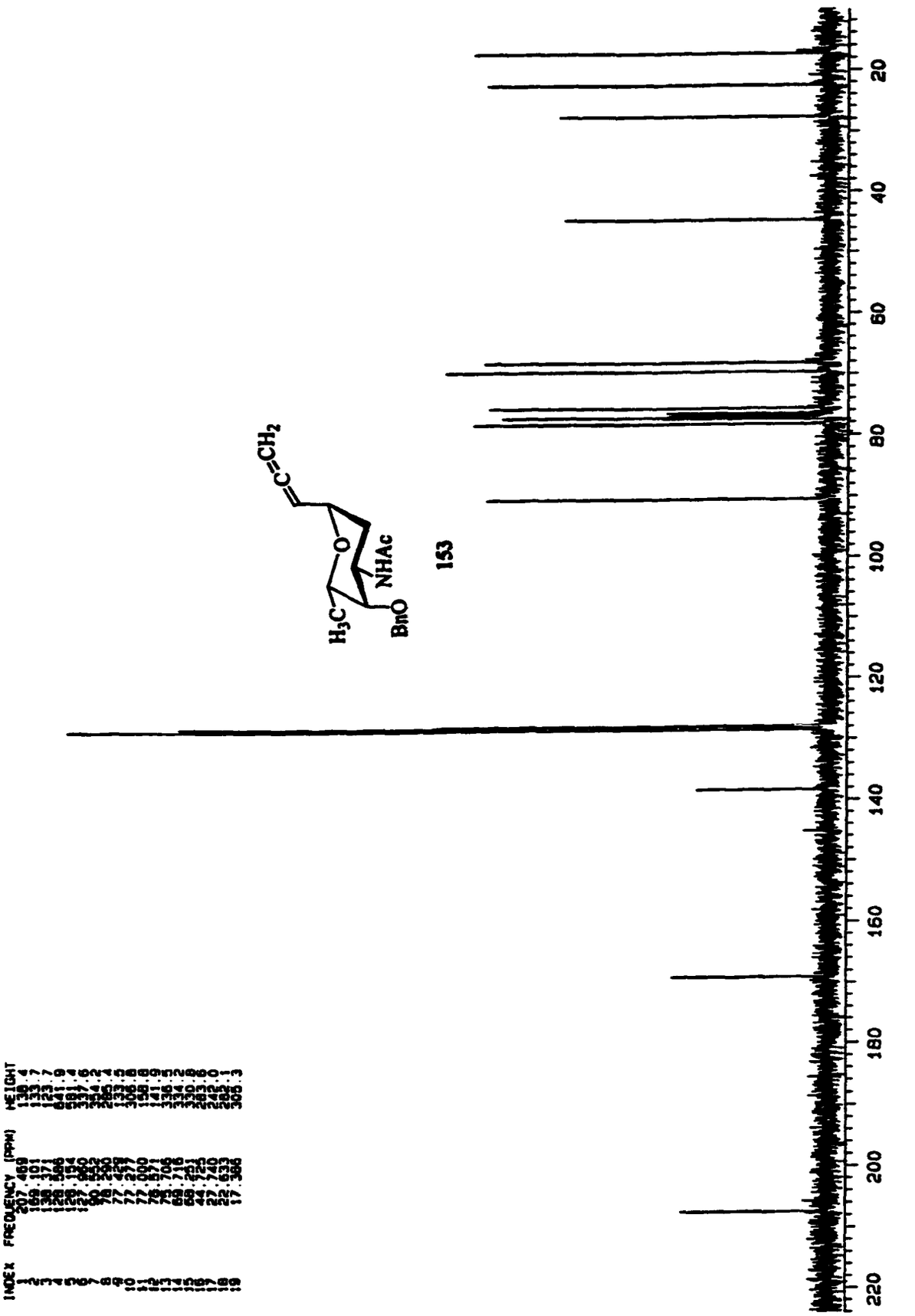

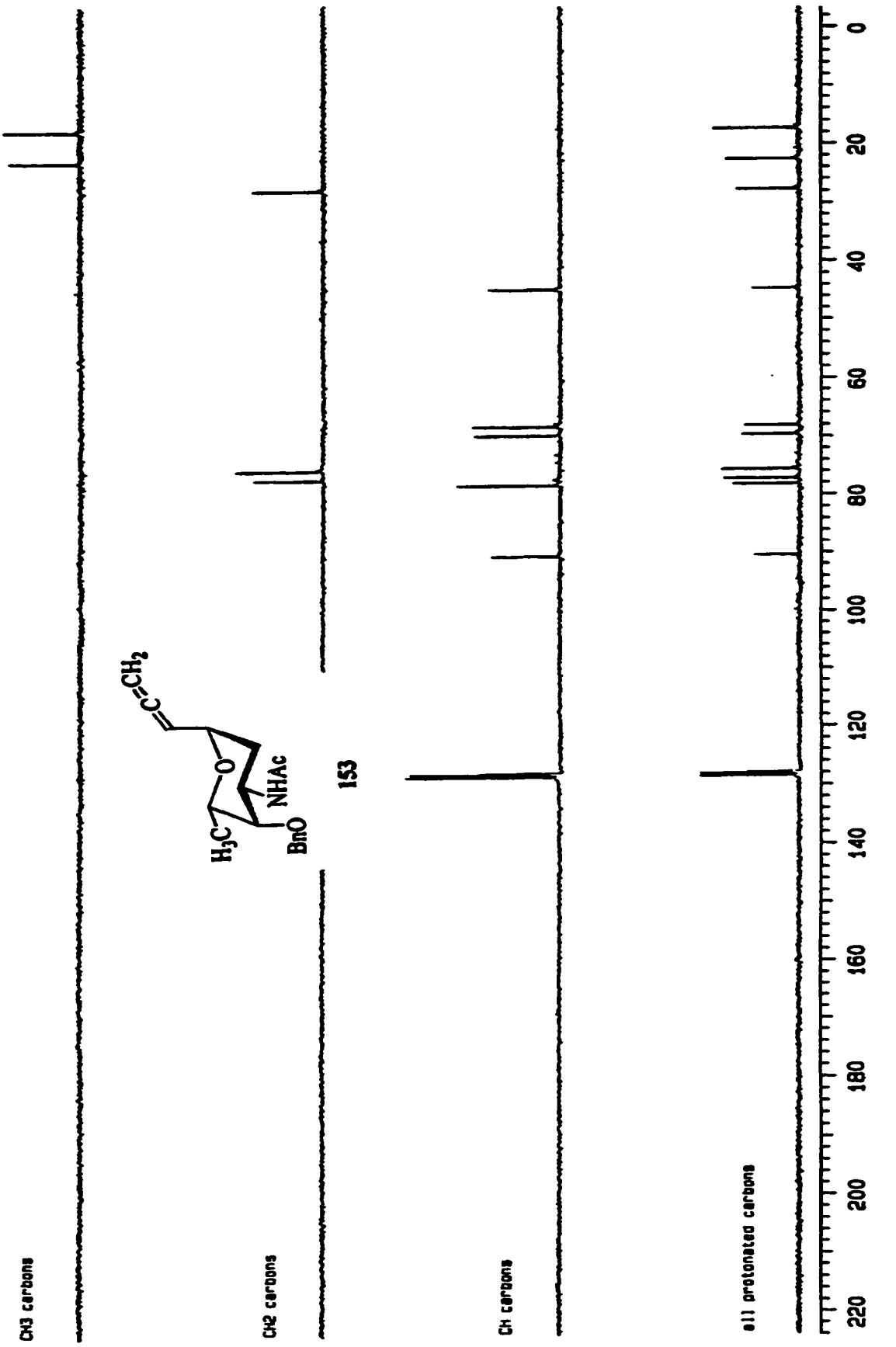

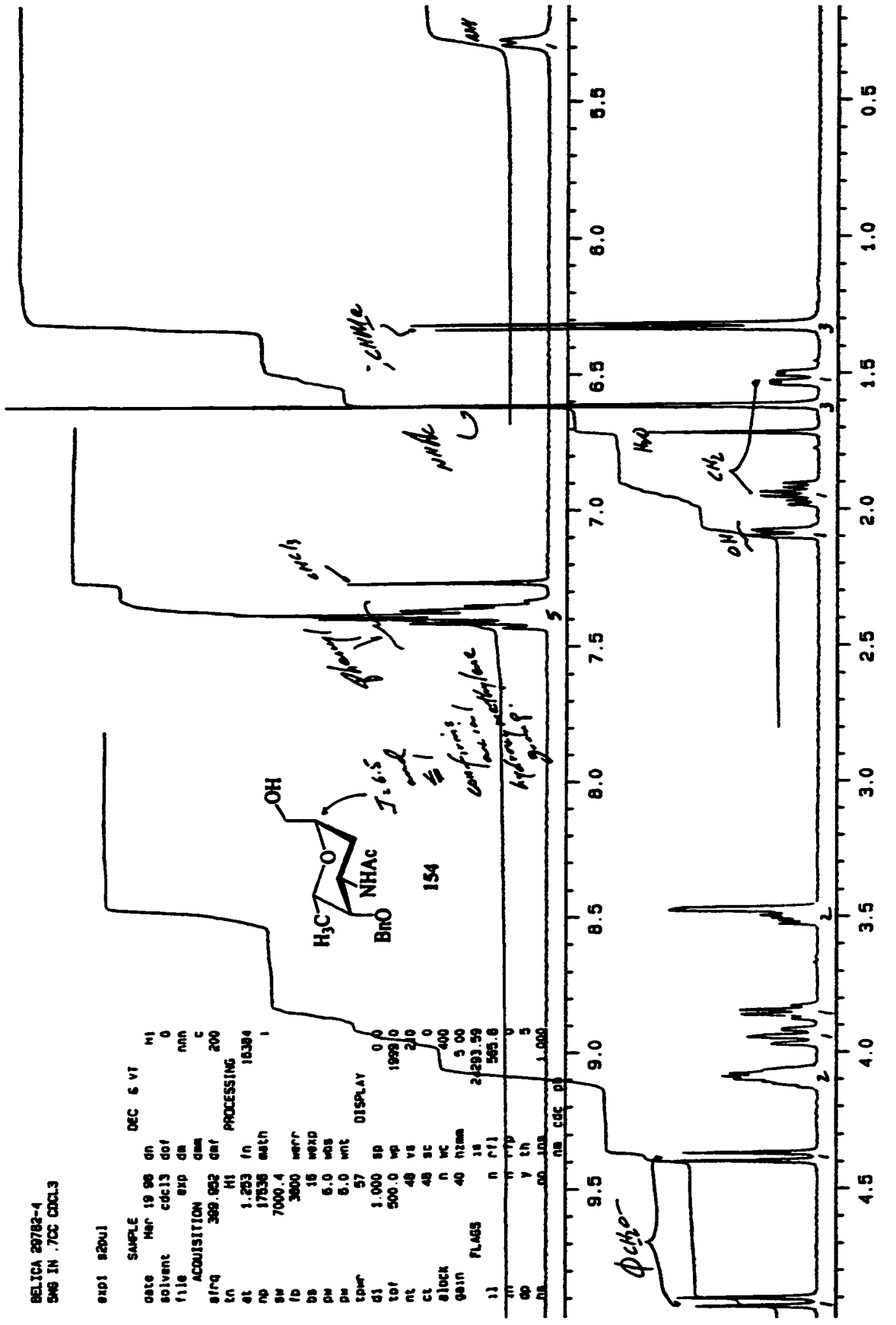

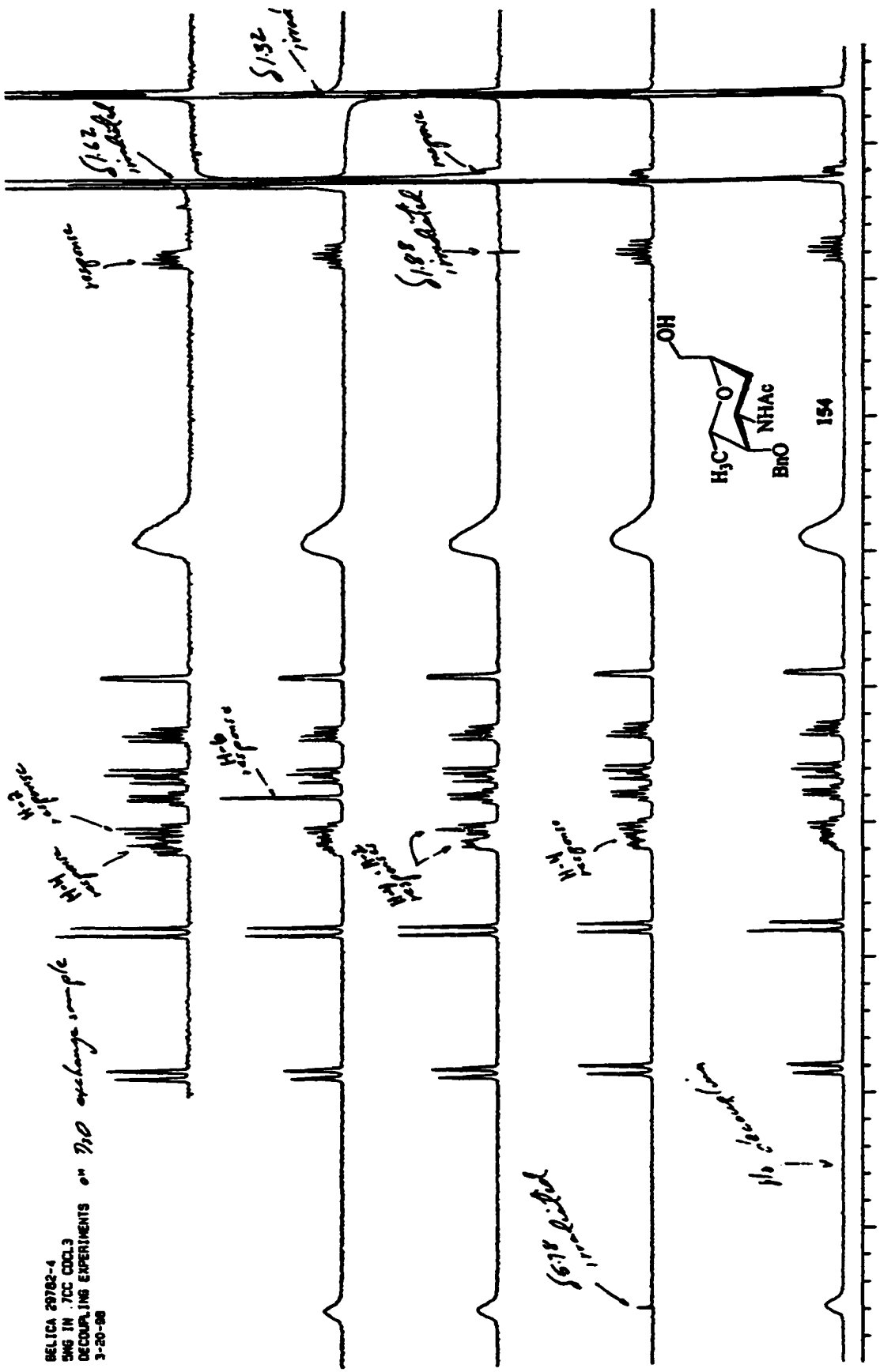

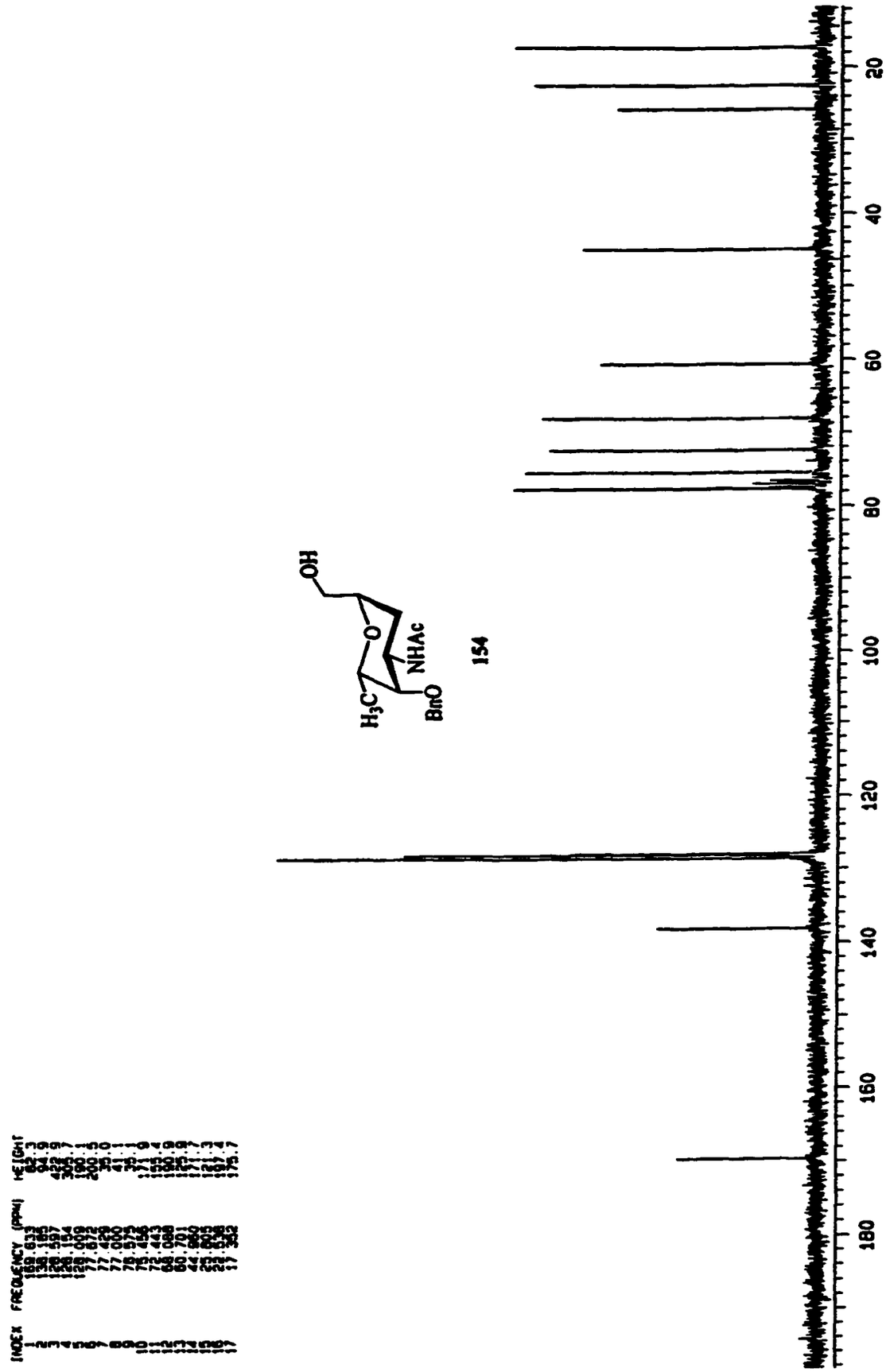

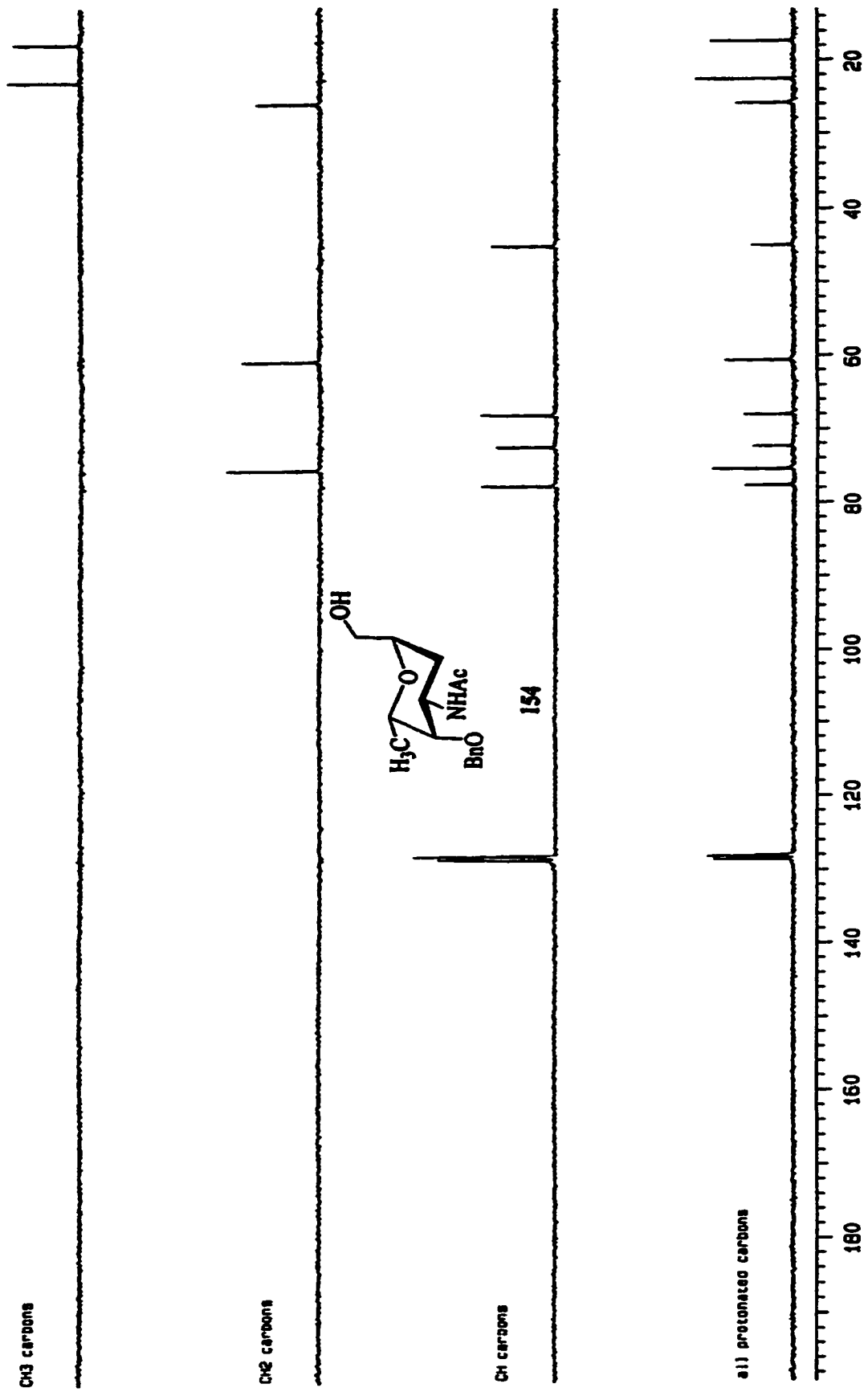

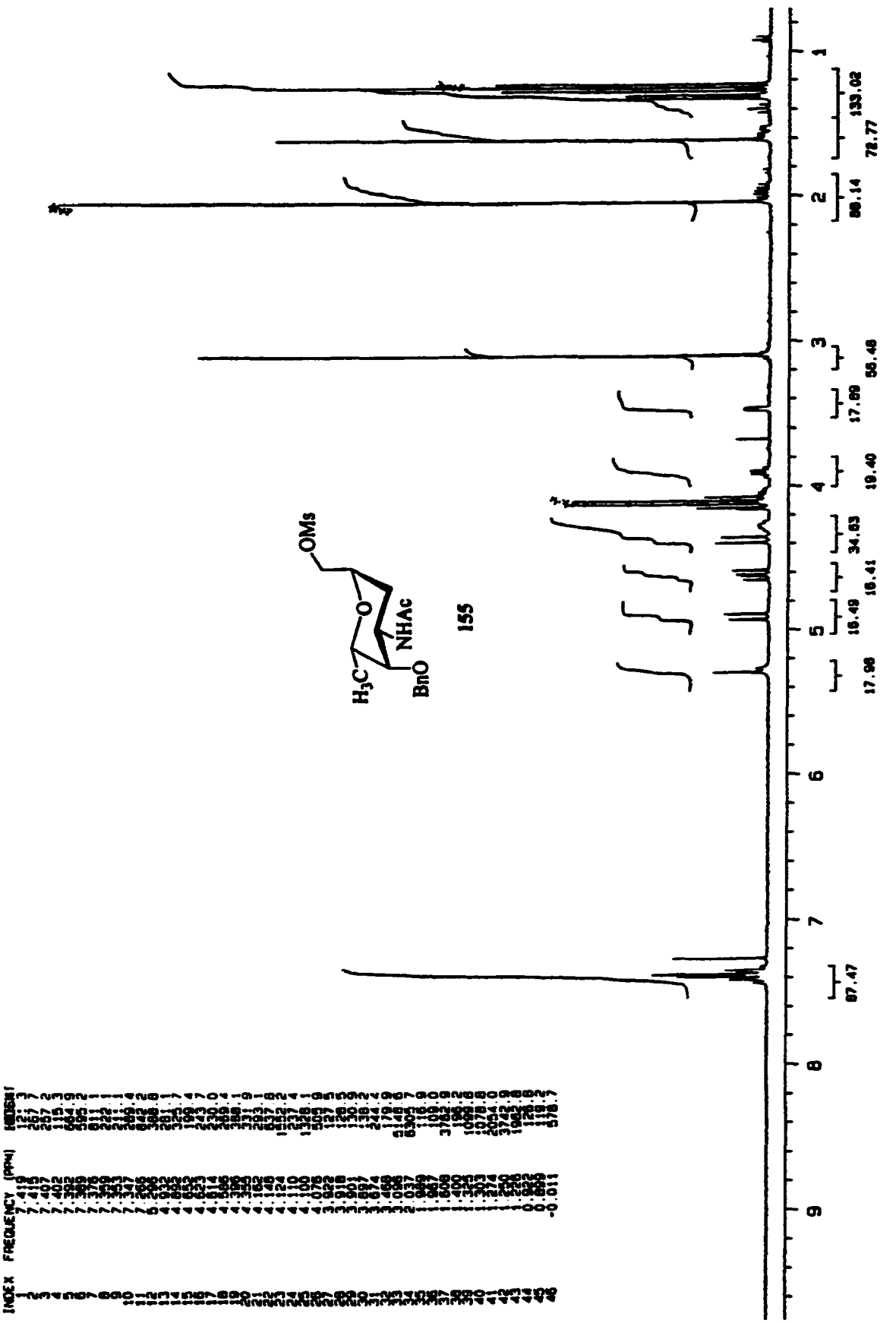

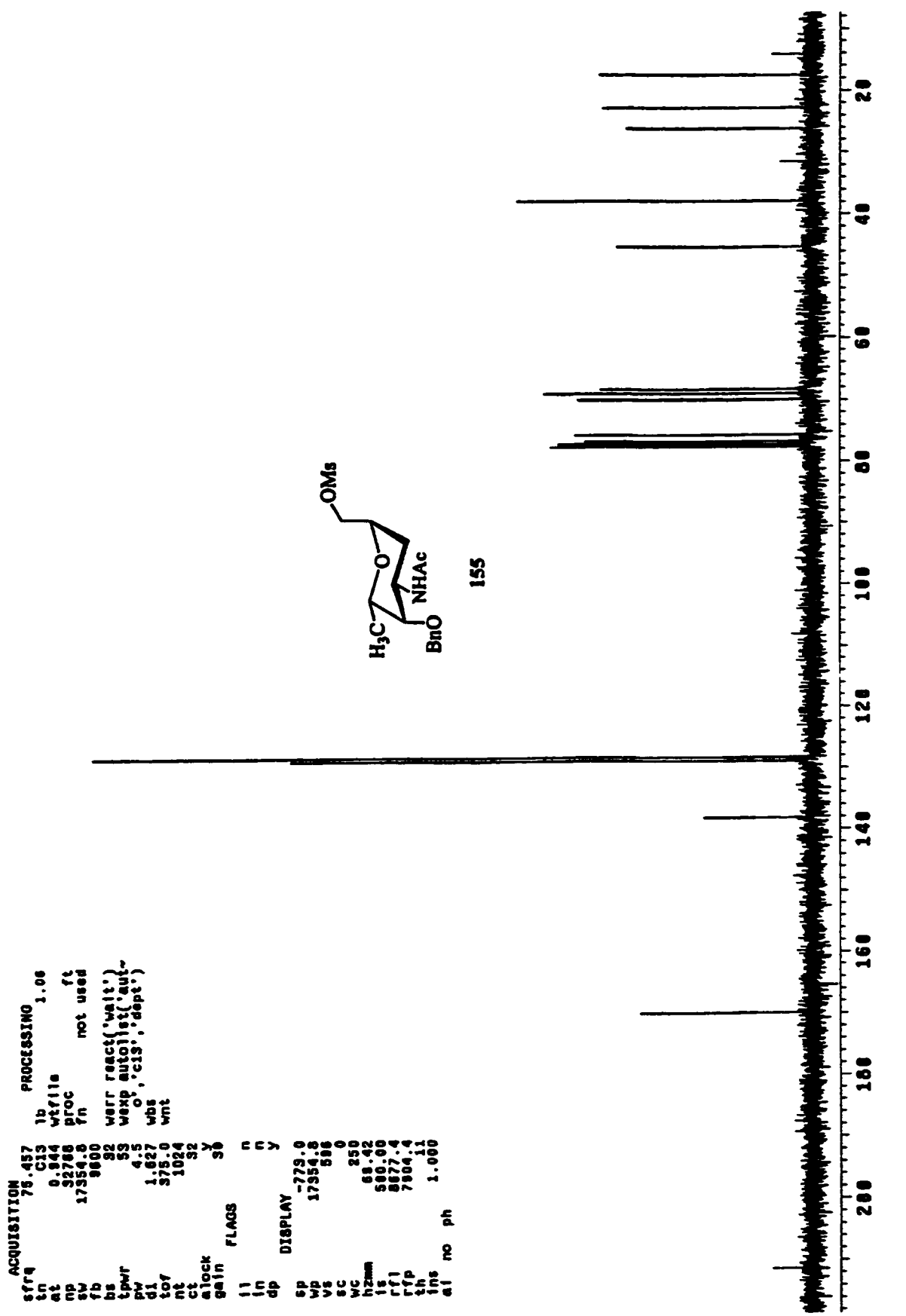

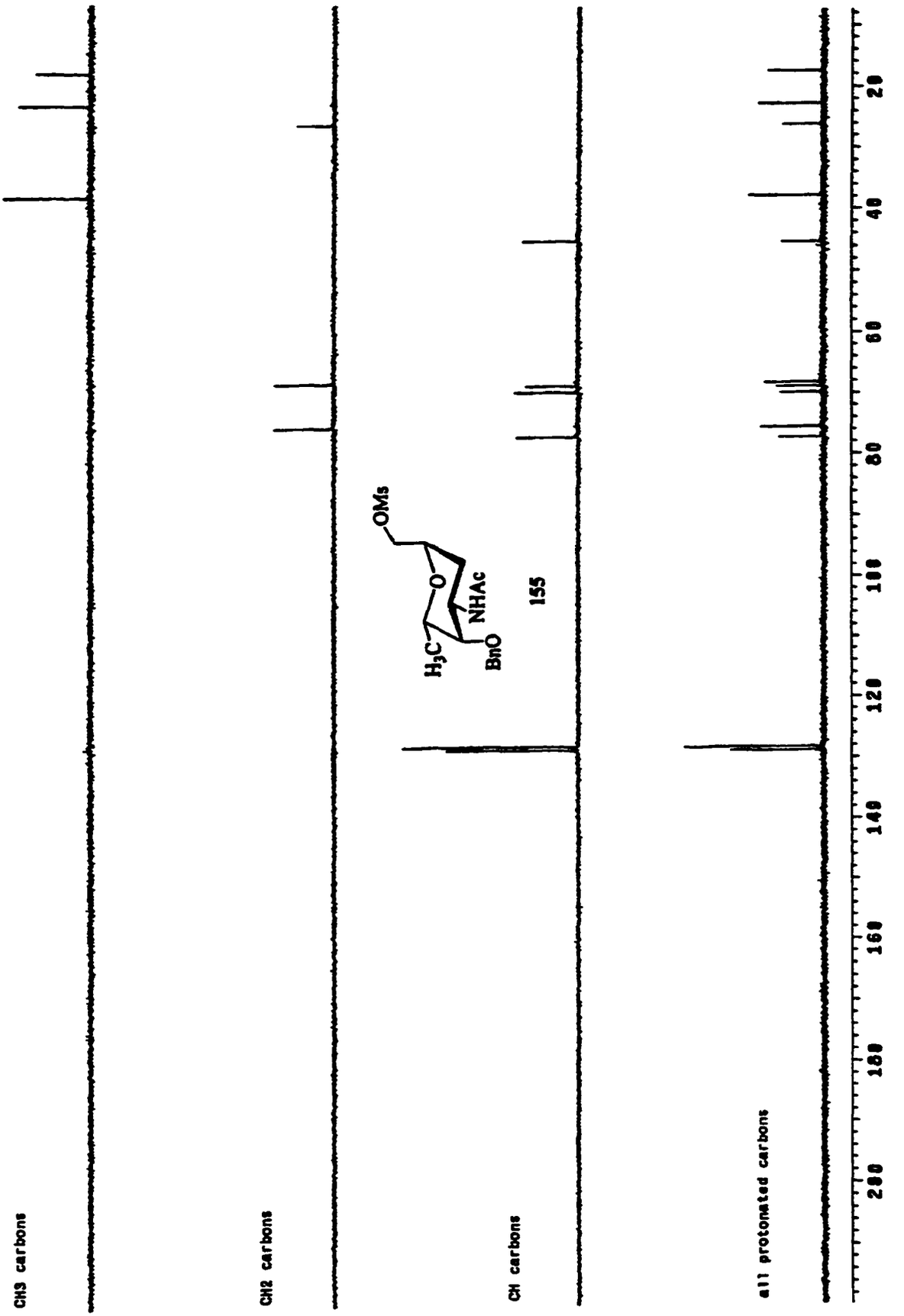

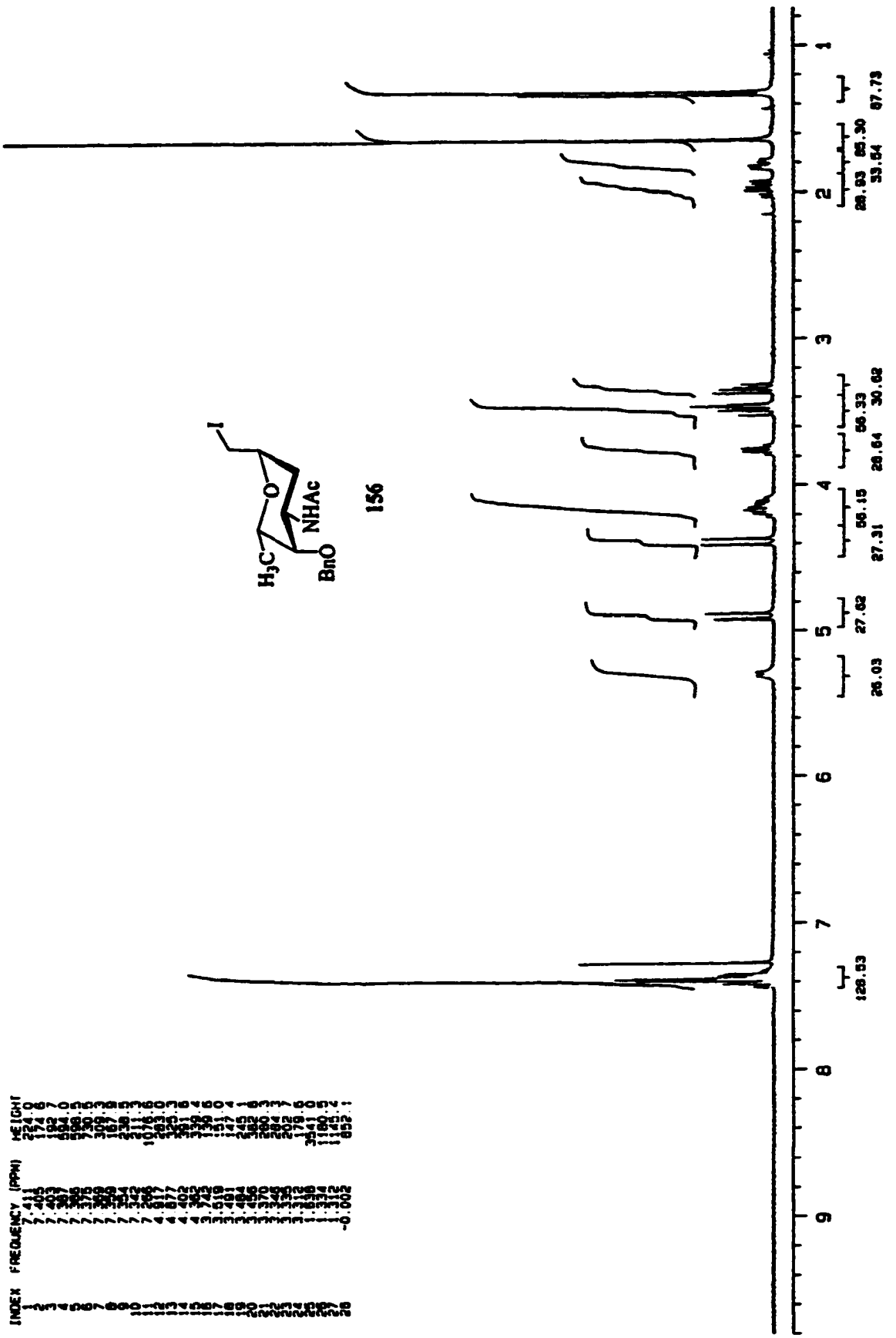

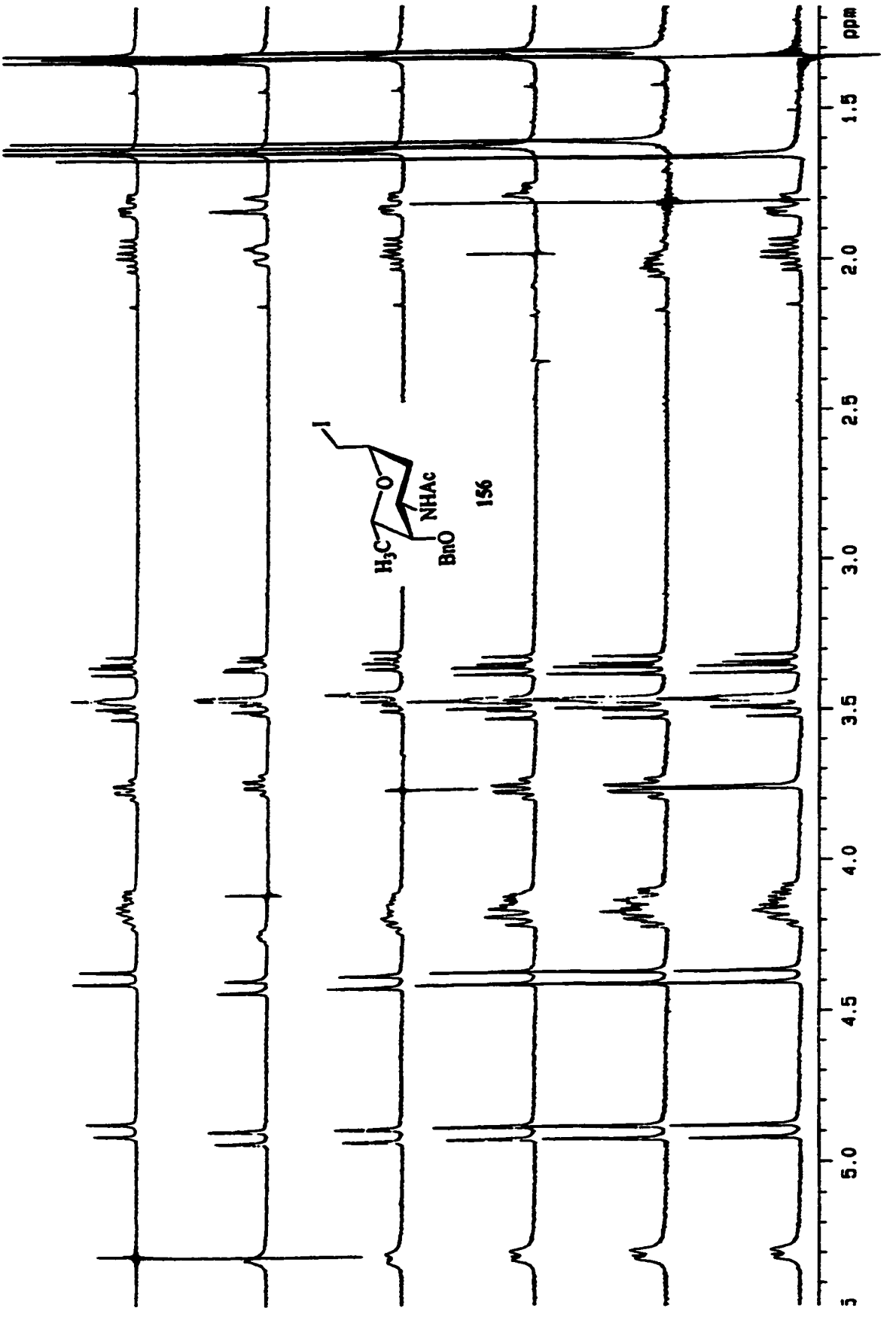

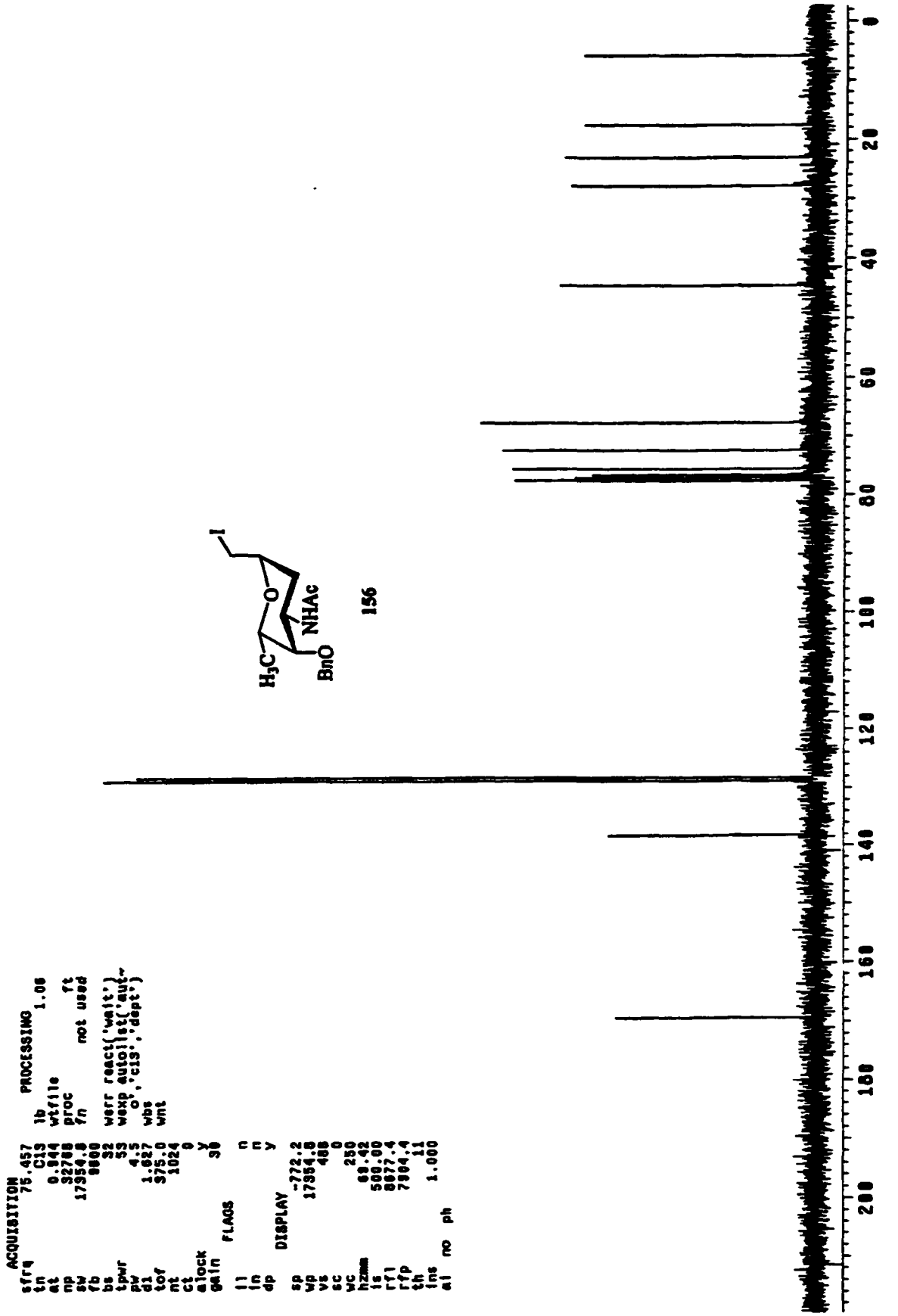

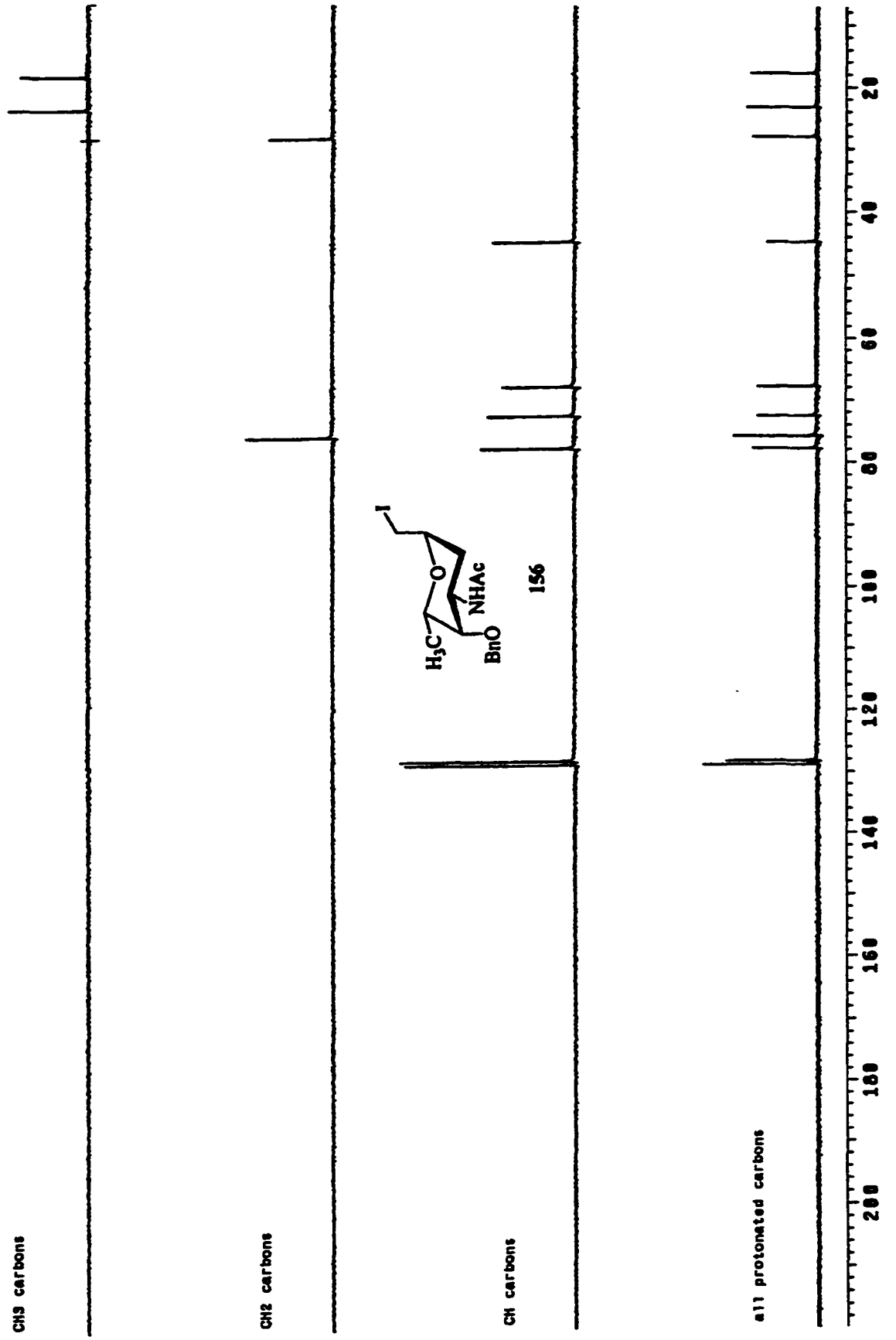

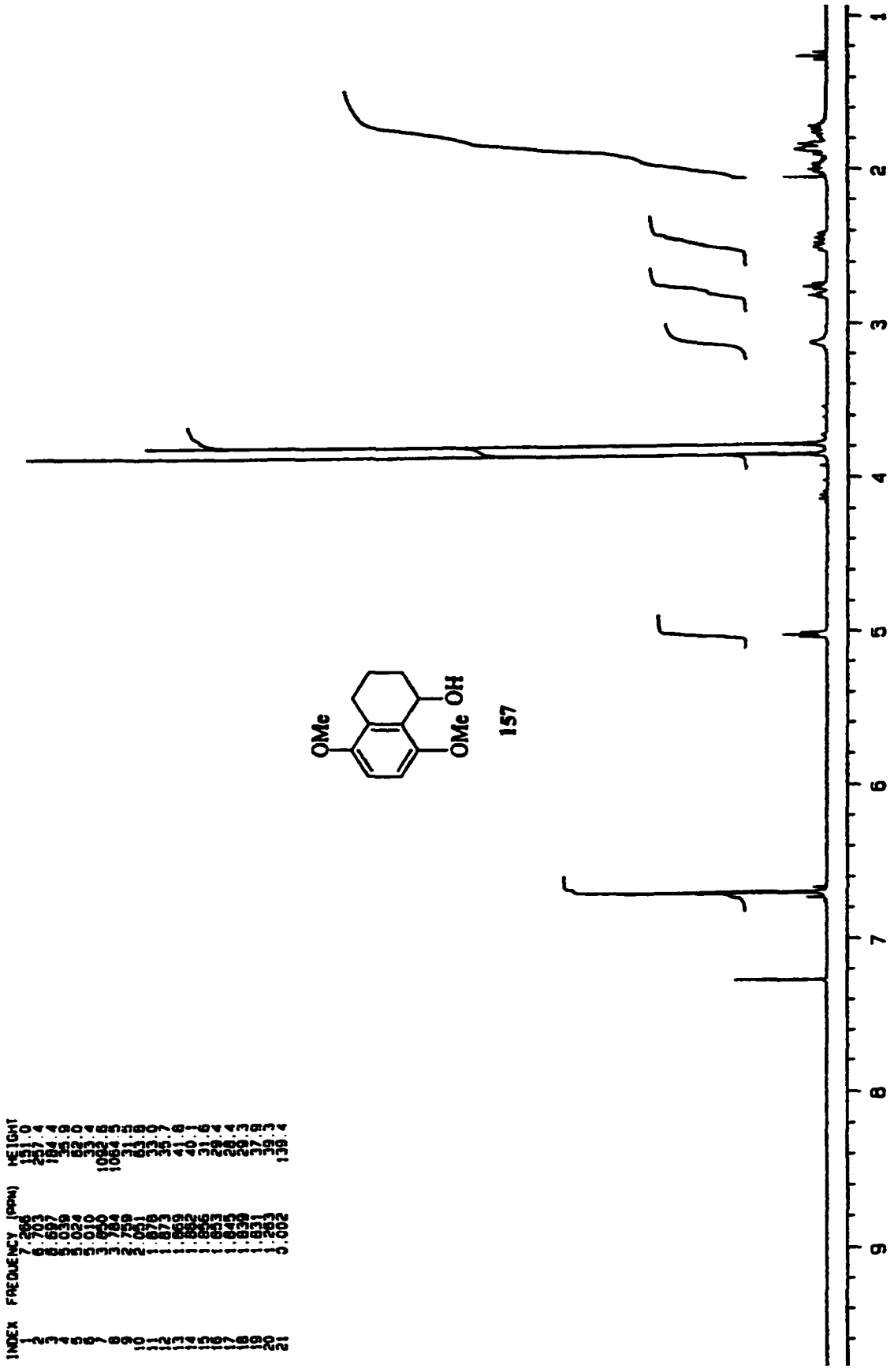

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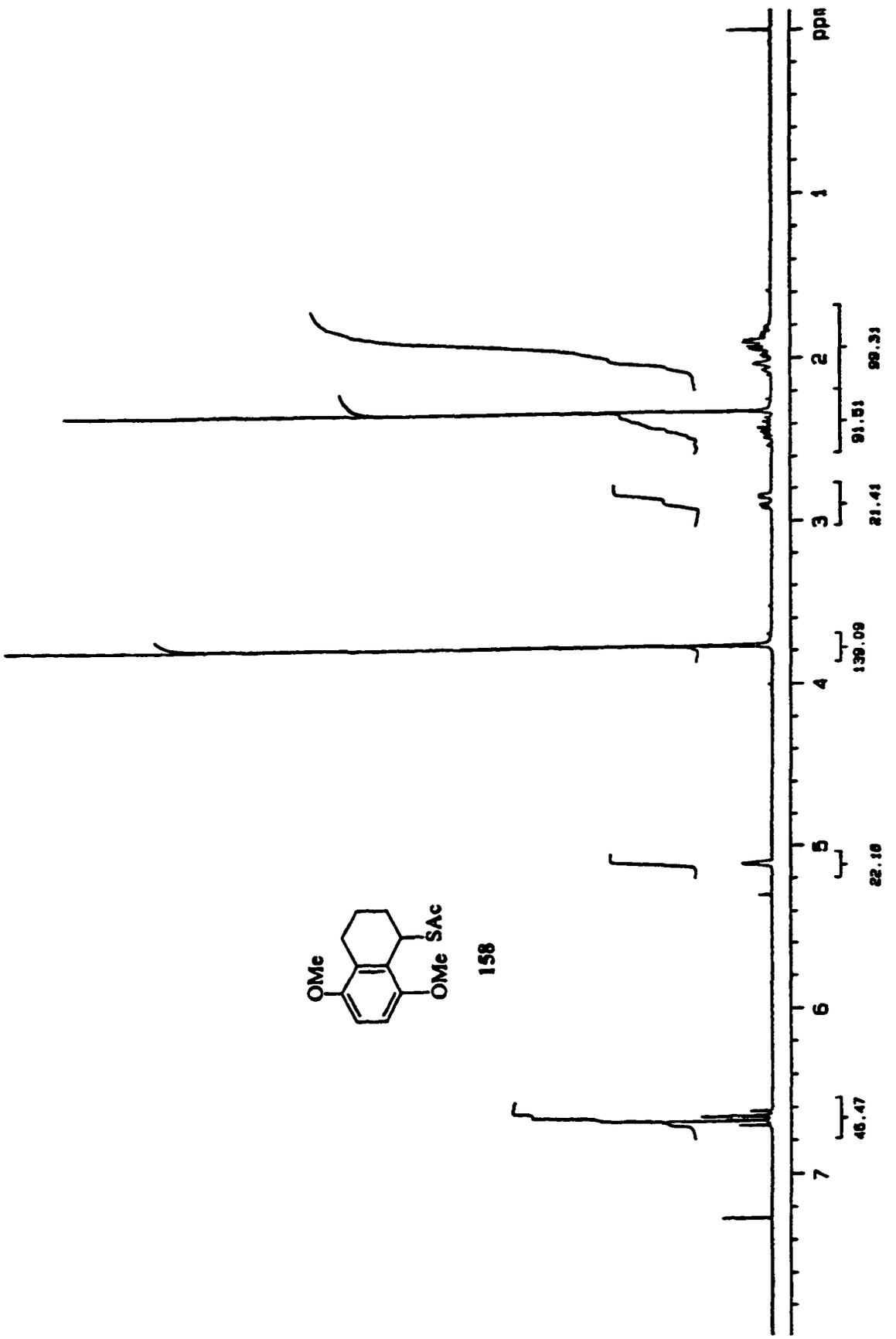
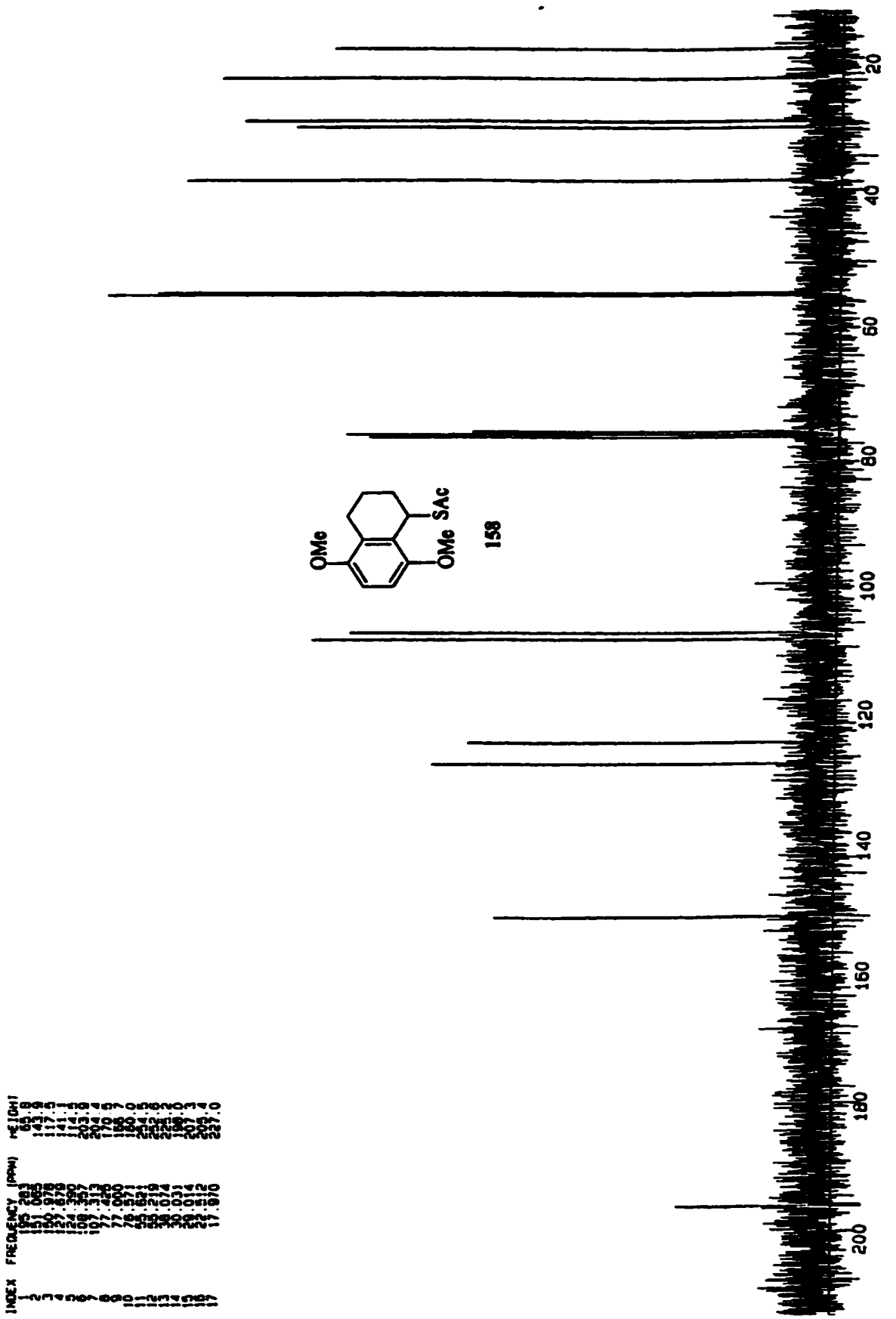
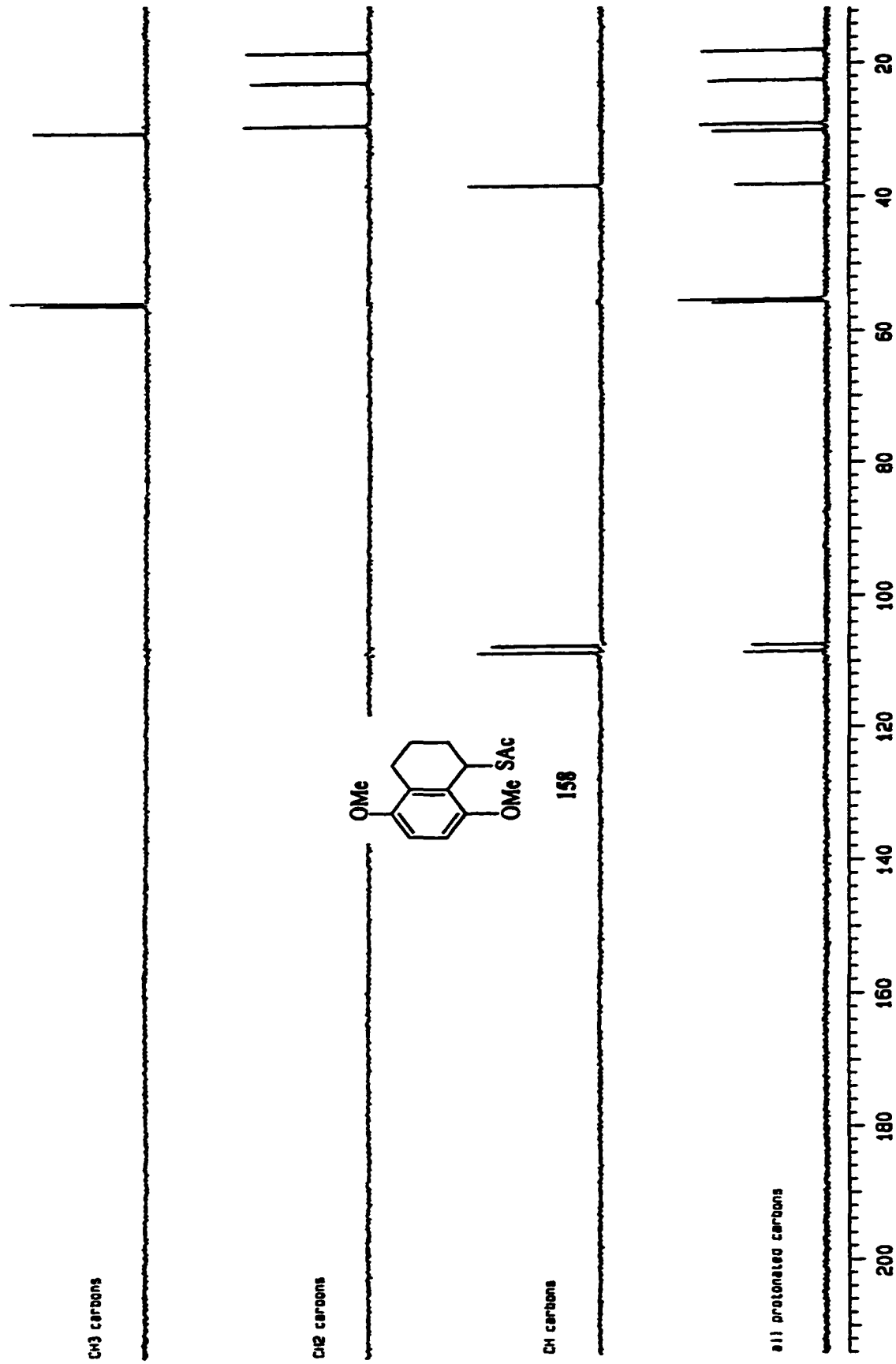
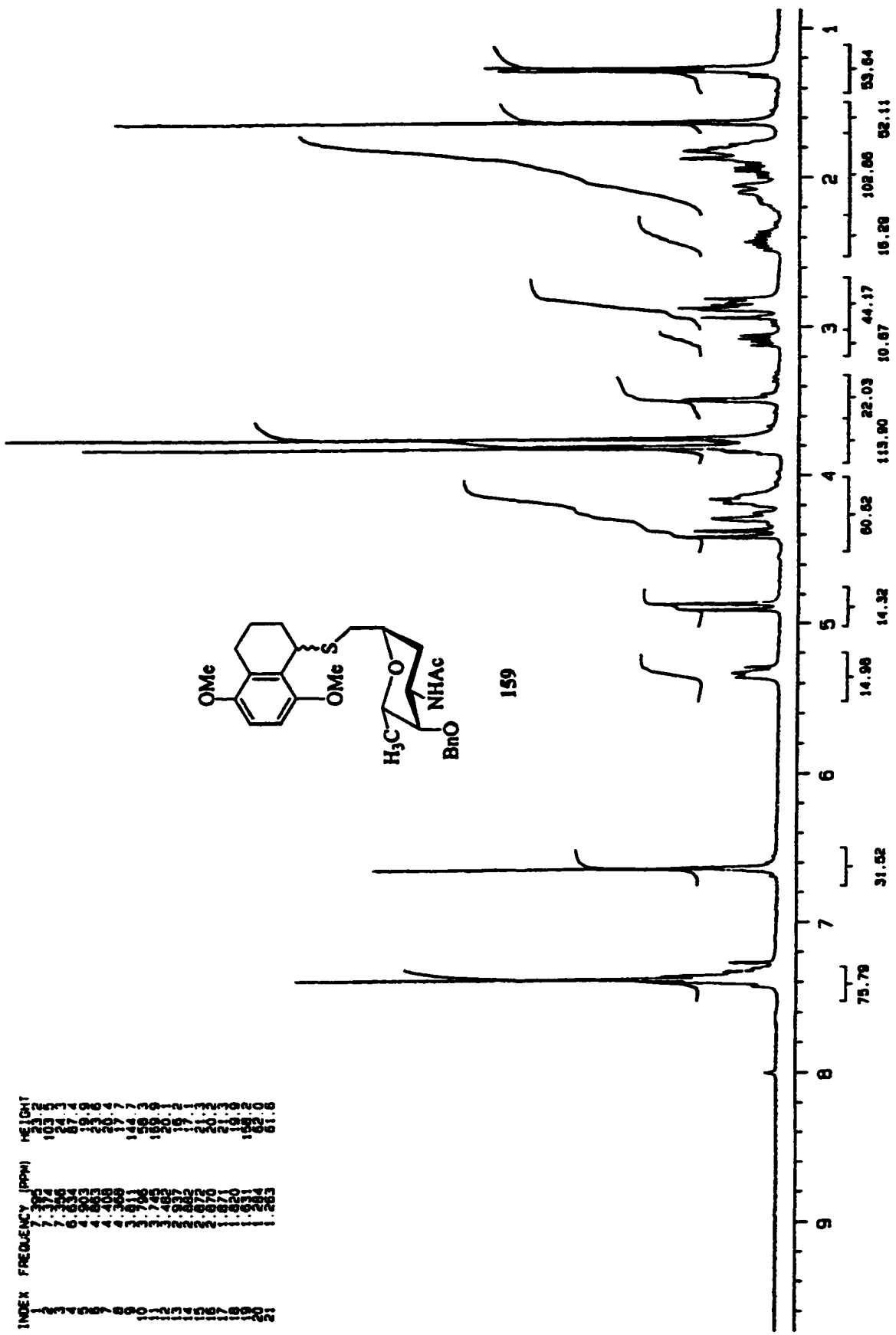
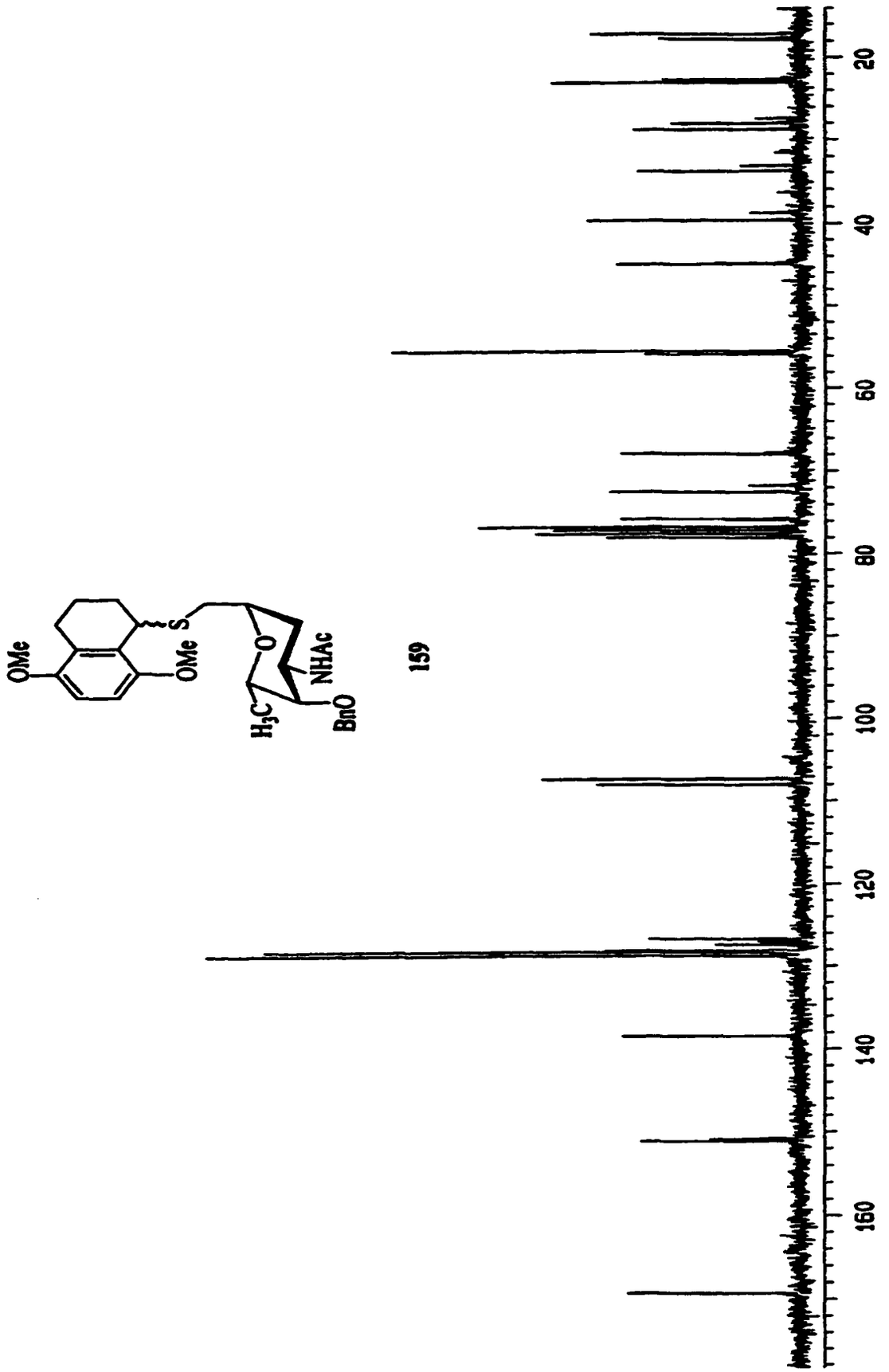
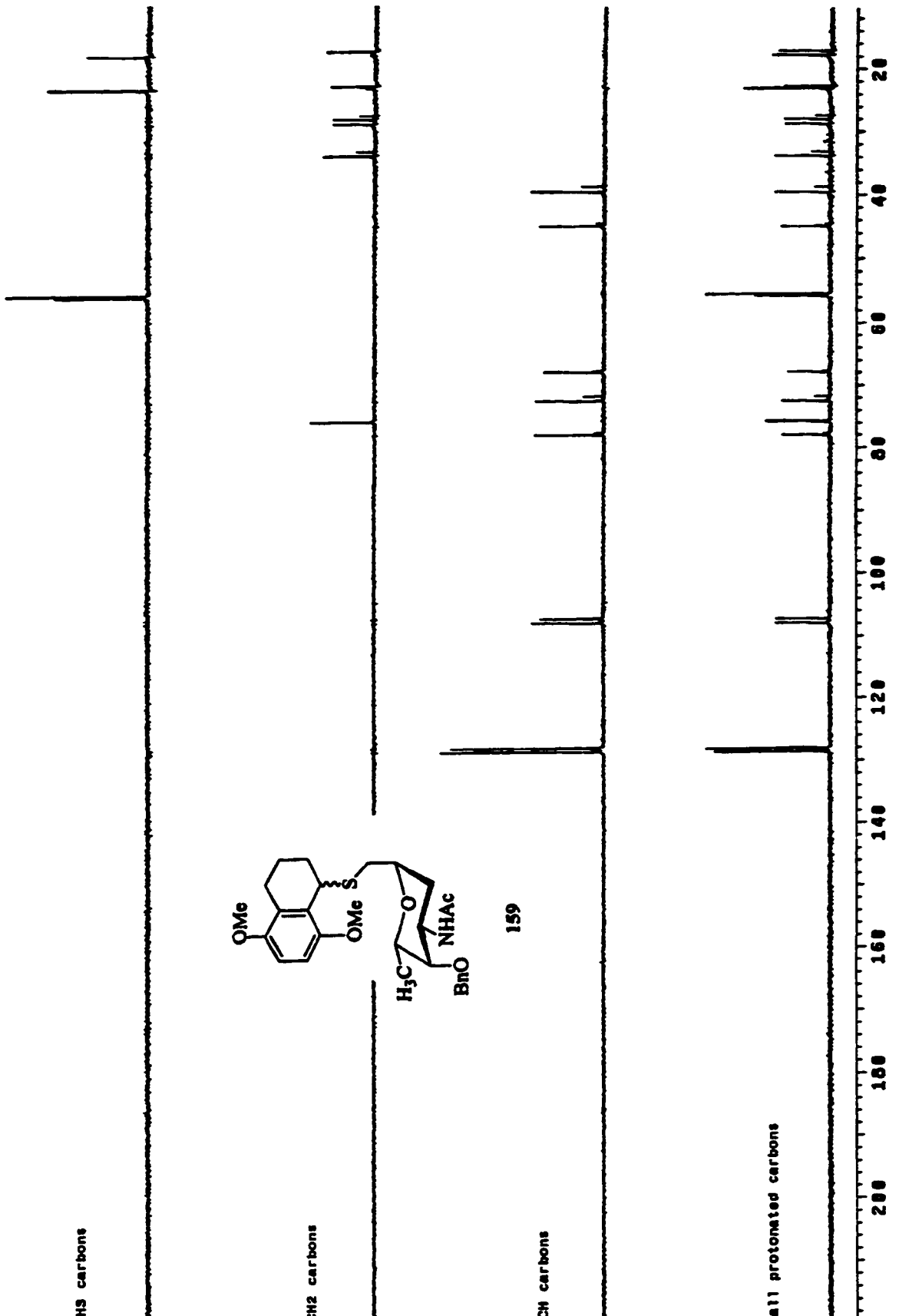


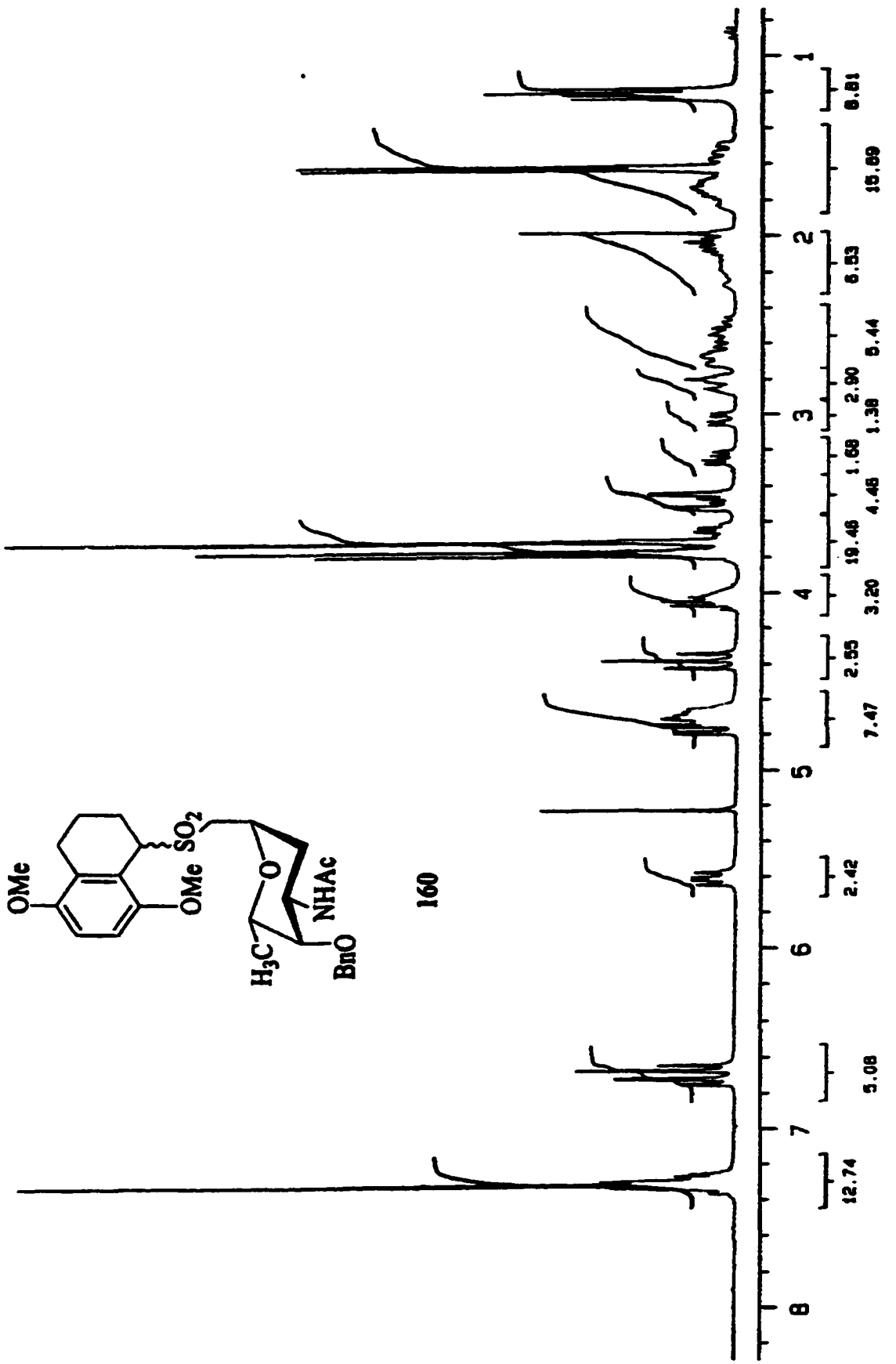


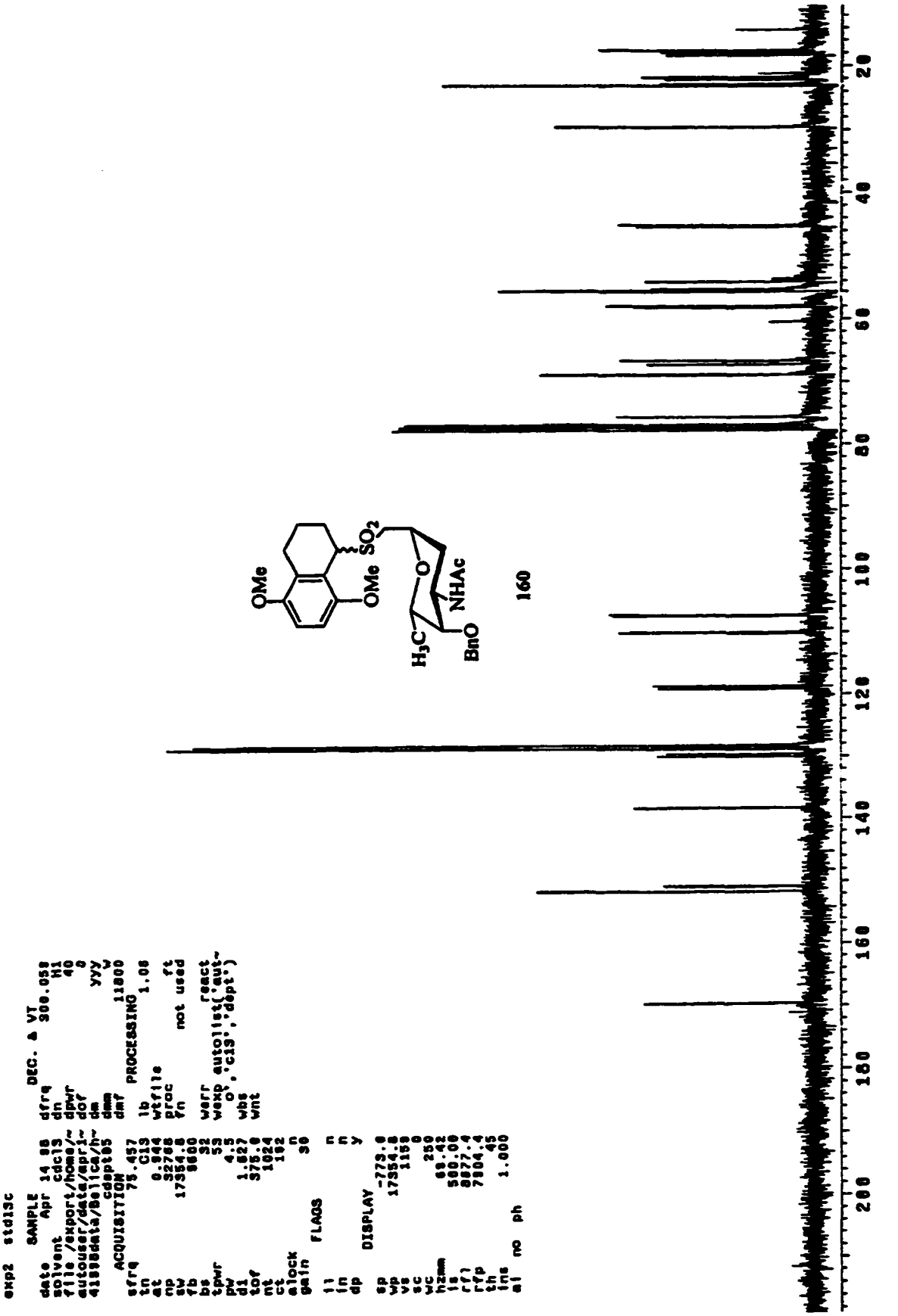


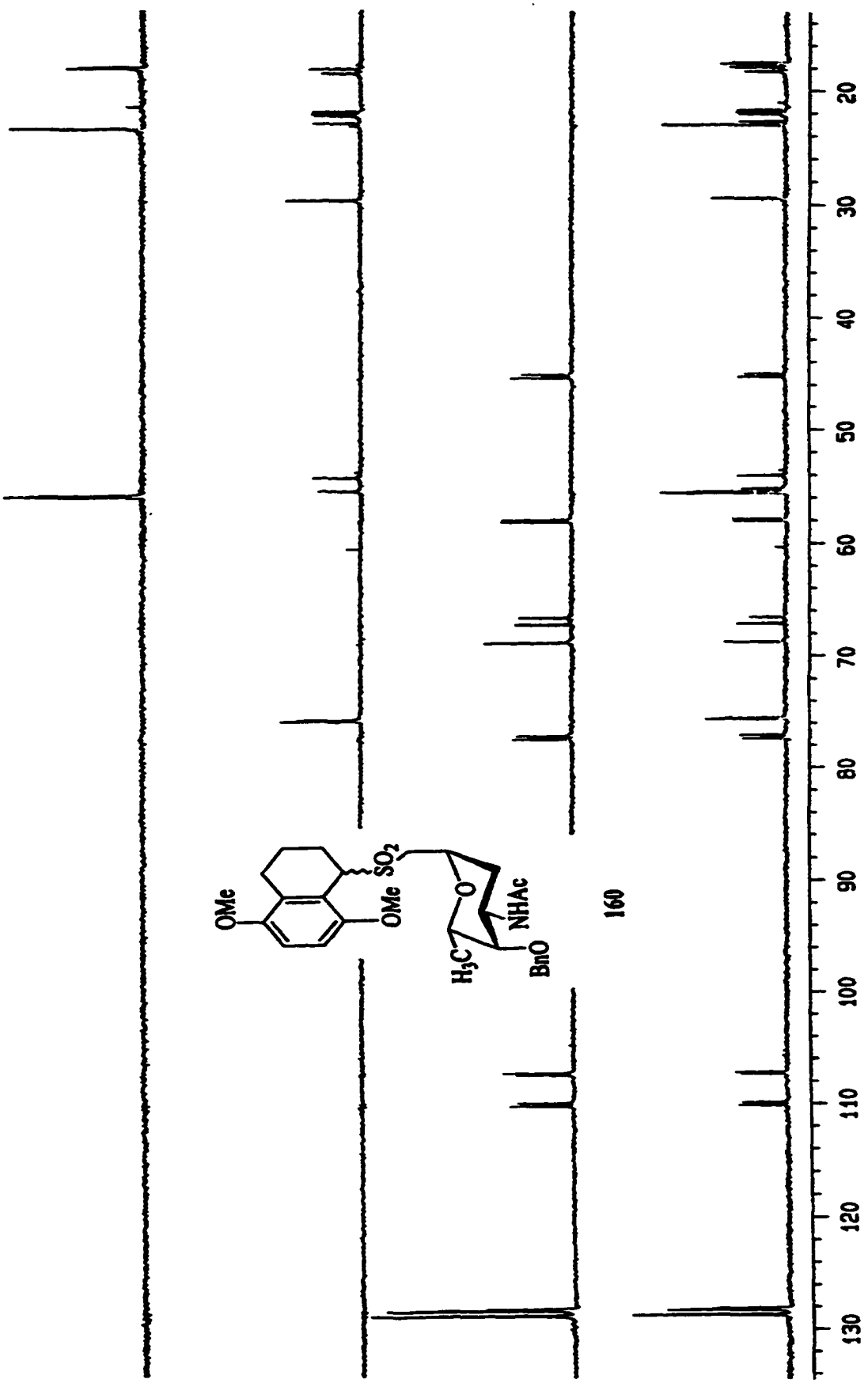


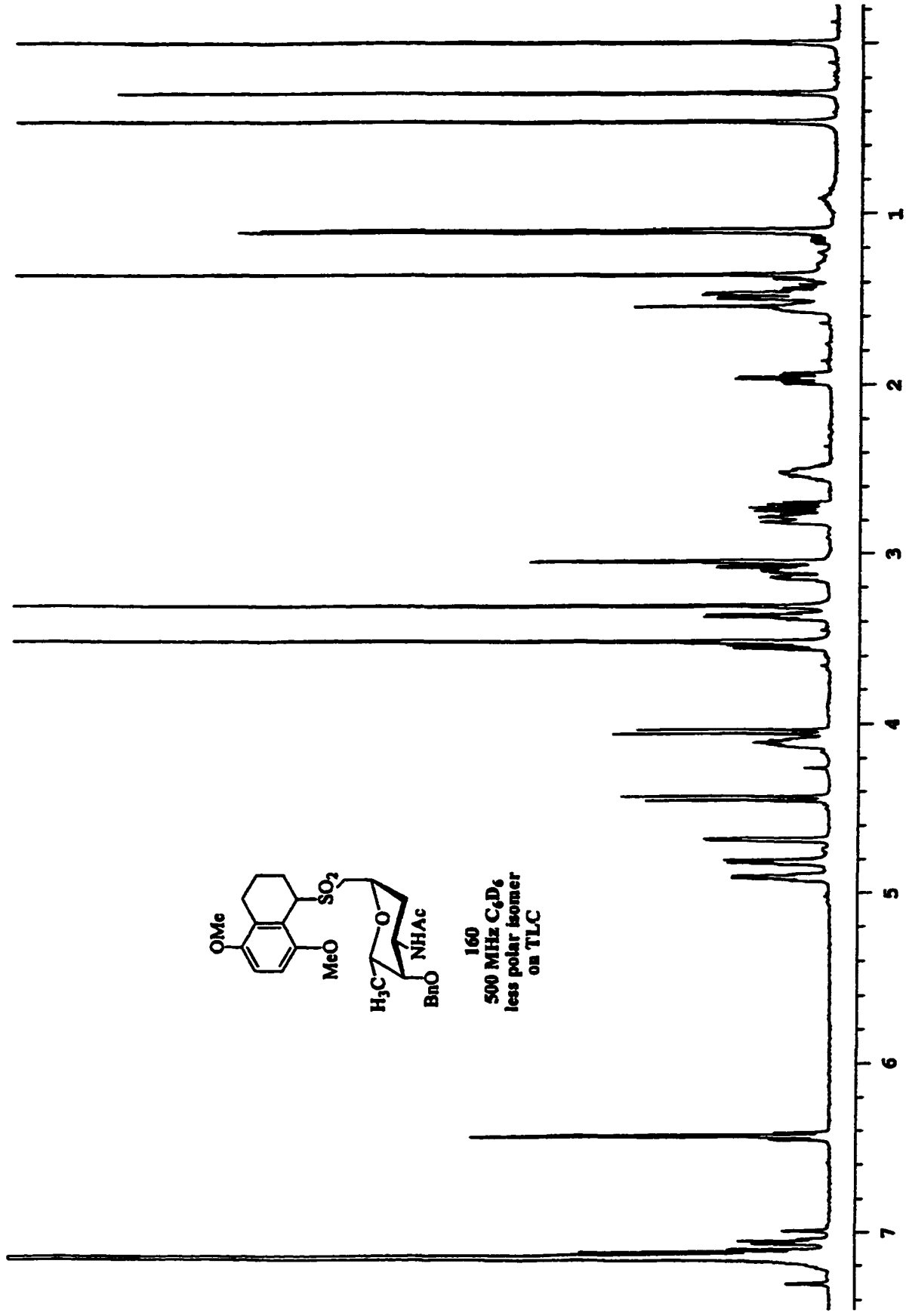


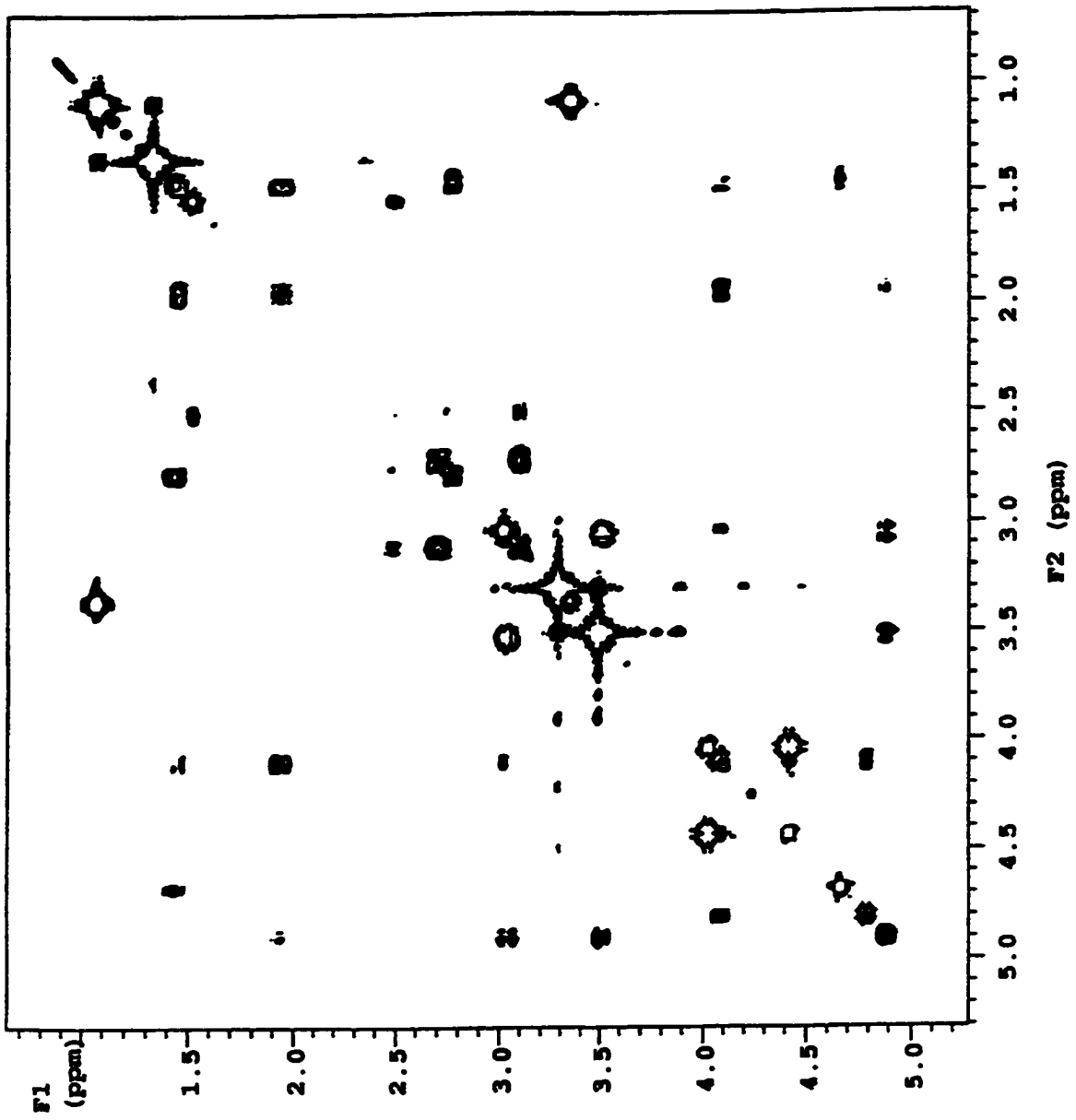


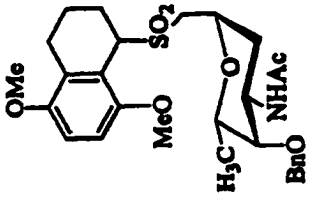




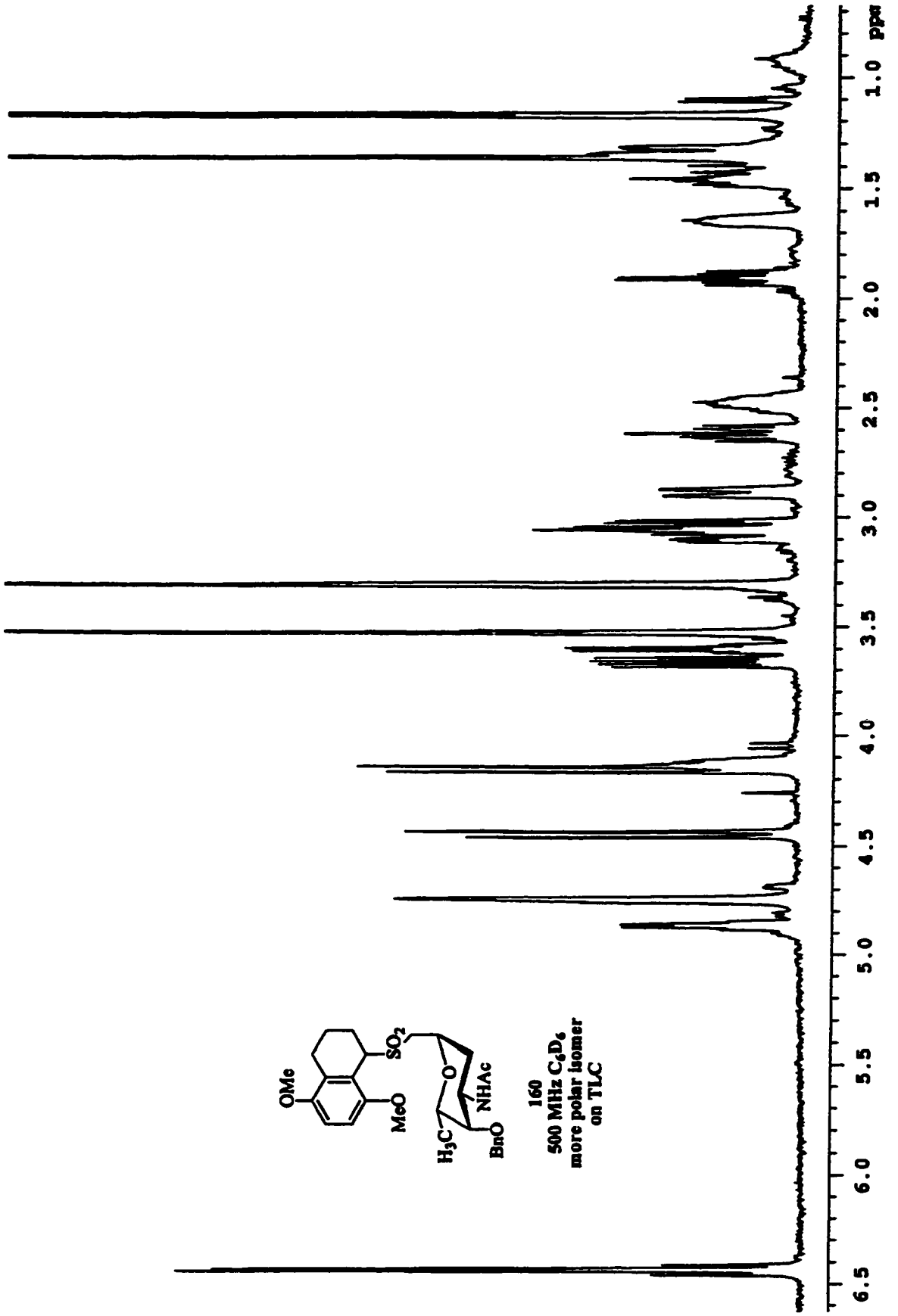


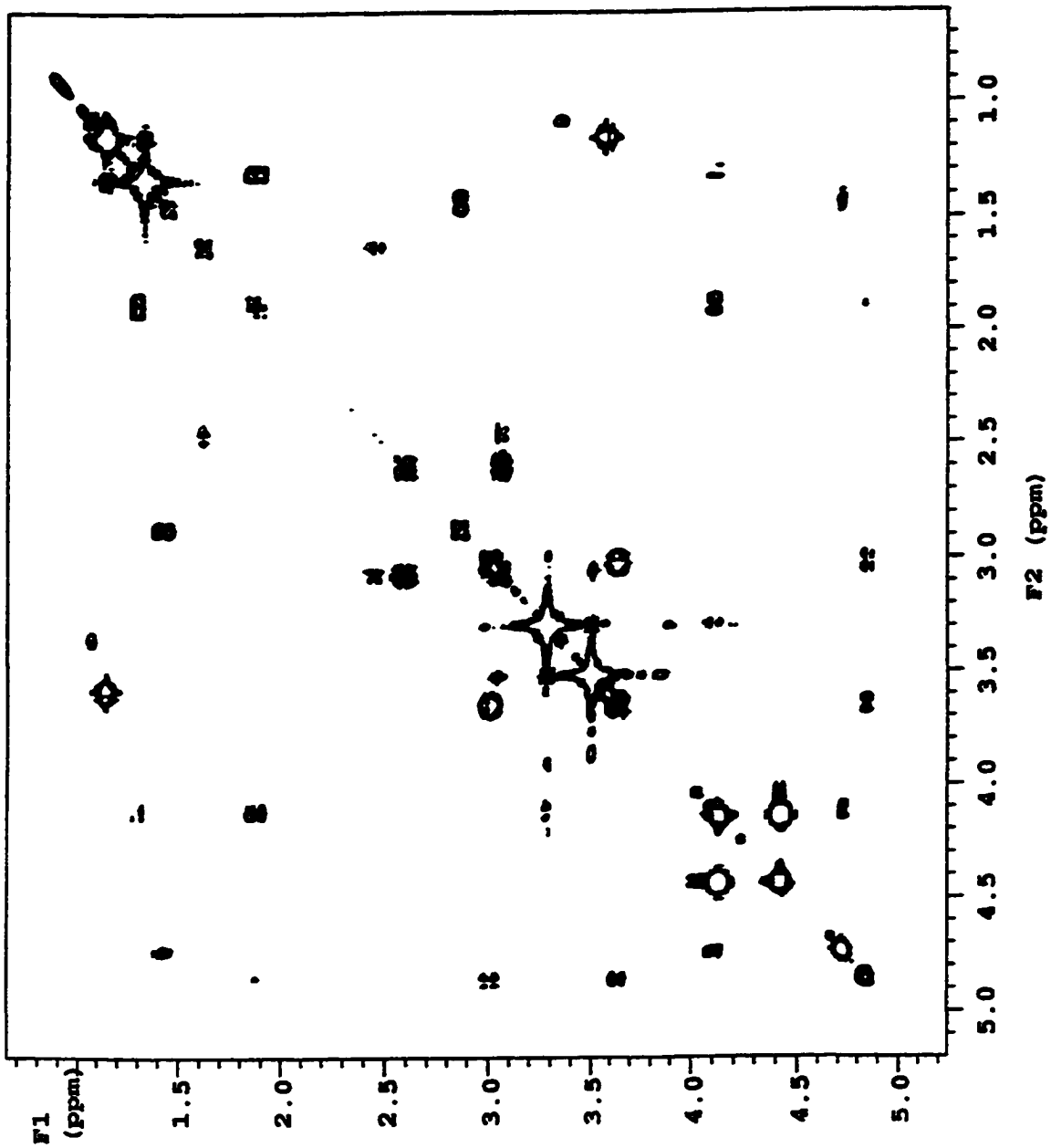


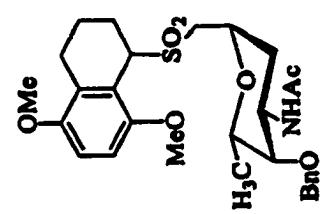




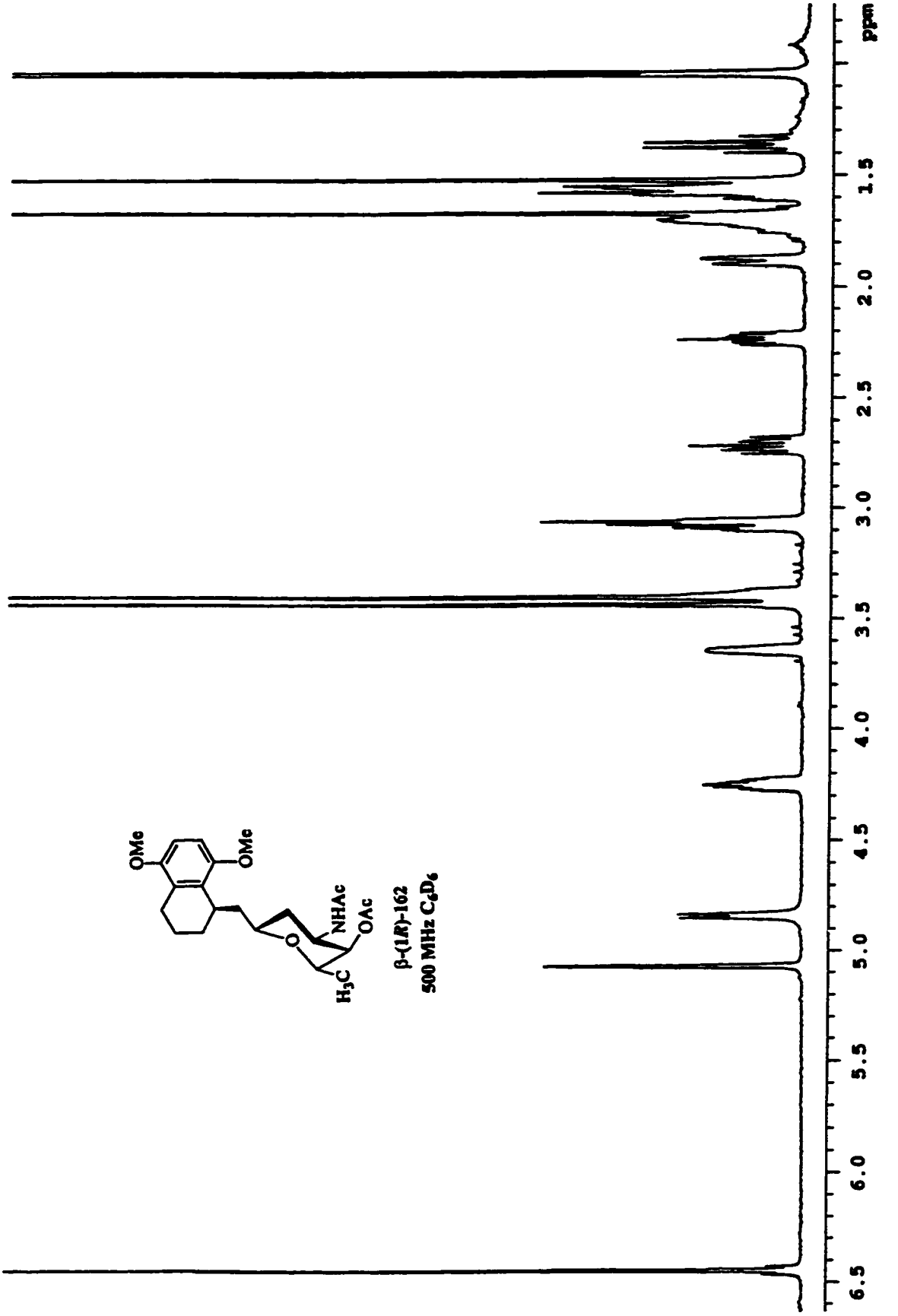
160
500 MHz C_6D_6
H, H COSY
less polar isomer
on TLC

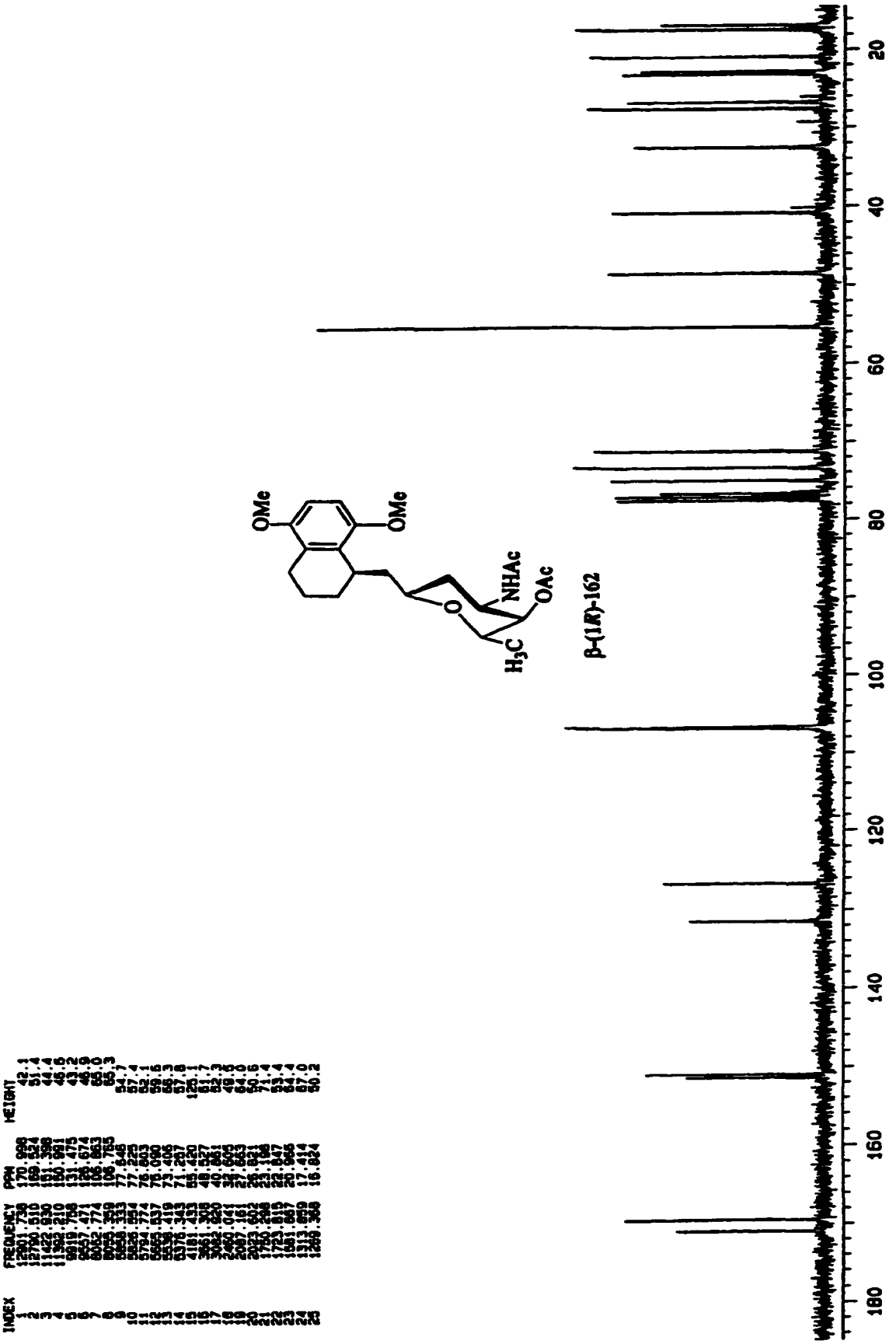


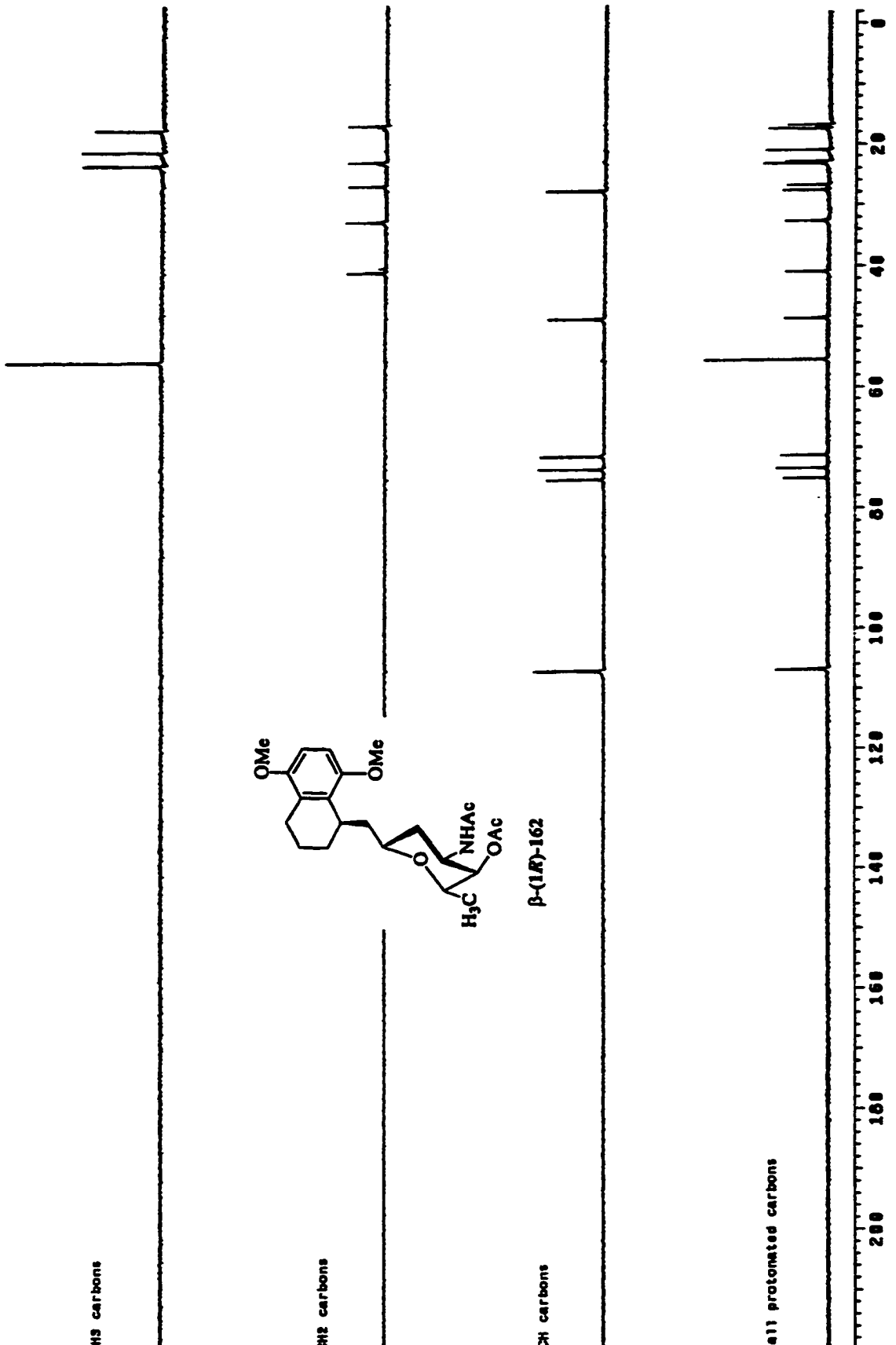


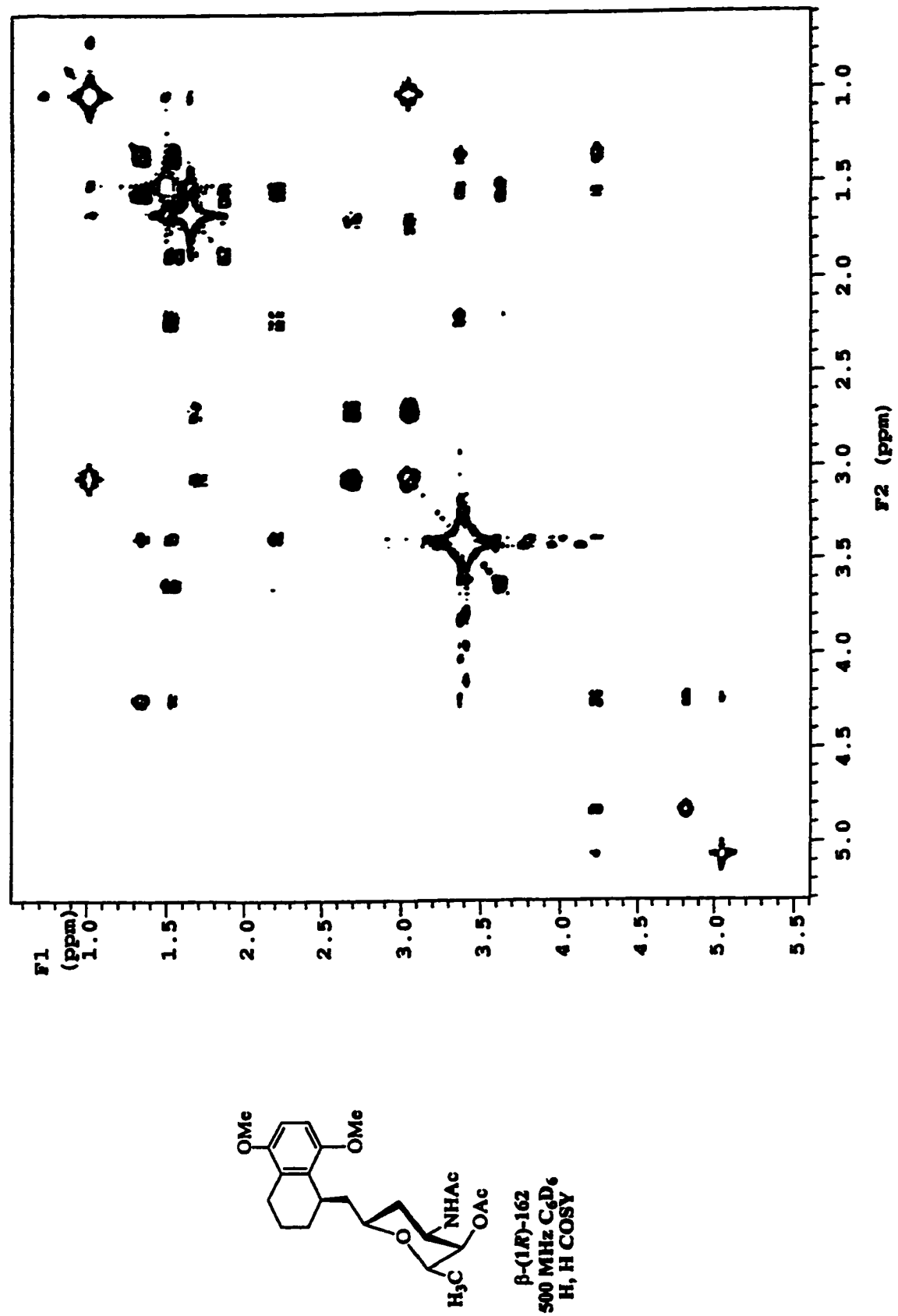


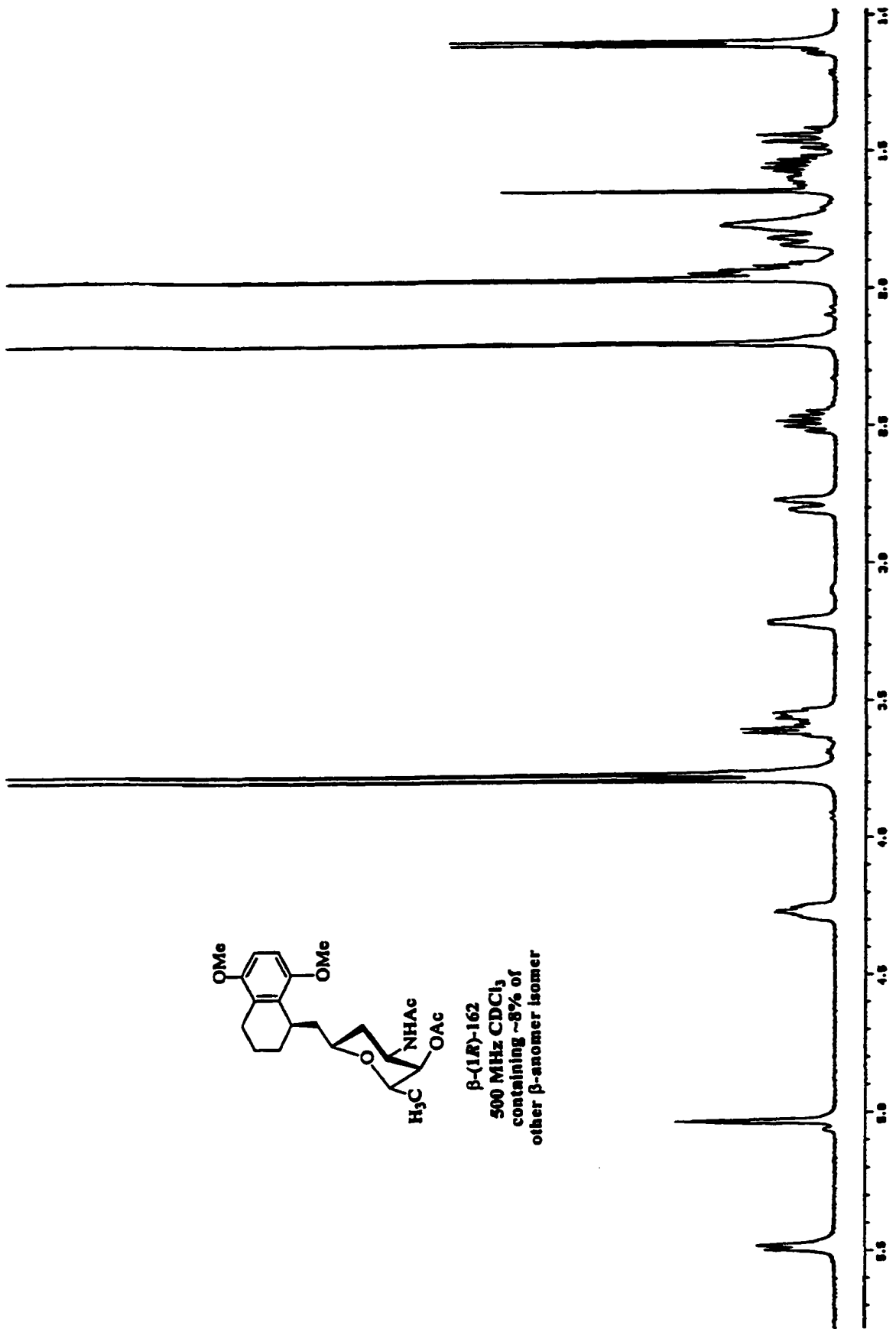
160
500 MHz C_6D_6
H, H COSY
more polar isomer
on TLC

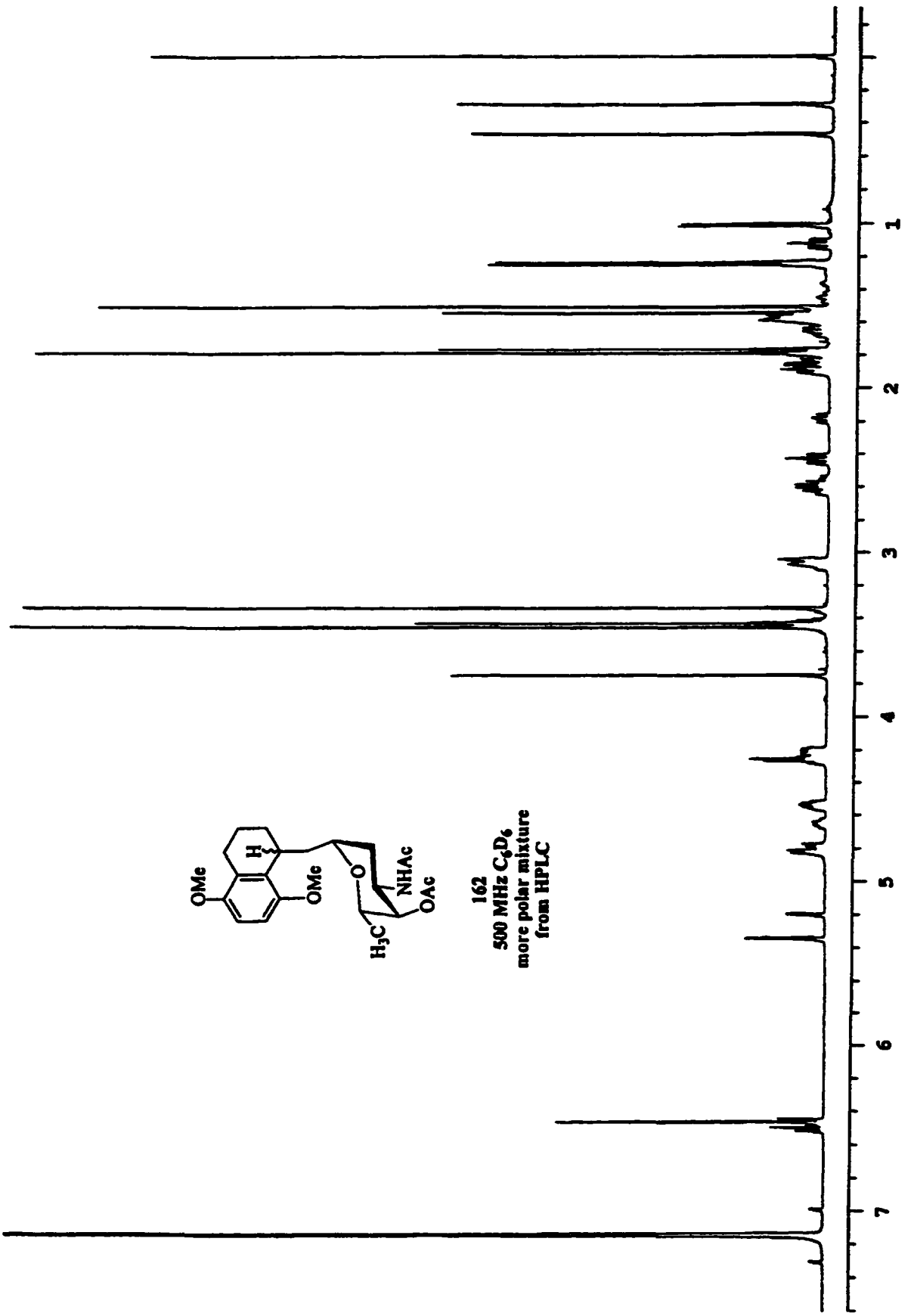


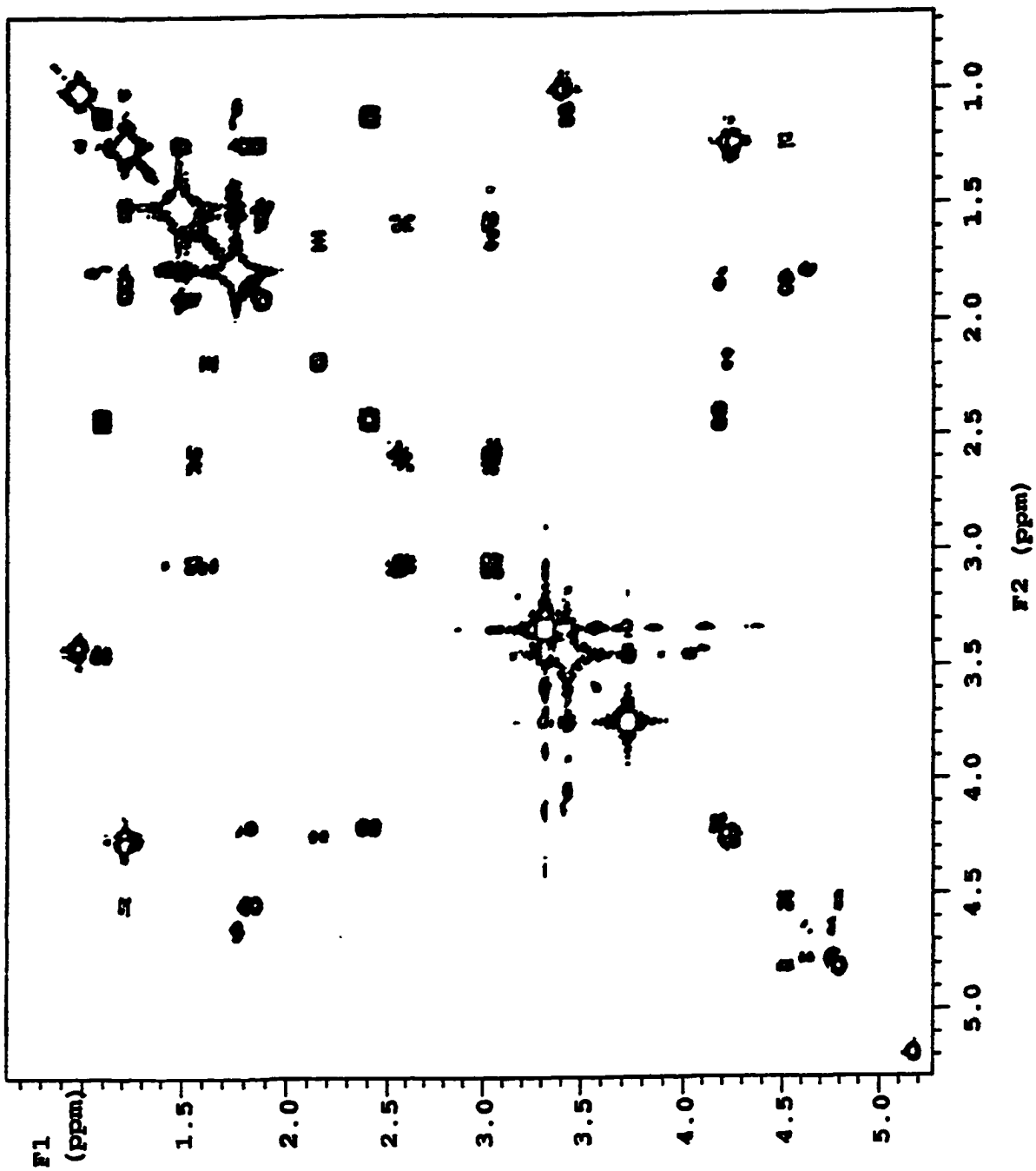


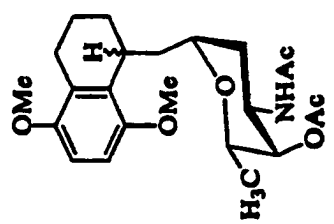












162
500 MHz C_6D_6
H, H COSY
more polar mixture
from HPLC

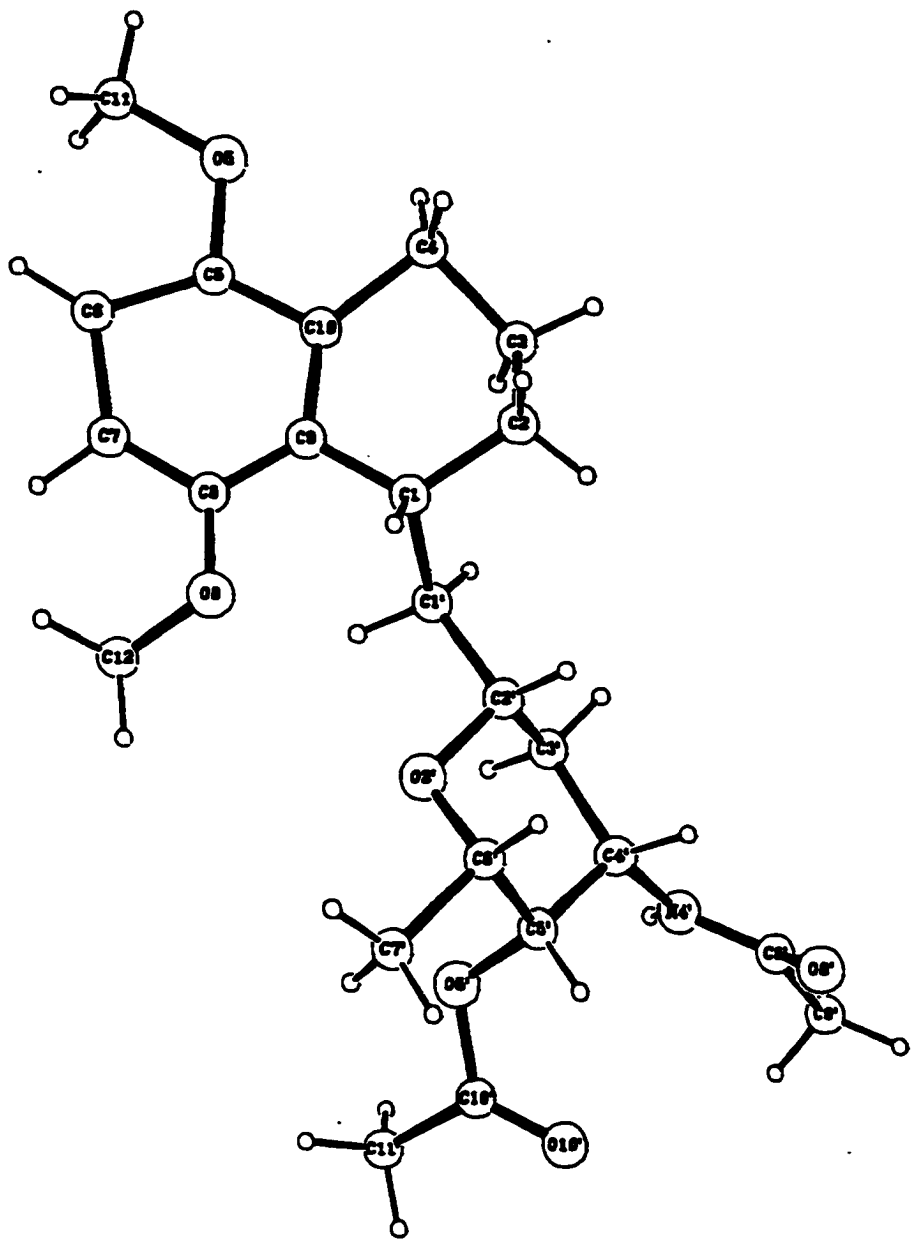


Figure 8. ORTEP drawing of the crystal structure of 4-(acetylamino)-2, 6-anhydro-1, 3, 4, 7-tetradeoxy-1-(1, 2, 3, 4-tetrahydro- 5,8-dimethoxy-1*R*-naphthyl)-5-O-(phenyl-methyl)-β-L-altro-heptitol [β-(1*R*)-162].

Table. X-ray Data for **[β-(1*R*)-162]** at **295 K**

Formula	$C_{23}H_{33}NO_6$
Formula weight	419.51
Crystal size (mm)	0.08 x 0.16 x 0.32
Crystal system	monoclinic
Space group	$P2_1$
a (Å)	15.553(3)
b (Å)	5.029(4)
c (Å)	16.257(4)
β (°)	117.76(2)
V (Å^3)	1125.3
Z	2
d_{calc} (g cm^{-3})	1.238
μ(Mo $K\alpha$) (cm^{-1})	0.83
Maximum θ (°)	25
Unique reflections	2013
Observed reflections [$I > 3.0\sigma(I)$]	498
Number of variables	120
R	0.128
R_w	0.131
$(\Delta\rho)_{max}$ (e Å^{-3})	1.2
$(\Delta\rho)_{min}$ (e Å^{-3})	–0.9

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IMAGE EVALUATION
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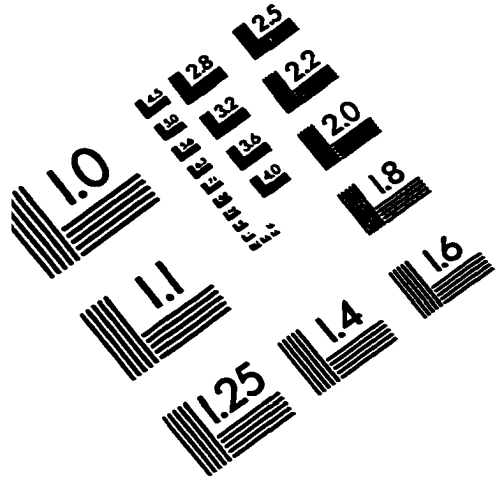

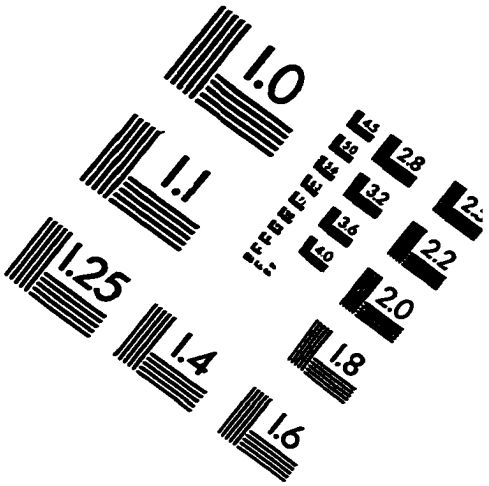

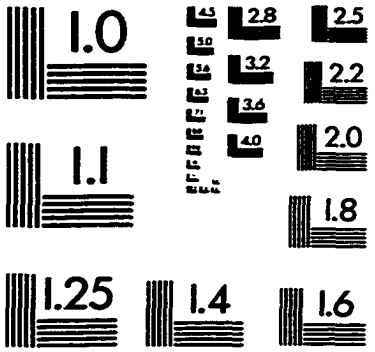

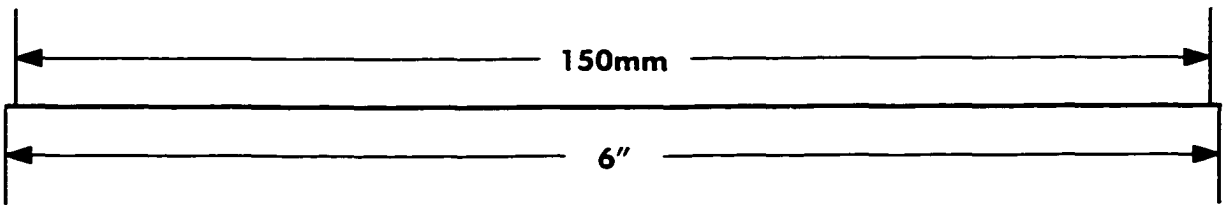

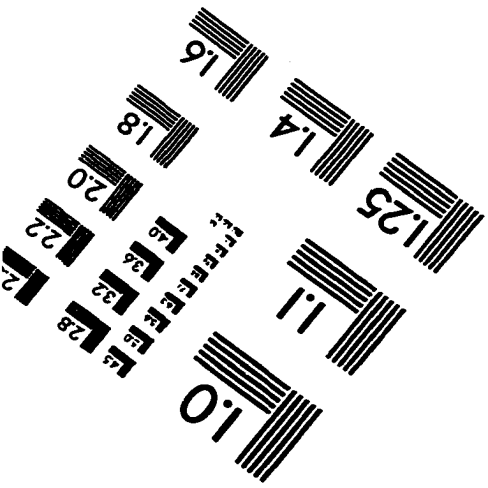

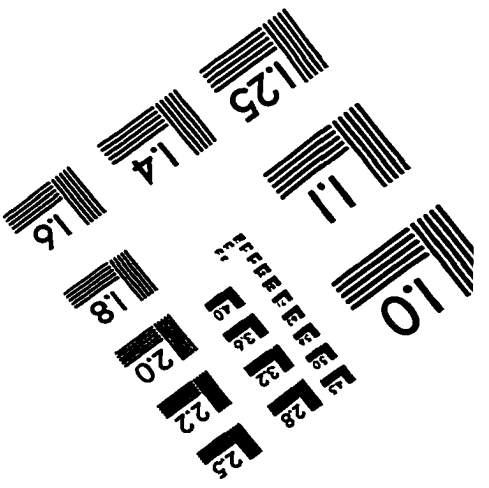

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