Synthesis of C-Glycoside Probes for Sialyl Lewis X-Selectin Recognition

By

Richard W. Denton

A dissertation submitted to the Graduate Faculty in Chemistry in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York

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Abstract

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Richard W. Denton

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Interest in C-glycosides as glycomimetics has led to the development of several methodologies for their synthesis. The Mootoo's group has shown that 1-thio-1,2-O-isopropylidene acetals (TIAs) are precursors to β-C-galactodisaccharides. In this thesis, application of the TIA methodology to five C-glycoside analogs of the Gal1β->1αMan O-disaccharide mimetic of sialyl Lewis X is described: two conformationally restrained analogs which have different conformational properties with respect to the intersaccharide linkages and three unrestrained structures with one or two fluorines on the intersaccharide carbon. These C-glycoside analogs are important because they are more hydrolytically stable than O-glycosides and could be more practical for drug development. The restrained C-glycosides are designed to restrict the conformational mobility around the Gal pseudoglycosidic linkage and only allow free rotation around the Man linkage. The fluorine substituent in the mono- and difluoro C-glycosides are also expected to effect conformational bias about the intersaccharide bond. Therefore these compounds could be useful as probes for interrogation of the conformational requirements for binding.

Conformational analysis of these C-glycosides was performed by a combination of NMR spectroscopy and molecular mechanics (MM) and molecular dynamics (MD)

calculations. The P-selectin binding of these mimetics in a Biacore assay was also determined. At 12 mM, the O-glycoside showed 48% inhibition of binding, while the C-glycoside analogs exhibited between 25 - 39% inhibition. The conformational and selectin binding data is discussed within the context of the crystal structure of sLe^x-P-selectin.

The application of the TIA methodology to the preparation of the C-glycoside of methyl α-D-altropyranosyl-(1→4)-α-D-glucopyranoside is also presented. This synthesis illustrates the suitability of the C-glycoside methodology to C-disaccharides with unusual glycone segments, and is also pertinent to the altromycins, a naturally occurring class of aryl-α-C-altrosides.

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At times one may wonder when this journey will end; this experience opened the doors to valuable relationships and carved out wonderful friendships that cannot go unappreciated. I would like to express sincere thanks to everyone who has contributed to making my years as a graduate student memorable.

First of all, I am deeply thankful to my Savior Jesus Christ who has given me the impetus and the strength to complete this thesis. I know that He has led me to the best mentor any graduate student could ever desire.

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Brethren, I count not myself to have apprehended: but this one thing I do, forgetting those things that which are behind, and reach forth unto those things which are before, I press towards the mark for the prize of the high calling of God in Christ.

Philippians 4 vs.13-14.

To the people dearest to me

My beautiful wife

My adorable sons

My encouraging parents

My prayerful pastor

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Symbols and Abbreviations

Ac	acetyl
Ac_2O	acetic anhydride
Avg.	average
BF_3.EtO	boron trifluoride etherate
Bn	benzyl
br	broad
Brine	saturated aqueous sodium chloride solution
Bu_4NI	tetrabutyl ammonium iodide
Bz	benzoyl
^{13}C NMR	carbon-13 nuclear magnetic resonance
ca.	about
calcd	calculated
COSY	correlation spectroscopy
CR	complement regulatory-like unit
CSA	camphorsulfonic acid
δ	chemical shift in ppm
d	doublet
DAST	(Diethylamino)sulfur trifluoride
DCC	dicyclohexylcarbodiimide
DDQ	2,3-dicholoro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate

DIB	iodobenzene diacetate
DMAP	4-dimethylaminopyridine
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
EGF	epidermal growth factor domain
ELAM-1	endothelial leukocyte adhesion molecule
eq	equivalent
ESL-1	E-selectin ligand-1
ESMS	electrospray mass spectroscopy
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
FABMS	Fast Atom Bombardment Mass Spectroscopy
FCC	Flash column chromatography
Fuc	L-fucose
g	gram
Gal	D-galactose
Glc	glucose
GluNAc	N-acetyl-D-glucosamine
GLYCAM-1	glycoprotein cell adhesion molecule-1
h	hour
HOAc	acetic acid
HRMS	High resolution mass spectroscopy
^1H NMR	Proton nuclear magnetic resonance spectroscopy
Hz	hertz
IC_{50}	Concentration of inhibitor resulting in the reduction of bonding to 50% of

	maximum.
J	coupling constant in hertz
L	liter
Le^x	Lewis X
m	multiplet
MadCAM-1	mucosal addressin cell adhesion molecule-1
man	mannopyranoside
m-CPBA	meta-chloroperoxybenzoic acid
MD	Molecular dynamics
Me	Methyl
mg	milligram
min	minute
MM3	Force fields for molecular mechanics calculations
mmol	millimole
MOM	methoxy methyl
ms	molecular sieves
NaH	Sodium Hydride
neu	Sialic acid
NMO	N-Methylmorpholine-N-oxide
NMR	Nuclear magnetic resonance
NOE	Nuclear overhauser effect
^oC	degree Celsius
Ph	phenyl
PhSH	thiophenol

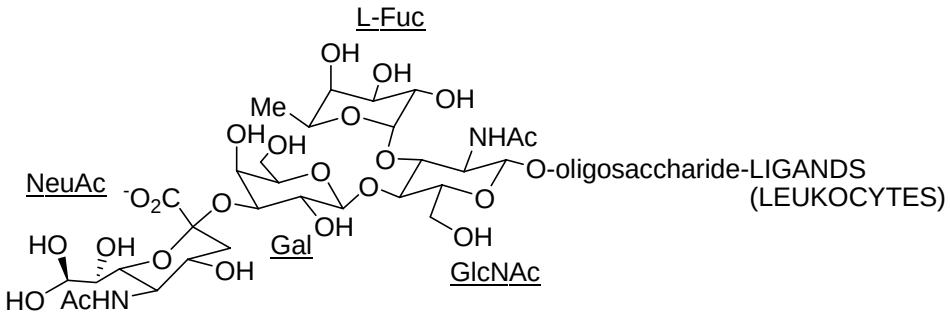
PMB	*para*-methoxy benzyl
ppm	parts per million
PSGL-1	P-selectin glycoprotein ligand-1
pyr	pyridine
q	quartet
rt	room temperature
s	singlet
sd	standard deviation
sLe^x	sialyl Lewis X
t	triplet
TBDPS	*tert*-butyl diphenyl silyl
TfOH	trifluoromathanesulfonic acid
THF	tetrahydrofuran
TIA	1-thio-1,2-*O*-isopropylidene acetal
TLC	thin layer chromatography
TMEDA	N,N,N',N'-tetramethylethylenediamine
TMS	trimethyl silyl
TMSOTf	trimethyl trifluoromethanesulfonate
Trityl	triphenylmethyl
TsCl	*p*-toluenesulfonyl chloride (p-$CH_3C_6H_4SO_2Cl$)
vs	versus

Chapter 1

Introduction

1.1 Background

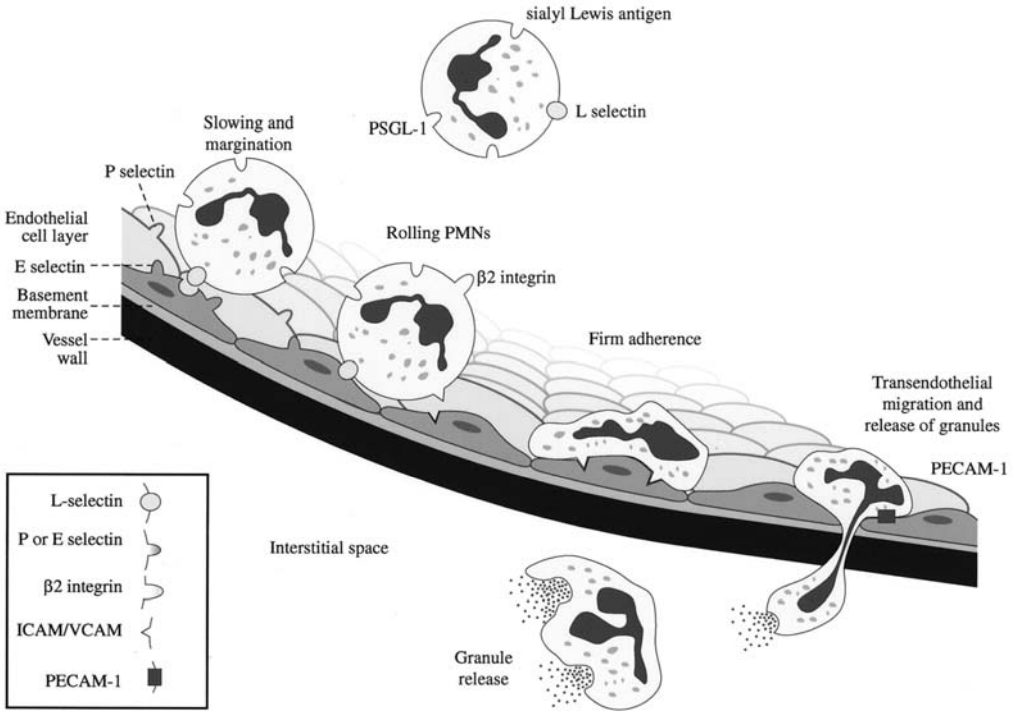
Figure 1.1: Sialyl Lewis X (sLe^x)



In the response to injury, the inflammation cascade begins with the release of cytokines at the site of injury within the tissue.[1] This stimulates the upregulation of two proteins E- and P-selectin on the endothelial surface. E- and P-selectin recognize the tetrasaccharide sialyl Lewis x (sLe^X) (Figure 1.1), and its glycoprotein derivatives on the surface of leukocytes and promote leukocyte adhesion to endothelial cells. A third selectin, L-selectin is constitutively expressed on leukocytes, and recognizes similar carbohydrate ligands found on the endothelium. This relatively weak, sLe^x mediated adhesion processes result in "rolling" of leukocytes across the endothelium leading to higher affinity adhesion between integrins on the leukocytes and endothelial proteins, ICAM-1 (intercellular adhesion molecule-1) and VCAM-1. Proteolytic cleavage of L-

selectin from the surface of the leukocytes occurs and PECAM receptors on endothelial cell surfaces mediate migration of the leukocytes through the endothelial layer to the damaged or infected tissue, where accumulation of leukocytes occurs (Figure 1.2). While inflammation plays a key role in controlling infections and repairing injuries, excessive accumulation of leukocytes may lead to damage of healthy cells and result in disease states such as reperfusion injuries, stroke, psoriasis, rheumatoid arthritis and respiratory diseases.[2, 3] Since E- and P-selectin are activated in response to injury, regulation of sLe^x-selectin binding has been examined as a new strategy for treating inflammation disorders.[2]

Figure 1.2: Inflammation cascade

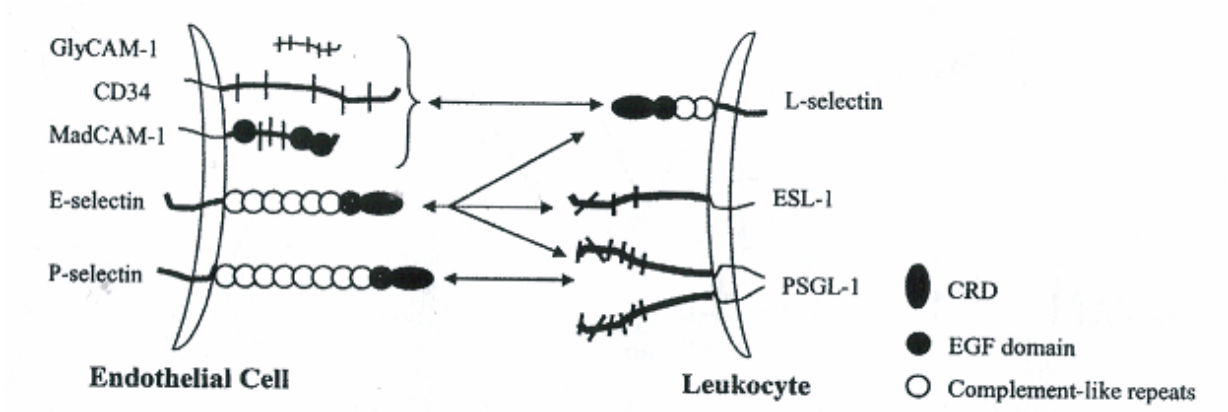


1.2 Selectin structure and their ligands:

The selectins are composed of five domains. A N-terminal calcium dependent lectin domain, an epidermal growth factor domain (EGF), a variable number of complement regulatory-like unit (CR), a transmembrane domain, and an intracellular tail.[4, 5]

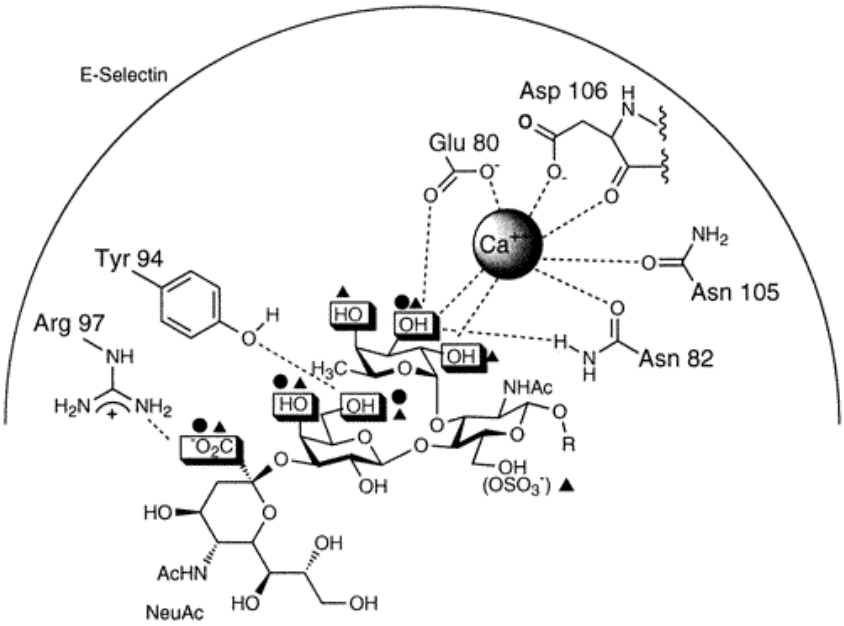
L-selectin interacts with three glycoprotein ligands on the endothelial cell surface. These are the glycoprotein cell adhesion molecule-1 (GLYCAM-1), CD34 and the mucosal addressin cell adhesion molecule-1 (MadCAM-1) ligands. E-Selectin recognize by P-selectin glycoprotein ligand-1 (PSGL-1) and E-selectin ligand-1 (ESL-1). P-selectin only interacts with PSGL-1, which is the best characterized ligand to date (figure 1.3).[6, 7] PSGL-1 is a glycoprotein with N- and O-linked glycans containing sLe^x, and a cluster of three N-terminal tyrosine sulfated groups. A truncated form of PSGL-1 was found to be effective against P-selectin and this led to numerous syntheses of analogs of PSGL-1 as potential anti-inflammatory agents.[8, 9]

Figure 1.3: The interaction between the selectins and their ligands.[7]



sLe^x is one of the key selectin binding epitopes on all of these ligands (Figure 1.4). Classical homology modeling and structural activity studies with nuclear magnetic resonance (NMR), along with computational analysis of bound sLe^x have led to a general model for sLe^x-selectin recognition.[7] The key receptor contact points are the 4-OH and the 6-OH groups of galactose, the COOH of the sialic acid, and the hydroxyl groups of fucose. The GlcNHAc residue is believed to act as a conformationally restricted spacer that maintains the binding region on the fucose and the COOH in a preferred spatial orientation (See figure 1.4).[10]

Figure 1.4: Model showing the structure and functional groups of sLe^x interacting with E-selectin (□), and the groups recognized by P- (•) and L-selectin (▲).[10]



Recently, X-ray structures of sLe^x bound to E-selectin and P-selectin have been reported.[11] The data obtained for both complexes suggested that the binding interactions

were almost electrostatic in nature. Both structures indicated that the 3- and 4- hydroxyl groups of the fucose bound to calcium. This mode of binding was in contrast to the earlier prediction of the fucose 2- and 3- hydroxyl groups being ligated to calcium, a concept originating from the structure of the rat mannose binding protein complexed with oligomannose.[11] It was also shown that the fucose hydroxyl groups form hydrogen bonds with specific selectin residues; the 4-OH group shows hydrogen bond to Asn82 and Glu80, while the 3-OH group hydrogen bonds to Asn85. In E-selectin, additional hydrogen bonding interactions are observed between Asn83 and Fuc 2-, 3- hydroxyl groups and Glu107. These interactions are not seen in the P-selectin/sLe^x complex. It was suggested that the overall fucose interactions provide a large amount of the sLe^x binding energy. In both P- and E- complexes, the sLe^x galactose residue hydrogen bonds to Tyr94 and Glu92, and the carboxylate group of the sialic acid moiety hydrogen bonds to Tyr48. These interactions combined with differences in the fucose binding seem to be the reason for the higher affinity of E-selectin/sLe^x interaction.

This binding model has been widely used to design small molecule mimetics of sLe^x. The majority are carbohydrate derived mimetics that appear to adapt similar contact points as sLe^x. As O-glycosides are prone to enzymatic and chemical degradation, and possess poor pharmacokinetic and bioavailability profiles, there has been interest in non-carbohydrate type mimetics.[7] The latter may also be easier to synthesize and more compatible with combinatorial chemistry.

A brief summary of sLe^x mimetics grouped according to tri-, di- and mono-saccharide and non-carbohydrate structures will be presented.

1.3 Trisaccharide mimetics

Trisaccharide mimetics were essentially used to identify the key hydroxyl groups of galactose and fucose residues. The expensive sialic acid was substituted by simplier species like sulfate **1.1**,[4] carboxymethyl and cyclohexyl lactic acid groups. These provided some active mimetics of which compound **1.2** has one of the highest potency against E-selectin.[7, 12] Interestingly the Gal 2-OH group compound **1.3** was less active than **1.2**. This increase in activity was believed to be due to preorganization of the bioactive conformation **1.2** compared to sLe^x and not additional interactions between the benzoate group and E-selectin.[12]

1.4 Disaccharide mimetics

An important disaccharide mimetic reported by Hiruma and coworkers was the O-glycoside **1.4**.[13] This was a β-D-galactopyranosyl-(1→1)-α-D-mannopyranoside with a flexible carboxymethyl group. It was reported to be five and forty times more active than sLe^x against E- and P-selectin respectively, in a cell based assay. Existing models for sLe^x-selectin binding suggested that the galactose and fucose recognition sites for sLe^x are homogeneous with the binding regions for the galactose and mannose residues in **1.4**.

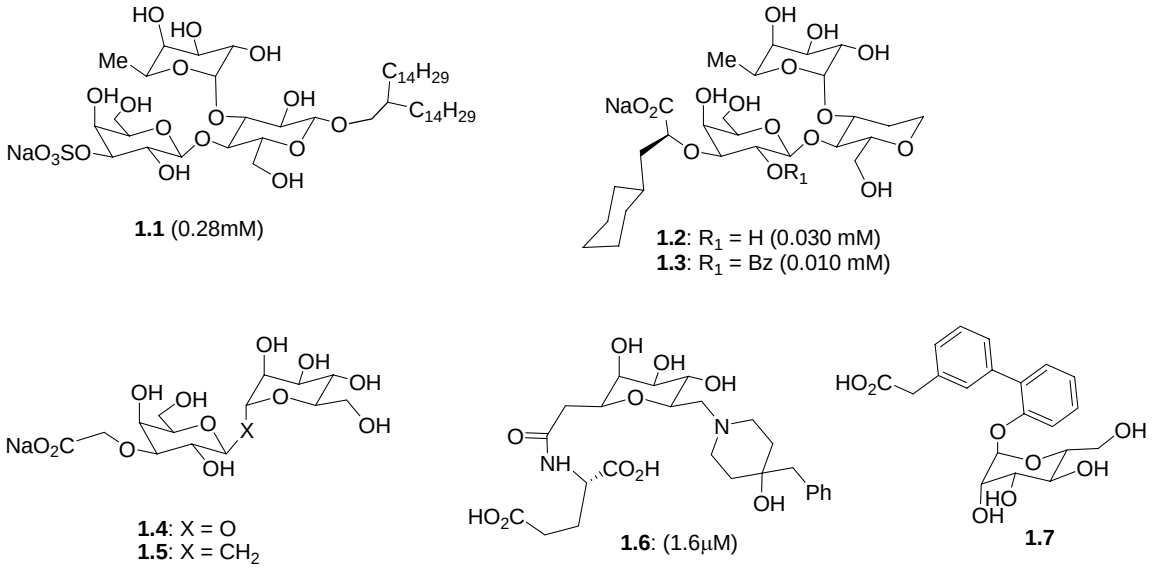
These encouraging results led to the synthesis of the exact C-glycoside **1.5** by the Mootoo group,[14] as the C-glycoside was more hydrolytically stable than O-glycosides and therefore more attractive for drug development. Conformational studies, performed in collaboration with Jiménez-Barbero on **1.4** and **1.5** revealed that the unbound O-glycoside existed essentially in a single conformation, while the C-glycoside displayed five significant conformations about its intersaccharide linkages.[15] The P-selectin

binding of **1.4** and **1.5** using the BIAcore surface plasmon resonance technique showed good dosage response with similar activity to sLe^x. The similarity in binding of **1.4** and **1.5** was interesting because these compounds were found to be very different in their conformational behavior with respect to their intersaccharide bonds.

1.5 Monosaccharide mimetics

In these types of sLe^x mimetics the lactosamine moiety was replaced with a flexible or rigid scaffold. The majority of these analogs retained the fucose residue but *D*-galactose or *D*-mannose sugar substitutes have also been popular. Two of the more potent groups of monosaccharide mimetics contained glycopeptide (**1.6**) or biphenyl residues (**1.7**)[7] as lactose-amine replacements (figure 1.5)

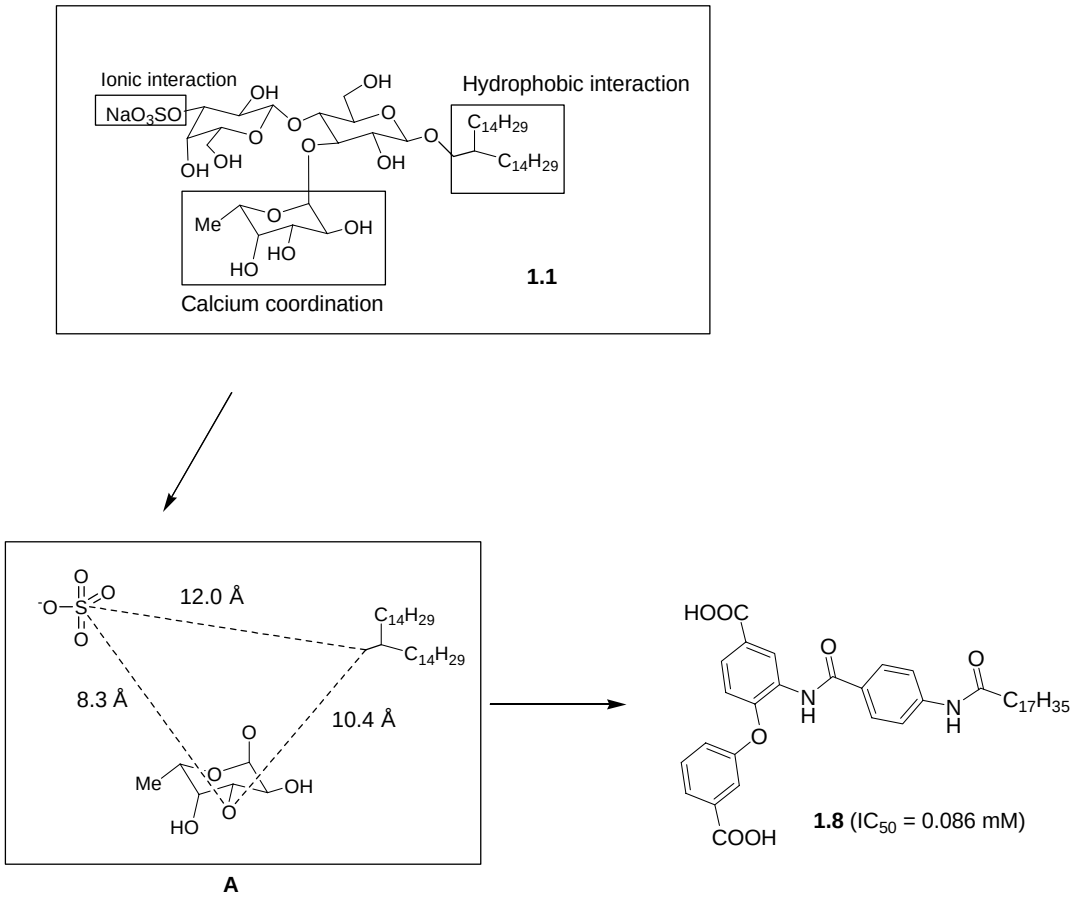
Figure 1.5: Selected carbohydrate mimetics of sLe^x and their binding activities



1.6 Non-carbohydrate mimetics

The analogs in this group are attractive because of their synthetic accessibility, stability, and their pharmacokinetic and bioavailability profiles. A potent E-selectin antagonist, compound **1.8** (IC_{50} = 0.086 mM) was designed using a 3D-pharmacophore model from the sulfated trisaccharide **1.1**/E-selectin complex model.[7, 16] In this approach, the fucose unit and the negatively charged sulfonic acid were replaced with the diaryletherdioic acid residue, and the hydrophobic branched chain was replaced with a single alkyl chain (Figure 1.6).

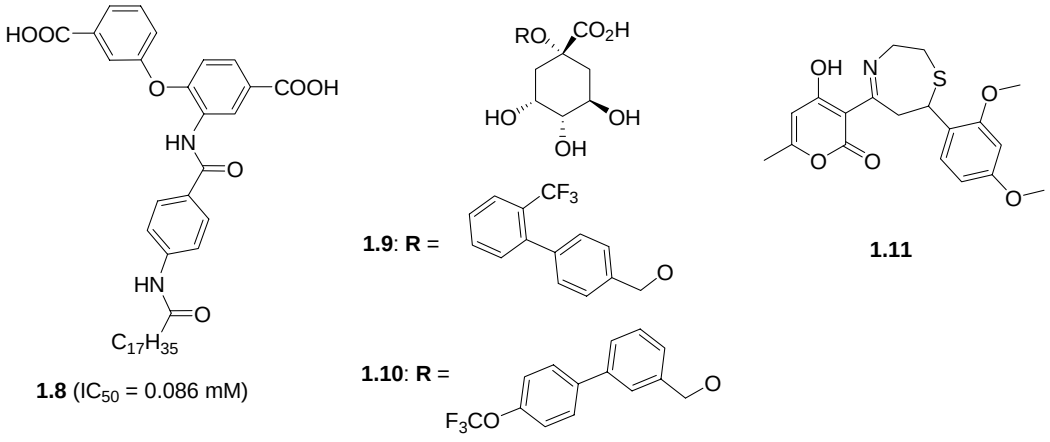
Figure1.6: Design of **1.8** *via* a pharmacophore model approach.[16]



A cocrystal structure of a small quinic acid derivative with E-selectin led to the hypothesis that two of the hydroxyl groups of quinic acid mimicked the calcium-bound fucose of sLe^x.[17] The X-ray structure data was used to design related **1.9** and **1.10**, which showed IC_{50}'s of approximately 10 mM in a Biacore P-selectin assay. The IC_{50} of sLe^x was 15 mM.

The non-carbohydrate mimetic 7-phenyl-1,4-thiazepine **1.11** (KF38789) with IC_{50} of 1.97μM for P-selectin, and weaker binding for E and L-selectin, was fortuitously discovered.

Figure 1.7: Non-carbohydrate mimetics of sLe^x and their binding activities.



The aforementioned examples represent a fraction of the large number of sLe^x mimetics synthesized to date. The promising activity reported for the relatively simple *O*-disaccharide **1.4** and its C-glycoside **1.5** prompt a more extensive investigation on the synthesis, conformational behavior and selecting binding of related disaccharide analogs. This is the thrust of this thesis.

Chapter 2

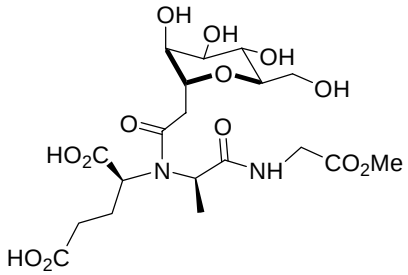
Synthesis of conformationally restrained C-disaccharide sLe^X mimetics.

2.10 Introduction

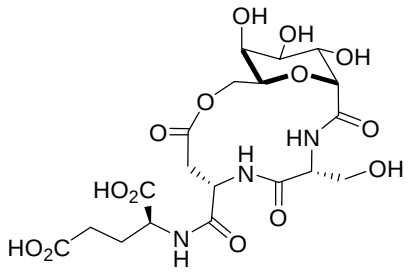
As previously mentioned, the exact C-glycoside **1.5** of O-glycoside **1.4** has been synthesized by the Mootoo group.[14] There were two reasons for interest in this C-glycoside; first, C-glycosides are more hydrolytically stable than O-glycosides and therefore more attractive for drug development.[18] Second, the presence of the carbon linker in the C-glycoside allows for design of analogs with different conformational properties with respect to the intersaccharide linkages[19], thereby leading to disaccharide analogs with different spatial orientation of the galactose and mannose segments. Evaluation of the selectin affinity of such structures could provide insight on the most active conformation of the disaccharide framework and in general, a clearer picture on the optimal requirements for binding to the selectins. Rigid compounds with all the recognition elements pre-organized in a conformation that is favorable for binding are expected to show higher affinity because of entropy considerations.[20] An example of this concept is illustrated in the relative binding of sLe^x mimetic **2.1** and the rigid macrocyclic glycoprotein **2.2**.[20] The more rigid analog was approximately 120 fold more active in a P-selectin assay.

Against this backdrop, the synthesis of conformationally restrained C-glycoside **2.3** and **2.4** was undertaken. These analogs present the Man residue in more defined regions of conformational space compared to **1.5**, and could provide more precise structure activity information.

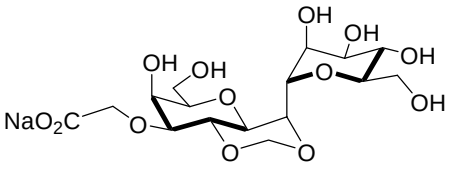
Figure 2.1: Conformationally restrained sLe^x mimetics.



2.1 (IC_{50} = 118 μM)

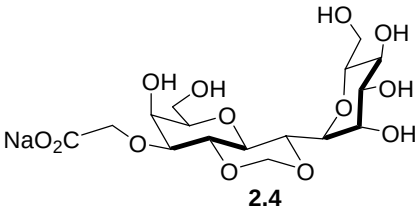


2.2 (IC_{50} = 1 μM)



2.3

Gal-aglyconic torsion locked in "anti" conformation relative to C1 of Man



2.4

Gal-aglyconic torsion locked in "exo" conformation relative to C1 of Man

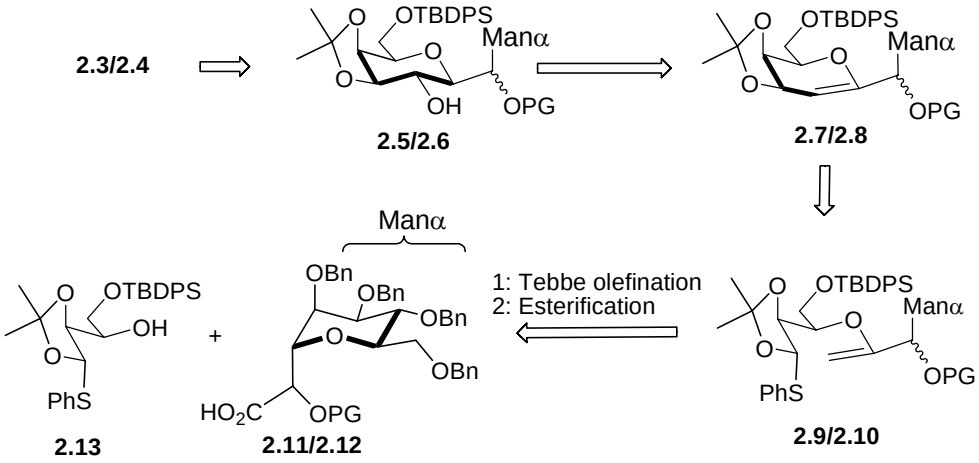
Results and Discussion

2.2 Retrosynthesis

The synthesis of **2.3** and **2.4** entailed the *de novo* construction of the galactose residue and centered on the oxocarbenium ion-enol ether cyclization [14] that was previously applied to **1.5** (Scheme 2.1).[14, 21] Thus, **2.3** and **2.4** could be obtained from the elaboration of C-disaccharides like **2.5** and **2.6** with an appropriate protecting group on the alcohol in the intersaccharide position. Compounds **2.5** and **2.6** should be available from the stereoselective hydroboration of C-1 substituted glycals **2.7** and **2.8**, which are the expected products of the oxocarbenium cyclization on thioacetal - enol ether substrates **2.9** and **2.10**, respectively. Precursors **2.9** and **2.10** would be obtained in a

convergent fashion from thioacetal fragment **2.13** and mannose derived α-alkoxy acids **2.11** and **2.12**.

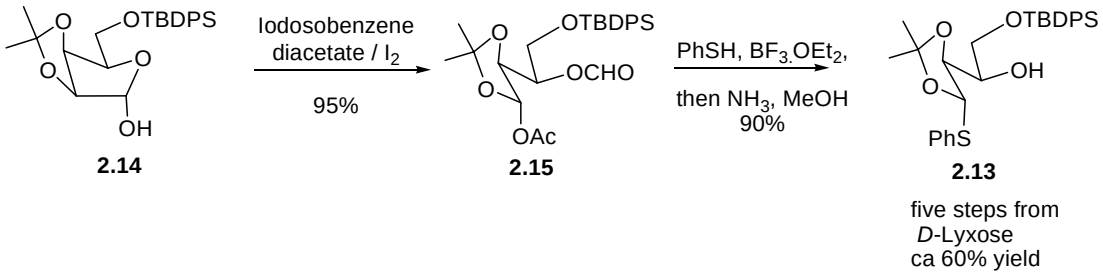
Scheme 2.1: Oxocarbenium ion cyclization strategy for hydroxymethyl linked C-disaccharides.



2.3 Synthesis of the thioacetal glycone and the acid segments.

The synthesis of the glycone **2.13** involved the Suarez radical fragmentation of the 1,2-O-isopropylidene furanose **2.14** to give the 1-O-acetyl-1,2-isopropylidene **2.15**.[22] Acetal exchange of **2.15** with thiophenol followed by basic hydrolysis of the resulting formate ester gave the 1-thiophenyl-1,2-isopropylidene alcohol **2.13** (Scheme 2.2).[14]

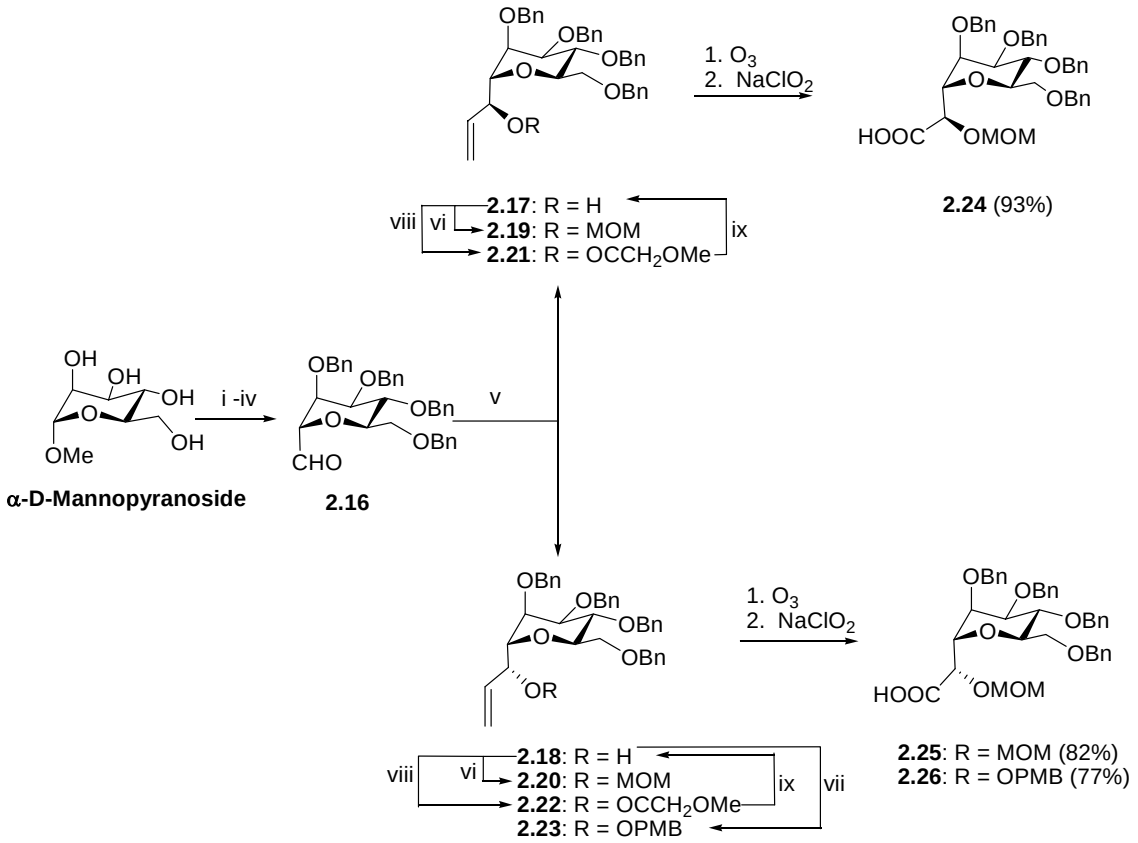
Scheme 2.2: Synthesis of the glycone synthon



The acid components were prepared *via* a straightforward sequence of reactions from the known C-formylmannoside **2.16**, available in four steps from methyl α-D-mannopyranoside.[10] Treatment of **2.16** with vinylmagnesium bromide provided a mixture of alcohols **2.17** and **2.18** that was separated as the methoxymethyl ether derivatives **2.19** and **2.20** (66% from **2.16**, 3:2 respectively, scheme 2.3). Ozonolysis of MOM-protected allylic alcohols **2.19** and **2.20** followed by sodium chlorate oxidation of the resulting aldehydes led to the acids **2.24** and **2.25** (Scheme 2.3). The *p*-methoxybenzyl acid derivative **2.26** was also synthesized from the vinyl alcohol **2.18**.

Two points in the synthesis of **2.19** and **2.20** are noteworthy. First, for easier chromatographic separation of these compounds, the alcoholic mixture **2.17**/**2.18** was converted to the methoxyacetate esters **2.21** and **2.22**. These esters were easily separated and individually hydrolyzed to **2.17** and **2.18** respectfully, which was then transformed to **2.19** and **2.20** as before (Scheme 2.3).

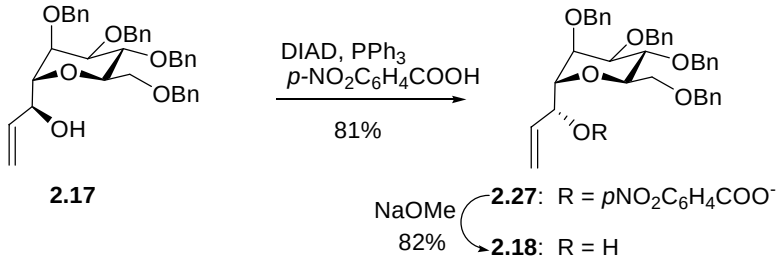
Scheme 2.3: Synthesis of the C-mannoside acid components



(i) NaH, BnBr, Bu_4NI, 95%; (ii) $CH_2CHCH_2Si(CH_3)_3$, TMSOTf, 90%; (iii) $PdCl_2(CH_3CN)_2$, C_6H_6, reflux, 88% (iv) O_3, PPh_3, 93%; (v) vinylMgBr, THF,73%; (vi) MOMCl, i-Pr_2NEt, 50 ^{0}C, 90%, isomers separation; (vii) NaH, PMBCl, Bu_4NI, 90%; (vii) DCC, DMAP, HO_2CCH_2OMe, 88%, isomer separation; (ix) NaOMe, then HCl in MeOH, **2.17** (quantitative yield), **2.18** (90%).

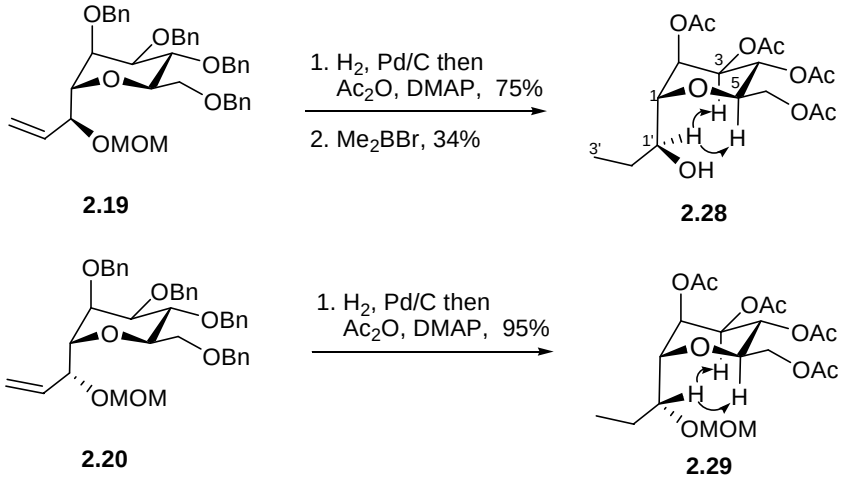
Second, a procedure for conversion of the major alcohol **2.17** to the minor isomer **2.18** was developed. This transformation was achieved *via* the Mitsunobu protocol [23] followed by base hydrolysis of the resulting ester (Scheme 2.4).

Scheme 2.4: Conversion of compound **2.17** to **2.18**



In order to confirm the axial orientation of the C1 substituent in the C-mannoside segments, **2.19** and **2.20** were converted to their tetraacetate-dihydro derivatives **2.28** and **2.29** respectively, and their stereochemical integrity verified by NOESY experiments (Scheme 2.5). The configuration at the allylic position of **2.19** and **2.20** was later assigned from ^{1}H NMR analysis of the conformationally restrained derivatives **2.45** and **2.46** (*vide infra*).

Scheme 2.5: Conformation of stereochemistry in C-mannoside segments



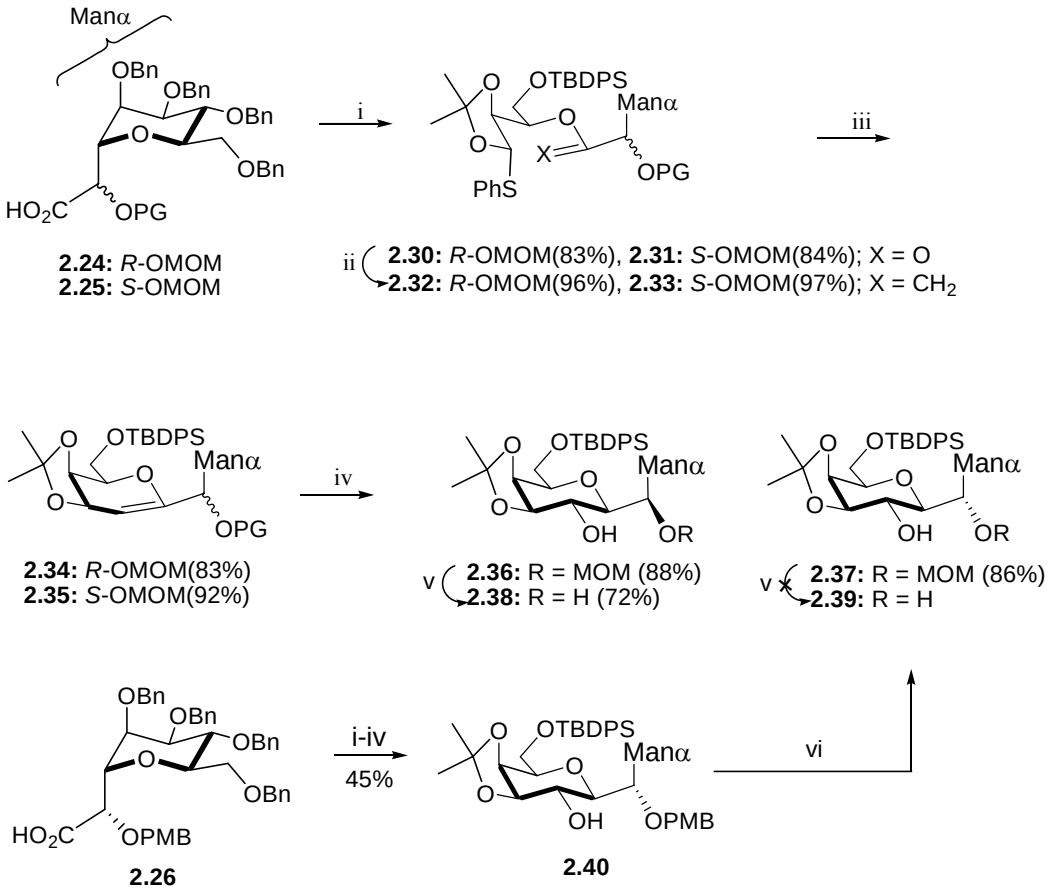
2.4 C-glycoside synthesis

The aglycone segments **2.24** and **2.25** were individually partnered with the alcohol **2.13** for the C-glycoside sequence (Scheme 2.6). DCC mediated esterification of **2.13** with **2.24** and **2.25** followed by treatment of the resulting esters with Tebbe reagent gave enol ethers **2.32** and **2.33** respectively, in 80% and 81% yield from **2.13**. The key cyclization reactions on **2.32** and **2.33** were promoted by methyl triflate in the presence of 2,6-di-tert-butyl-4-methylpyridine (DTBMP). This gave the C-1 substituted glycals **2.34**

(83%) and **2.35** (92%) respectively as the only cyclization products. Hydroboration of the glycals provided the β-C-galactosides **2.36** (88%) and **2.37** (86%), each as a single diastereomer.

The next step was the introduction of the methylene acetal residue in **2.38** and **2.39** (Scheme 2.7). The initial plan was to convert, these C-glycosides **2.36** and **2.37** directly to their cyclic methylene acetal derivatives using the conditions developed by Roush and co-workers.[24] However, the acidic conditions required for this transformation led to competing cleavage of the isopropylidene and methoxymethyl ether protecting groups. Therefore, in an alternative stepwise strategy selective removal of MOM acetals in **2.36** and **2.37** to diols **2.38** and **2.39**, was next attempted. Dimethylboronbromide was found to be the optimal acid promoter for this transformation, but this procedure was only useful for the conversion of **2.36** to **2.38**. Application of these conditions to **2.37** led to a mixture of several products, which afforded a low yield of **2.39** after purification. A more practical route to **2.39** was to use the PMB protected hydroxy-acid precursor **2.26** (instead of MOM ether **2.23**) in the C-glycoside synthesis. Thus, **2.26** was taken uneventfully, through the standard four-step C-glycosidation protocol to the PMB protected C-disaccharide **2.40** (45% overall yield from **2.13**). Conversion of **2.40** to diol **2.39** was best accomplished by first converting **2.40** to the acetate derivative, followed by DDQ mediated removal of the *p*-methoxybenzyl ether, and deacetylation of the product (Scheme 2.6).

Scheme 2.6: Synthesis of diols **2.38** and **2.39**



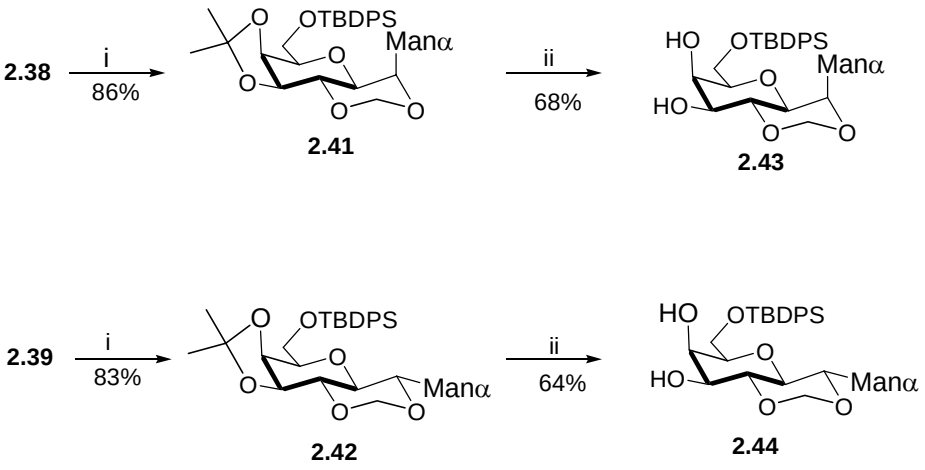
(i) DCC, DMAP, PhH; **2.13** (ii) Tebbe; (iii) MeOTf, DTBMP, CH_2Cl_2; (iv) BH_3.DMS then Na_2O_2; (v) Me_2BBr, DTBMP, CH_2Cl_2, -78 - 0 ^{O}C; (vi) (a) Ac_2O, DMAP, EtOAc; (b) DDQ, CH_2Cl_2-H_2O; (c) NaOMe, MeOH, 74%

2.5 Introduction of conformational restraints

The methylene acetal derivatives **2.41** and **2.42** were obtained by individual treatment of **2.38** and **2.39** with a mixture of dibromomethane and aqueous sodium hydroxide under phase transfer conditions.[25] These reactions were sometimes accompanied by small amounts of desilylated products, which could be easily reprotected. It was also found that small amounts of methyl ether side products were obtained and these were suppressed by performing the reaction in the presence of 2,3-

dimethylbutene. In preparation for the final alcohol protecting group modifications, the isopropylidene residue in **2.41** and **2.42** was selectively removed to give the respective diols **2.43** and **2.44** (Scheme 2.7).

Scheme 2.7: Synthesis of diols **2.43** and **2.44**



(i) n-Bu_4NBr, CH_2Br_2, 50% aq. NaOH; (ii) MeOH, HCl.

2.6 Stereochemical analysis of C-glycoside products

For characterization purposes **2.43** and **2.44** were transformed *via* straightforward alcohol protecting group changes to their peracetates **2.45** and **2.46** (Scheme 2.8, Table 2.1). The stereochemistry of the aglycone segment and the configuration at the intersaccharide carbon were assigned on the basis of vicinal J values. Thus, $J_{1,2}$ = 10.0, $J_{2,3}$ = 10.0, $J_{3,4}$ = 3.0, $J_{4,5}$ = 0 Hz for **2.45**, and $J_{1,2}$ = 9.8, $J_{2,3}$ = 9.8, $J_{3,4}$ = 3.0, $J_{4,5}$ = 0 Hz for **2.46** are consistent with the 3,4-O-isopropylidene-β-C-galacto motif.[26] A $J_{1,1'}$ value of 9.8 Hz and a NOE between H-2 of the galactose residue and the intersaccharide proton for **2.45** pointed strongly to an equatorial like attachment of the mannose residue onto a

chair-like dioxane ring. The corresponding $J_{1,1,}$ value for **2.45** (6.5 Hz), is somewhat larger than expected for equatorial-axial arrangement of vicinal protons on a chair-like dioxane. It appears that in this case, the bulky pseudo-axial substituent results in a distorted, half-chair-like geometry for ring **B** leading to the unexpectedly large J value. Similar NMR data was obtained for the later derivatives **2.45** and **2.46** (*vide infra*).

Scheme 2.8: Synthesis of restrained peracetylated C-glycosides

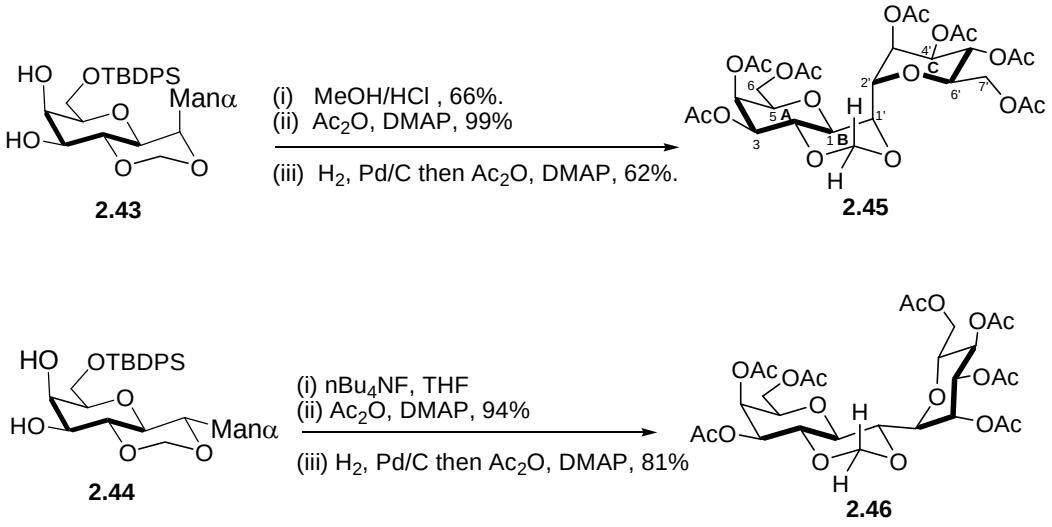


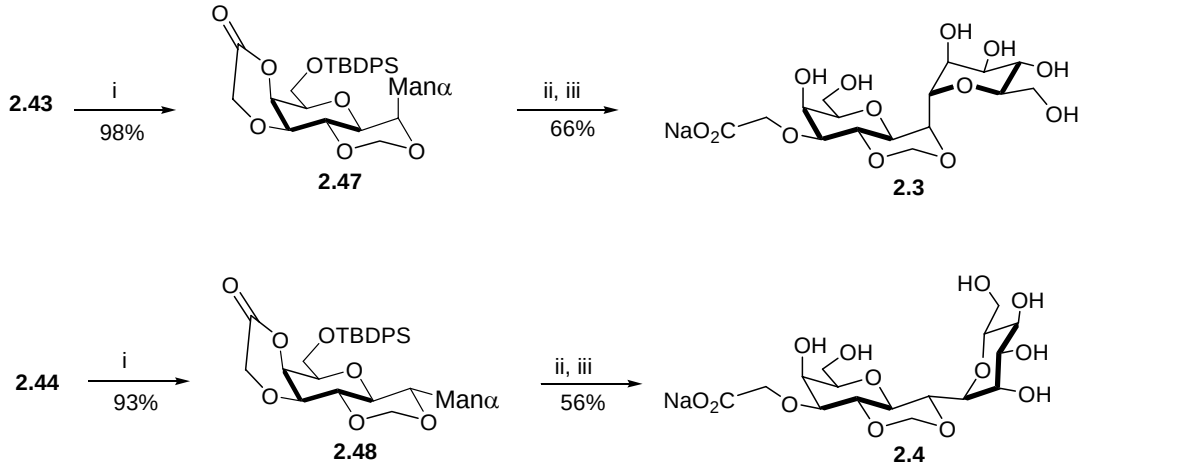
Table 2.1: ^{1}H-NMR of C-glycosides **2.45** and **2.46**.

Position	**2.45/ ^{1}H NMR (J, Hz)**	**2.46/ ^{1}H NMR (J, Hz)**
1′	4.19 (m)	3.77 (dd, J = 2.2, 9.8)
2’	4.56 (m)	4.46 (s)
3’	5.78 (dd, J = 3.0, 6.0)	5.84 (bs)
4’	5.70 (dd, J = 3.5, 5.8)	5.96 (dd, J = 4.0, 9.0)
5’	5.47 (t, J = 5.8)	5.72 (t, J = 9.0)
6’	4.07, (q, J = 5.7)	4.28 (m)
7’a	4.56 (m)	4.56 (dd, J = 5.0, 11.0)
7’b	4.56 (m)	4.28 (m)
1	3.47 (dd, J = 6.5, 10.0)	3.23 (t, J = 9.8)
2	4.51 (t, J = 10.0)	3.69 (t, J = 9.8)
3	5.19 (dd, J = 3.0, 10.0)	5.15 (dd, J = 3.0, 9.8)
4	5.55 (t, J = 3.0)	5.47 (d, J = 3.0)
5	3.33 (t, J = 6.0)	3.30 (t, J = 6.5)
6a	4.00 (dd, J = 6.0, 11.6)	3.99 (dd, J = 6.5, 10.8)
6b	4.19 (m)	4.10 (m)
O-CHa-O	5.06 (d, J = 6.0)	4.62 (d, J = 6.5)
O-CHbO	4.71 (d, J = 6.0)	buried at 4.10
CH_3CO-	1.56, 1.65, 1.67,1.68, 1.75, 1.96	1.63, 1.68, 1.73,1.74, 1.75, 1.78

2.7 "End games" for conformationally restrained mimetics 2.3 and 2.4

Finally, diols **2.43** and **2.44** were transformed to **2.3** and **2.4** *via* a reaction sequence that involved the selective dibutyltin oxide mediated alkylation of diol **2.43** and **2.44** with methyl bromoacetate.[14] This led to selective 3-O-alkylation followed by *in situ* lactonization to give **2.47** and **2.48** respectively. Exposure of these products to aqueous sodium hydroxide led to concomitant saponification and desilylation to give the corresponding dihydroxy acids, which were subjected to hydrogenolysis (Scheme 2.9). The target compounds **2.3** and **2.4** were obtained after purification using both reverse and normal phase chromatography, and lyophilization from aqueous solutions.

Scheme 2.9: Synthesis of the **2.3** and **2.4**



(i) Bu_2SnO, $PhCH_3$, $BrCH_2CO_2Me$, n-Bu_4NI; (ii) aq. NaOH, EtOH; (iii) H_2, Pd/C, HCOOH, MeOH, then aq. NaOH

2.8 Summary

The conformationally restrained C-glycosides **2.3**/**2.4** were prepared using the oxocarbenium ion-enol cyclization methodology that was developed in our group. These structures were designed to probe the optimal conformation requirements for binding of

their disaccharide framework to P-selectin. The conformational behavior and P-selectin binding of **2.3** and **2.4** will be discussed in chapter 4. The stereochemistry was assigned through analysis of vicinal J values from ^{1}H-NMR data.

2.9 Experimental section

General

Unless otherwise stated, all reactions were carried out under nitrogen atmosphere in oven-dried glassware using standard syringe and septa technique. Chemical shifts are relative to the deuterated solvent peak or the tetramethylsilane (TMS) peak at (δ 0.00) and are in parts per million. The ^{1}H and ^{13}C NMR spectra were recorded on 300, 400 or 500 MHz MHz instruments. Signals for selected nuclei were assigned through ^{1}H COSY experiments. High resolution mass spectroscopic (HRMS) data was obtained at the Mass Spectrometry Facility at University of Illinois, Urbana. Optical rotations are given in units of 10^{-1} deg/cm^2 g at 589 nm (sodium D-line).

Thin layer chromatography (TLC) was done on 0.25 mm thick precoated silica gel HF_{254} alumina sheets (Whatman). The chromatograms were observed under UV light and, or were visualized by heating plates that were dipped in ammonium molybdate solution. Unless otherwise stated, flash column chromatography (FCC) was performed using silica gel 60 (230-400 mesh) and employed a stepwise solvent polarity gradient, correlated with TLC mobility.

1-Thio-1,2-*O*-isopropylidene acetal 2.13.

Compound **2.13** was prepared by the previously reported procedures.[14] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (s, 9H), 1.47, 1.49 (both s, 6H), 2.32 (br s, 1H, D_2O), 3.80 (m, 3H), 4.18 (dd, J = 2.0, 7.0 Hz, 1H), 5.44 (d, J = 7.0 Hz, 1H), 7.20-7.80 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.5, 26.3, 27.1, 27.5, 65.3, 70.1, 80.4, 85.4, 111.5, 127.6, 127.9, 129.1, 129.9, 132.0, 133.3, 134.0, 135.7; ESMS 531 (M + Na). FABHRMS calcd for $C_{23}H_{31}O_4Si$ (M – SC_6H_6) 399.1992, found 399.1992.

Aldehyde 2.16

To a solution of methyl-α-D-mannopyranoside (5.0 g, 25.8 mmol) in dry DMF (50 mL) at 0 ^{o}C was added NaH (5.15 g, 60% in mineral oil, 0.13 mol) and Bu_4NI (0.95 mg, 0.26 mol) followed by BnBr (15.3 mL, 0.13 mmol). The reaction was stirred for 0.5 hour at rt under an argon atmosphere, then quenched with water and extracted with ether (2×50 mL). The organic layer was washed with water (5 × 10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. FCC of the crude material gave the tetrabenzylated product (13.6 g, 95%), R_f = 0.80 (15% EtOAc/petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.30 (s, 3H), 3.38 (m, 6H), 4.70 (m, 9H), 7.40 (m, 20H).

Trimethylsilyl triflate (1.8 mL, 10.1 mmol) was added dropwise to a solution of the tetrabenzylated methyl- α-*D*-mannoside (11.2 g, 20.2 mmol) and allytrimethylsilane (6.5 mL, 40.5 mmol) in anhydrous acetonitrile (50 mL) at 0 ^{o}C under an atmosphere of argon. The solution was warmed to rt and stirred for an additional 16 hours. The resulting deep-orange solution was diluted with CH_2Cl_2. The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. FCC of the crude

material gave the α-C-allyl derivative (9.4 g, 90%); colorless oil; R_f = 0.20 (5% EtOAc/petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29-2.38 (m, 2H), 3.62 (dd, J = 3.5, 4.6 Hz, 1H), 3.70 (dd, J = 3.5, 10.3 Hz, 1H), 3.82 (m, 2H), 3.82 (m, 1H), 3.87 (dd, J = 6.8, 13.0 Hz, 1H), 4.05 (ddd, J = 4.8, 6.2, 7.8 Hz, 1H), 4.51-4.61 (m, 7H), 4.70 (d, J = 11.3 Hz, 1H), 5.00-5.75 (m, 1H), 7.18-7.34 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.6, 69.1, 71.5, 72.2, 72.3, 73.2, 73.6, 73.9, 74.8, 76.9, 117.2, 127.6, 128.0, 128.1, 128.3, 134.3, 138.2, 138.4.

The product from the previous step (1.27 g, 2.25 mmol) and $PdCl_2(CH_3CN)_2$ (18 mg, 0.07 mmol) were dissolved in anhydrous benzene (75 mL) and refluxed for 16 hours.[26] Evaporation of the solvent *in vacuo* followed by FCC of the crude mixture gave the α-C-1-propenyl derivative (11 g, 88%) as a mixture of *E/Z* isomers (4:1 from ^{1}H-NMR); R_f = 0.45 (10% EtOAc/petroleum ether; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.64, 1.71 (d, J = 6.4 Hz, 3H ea), 4.53-4.55 (m), 4.53-4.91(m), 5.46 (dd, J = 1.5, 4.03 Hz, 1H), 5.52 (dd, J = 1.4, 5.1 Hz, 1H), 5.59-5.71 (m, 2H), 7.21-7.42 (m, 40H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 18.2, 69.8, 70.7, 71.9, 72.2, 73.5, 74.0, 74.5, 75.5, 76.6, 78,8, 79.4, 127.4-128.2 (several lines), 138.4, 138.5; FABMS 587.2 (M + Na).

A solution of the product from the previous step (1.44 g, 2.55 mmol) in CH_2Cl_2 (50 mL) was cooled to -78 ^{o}C. Then a mixture of O_3/O_2 was bubbled through the solution until TLC indicated complete disappearance of the starting material. The solution was then purged with nitrogen, warmed to rt and treated with triphenylphosphine (0.73 g, 2.81 mmol) and stirred vigorously for 30 min. Evaporation of the solvent *in vacuo* gave a yellow oil. FCC of the crude product afforded the aldehyde **2.16** (1.31 g, 93%), R_f = 0.44 (30% EtOAc/petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.63 (m,

1H), 3.93 (m, 2H), 4.11 (t, J = 8.4 Hz, 1H), 4.36 (d, J = 2.6 Hz, 1H), 4.54-4.56 (m, 8H), 4.97 (d, J = 11.0 Hz, 1H), 7.44 (m, 20 H), 9.91 (d, J = 1.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 69.3, 72.0, 72.1, 72.9, 73.3, 74.1, 74.5,76.6, 79.1, 79.8, 127.4, 127.5, 127.6, 127.8, 128.1, 128.2, 137.7, 137.8, 138.1, 202.9; FABMS 575.2 (M + Na).

Allylic alcohols 2.17 and 2.18

Vinylmagnesium bromide (31.0 mL, 1M in THF, 31.0 mmol) was slowly added to a solution of aldehyde **2.16** (5.78 g, 10.0 mmol) in dry THF (25 mL) at -15 ^{o}C. The reaction mixture was stirred at this temperature for 1.75 hours then at rt for 0.5 hour. The reaction mixture was the poured into saturated aqueous NH_4Cl at 0 ^{o}C and extracted with ether. The organic phase was dried (Na_2SO_4), filtered and evaporated *in vacuo*. FCC of residue gave the mixture of alcohols **2.17/2.18** (rel. ratio ca 3/2, 4.45 g, 73%) as a colorless oil; R_f = 0.62 (15% EtOAc/petroleum ether). For characterization purposes a sample of this mixture was separated by repeated FCC.

For allylic alcohol 2.17: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.50 (s, D_2O ex, 1H), 3.70 (dd, J = 4.6, 10.3 Hz, 1H), 3.75-3.89 (m, 5H), 4.01 (m, 1H), 4.33 (apparent t, J = 5.3 Hz, 1H), 4.49-4.62 (m, 8H), 5.18 (dt, J = 1.6, 10.5 Hz, 1H), 5.33 (dt, J = 1.6, 17.2 Hz, 1H), 5.90 (ddd, J = 5.8, 10.7, 16.1 Hz, 1H), 7.24-7.41 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 69.0, 70.6, 72.1, 72.7, 72.9, 73.4, 74.1, 74.9, 76.0, 116.6, 127.6-128.4 (several lines), 137.9, 138.2, 138.4; FABMS 603.2 (M + Na).

For allylic alcohol 2.18: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.36 (brd s, D_2O ex, 1H), 3.72 (dd, J = 5.1, 10.3 Hz, 1H), 3.85 (m, 2H), 3.94 (m, 2H), 4.02 (t, J = 6.2 Hz, 1H), 4.10 (m, 1H), 4.49-4.64 (m, 8H), 5.25 (d, J = 10.5 Hz, 1H), 5.35 (d, J = 17.6 Hz, 1H), 6.04 (ddd, J

= 6.4, 10.6, 17.2 Hz, 1H), 7.24-7.43 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 68.7, 71.4, 72.5, 72.85, 72.93, 73.4, 73.6, 74.3, 74.6, 75.2, 75.3, 116.8, 127.7-128.6 (several lines), 137.1, 138.1, 138.3, 138.4; ESMS 598.4 ($M+NH_4^+$).

MOM-protected alcohols 2.19 and **2.20**

MOMCl (0.91 mL, 11.9 mmol) was added to a mixture of **2.17/2.20** (2.30 g, 3.97 mmol), *i*-Pr_2NEt (2.76 mL, 15.9 mmol) and anhydrous CH_2Cl_2 (40 mL) at 0 ^{0}C. The mixture was refluxed for 4 hours at 50 ^{0}C, then washed with brine and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure and FCC of the residue provided **2.19** (0.65 g), **2.20** (0.88 g) and a mixture of MOM products **2.19/2.10** (0.62 g) (ca. 90% overall yield).

For **2.19**: R_f = 0.63 (20% EtOAc/petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.29 (s, 3H), 3.42 (m, 1H), 3.72-4.19 (m, 6H), 4.40 (t, J = 7.7 Hz, 1H), 4.53-4.89 (m, 10H), 5.11 (d, J = 10.6 Hz, 1H), 5.35 (d, J = 14.6 Hz, 1H), 5.89 (ddd, J = 6.7, 8.0, 11.7 Hz, 1H), 7.28-7.51 (m, 20 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.8, 69.6, 71.7, 72.1, 73.4, 74.1, 75.1, 75.6, 76.1, 78.4, 94.1, 119.6, 127.4-128.3 (several lines), 134.9, 138.5; FABHRMS calcd for $C_{39}H_{44}O_7Na$ (M + Na) 647.2985, found 647.2985.

For **2.20**: R_f = 0.66 (20% EtOAc/petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.34 (s, 3H), 3.72-4.03 (m, 7H), 4.32 (t, J = 7.1 Hz, 1H), 4.53-4.77 (m, 10H), 5.15 (d, J = 11.4 Hz, 1H), 5.20 (d, J = 18.0 Hz, 1H), 5.61 (ddd, J = 5.3, 9.1, 15.9 Hz, 1H), 7.24-7.38 (m, 20 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.0, 69.9 71.8, 72.3, 73.6, 73.9, 74.0, 75.1, 75.5, 76.1, 94.2, 119.3, 127.5-128.5 (several lines), 138.5, 138.7, 138.9; FABHRMS calcd for $C_{39}H_{44}O_7Na$ (M + Na) 647.2985, found 647.2985.

MOM-protected acid 2.24

Alkene **2.19** (3.90 g, 6.25 mmol) was subjected to the ozonolysis procedure described for the preparation of **2.16**. The aldehyde derivative was obtained (1.47 g, 94%). R_f = 0.63 (20% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.34 (s, 3H), 3.62 (dd, J = 6.0, 10.0 Hz, 1H), 3.66 (t, J = 3.8 Hz, 1H), 3.75 (m, 3H), 3.97 (dd, J = 3.0, 8.5 Hz, 1H), 4.05 (dt, J = 2.5, 6.5 Hz, 1H), 4.16 (m, 1H), 4.26 (dd, J = 3.0, 8.0 Hz, 1H), 4.35-4.52 (m, 8H), 4.58 (dd, J = 3.3, 8.6 Hz, 1H), 4.74 (q, J = 6.5 Hz, 2H), 7.13-7.32 (m, 20H), 9.48 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.2, 68.5, 71.7, 72.2, 72.8, 73.4, 74.4, 74.9, 75.4, 82.7, 97.5, 127.6, 127.7, 128.1, 128.2, 128.4, 138.0, 138.2, 138.4, 202.4; ESIMS 649.2 (M+Na).

To a mixture of the aldehyde from the previous step (1.48 g, 2.36 mmol) and $NaH_2PO_4.H_2O$ (3.26 mg, 23.6 mmol), in 5:1 CH_3CN-H_2O (30 mL) were successively added 30% H_2O_2 solution (1.0 mL) and a solution of $NaClO_2$ (1.1 g, 12.2 mmol) in water (10 mL) at 0 ^{o}C. The reaction mixture was stirred for 1 hour at rt, then quenched by addition of Na_2SO_3 (1.50 g) and extracted with EtOAc. The organic phase washed with water, brine, dried (Na_2SO_4) and concentrated under reduced pressure. FCC of the residue afforded acid **2.24** (1.50 g, 99%): colorless oil; R_f = 0.51 (10% MeOH/$CHCl_3$); ^{1}H NMR (300 MHz, C_6D_6) δ 3.23 (s, 3H), 3.85 (d, J = 5.5 Hz, 1H), 3.88 (m, 1H), 3.95 (t, J = 4.8 Hz, 1H), 4.30-4.44 (m, 8H), 4.51 (t, J = 11.0 Hz, 1H), 4.61-4.71 (m, 5H), 4.81 (dd, J = 4.0, 7.0 Hz, 1 H), 7.01-7.45 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.0, 68.7, 71.7, 72.3, 72.6, 72.9, 73.1, 74.7, 75.1, 75.8, 76.8, 77.2, 77.6, 96.4, 127.4-128.2 (several lines), 138.0, 173.4; EIHRMS calcd for $C_{38}H_{46}O_9SiN$ (M + NH_4^+) 660.2; FABHRMS calcd for $C_{38}H_{42}O_9Na$ (M + Na) 665.2724, found 665.2727.

MOM-protected acid 2.25

Alkene **2.20** (3.90 g, 6.25 mmol) was subjected to the ozonolysis procedure described for the preparation of **2.24**. The aldehyde derivative (3.31 g, 85%) was obtained: R_f = 0.44 (30% EtOAc/petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.40 (s, 3H), 3.74 (m, 3H), 3.93 (t, J = 3.3 Hz, 1H), 4.01 (dd, J = 3.0, 6.0 Hz, 1H), 4.17 (m, 2H), 4.32-4.53 (m, 8H), 4.58 (dd, J = 3.3, 8.6 Hz, 1H), 4.73 (d, J = 6.9 Hz, 1H), 7.17-7.37 (m, 20H), 9.72 (d, J = 1.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.3, 68.3, 70.8, 71.3, 71.9, 72.3, 72.4, 73.2, 73.5, 73.9, 75.0, 82.1, 97.7, 127.4-128.3 (several lines), 137.7, 137.8, 137.9, 138.2, 202.6 FABHRMS calcd for $C_{38}H_{42}O_8Na$ (M + Na) 649.2769, found 649.2777.

The aldehyde (416 mg, 0.66 mmol) from the previous step was converted, following the procedure that was used for **2.24**, to acid **2.25** (410 mg, 97%): colorless oil; R_f = 0.47 (10% MeOH/$CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.49 (s, 3H), 3.74 (m, 3H), 3.91 (m, 2H), 4.01 (t, J = 3.7 Hz, 1H), 4.17 (m, 2H), 4.39 (m, 1H), 4.55-4.71 (m, 10H), 4.77 (d, J = 7.3 Hz, 1H), 4.85 (d, J = 6.9 Hz, 1H), 7.31-7.49 (m, 20H), 11.22 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.5, 68.6, 70.8, 72.1, 72.2, 72.8, 73.2, 74.1, 74.4, 74.9, 75.7, 97.2, 127.4-128.3 (several lines), 137.8, 137.9, 138.0, 138.2, 174.5; FABHRMS calcd for $C_{38}H_{42}O_9Na$ (M + Na) 665.2727, found 665.2722.

***p*-Methoxybenzyl-protected acid 2.26**

To a solution of alcohol **2.18** (1.56 g, 2.69 mmol) in dry DMF (10 mL) at 0 ^{o}C under an argon atmosphere was added NaH (0.54 g, 60% in mineral oil, 13.4 mmol) and Bu_4NI (0.40 g, 1.08 mol) followed by *p*-methoxybenzyl chloride (2.20 mL, 16.1 mmol).

The reaction was stirred for 1 hour, then quenched with methanol (1 mL) and extracted with ether. The organic layer was washed with water, dried (Na_2SO_4) and concentrated *in vacuo*. FCC of the residue gave *p*-methoxybenzylated derivative **2.23** (1.70 g, 90%); R_f = 0.58 (20% EtOAc/petroleum ether); ^{13}C NMR (75 MHz, $CDCl_3$) 55.4, 70.0, 71.7, 72.0, 73.0, 74.7, 75.3, 76.4, 78.2, 79.5, 114.1, 119.4, 127.5-129.7 (several lines), 130.4, 135.7, 138.7, 138.8, 159.4; FABHRMS calcd for $C_{45}H_{48}O_7Na$ (M + Na) 723.3298, found 723.3300.

Treatment of **2.23** (2.64 g, 3.77 mmol) according to the standard ozonolysis procedure provided the derived aldehyde (2.20 g, 83%); R_f = 0.31 (20% EtOAc/petroleum ether); ^1H NMR (500 MHz, $CDCl_3$) δ 3.64 (dd, J = 5.0, 10.0 Hz, 1H), 3.70-3.84 (m, 4H), 3.78 (s, 3H buried), 4.04 (m, 2H), 4.32 (m, 2H), 4.47-4.57 (m, 8H), 4.65 (d, J = 9.0 Hz, 1H), 6.83 (d, J = 8.5 Hz, 2H), 7.20-7.37 (m, 22H), 9.52 (d, J = 1.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 55.1, 68.5, 71.5, 72.3, 72.6, 72.8, 73.0, 73.1, 75.1, 83.4, 113.9, 127.5-129.7 (several lines), 138.0, 138.2, 138.4, 159.4, 200.2; ESIMS 741.0 (M + K)

The aldehyde from the previous step (2.20 g, 3.13 mmol), was oxidized to the acid derivative, following the procedure that was used for acid **2.24**. Compound **2.26** (2.10 g, 93%) was obtained as a colorless oil; R_f = 0.36 (10% MeOH/$CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 3.64 (dd, J = 5.0, 10.0 Hz, 1H), 3.72 (m, 2H), 3.78 (s, 3H), 4.06 (dd, J = 2.5, 7.5 Hz, 1H), 4.12 (m, 1H), 4.30 (d, J = 3.0 Hz, 1H), 4.34 (m, 1H), 4.37 (bs, 1H), 4.42-4.64 (m, 10H), 6.81 (d, J = 9.0 Hz, 1H), 7.31-7.49 (m, 22H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.2, 68.9, 71.7, 72.4, 72.8, 73.0, 75.0, 75.5, 76.4, 114.0, 127.6-129.9, 138.1,

138.3, 159.6, 172.9; ESIHRMS calcd for $C_{44}H_{46}O_9Na$ (M + Na) 741.3037, found 741.3040.

4-Nitrobenzoate ester 2.27

A mixture of alcohol **2.17** (2.78 g, 4.79 mmol), triphenylphosphine (5.04 g, 19.2 mmol), and 4-nitrobenzoic acid (3.21 g, 19.2 mmol) was dissolved in dry toluene (150 mL). DIAD (3.78 mL, 19.2 mmol) was then added dropwise at 0 ^oC under an atmosphere of nitrogen. The mixture was allowed to warm to rt, and stirred for an additional 1 hour. After concentration under reduced pressure the mixture was neutralized with aqueous $NaHCO_3$, and extracted with ether. The ethereal extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo.* The crude product was purified by FCC to give the ester **2.27** (2.83 g, 81%), colorless oil, R_f = 0.44 (20% EtOAc/petroleum ether); ^1H NMR (300 MHz, $CDCl_3$) δ 3.73 (dd, J = 3.0, 10.3 Hz, 1H), 3.86-4.11(m, 5H), 4.33 (t, J = 5.7 Hz, 1H), 4.50-4.71 (m, 8H), 5.41 (d, J = 7.3 Hz, 1H), 5.46 (d, J = 16.1 Hz, 1H), 6.14 (ddd, J = 7.3, 7.9, 16.1 Hz, 1H), 7.29-739 (m, 20H), 8.12 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 68.7, 71.3, 72.7, 73.1, 73.3, 74.6, 75.0, 75.2, 75.5, 120.5, 123.4, 127.5-128.3 (several lines), 130.7, 132.0, 135.3, 137.8, 137.9, 138.1, 138.2, 150.4, 163.6; ESIMS 752.2 (M + Na).

Tetra-O-acetate 2.28

MOM protected alkene **2.19** (86 mg, 0.14 mmol), 10% Pd on carbon (170 mg), formic acid (0.25 mL) and methanol (5 mL) was stirred under an atmosphere of hydrogen (balloon), for 12 hours. The reaction mixture was purged with argon and filtered through

a bed of Celite. The filtrate was concentrated *in vacuo*, dissolved in EtOAc (5 mL) and treated with acetic anhydride (0.1 mL) and DMAP (5 mg). FCC of the crude mixture afforded the dihydro-tetraacetate derivative (57 mg, 92%) as a colorless oil; R_f = 0.50 (40% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, C_6D_6) δ 0.90 (t, J = 7.3 Hz, 3H, H-3'), 1.49, 1.60 (m, 1H ea, H-2'), 1.65, 1.66, 1.73, 1.74, (all s, 3H ea, C$\underline{H_3}$CO x 4), 3.33 (s, 3H, C$\underline{H_3}$O-), 3.60 (m, 1H, H-5), 3.82 (ddd, J = 6.5, 8.5, 12.5 Hz, 1H, H-1'), 4.01 (dd, J = 2.0, 6.5 Hz, 1H, H-1), 4.16 (dd, J = 2.0, 12.0 Hz, 1H, H-6a), 4.36 (dd, J = 6.0, 12.0 Hz, 1H, H-6b), 4.53 (q, J = 6.0 Hz, 2H, O-CH_2-O), 5.57 (dd, J = 3.5, 10.0 Hz, 1H, H-3), 5.63 (apparent t, J = 9.5 Hz, 1H, H-4), 6.02 (br s, 1H, H-2); FABHRMS calcd for $C_{19}H_{31}O_{11}$ (M + Na) 458.1765, found 458.1764.

To a solution of the product from the previous step (40 mg, 0.09 mmol) in anhydrous CH_2Cl_2 (2 mL), at -78 ^{o}C, was added dimethylboron bromide (1.14 M, 0.29 mL, 0.33 mmol). The reaction mixture was stirred at rt for 30 min, then poured into a 1:1 mixture of THF in saturated $NaHCO_3$ and extracted with ether. The organic layer was washed with aqueous $NaHSO_4$ and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. FCC of the residue afforded **2.28** (12 mg, 34%): colorless oil; ^{1}H NMR (500 MHz, C_6D_6) δ 0.84 (t, J = 7.5 Hz, 3H, H-3'), 1.47 (m, 2H, H-2'), 1.61, 1.67, 1.71 (all s, 3H, 3H 6H resp. C$\underline{H_3}$CO), 1.86 (br s, 1H, D_2O exchange) 3.38 (m, 1H, H-1'), 3.78 (t, J = 4.0 Hz, 1H, H-1), 4.10 (dd, J = 3.5, 12.0 Hz, 1H, H-6a), 4.24 (dt, J = 3.0, 7.0 Hz, 1H, H-5), 4.55 (dd, J = 6.5, 12.0 Hz, 1H, H-6b), 5.44 (t, J = 7.5 Hz, 1H, H-4), 5.69 (t, J = 4.0 Hz, 1H, H-2), 5.91 (dd, J = 3.5, 7.5 Hz, 1H, H-3); FABHRMS calcd for $C_{17}H_{27}O_{10}$ (M + H) 391.1604, found 391.1604.

MOM-tetra-O-acetate 2.29

Treatment of MOM protected alkene **2.20** (70 mg, 0.11 mmol) following the hydrogenation-acetylation sequence described in the synthesis of **2.28** provided MOM-tetraacetate **2.29** (36 mg, 75%) as a colorless oil; ^{1}H NMR (500 MHz, C_6D_6) δ 0.79 (t, J = 7.5 Hz, 3H, H-3'), 1.65, 1.78 (m, 2H, H-2'a, b), 1.63, 1.70, 1.73, 1.74 (all s, 3H ea, $C\underline{H_3}CO$ x 4), 3.26 (s. 3H, $C\underline{H_3}O$-), 3.52 (m, 1H, H-1'), 4.00 (t, J = 3.3 Hz, 1H, H-1), 4.23 (dd, J = 3.0, 12.5 Hz, 1H, H-6a), 4.36 (m, 1H, H-5), 4.46 (A of ABq, Δδ = 0.13 ppm, J = 6.5 Hz, 1H, O-CH_a-O), 4.49 (dd, J = 6.0, 12.0 Hz, 1H, H-6b), 4.59 (B of ABq, Δδ = 0.13 ppm, J = 6.5 Hz, 1H, O-CH_b-O), 5.62 (t, J = 9.0 Hz, 1H, H-4), 5.69 (t, J = 3.0 Hz, 1H, H-2), 5.91 (dd, J = 3.5, 9.0 Hz, 1H, H-3).

Thioacetal ester 2.30

DCC (324 mg, 1.58 mmol) was added at 0 ^{o}C to a solution of alcohol **2.13** (478 mg, 0.94 mmol), acid **2.24** (400 mg, 0.63 mmol), and DMAP (16 mg, 0.13 mmol) in anhydrous benzene (50 mL). The reaction was warmed to rt and stirred for 2 hours at this temperature. The mixture was diluted with ether (10 mL) and filtered. The filtrate was washed with 0.1 N aqueous HCl and brine, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by FCC to give ester **2.30** (525 mg, 74% based on recovered **2.13**): colorless oil; R_f = 0.32 (10% EtOAc/petroleum ether); IR (neat) 1759 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (s, 9H), 1.47, 1.54, (both s, 3H ea), 3.38 (s, 3H), 3.62 (dd, J = 5.2, 9.4 Hz, 1H), 3.88-3.97 (m, 3H), 4.08-4.24 (m, 3H), 4.30-4.80 (m, 14H), 5.51 (m, 1H), 5.57 (d, J = 6.6 Hz, 1H), 7.34-7.49 (m, 29H), 7.66 (m, 2H), 7.81 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.5, 27.0, 27.4, 56.4, 62.5, 69.5, 71.2, 72.2,

72.6, 72.9, 73.2, 74.9, 75.8, 79.2, 84.8, 96.1, 111.6, 127.3-129.8 (several lines), 132.8, 133.0, 133.4, 135.6, 135.7, 138.2, 138.4 (three signals), 138.8, 169.7; FABHRMS calcd for $C_{67}H_{76}O_{12}NaSiS$ (M + Na) 1155.4724, found 1155.4709.

Thioacetal ester 2.31

Thioacetal ester **2.31** (1.63 g, 84% based on **2.13**): colorless oil; R_f = 0.48 (15% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, C_6D_6) δ 1.15 (s, 9H), 1.48, 1.49 (both s, 3H ea.), 3.08 (s, 3H), 3.66 (dd, J = 4.0, 10.3 Hz, 1H), 3.76 (m, 2H), 4.09-4.28 (m, 6H), 4.39-4.62 (m, 10H), 4.71 (t, J = 6.0 Hz, 1H), 4.78, (dd, J = 2.5, 7.0 Hz, 1H), 5.71 (m, 1H), 5.89 (d, J = 7.0 Hz, 1H), 6.90-7.34 (m, 31H), 7.69-7.81 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.6, 27.0, 27.4, 56.2, 61.6, 69.1, 71.6, 72.2, 73.2, 73.3, 73.7, 75.3, 75.5, 76.8, 77.0, 77.2, 77.7, 78.7, 84.1, 96.8, 111.4, 127.4, 127.6-129.6 (several lines), 133.0, 133.3, 135.5, 135.6, 138.3, 138.4, 138.6, 169.5; FABHRMS calcd for $C_{67}H_{76}O_{12}SiSK$ (M + K) 1171.4464, found 1171.4464.

Thioacetal enol ether 2.32

Tebbe reagent in THF (20.8 mL, 0.5 M, 10.4 mmol), was added dropwise under an atmosphere of argon at -78 ^{o}C to a solution of ester **2.30** (3.36 g, 2.97 mmol) and pyridine (0.3 mL) in anhydrous 3:1 toluene/THF (40 mL). The reaction mixture was warmed to rt, stirred at this temperature for 3 hours, and then slowly poured into a solution of 1 N aqueous NaOH at 0 ^{o}C. The resulting suspension was extracted with ether, and the organic phase washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by FCC on basic alumina

(Brockmann I, 150 mesh) to give the thioacetal enol ether **2.32** (2.56 g, 96% based on recovered **2.30**): colorless oil, R_f = 0.56 (15% EtOAc/petroleum ether); ^{1}H NMR (300 MHz, C_6D_6) δ 1.13 (s, 9H), 1.45, 1.46 (both s, 3H ea.), 3.15 (s, 3H), 3.82 (m, 5H), 3.91 (bs, 1H), 3.95 (dd, J = 4.5, 10.0 Hz, 1H), 4.05 (m, 1H), 4.12 (t, J = 9.5 Hz, 1H), 4.24 (d, J = 7.0 Hz, 1H), 4.34 (m, 3H), 4.42 (d, J = 12.0 Hz, 1H), 4.47 (d, J = 12.0 Hz, 1H), 4.51 (d, J = 12.0 Hz, 1H), 4.52-4.62 (m, 4H), 4.74 (m, 3H), 4. 97 (d, J = 11.0 Hz, 1H), 5.92 (d, J = 7.5 Hz, 1H), 7.00-7.38 (m, 28H), 7.50 (d, J = 7.0 Hz, 2H), 7.71 (d, J = 7.0 Hz, 2H), 7.77 (m, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 27.1, 27.5, 28.0, 56.1, 62.1, 71.2, 72.1, 72.3, 74.2, 75.4, 75.6, 75.7, 75.8, 76.0, 76.3, 80.4, 80.7, 84.8, 88.0, 94.6, 112.1, 127.8-130.6 (several lines), 132.3, 133.6, 133.8, 135.2, 136.3, 139.5, 139.7, 139.9, 158.1; FABHRMS calcd for $C_{68}H_{78}O_{11}NaSiS$ (M + Na) 1153.4932 found 1153.4966.

Thioacetal enol ether 2.33

Thioacetal enol ether **2.33** (0.88 g, 96% based on recovered **2.32**): colorless oil, R_f = 0.67 (15% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, C_6D_6) δ 1.16 (s, 9H), 1.56, 1.59 (both s, 3H ea.), 2.94 (s, 3H), 3.55 (dd, J = 5.5, 10.5 Hz, 1H), 3.81 (t, J = 6.5 Hz, 1H), 3.96 (s, 1H), 4.01 (d, J = 9.5 Hz, 1H), 4.15 (m, 2H), 4.20-4.29 (m, 5H), 4.36-4.46 (m, 4H), 4.57-4.71 (m, 5H), 4.81-4.88 (m, 3H), 4.99 (d, J = 11.0 Hz, 1H), 6.31 (d, J = 6.0 Hz, 1H), 6.94-7.39 (m, 29H), 7.53 (d, J = 7.0 Hz, 2H), 7.75 (m, 4H); ^{13}C NMR (75 MHz, C_6D_6) δ 27.2, 27.7, 55.7, 62.0, 70.8, 71.7, 71.9, 73.6, 73.9, 75.2, 75.7, 75.9, 76.0, 76.1, 80.5, 80.7, 84.3, 94.4, 112.4, 127.0-130.1 (several lines), 131.7, 133.4, 133.7, 135.0, 136.0, 139.3, 139.6, 139.7, 156.8; FABHRMS calcd for $C_{68}H_{78}O_{11}NaSiS$ (M + Na) 1153.4938, found 1153.4932.

Glycal. 2.34

A mixture of enol ether **2.32** (2.56 g, 2.27 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (5.57 g, 27.3 mmol), and freshly activated, powdered 4A molecular sieves (3.0 g) in anhydrous CH_2Cl_2 (100 mL) were stirred for 15 min at rt under an argon atmosphere and then cooled to 0 ^oC. Methyl triflate (2.56 mL, 22.7 mmol) was then introduced, and the mixture was warmed to rt and stirred for an additional 2 days, at which time triethylamine (4.75 mL) was added. The mixture was diluted with ether, washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was purified by FCC over basic alumina (Brockmann I, 150 mesh) to give glycal **2.34** (1.91 g, 83%), clear oil, R_f = 0.60 (20% EtOAc/petroleum ether); ^1H NMR (300 MHz, C_6D_6) δ 1.20 (s, 9H), 1.38, 1.53, (both s, 3H ea), 3.33 (s, 3H), 3.82 (t, J = 7.0 Hz, 1H), 3.89-3.93 (m, 7H), 4.18 (m, 2H), 4.32-4.71 (m, 11H), 4.87 (m. 2H), 4.95 (d, J = 11.4 Hz, 1H), 7.12-7.39 (m, 24H), 7.45 (d, J = 7.0 Hz, 2H), 7.82 (m, 4H); ^{13}C NMR (75 MHz, C_6D_6) δ 27.4, 27.6, 29.2, 56.3, 63.9, 69.6, 71.0, 72.1, 72.4, 72.7, 73.5, 74.2, 75.1, 75.6, 76.3, 76.6, 80.8, 95.3, 102.8, 110.8, 127.8-130.5 (several lines), 134.0, 136.3, 136.4, 139.7, 139.8, 139.9, 151.9; FABHRMS calcd for $C_{62}H_{72}O_{11}NaSi$ (M + Na) 1043.4742, found 1043.4734.

Glycal 2.35

Glycal **2.35** (435 mg, 92% based on recovered **2.33**): clear oil, R_f = 0.43 (20% EtOAc/petroleum ether); ^1H NMR (500 MHz, C_6D_6) δ 1.18 (s, 9H), 1.35, 1.50 (both s, 3H ea), 3.10 (s, 3H), 3.81 (d, J = 10.0 Hz, 1H), 3.89 (dd, J = 4.0, 10.8 Hz, 1H), 4.05-4.11 (m, 3H), 4.17 (m, 2H), 4.32-4.47 (m, 6H), 4.50 (br s, 1H), 4.57 (d, J = 7.0 Hz, 1H), 4.66

(m, 2H), 4.95 (m, 2H), 7.00-7.43 (m, 26 H), 7.80 (m, 4H); ^{13}C NMR (75 MHz, C_6D_6) δ 27.1, 27.2, 28.8, 56.0, 63.7, 69.6, 70.3, 72.2, 72.4, 73.8, 74.5, 74.7, 75.5, 75.8, 75.9, 76.1, 76.6, 76.7, 80.2, 95.1, 102.0, 110.4, 127.4-130.0 (several lines), 133.7, 133.8, 136.0, 139.4, 139.6, 152.8; FABHRMS calcd for $C_{62}H_{72}O_{11}NaSi$ (M + Na) 1043.4740, found 1043.4742.

1,3,4,5-Tetra-*O*-benzyl-13-*O*-*tert*-butyldiphenylsilyl-2,6:8,12-dianhydro-10,11-*O*-isopropylidene-7-*O*-methoxymethyl-D-*lyxo*-D-*galacto*-D-*manno*-tridecitol 2.36.

$BH_3.Me_2S$ (0.02 mL, 0.23 mmol) was added at 0 ^oC to a solution of the glycal **2.34** (24 mg, 0.02 mmol) in anhydrous THF (2 mL) under an atmosphere of argon. The mixture was warmed to rt and stirred for an additional 1.5 hours at this temperature. At that time the solution was cooled to 0 ^oC and treated with a mixture of 3N NaOH (0.12 mL) and 30% aqueous H_2O_2 (0.05 mL) for 30 min. The mixture was diluted with ether, washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was purified by FCC to give MOM-protected C-galactoside as the only product: **2.36** (21 mg, 88% from **2.34**), colorless oil, R_f = 0.61 (30% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00 (s, 9H), 1.33, 1.44, (both s, 3H ea), 2.29 (d, J = 8.5 Hz, 1H, D_2O ex), 3.23 (s, 3H), 3.33 (br s, 1H), 3.43 (d, J = 8.8 Hz, 1H), 3.58-3.73 (m, 5H), 3.76 (d, J = 4.5 Hz, 1H), 3.80 (t, J = 8.0 Hz, 1H), 3.83 (dd, J = 2.0, 7.5 Hz, 1H), 3.90 (t, J = 9.5 Hz, 1H), 3.95 (dd, J = 2.0, 7.5 Hz, 1H), 4.14 (dd, J = 2.0, 7.5 Hz, 1H), 4.25 (m, 2H), 4.34 (d, J = 12.0 Hz, 1H), 4.46 (m, 4H), 4.53 (d, J = 6.0 Hz, 1H), 4.65 (d, J = 6.0 Hz, 1H), 4.72 (d, J = 6.0 Hz, 1H), 4.75 (d, J = 12.0 Hz, 1H), 5.52 (d, J = 6.2 Hz, 1H), 7.13-7.31 (m, 26H), 7.60 (m, 4H); ^{13}C NMR (75

MHz, $CDCl_3$) δ 26.6, 28.7, 56.1, 62.5, 69.4, 70.0, 71.9, 72.6, 73.2, 73.5, 74.6, 74.8, 75.7, 76.0, 77.0, 78.7, 78.9, 98.6, 109.4, 127.7-129.9 (several lines), 133.6, 135.6, 135.8, 138.4, 138.5, 138.9; FABHRMS calcd for $C_{62}H_{74}O_{12}NaSi$ (M + Na) 1061.4847, found 1061.4840.

1,3,4,5-Tetra-*O*-benzyl-13-*O*-*tert*-butyldiphenylsilyl-2,6:8,12-dianhydro-10,11-*O*-isopropylidene-7-O-methoxymethyl-D-*lyxo*-D-*gulo*-D-*manno*-tridecitol 2.37.

Application of the procedure that was used for **2.36** to glycal **2.35** (558 mg, 0.55 mmol) provided MOM protected C-glycoside **2.37** (415 mg, 86% based on recovered **2.35**): oil, R_f = 0.61 (30% EtOAc/petroleum ether); ^1H NMR (500 MHz, C_6D_6) δ 1.18 (s, 9H), 1.35, 1.56 (both s, 3H ea), 3.13 (s, 3H), 3.52 (t, J = 9.0 Hz, 1H), 3.77 (d, J = 9.5 Hz, 1H), 3.81 (dd, J = 2.0, 10.5 Hz, 1H), 3.86 (m, 2H), 3.94 (t, J = 9.5 Hz, 1H), 4.12 (t, J = 6.0 Hz, 1H), 4.16-4.27 (m, 5H), 4.32-4.62 (m, 12H), 4.88 (d, J = 11.0 Hz, 1H), 4.96 (d, J = 8.0 Hz, 1H), 7.00-7.38 (m, 26H), 7.82 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.7, 27.0, 28.6, 55.9, 63.0, 69.9, 70.0, 71.9, 72.3, 73.0, 73.6, 73.7, 73.9, 74.3, 74.5, 74.7, 74.8, 75.2, 77.2, 78.2, 79.4, 80.4, 97.1, 109.2, 127.5, 127.7, 128.0, 128.2, 128.4, 133.6, 135.6, 135.6, 135.7, 138.2, 138.4, 138.6; ESIHRMS calcd for $C_{62}H_{74}O_{12}NaSi$ (M + Na) 1061.4847, found 1061.4847.

1,3,4,5-Tetra-*O*-benzyl-13-*O*-*tert*-butyldiphenylsilyl-2,6:8,12-dianhydro-10,11-*O*-isopropylidene-D-*lyxo*-D-*galacto*-D-*manno*-tridecitol 2.38.

Dimethylboron bromide (0.18 mL, 1.85 mmol) was added at -78 ^oC, to a mixture of MOM-protected C-glycoside **2.36** (320 mg, 0.31 mmol), 2,6-di-*tert*-butyl-4-

methylpyridine (252 mg, 1.23 mmol), freshly activated, powdered 4A molecular sieves (624 mg) and anhydrous CH_2Cl_2 (20 mL). The reaction mixture was stirred at this temperature for 30 min, at rt for an additional 30 min, quenched by addition of a 1:1 mixture of THF and saturated aqueous $NaHCO_3$ (10 mL), and extracted with ether. After washing of the organic layer with 10% aqueous $NaHSO_4$ and brine, the organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure. FCC of the crude product afforded **2.38** (221 mg, 72% yield based on **2.36**) as a colorless oil; R_f = 0.17 (30% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, C_6D_6) δ 0.95 (s, 9H), 1.25 (s, 3H), 1.40 (s, 3H), 3.13 (bs, 1H, D_2O ex), 3.25 (dd, J = 5.5, 9.0 Hz, 1H), 3.45 (dd, J = 3.0, 10.0 Hz, 1H), 3.49 (t, J = 5.0 Hz, 1H), 3.56 (d, J = 6.0 Hz, 1H), 3.75-3.93 (m, 5H), 4.00 (m, 2H), 4.11 (m, 1H), 4.27 (dd, J = 2.0, 4.8 Hz, 1H), 4.30 (dd, J = 4.37 Hz, 1H), 4.45 - 4.63 (m, 9H), 7.25-7.42 (m, 26H), 7.70 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.6, 27.1, 28.6, 63.1, 69.4, 71.0, 71.2, 71.5, 72.4, 72.8, 73.1, 73.3, 73.8, 74.2, 75.0, 75.8, 76.3, 77.9, 80.3, 109.4, 127.7 - 129.8 (several lines), 133.7, 135.7, 137.9, 138.2, 138.5, 138.6; FABHRMS calcd for $C_{60}H_{70}O_{11}NaSi$ (M + Na) 1017.4585, found 1017.4557.

1,3,4,5-Tetra-*O*-benzyl-13-*O*-*tert*-butyldiphenylsilyl-2,6:8,12-dianhydro-10,11-*O*-isopropylidene-D-*lyxo*-D-*gulo*-D-*manno*-tridecitol 2.39.

Acetylation of PMB-protected C-glycoside **2.40** (155 mg, 0.13 mmol) following the procedure described in the synthesis of **2.28** provided the acetate derivative (156 mg, 98%) as a colorless oil; R_f = 0.34 (20% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.10 (s, 9H), 1.36 (s, 3H), 1.63 (s, 3H), 2.06 (s, 3H), 3.38 (dd, J = 3.0, 9.0 Hz, 1H), 3.60 (t, J = 8.8 Hz, 1H), 3.68 (dd, J = 6.8, 11.0 Hz, 1H), 3.75 (dt, J = 2.5, 7.5 Hz,

1H), 3.83-4.00 (m, 7H), 4.02 - 4.09 (m, 4H), 4.18 (dd, J = 2.0, 3.3 Hz, 1H), 4.32-4.85 (m, 8H), 5.34 (dd, J = 7.5, 9.7 Hz, 1H), 6.75 (d, J = 8.6 Hz, 2H), 7.11 (d, J = 8.6 Hz, 2H), 7.21 - 7.43 (m, 26H), 7.75 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 26.6, 27.1, 27.9, 55.2, 70.3, 70.4, 71.8, 72.8, 73.6, 73.8, 74.7, 75.0, 75.2, 75.4, 75.9, 76.5, 77.4, 78.3, 80.1, 109.9, 113.9, 127.5-130.5 (several lines), 133.7, 133.8, 135.7, 138.5, 138.6, 138.7, 159.4, 169.2.

DDQ (62 mg, 0.27 mmol) was added to a solution of the product from the previous step (155 mg, 0.13 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at rt for 2 hours, then diluted with saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2, dried (Na_2SO_4), and evaporated under reduced pressure. FCC of the residue afforded the derived alcohol (107 mg, 77%) as a colorless oil; R_f = 0.33 (20% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.34 (s, 3H), 1.46 (s, 3H), 1.99 (s, 3H), 3.06 (d, J = 3.5 Hz, D_2O exchange, 1H) 3.66-3.89 (m, 9H), 3.94 (dd, J = 3.5, 9.0 Hz, 1H), 4.00 (m, 1H), 4.24 (bs, 1H), 4.30 (d, J = 6.0 Hz, 1H), 4.48-4.63 (m, 7H), 4.77 (d, J = 11.5 Hz, 1H), 5.30 (t, J = 5.5 Hz, 1H), 7.21 - 7.41 (m, 26H), 7.68 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 26.1, 27.1, 62.8, 68.1, 69.8, 71.2, 71.9, 72.1, 73.3, 73.5, 74.1, 74.2, 75.1, 75.3, 76.2, 78.1, 78.3, 81.4, 82.2, 110.1, 127.6 - 129.8 (several lines), 133.6, 133.7, 135.7, 138.5, 138.7, 170.0; ESIHRMS calcd for $C_{62}H_{72}O_{12}SiNa$ (M + Na) 1059.4695, found 1059.4691.

NaOMe (50 mg, 1.14 mmol) was added to a solution of the product from the previous step (106 mg, 0.11 mmol) in anhydrous CH_3OH (5 mL). The reaction was stirred at rt for 2 hours and the pH was then adjusted to 7 by addition of 2N methanolic HCl. The mixture was concentrated under reduced pressure and the residue purified by

FCC to give the **2.39** (100 mg, 98%) as a colorless oil; R_f = 0.51 (25% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07 (s, 9H), 1.34 (s, 3H), 1.51 (s, 3H), 2.42 (d, J = 9.5 Hz, D_2O exchange, 1H), 3.34 (dd, J = 2.0, 9.0 Hz, 1H), 3.44 (t, J = 9.0 Hz, 1H), 3.63 (m, 2H), 3.77 (dd, J = 2.5, 8.5 Hz, 1H), 3.78-4.00 (m, 6H), 4.09 (m, 1H), 4.15 (t, J = 2.5 Hz, 1H), 4.21 (dd, J = 2.5, 9.5 Hz, 1H), 4.26 (d, J = 3.0 Hz, 1H), 4.48 - 4.71 (m, 8H), 7.13-7.45 (m, 26H), 7.71 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.6, 27.0, 28.5, 63.1, 69.2, 69.9, 72.2, 72.6, 73.6, 73.7, 74.0, 74.1, 75.1, 80.0 (two signals), 109.5, 127.8-129.9 (several lines), 133.5, 133.7, 135.7, 135.9, 137.3, 138.2, 138.4; FABHRMS calcd for $C_{60}H_{70}O_{11}SiNa$ (M + Na) 1017.4588, found 1017.4585.

1,3,4,5-Tetra-*O*-benzyl-13-*O*-*tert*-butyldiphenylsilyl-2,6:8,12-dianhydro-10,11-*O*-isopropylidene-7-O-*p*-methoxybenzyl-D-*lyxo*-D-*gulo*-D-*manno*-tridecitol 2.40.

OPMB protected thioacetal ester (2.61 g, 87%) as a colorless oil; R_f = 0.55 (15% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, C_6D_6) δ 1.05 (s, 9H), 1.41 (s, 3H), 1.47, (s, 3H), 3.42 (dd, J = 3.0, 10.0 Hz, 1H), 3.51 (dd, J = 3.0, 7.7 Hz, 1H), 3.61 (dd, J = 4.7, 10.0 Hz, 1H), 3.74 (m, 4H), 3.87 (m, 3H), 3.99 (t, J = 3.4 Hz, 1H), 4.14-4.45 (m, 10H), 4.57 (m, 3H), 5.34 (m, 2H), 6.75 (d, J = 8.6 Hz, 2H), 7.12-7.55 (m, 28H), 7.65 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.7, 27.0, 27.5, 55.3, 62.2, 69.3, 71.8, 72.0, 72.2, 72.9, 73.4, 74.3, 74.7, 75.7, 78.0, 79.1, 84.7, 111.6, 114.0, 127.3-129.8 (several lines), 132.7, 132.8, 133.0, 133.4, 135.5, 135.6, 138.3, 138.5, 138.7, 159.5, 169.6; FABHRMS calcd for $C_{73}H_{80}O_{12}SiSNa$ (M + Na) 1231.5038, found 1231.5037.

OPMB protected thioacetal enol ether (1.11 g, 79%) as a colorless oil; R_f = 0.60 (10% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, C_6D_6) δ 1.17 (s, 9H), 1.56 (s, 3H),

1.60 (s, 3H), 3.25 (s, 3H), 3.57 (dd, J = 5.0, 11.0 Hz, 1H), 3.68 (d, J = 11.0 Hz, 1H), 3.75 (dd, J = 5.0, 9.5 Hz, 1H), 3.80 (m, 1H), 3.96 (d, J = 9.5 Hz, 1H), 4.03 (m, 2H), 4.19-4.29 (m, 5H), 4.36-4.52 (m, 6H), 4.56 (A, of ABq, J = 11.5 Hz, $\Delta\delta$ = 0.16 ppm, 1H), 4.61 (A of ABq, J = 12.5 Hz, $\Delta\delta$ = 0.41 ppm, 1H), 4.78 (B of ABq, J = 11.5 Hz, $\Delta\delta$ = 0.16 ppm, 1H), 4.81 (d, J = 9.5 Hz, 1H), 4.85 (d, J = 6.0 Hz, 1H), 4.97 (B of ABq, J = 11.0 Hz, $\Delta\delta$ = 0.41 ppm, 1H), 6.27 (d, J = 6.0 Hz, 1H), 6.71 (d, J = 8.0 Hz, 2H), 6.95-7.28 (m, 29H), 7.32 (s, 1H), 7.39 (t, J = 7.0 Hz, 2H), 7.46 (d, J = 7.0 Hz, 1H), 7.76 (m, 4H); ^{13}C NMR (75 MHz, C_6D_6) δ 27.6, 28.1, 55.3, 62.4, 70.6, 71.3, 71.9, 74.0, 75.0, 75.4, 75.8, 76.1, 76.4, 78.4, 81.0, 85.0, 88.2, 112.8, 114.5, 126.8-129.5 (several lines), 130.5, 132.2, 133.3, 133.8, 134.0, 135.4, 136.4, 139.7, 140.0, 157.8, 160.2; ESIHRMS calcd for $C_{72}H_{82}O_{13}SiSNa$ (M + Na) 1229.5414, found 1229.5422.

OPMB protected glycal (0.92 g, 87% based on recovered starting material) as a clear oil, R_f = 0.27 (10% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, C_6D_6) δ 1.30 (s, 9H), 1.50 (s, 3H), 1.69 (s, 3H), 3.38 (s, 3H), 3.91 (dd, J = 2.3, 13.0 Hz, 1H), 3.98 (dd, J = 4.7, 13.0 Hz, 1H), 4.08 (dd, J = 3.0, 9.0 Hz, 1H), 4.19 (m, 3H), 4.32 (m, 3H), 4.40 (t, J = 5.3 Hz, 1H), 4.46 (d, J = 9.0 Hz, 1H), 4.50 (d, J = 7.2 Hz, 1H), 4.58-4.66 (m, 5H), 4.69 - 4.77 (m, 5H), 5.06 (d, J = 11.4 Hz, 1H), 5.18 (d, J = 2.0 Hz, 1H), 6.86 (d, J = 8.6 Hz, 2H), 7.11-7.50 (m, 28H), 7.90 (m, 4H); ^{13}C NMR (125 MHz, C_6D_6) δ 26.8, 26.9, 28.6, 54.5, 63.4, 69.5, 70.3, 71.0, 71.8, 71.9, 72.2, 73.5, 73.8, 74.5, 75.5, 76.1, 76.5, 77.4, 80.2, 101.2, 110.2, 114.0, 127.2-129.9 (several lines), 135.8 (two signals), 139.3, 153.2, 159.7; ESIHRMS calcd for $C_{68}H_{76}O_{11}SiNa$ (M + Na) 1119.5050, found 1119.5047.

OPMB protected C-glycoside **2.40** (0.52 g, 75% based on recovered starting material) as a clear oil; R_f = 0.40 (30% EtOAc/petroleum ether); ^{1}H NMR (500 MHz,

C_6D_6) δ 1.08 (s, 9H), 1.40 (s, 3H), 1.55 (s, 3H), 3.56 (m, 3H), 3.71 - 3.83 (m, 9H), 3.90 - 4.00 (m, 4H), 4.07 (apparent t, J = 5.8 Hz, 1H), 4.22 - 4.36 (m, 4H), 4.40 (dd, J = 2.5, 8.0 Hz, 1H), 4.47 - 4.68 (m, 7H), 4.81 (d, J = 11 Hz, 1H), 6.77 (d, J = 8.5 Hz, 2H), 7.11 (d, J = 8.5 Hz, 2H), 7.17 - 7.44 (m, 26H), 7.75 (m, 13.5 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.7, 27.1, 28.6, 55.3, 63.1, 70.1, 70.5, 71.8, 72.1, 72.5, 73.5, 74.6, 74.8, 75.2, 79.6, 80.5, 82.2, 109.3, 114.0, 127.7 - 129.8 (several lines), 130.1, 133.6, 133.8, 135.6, 135.7, 138.0, 138.4, 138.6, 159.4; ESIHRMS calcd for $C_{68}H_{78}O_{12}SiNa$ (M + Na) 1137.5161, found 1137.5160.

1,3,4,5-Tetra-*O*-benzyl-13-*O*-*tert*-butyldiphenylsilyl-2,6,8,12-dianhydro-10,11-*O*-isopropylidene-7,9-O-methylene-D-*lyxo*-D-*galacto*-D-*manno*-tridecitol 2.41.

A mixture of diol **2.38** (260 mg, 0.26 mmol), nBu_4Br (42 mg, 0.13 mmol), CH_2Br_2 (0.91 mL, 13.3 mmol) and 2,3-dimethylbutene (0.70 mL) was stirred at 65 ^oC for 15 min. 20% aqueous NaOH (8 mL) was then added dropwise to the reaction mixture and stirring continued at 65 ^oC for 3 hours. The mixture was then cooled to rt and extracted with ether. The organic layer was washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. FCC afforded **2.41** (204 mg, 86% based on recovered **2.38**) as a colorless oil; R_f = 0.44 (15% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.39 (s, 3H), 1.51 (s, 3H), 3.49 (dd, J = 6.9, 10.6 Hz, 1H), 3.63 (dd, J = 5.7, 10.1 Hz, 1H), 3.74 (dd, J = 5.7, 10.1 Hz, 1H), 3.81 (m, 3H), 3.90 (m, 2H), 3.96 (m, 2H), 4.06 (dd, J = 5.4, 7.6 Hz, 1H), 4.24 (dd, J = 7.8, 10.5 Hz, 1H), 4.30 - 4.58 (m, 11H), 4.82 (A of ABq, J = 5.9 Hz, Δδ = 0.59 ppm, 1H), 5.42 (B of ABq, J = 5.9 Hz, Δδ = 0.59 ppm, 1H), 7.15-7.40 (m, 26H), 7.68 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) 26.7, 27.0, 28.6,

62.0, 62.8, 68.9, 70.5, 71.5, 72.1, 72.6, 72.7, 73.5, 73.8, 73.9, 74.7, 74.8, 75.2, 76.0, 76.8, 77.6, 91.2, 109.9, 127.6 - 130.0 (several lines), 133.6, 133.7, 135.7, 135.8 (two signals), 138.5, 138.6, 138.7, 138.9; ESIHRMS calcd for $C_{61}H_{71}O_{11}Si$ (M + H) 1007.4766, found 1007.4810.

1,3,4,5-Tetra-*O*-benzyl-13-*O*-*tert*-butyldiphenylsilyl-2,6:8,12-dianhydro-10,11-*O*-isopropylidene-7,9-O-methyleneD-*lyxo*-D-*gulo*-D-*manno*-tridecitol 2.42.

Application of the procedure that was used for **2.41** to diol **2.39** (260 mg, 0.26 mmol) provided **2.42** (175 mg, 83% based on recovered **2.39**); colorless oil; R_f = 0.50 (20% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.34 (s, 3H), 1.55 (s, 3H), 3.03 (t, J = 9.0 Hz, 1H), 3.36 (t, J = 9.0 Hz, 1H), 3.66 (m, 2H), 3.74 (dd, J = 2.0, 9.5 Hz, 1H), 3.80 (m, 3H), 3.86 - 4.00 (m, 4H), 4.04 (q, J = 5.0 Hz, 1H), 4.18 (d, J = 3.5 Hz, 1H), 4.35 (d, J = 4.0 Hz, 1H), 4.44 - 4.58 (m, 7H), 4.63 (d, J = 10.5 Hz, 1H), 4.65 (A of ABq, J = 6.5 Hz, Δδ = 0.39 ppm, 1H), 5.04 (B of ABq, J = 6.5 Hz, Δδ = 0.39 ppm, 1H), 7.17-7.43 (m, 26H), 7.69 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.6, 27.2, 28.8, 62.7, 69.7, 69.3, 70.6, 71.9, 72.2, 72.8, 73.4, 73.8, 75.4, 76.0, 77.0, 80.1, 80.4, 93.7, 109.8, 127.5 - 129.9 (several lines), 133.7, 133.8, 135.7, 135.8, 138.7, 138.8; FABHRMS calcd for $C_{61}H_{70}O_{11}SiNa$ (M + Na) 1029.4584, found 1029.4585.

1,3,4,5-Tetra-*O*-benzyl-13-*O*-*tert*-butyldiphenylsilyl-2,6:8,12-dianhydro-7,9-O-methylene-D-*lyxo*-D-*galacto*-D-*manno*-tridecitol 2.43.

A saturated solution of HCl in ether (0.1 mL) was added to a solution of **2.41** (200 mg, 1.29 mmol) in dry CH_3OH (30 mL). The reaction mixture was stirred at rt for 2.5

hours then neutralized with a solution of NaOMe in methanol. Removal of the volatiles under reduced pressure and FCC of the residue provided **2.43** (130 mg, 68%) as a colorless oil; R_f = 0.53 (40% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95 (s, 9H), 2.49 (d, J = 7.5 Hz, 1H, D_2O ex), 2.92 (d, J = 11 Hz, 1H), 3.02 (d, J = 10.0 Hz, 1H, D_2O ex), 3.21 (s, 1H), 3.52 (m, 2H), 3.59 (m, 1H), 3.78 (m, 3H), 3.83 (t, J = 10.0 Hz, 1H), 3.88 - 4.00 (m, 3H), 4.05 (dd, 3.0, 9.8 Hz, 1H), 4.20 - 4.52 (m, 10H), 4.83 (A of ABq, J = 5.5 Hz, Δδ = 0.45 ppm, 1H), 5.38 (B of ABq, J = 5.5 Hz, Δδ = 0.45 ppm, 1H), 7.00-7.38 (m, 26H), 7.58 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) 27.1, 63.0, 66.4, 69.4, 69.7, 70.4, 71.9, 72.4, 72.8, 73.2, 73.4, 73.5, 74.7, 74.8, 75.0, 75.4, 80.0, 92.1, 127.6 - 129.9 (several lines), 133.4, 133.5, 135.7, 137.9, 138.1, 138.3, 138.7; FABHRMS calcd for $C_{58}H_{66}O_{11}NaSi$ (M + Na) 989.4272, found 989.4251.

1,3,4,5-Tetra-*O*-benzyl-13-*O*-*tert*-butyldiphenylsilyl-2,6:8,12-dianhydro-7,9-O-methylene-D-*lyxo*-D-*gulo*-D-*manno*-tridecitol 2.44.

Application of the procedure that was used for **2.43** to **2.42** (175 mg, 0.17 mmol) provided **2.44** (92 mg, 64% based on recovered **2.42**) as a colorless oil; R_f = 0.44 (40% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95 (s, 9H), 2.44 (d, J = 6.0 Hz, 1H, D_2O ex), 2.83 (b s, 1H, D_2O ex), 2.94 (t, J = 9.0 Hz, 1H), 3.25 (t, J = 5.0 Hz, 1H), 3.50 (m, 2H), 3.59 (m, 2H), 3.73 (m, 4H), 3.86 (m, 2H), 4.07 (m, 1H), 4.11 (d, J = 3.0 Hz, 1H), 4.35-4.61 (m, 10H), 4.97 (d, J = 6.0 Hz, 1H), 7.08-7.35 (m, 26H), 7.56 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.2, 63.6, 69.8, 70.0, 72.0, 72.2, 72.3, 72.6, 72.9, 73.6, 75.5, 76.1, 76.6, 77.4, 77.5, 78.0, 78.8, 80.4, 93.8, 127.5 - 130.1 (several lines), 132.9,

133.1, 135.7, 135.8, 138.6, 138.8; FABHRMS calcd for $C_{58}H_{66}O_{11}NaSi$ (M + Na) 989.4272, found 989.4254.

1,3,4,5,10,11,13-Hepta-*O*-acetyl-2,6:8,12-dianhydro-7,9-O-methylene-D-*lyxo*-D-*galacto*-D-*manno*-tridecitol 2.45.

A solution of conc HCl in ether (0.1 mL) was added to diol **2.44** (110 mg, 0.14 mmol) in dry methanol (10 mL). The reaction was stirred at rt for approximately 2 hours and neutralized with sodium methoxide in methanol. Removal of the volatiles under reduced pressure and FCC of the residue provided the corresponding triol (69 mg, 66%), colorless oil, R_f = 0.20, (70% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.02 (dd, J = 4.5, 8.0 Hz, 1H, D_2O ex), 2.50 (d, J = 8.0 Hz, 1H, D_2O ex) 3.16 (d, J = 9.0 Hz, 1H), 3.33 (d, J = 9.0 Hz, 1H, D_2O ex), 3.36 (d, J = 3.5 Hz, 1H), 3.59 (dt, J = 3.0, 8.8 Hz, 1H), 3.67 (m, 2H), 3.74 (m, 1H), 3.82 (m, 1H), 3.87 (m, 1H), 3.93 (dd, J = 3.5, 9.5 Hz, 1H), 4.05 (dd, J = 3.0, 9.8 Hz, 1H), 4.08-4.15 (m, 3H), 4.33-4.64 (m, 10H), 4.93 (d, J = 5.5 Hz, 1H), 5.50 (d, J = 5.5 Hz, 1H), 7.18 (t, J = 7.0 Hz, 6H), 7.25-7.39 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) 63.0, 66.8, 69.1, 71.0, 72.0, 72.5, 73.0, 73.1, 73.1, 73.2, 73.3, 74.6, 75.1, 79.5, 92.0, 128.3, 128.4, 128.5, 128.6, 137.9, 138.1, 138.4; FABHRMS calcd for $C_{42}H_{48}O_{11}Na$ (M + Na) 751.3094, found 751.3094.

A solution of the above triol (14.0 mg, 0.02 mmol), DMAP (1.0 mg, 0.01 mmol), and acetic anhydride (0.07 mL, 0.64 mmol) in EtOAc (3 mL), was stirred at rt for 20 min. Then MeOH was added and the reaction mixture evaporated to dryness under reduced pressure. The residue was purified by FCC to afford the triacetate (16.3 mg, 99%), R_f = 0.34 (30 % EtOAc/petroleum ether); ^{1}H NMR (500 MHz, C_6D_6) δ 1.73, 1.76, 1.60 (all, s, 9 H), 3.32 (t, J = 6.3 Hz), 3.52 (dd, J = 7.00, 9.8 Hz, 1H), 3.91 (dd, J = 7.0, 9.8 Hz, 1H),

4.03 (m, 3H), 4.15-4.60 (m, 13H), 4.67 (dd, J = 2.5, 7.8 Hz, 1H), 4.89 (d, J = 5.5 Hz, 1H), 4.95, (t, J = 10.0 Hz, 1H), 5.19 (dd, J = 3.0, 11.0 Hz, 1H), 5.56 (d, J = 2.0 Hz, 1H), 5.65 (d, J = 5.5 Hz, 1H), 7.07-7.29 (m, 18H), 7.36 (d, J = 7.5 Hz, 2H); FABHRMS calcd for $C_{42}H_{54}O_{14}Na$ (M + Na) 877.3411, found 877.3412.

The above triacetate was subjected to the hydrogenation-acetylation sequence out lined for the synthesis of **2.28** to give the peracetylated compound **2.45** (7.9 mg, 62%) as a colorless oil; R_f = 0.30 (40% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, C_6D_6) δ 1.56, 1.65, 1.67,1.68, 1.75, 1.96 (all s, 21H), 3.33 (t, J = 6.0 Hz, 1H), 3.47 (dd, J = 6.5, 10.0 Hz, 1H), 4.00 (dd, J = 6.0, 11.6 Hz, 1H), 4.07 (q, J = 5.7 Hz, 1H), 4.19 (m, 2H), 4.51 (t, J = 10.0 Hz, 1H), 4.56 (m, 3H), 4.71 (d, J = 6.0 Hz, 1H), 5.06 (d, J = 6.0 Hz, 1H), 5.19 (dd, J = 3.0, 10.0 Hz, 1H), 5.47 (t, J = 5.8 Hz, 1H), 5.55 (d, J = 3.0 Hz, 1H), 5.70 (dd, J = 3.5, 5.8 Hz, 1H), 5.78 (dd, J = 3.0, 6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 20.7, 20.9, 21.0 (two signals), 21.1 (two signals), 61.8, 62.3, 67.4, 68.0, 68.1, 68.2, 68.7, 70.7, 71.1, 71.9, 72.6, 73.1, 75.5, 90.5, 169.3, 169.7, 170.0 (two signals), 170.2, 170.5 (two signals); FABHRMS calcd for $C_{28}H_{38}O_{18}Na$ (M + Na) 685.1956, found 685.1952.

1,3,4,5,10,11,13-Hepta-*O*-acetyl-2,6:8,12-dianhydro-7,9-O-methylene-D-*lyxo*-D-*gulo*-D-*manno*-tridecitol 2.46.

A solution of diol **2.44** (12.0 mg, 0.01 mmol) in THF (3 mL) was treated with tetrabutyl ammonium fluoride in THF (1M, 0.05 mL, 0.05 mmol) for 1.5 hours. The solvent was then evaporated *in vacuo* to give the crude triol. The crude product, DMAP (1.0 mg, 0.01 mmol), and acetic anhydride (0.10 mL, 1.06 mmol) in EtOAc (3 mL), was stirred at rt for 30 min. Then MeOH was added and the reaction mixture evaporated to

dryness under reduced pressure. The residue was purified by FCC to give the triacetate (10.0 mg, 94%): R_f = 0.62 (50 % EtOAc/petroleum ether); ^{1}H NMR (500 MHz, C_6D_6) δ 1.62 (s, 3H), 1.73 (s, 6 H), 3.36 (t, J = 6.5 Hz, 1H), 3.59 (t, J = 9.5 Hz, 1H), 3.79 (t, J = 9.8 Hz, 1H), 3.92 (m, 2H), 3.98-4.10 (m, 6H), 4.28 (m, 2H), 4.44 (m, 1H), 4.53-4.64 (m, 8H), 4.83 (d, J = 6.5 Hz, 1H), 5.27 (dd, J = 3.0, 10.3 Hz, 1H), 5.48 (d, J = 3.0 Hz, 1H), 7.10-7.33 (m, 18H), 7.45 (d, J = 7.5 Hz, 2H). FABHRMS calcd. for $C_{42}H_{54}O_{14}Na$ (M + Na) 877.3411, found 877.3405.

Peracetylated compound **2.46** (6.3 mg, 81%) colorless oil; R_f = 0.29 (50 % EtOAc/petroleum ether); ^{1}H NMR (500 MHz, C_6D_6) δ 1.63, 1.68, 1.73,1.74, 1.75, 1.78 (all s, 21H), 3.23 (t, J = 9.8 Hz, 1H), 3.30 (t, J = 6.5 Hz, 1H), 3.69 (t, J = 9.8 Hz, 1H), 3.77 (dd, J = 2.2, 9.8 Hz, 1H), 3.99 (dd, J = 6.5, 10.8 Hz, 1H), 4.10 (m, 2H), 4.28 (m, 2H), 4.46 (s, 1H), 4.56 (dd, J = 5.0, 11.0 Hz, 1H), 4.62 (d, J = 6.5 Hz, 1H), 5.15 (dd, J = 3.0, 9.8 Hz, 1H), 5.47 (d, J = 3.0 Hz, 1H), 5.72 (t, J = 9.0 Hz, 1H), 5.84 (br s, 1H), 5.96 (dd, J = 4.0, 9.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8 (two signals), 20.9 (two signals), 21.0, (two signals), 21.2, 61.7, 62.9, 67.3, 68.4 (two signals), 69.9, 71.1, 72.8, 73.7, 74.6, 75.5, 75.7, 80.4, 93.5, 169.7, 168.8 (two signals), 169.9, 170.0, 170.3, 170.7.

Lactone 2.47.

A mixture of diol **2.44** (54 mg, 0.06 mmol), Bu_2SnO (27 mg, 0.11 mmol), and anhydrous toluene (5 mL) was heated at reflux using a Dean-Stark set-up for 1 hour. The solution was then evaporated *in vacuo* and the residue was dissolved in dry toluene (3 mL). n-Bu_4NI (22 mg, 0.06 mmol) and methyl 2-bromoacetate (0.10 mL, 1.08 mmol) were added and the solution heated at reflux for 1 hour, at which time the volatiles were

removed under reduced pressure. FCC of the residue afforded lactone **2.47** (55 mg, 98%) as a colorless oil; R_f = 0.35 (20 % EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41 (s, 9H), 3.42 (t, J = 7.0 Hz, 1H), 3.38 (dd, J = 6.5, 9.0 Hz, 1H), 3.58 (dd, J = 3.5, 10.0 Hz, 1H), 3.84 - 4.48 (m, 16H), 4.51 (d, J = 12.0 Hz, 1H), 4.56 (d, J = 3.0 Hz, 1H), 4.61 (dd, J = 1.5, 6.5 Hz, 1H), 4.66 (dd, J = 1.5, 9.5 Hz, 1H), 4.76 (d, J = 12 Hz, 1H), 4.93 (d, J = 6.0 Hz, 1H), 4.98 (t, J = 10.0 Hz, 1H), 5.74 (d, J = 6.0 Hz, 1H), 7.04 - 7.36 (m, 26H), 7.82 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.1, 60.9, 61.2, 68.4, 69.0, 70.5, 71.9, 72.1, 72.7, 73.2, 73.6, 74.2, 74.3, 74.7, 78.2, 91.7, 127.2 - 130.0 (several lines), 133.0, 133.2, 135.6, 138.3, 138.4, 138.5, 138.7, 166.5; FABHRMS calcd for $C_{60}H_{66}O_{12}NaSi$ (M + Na) 1029.4221, found 1029.4197.

Lactone 2.48.

Application of the procedure that was used for **2.47** to diol **2.45** (90 mg, 0.09 mmol) provided **2.48** (75 mg, 93% based on recovered **2.45**) as a colorless oil; R_f = 0.33 (20 % EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.06 (s, 9H), 3.55 (t, J = 9.5 Hz ,1H), 3.61-3.82 (m, 6H), 3.90 - 3.97 (m, 4H), 4.14 (d, J = 7.0 Hz, 1H), 4.22 (s, 1H), 4.35 - 4.51 (m, 11H), 4.68 (d, J = 6.5 Hz, 1H), 4.88 (d, J = 3.0 Hz, 1H), 5.10 (d, J = 6.5 Hz, 1H), 7.15 - 7.44 (m, 26H), 7.67 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.2, 60.6, 61.1, 68.4, 69.5, 71.0, 71.9, 72.3, 72.8, 73.5, 73.6, 74.1, 74.2, 75.2, 75.8, 76.1, 77.5, 79.4, 93.8, 127.6 - 130.1 (several lines), 132.9, 133.2, 135.6, 135.7, 138.3, 138.5, 138.6, 138.7, 166.8; FABHRMS calcd for $C_{60}H_{66}O_{12}SiNa$ (M + Na) 1029.4222, found 1029.4221.

(2,6:8,12-dianhydro-7,9-O-methylene-D-*lyxo*-D-*galacto*-D-*manno*-tridecit-10-yloxy)-ethanoic acid sodium salt 2.3.

Lactone **2.47** (99 mg, 0.10 mmol) was dissolved in ethanol (5 mL) and treated with 3N NaOH (2 mL). After 2 hours the solvent was removed under reduced pressure, and the residue purified by FCC to give the dihydroxy sodium salt resulting from saponification of the lactone and cleavage of the silyl ether (56 mg, 73%), as a colorless oil; R_f = 0.46 (30 % CH_3OH/acetone); ^1H NMR (500 MHz, CD_3OD) δ 3.54 (dd, J = 3.0, 9.5 Hz, 1H), 3.59 (t, J = 5.3 Hz, 1H), 3.66 (dd, J = 7.0, 9.5 Hz, 1H), 3.73 (m, 3H), 3.80 (m, 2H), 3.86 (m, 1H), 3.91 (q, J = 5.3Hz, 1H), 4.11 (m, 2H), 4.27 (A of ABq, Δδ = 0.11 ppm, J = 16.5 Hz, 1H), 4.36 (apparent t, J = 5.5 Hz, 1H), 4.38 (B of ABq, Δδ = 0.11 ppm, J = 16.5 Hz, 1H), 4.51-4.60 (m, 13H), 4.77 (d, J = 6.0 Hz, 1H), 5.29 (d, J = 6.0 Hz, 1H), 7.20-7.37 (m, 20H); ^{13}C NMR (100 MHz, CD_3OD) δ 61.7, 68.1, 68.4, 68.7, 70.1, 71.7, 72.7, 72.9, 73.1, 73.6, 74.0, 74.2, 74.5, 76.4, 79.3, 80.3, 90.4, 127.4, 128.1, 138.6, 174.1; ESIHRMS calcd for $C_{44}H_{51}O_{13}$ 787.3330, found 787.3358.

A mixture of the product from the previous step (52 mg, 0.06 mmol), 10% Pd on carbon (100 mg), formic acid (0.1 mL) and CH_3OH (3 mL) was stirred under an atmosphere of hydrogen (balloon), for 12 hours. The reaction mixture was purged with argon, filtered through a bed of Celite and the filtrate concentrated under reduced pressure. The residue was dissolved in ethanol (5 mL) and treated with 3M NaOH (1 mL). After stirring at rt for 2 hours the mixture was evaporated *in vacuo* and residue purified by sequential FCC on C18 silica gel (CH_3OH/H_2O) and Sephadex LH-20 (H_2O). Lyophilization of the eluate provided **2.3** as an amorphous solid (27 mg, 90%); $[\alpha]_D$ + 13.5 (*c* 0.40 H_2O); ^1H NMR (500 MHz, D_2O) δ 3.61 (dt, J = 2.6, 7.4 Hz, 1H), 3.65-3.74

(m, 5H), 3.75 (d, J = 2.6 Hz, 1H), 3.81 (m, 2H), 3.87 (dd, J = 3.5, 8.3 Hz, 1H), 4.13 (ABq, J = 16.3 Hz, Δδ = 0.09 ppm, 2H), 4.16 (d, J = 3.1Hz, 1H), 4.20 (t, J = 3.1 Hz, 1H). 4.26 (t, J = 9.9 Hz, 1H), 4.31 (dd, J = 3.4, 9.3 Hz, 1H), 4.50 (dd, J = 5.9, 9.3 Hz, 1H), 4.91 (A of ABq, J = 6.8 Hz, Δδ = 0.18 ppm, 1H), 5.09 (B of ABq, J = 6.8 Hz, Δδ = 0.18 ppm, 1H); ^{13}C NMR (125 MHz, D_2O) δ 60.7, 61.7, 66.5, 67.6, 68.0, 68.5, 69.0, 70.6, 72.3, 72.4, 72.5, 76.4, 79.5, 80.4, 89.6, 178.3; FABHRMS calcd for $C_{16}H_{26}O_{13}Na$ 449.1288, found 449.1271.

(2,6:8,12-dianhydro-7,9-O-methylene-D-*lyxo*-D-*gulo*-D-*manno*-tridecit-10-yloxy)-ethanoic acid sodium salt 2.4.

Lactone **2.48** (75 mg, 0.07 mmol) was subjected to the similar saponification procedure that was described for lactone **2.47**. The corresponding dihydroxy sodium salt (38 mg, 67%) was obtained as a colorless oil; R_f = 0.28 (30 % CH_3OH/acetone); ^{1}H NMR (500 MHz, CD_3OD) δ 3.16 (t, J = 9.0 Hz, 1H), 3.45 (dd, J = 3.0, 9.5 Hz, 1H), 3.53 (t, J = 6.3 Hz, 1H), 3.66 (d, J = 5.0 Hz, 1H), 3.71 (dd, J = 5.0, 11.5 Hz, 1H), 3.77 (m, 2H), 3.91 (d, J = 9.5 Hz, 1H), 3.96 (q, J = 5.0 Hz, 1H), 4.00 (m, 1H), 4.06 (m, 3H), 4.28 (m, 2H), 4.48-4.69 (m, 10H), 4.73 (d, J = 6.5 Hz, 1H), 5.04 (d, J = 6.5 Hz, 1H), 7.25-7.43 (m, 20H); ^{13}C NMR (75 MHz, CD_3OD) δ 63.0, 68.7, 70.8, 71.0, 73.1, 73.6, 73.8, 74.0, 74.5, 74.9, 76.6, 77.2, 78.7, 79.1, 80.7, 81.2, 81.9, 94.5, 128.5, 128.7, 128.8, 129.0, 129.1, 129.4, 139.7, 139.8, 178.4; FABHRMS calcd for $C_{44}H_{51}O_{13}$ (M + H) 787.3330, found 787.3327.

The product from the previous step (37 mg, 0.05 mmol) was subjected to the hydrogenation procedure that was described for **2.3**. Compound **2.4** (17 mg, 84%) was

obtained as an amorphous solid; $[\alpha]_D$ + 41.6 (*c* 0.30 H_2O); ^1H NMR (500 MHz, D_2O) δ 3.32 (t, J = 9.4 Hz, 1H), 3.60 (t, J = 8.6 Hz, 1H), 3.65 (dd, J = 2.5, 12.4 Hz, 1H), 3.68 - 3.71 (m, 8H), 3.97 (dd, J = 3.6, 8.6 Hz, 1H), 4.02 (dd, J = 2.7, 9.6 Hz, 1H), 4.10 - 4.15 (m, 5H), 4.17 (m, 3H), 4.79 (A of ABq J = 6.5 Hz, Δδ = 0.29 ppm, 1H), 5.08 (B of ABq, J = 6.5 Hz, Δδ = 0.29 ppm, 1H); ^{13}C NMR (125 MHz, D_2O) δ 61.2, 61.5, 66.4, 67.5 (two signals), 68.6, 71.3, 72.7, 76.1, 77.1, 77.4, 79.2, 79.3, 79.7, 93.2, 178.3; FABHRMS calcd for $C_{16}H_{26}O_{13}Na$ (M + Na) 449.1286, found 449.1295.

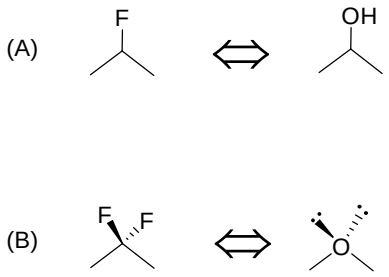
Chapter 3

Synthesis of fluorinated C-disaccharide sLe^X mimetics.

3.1 Introduction

Fluorinated carbohydrates are increasingly being utilized as tools for the investigation of various biological processes.[28-32] Interest in these compounds is related to the intrinsic properties of fluorine. The van der Waals radii of fluorine (1.47 Å) lies between oxygen (1.57 Å) and hydrogen (1.2 Å) and thus fluorine may behave as a less sterically demanding isostere of oxygen, or replaces hydrogen without any considerable sterical or geometrical demands.[33] Hence, fluoroalkanes and difluoromethylene groups are isosterical substituents of alkanols and ethers, respectively (Figure 3.1).[34]

Figure 3.1: Isosterical fluorine substituents

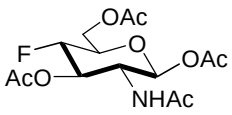


Fluorinated carbohydrates have previously been examined for their effects on selectin mediated cellular adhesion. A recent study by Descheny and coworkers revealed that 2-acetamido-1,3,6-tri-O-acetyl-4-deoxy-4-fluoro-D-glucopyranose **3.1** was able to inhibit selectin binding activity.[35] This effect was related to the ability of **3.1** to function as a potent metabolic inhibitor of N-acetyllactosamine and sLe^x biosynthesis.

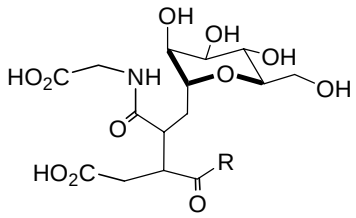
Other studies imply that the introduction of fluorine substituents on selectin ligands may increase their selectin binding affinity.[36, 37] This property of such fluorinated compounds may be due to their increased lipophilicity in comparison to their non-fluorinated analogs. Such characteristic seems to rationalize the two fold increase in binding of the fluorinated sLe^x mimetic **3.2**, to its non-fluoro analog **3.3** in a cell-free sLe^a-polymer/ E-selectin assay.[36] The fluorinated glycolipid sLeXF188 (**3.4**) was used to gain deeper insight into the effect of clustering of sLe^X glycolipids and their ability to induce cell rolling.[37] This study seems to imply that fluorination in the alkyl chain of **3.4** leads to an increase in its cluster size. This causes an impediment of cell rolling when compared to its unfluorinated analog at higher ligand concentrations in a dynamic cell assay.

Fluorine substitution on the pseudo-anomeric carbon in C-glycosides is expected to alter the conformational behavior in the intersaccharide torsions. This situation is analogous to distortion of the natural conformation of the sugar residue in nucleosides by introduction of a 2-fluoro substituents.[38] These expected characteristics of fluoro carbohydrates led to the synthesis of the epimeric fluoro C-glycosides **3.5** and **3.6**, and the difluoro-C-glycoside **3.7** (Figure 3.2).

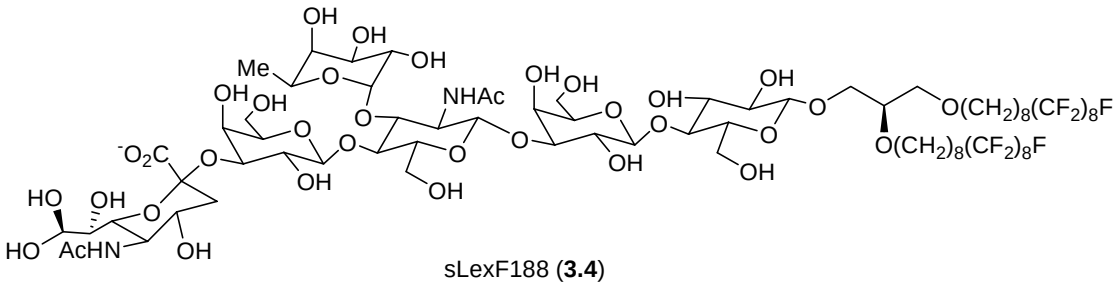
Figure 3.2: Fluorinated carbohydrate mimetics of sLe^x



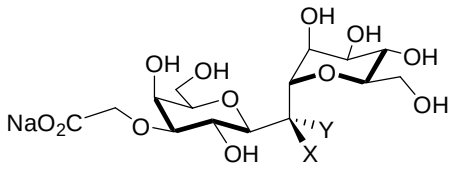
3.1



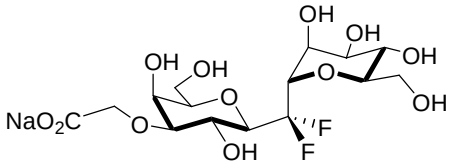
3.2: R = CF_3 (42% inhibition of E-selectin at 3 mM)
3.3: R = CH_3 (28% inhibition of E-selectin at 3 mM)



sLexF188 (**3.4**)



3.5: X = F, Y = H
3.6: X = H, Y = F



3.7

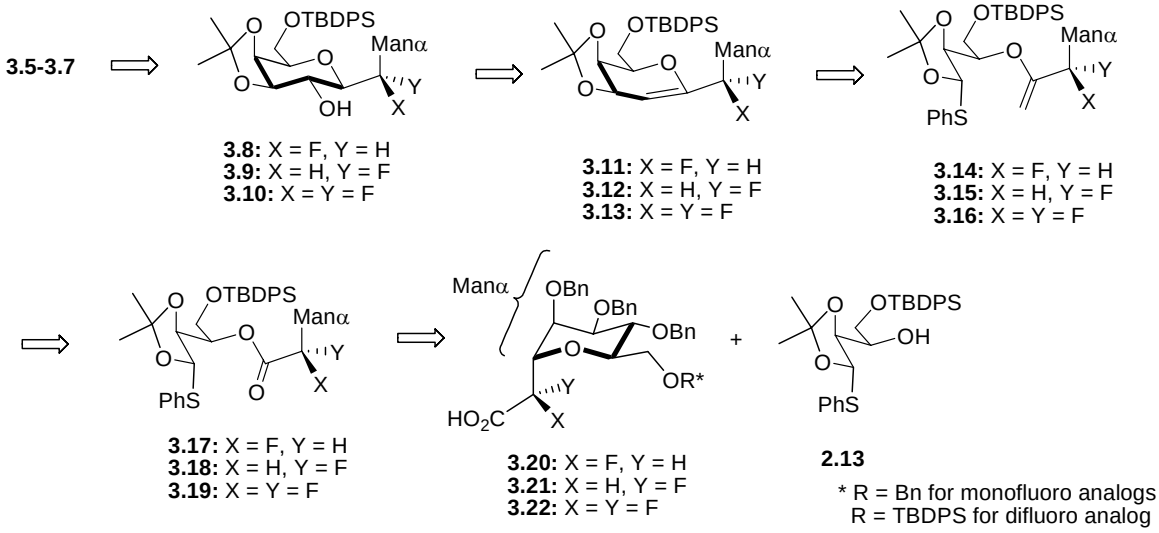
Results and Discussion

3.2 Retrosynthesis

We envisioned that the TIA methodology previously described could be used for the synthesis of the fluoro-C-glycosides **3.5-3.7**. Stereoselective hydroboration of the fluoro glycals **3.11-3.13** should provide **3.8-3.10.** These glycals may be obtained from the methyl triflate mediated cyclization of the enol ethers **3.14 - 3.16**. An important question about the later reaction is whether the electronegativity of the fluorine substituent would have an unfavorable effect on the key oxocarbeniunm cyclization step.

The enol ethers **3.14-3.16** could be synthesized from olefination of the corresponding α-fluoro esters **3.17-3.19**. These esters may be obtained from the DCC coupling of the fluoro acids **3.20-3.22** and the known TIA alcohol **2.13** (Scheme 3.1).

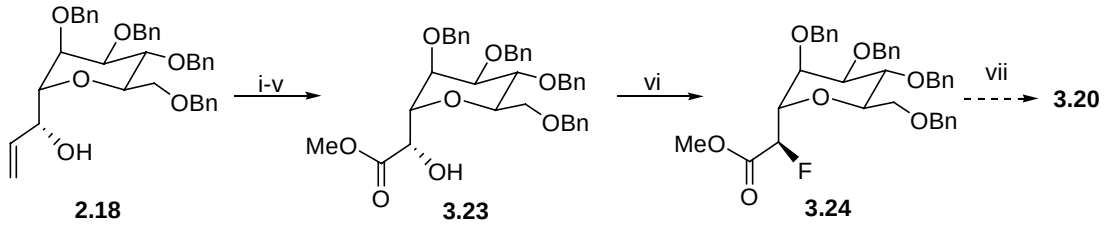
Scheme 3.1: Retrosynthesis of the fluoro-C-glycosides **3.5-3.7**.



3.3 Synthesis of the fluoro acid precursors 3.20-3.22.

We first attempted the synthesis of the acid **3.20** by treatment of the α-hydroxy ester derivative **3.23** with diethylaminosulfur trifluoride (DAST).[31] Previously prepared vinyl alcohol **2.18** was transformed to **3.23** in five steps (Scheme 3.2). The reaction of **3.23** with DAST gave the desired fluoro ester **3.24** in 16% yield. Both the ^{1}H and ^{13}C NMR spectra of **3.24** revealed a $^{2}J_{H,\,F}$ coupling of 48.8 Hz at δ 5.18 and $^{1}J_{C,\,F}$ coupling of 191.8 Hz t at δ 89.6 respectively, that was indicative of the α-fluoro ester. However, the low yield of the reaction prompted the development of an alternative synthesis of the fluoro acids **3.20/3.21**.

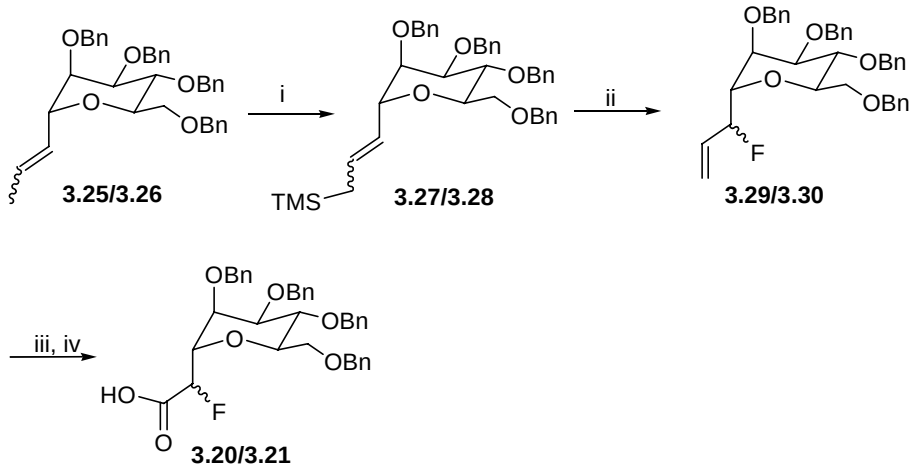
Scheme 3.2: Attempted synthesis of fluoro acid **3.20**.



i. AcO_2, DMAP, quant. yield; ii. O_3, PPh_3, 97%; iii $NaClO_2$, 99%; iv. $TMSCHN_2$, ether, quant. yield; v. NaOMe/MeOH, 80%; vi. DAST, CH_2Cl_2, 16%; vii. NaOH/EtOH, HCl

A more practical method for the synthesis of the fluoro acids **3.20/3.21** involved the coupling of the known α-C-1-propenyl derivatives **3.25/3.26** with allytrimethylsilane using a cross metathesis protocol. An *E/Z* (3/1) mixture of allylsilane **3.27/3.28** was obtained in 88% yield when the reaction was done under an ethylene atmosphere with 15 mol % of second-generation Grubbs' catalyst.[39] The mixture **3.27/3.28** was identified mainly as the *E* isomer in 88% yield. Treatment of **3.27/3.28** with Selectfluor™ led to a 1:1 mixture of the epimeric allylic fluorides **3.29/3.30** in 60% yield. In this reaction, the trimethylsilyl group enhances the reactivity of the alkene toward the addition of Selectfluor™ and controls the regioselectivity because of stabilization of the incipient cation β to the silicon.[40] Ozonolysis of **3.29/3.30** followed by sodium chlorate oxidation of the resulting mixture of aldehyde afforded the required fluoro acids **3.20/3.21** as an inseparable mixture (Scheme 3.3).

Scheme 3.3: Synthesis of fluoro acids **3.20/3.21**.

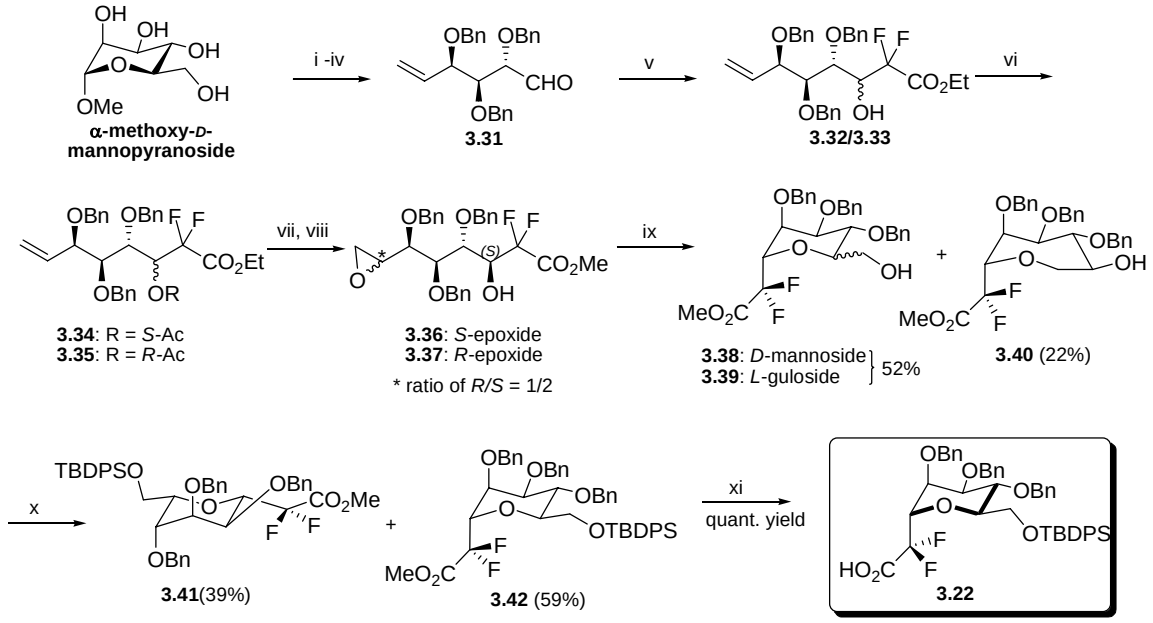


i. Grubbs 2, CH_2=CH_2 atm $CH_2CHCH_2Si(CH_3)_3$, 2 days, 89%; ii. selectfluor^{TM},CH_3CN, 60%; iii. O_3, PPh_3, 97%; iv. $NaClO_2$, 99%

The synthesis of the difluoro acid **3.22** was accomplished using the protocol developed by Quirion and coworkers.[41] Starting with the known enal **3.31** [42] (available in five steps from methyl α-*D*-mannopyranoside), Reformatsky reaction was done using the enolate ion generated from ethyl bromodifluoroacetate. This provided a diastereomeric mixture of alcohols **3.32/3.33** in 54% yield.[41] Attempts to separate this mixture by column chromatography was unsuccessful. However, acetylation enabled their separation as the acetates **3.34** and **3.35** in a ratio of ca. 3:1. At this juncture, the major product **3.34** was assumed to be the *anti* isomer based on evidence provided by literature.[43] The outcome of such transformation was later established in the ^{1}H NMR analysis of the later derivatives **3.45** and **3.46** (*vide infra*) and the major product was in fact the *anti* isomer. Therefore, the Reformatsky reaction probably preceded by the Felkin-Anh transition state.[43] Deacetylation of **3.34** followed by treatment of the resulting alcohol with *m*-CPBA yielded a 2:1 mixture of C-5 epimeric epoxides

3.36/3.37. Cyclization of the mixture of epoxides was initially performed under acidic conditions (CSA, CH_2Cl_2). This gave a mixture of several compounds. However, under basic conditions (NaOMe, MeOH), the crude products obtained were treated with $TMSN_2CH$ to mainly give the difluoro-C-glycoside mixture **3.38/3.39**, and the difluoro-C-heptoside derivative **40** as the minor product (Scheme 3.4). Protection of **3.38/3.39** as the *tert*-butyldiphenylsialyl ethers enabled their separation as the *D*- and *L*-sugars **3.41** and **3.42** respectively.

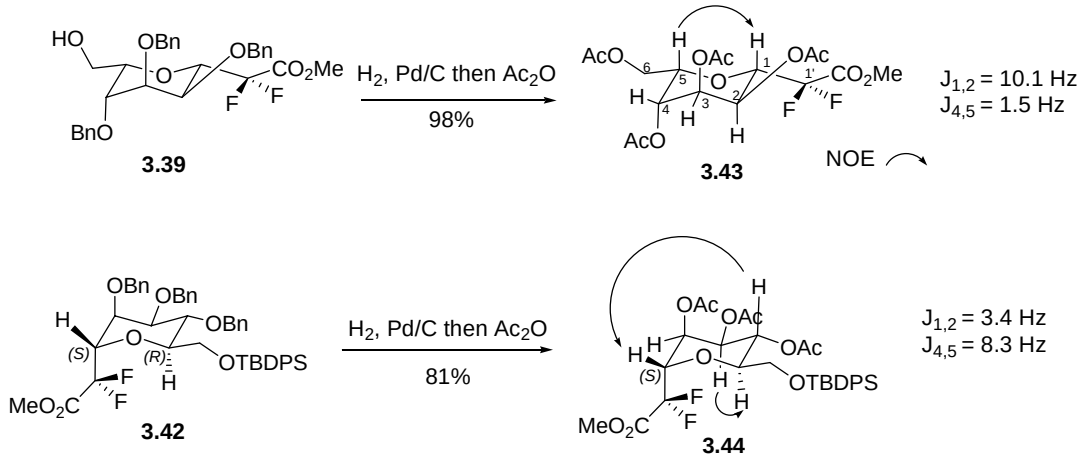
Scheme 3.4: Synthesis of the difluoro acid **3.22.**



i. Ph_3CCl, py, 99%; ii. (a) BnBr, NaH (b) TsOH, MeOH, 86% (2 steps); iii. Ph_3P, I_2, imdzl, 93%; iv. n-BuLi/THF, 94%; v. $BrCF_2COOEt$, Zn, 54%; vi. Ac_2O, DMAP, 85% (isomer separation, 3/1 ratio); vii. NaOMe/MeOH, 83%; viii. m-CPBA, Na_2SO_4/$NaHSO_4$ buffer, 74%, (2:1 ratio) ; ix. (a),NaOMe/MeOH then $TMSN_2CH$ in PhMe/MeOH; x. TBDPSCl, imid. isomer separation; xi. NaOH, EtOH then HCl.

The axial orientation at C-1 and the stereochemistry at C-5 in the difluoro-C-glycosides **3.41** and **3.42** were verified from the ^1H-^1H coupling constants and NOESY experiments of their acetylated derivatives **3.43** and **3.44** respectively (Scheme 3.5).

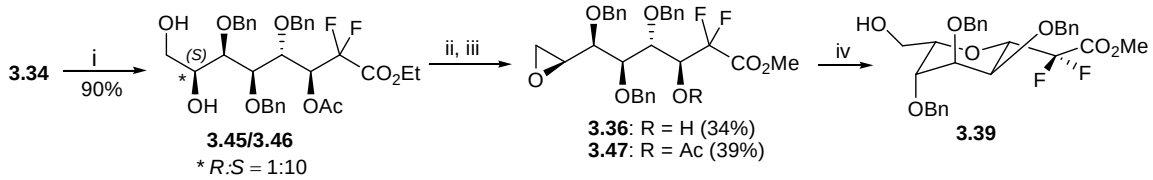
Scheme 3.5: Stereochemical analysis of difluoro-*D*-mannoside **3.39** and difluoro-*L*-guloside **3.41**.



Base hydrolysis of the required difluoro-C-mannoside **3.42** followed by acid workup led to the isolation of acid **3.22**. (Scheme 3.4)

An attempt was made to increase the selectivity of the required epoxide **3.37** (Scheme 3.6). Thus, the acetate **3.34** was subjected to dihydroxylation with osmium tetroxide and the product obtained selectively tosylated and treated under basic conditions to give the hydroxyl epoxide **3.36** and its acetylated derivative **3.47** instead. These compounds were individually cyclized to give the difluoro-C-glycoside **3.39** (Scheme 3.6).

Scheme 3.6: Synthesis of *L*-guloside **3.39**

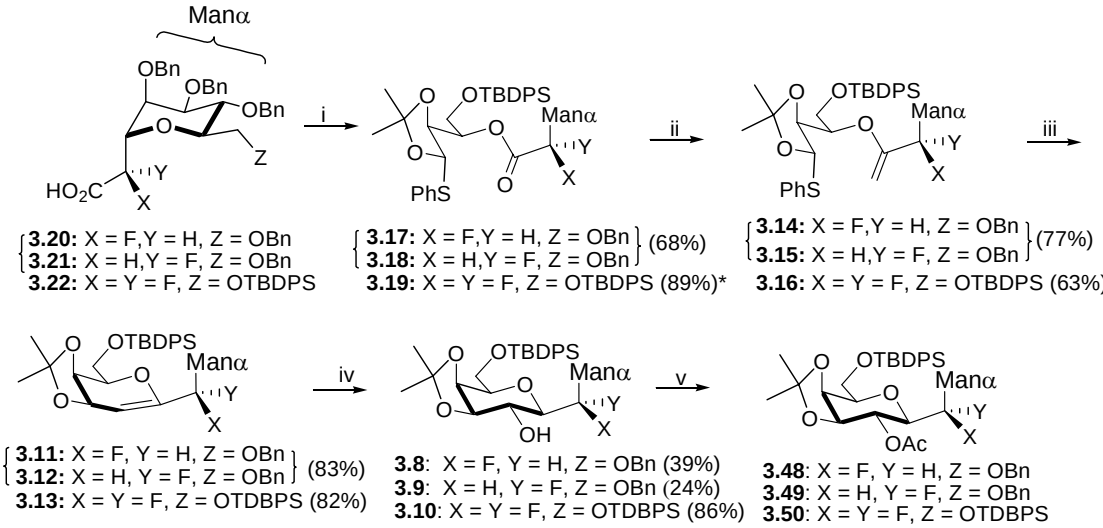


i. OsO_4/NMO, 90%; ii. TsCl/pyr, 87%; iii. 2eq. NaOMe, MeOH, 18h; iv. NaOMe/MeOH then HCl, 62% from **3.36** and 69% from **3.47.**

3.4 Synthesis of fluoro-C-glycosides 3.8-3.10.

The acid segments **3.20/3.21** and **3.22** were coupled with the alcohol **2.13** for the fluoro-C-glycoside sequence (Scheme 3.7). DCC mediated esterification of **3.20/3.21** and **3.22** with **2.13** gave a mixture of α-fluoro esters **3.17/3.18** (68%) and the difluoro ester **3.19** respectively. As the conversion of **3.19** from acid **3.22** was very low, the Yamaguchi esterification protocol[44] was attempted. Thus, **3.19** was prepared in 91% yield (based on recovered **2.13**) with 76% conversion from **3.22**. Tebbe methylenation on esters **3.17/3.18** provided a mixture of enol ethers **3.14/3.15**. However the reaction was not successful for difluoro ester **3.19**. The Takai methylenation[45] on **3.19** afforded the difluoro enol ether **3.16** in 63% yield. It should be noted that the difluoro ester **3.19** was labile to basic condition upon purification of the crude product. To overcome this, the purification process was performed with silica gel chromatography. The key cyclization reaction on **3.14/3.15** and **3.16**, was promoted by methyl triflate in the presence of 2,6-di-tert-butyl-4-methylpyridine (DTBMP). The feasibility of this reaction was of concern because the presence of the electronegative fluorine atom could reduce the nucleophilicity of the alkene in the oxocarbenium ion cyclization. In the event, the reaction proceeded to give the fluoro glycals **3.11/3.12** and **3.13** in high yields. Selective hydroboration of **3.11/3.12** and **3.13** provided the fluoro-C-galactosides **3.8** (39%), **3.9** (24%) and **3.10** (86%) respectively, each as a single diastereomer (Scheme 3.7). Alcohols **3.8** and **3.9** were readily separated on silica gel column chromatography (Rf's: 0.63 and 0.75 respectively, 30% ethyl acetate/petroleum ether).

Scheme 3.7: Synthesis of the fluorinated C-glycosides **3.8-3.10.**

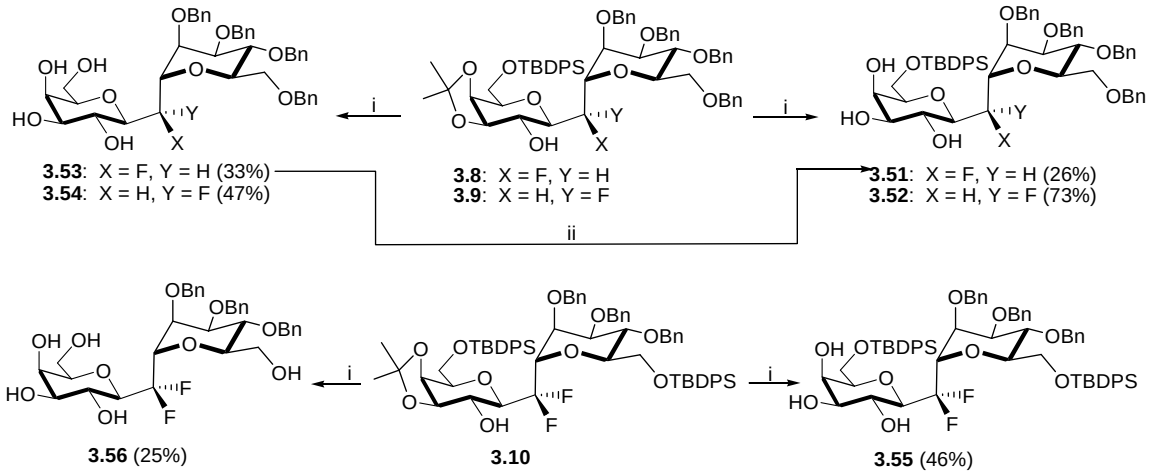


i. (a) DCC, DMAP, **2.13**, PhH* and/or (b) Et_3N, DMAP, 2,4,6-trichlorobenzoyl chloride, then **2.13**, DMAP, **3.22** (91%) ;
ii. (a) Tebbe or (b) $TiCl_4$, CH_2Br_2, Zn, TMEDA#; iii. MeOTf, DTBMP, CH_2Cl_2; iv. BH_3.DMS then Na_2O_2; v. Ac_2O, DMAP.

The stereochemistry at the C-1 position of galactose in these fluoro-C-glycosides was confirmed from the $J_{H\text{-}1,H\text{-}2}$ couplings of 8.4, 8.2 and 9.5 Hz for the acetates **3.48**, **3.49** and **3.50** respectively,[4] and subsequent derivatives **3.59** and **3.60** (*vide infra*).

Compounds **3.8**, **3.9** and **3.10** were converted to their respective triols **3.51** (26%), **3.52** (73%) and **3.55** (46%) upon treatment with methonolic HCl. These reactions on **3.8** and **3.9** were also accompanied by desilylation to give the tetrol **3.52** (33%) and the pentol **3.55** (25%) respectively. Resilylation of **3.52** gave the required **3.50** in a moderate yield of 67% (Scheme 3.8).

Scheme 3.8: Acid hydrolysis of fluoro-C-glycosides **3.8-3.10.**



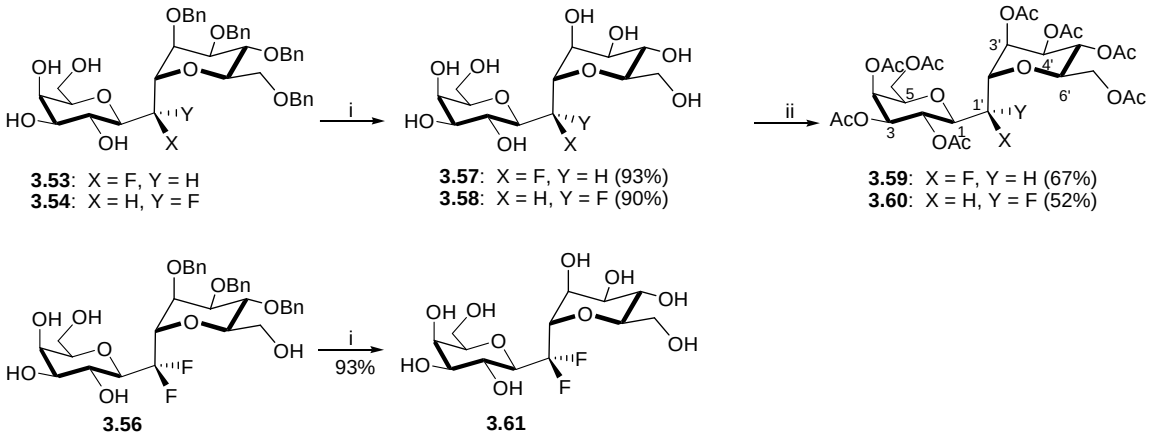
(i) MeOH/HCl; (ii) TBDPSCl, imidazole 67%.

3.5 Stereochemical analysis of fluoro-C-glycosides 3.59 and 3.60.

The structures **3.53** and **3.54** were confirmed by NMR analysis of their peracetate derivatives **3.59** and **3.60** (Scheme 3.9, Table 3.1). The stereochemistry of the aglycone segment was assigned on the basis of vicinal J values. Thus, $J_{1,2}$ = 10.0 Hz, $J_{2,3}$ = 10.0 Hz, $J_{3,4}$ = 3.3 Hz , $J_{4,5}$ = 0 Hz for both **3.59** and **3.60** were consistent with the 3,4,6-acetylated-β-C-galacto motif of recently synthesized restrain disaccharides.[26]

The stereochemistry of the fluorine substituents at the C-1' could not be determined at this point. This was subsequently assigned from NMR experiments performed by our collaborator Jiménez-Barbero in Spain. (See chapter 4)

Scheme 3.9: Synthesis of the peracetylated fluoro-C-glycosides **3.36** and **3.37**



3.53: X = F, Y = H
3.54: X = H, Y = F

3.57: X = F, Y = H (93%)
3.58: X = H, Y = F (90%)

3.59: X = F, Y = H (67%)
3.60: X = H, Y = F (52%)

3.56

3.61

(i) Pd/C, H_2, MeOH; (ii) DMAP, Ac_2O, EtOAc

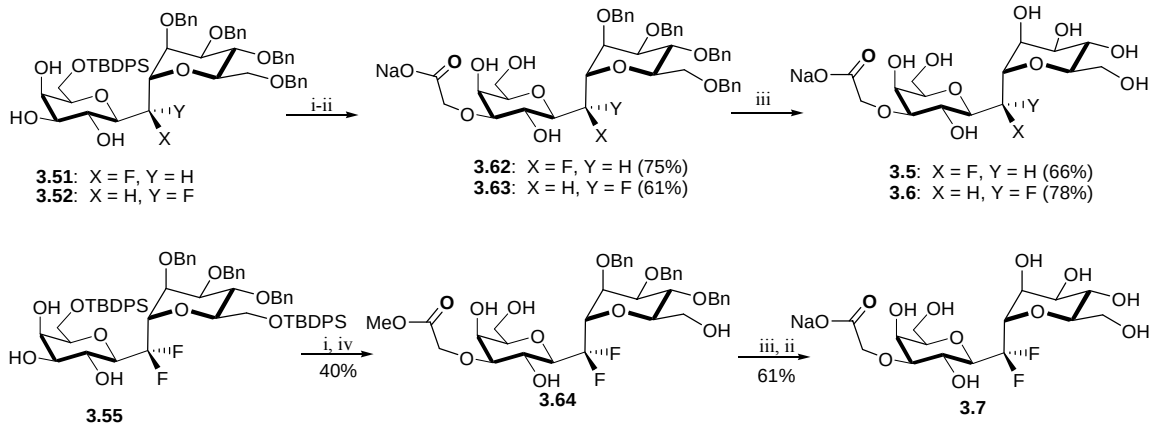
Table 3.1: ^{1}H-NMR of the peracetylated fluoro-C-glycosides **3.59** and **3.60**.

Positions	**^{1}H NMR (J, Hz) fluoro derivative 3.59**	**^{1}H NMR (J, Hz) fluoro derivative 3.60**
1′	4.85 (ddd, J = 2.2, 7.7, 46.6)	5.01 (ddd, J = 2.7, 5.5, 47.4)
2’	4.66 (ddd, J = 2.6, 7.7, 17.7)	4.61 (dt, J = 3.5, 31.5)
3’	5.80 (t, 2.6)	6.02 (t, J = 3.0)
4’	5.41 (dd, J = 2.6, 9.4)	5.78 (dd, J = 3.5, 8.8)
5’	5.66 (t, J = 9.4)	5.69 (t, J = 8.8)
6’	4.03 (m)	4.22 (m)
7’a	4.45 (dd, J = 5.3, 12.2)	4.49 (q, J = 5.9)
7’b	4.15 (dd, J = 6.9, 11.4)	4.10 (m)
1	3.72 (ddd, J = 2.4, 9.8, 20.1)	3.66 (m)
2	5.91 (t, J = 10.0)	5.62 (t, J = 10.0)
3	5.20 (dd, J = 3.3, 10.0)	5.08 (dd, J = 3.3, 10.0)
4	5.49 (d, J = 3.3)	5.45 (d, J = 3.3)
5	3.37 (t, J = 6.3)	3.27 (t, J = 6.5)
6a	4.22 (dd, J = 6.3, 11.4)	4.10 (m)
6b	4.24 (dd, J = 2.6, 12.2)	4.22 (m)
CH_3CO-	1.60, 1.65, 1.67, 1.69 (2), 1.730, 1.733, 1.76	1.61, 1.64, 1.667, 1.671, 1.71, 1.72, 1.76

3.6 Synthesis of the fluorinated sLe^x mimetics 3.5-3.7.

The triols **3.51**, **3.52** and **3.55** were next transformed to the targeted fluorinated sLe^x **3.5**, **3.6**, and **3.7** respectively (Scheme 3.10). Thus, selective dibutyltin oxide mediated alkylation of **3.51**, **3.52** and **3.55** with methyl bromoacetate led to 3-O-alkylation followed by *insitu* lactonization to give in each case a mixture of 2-O and 4-O-lactone products. Exposure of the mono fluoro crude products to aqueous sodium hydroxide led to concomitant saponification and desilylation to give the corresponding trihydroxy sodium salts **3.62** and **3.63**, which were subjected to hydrogenolysis. Exposure of the crude difluoro lactonized products to excess tetrabutyl ammonium fluoride followed by acid work up afforded the methyl ester **3.64**. The latter was then subjected to hydrogenolysis and base hydrolysis (Scheme 3.10). The target compounds **3.5**, **3.6** and **3.7** were obtained after purification using reverse and normal phase chromatography, and lyophillization from aqueous solutions.

Scheme 3.10: Final synthesis of the fluoro sLe^x mimetics **3.5-3.7**.



3.51: X = F, Y = H
3.52: X = H, Y = F

3.62: X = F, Y = H (75%)
3.63: X = H, Y = F (61%)

3.5: X = F, Y = H (66%)
3.6: X = H, Y = F (78%)

3.55

3.64

3.7

(i) Bu_2SnO then $BrCH_2CO_2Me$, nBu_4NI; (ii) EtOH/NaOH; (iii) H_2, Pd/C, MeOH; (iv) TBAF, THF, then HCl in MeOH.

3.7 Conclusion:

The fluorinated C-glycosides **3.5**, **3.6** and **3.7** were prepared, *via* a convergent *de novo* synthesis of the β-galacto- residue starting from the readily available 1-thio-1,2-*O*-isopropylidene precursor **2.13** and the mono- and difluoro acids **3.20**, **3.21** and **3.22**. The key step in the synthesis of the monofluoro acids **3.20/3.21** was the reaction of an allylsilane precursor with Selectfluor^{TM} to give a mixture of allylic fluorides. The synthesis of the difluoro acid **3.22** proceeded *via* the Reformatsky type addition of ethyl bromodifluoroacetate on the known aldehyde **3.31**. The mono-fluoro-C-glycosides **3.5** and **3.6** were tested for their P-selectin binding affinities as well as their conformational properties (See chapter 4).

3.8 Experimental section

Hydroxy ester 3.23

The α-acetoxy acid (0.74 g, 1.16 mmol), derived from the vinyl alcohol **2.18** was dissolved in methanol (10 mL) and toluene (25 mL) and to it was added TMS diazomethane (3.0 mL, 6.00 mmol, 2.0 M solution in ether) dropwise. After 5 min, the reaction was quenched with acetic acid (2 drops) and the solvent removed under reduced pressure. FCC of the crude residue provided the methoxy ester (0.75 g, quantitative yield) as a colorless oil. This ester was then dissolved in dry methanol (10 mL) and NaOMe in methanol (1M, 2.0 mL, 2.0 mmol) was added to the solution. The mixture was stirred for 1 hour and the volatiles removed *in vacuo*. FCC provided the hydroxy ester **3.23** (567 mg, 80%) as colorless oil: R_f = 0.43 (30% Ethyl acetate/petroleum ether);

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.98 (d, J = 7.0 Hz, 1H), 3.57 (m, 1H), 3.60 (dd, J = 6.3, 10.3 Hz, 1H), 3.63 (s, 3H), 3.66 (dd, J = 7.1, 10.2 Hz, 1H), 3.76 (t, J = 3.1 Hz, 1H), 3.97 (dd, J = 2.7, 9.5 Hz, 1H), 4.06 (t, J = 6.5 Hz, 1H), 4.18 (dd, J = 1.4, 9.5 Hz, 1H), 4.27-4.52 (m, 9H), 7.11-7.26 (m, 20H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 52.7, 68.3, 70.5, 71.0, 71.8, 72.2, 72.5, 72.9, 73.3, 73.9, 74.3, 75.2, 127.7-128.6 (several lines), 138.1, 138.2, 138.3, 138.4, 173.8.

α-Fluoro ester 3.24.

To a solution of alcohol **3.23** (490 mg, 0.81 mmol) in dichloromethane (10 mL) was added DAST (0.23 mL, 2.42 mmol) at rt. The mixture was then stirred at rt for 1 hour. The reaction was then quenched with a saturated solution of $NaHCO_3$ in water (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was washed with brine, dried (Na_2SO_4) and evaporated *in vacuo*. FCC of the residue gave two unidentified compounds and **3.24** (60 mg, 16%) as a colorless oil: R_f = 0.78 (30% Ethyl acetate/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.58 (s, 3H), 3.69 (dd, J = 5.5, 10.3 Hz, 1H), 3.72 (t, J = 3.7 Hz, 1H), 3.79 (dd, J = 6.7, 10.3 Hz, 1H), 3.82 (t, J = 6.8 Hz, 1H), 4.39 (dd, J = 3.2, 8.7 Hz, 1H), 4.42-4.59 (m, 8H), 5.18 (dd, J = 1.9, 48.8 Hz, 1H), 7.21-7.23 (m, 20H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 52.4, 68.4, 71.5 (d, J = 19.9 Hz), 71.8, 72.2, 72.3, 72.9, 73.4, 74.2, 74.6, 75.5, 89.6 (d, J = 191.8 Hz), 127.8-128.6 (several lines), 138.0, 138.2, 138.3, 138.4, 168.0 (d, J = 24.4 Hz).

Allyl trimethylsilanyl derivatives 3.27/3.28.

Grubbs II catalyst (0.45 g, 0.53 mmol) was added as a solid (in three portions over 24 hours) to a solution of the α-C-1-propenyl derivative **3.25/3.26** (5.60 g, 9.93 mmol), and allyltrimethylsilane (6.24 mL, 39.7 mmol) in dichloromethane (60 mL) under an ethylene atmosphere, and the mixture maintained at reflux for 3 days. Anhydrous DMSO (3 mL) was then introduced and stirring continued at reflux for an additional 30 min. The mixture was then concentrated *in vacuo* and the residue purified by FCC to afford allylTMS mannoside **3.27/3.28** (4.41 g, 89% based on recovered **3.25/3.26**) (E/Z ratio: 3/1) as a colorless oil; R_f = 0.50 (10% EtOAc/petroleum ether); ^{1}H NMR ($CDCl_3$) δ 0.03 (s, Me_3Si, 9H), 1.45 (m, 1H, H-3'), 3.69 (t, J = 2.9 Hz, 1H, H-6_b), 3.71-3.82 (m, 4H, H-2, 3, 5, 6_a), 3.94 (t, J = 8.6 Hz, 1H, H-4), 4.52 (A of ABq, J = 10.9 Hz, Δδ = 0.33 ppm, 1H, Ar-CH), 4.52-4.66 (m, 5H, H-1, Ar-CH_2 × 2), 4.73 (ABq, J = 12.4 Hz, Δδ = 0.07 ppm, 2H, Ar-CH_2), 4.84 (B of ABq, J = 10.9 Hz, Δδ = 0.33 ppm, 1H, Ar-CH), 5.32 (dd, J = 6.2, 15.5 Hz, 1H, H-1'), 5.61 (ddt, J = 1.0, 7.7, 25.4 Hz, 1H, H-2'), 7.19 (m, 2H, Ar-H), 7.25-7.37 (m, 16H, Ar-H) 7.40 (m, 2H, Ar-H); ^{13}C NMR (125 MHz) $CDCl_3$) δ 1.90, 23.5, 69.9, 71.8, 72.1, 73.5, 73.7, 74.8, 74.9, 75.6, 76.5, 79.3, 123.7-129.1 (several lines), 138.3, 138.6, 138.7; ESIHRMS calcd for $C_{40}H_{49}O_5Si$ (M + H) 637.3349, found 637.3345.

Fluoro-C-glycoside derivatives 3.29/3.30.

A solution of **3.27/3.28** (4.40 g, 6.92 mmol) and Selectfluor^{TM} (3.18 g, 8.98 mmol) in CH_3CN (70 mL) was stirred at rt for 16 hours. The mixture then concentrated *in vacuo*. Purification by FCC afforded **3.29/3.30** (*R/S* ratio : 1/1) (2.35 g, 60% based on recovered starting material) as a colorless oil: R_f = 0.32 (30% EtOAc/petroleum ether);

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.69 (dd, 5.1, 10.7 Hz, 0.5H), 3.72 (dd, J = 4.0, 10.5 Hz, 0.5H), 3.74-3.82 (m, 2H), 3.87 (m, 1H), 3.95 (apparent dt, J = 4.4, 20.1 Hz, 0.5H), 4.11 (m, 0.5H), 4.49-4.70 (m, 8H), 5.16 (dm, J = 45.4 Hz, 1H), 5.29 (d, J = 10.5Hz, 0.5H), 5.31 (d, J = 10.5Hz, 0.5H), 5.33 (dt, J = 3.2, 17.3 Hz, 0.5H), 5.39 (dm, 17.3 Hz, 0.5H), 5.92 (dddd, J = 6.2, 10.1, 16.7, 18.9 Hz, 0.5H), 6.03 (dddd, J = 6.2, 10.9, 17.3, 20.2 Hz, 0.5H), 7.15-7.37 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 68.5, 69.1, 71.8, 72.3, 72.5, 72.6 (d, J = 4.2 Hz), 72.9 (d, J = 9.2 Hz), 73.0 (d, J = 4.0 Hz), 73.4, 73.5, 73.8, 74.4, 74.6, 75.3 (× 2), 75.5, 91.6 (d, J = 175.2 Hz), 93.5 (d, J = 175.2 Hz), 119.0 (d, J = 11.7 Hz), 119.4 (d, J = 12.1 Hz), 127.7-128.6 (several lines), 132.9 (d, J = 19.4 Hz), 133.4 (d, J = 20.2 Hz), 138.9, 138.2, 138.3 (× 2), 138.4, 138.5; ESIHRMS calcd for $C_{37}H_{40}O_5F$ (M + H) 583.2860, found 583.2904.

Fluoro acids 3.20/3.21.

Fluoro alkenes **3.29/3.30** (2.35 g, 4.04 mmol) were subjected to the ozonolysis procedure described for the preparation of **2.16**. The aldehyde derivatives (2.30 g, 97%) were produced: R_f = 0.36 (30% EtOAc/petroleum ether); ^{1}H NMR ($CDCl_3$) δ 3.63-3.79 (m, 2.4H), 3.86-3.92 (m, 1.6H), 4.07 (dd, J = 2.6, 9.6 Hz, 0.4H), 4.12 (dd, J = 2.8, 9.7 Hz, 0.6H), 4.18 (t, J = 5.9 Hz, 0.6H), 4.24 (t, J = 6.2 Hz, 0.4H), 4.36-4.69 (m, 9H), 5.01 (dd, J = 0.8, 49.6 Hz, 0.4H), 5.07 (dd, J = 1.4, 48.0 Hz, 0.6H), 7.19-7.38 (m, 20H), 9.59 (d, J = 6.4 Hz, 0.4H), 9.82 (d, J = 5.9 Hz, 0.6H); ^{13}C NMR ($CDCl_3$) δ 67.9, 68.0, 70.5 (d, J = 17.4 Hz), 71.1 (d, J = 19.2 Hz), 71.9 (3 peaks), 72.0, 73.0 (2 peaks), 73.3, 73.4, 73.6, 74.1, 74.4, 75.3, 75.7, 93.6 (d, J = 187.9 Hz), 95.5 (d, J = 187.0 Hz), 127.8-128.7 (several

lines), 137.6, 137.8, 138.0 (2 peaks), 138.1, 138.3, 138.4, 196.8 (d, J = 34.8 Hz), 199.8 (d, J = 35.7 Hz).

The aldehyde mixture from the previous step (2.70 g, 3.94 mmol) was subjected to the procedure that was used to synthesize **2.24**, to give the fluoro acid mixture **3.20/3.21** (2.75 g, 99%): colorless oil; R_f = 0.29 (10% MeOH/$CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.66-3.77 (m, 3H), 3.82 (dd, J = 6.9, 10.3 Hz, 0.4H), 3.89 (t, J = 3.1 Hz, 0.6H), 4.03 (dd, J = 2.7, 9.4 Hz, 0.6H), 4.10 (dd, J = 2.8, 9.1 Hz, 0.4H), 4.17 (m, 1H), 4.36-4.57 (m, 9H), 5.17 (dd, J = 1.7, 48.4 Hz, 0.4H), 5.01 (dd, J = 1.7, 47.5 Hz, 0.6H), 7.16-7.38 (m, 20H); ^{13}C NMR ($CDCl_3$) δ 68.1, 68.2, 70.4 (d, J = 18.3 Hz), 71.1 (d, J = 20.2 Hz), 71.9, 72.0, 72.2 (d, J = 5.5 Hz), 72.3 (d, J = 2.7 Hz), 72.9 (2 peaks), 73.3, 74.0, 74.2, 74.3, 75.2, 75.6, 87.8 (d, J = 192.5 Hz), 89.0 (J = 190.6 Hz), 127.8-128.6 (several lines), 137.8 (2 peaks), 138.0 (2 peaks), 138.2 (2 peaks), 171.3 (d, J = 24.7 Hz), 172.0 (d, J = 25.7 Hz); ESIHRMS calcd for $C_{36}H_{38}O_7F$ (M + H) 601.2602, found 601.2623.

2,3,4-tris(benzyloxy)hex-5-enal 3.31.

A solution of methyl-α-D-mannopyranoside (25.0 g, 0.13 mol), trityl chloride (43.1 g, 1.55 mol), DMAP (0.16 g, 0.13 mmol) in dry DMF (50 mL) and pyridine (50 mL) was stirred for 12 hours. Removal of the solvents *in vacuo* gave the crude product. FCC of the residue yielded the 6-O-trityl derivative (58 g, 99%): colorless oil; R_f = 0.43 (100% Ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.35 (broad s, 1H, D_2O exchange), 2.75 (broad s, 1H, D_2O exchange), 3.29 (s, 3H), 3.35 (m, 2H), 3.55-3.64 (m, 2H), 3.68 (dd, J = 3.0, 8.7 Hz, 1H), 3.82 (m, 1H), 4.63 (s, 1H), 7.15-7.34 (m, 15H); ^{13}C NMR (125

MHz, $CDCl_3$) δ 55.0, 65.0, 70.2, 70.3, 71.9, 85.4, 100.9, 127.3-128.9 (several lines), 143.9, 144.0.

To a solution of methyl 6-O-trityl-α-D-mannopyranoside (53.2 g, 0.12 mol) in dry DMF (300 mL) at 0 ^oC was added NaH (19.5 g, 60% in mineral oil, 0.48 mol) and Bu_4NI (4.50 mg, 0.01 mol) followed by BnBr (49.4 mL, 0.41 mmol). The reaction was stirred for 14 hours at rt under an argon atmosphere, then diluted with water (280 mL) and extracted with ether (2 × 50 mL). The organic layer was washed with water (3 × 250 mL), dried (Na_2SO_4) and concentrated *in vacuo*. FCC of the crude methyl-2,3,4-trio-O-benzyl-6-O-trityl- α-*D*-mannoside. This crude product was dissolved in 9:1 MeOH:EtOAc (430 mL) and *p*-toluenesulfonic acid (4.9 g, 0.02 moles) was added to the solution. The reaction was stirred for 3 hours at rt. Triethylamine (3 mL) was added and the solvents was evaporated under reduced pressure, and the residue was purified by FCC to provide methyl-2,3,4-trio-O-benzyl-α-D-mannopyranoside (48.7 g, 86% over two steps); R_f = 0.47 (30% EtOAc/petroleum ether); ^1H NMR (500 MHz, $CDCl_3$) δ 2.04 (broad s, 1H, D_2O exchange), 3.32 (s, 3H), 3.64 (ddd, J = 3.0, 4.6, 9.5 Hz, 1H), 3.77-3.87 (m, 3H), 3.92 (dd, J = 3.0, 9.4 Hz, 1H), 3.99 (t, J = 9.4 Hz, 1H), 4.60-4.82 (m, 6H), 4.95 (d, J = 11.0 Hz, 1H), 7.20-7.44 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.0, 62.8, 72.3, 72.5, 73.2, 75.0, 75.2, 75.4, 80.5, 99.6, 127.8-128.6 (several lines), 138.5, 138.67, 138.71.

A mixture of the product from the previous step (36.0 g, 0.08 mol), triphenylphosphine (50.8 g, 0.19 mol), imidazole (10.6 g, 0.16 mol) and iodine (49.0 g, 0.19 mol) in anhydrous toluene (300 mL) was heated at reflux for 2 hours. The mixture was then cooled to rt and diluted with ether (400 ml), filtered through a bed of Celite and

evaporated under reduced pressure. FCC of the residue gave the iodide (41.5 g, 93%) as colorless oil: R_f = 0.37 (10% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.34 (dd, J = 7.7, 10.3 Hz, 1H), 3.39 (s, 3H), 3.54 (ddd, J = 2.3, 7.9, 9.1 Hz, 1H), 3.58 (dd, J = 2.3, 10.3 Hz, 1H), 3.79 (m, 2H), 3.91 (dd, J = 3.1, 9.3 Hz, 1H), 4.63-4.79 (m, 6H), 5.00 (d, J = 11.0 Hz, 1H), 7.28-7.40 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.2, 55.3, 71.7, 72.3, 73.0, 74.9, 75.6, 78,9, 80.2, 99.3, 127.8-128.7 (several lines), 138.4, 138.50, 138.53; ESIHRMS calcd for $C_{28}H_{35}O_5IN$ $[M + NH_4]^+$ 592.1554, found 592.1557.

To a solution of the above iodide (44.5 g, 0.08 mol) in THF (200 mL) was added n-BuLi (37.2 mL of 2.5 M solution in THF, 0.09 mol) dropwise at -78 ^{o}C, under an atmosphere of argon. The reaction was stirred at this temperature for 1.5 hours, then poured into saturated aqueous $NaHCO_3$ and extracted with ether. The combined organic phase was dried (Na_2SO_4), filtered and evaporated *in vacuo*. FCC of the residue afforded 2,3,4-tris(benzyloxy)hex-5-enal **3.31** (30.5 g, 94%), R_f = 0.29 (10% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.92 (dd, J = 3.8, 5.6 Hz, 1H), 4.10 (dd, J = 1.3, 3.4 Hz, 1H), 4.13 (dd, J = 6.7, 7.4 Hz, 1H), 4.38-4.74 (m, 6H), 5.37 (d, J = 10.1 Hz, 1H), 5.41 (d, J = 17.1 Hz, 1H), 5.90 (ddd, J = 7.8, 10.3, 17.7 Hz, 1H), 7.27-7.39 (m, 15H), 9.69 (d, J = 1.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 70.9, 72.9, 74.2, 80.7, 83.0, 83.8, 119.9, 127.7-128.6 (several lines), 135.3, 137.5, 138.1, 138.3, 201.7; ESIHRMS calcd for $C_{27}H_{32}O_4N$ $[M + NH_4]^+$ 434.2326, found 434.2250.

(3*R*,3*S*)-Ethyl 4,5,6-tris(benzyloxy)-2,2-difluoro-3-hydroxyoct-7-enoate 3.48/3.49.

To a suspension of activated zinc dust (13.2 g, 0.21 mol) in dry THF (30 mL) at reflux was added ethyl bromodifluoroacetate (30.0 g, 19.1 mL, 0.15 mol). After 10 min, a solution of **3.31** (20.0 g, 0.05 mmol) in THF (60 mL) was added dropwise over 30 min and the reaction mixture heated to reflux for a further 3 hours. The mixture was cooled to rt and carefully poured into 1M HCl (40 mL) and ice (40 g). The mixture was extracted with EtOAc (3 × 150 mL) and the organic layer washed with saturated aqueous $NaHCO_3$ and brine. This was then dried (Na_2SO_4) and concentrated *in vacuo* to give a dark brown residue. FCC of the crude gave (3*R,*3*S*)-ethyl 4,5,6-tris(benzyloxy)-2,2-difluoro-3-hydroxyoct-7-enoate (**3.32/3.33**) as a mixture of epimeric alcohols (13.9 g, 54%) in a 3:1 ratio (^{1}H-NMR): colorless oil; R_f = 0.29 (10% EtOAc/ petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.74 (t, J = 7.1 Hz, 2.3H), 1.32 (t, J = 7.1 Hz, 0.7H), 3.38 (dd, J = 3.2, 10.0 Hz, 0.3H), 3.58 (m, 0.7H) 3.77 (m, 0.3H), 3.86 (m, 1.7H), 3.94-4.08 (m, 1.7H), 4.11-4.22 (m, 0.7H), 4.31 (q, J = 7.1 Hz 0.6H), 4.40-4.87 (m, 7H), 5.37-5.50 (m, 2H), 5.92 (m, 0.7H), 6.03 (m, 0.3H), 7.27-7.39 (m, 15H); major isomer, ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 62.5, 70.4, 75.2, 78.9 (d, J = 3.9 Hz), 81.6, 82.9, 114.8 (dd, J = 257.3, 257.4 Hz), 120.0, 127.9, 128.1-128.6 (several lines), 135.3, 137.4, 138.01, 138.4, 163.4 (t, J = 30.8 Hz). Minor isomer; 14.0, 63.2, 70.4, 70.6, 73.9 (d, J = 3.4 Hz), 74.3, 75.3, 80.0, 81.7, 119.5, 127.8, 135.8, 137.6, 137.99, 138.2, 163.6 (dd, J = 30.0, 33.1 Hz); ESIHRMS calcd for $C_{31}H_{38}O_6F_2N$ $[M + NH_4]^+$ 558.2662, found 558.2651.

(3S)- and (3R)-ethyl 3-acetoxy-4,5,6-tris(benzyloxy)-2,2-difluorooct-7-enoate 3.34 and 3.35.

Treatment of the mixture **3.32/3.33** (0.54 g, 1.09 mmol) following the acetylation procedure described in the synthesis of **2.28** provided compounds **3.34** (0.40 g, 64%) and **3.35** (0.13 g, 21%) as colorless oils.

For (3S)-ethyl 3-acetoxy-4,5,6-tris(benzyloxy)-2,2-difluorooct-7-enoate (3.34): R_f = 0.38 (10% EtOAc/ petroleum ether); ^{1}H NMR ($CDCl_3$) δ 1.08 (t, J = 7.1 Hz, 3H), 2.20, (s, 3H), 3.74 (d, J = 8.1 Hz, 1H), 3.92 (q, J = 7.1 Hz, 1H), 4.06 (m, 3H), 4.41 (A of ABq, J = 10.8 Hz, Δδ = 0.15 ppm, 1H), 4.44 (A of ABq, J = 12.2 Hz, Δδ = 0.25 ppm, 1H), 4.56 (B of ABq, J = 10.8 Hz, Δδ = 0.15 ppm, 1H), 4.68 (B of ABq, J = 12.2 Hz, Δδ = 0.25 ppm, 1H), 4.87 (ABq, J = 12.0 Hz, Δδ = 0.04 ppm, 2H), 5.39 (d, J = 17.1 Hz, 1H), 5.46 (dd, J = 1.2, 10.5 Hz, 1H), 5.81 (ddd, J = 7.8, 10.5, 17.4 Hz, 1H), 6.00 (ddd, J = 3.2, 10.5, 20.8 Hz, 1H), 7.19-7.44 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7, 20.6, 62.8, 69.4 (t, J = 22.0 Hz), 70.5, 73.0, 75.0, 77.3 (d, J = 2.7 Hz), 81.2, 81.8, 113.3 (dd, J = 251.1, 257.5 Hz), 120.4, 127.9-128.7 (several lines), 135.0, 137.1, 138.4, 138.8, 162.3 (dd, J = 28.9, 33.1 Hz), 168.4; ESIHRMS calcd. for $C_{33}H_{40}O_7F_2N$ $[M + NH_4]^+$ 600.2767, found 600.2761.

For (3R)-ethyl 3-acetoxy-4,5,6-tris(benzyloxy)-2,2-difluorooct-7-enoate (3.35): R_f = 0. 28 (10% EtoAc/ petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (t, J = 7.1 Hz, 3H), 2.07 (s, 3H), 3.78 (dd, J = 4.2, 6.5 Hz, 1H), 4.20 (m, 4H), 4.38-4.25 (m, 2H), 4.64-4.80 (m, 4H), 5.42 (d, J = 10.4 Hz, 1H), 5.48 (d, J = 17.3Hz, 1H), 5.80 (ddd, J = 2.2, 12.7, 19.9 Hz, 1H), 6.01 (ddd, J = 7.8, 10.4, 17.6 Hz, 1H), 7.28-7.43 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 20.7, 63.3, 70.0 (dd, J = 24.6, 28.6 Hz) 73.2, 74.2, 75.1, 80.6, 81.8,

113.2 (dd, J = 255.2, 257.4 Hz), 119.4, 127.7-128.5 (several lines), 135.9, 138.1, 138.4, 138.5, 162.8 (dd, J = 30.3, 32.9 Hz), 168.5; ESIHRMS calcd for $C_{33}H_{40}O_7F_2N$ [M + NH_4]$^+$ 600.2767, found 600.2753.

Epoxides 3.36/2.37

A solution of acetate **3.34** (1.11 g, 1.90 mmol) in dry MeOH (20 mL) was treated with MeONa/MeOH solution (1M, 5.7 mL, 5.70 mmol). After stirring for 1 hour at rt, the reaction was neutralized with 2M HCl and the solvent evaporated at reduced pressure. FCC of the crude product gave (3S)-methyl 4,5,6-tris(benzyloxy)-2,2-difluoro-3-hydroxyoct-7-enoate (0.79 g, 83%) as a colorless oil: R_f = 0.54, (10% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.50 (s, 3H), 3.52 (m, 1H), 3.84 (m, 2H), 4.11 (t, J = 7.1 Hz, 1H), 4.36-4.73 (m, 5H), 4.83 (s, 2H), 5.37 (d, J = 18.6 Hz, 1H), 5.41 (d, J = 18.6 Hz, 1H), 5.90 (ddd, J = 8.3, 10.0, 17.6 Hz, 1H), 7.14-7.46 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.9, 70.7 (t, J = 22.9 Hz), 70.8, 72.9, 75.3, 77.3 (d, J = 2.7 Hz), 81.2, 81.8, 113.3 (dd, J = 251.1, 257.5 Hz), 120.4, 127.9-128.7 (several lines), 135.0, 137.1, 138.4, 138.8, 163.8 (dd, J = 30.2, 32.1 Hz); ESIHRMS calcd for $C_{30}H_{36}O_6F_2N$ [M + NH_4]$^+$ 544.2505, found 544.2505.

To a solution of the above alcohol (0.79 g, 1.50 mmol) in CH_2Cl_2 (20 mL) was added a mixture of *m*-CPBA (2.61 g, 15.1 mmol), in CH_2Cl_2 (20 mL), NaH_2PO_4 (4.30 g, 30.3 mmol) and Na_2HPO_4 (4.14 g, 30.0 mmol) in water (40 mL). The suspension was stirred for 26 hours at rt and poured into 10% Na_2SO_3 in saturated $NaHCO_3$ solution. After stirring for 1 hour, the organic layer was separated, washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure. FCC of this residue afforded a mixture

of epimeric epoxides **3.36/3.37** (0.50 g, 74% based on recovered alkene, 2:1 ratio) as an oil: R_f = 0.30 (15% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.47 (dd, J = 2.7, 4.9 Hz, 0.6H), 2.60 (t, J = 4.5 Hz, 0.6H), 2.68 (dd, J = 2.6, 4.9 Hz, 0.4H), 2.84 (t, J = 4.6 Hz, 0.4H), 3.09 (m, 0.4H), 3.36 (m, 0.6H), 3.30 (m, 0.6H), 3.53 -3.60 (m, 3.8H), 3.68 (m, 0.6H), 3.91 (m, 1.6H), 4.01 (d, J = 5.9 Hz, 0.4H), 4.45-4.90 (m, 7H), 7.18-7.40 (m, 15H); ^{13}C NMR ($CDCl_3$) δ (major isomer) 43.9, 52.7, 53.1, 70.6 (t, J = 22.5 Hz), 73.9, 74.4, 78.9 (d, J = 3.3 Hz), 80.8, 80.9, 114.9 (dd, J =250.0, 258.1 Hz), 122.9-128.7 (several lines), 137.4, 137.9, 1381, 138.4, 138.8, 163.8 (dd, J = 30.2, 32.3 Hz); ESIHRMS calcd for $C_{30}H_{36}O_7F_2N$ $[M + NH_4]^+$ 560.2454, found 560.2452.

Difluoro-C-glycosides 3.38/3.39.

A solution of the epoxide mixture **3.36/3.37** in dry MeOH (400 mL) was treated with MeONa/MeOH solution (1M, 23.2 mL, 23.2 mmol). After stirring for 23 hours at rt, the reaction was acidified to pH 2 with a solution of HCl in ether and the solvent evaporated at reduced pressure. The crude product was then dissolved in MeOH (20 mL) and toluene (60 mL) and treated with $TMSN_2CH$ (5.8 mL, 11.6 mmol, 2M solution in ether) at 0 ^oC. After 30 min, acetic acid (1 mL) was added to the reaction and the solvents evaporated at the pump. FCC of the crude product yielded the difluorinated monosaccharides **3.38/3.39** (2.16 g, 52%) as an inseparable mixture of *D*/*L*- sugars and a second compound that was presumed to be the heptoside derivative **3.40** (0.95 g, 22%).

For 3.38/3.39. Colorless oil: R_f = 0.49 (30% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.66 (d, J = 8.9 Hz, D_2O exchange, 0.5H), 1.87 (t, J = 6.2 Hz, D_2O exchange, 0.5H), 3.42 (dd, J = 1.2, 3.3 Hz, 0.5H), 3.50 (m, 0.5H), 3.65 (m, 2H), 3.75-

3.98 (m, 5.5H), 4.08 (dd, J = 3.2, 5.2 Hz, 0.5H), 4.28-4.72 (m, 7H), 7.15-7.38 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 53.0, 53.4, 61.7, 62.0, 71.4, 71.9, 72.0, 72.4, 72.5, 72.7-73.2 (several lines), 73.4, 74.3, 74.8, 75.7, 76.9, 114.0 (t, J = 254.7 Hz), 114.9 (dd, J = 256.3, 260.3 Hz), 127.7-128.6 (several lines), 137.4, 137.6, 137.9, 138.0, 163.37 (t, J = 30.9 Hz), 163.40 (dd, J = 27.0, 31.8 Hz); ESIHRMS calcd for $C_{30}H_{36}O_7F_2N$ $[M + NH_4]^+$ 560.2454, found 560.2489.

For compound 3.40: colorless oil: R_f = 0.60 (30% EtOAc/petroleum ether); ^1H NMR (500 MHz, $CDCl_3$) δ 3.13 (d, J = 8.3 Hz, D_2O exchange, 1H), 3.62 (s, 3H), 3.71 (m, 1H), 3.77 (dd, J = 4.9, 12.6 Hz, 1H), 3.83 (t, J = 5.2, 1H), 4.02 (d, J = 6.0 Hz, 1H), 4.06 (d, J = 12.7 Hz, 1H), 4.33-4.44 (m, 4H), 4.60 (s, 2H), 4.70 (ABq, J = 11.8 Hz, Δδ = 0.03 ppm, 2H),7.25-7.37 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 53.3, 66.5, 67.2, 72.0, 72.5, 73.3, 74.1, 75.2, 80.1, 115.7 (t, J = 255.7 Hz), 127.1-128.8 (several lines), 137.5, 137.7, 138.0, 163.8 (t, J = 31.5 Hz); ESIHRMS calcd for $C_{30}H_{36}O_7F_2N$ $[M + NH_4]^+$ 560.2454, found 560.2451.

β-C-L-*gulo* pyranosides 3.41 and α-C-D-*manno* pyranosides 3.42.

The mixture **3.38/3.39** (213.0 mg, 0.39 mmol), TBDPSCl (0.03 mL, 1.18 mmol), and imidazole (106.0 mg, 1.56 mmol) in anhydrous DMF (5 mL) was stirred at 50 ^oC for 2.5 hours. The reaction was then quenched with methanol (1 mL) and extracted with ether. The combined organic phase was washed with brine, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by gravity column chromatography to give the *L*-guloside **3.41** (119.0 mg, 39%) and *D*-mannoside **3.42** (180.0 mg 59%) as colorless oils.

For β-C-L-*gulo* pyranosides 3.41: R_f = 0.62 (10% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.09 (s, 9H), 3.61 (s, 3H), 3.67 (dd, J = 1.1, 3.7 Hz, 1H), 3.75 (t, J = 2.7 Hz, 1H), 3.81 (m, 2H), 3.96 (dd, J = 2.6, 10.0 Hz, 1H), 4.03 (t, J = 6.8 Hz, 1H), 4.32-4.70 (m, 5H), 4.48 (A of ABq, J = 12.1 Hz, Δδ = 0.21 ppm, 1H), 4.69 (B of ABq, J = 12.1 Hz, Δδ = 0.21 ppm, 1H), 7.16 (m, 2H), 7.28-7.47 (m, 19H), 7.67 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.0, 53.2, 62.3, 72.0, 72.1, 73.1, 73.2, 73.4 (two signals, a singlet and an apparent t, J = 23.0 Hz), 74.8, 75.7, 114.3 (t, J = 254.5 Hz), 127.9-128.8 (several lines), 133.4, 133.7, 135.7, 135.8, 137.8, 138.4 (two signals), 163.7 (t, J = 31.3 Hz); ESIHRMS calcd for $C_{46}H_{54}O_7SiF_2N$ $[M + NH_4]^+$ 798.3632 found 798.3630.

For α-C-D-*manno* pyranosides 3.42: R_f = 0.68 (10% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.11 (s, 9H), 3.69 (s, 3H), 3.91 (dd, J = 6.4, 12.5 Hz, 1H), 3.94-4.00 (m, 3H), 4.07 (t, J = 5.9 Hz, 1H), 4.13 (dd, J = 3.2, 5.6 Hz, 1H), 4.51 (dd, J = 5.6, 10.5, 19.0 Hz, 1H), 4.60-4.71 (m, 6H), 7.26 (m, 2H), 7.34-7.50 (m, 19H), 7.72 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.9, 53.4, 62.8. 72.3, 72.87, 72.94 (dd, J = 22.3, 27.0 Hz), 73.5, 74.1, 77.4, 115.2 (dd, J = 256.5, 258.8 Hz), 127.8-129.8 (several lines), 133.5, 133.8, 135.8, 136.0, 137.9, 138.3, 138.4, 163.6 (t, J = 31.4 Hz); ESIHRMS calcd for $C_{46}H_{54}O_7SiF_2N$ $[M + NH_4]^+$ 798.3632 found 798.3637.

β-C-L-tetra-O-guloside 3.43

Treatment of *L*-guloside **3.39** (50.0 mg, 0.09 mmol) following the hydrogenation-acetylation sequence described in the synthesis of **2.28** provided the tetra-O-acetylated derivative **3.43** (40.0 mg, 98%): colorless oil; R_f = 0.42 (40% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, C_6D_6) δ 1.98, 2.06, 2.20 (all s, 12H, $C\underline{H_3}CO$ × 4), 3.91 (s. 3H,

C$\underline{H_3}$O-), 4.14-4.66 (m, 2H, H-5, 6a), 4.17 (t, J = 5.9 Hz, 1H, H-6b), 4.34 (ddd, J = 7.8, 8.3, 14.4 Hz, 1H, H-1), 5.00 (dd, J = 1.5, 3.9 Hz, 1H, H-4), 5.40 (dd, J = 3.2, 10.1 Hz, 1H, H-2), 5.43 (t, J = 3.2 Hz, 1H, H-3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.6, 20.8, 20.9 (two signals), 53.6, 61.9, 63.9 (d, J = 4.2 Hz), 66.6, 67.8, 72.9 (dd, J = 23.8, 28.4 Hz), 73.0, 113.6 (dd, J = 252.0, 261.5 Hz), 163.2 (dd, J = 30.2, 32.2 Hz), 169.0 (two signals), 169.7, 170.5; ESIHRMS calcd for $C_{17}H_{26}O_{11}F_2N$ $[M + NH_4]^+$ 458.1468, found 458,1467.

6-O-tertbutyldiphenylsilyl-α-C-D-tri-O-acetyl mannoside 3.44.

Treatment of *D*-mannoside **3.42** (45.0 mg, 0.06 mmol) following the hydrogenation-acetylation sequence described in the synthesis of **2.28** provided the tri-O-acetate derivative **3.44** (30.0 mg, 81%): colorless oil; R_f = 0.44 (30% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08 (s, 9H, $(CH_3)_3$-), 1.99, 2.00, 2.12 (all s, 9H, C$\underline{H_3}$CO × 3), 3.71 (dd, J = 3.2, 11.7 Hz, 1H, H-6a), 3.75 (dd, J = 4.7, 11.7 Hz, 1H, H-6b), 3.82 (s, 3H, CH_3O-), 3.98 (m, 1H, H-5), 4.42 (ddd, J = 3.6, 6.6, 23.4 Hz, 1H, H-1), 5.38 (dd, J = 3.6, 8.3 Hz, 1H, H-3), 5.43 (t, J = 8.3 Hz, 1H, H-4), 5.65 (t, J = 3.4 Hz, 1H, H-2), 7.36-7.42 (m, 6H), 7.64-7.71 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.8 (two signals), 20.9, 26.9, 53.9, 62.5, 65.7, 66.1, 69.4 (d, J = 4.3 Hz), 74.3 (dd, J = 22.0, 30.0 Hz), 76.4, 114.5 (dd, J = 258.1, 262.1 Hz), 127.9 (two signals), 128.5, 130.0, 133.2, 133.4, 135.8, 135.9, 162.9 (dd, J = 29.2, 32.7 Hz), 169.5, 169.7, 169.9; ESIHRMS calcd for $C_{31}H_{42}O_{10}SiF_2N$ $[M + NH_4]^+$ 654.2541, found 654. 2537.

(3*S*,7*R*)-ethyl-3-acetoxy-4,5,6-tris(benzyloxy)-2,2-difluoro-7,8-dihydroxyoctanoate 3.45/3.46.

To a solution of **3.34** (0.70 g, 1.72 mmol) in acetone (30 mL) was added OsO_4 (0.1 mL, 0.10 mmol, 1M in butanol) and NMO (1.20 mL, 5.16 mmol, 50% wv in water). The mixture was stirred for 5 hours at rt then quenched with solid Na_2SO_3 (0.40 g). Ethyl acetate (20 mL) was added to the reaction mixture, and after separation of the layers, the aqueous phase was further extracted with the ethyl acetate (2 × 10 mL). The combined organic phase was washed with brine and dried over Na_2SO_4. After removal of the solvents *in vacuo*. FCC afforded **3.45/3.46** (0.67 g, 90%) as a 10:1 mixture of epimeric alcohol: colorless oil; R_f = 0.48 (50% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04 (t, J = 7.1 Hz, 0.3H), 1.08 (t, J = 7.1 Hz, 2.7H), 1.98 (t, J = 6.0 Hz, 1H), 2.09 (s, 0.3H), 2.12 (s, 2.7 H), 2.59 (d, J = 5.1 Hz, 0.1H), 2.61 (d, J = 6.1 Hz, 0.9H), 3.65 (m, 3H), 3.80 (m, 1H), 3.80-4.01 (m, 3H), 4.10 (dd, J = 1.9, 9.1 Hz, 1H), 4.50-4.83 (m, 6H), 6.08 (ddd, 3.2, 9.2, 20.6 Hz, 1H), 7.21-7.38 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (major isomer) 13.7, 20.8, 63.0, 63.4, 69.3 (t, J = 24.1 Hz), 71.6, 74.0,74.4, 74.7, 77.2, 79.1, 78.0, 114.6 (t, J = 257.0 Hz), 127.8-128.9 (several lines), 136.9, 137.8, 138.0, 163.4 (t, J = 31.7 Hz), 168.9; ESIHRMS calcd for $C_{33}H_{42}O_9F_2N$ $[M + NH_4]^+$ 634.2822 found 634.2825.

Epoxides 3.36 and 3.47.

To a solution of the diol mixture **3.45/3.46** (0.65 g, 1.04 mmol) in pyridine (10 mL) at 0 ^{o}C was added *p*-toluenesulfonyl chloride (0.24 g, 1.24 mmol) at 0 ^{0}C. The reaction was then stirred at rt 4 hours. The solvent was removed under reduced pressure,

and the residue purified by FCC to give a mixture of mono tosylates (0.53 g, 87% based on recovered diol): colorless oil, R_f = 0.44 (30% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12 (t, J = 7.1 Hz, 3H), 2.12 (s, 3H), 2.45 (s, 3H), 2.62 (s, 1H, D_2O exchange, 1H), 3.65 (t, J = 6.3 Hz, 1H), 3.93-4.02 (m, 4H), 4.14 (m, 2H), 4.24 (dd, J = 2.6, 10.1 Hz, 1H), 4.46-4.84 (m, 6H), 6.12 (ddd, 2.4, 8.5, 20.7 Hz, 1H), 7.17-7.41 (m, 17H), 7.81 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (major isomer) 13.7, 20.7, 21.7, 62.9, 68.9 (t, J = 22.1 Hz), 70.1, 71.3, 73.9, 74.6, 77.1, 78.3, 79.5, 113.1 (dd, J = 251.3, 258.8 Hz), 128.0-128.7 (several lines), 130.1, 132.8, 136.9, 137.8 (two signals), 145.2, 162.2 (dd, J = 29.6, 32.7 Hz), 168.8; ESIHRMS calcd for $C_{40}H_{48}O_{11}SF_2N$ $[M + NH_4]^+$ 788.2911 found 788.2910.

The mixture from the previous step (0.53 g, 0.69 mmol) was treated with base following the procedure described for the synthesis of **3.38/3.39**. The hydroxy epoxide **3.36** (0.16 g, 34%) and the acetylated derivative **3.47** (0.13 g, 39%) were produced.

For hydroxyl epoxide 3.36: colorless oil; R_f = 0.38 (30% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.69 (dd, J = 2.7, 4.9 Hz, 1H), 2.84 (t, J = 4.7 Hz, 1H), 3.09 (m, 1H), 3.53 (s, 3H), 3.56 (t, J = 6.2 Hz, 1H), 3.58 (dd, J = 1.6, 8.5 Hz, 1H), 3.93 (d, J = 9.1 Hz, 1H), 4.02 (d, J = 5.9 Hz, 1H), 4.47-4.88 (m, 7H), 7.27-7.41 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 47.3, 51.1, 52.9, 70.3 (t, J = 22.0 Hz), 73.3, 73.9, 75.2, 78.3 (d, J = 3.4 Hz), 79.5, 81.5, 114.9, (dd, J = 249.9, 256.8 Hz), 127.7-128.7 (several lines), 137.2, 137.7, 138.3, 163.8 (t, J = 31.6 Hz); ESIHRMS calcd for $C_{30}H_{36}O_7F_2N$ $[M + NH_4]^+$ 560.2454, found 560.2457.

For epoxide 3.47: R_f = 0.41 (30% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.06 (s, 3H), 2.71 (dd, J = 2.6, 5.2 Hz, 1H), 2.78 (m, 1H), 3.16 (m, 1H), 3.49 (s, 3H),

3.59 (t, J = 5.2 Hz, 1H), 3.79 (dd, J = 2.9, 5.4 Hz, 1H), 4.16 (dd, J = 2.9, 8.4 Hz, 1H), 4.55-4.83 (m, 6H), 6.02 (ddd, J = 4.2, 8.4, 19.3 Hz, 1H), 7.28-7.42 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 45.9, 51.1, 53.1, 69.6 (t, J = 22.0 Hz), 73.9, 74.1, 74.4, 77.1, 77.7, 80.6, 113.2 (dd, J = 251.4, 258.2 Hz), 127.8-128.6 (several lines), 137.1, 138.0, 138.1, 138.2, 162.7 (dd, J = 29.6, 32.7 Hz), 168.7.

Difluoro *L*-guloside 3.39

Hydroxy epoxide **3.36** (128.0 mg, 0.24 mmol) was treated with base as described for the synthesis of **3.38**/**3.39**. This afforded the *L*-guloside **3.39** (58.0 mg, 62%) and the heptose sugar **40** (12.7 mg, 14%) based on recovered epoxides. The acetoxy derivative **3.47** (158.0 mg, 0.27 mmol) also gave **3.39** (108.6 mg, 69%): colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.75 (d, J = 7.1 Hz, D_2O exchange, 1H), 3.45 (s, 3H), 3.71 (dd, J = 1.7, 4.2 Hz, 1H), 3.53 (m, 1H), 3.80 (apparent t, J = 3.4 Hz, 1H), 3.84 (dd, J = 7.8, 11.4 Hz, 1H), 3.97 (m, 2H), 4.32-4.72 (m, 7H), 7.19-7.38 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 53.2, 62.3, 71.7, 72.2, 72.7, 73.3 (apparent d, J = 2.0 Hz), 73.5 (two signals, s and an apparent t, J = 23.1 Hz), 75.1, 76.0, 114.2 (t, J = 254.8 Hz), 127.9-128.8 (several lines), 137.6, 137.8, 138.3, 163.6 (t, J = 31.3 Hz); ESIHRMS calcd for $C_{30}H_{36}O_7F_2N$ $[M + NH_4]^+$ 560.2454, found 560.2456.

Difluoro acid 3.22.

The difluoro-C-mannoside **3.42** (1.70 g, 2.18 mmol) was treated with a mixture of 3N NaOH (2.2 mL, 6.54 mmol) and ethanol (40 mL). After 1 hour the reaction mixture concentrated *in vacuo* and acidified with 2N HCl (20 mL). The mixture was then

extracted with ethyl acetate (3 × 20 mL) and the organic phase washed with water and dried (Na_2SO_4). The solvent was removed under reduced pressure, to provide the acid **3.22** (1.66 g, quantitative yield): colorless oil, R_f = 0.34 (20% MeOH/$CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.10 (s, 9H), 3.87-4.05 (m, 5H), 4.14 (dd, J = 2.9, 6.2 Hz, 1H), 4.48-4.66 (m, 7H), 7.24-7.48 (m, 21H), 7.71 (m, 4H), 9.49 (br s, D_2O exchange, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.0, 27.2, 62.6, 72.1 (t, J = 24.1 Hz), 72.37, 72.43, 72.9, 73.1, 73.8, 76.2, 77.5, 114.6 (t, J = 257.0 Hz), 127.7-129.9 (several lines), 133.4, 133.6, 135.8, 135.9, 137.6, 138.0, 138.2, 166.4 (t, J = 31.7 Hz); ESIHRMS calcd for $C_{45}H_{52}O_7SiF_2N$ $[M + NH_4]^+$ 784.3476 found 784.3464.

Mono-fluoro-thioacetal esters 3.17/3.18.

TIA alcohol **2.13** (2.27 g, 4.46 mmol) and acid mixture **3.20/3.21** (2.69 g, 4.51 mmol) was subjected to the same procedure used to synthesize compound **2.30**. An inseparable mixture of fluoro esters **3.17/3.18** (2.63 g, 68% based on recovered alcohol) was obtained: colorless oil; R_f = 0.20 (10% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03 (s, 9H), 1.34, 1.39, 1.43, 1.46 (all s, 6H), 3.40 (dd, J = 5.0, 9.0 Hz, 0.4H), 3.60 (m, 1H), 3.70 (m, 1H), 3.72-3.88 (m, 4H), 3.99 (m, 1.6H), 4.27 (m, 2H), 4.35-4.55 (m, 7H), 5.18 (dm, J = 47.2 Hz, 1H), 5.20-5.45 (m, 2H), 7.11(m, 1H), 7.20-7.40 (m, 29H), 7.53 (m, 1H), 7.66 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.4, 26.6, 26.9, 27.0, 27.3, 27.4, 61.5, 62.3, 68.3, 68.8, 70.9, 71.1, 71.5, 71.5, 71.9, 72.0, 72.4 (d, J = 7.1 Hz), 72.5, 72.6, 72.7, 73.1, 73.3, 74.1 (d, J = 23.6 Hz), 74.8, 75.5, 78.6, 78.8, 84.4, 85.1, 88.1 (d, J = 194.3 Hz), 89.2 (d, J = 193.4 Hz), 111.7, 111.9, 127.6-129.2 (several lines), 130.0, 132.0, 132.4, 132.5, 135.7, 135.8, 135.9, 138.0 (×2), 138.2, 138.3, 138.4, 138.7, 166.9 (d,

J = 24.8 Hz), 167.5 (d, J = 25.7 Hz); ESIHRMS calcd for $C_{65}H_{75}O_{10}NFSiS$ (M + NH_4) 1108.4865, found 1108.4918.

Difluoro thioacetal ester 3.19.

Procedure 1: TIA alcohol **2.13** (85.5 mg, 0.17 mmol) and difluoro acid **3.22** (140.0 mg, 0.18 mmol) was subjected to the same procedure used to synthesize compound **2.30**. This provided ester **3.19** (83.2 mg, 89% based on recovered **2.13** and 34% conversion based on **3.22**).

Procedure 2: A mixture of difluoro acid **3.22** (43.0 mg, 0.06 mmol), 2,4,6-trichlorobenzoyl chloride (0.01 mL, 0.06 mmol) and triethylamine (0.02 mL, 0.12 mmol) in THF (3 mL) was stirred for 3.5 hours at 0^0 C. TIA alcohol **2.13** (30.7 mg, 0.06 mmol) and DMAP (10.0 mg, 0.08 mmol) in toluene were then added, and the mixture stirred for another 1 hour. The mixture was then diluted with diethyl ether (10 mL) and washed with saturated aqueous $NaHCO_3$ solution, brine, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by FCC to give ester **3.19** (53.9 mg, 91% based on recovered **2.13** and 76% conversion based on **3.22**): colorless oil; R_f = 0.33 (10% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04 (two singlets, 18H), 1.31, 1.43, (both s, 6H), 3.77-3.89 (m, 5H), 3.91 (q, J = 5.1 Hz, 1H), 3.99 (t, J = 5.9 Hz, 1H), 4.07 (dd, J = 3.0, 5.6 Hz, 1H), 4.39-4.60 (m, 8H), 5.22 (m, 1H), 5.42 (d, J = 6.6 Hz, 1H), 7.16-7.42 (m, 30H), 7.52 (m, 2H), 7.65 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.7, 26.9, 27.0, 27.2, 61.6, 62.8, 72.5, 72.6, 72.7, 72.9, 73.2, 74.0, 74.5, 77.1, 77.6, 78.7, 84.7, 112.1, 114.9 (t, J = 257.4 Hz), 127.8-129.8 (several lines), 130.0, 132.6, 132.9, 133.0, 133.4, 133.5, 133.8, 135.8 (three signals), 135.9, 136.0, 137.8, 138.4, 138.5, 162.4

(t, J = 31.8 Hz); ESIHRMS calcd for $C_{74}H_{86}O_{10}SSi_2F_2N$ $[M + NH_4]^+$ 1274.5474, found 1274.5476.

Mono-fluoro thioacetal enol ethers 3.14/3.15.

Treatment of ester **3.17/3.18** (1.37 g, 1.26 mmol) under similar conditions used to prepare **2.32** afforded the fluoro enol ether mixture **3.14/3/15** (1.06 g, 77%): colorless oil, R_f = 0.58 (15% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, C_6D_6) δ 1.14, 1.15 (both s, 9H), 1.39, 1.47, 1.49, 1.51 (all s, 6H), 3.57 (dd, J = 5.5, 10.8 Hz, 0.6H), 3.65 (m, 1H), 3.81 (ddd, J = 2.8, 6.2, 8.9 Hz, 0.6H), 3.88-3.91 (m, 1.6H), 4.02 (dd, J = 5.1, 10.3 Hz, 0.4H), 4.05-4.10 (m, 5H), 4.33-4.65 (m, 9.2H), 4.71 (dd, J = 2.4, 6.7 Hz, 0.6H), 4.77 (dd, J = 2.2, 6.2 Hz, 0.6H), 4.80-4.86 (m, 1H), 4.89 (d, J = 12.0 Hz, 0.6H), 4.94 (d, J = 7.8 Hz, 0.4H), 5.11 (dd, J = 2.6, 46.4 Hz, 0.4H), 5.95 (d, J = 6.8 Hz, 0.4H), 6.05 (d, J = 6.2 Hz, 0.6H), 6.92-7.42 (m, 29H), 7.68-7.76 (m, 6H); ^{13}C NMR (C_6D_6) δ 26.9, 27.2, 27.4 (2 peaks), 27.6, 27.9, 62.0, 70.4, 70.8, 72.0, 72.3, 72.5, 72.8, 73.5 (d, J = 9.3 Hz), 73.6 (d, J = 16.7 Hz), 73.9, 74.6, 75.4, 75.5, 75.6, 76.5, 76.7, 80.3, 80.5, 80.8, 84.8, 85.3, 88.5 (d, J = 6.1 Hz), 90.5 (d, J = 183.5 Hz), 91.6 (d, J = 178.4 Hz), 127.6-129.5 (several lines), 130.5, 130.6, 132.2, 132.9, 133.6, 133.8, 134.8, 135.2, 136.4, 136.5, 139.3, 139.4, 139.5, 139.8, 139.9, 156.4 (d, J = 17.9 Hz), 156.9 (d, J = 24.7 Hz); ESIHRMS calcd for $C_{66}H_{77}O_9NFSiS$ $(M + NH_4)$ 1106.5072, found 1106.5103.

Difluoro thioacetal enol ethers 3.16.

A solution of titanium tetrachloride (4.98 mL, 4.98 mmol, 1M) was added to THF (6 mL) at 0 ^{o}C. The mixture was stirred for 30 min at which point TMEDA (1.2 mL,

7.96 mmol) was added in one portion. The resulting yellow-brown suspension was allowed to warm to rt and stirred for an additional 30 min. At this time freshly activated zinc dust (546.0 mg, 8.36 mmol) and lead (II) chloride (27.7 mg, 0.10 mmol) were added in portion and stirred at rt for a further 10 min. To the resulting bluish-green mixture was added a solution of ester **3.19** (257.0 mg, 0.20 mmol) and dibromomethane (0.28 mL, 3.98 mmol) in THF (6 mL) in one portion. The mixture was stirred at 60 ^{o}C for 3.5 hours and then diluted with brine. The mixture was stirred for 30 min at rt, diluted with ether (20 mL) and stirred vigorously for an additional 20 min. The resulting suspension was filtered through neutral alumina and the residue washed with ether. The ethereal extract was concentrated *in vacuo* and gravity chromatography of the residue over silica gel afforded enol ether **3.16** (100.9 mg, 63%, based on recovered **3.19**): colorless oil, R_f = 0.53 (5% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, C_6D_6) δ 1.15, 1,17 (both s, 18H), 1.47, 1.55, (both s, 6H), 3.81 (dd, J = 5.9, 11.0 Hz, 1H), 4.01-4.15 (m, 5H), 4.18 (dd, J = 7.3, 11.0 Hz, 1H), 4.31 (apparent t, J = 2.5 Hz, 1H), 4.35 (t, J = 3.7 Hz, 1H), 4.43-4.49 (m, 4H), 4.62 (A of ABq, J = 11.9 Hz, Δδ = 0.14 ppm, 1H), 4.69 (B of ABq, J = 11.9 Hz, Δδ = 0.14 ppm, 1H), 4.75 (d, J = 3.7 Hz, 1H), 4.79 (dd, J = 2.7, 5.6 Hz, 1H), 4.87 (d, J = 11.3 Hz, 1H), 5.08 (ddd, J = 1.7, 7.6, 26.7 Hz, 1H), 6.89-7.43 (m, 30H), 7.65-7.88 (m, 10H); ^{13}C NMR (125 MHz, C_6D_6) δ 27.3, 27.4, 27.6, 27.9, 62.1, 65.2, 72.6, 73.0, 73.5, 74.7 (dd, J = 22.0, 32.1 Hz), 75.0, 75.2, 78.9 (d, J = 4.6 Hz), 81.0, 84.9, 88.3 (t, J = 4.6 Hz), 113.1, 119.8 (dd, J = 248.4, 253.9 Hz), 127.3-129.5 (several lines), 130.2 (two signals), 130.6 (two signals), 131.6, 133.6, 133.8, 134.5, 134.6, 135.5, 136.4, 136.5, 139.1, 139.5, 139.7, 154.3 (dd, J = 23.8, 31.2 Hz); ESIHRMS calcd for $C_{75}H_{88}O_9SSi_2F_2N$ $[M + NH_4]^+$ 1272.5681, found 1272.5671.

Mono-fluoro glycals 3.11/3.12.

Treatment of the fluoro enol ether mixture **3.14/3/15** (1.06 g, 0.98 mmol) under similar conditions used to prepare **2.34** afforded the mono-fluoro glycal mixture **3.10/3.11** (0.68 g, 83% based on recovered **3.14/3/15**): clear oil; R_f = 0.39 (15% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, C_6D_6) δ 1.17 (s, 9H), 1.32, 1.36, 1.47, 1.60 (all s, 6H), 3.76 (dd, J = 2.9, 10.7 Hz, 0.5H), 3.85 (m, 1.5H), 3.93 (m, 1H), 4.01 (m, 1H), 4.04-4.14 (m. 3H), 4.18 (dd, J = 2.8, 7.6 Hz, 0.5H), 4.24 (m, 1.5H), 4.30 (m, 1H), 4.38-4.62 (m, 9.5H), 4.84 (d, J = 11.5 Hz, 0.5H), 4.97 (m, 0.5H), 5.03 (dd, J = 5.3, 46.6 Hz, 0.5H), 5.18 (dd, J = 2.0, 46.1 Hz, 0.5H), 5.38 (m, 0.5H), 7.03-7.34 (m, 26H), 7.78 (m, 4H); ^{13}C NMR (125 MHz, C_6D_6) δ 27.4 (×2), 27.8, 28.9, 63.8, 64.1, 69.6, 69.8, 70.3, 71.3 (d, J = 19.0 Hz), 72.2, 72.4, 72.7, 72.9, 73.0, 73.9 (×2), 74.0 (d, J = 4.0 Hz), 74.6, 74.7, 74.8, 88.6 (d, J = 182.0 Hz), 91.6 (d, J = 180.0 Hz), 100.8 (d, J = 8.8 Hz), 102.2 (d, J = 8.8 Hz), 111.0, 111.1, 127.9-128.9 (several lines), 133.9, 134.0, 134.1 (×2), 136.3, 136.4, 139.2, 139.3, 139.4, 139.5 (×2), 139.6, 139.7, 139.8, 150.7 (d, J = 25.6 Hz), 150.9 (d, J = 22.0 Hz); ESIHRMS calcd for $C_{60}H_{68}O_9FSi$ (M + H) 979.4617, found 979.4645.

Difluoro glycal 3.13.

The enol ether **3.16** (0.20 g, 0.16 mmol) was subjected to similar conditions used to prepare **2.34.** This provided the difluoro glycal **3.13** (0.12 g, 82% based on recovered **3.16**): clear oil, R_f = 0.54 (10% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, C_6D_6) δ 1.16, 1.18 (both s, 18H), 1.27, 1.28, (both s, 6H), 3.86 (t, J = 6.9 Hz, 1H), 4.03-4.17 (m, 7H), 4.30 (t, J = 2.9 Hz, 1H), 4.38 (m, 1H), 4.50-4.60 (m, 5H), 4.72 (A of ABq, J = 11.5 Hz, Δδ = 0.23 ppm, 1H), 4.79 (apparent ddd, J = 2.9, 10.0, 22.7 Hz, 1H), 4.98 (B of ABq,

J = 11.5 Hz, Δδ = 0.23 ppm, 1H), 5.41 (d, J = 2.7 Hz, 1H), 7.08-7.38 (m, 27H), 7.70-7.87 (m, 8H); ^{13}C NMR (125 MHz, C_6D_6) δ 27.4, 27.5, 28.8, 63.7, 63.8, 69.3, 72.2, 73.0, 73.3, 74.0, 74.9, 75.2 (dd, J = 24.7, 30.2 Hz), 77.5, 78.5, 80.3 (d, J = 2.7 Hz), 102.7 (t, J = 5.5 Hz), 111.3, 118.8 (dd, J = 247.4, 252.0 Hz), 127.9-128.9 (several lines), 133.9, 134.1 (two signals), 136.2, 136.3, 136.4, 136.7, 139.2, 139.5, 139.9, 148.5 (dd, J = 26.6, 31.2 Hz); ESIHRMS calcd for $C_{69}H_{82}O_9Si_2F_2N$ $[M + NH_4]^+$ 1162.5491, found 1162.5497.

1,3,4,5-Tetra-*O*-benzyl-13-*O*-*tert*-butyldiphenylsilyl-2,6:8,12-dianhydro-10,11-*O*-isopropylidene-7-fluoro-D-*lyxo*-D-*galacto*-D-*manno*-tridecitol 3.8 and 1,3,4,5-Tetra-*O*-benzyl-13-*O*-*tert*-butyldiphenylsilyl-2,6:8,12-dianhydro-10,11-*O*-isopropylidene-7-fluoro-D-*lyxo*-D-*gulo*-D-*manno*-tridecitol 3.9.

Application of the procedure that was used for **2.36** to the glycal mixture **3.11/3.12** (0.91 g, 0.94 mmol) provided the mono-fluoro-β-C-glycosides **3.8** (0.36 g, 39%) and **3.9** (0.23 g, 24%).

For C-glycoside 3.8: colorless oil; R_f = 0.63 (30% EtOAc/petroleum ether); ^{1}H NMR ($CDCl_3$) δ 1.07 (s, 9H, $CH_3)_3CSi$), 1.36, 1.49 (both s, 6H, $C(CH_3)_2$), 3.34 (d, J = 6.9 Hz, 1H, D_2O exchange, OH), 3.40 (dd, J = 3.5, 10.6 Hz, 1H, H-6a), 3.47 (ddd, J = 6.1, 9.2, 14.0 Hz, 1H, H-1'), 3.53 (t, J = 4.4 Hz, 1H, H-4), 3.69-3.79 (m, 3H, H-2', 3, 4), 3.84-3.95 (m, 5H, H-2, 3', 5' 6'a, 6'b), 4.09 (m, 1H, H-5), 4.30 (dd, J = 2.2, 5.6 Hz, 1H, H-4'), 4.40 (ddd, J = 2.7, 8.1, 27.1 Hz, 1H, H-1), 4.31-4.61 (m, 8H, 4 x PhC$\underline{H_2}$), 4.84 (ddd, J = 2.5, 6.1, 46.7 Hz, 1H, H-1''), 7.05-7.47 (m, 26H, Ph), 7.70 (m, 4H, Ph); ^{13}C NMR ($CDCl_3$) δ 26.4, 26.9, 28.3, 62.8, 68.1, 69.6 (d, J = 17.8 Hz), 69.9 (d, J = 3.7 Hz), 72.3, 73.1, 73.2, 73.4, 75.0, 75.1, 76.9, 77.7, 79.9, 91.1 (d, J = 181.2 Hz), 109.6, 127.8-129.8 (several

lines), 133.6 (2 peaks), 135.9 (2 peaks), 137.8, 138.0, 138.1, 138.3; FABHRMS calcd for $C_{60}H_{70}O_{10}FSi$ (M + H) 997.4722, found 997.5031.

For C-glycoside 3.9: colorless oil; R_f = 0.75 (30% EtOAc/petroleum ether); ^{1}H NMR ($CDCl_3$) δ 1.07 (s, 9H, $(CH_3)_3CSi$), 1.38, 1.52, (both s, 6H, $C(CH_3)_2$), 3.43 (dd, J = 8.6, 9.8 Hz, 1H, H-6a), 3.51 (ddd, J = 2.5, 10.0, 16.0 Hz, 1H, H-1'), 3.66 (m, 2H, H-4, 6b), 3.72 (dd, J = 2.6, 8.6 Hz, 1H, H-3), 3.82 (dt, J = 2.0, 8.8 Hz, 1H, H-5), 3.84 - 4.00 (m, 5H, H-2', 3', 5,' 6'a, 6'b), 4.02 (q, J = 2.8 Hz, 1H, H-2), 4.05 (d, J =5.9 Hz, D_2O exchange, 1H, OH), 4.34 (dd, J = 1.7, 4.9 Hz, 1H, H-4'), 4.41-4.64 (m, 8H, H-1, 7 x PhC<u>H</u>), 4.81 (B of ABq, J = 11.0 Hz, Δδ = 0.38 ppm, 1H, PhC<u>H</u>), 5.02 (ddd, J = 2.5, 9.1, 44.8 Hz, 1H, H-1''), 7.11-7.47 (m, 26H, Ph), 7.72 (m, 4H, Ph); ^{13}C NMR ($CDCl_3$) δ 26.6, 26.9, 28.6, 62.7, 69.3 (d, J = 29.1 Hz), 69.9, 71.2 (d, J = 23.5 Hz), 72.1, 72.8, 73.2 (d, J = 3.9 Hz), 73.7, 74.6, 74.7, 74.9, 76.9, 78.2 (d, J = 18.7 Hz), 79.8, 80.0, 86.6 (d, J = 178.6 Hz), 109.4, 127.8-129.9 (several lines), 133.6, 133.7, 135.8, 135.9, 137.3, 138.1 (2 peaks), 138.2; FABHRMS calcd for $C_{60}H_{70}O_{10}FSi$ (M + H) 997.4722, found 997.4759.

3,4,5-Tri-*O*-benzyl-1,13-*O*-di-*tert*-butyldiphenylsilyl-2,6:8,12-dianhydro-10,11-*O*-isopropylidene-7-deoxy-7,7-difluoro-D-*threo*-L-*gulo*-D-*manno*-tridecitol 3.10.

Application of the procedure that was used for **2.36** to the glycal **3.13** (0.12 g, 0.11 mmol) provided the difluoro-β-C-galactoside **3.10** (0.11 g, 86%) as colorless oil, colorless oil; R_f = 0.48 (20% EtOAc/petroleum ether); ^{1}H NMR ($CDCl_3$) δ 1.07 (s, 18H, 2 x $(CH_3)_3CSi$), 1.35, 1.47, (both s, 6H, $C(CH_3)_2$), 2.93 (d, J = 5.3 Hz, 1H, D_2O exchange, -OH), 3.54 (m, 1H, H-1'), 3.68 (t, J = 7.6 Hz, 1H, H-4), 3.79 (ddd, J = 2.2, 6.1, 7.8 Hz, 1H, H-5'), 3.80-3.97 (m, 8H, H-2', 3', 6'a, 6'b, 3, 5, 6a, 6b), 4.09 (t, J = 3.4, Hz, 1H, H-

2), 4.27 (dd, J = 2.5, 5.1 Hz, 1H, H-4'), 4.36 (d, J = 11.3 Hz, 1H, PhCH), 4.50-4.62 (m, 6H, H-1, 5 x PhCH), 7.06 (m, 2H, Ph), 7.22-7.42 (m, 25H, Ph), 7.65-7.73 (m, 8H, Ph); ^{13}C NMR ($CDCl_3$) δ 26.5, 27.0, 27.3, 28.5, 62.7, 64.3, 69.7, 72.8 (two signals), 72.9, 73.4, 74.0, 74.5, 76.6 (apparent t, J = 31.9 Hz), 78.2, 78.7, 80.2, 109.9, 121.2 (t, J = 254.2 Hz), 127.8-130.0 (several lines), 133.2, 133.5, 133.7, 135.8, 135.9, 136.0, 138.2, 138.3, 138.5; ESIHRMS calcd for $C_{69}H_{84}O_{10}Si_2F_2N$ $[M + NH_4]^+$ 1180.5596, found 1180.5601

1,3,4,5-Tetra-*O*-benzyl-9-*O*-acetyl-13-*O*-*tert*-butyldiphenylsilyl-2,6:8,12-dianhydro-10,11-*O*-isopropylidene-7-fluoro-D-*lyxo*-D-*galacto*-D-*manno*-tridecitol 3.48 and 1,3,4,5-Tetra-*O*-benzyl-9-*O*-acetyl-13-*O*-*tert*-butyldiphenylsilyl-2,6:8,12-dianhydro-10,11-*O*-isopropylidene-7-fluoro-D-*lyxo*-D-*gulo*-D-*manno*-tridecitol 3.49.

Fluoro-β-C-galactoside acetate **3.48**: colorless oil; R_f = 0.29 (20% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07 (s, 9H), 1.37, 1.54, (both s, 3H ea), 2.02 (s, 3H), 3.22 (ddd, J = 3.8, 7.8, 20.9 Hz, 1H), 3.63 (m, 3H), 3.72 (m, 2H), 3.78 (dd, J = 5.6, 14.9 Hz, 1H), 3.88 (q, J = 5.0 Hz, 1H), 3.95 (m, 2H), 4.07 (t, J = 6.2 Hz, 1H), 4.18 (dt, J = 5.3, 23.0 Hz, 1H), 4.35 (dd, J = 1.9, 5.5 Hz, 1H), 4.40-4.64 (m, 9H), 5.14 (dd, J = 7.1, 8.4 Hz, 1H), 7.12-7.48 (m, 26H), 7.75 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.3, 26.4, 27.0, 27.5, 62.3, 68.9, 69.1 (d, J = 5.5 Hz), 71.9, 73.0, 73.1, 73.4, 73.8, 74.2 (d, J = 6.0 Hz), 74.7, 75.1 (d, J = 19.6 Hz), 76.0, 76.6, 87.4 (d, J = 186.1 Hz), 110.4, 127.6-129.9 (several lines), 133.2, 133.5, 135.7, 135.8, 169.4; ESMS 1056.3 (M + NH_4)

Fluoro-β-C-galactoside acetate **3.49**: colorless oil; R_f = 0.29 (20% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03 (s, 9H), 1.34, 1.51, (both s,

3H ea), 2.02 (s, 3H), 3.60 (m, 1H), 3.67 (dd, J = 3.2, 7.1 Hz, 1H), 3.69-3.87 (m, 7H), 3.94 (m, 1H), 4.13 (dd, J = 5.1, 10.9 Hz, 1H), 4.25 (dt, J = 4.2, 23.4 Hz, 1H), 4.31 (dd, 1.5, 5.6 Hz, 1H), 4.41-4.68 (m, 8H), 4.77 (dt, J = 47.5, 4.9 Hz, 1H), 5.16 (dd, J = 9.9, 8.2 Hz, 1H), 7.14-7.40 (m, 26H), 7.68 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.3, 26.2, 26.9, 27.6, 69.4, 70.2 (d, J = 4.4 Hz), 71.9, 72.4, 73.0, 73.5, 74.1, 74.7, 75.9 (d, J = 10.6 Hz), 76.5, 93.3 (d, J = 180.1 Hz), 110.2, 127.7-129.9 (several lines), 130.0, 133.3, 133.5, 135.7, 135.9, 138.3, 138.4, 138.5 (×2), 138.6, 169.9; ESMS 1056.3 ($M + NH_4$)

3,4,5-Tri-*O*-benzyl-9-*O*-acetyl-1,13-*O*-di-*tert*-butyldiphenylsilyl-2,6:8,12-dianhydro-10,11-*O*-isopropylidene-7-deoxy-7,7-difluoro-D-*threo*-L-*gulo*-D-*manno*-tridecitol 3.50:

Difluoro-β-C-galactoside Acetate **3.50:** colorless oil; R_f = 0.29 (10% EtOAc/petroleum ether), ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02, 1.04 (both s, 18H), 1.36, 1.52, (both s, 6H), 1.99 (s, 3H), 3.65 (m, 2H), 3.78-3.92 (m, 7H), 3.98 (t, J = 3.4 Hz, 1H), 4.02 (t, J = 7.1 Hz, 1H), 4.10 (dd, J = 5.6, 7.1 Hz, 1H), 4.24 (m, 1H), 4.31 (dd, J = 2.0, 5.4 Hz, 1H), 4.47-4.73 (m, 6H), 5.26 (dd, J = 7.3, 9.5 Hz, 1H), 7.18-7.41 (m, 27H), 7.66 (m, 8H); ESIHRMS calcd for $C_{71}H_{86}O_{11}Si_2F_2N$ $[M + NH_4]^+$ 1222.5702, found 1222.5696

1,3,4,5-Tetra-*O*-benzyl-13-*O*-*tert*-butyldiphenylsilyl-2,6:8,12-dianhydro-7-fluoro-D-*lyxo*-D-*galacto*-D-*manno*-tridecitol 3.51 and 1,3,4,5-Tetra-*O*-benzyl-2,6:8,12-dianhydro-7-fluoro-D-*lyxo*-D-*galacto*-D-*manno*-tridecitol 3.53.

Application of the procedure that was used for **2.43** to **3.8** (407 mg, 0.41 mmol) provided the corresponding triol **3.51** (101 mg, 26%) and the tetrol **3.53** (78 mg, 33%).

The above tetrol **3.53** (78.0 mg, 0.11 mmol), TBDPSCl (0.04 mL, 0.14 mmol), and imidazole (15 mg, 0.22 mmol) in anhydrous DMF (3 mL) was stirred at 50 ^{o}C for 1.5 hours. The reaction mixture was then diluted with water (2 mL) and extracted with ether. The combined organic phase was washed with brine, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by FCC to give the triol **3.51** (70.0 mg, 67% yield).

For triol 3.51: colorless oil; R_f = 0.37 (40% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (s, 9H), 2.59 (d, J = 4.1 Hz, 1H, D_2O exchange), 2.67 (d, J = 3.0 Hz, 1H, D_2O exchange), 3.33 (dt, J = 3.7, 9.2 Hz, 1H), 3.41-3.47 (m, 3H), 3.50 (t, J = 4.8 Hz, 1H), 3.58 (d, J = 6.4 Hz, 1H), 3.78 (apparent t, J = 4.2 Hz, 1H), 3.79-3.96 (m, 5H), 4.13 (m, 2H), 4.35 (apparent ddd, J = 1.8, 7.8, 26.1 Hz, 1H), 4.38-4.64 (m, 8H), 4.84 (ddd, 2.0, 4.8, 45.1 Hz, 1H), 7.19 (m, 2H), 7.23-7.41 (m, 24H), 7.67-7.72 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.0, 63.5, 68,6, 69.0, 69.9 (d, J = 17.8 Hz), 72.3, 72.6, 73.2, 73.3, 73.5 (d, J = 3.0 Hz), 75.0, 75.1, 75.5, 75.6, 77.8, 78.0, 78.5, 91.2 (d, J = 181.5 Hz), 127.9-130.0 (several lines), 133.1, 133.4, 135.8, 135.9, 137.8, 138.0 (×2), 138.3; ESMS 979.3 (M + Na).

For tetrol 3.53: colorless oil: R_f = 0.13 (40% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.41 (dd, J = 3.8, 8.0 Hz, 1H, D_2O exchange), 2.75, 2.80 (both br s, 1H ea, D_2O exchange), 3.28 (dt, J = 3.4, 9.3 Hz, 1H), 3.43 (m, 1H), 3.47 (t, J = 4.6 Hz, 1H), 3.50 (ddd, J = 4.8, 9.7, 14.6 Hz, 1H), 3.65 (d, J = 6.8 Hz, 1H), 3.72 (ddd, J = 4.1, 8.5, 12.0 Hz, 1H), 3.82-3.94 (m, 5H), 3.97 (dd, J = 2.6, 7.9 Hz, 1H), 4.16 (m, 1H), 4.39 (ddd, J = 1.9, 8.0, 29.2 Hz, 1H), 4.34-4.64 (m, 9H), 4.89 (ddd, J = 1.9, 4.8, 45.2 Hz, 1H), 7.25 (m, 2H), 7.26-7.38 (m, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 63.4, 63.5, 68.4, 68.8, 69.7,

69.9 (d, J = 17.8 Hz), 72.4, 72.5, 73.2, 73.4 (d, J = 3.2 Hz), 74.9, 75.1, 75.3, 75.4, 77.9, 78.0, 78.6, 91.2 (J = 181.5 Hz), 128.0-128.7 (several lines), 137.7, 137.9, 138.0, 138.2.

1,3,4,5-Tetra-*O*-benzyl-13-*O*-*tert*-butyldiphenylsilyl-2,6:8,12-dianhydro-7-fluoro-D-*lyxo*-D-*gulo*-D-*manno*-tridecitol 3.52.

The fluoro disaccharide **3.9** (280 mg, 0.28 mmol) was subjected to similar conditions as used in the synthesis of **3.51**. This gave the triol **3.52** (152 mg, 73 % based on recovered **3.9**): colorless oil; R_f = 0.22 (40% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.09 (s, 9H), 2.27 (d, J = 4.1 Hz, 1H, D_2O exchange), 2.67 (d, J = 3.0 Hz, 1H, D_2O exchange), 3.39 (dt, J = 3.7, 9.2 Hz, 1H), 3.52-3.59 (m, 2H), 3.61 (apparent t, J = 8.8 Hz, 1H), 3.75-3.84 (m, 5H), 3.97 (apparent dd, J = 6.9, 10.0 Hz, 1H), 4.01 (m, 1H), 4.09 (m, 2H), 4.15 (t, J = 2.8 Hz, 1H), 4.49-4.91 (m, 9H), 5.04 (ddd, 2.0, 9.1, 44.4 Hz, 1H), 7.24-7.46 (m, 26H), 7.76 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.9, 63.0, 67.3 (d, J = 7.6 Hz), 68.9, 70.6, 71.1 (d, J = 23.5 Hz), 72.0, 72.5, 72.8, 73.4 (d, J = 3.9 Hz), 73.9, 74.4, 74.8, 75.0, 75.2, 78.1, 79.2, 79.4, 79.8, 86.6 (J = 179.6 Hz), 127.7-130.0 (several lines), 133.2, 133.4, 135.7, 135.8, 137.2, 138.2 (×4); ESMS 979.3 (M + Na)

1,3,4,5-Tetra-*O*-benzyl-13-2,6:8,12-dianhydro-7-fluoro-D-*lyxo*-D-*gulo*-D-*manno*-tridecitol 3.54.

Compound **3.9** (62 mg, 0.06 mmol) was again subjected to similar acid hydrolysis conditions as used in synthesis of **3.51**. Thus after a much longer time period provided the fluoro tetrol derivative **3.54** (21 mg, 47%), colorless oil: R_f = 0.39 (30% MeOH/$CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.45 (br s, 2H, D_2O exchange), 2.89 (br s,

1H, D_2O exchange), 3.36 (m, 1H), 3.45 (m, 1H), 3.56 (m, 1H), 3.62 (t, J = 9.0 Hz, 1H), 3.74-3.96 (m, 7H), 4.10 (m, 2H), 4.47-4.74 (m, 9H), 5.01 (ddd, J = 2.0, 8.8, 44.5 Hz, 1H), 7.25-7.42 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 62.8, 67.3 (d, J = 7.3 Hz), 69.6, 70.5, 71.3, 72.1, 72.7, 73.2 (d, J = 3.7 Hz), 73.9, 74.4, 74.8, 74.8 (d, J = 8.4 Hz), 78.2, 79.0 (d, J = 18.8 Hz), 79.5, 86.9 (d, J = 178.2 Hz), 127.9-128.8 (several lines), 137.2, 138.1 (×2), 138.2.

3,4,5-Tri-*O*-benzyl-1,13-di-*O*-*tert*-butyldiphenylsilyl-2,6:8,12-dianhydro-7-deoxy-7,7-difluoro-D-*threo*-L-*gulo*-D-*manno*-tridecitol 3.55 and 3,4,5-Tri-*O*-benzyl-2,6:8,12-dianhydro-7-deoxy-7,7-difluoro-D-*threo*-L-*gulo*-D-*manno*-tridecitol 3.56.

Application of the procedure that was used for **2.43** to C-glycoside **3.10** (80.0 mg, 0.07 mmol) provided the triol **3.55** (30 mg, 46%) and the desilylated product **3.56** (9.3 mg, 25% yield) based on recovered **3.10**, both as colorless oils;

For triol 3.54: R_f = 0.51 (40% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07, 1.08 (both s, 18H), 2.78 (broad s, D_2O exchange, 3H), 3.42 (dd, J = 3.2, 9.5 Hz, 1H), 3.49 (t, J = 5.9 Hz, 1H), 3.60 (q, J = 9.5 Hz, 1H), 3.68 (t, J = 7.6 Hz, 1H), 3.83-3.92 (m, 4H), 3.95 (dd, J = 5.9, 10.8 Hz, 1H), 4.03 (m, 1H), 4.09 (t, J = 9.3 Hz, 1H), 4.11 (d, J = 2.9 Hz, 1H), 4.14 (t, J = 3.1 Hz, 1H), 4.40 (d, J = 11.3 Hz, 1H), 4.54-4.70 (m, 6H), 7.10 (m, 2H), 7.20-7.47 (m, 25H), 7.63-7.77 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.0, 27.2, 63.3, 64.7, 67.8, 68.9, 72.8, 72.9, 72.8, 72.9, 74.1, 74.5, 75.4, 77.4, 78.3 (d, J = 7.4 Hz), 78.5, 78.7, 121.1 (t, J = 254.8 Hz), 127.8-128.6 (several lines), 130.0 (two signals), 130.1, 133.1, 133.2, 133.4, 133.5, 135.7, 135.8 (two signals), 135.9 (two signals), 138.2,

(two signals), 138.4; ESIHRMS calcd for $C_{66}H_{76}O_{10}Si_2F_2Na$ $[M + Na]^+$ 1145.4837, found 1145.4838.

For pentol 3.56: R_f = 0.28 (95% EtOAc/petroleum ether); ^1H NMR (500 MHz, $CDCl_3$) δ 2.24 (br s, D_2O exchange, 2H), 3.41 (s, 2H), 3.53 (m, 2H), 3.70 (m, 3H). 3.79 (m, 1H), 3.85 (t, J = 9.5 Hz, 1H), 3.96 (apparent t, J = 5.0 Hz, 1H), 4.02 (s, 1H), 4.11 (m, 2H), 4.38-4.61 (m, 7H), 4.84 (br s, 1H), 7.17-7.33 (m, 15H); ESIHRMS calcd for $C_{34}H_{40}O_{10}F_2Na$ $[M + Na]^+$ 669.2482, found 669.2480.

1,3,4,5,9,10,11,13-Octa-*O*-acetyl-2,6:8,12-dianhydro-7-fluoro-D-*lyxo*-D-*galacto*-D-*manno*-tridecitol 3.59.

The tetrol **3.53** (28 mg, 0.04 mmol), 10% Pd on carbon (60 mg), formic acid (0.05 mL) and methanol (2 mL) were stirred under an atmosphere of hydrogen (balloon), for 12 hours. The reaction mixture was purged with argon and filtered through a bed of Celite. The filtrate was then concentrated and the crude fluoro disaccharide **3.56** (13 mg, 93%) was collected as an amorphous solid; R_f = 0.43 (60% MeOH/ $CHCl_3$); ^1H NMR (500 MHz, D_2O) δ 3.39 (dd, J = 2.2, 13.2 Hz, 1H), 3.59-3.77 (m 7H), 3.82 (apparent t, J = 9.7 Hz, 1H), 3.87 (m, 2H), 3.94 (d, J = 3.3 Hz, 1H), 4.25 (m, 1H), 4.36 (ddd, J = 1.6, 7.4, 15.3 Hz, 1H), 5.16 (ddd, J = 1.6, 7.4, 46.6 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) 61.8 (×2), 67.3, 67.4 (d, J = 6.4 Hz), 69.1, 69.4, 71.3, 74.7, 76.2 (d, J = 23.1 Hz), 76.8, 78.7 (d, J = 20.5 Hz), 79.4, 91.7 (d, J = 176.8 Hz); ESIHRMS calcd for $C_{13}H_{23}O_{10}Na$ (M + Na) 381.1173, found 381.1182.

Compound **3.56** (13 mg, 0.04 mmol) was then taken up in ethyl acetate (5 mL), DMAP (3.0 mg, 0.02 mmol), acetic anhydride (0.2 mL, 2.12 mmol). This was stirred for

2 hours and the solvent removed *in vacuo*. FCC of the crude residue gave fluoro peracetate **3.59** (17 mg, 67%), colorless oil: R_f = 0.50 (60% EtOAc /petroleum ether); ^{1}H NMR (500 MHz, C_6D_6) δ 1.60, 1.65, 1.67, 1.69 (2), 1.730, 1.733, 1.76 (all s, 3H ea), 3.37 (t, J = 6.3 Hz, 1H, H-5), 3.72 (ddd, J = 2.4, 9.8, 20.1 Hz, 1H, H-1), 4.03 (m, 1H, H-6'), 4.15 (dd, J = 6.9, 11.4 Hz, 1H, H-7'b), 4.22 (dd, J = 6.3, 11.4 Hz, 1H, H-6a), 4.24 (dd, J = 2.6, 12.2 Hz, 1H, H-6b), 4.45 (dd, J = 5.3, 12.2 Hz, 1H, H-7'a), 4.66 (ddd, J = 2.6, 7.7, 17.7 Hz, 1H, H-2'), 4.85 (ddd, J = 2.2, 7.7, 46.6 Hz, 1H, H-1'), 5.20 (dd, J = 3.3, 10.0 Hz, 1H, H-3), 5.41 (dd, J = 2.6, 9.4 Hz, 1H, H-4'), 5.49 (d, J = 3.3, 1H, H-4), 5.66 (t, J = 9.4 Hz, 1H, H-5'), 5.80 (t, J = 2.6 Hz, 1H, H-3), 5.91 (t, J = 10.0 Hz, 1H, H-2); ^{13}C-NMR (125 MHz, C_6D_6) δ 20.4, 20.5 (×3), 20.6 (×3), 20.7, 61.9, 62.7, 66.1 (d, J = 2.8 Hz), 67.0, 68.0, 68.5 (d, J = 6.9 Hz), 70.5, 72.8, 73.1, 75.3 (d, J = 22.0 Hz), 75.5, 76.6 (d, J = 20.9 Hz), 86.5 (d, J = 185.6 Hz), 169.5, 169.7, 170.1, 170.2 (×2), 170.3, 170.5 170.6; ESIHRMS calcd for $C_{29}H_{40}O_{18}F$ (M + H) 695.2199, found 695.2216.

1,3,4,5,9,10,11,13-Octa-*O*-acetyl-2,6:8,12-dianhydro-7-fluoro-D-*lyxo*-D-*gulo*-D-*manno*-tridecitol 3.60.

The tetrol **3.54** (20 mg, 0.03 mmol) was subjected to hydrogenation condition as described in the synthesis of **3.56** to give crude fluoro disaccharide **3.58** (9 mg, 90%); amorphous solid; R_f = 0.29 (60% MeOH/ $CHCl_3$); ^{1}H NMR (500 MHz, D_2O) δ 3.70 (ddd, J = 1.1, 9.6, 28.8 Hz, 1H), 3.63-3.77 (m 8H), 3.90 (m, 2H), 3.95 (d, J = 3.1 Hz, 1H), 4.02 (t, J = 1.3 Hz, 1H), 4.37 (ddd, J = 1.4, 8.9, 16.8 Hz, 1H), 5.20 (dd, J = 8.9, 47.6 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) 61.5, 61.9, 66.5 (d, J = 5.2 Hz), 67.4, 68.5 (d, J = 7.6 Hz), 69.4, 71.6, 74.4, 74.7, 75.5, 77.8 (d, J = 20.1 Hz), 78.0 (d, J = 18.1 Hz), 85.8 (d, J =

179.1 Hz); ESIHRMS calcd for $C_{13}H_{24}O_{10}F$ (M + H) 359.1354, found 359.1367.

Treatment of the fluoro C-glycoside **3.58** (9 mg, 0.03 mmol) following the acetylation procedure as described in the synthesis of **3.59**, yielded the fluoro peracetate **3.60** (13 mg, 52%): colorless oil; R_f = 0.21 (60% Ethyl acetate/petroleum ether); ^{1}H NMR (500 MHz, C_6D_6) δ 1.61, 1.64, 1.67 (×2), 1.71, 1.72, 1.76 (all s, 3H ea), 3.27 (t, J = 6.5 Hz, 1H, H-5), 3.66 (m, 1H, H-1), 4.10 (m, 2H, H-6a, 7'b), 4.22 (m, 2H, H-6b, 6'), 4.49 (q, J = 5.9 Hz, 1H, H-7'a), 4.61 (dt, J = 3.5, 31.5 Hz, 1H, H-2'), 5.01 (ddd, J = 2.7, 5.5, 47.4 Hz, 1H, H-1'), 5.08 (dd, J = 3.3, 10.0 Hz, 1H, H-3), 5.45 (d, J = 3.3 Hz, 1H, H-4), 5.62 (t, J = 10.0 Hz, 1H, H-2), 5.69 (t, J = 8.8 Hz, 1H, H-5'), 5.78 (dd, J = 3.5, 8.8 Hz, 1H, H-4'), 6.02 (t, J = 3.0 Hz, 1H, H-3'); ^{13}C-NMR (125 MHz, C_6D_6) δ 20.8 (×3), 20.9 (×2), 21.0 (×2), 21.1, 61.4, 62.8, 66.4, 67.1 (d, J = 3.7 Hz), 67.4, 68.1, 69.9 (d, J = 6.0 Hz), 71.9, 73.5 (d, J = 1.8 Hz), 74.4 (d, J = 19.2 Hz), 74.6, 76.1 (d, J = 24.1 Hz), 94.8 (d, J = 181.4 Hz), 169.9, 170.0, 170.1 (×2), 170.2, 170.3, 170.6, 170.9; ESIHRMS calcd for $C_{29}H_{39}O_{18}FNa$ (M + Na) 717.2018, found 717.2050.

2,6:8,12-dianhydro-7-deoxy-7,7-difluoro-D-*threo*-L-*gulo*-D-*manno*-tridecitol 3.61.

The pentol **3.56** (12.0 mg, 0.02 mmol) was then subjected to hydronolysis condition as above. This gave difluoro C-glycoside **3.61** (7.5 mg, 93%) as a colorless oil; R_f = 0.32 (50% MeOH/CH_3Cl); ^{1}H NMR (500 MHz, D_2O) δ 3.76-3.93 (m, 8H), 3.96 (dd, 2.1, 12.2 Hz, 1H), 4.00 (dd, J = 3.6, 9.0 Hz, 1H), 4.05 (t, J = 9.5 Hz, 1H), 4.07 (d, J = 3.2 Hz, 1H), 4.41 (t, J= 2.2 Hz, 1H), 4.59 (ddd, J = 1.9, 14.6, 20.3 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) δ 61.2, 61.4, 66.3, 66.7, 66.9, 68.8, 71.1 (d, J = 2.6 Hz), 73.9, 76.3 (dd, J =

22.9, 26.6 Hz), 76.9 (t, J = 22.9 Hz), 77.9, 79.3, 121.6 (dd, J = 251.1, 253.9 Hz); ESIHRMS calcd for $C_{13}H_{22}O_{10}F_2Na$ $[M + Na]^+$ 399.1073, found 399.1070.

(1,3,4,5-tetra-*O*-benzyl-2,6:8,12-dianhydro-7-fluoro-D-*lyxo*-D-*galacto*-D-*manno*-tridecit-10-yloxy)-ethanoic acid sodium salt 3.62.

A mixture of triol **3.51** (100 mg, 0.10 mmol), dibutyltin oxide (39 mg, 0.16 mmol), and anhydrous toluene (20 mL) was heated at reflux in a Dean-Stark apparatus for 1 hour. The solution was then evaporated *in vacuo*, and the residue was dissolved in dry toluene (3 mL). n-Bu_4NI (58 mg, 0.16 mmol) and methyl 2-bromoacetate (0.20 mL, 1.08 mmol) were added and the solution heated at reflux for 1 hour, at which time the volatiles were removed. Partial purification of the crude material by FCC provided a mixture (75 mg) of three components; Rf's 0.18, 0.32 and 0.51 (30 % EtOAc/petroleum ether).

The above mixture (209 mg) was treated with a 1/1 mixture of aqueous 3N NaOH/ethanol (2 mL). After 4 hours, the solvent was removed under reduced pressure, and the residue was purified by chromatography to give **3.62** (106 mg, 75% from triol **3.51**): clear oil; R_f = 0.26 (30% MeOH/ $CHCl_3$); ^{1}H NMR (500 MHz, CD_3OD) δ 3.05 (ddd, J = 1.8, 9.2, 26.3 Hz, 1H), 3.37 (dd, J = 2.7, 9.4 Hz, 1H), 3.42 (t, J = 5.9 Hz, 1H), 3.68-3.78 (m 5H), 3.94 (J = 7.8 Hz, 1H), 3.99 (t, J = 9.4 Hz, 1H), 4.10 (d, J = 2.8 Hz, 1H), 4.32 (ABq, J = 16.8 Hz, Δδ = 0.05 ppm, 1H), 4.45-4.76 (m, 9H), 5.10 (ddd, J = 2.0, 7.2, 47.2 Hz, 1H), 7.23-7.35 (m, 18H), 7.42 (m, 2H); ^{13}C NMR (125 MHz, CD_3OD) 62.8, 67.0, 68.6, 70.1, 73.0, 73.6, 74.3, 74.7 (d, J = 2.0 Hz), 75.3, 75.5, 76.0, 79.4, 79.6, (d, J =

18.2 Hz), 80.2, 85.4, 87.2 (d, J = 176.8 Hz), 128.8-130.2 (several lines), 139.6, 139.8 (×2), 139.9, 176.3; ESIHRMS calcd for $C_{43}H_{50}O_{12}F$ (M + H) 777.3287, found 777.3292.

(1,3,4,5-tetra-*O*-benzyl-2,6:8,12-dianhydro-7-fluoro-D-*lyxo*-D-*gulo*-D-*manno*-tridecit-10-yloxy)-ethanoic acid sodium salt 3.63.

The triol **3.52** (152 mg, 0.16 mmol) was subjected to similar alkylation and saponification conditions as described for **3.62** to give **3.63**. (78 mg, 61% from triol **3.52**); clear oil; R_f = 0.22 (30% MeOH/ $CHCl_3$); ^{1}H NMR (500 MHz, CD_3OD) δ 3.45 (t, J = 5.9 Hz, 1H), 3.53-3.73 (m, 7H), 3.85 (m, 2H), 3.94 (m 1H), 4.13 (m, 2H), 4.24 (br s, 1H), 4.41-4.58 (m, 6H), 4.59 (ddd, J = 1.7, 5.9, 17.7 Hz, 1H), 4.66 (B of ABq, J = 11.9 Hz, Δδ = 0.20 ppm, 1H), 4.73 (B of ABq, J = 11.1 Hz, Δδ = 0.30 ppm, 1H), 5.04 (ddd, J = 1.1, 5.8, 46.6 Hz, 1H), 7.11 (m, 2H), 7.17-7.27 (m, 16H), 7.37 (m, 2H); ^{13}C NMR (125 MHz, CD_3OD) 62.9, 67.6, 67.7, 69.2, 70.7, 72.8, 73.2, 74.1 (d, J = 22.6 Hz), 74.5, 75.4, 75.8 (d, J = 4.5 Hz), 76.5, 80.3, 81.3, 81.4 (d, J = 21.3 Hz), 86.1, 93.2 (d, J = 178.9 Hz), 128.7-130.1 (several lines), 139.6, 139.8, 139.9, 140.0, 177.3; ESIHRMS calcd for $C_{43}H_{50}O_{12}F$ (M + H) 777.3287, found 777.3293.

(3,4,5-Tri-*O*-benzyl-2,6:8,12-dianhydro-7-deoxy-7,7-difluoro-D-*threo*-L-*gulo*-D-*manno*-tridecit-10-yloxy)-ethanoate methyl ester 3.64.

The triol **3.55** (50.0 mg, 0.05 mmol) was subjected to alkylation procedure as that of triol **3.62**. This afforded a mixture of two lactones (26.9 mg, 66% based on recovered **3.55**). To the above mixture of lactones in THF (3 mL) was added tetrabutyl ammonium fluoride (0.09 mL, 0.09 mmol, 1M solution in THF) and stirred for 2 hours. The solvent

was then evaporated and the residue taken up in concentrated methanolic HCl (0.5 mL) and stirred for 30 min at pH 2.0. Removal of the volatiles under reduced pressure and FCC of the residue provided the methanol ester 27 (10.0 mg, 40% based on recovered **3.55**): colorless oil; R_f = 0.59 (10% MeOH/CH_3Cl); ^{1}H NMR (500 MHz, CD_3OD) δ 3.45 (dd, J = 3.2, 9.3 Hz, 1H), 3.46 (t, J = 6.1 Hz, 1H), 3.68 (dd, J = 2.6, 12.1 Hz, 1H), 3.73-.82 (m, 5H), 3.85 (s, 3H), 3.92 (m, 1H), 3.97 (dd, J = 3.2, 7.3 Hz, 1H), 4.16 (d, J = 2.4 Hz, 1H), 4.20 (t, J = 9.3 Hz, 1H), 4.25 (t, J = 3.9 Hz, 1H), 4.45 (ABq, J = 16.8 Hz, Δδ = 0.04 ppm, 2H), 4.58-4.79 (m, 7H), 7.34-7.47 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 53.2, 62.4, 62.6, 67.6, 67.8, 68.5, 73.6 (two signals), 74.1, 74.9, 75.8, 79.2 (apparent t, J = 35.2 Hz), 79.4, 80.6, 85.9, 128.9-128.6 (several lines), 139.6, 139.8, 139.9, 174.2; ESIHRMS calcd for $C_{37}H_{48}O_{12}F_2N$ $[M + NH_4]^+$ 736.3139, found 736.31840.

(2,6:8,12-dianhydro-7-fluoro-D-*lyxo*-D-*galacto*-D-*manno*-tridecit-10-yloxy)-ethanoic acid sodium salt 3.5.

The sodium salt **3.62** (106 mg, 0.13 mmol), 20% Pd $(OH)_2$ (300 mg) and methanol (20 mL) were stirred under an atmosphere of hydrogen (balloon), for 24 hours. The reaction mixture was purged with argon and filtered through a bed of Celite. The filtrate was then concentrated and the residue taken up into methanol (10 mL) and 3N NaOH (1 mL). This was stirred for 2 hours and the solvent removed. This gave the crude compound **3.5** (38 mg, 66%) as a white solid. In order to obtain pure samples for bioassay, this crude was repeatedly columned using Sephadex LH-20 (water) to provide an amorphous solid (10.2 mg) after lyphillization. $[\alpha]_D$ + 40.8 (c 0.25 H_2O); R_f = 0.45 (70% MeOH/$CHCl_3$); ^{1}H NMR (500 MHz, D_2O) δ 3.34 (ddd, J = 1.4, 10.0, 29.1 Hz, 1H,

H-1), 3.41 (dd, J = 3.3, 9.4 Hz, 1H, H-3), 3.50-3.72 (m, 7H, H-4', 5', 6', 7'a, 5, 6a, 6b), 3.77 (apparent, dd, J = 1.6, 12.3 Hz, 1H, H-7'b), 3.88 (t, J = 9.6 Hz, 1H, H-2), 3.92 (m, 1H, H-3'), 3.98 (m, 2H, O=C-$\underline{CH_2}$-O), 4.01 (d, J = 2.9 Hz, 1H, H-4), 4.28 (ddd, J = 1.4, 8.8, 16.9 Hz, 1H, H-2'), 5.08 (ddd, J = 1.4, 8.5, 47.5 Hz, 1H, H-1'); ^{13}C NMR (125 MHz, D_2O) δ 61.5, 62.0, 65.5 (d, J = 6.4 Hz), 66.3, 67.4, 68.6 (J = 7.8 Hz), 68.7, 71.5, 75.5, 77.8 (d, J = 19.7 Hz), 78.1 (d, J = 17.4 Hz), 79.6, 83.6, 85.8 (d, J = 178.7 Hz), 179.1; ESIHRMS calcd for $C_{15}H_{25}O_{12}FNa$ (M + Na) 439.1228, found 439.1238.

(2,6:8,12-dianhydro-7-fluoro-D-*lyxo*-D-*gulo*-D-*manno*-tridecit-10-yloxy)-ethanoic acid sodium salt 3.6:

The sodium salt **3.63** was subjected to similar hydrogenation and saponification conditions as described for the synthesis of **3.5** to give crude product **3.6** (30 mg, 78%). Repeated sephadex LH-20 (water) and reverse phase chromatography provided **3.6** as an amorphous solid after lyphillization. $[\alpha]_D$ + 14.4 (c 0.25 H_2O); R_f = 0.43 (70% MeOH/$CHCl_3$); ^{1}H NMR (500 MHz, D_2O) δ 3.37 (dd, J = 3.0, 9.4 Hz, 1H, H-3), 3.50-3.77 (m, 7H, H-1, 5, 6a, 6b, 5', 6', 7'a), 3.76 (d, J = 12.5 Hz, 1H, H-7'b), 3.79 (dd, J = 3.3, 9.2 Hz, 1H, H-4'), 3.84 (t, J = 9.7 Hz, 1H, H-2), 3.97 (m, 1H, O=C-$\underline{CH_2}$-O), 4.01 (d, J = 2.7 Hz, 1H, H-4), 4.16 (br s, 1H, H-3'), 4.29 (dd, J =7.2, 15.4 Hz, 1H, H-2'), 5.04 (dd, J = 7.1, 46.6 Hz, 1H, H-1'); ^{13}C NMR (125 MHz, D_2O) δ 61.8, 61.9, 66.2, 66.4 (d, J = 8.5 Hz), 67.2, 68.8, 69.1, 71.4, 76.2 (d, J = 23.6 Hz), 76.8, 78.9 (d, J = 20.4 Hz), 79.1, 84.0, 91.7 (d, J = 177.1 Hz), 179.1; ESIHRMS calcd for $C_{15}H_{25}O_{12}FNa$ (M + Na) 439.1228, found 439.1235.

(2,6:8,12-dianhydro-7-deoxy-7,7-difluoro-D-*threo*-L-*gulo*-D-*manno*-tridecit-10-yloxy)-ethanoic sodium salt 3.7.

The difluoro C-glycoside **3.64** (4.1 mg, 5.71 μmol) was subjected to the hydrogenation and saponification conditions as described for the synthesis of **3.5** to give crude product **3.7** (1.6 mg, 61%): an amorphous solid; ^{1}H NMR (500 MHz, D_2O) δ 3.62 (dd, J = 3.1, 9.4 Hz, 1H), 3.77-3.98 (m, 8H), 4.00 (dd, J = 3.4, 9.0 Hz, 1H), 4.14-4.19 (m, 4H), 4.42 (brd s, 1H), 4.61 (t, J = 17.9 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) δ 61.2, 61.3, 65.2, 65.5, 66.5, 66.8, 68.5, 70.9, 76.2 (dd, J = 14.6, 21.9 Hz), 76.8 (t, J = 23.2 Hz), 78.9, 83.1, 121.4 (dd, J = 251.1, 254.8 Hz), 178.5; ESIHRMS calcd for $C_{15}H_{24}O_{12}F_2Na$ $[M + H]^+$ 457.1128, found 457.1125.

Chapter 4

Conformational and biological evaluation of sLe^x mimetics.

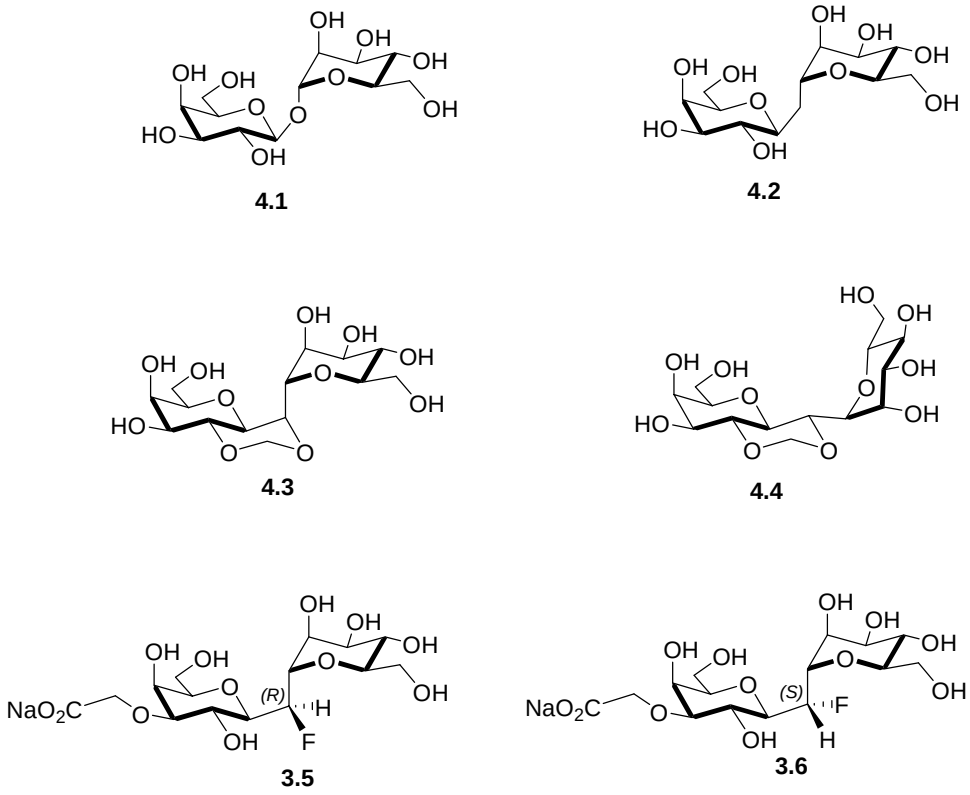
4.1 Introduction.

Carbohydrate-protein interactions are involved in a variety of important biological processes,[46,47] including attachment of pathogens to host cells, inflammation, metastasis, and immunological defense mechanisms.[48] *C*-glycosides (where the *exo* glycosidic oxygen in the natural *O*-glycosides is replaced with a methylene) are attractive mimetic of *O*-glycosides because of their enzymatic and chemical stability.[48] The substitution of the acetal oxygen atoms by methylene groups also increases the flexibility and the number of low energy conformations with respect to the inter-residue linkages. This conformational behaviour has been explained on the basis of the *exo*-anomeric effect.[48] The smaller energy difference between low energy conformation of *C*-glycoside (compare to *O*-glycoside) may lead to increase binding affinity of *C*-glycoside ligands if there is an enthalpic gain that exceeds the entropic penalty.

Previously the Mootoo laboratory in collaboration with Professor Jiménez-Barbero used a combination of NMR spectroscopy, molecular mechanics (MM) and molecular dynamics (MD) calculations to investigated the conformational properties of **1.4** and **1.5**, and their analogs without the glycolate residue at position 3 of the galactose segment, **4.1** and **4.2** (Figure 4.1).[49, 50] These studies indicated that the presence or absence of glycolate substituent did not have a significant effect on the conformational behavior with respect to the intersaccharide torsions. For simplicity in ^{1}H NMR signal

resolution a similar study on the restrained *C*-glycosides **4.3/4.4** [51], and the fluoro C-glycosides **3.5** and **3.6** was undertaken.

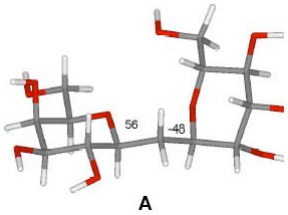
Figure 4.1: Compounds for conformational analysis



4.9. Preliminary results for 4.1 and 4.2

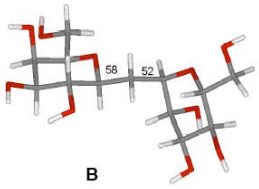
C-glycoside **4.2** in water populates five different conformational families defined by the glyconic torsions (Φgal,Φman): **A** (56, -48; 30%), **B** (58, 52; 42%), **C** (-57, -67; 12%), **D** (-171, 57; 10%) and **E** (176, -45; 6%) (Figure 4.2). In comparison, O-glycoside **4.1** exists in greater than 93% in conformational family **A** with very minor populations of conformational families **B**, **D** and **E**. Structures and exact dihedrals are shown for C-glycoside **4.2**.

Figure 4.2: Conformations for **4.1** and **4.2**



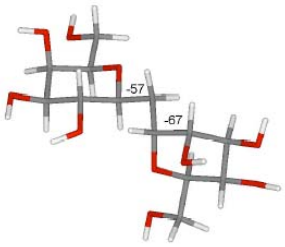
A

4.1 (>93%); **4.2** (30%)



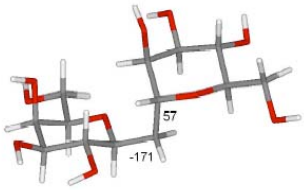
B

4.1 (4%); **4.2** (42%)



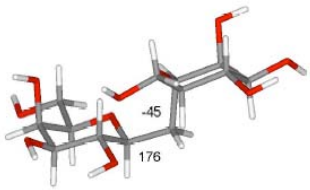
C

4.1 (not obs.); **4.2** (12%)



D

4.1 (<1%); **4.2** (10%)



E

4.1 (2%); **4.2** (6%)

Structures and exact dihedrals are shown for C-glycoside **4.2**. The % populations of the conformational families for **4.1** and **4.2** are given in parentheses.

The torsion angles ΦGal and ΦMan is defined as H1Gal-C1Gal-X-C1Man and H1Man-C1Man-X-C1Gal for **4.2.** Where the Φ shows a +60° value adopts an exo-orientation in β-glycosides, Φ value of -60° value adopts an exo-orientation in α-glycoside and Φ value of ±180° value adopts an anti-type arrangement. These

conformers can also be depicted as (**A**) exo-Φ_{Gal}/exo-Φ_{Man}, (**B**) exo-Φ_{Gal}/non-exo-Φ_{Man}, (**C**) non-exo-Φ_{Gal}/exo–Φ_{Man}, (**D**) anti-Φ_{Gal}/non-exo-Φ_{Man}, (**E**) anti-Φ_{Gal}/exo-Φ_{Man}.

Results and discussion

4.3 Conformational analysis of restrained *C*-glycosides 4.3 and 4.4

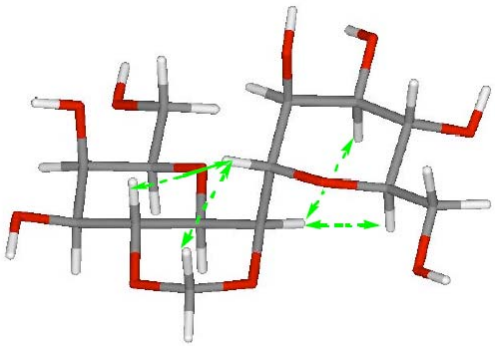
As for **4.1** and **4.2**, the conformationally restrained analogs **4.3** and **4.4**, molecular mechanics and dynamics calculations were performed using the MM3* force field,[52] as implemented in MACROMODEL 7.1.[53] However, unlike the case of the more flexible C-glycoside **4.2**, for which a time-averaged restrained MD protocol was used, no restraints were used for modeling the conformational behavior of **4.3** and **4.4**. Clearly, the presence of the cyclic acetal in these latter structures severely restricted the conformational mobility around the Gal pseudoglycosidic linkage and only the torsional degree of freedom around the Man linkage remained. This made the problem highly simplified, and the conformers around ΦMan were generated and optimized with MM3* with ΦGal left free during the minimization process. The GB/SA solvation model for water was used.[54] The probability distribution was calculated from the energy values according to a Boltzmann function at 300 K. Three low energy minima were obtained for **4.3** (Figure 4.3, Table 4.1). The lowest energy and one of the high-energy conformations (Φgal, Φman: 175, 51 and 151, -59), corresponded to conformational families **D** and **E** that were previously observed for **4.1** and **4.2**. Also, the highest energy conformation, **F** (Φgal,Φman: 168, 140) was detected. The latter was not observed for **4.1** and **4.2**. Intersaccharide coupling constants for these three conformations were obtained from the Karplus-Altona relationship[55] and compared with the values measured from the ^{1}H NMR

(Table 4.1). Accordingly **4.3** existed predominantly in conformation **D** (i.e. ca 85%), with minor populations of **E** and **F** (i.e. 10 and 5% respectively). Thus the relative population distribution was in qualitative agreement with the result predicted by MM3* calculations. The observation of strong key NOE contacts ($H_{intersac}$- $H3_{man}$, $H_{intersac}$- $H5_{man}$, OCH_2O_{ax}- $H1_{man}$ and $H2_{gal}$ -$H1_{man}$) is also in agreement with a high population of conformation **D**.

Table 4.1: MM3* and ^{1}H NMR data for **4.3**

Conformation	**D**	**C**	**F**	**Exp**
ΔE (kJ/mol)	0	28	32	
Φ Gal (^{o})	175	151	168	
Φ Man (^{o})	51	-59	140	
J $H1_{gal}$-$H_{intersac}$ (Hz)	5.0	7.0	5.8	5.9
J $H1_{man}$-$H_{intersac}$ (Hz)	10.2	1.1	0.5	8.8
% population	85	10	5	

Figure 4.3: Conformation **D** for **4.3**



key NOE's indicated by double headed arrows

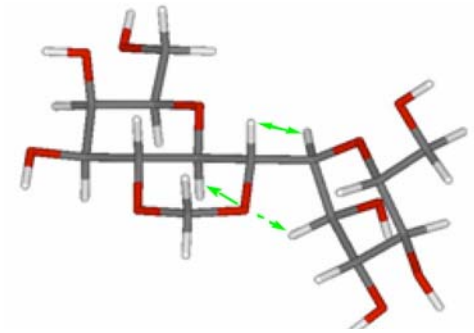
The MM3* calculations for **4.4** indicated low and high energy minima corresponding to conformational families **A** and **B** respectively (Figure 4.4). Analysis of the experimental J values as before indicated that **4.4** existed as a 20:80 ratio of **A**:**B**

(Table 4.2). Thus, in the case of **4.4**, the presence of conformation **A** was overestimated by the MM3*calculations. Observed strong key NOE contacts ($H_{intersac}$- $H1_{man}$ and $H1_{gal}$ - $H2_{man}$) were also in agreement with a major presence of conformation **B**.

Table 4.2: MM3* and ^{1}H NMR data for **4.4**

Conformation	**A**	**B**	**Exp**
ΔE (kJ/mol)	0.0	6.0	
Φ Gal (^{o})	54.7	58.2	
Φ Man (^{o})	-50.8	42.0	
J $H1_{gal}$-$H_{intersac}$ (Hz)	9.9	9.9	10.0
J $H1_{man}$-$H_{intesac}$ (Hz)	9.8	0.9	3.0
% population (soln.)	20	80	

Figure 4.4: Conformation **B** for **4.4**



key NOE's indicated by double headed arrows

4.4 Conformational analysis and epimer identification of fluoro-*C*-glycosides 3.5 and 3.6

At first, the configuration at the fluorinated carbon in **3.5** and **3.6** was not known. Again using the MM3* force field, the potential energy surfaces of both isomers were calculated by our collaborator Jesus Jiménez-Barbero. These calculations enabled the prediction of the major low energy conformers of **3.5** and **3.6** about the glycosidic torsion

angles Φ_{Gal} and Φ_{Man} (Table 4.3). These results showed that the compounds **3.5** and **3.6** had distinct conformational behavior depending on their stereochemical nature and five low-energy conformers with appreciable populations (Figure 4.4) were calculated for both compounds.

Table 4.3: Comparison between the inter-residue proton–proton distances deduced by MM3* calculations for the **A–E** conformers of 3.5-3.6 (approximated Φ_{Gal} and Φ_{Man} angles between brackets) and their observed NOEs (%, distance Å)

Conformer Φ/Ψ	**(3.5) NOE exp.**	**(3.6) NOE exp.**	**A 50/−50 (R/S)**	**B 60/60 (R/S)**	**C −70/−70 (R/S)**	**D −170/60 (R/S)**	**E 180/-70 (R/S)**
ΔE **(R)**	—	—	0.97	0.0	4.17	5.74	10.54
ΔE **(S)**	—	—	0.0	3.57	0.54	5.14	2.72
1G-1M	—	—	**2.47**	3.15	3.39	3.85	3.83
1G-2M	S (13) /2.30	—	4.35	**2.28**	4.78	3.96	4.77
1G-3M	Overlap	Overlap	5.16	3.45	4.40	4.28	4.89
1G-5M	Overlap	Overlap	4.28	4.54	**2.49**	4.59	4.13
CHF-2G	M (3)/3.16	M (3) /3.07	3.18/**2.57**	3.14/3.24	**2.53**/4.06	3.81/3.24	3.85/3.18
CHF-2M	M (2)/3.19	M (3) /3.07	2.49/3.27	3.17/3.13	2.69/3.02	3.37/3.90	2.45/2.90
CHF-3M	S (13) /2.32	MS (7)/2.66	3.36/2.49	**2.44**/2.36	3.73/2.42	**2.51**/4.05	3.43/2.39
CHF-5M	Overlap	S (11)/2.47	4.02/2.32	**2.34**/2.20	4.06/2.39	**2.11**/2.94	3.86/2.51
1M-2G	VW (0.5)/4.00	M (4) /3.03	4.71	4.35	3.00	**2.52**	3.28
1M-3G	—	—	5.13	5.42	4.95	5.10	5.53
1M-5G	—	—	4.14	3.98	5.48	5.44	4.75
2M-2G	—	—	5.34	5.02	4.82	**2.73**	5.11

According to the MM3* calculations, in the *S* isomer the exo-Φ_{Gal}/exo-Φ_{Man} conformer **A** is the major one (40%), followed by the non-*exo*-Φ_{Gal}/*exo*-Φ_{Man} conformer **C** (28%), *anti*-Φ_{Gal}/*exo*-Φ_{Man} **E** (15%) and **B** (12%). For the R isomer the same energy minima was shown, although with different relative steric energies and populations. In this case the major conformer was **B** (65%) followed by the double exo conformer **A** (26%). In this isomer, *anti*-conformers were more destabilized.

A qualitative analysis of **3.5** and **3.6** using NMR experiments, MM3* and dynamics calculations, were done. Also analysis of the measured interglycosidic *J* values between the methylene proton or the fluorine atom and the H-1Gal and H-1Man protons at the glycosidic positions were carried out. For the theoretical values of the $J_{H,F}$ constants the Karplus-type equation developed by Chattopadhyaya was used.[55]

Table 4.4: Expected *J* values (Hz) for conformations **A-E** for the basic conformations around Φ and Ψ angles for **3.5** and **3.6**, deduced by applying the generalized Karplus[57] equation proposed by Altona to the geometries provided by MM3* molecular mechanics calculations and Karplus type equation for the $J_{H,F}$ constants.[56]

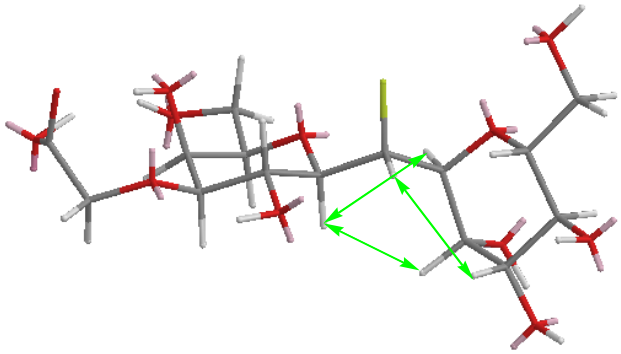
Pair	**Conformer (*J*, Hz)**					**Exp. (*J*, Hz)**	
	A	***B***	**C**	***D***	***E***	**3.5**	**3.6**
R *epimer*							
G-1′H/CHF	-0.3	0.4	7.9	4.7	4.2	1.4	
G-1′H/F	36.2	34.2	15.1	12.2	16.2	29.1	overlap
M-1H/CHF	-0.4	9.7	0.8	8.0	0.4	8.8	7.2
M-1H/F	35.9	11.0	30.1	14.5	36.1	16.9	15.4
S *epimer*							
G-1′H/CHF	9.5	9.5	0.8	2.9	3.3	1.4	
G-1′H/F	11.0	8.3	33.5	14.5	14.5	29.1	overlap
M-1H/CHF	9.5	0.8	8.7	0.8	9.5	8.8	7.2
M-1H/F	11.0	32.1	14.5	33.5	15.0	16.9	15.4

From the calculated coupling constant data for the different conformations, compound **3.5** might be predominantly the conformer **B** of epimer R or **C**/**E** of epimer S (Table 4.4). The presence of a strong 1G-2M NOE which is exclusive for conformer B suggested that **3.5** was the epimer R. Therefore for **3.5**, the experimental J values suggest 90% of the *exo*-Gal/non-*exo*-Man conformer **B**, and less than 10% of the double *exo*-anomeric conformer **A.** Thus, the population of conformer **A** of epimer R seemed to be overestimated by the MM3* simulations (from 26% to less than 10%). A strong NOE observed between CHF and 3M indicated that conformer **B** was a significant conformation in solution and also supports the population distribution (Figure 4.5).

Table 4.5: MM3* and ^{1}H NMR data for *R epimer* **3.5.**

Conformation	***A***	***B***	**Exp.**
ΔE (kJ/mol)	0.97	0	
J G-1′H/CHF (Hz)	-0.3	0.4	1.4
J G-1′H/F (Hz)	36.2	34.2	29.1
J M-1H/CHF(Hz)	-0.4	9.7	8.8
J M-1H/F (Hz)	35.9	11.0	16.9
1G-1M (NOE, dist. Å)	**2.47**	3.15	-
1G-2M (NOE, dist. Å)	4.35	**2.28**	(s, 2.30)
CHF-3M (NOE, dist. Å)	3.3	**2.44**	(s, 2.32)
% population (soln.)	10	90	-

Figure 4.5: Conformation B for **3.5**



key NOE's indicated by doubly headed arrows

The values of the coupling constants for compound **3.6** were in the same range of that of **3.5**, therefore the same possibility; **B**-*R* epimer or **C**/**E**-*S* epimer. The strong 1G-2M NOE, which is exclusive for **B**-*R* epimer was not observed in **3.6** (where as it is for **3.5**). Thus **C**/**E**-*S* epimer were considered more likely possibilities. The presence of strong CHF-3M and CHF-5M NOE's are consistent with both conformers **C** and **E**, but an estimation of the ratio of each conformer was impossible because of the experimental J values were similar to the to that predicted for **C** and **E** (Table 4.6).

Table 4.6: MM3* and ^{1}H NMR data for S e*pimer* **3.6.**

Conformation	***C***	***E***	**Exp.**
ΔE (kJ/mol)	0.54	2.72	
J G-1′H/CHF (Hz)	0.8	3.3	
J G-1′H/F (Hz)	33.5	14.5	overlap
J M-1H/CHF(Hz)	8.7	9.5	7.2
J M-1H/F (Hz)	14.5	15.0	15.4
1G-2M (NOE, dist. Å)	3.39	3.85	-
CHF-3M (NOE, dist. Å)	2.42	2.39	(MS, 2.66)
CHF-5M (NOE, dist. Å)	2.39	2.51	(S, 2.47)
1M-2G (NOE, dist. Å)	3.00	3.28	(M, 3.03)

4.5 P-Selectin binding data for sLe^x mimetics 1.4, 1.5, 2.3, 2.4, 3.5 and 3.6.

The competitive binding of O-disaccharide **1.4** and C-disaccharides **1.5, 2.3, 2.4, 3.5** and **3.6** to a soluble truncated form of human P-selectin was next evaluated in a Biacore assay with an immobilized monomeric truncated form of human PSGL-1 as the reference ligand.[17] The data revealed that at 12 mM, **1.4**, **1.5**, **2.3**, **2.4**, **3.5** and **3.6** showed 48, 26, 25, 31, 39, and 26% inhibition respectively (Table 4.7). The IC_{50} of sLe^x under these conditions was previously found to be 15 mM.[13] It should be noted that our result for O-disaccharide **1.4** is in disagreement with an earlier study in which the binding of **1.4** to P-selectin was found to be 40 times greater than sLe^x.[13] This inconsistency could be due to the fact that the latter investigation used a cell-based assay,[57] but this explanation is not completely satisfying because the IC_{50}'s for sLe^x in both the Biacore and cell-based measurement were similar (ca 8 vs. 15 mM respectively).

Table 4.7: P-selectin Biacore inhibition assay results for sLe^x mimetics.

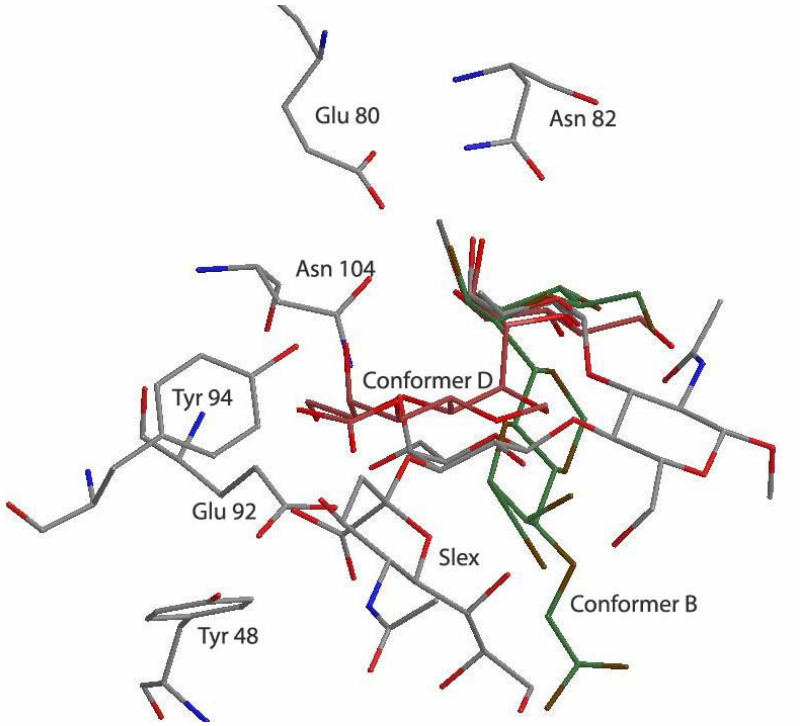
Samples	**Concentration** /mM	**Avg. % inhib**	**sd**
Glycyrrhizin **(control)**	1	**52**	0.99
O-Glycoside **1.4**	12	48	0.53
	6	33	0.52
C-Glycoside **1.5**	12	26	0.65
	6	12	0.63
Rigid C-glycoside **2.3**	12	25	0.57
	6	10	0.60
Rigid C-glycoside **2.4**	12	31	0.46
	6	13	0.50
R-Fluoro-*C*-glycoside **3.5**	12	39	0.41
	6	19	0.56
S-Fluoro-*C*-glycoside **3.6**	12	26	0.36
	6	13	0.45
Glycyrrhizin **(control)**	1	**51**	0.88

4.6 Discussion

It was anticipated that because of the different relative spatial positioning of the two sugar residues in **1.4**, **1.5**, **2.3**, **2.4**, **3.5** and **3.6**, these analogs would have very different activities. In so far as % inhibition could be used as a measure of binding, this information could provide insight on the optimal conformation requirements for binding of the disaccharide framework. However, the similarity of activities of these mimetics of sLe^x made any such conclusions somewhat speculative. Nevertheless, analysis of possible bound conformations in terms of the sLe^x-P-selectin recognition model may be useful for the design of more active P-selectin ligands (Figure 1.4). In this regard, the more conformationally rigid analogs **2.3** and **2.4** had more limited modes of binding and were an appropriate starting point. Accordingly, the galactose and mannose residues of **2.3** and **2.4** can individually, but not simultaneously mimic the interaction of the galactose and fucose residues in sLe^x, respectively (Figure 4.5). The selection of which of the two subunits of the disaccharide framework to use as a mimic of the analogous segment of sLe^x, was guided by the crystal structure of the sLe^x-P-selectin complex and existing structure activity data which suggested that the fucose residue accounted for the major part of the overall binding energy of sLe^x.[4,58,59] Therefore, it was speculated that the binding of the mannose segment of these disaccharide frameworks was conserved, and closely mimics that of the fucose in sLe^x (i.e. the 2-, 3- and 4- OH of the mannose residue map to the 4-, 3- and 2- OH of fucose). In the case of the restrained mimetics **2.3** and **2.4** this meant that individual galactose substituents must occupy different spatial positions relative to the mannose segment, and would therefore interact differently with the receptor sites in the galactose binding domain of sLe^x. Inspection of the sLe^x-P

selectin complex indicated these to be Tyr48, Tyr94 and Glu92, which interacted with Neu-COO-, Gal-4-OH and Gal-6-OH of sLex.[59] The assumption that the mannose mimics the fucose of sLe^x, the conformational restraints on **2.3** and **2.4**, and the notion that the relative position of the carboxylate of neuraminic acid in sLe^x and the fucose is critical for binding,[4,60] point to conformations like **D** (Φgal, Φman; 180°, 60°) and **B** (Φgal,Φman; 60°, 60°) as possible bound orientations for **2.3** and **2.4** respectively (Figure 4.6). Considering the P-selectin sites in the vicinity of the galactose binding domain of sLe^x, conformations like **B** and **D** appeared to give the best fit to the receptor, relative to their rotamers with respect to the unrestrained Φman torsion.

Figure 4.6: Comparison of binding of sLe^x, and conformations **B** and **D** using Chem3D program.



Thus with a restrained Φgal of approximately 170°, a Φman of 60° in **2.3** gave a **D**-like conformation (Φgal, Φman; 170, 60), which positions the carboxylate oxygen in **2.3** close to the Tyr48 binding site for Neu-COO- in sLe^x. The respective COO-/OTyr48 distances for this conformation and that of bound sLe^x were 4.8 and 3.6 Å. In this **D**-like conformation Gal-6-O in **2.3**, is farther away from the carboxylate oxygen of Glu92, compared with Gal-6-O in sLe^x (3.5 vs. 2.5 Å), while the Gal-4-O/Tyr94-O distance is closer for **2.3** compared with sLe^x (2.5 vs 3.5 Å). For **2.4**, in which Φgal is restrained to 60°, a Φman of 60° leads to conformation **B** which places the carboxylate of the glycolate in very similar proximity to Tyr 48-O compared with the carboxylate in sLe^x (3.4 vs 3.6 A respectively). However, in conformation **B** the oxygens at position 4 and 6 of the galactose segment were at a much further distance from Tyr94-O and Glu92-COO- respectively, compared with the corresponding galactose positions in sLe^x, and apparently out of binding range (i.e. ca 7 Å for gal-4-O/Tyr94-O, ca 9 Å for gal-6-O/Glu92-COO-). Instead, Gal-6-O in conformation **B** was relatively close toTyr94-O (5.2 Å), and appeared more likely to interact with this residue. Therefore, to summarize, the most important points on the binding of **B** and **D** type frameworks were an essentially identical mode of binding of their mannose segments but differences in the receptor interactions in their galactose segments, i.e. **2.3** appeared capable of a relatively strong Gal-4-OH/Tyr94 and weak COO-/Tyr48 and Gal-6-OH/Glu92 interactions, whereas for **2.4** a strong COO-/Tyr48, and weak Gal-6-OH/Tyr94 appeared to be the case. Since unbound **2.3** and **2.4** favored conformations like **D** and **B** respectively, and therefore expected to incur relatively small reorganizational energetic costs on binding, their similar binding might be an indication that these galactose interactions are relatively

weak compared to the binding of the mannose segment. This situation is analogous to the apparent dominant binding of the fucose residue in sLe^x noted earlier. However, an alternative explanation is that the combined magnitude of the carboxylate and galactose interactions in **D** and **B** are similar. Analogs of **2.3** and **2.4** with appropriate deletions of alcohol groups may be useful in probing this issue.

If the active conformation for restrained glycosides **1.4** and **1.5** were considered in terms of conformers **B** and **D**, the O-glycoside; which was preorganized in conformation **A** (Φgal, Φman; ca 60^o, -60^o), was closer in enthalpy to conformation **B** than **D** and may prefer a **B**-type bound conformation. Interestingly, minor reduction in the dihedral angles for the idealized **B** conformation (Φgal, Φman; 60^o, 60^o), which would be energetically less demanding for **1.4** (compared with the more rigid framework **2.4**), allows for **B**-like conformations that have closer COO-/Tyr48 and Gal-6-O/Tyr94 contacts. Thus the larger enthalpy cost (compared to **2.4**), required for the O-glycoside **1.4** to adopt a **B** like conformation may be offset by a more intimate fit of **1.4** to the receptor. The larger entropy cost (relative to **2.4**) that the flexible C-glycoside **1.5** would incur on binding in a **B**-like conformation, may be compensated in a similar way. Thus, a **B**-like active conformation for **1.4** and **1.5** may also account for the similarity of their binding compared with **2.4** (and **2.3**).

In the case of the monofluoro-*C*-glycosides **3.5** and **3.6**, the binding affinity for P-selectin was also similar that of the natural *O*-glycoside **1.4** and its C-glycoside analogs **1.5**, **2.3** and **2.4**. This similarity may be an indication that all these analogs are not properly preorganized in an optimal conformation for binding and hence pay similar energetic penalties in order to do so. However, it should be noted that the *R*-fluoro-C-

glycoside **3.5** which existed predominantly (< 90%) in the **B** conformation (exo-Φ_{Gal}/non-exo-Φ_{Man}) was twice as active as the *S*-isomer **3.6** which does not posses any **B** conformers.

4.7 Summary

C-disaccharides with different conformational properties about the intersaccharide linker were synthesized and evaluated together with their parent O-disaccharide for binding to P-selectin. These analogs were found to have comparable activity to sLe^x. However, the small differences in their activity did not permit any clear conclusions on a favored bound conformation. Possible bound conformations were considered based on the torsional constraints of conformationally restrained analogs and the structure of the sLe^x-P-selectin complex. That such conformationally different analogs show similar activity as sLe^x, raises questions about the extent to which the substituents on the galactose residue of sLe^x contribute to binding. Studies with more finely tuned analogs of **2.3, 2.4, 3.5** and **3.6** could give a clearer understanding of this disaccharide framework. On a general note the C-glycosides used in this study represent conformational mimetics of O-glycosides that could find wider use as recognition probes.

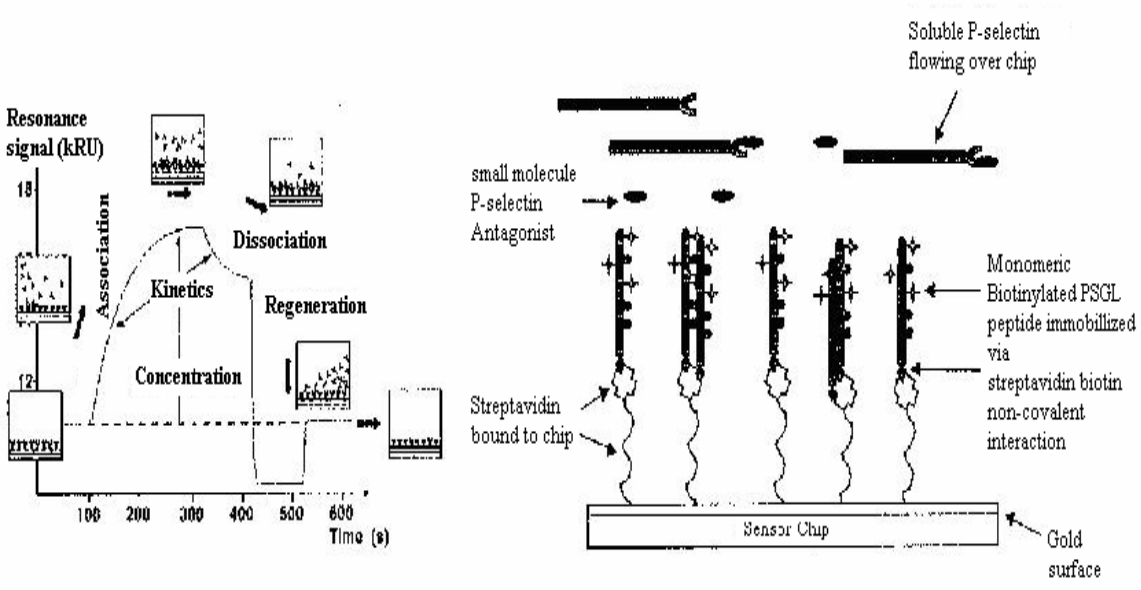
4.8 Experimental section

P-selectin-Biacore Inhibition Assay

P-selectin inhibition assays for **1.4**, **1.5**, **2.3**, **2.4, 3.5** and **3.6** were performed using a surface plasmon (Biacore) assay on a Biacore instrument, following the published

protocol.[17] Biotinylated 19ek (a purified monomeric truncated form of human PSGL-1) was immobilized on SA sensor chip 11 and a soluble recombinant truncated form of human P-selectin was delivered to the coated 19ek sensor chip at 30 μL/min and 25 ^{o}C in the presence and absence of the test ligands (Figure 4.7).

Figure 4.7: Characteristics of a sensogram, the readout of the Biacore instrument, inset picture shows events at the sensor chip surface.[4]



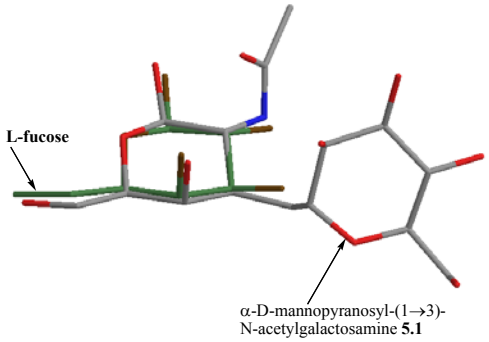
Chapter 5

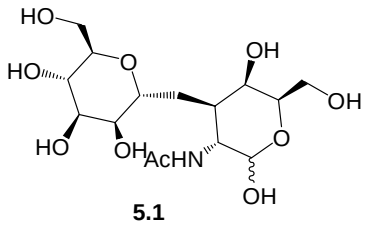
Synthesis of the C-glycoside of methyl α-*D*-altropyranosyl-(1→4)-α-*D*-glucopyranoside.

5.1 Introduction

The interest in disaccharide analogues as specific inhibitors of glycosidases and glycotransferases is based on the idea that they may act as bisubstrate-type transition state mimetics.[61, 62] C-disaccharides have attracted attention as hydrolytically stable glycomimetics because of their subtle conformational differences compared to O-glycosides.[63-66] These concepts inspired a recent investigation on the C-disaccharide of α-*D*-mannopyranosyl-(1→3)-N-acetylgalactosamine **5.1** (Figure 5.1).[61] Compound **5.1** was found to be a good bisubstrate inhibitor of human α-(1,3)-fucosyltransferase VI (which catalyzes the transfer of GDP-fucose to N-acetyllactosamine). Presumably, the α-L-fucopyranosyl and the D-GlcNAc binding sites of the enzyme are analogous to the respective binding regions for the C-α-*D*-mannopyranosyl and the D-GalNAc residues of **5.1**. Thus as illustrated in this example, disaccharide analogues[67-70] with "unnatural" glycone substituents are of interest. In this vein, we explored the use of our oxocarbenium ion cyclization methodology[14, 51, 71] for the synthesis of methyl C-α-*D*-altropyranosides.

Figure 5.1: A Chem 3D overlay for the N-acetyl galactosamine moiety of the α-(1,3)-fucosyltransferase VI inhibitor **5.1** with L-fucose.

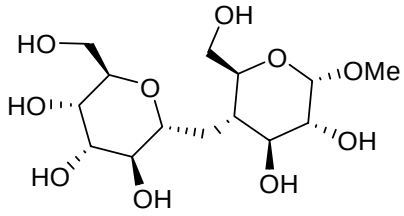




5.1

Accordingly, the C-glycoside of methyl-α-D-altropyranosyl-(1→4)-α-*D*-glucopyranoside **5.2** was targeted (Figure 5.2). This synthesis may also be significant to the synthesis of the naturally occurring class of aryl-α-C-altroside, the altromycins.[72, 73]

Figure 5.2: C-glycoside **5.2**



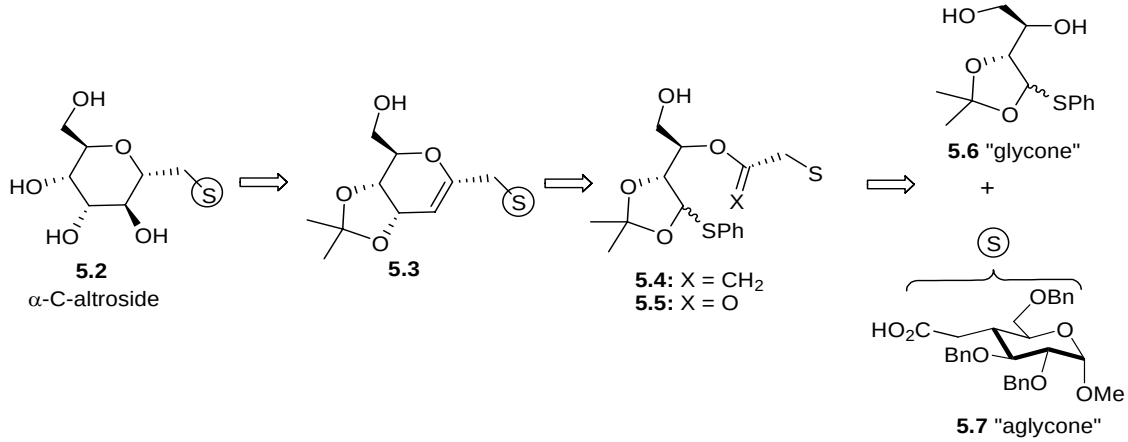
5.2

Results and discussion

5.2 Retrosynthesis

The synthesis of compound **5.2** requires a glycone segment **5.6**, and an aglycone **5.7**. Thus **5.2** can be derived from the selective hydroboration of the glycal **5.3**. Methyl triflate cyclization of **5.4** would give the glycal **5.3** as the only regioisomer. The enol ether **5.4** should be readily obtained from Tebbe olefination of the ester **5.5**. DCC mediated esterification of **5.6** and **5.7** would provide **5.5** (Scheme 5.1).

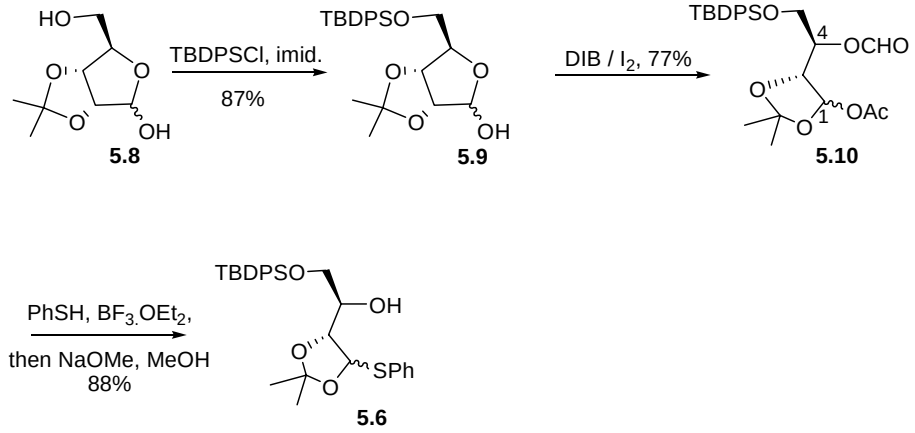
Scheme 5.1: Retrosynthesis of compound 5.2



5.3 Synthesis of 1-thio-1,2-isopropylidene acetals 5.6.

The TIA segment **5.6** was obtained from 2,3-*O*-isopropylidene-*D*-ribofurose **5.8**.[74] Thus conversion of **5.8** to the silyl ether **5.9**, and treatment of this material with diacetoxyiodosobenzene (DIB) and iodine gave the 1-*O*-acetyl-1,2-*O*-isopropylidene **5.10**, according to the Suarez protocol.[22] Compound **5.10** was exposed to thiophenol and $BF_3.OEt_2$ at -78 ^oC and the crude subjected to base hydrolysis of the formate ester. Thus **5.6** was made in 59% overall yield from 2,3-*O*-isopropylidene-*D*-ribofurose **5.8**.

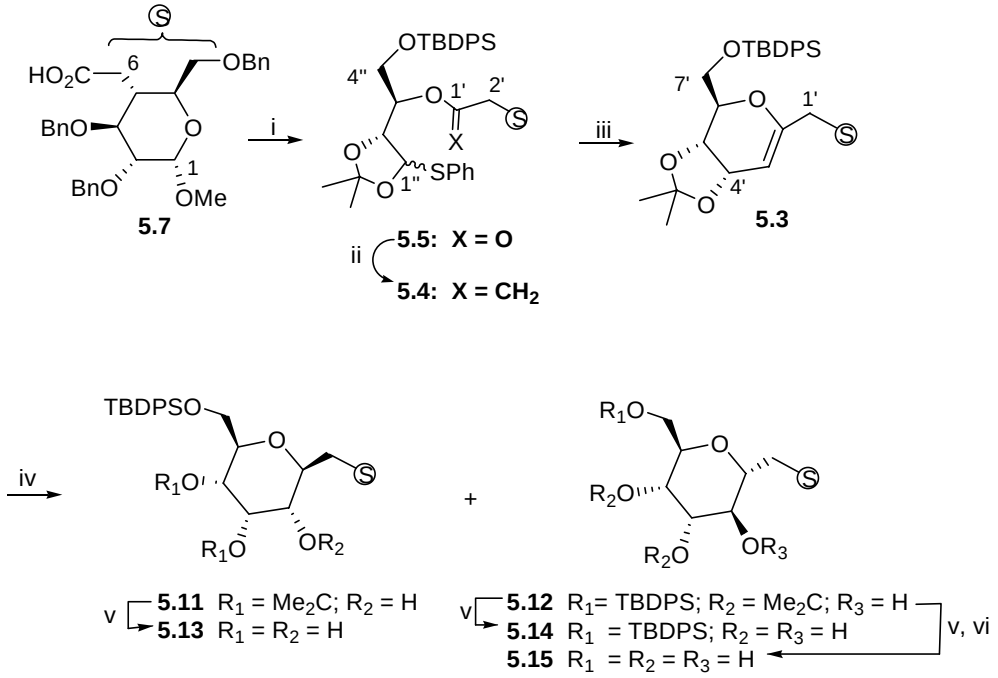
Scheme 5.2: Synthesis of the 1-thio-1,2-isopropylidene acetals **5.6**



5.4 C-glycoside synthesis

The aglycone segment **5.7** was obtained from the hydrolysis of the known ethyl ester derivative.[75, 76] The DCC coupling of alcohol **5.6** and acid **5.7** afforded the ester **5.5** which was transformed to the enol ether **5.4** by treatment with Tebbe reagent (Scheme 5.3). The key cyclization step on **5.4** was promoted by methyl triflate in the presence of 2,6-di-tert-butyl-4-methylpyridine, and led to C1 substituted glycal **5.3** in 70% yield. Hydroboration of **5.3** provided an approximately 1:5 ratio of two stereoisomers **5.11** and **5.12** respectively, in a combined yield of 84%. Chromatography of this mixture provided partial separation, giving a sample of pure **5.12** and an unseparated mixture of **5.11** and **5.12**.

Scheme 5.3: Synthesis of C-glycosides

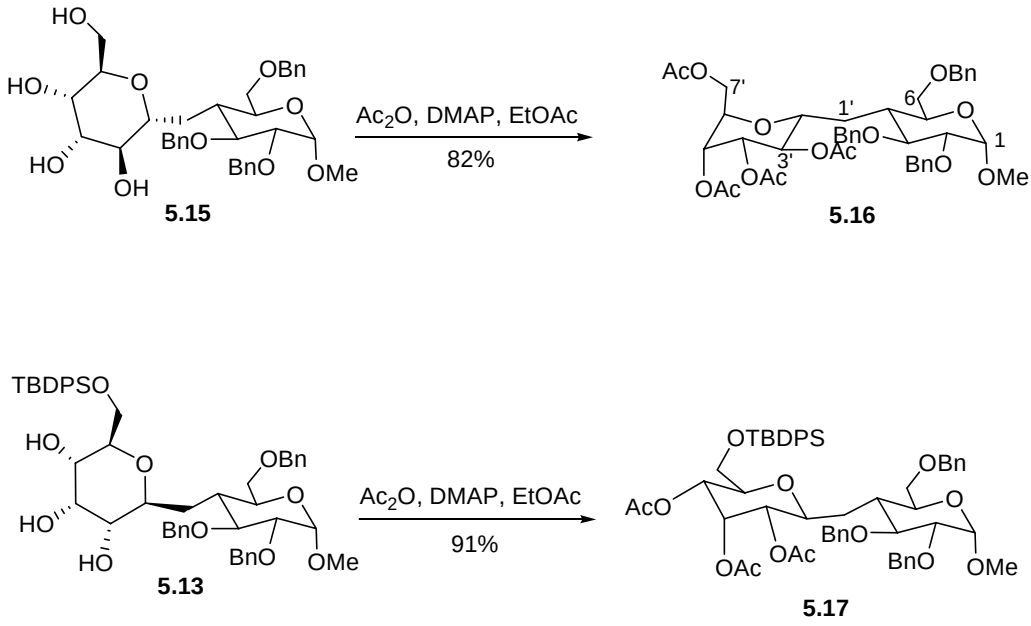


(i) **5.6**, DCC, DMAP, PhH, 85%; (ii) Tebbe, 60%; (iii) MeOTf, DTBMP, CH_2Cl_2, 70%; (iv) BH_3.DMS then Na_2O_2, 84%; (v) HCl, MeOH ; (vi) Bu_4NF, THF.

5.5 Conformational analysis of hydroboration products.

The stereochemistry of **5.12** was determined by conversion to the tetraacetate **5.16**. The J values ($J_{1',2'} = J_{2',3'} = 8.5$, $J_{3',4'} = 2.5$, $J_{4',5'} < 2.0$ Hz) for **5.16** were in agreement with an α-C-altroside in primarily the $^1C_4$ conformation.[77] The minor product of the hydroboration reaction, **5.11** was characterized as the triacetate **5.17**. Acid hydrolysis of the mixture of hydroboration products **5.11** and **5.12** provided an easily separable mixture of the corresponding triols **5.13** and **5.14**. Acetylation of **5.13** provided **5.17**. The data for **5.17** ($J_{1',2'} = 10.0$, $J_{2',3'} = 2.7$, $J_{3',4'} = 2.7$ $J_{4',5'} = 9.5$ Hz) supported a β-alloside in the $^4C_1$ conformation,[77] a result that is self consistent with the stereochemistry of the hydroboration reaction (Scheme 5.4).

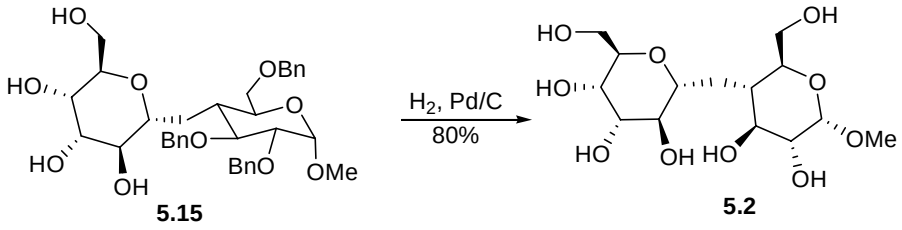
Scheme 5.4: Synthesis of acetylated products 5.16 and 5.17.



5.6 Synthesis of disaccharide 5.2

The targeted α-C-altroside **5.2** was obtained by hydrogenolysis of the tetraol **5.15**. The stereochemical integrity of **5.2** resides in the assignment of the aforementioned tetraacetate derivative **5.16**. Poor signal resolution in the ^{1}H-NMR resolution did not allow for conformational analysis of the altropyranoside ring.

Scheme 5.5: Final synthesis of α-C-altroside 5.2.



5.7 Summary

The synthesis of the **5.2** shows that the TIA C-glycoside methodology may also be used to prepare stereoselectively of α-C-altro-disaccharides. An attractive feature is the convergent nature of this strategy, which allows for incorporation of different aglycone subunits. Elaboration of the intermediate disaccharide glycal intermediates provides additional possibilities for variation of the glycone segment. These attributes are especially relevant to the synthesis of libraries of C-disaccharides with unusual substitution patterns.

5.8 Experimental section

2,3-*O*-Isopropylidene-5-*O*-*tert*-butyldiphenylsilyl-α/β-*D*-ribofuranose 5.9.

A solution of 2,3-*O*-isopropylidene-*D*-ribofuranose **5.8α/β**[74] (7.86 g, 41.0 mmol), TBDPSCl (11.4 mL, 41.0 mmol), and imidazole (5.64 g, 85.0 mmol) in anhydrous DMF (100 mL) was stirred at 50 ^{o}C for 1.5 hours. The reaction mixture was then diluted with water and extracted with ether. The combined organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by FCC to give an inseparable mixture **5.9**α/β (15.2 g, 87%) as a colorless oil; R_f = 0.42 (20% EtOAc/petroleum ether); IR (neat) 3423 cm^{-1}. Compound **5.9**α had ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 [s, 9H, $(CH_3)_3CSi$], 1.33, 1.48 [both s, 3H ea, $C(CH_3)_2$], 3.66 (dd, J = 2.6, 11.4 Hz, 1H, H-5a), 3.83 (dd, J = 2.6, 11.4 Hz, 1H, H-5b), 4.29 (bs, 1H, H-4), 4.54 (d, J = 10.6 Hz, D_2O ex, 1H, OH), 4.61 (d, J = 6.2 Hz, 1H, H-3), 4.72 (d, J = 5.9 Hz, 1H, H-2), 5.38 (d, J = 10.3 Hz, 1H, H-1), 7.43–7.80 (m, 10H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.3, 26.8 [$C(CH_3)_2$], 27.2 $(CH_3)_3CSi$], 65.8, 82.0, 87.4, 87.5 (4C, C-2, 3, 4, 5), 103.6 (C-1), 112.3 [$C(CH_3)_2$], 128.0–135.9 (Ph). Compound **5.9**β had ^{1}H NMR (300 MHz, $CDCl_3$) δ (selected signals) 1.06 [s, 9H, $(CH_3)_3CSi$], 1.41, 1.56 [both s, 3H ea, $C(CH_3)_2$], 3.94 (d, J = 11.4 Hz, 1H, D_2O ex, OH), 4.16 (bs, 1H, H-4), 5.67 (dd, J = 4.0, 11.4 Hz, 1H, H-1); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.1, 26.5 [$C(CH_3)_2$], 27.2 $(CH_3)_3CSi$], 66.2, 79.8, 81.6, 82.2 (4C, C-2, 3, 4, 5), 98.2 (C-1), 113.3 [$C(CH_3)_2$]; Mixture **5.9**α/β had HRMS(EI) m/z calcd for $C_{23}H_{29}O_5Si$ (M-CH_3) 413.1784. Found 413.1777.

1-*O*-Acetyl-4-*O*-*tert*-buty1diphenylsilyl-3-*O*-formyl-1,2-*O*-isopropylidene-*D*-*erythro*-hemiacetal 5.10.

A solution of compound **5.9** (5.82 g, 13.6 mmol) in anhydrous cyclohexane (90 mL) containing diacetoxyiodosobenzene (4.39 g, 15.2 mmol) and iodine (3.45 g, 13.5 mmol) was stirred under an atmosphere of argon at rt for 4 hours. The reaction mixture was then diluted with water and extracted with ether. The organic phase was washed with aqueous $Na_2S_2O_3$ and brine, then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was separated by FCC to give major (4.00 g, 61%) and minor (1.08 g, 16%) isomers of **5.10**. The major isomer was isolated as a white solid; R_f = 0.23 (5% EtOAc/petroleum ether); IR (film) 1732, 1752 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.09 (s, 9H, $(CH_3)_3CSi$], 1.41, 1.50 [both s, 3H ea, $C(CH_3)_2$], 2.04 (s, 3H, CH_3CO), 3.91 (m, 2H, H-4a, 4b), 4.52 (dd, J = 1.8, 5.9 Hz, 1H, H-2), 5.18 (q, J = 4.8 Hz, 1H, H-3), 6.27 (d, J = 1.8 Hz, 1H, H-1), 7.38-7.70 (m 10H, Ph), 8.02 (s, 1H, HCO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.9 (CH_3CO), 27.5, $(CH_3)_3CSi$, $C(CH_3)_2$,1C], 28.1 [$C(CH_3)_2$,1C), 62.9, 73.4, 81.2 (3C, C-2, 3, 4), 96.8 (C-1), 113.6 [$C(CH_3)_2$], 128.4, 130.4, 133.6, 136.2 (Ph), 160.3 (HCO), 170.2 (CH_3CO). HRMS (EI) m/z calcd for $C_{24}H_{31}O_5Si$ (M-$C_2H_3O_2$) 427.1941, found 427.1932.

The minor isomer was isolated as a colorless oil; R_f = 0.28 (5% EtOAc/petroleum ether); ^1H NMR (300 MHz, $CDCl_3$) δ 1.09 (s, 9H), 1.42, 1.51 [both s, 3H ea, $C(CH_3)_2$], 2.04 (s, 3H, CH_3CO), 3.98 (m, 2H, H-4a,b), 4.54 (dd, J = 3.3, 9.2 Hz, 1H, H-2), 5.33 (m, 1H, H-3), 6.33 (d, J = 3.3 Hz, 1H, H-1), 7.40–7.70 (m 10H, Ph), 7.91 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3 (CH_3CO), 26.3 [$C(CH_3)_2$, 1C], 27.1 $(CH_3)_3CSi$], 28.4 [$C(CH_3)_2$,

1C], 63.4, 71.3, 76.0 (3C, C-2, 3, 4), 93.5 (C-1), 112.7 [$C(CH_3)_2$], 127.8, 129.9, 133.3, 135.7 (Ph), 159.5 (HC = O), 170.0 (CH_3C=O); ESMS m/z 504.3 $[M + NH_4]^+$.

4-*O*-*tert*-Butyldiphenylsilyl-1,2-*O*-isopropylidene-*D*-*erythro*-*S*-phenyl monothiohemiacetal 5.6.

$BF_3.OEt_2$ (1.60 mL, 12.7 mmol) was slowly added to a solution of **5.10** (4.10 g, 8.4 mmol) and thiophenol (2.16 mL, 21.1 mmol) in anhydrous CH_2Cl_2 (40 mL) at -78 ^oC under an atmosphere of argon. The reaction was warmed to -40 ^oC and stirred at this temperature for 1 hour, or until TLC indicated complete disappearance of the starting material. Triethylamine (6.0 mL) was then added, and the reaction mixture was diluted with satd. aq $NaHCO_3$ and extracted with ether. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude material was dissolved in methanol (50 mL) and treated with a solution of NaOMe in methanol at rt for 30 min. Most of the solvent was then removed under reduced pressure. FCC of the residue provided **5.6** (3.49 g, 81%) as a colorless oil; R_f = 0.42 (10% EtOAc/petroleum ether); IR (neat) 3485 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.07 (s, 9H, $(CH_3)_3CSi$], 1.40, 1.53 [both s, 3H ea, $C(CH_3)_2$], 2.55 (d, J = 4.4 Hz, 1H, D_2O ex, OH), 3.81 (m, 3H, H-4a, 4b, H-3), 4.18 (t, J = 5.7 Hz, 1H, H-2), 5.58 (d, J = 5.5 Hz, 1H, H-1), 7.26–7.71 (m, 15H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.3 [$C(CH_3)_2$, 1C], 26.8 $(CH3)_3CSi$), 27.1 $(CH_3)_3CSi$), 27.8 [$C(CH_3)_2$, 1C], 64.6, 72.4, 81.2 (3C, C-2, 3, 4), 86.0 (C-1), 111.7 [C(CH3)2], 127.2–135.6 (Ph); HRMS(EI) m/z calcd for $C_{23}H_{31}O_4Si$ (M–SPh) 399.1992, found 399.1996.

Methyl 2,3,6-tri-*O*-benzyl-4-*C*-(carboxymethyl)-4-deoxy-α-*D*-glucopyranoside 5.7.

The ethyl ester of **5.7**[76] (7.20 g, 10.0 mmol) was treated with a 1:1 mixture of aq 3N NaOH:ethanol (120 mL). After 4 hours most of the ethanol was removed under reduced pressure. The resulting mixture was acidified with concentrated HCl to pH 4-5 and extracted with ethyl acetate. The combined organic layer was concentrated *in vacuo*. The residue was purified by FCC to give unreacted starting material and acid **5.7** (3.63g, 86% based on recovered starting material) as a colorless oil; R_f = 0.49 (40% EtOAc/petroleum ether); IR (film) 2500–3200 (br), 1707 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.03 (m, 2H, H-4, H-2'a), 2.57 (dd, J = 5.5, 16.5 Hz, 1H, H-2'b), 3.38 (s, 3H, OCH_3), 3.61, 3.83 (both m, 3H, 2H resp, H-2, 3, 5, 6a, 6b), 4.47 (d, J = 11.7 Hz, 1H, PhCH), 4.57–4.81 (m, 5H, H-1, 4 × PhCH), 5.02 (d, J = 11.0 Hz, 1H, PhCH), 7.20–7.35 (m, 15H, Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.3, 40.6 (C-4, 2'), 55.5 (OCH_3), 69.8, 70.4, 73.1, 73.6, 75.5, 78.1, 81.8 (7C, C-2, 3, 5, 6, $PhCH_2$), 98.7 (C-1), 127.8–138.7 (Ph), 176.5 (C = O); HRMS (FAB) m/z calcd for $C_{30}H_{34}O_7Na$ $[M + Na]^+$ 529.2201, found 529.2202.

Methyl 2,3,6-tri-*O*-benzyl-[(4-C-(4-*O*-*tert*-buty1diphenylsilyl-1,2-*O*-isopropylidene-D-*erythro*-*S*-phenyl monothiohemiacetal)-2-ethanoate]-4-deoxy-α-D-glucopyranoside 5.5.

DCC (2.71 g, 13.15 mmol) was added at 0 ^0C to a solution of alcohol **5.6** (2.67 g, 5.26 mmol), acid **5.7** (3.63 g, 7.17 mmol), and DMAP (128 mg, 1.05 mmol) in anhydrous benzene (50 mL). The reaction was warmed to rt and stirred for 2 hours. The mixture was then diluted with ether (20 mL) and filtered. The filtrate was washed with 0.1 N aq

HCl and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by FCC to give **5.5** (4.47 g, 85%) as a colorless oil; R_f = 0.42 (20% EtOAc/petroleum ether); IR (neat) 1734 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.00 [s, 9H, $(CH_3)_3CSi$], 1.31, 1.42 [both s, 3H ea, $C(CH_3)_2$], 2.26 (m, 2H, H-4, 2'a), 2.55 (m, 1H, H-2'b), 3.10 (s, 3H, OCH_3), 3.33 (m, 1H, H-1), 3.52 (m, 2H, H-6a, 6b), 3.79 (m, 4H, H-3, 5, 4a, 4b), 4.31 (t, J = 6.0 Hz, 1H, H-2''), 4.39 (d, J = 12.0 Hz, 1H, PhCH), 4.51 (m, 3H, 3 × PhCH), 4.61 (d, J = 11.0 Hz, 1H, PhCH), 4.62 (d, J = 4.0 Hz, 1H, H-1), 4.89 (m, 1H, H-3"), 4.91 (d, J = 11.0 Hz, 1H, PhCH), 5.37 (d, J = 6.5 Hz, 1H, H-1"), 7.10–7.70 (m, 30 H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.7 [$C(CH_3)_2$, 1C], 27.6 $(CH_3)_3CSi$), 28.1 [$C(CH_3)_2$, 1C], 33.5 (C-2'), 41.2 (C-4), 55.9 (OCH_3), 62.8 (C-4"), 70.6, 71.1, 73.5, 74.1, 74.4, 75.9, 78.9, 79.5, 82.5 (9C, C-2, 3, 5, 6, 2", 3", $PhCH_2$), 85.6 (C-1"), 99.1 (C-1), 112.2 [$C(CH_3)_2$], 127.8–139.3 (Ph), 171.6 (C=O); HRMS(FAB)m/z calcd for $C_{59}H_{68}O_{10}SSiNa$ $[M + Na]^+$ 1019.4203, found 1019.4200.

Methyl 2,3,6-tri-*O*-benzyl-4-*C*-[(4-*O*-*tert*-buty1diphenylsilyl-1,2-*O*-isopropylidene-D-*erythro*-*S*-phenyl monothiohemiacetal)-2-propene]-4-deoxy-α-D-glucopyranoside 5.4.

A solution of Tebbe reagent in THF (9.3 mL, 0.5 M, 4.7 mmol) was added dropwise, under an atmosphere of argon at -78 °C to ester **5.5** (1.82 g, 1.86 mmol) and pyridine (0.15 mL) in anhydrous 3:1 toluene/THF (20 mL). The reaction mixture was warmed to rt, stirred for 2 hours, and then slowly poured into a solution of 1 N aq NaOH at 0 °C. The resulting suspension was extracted with ether, and the organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure.

The residue was purified by FCC on basic alumina (Brockmann I, 150 mesh) to give enol ether **5.4** (1.09 g, 60%) as a colorless oil, R_f = 0.61 (15% EtOAc/petroleum ether); ^{1}H NMR (300 MHz, C_6D_6) δ 1.10 [s, 9H, $(CH_3)_3CSi$], 1.47, 1.62 [both s, 3H ea, $C(CH_3)_2$], 2.30 (dd, J = 4.8, 14.5 Hz, 1H, H-2'a), 2.40 (m, 1H, H-4), 2.69 (dd, J = 3.6, 14.5 Hz, 1H, H-2'b), 3.16 (s, 3H, OCH_3), 3.54 (dd, J = 3.5, 9.7 Hz, 1H, H-2), 3.75–4.15, 4.28 (both m, 8H, 1H, resp, H-3, 5, 6a, 6b. 3", 4"a, 4"b, = CH_2), 4.30–4.65 (m, 4H, 2 × $PhCH_2$), 4.74 (m, 2H, H-1, PhCH), 4.88 (bt, J = 5.0 Hz, 1H, H-2"), 5.19 (d, J = 11.2 Hz, 1H, PhCH), 6.10 (d, J = 6.2 Hz, 1H, H-1"), 6.94–7.84 (m, 30H, Ph); ^{13}C NMR (75 MHz, C_6D_6) δ 26.8 [$C(CH_3)_2$, 1C], 27.6 $(CH_3)_3CSi$], 28.2 [$C(CH_3)_2$, 1C], 33.8 (C-2'), 42.1 (C-4), 55.2 (OCH_3), 62.3 (C-4"), 71.5, 71.9, 72.7, 74.1, 75.2, 77.4, 78.6, 81.4, 83.8, 85.7 (10C, C-2, 3, 5, 6, 2", 3", $=CH_2$, $PhCH_2$) 86.1 (C-1"), 98.7 (C-1), 112.4 [$C(CH_3)_2$], 127.5–140.7 (Ph), 160.1 ($O\underline{C} = CH_2$). HRMS (FAB) m/z calcd for $C_{60}H_{71}O_9SSiH$ $[M + H]^+$ 995.4587, found 995.4588.

Methyl 4-*C*-(2,6-anhydro-7-*O*-*tert*-butyldiphenylsilyl-4,5-*O*-isopropylidene-1,3-dideoxy-D-*ribo*-hept-2-enitol-1-*C*-yl)-2,3,6-tri-*O*-benzyl-4-deoxy-α-D-glucopyranoside 5.3.

A mixture of enol ether **5.4** (740 mg, 0.08 mmol), 2,6-di-tert-butyl-4-methylpyridine (1.54 g, 7.51 mmol), and freshly activated, powdered 4 Å molecular sieves (300 mg) in anhydrous CH_2Cl_2 (25 mL) was stirred for 15 min at rt under an argon atmosphere, then cooled to 0 ^oC. Methyl triflate (1.0 mL, 7.55 mmol) was introduced, and the mixture was warmed to rt and stirred for an additional 18 hours, or until all the starting material had disappeared, at which time triethylamine (2.5 mL) was added. The

mixture was diluted with ether, washed with satd aq $NaHCO_3$ and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by FCC over basic alumina (Brockmann I, 150 mesh) to give **5.3** (460 mg, 70%) as a clear oil, R_f = 0.60 (20% EtOAc/petroleum ether); IR (film) 1647 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 1.24 [s, 9H, $(CH_3)_3CSi$], 1.31, 1.37 [both s, 3H ea, $C(CH_3)_2$], 2.40 (dd, J = 5.7, 14.4 Hz, 1H, H-1'a), 2.56 (m, 2H, H1'b, 4), 3.24 (s, 3H, OCH_3), 3.70 (m, 2H, H-2, 7'a), 3.85 4.00–4.20 (both m, 2H, 5H resp., H-3, 5, 6a, 6b, 3', 6', 7'b), 4.27 (t, J = 5.0 Hz, 1H, H-5'), 4.60 (m, 4H, 2 × $PhCH_2$), 4.83 (m, 2H, H-1, PhCH), 4.93 (d, J = 5.6 Hz, 1H, H-4'), 5.27 (d, J = 11.7 Hz, 1H, PhCH), 7.11–7.46 and 7.90 (both m, 25H, Ph); ^{13}C NMR (75 MHz, C_6D_6) δ 26.8 [$C(CH_3)_2$, 1C], 27.7 $(CH_3)_3CSi$], 28.2 [$C(CH_3)_2$, 1C], 33.9 (C-1'), 42.2 (C-4), 55.3 (OCH_3), 62.4 (C-7'), 71.6, 72.0, 72.8, 74.2, 75.3, 77.5, 78.7, 81.6, 83.9, 85.7, 86.2 (11C, C2, 3, 5, 6, 3', 4', 5', 6', 3 × $PhCH_2$), 100.0 (C-1), 112.5 [$C(CH_3)_2$], 128.0–140.8 (Ph), 160.2 (C-2'); HRMS (FAB) m/z calcd for $C_{54}H_{65}O_9Si$ $[M + H]^+$ 885.4399, found 885.4398.

Methyl 4-*C*-(2,6-anhydro-4,5-*O*-isopropylidene-7-*O*-*tert*-butyldiphenylsilyl-1-*deoxy*-D-*glycero*-D-*allo*-heptitol-1-*C*-yl)-2,3,6-tri-*O*-benzyl-4-deoxy-α-D-glucopyranoside (5.11) and Methyl 4-*C*-(2,6-anhydro-4,5-*O*-isopropylidene-7-*O*-*tert*-butyldiphenylsilyl-1-deoxy-D-*glycero*-D-*manno*-heptitol-1-*C*-yl)-2,3,6-*tri*-*O*-benzyl-4-deoxy-α-D-glucopyranoside (5.12).

$BH_3.Me_2S$ (2.7 mL of 1 M solution in CH_2Cl_2, 2.7 mmol) was added at 0 °C to a solution of the glycal **5.3** (340 mg, 0.39 mmol) in anhydrous THF (15 mL) under an atmosphere of argon. The mixture was warmed to rt and stirred for an additional 1 hour.

At that time the solution was cooled to 0 ^{o}C and treated with a mixture of 3N NaOH (2.5 mL) and 30% aqueous H_2O_2 (2.5 mL) for 30 min. The mixture was diluted with ether, washed with satd aq $NaHCO_3$ and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. FCC of the residue afforded a mixture of **5.11** and **5.12** (264 mg, ca. ratio 1:5, 84%) which had identical TLC mobilities (R_f = 0.25, 10% EtOAc/petroleum ether). For characterization purposes, a pure sample of **5.12** was obtained by resubjecting this material to a second chromatography and collection of a later eluting fraction. Compound **5.12** was isolated as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 [s, 9H, $(CH_3)_3CSi$], 1.29, 1.46 [both s, 3H ea, $C(CH_3)_2$], 1.51 (m, 1H, H-1'a), 1.75 (m, 1H, H-1'b), 2.05 (m, 1H, H-4), 3.00 (bs, 1H, D_2O ex), 3.32 (m, 1H), 3.37 (s, 3H), 3.41 (m, 1H), 3.55 (m, 2H), 3.60–3.95 (m, 7H), 4.12 (m, 1H), 4.44 (s, 2H), 4.65–4.85 (m, 4H), 5.03 (d, J = 12.0 Hz, 1H), 7.26–7.78 (m, 25H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.7 $(CH_3)_3CSi$, $C(CH_3)_2$, 1C), 28.8 [$C(CH_3)_2$, 1C], 33.1 (C-1'), 40.5 (C-4), 55.9 (OCH_3), 65.4 (C-7'), 71.4, 72.4, 73.5, 74.0, 74.6, 75.5, 76.6, 78.8, 81.2, 82.6 (12C, C-2, 3, 5, 6, 2', 3', 4', 5' 6', 3 × $PhCH_2$), 99.0 (C-1), 109.5 [$C(CH_3)_2$], 128.1–139.1 (Ph); HRMS (FAB) m/z calcd for $C_{54}H_{66}O_{10}SiNa$ $[M + Na]^+$ 925.4321, found 925.4323. Compound **5.11** was characterized as triol **5.13** and triacetate **5.17** (*vide infra*).

Methyl 4-C-(2,6-anhydro-7-*O*-*tert*-butyldiphenylsilyl-1-deoxy-D-glycero-D-*allo*-heptitol-1-*C*-yl)-2,3,6-tri-*O*-benzyl-4-deoxy-α-D-glucopyranoside 5.13 and Methyl 4-*C*-(2,6-anhydro-7-*O*-*tert*-butyldiphenylsilyl-1-deoxy-D-*glycero*-D-*manno*-heptitol-1-*C*-yl)-2,3,6-tri-*O*-benzyl-4-deoxy-α-D-glucopyranoside 5.14.

To a portion of the mixture of **5.11** and **5.12** from the previous step (103 mg, 0.11 mmol) in dry methanol was added a 1 M solution of HCl in ether (0.7 mL). The reaction was stirred for 1.5 hours and then neutralized with a solution of NaOMe in methanol. Removal of the volatiles followed by FCC of the residue provided triols **5.13** (12 mg, 12%) and **5.14** (65 mg, 66%).

Compound **5.13** was isolated as a clear gum; R_f = 0.64 (50% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, C_6D_6) δ 1.16 [s, 9H, $(CH_3)_3CSi$], 1.68 (m, 1H, H-1'a), 2.20 (m, 1H, H-1'b), 2.42 (m, 1H, H-4), 2.44 (bs, 1H, D_2O ex, OH), 2.58 (d, J = 7.5 Hz, 1H, D_2O ex, OH), 2.93 (d, J = 5.5 Hz, 1H, D_2O ex, OH), 3.07 (t, J = 7.3 Hz, 1H), 3.18 (s, 3H, OCH_3), 3.60 (m, 3H), 3.80 (m, 3H), 3.88–4.00 (m, 4H), 4.04 (dd, J = 4.5, 11.0 Hz, 1H), 4.42 (ABq, J = 12.0 Hz, Δδ = 0.05 ppm, 2H, $PhCH_2$), 4.48 (ABq, Δδ = 0.04 ppm, J = 12.0 Hz, 2H, $PhCH_2$), 4.76 (d, J = 3.0 Hz, 1H, H-1), 4.89 (ABq, Δδ = 0.44 ppm, J = 11.0 Hz, 2H, $PhCH_2$), 7.05–7.82 (m, 25H); HRMS (FAB) m/z calcd for $C_{51}H_{62}O_{10}NaSi$ $[M + Na]^+$ 885.4010. Found 885.4030.

Compound **5.14** was isolated as a clear gum; R_f = 0.50 (50% EtOAc/petroleum ether); ^{1}H NMR (300 MHz, C_6D_6) δ 1.18 [s, 9H, $(CH_3)_3CSi$], 1.82 (m, 1H, H-1'a), 1.98 (m, 1H, H-1'b), 2.32 (m, 1H, H-4), 2.75 (s, 1H, D_2O ex, OH), 2.92 (s, 1H, D_2O ex, OH), 3.22 (s, 3H, OCH_3), 3.51 (s, 1H, D_2O ex, OH), 3.52 (dd, J = 3.3, 9.9 Hz, partially hidden by s at δ 3.51, 1H), 3.60 (dd, J = 2.6, 8.4 Hz, 1H), 3.72 (m, 2H), 3.82 (m, 4H), 3.93 (dd, J = 6.3, 9.3 Hz, 1H), 4.01 (t, J = 9.6 Hz, 1H), 4.09 (bs, 1H), 4.26 (t, J = 6.2 Hz, 1H), 4.44 (ABq, Δδ = 0.06 ppm, J = 11.7 Hz, 1H), 4.49 (ABq, Δδ = 0.05 ppm, J = 12.4 Hz, 1H), 4.74 (d, J = 3.3 Hz, 1H, H-1), 4.87 (ABq, Δδ = 0.41 ppm, J = 10.6 Hz, 1H), 7.10–7.76 (m, 25H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.2 $(CH_3)_3CSi$], 33.4 (C-1'), 40.0 (C-4), 55.4 (OCH_3),

62.9 (C-7'), 69.0, 69.1, 70.8, 72.0, 72.9, 73.6, 73.7, 73.8, 74.4, 76.5, 81.3, 82.2, (12C, C-2, 3, 5, 6, 2', 3', 4' 5' 6', 3 × $PhCH_2$), 98.4 (C-1), 127.6–138.4 (Ph). HRMS (FAB) m/z calcd for $C_{51}H_{62}O_{10}NaSi$ $[M + Na]^+$ 885.4010, found 885.4013.

Methyl 4-*C*-(2,6-anhydro-1-deoxy-D-*glycero*-D-*manno*-heptitol-1-C-yl)-2,3,6-tri-*O*-benzyl-4-deoxy-α-D-glucopyranoside 5.15.

A solution of HCl in ether (0.3 mL of ca.1M) was added to **5.12** (419 mg, 0.49 mmol) in dry methanol (30 mL). The reaction was stirred at rt for approximately 4 hours, then neutralized with a solution of NaOMe in methanol. Addition of Bu_4NF (2.8 mL of a 1 M solution in THF, 2.8 mmol) to the reaction mixture, followed by stirring for an additional 1 hour, then removal of the volatiles under reduced pressure, and FCC of the residue, provided **5.15** (164 mg, 58%) as a colorless oil; R_f = 0.37, (20% acetone/EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 1.62 (m, 1H, H-1'a), 1.77 (m, 1H, H-1'b), 2.07 (m, 1H, H-4), 2.86 (bs, 1H, D_2O ex, OH), 3.29 (m, 2H), 3.38 (s, 3H, OCH_3), 3.43–3.67 (m, 8H), 3.85 (m, 2H), 4.50–4.76 (m, 6H, H-1, 5 × PhCH), 5.03 (d, J = 10.6 Hz, 1H, PhCH), 7.24–7.37 (m, 15H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.3 (C-1'), 39.4 (C-4), 55.5 (OCH_3), 59.4 (C-7'), 68.6,70.6, 71.5, 72.3, 72.5, 73.0, 73.4, 73.6, 76.3, 77.5, 81.6, 82.0 (12C, C-2, 3, 5, 6, 2', 3', 4', 5', 6', 3 × $PhCH_2$), 98.3 (C-1), 127.7–138.2 (Ph); HRMS (FAB) m/z calcd for $C_{35}H_{44}O_{10}Na$ $[M + Na]^+$ 647.2832, found 647.2834.

Methyl 4-C-(2,6-anhydro-3,4,5,7-*tetra*-*O*-acetyl-1-deoxy-D-*glycero*-D-mannoheptitol-1-*C*-yl)-2,3,6-tri-*O*-benzyl-4-deoxy-α-D-glucopyranoside 5.16.

A solution of tetraol **5.15** (25.5 mg, 0.04 mmol), DMAP (1.00 mg, 4 mmol), and acetic anhydride (0.04 mL, 0.40 mmol) in ethyl acetate (3.0 mL), was stirred at rt for 20 min. Methanol was then added and the reaction mixture concentrated under reduced pressure. The residue was purified by FCC to give **5.16** (26.7 mg, 82%) as a colorless oil; R_f = 0.66 (40% EtOAc/petroleum ether); $[\alpha]_D$ + 23° (c 1.3 $CHCl_3$); IR (film) 1743 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 1.59 (s, 3H, CH_3CO), 1.64, (m, buried under s at d 1.64, 1H, H- 1'a) 1.64, 1.69, 1.78 (all s, 3H ea, 3 × CH_3CO), 2.12 (t, J = 10.5 Hz, 1H, H-1'b), 2.23 (apparent q, J = 7.5 Hz, 1H, H-4), 3.25 (s, 3H, OCH_3), 3.56 (bd, J = 9.0 Hz, 1H, H-2), 3.62 (m, 1H, H-6a), 3.70 (bd, J = 10.5 Hz, 1H, H-6b), 3.81 (bd, J = 10.5 Hz, 1H, H-5), 3.89 (bd, J = 11.0 Hz, 1H, H-7'a), 4.06 (m, 2H, H-3, 6'), 4.28 (m, 2H, H-2', 7'b), 4.43 (m. 4H, 2 × $PhCH_2$), 4.74 (bs, 1H, H-1), 4.94 (ABq, Δδ = 0.49 ppm, J = 10.5 Hz, 2H, $PhCH_2$), 5.33 (t, J = 8.5 Hz, 1H, H-3'), 5.43 (dd, J = 2.5, 8.5 Hz, 1H, H-4'), 5,49 (d, J = 2.5 Hz, 1H, H-5'), 7.10-7.51 (m, 15H, Ph); ^{13}C NMR (75 MHz, C_6D_6) δ 20.7, 20.8, 20.9 (CH_3CO, 4C), 31.8 (C-1'), 41.1 (C-4), 55.5 (OCH_3), 62.3, 69.5, 70.6, 71.7, 72.0, 72.3, 72.9, 73.3 (2C), 74.2, 75.8, 81.4, 83.5 (13C, C-2, 3, 5, 6, 2', 3', 4', 5', 6', 7', 3 x $PhCH_2$), 99.0 (C-1) 128.0-130.0 (Ph), 169.6, 169.7, 169.8, 170.1 (CH_3CO). HRMS (FAB) m/z calcd for $C_{43}H_{52}O_{14}Na$ $[M + Na]^+$ 815.8355, found 815.3256.

Methyl 4-*C*-(2,6-anhydro-7-*O*-*tert*-butyldiphenylsilyl-3,4,5-tri-*O*-acetyl-1-deoxy-D-*glycero*-D-*allo*-heptitol-1-*C*-yl)-2,3,6-tri-*O*-benzyl-4-deoxy-α-D-glucopyranoside 5.17.

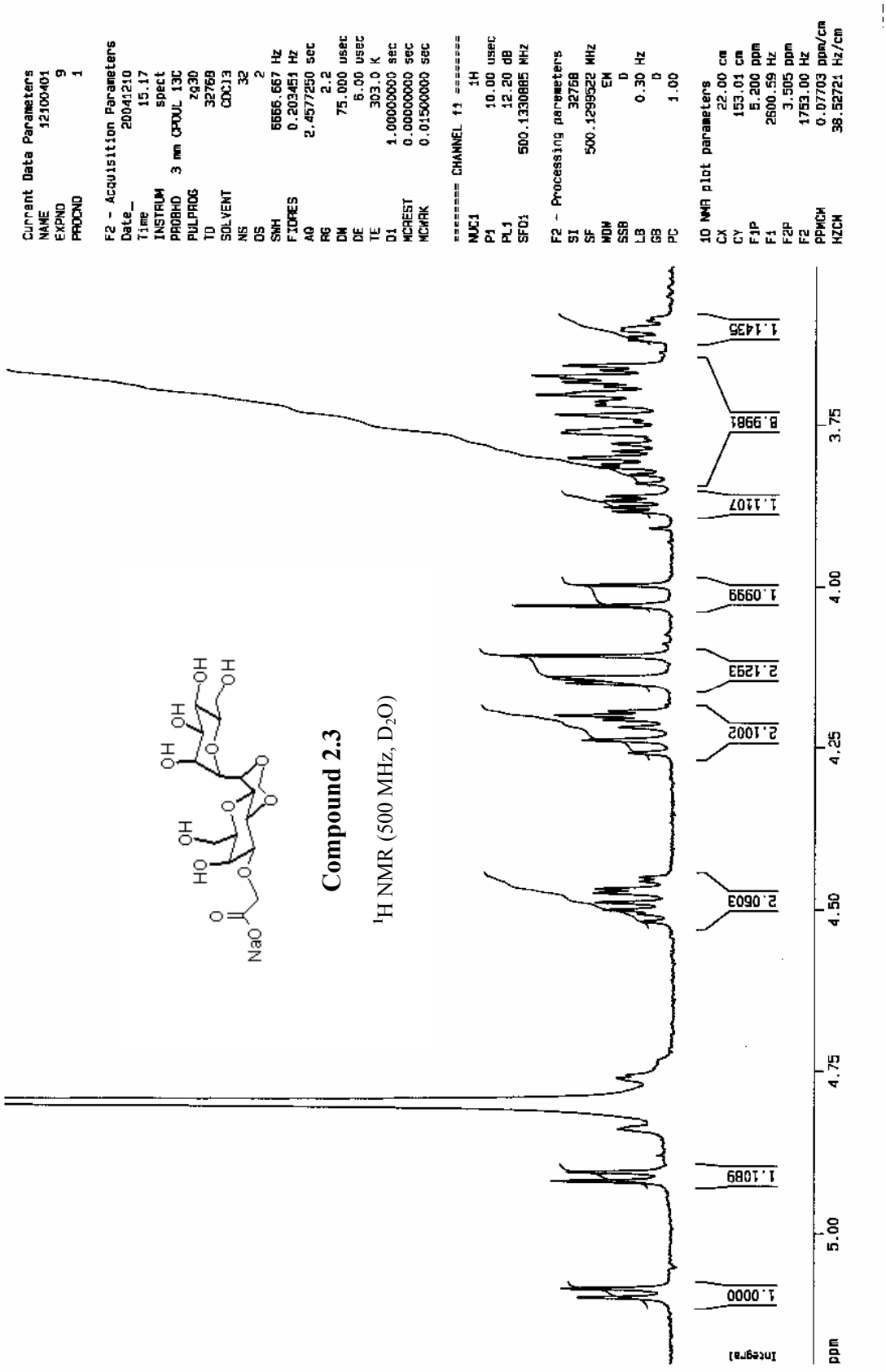
Triol **5.13** (4.0 mg, 0.005 mmol) was subjected to the identical acetylation procedure that was described for the preparation of **5.16**. FCC of the crude reaction product provided **5.13** (4.2 mg, 91%) as a clear gum; R_f = 0.50 (30% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, C_6D_6) δ 1.72 [s, 9H, $(CH_3)_3CSi$], 1.50, 1.63, 1.64 (all s, 3H ea, CH_3CO), 1.75 (m, 1H, H-1'a), 2.15 (bdd, J = 4.5, 14.0 Hz, 1H, H-1'b), 2.62 (m, 1H, H-4), 3.16 (s, 3H, OCH_3), 3.70 (dd, J = 3.0, 8.8 Hz, 1H, H-2), 3.76 (dd, J = 3.5, 11.5 Hz, 1H, H-7'a), 3.84 (m, 2H, H-6a, 6'), 3.88 (bd, J = 11.5 Hz, 1H, H-7'b), 3.98 (dd, J = 3.5, 11.0 Hz, 1H, H-6b), 4.12, (t, J = 10.5 Hz, 1H, H-3), 4.23 (m, 2H, H-5, H-2'), 4.44 (ABq, Δδ = 0.03 ppm, J = 12.0 Hz, 2H, $PhCH_2$), 4.54 (ABq, Δδ = 0.07 ppm, J = 12.0 Hz, 2H, $PhCH_2$), 4.81, (d, J = 3.0 Hz, 1H, H-1), 4.90 (dd, J = 2.0, 9.5 Hz, 1H, H-3'), 4.99 (ABq, Δδ = 0.55 ppm, J = 11.5 Hz, 2H, $PhCH_2$), 5.43 (dd, J = 2.0, 9.9 Hz,1H, H-5'), 6.20 (bt, J = 2.0 Hz, 1H, H-4'), 7.20, 7.80 (both m, 25H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7, 20.8, 20.9 (CH_3CO), 27.2, 27.6 $(CH_3)_3CSi$), 30.0 (C-1'), 40.4 (C-4), 55.3 (OCH_3), 63.1, 64.5, 66.8, 68.8, 70.3, 70.7, 71.0, 71.8, 73.1, 73.8, 74.7, 75.0, 82.5 (13C, C-2, 3, 5, 6, 2', 3', 4', 5', 6', 7', 3 × $PhCH_2$), 98.6 (C-1), 127.4-139.3 (Ph),168.9, 169.3, 169.9 (CH_3CO). ESMS m/z 1006.5 $[M + NH_4]^+$.

Methyl 4-*C*-(2,6-anhydro-1-deoxy-D-*glycero*-D-manno-heptitol-1-*C*-yl)-4-deoxy-α-D-glucopyranoside 5.2.

A mixture of **5.15** (124 mg, 0.20 mmol), 20% Pd on carbon (400 mg), formic acid (0.35 mL) and methanol (7.0 mL) was stirred under an atmosphere of hydrogen (balloon),

for 12 hours. The reaction mixture was purged with argon and filtered through a bed of Celite. The filtrate was concentrated *in vacuo*, and the residue was purified by FCC to provide **5.2** (55.0 mg, 83%) as a white solid; R_f = 0.68 (50% MeOH/$CHCl_3$); $[\alpha]_D$ + 93 (c 0.54 MeOH); ^{1}H NMR (500 MHz, D_2O, 25 ^oC) δ 1.71 (ddd, J = 2.8, 10.1, 15.1 Hz, 1 H, H-1'a), 1.83 (m, 1H, H-4), 2.08 (ddd, J = 2.0, 6.0, 15.1 Hz, 1H, H-1'b), 3.42 (s, 3H, OCH_3), 3.50 (apparent t, J = 9.0 Hz, 1H, H-7'a), 3.64 (dd, J = 3.7, 9.6 Hz, 1H, H-2), 3.66–3.76 (m, 4H, H-5, 2', 3', 6'), 3.82 (m, 3H, H-4', 7'a, 7'b), 3.93 (bdd, J = 9.1, 12.0 Hz, H-6a), 3.99 (m, 2H, H-6b, 5'), 4.85 (d, J = 3.7 Hz, H-1); ^{13}C NMR (125 MHz, D_2O) δ 29.9 (C-1'), 39.0 (C-4), 54.9 (OCH_3), 58.0, 61.5 (C-6, 7'), 68.5, 70.9, 71.4, 71.7, 72.4 (two carbons), 72.9, 78.4 (8C, C-2, 3, 5, 2', 3', 4', 5', 6'), 99.5 (C-1); HRMS (FAB) m/z calcd for $C_{14}H_{27}O_{10}Na$ $[M + Na]^+$ 355.1604, found 355.1602.

Appendix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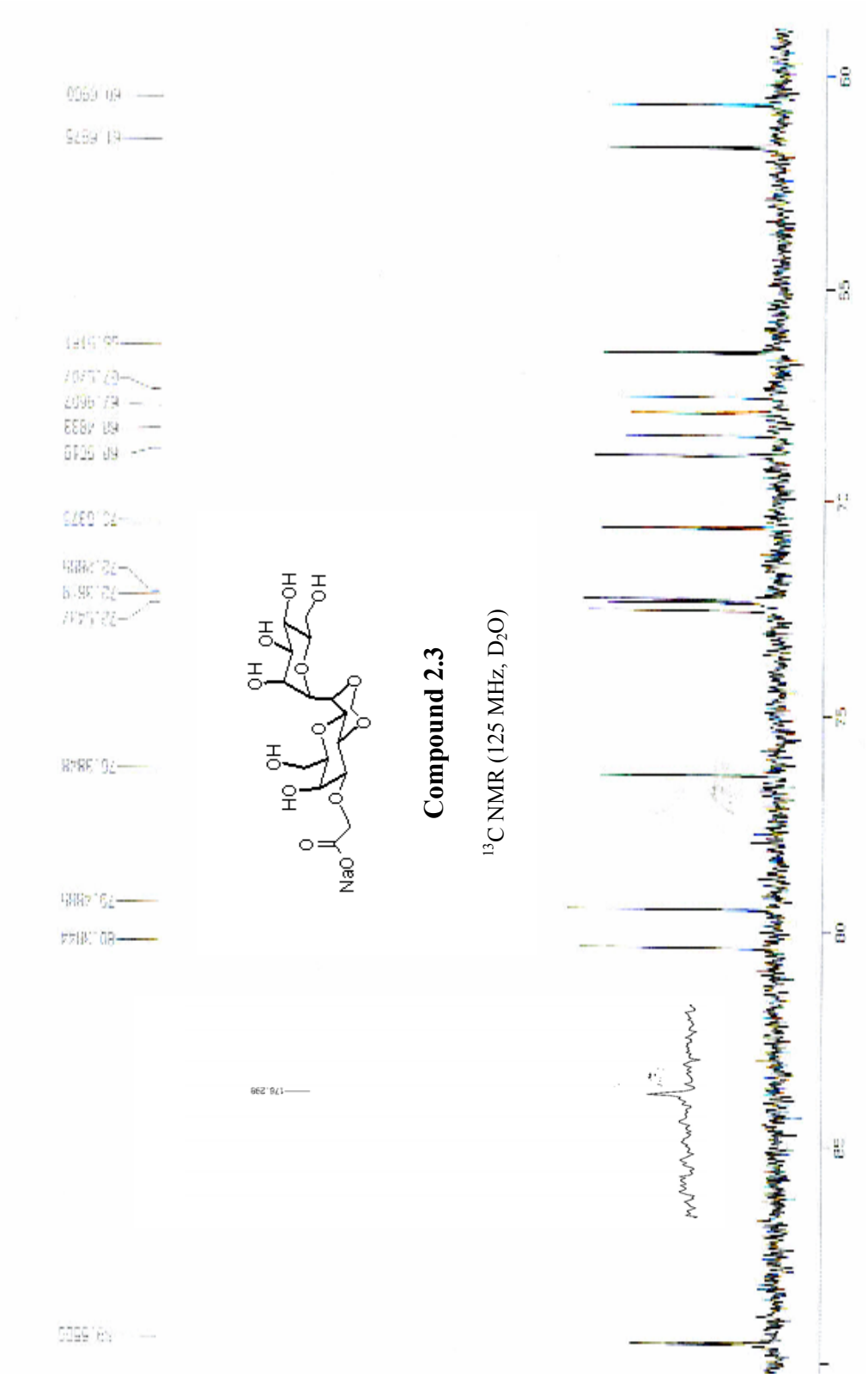

Compound 2.3

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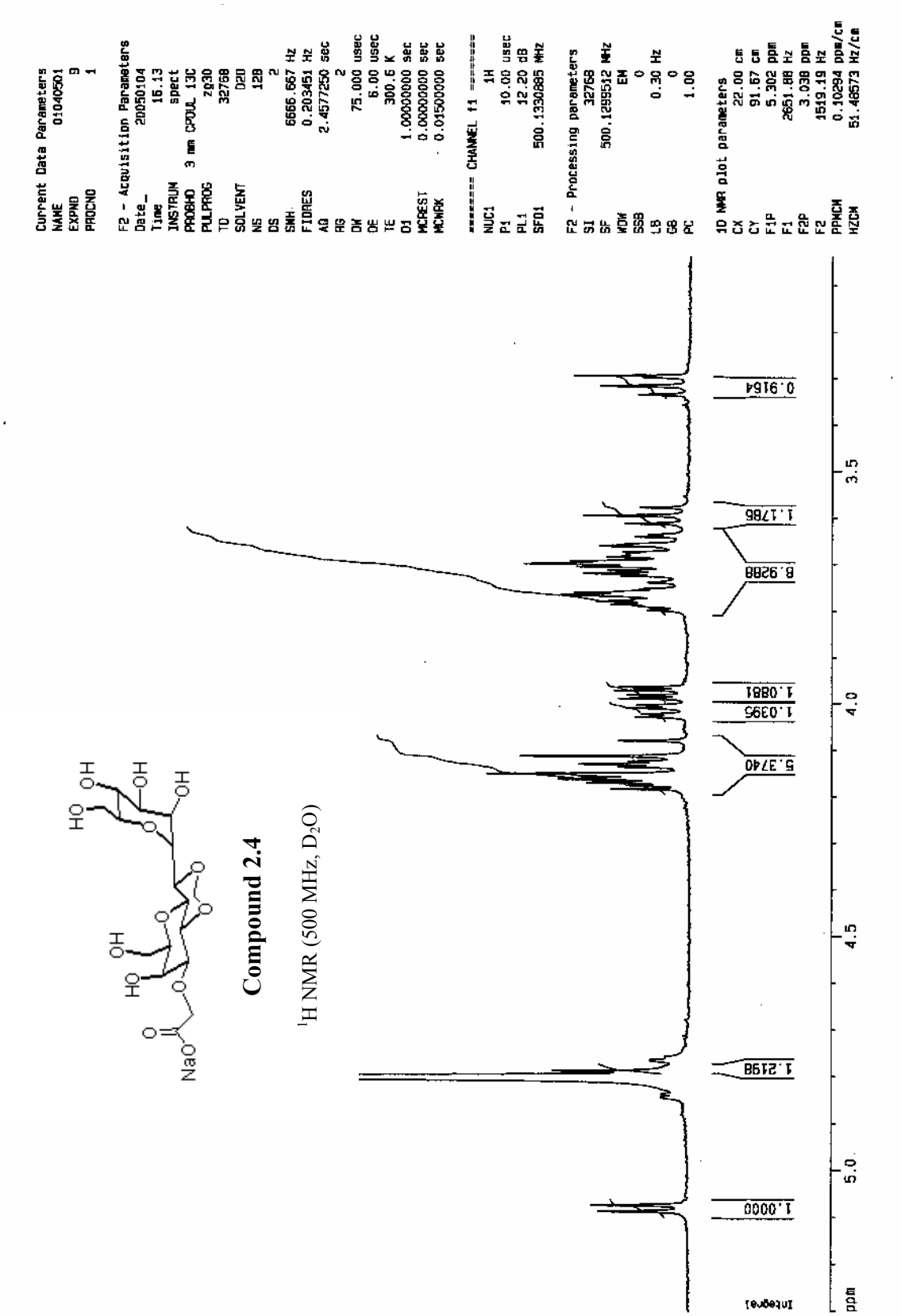
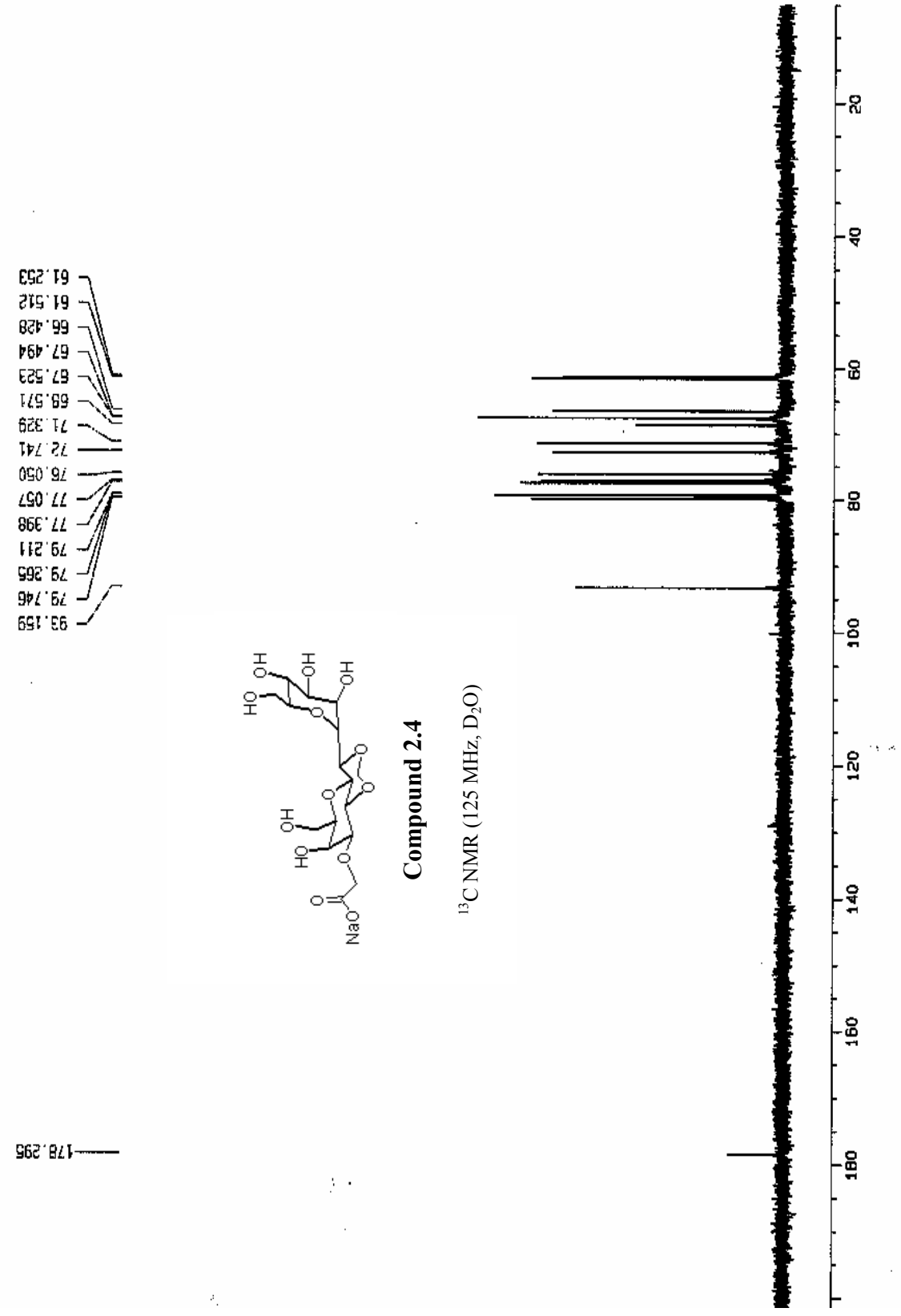


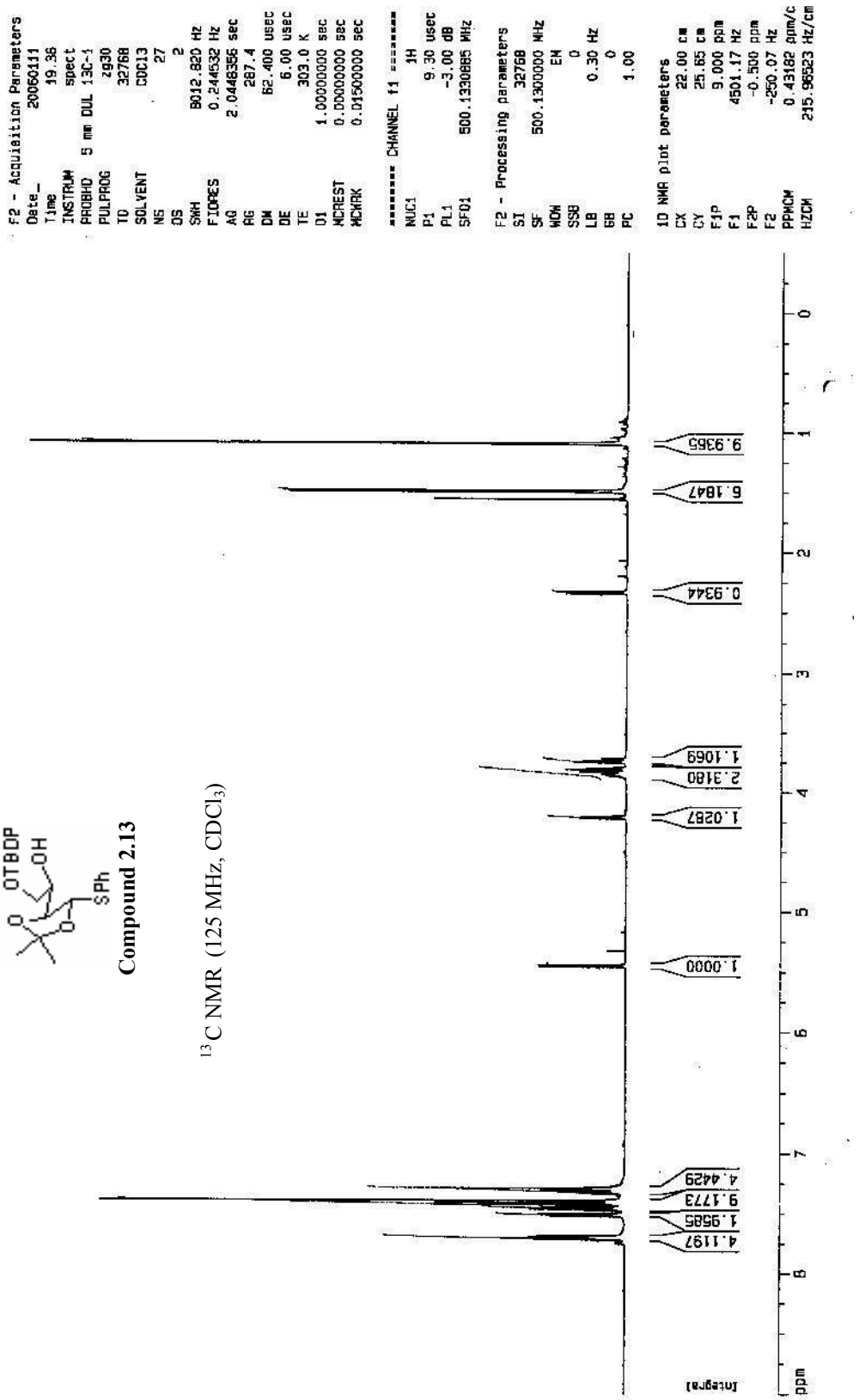
Compound 2.4

^{1}H NMR (500 MHz, D_2O)



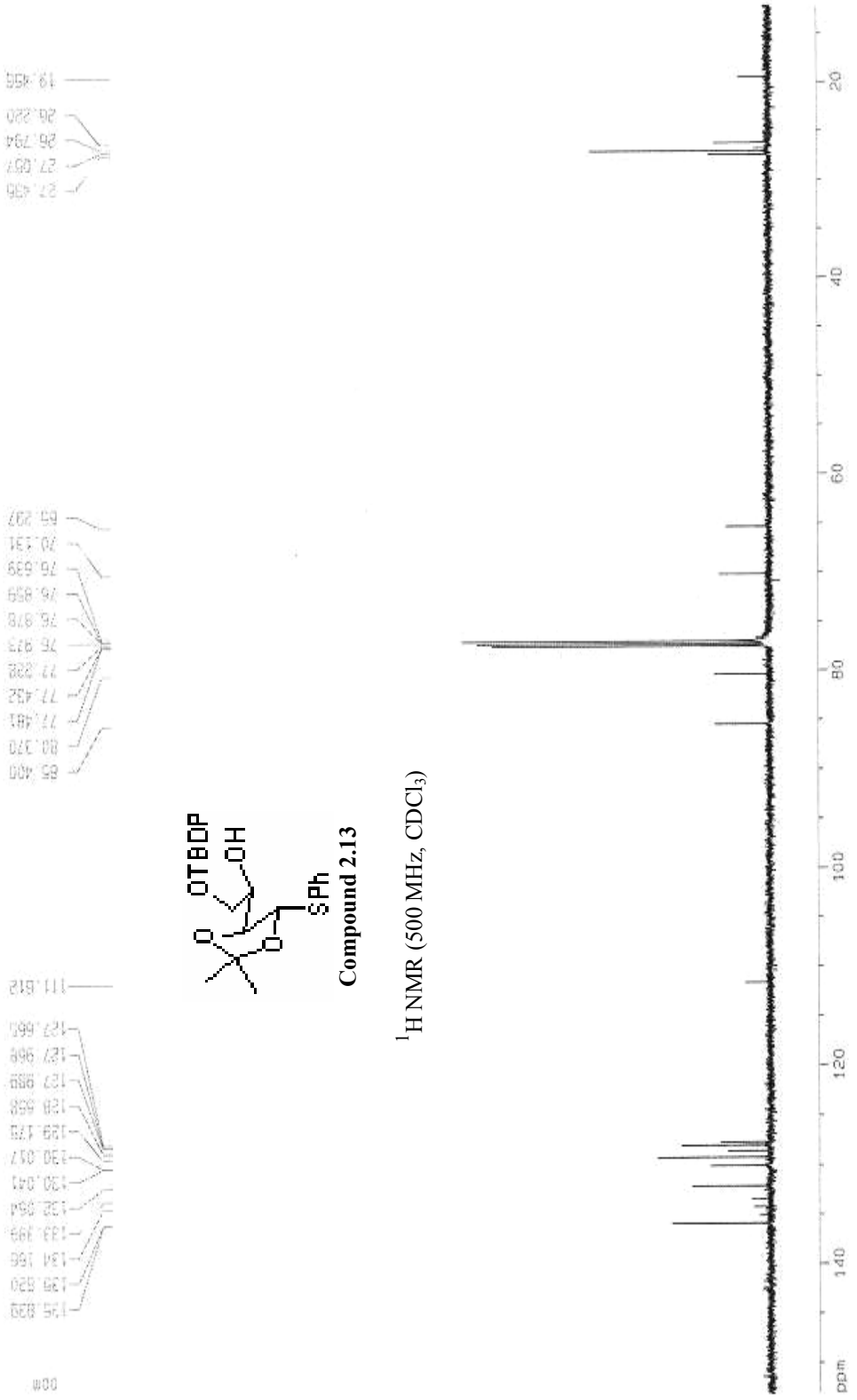
Compound 2.4

^{13}C NMR (125 MHz, D_2O)



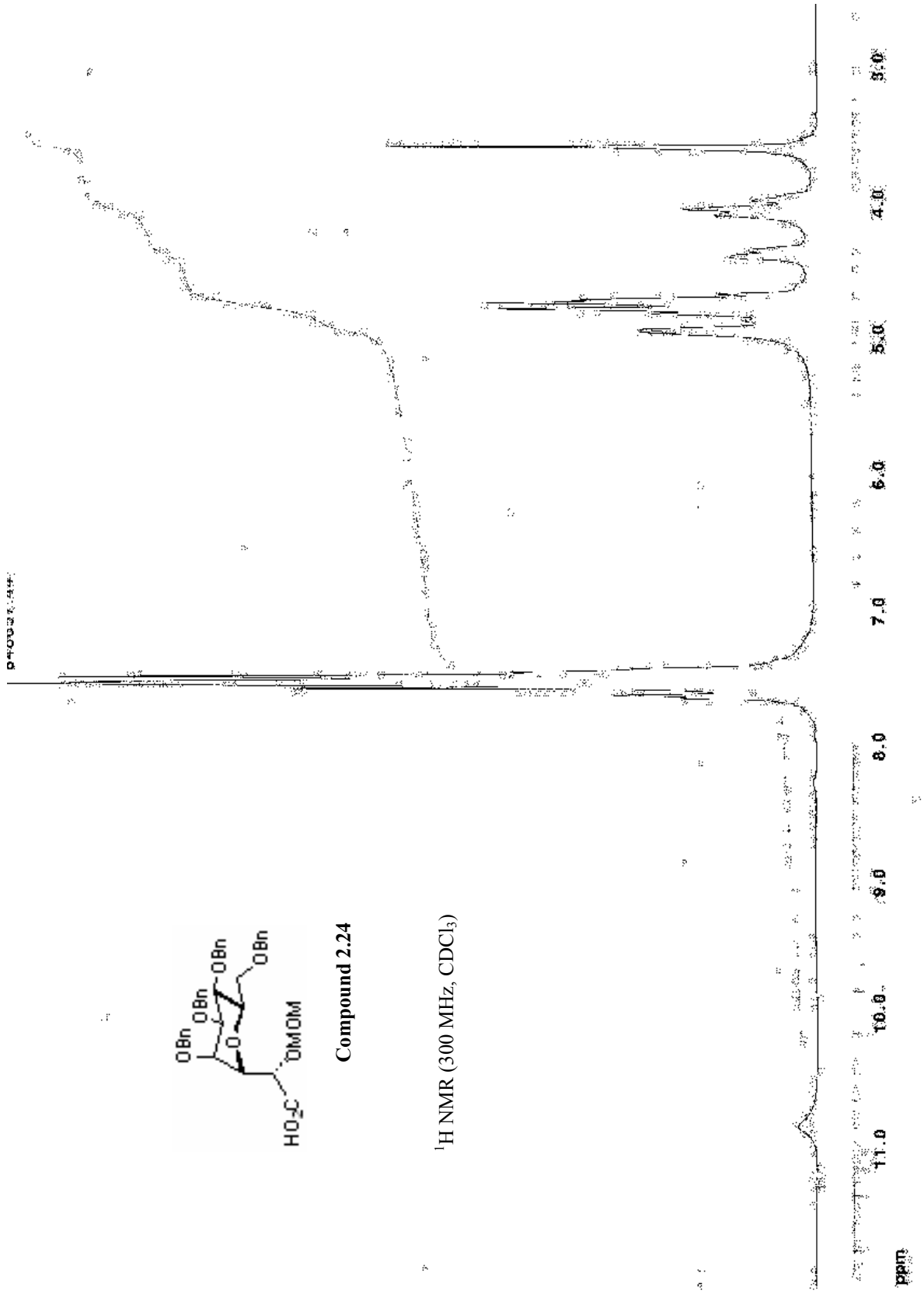
Compound 2.13

^{13}C NMR (125 MHz, $CDCl_3$)



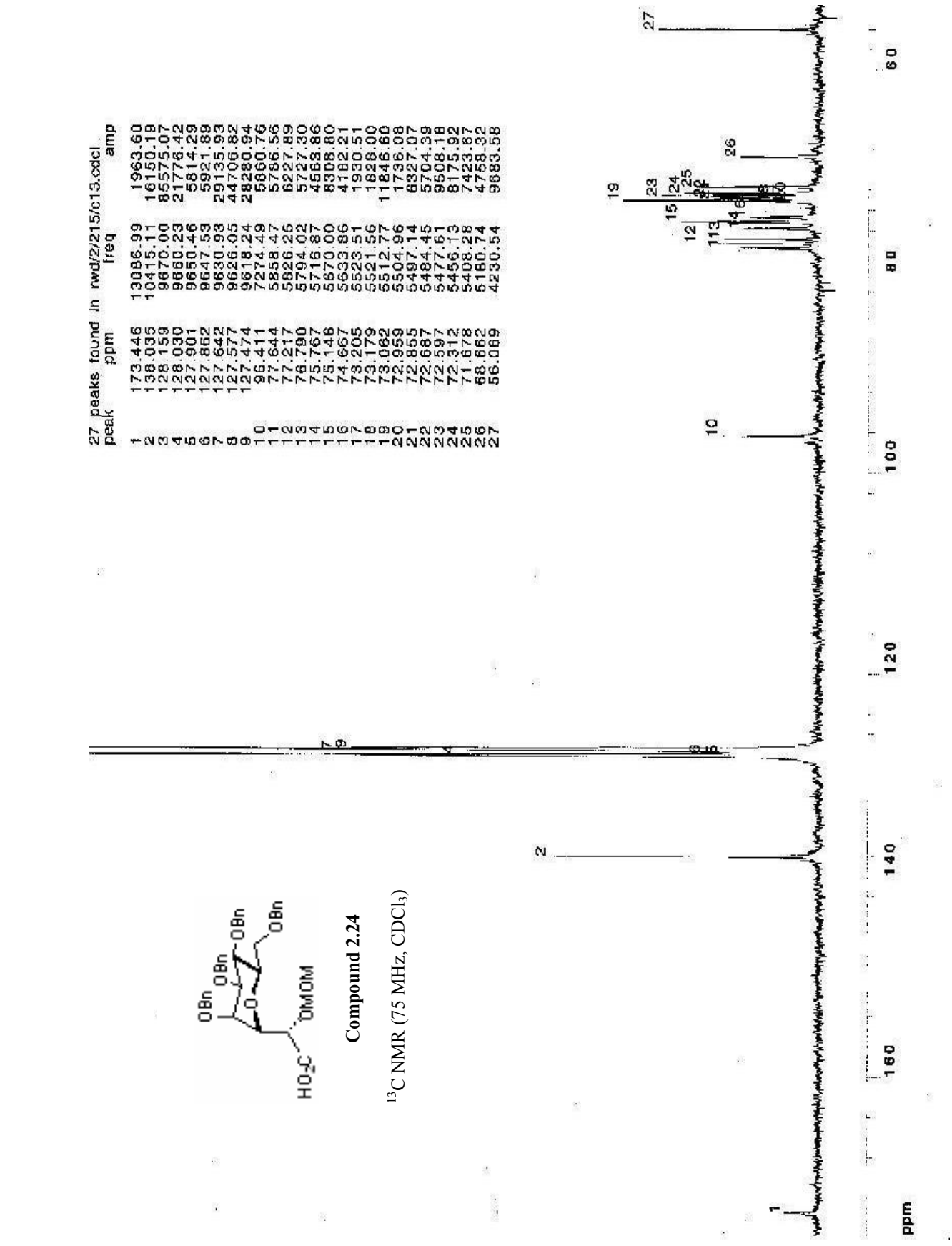
Compound 2.13

^{1}H NMR (500 MHz, $CDCl_3$)



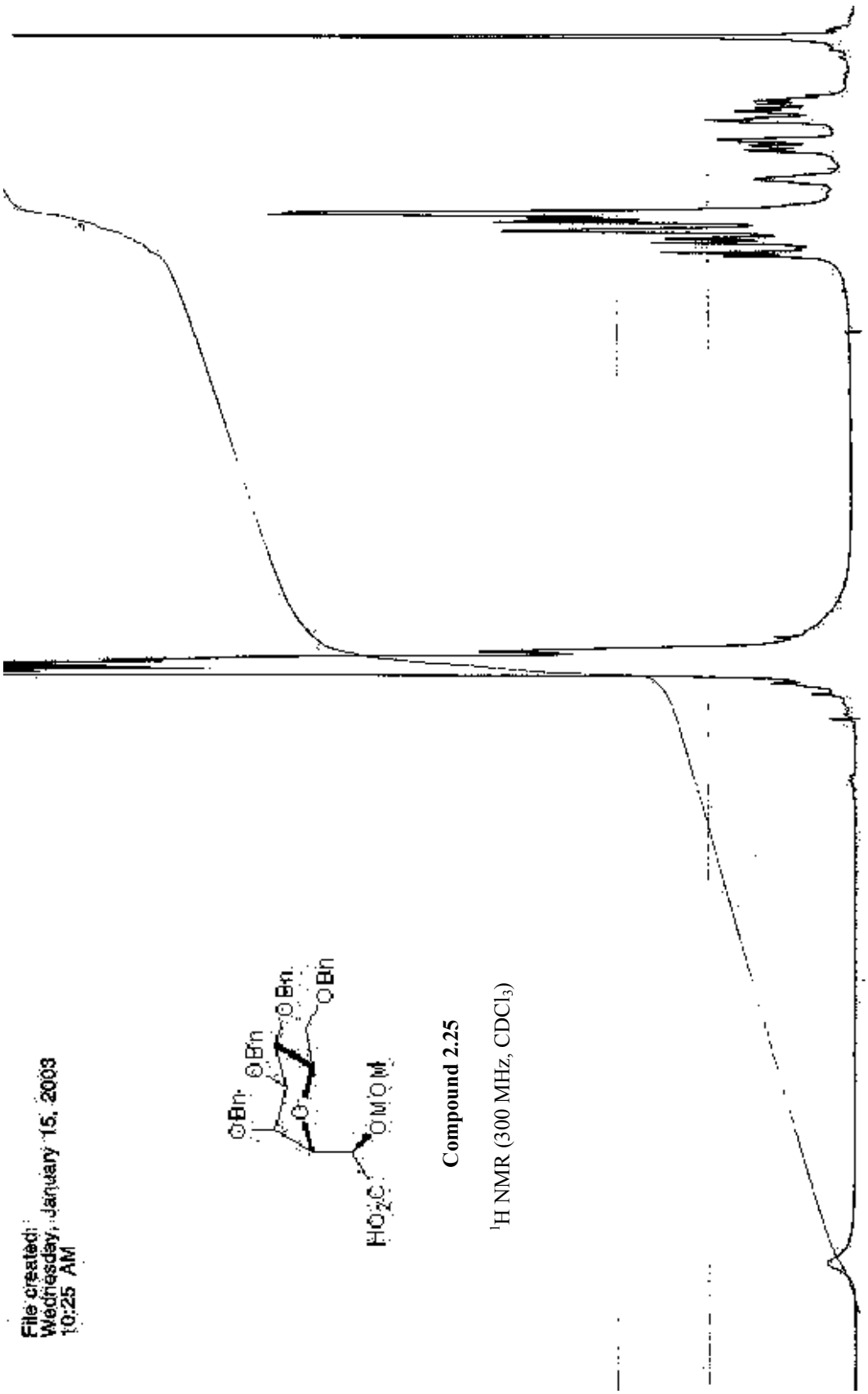
Compound 2.24

^{1}H NMR (300 MHz, $CDCl_3$)



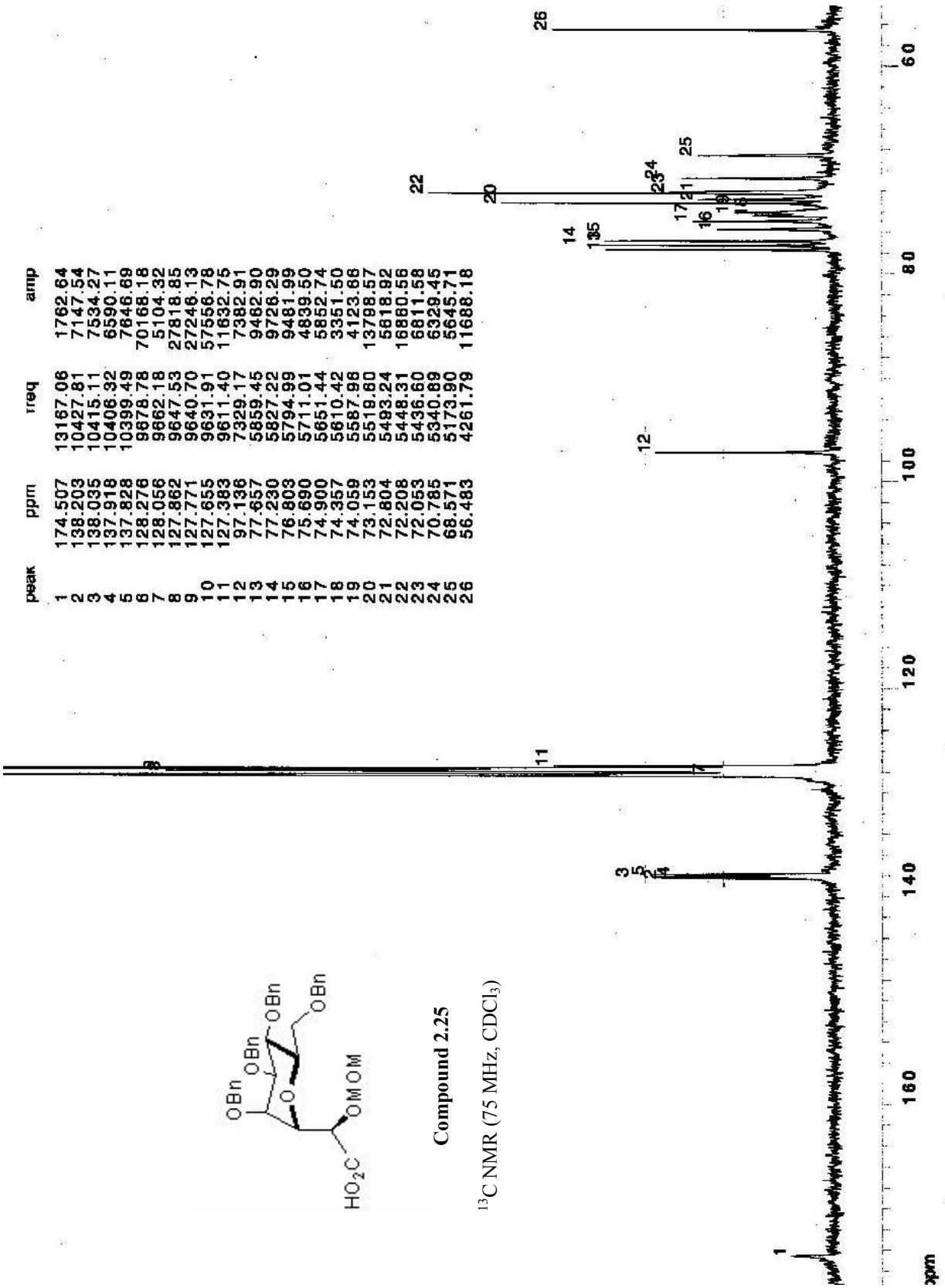
Compound 2.24

^{13}C NMR (75 MHz, $CDCl_3$)



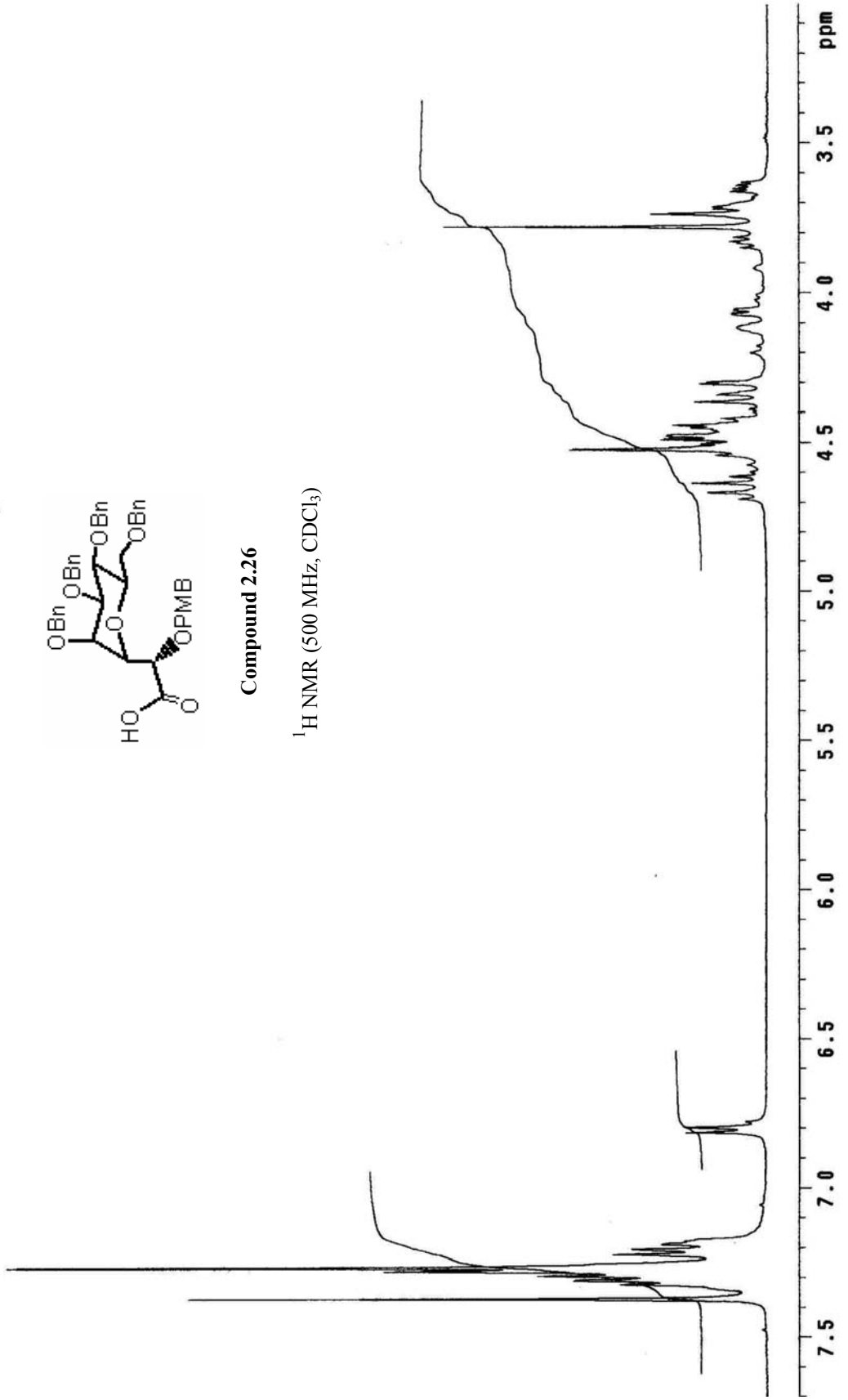
Compound 2.25

^{1}H NMR (300 MHz, $CDCl_3$)



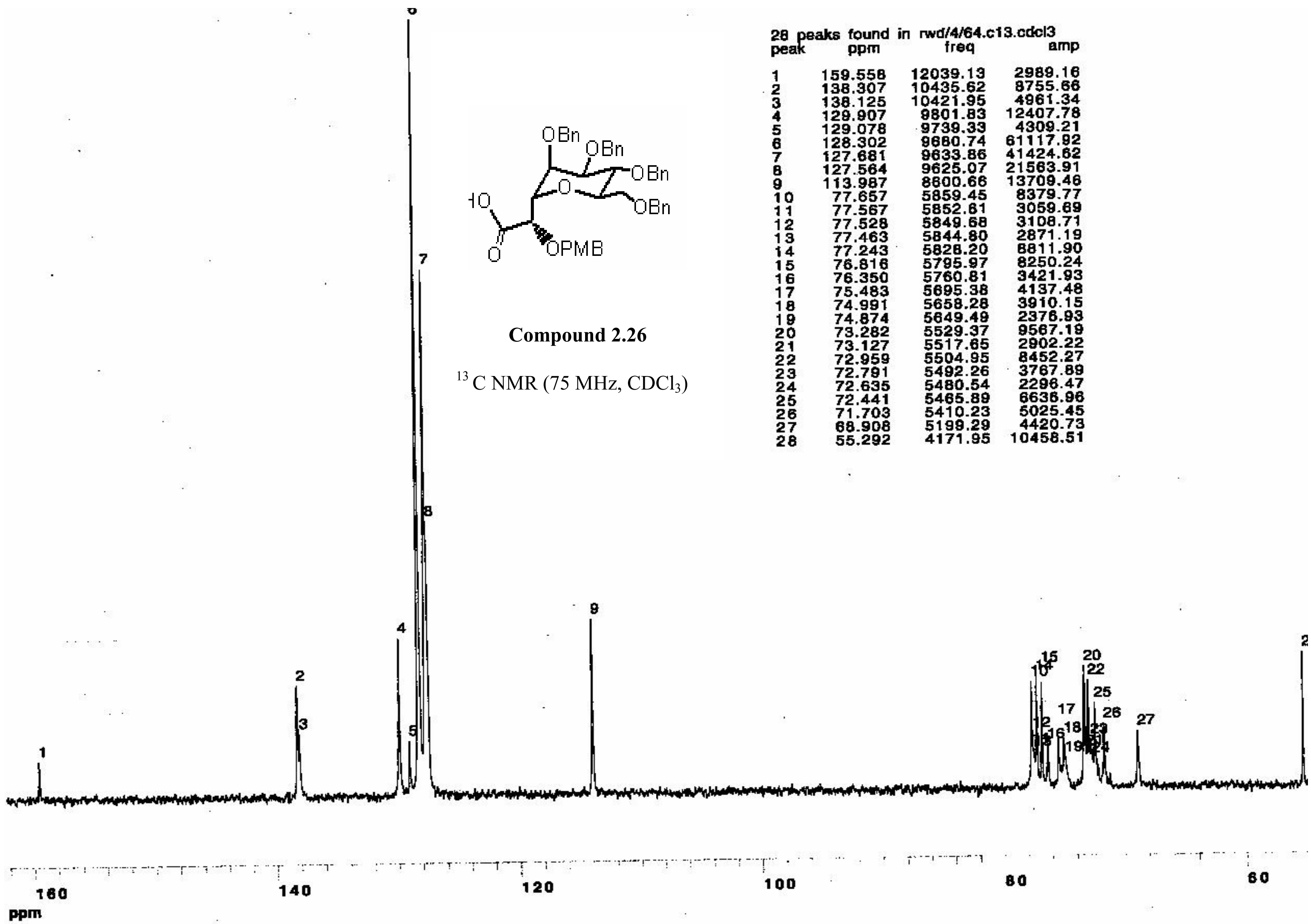
Compound 2.25

^{13}C NMR (75 MHz, $CDCl_3$)



Compound 2.26

^{1}H NMR (500 MHz, $CDCl_3$)

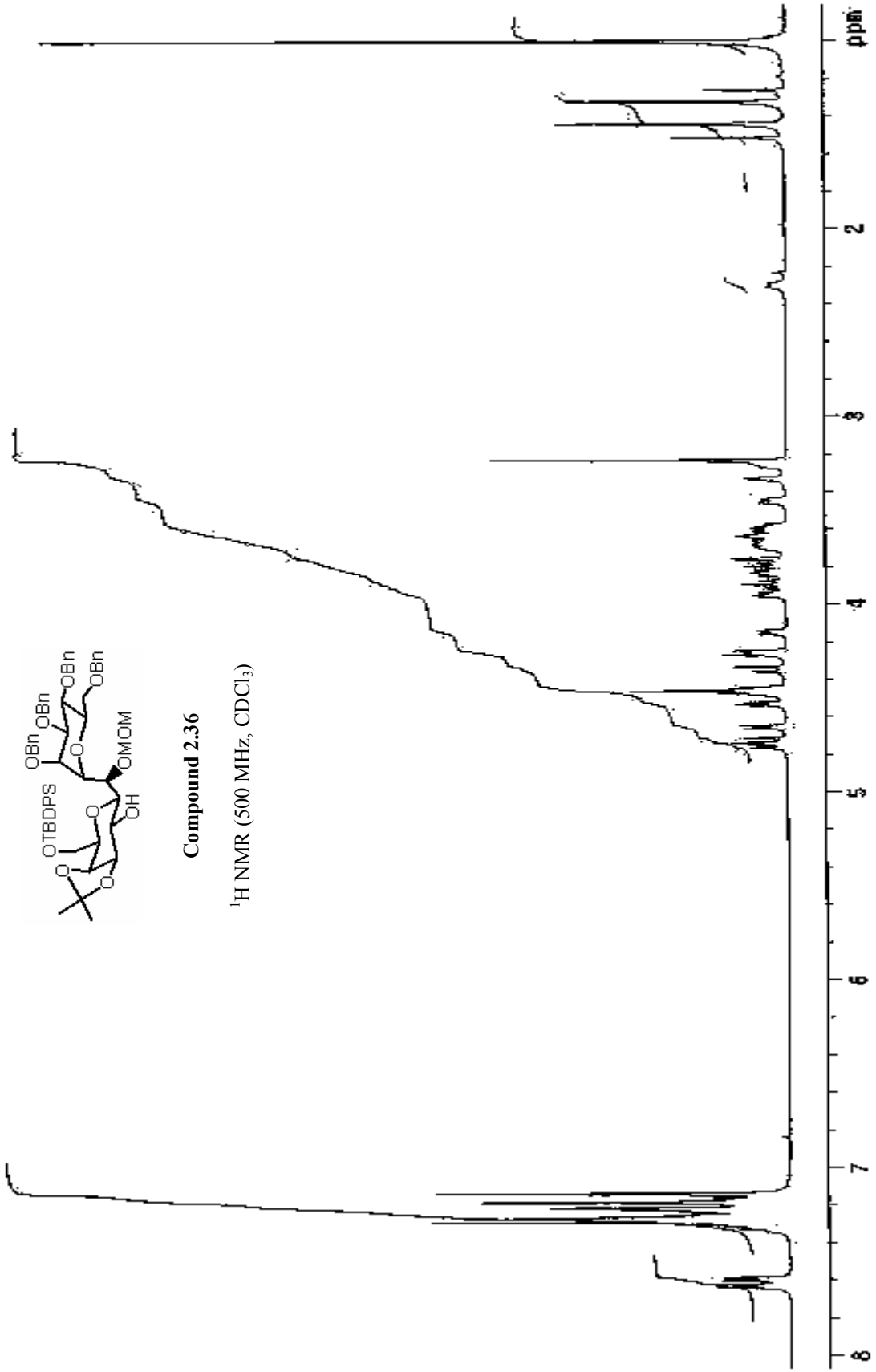


Compound 2.26

^{13}C NMR (75 MHz, $CDCl_3$)

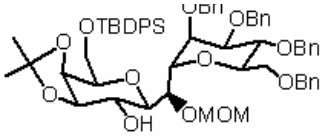
28 peaks found in rwd/4/64.c13.cdcl3

peak	ppm	freq	amp
1	159.558	12039.13	2989.16
2	138.307	10435.62	8755.66
3	138.125	10421.95	4961.34
4	129.907	9801.83	12407.78
5	129.078	9739.33	4309.21
6	128.302	9680.74	61117.92
7	127.681	9633.86	41424.62
8	127.564	9625.07	21563.91
9	113.987	8600.66	13709.46
10	77.657	5859.45	8379.77
11	77.567	5852.61	3059.69
12	77.528	5849.68	3108.71
13	77.463	5844.80	2871.19
14	77.243	5828.20	6811.90
15	76.816	5795.97	8250.24
16	76.350	5760.81	3421.93
17	75.483	5695.38	4137.48
18	74.991	5658.28	3910.15
19	74.874	5649.49	2376.93
20	73.282	5529.37	9567.19
21	73.127	5517.65	2902.22
22	72.959	5504.95	8452.27
23	72.791	5492.26	3767.89
24	72.635	5480.54	2296.47
25	72.441	5465.89	6636.96
26	71.703	5410.23	5025.45
27	68.908	5199.29	4420.73
28	55.292	4171.95	10458.51



Compound 2.36

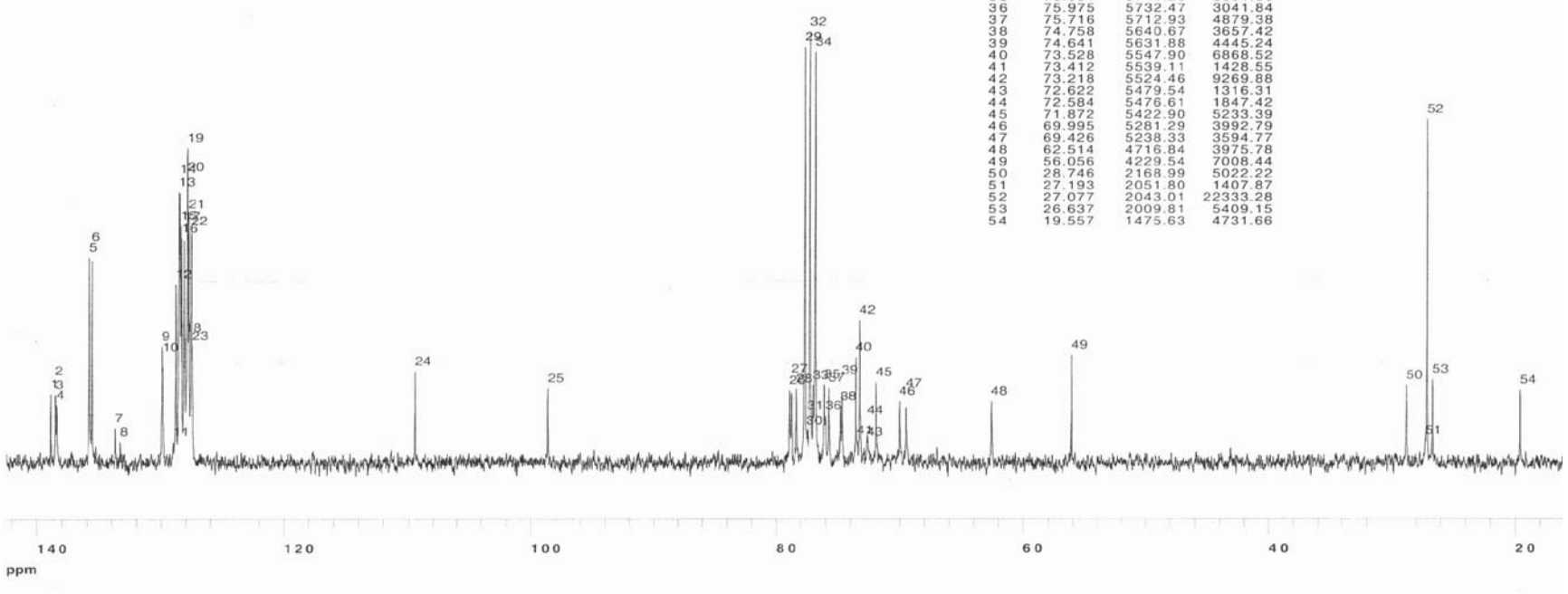
^{1}H NMR (500 MHz, $CDCl_3$)

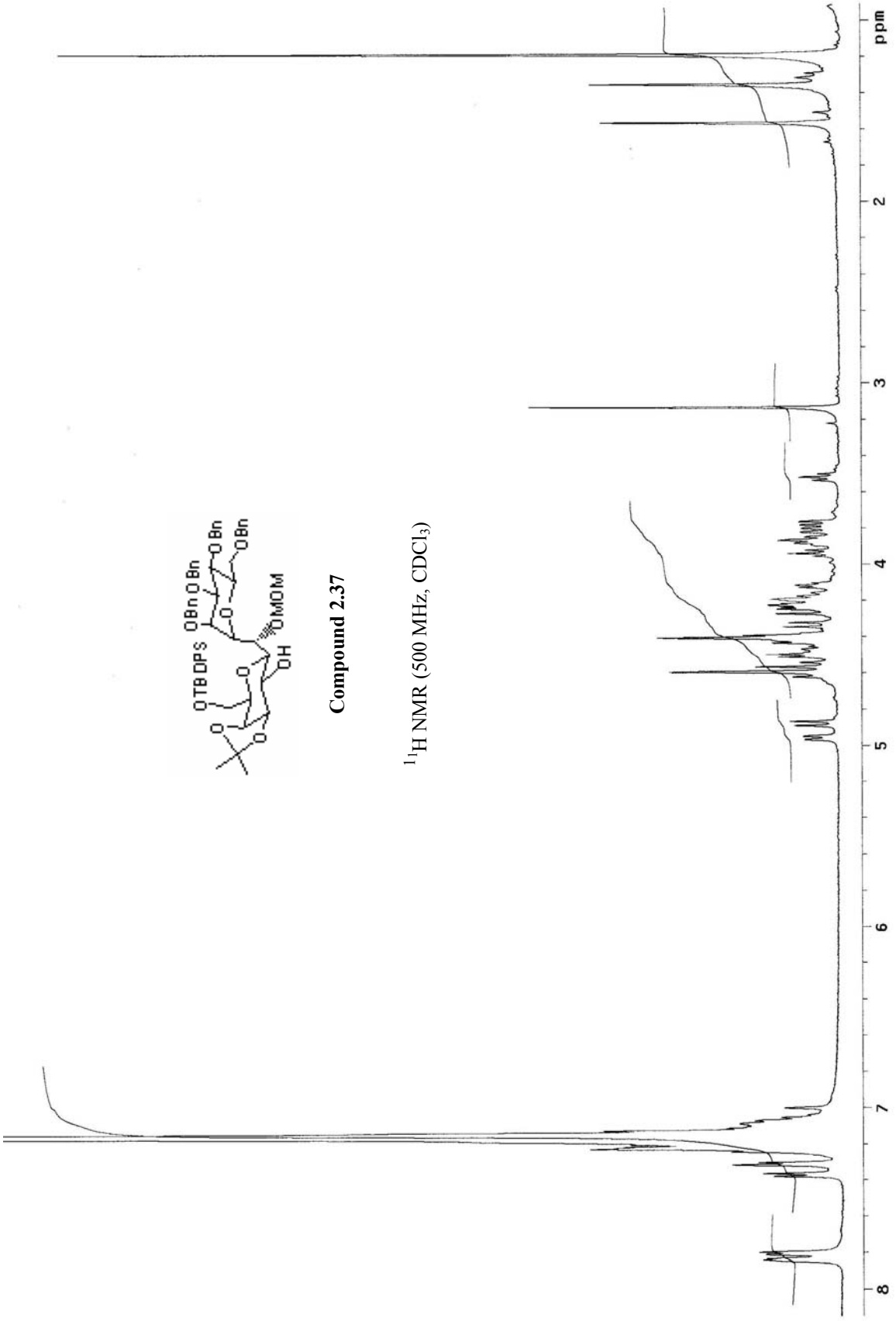


Compound 2.36

^{13}C NMR (75 MHz, $CDCl_3$)

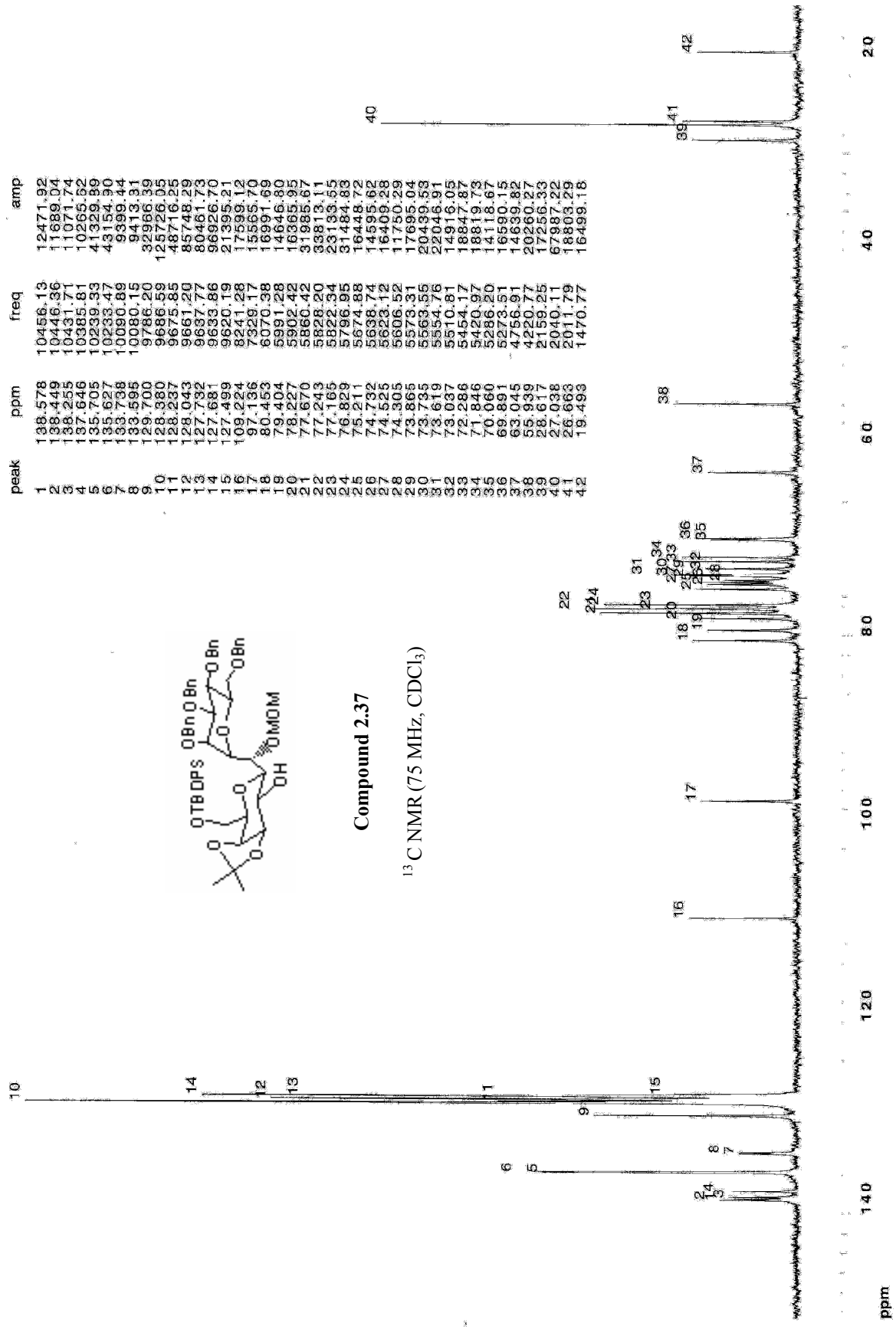
peak	ppm	freq	amp
1	138.850	10476.61	4491.67
2	138.501	10450.24	4416.36
3	138.475	10448.29	4427.38
4	138.385	10441.45	3775.69
5	135.757	10243.21	13341.56
6	135.550	10227.58	13109.63
7	133.647	10084.03	2238.30
8	133.259	10054.73	1325.70
9	129.868	9798.87	7566.71
10	129.829	9795.94	6863.62
11	128.962	9730.51	1348.66
12	128.755	9714.89	11605.51
13	128.522	9697.31	17585.02
14	128.444	9691.45	17522.78
15	128.367	9685.59	15403.92
16	128.289	9679.73	14573.12
17	128.095	9665.08	14457.95
18	128.017	9659.22	8118.92
19	127.836	9645.55	20460.14
20	127.797	9642.62	18581.94
21	127.720	9636.76	16152.23
22	127.526	9622.11	15054.76
23	127.461	9617.23	7604.55
24	109.393	8253.95	5953.14
25	98.586	7438.52	4855.93
26	78.874	5951.22	4711.57
27	78.718	5939.50	4544.38
28	78.317	5909.22	4811.53
29	77.657	5859.42	27056.20
30	77.528	5849.65	2053.16
31	77.424	5841.84	2145.74
32	77.230	5827.19	28038.29
33	76.984	5808.64	5041.49
34	76.803	5794.97	26736.22
35	76.091	5741.25	5091.30
36	75.975	5732.47	3041.84
37	75.716	5712.93	4879.38
38	74.758	5640.67	3657.42
39	74.641	5631.88	4445.24
40	73.528	5547.90	6868.52
41	73.412	5539.11	1428.55
42	73.218	5524.46	9269.88
43	72.622	5479.54	1316.31
44	72.584	5476.61	1847.42
45	71.872	5422.90	5233.39
46	69.995	5281.29	3992.79
47	69.426	5238.33	3594.77
48	62.514	4716.84	3975.78
49	56.056	4229.54	7008.44
50	28.746	2168.99	5022.22
51	27.193	2051.80	1407.87
52	27.077	2043.01	22333.28
53	26.637	2009.81	5409.15
54	19.557	1475.63	4731.66

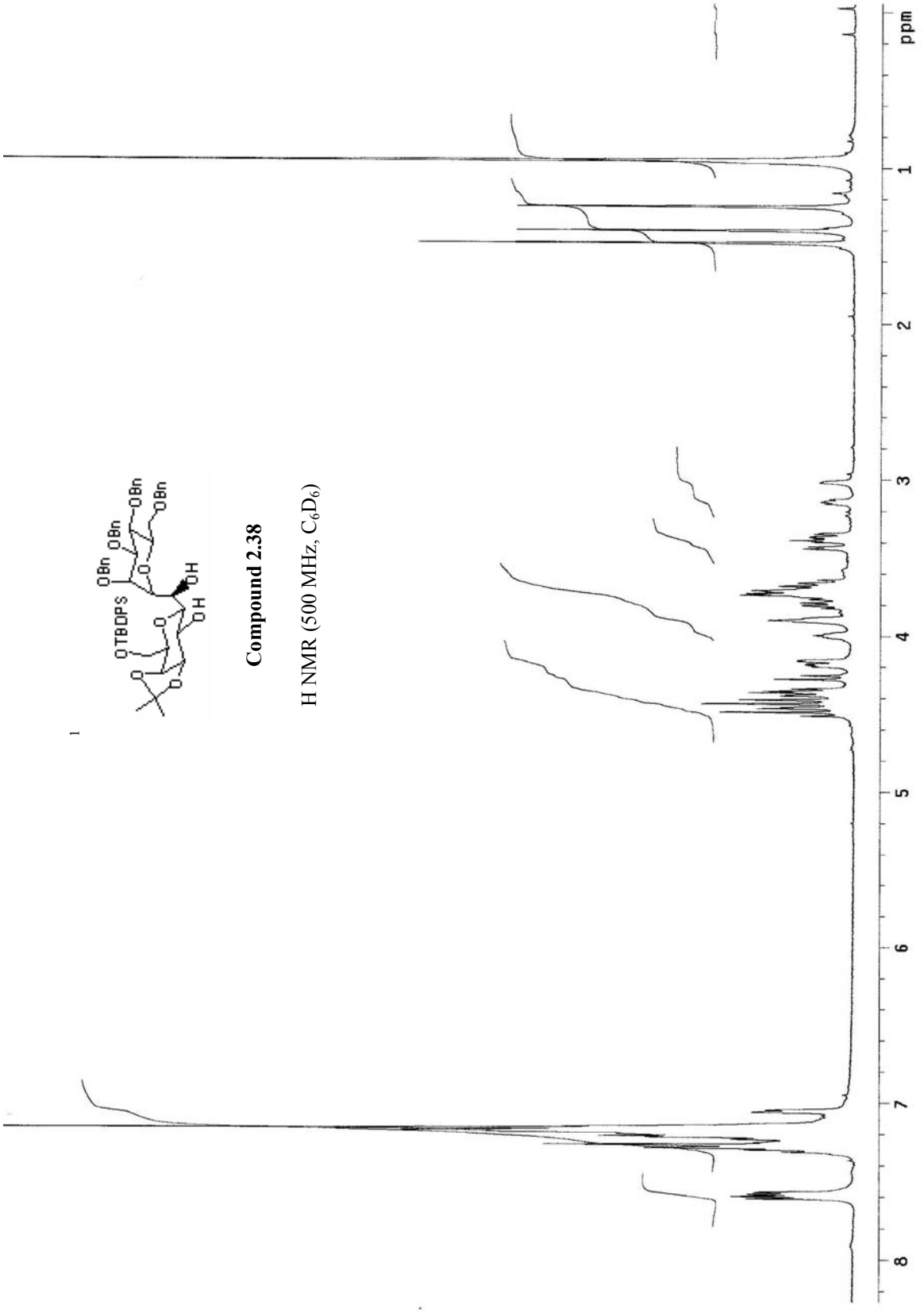




Compound 2.37

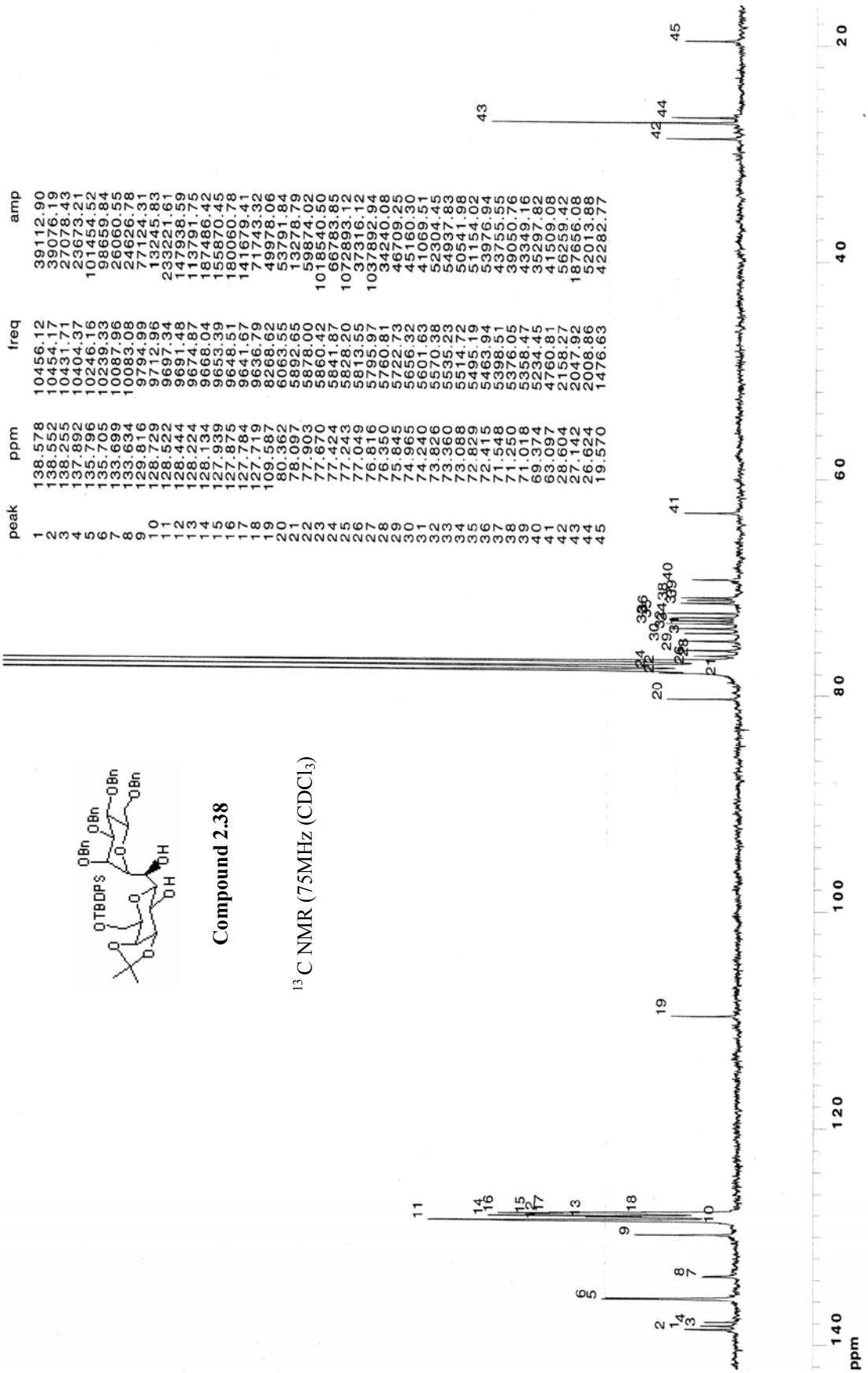
^{1}H NMR (500 MHz, $CDCl_3$)

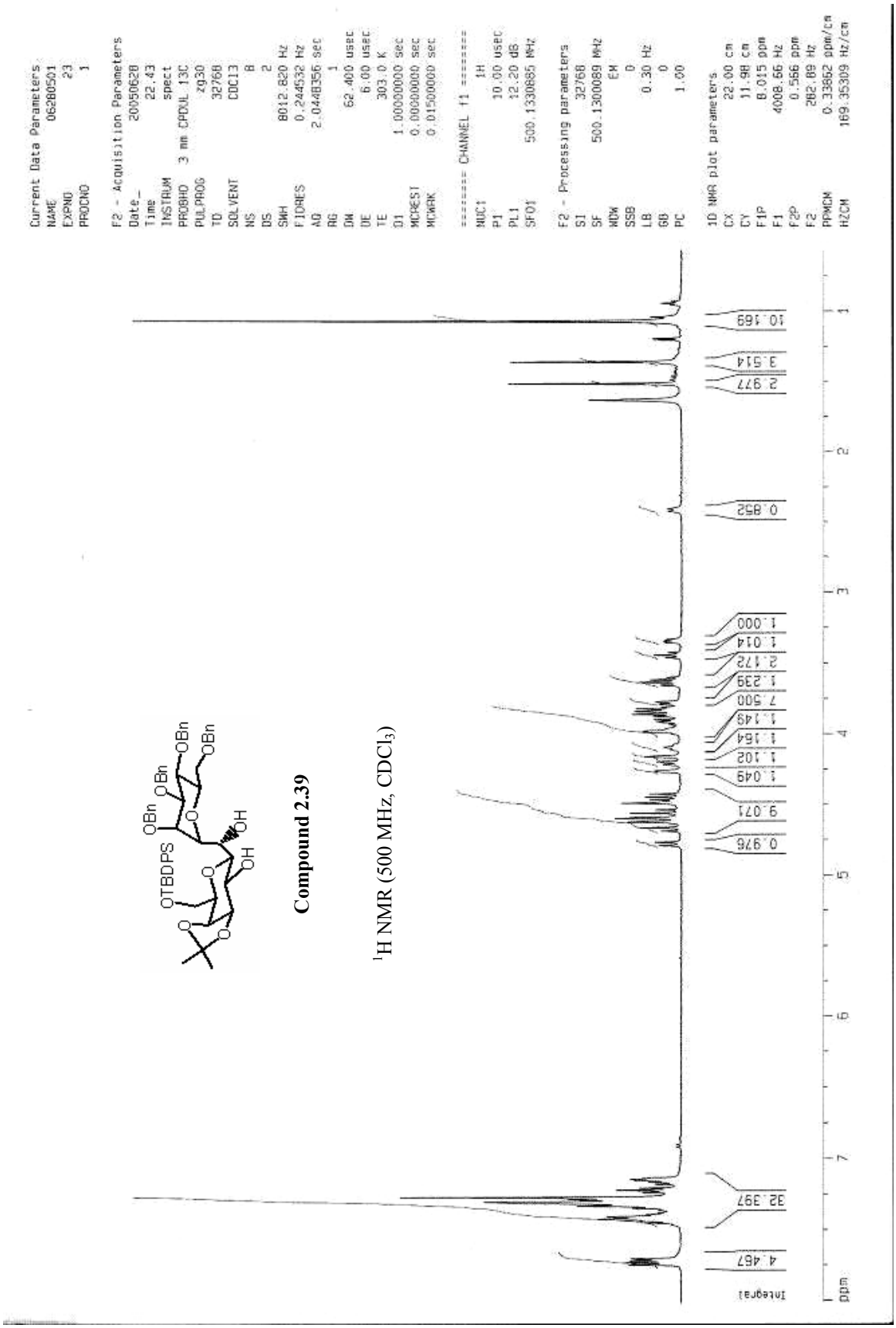

peak ppm freq amp
1 138.578 10456.13 12471.92
2 138.449 10446.36 11689.04
3 138.255 10431.71 11071.74
4 137.646 10385.81 10265.52
5 135.705 10239.33 41329.89
6 135.627 10233.47 43154.30
7 133.738 10090.89 9399.44
8 133.595 10080.15 9413.31
9 129.700 9786.20 32966.39
10 128.380 9686.59 125726.05
11 128.237 9675.85 48716.25
12 128.043 9661.20 85748.29
13 127.732 9637.77 80461.73
14 127.681 9633.86 96926.70
15 127.499 9620.19 21395.21
16 109.224 8241.28 17599.12
17 97.136 7329.17 15565.70
18 80.453 6070.38 16991.69
19 79.404 5991.28 14646.80
20 78.227 5902.42 16365.95
21 77.670 5860.42 31985.67
22 77.243 5828.20 33813.11
23 77.165 5822.34 23133.55
24 76.829 5796.95 31484.83
25 75.211 5674.88 16448.72
26 74.732 5638.74 14595.62
27 74.525 5623.12 16409.28
28 74.305 5606.52 11750.29
29 73.865 5573.31 17695.04
30 73.735 5563.55 20439.53
31 73.619 5554.76 22046.91
32 73.037 5510.81 14916.05
33 72.286 5454.17 18847.87
34 71.846 5420.97 18819.73
35 70.060 5286.20 14118.67
36 69.891 5273.51 16590.15
37 63.045 4756.91 14639.82
38 55.939 4220.77 20260.27
39 28.617 2159.25 17256.33
40 27.038 2040.11 67987.22
41 26.663 2011.79 18803.29
42 19.493 1470.77 16499.18
OTBDPS
OBn
OBn
OBn
OMOM
OH
Compound 2.37
^{13}C NMR (75 MHz, $CDCl_3$)
ppm

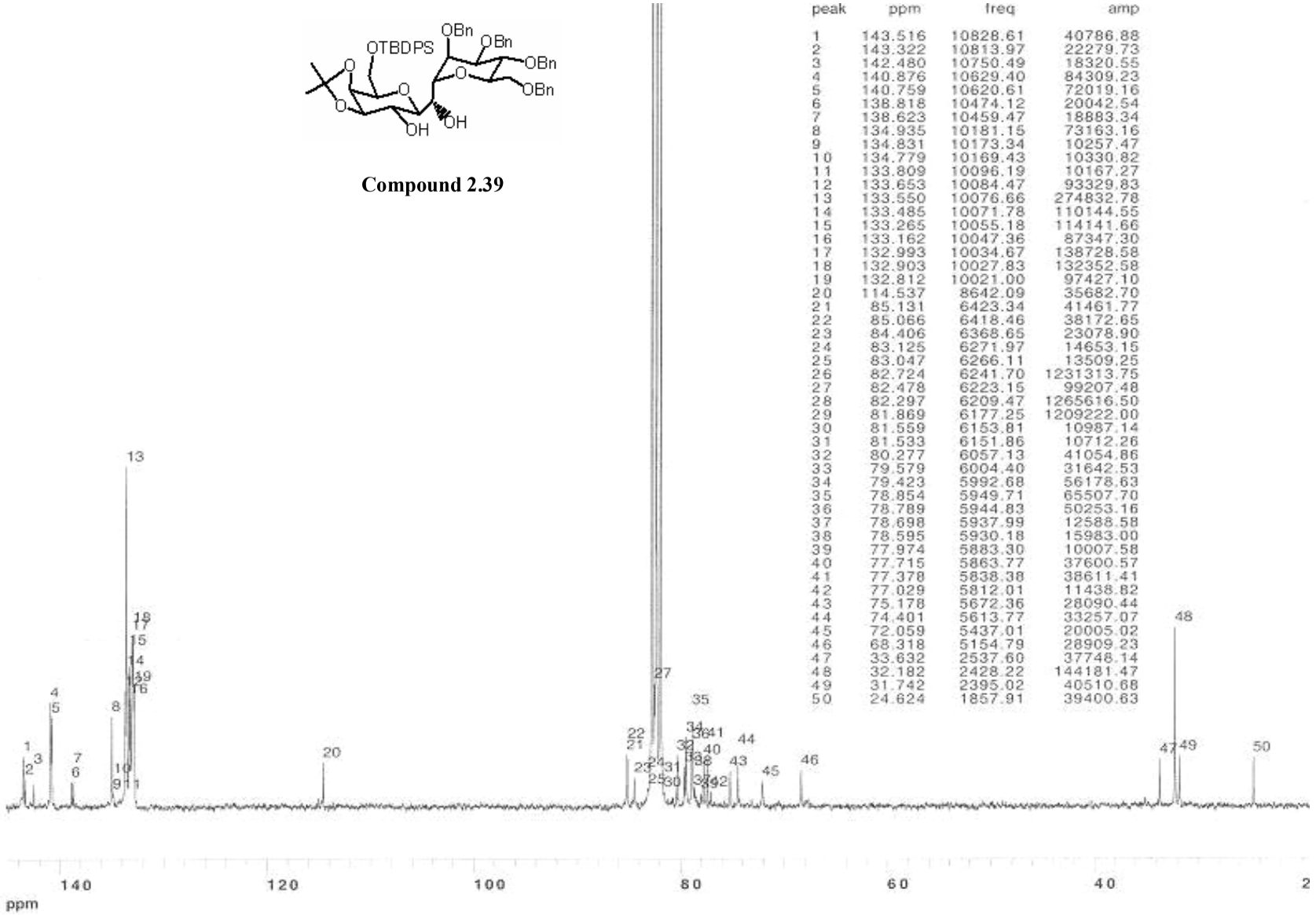


Compound 2.38

H NMR (500 MHz, C_6D_6)

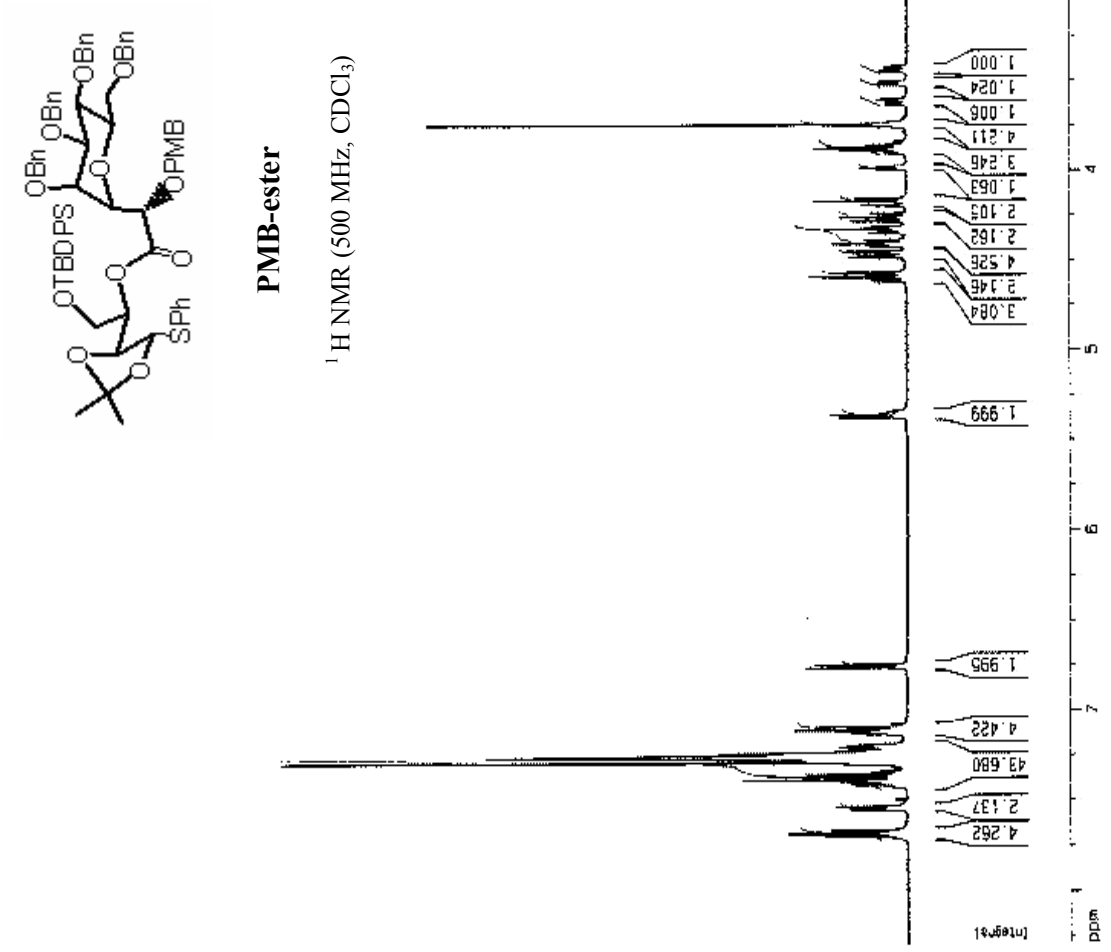

OTBDPS
OBn
OBn
OBn
OBn
OH
OH
Compound 2.38
^{13}C NMR (75MHz ($CDCl_3$)
peak ppm freq amp
1 138.578 10456.12 39112.90
2 138.552 10454.17 39076.19
3 138.255 10431.71 27078.43
4 137.892 10404.37 23673.21
5 135.796 10246.16 101454.52
6 135.705 10239.33 98659.84
7 133.699 10087.96 26060.55
8 133.634 10083.08 24626.78
9 129.816 9794.99 77124.31
10 128.729 9712.96 13245.83
11 128.522 9697.34 233221.61
12 128.444 9691.48 147938.59
13 128.224 9674.87 113791.75
14 128.134 9668.04 187486.42
15 127.939 9653.39 155870.45
16 127.875 9648.51 180060.78
17 127.784 9641.67 141679.41
18 127.719 9636.79 71743.32
19 109.587 8268.62 49978.06
20 80.362 6063.55 53791.84
21 78.097 5892.65 13278.79
22 77.903 5878.00 59874.02
23 77.670 5860.42 1018540.50
24 77.424 5841.87 66783.85
25 77.243 5828.20 1072893.12
26 77.049 5813.55 37316.12
27 76.816 5795.97 1037892.94
28 76.350 5760.81 34240.08
29 75.845 5722.73 46709.25
30 74.965 5656.32 45160.30
31 74.240 5601.63 41069.51
32 73.826 5570.38 52304.45
33 73.360 5535.23 54937.83
34 73.088 5514.72 50541.98
35 72.829 5495.19 51154.02
36 72.415 5463.94 53976.94
37 71.548 5398.51 43755.55
38 71.250 5376.05 39050.76
39 71.018 5358.47 43349.16
40 69.374 5234.45 35297.82
41 63.097 4760.81 41509.08
42 28.604 2158.27 56259.42
43 27.142 2047.92 187656.08
44 26.624 2008.86 52013.88
45 19.570 1476.63 42282.77
ppm

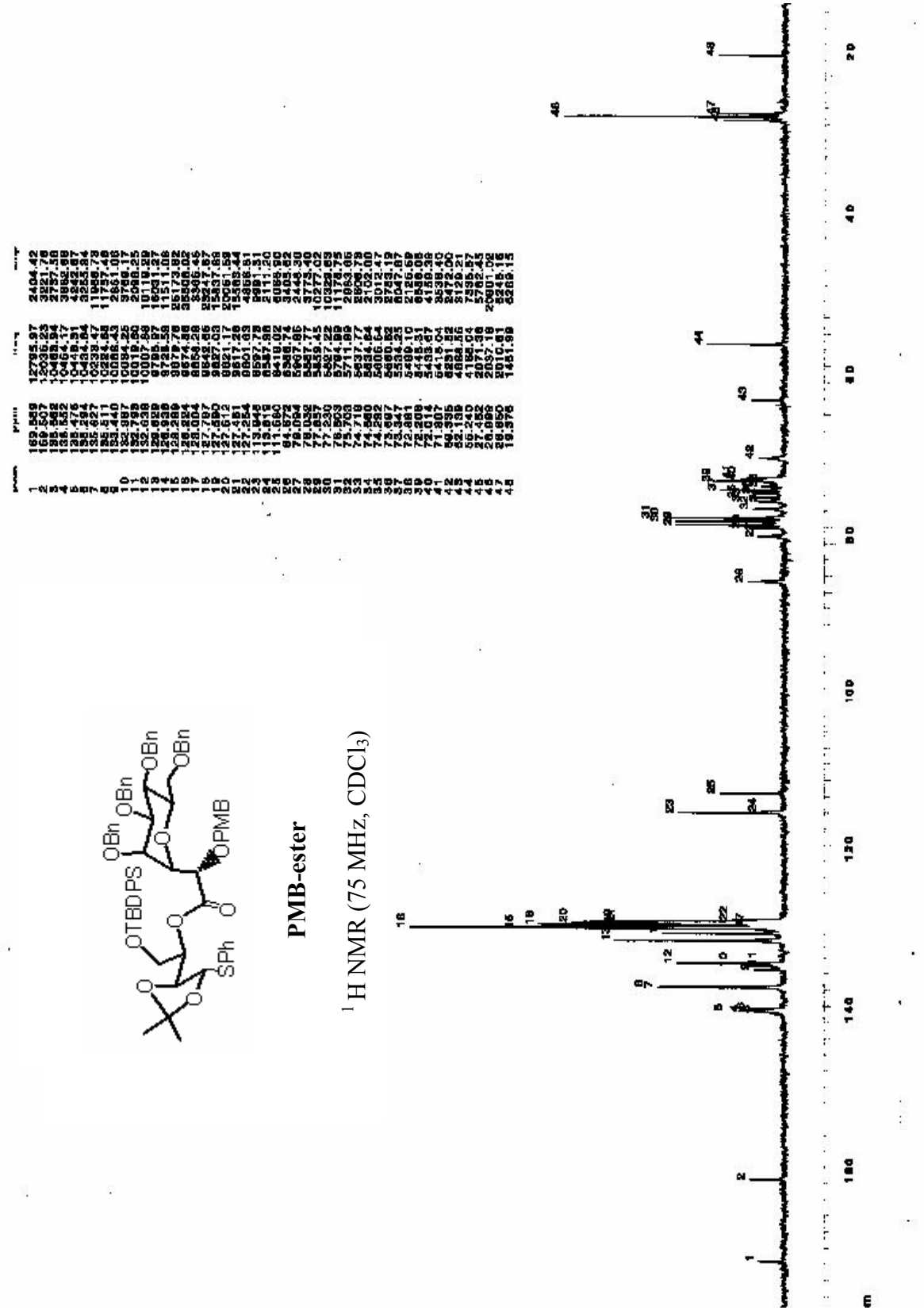

OTBDPS
OBn
OBn
OBn
OH
OH
Compound 2.39
^{1}H NMR (500 MHz, $CDCl_3$)
Current Data Parameters
NAME 06280501
EXPNO 23
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050628
Time 22.43
INSTRUM spect
PROBHD 3 mm CPDUL 13C
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 8
DS 2
SWH 8012.820 Hz
FIDRES 0.244532 Hz
AQ 2.0448356 sec
RG 1
DW 62.400 usec
DE 6.00 usec
TE 303.0 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 10.00 usec
PL1 12.20 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300089 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 22.00 cm
CY 11.98 cm
F1P 8.015 ppm
F1 4008.56 Hz
F2P 0.566 ppm
F2 282.89 Hz
PPMCM 0.33862 ppm/cm
HZCM 169.35309 Hz/cm
integral
4.487
32.397
0.976
9.071
1.049
1.102
1.164
1.149
7.500
1.239
2.172
1.014
1.000
0.852
2.977
3.514
10.189
ppm



Compound 2.39

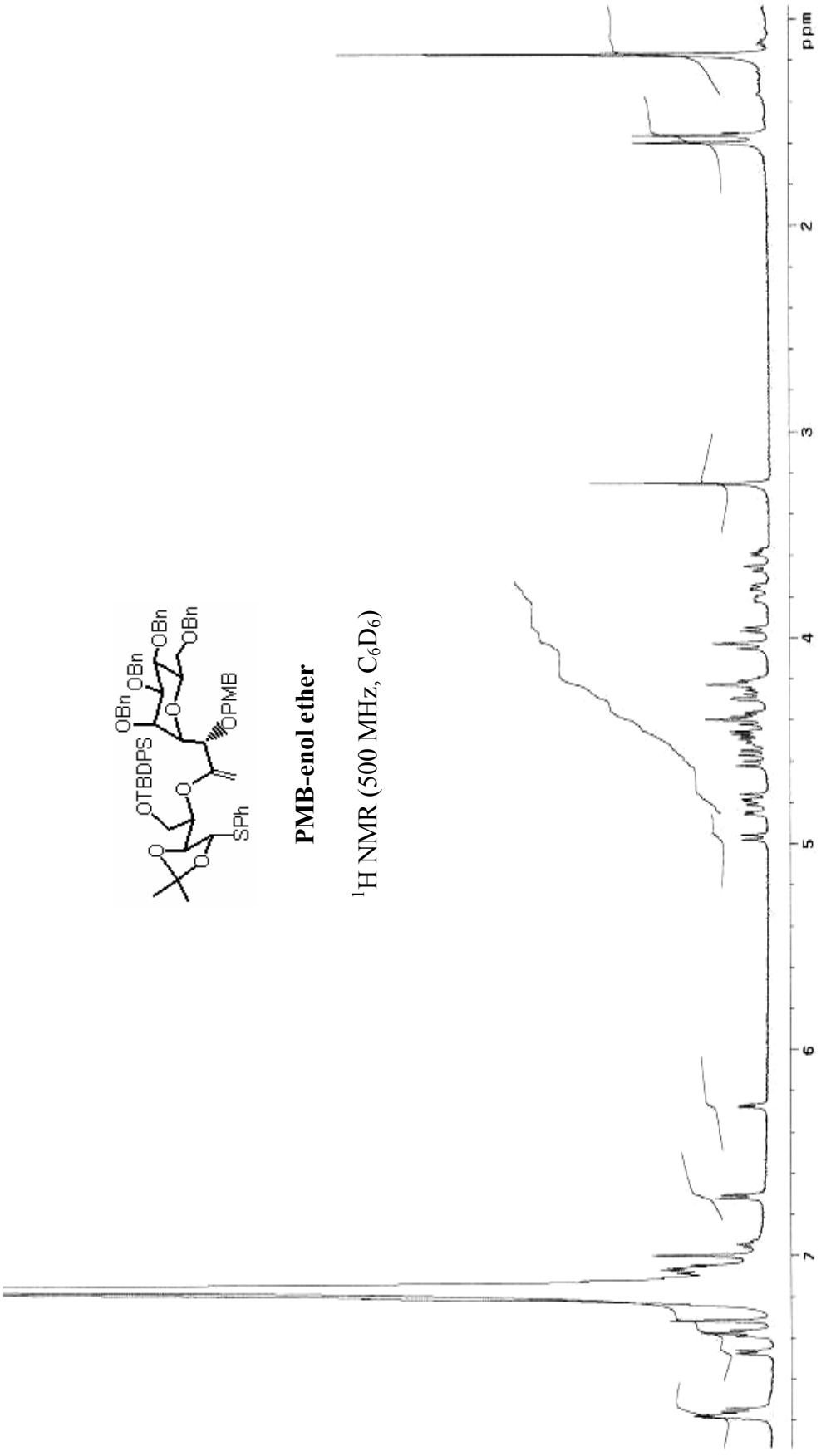
peak	ppm	freq	amp
1	143.516	10828.61	40786.88
2	143.322	10813.97	22279.73
3	142.480	10750.49	18320.55
4	140.876	10629.40	84309.23
5	140.759	10620.61	72019.16
6	138.818	10474.12	20042.54
7	138.623	10459.47	18883.34
8	134.935	10181.15	73163.16
9	134.831	10173.34	10257.47
10	134.779	10169.43	10330.82
11	133.809	10096.19	10167.27
12	133.653	10084.47	93329.83
13	133.550	10076.66	274832.78
14	133.485	10071.78	110144.55
15	133.265	10055.18	114141.66
16	133.162	10047.36	87347.30
17	132.993	10034.67	138728.58
18	132.903	10027.83	132352.58
19	132.812	10021.00	97427.10
20	114.537	8642.09	35682.70
21	85.131	6423.34	41461.77
22	85.066	6418.46	38172.65
23	84.406	6368.65	23078.90
24	83.125	6271.97	14653.15
25	83.047	6266.11	13509.25
26	82.724	6241.70	1231313.75
27	82.478	6223.15	99207.48
28	82.297	6209.47	1265616.50
29	81.869	6177.25	1209222.00
30	81.559	6153.81	10987.14
31	81.533	6151.86	10712.26
32	80.277	6057.13	41054.86
33	79.579	6004.40	31642.53
34	79.423	5992.68	56178.63
35	78.854	5949.71	65507.70
36	78.789	5944.83	50253.16
37	78.698	5937.99	12588.58
38	78.595	5930.18	15983.00
39	77.974	5883.30	10007.58
40	77.715	5863.77	37600.57
41	77.378	5838.38	38611.41
42	77.029	5812.01	11438.82
43	75.178	5672.36	28090.44
44	74.401	5613.77	33257.07
45	72.059	5437.01	20005.02
46	68.318	5154.79	28909.23
47	33.632	2537.60	37748.14
48	32.182	2428.22	144181.47
49	31.742	2395.02	40510.68
50	24.624	1857.91	39400.63


PMB-ester
^{1}H NMR (500 MHz, $CDCl_3$)
H_2O
OBn
OBn
OBn
OTBDPS
OPMB
SPh
O
Current Data Parameters
NAME 05070401
EXPNO 5
PROCNO 1
F2 - Acquisition Parameters
Date_ 20040507
Time 13.13
INSTRUM spect
PROBHD 5 mm DUL 13C-H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 8
DS 2
SWH 6666.667 Hz
FIDRES 0.203451 Hz
AQ 2.4577250 sec
RG 406.4
DW 75.000 usec
DE 6.00 usec
TE 303.0 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 8.45 usec
PL1 -3.00 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMH plot parameters
CX 22.00 cm
CY 46.55 cm
F1P 8.285 ppm
F1 4143.57 Hz
F2P 0.654 ppm
F2 326.84 Hz
PPMCM 0.34685 ppm/cm
HZCM 173.48772 Hz/cm
9.721
3.413
3.150
1.000
1.024
1.006
4.211
3.246
1.063
2.105
2.162
4.526
2.146
3.084
1.999
1.995
4.422
43.680
2.137
4.262
Integral
ppm



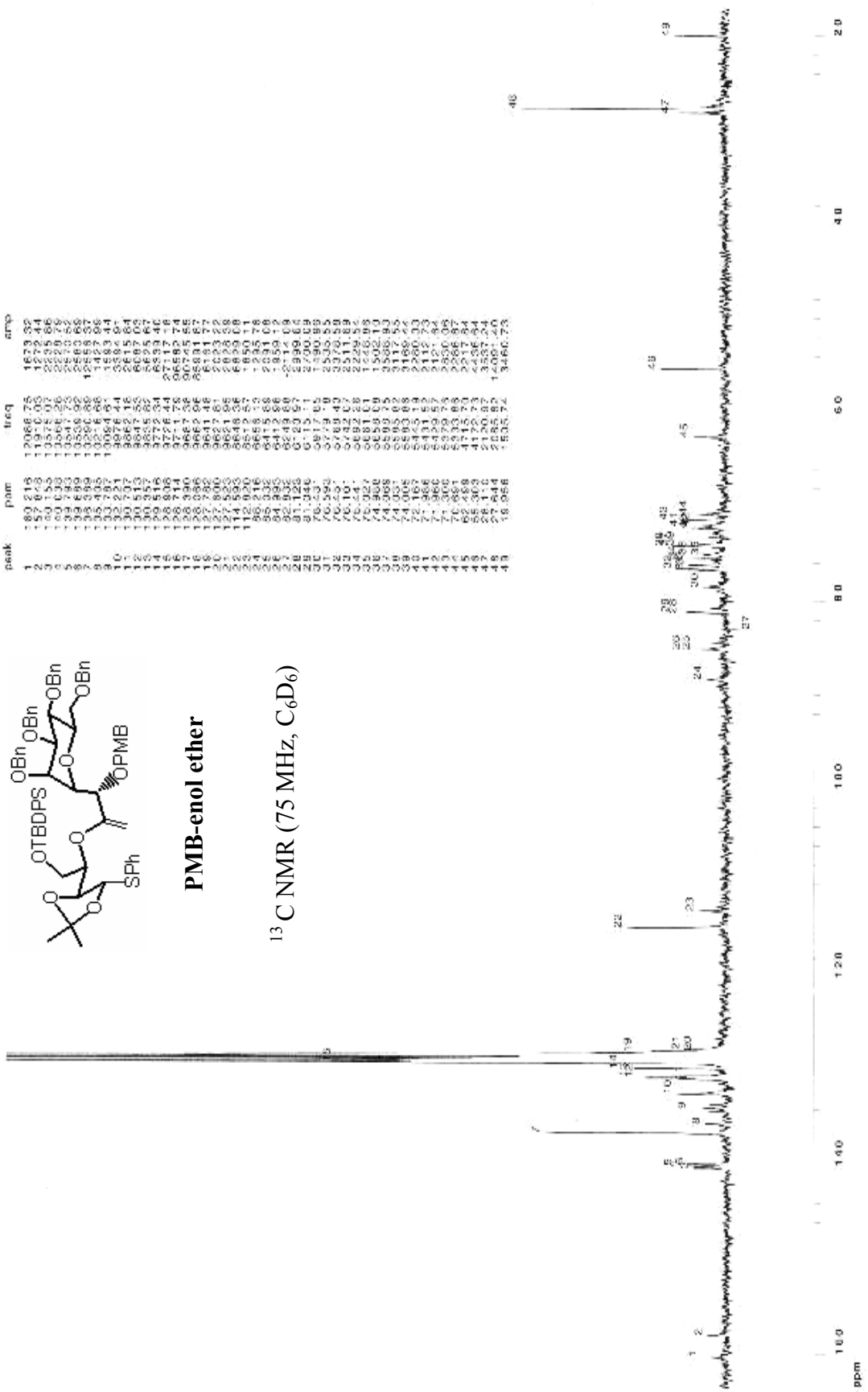
PMB-ester

^{1}H NMR (75 MHz, $CDCl_3$)



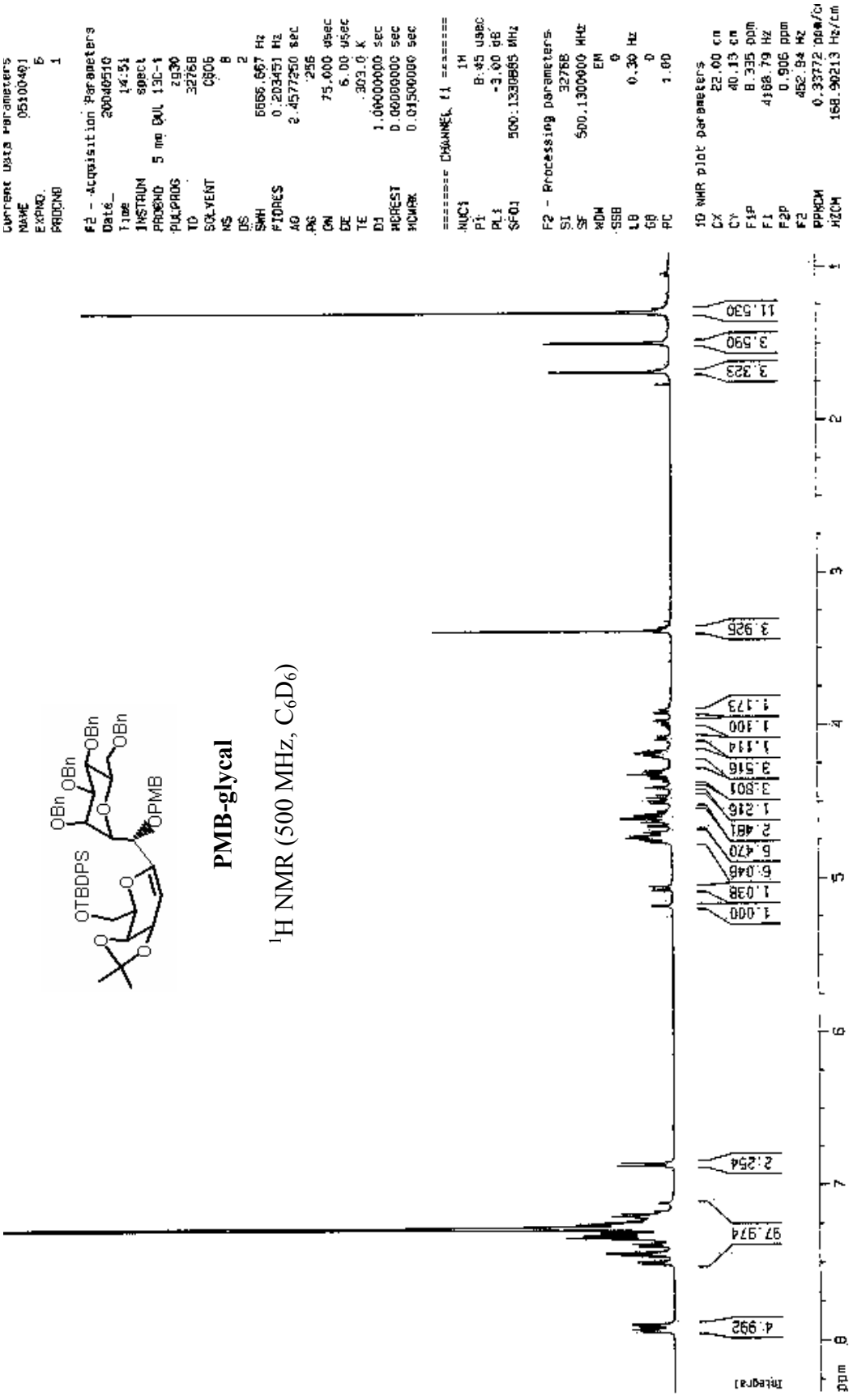
PMB-enol ether

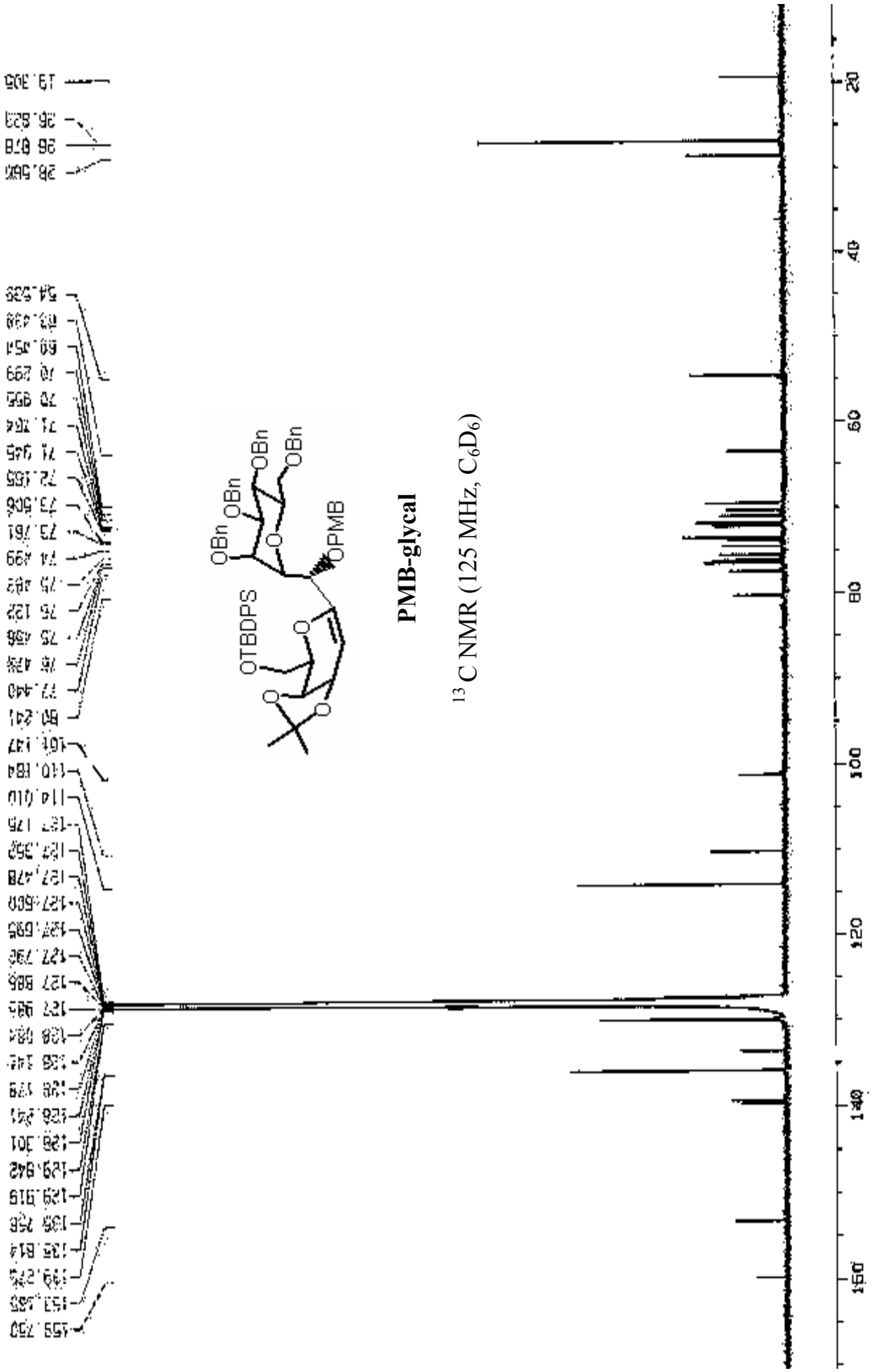
^{1}H NMR (500 MHz, C_6D_6)



PMB-enol ether

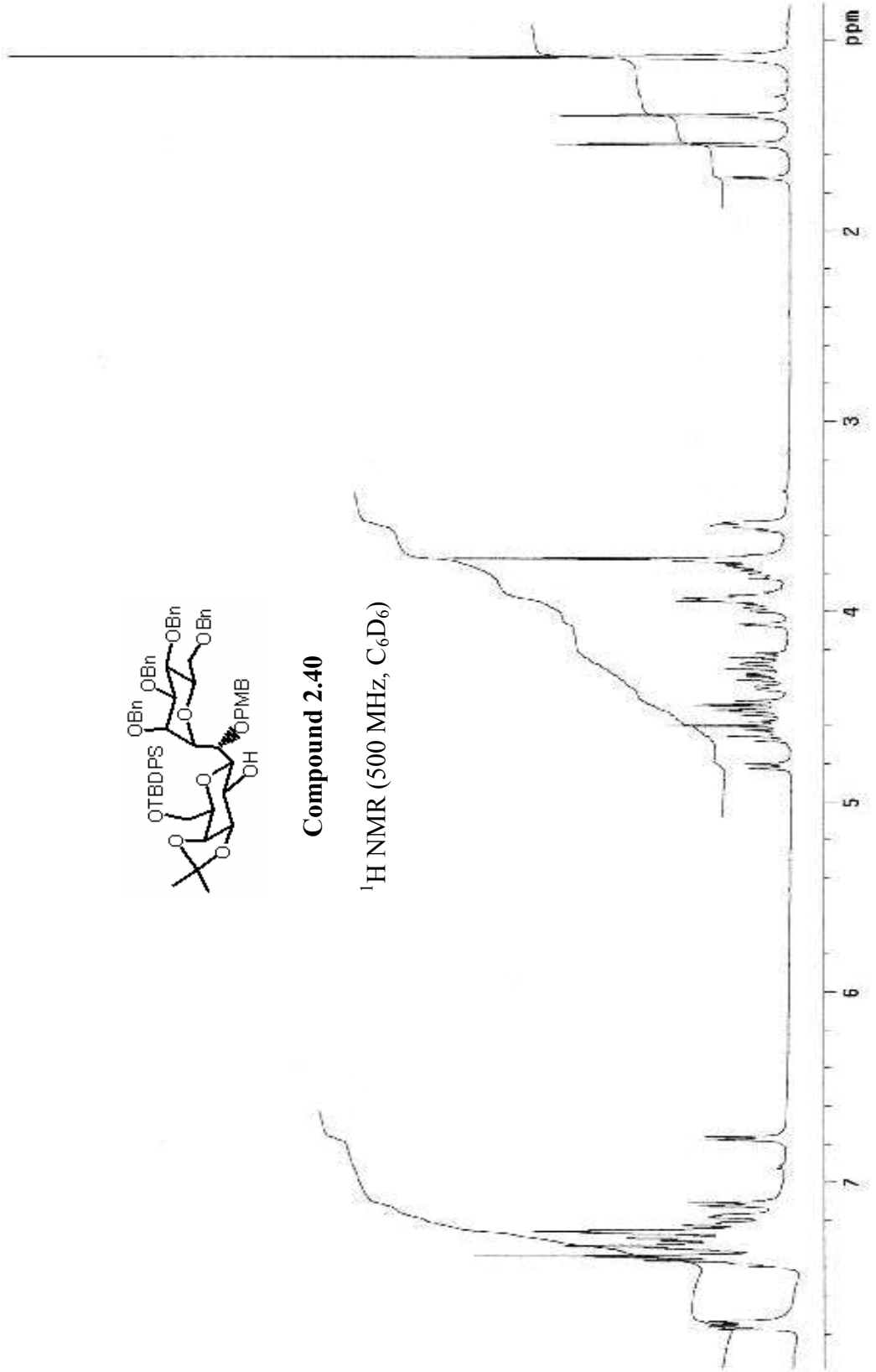
^{13}C NMR (75 MHz, C_6D_6)


OTBDPS
OBn
OBn
OBn
OBn
OPMB
PMB-glycal
^{1}H NMR (500 MHz, C_6D_6)



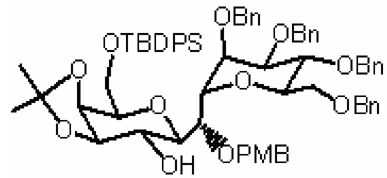
PMB-glycal

^{13}C NMR (125 MHz, C_6D_6)



Compound 2.40

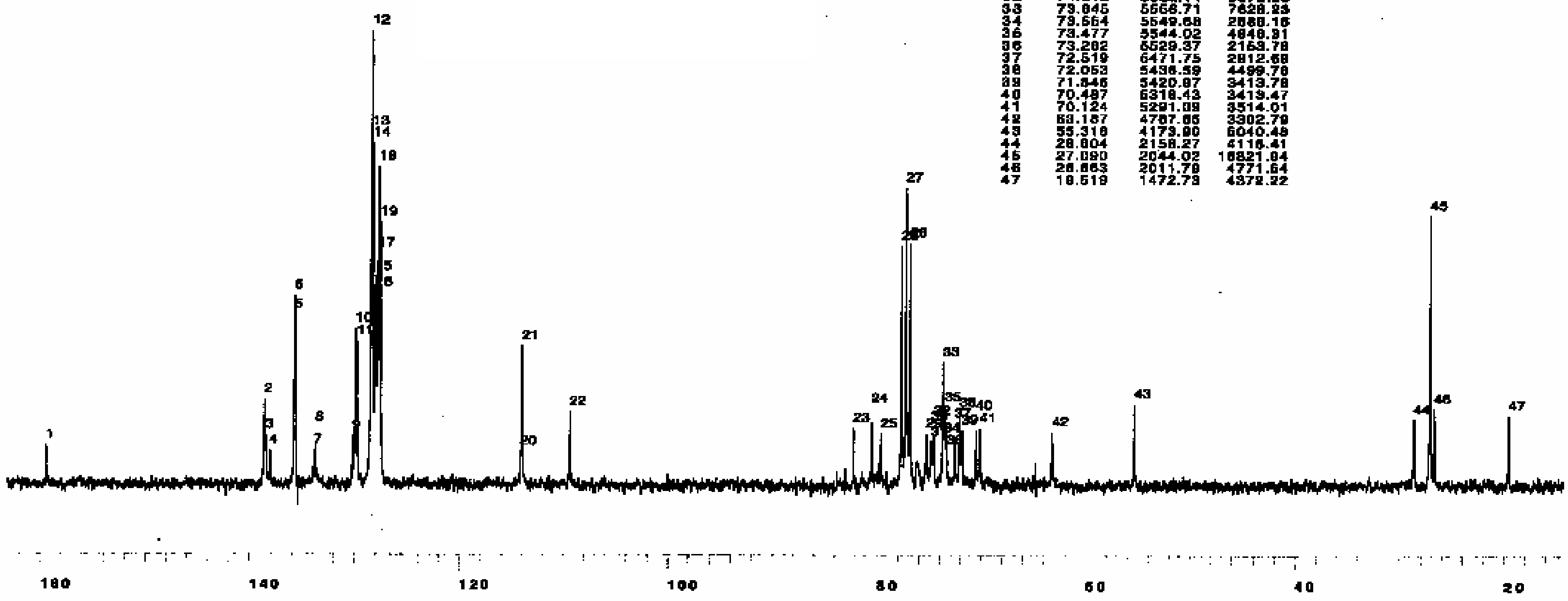
^{1}H NMR (500 MHz, C_6D_6)

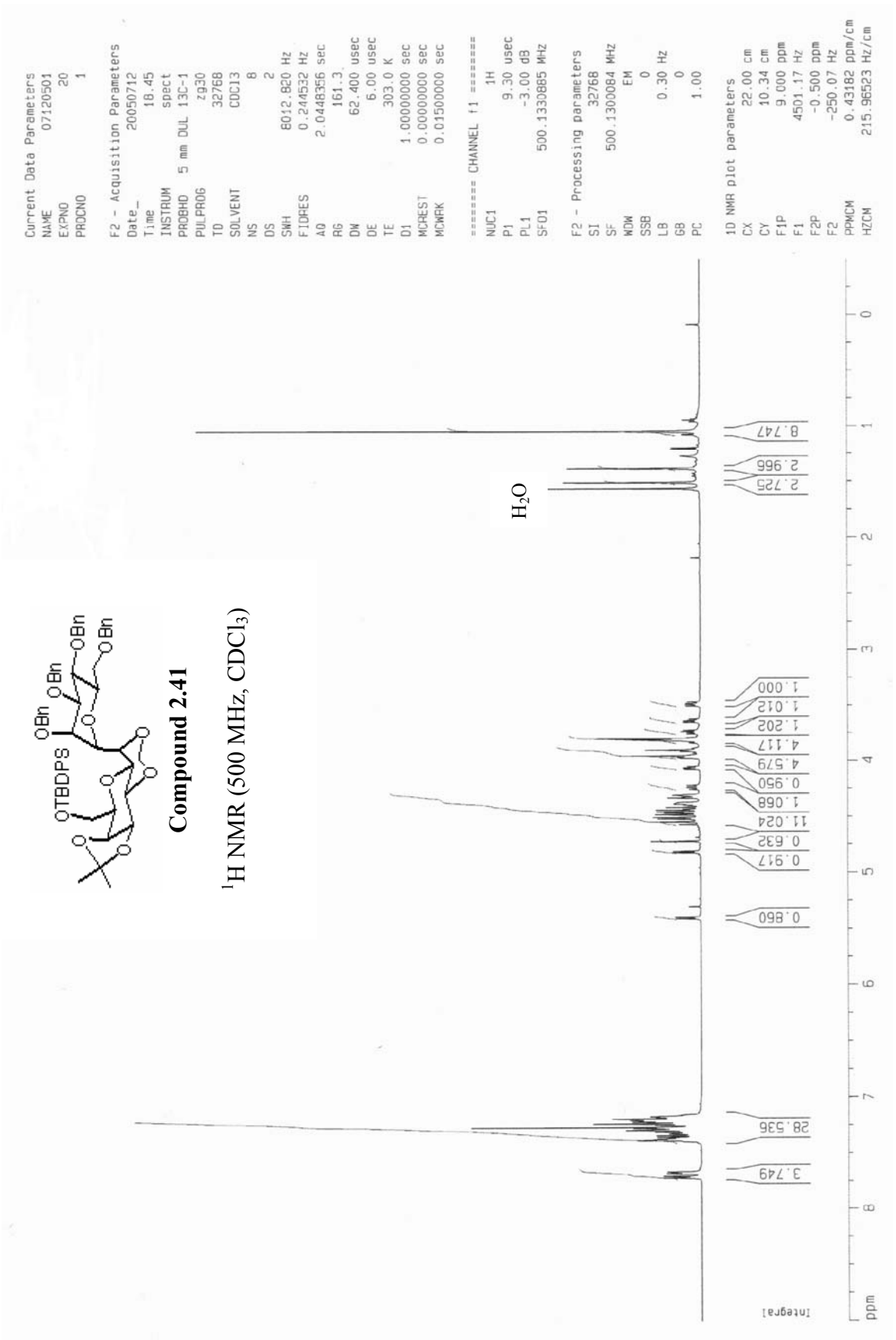


Compound 2.40

^{13}C NMR (75 MHz, $CDCl_3$)

peak	ppm	freq	amp
1	159.429	12029.37	2366.62
2	138.565	10455.15	5267.01
3	138.436	10445.38	3063.58
4	138.022	10414.13	2085.24
5	135.718	10240.31	10519.96
6	135.653	10235.42	11736.64
7	133.815	10096.75	2111.93
8	133.686	10086.98	2819.08
9	130.114	9817.46	3039.57
10	129.842	9796.95	6664.33
11	129.700	9786.20	8880.68
12	128.380	9686.59	28293.58
13	128.328	9682.69	21972.30
14	128.263	9677.81	21283.70
15	127.991	9657.30	12901.61
16	127.952	9654.37	11902.14
17	127.758	9639.72	14382.39
18	127.681	9633.86	19795.37
19	127.536	9623.12	16297.66
20	114.065	8606.62	2049.88
21	113.981	8598.70	8823.77
22	109.341	8250.07	4534.37
23	82.187	6201.24	3529.76
24	80.453	6070.36	3866.91
25	79.673	6009.86	3189.00
26	77.657	5859.46	14848.22
27	77.230	5827.22	18507.35
28	76.815	5795.97	15051.84
29	75.237	5676.83	3194.78
30	74.810	5644.60	2743.06
31	74.771	5641.67	2685.19
32	74.512	5622.14	3073.26
33	73.845	5566.71	7628.23
34	73.564	5549.68	2868.16
35	73.477	5544.02	4848.31
36	73.282	5529.37	2163.78
37	72.519	5471.75	2812.68
38	72.053	5436.59	4499.78
39	71.846	5420.87	3413.78
40	70.487	5318.43	3419.47
41	70.124	5291.09	3514.01
42	63.187	4767.66	3302.79
43	55.318	4173.90	6040.49
44	28.604	2158.27	4116.41
45	27.090	2044.02	16821.84
46	26.663	2011.79	4771.64
47	19.519	1472.73	4372.22




OBn
OBn
OBn
OBn
OTBDPS
Compound 2.41
^{1}H NMR (500 MHz, CDCl$_3$)
H$_2$O
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EXPNO 20
PROCNO 1
F2 - Acquisition Parameters
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Time 18.45
INSTRUM spect
PROBHD 5 mm DUL 13C-1
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 8
DS 2
SWH 8012.820 Hz
FIDRES 0.244532 Hz
AQ 2.0448356 sec
RG 161.3
DW 62.400 usec
DE 6.00 usec
TE 303.0 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
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P1 9.30 usec
PL1 -3.00 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
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SF 500.1300084 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
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CY 10.34 cm
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F1 4501.17 Hz
F2P -0.500 ppm
F2 -250.07 Hz
PPMCM 0.43182 ppm/cm
HZCM 215.96523 Hz/cm
8.747
7.966
7.725
1.000
1.012
1.202
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0.950
1.068
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0.917
0.860
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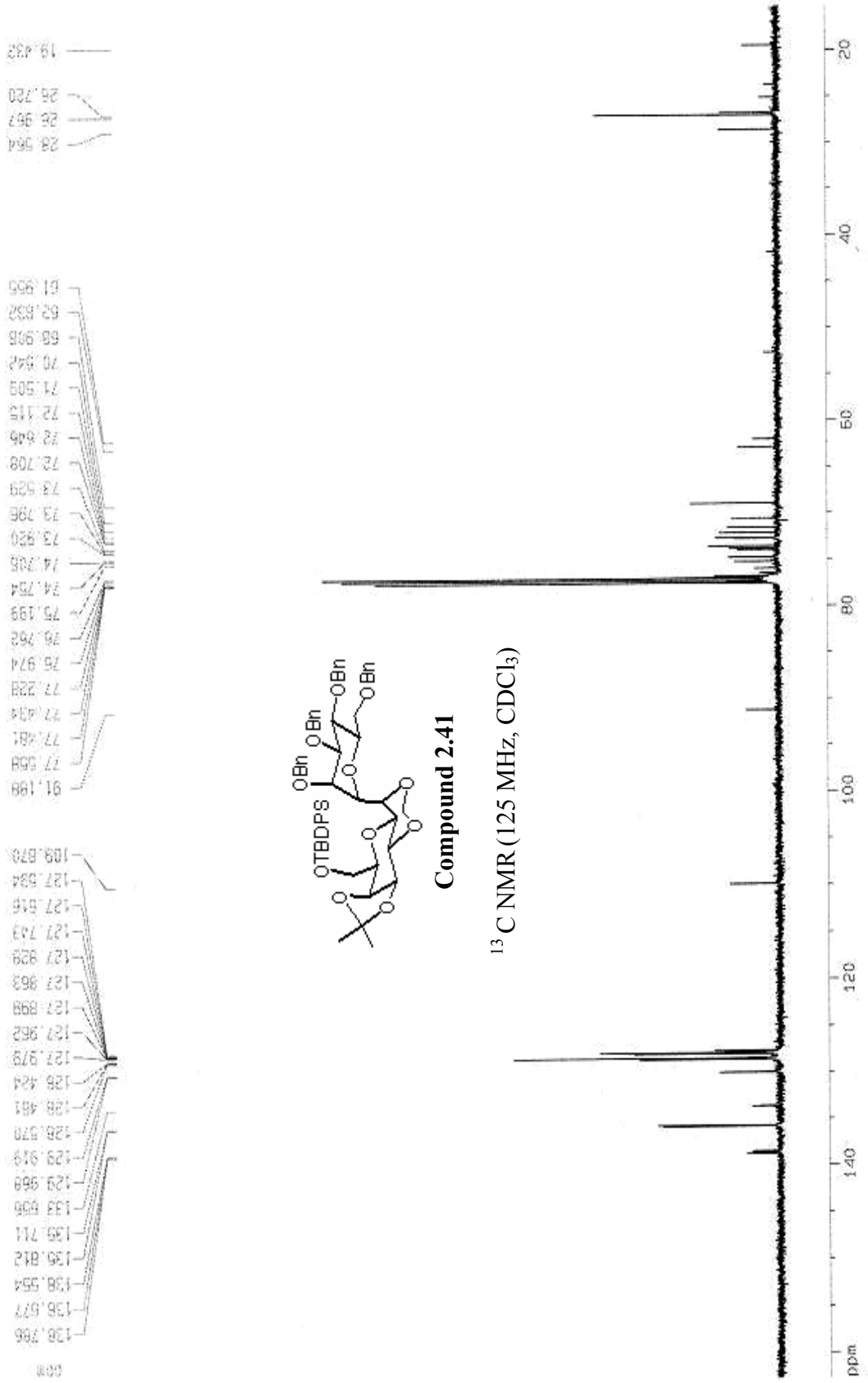
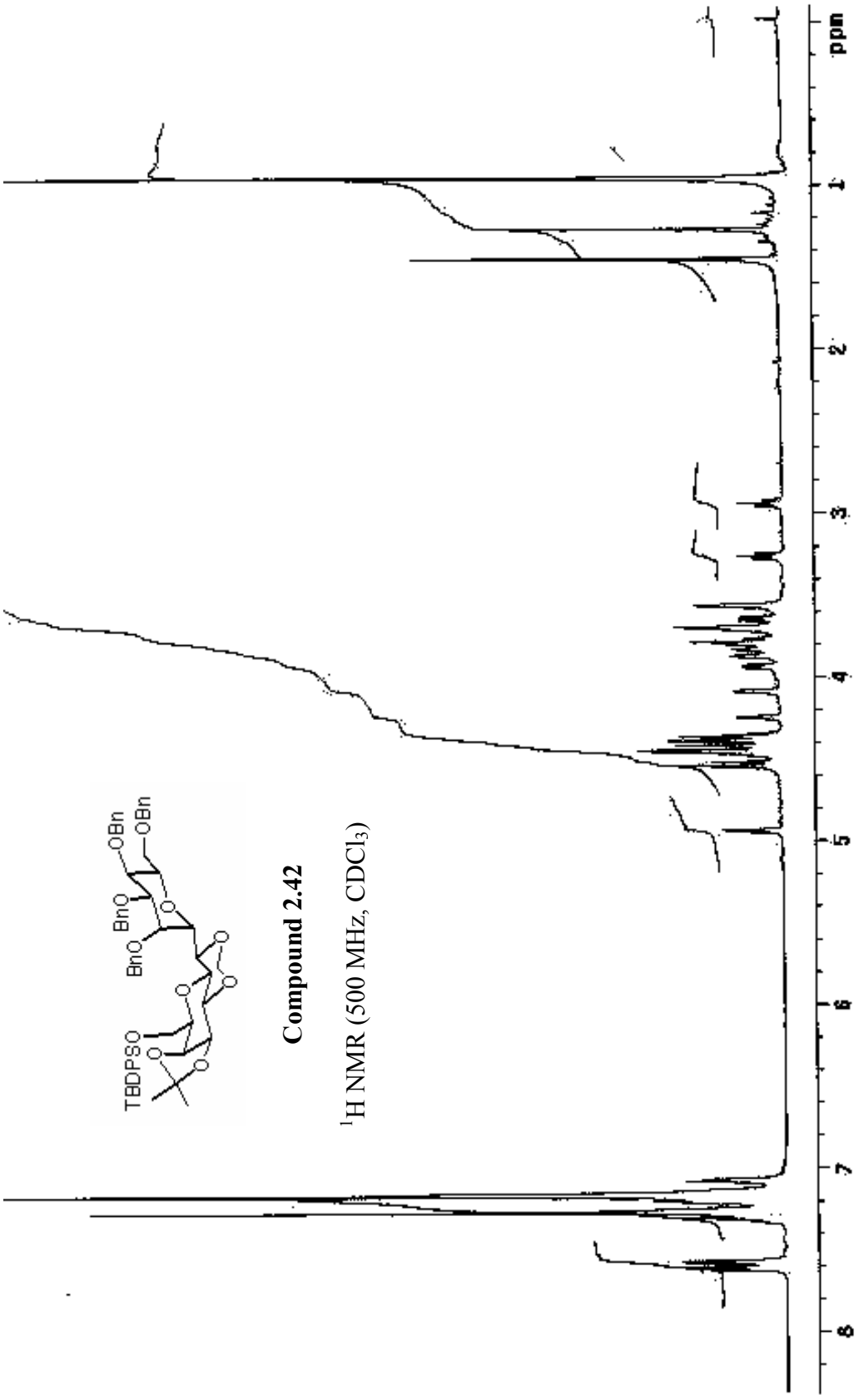
integral
ppm



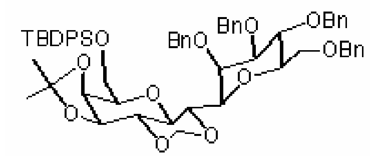
Compound 2.41

^{13}C NMR (125 MHz, $CDCl_3$)



Compound 2.42

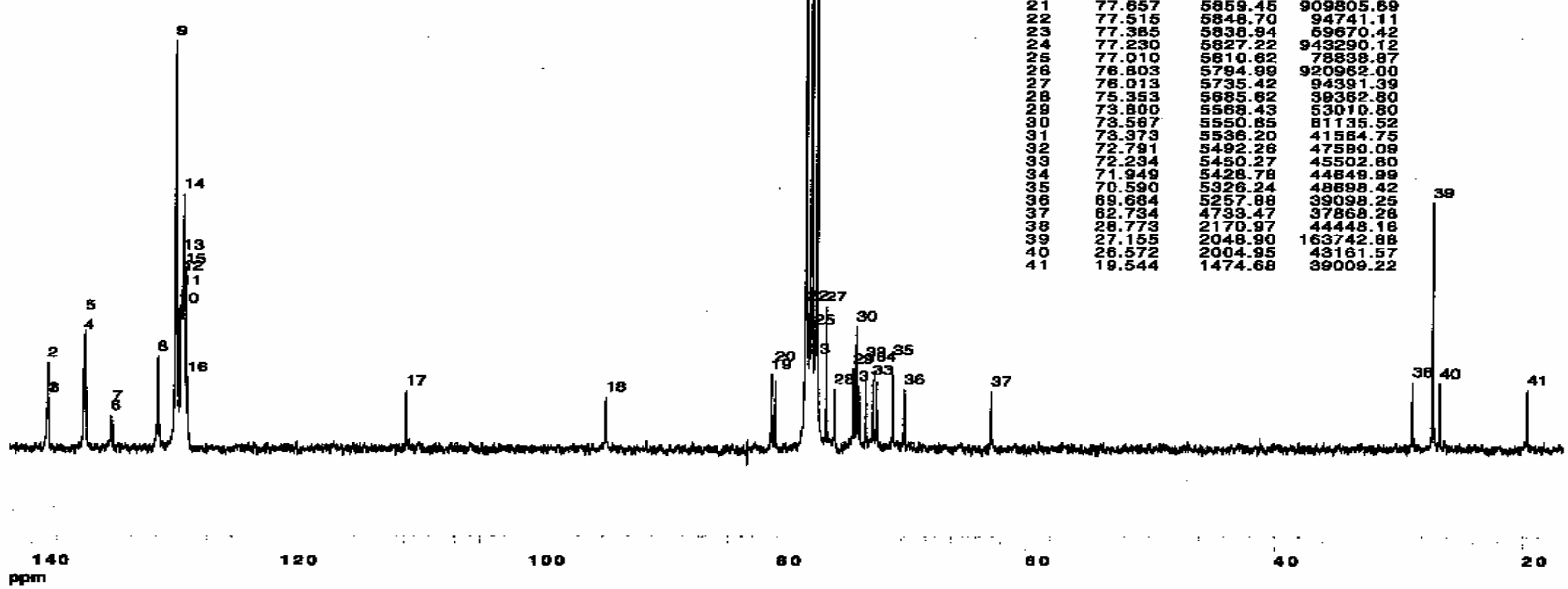
^{1}H NMR (500 MHz, $CDCl_3$)

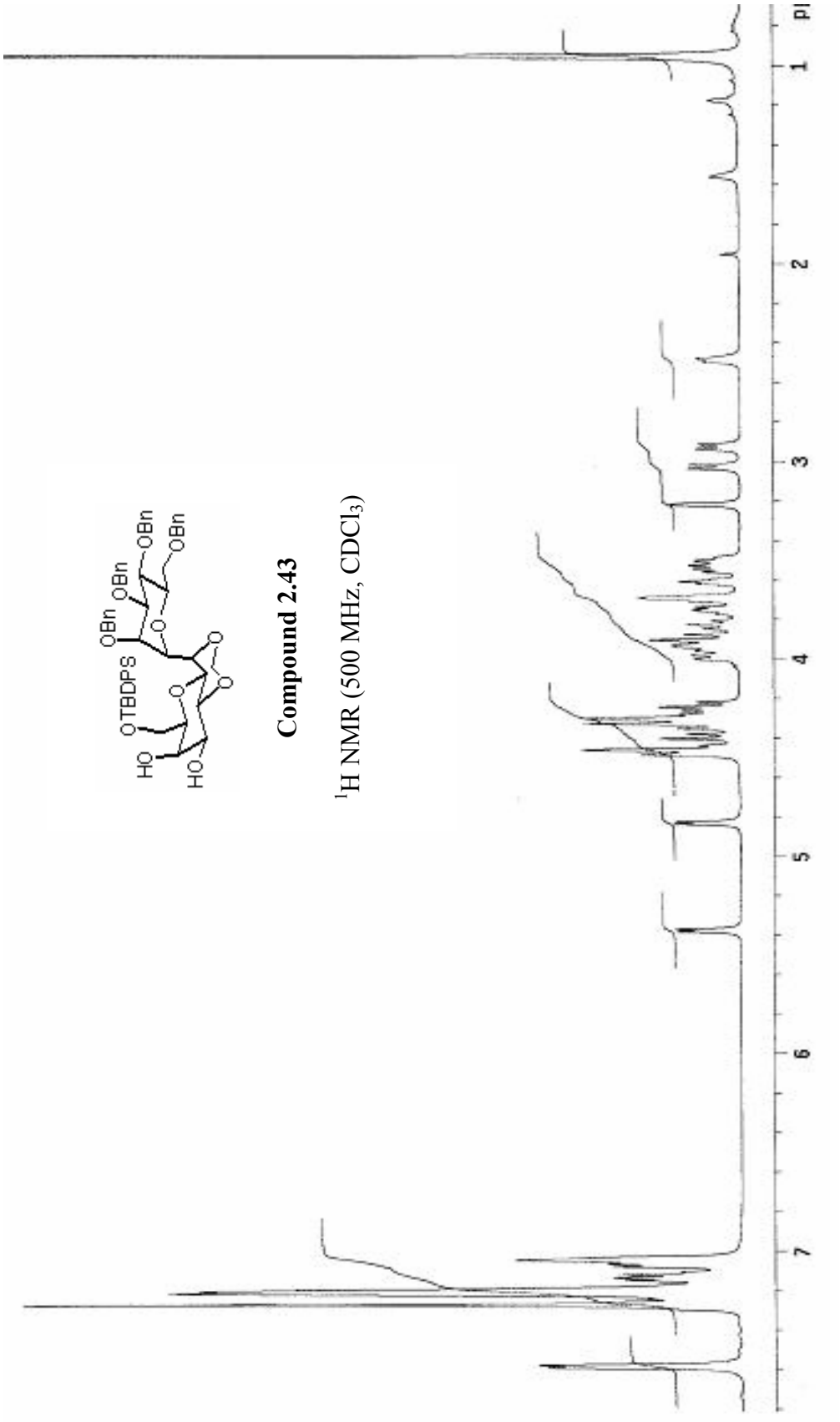


Compound 2.42

^{13}C NMR (75 MHz, $CDCl_3$)

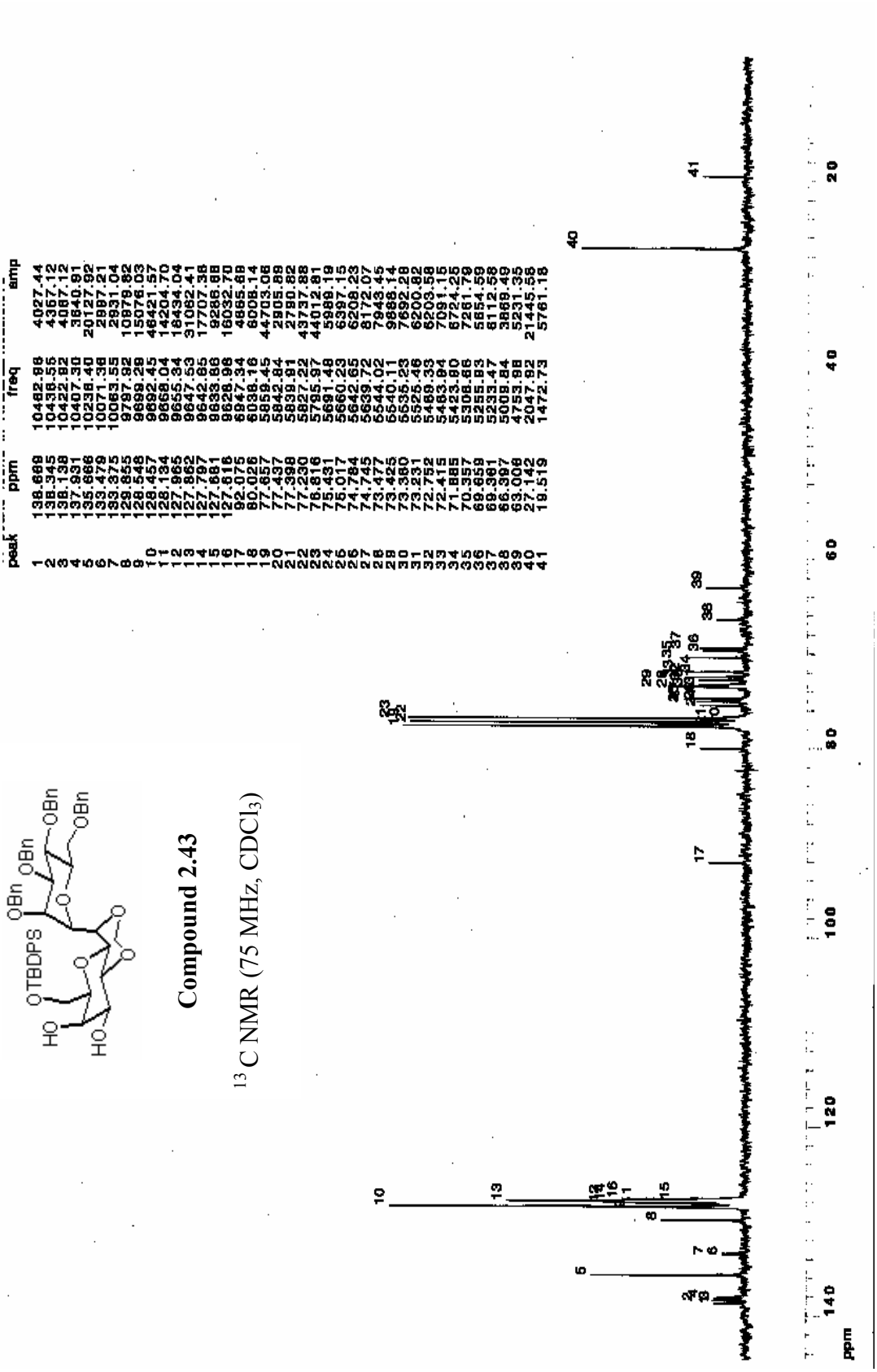
peak	ppm	freq	amp
1	138.811	10473.70	33575.13
2	138.747	10468.82	56679.42
3	138.669	10462.96	33464.57
4	135.822	10248.12	75139.92
5	135.705	10239.33	78202.79
6	133.647	10084.05	21568.16
7	133.516	10074.29	18188.94
8	129.856	9797.92	60759.65
9	128.444	9691.48	271457.34
10	128.276	9678.78	92726.41
11	128.043	9661.20	94622.93
12	127.985	9655.34	104636.52
13	127.875	9648.51	118463.52
14	127.787	9642.66	169031.09
15	127.707	9636.81	119085.73
16	127.512	9621.16	47019.79
17	109.820	8286.20	38288.21
18	93.745	7073.31	34003.15
19	80.440	6069.41	49183.33
20	80.129	6045.97	44799.47
21	77.657	5859.45	909805.69
22	77.515	5848.70	94741.11
23	77.365	5838.94	59670.42
24	77.230	5827.22	943290.12
25	77.010	5810.62	78838.87
26	76.803	5794.99	920962.00
27	76.013	5735.42	94391.39
28	75.353	5685.62	39362.80
29	73.800	5568.43	53010.80
30	73.567	5550.85	81135.52
31	73.373	5536.20	41564.75
32	72.791	5492.26	47580.09
33	72.234	5450.27	45502.80
34	71.949	5428.78	44649.99
35	70.590	5326.24	48698.42
36	69.684	5257.88	39098.25
37	62.734	4733.47	37868.28
38	28.773	2170.97	44448.16
39	27.155	2048.90	163742.88
40	26.572	2004.95	43161.57
41	19.544	1474.68	39009.22

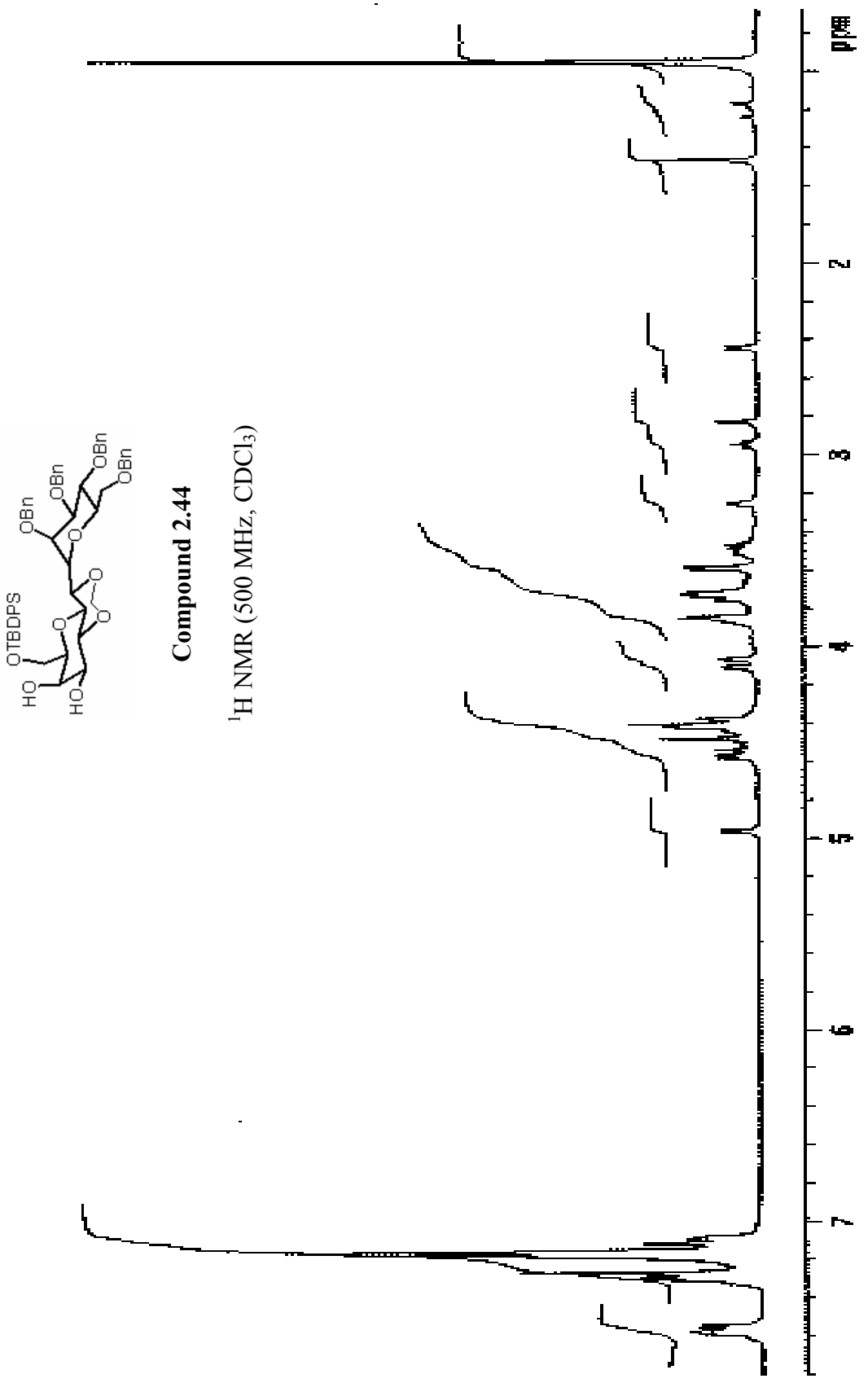


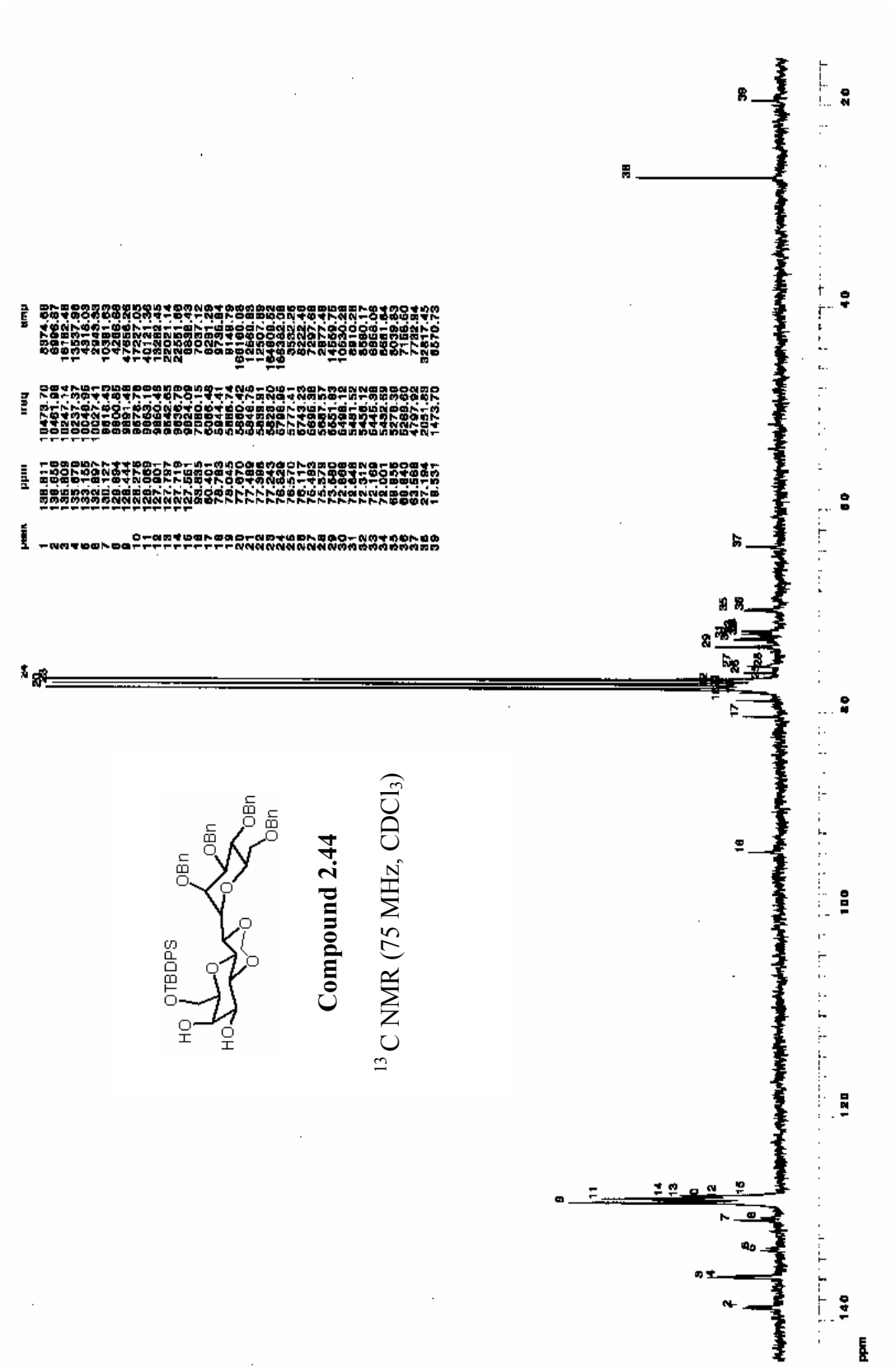


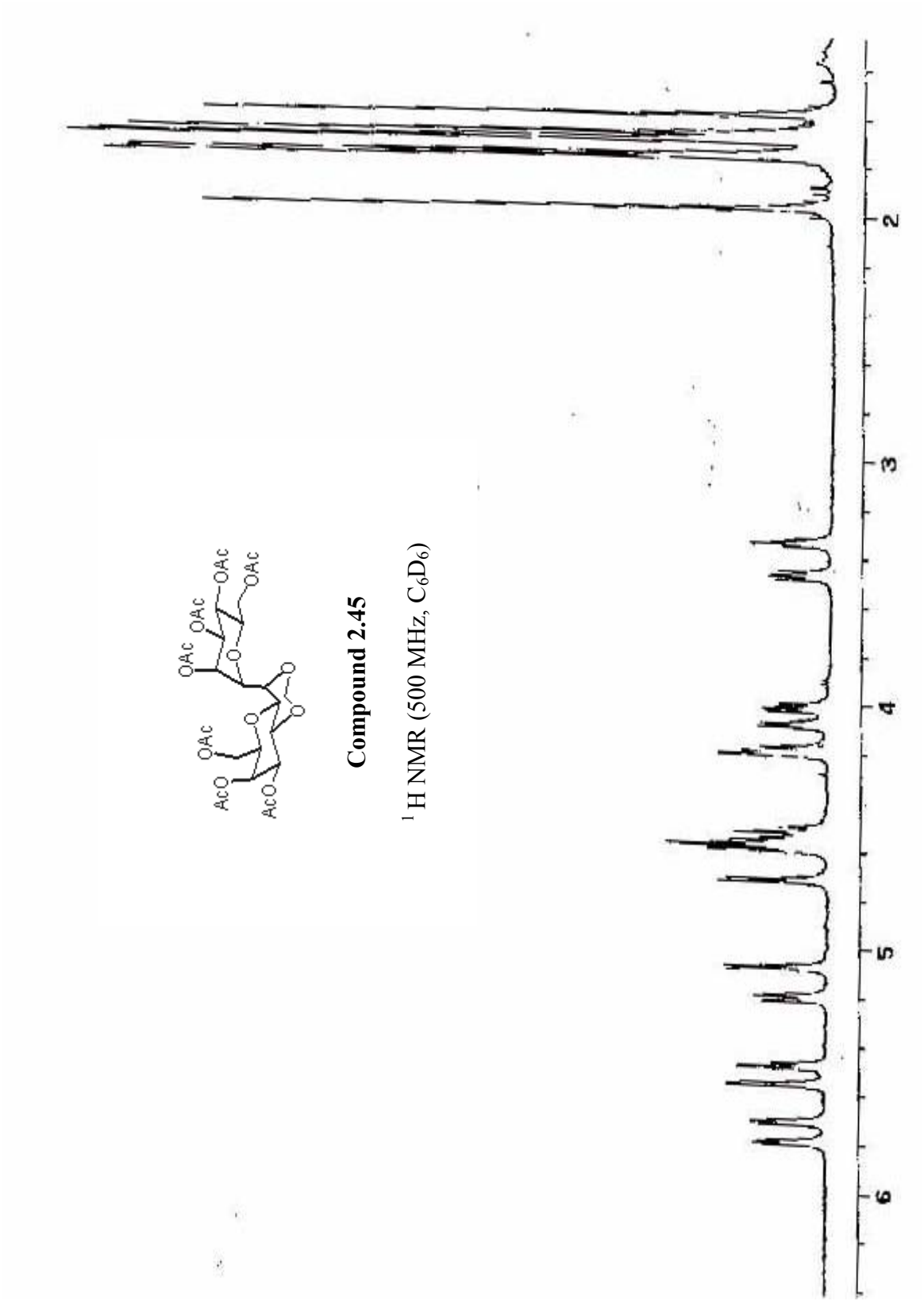
Compound 2.43

^{1}H NMR (500 MHz, $CDCl_3$)


OBn
OBn
OBn
OBn
OTBDPS
HO
HO
O
O
O
O
O
Compound 2.43
^{13}C NMR (75 MHz, $CDCl_3$)
peak ppm freq amp
1 138.688 10482.98 4027.44
2 138.345 10436.56 4367.12
3 138.138 10422.82 4087.12
4 137.931 10407.30 3640.91
5 135.666 10238.40 20127.92
6 133.479 10071.38 2867.21
7 133.375 10063.55 2931.04
8 128.855 9797.82 10879.82
9 128.548 9699.28 15076.03
10 128.457 9692.45 46421.57
11 128.134 9668.04 14204.70
12 127.965 9655.34 18434.04
13 127.862 9647.53 31062.41
14 127.797 9642.65 17707.38
15 127.681 9633.86 8286.88
16 127.616 9628.98 16032.70
17 92.075 6947.34 4865.88
18 80.026 6038.16 6008.14
19 77.657 5859.45 44703.06
20 77.437 5842.84 2905.88
21 77.398 5839.91 2790.82
22 77.230 5827.22 43737.88
23 76.816 5795.97 44012.81
24 75.431 5691.48 5989.19
25 75.017 5660.23 5397.15
26 74.784 5642.65 6208.23
27 74.745 5639.72 8172.07
28 73.477 5544.02 7943.45
29 73.425 5540.11 9888.14
30 73.380 5535.23 7692.28
31 73.231 5525.46 6200.82
32 72.752 5489.33 6203.58
33 72.415 5463.94 7091.15
34 71.885 5423.80 6724.25
35 70.557 5308.86 7261.79
36 68.659 5255.83 5854.59
37 68.361 5233.47 8112.58
38 66.397 5008.84 3869.49
39 63.008 4753.98 5231.35
40 27.142 2047.92 21445.58
41 19.519 1472.73 5761.18
ppm

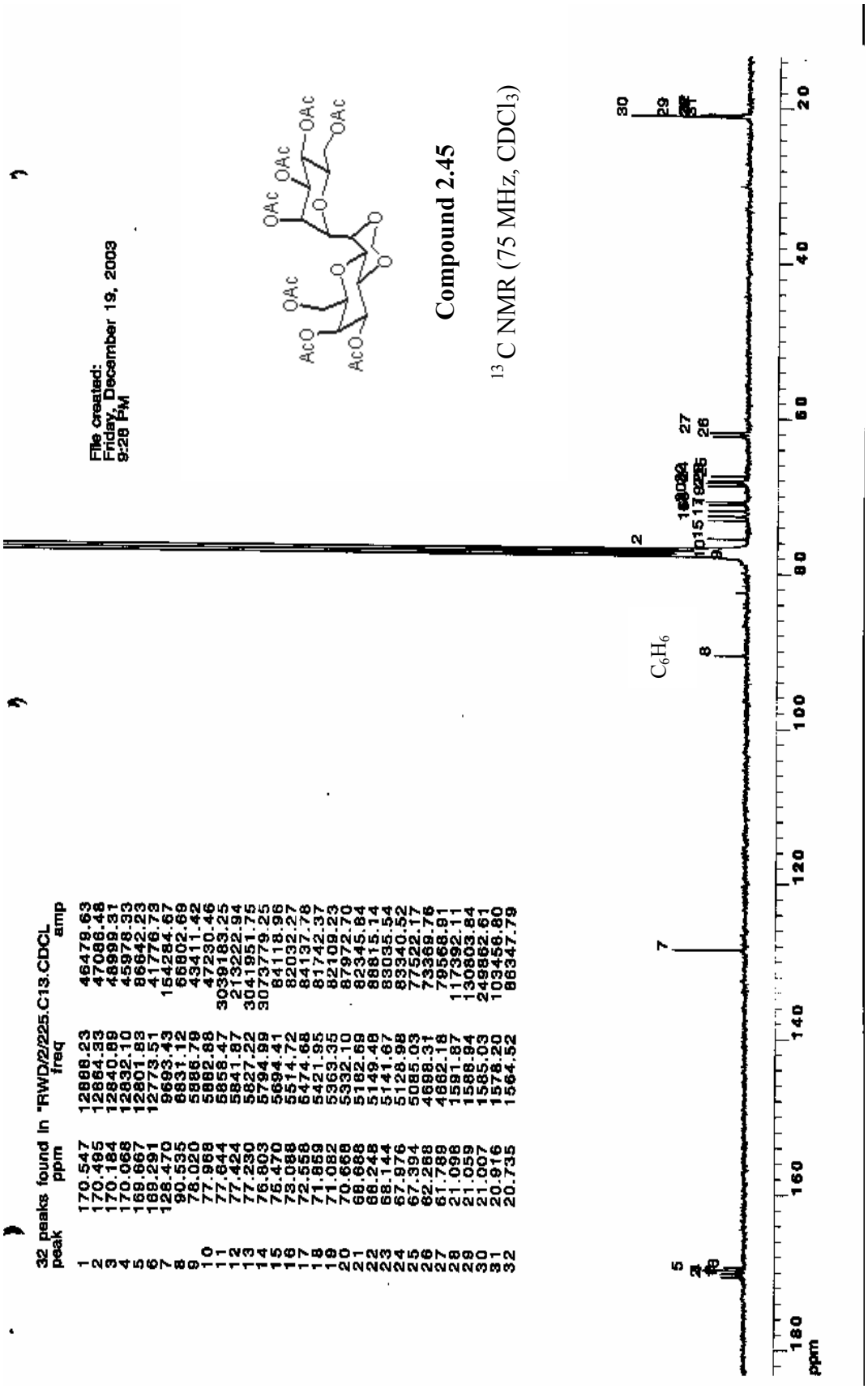

OTBDPS
HO
HO
OBn
OBn
OBn
OBn
O
O
O
O
Compound 2.44
^{1}H NMR (500 MHz, $CDCl_3$)
ppm
2
3
4
5
6
7


OTBDPS
HO
HO
OBn
OBn
OBn
OBn
Compound 2.44
^{13}C NMR (75 MHz, $CDCl_3$)
ppm

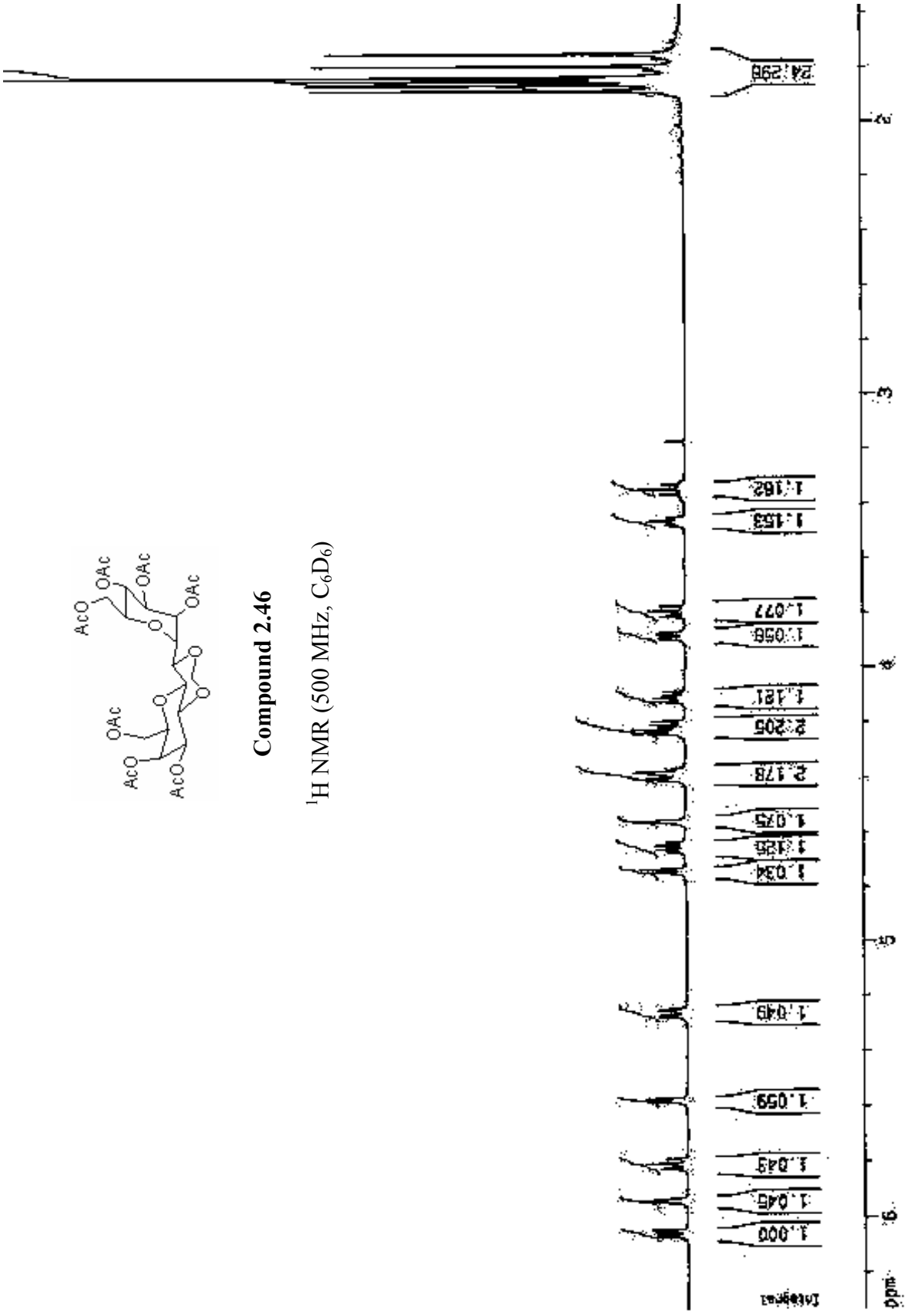


Compound 2.45

^{1}H NMR (500 MHz, C_6D_6)

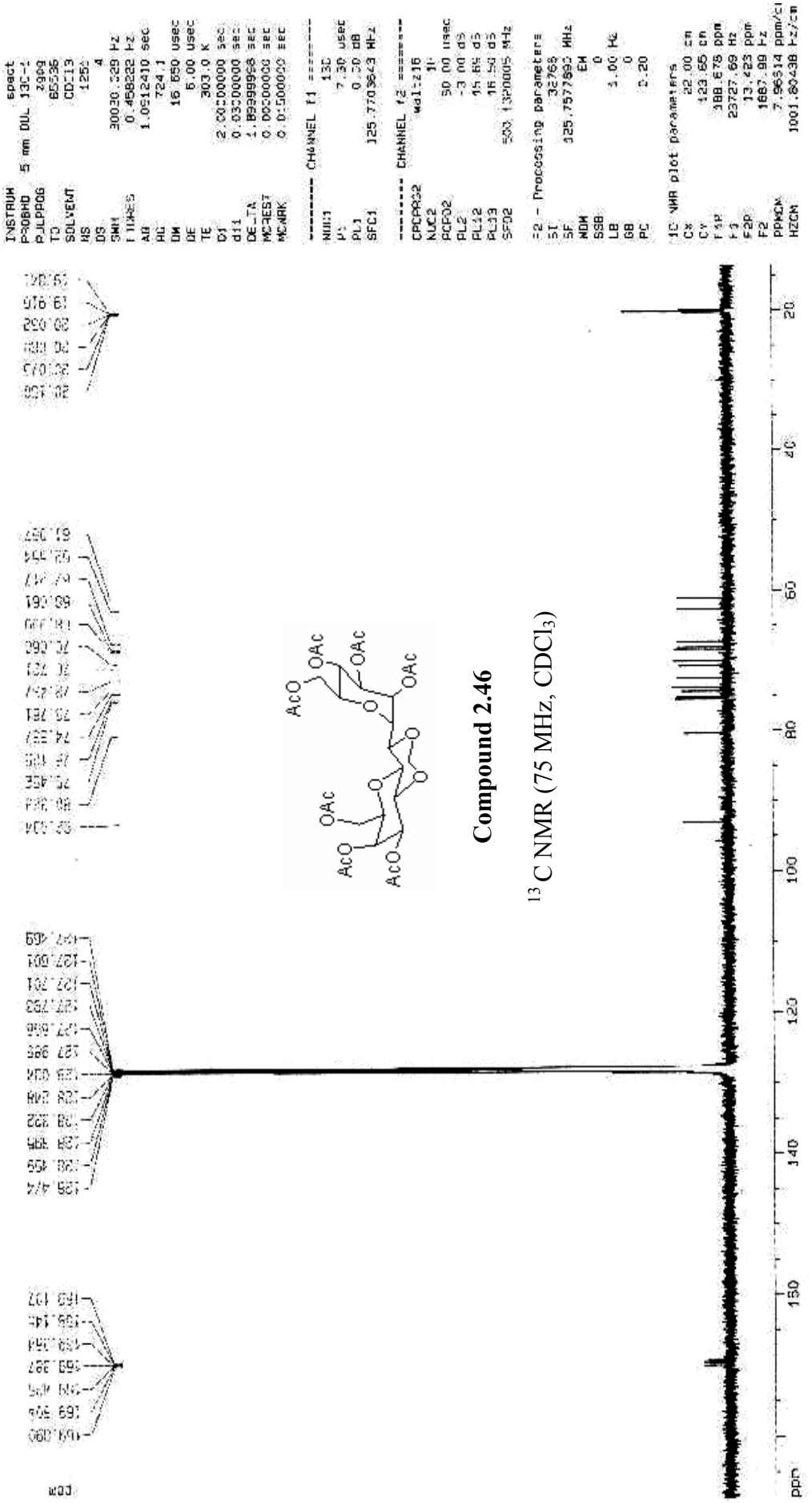


32 peaks found in "RWD/2/225.C13.CDCL			
peak	ppm	freq	amp
1	170.547	12868.23	46479.63
2	170.485	12864.33	47086.48
3	170.184	12840.89	48999.31
4	170.068	12832.10	45978.33
5	169.667	12801.83	86642.23
6	169.291	12773.51	41776.79
7	128.470	9693.43	154284.67
8	90.535	6831.12	66602.69
9	78.020	5886.79	43411.42
10	77.968	5882.88	47230.46
11	77.644	5858.47	3039183.25
12	77.424	5841.87	213222.94
13	77.230	5827.22	3041951.75
14	76.803	5794.99	3073779.25
15	76.470	5694.41	84118.96
16	73.088	5514.72	82032.27
17	72.558	5474.68	84137.78
18	71.859	5421.95	81742.37
19	71.082	5363.35	82109.23
20	70.668	5332.10	87972.70
21	68.668	5182.69	82345.84
22	68.248	5149.48	88815.14
23	68.144	5141.67	83035.54
24	67.976	5128.98	83340.52
25	67.394	5085.03	77522.17
26	62.268	4698.31	73369.76
27	61.789	4662.18	79568.81
28	21.098	1591.87	117392.11
29	21.059	1588.94	130803.84
30	21.007	1585.03	249862.61
31	20.916	1578.20	103456.80
32	20.735	1564.52	88347.79



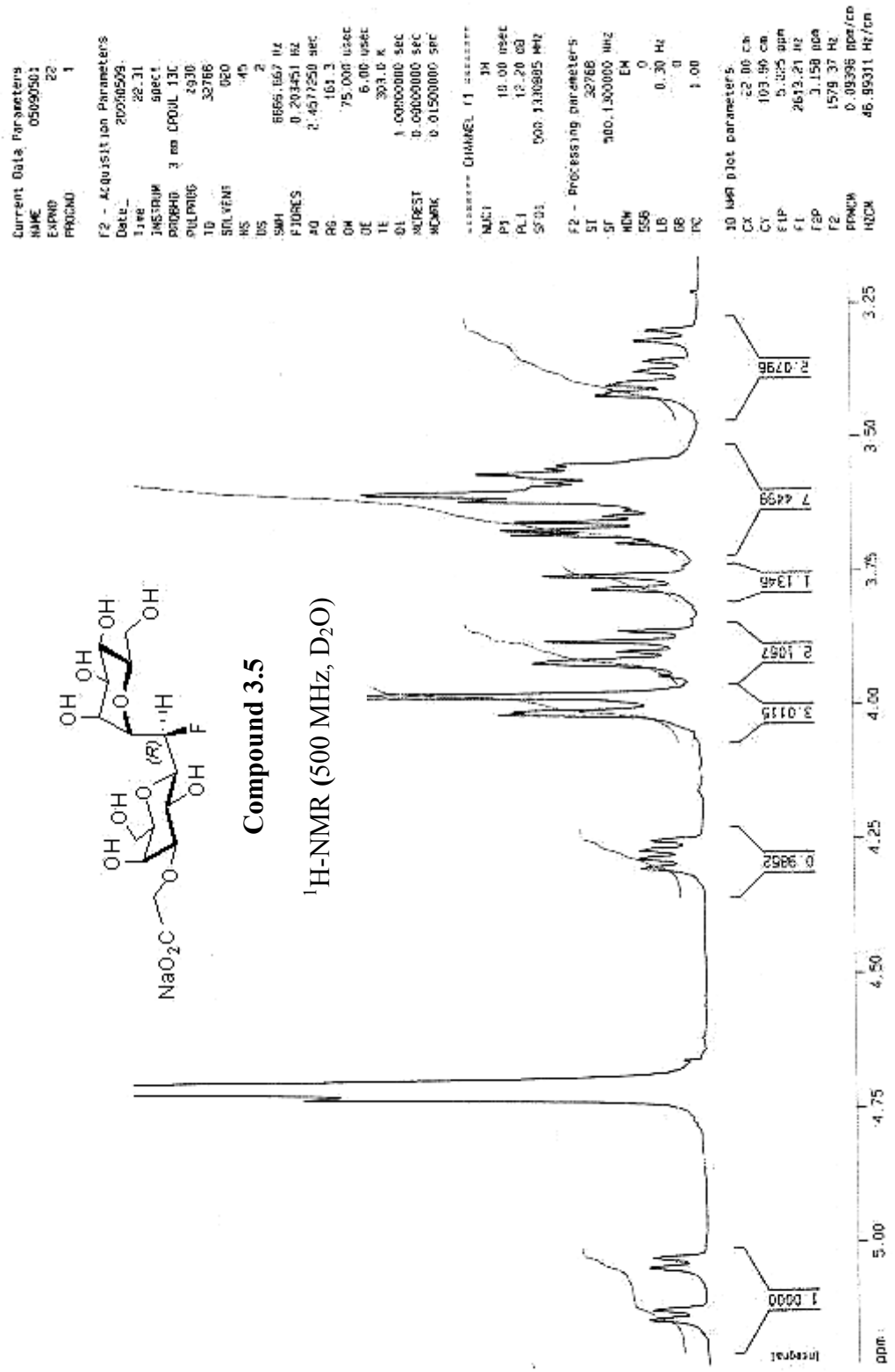
Compound 2.46

^{1}H NMR (500 MHz, C_6D_6)



Compound 2.46

^{13}C NMR (75 MHz, $CDCl_3$)


Compound 3.5
^{1}H-NMR (500 MHz, D_2O)
NaO2C
OH
F
(R)
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3.0135
2.1057
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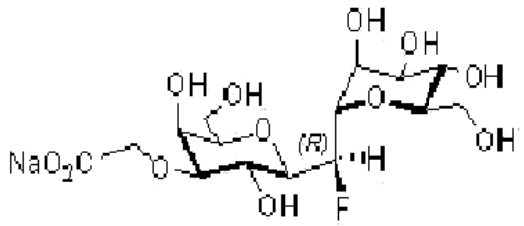
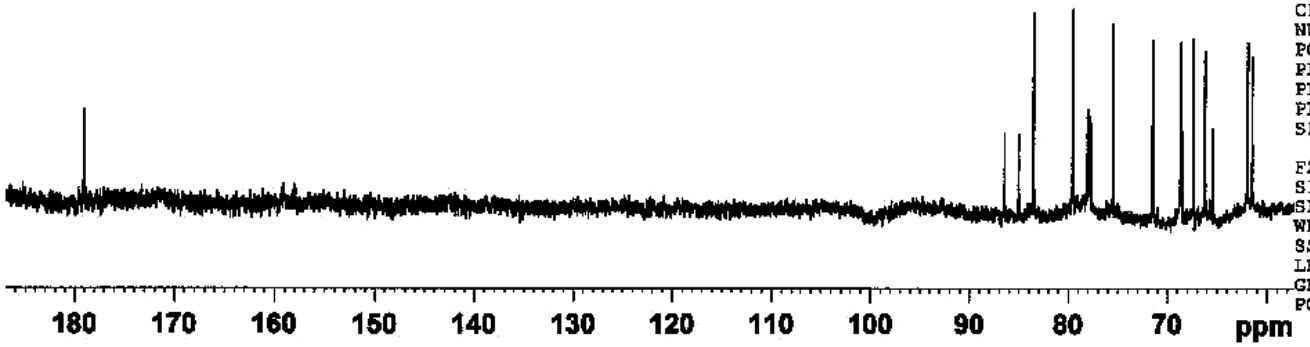
7.4499
2.0796
5.00
4.75
4.50
4.25
4.00
3.75
3.50
3.25
ppm



Compound 3.5

^{13}C-NMR (125 MHz, D_2O)

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PROCNO                        1

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PULPROG              zgpg
TD                  65418
SOLVENT             GB~~c13~~
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DS                       4
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FIDRES               0.459048 Hz
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DE                   6.00 usec
TE                  303.0 K
D1               2.00000000 sec
d11              0.03000000 sec
DELTA            1.89999998 sec
MCREST           0.00000000 sec
MCWRK            0.01500000 sec

======== CHANNEL f1 ========
NUC1                   13C
P1                   10.00 usec
PL1                  18.00 dB
SFO1           125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                   1H
PCPD2                80.00 usec
PL2                  12.20 dB
PL12                 29.00 dB
PL13                 29.00 dB
SFO2           500.1320005 MHz

F2 - Processing parameters
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LB                   2.00 Hz
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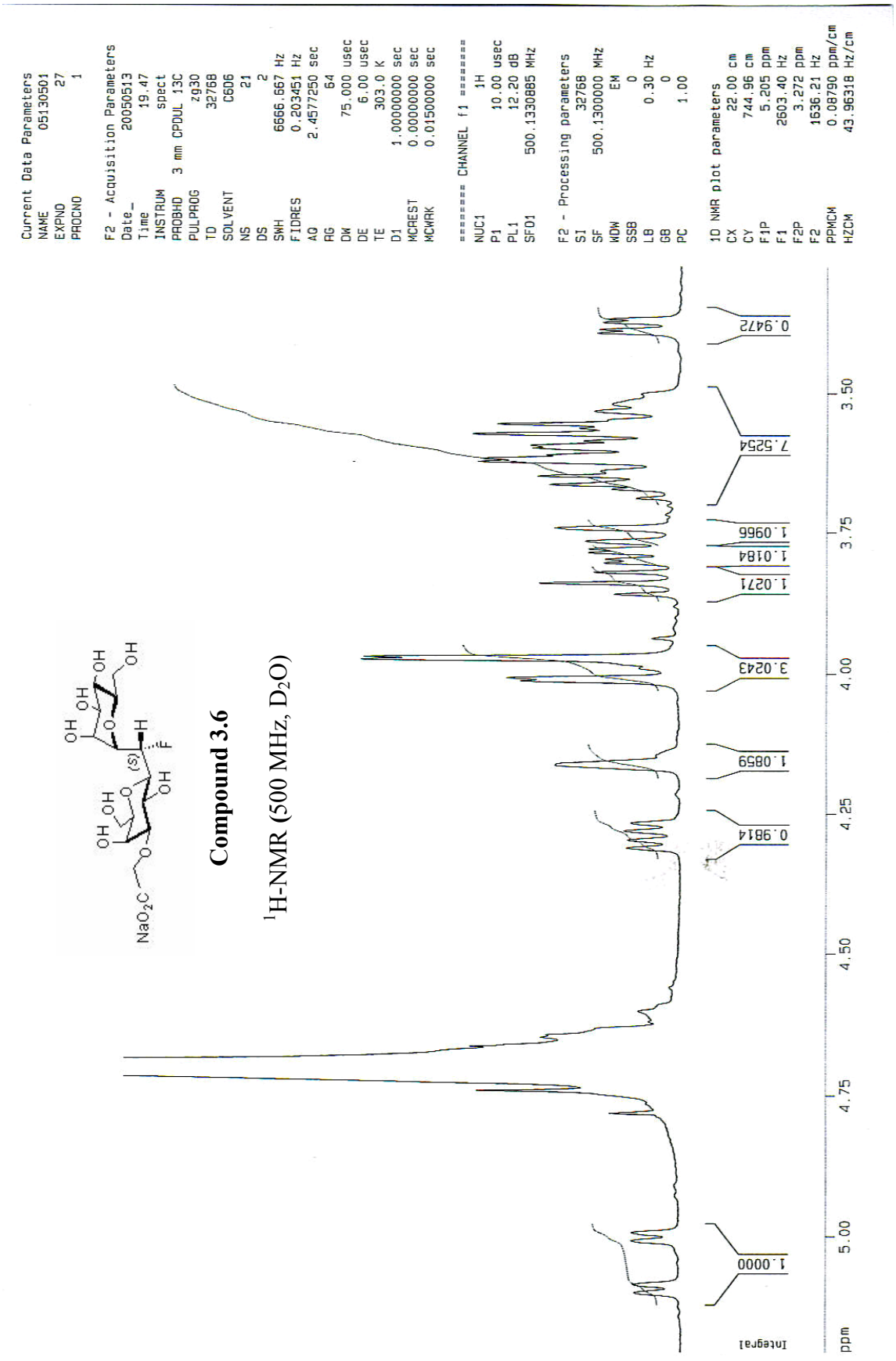
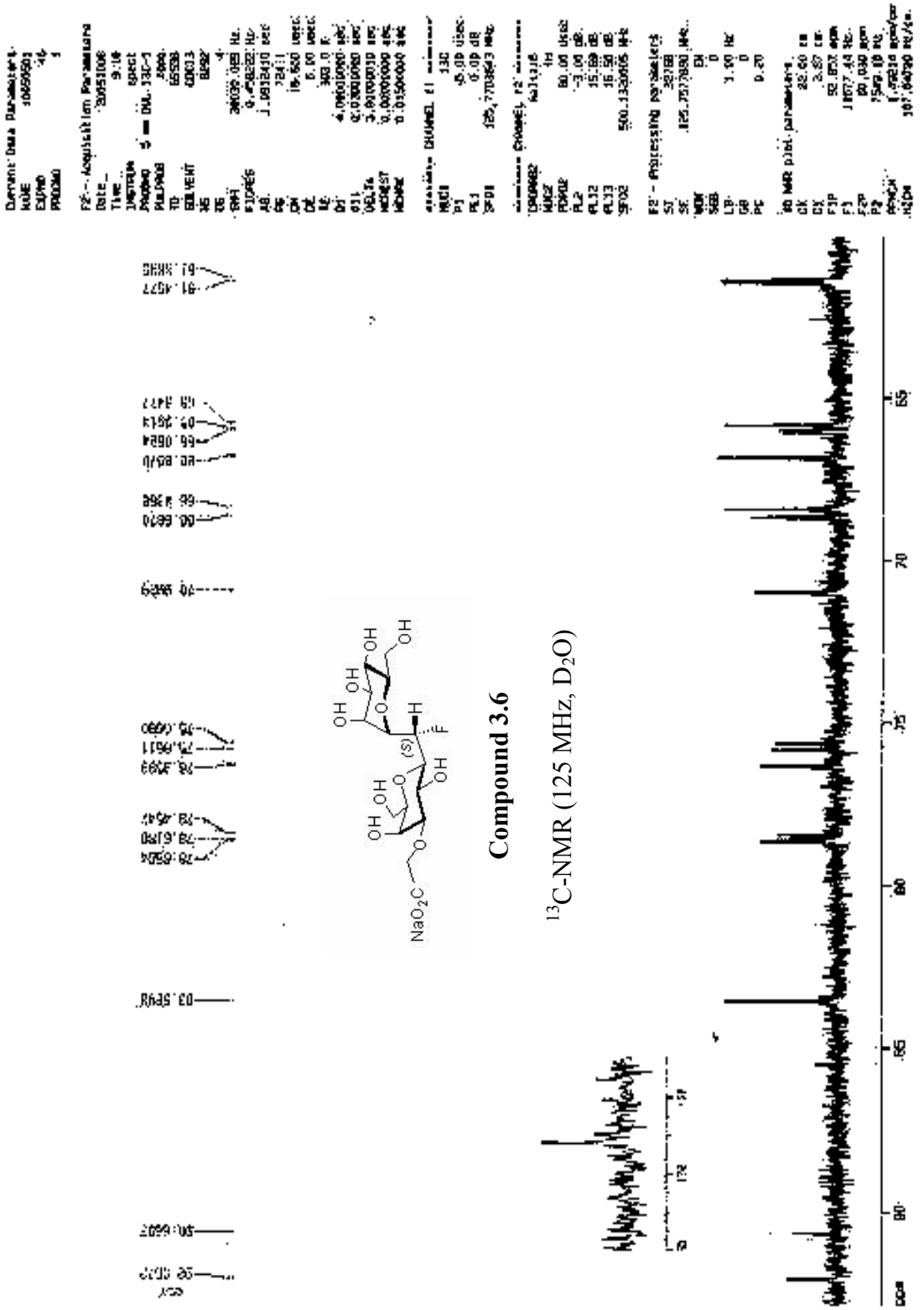


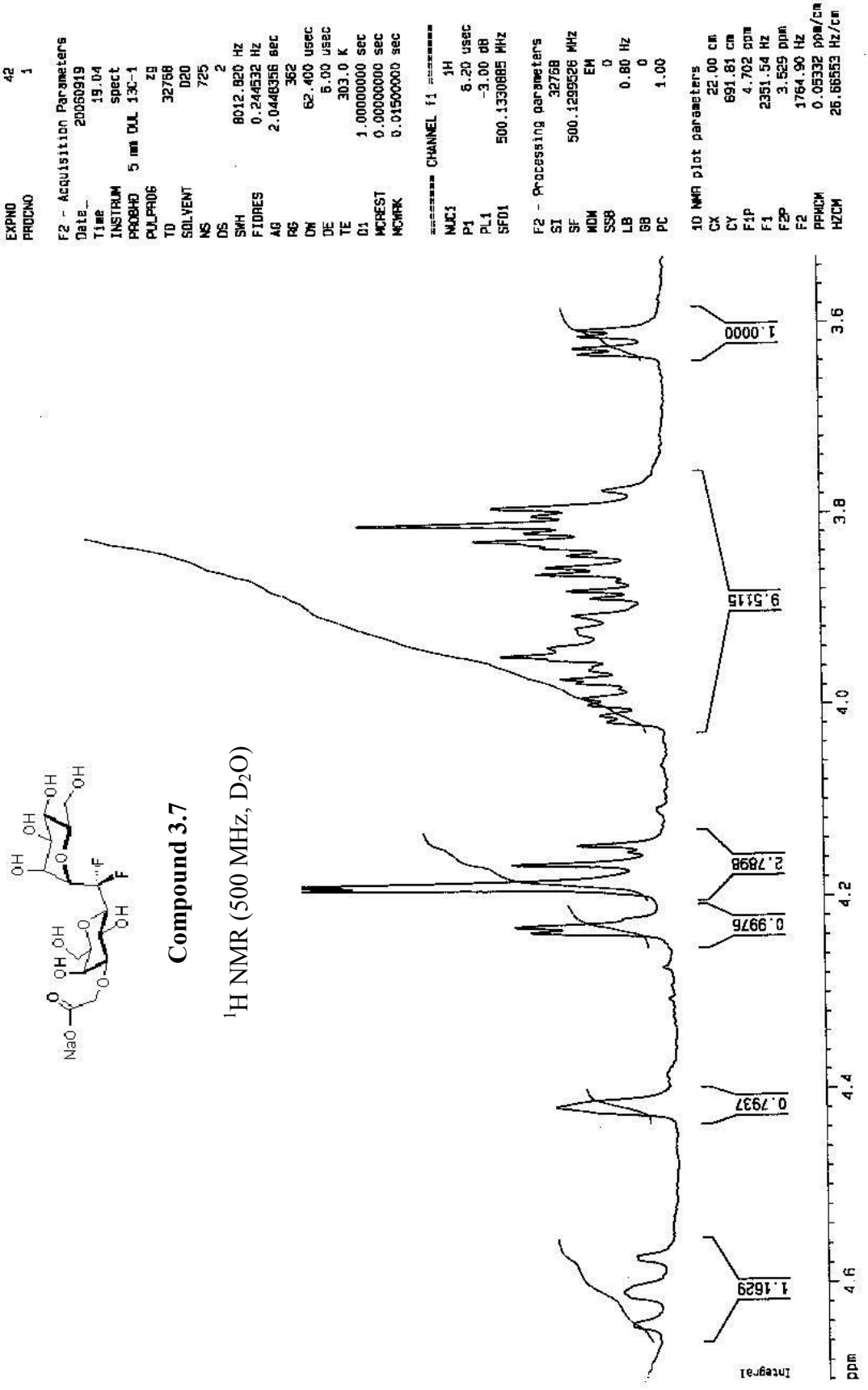
Compound 3.6

^{1}H-NMR (500 MHz, D_2O)



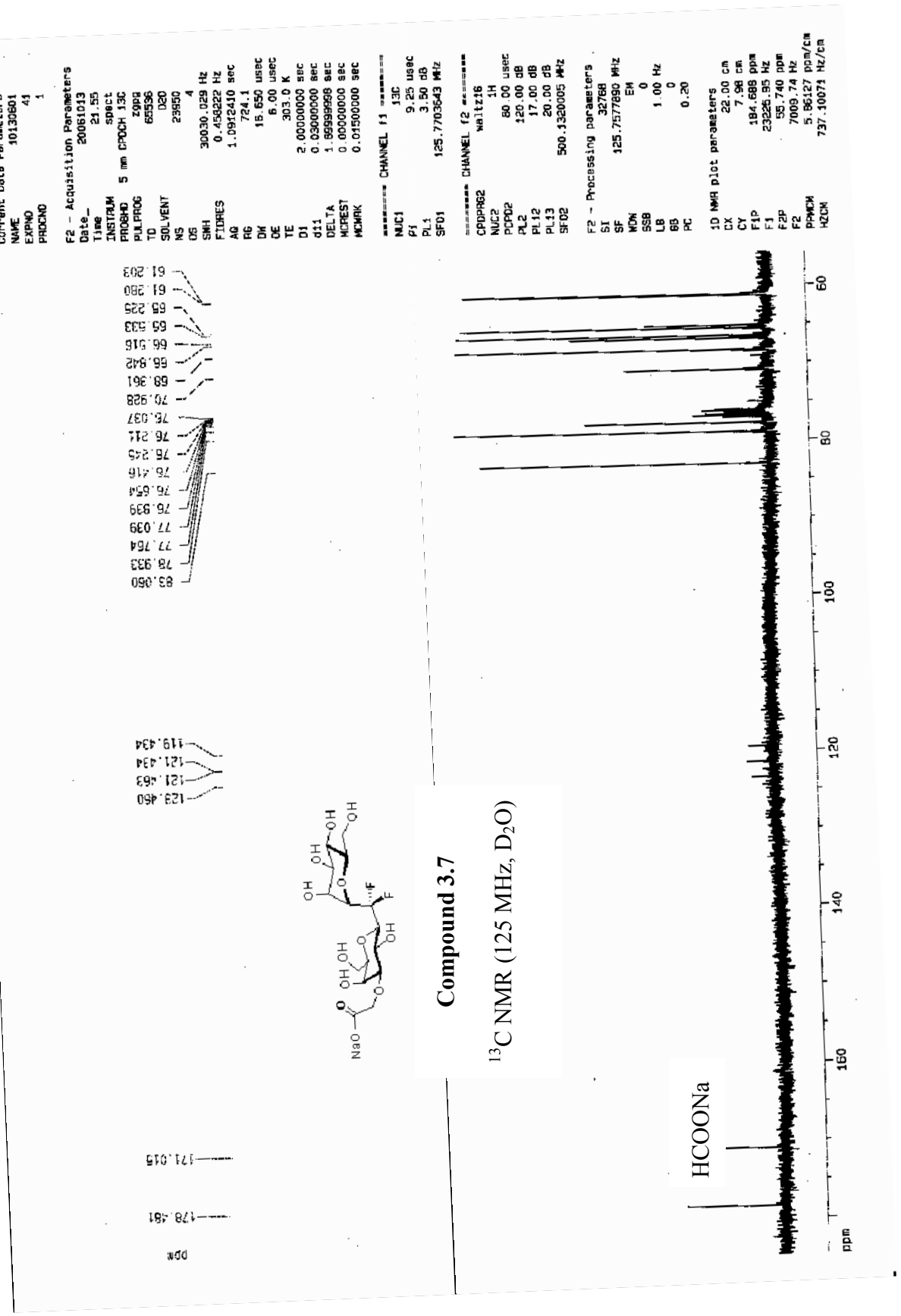
Compound 3.6

^{13}C-NMR (125 MHz, D_2O)



Compound 3.7

^{1}H NMR (500 MHz, D_2O)


Compound 3.7
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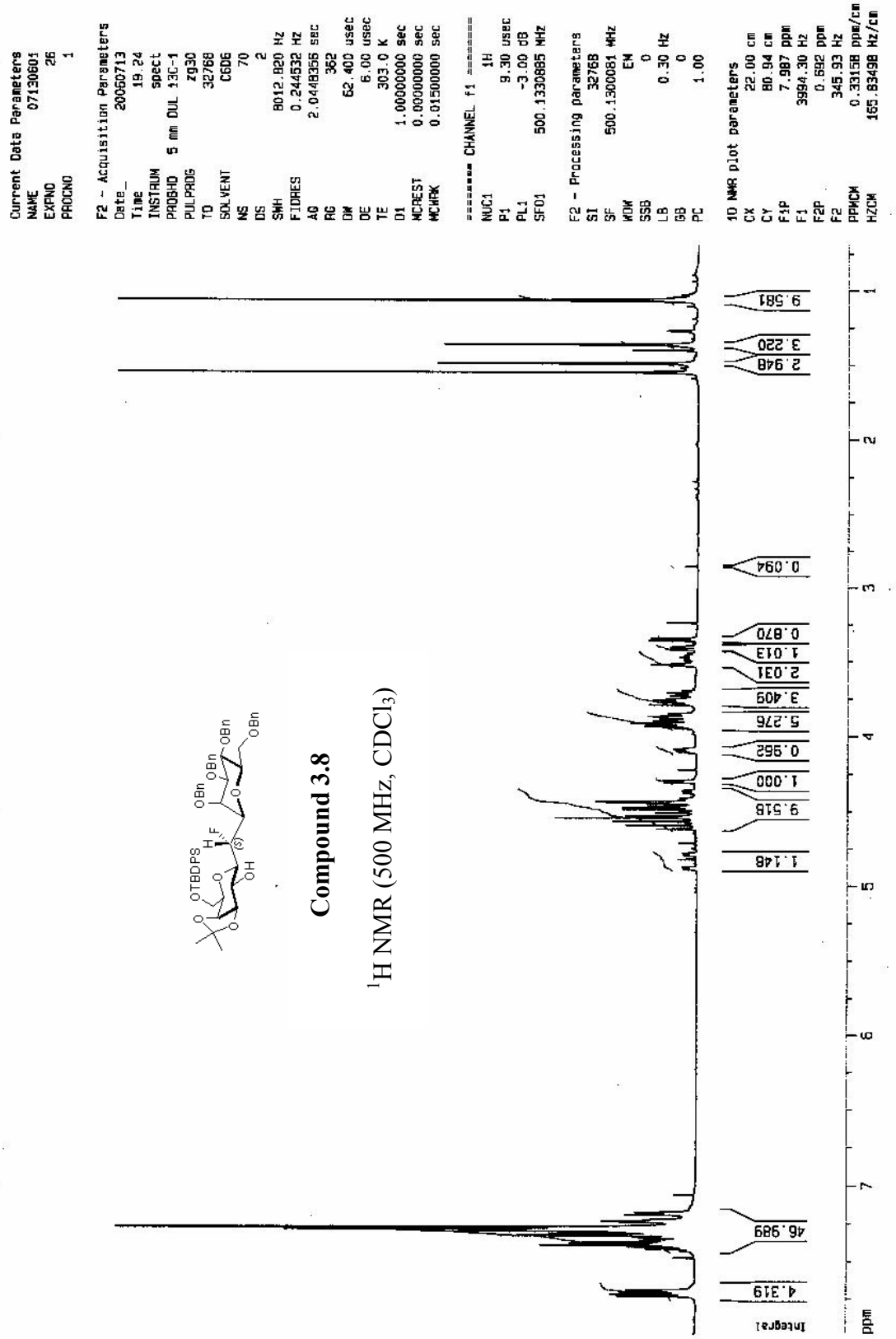
HCOONa
ppm


Compound 3.8
^{1}H NMR (500 MHz, $CDCl_3$)
OTBDPS
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OBn
OBn
OBn
F
H
OH
Current Data Parameters
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EXPNO 26
PROCNO 1
F2 - Acquisition Parameters
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Time 19.24
INSTRUM spect
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PULPROG zg30
TD 32768
SOLVENT C6D6
NS 70
DS 2
SWH 8012.820 Hz
FIDRES 0.244532 Hz
AQ 2.0449356 sec
RG 362
DW 62.400 usec
DE 6.00 usec
TE 303.0 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 9.30 usec
PL1 -3.00 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300081 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
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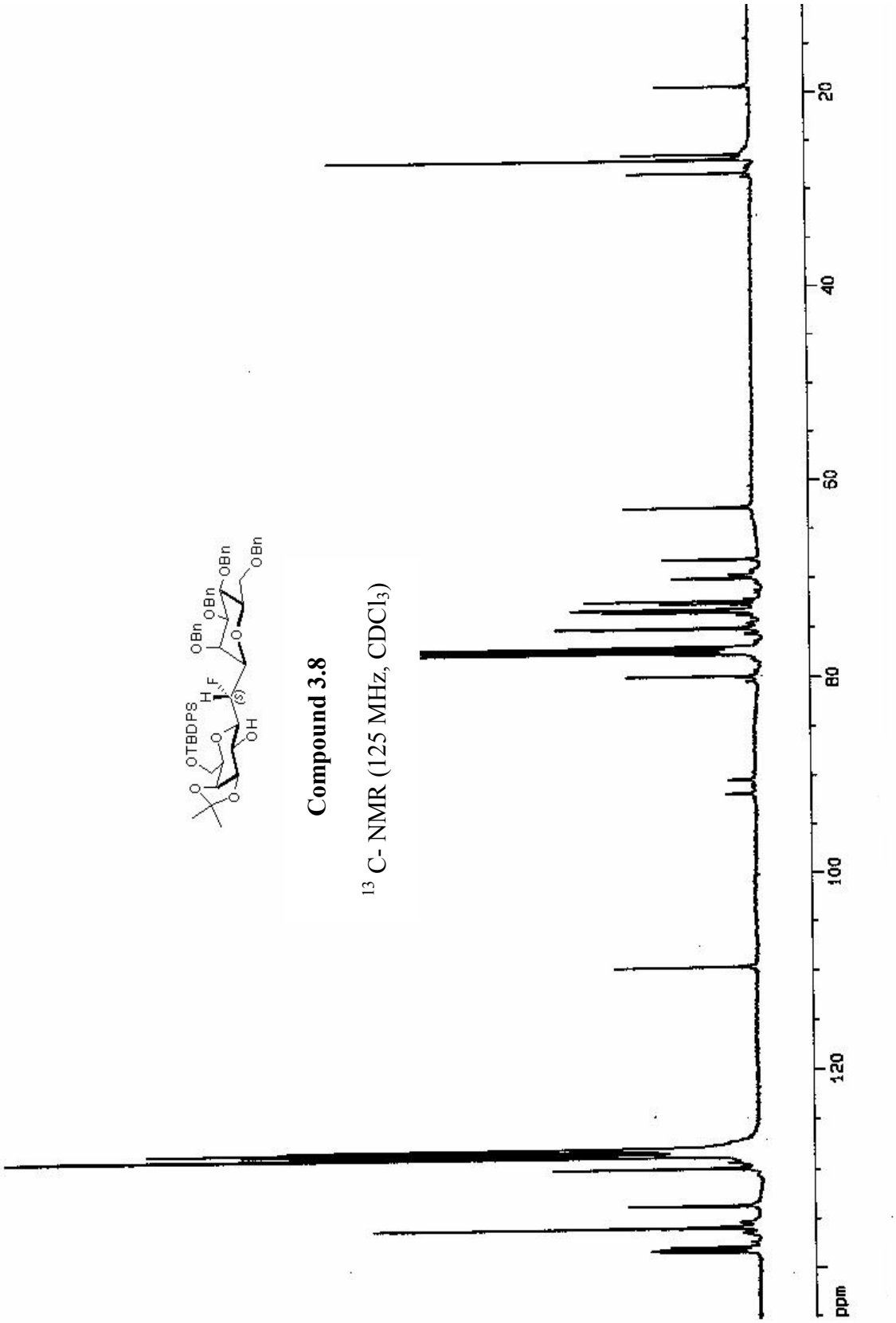
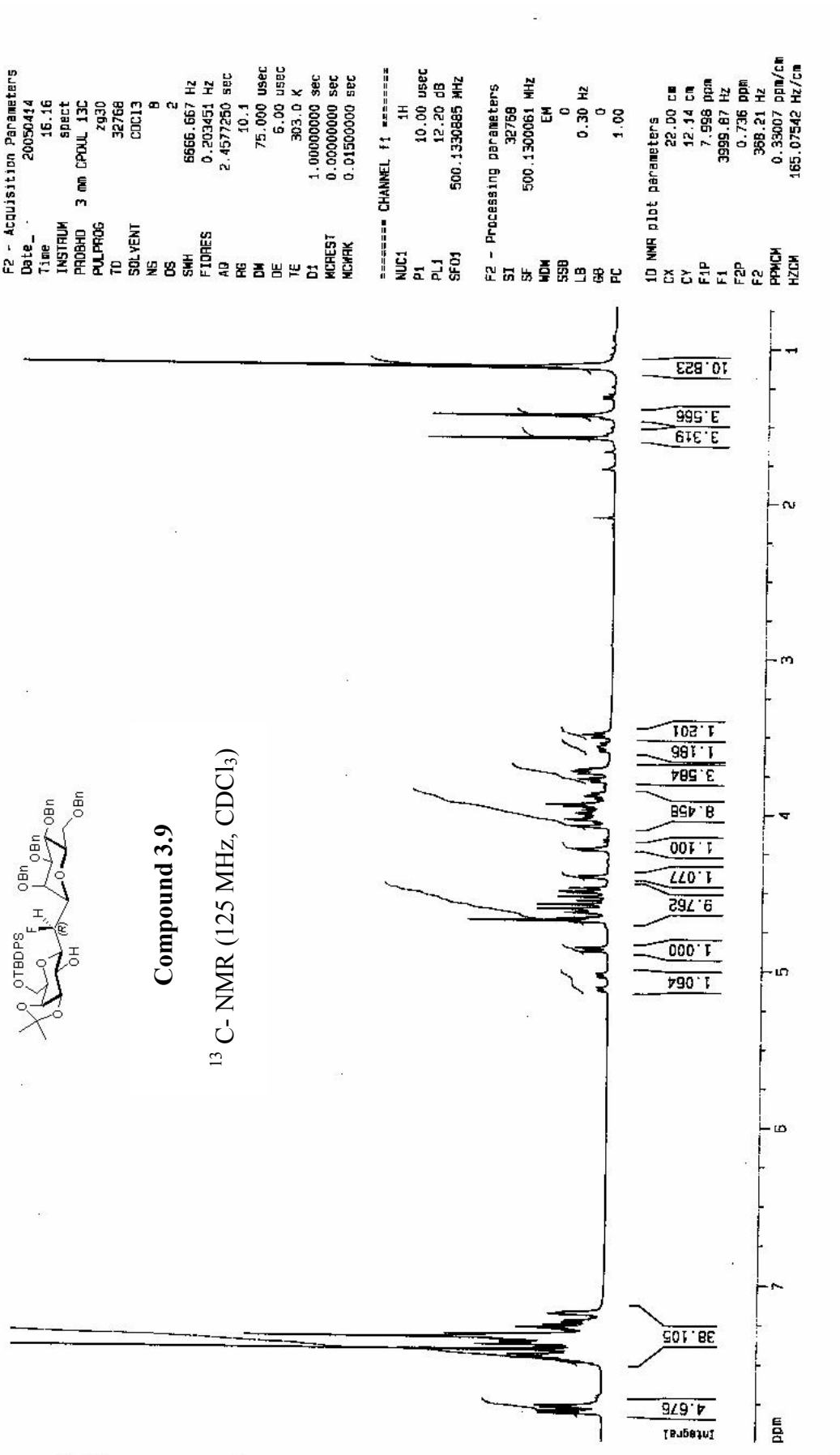
CY 80.94 cm
F1P 7.987 ppm
F1 3994.30 Hz
F2P 0.692 ppm
F2 345.93 Hz
PPMCM 0.33158 ppm/cm
HZCM 165.83498 Hz/cm
9.581
3.220
2.948
0.094
0.870
1.013
2.031
3.409
5.276
0.962
1.000
9.518
1.148
46.989
4.319
Integral
ppm



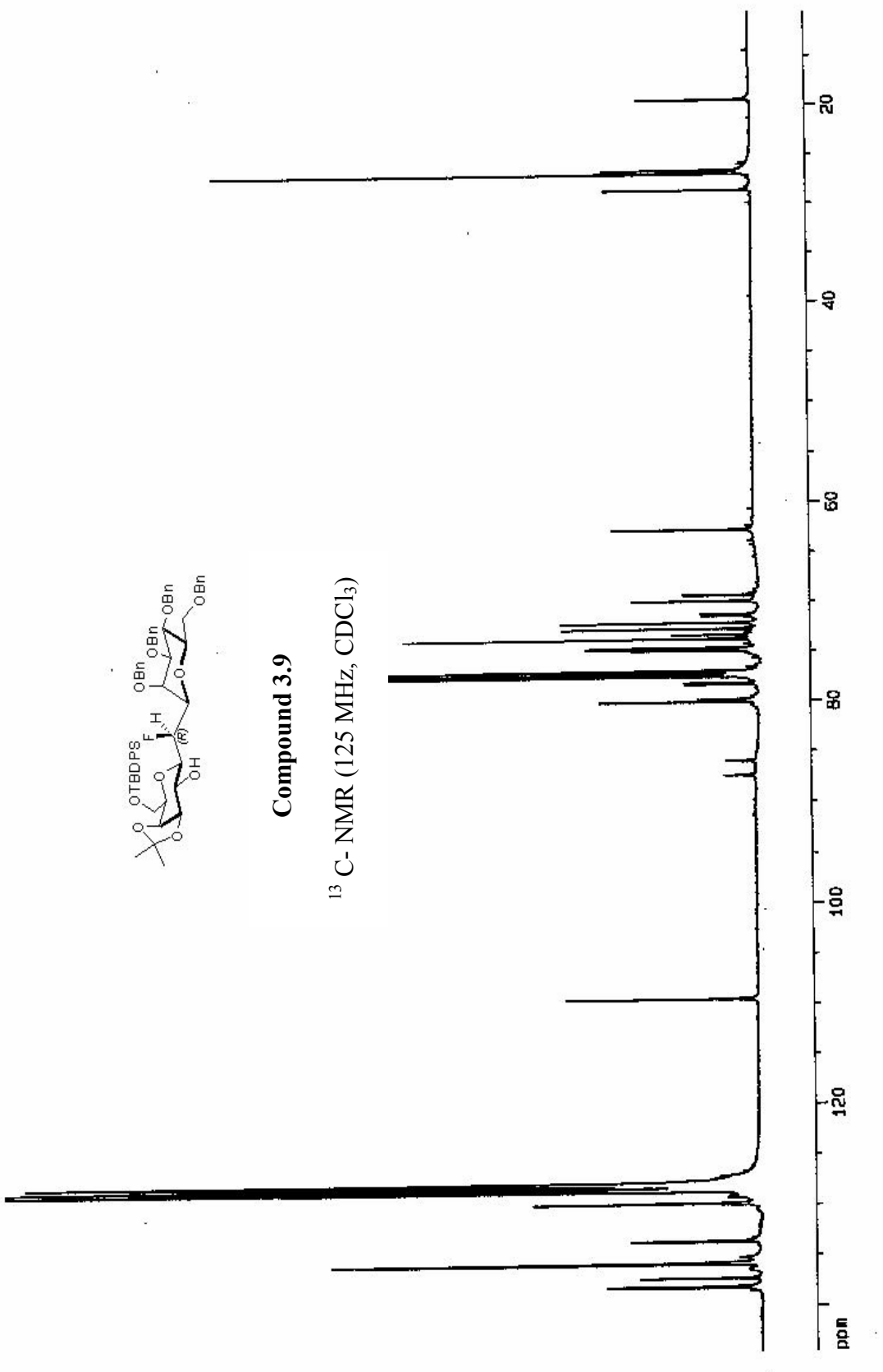
Compound 3.8

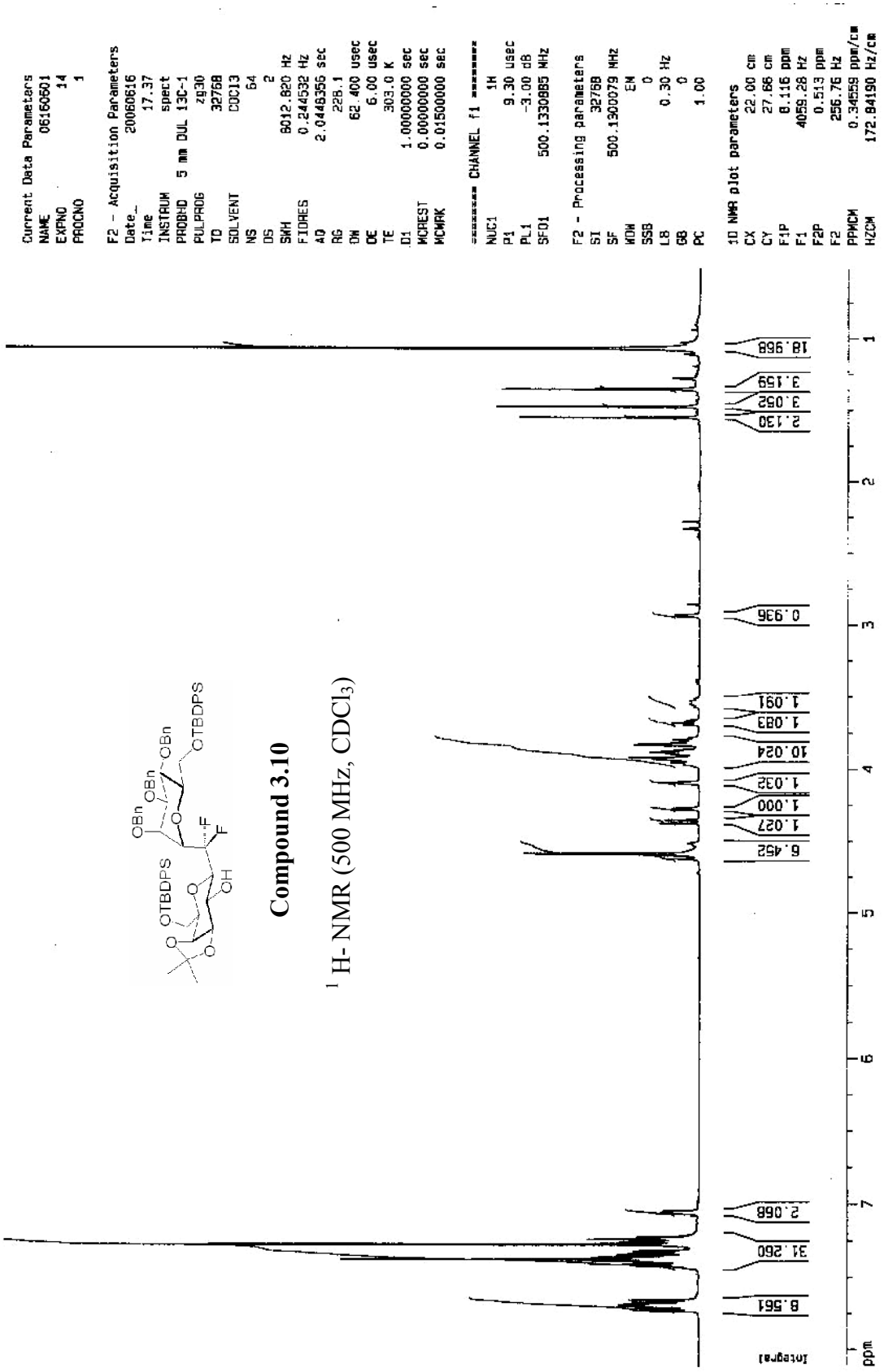
^{13}C- NMR (125 MHz, $CDCl_3$)



Compound 3.9

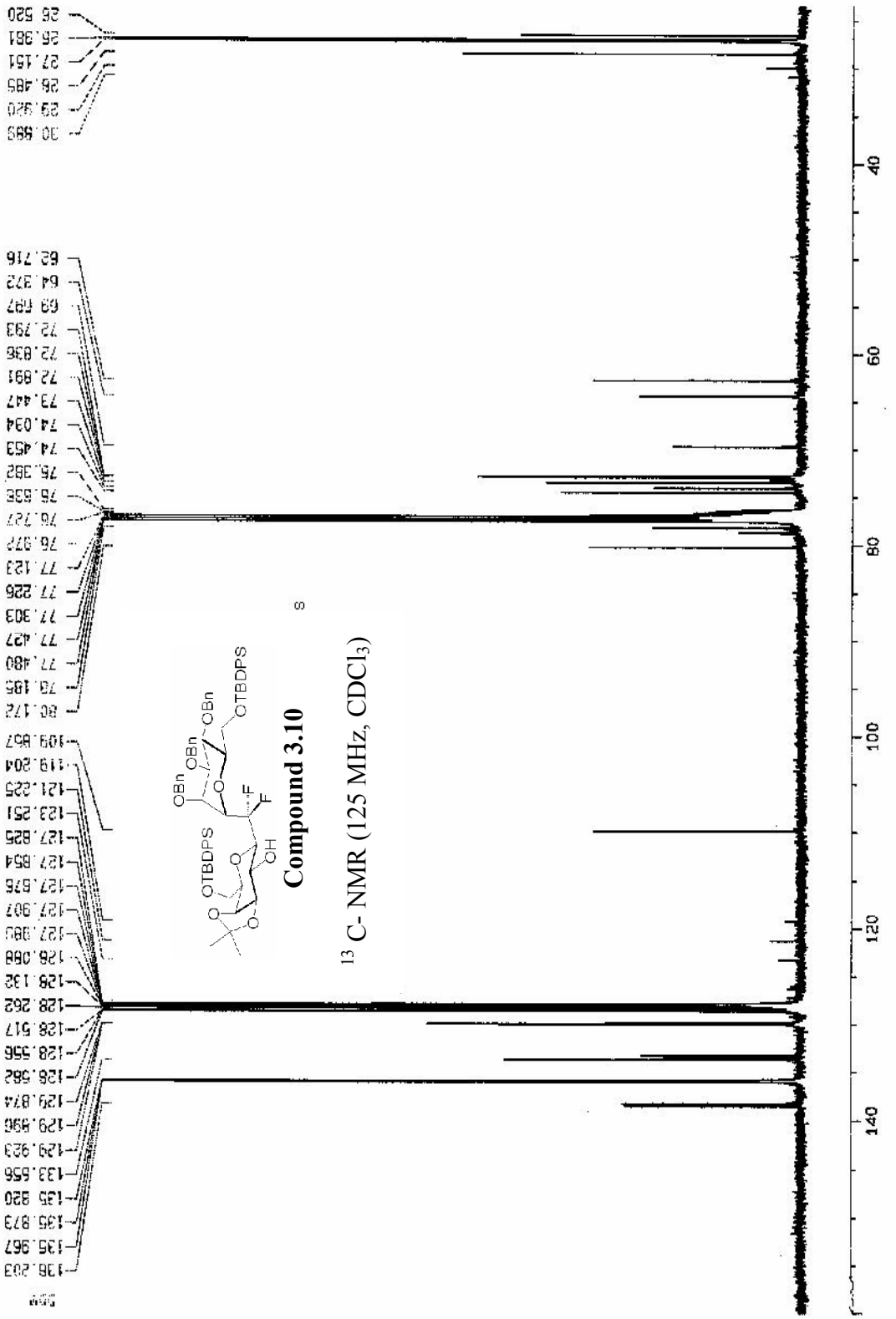
^{13}C- NMR (125 MHz, $CDCl_3$)


OTBDPS
OBn
OBn
OBn
OBn
F
H
OH
Compound 3.9
13 C- NMR (125 MHz, CDCl3)
ppm
20
40
60
80
100
120



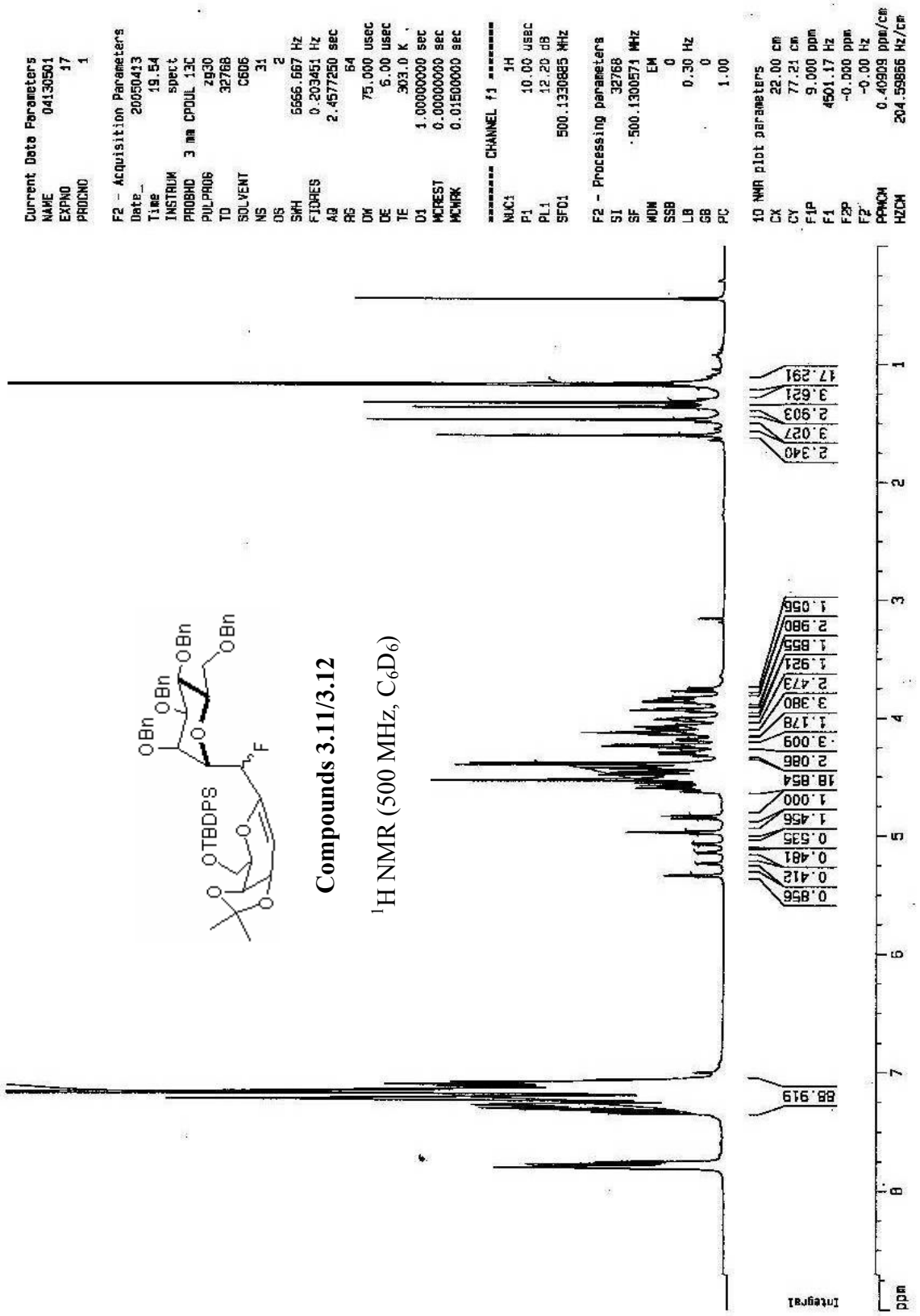
Compound 3.10

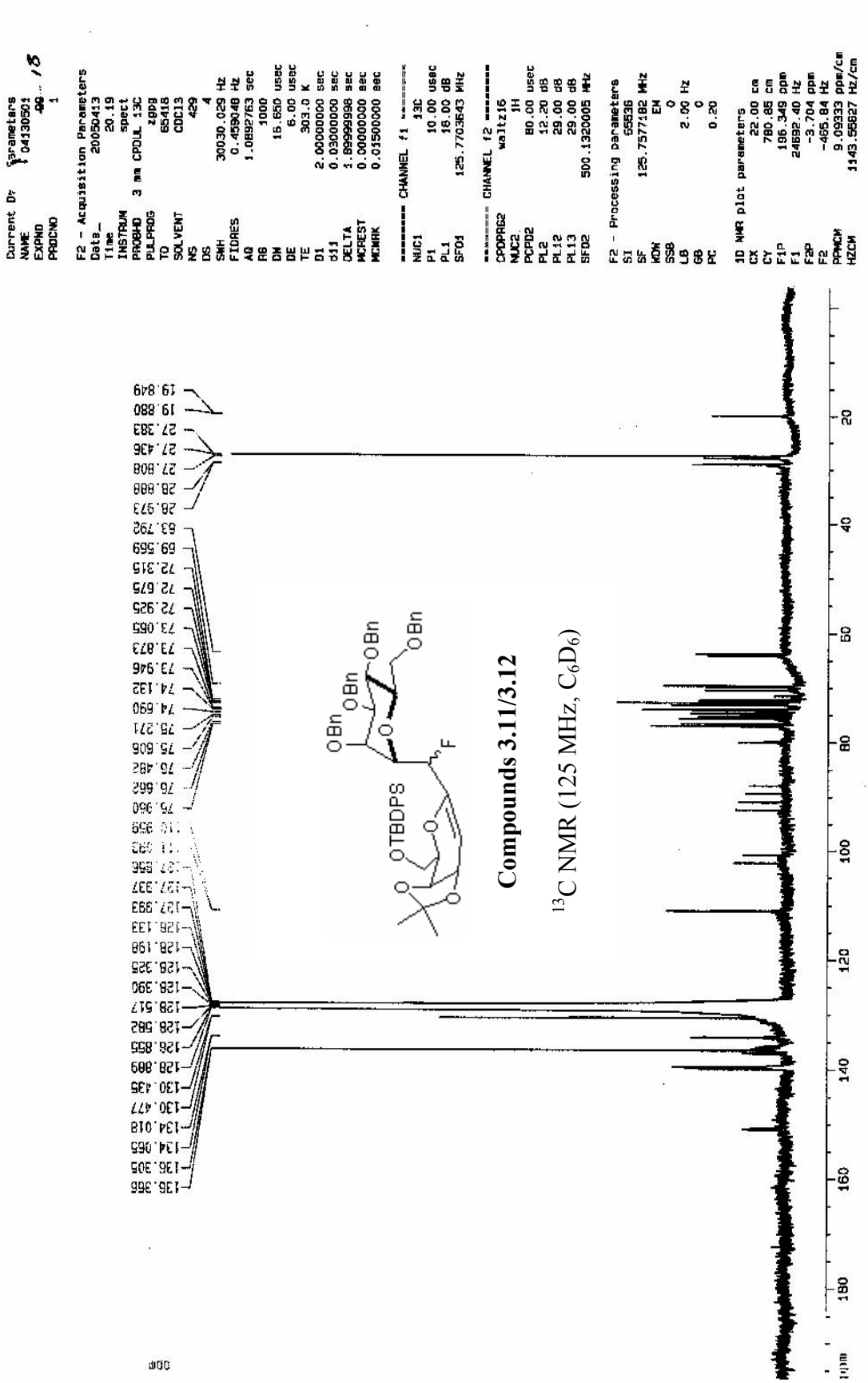
^{1}H- NMR (500 MHz, $CDCl_3$)

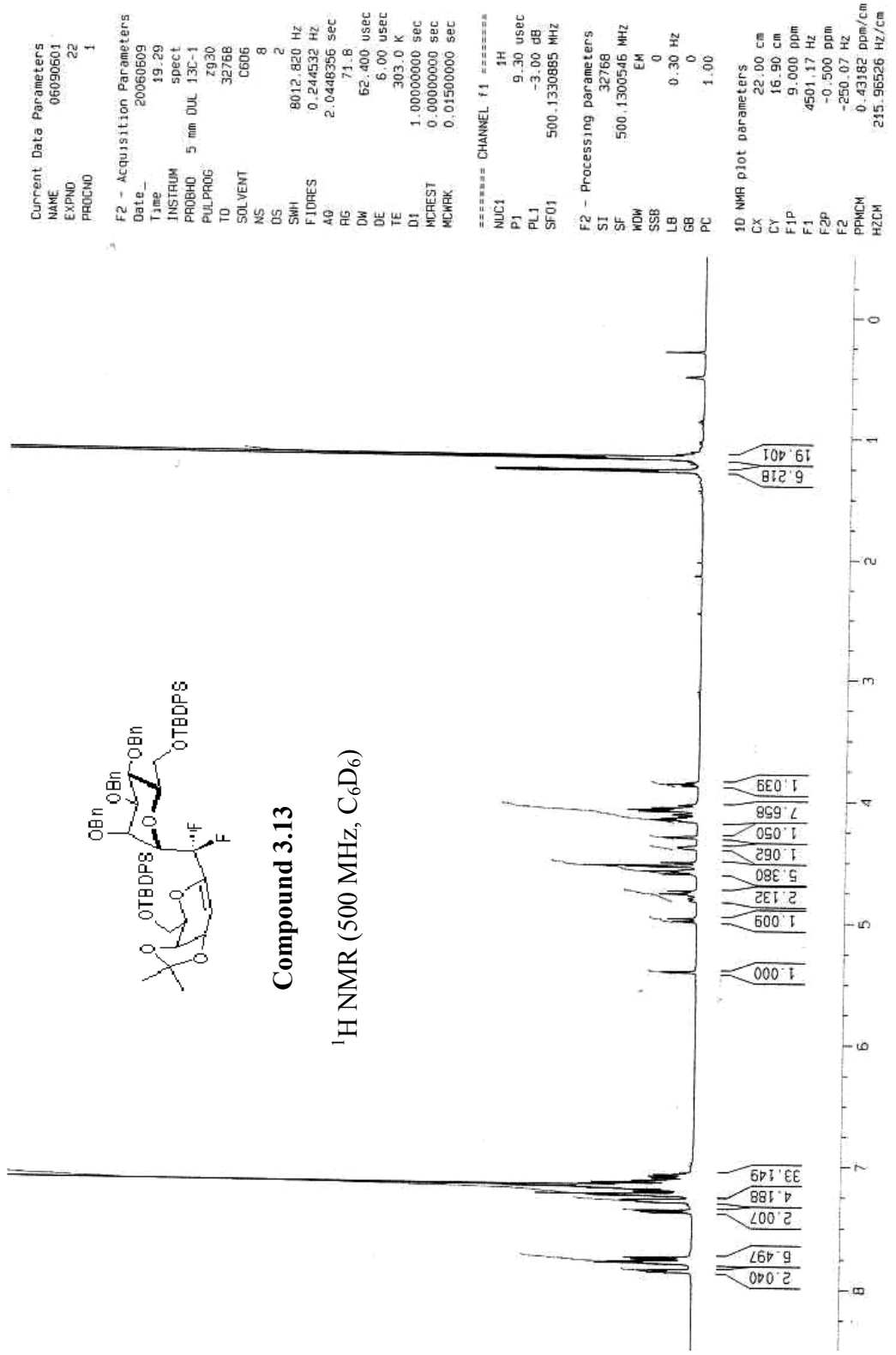


Compound 3.10

^{13}C- NMR (125 MHz, $CDCl_3$)

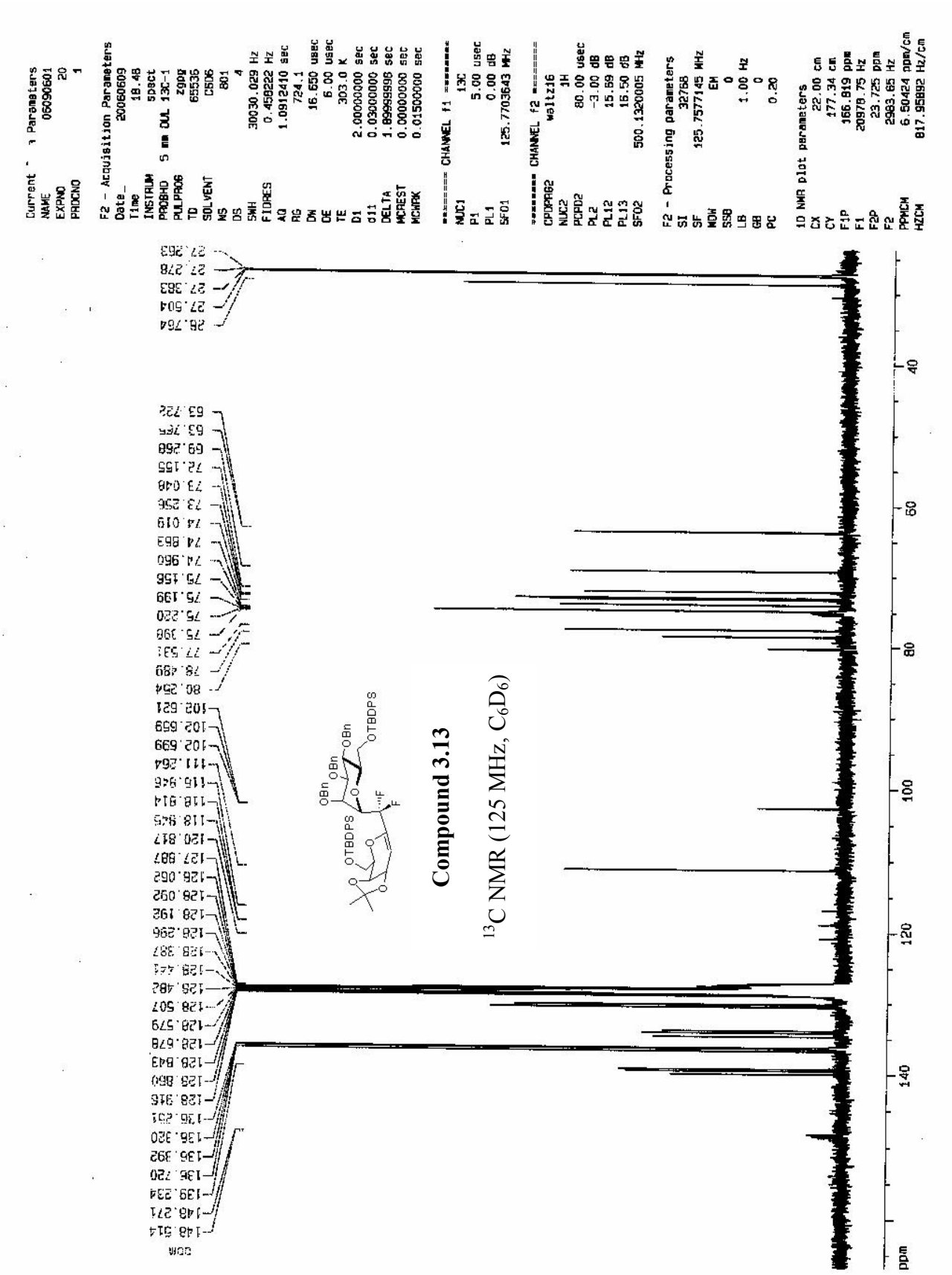

OBn
OBn
OBn
OBn
O
O
F
OTBDPS
O
O
O
Compounds 3.11/3.12
^{1}H NMR (500 MHz, C_6D_6)
Current Data Parameters
NAME 04130501
EXPNO 17
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050413
Time 19.54
INSTRUM spect
PROBHD 3 mm CPDUL 13C
PULPROG zg30
TD 32768
SOLVENT C6D6
NS 31
DS 2
SWH 5566.667 Hz
FIDRES 0.203451 Hz
AQ 2.4577250 sec
RG 64
DW 75.000 usec
DE 6.00 usec
TE 303.0 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 10.00 usec
PL1 12.20 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300571 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 22.00 cm
CY 77.21 cm
F1P 9.000 ppm
F1 4501.17 Hz
F2P -0.000 ppm
F2 -0.00 Hz
PPMCM 0.40909 ppm/cm
HZCM 204.59886 Hz/cm
88.919
17.291
3.621
2.903
3.027
2.340
1.056
2.980
1.855
1.921
2.473
3.380
1.178
3.009
2.086
18.854
1.000
1.456
0.535
0.481
0.412
0.856
Integral
ppm

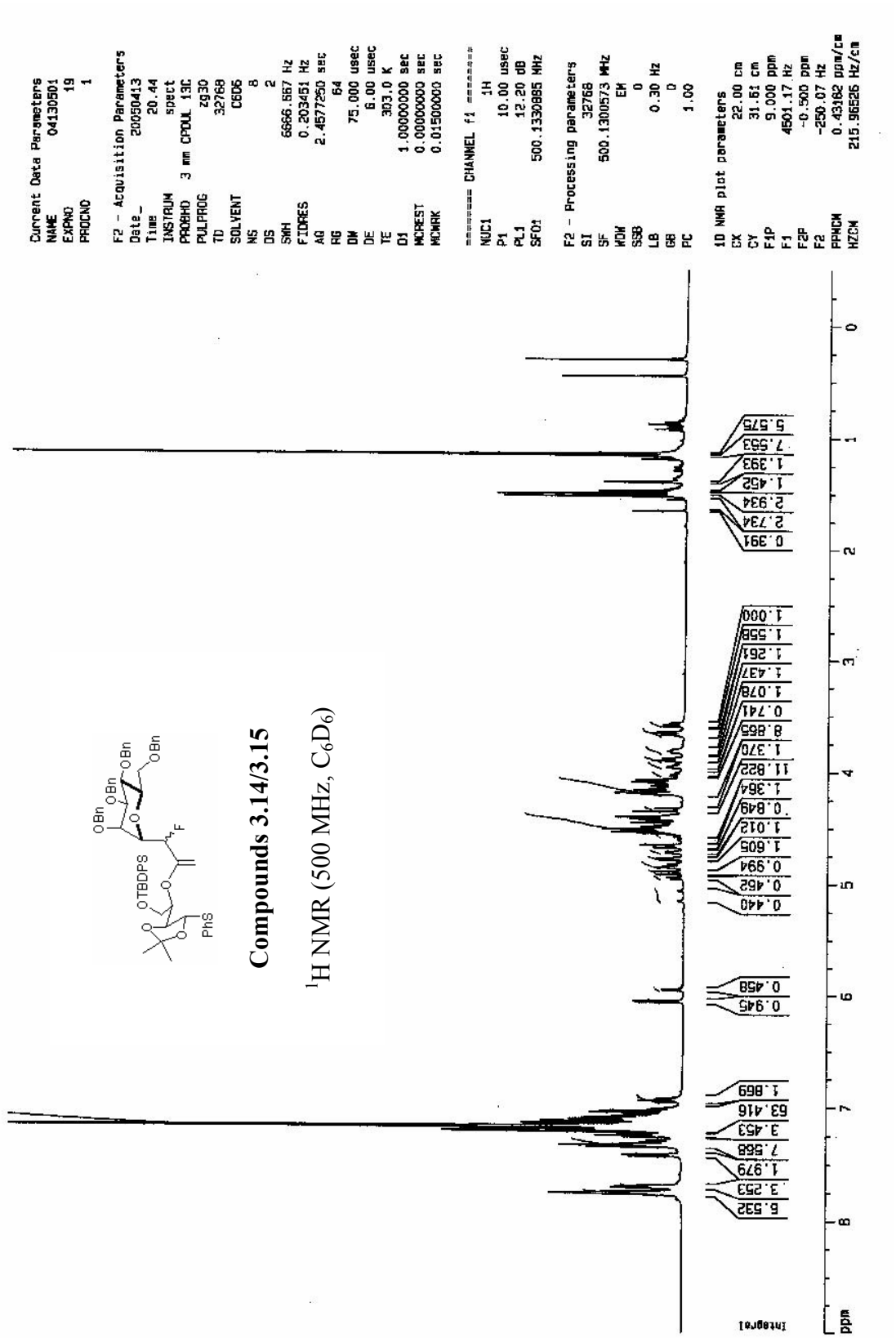

Compounds 3.11/3.12
^{13}C NMR (125 MHz, C_6D_6)
OBn
OBn
OBn
OBn
OTBDPS
F

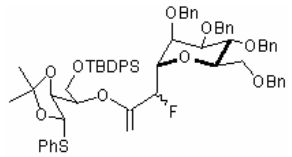


Compound 3.13

^{1}H NMR (500 MHz, C_6D_6)


Compound 3.13
^{13}C NMR (125 MHz, C_6D_6)
OBn
OBn
OBn
OTBDPS
OTBDPS
F
ppm

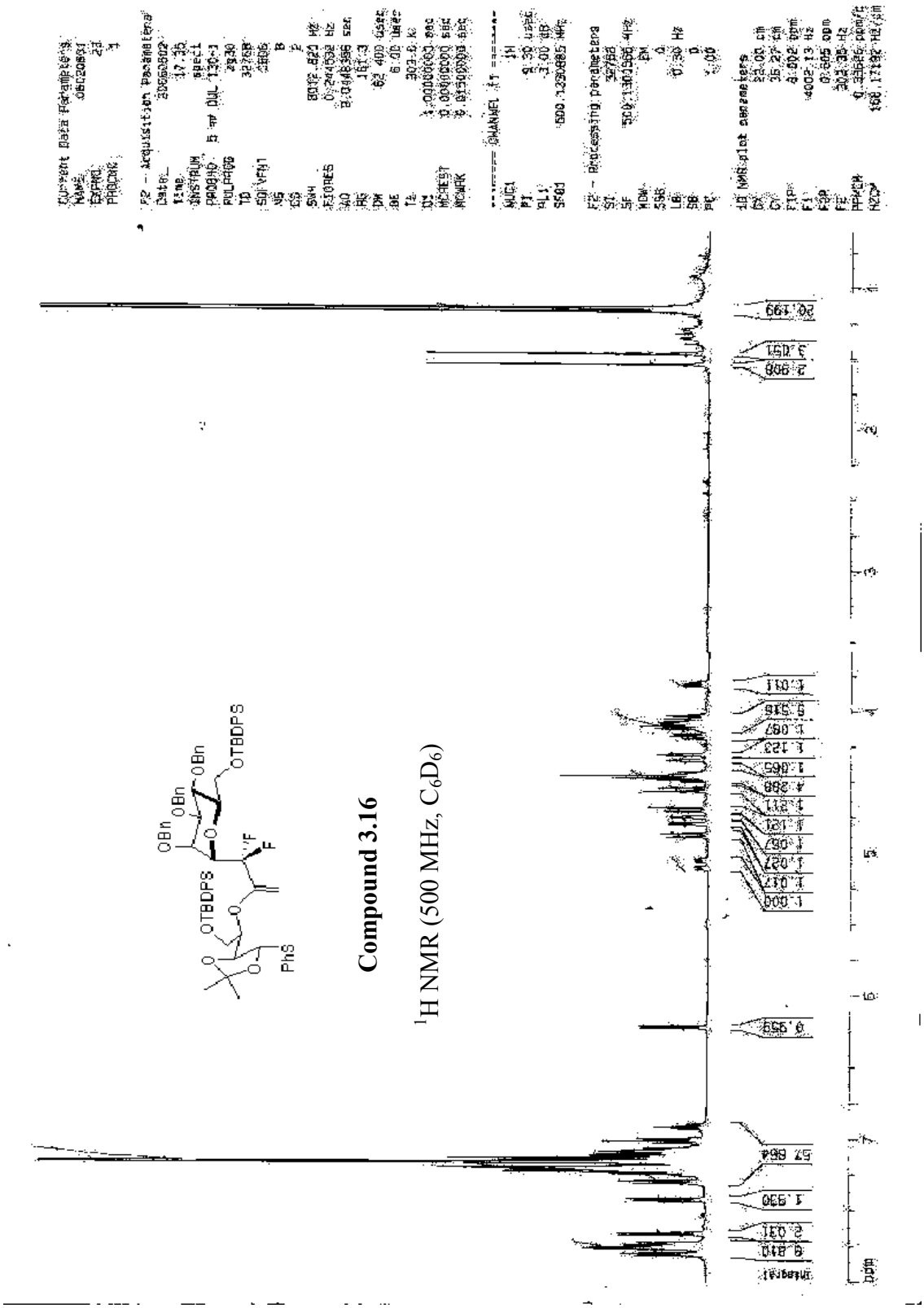

Current Data Parameters
NAME 04130501
EXPNO 19
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050413
Time 20.44
INSTRUM spect
PROBHD 3 mm CPDUL 13C
PULPROG zg30
TD 32768
SOLVENT C6D6
NS 8
DS 2
SWH 6666.667 Hz
FIDRES 0.203451 Hz
AQ 2.4577250 sec
RG 64
DW 75.000 usec
DE 6.00 usec
TE 303.0 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 10.00 usec
PL1 12.20 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300573 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 22.00 cm
CY 31.61 cm
F1P 9.000 ppm
F1 4501.17 Hz
F2P -0.500 ppm
F2 -250.07 Hz
PPMCM 0.43182 ppm/cm
HZCM 215.96526 Hz/cm
OBn
OBn
OBn
OBn
O
F
OTBDPS
O
O
O
O
PhS
Compounds 3.14/3.15
^{1}H NMR (500 MHz, C_6D_6)
5.575
7.553
1.393
1.452
2.934
2.734
0.391
1.000
1.558
1.261
1.437
1.078
0.741
8.865
1.370
11.822
1.364
0.849
1.012
1.605
0.994
0.462
0.440
0.458
0.945
1.869
53.416
3.453
7.568
1.979
3.253
5.532
Integral
ppm
0
1
2
3
4
5
6
7
8



Compounds 3.14/3.15

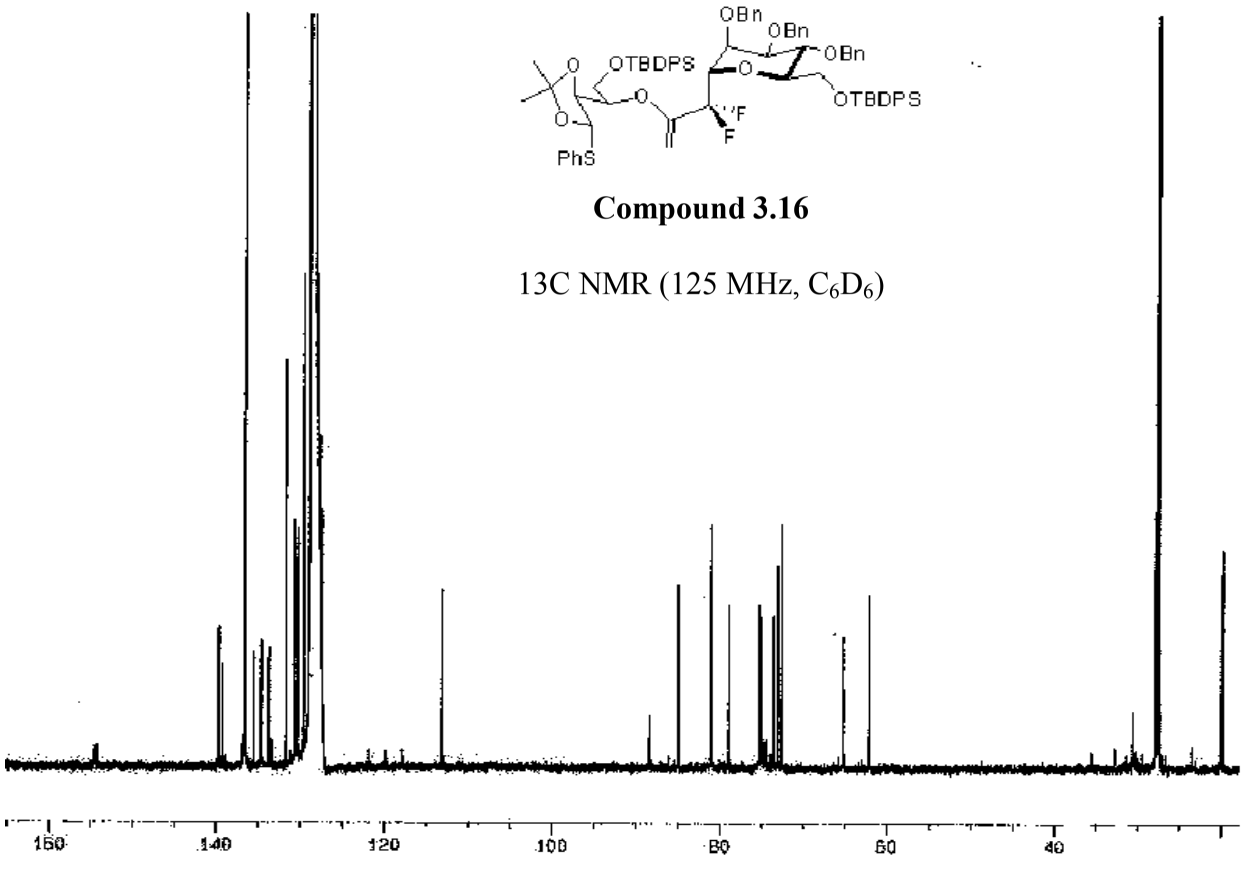
^{13}C NMR (125 MHz, C_6D_6)


```
Current Parameters
NAME                 04130501
EXPNO                      99
PROCNO                      1

F2 - Acquisition Parameters
Date_              20050413
Time                 21.02
INSTRUM              spect
PROBHD   3 mm CPDUL 13C
PULPROG              zgpg
TD                  65418
SOLVENT             CDCl3
NS                    512
DS                      4
SWH              30030.029 Hz
FIDRES           0.459048 Hz
AQ               1.0892763 sec
RG                   1000
DW                 16.650 usec
DE                  6.00 usec
TE                303.0 K
D1             2.00000000 sec
d11            0.03000000 sec
DELTA          1.89999998 sec
MCREST         0.00000000 sec
MCWRK          0.01500000 sec

======== CHANNEL f1 ========
NUC1                  13C
P1                 10.00 usec
PL1                18.00 dB
SFO1         125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                  1H
PCPD2              80.00 usec
PL2                12.20 dB
PL12               29.00 dB
PL13               29.00 dB
SFO2         500.1320005 MHz

F2 - Processing parameters
SI                  65536
SF           125.7577182 MHz
WDW                   EM
SSB                    0
LB                  2.00 Hz
GB                     0
PC                  0.20

1D NMR plot parameters
CX                 22.00 cm
CY                316.12 cm
F1P              166.355 ppm
F1               20920.49 Hz
F2P               14.287 ppm
F2                1795.70 Hz
PPMCM            6.91221 ppm/cm
HZCM          869.26318 Hz/cm
```



Compound 3.16

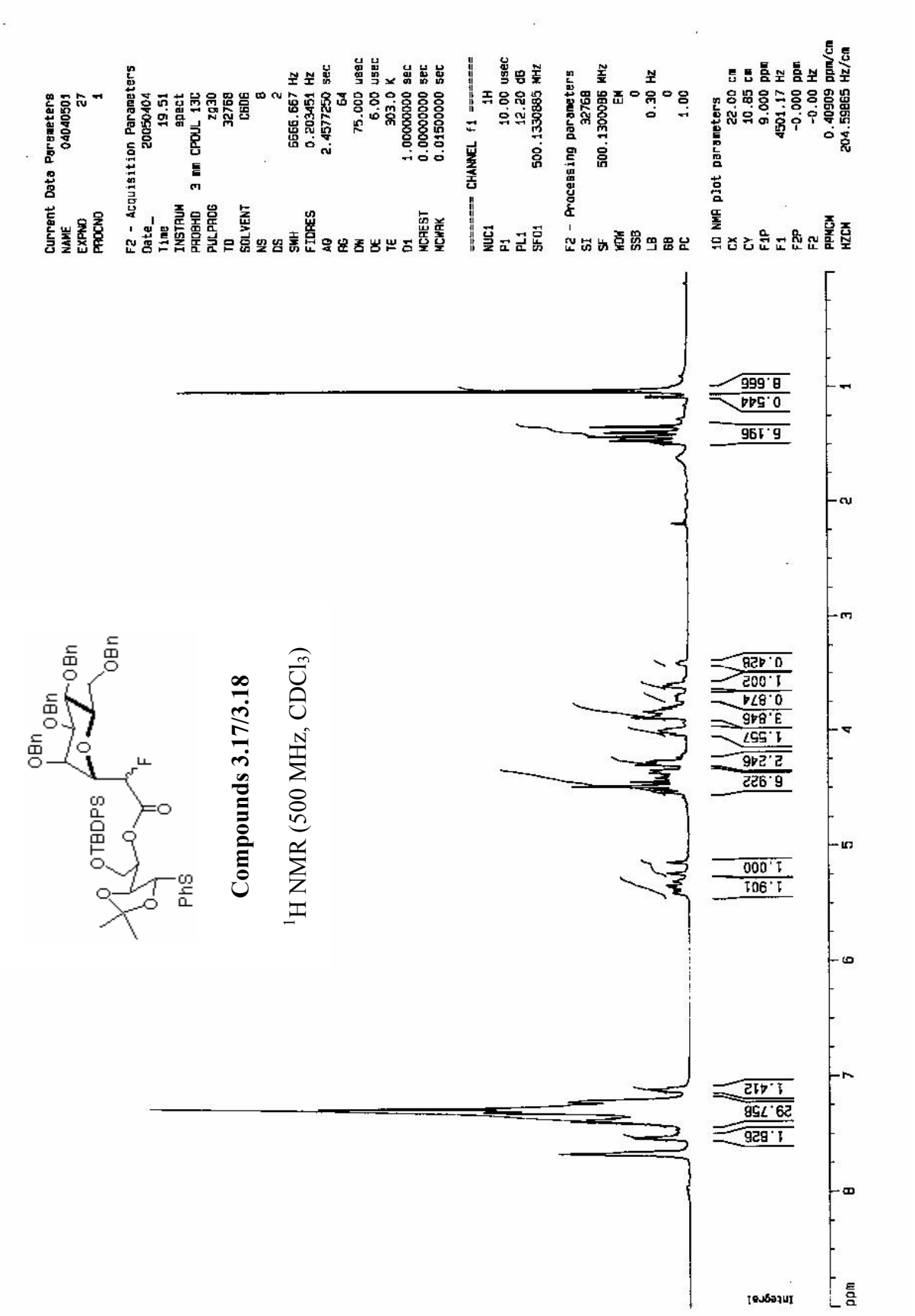
^{1}H NMR (500 MHz, C_6D_6)

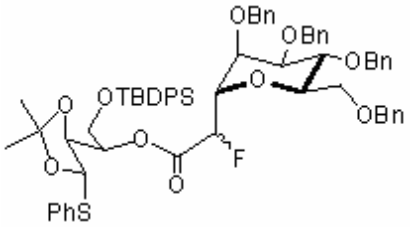


Compound 3.16

13C NMR (125 MHz, C_6D_6)

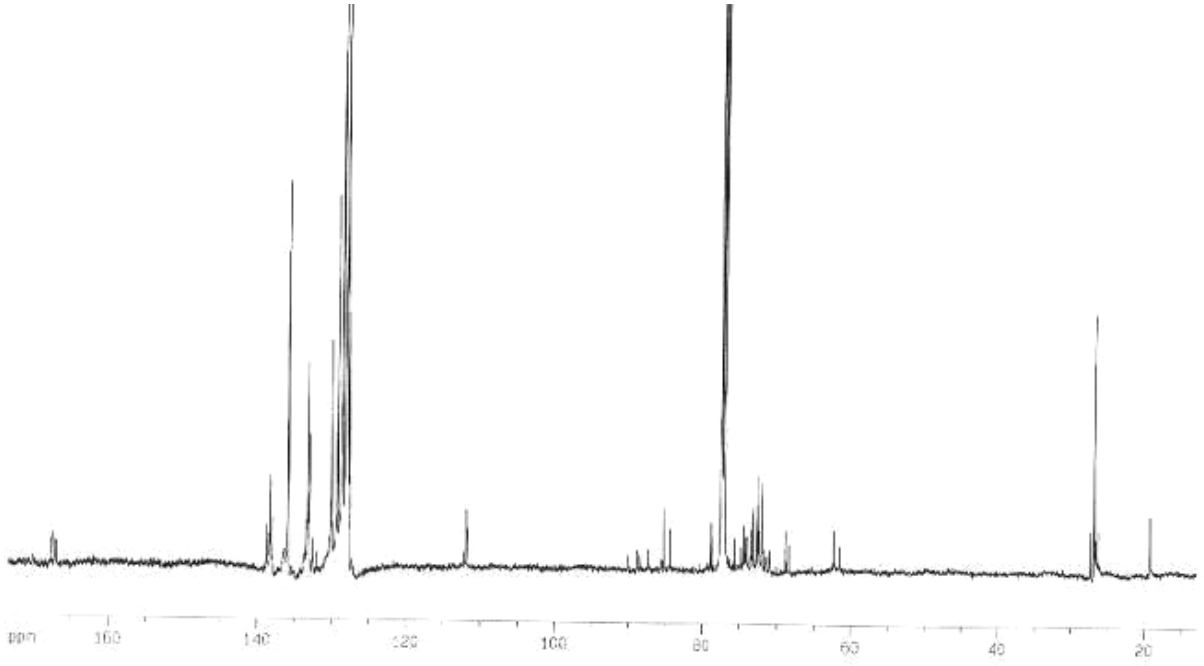
```
Current Da  Parameters
NAME        06020601
EXPNO             26
PROCNO             1

F2 - Acquisition Parameters
Date_        20060602
Time            18.33
INSTRUM         spect
PROBHD  5 mm DUL 13C-1
PULPROG         zgpg
TD             65536
SOLVENT         CDCl3
NS              21565
DS                  4
SWH         30030.029 Hz
FIDRES      0.458222 Hz
AQ          1.0912410 sec
RG              724.1
DW             16.650 usec
DE              6.00 usec
TE             303.0 K
D1          2.00000000 sec
d11         0.03000000 sec
DELTA       1.89999998 sec
MCREST      0.00000000 sec
MCWRK       0.01500000 sec

======== CHANNEL f1 ========
NUC1              13C
P1               5.00 usec
PL1              0.00 dB
SF01        125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG2       waltz16
NUC2              1H
PCPD2           80.00 usec
PL2             -3.00 dB
PL12            15.69 dB
PL13            15.59 dB
SF02        500.1320005 MHz

F2 - Processing parameters
SI              32768
SF        125.7577136 MHz
WDW               EM
SSB               0
LB             1.00 Hz
GB                0
PC             0.20

1D NMR plot parameters
CX             22.00 cm
CY            371.91 cm
F1P           187.492 ppm
F1          23578.61 Hz
F2P            17.831 ppm
F2           2242.40 Hz
PPMCM          7.71188 ppm/cm
HZCM         968.82806 Hz/cm
```


OBn
OBn
OBn
OBn
O
F
OTBDPS
O
O
O
O
PhS
Compounds 3.17/3.18
^{1}H NMR (500 MHz, $CDCl_3$)
Current Data Parameters
NAME 04040501
EXPNO 27
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050404
Time 19.51
INSTRUM spect
PROBHD 3 mm CPDUL 13C
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 8
DS 2
SWH 5666.667 Hz
FIDRES 0.203451 Hz
AQ 2.4577250 sec
RG 64
DW 75.000 usec
DE 6.00 usec
TE 303.0 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 10.00 usec
PL1 12.20 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300086 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 22.00 cm
CY 10.85 cm
F1P 9.000 ppm
F1 4501.17 Hz
F2P -0.000 ppm
F2 -0.00 Hz
PPMCM 0.40909 ppm/cm
HZCM 204.59865 Hz/cm
8.666
0.544
6.196
6.922
2.246
1.557
3.846
0.874
1.002
0.428
1.901
1.000
1.826
29.758
1.412
Integral
ppm



Compounds 3.17/3.18

^{1}H NMR (125 MHz, $CDCl_3$)



Current Parameters
NAME 04040501
EXPNO 99
PROCNO 1

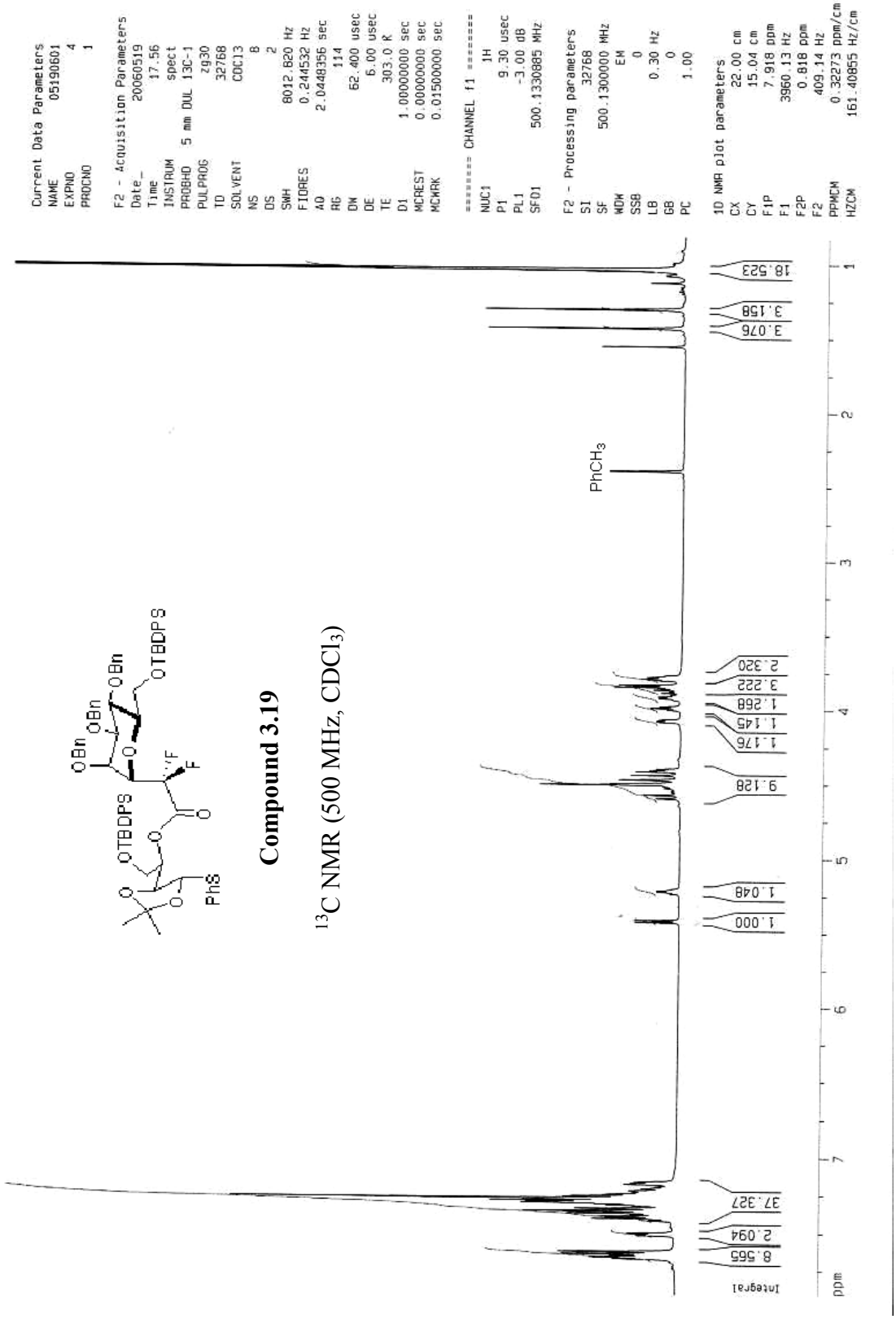
F2 - Acquisition Parameters
Date_ 20050404
Time 20.02
INSTRUM spect
PROBHD 5 mm CPDUL 13C
PULPROG 7000
TD 65416
SOLVENT CDCl3
NS 256
DS 4
SWH 30030.029 Hz
FIDRES 0.459045 Hz
AQ 1.0892753 sec
RG 1000
DW 16.650 usec
DE 6.00 usec
TE 303.0 K
D1 2.00000000 sec
D11 0.03000000 sec
DELTA 1.89999998 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

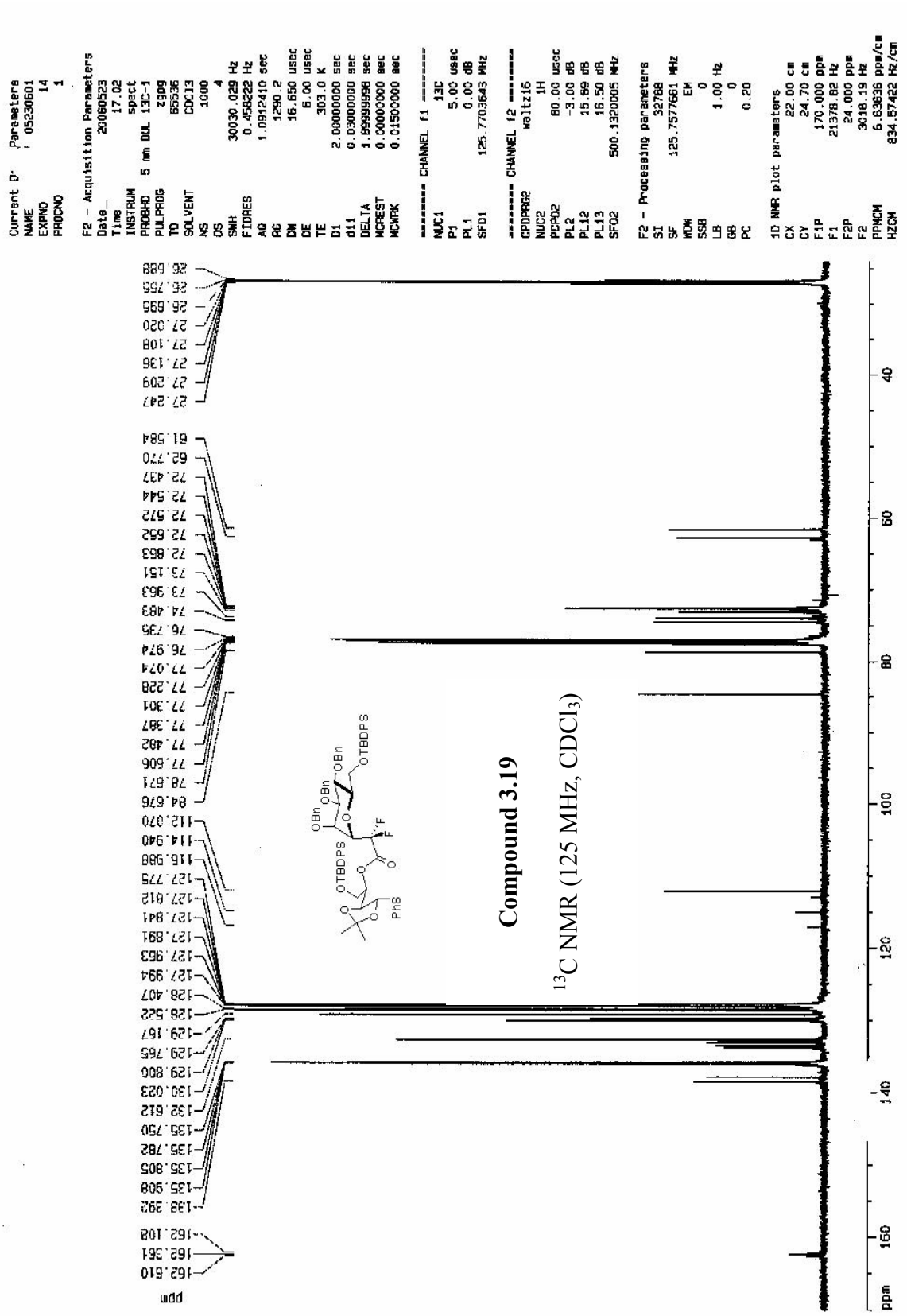
======== CHANNEL f1 ========
NUC1 13C
P1 10.00 usec
PL1 18.00 dB
SFO1 125.7703643 MHz

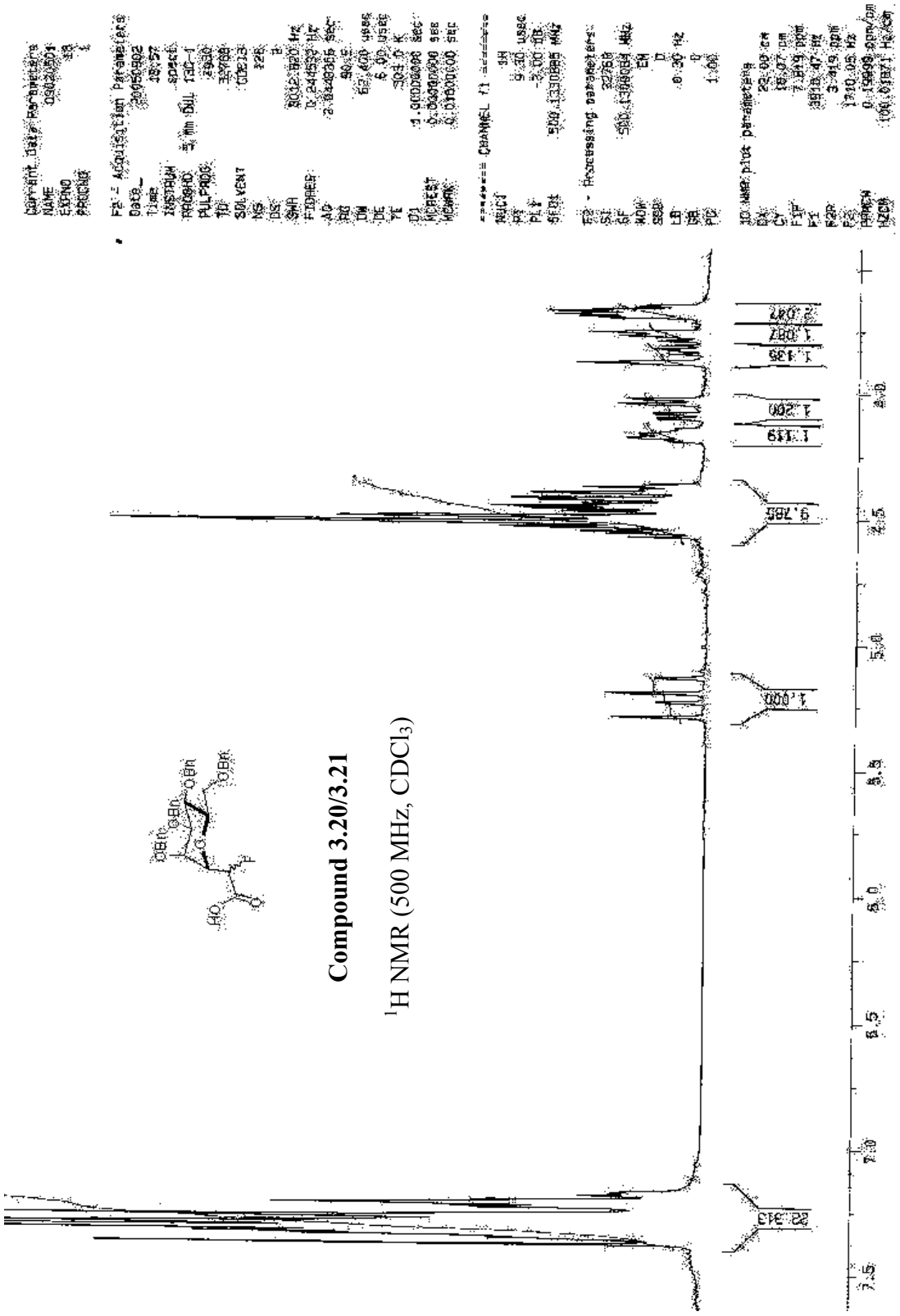
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 12.30 dB
PL12 29.00 dB
PL13 29.00 dB
SFO2 500.1320005 MHz

F2 - Processing parameters
SI 65536
SF 125.7577575 MHz
WDW EM
SSB 0
LB 2.00 Hz
GB 0
PC 0.20

1D NMR plot parameters
CX 22.00 cm
CY 20.61 cm
F1P 173.297 ppm
F1 21793.47 Hz
F2P 13.008 ppm
F2 1635.81 Hz
PPMCM 7.28569 ppm/cm
HZCM 915.25720 Hz/cm

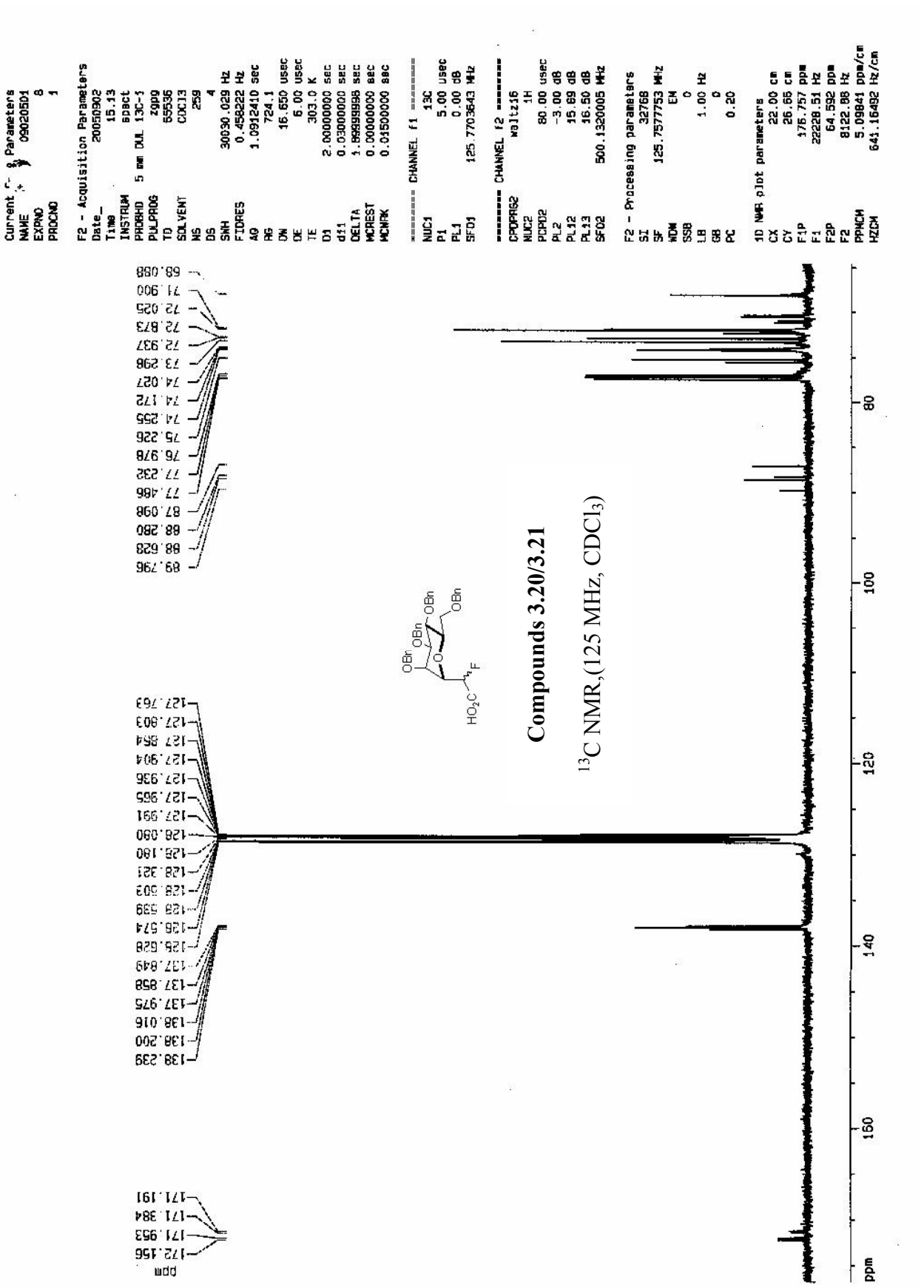

Current Data Parameters
NAME 05190601
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060519
Time 17.56
INSTRUM spect
PROBHD 5 mm DUL 13C-1
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 8
DS 2
SWH 8012.820 Hz
FIDRES 0.244532 Hz
AQ 2.0448356 sec
RG 114
DW 62.400 usec
DE 6.00 usec
TE 303.0 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 9.30 usec
PL1 -3.00 dB
SF01 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 22.00 cm
CY 15.04 cm
F1P 7.918 ppm
F1 3960.13 Hz
F2P 0.818 ppm
F2 409.14 Hz
PPMCM 0.32273 ppm/cm
HZCM 161.40855 Hz/cm
OBn
OBn
OBn
OTBDPS
OTBDPS
F
F
PhS
Compound 3.19
13C NMR (500 MHz, CDCl3)
PhCH3
18.523
3.076
3.158
2.320
3.222
1.268
1.145
1.176
9.128
1.000
1.048
8.565
2.094
37.327
Integral
ppm

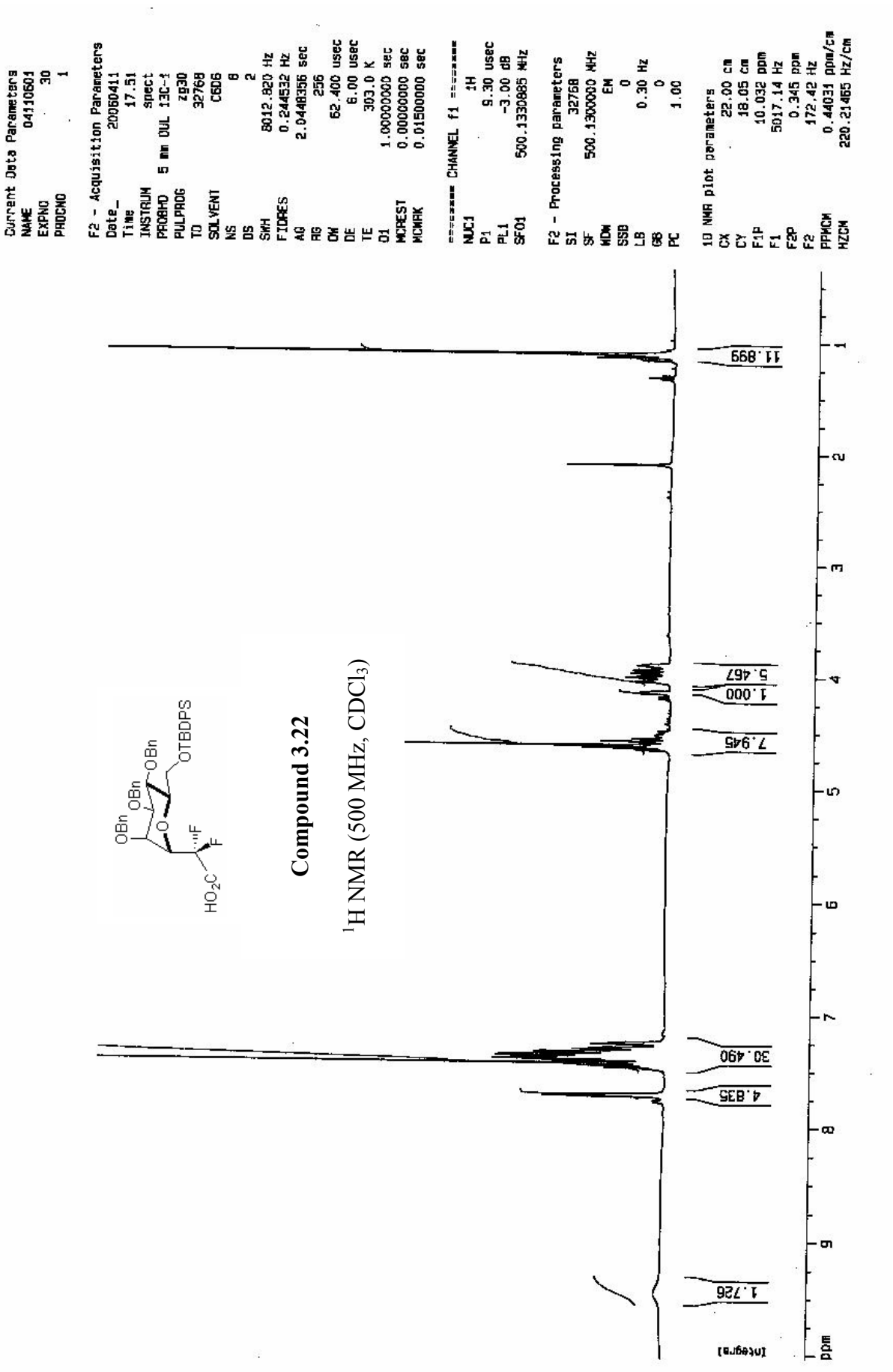

Compound 3.19
^{13}C NMR (125 MHz, $CDCl_3$)



Compound 3.20/3.21

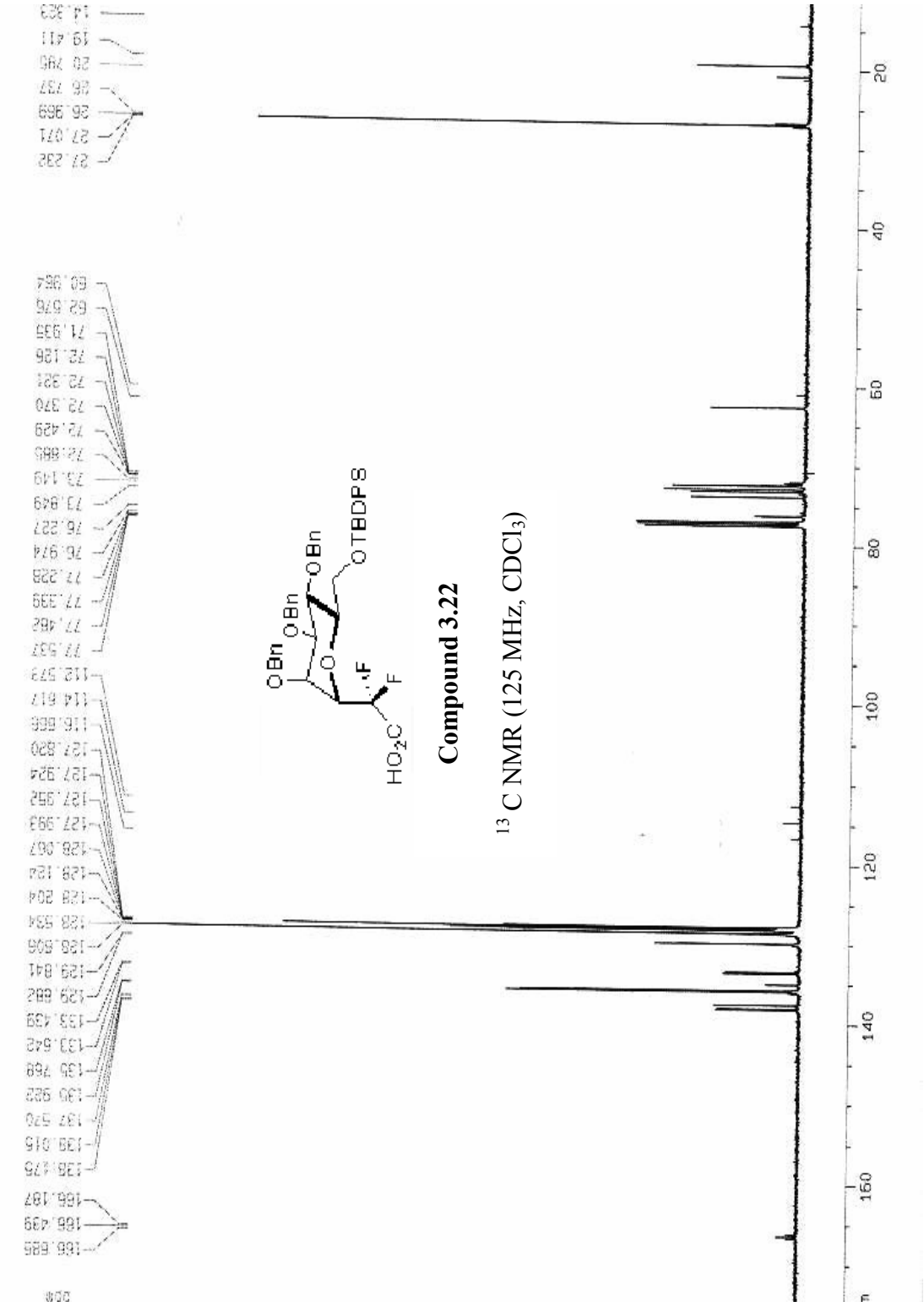
^{1}H NMR (500 MHz, $CDCl_3$)

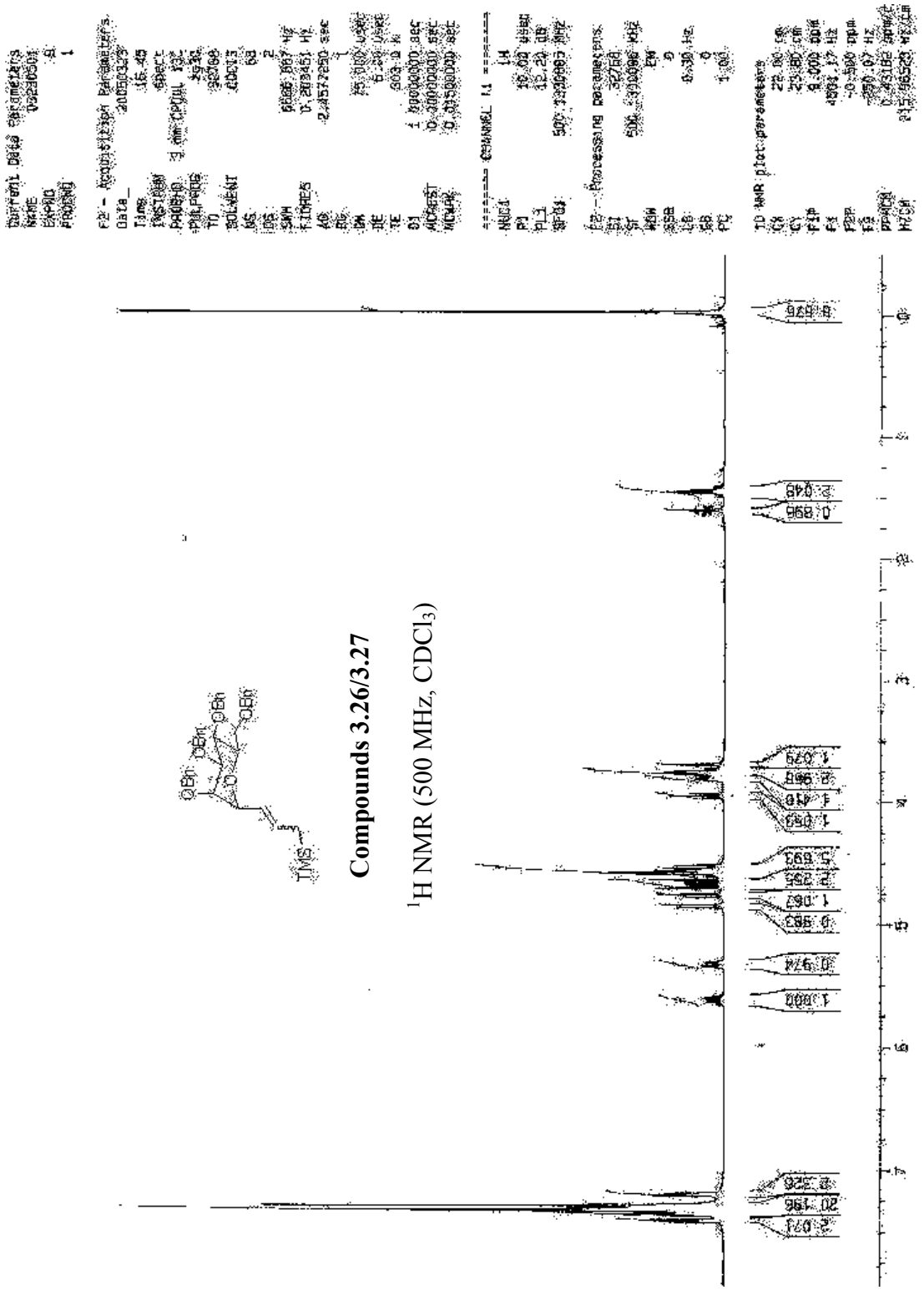

Compounds 3.20/3.21
^{13}C NMR,(125 MHz, $CDCl_3$)
OBn
OBn
OBn
O
F
HO_2C
ppm
20
40
60
80
100
120
140
160



Compound 3.22

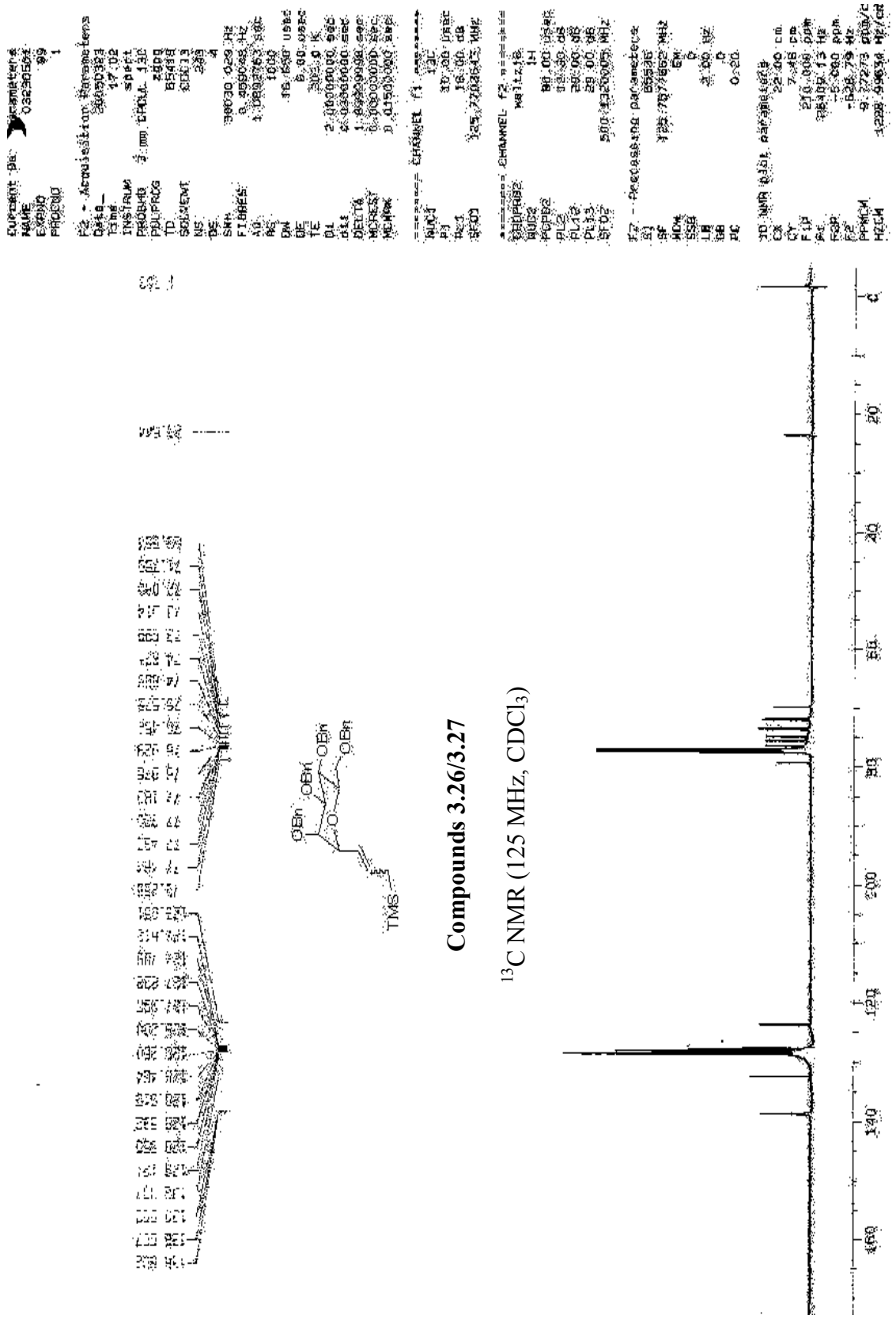
^{1}H NMR (500 MHz, $CDCl_3$)


OBn
OBn
OBn
OTBDPS
O
F
HO2C
Compound 3.22
13 C NMR (125 MHz, CDCl3)



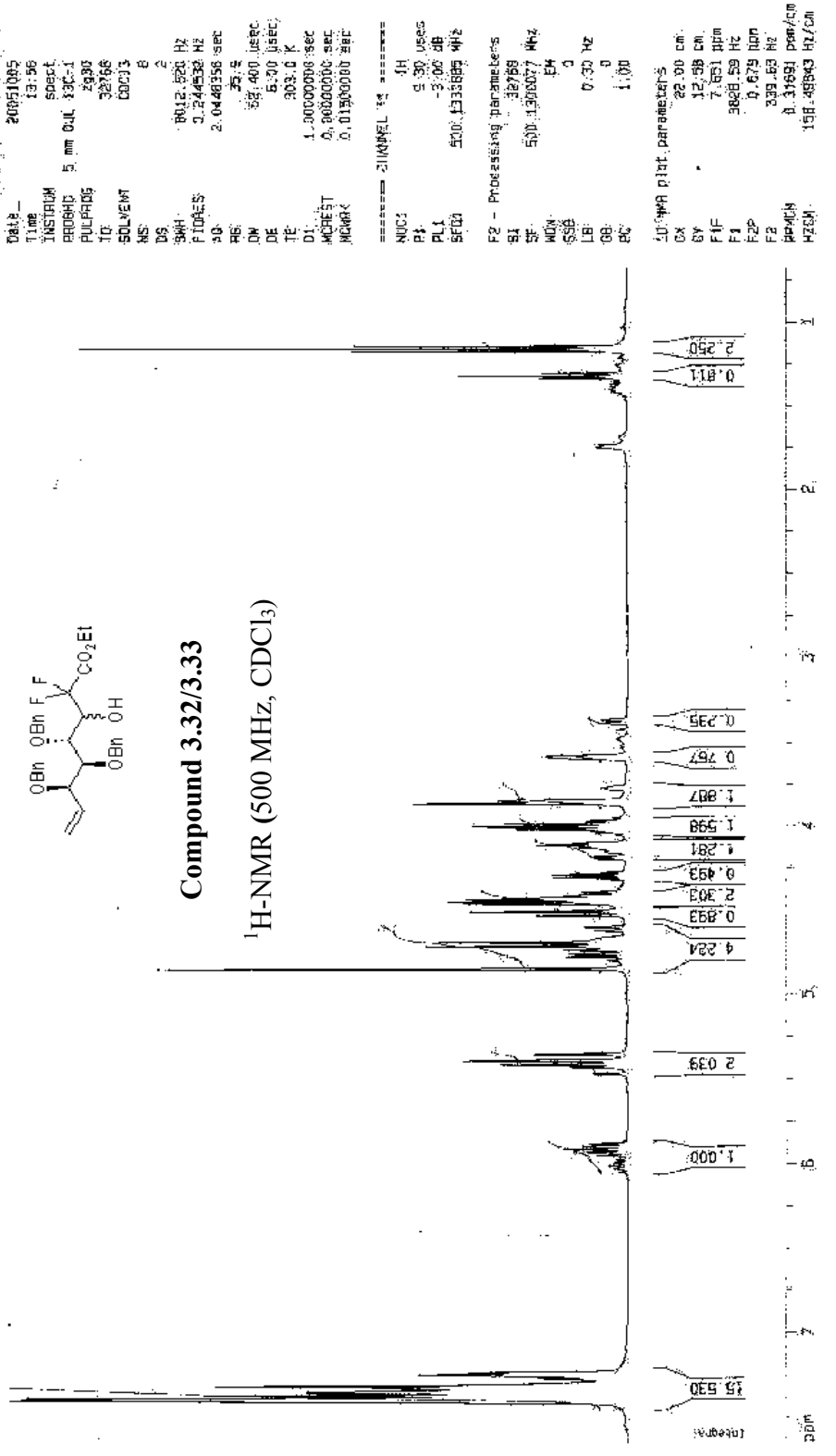
Compounds 3.26/3.27

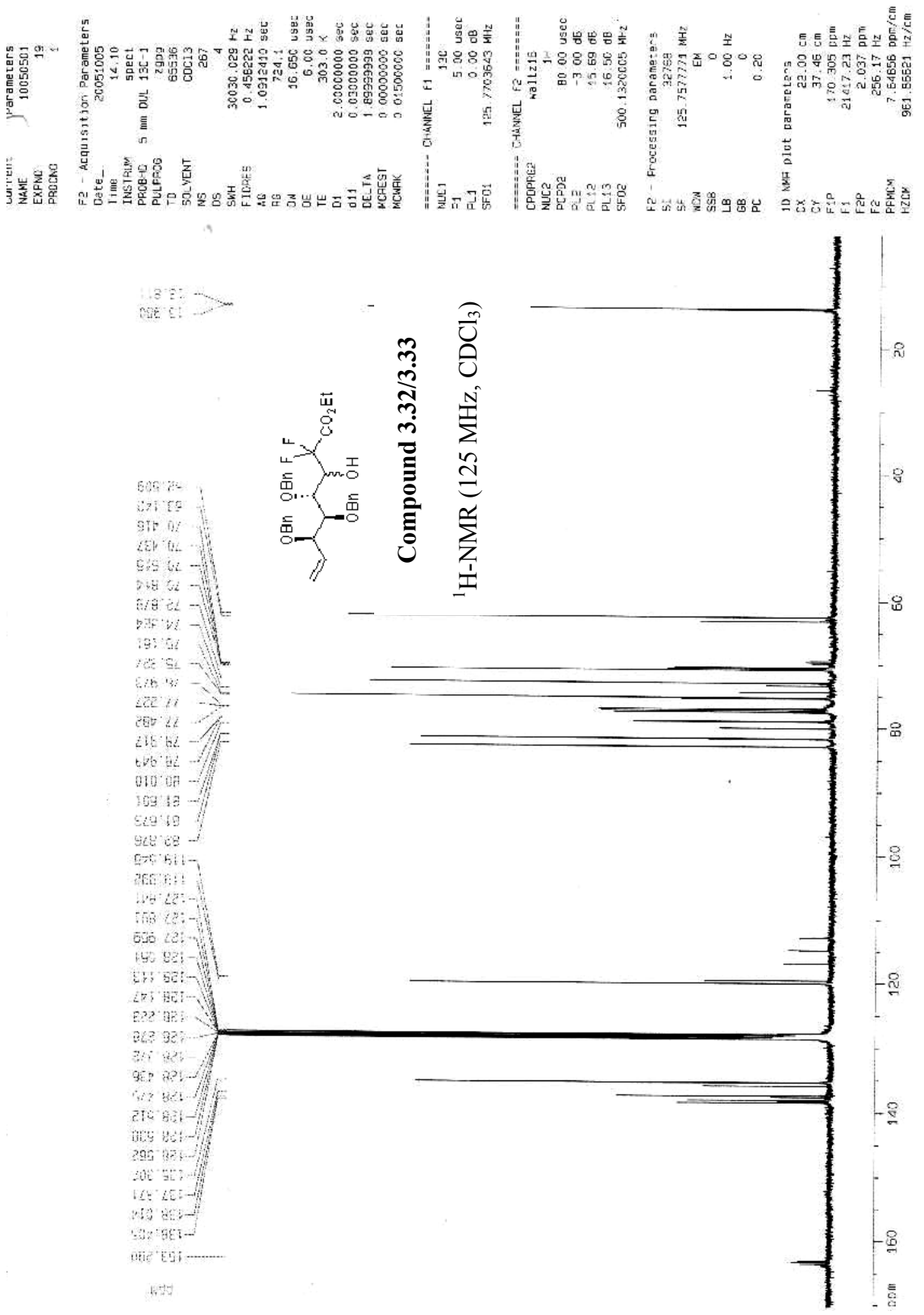
^{1}H NMR (500 MHz, $CDCl_3$)

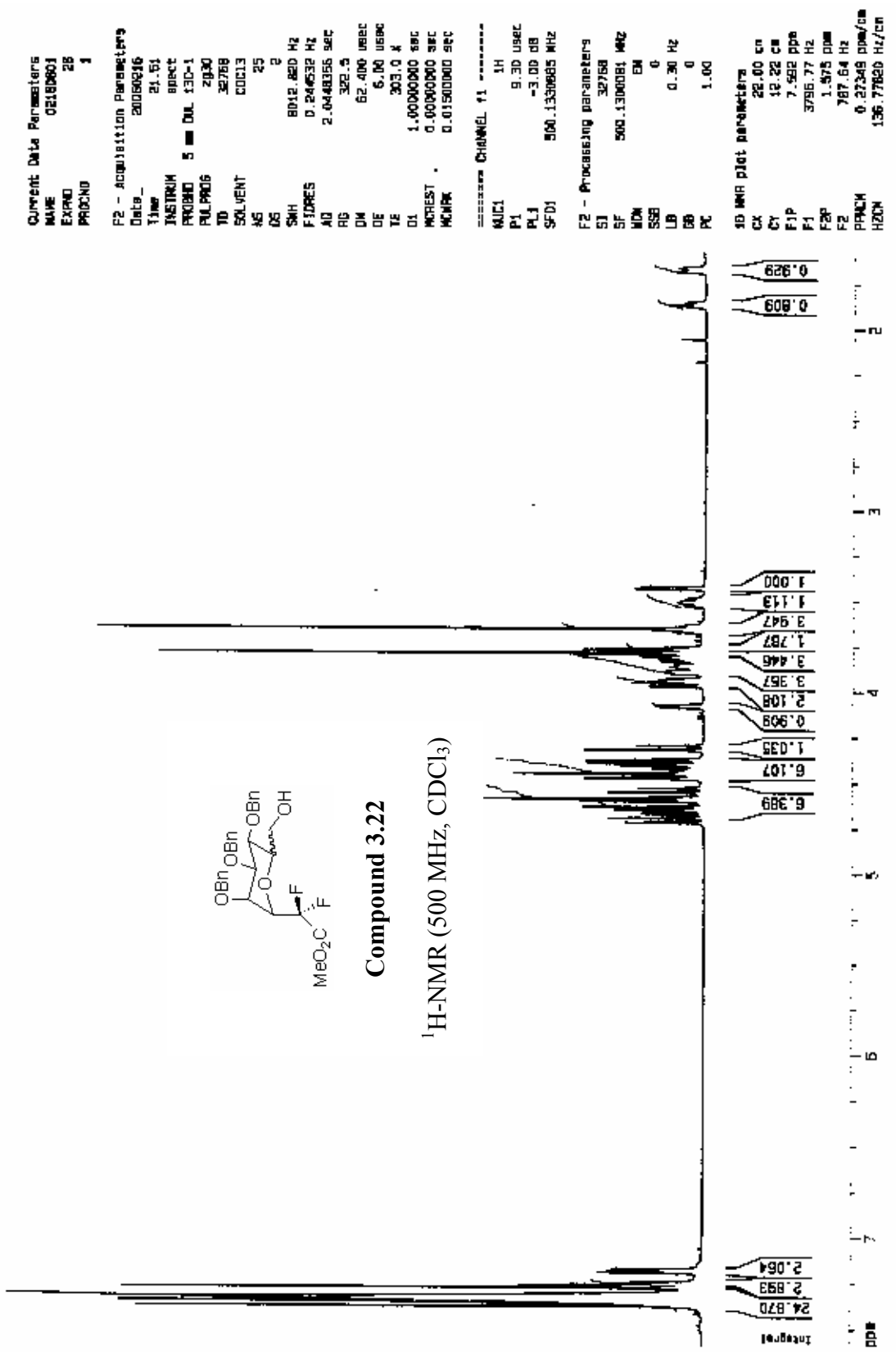


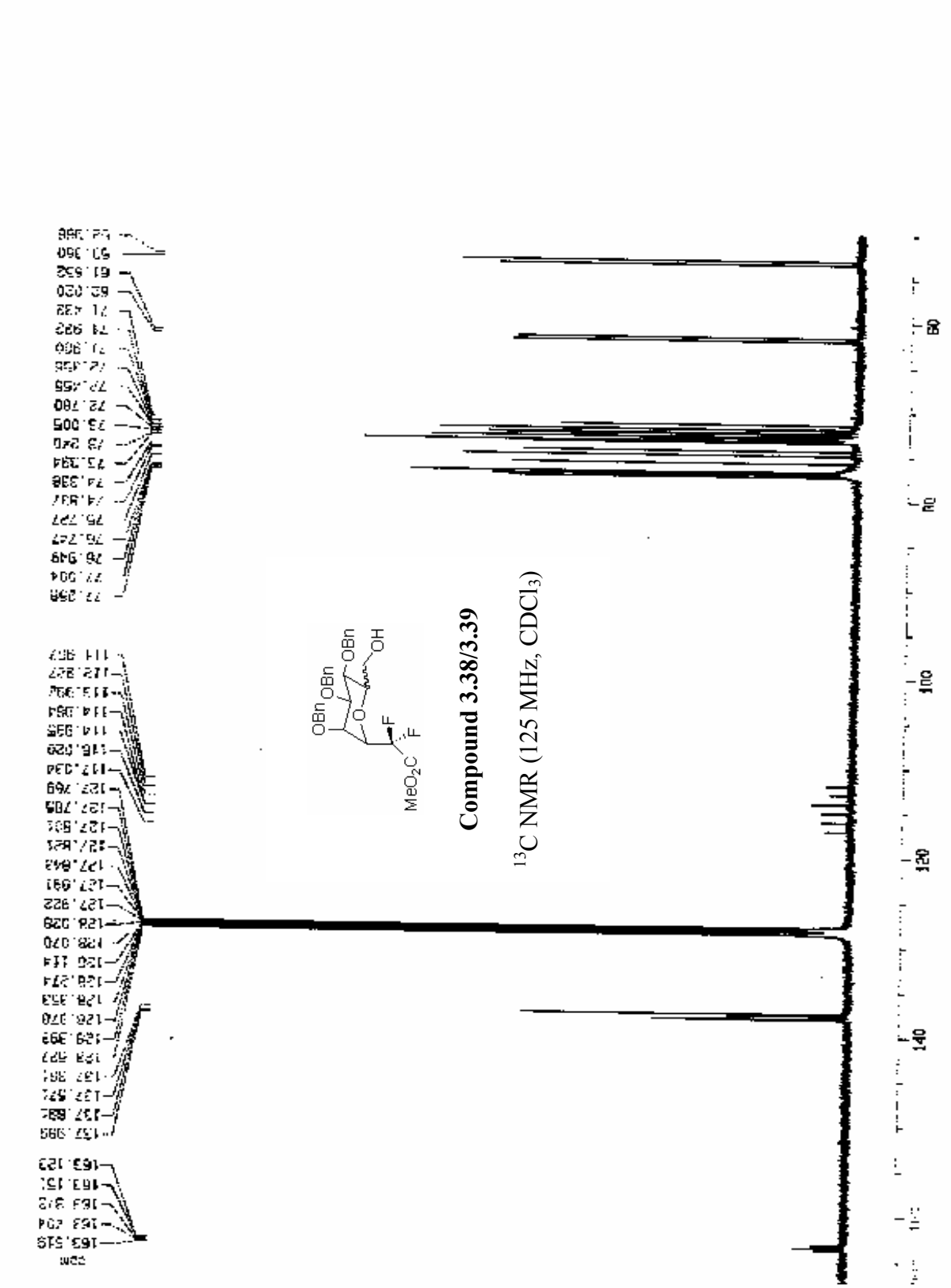
Compounds 3.26/3.27

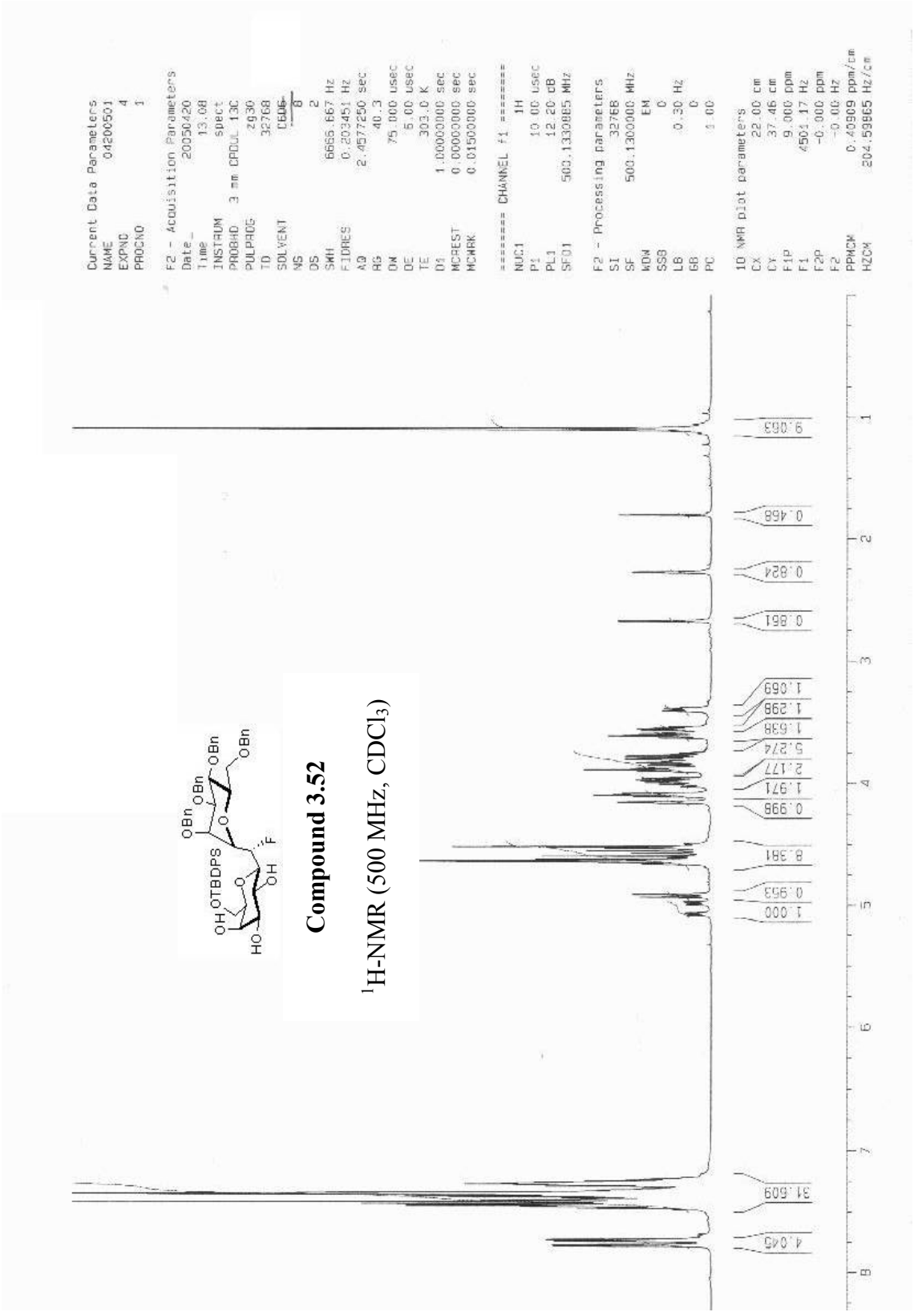
^{13}C NMR (125 MHz, $CDCl_3$)


OBn OBn F F
CO2Et
OBn OH
Compound 3.32/3.33
1H-NMR (500 MHz, CDCl3)
15.530
1.000
2.039
4.234
0.993
2.303
0.993
4.281
1.598
1.887
0.767
0.735
0.811
2.250
ppm


Compound 3.32/3.33
^{1}H-NMR (125 MHz, $CDCl_3$)
OBn OBn F F
CO_2Et
OBn OH


Compound 3.22
^{1}H-NMR (500 MHz, $CDCl_3$)


OBn
OBn
OBn
OH
O
F
F
MeO2C
Compound 3.38/3.39
13C NMR (125 MHz, CDCl3)


OBn
OBn
OBn
OBn
OTBDPS
OH
HO
F
Compound 3.52
^{1}H-NMR (500 MHz, $CDCl_3$)
Current Data Parameters
NAME 04200501
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050420
Time 13.08
INSTRUM spect
PROBHD 3 mm CPDUL 13C
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 8
DS 2
SWH 6665.667 Hz
FIDRES 0.203451 Hz
AQ 2.4577250 sec
RG 40.3
DW 75.000 usec
DE 5.00 usec
TE 303.0 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 10.00 usec
PL1 12.20 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 22.00 cm
CY 37.46 cm
F1P 9.000 ppm
F1 4501.17 Hz
F2P -0.000 ppm
F2 -0.00 Hz
PPMCM 0.40909 ppm/cm
HZCM 204.59865 Hz/cm
9.063
0.468
0.824
0.861
1.069
1.298
1.638
5.274
2.177
1.971
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8.381
1.000
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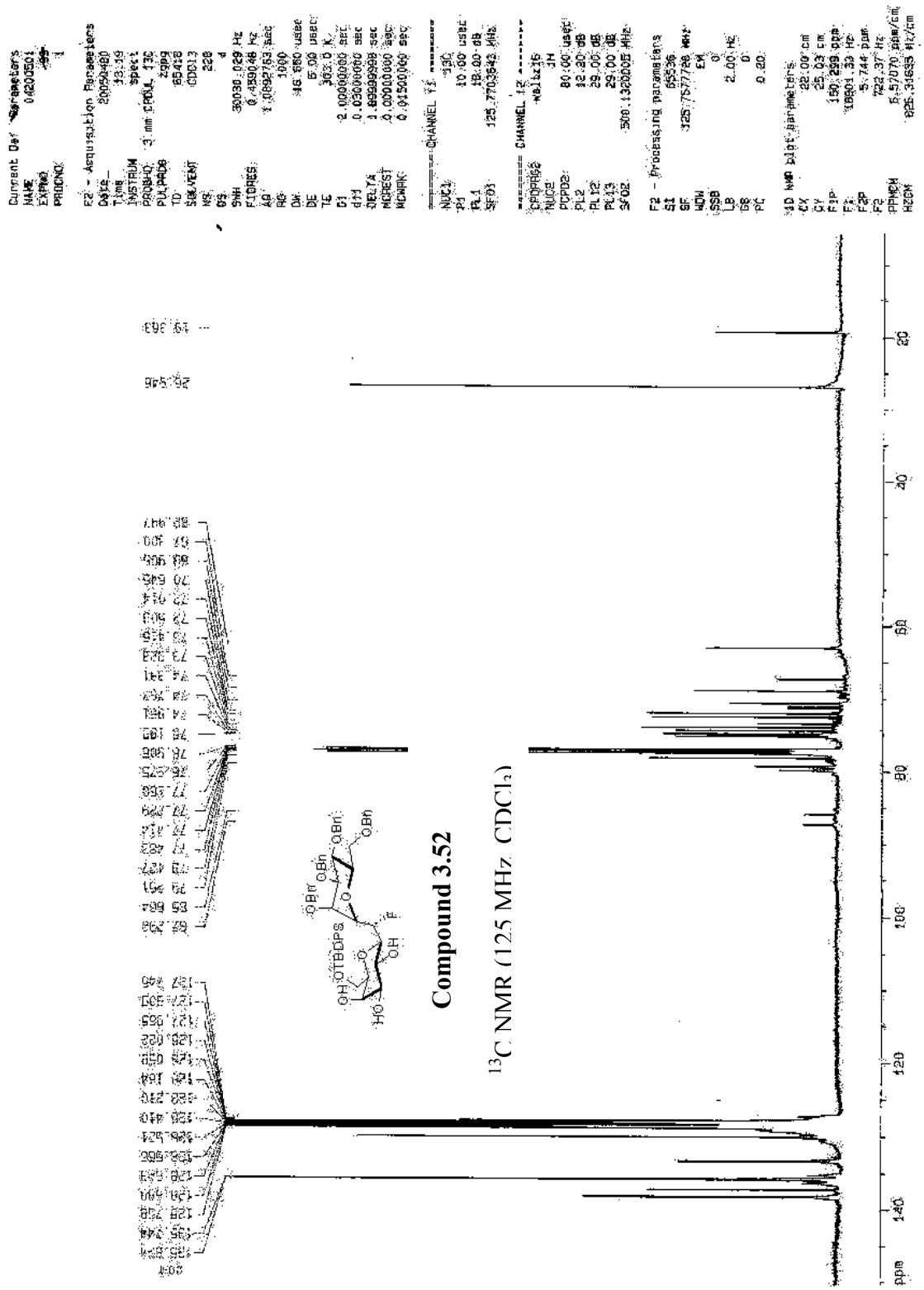
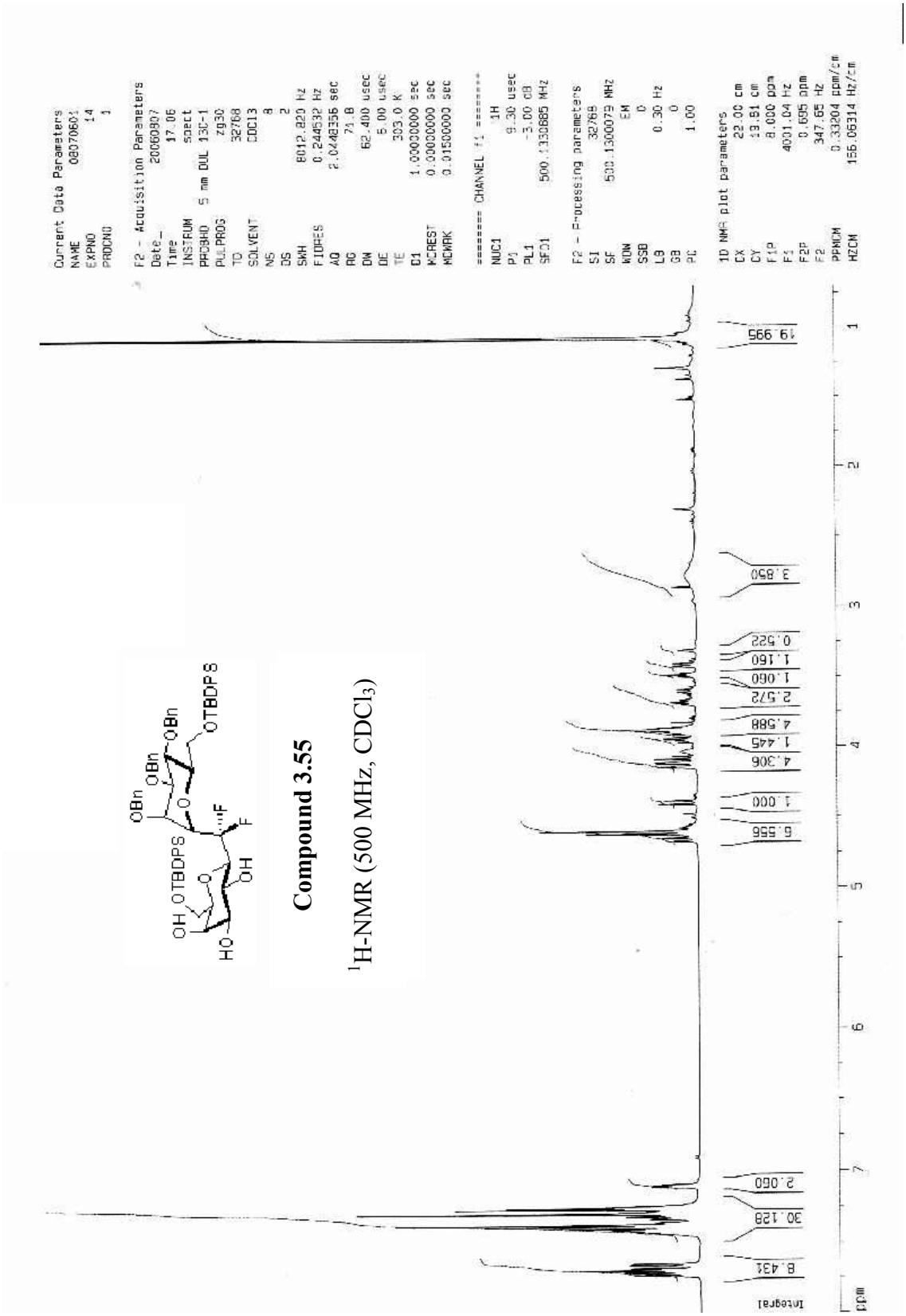
4.045
8
7
6
5
4
3
2
1



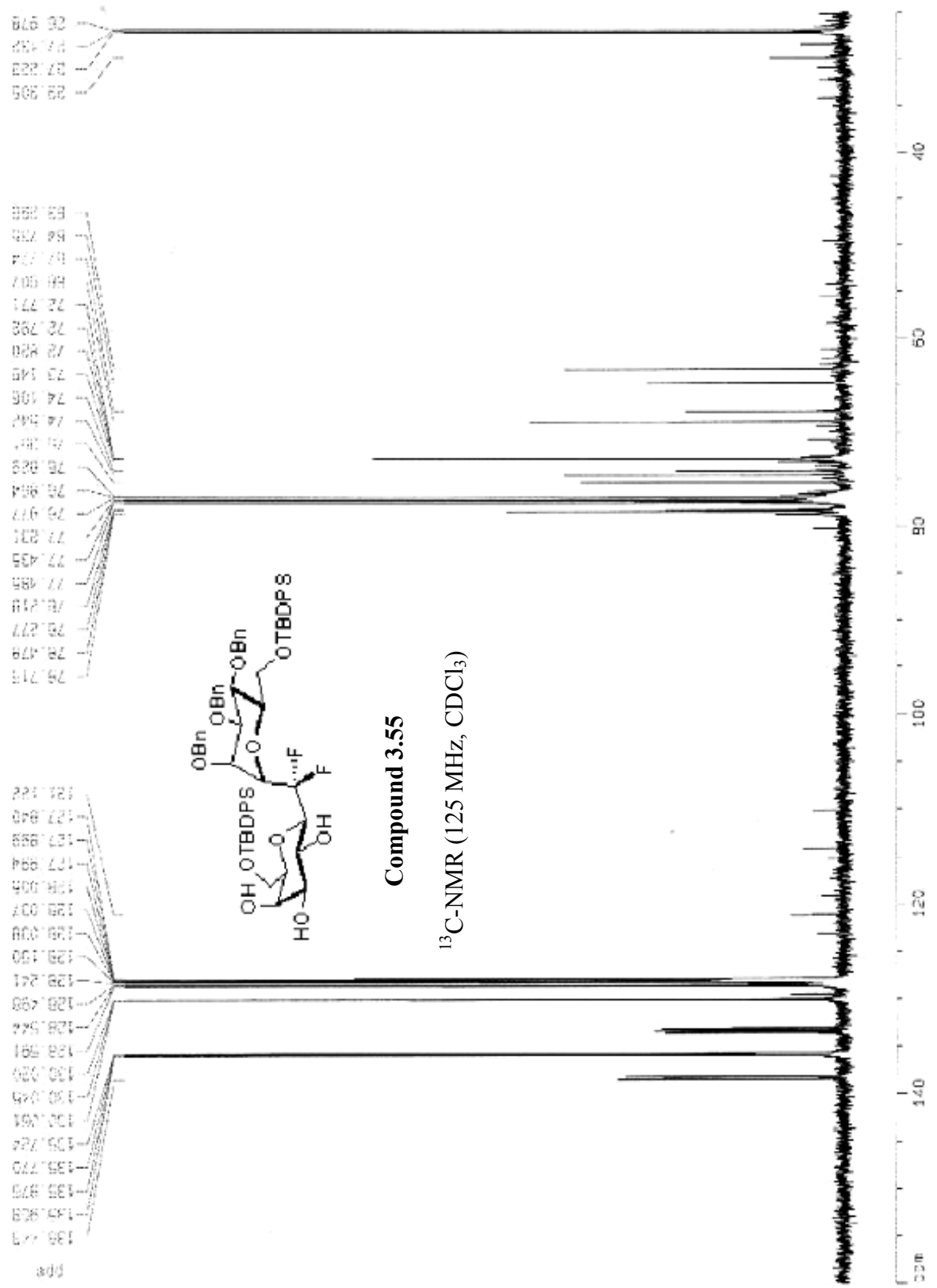
Compound 3.52

^{13}C NMR (125 MHz, $CDCl_3$)



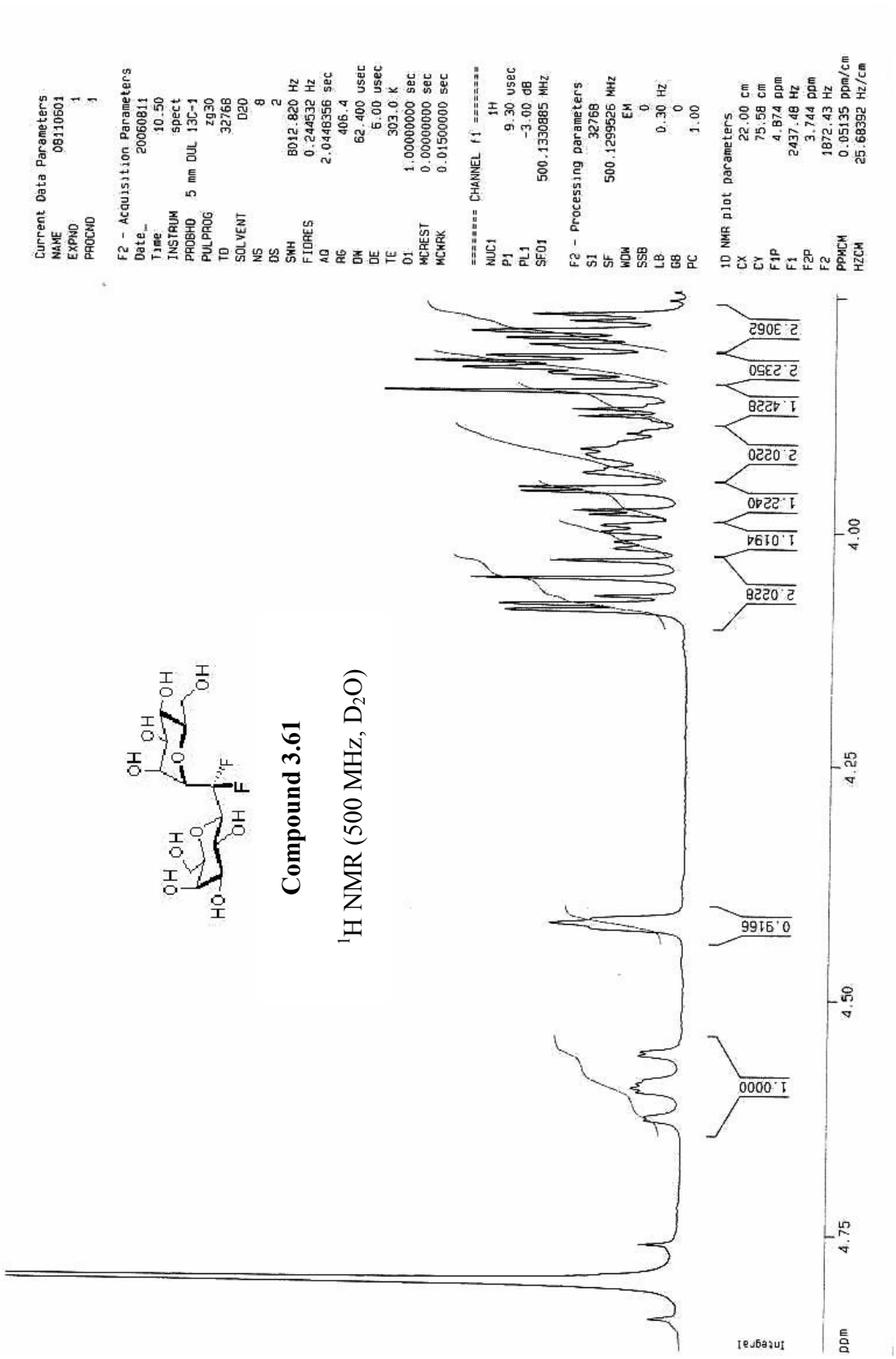
Compound 3.55

^{1}H-NMR (500 MHz, $CDCl_3$)



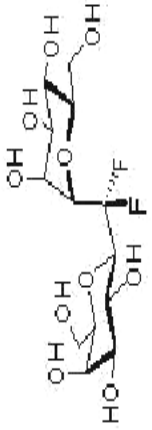
Compound 3.55

^{13}C-NMR (125 MHz, $CDCl_3$)



Compound 3.61

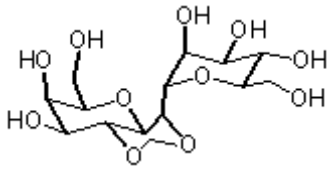
^{1}H NMR (500 MHz, D_2O)



Compound 3.61

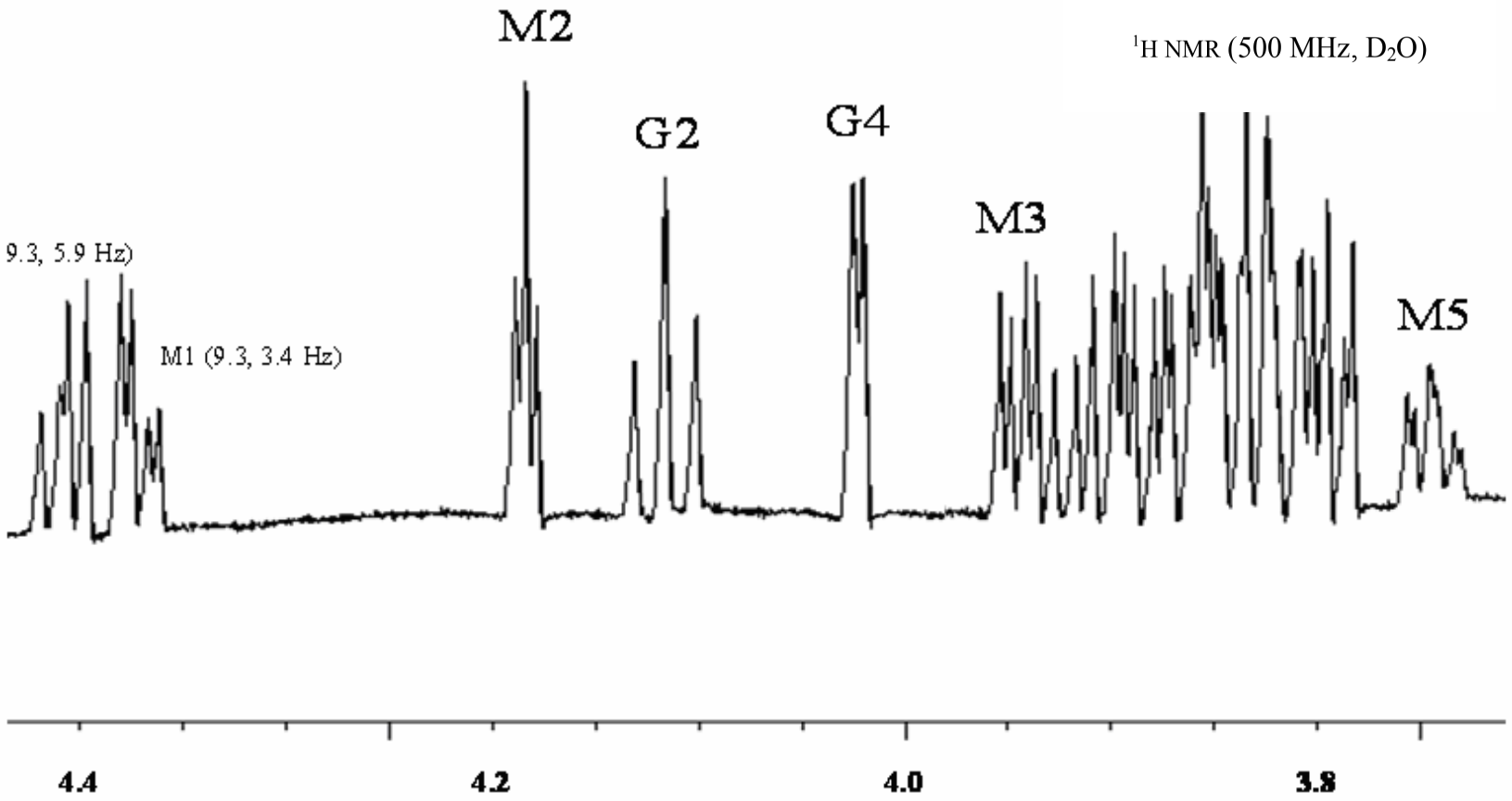
^{13}C NMR (125 MHz, D_2O)

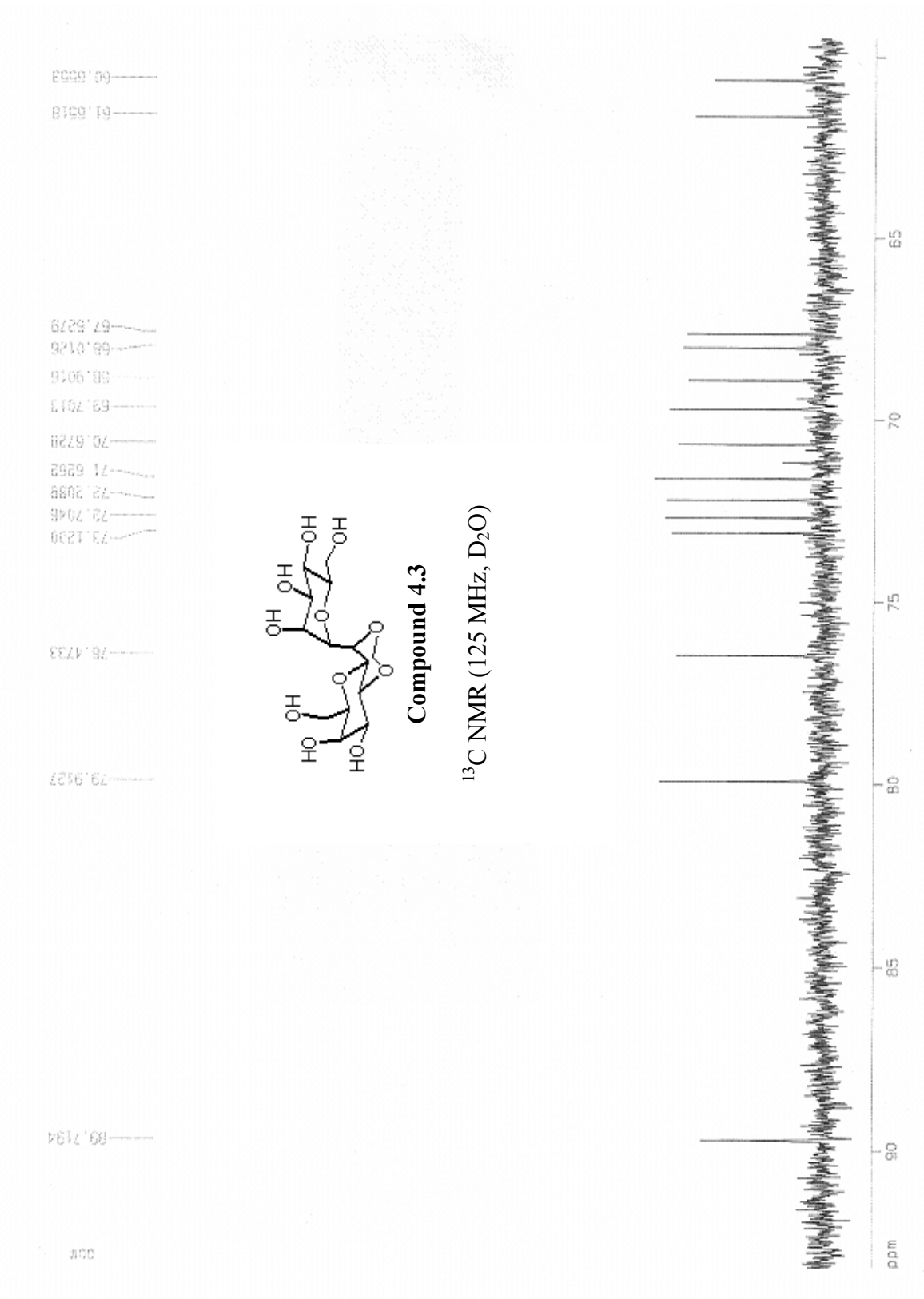
1H NMR spectrum and key coupling constants



Compound 4.3

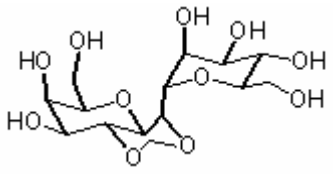
^{1}H NMR (500 MHz, D_2O)





Compound 4.3

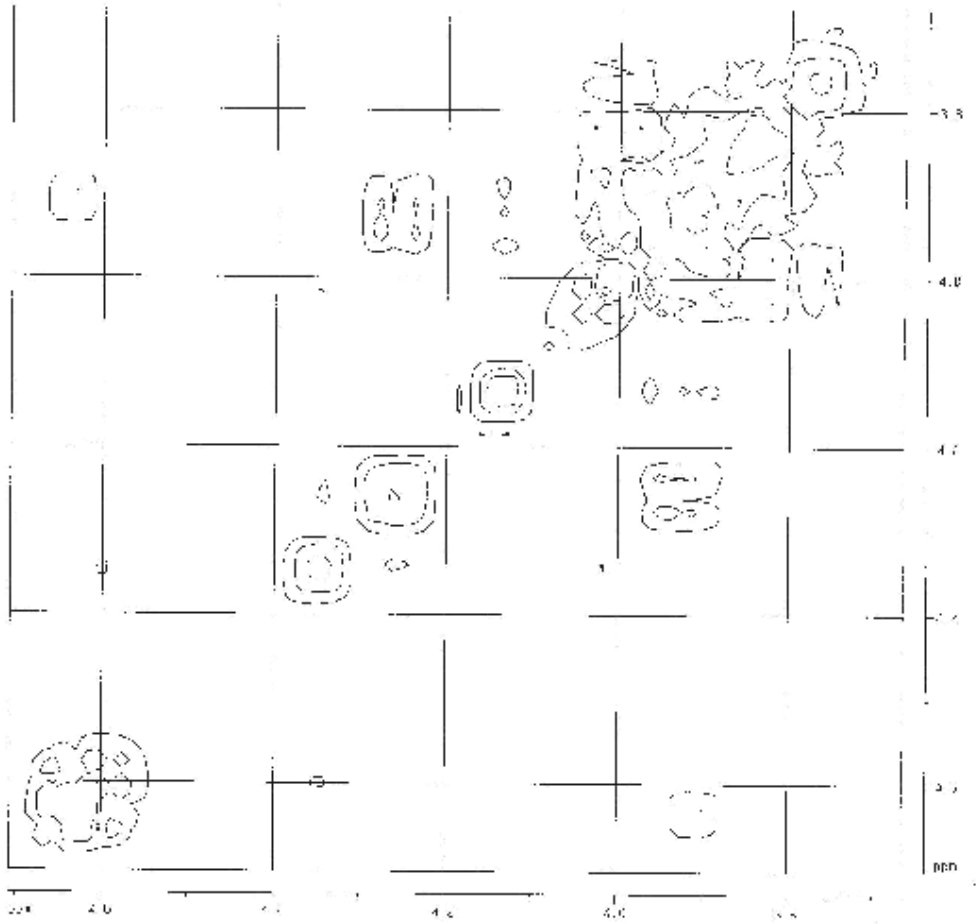
^{13}C NMR (125 MHz, D_2O)

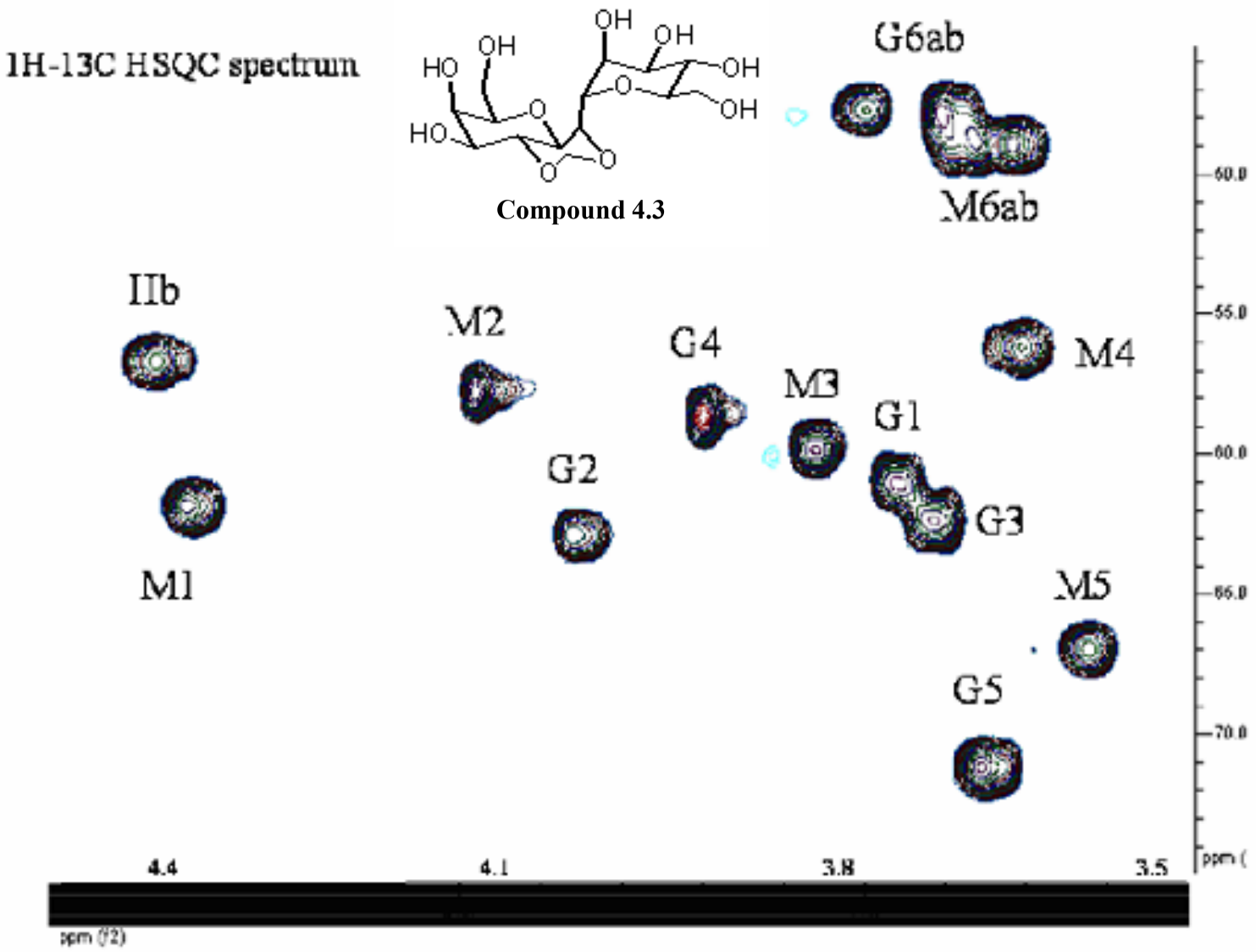


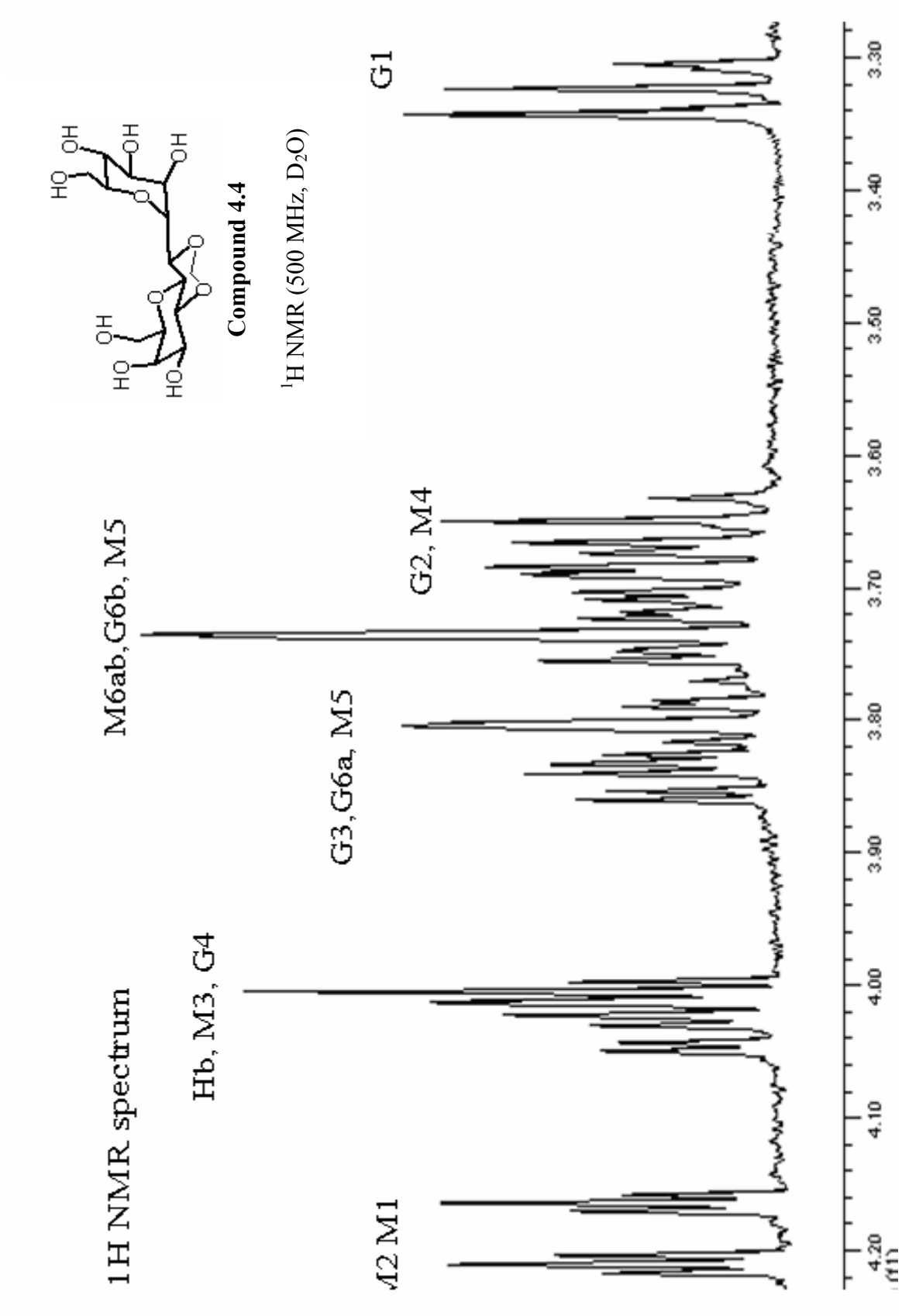
Compound 4.3

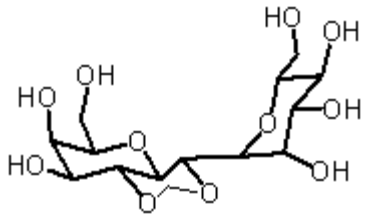
(1H-1H COSY)

	δ (ppm)	*J (Hz)*	
M1	4.39	**8.8**	3.4
M2	4.14	3.3	
M3	3.82	3.7	8.3
M4	3.63		
M5	3.56	2.4	7.5
M6a	3.69		
M6b	3.64		
Hintersac	4.44	8.8	**5.9**
G1	3.75	5.9	
G2	4.05	9.2	
G3	3.74		
G4	3.92	3.3	
G5	3.67		
G6a	3.79		
G6b	3.70		
OCH_2Oax	5.04	6.5	
OCH_2Oac	4.86	6.5	




1H-13C HSQC spectrum
OH
OH
OH
HO
OH
HO
O
O
O
O
Compound 4.3
G6ab
M6ab
IIb
M2
G4
M3
M4
G1
G2
G3
M1
M5
G5
60.0
55.0
50.0
65.0
70.0
4.4
4.1
3.8
3.5
ppm (f2)

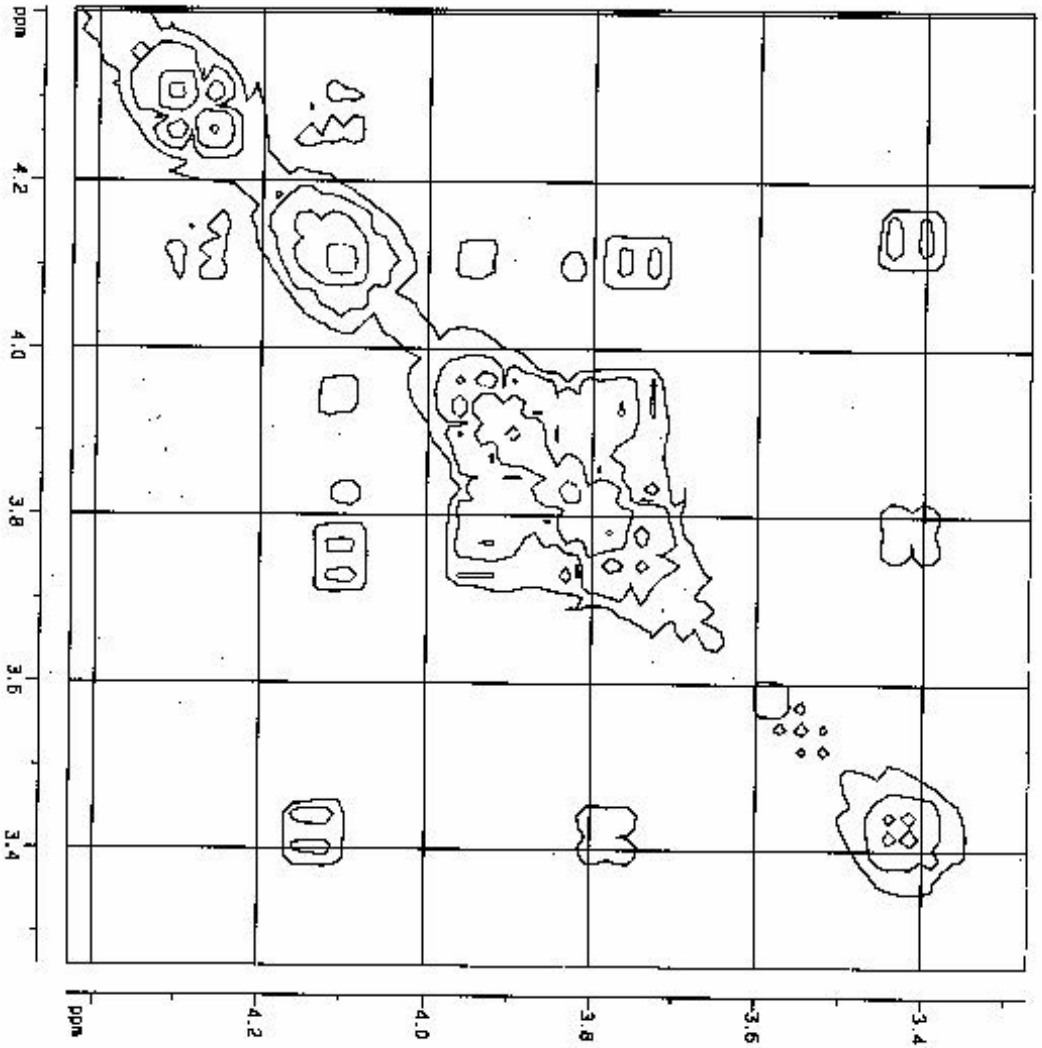

1H NMR spectrum
M6ab,G6b, M5
Hb, M3, G4
G3,G6a, M5
G2, M4
G1
M1
Compound 4.4
^{1}H NMR (500 MHz, D_2O)
4.20
4.10
4.00
3.90
3.80
3.70
3.60
3.50
3.40
3.30



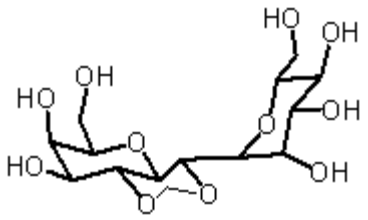
Compound 4.4

(1H-1H COSY)

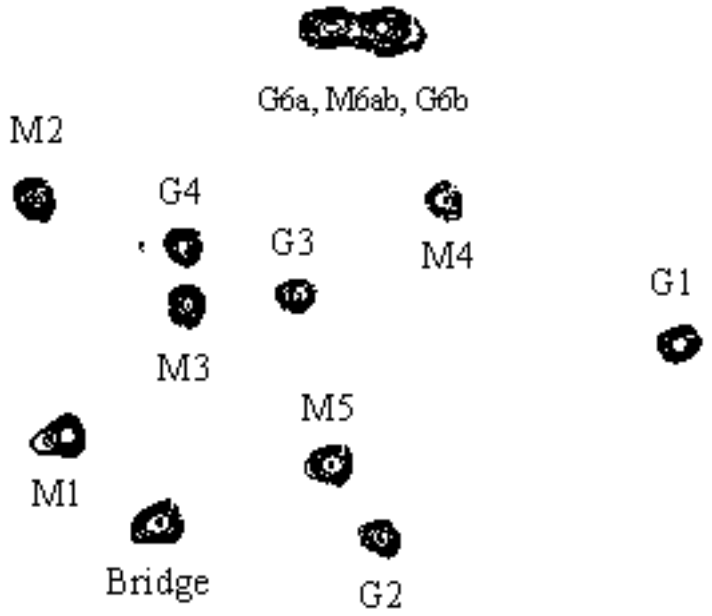
	δ (ppm)	*J (Hz)*	
M1	4.16	**3.0**	3.0
M2	4.21	3.3	3.3
M3	4.01		
M4	3.65	8.7	8.7
M5	3.80		
M6a	3.74*		
M6b	3.74*		
H bridge	4.04	3.3	**10.0**
G1	3.32	9.4	9.4
G2	3.69		
G3	3.85		
G4	4.01		
G5	3.73		
G6a	3.74*		
G6b	3.80*		
OCH_2Oax	4.84	6.5	
OCH_2Oeq	5.15	6.5	

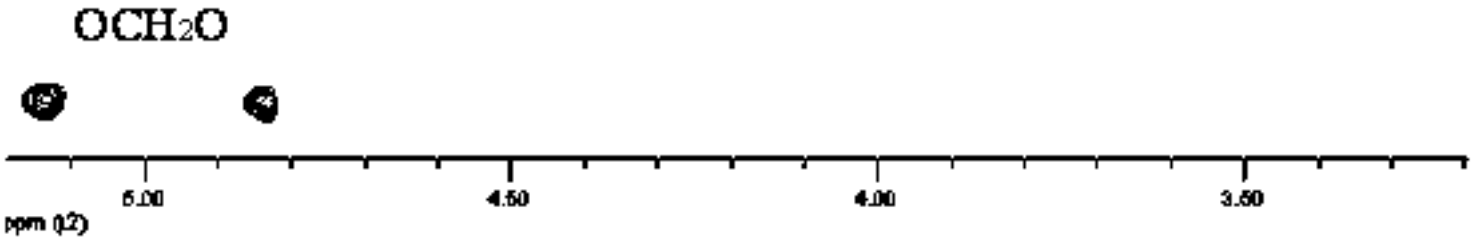


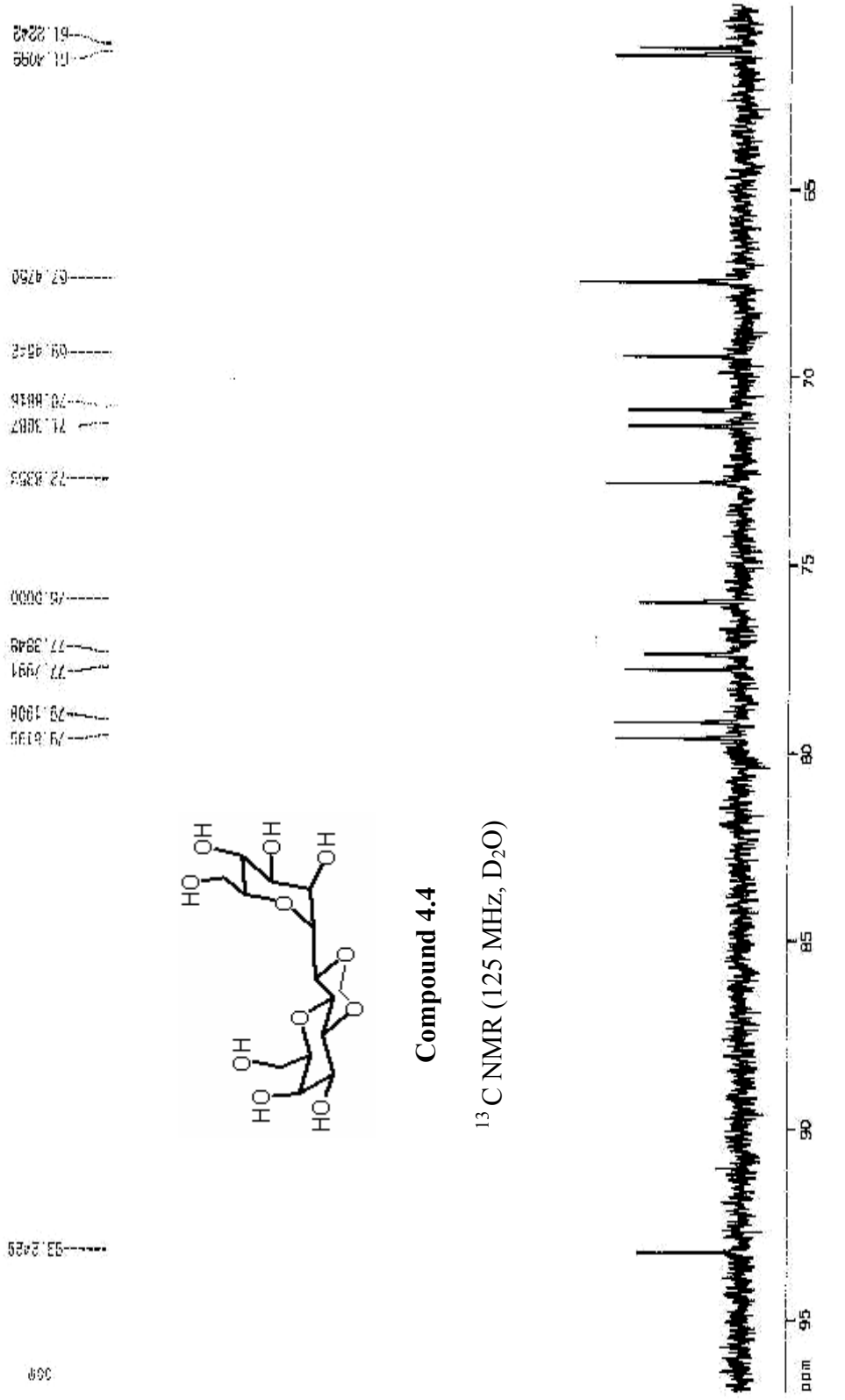
1H-13C HSQC spectrum



Compound 4.4

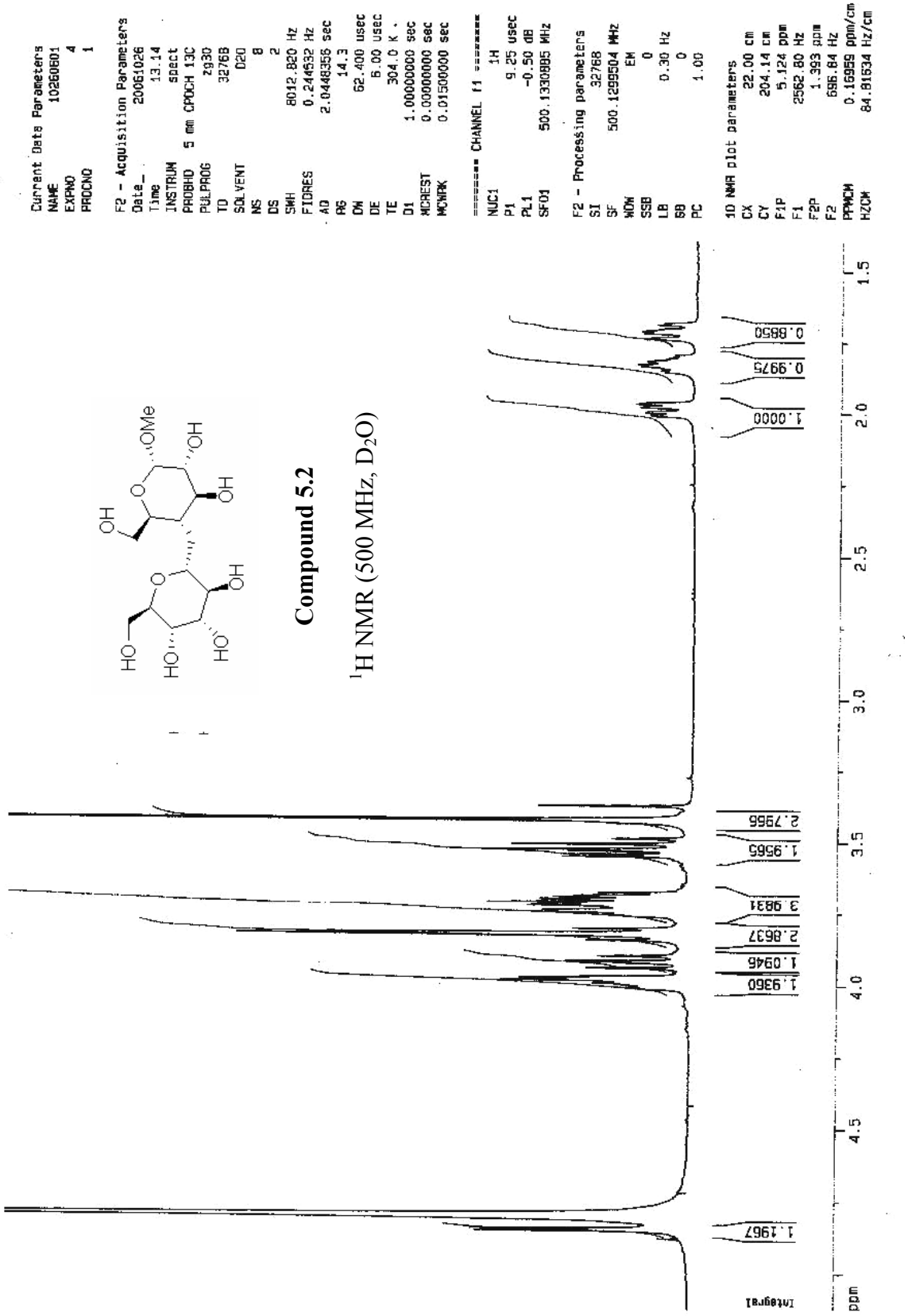






Compound 4.4

^{13}C NMR (125 MHz, D_2O)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EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
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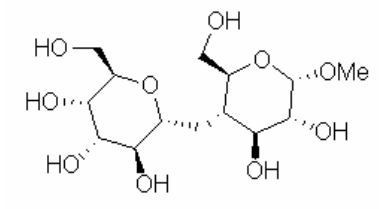
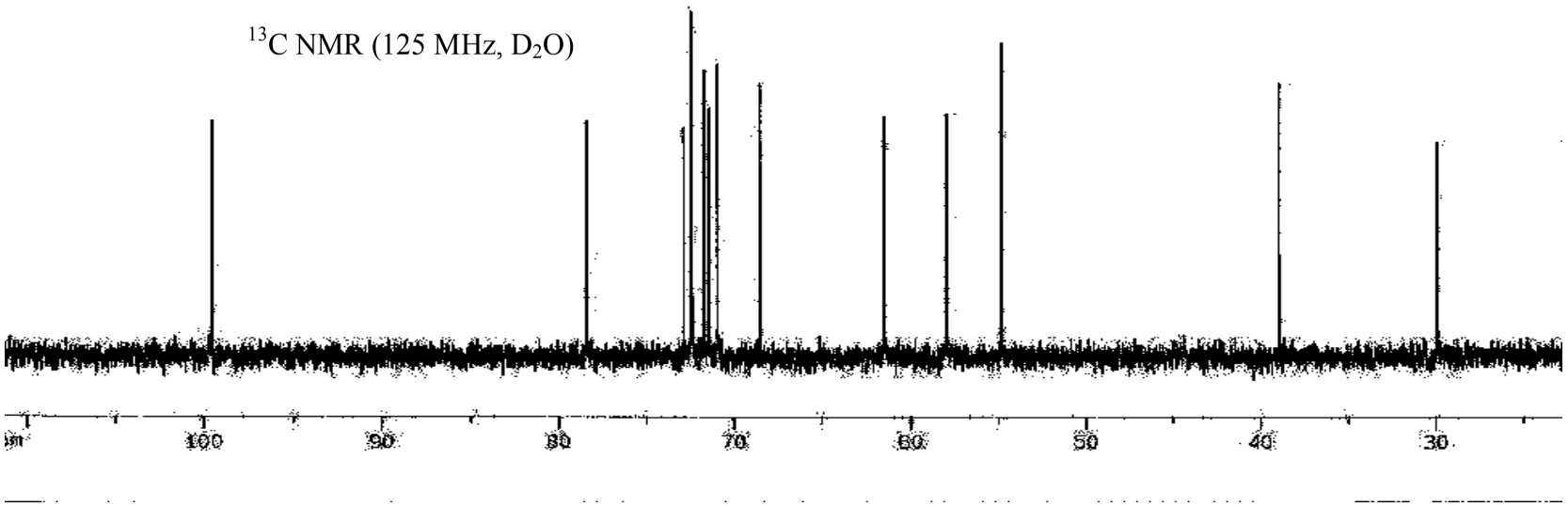
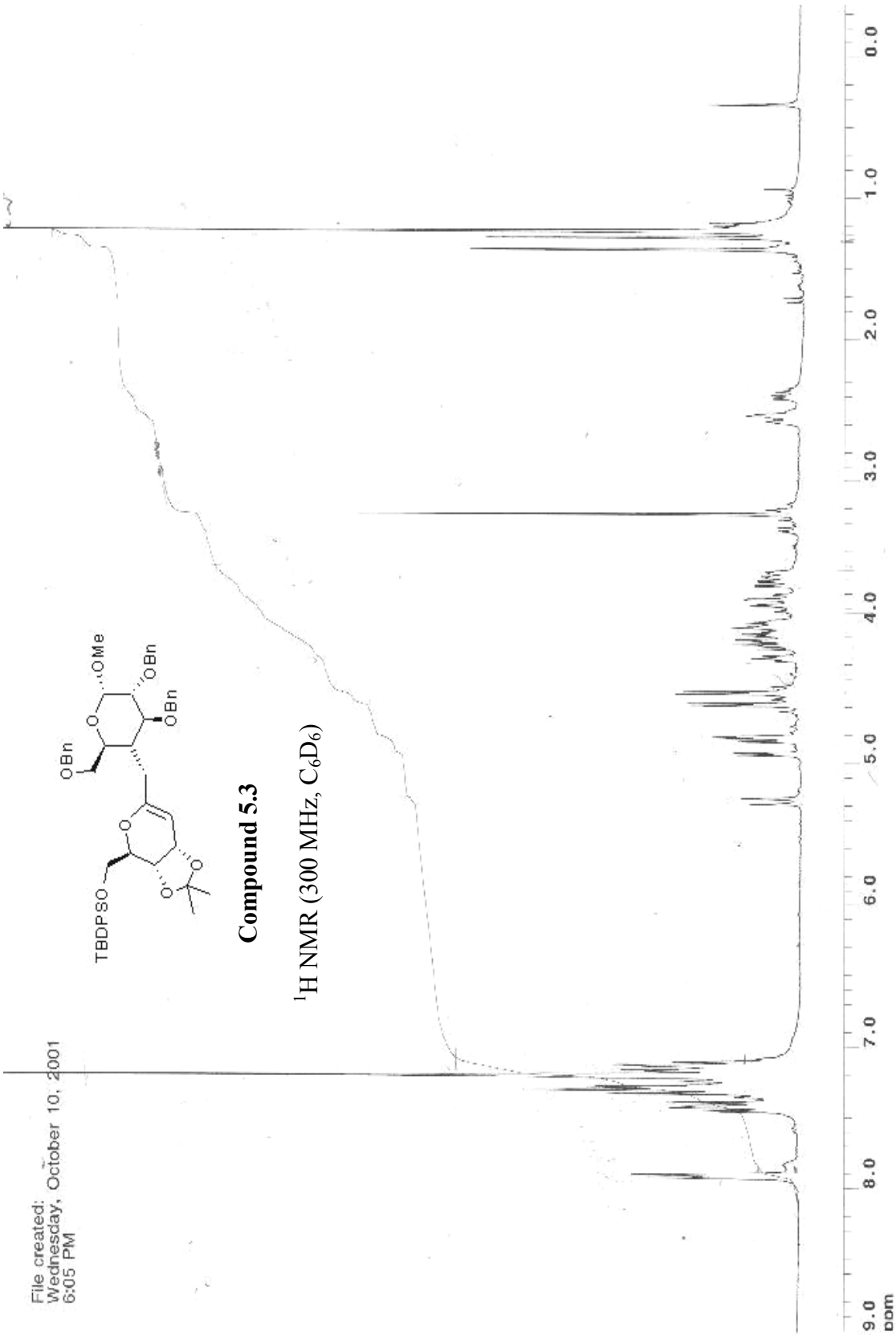
Time 13.14
INSTRUM spect
PROBHD 5 mm CPDCH 13C
PULPROG zg30
TD 32768
SOLVENT D2O
NS 8
DS 2
SWH 8012.820 Hz
FIDRES 0.244532 Hz
AQ 2.0448356 sec
RG 14.3
DW 62.400 usec
DE 6.00 usec
TE 304.0 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 9.25 usec
PL1 -0.50 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1299504 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 22.00 cm
CY 204.14 cm
F1P 5.124 ppm
F1 2562.80 Hz
F2P 1.393 ppm
F2 696.84 Hz
PPMCM 0.16959 ppm/cm
HZCM 84.81634 Hz/cm
OMe
OH
HO
Compound 5.2
^{1}H NMR (500 MHz, D_2O)
1.1967
2.7956
1.9565
3.9831
2.8637
1.0946
1.9360
1.0000
0.9975
0.8850
Integral
ppm
4.5
4.0
3.5
3.0
2.5
2.0
1.5



Compound 5.2

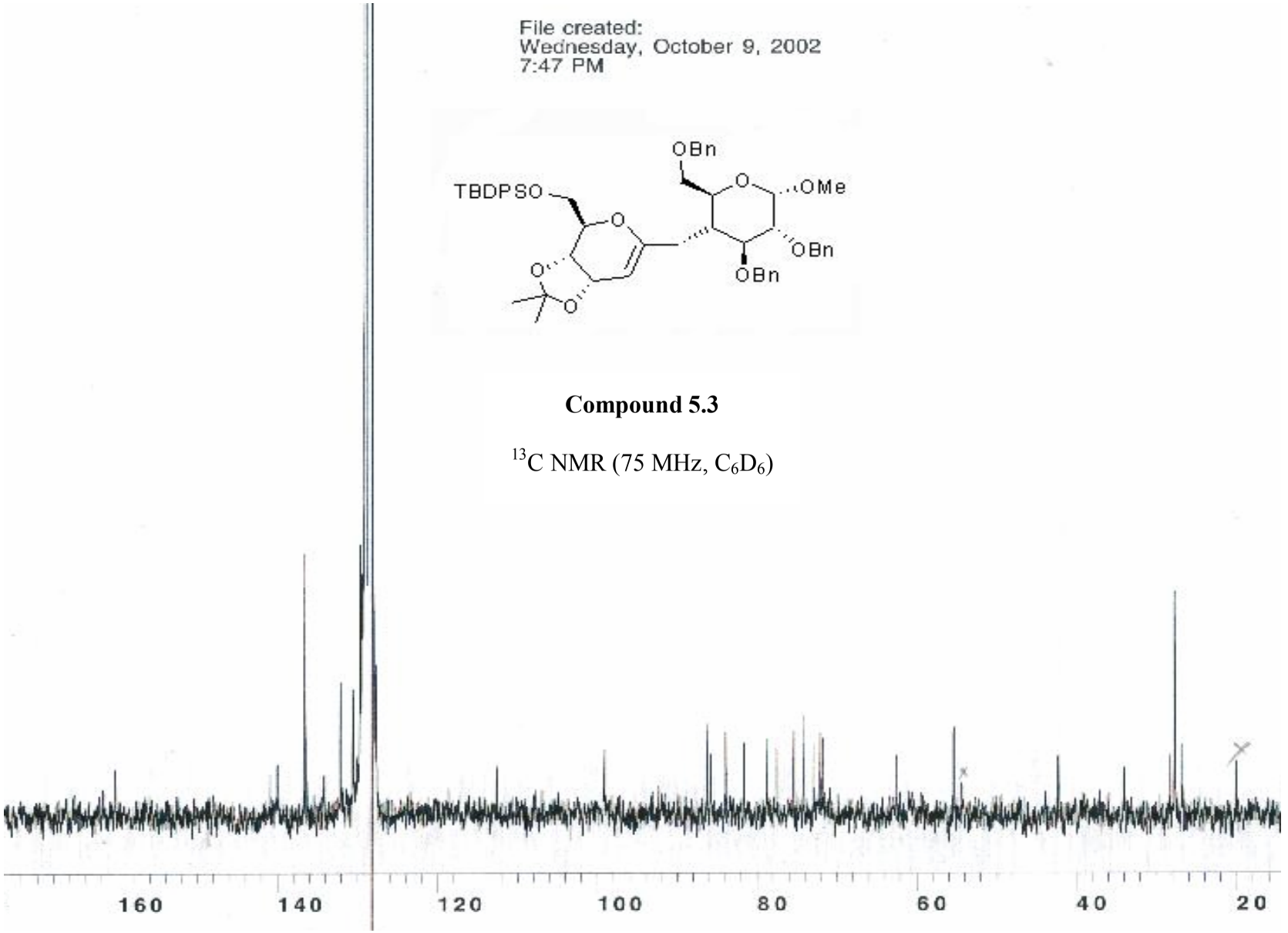
^{13}C NMR (125 MHz, D_2O)





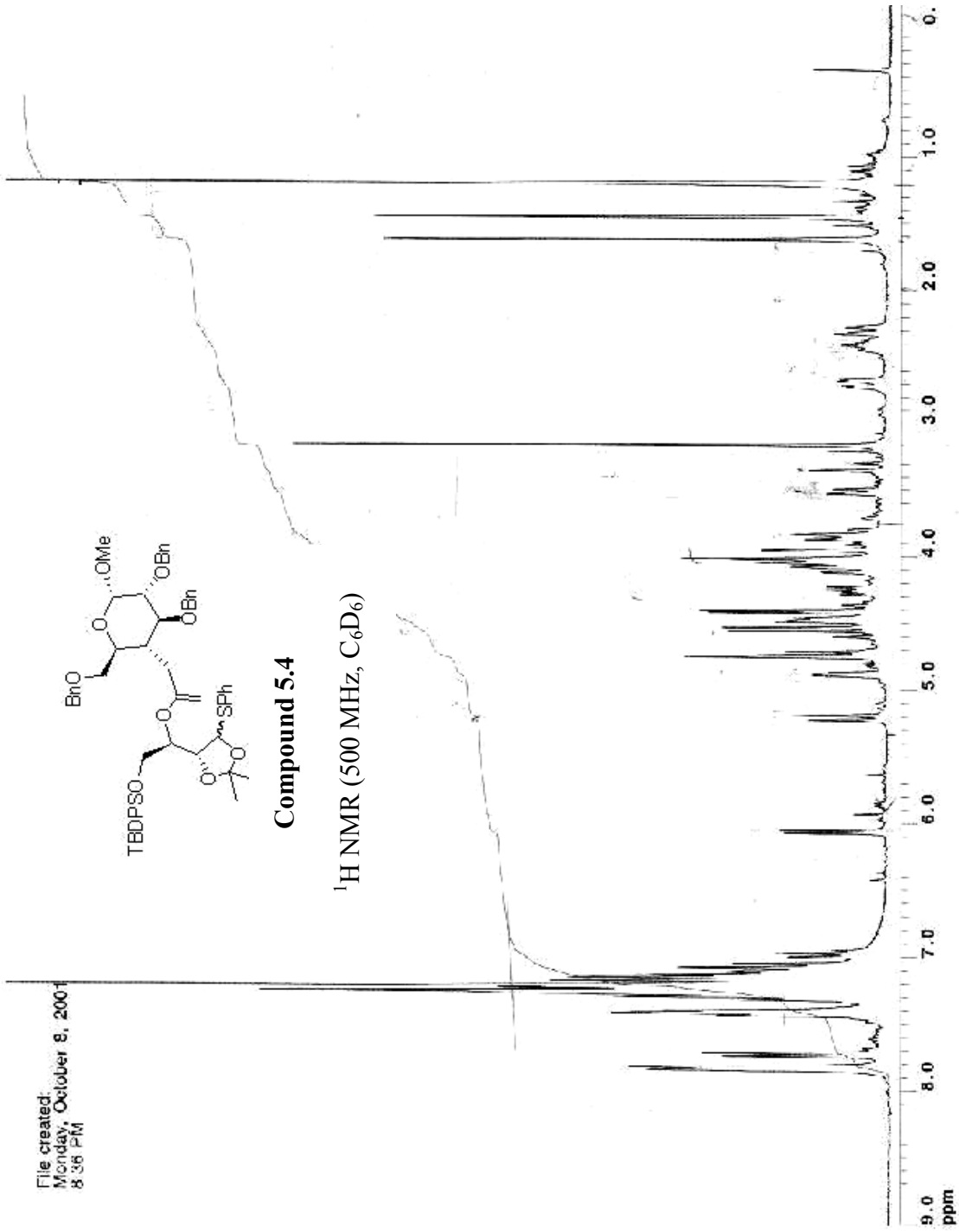
Compound 5.3

^{1}H NMR (300 MHz, C_6D_6)



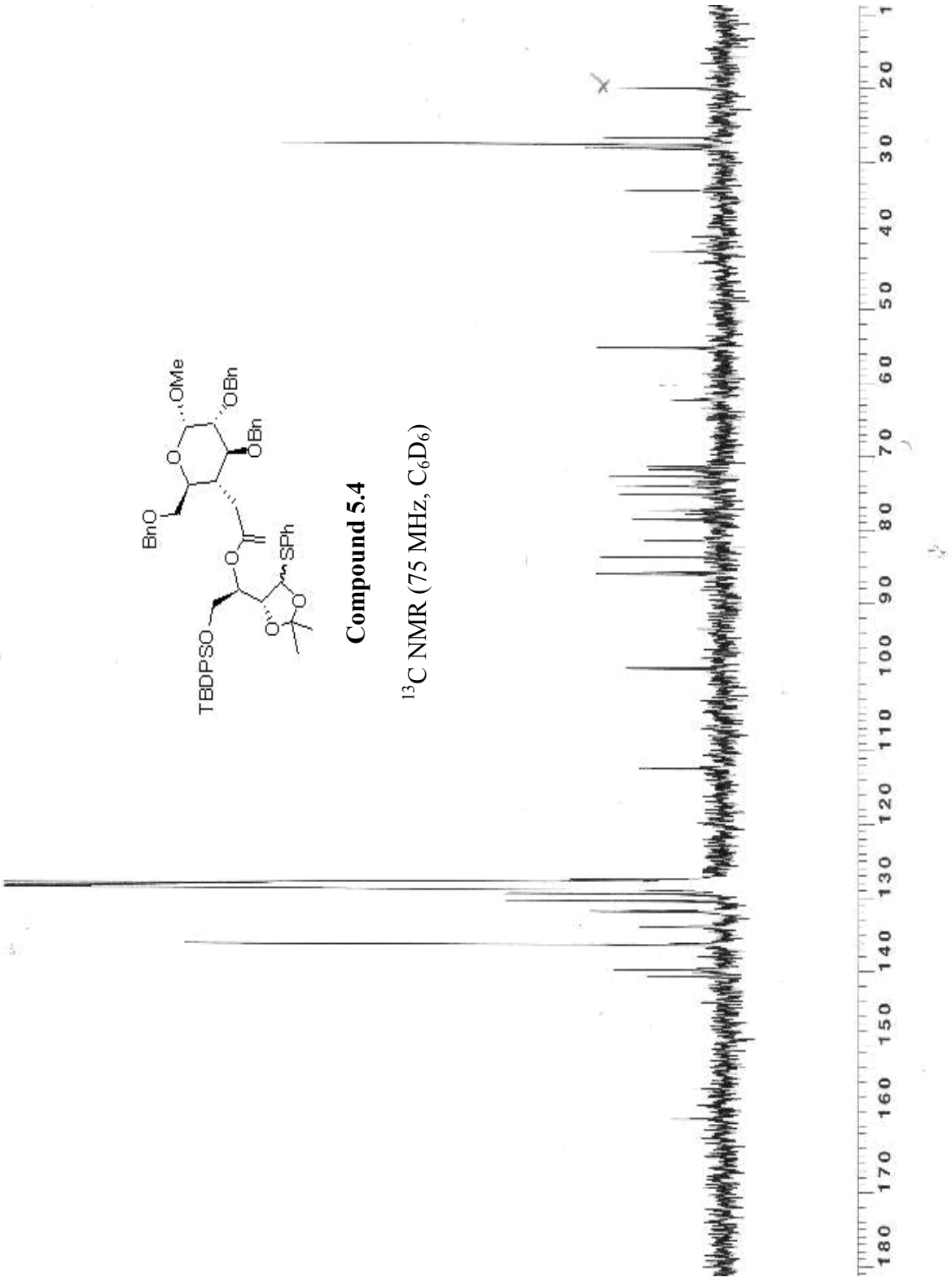
Compound 5.3

^{13}C NMR (75 MHz, C_6D_6)



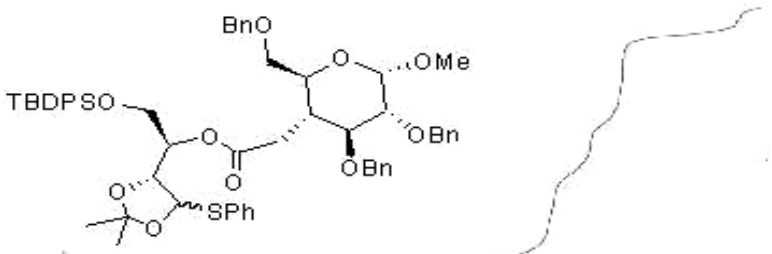
Compound 5.4

^{1}H NMR (500 MHz, C_6D_6)



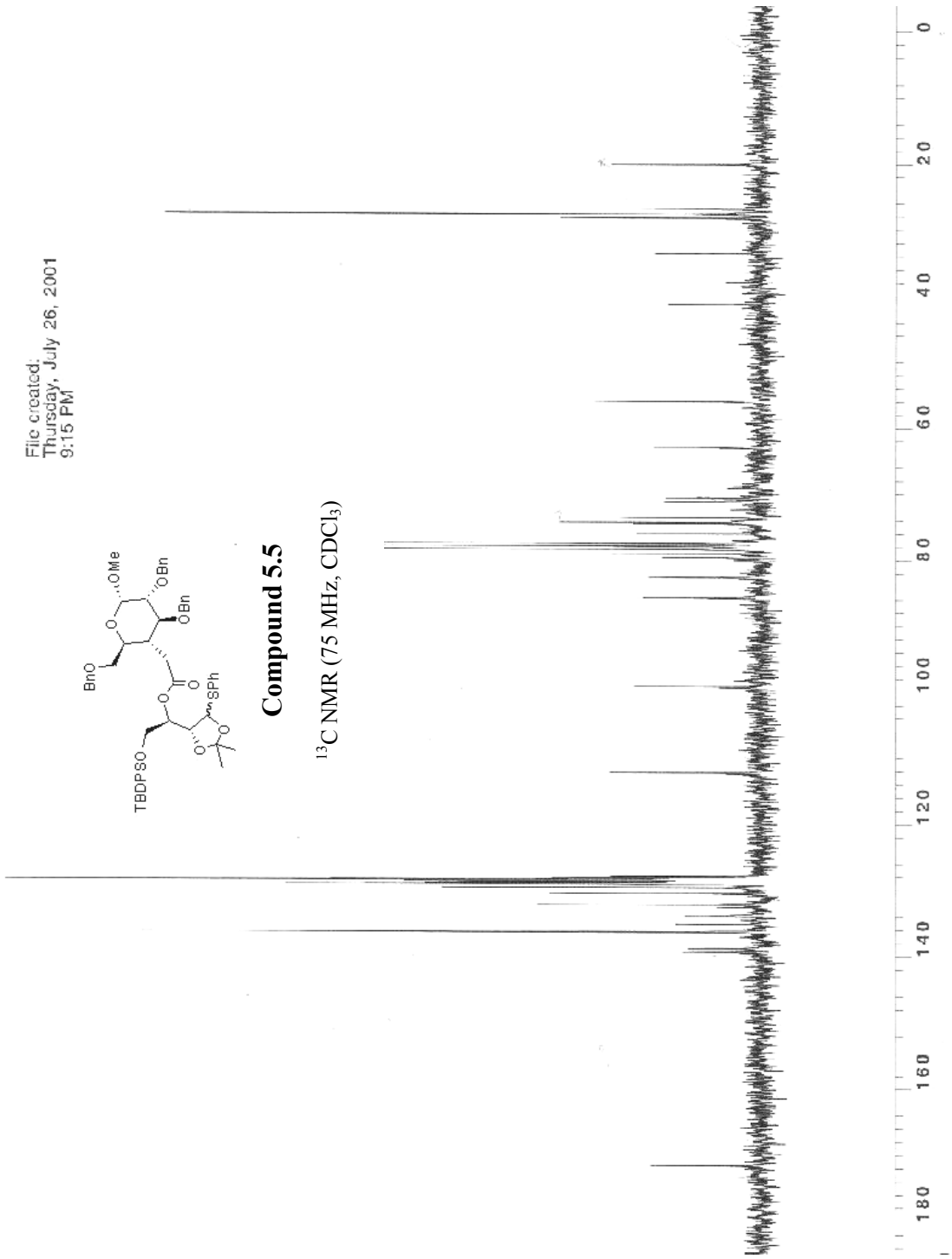
Compound 5.4

^{13}C NMR (75 MHz, C_6D_6)



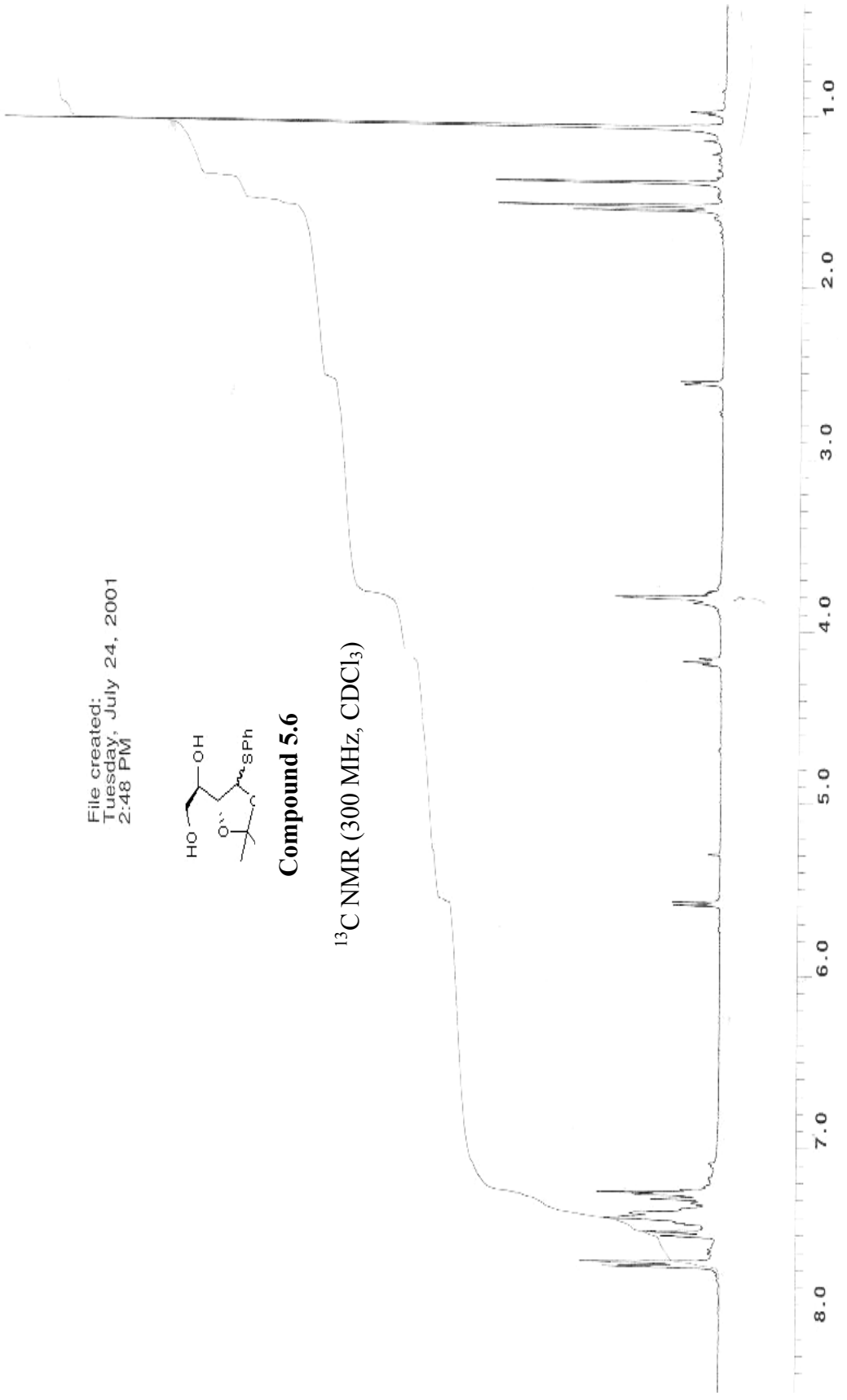
Compound 5.5

^{1}H NMR (500 MHz, $CDCl_3$)



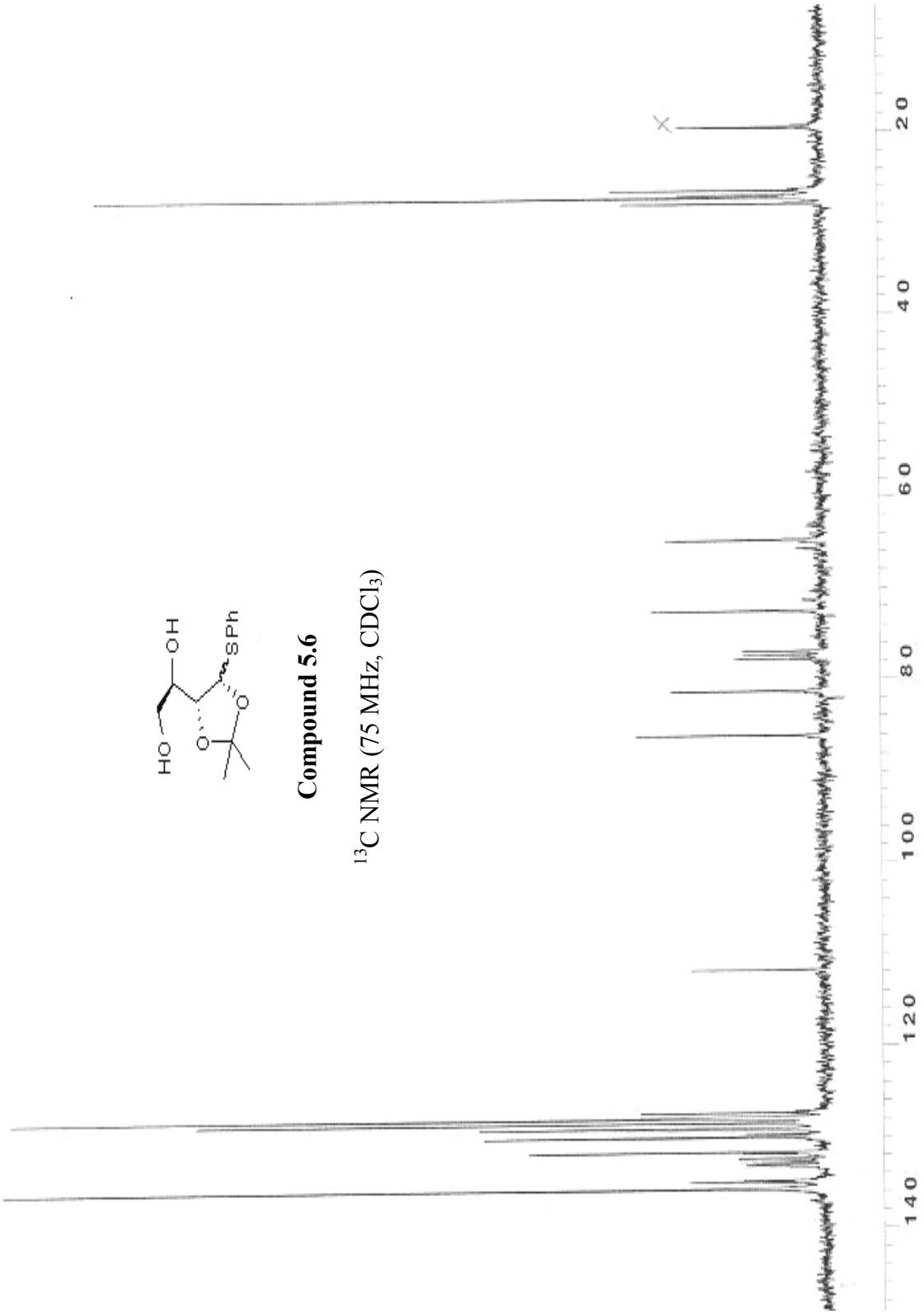
Compound 5.5

^{13}C NMR (75 MHz, $CDCl_3$)



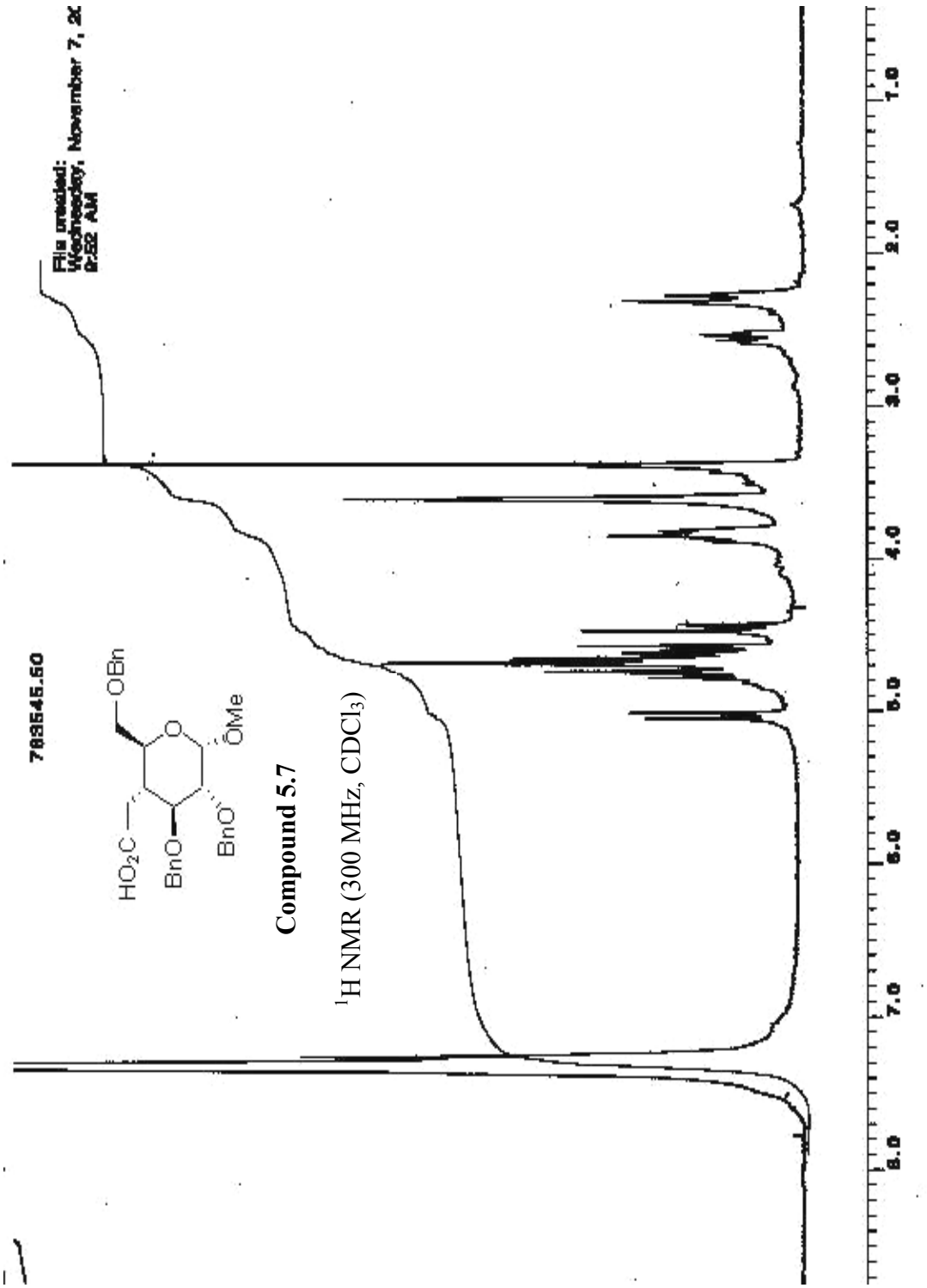
Compound 5.6

^{13}C NMR (300 MHz, $CDCl_3$)



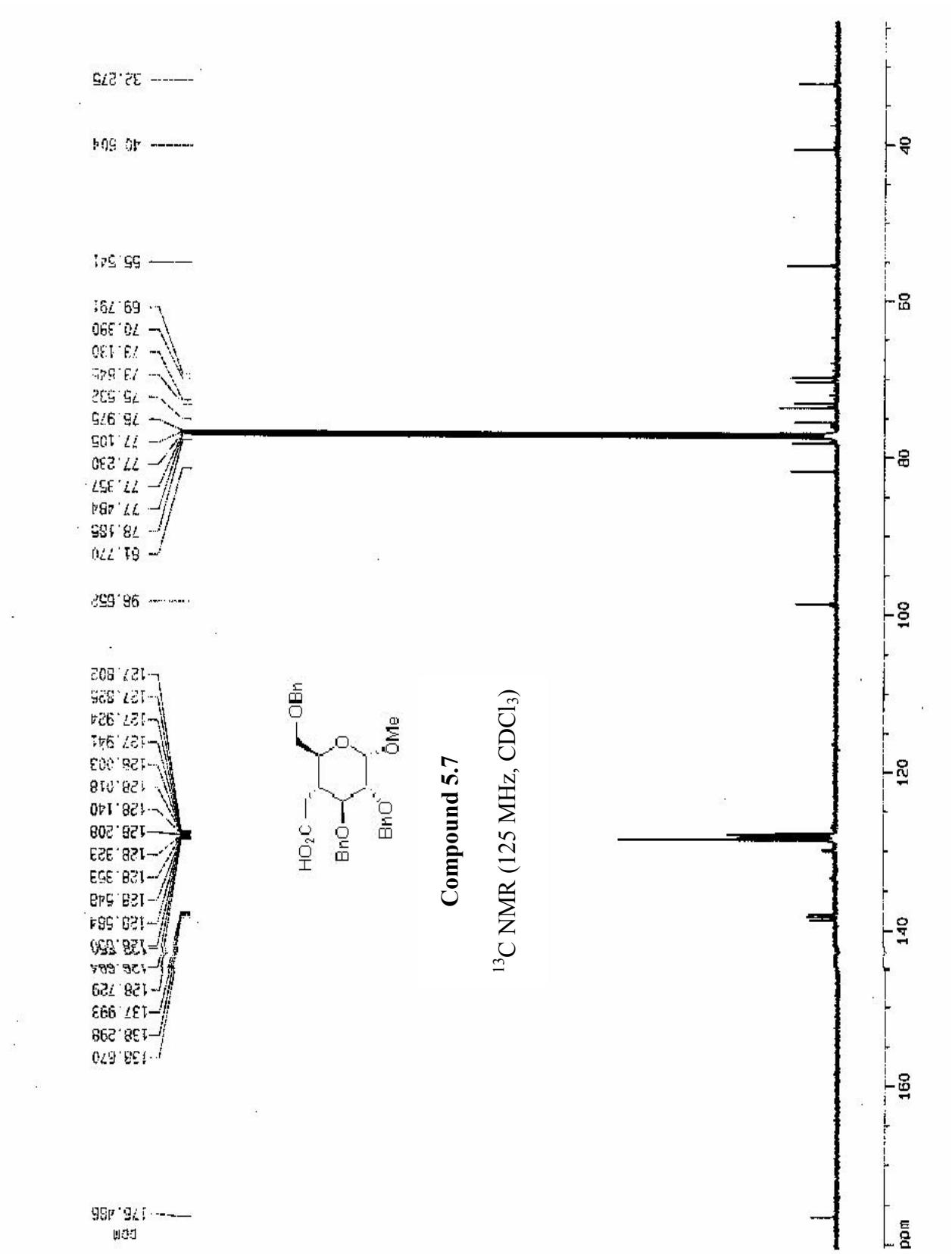
Compound 5.6

^{13}C NMR (75 MHz, $CDCl_3$)



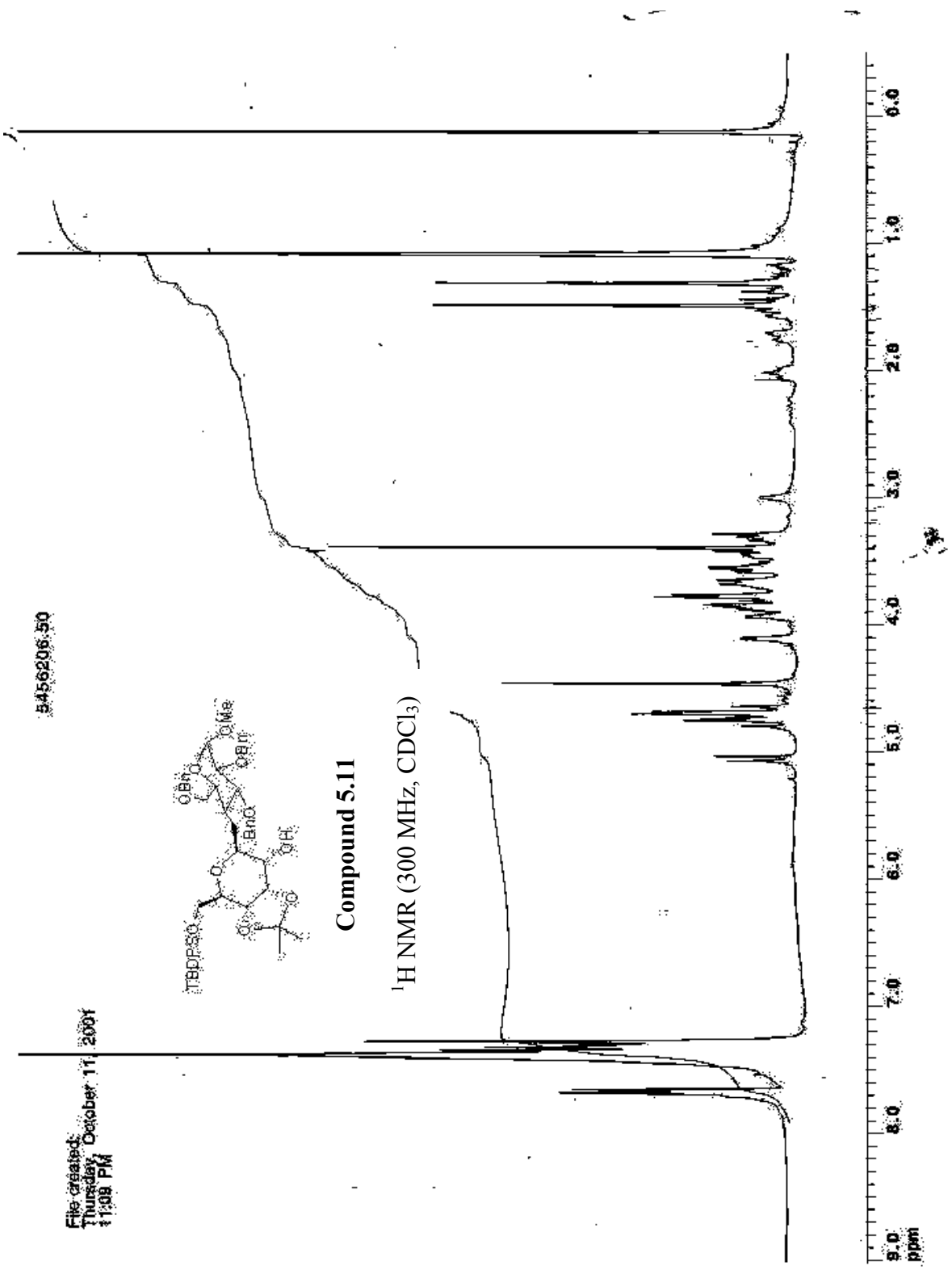
Compound 5.7

^{1}H NMR (300 MHz, $CDCl_3$)



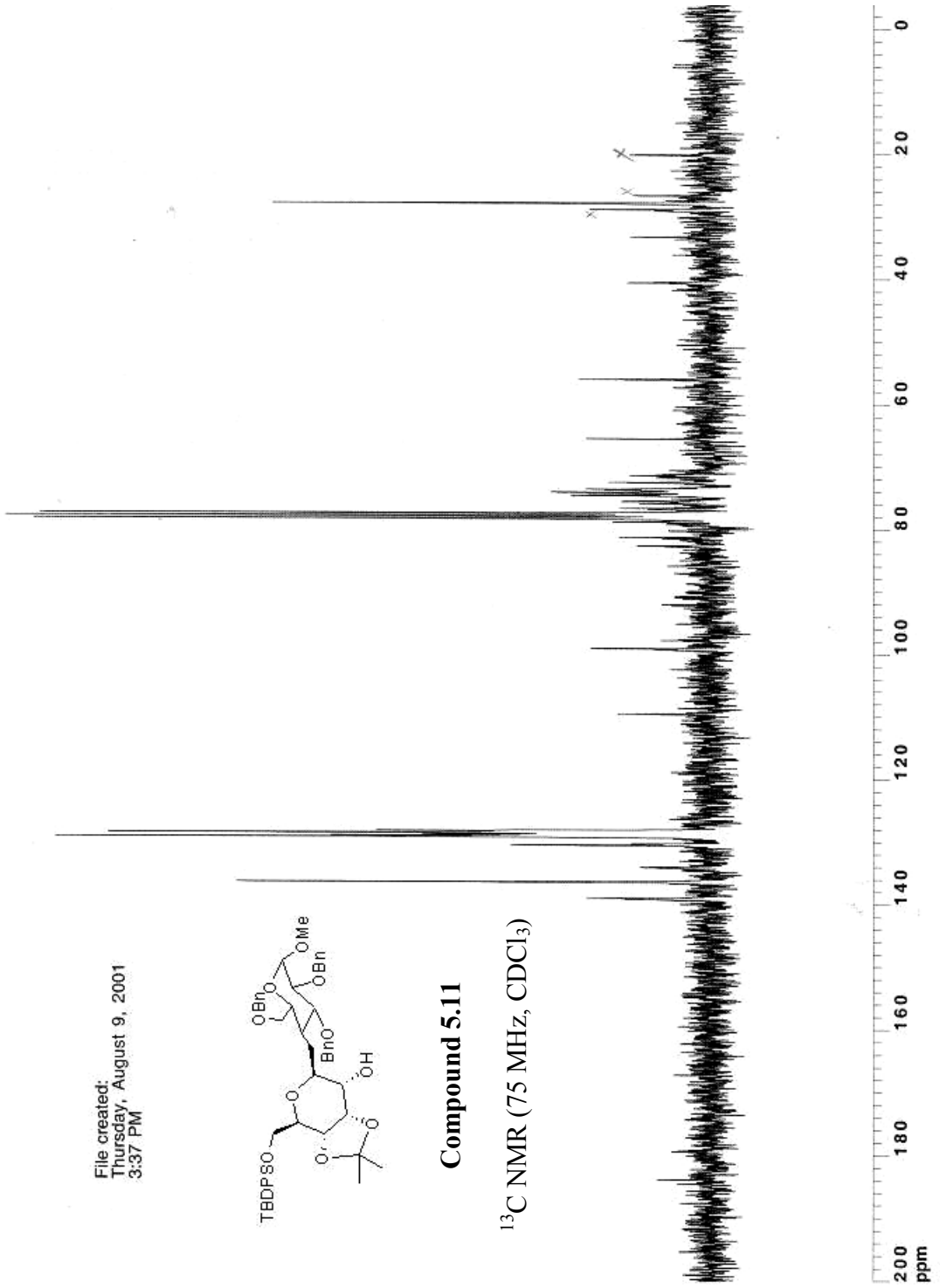
Compound 5.7

^{13}C NMR (125 MHz, $CDCl_3$)



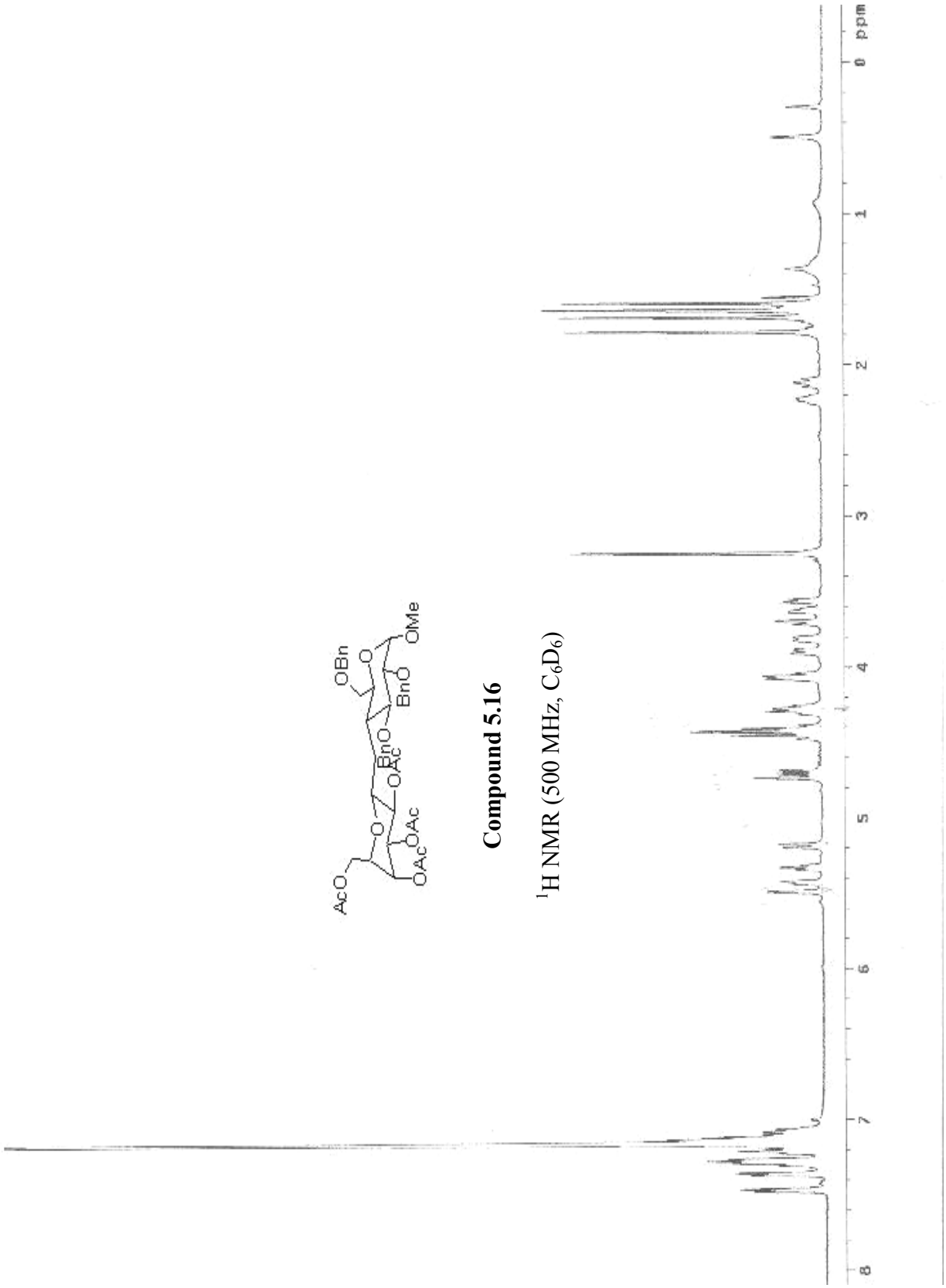
Compound 5.11

^{1}H NMR (300 MHz, $CDCl_3$)



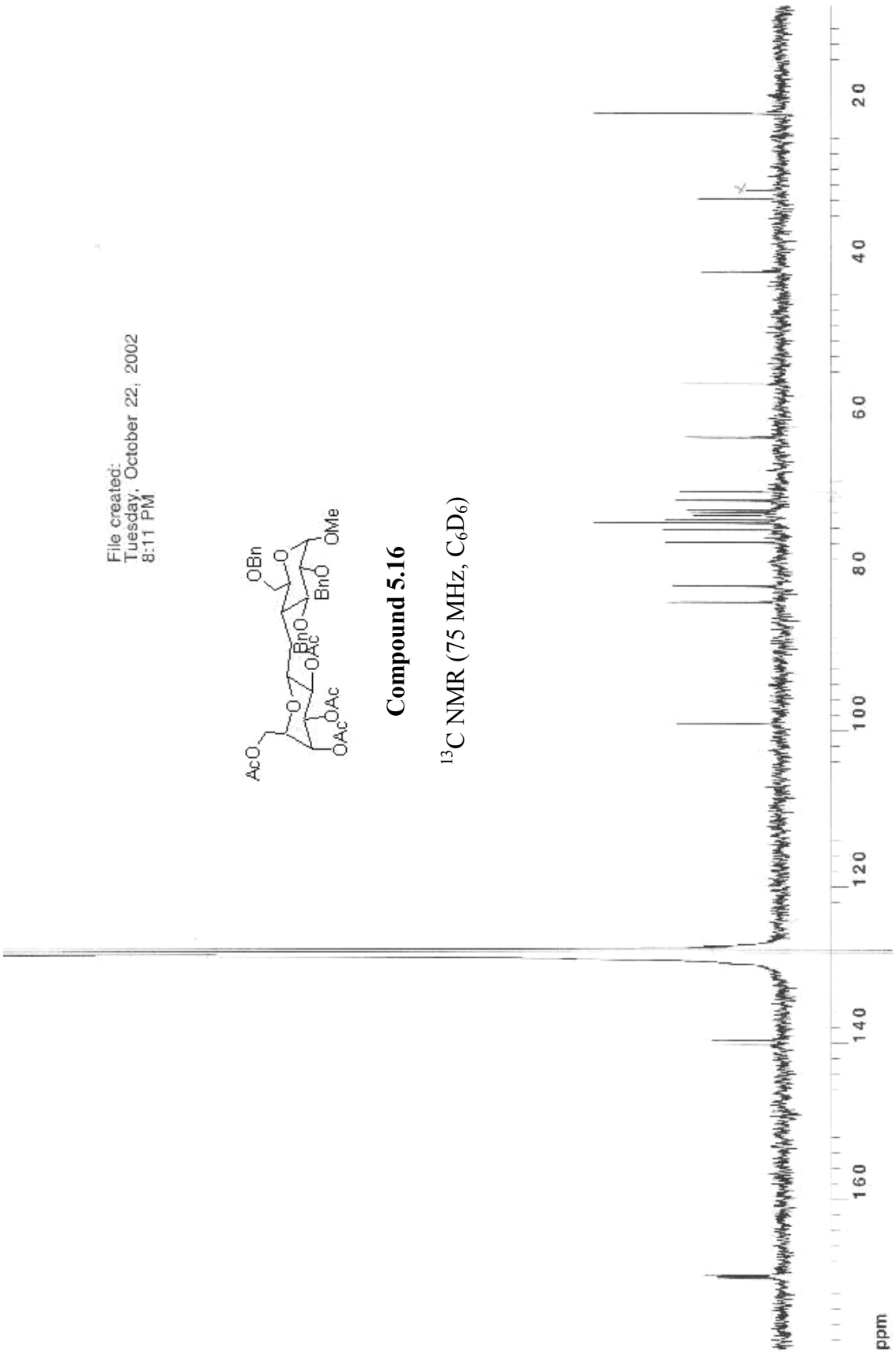
Compound 5.11

^{13}C NMR (75 MHz, $CDCl_3$)



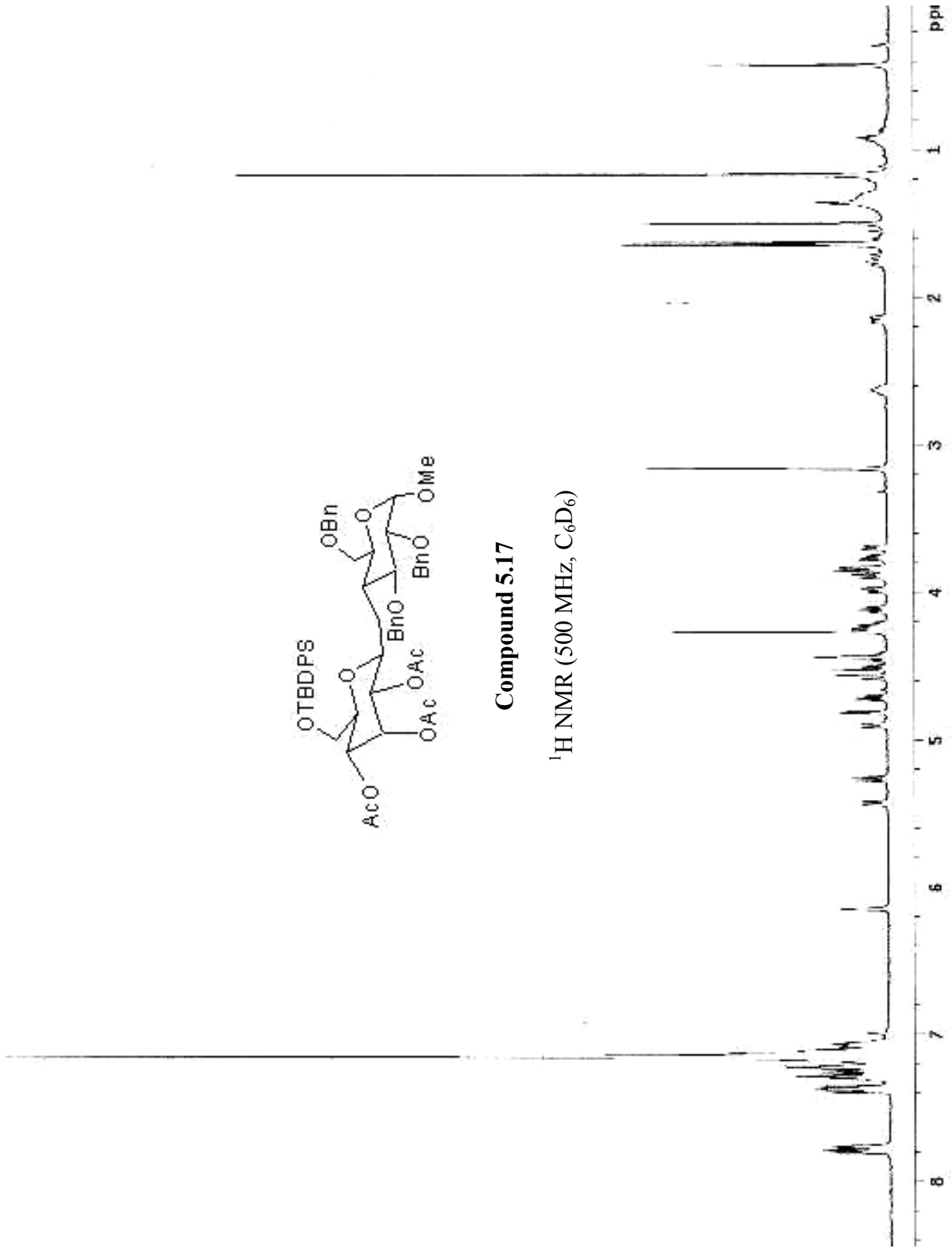
Compound 5.16

^{1}H NMR (500 MHz, C_6D_6)



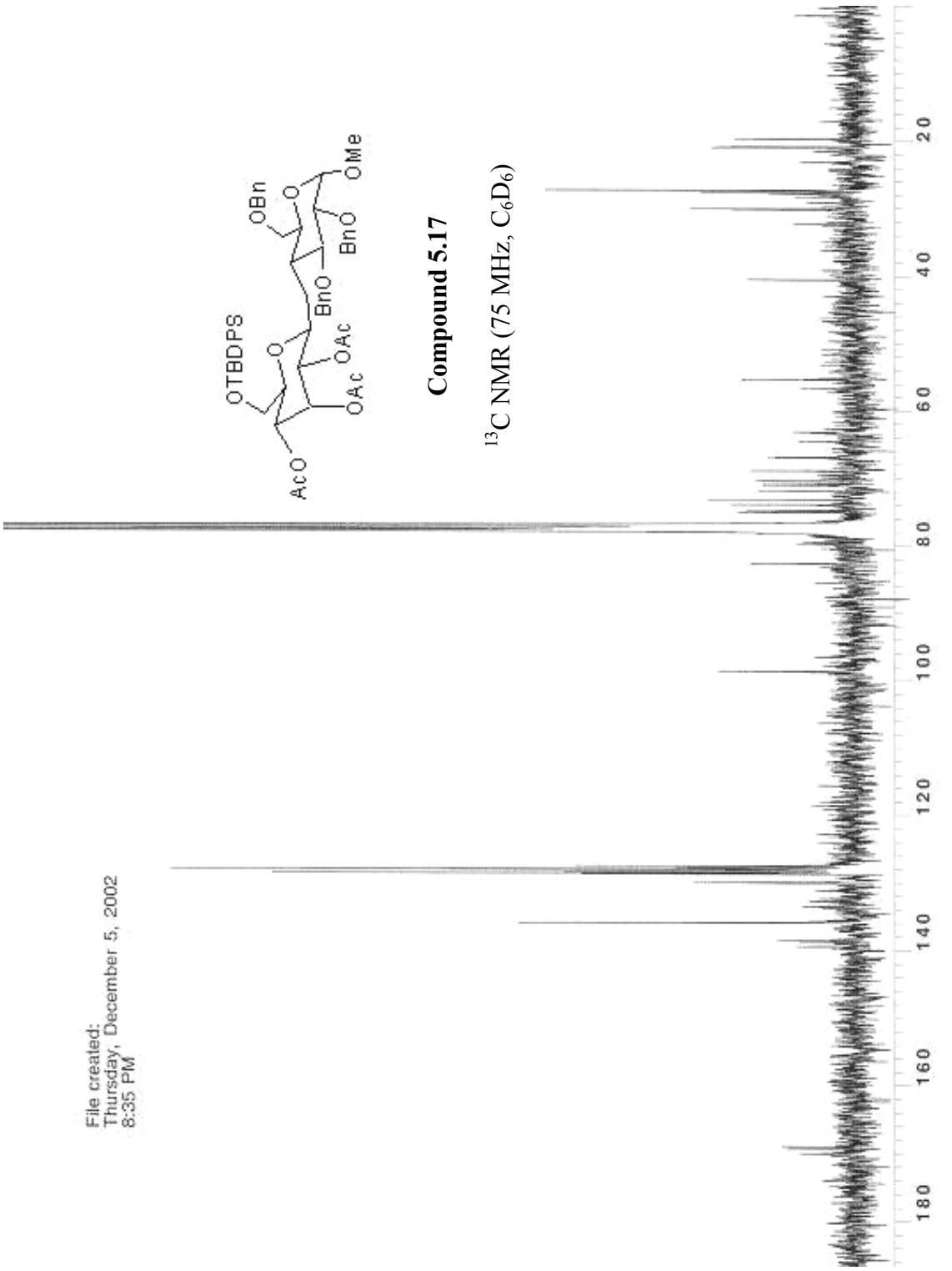
Compound 5.16

^{13}C NMR (75 MHz, C_6D_6)



Compound 5.17

^{1}H NMR (500 MHz, C_6D_6)



Compound 5.17

^{13}C NMR (75 MHz, C_6D_6)

References

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