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Aglycon Modifications of Ipomoeassin F: Synthetic Route Development and Analog Synthesis to Enable Further SAR Studies

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy in Chemistry

by

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Harding University
Bachelor of Science in Chemistry, 2012

December 2019
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Abstract

The ipomoeassin family of resin glycosides were discovered to have a high potency against numerous cancer cell line, with ipomoeassin F being the most potent among the family of natural products. Interestingly, one of the few differences between ipomoeassin F and the other compounds is the length of the fatty-acid derived aglycon. As the mechanism of action for this family of resin glycosides is unknown and didn’t have any significant COMPARE correlation with the recorded anticancer agents in the National Cancer Institute (NCI), further SAR studies are needed. Drawing on the differences between ipomoeassin F and the other ipomoeassins, it seemed logical to explore the effect of the aglycon on the bioactivity of these compounds. To achieve this, we sought to synthesize an epimer of ipomoeassin F, changing the configuration of the sole chiral center contained in the aglycon, as well as developing a synthesis that would enable us to modify the tail of the aglycon and explore in more depth the role of the critical region of the molecule.

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As I finish up this stage in my life, I’d like to thank all the people who have helped me get to this point, those who led my life in this direction, those who helped me get through this challenging time, and those who blessed me with their invaluable insight and knowledge along the way.

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Abbreviations

μM – micromolar

A2780 – human ovarian cancer cell line

ABPP – activity-based protein profiling

Ac – acetyl or acetic acid

Alloc – allyloxycarbonyl

Bn – benzyl

C_{14} ¬ tetradecanoic acid

C_{16} ¬ hexadecanoic acid

CA – chloroacetyl

cinn ¬ cinnamoyl or cinnamic acid

CMPI – 2,4,6-trichlorobenzoyl chloride

CSA – camphorsulfonic acid

DABCO - 1,4-diazabicyclo[2.2.2]octane

DCC – *N,N'*-dicyclohexylcarbodiimide

DCE – dichloroethane

DCM – dichloromethane

DDQ – 2,3-Dichloro-5,6-Dicyanobenzoquinone

DMAP ¬ 4-dimethylaminopyridine

DMF – Dimethylformamide

E7389 – Eribulin clinical anti-cancer drug

Et_2O – diethyl ether

EtOH – ethanol

Fuc*p* – fucose

Gal – galactose

Glc*p* – glucose

H522-T1 – non-small cell lung cancer cell line

HCl – hydrochloric acid

Hex – hexanes

HPLC – High-performance liquid chromatography

hrs. – hours

HT-29 – human colorectal adenocarcinoma cell line

Ipomo – Ipomoeassin

KOH – potassium hydroxide

KOMe – potassium methoxide

MDA-MBA-435 – metastatic human breast cancer cell line

MeCN – acetonitrile

MeOH- methanol

MS – molecular sieves

n – number of carbons

nm – nanometer

nM – nanomolar

NMR – Nuclear Magnetic Resonance

Ph – phenyl

PMB – 4-methoxylbenozyl

PMP– 4-methoxylphenyl

Qui – quinovose

RCAM – ring closing alkyne metathesis

RCM – Ring Closing Metathesis

Rha – rhamnose

RT – room temperature

SAR – structure-activity relationships

TBS – tert-butyldimethylsilyl

TFA – trifluoracetic acid

THF – tetrahydrofuran

tig – tiglic or tigloyl

TMS – trimethylsilyl

TMSCl – trimethylsilyl chloride

TMSOTf -trimethylsilyl trifluoromethanesulfonate

Tol – toluene

TPP – triphenyl phosphine

TsOH – *p*-toluenesulfonic acid

U937 – human lung(lymphoblast) cell line

[redacted] BACKGROUND AND INTRODUCTION

1.1 Carbohydrate Derived Macrocyclic Natural Products

Macrocyclic compounds have been extensively studied and synthesized due to their interesting biological and physicochemical properties and due to their abundance in nature. These macrocycle-containing natural products have been the target of many synthetic organic chemists over the years and have found diverse uses biologically, chemically, analytically, and medically. Among these naturally occurring macrocyclic compounds are macrocycles with embedded carbohydrates. In these structures, such as resin glycosides or other glycolipids, at least two bonds from a monosaccharide residue form a macrocycle[1,2,3]. Due to the interesting structures and bioactivity of many of these natural products, a number of carbohydrate derived macrocycles have been synthesized, including Tricolorin A and G, Woodrosin I, Sophorolipid Lactone, Glucolipsin, Cycloviracin B_1, and Ipomoeassin A-F[2]. These syntheses have employed a variety of intramolecular strategies to form the macrocyclic ring including the Diels-Alder reaction, aldol reaction, copper catalyzed azide-alkyne cycloaddition (CuAAC), lactonization, glycosylation[4] and metathesis, both ring closing alkene metathesis (RCM) and ring closing alkyne metathesis (RCAM)[1,5]. With the advancements to metathesis in recent years, this has become a popular method for constructing large rings intramolecularly. The reaction conditions are less harsh than many other reactions. The homogeneous transition metal catalysts can be used in standard organic solvents, are stable at room temperature and are highly reactive under mild conditions. Many of the catalysts also are tolerant to a wide range of functional groups and protecting groups and exhibit good selectivity, leading them to be a quite popular choice for many recent macrocyclic natural product syntheses.

1.2 Resin Glycosides

Resin glycosides are a class of natural products unique to the morning glory family, Convolvulaceae[6]. The Latin *convolvo*, from which the name of this family is derived, means interlaced and refers to the interlacing vines of the plants. Resin glycosides are secreted from cells in both foliar tissues and roots of this family of plants. Traditionally, these plants have been used extensively by various cultures throughout the world for their purgative properties. The active principles responsible for the purgative action of these botanical drugs are the unique glycoresins[7]. Due to the potent biological activity many of the resin glycosides have shown and their historical prevalence in botanical medicine, many have been isolated, characterized, and assayed over the years. The morning glory family of flowering plants is quite extensive, containing over 1,000 different species, and has yielded a wide variety of resin glycosides with a host of different bioactivities. Calysolins I-XVII were isolated from *Calystegia soldanella* and many showed anti-viral activity in an anti-HSV-1 assay[8,9,10,11]. Eleven pentasaccharide macrocycles, aquaterins I-XI, were isolated from *Ipomoea aquatica* and exhibited potent anti-cancer activity in HepG2 liver carcinoma cells. Most of the compounds were shown to elevate Ca^{2+} concentrations in the HepG2 cells, possibly contributing to the cytotoxicity observed[12]. Alinosides I-IX, isolated from the seeds of *Ipomoea alba*, and wolcottine I and wolcottinosides I-IV, isolated from *Ipomoea wolcottiana*, all showed potential as multidrug-resistance-modifying agents[13,14,15]. Purgins I-III and Purginosides I-IV were obtained from *Ipomoea purga* and also showed reversal of multidrug resistance, particularly Purgin II which enhanced vinblastine activity more than 2,000 fold in vinblastine-resistant human breast carcinoma cells (MCF-7/Vin)[16,17]. Cairicosides A and B were isolated from *Ipomoea cairica* and displayed α-glucosidase inhibitory activity[18]. Cairicosides A-E all exhibited moderate cytotoxicity against a small panel of human tumor cell lines[19]. The tyrianthinic acid tyrianthin series of resin glycosides were isolated from *Ipomoea tyrianthina* and showed biological activity in some central nervous system models as well as vasodilators. Tyrianthins C-E increased the sleeping time induced by sodium pentobarbital and the release of gamma-aminobutyric acid (GABA) in the brain cortex of mice[20,21]. Ipomotaosides A-D were extracted from the dried aerial parts of *Ipomoea batatas* and some anti-inflammatory activity was displayed by inhibiting two isoforms of the cyclooxygenase enzymes, COX-1 and COX-2. A xylose-containing oligosaccharide bacterial efflux pump inhibitor, Pescaprein XVIII, was obtained from *Ipomoea pes-caprae*. The resin glycoside was shown to potentiate the action of norfloxacin when treating multidrug resistant strains of *Staphylococcus aureus*[22].

[redacted] Synthesis of Resin Glycosides

To date, there have been a number of total syntheses of resin glycosides published from various groups. Structurally, these compounds all consist of two main regions. One being the hydrophilic glycon moiety and the other being the hydrophobic aglycon moiety. The glycon is composed of up to six monosaccharides, typically D-glucose, L-rhamnose, D-fucose, D-quinovose, and D-xylose, and are found in their pyranose forms. The fatty acid derived aglycon typically is composed of either a mono- or dihydroxy C_{14} or C_{16} fatty acid which spans two or more saccharide units to form a macrolactone. Usually a number of short-chain aliphatic acids decorate the periphery of the saccharide core as well[6].

Synthetically, these various molecules have proved challenging to synthesize and numerous strategies have been employed to construct these natural products and their analogs. The most notable challenge has been the formation of the macrocycle. Among the different strategies employed over the years, the most notable and prolific are various lactonizations conditions and RCM, the latter being the most favored in recent years[23].

[redacted] Synthesis of Calonyctin A

To date, two total synthesis of Calonyctin A (Figure 1-1) have been reported, first by Schmidt in 1995 and by Sakairi in 2000. Calonyctin A is one of the few resin glycosides that isn't isolated from the morning glory family but from *Calonyction aculeatum*. This compound strongly promotes the growth of various crops such as peanuts, beans, wheat, and potatoes[24,25]. The structure consists of three D-quinovose and one L-rhamnose units forming a tetrasaccharide and an 11-hydroxyhexadecanoic acid aglycon forming a 22-membered macrocycle.

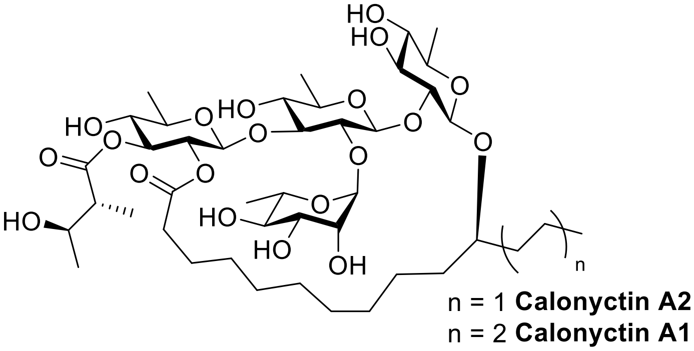
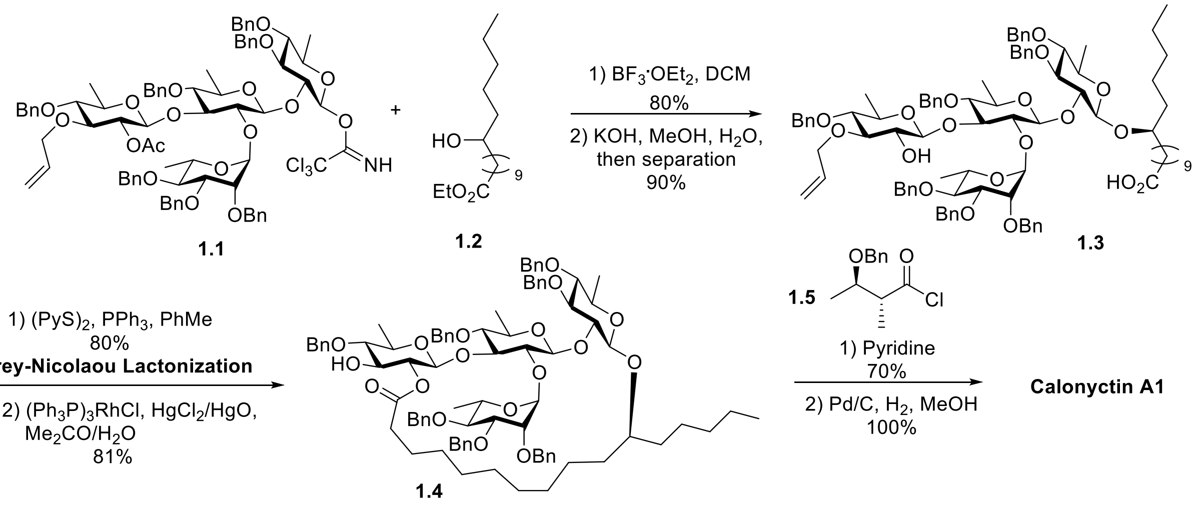


Figure 1-1. Structure of the Calonyctins

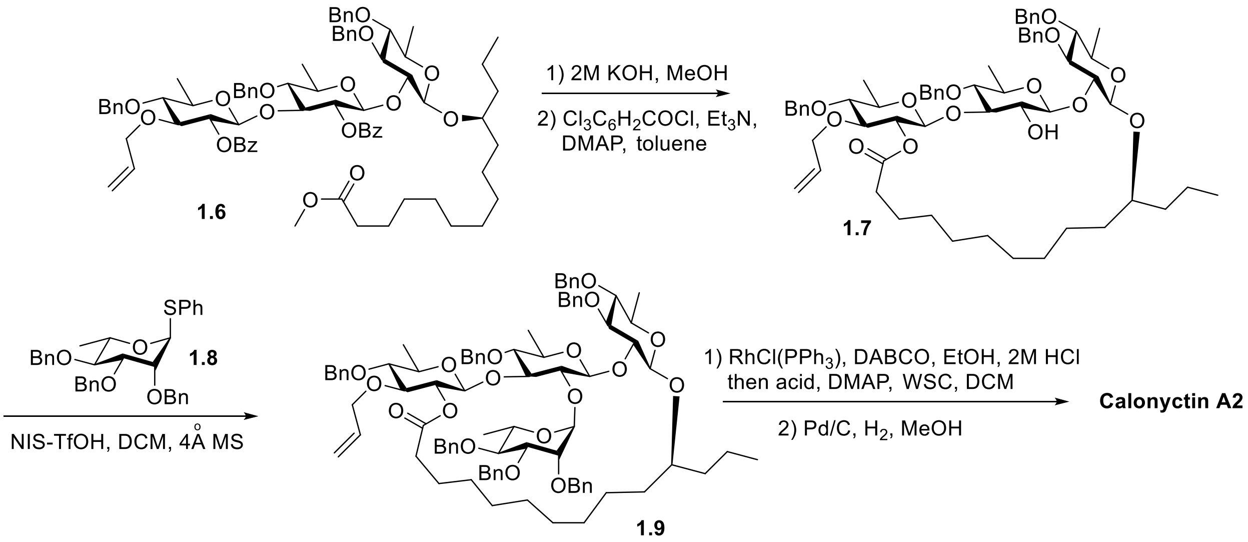
Schmidt's group was the first to synthesize the tetrasaccharidic macrolide, Calonyctin A1 (Figure 1-1). Schmidt's strategy for the synthesis relied on appropriately protecting the four carbohydrate residues and assembling the key tetrasaccharide fragment via a series of glycosylations using the trichloroacetimidate donor method[26]. Following the tetrasaccharide construction, desilylation with tetrabutylammonium fluoride (TBAF) and subsequent treatment with trichloroacetonitrile and DBU furnished the tetraosyl acetimidate donor. The donor was then coupled with the aglycon acceptor. Because the absolute stereochemistry was unknown at the time, a racemic mixture of the acceptor was used to form a 1:1 mixture of diastereomeric glycosides which were separated after saponification. Macrolactone formation was then accomplished using a Corey-Nicolaou macrolactonization, an established method for forming macrolactones in natural products[27] and has been successfully used in the synthesis of other resin glycosides as well[28]. Allyl removal followed by acylation with 3-benzyloxy-2-methylbutyric acid chloride and a final deprotection provided Calonyctin A1 for the first time[25,29].



1.1
1.2
1) BF$_3$·OEt$_2$, DCM
80%
2) KOH, MeOH, H$_2$O, then separation
90%
1.3
1) (PyS)$_2$, PPh$_3$, PhMe
80%
Corey-Nicolaou Lactonization
2) (Ph$_3$P)$_3$RhCl, HgCl$_2$/HgO, Me$_2$CO/H$_2$O
81%
1.4
1.5
1) Pyridine
70%
2) Pd/C, H$_2$, MeOH
100%
Calonyctin A1

Scheme 1-1. Schmidt Synthesis of Calonyctin A1

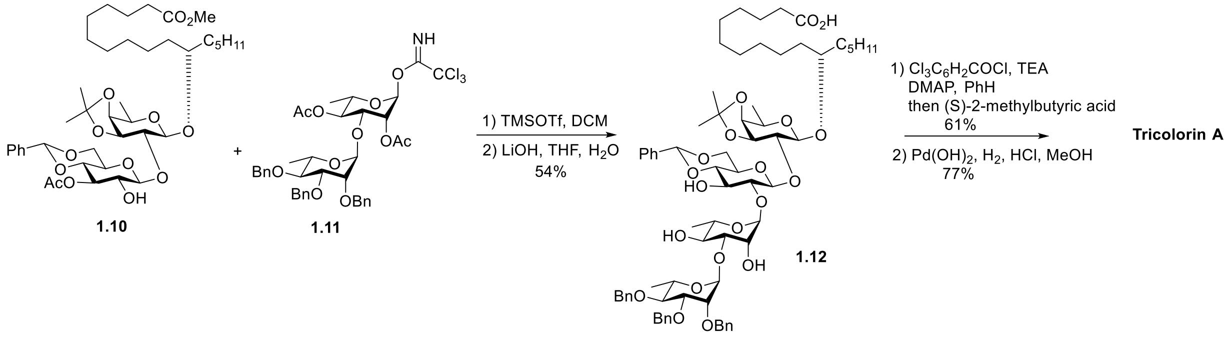
In 2000, the Sakairi group targeted Calonyctin A2, which differs from Calonyctin A1 only in the length of the aglygon. Their approach started from the β-(1,3)-linked disaccharide, laminaribiose in order to reduce the number of glycosylations in the synthesis. Following appropriate protection of the disaccharide and conversion to the corresponding thioglycoside, a glycosylation with the glucoside acceptor in the presence of NIS and a catalytic amount of TfOH smoothly afforded the trisaccharide. After subsequent treatment with aqueous KOH, the macrolactone was constructed by employing the Yamaguchi mixed anhydride procedure. An additional glycosylation with the L-rhamnosyl donor completed the formation of the tetrasaccharidic macrocycle, albeit in low yield. The allyl group was removed to allow for introduction of the 2-methylbutyric acid derivative and a final deprotection afforded Calonyctin A2.


1.6
1) 2M KOH, MeOH
2) Cl3C6H2COCl, Et3N, DMAP, toluene
1.7
1.8
NIS-TfOH, DCM, 4Å MS
1.9
1) RhCl(PPh3), DABCO, EtOH, 2M HCl then acid, DMAP, WSC, DCM
2) Pd/C, H2, MeOH
Calonyctin A2

Scheme 1-2. Sakairi Synthesis of Calonyctin A2

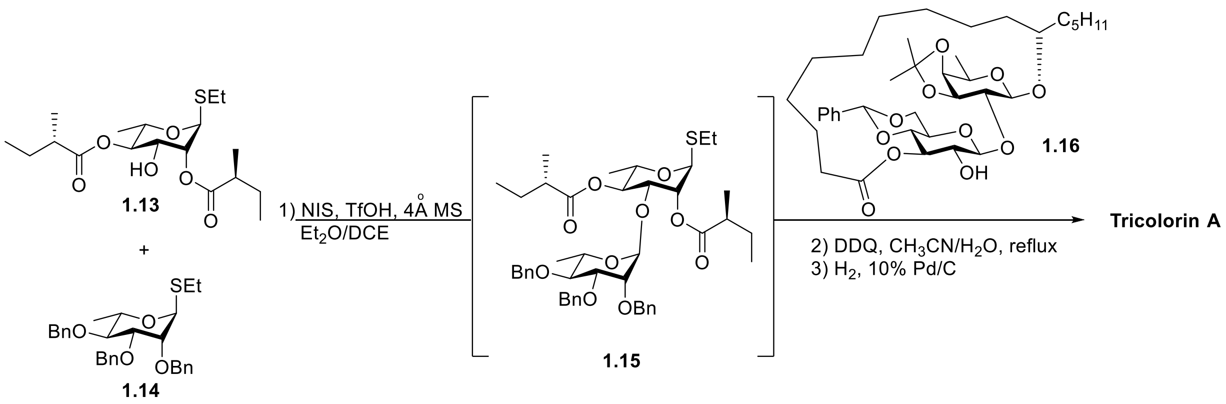
[redacted] Synthesis of the Tricolorins

Ipomoea tricolor had long been used as a cover crop in Mexican traditional agriculture due to its ability to control weed growth. In 1993, Pereda-Miranda and co-workers isolated and characterized the resin glycoside tricolorin A, the most abundant and easy to purify of the tricolorins, from *Ipomoea tricolor*[30]. The isolated compound also showed significant cytotoxic activity against P-388 lymphocytic leukemia cells and in human breast cancer cells. Its unique structure and biological activity spurred several total syntheses. The first synthesis was completed by Heathcock in 1997. He envisioned a coupling of two disaccharide units using a rhamnose-rhamnose disaccharide glycosyl donor and a lactone disaccharide glycosyl acceptor. However, he found that with the macrolactone already formed, the acceptor was too sterically hindered to efficiently couple. In order to circumvent this issue, a new strategy was formed in which the tetrasaccharide would be formed prior to macrolactonization. To prepare the tetrasaccharide, the C-3 position of the glucose moiety was selectively acetylated to allow the glycosylation between the rhamnosyl trichloroacetimidate donor and the C-2 hydroxyl group of glucose. Following the glycosylation and a subsequent saponification, a one-pot Yamaguchi macrolactonization and esterification with (S)-2-methylbutyric acid gave tricolorin A after a final deprotection.


CO_2Me
C_5H_{11}
Ph
AcO
OH
1.10
+
NH
CCl_3
AcO
OAc
BnO
BnO
OBn
1.11
1) TMSOTf, DCM
2) LiOH, THF, H_2O
54%
CO_2H
C_5H_{11}
Ph
HO
HO
OH
1.12
BnO
BnO
OBn
1) $Cl_3C_6H_2COCl$, TEA
DMAP, PhH
then (S)-2-methylbutyric acid
61%
2) $Pd(OH)_2$, H_2, HCl, MeOH
77%
Tricolorin A

Scheme 1-3. Heathcock Synthesis of Tricolorin A

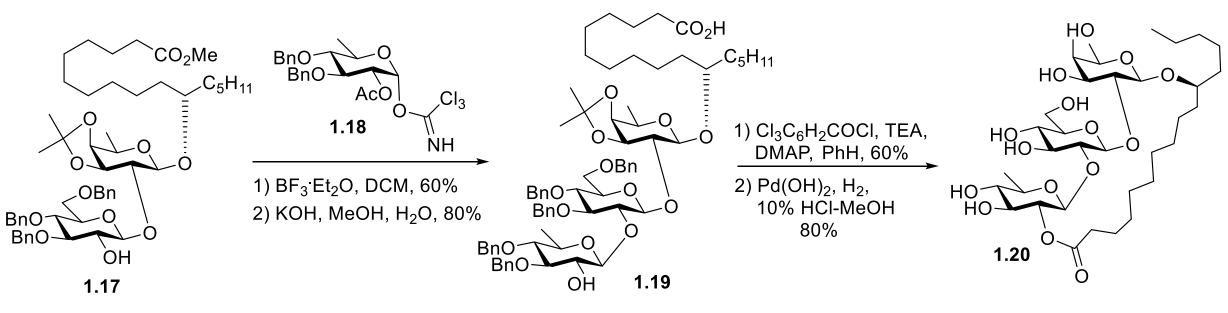
An additional total synthesis of tricolorin A was also published by the Yu and Hui group[31]. Their strategy utilized thioglycosides as the glycosylating reagents employed in a one-pot stepwise glycosylation to form the tetrasaccharide portion of the molecule. The disaccharide macrolactone was assembled via a Schmidt glycosylation, subsequent deprotection and a regioselective Corey-Nicolaou macrolactonization. To add the remaining carbohydrates a one-pot, two step glycosylation was performed. First, the two thioglycosides were coupled using NIS/TfOH followed by addition of the previously synthesized disaccharidic macrolactone. After deprotection of the isopropylidene and benzylidene using DDQ, the benzyl groups were removed by hydrogenation to afford tricolorin A[29,31].



SEt
O
HO
O
O
O
O
1.13
+
SEt
BnO
BnO
OBn
1.14
1) NIS, TfOH, 4Å MS
Et2O/DCE
SEt
BnO
BnO
OBn
1.15
C5H11
Ph
OH
O
1.16
2) DDQ, CH3CN/H2O, reflux
3) H2, 10% Pd/C
Tricolorin A

Scheme 1-4. Hui and Yu Synthesis of Tricolorin A

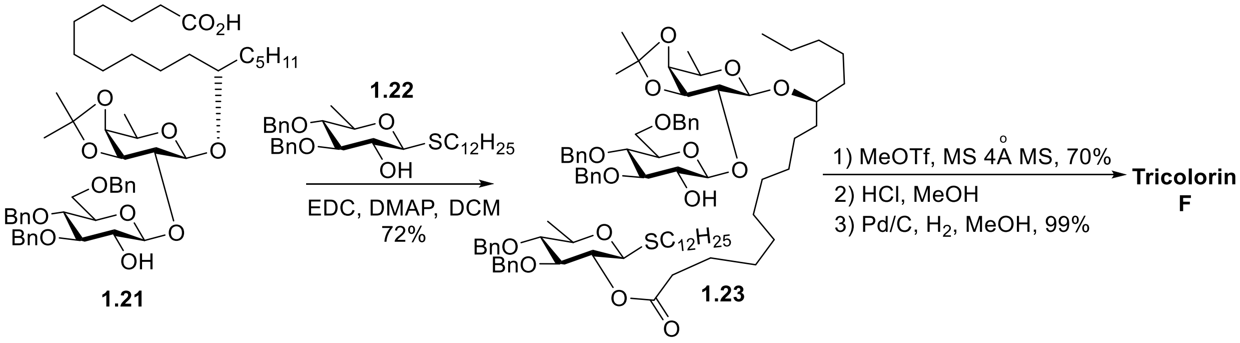
Sakairi's group chose to use a different strategy to form the macrocyclic core of Tricolorin A. They closed the macrolactone using an intramolecular glycosylation, a strategy they would go on to us for making Tricolorin F (Scheme 1-6). They first coupled the dodecyl thiofucoside donor with methyl 11(S)-jalapionate and following a Zemplan transesterification and subsequent saponification introduced the thioglucoside via an esterification reaction to give the disaccharide in poor yield (12%). At this point, a MeOTf-promoted intramolecular glycosylation afforded the key disaccharide macrolactone.



CO2Me
C5H11
OBn
BnO
BnO
OH
1.17
BnO
BnO
AcO
Cl3
NH
1.18
1) BF3·Et2O, DCM, 60%
2) KOH, MeOH, H2O, 80%
CO2H
C5H11
OBn
BnO
BnO
BnO
BnO
OH
1.19
1) Cl3C6H2COCl, TEA, DMAP, PhH, 60%
2) Pd(OH)2, H2, 10% HCl-MeOH 80%
HO
HO
OH
HO
HO
HO
HO
1.20

Scheme 1-5. Heathcock Synthesis of Tricolorin F

In addition to Tricolorin A, the Heathcock group also successfully completed the first synthesis of the trisaccharide macrolactone, tricolorin F in 2004[32]. They followed a similar synthetic strategy they had previously employed for tricolorin A[33]. After preparing the disaccharide acceptor, it was glycosylated with quinovosyl trichloroacetimidate and saponified (Scheme 1-5). The macrolactone was then formed following Yamaguchi's procedure and a subsequent debenzylation gave tricolorin F[29,32].



Scheme 1-6. Sakairi Synthesis of Tricolorin F

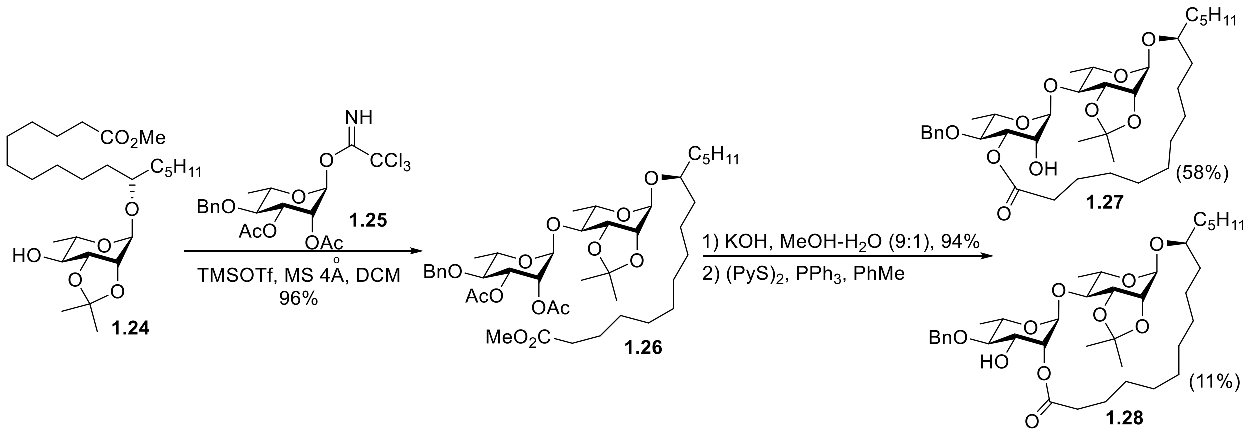
The Sakairi group also completed the synthesis of tricolorin F applying the intramolecular glycosylation strategy previously employed for tricolorin A. Following the preparation of the disaccharide fragment, the thioquinovoside was coupled via an EDC mediated esterification reaction to furnish the trisaccharide. An intramolecular glycosylation then completed the macrocycle and two final deprotections gave the desired tricolorin F[4,29].

[redacted] Synthesis of the Merremosides

The merremosides were isolated from the tuber of *Merremia mammosa* (Lour.) Hall. F. (Convolvulaceae). The plant had been used in Indonesia for treating diabetes as well as treating throat and respiratory issues. These compounds were shown to exhibit ionophoretic activity with the ability to transport Na^+, K^+, and Ca^{2+} across human erythrocyte membranes[29].

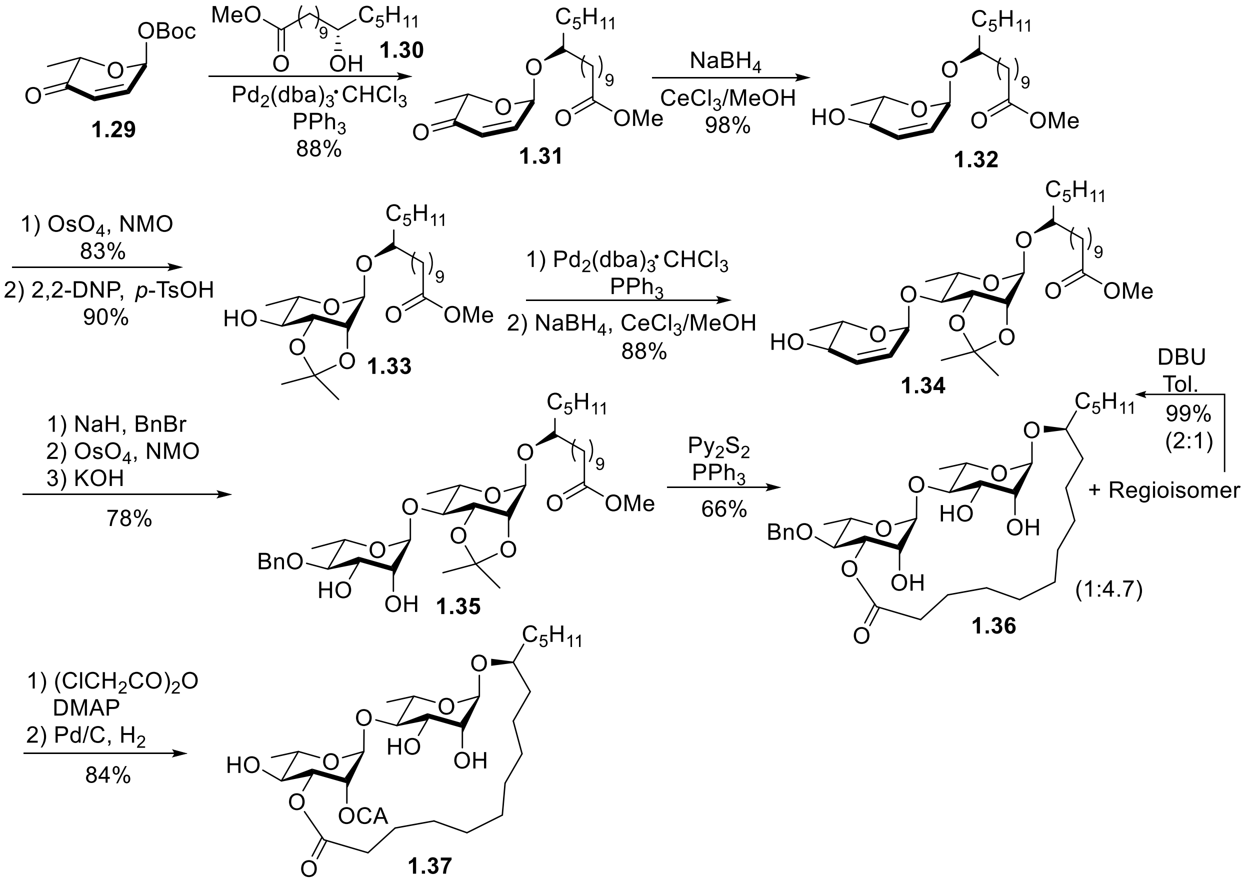
In 2006, Yang's group first synthesized the macrolactone core of the Merremosides[34].

After coupling the 11(S)-jalapionate with the L-rhamnopyranosyl trichloroacetimidate donor, the resulting rhamnoside was deacetylated and isopropylidinated to furnish the acceptor for a subsequent glycosylation. An additional L-rhamnopyranosyl donor was prepared and coupled with the rhamnoside acceptor to afford the desired disaccharide which was deacetylated. They then tried to form the macrolactonization under Yamaguchi's conditions but were unsuccessful so the Corey-Nicolaou macrolactonization method was employed with decent regioselectivity to complete the macrolactone core.



Scheme 1-7. Yang Synthesis of the Merremosides Core

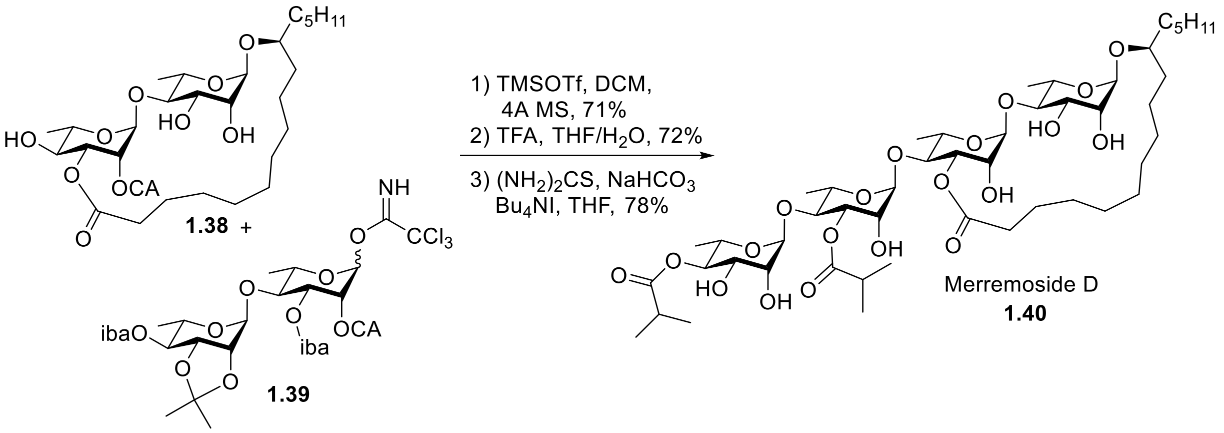
The first complete synthesis of any merremoside family member was reported in 2014 when O'Doherty *et al.* achieved the *de novo* synthesis of merremoside D[35]. Using a strategy common to the O'Doherty group, they began their synthesis from a pool of achiral starting materials and relied on asymmetric catalysis to install the 21 stereocenters of merremoside D. Their synthesis begins from a key pyranone building block which is obtained in 3 steps from acetylfuran. The jalapinolic ester used for the aglycon was synthesized following a modified asymmetric version of Heathcock's protocol employed in his synthesis of Tricolorin A[33]. The jalapinolic ester and the pyranone building block were then coupled via a stereoselective Pd-catalyzed glycosylation. This enone was then converted to the rhamnopyranoside acceptor through a Luche reduction, dihoydroxylation and a subsequent isopropylidination. An additional glycosylation with the same pyranone precursor followed by enone reduction, benzyl protection, alkene dihydroxylation and ester saponification gave the key disaccharide intermediate which would be the precursor for macrolactonization. Macrolactonization was accomplished using the Corey-Nicolaou method, however it gave the undesired regioisomer as the major product. Fortunately, they found they could isomerize the undesired compound to the desired isomer upon treatment with DBU in toluene. The remaining free hydroxyl group was then protected, and the benzyl ether was cleaved to afford the disaccharide acceptor.



OBoc
1.29
MeO
9
C5H11
O
OH
1.30
Pd2(dba)3·CHCl3
PPh3
88%
C5H11
9
OMe
1.31
NaBH4
CeCl3/MeOH
98%
HO
1.32
1) OsO4, NMO
83%
2) 2,2-DNP, p-TsOH
90%
1.33
1) Pd2(dba)3·CHCl3
PPh3
2) NaBH4, CeCl3/MeOH
88%
1.34
DBU
Tol.
99%
(2:1)
1) NaH, BnBr
2) OsO4, NMO
3) KOH
78%
BnO
1.35
Py2S2
PPh3
66%
+ Regioisomer
(1:4.7)
1.36
1) (ClCH2CO)2O
DMAP
2) Pd/C, H2
84%
OCA
1.37

Scheme 1-8. O'Doherty Synthesis of Macrolactone Intermediate

The disaccharide trichloroacetimidate donor was then prepared following a similar *de novo* synthetic route. The donor and acceptor were coupled to form the desired tetrasaccharide upon treatment with TMSOTf. The remaining acetonide and chloroacetate protecting groups were cleaved to complete the synthesis of merremoside D in 22 longest linear steps with a 3% overall yield[35].



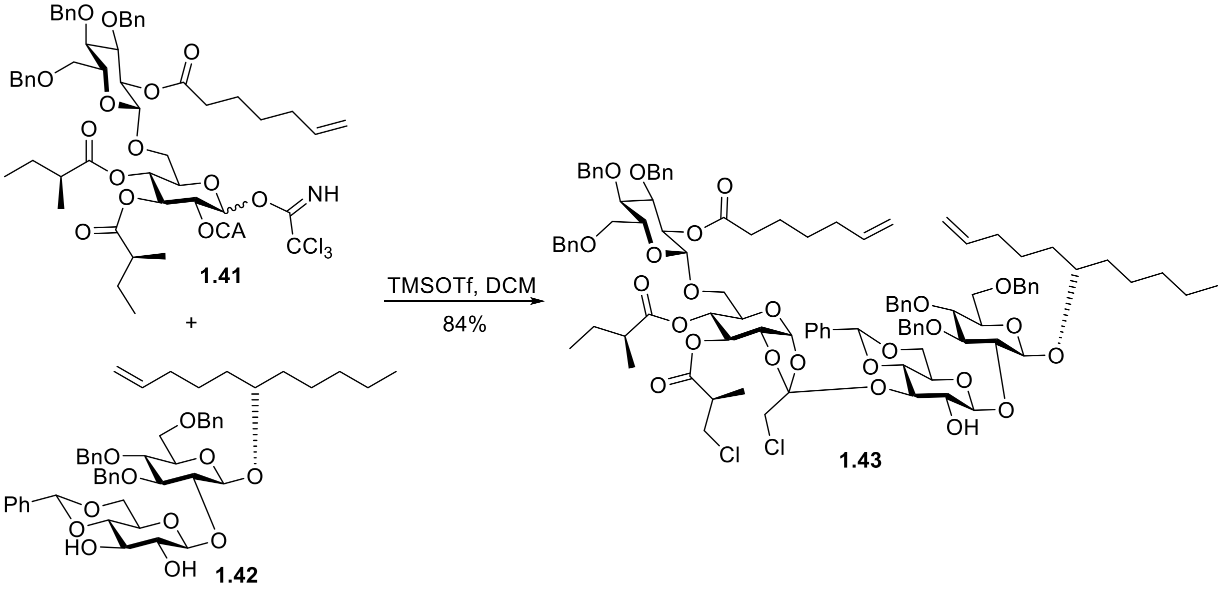
Scheme 1-9. O'Doherty Synthesis of Merremoside D

[redacted] Ring-Closing Metathesis in the Synthesis of Carbohydrate Containing Macrolides

[redacted] Synthesis of Woodrosin I

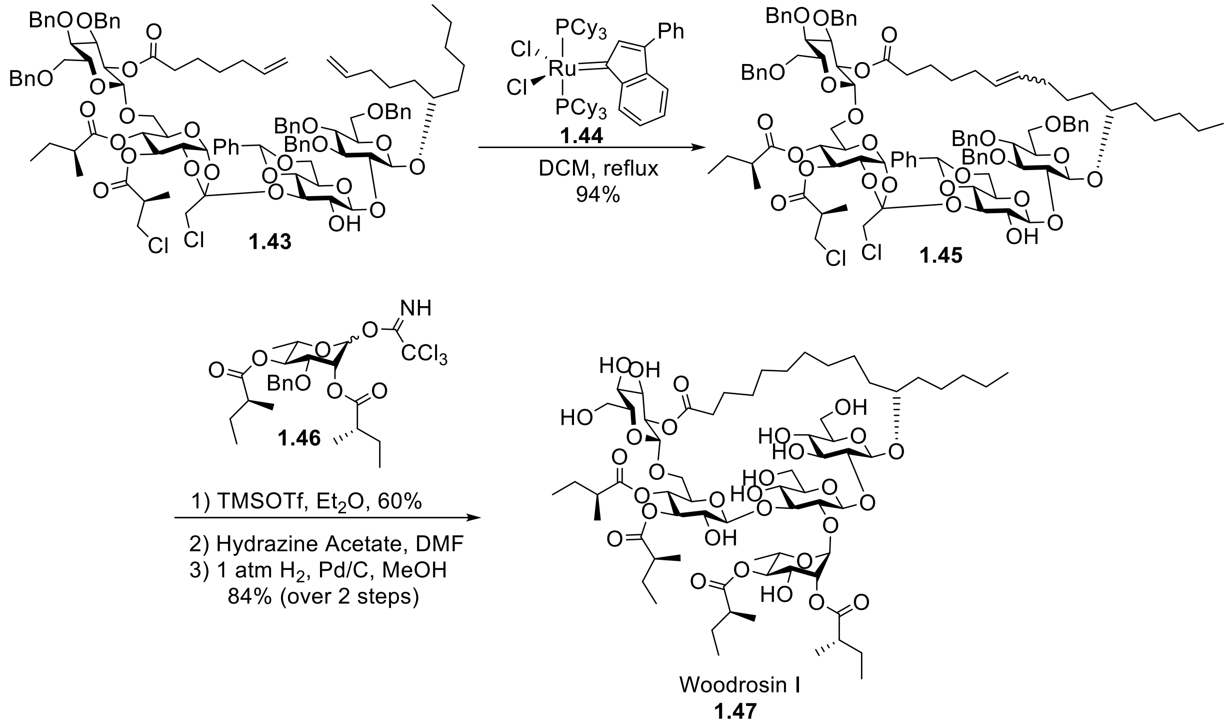
Woodrosin I, isolated from the stems of *Ipomoea tuberosa* L. (*Merremia tuberosa* (L.) Rendle), is one of the most complex resin glycosides known[36]. It is a pentasaccharide with an aglycon that spans four glucose units to form a 27-membered macrocycle[37]. Alois Fürstner, a pioneer in the use of ring-closing metathesis (RCM) in the synthesis of macrocyclic natural products, first reported the synthesis of Woodrosin I in 2002[37].

The Fürstner synthesis of Woodrosin I began with the preparation of the two disaccharide glucosides[38]. After synthesizing the donor and acceptor, they attempted a regioselective glycosylation at the 3'-OH position. Model studies had shown the 3'-OH functionality to be much more active than the 2’-OH location which would free them from having to do additional protection. While the glycosylation did achieve the desired regioselectivity, unexpectedly, NMR showed the formation of an orthoester by participation of the chloroacetyl protecting group. The chloroacetyl moiety had been chosen to be an orthogonal protecting group as well as providing stereochemical control through neighboring group participation to achieve the desired β-selectivity for the glycosylation reaction. Despite this obstacle, they attempted to carry on and introduce the rhamnosyl moiety. However, they found the site to be too sterically congested for the glycosylation to be successful. Before re-routing and starting over, they speculated that perhaps forming the macrocycle first might alter the conformation enough to open up the sterically hindered 2’-OH so that the rhamnosyl donor could freely be introduced.



Scheme 1-10. Fürstner Synthesis of RCM Precurser

Carrying forward with the synthesis, they decided they would attempt to form the macrocycle by RCM before completing the oligosaccharide backbone. The ring closure proceeded uneventfully and in excellent yield upon treatment with either Grubbs carbene or phenylindenylidene complex in a dilute, refluxing solution of DCM. They then turned their attention once again to introducing the rhamnose moiety. The rhamnosyl donor was particularly labile so Schmidt's "inverse glycosylation procedure"[39] was implemented by premixing catalytic amounts of TMSOTf in anhydrous Et_2O with the acceptor before slowly adding the donor. This time the glycosylation proceeded rather smoothly to complete the oligosaccharide backbone and rearranged the orthoester junction to the desired *β*-glycosidic linkage in 60% yield. The synthesis was completed by removing the chloroacetyl protecting group with hydrazine acetate followed by hydrogenation over palladium on charcoal to reduce the alkene in the aglycon and cleave the remaining protecting groups affording, for the first time, woodrosin I[37,40].



1.43
1.44
DCM, reflux
94%
1.45
1.46
1) TMSOTf, Et_2O, 60%
2) Hydrazine Acetate, DMF
3) 1 atm H_2, Pd/C, MeOH
84% (over 2 steps)
Woodrosin I
1.47

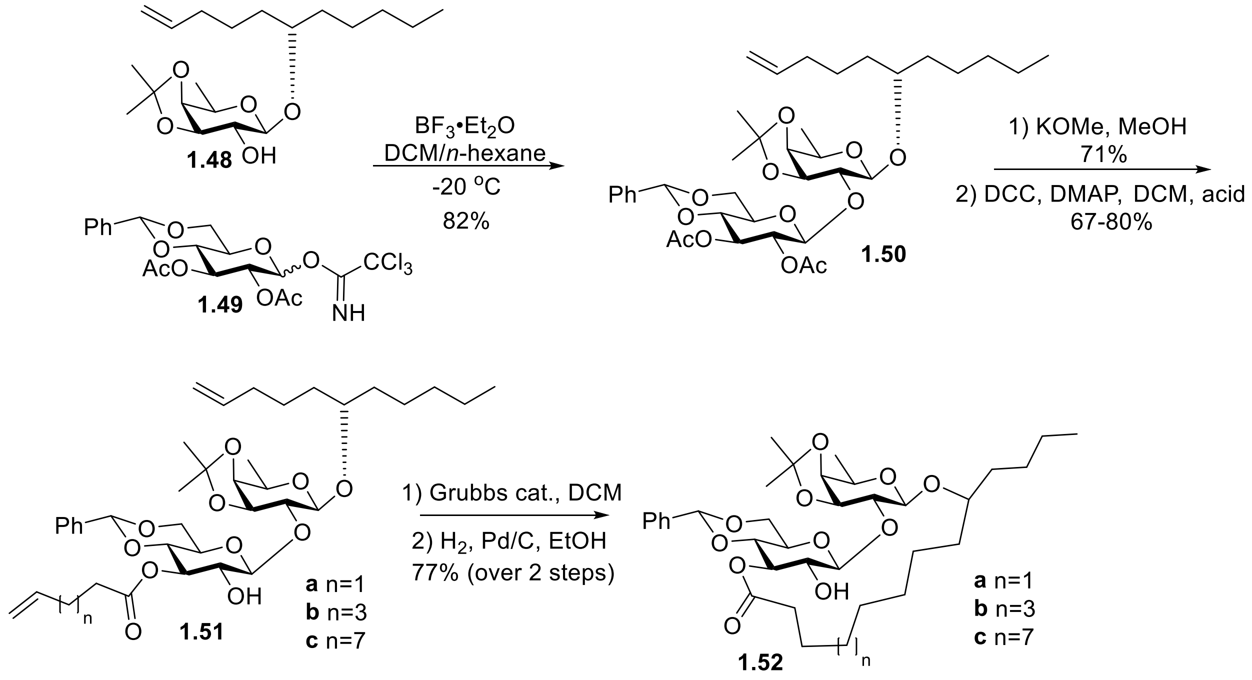
Scheme 1-11. Completion of Woodrosin I

[redacted] Synthesis of Tricolorin A and G (and Analogs)

As exemplar members of the Morning Glory family of resin glycosides, Tricolorin A and

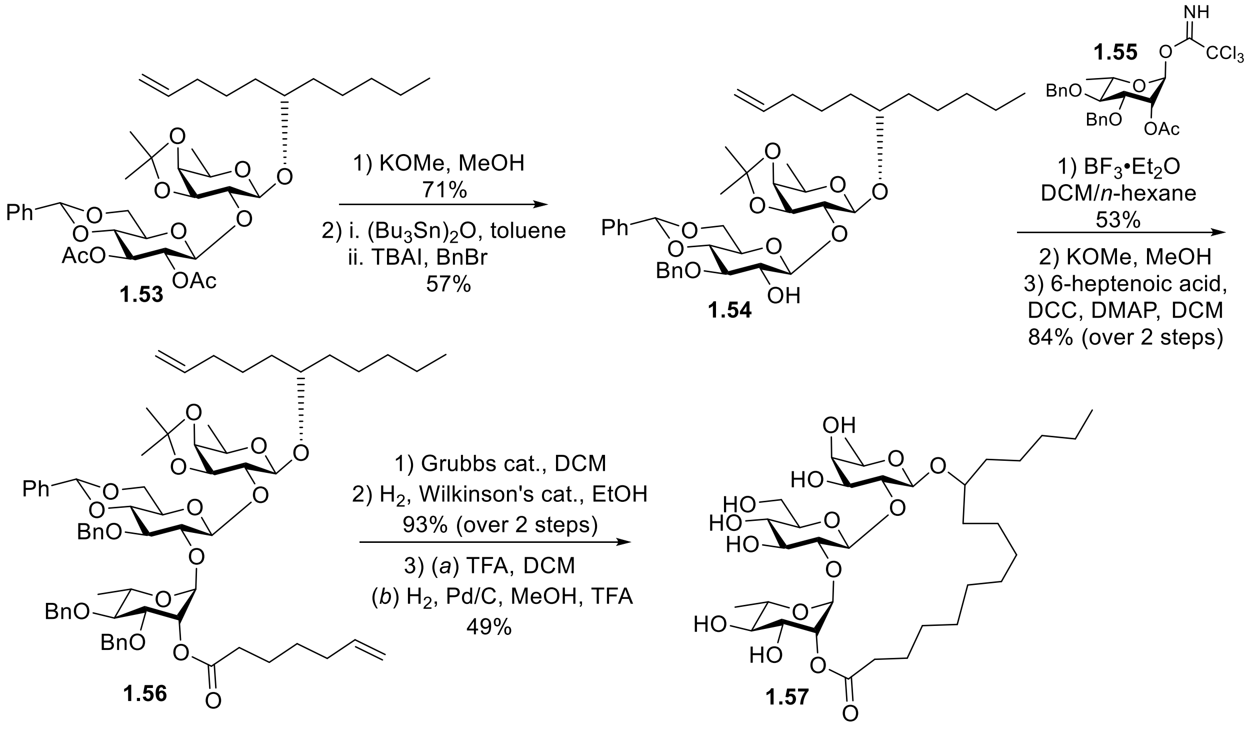
G are obvious targets to demonstrate the flexibility and utility of ring-closing metathesis for the synthesis of macrocycles. Though tricolorin A had been previously synthesized utilizing a traditional macrolactonization strategy to close the ring, this approach doesn't offer the flexibility to easily generate the wide range of analogs needed to further advance SAR studies.

To assemble the precursor for RCM, an acetonide protected fucoside acceptor was coupled with a glucosyl acetimidate donor via standard Lewis acid-catalyzed glycosylation conditions. Following a deacetylation, the 3"-OH group could then be regioselectively esterified with unsaturated carboxylic acids of varying lengths to give the desired RCM precursor and showcase the flexibility of late-stage ring-closure for accessing a variety of analogs. The subsequent RCM and hydrogenation proceeded smoothly to afford the macrocyclic core of tricolorin A. The remainder of the synthesis involved glycosylation at the free 2"-OH position with a suitably protected disaccharide acceptor and subsequent deprotection to provide tricolorin A and its analogs of various ring sizes.


1.48
OH
Ph
AcO
OAc
CCl3
NH
1.49
BF3•Et2O
DCM/n-hexane
-20 °C
82%
1.50
1) KOMe, MeOH
71%
2) DCC, DMAP, DCM, acid
67-80%
1.51
a n=1
b n=3
c n=7
1) Grubbs cat., DCM
2) H2, Pd/C, EtOH
77% (over 2 steps)
1.52
a n=1
b n=3
c n=7

Scheme 1-12. Fürstner Synthesis of Tricolorin Core

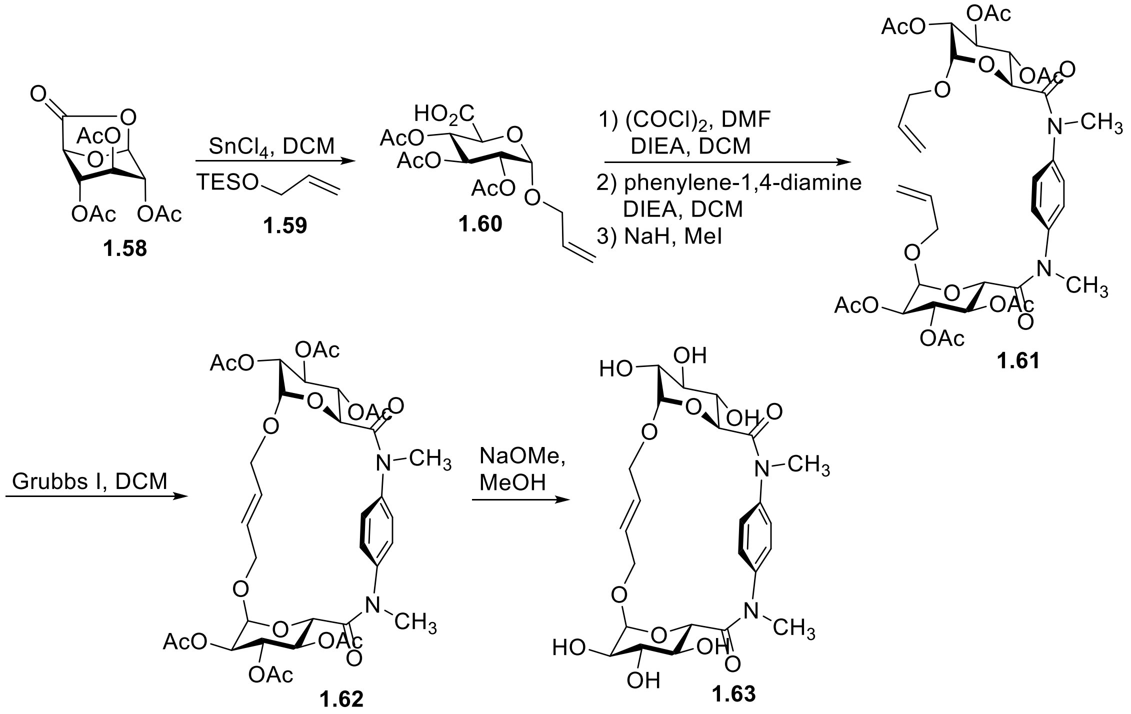
In addition to tricolorin A, the key intermediate **1.53** also could be used to access tricolorin G. In order to realize this compound, intermediate **1.53** had to be deacetylated and the more reactive C3” position was protected, allowing for the introduction of a rhamnosyl moiety at the less reactive C2” hydroxyl group. Another base-catalyzed deacetylation freed the C2 position of the rhamnosyl moiety for a subsequent introduction of 6-heptenoic acid ester to furnish the RCM precursor **1.56**. Once again showcasing the versatility of RCM for the preparation of macrocycles of varying lengths, metathesis following by hydrogenation smoothly yielded the desired compound, this time spanning three saccharide units. A final global deprotection would then afford tricolorin G for the first time.



1.53
1) KOMe, MeOH
71%
2) i. $(Bu_3Sn)_2O$, toluene
ii. TBAI, BnBr
57%
1.54
1.55
1) $BF_3•Et_2O$
DCM/*n*-hexane
53%
2) KOMe, MeOH
3) 6-heptenoic acid,
DCC, DMAP, DCM
84% (over 2 steps)
1.56
1) Grubbs cat., DCM
2) H_2, Wilkinson's cat., EtOH
93% (over 2 steps)
3) (*a*) TFA, DCM
(*b*) H_2, Pd/C, MeOH, TFA
49%
1.57

Scheme 1-13. Fürstner Synthesis of Tricolorin G

[redacted] Synthesis of Glycophanes

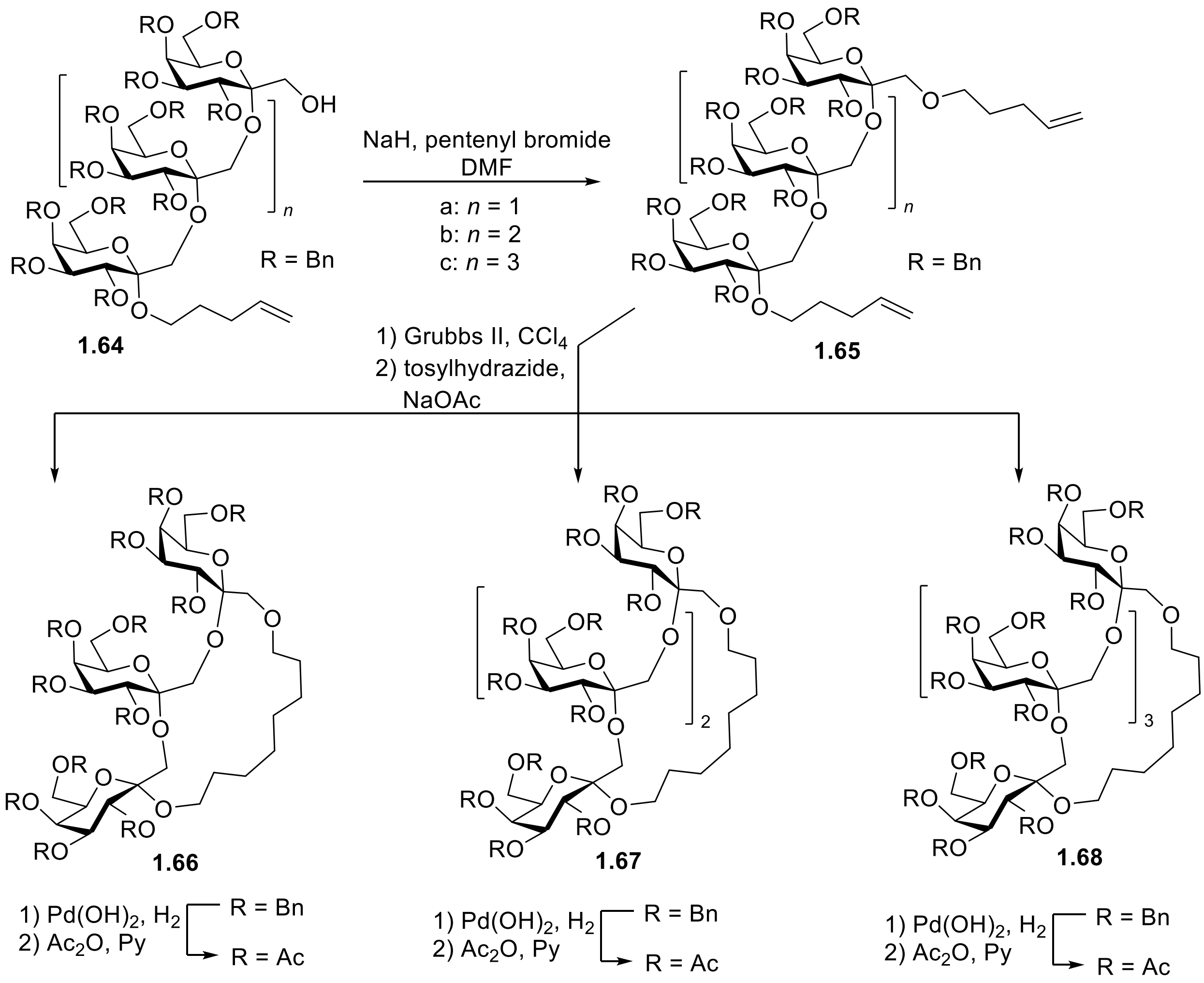


Scheme 1-14. Murphy Synthesis of Glycophanes

Glycophanes are macrocyclic hybrids of cyclophanes and carbohydrates. The synthesis of these highly functionalized scaffolds illustrates once again the versatility of RCM for assembling carbohydrate containing macrocycles, this time using much shorter aglycons. To prepare the first glycophane **1.63**, the Murphy group commenced with a glucuronic acid 6,1-anhydro derivative which was used to prepare the glycoside **1.60**. Treatment with oxalyl chloride furnished the corresponding acid chloride which was reacted with phenylene-1,4-diamine to generate the diamide. Subsequent N-methylation gave the RCM precursor **1.61**. Ring closure using Grubbs first generation catalyst smoothly afforded the desired product as a 4:1 mixture of isomers, favoring the *E*-isomer. A final deacetylation gave glycophane **1.63**. The authors noted that the N-methylation of the secondary amides was crucial for achieving RCM versus cross-metathesis. It is believed that the more conformationally restricted tertiary amide structure helps to facilitate the ring closure. A similar strategy was also employed to synthesize a variety of glycophane derivatives with varying lengths of aglycons using both RCM and ring-closing alkyne metathesis (RCAM). While using longer, more flexible alkanes and alkynes, N-methylation was not necessary to achieve ring-closure.

[redacted] Synthesis of Macrocyclic Neoglycoconjugate

An additional class of carbohydrate-containing macrocycles whose syntheses were achieved using RCM are neoglycoconjugates. Dondoni and Marra synthesized these neoglycoconjugate analogs beginning with oligosaccharides **1.64a-c**. Treatment with pentenyl bromide and NaH in DMF gave the corresponding dialkenyl RCM precursors. RCM facilitated by Grubbs second generation catalyst in carbon tetrachloride followed by alkene reduction gave the desired macrocyclic compounds. Debenzylation and subsequent acetylation afforded the final compounds **1.66 – 1.68**. Various other macrocyclic neoglycoconjugates were synthesized by Kirschning[41], Westermann[42], Krausz[43], Danishefsky[44], and Len[45], all employing RCM to complete their various syntheses.

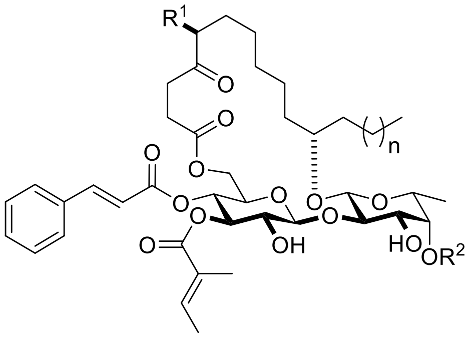

NaH, pentenyl bromide
DMF
a: n = 1
b: n = 2
c: n = 3
R = Bn
1.64
1.65
1) Grubbs II, CCl4
2) tosylhydrazide, NaOAc
1.66
1.67
1.68
1) Pd(OH)2, H2
2) Ac2O, Py
R = Bn
R = Ac

Scheme 1-15. Dondoni and Marra Synthesis of Neoglycoconjugates

■ Ipomoeassins

The ipomoeassins are a family of resin glycosides isolated from the leaves of *Ipomoea squamosa* Choisy from the Suriname rainforest. Initially, five compounds were isolated and characterized by David Kingston and colleagues in 2005, ipomoeassins A-E[46]. In 2007, one fraction from the previous isolation work was re-examined and discovered to contain an additional compound, ipomoeassin F, with a different retention time on HPLC[47]. Much interest was shown in the originally isolated ipomoeassins A-E due to their high cytotoxicity against the

A2780 ovarian cancer cell line. Later, when ipomoeassin F was isolated, it was shown to have IC_{50} values around 14 times more potent than ipomoeassin A, even though the only structural difference between the two compounds is two methylene units in the aglycon[48]. Structurally, the ipomoeassins consist of a fucose and glucose-derived (1→2)-β-disaccharide joined at *O*-1' and *O*-6'' by a 14 or 16 carbon fatty-acid-derived chain, forming a macrocyclic structure. The ipomoeassins vary in three different positions (Figure **1-2**), one being acylation of the C-4 hydroxyl group of the fucosyl moiety. The other differences are found on the aglycon where C-5 can have an acetyl group, hydroxyl group, or no substituent, and the length of the aglycon can be 14 or 16 carbons. These small changes can have a drastic impact on the potency of the compound as seen with the difference in activity between ipomoeassin F and A.



Ipomoeassin A: n = 1, R_1 = H, R_2 = Ac
Ipomoeassin B: n = 1, R_1 = H, R_2 = H
Ipomoeassin C: n = 1, R_1 = OH, R_2 = Ac
Ipomoeassin D: n = 1, R_1 = OAc, R_2 = Ac
Ipomoeassin E: n = 1, R_1 = OAc, R_2 = H
Ipomoeassin F: n = 3, R_1 = H, R_2 = Ac

Figure 1-2. General Structure of Ipomoeassins A-F

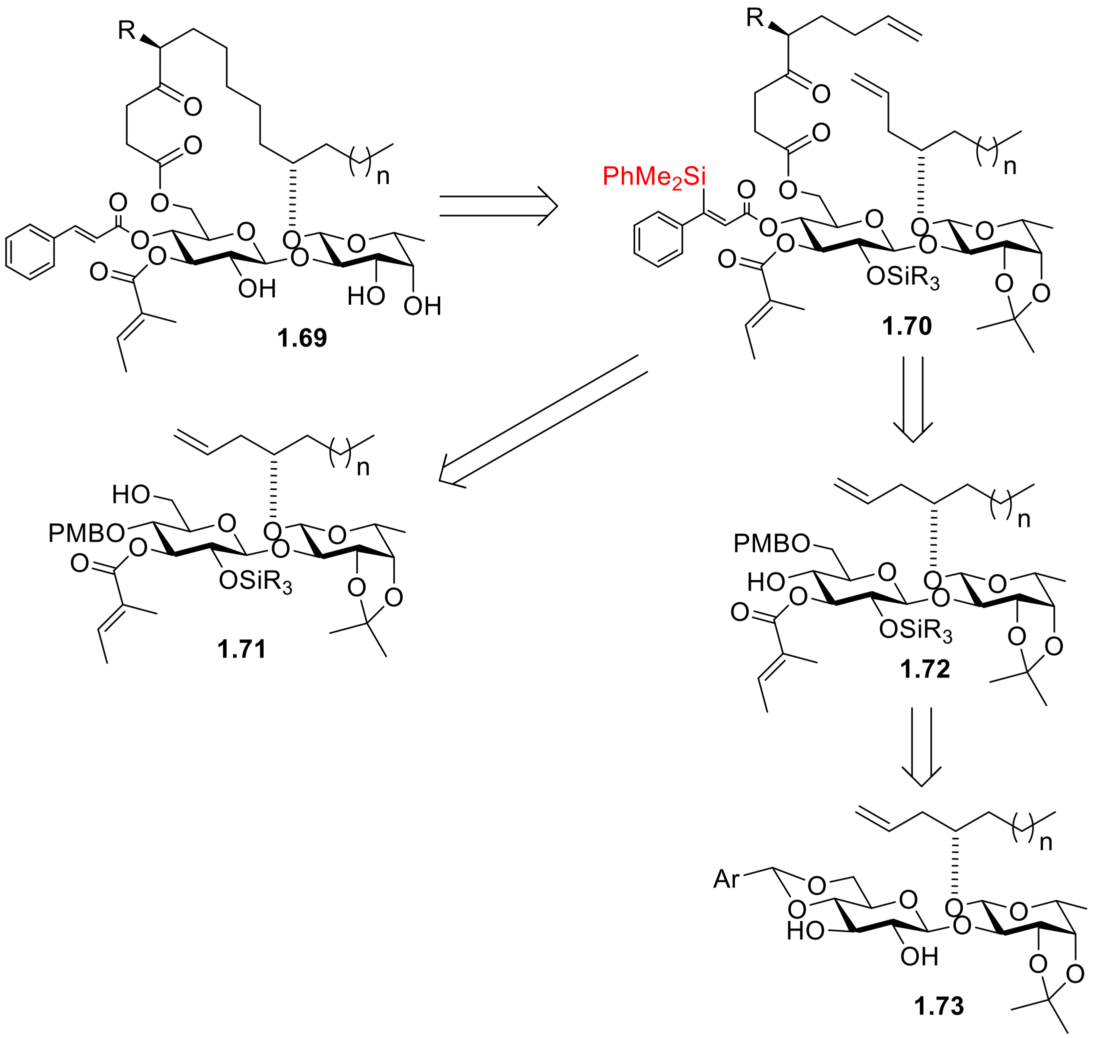
[redacted]

F	H	Ac	3		7.4	36	2.6	4.2	9.4	12.9

[redacted]

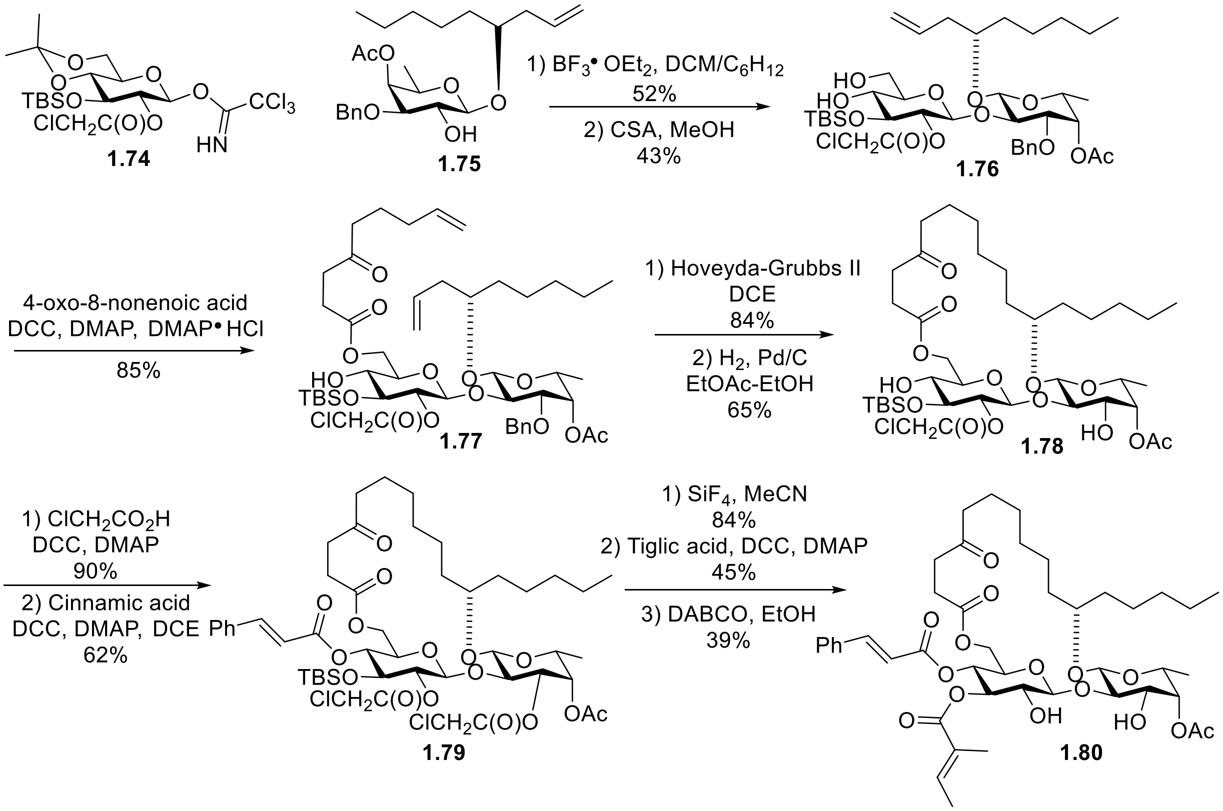
[redacted] Synthesis of the Ipomoeassins

Prior to the work by the Shi group, two different methodologies across three publications existed on the synthesis of the ipomoeassin family, both relying on a key RCM for construction of the macrocycle. The first of these publications came in 2007, by Fürstner et al. They reported the first total synthesis of ipomoeassin B and E[49]. Two years later, in 2009 they published the total synthesis of all the ipomoeassins, A-F[50], employing a flexible synthetic route that could give them access to all members of the family. In the Fürstner work, they relied on a multitasking C-silylation strategy to create a surrogate for the cinnamic acid moiety, allowing them to introduce this unsaturated group at an early stage of the synthesis without it interfering with the RCM or being unintentionally reduced during the subsequent hydrogenation[50]. Their synthesis commenced with the assembly of disaccharide **1.73** followed by a selective esterification to introduce the tiglate group followed by a TBS introduction to protect the remaining free hydroxyl. A reductive opening of the benzylidene acetal was expected to give compound **1.71** but was unsuccessful. Instead, compound **1.72** was obtained in a 4:1 ratio causing them to employ the aforementioned C-silylation strategy and introduce the cinnamate prior to RCM instead of afterwards as was initially planned. With the cinnamate installed, the remaining portion of the aglycon could be introduced via a Yamaguchi esterification to give the key RCM precursor **1.70**. RCM followed by hydrogenation, desilylation, and acetonide removal gave triol **1.69**. The triol could then be appropriately acetylated to form ipomoeassins A, C, D, or F or left as the hydroxyl to form ipomoeassins B or E. This route was flexible enough to allow the synthesis of all the natural ipomoeassins by introducing the appropriate aglycons as well as the first synthesis of 3 ipomoeassin derived analogs.



Scheme 1-16. Retrosynthesis for the Fürstner Synthesis of the Ipomoeassins

Though the first of the ipomoeassins were synthesized by Fürstner et al., Postema and colleagues were the first to report the synthesis of ipomoeassin F in 2009[48]. Their approach began with the preparation of the trichloroacetimidate glucosyl donor **1.74** and fucoside acceptor **1.75**. Schmidt glycosylation conditions coupled the two monosacharride fragments and was followed by treatment with CSA to remove the isopropylidene unit. A regioselective DCC-mediated esterification gave the RCM precursor **1.77**. Using the Hoveyda-Grubbs second generation catalyst they were easily able to use RCM to form the macrocycle. Hydrogenation then cleanly reduced the resulting double bond and cleaved the benzyl protecting group. Since they closed the ring prior to introduction of any other unsaturated groups, they didn't have to be concerned with any undesired reductions. They then selectively protected the C-3 position of fucose using chloroacetic acid to allow for the subsequent introduction of the cinnamate moiety. Desilylation then allowed for the installation of the tigloyl group in the pennultimate step. A final deprotection yielded ipomoeassin F for the first time. The synthetic material proved to be identical to the sample isolated by the Kingston group.


TBSO
ClCH2C(O)O
CCl3
HN
1.74
AcO
BnO
OH
1.75
1) BF3• OEt2, DCM/C6H12
52%
2) CSA, MeOH
43%
HO
HO
TBSO
ClCH2C(O)O
BnO
OAc
1.76
4-oxo-8-nonenoic acid
DCC, DMAP, DMAP• HCl
85%
1.77
1) Hoveyda-Grubbs II
DCE
84%
2) H2, Pd/C
EtOAc-EtOH
65%
1.78
1) ClCH2CO2H
DCC, DMAP
90%
2) Cinnamic acid
DCC, DMAP, DCE
62%
Ph
ClCH2C(O)O
1.79
1) SiF4, MeCN
84%
2) Tiglic acid, DCC, DMAP
45%
3) DABCO, EtOH
39%
1.80

Scheme 1-17. Postema Synthesis of Ipomoeassin F

[redacted] SYNTHESIS OF THE C11 EPIMER OF IPOMOEASSIN F

While two groups had already published the syntheses of the ipomoeassins[48–50], SAR studies were still necessary to further interrogate the protein-drug interactions of the ipomoeassins. Although these compounds show a high cytotoxicity towards a number of cancer cell lines, little was known about their mode of action. In fact, the cytotoxicity profile of ipomoeassin A had no significant COMPARE correlation with any of the recorded anticancer agents in the National Cancer Institute (NCI)[51], possibly suggesting a new potential druggable target. SAR studies could help to reveal the pharmacophore of the ipomoeassins and eventually lead to the development of chemicals probes for use in target identification. In later work, the Shi group discovered Ipomoeassin F binds Sec61α[52].

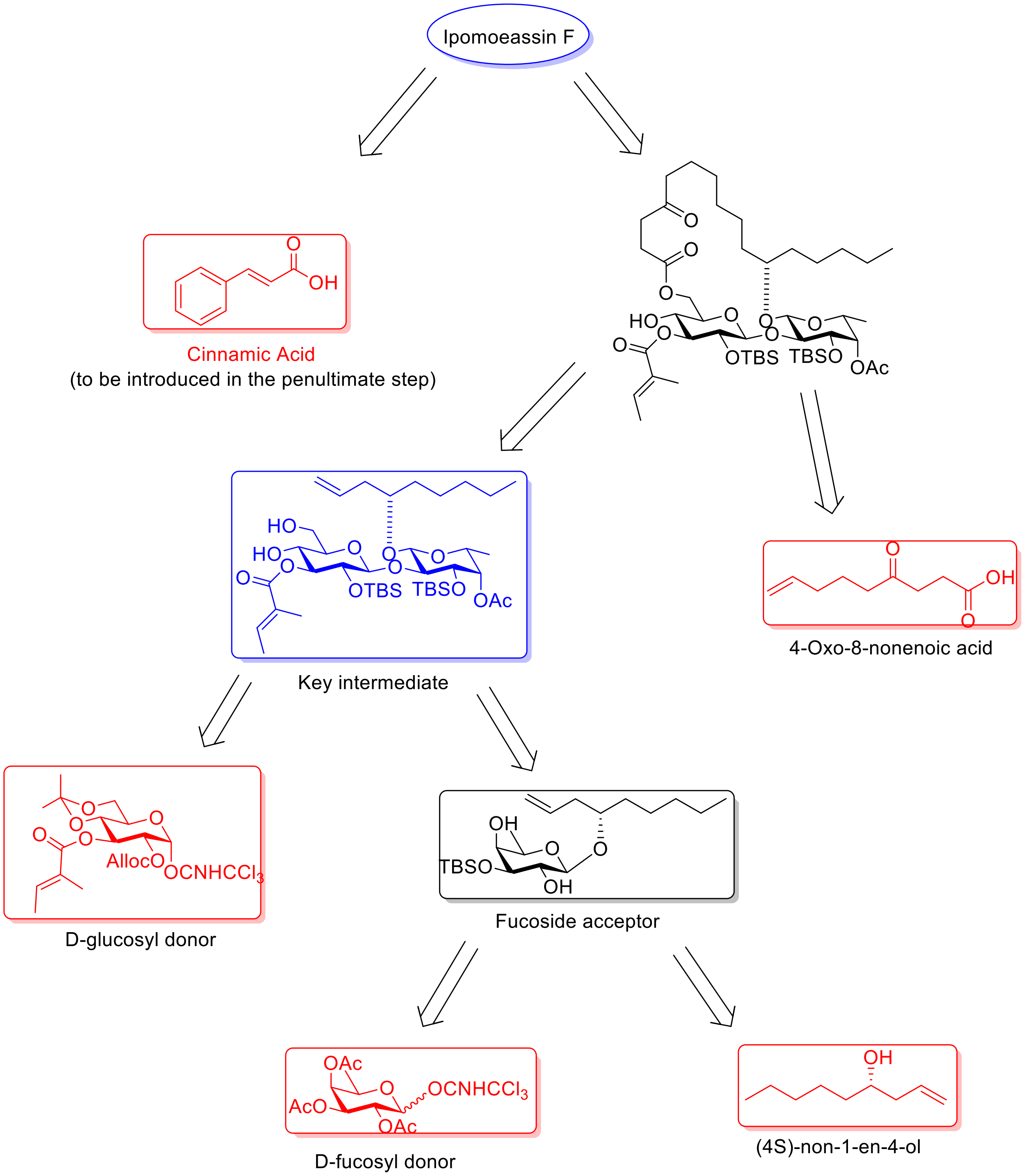
In order to begin the SAR studies, we first needed a flexible and scalable synthetic route that would facilitate the synthesis and biological studies of the scarcely available natural product, as well as its various analogs. We initially chose ipomoeassin F as our target due to its higher potency compared to the other ipomoeassins. We also used the same route to synthesize the C-11R epimer of ipomoeassin F to explore the effect of stereochemistry on the bioactivity[53,54]. While most all of the resin glycosides contain a chiral center in the aglycon, interestingly, they all have the same relative configuration. The role of this chiral center has never been explored for not only the ipomoeassins, but for all of the resin glycosides.

[redacted] Retrosynthetic Strategy

To begin planning an appropriate synthetic route for ipomoeassin F and it’s epimer, we first carefully evaluate the two previous syntheses of this natural product[48,50]. It seemed clear that an RCM approach would be the most favorable way to construct the 20-membered macrolactone ring as its utility had been demonstrated in a wide variety of resin glycosides. However, as shown by Postema and Fürstner, it is not without its challenges, primarily the unsaturated ester functionalities decorating the disaccharide core. To circumvent these issues we chose to introduce the cinnamoyl moiety in the penultimate step of the synthesis[53], in part due to the incompatibly with the necessary hydrogenation step, but also to enable the synthesis of various analogs at the position. Cinnamoyl-containing compounds have received much attention in medicinal research due to their antitumor properties[55] and the α,β-unsaturated Michael system as contained by cinnamic acid is known to function as a covalent protein modifier through conjugate addition[56]. Bearing these things in mind, we anticipated that this group could play an important role in the activity of the ipomoeassins and wanted a synthesis that could later be used to construct analogs at this position. In later work from the Shi group, this theory was validated as the cinnamte and tiglate were critical to the cytotoxicity[57,58]

From here, we envisioned constructing the RCM precursor by relying on a regioselective esterification to introduce the unsaturated ester fragment. This would free us from having to protect and subsequently deprotect the 4-*O*-Glc*p* position before introducing the cinnamate. We proposed assembling the key diol intermediate from a D-glucosyl donor and a fucoside acceptor with one aglycon fragment already installed. Appropriate protecting groups were a key consideration for this intermediate as they would need to be stable to hydrogenation conditions and also be removed without disturbing the other ester groups. This led us to protecting both the 3-*O*-Glc*p* and the 3-*O*-Fuc*p* with TBS which could both be easily removed in the final step.

The glycosylation to form the disaccharide core would be accomplished using Schmidt glycosylation conditions, but the requisite β-(1→2) glycosidic linkage meant there would need to be a protecting group which could direct the glycosylation through neighboring group participation. We chose to use the allyloxycarbonyl (Alloc) group for this purpose because it could be removed under mild conditions, leaving the isopropylidene protection unaltered. It



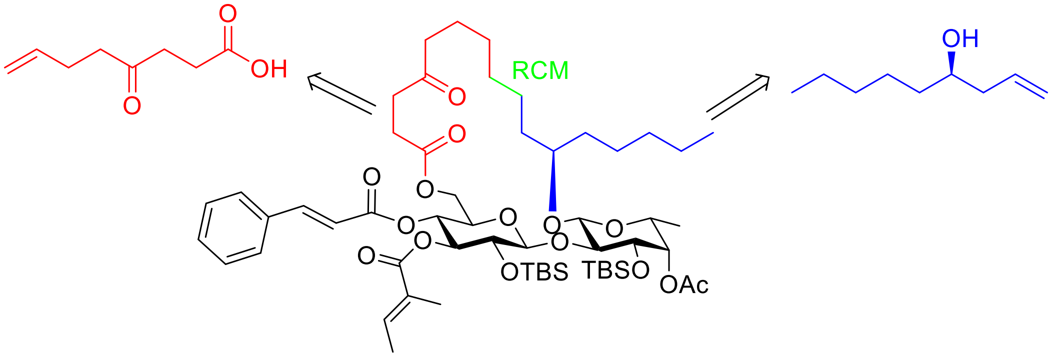
Ipomoeassin F
Cinnamic Acid
(to be introduced in the penultimate step)
Key intermediate
4-Oxo-8-nonenoic acid
D-glucosyl donor
Fucoside acceptor
D-fucosyl donor
(4S)-non-1-en-4-ol

Scheme 2-1. Retrosynthetic Strategy for Ipomoeassin F and its Epimer would later have to be exchanged for a TBS group due to incompatibility with the RCM/hydrogenation step. The tiglate could be installed prior to RCM/hydrogenation as Fürstner previously demonstrated a trisubstituted olefin would not be reduced if Wilkinson's catalyst was used for hydrogenation. After a deprotection to form the glucosyl hemiacetal, the trichloroacetimidate donor could be formed for coupling with the fucoside acceptor. An appropriately protected fucoside acceptor could be generated from a glycosylation with a peracetylated fucosyl donor and non-1-en-4-ol. This would introduce one half of the aglycon and install the desired stereochemistry for both ipomoeassin F and it's epimer.

[redacted] Synthesis of the Aglycon for the 11*R*-Epimer of Ipomoeassin F

As previously mentioned, it is known that the aglycon of the ipomoeassins can drastically impact the bioactivity of the compounds, as seen with ipomoeassin A and F. There are various changes to this region that could potentially be explored, but the first obvious modification was changing the configuration of the sole stereocenter. The planned synthetic route sets the configuration of the chiral center early in synthesis by using commercially available *R* or *S*-epichlorohydrin. In order to synthesize the epimer of ipomoeassin F it would be necessary to start from the beginning of the synthesis.

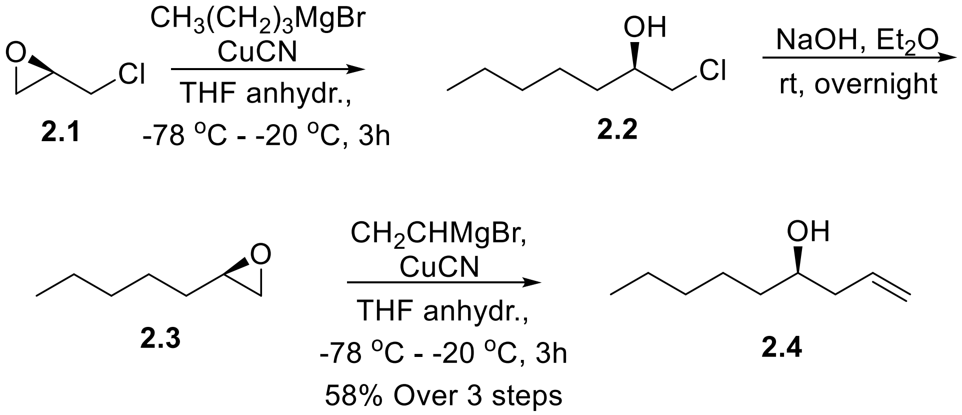
The aglycon in its entirety consists of 16 carbons. However, it would be assembled as two fragments. One fragment (highlighted red in Scheme 2-2), (4R)-non-1-en-4-ol would be coupled via glycosylation to a fucosyl donor while the other (highlighted blue in Scheme 2-2), 4-oxo-8-nonenoic acid, would be attached after the formation of the disaccharide through an esterification. The two olefin containing fragments would then be coupled using RCM.



Scheme 2-2. Aglycon of the 11*R*-Epimer of Ipomoeassin F

[redacted] Preparation of (4R)-nonen-4-ol

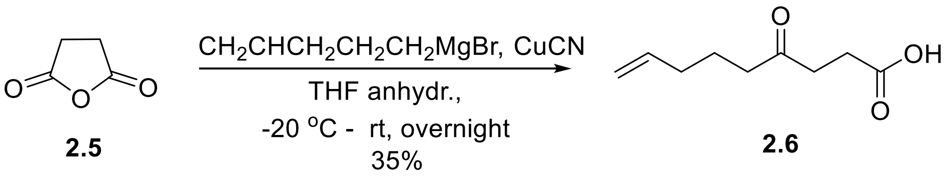
The first portion of the aglycon to be synthesized was (4*R*)-nonen-4-ol as it would serve as the acceptor for glycosylation with the peracetylated fucosyl acetimidate donor. The synthesis relies on commercially available (4*R*)-epichlorohydrin as a source of the desired chirality. The epoxide was opened up by addition of butylmagnesium bromide in the presence of copper (I) cyanide (CuCN) to give (*R)*-1-chloro-2-heptanol as a single enantiomer. Treatment with an excess of sodium hydroxide in diethyl ether would re-form the epoxide through a base-catalyzed intramolecular S_N2 reaction. An additional Grignard reaction with vinylmagnesium bromide would open the epoxide once again to give the desired (4*R*)-nonen-4-ol. After completion of the three step sequence, the final product was then purified by column chromatography to give the final compound with a 58% yield across all three steps.


2.1
$CH_3(CH_2)_3MgBr$
CuCN
THF anhydr.,
-78 °C - -20 °C, 3h
OH
Cl
2.2
NaOH, Et_2O
rt, overnight
O
2.3
$CH_2CHMgBr$,
CuCN
THF anhydr.,
-78 °C - -20 °C, 3h
58% Over 3 steps
OH
2.4

Scheme 2-3. Synthesis of (4*R*)-nonen-4-ol

[redacted] Preparation of 4-oxo-8-nonenoic acid

The remaining fragment of the aglycon, 4-oxo-8-nonenoic acid could be prepared on a multi-gram scale in a single, albeit low yielding, step starting from succinic anhydride. The succinic anhydride was opened through a Grignard reaction with pentenylmagnesium bromide in the presence of CuCN. It was necessary to use an excess of the Grignard reagent to drive the reaction to completion, however, the extra reagent could then add to the ketone as well, diminishing the yield. While there are other options to synthesize this compound, practically, it was more efficient to be able to make the compound in a single step rather than using multiple steps.


O
O
O
2.5
$CH_2CHCH_2CH_2CH_2MgBr$, CuCN
THF anhydr.,
-20 °C - rt, overnight
35%
O
OH
O
2.6

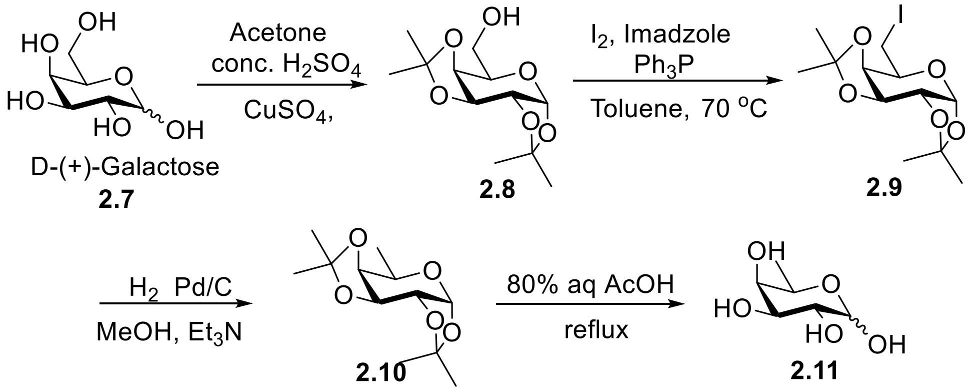
Scheme 2-4. Synthesis of 4-oxo-8-pentenoic acid

[redacted] Synthesis of the Fucoside Acceptor

To prepare the fucoside acceptor for coupling with the glucosyl donor, we first established a route to synthesize a fully protected fucosyl donor which would then undergo an anomeric deprotection to form the hemiacetal, followed by the formation of the trichloroacetimidate donor and subsequent glycosylation with aglycon fragment **2.4**. A single deprotection would then free 2-*O*-fuc*p* and provide the fucoside acceptor. This route was successfully used to synthesize the epimer of ipomoeassin F, however further investigation into the regioselectivity of installing protecting groups on fucose during the synthesis of the natural product ipomoeassin F inspired a much more efficient route for the synthesis of the fucoside acceptor which was shorter, and much easier to scale up a sufficient amount of material and was effectively used during the synthesis of both the epimer and the natural product. The new route first prepared a peracetylated fucosyl donor which was then coupled with the aglycon fragment **2.4**. While installing this fragment earlier made it necessary to synthesize a larger amount of the chiral alcohol, it also eliminated the need to protect and deprotect the anomeric position and ultimately shortened the total number of steps needed. The new route also relied a regioselective protection in which TBS could be introduced with high selectivity to the 3-*O*-fuc*p* position, eliminating the need to protect any of the other positions.

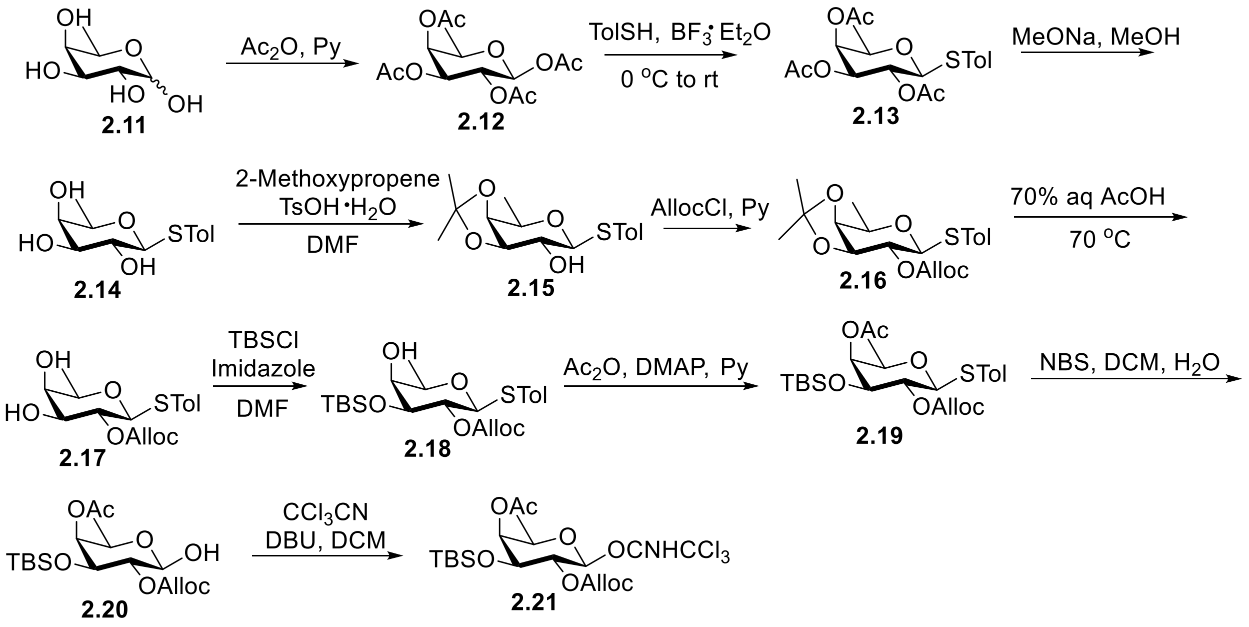
[redacted] Original Preparation of the Fucoside Acceptor

The first synthesis the fucoside acceptor began with the preparation of D-fucose, as did the improved synthesis. While fucose is commercially available, it is rather expensive and as it a starting material for the synthesis of the epimer, substantial quantities are required. A more cost-effective way of obtaining the material is from the readily available and inexpensive D-galactose. Diisopropylidene galactose is first made followed by iodination of the remaining hydroxyl group. Reductive dehalogenation using hydrogen gas gives the deoxy sugar. Treatment with acetic acid cleaves the acetonide protecting groups to give D-fucose, as reported in the literature[59].



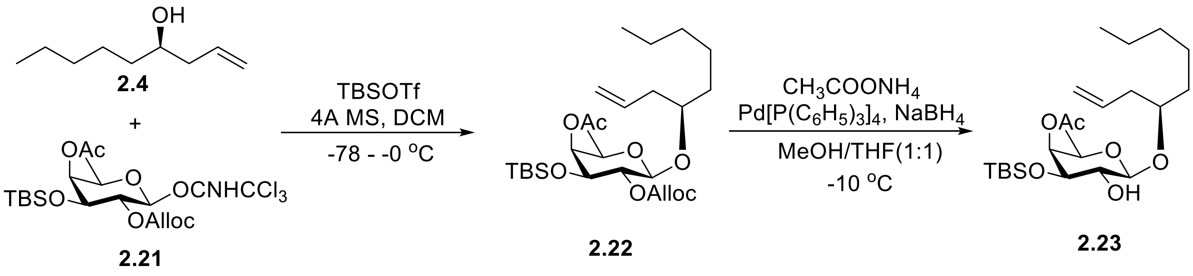
Scheme 2-5. Synthesis of D-Fucose

With D-fucose in hand, is was then globally acetylated to give peracetylated fucose. Thioglycoside **2.13** was then prepared directly with lewis acid-catalyzed glycosylation with thiotoluene. Deacetylation using sodium methoxide (NaOMe) gave the deprotected thioglycoside **2.14**. At this point, isopropylidenation could protect the 3-*O* and 4-*O*-fuc*p* hydroxyl groups leaving the 2-*O* position open for a subsequent orthogonal protection with an allyoxycarbonyl (Alloc) group. Cleavage of the acetonide would then allow for a regioselective TBS introduction to the favored 3-*O* position and the remaining hydroxyl group was acetylated. With all of the hydroxyl groups appropriately protected, the anomeric position was then deprotected using NBS to give the hemiacetal **2.20**. The hemiacetal was then converted to the fucosyl donor **2.21** with trichloroacetonitrile in the presence of DBU.


2.11
Ac₂O, Py
2.12
TolSH, BF₃·Et₂O
0 °C to rt
2.13
MeONa, MeOH
2.14
2-Methoxypropene
TsOH·H₂O
DMF
2.15
AllocCl, Py
2.16
70% aq AcOH
70 °C
2.17
TBSCl
Imidazole
DMF
2.18
Ac₂O, DMAP, Py
2.19
NBS, DCM, H₂O
2.20
CCl₃CN
DBU, DCM
2.21
OH
HO
O
OAc
AcO
STol
OAlloc
TBSO
OCNHCCl₃

Scheme 2-6. Original Synthesis of the Fucosyl Donor

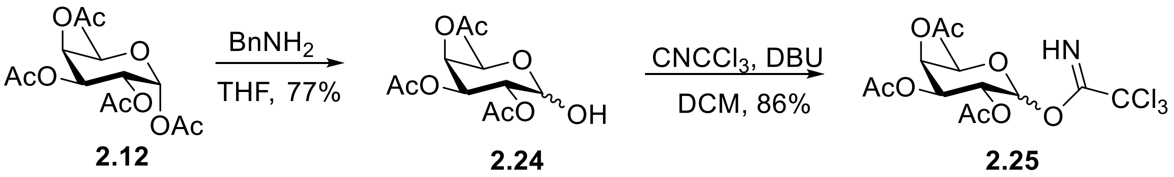
With the fully protected fucosyl donor established, it could then be coupled to the alcohol acceptor **2.4** via standard Schmidt glycosylation conditions. The Alloc protecting group could then be removed to furnish the fucoside acceptor to be coupled with the glucosyl donor. The main advantage of this route was the fact the aglycon was attached in the penultimate step, reducing the total amount of alcohol **2.4** that needed to be synthesized. Overall, this synthesis was much too lengthy though and it was much more efficient and scalable to introduce the aglycon earlier on do less manipulation of protecting groups.


2.4
+
2.21
TBSOTf
4A MS, DCM
-78 - -0 °C
2.22
CH₃COONH₄
Pd[P(C₆H₅)₃]₄, NaBH₄
MeOH/THF(1:1)
-10 °C
2.23
OH
OAc
TBSO
O
OCNHCCl₃
OAlloc

Scheme 2-7. Original Synthesis of Fucoside Acceptor

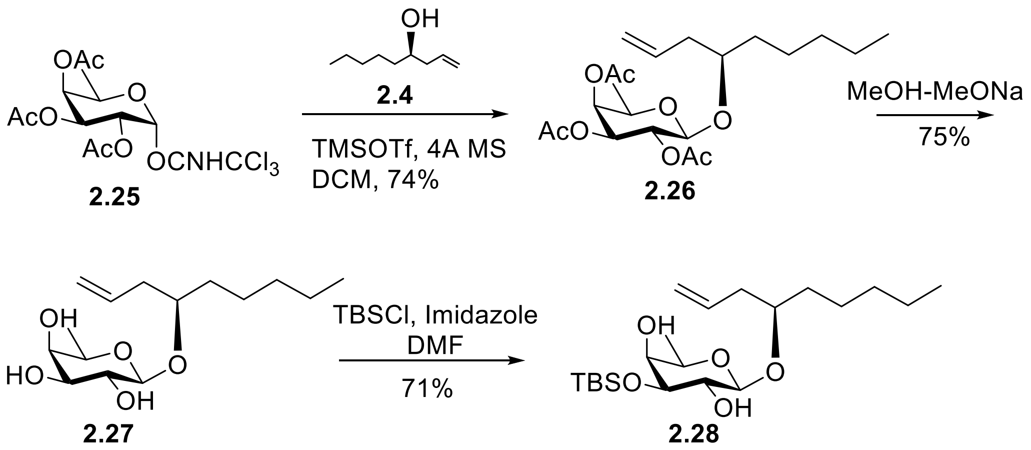
[redacted] Updated Preparation of the Fucoside Acceptor

As mentioned, our original synthetic route was successful in preparing the desired fucoside acceptor, but it was a very time-consuming process to scale up enough acceptor to complete a total synthesis. One way we addressed this problem was to introduce the aglycon early in the synthesis. With the aglycon already in place, there is one less hydroxyl group to protect and deprotect. Our synthesis still began with preparation of peracetylated D-fucose **2.12**, but afterwards we performed an anomeric deacylation with benzylamine ($BnNH_2$) to give the fucose hemiacetal which was converted to the fucosyl donor **2.25**.



Scheme 2-8. Updated Synthesis of Fucosyl Donor

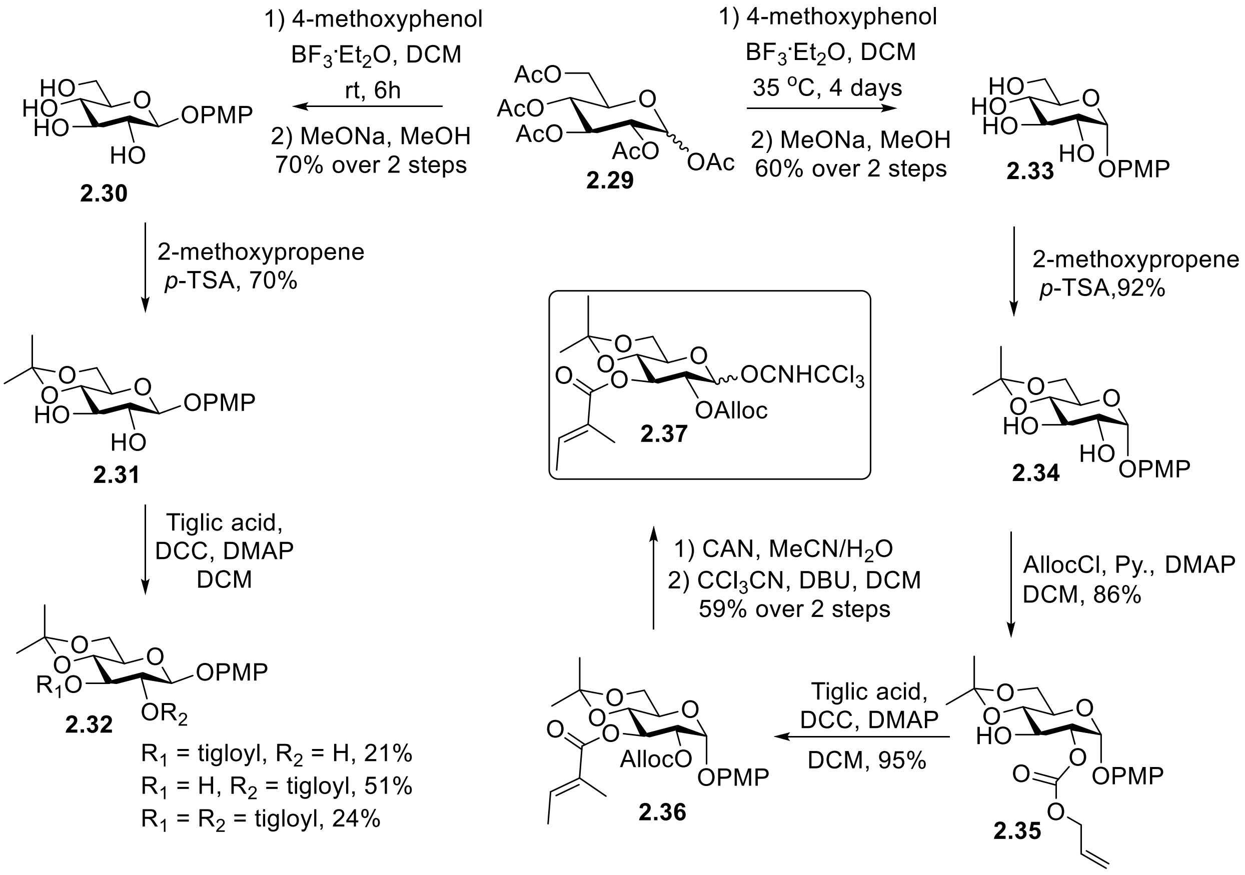
At this point, a glycosylation coupled the donor and aglycon acceptor to furnish fucoside **2.26**. A global deacylation then gave triol **2.27**. We then greatly shortened the synthesis by exploiting the difference in reactivity of the three hydroxyl groups. The reactivity of secondary hydroxyl groups in the galacto configuration had been previously established in the literature[60] as 3-OH > 2-OH > 4-OH. We anticipated this trend would hold true with 6-deoxy galactopyranose (D-fucose) as well and the 3-OH would be the most nucleophilic due to hydrogen bonding with the axial 4-OH. To our delight, we obtained regioselective silylation at the 3-OH position of the triol in good yield (71%). We followed this trend in regioselectivity and assumed we could directly use diol **2.28** as the fucoside acceptor for a regioselective glycosylation at the more reactive equatorial 2-OH position of fucose without having to first protect the 4-OH.


OAc
AcO
AcO
O
OCNHCCl3
2.25
OH
2.4
TMSOTf, 4A MS
DCM, 74%
OAc
AcO
O
O
OAc
2.26
MeOH-MeONa
75%
OH
HO
O
O
OH
2.27
TBSCl, Imidazole
DMF
71%
OH
TBSO
O
O
OH
2.28

Scheme 2-9. Updated Synthesis of Fucoside Acceptor

Synthesis of the Glucosyl Donor

With the successful completion of the fucoside acceptor, we then turned our attention to its coupling partner, the glucosyl donor. Before the glycosylation, we sought to already have the tiglate group established at the 3-OH position and have the remaining hydroxyl groups appropriately protected as well as a 2-OH protecting group that would serve as a directing group for the glycosylation through neighboring group participation so that we could form the requisite *β*-glycosidic linkage. With these requirements in mind we planned glucosyl donor **2.37**. The synthesis commenced with peracetylated D-glucopyranose. It is known for *β*-D-glucopyranosides that esterification reactions favor the 3-OH position over the 2-OH position[60], so we first synthesized *p*-methoxyphenyl (PMP)- *β*-D-glucopyranoside to try to exploit this difference in reactivity

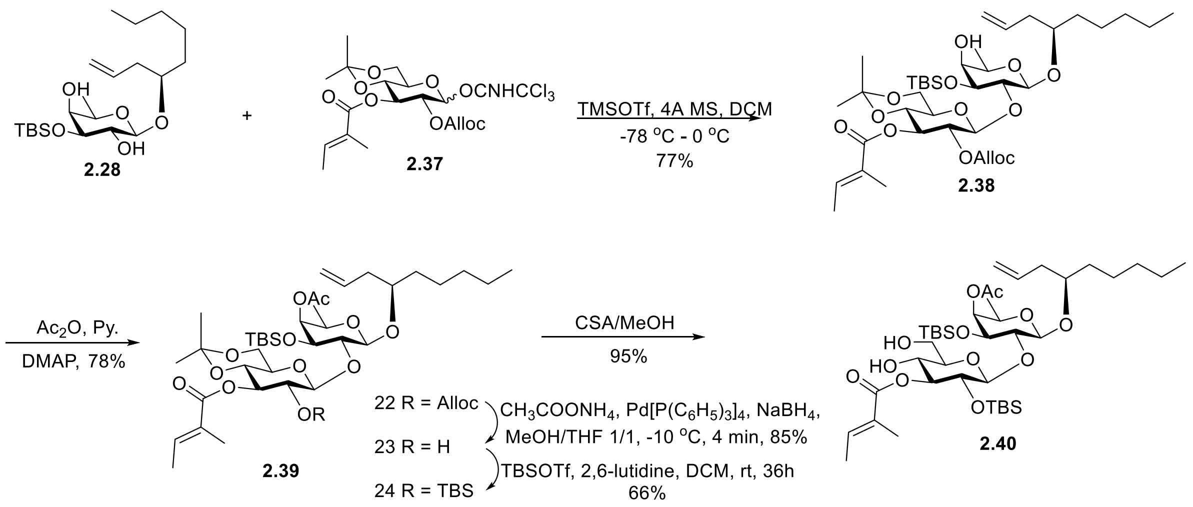

1) 4-methoxyphenol
$BF_3 \cdot Et_2O$, DCM
rt, 6h
2) MeONa, MeOH
70% over 2 steps
1) 4-methoxyphenol
$BF_3 \cdot Et_2O$, DCM
35 °C, 4 days
2) MeONa, MeOH
60% over 2 steps
2.30
2.29
2.33
2-methoxypropene
p-TSA, 70%
2-methoxypropene
p-TSA,92%
2.31
2.37
2.34
Tiglic acid,
DCC, DMAP
DCM
1) CAN, MeCN/H_2O
2) CCl_3CN, DBU, DCM
59% over 2 steps
AllocCl, Py., DMAP
DCM, 86%
2.32
R_1 = tigloyl, R_2 = H, 21%
R_1 = H, R_2 = tigloyl, 51%
R_1 = R_2 = tigloyl, 24%
Tiglic acid,
DCC, DMAP
DCM, 95%
2.36
2.35

Scheme 2-10. Synthesis of the Glucosyl Donor

To make the PMP-glucoside **2.30**, the peracetylated glucose was reacted with 4-methoxylphenol in the presence of a Lewis acid and stirred for six hours at ambient temperature. The acetyl groups were then removed using sodium methoxide in methanol. The 4-OH and 6-OH positions could then be protected by isopropylidenation. At this point, a Steglich esterification could be attempted to try to regioselectively install the tiglate at the 3-OH position relying on the reactivity trend mentioned above. To our dismay, we found that the reaction favored the 2-OH position in a ratio of 2.4:1. Since esterification reactions should favor the 2-OH position in α-D-glucopyranosides[60], we turned our attention to making the α-anomer of the previously mentioned compound. To synthesize this molecule, we followed the same reaction sequence but by relying on the anomeric effect and leaving the glycosylation for four days at an elevated temperature, we were able to obtain the anomer. Using compound **2.34**, we now tried to regioselectively install the Alloc protecting group at the 2-OH position and much to our delight, found that we exclusively obtained the desired regioisomer. We chose the Alloc group for this position due to the fact that it should direct our glycosylation to the desired anomer and could be removed under mild conditions. Acylation of the remaining 3-OH with tiglic acid successfully yielded the glucosyl donor precursor **2.36**. Cleavage of the PMP group in a solution of ceric ammonium nitrate (CAN) gave the hemiacetal which was subsequently converted to the trichloroacetimidate donor **2.37** upon treatment with trichloroacetonitrile and DBU.

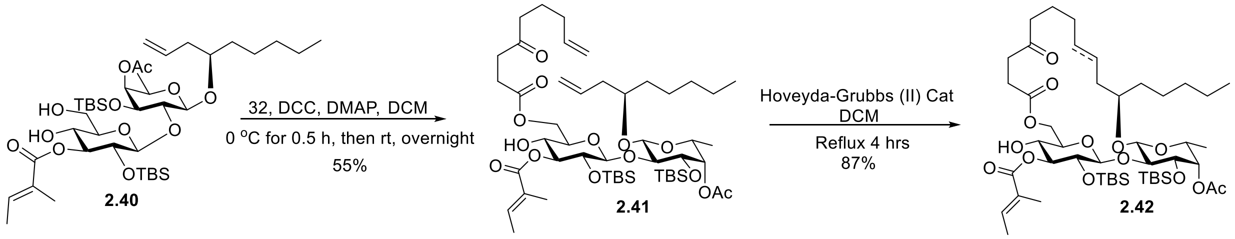
[redacted] Completion of C11 Epimer Synthesis

With all of the fragments complete, the disaccharide intermediate could finally be prepared. Fucoside **2.28** and glucosyl donor **2.37** were coupled by a regio- and stereoselective glycosylation to exclusively form the key β-(1 → 2)-linked disaccharide intermediate **2.38**, as confirmed by ^{1}H, COSY, and HSQC NMR spectra. The 4-*O*-fuc*p* acetyl group was then installed followed by deisopropylidenation with camphorsulfonic acid (CSA) in methanol. The Alloc group could then be removed and regioselectively replaced with TBS which would be undisturbed by the RCM/hydrogenation step.


TBSO
OH
O
OH
2.28
+
O
O
O
O
OCNHCCl$_3$
OAlloc
2.37
TMSOTf, 4A MS, DCM
-78 °C - 0 °C
77%
OH
TBSO
O
O
O
OAlloc
2.38
Ac$_2$O, Py.
DMAP, 78%
OAc
TBSO
OR
2.39
22 R = Alloc
23 R = H
24 R = TBS
CH$_3$COONH$_4$, Pd[P(C$_6$H$_5$)$_3$]$_4$, NaBH$_4$,
MeOH/THF 1/1, -10 °C, 4 min, 85%
TBSOTf, 2,6-lutidine, DCM, rt, 36h
66%
CSA/MeOH
95%
OAc
HO
TBSO
HO
OTBS
2.40

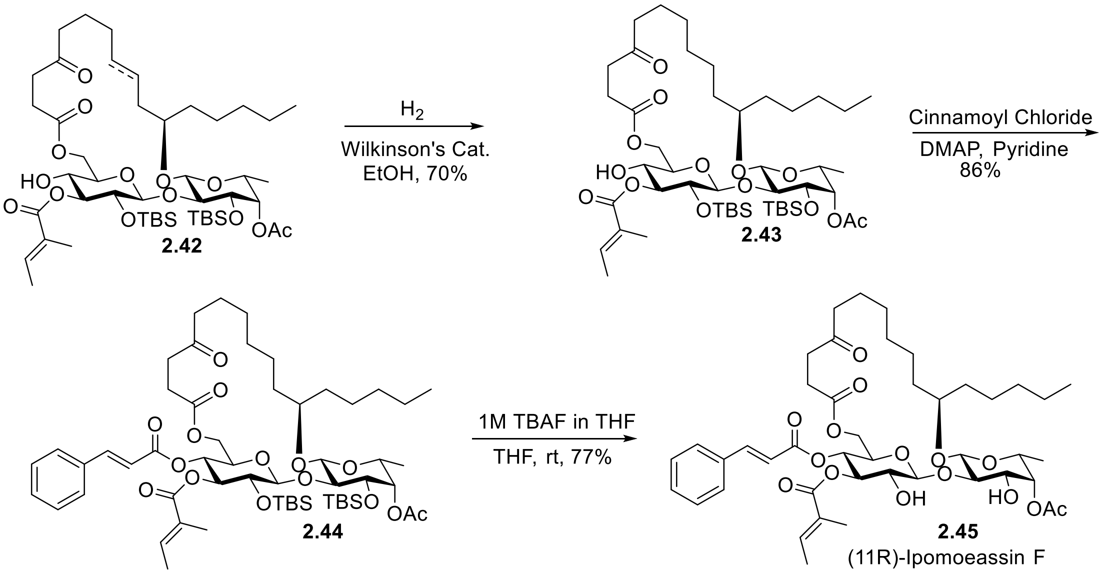
Scheme 2-11. Synthesis of Disaccharide Intermediate

After completion of key disaccharide intermediate **2.40**, the remaining portion of the aglycon was regioselectively introduced to the 6-*O*-glc*p* position via Steglich esterification to form the RCM precursor **2.41**. RCM with Hoveyda-Grubbs second generation catalyst was then used to smoothly close the ring.


OAc
HO
TBSO
HO
OTBS
2.40
32, DCC, DMAP, DCM
0 °C for 0.5 h, then rt, overnight
55%
O
O
HO
OTBS
TBSO
OAc
2.41
Hoveyda-Grubbs (II) Cat
DCM
Reflux 4 hrs
87%
HO
OTBS
TBSO
OAc
2.42

Scheme 2-12. Synthesis of Ring-Closed Intermediate

To complete the synthesis of the epimer, the resulting olefin from the RCM step was reduced using hydrogenation with Wilkinson’s catalyst leaving the unsaturated tiglate moiety intact. Then, in the penultimate step, cinnamate was introduced followed by a final deprotection in 1M TBAF in THF to yield, for the first time, the 11*R*-epimer of ipomoeassin F over 17 steps of the longest linear sequence, from commercially available starting materials.


H2
Wilkinson's Cat.
EtOH, 70%
Cinnamoyl Chloride
DMAP, Pyridine
86%
1M TBAF in THF
THF, rt, 77%
2.42
2.43
2.44
2.45
(11R)-Ipomoeassin F
OTBS
TBSO
OAc
HO
OH

Scheme 2-13. Completion of the 11*R*-Epimer of Ipomoeassin F

Cytotoxicity of the 11*R*-Epimer of Ipomoeassin F

After synthesizing the 11*R*-epimer of ipomoeassin F, the cytotoxicity was evaluated across a number of cancer cell lines in an effort to determine the role the stereochemistry of the aglycon plays in ipomoeassin F's biological activity. The cytotoxicity was obtained by using the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) colorimetric assay with Taxol as the positive control. The results were compared with those obtained from the synthetic sample of ipomoeassin F. The cytotoxicity was evaluated against a total of seven cell lines. Five of these (MDA-MB-231, MCF7, HeLa, U937, and Jurkat) are human tumor cell lines, one was an immortalized normal human mammary epithelial cell line (MCF-10A) and the last one was an immortalized normal mouse embryo fibroblast cell line. Table **2-1** below summarizes the results of the assay, showing the concentrations required for 50% cell death (IC_{50} values) when compared to the vehicle-treated negative control (IC_{50} values). Although the 11*R* epimer was still quite toxic to the cells, it was significantly (20-80 fold) less potent than ipomoeassin F in its native configuration, illustrating the importance of the molecule’s overall conformation to its biological activity.

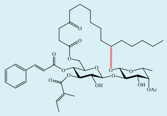
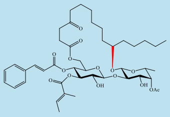
Code	Structures	IC_{50} (231, nM)	IC_{50} (MCF7, nM)	IC_{50} (HeLa, nM)	IC_{50} (U937, nM)	IC_{50} (Jurkat, nM)	IC_{50} (MCF-10A, nM)	IC_{50} (3T3, nM)
	Taxol	5.1	11.0	1.6	2.7	2.8	41.0	344.0
ZIF (IpomF)		6.5	43.7	11.7	5.4	6.1	4.1	16.8
BIF (R IpomF)		120.2	830.7	440.2	190.1	325.1	159.2	1370.5

Table 2-1. Cell Cytotoxicity of Ipm F and Epimer

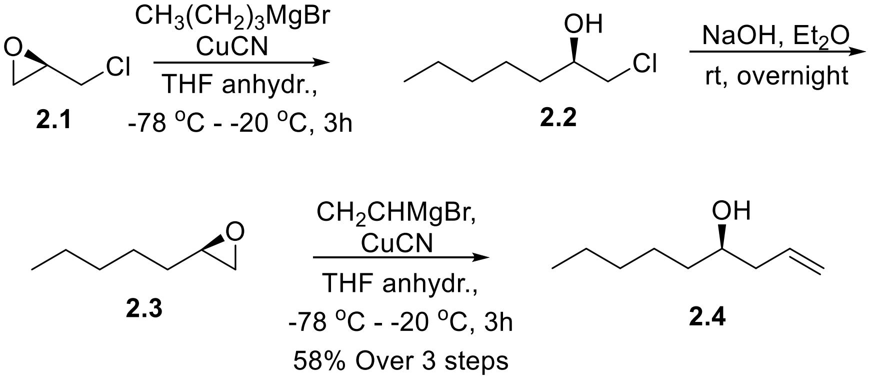
[redacted] Experimental Procedures

Reactions were carried out in oven-dried glassware. All reagents were purchased from commercial sources and were used without further purification unless specified. Except stated otherwise, all reactions were carried out under a nitrogen atmosphere and monitored by thin layer chromatography (TLC) using Silica Gel GF254 plates (Agela) with detection by charring with 5% (v/v) H2SO4 in EtOH or by visualizing in UV light (254 nm). Column chromatography was performed on silica gel (230–450 mesh, Sorbent). The ratio between silica gel and crude product ranged from 100 to 50:1 (w/w). NMR data were collected on a Bruker 300 or 400 MHz NMR spectrometer and a Bruker 300 or 400 MHz system. 1H NMR spectra were obtained in deuterochloroform (CDCl3) with chloroform (CHCl3, δH = 7.27 for 1H) as an internal reference. 13C NMR spectra were proton decoupled and were in CDCl3 with CHCl3 (δC = 77.0 for 13C) as an internal reference. Chemical shifts are reported in ppm (δ). Data are presented in the form:

chemical shift (multiplicity, coupling constants, and integration). 1H data are reported as though they were first order. The errors between the coupling constants for two coupled protons were less than 0.5 Hz, and the average number was reported. Proton assignments, when made, were done so with the aid of COSY NMR spectra. For some compounds, HSQC and HMBC NMR were also applied to assign the proton signals. Optical rotations were measured on an Autopol III Automatic Polarimeter at 25 ± 1 °C for solutions in a 1.0 dm cell. High resolution mass spectrum (HRMS) and were acquired in the ESI mode.

[redacted] Synthesis of the Epimer Aglycon

[redacted] Preparation of (4R)-non-1-en-4-ol



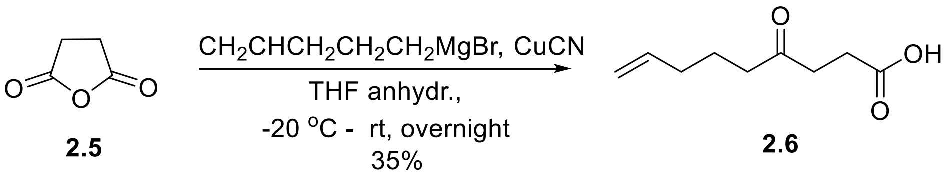
(2*R*)-1-chloro-2-heptanol **2.2**. A mixture of Mg (4.08 g, 144.4 mmol), catalytic I_2 and dry THF (120 mL) were heated to reflux (68-70 °C). While heating, 0.5 mL of bromobutane was added to the mixture. One the refluxing temperature was reached, the remaining bromobutane (17.4 mL, 144.4 mmol) was added dropwise to the mixture under a nitrogen atmosphere. After all the Mg had been consumed to form the Grignard reagent the solution was cooled to RT. The butyl magnesium bromide was added using an addition funnel to a solution of (*R*)-epichlorohydrin **2.1** (10.16 g, 130.3 mmol) and CuCN (1.17 g, 116.0 mmol) at -78 °C over 1 hr.

The reaction was slowly warmed to -20 °C over 3-4 hrs. The reaction was quenched with sat. aq. NH_4Cl (200 mL) and the solvent removed under reduced pressure. The organic layer was extracted with Et_2O (250 mL x 2), dried over Na_2SO_4, filtered, and solvent carefully removed under reduced pressure. Compound **2.2** was taken to the next step without further purification. ^1H NMR (300 MHz, $CDCl_3$) δ_H 3.80 (m, 1H, 2 C*H*), 3.49 (dd, *J* = 6.12 Hz, 1H Cl-CH_2), 2.27 (m, 1H), 1.52 (m, 2H), 1.31 (m, 6H), 0.89 (t, *J* = 6 Hz, 3H, –CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 71.5 (–CH_2), 50.6 (–CH_2), 34.3 (–CH_2), 31.7 (–CH_2), 25.2 (–CH_2), 22.6 (–CH_2), 14.0 (–CH_3).[61]

2-pentyl-(2*R*)-oxirane **2.3**. NaOH (36.0 g, 361.2 mmol) was added to a solution of the crude *α*-chloro alcohol **2.2** (18.14 g, 120.4 mmol) at RT and allowed stirred for 4-5 hrs. The reaction was monitored by TLC (silica, Hex-EtOAc 4:1, R_f = 0.74). Upon completion the reaction was poured into ice water and extracted with Et_2O (200 mL x 3). The organic layers were combined, dried over Na_2SO_4, filtered, and the Et_2O was removed under reduced pressure. The epoxide **2.3** was used directly in the next step without further purification. ^1H NMR ($CDCl_3$, 400 MHz) δ_H 2.94–2.88 (m, 1 H), 2.75 (dd, *J* = 5.0, 4.0, Hz, 1H), 2.46 (dd, *J* = 5.0, 2.8 Hz, 1H), 1.56–1.28 (m, 8H), 0.90 (m, 3H, –CH_3).^{13}C NMR (100 MHz, $CDCl_3$) δ_C 195.6 (O–C–O), 64.2 (O–CH_2), 32.2(–CH_2), 31.3 (–CH_2), 25.4 (–CH_2), 22.6 (–CH_2), 14.1 (–CH_3).[62,63]

(4*R*)-nonen-4-ol **2.4**. Vinylmagnesium bromide (175 mL, 109.4 mmol, 0.7 M in THF) was added dropwise at -78 °C to a solution of the crude epoxide **2.3** (9.61 g, 66.6 mmol), CuCN (845 mg, 66.6 mmol), and dry THF (200 mL). The reaction was kept at -78 °C for 0.5 hrs and slowly warmed to 0 °C over 3-4 hrs. The reaction was quenched with sat. aq. NH_4Cl (150 mL) and the THF removed under reduce pressure. The organic layer was extracted with Et$_2$O (225 mL x 3) and the combined organic layers were washed with brine (200 mL). The organic layer was dried over Na$_2$SO$_4$, filtered, and solvent removed under reduced pressure. The oil was purified by column chromatography (silica, Hex-EtOAc, 10:1 → 6:1) to give the alcohol **2.4** in 64% (12.12 g) from (*R*)-epichlorohydrin. ^{1}H NMR (300 MHz, CDCl$_3$) δ_H 5.84 (dd, *J* =17.2, 10.2, 7.1 Hz, 1H, *H*C=), 5.19–5.09 (m, 2H, =C*H*$_2$), 3.65 (br, s, 1H, C–O*H*), 2.37–2.25 (m, 1H, *H*C–O), 2.20–2.07 (m, 2H), 1.67–1.56 (m, 2H), 1.53–1.21(m, 8H), 0.89 (t, *J* = 6.6 Hz, 3H, –C*H*$_3$). ^{13}C NMR δ_C (75 MHz, CDCl$_3$) δ_C 134.9 (=CH), 118.0 (H$_2$C=), 70.7 (C–H), 41.9 (–CH$_2$), 36.8 (–CH$_2$), 31.8 (–CH$_2$), 25.3 (–CH$_2$), 22.6 (–CH$_2$), 14.0 (–CH$_3$).[64–66]

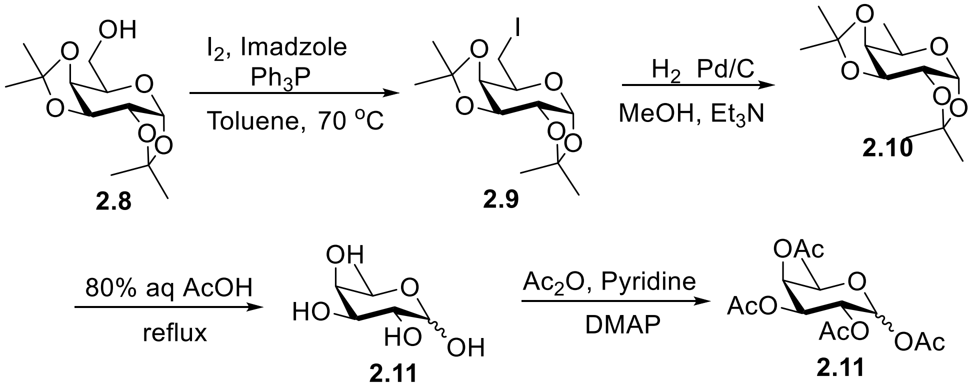
[redacted] Preparation of 4-oxo-8-nonenoic acid



4-oxo-8-nonenoic acid **2.6**. Mg (1.64 g, 6.8 mmol), I$_2$ (trace), and 5-bromopentene **X** (few drops, initiate the Grignard reaction) dry THF (100 mL) were combined, then heated to reflux under a N$_2$ atmosphere. Then 5-bromopentene **2.5** (8.1 mL, 67.1 mmol) was added to the reaction mixture dropwise over 30 mins and continued to heat at reflux for 2 hrs (trace amount of Mg). The Grignard reagent was cooled to RT, while a solution of succinic anhydride (7.35 g, 73.8 mmol) in THF (60 mL) was cooled to 0°C. After cooling to RT, the Grignard reagent was added dropwise (1 hr.) to the succinic anhydride and THF, then slowly warmed to RT overnight. TLC showed the reaction complete (Hex:EtOAc:AcOH, 79.5:20:0.5). 1 M HCl (75 mL) quenched the reaction and the mixture was stirred for 10 mins. The THF was then removed under reduced pressure. The aqueous layer was extracted with DCM (75 mL x 2) then acidified with conc. HCl to a pH of 2-3. The aqueous layer was extracted with DCM (40 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to dryness under reduced pressure. Purification by column chromatography gave the acid **2.6** in 32% yield (silica, Hex–EtOAc–AcOH 100:0:0→75:25:0.5). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.81-5.71 (m, 1H), 5.04-4.97 (m, 2H), 2.72 (t, 2H, *J* = 6.4 Hz), 2.63 (t, 2H, *J* = 6.4 Hz), 2.46 (t, 2H, *J* = 7.2), 2.05 (t, 2H, *J* = 6.0 Hz), 1.70 (app. qui., 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 208.7 (C=O), 178.1, 137.8 (C=C), 115.9 (C=C), 41.7, 36.8, 32.9, 27.7, 24.7.[67,68]

[redacted] Synthesis of the Fucoside Acceptor

[redacted] Preparation of *D*-Fucose



1,2:3,4-bis-*O*-(1-methylethylidene)-6-deoxy-6-iodo-*α*-D-galactopyranose **2.9**. To a 1L RBF was added toluene (500 mL) and diisopropylidene-galactose **2.8** (52.28 g, 200.8 mmol), PPh_3 (63.21 g, 241.0 mmol), and imidazole (49.22 g, 723.1 mmol) at RT. Then I_2 (63.21 g, 241.0 mmol) was added to the reaction mixture and allowed to stir at 80 °C overnight as the reaction turned a dark brown color. After completion of the reaction (silica, Hex-EtOAc 2:1, R_f = 0.76), the reaction mixture was quenched with MeOH (10 mL) and the resulting solution was concentrated to a residue. The reaction mixture was filtered through a pad of Celite and a sat. aq. solution of $Na_2S_2O_3$ was added until the slurry turned almost clear (yellow). The aqueous layer was extracted with DCM (400 mL x 2), dried over Na_2SO_4, and the solvent evaporated under reduced pressure. The syrup was purified by column chromatography (silica, Hex-EtOAc 5:1→3:1) to give **2.9** in 70% (52.47 g). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 5.54 (d, *J* = 5.1 Hz, 1H, 1-H-Glc*p*), 4.61 (dd, *J* = 7.9, 2.5 Hz, 1H), 4.41 (dd, *J* = 7.9, 1.8 Hz, 1H), 4.30 (dd, *J* = 5.1, 2.5 Hz, 1H), 3.95 (td, *J* = 7.0, 1.8 Hz, 1H), 3.32 (dd, *J* = 10.1, 6.9 Hz, 1H), 3.20 (dd, *J* = 10.1, 7.2 Hz, 1H), 1.55 (s, 3H, $–CH_3$), 1.45 (s, 3H, $–CH_3$), 1.36 (s, 3H, $–CH_3$), 1.37 (s, 3H, $–CH_3$), 1.33 (s, 3H, $–CH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 109.6 (O–C–O), 108.8 (O–C–O), 96.8 (C-1), 71.7, 71.1, 70.6, 69.1, 26.1 ($–CH_3$), 26.0 ($–CH_3$), 25.1 ($–CH_3$), 24.6 ($–CH_3$).[69,70]

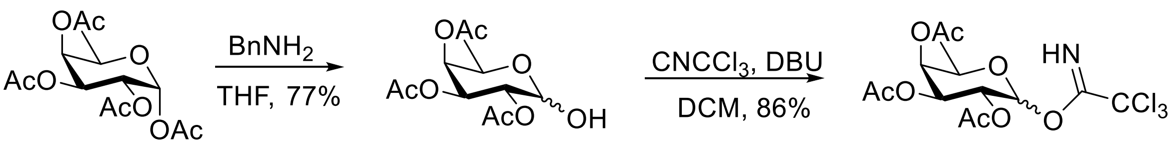
1,2:3,4-bis-*O*-(1-methylethylidene)-6-deoxy-*α*-D-galactopyranose **2.10**. Pd/C (10 g) was added to a solution of the iodo intermediate **2.9** (31.23 g, 84.3 mmol), DIEA (21.9 mL, 126.5 mmol), and MeOH (150 mL). Under a H_2 atmosphere, the pressure was increased to 80 pounds per square inch (PSI) and allowed to shake at RT overnight (Parr shaker). TLC (silica, Hex-EtOAc 2:1) showed the reaction was complete and the reaction was quenched with NEt_3 and filtered through a pad of Celite. The crude product **2.10** was used directly in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.57 (d, *J* = 5.2 Hz, 1H, H-1-Fuc*p*), 5.48 (dd, *J* = 8.1 Hz, 2.8 Hz, 1H, H-3-Fuc*p*), 4.26 (dd, *J* = 5.3 Hz, 2.4 Hz, 1H, H-2-Fuc*p*), 4.06 (dd, *J* = 1.6 Hz, 8.0 Hz, 1H, H-4-Fuc*p*), 3.89 (ddd, 1H, H-5-Fuc*p*), 1.50 (s, 3H, $–CH_3$), 1.44 (s, 3H, $–CH_3$), 1.33 (s, 3H, $–CH_3$), 1.30 (s, 3H, $–CH_3$), 1.23 (d, *J* = 6.4 Hz, 3H, $–CH_3$). ^{13}C NMR (75 MHz, CDCl3) δ_C 109.0, 108.3, 96.6, 73.5, 70.9, 70.4, 63.5, 26.0 • 2, 24.9, 24.4, 15.9.[71,72]

6-deoxy-*α*,*β*-D-galactopyranose **2.11**. The crude intermediate **2.10** (44 g) was dissolved in 80% acetic acid (400 mL) and heated to reflux (125 °C). The reaction was allowed to reflux overnight at which point TLC (silica, Hex-EtOAc 6:1, $R_f = 0.11$) indicated the reaction was finished. The reaction was cooled to RT, then co-evaporated with toluene (200 mL x 3). The slurry was diluted with sat. aq. $NaHCO_3$ (300 mL) and extracted with DCM (300 mL · 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to dryness. The crude D-Fuc*p* **2.11** was used directly in the next step without further purification. ^{1}H NMR (400 MHz, D_2O) δ_H 5.05 (d, *J* = 3.8 Hz, 1H, 1-H-Fuc*p*), 4.41 (d, *J* = 7.9 Hz, 1H, H-1-Fuc*p*), 4.06 (q, *J* = 6.7 Hz, 1H, H-5-Fuc*p*), 3.74-3.64 (m, 4H, H-2-Fuc*p*, H-3-Fuc*p*, H-4-Fuc*p*, H-5-Fuc*p*), 3.59 (d, *J* = 2.8, 4-OH-Fuc*p*), 3.50 (dd, *J* = 10.1 Hz, 3.4 Hz, 3-OH-Fuc*p*), 3.31 (dd, *J* = 10.1 Hz, 7.9 Hz, 2-OH-Fuc*p*), 1.10 (d, *J* = 6.3 Hz, 3H, H-6-Fuc*p*), 1.07 (d, *J* = 6.4 Hz, 3H, H-6-Fuc*p*).[73,74]

1,2,3,4-*O*-tetracetate-6-deoxy-*α*,*β*-D-galactopyranose **2.12**. The crude D-Fuc*p* **2.11** (32.1 g, 195 mmol) was dissolved in acetic anhydride (75 mL) and pyridine (140 mL) and cat. DMAP was added. The reaction was allowed to stir at RT overnight, while turning a deep orange color. TLC (silica, Hex-EtOAc 2:1, $R_f = 0.61$) showed the reaction to be complete and the solution was co-evaporated with toluene (200 x 3). To the residue was added sat. aq. $NaHCO_3$ (300 mL) which was extracted with DCM (300 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and solvent removed under reduce pressure. The residue was purified by column chromatography (silica, Hex-EtOAc, 4:1→3:1) to the peracetylated D-Fuc*p* **2.12** in 48% yield over three steps from **2.9**. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.30 (d, *J* = 3.0 Hz, 1H), 5.65 (d, *J* = 8.5 Hz, 1H), 5.30-5.23 (m, 5H), 5.05 (dd, *J* = 10.5, 3.5 Hz, 1H), 4.24 (q, *J* = 6.5 Hz, 1H), 3.93 (q, *J* = 6.5 Hz, 1H), 2.15-1.95 (series of s, 3H, $–CH_3$), 1.19 (d, *J* = 6.5 Hz, 3H, $–CH_3$), 1.12

(d, J = 6.5 Hz, 3H, –CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 170.48, 170.46, 170.11, 169.94, 169.90, 169.4, 169.1, 166.4, 92.2, 89.9, 71.3, 70.6, 70.3, 70.0, 68.0, 67.9, 67.3, 66.5, 22.1, 20.9, 20.8, 20.63, 20.60, 20.57, 20.53, 15.92, 15.91.[75–77]

[redacted] Preparation of the Fucosyl Donor



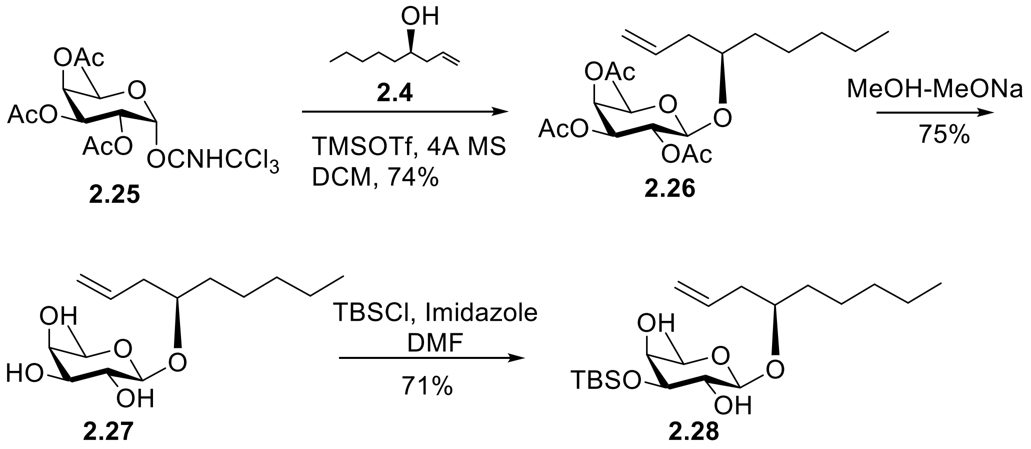
2.12 **2.24** **2.25**

2,3,4-*O*-triacetate-6-deoxy-*α*,*β*-D-galactopyranose **2.24**. The peracetylated D-Fuc*p* **2.12** (10.55 g, 31.7 mmol) was dissolved in dry THF (150 mL) and $BnNH_2$ (4.6 mL, 47.6 mmol). The reaction was stirred at RT overnight at which point TLC showed the reaction to be complete (silica, Hex-EtOAc 1:1, R_f = 0.54, 0.49). The THF was removed under reduced pressure, the residue diluted with DCM (200 mL), washed with 5% HCl, then sat. aq. $NaHCO_3$. The organic layer was collected, dried over $NaSO_4$, filtered, and concentrated to dryness. The syrup was purified by column chromatography (silica, Hex-EtOAc, 2:1→1:2) to give the *α*,*β*-hemiacetal D-fucose **2.24** in 77% (7.15 g) and carried directly to the next step.[78]

1-(2,2,2-trichloroethanimidate)-2,3,4-triacetate-6-deoxy-*α*,*β*-D-galactopyranose **2.25**. Trichloroacetonitrile (12.8 mL, 128 mmol) and DBU (0.68 mL, 3.2 mmol) were added to a solution of DCM (100 mL) and the hemiacetal **2.24** (9.30 g, 32.0 mmol) at RT. The reaction was stirred at RT for 3-4 hrs, when TLC (silica, Hex-EtOAc 1:1, R_f = 0.71 and 0.77) indicated that the starting material had been consumed. The reaction was quenched with NEt_3 (0.5 mL) and the

DCM evaporated under reduced pressure. The residue was purified by column chromatography (silica, Hex-EtOAc, 4:1→1:1, 0.1% NEt_3) to give the *α*,*β*-Schmidt donor **2.25** in 86% yield (10.6 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.64 (s, 1H), 6.59 (d, *J* = 3.5 Hz, 1H), 5.51-5.35 (m, 3 H), 4.43-4.37 (br q, J= 6.6 Hz, 1 H), 2.22, 2.05, and 2.04 (3 s, 3H), 1.15 (d, *J* = 6.6 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 170.4-170.0 · 3, 161.1, 93.9, 77.2, 70.5, 67.9, 66.9, 67.5, 20.7-20.6 · 3, 15.9.[79]

[redacted] Preparation of the Fucoside Acceptor



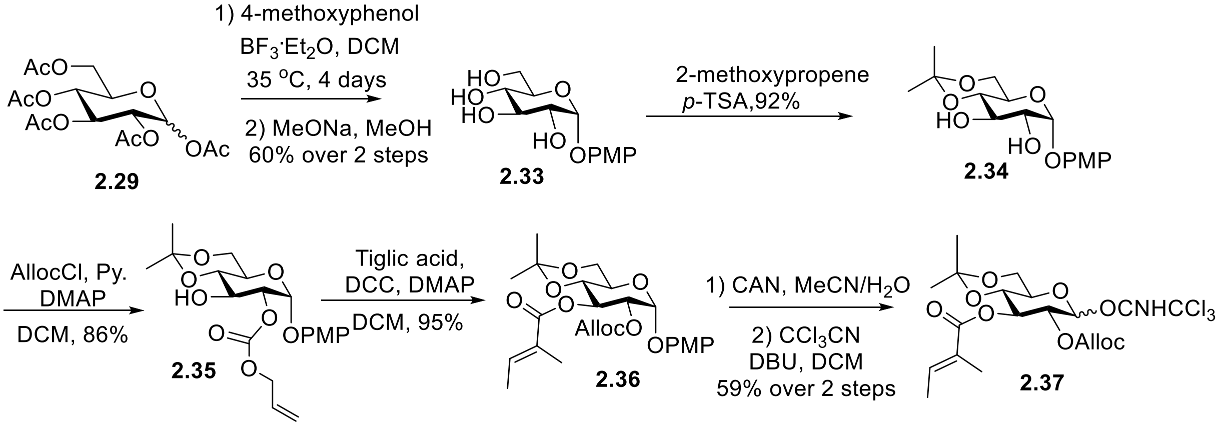
OAc
AcO
AcO
OCNHCCl3
O
2.25
OH
2.4
TMSOTf, 4A MS
DCM, 74%
OAc
AcO
OAc
O
2.26
MeOH-MeONa
75%
OH
HO
OH
2.27
TBSCl, Imidazole
DMF
71%
OH
TBSO
OH
2.28

1-Nonen-4R-yl 2,3,4-Tri-O-acetyl-β-D-fucopyranoside **2.26**. A mixture of acceptor **2.4** (1.32 g, 9.3 mmol), donor **2.25** (4.28 g, 9.8 mmol), and 4 Å molecular sieves (3 g) in anhydrous, redistilled CH_2Cl_2 (120 mL) was stirred under an N_2 atmosphere for 30 min and then cooled to −10 °C. TMSOTf(168 μL, 0.95 mmol) was added to the mixture, and then the reaction mixture was allowed to gradually warm to ambient temperature with the cold bath in place and was stirred for 1 h. TLC (silica, 1:3 EtOAc−hexanes) indicated that the reaction was complete. The reaction mixture was quenched with Et_3N (320 μL) and filtered. The filtrate was evaporated in vacuo to give a residue, which was purified by silica gel column chromatography (silica, EtOAc−hexanes, 1:7 → 1:5) to give compound **2.26** (2.80 g, 74%) as a yellowish syrup. $[\alpha]^{25}_{D}$ +9.7 (*c* 1 CHCl3); ^{1}H NMR (400 MHz, CDCl3) δ 5.88−5.75 (m, 1H, CH2=CHCH2−), 5.25−5.13 (m, 2H, H-4-Fuc*p*, H-2-Fuc*p*), 5.09−4.96 (m, 3H, H-3-Fuc*p*, CH2=CHCH2−), 4.49 (d, *J* = 7.6 Hz, 1H, H-1-Fuc*p*), 3.84−3.74 (m, 1H, H-5-Fucp), 3.65−3.56 (m, 1H, −CH2CHCH2−), 2.51−2.27 (m, 2H), 2.18 (s, 3H, CH3C=O), 2.04 (s, 3H, CH3C=O), 1.99 (s, 3H, CH3C=O), 1.50−1.40 (m, 2H), 1.40−1.23 (m, 6H), 1.24 (d, *J* = 6.4 Hz, 3H, H-6-Fuc*p*), 0.89 (t, *J* = 6.8 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 170.8, 170.3, 169.4, 134.7, 116.9, 101.2, 81.0, 71.5, 70.3, 69.3, 69.0, 39.7, 33.5, 31.9, 24.7, 22.6, 20.8, 20.7, 20.7, 16.1, 14.0. IR (film) *ν* = 2936, 2856, 1755, 1600, 1368, 1254, 1229, 1078; HRMS (ESI) m/z calcd for $C_{21}H_{34}NaO_8$ $[M + Na]^+$ 437.2151, found 437.2148.

1-Nonen-4S-yl β-D-fucopyranoside **2.27**. MeONa (80 mg, 1.48 mmol) was added in one portion to a solution of **2.26** (2.69 g, 6.49 mmol) in MeOH (50 mL) at room temperature. The reaction mixture was stirred at room temperature overnight. TLC (silica, 3:1 EtOAc–hexanes) showed the reaction was complete. Neutralization of the reaction mixture with acidic ion exchange resin (Amberlite IR-120 (H+), Alfa Aesar) and the organic phase was concentrated *in vacuo*. The residue was purified by column chromatography (silica, EtOAc–hexanes, 3:1 → 5:1) gave triol **2.27** (1.37 g, 73%) as a colorless syrup. $[\alpha]_D^{25}$ +2.0° (*c* 1 $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 – 5.78 (m, 1H, CH_2=C*H*-CH_2-), 5.11 – 4.99 (m, 2H, CH_2=CH-CH_2-), 4.25 (d, *J* = 7.6 Hz, 1H, H-1-Fuc*p*), 3.76 – 3.54 (m, 5H, H-2-Fuc*p*, H-3-Fuc*p*, H-4-Fuc*p*, H-5-Fuc*p*, -CH_2-C*H*-CH_2-), 3.90 (br 1H, O*H*), 3.41 (br, 1H, O*H*), 3.24 (br, 1H, O*H*), 2.46 – 2.30 (m, 2H), 1.57 – 1.48 (m, 2H), 1.45 – 1.21 (m, 9H), 0.89 (d, *J* = 6.8 Hz, 3H, H-6-Fuc*p*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.98, 116.75, 102.58, 79.72, 73.94, 71.68, 71.60, 70.47, 39.55, 33.52, 31.88, 24.79, 22.55, 16.36, 14.04; IR (film) *v* = 3381, 2928, 2859, 1639, 1070, 995, 912, 756; HRMS (ESI) *m/z* calcd for $C_{15}H_{28}NaO_5$ $[M + Na]^+$ 311.1834, found 311.1830.

1-Nonen-4S-yl 3-O-tert-butyldimethylsilyl-β-D-fucopyranoside **2.28**. To a cold (0 °C) solution of triol **2.27** (0.36 g, 1.2 mmol) and 1H-Imidazole (0.24 g, 3.5 mmol) in DMF (15 mL) was added *t*-butyldimethylsilyl chloride (0.26 g, 1.7 mmol). The reaction was stirred at 0 °C for 30 min and then was allowed to warm to ambient temperature and stirred for another 2 h. At this point, TLC (silica, 1:9 EtOAc–hexanes) showed the reaction was complete. The reaction mixture was diluted with ether (25 ml), washed with water (3 × 15 mL) and brine (15 mL). The aqueous layer was extracted with ether (25 ml). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (silica, EtOAc–hexanes, 1:3 → 1:2) to afford compound **2.28** (0.36 g, 71%) as a colorless syrup. $[\alpha]_D^{25}$ +7.8° (*c* 1 $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 5.91 – 5.74 (m, 1H, CH_2=C*H*-CH_2-), 5.14 – 4.98 (m, 2H, CH_2=CH-CH_2-), 4.20 (d, *J* = 7.8 Hz, 1H, H-1-Fuc*p*), 3.73 – 3.65 (m, 1H, -CH_2-C*H*-CH_2-), 3.63 (dd, *J* = 9.2, 3.6 Hz, 1H, H-3-Fuc*p*), 3.59 – 3.48 (m, 3H, H-2-Fuc*p*, H-4-Fuc*p*, H-5-Fuc*p*), 2.62 (br, 1H, O*H*), 2.38 – 2.21 (m, 2H), 2.17 (d, *J* = 1.6 Hz, 1H, O*H*), 1.67 – 1.47 (m, 2H), 1.39 – 1.22 (m, 9H), 0.96 – 0.84 (m, 12H), 0.15 (s, 3H, CH_3-Si), 0.13 (s, 3H, CH_3-Si). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.06, 117.37, 102.24, 78.88, 74.86, 72.14, 72.08, 70.00, 38.54, 34.73, 31.81, 25.75(3), 24.73, 22.56, 18.10, 16.37, 14.09, –4.42, –4.97; IR (film) *v* = 3379, 2930, 2856, 1653, 1074, 997, 800, 760; HRMS (ESI) *m/z* calcd for $C_{21}H_{42}NaO_5Si$ $[M + Na]^+$ 425.2699, found 425.2693.

[redacted] Synthesis of the Glucosyl Donor


AcO
AcO
AcO
O
AcO
OAc
2.29
1) 4-methoxyphenol
BF3·Et2O, DCM
35 °C, 4 days
2) MeONa, MeOH
60% over 2 steps
HO
HO
HO
O
HO
OPMP
2.33
2-methoxypropene
p-TSA,92%
O
O
O
HO
HO
OPMP
2.34
AllocCl, Py.
DMAP
DCM, 86%
O
O
O
HO
O
O
O
OPMP
2.35
Tiglic acid,
DCC, DMAP
DCM, 95%
O
O
O
O
O
AllocO
OPMP
2.36
1) CAN, MeCN/H2O
2) CCl3CN
DBU, DCM
59% over 2 steps
O
O
O
O
O
OCNHCCl3
OAlloc
2.37

p-Methoxyphenyl 4,6-*O*-isopropylidene-α-D-glucopyranoside **2.34**. To a cold (0 °C) solution of the penta-*O*-acetyl-β-D-glucopyranose **2.29** (70.0 g, 179 mmol) and *p*-methoxyphenol (33.4 g, 269 mmol) in dry CH_2Cl_2 (800 mL) was added boron trifluoride diethyl etherate (111 mL, 897 mmol) over 30 min. The mixture was then heated to 35 °C and agitated for 4 days, at the end of which time TLC (EtOAc–hexanes, 1:2) indicated that the reaction was complete. The reaction mixture was poured into crushed ice, and the excess boron trifluoride diethyl etherate was neutralized by the careful addition of saturated aqueous $NaHCO_3$ solution. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo to provide a yellowish syrup. The syrup was dried under high vacuum for 2 hours before being dissolved in MeOH (500 mL). Sodium methoxide (2 g) was added to the reaction mixture and stirred at room temperature for 2 hours. The residue was purified by column chromatography (silica, EtOAc–MeOH, 1:20 → 1:5) to afford *p*-methoxyphenyl α-D-glucopyranoside **2.33** (30.8 g, 60% over 2 steps) as a white solid. To a solution of compound **2.33** (28.8 g, 101 mmol) in DMF (200 mL) containing *p*-TsOH·H_2O (0.38 g, 2.0 mmol) was added 2-methoxypropene (11.6 mL, 121 mmol) under nitrogen atmosphere. The resulting mixture was stirred for 6 hours at room temperature until completion (EtOAc–hexanes, 2:1). The reaction was quenched with Et_3N (0.5 mL) and then diluted with EtOAc (400 mL), washed with water (400 mL × 3) and brine (100 mL). The aqueous layer was extracted with EtOAc (400 mL × 2). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica, EtOAc–hexanes, 1:1 → 2:1) to give compound **2.34** (30.2 g, 92%) as a white foam. $[\alpha]_D^{25}$ +124.7° (*c* 1 $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.02 – 6.96 (m, 2H, 2 × Ar*H*), 6.84 – 6.79 (m, 2H, 2 × Ar*H*), 5.41 (d, *J* = 3.6 Hz, 1H, H-1), 4.00 (td, *J* = 9.2, 2.0 Hz, 1H), 3.88 – 3.66 (m, 7H, H-2, H-5, 2 × H-6, -OCH_3), 3.61 (t, *J* = 8.8 Hz, 1H), 3.45 – 3.40 (m, 1H, O*H*), 3.00 – 2.92 (m, 1H, O*H*), 1.52 (s, 3H, (CH_3)$_2$C), 1.44 (s, 3H, (CH_3)$_2$C). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.41, 150.17, 118.40(2), 114.63(2), 99.80, 98.62, 73.43, 72.81, 71.85, 63.99, 62.13, 55.59, 29.01, 19.08.

p-Methoxyphenyl 2-*O*-allyloxycarbonyl-4,6-*O*-isopropylidene-α-D-glucopyranoside **2.35**. Compound **2.34** (20.4 g, 62.5 mmol) was dissolved in CH_2Cl_2 (300 mL) containing pyridine (20 mL, 250 mmol) and DMAP (0.76 g, 6.3 mmol), then under a N_2 atmosphere, allyl chloroformate (7.3 mL, 68.8 mmol) in CH_2Cl_2 (50 mL) was added drop wise to the solution at –35 °C over 30 min. Then the reaction mixture was allowed to gradually warm to 0 °C over 30 min, at the end of which time TLC (silica, 1: 2 EtOAc–hexanes) showed it was complete. Then the reaction mixture was quenched with MeOH (0.5 mL) and washed with 1M HCl (200 mL), saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL). The aqueous layer was extracted with CH_2Cl_2 (200 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica, EtOAc–hexanes, 1:4 → 1:3) to give compound **2.35** (22.1 g, 86%) as a white foam. $[\alpha]_D^{25}$ +153.2° (*c* 1 $CHCl_3$).

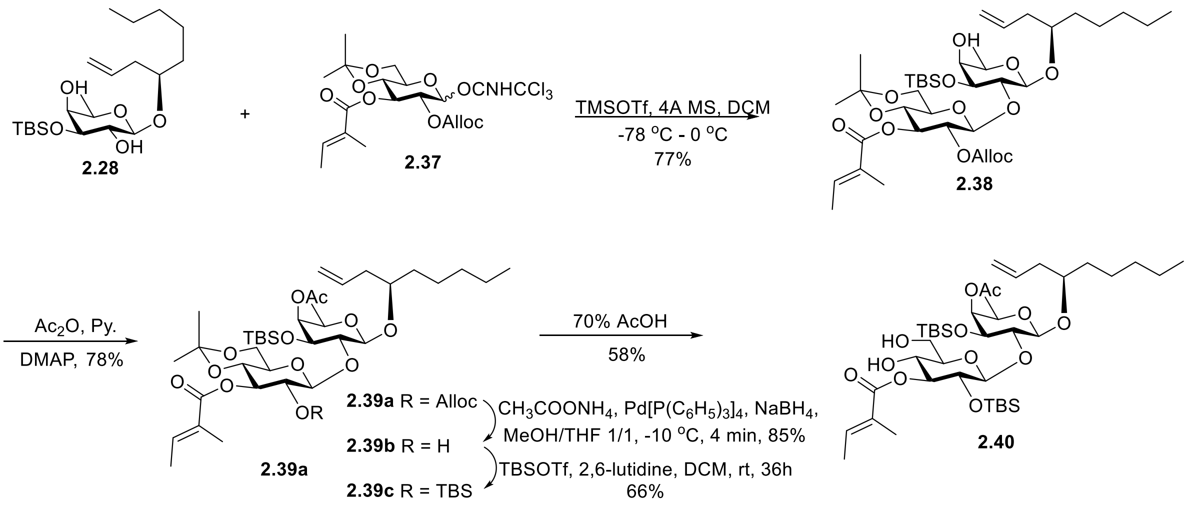
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 – 6.94 (m, 2H, 2 × Ar*H*), 6.85 – 6.77 (m, 2H, 2 × Ar*H*), 5.96 – 5.85 (m, 1H, CH_2=C*H*-CH_2-), 5.65 (d, *J* = 3.6 Hz, 1H, H-1), 5.38 – 5.22 (m, 2H, CH_2=CH-CH_2-), 4.72 (dd, *J* = 9.6, 3.6 Hz, 1H, H-2), 4.66 – 4.59 (m, 2H, CH_2=CH-CH_2-), 4.26 (t, *J* = 9.2 Hz, 1H, H-3), 3.92 – 3.81 (m, 2H, H-5, H-6), 3.81 – 3.74 (m, 4H, H-6, -OCH_3), 3.75 – 3.64 (m, 1H, H-4), 3.04 (br, 1H, O*H*), 1.54 (s, 3H, (CH_3)$_2$C), 1.45 (s, 3H, (CH_3)$_2$C). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.27, 154.43, 150.25, 131.07, 119.19, 118.16(2), 114.54(2), 99.97, 95.83, 76.68, 73.68, 68.92, 68.77, 63.67, 62.05, 55.57, 28.93, 19.06.

p-Methoxyphenyl 2-*O*-allyloxycarbonyl-3-*O*-tigloyl-4,6-*O*-isopropylidene-α-D-glucopyranoside **2.36**. DCC (8.60 g, 41.7 mmol) was added in one portion to a 0 ºC CH_2Cl_2 (100 mL) solution of **2.35** (11.4 g, 27.8 mmol), tiglic acid (4.17 g, 41.7 mmol) and 4-dimethylaminopyridine (0.34 g, 2.78 mmol). The reaction was allowed to warm to ambient temperature and stirred overnight. At this point, TLC (silica, 1:2 EtOAc–hexanes) showed the reaction was complete. The reaction mixture was diluted with ether (100 mL) and hexanes (50 mL), stirred for 20 minutes, then filtered thru a pad of Celite using ether (50 mL) as the eluent and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (silica, EtOAc–hexanes, 1:6 → 1:5) to give **2.36** (13.1 g, 95%) as a colorless syrup. $[\alpha]_D^{25}$ +127.9° (*c* 1 $CHCl_3$). ^{1}H NMR (400 MHz, MeOD) δ 7.05 – 6.99 (m, 2H, 2 × Ar*H*), 6.93 – 6.83 (m, 3H, Me-C*H*-C(Me)-C=O, 2 × Ar*H*), 5.94 – 5.75 (m, 1H, CH_2=C*H*-CH_2-), 5.67 (d, *J* = 3.6 Hz, 1H, H-1), 5.57 (t, *J* = 10.0 Hz, 1H, H-3), 5.29 – 5.15 (m, 2H, CH_2=CH-CH_2-), 4.97 (dd, *J* = 10.0, 3.6 Hz, 1H, H-4), 4.65 – 4.51 (m, 2H, CH_2=CH-CH_2-), 4.01 – 3.79 (m, 4H, H-4, H-5, 2 × H-6), 3.75 (s, 3H, -OCH_3), 3.75 (d, *J* = 4.7 Hz, 3H), 1.86 – 1.78 (m, 6H, CH_3-CH-C(CH_3)-C=O), 1.50 (s, 3H, (CH_3)$_2$C), 1.34 (s, 3H, (CH_3)$_2$C). ^{13}C NMR (100 MHz, MeOD) δ 168.42, 157.02, 155.64, 151.67, 139.55, 132.84, 129.20, 119.40(2), 118.87, 115.73(2), 101.15, 97.66, 75.89, 73.09, 70.83, 69.81, 65.65, 63.06, 56.04, 29.33, 19.38, 14.50, 12.23.

2-*O*-Allyloxycarbonyl-3-*O*-tigloyl-4,6-*O*-isopropylidene-α-D-glucopyranosyl trichloroacetimidate **2.37**. To a solution of compound **2.36** (10.9 g, 22.1 mmol) in acetonitrile (120 mL) and water (30 mL) was added a solution of ceric ammonium nitrate (CAN) (24.3 g, 44.3 mmol) in water (30 mL) over 5 min at -10 ^{o}C. The mixture was stirred for 15 min at the same temperature, at the end of which time TLC (silica, 1:2 EtOAc–hexanes) indicated that the reaction was complete. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc (400 mL × 2). The combined organic phase was dried over Na_2SO_4 and concentrated. The obtained residue was purified by column chromatography (silica, EtOAc–hexanes, 1:4 → 1:2) to afford the desired hemiacetal. To a solution of the obtained hemiacetal in CH_2Cl_2 (100 mL) was added trichloroacetonitrile (8.9 mL, 88 mmol), and 1,8-diazabicyclo[5.4.0]undecene (DBU) (0.33 mL, 2.2 mmol). The mixture was stirred overnight at room temperature and then was concentrated. The residue was purified by column chromatography (silica, EtOAc–hexanes, 1:5 → 1:3) to afford the glucosyl donor **2.37** (6.93 g, 59% over 2 steps) as a colorless syrup. $[\alpha]_D^{25}$ ° +59.6 (*c* 1 $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H, CN*H*CCl_3), 6.90 – 6.83 (m, 1H, Me-C*H*-C(Me)-C=O), 6.57 (d, *J* = 4.0 Hz, 1H, H-1), 5.93 – 5.76 (m, 1H, CH_2=C*H*-CH_2-), 5.61 (t, *J* = 9.6 Hz, 1H, H-3), 5.36 – 5.17 (m, 2H, CH_2=CH-CH_2-), 5.03 (dd, *J* = 9.6, 4.0 Hz, 1H, H-2), 4.65 – 4.54 (m, 2H, CH_2=CH-CH_2-), 4.05 – 3.72 (m, 4H, H-2, H-4, H-5, 2 × H-6), 1.90 – 1.76 (m, 6H, CH_3-CH-C(CH_3)-C=O), 1.49 (s, 3H, (CH_3)$_2$C), 1.41 (s, 3H, (CH_3)$_2$C). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.63, 161.15, 154.17, 138.02, 131.10, 128.03, 118.80, 99.95, 93.56, 73.99, 71.65, 69.01, 68.91, 66.19, 62.02, 28.82, 18.93, 14.44, 12.12.

[redacted] Completion of C11 Epimer Synthesis

[redacted] Preparation of Key Disaccharide Intermediate



2.28
+
2.37
OCNHCCl3
OAlloc
TMSOTf, 4A MS, DCM
-78 °C - 0 °C
77%
2.38
Ac2O, Py.
DMAP, 78%
2.39a
2.39a R = Alloc
2.39b R = H
2.39c R = TBS
CH3COONH4, Pd[P(C6H5)3]4, NaBH4,
MeOH/THF 1/1, -10 °C, 4 min, 85%
TBSOTf, 2,6-lutidine, DCM, rt, 36h
66%
70% AcOH
58%
2.40

1-Nonen-4*S*-yl 2-*O*-allyloxycarbonyl-3-*O*-tigloyl-4,6-di-*O*-isopropylidene-β-D-glucopyranosyl-(1→2)-3-*O*-*tert*-butyldimethylsilyl-β-D-fucopyranoside **2.38**. A mixture of acceptor **2.28** (0.450 g, 1.1 mmol), donor **2.37** (0.540 g, 1.0 mmol), and 4 Å molecular sieves (1 g) in anhydrous, redistilled CH_2Cl_2 (20 mL) was stirred under a N_2 atmosphere for 30 min and then cooled to -60 °C. TMSOTf (38.6 µL, 0.18 mmol) was added to the mixture. Then the reaction mixture was allowed to gradually warm to -20 °C over 1 h, at the end of which time TLC (silica, 1:6 EtOAc–hexanes) showed it was complete. Then the reaction mixture was quenched with Et_3N and filtered. The filtrate was evaporated *in vacuo* to give a residue, which was purified by silica gel column chromatography (silica, EtOAc–hexanes, 1:20 → 1:10) to give compound **2.38** (0.510 g, 66%) as a colorless syrup. $[\alpha]_D^{25}$ –3.9° (*c* 1 $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 – 6.79 (m, 1H, Me-C*H*=C(Me)-C=O), 5.85 – 5.79 (m, 2H, 2 x CH_2=C*H*-CH_2-), 5.34 – 4.99 (m, 6H, 2 × CH_2=CH-CH_2-, H-3-Glu*p*, H-1-Glu*p*), 4.72 (dd, *J* = 9.6, 8.0 Hz, 1H, H-2-Glu*p*), 4.62 – 4.49 (m, 2H, CH_2=CH-CH_2-O-), 4.28 (d, *J* = 7.6 Hz, 1H, H-1-Fuc*p*), 3.97(dd, *J* = 11.2, 5.6 Hz, 1H, H-6-Glu*p*), 3.86 – 3.67 (m, 4H, H-2-Fuc*p*, H-3-Fuc*p*, H-4-Glu*p*, H-6-Glu*p*), 3.68 – 3.59 (m, 1H), 3.56 – 3.47 (m, 2H), 3.31 (m, 1H, H-5-Glu*p*), 2.37 (br, 1H, O*H*), 2.36 (t, *J* = 6.8 Hz, 2H), 1.83 – 1.75 (m, 6H, CH_3-CH-C(CH_3)-C=O), 1.55 – 1.46 (m, 2H), 1.46 (s, 3H), 1.41 – 1.20 (m, 12H), 1.00 – 0.82 (m, 12H), 0.18 (s, 3H, CH_3-Si), 0.11 (s, 3H, CH_3-Si). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.85, 154.19, 137.92, 135.21, 131.42, 128.05, 118.32, 116.53, 1001.12, 99.61, 99.60, 79.94, 77.21, 75.78, 75.72, 72.36, 72.26, 71.83, 69.49, 68.37, 67.15, 62.18, 39.41, 33.45, 32.26, 28.90, 25.92(3), 24.72, 22.87, 18.79, 17.97, 16.47, 14.39, 14.03, 12.06, -4.59(2).

1-Nonen-4*S*-yl 2-*O*-allyloxycarbonyl-3-*O*-tigloyl-4,6-di-*O*-isopropylidene-β-D-glucopyranosyl-(1→2)-4-*O*-acetyl-3-*O*-*tert*-butyldimethylsilyl-β-D-fucopyranoside **2.39**. To a cold (0 °C) solution of compound **2.38** (392.2 mg, 0.509 mmol) and DMAP (6.2 mg, 0.051 mmol) in pyridine (3 mL) was added acetic anhydride (1 mL). The reaction mixture was heated to 60 °C and stirred for an additional 24 h, at the end of which time TLC (silica, 1:6 EtOAc–hexanes) indicated that the reaction was complete. The mixture was concentrated under diminished pressure and then co-evaporated with toluene (2 × 20 mL) to give the crude product. The residue was purified by column chromatography (silica, EtOAc–hexanes, 1:20 → 1:10) to afford compound **2.39a** (321.2 mg, 78%,) as a colorless syrup. $[\alpha]_D^{25}$ –0.6° (*c* 1 $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 – 6.80 (m, 1H, Me-C*H*=C(Me)-C=O), 5.91 – 5.78 (m, 2H, 2 x CH_2=C*H*-CH_2-), 5.33 – 5.02 (m, 6H, 2 × CH_2=CH-CH_2-, H-3-Glu*p*, H-1-Glu*p*), 5.00 (m, 1H, H-4-Fuc*p*), 4.74 (dd, *J* = 9.6, 8.0 Hz, 1H, H-2-Glu*p*), 4.62 – 4.47 (m, 2H, CH_2=CH-CH_2-O-), 4.30 (d, *J* = 7.6 Hz, 1H, H-1-Fuc*p*), 4.01 (dd, *J* = 10.8, 5.2 Hz, 1H, H-6-Glu*p*), 3.92 (dd, *J* = 9.2, 8.0 Hz, 1H, H-2-Fuc*p*), 3.80 – 3.67 (m, 3H, H-3-Fuc*p*, H-4-Glu*p*, H-6-Glu*p*), 3.66 – 3.57 (m 2H), 3.31 (m, 1H, H-5-Glu*p*), 2.35 (br, 2H), 2.11 (s, 3H, CH_3-C=O), 1.82 – 1.72 (m, 6H, CH_3-CH-

C(C*H*$_3$)-C=O), 1.62 – 1.48 (m, 2H), 1.43 (s, 3H, (C*H*$_3$)$_2$C), 1.41 – 1.25 (m, 9H), 1.13 (d, *J* = 6.4 Hz, 3H, H-6-Fuc*p*), 0.98 – 0.82 (m, 12H), 0.12 (s, 3H, C*H*$_3$-Si), 0.09 (s, 3H, C*H*$_3$-Si). ^{13}C NMR (100 MHz, CDCl$_3$) δ 170.80, 166.81, 154.25, 137.93, 135.01, 131.43, 128.04, 118.26, 116.73, 101.56, 99.62, 99.50, 81.02, 77.10, 75.18, 73.54, 73.41, 72.23, 71.96, 68.86, 68.35, 67.20, 62.26, 39.42, 33.66, 32.30, 28.91, 25.82(3), 24.88, 22.91, 20.94, 18.80, 17.71, 16.60, 14.39, 14.23, 12.00, -4.22, -4.95.

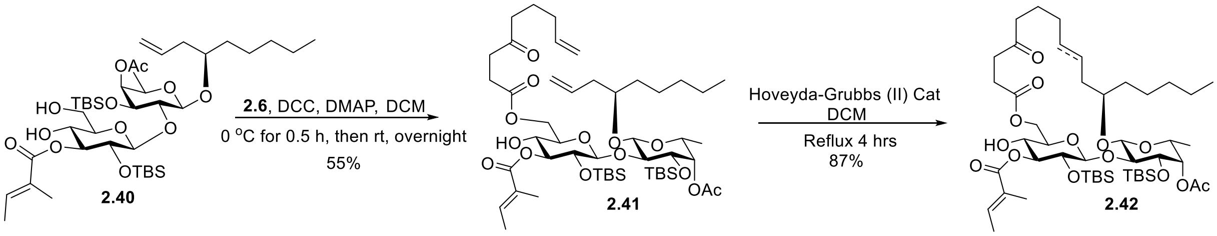
1-Nonen-4*S*-yl 3-*O*-tigloyl-4,6-di-*O*-isopropylidene-β-D-glucopyranosyl-(1→2)-4-*O*-acetyl-3-*O*-*tert*-butyldimethylsilyl-β-D-fucopyranoside **2.39b**. To a cooled (-10 °C) solution of compound **2.39a** (449.8 mg, 0.55 mmol) in 1:1 MeOH–THF (15 mL) was added CH_3COONH_4 (426.8 mg, 5.53 mmol). With vigorous stirring, $Pd[P(C_6H_5)_3]_4$ (25.6 mg, 0.02 mmol), and $NaBH_4$ (31.2 mg, 0.82 mmol) was added in 3 portions immediately one after another. Four minutes after the addition of the second portion of $NaBH_4$, TLC (EtOAc–hexanes, 1:6) indicated that the reaction was complete. The reaction mixture was concentrated under diminished pressure, the residue was dissolved in CH_2Cl_2 (20 mL) and washed with water (10 mL), then the organic layer was dried over Na_2SO_4. Evaporation and purification by column chromatography (silica, EtOAc–hexanes, 1:10) afforded compound **2.39b** (343.2 mg, 85%). $[\alpha]_D^{25}$ –1.5° (*c* 1 CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.90 – 6.80 (m, 1H, Me-C*H*=C(Me)-C=O), 5.93 – 5.79 (m, 1H, CH$_2$=C*H*-CH$_2$-), 5.15 (t, *J* = 9.6 Hz, 1H, H-3-Glu*p*), 5.10 – 5.00 (m, 3H, C*H*$_2$=CH-CH$_2$-, H-4-Fuc*p*), 4.70 (d, *J* = 8.0 Hz, 1H, H-1-Glu*p*), 4.39 (d, *J* = 7.6 Hz, 1H, H-1-Fuc*p*), 3.99 – 3.85 (m, 2H, H-6-Glu*p*, H-2-Fuc*p*), 3.83 – 3.72 (m, 2H, H-6-Glu*p*, H-3-Fuc*p*), 3.72 – 3.69 (m, 2H, H-4-Glu*p*), 3.62 – 3.58 (m, 1H, H-5-Fuc*p*), 3.57 – 3.43 (m, 2H, H-2-Glu*p*, O*H*), 3.40 – 3.35 (m, 1H, H-5-Glu*p*), 2.49 – 2.30 (m, 2H), 2.10 (s, 3H, C*H*$_3$-C=O), 1.90 – 1.73 (m, 6H, C*H*$_3$-CH-C(C*H*$_3$)-

C=O), 1.60 – 1.50 (m, 2H), 1.46 (s, 3H, (C*H*$_3$)$_2$C), 1.41 – 1.21 (m, 9H), 1.15 (d, *J* = 6.4 Hz, 3H, H-6-Fuc*p*), 0.94 – 0.80 (m, 12H), 0.18 (s, 3H, C*H*$_3$-Si), 0.15 (s, 3H, C*H*$_3$-Si). ^{13}C NMR (75 MHz, CDCl$_3$) δ 170.85, 167.63, 137.40, 134.55, 128.40, 116.99, 104.48, 101.49, 99.61, 79.48, 78.80, 75.38, 72.83, 72.77, 72.68, 71.67, 68.80, 68.25, 62.26, 38.73, 32.91, 32.12, 28.96, 25.79(3), 24.66, 22.64, 20.92, 18.91, 17.82, 16.50, 14.37, 14.11, 12.12, -4.49, -4.52.

1-Nonen-4*S*-yl 3-*O*-tigloyl-2-*O*-*tert*-butyldimethylsilyl-4,6-di-*O*-isopropylidene-β-D-glucopyranosyl-(1→2)-4-*O*-acetyl-3-*O*-*tert*-butyldimethylsilyl-β-D-fucopyranoside **2.39c**. TBSOTf (0.43 mL, 1.9 mmol) was added to a solution of compound **2.39b** (343.2 mg, 0.47 mmol) and 2,6-lutidine (0.55 mL, 4.7 mmol) in distilled CH$_2$Cl$_2$ (5 mL) at 0 °C. The reaction was allowed to warm to ambient temperature and stirred for 24 h. At this point, TLC (silica, 1:6 EtOAc–hexanes) showed the reaction was complete. Evaporation of the solvent followed by purification of the residue by flash chromatography (silica, EtOAc–hexanes, 1:20 → 1:10) gave compound **2.39c** (298.4 mg, 75%) as a colorless syrup. $[\alpha]_D^{25}$ –6.0° (*c* 1 CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.89 – 6.79 (m, 1H, Me-C*H*=C(Me)-C=O), 5.92 – 5.80 (m, 1H, CH$_2$=C*H*-CH$_2$-), 5.14 – 5.01 (m, 3H, H-3-Glu*p*, C*H*$_2$=CH-CH$_2$-), 5.00 – 4.91 (m, 2H, H-1-Glu*p*, H-4-Fuc*p*), 4.32 (d, *J* = 7.6 Hz, 1H, H-1-Fuc*p*), 4.04 (dd, *J* = 9.2, 7.6 Hz, 1H, H-2-Fuc*p*), 3.95 (dd, *J* = 10.8, 5.2 Hz, 1H, H-6-Glu*p*), 3.85 (dd, *J* = 9.2, 4.0 Hz, 1H, H-3-Fuc*p*), 3.72 (t, *J* = 10.4 Hz, 1H, H-6-Glu*p*), 3.69 – 3.58 (m, 2H, H-5-Fuc*p*, -CH$_2$-C*H*-CH$_2$-), 3.57 – 3.50 (m, 2H, H-2-Glu*p*, H-4-Glu*p*), 3.30 – 3.21 (m, 1H, H-5-Glu*p*), 2.35 (t, *J* = 6.4 Hz, 2H), 2.11 (s, 3H, C*H*$_3$-C=O), 1.87 – 1.75 (m, 6H, C*H*$_3$-CH-C(C*H*$_3$)-C=O), 1.61 – 1.46 (m, 2H), 1.45 (s, 3H, (C*H*$_3$)$_2$C), 1.40 – 1.21 (m, 9H), 1.12 (d, *J* = 6.4 Hz, 3H, H-6-Fuc*p*), 1.00 – 0.81 (m, 12H), 0.78 (s, 9H), 0.16 (s, 3H, C*H*$_3$-Si), 0.10 (s, 3H, C*H*$_3$-Si), 0.08 (s, 3H, C*H*$_3$-Si), –0.05 (s, 3H, C*H*$_3$-Si). ^{13}C NMR (100 MHz, CDCl$_3$) δ 170.91, 166.79, 136.88, 134.94, 128.73, 116.79, 101.61, 100.56, 99.33, 81.61, 76.65, 75.07, 74.30, 73.54, 73.30, 72.60, 68.75, 66.94, 62.55, 39.65, 33.97, 32.29, 28.95, 25.83(3), 25.80(3), 25.02, 22.85, 21.00, 18.82, 18.10, 17.69, 16.75, 14.28, 14.19, 12.05, –3.06, –3.9, –4.17, –4.22.

1-Nonen-4*S*-yl 3-*O*-tigloyl-2-*O*-*tert*-butyldimethylsilyl-β-D-glucopyranosyl-(1→2)-4-*O*-acetyl-3-*O*-*tert*-butyldimethylsilyl-β-D-fucopyranoside **2.40**. Compound **2.39c** (298.4 mg, 0.35 mmol) was dissolved in a 70% solution of acetic acid and water (10 mL). The reaction mixture was stirred at 70 ^{o}C for 1 hour at which point TLC (silica, 1:3 EtOAc–hexanes) showed it was complete. The reaction was concentrated and then co-evaporated with toluene (3 x 5 mL). The residue was purified by column chromatography (silica, EtOAc–hexanes, 1:3 → 1:2) and gave compound **2.40** (165.0 mg, 58%) as a white foam. $[\alpha]_D^{25}$ +15.4° (*c* 1 CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.96 – 6.85 (m, 1H, Me-C*H*=C(Me)-C=O), 5.90 – 5.79 (m, 1H, CH$_2$=C*H*-CH$_2$-), 5.11 – 5.01 (m, 2H, C*H*$_2$=CH-CH$_2$-), 5.01 – 4.90 (m, 3H, H-1-Glu*p*, H-3-Glu*p*, H-4-Fuc*p*), 4.31 (d, *J* = 7.6 Hz, 1H, H-1-Fuc*p*), 4.08 (t, *J* = 8.4 Hz, 1H, H-2-Fuc*p*), 3.88 (dd, *J* = 12.0, 3.6 Hz, 1H, H-6-Glu*p*), 3.85 (dd, *J* = 9.2, 3.6 Hz, 1H, H-3-Fuc*p*), 3.77 (dd, *J* = 12.0, 4.4 Hz, 1H, H-6-Glu*p*), 3.69 – 3.56 (m, 3H, H-4-Glu*p*, H-5-Fuc*p*, -CH$_2$-C*H*-CH$_2$-), 3.55 – 3.49 (m, 1H, H-2-Glu*p*), 3.40 – 3.31 (m, 1H, H-5-Glu*p*), 2.50 – 2.28 (m, 4H), 2.13 (s, 3H, C*H*$_3$-C=O), 1.88 – 1.78 (m, 6H, C*H*$_3$-CH-C(C*H*$_3$)-C=O), 1.60 – 1.46 (m, 2H), 1.40 – 1.22 (m, 6H), 1.14 (d, *J* = 6.4 Hz, 3H, H-6-Fuc*p*), 0.97 – 0.83 (m, 12H), 0.80 (s, 9H), 0.15 (s, 3H, C*H*$_3$-Si), 0.11 (s, 6H, 2 × C*H*$_3$-Si), 0.05 (d, *J* = 11.9 Hz, 3H, C*H*$_3$-Si). ^{13}C NMR (100 MHz, CDCl$_3$) δ 170.91, 169.14, 138.60, 134.79, 128.19, 116.91, 101.62, 99.97, 81.53, 79.16, 75.32, 74.35, 73.89, 73.36, 73.27, 70.76, 68.81, 62.14, 39.55, 33.88, 32.13, 25.83(3), 25.79(3), 25.32, 22.72, 21.01, 18.06, 17.59, 16.70, 14.39, 14.02, 11.97, –3.00, –3.94, –4.21, –5.17.

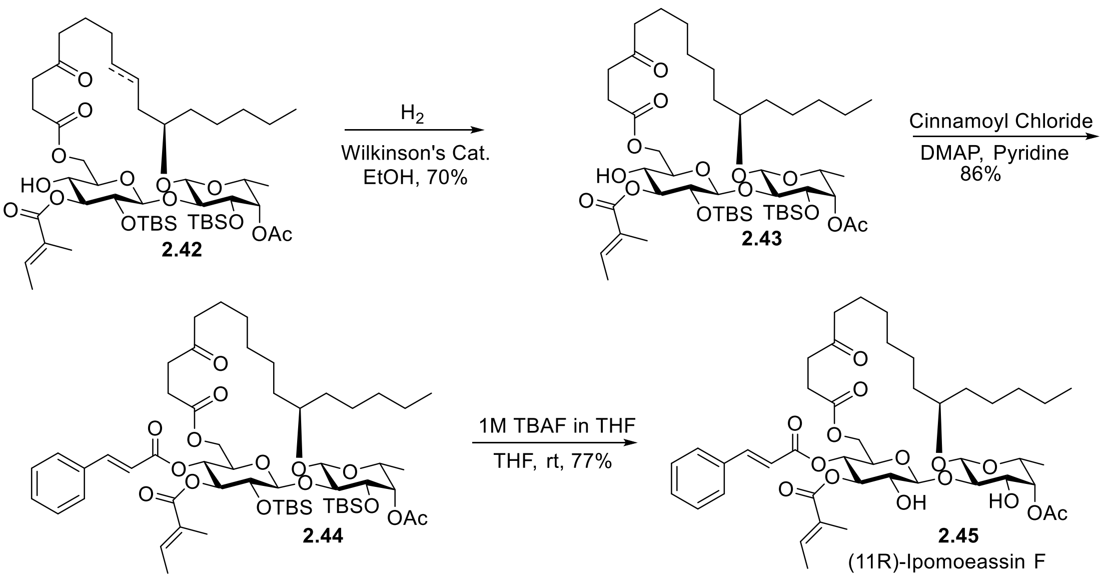
[redacted] Preparation of Ring-Closed Intermediate


OAc
HO
TBSO
HO
O
OTBS
2.40
2.6, DCC, DMAP, DCM
0 °C for 0.5 h, then rt, overnight
55%
HO
OTBS
TBSO
OAc
2.41
Hoveyda-Grubbs (II) Cat
DCM
Reflux 4 hrs
87%
HO
OTBS
TBSO
OAc
2.42

Diene **2.41**. DCC (50.3 mg, 0.241 mmol) was added in one portion to a 0 ºC CH_2Cl_2 (10 mL) solution of **2.40** (175.9 mg, 0.219 mmol), 4-oxonon-8-eneoic acid **2.6** (41.0 mg, 0.241 mmol) and 4-dimethylaminopyridine (DMAP) (2.5 mg, 0.022 mmol). The reaction was allowed to warm to ambient temperature and stirred overnight. At this point, TLC (silica, 1:3 EtOAc–hexanes) showed the reaction was complete. The reaction mixture was diluted with ether (20 ml) and hexanes (10 ml), stirred for 20 minutes then filtered thru a pad of celite using ether (20 ml) as the eluent and the filtrate concentrated *in vacuo*. The residue was purified by column chromatography (silica, EtOAc–hexanes, 1:6) gave diene **2.41** (110.0 mg, 55%) as a colorless syrup. $[\alpha]_D^{25}$ +4.2° (*c* 1 $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 – 6.89 (m, 1H, Me-C*H*-C(Me)-C=O), 5.95 – 5.69 (m, 2H, 2 x CH_2=C*H*-CH_2-), 5.12 – 4.89 (m, 7H, 2 × CH_2=CH-CH_2-, H-1-Glu*p*, H-3-Glu*p*, H-4-Fuc*p*), 4.41 (dd, *J* = 12.0, 4.4 Hz, 1H, H-6-Glu*p*), 4.39 (d, *J* = 8.0 Hz, 1H, H-1-Fuc*p*), 4.35 – 4.33 (dd, *J* = 12.0, 2.0 Hz, 1H, H-6-Glu*p*), 4.08 (t, *J* = 9.2, 7.6 Hz, 1H, H-2-Fuc*p*), 3.90 (dd, *J* = 9.2, 3.6 Hz, 1H, H-3-Fuc*p*), 3.70 – 3.49 (m, 4H, H-2-Glu*p*, H-4-Glu*p*, H-5-Fuc*p*, -CH_2-C*H*-CH_2-), 3.48 – 3.40 (m, 1H, H-5-Glu*p*), 2.94 (d, *J* = 4.8 Hz, 1H, O*H*), 2.82 – 2.55 (m, 4H), 2.52 – 2.41 (m, 2H), 2.38 (t, *J* = 6.0 Hz, 2H), 2.13 (s, 3H, CH_3-C=O), 2.11 – 2.01 (m, 2H), 1.89 – 1.77 (m, 6H, CH_3-CH-C(CH_3)-C=O), 1.76 – 1.65 (m, 4H), 1.42 – 1.21 (m, 6H), 1.14 (d, *J* = 6.4 Hz, 3H, H-6-Fuc*p*), 0.97 – 0.85 (m, 12H), 0.80 (s, 9H), 0.15 (s, 3H, CH_3-Si), 0.11 (s, 6H, 2 × C*H*$_3$-Si), 0.04 (s, 3H, C*H*$_3$-Si). ^{13}C NMR (75 MHz, CDCl$_3$) δ 208.66, 173.08, 170.95, 169.08, 138.67, 137.89, 134.99, 128.20, 116.87, 115.31, 101.11, 99.95, 80.99, 79.01, 74.25, 73.87, 73.80, 73.43, 70.40, 68.84, 63.57, 41.82, 39.59, 37.13, 33.77, 33.03, 32.26, 27.70, 25.83(3), 25.82(3), 25.32, 22.85, 22.71, 21.05, 18.09, 17.63, 16.72, 14.46, 14.26, 12.04, –3.08, –3.94, –4.24, –5.13.

RCM Product **2.42**. To a solution of diene **2.41** (110.0 mg, 0.12 mmol) in CH$_2$Cl$_2$ (40 mL) was added Hoveyda-Grubbs catalyst 2nd generation (7.2 mg, 0.01 mmol) in one portion at room temperature. The reaction mixture was refluxed for 4 h. At this point, TLC (silica, 1:2 EtOAc–hexanes) showed the reaction was complete. The reaction was cooled to ambient temperature and then concentrated. Flash chromatography (silica, EtOAc–hexanes, 1:4 → 1:2) gave isomers **2.42** (92.8 mg, 87%) as a white foam which was not fully characterized. The obtained isomer was subjected to hydrogenation in next step and the product was fully characterized.

Completion of C11 Epimer



2.42
H2
Wilkinson's Cat.
EtOH, 70%
2.43
Cinnamoyl Chloride
DMAP, Pyridine
86%
2.44
1M TBAF in THF
THF, rt, 77%
2.45
(11R)-Ipomoeassin F

Hydrogenation Product **2.43**. To a solution of cycloalkene **2.42** (51.4 mg, 0.055 mmol) in EtOH (2 mL) was added Wilkinson's catalyst (22 mg, 0.024 mmol) in one portion at room temperature. The reaction was then stirred under an atmosphere of hydrogen (1 atm) overnight. At this point, TLC (silica, 1:2 EtOAc–hexanes) showed the reaction was complete. The reaction mixture was filtered thru a pad of celite using EtOAc (2 mL) as the eluent and the resulting filtrate concentrated. Flash chromatography (silica, EtOAc–hexanes, 1:5 → 1:3) gave **2.43** (36.1 mg, 70%) as a colorless syrup. $[\alpha]_D^{25}$ +18.0° (*c* 1 $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.00 – 6.89 (m, 1H, Me-C*H*-C(Me)-C=O), 5.03 – 4.85 (m, 3H, H-1-Glu*p*, H-3-Glu*p*, H-4-Fuc*p*), 4.51 (m, 1H, H-6-Glu*p*), 4.47 (br, 1H, H-1-Fuc*p*), 4.35 – 4.21 (m, 2H, H-6-Glu*p*, H-2-Fuc*p*), 3.99 – 3.89 (m, 1H, H-3-Fuc*p*), 3.72 – 3.61 (m, 1H, H-5-Fuc*p*), 3.59 (br, 1H, H-5-Glu*p*), 3.51 – 3.40 (m, 3H, H-2-Glu*p*, H-4-Glu*p*, -CH_2-C*H*-CH_2-), 3.08 – 2.95 (m, 1H, O*H*), 2.95 – 2.89 (m, 1H), 2.78 – 2.60 (m, 3H), 2.60 – 2.48 (m, 1H), 2.38 – 2.27 (m, 1H), 2.12 (s, 3H, CH_3-C=O), 1.89 –

1.78 (m, 6H, CH_3-CH-C(CH_3)-C=O), 1.75 – 1.51 (m, 6H), 1.49 – 1.21 (m, 12H), 1.12 (d, *J* = 6.4 Hz, 3H, H-6-Fuc*p*), 0.95 – 0.86 (m, 12H), 0.79 (s, 9H), 0.16 (s, 3H, CH_3-Si), 0.12 (s, 3H, CH_3-Si), 0.11 (s, 3H, CH_3-Si), 0.05 (s, 3H, CH_3-Si). ^{13}C NMR (75 MHz, CDCl$_3$) δ 210.09, 172.51, 170.93, 169.37, 138.89, 128.11, 99.84, 100.21, 79.44, 74.29, 74.08, 73.79, 73.54, 61.08, 68.65, 63.78, 41.74, 37.21, 33.27, 32.78, 32.27, 28.83, 26.96, 26.72, 25.97, 25.85(6), 24.94, 23.04, 22.71, 22.62, 21.05, 18.11, 17.66, 16.56, 14.47, 14.19, 12.04, –3.25, –3.88, –4.27, –5.24.

Compound **2.44**. To a cold (0 °C) solution of compound **2.43** (28.1 mg, 0.030 mmol) and DMAP (9.0 mg, 0.060 mmol) in pyridine (2 mL) was added cinnamoyl chloride (20.1 mg, 0.120 mmol). The reaction mixture was allowed to warm to ambient temperature and stirred for 24 h. At the end of this time, TLC (silica, 1:2 EtOAc–hexanes) indicated that the reaction was complete. The reaction was quenched with MeOH (10 µL) and diluted with CH_2Cl_2 (10 mL), washed with 1 M HCl (10 mL), saturated aqueous $NaHCO_3$ (10 mL), and dried (Na_2SO_4). The solvent was evaporated under vacuum and the residue was purified by column chromatography (silica, EtOAc–hexanes, 1:6) to afford compound **2.44** (27.5 mg, 86%) as a white foam. $[\alpha]_D^{25}$ –1.8° (*c* 0.5 CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.62 (d, *J* = 16.0 Hz, 1H, Ph-C*H*=C-), 7.54 – 7.47 (m, 2H, 2 × Ar*H*), 7.44 – 7.35 (m, 3H, 3 × Ar*H*), 6.85 – 6.75 (m, 1H, Me-C*H*-C(Me)-C=O), 6.33 (d, *J* = 16.0 Hz, 1H, Ph-CH=C*H*-), 5.25 (t, *J* = 9.2 Hz, 1H, H-3-Glu*p*), 5.09 – 4.93 (m, 3H, H-1-Glu*p*, H-4-Glu*p*, H-4-Fuc*p*), 4.51 (br, 1H, H-1-Fuc*p*), 4.34 – 4.27 (m, 1H, H-6-Glu*p*), 4.20 – 4.11 (m, 1H, H-6-Glu*p*), 4.06 – 4.00 (m, 1H, H-3-Fuc*p*), 3.99 – 3.92 (m, 1H, H-2-Fuc*p*), 3.78 – 3.70 (m, 3H, H-5-Glu*p*, H-5-Fuc*p*, -CH$_2$-C*H*-CH$_2$-), 3.66 (dd, *J* = 8.8, 7.6 Hz, 1H, H-2-Glu*p*), 3.01 – 2.70 (m, 2H), 2.78 – 2.46 (m, 4H), 2.12 (s, 3H, CH_3-C=O), 1.76 – 1.70 (m, 9H), 1.70 – 1.55 (m, 3H), 1.46 – 1.22 (m, 12H), 1.12 (d, *J* = 6.4 Hz, 3H, H-6-Fuc*p*), 0.99 – 0.84 (m, 12H), 0.80 (s, 9H), 0.20 (s, 3H, C*H*$_3$-Si), 0.13 (s, 3H, C*H*$_3$-Si), 0.12 (s, 3H, C*H*$_3$-Si), 0.03 (s, 3H, C*H*$_3$-Si). ^{13}C NMR (100 MHz, CDCl$_3$) δ 210.05, 172.06, 170.94, 166.95, 165.80, 146.27, 138.03, 134.11, 130.57, 128.87(2), 128.29(2), 128.17, 116.70, 100.06, 99.99, 74.97, 73.95, 73.77, 71.63, 70.07, 68.61, 41.69, 37.14, 33.76, 31.94, 28.75, 27.88, 27.40, 25.88(3), 25.82(3), 24.89, 24.72, 22.97, 22.71, 21.05, 18.12, 17.71, 16.61, 14.40, 14.14, 11.94, –3.49, –3.85, –4.34, –5.27.

11R epimer **2.45**. To a solution of **2.44** (20.0 mg, 0.019 mmol) in THF (2 mL) was added TBAF (1M solution in THF, 0.11 mL, 0.113 mmol) at -10 °C. The reaction mixture was stirred at the same temperature for 4 h at which point TLC (silica, 1:1 EtOAc–hexanes) showed it was complete. The reaction mixture was diluted with Et$_2$O (10 mL), washed with 1M HCl (10 mL), saturated NaHCO$_3$ (10 mL), and brine (5 mL). The aqueous layer was extracted with Et$_2$O (20 mL x 2). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (silica, EtOAc–hexanes, 1:2 → 1:1) gave compound **2.45** (12.0 mg, 77%) as a white foam. $[\alpha]_D^{25}$ –17.0° (*c* 1.0 CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.68 (d, *J* = 16.0 Hz, 1H, Ph-C*H*=C-), 7.55 – 7.48 (m, 2H, 2 × Ar*H*), 7.43 – 7.35 (m, 3H, 3 × Ar*H*), 6.93 – 6.84 (m, 1H, Me-C*H*-C(Me)-C=O), 6.38 (d, *J* = 16.0 Hz, 1H, Ph-CH=C*H*-), 5.23 (t, *J* = 9.6 Hz, 1H, H-4-Glu*p*), 5.20 – 5.16 (m, 2H, H-3-Glu*p*, H-4-Fuc*p*), 4.67 (d, *J* = 8.0 Hz, 1H, H-1-Glu*p*), 4.22 (br, 1H, O*H*), 4.49 (dd, *J* = 12.4, 3.6 Hz, 1H, H-6-Glu*p*), 4.46 (d, *J* = 7.6 Hz, 1H, H-1-Fuc*p*), 4.16 (dd, *J* = 12.4, 2.4 Hz, 1H, H-6-Glu*p*), 3.95 – 3.86 (m, 2H, O*H*, H-3-Fuc*p*), 3.85 – 3.81 (m, 1H, H-5-Glu*p*), 3.81 – 3.66 (m, 4H, H-2-Glu*p*, H-2-Fuc*p*, H-5-Fuc*p*, -CH$_2$-C*H*-CH$_2$-), 3.00 – 2.91 (m, 1H), 2.75 – 2.42 (m, 5H) 2.20 (s, 3H, C*H*$_3$-C=O), 1.80 – 1.75 (m, 6H, C*H*$_3$-CH-C(C*H*$_3$)-C=O), 1.75 – 1.70 (m, 2H), 1.70 – 1.52 (m, 4H), 1.51 – 1.20 (m, 12H), 1.19 (t, *J* = 6.4 Hz, 3H, H-6-Fuc*p*), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C

NMR (100 MHz, $CDCl_3$) δ 209.40, 171.76, 171.50, 168.22, 165.60, 146.24, 139.11, 134.00, 130.69, 128.95(2), 128.27(2), 127.75, 116.71, 103.13, 97.95, 78.48, 77.45, 75.99, 74.56, 72.66, 72.15, 71.75, 69.22, 68.61, 62.46, 41.95, 37.38, 33.15, 32.57, 32.05, 29.71, 28.79, 28.12, 27.44, 24.68, 23.50, 23.14, 22.63, 20.96, 16.34, 14.54, 14.10, 12.04. HRMS for $C_{44}H_{62}NaO_{15}$ $(M+Na)^+$ 853.3981. Found: 853.3986

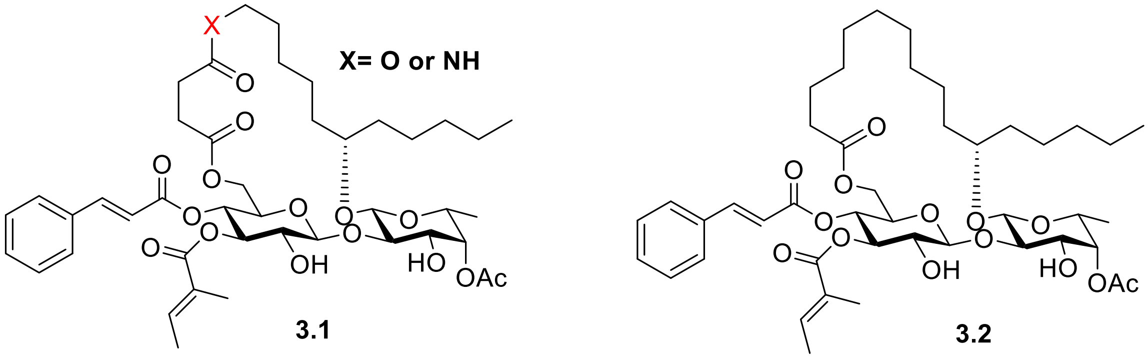
[redacted] DEVELOPMENT OF A SYNTHESIS TO ACCESS TAIL-MODIFIED ANALOGS OF IPOMOEASSIN F

Having already demonstrated the importance of the aglycon’s chiral center and knowing the major role the length of the aglycon plays in the bioactivity of ipomoeassin F, we sought to further investigate this key component of the ipomoeassins. As previously mentioned, the only difference between ipomoeassin F and ipomoeassin A are two methylene units in the tail of the aglycon so we were curious if further increasing the length, and thus increasing the lipophilicity, of the aglycon could improve potency. If this region of the molecule could tolerate modification, it would also be interesting to see what other functional groups could be tolerated and what effect they would have.

In order to investigate this region of the molecule, a new synthetic route would need to be established. While we could synthesize modified aglycons and attach them with our current synthesis (as demonstrated with the epimer), this really would be inefficient for the synthesis of a small library of analogs as each new compound would need to be synthesized from scratch. Though we explored a few strategies, ultimately we decided the most practical and flexible route would be one that gave us some type functional handle which could be modified either in the final step, or at least near the final step of the synthesis.

[redacted] Retrosynthetic Strategy

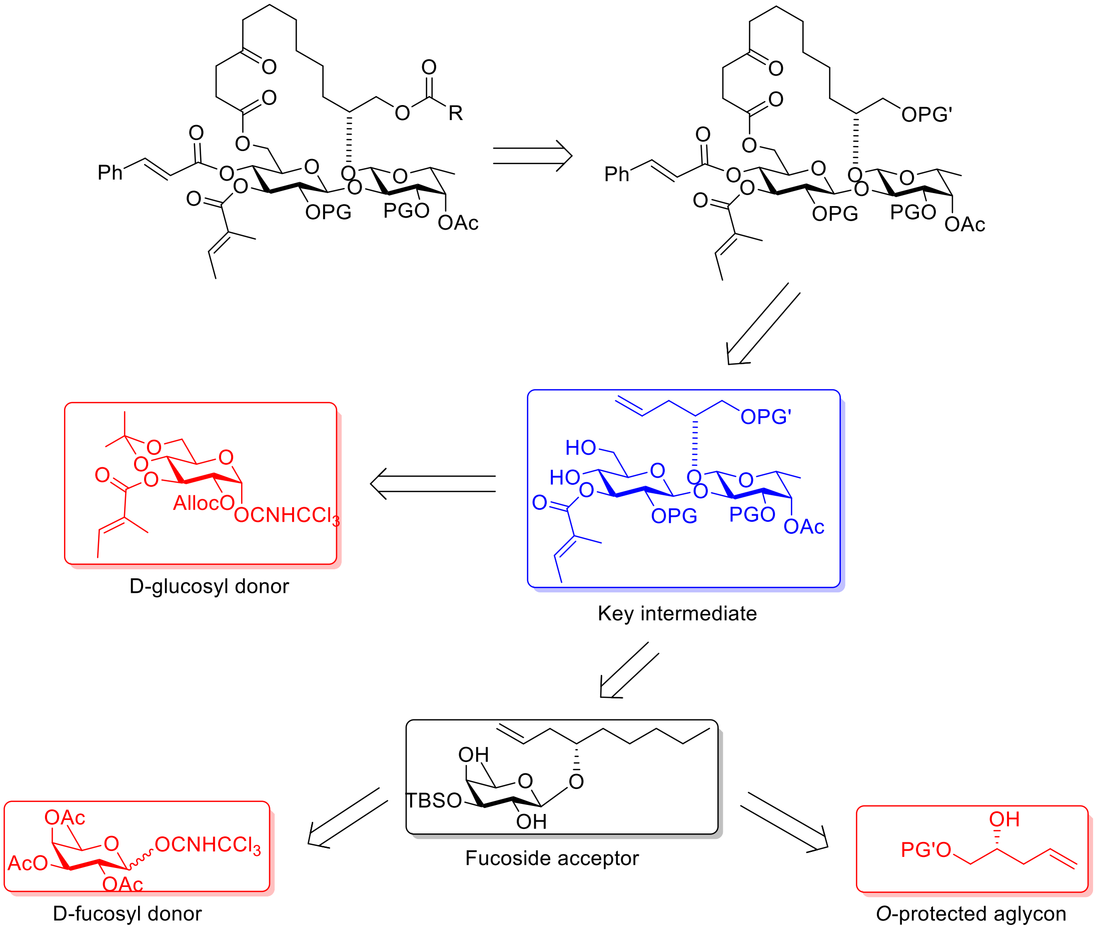
As we set out to design a synthesis that would allow the tail of the aglycon to be modified, we decided incorporating a hydroxyl group into the aglycon would give us the most flexibility in the way of analog synthesis. With a terminal hydroxyl group in the tail, we would be able to attach a wide variety of compounds through mild esterification conditions without disturbing the other esters already decorating the periphery of the molecule. We acknowledged that this strategy would be incorporating other variables besides solely modifying the length of the tail, but we were hopeful that an ester functionality could be tolerated at this position and any decrease in lipophilicity due to the ester could be overcome with a sufficiently lipophilic sidechain. We were also encouraged by results previously obtained by our lab during the synthesis of bioisosteric 5-oxa/aza analogs of ipomoeassin F[80]. In this work, the ketone functionality of the aglycon was substituted for various amides and esters. Several of these analogs (Figure 3-1) maintained quite similar potency to ipomoeassin F, encouraging us that perhaps an ester could be tolerated in the tail of the aglycon as well. Another earlier successful modification to the aglycon from our lab removed the ketone from the aglycon altogether with very little drop in activity[81].



3.1 **3.2**

Figure 3-1. Previously Synthesized Aglycon Modified Analogs

When designing the synthesis, we initially planned to use a route as close as possible to our original ipomoeassin F/epimer route so that most of the chemistry would already be established. The main challenge would be the addition of an extra hydroxyl group in the aglycon that would need to be protected throughout the entirety of the synthesis. Ideally this group would be orthogonal to the other protecting group so that it could be selectively removed at the end of the synthesis and the corresponding hydroxyl group could be modified. We hypothesized that the primary alcohol on the tail would be more selective towards esterification reactions than the secondary carbohydrate alcohols, but orthogonal protection would free us from needing to rely on any selectivity differences. Not only did we desire orthogonal protection, but we also needed a group that could withstand the various reaction conditions throughout the entirety of the synthesis which limited our selection of possible protecting groups considerably. In the end, we had to stray from our initial route in a few locations which will be described in detail below.



Ph
OPG
PGO
OAc
R
OPG'
HO
AllocO
OCNHCCl3
D-glucosyl donor
Key intermediate
OH
TBSO
Fucoside acceptor
OAc
AcO
D-fucosyl donor
PG'O
O-protected aglycon

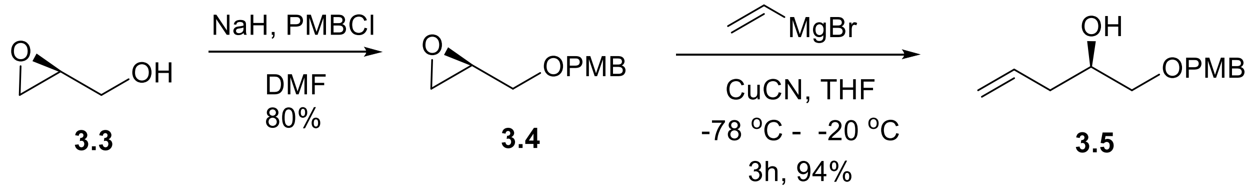
Scheme 3-1. Initial Retrosynthetic Strategy

[redacted] Synthesis of the Protected Aglycon

Fundamental to the success of our synthesis was the selection of a suitable protecting group for the hydroxyl group in the tail of the aglycon. We began the synthesis with *S*-glycidol as our source of chirality as well as for the inclusion of a hydroxyl group that we would be able to modify. We started by protecting the alcohol and then opening up the epoxide with vinylmagnesium bromide to form the protected aglycon. We initially chose the *p*-methoxybenzyl (PMB) protecting group as it should be stable enough to remain in place throughout the synthesis but be easily removed under mild oxidizing condition without disturbing the TBS protecting groups we anticipated using to protect the secondary hydroxyl groups of the glycon. However, after further optimization we found the *tert*-butyldiphenylsilyl (TBDPS) protecting group to be more suitable.

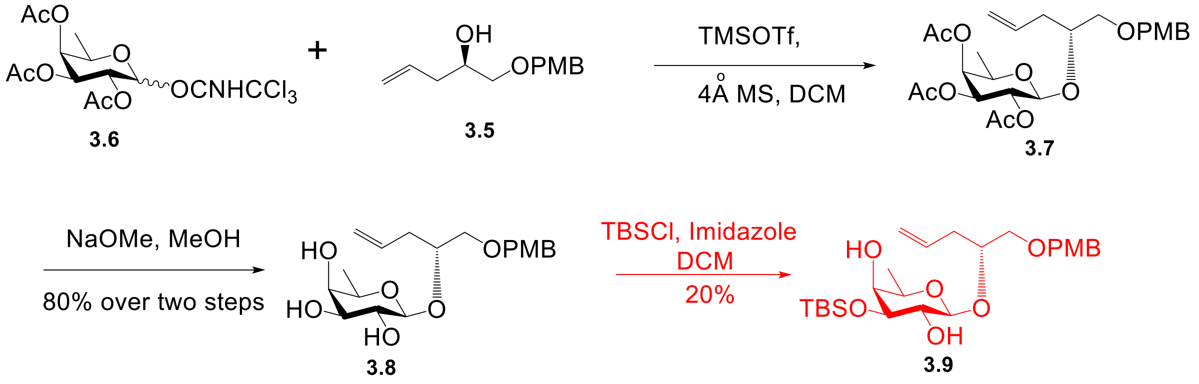
[redacted] Preparation of the PMB Protected Aglycon

Originally, we chose to protect the aglycon using PMB due to its stability and desirable deprotection conditions. We commenced by reacting commercially available *S*-glycidol with PMBCl using NaH as the base to furnish the protected glycidol. We could then open the epoxide with vinylmagnesium bromide to form the chiral alcohol **3.5** which would be used as the aglycon in a subsequent glycosylation with the fucosyl donor.



Scheme 3-2. Synthesis of the PMB Protected Aglycon

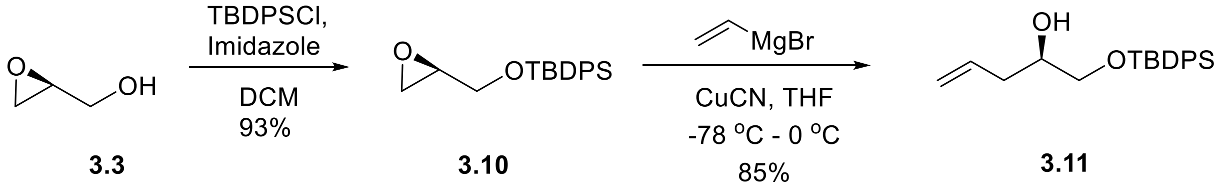
We carried on with the synthesis by coupling this PMB protected aglycon with the fucosyl donor **3.6** via glycosylation catalyzed by the Lewis acid TMSOTf under anhydrous conditions. A subsequent deacetylation smoothly gave fucoside **3.8** in good yield. At this stage in the synthesis we rely on a regioselective introduction of TBS to the 3-*O*-fuc*p* position. Unfortunately, we were unable to replicate our previous results with this reaction on this particular substrate. It seems the selectivity among the three hydroxyl groups is heavily dependent on the aglycon of the substrate. While using the OPMB containing aglycon, only 20% yield of the desired compound was isolated. While the 3-*O* position is still the most reactive position, the yield seems to be hindered by potential hydrogen bonding with the OPMB group of the aglycon. Although we could use a different route to synthesize the desired fucoside acceptor, we would have to drastically lengthen the synthetic route so we decided it would be more efficient to first investigate other aglycon protecting groups before altogether changing our strategy.


AcO
AcO
AcO
O
OCNHCCl3
3.6
+
OH
OPMB
3.5
TMSOTf,
4Å MS, DCM
AcO
AcO
AcO
O
O
OPMB
3.7
NaOMe, MeOH
80% over two steps
HO
HO
HO
O
O
OPMB
3.8
TBSCl, Imidazole
DCM
20%
HO
TBSO
OH
O
O
OPMB
3.9

Scheme 3-3. Synthesis of OPMP Fucoside Acceptor

[redacted] Preparation of the TBDPS-Protected Aglycon

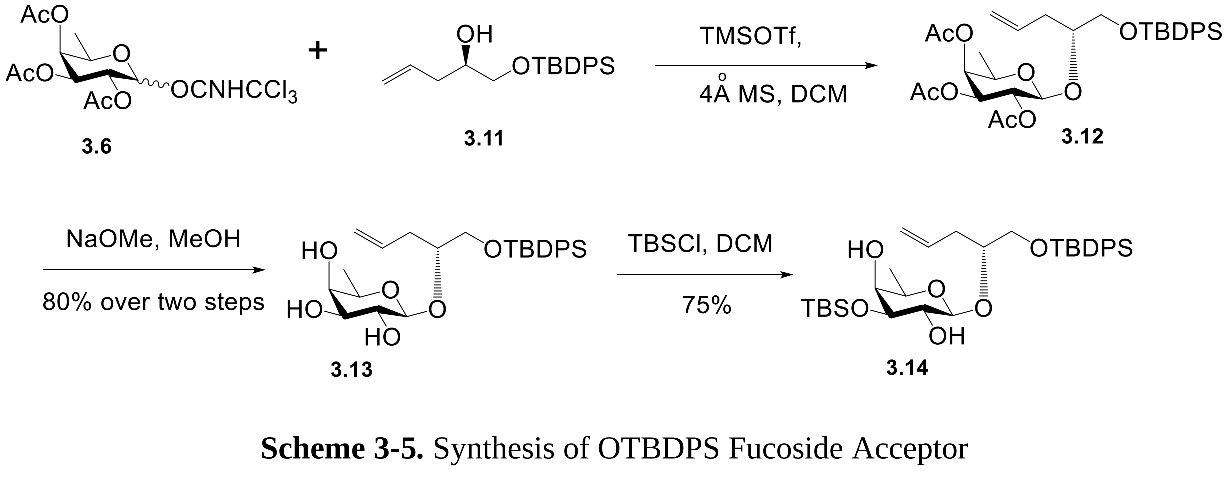
Hypothesizing that the 3-*O*-fuc*p* position was unreactive due to hydrogen bonding from the PMB, we decided to try TBDPS. While this wasn't our most desirable choice due to lack of selectivity with its removal, we were drawn to its robustness and were fairly confident in its stability towards the various reaction conditions it would encounter. The synthesis began in a similar fashion, reacting *S*-glycidol with TBDPSCl and imidazole to protect the free hydroxyl group. Upon successful protection, we once again opened the epoxide using vinylmagnesium bromide to afford the desired TBDPS-protected chiral alcohol **3.11**.



OH
3.3
TBDPSCl,
Imidazole
DCM
93%
OTBDPS
3.10
MgBr
CuCN, THF
-78 °C - 0 °C
85%
OH
OTBDPS
3.11

Scheme 3-4. Synthesis of the TBDPS Protected Aglycon

With the new aglycon in hand we once again attempted to synthesize the fucoside acceptor. Using the same sequence of reactions, we coupled the aglycon and the fucosyl donor which upon deacetylation with NaOMe in MeOH gave fucoside **3.13**. To our delight, the following TBS introduction gave the desired selectivity and with good conversion, so we decided to carry forward using TBDPS as our protecting group of choice for the aglycon.



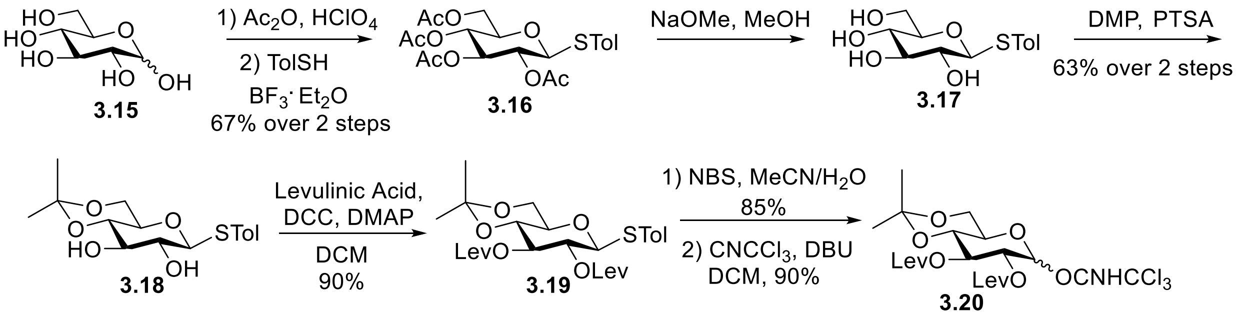
AcO
AcO
AcO
O
OCNHCCl3
3.6
+
OH
OTBDPS
3.11
TMSOTf,
4Å MS, DCM
AcO
AcO
AcO
O
O
OTBDPS
3.12
NaOMe, MeOH
80% over two steps
HO
HO
HO
O
O
OTBDPS
3.13
TBSCl, DCM
75%
HO
TBSO
OH
O
O
OTBDPS
3.14

Scheme 3-5. Synthesis of OTBDPS Fucoside Acceptor

Synthesis of the Glucosyl Donor

With the successful completion of the protected fucoside acceptor, we then turned our attention to the glucosyl donor. One of the biggest hurdles for quickly scaling up more intermediates for our original ipomoeassin F (and epimer) synthesis was the synthesis of the glucosyl donor. Our need for the α-PMP glucoside required us to wait for days for the reaction to finish and also required a difficult large-scale purification to remove any anomer that might remain. The protecting strategy used also required more steps. Fortunately, during an effort in our lab to study the role of the tiglate and cinnamate moietys[58], a new route for the glucosyl donor was established which we also opted to use for this work.

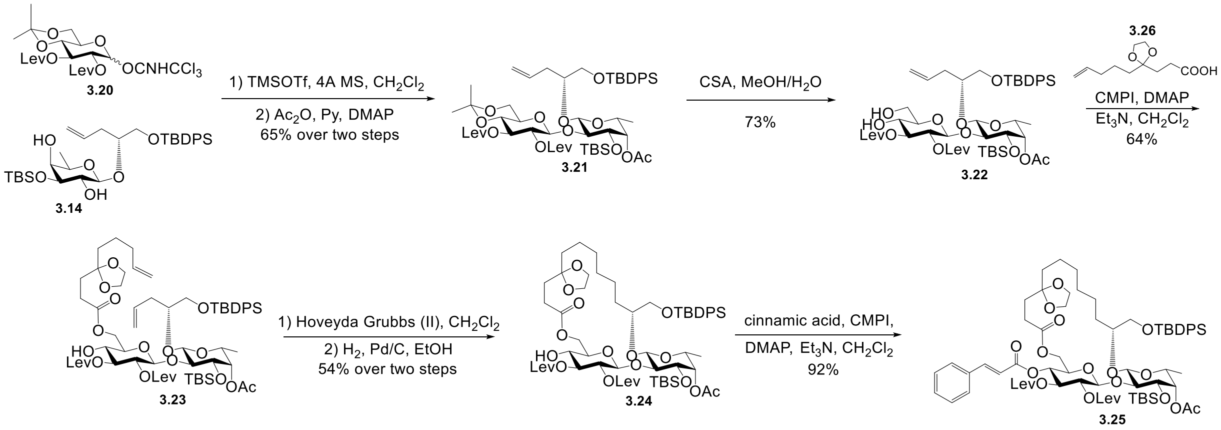
The synthesis begins with D-glucose which was globally acetylated. Glycosylation with thiotoluene followed by deacylation gave the thioglycoside **3.16**. Subsequent isopropylidenation efficiently protected the 4- and 6-*O* positions leaving the other positions open for orthogonal protection with levulinic acid. The anomeric thiotoluene could then be removed upon treatment with NBS and the corresponding hemiacetal was converted to the trichloroacetimidate glucosyl donor **3.20**.


3.15
1) Ac_2O, $HClO_4$
2) TolSH
$BF_3 \cdot Et_2O$
67% over 2 steps
3.16
NaOMe, MeOH
3.17
DMP, PTSA
63% over 2 steps
3.18
Levulinic Acid,
DCC, DMAP
DCM
90%
3.19
1) NBS, $MeCN/H_2O$
85%
2) $CNCCl_3$, DBU
DCM, 90%
3.20
STol
LevO
$OCNHCCl_3$

Scheme 3-6. Synthesis of the Glucosyl Donor

Synthesis of Macrocyclic Disaccharide Intermediate

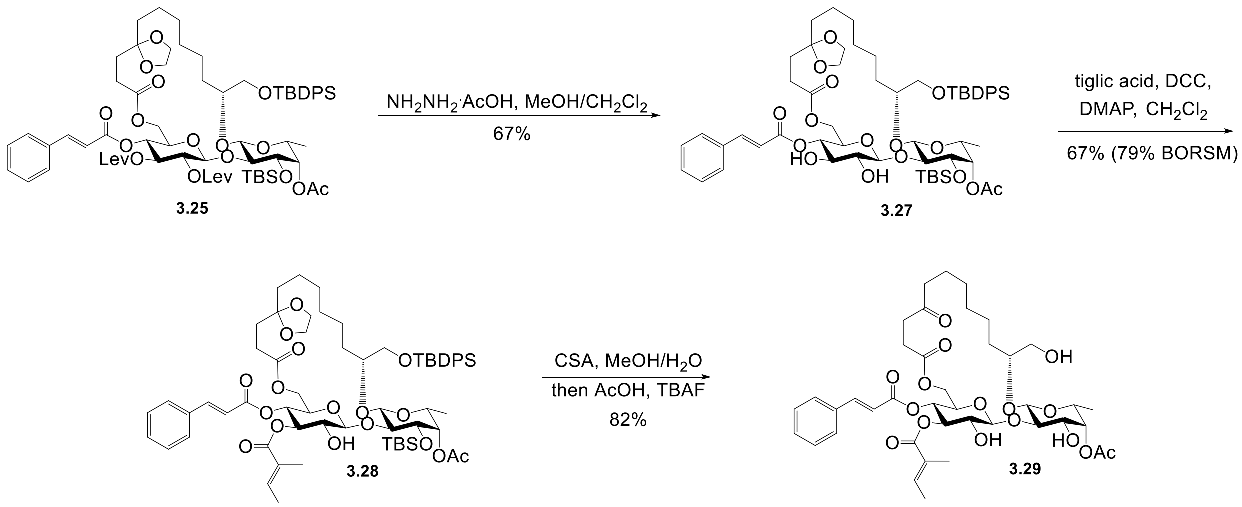
After obtaining both the glucosyl donor and the fucoside acceptor, a regio- and stereoselective glycosylation provided the disaccharide intermediate in good yield. An acylation of the remaining free hydroxyl group afforded compound **3.21**. At this point, deisopropylidenation followed by a regioselective esterification successfully introduced the other fragment of the aglycon to furnish the RCM precursor **3.23**. RCM catalyzed by Hoveyda-Grubbs second generation catalyst followed by hydrogenation completed the formation of the macrocycle. In this case, the hydrogenation could be performed using palladium on carbon as the catalyst since no other unsaturated groups would be present until after the reduction. Following hydrogenation, the cinnamate moiety was introduced to the 4-*O*-glc*p* position via Mukaiyama esterification to give intermediate **3.25**.


LevO
LevO
OCNHCCl3
3.20
HO
OTBDPS
TBSO
OH
3.14
1) TMSOTf, 4A MS, CH2Cl2
2) Ac2O, Py, DMAP
65% over two steps
OTBDPS
LevO
OLev
TBSO
OAc
3.21
CSA, MeOH/H2O
73%
OTBDPS
HO
HO
LevO
OLev
TBSO
OAc
3.22
3.26
COOH
CMPI, DMAP
Et3N, CH2Cl2
64%
OTBDPS
HO
LevO
OLev
TBSO
OAc
3.23
1) Hoveyda Grubbs (II), CH2Cl2
2) H2, Pd/C, EtOH
54% over two steps
OTBDPS
HO
LevO
OLev
TBSO
OAc
3.24
cinnamic acid, CMPI,
DMAP, Et3N, CH2Cl2
92%
OTBDPS
LevO
OLev
TBSO
OAc
3.25

Scheme 3-7. Synthesis of Ring-Closed Intermediate

Synthesis of Key Intermediate for Analog Synthesis

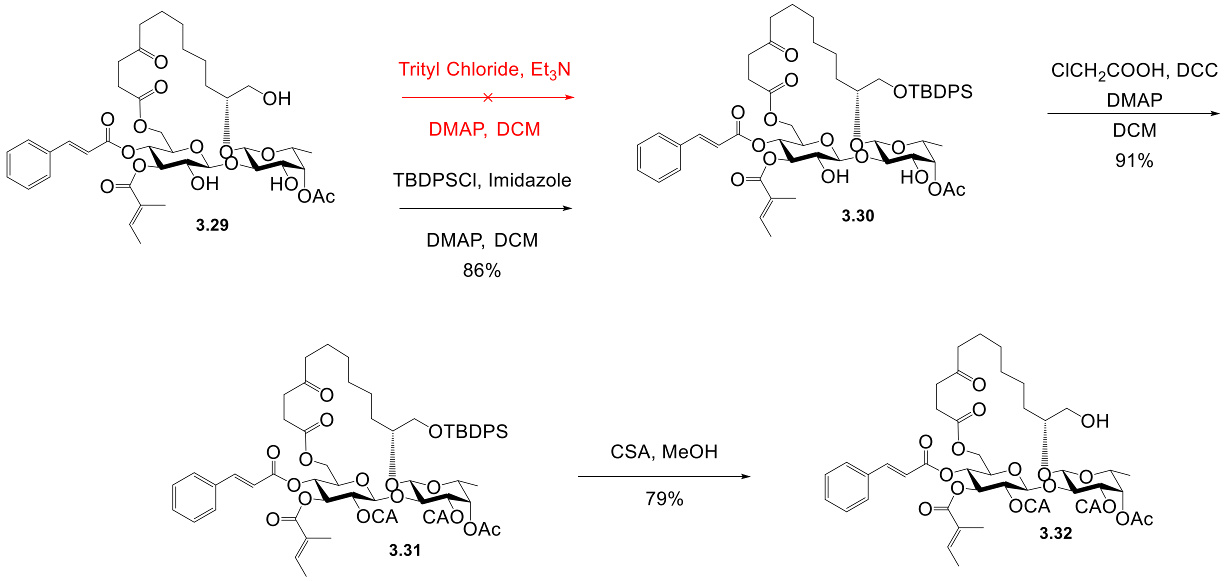
Following the installation of the cinnamate, we could begin to attempt our end strategy. We first removed the levulinoyl protecting groups using hydrazine acetate and then regioselectively introduced the tiglate to the 3-*O*-glc*p* position. From here our strategy was to do a global deprotection, removing the TBDPS, TBS, and ketal in one pot, and attempt to selectively modify the primary tail hydroxyl group. Because we used TBDPS as our protecting group for the tail, we were unable to selectively deprotect this position, but we hoped that a regioselective esterification would be possible since we anticipated the terminal tail hydroxyl group to be less hindered than the secondary glycon hydroxyl groups and thus more reactive. Unfortunately, all of the esterification conditions we tried resulted in an inseparable mixture of regioisomers. Triol **3.29** was tested in our cytotoxicity assay as a new analog to understand what kind of an impact such an increase in hydrophilicity would have on activity. As expected, this compound showed a decrease of more than 400-fold when compared to ipomoeassin in MDA-MB-231 or MCF7 cells (Table 3-1).



OTBDPS
LevO
OLev
TBSO
OAc
3.25
NH2NH2·AcOH, MeOH/CH2Cl2
67%
HO
OH
3.27
tiglic acid, DCC, DMAP, CH2Cl2
67% (79% BORSM)
3.28
CSA, MeOH/H2O
then AcOH, TBAF
82%
OH
HO
3.29

Scheme 3-8. Synthesis of Triol Intermediate

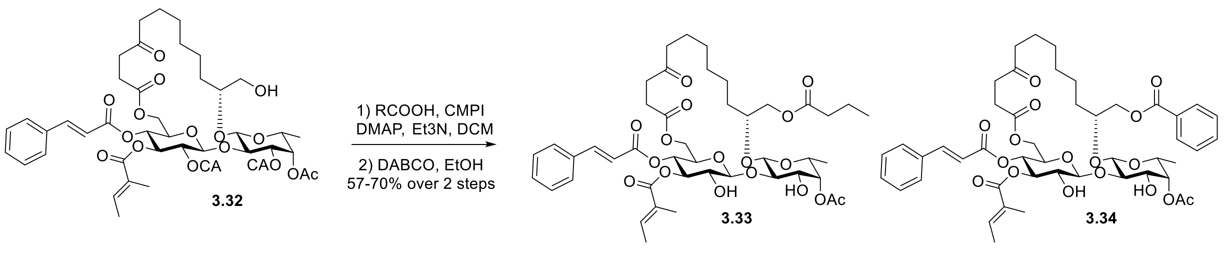
Knowing that a regioselective modification of the terminal hydroxyl group might not be possible, we decided to employ an alternative strategy. We hoped that an introduction of a bulky protecting group would be selective to the primary position. Our first trial was with a trityl group which is normally very selective to primary alcohols. However, it seemed our terminal hydroxyl group was still too hindered. Even with a large excess of trityl chloride, no reaction at all was observed. Since we knew TBDPS had previously been installed at that position, we attempted to reinstall it. Fortunately, we were able to introduce it with good selectivity upon addition of an excess of TBDPSCl. At this stage of the synthesis we needed to now install an orthogonal protecting group at the remaining secondary hydroxyl positions so that we could selectively remove the TBDPS group. For this we chose a chloroacetyl group since it was small enough to be easily introduced and would be stable to the acidic conditions needed to remove the TBDPS. This strategy worked in our favor and the chloroacetyl groups were easily installed using Steglich esterification conditions and the TBDPS group was subsequently removed using CSA.



Scheme 3-9. Completion of Intermediate for Further Analog Synthesis

Synthesis of Tail-Modified Ipomoeassin Analogs

Having successfully developed a route to enable the synthesis of multiple analogs with a modified aglycon, we chose a small set of ester analogs to test the effect of lipophilicity and the tolerability of different functional groups. For an initial study, we attempted to introduce a series of aliphatic chains of increasing length as well as an aromatic group. The ester was first formed via Mukaiyama esterification. The solvent was then evaporated and DABCO and ethanol were added to remove the chloroacetyl protecting groups in the same pot. The final compounds could then be purified by chromatography and submitted to a cytotoxicity assay. Unfortunately, two of the isolated compounds, the acetyl and hexyl ester analogs, were determined to have an incorrect structure. The two successful analogs, the benzyl and butyl esters, provided some useful cytotoxicity data summarized in Table 3-1. As we expected, the butyl ester analog showed an increase in potency relative to the corresponding alcohol, although still not as potent as ipomoeassin F. While the overall length of the aglycon tail is similar to that of ipomoeassin F, the overall lipophilicity was decreased by the presence of the ester and presumably is responsible for the decrease in activity. In the future we would like to investigate if lengthening the ester could make up for this difference in potency. The benzyl ester analog also showed improved potency but much less than the butyl analog indicating that this area of the molecule is probably not tolerant of aromatic groups. This exploratory synthesis unfortunately did not provide enough material for a large array study, but with the establishment of a viable route for the synthesis of tail-modified ipomoeassin analogs, a future scale-up of material could give access to a new library of ipomoeassin analogs for further SAR studies.



Scheme 3-10. Synthesis of Tail-Modified Analogs

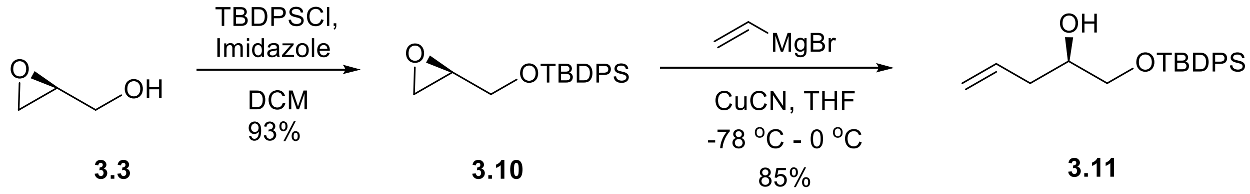
	Ipom F	Cmpd **3.29**	Cmpd **3.33**	Cmpd **3.34**
MDA-MB-231 (IC_{50}, nM)	6.3	2722.2	700.3	858.7
MCF-7 (IC_{50}, NM)	36.5	19013.2	1960.2	4254.7

Table 3-1. Cell Cytotoxicity Data

[redacted] Experimental Procedures

Reactions were carried out in oven-dried glassware. All reagents were purchased from commercial sources and were used without further purification unless specified. Except stated otherwise, all reactions were carried out under a nitrogen atmosphere and monitored by thin layer chromatography (TLC) using Silica Gel GF254 plates (Agela) with detection by charring with 5% (v/v) H2SO4 in EtOH or by visualizing in UV light (254 nm). Column chromatography was performed on silica gel (230–450 mesh, Sorbent). The ratio between silica gel and crude product ranged from 100 to 50:1 (w/w). NMR data were collected on a Bruker 300 or 400 MHz NMR spectrometer and a Bruker 300 or 400 MHz system. 1H NMR spectra were obtained in deuterochloroform (CDCl3) with chloroform (CHCl3, δH = 7.27 for 1H) as an internal reference. 13C NMR spectra were proton decoupled and were in CDCl3 with CHCl3 (δC = 77.0 for 13C) as an internal reference. Chemical shifts are reported in ppm (δ). Data are presented in the form: chemical shift (multiplicity, coupling constants, and integration). 1H data are reported as though they were first order. The errors between the coupling constants for two coupled protons were less than 0.5 Hz, and the average number was reported. Proton assignments, when made, were done so with the aid of COSY NMR spectra. For some compounds, HSQC and HMBC NMR were also applied to assign the proton signals. Optical rotations were measured on an Autopol III Automatic Polarimeter at 25 ± 1 °C for solutions in a 1.0 dm cell. High resolution mass spectrum (HRMS) and were acquired in the ESI mode.

Synthesis of the Tail-Protected Aglycon

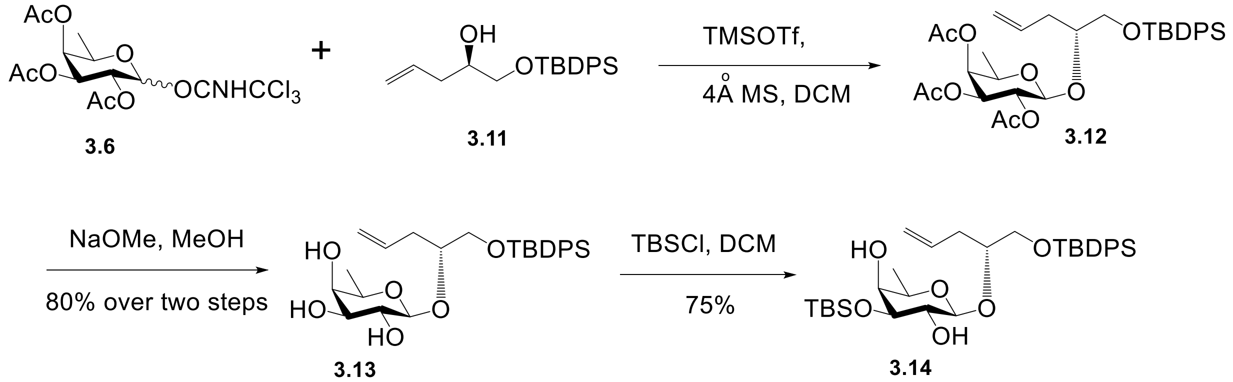


3.3 **3.10** **3.11**

(R)-tert-butyl(oxiran-2-ylmethoxy)diphenylsilane **3.10**. A stirred solution of (S)-glycidol (1.0 g, 1.0 eq) and imidazole (2.02 g, 2.2 eq) in DCM (15 mL) was cooled to 0 °C and TBDPSCl (4.56 mL, 1.2 eq) was slowly added under a nitrogen atmosphere. The reaction was allowed to warm to RT and was stirred overnight at which point TLC (EtOAc-Hexanes, 1:7) showed the reaction to be complete. The reaction mixture was diluted with water and extracted with DCM (x3). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated to dryness. The crude reside was purified via column chromatography (silica, EtOAc-Hexanes, 1:20 → 1:10) to give compound **3.10** (3.92 g, 93%).

(R)-1-((tert-butyldiphenylsilyl)oxy)pent-4-en-2-ol **3.11**. A solution of compound **3.10** (0.182 g, 1.0 eq) and CuCN (0.010 g, 0.2 eq) in THF (5 mL) was cooled to -30 °C and stirred for 10 min. Vinylmagnesium bromide (1.24 mL, 1.5 eq, 0.7 M in THF) was then slowly dripped in and stirred for 30 min before slowly warming to 0 °C and stirring for an additional 30 minutes at which point TLC (EtOAc-Hexanes, 1:7) showed the reaction to be complete. The reaction was then quenched with saturated NH_4Cl (aq.) still at 0 °C. The mixture was extracted with diethyl ether (3 x 10 mL) and the combined organic layers were washed with brine, dried over sodium sulfate, filtered evaporated and concentrated. The residue was purified via column chromatography (silica, EtOAc-Hexanes, 1:20 → 1:10) to give alcohol **3.11** (0.169 g, 85%).

Synthesis of TBDPS-Protected Fucoside Acceptor

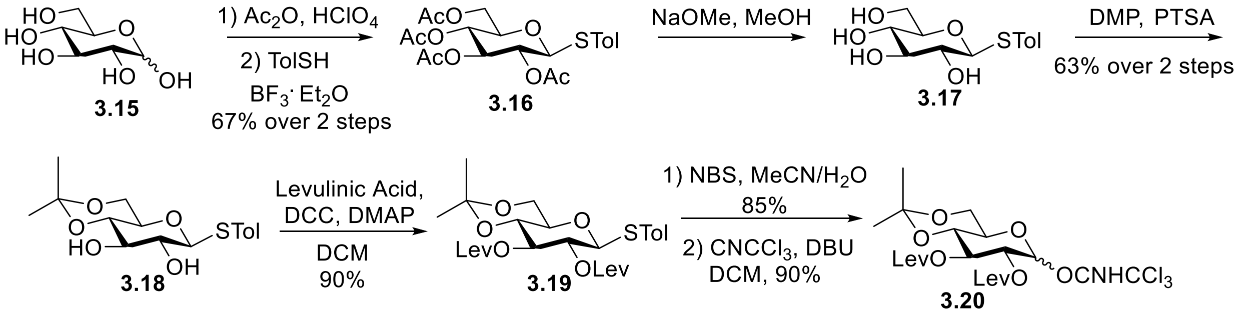

AcO
AcO
AcO
O
OCNHCCl3
3.6
+
OH
OTBDPS
3.11
TMSOTf,
4Å MS, DCM
AcO
AcO
AcO
O
O
OTBDPS
3.12
NaOMe, MeOH
80% over two steps
HO
HO
HO
O
O
OTBDPS
3.13
TBSCl, DCM
75%
HO
TBSO
OH
O
O
OTBDPS
3.14

Peracetylated fucoside **3.12**. A solution of fucosyl donor **3.6** (5.02 g, 1.1 eq) and acceptor **3.11** (3.62 g, 1.0 eq) in dry DCM (100 mL) was stirred over 4Å molecular sieves (5 g) for 30 min and then chilled to -78 ^{o}C. TMSOTf (0.209 mL, 0.1 eq) was added to the chilled solution and the reaction was slowly warmed to RT over 3 hours and left to stir overnight at which point TLC (EtOAc-hexanes, 1:2) showed the reaction to be mostly complete. The reaction was quenched with Et_3N (0.3 mL), filtered and purified by chromatography (silica, EtOAc-Hexanes, 1:10 → 1:6). After purification, NMR and TLC showed some impurities to remain but the crude residue was taken to the next step without any complications. Following the deprotection the triol could be easily separated from the impurities and fully characterized.

Fucoside **3.13**. A solution of crude compound **3.12** (4.98 g) was dissolved in MeOH at RT and NaOMe was stirred in until the solution was sufficiently basic (pH ~10). The reaction was left to stir overnight at which point TLC (EtOAc-Hexanes, 1:2) showed all of the SM had been consumed. The reaction was then neutralized by the addition of ion-exchange resin (to pH ~7). The suspension was filtered and then concentrated to dryness. The residue was purified via column chromatography (silica, EtOAc-Hexanes, 1:3 → 1:0) to give compound **3.13** (4.14 g, 80% over 2 steps).

Fucoside acceptor **3.14**. To a stirred solution of triol **3.13** (1.46 g, 1 eq) and imidazole (0.61 g, 3 eq) in DCM (40 mL) was added TBSCl (0.63 g, 1.4 eq) at 0 ^oC. The reaction was allowed to warm to RT after addition of TBSCl and was left to stir overnight at which point TLC (EtOAc-hexanes, 1:2) showed all the SM had been consumed and one major product was observed as well as small amounts of a regioisomer. The reaction mixture was transferred to a separatory funnel and washed with water (2 x 25 mL). The aqueous layers were extracted with DCM (2 x 25 mL) and the combined organic layers were washed with brine (30 mL), dried over sodium sulfate, filtered, and concentrated to dryness. The residue was purified via column chromatography (silica, EtOAc-Hexanes, 1:10 → 1:8) to give the desired compound **3.14** (1.35 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 6.8 Hz, 4H), 7.46 – 7.38 (m, 6H), 5.92 – 5.82 (m, 1H), 5.12 (t, *J* = 14.1 Hz, 2H), 4.17 (d, *J* = 7.8 Hz, 1H), 3.98 – 3.95 (m, 1H), 3.79 – 3.73 (m, 1H), 3.64 – 3.59 (m, 2H), 3.53 – 3.44 (m, 3H), 2.66 – 2.59 (m, 2H), 2.37 – 2.30 (m, 2H), 1.24 (d, *J* = 6.5 Hz, 3H), 1.09 (s, 9H), 0.93 (s, 10H), 0.15 (d, *J* = 8.1 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.59, 135.54, 135.06, 133.66, 133.41, 129.60, 129.59, 127.60, 127.59, 117.49, 103.17, 79.63, 77.32, 77.00, 76.68, 74.68, 72.05, 71.75, 70.04, 65.78, 36.43, 26.86, 25.73, 19.22, 18.07, 16.22, -4.44, -5.03.

[redacted] Synthesis of the Glucosyl Donor


1) Ac2O, HClO4
2) TolSH
BF3·Et2O
67% over 2 steps
3.15
3.16
NaOMe, MeOH
3.17
DMP, PTSA
63% over 2 steps
3.18
Levulinic Acid, DCC, DMAP
DCM
90%
3.19
1) NBS, MeCN/H2O
85%
2) CNCCl3, DBU
DCM, 90%
3.20
STol
OAc
OLev
LevO
OCNHCCl3

1,2,3,4,6-pentaacetate-*α,β*-D-glucopyranose **3.15b**. D-Glc*p* **3.15** (20.65 g, 0.14 mol) was slowly added to a mixture of acetic anhydride (90 mL) and $HClO_4$ (0.7 mL) over 0.5-1 hr at 0 ^{o}C. The reaction was allowed to warm slowly over 30 mins as the reaction turned from yellow to clear. TLC (silica, 2:1 Hex-EtOAc) showed the reaction to be complete. The reaction mixture was co-evaporated with toluene (150 mL) three times after quenching reaction with Et_3N. The residue was dissolved in sat. aq. $NaHCO_3$ (100 mL) and extracted twice with DCM (150 mL). The organic layers were combined, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Compound **3.15b** was carried on to the next step without further purification. ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 6.29 (d, *J* = 3.2 Hz, 1 H, H-1$_{\alpha}$), 5.67 (d, *J* = 7.7 Hz, c0.4 H, H-1$_{\beta}$), 5.44-5.35 (dd, *J* = 10.2 and 10.0 Hz, 1 H, H-3$_{\alpha}$), 5.29-5.21 (m, 0.4 H, H-3$_{\beta}$), 5.17-5.04 (m, 2.8 H, H-2$_{\alpha}$, H-2$_{\beta}$, H-4$_{\beta}$, H-4$_{\alpha}$), 4.30-4.26 (m, 1.4 H, H-6$_{\alpha}$, H-6$_{\alpha\beta}$), 4.12-4.01 (m, 2.4 H, H-6$_{\alpha}$, H-6$_{\beta}$, H-5$_{\alpha}$), 3.84-3.79 (0.4 H, H-5$_{\beta}$), 2.19 (s, 4.2 H), 2.13 (s, 1.2 H), 2.09 (s, 4.2 H), 2.02 (s, 8.4 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_c 170.4, 170.1, 169.5, 169.3, 168.6, 92.0 (C-1$_{\beta}$), 89.4 (C-1$_{\alpha}$), 73.2 (C$_{\beta}$), 70.6 (C$_{\beta}$), 70.2 (2C$_{\alpha,\beta}$), 69.5 (C$_{\alpha}$), 68.2 (C$_{\alpha}$), 61.7 (C$_{\alpha,\beta}$), 21.0, 21.0, 20.8, 20.7.[82]

4-(methylthio)phenyl-2,3,4,6-tetraacetate-*β*-D-glucopyranoside **3.16**. Peracetylated glucose **3.15b** (27 g, 69.3 mmol) was dissolved in dry DCM (300 mL) with 4-methylthiophenol (12.9 g, 138.7 mmol) and cooled to -10 °C. Then, $BF_3 \cdot OEt_2$ was slowly added and reaction stirred 12-48 hrs at RT. The reaction was monitored by TLC (silica, Hex-EtOAc 2:1, $R_f = 0.54$). The reaction mixture was slowly poured into crushed ice and stirred for 10 mins. The reaction was neutralized with careful addition of sat. aq. $NaHCO_3$ (200 mL) and extracted (300 mL x 2) with DCM. The combined organic layers were dried over $NaSO_4$, filtered, and the solvent removed under reduced pressure. The residue was purified with column chromatography (silica, Hex-EtOAc, 5:1-1:1) to give the *β*-thioGlc*p* **3.16** in 70% (85% BORSM). ^{1}H NMR (400 MHz, CDCl3) δ_H 7.38 (d, *J* = 7.8 Hz, 2H, 2 · Ar–*H*), 7.12 (d, *J* = 7.8 Hz, 2H, 2 · Ar–*H*), 5.20 (t, *J* = 9.6 Hz, 1H, H-3-Glc*p*), 5.01 (t, *J* = 9.6 Hz, 1H, H-4-Glc*p*), 4.93 (t, *J* = 9.7 Hz, 1H, H-2-Glc*p*), 4.62 (d, *J* = 10.1 Hz, 1H, H-1-Glc*p*), 4.23-4.14 (m, 2H, H-6-Glc*p*), 3.69 (ddd, *J* = 2.3, 4.3, 7.4 Hz, 1H, H-5-Glc*p*), 2.34 (s, 3H, S–Tol–C*H*3), 2.08 (s, 3H, –C*H*3), 2.08 (s, 3H, –C*H*3), 2.00 (s, 3H, –C*H*3), 1.99 (s, 3H, –C*H*3). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 170.6 (C=O), 170.1 (C=O), 169.4 (C=O), 169.3 (C=O), 138.7 (C=C), 133.7 · 2 (C=C), 129.6 · 2 (C=C), 127.4 (C=C), 85.7 (C-1), 75.8, 73.8, 69.8, 68.2, 62.1, 21.2 ($-CH_3$), 20.7 ($-CH_3$), 20.7 ($-CH_3$), 20.5($-CH_3$), 20.4 ($-CH_3$).[83,84]

4-(methylthio)phenyl-*β*-D-glucopyranoside **3.17**. The *β*-thioGlc*p* **3.16** (23.6 g, 51.9 mmol) was dissolved in MeOH (200 mL) and catalytic NaOMe (0.280 g, 5.2 mmol). The reaction was stirred at RT for 6-12 hrs, when the TLC (silica, EtOAc: MeOH 10:1, $R_f = 0.15$) showed the reaction to be complete. The reaction was neutralized with Amberlite IR-120 (H) ion exchange resin and filtered. The solvent was removed under reduced pressure. The crude tetraol **3.17** was used directly in the next step without further purification. ^{1}H NMR (400 MHz,

CD_3OD) δ_H 7.44 (d, *J* = 7.7, 2H, 2 • Ar–*H*), 7.11 (d, *J* = 7.8, 2H, 2 • Ar–*H*), 4.50 (d, *J* = 9.5, 1H, H-1-Glc*p*), 3.89 (d, *J* = 2.5, 1H), 3.76-3.71 (m, 2H), 3.59 (t, *J* = 9.2, 1H), 3.56-3.48 (m, 2H, H-5-Glc*p*), 2.30 (s, 3H, Ph –C*H*$_3$). ^{13}C NMR (100 MHz, CD_3OD) δ 138.5 (C=C), 133.0 • 2 (C=C), 132.2 • 2 (C=C), 130.7 (C=C), 90.8 (C-1), 80.7, 76.5, 71.1, 70.5, 62.7, 21.2 (Ph–CH_3).[85]

4-(methylthio)phenyl-4,6-*O*-isopropylidine-*β*-D-glucopyranoside **3.18**. The crude tetraol **3.17** (16.8 g, 58.6 mmol) was dissolved in the minimal amount of DMF (80 mL), then DMP (66 mL, 234 mmol) and catalytic *p*-TsOH (223 mg, 1.1 mg) were added to the solution at RT. The reaction was allowed to stir at RT overnight, while monitoring the reaction though TLC (Hex-EtOAc, 2:1, R_f = 0.49). The reaction was quenched with NEt_3 (0.5 mL), diluted with toluene, and solvent removed under reduced pressure. The crude syrup was dissolved in EtOAc (150 mL), washed with brine, dried over $NaSO_4$, filtered, and the EtOAc under reduced pressure. The syrup was purified using column chromatography (silica, Hex-EtOAc 4:1→1:2) to the C-4,C-6-protected glucoside **3.18** in 75% (15.75 g) clear syrup; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.40 (d, *J* = 8.2 Hz, 2H, 2 • Ar–*H*), 7.13 (d, *J* = 8.1 Hz, 2H, 2 • Ar–*H*), 4.58 (d, *J* = 9.6 Hz, 1H, C-1-Glc*p*), 3.94 (dd, *J* = 10.4, 5.2 Hz, 1H), 3.76 (t, *J* = 10.8 Hz, 1H), 3.68 (t, *J* = 8.4 Hz, 1H), 3.51 (t, *J* = 9.6 Hz, 1H), 3.41– 3.27 (m, 2H), 3.10 (br, 1H, –O*H*), 2.90 (br, 1H, –O*H*), 2.61 (s, 3H, Ph–C*H*$_3$), 1.49 (s, 3H, O–C–C*H*$_3$), 1.42 (s, 3H, O–C–C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ_H 138.68 (C=C), 133.43 • 2 (C=C), 129.84 • 2 (C=C), 127.50 (C=C), 99.80 (O–C–O), 88.80 (C-1), 74.91, 72.89, 72.66, 71.52, 61.97, 28.94 (Ph–CH_3), 21.12 (O–C–CH_3), 19.10 (O–C–CH_3).

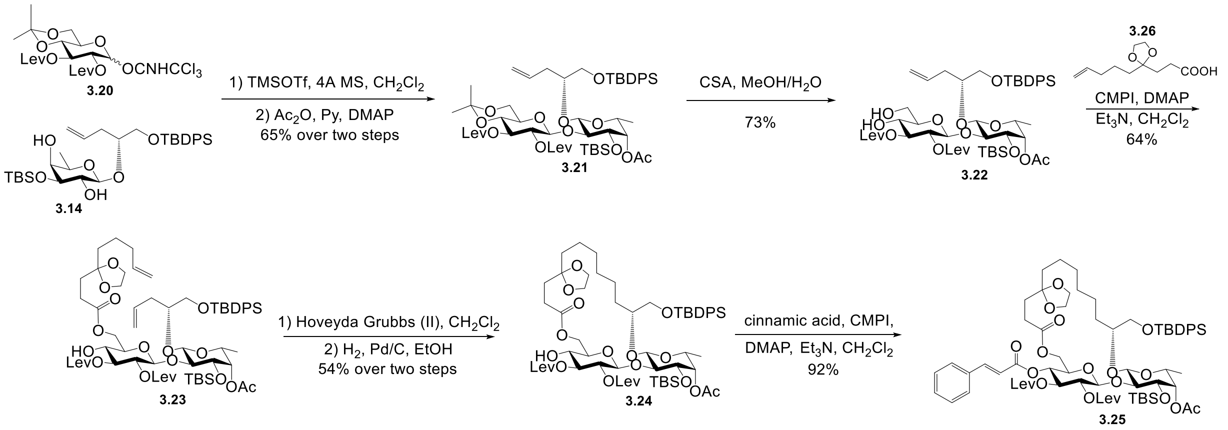
4-(methylthio)phenyl-2,3-*O*-levulinoyl-4,6-isopropylidine-*β*-D-glucopyranoside **3.19**. DCC (23.13 g, 112 mmol) was added in one portion to a cooled solution (0 °C) of DCM (300 mL), the diol **3.18** (12.2 g, 37.3 mmol), levulinic acid (13.0 g, 112mmol), and DMAP (991 mg, 7.4 mmol). The reaction was stirred at RT overnight, as the reaction started to form white precipitate (DCU), and the reaction turned a reddish-brown color. After TLC (silica, Hex-EtOAc, 3:1, $R_f = 0.58$) showed the reaction to be complete the DCM was partially removed under reduced pressure. The reaction was diluted with Et_2O (200 mL) and Hex (100 mL) to cause the DCU to crash out of the solution. The slurry was filtered through a pad of Celite and concentrated under reduced pressure. The residue was purified through column chromatography (silica, Hex-EtOAc, 2:1→1:1) to give the 2,3-lev-glucoside **3.19** in 90% (17.5 g). The material was carried through to the next step without characterization.

Hemiacetal-2,3-*O*-levulinoyl-4,6-*O*-isopropylidene-*α*,*β*-D-glucopyranoside **3.19b**. The 2,3-*O*-lev glucoside **3.19** was dissolved in the mixture of MeCN/H_2O (9:1, 108 mL:12 mL) and cooled to -10 °C. Then, NBS (15.1 mmol, 89.2 mmol) was slowly added over five mins to the mixture and stirred at -10 °C for 5-10 mins. After TLC (silica, Hex-EtOAc, $R_f = 0.51, 0.42$) showed the reaction to be complete, sat. aq. $Na_2S_2O_3$ (40 mL, orange to clear) was added followed by sat. aq. $NaHCO_3$ (120 mL). The mixture was partially concentrated under reduced pressure and the organic layer extracted with DCM (2 x 150 mL). The combined organic layers were collected, dried over $NaSO_4$, filtered, and concentrated under reduced pressure. The residue was purified with column chromatography (silica, Hex-EtOAc, 4:1→EtOAc) to the give the α,β-hemiacetal **3.19b** in 80%.

Trichloroacetimidate-2,3-*O*-levulinoyl-4,6-*O*-isopropylidene-*α,β*-D-glucopyranoside **3.20**. CCl_3CN (8.35 g, 83.0 mmol) and DBU (0.31 mL, 2.01 mmol) were are added to the mixture of the α*,β*-hemiacetal **3.19b** (8.64 g, 20.8 mmol). The reaction was allowed to stir at RT for 3-5 hrs. as the mixture turned an orange-brown color. The reaction was quenched with 0.5 mL of NEt_3 after the TLC (silica Hex-EtOAc 1:1 $R_{f\,=}$ 0.65) showed the reaction to be complete. The mixture was concentrated under reduced pressure. The Schmidt donor **3.20** was obtained in 85% (9.90 g), after purification by column chromatography (silica, Hex-EtOAc 4:1 →1:1, few drops of NEt_3). $[\alpha]^{25}_D$ + 52.4° (*c* 1 $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ_H 8.71, 8.64 (2s, 1H, OCN*H*CCl_3), 6.45 (d, *J* = 4.5 Hz, 1H, H-1-Glc*p*), 5.49 (t, *J* = 9.6 Hz, 1H, H-3-Glc*p*), 5.12 (dd, *J* = 10.0, 4.0 Hz, 1H, H-2-Glc*p*), 3.98 – 3.87 (m, 2H, H-5, H-6-Glc*p*), 3.84 – 3.68 (m, 2H, H-4-Glc*p*, H-6-Glc*p*), 2.90 – 2.46 (m, 8H, 2 · CH_3–C=O(C*H*$_2$)$_2$C–O), 2.17 (s, 3H, C*H*$_3$-C=O(CH_2)$_3$C-O), 2.16, 2.15 (2s, 3H, C*H*$_3$–C=O(CH_2)$_2$C–O), 1.49, 1.48 (2s, 3H, (C*H*$_3$)$_2$C–O), 1.40, 1.39 (2s, 3H, (C*H*$_3$)$_2$C–O). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 206.3, 206.2, 171.81, 171.7, 160.9, 99.9, 93.6, 90.7, 71.3, 70.3, 69.1, 66.0, 61.94, 37.7, 37.5, 29.7, 29.7, 28.7, 27.8, 27.5, 18.9.

[redacted] Synthesis of Key Triol Intermediate

[redacted] Preparation of Ring-Closed Intermediate


LevO
LevO
OCNHCCl3
3.20
HO
OTBDPS
TBSO
OH
3.14
1) TMSOTf, 4A MS, CH2Cl2
2) Ac2O, Py, DMAP
65% over two steps
OTBDPS
LevO
OLev
TBSO
OAc
3.21
CSA, MeOH/H2O
73%
OTBDPS
HO
HO
LevO
OLev
TBSO
OAc
3.22
3.26
COOH
CMPI, DMAP
Et3N, CH2Cl2
64%
OTBDPS
HO
LevO
OLev
TBSO
OAc
3.23
1) Hoveyda Grubbs (II), CH2Cl2
2) H2, Pd/C, EtOH
54% over two steps
OTBDPS
HO
LevO
OLev
TBSO
OAc
3.24
cinnamic acid, CMPI,
DMAP, Et3N, CH2Cl2
92%
OTBDPS
LevO
OLev
TBSO
OAc
3.25

Disaccharide **3.21**. To a stirred solution of donor **3.20** (4.01 g, 1.0 eq) and acceptor **3.14** (4.30 g, 1.0 eq) in DCM was added 4 Å molecular sieves at RT. The mixture was stirred for 30 min and cooled to -78 ^{o}C. TMSOTf (0.13 mL, 0.1 eq) was then added to the reaction mixture and left to stir for an hour. After an hour, the reaction was allowed to warm to 0 ^{o}C at which point TLC (EtOAc-hexanes, 1:2) showed the reaction to be complete. The reaction was quenched with pyridine, filtered, and concentrated to dryness. The crude product was carried on to the next step without purification. To a cold (0 ^{o}C) solution of the crude disaccharide and DMAP (trace) in pyridine (40 mL) was added acetic anhydride (12 mL). The reaction mixture was heated to 40 ^{o}C and stirred for an additional 24 h, at the end of which time TLC (silica, 1:2 EtOAc–hexanes) indicated that the reaction was complete. The mixture was concentrated under reduced pressure and then co-evaporated with toluene (2 × 50 mL) gave the crude product. The residue was purified by column chromatography (silica, EtOAc–hexanes, 1:3 → 1:2) to afford compound **3.21** (4.84 g, 65% over 2 steps) as a colorless syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.70 – 7.67 (m, 4H), 7.44 – 7.36 (m, 6H), 6.07 – 5.97 (m, 1H), 5.15 – 5.04 (m, 4H), 4.96 – 4.90 (m, 2H), 4.27 (d, *J* = 7.6 Hz, 1H), 3.95 – 3.81 (m, 3H), 3.77 – 3.62 (m, 5H), 3.47 (q, *J* = 6.3 Hz, 1H), 3.29 – 3.22 (m, 1H), 2.84 – 2.51 (m, 10H), 2.43 – 2.37 (m, 1H), 2.17 (d, *J* = 5.8 Hz, 6H), 2.10 (s, 3H), 1.44 (s, 3H), 1.37 (s, 3H), 1.07 (s, 10H), 0.97 (d, *J* = 6.4 Hz, 3H), 0.87 (s, 10H), 0.15 (s, 3H), 0.10 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 206.33, 206.11, 171.89, 171.33, 170.65, 135.61, 135.58, 135.08, 133.74, 133.54, 129.53, 127.56, 127.54, 116.69, 102.19, 99.67, 99.37, 81.15, 77.32, 76.68, 75.22, 73.42, 73.37, 73.33, 72.44, 71.53, 68.83, 67.37, 65.60, 62.14, 37.73, 36.19, 29.77, 29.75, 28.88, 27.88, 27.86, 26.83, 25.82, 20.84, 19.21, 18.85, 17.74, 16.34, -4.46, -4.47

Diol **3.22**. CSA (214 mg, 0.20 eq) was added in one portion to a solution of compound **3.21** (4.80 g, 1.0 eq) in MeOH (50 mL) at room temperature. The reaction mixture was stirred for 2 hours at which point TLC (silica, 1:2 EtOAc–hexanes) showed it was complete. The solvent was removed, and the residue was purified by column chromatography (silica, EtOAc–hexanes, 1:2) gave compound **3.22** (3.37 g, 73%) as a colorless syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.68 – 7.66 (m, 4H), 7.43 – 7.35 (m, 6H), 6.03 – 5.94 (m, 1H), 5.14 – 4.90 (m, 6H), 4.26 (d, *J* = 7.7 Hz, 1H), 3.92 – 3.83 (m, 3H), 3.79 – 3.67 (m, 4H), 3.64 – 3.60 (m, 1H), 3.46 (q, *J* = 6.3 Hz, 1H) 3.41 – 3.39 (m, 2H), 2.85 – 2.77 (m, 3H), 2.71 – 2.51 (m, 6H), 2.39 – 2.31 (m, 2H), 2.17 (d, *J* = 8.5 Hz, 6H), 2.11 (s, 3H), 1.06 (s, 9H), 0.97 (d, *J* = 6.4 Hz, 3H), 0.88 (s, 9H), 0.14 (s, 3H), 0.10 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 208.11, 206.07, 173.06, 171.34, 170.70, 135.58, 135.56, 134.92, 133.74, 133.51, 129.55, 129.53, 127.57, 127.53, 116.89, 102.27, 98.75, 81.62, 77.32, 76.68, 76.24, 74.98, 74.75, 73.47, 73.21, 72.06, 69.72, 68.84, 65.67, 62.00, 38.34, 37.64, 36.22, 29.74, 29.72, 28.08, 27.88, 26.82, 25.75, 20.89, 19.20, 17.66, 16.34, -4.35, -4.60

Diene **3.23**. To a stirred solution diol **3.22** (3.32 g, 1.0 eq) in dry DCM (50 mL) was added 1-methyl-2-chloropyrdium iodide (CMPI) (1.69 g, 2.0 eq), DMAP (203 mg, 0.5 eq), and the acid **3.26** (0.781 g, 1.1 eq). After the reaction was cooled to 0 ^oC, NEt_3 (3.36 g, 4.62 mL, 10 eq) was added and the reaction was allowed to slowly warm to RT over 1-2 hrs. At this point TLC showed the reaction to be complete (silica, Hex–EtOAc 1:1). The reaction was concentrated under reduced pressure and purified by column chromatography (silica, Hex−EtOAc, 5:1 → 1:1) to give the diene **3.23** (2.54 g, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.69 – 7.66 (m, 4H), 7.43 – 7.35 (m, 6H), 6.09 – 5.99 (m, 1H), 5.83 – 5.73 (m, 1H), 5.14 – 4.89 (m, 8H), 4.44 (dd, *J* = 12.2, 3.8 Hz, 1H), 4.30 – 4.23 (m, 2H), 3.95 – 3.60 (m, 10H), 3.48 – 3.45

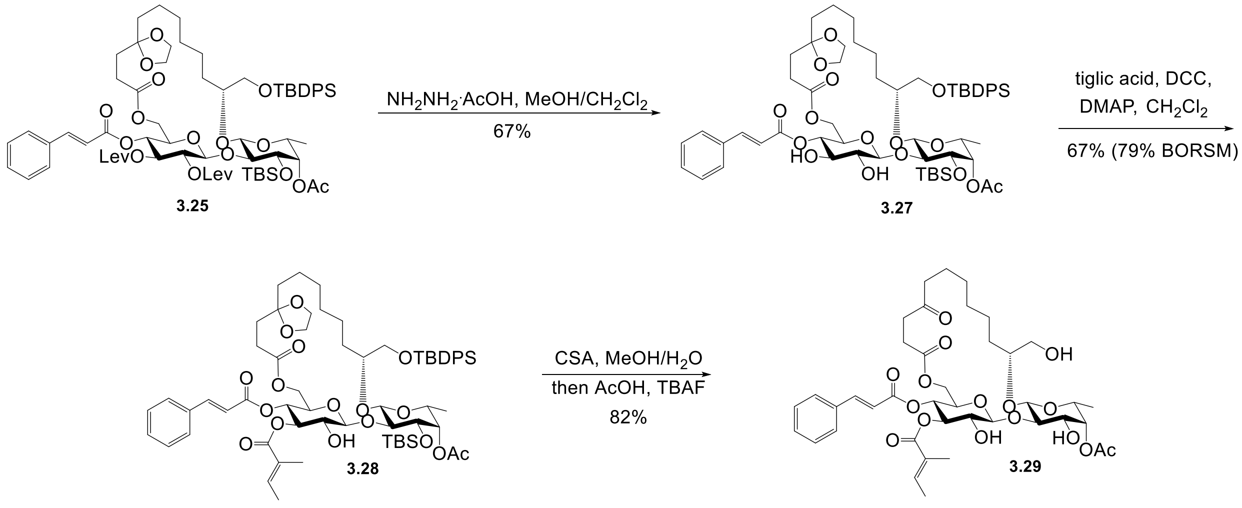
(m, 3H), 2.82 – 2.76 (m, 3H), 2.73 – 2.48 (m, 6H), 2.44 – 2.35 (m, 3H), 2.16 (d, *J* = 10.0 Hz, 6H), 2.10 (s, 3H), 2.05 – 1.99 (m, 4H), 1.61 – 1.57 (m 2H), 1.49 – 1.43 (m, 2H), 1.06 (s, 9H), 0.97 (d, *J* = 6.4 Hz, 3H), 0.87 (s, 9H), 0.15 (s, 3H), 0.10 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 207.34, 206.06, 174.01, 172.78, 171.24, 170.63, 138.37, 135.58, 135.56, 135.25, 133.72, 133.51, 129.53, 127.56, 127.53, 116.73, 114.77, 110.81, 102.30, 98.90, 81.57, 77.32, 77.00, 76.68, 75.36, 75.09, 73.94, 73.43, 73.37, 72.34, 68.86, 68.72, 65.72, 65.09, 65.01, 62.84, 38.11, 37.69, 36.83, 36.34, 33.72, 32.04, 29.72, 28.64, 27.97, 27.85, 26.80, 25.80, 22.94, 20.83, 19.19, 17.71, 16.34, -4.46, -4.52.

Ring-Closed Intermediate **3.24**. To a solution of diene **3.23** (2.49 g, 1.0 eq) in DCM (500 mL) was added Hoveyda-Grubbs catalyst 2nd generation (0.26 g, 0.2 eq) in one portion at room temperature. The reaction mixture was refluxed for 4 h. At this point, TLC (silica, 1:2 EtOAc–hexanes) showed the reaction was complete. The reaction was cooled to ambient temperature and then concentrated. Flash chromatography (silica, EtOAc–hexanes, 1:2 → 1:1) gave the mixture of isomers as a colorless syrup. The obtained isomer was subjected to hydrogenation in next step and the product was fully characterized. To a solution of the cycloalkene isomers in EtOH (50 mL) was added 10% Pd/C (0.5 g) in one portion at room temperature. The reaction was then stirred under an atmosphere of hydrogen for 4 hours at the same temperature. At this point, TLC (silica, 1:2 EtOAc–hexanes) showed the reaction was complete. The reaction mixture was filtered thru a pad of celite using EtOAc as the eluent and the resulting filtrate concentrated. Flash chromatography (silica, EtOAc–hexanes, 1:2 → 1:1) gave compound **3.24** (1.32 g, 54% over 2 steps) as a colorless syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.68 – 7.66 (m, 4H), 7.43 – 7.35 (m, 6H), 5.11 – 5.03 (m, 2H), 4.95 – 4.84 (m, 3H), 4.17 (d, *J* = 7.7 Hz, 1H), 4.03 – 3.88 (m, 8H), 3.82 (dd, *J* = 9.2, 3.4 Hz, 1H), 3.60 – 3.58 (m, 2H), 3.47 – 3.34 (m, 3H), 2.79 – 2.75 (m, 4H), 2.64 – 2.55 (m, 5H), 2.44 – 2.38 (m, 2H), 2.17 (d, *J* = 1.7 Hz, 6H), 2.08 (s, 3H), 1.98 – 1.92 (m, 1H), 1.70 – 1.26 (m, 15H), 1.06 (s, 9H), 0.95 (d, *J* = 6.4 Hz, 3H), 0.88 (s, 9H), 0.18 (s, 3H), 0.13 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 206.83, 206.24, 175.34, 172.37, 171.25, 170.70, 135.63, 135.62, 133.97, 133.77, 129.51, 129.49, 127.55, 127.51, 111.08, 102.58, 98.93, 82.97, 77.32, 76.68, 74.99, 74.89, 74.56, 73.54, 73.33, 72.13, 68.75, 67.35, 66.07, 64.68, 64.52, 62.26, 53.79, 37.93, 37.77, 35.70, 31.95, 31.65, 29.83, 29.80, 29.77, 29.26, 28.92, 28.24, 27.90, 26.88, 25.83, 23.50, 23.06, 20.89, 19.25, 17.61, 16.43, -4.10, -4.56.

Compound **3.25**. CMPI (419 mg, 1.5 eq), DMAP (66.7 mg, 0.5 eq) and NEt_3 (1.11 g, 1.53 mL, 10 eq) were added to a solution of **3.24** (1.28 g, 1 eq) and cinnamic acid (243 mg, 1.5 eq) in dry DCM (30 mL) at -10 °C. The reaction was allowed to slowly warm to ambient temperature and stirred overnight. At this point, TLC (silica, 2:1 Hex–EtOAc) showed the reaction was complete. The reaction mixture was diluted with DCM (30 mL) washed with sat. $NaHCO_3$ (30 mL) and extracted with DCM (30 mL). The combined organic extracts were dried over Na_2SO_4. Evaporation of the solvent followed by purification of the residue by column chromatography (silica, Hexanes−EtOAc, 3:1 → 1:2) to give **3.25** (1.31 g, 92%) as a colorless syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.70 – 7.66 (m, 4H), 7.53 – 7.51 (m, 2H), 7.42 – 7.38 (m, 9H), 6.36 (d, *J* = 16.0 Hz, 1H), 5.29 – 5.20 (m, 3H), 5.01 – 4.95 (m, 2H), 4.36 (dd, *J* = 12.3, 2.6 Hz, 1H), 4.26 (d, *J* = 7.6 Hz, 1H), 4.07 (dd, *J* = 12.3, 2.2 Hz, 1H), 3.99 – 3.82 (m, 7H), 3.69 – 3.59 (m, 3H), 3.48 – 3.42 (m, 1H), 2.79 – 2.76 (m, 2H), 2.70 – 2.64 (m, 2H), 2.61 – 2.47 (m, 5H), 2.39 – 2.35 (m, 2H), 2.15 (s, 3H), 2.09 (s, 6H), 2.01 – 1.96 (m, 1H), 1.73 – 1.26 (m, 15H), 1.07 (s, 9H), 0.96 (d, *J* = 6.4 Hz, 3H), 0.91 (s, 9H), 0.20 (s, 3H), 0.14 (s, 3H). ^{13}C NMR (100

MHz, CDCl$_3$) δ_C 206.16, 206.05, 172.94, 171.88, 171.12, 170.66, 165.00, 146.07, 135.62, 135.61, 134.09, 133.88, 133.60, 130.52, 129.55, 129.52, 128.82, 128.26, 127.59, 127.54, 116.76, 111.23, 102.24, 98.86, 82.67, 77.32, 76.68, 74.29, 74.04, 73.50, 73.05, 72.19, 71.89, 68.86, 68.46, 66.02, 64.52, 64.49, 61.63, 37.76, 37.68, 34.60, 31.93, 31.24, 30.01, 29.77, 29.56, 29.24, 29.00, 28.20, 27.91, 27.82, 26.87, 25.88, 23.92, 22.93, 20.84, 19.23, 17.73, 16.37, -4.31, -4.50.

[redacted] Preparation of Triol Intermediate


OTBDPS
LevO
OLev
TBSO
OAc
3.25
NH$_2$NH$_2$·AcOH, MeOH/CH$_2$Cl$_2$
67%
HO
OH
3.27
tiglic acid, DCC,
DMAP, CH$_2$Cl$_2$
67% (79% BORSM)
3.28
CSA, MeOH/H$_2$O
then AcOH, TBAF
82%
OH
HO
3.29

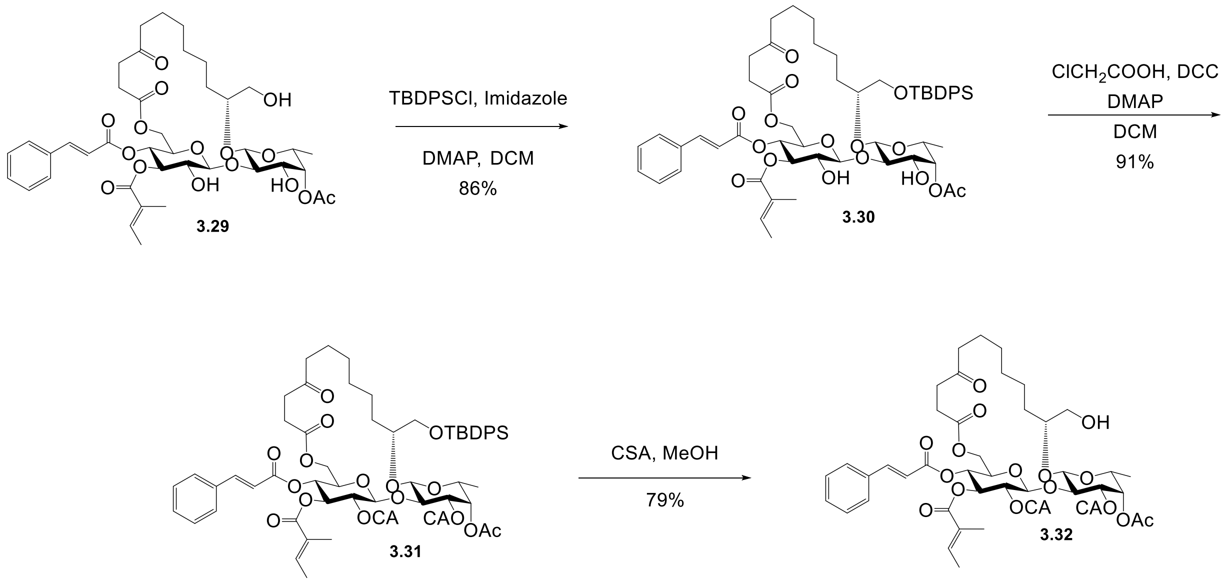
Diol **3.27**. Hydrazine acetate (0.535 g, 6.0 eq) was added in one portion to a solution of compound **3.25** (1.26 g, 1.0 eq) in 2:1 DCM/MeOH (16 mL) at room temperature. The reaction mixture was stirred for 2 hr, at which point TLC (silica, 2:1 Hex–EtOAc) showed the reaction was complete. Then the reaction was quenched with sat. aq. NaHCO$_3$ (20 mL) and extracted with DCM (25 mL x 2). The combined organic extracts were dried over Na$_2$SO$_4$, evaporated and purified by column chromatography (silica, Hex–EtOAc, 3:1→ 1:1) to afford compound **3.27** (717 mg, 67%) as a colorless syrup. ^{1}H NMR (400 MHz, CDCl$_3$) δ_H 7.71 – 7.68 (m, 4H), 7.55 –

7.53 (m, 2H), 7.45 – 7.38 (m, 9H), 6.46 (d, *J* = 16.0 Hz, 1H), 5.12 – 5.05 (m, 2H), 4.62 (d, *J* = 7.7 Hz, 1H), 4.40 (d, *J* = 7.6 Hz, 1H), 4.25 (dd, *J* = 11.9, 3.8 Hz, 1H), 4.14 – 4.08 (m, 1H), 3.95 – 3.80 (m, 9H), 3.77 – 3.63 (m, 5H), 3.51 – 3.42 (m, 2H), 2.66 (d, *J* = 2.4 Hz, 1H), 2.35 – 2.30 (m, 2H), 2.11 (s, 3H), 2.05 – 1.90 (m, 3H), 1.76 – 1.55 (m, 5H), 1.43 – 1.25 (br, m, 10H), 1.07 (s, 9H), 1.02 (d, *J* = 6.4 Hz, 3H), 0.92 (s, 9H), 0.22 (s, 3H), 0.18 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 173.06, 170.58, 166.17, 146.13, 135.64, 135.62, 134.15, 133.79, 133.61, 130.50, 129.60, 129.60, 128.86, 128.21, 127.59, 127.56, 117.12, 111.21, 103.34, 102.14, 80.97, 78.13, 77.32, 77.20, 76.68, 75.99, 73.46, 72.99, 72.69, 72.40, 71.46, 68.71, 65.74, 64.59, 64.46, 63.61, 60.34, 35.08, 31.60, 31.31, 29.70, 29.02, 28.53, 26.87, 25.86, 24.04, 22.71, 21.00, 20.75, 19.25, 17.84, 16.37, 14.16, -4.37, -4.63.

Intermediate **3.28**. A solution of compound **3.27** (711 mg, 1.0 eq), tiglic acid (70.8 mg, 1.1 eq) DCC (159 mg, 1.2 eq), and DCM (20 mL) were cooled to -10 ^{o}C. Then DMAP (7.8 mg, 0.1 eq) was added to the solution in portion and the reaction allowed to slowly warm to RT overnight. TLC (silica, Hex-EtOAc, 2:1) showed the reaction to be mostly complete. The solvent was partially removed, then Hex (16 mL) and Et_2O (8 mL) were added, then stirred for 20 min to precipitate the DCU byproduct. The mixture was filtered through a pad of Celite using cold Et_2O (20 mL) as the eluent, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica, Hex-EtOAc 6:1 → 1:1) to give intermediate **3.28** (512 mg, 67%) (603 mg, 79% BORSM). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.71 – 7.68 (m, 4H), 7.53 – 7.50 (m, 2H), 7.45 – 7.38 (m, 9H), 6.85 – 6.80 (m, 1H), 6.36 (d, *J* = 16.0 Hz, 1H), 5.34 – 5.20 (m, 2H), 5.04 (d, *J* = 3.1 Hz, 1H), 4.70 (d, *J* = 7.6 Hz, 1H), 4.39 (d, *J* = 7.6 Hz, 1H), 4.23 (dd, *J* = 11.9, 3.7 Hz, 1H), 4.08 (dd, *J* = 11.9, 4.6 Hz, 1H), 3.96 – 3.67 (m, 12H), 3.61 – 3.56 (m, 1H), 3.49 (q, *J* = 6.36 Hz, 1H), 2.39 – 2.25 (m, 2H), 2.09 (s, 3H), 2.05 – 1.88 (m, 2H), 1.76 – 1.72 (m, 7H), 1.66 – 1.54 (m, 5H), 1.34 (br, 10H), 1.08 (s, 9H), 1.01 (d, *J* = 6.4 Hz, 3H), 0.89 (s, 9H), 0.21 (s, 3H), 0.17 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 173.06, 170.70, 167.47, 165.60, 146.03, 138.10, 135.66, 134.10, 133.80, 133.62, 130.51, 129.64, 128.85, 128.24, 127.91, 127.62, 127.59, 116.87, 111.25, 103.82, 102.22, 80.98, 78.40, 77.32, 76.68, 74.43, 72.95, 72.83, 72.69, 72.26, 69.73, 68.74, 65.70, 64.60, 64.48, 63.56, 35.06, 31.68, 31.38, 29.69, 29.11, 28.56, 26.90, 25.78, 24.03, 22.80, 20.83, 19.26, 17.82, 16.36, 14.35, 11.97, -4.43, -4.55.

Triol **3.29**. To a stirred solution of compound **3.28** (504 mg, 1.0 eq) in MeOH (10 mL) and H_2O (0.1 mL) was added CSA (19.7 mg, 0.2 eq) at RT. The reaction was stirred for 12 hours at which point TLC (silica, Hex-EtOAc, 2:1) showed the SM to be consumed. After the initial reaction was complete, to the same pot was added TBAF (1M in THF, 8.48 mL, 20 eq) and AcOH (2.9 mL, 50 eq) at 0 ^{o}C. The reaction was allowed to warm to RT and stir overnight at which point TLC (silica, Hex-EtOAc, 1:1) indicated that the reaction was fully deprotected. The reaction mixture was then diluted with Et_2O (20 mL) and washed with 1M HCl (10 mL), then saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL). The aqueous layers were extracted with Et_2O (20 mL x 2) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was then purified via column chromatography (silica, Hex-EtOAc 2:1 → 0:1) to give compound **3.29** (275 mg, 82%). δ_H 7.64 (d, *J* = 16.0 Hz, 1H), 7.52 – 7.49 (m, 2H), 7.40 – 7.39 (m, 3H), 6.94 – 6.89 (m, 1H), 6.35 (d, *J* = 16.0 Hz, 1H), 5.36 (t, *J* = 9.8 Hz, 1H), 5.19 (d, *J* = 3.1 Hz, 1H), 5.07 (t, *J* = 9.5 Hz, 1H), 4.66 (d, *J* = 7.8 Hz, 1H), 4.53 (dd, *J* = 12.5, 3.1 Hz, 1H), 4.42 (d, *J* = 7.7 Hz, 1H), 4.16 – 4.09 (m, 2H), 3.92 (dd, *J* = 9.6, 3.5 Hz, 1H), 3.83 – 3.47 (m, 7H), 2.89 – 2.44 (m, 7H), 2.19 (s, 3H), 2.07 – 2.05 (m, 2H), 1.79 – 1.61 (m, 10H), 1.45 – 1.21 (m, 12H), 0.98 – 0.86 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$) δ_C 209.85, 171.72, 171.30, 169.40, 165.32, 146.19, 140.42, 133.94, 130.67, 128.89, 128.25, 127.40, 116.63, 106.13, 101.51, 84.62, 83.61, 74.18, 72.49, 72.20, 69.40, 67.10, 65.09, 61.82, 60.36, 41.75, 37.39, 31.52, 28.96, 28.63, 28.27, 25.39, 23.07, 21.00, 20.82, 16.21, 14.63, 14.16, 13.66, 11.89. HRMS for $C_{40}H_{54}NaO_{16}$ (M+Na)$^+$ 813.3304. Found: 813.3292

[redacted] Completion of Intermediate for Analog Synthesis

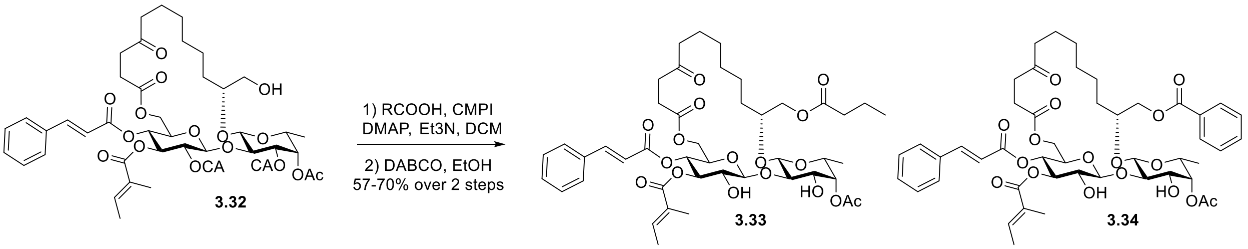


Diol **3.30**. To a stirred solution of triol **3.29** (265 mg, 1 eq) and imidazole (68.4 mg, 3 eq) in DCM (10 mL) was added TBDPSCl (276 mg, 3 eq) and DMAP (20.5 mg, 0.5 eq) at 0 °C. The reaction was allowed to warm to RT after addition of TBDPSCl and was left to stir overnight at which point TLC (EtOAc-hexanes, 1:1) showed all the SM had been consumed and one major product was observed. The reaction mixture was transferred to a separatory funnel and washed with water (2 x 10 mL). The aqueous layers were extracted with DCM (2 x 10 mL) and the combined organic layers were washed with brine (10 mL), dried over sodium sulfate, filtered, and concentrated to dryness. The residue was purified via column chromatography (silica, EtOAc-Hexanes, 1:2 → 1:0) to give the desired compound **3.30** (297 mg, 86%). ^{1}H NMR (400 MHz, CDCl$_3$) δ_H 7.70 – 7.68 (m, 4H), 7.63 (d, *J* = 16.0 Hz, 1H) 7.52 – 7.50 (m, 2H), 7.46 – 7.37 (m, 9H), 6.92 – 6.87 (m, 1H), 6.35 (d, *J* = 16.0 Hz, 1H), 5.29 (t, *J* = 9.8 1H), 5.11 – 5.06 (m, 2H), 4.59 (br, 1H), 4.54 (d, *J* = 7.8 Hz, 1H), 4.43 (dd, *J* = 12.4, 3.1 Hz, 1H), 4.39 (d, *J* = 7.7 Hz, 1H), 4.02 – 3.98 (m, 2H), 3.90 – 3.84 (m, 2H), 3.75 – 3.57 (m, 6H), 2.76 – 2.43 (m, 6H), 2.16 (s, 3H), 1.76 – 1.61 (m, 14H), 1.34 – 1.22 (m, 7H), 1.07 (s, 12H). ^{13}C NMR (100 MHz, CDCl$_3$) δ_C 210.05, 171.71, 171.57, 169.05, 165.38, 146.11, 140.00, 134.00, 133.90, 133.70, 130.64, 129.64, 129.61, 128.90, 128.26, 127.62, 127.58, 127.51, 116.72, 105.84, 101.06, 83.10, 80.64, 77.20, 76.12, 74.21, 72.68, 72.46, 72.43, 68.78, 67.45, 66.01, 61.86, 41.77, 37.61, 36.62, 31.32, 29.18, 29.07, 28.40, 26.91, 24.77, 24.67, 23.59, 20.88, 19.29, 16.27, 14.60, 11.94.

Protected intermediate **3.31**. DCC (232 mg, 4.0 eq) was added in one portion to a 0 ºC DCM (10 mL) solution of **3.30** (289 mg, 1.0 eq), chloroacetyl acid (127 mg, 4.0 eq) and 4-dimethylaminopyridine (34.3 mg, 1.0 eq). The reaction was allowed to warm to ambient temperature and stirred overnight. At this point, TLC (silica, 1:1 EtOAc–hexanes) showed the reaction was complete. The reaction mixture was diluted with ether (10 mL) and hexanes (5 mL), stirred for 20 minutes then filtered thru a pad of celite using ether (10 mL) as the eluent and the filtrate concentrated *in vacuo*. The residue was purified by column chromatography (silica, EtOAc–hexanes, 1:5 → 1:2) gave compound **3.31** (302 mg, 91 %). Some DCU remained after purification but the crude material was carried forward to the next step and characterized following deprotection.

Compound **3.32**. To a stirred solution of **3.31** (290 mg, 1.0 eq) in MeOH (10 mL) was added CSA (11.4 mg, 0.2 eq) at 0 ^{o}C. The reaction was allowed to warm to RT as it stirred overnight. TLC (Silica, 1:1 EtOAc–hexanes) indicated that the reaction was complete. The reaction mixture was diluted concentrated and then diluted with DCM (15 mL) and washed with a saturated solution of $NaHCO_3$ (10 mL). The aqueous layer was extracted with DCM (2 x 10 mL) and the combined organic layers were washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated to dryness. The residue was purified via column chromatography (Silica, EtOAc–hexanes, 1:4 → 1:1) to give compound **3.32** (183 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.62 (d, *J* = 16 Hz, 1H), 7.51 – 7.49 (m, 2H), 7.40 – 7.39 (m, 3H), 6.82 – 6.78 (m, 1H), 6.32 (d, *J* = 16.0 Hz, 1H), 5.35 (p, *J* = 8.4 Hz, 2H), 5.19 (m, *J* = 3.1 Hz, 1H), 5.13 – 4.96 (m, 3H), 4.52 – 4.47 (m, 2H), 4.20 – 4.14 (m, 3H), 4.05 – 3.83 (m, 6H), 3.65 – 3.56 (m, 4H), 3.17 – 3.16 (m, 1H), 2.99 – 2.92 (m, 1H), 2.75 – 2.40 (m, 6H), 2.20 (s, 2H), 1.96 – 1.93 (m, 1H), 1.75 – 1.58 (m, 18H), 1.37 – 1.22 (m, 20H), 0.90 – 0.87 (m, 2H).

[redacted] Synthesis of Tail-Modified Analogs



Analog **3.33**. To a stirred solution of compound **3.32** (20.0 mg, 1.0 eq) in dry DCM (5 mL) was added 1-methyl-2-chloropyrdium iodide (CMPI) (1.69 g, 2.0 eq), DMAP (203 mg, 0.5 eq), and butanoic acid (0.781 g, 1.5 eq). After the reaction was cooled to 0 ^{o}C, NEt_3 (3.36 g, 4.62 mL, 10 eq) was added and the reaction was allowed to slowly warm to RT over 1-2 hrs. At this point TLC showed the reaction to be complete (silica, Hex–EtOAc 1:1). The reaction mixture was then concentrated and re-dissolved in ethanol (5 mL). To the solution was added DABCO (4.8 mg, 2.0 eq) at rt. The reaction was stirred for one hour, at which point TLC (silica, 1:1 EtOAc–hexanes) showed it was complete. The reaction mixture was diluted with DCM (5 mL), washed with 1M HCl (5 mL) and saturated aqueous $NaHCO_3$ (5 mL). The aqueous layer was extracted with DCM (2 x 5 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica, EtOAc–hexanes, 1:3 → 1:0) to give compound **3.33** (12.7 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.65 (d, *J* = 16 Hz, 1H), 7.53 – 7.50 (m, 2H), 7.40 – 7.39 (m, 3H), 6.94 – 6.90 (m, 1H), 6.36 (d, *J* = 16.0 Hz, 1H), 5.35 – 5.31 (m, 2H), 5.16 – 5.07 (m, 3H), 4.64 – 4.48 (m, 1H), 4.49 – 4.41 (m, 1H), 4.23 – 4.12 (m, 3H), 3.96 – 3.68 (m, 10H), 2.75 – 2.21 (m, 8H), 2.18 (s, 2H), 2.05 – 2.01 (m, 1H), 1.96 – 1.93 (m, 1H), 1.77 – 0.86 (m, 38H). HRMS for $C_{44}H_{60}NaO_{17}$ $(M+Na)^+$ 883.3723. Found: 883.3716

Analog **3.34** (10.8 mg, 57%). Synthesized from compound **3.32** (20.0 mg) in the same method as above. HRMS for $C_{47}H_{58}NaO_{17}$ $(M+Na)^+$ 917.3566. Found: 853.3565

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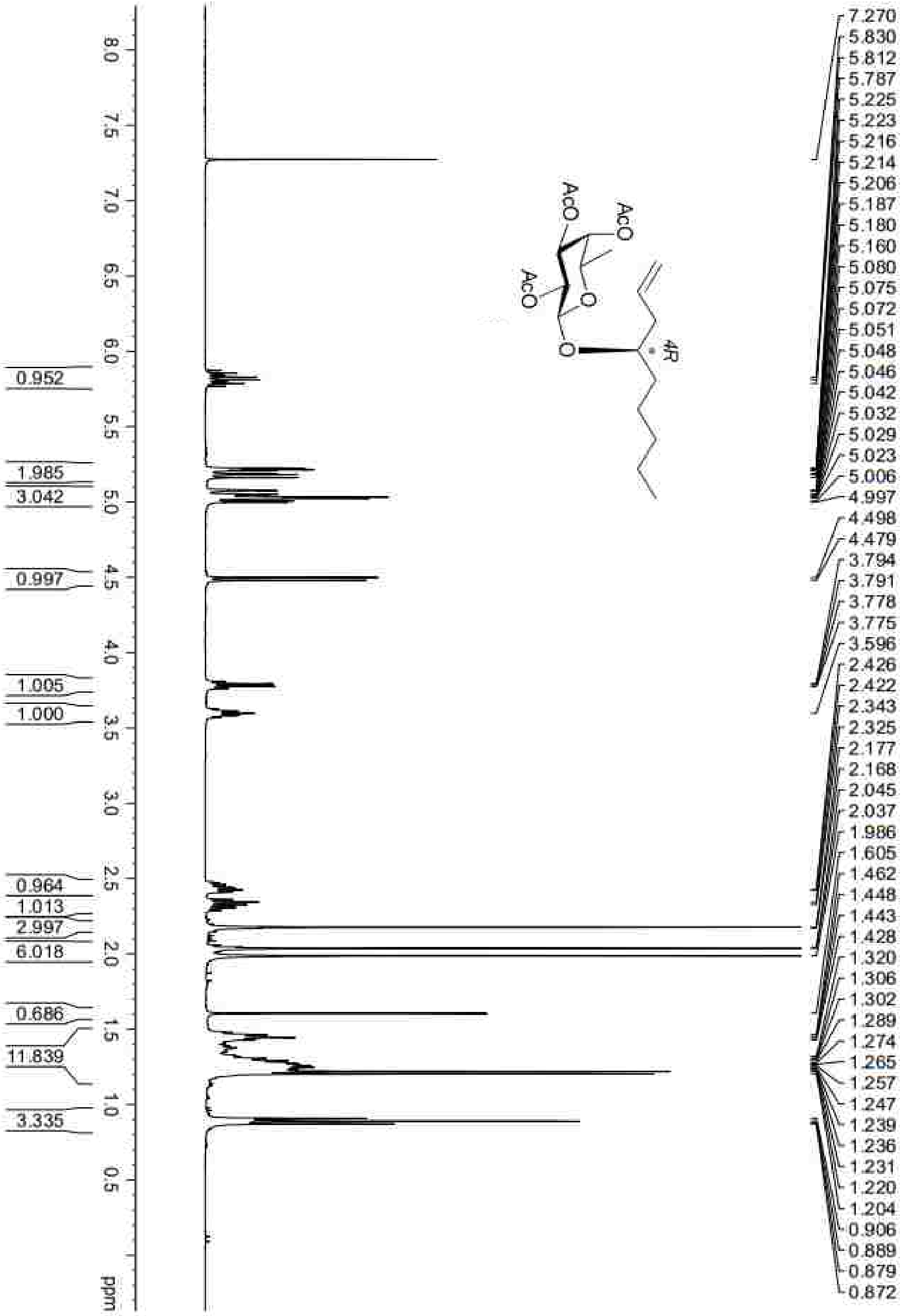
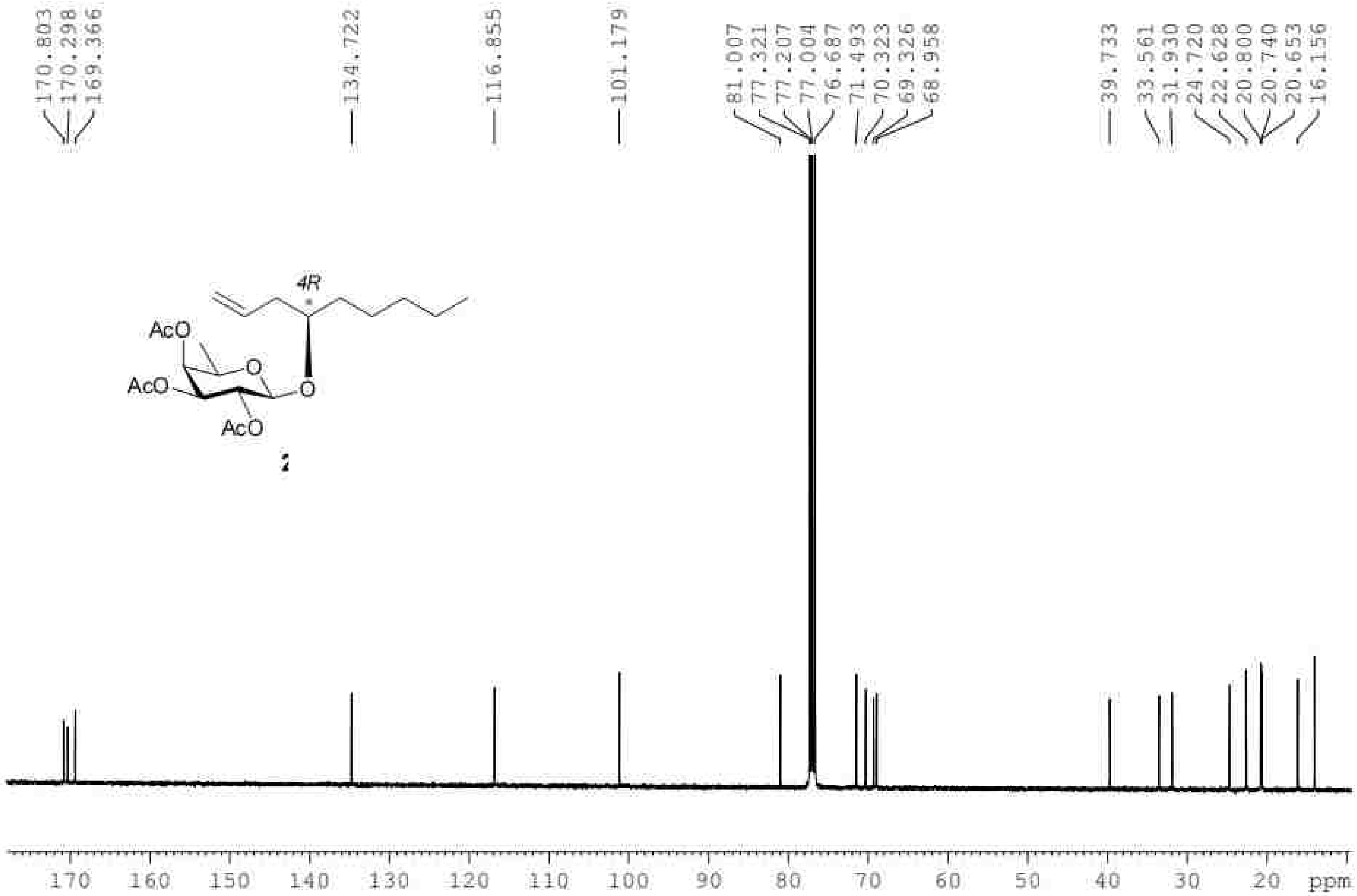
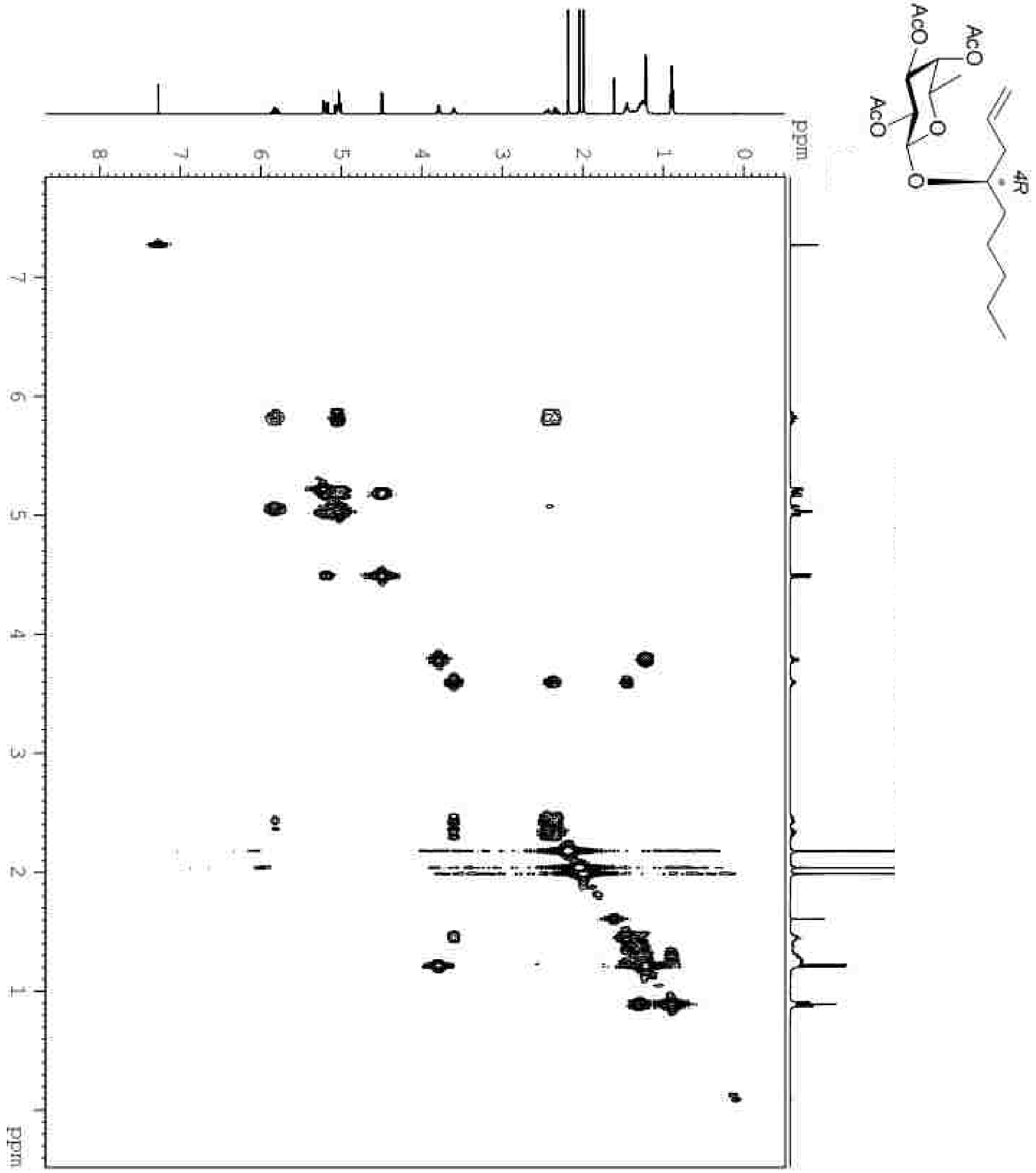
[redacted] APPENDIX

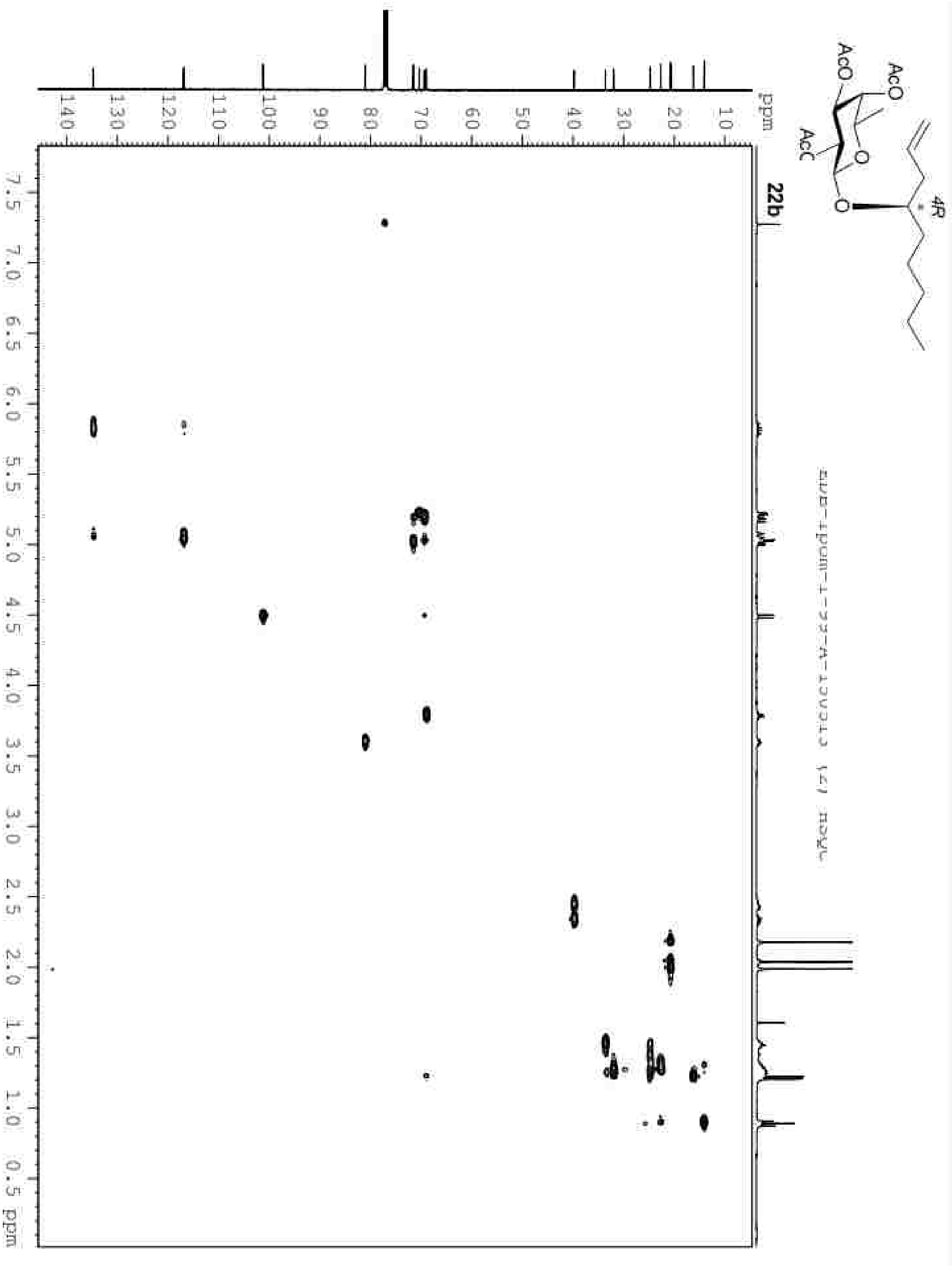
[redacted] Supplemental Information: Spectra and Chromatograms of Key Compounds



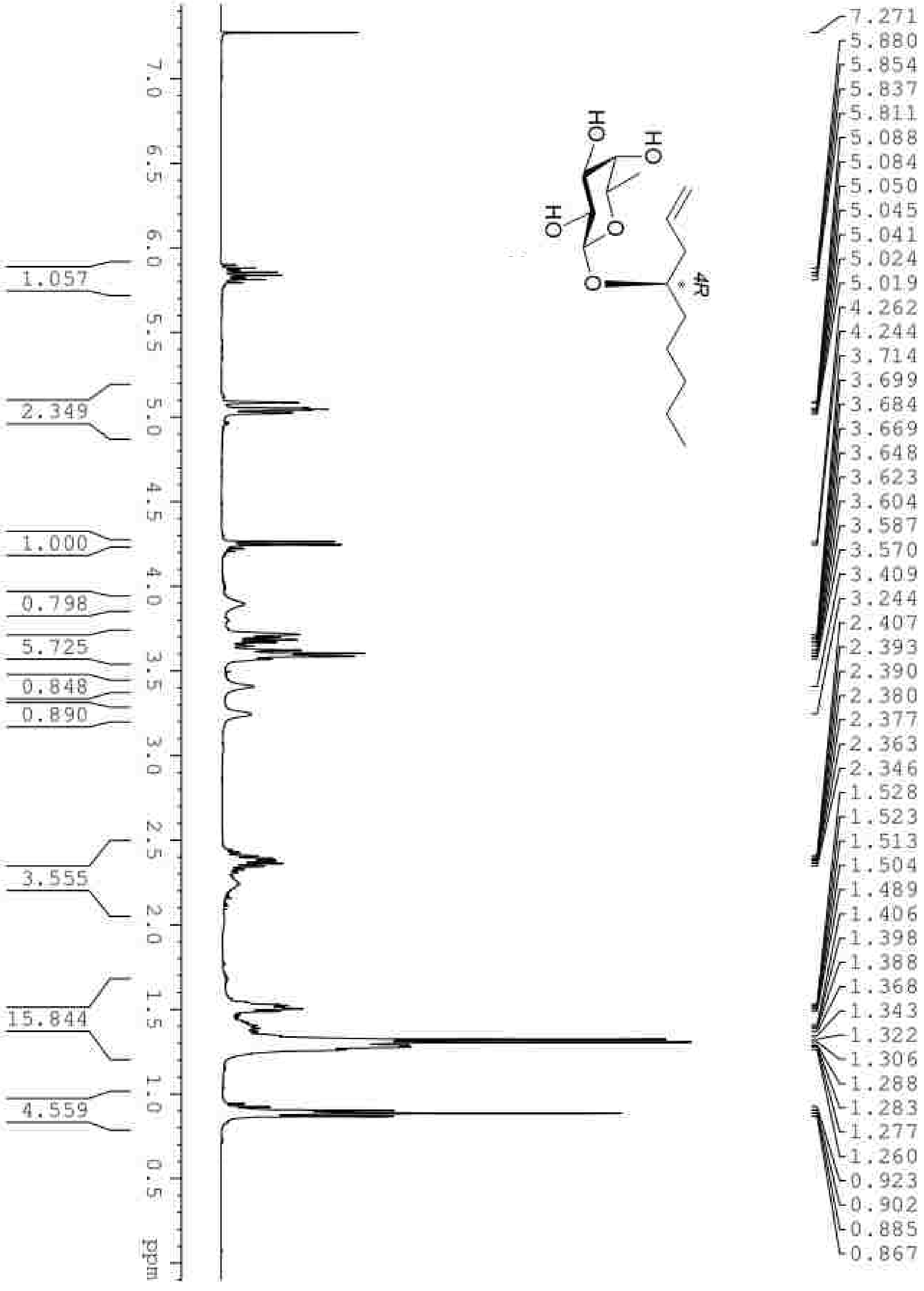

170.803
170.298
169.366
134.722
116.855
101.179
81.007
77.321
77.207
77.004
76.687
71.493
70.323
69.326
68.958
39.733
33.561
31.930
24.720
22.628
20.800
20.740
20.653
16.156
4R
AcO
AcO
AcO
O
O
2
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm



AcO
AcO
AcO
O
O
4R
ppm
8
7
6
5
4
3
2
1
0
ppm
7
6
5
4
3
2
1


22b

AcO
AcO
AcO
O
O
4R
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm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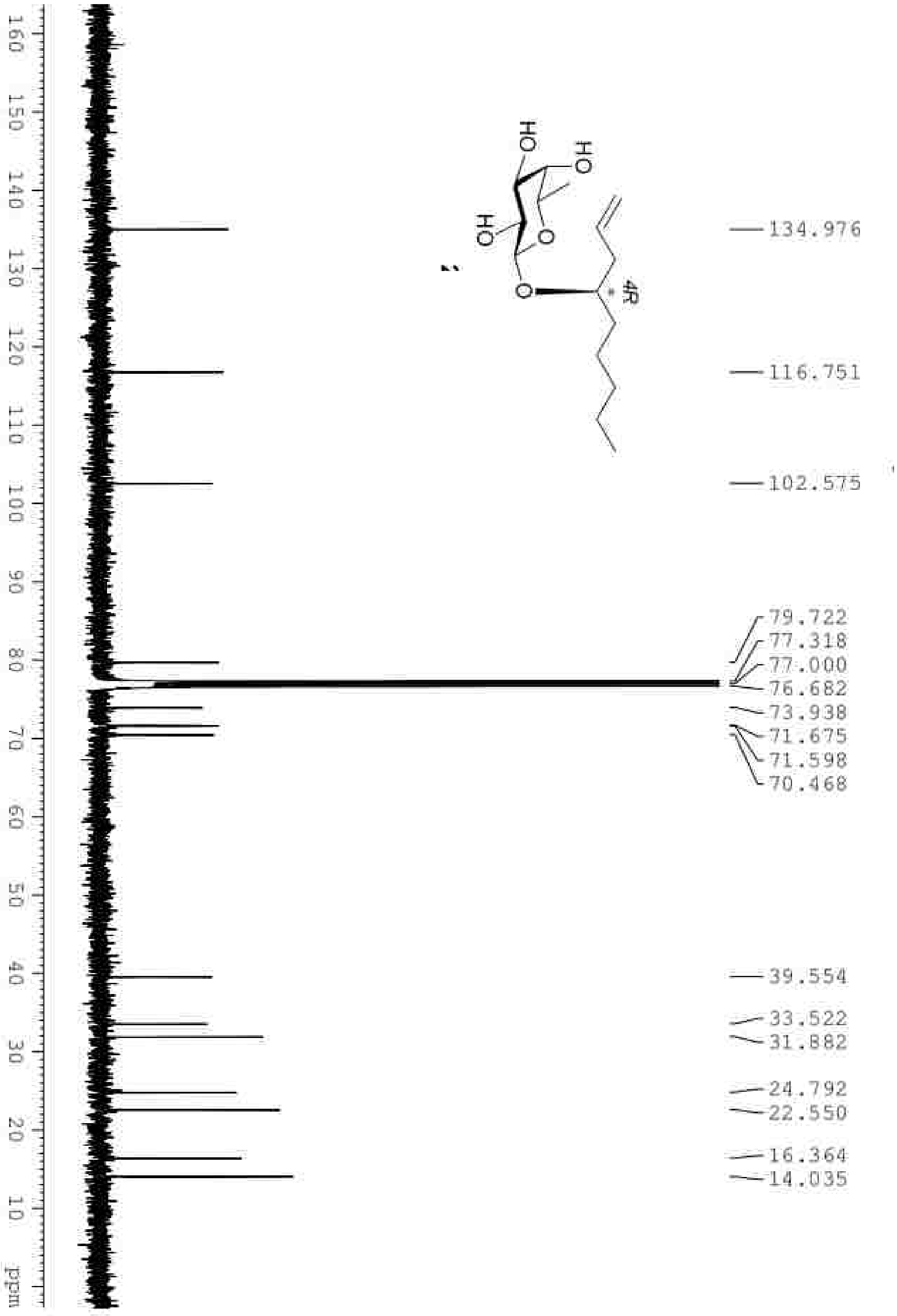
5.880
5.854
5.837
5.811
5.088
5.084
5.050
5.045
5.041
5.024
5.019
4.262
4.244
3.714
3.699
3.684
3.669
3.648
3.623
3.604
3.587
3.570
3.409
3.244
2.407
2.393
2.390
2.380
2.377
2.363
2.346
1.528
1.523
1.513
1.504
1.489
1.406
1.398
1.388
1.368
1.343
1.322
1.306
1.288
1.283
1.277
1.260
0.923
0.902
0.885
0.867
HO
HO
HO
O
O
4R
1.057
2.349
1.000
0.798
5.725
0.848
0.890
3.555
15.844
4.559
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm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77.000
76.682
73.938
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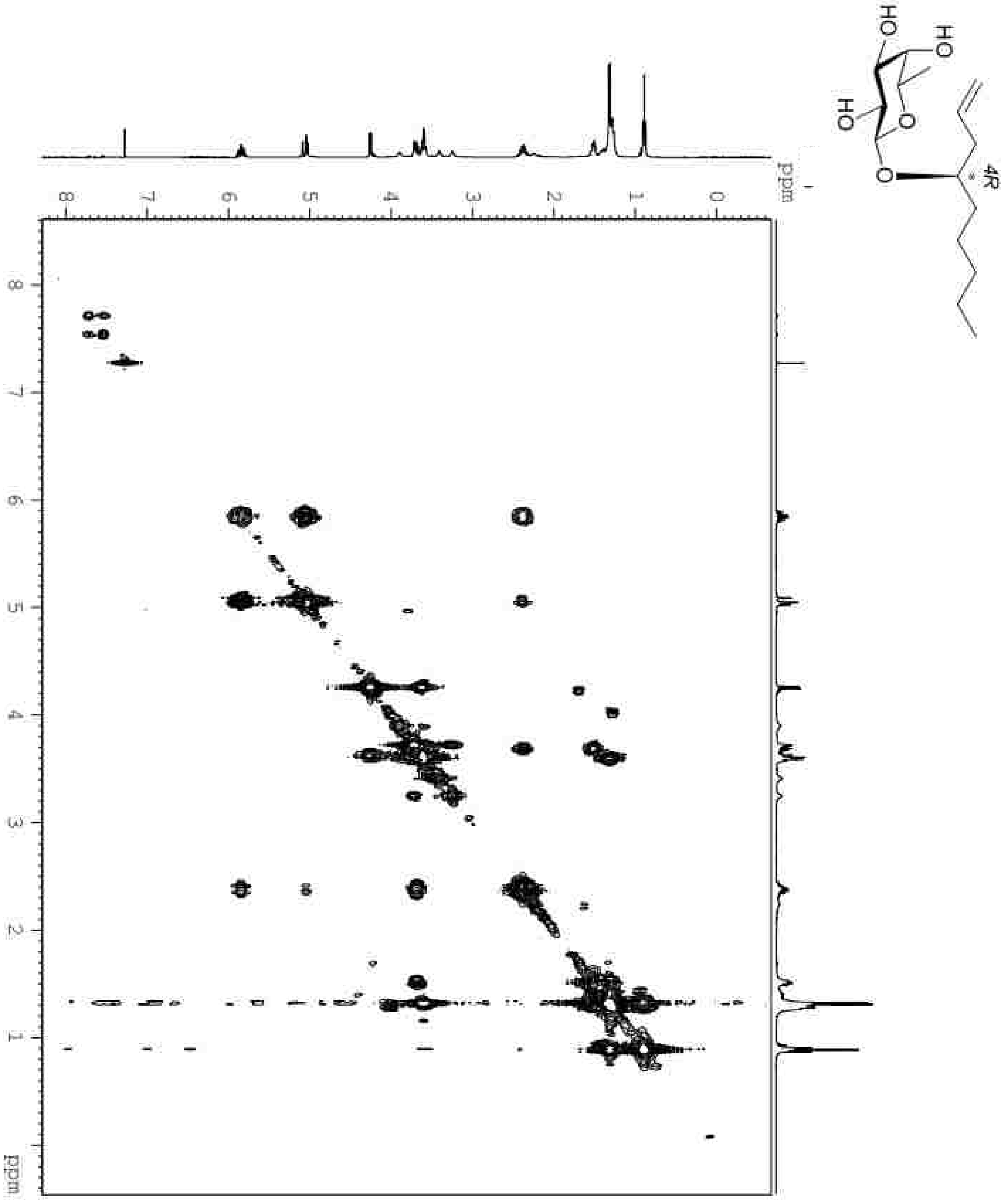
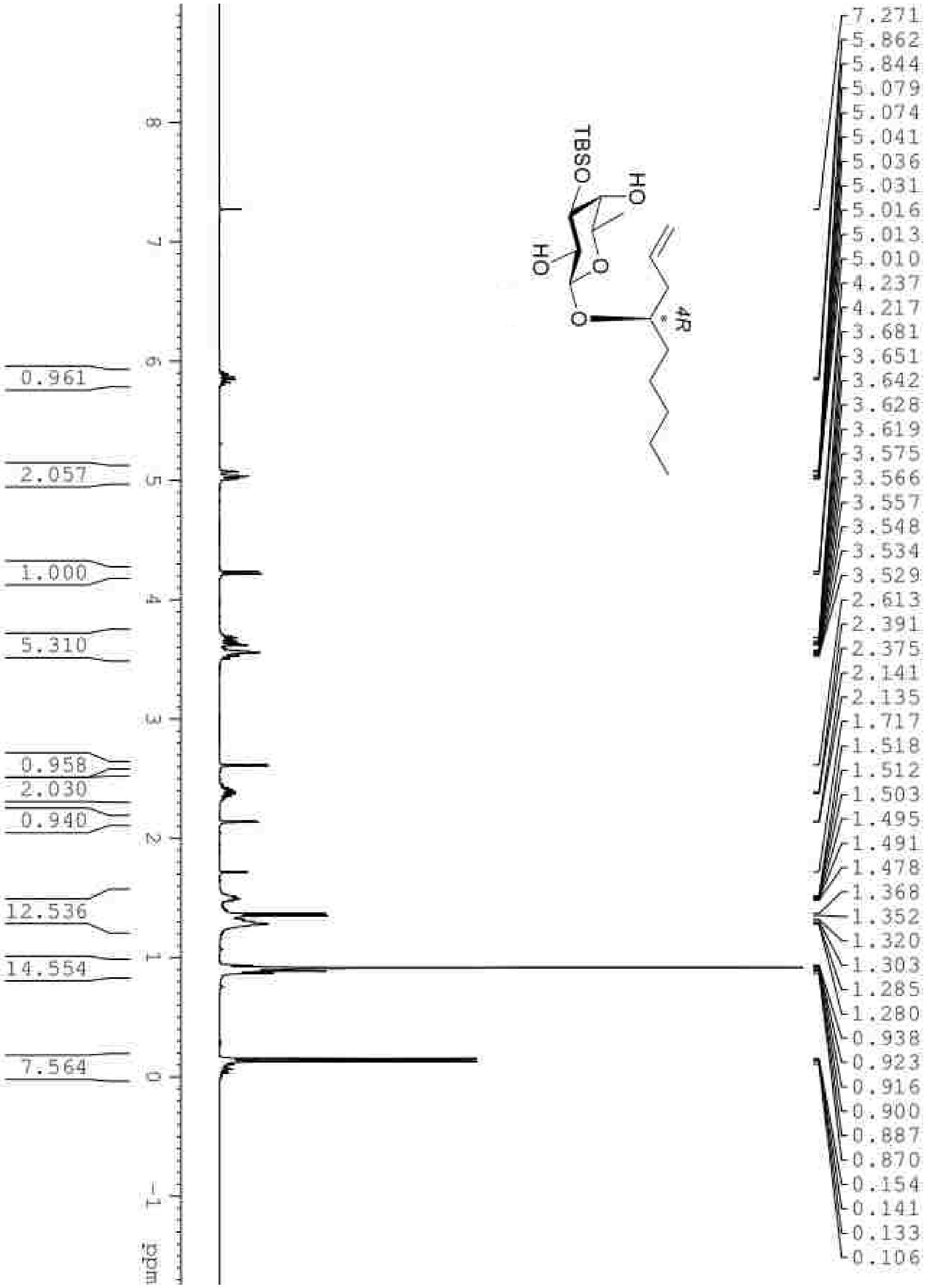
71.598
70.468
39.554
33.522
31.882
24.792
22.550
16.364
14.035
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm
HO
HO
HO
O
O
4R
2



4R
HO
HO
HO
O
O
ppm
8
7
6
5
4
3
2
1
0
ppm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HO
O
4R
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2.057
1.000
5.310
0.958
2.030
0.940
12.536
14.554
7.564
8
7
6
5
4
3
2
1
0
−1
ppm
7.271
5.862
5.844
5.079
5.074
5.041
5.036
5.031
5.016
5.013
5.010
4.237
4.217
3.681
3.651
3.642
3.628
3.619
3.575
3.566
3.557
3.548
3.534
3.529
2.613
2.391
2.375
2.141
2.135
1.717
1.518
1.512
1.503
1.495
1.491
1.478
1.368
1.352
1.320
1.303
1.285
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0.923
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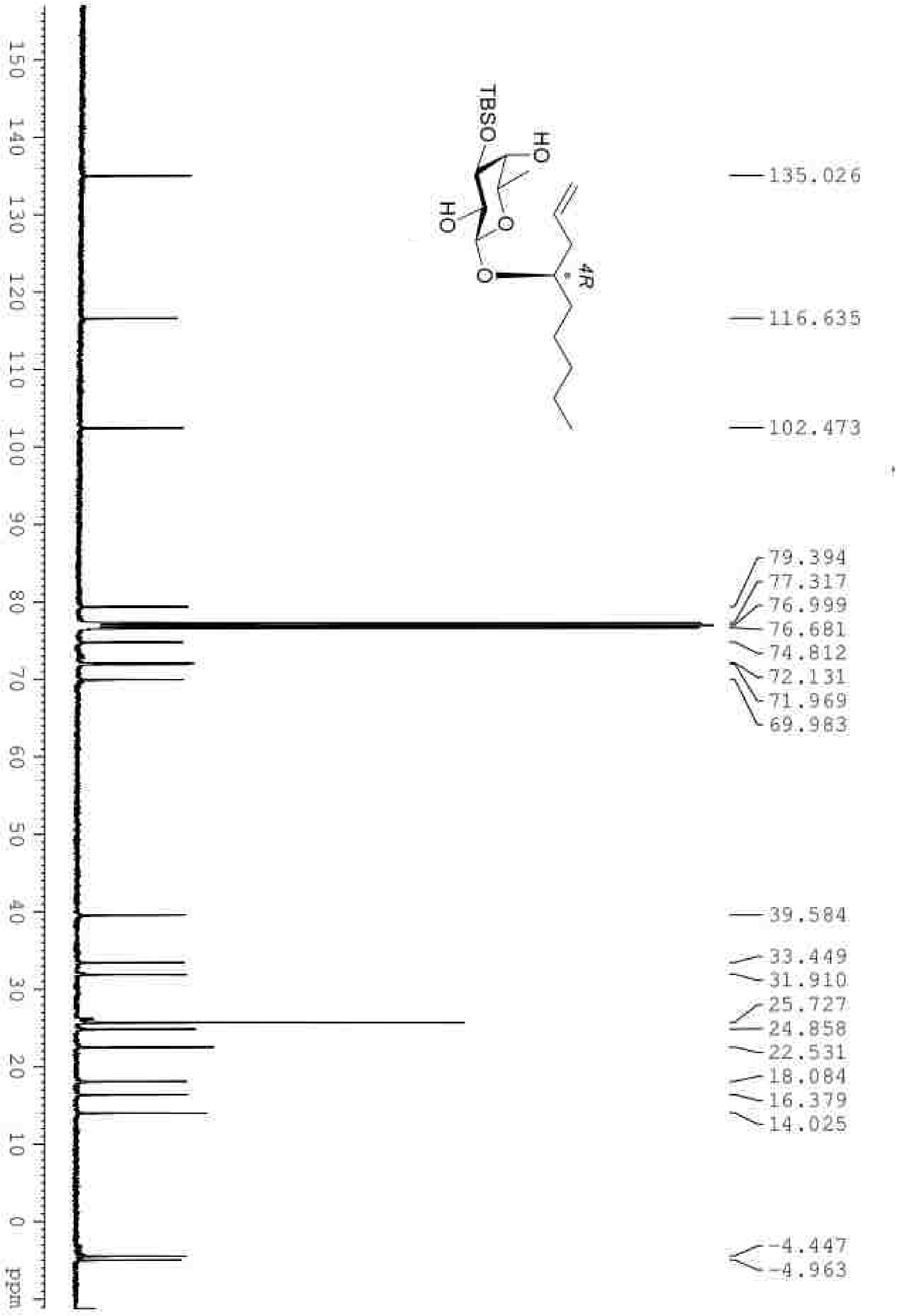
0.870
0.154
0.141
0.133
0.106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HO
O
O
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116.635
102.473
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77.317
76.999
76.681
74.812
72.131
71.969
69.983
39.584
33.449
31.910
25.727
24.858
22.531
18.084
16.379
14.025
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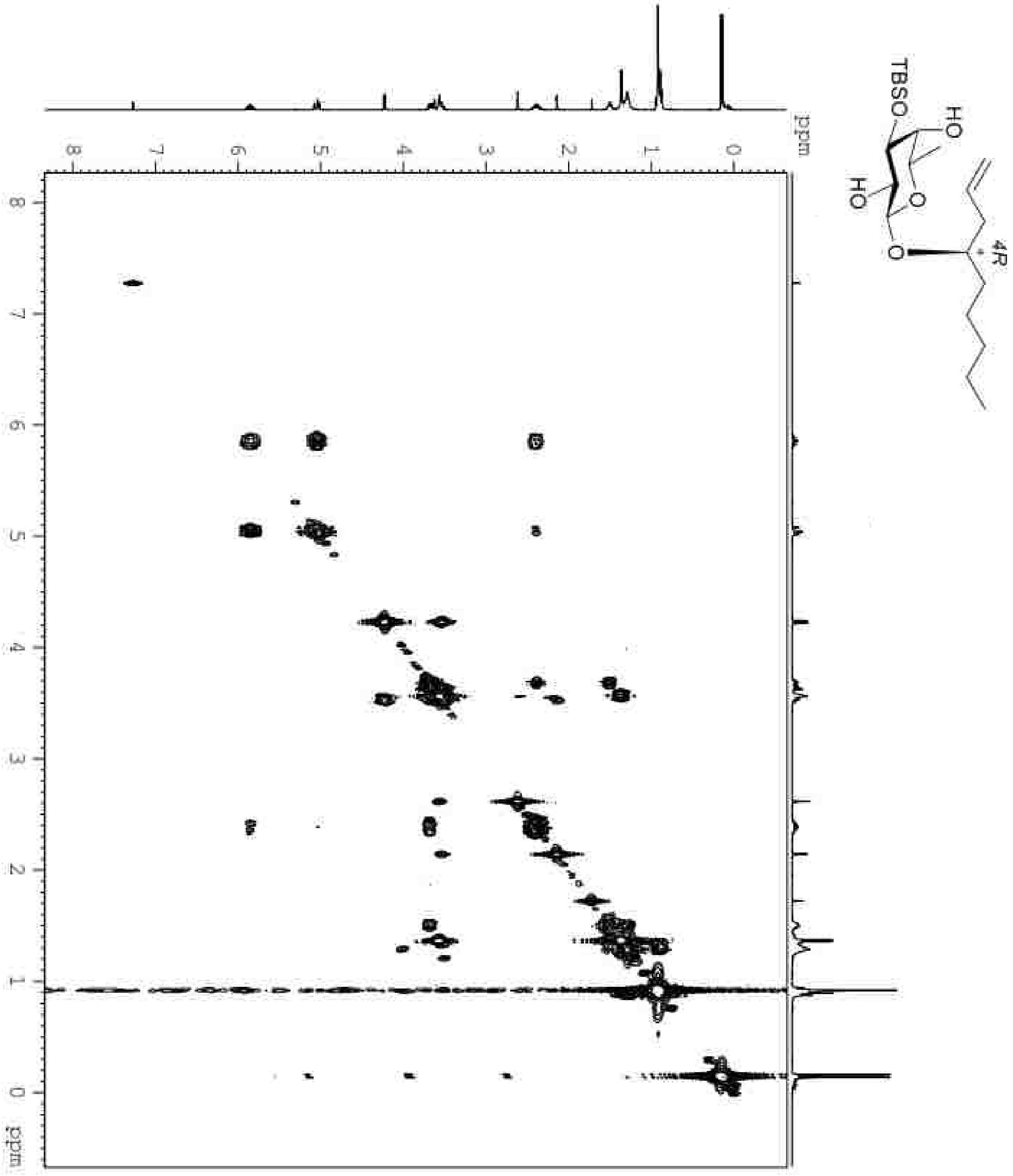
60
50
40
30
20
10
0
ppm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TBSO
HO
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7
6
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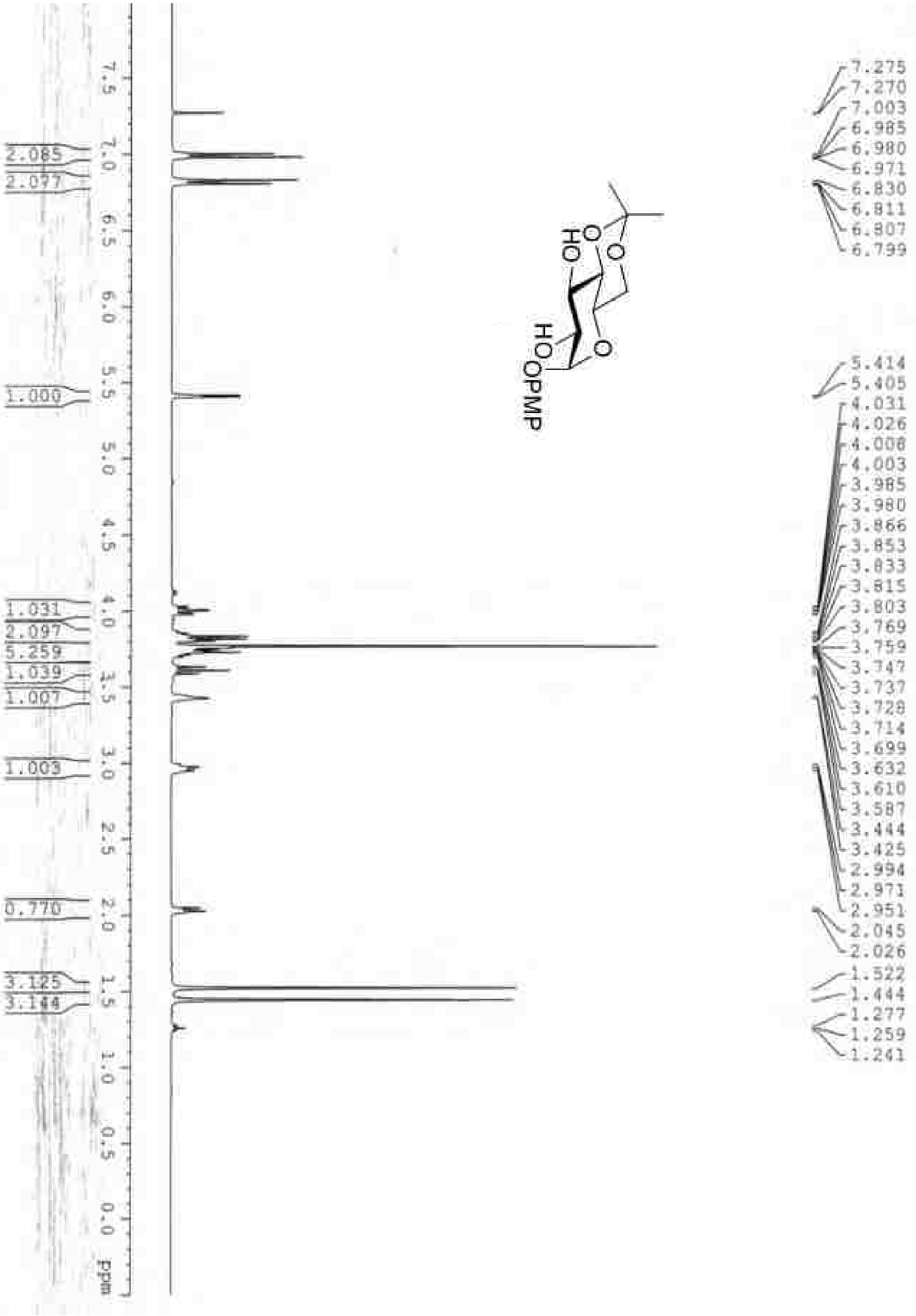
3
2
1
0
ppm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7.003
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5.405
4.031
4.026
4.008
4.003
3.985
3.980
3.866
3.853
3.833
3.815
3.803
3.769
3.759
3.747
3.737
3.728
3.714
3.699
3.632
3.610
3.587
3.444
3.425
2.994
2.971
2.951
2.045
2.026
1.522
1.444
1.277
1.259
1.241
O
O
O
HO
HO
OPMP
2.085
2.077
1.000
1.031
2.097
5.259
1.039
1.007
1.003
0.770
3.125
3.144
7.5
7.0
6.5
6.0
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4.0
3.5
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2.0
1.5
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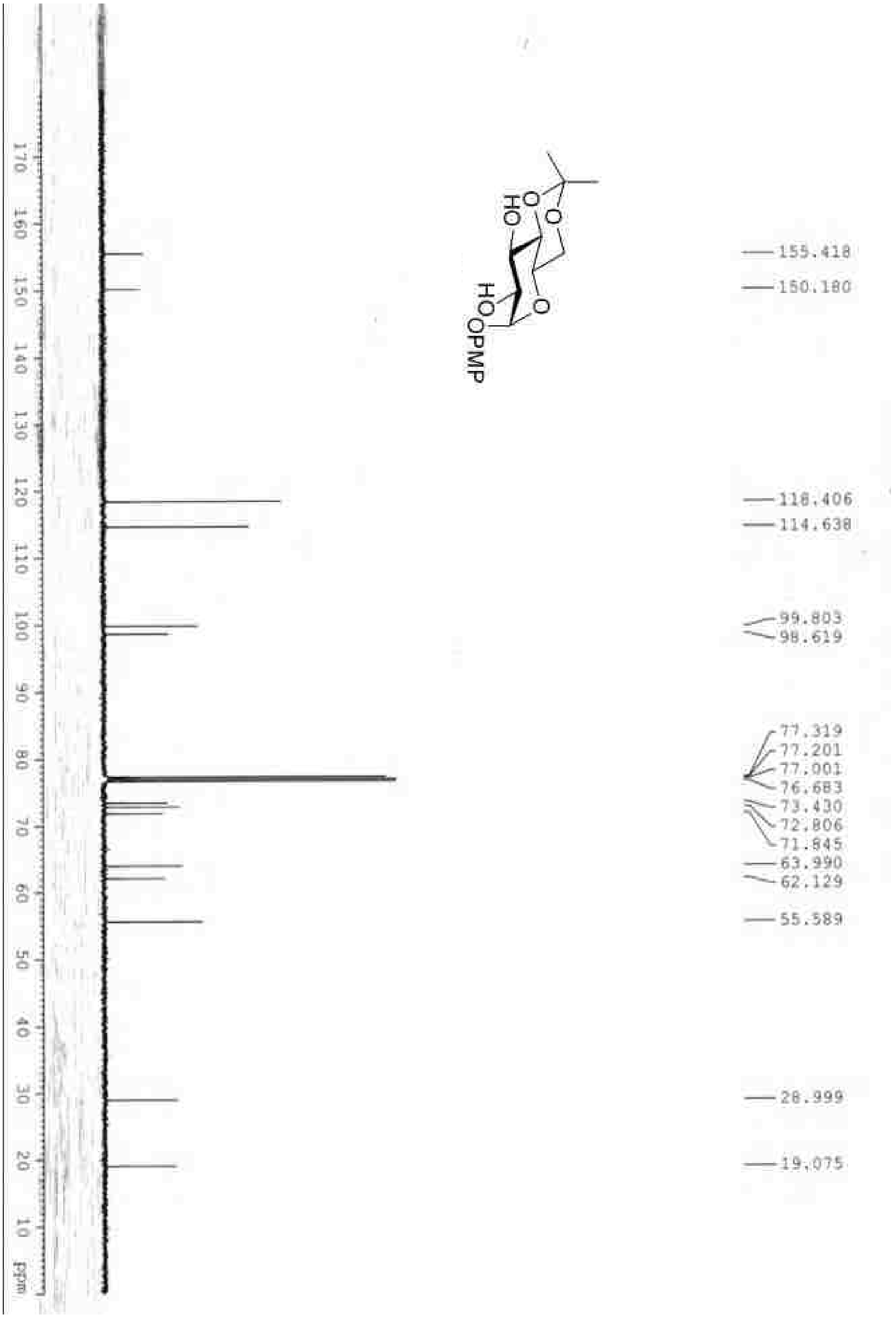
0.5
0.0
ppm



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150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm
O
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HO
HO
O
OPMP
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150.180
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114.638
99.803
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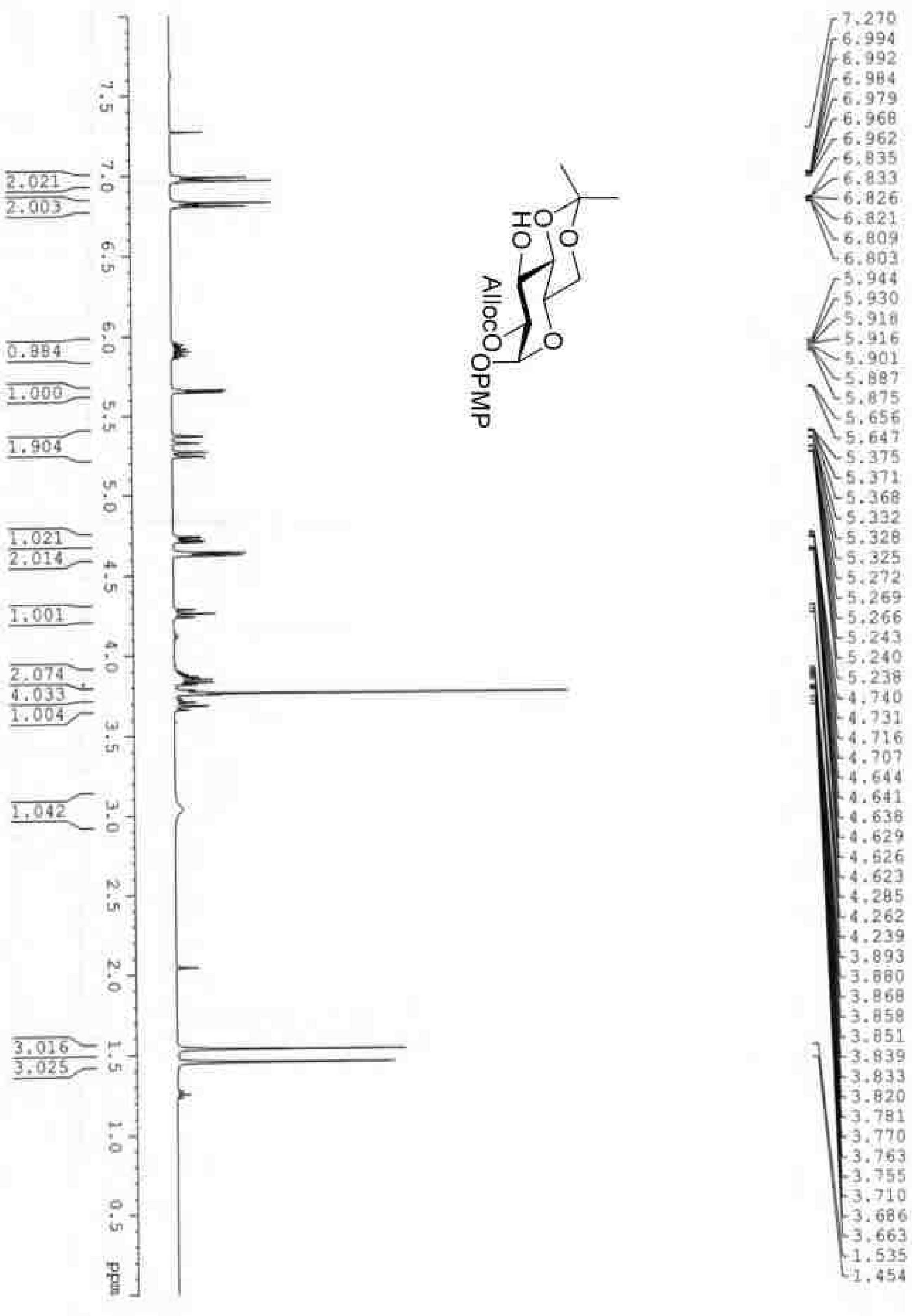
19.075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6.809
6.803
5.944
5.930
5.918
5.916
5.901
5.887
5.875
5.656
5.647
5.375
5.371
5.368
5.332
5.328
5.325
5.272
5.269
5.266
5.243
5.240
5.238
4.740
4.731
4.716
4.707
4.644
4.641
4.638
4.629
4.626
4.623
4.285
4.262
4.239
3.893
3.880
3.868
3.858
3.851
3.839
3.833
3.820
3.781
3.770
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3.755
3.710
3.686
3.663
1.535
1.454
O
O
HO
O
AllocO
OPMP
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2.003
0.984
1.000
1.904
1.021
2.014
1.001
2.074
4.033
1.004
1.042
3.016
3.025
7.5
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6.5
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3.0
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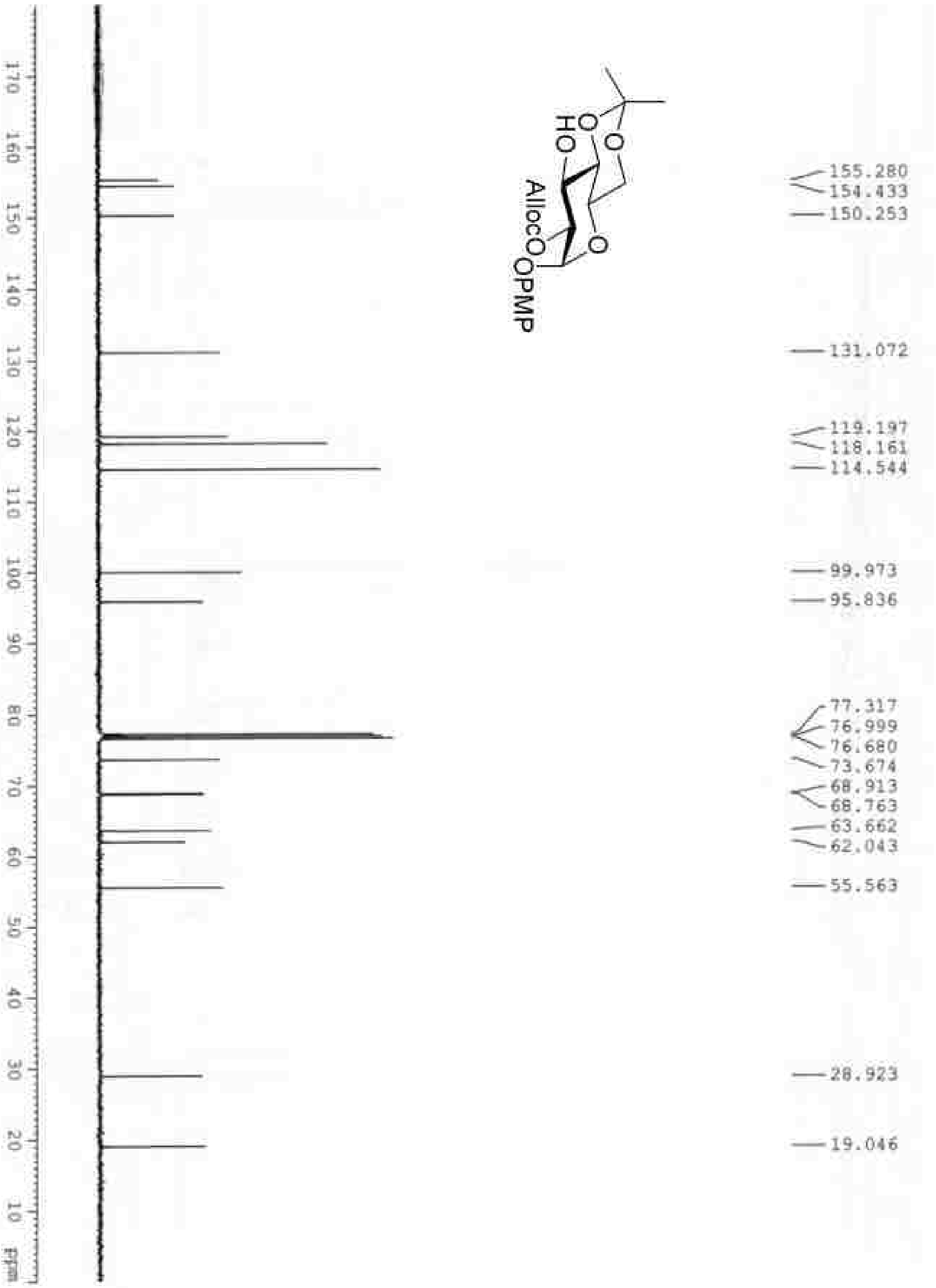
0.5
ppm



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95.836
77.317
76.999
76.680
73.674
68.913
68.763
63.662
62.043
55.563
28.923
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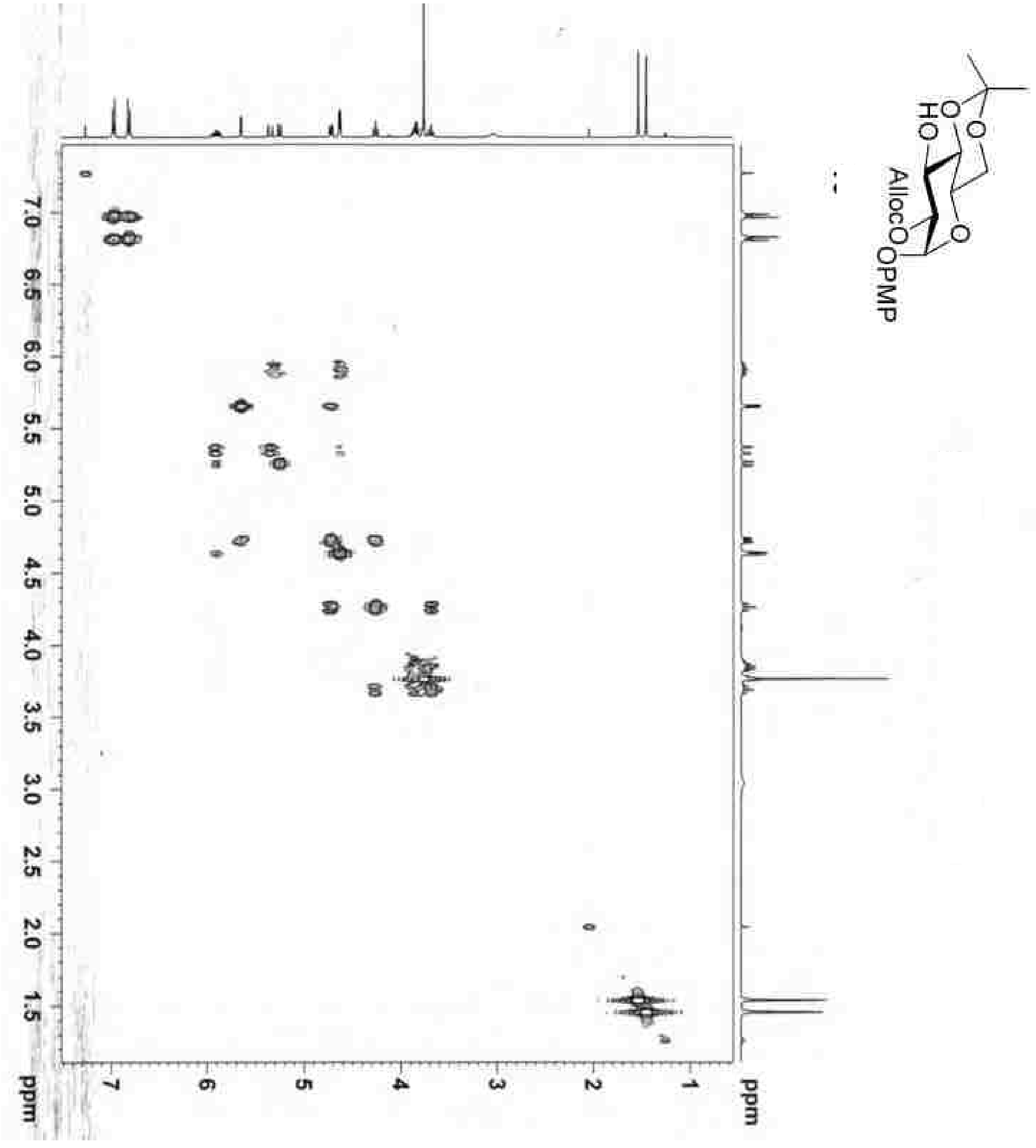
30
20
10
ppm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4.5
4.0
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3.0
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2.0
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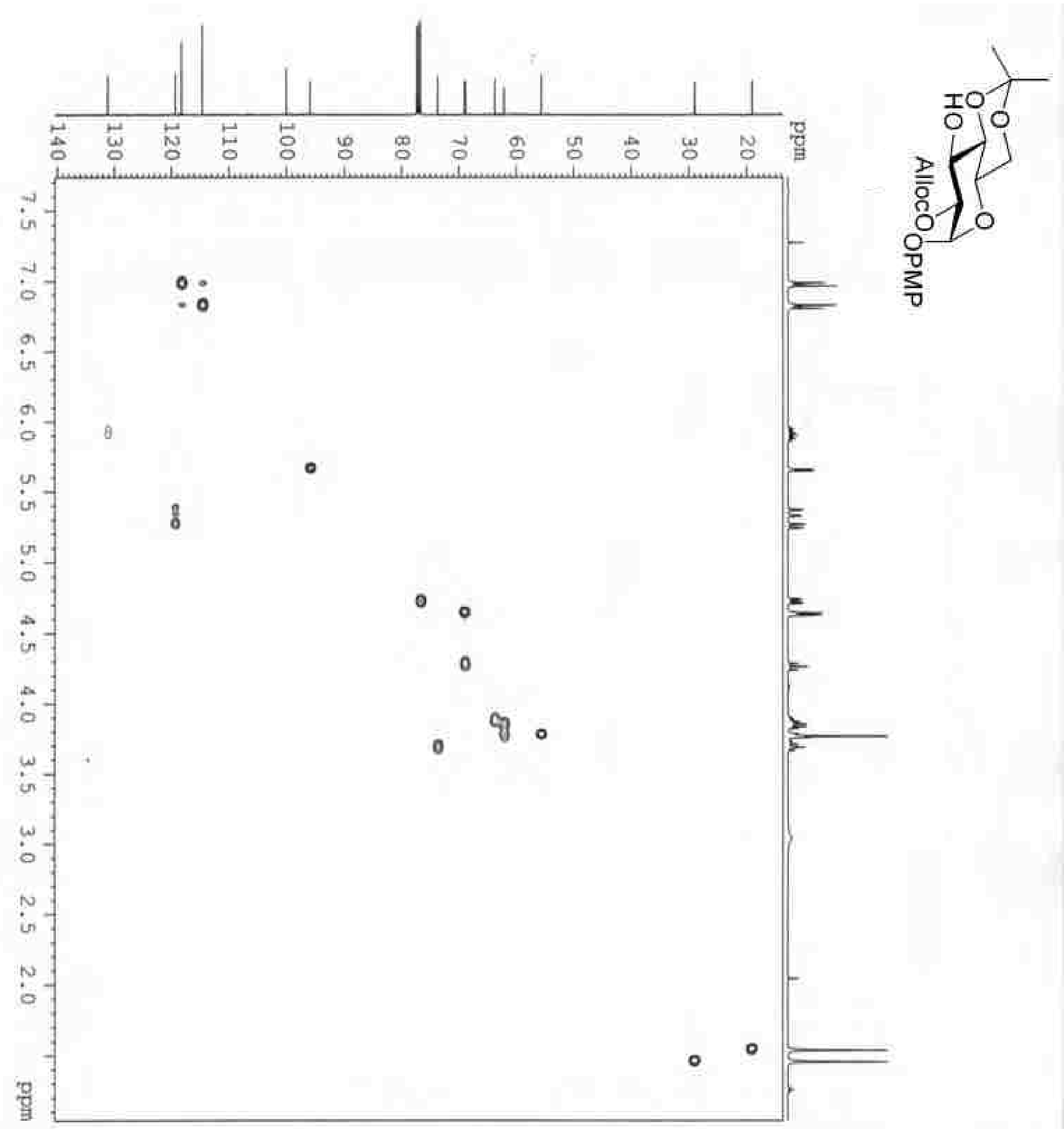
ppm
7
6
5
4
3
2
1
ppm
O
O
HO
AllocO
O
OPMP



HO
O
O
O
AllocO
OPMP
ppm
20
30
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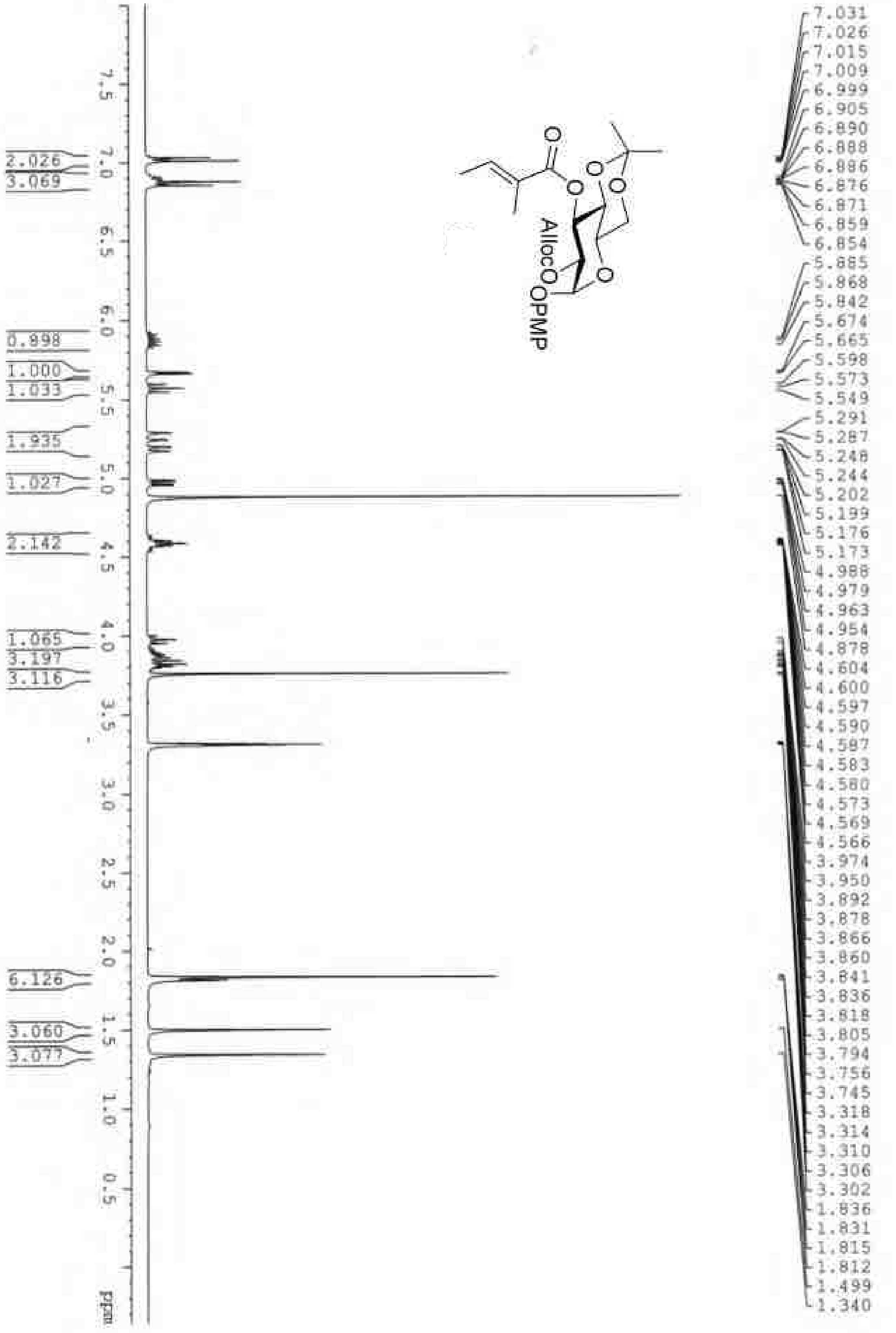

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1.0
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1.027
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3.077
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7.009
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6.888
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4.590
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4.573
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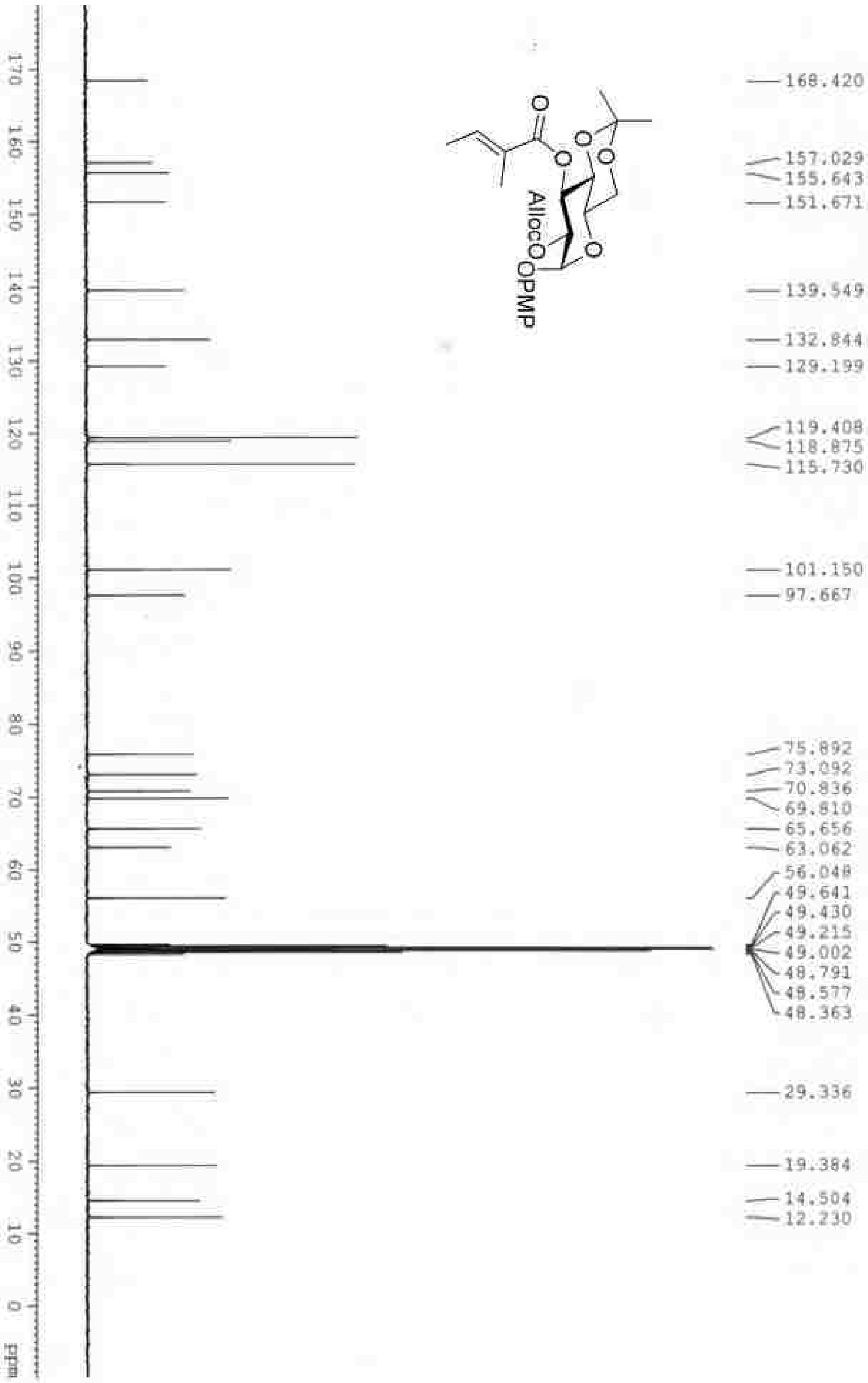
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63.062
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49.002
48.791
48.577
48.363
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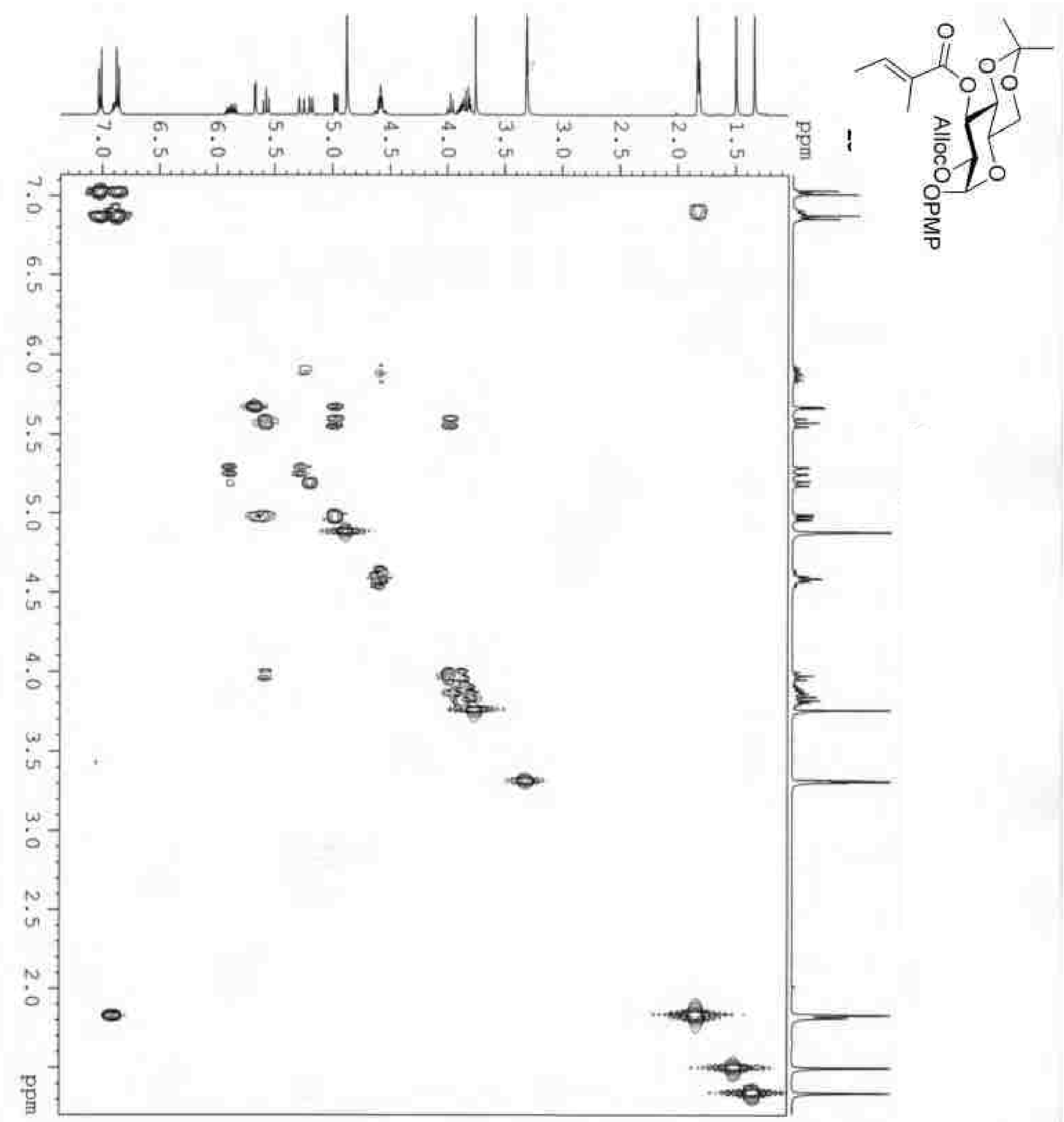
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OPMP
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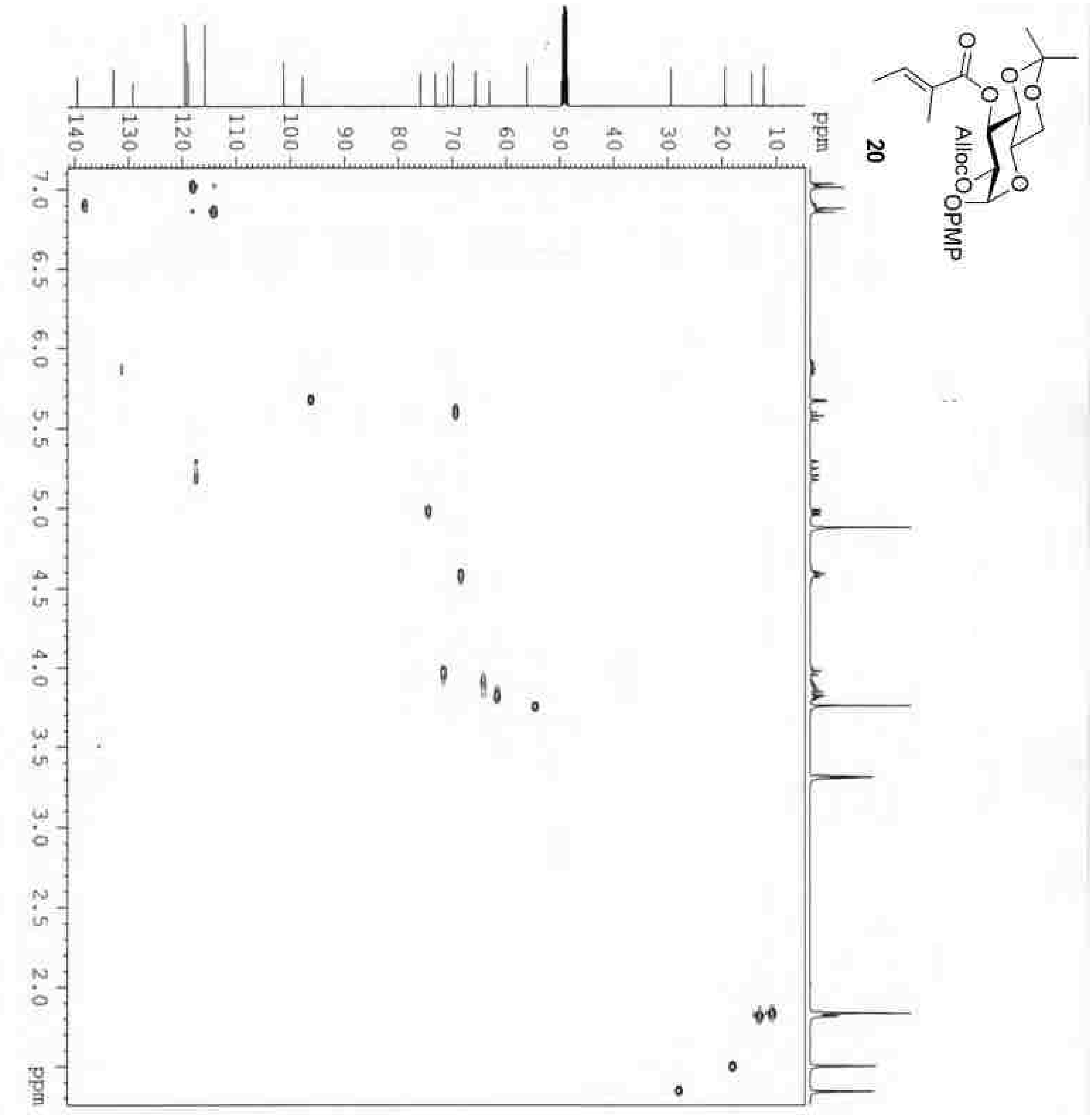
ppm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OPMP
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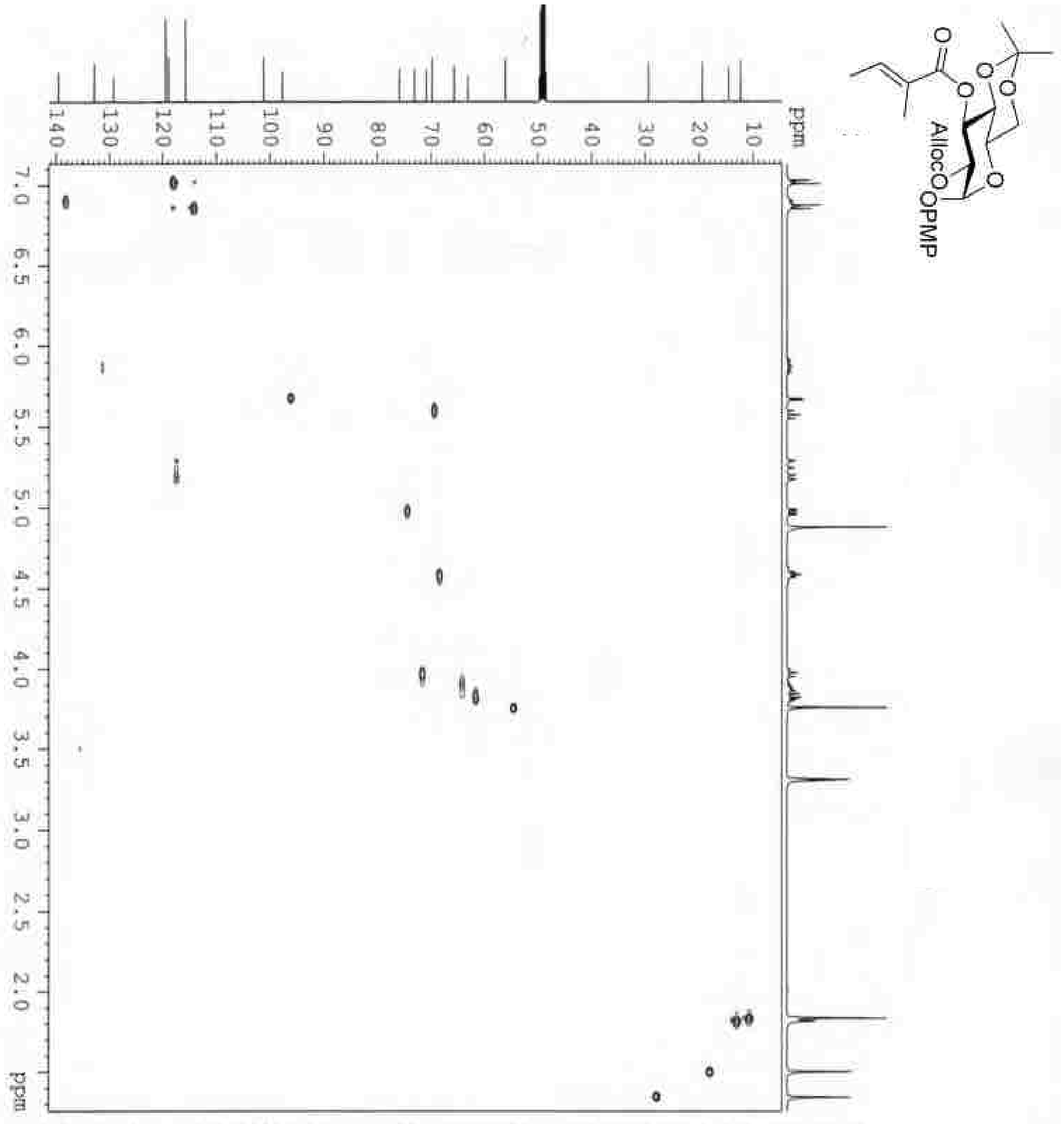
2.0
ppm

20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ppm
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80
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30
20
10
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5.0
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3.5
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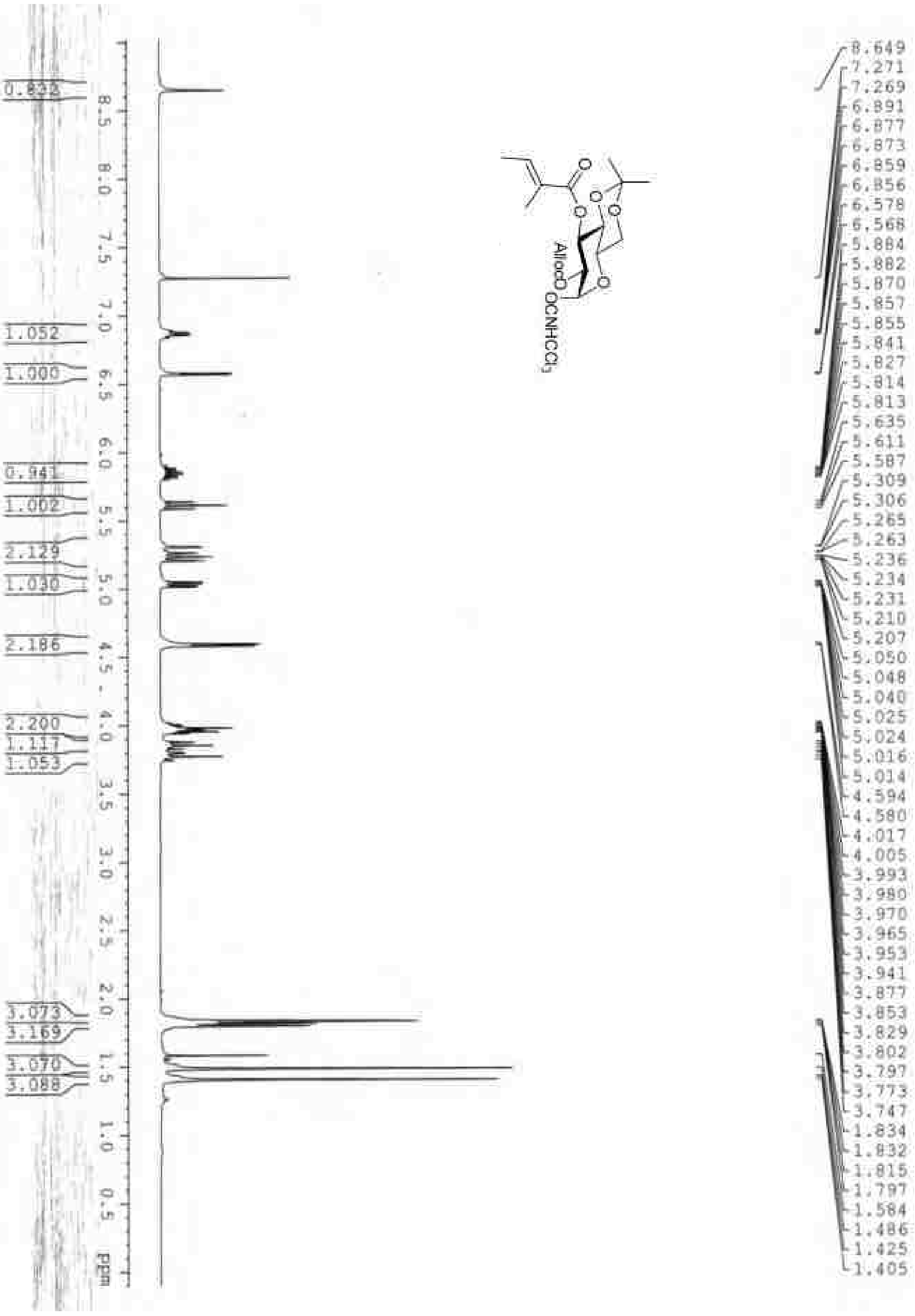
2.5
2.0
ppm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4.0
3.5
3.0
2.5
2.0
1.5
1.0
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1.000
0.941
1.002
2.129
1.030
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2.200
1.117
1.053
3.073
3.169
3.070
3.088
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7.269
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6.859
6.856
6.578
6.568
5.884
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5.870
5.857
5.855
5.841
5.827
5.814
5.813
5.635
5.611
5.587
5.309
5.306
5.265
5.263
5.236
5.234
5.231
5.210
5.207
5.050
5.048
5.040
5.025
5.024
5.016
5.014
4.594
4.580
4.017
4.005
3.993
3.980
3.970
3.965
3.953
3.941
3.877
3.853
3.829
3.802
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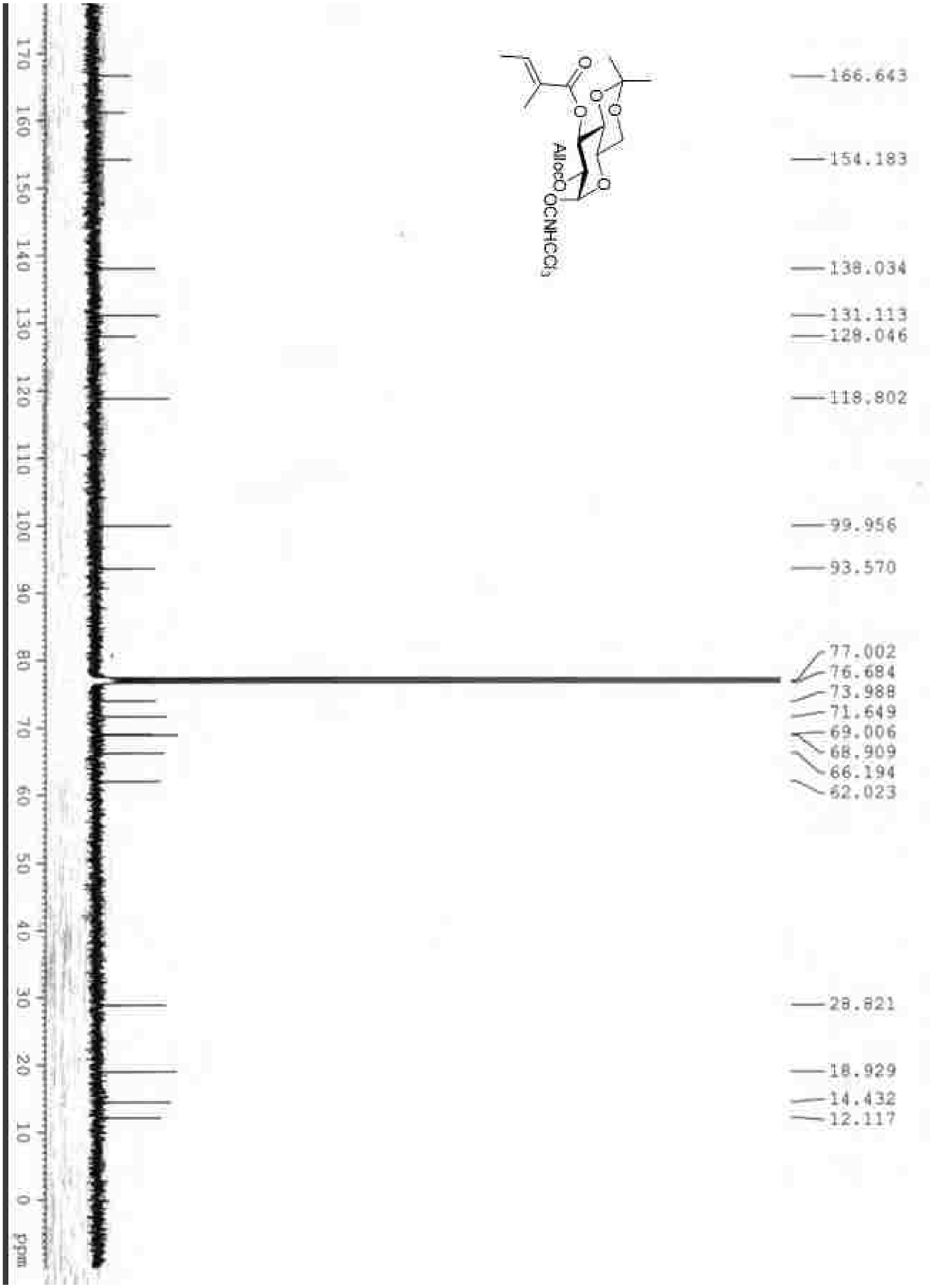
1.425
1.405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128.046
118.802
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93.570
77.002
76.684
73.988
71.649
69.006
68.909
66.194
62.023
28.821
18.929
14.432
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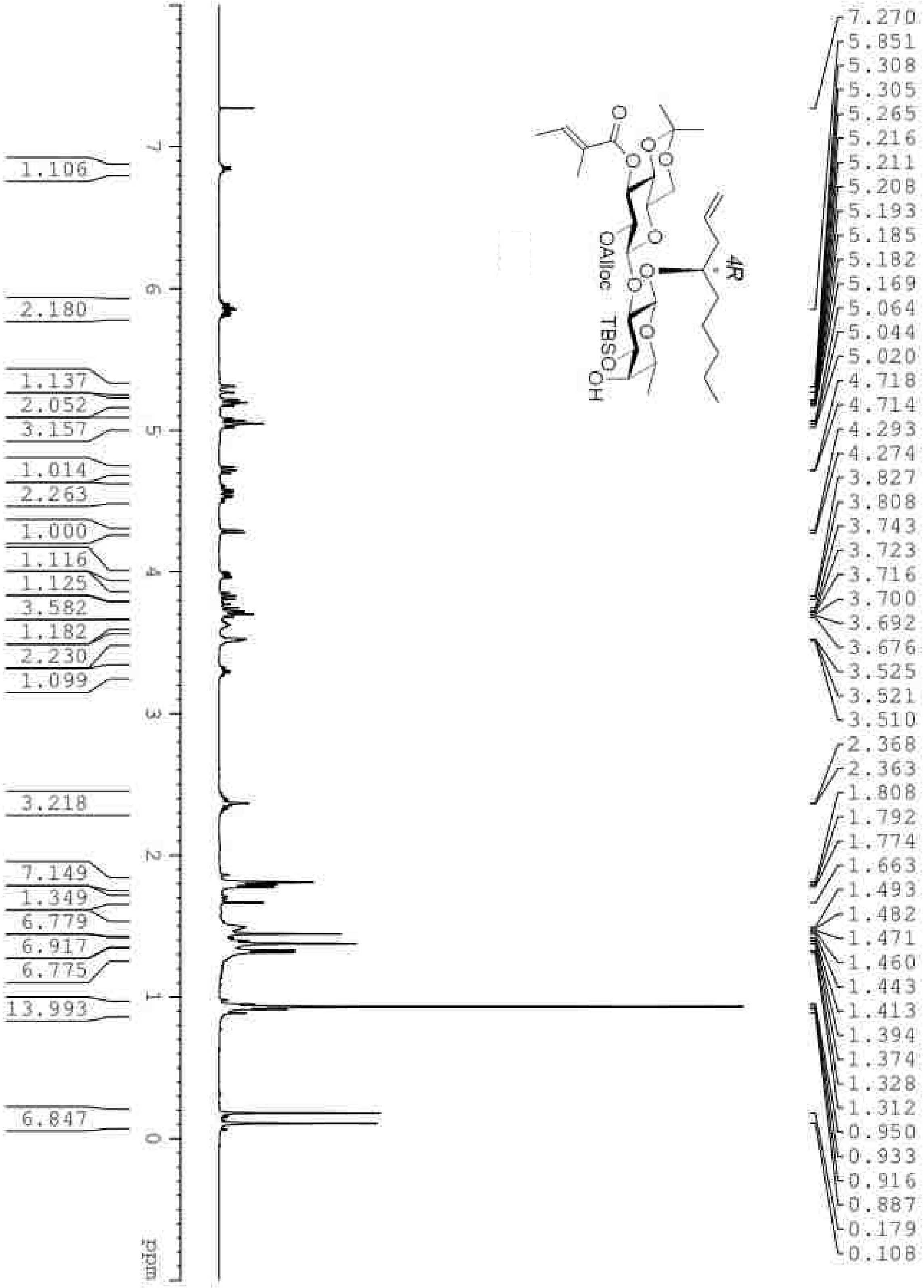

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5.216
5.211
5.208
5.193
5.185
5.182
5.169
5.064
5.044
5.020
4.718
4.714
4.293
4.274
3.827
3.808
3.743
3.723
3.716
3.700
3.692
3.676
3.525
3.521
3.510
2.368
2.363
1.808
1.792
1.774
1.663
1.493
1.482
1.471
1.460
1.443
1.413
1.394
1.374
1.328
1.312
0.950
0.933
0.916
0.887
0.179
0.108
1.106
2.180
1.137
2.052
3.157
1.014
2.263
1.000
1.116
1.125
3.582
1.182
2.230
1.099
3.218
7.149
1.349
6.779
6.917
6.775
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ppm
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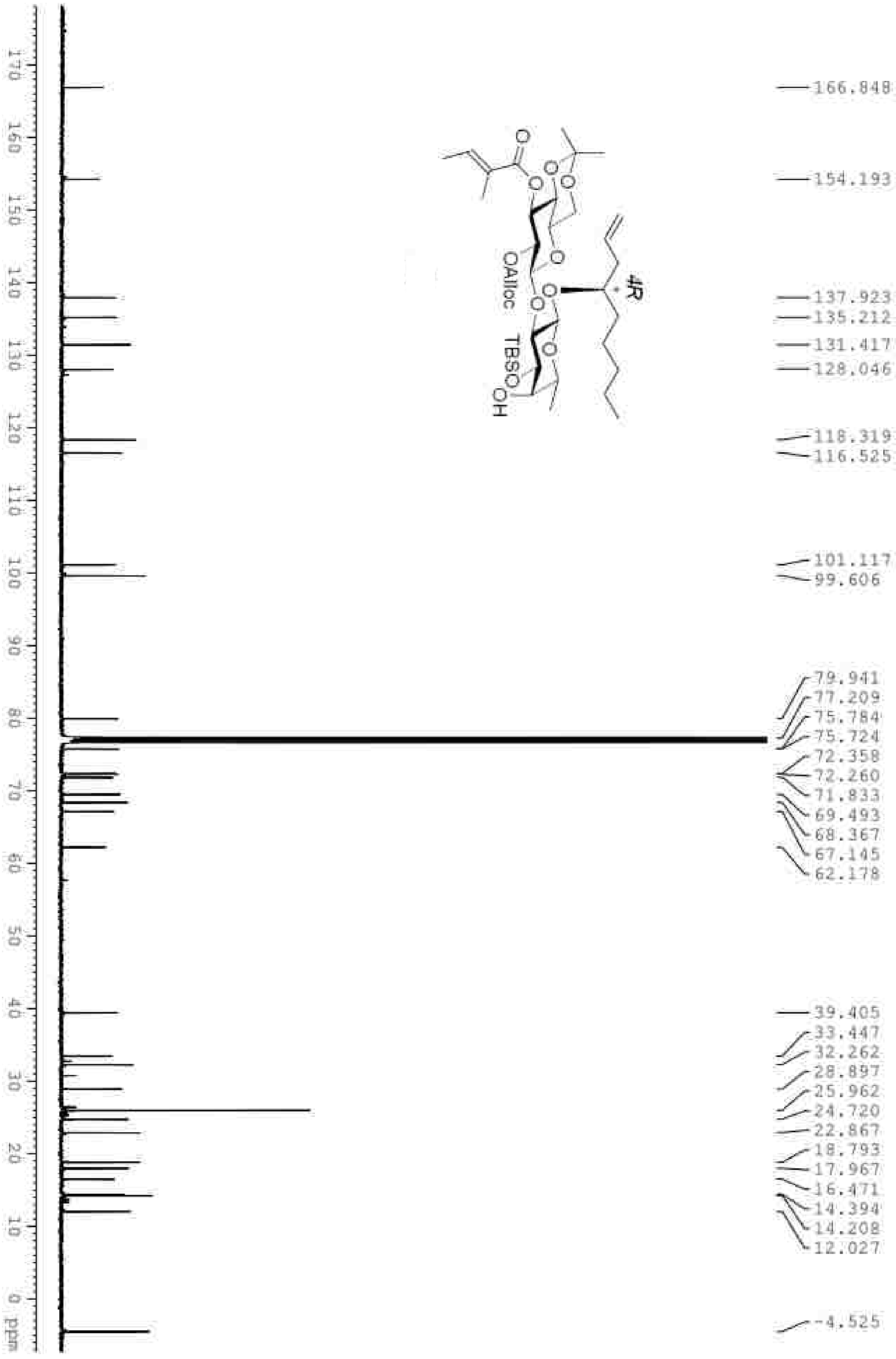
TBSO
OH
O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116.525
101.117
99.606
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77.209
75.784
75.724
72.358
72.260
71.833
69.493
68.367
67.145
62.178
39.405
33.447
32.262
28.897
25.962
24.720
22.867
18.793
17.967
16.471
14.394
14.208
12.027
-4.525
170
160
150
140
130
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80
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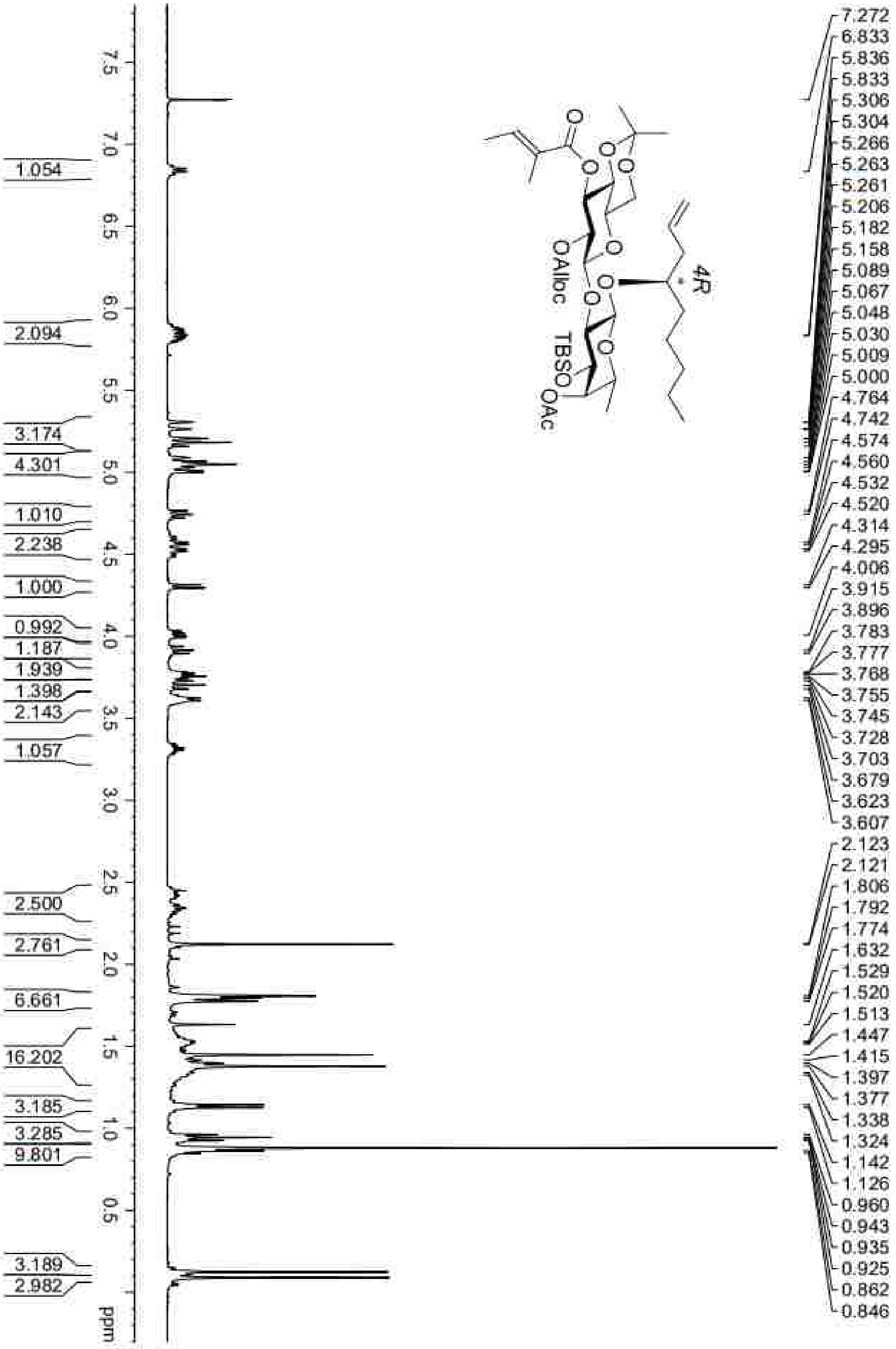
O
OAlloc
TBSO
OH
4R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TBSO
OAc
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5.0
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4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
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3.174
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2.238
1.000
0.992
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1.939
1.398
2.143
1.057
2.500
2.761
6.661
16.202
3.185
3.285
9.801
3.189
2.982
7.272
6.833
5.836
5.833
5.306
5.304
5.266
5.263
5.261
5.206
5.182
5.158
5.089
5.067
5.048
5.030
5.009
5.000
4.764
4.742
4.574
4.560
4.532
4.520
4.314
4.295
4.006
3.915
3.896
3.783
3.777
3.768
3.755
3.745
3.728
3.703
3.679
3.623
3.607
2.123
2.121
1.806
1.792
1.774
1.632
1.529
1.520
1.513
1.447
1.415
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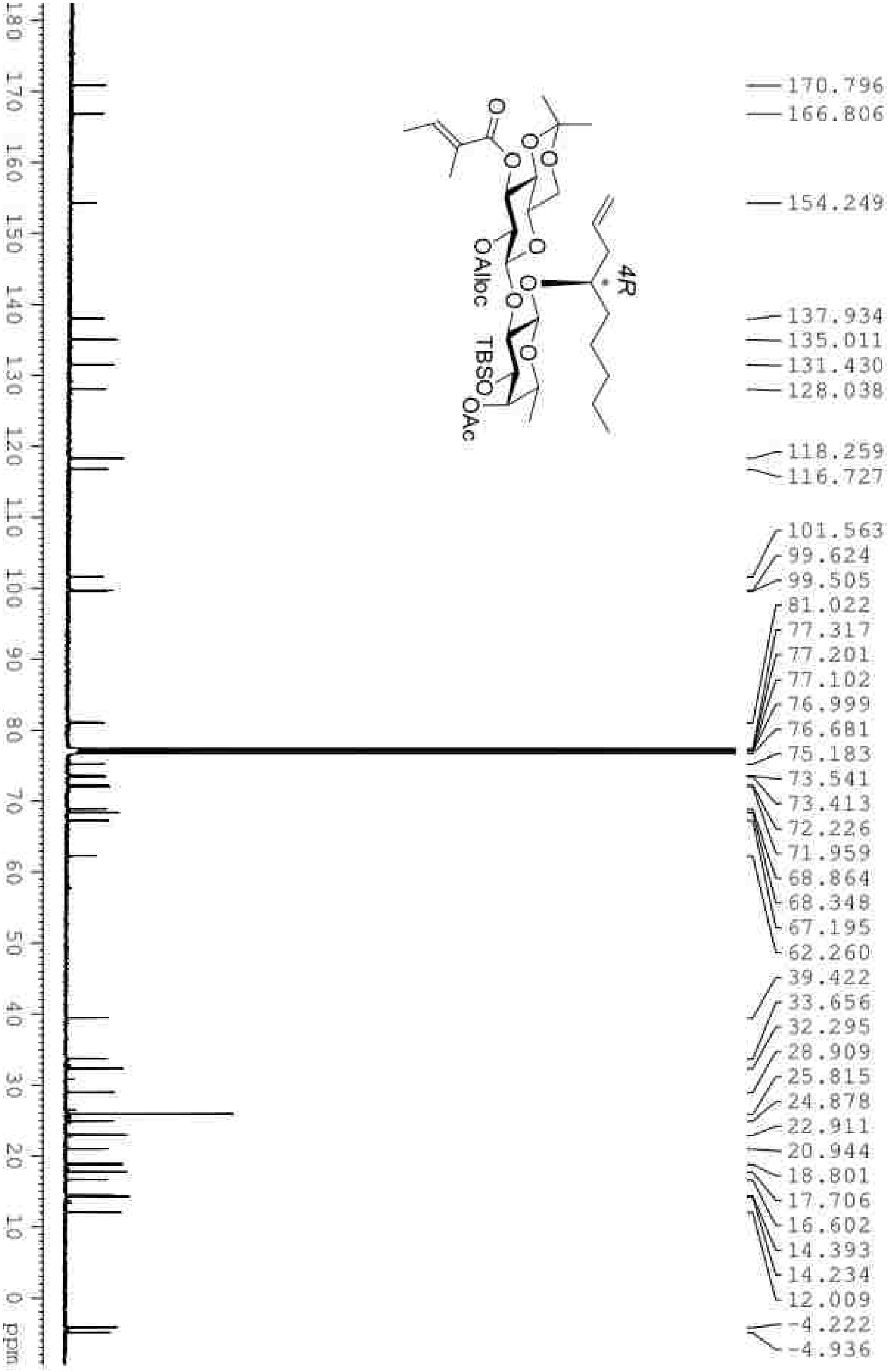
180
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160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
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166.806
154.249
137.934
135.011
131.430
128.038
118.259
116.727
101.563
99.624
99.505
81.022
77.317
77.201
77.102
76.999
76.681
75.183
73.541
73.413
72.226
71.959
68.864
68.348
67.195
62.260
39.422
33.656
32.295
28.909
25.815
24.878
22.911
20.944
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4R
O
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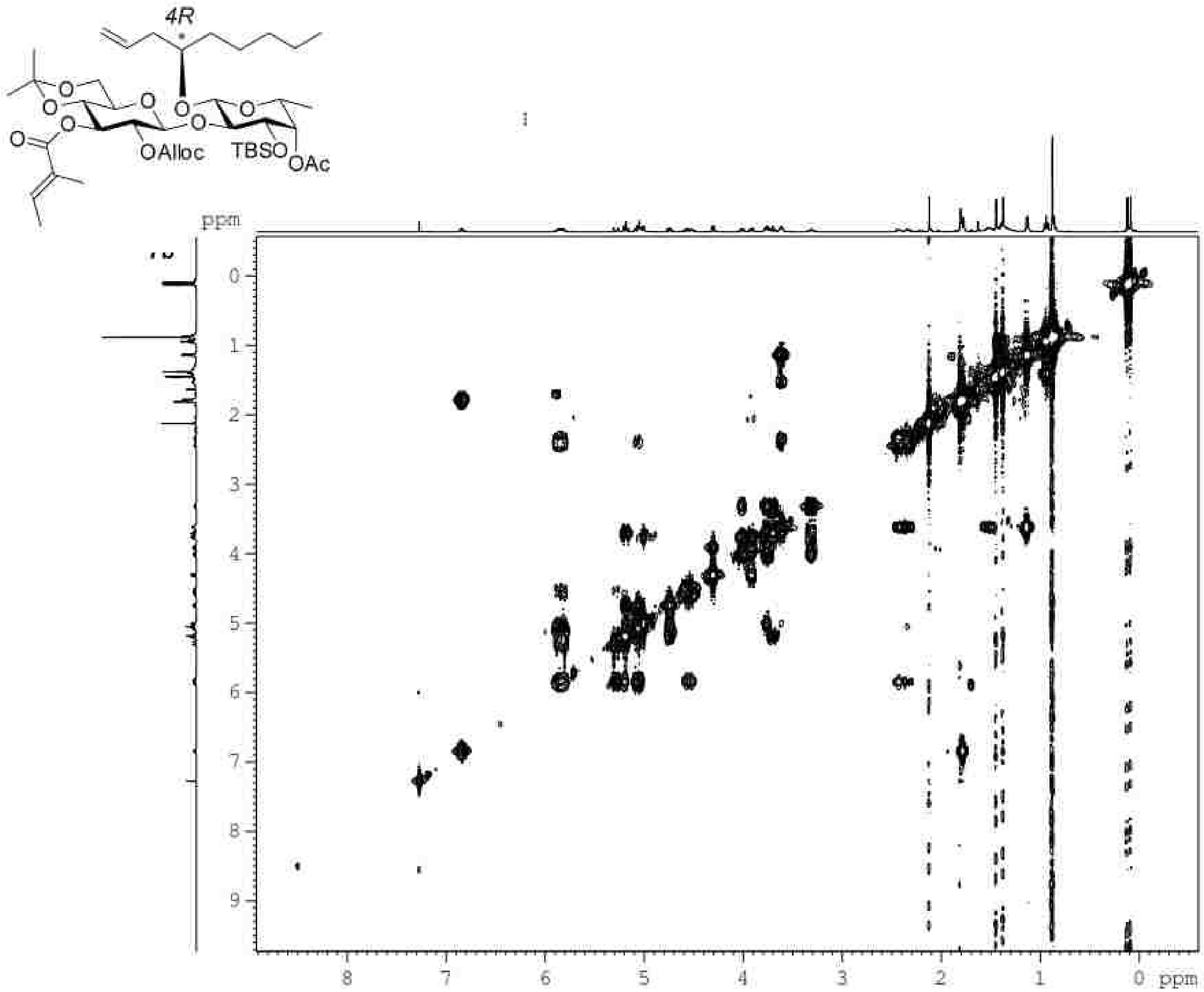
TBSO
OAc


4R
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TBSO
OAc
ppm
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5
6
7
8
9
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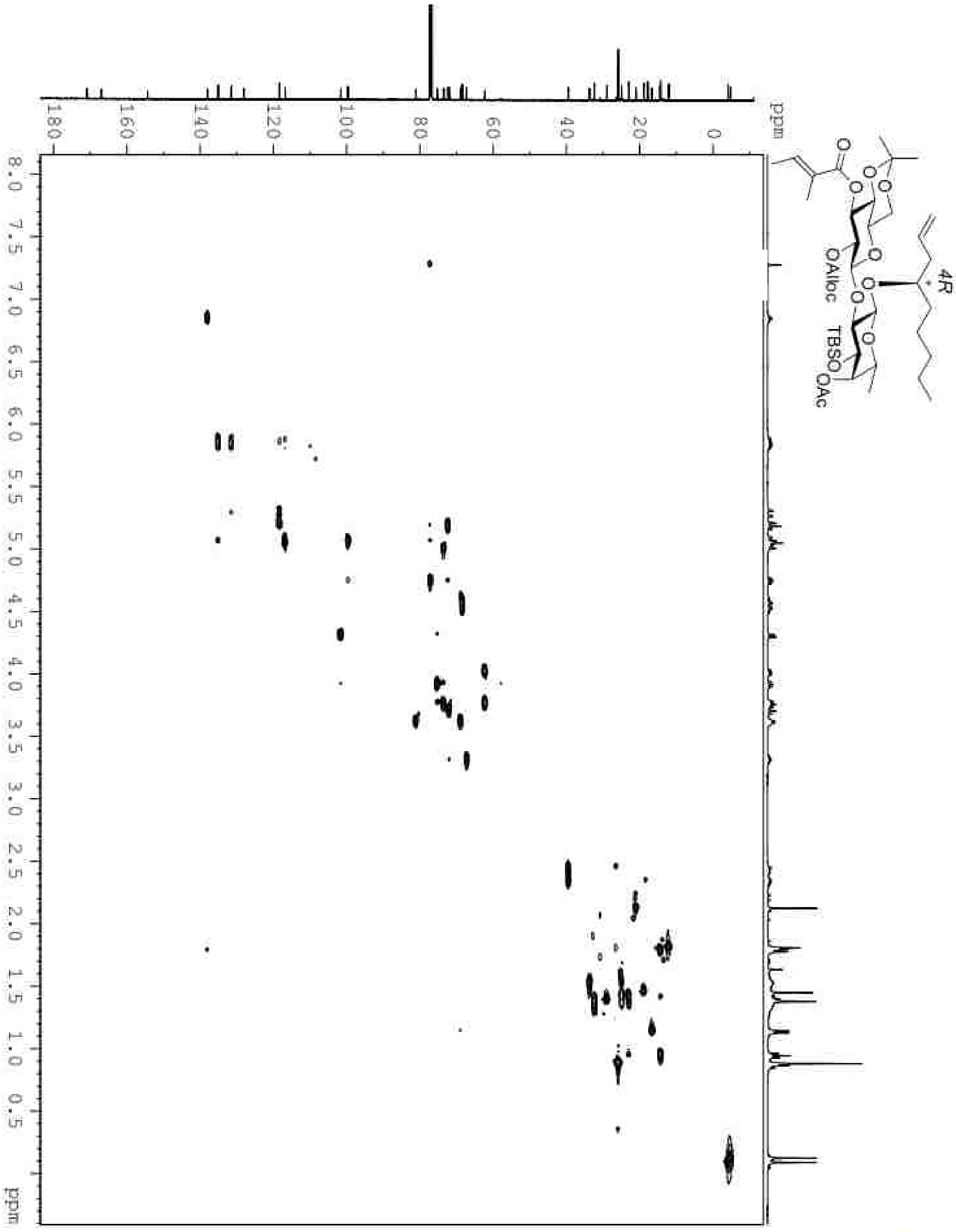
5
4
3
2
1
0 ppm


4R
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TBSO
OAc
ppm
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160
140
120
100
80
60
40
20
0
8.0
7.5
7.0
6.5
6.0
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4.5
4.0
3.5
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2.0
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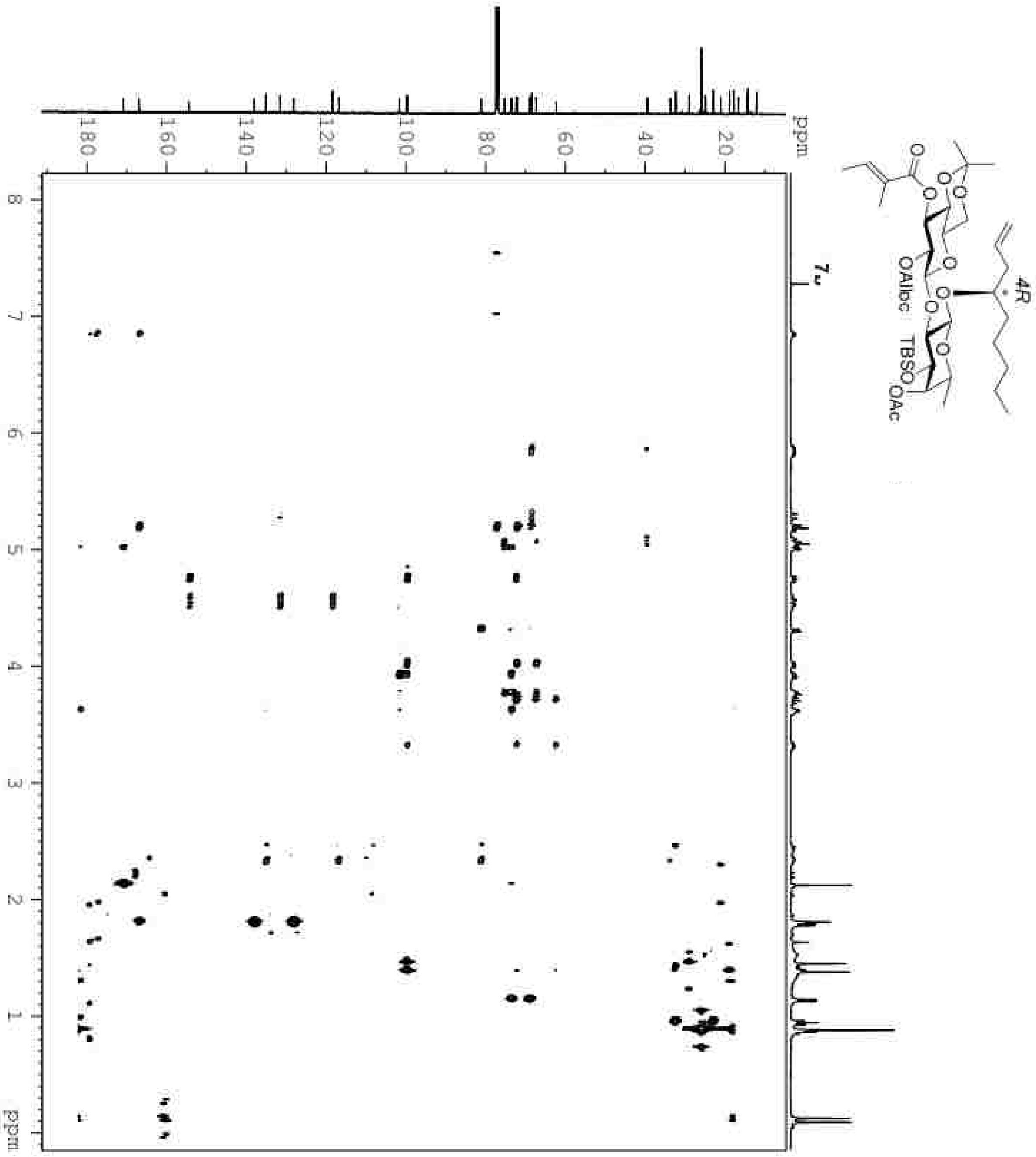

4R
O
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TBSO
OAc
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100
120
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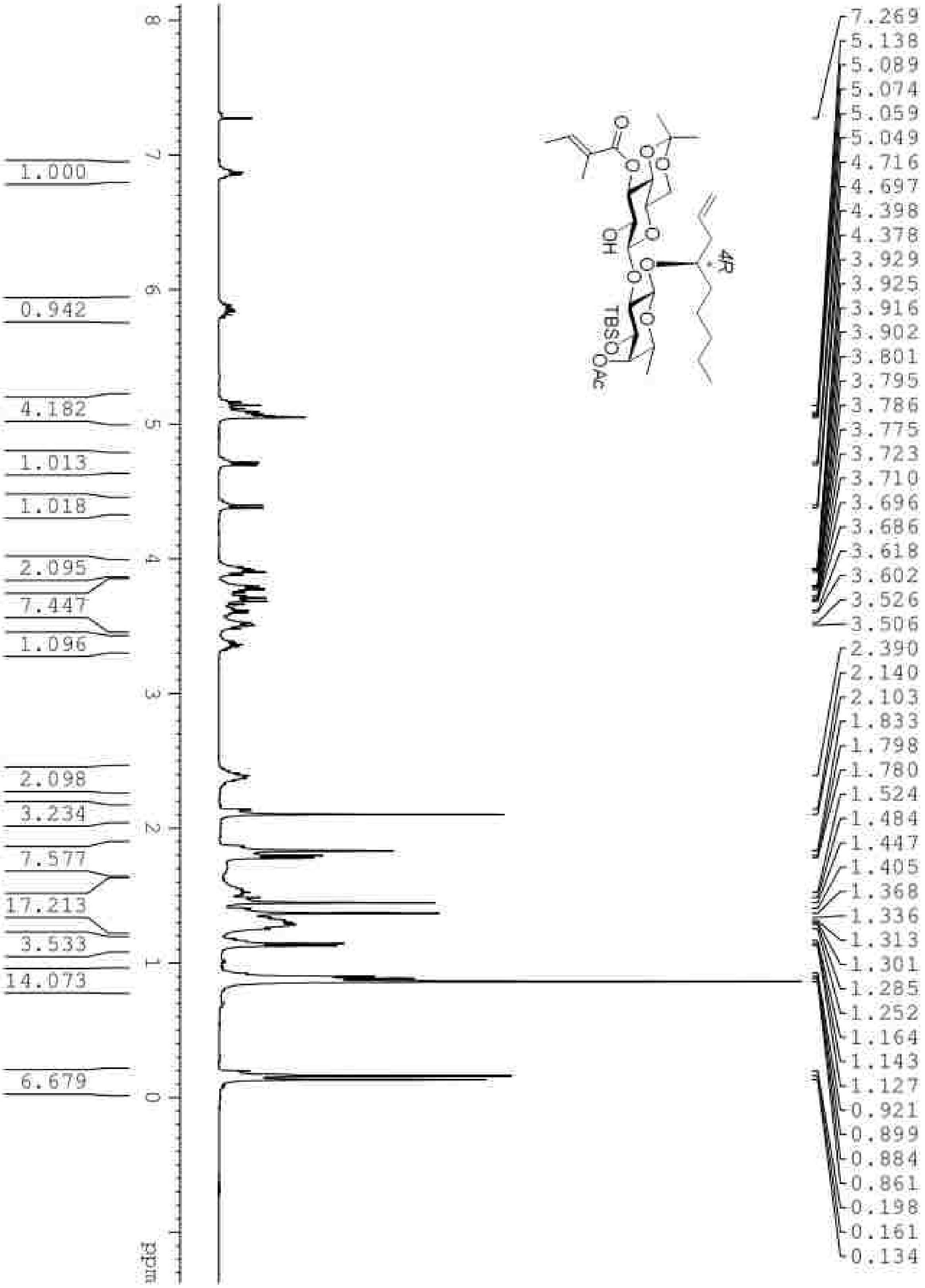
160
180
8
7
6
5
4
3
2
1
ppm

7u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6
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4
3
2
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3.925
3.916
3.902
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3.723
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3.506
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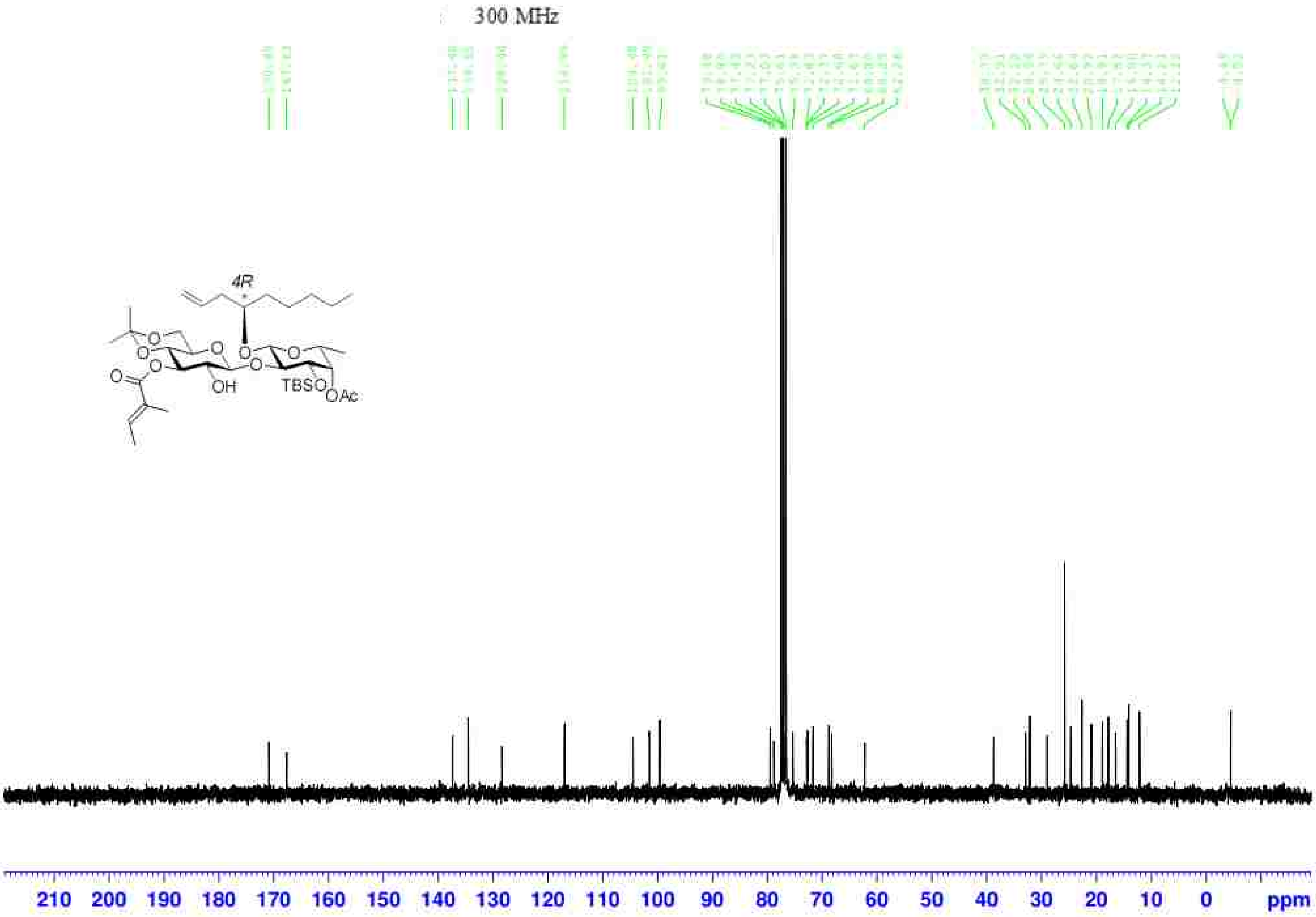
4R
O
OH
TBSO
OAc


300 MHz
4R
O
O
O
O
O
O
O
OH
TBSO
OAc
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200
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130
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110
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30
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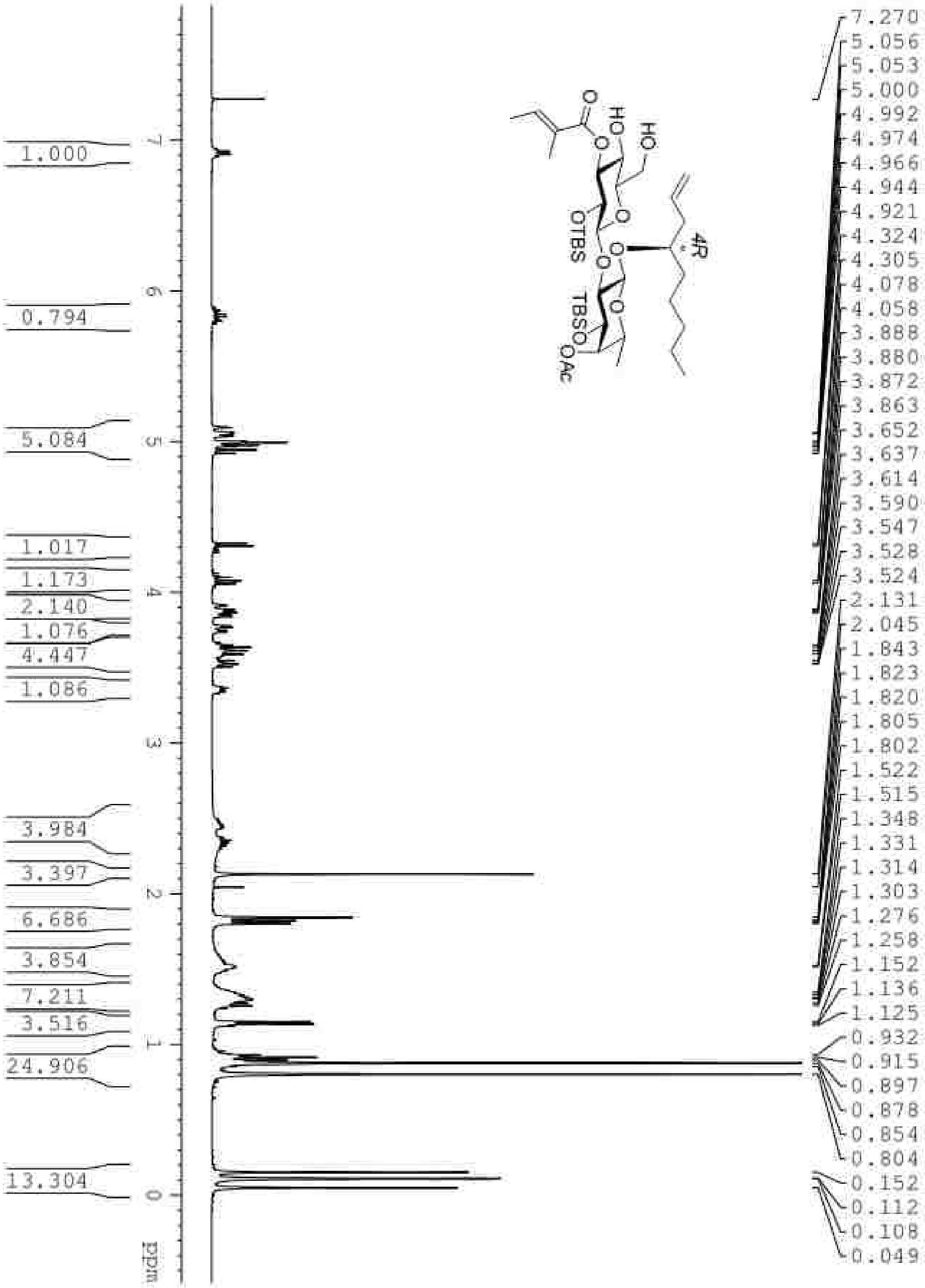

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4.058
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3.547
3.528
3.524
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1.802
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1.515
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1.276
1.258
1.152
1.136
1.125
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0.854
0.804
0.152
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1.000
0.794
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1.017
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2.140
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3.397
6.686
3.854
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3.516
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13.304
7
6
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0
ppm
4R
HO
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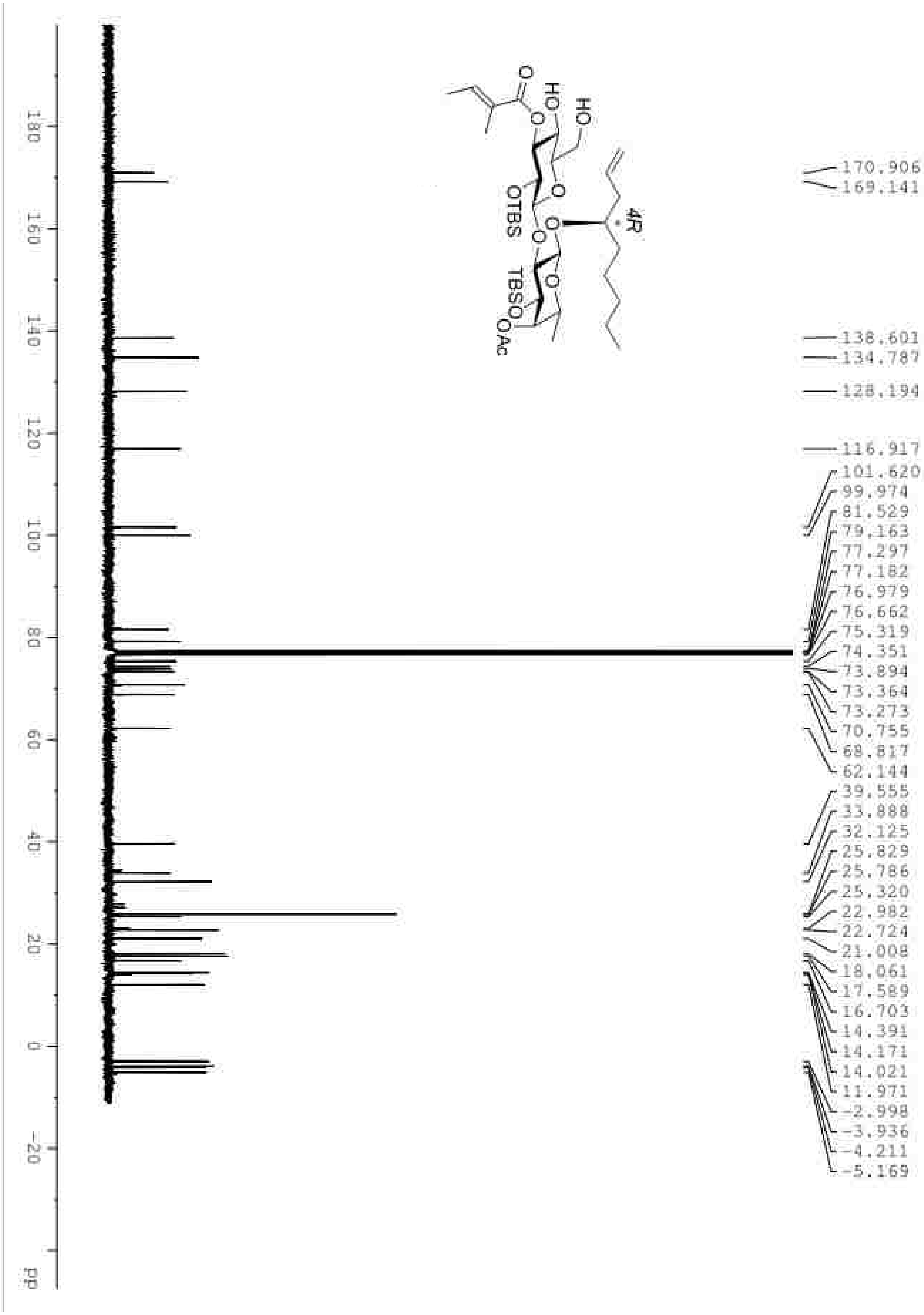
O
O
O
O
OTBS
TBSO
OAc
O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HO
O
OTBS
TBSO
OAc
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25.320
22.982
22.724
21.008
18.061
17.589
16.703
14.391
14.171
14.021
11.971
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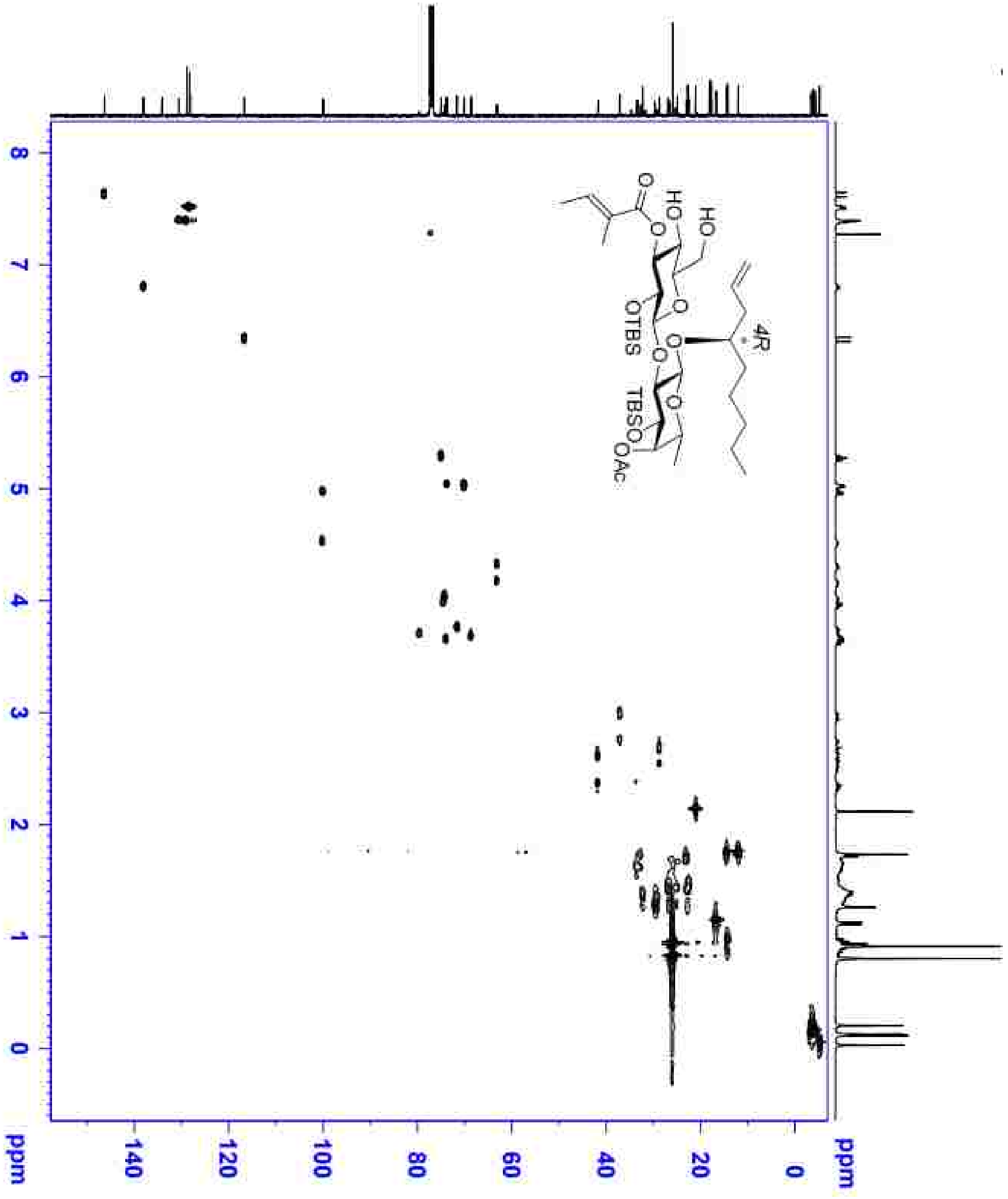
4R
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HO
O
O
O
O
O
OTBS
TBSO
OAc
ppm
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3
2
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ppm
140
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60
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20
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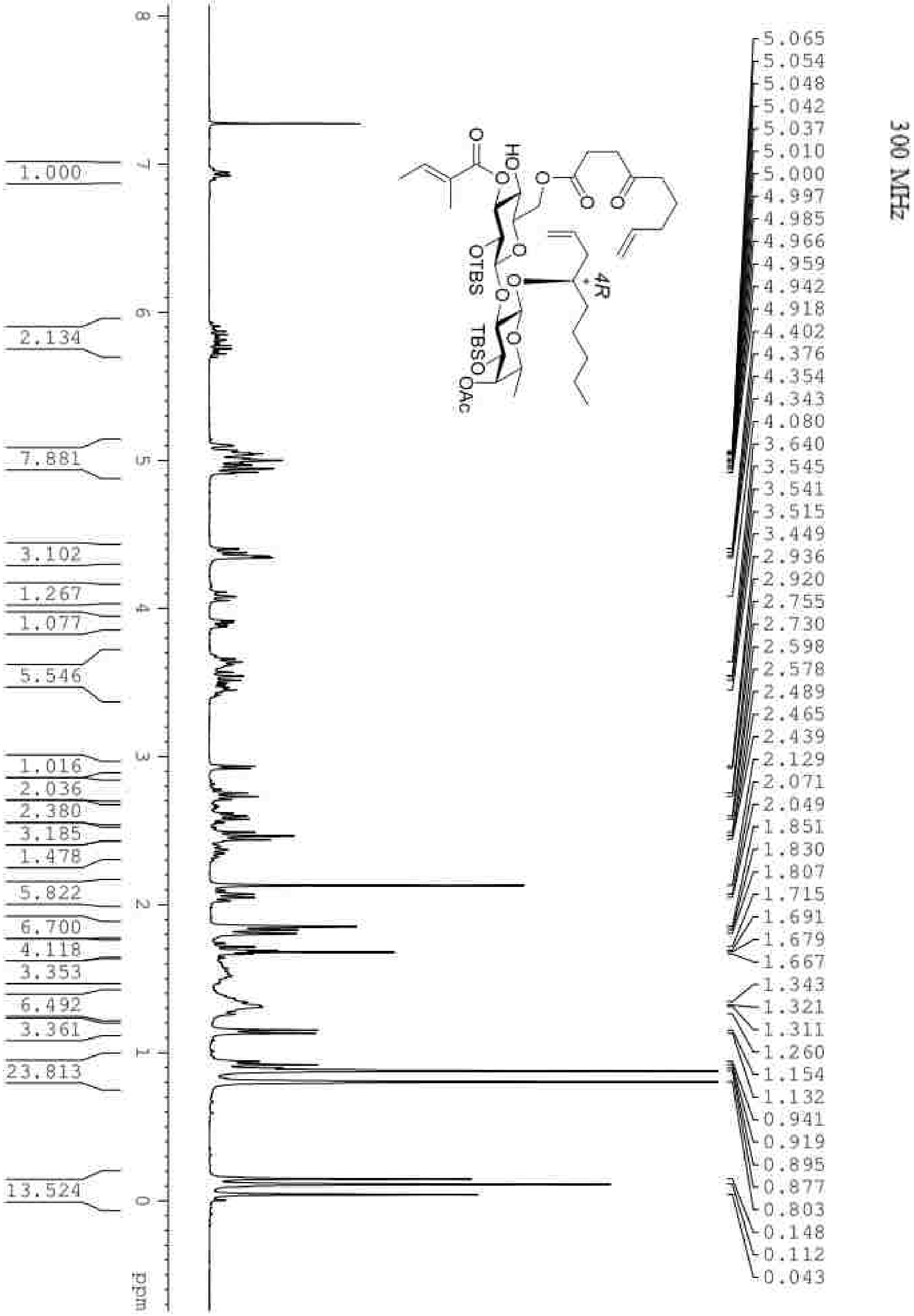
300 MHz
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O
OTBS
TBSO
OAc
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2.920
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2.730
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2.578
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2.465
2.439
2.129
2.071
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1.851
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1.132
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0.043
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1.016
2.036
2.380
3.185
1.478
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6.700
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3.361
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4
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2
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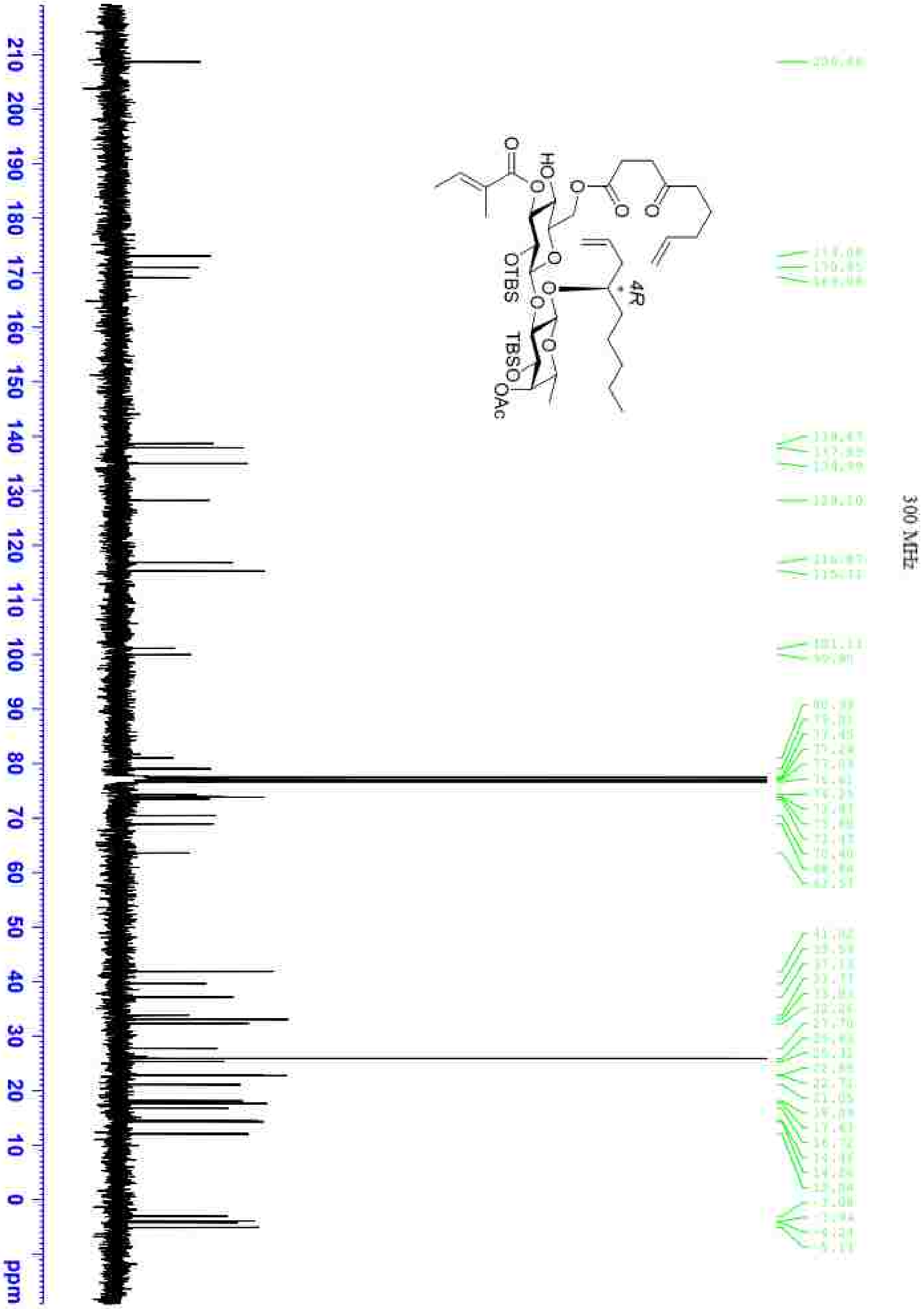
0
ppm


300 MHz
4R
HO
O
OTBS
TBSO
OAc
210
200
190
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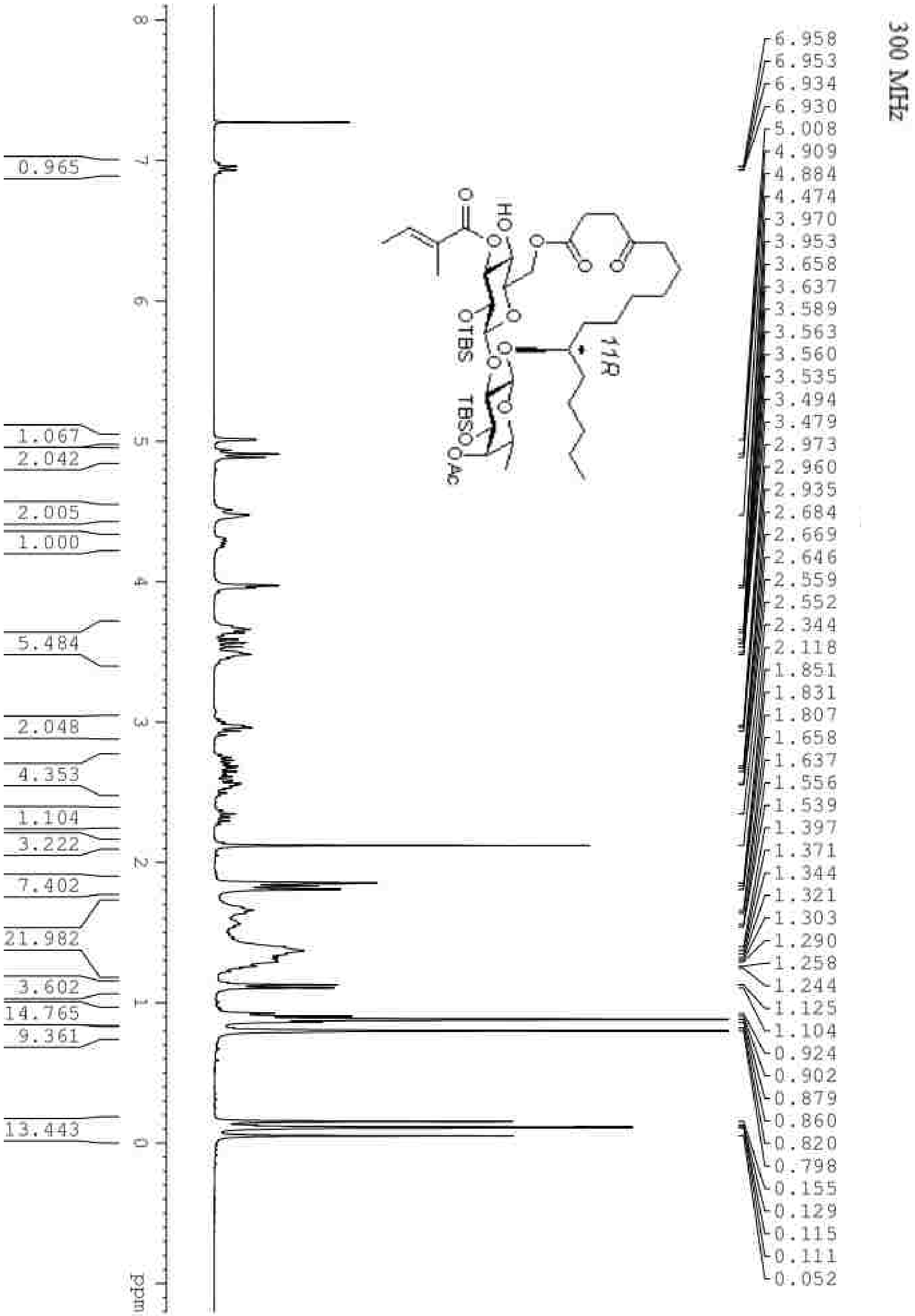
0
ppm


300 MHz
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4.474
3.970
3.953
3.658
3.637
3.589
3.563
3.560
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3.494
3.479
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9.361
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7
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5
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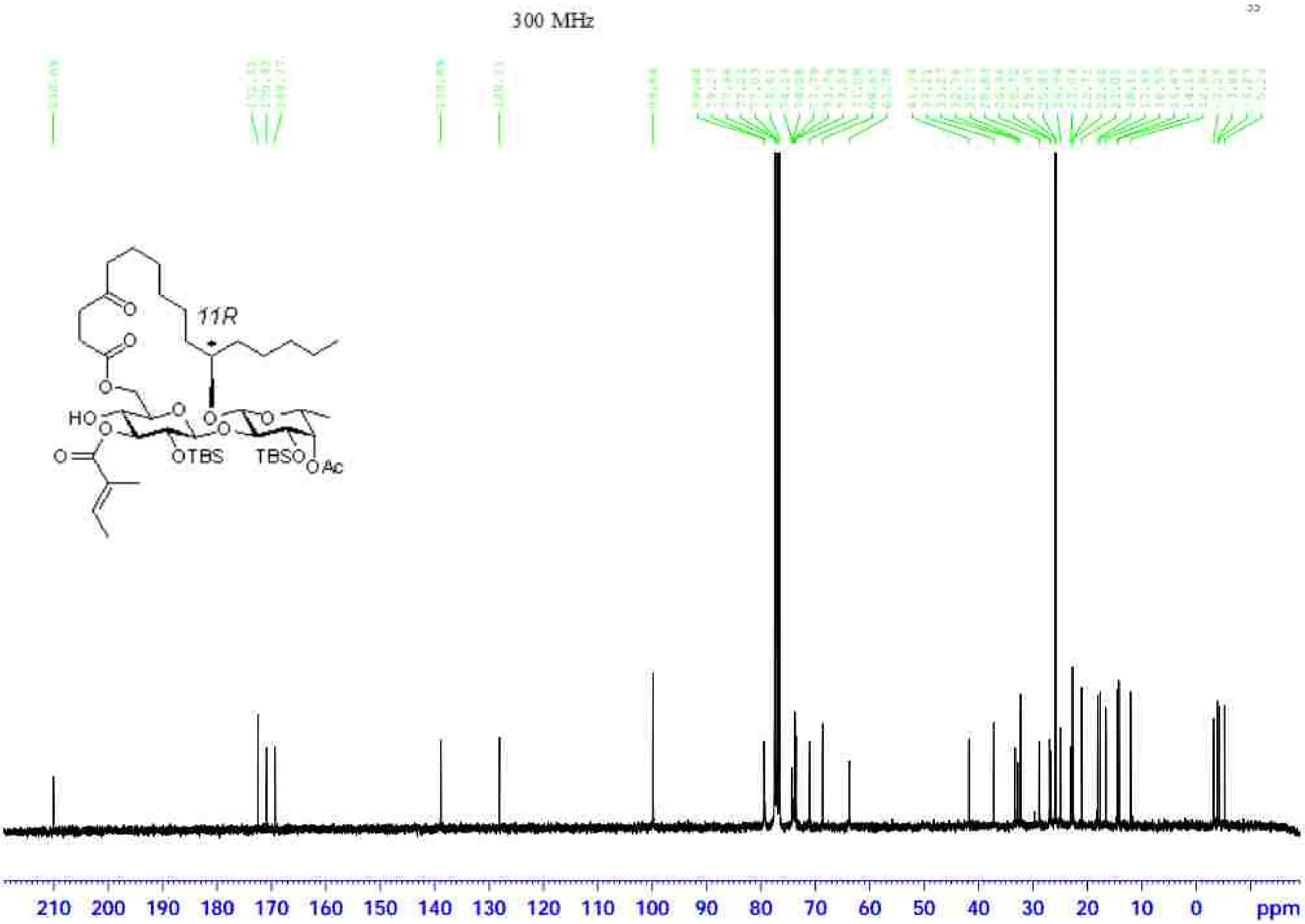
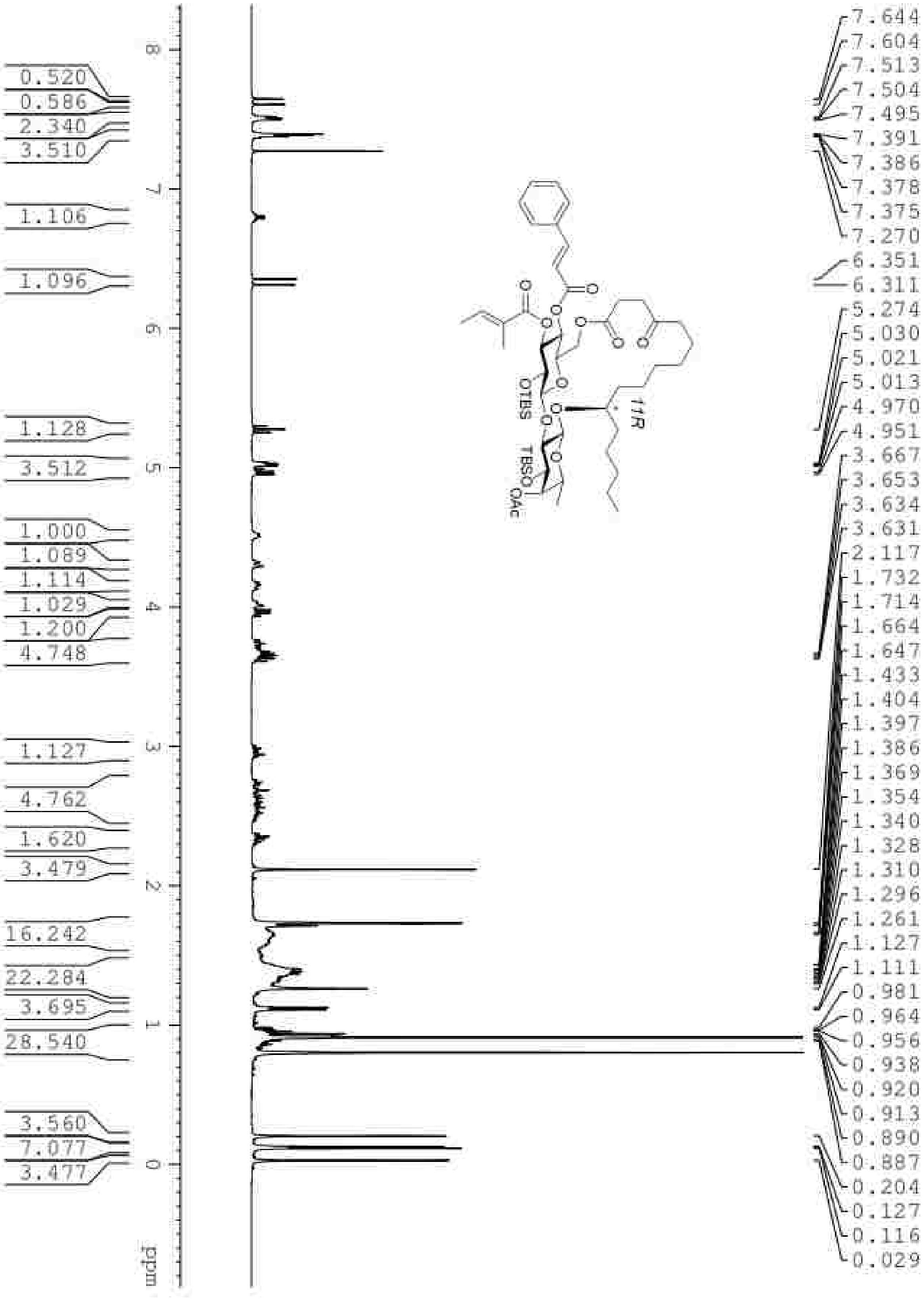
1
0
ppm
11R
HO
O
OTBS
TBSO
OAc


300 MHz
11R
HO
OTBS
TBSO
OAc
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm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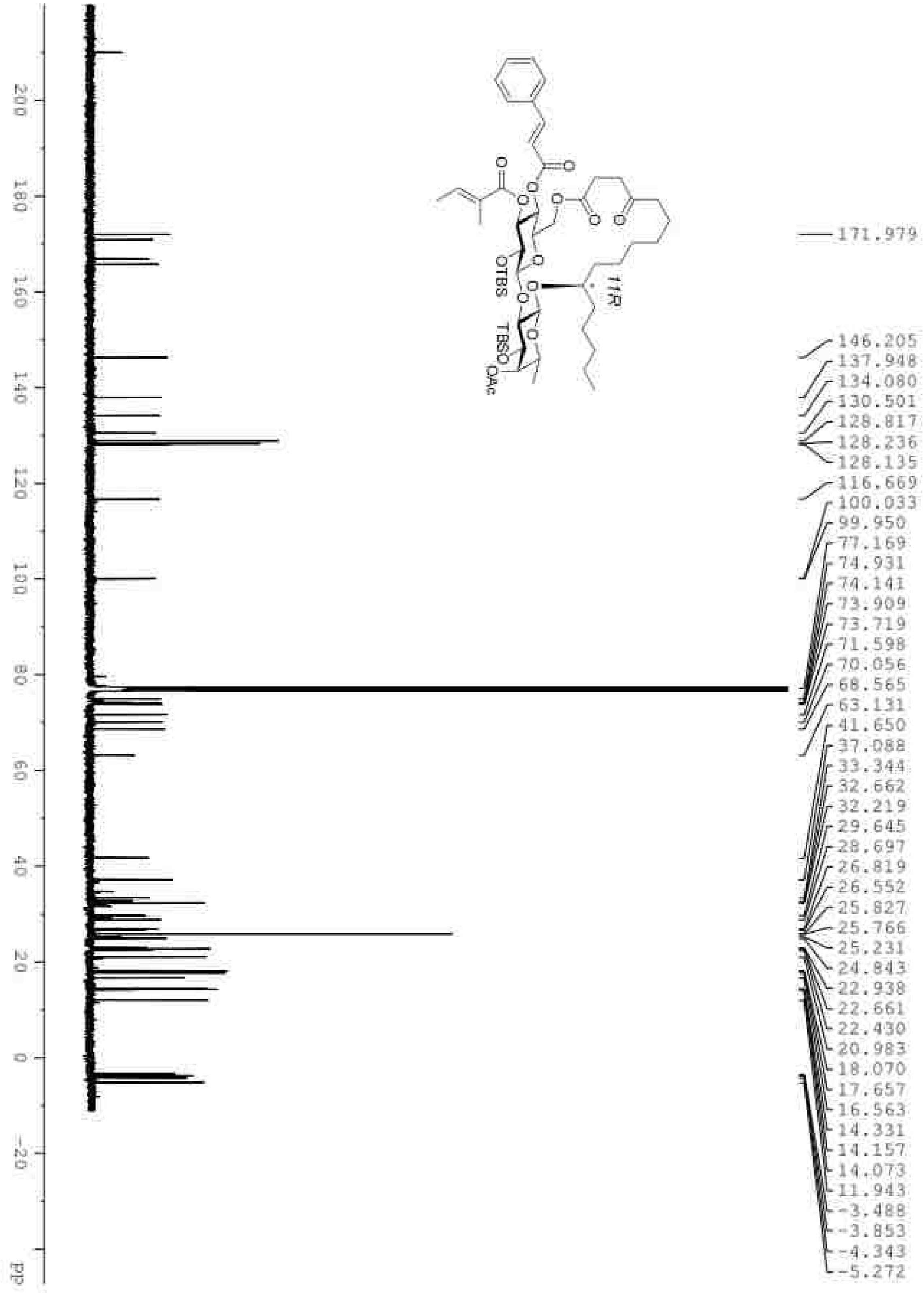
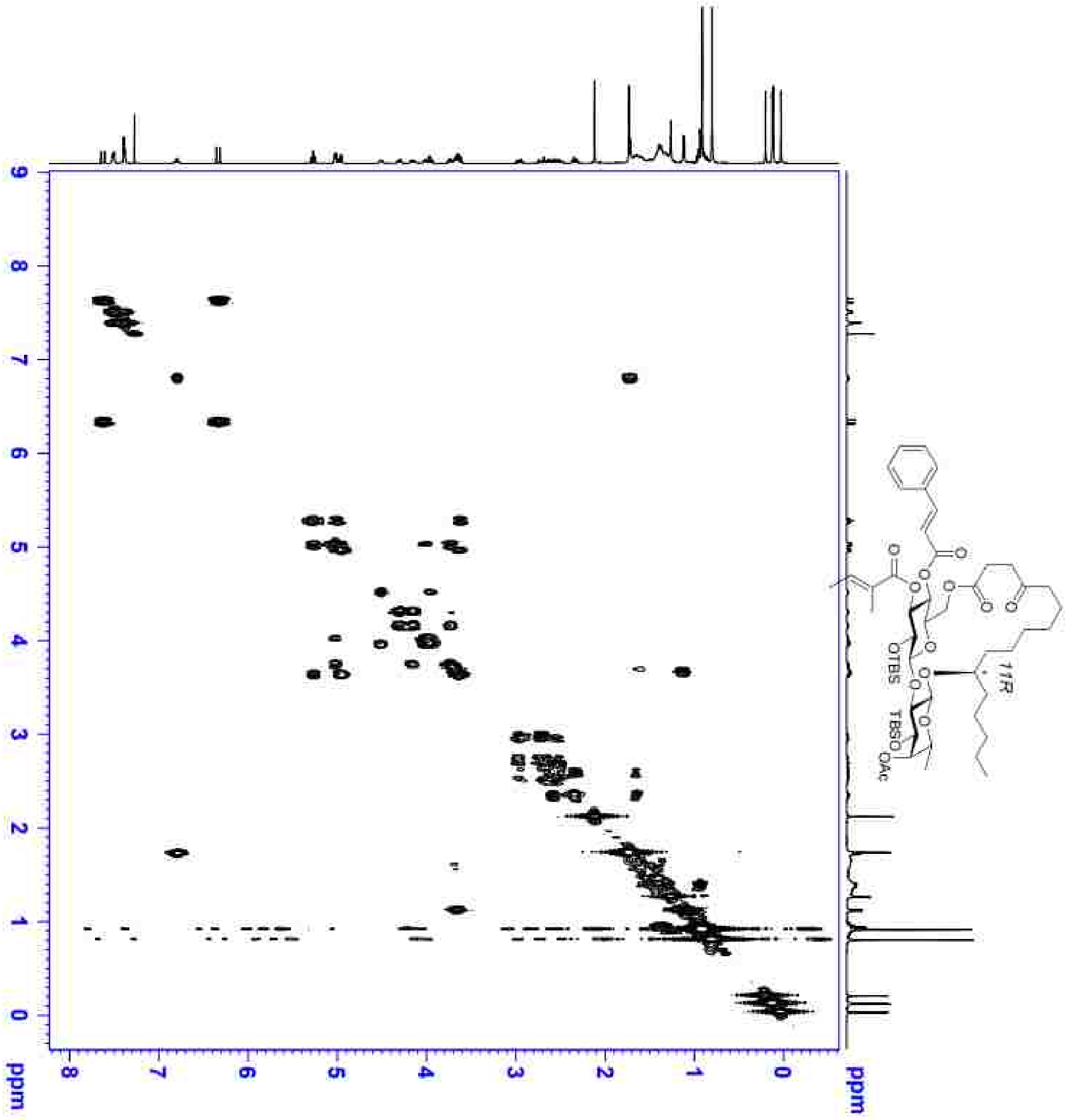
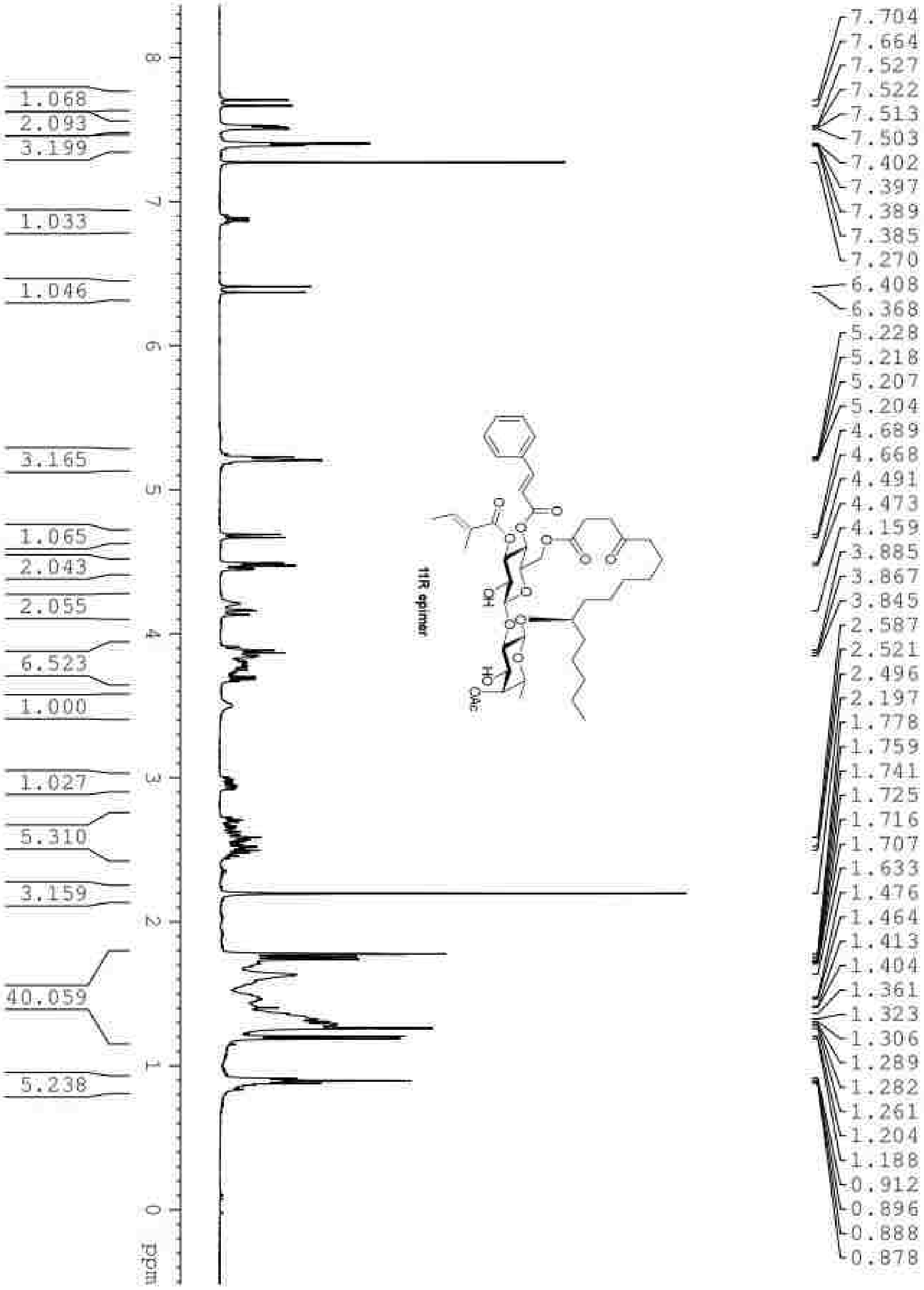
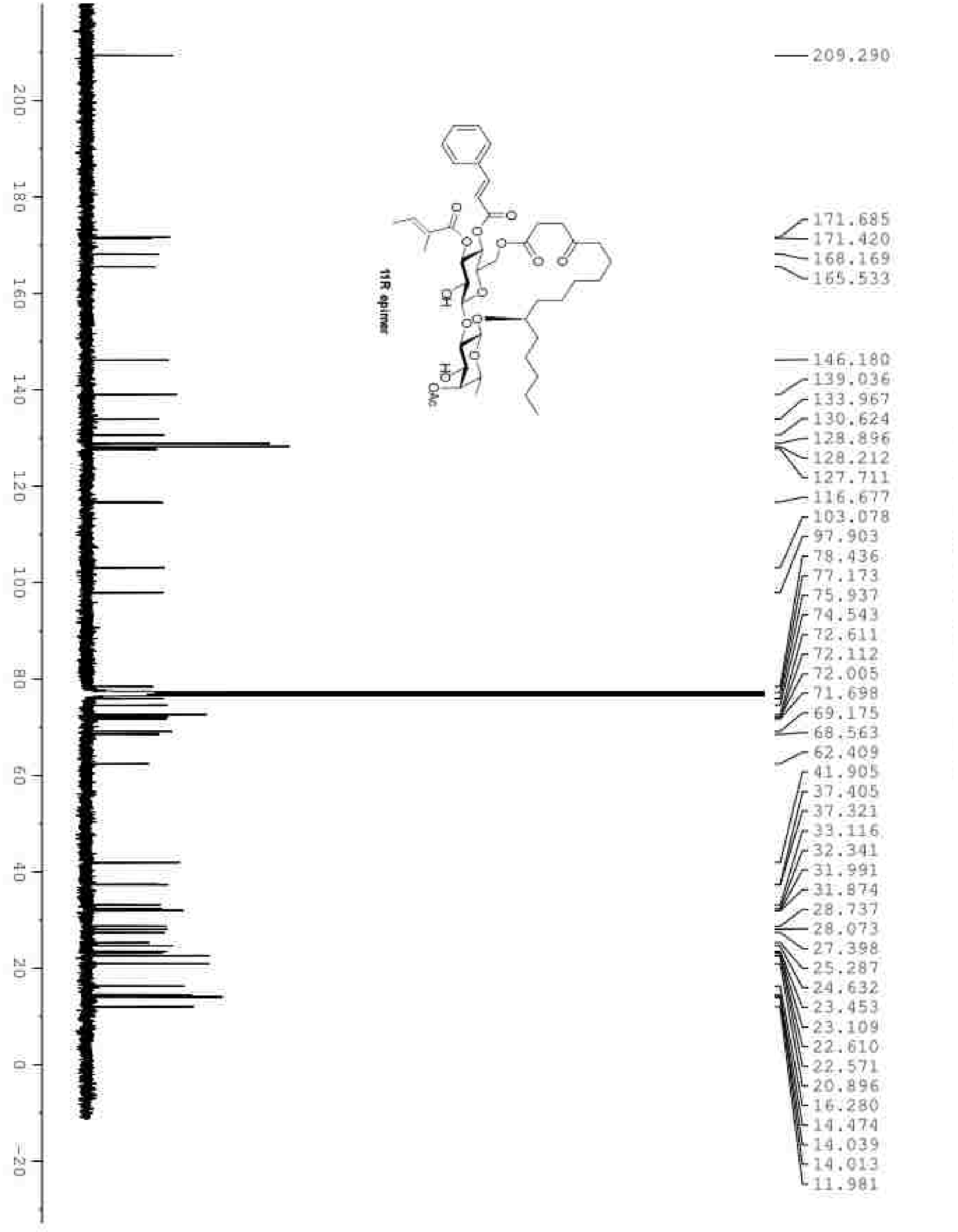
0.586
2.340
3.510
1.106
1.096
1.128
3.512
1.000
1.089
1.114
1.029
1.200
4.748
1.127
4.762
1.620
3.479
16.242
22.284
3.695
28.540
3.560
7.077
3.477
8
7
6
5
4
3
2
1
0
ppm
O
OTBS
TBSO
OAc
11R
7.644
7.604
7.513
7.504
7.495
7.391
7.386
7.378
7.375
7.270
6.351
6.311
5.274
5.030
5.021
5.013
4.970
4.951
3.667
3.653
3.634
3.631
2.117
1.732
1.714
1.664
1.647
1.433
1.404
1.397
1.386
1.369
1.354
1.340
1.328
1.310
1.296
1.261
1.127
1.111
0.981
0.964
0.956
0.938
0.920
0.913
0.890
0.887
0.204
0.127
0.116
0.029

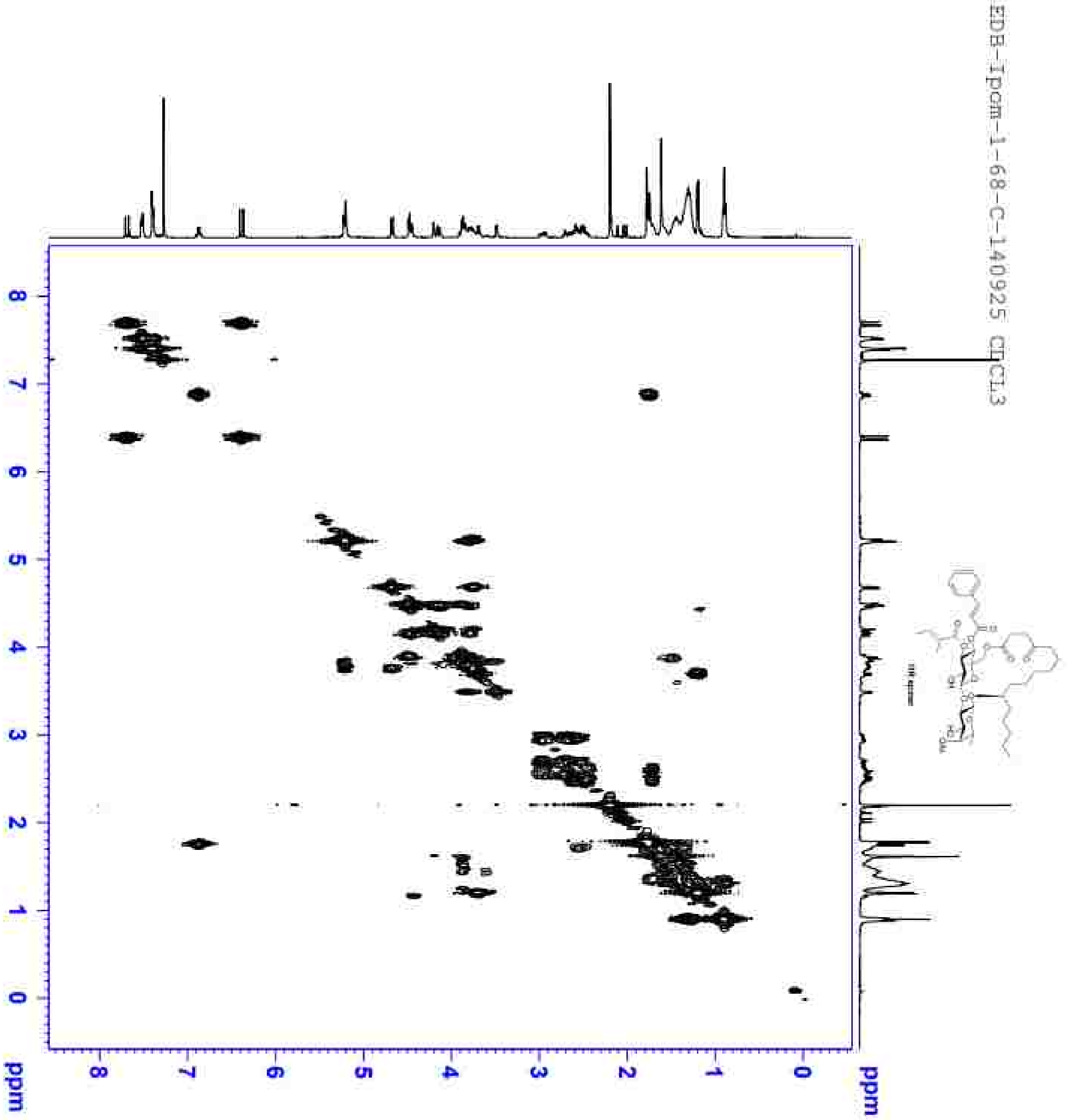


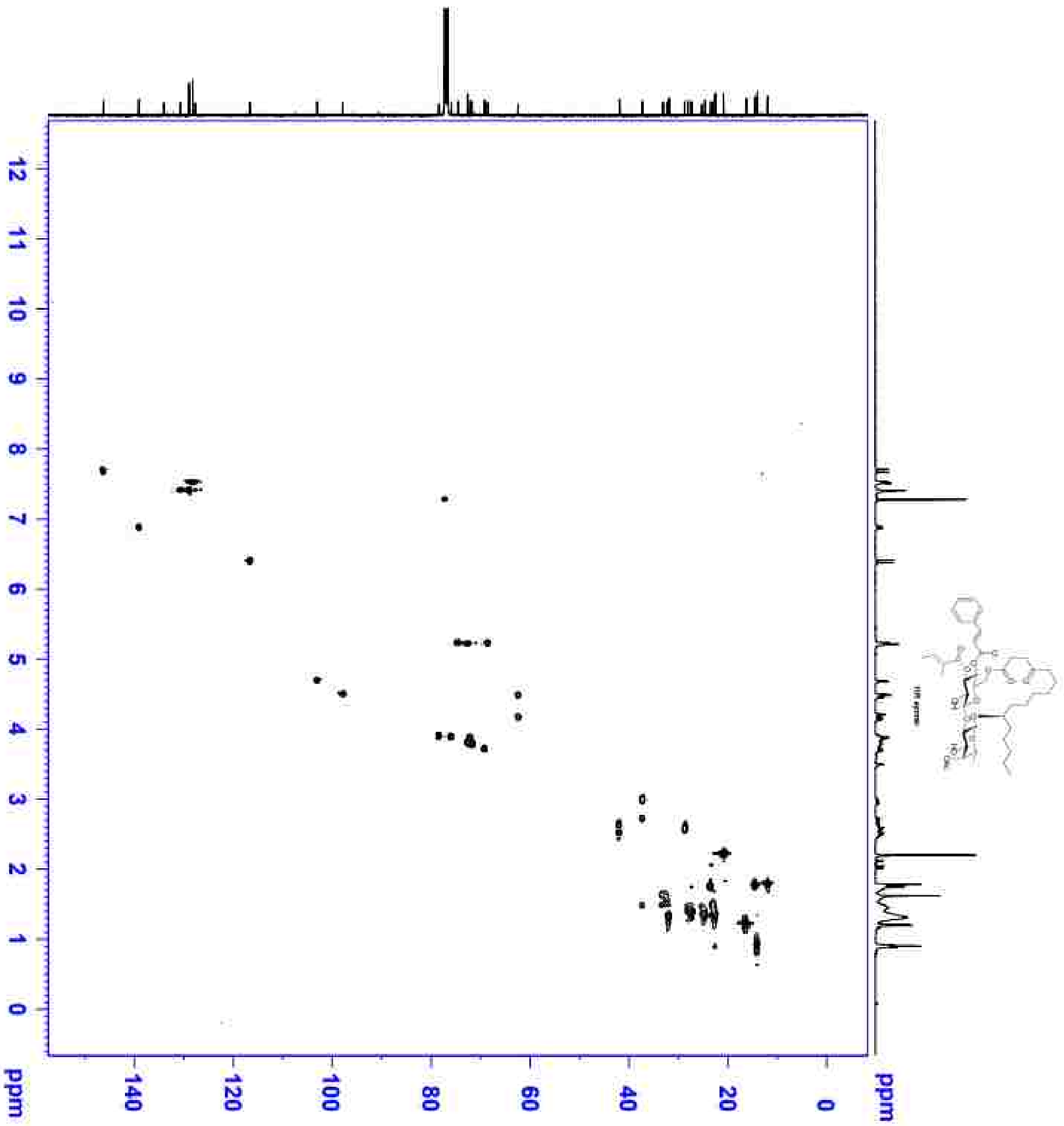
200
180
160
140
120
100
80
60
40
20
0
-20
PP
O
O
O
O
O
O
O
O
O
O
OTBS
TBSO
OAc
11R
171.979
146.205
137.948
134.080
130.501
128.817
128.236
128.135
116.669
100.033
99.950
77.169
74.931
74.141
73.909
73.719
71.598
70.056
68.565
63.131
41.650
37.088
33.344
32.662
32.219
29.645
28.697
26.819
26.552
25.827
25.766
25.231
24.843
22.938
22.661
22.430
20.983
18.070
17.657
16.563
14.331
14.157
14.073
11.943
-3.488
-3.853
-4.343
-5.272


ppm
9
8
7
6
5
4
3
2
1
0
ppm
8
7
6
5
4
3
2
1
0
OTBS
TBSO
OAc
11R


11R epimer
OAc
HO
OH
ppm
8
7
6
5
4
3
2
1
0
1.068
2.093
3.199
1.033
1.046
3.165
1.065
2.043
2.055
6.523
1.000
1.027
5.310
3.159
40.059
5.238
7.704
7.664
7.527
7.522
7.513
7.503
7.402
7.397
7.389
7.385
7.270
6.408
6.368
5.228
5.218
5.207
5.204
4.689
4.668
4.491
4.473
4.159
3.885
3.867
3.845
2.587
2.521
2.496
2.197
1.778
1.759
1.741
1.725
1.716
1.707
1.633
1.476
1.464
1.413
1.404
1.361
1.323
1.306
1.289
1.282
1.261
1.204
1.188
0.912
0.896
0.888
0.878


11R epimer
OH
HO
OAc
200
180
160
140
120
100
80
60
40
20
0
−20
209.290
171.685
171.420
168.169
165.533
146.180
139.036
133.967
130.624
128.896
128.212
127.711
116.677
103.078
97.903
78.436
77.173
75.937
74.543
72.611
72.112
72.005
71.698
69.175
68.563
62.409
41.905
37.405
37.321
33.116
32.341
31.991
31.874
28.737
28.073
27.398
25.287
24.632
23.453
23.109
22.610
22.571
20.896
16.280
14.474
14.039
14.013
11.981


EDB-Ipgm-1-68-C-140925 CDCL3
ppm
8
7
6
5
4
3
2
1
0
ppm
8
7
6
5
4
3
2
1
0

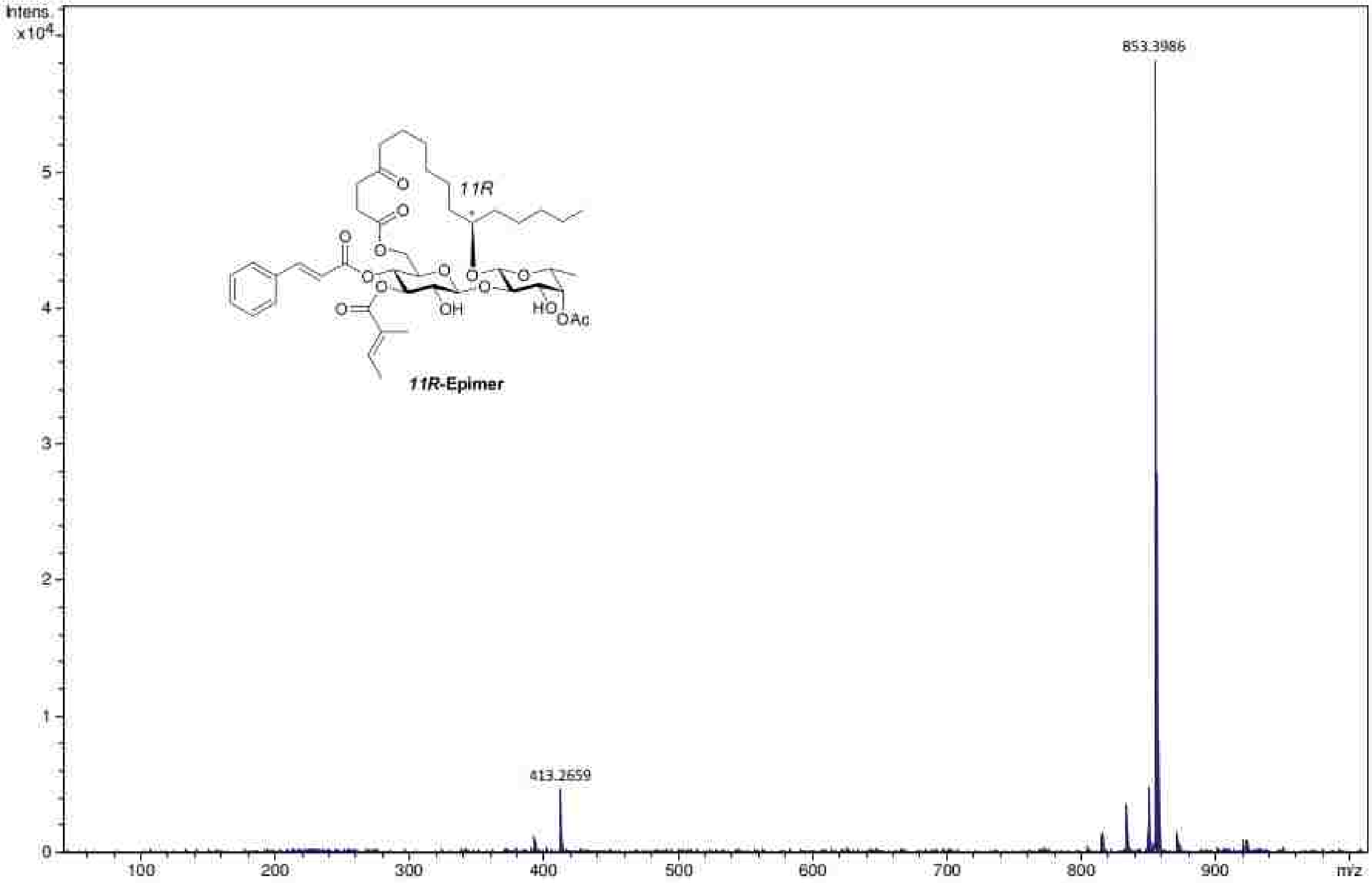


ppm
140
120
100
80
60
40
20
0
ppm
12
11
10
9
8
7
6
5
4
3
2
1
0

ESI Mass Spectrum

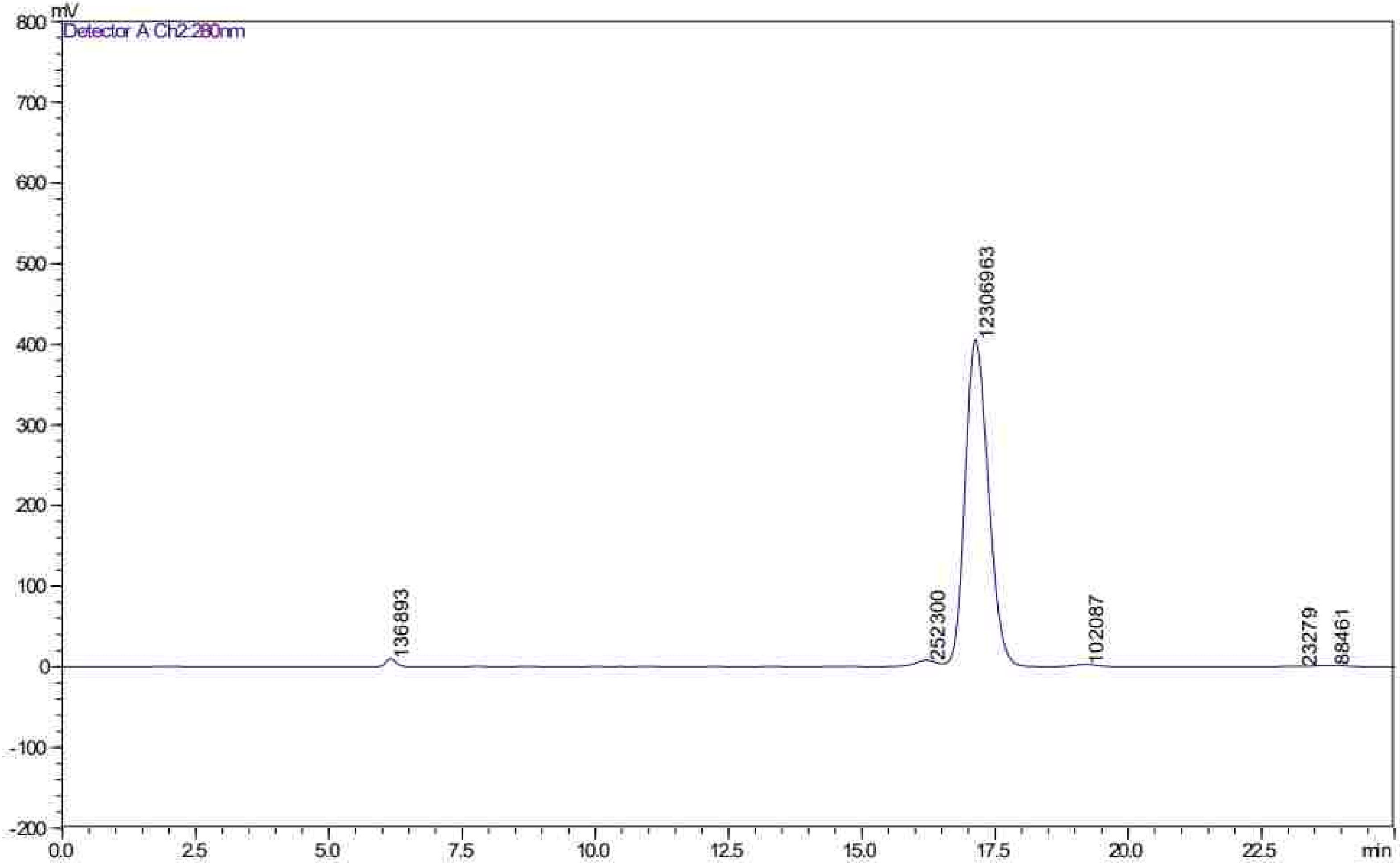
Sample Name: EI-68
Sample id#: 982220
Instrument: ultrOTOF-Q

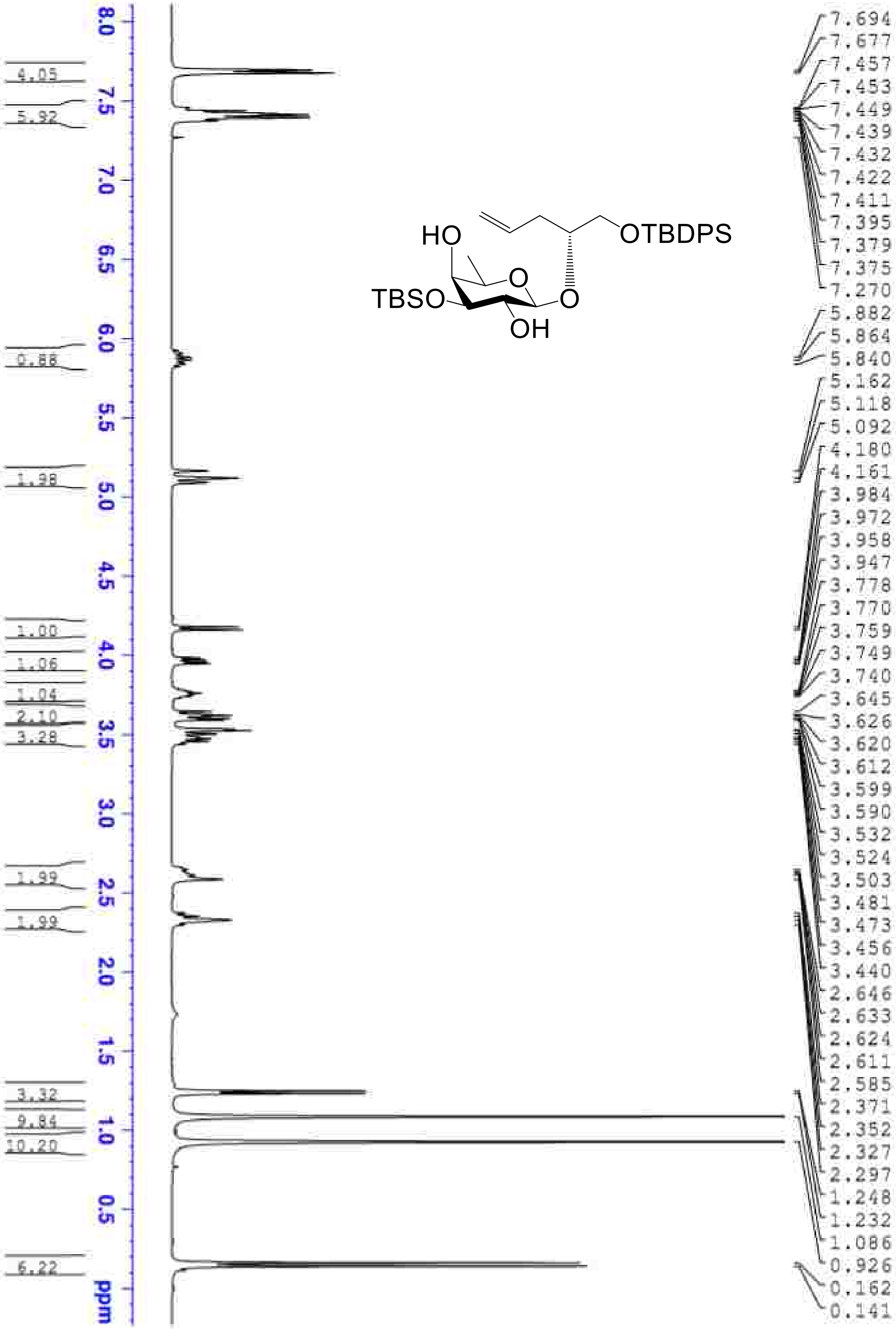
11/6/2014



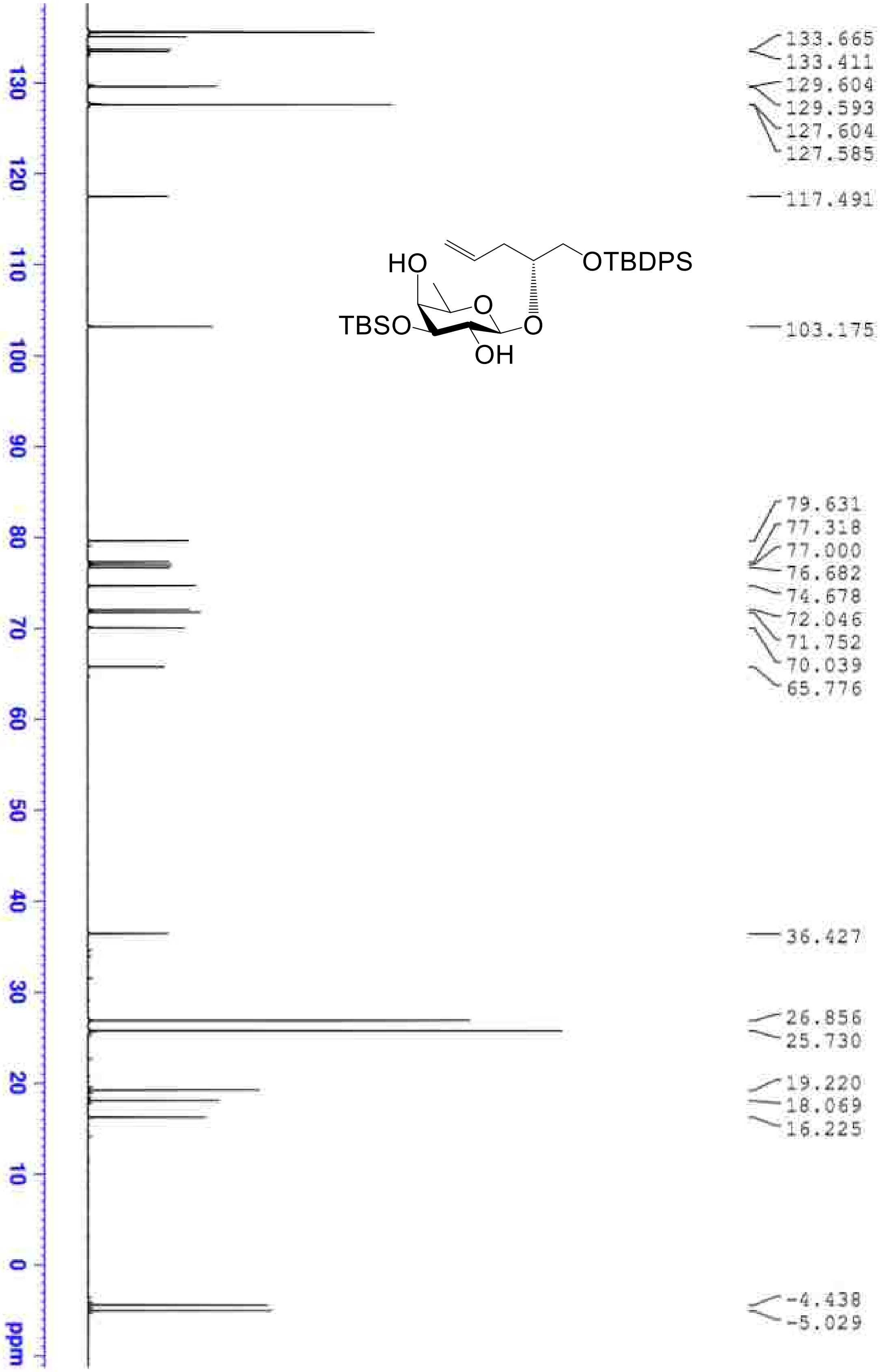
***11R*-Epimer**

HPLC for **11R-Epimer** (95.3%; MeCN/H_2O 3:1; 1 mL/min, t_R = 17.1 min)





HO
TBSO
O
O
OH
OTBDPS
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
4.05
5.92
0.88
1.98
1.00
1.06
1.04
2.10
3.28
1.99
1.99
3.32
9.84
10.20
6.22
7.694
7.677
7.457
7.453
7.449
7.439
7.432
7.422
7.411
7.395
7.379
7.375
7.270
5.882
5.864
5.840
5.162
5.118
5.092
4.180
4.161
3.984
3.972
3.958
3.947
3.778
3.770
3.759
3.749
3.740
3.645
3.626
3.620
3.612
3.599
3.590
3.532
3.524
3.503
3.481
3.473
3.456
3.440
2.646
2.633
2.624
2.611
2.585
2.371
2.352
2.327
2.297
1.248
1.232
1.086
0.926
0.162
0.141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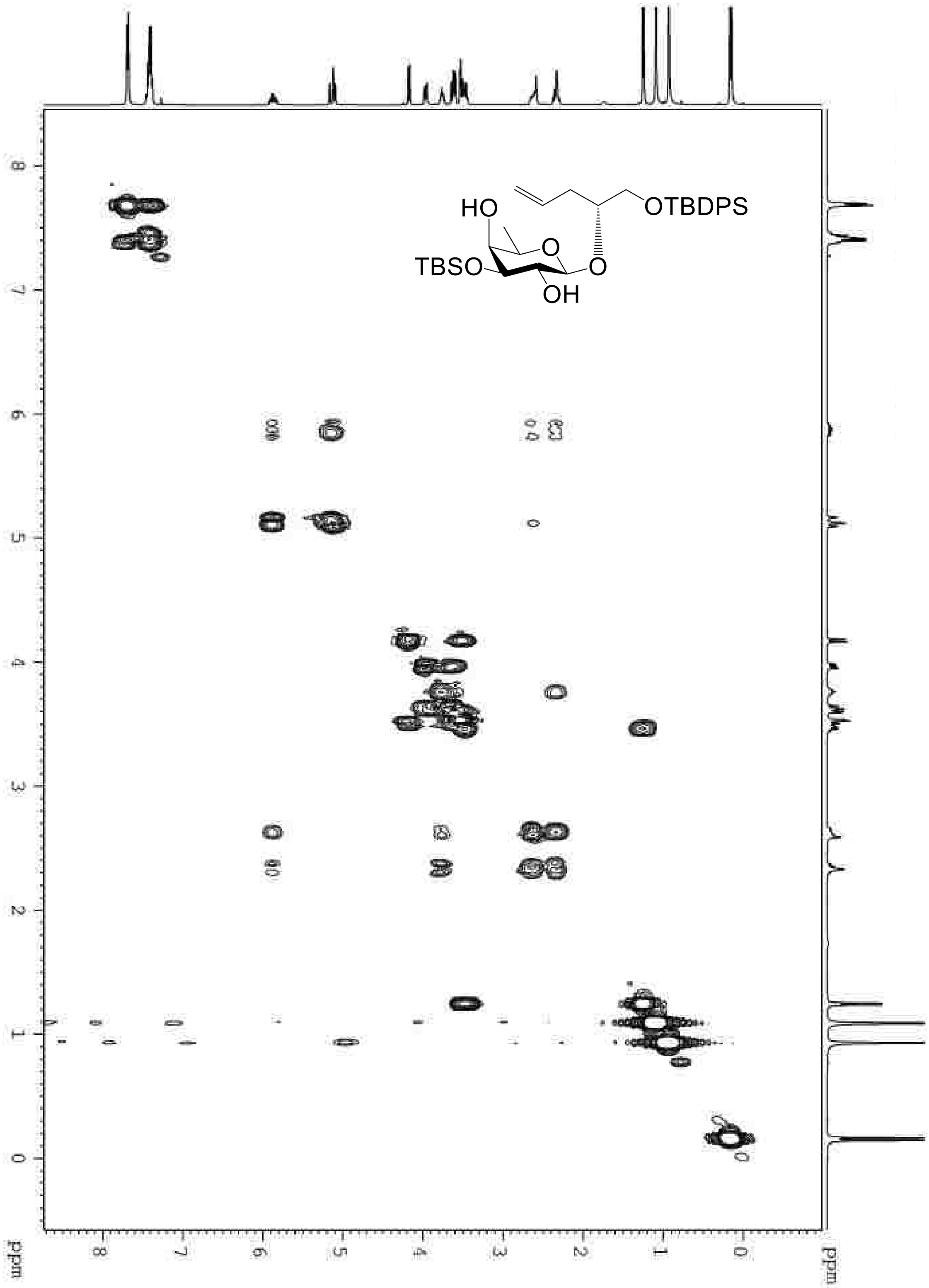
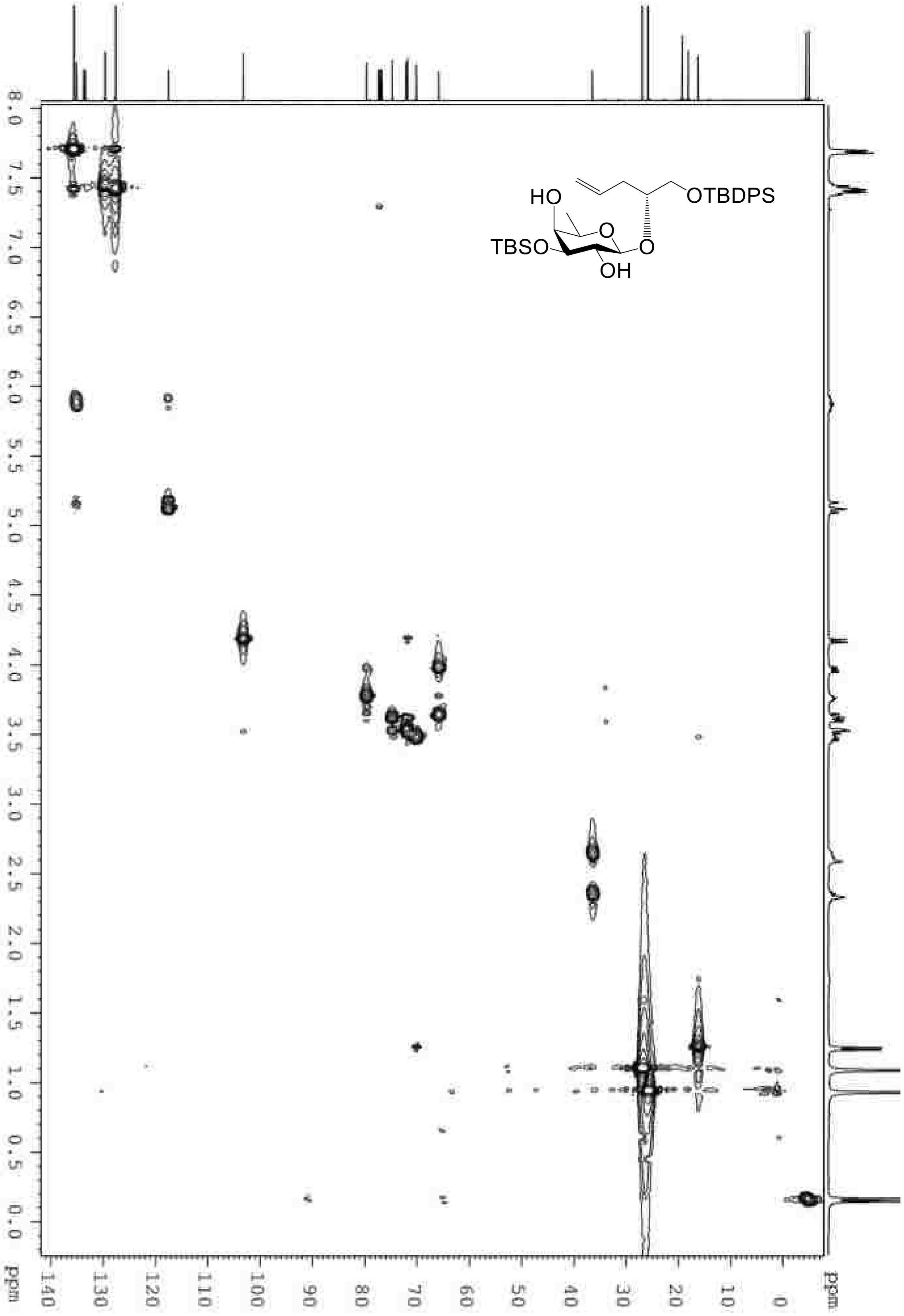
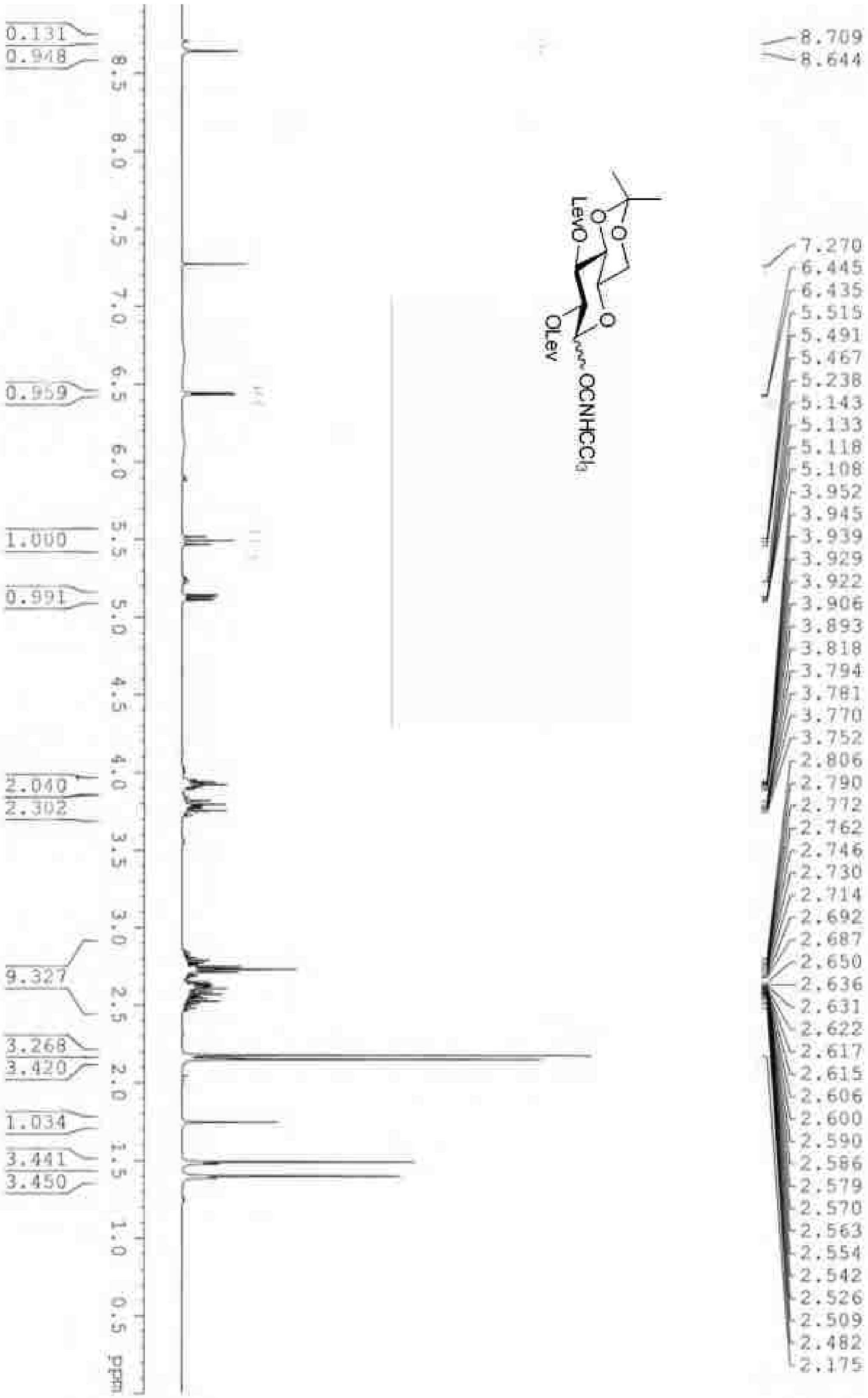
133.411
129.604
129.593
127.604
127.585
117.491
103.175
79.631
77.318
77.000
76.682
74.678
72.046
71.752
70.039
65.776
36.427
26.856
25.730
19.220
18.069
16.225
-4.438
-5.029
HO
OTBDPS
TBSO
O
O
OH
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


HO
OTBDPS
O
TBSO
O
OH
ppm
8
7
6
5
4
3
2
1
0
ppm
8
7
6
5
4
3
2
1
0


HO
OTBDPS
TBSO
O
O
OH
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


0.131
0.948
0.959
1.000
0.991
2.040
2.302
9.327
3.268
3.420
1.034
3.441
3.450
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
LevO
O
O
O
OLev
OCNHCCl3
8.709
8.644
7.270
6.445
6.435
5.515
5.491
5.467
5.238
5.143
5.133
5.118
5.108
3.952
3.945
3.939
3.929
3.922
3.906
3.893
3.818
3.794
3.781
3.770
3.752
2.806
2.790
2.772
2.762
2.746
2.730
2.714
2.692
2.687
2.650
2.636
2.631
2.622
2.617
2.615
2.606
2.600
2.590
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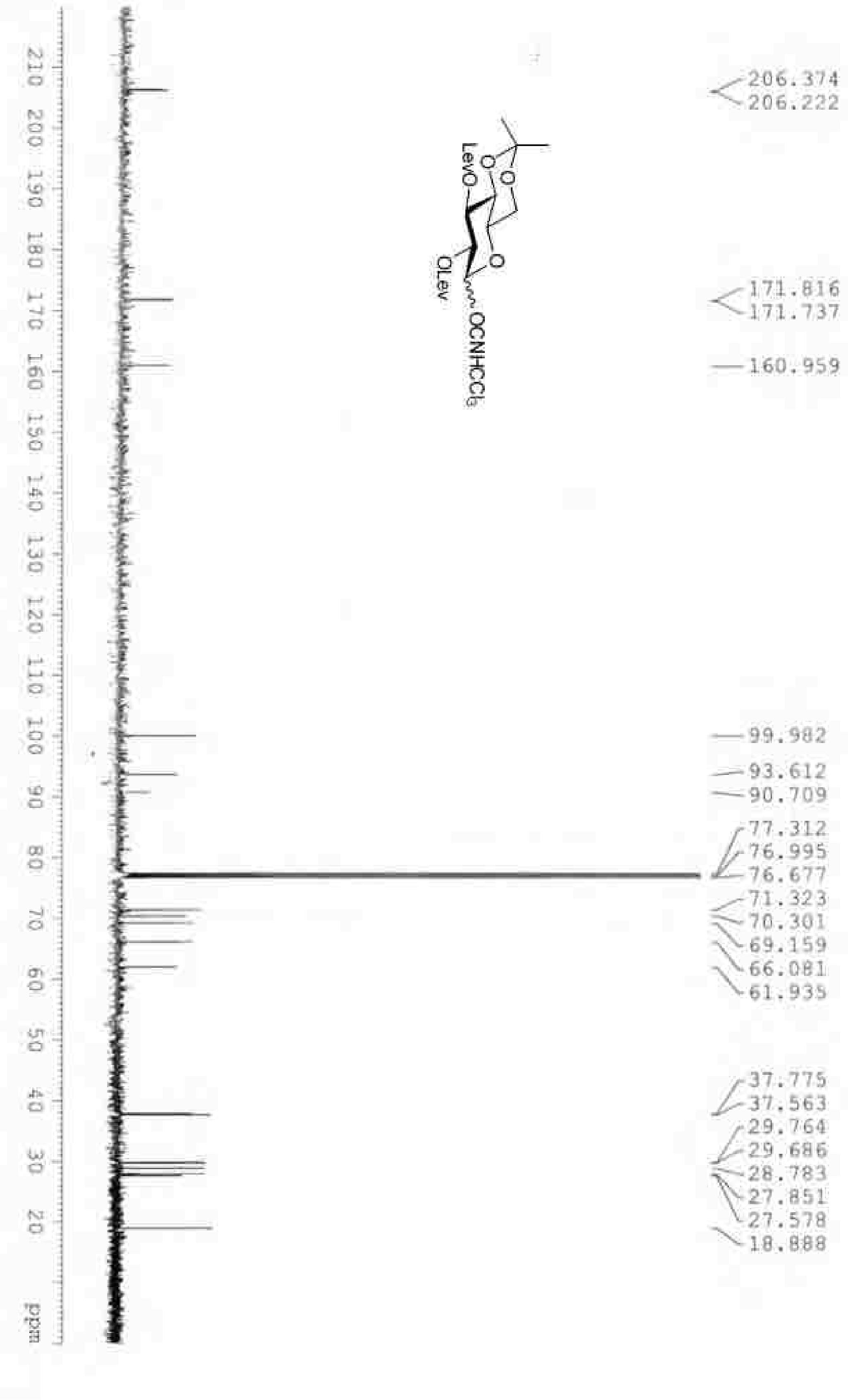
2.554
2.542
2.526
2.509
2.482
2.175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206.222
171.816
171.737
160.959
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93.612
90.709
77.312
76.995
76.677
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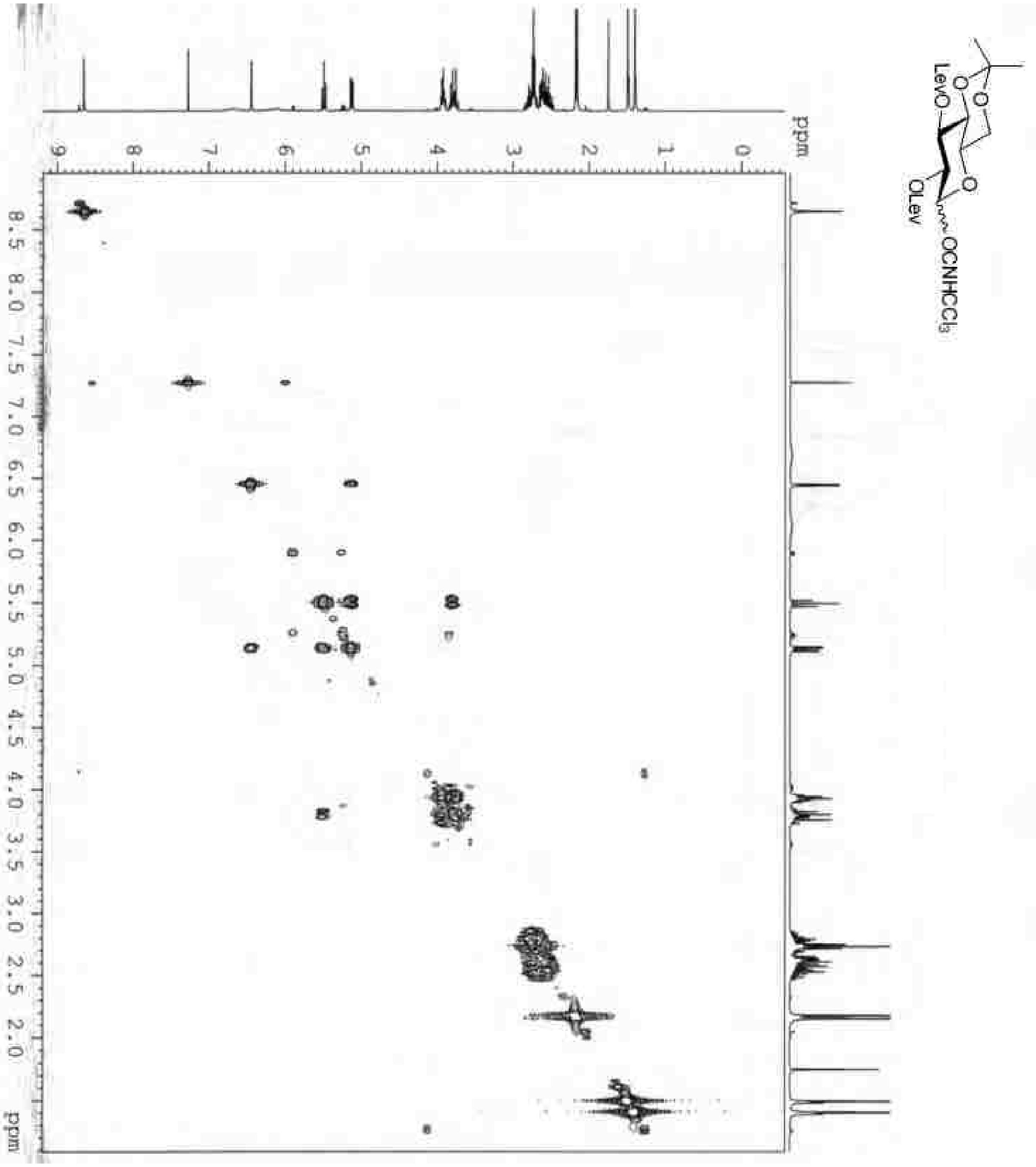
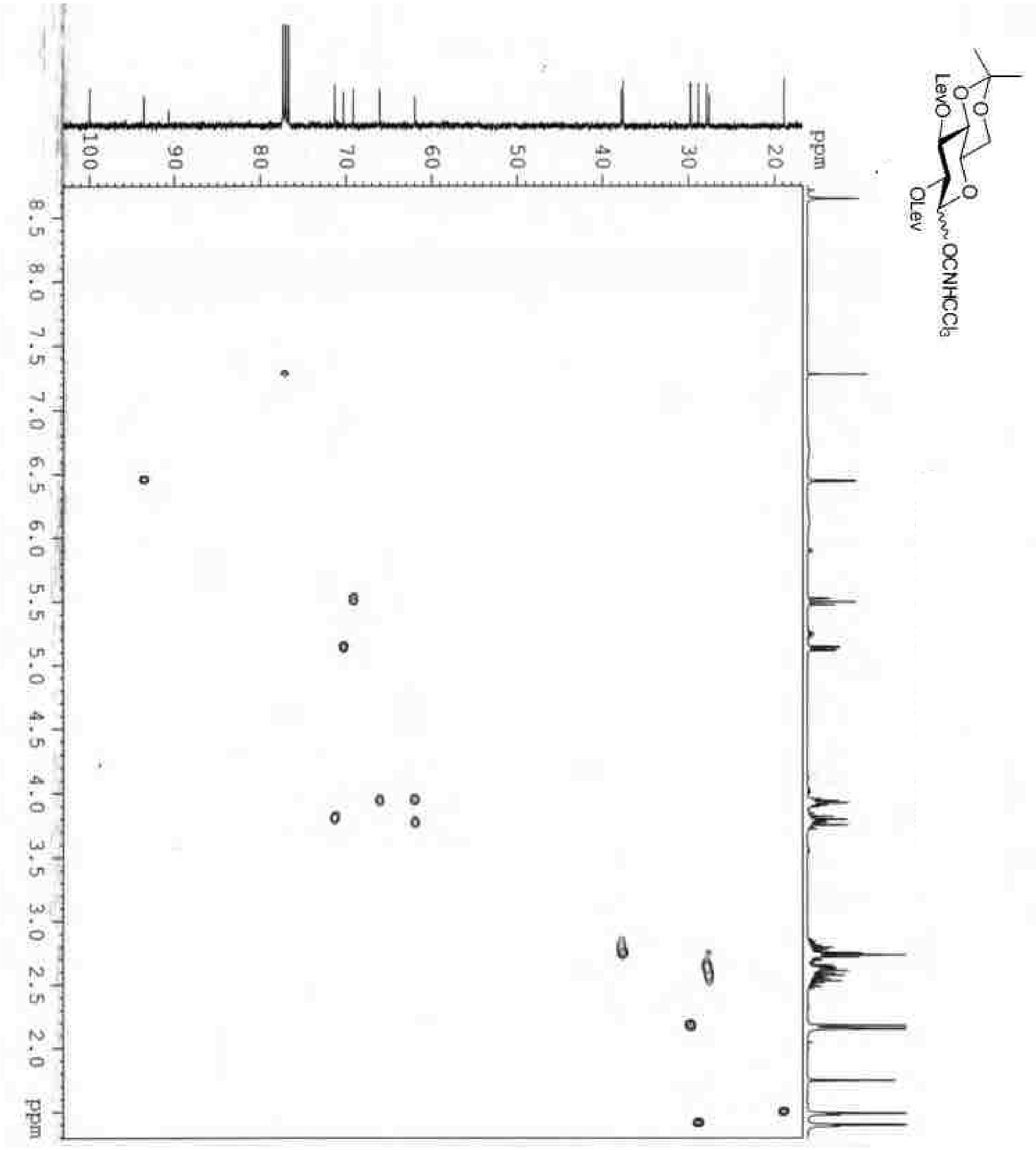
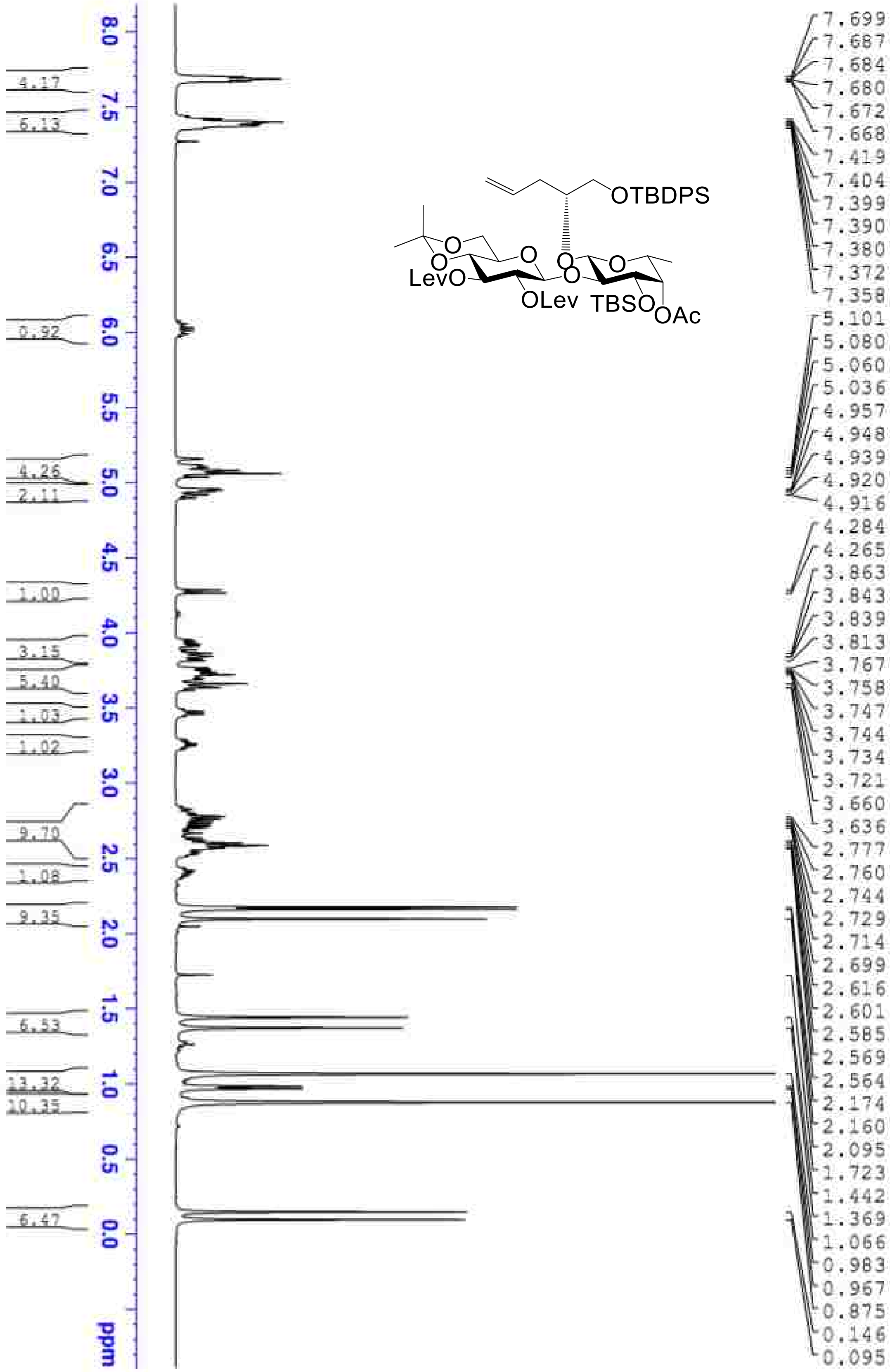
70.301
69.159
66.081
61.935
37.775
37.563
29.764
29.686
28.783
27.851
27.578
18.888
LevO
OLev
OCNHCCl3
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


LevO
O
O
O
OLev
OCNHCCl3
ppm
9
8
7
6
5
4
3
2
1
0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm



LevO
OLev
O
OCNHCCl3
ppm
100
90
80
70
60
50
40
30
20
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0


8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
4.17
6.13
0.92
4.26
2.11
1.00
3.15
5.40
1.03
1.02
9.70
1.08
9.35
6.53
13.32
10.35
6.47
OTBDPS
O
LevO
OLev
TBSO
OAc
7.699
7.687
7.684
7.680
7.672
7.668
7.419
7.404
7.399
7.390
7.380
7.372
7.358
5.101
5.080
5.060
5.036
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4.939
4.920
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3.767
3.758
3.747
3.744
3.734
3.721
3.660
3.636
2.777
2.760
2.744
2.729
2.714
2.699
2.616
2.601
2.585
2.569
2.564
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1.442
1.369
1.066
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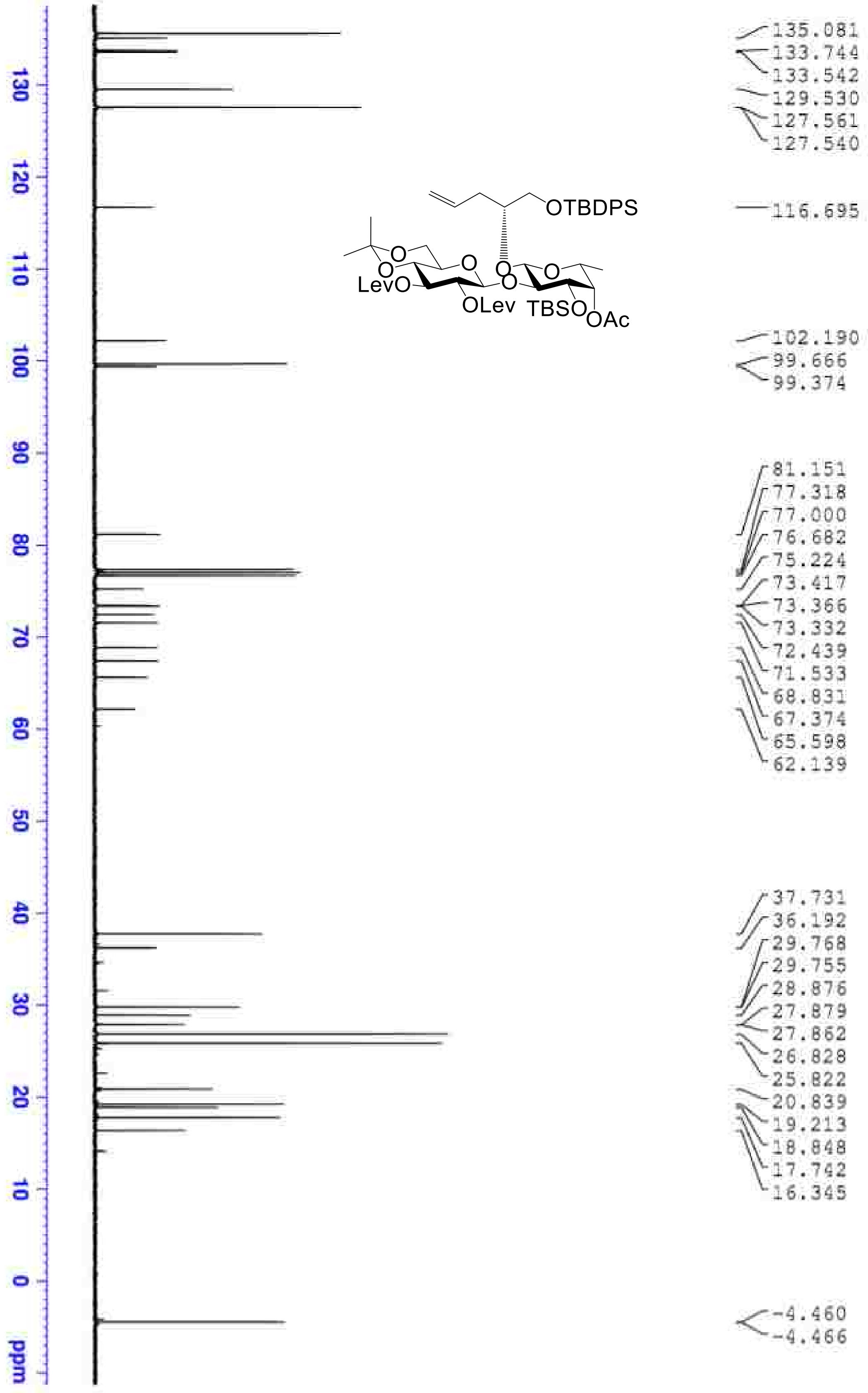
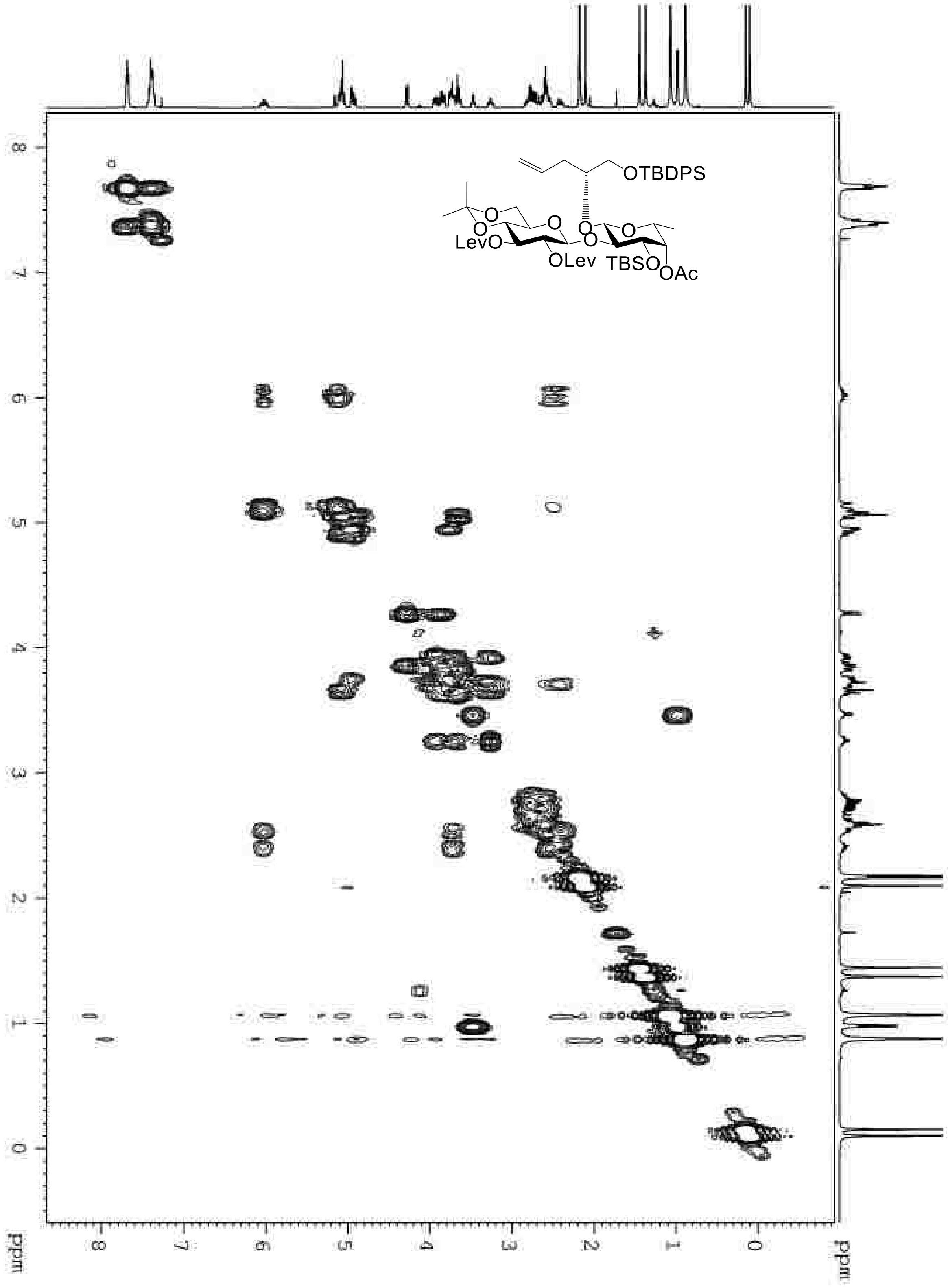
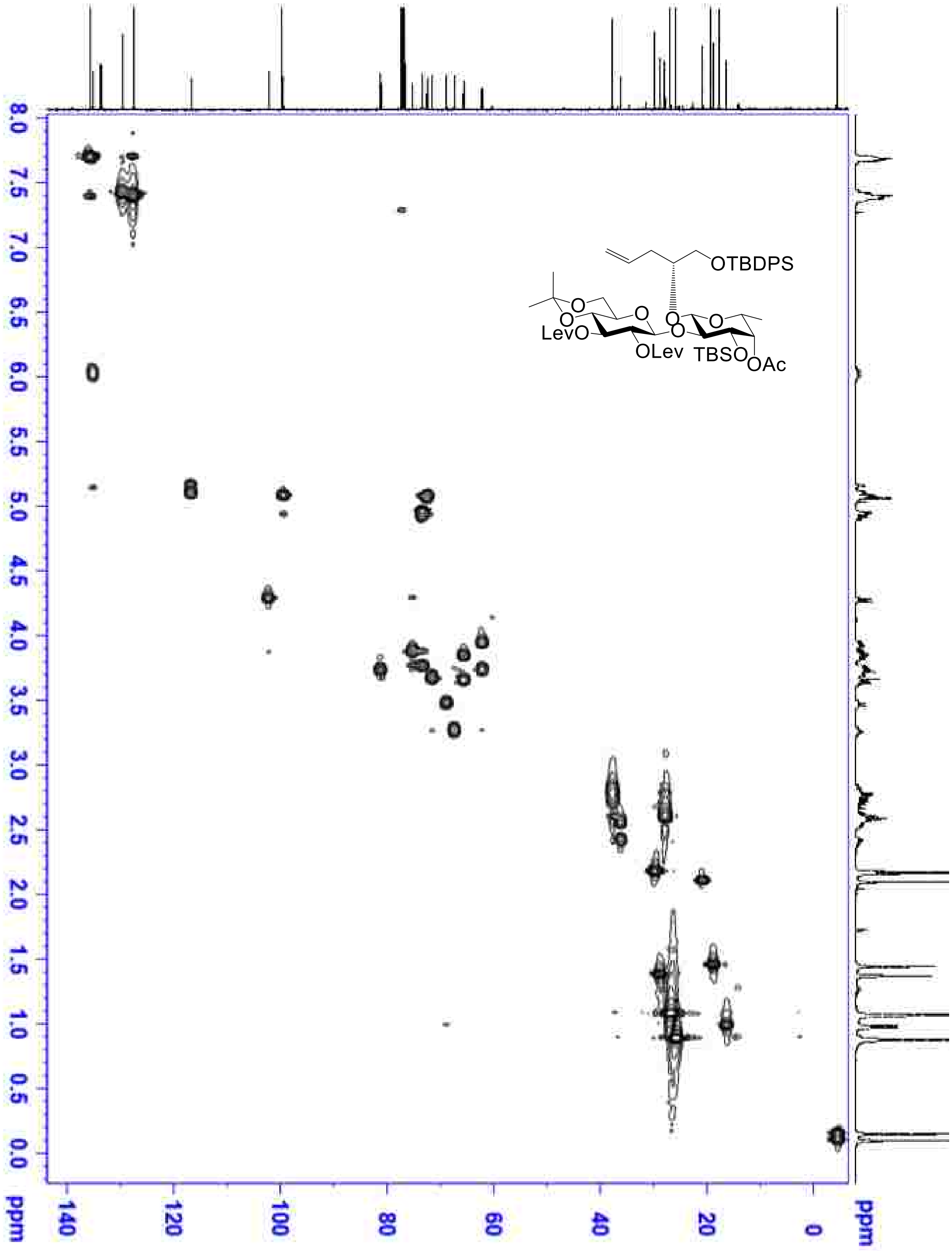
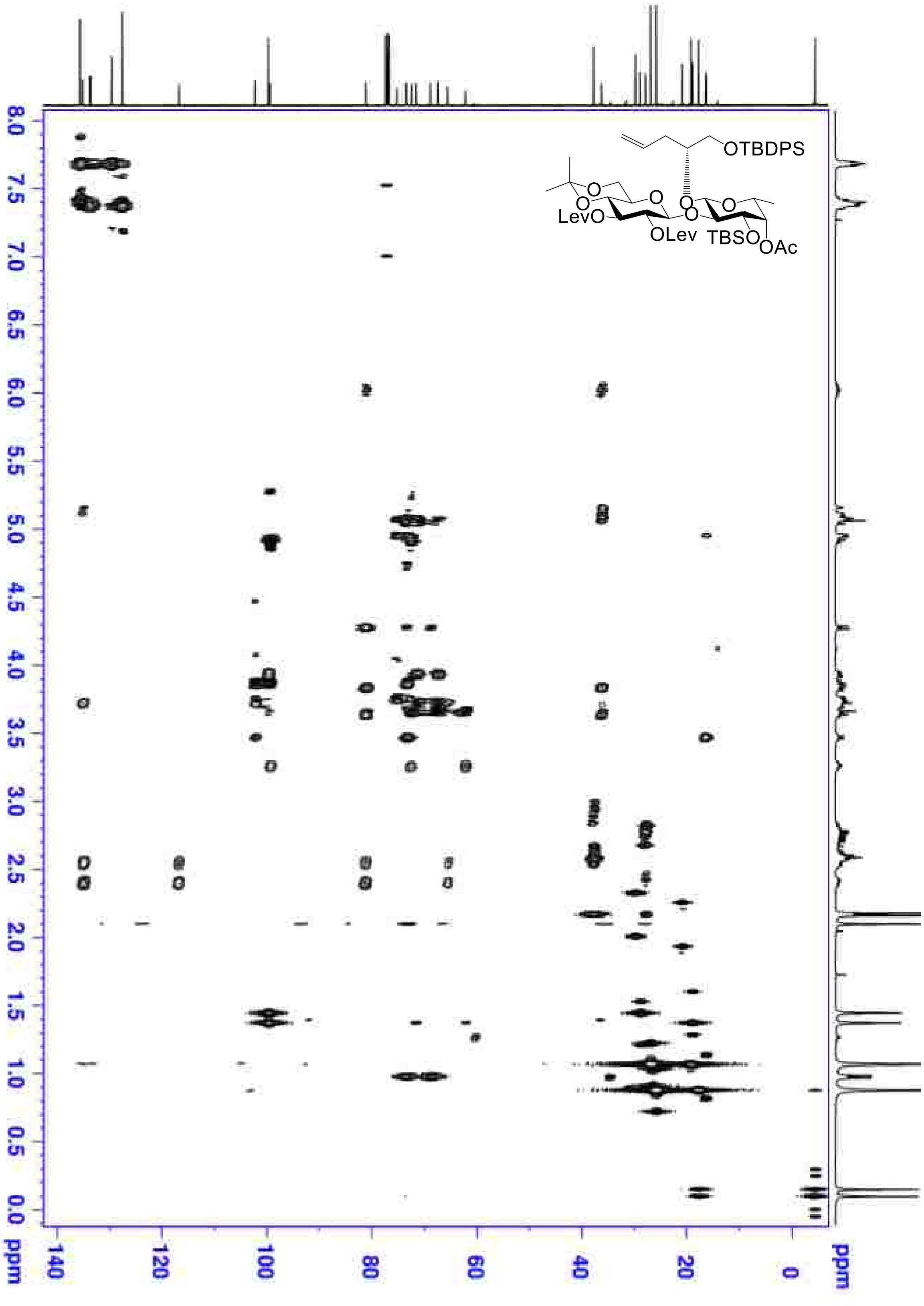
0.095


OTBDPS
O
O
LevO
O
OLev
O
O
O
TBSO
OAc
135.081
133.744
133.542
129.530
127.561
127.540
116.695
102.190
99.666
99.374
81.151
77.318
77.000
76.682
75.224
73.417
73.366
73.332
72.439
71.533
68.831
67.374
65.598
62.139
37.731
36.192
29.768
29.755
28.876
27.879
27.862
26.828
25.822
20.839
19.213
18.848
17.742
16.345
-4.460
-4.466
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


OTBDPS
O
O
O
O
O
LevO
OLev
TBSO
OAc
ppm
8
7
6
5
4
3
2
1
0
ppm


OTBDPS
O
LevO
OLev
TBSO
OAc
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
140
120
100
80
60
40
20
0
ppm


OTBDPS
LevO
OLev
TBSO
OAc
ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
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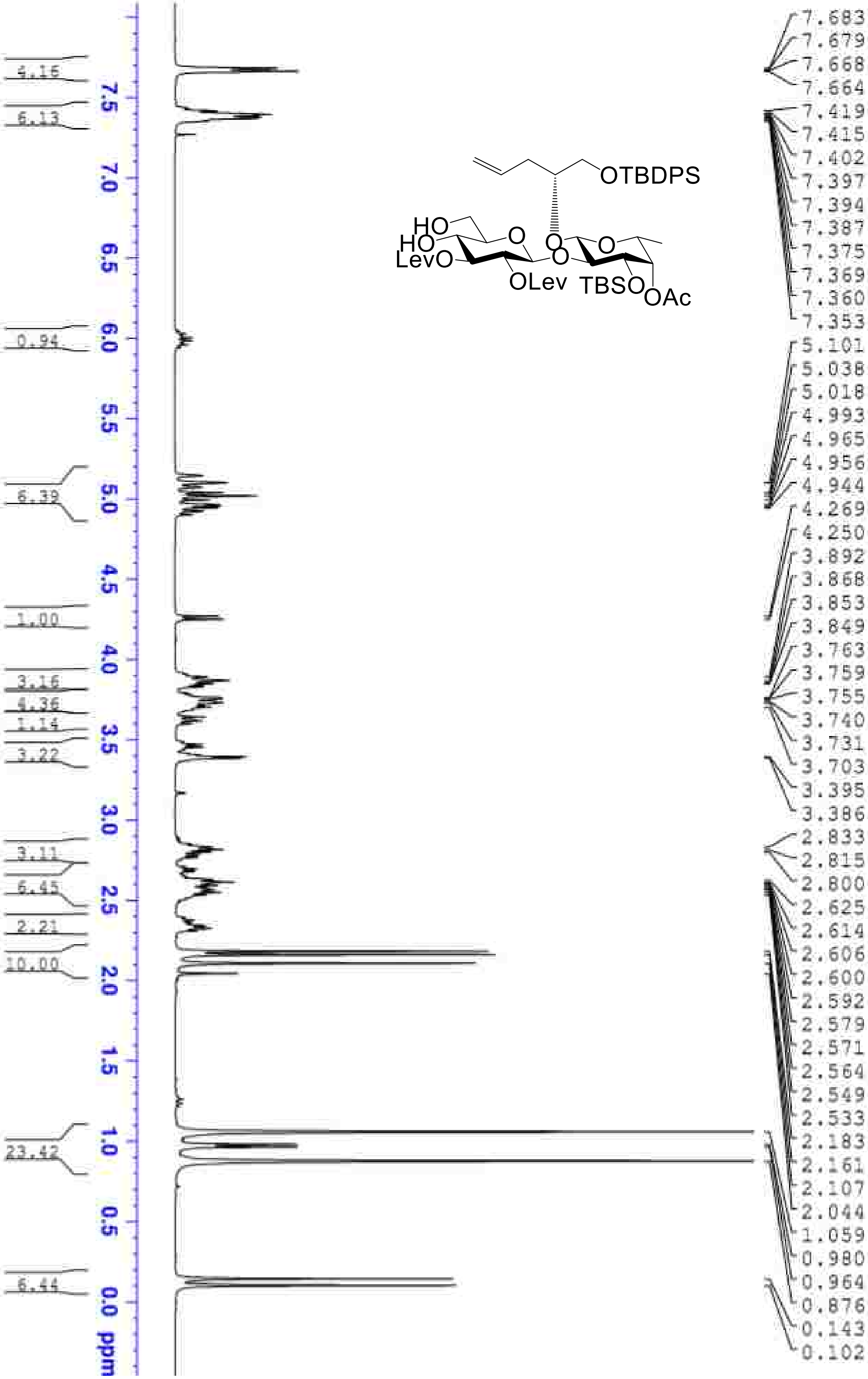
140
120
100
80
60
40
20
0



OTBDPS
HO
HO
LevO
O
O
O
O
OLev
TBSO
OAc
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0 ppm
4.16
6.13
0.94
6.39
1.00
3.16
4.36
1.14
3.22
3.11
6.45
2.21
10.00
23.42
6.44
7.683
7.679
7.668
7.664
7.419
7.415
7.402
7.397
7.394
7.387
7.375
7.369
7.360
7.353
5.101
5.038
5.018
4.993
4.965
4.956
4.944
4.269
4.250
3.892
3.868
3.853
3.849
3.763
3.759
3.755
3.740
3.731
3.703
3.395
3.386
2.833
2.815
2.800
2.625
2.614
2.606
2.600
2.592
2.579
2.571
2.564
2.549
2.533
2.183
2.161
2.107
2.044
1.059
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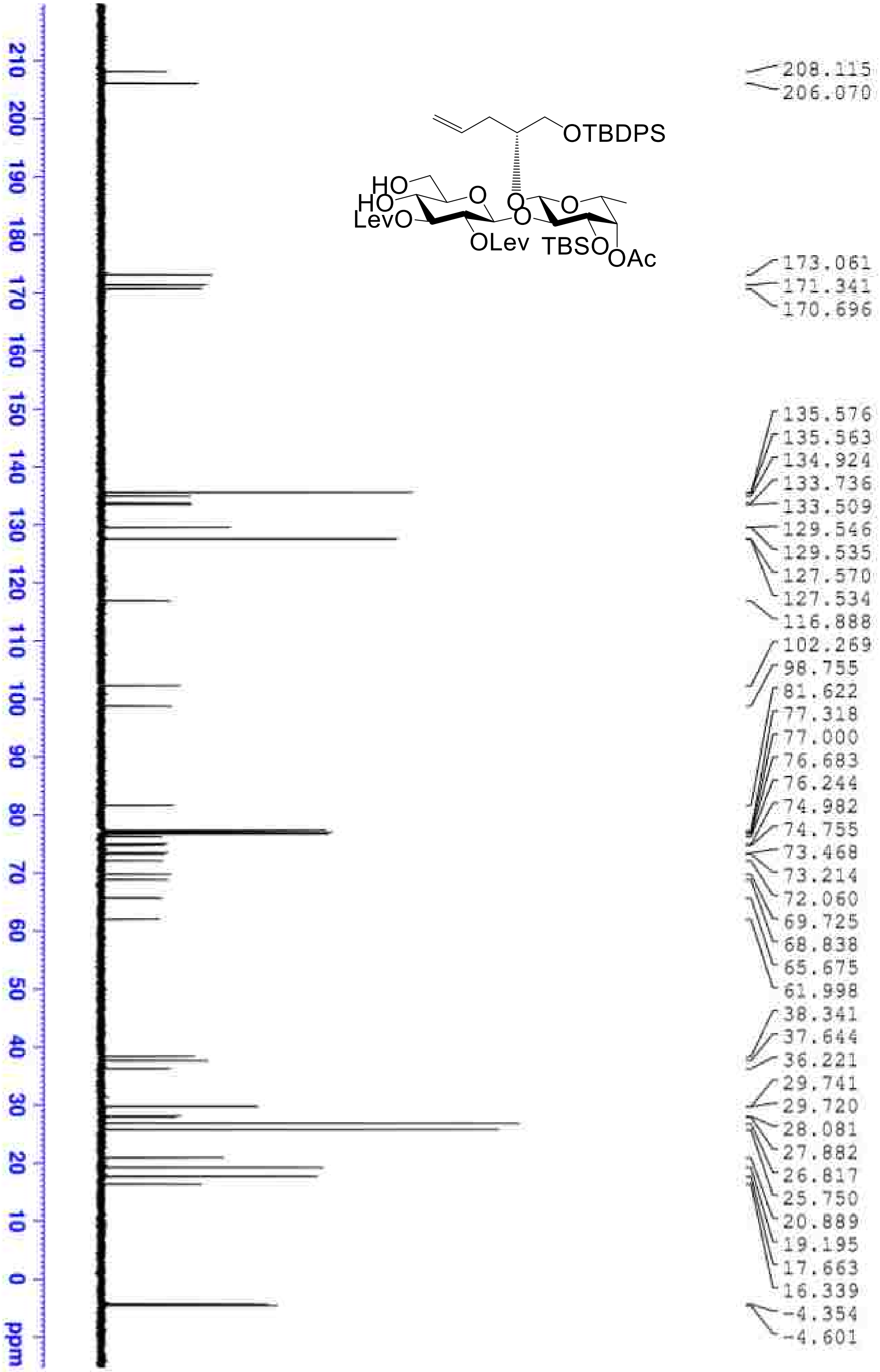
0.876
0.143
0.102


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm
OTBDPS
HO
HO
LevO
O
OLev
O
O
O
TBSO
OAc
208.115
206.070
173.061
171.341
170.696
135.576
135.563
134.924
133.736
133.509
129.546
129.535
127.570
127.534
116.888
102.269
98.755
81.622
77.318
77.000
76.683
76.244
74.982
74.755
73.468
73.214
72.060
69.725
68.838
65.675
61.998
38.341
37.644
36.221
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27.882
26.817
25.750
20.889
19.195
17.663
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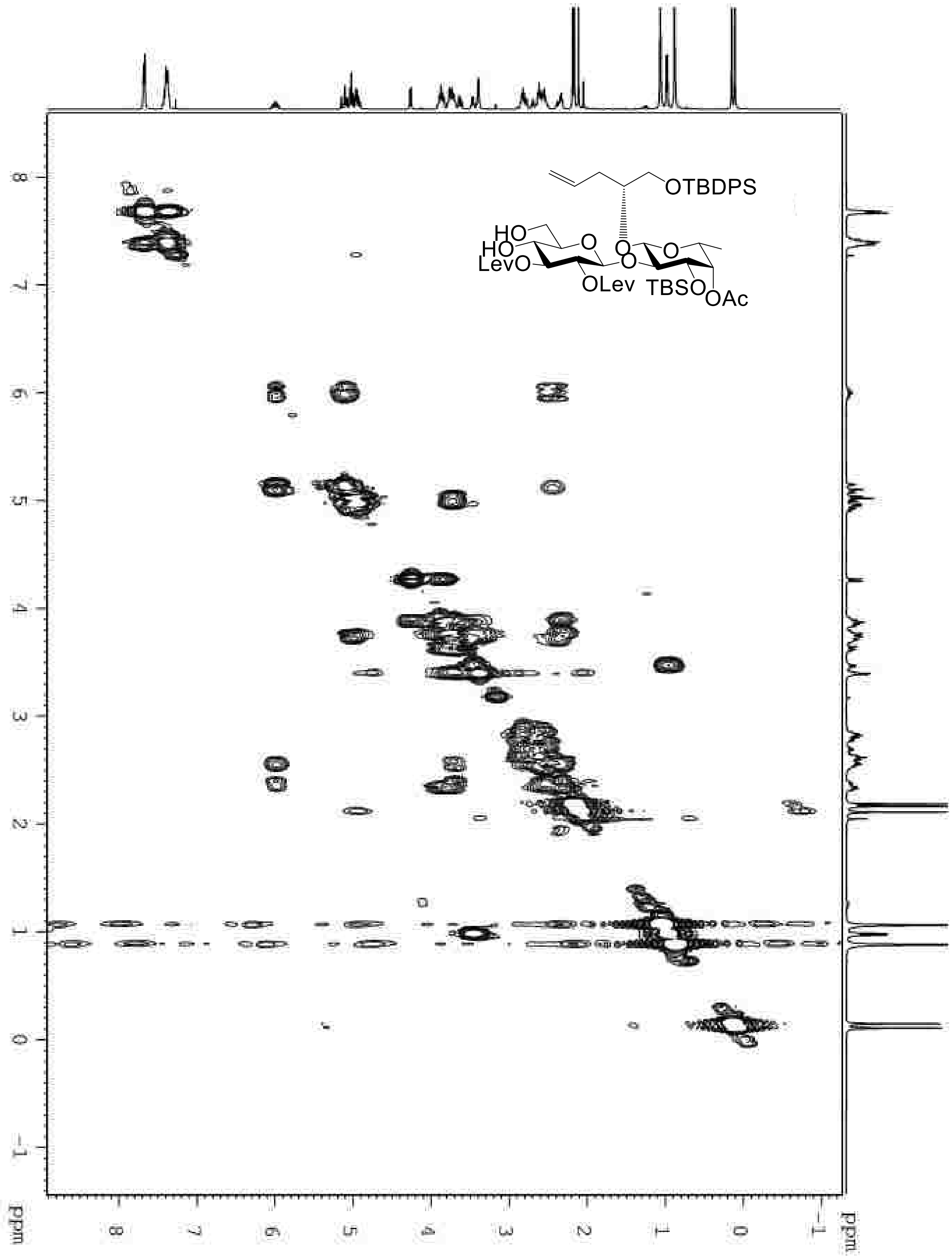
-4.601


OTBDPS
HO
HO
LevO
O
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O
O
OLev
TBSO
OAc
ppm
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4
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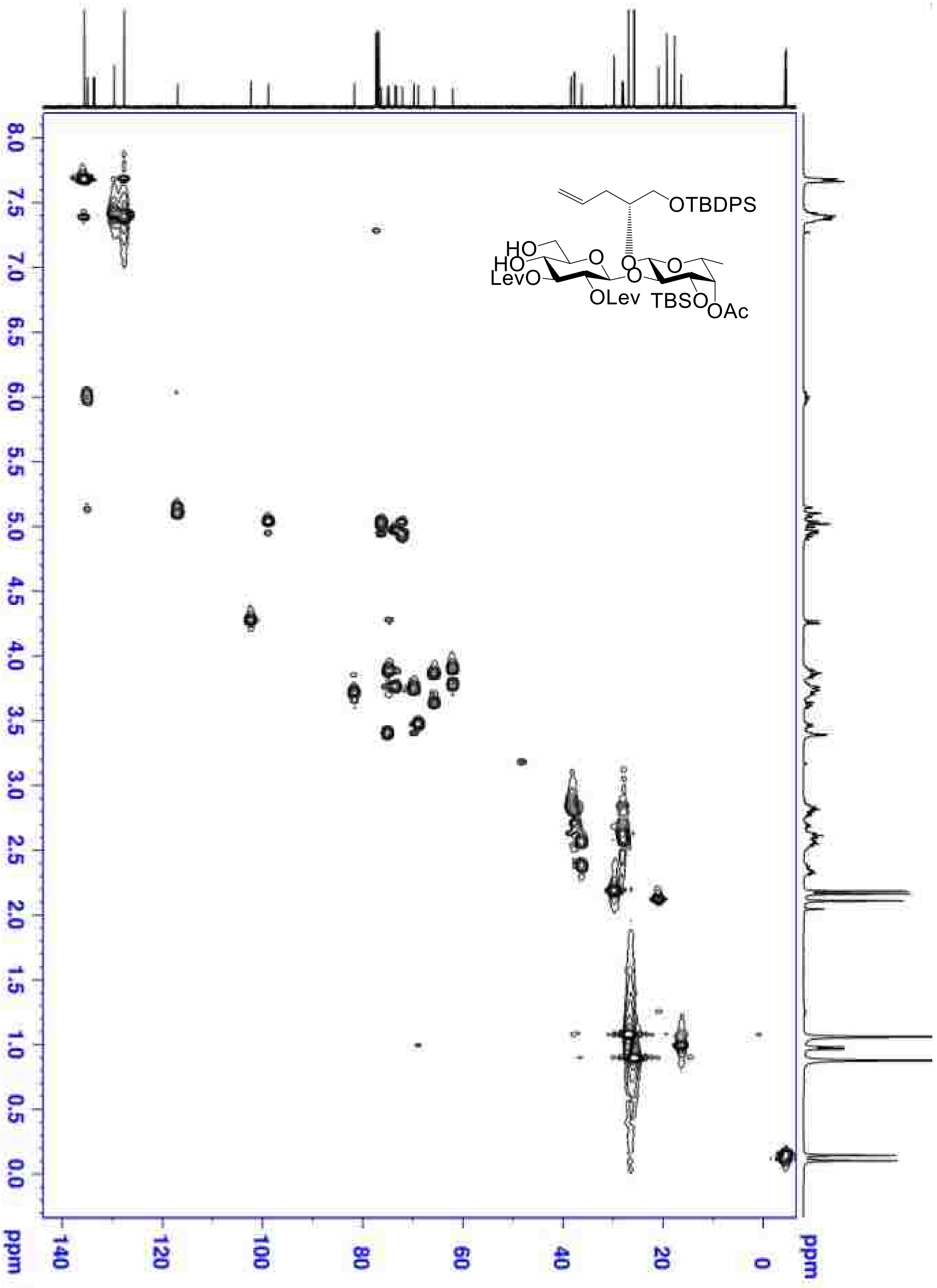
−1
ppm



OTBDPS
HO
HO
LevO
O
O
O
O
OLev
TBSO
OAc
ppm
8.0
7.5
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6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
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ppm
140
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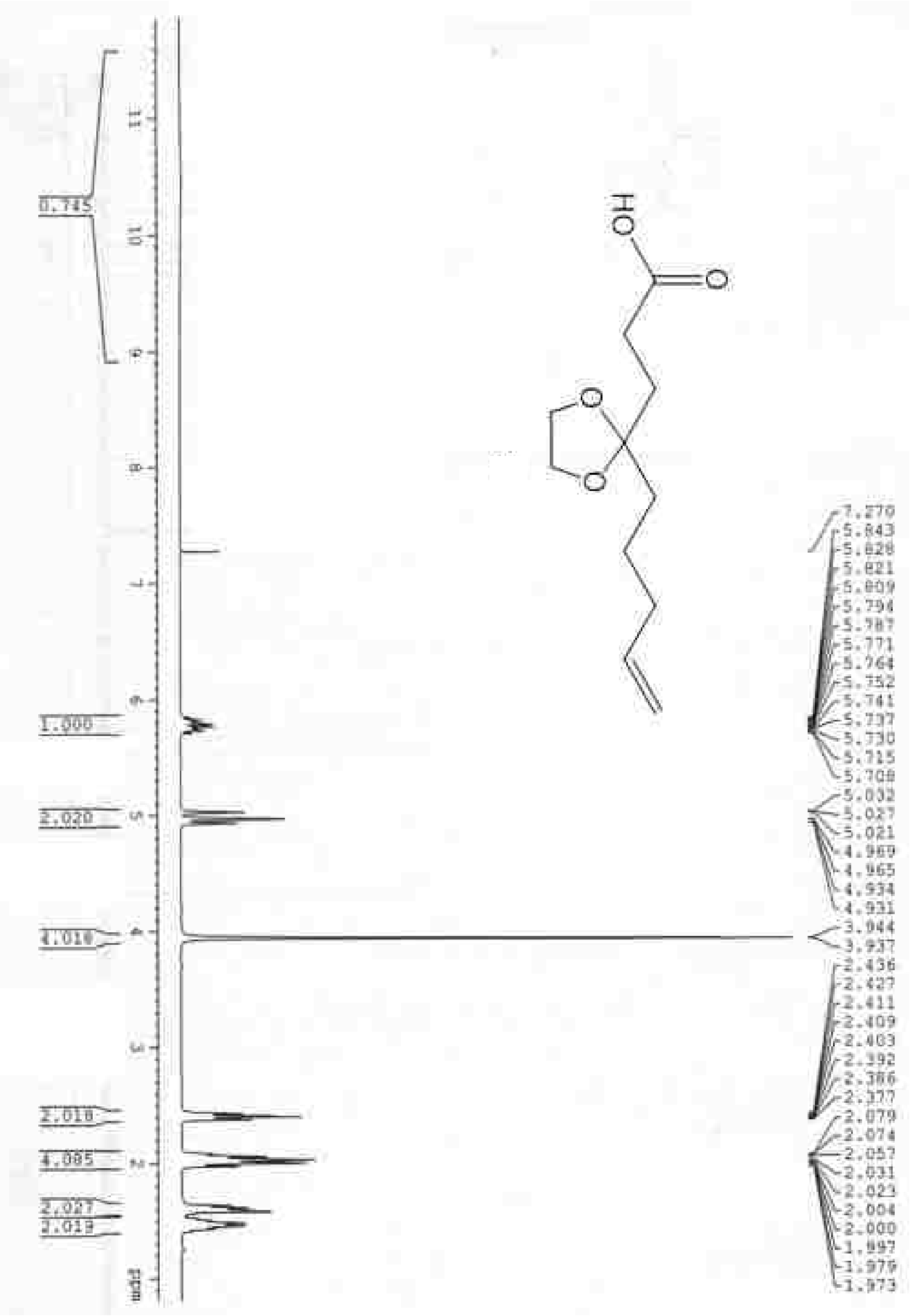
80
60
40
20
0



HO
O
O
O
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2.018
4.085
2.027
2.019
11
10
9
8
7
6
5
4
3
2
ppm
7.270
5.843
5.828
5.821
5.809
5.794
5.787
5.771
5.764
5.752
5.741
5.737
5.730
5.715
5.708
5.032
5.027
5.021
4.969
4.965
4.934
4.931
3.944
3.937
2.436
2.427
2.411
2.409
2.403
2.392
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2.074
2.057
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2.023
2.004
2.000
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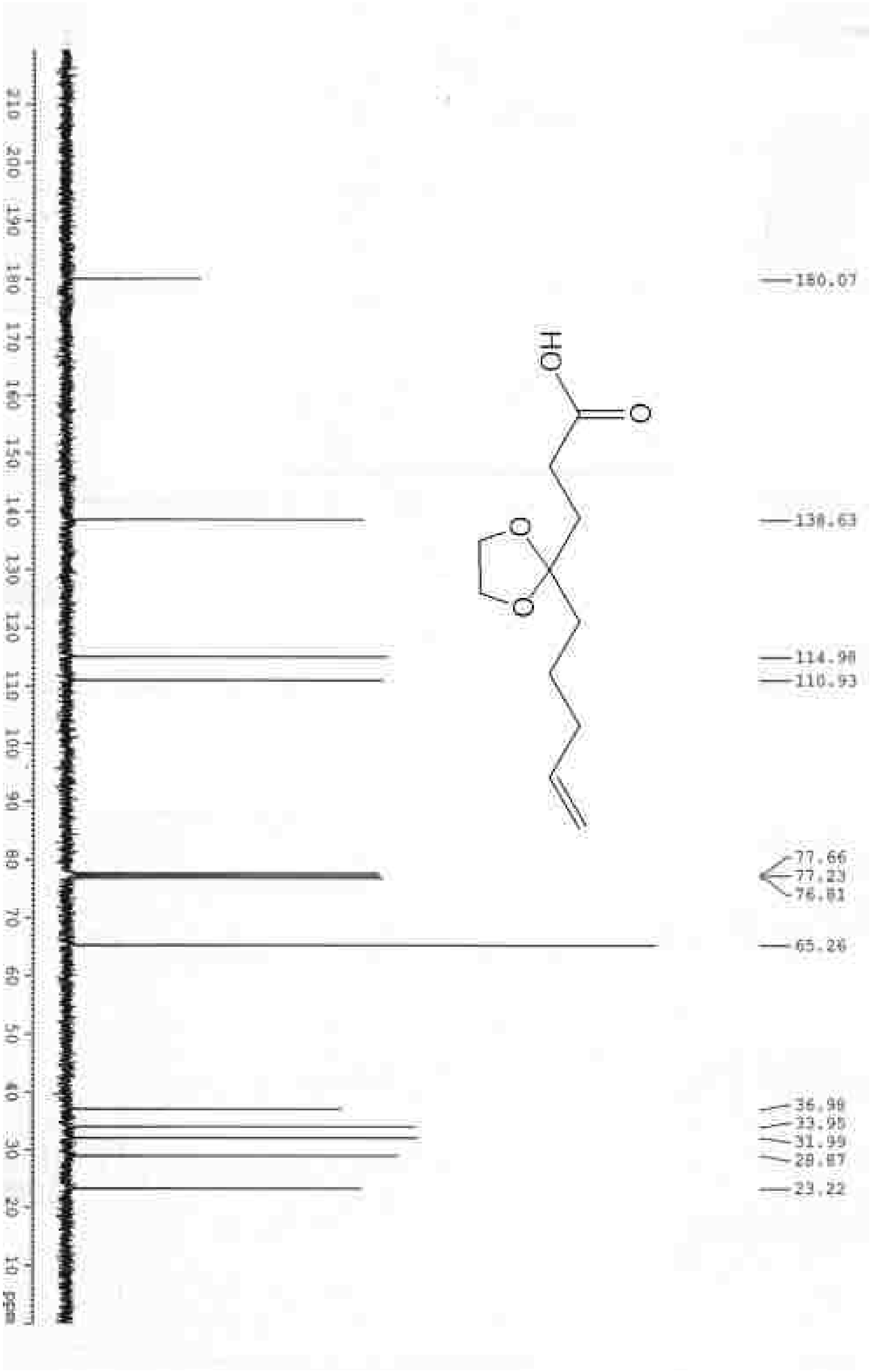
1.979
1.973



210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10 ppm
180.07
138.63
114.98
110.93
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76.81
65.26
36.98
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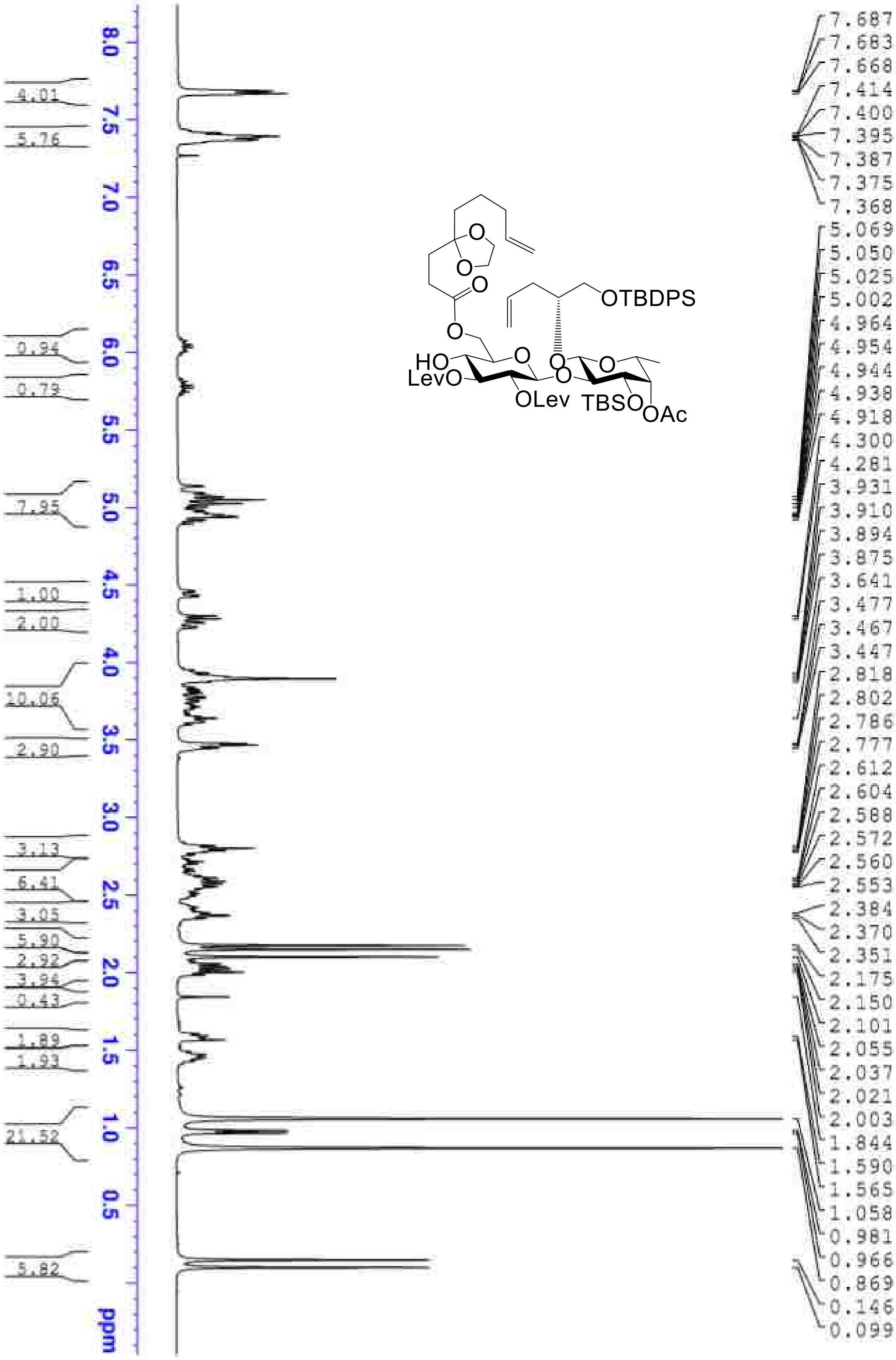
31.99
28.87
23.22
HO
O
O
O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3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
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0.94
0.79
7.95
1.00
2.00
10.06
2.90
3.13
6.41
3.05
5.90
2.92
3.94
0.43
1.89
1.93
21.52
5.82
O
O
O
O
OTBDPS
HO
O
LevO
O
O
O
OLev
TBSO
OAc
7.687
7.683
7.668
7.414
7.400
7.395
7.387
7.375
7.368
5.069
5.050
5.025
5.002
4.964
4.954
4.944
4.938
4.918
4.300
4.281
3.931
3.910
3.894
3.875
3.641
3.477
3.467
3.447
2.818
2.802
2.786
2.777
2.612
2.604
2.588
2.572
2.560
2.553
2.384
2.370
2.351
2.175
2.150
2.101
2.055
2.037
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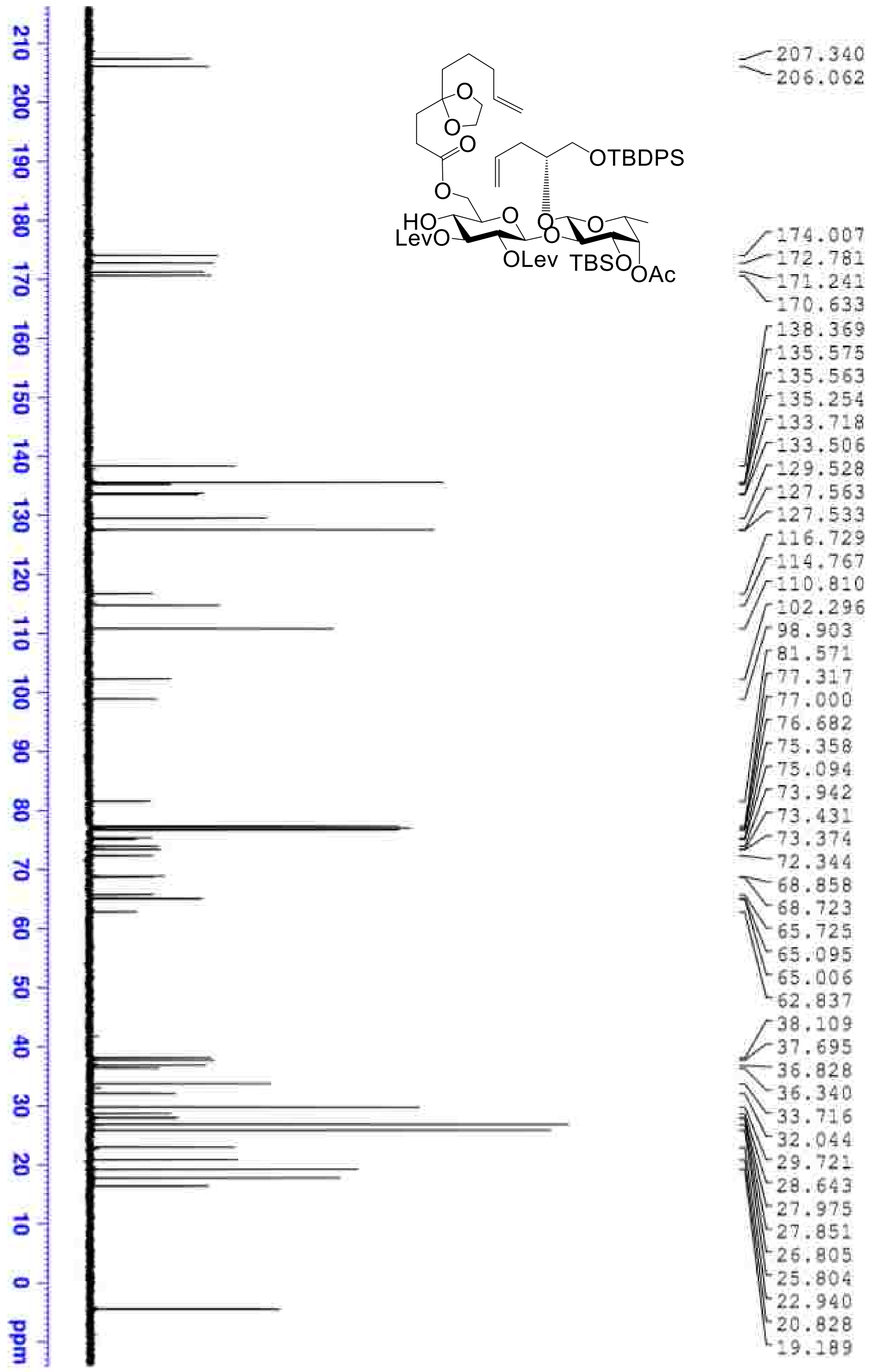
0.099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180
170
160
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140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm
O
O
O
OTBDPS
O
HO
O
O
O
LevO
O
OLev
TBSO
OAc
207.340
206.062
174.007
172.781
171.241
170.633
138.369
135.575
135.563
135.254
133.718
133.506
129.528
127.563
127.533
116.729
114.767
110.810
102.296
98.903
81.571
77.317
77.000
76.682
75.358
75.094
73.942
73.431
73.374
72.344
68.858
68.723
65.725
65.095
65.006
62.837
38.109
37.695
36.828
36.340
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28.643
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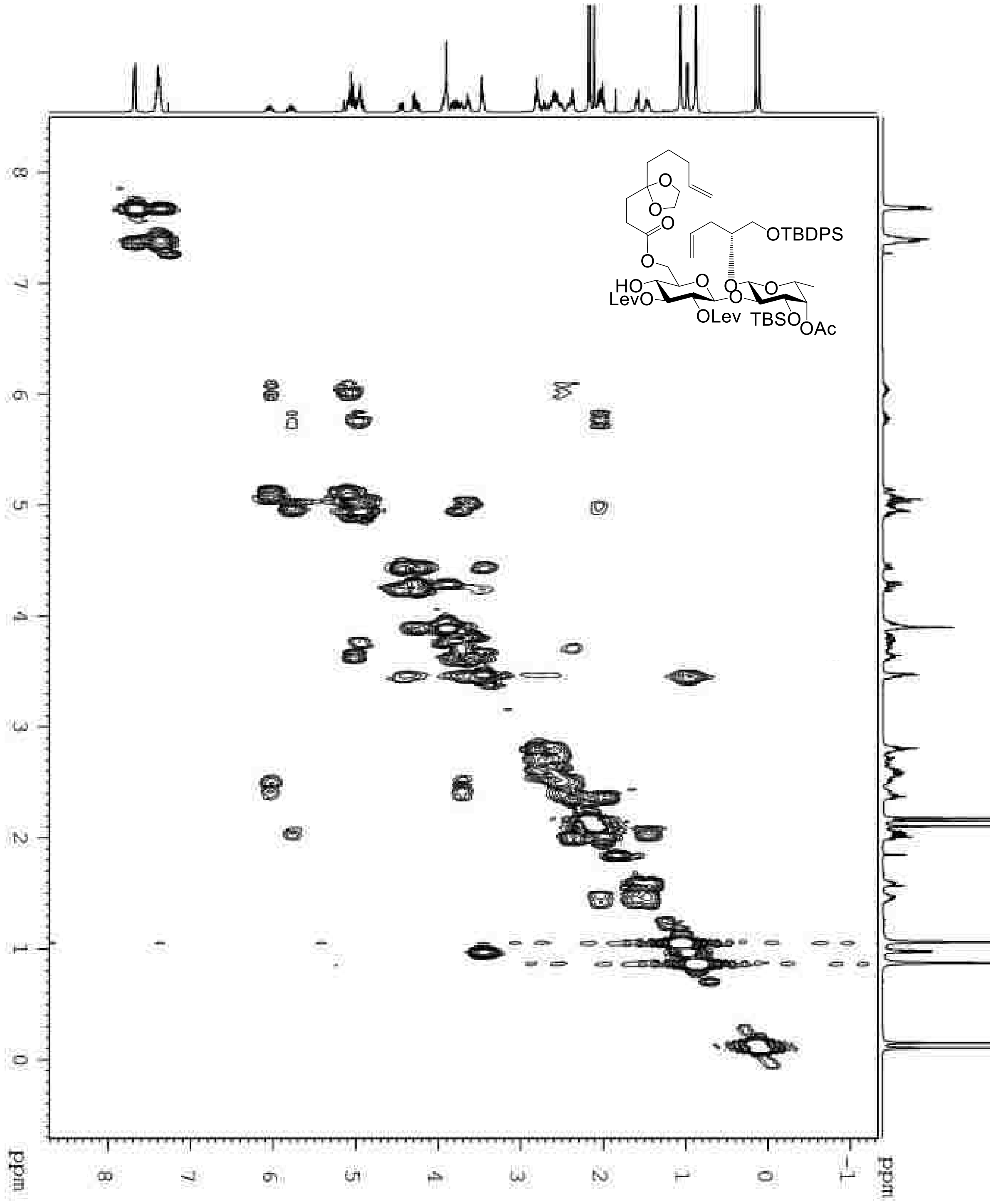
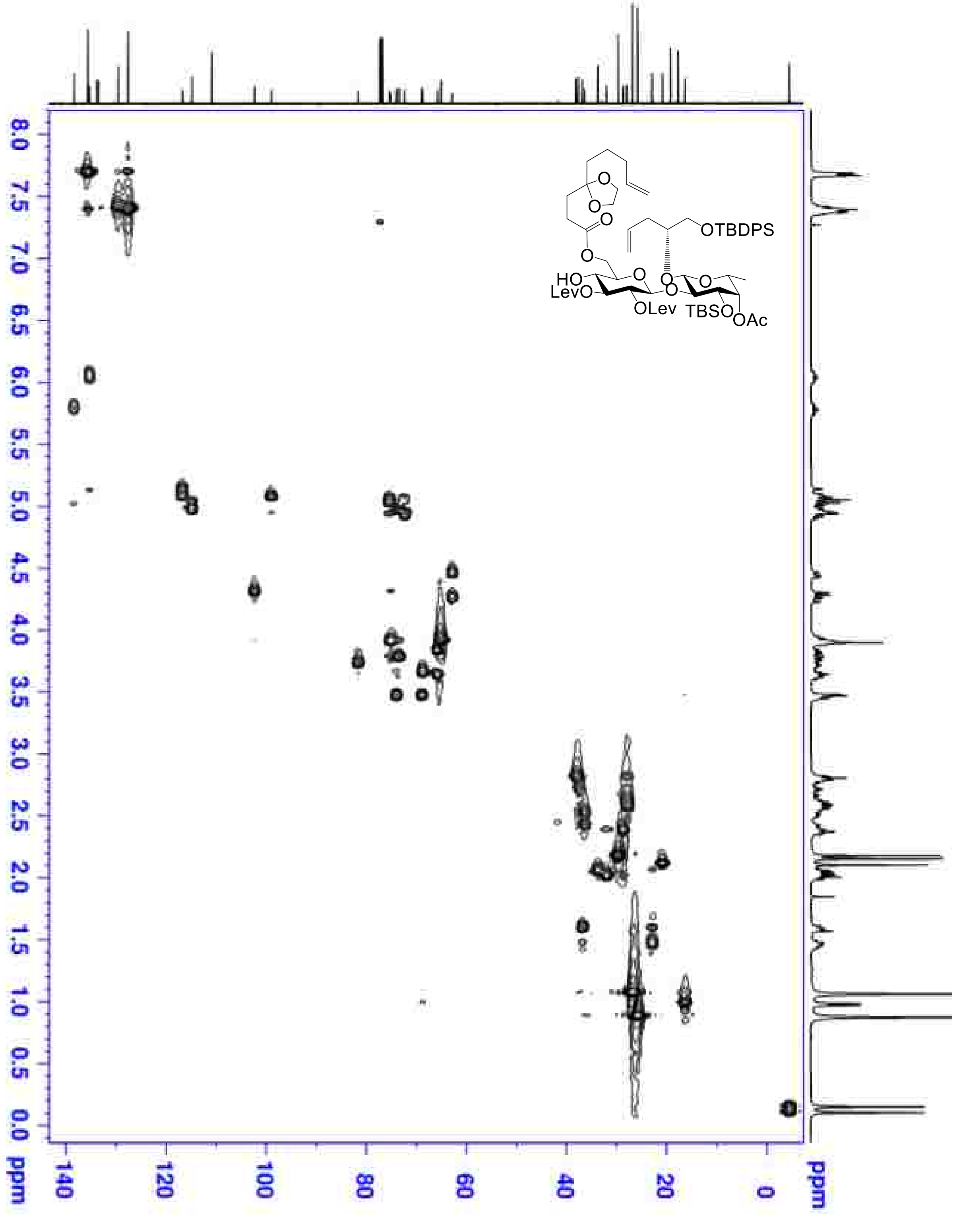
25.804
22.940
20.828
19.189



OTBDPS
HO
LevO
OLev
TBSO
OAc
ppm
8
7
6
5
4
3
2
1
0
−1


O
O
O
OTBDPS
O
HO
LevO
O
O
O
OLev
TBSO
OAc
8.0
7.5
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6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
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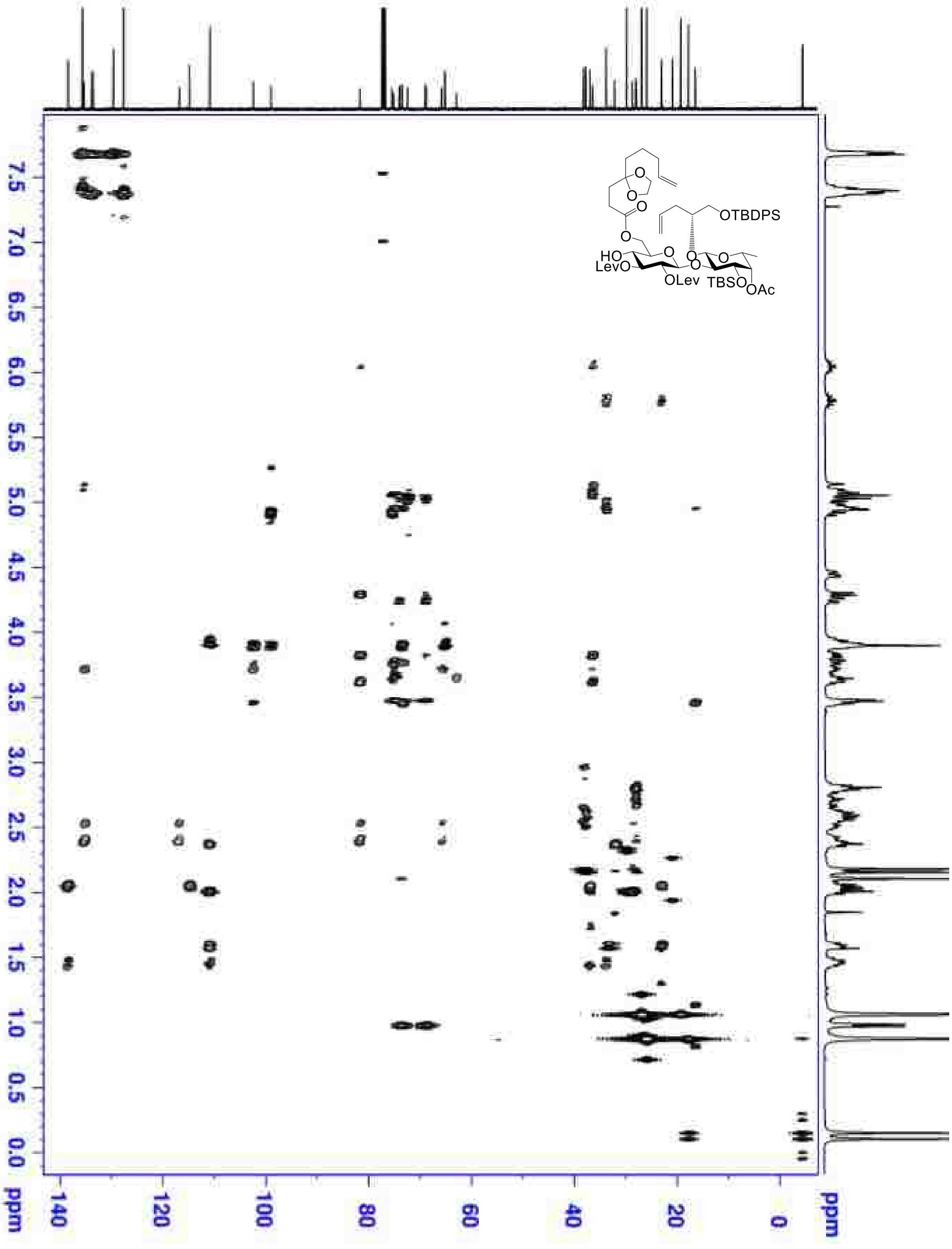
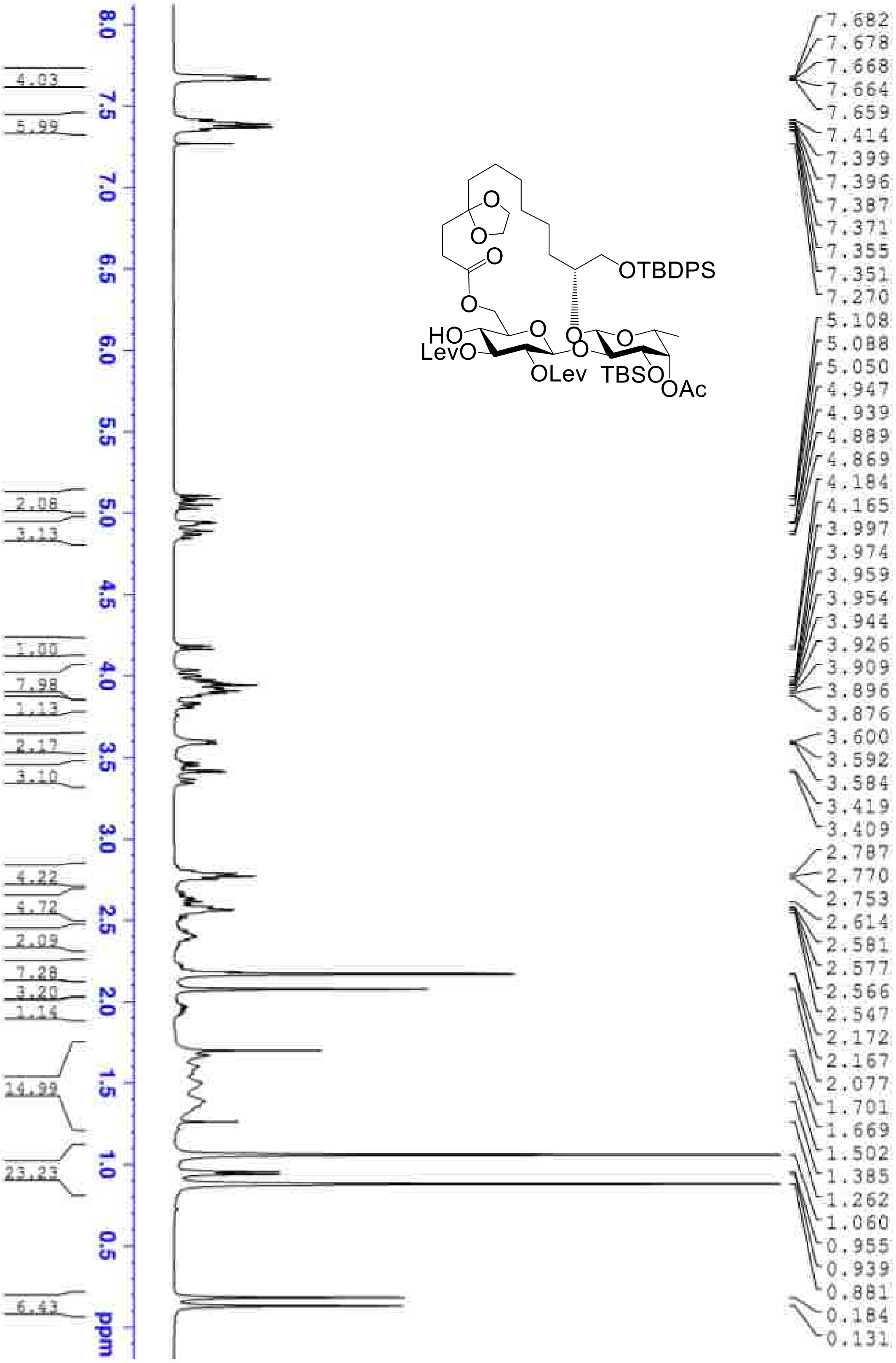
120
100
80
60
40
20
0
ppm



ppm
140
120
100
80
60
40
20
0
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
OTBDPS
HO
LevO
OLev
TBSO
OAc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5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
4.03
5.99
2.08
3.13
1.00
7.98
1.13
2.17
3.10
4.22
4.72
2.09
7.28
3.20
1.14
14.99
23.23
6.43
OTBDPS
HO
LevO
OLev
TBSO
OAc
O
7.682
7.678
7.668
7.664
7.659
7.414
7.399
7.396
7.387
7.371
7.355
7.351
7.270
5.108
5.088
5.050
4.947
4.939
4.889
4.869
4.184
4.165
3.997
3.974
3.959
3.954
3.944
3.926
3.909
3.896
3.876
3.600
3.592
3.584
3.419
3.409
2.787
2.770
2.753
2.614
2.581
2.577
2.566
2.547
2.172
2.167
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1.502
1.385
1.262
1.060
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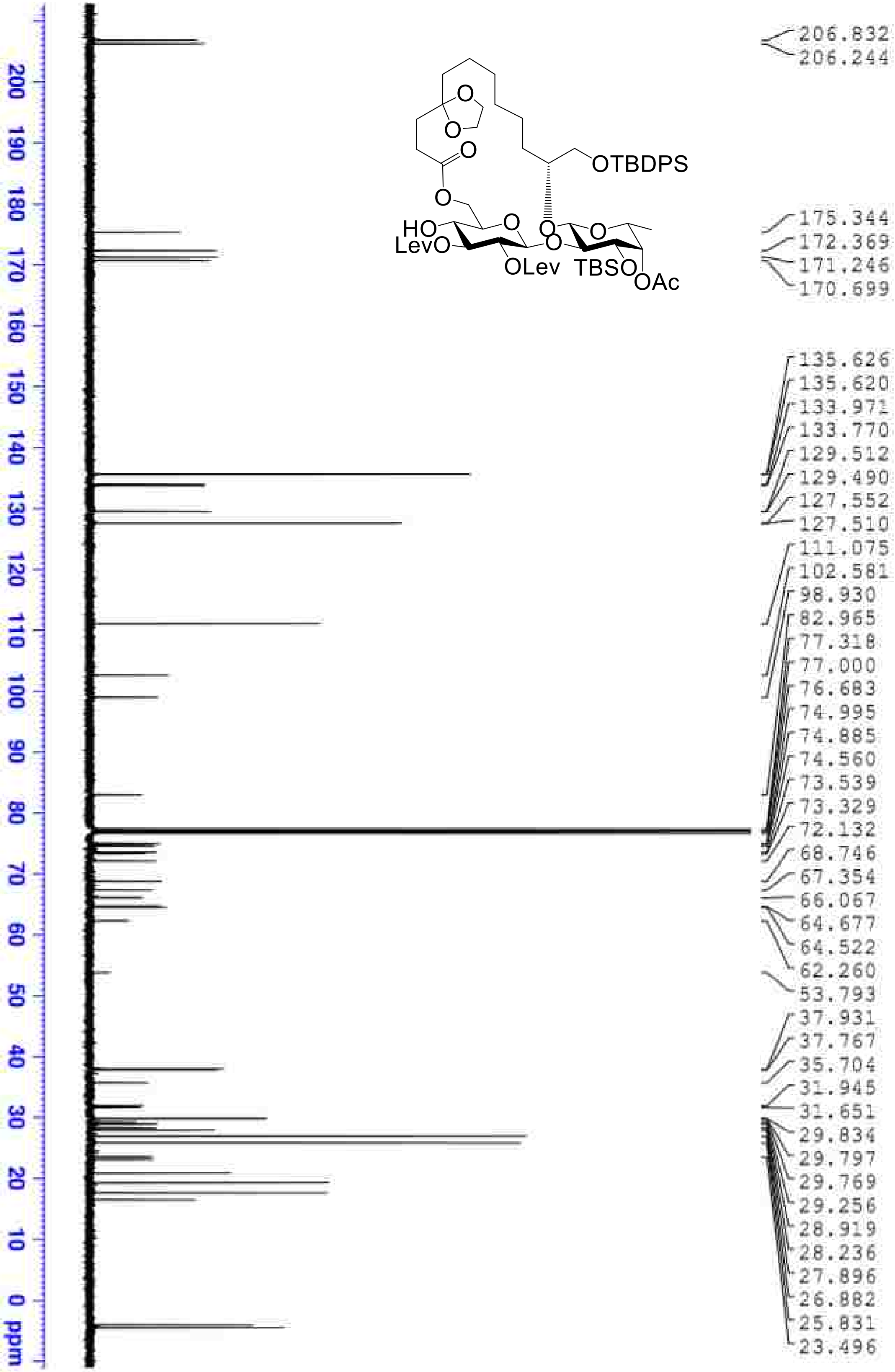
0.939
0.881
0.184
0.131


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm
OTBDPS
O
O
O
O
HO
LevO
OLev
TBSO
OAc
206.832
206.244
175.344
172.369
171.246
170.699
135.626
135.620
133.971
133.770
129.512
129.490
127.552
127.510
111.075
102.581
98.930
82.965
77.318
77.000
76.683
74.995
74.885
74.560
73.539
73.329
72.132
68.746
67.354
66.067
64.677
64.522
62.260
53.793
37.931
37.767
35.704
31.945
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29.769
29.256
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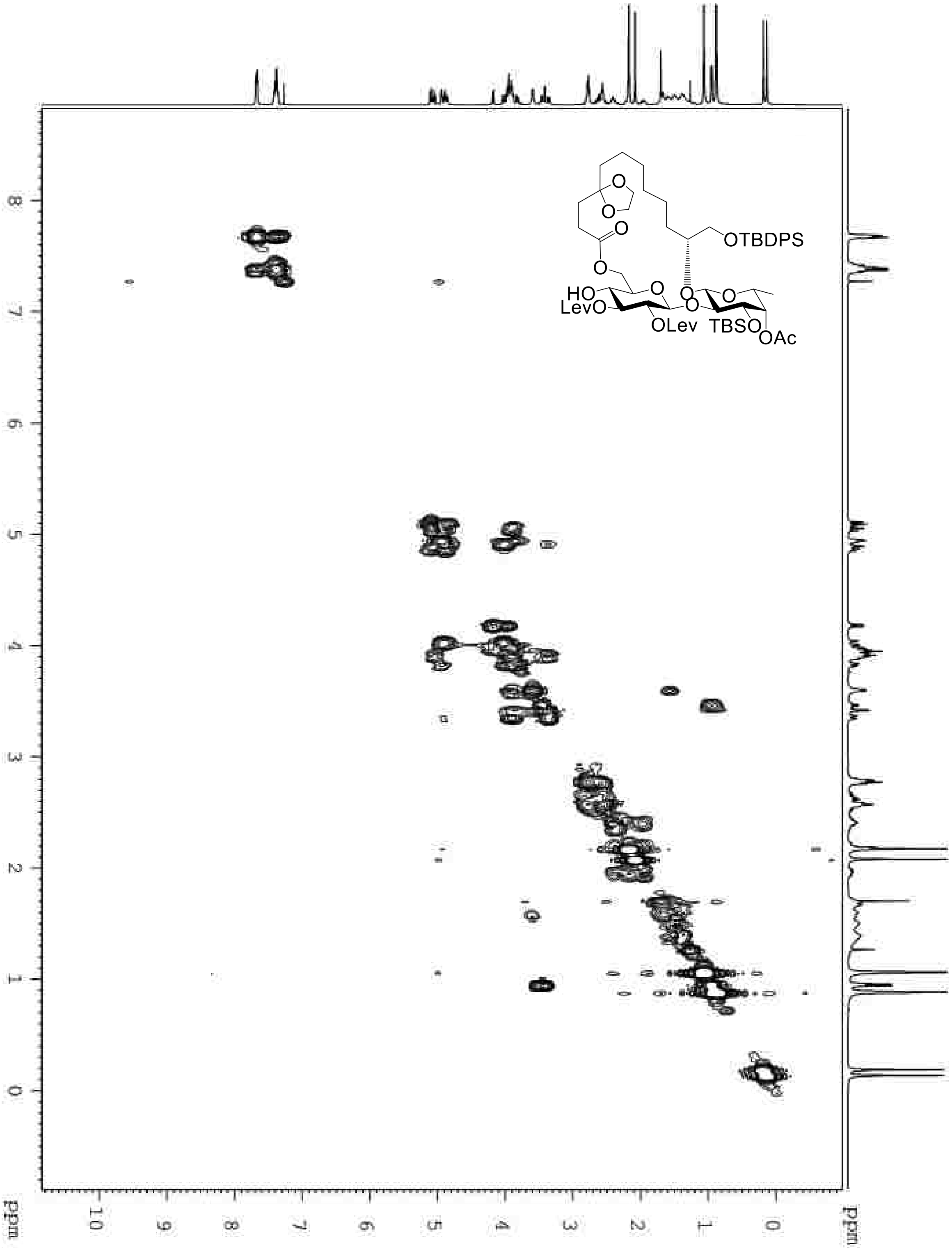
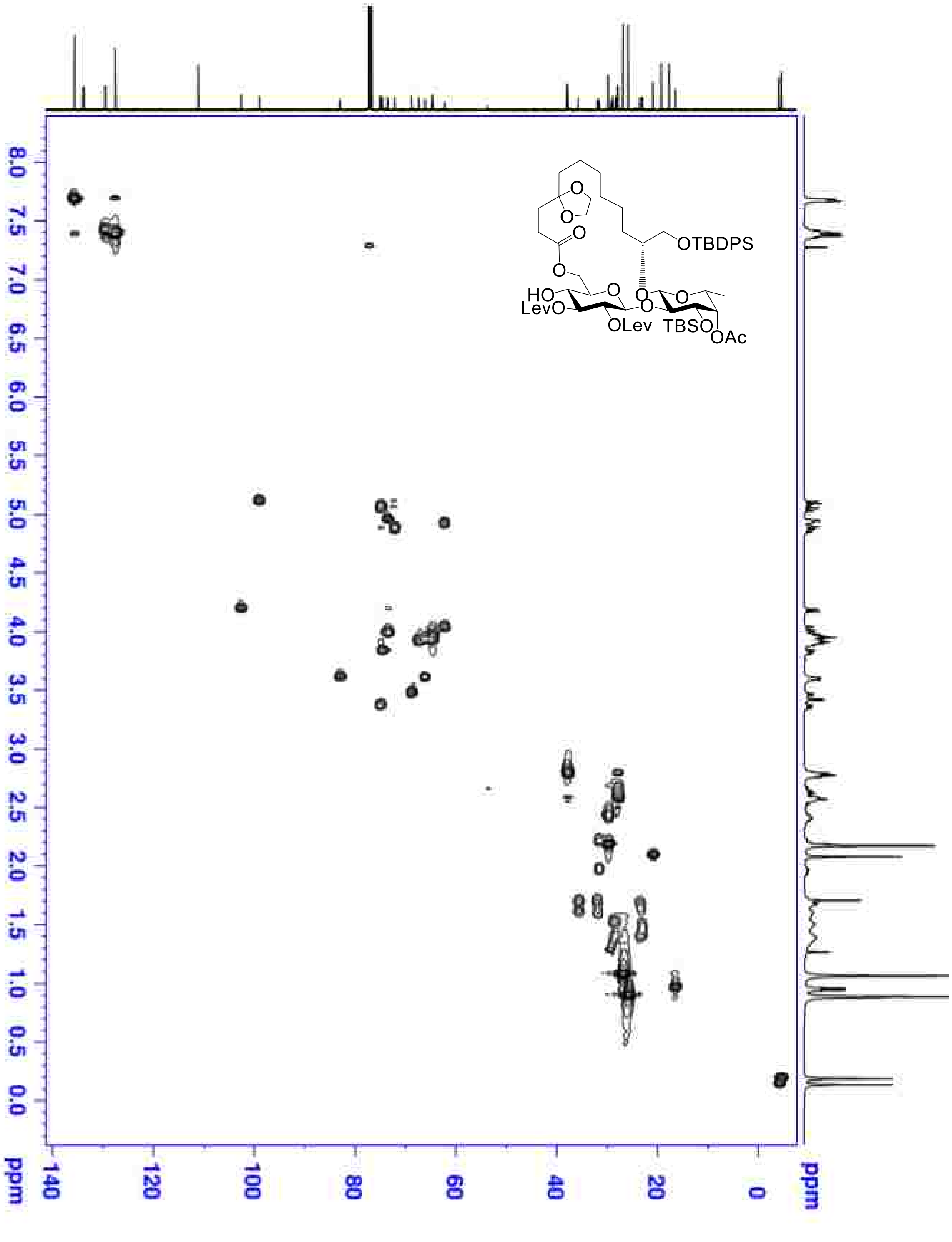
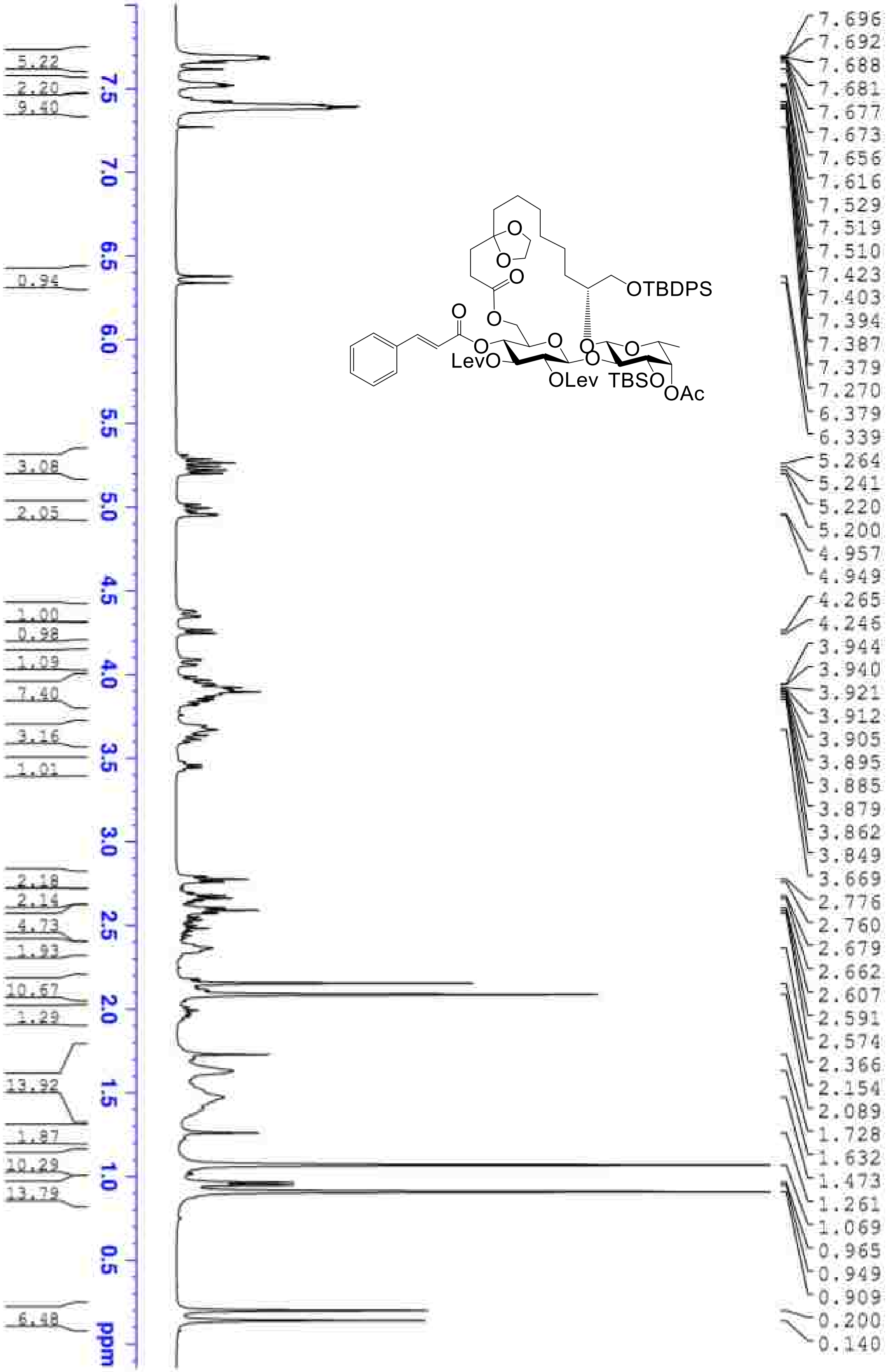
25.831
23.496


O
O
O
OTBDPS
O
HO
LevO
O
OLev
O
O
TBSO
O
OAc
ppm
10
9
8
7
6
5
4
3
2
1
0
ppm
8
7
6
5
4
3
2
1
0



OTBDPS
HO
LevO
OLev
TBSO
OAc
ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
140
120
100
80
60
40
20
0
ppm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1.00
0.98
1.09
7.40
3.16
1.01
2.18
2.14
4.73
1.93
10.67
1.29
13.92
1.87
10.29
13.79
6.48
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
O
O
O
O
OTBDPS
O
O
O
O
O
LevO
OLev
TBSO
OAc
7.696
7.692
7.688
7.681
7.677
7.673
7.656
7.616
7.529
7.519
7.510
7.423
7.403
7.394
7.387
7.379
7.270
6.379
6.339
5.264
5.241
5.220
5.200
4.957
4.949
4.265
4.246
3.944
3.940
3.921
3.912
3.905
3.895
3.885
3.879
3.862
3.849
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2.662
2.607
2.591
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1.261
1.069
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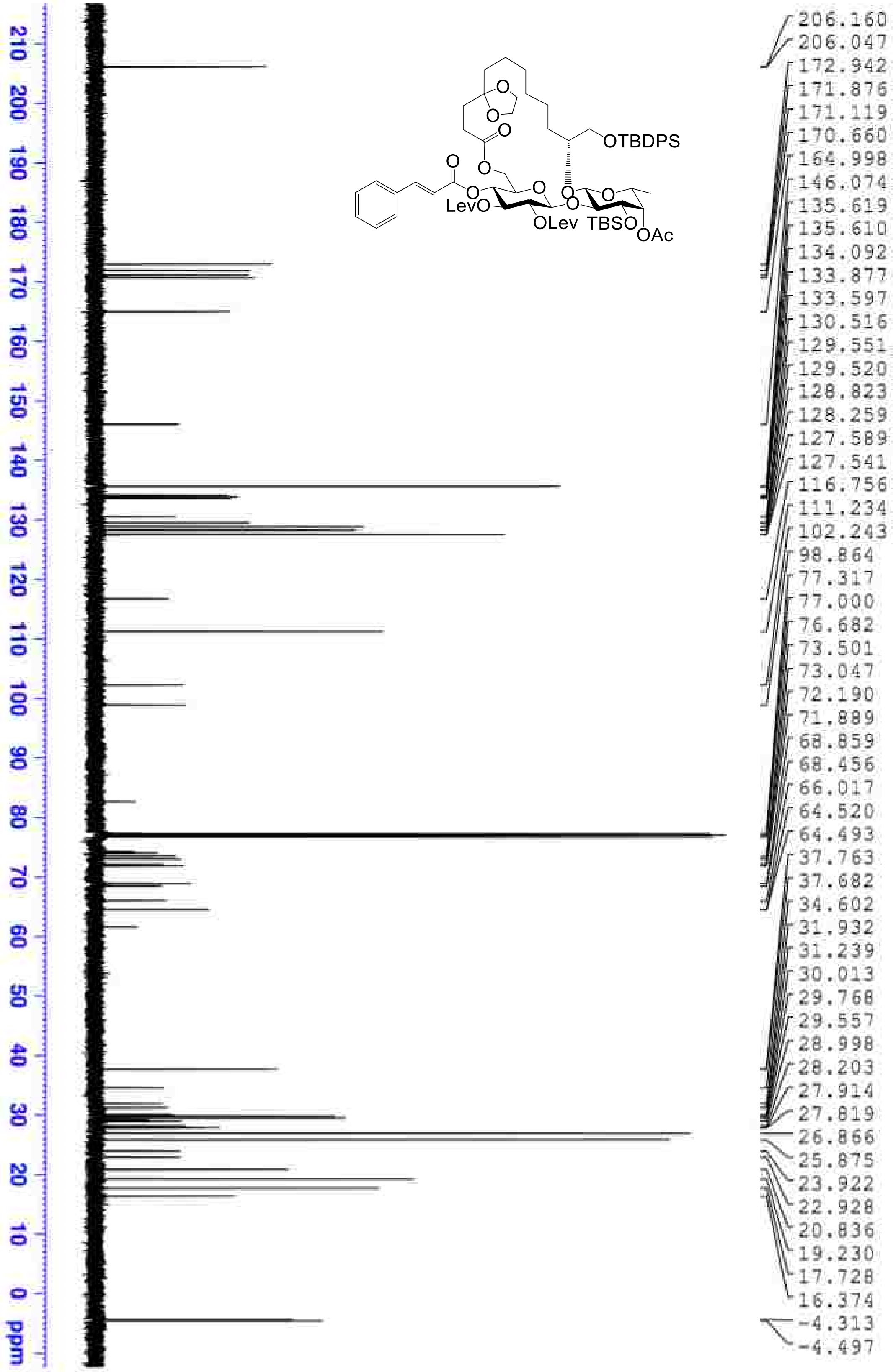
0.949
0.909
0.200
0.140


OTBDPS
LevO
OLev
TBSO
OAc
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm
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171.876
171.119
170.660
164.998
146.074
135.619
135.610
134.092
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133.597
130.516
129.551
129.520
128.823
128.259
127.589
127.541
116.756
111.234
102.243
98.864
77.317
77.000
76.682
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73.047
72.190
71.889
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66.017
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37.682
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31.932
31.239
30.013
29.768
29.557
28.998
28.203
27.914
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17.728
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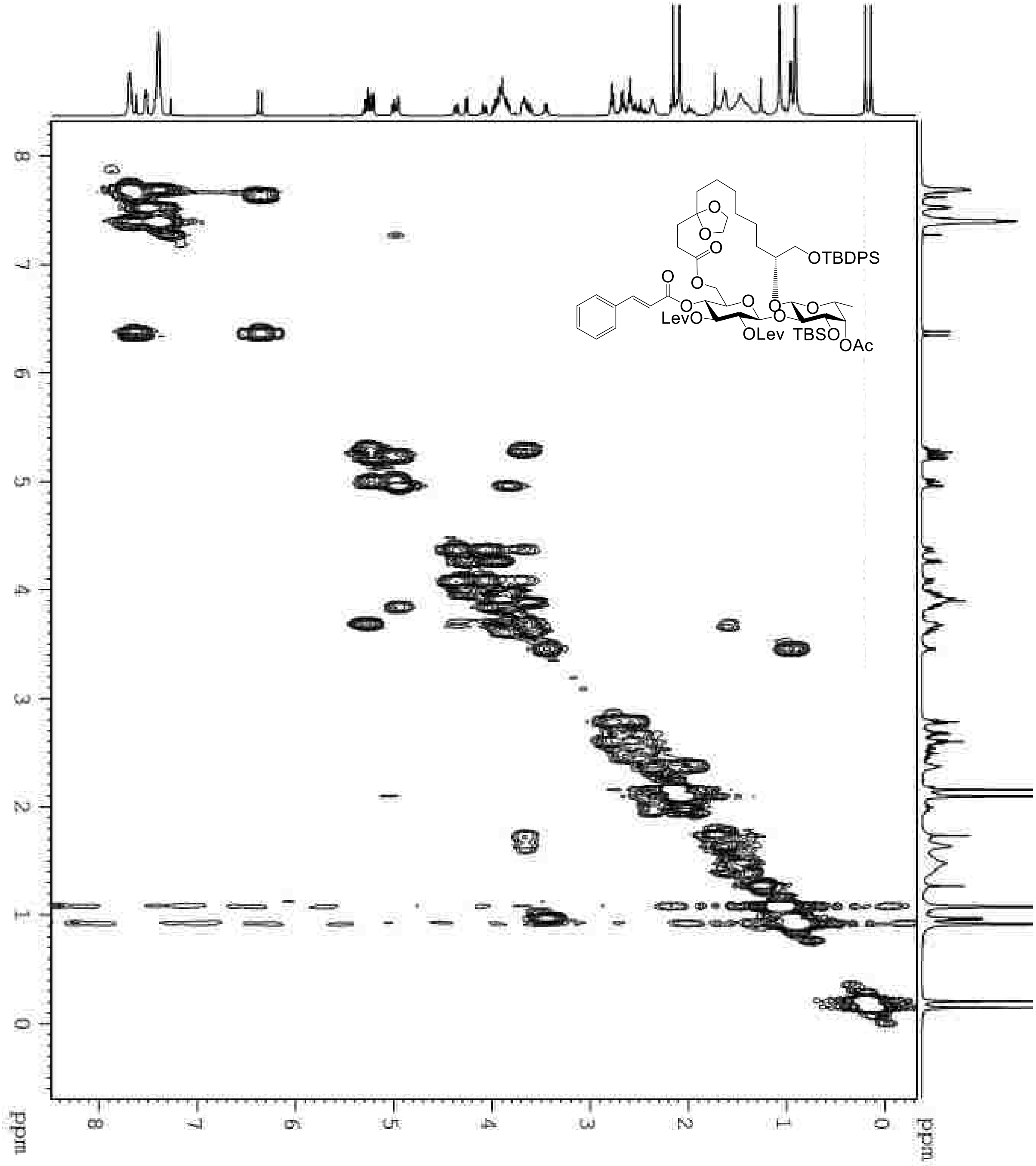
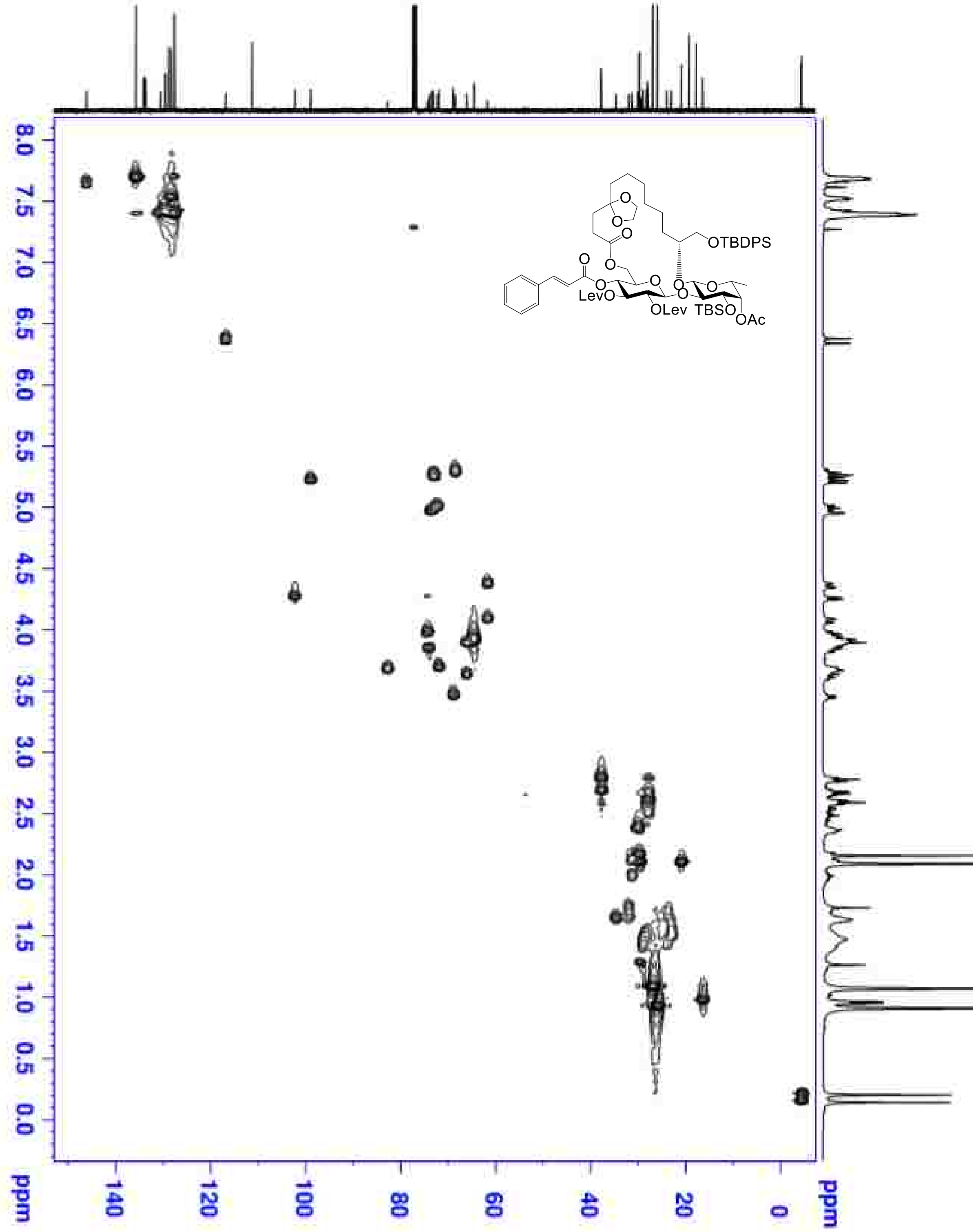
-4.497


OTBDPS
LevO
OLev
TBSO
OAc
ppm
8
7
6
5
4
3
2
1
0
ppm


ppm
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6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
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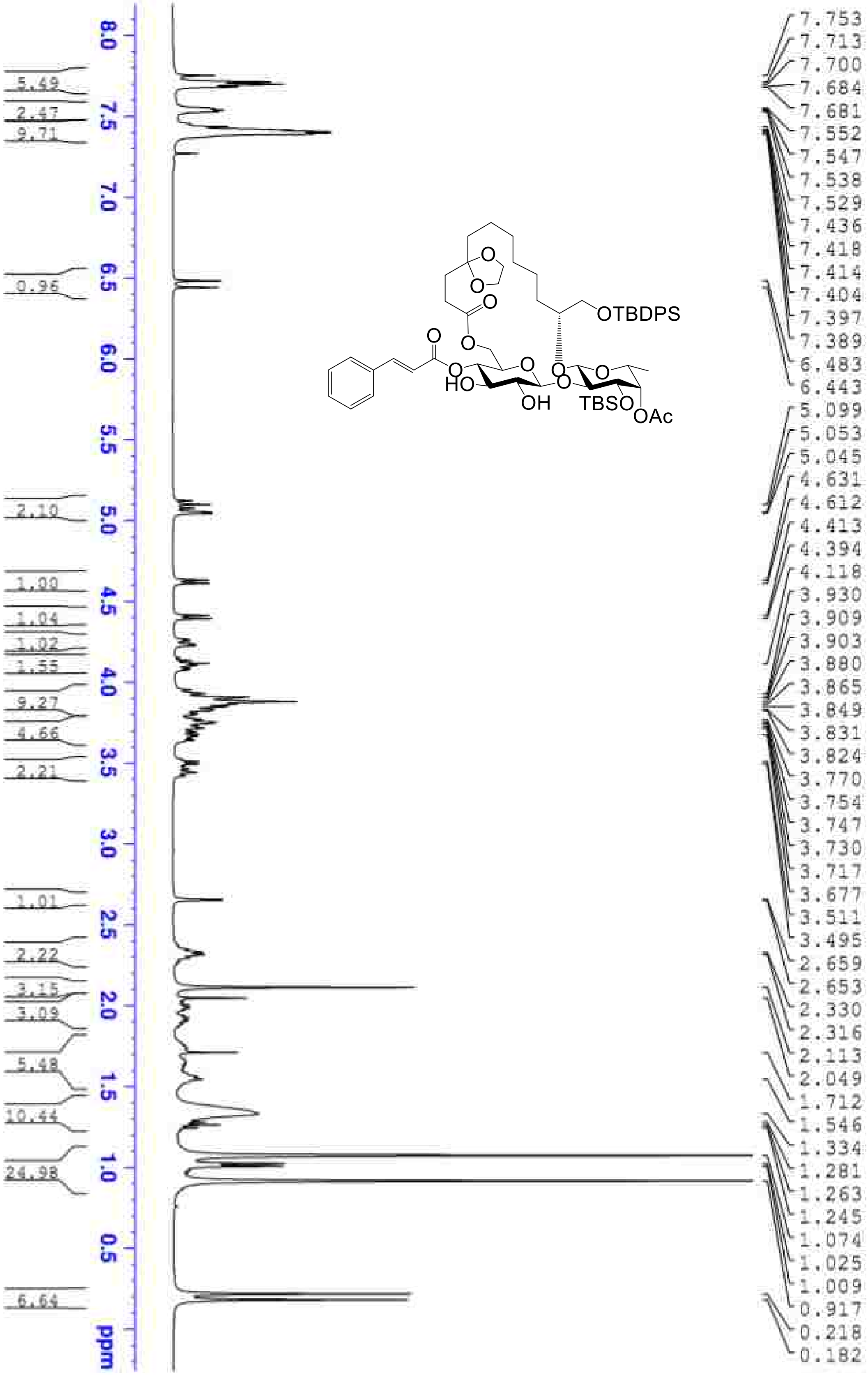
120
100
80
60
40
20
0
OTBDPS
O
LevO
OLev
TBSO
OAc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5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
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2.47
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0.96
2.10
1.00
1.04
1.02
1.55
9.27
4.66
2.21
1.01
2.22
3.15
3.09
5.48
10.44
24.98
6.64
7.753
7.713
7.700
7.684
7.681
7.552
7.547
7.538
7.529
7.436
7.418
7.414
7.404
7.397
7.389
6.483
6.443
5.099
5.053
5.045
4.631
4.612
4.413
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4.118
3.930
3.909
3.903
3.880
3.865
3.849
3.831
3.824
3.770
3.754
3.747
3.730
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2.659
2.653
2.330
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2.113
2.049
1.712
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1.334
1.281
1.263
1.245
1.074
1.025
1.009
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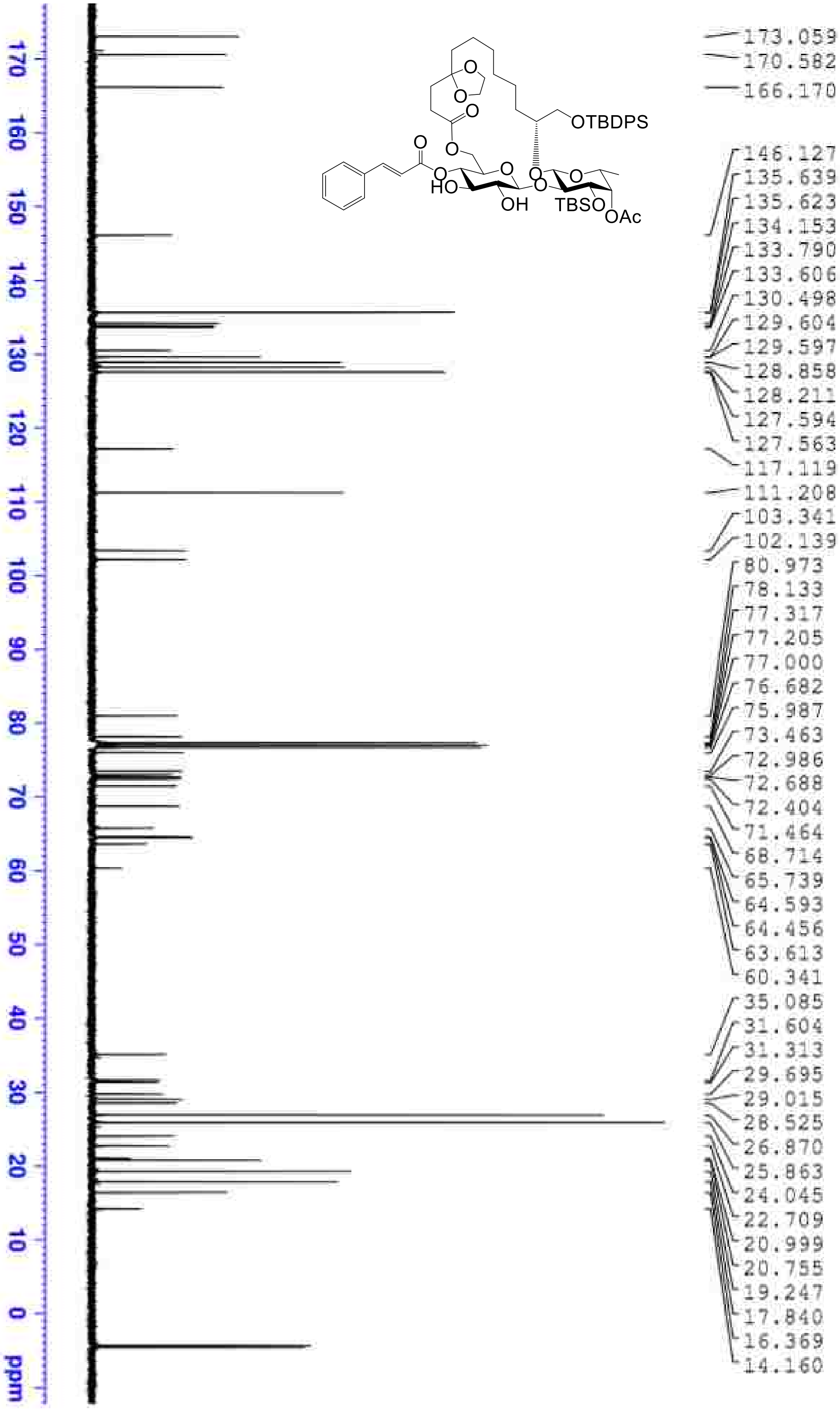
O
O
O
OTBDPS
O
O
O
O
O
O
HO
OH
TBSO
OAc



OTBDPS
HO
OH
TBSO
OAc
O
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166.170
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135.623
134.153
133.790
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130.498
129.604
129.597
128.858
128.211
127.594
127.563
117.119
111.208
103.341
102.139
80.973
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77.205
77.000
76.682
75.987
73.463
72.986
72.688
72.404
71.464
68.714
65.739
64.593
64.456
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60.341
35.085
31.604
31.313
29.695
29.015
28.525
26.870
25.863
24.045
22.709
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16.369
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140
130
120
110
100
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60
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40
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20
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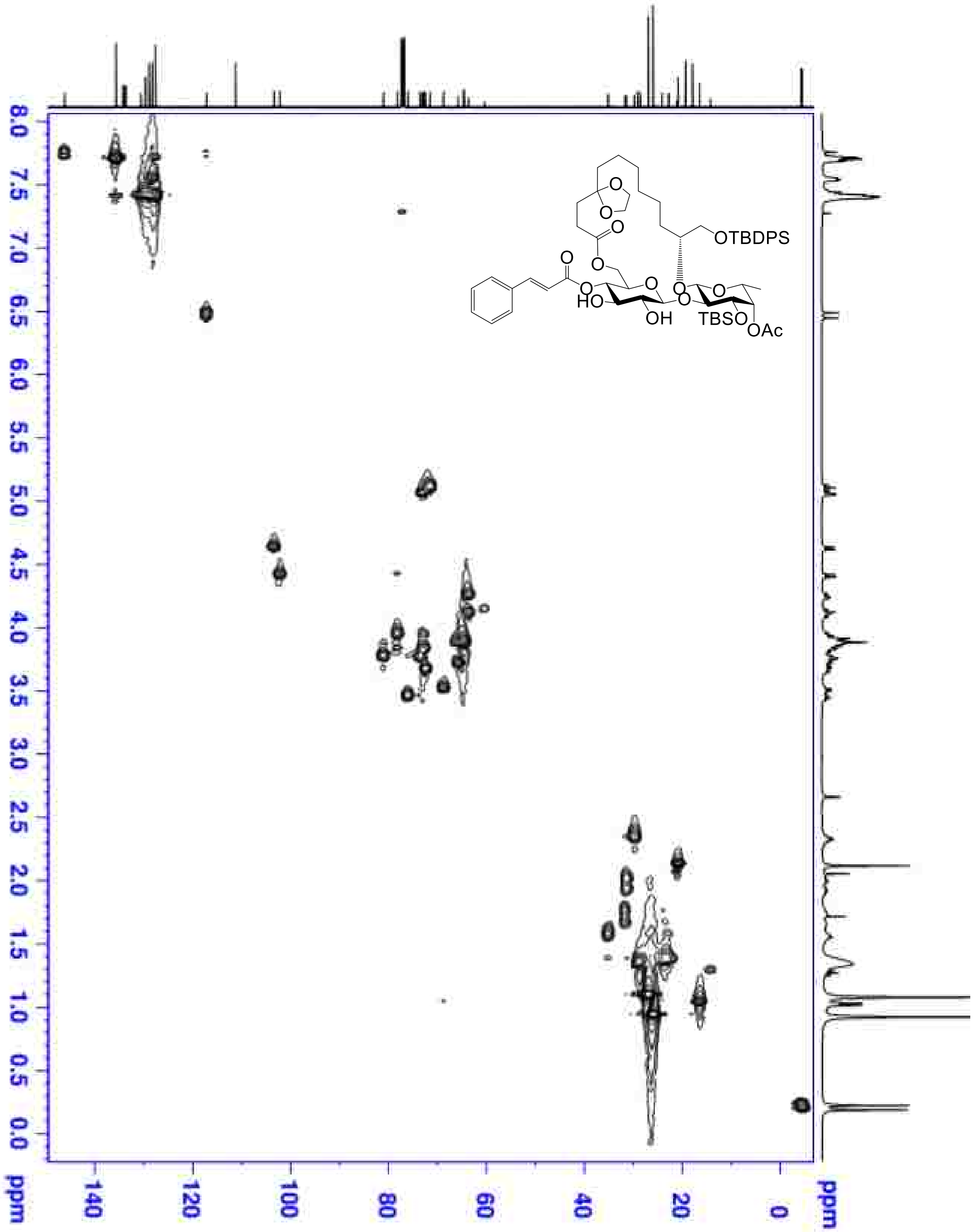
0
ppm


OTBDPS
O
O
O
O
O
HO
OH
TBSO
OAc
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6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
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1.0
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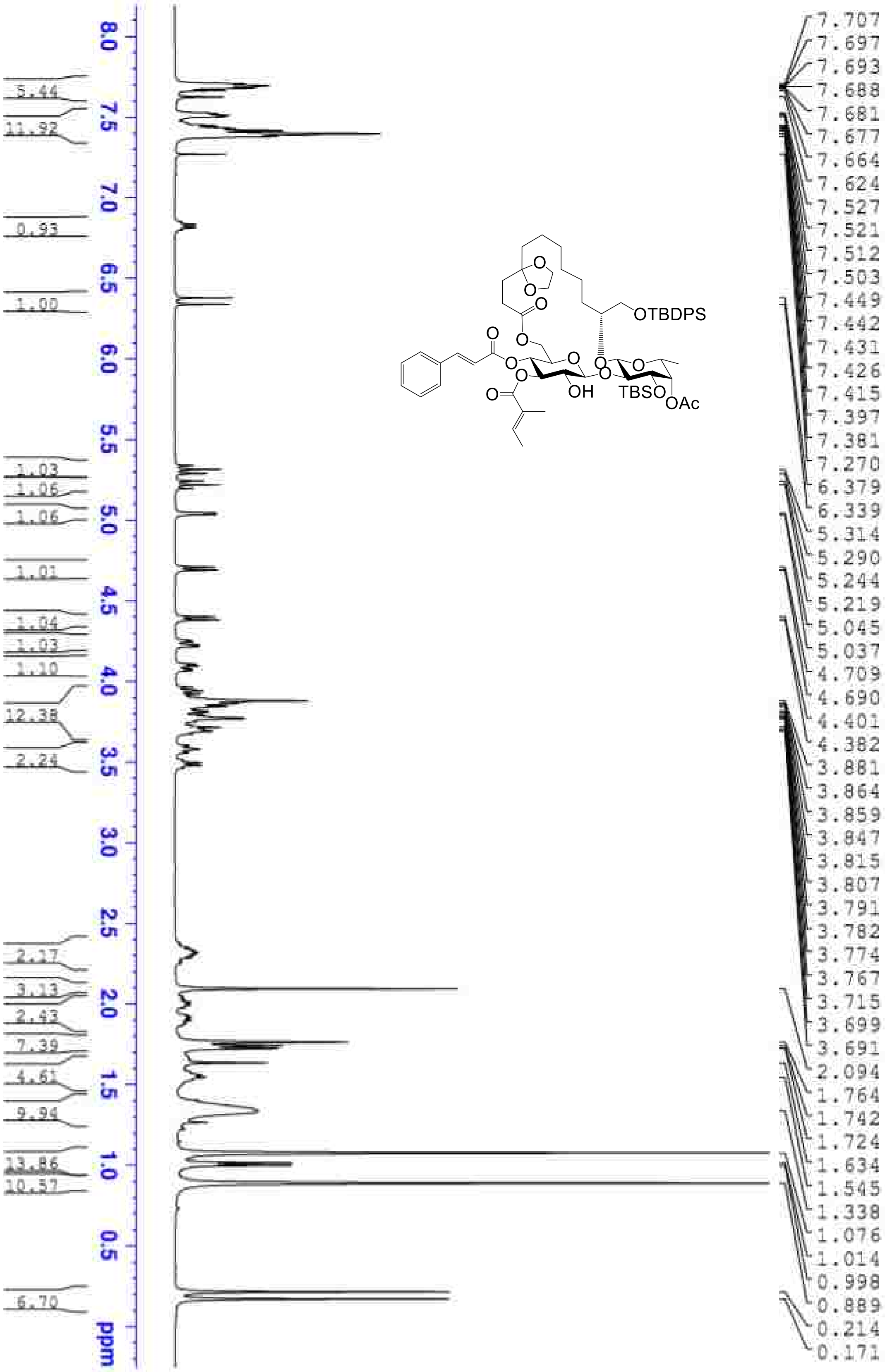
ppm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3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
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1.06
1.06
1.01
1.04
1.03
1.10
12.38
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2.17
3.13
2.43
7.39
4.61
9.94
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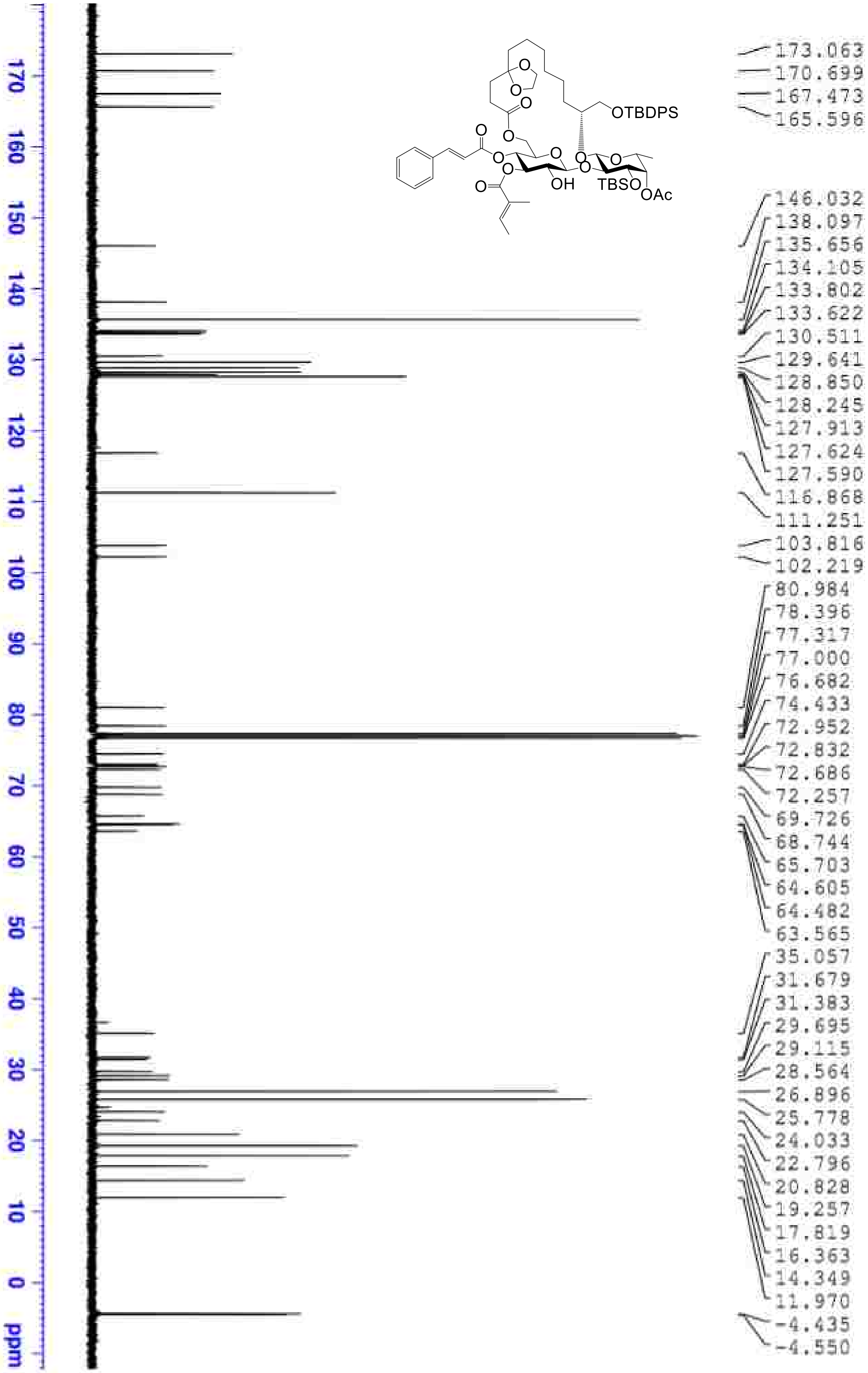
1.076
1.014
0.998
0.889
0.214
0.171
O
O
O
O
O
OTBDPS
O
O
O
O
O
O
O
OH
TBSO
OAc
O


OTBDPS
O
O
O
O
O
O
O
O
OH
O
O
TBSO
OAc
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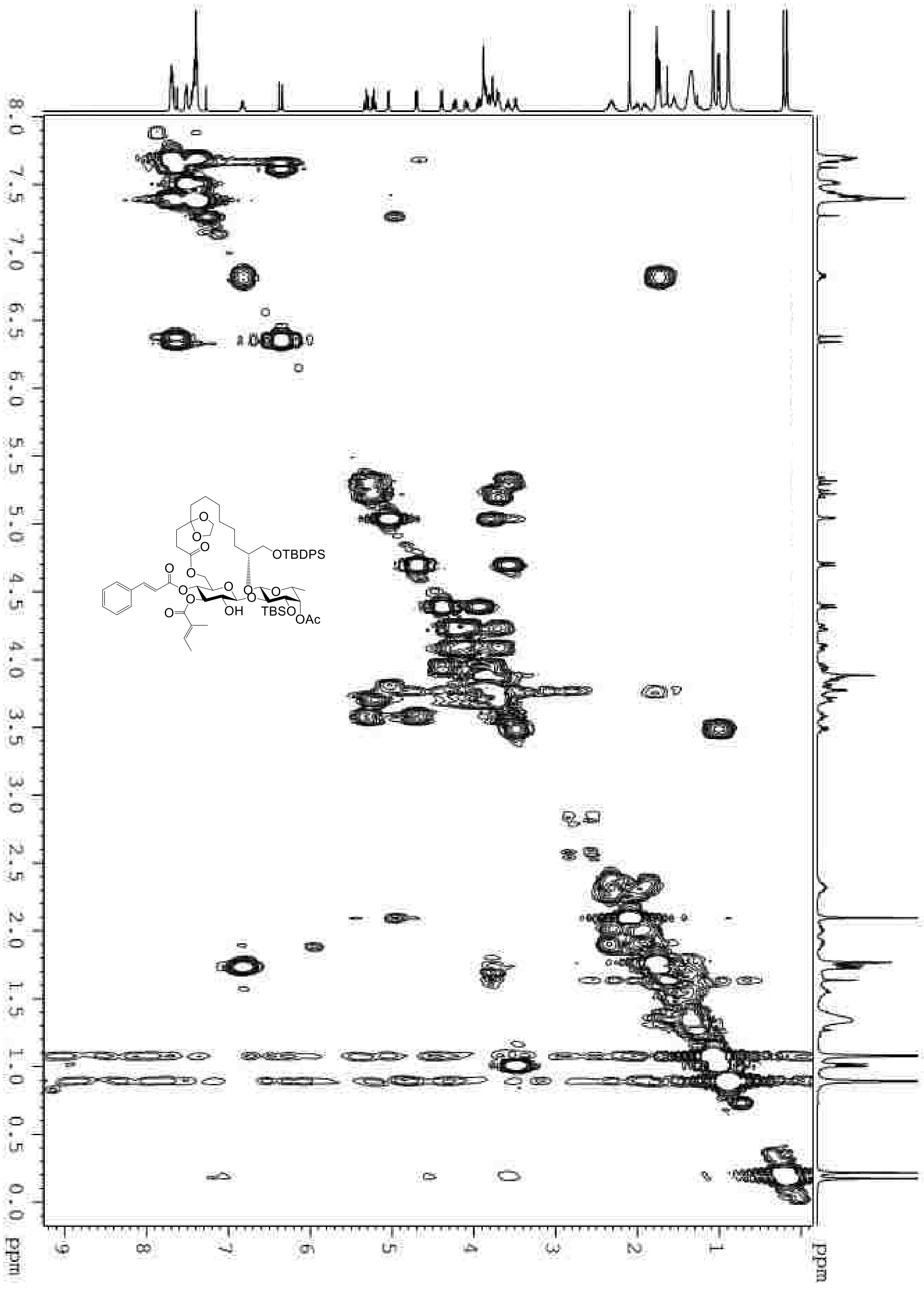
170.699
167.473
165.596
146.032
138.097
135.656
134.105
133.802
133.622
130.511
129.641
128.850
128.245
127.913
127.624
127.590
116.868
111.251
103.816
102.219
80.984
78.396
77.317
77.000
76.682
74.433
72.952
72.832
72.686
72.257
69.726
68.744
65.703
64.605
64.482
63.565
35.057
31.679
31.383
29.695
29.115
28.564
26.896
25.778
24.033
22.796
20.828
19.257
17.819
16.363
14.349
11.970
-4.435
-4.550
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


OTBDPS
OH
TBSO
OAc
ppm
9
8
7
6
5
4
3
2
1
ppm
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7.5
7.0
6.5
6.0
5.5
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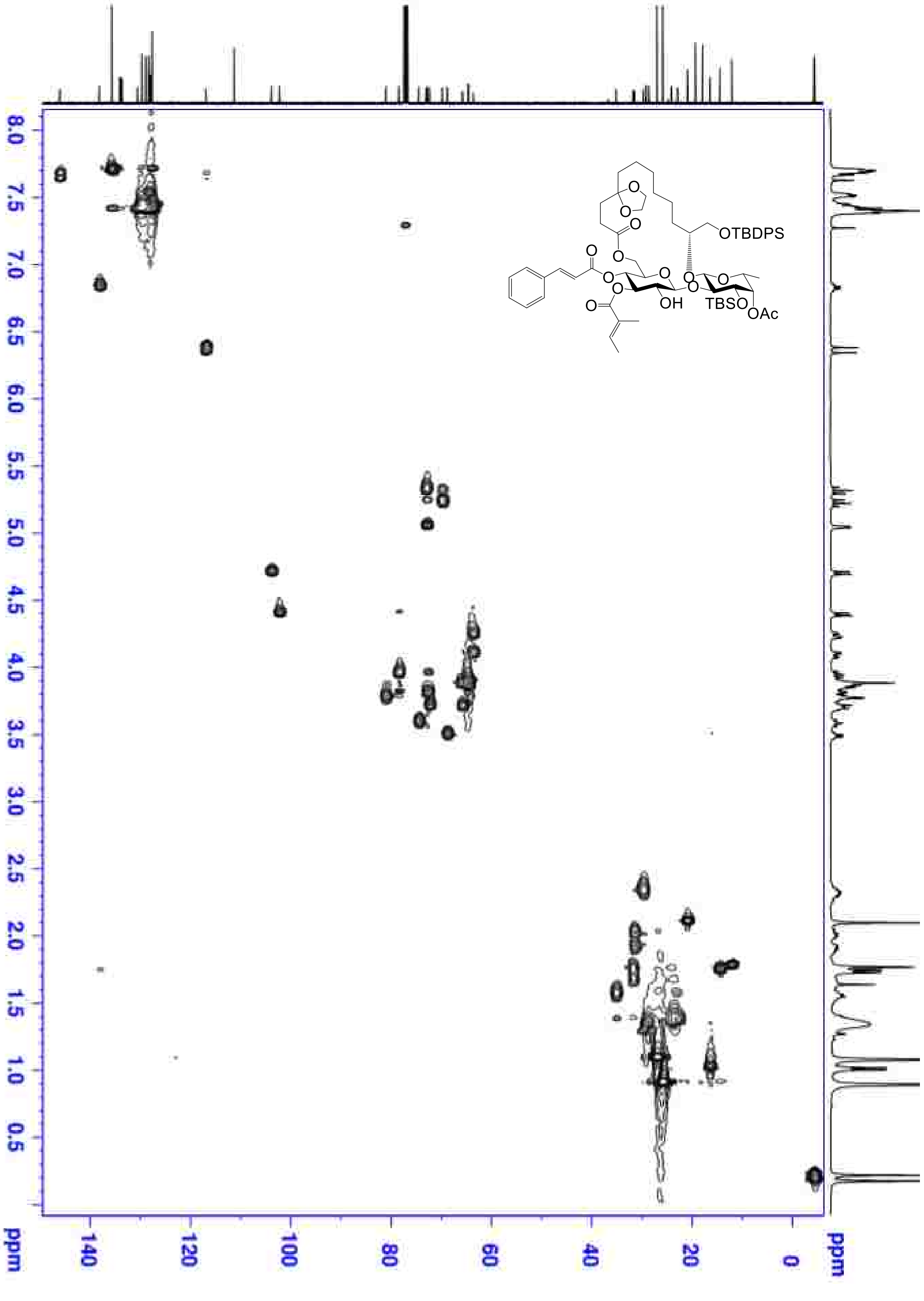
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

ppm
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6.0
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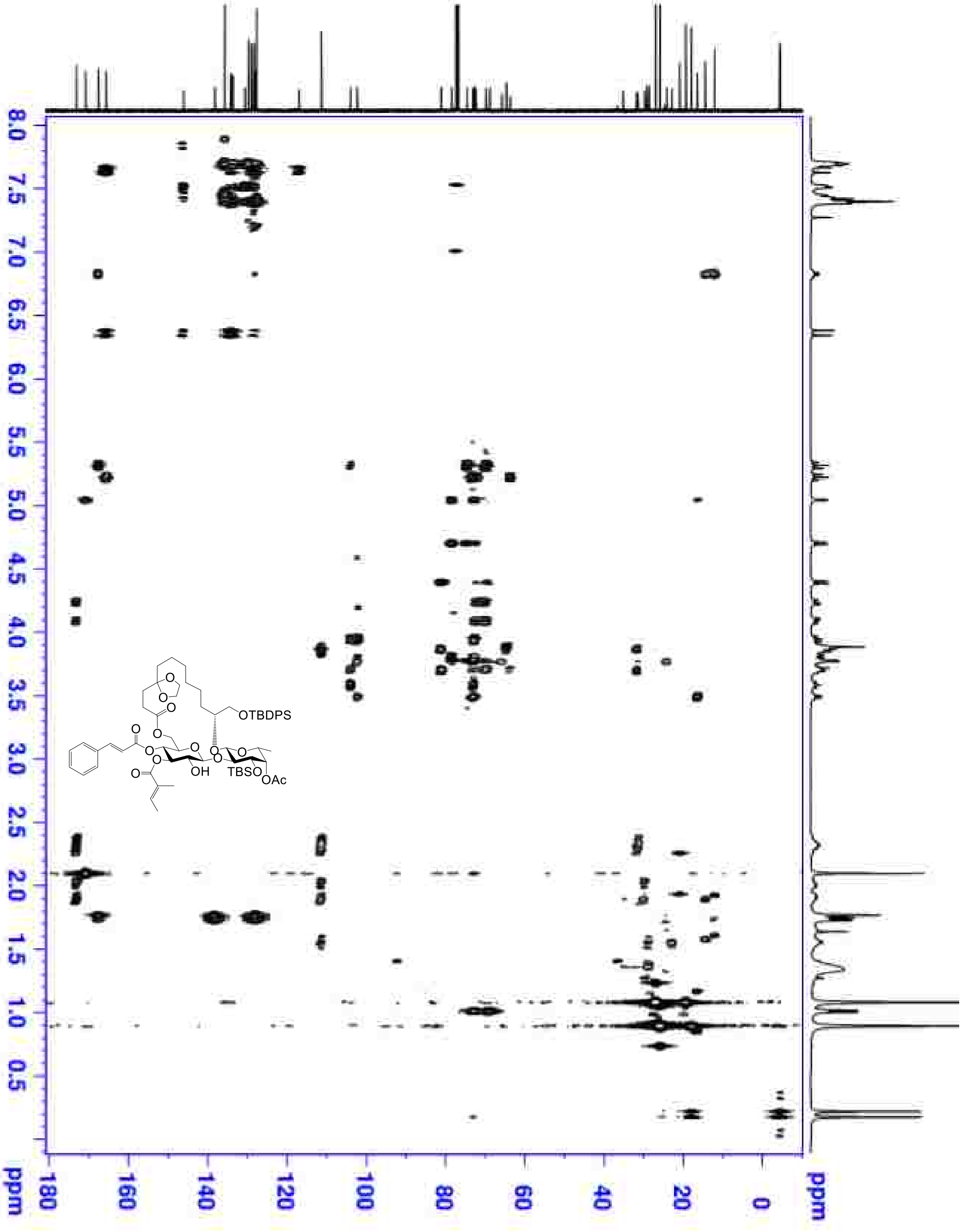
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
140
120
100
80
60
40
20
0
OTBDPS
OH
TBSO
OAc


ppm
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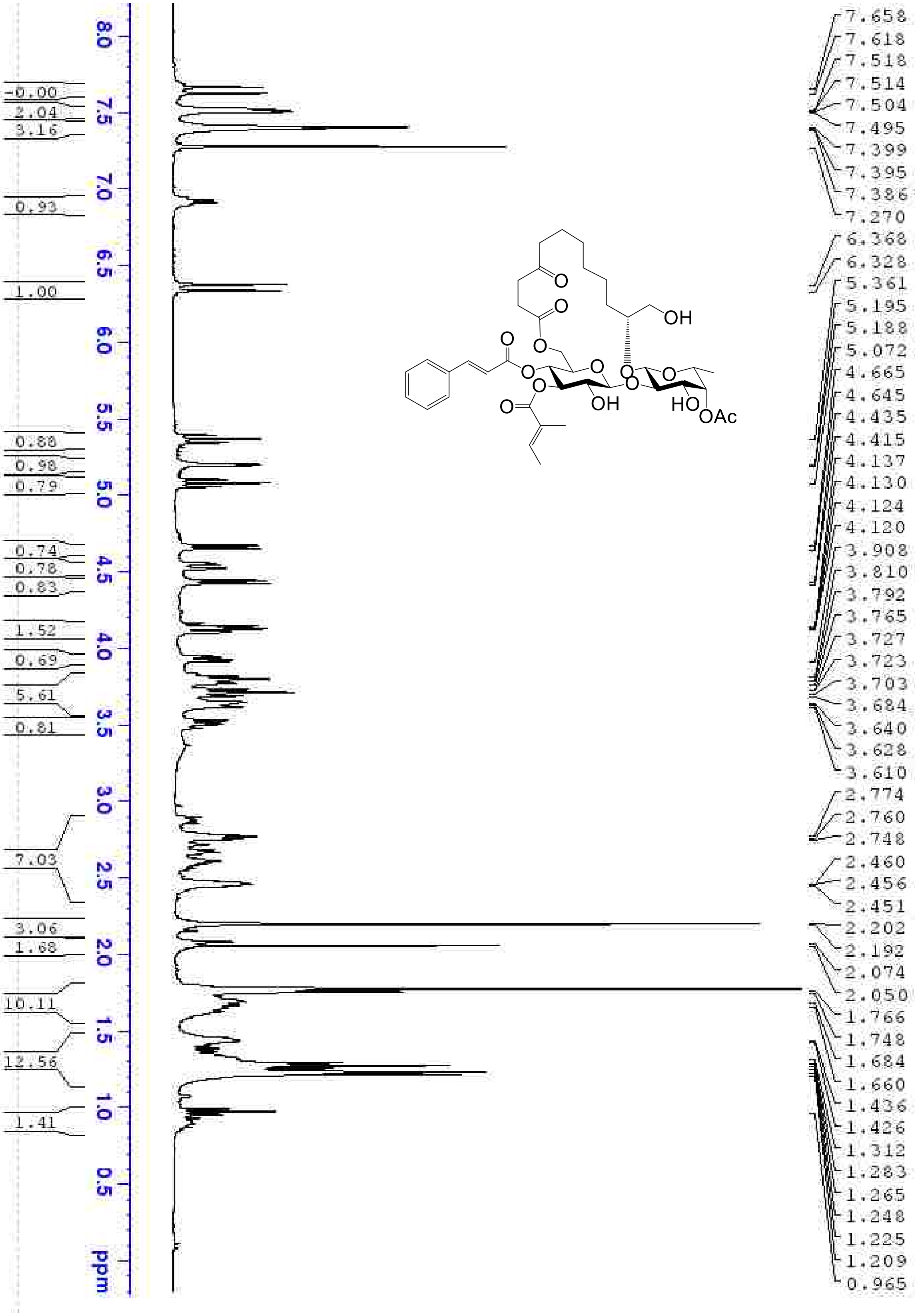
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
180
160
140
120
100
80
60
40
20
0
OTBDPS
OH
TBSO
OAc



-0.00
2.04
3.16
0.93
1.00
0.88
0.98
0.79
0.74
0.78
0.83
1.52
0.69
5.61
0.81
7.03
3.06
1.68
10.11
12.56
1.41
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
O
O
OH
O
O
O
O
O
O
OH
HO
OAc
O
7.658
7.618
7.518
7.514
7.504
7.495
7.399
7.395
7.386
7.270
6.368
6.328
5.361
5.195
5.188
5.072
4.665
4.645
4.435
4.415
4.137
4.130
4.124
4.120
3.908
3.810
3.792
3.765
3.727
3.723
3.703
3.684
3.640
3.628
3.610
2.774
2.760
2.748
2.460
2.456
2.451
2.202
2.192
2.074
2.050
1.766
1.748
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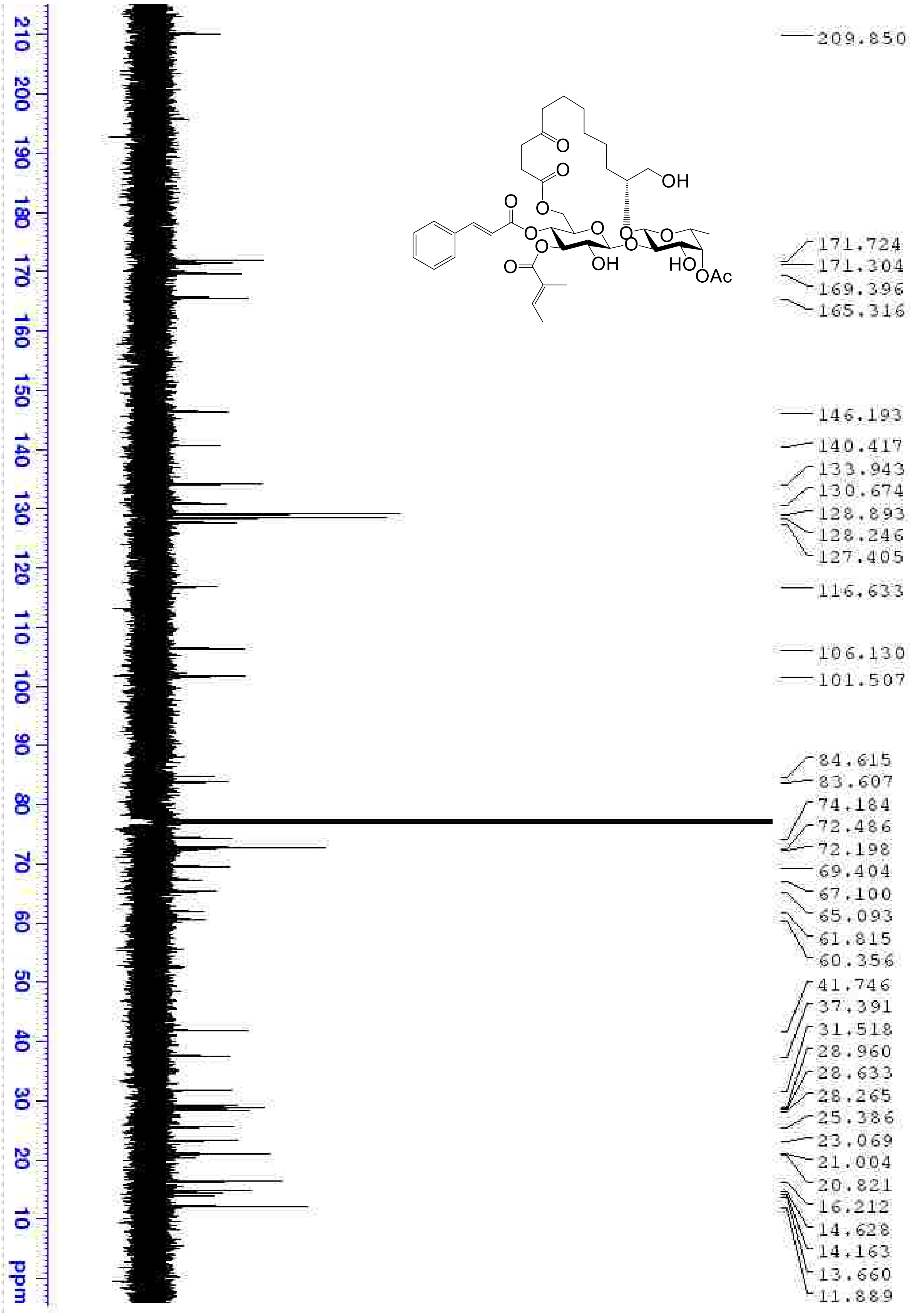
1.436
1.426
1.312
1.283
1.265
1.248
1.225
1.209
0.965



209.850
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171.304
169.396
165.316
146.193
140.417
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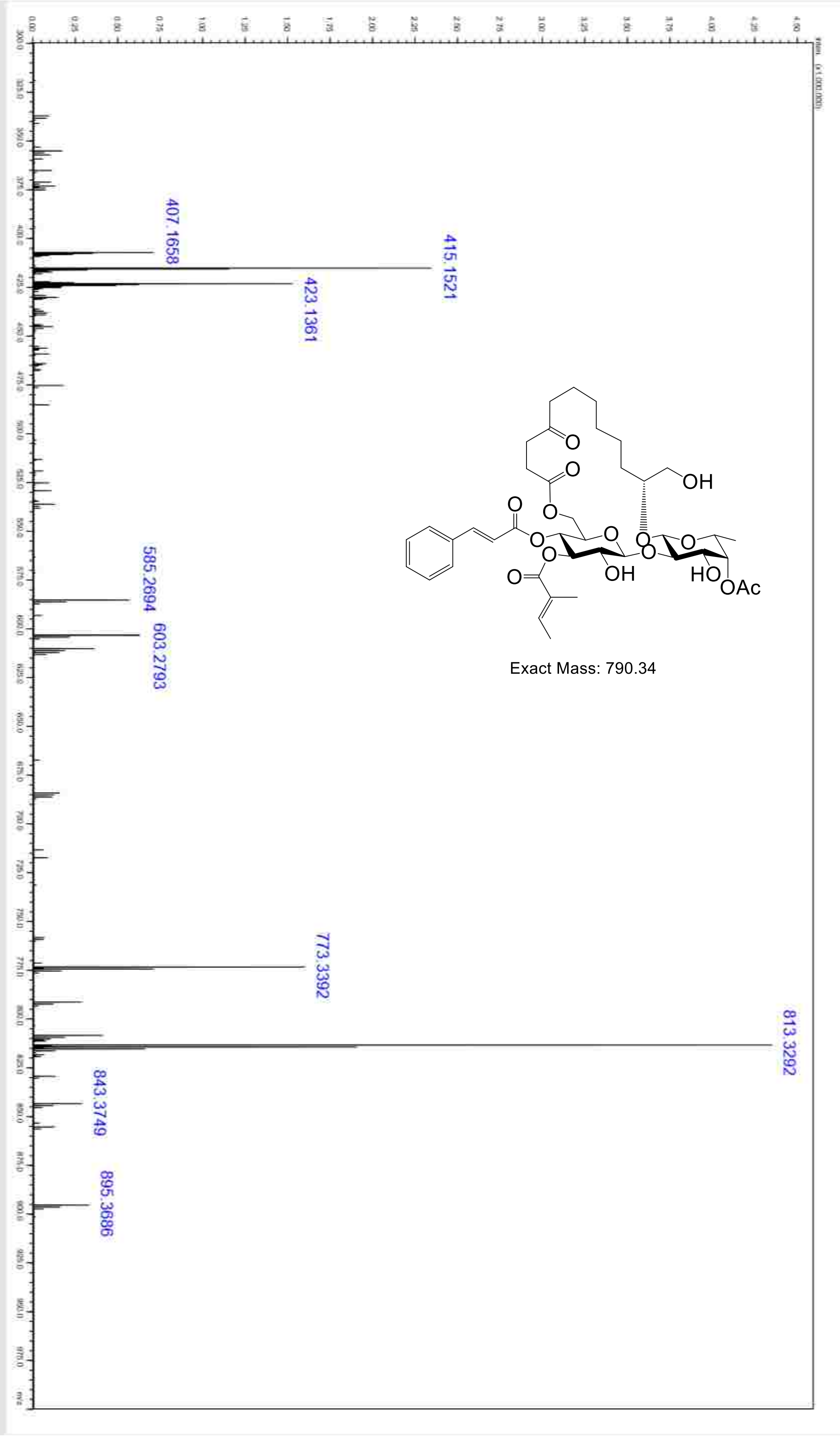
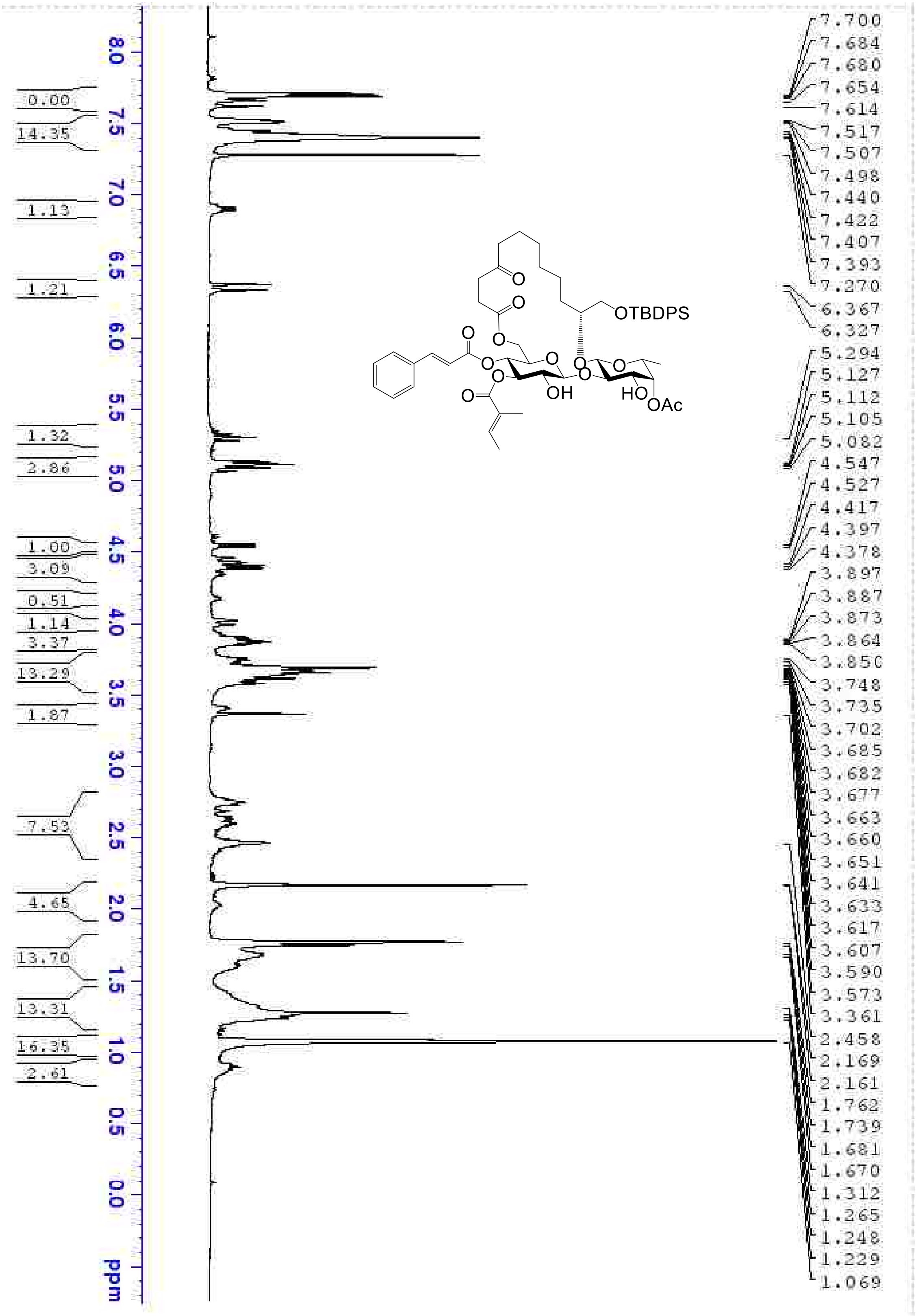
128.246
127.405
116.633
106.130
101.507
84.615
83.607
74.184
72.486
72.198
69.404
67.100
65.093
61.815
60.356
41.746
37.391
31.518
28.960
28.633
28.265
25.386
23.069
21.004
20.821
16.212
14.628
14.163
13.660
11.889
O
O
OH
O
O
O
O
O
OH
HO
OAc
ppm
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10



Exact Mass: 790.34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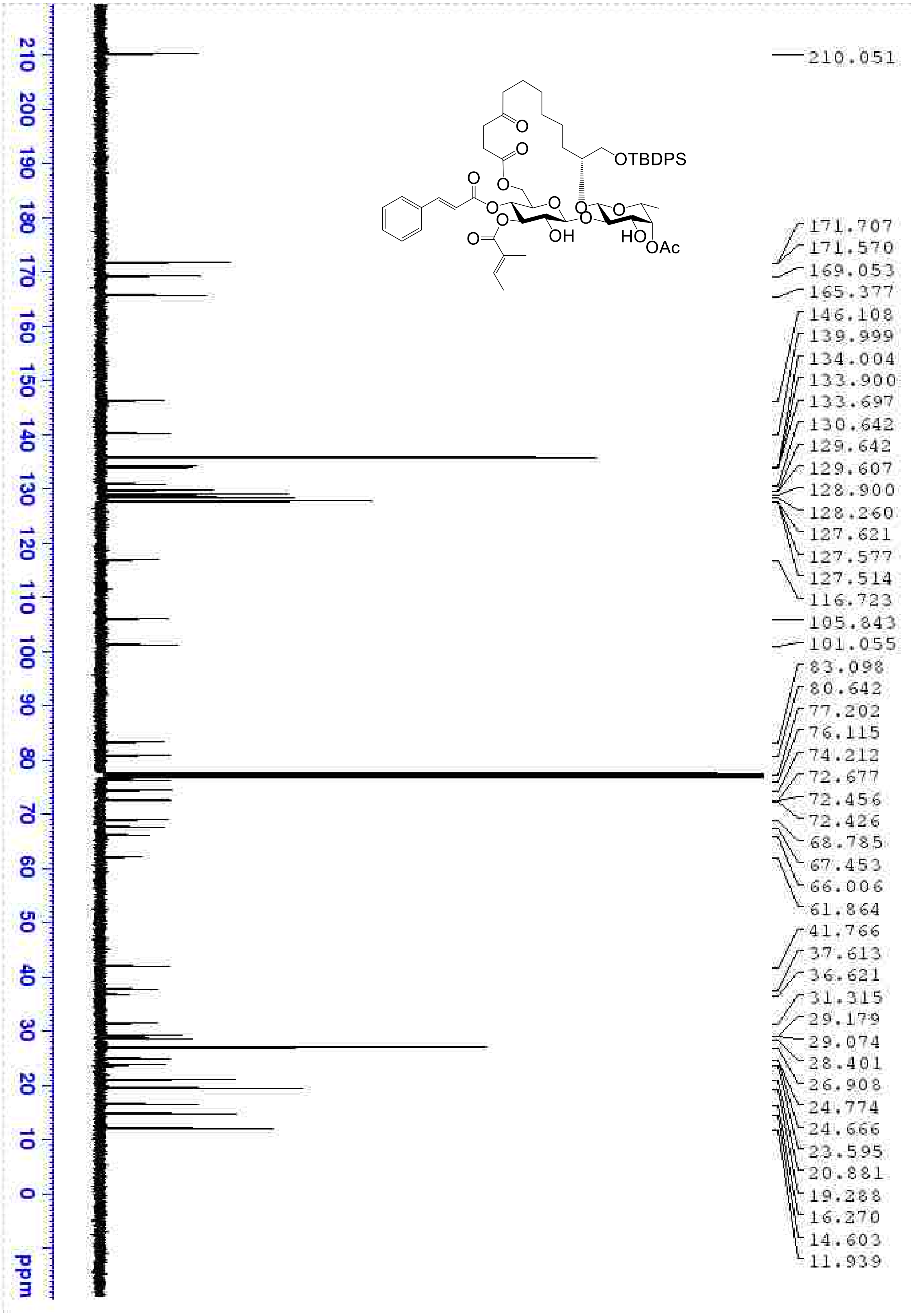
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
0.00
14.35
1.13
1.21
1.32
2.86
1.00
3.09
0.51
1.14
3.37
13.29
1.87
7.53
4.65
13.70
13.31
16.35
2.61
7.700
7.684
7.680
7.654
7.614
7.517
7.507
7.498
7.440
7.422
7.407
7.393
7.270
6.367
6.327
5.294
5.127
5.112
5.105
5.082
4.547
4.527
4.417
4.397
4.378
3.897
3.887
3.873
3.864
3.850
3.748
3.735
3.702
3.685
3.682
3.677
3.663
3.660
3.651
3.641
3.633
3.617
3.607
3.590
3.573
3.361
2.458
2.169
2.161
1.762
1.739
1.681
1.670
1.312
1.265
1.248
1.229
1.069
O
O
OTBDPS
O
O
O
O
O
O
O
OH
HO
OAc
O



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171.570
169.053
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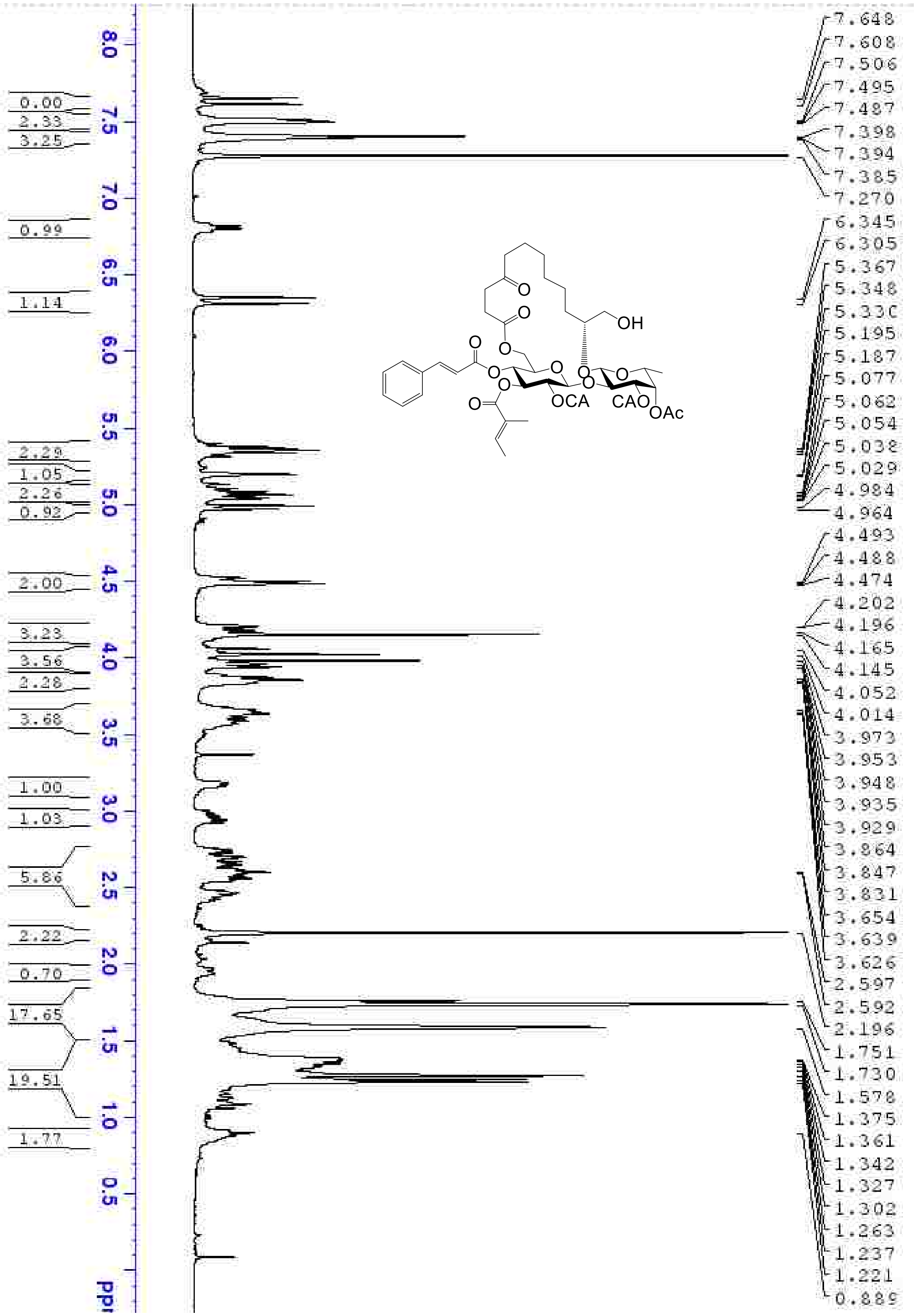
146.108
139.999
134.004
133.900
133.697
130.642
129.642
129.607
128.900
128.260
127.621
127.577
127.514
116.723
105.843
101.055
83.098
80.642
77.202
76.115
74.212
72.677
72.456
72.426
68.785
67.453
66.006
61.864
41.766
37.613
36.621
31.315
29.179
29.074
28.401
26.908
24.774
24.666
23.595
20.881
19.288
16.270
14.603
11.939
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm
O
O
OTBDPS
O
O
O
O
O
O
O
O
OH
HO
OAc
O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5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
0.00
2.33
3.25
0.99
1.14
2.29
1.05
2.26
0.92
2.00
3.23
3.56
2.28
3.68
1.00
1.03
5.86
2.22
0.70
17.65
19.51
1.77
7.648
7.608
7.506
7.495
7.487
7.398
7.394
7.385
7.270
6.345
6.305
5.367
5.348
5.330
5.195
5.187
5.077
5.062
5.054
5.038
5.029
4.984
4.964
4.493
4.488
4.474
4.202
4.196
4.165
4.145
4.052
4.014
3.973
3.953
3.948
3.935
3.929
3.864
3.847
3.831
3.654
3.639
3.626
2.597
2.592
2.196
1.751
1.730
1.578
1.375
1.361
1.342
1.327
1.302
1.263
1.237
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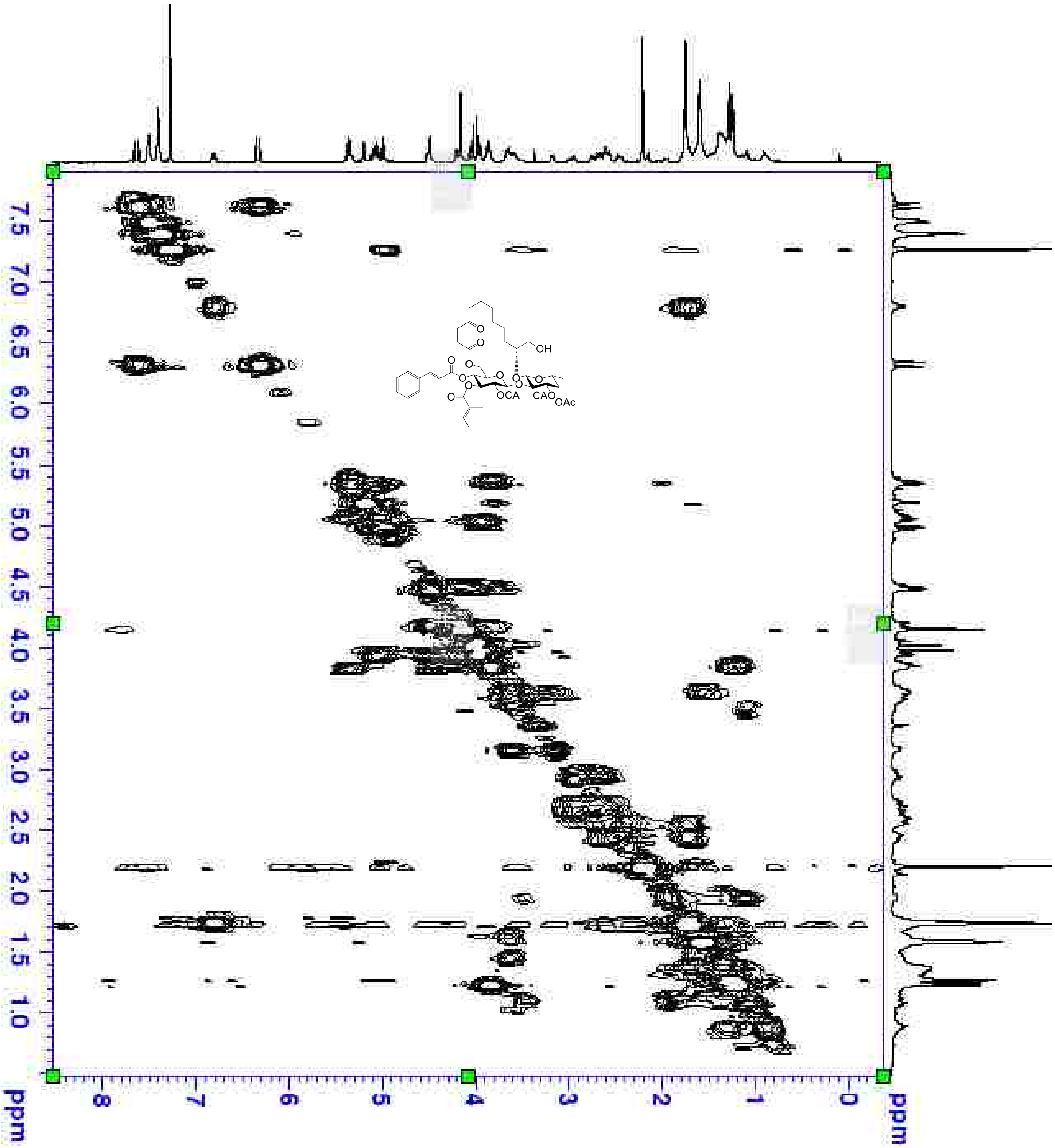
O
O
OH
O
O
O
O
O
O
O
OCA
CAO
OAc
O


ppm
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6
5
4
3
2
1
0
ppm
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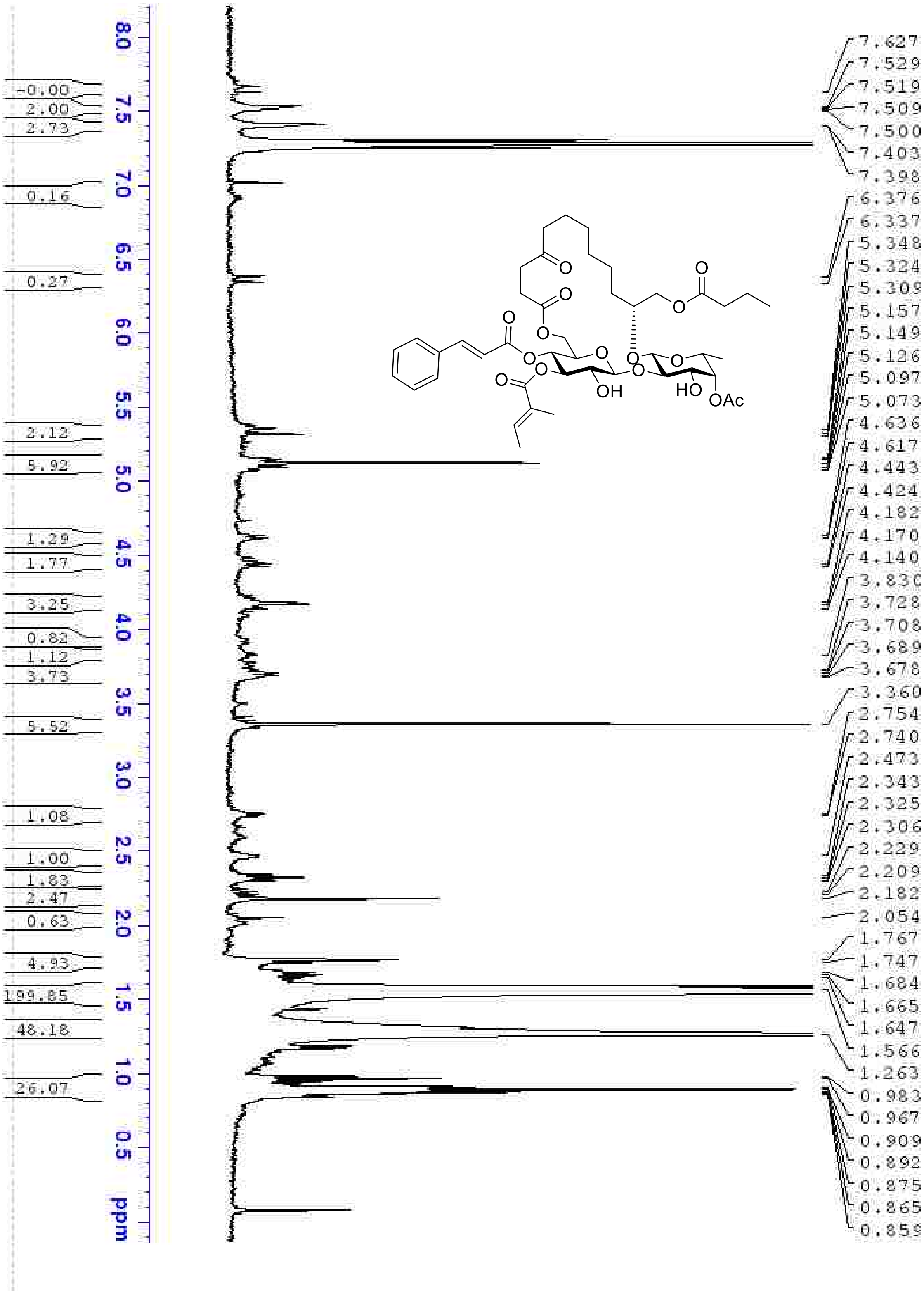
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
O
O
O
OH
O
O
O
O
O
O
OCA
CAO
OAc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6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
-0.00
2.00
2.73
0.16
0.27
2.12
5.92
1.29
1.77
3.25
0.82
1.12
3.73
5.52
1.08
1.00
1.83
2.47
0.63
4.93
199.85
48.18
26.07
7.627
7.529
7.519
7.509
7.500
7.403
7.398
6.376
6.337
5.348
5.324
5.309
5.157
5.149
5.126
5.097
5.073
4.636
4.617
4.443
4.424
4.182
4.170
4.140
3.830
3.728
3.708
3.689
3.678
3.360
2.754
2.740
2.473
2.343
2.325
2.306
2.229
2.209
2.182
2.054
1.767
1.747
1.684
1.665
1.647
1.566
1.263
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0.967
0.909
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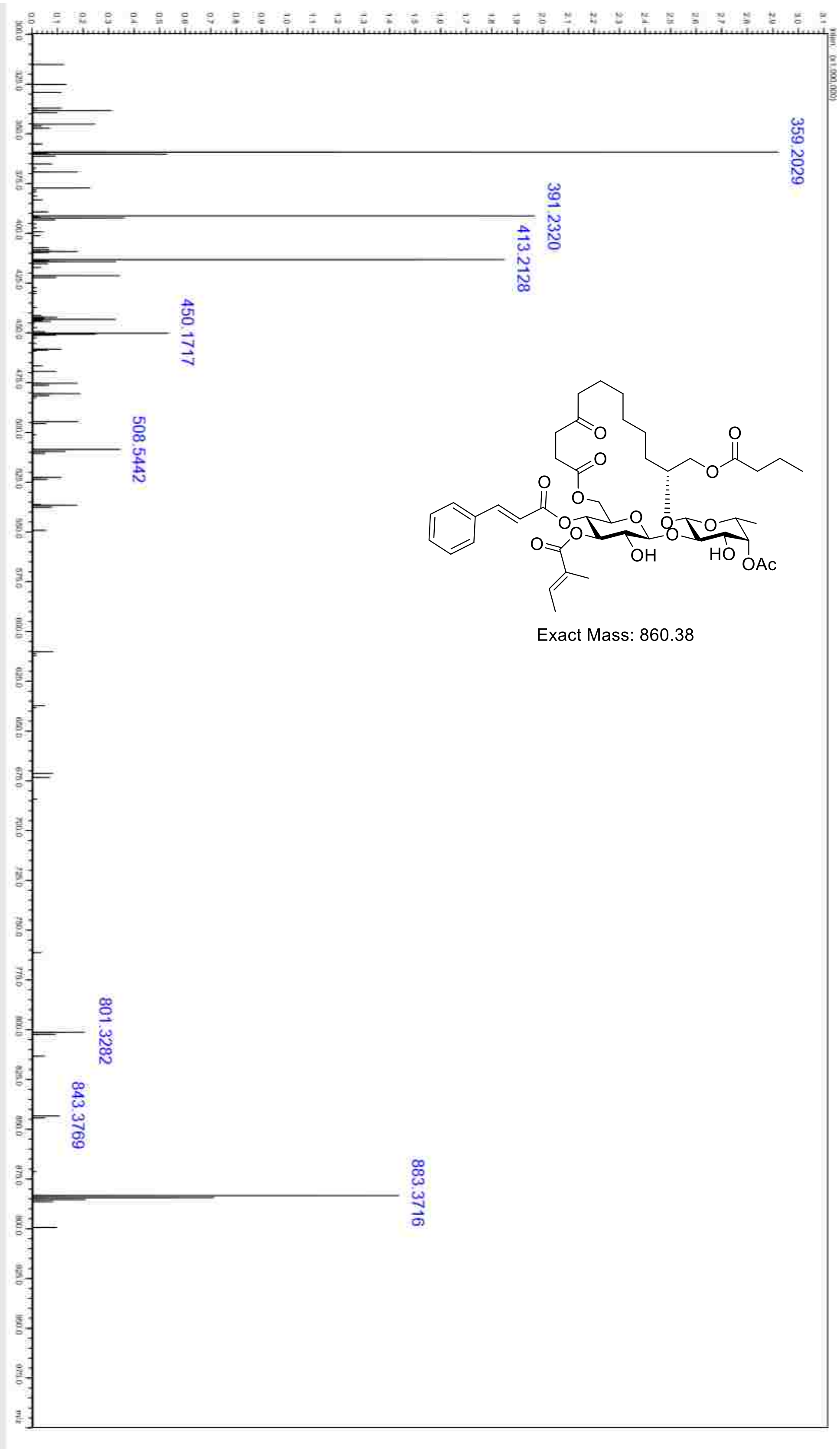
0.875
0.865
0.859
O
OH
HO
OAc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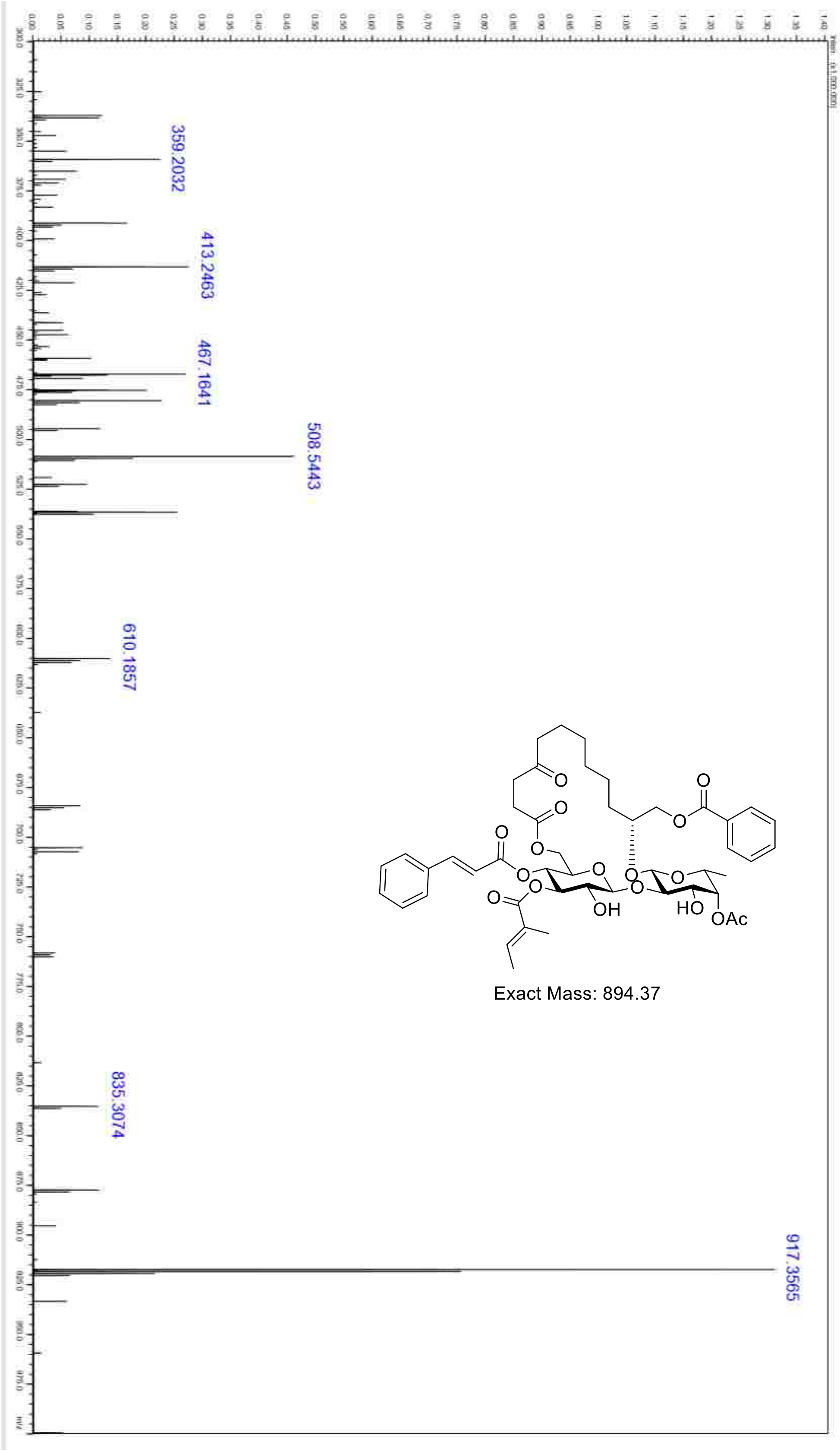
843.3769
883.3716
O
OH
HO
OAc
Exact Mass: 860.38



Exact Mass: 894.37