Development of Novel Glycosylation Reactions Using Transition Metals or Organocatalysts

by

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Haoyuan Wang

Under the Supervision of Professor Weiping Tang

at the University of Wisconsin-Madison

ABSTRACT:

Carbohydrates play a significant role in many biological events, such as cell-cell communications, intercellular recognitions, and blood group identifications. Monosaccharides, oligosaccharides, polysaccharides and their glycoconjugates such as glycoproteins and glycolipids are also involved in various diseases including tumor formation, metastasis, bacterial and viral infections. Numerous carbohydrate-based drugs and vaccines have been approved or are in different phases of clinical trials.

Although many methods have been developed for the synthesis of carbohydrates, stereoselective glycosidic bond formation is still challenging. One of the biggest bottleneck for glycobiology researchers is still the lack of a general way to obtain homogeneous forms of glycans in a reliable and scalable fashion.

Over the past 3 years, I have developed several novel glycosylation reactions that could be used to synthesize carbohydrates and glycoconjugates stereoselectively. In my first project, I developed two reactions that use transition metal catalysts such as iridium or palladium in combination with Brønsted acid promoter, to realize a dynamic kinetic diastereoselective glycosylation (DKDG) and a dynamic kinetic diastereoselective isomerization (DKDI). I also demonstrated the products of DKDG and DKDI could be applied to the synthesis of rare and unnatural mono- and oligo-saccharides.

Inspired by the mechanistic understandings on the first project, I developed an organocatalyst-directed dynamic kinetic diastereoselective acylation of lactols (DKDA) in my second project. This DKDA reaction provides a convenient solution to a long standing problem in Feringa-O'Doberty's de novo carbohydrate synthesis. The transition-state model of DKDA indicated a novel type of cation-lone pair electrostatic interaction. Based on this model, I developed a second generation of DKDA (DKDA-2.0) by using monosaccharide substrates to realize stereoselective synthesis of different 1-acyl sugars which exist in many natural products, drug metabolites and have been applied to drug delivery.

In the last project, I developed a novel stable glycosyl donor with a traceless isoquinoline-1-carboxylate (IsQ) leaving group that could be activated by copper salt for glycosylation reaction under neutral and extremely mild conditions (Glyco-IsQ). I also demonstrated the broad scope of the glycosylation donor in over a dozen of examples and its orthogonality with another ester glycosyl donor in a streamlined iterative synthesis of oligosaccharides, without involving any protection, deprotection, or activation steps during the assembly of the oligosaccharides. A tetra-saccharide was assembled in just 3 steps by using this iterative synthesis strategy.

Acknowledgements

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joined the lab.

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I want to thank professor Richards Hsung and his group. The joint group meeting we had together was very helpful to me. I also want to thank Prof. Dr. Jun Deng, Dr. Zhixiong Ma, Prof. Dr. Shuzhong He, Prof. Dr. Xiaona Wang and Dr. Lichao Fang for their generous suggestions to me. Group members of professor Jiang lab: Dr. Baobin Li, Dr. Chia-Wei Hu, Matthew Worth, Lei Lu, Dacheng Fan, Hao Li and Adam Kositzke are also greatly acknowledged for their kind discussions with me on topics related to glycobiology and carbohydrate synthesis.

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Haoyuan Wang

At Apt. 415, 4817 Sheboygan Avenue

On a typical Madison spring: Windy and 55 ^{o}F

Abbreviations and Acronyms

4Å MS = 4 Å molecular sieves

Ac = Acetyl

Ar = Aryl

Bn = Benzyl

Boc = *tert*-butyloxycarbonyl

BTM = Benzotetramisole

Bu or *n*-Bu = *n*-Butyl

*t*Bu = *tert*-Butyl

Bz = Benzoyl

Cod = Cyclooctadiene

Cp = Cyclopentadienyl

*m*CPBA = *meta*-Chloroperoxybenzoic acid

DABCO = 1,4-Diazabicyclo[2.2.2]octane, Triethylendiamine

DBU = 1,8-Diazabyciclo[5.4.0]undec-7-ene

DCC = 1,3-Dicyclohexylcarbodiimide

DCE = 1,2-Dichloroethene

DCM = Dichloromethane

DIBAL = Diisobutylaluminium hydride

DIPEA = N,N-Diisopropylethylamine

DMAP = 4-Dimethylaminopyridine

DMF = N,N-Dimethylformamide

DMSO = Dimethylsulphoxide

DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine

EDCI = 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide

Et = Ethyl

Et_2O = Diethyl ether

Fmoc = Fluorenylmethyloxycarbonyl

GT = Glycosyltransferase

IBO = Isobutylene oxide

LAH = Lithium aluminium hydride

LG = Leaving group

LDA = Lithium diisopropylamide

Me = Methyl

Ms = Mesylate

Nu = Nucleophile

NMI = N-Methyl imidazole

OAc = Acetate

OMe = Methoxy

OTf = Trifluoromethanesulfonate

PG = Protecting group

Ph = Phenyl

Piv = Pivaloyl, 2,2-dimethylacetyl

*i*Pr = *iso*-Propyl

Py = Pyridine

TBAF = Tetrabutylammonium fluoride

TBS = *tert*-Butyldimethylsilyl

TBPS = *tert*-Butyldiphenylsilyl

TBS = tert-Butyldimethylsilyl

TES = Triethylsilyl

Tf_2O = Triflic anhydride

THF = Tetrahydrofurane

TIPS = Triisopropylsilyl

TMB = 1,3,5-Tri-methoxybenzene

TMEDA = Tetramethylethylenediamine

TMS = Trimethylsilyl

Troc = 2,2,2-Trichloroethoxycarbonyl

Ts = *para*-Toluenesulphonyl

Table of Contents

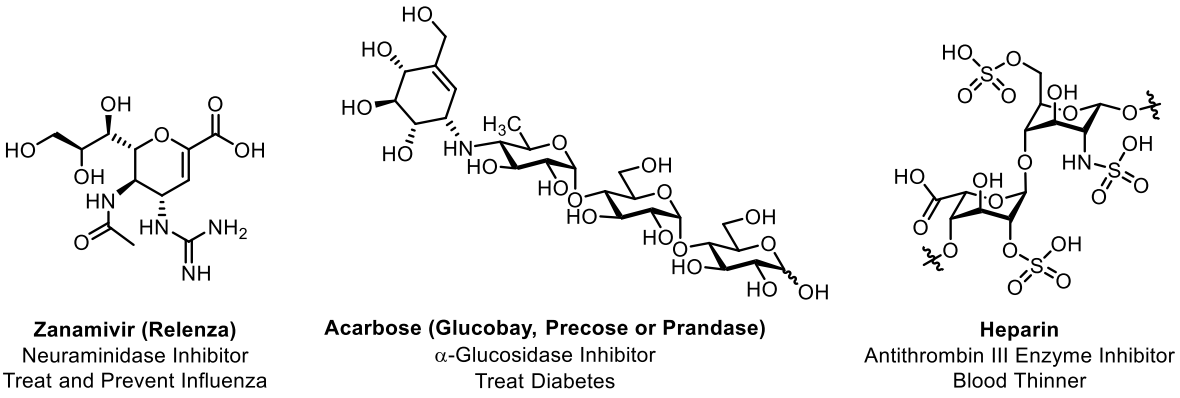
Chapter 1

Chiral Reagents in Glycosylation and Modification of Carbohydrates

1.1 Introduction

Carbohydrates play a significant role in many biological events, such as cell-cell communications, intercellular recognitions, and blood group identifications.[1] Monosaccharides, oligosaccharides, polysaccharides and their glycoconjugates (*e.g.* glycoproteins and glycolipids) are also involved in various diseases such as tumor formation, metastasis, bacterial and viral infections. Many carbohydrate scaffolds can be found in prescription drugs like zanamivir (influenza), acarbose (diabetes) and heparin (thrombosis) (**Scheme 1-1**).[2] In addition, a great number of carbohydrate-based vaccines has already been approved or in different phases of their developmental stages.[3]

Scheme 1-1. Examples of carbohydrate scaffolds in prescription drugs



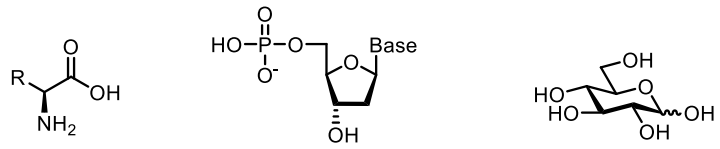
Zanamivir (Relenza)
Neuraminidase Inhibitor
Treat and Prevent Influenza

Acarbose (Glucobay, Precose or Prandase)
α-Glucosidase Inhibitor
Treat Diabetes

Heparin
Antithrombin III Enzyme Inhibitor
Blood Thinner

Carbohydrates, lipids, nucleic acids, and proteins are the primary macromolecules in cells. Compared to nucleic acids and proteins, the structures of carbohydrates are far more diverse. For example, two amino acids and two nucleotides will potentially have 2 different linear combinations, respectively. However, two monosaccharides will have a total of 20 different linear combinations, considering the attachment of different hydroxyl groups and α/β anomers (**Scheme 1-2**).

Scheme 1-2. Complexity of monosaccharides compared with amino acids and nucleotides



Amino Acids
Linear combination of two amino acids: **2**

Nucleotides
Linear combination of two necleotides: **2**

Monosaccharides
Linear combination of two monosaccharides: **20**

Although the biologically relevant carbohydrates can be isolated from natural sources, most of them are in heterogeneous

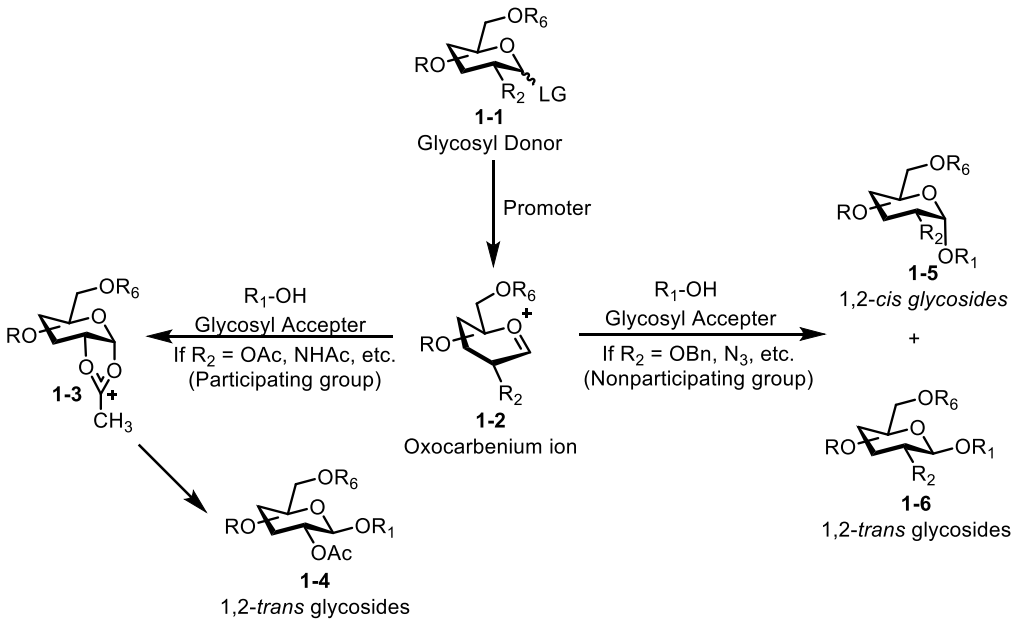
forms and it could be a huge liability as demonstrated by the incidence of heparin sulfate, where the use of contaminated heterogeneous forms of it had caused over 100 death.[4] Due to its structural complexity and lack of homogeneous form, the functions of carbohydrates are the least understood among those four essential biomolecules. The biggest bottleneck that slows glycobiology researches down is the lack of a general way to obtain homogeneous forms of glycans in a reliable and scalable fashion.

Since the pioneering work by 1902 Nobel Laureate Emil Fisher, carbohydrate chemistry has been evolved and numerous methods have been developed to overcome the challenges of carbohydrate synthesis in the last decades. Among them, solution phase based one-pot glycosylation[5] and solid phase based automated oligosaccharides synthesis[6] stand out and provide expedient ways to assemble oligosaccharides.[7] However, stereoselective glycosidic bond formation and protecting group (PG) manipulations, including regioselective protections and deprotections, are still hindering the carbohydrate synthesis and therefore, limiting our efforts toward understanding the functions of glycans in biological systems.[8]

Just like every single organic chemistry reaction, chemical glycosylation reactions are governed by the rule of reactivity and selectivity. The glycosyl donor must be reactive enough so that a nucleophile, for example, hydroxyl group on the glycosyl accepter, can react with and form the glycosidic linkage. However, the glycosyl donor cannot be too reactive so that the formation of glycosidic linkage occurs with proper selectivity. Thus, the selective synthesis of carbohydrates often relies on many factors such as PG, leaving group (LG), promoter, solvent, concentration, temperature, as well as the chemical properties of the glycosyl accepter. One or multiple factors above can dictate the stereo-outcome of glycosylation reactions and they are not always predictable. Laborious screenings of each of these factors are often necessary.

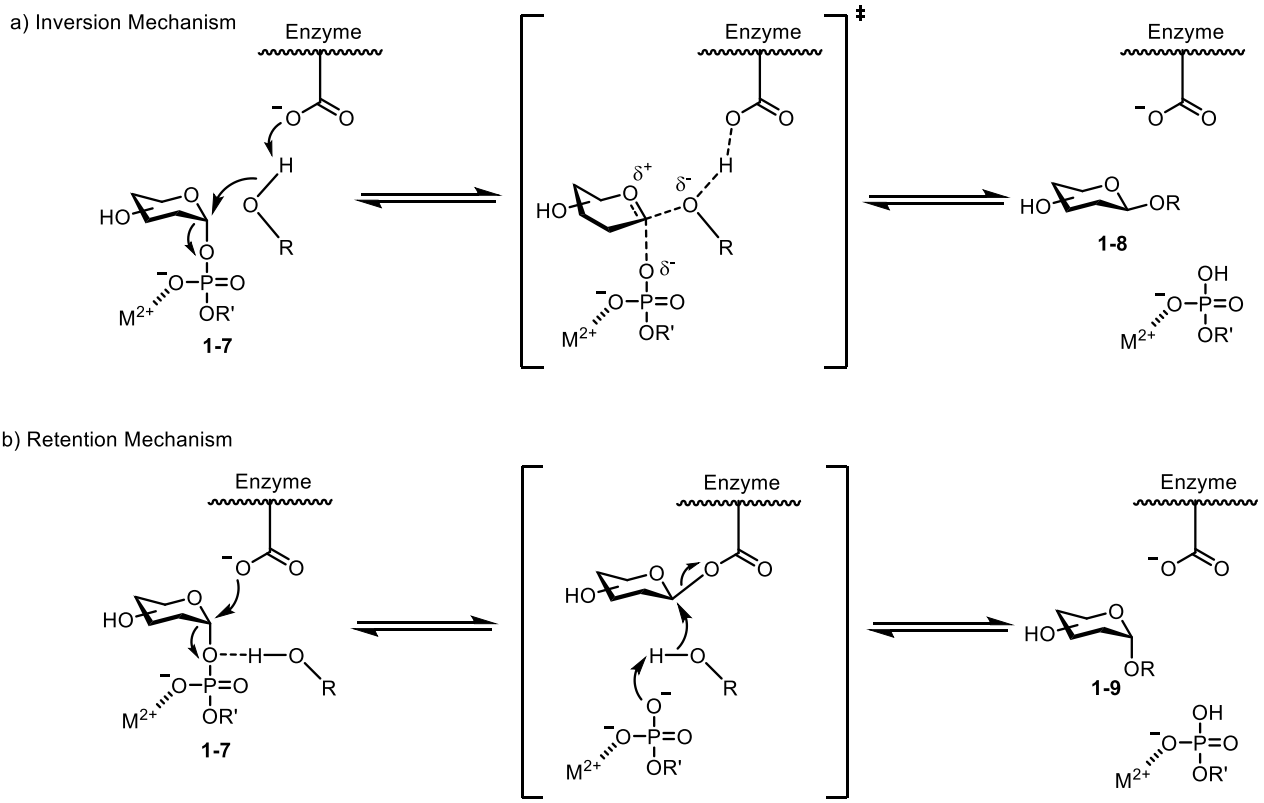
In particular, PGs can affect the electronic properties of glycosyl donors and intermediates, making it more reactive (armed, PG = Bn, *etc.*) or less reactive (disarmed, PG = Ac, Bz, *etc.*). PGs can also participate in glycosylation reaction through the classical neighboring group participation mechanism. Glycosyl donor **1-1** is activated with proper promoter to form oxocarbenium ion **1-2**, the acyl protecting group at C-2 can then participate and stabilize **1-2** by forming acetoxonium ion intermediate **1-3**, it can then react with glycosyl accepter to form 1,2-*trans* glycosides **1-4**. When non-participating group is at C-2, 1,2-*cis* glycosides **1-5** can be obtained, however, often with a mixture of 1,2-*trans* glycosides **1-6** (**Scheme 1-3**).

Scheme 1-3. General pathways for chemical glycosylation reactions



Compared to the laborious processes in chemical carbohydrate synthesis, enzymatic and chemoenzymatic synthesis of carbohydrates are more depend on the choice of LGs and its glycosyltransferases (GTs). Starting from the same nucleoside diphosphate sugar donor **1-7**, the inverting GTs catalyze the glycosylation reactions with inversion of the stereogenic center at the anomeric position through a S_N2-like displacement *via* an oxocarbenium ion-type transition state to form glycosylation product **1-8** (**Scheme 1-4-a**); the retaining GTs catalyze the glycosylation reactions with total retention of stereogenic center at anomeric position *via* an acyl-glycoside intermediate to form glycosylation product **1-9** (**Scheme 1-4-b**).[7, 9]

Scheme 1-4. General pathways for enzymatic glycosylation reactions



ROH: accepter group;
R': a nucleoside or nucleoside monophosphate or lipid phosphate or phosphate;
M^{2+}: Mn^{2+} or Mg^{2+}.

The enzymatic and chemoenzymatic synthesis of carbohydrates are very efficient and selective in oligosaccharides and glycoconjugates assembly. There are no PG manipulations and enzymatic glycosylation is specific and in aqueous solution under mild temperature. In mammals, most GTs are Leloir type, where nine basic nucleotide-phosphate monosaccharide glycosyl donors are utilized as building blocks for the stepwise synthesis of oligosaccharides. GTs remain to be the most reliable and the only efficient way to build challenging glycosidic linkages.[10] However, the use of GTs in the synthesis of carbohydrates is still limited by its commercial availability and sometimes solubility. Although several improvements have been made in enzymatic and chemoenzymatic synthesis of carbohydrates, chemical synthesis is often necessary for the preparation of non-naturally occurring carbohydrates and their analogues.

The number of applications of chiral axillaries and chiral catalysts in organic reactions has been growing rapidly. Small organic molecules could often achieve the same chemical transformations as good and specific as enzymes and other large organic molecules. In the past twenty years, several bio-mimetic chiral reagents have been developed for the glycosylation and

modification of carbohydrates with high efficiency and selectivity. In this review, we will summarize some of the most recent examples in this area, with a focus on their mechanisms.

1.2 Chiral Reagents in Glycosylation Reactions

1.2.1 Chiral Auxiliaries in Glycosylation Reactions

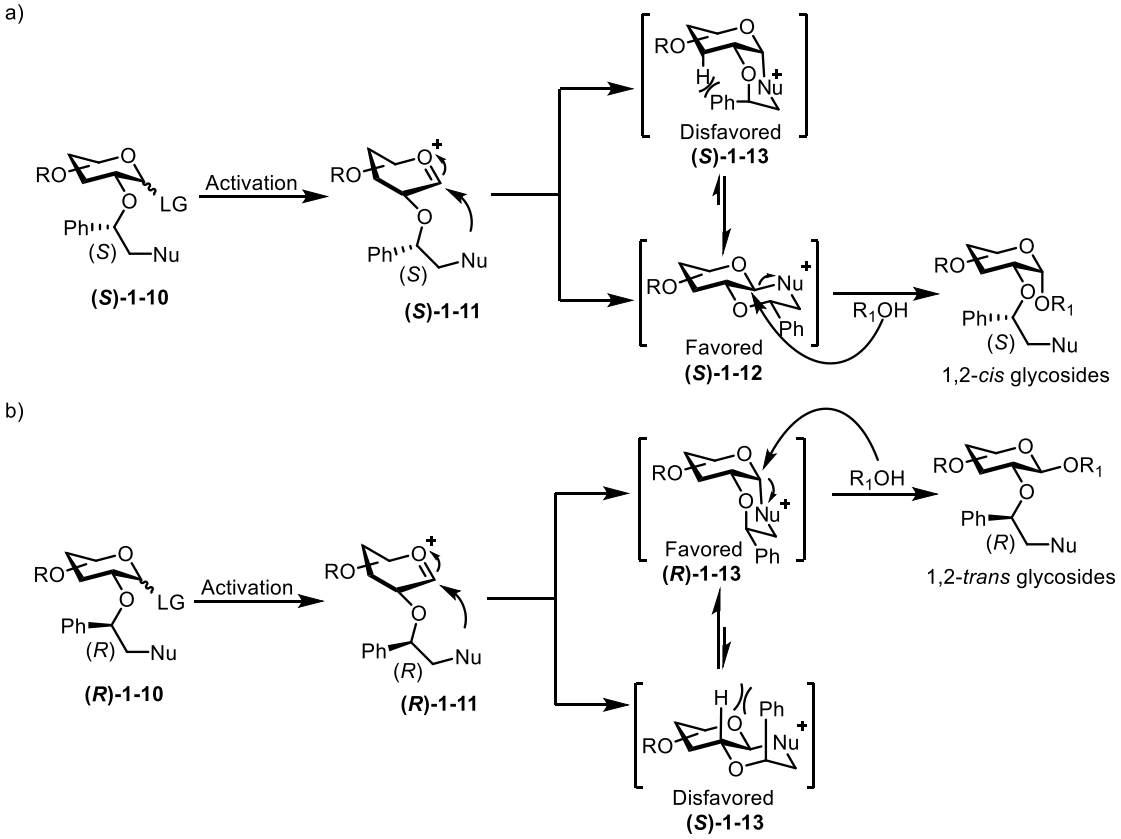
Chiral auxiliaries are a group of stereo-defined units that are temporarily installed into the substrate of organic reactions.[11] The presence of chiral auxiliary can bias the stereoselectivity of specific chemical transformations and therefore, influence the stereo-outcome of the reactions. After the reaction, the auxiliary can often be removed and recycled.

Carbohydrate chemists also designed many elegant chiral auxiliaries to improve stereoselectivity of glycosylation reactions.[12]

1.2.1.1 Chiral Auxiliaries at the C-2 Position of Carbohydrates

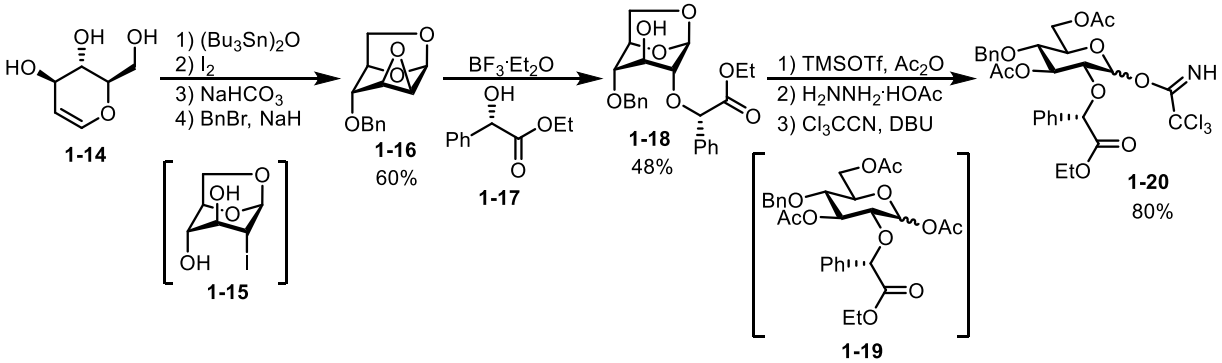
In 2005, Boons' group first reported a stereoselective glycosylation reaction by attaching chiral auxiliaries to the C-2 position of carbohydrates.[13] They proposed that a chiral auxiliary such as (*S*)- and (*R*)-mandelate derivatives at the C-2 position of glycosyl donors **1-10** could potentially influence the selectivity of glycosylation reactions. Upon activation of **1-10** to form oxocarbenium ion **1-11**, the (*S*)-**1-11** is favored to form the *trans*-decalin intermediate (*S*)-**1-12** to avoid the steric clash between the phenyl group on the chiral auxiliary and hydrogen on the C-3 as shown in (*S*)-**1-13**. The accepter will then attack intermediate (*S*)-**1-12** from the bottom to form 1,2-*cis* glycoside (**Scheme 1-5-a**). As for (*R*)-**1-11**, the *cis*-decalin intermediate (*R*)-**1-13** should be favored over the *trans*-decalin intermediate (*S*)-**1-13** to avoid the 1,3-diaxial steric clash and therefore 1,2-*trans* glycoside will be the product (**Scheme 1-5-b**). Since the 1,2-*trans* glycosides can be easily prepared by neighboring group participation, they focused their studies on the formation of the more challenging 1,2-*cis* glycosides.

Scheme 1-5. Boons' proposal of using chiral auxiliaries at the C-2 position to form 1,2-*cis* glycosides and 1,2-*trans* glycosides



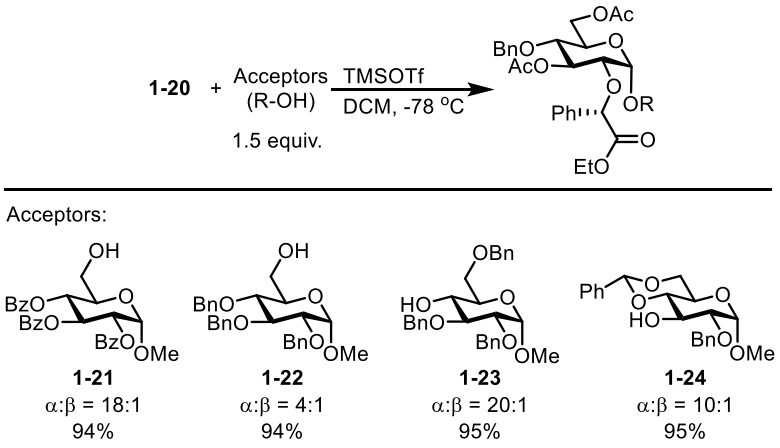
The first-generation[13] glycosyl donor **1-20** with a chiral auxiliary was synthesized from commercially available glucal **1-14** in 8 steps (**Scheme 1-6**). Intermediate **1-16** could be prepared in a four-step sequence *via* **1-15** following a known procedure in good yields.[14] This intermediate **1-16** was then treated with commercially available ethyl (*S*)-mandelate **1-17** and $BF_3{\cdot}Et_2O$ to form **1-18** in 48% yield. Glycosyl donor **1-20** could be obtained in great yield from **1-18** after 3 steps *via* intermediate **1-19**.

Scheme 1-6. Boons' synthesis of the first-generation of chiral auxiliary donor **1-20**



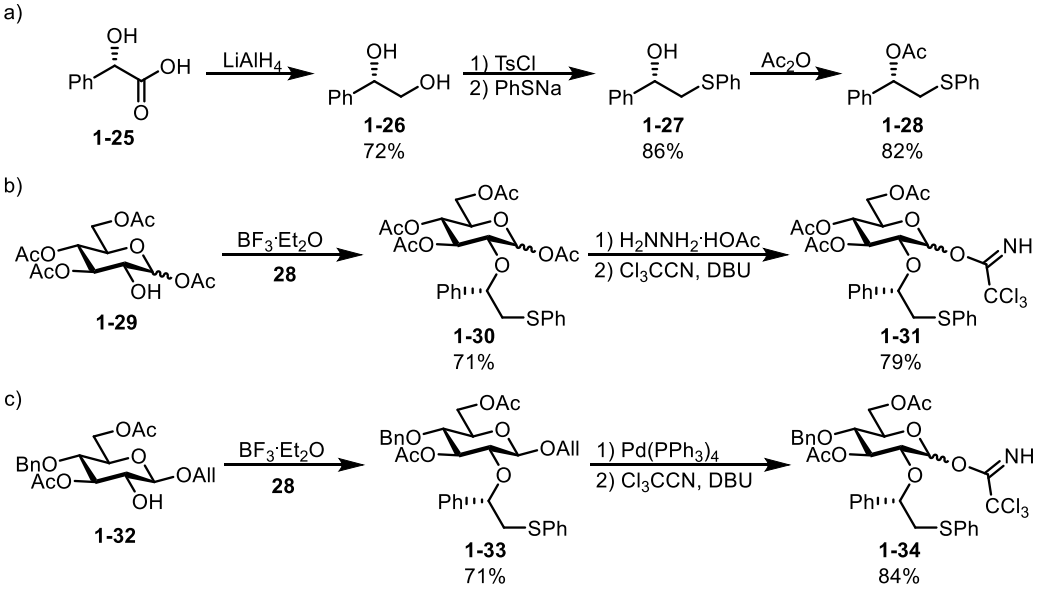
Glycosyl donor **1-20** was coupled with different glycosyl acceptors by using catalytic amount of TMSOTf in DCM at -78 ^{o}C (**Scheme 1-7**). As expected, the 1,2-*cis* disaccharides could be formed in moderate to great α-selectivity with high efficiency. These results indicated that the chiral auxiliary in the glycosyl donor didn't interfere the reaction and the donor was still very reactive. Clearly, the α-selectivity was depended on the different electronic and/or steric properties of the acceptors. The lower α-selectivity in certain cases was due to the direct glycosylation of oxocarbenium ion intermediate (*S*)-**1-11** before the participation of chiral moiety.

Scheme 1-7. Stereoselectivity of first-generation of chiral auxiliary donor **1-20** with different acceptors



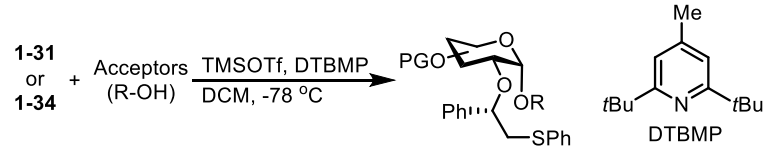
It was rationalized that the rate of participation of ethoxycarbonyl moiety in the first-generation chiral auxiliary was slower. A second-generation chiral auxiliary with a stronger nucleophilic moiety was then developed.[15] Similar to the first-generation, the chiral auxiliary was also derived from commercially available (*S*)-mandelic acid **1-25**. Chiral auxiliary moiety **1-28** could be synthesized from **1-25** in 4 steps (**Scheme 1-8-a**). After the installation of **1-28** at C-2, glycosyl donors **1-31** and **1-34** could be formed in good yields from **1-29** and **1-32** through a three-step sequence, respectively (**Scheme 1-8-b and c**).

Scheme 1-8. Boons' synthesis of the second-generation of chiral auxiliary donors **1-31** and **1-34**



Glycosyl donors **1-31** and **1-34** were treated with different acceptors under the standard condition, respectively (**Scheme 1-9**). Perfect α-selectivity was observed in all cases, indicating that the reaction went through the proposed intermediate (*S*)-**1-12** and the nucleophilicity of chiral auxiliary indeed played an important role in the formation of (*S*)-**1-12**. The addition of a steric bulkier base such as 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) is important in getting higher yields of disaccharide products. Later, they discovered that the electron-withdrawing protecting group at C-3 is crucial in gaining the perfect α -selectivity.[16] This second-generation chiral auxiliary donors have also been applied to the solid phase synthesis of several oligosaccharides with 1,2-*cis* linkages.[17] The second-generation chiral auxiliary could also be applied to the synthesis of β-mannosides.[18] When the chiral auxiliary was installed at C-6 position, the synthesis of α-2-deoxyglycosides was also realized.[19]

Scheme 1-9. Stereoselectivity of second-generation of chiral auxiliary donors **1-31** and **1-34** with different acceptors

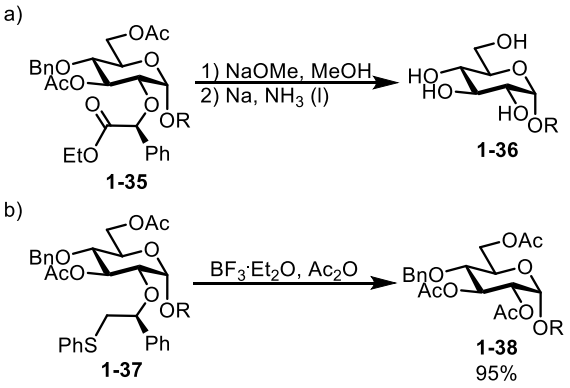


Acceptors:	**1-21**	**1-22**	**1-23**
	α only from **1-31**: 88% from **1-34**: 83%	α only from **1-31**: 90% from **1-34**: 95%	α only from **1-31**: 83% from **1-34**: 85%

For the synthesis of carbohydrates and glycoconjugates, the removal of chiral auxiliaries is as important as making the

glycosidic linkages. It was demonstrated that **1-35** bearing a first-generation chiral auxiliary could be deprotected by saponification to remove acetyl protecting groups and Birch reduction to remove the benzyl protecting group and chiral auxiliary to afford **1-36** (**Scheme 1-10-a**).[13] As for the second-generation chiral auxiliary, it could be selectively transformed to acetyl group in the presence of many other protecting groups by simply treating oligosaccharides of interest, such as **1-37**, with $BF_3{\cdot}Et_2O$ and acetic anhydride to form **1-38** *via* the formation of episulfonium ion (**Scheme 1-10-b**).[17]

Scheme 1-10. Removal of Boon's first- and second-generation chiral auxiliaries

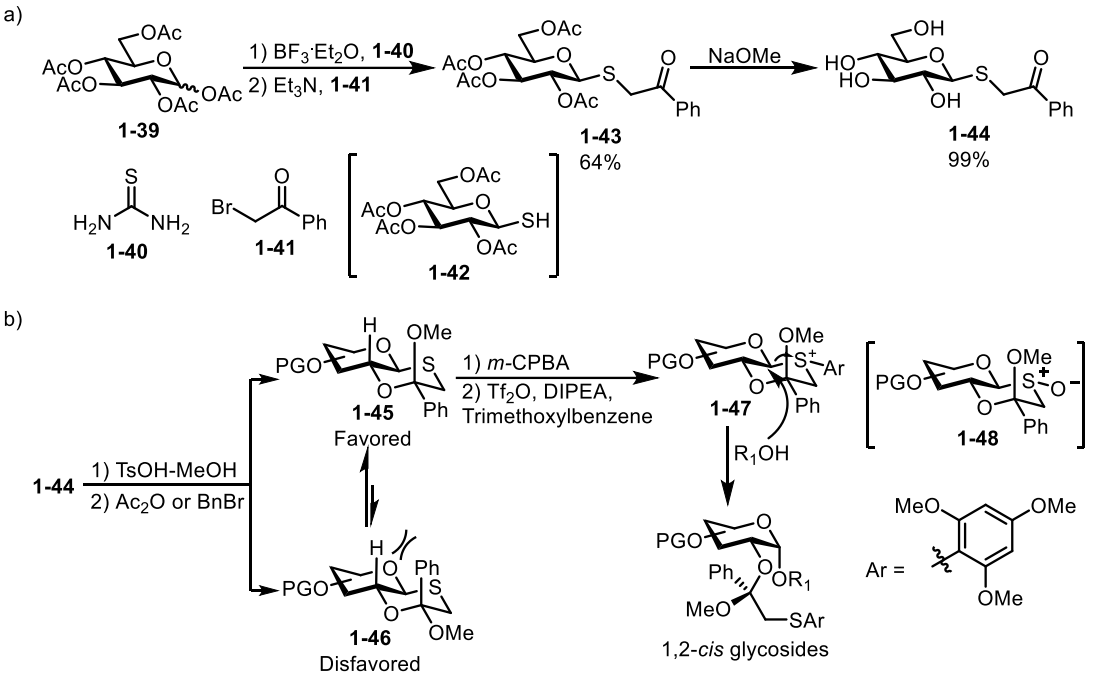


1.2.1.2 Conformationally Induced Chiral Auxiliaries

Although perfect 1,2-*cis* selectivity could be obtained by using Boon's chiral auxiliary donors, the synthesis of those donors, such as **1-31** and **1-34**, and chiral auxiliary **1-28**, requires significant efforts.

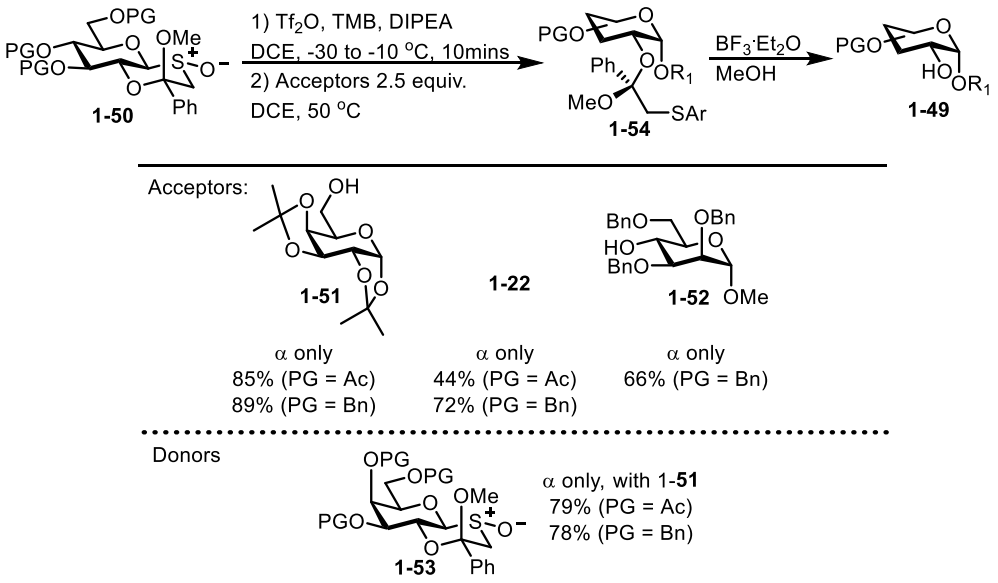
In 2009, Turnbull and coworkers reported an elegant example,[20] where the key oxathiane glycosyl donor precursor **1-44** was prepared from commercially available material **1-39** in 3 steps in good overall yield (**Scheme 1-11-a**). After the cyclization and acetylation to form the glycosyl donor **1-45** from **1-44**, the oxathiane ring became chiral and served as chiral auxiliary in the glycosylation reaction. Conformationally, the glycosyl donor **1-45** with a *trans*-decalin configuration was favored because it avoided the 1,3-diaxial repulsion between H and the bigger Ph group as shown in intermediate **1-46**. Oxidation of sulfide **1-45** to sulfoxide **1-48** and then followed by the activation of sulfoxide donor using electrophilic aromatic substitution with 1,3,5-*tri*-methoxybenzene (TMB) could give intermediate **1-47**. It could couple with different glycosyl accepters to give the 1,2-*cis* glycoside as product (**Scheme 1-11-b**).

Scheme 1-11. Turnbull's synthesis of glycosyl donor precursor **1-44** and his proposal of forming 1,2-*cis* glycosides



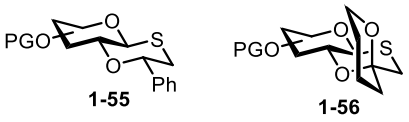
They also demonstrated that various of 1,2-*cis* glycosides could be prepared with perfect α-selectivity. After the reaction, chiral auxiliary could be easily removed by adding $BF_3{\cdot}Et_2O$ and methanol during the work up to form disaccharide products **1-49** (**Scheme 1-12**). The biggest drawback for this approach is the stability of acyclic ketal **1-54**. It was found that when disarmed (PG = Ac) donors were used, **1-54** would loss the methoxy group and undergo decomposition under the glycosylation conditions. The methoxy group can also act as acceptor and intercept intermediate **1-47** to give methyl-glycoside by-product, resulting in a lower yield of glycosylation reaction.

Scheme 1-12. Stereoselectivity of Turnbull's chiral auxiliary glycosyl donors **1-50** and **1-53** with different acceptors



To avoid the formation of by-product and improve the efficiency of the glycosylation reaction, Turnbull's group developed glycosyl donors **1-55**[21] and **1-56**[22] in order to form a more stable auxiliary-protecting group at C-2 after the reaction (**Scheme 1-13**). However, lower α-selectivity was observed in both cases when compared to the original donor **1-45**. Boons and coworkers further examined the influences of protecting groups on the selectivity of this glycosylation reaction by using glycosyl donor **1-55**.[23] They found that, like the previous studies on their chiral auxiliaries, an electron withdrawing protecting group at C-3 is significant in obtaining high α-selectivity. By using different orthogonally protected donors **1-55**, they achieved a branched tetra-saccharide synthesis with good overall yield and great 1,2-*cis* selectivity.[23]

Scheme 1-13. Next-generations of chiral auxiliary donors **1-55** and **1-56** developed by Turnbull



1.2.2 Chiral Catalysts in Glycosylation

Inspired by how nature assembles glycans, carbohydrate chemists have long been aspiring to develop chiral small molecule catalysts that can achieve glycosylation reactions in similar fashions.

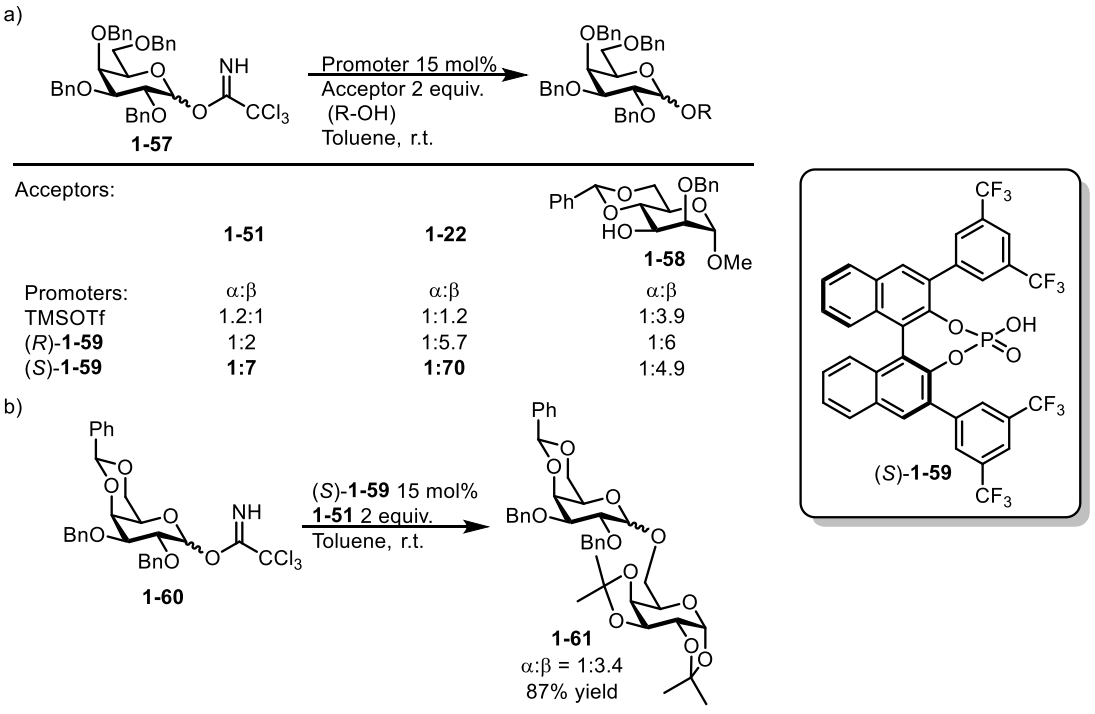
Since the pioneering work by Fairbanks,[24] over the past couple of years, many elegant examples have been reported by

using chiral catalysts in glycosylation reactions. Herein, we categorize those examples by the types of glycosyl donors that were used in the glycosylation reactions.

1.2.2.1 Glycosyl Trichloroacetimidates as Donors

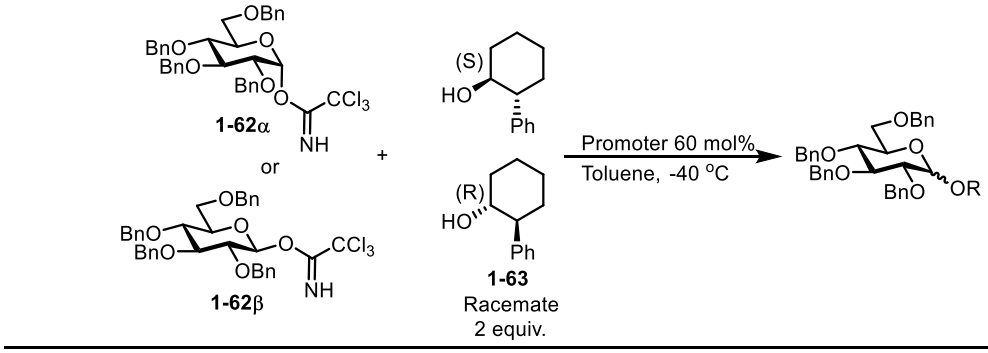
In 2010, Fairbanks and coworkers first reported that the stereo-outcome of glycosylation reactions can be influenced by the choice of chiral Brønsted acids.[24] In their report, galactosyl trichloroacetimidates donor **1-57** was coupled with different acceptors (**Scheme 1-14-a**). In the presence of TMSOTf, there was no obvious stereoselectivity preference for primary alcohol acceptors **1-51** and **1-22**, while the intrinsic preference for secondary alcohol acceptor **1-58** was the formation of β-galactoside product. Little differences were observed when (*R*)-**1-59** was used as promoter. However, by using (*S*)-**1-59** as promoter, good to great β-selectivity (or 1,2-*trans* selectivity) could be achieved for accepters **1-51** and **1-22**, respectively. While achiral phosphoric acid promoter such as $(PhO)_2P(O)OH$ was not effective in this transformation. As for secondary mannose-accepter **1-58**, no significant difference was observed between promoters TMSOTf, (*R*)-**1-59** and (*S*)-**1-59**. Although they didn't study the influences of protecting groups on the stereoselectivity, this glycosylation reaction seemed to be protecting group dependent. Simply switching the protecting groups on C-4 and C-6 from benzyl to benzylidene and using **1-60** as donor, disaccharides **1-61** could be obtained in 87% yield, but with lower β-selectivity (**Scheme 1-14-b**).

Scheme 1-14. Fairbanks' examples of using chiral Brønsted acid (*S*)-**1-59** for β-selective glycosylation reactions



Toshima group, in 2013, studied the influences of different chiral secondary acceptors on the stereoselectivity of glycosylation reaction by using the same **1-59** chiral catalyst (**Scheme 1-15**).[25] They found when **1-62α** was used as glycosyl donor and coupled with racemic **1-63** by TMSOTf, (*R*)-**1-63** was intrinsically more reactive than (*S*)-**1-63**. The formation of β-linkage was slightly favored for (*R*)-**1-63**, while the α-linkage was preferred for (*S*)-**1-63**. This result demonstrated that there was an inherent stereo-preference between the donor **1-62α** and acceptor **1-63** in the reaction. By using (*S*)-**1-59** as promoter, it could enhance the intrinsic reactivity of **1-63** and improve the stereoselectivity of the glycosylation reaction, making (β,*R*)-**1-64** the only glycosylation product. The use of (*R*)-**1-59** as promoter gave no obvious changes compared to TMSOTf. When **1-62β** was used as glycosyl donor and promoted by (*S*)-**1-59**, although the reaction became α-selective, multiple products could be obtained.

Scheme 1-15. Toshima's discoveries of chiral recognition between donor and accepter

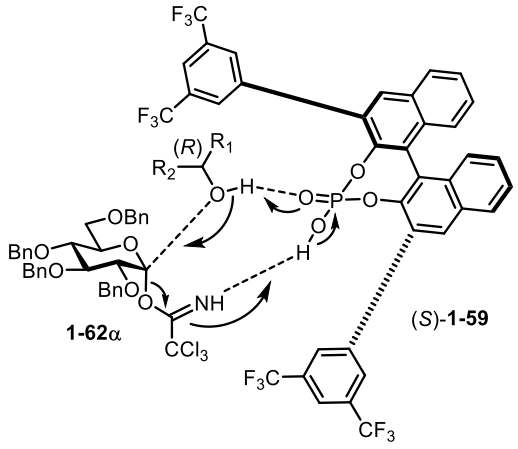


Yields of	(α,*R*)-**1-64**	(α,*S*)-**1-64**	(β,*R*)-**1-64**	(β,*S*)-**1-64**
TMSOTf with **1-62α**	13	17	**37**	7
(*R*)-**1-59** with **1-62α**	8	5	**31**	13
(*S*)-**1-59** with **1-62α**	0	0	**85**	0
(*S*)-**1-59** with **1-62β**	**32**	22	21	0

Based on their mechanistic studies, the authors believed that both α/β-stereoselectivity of the glycosylation reaction and (*R*)/(*S*)-diastereoselectivity of the accepter were under kinetic control and the reaction went through a concerted S_N2 process. A plausible mechanism was proposed (**Scheme 1-16**). Chiral Brønsted acid catalyst (*S*)-**1-59** activated both trichloroacetimidate leaving group on donor **1-62α** and the accepters and promoted the coupling through a S_N2 reaction. As for the chiral secondary accepters, they suggested that the (*R*)/(*S*)-diastereoselectivity was originated from the higher stability of **1-62α**/(*S*)-**1-59**/(*R*)-**1-**

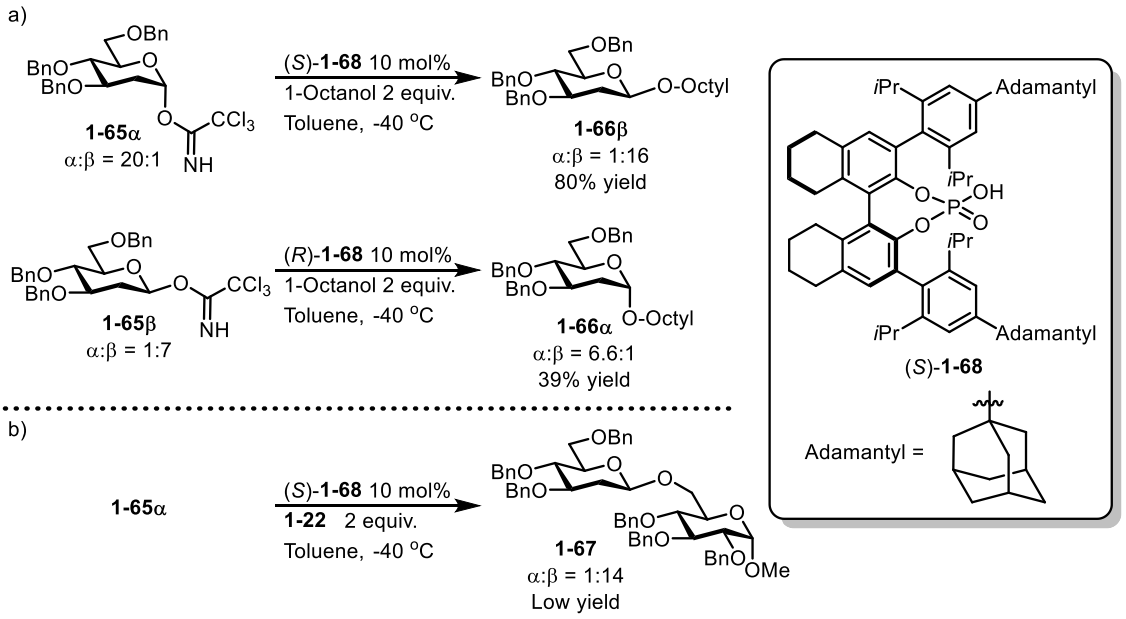
63 intermediate when compared to **1-62α**/(*S*)-**1-59**/(*S*)-**1-63** intermediate.[25]

Scheme 1-16. Glycosylation mechanism proposed by Toshima and coworkers



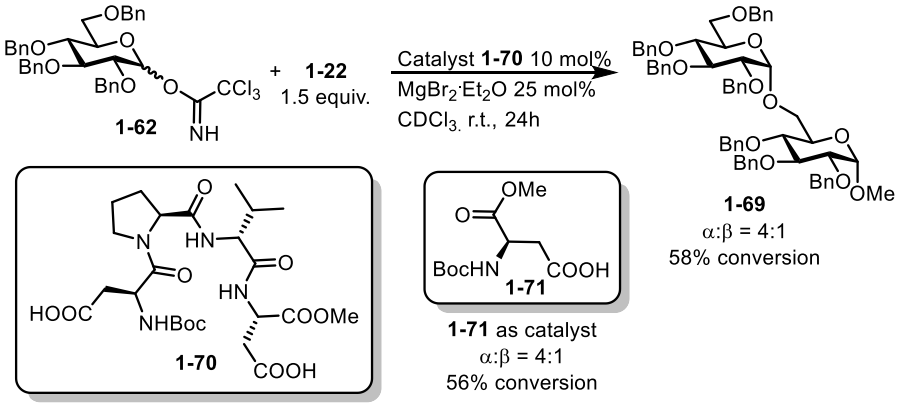
Bennett and coworkers later discovered that the similar chiral Brønsted acid catalyst could be used in the selective formation of the challenging β-2-deoxyl-glycosyl linkages (**Scheme 1-17-a**).[26] They found that by using (*S*)-**1-68** as catalyst, glycosyl donor **1-65α** could couple with 1-octanol to form **1-66β** as product in 80% yield with great selectivity. When **1-65β** was used as donor, **1-66α** could be obtained with great selectivity but in lower yield in the presence of chiral catalyst (*R*)-**1-68** and 1-octanol. Although the selectivity was great for **1-65β** with (*R*)-**1-68** catalyst, **1-65β** couldn't be isolated in pure form since it was not stable and quickly became the more stable **1-65α** isomer. They believed that this reaction proceeded through a S_N2 mechanism. Unfortunately, when glucose based primary alcohol accepter **1-22** was used, **1-67** was only obtained in low yield despite high β-selectivity (**Scheme 1-17-b**).

Scheme 1-17. Bennett's synthesis of 2-deoxyl-glycosides by using chiral **1-68** catalyst



In 2013, Miller lab, based on their previous studies on glycosylation[27] and inspired by the retention mechanism in enzymatic glycosylation process[9], found that aspartic acid derivative **1-71** or a synthetic tetrapeptide **1-70** could catalyze the glycosylation with $MgBr_2$ salt as co-catalyst to obtain **1-69** with moderate α-selectivity (**Scheme 1-18**).[28] It is worth to mention that when using **1-62** as the donor, $MgBr_2$ salt, **1-70** or **1-71** alone can't achieve a satisfactory conversion as catalyst. This example shows that there is a great potential of using synthetic peptides to control the selectivity of glycosylation reactions in a bio-mimetic manner.

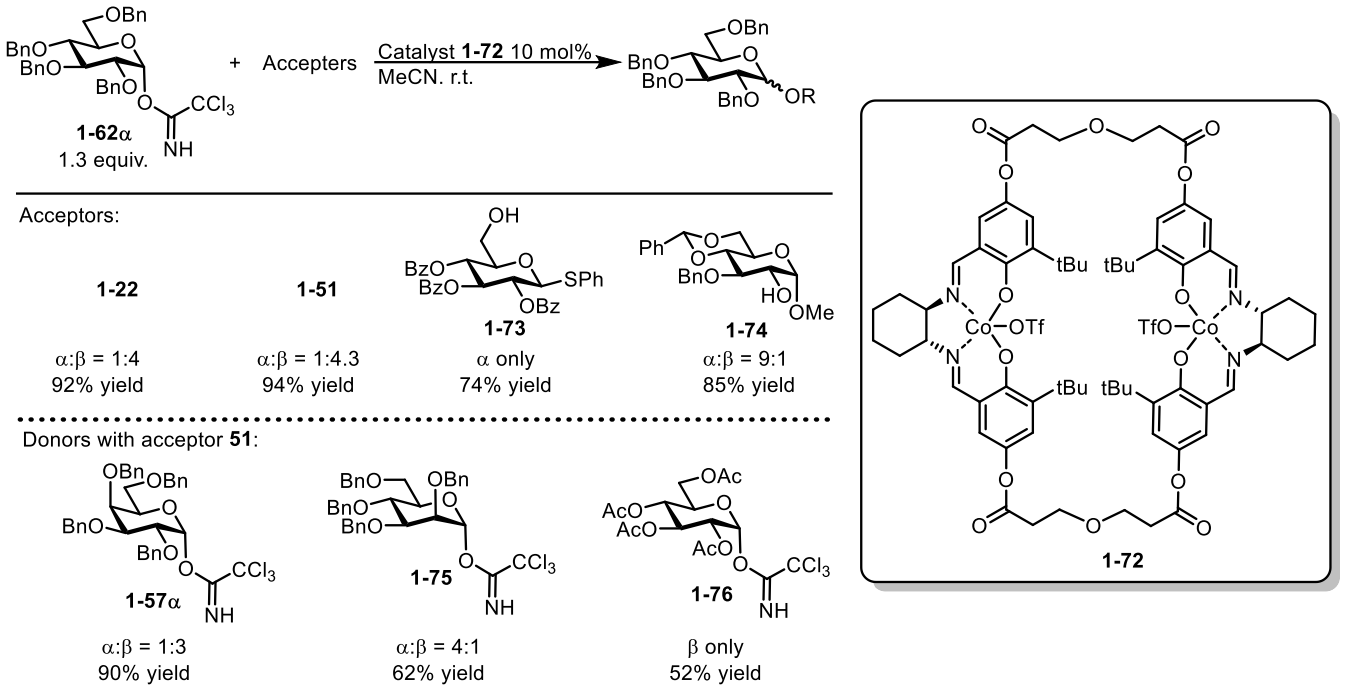
Scheme 1-18. Miller's application of using peptides to catalyze selective glycosylation reactions



Galan and coworkers in 2015 reported that a C_2 symmetrical dimeric-salen-Co catalyst **1-72** could act as chiral catalyst when

1-62α was used as glycosyl donor and coupled with different acceptors (**Scheme 1-19**).[29] The disaccharide products could be prepared in good yields with moderate to great selectivity. They found that both the chemical properties such as stereo- and electronical properties of acceptors and *C*$_2$ symmetry of **1-72** catalyst were essential in getting satisfactory α and β selectivity in this reaction. When donor **1-76** with a participating acetyl group at C-2 was used, the reaction was β-selective, suggesting the participation of the neighboring group.

Scheme 1-19. Galan's selective glycosylation using chiral catalyst **1-72**

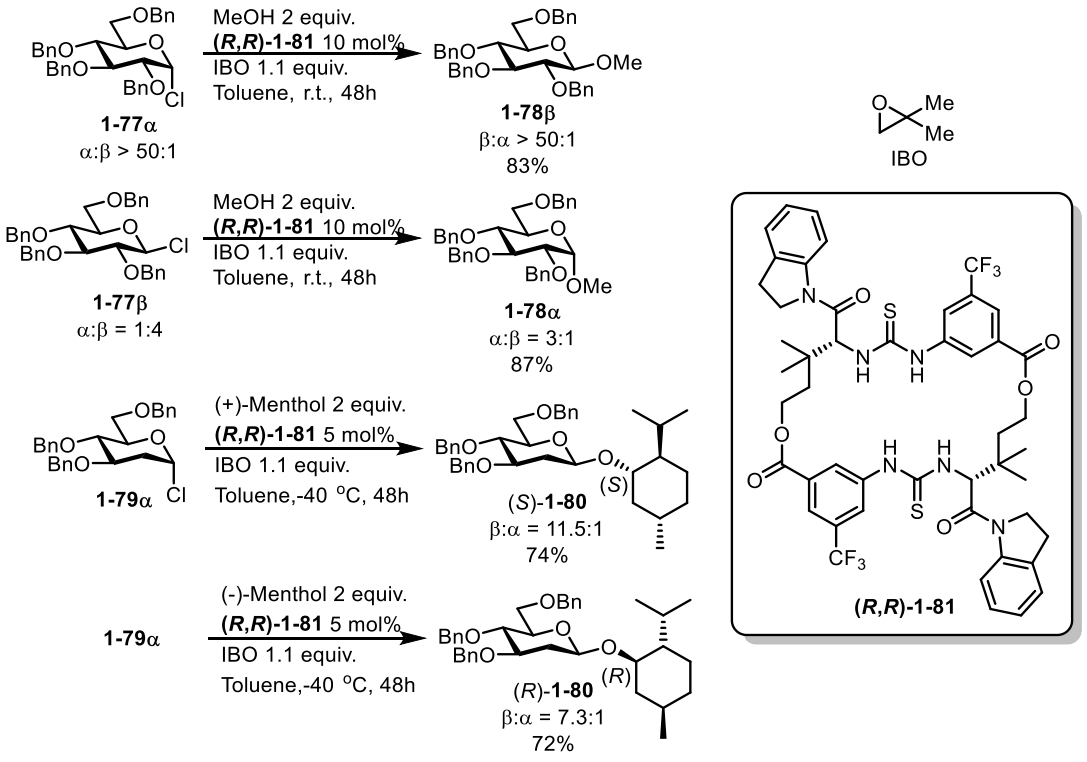


1.2.2.2 Glycosyl Chlorides as Donors

Early in 2017, Jacobsen's group, based on their previous studies[30], developed a stereoselective glycosylation reaction using glycosyl chloride donors and a *C*$_2$ symmetric macrocyclic bisthiourea chiral catalyst (*R*,*R*)-**1-81**.[31] In their report, the stereo-outcome of this reaction was totally dependent on the α- or β-configuration of glycosyl chloride donors (**Scheme 1-20**). They proposed that this transformation was *via* S$_N$2 process. When donor **1-77α** was coupled with methanol, **1-78β** could be formed in 83% yield with great selectivity. When β-enriched glycosyl chloride **1-77β** was treated with same nucleophile under the same condition, **1-78α** could be obtained as the major product. The β-glycosyl chloride can't be isolated in pure isomeric form. Although this method itself is highly selective, it is difficult to prepare α-glycosidic linkages selectively. They also found the chiral recognition process between donors and accepters in their transformations. For example, when (+)- and (-)-menthol was

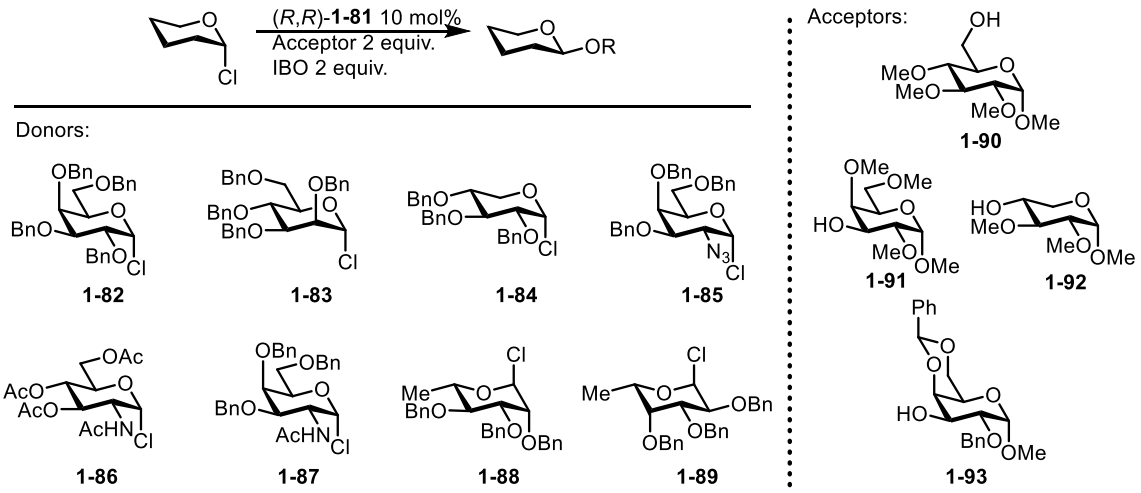
used as acceptor to react with **1-79α**, respectively, good β-selectivity could be obtained in both cases. But with (+)-menthol provided higher β-selectivity than (-)-menthol. Isobutylene oxide (IBO) was used as an electrophilic reagent to trap HCl by-product.

Scheme 1-20. Jacobsen's chiral bisthiourea catalyst **1-81** in glycosylation



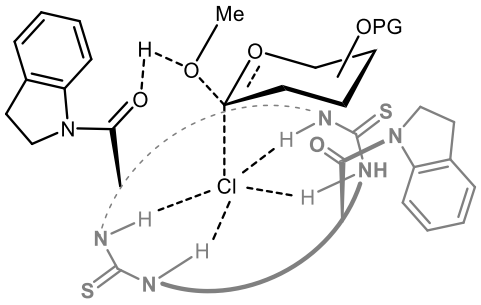
Unlike previous cases where the changes of different glycosyl donors and accepters will have significant impacts on α- and β-selectivity, this glycosylation reaction is predictable and always β-selective starting from α-glycosyl chlorides. Not only glucosyl donor **1-77α** and 2-deoxyglucosyl donor **1-79α** could be coupled with accepters listed below, different donors such as **1-82**, **1-83**, …, **1-89** could also be used to couple with different accepters such as **1-90**, **1-91**, **1-92** and **1-93** to afford disaccharide products in good yields with the β-selectivity ranging from 4:1 to greater 99:1 (**Scheme 1-21**). Among the acceptors, **1-92** is the mismatched secondary accepter and 59% yield with 6.7:1 β-selectivity were obtained when it was coupled with **1-82**.

Scheme 1-21. Substrates and acceptors scope for Jacobsen's β-selective glycosylation



They also measured the competitive secondary α-deuterium kinetic isotope effects (SDKIEs) at the anomeric position. For β-product, the value of SDKIE is greater than 1.2, while for the α-product, the SDKIE is smaller than 1.2 but greater than 1.[32] These results suggested that the formation of β-product was primarily *via* S_N2 mechanism and the α-product was more likely derived from oxocarbenium ion *via* S_N1 mechanism. A plausible working model was proposed based on experimental results and computed transition states (**Scheme 1-22**). The key interactions in the model involved the activation of alcohol nucleophile by a Lewis basic interaction with carbonyl oxygen of indoline amide moiety *via* hydrogen bonding and the activation of chloride leaving group on donors by bisthiourea moiety through hydrogen bonding.

Scheme 1-22. Proposed working model for Jacobsen's β-selective glycosylation

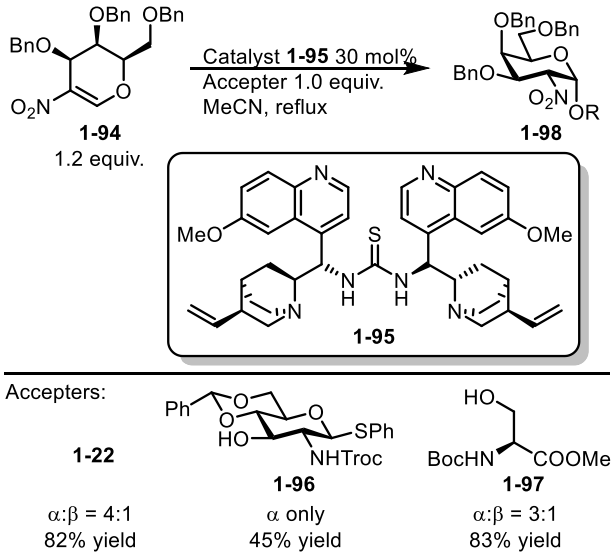


1.2.2.3 Glycals as Donors

About the same time, in 2016, Galan and coworkers, Yoshida, Takao and coworkers reported that a bifunctional chiral thiourea catalyst could promote the α-selective glycosylation to 2-nitroglycals. In Galan's report, 2-nitrogalactal **1-94** was used as glycosyl donor and coupled with different glycosyl acceptors in the presence of chiral catalyst **1-95** (**Scheme 1-23**).[33] For

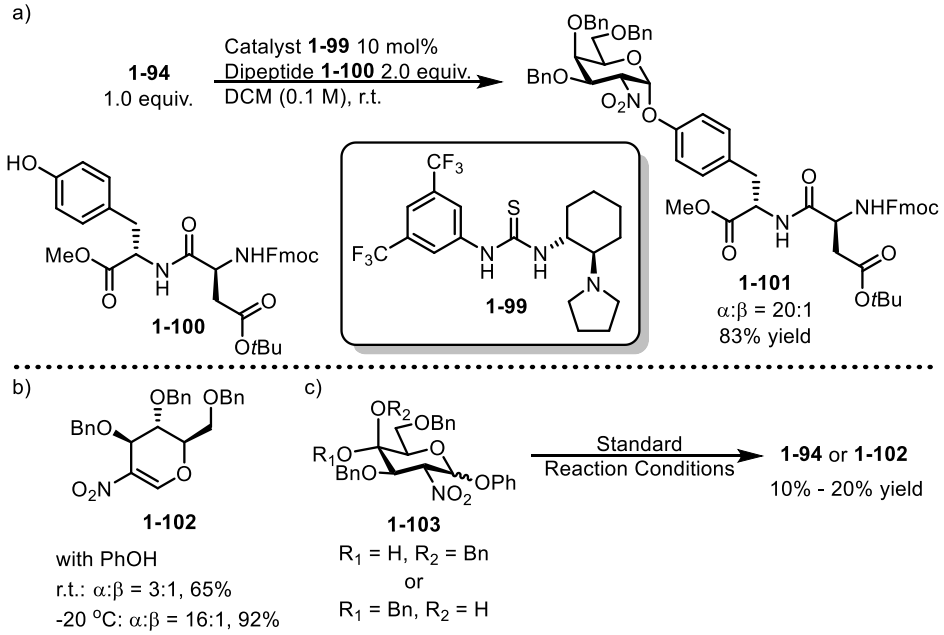
primary alcohol acceptors such as **1-22** and **1-97**, moderate α-selectivity could be obtained with good yields. While great α-selectivity could be achieved when secondary acceptor **96** was used, lower yield was observed. After the reduction of the nitro group at C-2, disaccharide products **1-98** could be converted to 1,2-*cis* galactosamine glycosides, which is generally challenging to synthesize.

Scheme 1-23. Galan's report of using chiral thiourea catalyst **1-95** for α-selective glycosylation



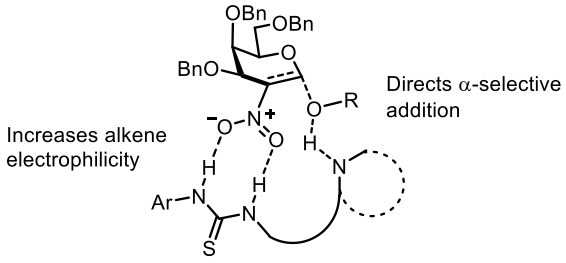
In Yoshida and Takao's report, 2-nitrogalactal **1-94** was coupled with different phenol derivatives, such as tyrosine containing dipeptide **1-100**, by using chiral catalyst **1-99**. Great α-selectivity could be obtained with good yield in most cases (**Scheme 1-24-a**).[34] Lower stereoselectivity (α:β = 2:1) was observed when the enantiomer of **1-99** was used as the catalyst. They also found that 2-nitroglucal **1-102** could be used as the donor in this reaction. Great α-selectivity of the corresponding product could be prepared at lower temperature in 92% yield (**Scheme 1-24-b**). However, the glycosylation products **1-103** from **1-94** and **1-102** could undergo elimination to form the glycal substrates **1-94** or **1-102** in 10-20% yield (**Scheme 1-24-c**).

Scheme 1-24. Yoshida and Takao's α-selective glycosylation of using chiral catalyst **1-99**



A working model was proposed in both reports. The thiourea moiety could coordinate with nitro group through hydrogen bonding and therefore increase the electrophilicity of alkene. The amine moiety of the catalysts at the same time could activate the alcohol nucleophile and direct the α-selective addition to alkene to form α-glycoside products (**Scheme 1-25**).

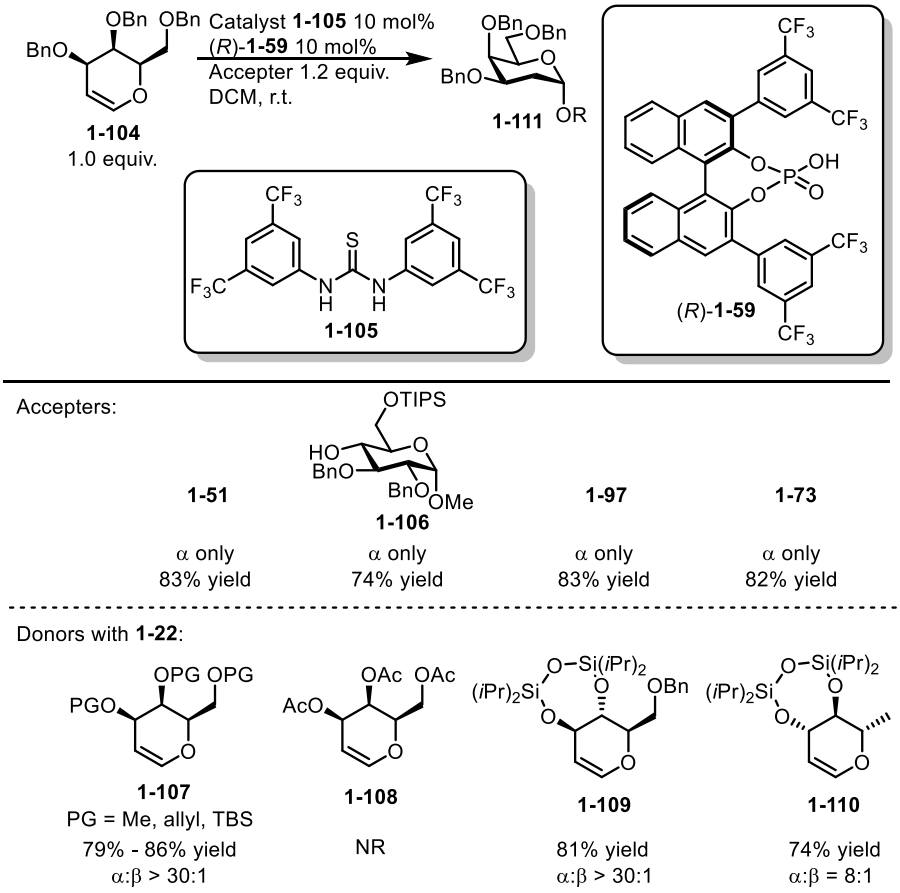
Scheme 1-25. Working model for bifunctional chiral thiourea catalyzed glycosylation reaction of glycals



In 2017, Galan group found that thiourea catalyst **1-105**, in combination with chiral Brønsted acid catalyst (*R*)-**1-59**, could cooperatively affect the stereo-outcome of glycosylation reaction (**Scheme 1-26**).[35] D-galactal donor **1-104** was coupled with different acceptors by using catalysts **1-105** and (*R*)-**1-59**, for primary alcohol acceptors such as **1-51**, **1-97** and **1-73**. Exclusive α-glycosides were obtained in great yields. For secondary acceptor **1-106**, the glycosylation was slower and when the reaction was conducted at 45 °C and α-glycoside product could be obtained in 74% yield. This reaction proceeded well with different protecting groups on galactal donor **1-107**, such as methyl, allyl and TBS groups. No reaction was observed when per-

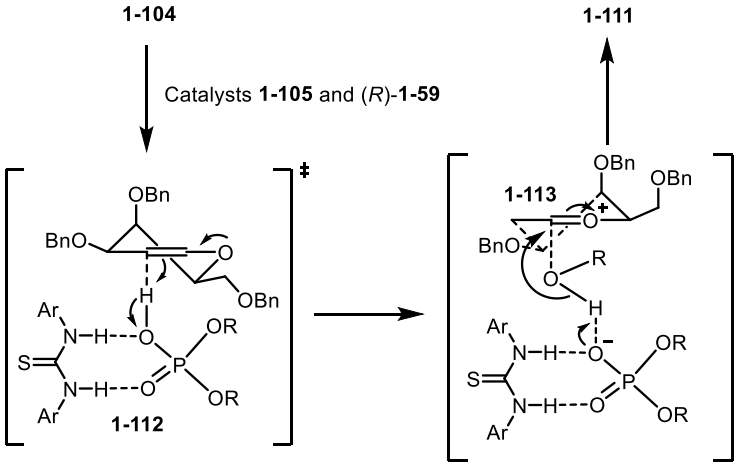
acetylated donor **1-108** was used. D-Glucal donor **1-109** and L-rhamnal donor **1-110** also worked well in this reaction with good selectivity. However, for these two donors, the 3,4-O-siloxane protecting group is necessary to avoid the Ferrier rearrangement byproduct.

Scheme 1-26. Galan's cooperative strategy for the synthesis of α-glycosides from glycals



They also found that no change in anomeric ratio was observed when they resubmitted an anomeric mixture of product **1-111** into the standard reaction conditions. This suggested that the formation of α-glycosides was not due to the self-isomerization to the more stable α-isomer. A plausible model was proposed in **Scheme 1-27**. Thiourea catalyst **1-105** could form hydrogen bonds with chiral catalyst (*R*)-**1-59** in complex **1-112**. Glycosyl donor **1-104** could be activated by complex **1-112** and this induced a proton addition to the alkene from the less hindered face to form oxocarbenium ion intermediate **1-113**. The phosphate anion could then activate and direct the accepter to react with **1-113** to afford product **1-111** in high stereoselectivity.

Scheme 1-27. Plausible working model proposed by Galan and coworkers



1.3 Chiral Catalysts in Regioselective Modifications of Carbohydrates

The chemical synthesis of oligosaccharides and glycoconjugates often requires regioselective manipulations of different hydroxy groups (OHs) of carbohydrates. The most established approaches are based on the steric or electronic differences in the intrinsic reactivity of different OHs.[36] Although these approaches are very effective, extensive synthetic efforts and careful separation of products are usually involved to selectively functionalize one OH in the presence of other OHs. Sometimes, it is impossible to do so because the reactivity differences between OHs are just too small.

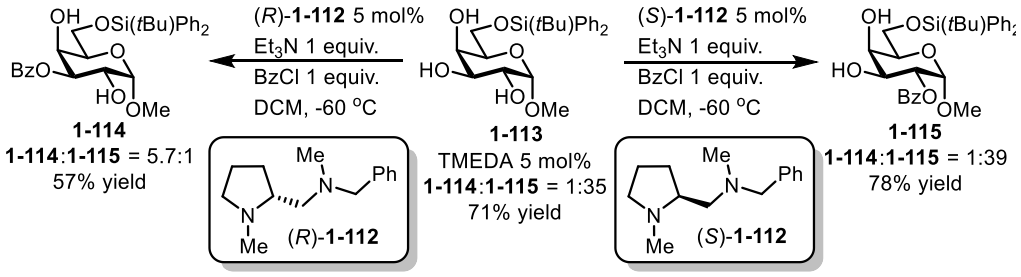
Given the fact that enzymatic carbohydrate synthesis displays a well-controlled regioselectivity stands on the substrate-enzyme recognition process, carbohydrate chemists in the last decades have developed several classes of chiral catalysts to mimic enzymatic transformations. The trivial reactivity differences of OHs can be recognized by these chiral catalysts and they could either enhance or override the intrinsic selectivity to make those products otherwise difficult to prepare.

1.3.1 Peptides and its Derivatives in Regioselective Modifications

In 2003, Vasella and coworkers first reported that proline-derived diamine catalysts (*R*)-**1-112** and (*S*)-**1-112**, originally developed by Oriyama's group for kinetic resolution of secondary alcohols and desymmetrization of *meso*-diols,[37] could be used in regioselective benzoylation for different mono- and di-protected monosaccharides.[38] They found that when substrate **1-113** was treated with Et_3N and BzCl, (*R*)-**1-112** catalyst gave 3-*O* benzoylated product **1-114** in good regioselectivity with 57% yield, while the (*S*)-**1-112** catalyst afforded 2-*O* benzoylated product **1-115** in great regioselectivity and yield. When tetramethylethylenediamine (TMEDA) was used as achiral catalyst, the intrinsic selectivity strongly favored **1-115** in this

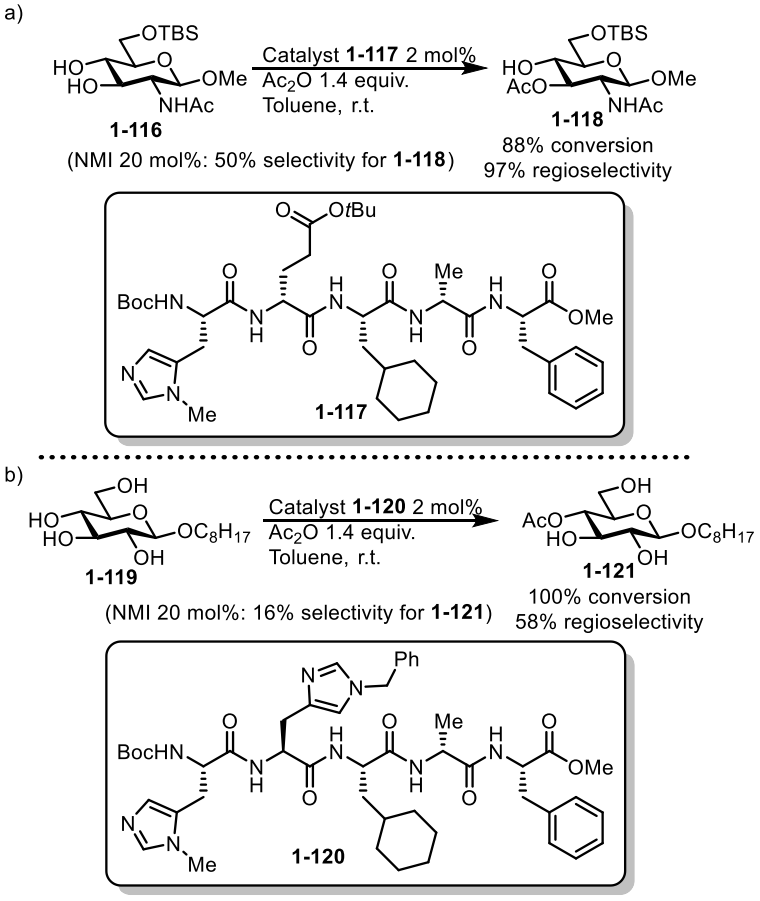
transformation. These results showed that (*S*)-**1-112** catalyst could enhance the intrinsic selectivity, while (*R*)-**1-112** catalyst could override it (**Scheme 1-28**). The authors suggested that the regioselectivity outcome of different monosaccharide substrates with different PGs patterns was depended on the structure of the OHs and intramolecular hydrogen bonding.

Scheme 1-28. Vasella's regioselective benzoylation by using proline-derived catalyst **1-112**



Later, Miller group, based on their previous studies on enantioselective acylation by using synthetic peptides[39], discovered that synthetic peptide catalysts **1-117** and **1-120** with modified histidine moieties on the side chain could be used to regioselectively acylate monosaccharide substrates.[40] For substrate **1-116**, 3-*O* could be acylated to afford product **1-118** in great yield with 97% regioselectivity (with 3% of 4-*O* acylated product) when catalyst **1-117** was used, while the intrinsic regioselectivity for **1-116** by using achiral N-methyl imidazole (NMI) catalyst was 50% for product **1-118** with 22% 4-*O* acylated product and 28% di-acylated product (**Scheme 1-29-a**). This result showed that peptide catalyst **1-117** could enhance the intrinsic selectivity for this substrate. When substrate **1-119** was used, 4-*O* acylated product **1-121** could be obtained as a major diastereomer with 58% of regioselectivity (other diastereomers are 2-*O* (9%), 3-*O* (11%) and 6-*O* (22%) mono-acylated products) by using catalyst **1-120** (**Scheme 1-29-b**). The intrinsic selectivity for substrate **1-119** was only 16% for product **1-121** (more reactive 6-*O* mono-acylated product is the major product with 64% of selectivity), indicating that the peptide catalyst **1-120** could override the intrinsic selectivity in this case. They also demonstrated that related synthetic peptide catalysts could be applied to regioselective Barton-McCombie deoxygenation reaction of carbohydrate substrates to form various deoxyglycosides.[41] They also applied this method to the modification carbohydrate moiety of natural products such as vancomycin.[42] The synthetic peptide catalysts have been applied to the phosphorylation of Inositols[43] and modification of other polyol nature products as well.[42]

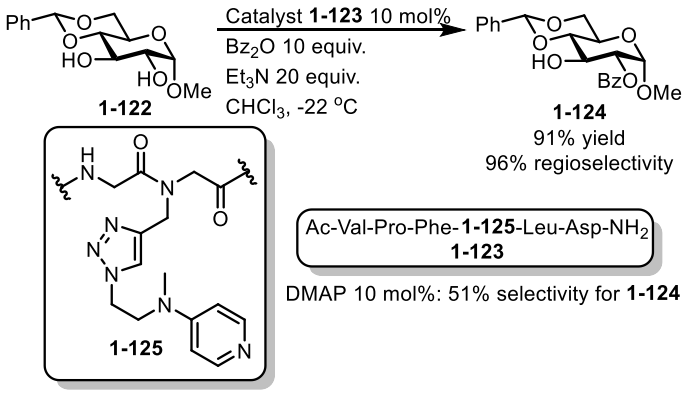
Scheme 1-29. Miller's regioselective acylation by using synthetic peptide catalysts



In 2016, Kirsch and coworkers reported an example where DMAP-based small molecular peptides could be synthesized by simply attaching DMAP into a side chain of peptide through click chemistry and used for regioselective benzoylation of carbohydrates.[44] A variety of peptide scaffolds could be synthesized from solid-phase peptide synthesis to form a library of DMAP-based small molecular peptides. After screening the library of catalysts, they found that substrate **1-122** could be selectively acylated at 2-*O* to form product **1-124** in 91% yield with 96% regioselectivity by using catalyst **1-123**. When DMAP was used as achiral catalyst, 51% of regioselectivity with 66% conversion was observed for product **1-124** with 18% of 3-*O* acylated product and 31% of di-acylated product. However, the peptide catalyst in this method is very substrate-specific. Different peptide catalysts must be screened for different monosaccharide substrates or even same monosaccharide with different protecting groups. The authors believed that in their DMAP-based peptide catalysts, the DMAP moiety was accountable for catalysis while the peptide chain influenced the regioselectivity of substrates. Early 2017, they discovered that better regioselectivity and easier purification process could be achieved when they attached the peptide catalysts on the solid

supports.[45]

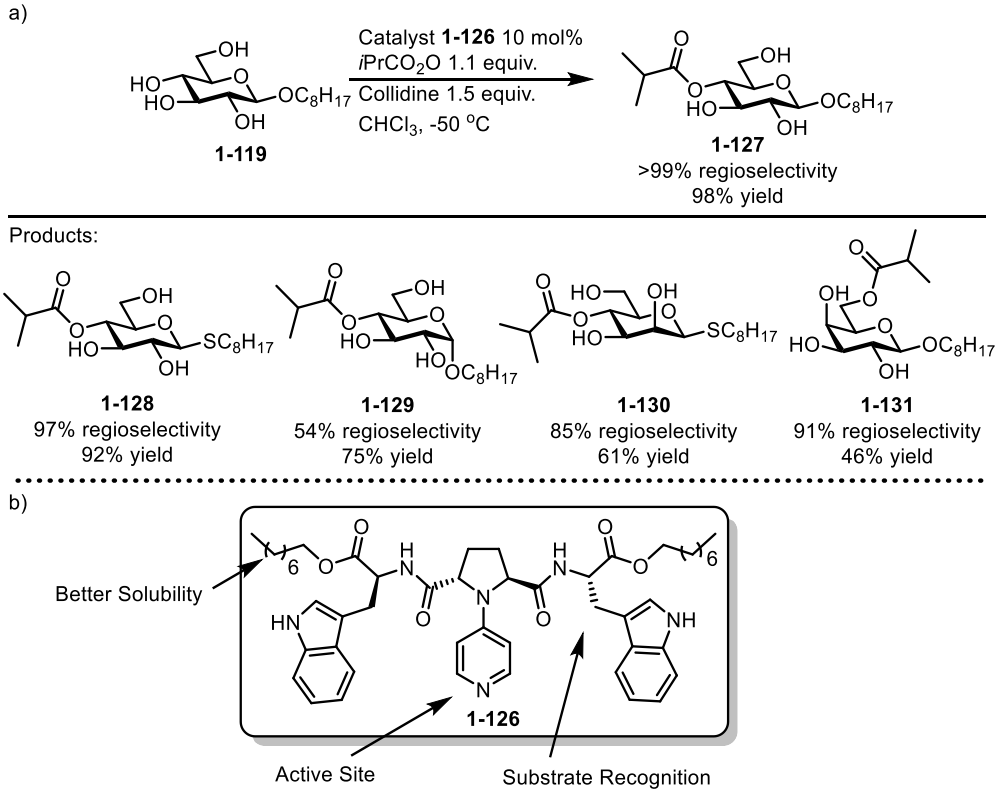
Scheme 1-30. Kirsch's regioselective acylation by using DMAP-based small molecular peptides



1.3.2 Chiral DMAP Derivatives in Regioselective Modifications

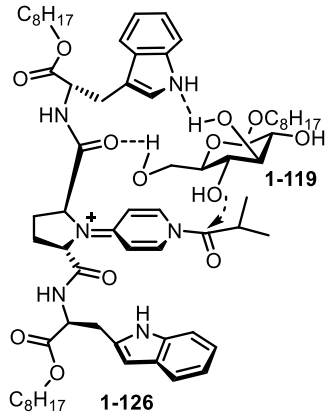
In 2007, Kawabata group reported that by using chiral 4-pyrrolidinopyridine (PPY) catalyst[46] **1-126**, octyl-β-D-glucopyranoside **1-119** could be acylated regioselectively at 4-*O* to form mono-acylated product **1-127** (**Scheme 1-31-a**).[47] Because tryptophan moieties are highly preserved in the recognition site of the family of β-glucosidase, they decided to install tryptophan to their catalyst as a functional side chain for the carbohydrate substrates recognition. In addition, octyl ester moiety was introduced to increase the solubility of the chiral catalyst in non-polar solvent, where the hydrogen bonding is stronger. They found the C_2-symmetry of catalyst **1-126** was essential in obtaining high regioselectivity. Under the standard condition, substrates **1-119**, **1-128** and **1-130** could all be selectively acylated at 4-*O* in good yields with high regioselectivity (>85%). Moderate 4-*O* selectivity (54%) was observed for substrate **1-129**. However, when **1-131** was used as substrate, the more reactive OH at C-6 was selectively acylated (**Scheme 1-31-a**). The authors believed that the equatorial orientation of OH at C-4 is significant in this selective acylation process.

Scheme 1-31. Kawabata's regioselective 4-*O* acylation by using chiral PPY catalyst **1-126**



Based on their experimental results, a working model for this transformation was proposed as shown in **Scheme 1-32**.[47] The key interactions for the substrate-catalyst recognition are the hydrogen bonding between 6-OH and carbonyl oxygen of the amide and the hydrogen bonding between 3-OH and indole nitrogen. According to this model, 4-OH has to be at equatorial position to be spatially closer to acylpyridinium moiety. They also suggested that lower regioselectivity for octyl-α-D-glucopyranoside **1-129** could be attributed to the unfavorable stereo-clash between α-octyloxy substituent and acylpyridinium moiety.

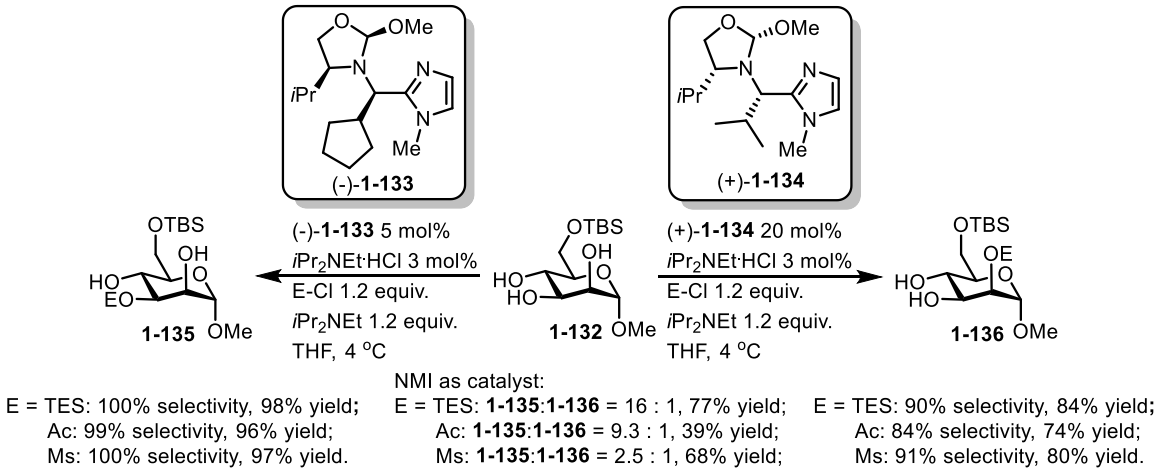
Scheme 1-32. Kawabata's proposed working model



1.3.3 Chiral Catalysts in Regioselective Modifications through Covalent Interactions

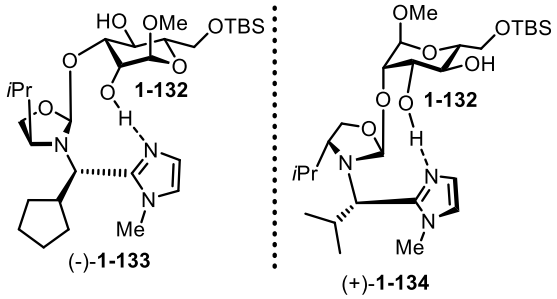
In 2013, based on their previous studies on the desymmetrization of *cis*-1,2-diols[48], Tan and coworkers reported an elegant example that the 1,2-*cis*-diol moiety in carbohydrates can be selectively functionalized by using different chiral imidazole-based catalysts (**Scheme 1-33**).[49] When substrate **1-132** was reacted with different electrophiles, (-)-**1-133** catalyst gave 3-*O* functionalized products **1-135** in great yield with greater than 99% regioselectivity. When (+)-**1-134** was used as the catalyst, 2-*O* functionalized products **1-138** could be obtained in good yield with high selectivity. The intrinsic selectivity in these reactions all favored product **1-135** using different electrophiles with achiral N-methyl imidazole (NMI) catalyst. They also demonstrated that other triols in carbohydrate substrates and 1,2-*cis*-diols in furanose substrate worked well under the standard condition. It is worth to mention that the catalysts were prepared in glove box and the reactions were also run in glove box due to the moisture sensitive nature of the catalysts and reactions.

Scheme 1-33. Tan's selective functionalization of 1,2-*cis*-diols by using chiral catalysts



Based on their experimental results, a plausible working model was proposed (**Scheme 1-34**). Firstly, a sterically matched OH was covalently attached onto the oxazolidine ring through transacetalation reaction and released a molecule of methanol. Due to the formation of the covalent bond, it makes the oxygen that attached to it chemically unreactive. The defined stereocenter on the catalyst made the imidazole moiety spatially closer to the OH *cis*- to the oxygen that bonded to the catalyst and activated the OH through hydrogen bonding. Final functionalized products could be released after trapping the activated OH with different electrophiles.

Scheme 1-34. Tan's model for selective functionalizations of 1,2-*cis*-diols

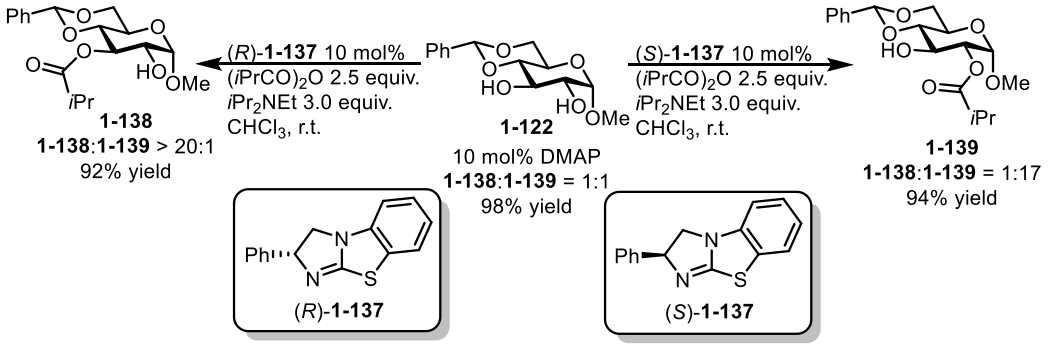


1.3.4 Chiral Catalysts in Regioselective and Siteselective Modifications through Cation-n Interactions

In 2017, Tang group, based on by their previous studies on acylations of anomeric hydroxy groups,[50] reported a chiral BTM catalysts directed regioselective acylation of 1,2-*tran*-diols (**Scheme 1-35**).[51] In their report, when **1-122** was subjected to

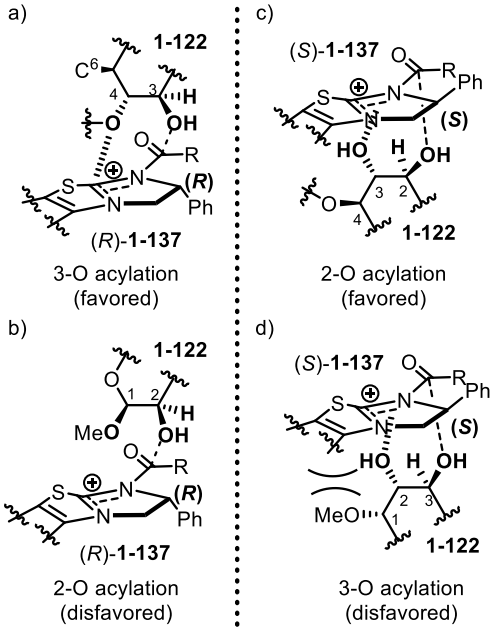
isobutyric anhydride, the (*R*)-**1-137** catalyst gave 3-*O* acylated product **1-138** in 92% yield with greater than 20:1 regioselectivity, while the (*S*)-**1-137** catalyst afforded 2-*O* acylated product **1-139** with great yield and selectivity. When DMAP was used as achiral catalyst, there was no selectivity for the formation of any of the two products. They also demonstrated that other 1,2-*tran*-diols in carbohydrates could be regioselectively acylated under the standard condition. In addition, the scope of the chiral catalyst-controlled acylation was further extended to site-selective acylation of several complex substrates, such as tetraol derived from trehalose and a diol where each hydroxyl group located in two different sugar unites in a disaccharide.

Scheme 1-35. Tang's regioselective acylation of *trans*-1,2-diols in carbohydrates



Based on experimental results and computational calculations, a plausible working model was proposed. The key interaction for substrate recognition is the cation-lone pair interaction between the acylated positively-charged BTM catalyst **1-137** and the lone pair on OR or OH group of the substrate. When substrate **1-122** was subjected to (*R*)-**1-137** catalyst, the 3-*O* acylated product was favored because the cation-lone pair interaction between 4-OR and catalyst was available and stronger, thus helped to recognize the substrate (**Scheme 1-36-a**). The cation-lone pair interaction between 1-OMe and (*R*)-**1-137** catalyst was not available due to the improper α orientation of OMe group (**Scheme 1-36-b**). When (*S*)-**1-137** catalyst was used, the 2-*O* acylated product was favored because the cation-lone pair interaction between 3-OH and catalyst was stronger (**Scheme 1-36-c**). Although the cation-lone pair interaction was also available between 2-OH and catalyst, this interaction was weakened by steric repulsion of between 1-OMe group and catalyst (**Scheme 1-36-d**). This model could also be used in predicting the regioselectivity of other carbohydrate 1,2-*trans*-diols and polyols.

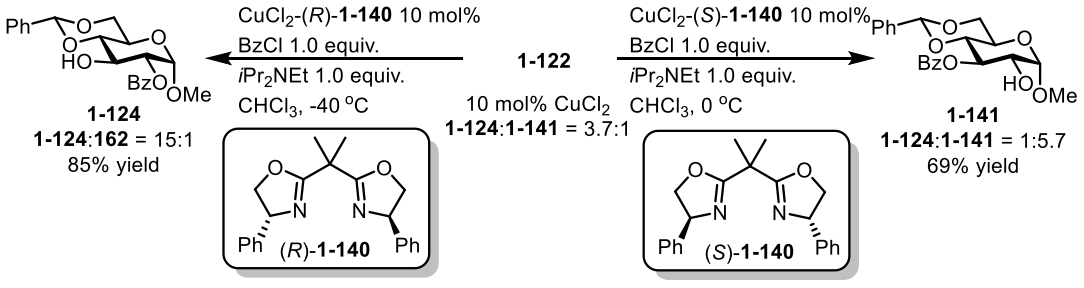
Scheme 1-36. Tang's proposed model for selective acylation of 1,2-*trans*-diols



1.3.5 Chiral Metal Complexes in Regioselective Modifications

Miller group in 2013 reported that chiral copper(II) complex could catalyze a regioselective benzoylation of various partially protected monosaccharides (**Scheme 1-37**).[52] When 10 mol% $CuCl_2$ was used with substrate **1-122** and BzCl, the intrinsic selectivity favors the formation of 2-*O* benzoylated product **1-124** over 3-*O* benzoylated product **1-141** in a 3.7:1 ratio. When chiral (*R*)-**1-140** ligand was added into the reaction, product **1-124** could be obtained in 85% yield with high regioselectivity. Product **1-141** could be prepared in good selectivity (5.7:1) and yield when (*S*)-**1-140** ligand was used. This method could also be applied to other 1,2-*trans*- and *cis*-diols coupled with different electrophiles with moderate to excellent regioselectivity.

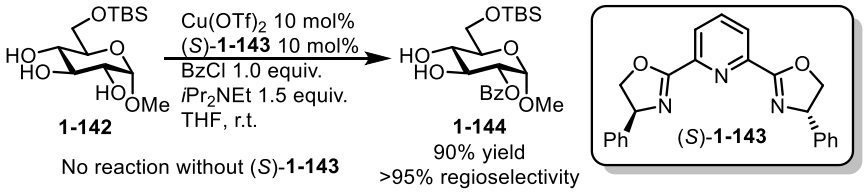
Scheme 1-37. Miller's application of chiral copper(II) complexes in benzoylation of diols in carbohydrates



Later, Dong and coworkers found the chiral copper(II) complex could also be applied to various triols in pyranoses and

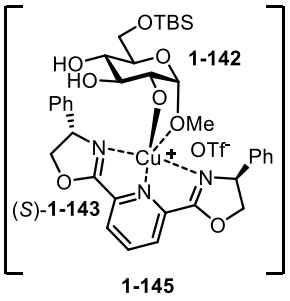
furanoses (**Scheme 1-38**).[53] In their studies, $Cu(OTf)_2$ catalyst alone without ligand was not effective. By adding chiral (*S*)-**1-143** ligand into the reaction, substrate **1-142** could be selectively benzoylated at 2-*O* and formed product **1-144** in 90% yield with greater than 95% regioselectivity. However, when (*R*)-**1-143** ligand was added, **1-144** remained as the major product with slightly lower regioselectivity (88%).

Scheme 1-38. Dong's chiral copper(II) complex in benzoylation of triols



A reaction mechanism was proposed in **Scheme 1-39**. Under the standard condition, chiral copper(II) complex could bind to 1,2-*cis*-dioxy moiety (1-OMe and 2-*O*) of the substrate **1-142** to form copper alkoxide intermediate **1-145**. The authors suggested that the nucleophilicity of 2-*O* was enhanced due to the binding with copper complex. **1-145** was then trapped by electrophile to give the final product. According to their kinetic studies, the nucleophilic addition to electrophile was the turnover limiting step in this transformation.

Scheme 1-39. Dong's proposed key intermediate for benzoylation of triols

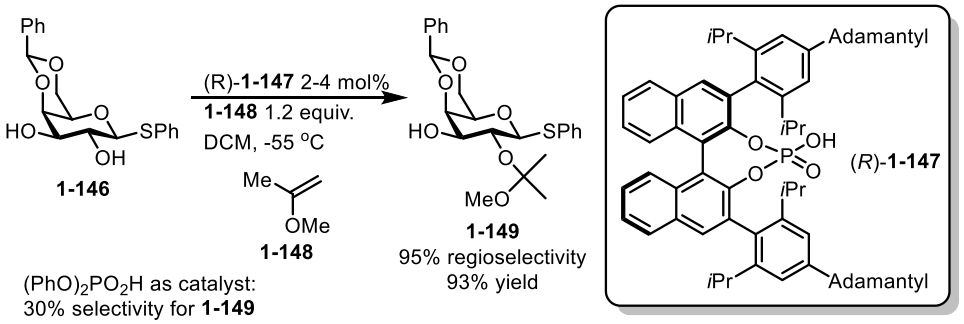


1.3.6 Chiral Brønsted Acids in Regioselective Modifications

Nargony's group in 2013 reported that chiral Brønsted acid derivatives could catalyze a regioselective acetalization of 1,2-diols in carbohydrates (**Scheme 1-40**).[54] In their report, when substrate **1-146** was subject to (*R*)-**1-147** catalyst and **1-148**, 2-*O* could be selectively protected to form product **1-149** in 93% yield and 95% regioselectivity. When achiral phosphoric acid $(PhO)_2P(O)OH$ was used, the intrinsic selectivity was in favor of 3-*O* protected product, and the regioselectivity of product **1-**

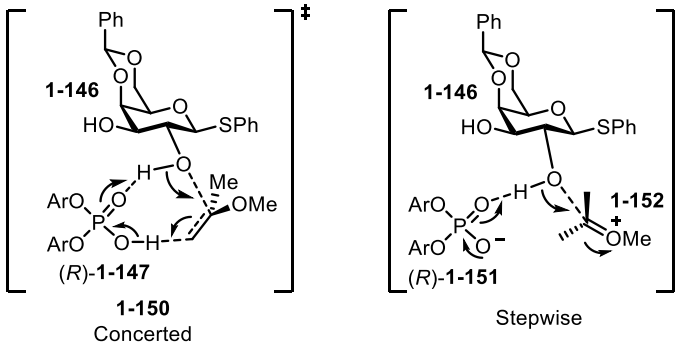
149 was only 30%. When (*S*)-**1-147** was used as catalyst in this transformation, in most cases, lower levels of regioselectivity were obtained.

Scheme 1-40. Nargony's regioselective protection by using chiral Brønsted acid (*R*)-**1-147**



As part of their mechanistic studies, they found that the regioselectivity of the product was under kinetic control and no isomerization occurred under the reaction temperature. Two plausible mechanisms involving a concerted pathway and a stepwise pathway were proposed based on their experimental results. In the concerted pathway through intermediate **1-150**, chiral phosphoric acid (*R*)-**1-147** could activate substrate **1-146** through hydrogen bonding and the regioselectivity was due to the more favored binding between 2-OH and chiral catalyst. In the stepwise pathway, chiral phosphate (*R*)-**1-151** and cationic intermediate **1-152** were formed from (*R*)-**1-147** and **1-148**, respectively. Because of the chiral backbone of (*R*)-**1-151**, the hydrogen bonding between catalyst and 2-OH was favored and the OH was then activated to form final product **1-149**.

Scheme 1-41. Nargony's proposed mechanisms

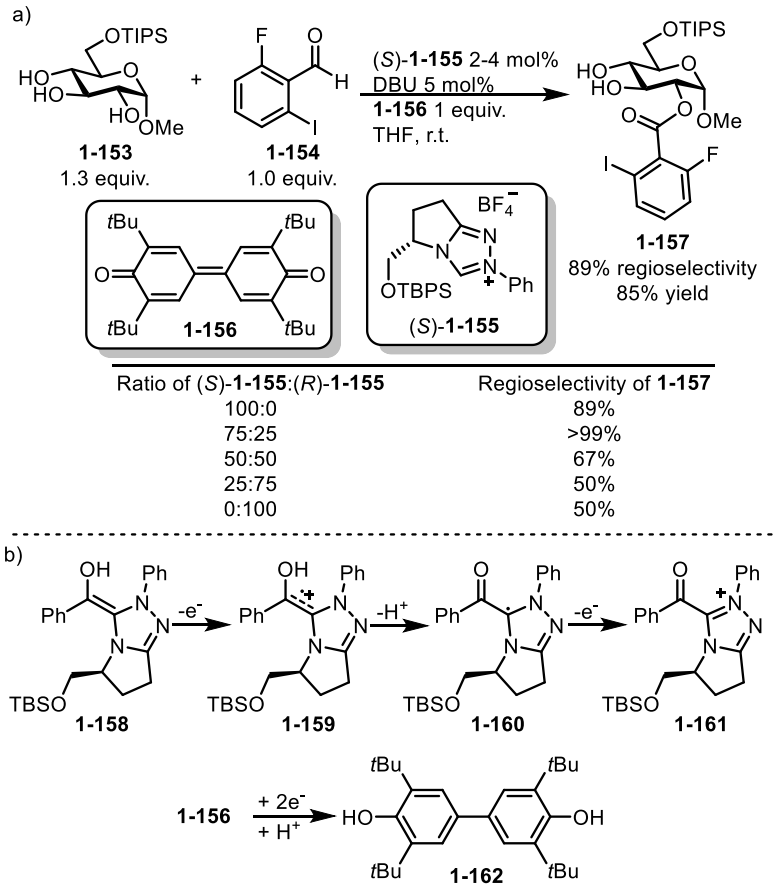


1.3.7 Chiral NHCs in Regioselective Modifications

Based on their previous studies,[55] Studer and coworkers reported the application of chiral N-Heterocyclic-Carbene (NHC) in regioselective acylation of diols and triols in carbohydrates (**Scheme 1-42-a**) in 2016.[56] Substrate **1-153** was treated with **1-154**

and **1-156** in the presence of chiral NHC catalyst (*S*)-**1-155**. 2-*O* acylated product **1-157** could be prepared in 85% yield with 89% regioselectivity. They believed that since a second equivalent of the free NHC catalyst was required in the acylation step, a nonlinear effect on the regioselectivity should be expected. They indeed found that when the ratio between (*S*)- and (*R*)-**1-155** was 3:1, a maximum regioselectivity for product **1-157** could be obtained at greater than 99%. These results indicated that a cooperative process was involved in this reaction and in the acylating step, one enantiomer of the **1-155** catalyst was part of acylating reagent, while the other enantiomer of **1-155** was likely to activate alcohol through hydrogen bonding. **1-156** was used as two-electron-oxidant to oxidize key Breslow intermediate **1-158** to **1-161** through radical cation **1-159** and radical **1-160** intermediates in this transformation and formed **1-162** (**Scheme 1-42-b**).[57]

Scheme 1-42. Studer's regioselective acylation using chiral NHC catalysts



1.4 Conclusions and Outlooks

During the past 15 years, a number of chiral reagents and catalysts have been developed for glycosylation and modification of carbohydrates. Complementary to some of the traditional approaches, those new developments significantly improved our

ability to synthesize various glycosidic linkages with high yields and selectivity. It is expected that these new methods will be applied to the synthesis of complexed carbohydrates, which could be used as probes to further improve our understandings of the functions of carbohydrates in biological systems and developed to novel therapeutics.

For glycosylation reactions, many major challenges remain unsolved. Here are some of them. 1) There is no universal method or a (pair of) catalyst(s) that can promote the formation of α and β glycosidic linkages selectively by using the same glycosyl donor similar to what the enzyme does. 2) The stereogenic center of the secondary alcohol nucleophile in glycosyl acceptors can often influence the stereo-outcome of glycosylation reactions. It is more challenging to achieve high selectivity in the mis-match scenarios. 3) There is still lack of a systematic study on how different hydroxyl protecting groups of carbohydrates may impact a specific type of glycosylation reaction.

For regio- and site-selective modifications, it is much more challenging to override the intrinsic selectivity of OH groups than enhance it. In addition, there is lack of evidence for many of the proposed mechanisms and key interactions. Simple, predictable, and regio- or site-selective protection methods are still in great needs. Very little attention has been paid to the equally important chiral catalyst mediated regioselective deprotection method and methods in this field are yet to be developed.

With the accumulation of more knowledge in both glycosylation reactions and site-selective modifications of carbohydrates mediated by chiral catalysts, we look forward to the realization of chemical glycosylation reactions that can match the stereo- and site-selectivity of enzymes. These new methods will truly transform glycoscience.

1.5 References

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Chapter 2

Iridium-Catalyzed Dynamic Kinetic Diastereoselective Isomerization (DKDI)

and

Dynamic Kinetic Diastereoselective Glycosylation Reactions(DKDG)

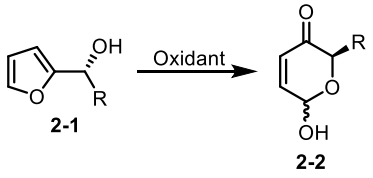
Part of this chapter was taken from the following published article.

H.-Y. Wang, K. Yang, S. R. Bennett, S.-R. Guo, W. Tang, *Angew. Chem. Int. Ed.* **2015**, *54*, 8756-8759.

2.1 Introduction

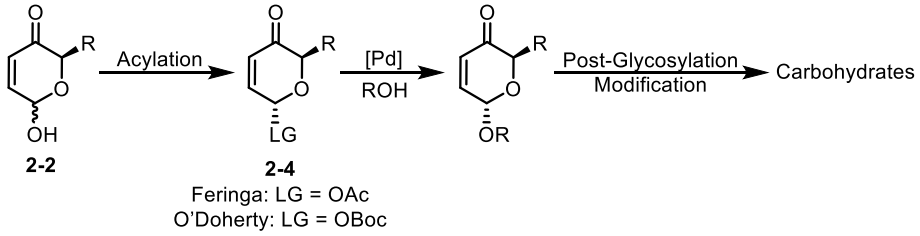
Biogenic furans are considered to be among the most promising sustainable raw materials for the production of fine chemicals.[1] Besides the defunctionalization methods developed for the synthesis of simple chemicals from furans,[2] the Achmatowicz rearrangement occupies a unique position as it efficiently converts a feedstock furan **2-1** into a much more structurally complex dihydropyranone **2-2** (**Scheme 2-1**).[3]

Scheme 2-1. Achmatowicz rearrangement



The potential of the Achmatowicz rearrangement for *de novo* synthesis of carbohydrates was immediately recognized after its initial discovery in the 1970s.[4] Later, the research groups of Feringa[5] and O'Doherty[6] reported that esters or carbonates of dihydropyranone **2-4** derived from hemiacetal **2-2** could undergo palladium-catalyzed stereospecific glycosylation reaction, which represented a unique glycosylation method (**Scheme 2-2**).[7] Although the glycosylation is stereospecific, the acylation step that makes **2-4** from **2-2** requires either substrate-dependent enzymatic resolution (R = H)[8] or separation of a mixture of diastereomers by column chromatography (R = Me and OTBS).[9]

Scheme 2-2. Feringa-O'Doherty's palladium-catalyzed stereospecific glycosylation reaction

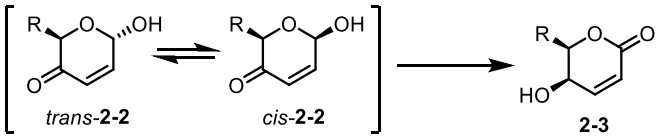


Besides its applications in carbohydrates synthesis, the Achmatowicz rearrangement has also been applied to the synthesis of diverse libraries[10] and complex natural products,[11] including hexacyclic harringtonolide completed by our group in 2012.[12]

Because of the importance of the Achmatowicz rearrangement, a variety of oxidation conditions have been developed for the conversion of **2-1** to **2-2**,[13] including recently reported practical catalysts based on vanadium[14] and monooxygenase.[15]

Efforts have also been devoted to the manipulation of hemiacetal and ketone groups in **2-2**, such as protection or oxidation of the hemiacetal and reduction of the ketone group to form osmundalactone derivatives **2-3** (**Scheme 2-3**).[16] Osumundalactone derivatives exists widely in many natural products and is also key intermediates in the synthesis of many natural products.[17] However, most transformations involving the anomeric center are not highly stereoselective.

Scheme 2-3. Synthesis of osmundalactone derivatives **2-3** *via* isomerization of **2-2**

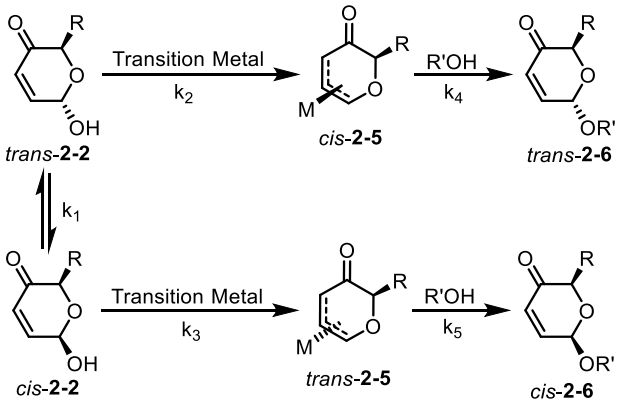


2.2 Results and Discussion

2.2.1 Optimization of Reaction Conditions

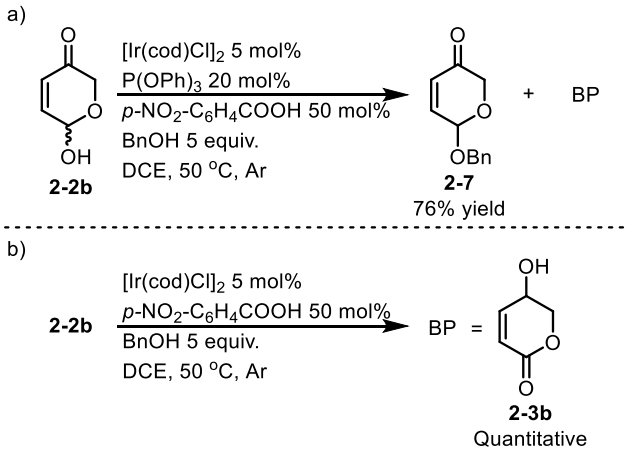
We envisioned that we could circumvent the acylation problem mentioned above for the synthesis of substrates in Feringa-O'Doherty's palladium-catalyzed stereospecific glycosylation reaction by directly using hemiacetal **2-2** derivatives as substrates in glycosylation through a dynamic kinetic diastereoselective process (**Scheme 2-4**). Upon treating **2-2** with transition metal catalyst, the allylic alcohol could be activated[18] and form π-allyl intermediates *cis*- and *trans*-**2-5**, respectively. Allylic alcohols *trans*-**2-2** and *cis*-**2-2** interconvert to each other in a dynamic equilibrium. Depending on the rate-determine step, either *trans*-**2-6** or *cis*-**2-6** could be formed as the major product. To avoid steric interactions between the R group and incoming metal-complex, the formation of metal-π-allyl intermediate *trans*-**2-5** should be faster than that of *cis*-**2-5**. Similarly, the formation of *trans*-**2-6** may be faster than that of *cis*-**2-6** to avoid steric interactions between the R group and incoming alcohol nucleophile. If the ionization to form metal-π-allyl is the rate-determine step, ether *cis*-**2-6** would be the major product; while ether *trans*-**2-6** would be major product if the nucleophilic addition is the rate-determine step. The stereo-outcome of the glycosylation product in this dynamic kinetic diastereoselective glycosylation (DKDG) could be influenced by the relative rates (k_1, k_2, k_3, k_4, and k_5) of each chemical step and we believe it could be altered by adding different promoters or additives. The glycosylation products **2-6** could be used to synthesize different carbohydrates, as demonstrated by Feringa and O'Doherty.

Scheme 2-4. Reaction design for metal-catalyzed DKDG



To this end, substrate **2-2b** was synthesized in one step from commercially available 2-furanmethanol through Achmatowicz rearrangement and it was subjected to the allylic alkylation condition developed by Carreira and coworkers (**Scheme 2-5-a**).[18] We were glad to find that product **2-7** could be obtained in 76% of yield alongside with a by-product (BP). When no triphenylphosphite ligand was added, we found that no alkylation product **2-7** was observed and the BP became the only product. It turned out that isomerization product **2-3b** was the BP and it was formed through internal hydrogen transfer process (**Scheme 2-5-b**).

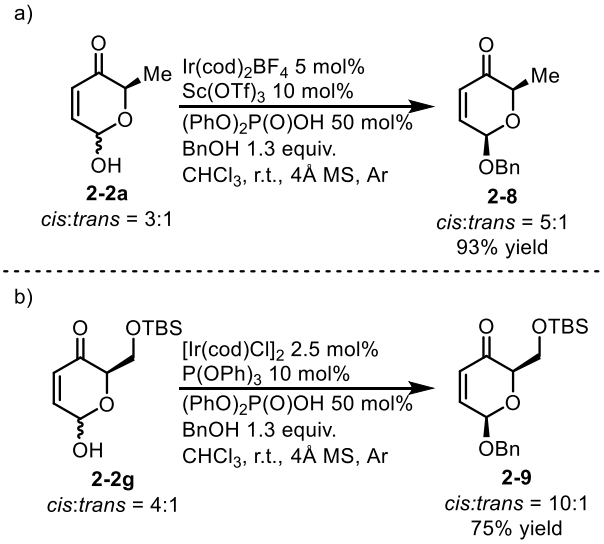
Scheme 2-5. Initial findings for iridium-catalyzed DKDG



In order to have a better understanding of the diastereo-outcome of this glycosylation reaction, substrates **2-2a** and **2-2g** were synthesized from commercially available starting material 2-acetylfuran in 2 and 5 steps, respectively. The hemiacetals **2-2a** and **2-2g** exist as a mixture of two epimers, and the diastereomeric ratio (d.r.) is around 3:1 for **2-2a** and 4:1 for **2-2g**, all favoring the *cis*-isomer. After screening various conditions, we discovered that the Brøsted acid played a very important role in

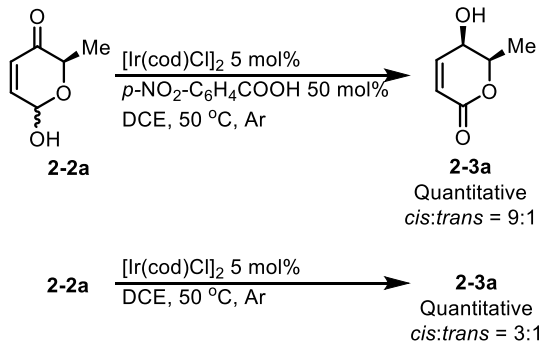
this glycosylation reaction. When no Brøsted acid was added, lower yield and selectivity was observed. We found that when substrate **2-2a** was used, cationic iridium $Ir(cod)_2BF_4$ was the best catalyst, $(PhO)_2P(O)OH$ was the best Brøsted acid promoter, and product **2-8** could be afforded in 93% yield with a ratio 5:1 (*cis*:*trans*, **Scheme 2-6-a**). The Lewis acid $Sc(OTf)_3$ was essential in improving overall conversion and diastereoselectivity for substrate **2-2a**. For substrate **2-2g**, the $[Ir(cod)Cl]_2$ became the best catalyst and $P(OPh)_3$ was the best ligand. When BnOH was employed, product **2-9** could be obtained in 75% yield with a diastereomeric ratio of 10:1, favoring *cis*-product (**Scheme 2-6-b**).

Scheme 2-6. Optimized condition for iridium-catalyzed DKDG



While a lot of efforts have been made to improve the overall efficiency and selectivity of this glycosylation reaction, the isomerization product was always a by-product and sometimes was even the major one. Thus, we decided to study the isomerization reaction first. When **2-2a** was used under the initial condition, product **2-3a** could be obtained in almost quantitative yield and the diastereomeric ratio of **2-3a** was 9:1 favoring *cis*-product. We also found that Brøsted acid promoter could affect the diastereo-outcome of this transformation. When no carboxylic acid was added, the diastereomeric ratio of the product stayed around the same with substrate **2-2a** (*cis*:*trans* = 3:1). These results (**Scheme 2-7**) clearly suggested that this reaction was going through a dynamic kinetic diastereoselective isomerization (DKDI) process and the rate of iridium-catalyzed isomerization is much faster than the equilibration of the two epimers.

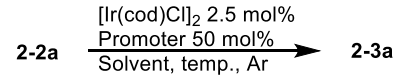
Scheme 2-7. Initial findings for iridium-catalyzed DKDI



Encouraged by the above results, the reaction conditions optimization was conducted. We first screened a number of transition metal catalysts, such as $[Ru(cod)Cl_2]_n$, $[Cp^*Ru(CH_3CN)_3]$, $[Rh(cod)Cl]_2$, $Rh(cod)BF_4$, $Ir(cod)BF_4$, $[Ir(cod)Cl]_2$, $Pd(OAc)_2$, $Pd_2(dba)_3$, $NiCl_2[P(C_6H_{11})_3]_2$, AgOAc, and CuBr. Interestingly, only iridium-based catalysts provided the desired isomerization product **2-3a**. Cationic $Ir(cod)BF_4$ only yielded a trace amount of product.

We next screened different Brøsted acids in an attempt to accelerate the rate of equilibration between epimers *cis*-**2-2a** and *trans*-**2-2a** (**Scheme 2-8**, entries 2–12). To our delight, the *cis*/*trans* ratio immediately increased to 12:1 upon the addition of benzoic acid (50 mol%; **Scheme 2-8**, entry 2). This result clearly indicated that the rate of equilibration between the two epimeric hemiacetals is accelerated by an acid additive, and that a dynamic kinetic transformation is possible. The use of benzoic acids with either an electron-withdrawing nitro group or an electron-donating methyl group led to a slight decrease in the diastereomeric ratio (**Scheme 2-8**, entries 3 and 4). The diastereomeric ratio was increased slightly by carrying out the reaction at room temperature (**Scheme 2-8**, entry 5). The yield was slightly lower when the amount of benzoic acid was increased to 100 mol% or decreased to 5 mol%, but the diastereomeric ratio remained the same (**Scheme 2-8**, entries 6 and 7). By screening several other carboxylic acids and different solvents (**Scheme 2-8**, entries 8–12), we found that the *cis*-prodcut could be obtained exclusively in nearly quantitative yield when 2,6-dichlorobenzoic acid was used as the cocatalyst (**Scheme 2-8**, entry 11).

Scheme 2-8. Screening of conditions for the iridium-catalyzed DKDI



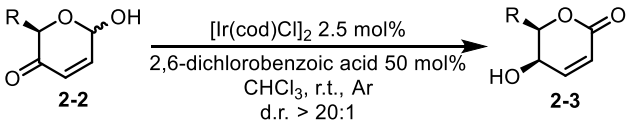
Entry	Promoter	Solvent	Temp.	Yield[a]	d.r. (*cis*:*trans*)[b]
1	-	DCE	50 °C	96%	3:1
2	PhCOOH	DCE	50 °C	97%	12:1
3	*p*-NO_2-C_6H_4COOH	DCE	50 °C	99%	9:1
4	*p*-Me-C_6H_4COOH	DCE	50 °C	97%	10:1
5	C_6H_5COOH	DCE	r.t	97%	14:1
6	C_6H_5COOH (100 mol%)	DCE	r.t	88%	14:1
7	C_6H_5COOH (5 mol%)	DCE	r.t.	86%	14:1
8	CH_3COOH	DCE	r.t.	89%	16:1
9	CF_3COOH	DCE	r.t.	82%	14:1
10	2,6-Cl-C_6H_3COOH	DCE	r.t.	99%	18:1
11	**2,6-Cl-C_6H_3COOH**	**$CHCl_3$**	**r.t.**	**98%**	**>20:1**
12	2,6-Cl-C_6H_3COOH	CH_2Cl_2	r.t.	87%	20:1

[a] NMR yield using CH_2Br_2 as internal standard, isolated yield in parentheses.
[b] Determined by ^{1}H-NMR of the crude mixture.
cod = 1,5-cyclooctadiene.
DCE = dichloroethane.

2.2.2 Substrate Scope and Applications

The scope of the iridium-catalyzed dynamic kinetic diastereoselective isomerization is shown in **Scheme 2-9**. Product **2-3a** was isolated in 91% yield when the reaction was carried out under the optimized conditions. The R group in substrate **2-2** can also be a hydrogen atom (**Scheme 2-9**, b). Product **2-3e** with a *tert*-butyl substituent was isolated in 63% yield over three steps from furan and pivalaldehyde (**Scheme 2-9**, e). Substrate **2-2e** was not stable and was subjected to isomerization immediately after its preparation by the addition of furanyl lithium to pivalaldehyde and subsequent Achmatowicz rearrangement. Cyclopropyl and silyl ether groups were also tolerated (**Scheme 2-9**, f and g). Product **3-3g** is a key intermediate in the synthesis of a number of carbohydrate lactones, such as gulonolactone and allonolactone.[19] Neither electron-withdrawing nor electrondonating groups on the aryl group impacted the yield significantly (**Scheme 2-9**, h, i, and j). The trifluoromethyl-substituted substrate **2-2k** was not stable and needed to be used immediately after its preparation (**Scheme 2-9**, k). An *ortho*-substituted phenyl group was also compatible with the transformation (**Scheme 2-9**, l). In all cases, the *cis*-product was observed exclusively.

Scheme 2-9. Substrate scope of iridium-catalyzed DKDI

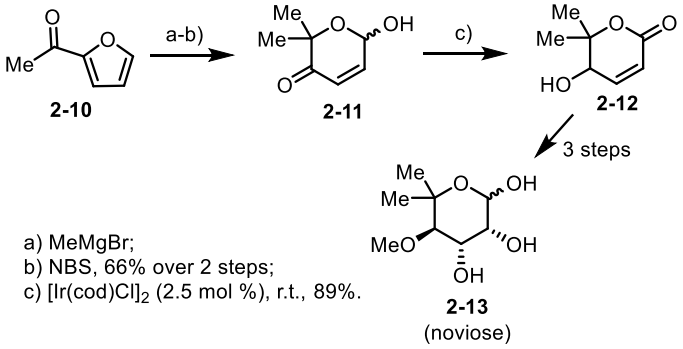


a, R = Me, 91%
b, R = H, 96%
c, R = *n*-Pr, 93%
d, R = *i*-Pr, 90%
e*, R = *t*-Bu, 63%
f, R = cyclopropyl, 94%
g**, R = CH_2OTBS, 84%
h, R = phenyl, 93%
i, R = *p*-F-C_6H_4, 95%
j, R = *p*-MeO-C_6H_4, 88%
k*, R = *p*-CF_3-C_6H_4, 60%
l, R = *o*-CH_3-C_6H_4, 75%

* Substrate was not stable and used without purification.
** The reaction was conducted at 50 °C.

A gem-dimethyl substituent was also tolerated in this isomerization reaction (**Scheme 2-10**). Substrate **2-11** was prepared in two steps from commercially available 2-acetylfuran **2-10**. The isomerization product **2-12** has been converted into noviose **2-13** in three steps through methylation, reduction, and dihydroxylation.[20] The combination of the Achmatowicz rearrangement and iridium-catalyzed isomerization provides a concise *de novo* synthesis of noviose.[21]

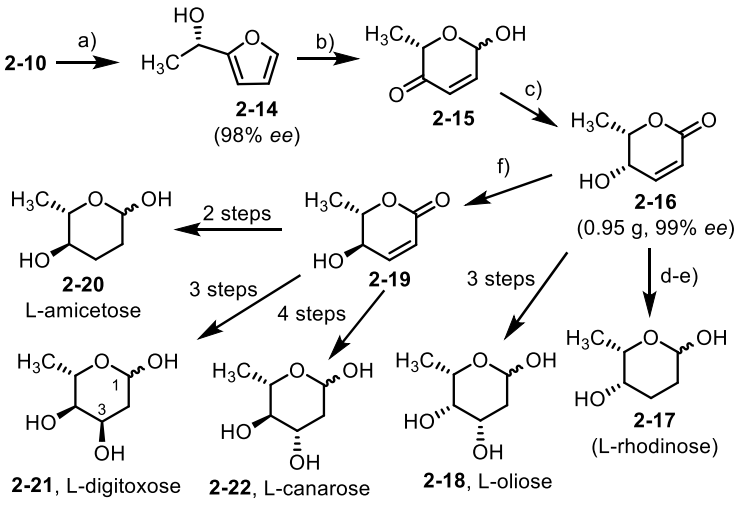
Scheme 2-10. Formal synthesis of noviose (all reactions in this scheme are completed by Mr. Ka Yang)



a) MeMgBr;
b) NBS, 66% over 2 steps;
c) $[Ir(cod)Cl]_2$ (2.5 mol %), r.t., 89%.

The secondary alcohol **2-14** could be prepared in 98% yield with 98% *ee* according to known protocols (**Scheme 2-11**).[22] The stereochemical integrity was retained under the isomerization conditions in a gram-scale synthesis. Reduction of the key intermediate **2-16** completed the enantioselective synthesis of L-rhodinose (**2-17**).[23] The same intermediate has been converted into L-oliose (**2-18**) in three steps.[24] Mitsunobu inversion of allylic alcohol **2-16**, followed by hydrolysis,[16a] afforded osmundalactone (**2-19**).[24-25] The synthesis of L-amicetose (**2-20**), L-digitoxose (**2-21**), and L-canarose (**2-22**) from intermediate **2-19** has been reported previously.[16b, 26] Intermediates **2-16** and **2-19** have also been converted into amino sugar derivatives, such as daunosamine and ristoamine.[27]

Scheme 2-11. Catalytic asymmetric synthesis of deoxysugars



a) $[Cp^*RhCl_2]_2$ (0.05 mol%), (*R*,*R*)-TsDPEN (0.12 mol%), HCO_2Na, 40 °C, 98%; b) NBS, 85%; c) $[Ir(cod)Cl]_2$ (2.5 mol %), rt, 76%; d) H_2, Pd/C; e) DIBAL-H, 40% over 2 steps; f) PPh_3, *p*-$NO_2C_6H_4CO_2H$, DEAD, then MeOH, Et_3N, 75% over 2 steps.

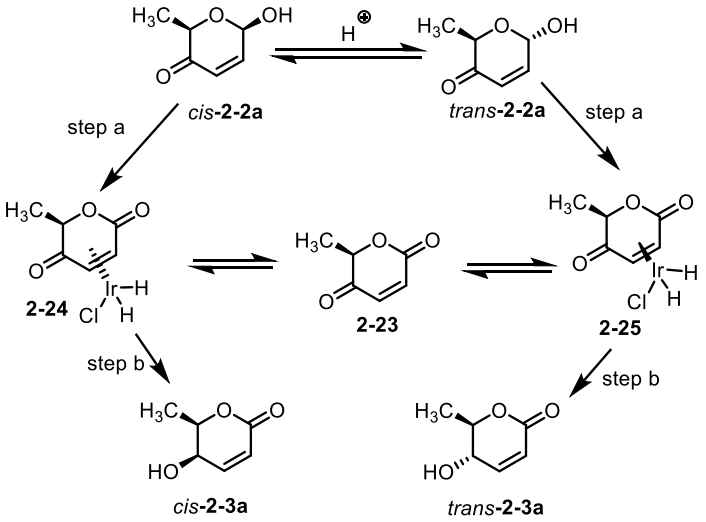
Very recently, this DKDI reaction was applied to the total synthesis of natural product angiopteralactone B by Lawrence and coworkers.[28]

2.2.3 Mechanism

A trace amount of ketolactone **2-23**[29] was isolated when the isomerization was conducted on a larger scale (**Scheme 2-12**). This intermediate decomposes quickly at room temperature.

A mechanism for the dynamic kinetic isomerization is proposed in **Scheme 2-12**. The dehydrogenation of *cis*-**2-2a** and *trans*-**2-2a** is thought to afford metal complexes **2-24** and **2-25**, from which products *cis*-**2-3a** and *trans*-**2-3a**, are formed, respectively, upon hydrogenation. Overall, this transformation is a rare example of stereoselective internal transfer hydrogenation. In the absence of an acid, the ratio of *cis*-**2-3a** to *trans*-**2-3a** is around 3:1, which is similar to the ratio of *cis*-**2-2a** to *trans*-**2-2a**. This observation suggests that the rate of equilibration between the two hemiacetals is slower than the rate of internal transfer hydrogenation in the absence of an acid. The rate of interconversion between the two hemiacetals became significantly faster than the internal transfer hydrogenation in the presence of an acid additive, thus making the stereoselective dynamic kinetic isomerization possible.

Scheme 2-12. Proposed mechanism for the iridium-catalyzed DKDI



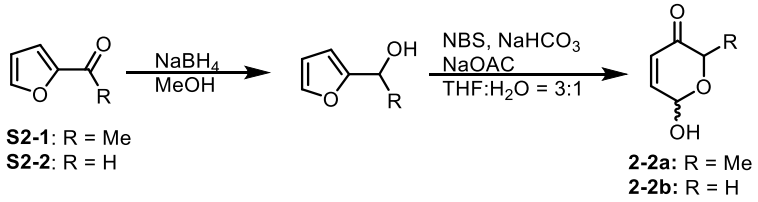
2.2.4 Conclusion

In summary, we have discovered a novel iridium-catalyzed stereoselective dynamic kinetic internal transfer hydrogenation reaction. This new method provides a practical and unified approach to the synthesis of deoxy- and amino sugars from simple furan derivatives.

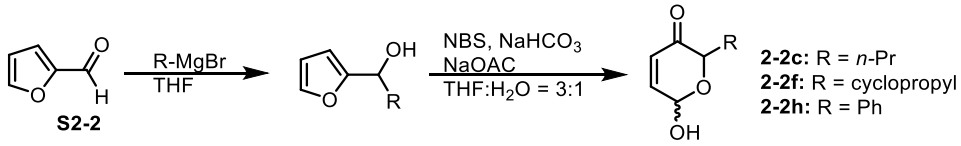
2.3 Experimental Section

2.3.1 Methods for the preparation of substrates

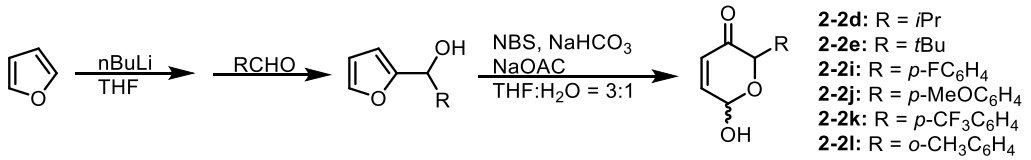
1) For substrates **2-2a** and **2-2b**:



2) For substrates **2-2c, 2-2f,** and **2-2h**:

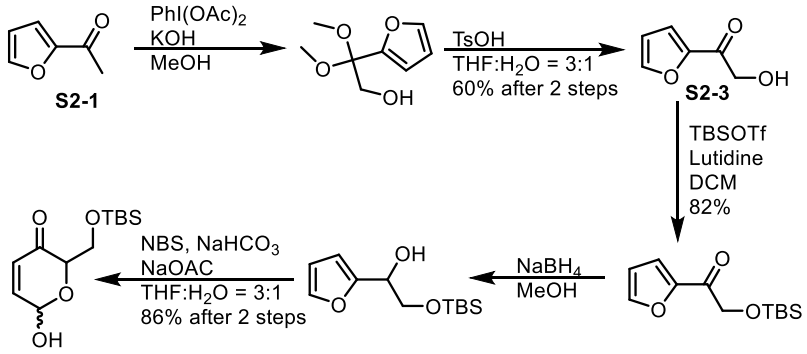


3) For substrates **2-2d, 2-2e, 2-2i, 2-2j, 2-2k,** and **2-2l**:



Note: **2-2e** and **2-2k** decomposed on silica gel and crude products were used directly

4) For substrate **2-2g**:



Representative experimental procedures for the preparation of substrates:

1) For substrates **2-2a** and **2-2b**:

Compound **2-2a**[6a] was prepared according to the literature procedure from commercially available material **S2-1**. Compound **2-2b**[30] was prepared according to the same procedure and the yield was 77% after 2 steps. Their spectra are identical to the literature.

2) For substrate **2-2f**:

To a stirred solution of **S2-2** (2.0 mmol) in anhydrous THF (10 mL) was added cyclopropyl Grignard reagent (1.3 equiv., 2.6 mmol) at 0 °C under argon. The mixture was then warmed up to ambient temperature. After completion, the reaction was quenched with saturated NH_4Cl solution, extracted by DCM. The combined organic phase was dried over Na_2SO_4 and concentrated under vacuum. The crude mixture was used in the next step without further purification.

To a stirred solution of crude mixture above in THF/H_2O (3:1, 16 mL) was added $NaHCO_3$ (2 equiv., 4 mmol), $NaOAc{\cdot}3H_2O$ (1

equiv., 2 mmol) and NBS (1 equiv, 2 mmol) at 0 °C. The mixture was stirred at the same temperature until completion as indicated by TLC. After completion, the reaction was quenched with saturated $NaHCO_3$ solution, extracted by ethyl acetate. The combined organic phase was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography (hexane/ethyl acetate = 3:1) to yield 212 mg of product **2-2f** (68% over two steps) as yellow oil.

Compounds **2-2c**[31] and **2-2h**[32] were also prepared according to this procedure and the yields were 72% (for **2-2c**) and 56% (for **2-2h**) after 2 steps. Their spectra are identical to the literature.

3) For substrate **2-2i**:

To a stirred solution of furan (2 mmol) in anhydrous THF (20 mL) was added *n*BuLi (1.1 equiv, 2.2 mmol) at -78 °C under argon. After the mixture was stirred at the same temperature for 30 min, 4-fluorobenzaldehyde (1.1 equiv, 2.2 mmol) was then added. The mixture was then warmed up to ambient temperature. After the reaction is completed as indicated by TLC, the reaction was quenched with saturated NH_4Cl solution, extracted by DCM. The combined organic phase was dried over Na_2SO_4 and concentrated under vacuum. The crude mixture was used in the next step without further purification.

To a stirred solution of crude mixture above in THF/H_2O (3:1, 16 mL) was added $NaHCO_3$ (2 equiv., 4 mmol), $NaOAc{\cdot}3H_2O$ (1 equiv, 2 mmol) and NBS (1 equiv, 2 mmol) at 0 °C. The mixture was stirred at the same temperature until it is completed as indicated by TLC. The reaction was then quenched with saturated $NaHCO_3$ solution and extracted by ethyl acetate. The combined organic phase was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography (hexane/ethyl acetate = 3:1) to yield 244 mg **2-2i** product (53% over two steps) as yellow oil. Their spectra are identical to the literature.[33]

Compounds **2-2d**,[31] **2-2j**,[33] **2-2l** were also prepared according to the same procedure and the yields were 50% (for **2-2d**), 48% (for **2-2j**), 53% (for **2-2l**) after 2 steps. Their spectra are identical to the literature. Compounds **2-2e** and **2-2k** are not stable on silica gel and were used for the next step without purification.

4) For substrate **2-2g**:

To a stirred solution of KOH (4.5 equiv., 90 mmol) in MeOH (50 mL) was added **S2-1** (20 mmol) at 0 °C under argon. Phenyliodine diacetate (1.5 equiv, 30 mmol) was then added proportionally. The mixture was then stirred at the same

temperature for 3h. The reaction was then quenched with brine and extracted by ethyl acetate. The combined organic phase was dried over Na_2SO_4 and concentrated under vacuum. The crude mixture was used in the next step without further purification.

To a stirred solution of crude mixture above in THF:H_2O (3:1, 16 mL) was added TsOH (2 equiv, 40 mmol) at ambient temperature. The mixture was heated to reflux and stirred for 5h. The reaction was then quenched with saturated $NaHCO_3$ solution and extracted by ethyl acetate. The combined organic phase was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography (hexane/ethyl acetate = 3:1) to yield product **S2-3** for 1.2 g (48% over two steps) as a yellow solid. The spectra are identical to literature.[34]

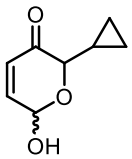
To a stirred solution of **S2-3** (1 mmol) in DCM (10 mL) was added 2,6-lutidine (1.5 equiv., 1.5 mmol) at 0 °C under argon. TBSOTf (1.3 equiv., 1.3 mmol) was then added at the same temperature. The mixture was then warmed up to ambient temperature and stirred for 30 min. After completion, the reaction was quenched with saturated NH_4Cl solution and extracted by DCM. The combined organic phase was dried over Na_2SO_4 and concentrated under vacuum. The crude mixture was used in the next step without further purification.

To a stirred solution of the above crude mixture in MeOH (10 mL) was added $NaBH_4$ (1.3 equiv., 1.3 mmol) at 0 °C. The mixture was stirred for 30 min at the same temperature. After completion, the reaction was quenched with saturated NH_4Cl solution and extracted by DCM. The combined organic phase was dried over Na_2SO_4 and concentrated under vacuum. The crude mixture was used in the next step without further purification.

To a stirred solution of the above crude mixture in THF/H_2O (3:1, 8 mL) was added $NaHCO_3$ (2 equiv., 2 mmol), $NaOAc{\cdot}3H_2O$ (1 equiv., 1 mmol) and NBS (1 equiv., 1 mmol) at 0 °C. The mixture was stirred at the same temperature until the reaction is completed as indicated by TLC. The reaction was then quenched with saturated $NaHCO_3$ solution and extracted by ethyl acetate. The combined organic phase was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography (hexane/ethyl acetate = 3:1) to yield 218 mg of product **2-2g** (64% over three steps) as yellow oil. The spectra are identical to literature.[6b]

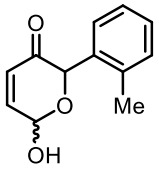
2.3.2 Characterization data for DKDI substrates

Substrates **2-2a**, **2-2b**, **2-2c**, **2-2d**, **2-2g**, **2-2h**, **2-2i**, and **2-2j** are known compounds as indicated previously. Substrates **2-2e** and **2-2k** are not stable on silica gel and were used for the next step without purification.



2-2f

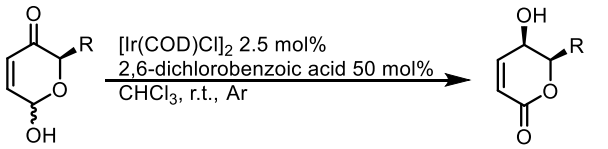
2-2f: 2-cyclopropyl-6-hydroxy-2H-pyran-3(6H)-one. Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, TMS) of the major isomer: δ 6.89 (dd, *J* = 10.5, 3.0 Hz, 1H), 6.13 (d, *J* = 10.0 Hz, 1H), 5.70 (d, *J* = 2.5 Hz, 1H), 3.98 (d, *J* = 7.5 Hz, 1H), 3.37 (s, 1H), 1.25 – 1.15 (m, 1H), 0.77 – 0.68 (m, 1H), 0.54 – 0.45 (m, 2H), 0.39 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$, TMS) for the major isomer: δ 196.0, 144.6, 127.9, 88.1, 78.0, 11.1, 3.1, 1.5. IR: ν 3405, 1694, 1371, 1086, 1032 cm^{-1}. HRMS (ESI) for $C_8H_{10}O_3$ (M+Na), 177.0522 (Calc.), found 177.0520.



2-2l

2-2l: 6-hydroxy-2-(*o*-tolyl)-2H-pyran-3(6H)-one. Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, TMS) of the major isomer: δ 7.27 – 7.19 (m, 4H), 6.96 (dd, *J* = 10.0, 3.0 Hz, 1H), 6.22 (d, *J* = 10.0 Hz, 1H), 5.79 (m, 1H), 5.72 (t, *J* = 3.5 Hz, 1H), 3.25 (d, *J* = 4.5 Hz, 1H), 2.31 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, TMS) for the major isomer: δ 195.0, 144.4, 137.4, 134.2, 130.9, 128.9, 128.7, 128.1, 126.1, 88.3, 75.4, 19.8. IR: ν 3408, 1692, 1371, 1224, 1086 cm^{-1}. HRMS (ESI) for $C_{12}H_{12}O_3$ (M+Na), 227.0679 (Calc.), found 227.0674.

2.3.3 Method for the iridium-catalyzed DKDI

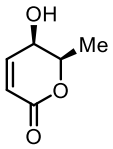


S4 *cis:trans* > 20:1

To an oven-dried flask was added substrate **S4** (0.2 mmol), $[Ir(cod)Cl]_2$ (0.005 mmol), 2,6-dichlorobenzoic acid (0.1 mmol) and anhydrous $CHCl_3$ (2 mL, amylene as stabilizer) under argon. The reaction was stirred at RT and monitored by TLC. After the

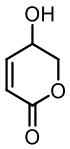
reaction was completed, the solvent was evaporated and the residue was purified by flash column chromatography.

2.3.4 Characterization data for products from the iridium-catalyzed DKDI



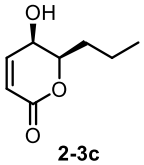
2-3a

2-3a: 5-hydroxy-6-methyl-5,6-dihydro-2H-pyran-2-one. Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.02 (dd, *J* = 10.0, 5.5 Hz, 1H), 6.12 (d, *J* = 9.5 Hz, 1H), 4.54 (m, 1H), 4.04 (dd, *J* = 6.0, 2.5 Hz, 1H), 1.50 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, TMS): δ 164.4, 144.9, 122.6, 77.5, 63.0, 15.8. All spectral data are in accordance with literature.[24]



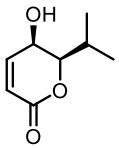
2-3b

2-3b: 5-hydroxy-5,6-dihydro-2H-pyran-2-one. Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 6.95 (dd, *J* = 7.5, 5.0 Hz, 1H), 6.09 (dd, *J* = 7.0, 1.0 Hz, 1H), 4.53 – 4.36 (m, 3H), 2.01 (br, 1H). ^{13}C NMR (101 MHz, $CDCl_3$, TMS): δ 163.2, 146.5, 122.1, 72.1, 61.0. IR: ν 3410, 2926, 1721, 1456, 1102 cm^{-1}. HRMS (ESI) for $C_5H_6O_3$ (M+H), 115.0390 (Calc.), found 115.0384.



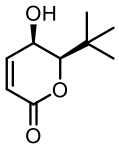
2-3c

2-3c: 5-hydroxy-6-propyl-5,6-dihydro-2H-pyran-2-one. Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.02 (dd, *J* = 10.0, 5.5 Hz, 1H), 6.08 (d, *J* = 10.0 Hz, 1H), 4.33 (m, 1H), 4.06 (dd, *J* = 5.5, 2.5 Hz, 1H), 3.00 (br, 1H), 1.99 – 1.85 (m, 1H), 1.84 – 1.72 (m, 1H), 1.63 – 1.40 (m, 2H), 0.99 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, TMS): δ 164.5, 144.8, 122.8, 81.0, 62.1, 32.1, 18.3, 14.0. IR: ν 3407, 2962, 1715, 1384, 1119 cm^{-1}. HRMS (ESI) for $C_8H_{12}O_3$ (M+Na), 179.0679 (Calc.), found 179.0675.



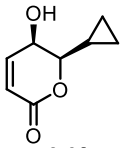
2-3d

2-3d: 5-hydroxy-6-isopropyl-5,6-dihydro-2H-pyran-2-one. Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.02 (dt, *J* = 9.5, 6.0 Hz, 1H), 6.09 (d, *J* = 10.0 Hz, 1H), 4.19 (dd, *J* = 6.0, 2.0 Hz, 1H), 3.85 (dd, *J* = 10.0, 2.0 Hz, 1H), 2.74 (br, 1H), 2.31 – 2.19 (m, 1H), 1.15 (d, *J* = 6.5 Hz, 3H), 1.04 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, TMS): δ 164.6, 144.7, 122.9, 86.5, 60.7, 28.6, 19.2, 18.3. IR: ν 3406, 2966, 1707, 1267, 1042 cm^{-1}. HRMS (ESI) for $C_8H_{12}O_3$ (M+Na), 179.0679 (Calc.), found 179.0675.



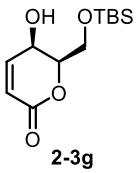
2-3e

2-3e: 6-(*tert*-butyl)-5-hydroxy-5,6-dihydro-2H-pyran-2-one. Yellow solid, m.p. = 77-80 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 6.99 (dd, *J* = 10.0, 6.0 Hz, 1H), 6.05 (d, *J* = 9.5 Hz, 1H), 4.30 (dd, *J* = 6.0, 2.0 Hz, 1H), 3.91 (d, *J* = 2.0 Hz, 1H), 3.01 (br, 1H), 1.16 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$, TMS): δ 165.4, 145.2, 122.4, 87.2, 62.0, 34.6, 26.6. IR: ν 3376, 2961, 1711, 1256, 1032 cm^{-1}. HRMS (ESI) for $C_9H_{14}O_3$ (M+Na), 193.0835 (Calc.), found 193.0831.



2-3f

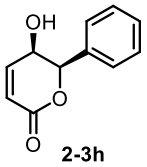
2-3f: 6-cyclopropyl-5-hydroxy-5,6-dihydro-2H-pyran-2-one. Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.02 (dd, *J* = 10.0, 4.5 Hz, 1H), 6.10 (d, *J* = 9.5 Hz, 1H), 4.22 (dd, *J* = 5.5, 2.5 Hz, 1H), 3.54 (dd, *J* = 9.5, 3.0 Hz, 1H), 2.84 (br, 1H), 1.51 – 1.41 (m, 1H), 0.80 – 0.65 (m, 2H), 0.56 (m, 1H), 0.34 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$, TMS): δ 162.1, 142.6, 120.8, 84.0, 60.6, 8.4, 1.7. IR: ν 3406, 2921, 1714, 1259, 1043 cm^{-1}. HRMS (ESI) for $C_8H_{10}O_3$ (M+Na), 177.0522 (Calc.), found 177.0520.



2-3g

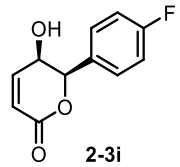
2-3g: 6-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-hydroxy-5,6-dihydro-2H-pyran-2-one. Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, TMS):

δ 7.01 (dd, *J* = 12.0, 7.0 Hz, 1H), 6.13 (d, *J* = 12.0 Hz, 1H), 4.44 – 4.34 (m, 2H), δ 4.09 (dd, *J* = 13.5, 9.5 Hz, 1H), 4.02 (dd, *J* = 13.0, 5.5 Hz, 1H), 3.19 (br, 1H), 0.91 (s, 9H), 0.13 (s, 3H), 0.13 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, TMS): δ 163.3, 144.3, 123.1, 78.9, 62.2, 61.4, 25.9, 18.3, -5.4. All spectral data are in accordance with literature.[17b]



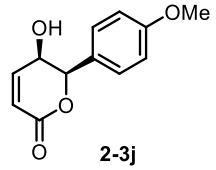
2-3h

2-3h: 5-hydroxy-6-phenyl-5,6-dihydro-2H-pyran-2-one. Yellow solid, m.p.: 121-122 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.51 – 7.36 (m, 5H), 7.08 (ddd, *J* = 9.6, 5.6, 0.8 Hz, 1H), 6.24 (dd, *J* = 9.6, 0.8 Hz, 1H), 5.47 (d, *J* = 6.4 Hz, 1H), 4.31 (dd, *J* = 6.4, 2.4 Hz, 1H), 2.00 (br, 1H). ^{13}C NMR (101 MHz, $CDCl_3$, TMS) δ 163.7, 143.8, 134.8, 129.04, 129.01, 126.8, 123.7, 81.9, 63.7. IR ν 3349, 3030, 1688, 1255, 1040 cm^{-1}. HRMS (ESI) for $C_{11}H_{10}O_3$ (M+Na), 213.0522 (Calc.), found 213.0519.



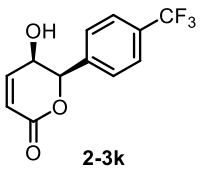
2-3i

2-3i: 6-(4-fluorophenyl)-5-hydroxy-5,6-dihydro-2H-pyran-2-one. Yellow solid, m.p.: 125-126 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.48 – 7.42 (m, 2H), 7.16 – 7.07 (m, 3H), 6.24 (d, *J* = 9.6 Hz, 1H), 5.45 (d, *J* = 2.4 Hz, 1H), 4.29 (s, 1H), 2.05 (br, 1H). ^{13}C NMR (101 MHz, $CDCl_3$, TMS) δ 163.5, 163.1 (d, *J* = 249 Hz), 143.9, 130.6 (d, *J* = 3.2 Hz), 128.8 (d, *J* = 8.4 Hz), 123.6, 116.0 (d, *J* = 21.7 Hz), 81.4, 63.6. IR ν 3417, 3006, 1708, 1362, 1222 cm^{-1}. HRMS (ESI) for $C_{11}H_9FO_3$ (M+Na), 231.0427 (Calc.), found 231.0426.



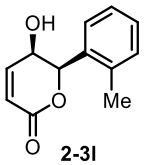
2-3j

2-3j: 5-hydroxy-6-(4-methoxyphenyl)-5,6-dihydro-2H-pyran-2-one. Yellow solid, m.p.: 150-151 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.44 – 7.33 (m, 2H), 7.08 (dd, *J* = 9.6, 5.6 Hz, 1H), 7.00 – 6.94 (m, 2H), 6.25 (d, *J* = 9.6 Hz, 1H), 5.44 (d, *J* = 2.8 Hz, 1H), 4.28 (dd, *J* = 6.0, 2.8 Hz, 1H), 3.83 (s, 3H), 1.79 (br, 1H). ^{13}C NMR (101 MHz, $CDCl_3$, TMS) δ 163.6, 160.2, 143.7, 128.1, 126.7, 123.8, 114.5, 81.6, 63.8, 55.6. IR ν 3375, 3005, 1707, 1363, 1026 cm^{-1}. HRMS (ESI) for $C_{12}H_{12}O_4$ (M+Na), 243.0628 (Calc.), found 243.0628.



2-3k

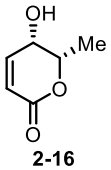
2-3k: 5-hydroxy-6-(4-(trifluoromethyl)phenyl)-5,6-dihydro-2H-pyran-2-one. Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.69 (d, *J* = 8.0 Hz, 2H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.12 (dd, *J* = 10.5, 6.0 Hz, 1H), 6.25 (d, *J* = 9.5 Hz, 1H), 5.53 (d, *J* = 1.5 Hz, 1H), 4.36 (dd, *J* = 6.0, 2.5 Hz, 1H), 2.11 (br, 1H). ^{13}C NMR (101 MHz, $CDCl_3$, TMS): δ 163.1, 143.8, 138.8, 131.1 (d, *J* = 32.7 Hz), 127.2, 125.8 (q, *J* = 3.8 Hz), 124.0 (d, *J* = 273.4 Hz), 123.6, 110.0, 81.3, 63.4. IR: ν 3551, 2929, 1689, 1336, 1082 cm^{-1}. HRMS (ESI) for $C_{12}H_9F_3O_3$ (M+Na), 281.0396 (Calc.), found 281.0394.



2-3l

2-3l: 5-hydroxy-6-(o-tolyl)-5,6-dihydro-2H-pyran-2-one. Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.63 (d, *J* = 6.5 Hz, 1H), 7.34 – 7.27 (m, 2H), 7.22 (d, *J* = 6.5 Hz, 1H), 7.09 (dd, *J* = 10.0, 6.0 Hz, 1H), 6.27 (d, *J* = 10.0 Hz, 1H), 5.69 (d, *J* = 2.0 Hz, 1H), 4.28 (dd, *J* = 5.5, 2.0 Hz, 1H), 2.34 (s, 3H), 1.76 (br, 1H). ^{13}C NMR (101 MHz, $CDCl_3$, TMS): δ 163.7, 143.5, 134.1, 132.5, 130.9, 128.9, 128.1, 126.7, 123.8, 79.0, 61.5, 19.3. IR: ν 3392, 2977, 1693, 1289, 1080 cm^{-1}. HRMS (ESI) for $C_{12}H_{12}O_3$ (M+H), 205.0859 (Calc.), found 205.0855.

2.3.5 HPLC chromatogram for 2-14 and 2-16

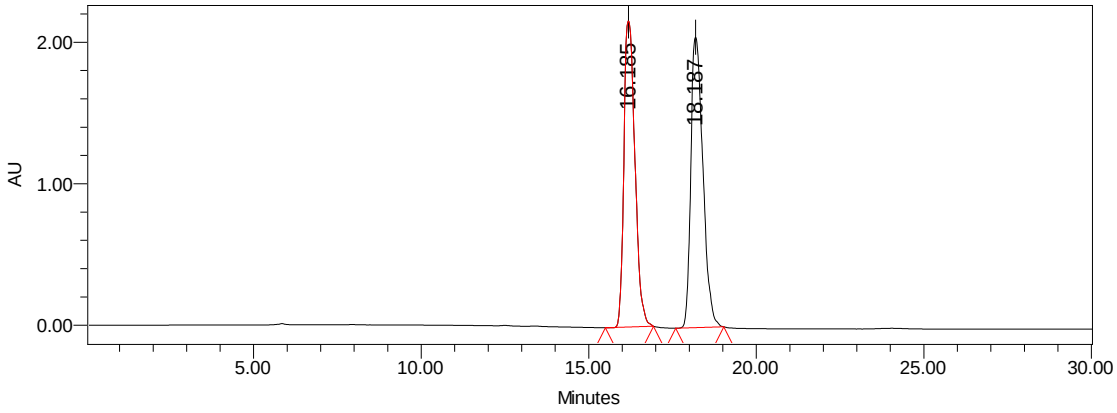


2-16

For optical pure compounds **2-14**, **2-15** and **2-16**: Secondary alcohol **2-14** was prepared in 76% yield (0.95 g) and 98% *ee* according to reported protocols.[22] For product **2-16**, see **2-3a** for the spectra data.

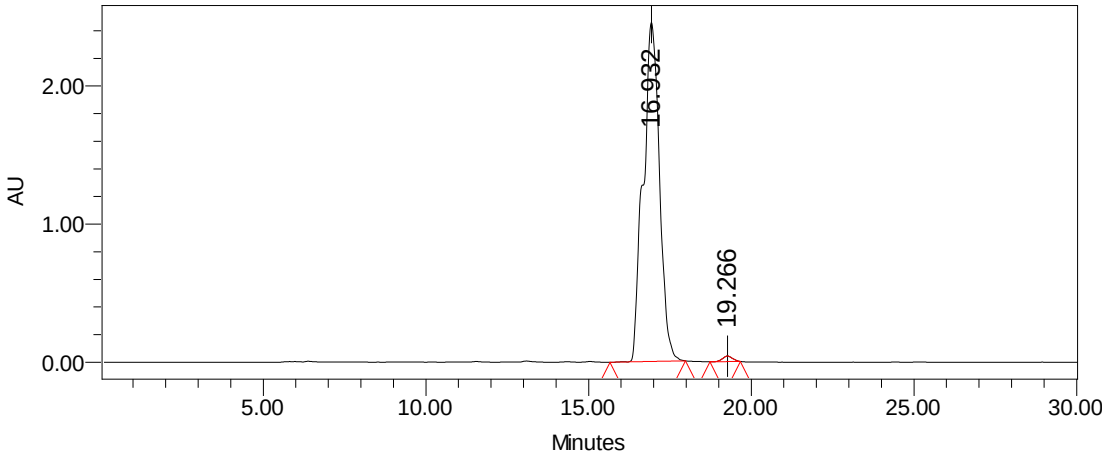
HPLC spectra of racemic and enantioenriched compound **2-14** (Chiralcel OJ-H, eluent: hexane/2-propanol = 95/5, flow rate: 1.0 mL/min, detection at 225 nm):

Racemic **2-14**:



	Retention Time	% Area
1	16.185	49.07
2	18.187	50.93

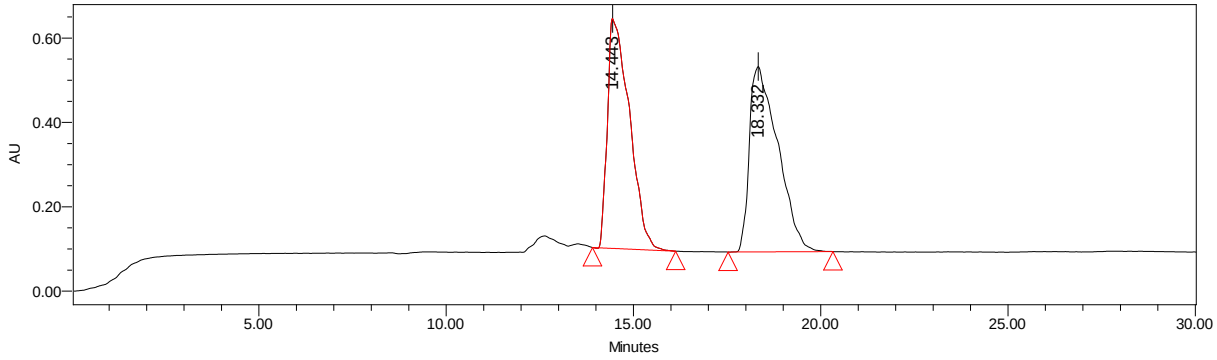
Enantio-enriched **2-14**:



	Retention Time	% Area
1	16.932	98.99
2	19.266	1.01

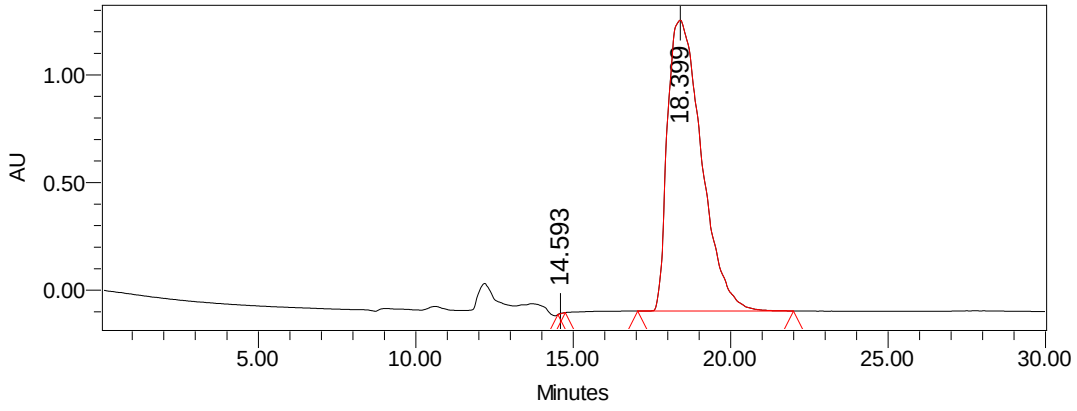
HPLC spectra of racemic and enantioenriched compound **2-16** (Chiralcel AD-H, eluent: hexane/2-propanol = 80/20, flow rate: 0.7 mL/min, detection at 222 nm):

Racemic **2-16**:



	Retention Time	% Area
1	14.443	49.07
2	18.332	50.93

Enantio-enriched **2-16**:

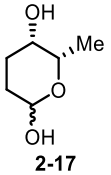


	Retention Time	% Area
1	14.593	0.01
2	18.399	99.99

2.3.6 Preparation and characterization data for 2-17

To a solution of **2-16** (64 mg, 0.5 mmol) in MeOH (3 mL) was added 5% Pd/C (50 mg) and the mixture was stirred under H_2 atmosphere at room temperature for 8h. After completion, the catalyst was filtered off through a short pad of Celite. The organic solution was subsequently washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The resulting crude volatile product was used in the next step without further purification.

To a solution of above crude mixture in DCM (3 mL) was added DIBAL-H (1M in DCM, 1.2 equiv., 0.6 mmol) at -78 °C under argon. The mixture was stirred at the same temperature for 5 min and quenched by water (0.02 mL). The solution was filtered off through a short pad of Celite, and the mixture was concentrated under vacuum. The residue was purified by flash column chromatography (hexane/ethyl acetate = 1:4) to yield 26 mg (40% over two steps) product **2-17** as yellow oil.



2-17

2-17: (5*S*,6*S*)-6-methyltetrahydro-2H-pyran-2,5-diol. Yellow oil. The product contains anomeric mixtures of pyranose and

furanose forms and the ratios of them are solvent and concentration dependent, which is consistent with literature.[35] $[\alpha]_D$ = -7.0 (acetone, c = 0.2), literature $[\alpha]_D$ = -6.7 to -9 (acetone).[35] ^{1}H NMR (500 MHz, $CDCl_3$, TMS) (The sample was allowed to be equilibrated for 1 h prior to recording the spectrum) δ 5.58 (d, *J* = 4.0 Hz), 5.52 (br), 5.30 (br), 4.78 (d, *J* = 5.0 Hz) (altogether 1H), 4.26 – 4.09 (m), 4.08 – 3.92 (m), 3.86 – 3.78 (m), 3.69 (m), 3.50 (br), 3.20 (br), 2.75 – 2.58 (m), 2.29 (br) (altogether 4H), 2.17 – 1.85 (m), 1.81 – 1.39 (m) (altogether 4H), 1.36 – 1.10 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, TMS) (The sample was allowed to be equilibrated for 1 h prior to recording the spectrum) δ 99.0, 98.4, 96.5, 91.9, 85.1, 83.1, 74.3, 70.7, 70.4, 68.2, 67.5, 66.6, 66.3, 63.0, 39.0, 34.3, 33.4, 32.7, 29.9, 29.8, 29.5, 29.3, 27.1, 26.0, 25.3, 23.7, 23.5, 22.1, 20.0, 19.4, 17.4. The spectral data are in accordance with literature.[35]

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Chapter 3

Chiral Catalyst-Directed Dynamic Kinetic Diastereoselective Acylation of Lactols for *De Novo* Synthesis of Carbohydrate (DKDA)

Part of this chapter was taken from the following published article.

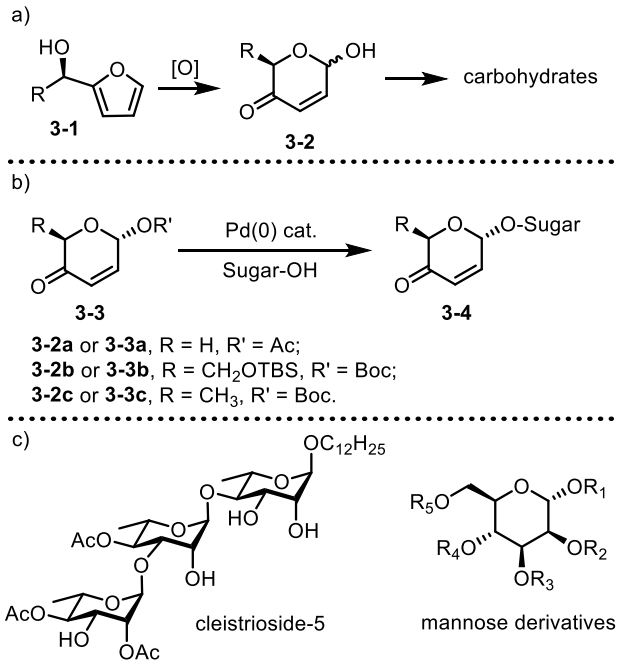
H.-Y. Wang, K. Yang, D. Yin, C. Liu, D. A. Glazier, W. Tang, *Org. Lett.* **2015**, *17*, 5272-5275.

3.1 Introduction

Carbohydrate, one of the four basic macromolecules of life, plays an essential role in numerous important biological processes such as immunological responses, cancer metastasis, and bacterial or viral infections.[1] Efficient and stereoselective synthetic methods, especially *de novo* synthetic methods that do not rely on naturally occurring sugars, may greatly facilitate the study of the biological functions of carbohydrate. It will also enable the development of carbohydrate analogues as novel therapeutic agents.

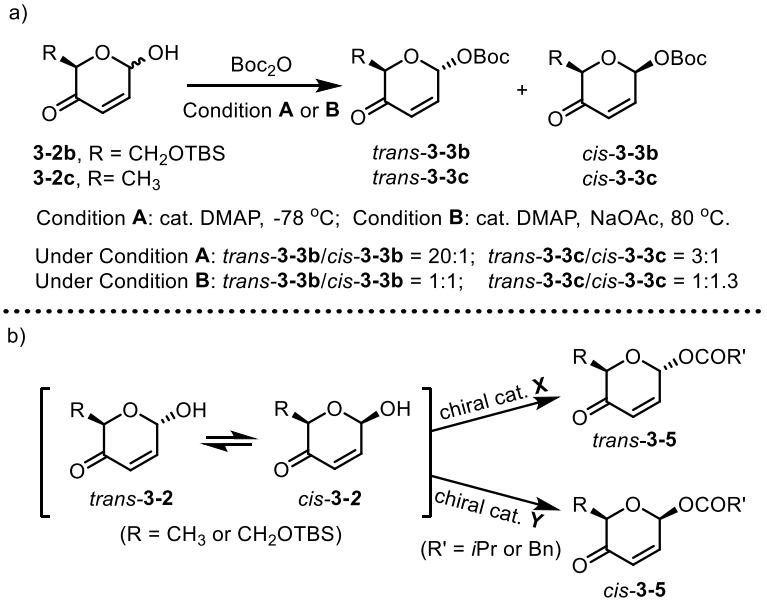
Since the seminal work by Sharpless and Masamune on *de novo* synthesis of hexopyranoses,[2] a number of new strategies have been developed for *de novo* synthesis of carbohydrates.[3] However, the stereochemistry at the anomeric position or stereoselective glycosylation remained largely unaddressed in these *de novo* synthesis.[4] Among various *O*-glycosylation methods,[5] Pd-catalyzed Tsuji–Trost allylic alkylation[6] has been recognized by Lee,[7] Feringa,[8] O'Doherty,[9] Liu,[10] and Rhee[11] as a powerful way to link monosaccharides. *De novo* synthesis of carbohydrate developed by Feringa[8] and O'Doherty[9] relies on Achmatowicz rearrangement[12] and stereoselective Pd-catalyzed glycosylation (**Scheme 3-1**). The former converts the biogenic feedstock furan derivatives **3-1** to dihydropyranone **3-2**, which has been extensively applied in *de novo* synthesis of carbohydrates since its initial discovery in the 1970s (**Scheme 3-1-a**).[3b, 13] In the latter process, esters or carbonates **3-3a-c** undergo Pd-catalyzed Tsuji–Trost allylic alkylation[6] to afford product **3-4** with retention of stereochemistry (**Scheme 3-1-b**). Feringa and co-workers primarily focused on the glycosylation of ester **3-3a**, which was derived from lipase mediated resolution.[8b, 14] In the past decade, O'Doherty and co-workers have applied the Pd-catalyzed glycosylation of **3-3b** and **3-3c** to the synthesis of numerous mono- and oligo-saccharides, such as mannose derivatives and cleistriosides shown in **Scheme 3-1-c.**[15] However, the overall transformation from lactol **3-2** to product **3-4** is often not stereoselective because of the low selectivity of the acylation of the lactol.

Scheme 3-1. *De novo* synthesis of carbohydrates



Although *trans*-**3-3b** could be prepared exclusively from the corresponding Achmatowicz rearrangement product **3-2b** (**Scheme 3-2-a**),[9] the best diastereomeric ratio favoring *cis*-**3-3b** was only 1:1. The ratios for the closely related carbonates *trans*-**3-3c** and *cis*-**3-3c** ranged from 3:1 to 1:1.3.[9, 16] Chromatographic separation of these isomers is required with the exception of *trans*-**3-3b**. We recently became interested in the dynamic kinetic diastereoselective transformations of lactol **3-2** and discovered an Ir-catalyzed dynamic kinetic diastereoselective isomerization of lactol **3-2** to its lactone.[17] We envisioned that chiral catalysts could either reinforce or override the intrinsic diastereoselectivity for the acylation of lactol **3-2** and provide a general solution for the synthesis of either *trans*-**3-5** or *cis*-**3-5** *via* chiral catalyst-directed dynamic kinetic diastereoselective acylation (DKDA) (**Scheme 3-2-b**).

Scheme 3-2. DKDA of lactols



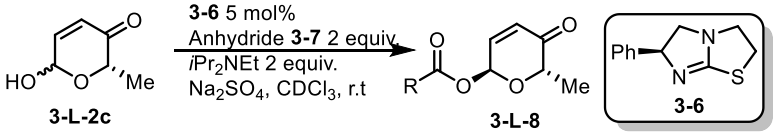
3.2 Results and Discussion

3.2.1 Optimization of Reaction Conditions

After we analyzed chiral organocatalysts that are known to mediate enantioselective acylation of alcohols,[18] commercially available levamisole (tetramisole) **3-6** with an (*S*)-configuration became attractive to us because of its broad utility in many different reactions.[19] This type of tetramisole-based catalyst has been extensively used by Birman and co-workers for the kinetic resolution of secondary alcohols,[20] azlactones,[21] and α-thiolcarboxylic acids.[22] Wiskur and co-workers also applied them to the asymmetric silylation of alcohols.[23]

Chiral lactol **3-L-2c** was prepared enantioselectively in two steps from 2-acetylfuran *via* catalytic asymmetric hydrogenation (98% *ee*) and Achmatowicz rearrangement according to known protocols.[17, 24] Using **3-6** as the catalyst, no reaction was observed when (Boc_2)O was employed. We were pleased to find that simple acetic anhydride provided product **3-L-8b** with a d.r. of 8:1 favoring the *trans*-isomer. Higher selectivity was observed by using more hindered anhydrides **3-7c** and **3-7d**. (**Scheme 3-3)** A similar trend was also observed by Birman and co-workers for the acylation of alcohols.[20]

Scheme 3-3. Screening of anhydride for DKDA

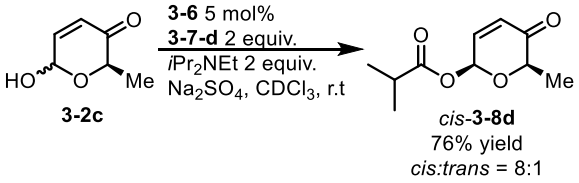


Entry	Anhydride **3-7**	Conversion[a]	d.r. (*trans:cis*)[a]
1	Boc_2O, **3-7a**	0%	-
2	Ac_2O, **3-7b**	>99%	8:1
3	$(EtCO)_2O$, **3-7c**	>99%	11:1
4	$(iPrCO)_2O$, **3-7d**	>99%	15:1
5	Bz_2O, **3-7e**	70%	1:1
6	Piv_2O, **3-7f**	<10%	-
7[b]	**3-7d**	92%[c]	15:1

[a] The conversion of **3-L-2c** and d.r. of **3-L-8** were determined by ^{1}H-NMR of crude product using CH_2Br_2 as internal standard.
[b] The reaction was carried out in $CHCl_3$.
[c] Isolated yield.

Since only one enantiomeric isomer was commercially available for catalyst **3-6**, we prepared substrate **3-D-2c** to explore the mismatched acylation. The d.r. dropped from 8:1 to 1:1 when **3-D-2c** was employed as the substrate using acetic anhydride as the acylation reagent. Under the conditions of entry 7 in **Scheme 3-3**, a d.r. of 8:1 favoring the mismatched *cis*-**3-8d** was observed, and this *cis*-isomer could be isolated in 76% yield (**Scheme 3-4**).

Scheme 3-4. DKDA for mismatched substrate



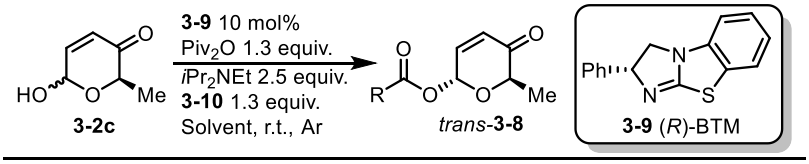
We then tried to acylate mismatched substrate **3-2b** under the conditions of entry 7 in **Scheme 3-3**. Unfortunately, low conversion and low d.r. were observed. No improvement was obtained by changing the TBS group to benzyl or benzoyl protecting groups.

While we were optimizing conditions for these challenging mismatched substrates, Ortiz and co-workers reported the dynamic kinetic asymmetric transformation (DYKAT) of lactol **3-2a** (R = H) and four related lactols with either two hydrogen or two methyl substituents on the 5-position to the corresponding esters with up to 88% *ee*.[25] Commercially available levamisole **3-6** was also employed as the chiral organocatalyst. The method was then applied to an elegant synthesis of anti-HIV drug BMS-

986001. Although the DYKAT of lactol **3-2a** was nicely demonstrated by Ortiz and co-workers, it was not obvious that the DKDA of substrates **3-2b** and **3-2c** could be easily achieved. In fact, our results have indicated that it is challenging to override the intrinsic diastereoselectivity for mismatched substrates.

We also tried to acylate substrates **3-L-2c** and **3-2c** under the conditions in entry 7 in **Scheme 3-3** using benzotetramisole (BTM) catalyst **3-9** (**Scheme 3-5**), which was first introduced by Birman for the kinetic resolution of alcohols.[20] We obtained products with d.r.s ranging from 8:1 to 1:7 for matched and mismatched substrates. We were then attracted by Shiina's mixed anhydride conditions for the kinetic resolution of alcohols because a wide variety of carboxylic acids are readily available.[26] We explored different carboxylic acids for the acylation of matched substrate **3-2c** using catalyst **3-9** as shown in **Scheme 3-5**. The diastereoselectivity for product **3-8b** was improved from 8:1 (**Scheme 3-3**, entry 2) to 13:1 (**Scheme 3-5**, entry 1) under these new conditions. We quickly found that simple phenylacetic acid yielded *trans*-**3-8g** exclusively (**Scheme 3-5**, entry 6). The reaction also worked well in $CHCl_3$ (**Scheme 3-5**, entries 8 and 9), and it became the choice of solvent since the catalyst is more soluble in $CHCl_3$ than ether.

Scheme 3-5. Screening of mixed anhydride for DKDA



Entry	Acid **3-10**	Solvent	Conversion[a]	d.r. (*trans:cis*)[a]
1	AcOH	Et_2O	85%	13:1
2	EtCOOH	Et_2O	>99%	18:1
3	*i*PrCOOH	Et_2O	>99%	9:1
4	PhCOOH	Et_2O	<10%	-
5	$Ph_2CHCOOH$	Et_2O	>99%	14:1
6	$PhCH_2COOH$	Et_2O	>99%	> 20:1
7	$PhCH_2COOH$	DCM	80%	16:1
8	$PhCH_2COOH$	$CHCl_3$	>99%	> 20:1
9	$PhCH_2COOH$	$CHCl_3$	76%[b]	> 20:1

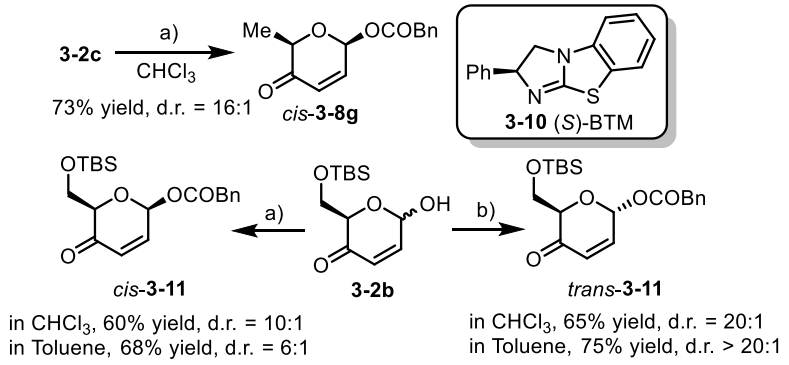
[a] The conversion of **3-2c** and d.r. of *trans*-**3-8** were determined by ^{1}H-NMR of crude product using CH_2Br_2 as internal standard.
[b] Isolated yield.

3.2.2 Substrate Scope and Applications

With these new conditions in hand, we examined the acylation of substrate **3-2c** using catalyst **3-10**, the more challenging mismatched scenario (**Scheme 3-6**). Product *cis*-**3-8g** was prepared in high yield and diastereoselectivity. We were also pleased

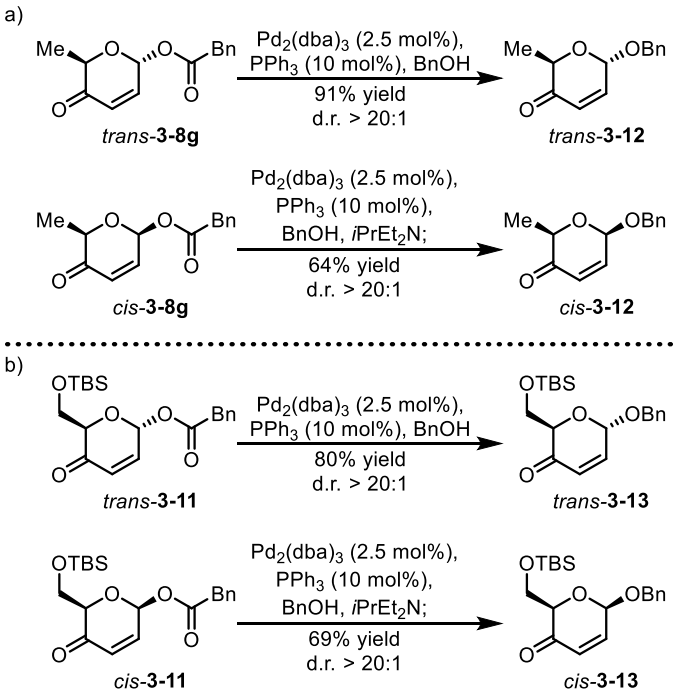
to find that both α-(*trans*-) and β-(*cis*-) isomeric products **3-11** could be prepared in high diastereoselectivity using catalyst **3-9** or **3-10**, though the reaction was much slower for the mismatched case in $CHCl_3$. Faster reaction and higher yield were observed in toluene for products *trans*-**3-11** and *cis*-**3-11**. Both enantiomers of substrates **3-2b** were prepared highly enantioselectively (98% *ee*) according to our previous protocols.[17] All diastereoisomers of **3-8g** and **3-11** could be easily separated by SiO_2 column chromatography, and the yield refers to the isolated yield of a single isomer. All of these isomers are basic chiral building blocks for the synthesis of various oligosaccharides *via* Pd-catalyzed glycosylation.[4, 15]

Scheme 3-6. Catalyst-directed DKDA of different lactols



Following O'Doherty's conditions,[16] glycosides **3-12** and **3-13** were prepared efficiently and stereospecifically from the corresponding esters *via* Pd−π-allyl intermediates (**Scheme 3-7**). All of the ester substrates (**3-8g** and **3-11**) employed here are single stereoisomers (d.r.s > 20:1). The standard conditions worked well for most substrates, including *trans*-**3-8g** and *trans*-**3-11**. However, the d.r. of the product dropped to 6:1 for *cis*-**3-8g**. The addition of organic base significantly improved the diastereomeric ratio. Similarly, the addition of base is required for the preparation of *cis*-**3-13**. Various post-glycosylation modification methods have been developed by O'Doherty and co-workers for the conversion of products in **Scheme 3-7** to diverse range of mono- and oligo-saccharides.[4, 15]

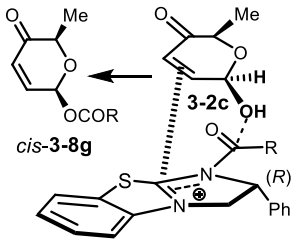
Scheme 3-7. Pd-catalyzed stereospecific glycosylation



3.2.3 Mechanism

According the transition-state model proposed by Profs. Houk and Birman for BTM catalyzed kinetic resolution of benzylic, allylic, and propargylic secondary alcohols,[20b, 27] the cation-π interaction between the cationic acylated-BTM catalyst and the π system of the substrates is the dominant factor for the high enantioselectivity in their transformations. We don't think the transition-state model they proposed is the model in our DKDA reaction for the following two major reasons: 1) The π system in our substrates **3-2b** and **3-2c** is part of enone moiety. The electron-withdrawing carbonyl group makes the alkene π system relatively electron-deficient and difficult to interact with the cationic acylated-catalyst through cation-π interaction; 2) When we tried to fit our substrate **3-2c** to their model, an opposite reaction outcome was predicted (**Scheme 3-8**). When (*R*)-BTM catalyst **3-9** was used in DKDA, *trans*-**3-8g** could be obtained as the major product, however, the model predicted *cis*-**3-8g** as the major one.

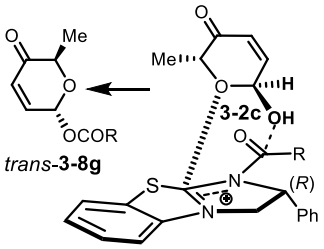
Scheme 3-8. Fitting DKDA substrate **3-2c** on model proposed by Profs. Houk and Birman



Model prediction: *cis*-**3-8g**
Observation: *trans*-**3-8g**

Obviously, if we flipped substrate **3-2c** 180°, the predicted product would correlate with the experimental results. For this model, a new type of cation-lone pair interaction is proposed between the cationic acylated-BTM catalyst and the lone pair of the oxygen on the pyranone ring (**Scheme 3-9**). While the detailed density functional theoretical calculations of this particular system is still ongoing in our collaborator Prof. Peng Liu's group, we have demonstrated that the nature of this cation-lone pair interaction is largely charge-dipole type of electrostatic interaction in a related site-selective acylation reaction.[28]

Scheme 3-9. Fitting DKDA substrate **3-2c** based on cation-lone pair interaction



Model prediction: *trans*-**3-8g**
Observation: *trans*-**3-8g**

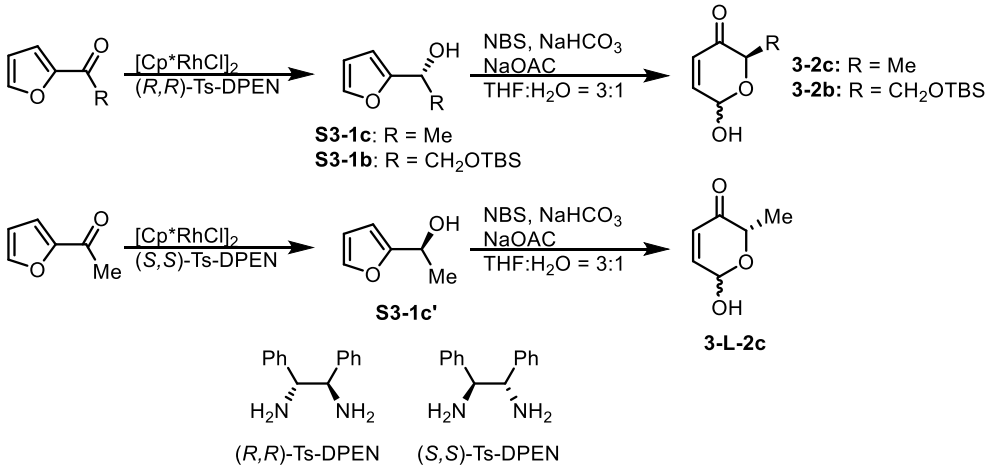
3.2.4 Conclusion

In summary, the combination of chiral organocatalyst-directed DKDA and Pd-catalyzed glycosylation allows the complete stereochemical control of the anomeric center and paves the way for highly stereoselective *de novo* synthesis of many natural and non-natural carbohydrates.

3.3 Experimental Section

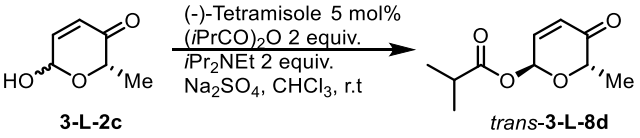
3.3.1 Methods for the preparation of substrates

Substrates **3-2c, 3-2b** and **3-L-2c** were prepared according to our previously reported procedures and their spectra are in accordance with literature.[17, 24] For **S3-1b**, $[\alpha]_D^{22}$= +14.7 (*c* = 0.95, CH_2Cl_2), literature[15a] $[\alpha]_D^{22}$= +14.5 (*c* = 1.0, CH_2Cl_2). For **S3-1c**, $[\alpha]_D^{22}$= +20.1 (*c* = 1.2, CH_2Cl_2), literature[29] $[\alpha]_D^{25}$= +20.8 (*c* = 1.0, CH_2Cl_2). For **S3-1c'**, $[\alpha]_D^{22}$= -19.4 (*c* = 1.0, CH_2Cl_2), literature[30] $[\alpha]_D^{20}$= -20.1 (*c* = 1.0, CH_2Cl_2).



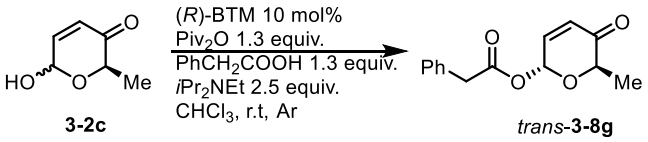
3.3.2 Methods for chiral catalyst-directed DKDA

1) Tetramisole-catalyzed DKDA of **3-L-2c**:



To an oven-dried flask was added **3-L-2c** (25.6 mg, 0.2 mmol), (-)-Tetramisole (2 mg, 0.01 mmol), *i*Pr_2NEt (66.1 µL, 0.4 mmol), Na_2SO_4 (80 mg) and anhydrous $CHCl_3$ (2 mL, amylene as stabilizer) under Ar. The mixture was stirred at RT for 5 min before (*i*PrCO)$_2$O (66.3 µL, 0.4 mmol) was added. The reaction was stirred at RT for 12 hours and monitored by TLC. After the reaction was completed, the solvent was evaporated and the residue was purified by flash column chromatography (eluent: Hex:EA=6:1, V/V) to afford product *trans*-**3-L-8d** as yellow oil (36.5 mg, 92% yield).

2) (*R*)-BTM-catalyzed DKDA of **3-2b** and **3-2c**:

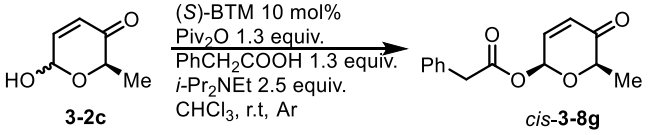


To an oven-dried flask was added **3-2c** (25.6 mg, 0.2 mmol), (*R*)-BTM (5 mg, 0.02 mmol), *i*Pr$_2$NEt (82.7 μL, 0.5 mmol) and anhydrous $CHCl_3$ (1.2 mL, amylene as stabilizer) under Ar. The mixture was stirred at RT for 5 min before Piv_2O (52.7 μL, 0.26 mmol) and phenyl acetic acid (35.4 mg, 0.26 mmol) were added. The reaction was stirred at RT for 12 h and monitored by TLC. After the reaction was completed, the solvent was evaporated and the residue was purified by flash column chromatography (eluent: Hex:EA=8:1, V/V) to afford product *trans*-**3-8g** as yellow oil (37.4 mg, 76% yield).

To an oven-dried flask was added **3-2b** (51.7 mg, 0.2 mmol), (*R*)-BTM (5 mg, 0.02 mmol), *i*Pr$_2$NEt (82.7 μL, 0.5 mmol) and anhydrous toluene (1.2 mL) under Ar. The mixture was stirred at RT for 5 min before Piv_2O (52.7 μL, 0.26 mmol) and phenyl acetic acid (35.4 mg, 0.26 mmol) were added. The reaction was stirred at RT for 5 h and monitored by TLC. After the reaction was completed, the solvent was evaporated and the residue was purified by flash column chromatography (eluent: Hex:EA=10:1, V/V) to afford product *trans*-**3-11** as yellow oil (56.5 mg, 75% yield).

Note: The acylation of substrate **3-2b** is much faster in toluene (5 h) than in $CHCl_3$ (2 d) and the d.r. can be retained as 20:1 or higher.

3) (*S*)-BTM-catalyzed DKDA of **3-2b** and **3-2c**:

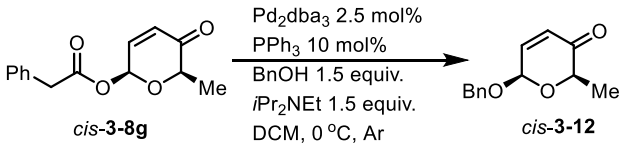


To an oven-dried flask was added **3-2c** (25.6 mg, 0.2 mmol), (*S*)-BTM (5 mg, 0.02 mmol), *i*Pr$_2$NEt (82.7 μL, 0.5 mmol) and anhydrous $CHCl_3$ (1.2 mL, amylene as stabilizer) under Ar. The mixture was stirred at RT for 5 min before Piv_2O (52.7 μL, 0.26 mmol) and phenyl acetic acid (35.4 mg, 0.26 mmol) was added. The reaction was stirred at RT for 24 h and monitored by TLC. After the reaction was completed, the solvent was evaporated and the residue was purified by flash column chromatography (eluent: Hex:EA=8:1, V/V) to afford product *cis*-**3-8g** as yellow oil (36.0 mg, 73% yield).

To an oven-dried flask was added **3-2b** (51.7 mg, 0.2 mmol), (*S*)-BTM (5 mg, 0.02 mmol), *i*Pr$_2$NEt (82.7 μL, 0.5 mmol) and anhydrous toluene (1.2 mL) under Ar. The mixture was stirred at RT for 5 min before Piv$_2$O (52.7 μL, 0.26 mmol) and phenyl acetic acid (35.4 mg, 0.26 mmol) was added. The reaction was stirred at RT for 6 h and monitored by TLC. After the reaction was completed, the solvent was evaporated and the residue was purified by flash column chromatography (eluent: Hex:EA=10:1, V/V) to afford product *cis*-**3-11** as yellow oil (51.2 mg, 68% yield).

Note: The acylation of substrate **3-2b** is much faster in toluene (6 h) than in $CHCl_3$ (4 d), though the d.r. drops from 10:1 to 6:1.

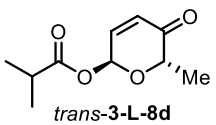
3.3.3 Method for Pd-catalyzed stereospecific glycosylation



To an oven-dried flask was added *cis*-**3-8g** (24.6 mg, 0.1 mmol), BnOH (15.5 μL, 0.15 mmol), *i*Pr$_2$NEt (24.8 μL, 0.15 mmol) and anhydrous DCM (0.8 mL). The mixture was stirred at 0 °C for 5 min before a DCM (0.2 mL) solution of Pd_2dba_3 (2.3 mg, 0.0025 mmol) and PPh_3 (2.6 mg, 0.01 mmol) was added. The reaction was stirred at 0 °C for 1 h under Ar and monitored by TLC. After the reaction was completed, the solvent was evaporated and the residue was purified by flash column chromatography (eluent: Hex:EA=10:1, V/V) to afford product *cis*-**3-12** as white oil (14.0 mg, 64% yield).

Note: *cis*-**3-13** (24.0 mg, 69% yield, eluent: Hex:EA=15:1) was also prepared according to this method from *cis*-**3-11** (37.7 mg, 0.1 mmol).

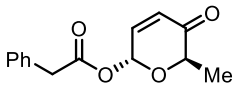
3.3.4 Characterization data for acylation products



trans-**3-L-8d**

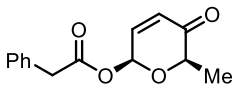
trans-**3-L-8d**: (2*S*,6*S*)-6-methyl-5-oxo-5,6-dihydro-2H-pyran-2-yl isobutyrate. Yellow oil. $[\alpha]_D^{22}$ = -130.9° ($CHCl_3$, c = 3.0). ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 6.92 – 6.86 (dd, *J* = 10.0, 3.5 Hz, 1H), 6.49 (d, *J* = 3.5 Hz, 1H), 6.21 (d, *J* = 10.5 Hz, 1H), 4.60 (q, *J* = 7.0 Hz, 1H), 2.63 (m, 1H), 1.41 (d, *J* = 6.5 Hz, 3H), 1.21 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 196.1, 175.8, 142.0, 128.4, 87.1,

72.5, 34.3, 19.1, 19.0, 15.6. IR: ν 2979, 1751, 1703, 1098, 759 cm^{-1}. HRMS (ESI) for $C_{10}H_{14}O_4$ (M+H), 199.0965 (Calc.), found 199.0963.



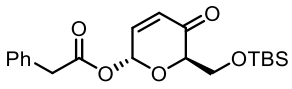
trans-**3-8g**

trans-**3-8g**: (2*R*,6*R*)-6-methyl-5-oxo-5,6-dihydro-2H-pyran-2-yl 2-phenylacetate. Yellow oil. $[\alpha]_D^{22}$ = -100.8° ($CHCl_3$, c = 1.0). ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 7.37 - 7.32 (m, 2H), 7.32 - 7.28 (m, 3H), 6.85 (dd, *J* = 10.0, 3.5 Hz, 1H), 6.49 (d, *J* = 3.5 Hz, 1H), 6.19 (d, *J* = 10.0 Hz, 1H), 4.45 (q, *J* = 7.0 Hz, 1H), 3.69 (s, 2H), 1.35 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 196.0, 170.4, 141.6, 133.5, 129.4, 129.0, 128.6, 127.7, 87.6, 72.6, 41.6, 15.5. IR: ν 3021, 1749, 1703, 1216, 756 cm^{-1}. HRMS (ESI) for $C_{14}H_{14}O_4$ (M+Na), 269.0784 (Calc.), found 269.0783.



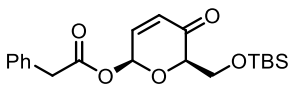
cis-**3-8g**

cis-**3-8g**: (2*S*,6*R*)-6-methyl-5-oxo-5,6-dihydro-2H-pyran-2-yl 2-phenylacetate. Yellow oil. $[\alpha]_D^{22}$ = 107.2° ($CHCl_3$, c = 0.5). ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 7.37 - 7.31 (m, 2H), 7.31 – 7.27 (m, 3H), 6.84 (dd, *J* = 10.0, 2.0 Hz, 1H), 6.58 – 6.55 (m, 1H), 6.20 (d, *J* = 10.0 Hz, 1H), 4.34 (q, *J* = 7.0 Hz, 1H), 3.69 (s, 2H), 1.36 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 196.1, 170.2, 143.2, 133.2, 129.6, 129.0, 128.4, 127.7, 88.2, 76.1, 41.6, 18.8. IR: ν 3020, 1753, 1699, 1217, 764 cm^{-1}. HRMS (ESI) for $C_{14}H_{14}O_4$ (M+Na), 269.0784 (Calc.), found 269.0780.



trans-**3-11**

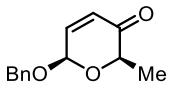
trans-**3-11**: (2*S*,6*S*)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-oxo-5,6-dihydro-2H-pyran-2-yl 2-phenylacetate. Yellow oil. $[\alpha]_D^{22}$ = -79.6° ($CHCl_3$, c = 3). ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 7.35 – 7.25 (m, 5H), 6.89 (dd, *J* = 10.5, 3.5 Hz, 1H), 6.62 (d, *J* = 3.5 Hz, 1H), 6.22 (d, *J* = 10.5 Hz, 1H), 4.38 (dd, *J* = 4.5, 2.5 Hz, 1H), 4.06 – 3.96 (m, 2H), 3.67 (s, 2H), 0.85 (s, 9H), 0.04 (d, *J* = 7.5 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 193.9, 170.2, 142.2, 133.4, 129.5, 129.0, 128.9, 127.6, 87.8, 78.2, 62.9, 41.5, 26.05, 26.03, 18.5, -5.1, -5.2. IR: ν 2931, 1751, 1702, 1134, 757 cm^{-1}. HRMS (ESI) for $C_{20}H_{28}O_5Si$ (M+Na), 399.1598 (Calc.), found 399.1610.



cis-**3-11**

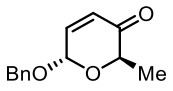
cis-**3-11**: (2*S*,6*R*)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-oxo-5,6-dihydro-2H-pyran-2-yl 2-phenylacetate. Yellow oil. $[\alpha]_D^{22}$ = 88.2° ($CHCl_3$, c = 0.5). ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.35 - 7.27 (m, 5H), 6.83 (dd, *J* = 10.0, 2.5 Hz, 1H), 6.59 (dd, *J* = 2.5, 1.5 Hz, 1H), 6.23 (dd, *J* = 10.5, 1.5 Hz, 1H), 4.31 (dd, *J* = 6.0, 4.5 Hz, 1H), 4.00 - 3.92 (m, 2H), 3.70 (s, 2H), 0.88 (s, 9H), 0.04 (d, *J* = 4.5 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 193.6, 170.2, 143.1, 133.3, 129.5, 129.3, 128.9, 127.7, 88.0, 80.8, 64.3, 41.5, 26.1, 18.6, -5.0, -5.1. IR: v 2929, 1756, 1697, 1136, 761 cm^{-1}. HRMS (ESI) for $C_{20}H_{28}O_5Si$ (M+Na), 399.1598 (Calc.), found 399.1602.

3.3.5 Characterization data for Pd-catalyzed stereospecific glycosylation products



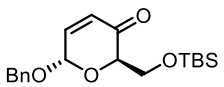
cis-**3-12**

cis-**3-12**: (2*R*,6*R*)-6-(benzyloxy)-2-methyl-2H-pyran-3(6H)-one. White oil. $[\alpha]_D^{22}$ = -38.4° ($CHCl_3$, c = 0.75; literature: $[\alpha]_D^{22}$ = -41.8°, c = 1.20 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.42 – 7.30 (m, 5H), 6.91 (dd, *J* = 10.0, 2.0 Hz, 1H), 6.14 (d, *J* = 10.0 Hz, 1H), 5k.40 (s, 1H), 4.95 (d, *J* = 12.0 Hz, 1H), 4.69 (d, *J* = 12.0 Hz, 1H), 4.24 (q, *J* = 10.8 Hz, 1H), 1.53 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, TMS): δ 197.1, 146.8, 137.1, 128.8, 128.4, 128.3, 94.6, 75.6, 70.4, 17.6. All spectral data are in accordance with literature.[31]



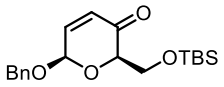
trans-**3-12**

trans-**3-12**: (2*R*,6*S*)-6-(benzyloxy)-2-methyl-2H-pyran-3(6H)-one. Yellow oil. $[\alpha]_D^{22}$ = -55.4° (CH_2Cl_2, c = 0.5; literature: $[\alpha]_D^{22}$ = -54.6°, c = 0.77 in CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.40 – 7.29 (m, 5H), 6.83 (dd, *J* = 10.5, 3.5 Hz, 1H), 6.09 (d, *J* = 10.5 Hz, 1H), 5.27 (d, *J* = 3.5 Hz, 1H), 4.84 (d, *J* = 12.0 Hz, 1H), 4.69 (d, *J* = 12.0 Hz, 1H), 4.55 (q, *J* = 7.0 Hz, 1H), 1.37 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, TMS): δ 197.2, 143.6, 137.4, 128.8, 128.4, 128.4, 127.8, 92.6, 71.1, 70.8, 15.5. All spectral data are in accordance with literature.[9b]



trans-**3-13**

trans-**3-13**: (2*R*,6*S*)-6-(benzyloxy)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-2H-pyran-3(6H)-one. Yellow oil. $[\alpha]_D^{22}$ = -44.4° (CH_2Cl_2, c = 0.18; literature: $[\alpha]_D^{22}$ = -45.8°, c = 1.0 in CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.40 – 7.29 (m, 5H), 6.87 (dd, *J* = 10.0, 3.0 Hz, 1H), 6.11 (d, *J* = 10.0 Hz, 1H), 5.40 (d, *J* = 3.5 Hz, 1H), 4.87 (d, *J* = 11.5 Hz, 1H), 4.68 (d, *J* = 11.5 Hz, 1H), 4.49 (dd, *J* = 5.5, 2.5 Hz, 1H), 4.09 – 4.00 (m, 2H), 0.89 (s, 9H), 0.08 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$, TMS): δ 195.0, 144.2, 137.3, 128.8, 128.5, 128.5, 128.4, 92.4, 76.5, 70.8, 62.8, 26.1, -5.0, -5.1. All spectral data are in accordance with literature.[15a]



cis-**3-13**

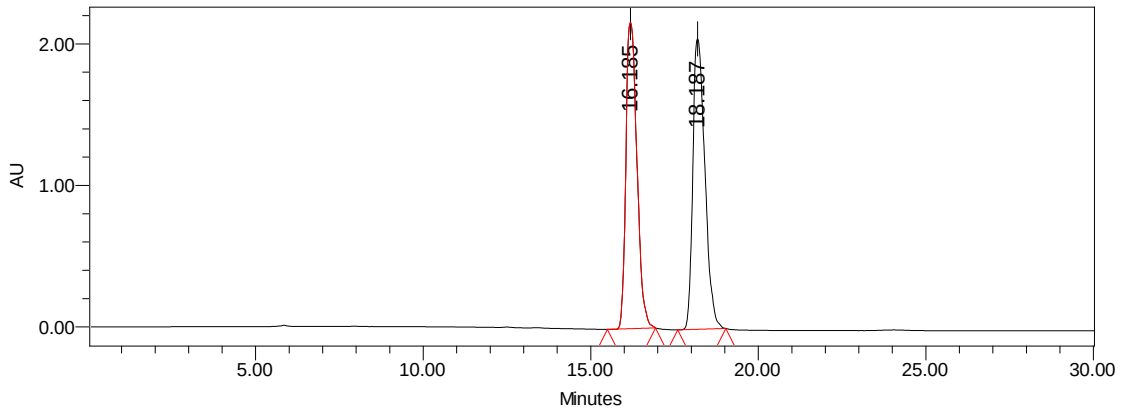
cis-**3-13**: (2*R*,6*R*)-6-(benzyloxy)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-2H-pyran-3(6H)-one. Yellow oil. $[\alpha]_D^{22}$ = -5.9° (CH_2Cl_2, c = 0.7; literature for its enantiomer: $[\alpha]_D^{22}$ = 5.8°, c = 1.2 in CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.45 – 7.31 (m, 5H), 6.90 (dd, *J* = 10.0, 2.5 Hz, 1H), 6.13 (dd, *J* = 10.5, 1.5 Hz, 1H), 5.40 (s, 1H), 4.99 (d, *J* = 12.0 Hz, 1H), 4.73 (d, *J* = 11.5 Hz, 1H), 4.25 – 4.22 (m, 1H), 4.11 – 4.00 (m, 2H), 0.91 (s, 9H), 0.08 (d, *J* = 4.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$, TMS): δ 194.8, 146.6, 137.1, 128.8, 128.8, 128.6, 128.3, 93.9, 80.7, 70.4, 64.0, 26.1, -5.0, -5.0. All spectral data are in accordance with literature.[31]

3.3.6 HPLC chromatogram for S3-1c, S3-1c' and S3-1b

For substrates **S3-1c** and **S3-1c'**

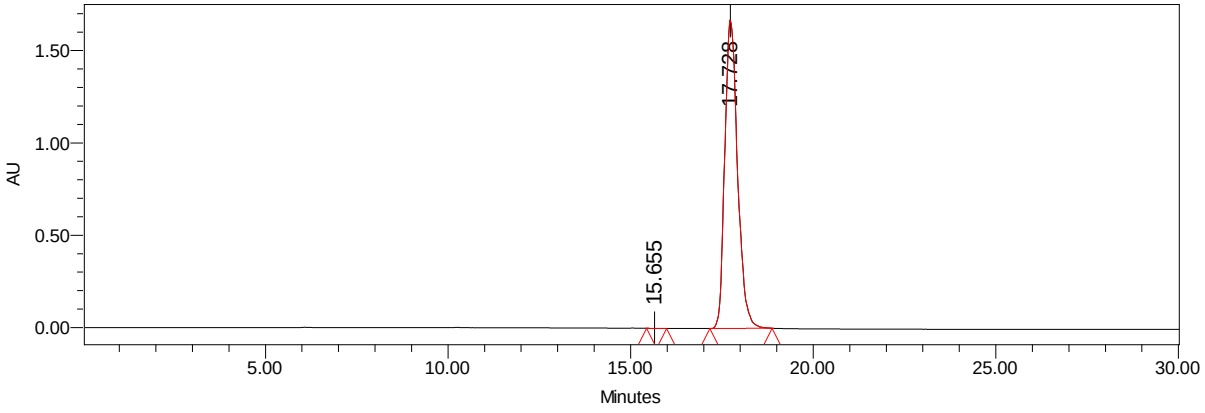
(Chiralcel OJ-H, eluent: hexane/2-propanol = 95/5, flow rate: 1.0 mL/min, detection at 225 nm)

Racemic **S3-1c**:



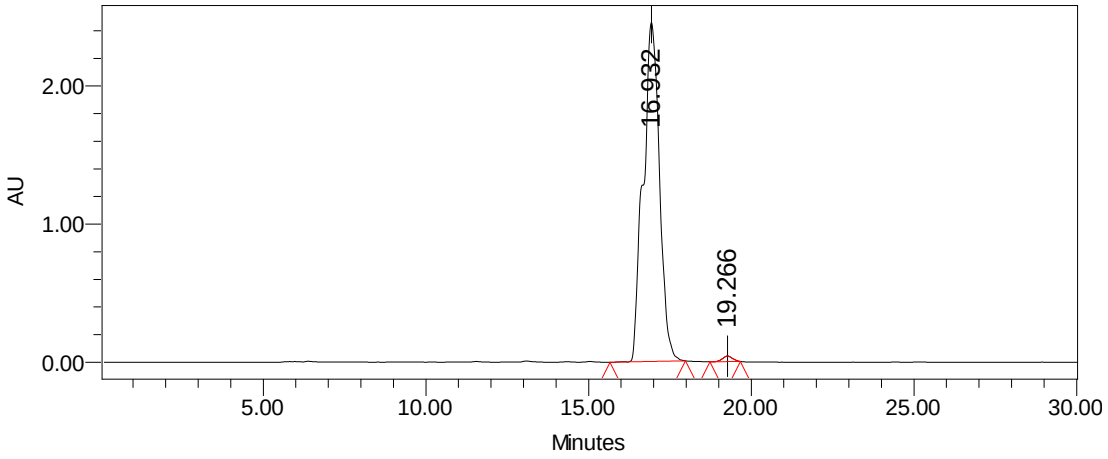
	Retention Time	Area	% Area	Height	Int Type
1	16.185	49481744	49.07	2163970	bb
2	18.187	51353017	50.93	2054504	bb

Enantioenriched **S3-1c**:



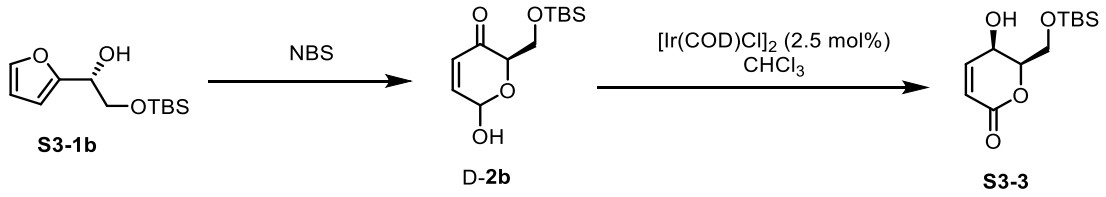
	Retention Time	Area	% Area	Height	Int Type
1	15.655	516	0.00	45	bb
2	17.728	40810626	100.00	1672195	bb

Enantioenriched **S3-1c'**:



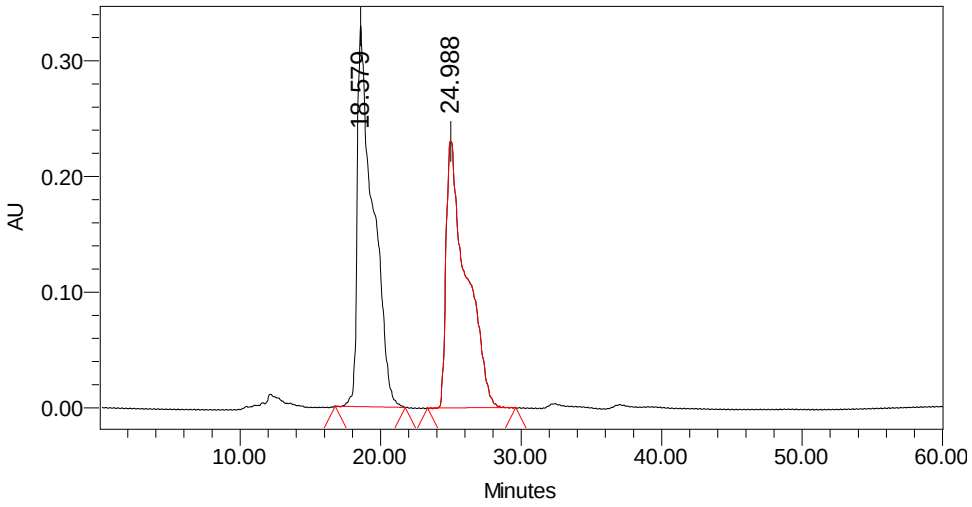
	Retention Time	Area	% Area	Height	Int Type
1	16.932	85396380	98.99	2454309	bb
2	19.266	867333	1.01	39701	Bb

We were not able to separate the racemic sample of **S3-1b** directly by HPLC. We derivatized racemic and enantioenriched **S3-1b** to **S3-3** in two steps following our previously established procedures.[17]



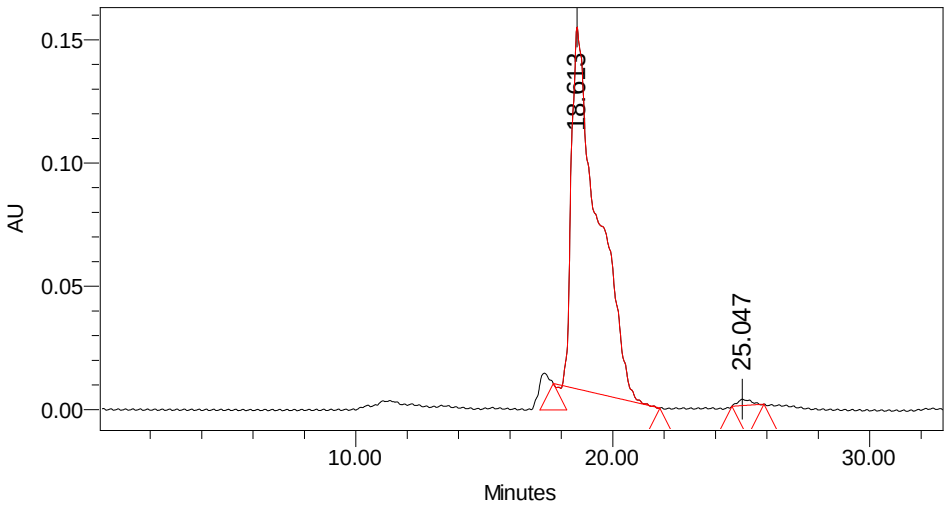
Racemic **S3**:

(Chiralcel OD-H, eluent: hexane/2-propanol = 90/10, flow rate: 0.7 mL/min, detection at 220 nm)



	Retention Time	Area	% Area	Height	Int Type
1	18.579	25486786	52.62	329563	bb
2	24.988	22951118	47.38	230462	bb

Enantioenriched **S3**:



	Retention Time	Area	% Area	Height	Int Type
1	18.613	10458377	99.12	146802	bb
2	25.047	92403	0.88	2616	bb

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Chapter 4

Dynamic Kinetic Diastereoselective Acylation of Carbohydrate Anomeric Hydroxyl Groups Directed by Chiral Catalysts (DKDA-2.0)

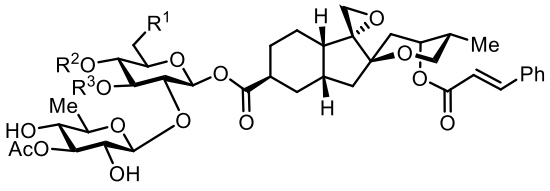
Part of this chapter was taken from the following published article.

H.-Y. Wang, C. J. Simmons, Y. Zhang, A. M. Smits, G. G. Balzer, S. Wang, W. Tang, *Org. Lett.* **2017**, *19*, 508-511.

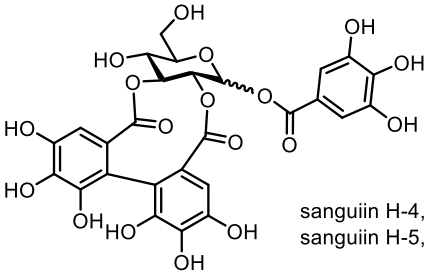
4.1 Introduction

The importance of complex carbohydrate-containing natural products continues to stimulate the development of efficient and stereoselective methods for their synthesis. 1-Acyl mono- or oligo-saccharides exist in many bioactive natural products, such as QS-21A, phyllanthoside, and phyllanthostatins (**Scheme 4-1**).[1] Numerous members of the ellagitannin family also have a 1-acylglycoside unit, such as sanguiin H-4 and sanguiin H-5 in **Scheme 4-1**.[1d] β-1-Acyl glucuronides are the major metabolites of most carboxylic acid containing drugs, and it has become critical to stereoselectively prepare β-1-acyl glucuronides for toxicity evaluation during drug development.[2] Several β-1-acyl glucosides were also identified as metabolites of bile acids and important biomarkers for patients with hepatic diseases.[3] In addition, numerous drugs have been linked to glucose and its derivatives to selectively target cancer cells.[4] Interestingly, the β-1-acyl glucose conjugate showed better activity than the corresponding α-form in the case of glucose−triptolide conjugates in recent studies.[5] However, a general and catalyst-controlled method has not been developed for the stereoselective acylation of the anomeric hydroxyl group to form either isomers.[6]

Scheme 4-1. Examples of 1-acyl sugar natural products



phyllanthoside, $R^1 = R^2 = H$, $R^3 = Ac$;
phyllanthostatin 1, $R^1 = R^3 = H$, $R^2 = Ac$;
phyllanthostatin 2, $R^1 = OH$, $R^2 = H$, $R^3 = Ac$.



sanguiin H-4, α–anomer
sanguiin H-5, β–anomer

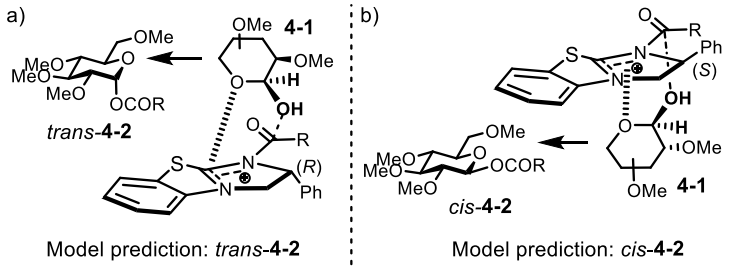
Recently, we[7] and others[8] reported that chiral catalysts could mediate the enantio- and diastereo-selective acylation of allylic alcohols in pyranones derived from Achmatowicz rearrangement[9]. The resulting allylic esters could then undergo Pd-catalyzed stereospecific *O*-alkylation for *de novo* synthesis of carbohydrates.[10] We proposed that the cation-lone pair

interaction between the cationic acylated-BTM catalyst and the lone pair of the oxygen on the pyranone ring is the dominant factor in the DKDA reaction.

To further explore the scope of this cation-lone pair interaction in catalysis, we studied the dynamic kinetic diastereoselective acylation of anomeric hydroxyl groups in naturally occurring mono- and oligosaccharides (DKDA-2.0). These substrates don't have an olefin moiety that could interact with catalyst through cation-π interaction. In general, it is still challenging to synthesize glycosyl esters in a diastereoselective manner.

According to our proposed model, when substrate **4-1** was used as substrate, (*R*)-BTM would give *trans*-**4-2** as the major product and (*S*)-BTM would give *cis*-**4-2** as the major one (**Scheme 4-2**).

Scheme 4-2. Our proposed model for DKDA-2.0



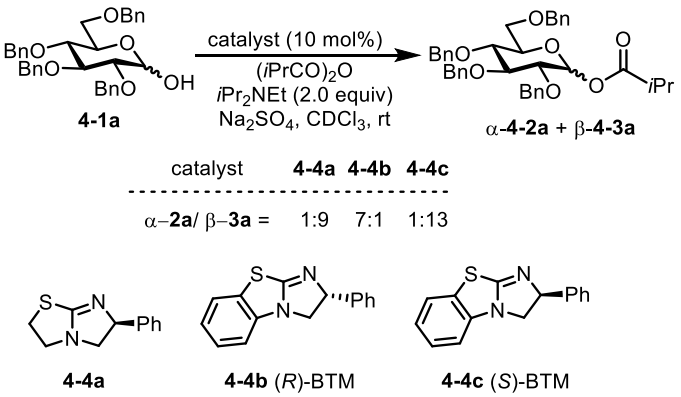
Our results in the following sections demonstrate that chiral catalysts can promote the stereoselective acylation of anomeric hydroxyl groups in a variety of carbohydrates to form either the α- or β-anomeric esters. The resulting α- and β-anomeric esters showed very different reactivity profiles toward reduction and glycosylation.

4.2 Results and Discussion

4.2.1 Optimization of Reaction Conditions

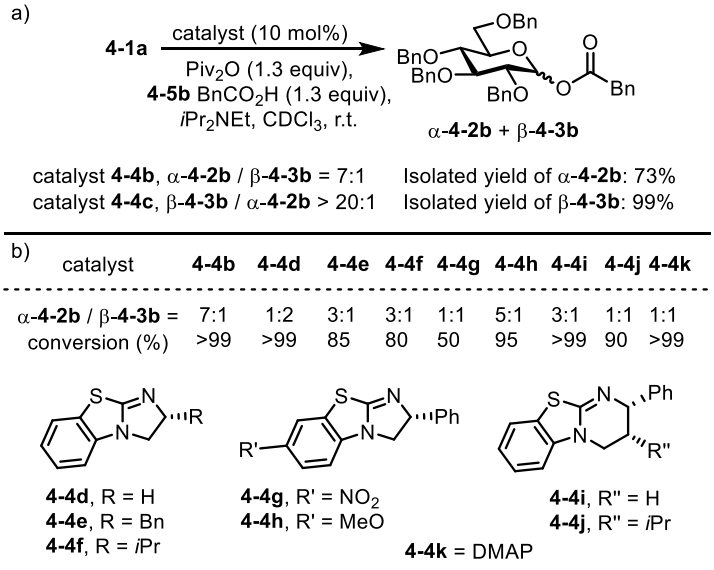
We first examined three commercially available chiral catalysts (**4-4a–c**) for the dynamic kinetic diastereoselective acylation (DKDA-2.0) of glucose derivative **4-1a** using isobutyric anhydride (**Scheme 4-3**). Both (*S*)-tetramisole[11] **4-4a** and (*S*)-benzotetramisole (BTM)[12] **4-4c** yielded the β-anomer as the major isomer, while (*R*)-BTM **4-4b** mainly provided the α-isomer. These results correlate with the predictions by using our proposed model.

Scheme 4-3. DKDA-2.0 with anhydride



We next turned our attention to the mixed anhydride method[13] due to the availability of diverse carboxylic acids and our previous success of using mixed anhydride method to further improve the diastereoselectivity[7] (**Scheme 4-4-a**). Exclusive formation of the β-anomer could be realized using (*S*)-BTM **4-4c** as the catalyst and phenyl acetic acid **4-5b** as the acylation reagent. We then screened various benzotetramisole catalysts[14] with different steric and electronic properties to further improve the selectivity for the α-isomer (**Scheme 4-4-b**). (*R*)-BTM **4-4b** remained the best catalyst for the highest α-selectivity. We also examined different solvents including toluene, *tert*-amyl alcohol, THF, dichloromethane, and acetonitrile. We found that the highest yield and d.r. for the α-isomer were obtained in chloroform.

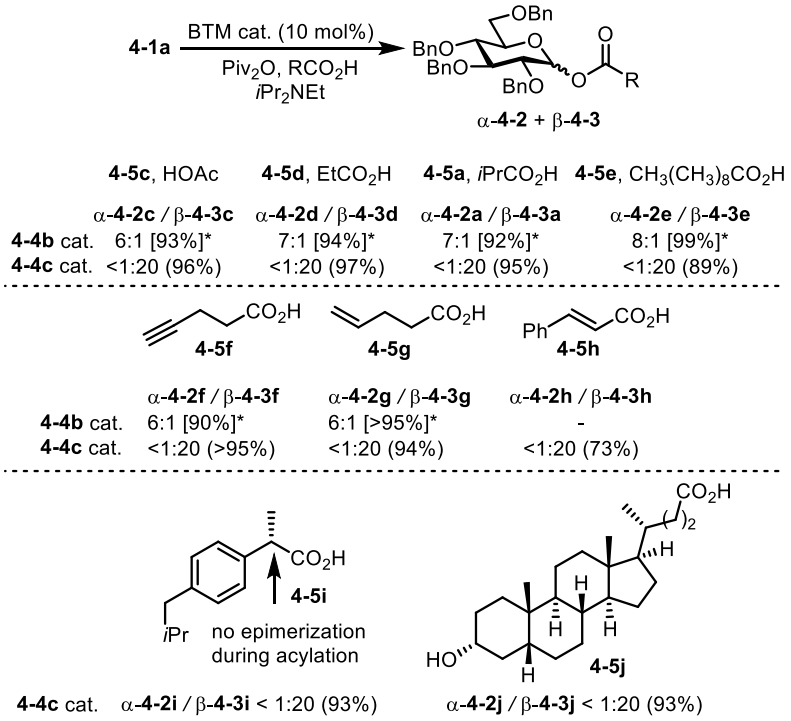
Scheme 4-4. Screening of catalysts for DKDA-2.0 of Glucose



4.2.2 Substrate Scope and Applications

We then investigated the scope of acids for the DKDA-2.0 of substrate **4-1a** (**Scheme 4-4**). Diverse carboxylic acids including α-substituted acid **5-5a**, acetic acid **5-5c**, long-chain carboxylic acid **5-5e**, and unsaturated carboxylic acids **5-5f**, **5-5g**, and **5-5h** all worked well. High selectivitity was observed for the formation of all β-isomers. The selectivity for the α-isomer ranges from 6:1 to 8:1. When (*S*)-ibuprofen **5-5i** was employed as the substrate, we did not observe any epimerization product. The β-glucosidic conjugates of acid **5-5j** and related bile acids are important biomarkers for patients with hepatic diseases.[3] We were pleased to find that the product β-**4-3j** was formed with high stereoselectivity under our standard conditions.

Scheme 4-4. Scope of carboxylic acids for DKDA-2.0 of glucose with mixed anhydrides



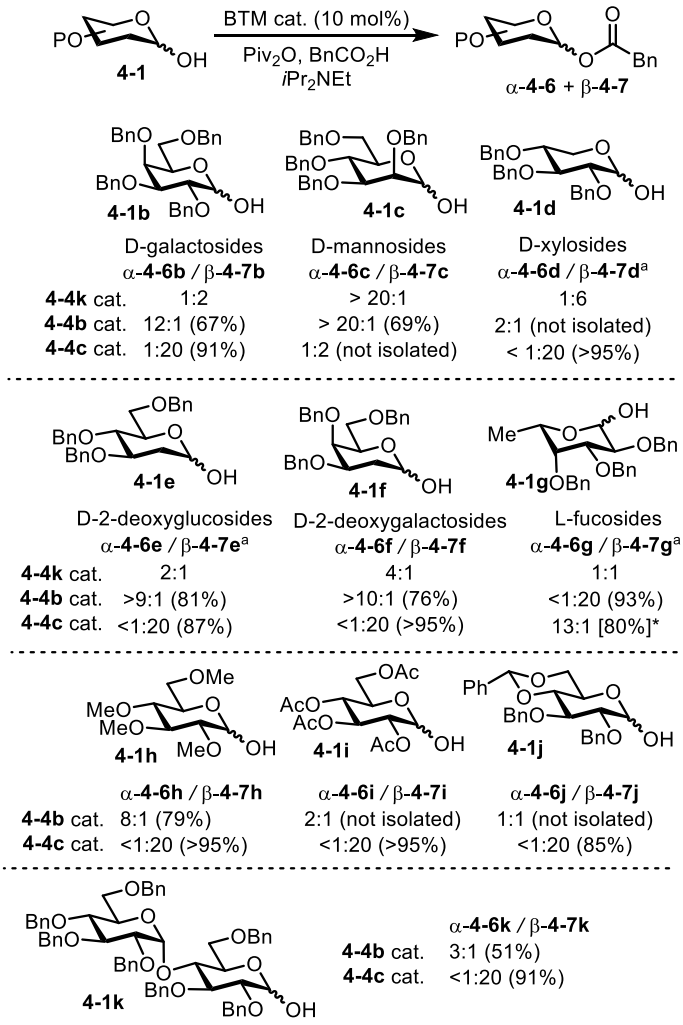
Note: The number in ( ) is the isolated yield of the major isomer.
The number in [ ]* is the isolated yield of the mixture of α–and β–isomer.

The scope of carbohydrates for the DKDA-2.0 of the anomeric hydroxyl group is examined in **Scheme 4-5**. We demonstrated that the preference for the β-isomer **4-7** remained high for protected D-galactose **4-1b**, D-xylose **4-1d**, 2-deoxy-D-glucose **4-1e**, 2-deoxy-D-galactose **4-1f**, and L-fucose **4-1g**. L-Fucose **4-1g** requires the opposite enantiomeric catalyst compared to D-sugars. It is worth mentioning that the intrinsic selectivity for most sugar substrates is low using DMAP as the catalyst. The intrinsic selectivity for mannose derivative **4-1c** is over 20:1 favoring the α-isomer. We were surprised that (*S*)-BTM catalyst was able to override this strong intrinsic bias and form β-mannoside **4-7c** as the major isomer. The intrinsic selectivity for xylose derivative **4-1d** is about 6:1 favoring the β-isomer. (*R*)-BTM catalyst is able to override the intrinsic bias, and α-xyloside **4-6d** is formed as

the major isomer.

We also briefly examined the effect of the protecting group on the diastereoselectivity using D-glucose as the example. The results for methyl ether **4-1h** are similar to those for benzyl ether **4-1a**. Interestingly, acetyl- and benzylidene-protected **4-1i** and **4-1j** showed decreased selectivity for the formation of α-esters, while the selectivity for the formation of the β-ester remained the same. A similar trend was also observed for disaccharide **4-1k**. The change of anomeric ratios by varying the protecting group is common in glycosylation reactions.[15] The mechanism for this intriguing selectivity change in acylation will be further investigated.[12c, 12d]

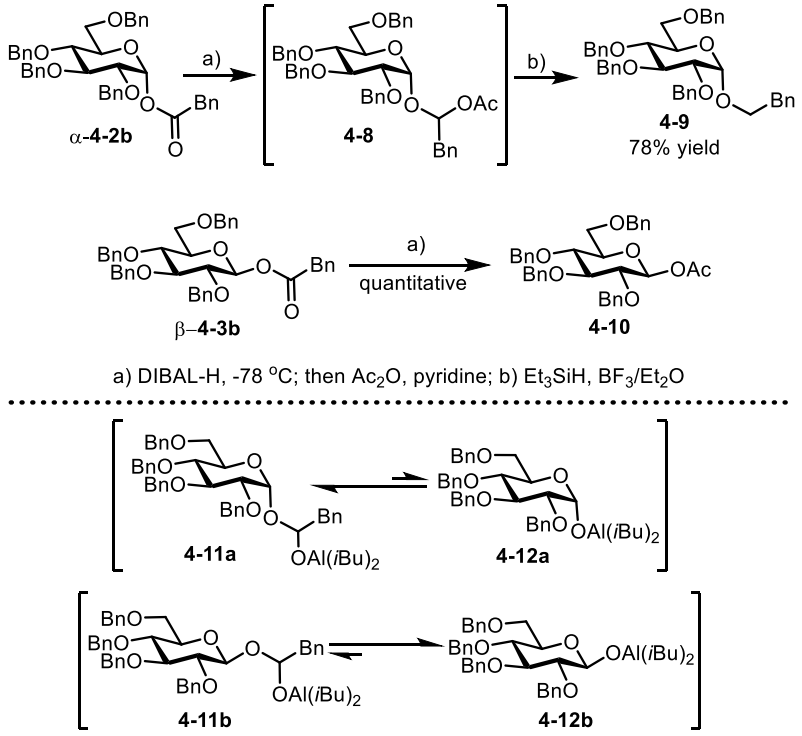
Scheme 4-5. Scope of sugar substrates for DKDA-2.0



Note: The number in ( ) is the isolated yield of the major isomer.
The number in [ ]* is the isolated yield of the mixture of α–and β–isomer.
[a] Data was acquired from Mr. Christopher Simmons

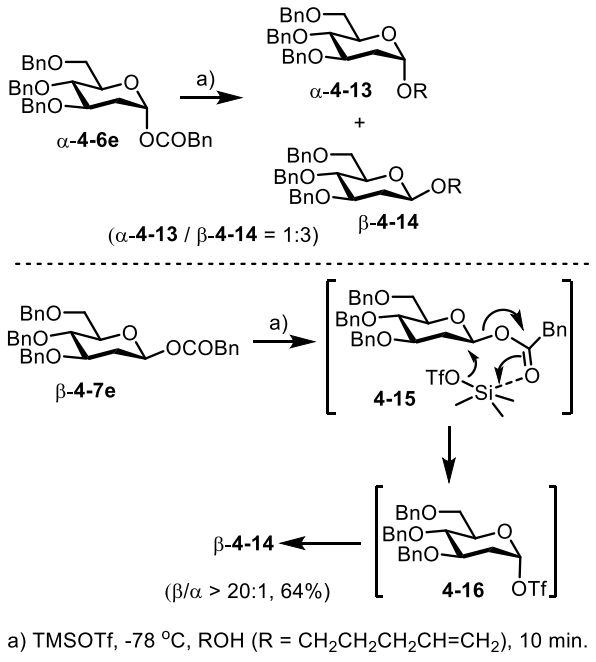
Reduction of the anomeric esters to ethers has been reported by Barrett *via* the formation of thionoester intermediates and desulfurization.[16] We investigated the possibility of one-pot reduction of esters to ethers based on a protocol reported by Rychnovsky (**Scheme 4-6**).[17] We found that α-glucoside **4-9** could be prepared from α-**4-2b** efficiently and there was no scrambling of stereochemistry. To our surprise, β-**4-3b** afforded simple acetyl ester **4-10** after the first step. The above results suggest that aluminum complex **4-11a** is stable under the reaction conditions and does not undergo further reduction to form **4-12a**, while aluminum complex **4-11b** is further reduced under the reaction conditions to form **4-12b**.

Scheme 4-6. Reduction of anomeric esters



Glycosylation of 2-deoxy sugars by stereospecific S_N2 displacement of 1-α-tosylate or 1-α-halo derivatives was recently reported.[18] When ester α-**4-6e** was employed as the substrate for glycosylation, a mixture of products α-**4-13** and β-**4-14** was obtained. In sharp contrast, β-2-deoxyglucoside β-**4-14** was selectively prepared from ester β-**4-7e**, presumably through a double S_N2 process (**Scheme 4-7**). The detailed mechanism and scope of this intriguing process is under further investigation.

Scheme 4-7. Synthesis of β-2-Deoxyglucosides



a) TMSOTf, -78 °C, ROH (R = $CH_2CH_2CH_2CH{=}CH_2$), 10 min.

4.2.3 Conclusion

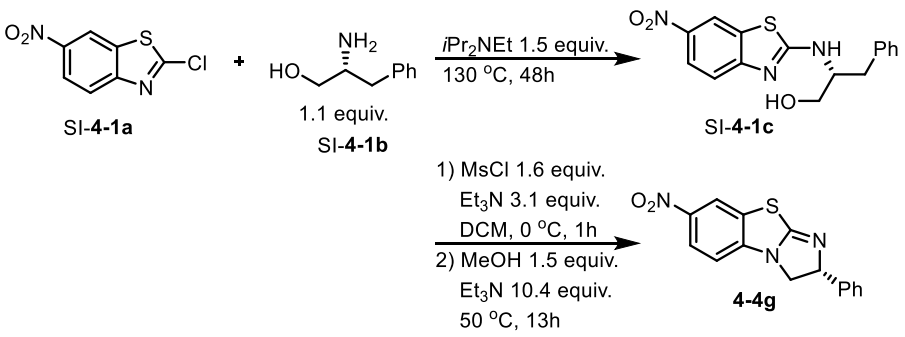
In summary, we have developed a chiral catalyst-directed dynamic kinetic stereoselective method for the acylation of anomeric hydroxyl groups in a variety of sugar substrates. The resulting α- or β-1-acylsugars have very different reactivity profiles in reduction and glycosylation reactions. The detailed mechanism for the catalyst-directed acylation is under investigation by our computational collaborators and will be reported in due course.

4.3 Experimental Section

4.3.1 Methods for the preparation of catalysts

Known catalyst **4-4a**, **4-4b**, **4-4c**, **4-4d**, **4-4e**, **4-4f** and **4-4j** were prepared according to literature procedure from commercially available materials.[12b, 13, 19] The spectra of catalyst **4-4a**,[12b] **4-4b**,[12b] **4-4c**,[12b] **4-4d**,[13] **4-4e**,[13] **4-4f**,[13] and **4-4j**[19] are in accordance with literature. Catalyst **4-4i** was purchased from Sigma-Aldrich.

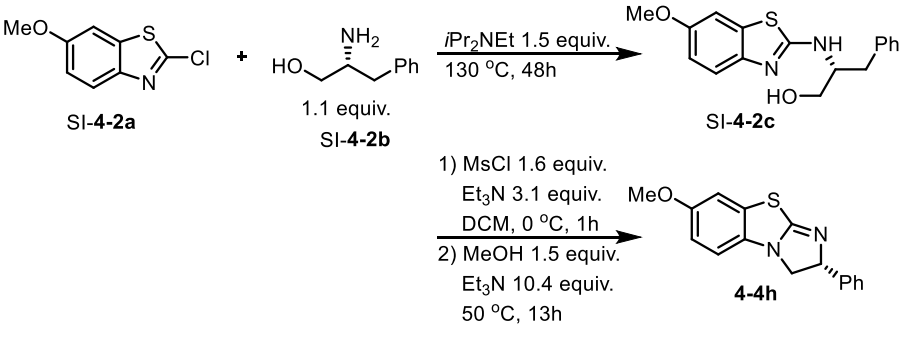
Catalyst **4-4g** was prepared according to literature procedures from commercially available materials as shown below.[13]



To a 30 mL pressure tube was added SI-**4-1a** (214.8 mg, 1 mmol), SI-**4-1b** (151 mg, 1.1 mmol) and *i*Pr$_2$NEt (0.2 mL to 1.0 mL). The tube was sealed and then stirred at 130 °C under argon. After 48 hours, the reaction was cooled to room temperature, diluted with MeOH:DCM = 1:1 solution (3-5 mL, it took around 8h to dissolve all the solid mixtures) and then transferred to a 50 mL flask. The mixture was concentrated in vacuo to afford SI-**1c**. The crude mixture was used in the next step without further purification.

To a solution of the above crude mixture in DCM (10 mL) at 0 °C were added Et$_3$N (0.45 mL, 3.1 mmol) and MsCl (0.13 mL, 1.6 mmol) under argon. The reaction was stirred at 0 °C for 1 h and warmed up to RT. MeOH (0.06 mL, 1.5 mmol) and Et$_3$N (1.5 mL, 10.4 mmol) were then added and the reaction was stirred at 50 °C. After 13 hours, the reaction was cooled to RT and quenched with saturated NaHCO$_3$(aq). The mixture was extracted with DCM (3x20 mL) and the organic phases were combined, dried over Na$_2$SO$_4$ and concentrated in vacuo. The crude product was purified by flash column chromatography (eluent: Hex:IPA=20:1, V/V with 1% Et$_3$N) to afford **4-4g** as product (yellow solid, 144 mg, 32% yield).

Catalyst **4-4h** was prepared according to literature procedures from commercially available materials as shown below.[13]



To a 30 mL pressure tube was added SI-**4-2a** (199.7 mg, 1 mmol), SI-**4-2b** (151 mg, 1.1 mmol) and *i*Pr$_2$NEt (0.2 mL to 1.0 mL). The tube was sealed and then stirred at 130 °C under argon. After 48 hours, the reaction was cooled to room temperature,

diluted with MeOH:DCM = 1:1 solution (3-5 mL, it took around 8h to dissolve all the solid mixtures) and then transferred to a 50 mL flask. The mixture was concentrated in vacuo to afford SI-**4-2c**. The crude mixture was used in the next step without further purification.

To a solution of the above crude mixture in DCM (10 mL) at 0 °C were added Et_3N (0.45 mL, 3.1 mmol) and MsCl (0.13 mL, 1.6 mmol) under argon. The reaction was stirred at 0 °C for 1 h and warmed up to RT. MeOH (0.06 mL, 1.5 mmol) and Et_3N (1.5 mL, 10.4 mmol) were then added and the reaction was stirred at 50 °C. After 13 hours, the reaction was cooled to RT and quenched with saturated $NaHCO_3$(aq). The mixture was extracted with DCM (3x20 mL) and the organic phases were combined, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (eluent: Hex:IPA=20:1, V/V with 1% Et_3N) to afford a crude mixture. **4-4h** (white solid, 125 mg, 22% yield) was then recrystallized from Et_2O (3-5 mL).

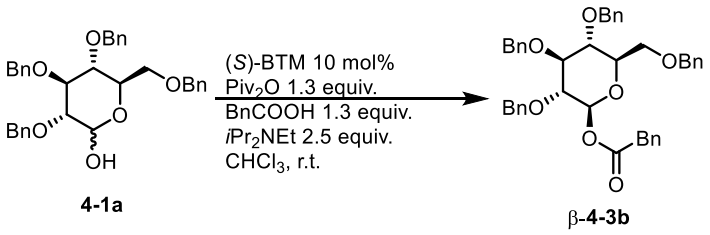
4.3.2 Methods for the preparation of substrates

Substrates **4-1a**, **4-1b** and **4-1c** were purchased from Chem-Impex.

Known substrate **4-1f**, **4-1h**, **4-1i**, **4-1j** and **4-1k** were prepared according to literature procedure from commercially available materials.[20] The spectra of substrates **4-1f**,[20a] **4-1h**,[20b] **4-1i**,[20c] **4-1j**[20d] and **4-1k**[20e] are in accordance with literature.

4.3.3 Methods for BTM-Catalyzed DKDA

Procedure A: (*S*)-BTM-Catalyzed DKDA of 1a:

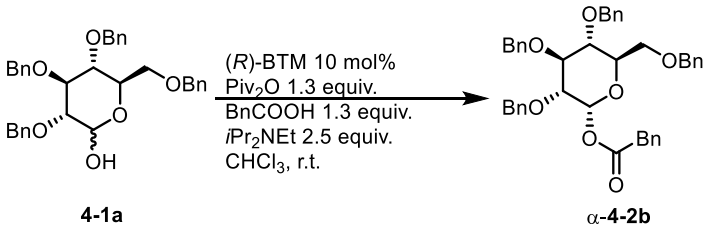


To an oven-dried flask was added **4-1a** (540.7 mg, 1.0 mmol), (*S*)-BTM catalyst (25.2 mg, 0.1 mmol), BnCOOH (177.1 mg, 1.3 mmol), *i*-Pr_2NEt (413 μL, 2.5 mmol), Piv_2O (253 μL, 1.3 mmol) and anhydrous $CHCl_3$ (6.0 mL, amylene as stabilizer) under Ar. The reaction was stirred at RT and monitored by TLC. After the reaction was completed (~16h), the reaction was quenched with saturated aqueous $NaHCO_3$ solution. The mixture was extracted with DCM for 3 times and the organic phases were combined, dried over Na_2SO_4 and concentrated in vacuo. Crude NMR was taken and was then purified by flash column chromatography

(eluent: Hex:EA=8:1, V/V) to afford β-**4-3b** as product (white solid, 657 mg, 99% yield).

Note: Dry toluene can also be used as solvent.

Procedure B: (*R*)-BTM-Catalyzed DKDA of 1a:

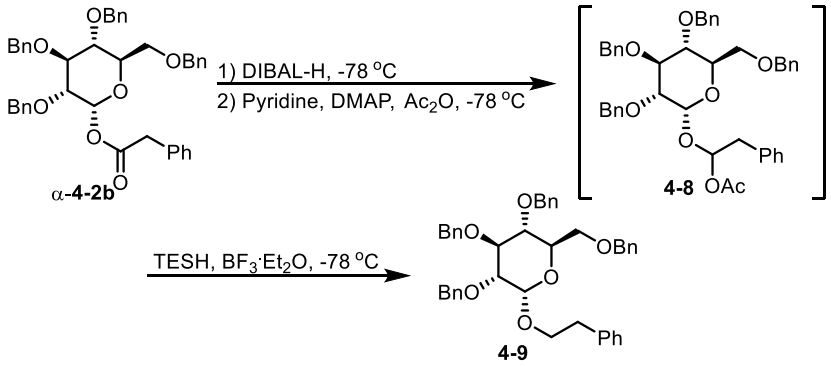


4-1a α-**4-2b**

To an oven-dried flask was added **4-1a** (540.7 mg, 1.0 mmol), (*R*)-BTM catalyst (25.2 mg, 0.1mmol), BnCOOH (177.1 mg, 1.3 mmol), *i*-Pr$_2$NEt (413 µL, 2.5 mmol), Piv$_2$O (253 µL, 1.3 mmol) and anhydrous CHCl$_3$ (6.0 mL, amylenes as stabilizer) under Ar. The reaction was stirred at RT and monitored by TLC. After the reaction was completed (~24h), the reaction was quenched with saturated aqueous NaHCO$_3$ solution. The mixture was extracted with DCM for 3 times and the organic phases were combined, dried over Na$_2$SO$_4$ and concentrated in vacuo. Crude NMR was taken and was then purified by flash column chromatography (eluent: Hex:EA=8:1, V/V) to afford α-**4-2b** as product (colorless oil, 481 mg, 73% yield).

Note: Dry toluene can also be used as solvent.

4.3.4 Method for the Deoxygenation of Ester to Form Ether 4-9



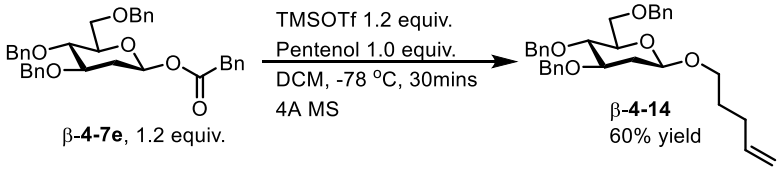
α-**4-2b** **4-8** **4-9**

The α-**4-2b** (131.8 mg, 0.2 mmol) was dissolved in dry DCM (0.8 mL) under Ar in an oven-dried flask. The solution was cooled to -78 °C and stirred for 5 mins. DIBAL-H (1 M in hexanes, 0.4 mL, 0.4 mmol) was then added and the reaction was stirred at -

78 °C. After 45 min, pyridine (48.6 µL, 0.6 mmol), DMAP (48.9 mg, 0.4 mmol) in DCM (0.3 mL) solution and acetic anhydride (113 µL, 1.2 mmol) was added into the reaction, respectively. The mixture was stirred at -78 °C and monitored by TLC. After completion (~4 h), the mixture was warmed up to 0 °C, and stirred for another 30 min and then was quenched with saturated aqueous NH_4Cl. The mixture was extracted with DCM for 3 times and the organic phases were combined, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (eluent: Hex:EA=6:1, V/V) to afford colorless oil **4-8** as a mixture of diastereomers.

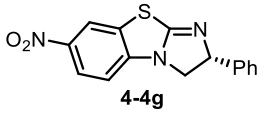
Compound **4-8** (0.2 mmol, 1.0 equiv.) was dissolved in dry DCM (4.0 mL) under Ar in an oven-dried flask. After cooling to -78 °C, triethylsilane (42.3 µL, 0.5 mmol) was added and the mixture was stirred for another 10 mins. $BF_3{\cdot}Et_2O$ (61.7 µL, 0.5 mmol) was then added dropwise. The reaction was stirred at -78 °C and monitored by TLC. After completion (~30 min), the reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with DCM for 3 times and organic phases were combined, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (eluent: Hex:EA=6:1, V/V) to afford **4-9** (colorless oil, 50 mg, 78% yield).

4.3.5 Method for the Synthesis of β-2-Deoxyglucoside



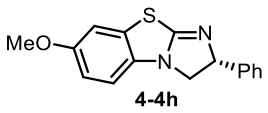
To an oven-dried flask was added β-**4-7e** (33.2 mg, 0.06 mmol), pentenol (5.2 µL, 0.05 mmol), 4Å MS (30 mg) and dry DCM (0.5 mL). The mixture was stirred at RT for 20 min and cooled to -78 °C. TMSOTf (10.9 µL, 0.06 mmol) was then added and the reaction was stirred at -78 °C. After 30 min, the reaction was quenched with 1 drop of Et_3N. The mixture was filtered through a pad of celite and washed with DCM and concentrated in vacuo. The crude product was purified by flash column chromatography (eluent: Hex:EA=8:1, V/V) to afford product β-**4-14**.

4.3.6 Characterization data for catalysts 4-4g and 4-4h



4-4g

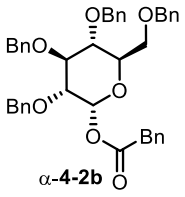
4-4g: (*R*)-7-nitro-2-phenyl-2,3-dihydrobenzo[d]imidazo[2,1-b]thiazole. Yellow soild, m.p. = 115-118 °C. $[\alpha]_D^{22}$ = 109.6° ($CHCl_3$, c = 0.5). ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.21 (d, J = 2.0 Hz, 1H), 8.15 (dd, J = 8.5, 2.0 Hz, 1H), 7.43 – 7.28 (m, 5H), 6.68 (d, J = 8.5 Hz, 1H), 5.77 (dd, J = 10.5, 7.5 Hz, 1H), 4.36 (t, J = 10.0 Hz, 1H), 3.80 (dd, J = 9.5, 7.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 165.4, 142.3, 142.2, 141.9, 129.2, 128.6, 128.2, 126.6, 124.3, 119.4, 107.2, 76.3, 52.3. IR: ν 3002, 1594, 1519, 1335, 1131 cm^{-1}. HRMS (ESI) for $C_{15}H_{11}N_3O_2S$ (M+Na), 320.0464 (Calc.), found 320.0460.



4-4h

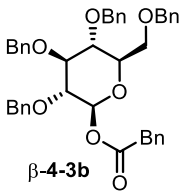
4-4h: (*R*)-7-methoxy-2-phenyl-2,3-dihydrobenzo[d]imidazo[2,1-b]thiazole. White solid, m.p. = 120-123 °C. $[\alpha]_D^{22}$ = 186.0° ($CHCl_3$, c = 0.8). ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.40 – 7.34 (m, 4H), 7.30 – 7.26 (m, 1H), 6.92 (d, J = 2.5 Hz, 1H), 6.73 (dd, J = 8.5, 2.5 Hz, 1H), 6.58 (d, J = 8.5 Hz, 1H), 5.63 (dd, J = 10.0, 8.5 Hz, 1H), 4.23 (dd, J = 10.0, 9.0 Hz, 1H), 3.78 (s, 3H), 3.69 – 3.63 (t, J = 8.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 167.3, 155.2, 143.2, 131.7, 128.9, 128.7, 127.7, 126.7, 112.3, 109.9, 109.0, 75.7, 56.2, 53.3. IR: ν 3010, 2943, 1574, 1492, 1038 cm^{-1}. HRMS (ESI) for $C_{16}H_{14}N_2OS$ (M+Na), 305.0719 (Calc.), found 305.0715.

4.3.7 Characterization data for DKDA Products



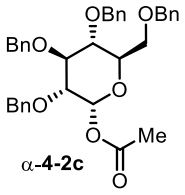
α-**4-2b**

α-**4-2b**: (*2R,3R,4S,5R,6R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl 2-phenylacetate. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.34 – 7.20 (m, 23H), 7.16 – 7.10 (m, 2H), 6.40 (d, J = 3.5 Hz, 1H), 4.90 (d, J = 11.0 Hz, 1H), 4.82 (d, J = 10.5 Hz, 1H), 4.77 (d, J = 11.0 Hz, 1H), 4.66 (d, J = 11.0 Hz, 1H), 4.61 – 4.53 (m, 2H), 4.49 (d, J = 11.0 Hz, 1H), 4.44 (d, J = 12.0 Hz, 1H), 3.85 (t, J = 9.0 Hz, 1H), 3.78 – 3.71 (m, 2H), 3.70 – 3.63 (m, 4H), 3.57 (dd, J = 11.0, 2.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$, TMS): δ 170.1, 138.8, 138.3, 138.0, 137.8, 133.8, 129.5, 128.7, 128.6, 128.2, 128.1, 128.1, 128.1, 128.0, 127.9, 127.9, 127.8, 127.3, 90.6, 81.7, 79.2, 77.0, 75.8, 75.3, 73.7, 73.3, 73.1, 68.2, 41.6. IR: ν 3033, 2492, 1746, 1454, 1074 cm^{-1}. HRMS (ESI) for $C_{42}H_{42}O_7$ (M+Na), 681.2823 (Calc.), found 681.2816.



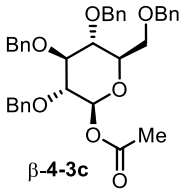
β-**4-3b**

β-**3b**: (*2S,3R,4S,5R,6R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl 2-phenylacetate. m.p. = 70-73 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.33 – 7.20 (m, 21H), 7.14 – 7.09 (m, 4H), 5.62 (d, J = 8.0 Hz, 1H), 4.85 (d, J = 11.0 Hz, 1H), 4.79 (m, 2H), 4.64 – 4.42 (m, 5H), 3.74 (m, 3H), 3.70 – 3.67 (m, 1H), 3.67 – 3.59 (m, 2H), 3.59 – 3.53 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$, TMS): δ 170.1, 138.6, 138.3, 138.2, 138.2, 133.4, 129.6, 128.9, 128.6, 128.6, 128.6, 128.2, 128.1, 128.1, 128.0, 128.0, 127.9, 127.9, 127.9, 127.5, 94.8, 85.0, 81.2, 77.4, 75.9, 75.8, 75.2, 75.0, 73.8, 68.3, 41.6. IR: ν 3001, 2944, 1756, 1376, 1074 cm^{-1}. HRMS (ESI) for $C_{42}H_{42}O_7$ (M+Na), 681.2823 (Calc.), found 681.2819.



α-**4-2c**

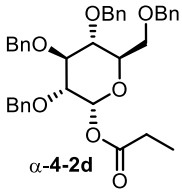
α-**4-2c**: (*2R,3R,4S,5R,6R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl acetate. ^{1}H NMR of the major α-isomer (500 MHz, $CDCl_3$, TMS): δ 7.35 – 7.25 (m, 18H), 7.13 (m, 2H), 6.36 (d, J = 3.5 Hz, 1H), 4.96 (d, J = 11.0 Hz, 1H), 4.83 (t, J = 10.5 Hz, 2H), 4.70 (d, J = 11.5 Hz, 1H), 4.62 (m, 2H), 4.49 (t, J = 11.0 Hz, 2H), 3.94 (t, J = 9.0 Hz, 1H), 3.87 (m, 1H), 3.78 – 3.66 (m, 3H), 3.64 (m, 1H), 2.13 (s, 3H). ^{13}C NMR of the major α-isomer (126 MHz, $CDCl_3$, TMS): δ 169.7, 138.9, 138.3, 138.0, 137.8, 128.7, 128.7, 128.6, 128.4, 128.2, 128.2, 128.2, 128.1, 128.1, 128.0, 128.0, 127.9, 90.2, 81.9, 79.1, 77.2, 75.9, 75.5, 73.8, 73.4, 73.1, 68.3, 21.4. Spectral data are in accordance with literature.[21]



β-**4-3c**

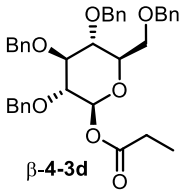
β-**4-3c**: (*2S,3R,4S,5R,6R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl acetate. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.33 – 7.21 (m, 18H), 7.15 – 7.09 (m, 2H), 5.63 (d, J = 8.0 Hz, 1H), 4.89 (d, J = 10.8 Hz, 1H), 4.83 – 4.79 (m, 2H), 4.76 (d, J = 4.0 Hz, 2H), 4.60 (d, J = 12.0 Hz, 1H), 4.52 (d, J = 10.8 Hz, 1H), 4.44 (d, J = 12.0 Hz, 1H), 3.79 – 3.67 (m, 4H), 3.63 – 3.53 (m, 2H), 2.00 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, TMS): δ 169.2, 138.4, 138.2, 138.1, 137.9, 128.5, 128.4, 128.4, 128.4, 128.2, 128.0, 127.9,

127.9, 127.8, 127.8, 127.7, 94.1, 84.8, 81.1, 77.3, 75.7, 75.5, 75.0, 75.0, 73.5, 68.1, 21.1. Spectral data are in accordance with literature.[21]



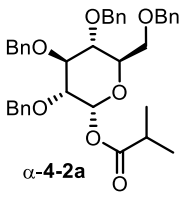
α-**4-2d**

α-**4-2d**: (*2R,3R,4S,5R,6R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl propionate. ^{1}H NMR of the major α-isomer (400 MHz, $CDCl_3$, TMS): δ 7.34 – 7.25 (m, 18H), 7.15 – 7.11 (m, 2H), 6.40 (d, J = 3.6 Hz, 1H), 4.95 (d, J = 10.8 Hz, 1H), 4.83 (t, J = 10.8 Hz, 2H), 4.70 (d, J = 11.2 Hz, 1H), 4.61 (m, 2H), 4.49 (m, 2H), 3.93 (t, J = 9.2 Hz, 1H), 3.89 – 3.83 (m, 1H), 3.77 – 3.67 (m, 3H), 3.66 – 3.61 (m, 1H), 2.45 – 2.36 (m, 2H), 1.19 – 1.12 (t, J = 7.6 Hz, 3H). ^{13}C NMR of the major α-isomer (126 MHz, $CDCl_3$, TMS): δ 173.1, 138.9, 138.3, 138.1, 137.9, 128.7, 128.6, 128.6, 128.3, 128.2, 128.2, 128.1, 128.1, 128.1, 128.0, 128.0, 127.9, 90.1, 81.9, 79.2, 77.2, 75.9, 75.5, 73.8, 73.3, 73.1, 68.3, 27.9, 9.2. IR: ν 3009, 2946, 1662, 1252, 1142 cm^{-1}. HRMS (ESI) for $C_{37}H_{40}O_7$ (M+Na), 619.2666 (Calc.), found 619.2664.

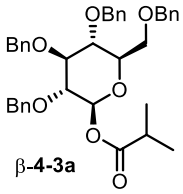


β-**4-3d**

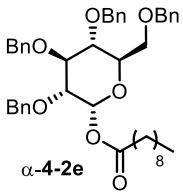
β-**4-3d**: (*2S,3R,4S,5R,6R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl propionate. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.34 – 7.24 (m, 18H), 7.15 – 7.11 (m, 2H), 5.63 (d, J = 8.0 Hz, 1H), 4.89 (d, J = 11.2 Hz, 1H), 4.81 (m, 2H), 4.76 (d, J = 1.2 Hz, 2H), 4.63 (d, J = 12.0 Hz, 1H), 4.52 (d, J = 10.8 Hz, 1H), 4.47 (d, J = 12.0 Hz, 1H), 3.77 – 3.68 (m, 4H), 3.58 (m, 2H), 2.45 – 2.21 (m, 2H), 1.13 (t, J = 7.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 173.0, 138.6, 138.3, 138.3, 138.1, 128.6, 128.6, 128.6, 128.2, 128.1, 128.1, 128.0, 128.0, 127.9, 94.3, 85.0, 81.3, 77.5, 75.9, 75.7, 75.2, 73.7, 68.3, 27.8, 9.0. IR: ν 3009, 2941, 1760, 1445, 1077 cm^{-1}. HRMS (ESI) for $C_{37}H_{40}O_7$ (M+Na), 619.2666 (Calc.), found 619.2663.



α-**4-2a**: (*2R,3R,4S,5R,6R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl isobutyrate. ^{1}H NMR of the major α-isomer (400 MHz, $CDCl_3$, TMS): δ 7.33 – 7.26 (m, 18H), 7.16 – 7.12 (m, 2H), 6.40 (d, J = 3.2 Hz, 1H), 4.95 (d, J = 11.2 Hz, 1H), 4.83 (dd, J = 13.6, 10.8 Hz, 2H), 4.68 (d, J = 11.6 Hz, 1H), 4.63 – 4.57 (m, 2H), 4.49 (m, 2H), 3.92 (t, J = 9.2 Hz, 1H), 3.86 (m, 1H), 3.72 (m, 4H), 2.60 (m, 1H), 1.19 (dd, J = 6.8, 1.2 Hz, 6H). ^{13}C NMR of the major α-isomer (126 MHz, $CDCl_3$, TMS): δ 175.7, 138.8, 138.3, 138.1, 138.0, 128.7, 128.6, 128.6, 128.3, 128.2, 128.2, 128.2, 128.1, 128.0, 127.9, 89.9, 81.9, 79.3, 77.1, 75.9, 75.6, 73.8, 73.2, 73.1, 68.3, 34.4, 19.2, 19.1. IR: ν 2979, 2942, 1744, 1376, 1026 cm^{-1}. HRMS (ESI) for $C_{37}H_{42}O_7$ (M+Na), 633.2823 (Calc.), found 633.2817.

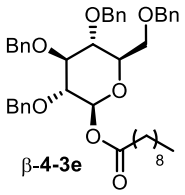


β-**4-3a**: (*2S,3R,4S,5R,6R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl isobutyrate. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.34 – 7.25 (m, 18H), 7.17 – 7.12 (m, 2H), 5.63 (d, J = 8.0 Hz, 1H), 4.88 (d, J = 10.8 Hz, 1H), 4.81 (d, J = 12.0 Hz, 2H), 4.77 (d, J = 2.0 Hz, 2H), 4.63 (d, J = 12.4 Hz, 1H), 4.54 (d, J = 10.8 Hz, 1H), 4.51 – 4.47 (d, J = 12.4 Hz, 1H), 3.79 – 3.69 (m, 4H), 3.63 – 3.55 (m, 2H), 2.58 (hept, J = 7.2 Hz, 1H), 1.19 (dd, J = 6.8, 4.8 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 175.7, 138.6, 138.3, 138.3, 138.2, 128.6, 128.6, 128.6, 128.2, 128.1, 128.1, 128.0, 127.9, 127.9, 94.4, 85.1, 81.2, 77.5, 75.9, 75.8, 75.2, 75.2, 73.7, 68.3, 34.2, 19.1, 18.8. Spectral data are in accordance with literature.[22]



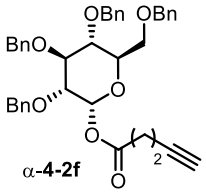
α-**4-2e**: (*2R,3R,4S,5R,6R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl decanoate. ^{1}H NMR of the major α-isomer (500 MHz, $CDCl_3$, TMS): δ 7.33 – 7.26 (m, 18H), 7.14 (m, 2H), 6.40 (d, J = 3.5 Hz, 1H), 4.95 (d, J = 11.0 Hz, 1H), 4.83 (dd, J = 14.5, 10.5 Hz, 2H), 4.69 (d, J = 11.5 Hz, 1H), 4.61 (dd, J = 11.5, 7.5 Hz, 2H), 4.52 – 4.45 (m, 2H), 3.93 (t, J = 9.5 Hz, 1H), 3.88 –

3.84 (m, 1H), 3.76 – 3.73 (m, 2H), 3.69 (dd, J = 9.5, 3.5 Hz, 1H), 3.64 (dd, J = 10.5, 1.5 Hz, 1H), 2.41 – 2.34 (m, 2H), 1.68 – 1.58 (m, 2H), 1.31 – 1.23 (m, 12H), 0.86 (t, J = 7.5 Hz, 3H). ^{13}C NMR of the major α-isomer (126 MHz, $CDCl_3$, TMS): δ 172.5, 138.9, 138.3, 138.1, 137.9, 128.6, 128.6, 128.3, 128.2, 128.2, 128.1, 128.1, 128.0, 128.0, 127.9, 90.0, 81.9, 79.2, 77.2, 75.9, 75.5, 73.8, 73.3, 73.1, 68.3, 34.6, 32.1, 29.7, 29.5, 29.5, 29.3, 25.2, 22.9, 14.3. IR: ν 3005, 2931, 1748, 1376, 1073 cm^{-1}. HRMS (ESI) for $C_{44}H_{54}O_7$ (M+Na), 717.3762 (Calc.), found 717.3766



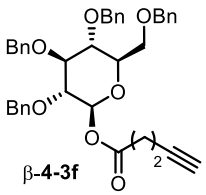
β-**4-3e**

β-**4-3e**: (*2S,3R,4S,5R,6R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl decanoate. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.34 – 7.25 (m, 18H), 7.14 (m, 2H), 5.63 (d, J = 8.0 Hz, 1H), 4.88 (d, J = 11.0 Hz, 1H), 4.84 – 4.78 (m, 2H), 4.76 (s, 2H), 4.62 (d, J = 12.5 Hz, 1H), 4.53 (d, J = 10.5 Hz, 1H), 4.48 (d, J = 12.0 Hz, 1H), 3.78 – 3.69 (m, 4H), 3.62 – 3.54 (m, 2H), 2.40 – 2.21 (m, 2H), 1.65 – 1.56 (m, 2H), 1.33 – 1.21 (m, 12H), 0.88 (t, J = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 172.4, 138.6, 138.3, 138.3, 138.2, 128.6, 128.6, 128.6, 128.2, 128.1, 128.1, 128.0, 128.0, 128.0, 127.9, 127.9, 94.2, 85.1, 81.3, 77.5, 75.9, 75.8, 75.2, 75.2, 73.7, 68.3, 34.5, 32.1, 29.6, 29.5, 29.3, 24.8, 22.9, 14.4. Spectral data are in accordance with literature.[23]



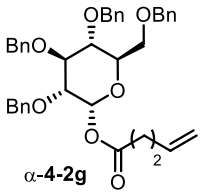
α-**4-2f**

α-**4-2f**: (*2R,3R,4S,5R,6R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl pent-4-ynoate. ^{1}H NMR of the major α-isomer (500 MHz, $CDCl_3$, TMS): δ 7.33 – 7.27 (m, 18H), 7.14 (m, 2H), 6.40 (d, J = 3.5 Hz, 1H), 4.95 (d, J = 11.0 Hz, 1H), 4.86 – 4.79 (m, 2H), 4.69 (d, J = 11.5 Hz, 1H), 4.61 (dd, J = 15.5, 11.5 Hz, 2H), 4.49 (dd, J = 15.5, 11.5 Hz, 2H), 3.93 (t, J = 9.5 Hz, 1H), 3.88 (d, J = 9.5 Hz, 1H), 3.74 – 3.67 (m, 3H), 3.66 – 3.61 (m, 1H), 2.66 – 2.59 (m, 2H), 2.54 – 2.49 (m, 2H), 1.94 – 1.93 (m, 1H). ^{13}C NMR of the major α-isomer (126 MHz, $CDCl_3$, TMS): δ 170.4, 138.8, 138.3, 138.0, 137.8, 128.7, 128.6, 128.6, 128.3, 128.2, 128.1, 128.0, 128.0, 127.9, 127.9, 90.6, 82.4, 81.8, 79.1, 77.1, 75.9, 75.5, 73.8, 73.4, 73.2, 69.5, 68.3, 33.6, 14.4. Spectral data are in accordance with literature.[24]



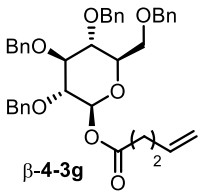
β-**4-3f**

β-**4-3f**: (*2S,3R,4S,5R,6R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl pent-4-ynoate. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.33 – 7.26 (m, 18H), 7.13 (m, 2H), 5.64 (d, J = 8.0 Hz, 1H), 4.88 (d, J = 10.5 Hz, 1H), 4.84 – 4.79 (m, 2H), 4.77 – 4.74 (m, 2H), 4.62 (d, J = 12.0 Hz, 1H), 4.52 (d, J = 11.0 Hz, 1H), 4.48 (d, J = 12.5 Hz, 1H), 3.77 – 3.70 (m, 4H), 3.62 – 3.54 (m, 2H), 2.63 – 2.54 (m, 1H), 2.50 – 2.44 (m, 3H), 1.93 (t, J = 2.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 170.4, 138.6, 138.3, 138.2, 138.1, 128.7, 128.6, 128.6, 128.2, 128.1, 128.1, 128.1, 128.0, 128.0, 94.5, 85.0, 82.4, 81.2, 77.4, 76.0, 75.8, 75.3, 73.8, 69.5, 68.3, 33.5, 14.2. Spectral data are in accordance with literature.[24]



α-**4-2g**

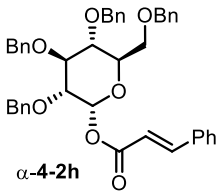
α-**4-2g**: (*2R,3R,4S,5R,6R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl pent-4-enoate. ^{1}H NMR of the major α-isomer (500 MHz, $CDCl_3$, TMS): δ 7.34 – 7.26 (m, 18H), 7.14 (m, 2H), 6.39 (d, J = 3.5 Hz, 1H), 5.86 – 5.77 (m, 1H), 5.07 – 5.04 (m, 1H), 5.00 – 4.93 (m, 2H), 4.86 – 4.79 (m, 2H), 4.69 (d, J = 11.0 Hz, 1H), 4.64 – 4.57 (m, 2H), 4.52 – 4.45 (m, 2H), 3.93 (t, J = 9.0 Hz, 1H), 3.88 – 3.83 (m, 1H), 3.74 – 3.67 (m, 3H), 3.63 (dd, J = 10.5, 1.5 Hz, 1H), 2.52 – 2.47 (m, 2H), 2.41 – 2.36 (m, 2H). ^{13}C NMR of the major α-isomer (126 MHz, $CDCl_3$, TMS): δ 171.7, 138.8, 138.3, 138.0, 137.9, 136.6, 128.7, 128.7, 128.6, 128.3, 128.2, 128.2, 128.1, 128.1, 128.0, 128.0, 128.0, 127.9, 115.9, 90.2, 81.9, 79.1, 77.2, 75.9, 75.5, 73.8, 73.3, 73.1, 68.3, 33.8, 28.9. Spectral data are in accordance with literature.[25]



β-**4-3g**

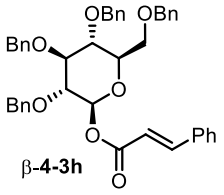
β-**4-3g**: (*2S,3R,4S,5R,6R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl pent-4-enoate. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.33 – 7.24 (m, 18H), 7.14 (m, 2H), 5.84 – 5.74 (m, 1H), 5.63 (d, J = 8.0 Hz, 1H), 5.04 (dd, J = 17.0, 1.5 Hz, 1H), 4.98 (dd, J = 12.5, 1.5 Hz, 1H), 4.88 (d, J = 11.0 Hz, 1H), 4.83 – 4.73 (m, 4H), 4.62 (d, J = 12.0 Hz, 1H), 4.53 (d, J = 11.0 Hz, 1H),

4.48 (d, J = 12.5 Hz, 1H), 3.78 – 3.68 (m, 4H), 3.62 – 3.54 (m, 2H), 2.50 – 2.40 (m, 1H), 2.39 – 2.31 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 171.6, 138.6, 138.3, 138.3, 138.2, 136.5, 128.6, 128.6, 128.6, 128.2, 128.1, 128.1, 128.0, 127.9, 127.9, 116.0, 94.3, 85.1, 81.3, 77.5, 75.9, 75.8, 75.2, 73.7, 68.3, 33.7, 28.6. Spectral data are in accordance with literature.[25]



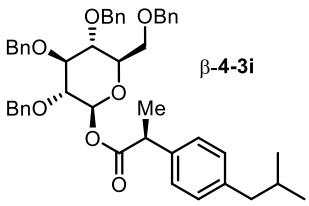
α-**4-2h**

α-**4-2h**: (*2R,3R,4S,5R,6R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl cinnamate. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.75 (d, J = 16.0 Hz, 1H), 7.55 – 7.53 (m, 2H), 7.42 – 7.38 (m, 3H), 7.37 – 7.25 (m, 18H), 7.18 – 7.13 (m, 2H), 6.50 – 6.47 (m, 2H), 4.99 (d, J = 11.0 Hz, 1H), 4.86 (dd, J = 11.0, 4.5 Hz, 2H), 4.74 (d, J = 11.5 Hz, 1H), 4.67 (d, J = 11.5 Hz, 1H), 4.60 (d, J = 12.0 Hz, 1H), 4.53 (d, J = 10.5 Hz, 1H), 4.48 (d, J = 12.0 Hz, 1H), 4.04 (t, J = 9.5 Hz, 1H), 3.94 (d, J = 10.0 Hz, 1H), 3.83 – 3.73 (m, 3H), 3.66 (dd, J = 11.0, 1.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 165.5, 146.4, 138.9, 138.3, 138.1, 137.8, 134.4, 130.8, 129.2, 128.7, 128.7, 128.6, 128.6, 128.5, 128.4, 128.3, 128.2, 128.2, 128.1, 128.1, 128.0, 127.9, 117.7, 90.4, 82.1, 79.2, 77.2, 75.9, 75.6, 73.8, 73.4, 73.1, 68.3. IR: ν 3001, 2942, 1721, 1638, 1452 cm^{-1}. HRMS (ESI) for $C_{43}H_{42}O_7$ (M+Na), 693.2823 (Calc.), found 693.2819



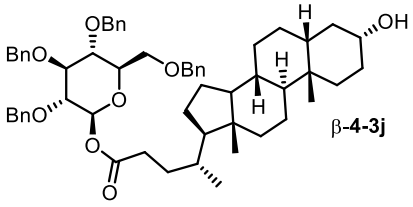
β-**4-3h**

β-**4-3h**: (*2S,3R,4S,5R,6R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl cinnamate. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.75 (d, J = 16.0 Hz, 1H), 7.52 (dd, J = 5.5, 2.0 Hz, 2H), 7.42 – 7.38 (m, 3H), 7.34 – 7.22 (m, 18H), 7.17 – 7.13 (m, 2H), 6.39 (d, J = 16.0 Hz, 1H), 5.78 (d, J = 8.0 Hz, 1H), 4.92 (d, J = 11.0 Hz, 1H), 4.84 (dd, J = 11.0, 8.5 Hz, 2H), 4.79 (s, 2H), 4.62 (d, J = 12.5 Hz, 1H), 4.55 (d, J = 10.5 Hz, 1H), 4.48 (d, J = 12.5 Hz, 1H), 3.82 – 3.73 (m, 4H), 3.69 (t, J = 8.5 Hz, 1H), 3.62 (d, J = 9.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 165.3, 146.7, 138.6, 138.3, 138.2, 138.1, 134.4, 130.9, 129.2, 128.7, 128.6, 128.6, 128.5, 128.3, 128.2, 128.1, 128.1, 128.0, 128.0, 127.9, 127.9, 117.4, 94.4, 85.1, 81.2, 77.5, 76.0, 75.8, 75.3, 75.2, 73.8, 68.3. Spectral data are in accordance with literature.[26]



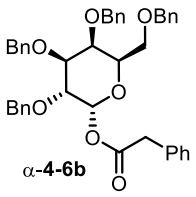
β-**4-3i**

β-**4-3i**: (*S*)-(*2S,3R,4S,5R,6R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl 2-(4-isobutylphenyl)propanoate. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.31 – 7.24 (m, 16H), 7.21 – 7.18 (m, 4H), 7.17 – 7.13 (m, 2H), 7.02 (d, J = 8.0 Hz, 2H), 5.62 (d, J = 8.0 Hz, 1H), 4.85 (d, J = 11.0 Hz, 1H), 4.79 (d, J = 11.0 Hz, 2H), 4.64 (d, J = 11.5 Hz, 1H), 4.60 – 4.52 (m, 3H), 4.46 (d, J = 12.5 Hz, 1H), 3.73 – 3.66 (m, 5H), 3.57 – 3.54 (m, 2H), 2.37 (d, J = 7.0 Hz, 2H), 1.82 – 1.72 (m, 1H), 1.51 (d, J = 7.0 Hz, 3H), 0.85 (d, J = 6.5 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 173.4, 140.9, 138.7, 138.3, 138.3, 138.3, 137.0, 129.5, 128.6, 128.6, 128.6, 128.6, 128.1, 128.0, 128.0, 127.9, 127.9, 127.8, 127.6, 94.7, 85.0, 81.1, 77.5, 76.0, 75.8, 75.2, 75.0, 73.7, 68.3, 45.4, 45.2, 30.3, 22.6, 18.7. Spectral data are in accordance with literature.[27]



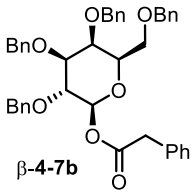
β-**4-3j**

β-**4-3j**: (*4R*)-(*2S,3R,4S,5R,6R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl 4-((*3R,5R,8R,9S,10S,13R,17R*)-3-hydroxy-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)pentanoate. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.28 (m, 18H), 7.16 – 7.11 (m, 2H), 5.61 (d, J = 8.0 Hz, 1H), 4.89 (d, J = 11.0 Hz, 1H), 4.81 (dd, J = 11.0, 5.0 Hz, 2H), 4.77 (d, J = 2.0 Hz, 2H), 4.63 (d, J = 12.0 Hz, 1H), 4.53 (d, J = 11.0 Hz, 1H), 4.48 (d, J = 12.0 Hz, 1H), 3.78 – 3.68 (m, 4H), 3.62 – 3.56 (m, 3H), 2.35 – 2.20 (m, 2H), 1.94 (d, J = 12.0 Hz, 1H), 1.86 – 1.70 (m, 6H), 1.65 (d, J = 11.0 Hz, 1H), 1.57 – 1.46 (m, 2H), 1.41 – 1.31 (m, 8H), 1.26 – 1.23 (m, 2H), 1.18 – 0.97 (m, 6H), 0.95 – 0.85 (m, 7H), 0.62 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 172.9, 138.6, 138.3, 138.3, 138.2, 128.6, 128.6, 128.6, 128.2, 128.1, 128.1, 128.0, 127.9, 127.9, 127.9, 94.2, 85.0, 81.3, 77.5, 75.9, 75.7, 75.2, 75.2, 73.7, 72.1, 68.3, 56.7, 56.1, 43.0, 42.3, 40.6, 40.4, 36.7, 36.1, 35.6, 35.5, 34.8, 31.4, 30.8, 30.8, 28.4, 27.4, 26.6, 24.4, 23.6, 21.0, 18.6, 12.3. Spectral data are in accordance with literature.[28]



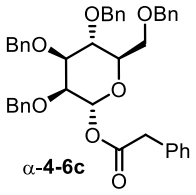
α-**4-6b**

α-**4-6b**: (*2R,3R,4S,5S,6R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl 2-phenylacetate. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.36 – 7.20 (m, 25H), 6.41 (d, J = 3.5 Hz, 1H), 4.92 (d, J = 11.0 Hz, 1H), 4.75 (d, J = 12.0 Hz, 1H), 4.70 – 4.62 (m, 3H), 4.55 (d, J = 11.5 Hz, 1H), 4.41 (d, J = 12.0 Hz, 1H), 4.36 (d, J = 12.0 Hz, 1H), 4.14 (dd, J = 10.0, 3.5 Hz, 1H), 3.95 (d, J = 1.5 Hz, 1H), 3.84 (t, J = 6.5 Hz, 1H), 3.74 (dd, J = 10.0, 2.5 Hz, 1H), 3.67 (s, 2H), 3.54 – 3.41 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 170.2, 138.8, 138.7, 138.3, 138.0, 134.0, 129.6, 128.7, 128.6, 128.6, 128.5, 128.5, 128.4, 128.2, 128.1, 128.0, 127.8, 127.8, 127.7, 127.3, 91.4, 78.7, 75.8, 75.1, 74.8, 73.7, 73.5, 73.3, 72.1, 68.6, 41.8. Spectral data are in accordance with literature.[29]



β-**4-7b**

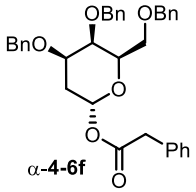
β-**4-7b**: (*2S,3R,4S,5S,6R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl 2-phenylacetate. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.34 – 7.19 (m, 23H), 7.11 (m, 2H), 5.59 (d, J = 8.0 Hz, 1H), 4.93 (d, J = 11.5 Hz, 1H), 4.68 (s, 2H), 4.63 (dd, J = 10.5, 6.5 Hz, 2H), 4.45 – 4.38 (m, 3H), 3.96 (d, J = 2.5 Hz, 1H), 3.92 (dd, J = 10.0, 8.5 Hz, 1H), 3.71 – 3.65 (m, 1H), 3.64 – 3.54 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 170.1, 138.7, 138.5, 138.4, 138.0, 133.5, 129.6, 128.8, 128.7, 128.6, 128.5, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.9, 127.8, 127.8, 127.5, 95.0, 82.5, 78.3, 75.3, 75.0, 74.4, 73.7, 73.3, 73.1, 68.1, 41.5. Spectral data are in accordance with literature.[29]



α-**4-6c**

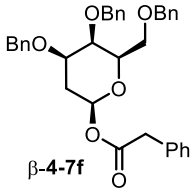
α-**4-6c**: (*2R,3S,4S,5R,6R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl 2-phenylacetate. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.38 – 7.16 (m, 25H), 6.23 (d, *J* = 2.0 Hz, 1H), 4.86 (d, *J* = 10.8 Hz, 1H), 4.69 (dd, *J* = 21.6, 12.4 Hz, 2H), 4.63 (d, *J* = 12.2 Hz, 1H), 4.53 – 4.45 (m, 4H), 4.04 (t, *J* = 9.5 Hz, 1H), 3.77 – 3.65 (m, 5H), 3.58 (d, *J* = 2.1 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$, TMS): δ 169.8, 138.5, 138.5, 138.4, 138.0, 133.6, 129.4, 128.9, 128.6, 128.5, 128.2, 128.1, 128.0, 127.9, 127.7, 127.5,

92.5, 92.5, 79.4, 75.4, 74.7, 74.3, 73.7, 73.6, 72.7, 72.3, 69.1, 41.6. Spectral data are in accordance with literature.[30]



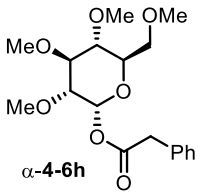
α-**4-6f**

α-**4-6f**: (*2R,4R,5R,6R*)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl 2-phenylacetate. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.37 – 7.23 (m, 20H), 5.67 (dd, *J* = 10.0, 2.4 Hz, 1H), 4.92 (d, *J* = 11.6 Hz, 1H), 4.64 (d, *J* = 11.6Hz, 1H), 4.56 (s, 2H), 4.43 (q, *J* = 11.7 Hz, 2H), 3.88 (d, *J* = 2Hz, 1H), 3.65 – 3.58 (m, 6H), 2.20 (td, *J* = 12.0, 10.1 Hz, 1H), 2.08 – 2.04 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$, TMS): δ 170.0, 138.9, 138.4, 138.1, 134.1, 129.4, 128.8, 128.7, 128.6, 128.5, 128.4, 128.2, 128.0, 127.9, 127.8, 127.5, 127.4, 93.5, 74.6, 74.2, 73.7, 72.7, 70.6, 69.1, 41.9, 30.1. IR: ν 2921, 2360, 2341, 1737, 1455, 1372, 1241, 1097, 1047, 910, 731, 697cm^{-1}. HRMS (ESI) for $C_{35}H_{36}O_6$ (M+Na), 575.2404 (Calc.), found 575.2378.



β-**4-7f**

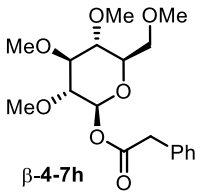
β-**4-7f**: (*2S,4R,5R,6R*)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl 2-phenylacetate. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.36 – 7.25 (m, 20H), 5.67 (dd, *J* = 10.0, 2.4 Hz, 1H), 4.92 (d, *J* = 11.6 Hz, 1H), 4.64 (d, *J* = 11.6 Hz, 1H), 4.56 (s, 2H), 4.43 (q, J = 11.7 Hz, 2H), 3.88 (d, J = 2.1 Hz, 1H), 3.65 – 3.58 (m, 6H), 2.20 (td, J = 12.0, 10.1 Hz, 1H), 2.08 – 2.04 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$, TMS): δ 170.1, 138.9, 138.1, 133.6, 129.6, 128.8, 128.7, 128.6, 128.5, 128.4, 128.2, 128.0, 128.0, 127.8, 127.6, 127.4, 93.2, 75.1, 74.6, 73.7, 71.5, 70.7, 68.7, 41.3, 31.6. IR: ν 3064, 3031, 2360, 2341, 1749, 1497, 1455, 1360, 1244, 1213, 1106, 1042, 732, 696 cm^{-1}. HRMS (ESI) for $C_{35}H_{36}O_6$ (M+Na), 575.2404 (Calc.), found 575.2395.



α-**4-6h**

α-**4-6h**: (*2R,3R,4S,5R,6R*)-3,4,5-trimethoxy-6-(methoxymethyl)tetrahydro-2H-pyran-2-yl 2-phenylacetate. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.34 – 7.26 (m, 5H), 6.33 (d, J = 3.5 Hz, 1H), 3.70 (s, 2H), 3.61 (s, 3H), 3.52 (s, 3H), 3.51 – 3.44 (m, 3H), 3.42 (s, 3H),

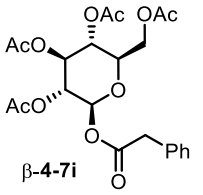
3.35 – 3.34 (m, 4H), 3.29 – 3.22 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 170.2, 133.9, 129.5, 128.8, 127.4, 90.1, 83.2, 81.1, 78.7, 72.8, 70.7, 61.1, 60.8, 59.4, 59.1, 41.6. IR: ν 3002, 2944, 1750, 1376, 1011 cm^{-1}. HRMS (ESI) for $C_{18}H_{26}O_7$ (M+Na), 377.1571 (Calc.), found 377.1573



β-**4-7h**

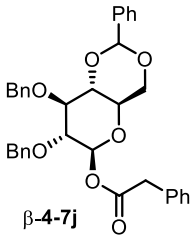
β-**4-7h**: (*2S,3R,4S,5R,6R*)-3,4,5-trimethoxy-6-(methoxymethyl)tetrahydro-2H-pyran-2-yl 2-phenylacetate. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.34 – 7.23 (m, 5H), 5.45 (d, J = 8.0 Hz, 1H), 3.69 (d, J = 2.5 Hz, 2H), 3.62 -3.61 (m, 4H), 3.56 (dd, J = 10.5, 3.5 Hz, 1H), 3.53 (s, 3H), 3.38 (s, 3H), 3.36 – 3.35 (m, 1H), 3.29 – 3.24 (m, 4H), 3.19 (t, J = 9.0 Hz, 1H), 3.08 (t, J = 9.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 170.1, 133.5, 129.6, 128.8, 127.4, 94.5, 86.7, 82.7, 78.8, 75.4, 70.7, 61.1, 60.6, 60.5, 59.5, 41.6.

IR: ν 2997, 2943, 1756, 1376, 1061 cm^{-1}. HRMS (ESI) for $C_{18}H_{26}O_7$ (M+Na), 377.1571 (Calc.), found 377.1579



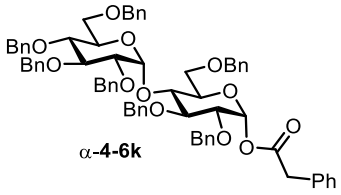
β-**4-7i**

β-**4-7i**: (*2R,3R,4S,5R,6S*)-2-(acetoxymethyl)-6-(2-phenylacetoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.35 – 7.24 (m, 5H), 5.69 (d, J = 8.0 Hz, 1H), 5.24 – 5.18 (m, 1H), 5.15 – 5.11 (m, 2H), 4.30 (dd, J = 12.5, 4.5 Hz, 1H), 4.11 (dd, J = 12.5, 2.0 Hz, 1H), 3.85 – 3.82 (m, 1H), 3.66 (s, 2H), 2.09 (s, 3H), 2.03 (s, 3H), 1.99 (s, 3H), 1.76 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 170.8, 170.3, 169.7, 169.6, 169.3, 133.1, 129.5, 129.0, 127.6, 92.1, 73.0, 72.9, 70.2, 68.0, 61.6, 41.4, 20.9, 20.8, 20.8, 20.5. IR: ν 3009, 2944, 1760, 1376, 919 cm^{-1}. HRMS (ESI) for $C_{22}H_{26}O_{11}$ (M+Na), 489.1367 (Calc.), found 489.1365



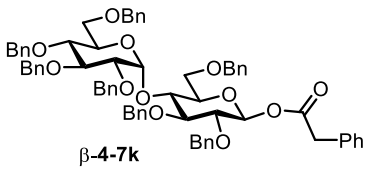
β-**4-7j**

β-**4-7j**: (*4aR,6S,7R,8S,8aR*)-7,8-bis(benzyloxy)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-6-yl 2-phenylacetate. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.47 (dd, J = 8.0, 2.0 Hz, 2H), 7.39 – 7.35 (m, 3H), 7.33 – 7.23 (m, 13H), 7.14 – 7.11 (m, 2H), 5.73 (d, J = 8.0 Hz, 1H), 5.54 (s, 1H), 4.90 (d, J = 11.5 Hz, 1H), 4.75 (d, J = 11.5 Hz, 1H), 4.64 (d, J = 11.5 Hz, 1H), 4.45 (d, J = 11.5 Hz, 1H), 4.36 (dd, J = 10.0, 4.5 Hz, 1H), 3.82 (t, J = 9.0 Hz, 1H), 3.75 – 3.67 (m, 2H), 3.63 (d, J = 9.5 Hz, 2H), 3.59 – 3.53 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 169.9, 138.5, 138.1, 137.4, 133.2, 129.6, 129.2, 128.9, 128.6, 128.5, 128.5, 128.3, 128.0, 128.0, 127.6, 126.2, 101.5, 94.7, 81.5, 81.2, 80.9, 75.4, 75.3, 68.8, 66.9, 41.5. IR: ν 3000, 2943, 1760, 1540, 1248 cm^{-1}. HRMS (ESI) for $C_{35}H_{34}O_7$ (M+Na), 589.2197 (Calc.), found 589.2188



α-**4-6k**

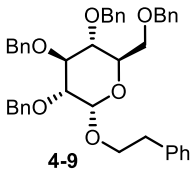
α-**4-6k**: (*2R,3R,5R,6R*)-3,4-bis(benzyloxy)-6-((benzyloxy)methyl)-5-(((*2R,3R,4S,5R,6R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)tetrahydro-2H-pyran-2-yl 2-phenylacetate. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.29 – 7.18 (m, 36H), 7.15 – 7.08 (m, 4H), 6.40 (d, J = 3.5 Hz, 1H), 5.67 (d, J = 3.5 Hz, 1H), 4.92 (dd, J = 18.0, 12.0 Hz, 2H), 4.79 (dd, J = 10.5, 8.0 Hz, 3H), 4.60 (d, J = 11.0 Hz, 1H), 4.56 (d, J = 2.5 Hz, 2H), 4.54 – 4.48 (m, 2H), 4.47 – 4.41 (m, 3H), 4.28 (d, J = 12.0 Hz, 1H), 4.12 (t, J = 9.5 Hz, 1H), 3.97 (t, J = 9.5 Hz, 1H), 3.91 (t, J = 9.5 Hz, 1H), 3.85 – 3.81 (m, 2H), 3.75 – 3.70 (m, 4H), 3.68 – 3.63 (m, 1H), 3.57 (d, J = 9.5 Hz, 1H), 3.51 (td, J = 10.0, 2.5 Hz, 2H), 3.42 – 3.37 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 170.3, 139.0, 138.7, 138.4, 138.2, 138.1, 137.6, 133.8, 129.6, 128.8, 128.6, 128.6, 128.6, 128.5, 128.5, 128.5, 128.4, 128.3, 128.1, 128.0, 128.0, 127.9, 127.9, 127.8, 127.7, 127.6, 127.4, 127.0, 97.2, 90.3, 82.2, 81.8, 79.6, 79.4, 77.9, 75.8, 75.2, 74.6, 73.7, 73.5, 73.5, 73.4, 72.9, 72.1, 71.3, 68.7, 68.4, 41.6. IR: ν 3002, 2941, 1751, 1258, 819 cm^{-1}. HRMS (ESI) for $C_{69}H_{70}O_{12}$ (M+Na), 1113.4759 (Calc.), found 1113.4742



β-**4-7k**

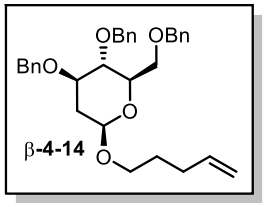
β-**4-7k**: (*2S,3R,5R,6R*)-3,4-bis(benzyloxy)-6-((benzyloxy)methyl)-5-(((*2R,3R,4S,5R,6R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)tetrahydro-2H-pyran-2-yl 2-phenylacetate. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.28 – 7.15 (m, 36H), 7.10 (dd, J = 7.5, 2.5 Hz, 2H), 7.03 (dd, J = 7.0, 1.5 Hz, 2H), 5.67 (d, J = 8.0 Hz, 1H), 5.59 (d, J = 3.5 Hz, 1H), 4.87 – 4.76 (m, 5H), 4.58 (d, J = 12.0 Hz, 1H), 4.53 – 4.46 (m, 5H), 4.43 (d, J = 10.0 Hz, 2H), 4.29 (d, J = 12.0 Hz, 1H), 4.15 (t, J = 9.0 Hz, 1H), 3.90 (t, J = 9.0 Hz, 1H), 3.86 (dd, J = 11.0, 3.5 Hz, 1H), 3.82 – 3.74 (m, 2H), 3.72 – 3.58 (m, 6H), 3.51 (ddd, J = 22.5, 10.5, 3.0 Hz, 2H), 3.41 (dd, J = 10.5, 1.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 170.1, 138.9, 138.8, 138.6, 138.5, 138.2, 138.1, 138.0, 133.4, 129.6, 128.9, 128.5, 128.5, 128.5, 128.4, 128.2, 128.1, 128.0, 128.0, 127.9, 127.9, 127.9, 127.8, 127.8, 127.7, 127.6, 127.0, 127.4, 126.9, 97.2, 94.6, 84.9, 82.2, 81.1, 79.6, 77.9, 75.8, 75.6, 75.2, 74.8, 74.3, 73.7, 73.5, 73.5, 72.8, 71.3, 68.8, 68.4, 41.6. IR: v 2994, 2940, 1753, 1541, 1245 cm^{-1}. HRMS (ESI) for $C_{69}H_{70}O_{12}$ (M+Na), 1113.4759 (Calc.), found 1113.4745

4.3.8 Characterization data for Deoxygenation Product 4-9



4-9: (*2R,3R,4S,5R,6S*)-3,4,5-tris(benzyloxy)-2-((benzyloxy)methyl)-6-phenethoxytetrahydro-2H-pyran. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.37 – 7.18 (m, 23H), 7.15 – 7.11 (m, 2H), 4.99 (d, J = 11.0 Hz, 1H), 4.82 (dd, J = 11.0, 2.0 Hz, 2H), 4.77 – 4.74 (m, 2H), 4.61 (d, J = 12.0 Hz, 1H), 4.57 (d, J = 12.0 Hz, 1H), 4.46 – 4.41 (m, 2H), 3.98 (t, J = 8.5 Hz, 1H), 3.85 – 3.78 (m, 1H), 3.70 – 3.58 (m, 4H), 3.57 – 3.50 (m, 2H), 2.99 – 2.88 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$, TMS): δ 139.1, 138.9, 138.6, 138.5, 138.2, 129.2, 128.6, 128.6, 128.6, 128.5, 128.2, 128.2, 128.1, 128.0, 128.0, 127.9, 127.8, 127.8, 126.5, 97.1, 82.2, 80.2, 77.9, 75.9, 75.1, 73.7, 73.4, 70.4, 69.0, 68.7, 36.2. Spectral data are in accordance with literature.[31]

4.3.9 Characterization data for β-2-Deoxyglucoside β-4-14



β-**4-14**: (2R,3S,4R,6R)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-6-(pent-4-en-1-yloxy)tetrahydro-2H-pyran. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.36 – 7.26 (m, 13H), 7.22 – 7.19 (m, 2H), 5.87 – 5.76 (m, 1H), 5.05 – 5.00 (m, 1H), 4.96 (d, *J* = 10.0 Hz, 1H), 4.89 (d, *J* = 10.5, 1H), 4.68 (d, *J* = 12.0 Hz, 1H), 4.62 (d, *J* = 12.5 Hz, 2H), 4.59 – 4.53 (m, 2H), 4.43 (dd, *J* = 9.5, 1.5 Hz, 1H), 3.93 – 3.89 (m, 1H), 3.76 (dd, *J* = 11.0, 2.0 Hz, 1H), 3.73 – 3.61 (m, 2H), 3.52 – 3.39 (m, 3H), 2.34 (ddd, *J* = 12.0, 4.5, 1.5 Hz, 1H), 2.12 (dd, *J* = 14.5, 7.0 Hz, 2H), 1.74 – 1.60 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, TMS): δ 138.6, 138.4, 128.7, 128.6, 128.6, 128.3, 128.0, 128.0, 127.9, 127.8, 115.0, 100.1, 79.7, 78.4, 75.5, 75.2, 73.7, 71.6, 69.6, 69.0, 37.0, 30.4, 29.1. IR: ν 3032, 2936, 2848, 1372, 916 cm^{-1}. HRMS (ESI) for $C_{32}H_{38}O_5$ (M+Na), 525.2611 (Calc.), found 525.2604

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Chapter 5

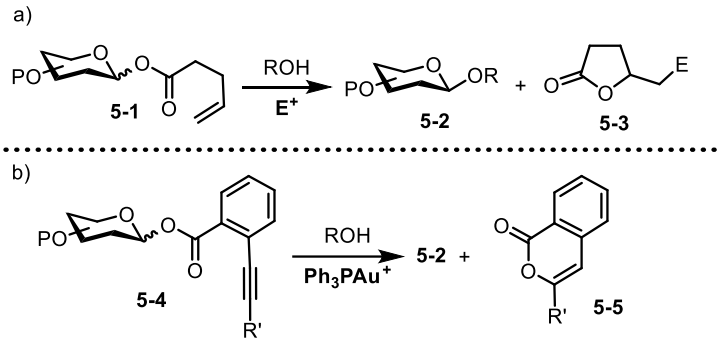
Isoquinoline-1-Carboxylate as a Traceless Leaving Group for Glycosylation under Neutral and Mild Conditions (Glyco-IsQ)

5.1 Introduction

Carbohydrates are essential in numerous fundamentally important biological events such as immunological responses, cancer metastasis, and bacterial or viral infections.[1] Chemical synthesis of oligosaccharides and glycoconjugates is crucial to decipher the complex carbohydrate-mediated biological events and develop novel therapeutics.[2] Numerous efficient and stereoselective glycosylation methods have been developed in the past century.[3] However, most of them involve strong Brønsted or Lewis acids with a few exceptions.[4] Efficient and general glycosylation methods that can operate under mild conditions are still highly desirable.[5]

Anomeric esters are attractive glycosyl donors as they are easy to prepare and generally benchtop stable. However, simple anomeric esters such as glycosyl acetates have not been widely used as glycosyl donors in the synthesis of oligosaccharides and glycoconjugates due to their low reactivity. The activation of anomeric ester donors generally requires harsh conditions that are not applicable for complex substrates. In the 1990's more practical glycosylation conditions were developed for anomeric esters with a remote alkene and later with alkyne or allene (*e.g.* **5-1**, **Scheme 5-1-a**), all of which could be activated by electrophiles.[6] In addition to the desired product **5-2**, byproduct **5-3** is also generated and it often reacts with glycosyl acceptor nucleophiles.[7] In 2008,[8] Yu reported that anomeric esters bearing a novel *ortho*-alkynybenzoate such as **5-4** could be activated by gold (I) complexes (**Scheme 5-1-b**). The mechanistic details of this novel method were elucidated subsequently.[9] This mild glycosylation method avoids strong acidic, nucleophilic, or electrophilic conditions and is orthogonal to most other glycosyl donors. It has become one of the most preferred glycosylation methods for the synthesis of complex oligosaccharides and glycosylated natural products.[10] Other related anomeric esters or carbonates bearing a remote alkyne were also developed as glycosyl donors.[11] In all cases, byproducts associated with the leaving group such as **5-5** need to be separated from the desired product **5-2**.

Scheme 5-1. Glycosylation using stable anomeric ester as the donor

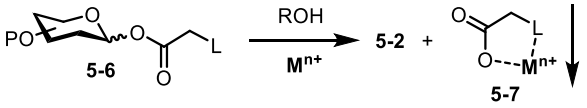


5.2 Results and Discussion

5.2.1 Optimization of Reaction Conditions

We envisioned that a transition metal complex might be able to chelate[5c] to an appropriately designed anomeric ester **5-6** to form salt **5-7**, which could be precipitated from the solution under mild conditions (**Scheme 5-2**). If by-products associated with the leaving group become undetectable in the solution by NMR, the leaving group can be considered as a "traceless leaving group". This strategy would leave **5-2** as the major product in the reaction system and greatly facilitate automated solution phase synthesis of libraries of oligosaccharides.[12] This new glycosylation is likely orthogonal to the Au(I)-promoted process.

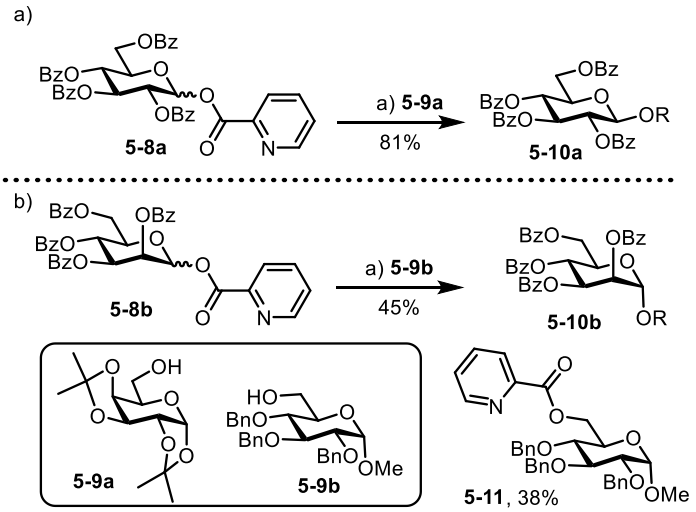
Scheme 5-2. Our proposed glycosylation by using stable anomeric ester



We then examined various anomeric esters with chelating ability and different types of transition metal complexes for glycosylation. As early as 1991, glycosyl pyridine-2-carboxylates or picolinic esters were introduced to armed glycosyl donors[13] for glycosylations, and they yielded a mixture of α- and β-isomeric products in low selectivity.[13] However, picolinic esters have rarely been applied to the synthesis of oligosaccharides as general glycosyl donors. We found that disarmed donors bearing an anomeric picolinic ester such as **5-8a** could be activated by 60 mol% of $Cu(OTf)_2$ to afford only β-isomeric product **5-9a** in 81% yield (**Scheme 5-3-a**). When we began to examine the scope of different glycosyl donors and acceptors using picolinic ester as the leaving group, we quickly realized that significant amount of transesterification by-products often accompanied the

glycosylation products. For example, only 45% yield of the desired product **5-10b** was obtained for disarmed donor **5-8b** and glycosyl acceptor **5-9b**. Transesterification by-product **5-11** was isolated in as much as 38% yield (**Scheme 5-3-b**).

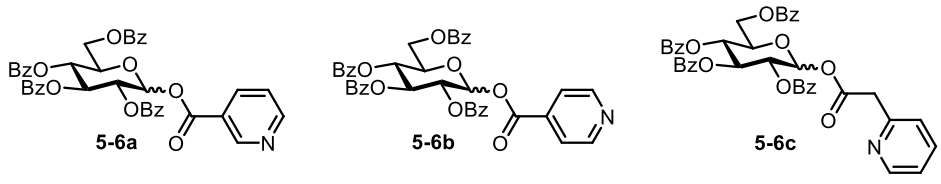
Scheme 5-3. Transesterification side reaction under optimized Kobayashi's condition



a) ROH (1.2 equiv.), $Cu(OTf)_2$ (60 mol%), DCM, r.t., 4Å MS, 12h

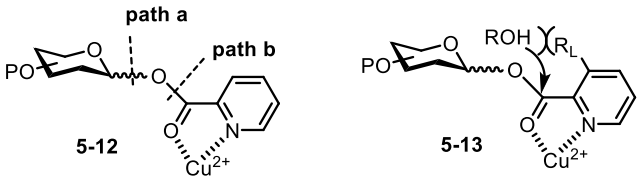
Interestingly, when the amount of $Cu(OTf)_2$ was decreased to 40 mol% or increased to 240 mol%, lower conversions were observed. Other anomeric esters such as glycosyl 3- or 4-pyridinecarboxylates (**5-6a** and **5-6b**) and glycosyl 2-pyridylacetates **5-6c** could not be activated by various metal complexes for glycosylation as shown in **Scheme 5-4**, suggesting that chelation *via* a five-membered ring in a conjugated system is critical for the activation.

Scheme 5-4. Substrates failed to be activated



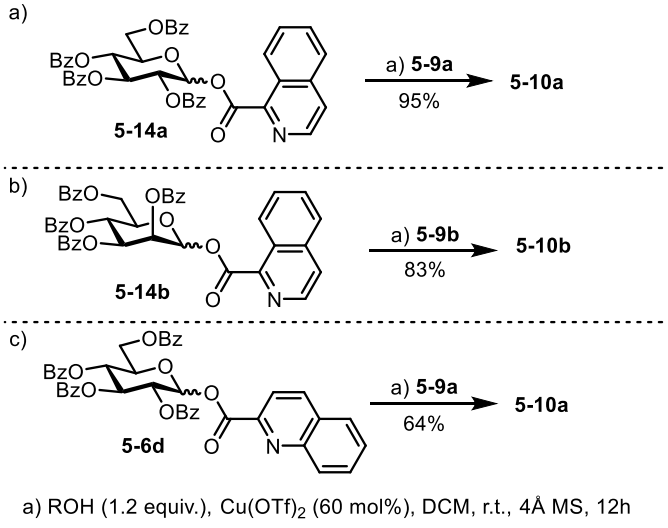
Clearly, the chelation of Cu^{2+} to picolinic ester **5-12** not only weakens the anomeric C-O bond towards glycosylation *via* path **a**, but also activates the carbonyl group towards nucleophilic attack *via* path **b** (**Scheme 5-5**). We envisioned that a bulky R_L substituent on the 3-position of the picolinic ester **5-13** might block the attack of alcohol ROH to the carbonyl carbon and minimize the formation of transesterification by-product.

Scheme 5-5. Possible pathways for glycosylation and transesterification reactions



After examining various commercially available pyridine-2-carboyxlic acids with a 3-substituent, isoquinoline-1-carboxylic acid was identified as the most affordable (e.g. $80/100g from Ark Pharm, Inc.) reagent with a bulky "3-substituent". Isoquinoline-1-carboxylate (IsQ) esters **5-14a** and **5-14b** were easily prepared from the corresponding lactols (**Scheme 5-6**). The desired glycosylation products **5-10a** and **5-10b** were isolated in high yields by using 60 mol% of $Cu(OTf)_2$. Lower conversions were observed with less copper salt. We did not observe any transesterification by-products in these two cases. No by-product associated with the leaving group was observed by NMR after removing the solid material including molecular sieves by filtration, suggesting that the IsQ copper salt is rather insoluble in DCM. This confirms our hypothesis that glycosyl donors with a traceless leaving group are possible. We also examined the corresponding quinoline-2-carboxylate donor **5-6d** and obtained much lower yields of the glycosylation product (**Scheme 5-6-c**).

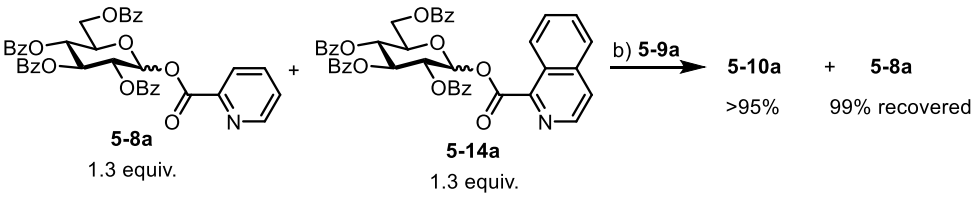
Scheme 5-6. Identification of a general and benchtop stable glycosyl donors with a traceless leaving group



To better understand the relative reactivity of anomeric picolinic and IsQ esters, we performed a competition experiment between glycosyl donors **5-8a** and **5-14a** (**Scheme 5-7**). When both donors were treated with 1.0 equiv. of acceptor **5-9a**, only **5-14a** was able to react. We could isolate disaccharide product **5-10a** in greater than 95% yield and the unreacted **5-8a** in 99%

yield. This indicated that our newly designed IsQ glycosyl donor was far more reactive than picolinic ester. We also stored IsQ ester **5-14a** at room temperature under air for months and no decomposition was observed, indicating excellent benchtop stability.

Scheme 5-7. Competition experiment

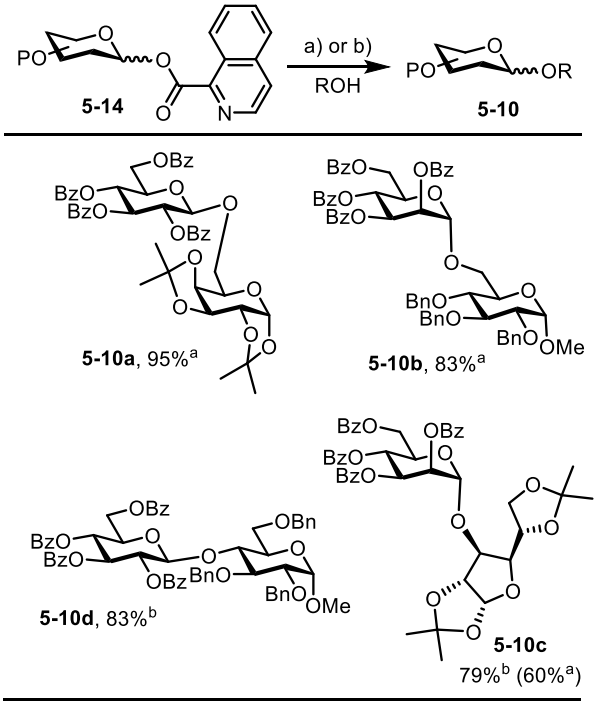


b) ROH (1.0 equiv.), $Cu(OTf)_2$ (60 mol%), DCM, r.t., 4Å MS, 12h

5.2.2 Substrate Scope and Applications

We then explored the general scope of $Cu(OTf)_2$-mediated glycosylation using Glyco-IsQ donors (**Scheme-5-8**). As previously discussed, high yields and high selectivity were observed for the formation of products **5-10a** and **5-10b** from mannosyl or glucosyl IsQ donors **5-14a**/**5-14b** and primary alcohols **5-9a**/**5-9b**. When these disarmed glycosyl donors reacted with secondary alcohols, lower yields were obtained in the presence of 60 mol% $Cu(OTf)_2$. The rate of glycosylation was slower in these cases and hydrolysis became competitive. By increasing the amount of copper salts to 120 mol%, we were able to improve the yields of glycosyl products **5-10c** and **5-10d** by nearly 20%.

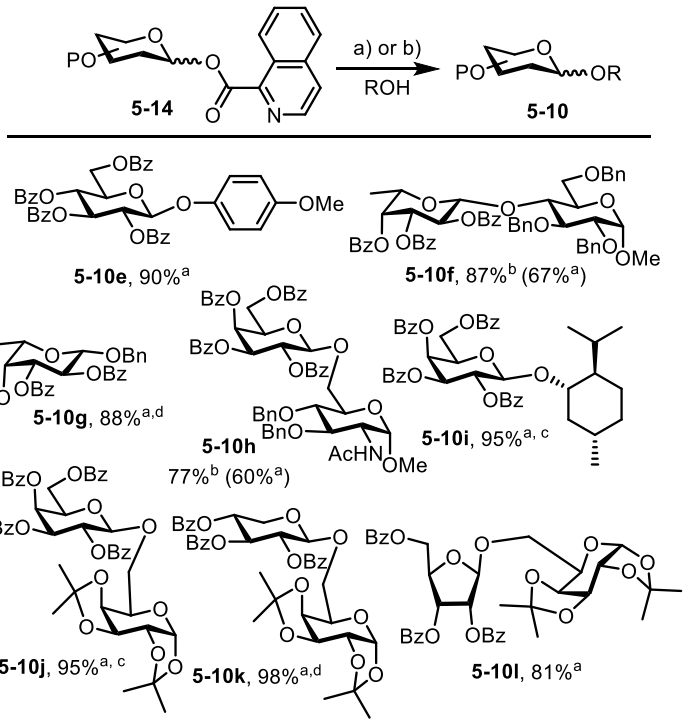
Scheme 5-8. Scope of $Cu(OTf)_2$-Mediated Glycosylation-I



a) ROH (1.3 equiv.), $Cu(OTf)_2$ (60 mol%), DCM, r.t., 4Å MS, 12h;
b) ROH (1.3 equiv.), $Cu(OTf)_2$ (120 mol%), DCM, r.t., 4Å MS, 12h.
c) The reaction was run in 1 mmol scale.

Product **5-10e** could be obtained in high yield by using phenol as the glycosyl acceptor. Other pyranose IsQ donors, such as those derived from L-fucose (*e.g.* donor of **5-10f** and **5-10g**), galactose (*e.g.* donor of **5-10h**, **5-10i** and **5-10j**), xylose (*e.g.* donor of **5-10k**), and furanose IsQ donors, such as those derived from ribose (*e.g.* donor of **5-10l**) could all react with diverse range of glycosyl acceptors to yield β-isomeric products exclusively, through the participation of the neighboring group. (**Scheme 5-9**)

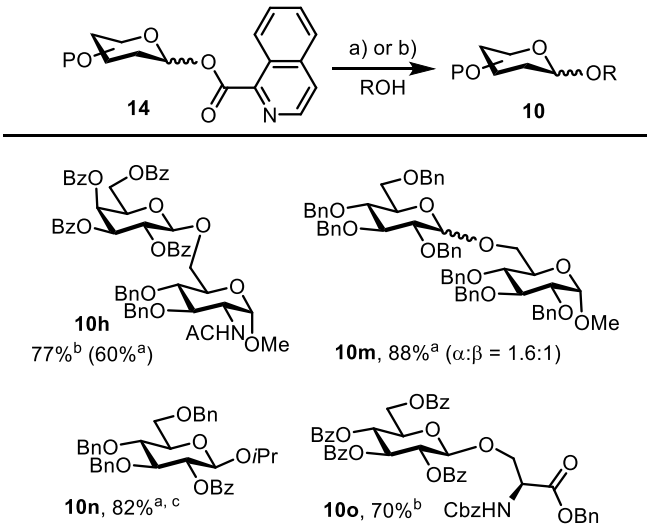
Scheme 5-9. Scope of $Cu(OTf)_2$-Mediated Glycosylation-II



a) ROH (1.3 equiv.), $Cu(OTf)_2$ (60 mol%), DCM, r.t., 4Å MS, 12h;
b) ROH (1.3 equiv.), $Cu(OTf)_2$ (120 mol%), DCM, r.t., 4Å MS, 12h.
c) The reaction was run in 1 mmol scale.
d) Data aquired from Mr. Christopher Simmons

The 6-OH of GlcNAc is generally considered an inert glycosyl acceptor for its tendency to form intermolecular hydrogen bonds.[14] Under our conditions, this poor glycosyl donor could react with galactosyl IsQ donor to afford product **5-10h** in 77% yield. This is in sharp contrast to previously reported <30% yields of glycosylation products derived from GlcNAc C(6)-OH acceptor and various donors.[14] Both armed and superarmed glucosyl donors[15] are also viable substrates, and products **5-10m** and **5-10n** were isolated in high yields. As expected, while only β-product **5-10n** was observed in the latter case, a mixture of isomeric products was obtained in the former case. Serine derivative can also be glucosylated smoothly to yield product **5-10o**.

Scheme 5-10. Scope of $Cu(OTf)_2$-Mediated Glycosylation-III

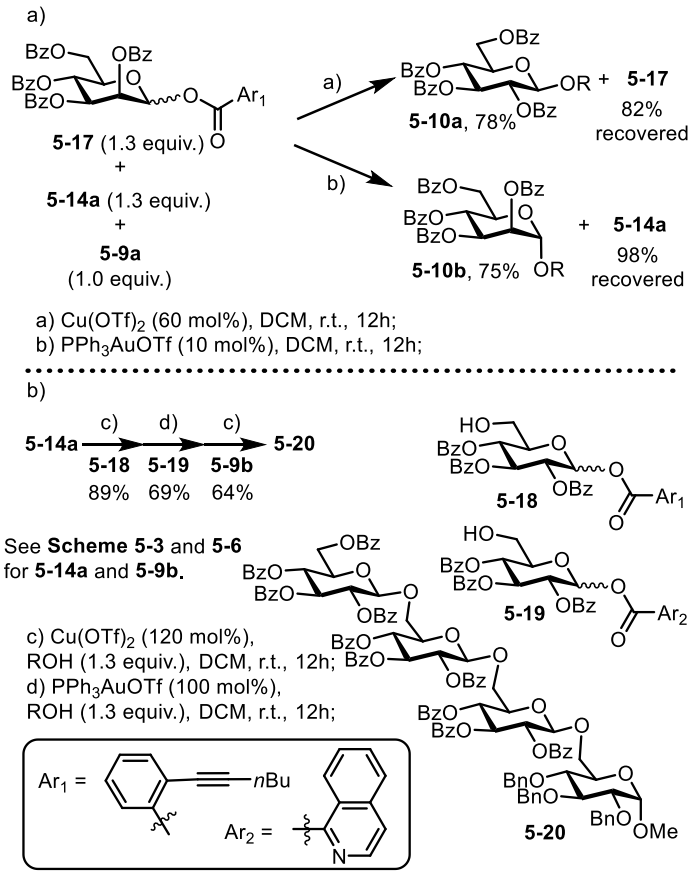


a) ROH (1.3 equiv.), $Cu(OTf)_2$ (60 mol%), DCM, r.t., 4Å MS, 12h;
b) ROH (1.3 equiv.), $Cu(OTf)_2$ (120 mol%), DCM, r.t., 4Å MS, 12h.
c) The reaction was run in 1 mmol scale.

Glycosylation using orthogonal leaving groups is one of the most efficient strategies for the assembly of oligosaccharides in solution.[16] However, it remains underdeveloped with limited known examples that are completely orthogonal.[17] There are even less examples of stable orthogonal glycosyl donors that can be activated under mild neutral conditions.

Both our Glyco-IsQ and Yu's esters are stable glycosyl donors that can be activated under mild and neutral conditions. These two donors may become an ideal pair if they are orthogonal to each other. We then tested this strategy in the synthesis of tetrasaccharide **5-20**, whose sulfated derivatives possessed potent proangiogenic activity.[18] Yu's donor **5-17** and our donor **5-14a** were mixed together with acceptor **5-9a** and treated with Au(I) and Cu(II) complexes under Yu's and our conditions, respectively. Under Yu's condition, we isolated product **5-10b** in 75% yield and **5-14a** was recovered in high yield. Under our conditions, we obtained product **5-10a** and **5-17** was recovered in high yield (**Scheme 5-11-a**). Based on the complete orthogonality of the two anomeric esters, we accomplished an iterative synthesis of tetrasaccharide **5-20** in three steps from four different building blocks (**Scheme 5-11-b**). Only 21% or 63% yields were obtained for the corresponding trisaccharide with 10 mol% or 50 mol% of Au(I) complex, respectively. The loading of Au(I) complex needs to be increased to 1.0 equivalent to achieve over 70% yields.

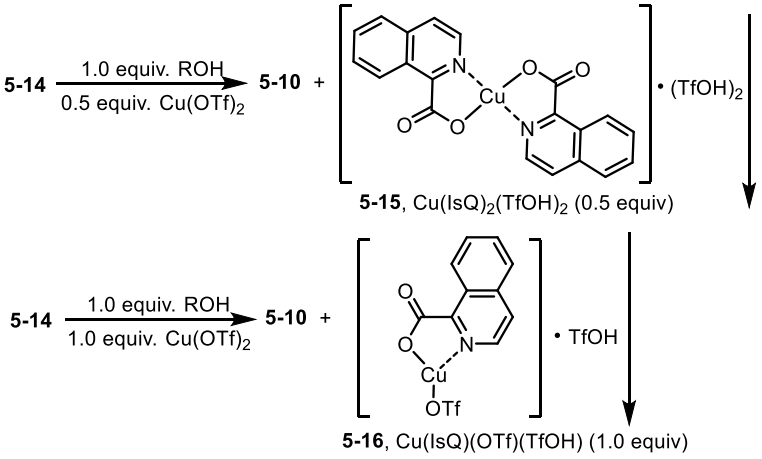
Scheme 5-11. Iterative synthesis based on orthogonal glycosyl esters (All reactions in this scheme are completed by Mr. Christopher Simmons)



5.2.3 Mechanism

If the proton after the glycosylation is in the free TfOH form after the formation of copper-IsQ complex, the resuling solution should be relatively acidic. We were surprised to find that the pH value of the solution after glycosylation was between 6 and 7. To exclude the effect of molecular sieves, we also mixed IsQ acid with $Cu(OTf)_2$ in either 2:1 or 1:1 ratios in DCM under the same concentration as the reaction conditions, and the pH values of the resulting solutions were both close to neutral. Under the same conditions, the pH value of IsQ acid alone in DCM was between 2 and 3. The details of these experiments are outlined in experimental section. These results indicated that free TfOH was not formed during the glycosylation. It has been reported that copper bispicolinic carboxylate can form 1:1 or 1:2 adducts with water, KSCN, or thiourea in different crystal forms.[19] We propose that copper-IsQ complexes co-precipitated with TfOH from the solution to form **5-15** and **5-16** after glycosylation under conditions a) or b) in **Scheme 5-8 to 5-10**, respectively (**Scheme 5-12**).

Scheme 5-12. Possible copper complexes formed after glycosylation



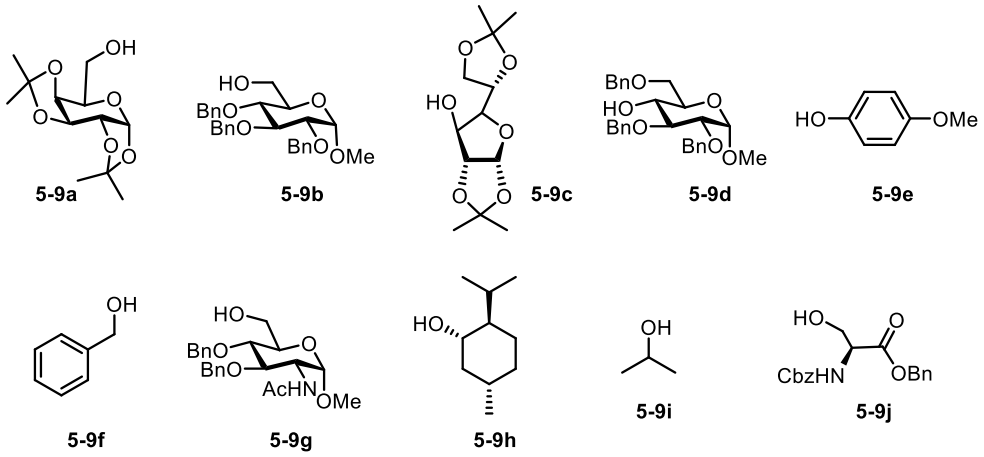
5.2.4 Conclusion

In summary, we have developed a novel stable glycosyl donor with a traceless IsQ leaving group that can be activated by $Cu(OTf)_2$ for glycosylation under neutral and extremely mild conditions (Glyco-IsQ). Mechanistic studies revealed that TfOH was co-precipitated with copper-IsQ salts. We also demonstrated the broad scope of the glycosylation donor in over a dozen examples and its orthogonality with Yu's donor in a streamlined iterative synthesis of oligosaccharides, without involving any protection, deprotection, or activation steps during the assembly of the oligosaccharides.

5.3 Experimental Section

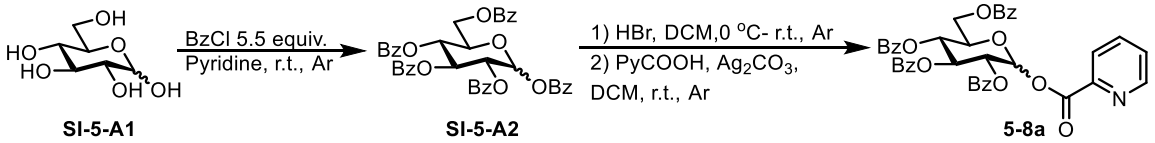
5.3.1 Methods for the preparation of glycosyl accepters

Known accepters **5-9b**, **5-9d** and **5-9g** were prepared according to literature procedure from commercially available materials[20]. The spectra of accepters **5-9b**,[20a] **5-9d**,[20a] and **5-9g**[20c] are in accordance with literature. Accepters **5-9a**, **5-9c**, **5-9e**, **5-9f**, **5-9h**, **5-9i** and **5-9j** were purchased and directly used into the reaction.



5.3.2 Methods for the preparation of glycosyl donors

1) Procedure 2A: Method for the preparation of glycosyl donor **5-8a**



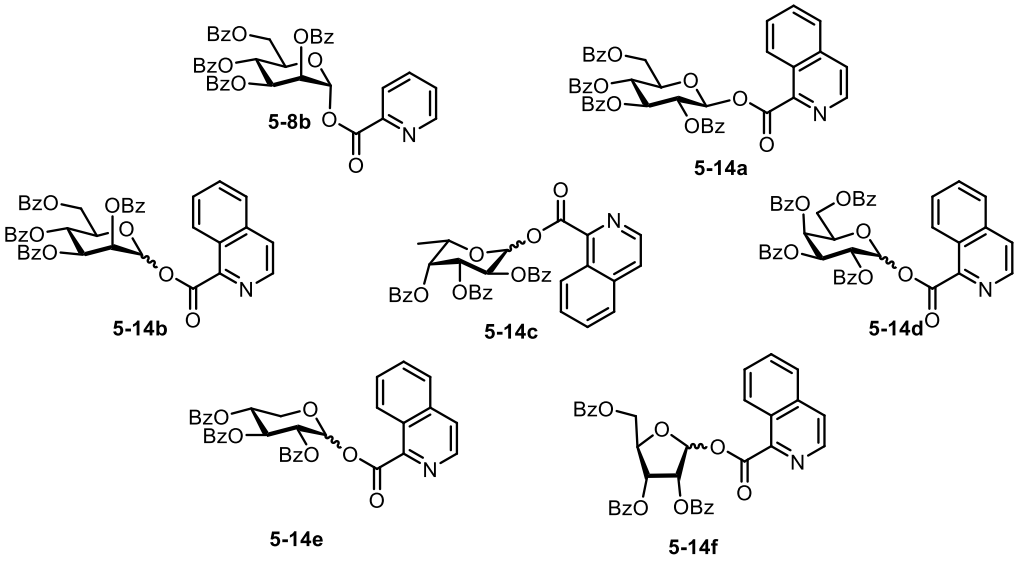
To an oven-dried flask was added D-glucose **SI-5-A1** (10 mmol, 1.8 g) and anhydrous pyridine (30 mL) under Ar. After cooling to 0 °C, BzCl (55 mmol, 6.5 mL) was added and the reaction was warmed up and stirred at RT. After completion (~16 h), the reaction was quenched with water. The mixture was extracted with EA for 3 times and the organic phases were combined, washed with 2M HCl solution, brine, dried over Na_2SO_4 and concentrated in vacuo. Crude product **SI-5-A2** was used in next step without further purification.

To an oven-dried flask was added **SI-5-A2** (1 mmol, 700.7 mg) and dry DCM (4.5 mL) under Ar. After cooling to 0 °C, HBr (1.8 mL, 33% in AcOH) was added and the reaction was warmed up and stirred at RT and monitored by TLC. After completion (~4 h), the reaction was quenched with saturated $NaHCO_3$ solution. The mixture was extracted with DCM for 3 times and organic phases were combined, dried over Na_2SO_4 and concentrated in vacuo.

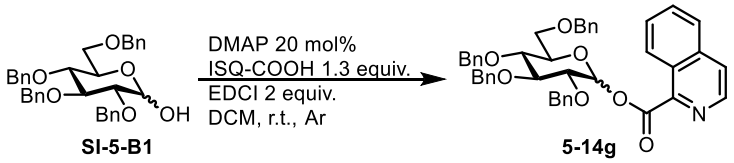
To an oven-dried flask was added above crude product, picolinic acid (1.2 mmol, 147.7 mg) and Ag_2CO_3 (0.6 mmol, 115.3 mg) and dry DCM (4.5 mL) under Ar. The reaction was stirred at RT and monitored by TLC. After the reaction was completed (~16 h), the reaction was quenched with saturated $NaHCO_3$ solution. The mixture was extracted with DCM for 3 times and the organic

phases were combined, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (eluent: Hex:EA=3:2, V/V) to afford **5-8a** as product (white solid, 512 mg, 73% yield over 3 steps).

Glycosyl donors **5-8b**, **5-14a**, **5-14b**, **5-14c**, **5-14d**, **5-14e**, and **5-14f** were all prepared from this procedure.

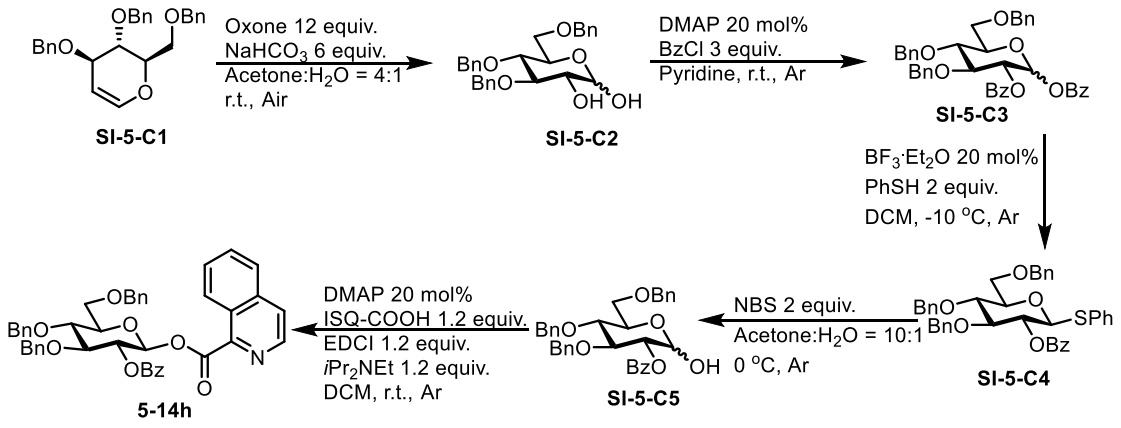


2) Procedure 2B: Method for the preparation of glycosyl donor **5-14g**



To an oven-dried flask was added commercially available starting material **SI-5-B1** (1 mmol, 540.7 mg), DMAP (0.2 mmol, 24.4 mg), 1-isoquinolinecarboxylic acid (1.3 mmol, 225.2 mg), EDCI (2 mmol, 383.3 mL) and dry DCM (5.0 mL) under Ar. The reaction was stirred at RT and monitored by TLC. After the reaction was completed (~12 h), the reaction was quenched with saturated $NaHCO_3$ solution. The mixture was extracted with DCM for 3 times and the organic phases were combined, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (eluent: Hex:EA=3:1, V/V) to afford **5-14g** as product (light yellow syrup, 644 mg, >99% yield).

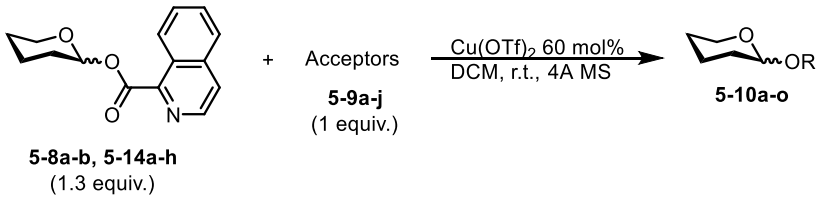
3) Procedure 2C: Method for the preparation of glycosyl donor **5-14h**



SI-5-C5 was prepared according to reference[21] from commercially available starting material **SI-5-C1** through a four-step sequence listed above.

To an oven-dried flask was added **SI-5-C5** (0.66 mmol, 367 mg), DMAP (0.132 mmol, 16.1 mg), 1-isoquinolinecarboxylic acid (0.792 mmol, 137.2 mg), EDCI (0.792 mmol, 383.3 mL), *i*Pr_2Net (0.792 mmol, 0.13 mL) and dry DCM (5.0 mL) under Ar. The reaction was stirred at RT and monitored by TLC. After the reaction was completed (~12 h), the reaction was quenched with saturated $NaHCO_3$ solution. The mixture was extracted with DCM for 3 times and the organic phases were combined, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (eluent: Hex:EA=3:1, V/V) to afford **5-14h** as product (light yellow syrup, 254 mg, 54% yield).

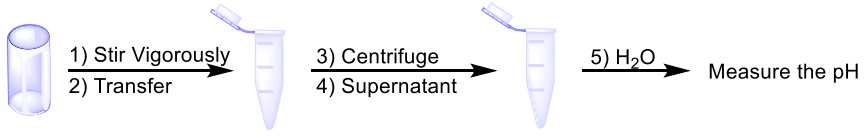
5.3.3 Method for Cu-mediated Glycosylation by using Glyco-IsQ donor



To an oven-dried vial was added IsQ donor (0.039 mmol), Accepter (0.03 mmol), 4Å MS (60 mg) and dry DCM (0.2 mL) under Ar. The suspension was stirred at RT for 15 mins and $Cu(OTf)_2$ (60 mol%) was added. The vial was recharged with Ar, stirred at RT and monitored by TLC. After completion (~12 h), the reaction was filtered through a pad of celite and concentrated in vacuo. The crude product was purified by flash column chromatography to afford final product.

Note: 1) The glycosylation can be ran under air, but it is better under argon; 2) For accepters **5-9c**, **5-9d**, **5-9g** and **5-9j**, 120 mol% of $Cu(OTf)_2$ was used instead of 60 mol%.

5.3.4 Methods for pH Experiments



Entry	Reagents dissolved in DCM	pH
1	0.1 mmol reaction mixture	6-7
2	0.1 mmol 1-isoquinolinecarboxylic acid **(IsQ)**	2-3
3	0.1 mmol **IsQ** with 0.05 mmol $Cu(OTf)_2$	6-7
4	0.1 mmol **IsQ** with 0.1 mmol $Cu(OTf)_2$	6-7

1) Entry 1:

To an oven-dried vial was added **5-14a** (0.13 mmol, 97.7 mg), **5-9a** (0.1 mmol, 26 mg), 4Å MS (180 mg) and dry DCM (0.7 mL) under Ar. The suspension was stirred at RT for 15 mins and $Cu(OTf)_2$ (60 mol%) was added. The vial was recharged with Ar, stirred at RT and monitored by TLC. After completion (~12 h), the reaction was centrifuged and 0.2 mL supernatant was taken. To this 0.2 mL supernatant, 0.2 mL water was added and pH was measured by pH test strips as 6-7.

2) Entry 2:

To an oven-dried vial was added **IsQ** (0.1 mmol, 17.3 mg) and dry DCM (0.7 mL) under Ar. The suspension was stirred at RT. After 10 mins, the suspension was centrifuged and 0.2 mL supernatant was taken. To this 0.2 mL supernatant, 0.2 mL water was added and pH was measured by pH test strips as 2-3.

3) Entry 3:

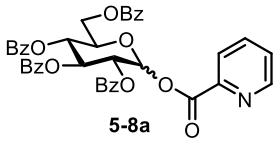
To an oven-dried vial was added **IsQ** (0.1 mmol, 17.3 mg), $Cu(OTf)_2$ (0.05 mmol, 18.1 mg) and dry DCM (0.7 mL) under Ar. The suspension was stirred at RT. After 10 mins, the suspension was centrifuged and 0.2 mL supernatant was taken. To this 0.2 mL supernatant, 0.2 mL water was added and pH was measured by pH test strips as 6-7.

4) Entry 4:

To an oven-dried vial was added **IsQ** (0.1 mmol, 17.3 mg), $Cu(OTf)_2$ (0.1 mmol, 36.2 mg) and dry DCM (0.7 mL) under Ar. The suspension was stirred at RT. After 10 mins, the suspension was centrifuged and 0.2 mL supernatant was taken. To this 0.2 mL supernatant, 0.2 mL water was added and pH was measured by pH test strips as 6-7.

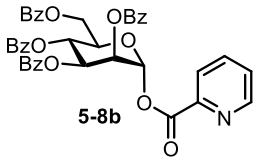
5.3.5 Characterization data for products

1) Characterization data and method for glycosyl donors:



5-8a

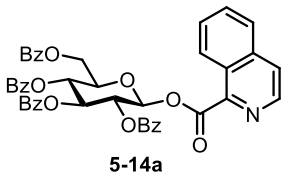
5-8a: 2,3,4,6-tetra-O-benzoyl-D-glucopyranosyl 2-pyridinecarboxylate. White solid. m.p. = 93-99 °C. $[\alpha]_D^{22}$ = 83.1° ($CHCl_3$, c = 1.0). ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.86 (d, J = 3.5 Hz, 1.6H), 8.75 (d, J = 4.5 Hz, 1H), 8.19 (d, J = 8.0 Hz, 1.7H), 8.11 (d, J = 7.5 Hz, 1H), 8.07 – 8.00 (m, 5.4H), 7.99 – 7.84 (m, 17.7H), 7.81 (td, J = 7.5, 2.0 Hz, 1.2H), 7.60 – 7.27 (m, 35.9H), 6.93 (d, J = 4.0 Hz, 1.7H), 6.42 (d, J = 8.0 Hz, 1H), 6.35 (t, J = 10.0 Hz, 1.7H), 6.04 (t, J = 9.5 Hz, 1H), 5.90 – 5.86 (m, 2.7H), 5.81 (t, J = 9.5 Hz, 1.1H), 5.70 (dd, J = 10.5, 3.5 Hz, 1.7H), 4.76 – 4.70 (m, 1.6H), 4.69 – 4.61 (m, 2.8H), 4.51 (td, J = 11.5, 4.5 Hz, 2.7H), 4.47 – 4.42 (m, 1.1H). ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 166.3, 166.1, 165.9, 165.6, 165.4, 165.4, 165.3, 163.3, 162.9, 150.7, 150.6, 147.3, 146.7, 137.4, 133.8, 133.8, 133.7, 133.7, 133.6, 133.4, 133.4, 130.1, 130.1, 130.1, 130.1, 130.0, 130.0, 129.8, 129.7, 129.1, 129.0, 128.9, 128.9, 128.9, 128.8, 128.7, 128.7, 128.6, 128.6, 128.6, 127.7, 126.1, 125.8, 93.3, 91.0, 73.6, 72.9, 71.2, 70.9, 70.7, 70.7, 69.2, 69.0, 63.0, 62.6. HRMS (ESI) for $C_{40}H_{31}NO_{11}$ (M+Na), 724.1789 (Calc.), found 724.1779.



5-8b

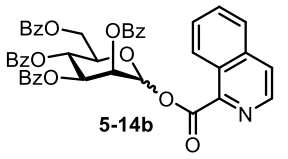
5-8b: 2,3,4,6-tetra-O-benzoyl-D-mannopyranosyl 2-pyridinecarboxylate. White solid. m.p. = 95-99 °C. $[\alpha]_D^{22}$ = -17.0° ($CHCl_3$, c = 1.0). ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.88 (d, J = 4.5 Hz, 1H), 8.26 (d, J = 8.0 Hz, 1H), 8.13 – 8.06 (m, 4H), 7.97 – 7.84 (m, 3H), 7.85 (d, J = 7.0 Hz, 2H), 7.66 – 7.34 (m, 14H), 7.28 (t, J = 7.5 Hz, 2H), 6.69 (d, J = 1.5 Hz, 1H), 6.30 (t, J = 10.0 Hz, 1H), 6.12 (dd, J = 10.0, 3.5 Hz, 1H), 5.98 – 5.92 (m, 1H), 4.73 – 4.66 (m, 2H), 4.51 (dd, J = 12.0, 3.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 166.3, 165.8, 165.5, 165.3, 162.9, 150.6, 147.2, 137.4, 133.9, 133.8, 133.6, 133.3, 130.2, 130.1, 130.0, 130.0, 129.2, 129.1, 129.1, 128.9, 128.7, 128.7, 128.6, 127.6, 126.0, 92.3, 71.6, 70.2, 69.6, 66.4, 62.5. HRMS (ESI) for $C_{40}H_{31}NO_{11}$ (M+Na), 724.1789

(Calc.), found 724.1760.



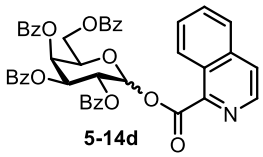
5-14a

5-14a: 2,3,4,6-tetra-O-benzoyl-D-glucopyranosyl isoquinoline-1-carboxylate. White solid. m.p. = 93-96 °C. $[\alpha]_D^{22}$ = 16.1° ($CHCl_3$, c = 1.0). ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.59 (d, J = 5.5 Hz, 1H), 8.48 (d, J = 8.0 Hz, 1H), 8.07 – 8.02 (m, 2H), 7.98 – 7.91 (m, 4H), 7.89 – 7.85 (m, 2H), 7.83 (d, J = 8.5 Hz, 1H), 7.77 (d, J = 5.5 Hz, 1H), 7.68 – 7.62 (m, 1H), 7.53 – 7.48 (m, 3H), 7.46 – 7.33 (m, 8H), 7.29 (t, J = 7.5 Hz, 2H), 6.59 (d, J = 8.0 Hz, 1H), 6.06 (t, J = 9.5 Hz, 1H), 5.92 – 5.89 (m, 1H), 5.84 (t, J = 9.5 Hz, 1H), 4.72 (dd, J = 12.5, 3.5 Hz, 1H), 4.60 (dd, J = 12.5, 5.0 Hz, 1H), 4.53 – 4.45 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 166.3, 165.9, 165.3, 165.1, 164.4, 147.6, 142.1, 137.0, 133.8, 133.7, 133.6, 133.3, 130.7, 130.2, 130.1, 130.1, 130.1, 129.8, 129.1, 129.0, 128.9, 128.9, 128.7, 128.6, 128.6, 127.4, 126.9, 126.0, 124.7, 93.4, 73.7, 73.1, 71.2, 69.2, 63.1. HRMS (ESI) for $C_{44}H_{33}NO_{11}$ (M+Na), 774.1946 (Calc.), found 774.1913.



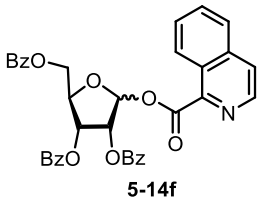
5-14b

5-14b: 2,3,4,6-tetra-O-benzoyl-D-mannopyranosyl isoquinoline-1-carboxylate. White solid. m.p. = 85-89 °C. $[\alpha]_D^{22}$ = -47.0° ($CHCl_3$, c = 1.0). ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.79 (d, J = 8.5 Hz, 1H), 8.76 (d, J = 5.5 Hz, 1H), 8.15 – 8.09 (m, 7H), 8.06 – 8.02 (m, 2H), 7.99 – 7.92 (m, 5H), 7.91 (d, J = 5.5 Hz, 1H), 7.86 – 7.82 (m, 2H), 7.81 – 7.76 (m, 3H), 7.76 – 7.71 (m, 1H), 7.63 (t, J = 7.5 Hz, 1H), 7.60 – 7.53 (m, 3H), 7.52 – 7.30 (m, 19H), 7.27 – 7.23 (m, 5H), 6.80 (d, J = 2.0 Hz, 1H), 6.31 (t, J = 10.5 Hz, 1H), 6.21 – 6.12 (m, 2H), 6.05 – 6.01 (m, 2H), 5.77 (dd, J = 3.5, 2.0 Hz, 1H), 5.56 (d, J = 1.5 Hz, 1H), 4.84 – 4.68 (m, 4H), 4.54 (dd, J = 12.5, 4.0 Hz, 1H), 4.47 (dd, J = 12.0, 3.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 166.5, 166.3, 165.8, 165.7, 165.7, 165.7, 165.6, 165.4, 163.6, 147.6, 142.0, 137.2, 133.9, 133.7, 133.7, 133.7, 133.6, 133.5, 133.3, 133.3, 133.3, 131.1, 130.4, 130.2, 130.1, 130.1, 130.1, 130.1, 130.1, 130.0, 130.0, 130.0, 129.6, 129.6, 129.5, 129.3, 129.3, 129.3, 129.2, 129.1, 128.9, 128.8, 128.7, 128.6, 128.5, 128.5, 127.5, 127.2, 126.3, 125.0, 92.6, 92.3, 71.6, 71.2, 70.2, 70.0, 69.7, 69.1, 67.2, 66.5, 63.0, 62.7. HRMS (ESI) for $C_{44}H_{33}NO_{11}$ (M+Na), 774.1946 (Calc.), found 774.1919.



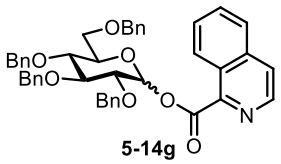
5-14d

5-14d: 2,3,4,6-tetra-O-benzoyl-D-galactopyranosyl isoquinoline-1-carboxylate. White solid. m.p. = 85-86 °C. $[\alpha]_D^{22}$ = 133.0° ($CHCl_3$, c = 1.2). ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.67 (d, J = 5.5 Hz, 1H), 8.61 (d, J = 5.5 Hz, 1H), 8.48 (d, J = 8.6 Hz, 1H), 8.42 (d, J = 8.6 Hz, 1H), 8.11 (t, J = 7.8 Hz, 4H), 7.97-8.04 (m, 7H), 7.78-7.90 (m, 8H), 7.59-7.734 (m, 5H), 7.25-7.52 (m, 23H), 7.16 (d, J = 3.5 Hz, 1H), 6.59 (d, J = 8.2 Hz, 1H), 6.13-6.20 (m, 4H), 6.08 (dd, J = 3.6, 10.4 Hz, 1H), 5.81 (dd, J = 3.4, 10.2 Hz, 1H), 5.04 (t, J = 6.5 Hz, 1H), 4.75-4.78 (m, 1H), 4.65-4.68 (m, 2H), 4.46-4.54 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 166.05, 165.94, 165.80, 165.60, 165.57, 165.12, 164.40, 164.29, 148.13, 147.60, 141.99, 136.75, 133.76, 133.70, 133.57, 133.50, 133.43, 133.38, 133.30, 133.21, 130.62, 130.56, 130.10, 130.00, 129.87, 129.80, 129.78, 129.42, 129.07, 128.97, 128.86, 128.83, 128.78, 128.71, 128.68, 128.49, 128.40, 128.37, 127.26, 127.20, 126.63, 126.60, 125.77, 125.65, 124.43, 124.38, 93.68, 91.38, 77.43, 72.91, 71.95, 69.92, 69.12, 68.78, 68.62, 68.05, 62.11. HRMS (ESI) for $C_{44}H_{33}NO_{11}$ (M+Na), 774.1945 (Calc.), found 774.1918.



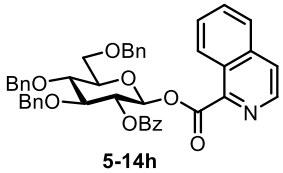
5-14f

5-14f: 2,3,5-tri-O-benzoyl-D-ribofuranosyl isoquinoline-1-carboxylate. White solid. m.p. = 80-83 °C. $[\alpha]_D^{22}$ = -95.5° ($CHCl_3$, c = 1.0). ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.75 (d, J = 8.5 Hz, 3.4H), 8.68 (d, J = 5.5 Hz, 3.5H), 8.10 – 8.06 (m, 7.3H), 8.05 – 7.86 (m, 28.5H), 7.78 – 7.75 (m, 3.8H), 7.71 – 7.69 (m, 3.9H), 7.60 – 7.48 (m, 14.6H), 7.41 – 7.28 (m, 28.9H), 6.79 (d, J = 3.0 Hz, 3.6H), 6.08 (t, J = 4.0 Hz, 3.6H), 6.00 (t, J = 3.0 Hz, 1H), 5.79 (t, J = 3.5 Hz, 3.6H), 5.75 (d, J = 3.0 Hz, 3.8H), 5.59 – 5.56 (m, 1H), 5.48 – 5.45 (m, 2H), 4.62 (dd, J = 13.0, 2.0 Hz, 3.7H), 4.43 (dd, J = 12.5, 3.0 Hz, 1H), 4.32 (dd, J = 13.0, 3.5 Hz, 3.7H), 4.11 (dd, J = 12.0, 5.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 166.3, 165.9, 165.5, 164.0, 147.7, 142.1, 137.1, 133.6, 133.6, 133.5, 133.4, 130.9, 130.4, 130.3, 130.2, 130.1, 130.0, 130.0, 129.9, 129.6, 129.5, 129.3, 128.7, 128.7, 128.6, 128.6, 127.5, 127.1, 126.2, 124.9, 93.8, 93.0, 70.4, 68.1, 67.9, 67.5, 67.4, 66.6, 63.7, 61.8, 61.7. HRMS (ESI) for $C_{36}H_{27}NO_9$ (M+Na), 640.1578 (Calc.), found 640.1568.



5-14g

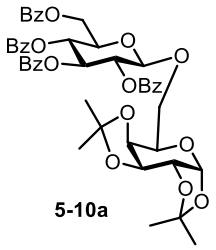
5-14g: 2,3,4,6-tetra-O-benzyl-D-glucopyranosyl isoquinoline-1-carboxylate. Yellow syrup. $[\alpha]_D^{22}$ = 37.5° ($CHCl_3$, c = 7.0). ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.77 (d, J = 8.5 Hz, 1H), 8.67 – 8.57 (m, 5H), 7.88 – 7.82 (m, 5H), 7.77 (d, J = 5.5 Hz, 2H), 7.74 – 7.58 (m, 5H), 7.51 – 7.45 (m, 3H), 7.41 – 7.39 (m, 4.0H), 7.36 – 7.21 (m, 48H), 7.21 – 7.17 (m, 3H), 7.16 – 7.07 (m, 7H), 6.82 (d, J = 3.5 Hz, 2H), 6.04 (d, J = 8.0 Hz, 1H), 5.05 – 4.93 (m, 4H), 4.92 – 4.77 (m, 11H), 4.65 – 4.59 (m, 4H), 4.56 – 4.45 (m, 5H), 4.09 – 4.05 (m, 4H), 3.89 – 3.74 (m, 13H), 3.70 (dd, J = 10.5, 2.0 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 165.1, 164.6, 149.7, 148.0, 142.0, 142.0, 138.8, 138.7, 138.3, 138.3, 138.3, 138.2, 138.0, 137.9, 137.0, 136.9, 130.8, 130.7, 130.2, 129.0, 128.7, 128.6, 128.6, 128.6, 128.5, 128.5, 128.4, 128.4, 128.2, 128.2, 128.1, 128.0, 128.0, 127.9, 127.9, 127.8, 127.8, 127.8, 127.3, 127.2, 127.2, 126.6, 126.6, 126.4, 124.6, 123.9, 95.7, 91.9, 85.0, 81.9, 81.1, 79.4, 77.6, 77.1, 76.3, 75.9, 75.5, 75.3, 75.2, 73.8, 73.7, 73.7, 73.4, 68.6, 68.2. HRMS (ESI) for $C_{44}H_{41}NO_7$ (M+Na), 718.2775 (Calc.), found 718.2757.



5-14h

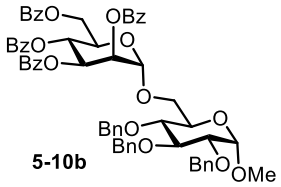
5-14h: 3,4,6-tri-O-benzyl-2-O-benzoyl- D-glucopyranosyl isoquinoline-1-carboxylate. Yellow syrup. $[\alpha]_D^{22}$ = 12.5° ($CHCl_3$, c = 7.3). ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.54 (d, J = 5.5 Hz, 1H), 8.36 (dd, J = 8.5, 0.5 Hz, 1H), 8.00 (dd, J = 8.5, 0.5 Hz, 2H), 7.77 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 5.5 Hz, 1H), 7.62 – 7.57 (m, 1H), 7.56 – 7.51 (m, 1H), 7.40 (t, J = 8.0 Hz, 2H), 7.37 – 7.19 (m, 11H), 7.17 – 7.10 (m, 5H), 6.28 (d, J = 8.0 Hz, 1H), 5.68 – 5.61 (m, 1H), 4.85 (d, J = 11.0 Hz, 1H), 4.79 (d, J = 11.5 Hz, 1H), 4.71 (d, J = 11.0 Hz, 1H), 4.65 (dd, J = 12.5, 7.5 Hz, 2H), 4.55 (d, J = 12.0 Hz, 1H), 4.00 – 3.98 (m, 2H), 3.86 – 3.85 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 165.2, 164.8, 148.3, 142.1, 138.2, 138.1, 137.8, 136.8, 133.5, 130.6, 130.1, 129.7, 128.7, 128.6, 128.6, 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.2, 126.6, 126.0, 124.3, 93.7, 82.8, 77.7, 76.6, 75.3, 75.3, 73.8, 72.9, 68.5. HRMS (ESI) for $C_{44}H_{39}NO_8$ (M+Na), 732.2568 (Calc.), found 732.2604.

5.3.6 Characterization data and method for products



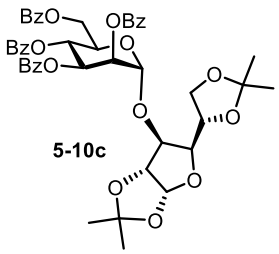
5-10a

5-10a. Colorless syrup. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.03 (d, J = 7.5 Hz, 2H), 7.97 (d, J = 7.5 Hz, 2H), 7.90 (d, J = 7.5 Hz, 2H), 7.83 (d, J = 7.5 Hz, 2H), 7.57 – 7.46 (m, 3H), 7.45 – 7.31 (m, 7H), 7.30 – 7.25 (m, 2H), 5.90 (t, J = 10.0 Hz, 1H), 5.68 (t, J = 10.0 Hz, 1H), 5.54 (t, J = 9.0 Hz, 1H), 5.42 (d, J = 5.0 Hz, 1H), 5.05 (d, J = 7.5 Hz, 1H), 4.64 (dd, J = 12.0, 2.0 Hz, 1H), 4.49 (dd, J = 12.0, 5.0 Hz, 1H), 4.46 – 4.39 (m, 1H), 4.25 – 4.15 (m, 2H), 4.10 (d, J = 8.0 Hz, 1H), 4.02 (dd, J = 12.0, 3.5 Hz, 1H), 3.93 – 3.82 (m, 2H), 1.37 (s, 3H), 1.24 (s, 3H), 1.20 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 166.4, 166.0, 165.4, 165.4, 133.6, 133.4, 133.3, 130.2, 130.1, 130.0, 129.9, 129.6, 129.1, 129.1, 128.6, 128.6, 128.5, 128.4, 109.5, 108.7, 101.5, 96.4, 73.3, 72.4, 72.1, 71.2, 70.8, 70.6, 70.1, 68.5, 67.8, 63.5, 26.1, 25.9, 25.1, 24.5. Spectral data are in accordance with literature[22].



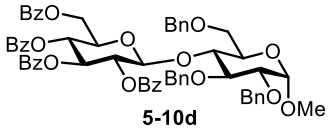
5-10b

5-10b. Colorless syrup. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.10 – 8.06 (m, 2H), 8.06 – 8.02 (m, 2H), 7.92 – 7.88 (m, 2H), 7.85 – 7.81 (m, 2H), 7.61 – 7.54 (m, 2H), 7.51 (t, J = 7.5 Hz, 1H), 7.45 – 7.24 (m, 24H), 6.06 (t, J = 10.0 Hz, 1H), 5.88 (dd, J = 10.0, 3.5 Hz, 1H), 5.72 (dd, J = 4.0, 2.0 Hz, 1H), 5.15 (d, J = 1.0 Hz, 1H), 5.01 (dd, J = 11.0, 4.0 Hz, 2H), 4.84 – 4.78 (m, 2H), 4.69 (dd, J = 12.5, 3.0 Hz, 2H), 4.63 (dd, J = 10.0, 2.0 Hz, 2H), 4.44 – 4.37 (m, 1H), 4.34 (dd, J = 12.0, 5.0 Hz, 1H), 4.03 (t, J = 9.5 Hz, 1H), 3.94 (dd, J = 11.0, 5.0 Hz, 1H), 3.86 (dd, J = 10.0, 5.5 Hz, 1H), 3.81 (dd, J = 11.0, 1.0 Hz, 1H), 3.57 (dd, J = 9.5, 3.5 Hz, 1H), 3.55 – 3.50 (m, 1H), 3.45 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 166.3, 165.7, 165.7, 165.5, 139.0, 138.4, 138.4, 133.7, 133.4, 133.3, 130.2, 130.1, 130.0, 129.9, 129.6, 129.4, 129.2, 128.8, 128.7, 128.7, 128.6, 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 98.2, 98.0, 82.4, 80.5, 78.0, 76.0, 75.3, 73.7, 70.5, 70.2, 70.1, 69.1, 67.1, 66.9, 63.0, 55.5. Spectral data are in accordance with literature[23].



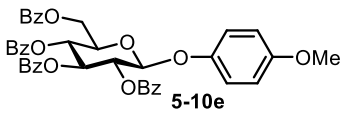
5-10c

5-10c. Colorless syrup. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.11 (d, J = 7.0 Hz, 2H), 8.06 (d, J = 8.0 Hz, 2H), 7.97 (d, J = 7.5 Hz, 2H), 7.82 (d, J = 7.5 Hz, 2H), 7.63 – 7.55 (m, 2H), 7.51 (t, J = 7.5 Hz, 1H), 7.45 – 7.35 (m, 7H), 7.28 – 7.25 (m, 2H), 6.11 – 6.02 (m, 2H), 5.88 (dd, J = 10.0, 2.5 Hz, 1H), 5.76 (s, 1H), 5.41 (s, 1H), 4.77 – 4.68 (m, 2H), 4.58 – 4.34 (m, 4H), 4.28 – 4.21 (m, 1H), 4.16 – 4.08 (m, 1H), 4.01 (dd, J = 8.5, 5.5 Hz, 1H), 1.51 (s, 3H), 1.38 (s, 3H), 1.32 (s, 3H), 1.28 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 166.5, 165.8, 165.7, 165.2, 133.8, 133.7, 133.5, 133.3, 130.1, 130.0, 129.5, 129.2, 129.1, 128.9, 128.7, 128.7, 128.6, 112.4, 109.8, 105.6, 99.0, 84.3, 81.9, 81.6, 72.5, 70.1, 70.0, 69.9, 68.1, 67.3, 63.5, 27.1, 27.0, 26.5, 25.2. Spectral data are in accordance with literature[23].



5-10d

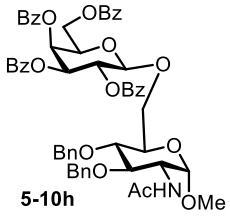
5-10d. Colorless syrup. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.95 (d, J = 8.0 Hz, 2H), 7.87 (d, J = 8.0 Hz, 4H), 7.78 (d, J = 7.5 Hz, 2H), 7.56 – 7.47 (m, 5H), 7.46 – 7.29 (m, 14H), 7.28 – 7.22 (m, 5H), 7.21 – 7.16 (m, 3H), 5.61 (t, J = 9.5 Hz, 1H), 5.54 (t, J = 9.5 Hz, 1H), 5.46 (t, J = 9.0 Hz, 1H), 5.07 (d, J = 11.0 Hz, 1H), 4.84 – 4.70 (m, 4H), 4.59 – 4.54 (m, 2H), 4.43 – 4.30 (m, 2H), 4.25 (dd, J = 12.0, 4.5 Hz, 1H), 3.96 (t, J = 9.5 Hz, 1H), 3.87 (t, J = 9.0 Hz, 1H), 3.70 (t, J = 9.5 Hz, 2H), 3.54 – 3.37 (m, 3H), 3.27 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 166.3, 166.0, 165.3, 165.0, 139.5, 138.6, 138.1, 133.6, 133.6, 133.4, 133.2, 130.0, 129.9, 129.9, 129.4, 129.2, 129.1, 129.1, 128.7, 128.6, 128.6, 128.6, 128.5, 128.3, 128.3, 128.0, 127.6, 127.4, 100.7, 98.7, 80.2, 79.0, 77.5, 75.6, 73.9, 73.8, 73.4, 72.5, 72.1, 70.1, 69.7, 67.8, 63.4, 55.6. Spectral data are in accordance with literature[9a].



5-10e

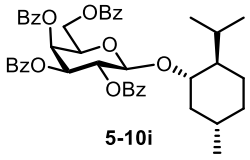
5-10e. Yellow syrup. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.04 (d, J = 7.5 Hz, 2H), 7.98 (d, J = 7.5 Hz, 2H), 7.93 (d, J = 7.5 Hz, 2H), 7.86 (d, J = 7.5 Hz, 2H), 7.60 – 7.48 (m, 3H), 7.47 – 7.34 (m, 7H), 7.30 (t, J = 7.5 Hz, 2H), 6.95 (d, J = 9.0 Hz, 2H), 6.67 (d, J = 8.5 Hz, 2H), 5.97 (t, J = 10.0 Hz, 1H), 5.77 (t, J = 9.5 Hz, 1H), 5.70 (t, J = 9.5 Hz, 1H), 5.26 (d, J = 8.0 Hz, 1H), 4.67 (dd, J = 12.0, 2.5 Hz, 1H),

4.56 – 4.52 (m, 1H), 4.30 – 4.26 (m, 1H), 3.71 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 166.3, 166.0, 165.5, 165.3, 156.0, 151.2, 133.8, 133.6, 133.6, 133.4, 130.1, 130.1, 130.0, 130.0, 129.8, 129.4, 129.0, 128.9, 128.7, 128.7, 128.6, 128.6, 119.3, 114.7, 101.1, 73.1, 72.8, 72.0, 70.0, 63.5, 55.8. Spectral data are in accordance with literature[24].



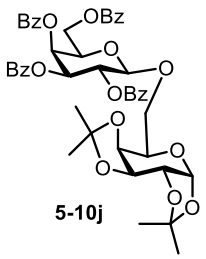
5-10h

5-10h. Yellow syrup. $[\alpha]_D^{22}$ = 167.1° ($CHCl_3$, c = 1.5). ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.09 (d, J = 7.0 Hz, 2H), 8.02 (d, J = 7.5 Hz, 2H), 7.89 (d, J = 7.0 Hz, 2H), 7.77 (d, J = 7.5 Hz, 2H), 7.61 (t, J = 7.5 Hz, 1H), 7.54 (t, J = 7.5 Hz, 1H), 7.48 (t, J = 7.5 Hz, 2H), 7.44 – 7.38 (m, 4H), 7.33 – 7.20 (m, 12H), 7.18 – 7.14 (m, 2H), 6.00 (d, J = 3.0 Hz, 1H), 5.86 (dd, J = 10.5, 8.0 Hz, 1H), 5.62 (dd, J = 10.5, 3.0 Hz, 1H), 5.25 (d, J = 9.5 Hz, 1H), 4.86 (d, J = 8.0 Hz, 1H), 4.72 – 4.69 (m, 2H), 4.60 – 4.46 (m, 3H), 4.43 – 4.39 (m, 2H), 4.32 (t, J = 6.5 Hz, 1H), 4.25 (d, J = 10.0 Hz, 1H), 4.17 (td, J = 10.0, 3.5 Hz, 1H), 3.79 – 3.71 (m, 2H), 3.59 (t, J = 10.5 Hz, 1H), 3.44 (t, J = 9.5 Hz, 1H), 3.08 (s, 3H), 1.81 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 169.8, 166.2, 165.8, 165.8, 165.3, 138.5, 138.1, 133.8, 133.5, 133.5, 133.4, 130.3, 130.0, 129.9, 129.6, 129.5, 129.2, 128.9, 128.8, 128.7, 128.6, 128.6, 128.5, 128.4, 128.4, 128.0, 128.0, 127.9, 102.2, 98.5, 80.5, 78.6, 75.0, 74.7, 71.9, 71.6, 70.4, 69.9, 69.2, 68.3, 62.1, 54.9, 52.5, 23.7. HRMS (ESI) for $C_{57}H_{55}NO_{15}$ (M+H), 994.3644 (Calc.), found 994.3643.



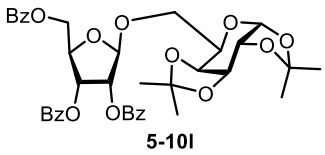
5-10i

5-10i. Colorless syrup. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.00 – 8.02 (m, 2H), 7.93 – 7.95 (m, 2H), 7.88 – 7.90 (m, 2H), 7.71 – 7.72 (m, 2H), 7.27 – 7.52 (m, 10H), 7.14 – 7.17 (m, 2H), 5.91 (d, J = 3.0 Hz, 1H), 5.65 – 5.69 (m, 1H), 5.51 (dd, J = 10.5, 3.5 Hz, 1H), 4.80 (d, J = 8.0 Hz, 1H), 4.52 – 4.56 (m, 1H), 4.33 – 4.36 (m, 1H), 4.22 (t, J = 6.5 Hz, 1H), 3.38 – 3.43 (m, 1H), 2.27 – 2.30 (m, 1H), 1.87 (d, J = 12. 5 Hz, 1H), 1.47 – 1.53 (m, 2H), 1.14 – 1.21 (m, 3H), 0.88 - 0.82 (m, 1H), 0.79 (d, J = 7.0 Hz, 3H), 0.68 (d, J = 6.5 Hz, 3H), 0.64 (d, J = 6.5 Hz, 3H), 0.63 – 0.57 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 166.3, 165.9, 165.8, 165.4, 133.7, 133.4, 133.3, 130.3, 130.0, 130.0, 129.9, 129.8, 129.7, 129.4, 129.1, 128.8, 128.6, 128.5, 100.1, 80.1, 72.3, 71.4, 70.3, 68.6, 62.6, 47.5, 41.4, 34.3, 31.6, 25.3, 23.2, 22.2, 21.1, 15.9. Spectral data are in accordance with literature[25].



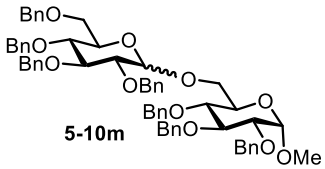
5-10j

5-10j. Colorless syrup. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.99 (d, J = 7.5 Hz, 2H), 7.93 (d, J = 7.5 Hz, 2H), 7.89 (d, J = 7.5 Hz, 2H), 7.69 (d, J = 7.5 Hz, 2H), 7.23-7.48 (m, 10H), 7.11 (t, J = 7.5 Hz, 2H), 5.92 (d, J = 3.0 Hz, 1H), 5.72-5.76 (m, 1H), 5.54 (dd, J = 3.5, 10.5 Hz, 1H), 5.32 (d, J = 5.0 Hz, 1H), 4.95 (d, J = 8.0 Hz, 1H), 4.56-4.60 (m, 1H), 4.26-4.36 (m, 3H), 4.11-4.12 (m, 1H), 3.97-4.03 (m, 2H), 3.81-3.86 (m, 2H), 1.29 (s, 3H), 1.13 (s, 3H), 1.12 (s, 3H), 1.09 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 166.1, 165.7, 165.7, 165.4, 133.7, 133.3, 133.2, 130.1, 130.1, 129.9, 129.9, 129.6, 129.2, 128.9, 128.7, 128.6, 128.5, 128.4, 128.3, 109.4, 108.5, 101.9, 96.3, 77.5, 72.0, 71.4, 71.1, 70.7, 70.5, 69.8, 68.6, 68.3, 67.6, 62.2, 26.0, 25.8, 25.0, 24.4. Spectral data are in accordance with literature[26].



5-10l

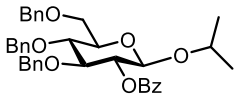
5-10l. Colorless syrup. $[\alpha]_D^{22}$ = 58.9° ($CHCl_3$, c = 1.5). ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.04 (dd, J = 8.0, 1.0 Hz, 2H), 8.00 (dd, J = 8.0, 1.5 Hz, 2H), 7.89 – 7.83 (m, 2H), 7.56 – 7.47 (m, 3H), 7.36 – 7.27 (m, 6H), 5.81 (t, J = 4.0 Hz, 1H), 5.60 (d, J = 2.5 Hz, 1H), 5.55 – 5.53 (m, 2H), 5.19 (d, J = 2.0 Hz, 1H), 4.64 (dd, J = 8.0, 2.5 Hz, 1H), 4.39 (dd, J = 13.5, 2.0 Hz, 1H), 4.35 – 4.30 (m, 2H), 4.11 – 4.04 (m, 2H), 3.97 (dd, J = 10.0, 6.5 Hz, 1H), 3.77 (dd, J = 10.0, 6.5 Hz, 1H), 1.54 (s, 3H), 1.47 (s, 3H), 1.37 (s, 3H), 1.33 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 166.5, 166.1, 165.5, 133.4, 133.4, 133.3, 130.3, 130.2, 130.2, 130.0, 130.0, 129.7, 128.6, 128.6, 128.5, 109.6, 109.0, 99.1, 96.6, 71.2, 70.9, 70.8, 68.9, 68.1, 67.1, 66.7, 66.5, 61.7, 26.3, 26.3, 25.2, 24.9. HRMS (ESI) for $C_{38}H_{40}O_{13}$ (M+Na), 727.2361 (Calc.), found 727.2351.



5-10m

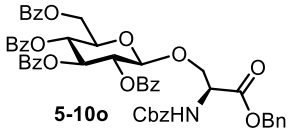
5-10m. White solid. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.33 – 7.11 (m, 84H), 4.98 – 4.89 (m, 9H), 4.85 – 4.39 (m, 30H), 4.34 (d, J = 8.0 Hz, 1H), 4.18 (d, J = 10.0 Hz, 1H), 4.01 – 3.94 (m, 4H), 3.87 – 3.41 (m, 25H), 3.35 – 3.32 (m, 7H). ^{13}C NMR (126 MHz, $CDCl_3$,

TMS): δ 139.1, 139.1, 139.0, 138.8, 138.7, 138.7, 138.7, 138.6, 138.6, 138.5, 138.4, 138.4, 138.3, 138.2, 128.7, 128.6, 128.6, 128.6, 128.6, 128.6, 128.5, 128.5, 128.4, 128.2, 128.2, 128.2, 128.2, 128.2, 128.1, 128.1, 128.1, 128.1, 128.0, 127.9, 127.9, 127.9, 127.9, 127.8, 127.8, 127.8, 127.8, 127.7, 104.0, 98.3, 98.2, 97.5, 85.0, 82.4, 82.3, 82.2, 81.9, 80.4, 80.2, 80.0, 78.2, 78.1, 78.0, 77.9, 76.0, 75.9, 75.7, 75.3, 75.2, 75.1, 73.7, 73.6, 73.6, 73.6, 72.6, 70.6, 70.5, 70.1, 69.3, 68.8, 68.7, 66.3, 66.1, 55.4, 55.4. Spectral data are in accordance with literature[27].



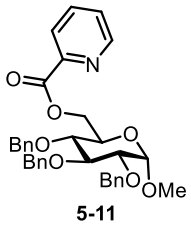
5-10n

5-10n. Colorless syrup. $[\alpha]_D^{22}$ = 18.3° ($CHCl_3$, c = 1.5). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.99-7.88 (m, 2H), 7.47 (t, J = 7.2 Hz, 1H), 7.34 (t, J = 7.6 Hz, 2H), 7.31-6.98 (m, 15H), 5.15 (dd, J = 9.2, 8.4 Hz, 1H), 4.75 (d, J = 11.2 Hz, 1H), 4.65 (d, J = 10.8 Hz, 1H), 4.61-4.45 (m, 5H), 3.88-3.78 (m, 1H), 3.77-3.58 (m, 4H), 3.52-3.43 (m, 1H), 1.12 (d, J = 6.0 Hz, 3H), 0.93 (d, J = 6.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, TMS): δ 165.3, 138.4, 138.2, 138.1, 133.1, 130.4, 129.9, 128.6, 128.6, 128.5, 128.4, 128.2, 128.0, 127.9, 127.8, 100.2, 83.1, 78.4, 75.5, 75.2, 75.1, 74.3, 73.7, 72.7, 69.2, 23.6, 22.2. HRMS (ESI) for $C_{37}H_{40}O_7$ (M+Na), 619.2666 (Calc.), found 619.2666.



5-10o

5-10o. Colorless syrup. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.00 (d, J = 7.5 Hz, 2H), 7.93 (d, J = 7.5 Hz, 2H), 7.89 (d, J = 7.0 Hz, 2H), 7.82 (d, J = 7.5 Hz, 2H), 7.56 – 7.47 (m, 2H), 7.46 – 7.23 (m, 20H), 5.85 (t, J = 10.0 Hz, 1H), 5.63 (t, J = 10.0 Hz, 1H), 5.55 (d, J = 8.0 Hz, 1H), 5.45 (dd, J = 9.5, 8.0 Hz, 1H), 5.14 (q, J = 12.0 Hz, 2H), 5.02 (d, J = 12.5 Hz, 1H), 4.94 (d, J = 12.0 Hz, 1H), 4.78 (d, J = 8.0 Hz, 1H), 4.60 (dd, J = 12.5, 3.5 Hz, 1H), 4.55 – 4.48 (m, 1H), 4.42 (dd, J = 12.5, 5.0 Hz, 1H), 4.37 (dd, J = 10.0, 2.5 Hz, 1H), 4.05 – 3.98 (m, 1H), 3.91 (dd, J = 10.0, 3.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 169.5, 166.3, 166.0, 165.4, 165.3, 156.1, 136.5, 135.5, 133.7, 133.5, 133.4, 130.1, 130.0, 130.0, 129.7, 129.3, 129.0, 129.0, 128.8, 128.7, 128.7, 128.7, 128.6, 128.6, 128.5, 128.3, 128.3, 101.6, 72.8, 72.5, 72.0, 69.7, 69.7, 67.7, 67.2, 63.2, 54.5. Spectral data are in accordance with literature[28].



5-11

5-11. Colorless syrup. $[\alpha]_D^{22}$ = 71.4° ($CHCl_3$, c = 1.0). ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.75 (d, J = 4.5 Hz, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.80 (t, J = 8.0 Hz, 1H), 7.45 (dd, J = 7.5, 5.0 Hz, 1H), 7.40 – 7.19 (m, 15H), 5.01 (d, J = 10.5 Hz, 1H), 4.91 (d, J = 11.0 Hz, 1H), 4.85 – 4.79 (m, 2H), 4.71 – 4.52 (m, 5H), 4.05 (t, J = 9.5 Hz, 1H), 4.03 – 3.95 (m, 1H), 3.65 – 3.54 (m, 2H), 3.38 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 164.9, 150.3, 148.0, 138.8, 138.3, 138.1, 137.0, 128.7, 128.7, 128.7, 128.3, 128.3, 128.3, 128.2, 128.1, 128.0, 127.1, 125.3, 98.2, 82.4, 80.2, 77.8, 76.1, 75.3, 73.6, 68.9, 64.5, 55.5. HRMS (ESI) for $C_{34}H_{35}NO_7$ (M+Na), 592.2306 (Calc.), found 592.2288.

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Appendix 1

Intermolecular Bromoesterification of Conjugated Enynes: an Efficient Synthesis of Bromoallenes

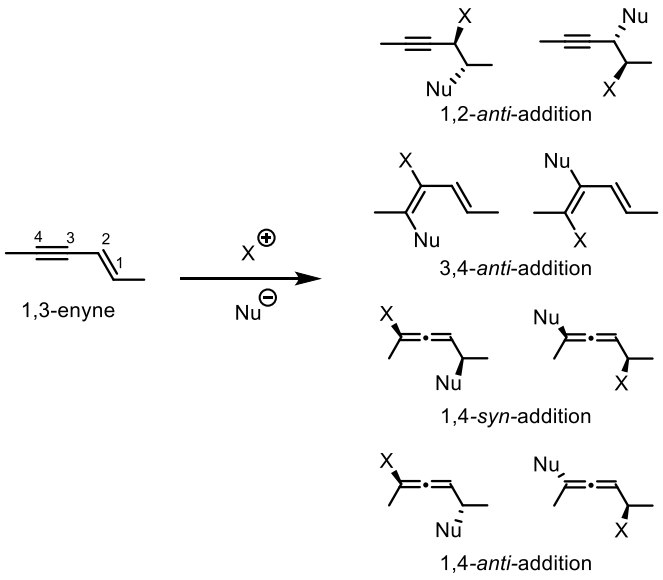
Part of this chapter was taken from the following published article.

H.-Y. Wang, W. Zhang, Y. Zhang, C. M. Schienebeck, S. R. Bennett, W. Tang, *Org. Chem. Front.* **2014**, *1*, 386-390.

1 Introduction

Halogen mediated addition of nucleophiles to alkenes is one of the fundamentally most important reactions.[1] It provides useful building blocks with up to two adjacent new stereogenic centers. Halogen-mediated 1,4-addition to conjugated enynes can produce chiral allenes[2] together with a stereogenic center. This potentially very useful reaction has, however, received very little attention partly due to the complex regio- and diastereo-selectivity issue as illustrated in **Scheme 1**.

Scheme 1. Potential isomeric products from halogen-mediated addition of nucleophiles to 1,3-enynes

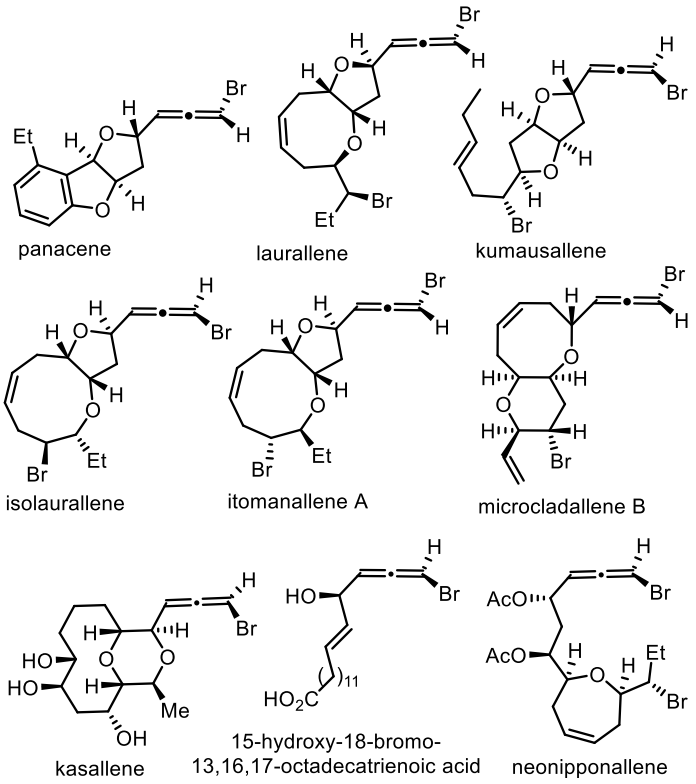


The regioselectivity can be overcome partially by tethering the nucleophile with the 1,3-enyne. Indeed, examples of intramolecular halocyclizations in a 1,4-addition fashion have been documented in the literature. In 1982, the first intramolecular bromoetherification of 1,3-enynes was reported in a biomimetic synthesis of racemic panacene (**Scheme 2**).[3] The diastereomeric ratio for this 1,4-addition was 1:1. It was later found that the relative stereochemistry of panacene was assigned wrong.[4] No or low diastereoselectivity was observed for similar intramolecular bromoetherification of 1,3-enynes in the synthesis of laurallene[5] and kumausallene[6], with a few exceptions.[7] The first stereoselective biomimetic synthesis of bromoallene-containing natural products was accomplished by us in 2011.[8] Nearly perfect diastereoselectivity was observed in the biomimetic intramolecular 1,4-bromoetherification of 1,3-enynes in our enantioselective synthesis of kumausallene.

In addition to panacene, laurallene, and kumausallene, the bromoallene moiety is also present in dozens of other natural products (**Scheme 2**).[9] Only a small number of them have been synthesized to date.[10] Interestingly, all haloallenes found in

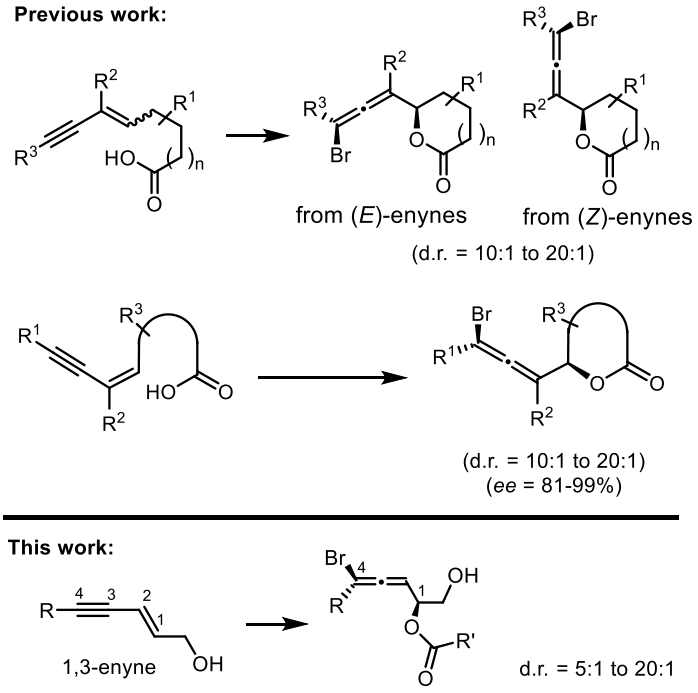
nature are disubstituted bromoallenes. Haloallene is also an important intermediate for the preparation of more complex allenes and other functional groups.[11]

Scheme 2. Selected bromoallene-containing natural products



In 2009, we reported the first 1,4-bromolactonization of 1,3- enynes (**Scheme 3**).[12] Subsequently, the catalytic asymmetric version of this halocyclization was developed by us,[13] which represents the first catalytic asymmetric halolactonization with more than 90% *ee*.[14] A number of groups[15] including us[16] also developed different catalysts for asymmetric halolactonization of substituted alkenes and alkynes. In addition to carboxylate nucleophiles, we also demonstrated that high diastereoselectivity could be achieved for certain nitrogen nucleophiles in several halocyclizations.[17] To the best of our knowledge, the much more challenging halogen-mediated intermolecular 1,4-addition to 1,3-enynes has never been reported for any nucleophiles. We herein describe the first example of intermolecular 1,4-addition of halogen and carboxylate to 1,3-enynes.

Scheme 3. Intra- and intermolecular 1,4-bromoesterification of 1,3-enynes

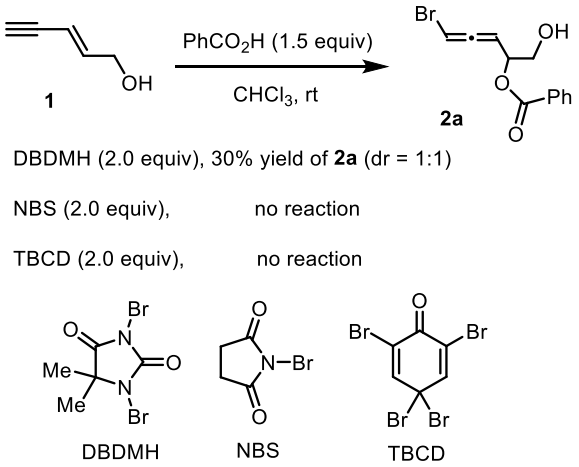


2 Results and Discussion

2.1 Optimization of Reaction Conditions

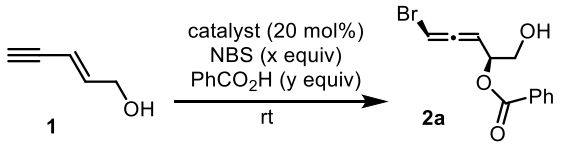
Since enyne **1** is commercially available, we began our investigation on the intermolecular bromoesterification with this substrate. We first examined the source of halogen in the absence of any additive (Scheme 4). Around 30% yield of the desired 1,4-addition product **2a** was observed with a 1:1 d.r. when DBDMH was employed, while no reaction occurred using NBS or TBCD.

Scheme 4. 1,4-Bromoesterification of 1,3-enyne **1** with different halogenation reagents



To avoid the background reaction, which provides low diastereoselectivity, we then examined different catalysts that can activate NBS (entries 1–5, **Scheme 5**). Similar to the intramolecular reaction,[12] DABCO afforded the highest diastereoselectivity (entry 1). The major diastereomer was assigned as the syn-addition product shown in **Scheme 5** based on our previous studies on halocyclization of enynes.[8, 12-13, 16] We next investigated the effect of the amount of NBS on the d.r. and yield in the presence of 1.1 equivalents of benzoic acid (entries 6–8). Both d.r. and yield were increased with less NBS reagent. Other solvents (entries 9 and 10) gave poor results. The best yield was obtained when the amount of benzoic acid was increased from 1.1 to 1.3 equivalents (entry 11). Although the yield of **2a** could be improved further with an increased equivalent of benzoic acid (entry 12), the d.r. dropped from 10:1 to 7:1.

Scheme 5. Screening of the conditions for 1,4-addition of benzoate and bromine to 1,3-enyne **1**



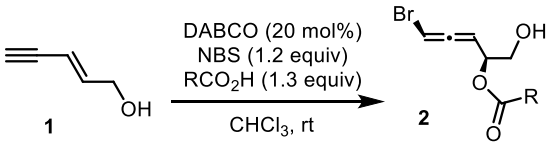
entry	catalyst	x	y	solvent	d.r.	Yield[a]
1	DABCO	2.0	1.5	$CHCl_3$	5:1	41%
2	DBU	2.0	1.5	$CHCl_3$	1:1	<10%
3	DMAP	2.0	1.5	$CHCl_3$	1:1	<10%
4	DMF	2.0	1.5	$CHCl_3$	3:1	31%
5	PPh_3	2.0	1.5	$CHCl_3$	no reaction	
6	DABCO	2.0	1.1	$CHCl_3$	3:1	46%
7	DABCO	1.5	1.1	$CHCl_3$	5:1	63%
8	DABCO	1.2	1.1	$CHCl_3$	10:1	65%
9	DABCO	1.2	1.1	DCE	3:1	73%
10	DABCO	1.2	1.1	toluene	no reaction	
11	DABCO	1.2	1.3	$CHCl_3$	10:1	75%
12	DABCO	1.2	1.5	$CHCl_3$	7:1	83%

[a.] Yield was based on NMR using CH_2Br_2 as the internal standard.

2.2 Substrate Scope and Applications

With the optimized conditions in hand, we then studied the scope of the carboxylic acids (**Scheme 6**). Similar results were obtained by using *ortho*- or *para*-methyl substituted benzoic acids (entries 2 and 3). A slower reaction was observed for benzoic acid with a strong electron-donating group (entry 4), while benzoic acid with a strong electron-withdrawing group yielded a complex mixture (entry 5). Halogen substituted benzoic acids gave 44% to 70% yields of the desired products (entries 6–8). Lower yields for entries 7 and 8 are likely due to the poor solubility of the corresponding benzoic acids. Aliphatic carboxylic acids generally worked well with slightly lower d.r.s (entries 9–11).

Scheme 6. Scope of carboxylic acids

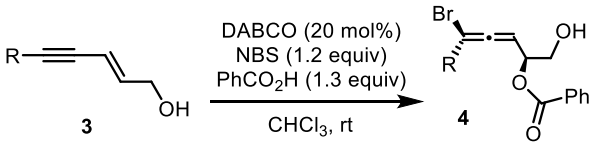


entry	carboxylic acid (R)	product	dr	Yield[a]
1	R = C_6H_5	**2a**	10:1	73%
2	R = *o*-$CH_3C_6H_4$	**2b**	10:1	65%
3	R = *p*-$CH_3C_6H_4$	**2c**	10:1	65%
4	R = *p*-$CH_3OC_6H_4$	**2d**	10:1	45%
5	R = *p*-$NO_2C_6H_4$	complex mixture		
6	R = *p*-FC_6H_4	**2e**	10:1	70%
7	R = *p*-ClC_6H_4	**2f**	10:1	45% (60%)[b]
8	R = *p*-BrC_6H_4	**2g**	10:1	44% (57%)[b]
9	R = CH_3	**2h**	8:1	67%
10	R = $C_6H_5CH_2$	**2i**	5:1	77%
11	R = CH_3CH_2	**2j**	5:1	61%

[a] Isolated yield. [b] Based on recovered starting material.

The scope of enynes was also examined (**Scheme 7**). Enynes with sterically bulky groups provided higher diastereoselectivity compared with **2** (entries 1 and 2). The d.r. and yield for enyne **3c** with a long-chain aliphatic substituent (entry 3) were similar to those of the parent substrate **1**. No reaction occurred for enynes with an aryl or cyclopropyl substituent (entries 4 and 5).

Scheme 7. Scope of enynes



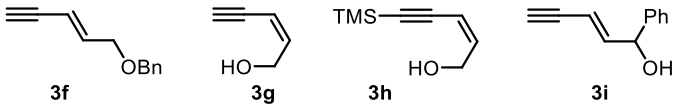
entry	enyne (R)	product	dr	Yield[a]
1	**3a**, R = *t*Bu	**4a**	20:1	71%
2	**3b**, R = TMS	**4b**	14:1	71%
3	**3c**, R = $CH_3(CH_2)_5$	**4c**	10:1	65%
4[b]	**3d**, R = C_6H_5		no reaction	
5	**3e**, R = cyclopropyl		no reaction	

[a.] Isolated yield.

b. Data acquired from Ms. Casi Schienebeck

We also found that the free hydroxyl group in **1** was required since no reaction occurred for substrate **3f**, where the OH group was masked as benzyl ether (Scheme 4). Surprisingly, enynes **3g** and **3h** with a *cis*-alkene also did not afford any desired products. Only a trace amount of the product was observed for secondary alcohol **3i** under standard conditions.

Scheme 8. Failed substrates.



2.3 Mechanism

Similar to the previously reported intramolecular 1,4-addition of halogen and nucleophile to 1,3-enynes, [8, 12-13, 16] the overall *syn*-addition is likely due to the interaction between the negatively charged carboxylate and the partially positively charged electrophile. The free OH group may facilitate the addition by forming a hydrogen-bond with the carboxylate.

2.4 Conclusion

In summary, we have developed the first intermolecular 1,4- bromoesterification of conjugated 1,3-enynes. Functionalized

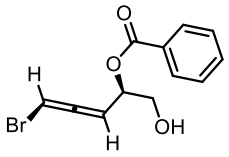
bromoallenes were prepared efficiently from relatively simple starting materials diastereoselectively. A broad range of carboxylic acids and enynes with either a terminal or internal alkyne can participate in the 1,4-addition reaction.

3. Experimental Section

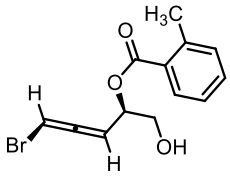
3.1 General methods for the preparation of conjugated enynes

Substrates **3a**, **3c**, **3e**, **3g**, **3h** were prepared according to our previously reported procedures[12] and their spectra are in accordance with literature.[12-13, 18] Substrates **3b**,[19] **3d**,[20] and **3f** [21] were prepared according to known procedures and their spectra are in accordance with literature.

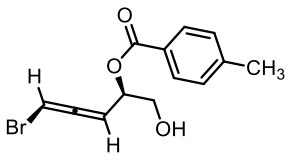
3.2 Characterization data for bromoesterification products



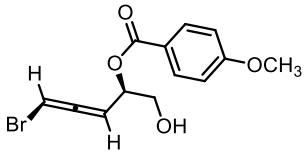
2a: 5-bromo-1-hydroxypenta-3,4-dien-2-yl benzoate. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.07 (d, *J* = 7.2 Hz, 2H), 7.59 (t, *J* = 7.2 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 6.18 – 6.08 (dd, *J* = 5.6, 2.0 Hz, 1H), 5.69 (qd, *J* = 5.2, 2.0 Hz, 1H), 5.58 (t, *J* = 5.6 Hz, 1H), 3.91 (br, s, 2H), 2.10 (br, s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.57, 166.03, 133.54, 129.92, 129.68, 128.61, 97.04, 75.28, 71.57, 64.22. IR (neat) ν 3454, 3061, 2934, 1719, 1265, 1069 cm^{-1}. HRMS (ESI) for $C_{12}H_{11}BrO_3$ (M+H), 282.9965 (Calc.), found 282.9967.



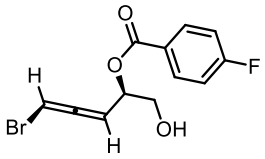
2b: 5-bromo-1-hydroxypenta-3,4-dien-2-yl 2-methylbenzoate. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.96 (d, *J* = 8.0 Hz, 1H), 7.43 (td, *J* = 7.5, 0.5 Hz, 1H), 7.29 – 7.23 (m, 2H), 6.14 (dd, *J* = 5.5, 2.0 Hz, 1H), 5.70 – 5.63 (m, 1H), 5.58 (t, *J* = 5.5 Hz, 1H), 3.98 – 3.86 (m, 2H), 2.61 (s, 3H), 2.03 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.63, 166.82, 140.67, 132.57, 131.93, 130.91, 129.02, 125.95, 97.12, 75.30, 71.36, 64.26, 21.95. IR (neat) ν 3425, 3060, 2927, 1719, 1250, 1073 cm^{-1}. HRMS (ESI) for $C_{13}H_{13}BrO_3$ ($M+NH_4$), 314.0387 (Calc.), found 314.0384.



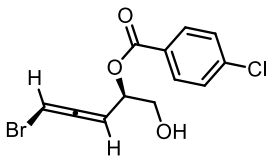
2c: 5-bromo-1-hydroxypenta-3,4-dien-2-yl 4-methylbenzoate. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.95 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 7.0 Hz, 2H), 6.12 (dd, *J* = 5.6, 2.0 Hz, 1H), 5.68 (m, 1H), 5.56 (t, *J* = 5.6 Hz, 1H), 3.98 – 3.85 (m, 2H), 2.42 (s, 3H), 1.25 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.56, 166.10, 144.37, 129.98, 129.34, 126.93, 97.17, 75.26, 71.41, 64.32, 21.86. IR (neat) ν 3440, 3060, 2924, 1719, 1268, 1105 cm^{-1}. HRMS (ESI) for $C_{13}H_{13}BrO_3$ (M+H), 297.0121 (Calc.), found 297.0123.



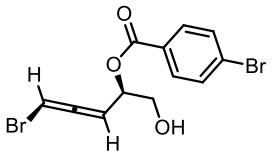
2d: 5-bromo-1-hydroxypenta-3,4-dien-2-yl 4-methoxybenzoate. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.02 (d, *J* = 9.0 Hz, 2H), 6.93 (d, *J* = 8.5 Hz, 2H), 6.12 (d, *J* = 5.5 Hz, 1H), 5.67 (d, *J* = 5.0 Hz, 1H), 5.58 (t, *J* = 5.5 Hz, 1H), 3.92 (d, *J* = 4.5 Hz, 2H), 3.87 (s, 3H), 2.02 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.53, 165.77, 163.89, 132.04, 122.01, 113.89, 97.27, 75.23, 71.31, 64.38, 55.64. IR (neat) ν 3453, 3060, 2923, 1711, 1254, 1101 cm^{-1}. HRMS (ESI) for $C_{13}H_{13}BrO_4$ (M+H), 313.0070 (Calc.), found 313.0066.



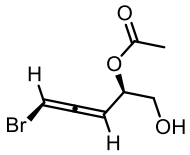
2e: 5-bromo-1-hydroxypenta-3,4-dien-2-yl 4-fluorobenzoate. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.05 – 8.12 (m, 2H), 7.17 – 7.08 (t, *J* = 8.4 Hz, 2H), 6.13 (ddd, *J* = 5.6, 2.0, 0.4 Hz, 1H), 5.72 – 5.64 (m, 1H), 5.57 (td, *J* = 5.6, 0.4 Hz, 1H), 3.98 – 3.88 (m, 2H), 2.00 (s, 1H).^{13}C NMR (100 MHz, $CDCl_3$): δ 202.62, 166.17 (d, *J* = 253 Hz), 165.06, 132.54 (d, *J* = 9.3 Hz), 125.95, 115.84 (d, *J* = 21.9 Hz), 96.93, 75.33, 71.69, 64.22. IR (neat) ν 3440, 3061, 2927, 1720, 1265, 1113 cm^{-1}. HRMS (ESI) for $C_{12}H_{10}BrFO_3$ (M+Na), 322.9689 (Calc.), found 322.9690.



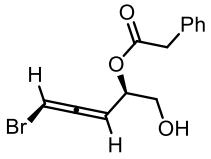
2f: 5-bromo-1-hydroxypenta-3,4-dien-2-yl 4-chlorobenzoate. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.01 (d, *J* = 8.5 Hz, 2H), 7.45 (d, *J* = 8.5 Hz, 2H), 6.13 (dd, *J* = 5.5, 2.0 Hz, 1H), 5.73 – 5.62 (m, 1H), 5.58 (t, *J* = 5.5 Hz, 1H), 3.99 – 3.85 (m, 2H), 2.00 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.65, 165.17, 140.09, 131.33, 129.01, 128.15, 96.85, 75.37, 71.79, 64.19. IR (neat) ν 3441, 3060, 2924, 1718, 1265, 1091 cm^{-1}. HRMS (ESI) for $C_{12}H_{10}BrO_3$ (M+Na), 338.9394 (Calc.), found 338.9392.



2g: 5-bromo-1-hydroxypenta-3,4-dien-2-yl 4-bromobenzoate. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.93 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 2H), 6.13 (dd, *J* = 6.0, 0.8 Hz, 1H), 5.72 – 5.65 (m, 1H), 5.57 (t, *J* = 6.0 Hz, 1H), 3.98 – 3.90 (m, 2H), 1.99 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.65, 165.31, 132.01, 131.44, 128.78, 128.61, 96.83, 75.38, 71.81, 64.18. IR (neat) ν 3424, 3060, 2923, 1720, 1265, 1116 cm^{-1}. HRMS (ESI) for $C_{12}H_{10}Br_2O_3$ (M+Na), 382.8888 (Calc.), found 382.8878.

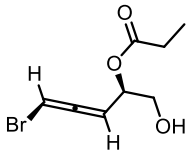


2h: 5-bromo-1-hydroxypenta-3,4-dien-2-yl acetate. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 6.17 – 6.11 (m, 1H), 5.47 (t, *J* = 5.5 Hz, 1H), 5.45 – 5.39 (m, 1H), 3.88 – 3.72 (m, 2H), 2.18 – 2.08 (s, 3H), 1.86 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.59, 170.40, 96.84, 75.02, 71.14, 64.04, 21.12. IR (neat) ν 3441, 3060, 2924, 1737, 1232, 1044 cm^{-1}. HRMS (ESI) for $C_7H_9BrO_3$ ($M+NH_4$), 238.0074 (Calc.), found 238.0078.

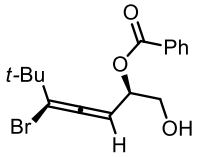


2i: 5-bromo-1-hydroxypenta-3,4-dien-2-yl 2-phenylacetate. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.38 – 7.27 (m, 5H), 6.03 – 5.95 (m, 1H), 5.47 – 5.37 (m, 2H), 3.77 (m, 2H), 3.69 (s, 2H), 1.71 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.43, 170.97,

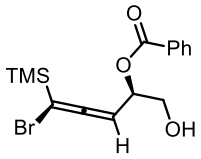
133.69, 129.37, 128.83, 127.44, 96.72, 75.23, 71.34, 63.98, 41.45. IR (neat) ν 3454, 3060, 2922, 1734, 1245, 1146 cm^{-1}. HRMS (ESI) for $C_{13}H_{13}BrO_3$ ($M+NH_4$), 314.0387 (Calc.), found 314.0395.



2j: 5-bromo-1-hydroxypenta-3,4-dien-2-yl propionate. Colorless oil. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 6.14 – 6.10 (m, 1H), 5.50 – 5.40 (m, 2H), 3.87 – 3.75 (m, 2H), 2.40 (q, *J* = 7.6 Hz, 2H), 1.26 (s, 1H), 1.21 – 1.13 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.52, 173.88, 97.02, 75.05, 70.87, 64.13, 27.73, 9.26. IR (neat) ν 3455, 3061, 2924, 1737, 1180, 1082 cm^{-1}. HRMS (ESI) for $C_8H_{11}BrO_3$ ($M+NH_4$), 252.0230 (Calc.), found 252.0234.



4a: 5-bromo-1-hydroxy-6,6-dimethylhepta-3,4-dien-2-yl benzoate. Colorless oil. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.07 (d, *J* = 7.2 Hz, 2H), 7.58 (td, *J* = 8.0, 1.2 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 5.70 – 5.62 (m, 1H), 5.45 (dd, *J* = 5.2, 1.2 Hz, 1H), 3.95 – 3.88 (m, 2H), 2.09 (s, 1H), 1.07 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.20, 166.16, 133.57, 130.03, 129.91, 128.66, 109.10, 94.74, 72.10, 64.40, 37.04, 31.17, 29.12, 28.99. IR (neat) ν 3442, 3063, 2969, 1721, 1267, 1113 cm^{-1}.



4b: 5-bromo-1-hydroxy-5-(trimethylsilyl)penta-3,4-dien-2-yl benzoate. Colorless oil. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.06 (d, *J* = 8.8Hz, 2H), 7.58 (t, *J* = 7.2 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 5.70 – 5.62 (m, 1H), 5.31 (d, *J* = 5.2 Hz, 1H), 3.97 – 3.83 (m, 2H), 2.04 (s, 1H), 0.09 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.76, 165.99, 133.49, 129.94, 129.83, 128.58, 91.75, 90.05, 71.65, 64.48, -2.05. IR (neat) ν 3440, 3063, 2958, 1721, 1266, 1112 cm^{-1}. HRMS (ESI) for $C_{15}H_{19}BrO_3Si$ ($M+NH_4$), 372.0626 (Calc.), found 372.0615.

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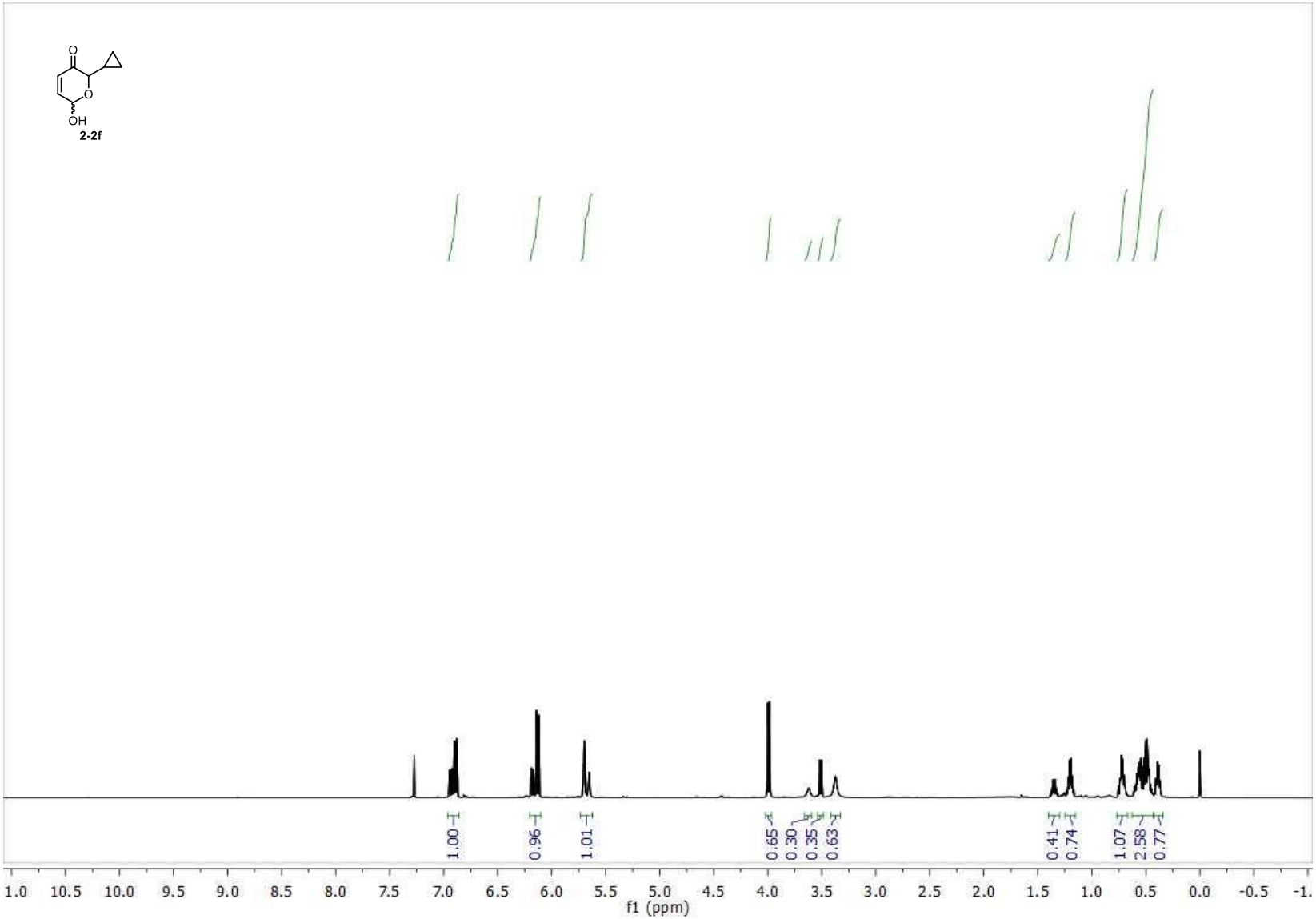
Appendix 2: NMR Spectra of Compounds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1.01
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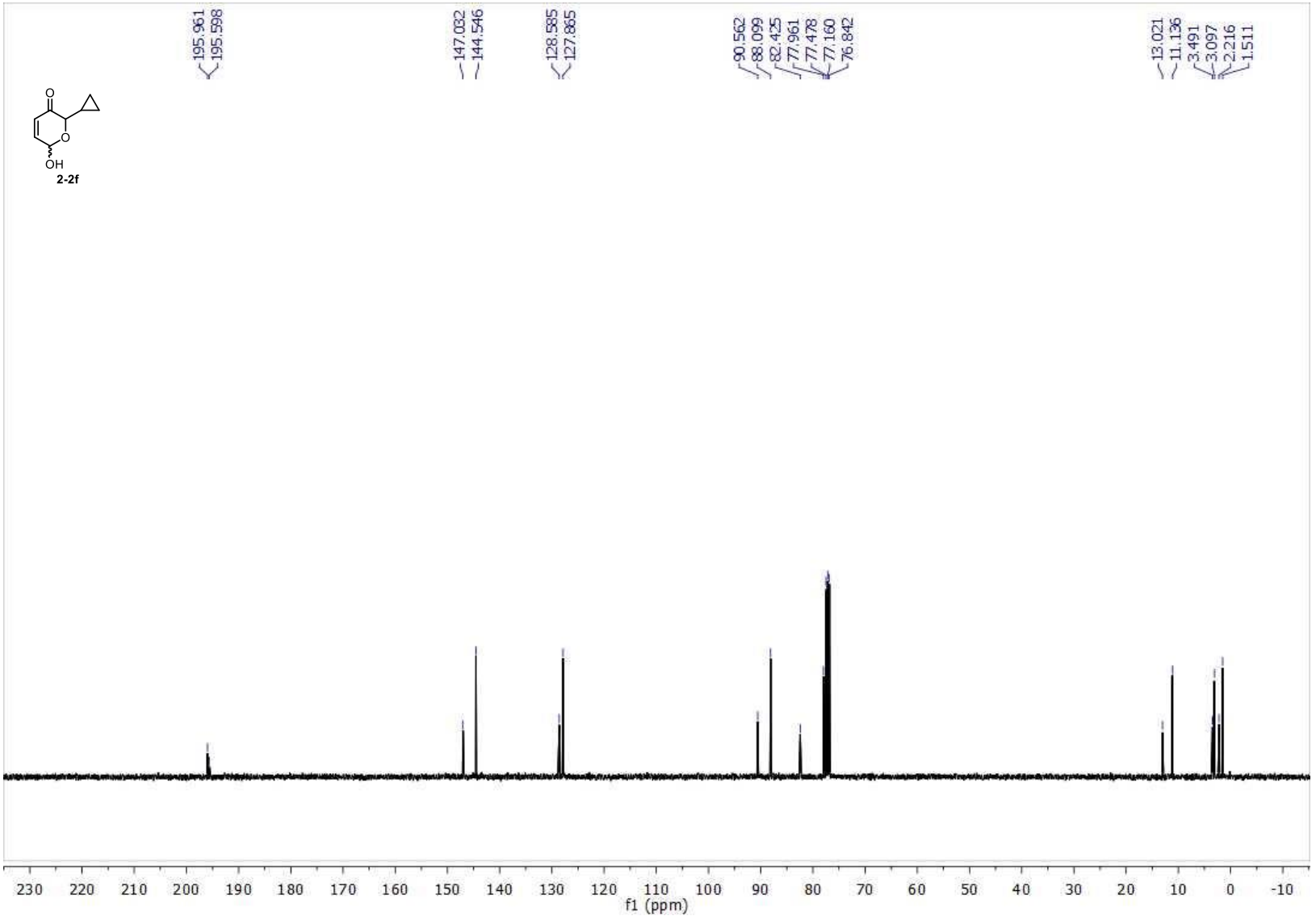
0.30
0.35
0.63
0.41
0.74
1.07
2.58
0.77
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.
f1 (ppm)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76.842
13.021
11.136
3.491
3.097
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O
OH
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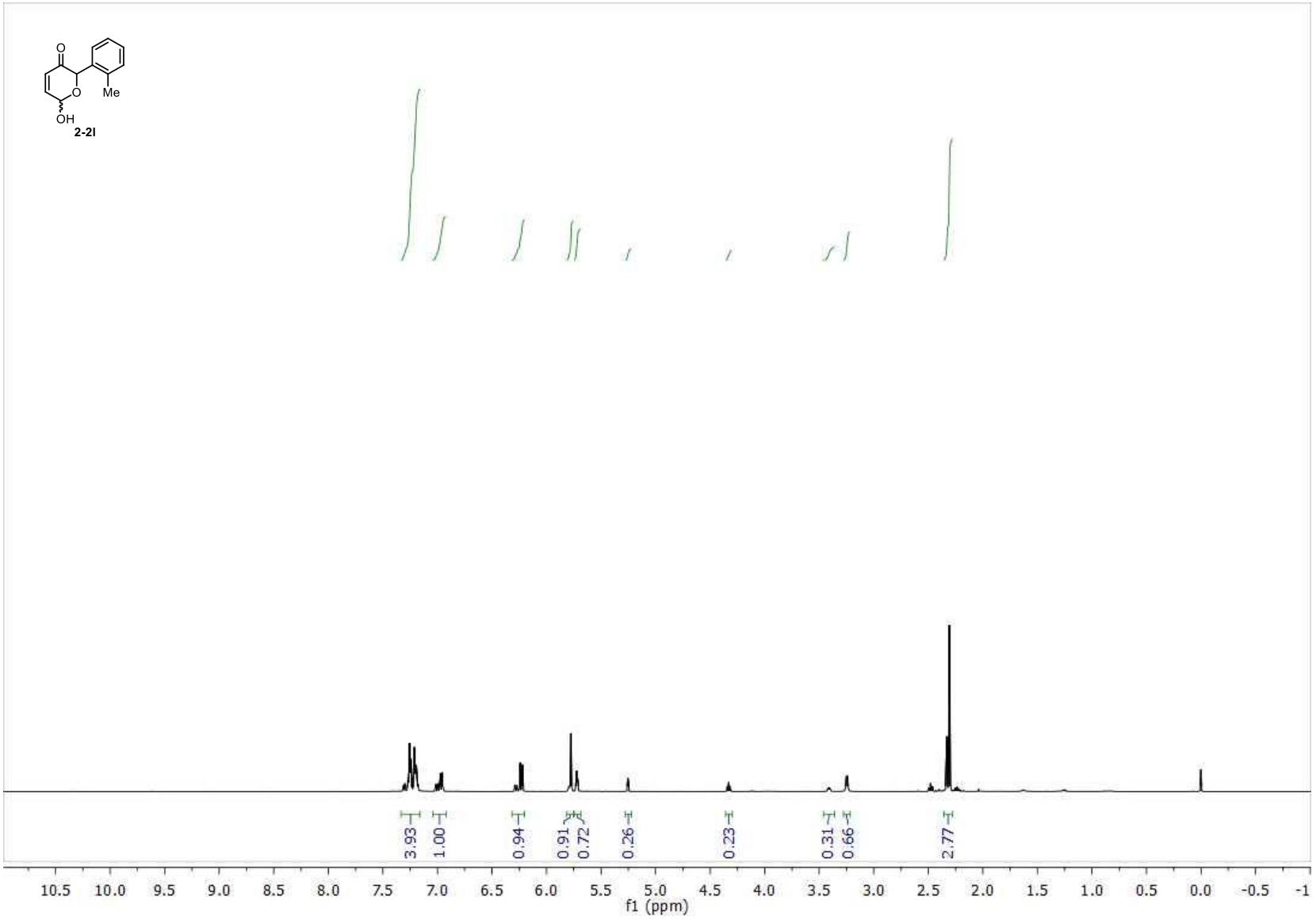
f1 (ppm)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0.31
0.66
2.77
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
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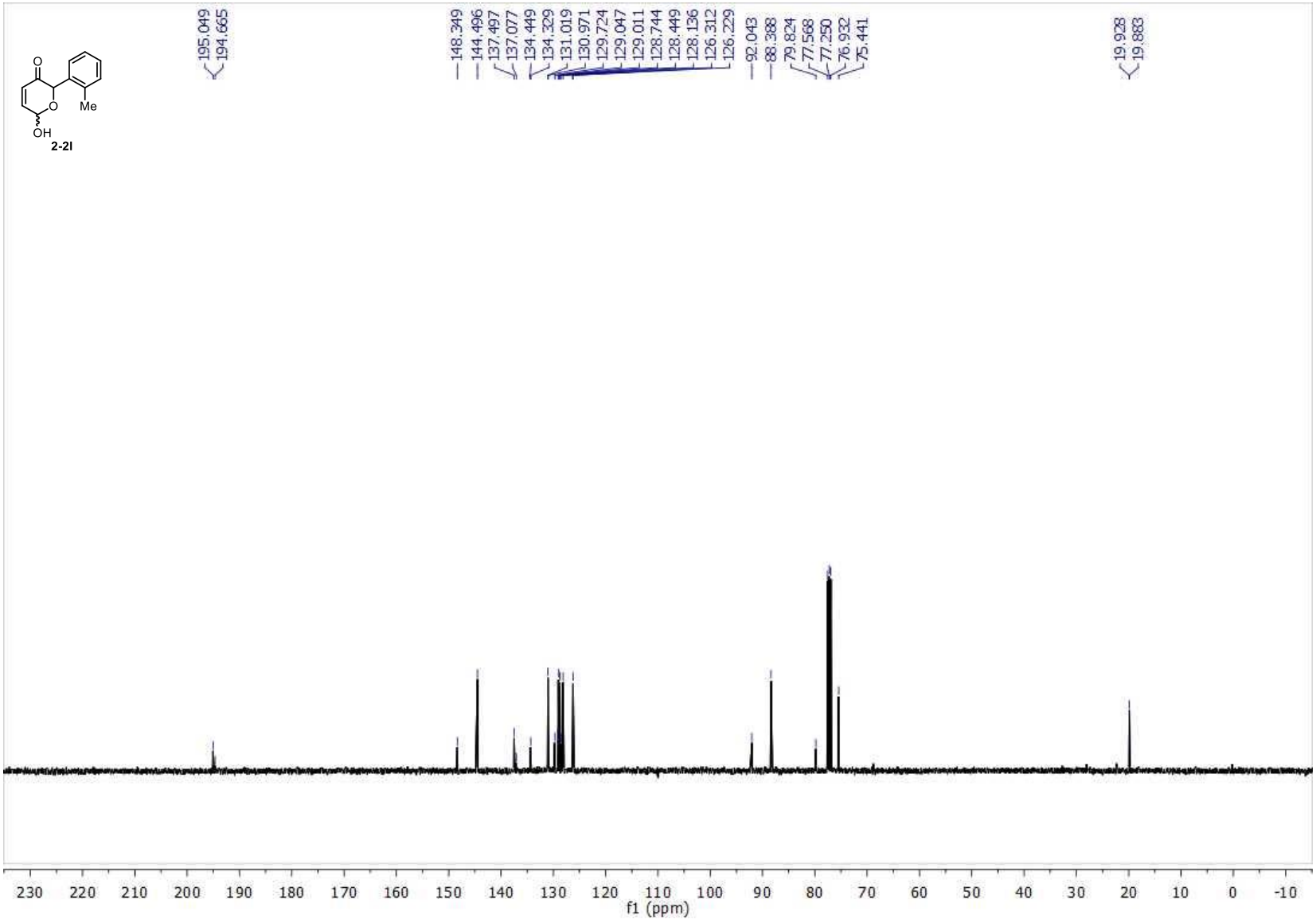
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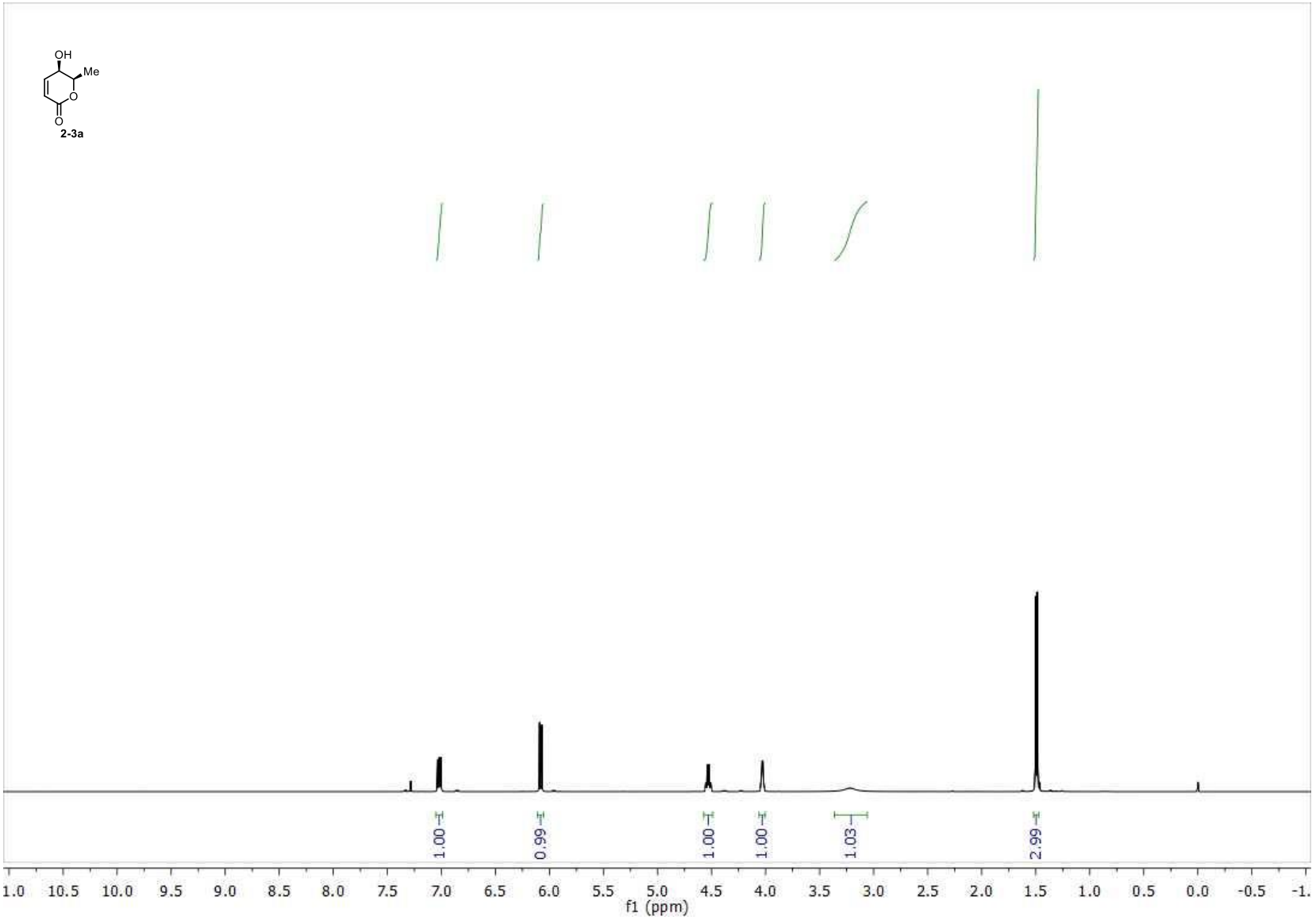
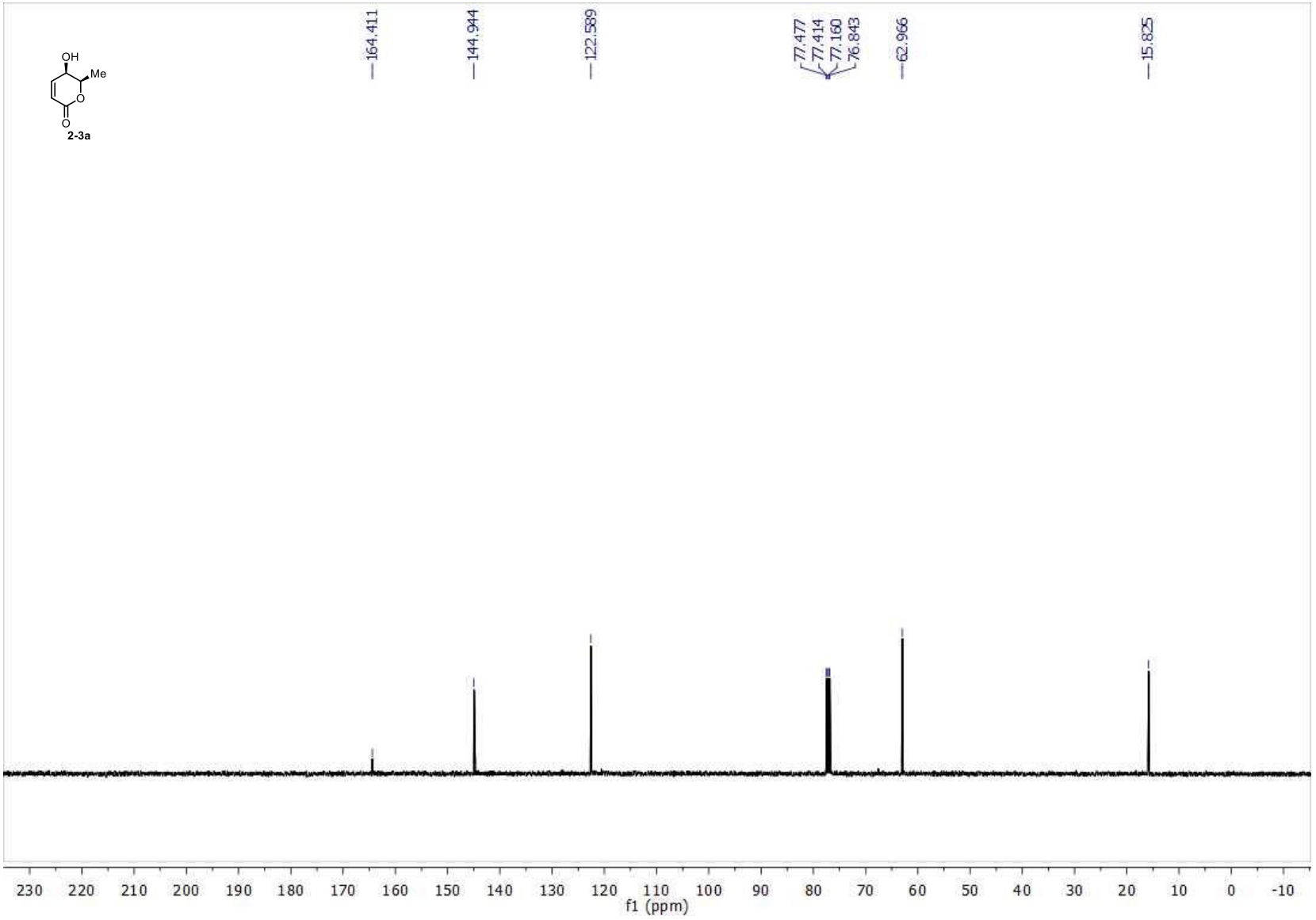
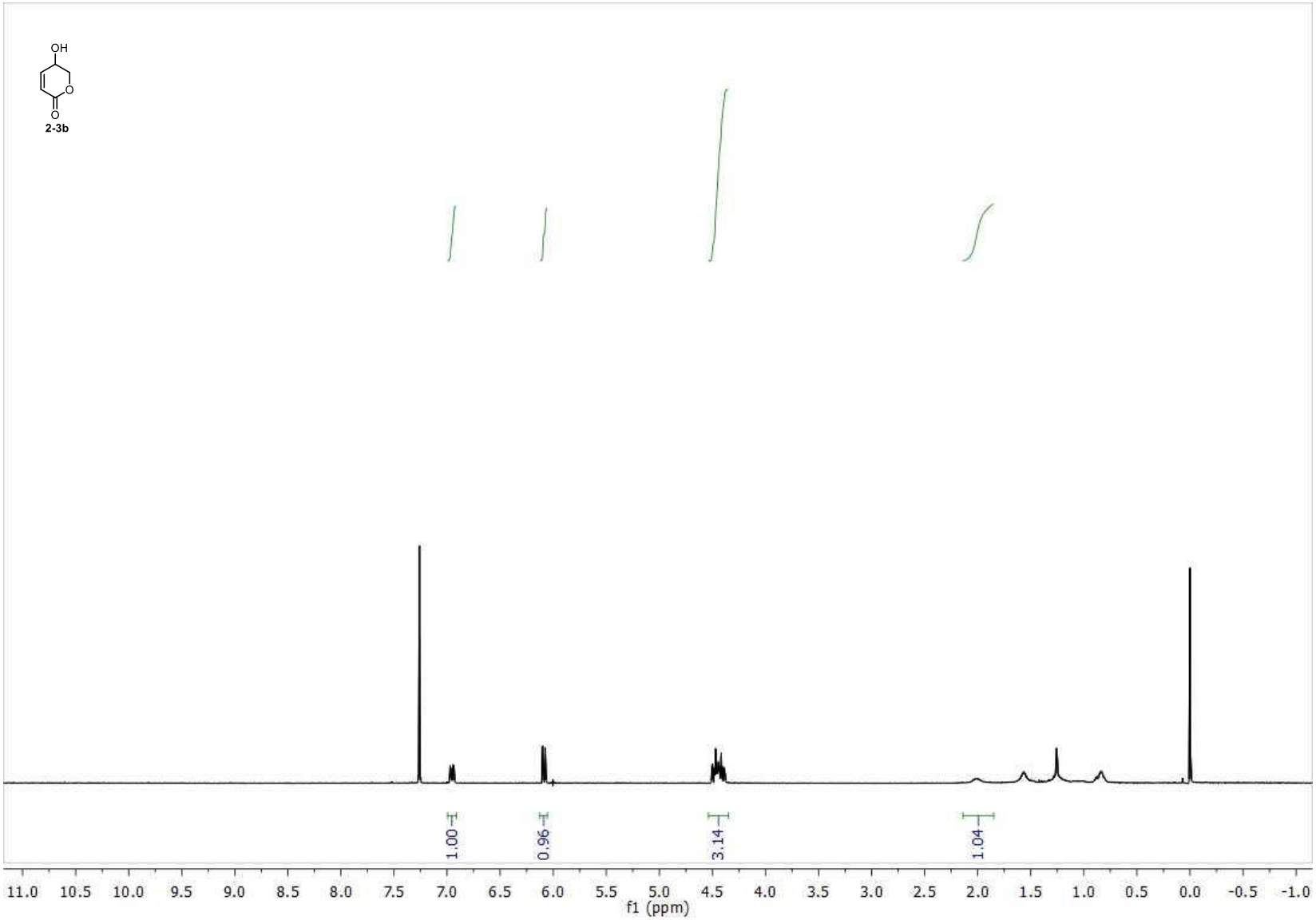
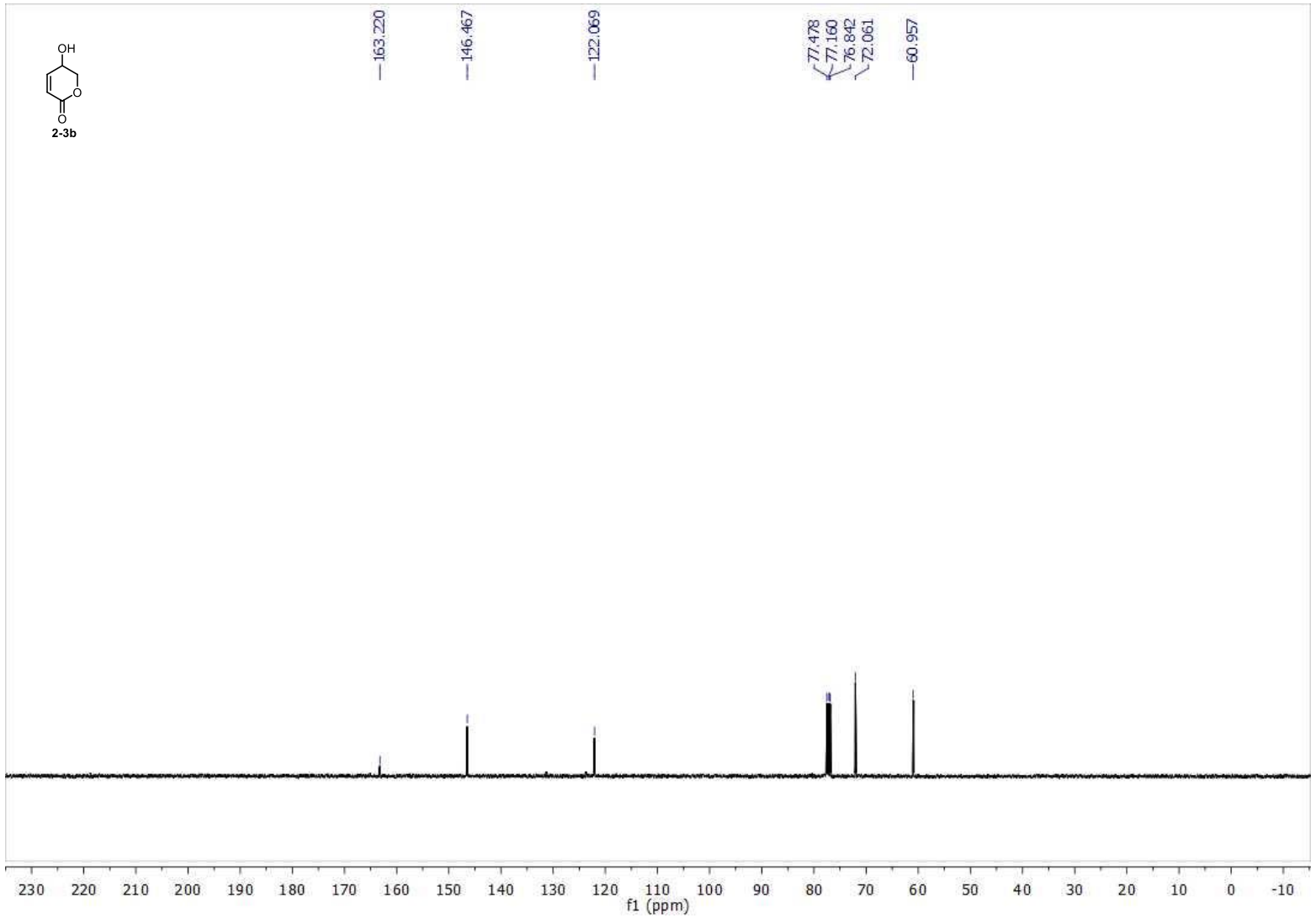
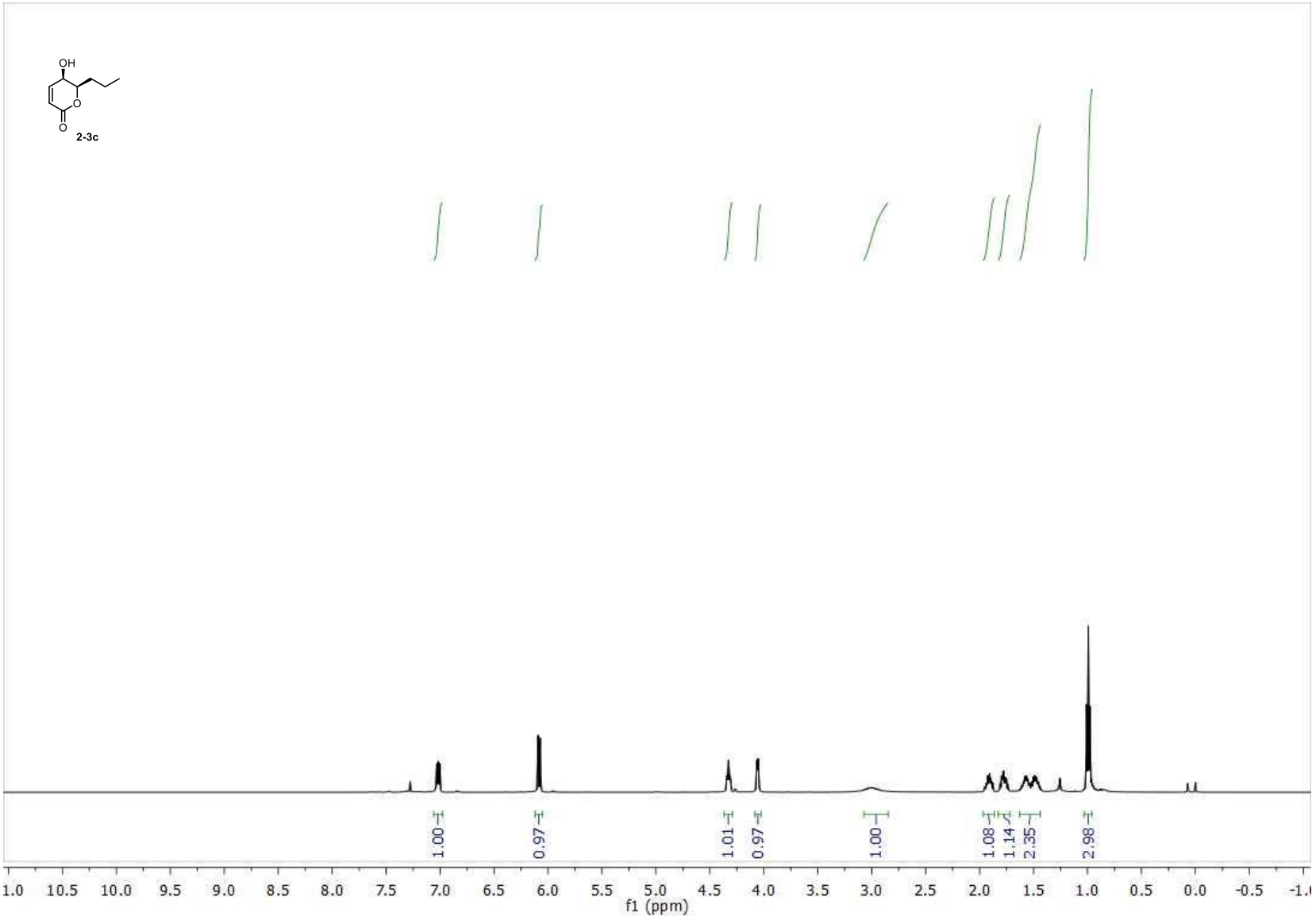
129.011
128.744
128.449
128.136
126.312
126.229
92.043
88.388
79.824
77.568
77.250
76.932
75.441
19.928
19.883
O
O
Me
OH
2-2l
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

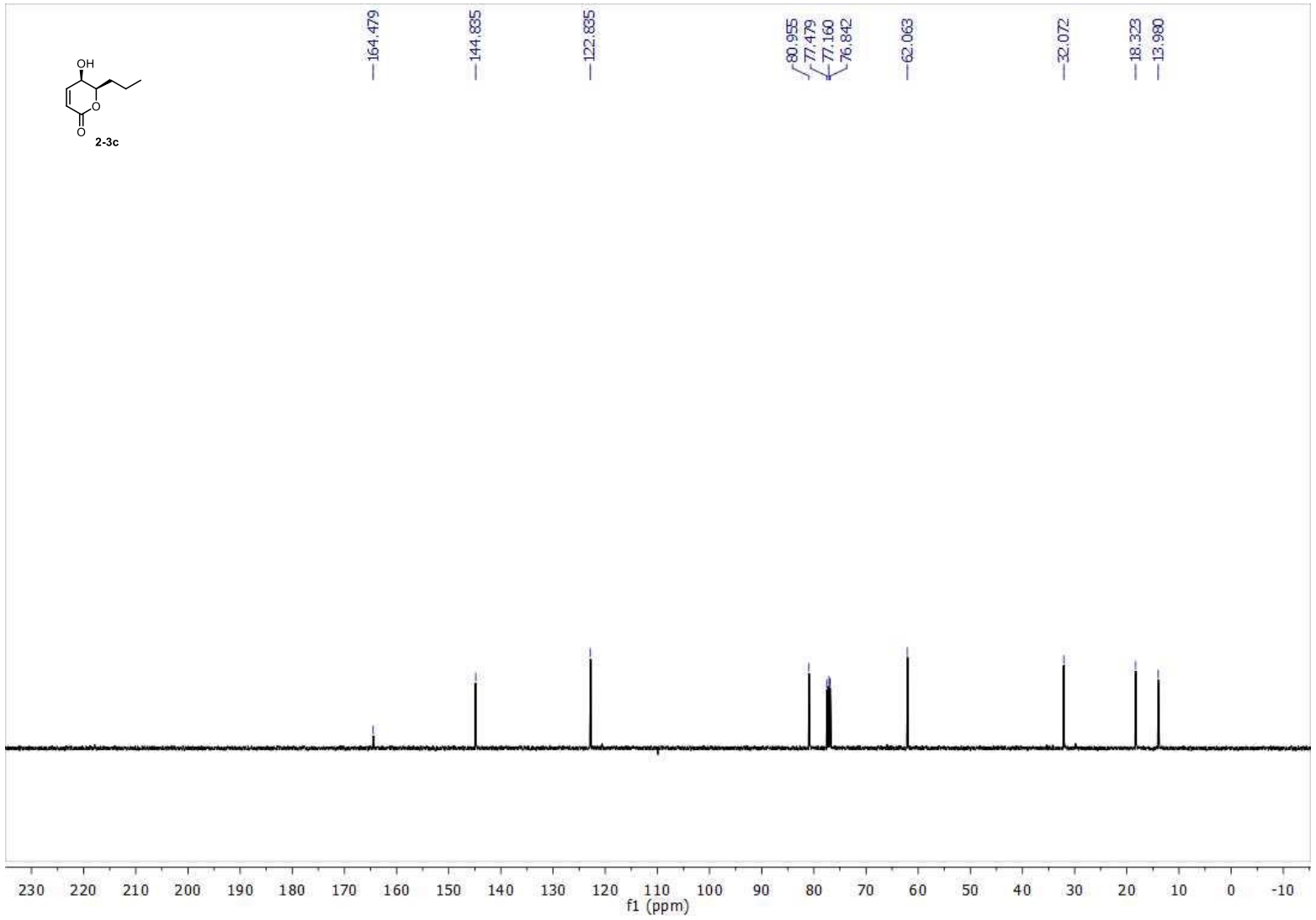

OH
Me
O
O
2-3a
1.00
0.99
1.00
1.00
1.03
2.99
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.
f1 (ppm)

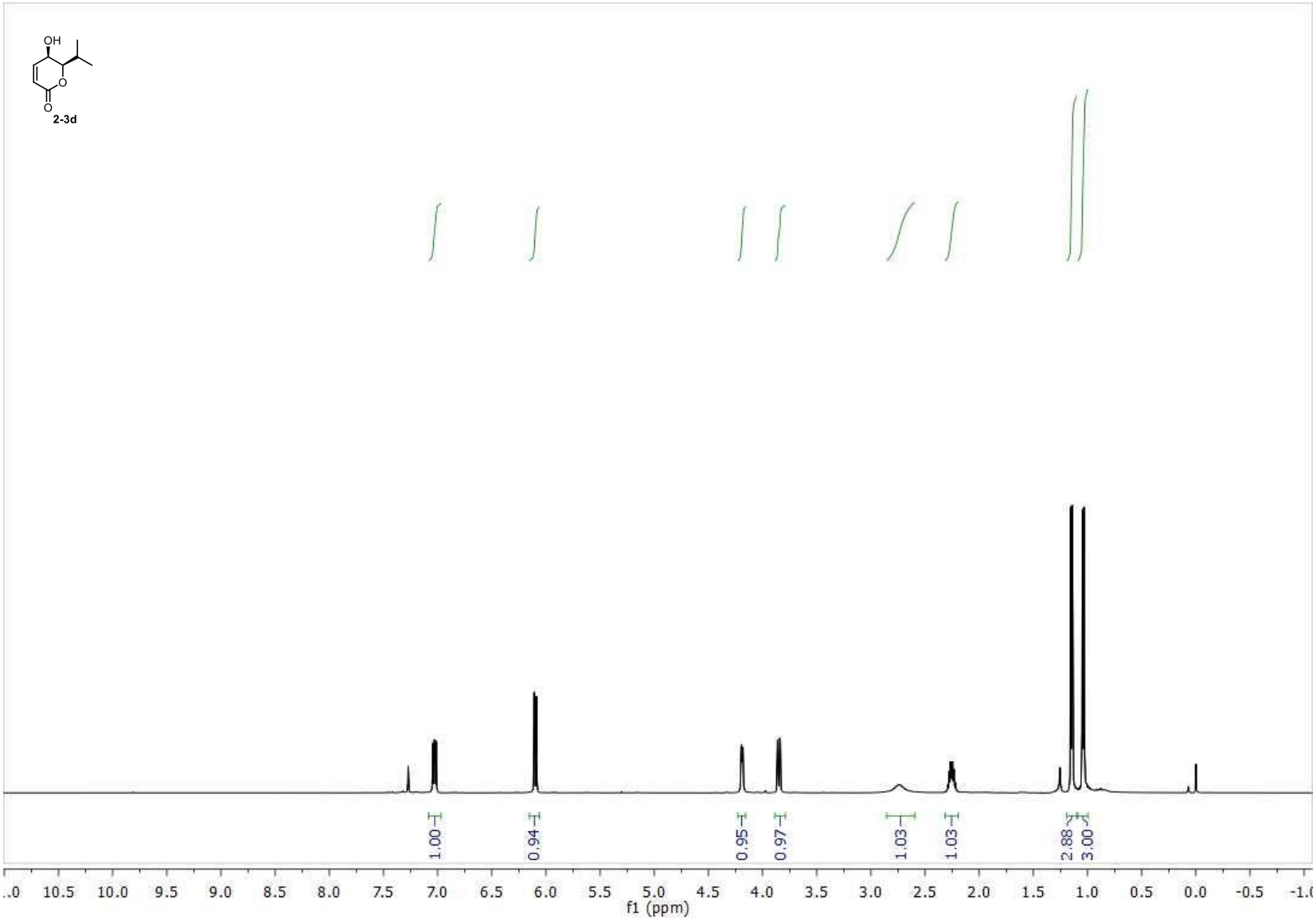

OH
Me
O
O
2-3a
164.411
144.944
122.589
77.477
77.414
77.160
76.843
62.966
15.825
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

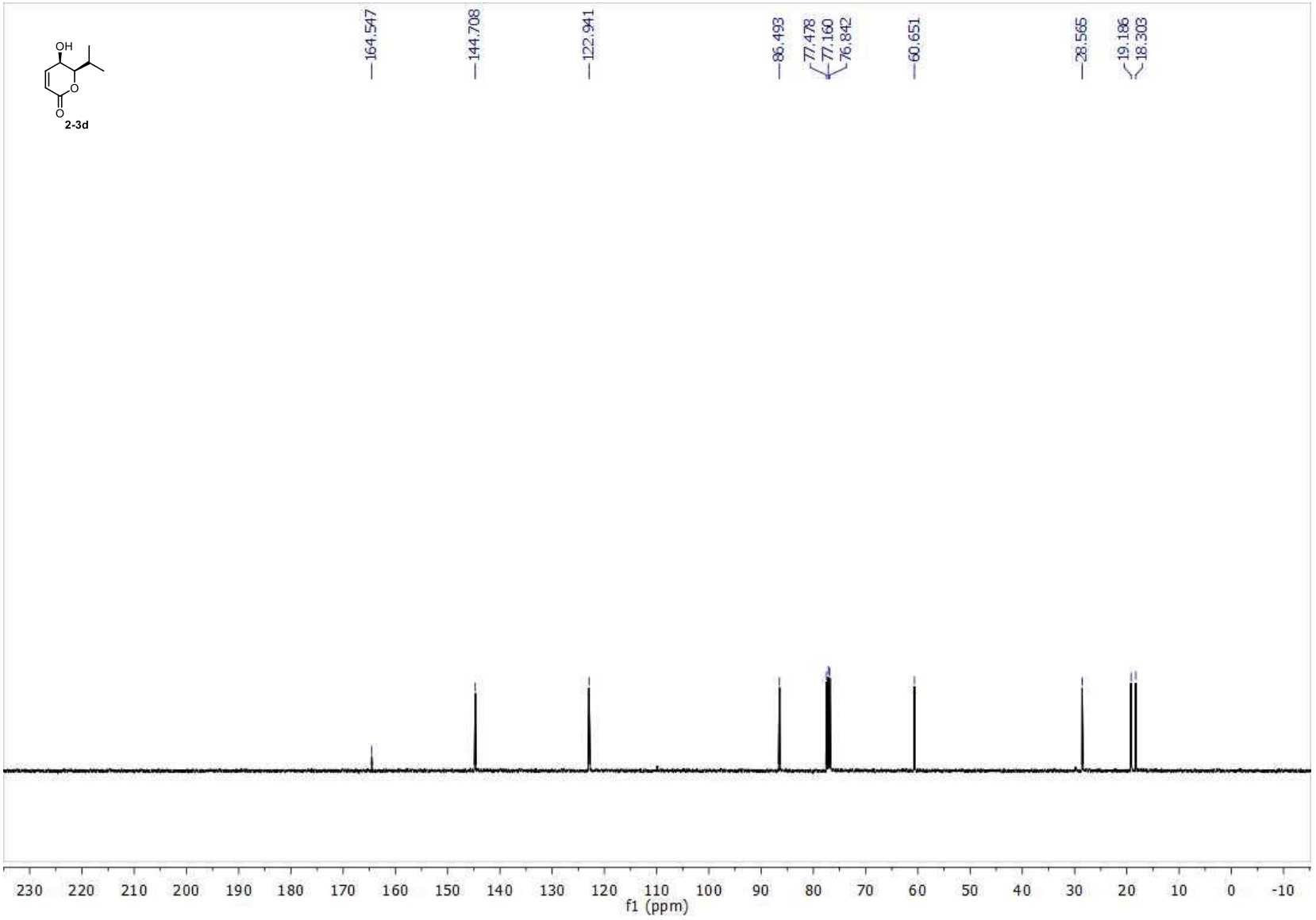

OH
O
O
2-3b
1.00
0.96
3.14
1.04
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

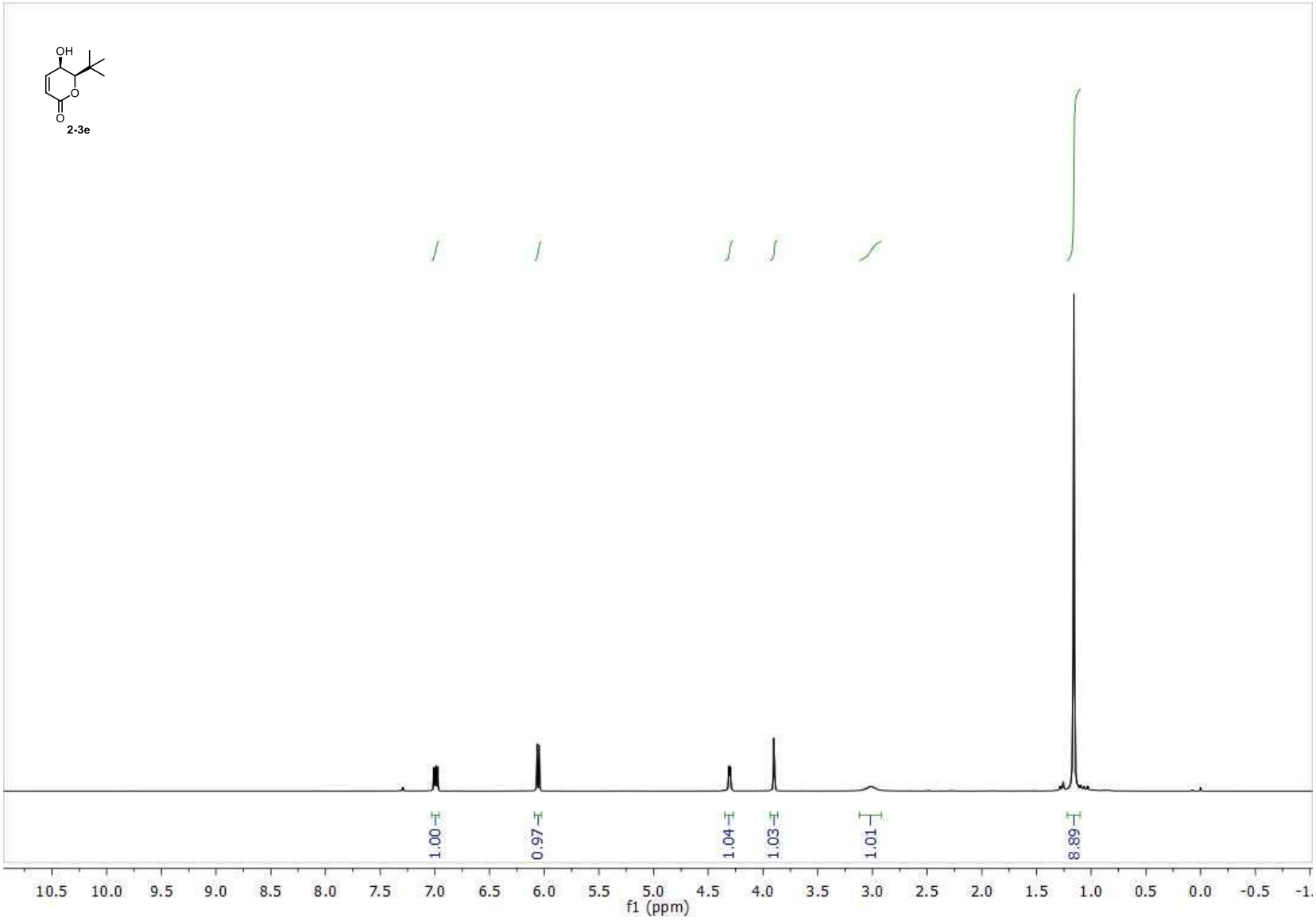

OH
O
O
2-3b
163.220
146.467
122.069
77.478
77.160
76.842
72.061
60.957
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

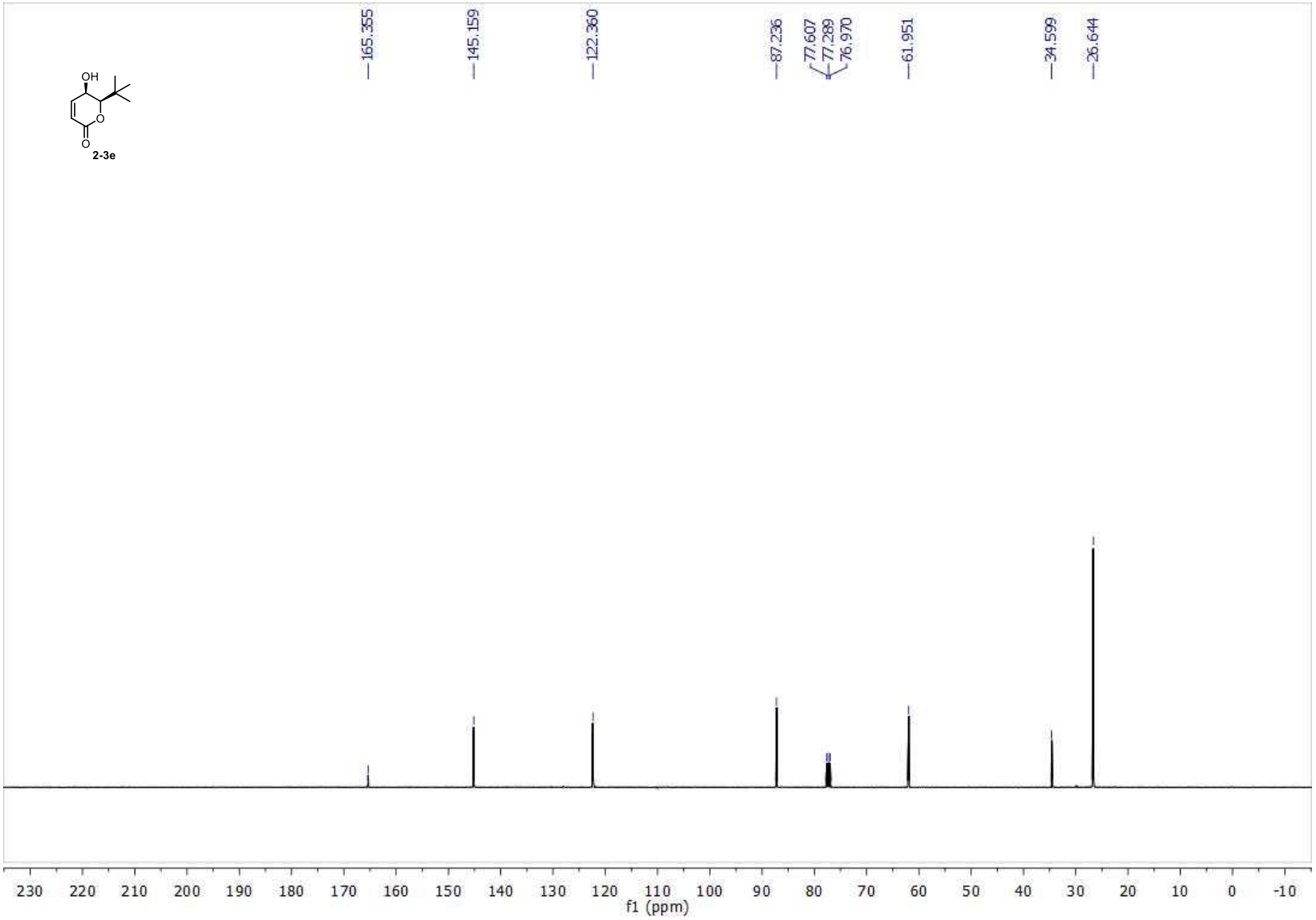

OH
O
O
2-3c
1.00
0.97
1.01
0.97
1.00
1.08
1.14
2.35
2.98
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

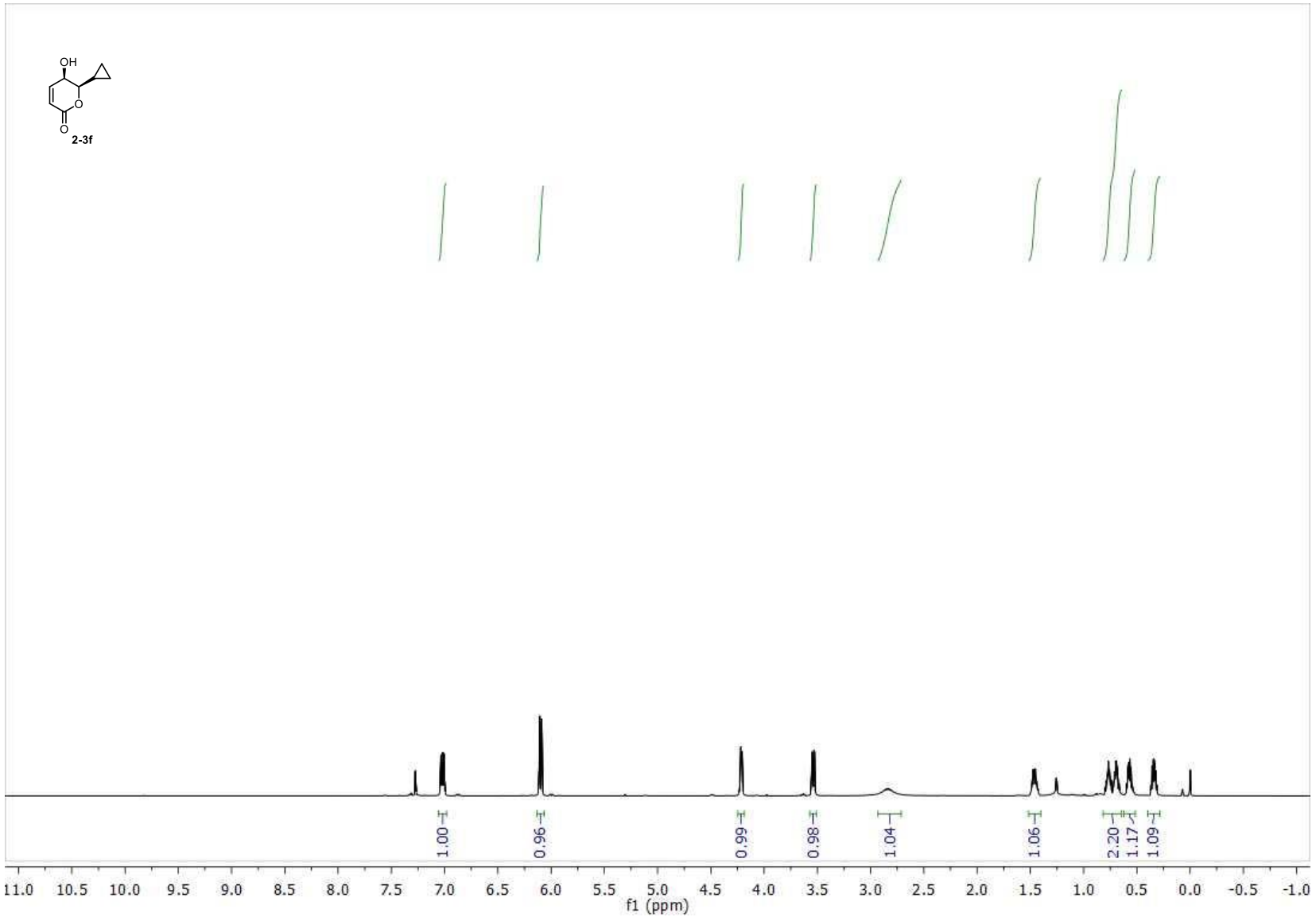

OH
O
O
2-3c
164.479
144.835
122.835
80.955
77.479
77.160
76.842
62.063
32.072
18.323
13.980
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

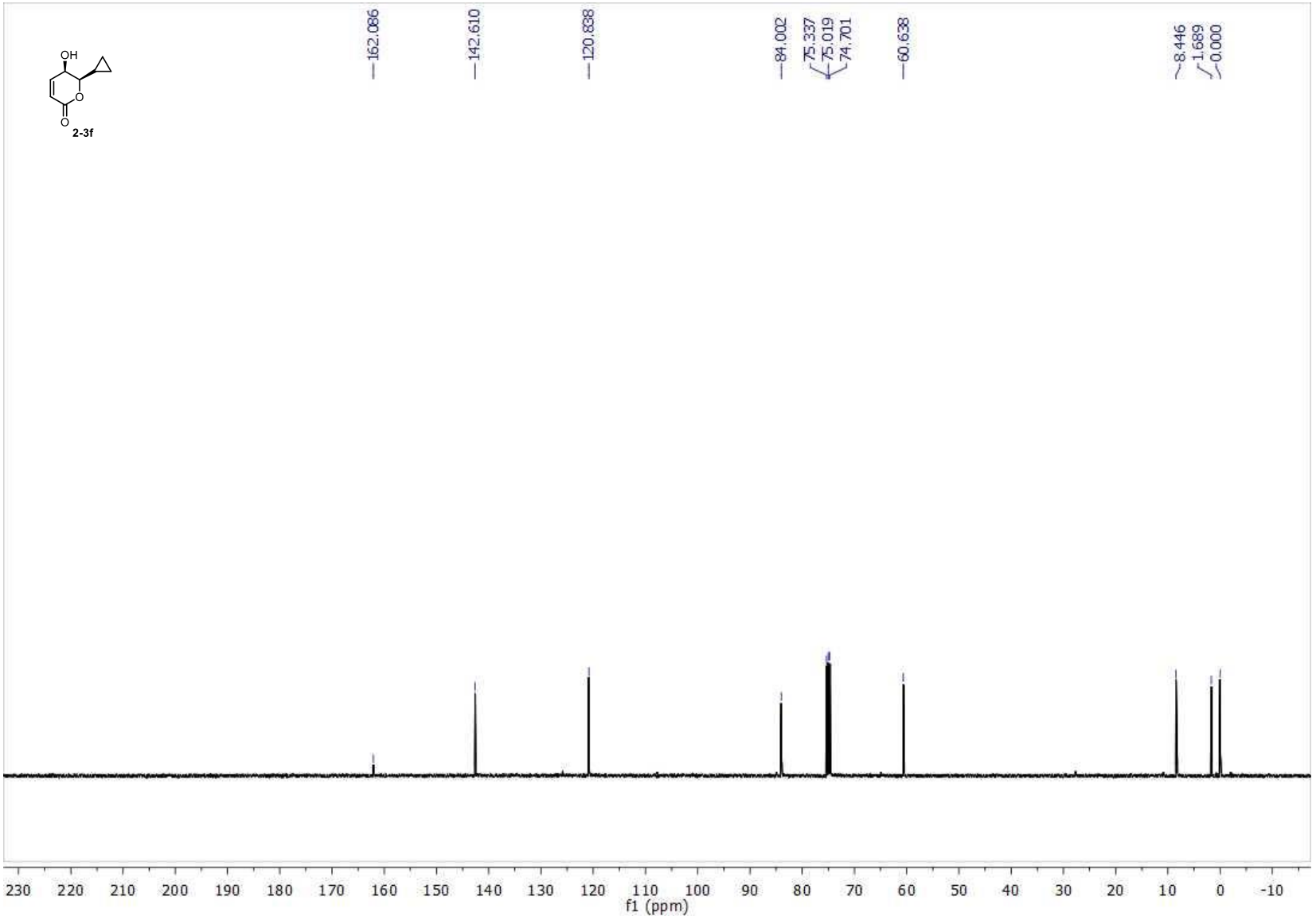

OH
O
O
2-3d
1.00
0.94
0.95
0.97
1.03
1.03
2.88
3.00
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

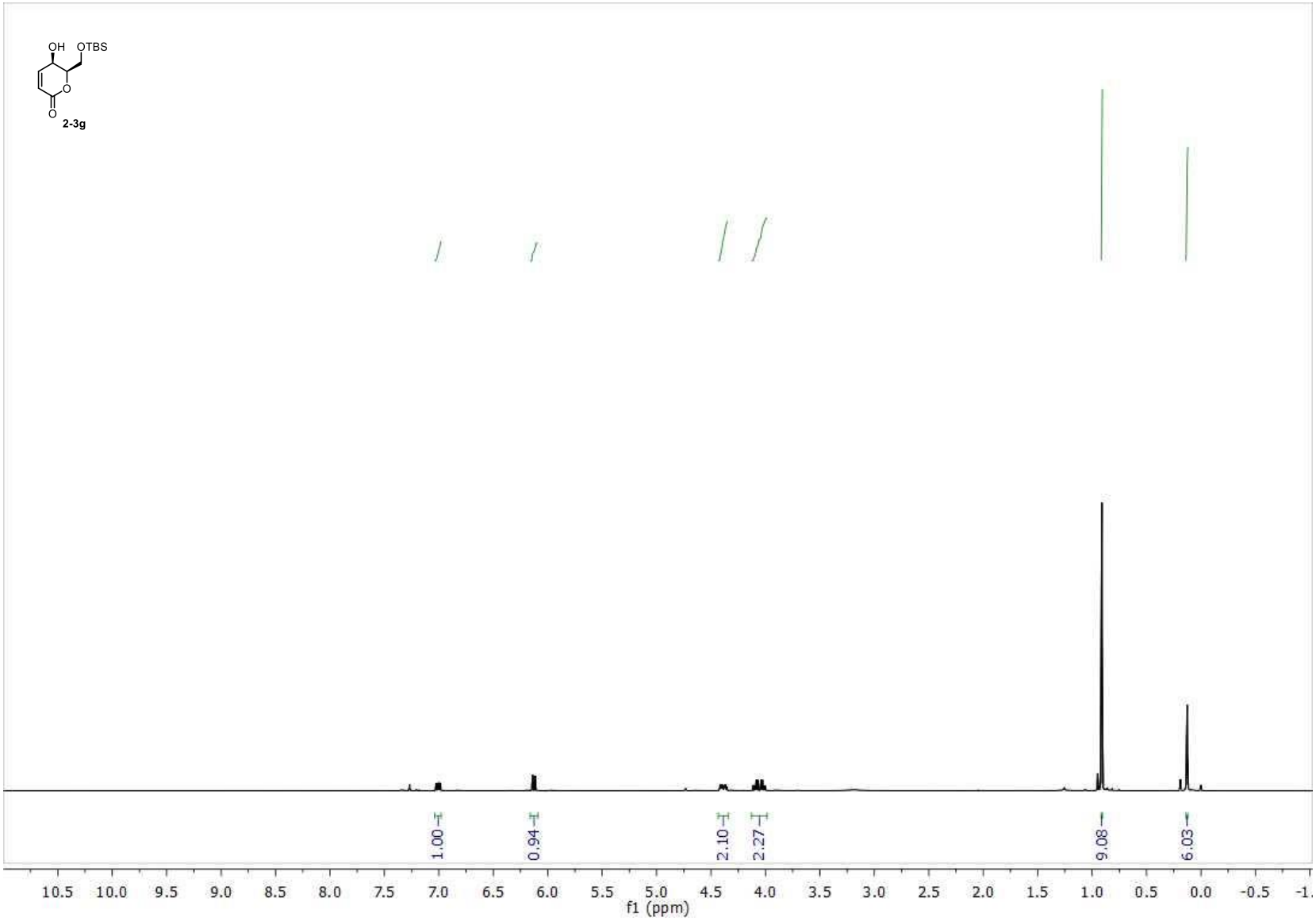

OH
O
O
2-3d
164.547
144.708
122.941
86.493
77.478
77.160
76.842
60.651
28.565
19.186
18.303
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

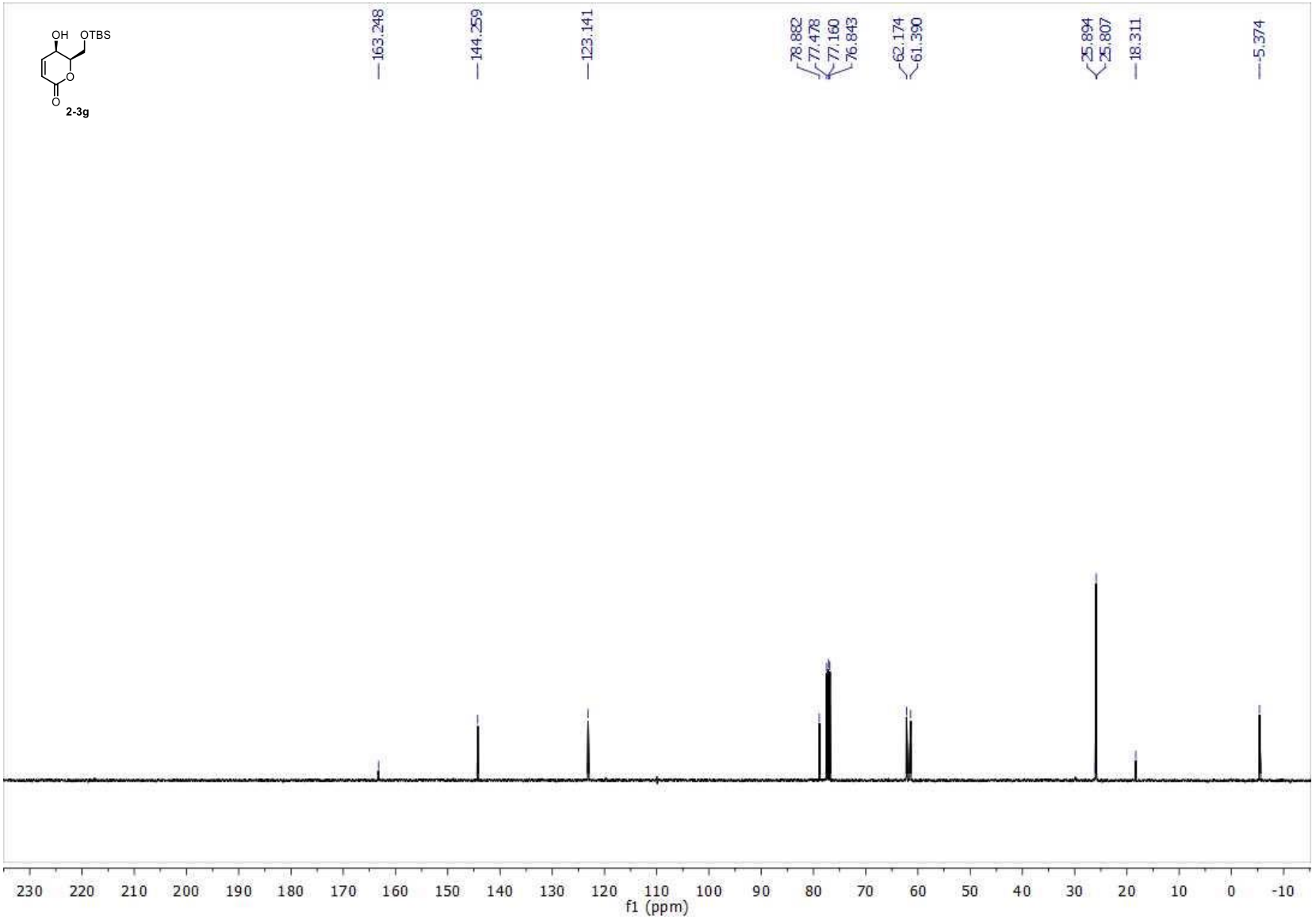

OH
O
O
2-3e
1.00
0.97
1.04
1.03
1.01
8.89
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

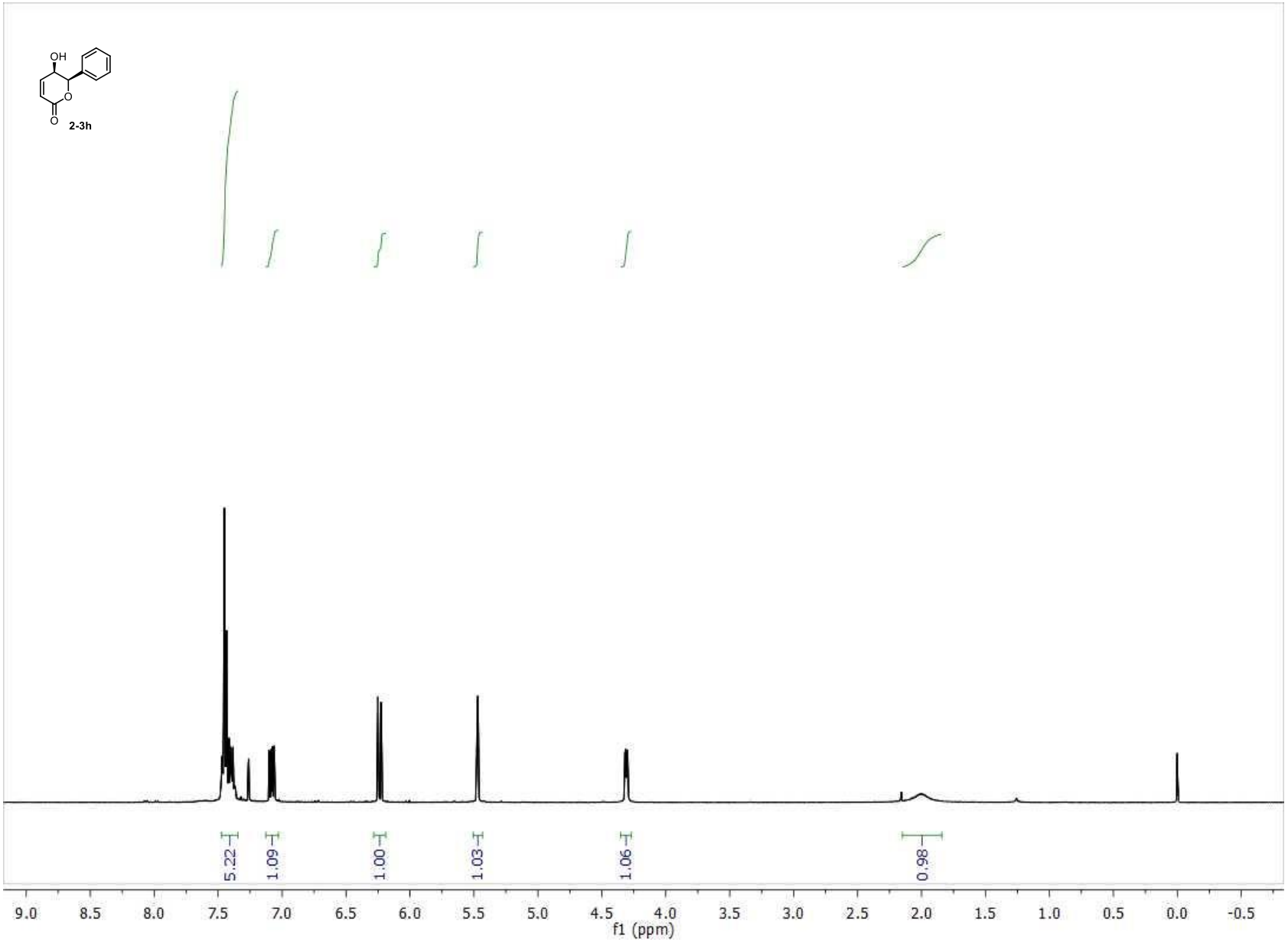

OH
O
O
2-3e
165.355
145.159
122.360
87.236
77.607
77.289
76.970
61.951
34.599
26.644
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

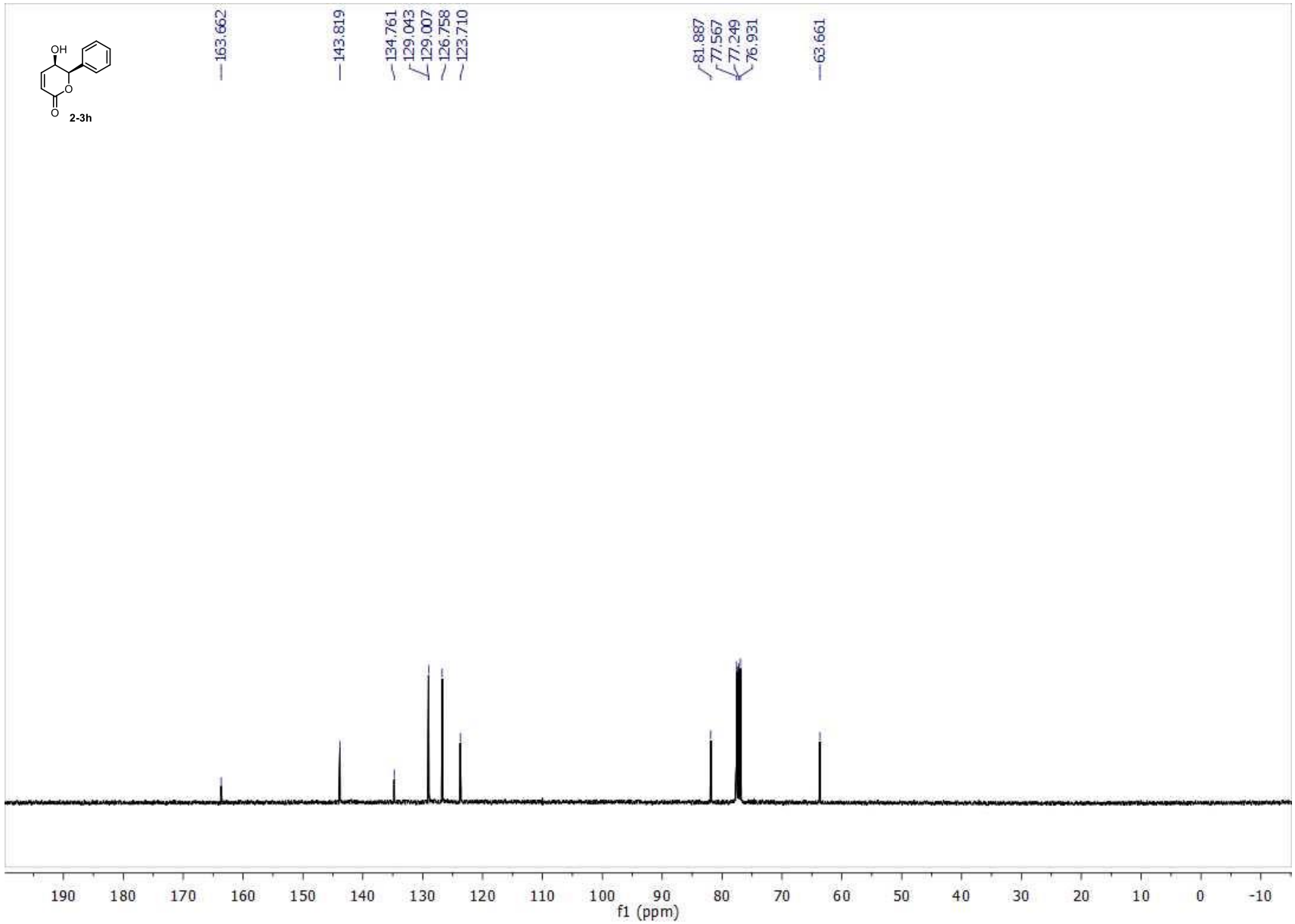

OH
O
O
2-3f
1.00
0.96
0.99
0.98
1.04
1.06
2.20
1.17
1.09
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

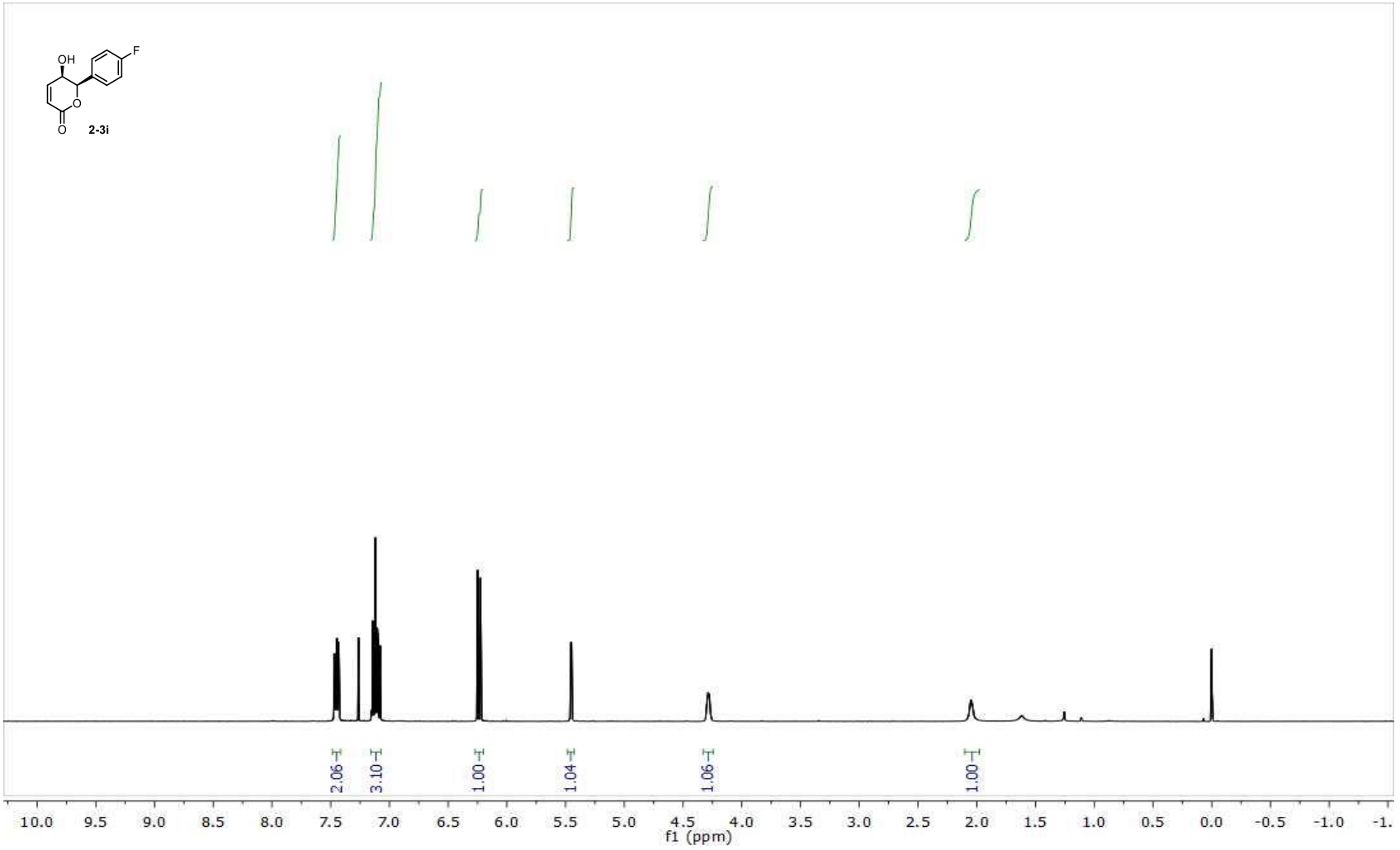

OH
O
O
2-3f
162.086
142.610
120.838
84.002
75.337
75.019
74.701
60.638
8.446
1.689
0.000
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

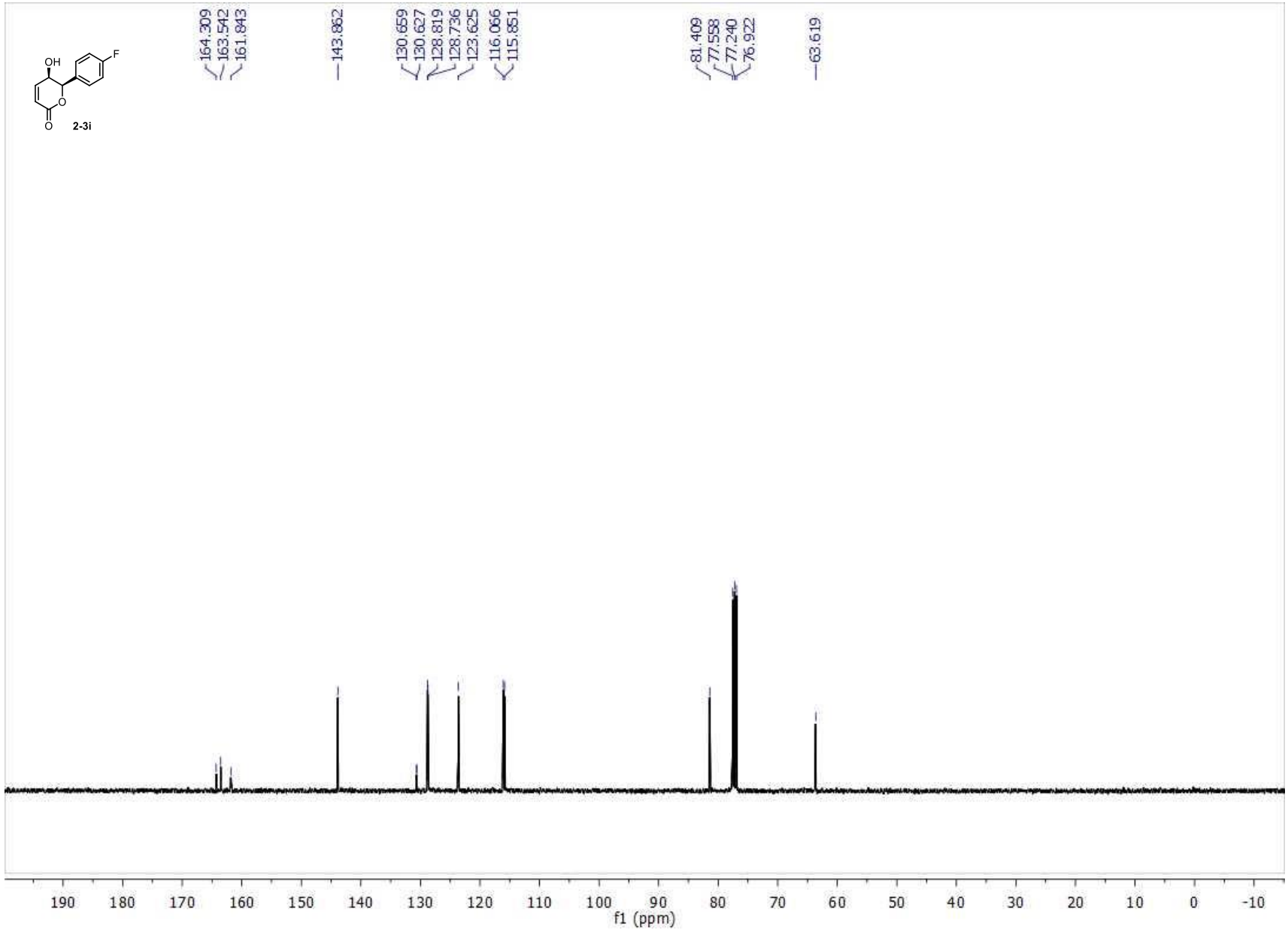

OH
OTBS
O
O
2-3g
1.00
0.94
2.10
2.27
9.08
6.03
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

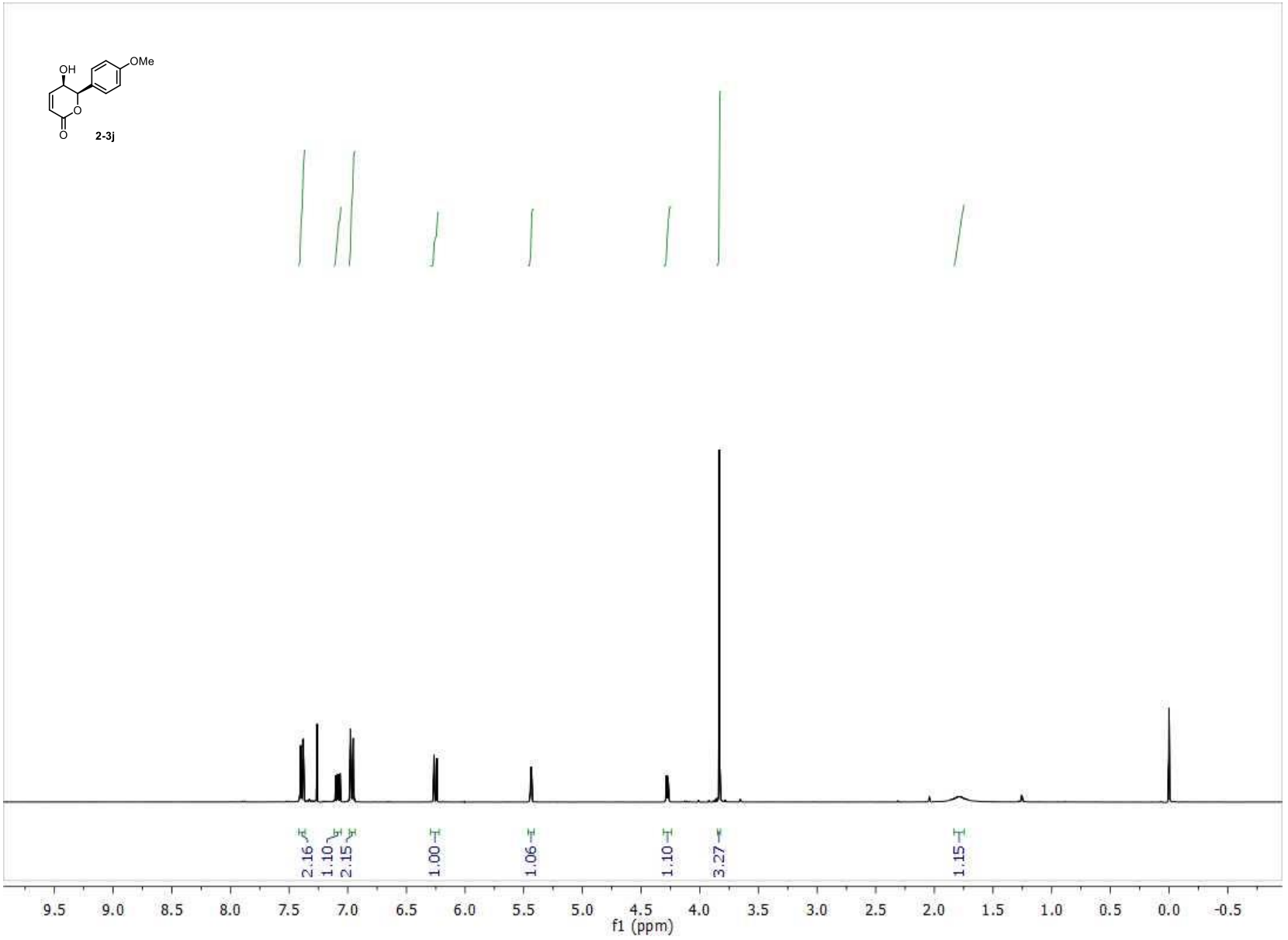

OH
OTBS
O
O
2-3g
163.248
144.259
123.141
78.882
77.478
77.160
76.843
62.174
61.390
25.894
25.807
18.311
-5.374
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

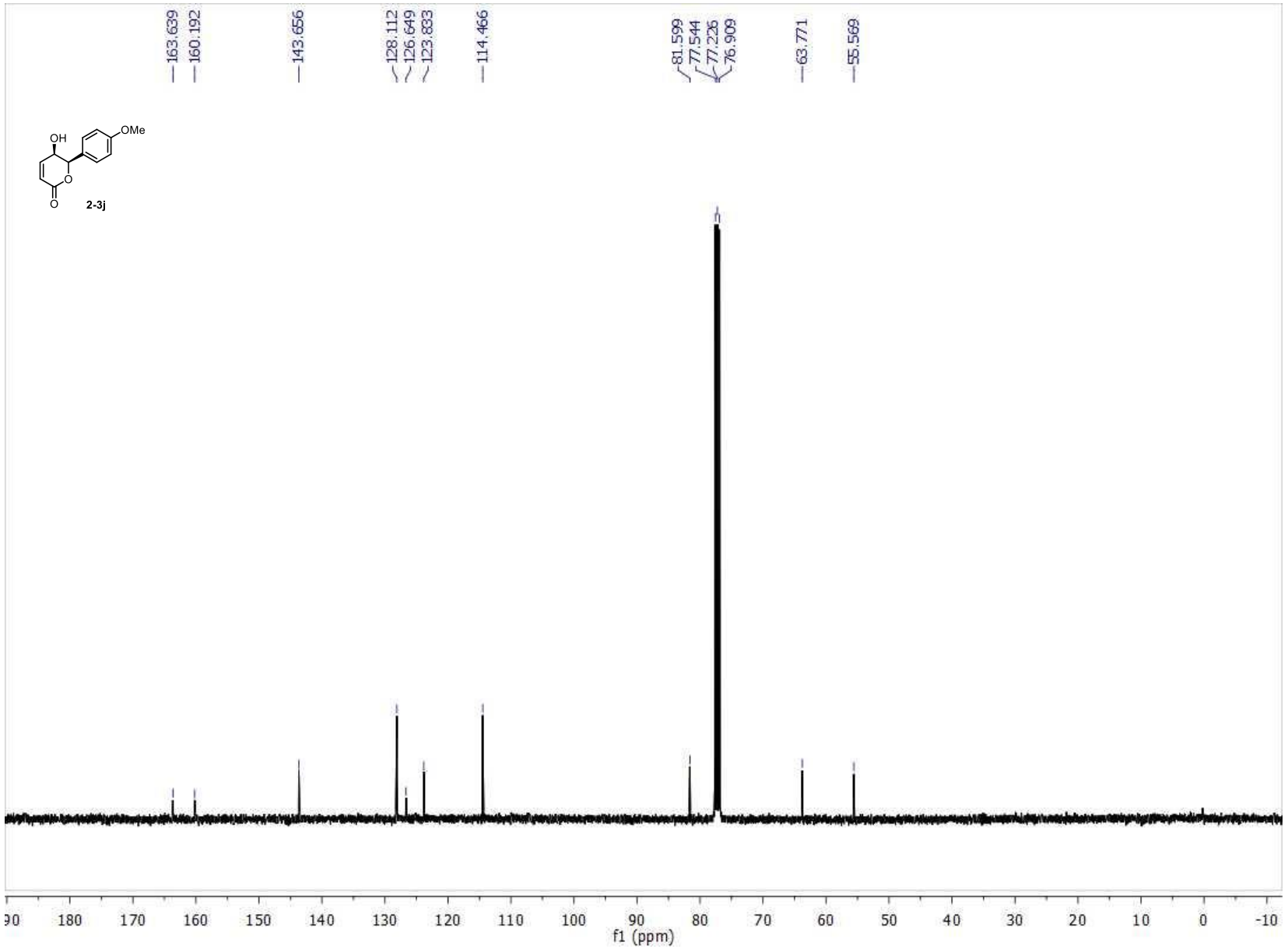

OH
O
O
2-3h
5.22
1.09
1.00
1.03
1.06
0.98
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

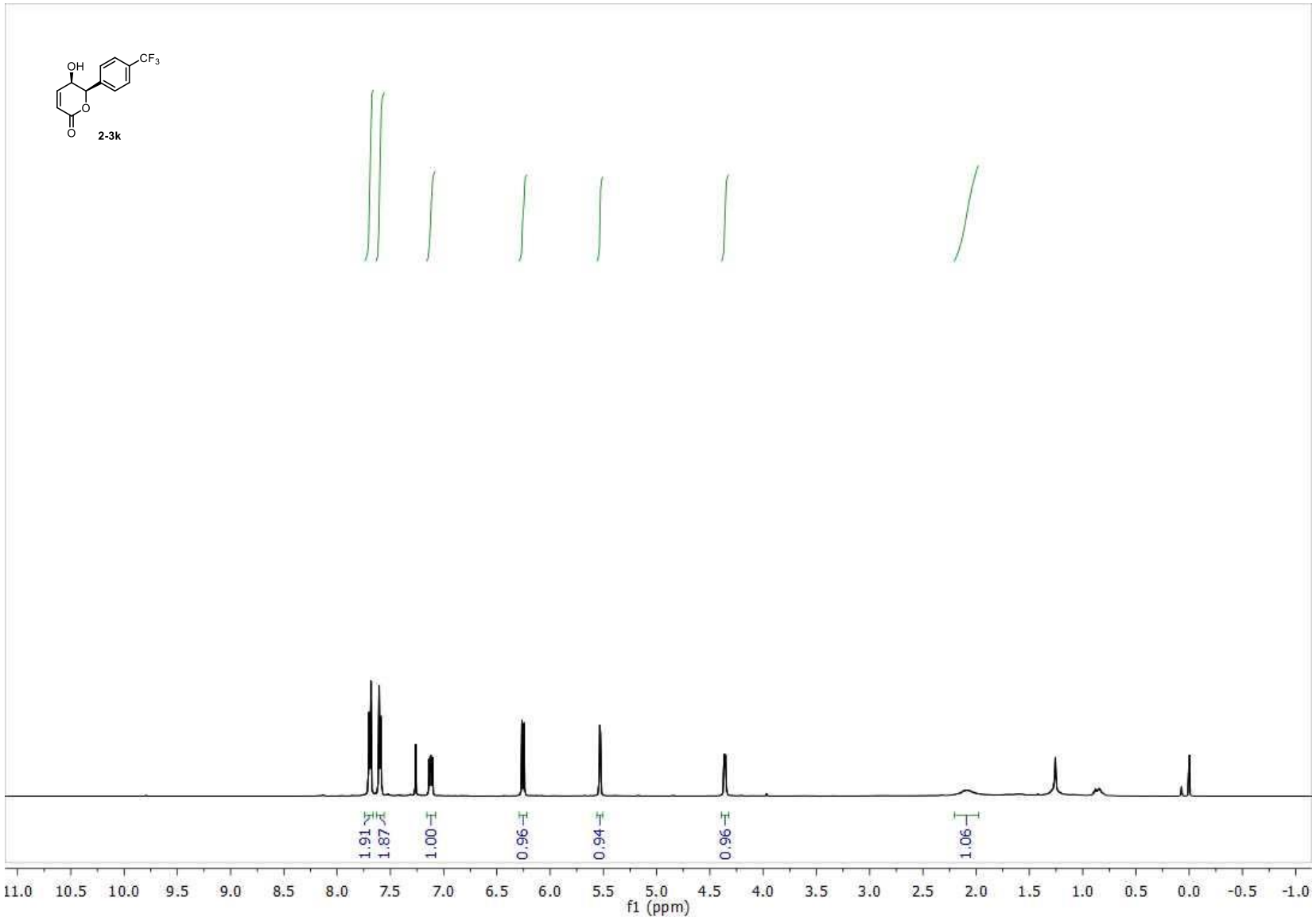

OH
O
O
2-3h
163.662
143.819
134.761
129.043
129.007
126.758
123.710
81.887
77.567
77.249
76.931
63.661
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

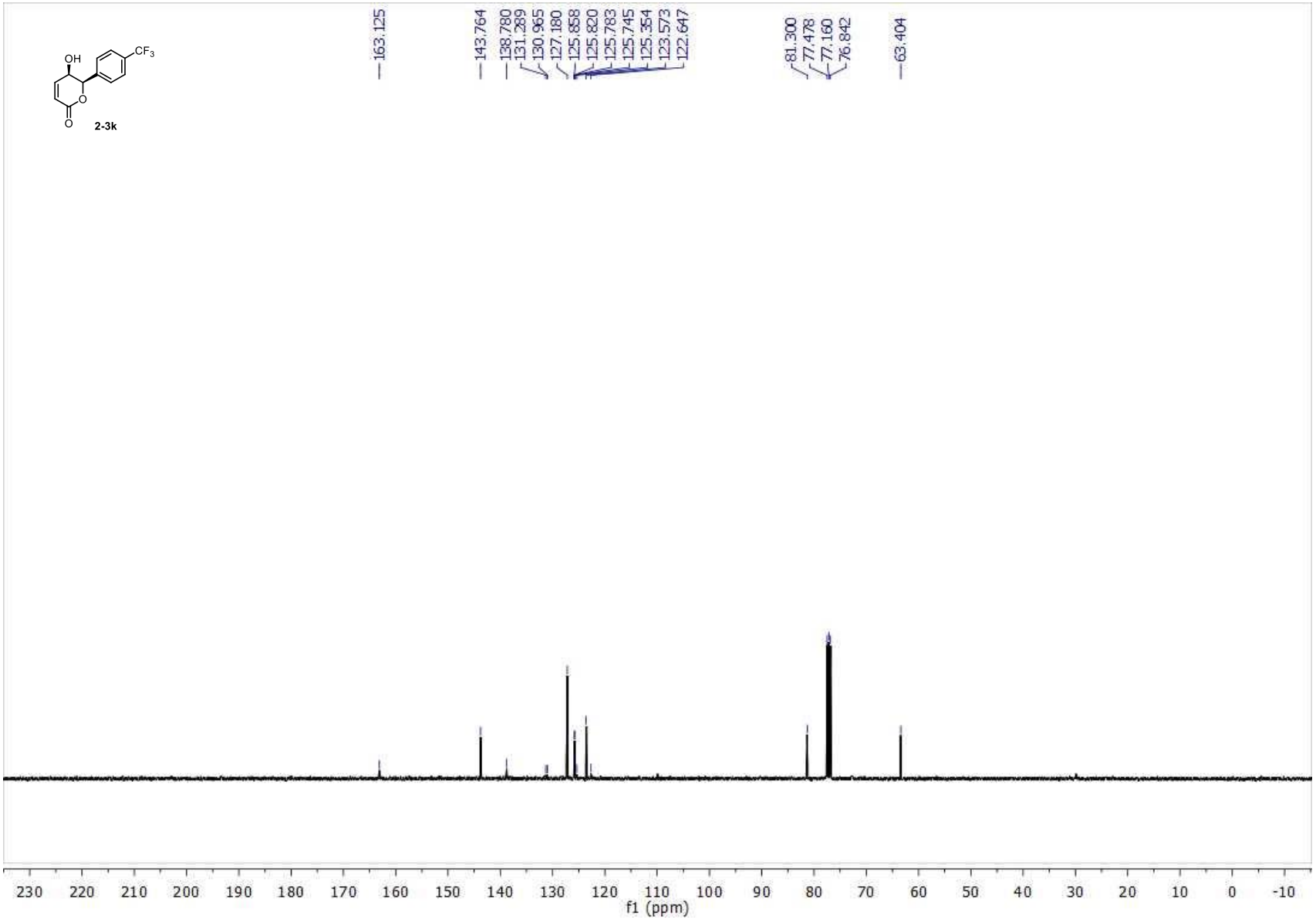

OH
F
O
O
2-3i
2.06
3.10
1.00
1.04
1.06
1.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.
f1 (ppm)

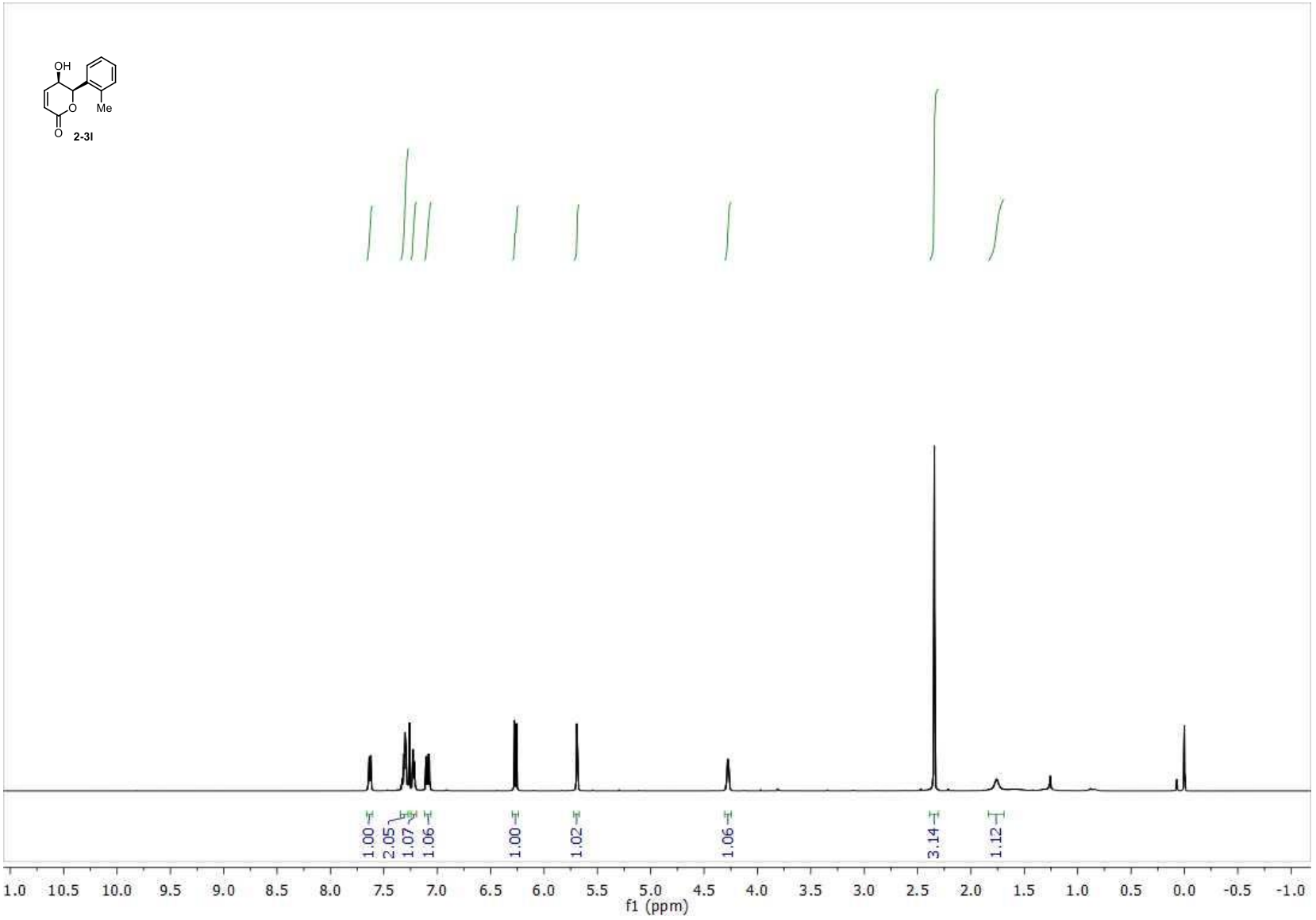

OH
F
O
O
2-3i
164.309
163.542
161.843
143.862
130.659
130.627
128.819
128.736
123.625
116.066
115.851
81.409
77.558
77.240
76.922
63.619
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

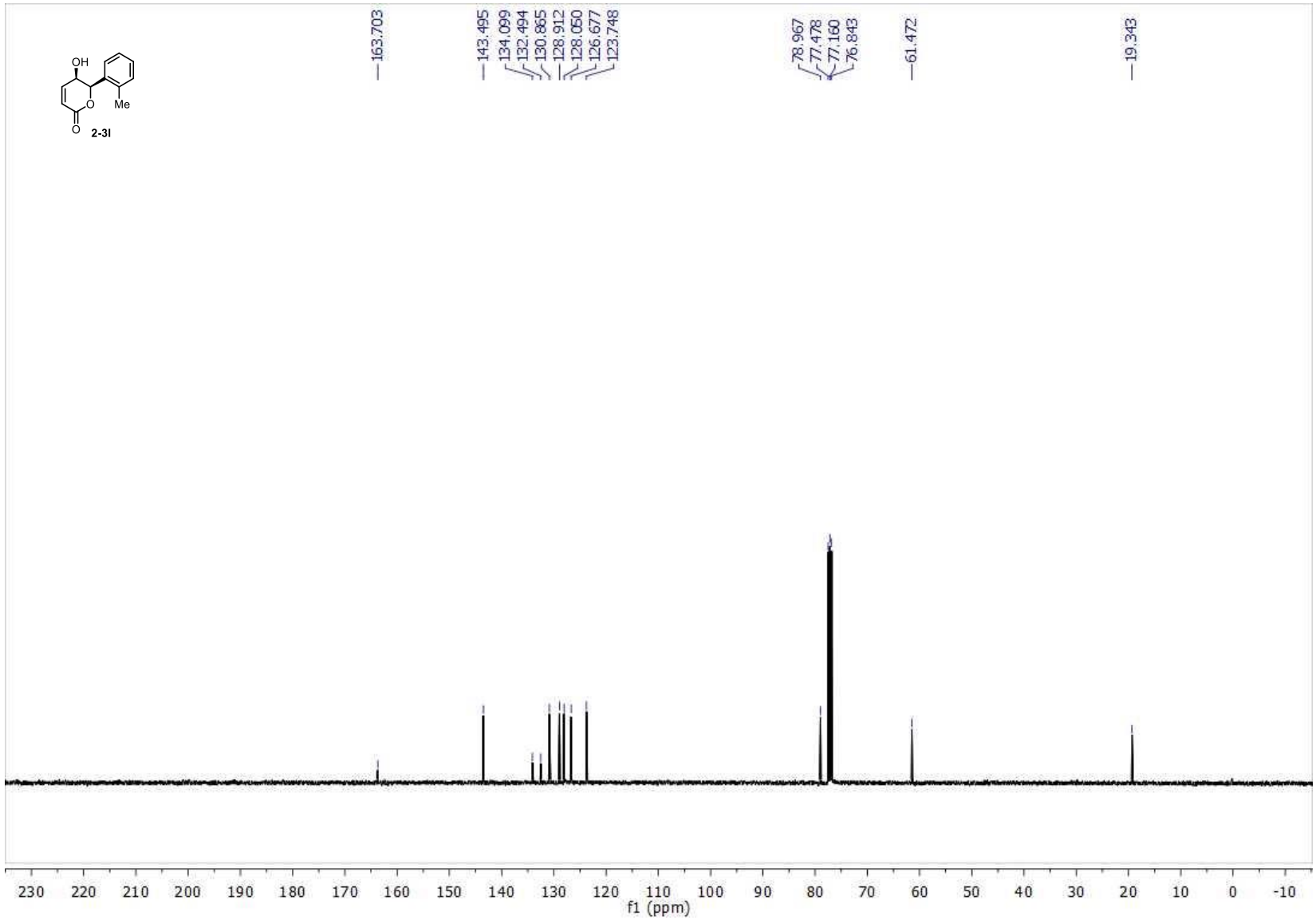

OH
OMe
O
O
2-3j
2.16
1.10
2.15
1.00
1.06
1.10
3.27
1.15
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

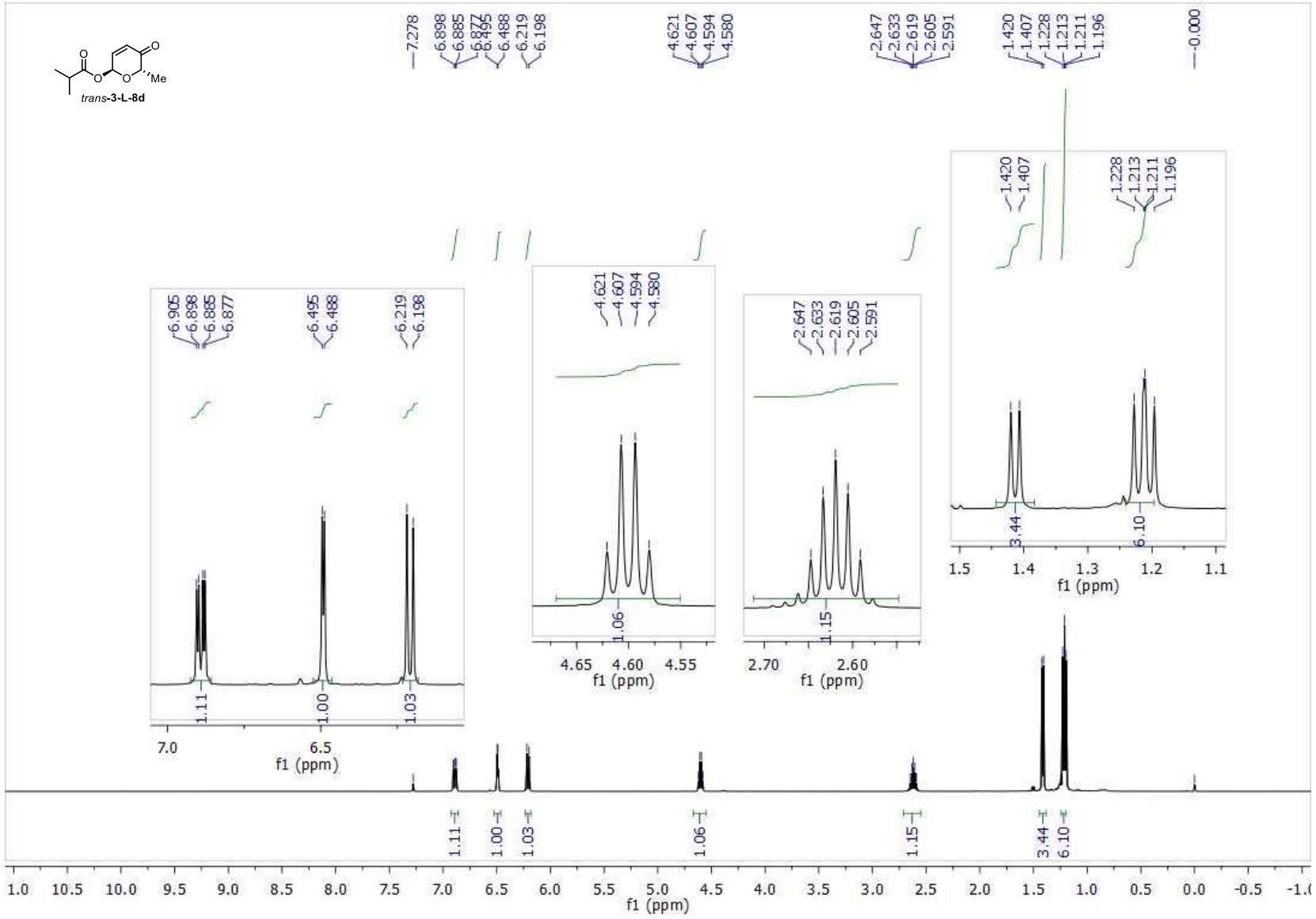

163.639
160.192
143.656
128.112
126.649
123.833
114.466
81.599
77.544
77.226
76.909
63.771
55.569
OH
OMe
O
O
2-3j
f1 (ppm)

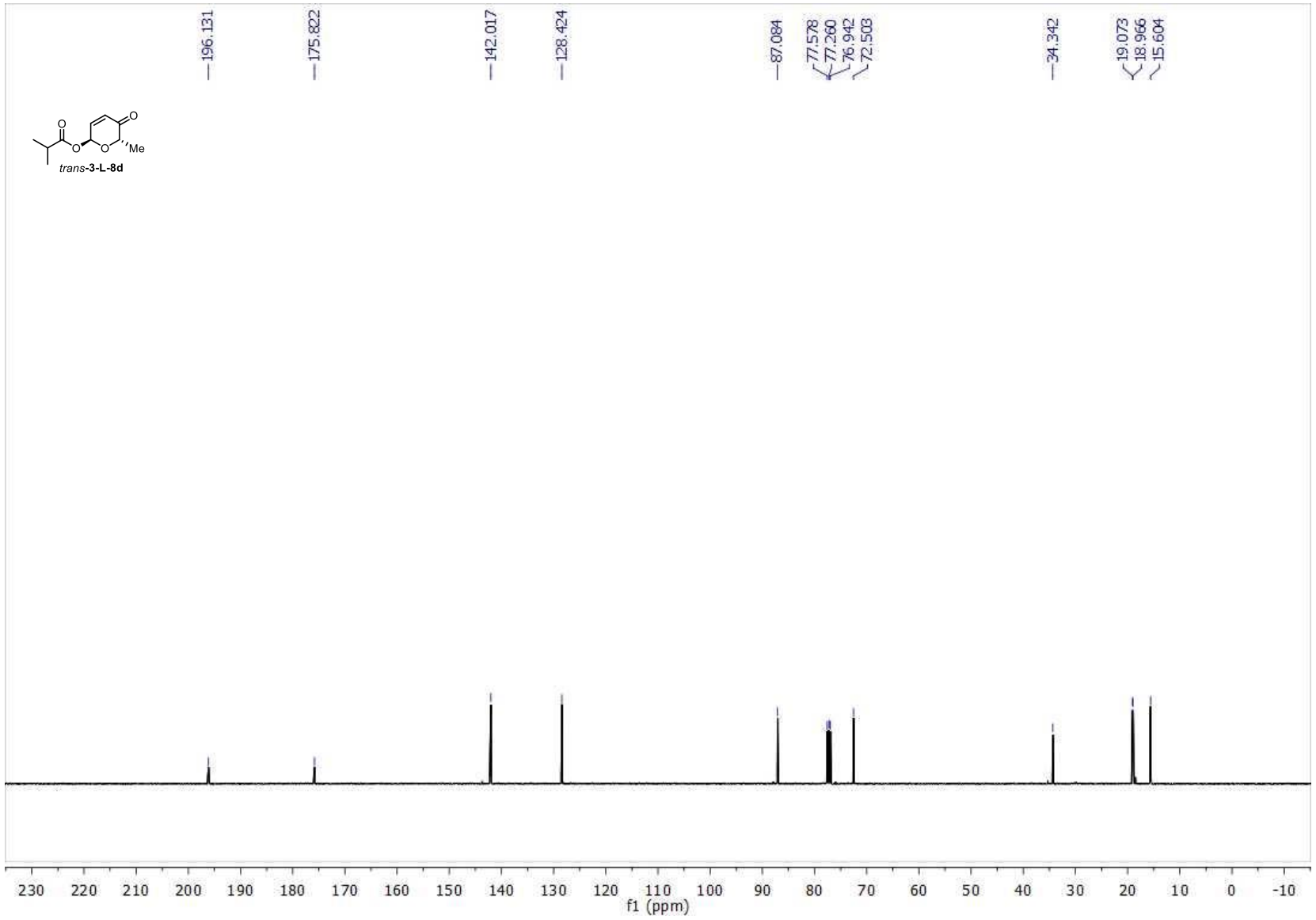

OH
CF3
O
O
2-3k
1.91
1.87
1.00
0.96
0.94
0.96
1.06
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

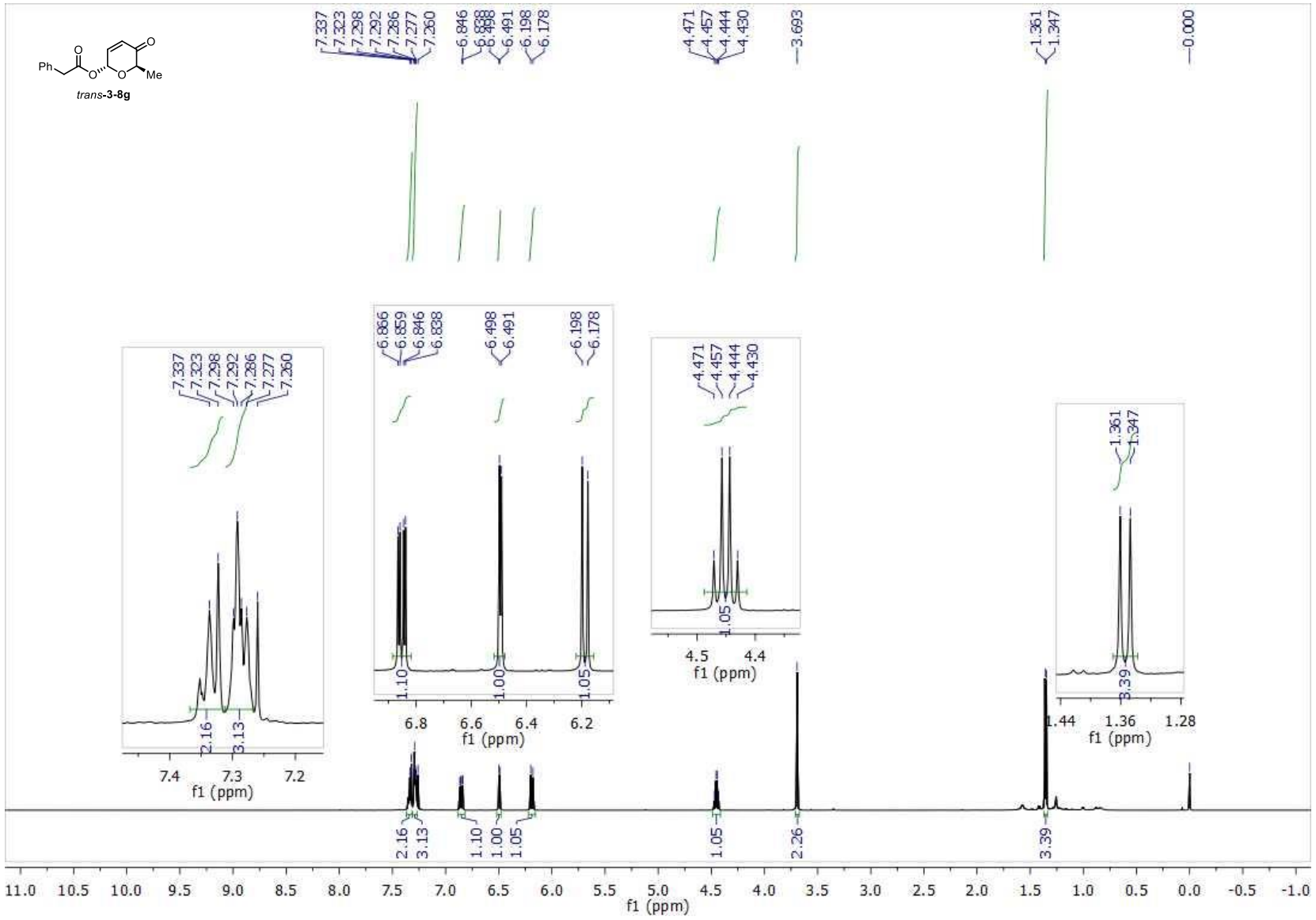

OH
CF3
O
O
2-3k
163.125
143.764
138.780
131.289
130.965
127.180
125.858
125.820
125.783
125.745
125.354
123.573
122.647
81.300
77.478
77.160
76.842
63.404
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

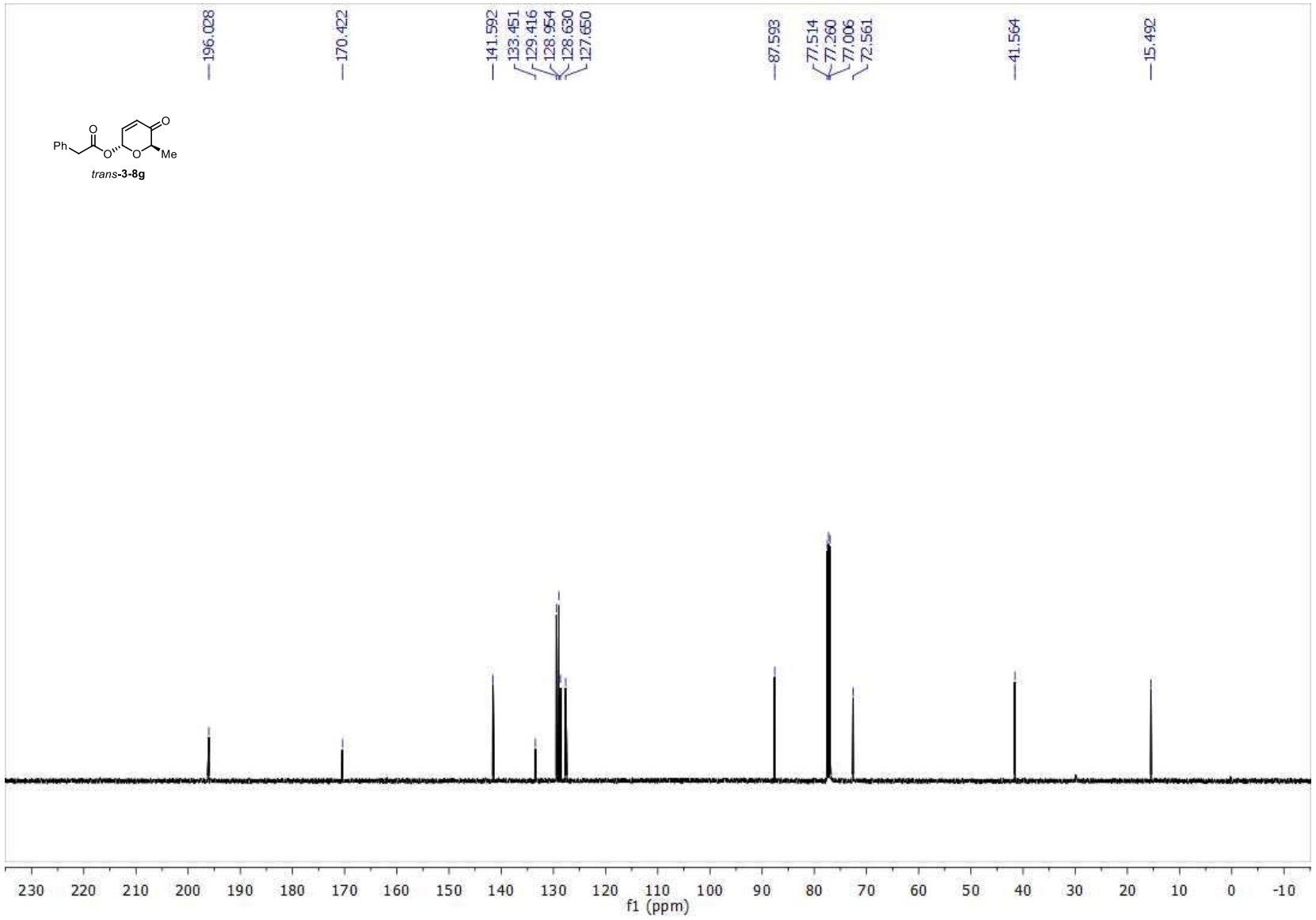

OH
O
Me
O
2-3l
1.00
2.05
1.07
1.06
1.00
1.02
1.06
3.14
1.12
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

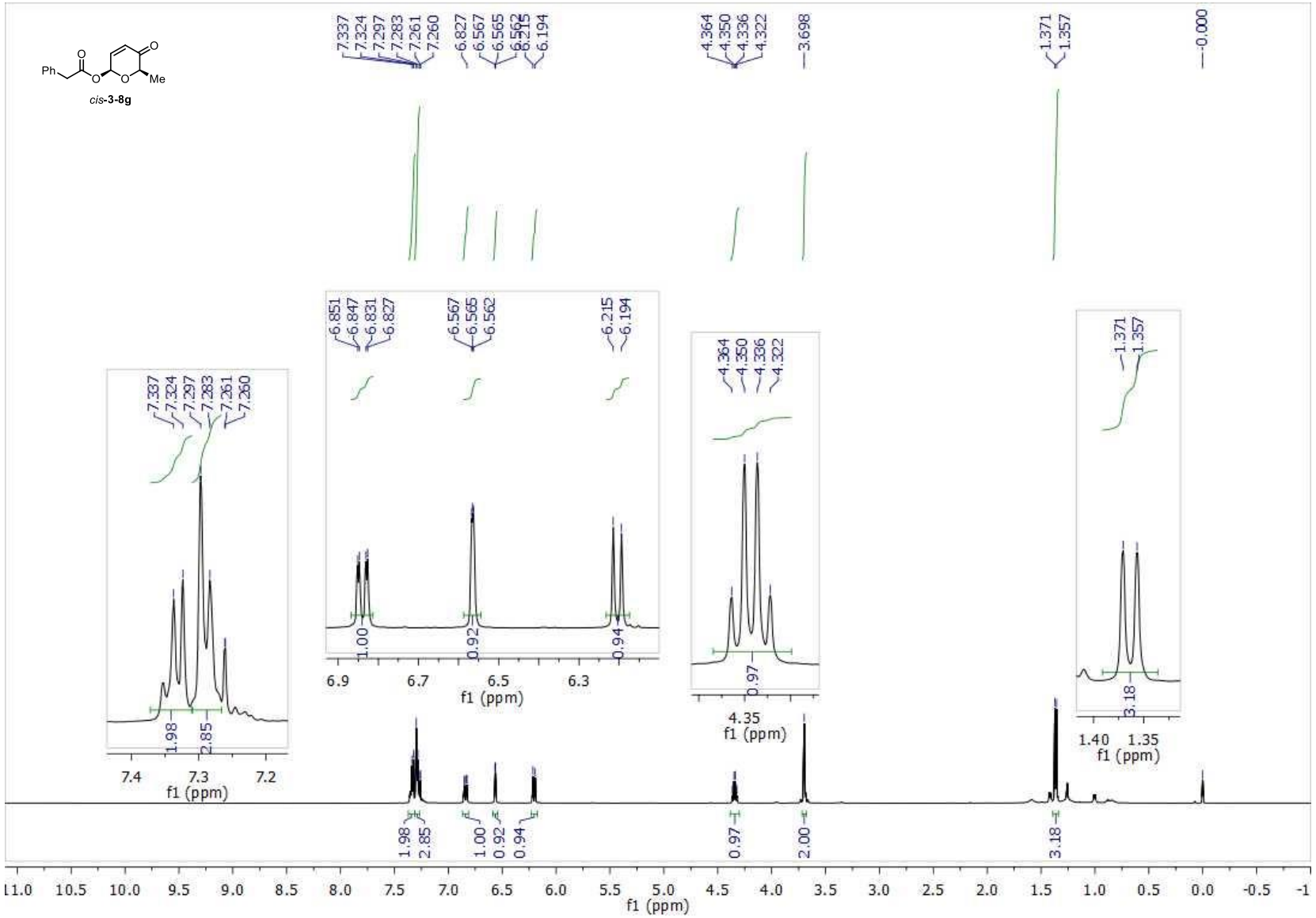

OH
O
Me
O
2-3l
163.703
143.495
134.099
132.494
130.865
128.912
128.050
126.677
123.748
78.967
77.478
77.160
76.843
61.472
19.343
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

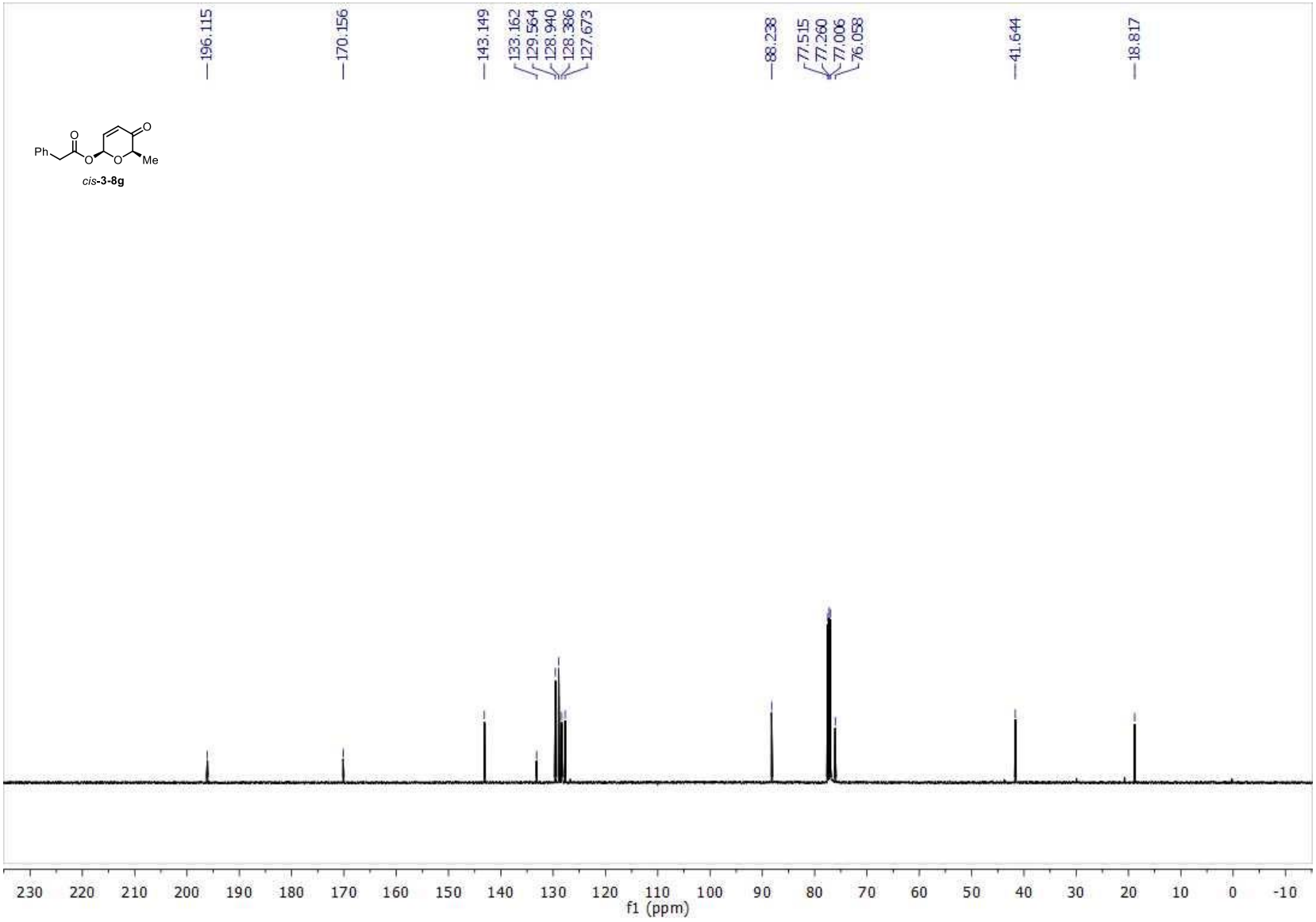

trans-3-L-8d
Me
7.278
6.898
6.885
6.877
6.495
6.488
6.219
6.198
4.621
4.607
4.594
4.580
2.647
2.633
2.619
2.605
2.591
1.420
1.407
1.228
1.213
1.211
1.196
-0.000
1.11
1.00
1.03
1.06
1.15
3.44
6.10
f1 (ppm)

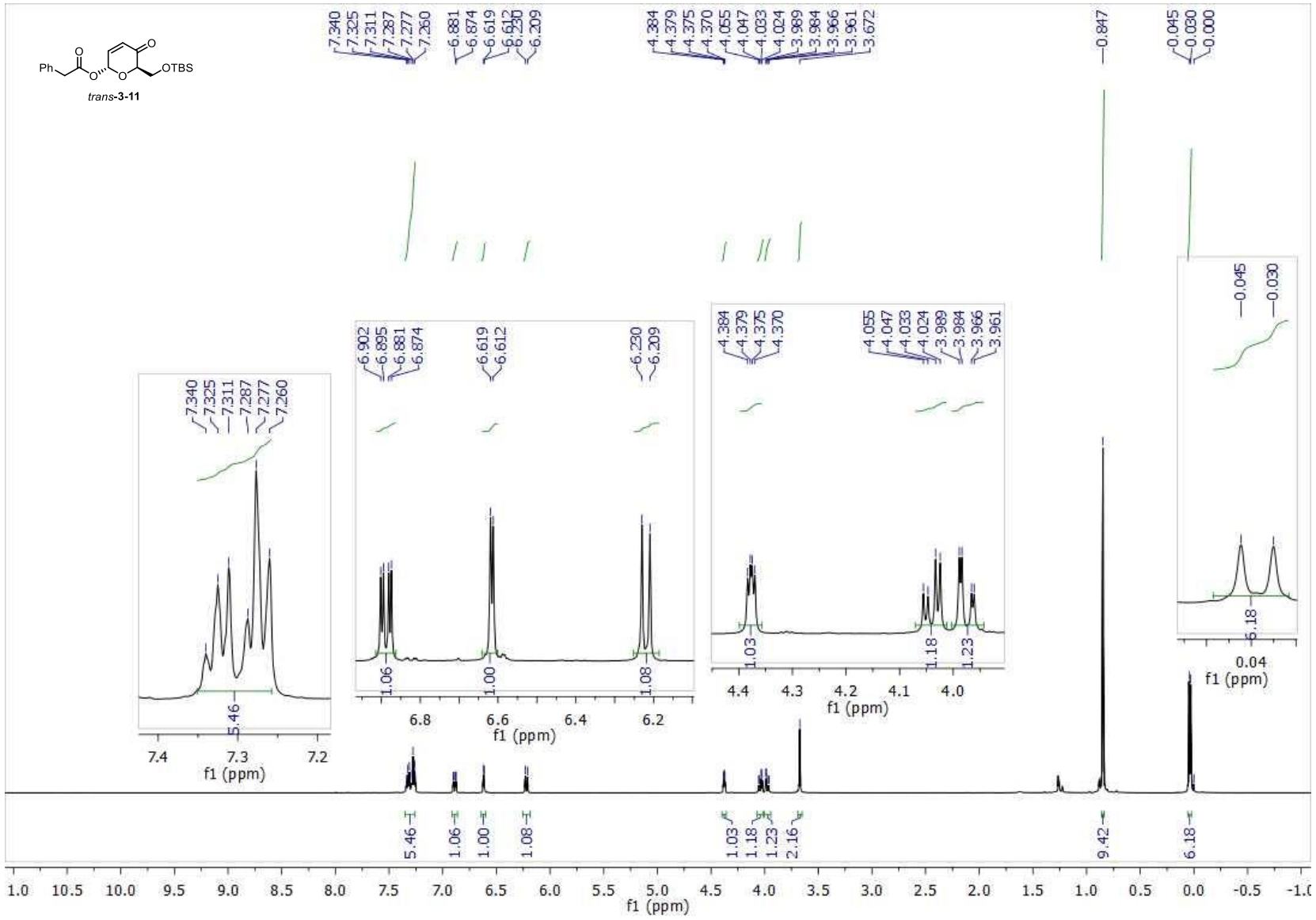

196.131
175.822
142.017
128.424
87.084
77.578
77.260
76.942
72.503
34.342
19.073
18.966
15.604
Me
trans-3-L-8d
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

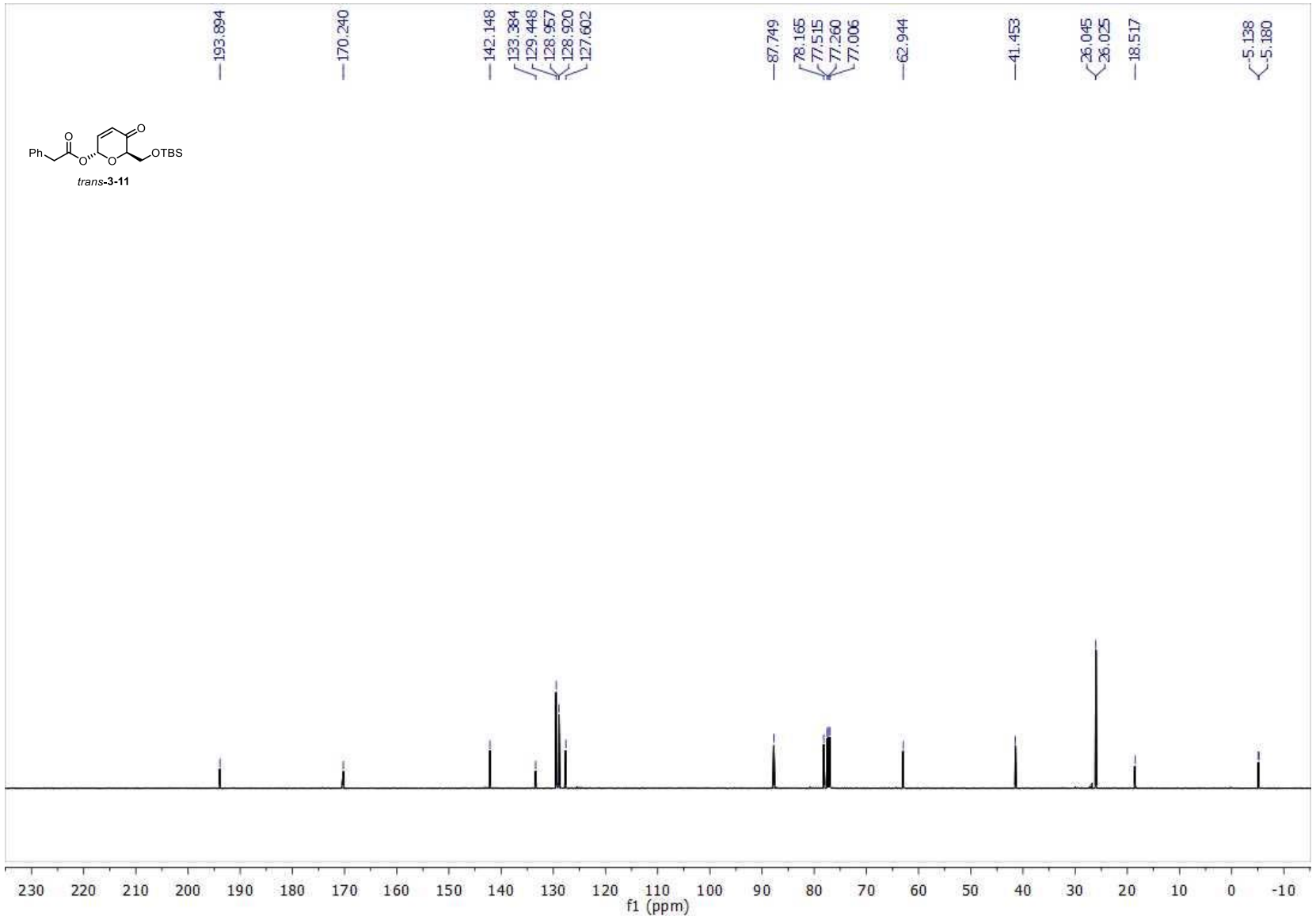

Ph
O
O
O
Me
trans-3-8g
7.337
7.323
7.298
7.292
7.286
7.277
7.260
6.846
6.838
6.498
6.491
6.198
6.178
4.471
4.457
4.444
4.430
3.693
1.361
1.347
0.000
f1 (ppm)
2.16
3.13
1.10
1.00
1.05
1.05
2.26
3.39

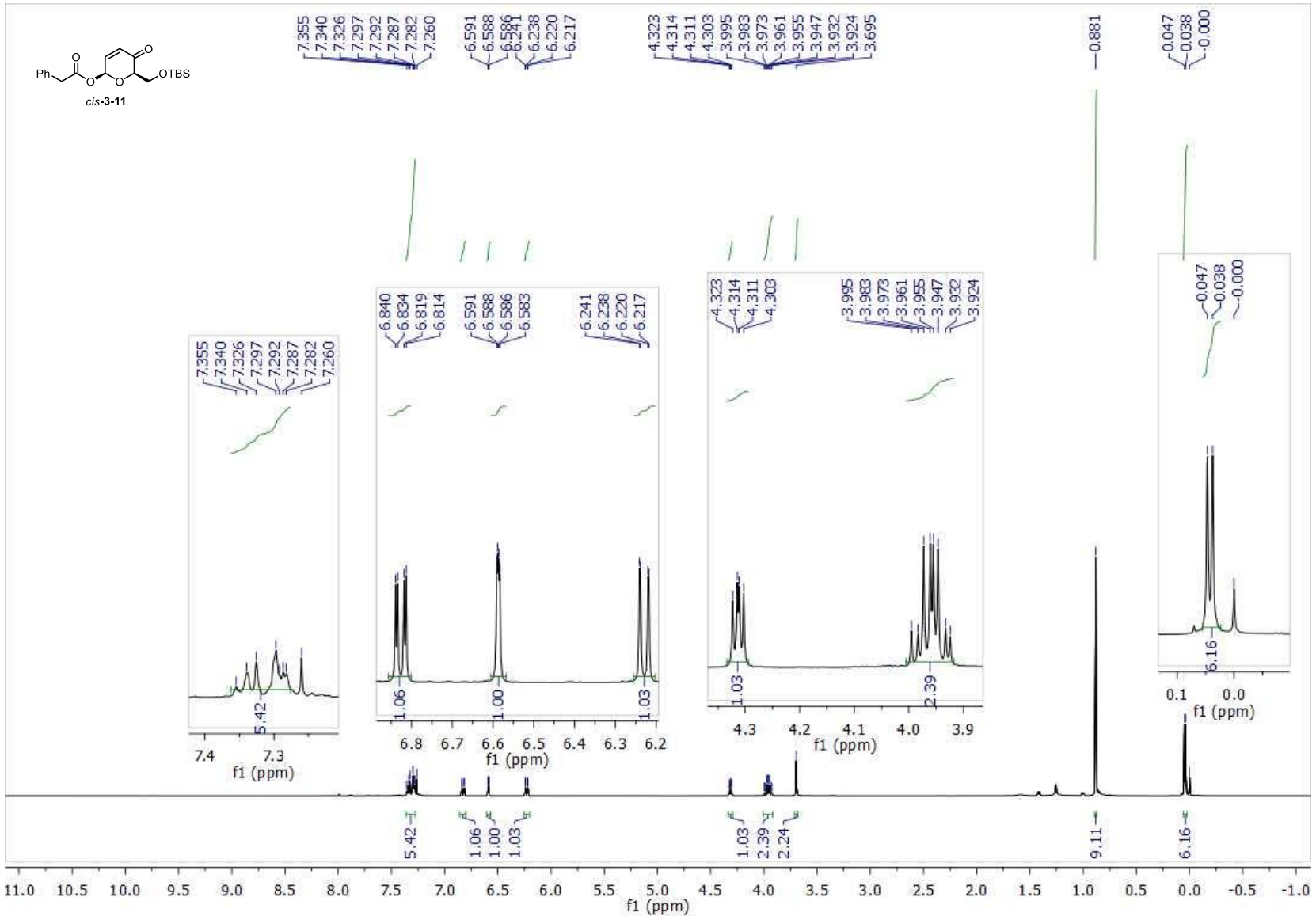

196.028
170.422
141.592
133.451
129.416
128.954
128.630
127.650
87.593
77.514
77.260
77.006
72.561
41.564
15.492
Ph
O
O
O
Me
trans-3-8g
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

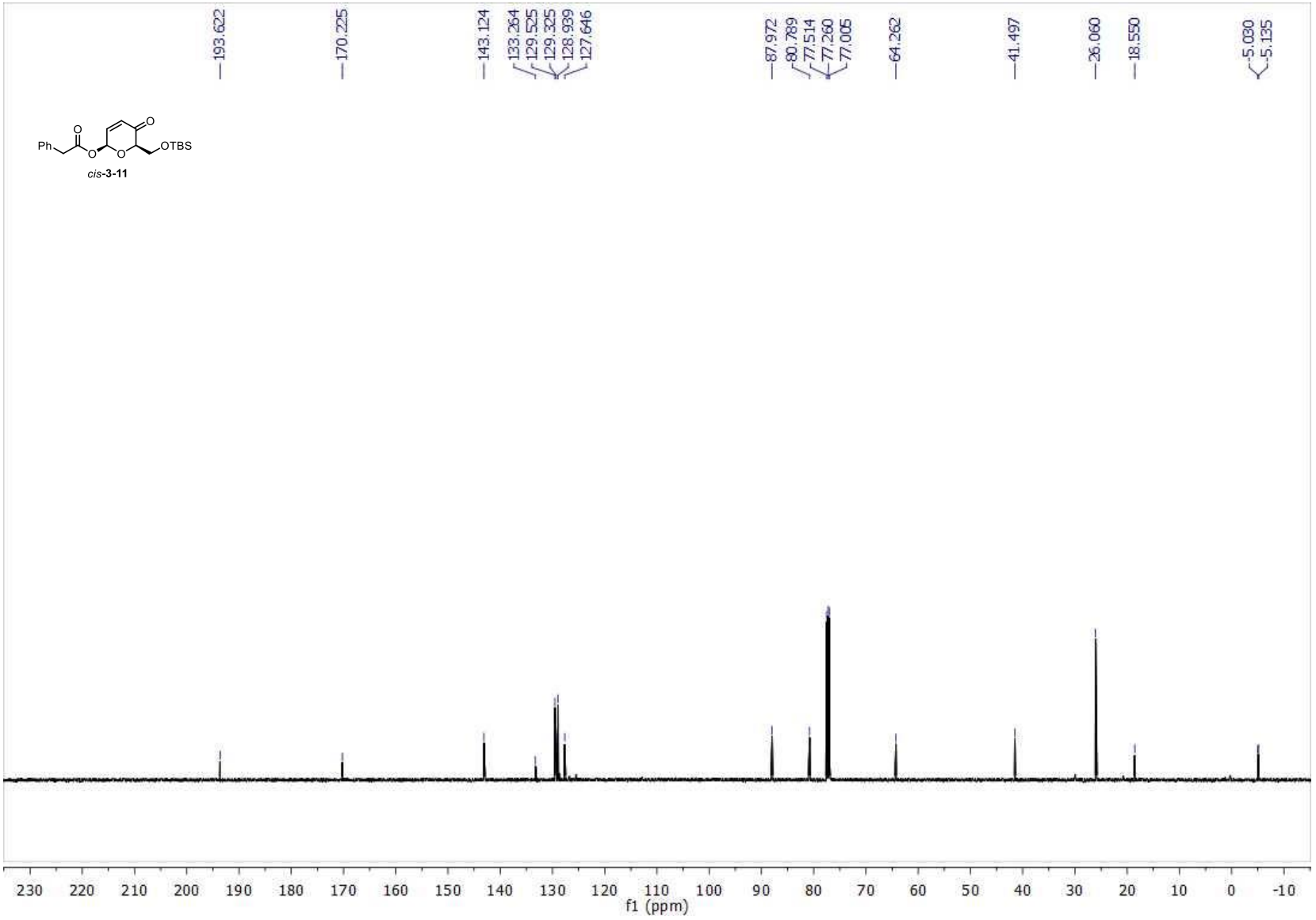

cis-3-8g
7.337
7.324
7.297
7.283
7.261
7.260
6.827
6.567
6.565
6.562
6.215
6.194
4.364
4.350
4.336
4.322
3.698
1.371
1.357
0.000
f1 (ppm)

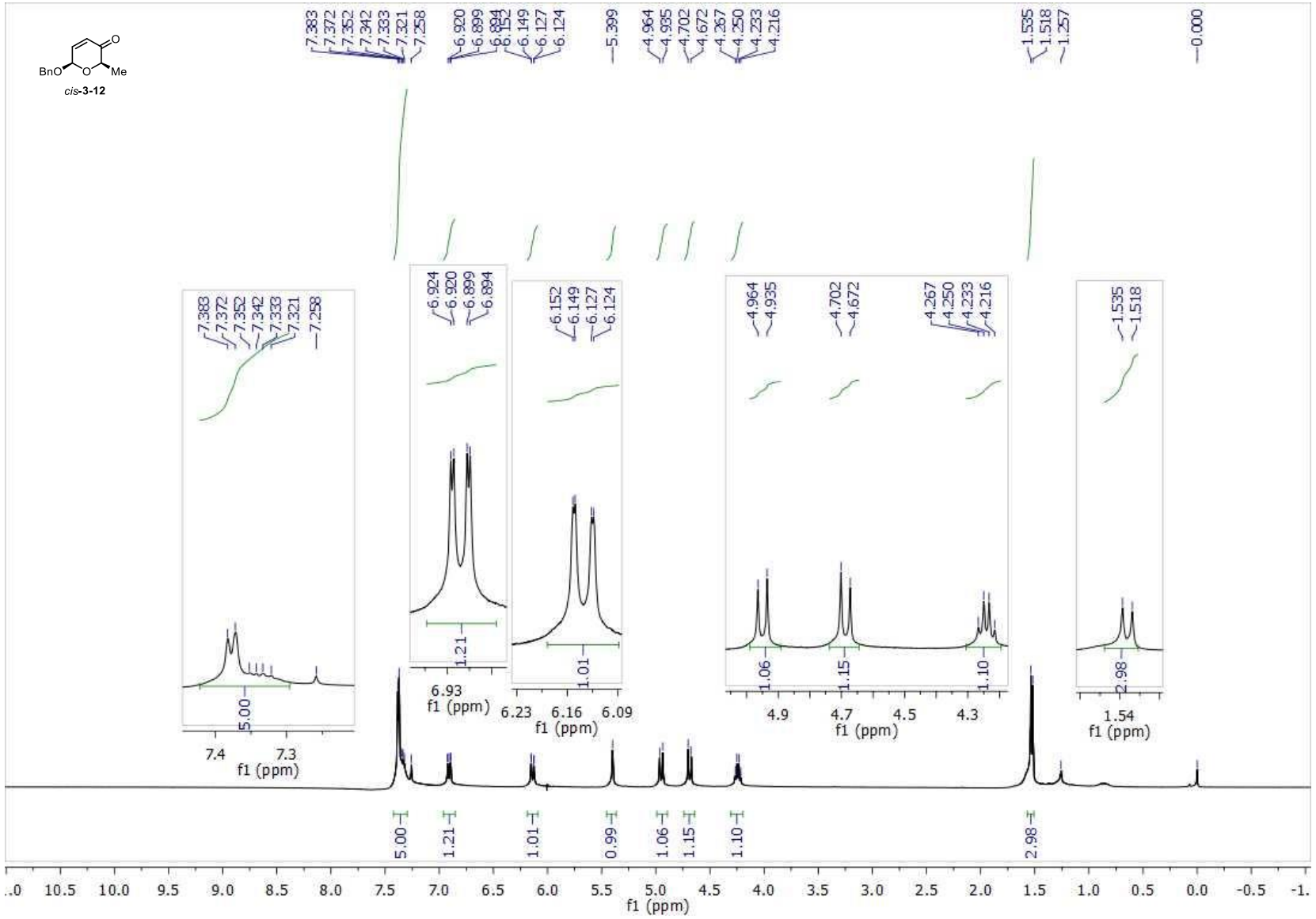

196.115
170.156
143.149
133.162
129.564
128.940
128.386
127.673
88.238
77.515
77.260
77.006
76.058
41.644
18.817
Ph
O
O
O
Me
cis-3-8g
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

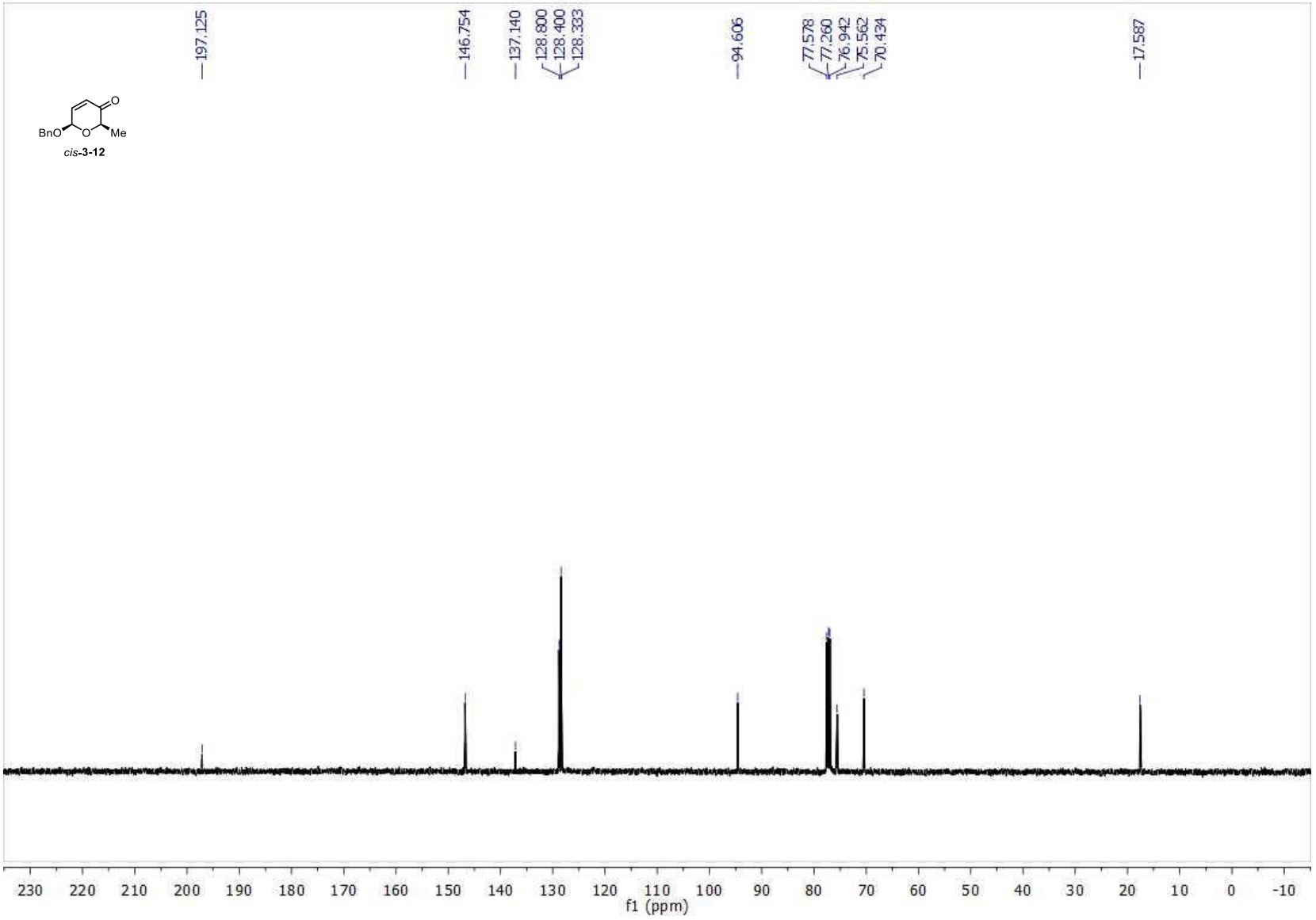

trans-3-11
Ph
OTBS
7.340
7.325
7.311
7.287
7.277
7.260
6.881
6.874
6.619
6.612
6.230
6.209
4.384
4.379
4.375
4.370
4.055
4.047
4.033
4.024
3.989
3.984
3.966
3.961
3.672
0.847
0.045
0.030
0.000
6.902
6.895
6.881
6.874
1.06
1.00
1.08
f1 (ppm)
5.46
1.03
1.18
1.23
2.16
9.42
6.18
0.04

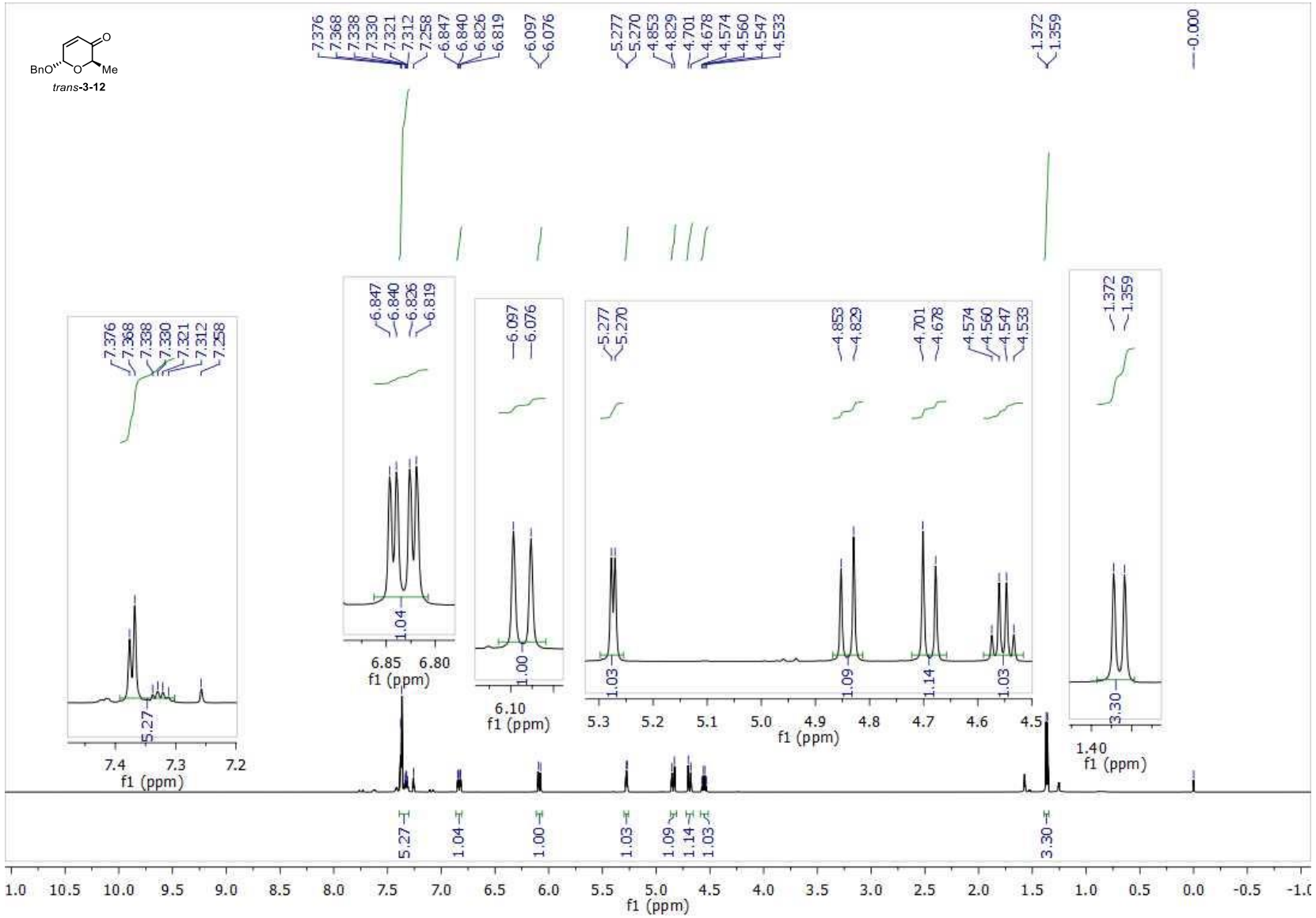

193.894
170.240
142.148
133.384
129.448
128.957
128.920
127.602
87.749
78.165
77.515
77.260
77.006
62.944
41.453
26.045
26.025
18.517
5.138
5.180
Ph
OTBS
trans-3-11
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

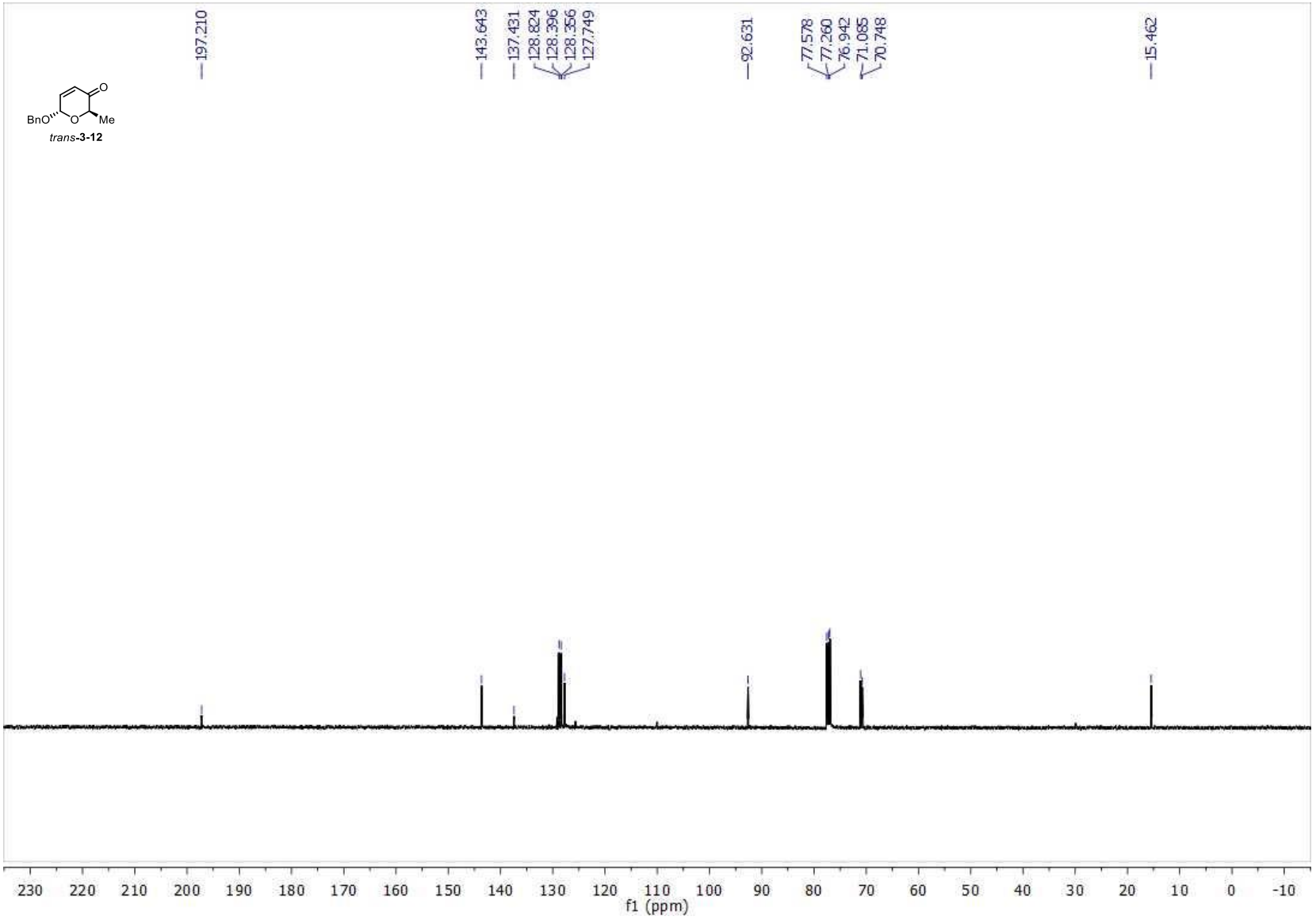

Ph
OTBS
cis-3-11
f1 (ppm)

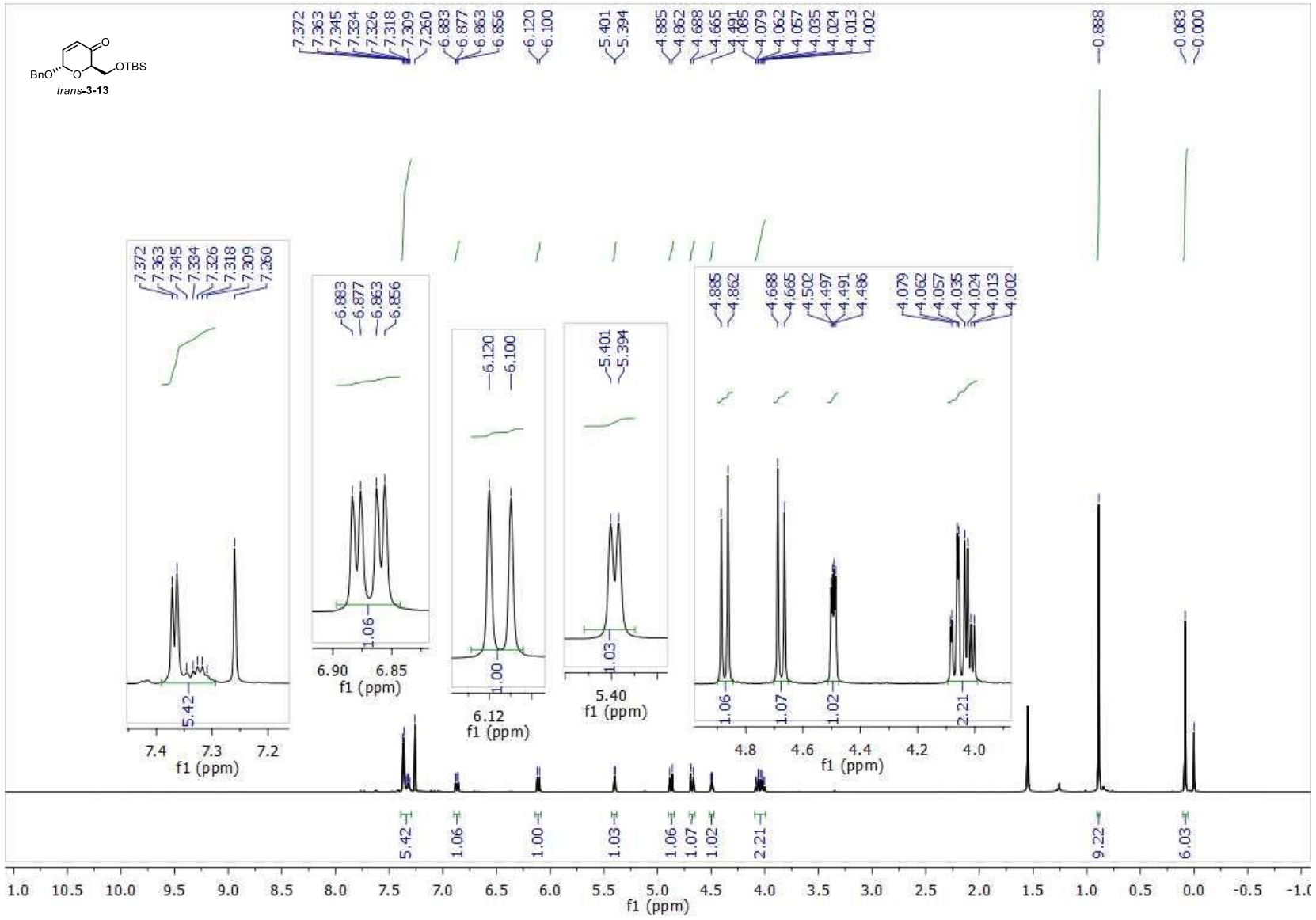

193.622
170.225
143.124
133.264
129.525
129.325
128.939
127.646
87.972
80.789
77.514
77.260
77.005
64.262
41.497
26.060
18.550
-5.030
-5.135
Ph
O
O
O
O
OTBS
cis-3-11
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

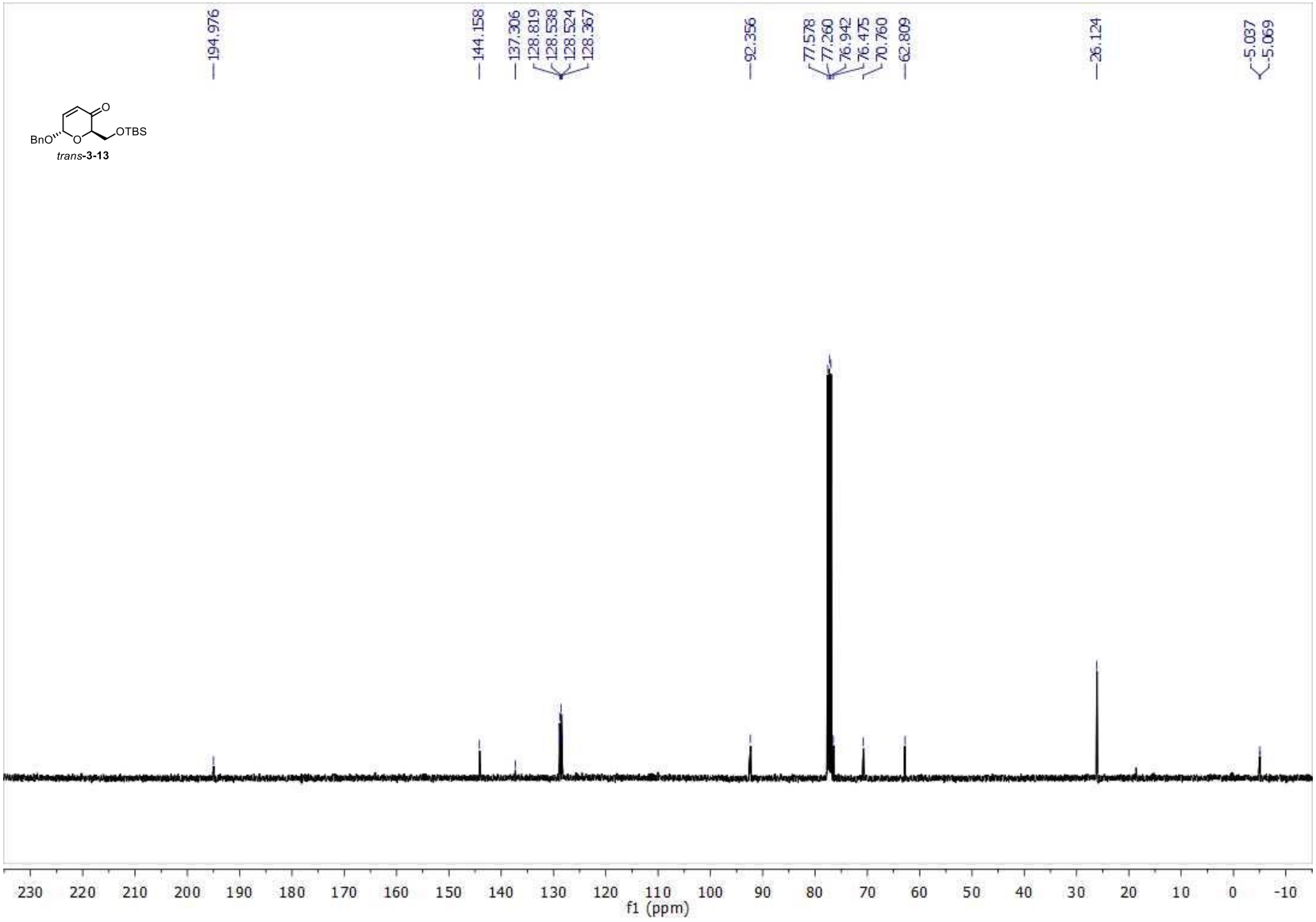

BnO
Me
cis-3-12
7.383
7.372
7.352
7.342
7.333
7.321
7.258
6.920
6.899
6.894
6.152
6.149
6.127
6.124
5.399
4.964
4.935
4.702
4.672
4.267
4.250
4.233
4.216
1.535
1.518
1.257
0.000
5.00
1.21
1.01
0.99
1.06
1.15
1.10
2.98
f1 (ppm)

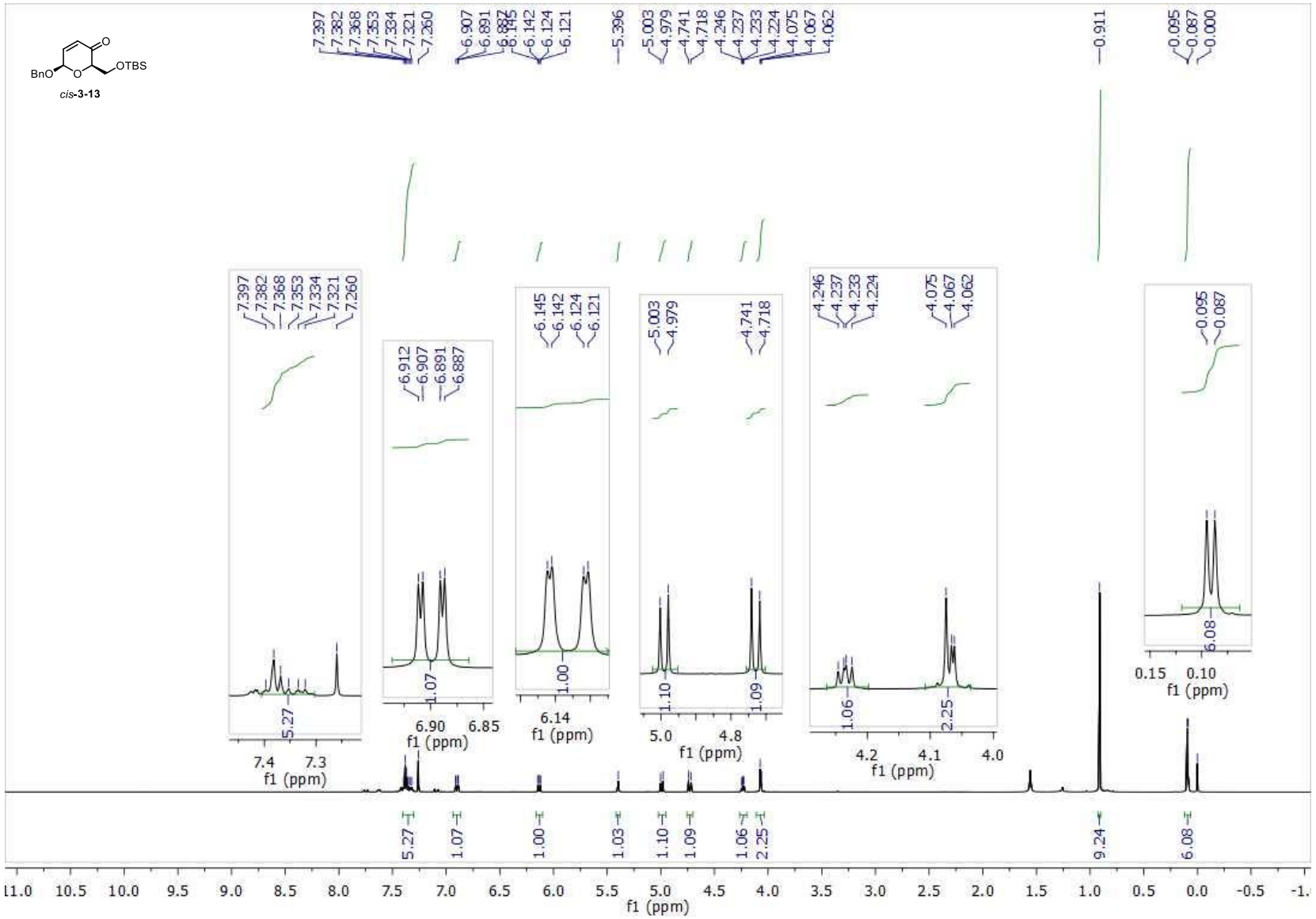

197.125
146.754
137.140
128.800
128.400
128.333
94.606
77.578
77.260
76.942
75.562
70.434
17.587
BnO
O
Me
cis-3-12
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

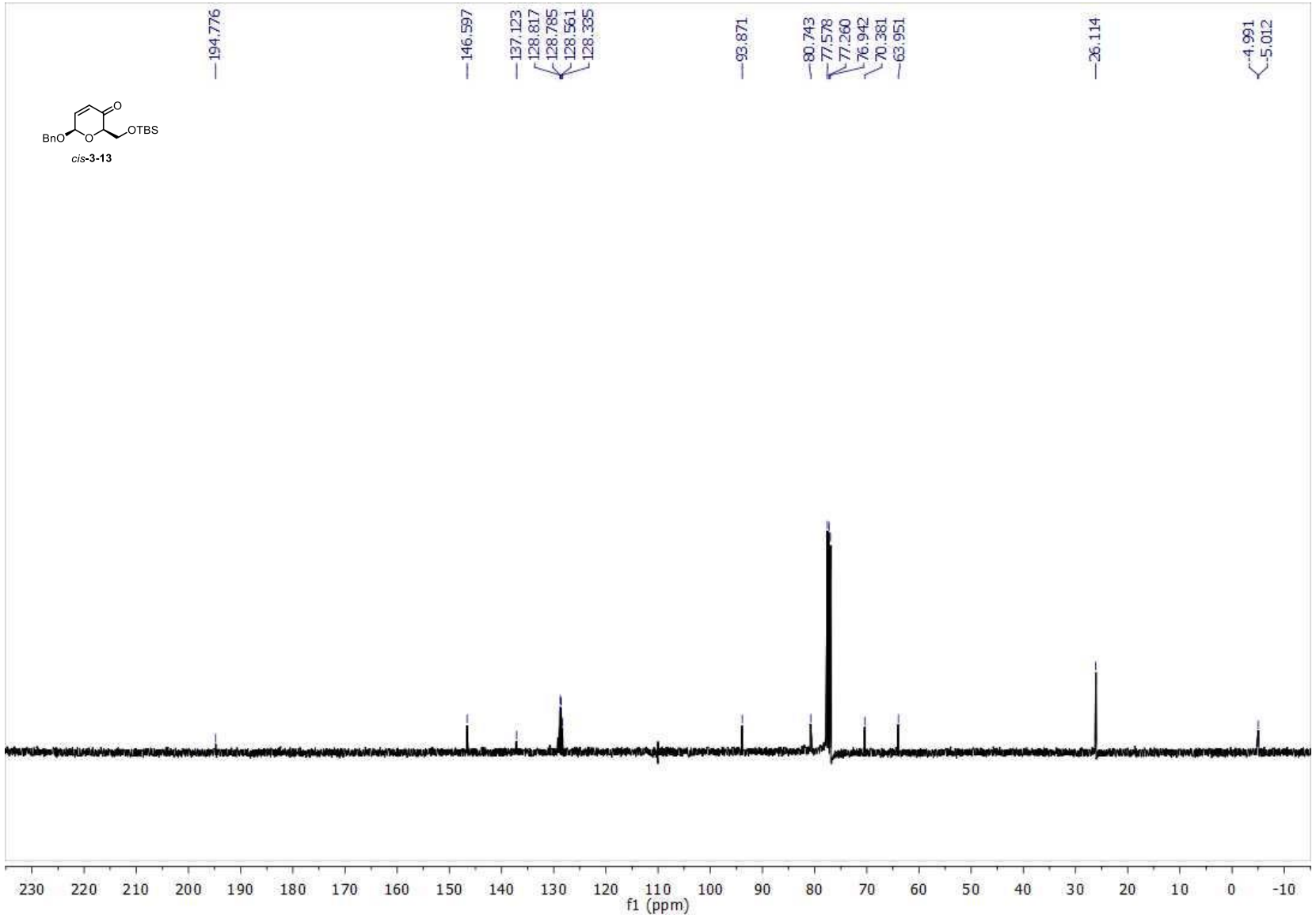

BnO
Me
trans-3-12
7.376
7.368
7.338
7.330
7.321
7.312
7.258
6.847
6.840
6.826
6.819
6.097
6.076
5.277
5.270
4.853
4.829
4.701
4.678
4.574
4.560
4.547
4.533
1.372
1.359
0.000
1.04
1.00
1.03
1.09
1.14
1.03
3.30
5.27
f1 (ppm)

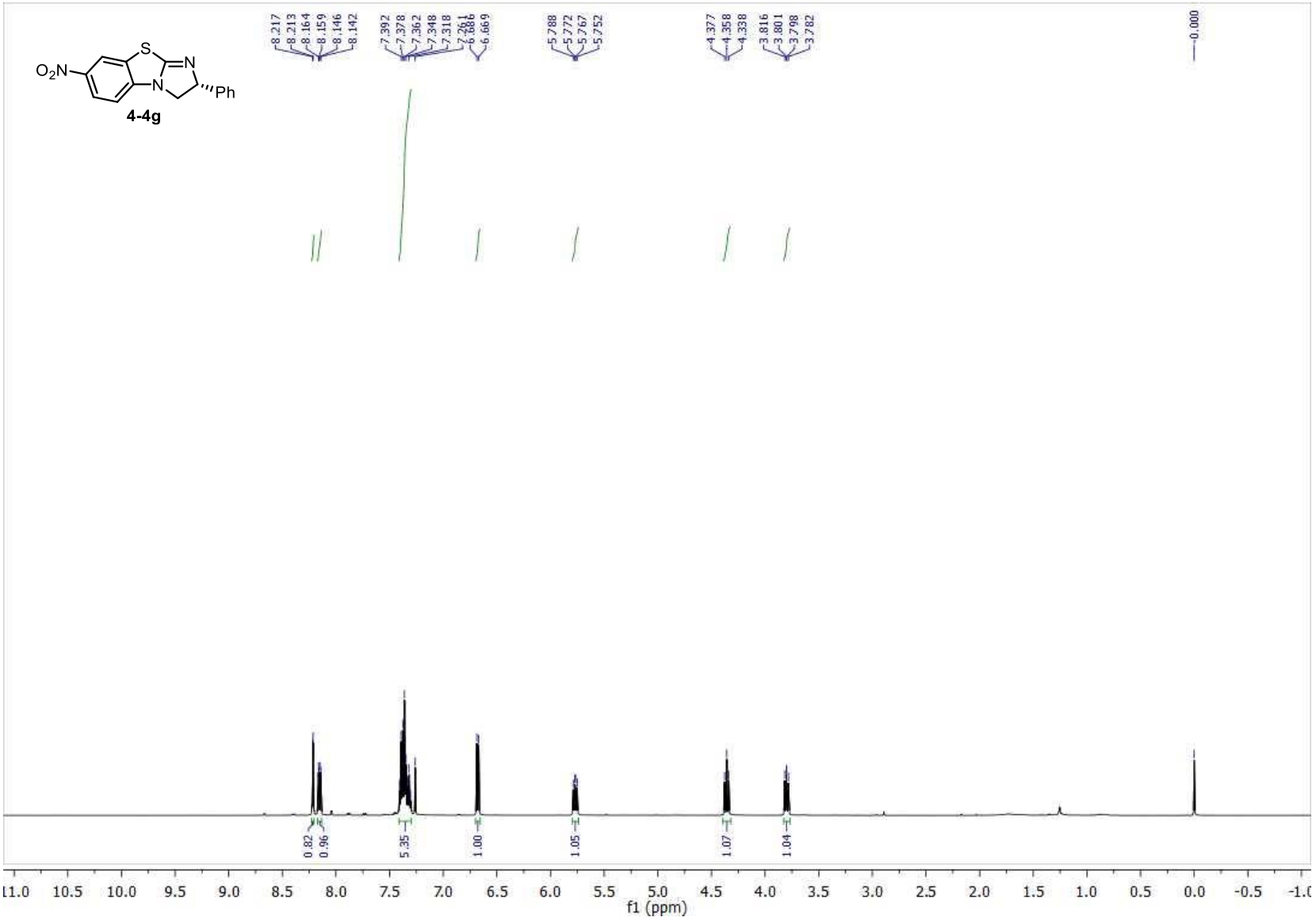

197.210
143.643
137.431
128.824
128.396
128.356
127.749
92.631
77.578
77.260
76.942
71.085
70.748
15.462
BnO
O
Me
trans-3-12
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

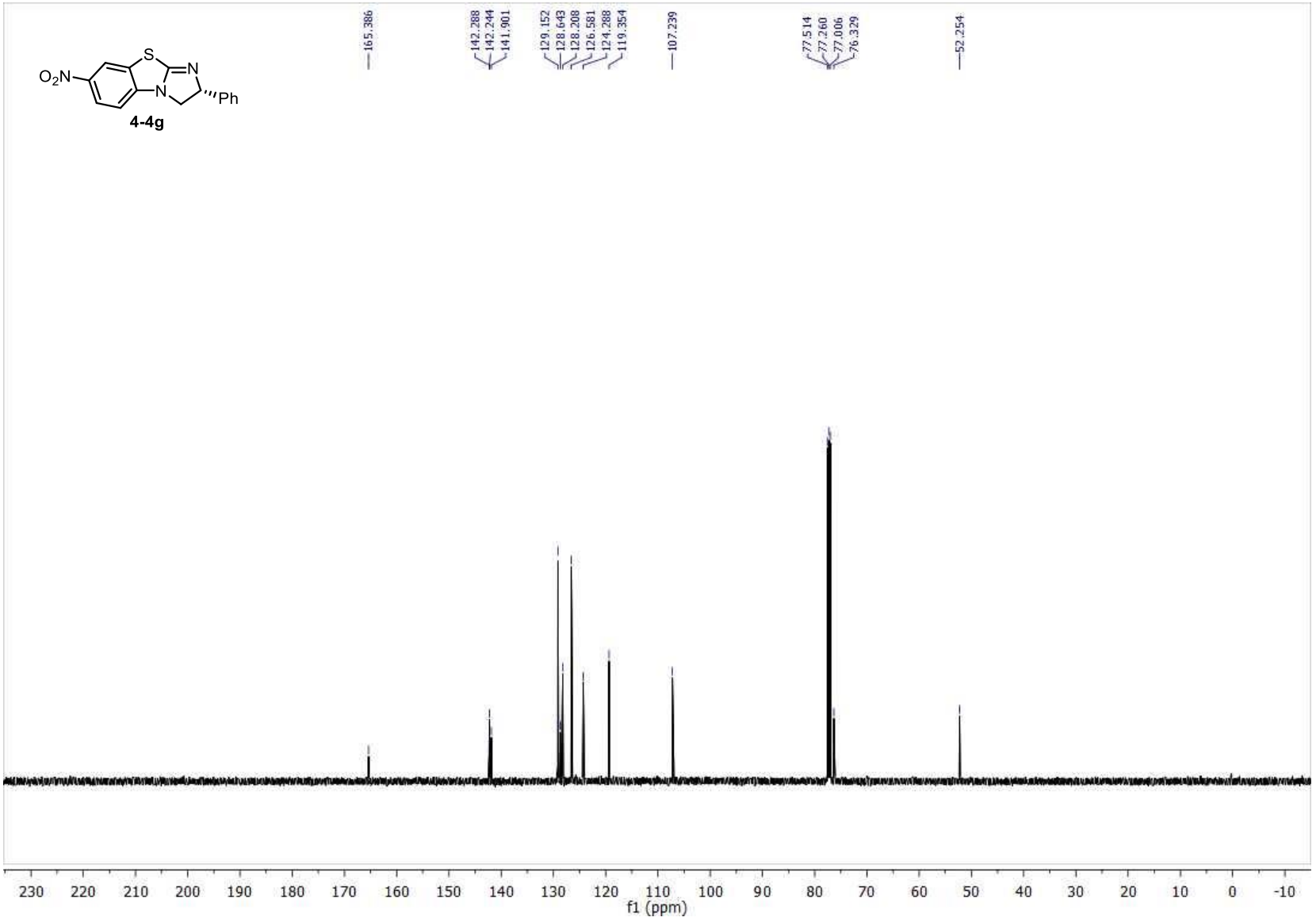

BnO
OTBS
O
trans-3-13
7.372
7.363
7.345
7.334
7.326
7.318
7.309
7.260
6.883
6.877
6.863
6.856
6.120
6.100
5.401
5.394
4.885
4.862
4.688
4.665
4.502
4.497
4.491
4.486
4.079
4.062
4.057
4.035
4.024
4.013
4.002
0.888
0.083
0.000
5.42
1.06
1.00
1.03
1.06
1.07
1.02
2.21
9.22
6.03
f1 (ppm)

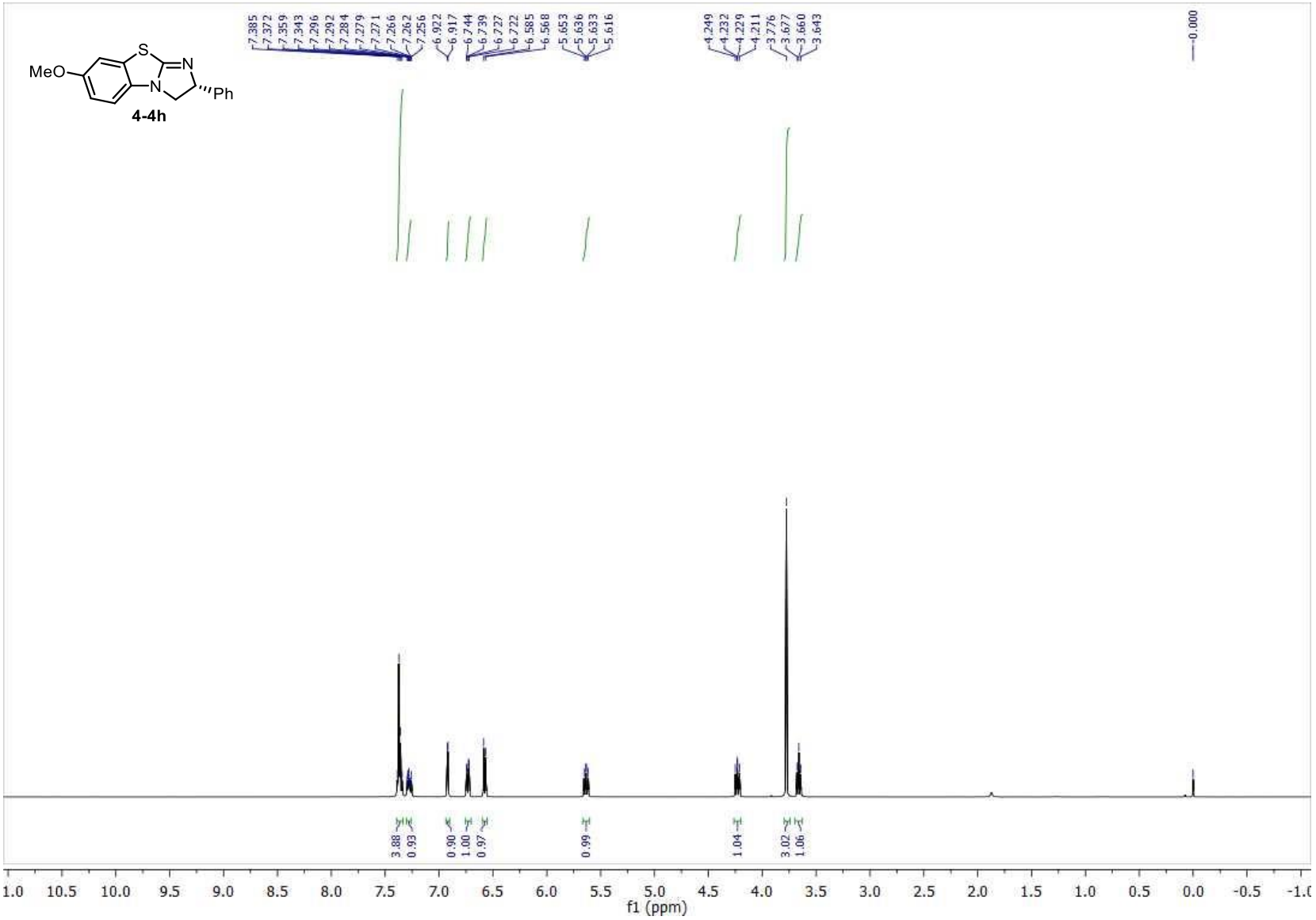

194.976
144.158
137.306
128.819
128.538
128.524
128.357
92.356
77.578
77.260
76.942
76.475
70.760
62.809
26.124
-5.037
-5.069
BnO
OTBS
trans-3-13
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

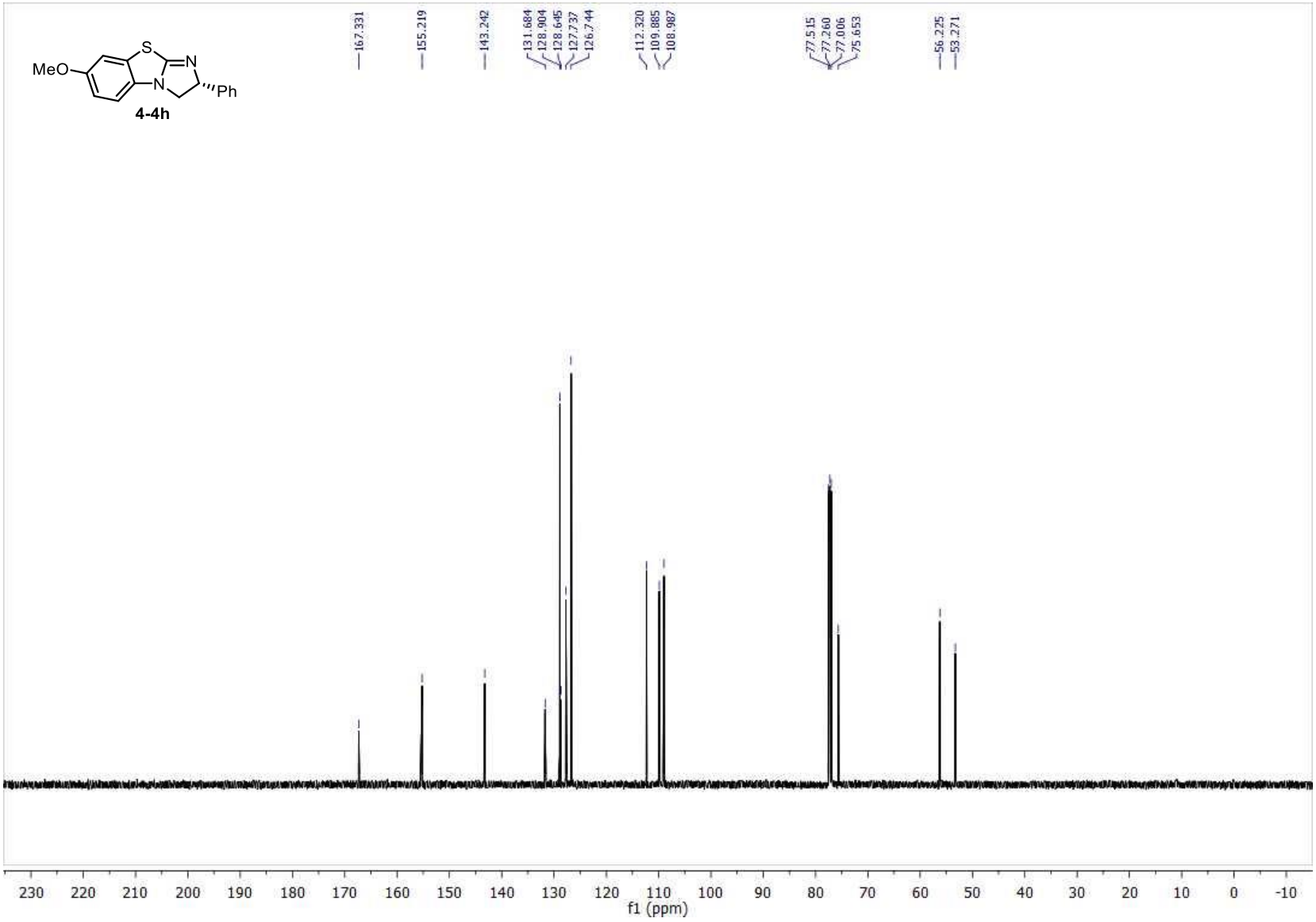

BnO
OTBS
cis-3-13
f1 (ppm)

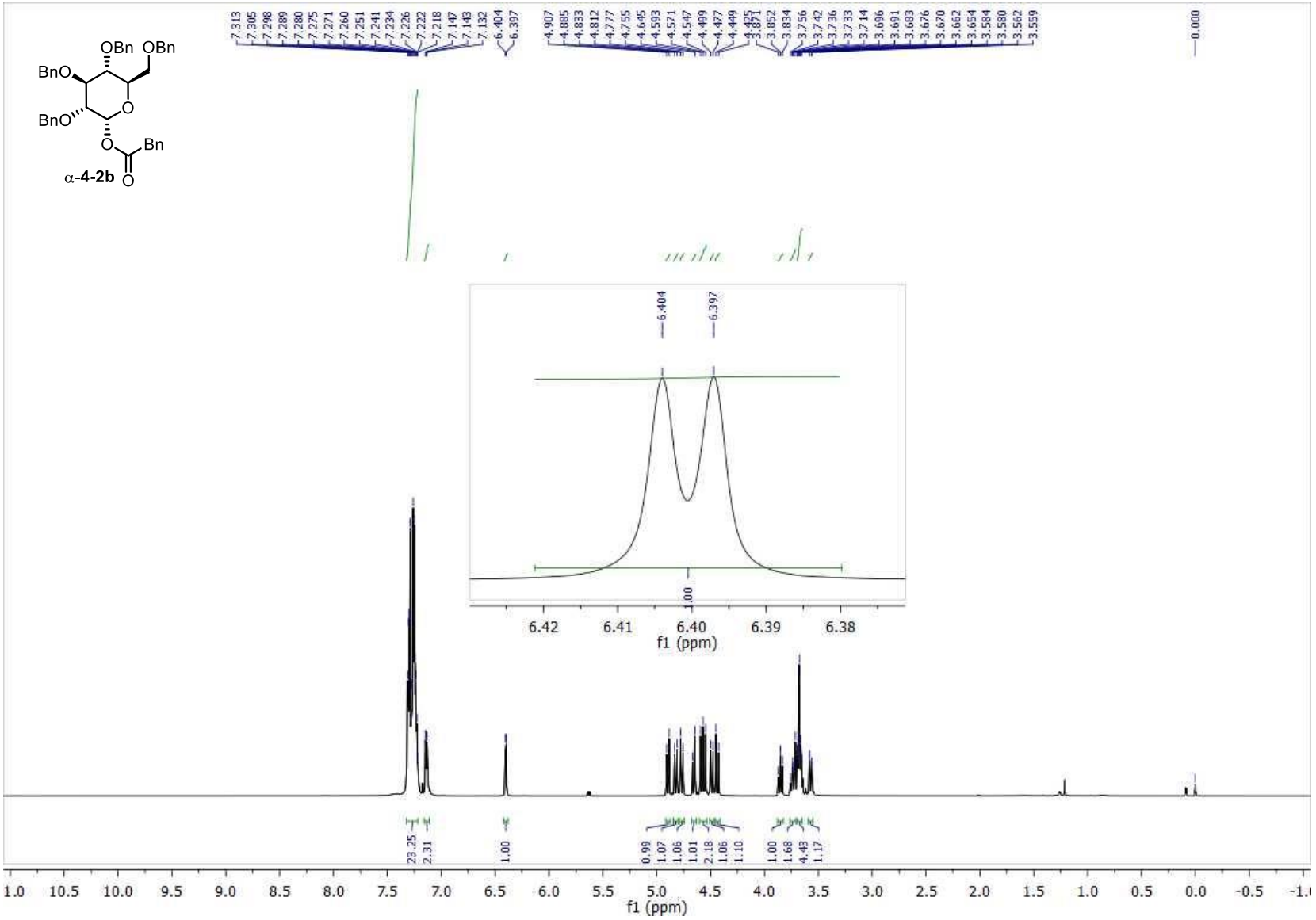

194.776
146.597
137.123
128.817
128.785
128.561
128.335
93.871
80.743
77.578
77.260
76.942
70.381
63.951
26.114
4.991
5.012
BnO
OTBS
cis-3-13
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

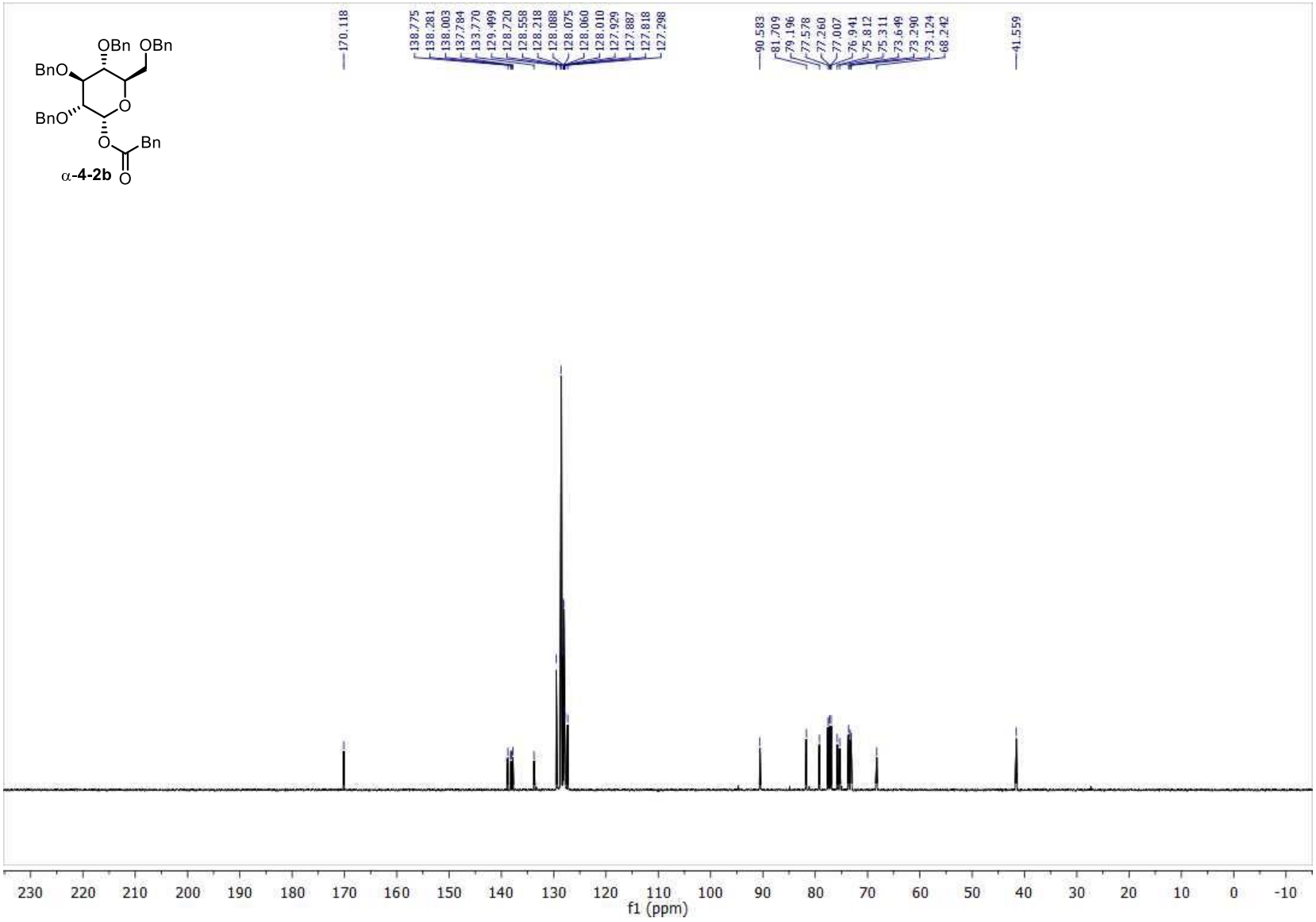

O2N
S
N
N
Ph
4-4g
8.217
8.213
8.164
8.159
8.146
8.142
7.392
7.378
7.362
7.348
7.318
7.261
6.886
6.669
5.788
5.772
5.767
5.752
4.377
4.358
4.338
3.816
3.801
3.798
3.782
0.000
0.82
0.96
5.35
1.00
1.05
1.07
1.04
f1 (ppm)

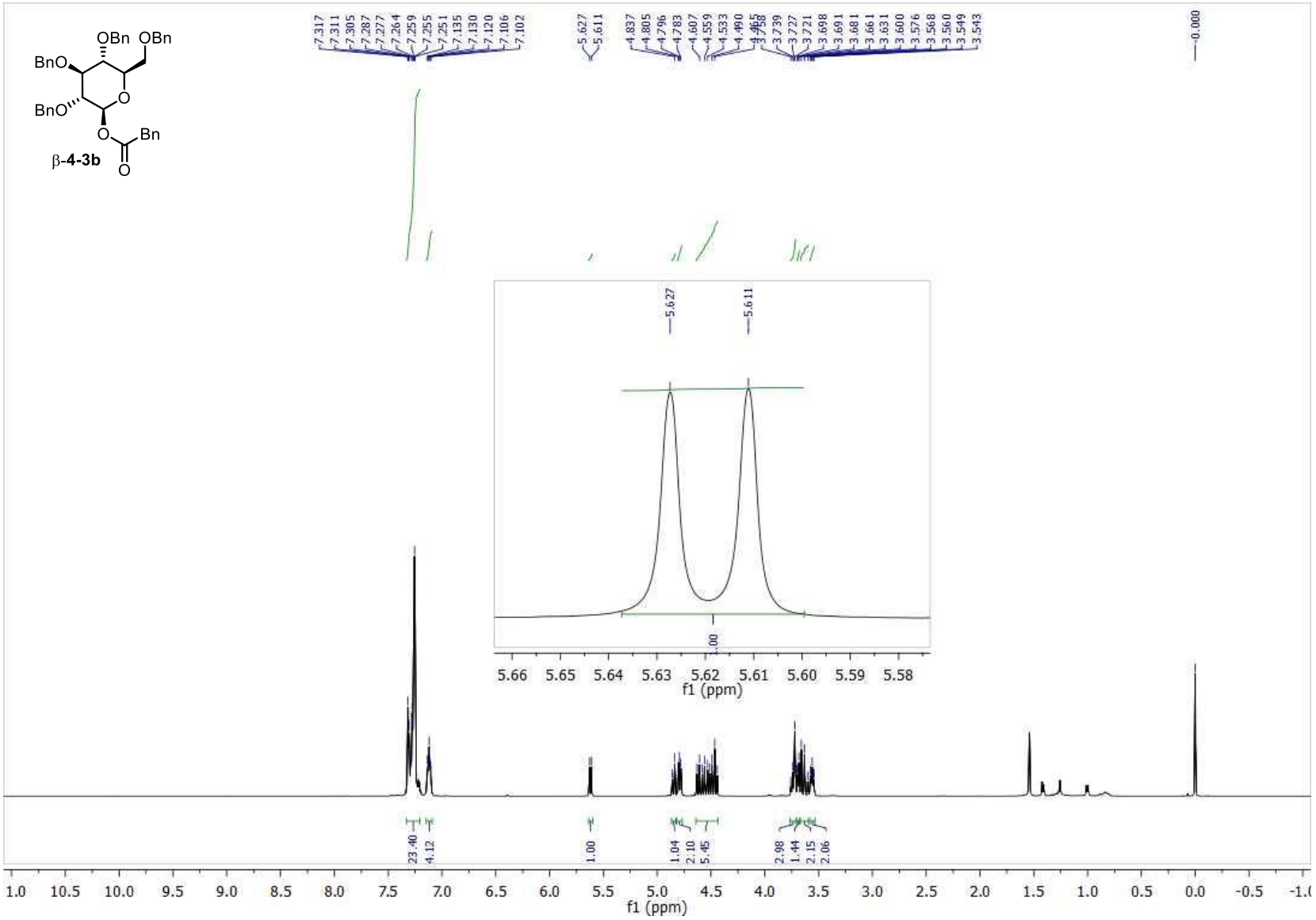

O2N
S
N
N
Ph
4-4g
165.386
142.288
142.244
141.901
129.152
128.643
128.208
126.581
124.288
119.354
107.239
77.514
77.260
77.006
76.329
52.254
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

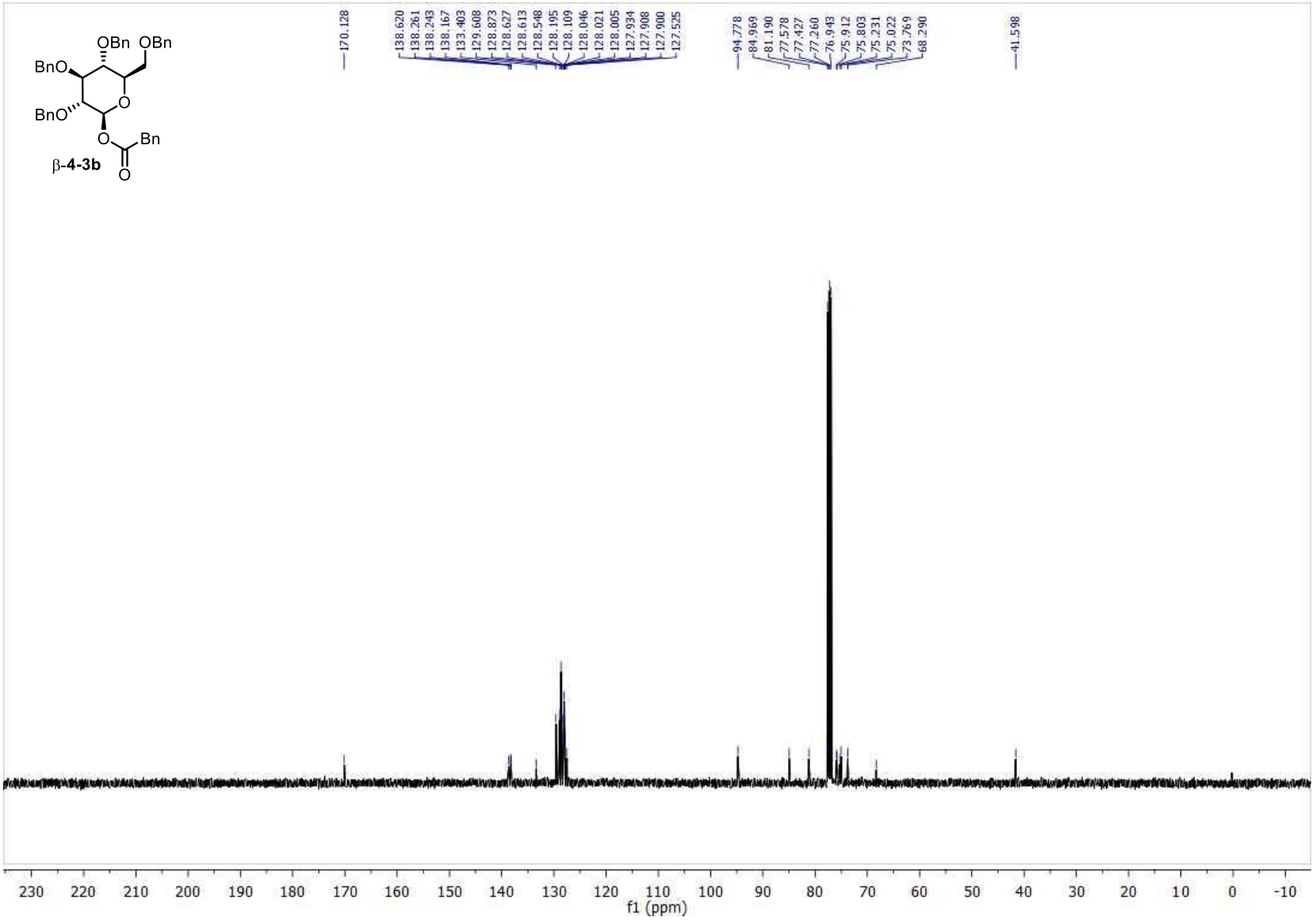

MeO
S
N
N
Ph
4-4h
7.385
7.372
7.359
7.343
7.296
7.292
7.284
7.279
7.271
7.266
7.262
7.256
6.922
6.917
6.744
6.739
6.727
6.722
6.585
6.568
5.653
5.636
5.633
5.616
4.249
4.232
4.229
4.211
3.776
3.677
3.660
3.643
0.000
3.88
0.93
0.90
1.00
0.97
0.99
1.04
3.02
1.06
f1 (ppm)

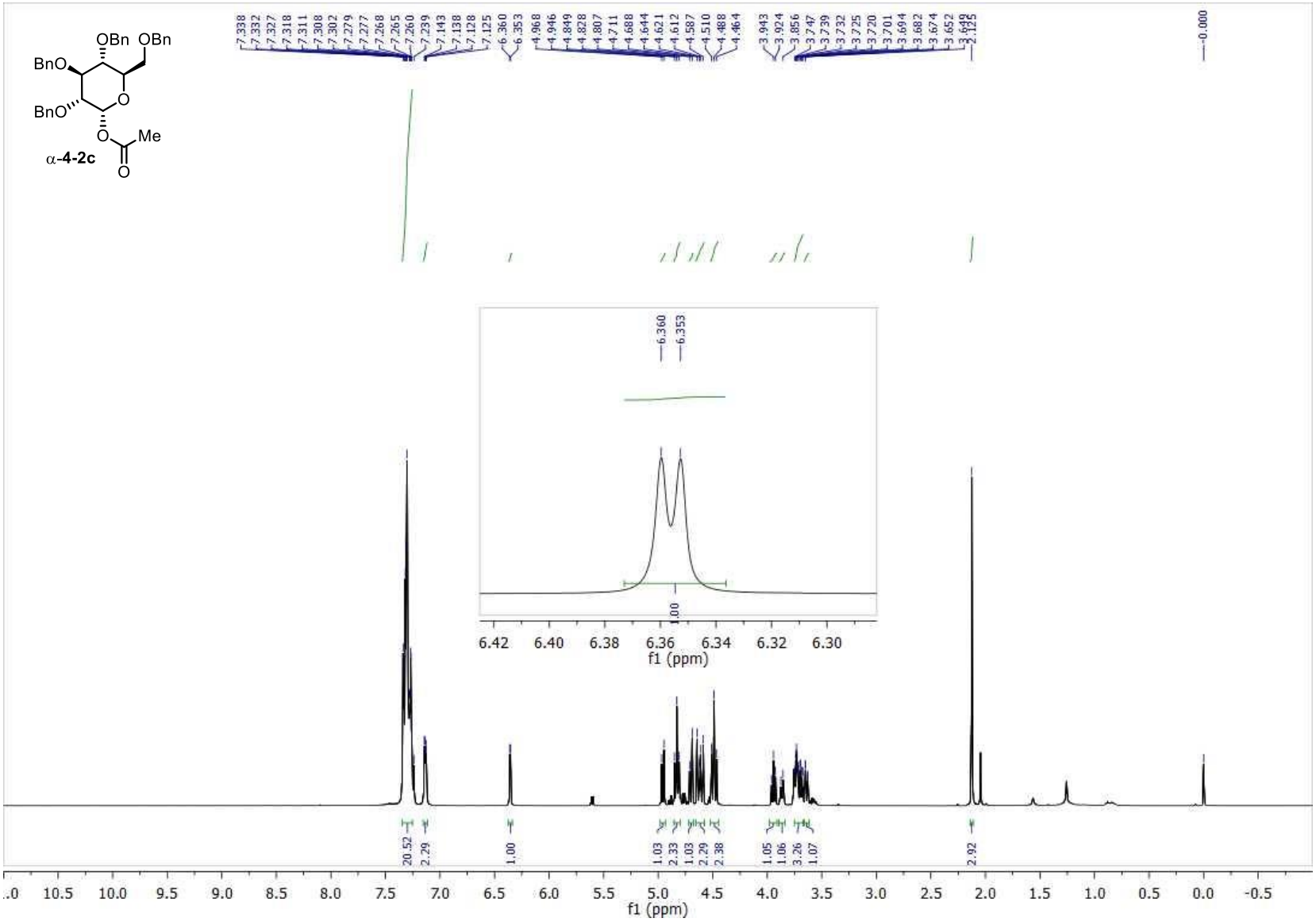

MeO
S
N
N
Ph
4-4h
167.331
155.219
143.242
131.684
128.904
128.645
127.737
126.744
112.320
109.885
108.987
77.515
77.260
77.006
75.653
56.225
53.271
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

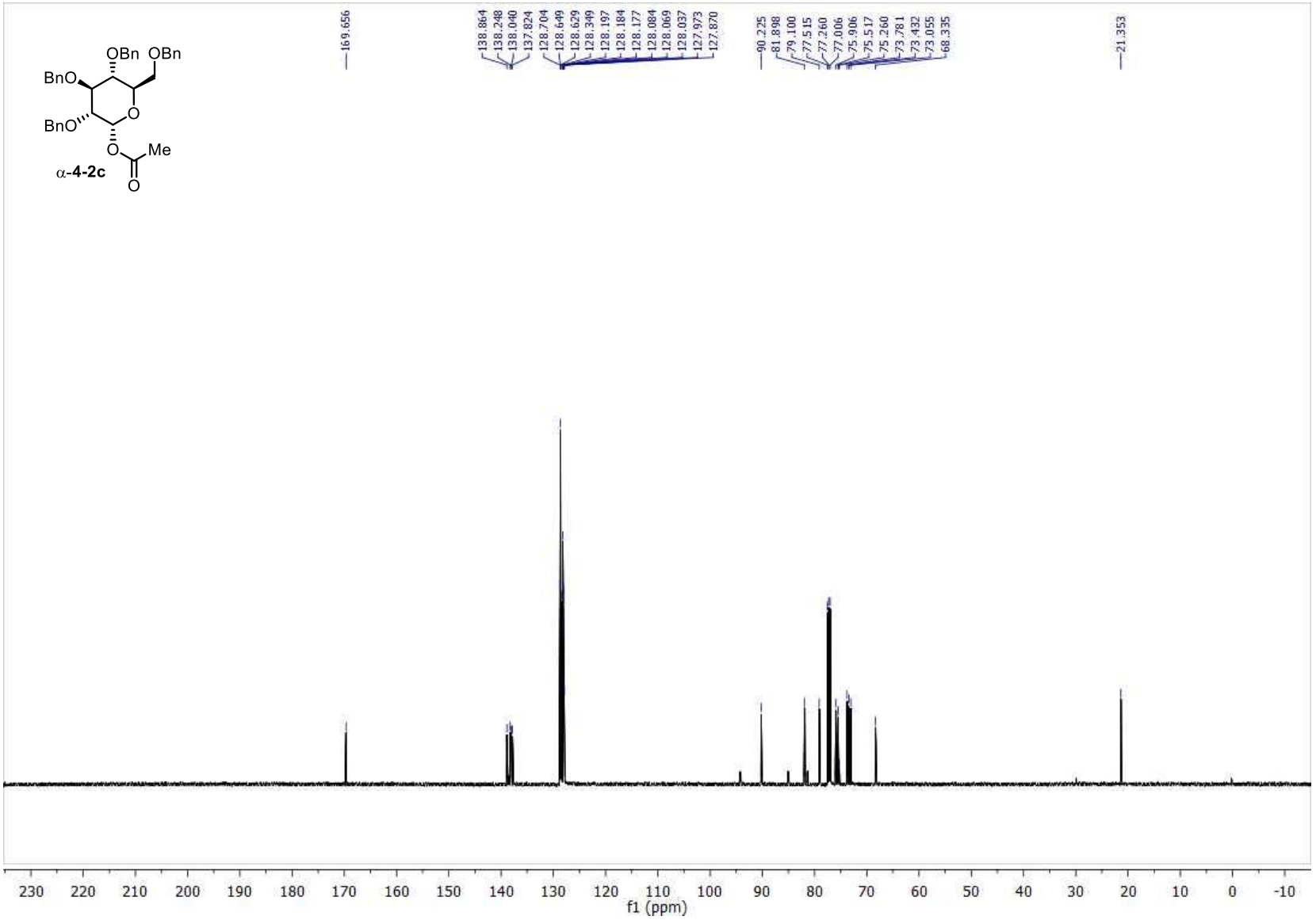

α-4-2b
f1 (ppm)
f1 (ppm)

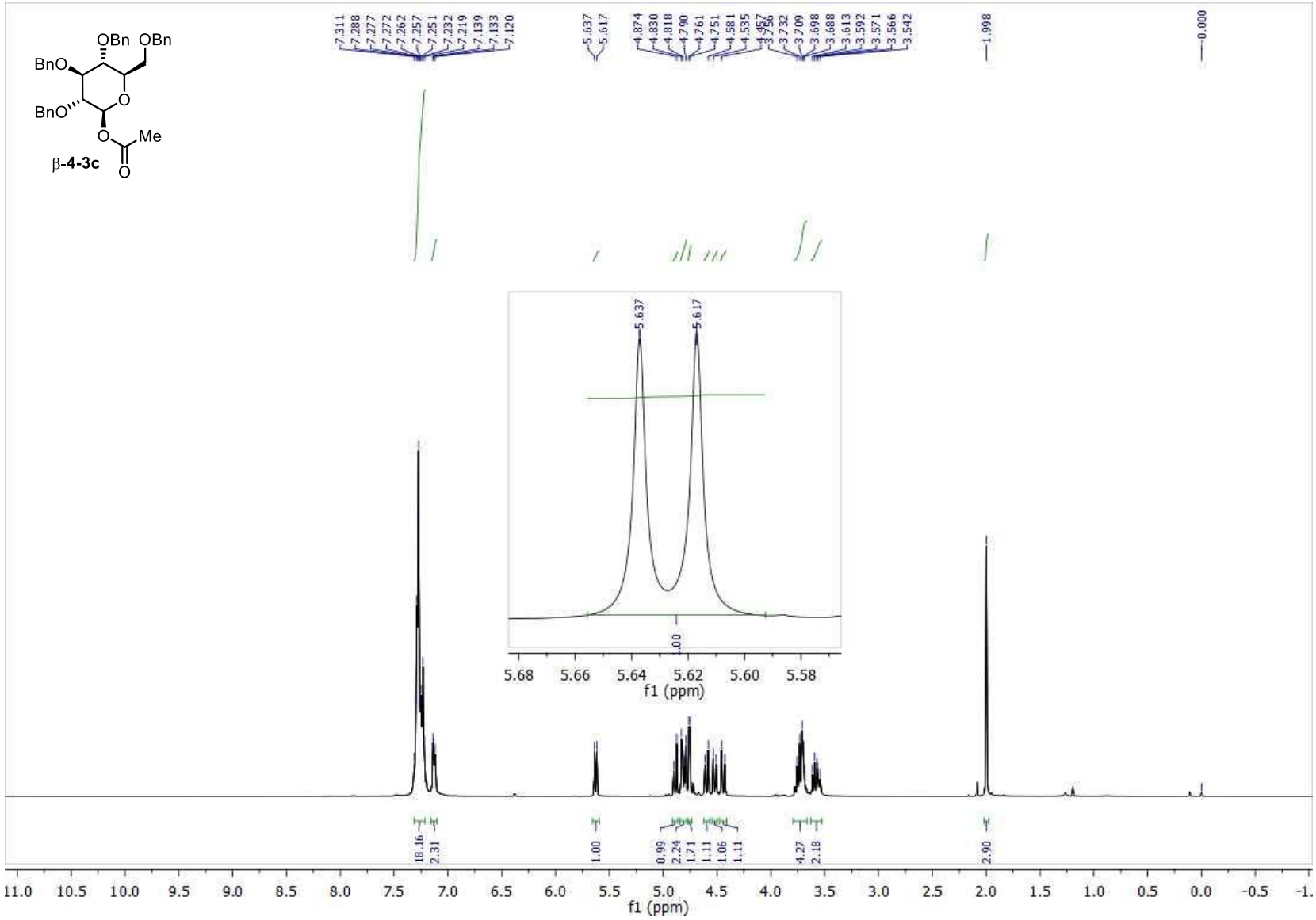

OBn OBn
BnO
BnO
O
O
Bn
O
α-4-2b
170.118
138.775
138.281
138.003
137.784
133.770
129.499
128.720
128.558
128.218
128.088
128.075
128.060
128.010
127.929
127.887
127.818
127.298
90.583
81.709
79.196
77.578
77.260
77.007
76.941
75.812
75.311
73.649
73.290
73.124
68.242
41.559
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

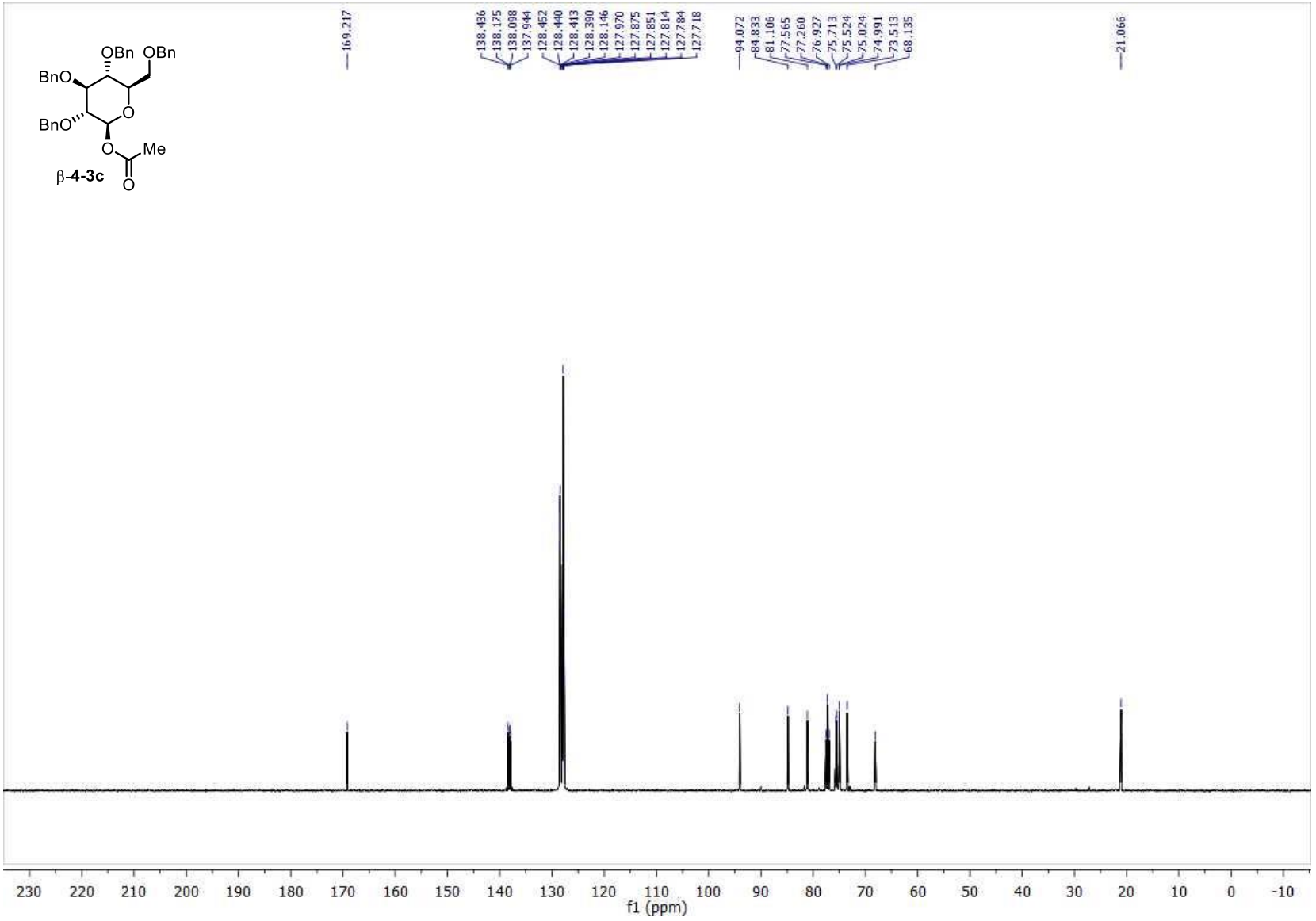

β-4-3b
7.317
7.311
7.305
7.287
7.277
7.264
7.259
7.255
7.251
7.135
7.130
7.120
7.106
7.102
5.627
5.611
4.837
4.805
4.796
4.783
4.607
4.559
4.533
4.490
3.758
3.739
3.727
3.721
3.698
3.691
3.681
3.661
3.631
3.600
3.576
3.568
3.560
3.549
3.543
0.000
5.66 5.65 5.64 5.63 5.62 5.61 5.60 5.59 5.58
f1 (ppm)
23.40
4.12
1.00
1.04
2.10
5.45
2.98
1.44
2.15
2.06
f1 (ppm)

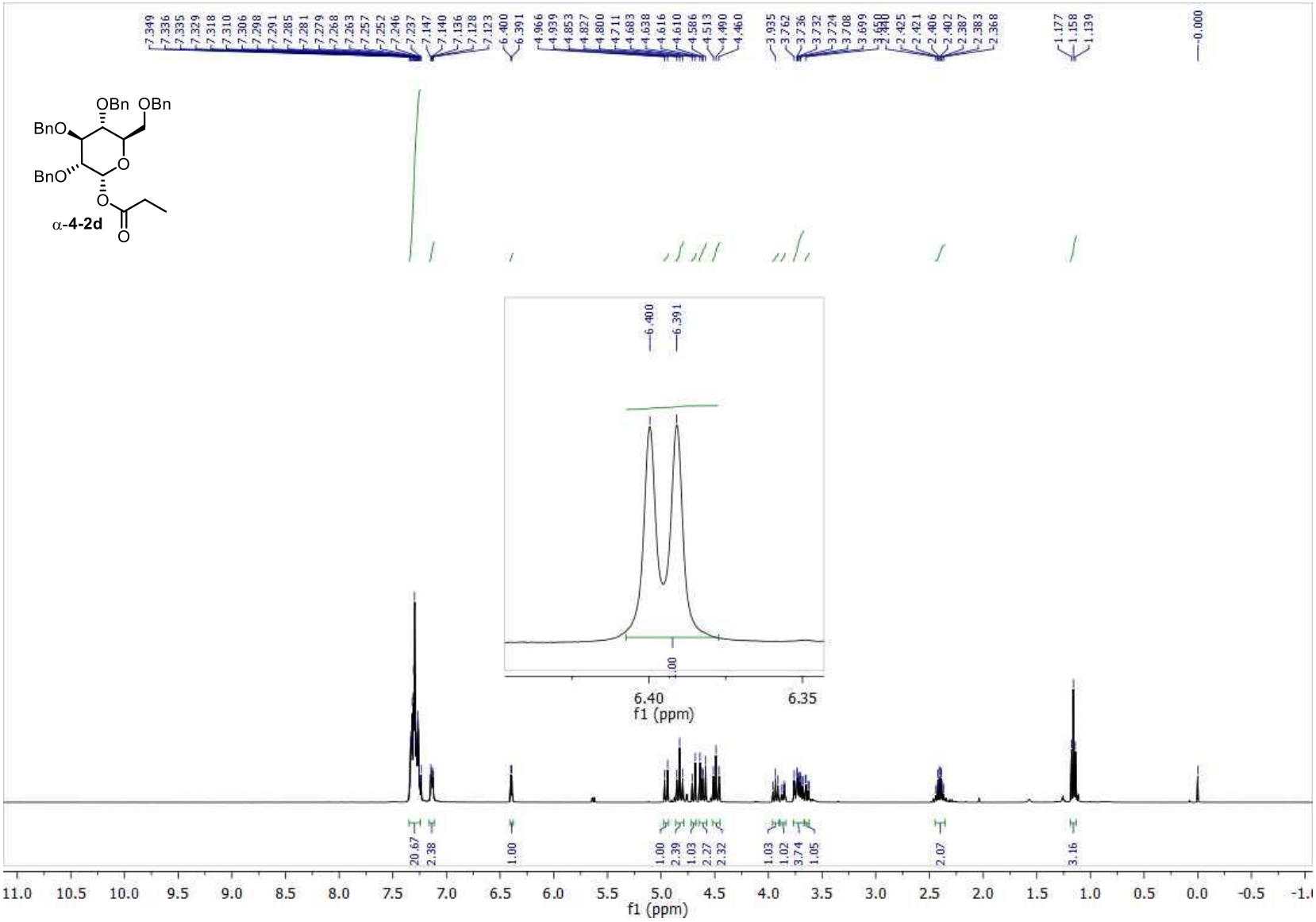

OBn OBn
BnO
BnO
O
O
Bn
O
β-4-3b
170.128
138.620
138.261
138.243
138.167
133.403
129.608
128.873
128.627
128.613
128.548
128.195
128.109
128.046
128.021
128.005
127.934
127.908
127.900
127.525
94.778
84.969
81.190
77.578
77.427
77.260
76.943
75.912
75.803
75.231
75.022
73.769
68.290
41.598
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

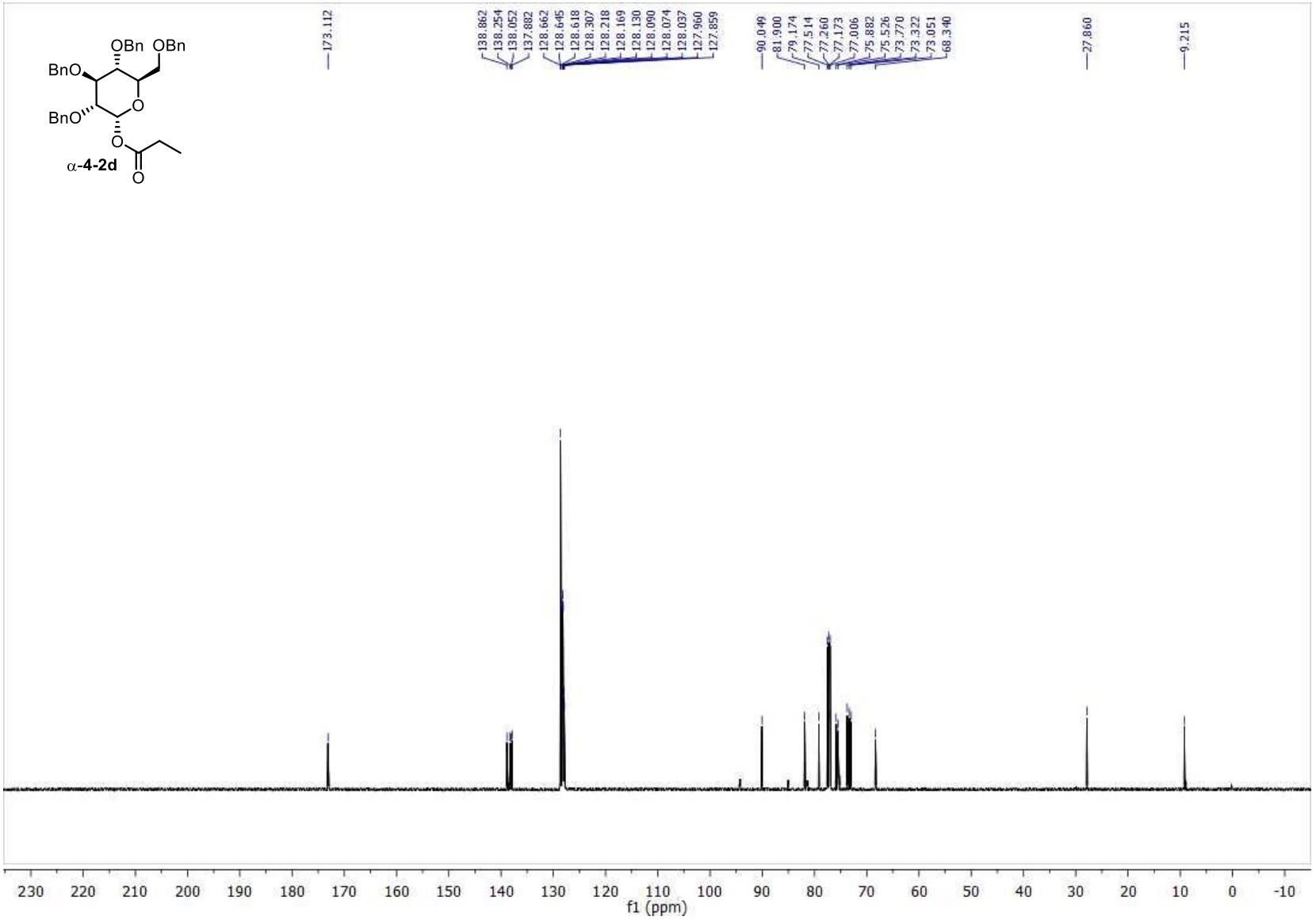

OBn OBn
BnO
BnO
O
O
Me
O
α-4-2c
7.338
7.332
7.327
7.318
7.311
7.308
7.302
7.279
7.277
7.268
7.265
7.260
7.239
7.143
7.138
7.128
7.125
6.360
6.353
4.968
4.946
4.849
4.828
4.807
4.711
4.688
4.644
4.621
4.612
4.587
4.510
4.488
4.464
3.943
3.924
3.856
3.747
3.739
3.732
3.725
3.720
3.701
3.694
3.682
3.674
3.652
3.648
2.125
-0.000
6.42
6.40
6.38
6.36
6.34
6.32
6.30
f1 (ppm)
20.52
2.29
1.00
1.03
2.33
1.03
2.29
2.38
1.05
1.06
3.26
1.07
2.92
f1 (ppm)

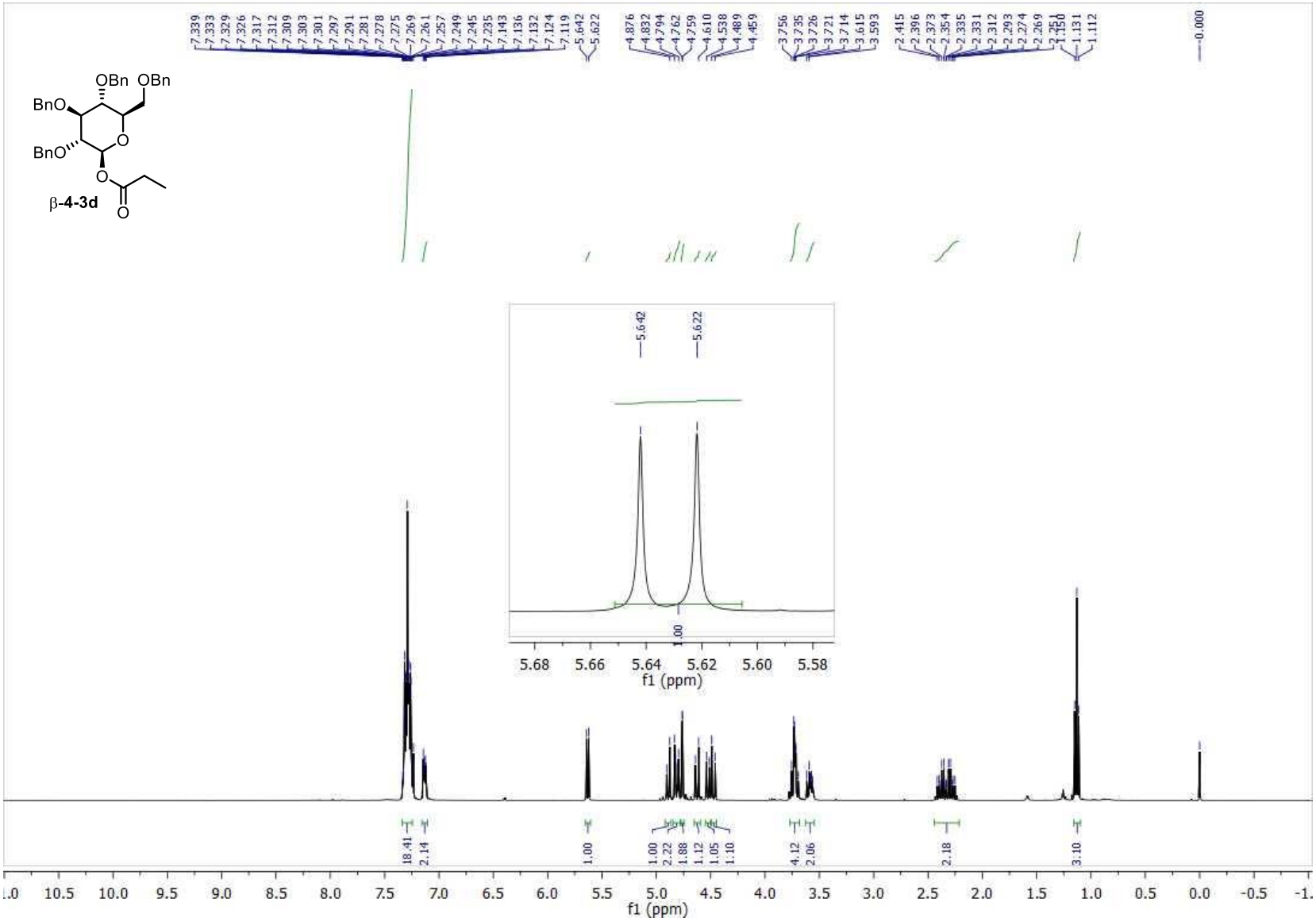

OBn
OBn
BnO
BnO
O
O
Me
O
α-4-2c
169.656
138.864
138.248
138.040
137.824
128.704
128.649
128.629
128.349
128.197
128.184
128.177
128.084
128.069
128.037
127.973
127.870
90.225
81.898
79.100
77.515
77.260
77.006
75.906
75.517
75.260
73.781
73.432
73.055
68.335
21.353
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

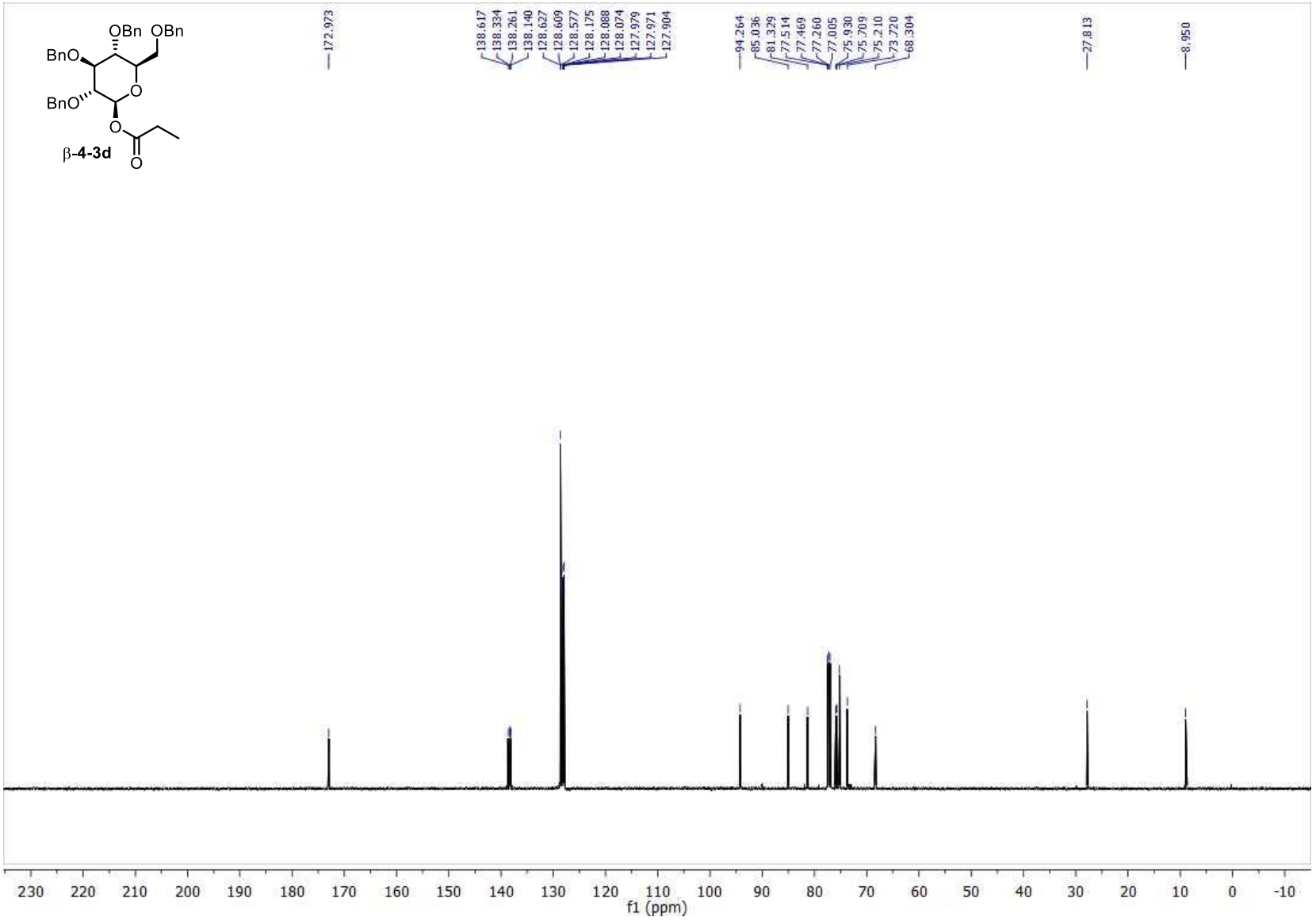

OBn OBn
BnO
BnO
O
O
Me
O
β-4-3c
7.311
7.288
7.277
7.272
7.262
7.257
7.251
7.232
7.219
7.139
7.133
7.120
5.637
5.617
4.874
4.830
4.818
4.790
4.761
4.751
4.581
4.535
3.732
3.709
3.698
3.688
3.613
3.592
3.571
3.566
3.542
1.998
0.000
5.637
5.617
1.00
5.68
5.66
5.64
5.62
5.60
5.58
f1 (ppm)
18.16
2.31
1.00
0.99
2.24
1.71
1.11
1.06
1.11
4.27
2.18
2.90
11.0
10.5
10.0
9.5
9.0
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
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

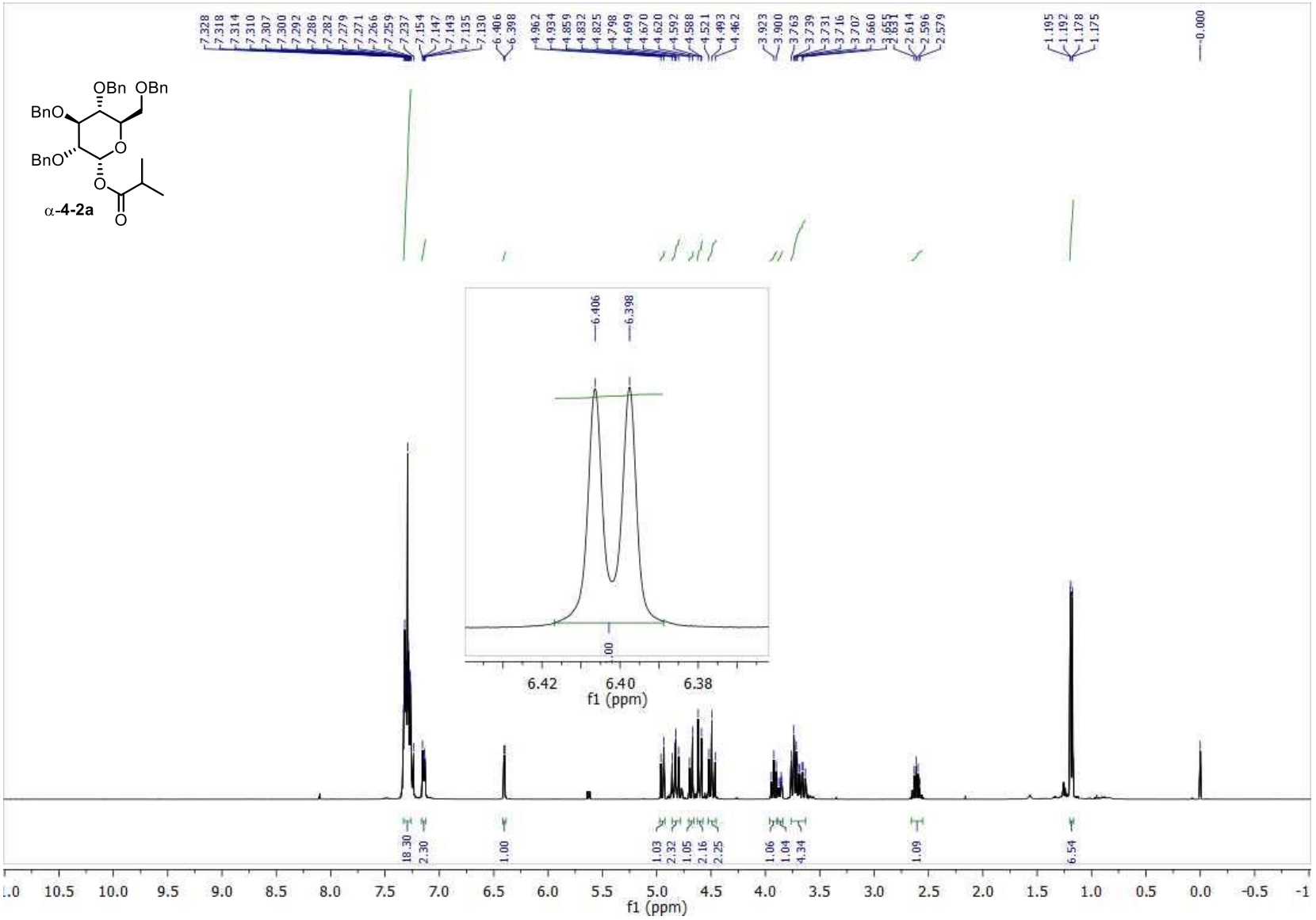

169.217
138.436
138.175
138.098
137.944
128.452
128.440
128.413
128.390
128.146
127.970
127.875
127.851
127.814
127.784
127.718
94.072
84.833
81.106
77.565
77.260
76.927
75.713
75.524
75.024
74.991
73.513
68.135
21.066
OBn
OBn
BnO
BnO
O
O
Me
O
β-4-3c
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

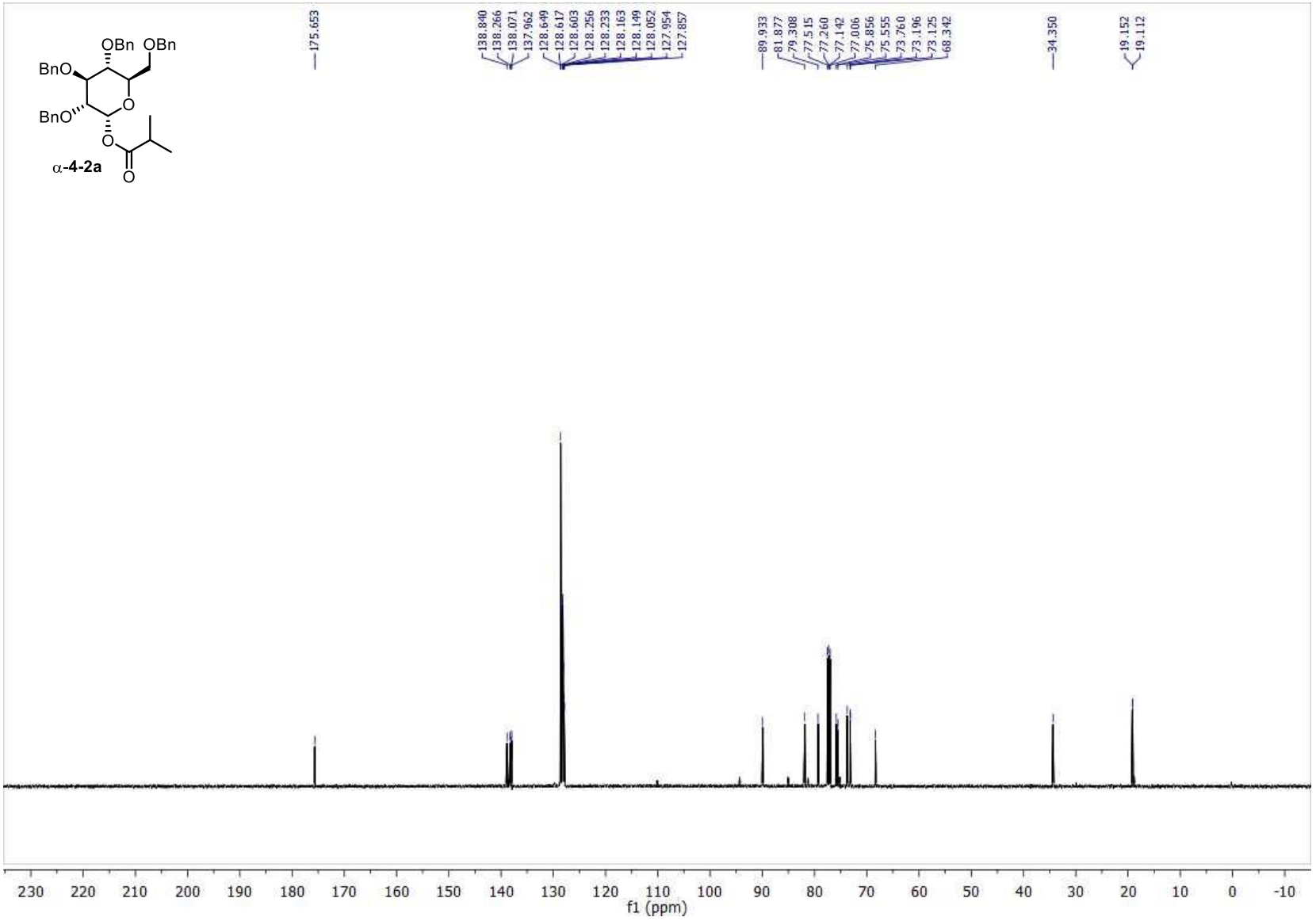

OBn OBn
BnO
BnO
O
O
α-4-2d
O
6.400
6.391
1.00
6.40
6.35
f1 (ppm)
20.67
2.38
1.00
1.00
2.39
1.03
2.27
2.32
1.03
1.02
3.74
1.05
2.07
3.16
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

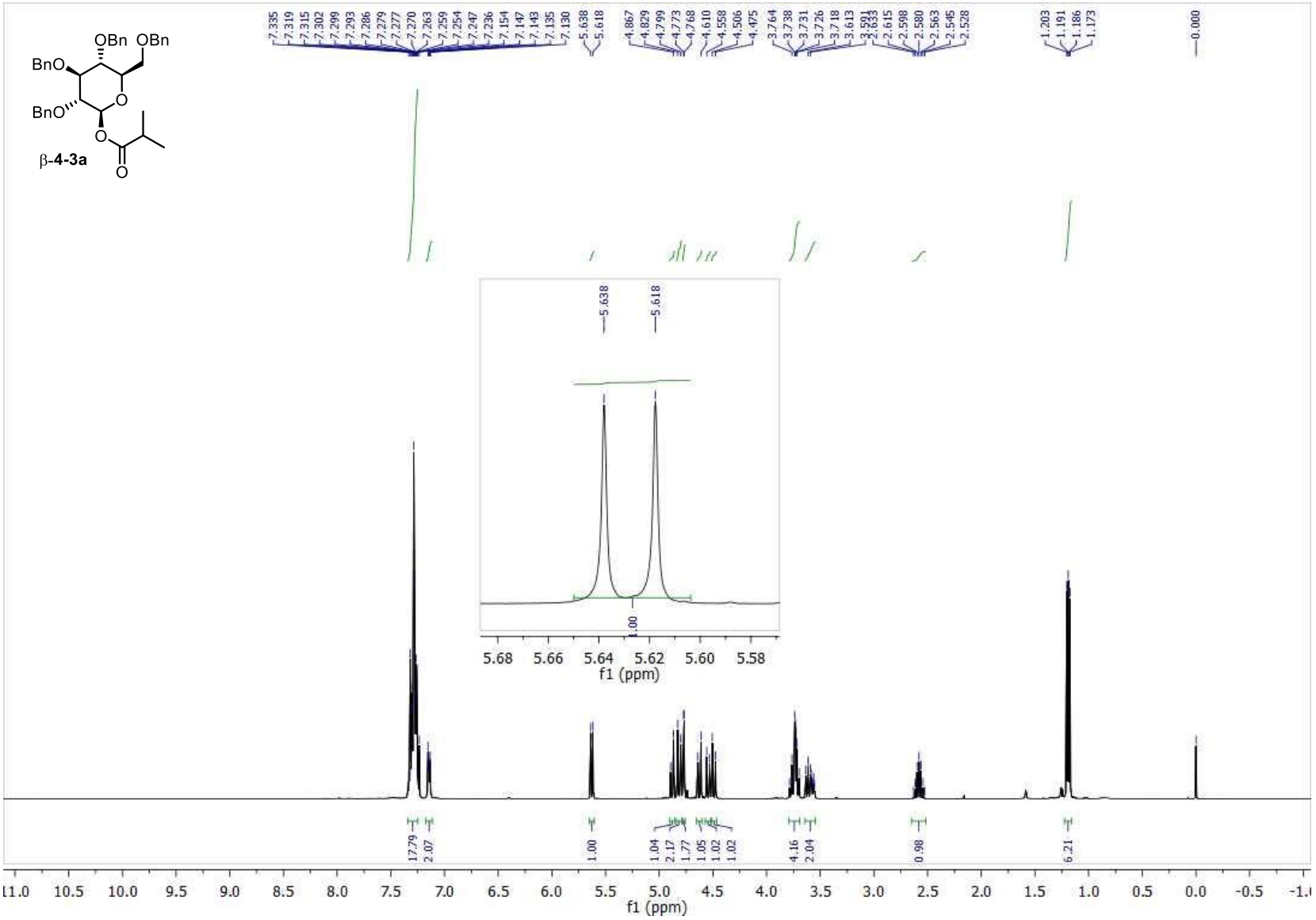

OBn OBn
BnO
BnO
O
O
O
α-4-2d
173.112
138.862
138.254
138.052
137.882
128.662
128.645
128.618
128.307
128.218
128.169
128.130
128.090
128.074
128.037
127.960
127.859
90.049
81.900
79.174
77.514
77.260
77.173
77.006
75.882
75.526
73.770
73.322
73.051
68.340
27.860
9.215
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

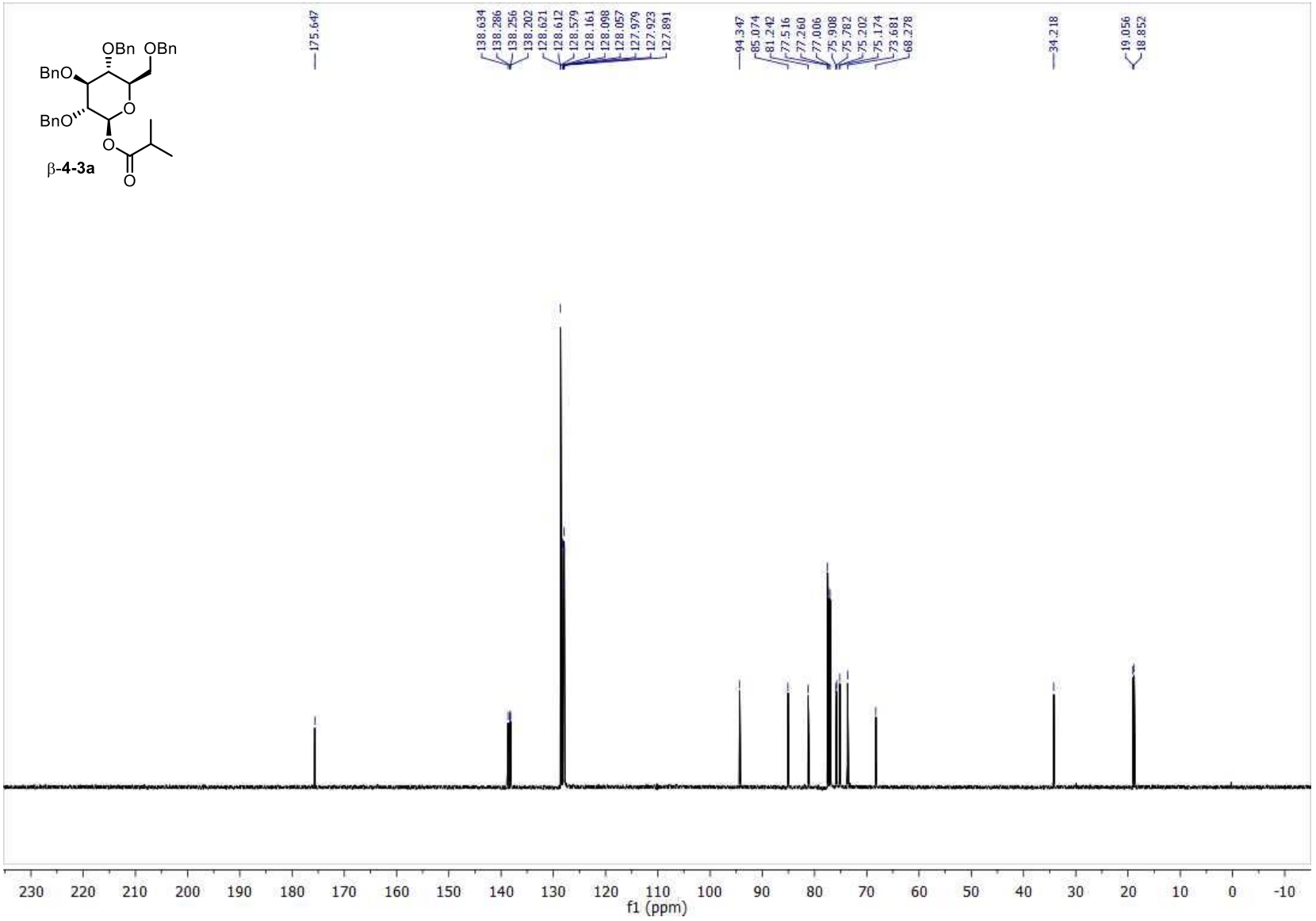

OBn OBn
BnO
BnO
O
O
β-4-3d
O
7.339
7.333
7.329
7.326
7.317
7.312
7.309
7.303
7.301
7.297
7.291
7.281
7.278
7.275
7.269
7.261
7.257
7.249
7.245
7.235
7.143
7.136
7.132
7.124
7.119
5.642
5.622
4.876
4.832
4.794
4.762
4.759
4.610
4.538
4.489
4.459
3.756
3.735
3.726
3.721
3.714
3.615
3.593
2.415
2.396
2.373
2.354
2.335
2.331
2.312
2.293
2.274
2.269
1.150
1.131
1.112
0.000
5.642
5.622
1.00
5.68
5.66
5.64
5.62
5.60
5.58
f1 (ppm)
18.41
2.14
1.00
1.00
2.22
1.88
1.12
1.05
1.10
4.12
2.06
2.18
3.10
10.5
10.0
9.5
9.0
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
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

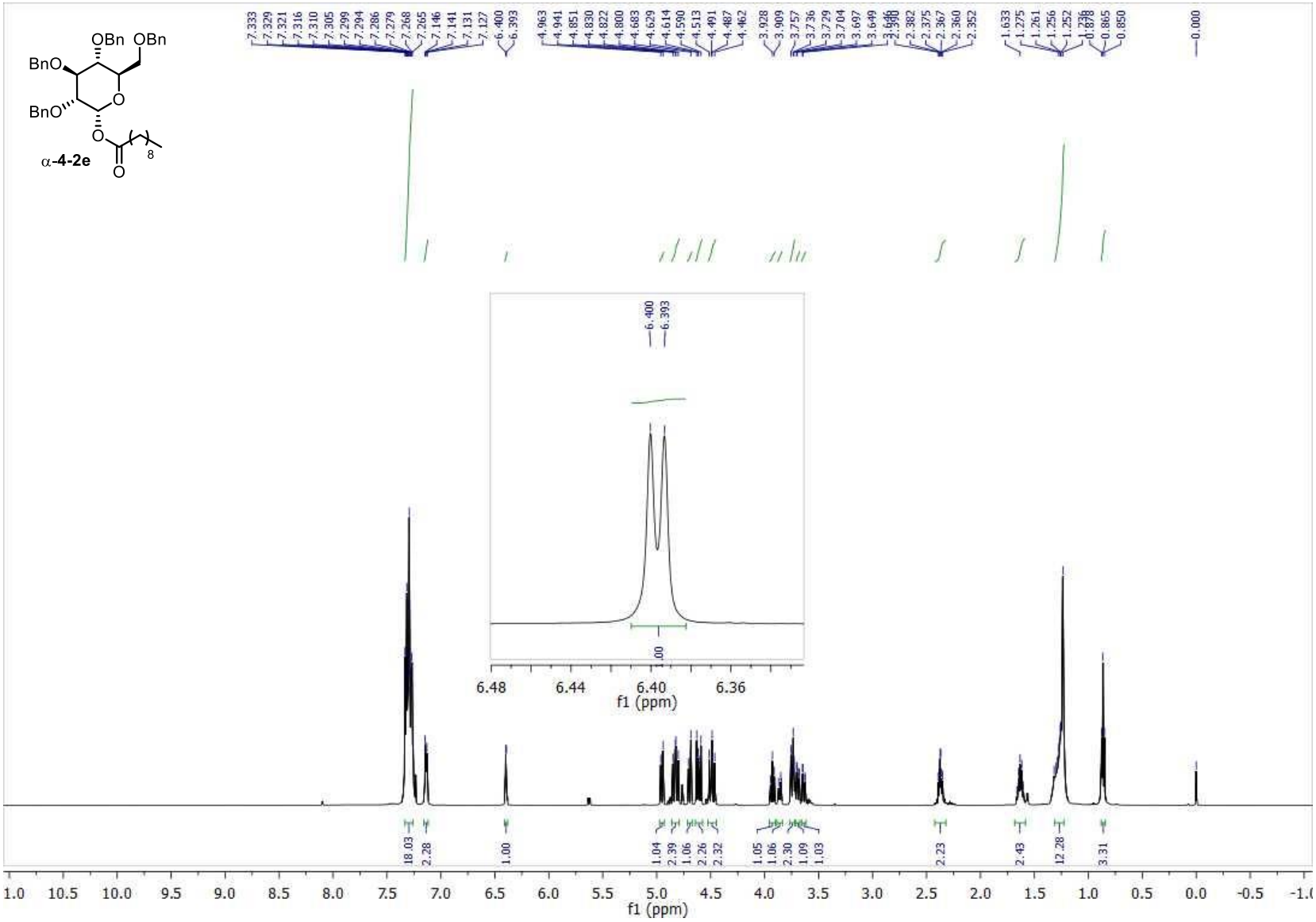

OBn
OBn
BnO
BnO
O
O
O
β-4-3d
172.973
138.617
138.334
138.261
138.140
128.627
128.609
128.577
128.175
128.088
128.074
127.979
127.971
127.904
94.264
85.036
81.329
77.514
77.469
77.260
77.005
75.930
75.709
75.210
73.720
68.304
27.813
8.950
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

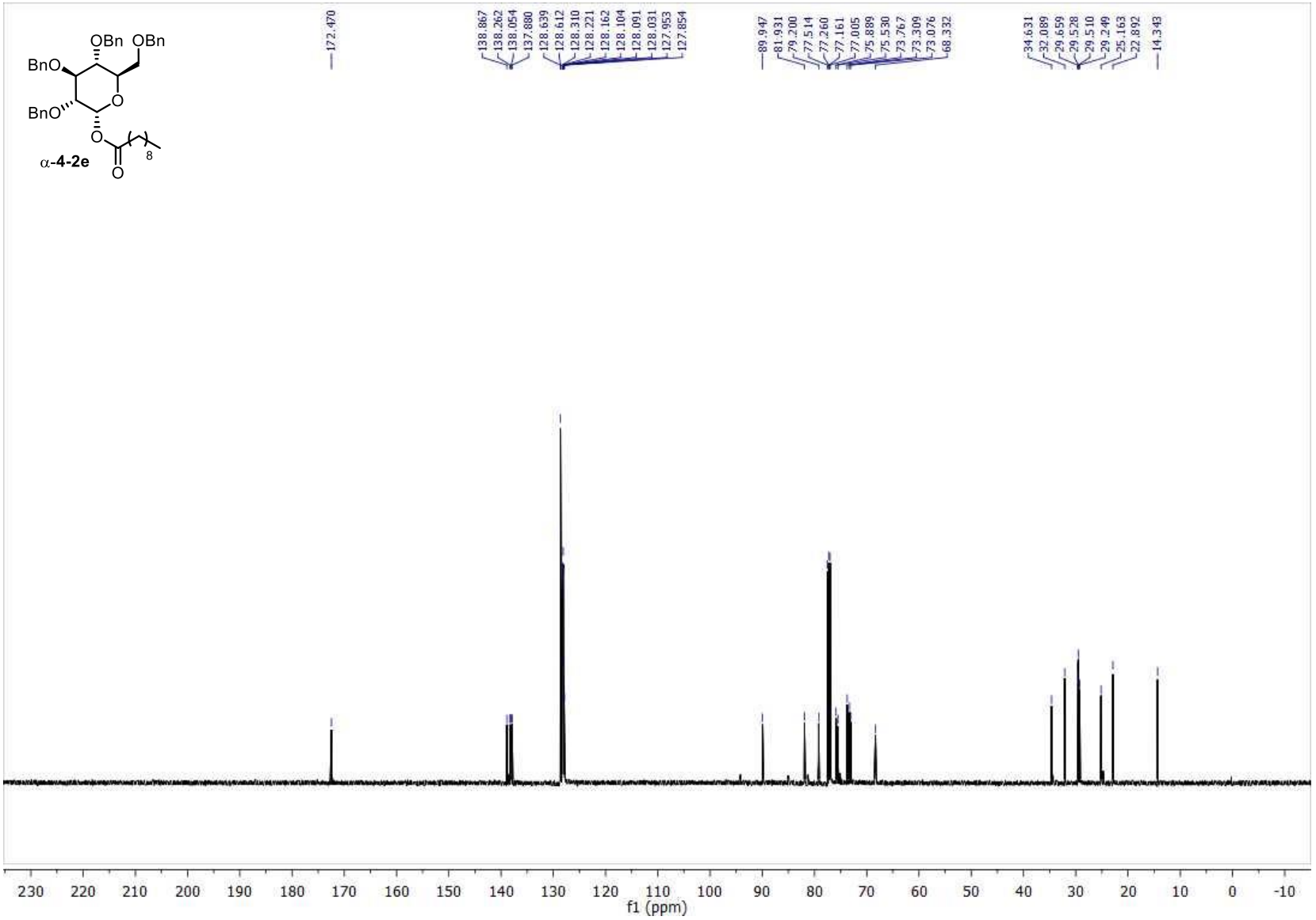

OBn OBn
BnO
BnO
O
O
O
α-4-2a
7.328 7.318 7.314 7.310 7.307 7.300 7.292 7.286 7.282 7.279 7.271 7.266 7.259 7.237 7.154 7.147 7.143 7.135 7.130 6.406 6.398
4.962 4.934 4.859 4.832 4.825 4.798 4.699 4.670 4.620 4.592 4.588 4.521 4.493 4.462
3.923 3.900 3.763 3.739 3.731 3.716 3.707 3.660 3.655 3.631
2.614 2.596 2.579
1.195 1.192 1.178 1.175
0.000
6.406
6.398
1.00
6.42 6.40 6.38
f1 (ppm)
18.30 2.30 1.00 1.03 2.32 1.05 2.16 2.25 1.06 1.04 4.34 1.09 6.54
10.5 10.0 9.5 9.0 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 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

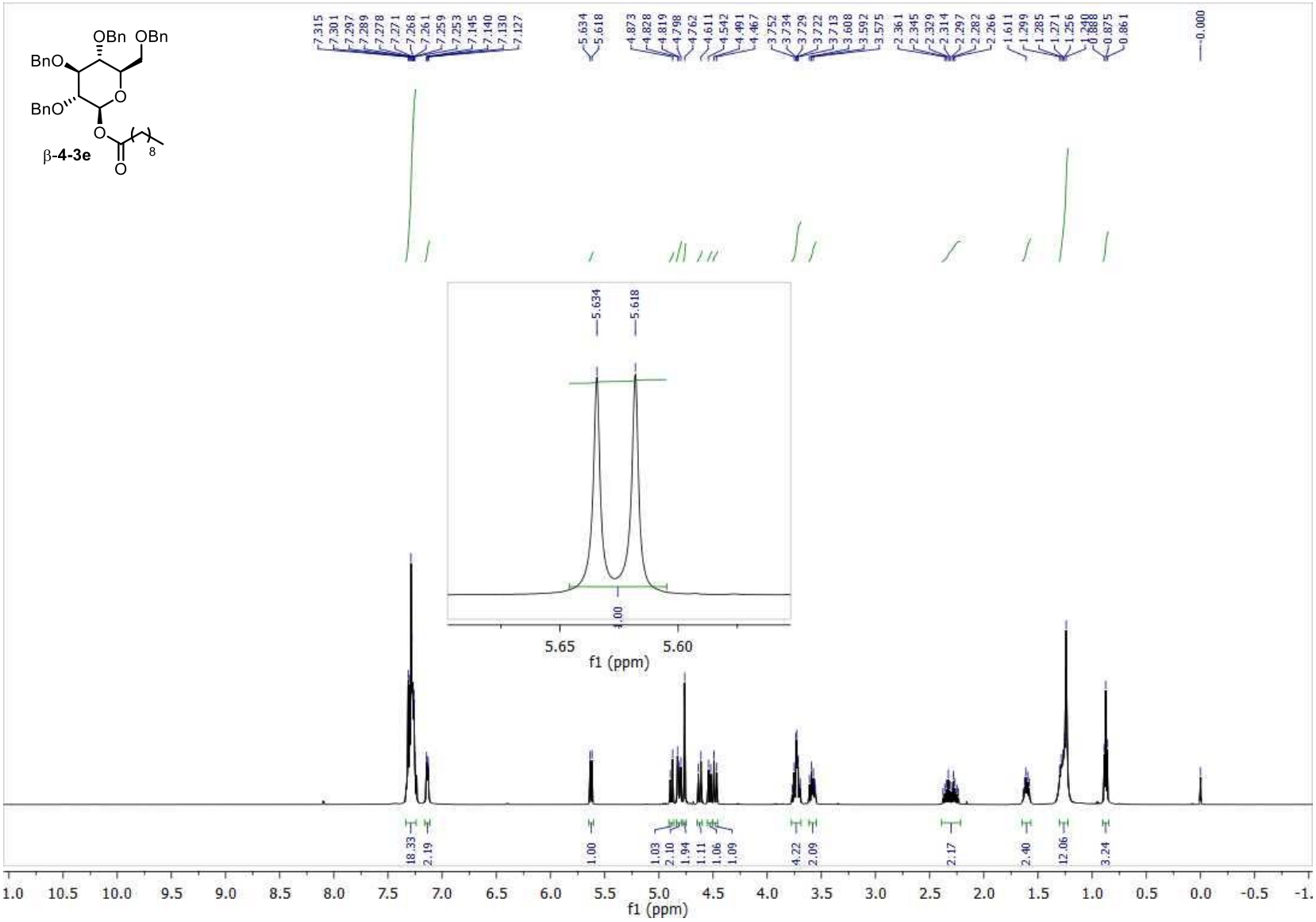

OBn OBn
BnO
BnO
O
O
O
α-4-2a
175.653
138.840
138.266
138.071
137.962
128.649
128.617
128.603
128.256
128.233
128.163
128.149
128.052
127.954
127.857
89.933
81.877
79.308
77.515
77.260
77.142
77.006
75.856
75.555
73.760
73.196
73.125
68.342
34.350
19.152
19.112
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

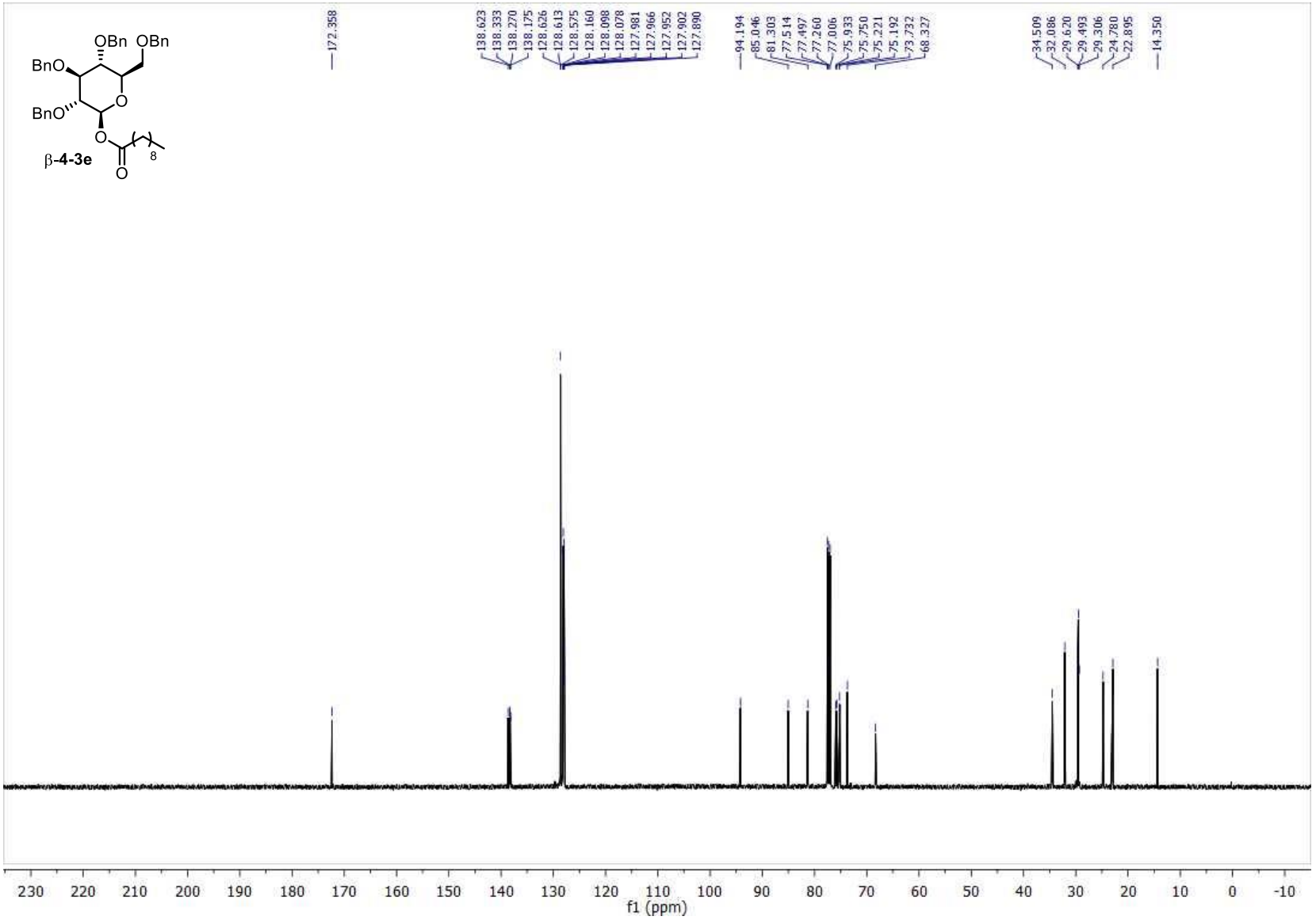

OBn OBn
BnO
BnO
O
O
O
β-4-3a
7.335 7.319 7.315 7.302 7.299 7.293 7.286 7.279 7.277 7.270 7.263 7.259 7.254 7.247 7.236 7.154 7.147 7.143 7.135 7.130 5.638 5.618 4.867 4.829 4.799 4.773 4.768 4.610 4.558 4.506 4.475 3.764 3.738 3.731 3.726 3.718 3.613 3.591 2.633 2.615 2.598 2.580 2.563 2.545 2.528 1.203 1.191 1.186 1.173 0.000
5.638
5.618
1.00
5.68 5.66 5.64 5.62 5.60 5.58
f1 (ppm)
17.79 2.07 1.00 1.04 2.17 1.77 1.05 1.02 1.02 4.16 2.04 0.98 6.21
11.0 10.5 10.0 9.5 9.0 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 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

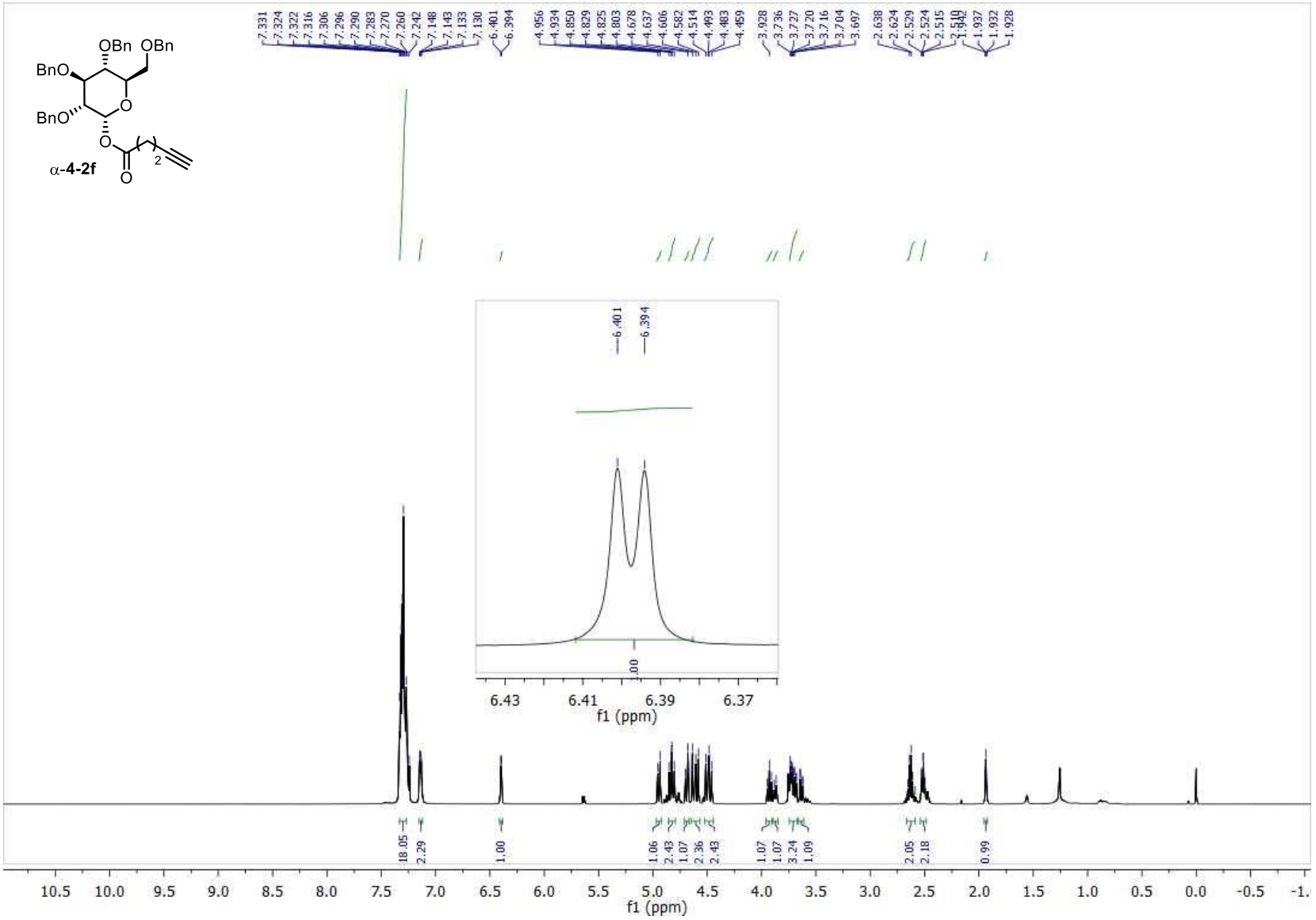

OBn
OBn
BnO
BnO
O
O
O
β-4-3a
175.647
138.634
138.286
138.256
138.202
128.621
128.612
128.579
128.161
128.098
128.057
127.979
127.923
127.891
94.347
85.074
81.242
77.516
77.260
77.006
75.908
75.782
75.202
75.174
73.681
68.278
34.218
19.056
18.852
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

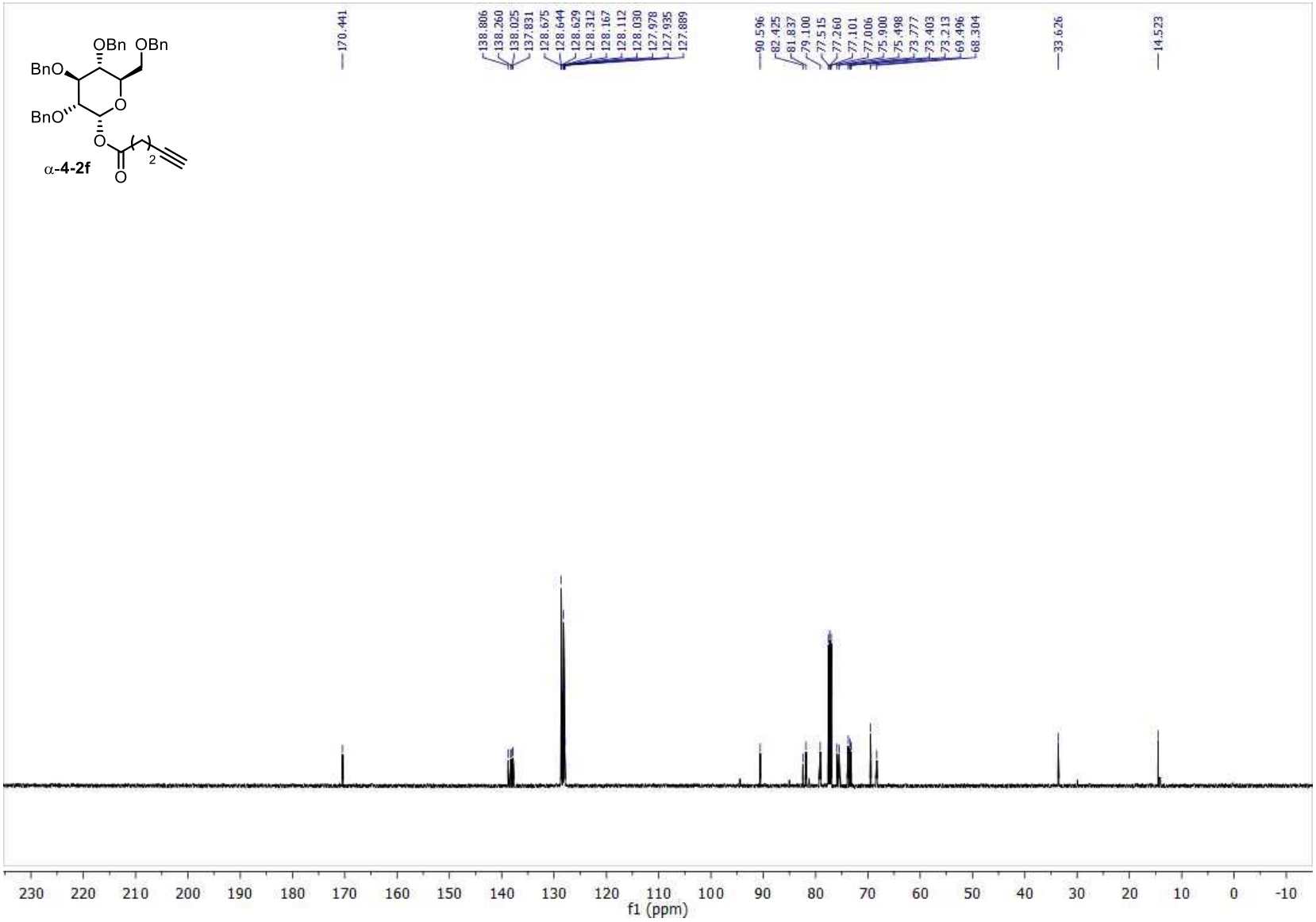

OBn OBn
BnO
BnO
O
O
8
O
α-4-2e
f1 (ppm)

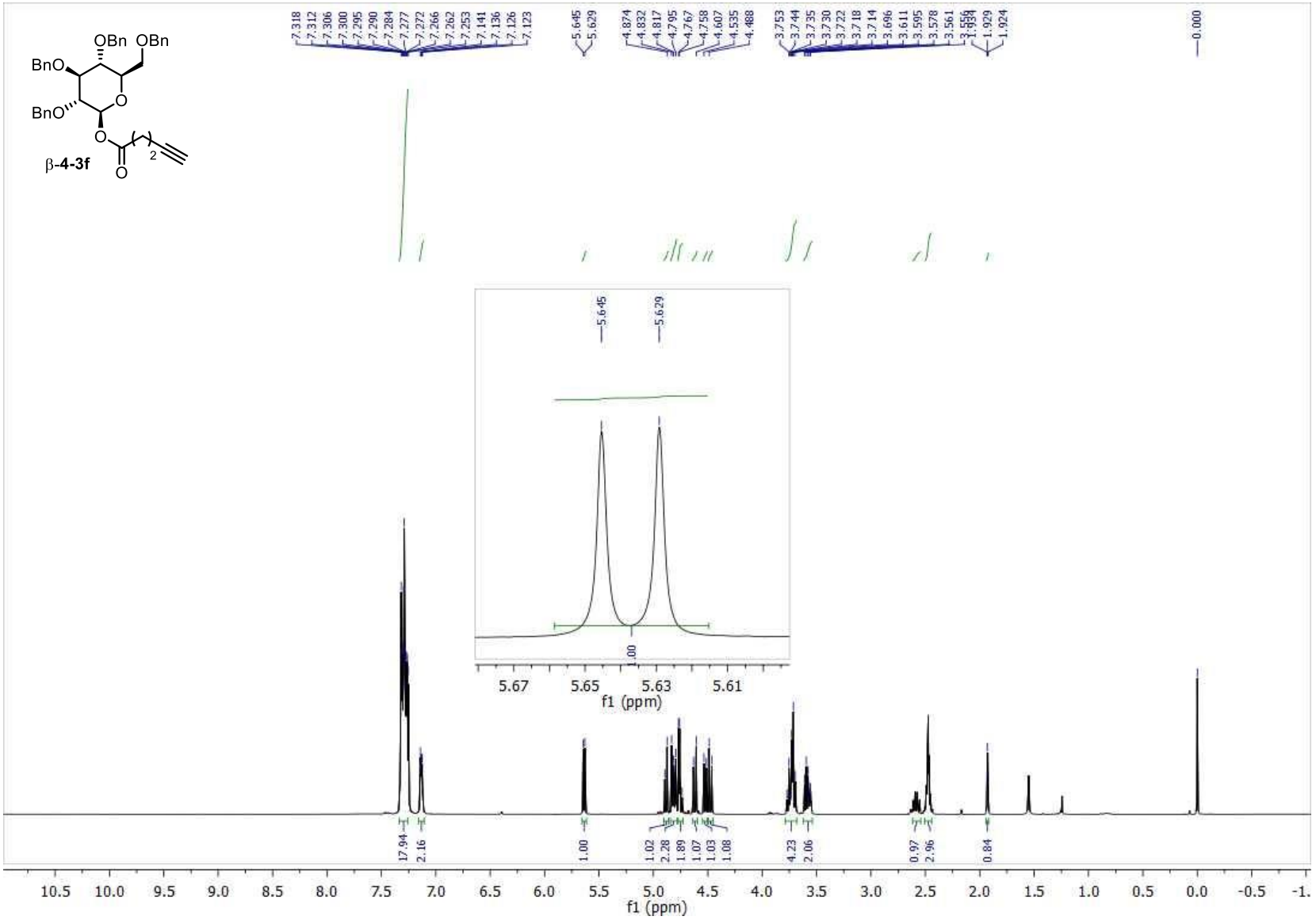

OBn OBn
BnO
BnO
O
O
8
α-4-2e
172.470
138.867
138.262
138.054
137.880
128.639
128.612
128.310
128.221
128.162
128.104
128.091
128.031
127.953
127.854
89.947
81.931
79.200
77.514
77.260
77.161
77.005
75.889
75.530
73.767
73.309
73.076
68.332
34.631
32.089
29.659
29.528
29.510
29.249
25.163
22.892
14.343
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

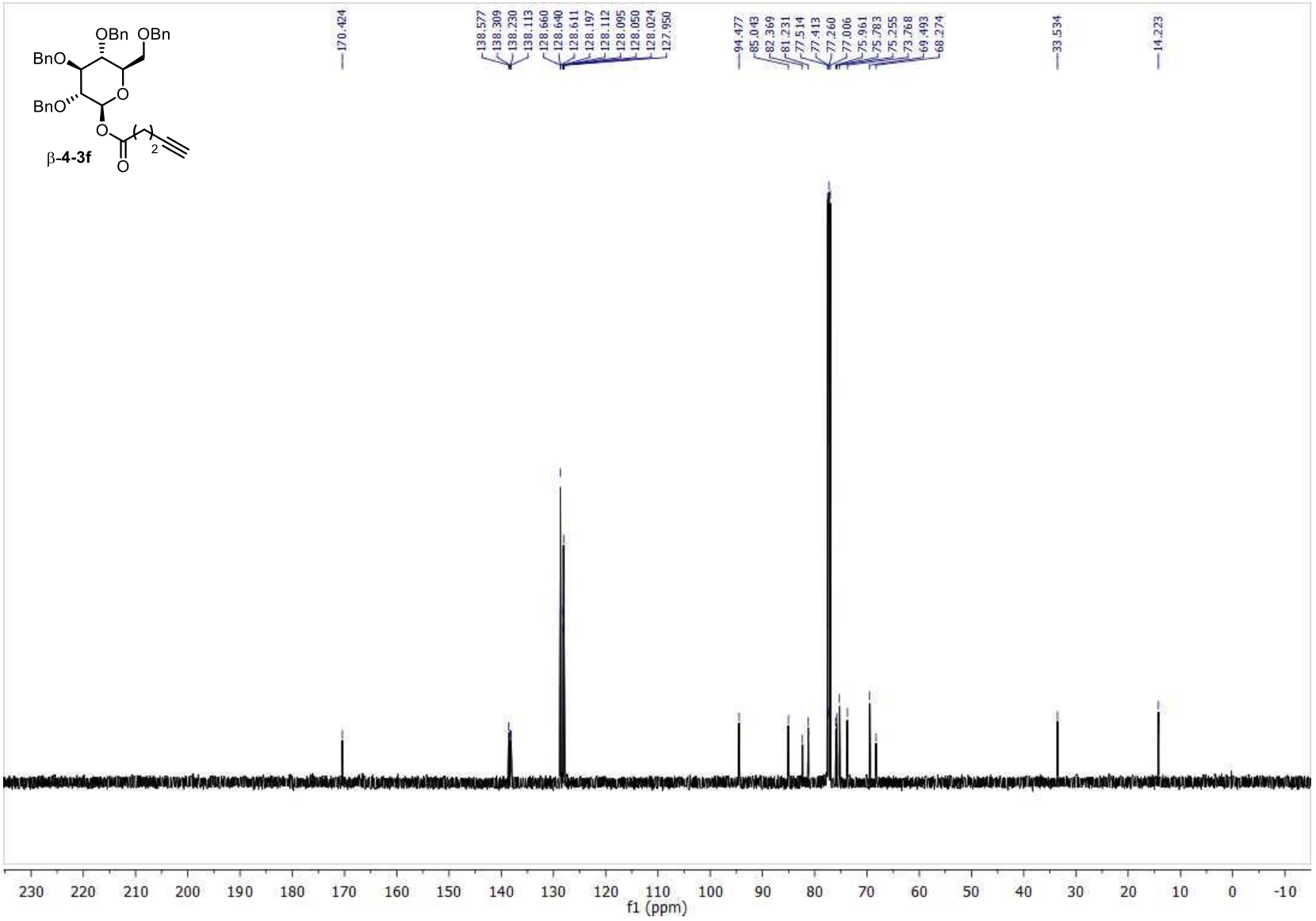

β-4-3e
5.634
5.618
5.65
5.60
f1 (ppm)
f1 (ppm)

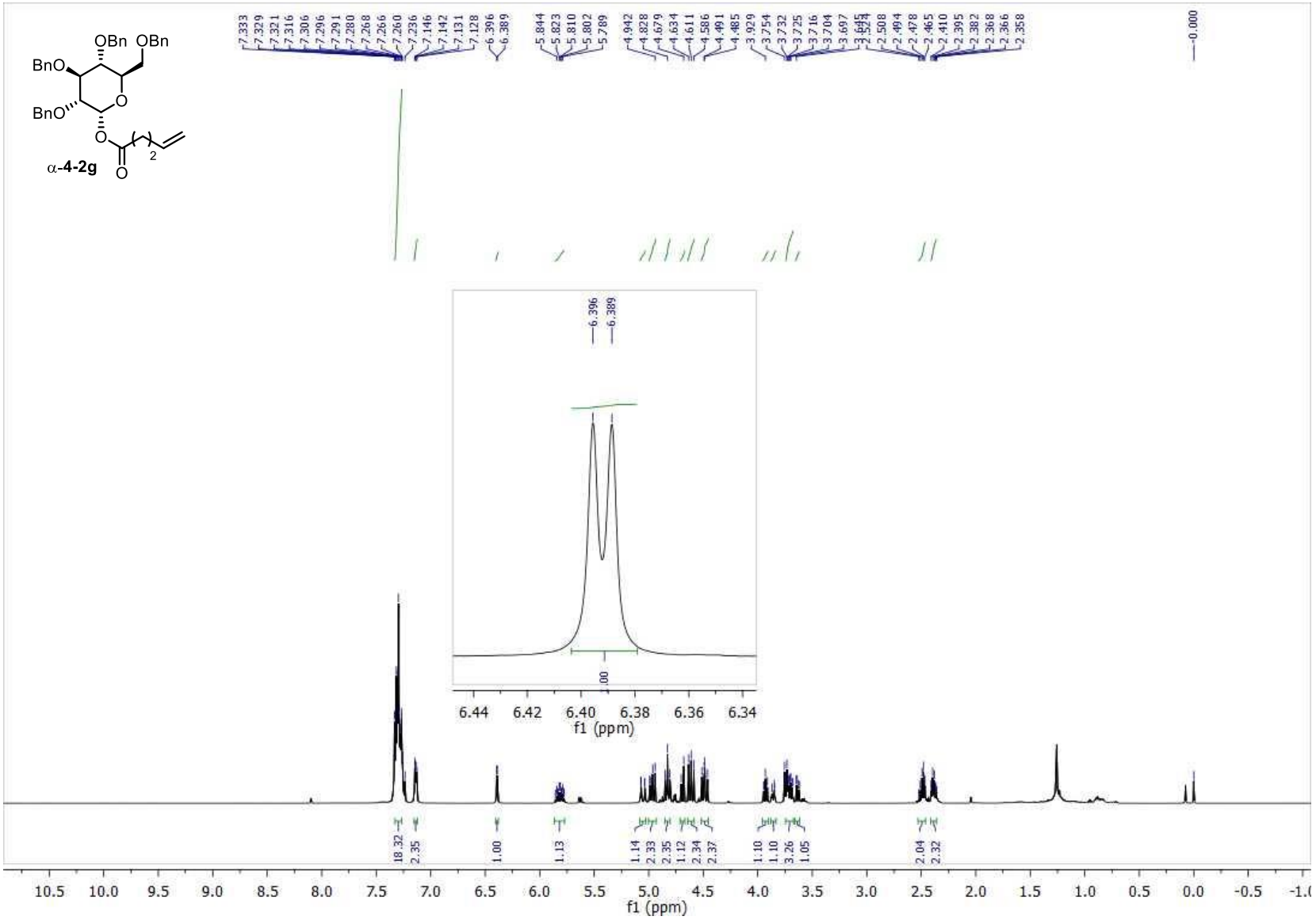

OBn
OBn
BnO
BnO
O
O
O
8
β-4-3e
172.358
138.623
138.333
138.270
138.175
128.626
128.613
128.575
128.160
128.098
128.078
127.981
127.966
127.952
127.902
127.890
94.194
85.046
81.303
77.514
77.497
77.260
77.006
75.933
75.750
75.221
75.192
73.732
68.327
34.509
32.086
29.620
29.493
29.306
24.780
22.895
14.350
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

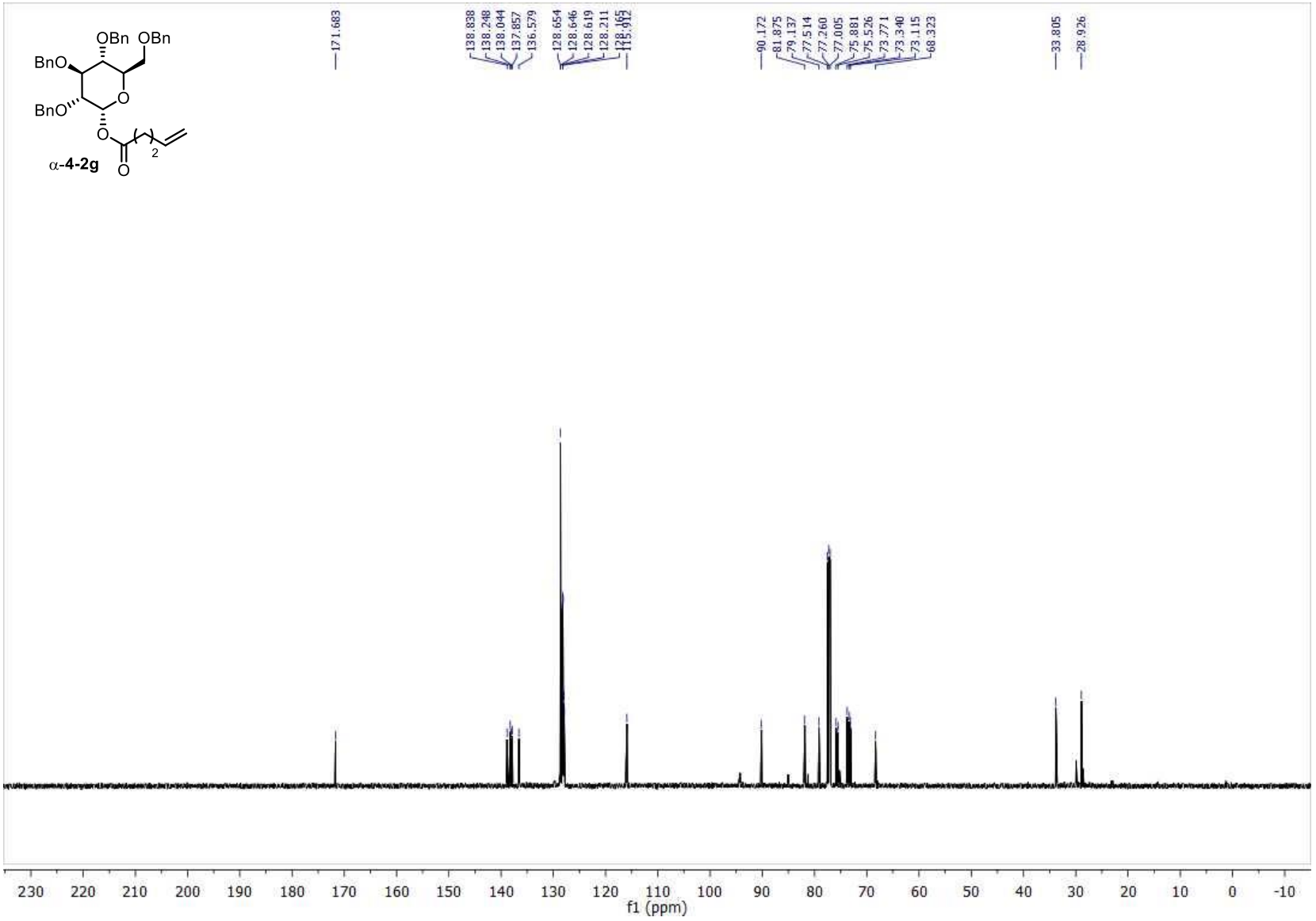

OBn OBn
BnO
BnO
O
O
2
O
α-4-2f
7.331 7.324 7.322 7.316 7.306 7.296 7.290 7.283 7.270 7.260 7.242 7.148 7.143 7.133 7.130 6.401 6.394
4.956 4.934 4.850 4.829 4.825 4.803 4.678 4.637 4.606 4.582 4.514 4.493 4.483 4.459
3.928 3.736 3.727 3.720 3.716 3.704 3.697
2.638 2.624 2.529 2.524 2.515 1.937 1.932 1.928
6.401
6.394
1.00
6.43 6.41 6.39 6.37
f1 (ppm)
18.05 2.29 1.00 1.06 2.43 1.07 2.36 2.43 1.07 1.07 3.24 1.09 2.05 2.18 0.99
10.5 10.0 9.5 9.0 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 1.5 1.0 0.5 0.0 -0.5 -1.
f1 (ppm)

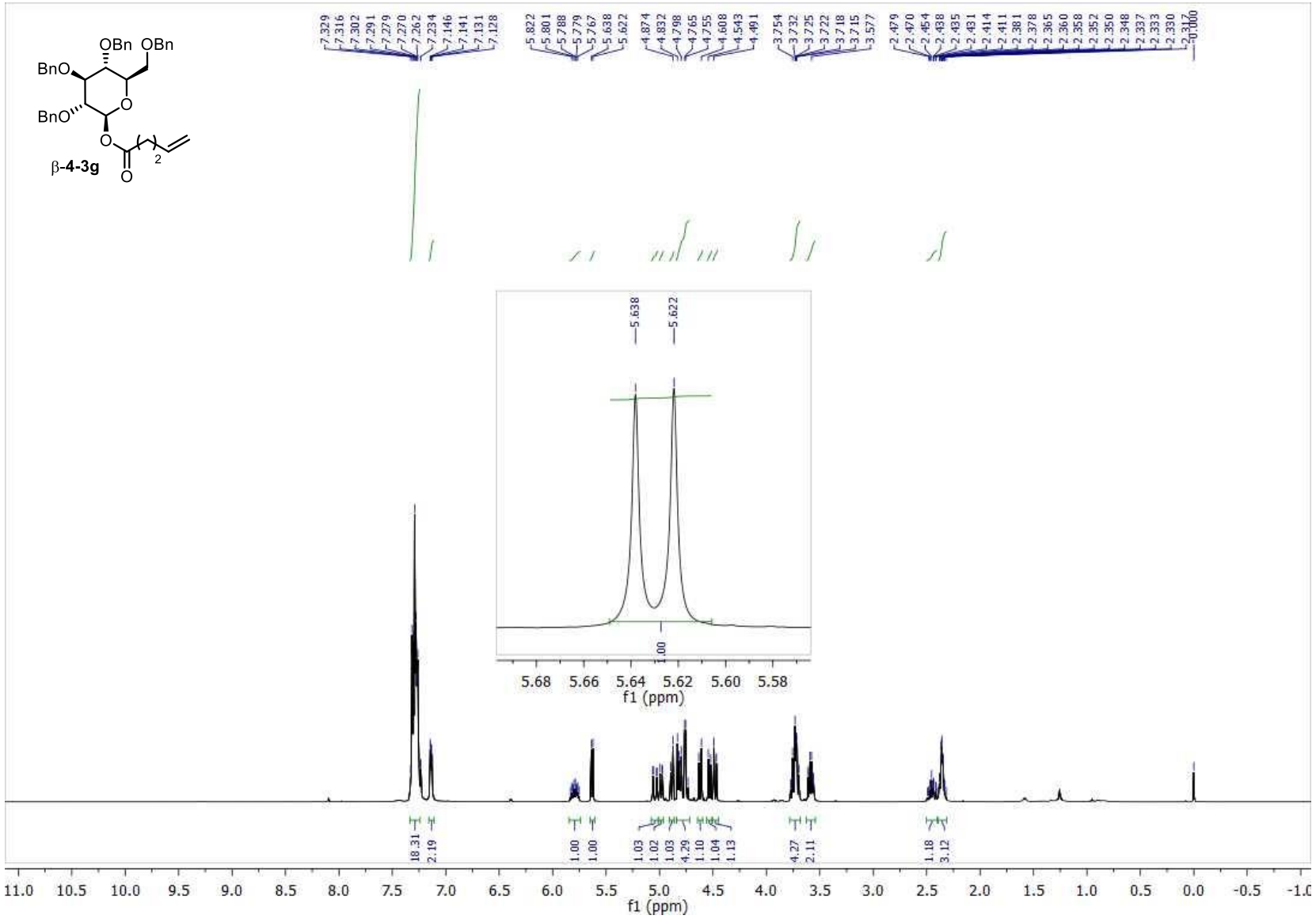

OBn OBn
BnO
BnO
O
O
2
O
α-4-2f
170.441
138.806
138.260
138.025
137.831
128.675
128.644
128.629
128.312
128.167
128.112
128.030
127.978
127.935
127.889
90.596
82.425
81.837
79.100
77.515
77.260
77.101
77.006
75.900
75.498
73.777
73.403
73.213
69.496
68.304
33.626
14.523
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

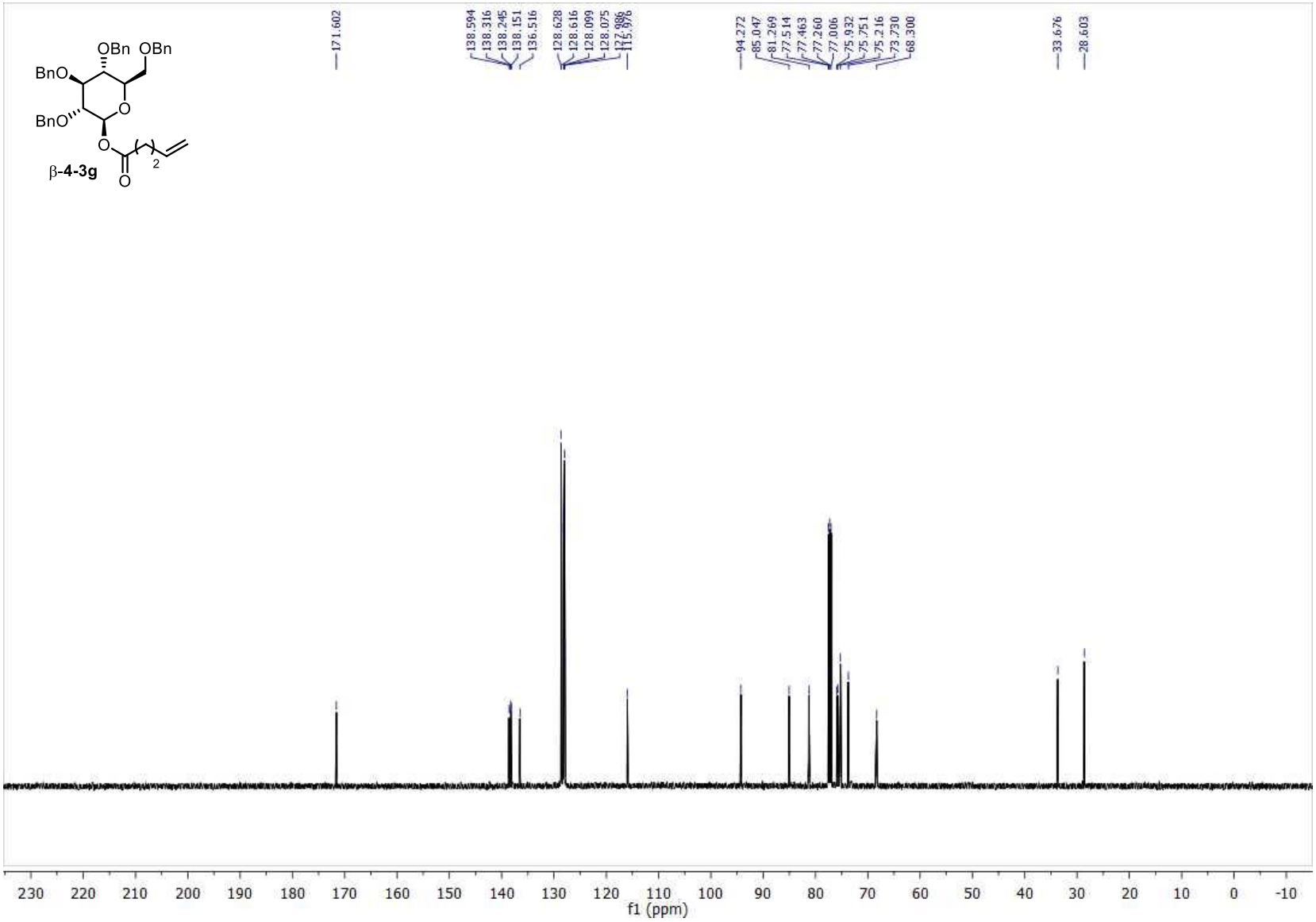

OBn OBn
BnO
BnO
O
O
2
O
β-4-3f
7.318
7.312
7.306
7.300
7.295
7.290
7.284
7.277
7.272
7.266
7.262
7.253
7.141
7.136
7.126
7.123
5.645
5.629
4.874
4.832
4.817
4.795
4.767
4.758
4.607
4.535
4.488
3.753
3.744
3.735
3.730
3.722
3.718
3.714
3.696
3.611
3.595
3.578
3.561
1.929
1.924
0.000
5.67
5.65
5.63
5.61
f1 (ppm)
17.94
2.16
1.00
1.02
2.28
1.89
1.07
1.03
1.08
4.23
2.06
0.97
2.96
0.84
10.5
10.0
9.5
9.0
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
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

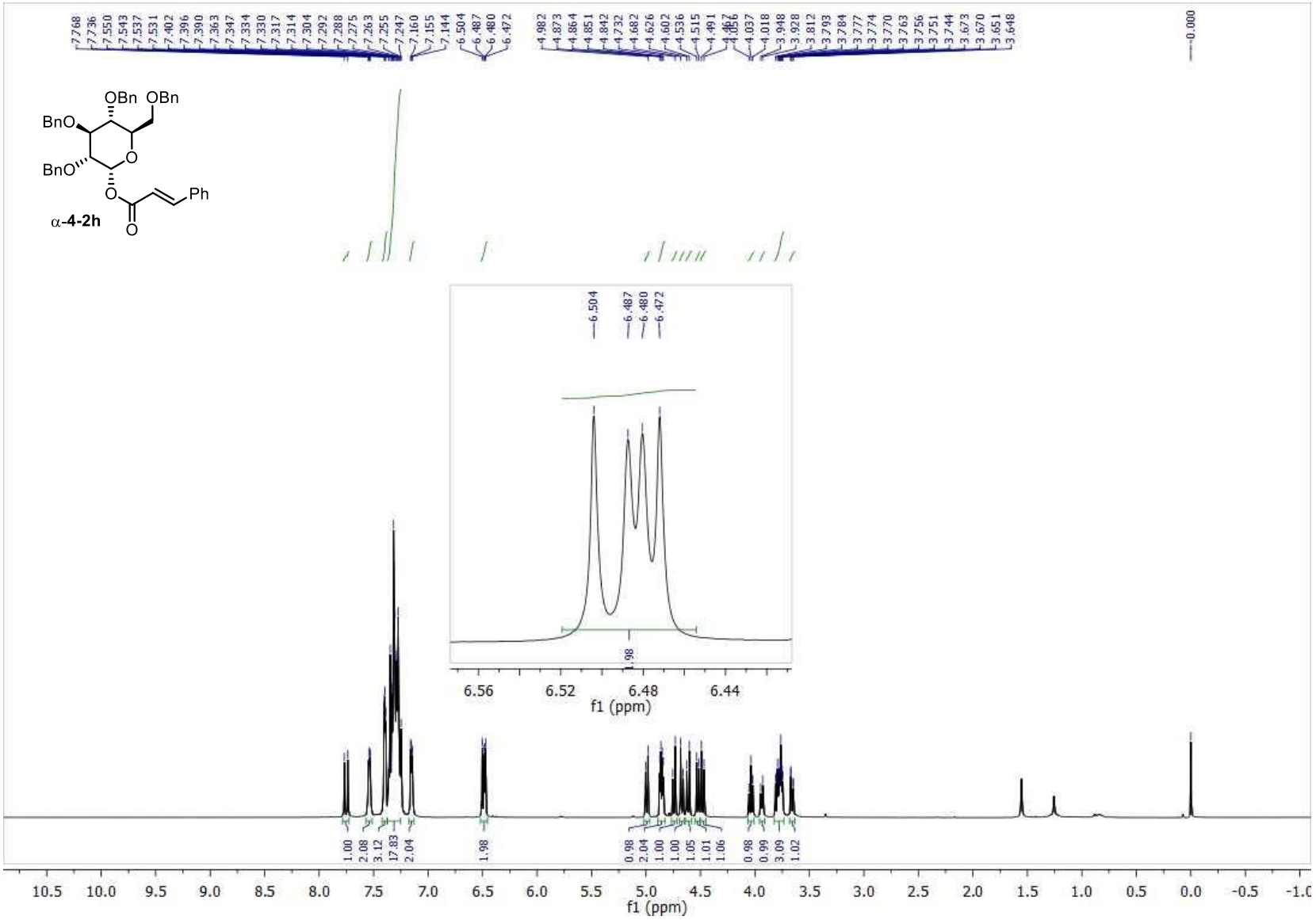

OBn OBn
BnO
BnO
O
O
2
β-4-3f
170.424
138.577
138.309
138.230
138.113
128.660
128.640
128.611
128.197
128.112
128.095
128.050
128.024
127.950
94.477
85.043
82.369
81.231
77.514
77.413
77.260
77.006
75.961
75.783
75.255
73.768
69.493
68.274
33.534
14.223
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

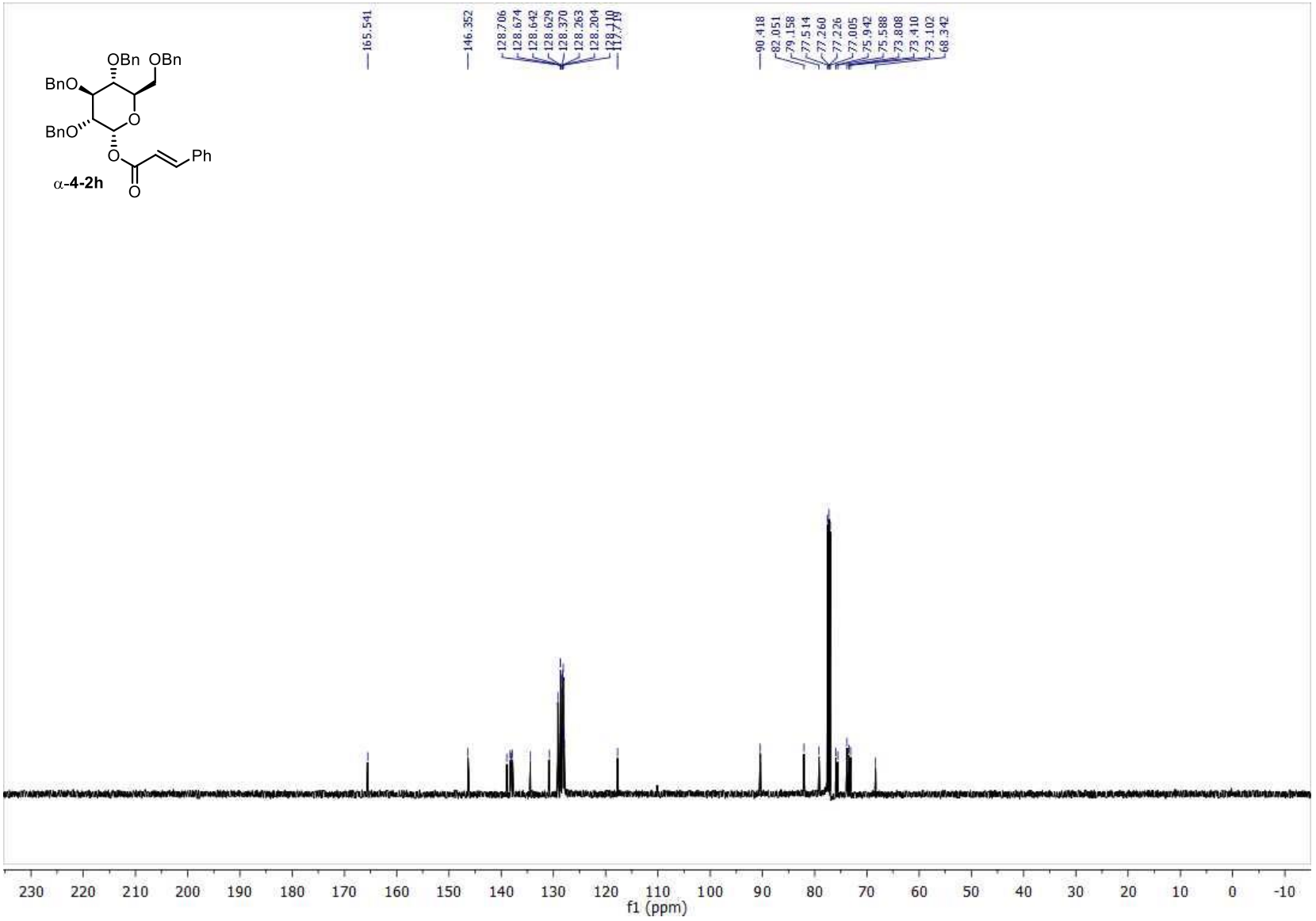

OBn OBn
BnO
BnO
O
O
2
O
α-4-2g
7.333
7.329
7.321
7.316
7.306
7.296
7.291
7.280
7.268
7.266
7.260
7.236
7.146
7.142
7.131
7.128
6.396
6.389
5.844
5.823
5.810
5.802
5.789
4.942
4.828
4.679
4.634
4.611
4.586
4.491
4.485
3.929
3.754
3.732
3.725
3.716
3.704
3.697
3.645
3.624
2.508
2.494
2.478
2.465
2.410
2.395
2.382
2.368
2.366
2.358
-0.000
6.396
6.389
1.00
6.44
6.42
6.40
6.38
6.36
6.34
f1 (ppm)
18.32
2.35
1.00
1.13
1.14
2.33
2.35
1.12
2.34
2.37
1.10
1.10
3.26
1.05
2.04
2.32
10.5
10.0
9.5
9.0
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
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

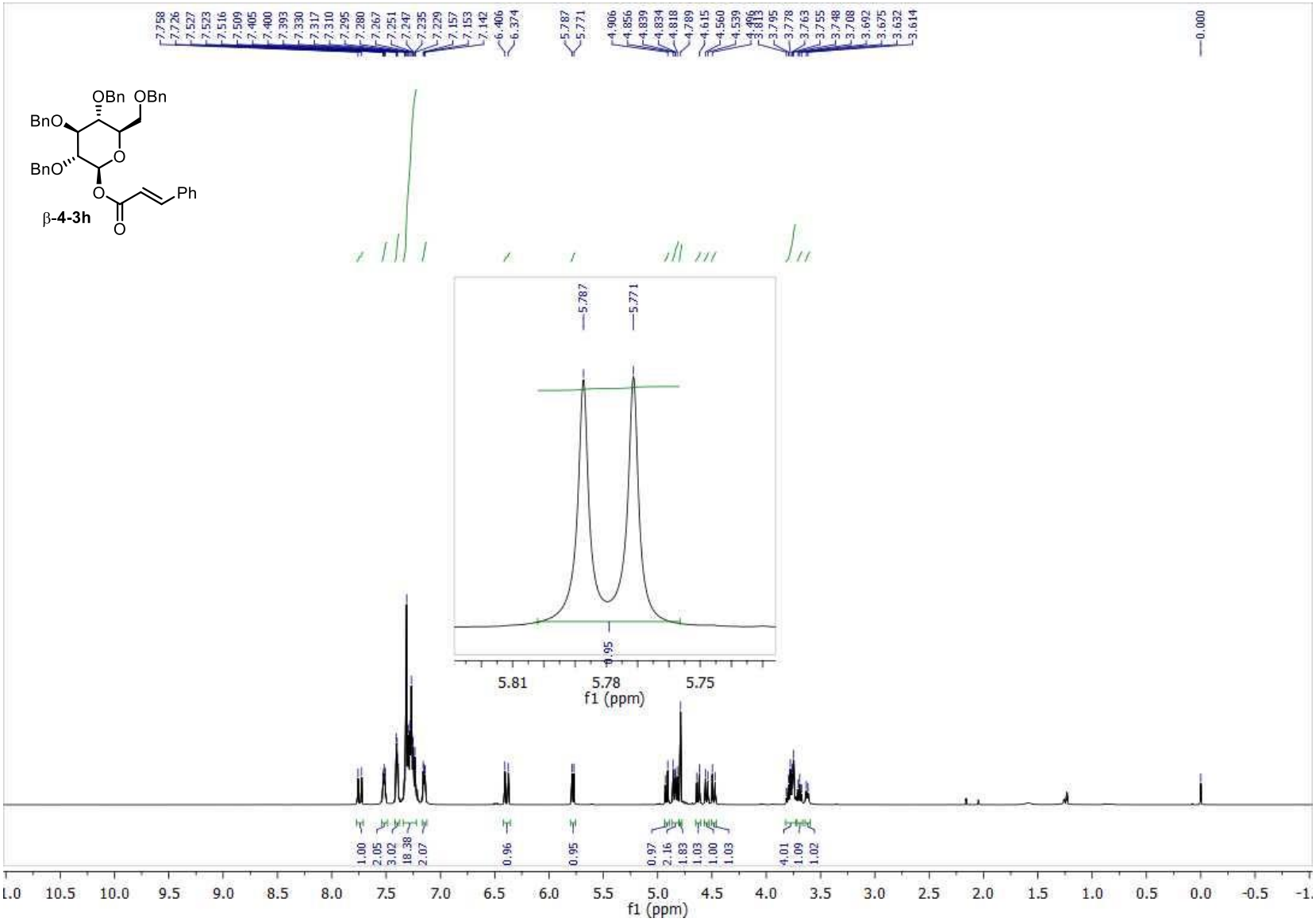

OBn OBn
BnO
BnO
O
O
O
2
α-4-2g
171.683
138.838
138.248
138.044
137.857
136.579
128.654
128.646
128.619
128.211
115.912
90.172
81.875
79.137
77.514
77.260
77.005
75.881
75.526
73.771
73.340
73.115
68.323
33.805
28.926
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

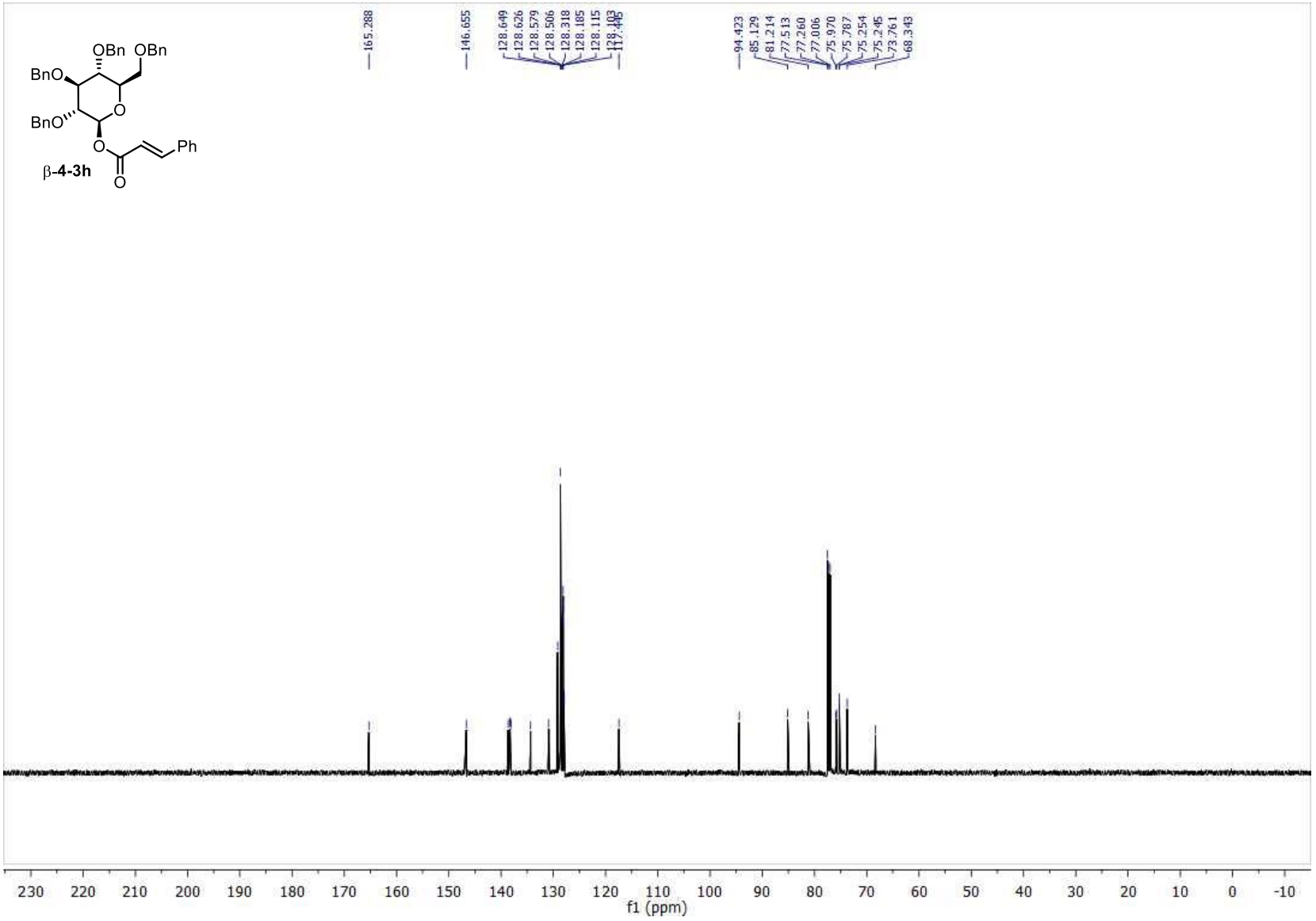

OBn OBn
BnO
BnO
O
O
2
O
β-4-3g
7.329
7.316
7.302
7.291
7.279
7.270
7.262
7.234
7.146
7.141
7.131
7.128
5.822
5.801
5.788
5.779
5.767
5.638
5.622
4.874
4.832
4.798
4.765
4.755
4.608
4.543
4.491
3.754
3.732
3.725
3.722
3.718
3.715
3.577
2.479
2.470
2.454
2.438
2.435
2.431
2.414
2.411
2.381
2.378
2.365
2.360
2.358
2.352
2.350
2.348
2.337
2.333
2.330
2.317
0.000
5.638
5.622
1.00
5.68 5.66 5.64 5.62 5.60 5.58
f1 (ppm)
18.31
2.19
1.00
1.00
1.03
1.02
1.03
4.29
1.10
1.04
1.13
4.27
2.11
1.18
3.12
11.0 10.5 10.0 9.5 9.0 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 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

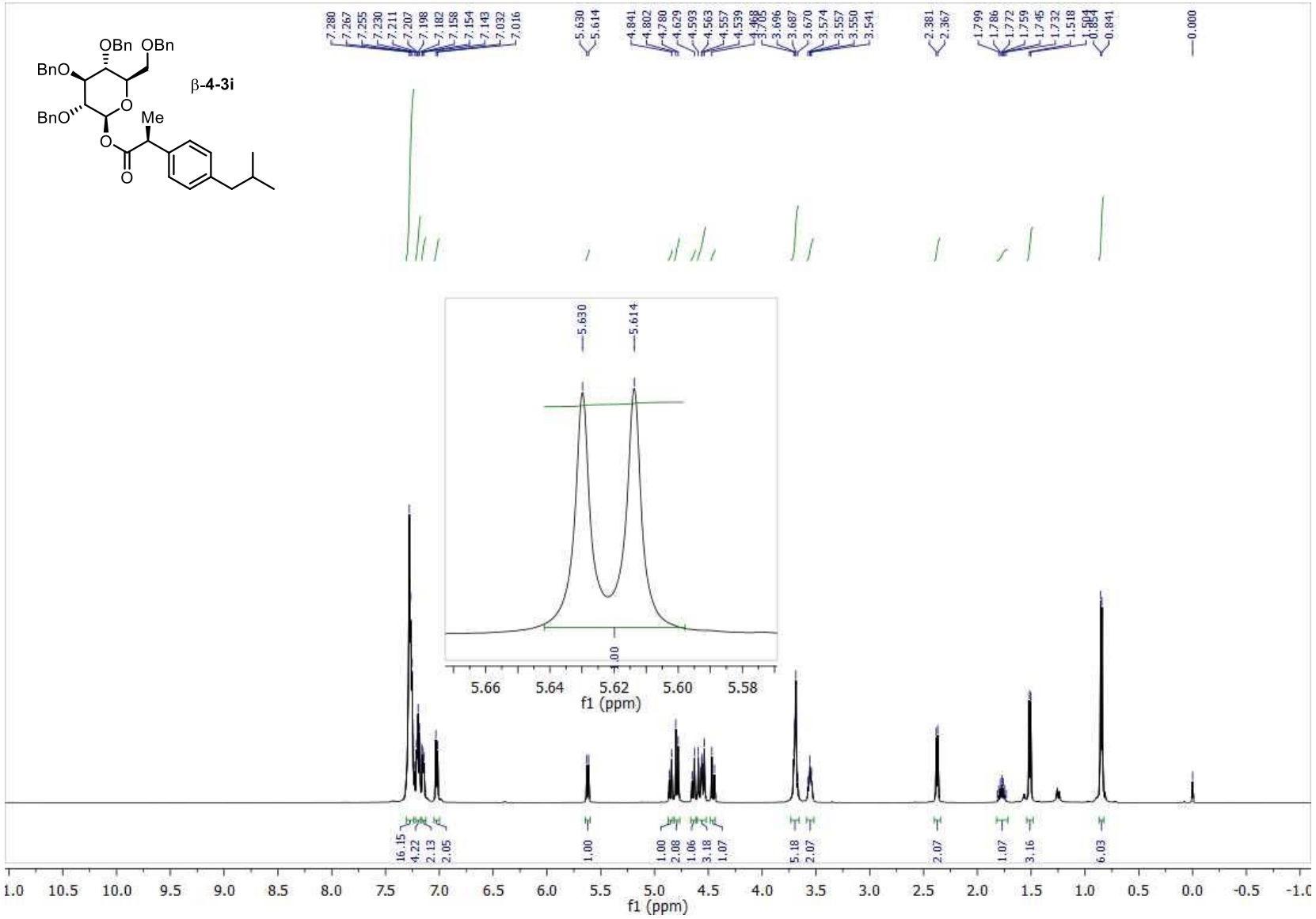

OBn OBn
BnO
BnO
O
O
2
O
β-4-3g
171.602
138.594
138.316
138.245
138.151
136.516
128.628
128.616
128.099
128.075
94.272
85.047
81.269
77.514
77.463
77.260
77.006
75.932
75.751
75.216
73.730
68.300
33.676
28.603
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

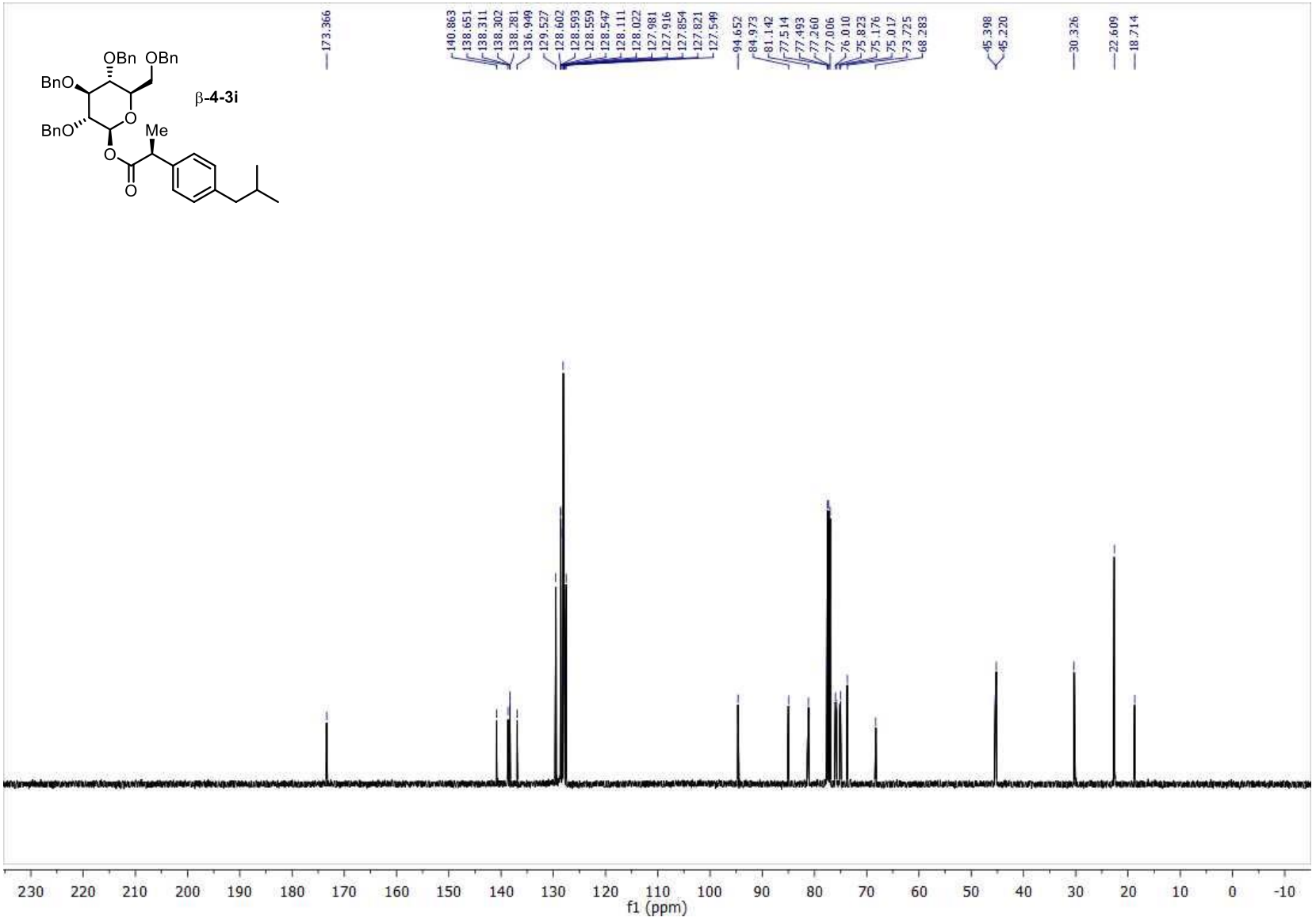

OBn OBn
BnO
BnO
O
O
Ph
O
α-4-2h
f1 (ppm)

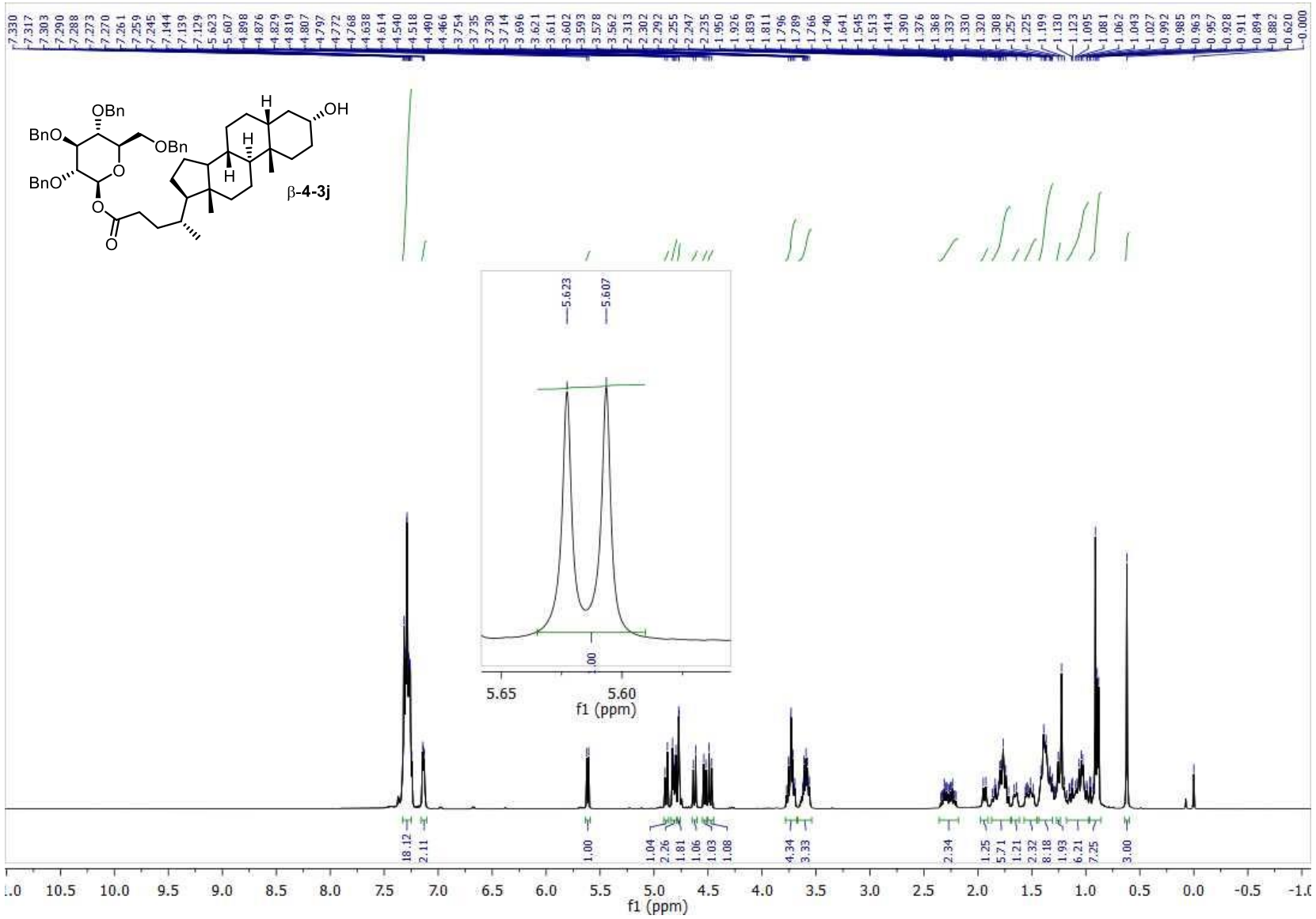

OBn OBn
BnO
BnO
O
O
Ph
O
α-4-2h
165.541
146.352
128.706
128.674
128.642
128.629
128.370
128.263
128.204
90.418
82.051
79.158
77.514
77.260
77.226
77.005
75.942
75.588
73.808
73.410
73.102
68.342
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

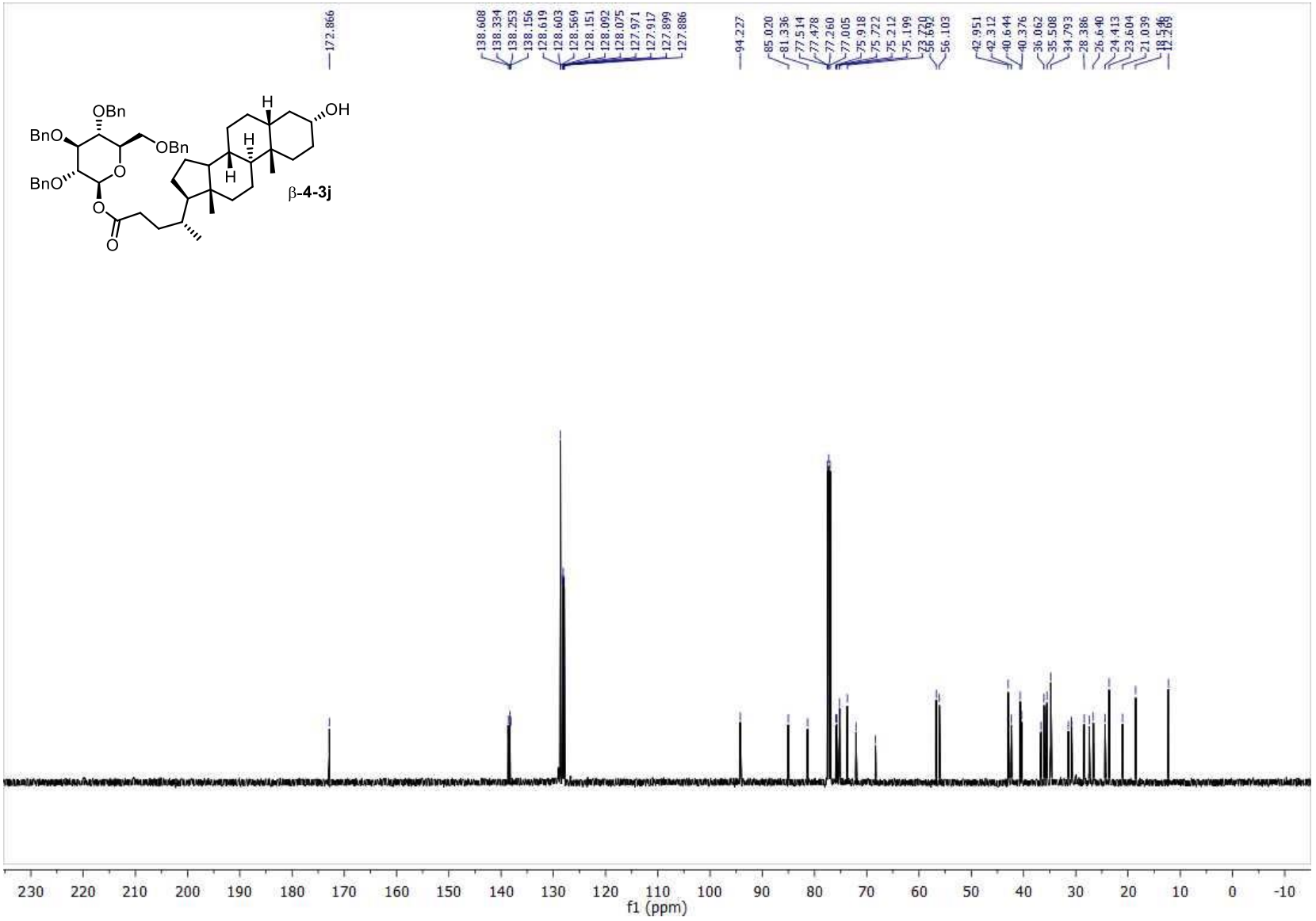

OBn OBn
BnO
BnO
O
O
Ph
O
β-4-3h
5.787
5.771
0.95
5.81
5.78
5.75
f1 (ppm)
1.00
2.05
3.02
18.38
2.07
0.96
0.95
0.97
2.16
1.83
1.03
1.00
1.03
4.01
1.09
1.02
f1 (ppm)

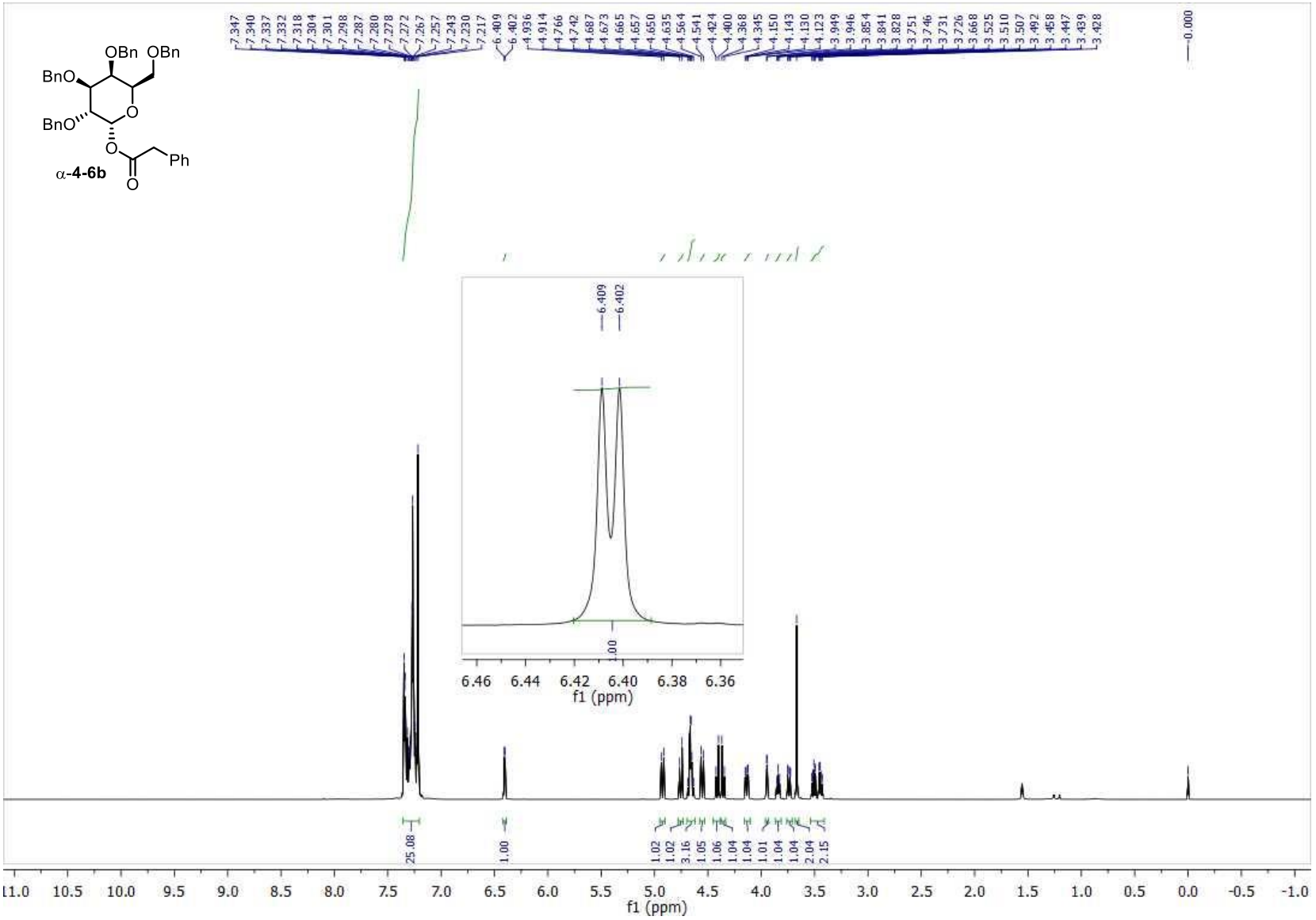

OBn OBn
BnO
BnO
O
O
Ph
O
β-4-3h
165.288
146.655
128.649
128.626
128.579
128.506
128.318
128.185
128.115
94.423
85.129
81.214
77.513
77.260
77.006
75.970
75.787
75.254
75.245
73.761
68.343
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

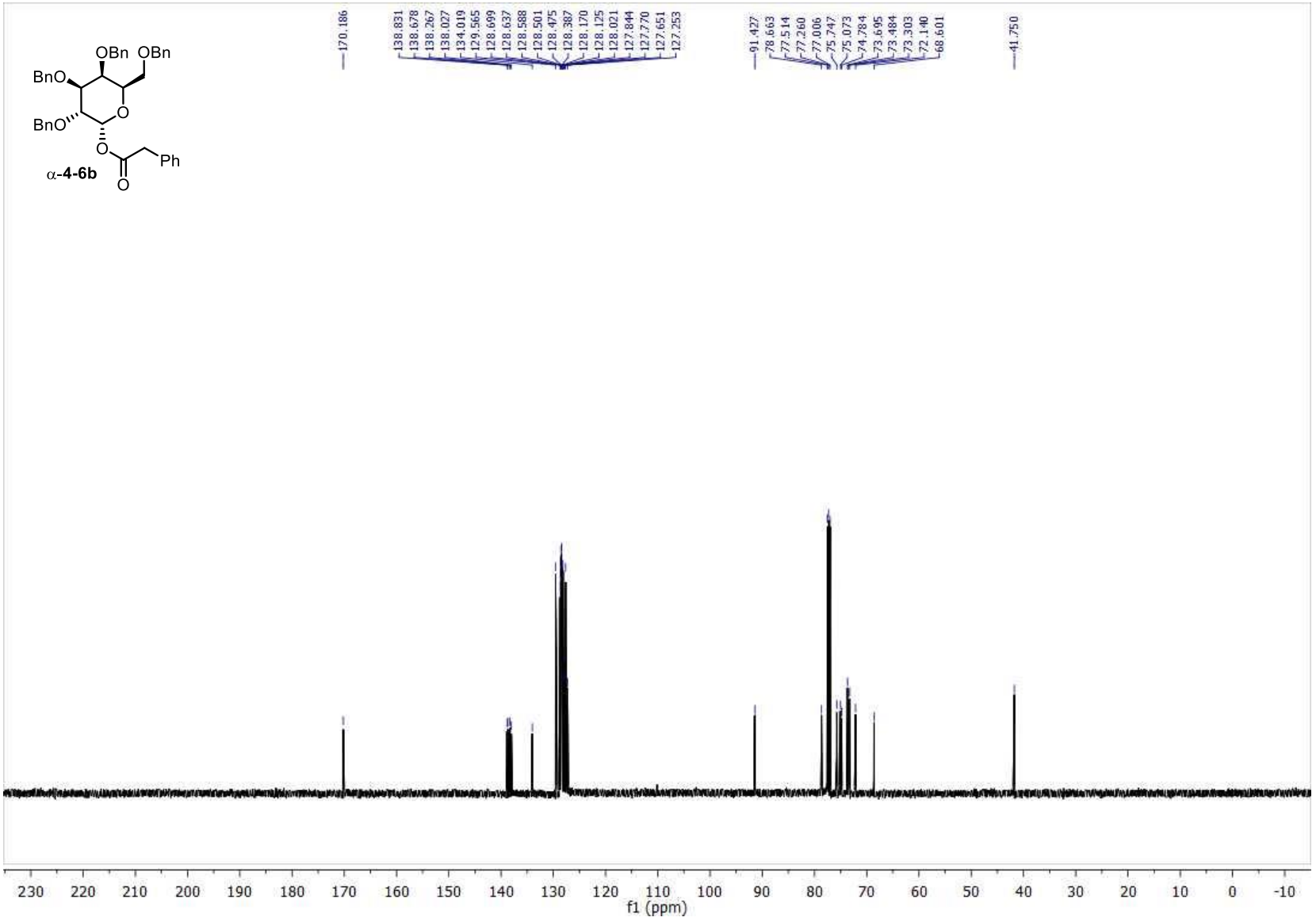

β-4-3i
OBn
OBn
BnO
BnO
O
Me
O
O
7.280
7.267
7.255
7.230
7.211
7.207
7.198
7.182
7.158
7.154
7.143
7.032
7.016
5.630
5.614
4.841
4.802
4.780
4.629
4.593
4.563
4.557
4.539
3.705
3.696
3.687
3.670
3.574
3.557
3.550
3.541
2.381
2.367
1.799
1.786
1.772
1.759
1.745
1.732
1.518
0.884
0.841
0.000
5.630
5.614
1.00
5.66
5.64
5.62
5.60
5.58
f1 (ppm)
16.15
4.22
2.13
2.05
1.00
1.00
2.08
1.06
3.18
1.07
5.18
2.07
2.07
1.07
3.16
6.03
1.0
10.5
10.0
9.5
9.0
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
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

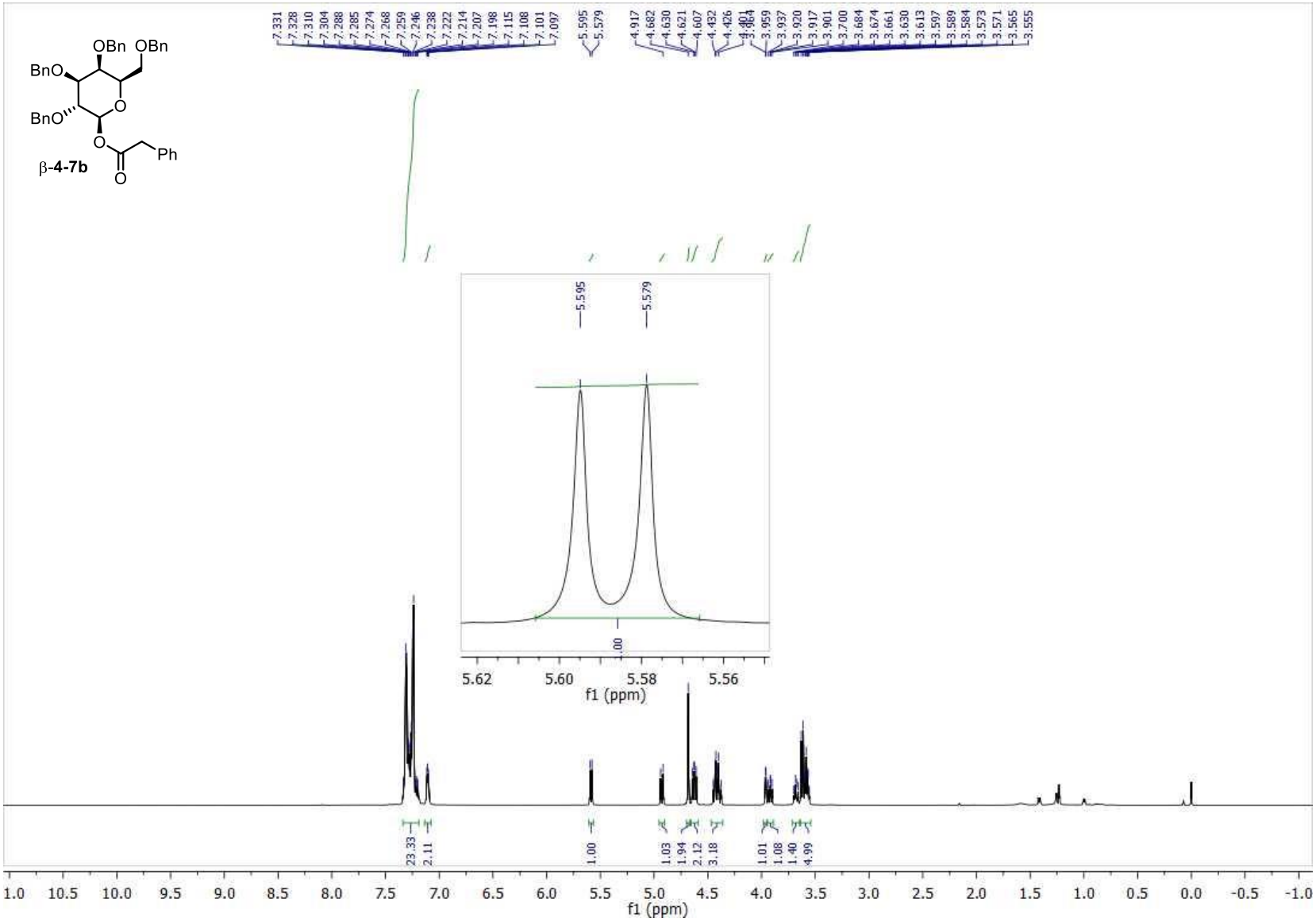

OBn OBn
BnO
BnO
O
Me
O
O
β-4-3i
173.366
140.863
138.651
138.311
138.302
138.281
136.949
129.527
128.602
128.593
128.559
128.547
128.111
128.022
127.981
127.916
127.854
127.821
127.549
94.652
84.973
81.142
77.514
77.493
77.260
77.006
76.010
75.823
75.176
75.017
73.725
68.283
45.398
45.220
30.326
22.609
18.714
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

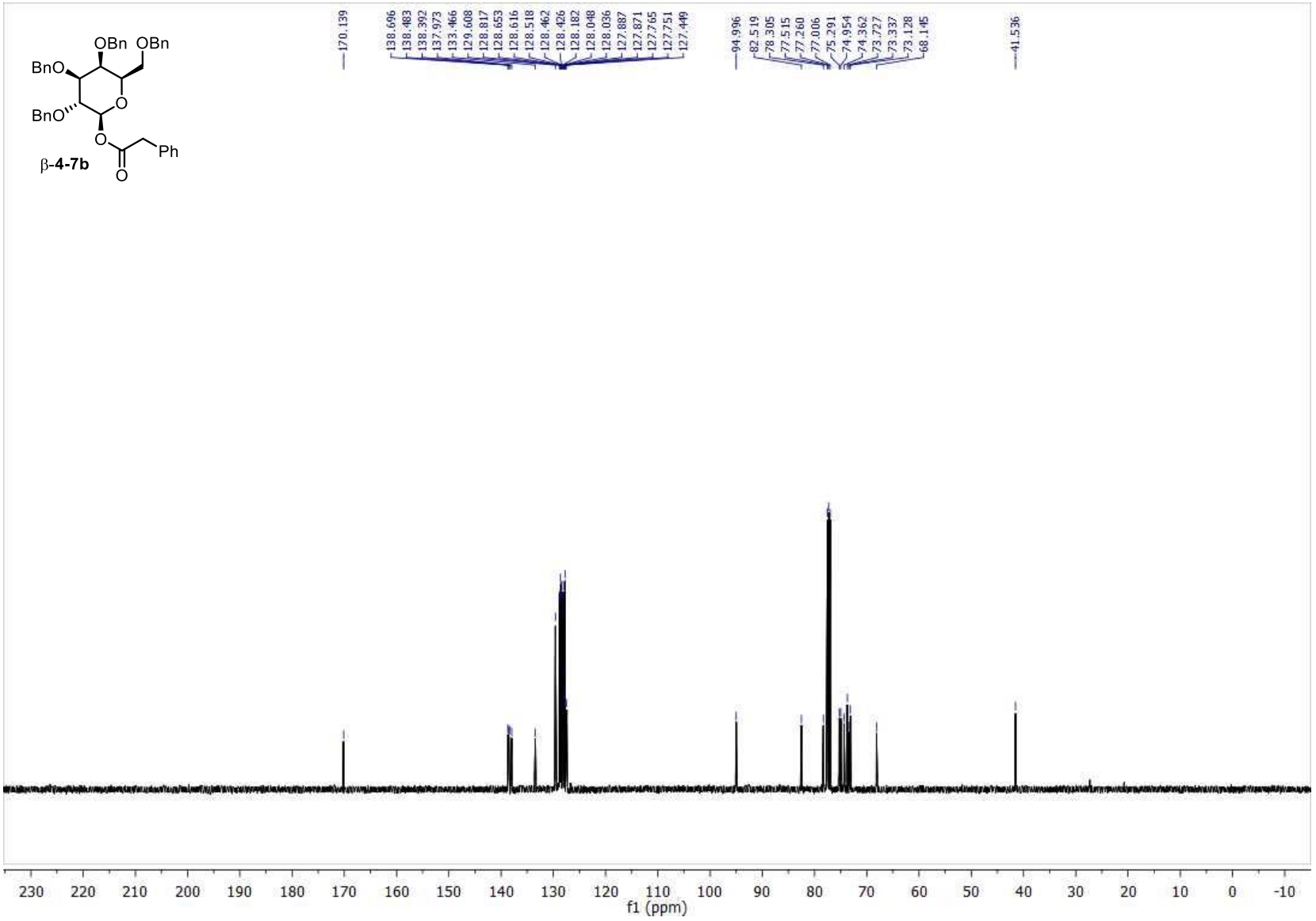

OBn
BnO
OBn
BnO
O
O
O
H
H
H
OH
β-4-3j
5.623
5.607
5.65
5.60
f1 (ppm)
18.12
2.11
1.00
1.04
2.26
1.81
1.06
1.03
1.08
4.34
3.33
2.34
1.25
5.71
1.21
2.32
8.18
1.93
6.21
7.25
3.00
f1 (ppm)

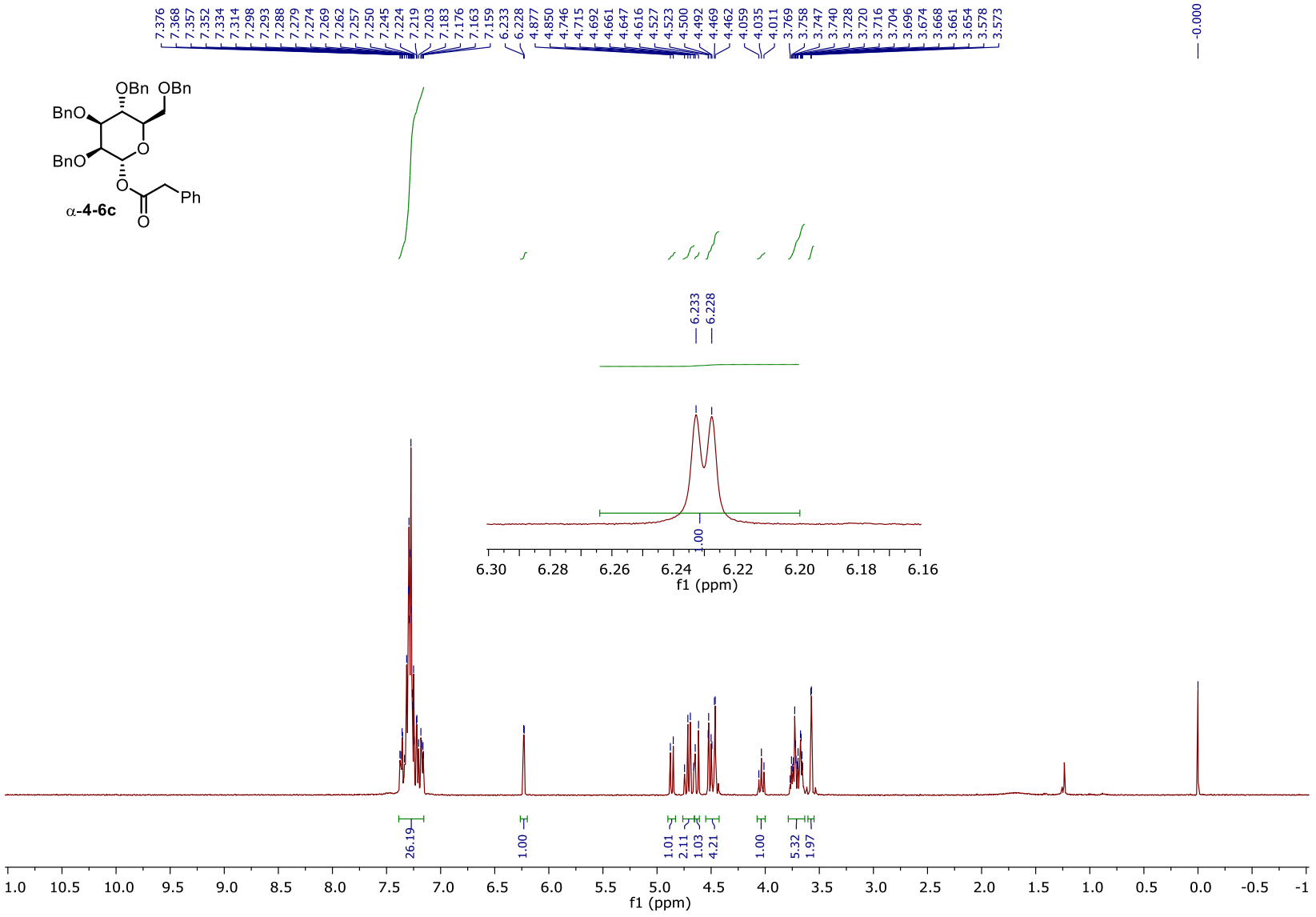

172.866
138.608
138.334
138.253
138.156
128.619
128.603
128.569
128.151
128.092
128.075
127.971
127.917
127.899
127.886
94.227
85.020
81.336
77.514
77.478
77.260
77.005
75.918
75.722
75.212
75.199
73.720
73.692
56.103
42.951
42.312
40.644
40.376
36.062
35.508
34.793
28.386
26.640
24.413
23.604
21.039
18.546
12.289
OBn
BnO
OBn
BnO
O
O
O
H
H
H
OH
β-4-3j
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

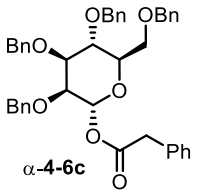

OBn OBn
BnO
BnO
O
O
Ph
O
α-4-6b
7.347 7.340 7.337 7.332 7.318 7.304 7.301 7.298 7.287 7.280 7.278 7.272 7.267 7.257 7.243 7.230 7.217 6.409 6.402 4.936 4.914 4.766 4.742 4.687 4.673 4.665 4.657 4.650 4.635 4.564 4.541 4.424 4.400 4.368 4.345 4.150 4.143 4.130 4.123 3.949 3.946 3.854 3.841 3.828 3.751 3.746 3.731 3.726 3.668 3.525 3.510 3.507 3.492 3.458 3.447 3.439 3.428
0.000
6.409
6.402
1.00
6.46 6.44 6.42 6.40 6.38 6.36
f1 (ppm)
25.08
1.00
1.02 1.02 3.16 1.05 1.06 1.04 1.04 1.01 1.04 1.04 2.04 2.15
11.0 10.5 10.0 9.5 9.0 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 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


OBn OBn
BnO
BnO
O
O
Ph
O
α-4-6b
170.186
138.831
138.678
138.267
138.027
134.019
129.565
128.699
128.637
128.588
128.501
128.475
128.387
128.170
128.125
128.021
127.844
127.770
127.651
127.253
91.427
78.663
77.514
77.260
77.006
75.747
75.073
74.784
73.695
73.484
73.303
72.140
68.601
41.750
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


β-4-7b
f1 (ppm)
f1 (ppm)

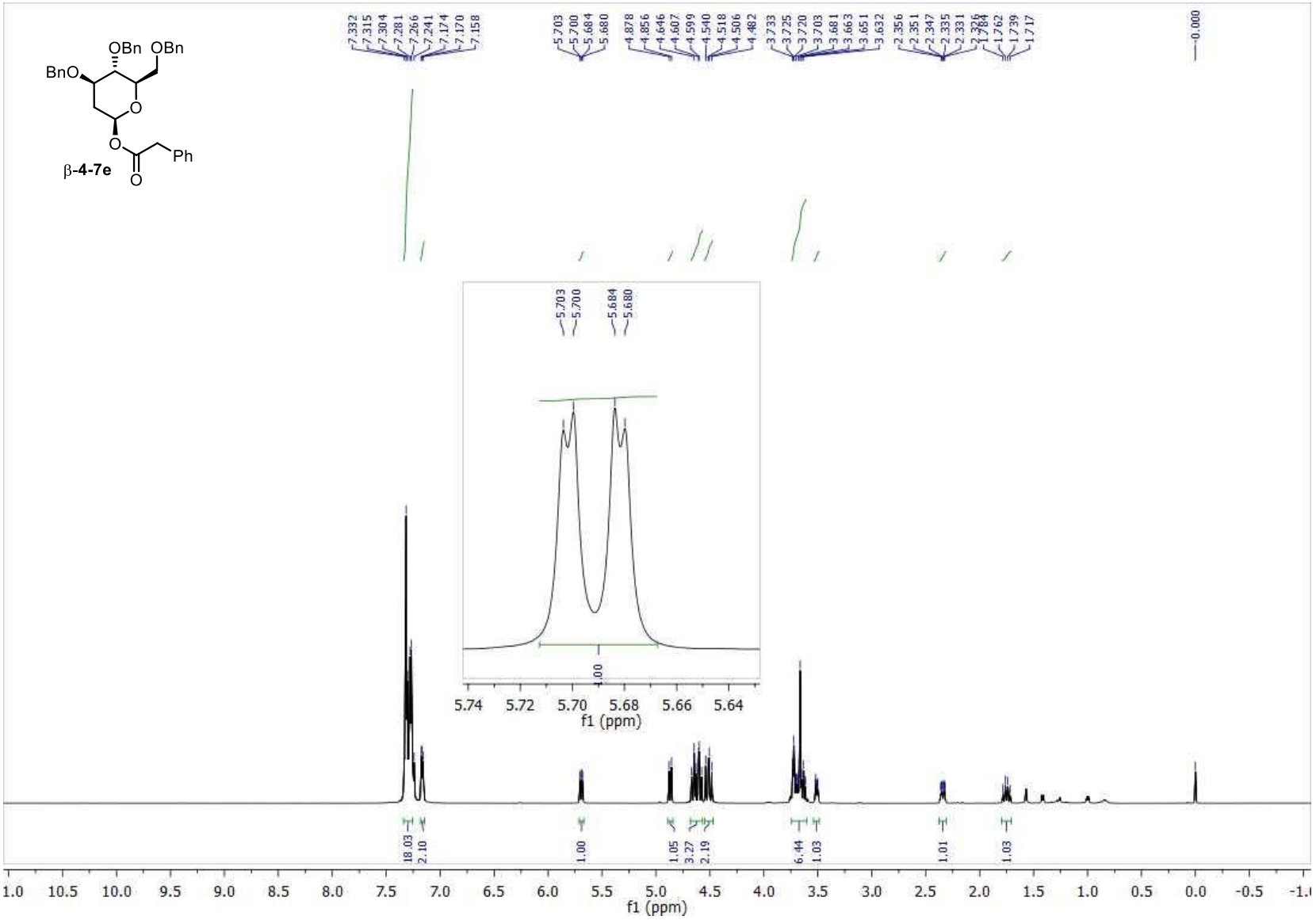

OBn OBn
BnO
BnO
O
O
Ph
O
β-4-7b
170.139
138.696
138.483
138.392
137.973
133.466
129.608
128.817
128.653
128.616
128.518
128.462
128.426
128.182
128.048
128.036
127.887
127.871
127.765
127.751
127.449
94.996
82.519
78.305
77.515
77.260
77.006
75.291
74.954
74.362
73.727
73.337
73.128
68.145
41.536
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

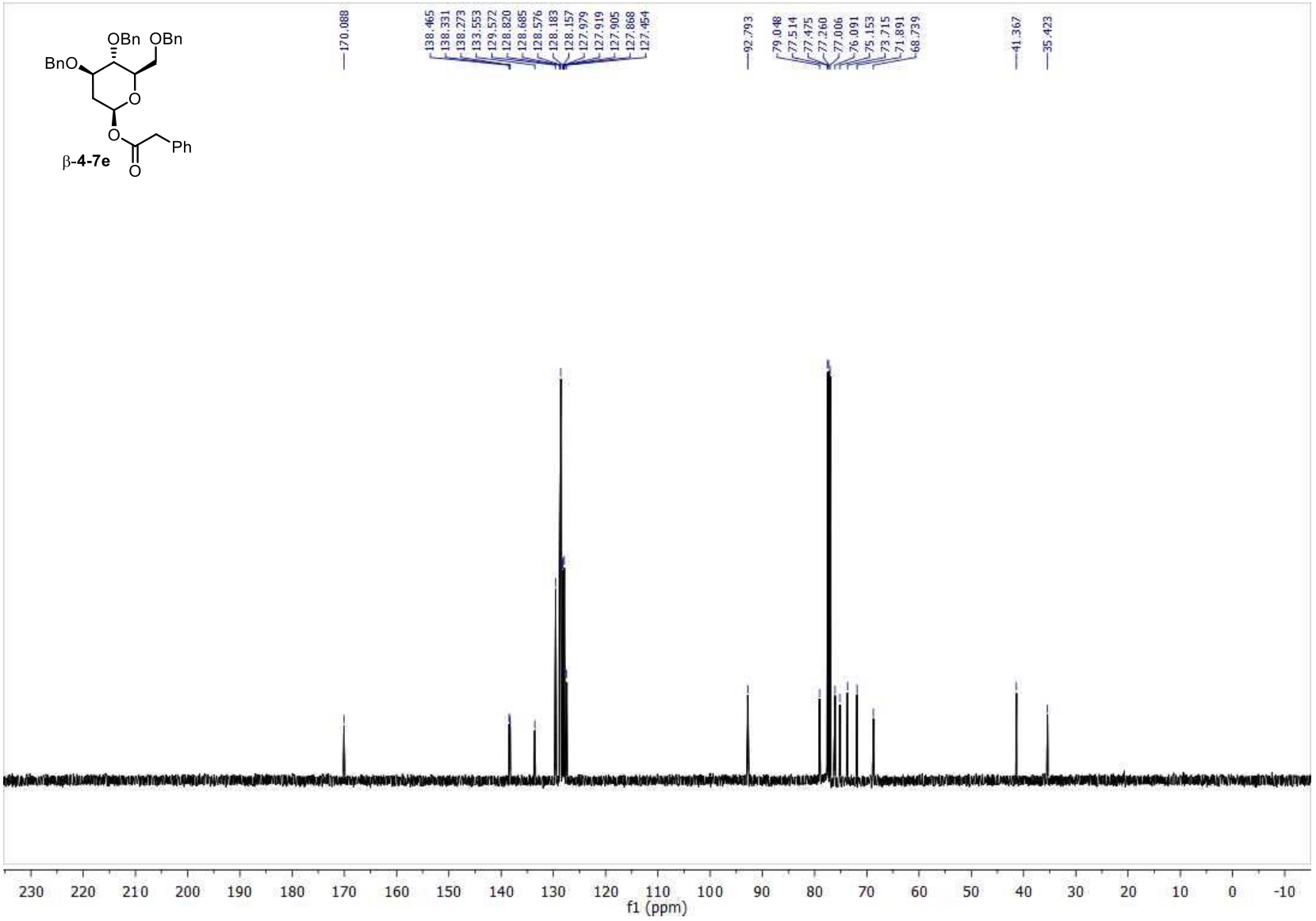

OBn OBn
BnO
BnO
O
O
Ph
O
α-4-6c
7.376 7.368 7.357 7.352 7.334 7.314 7.298 7.293 7.288 7.279 7.274 7.269 7.262 7.257 7.250 7.245 7.224 7.219 7.203 7.183 7.176 7.163 7.159 6.233 6.228 4.877 4.850 4.746 4.715 4.692 4.661 4.647 4.616 4.527 4.523 4.500 4.492 4.469 4.462 4.059 4.035 4.011 3.769 3.758 3.747 3.740 3.728 3.720 3.716 3.704 3.696 3.674 3.668 3.661 3.654 3.578 3.573
-0.000
6.233
6.228
1.00
6.30 6.28 6.26 6.24 6.22 6.20 6.18 6.16
f1 (ppm)
26.19
1.00
1.01
2.11
1.03
4.21
1.00
5.32
1.97
1.0 10.5 10.0 9.5 9.0 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 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

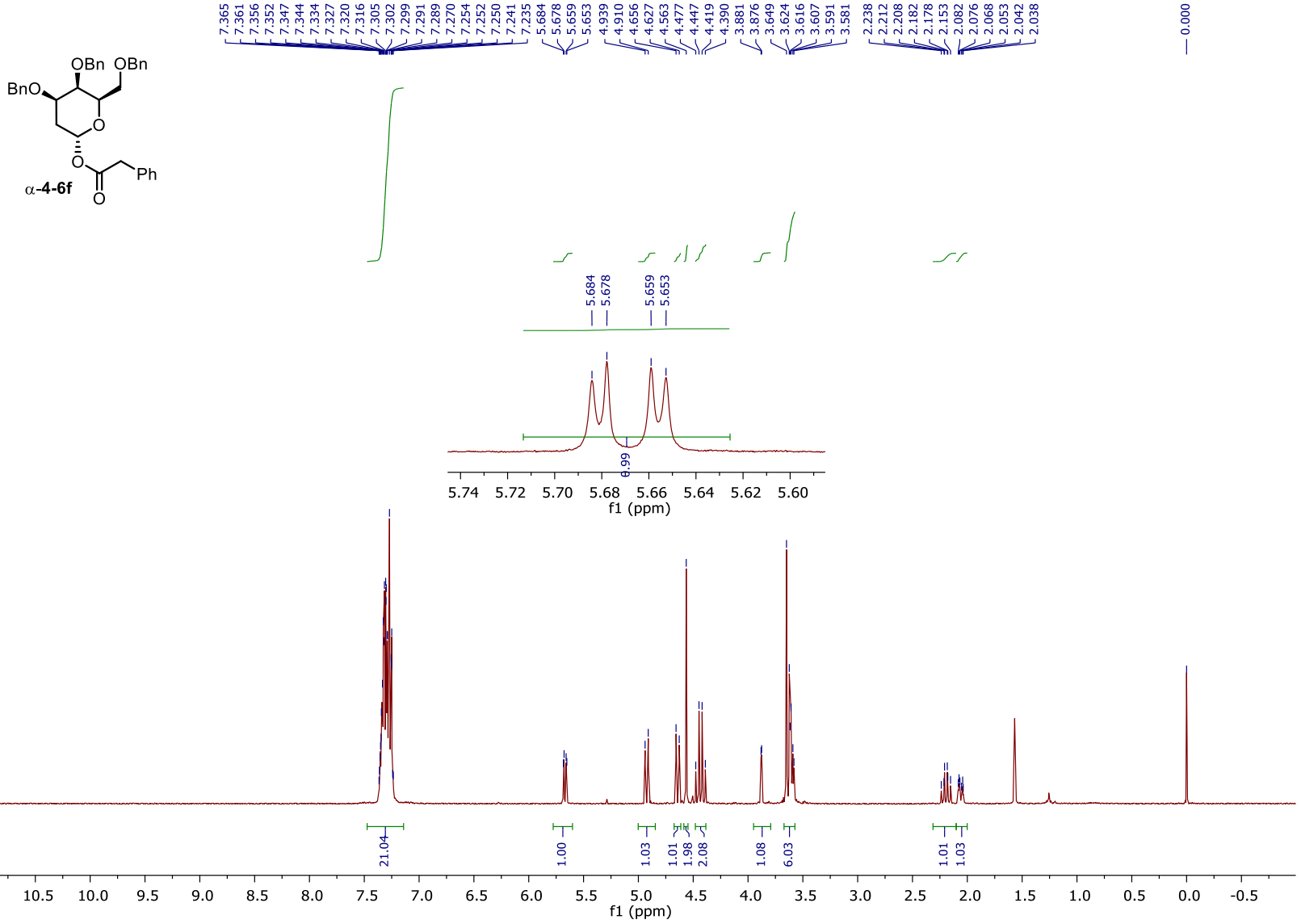

OBn
OBn
BnO
BnO
O
O
Ph
O

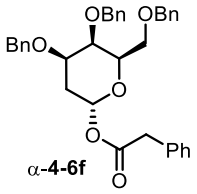
α-**4-6c**

169.759
138.504
138.450
138.363
138.004
133.561
129.384
128.903
128.550
128.510
128.194
128.127
128.037
127.894
127.710
127.521
92.538
92.484
79.425
77.548
77.230
76.913
75.363
74.734
74.332
73.726
73.639
72.704
72.289
69.057
41.609
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


OBn
OBn
BnO
O
O
Ph
O
β-4-7e
7.332
7.315
7.304
7.281
7.266
7.241
7.174
7.170
7.158
5.703
5.700
5.684
5.680
4.878
4.856
4.646
4.607
4.599
4.540
4.518
4.506
4.482
3.733
3.725
3.720
3.703
3.681
3.663
3.651
3.632
2.356
2.351
2.347
2.335
2.331
1.762
1.739
1.717
0.000
18.03
2.10
1.00
1.05
3.27
2.19
6.44
1.03
1.01
1.03
f1 (ppm)

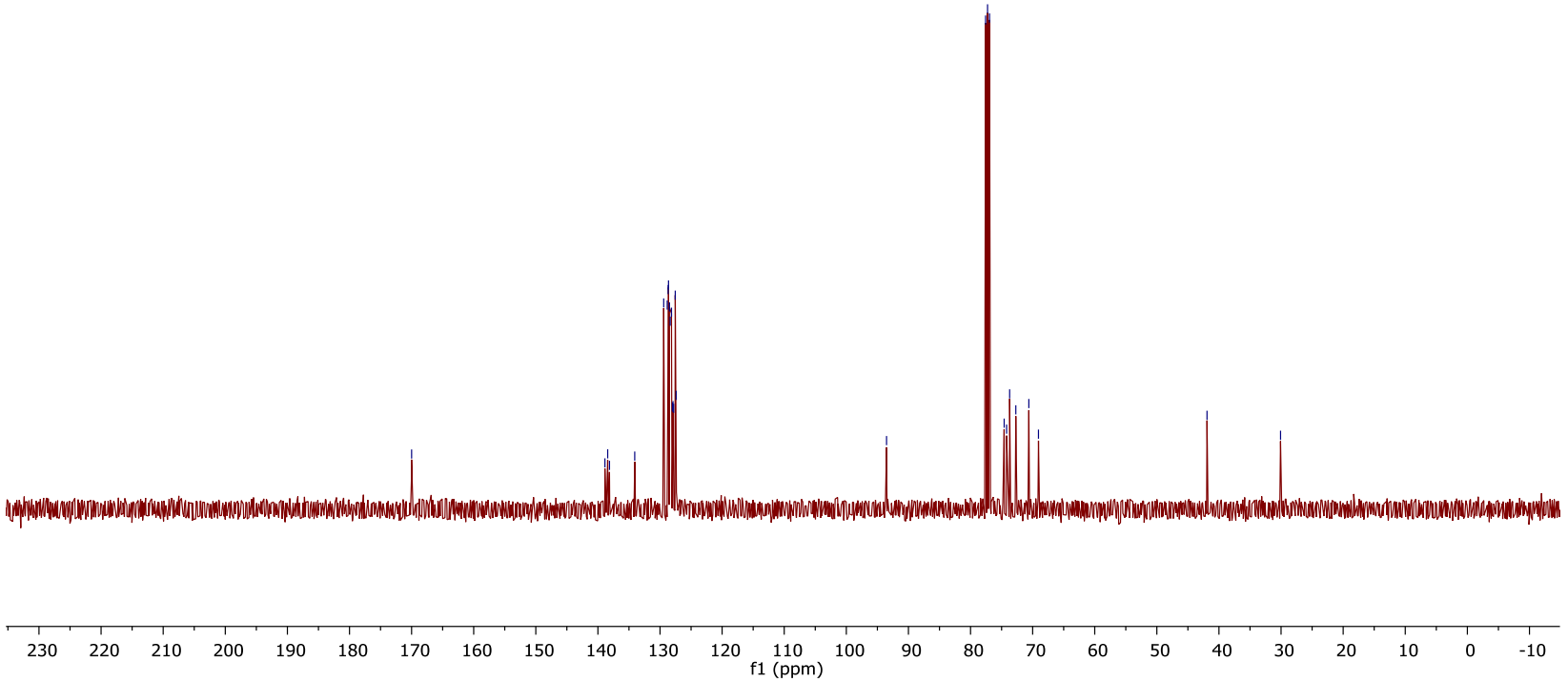

OBn OBn
BnO
O
O
O
Ph
β-4-7e
170.088
138.465
138.331
138.273
133.553
129.572
128.820
128.685
128.576
128.183
128.157
127.979
127.919
127.905
127.868
127.454
92.793
79.048
77.514
77.475
77.260
77.006
76.091
75.153
73.715
71.891
68.739
41.367
35.423
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

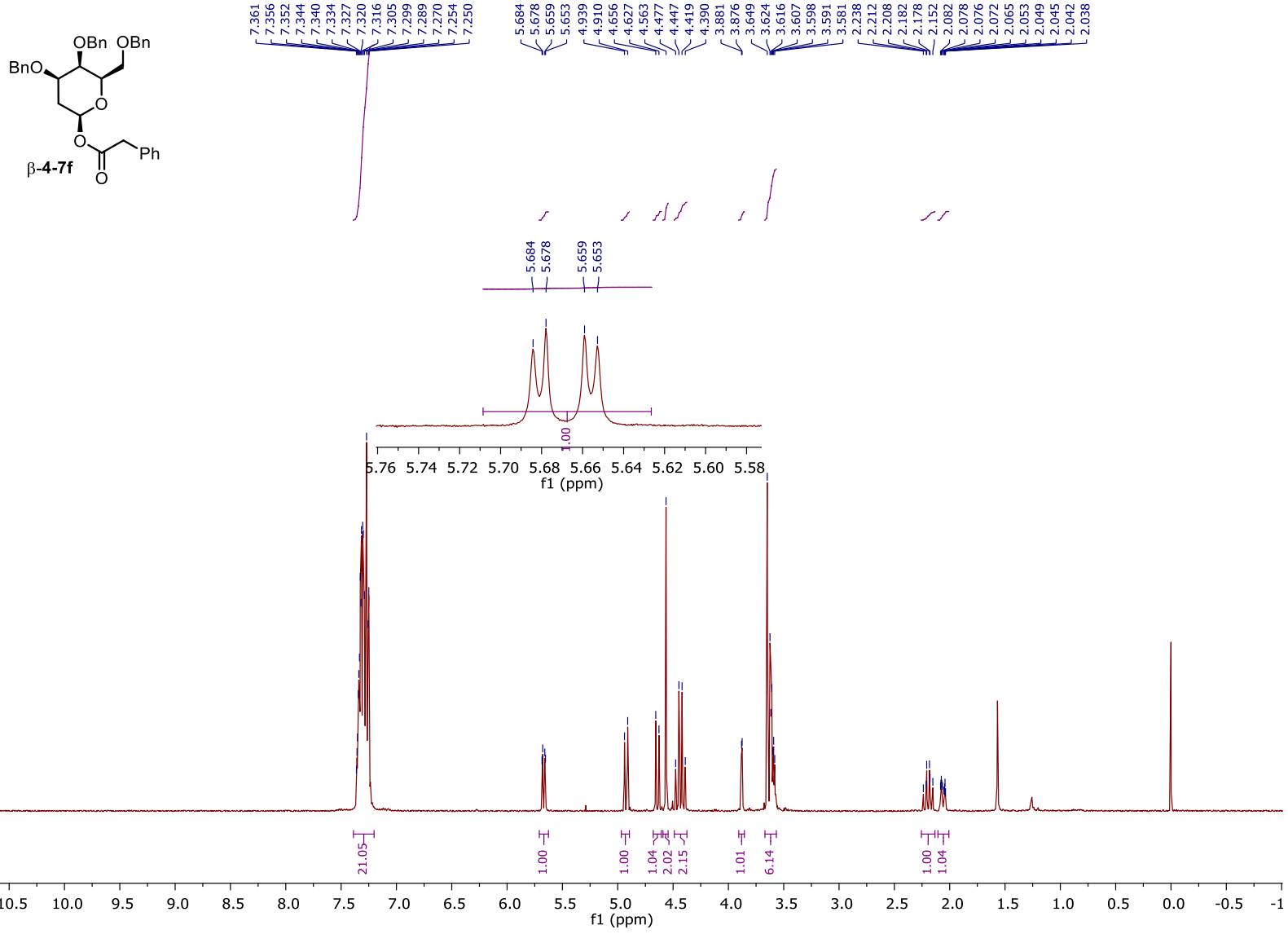

7.365
7.361
7.356
7.352
7.347
7.344
7.334
7.327
7.320
7.316
7.305
7.302
7.299
7.291
7.289
7.270
7.254
7.252
7.250
7.241
7.235
5.684
5.678
5.659
5.653
4.939
4.910
4.656
4.627
4.563
4.477
4.447
4.419
4.390
3.881
3.876
3.649
3.624
3.616
3.607
3.591
3.581
2.238
2.212
2.208
2.182
2.178
2.153
2.082
2.076
2.068
2.053
2.042
2.038
0.000
OBn
OBn
BnO
O
O
Ph
O
α-4-6f
5.684
5.678
5.659
5.653
6.99
5.74
5.72
5.70
5.68
5.66
5.64
5.62
5.60
f1 (ppm)
21.04
1.00
1.03
1.01
1.98
2.08
1.08
6.03
1.01
1.03
1.0
10.5
10.0
9.5
9.0
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
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

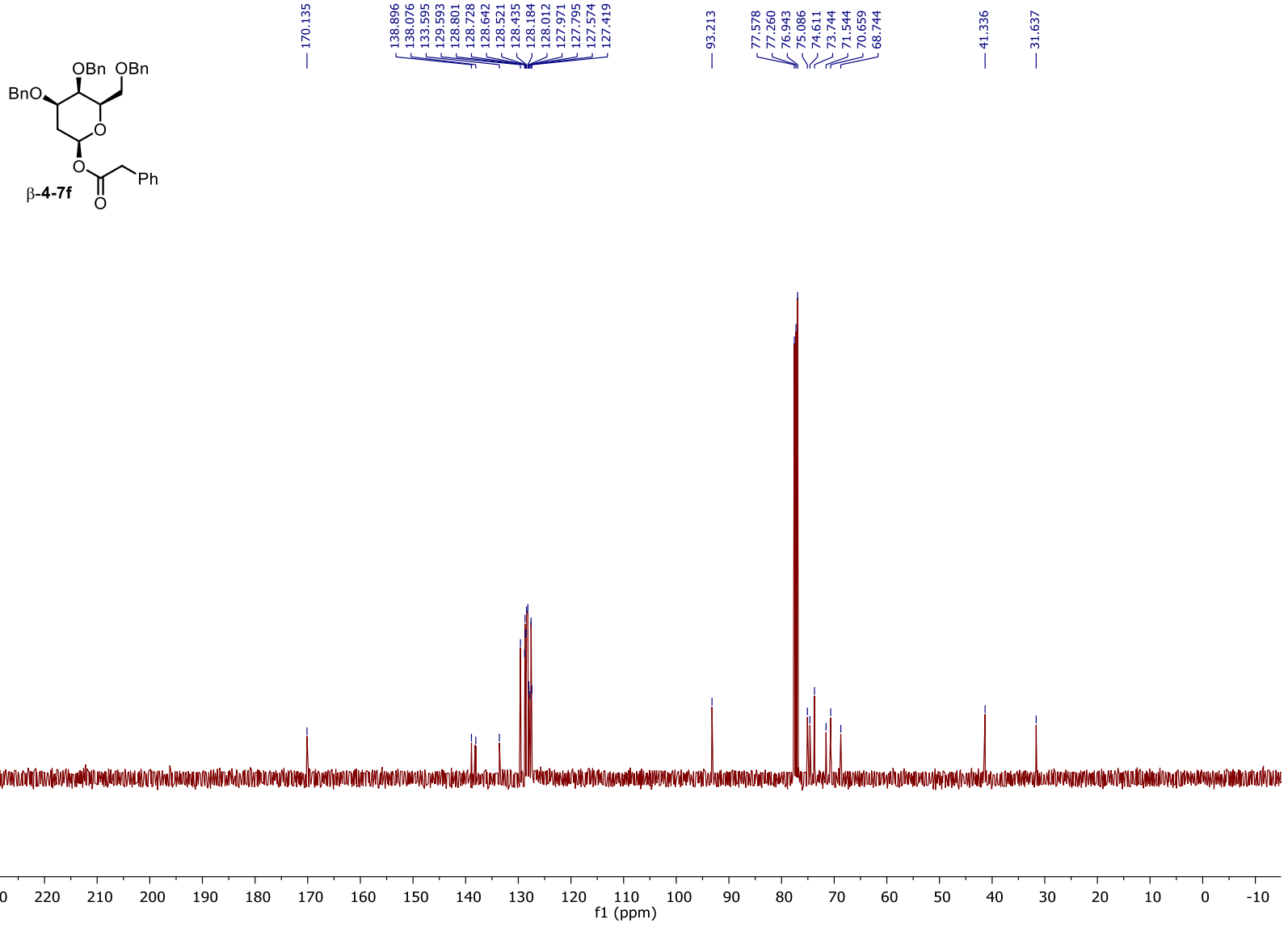


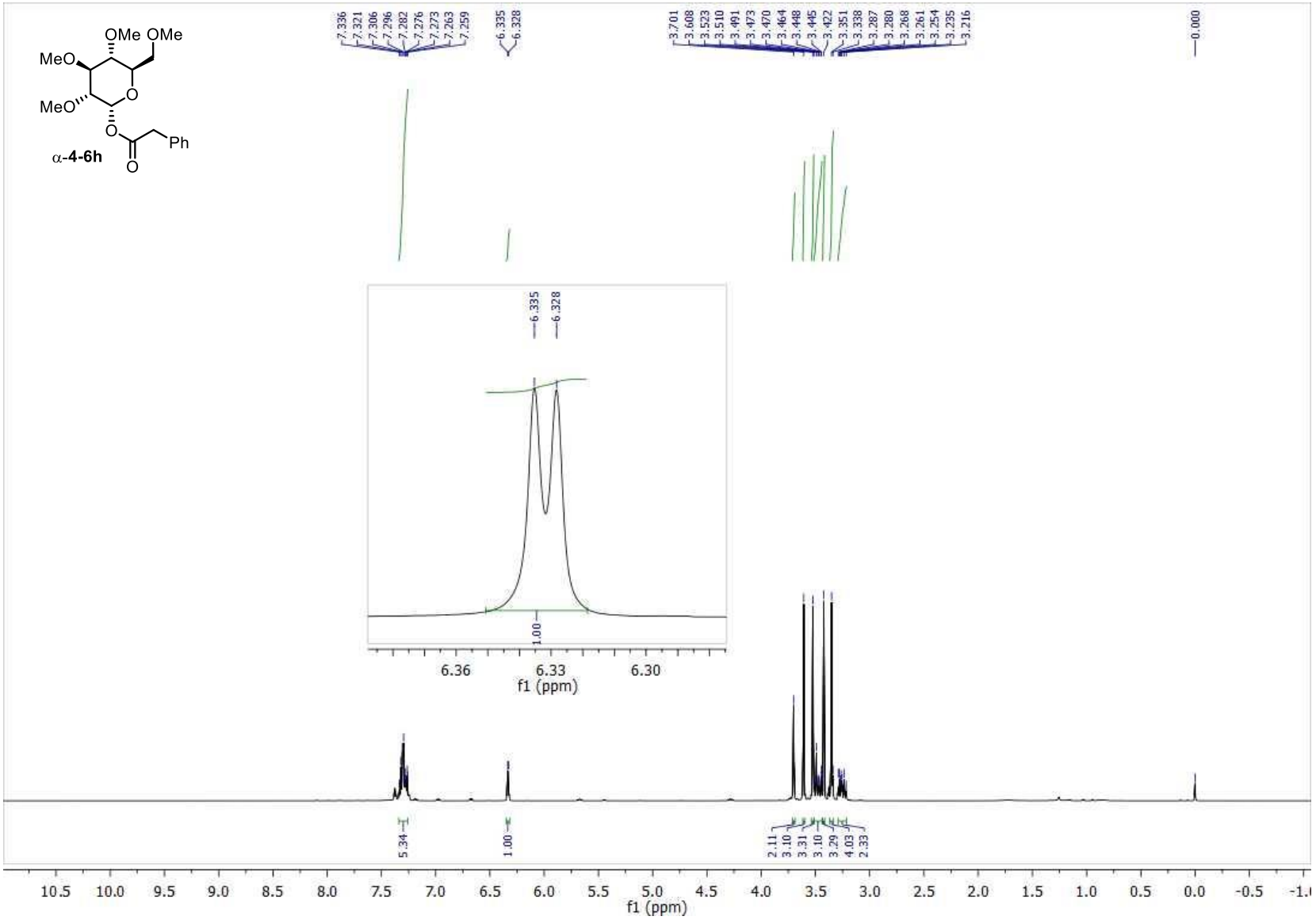
α-**4-6f**

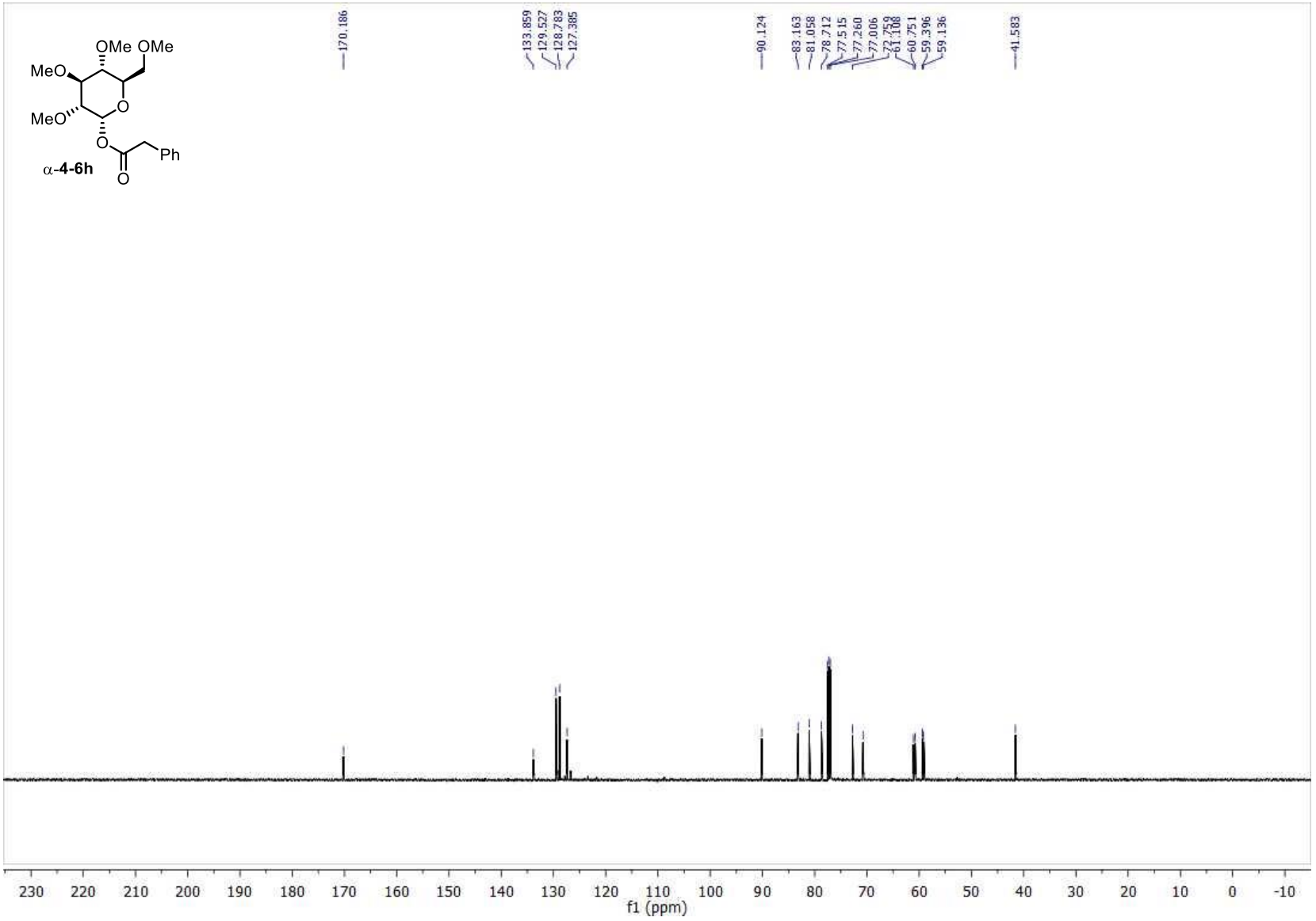
169.999
138.871
138.424
138.136
134.070
129.407
128.839
128.690
128.634
128.476
128.364
128.152
127.997
127.910
127.807
127.545
127.404
93.524
77.578
77.260
76.942
74.587
74.194
73.702
72.709
70.613
69.061
41.920
30.082

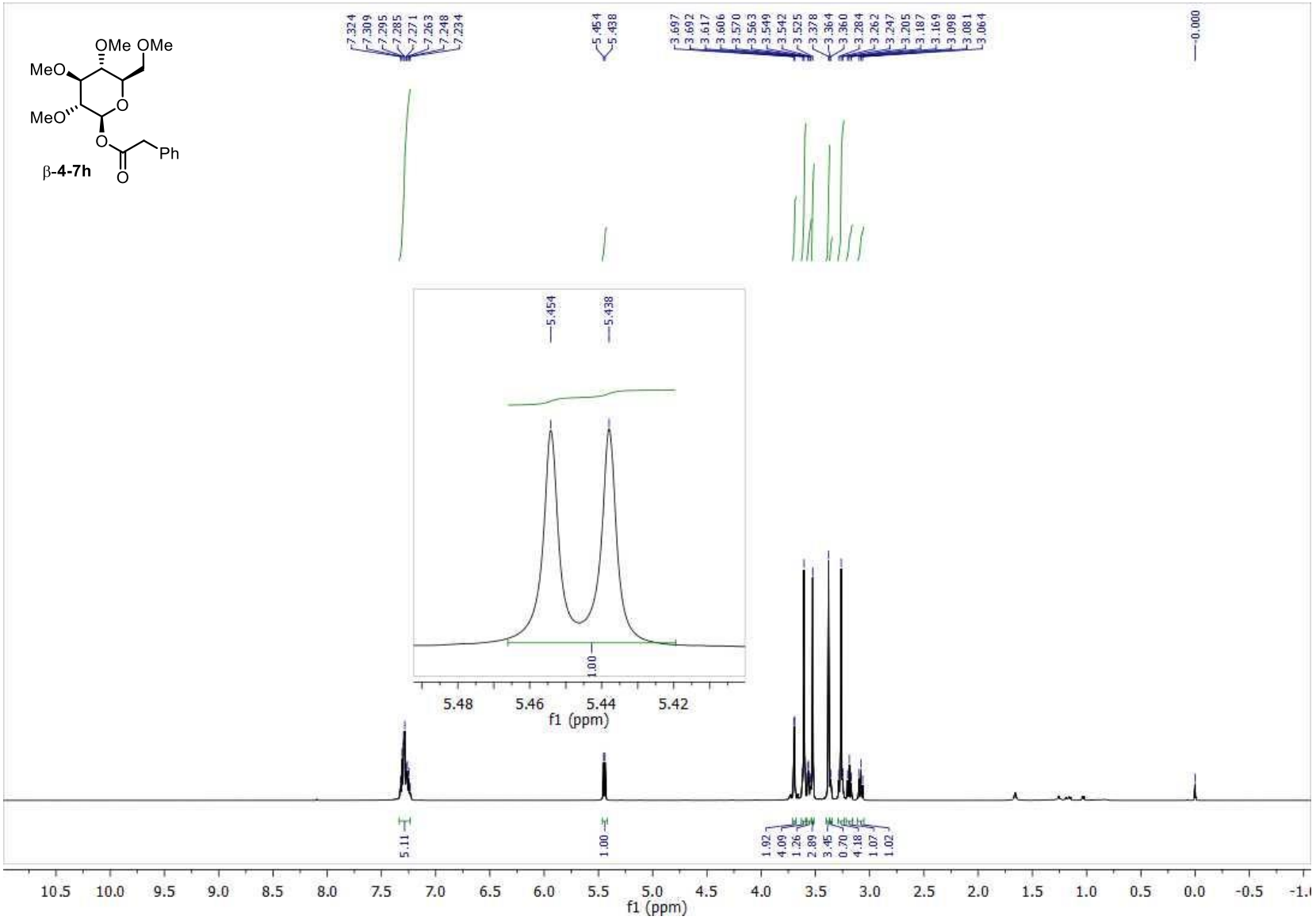


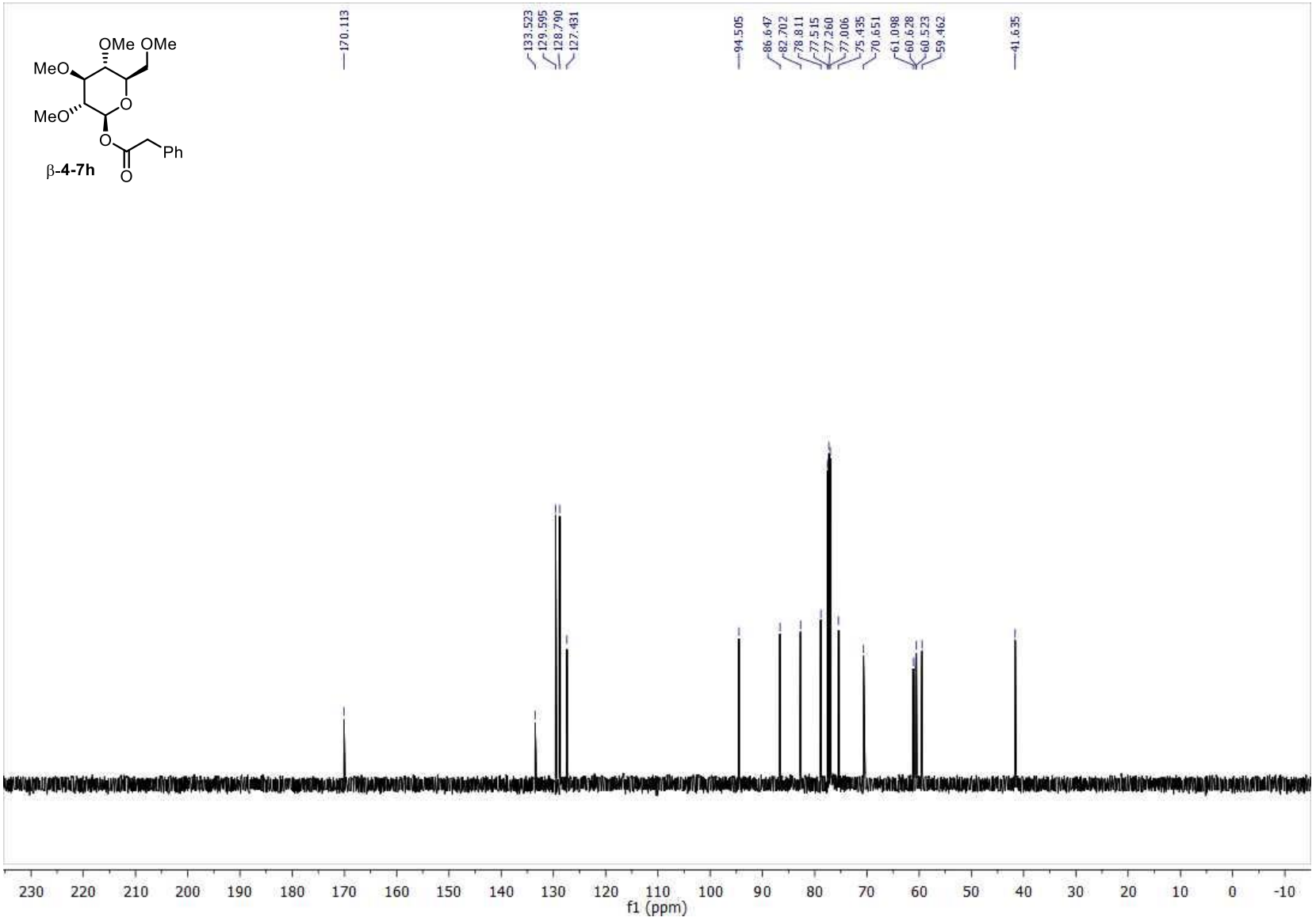

OBn OBn
BnO
O
O
Ph
O
β-4-7f
7.361 7.356 7.352 7.344 7.340 7.334 7.327 7.320 7.316 7.305 7.299 7.289 7.270 7.254 7.250
5.684 5.678 5.659 5.653 4.939 4.910 4.656 4.627 4.563 4.477 4.447 4.419 4.390 3.881 3.876 3.649 3.624 3.616 3.607 3.598 3.591 3.581 2.238 2.212 2.208 2.182 2.178 2.152 2.082 2.078 2.076 2.072 2.065 2.053 2.049 2.045 2.042 2.038
1.00
5.76 5.74 5.72 5.70 5.68 5.66 5.64 5.62 5.60 5.58
f1 (ppm)
21.05 1.00 1.00 1.04 2.02 2.15 1.01 6.14 1.00 1.04
10.5 10.0 9.5 9.0 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 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

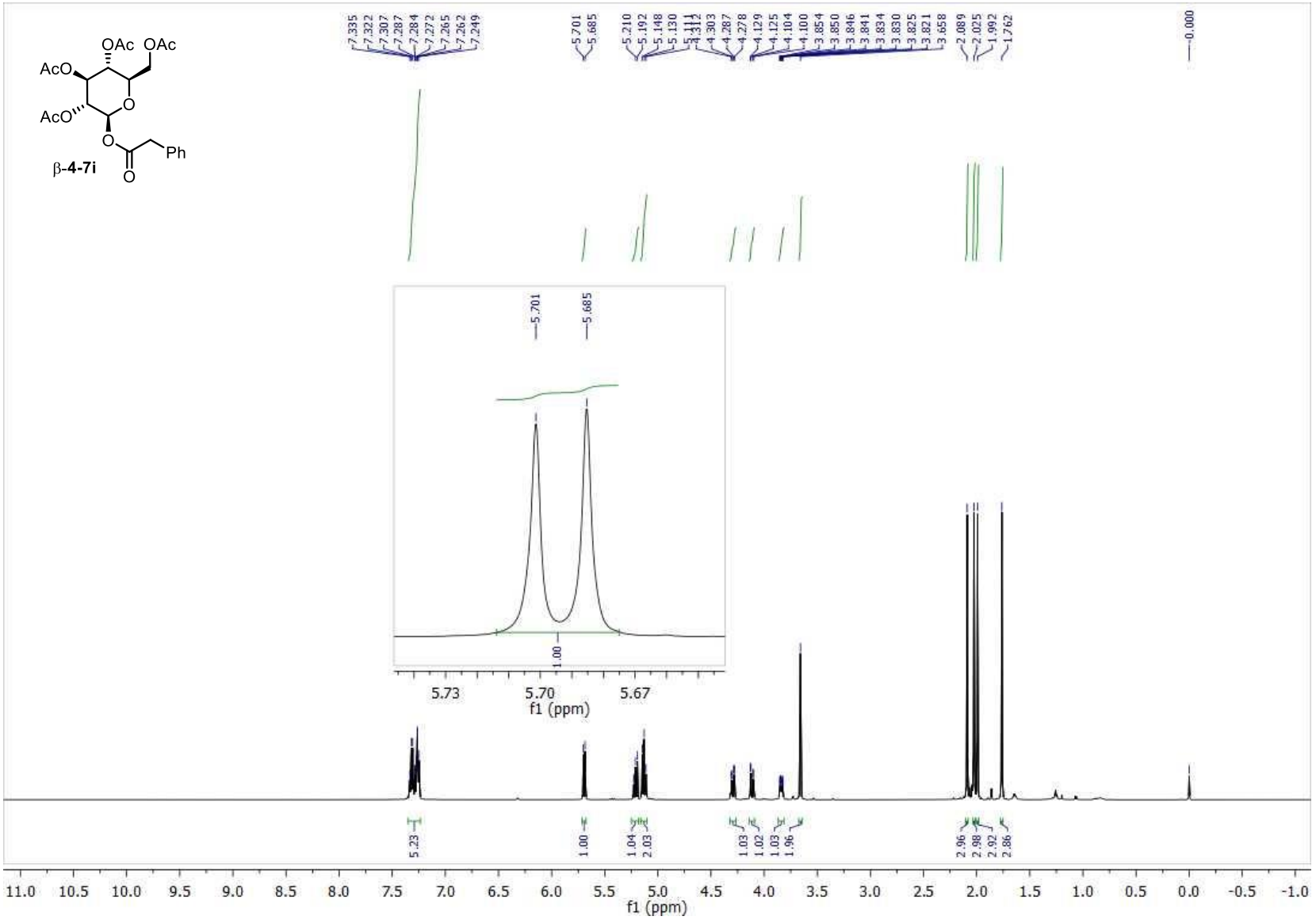

170.135
138.896
138.076
133.595
129.593
128.801
128.728
128.642
128.521
128.435
128.184
128.012
127.971
127.795
127.574
127.419
93.213
77.578
77.260
76.943
75.086
74.611
73.744
71.544
70.659
68.744
41.336
31.637
OBn
OBn
BnO
O
O
Ph
O
β-4-7f
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

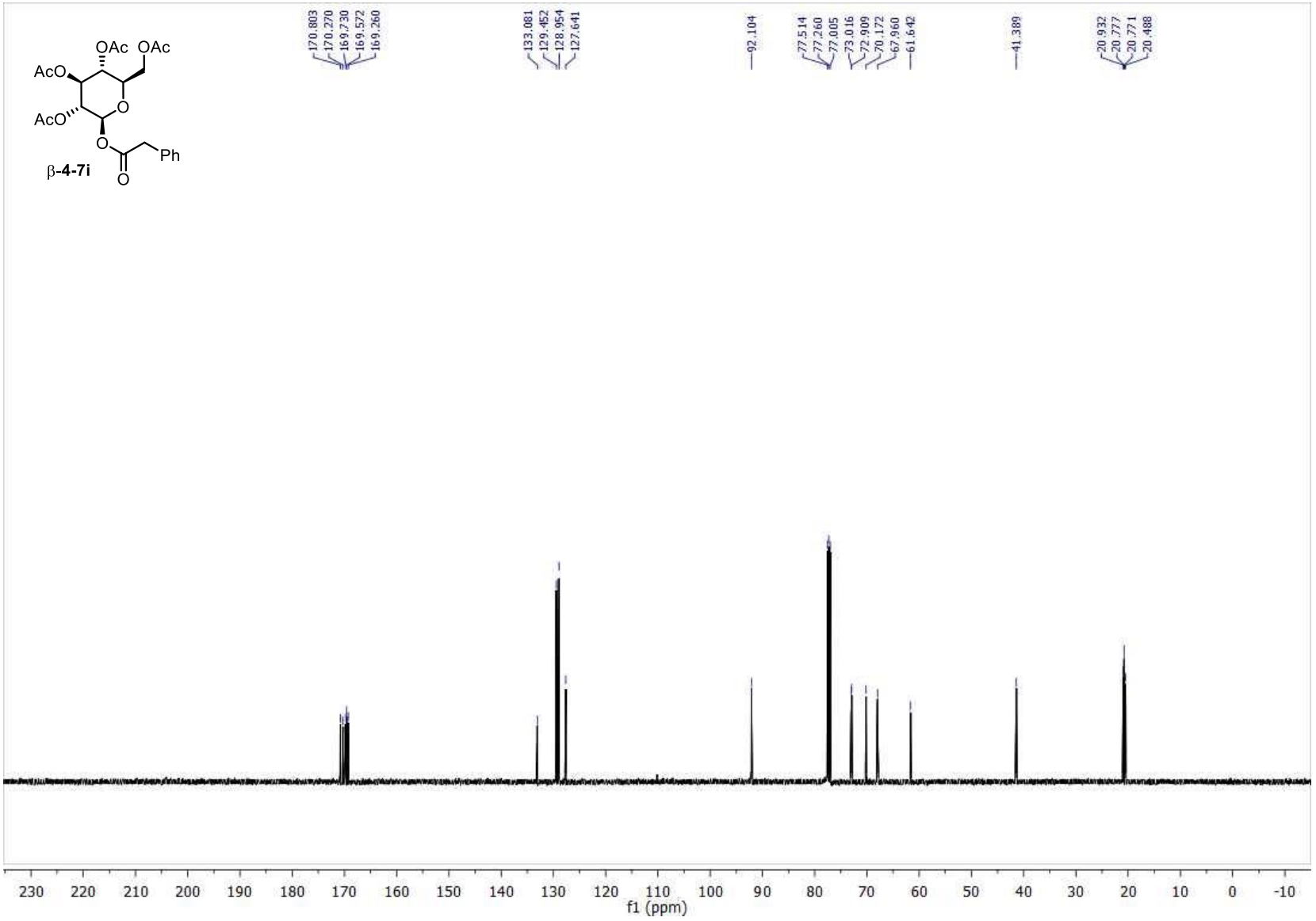

OMe OMe
MeO
MeO
O
O
Ph
O
α-4-6h
7.336
7.321
7.306
7.296
7.282
7.276
7.273
7.263
7.259
6.335
6.328
3.701
3.608
3.523
3.510
3.491
3.473
3.470
3.464
3.448
3.445
3.422
3.351
3.338
3.287
3.280
3.268
3.261
3.254
3.235
3.216
0.000
6.335
6.328
1.00
6.36
6.33
6.30
f1 (ppm)
5.34
1.00
2.11
3.10
3.31
3.10
3.29
4.03
2.33
10.5
10.0
9.5
9.0
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
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

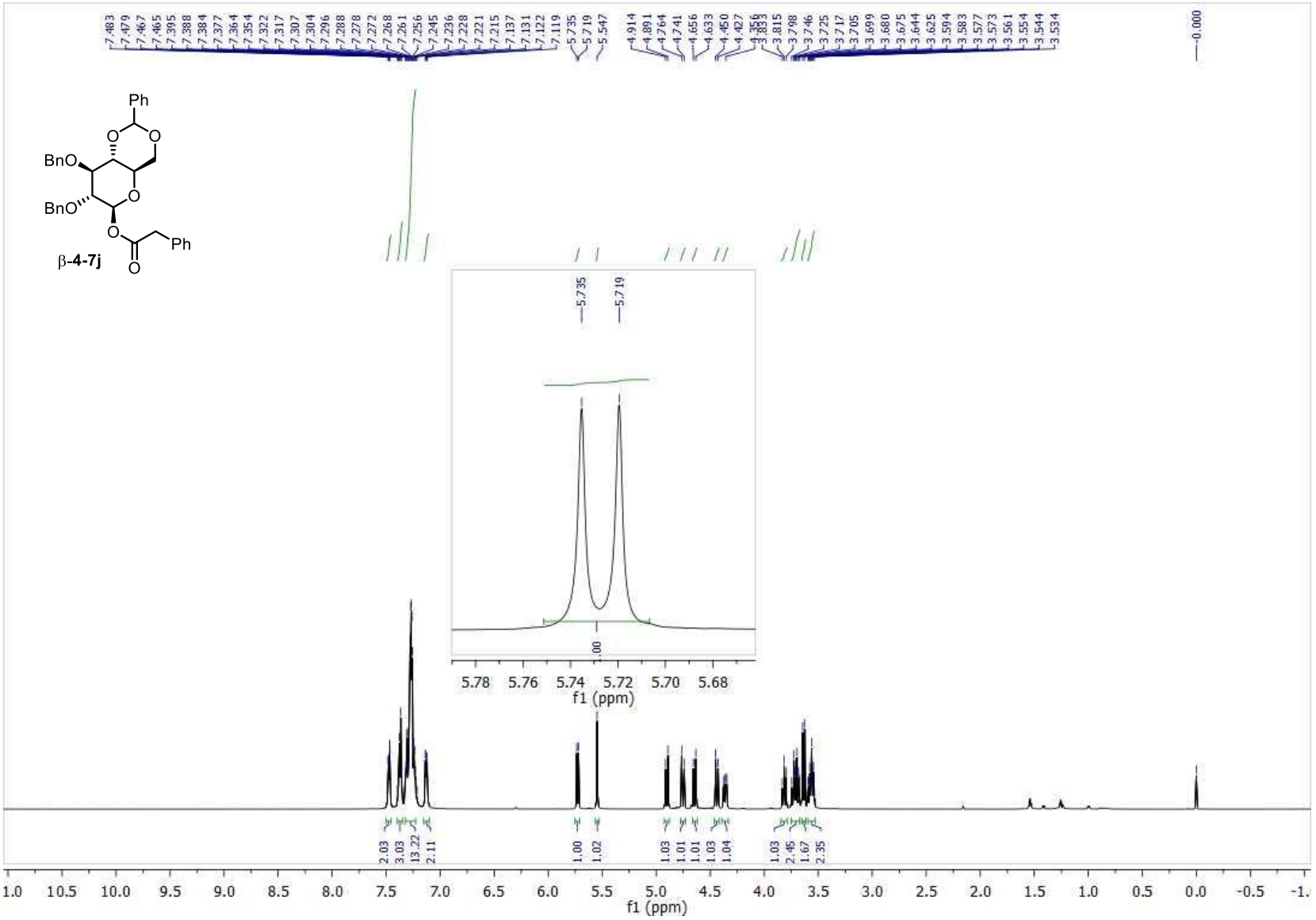

OMe OMe
MeO
MeO
O
O
Ph
O
α-4-6h
170.186
133.859
129.527
128.783
127.385
90.124
83.163
81.058
78.712
77.515
77.260
77.006
72.759
61.108
60.751
59.396
59.136
41.583
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

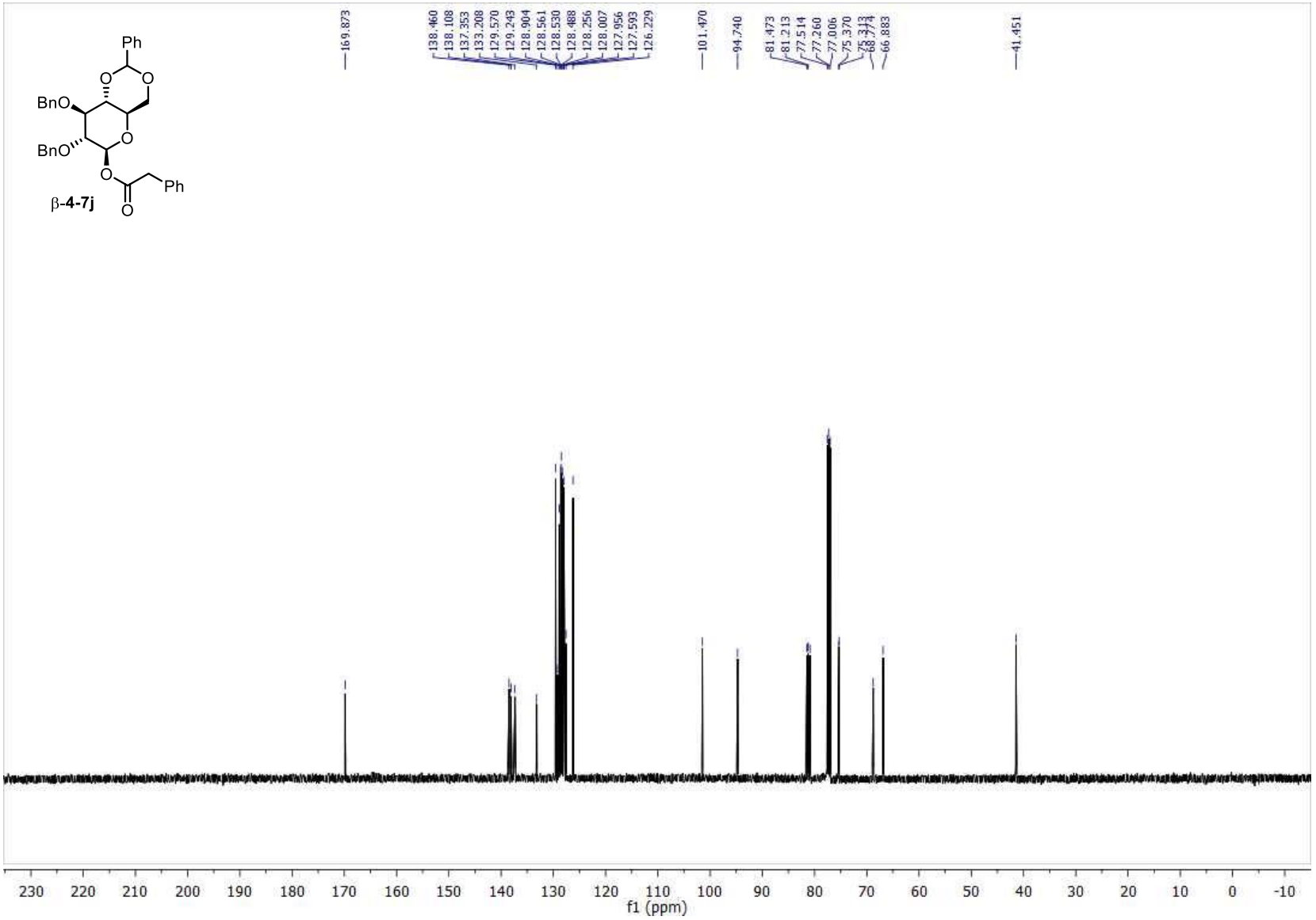

β-4-7h
f1 (ppm)
f1 (ppm)

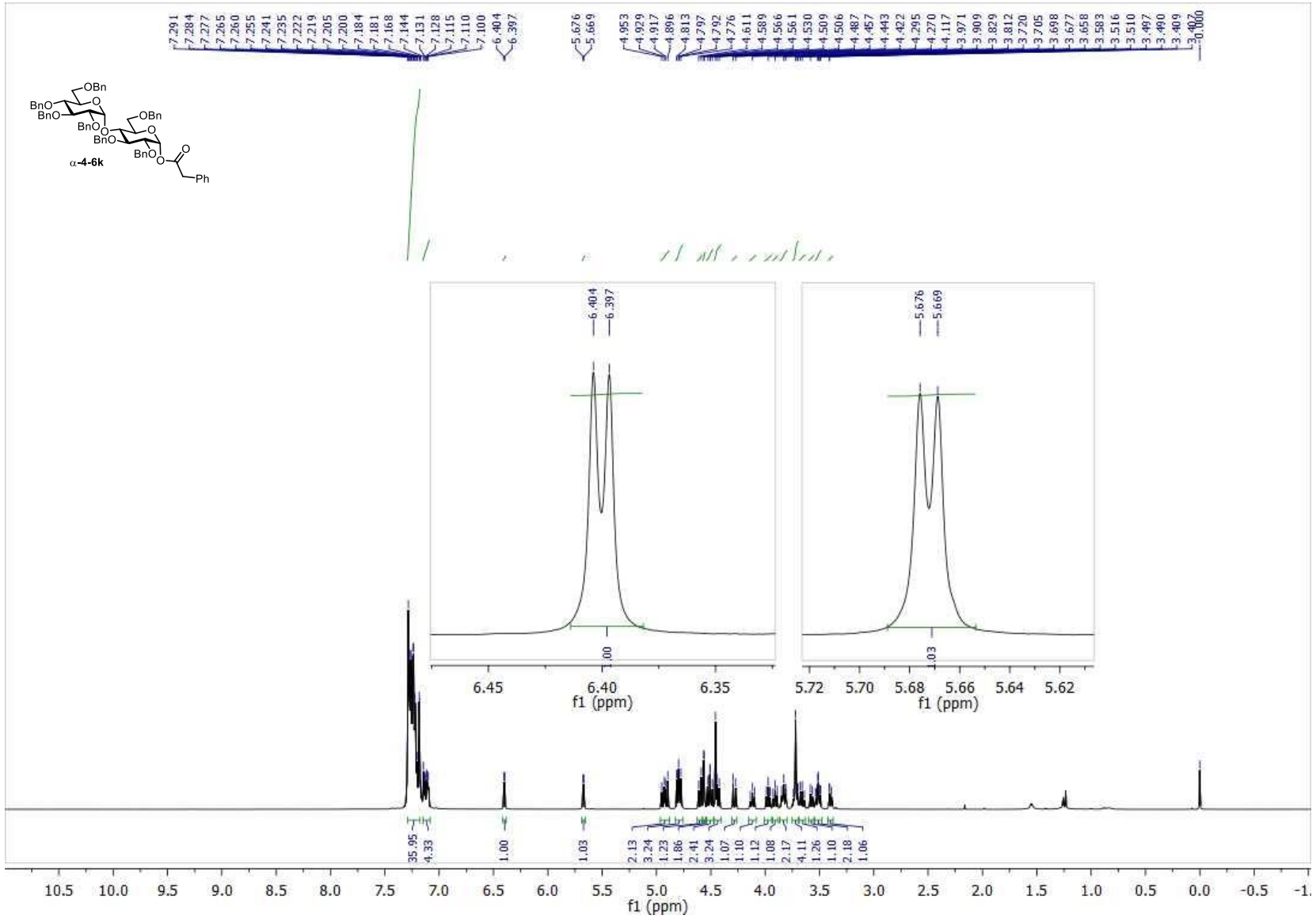

OMe OMe
MeO
MeO
O
O
Ph
O
β-4-7h
170.113
133.523
129.595
128.790
127.431
94.505
86.647
82.702
78.811
77.515
77.260
77.006
75.435
70.651
61.098
60.628
60.523
59.462
41.635
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

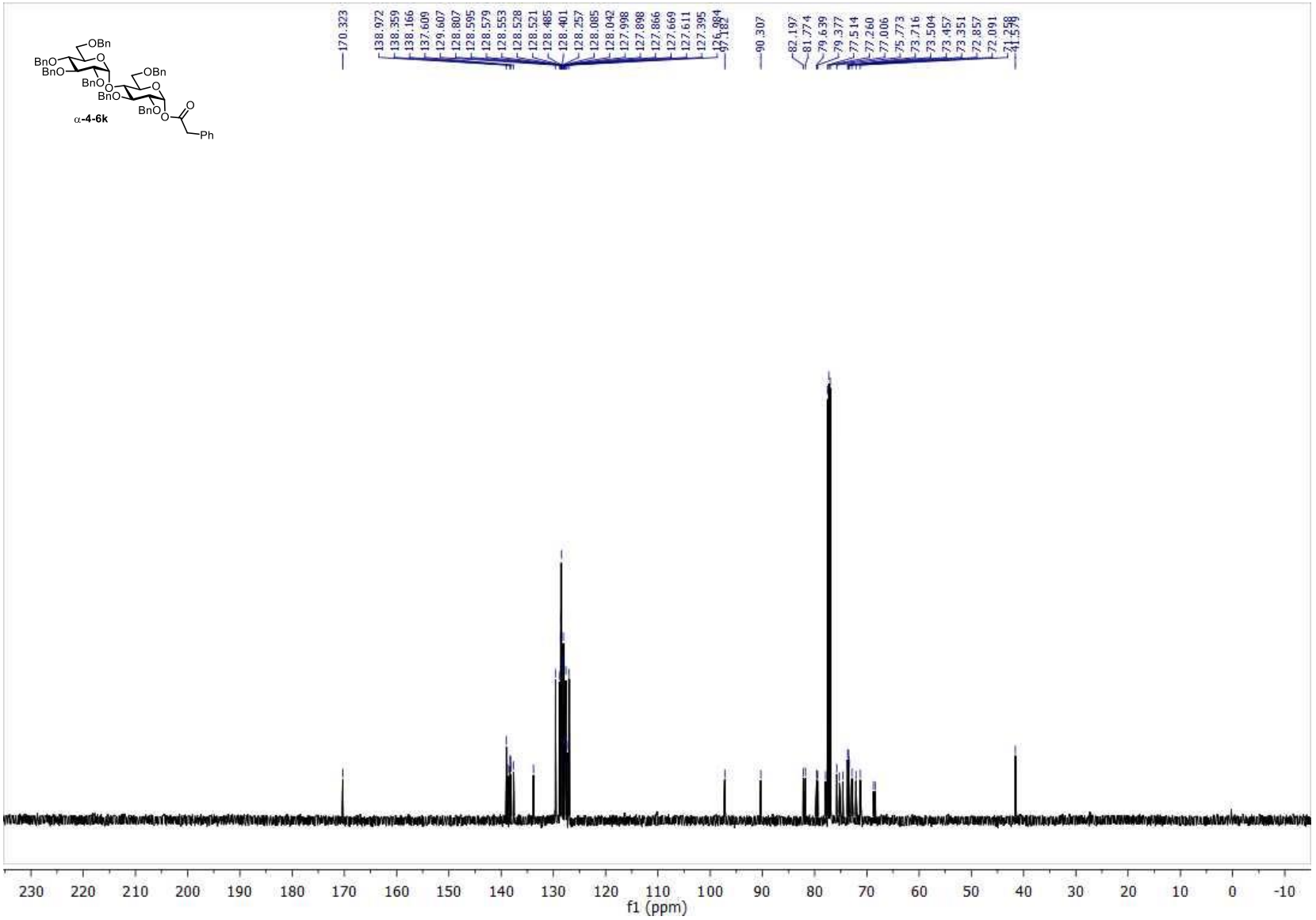

β-4-7i
f1 (ppm)

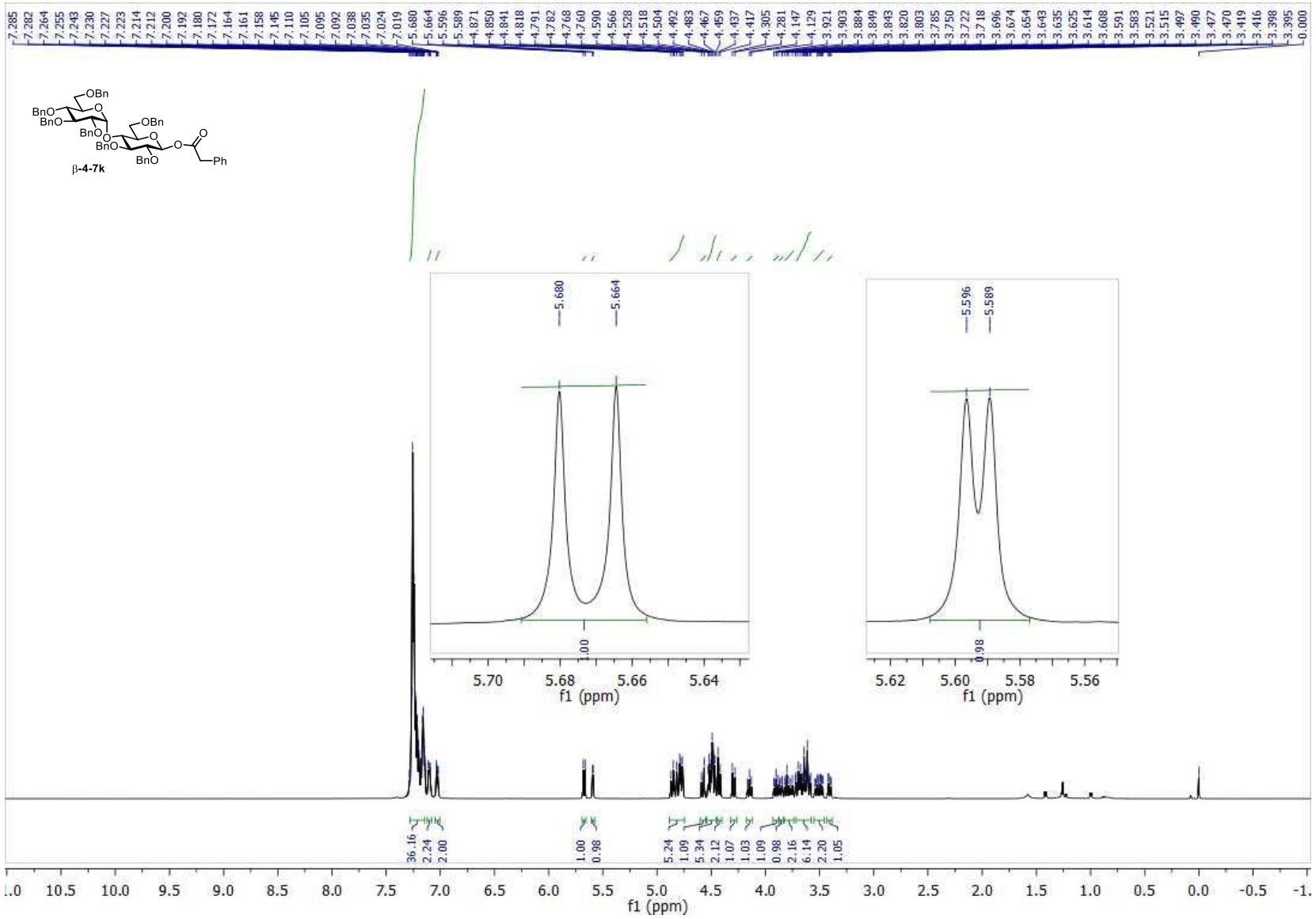

OAc
OAc
AcO
AcO
O
O
O
Ph
β-4-7i
170.803
170.270
169.730
169.572
169.260
133.081
129.452
128.954
127.641
92.104
77.514
77.260
77.005
73.016
72.909
70.172
67.960
61.642
41.389
20.932
20.777
20.771
20.488
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

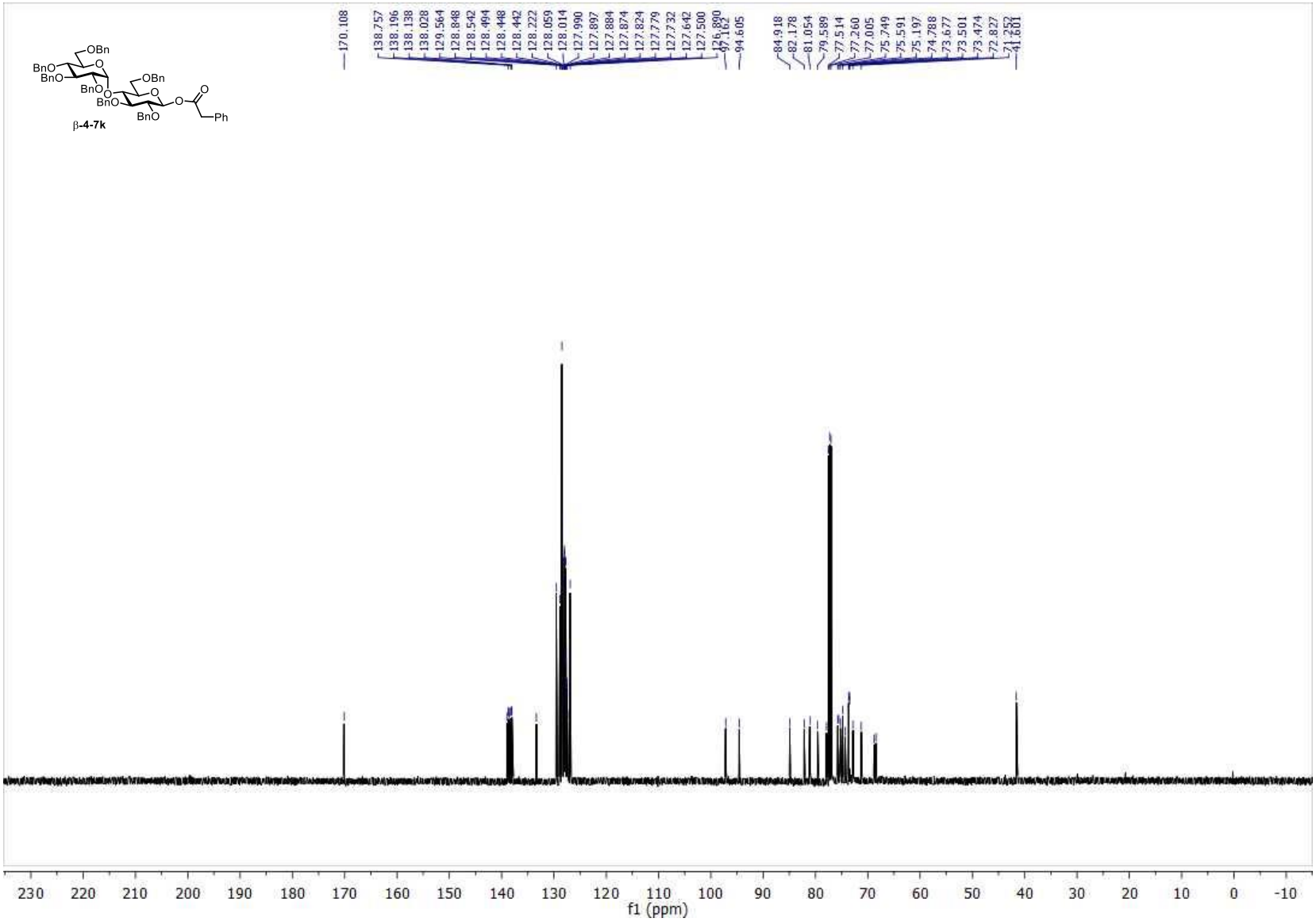

β-4-7j
f1 (ppm)

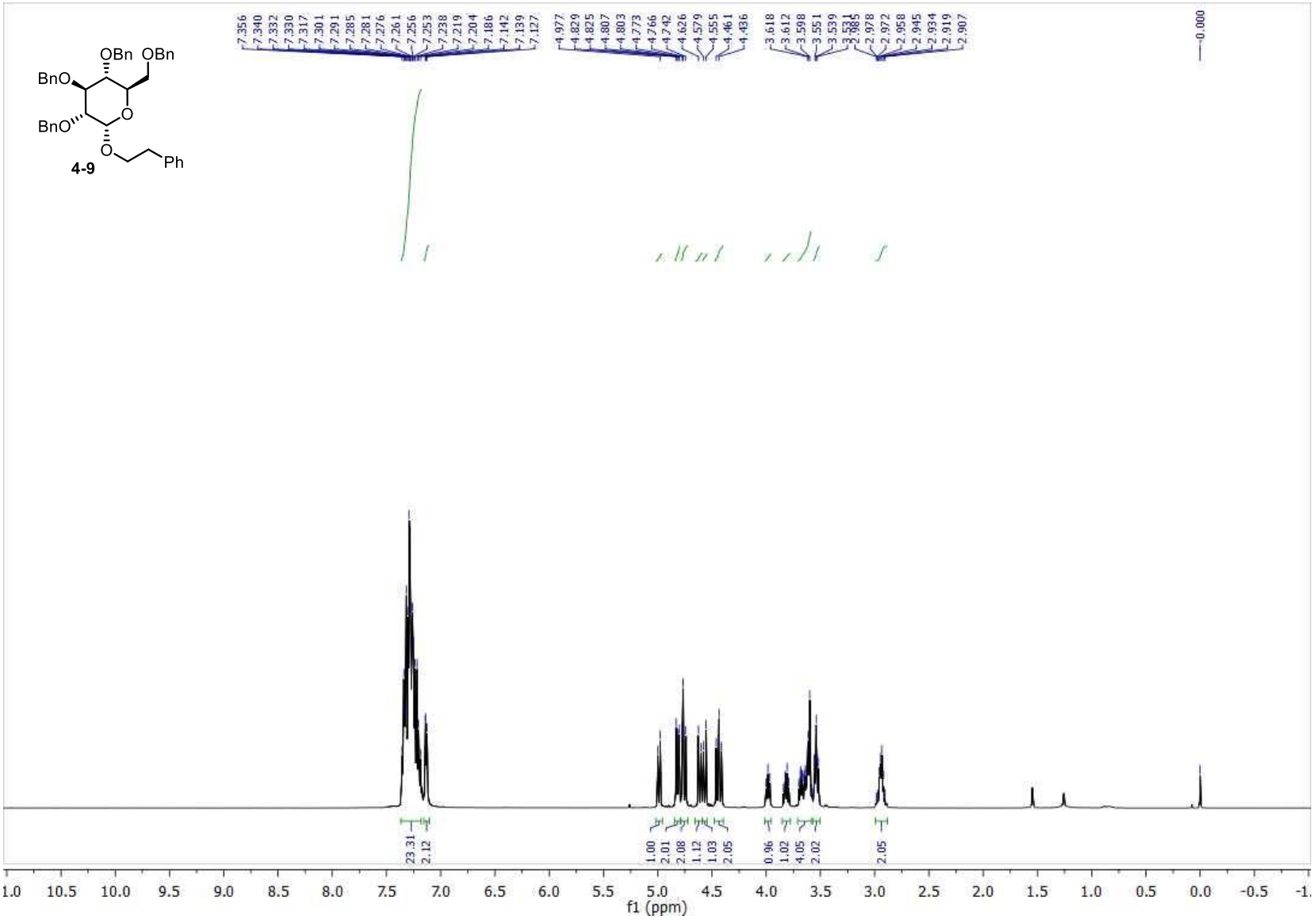

Ph
BnO
BnO
O
Ph
O
β-4-7j
169.873
138.460
138.108
137.353
133.208
129.570
129.243
128.904
128.561
128.530
128.488
128.256
128.007
127.956
127.593
126.229
101.470
94.740
81.473
81.213
77.514
77.260
77.006
75.370
66.883
41.451
f1 (ppm)


α-4-6k
f1 (ppm)


α-4-6k
170.323
138.972
138.359
138.166
137.609
129.607
128.807
128.595
128.579
128.553
128.528
128.521
128.485
128.401
128.257
128.085
128.042
127.998
127.898
127.866
127.669
127.611
127.395
126.984
97.182
90.307
82.197
81.774
79.639
79.377
77.514
77.260
77.006
75.773
73.716
73.504
73.457
73.351
72.857
72.091
41.578
f1 (ppm)


β-4-7k
5.680
5.664
5.596
5.589
1.00
0.98
f1 (ppm)
36.16
2.24
2.00
1.00
0.98
5.24
1.09
5.34
2.12
1.07
1.03
1.09
0.98
2.16
6.14
2.20
1.05


β-4-7k
170.108
138.757
138.196
138.138
138.028
129.564
128.848
128.542
128.494
128.448
128.442
128.222
128.059
128.014
127.990
127.897
127.884
127.874
127.824
127.779
127.732
127.642
127.500
126.880
97.162
94.605
84.918
82.178
81.054
79.589
77.514
77.260
77.005
75.749
75.591
75.197
74.788
73.677
73.501
73.474
72.827
71.757
41.601
f1 (ppm)


OBn OBn
BnO
BnO
O
O
Ph
4-9
7.356
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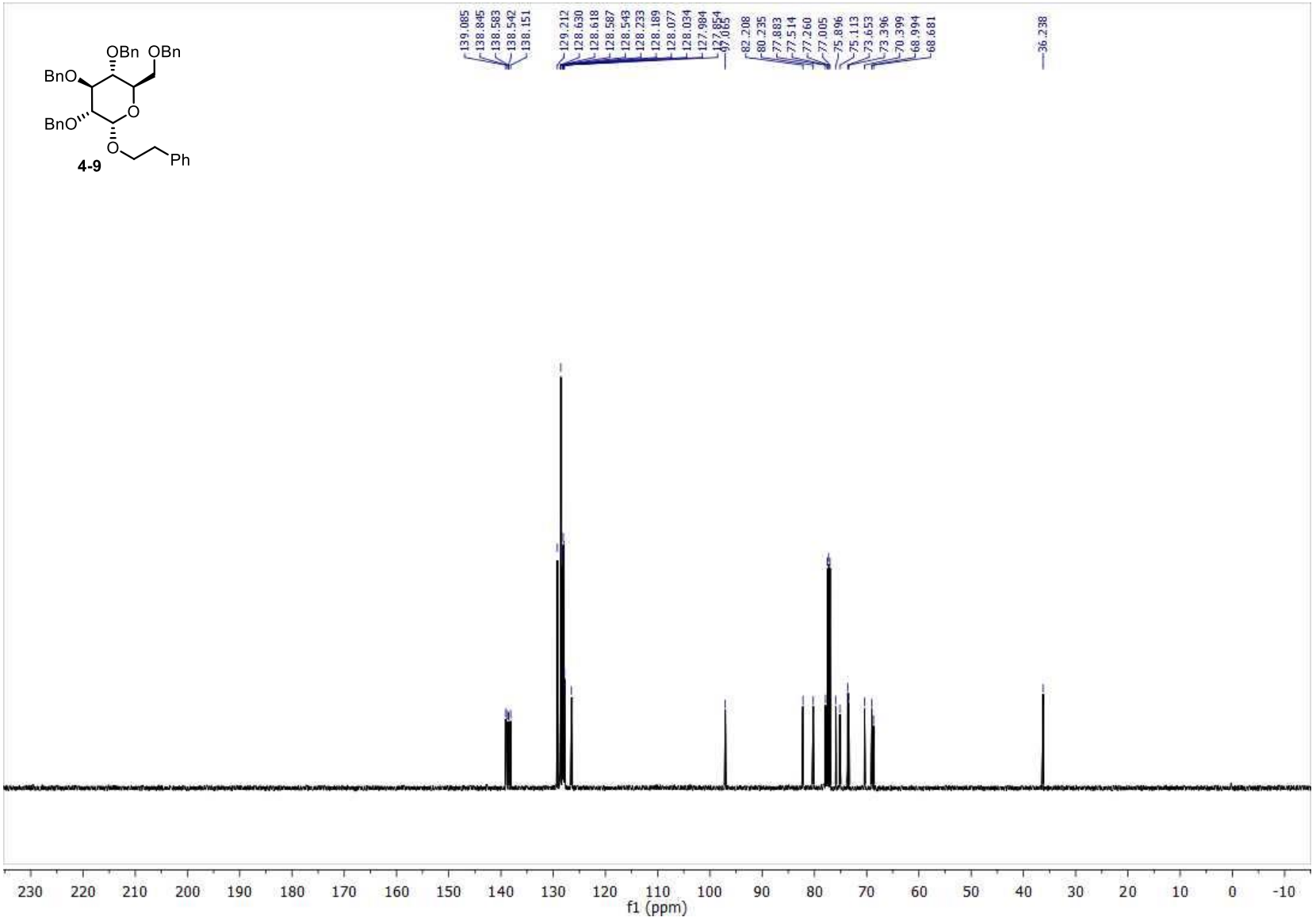
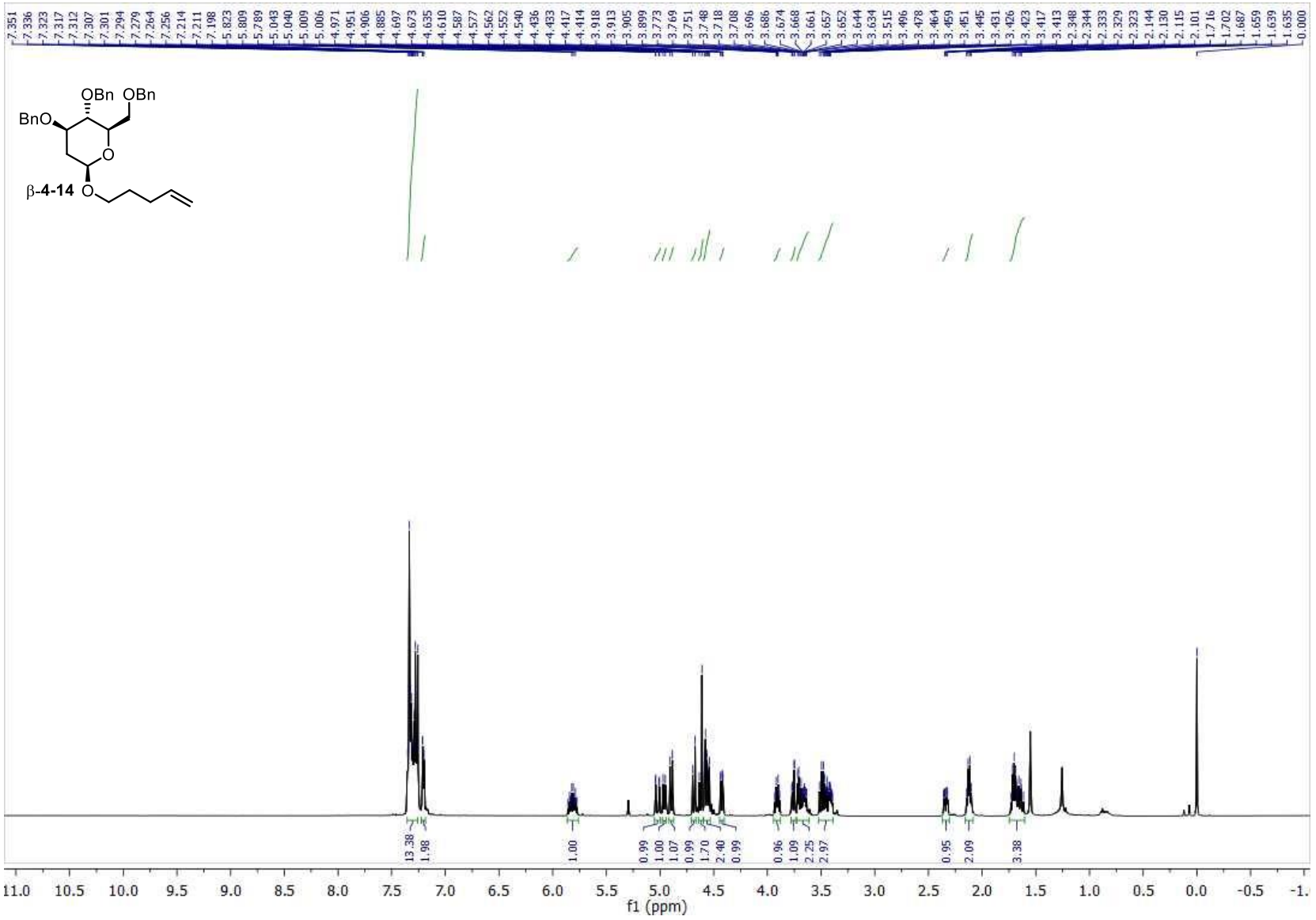
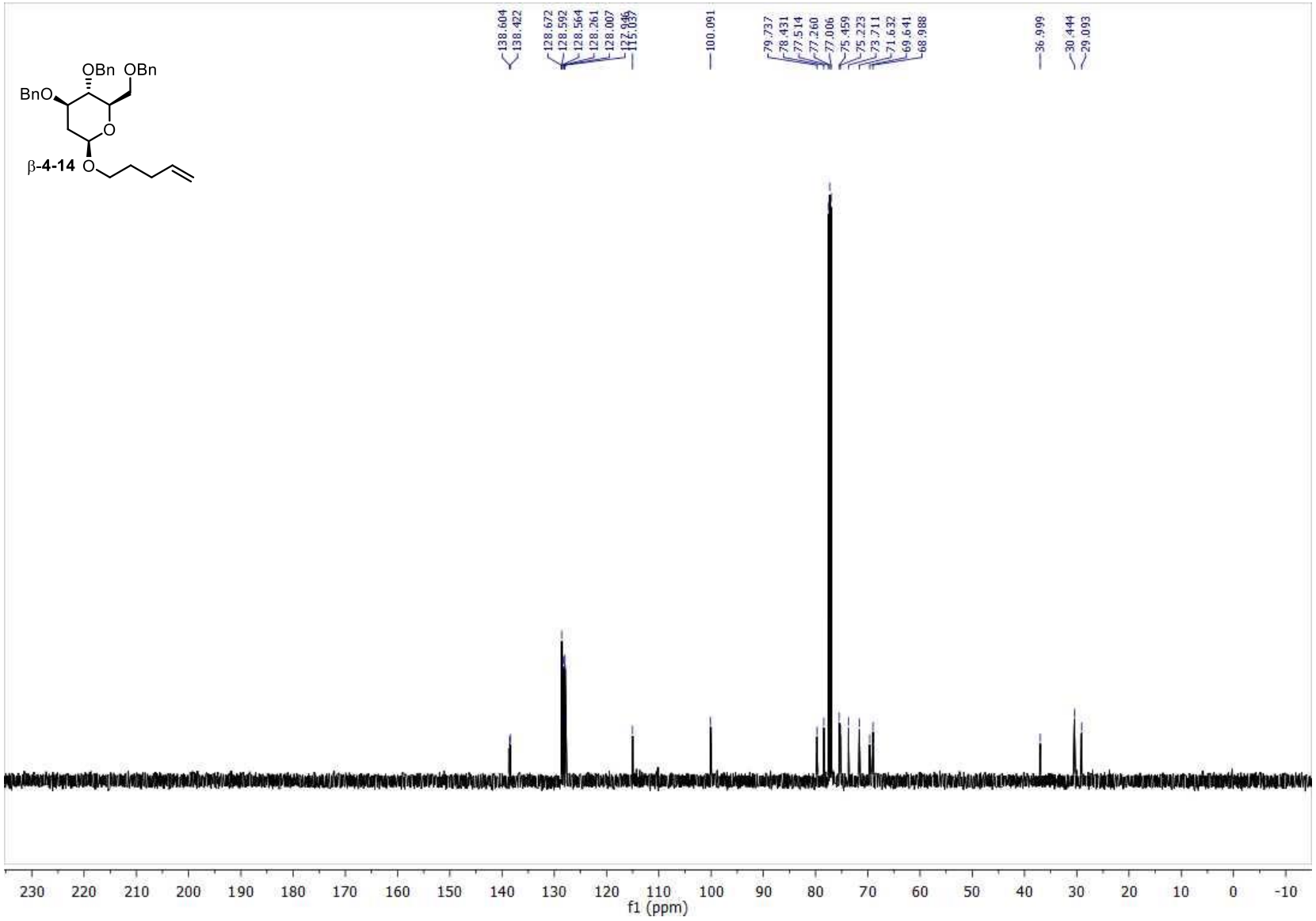
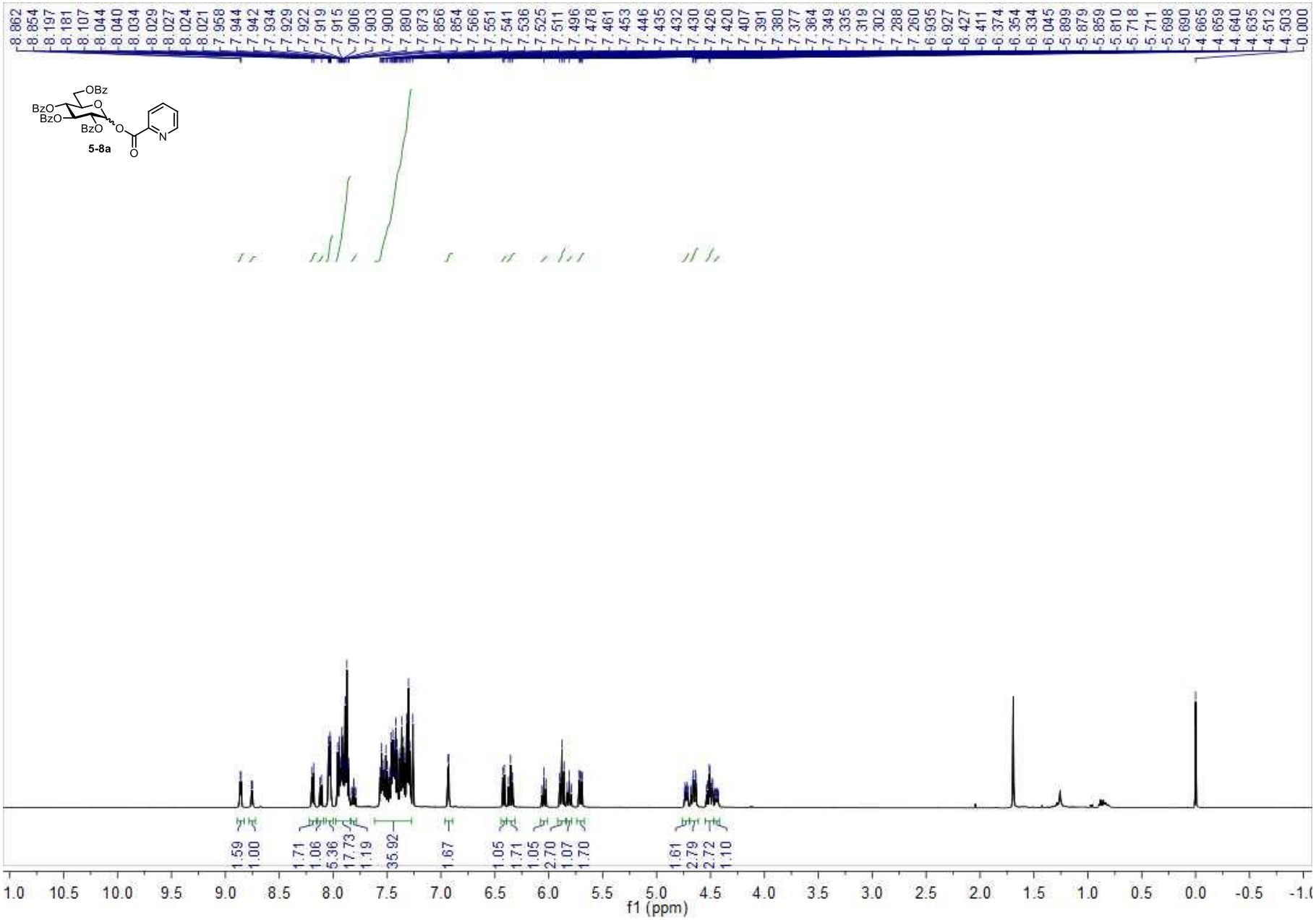
7.330
7.317
7.301
7.291
7.285
7.281
7.276
7.261
7.256
7.253
7.238
7.219
7.204
7.186
7.142
7.139
7.127
4.977
4.829
4.825
4.807
4.803
4.773
4.766
4.742
4.626
4.579
4.555
4.461
4.436
3.618
3.612
3.598
3.551
3.539
3.531
3.485
2.978
2.972
2.958
2.945
2.934
2.919
2.907
0.000
23.31
2.12
1.00
2.01
2.08
1.12
1.03
2.05
0.96
1.02
4.05
2.02
2.05
f1 (ppm)


OBn OBn
BnO
BnO
O
O
Ph
4-9
139.085
138.845
138.583
138.542
138.151
129.212
128.630
128.618
128.587
128.543
128.233
128.189
128.077
128.034
127.984
127.854
127.065
82.208
80.235
77.883
77.514
77.260
77.005
75.896
75.113
73.653
73.396
70.399
68.994
68.681
36.238
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


OBn
OBn
BnO
O
β-4-14
O
f1 (ppm)


OBn
OBn
BnO
O
β-4-14
O
138.604
138.422
128.672
128.592
128.564
128.261
128.007
100.091
79.737
78.431
77.514
77.260
77.006
75.459
75.223
73.711
71.632
69.641
68.988
36.999
30.444
29.093
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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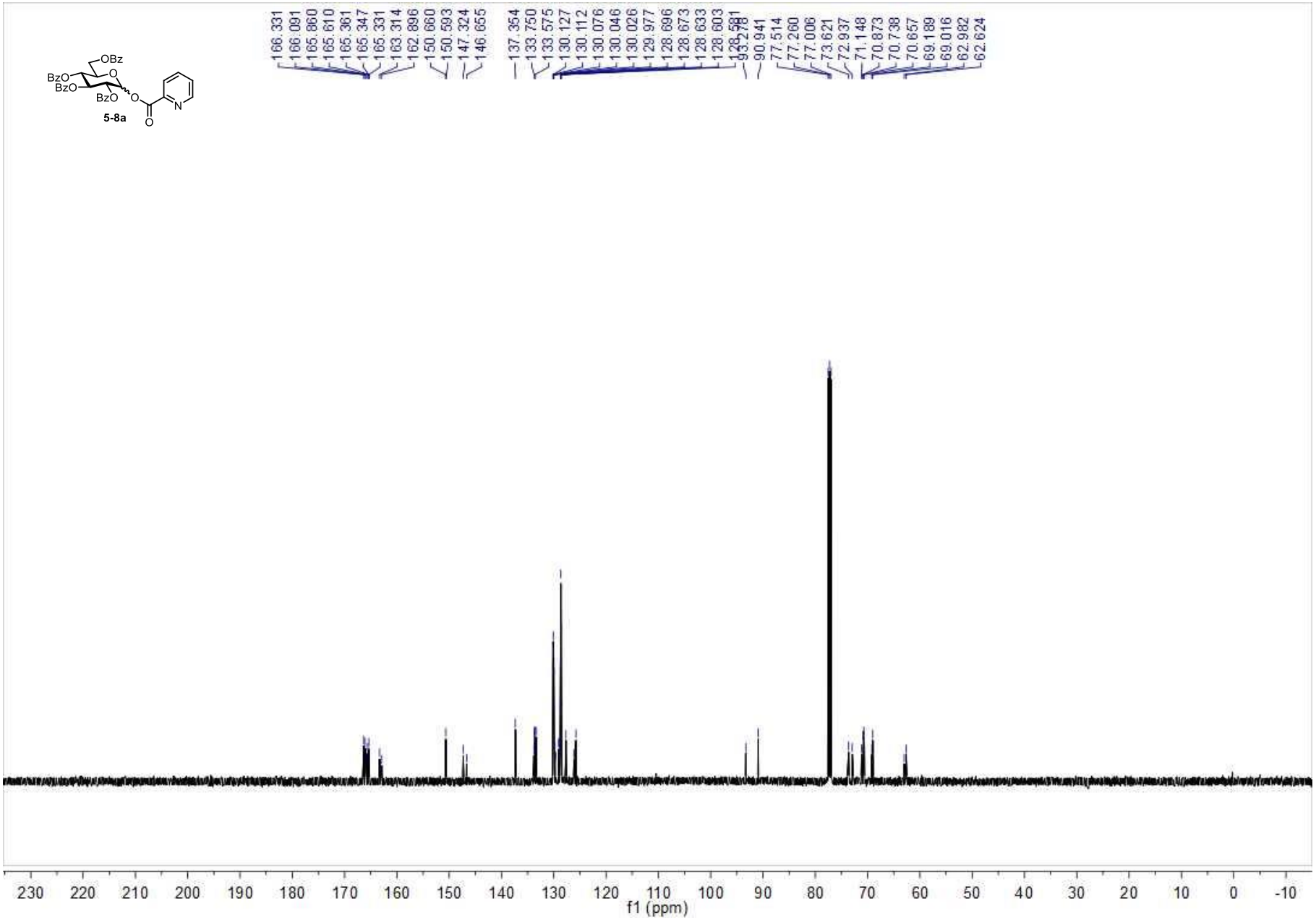
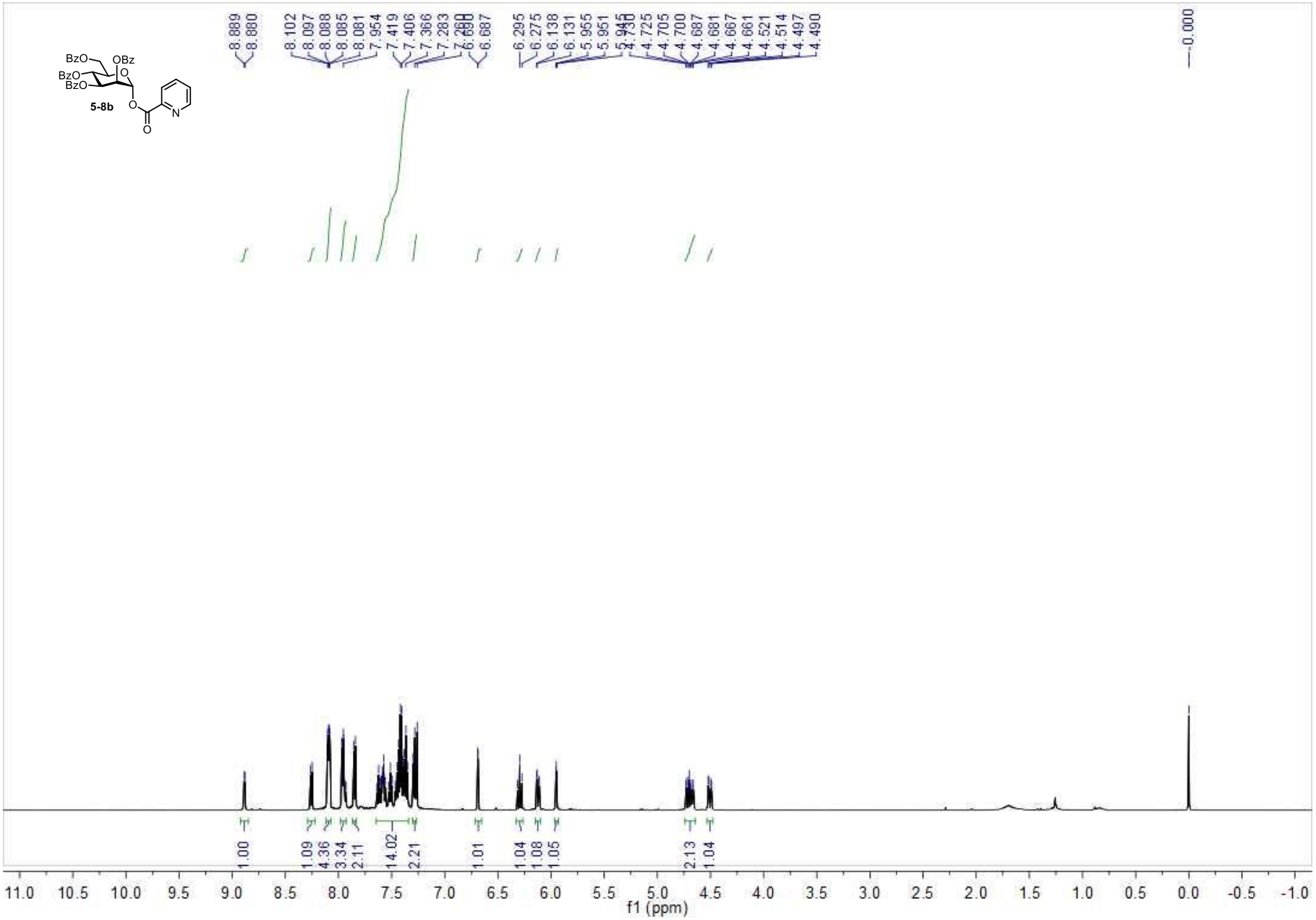
8.040
8.034
8.029
8.027
8.024
8.021
7.958
7.944
7.942
7.934
7.929
7.922
7.919
7.915
7.906
7.903
7.900
7.890
7.873
7.856
7.854
7.566
7.551
7.541
7.536
7.525
7.511
7.496
7.478
7.461
7.453
7.446
7.435
7.432
7.430
7.426
7.420
7.407
7.391
7.380
7.377
7.364
7.349
7.335
7.319
7.302
7.288
7.260
6.935
6.927
6.427
6.411
6.374
6.354
6.334
6.045
5.899
5.879
5.859
5.810
5.718
5.711
5.698
5.690
4.665
4.659
4.640
4.635
4.512
4.503
0.000
OBz
BzO
BzO
BzO
O
O
N
5-8a
1.59
1.00
1.71
1.06
5.36
17.73
1.19
35.92
1.67
1.05
1.71
1.05
2.70
1.07
1.70
1.61
2.79
2.72
1.10
1.0
10.5
10.0
9.5
9.0
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
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


166.331
166.091
165.860
165.610
165.361
165.347
165.331
163.314
162.896
150.660
150.593
147.324
146.655
137.354
133.750
133.575
130.127
130.112
130.076
130.046
130.026
129.977
128.696
128.673
128.633
128.603
128.581
93.278
90.941
77.514
77.260
77.006
73.621
72.937
71.148
70.873
70.738
70.657
69.189
69.016
62.982
62.624
OBz
BzO
BzO
BzO
O
O
N
5-8a
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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BzO
BzO
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O
N
O
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8.088
8.085
8.081
7.954
7.419
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7.283
6.687
6.295
6.275
6.138
6.131
5.955
5.951
4.725
4.705
4.700
4.687
4.681
4.667
4.661
4.521
4.514
4.497
4.490
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1.09
4.36
3.34
2.11
14.02
2.21
1.01
1.04
1.08
1.05
2.13
1.04
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10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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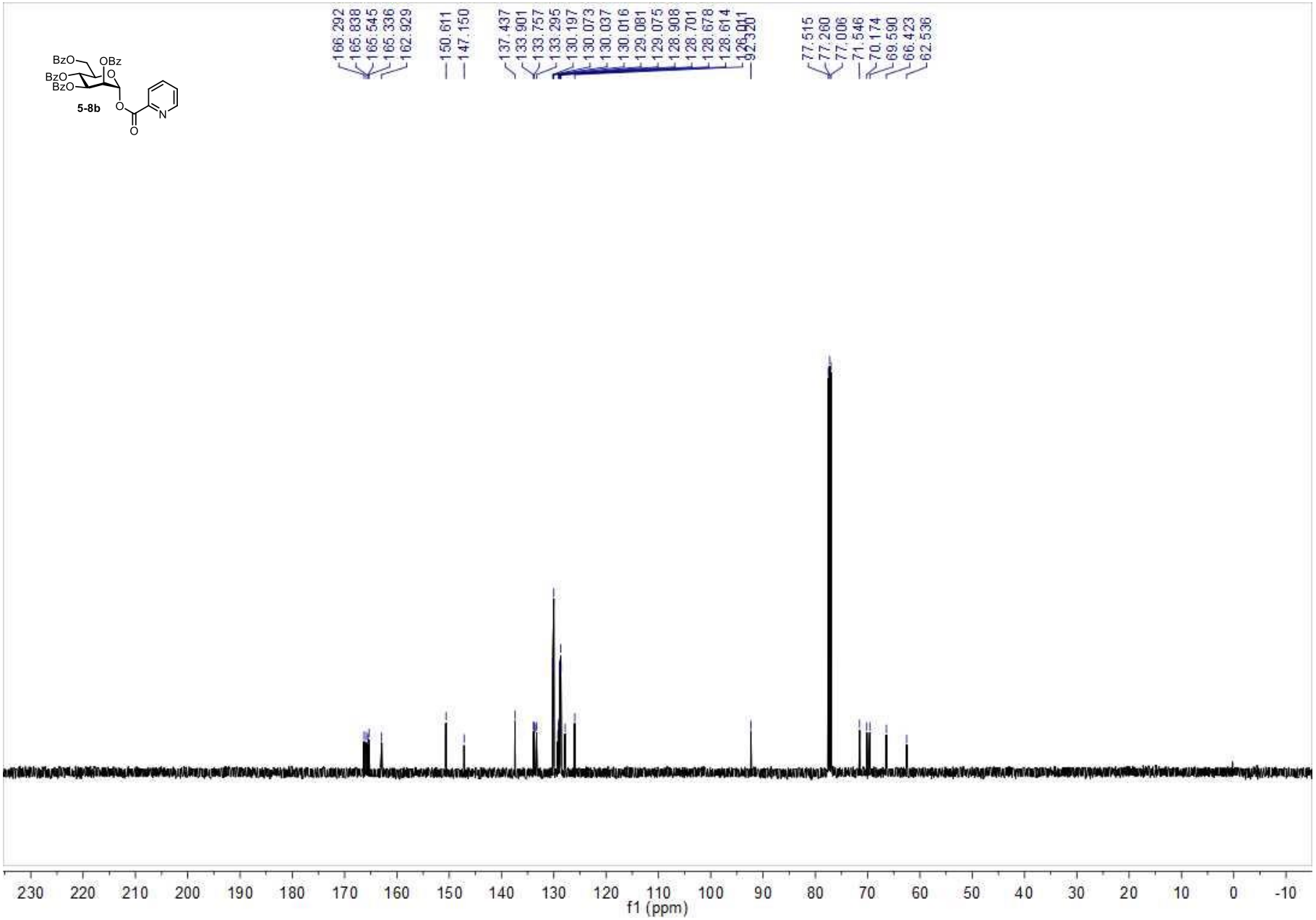
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)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128.678
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77.260
77.006
71.546
70.174
69.590
66.423
62.536
BzO
OBz
BzO
BzO
O
O
N
5-8b
230
220
210
200
190
180
170
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30
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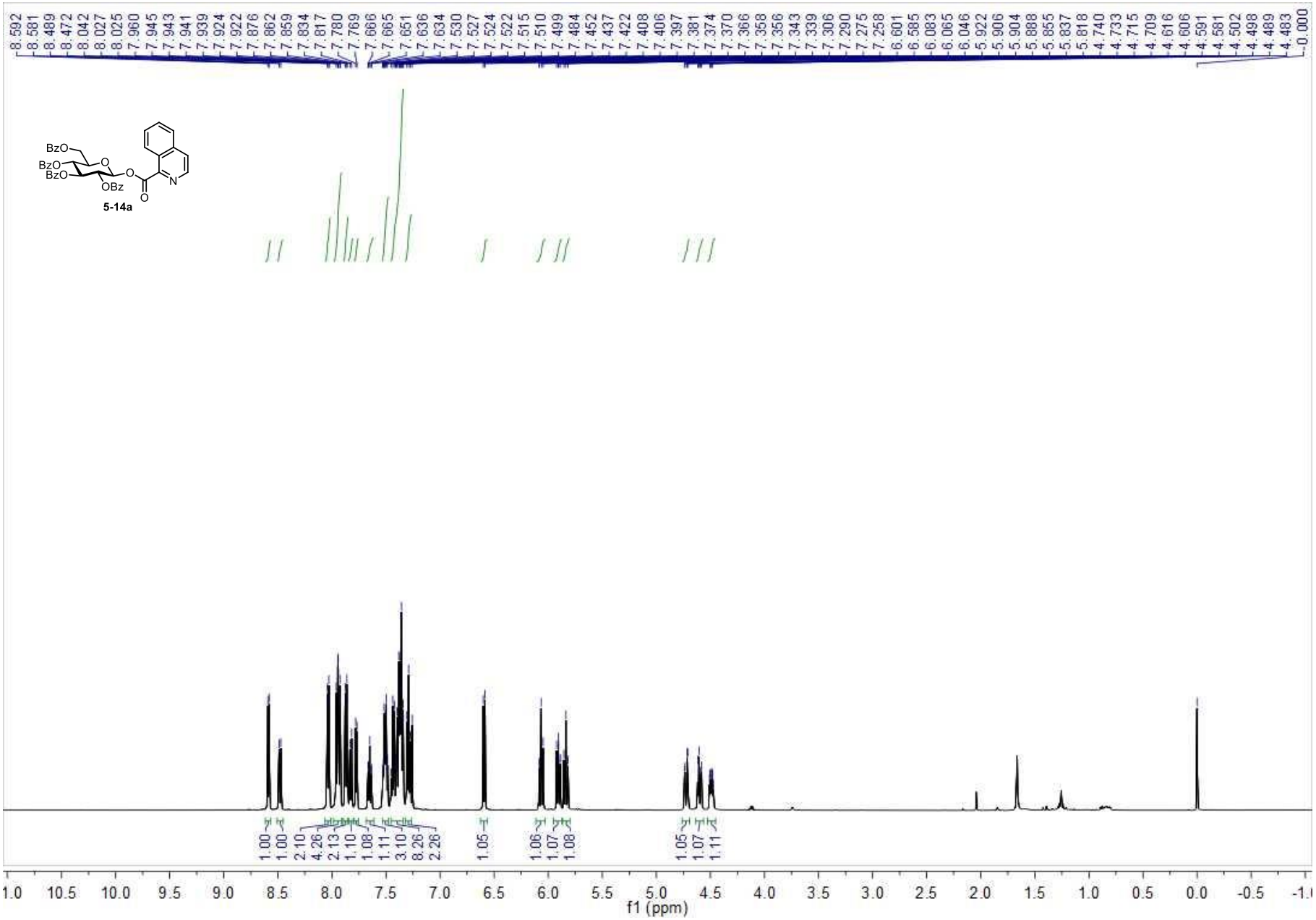
f1 (ppm)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7.859
7.834
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7.780
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7.651
7.636
7.634
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7.527
7.524
7.522
7.515
7.510
7.499
7.484
7.452
7.437
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7.406
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4.606
4.591
4.581
4.502
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4.489
4.483
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BzO
BzO
BzO
OBz
O
N
5-14a
1.00
1.00
2.10
4.26
2.13
1.10
1.08
1.11
3.10
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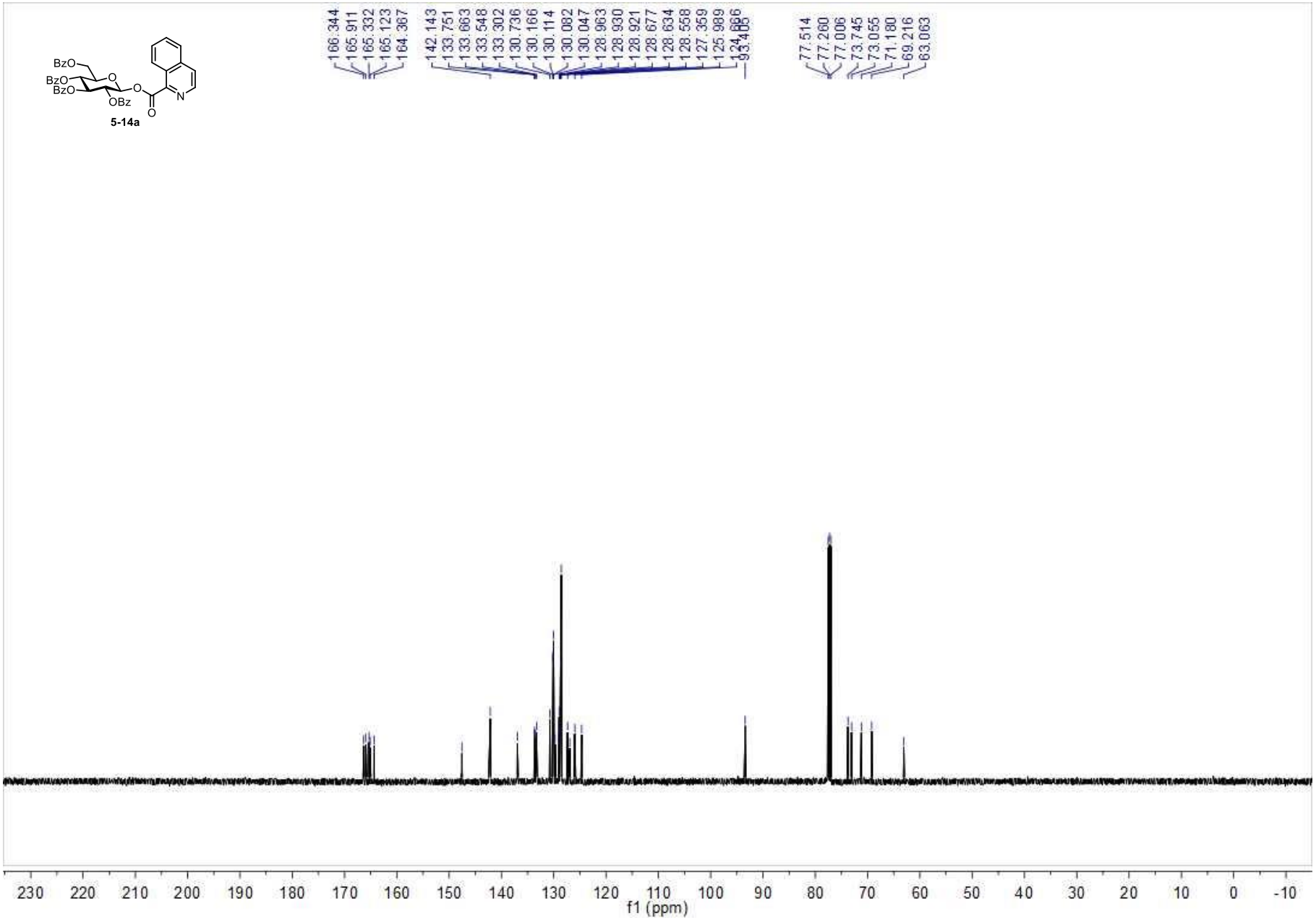
2.26
1.05
1.06
1.07
1.08
1.05
1.07
1.11
f1 (ppm)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BzO
OBz
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N
O
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133.548
133.302
130.736
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130.114
130.082
130.047
128.963
128.930
128.921
128.677
128.634
128.558
127.359
125.989
93.405
77.514
77.260
77.006
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71.180
69.216
63.063
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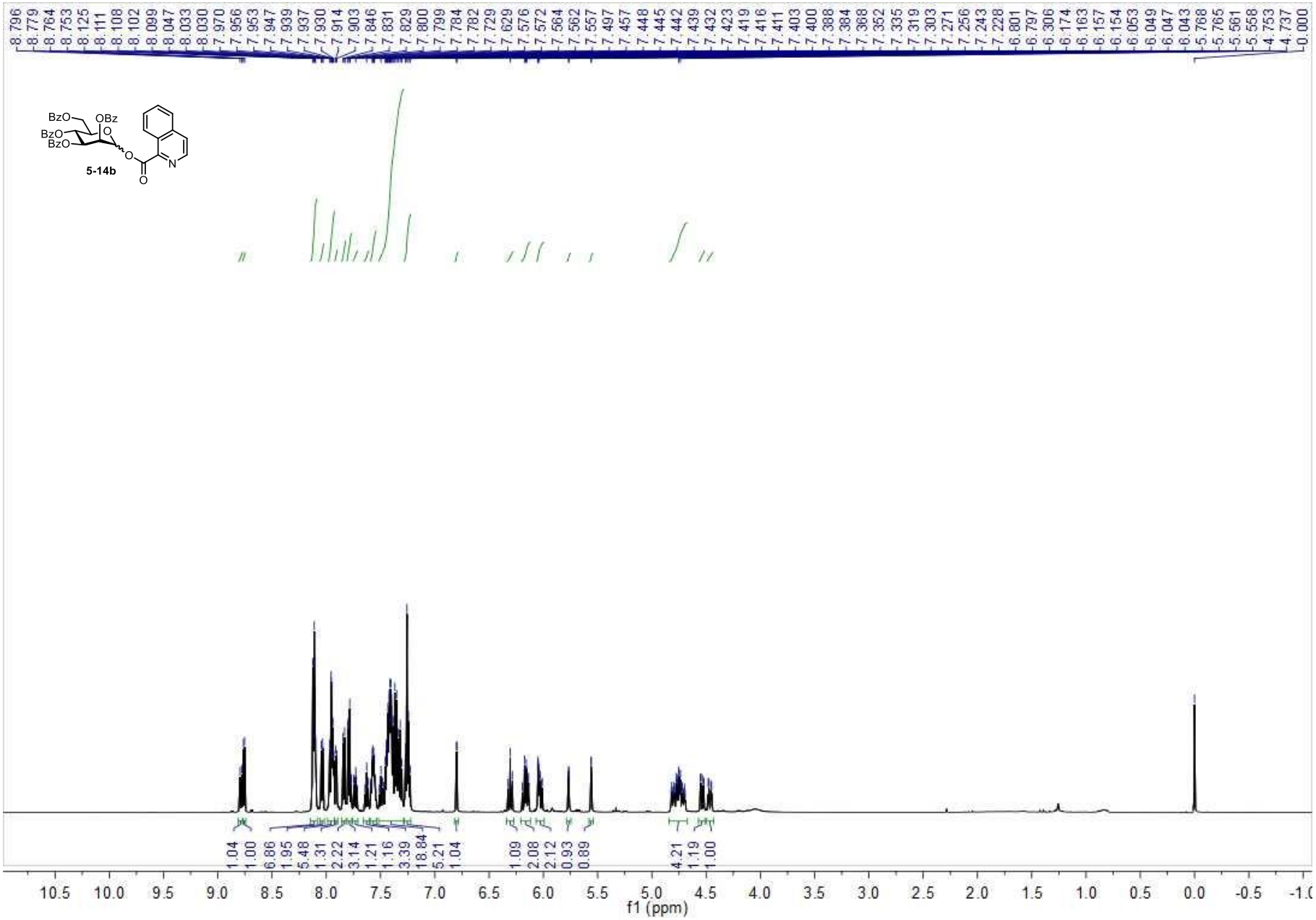
f1 (ppm)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8.102
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8.047
8.033
8.030
7.970
7.956
7.953
7.947
7.939
7.937
7.930
7.914
7.903
7.846
7.831
7.829
7.800
7.799
7.784
7.782
7.729
7.629
7.576
7.572
7.564
7.562
7.557
7.497
7.457
7.448
7.445
7.442
7.439
7.432
7.423
7.419
7.416
7.411
7.403
7.400
7.388
7.384
7.368
7.352
7.335
7.319
7.303
7.271
7.256
7.243
7.228
6.801
6.797
6.306
6.174
6.163
6.157
6.154
6.053
6.049
6.047
6.043
5.768
5.765
5.561
5.558
4.753
4.737
0.000
BzO
OBz
BzO
BzO
O
O
N
O
5-14b
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1.00
6.86
1.95
5.48
1.31
2.22
3.14
1.21
1.16
3.39
18.84
5.21
1.04
1.09
2.08
2.12
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0.89
4.21
1.19
1.00
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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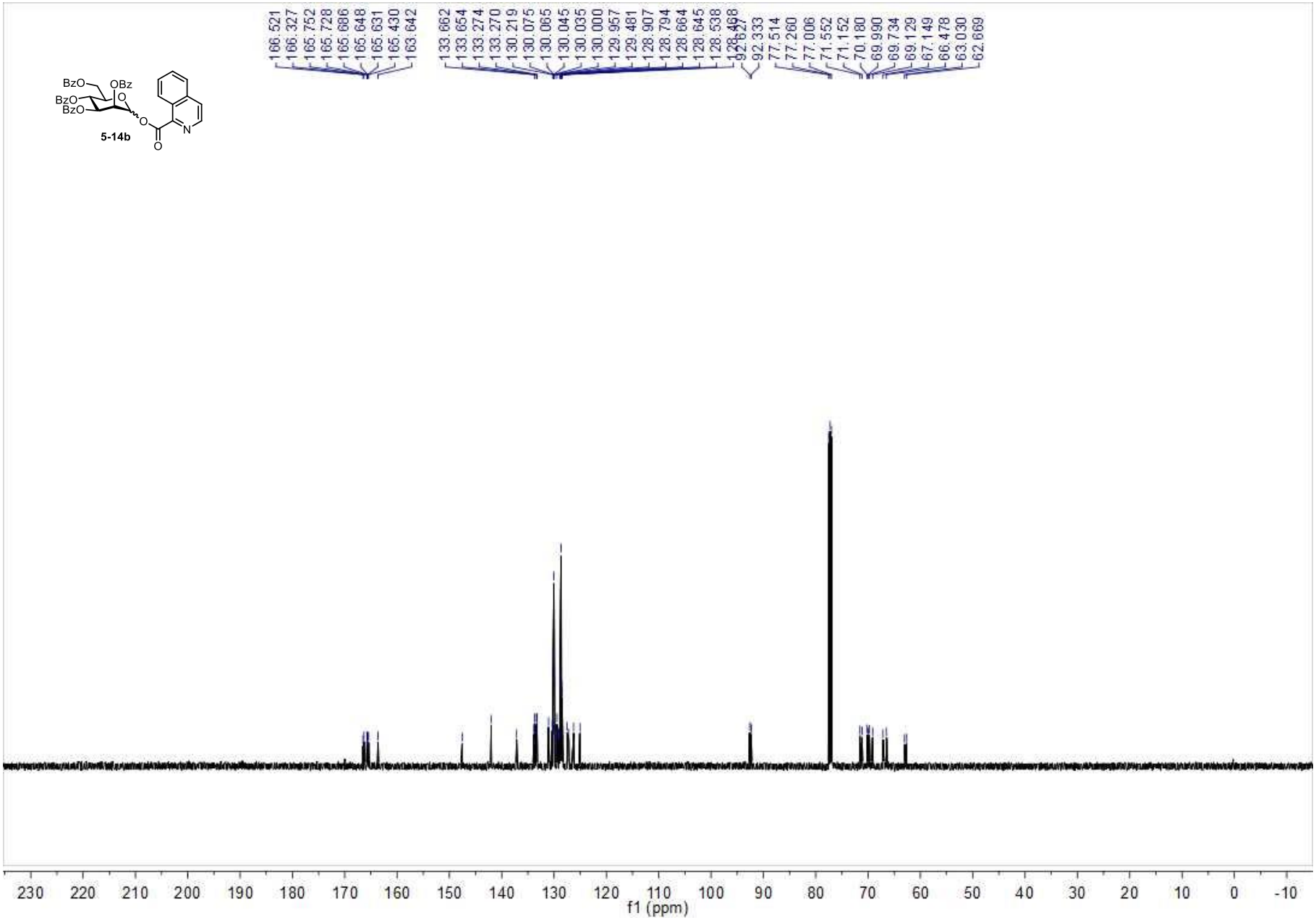
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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130.065
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130.035
130.000
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128.645
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92.333
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77.260
77.006
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71.152
70.180
69.990
69.734
69.129
67.149
66.478
63.030
62.669
BzO
OBz
BzO
BzO
O
O
N
O
5-14b
230
220
210
200
190
180
170
160
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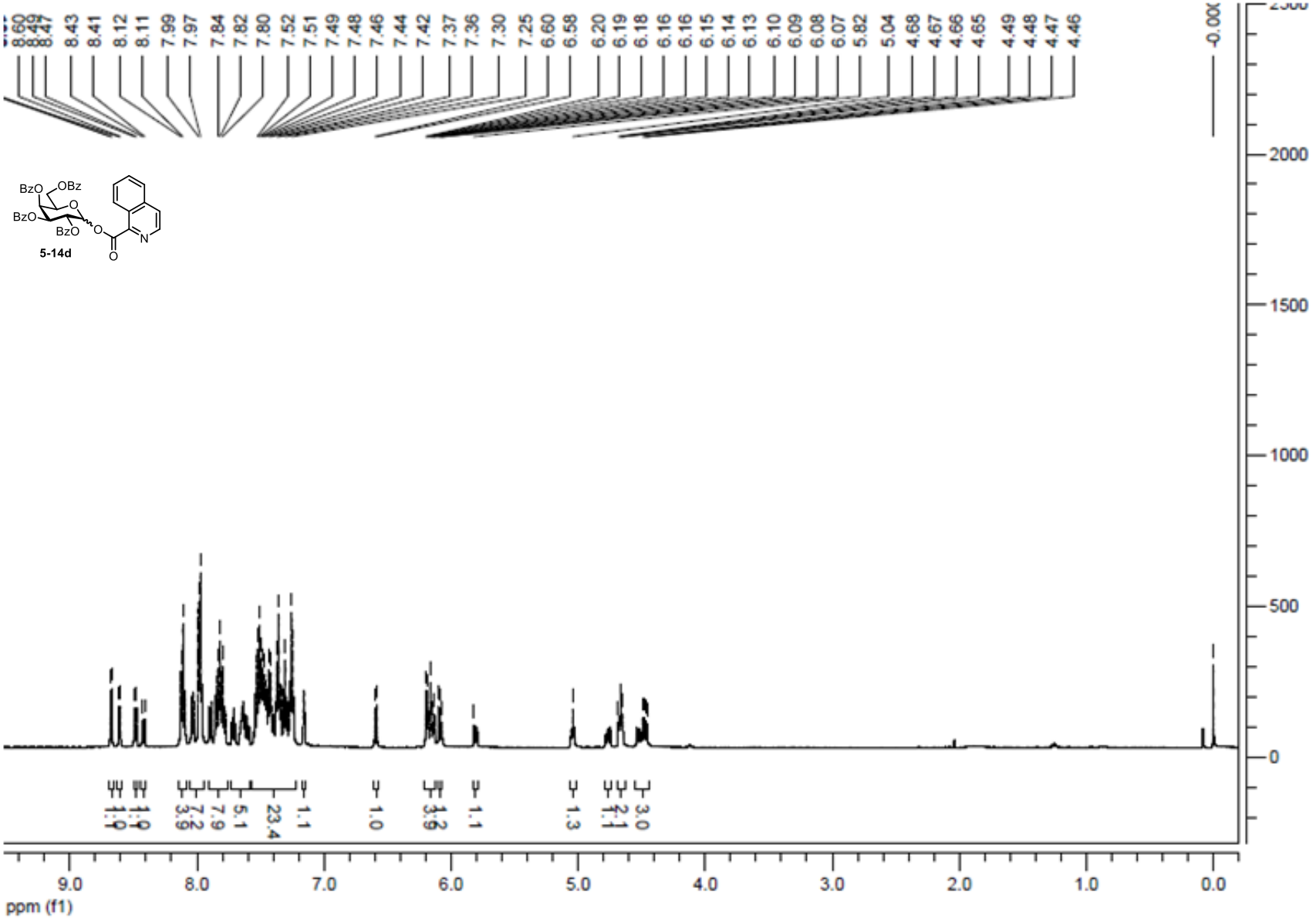
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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7.80
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7.51
7.49
7.48
7.46
7.44
7.42
7.37
7.36
7.30
7.25
6.60
6.58
6.20
6.19
6.18
6.16
6.16
6.15
6.14
6.13
6.10
6.09
6.08
6.07
5.82
5.04
4.68
4.67
4.66
4.65
4.49
4.48
4.47
4.46
BzO
OBz
BzO
BzO
O
O
N
O
5-14d
2000
1500
1000
500
0
1.0
1.0
1.0
3.9
7.2
7.9
5.1
23.4
1.1
1.0
3.9
1.2
1.1
1.3
2.1
1.1
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6.0
5.0
4.0
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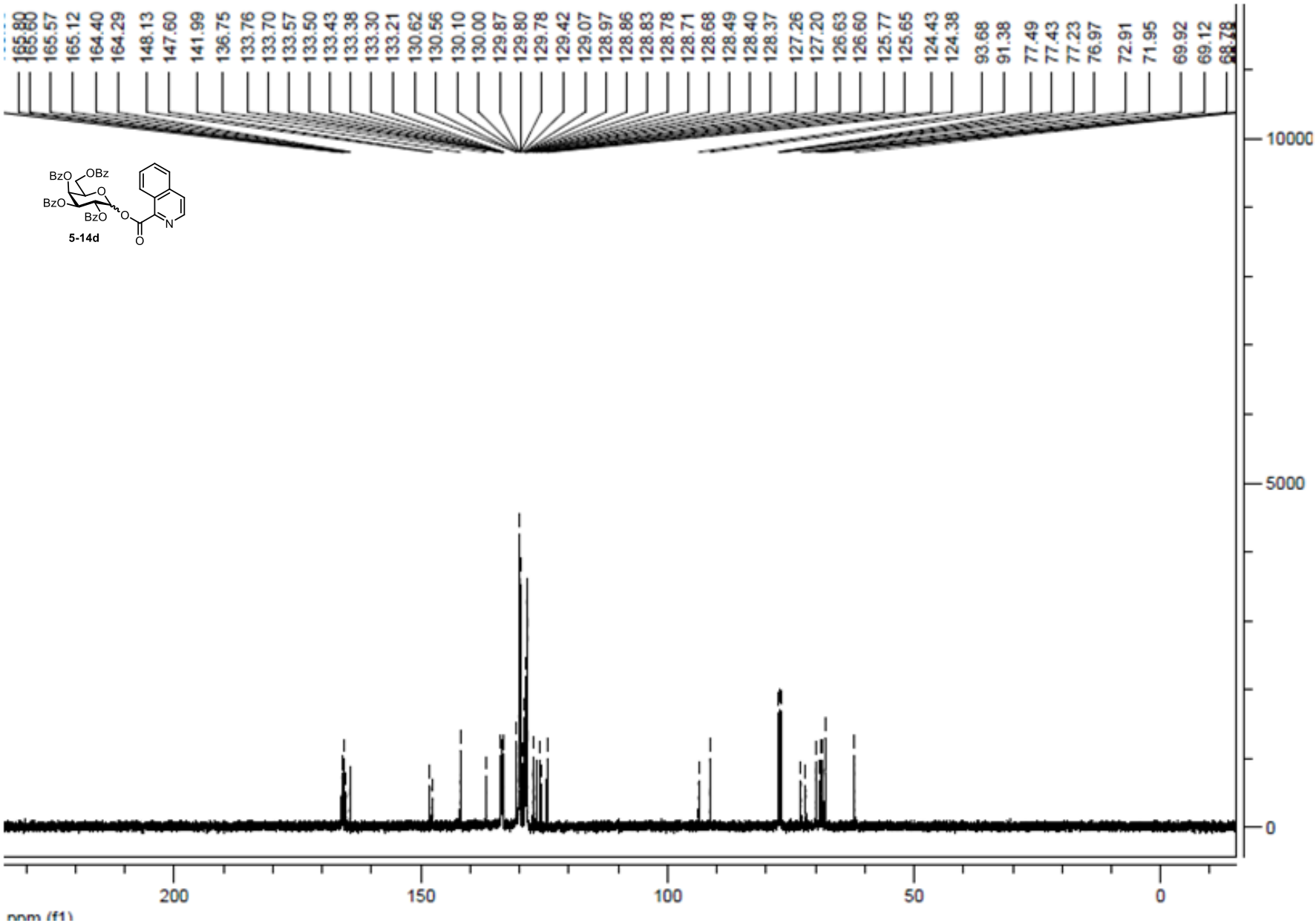
2.0
1.0
0.0
ppm (f1)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141.99
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133.38
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133.21
130.62
130.56
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128.37
127.26
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126.60
125.77
125.65
124.43
124.38
93.68
91.38
77.49
77.43
77.23
76.97
72.91
71.95
69.92
69.12
68.78
BzO
OBz
BzO
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O
O
N
O
5-14d
10000
5000
0
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50
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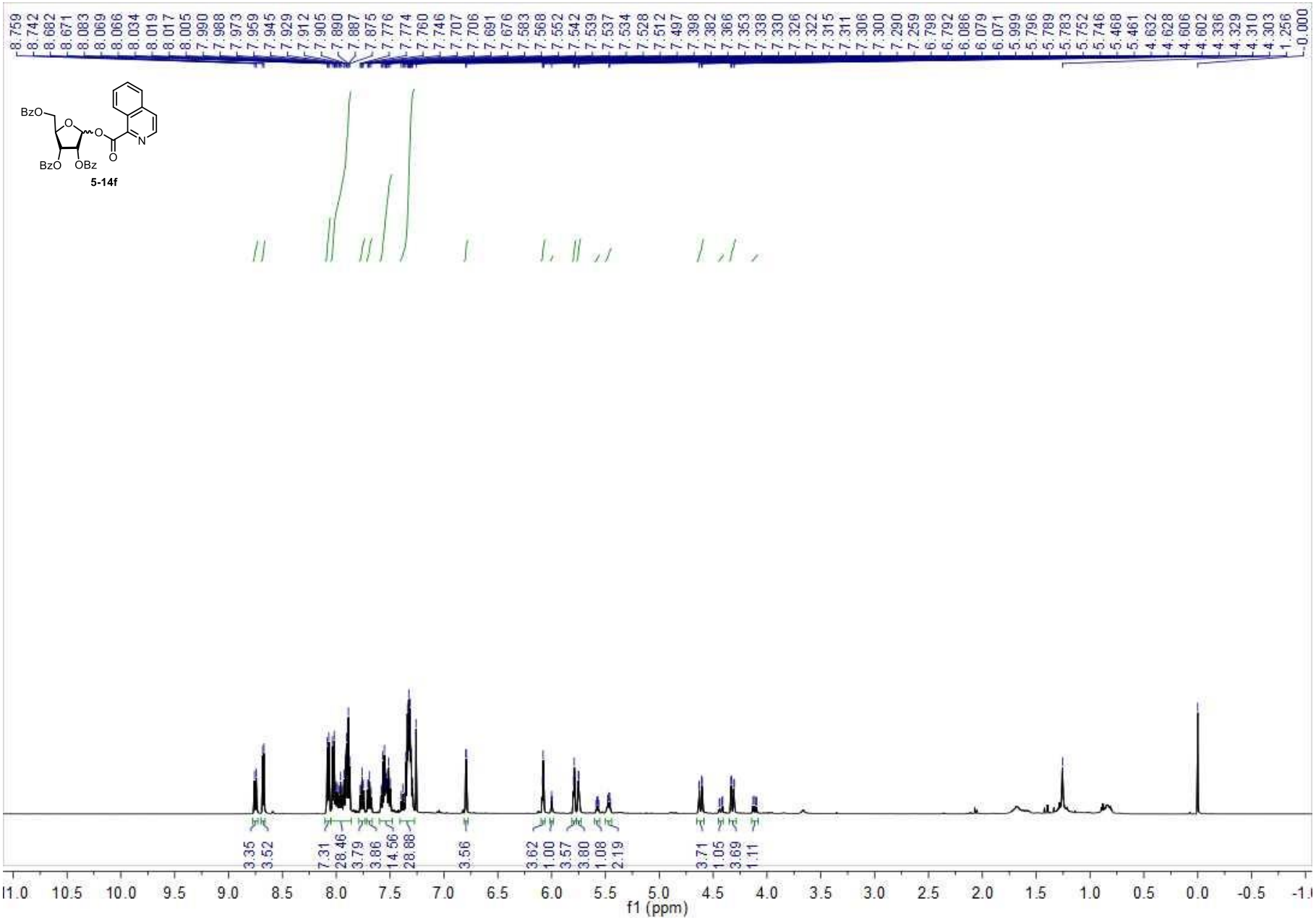
ppm (f1)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7.973
7.959
7.945
7.929
7.912
7.905
7.890
7.887
7.875
7.776
7.774
7.760
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7.706
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7.676
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7.534
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7.306
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6.071
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5.783
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4.628
4.606
4.602
4.336
4.329
4.310
4.303
1.256
0.000
BzO
BzO
OBz
5-14f
3.35
3.52
7.31
28.46
3.79
3.86
14.56
28.88
3.56
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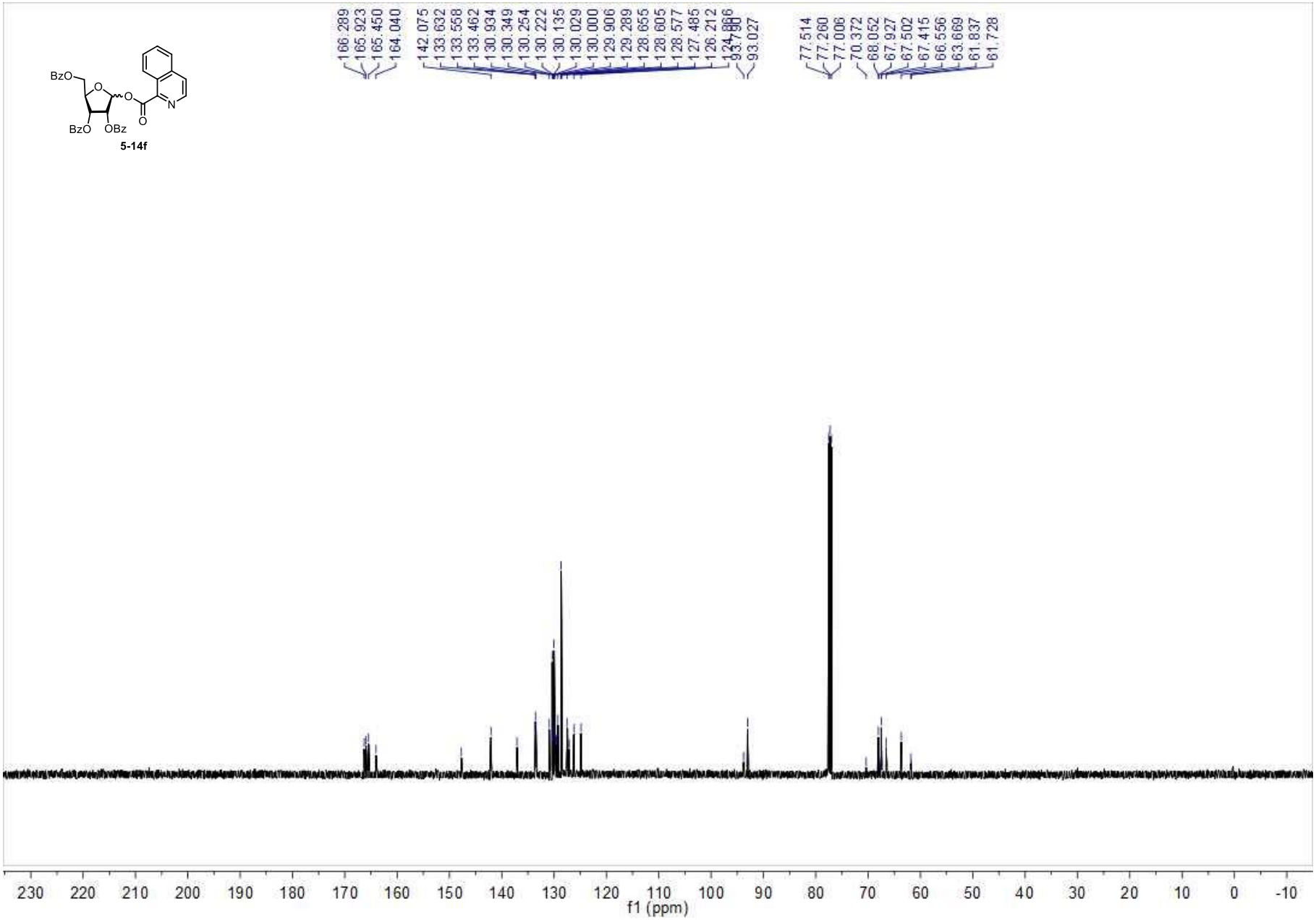
3.57
3.80
1.08
2.19
3.71
1.05
3.69
1.11
f1 (ppm)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BzO
OBz
5-14f
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130.254
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130.135
130.029
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126.212
93.790
93.027
77.514
77.260
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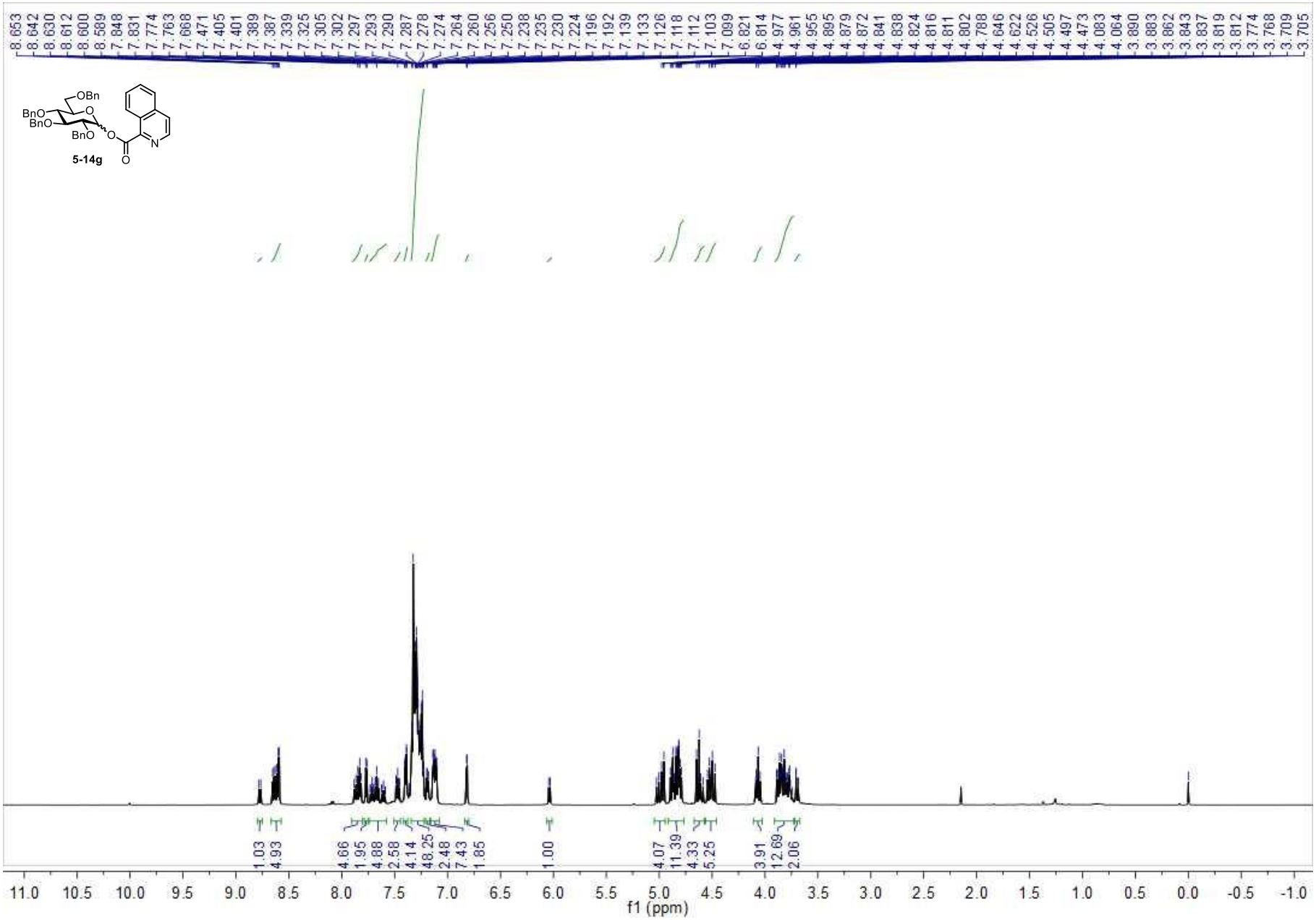
63.669
61.837
61.728
f1 (ppm)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7.302
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7.290
7.287
7.278
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7.260
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7.133
7.126
7.118
7.112
7.103
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6.814
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4.811
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3.843
3.837
3.819
3.812
3.774
3.768
3.709
3.705
OBn
BnO
BnO
BnO
O
O
N
O
5-14g
1.03
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1.95
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2.58
4.14
48.25
2.48
7.43
1.85
1.00
4.07
11.39
4.33
5.25
3.91
12.69
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10.5
10.0
9.5
9.0
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8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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0.0
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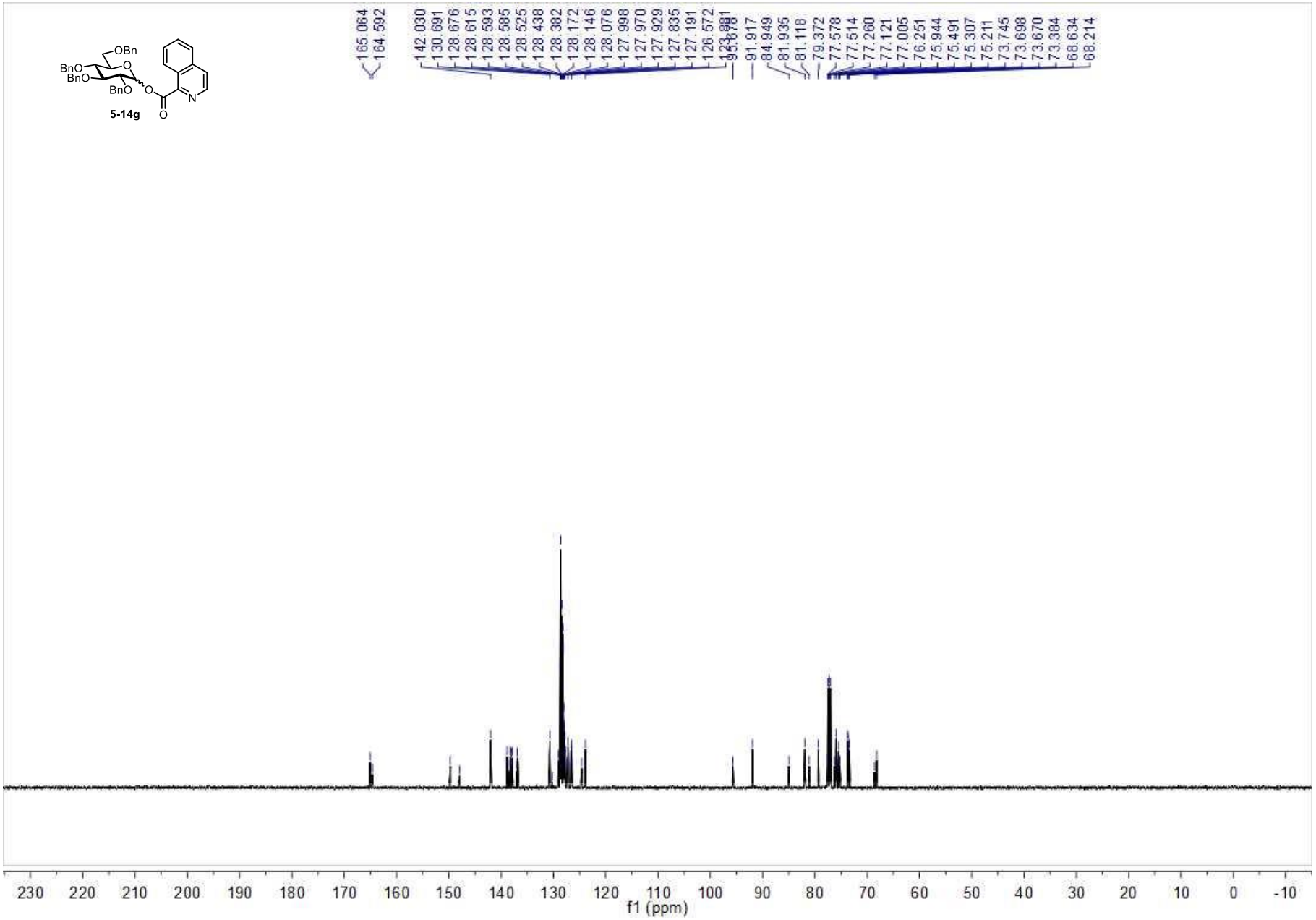
-1.0
f1 (ppm)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BnO
BnO
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N
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128.615
128.593
128.585
128.525
128.438
128.382
128.172
128.146
128.076
127.998
127.970
127.929
127.835
127.191
126.572
91.917
84.949
81.935
81.118
79.372
77.578
77.514
77.260
77.121
77.005
76.251
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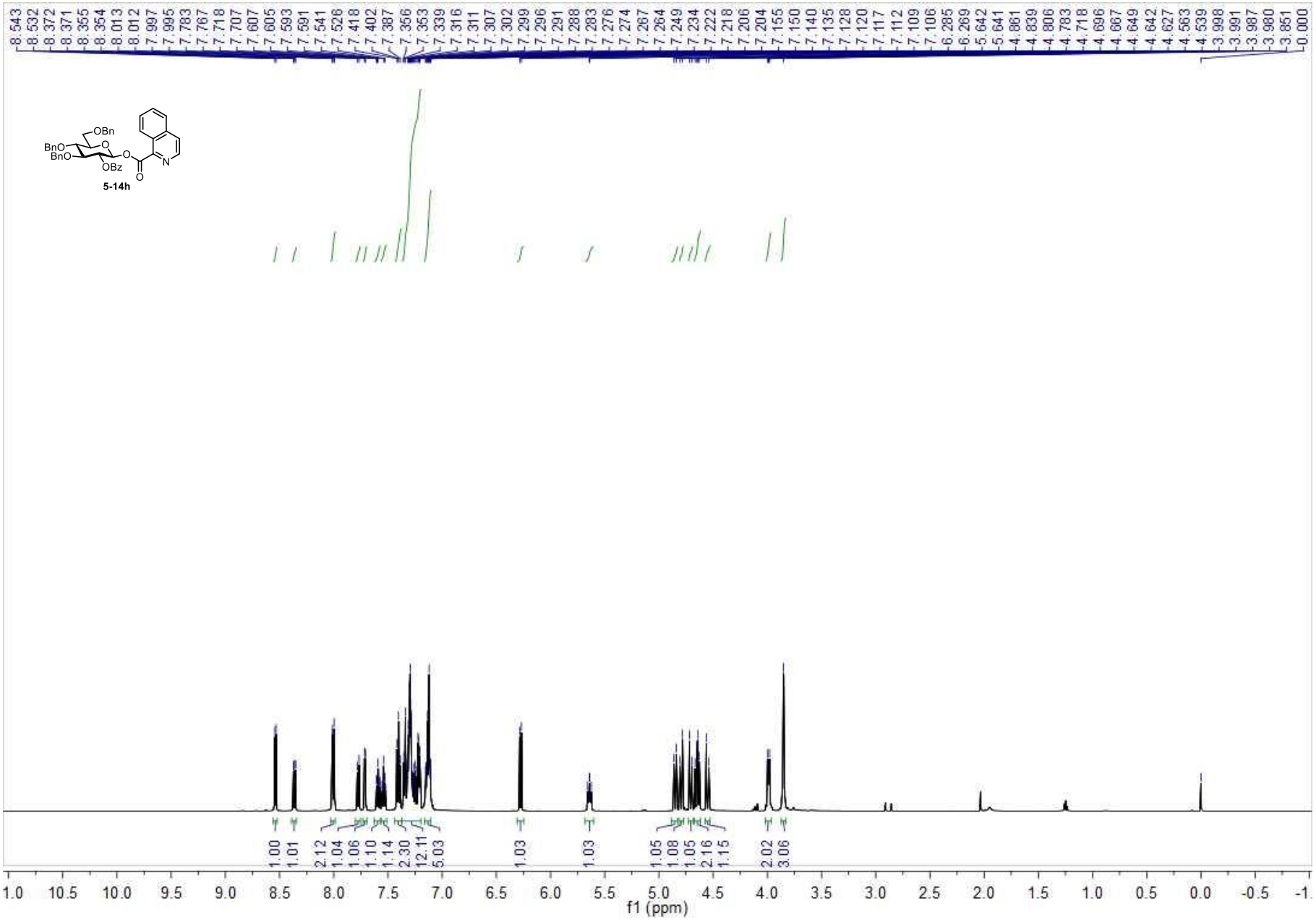
75.307
75.211
73.745
73.698
73.670
73.384
68.634
68.214
f1 (ppm)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7.718
7.707
7.607
7.605
7.593
7.591
7.541
7.528
7.418
7.402
7.387
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7.353
7.339
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7.311
7.307
7.302
7.299
7.296
7.291
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7.276
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7.140
7.135
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7.109
7.106
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4.642
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4.539
3.998
3.991
3.987
3.980
3.851
0.000
OBn
BnO
BnO
OBz
O
N
5-14h
1.00
1.01
2.12
1.04
1.06
1.10
1.14
2.30
12.11
5.03
1.03
1.03
1.05
1.08
1.05
2.16
1.15
2.02
3.06
1.0
10.5
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9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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2.5
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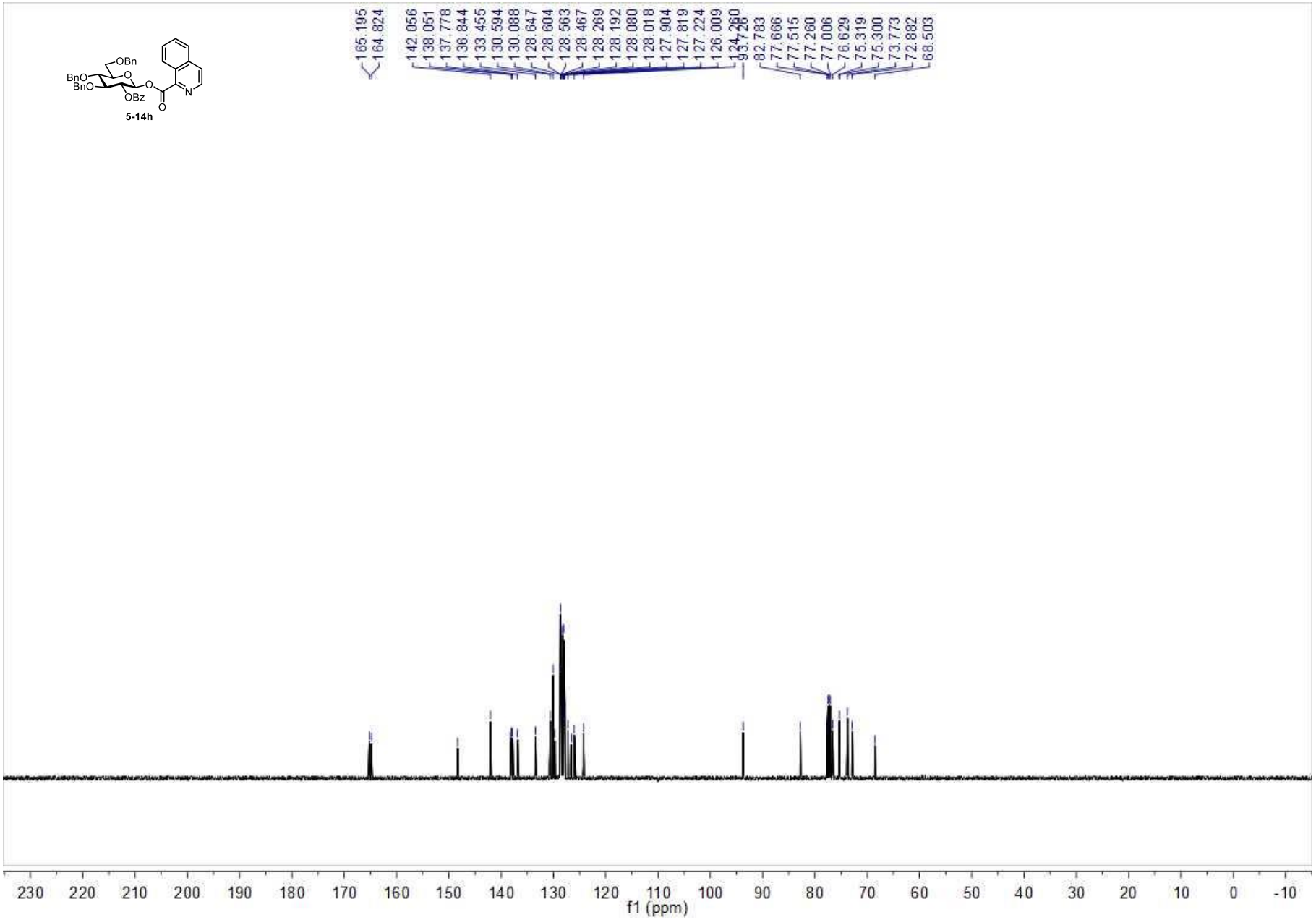
f1 (ppm)


OBn
BnO
BnO
O
OBz
O
N
O
5-14h
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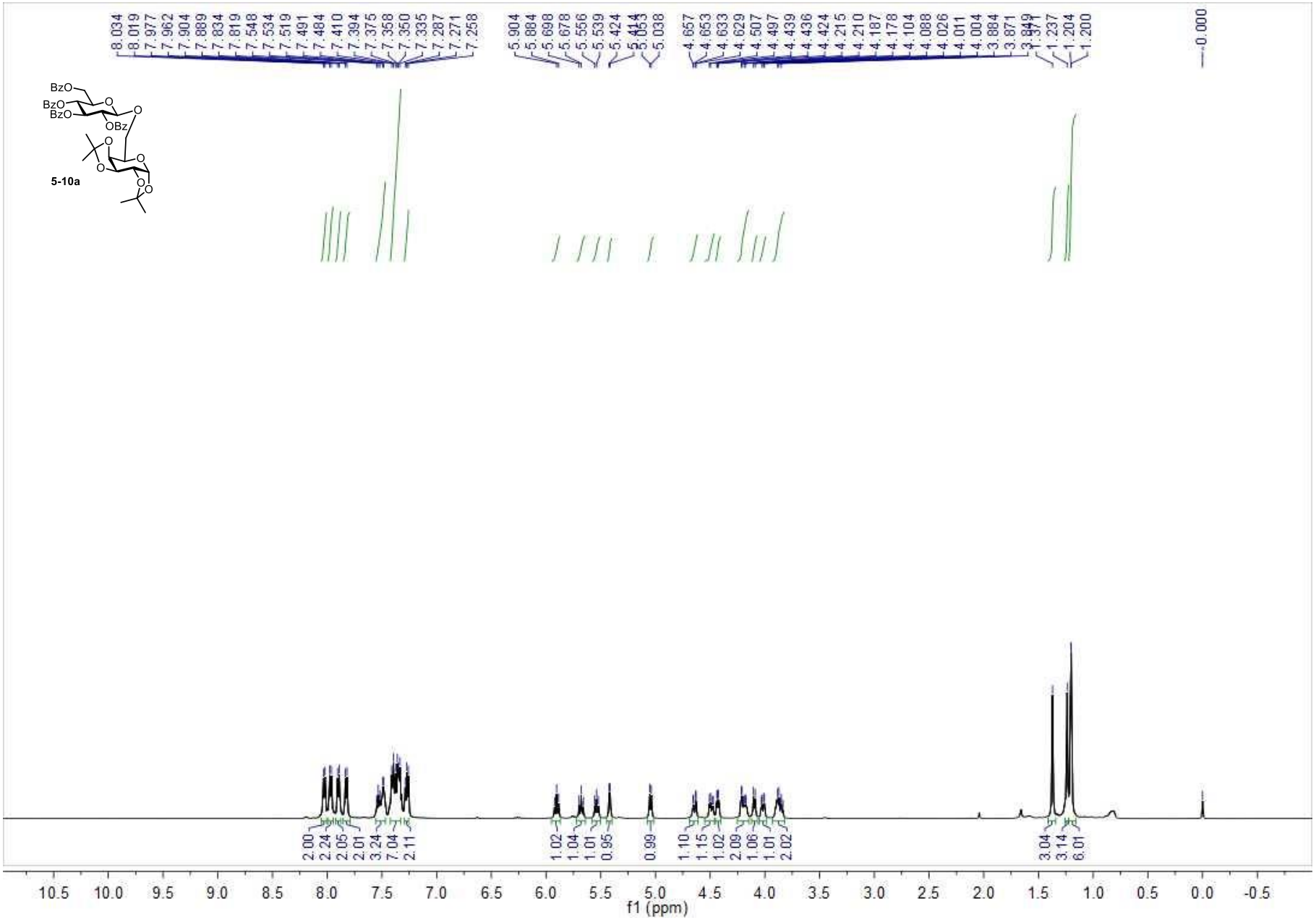
142.056
138.051
137.778
136.844
133.455
130.594
130.088
128.647
128.604
128.563
128.467
128.269
128.192
128.080
128.018
127.904
127.819
127.224
126.009
124.260
93.728
82.783
77.666
77.515
77.260
77.006
76.629
75.319
75.300
73.773
72.882
68.503
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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7.484
7.410
7.394
7.375
7.358
7.350
7.335
7.287
7.271
7.258
5.904
5.884
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5.678
5.556
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5.424
5.414
5.053
5.038
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4.653
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4.497
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4.436
4.424
4.215
4.210
4.187
4.178
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4.088
4.026
4.011
4.004
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1.200
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BzO
BzO
BzO
OBz
5-10a
2.00
2.24
2.05
2.01
3.24
7.04
2.11
1.02
1.04
1.01
0.95
0.99
1.10
1.15
1.02
2.09
1.06
1.01
2.02
3.04
3.14
6.01
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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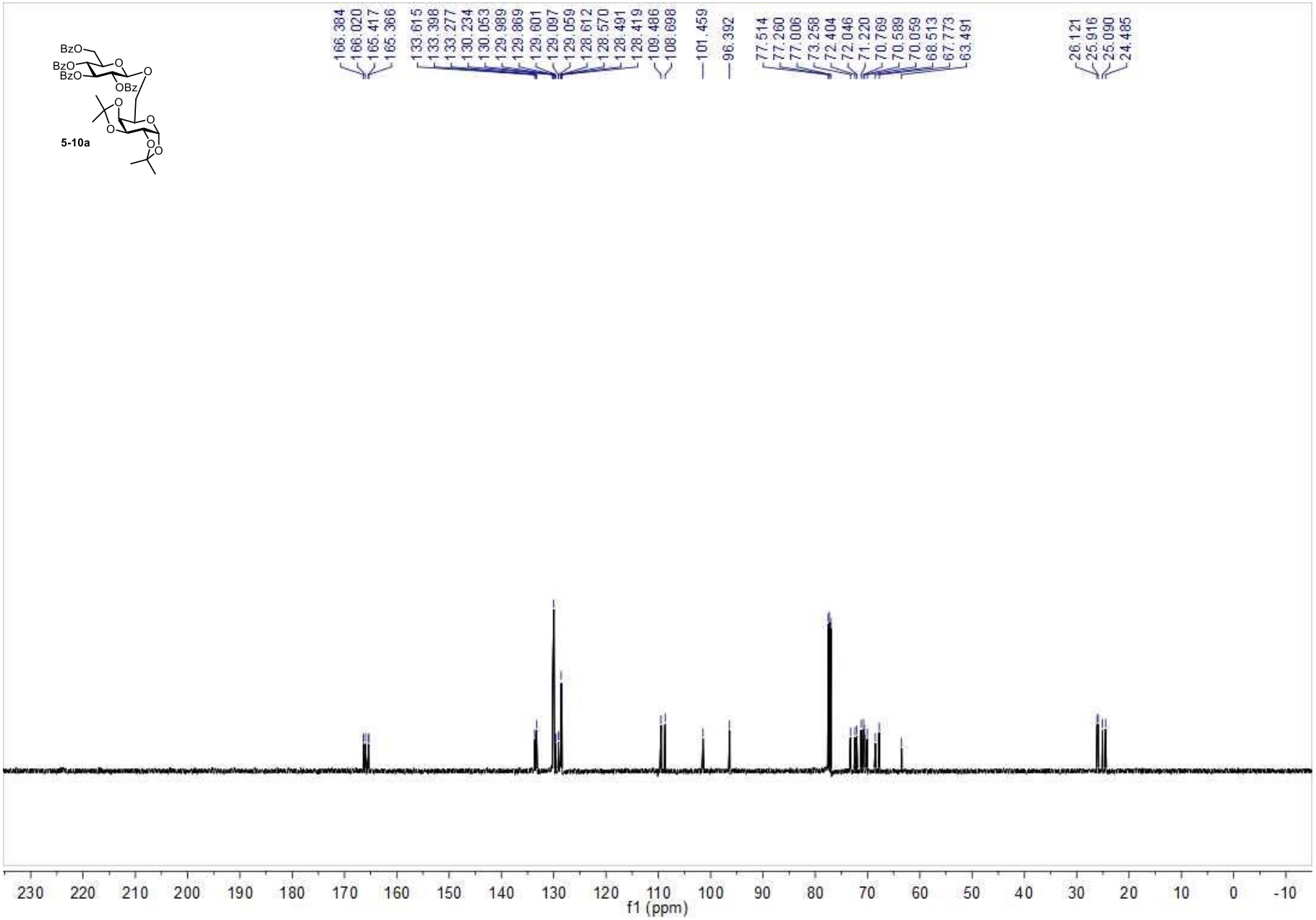
f1 (ppm)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129.059
128.612
128.570
128.491
128.419
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108.698
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96.392
77.514
77.260
77.006
73.258
72.404
72.046
71.220
70.769
70.589
70.059
68.513
67.773
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25.916
25.090
24.485
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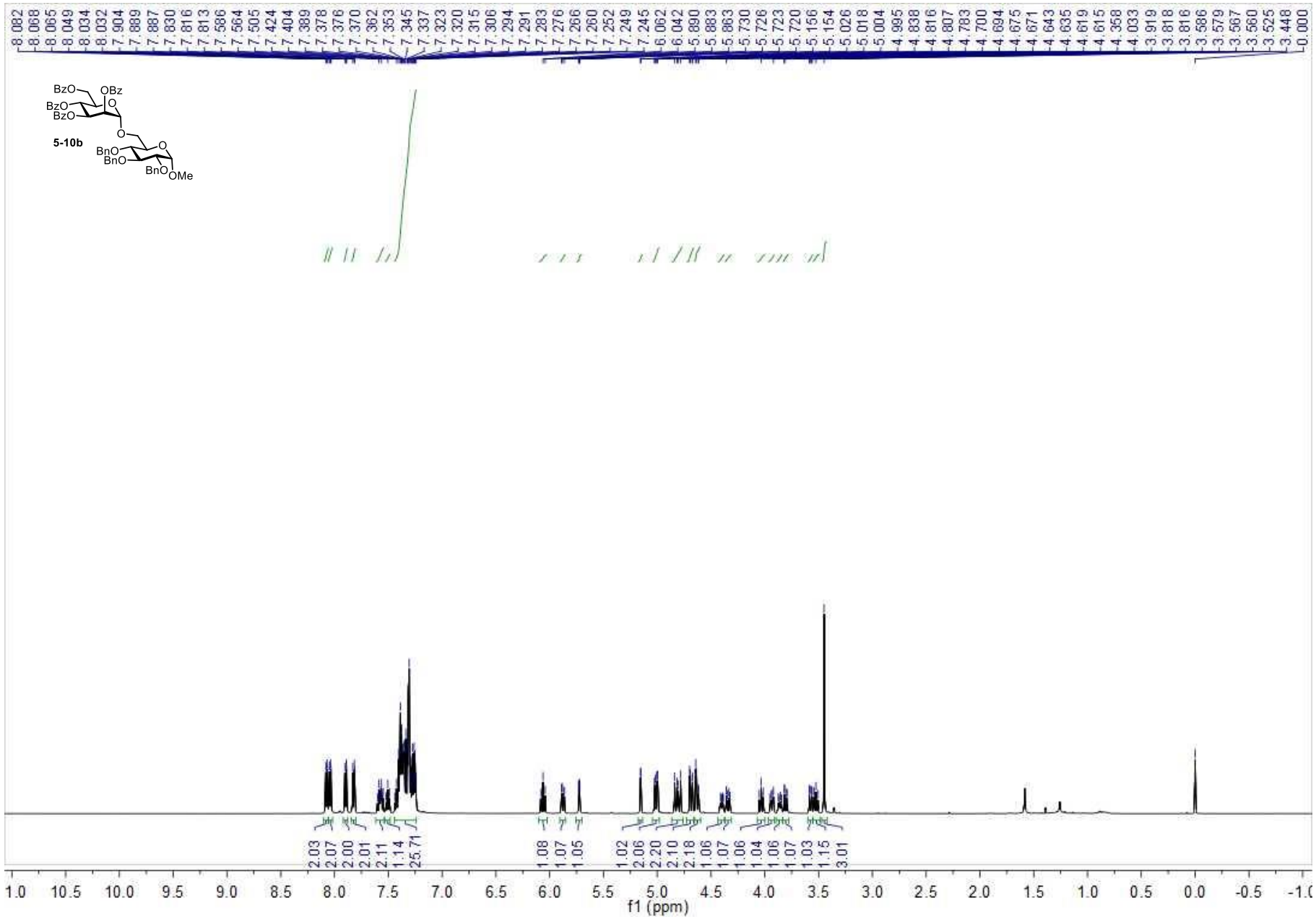
BzO
BzO
OBz
5-10a
f1 (ppm)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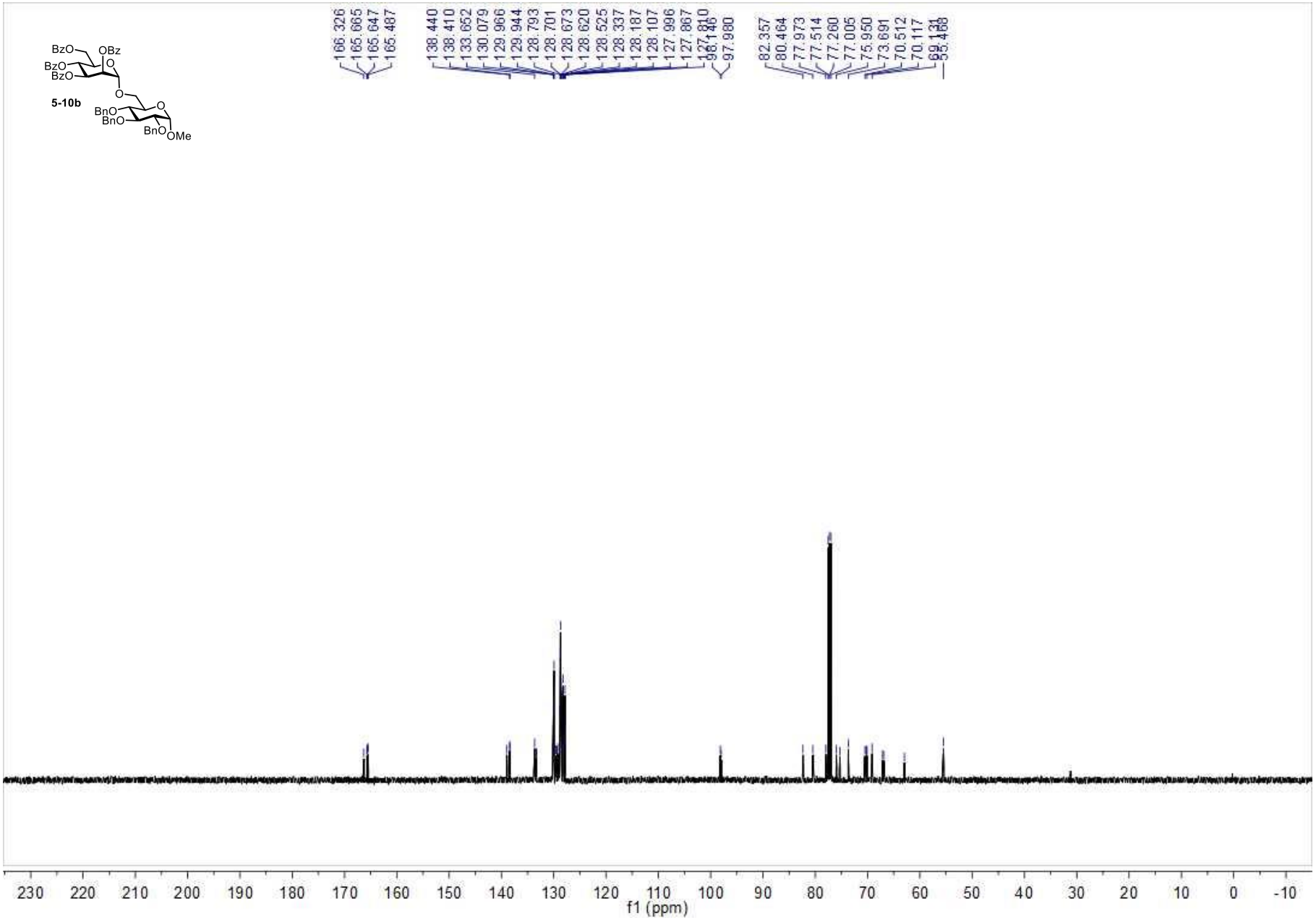
f1 (ppm)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128.337
128.187
128.107
127.996
127.867
127.810
97.980
82.357
80.464
77.973
77.514
77.260
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75.950
73.691
70.512
70.117
69.131
55.468
BzO
OBz
BzO
BzO
O
O
BnO
BnO
BnO
OMe
5-10b
230
220
210
200
190
180
170
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30
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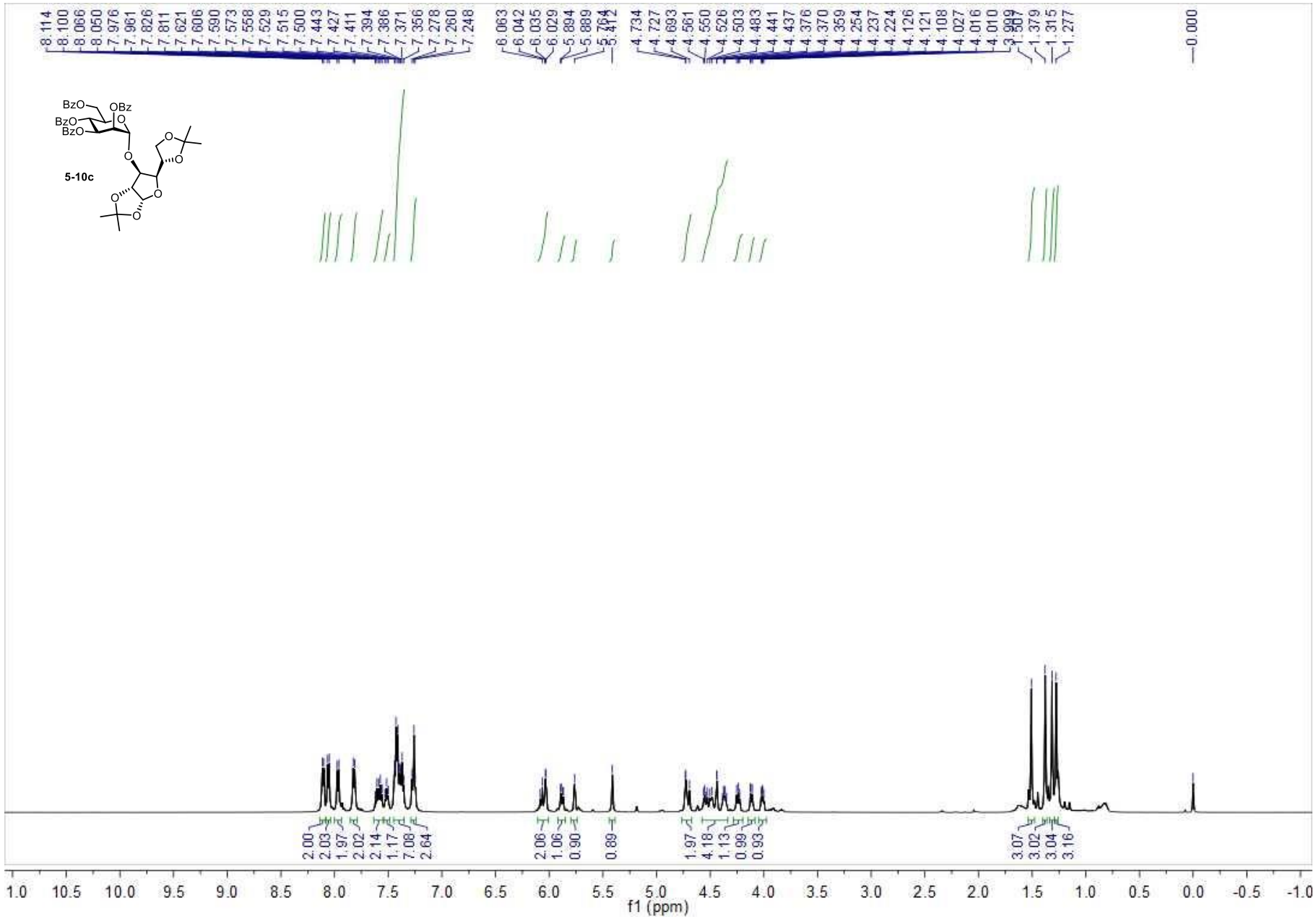
-10
f1 (ppm)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7.573
7.558
7.529
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7.500
7.443
7.427
7.411
7.394
7.386
7.371
7.356
7.278
7.260
7.248
6.063
6.042
6.035
6.029
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5.889
5.764
5.412
4.734
4.727
4.693
4.561
4.550
4.526
4.503
4.483
4.441
4.437
4.376
4.370
4.359
4.254
4.237
4.224
4.126
4.121
4.108
4.027
4.016
4.010
3.909
3.907
1.379
1.315
1.277
0.000
BzO
OBz
BzO
BzO
5-10c
2.00
2.03
1.97
2.02
2.14
1.17
7.08
2.64
2.06
1.06
0.90
0.89
1.97
4.18
1.13
0.99
0.93
3.07
3.02
3.04
3.16
1.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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2.0
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0.0
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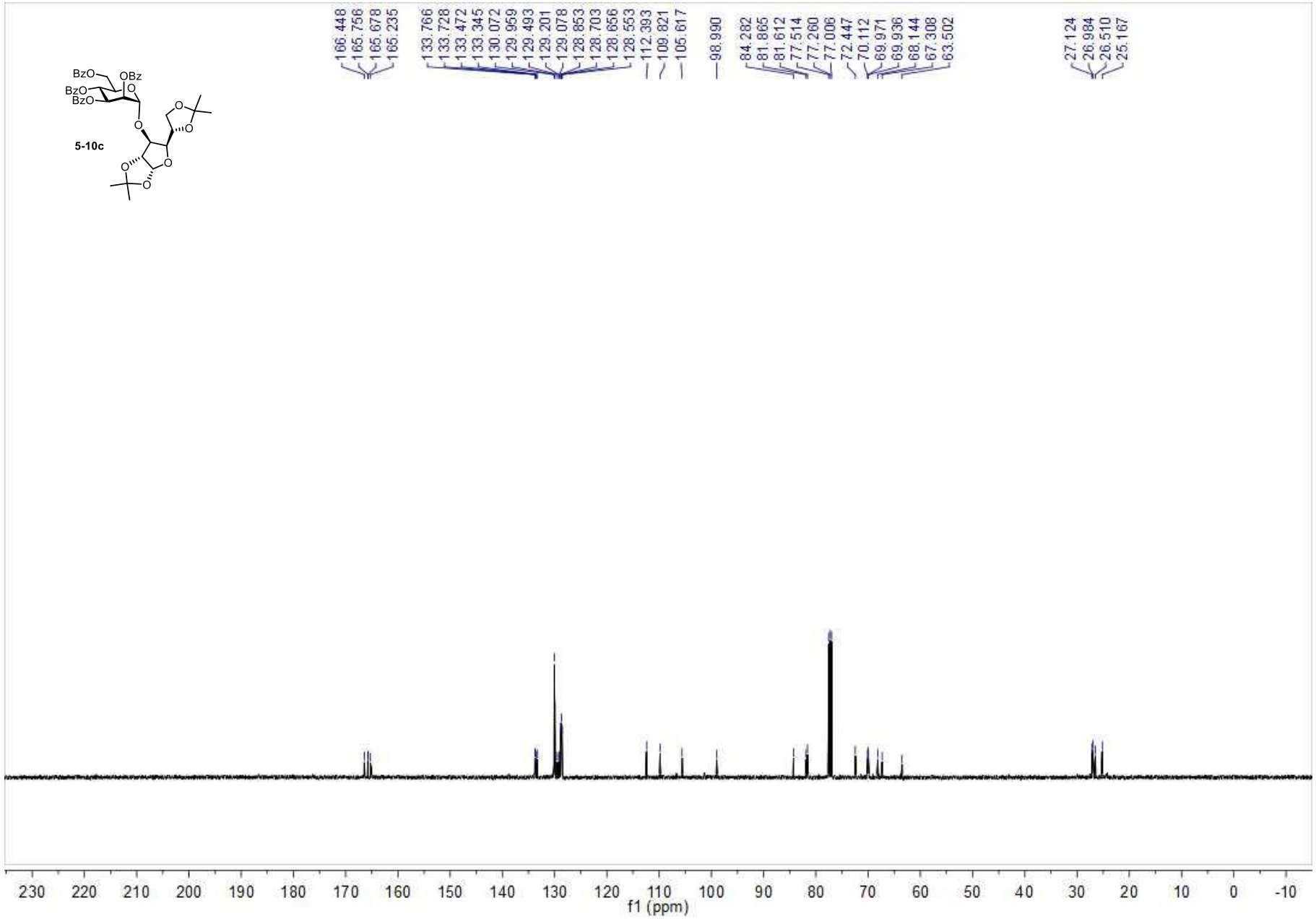
f1 (ppm)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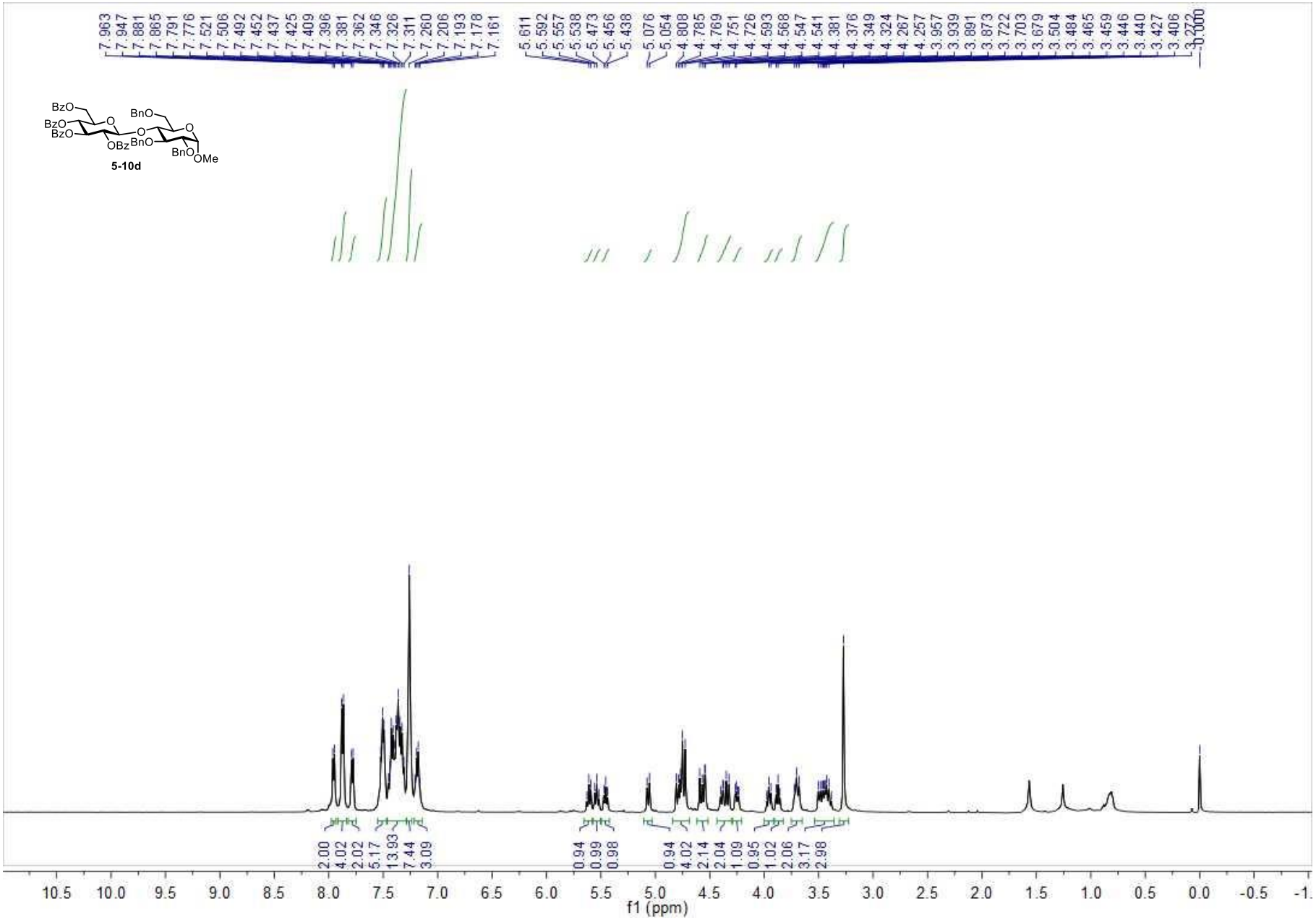
129.078
128.853
128.703
128.656
128.553
112.393
109.821
105.617
98.990
84.282
81.865
81.612
77.514
77.260
77.006
72.447
70.112
69.971
69.936
68.144
67.308
63.502
27.124
26.984
26.510
25.167
BzO
OBz
BzO
BzO
5-10c
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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7.409
7.396
7.381
7.362
7.346
7.326
7.311
7.260
7.206
7.193
7.178
7.161
5.611
5.592
5.557
5.538
5.473
5.456
5.438
5.076
5.054
4.808
4.785
4.769
4.751
4.726
4.593
4.568
4.547
4.541
4.381
4.376
4.349
4.324
4.267
4.257
3.957
3.939
3.891
3.873
3.722
3.703
3.679
3.504
3.484
3.465
3.459
3.446
3.440
3.427
3.406
3.272
0.000
BzO
BzO
BzO
OBz
BnO
BnO
O
O
BnO
OMe
5-10d
2.00
4.02
2.02
5.17
13.93
7.44
3.09
0.94
0.99
0.98
0.94
4.02
2.14
2.04
1.09
0.95
1.02
2.06
3.17
2.98
10.5
10.0
9.5
9.0
8.5
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6.5
6.0
5.5
5.0
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0.5
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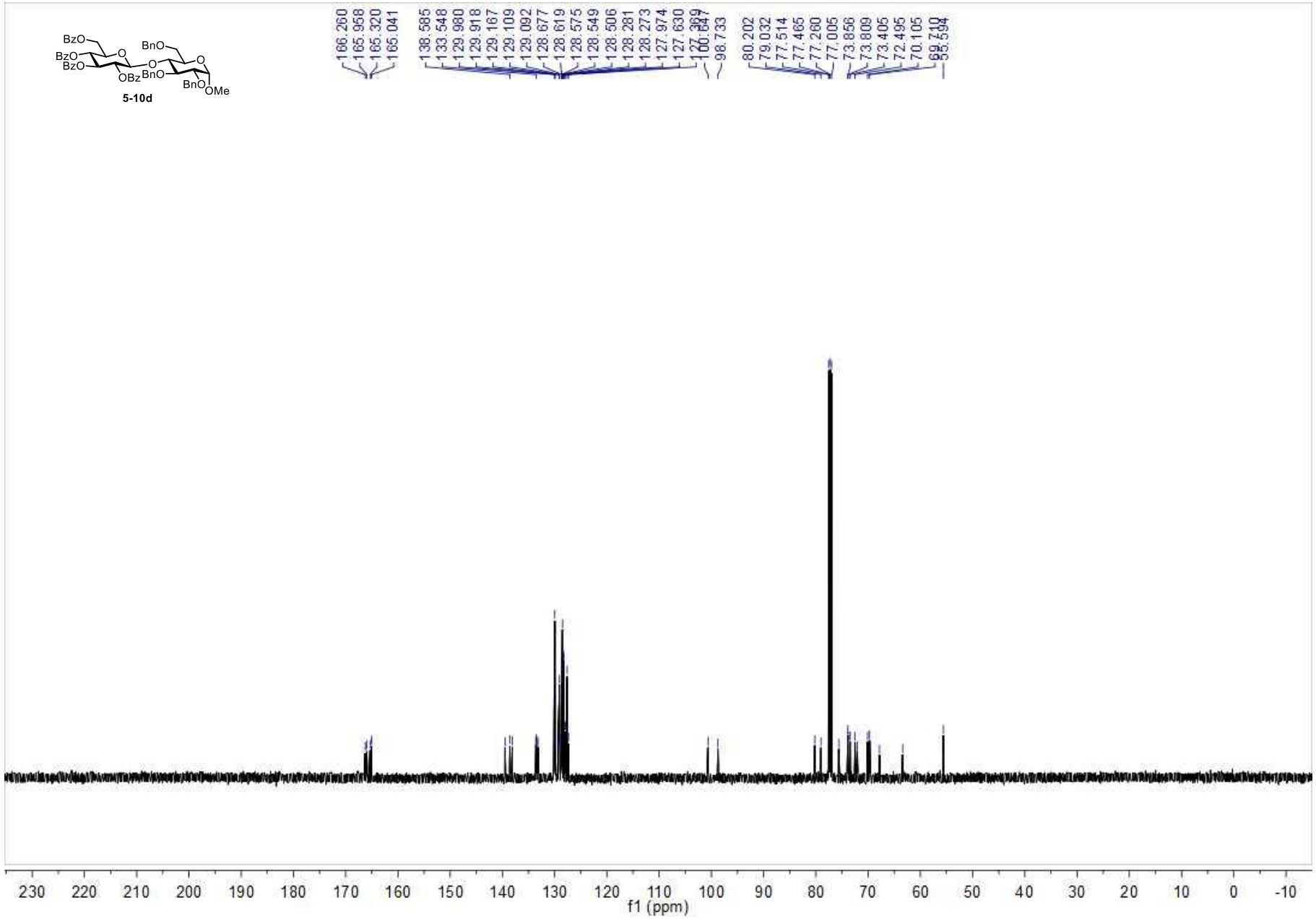
f1 (ppm)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BzO
BzO
OBz
BnO
BnO
BnO
OMe
5-10d
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138.585
133.548
129.980
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129.167
129.109
129.092
128.677
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128.506
128.281
128.273
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98.733
80.202
79.032
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77.005
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73.809
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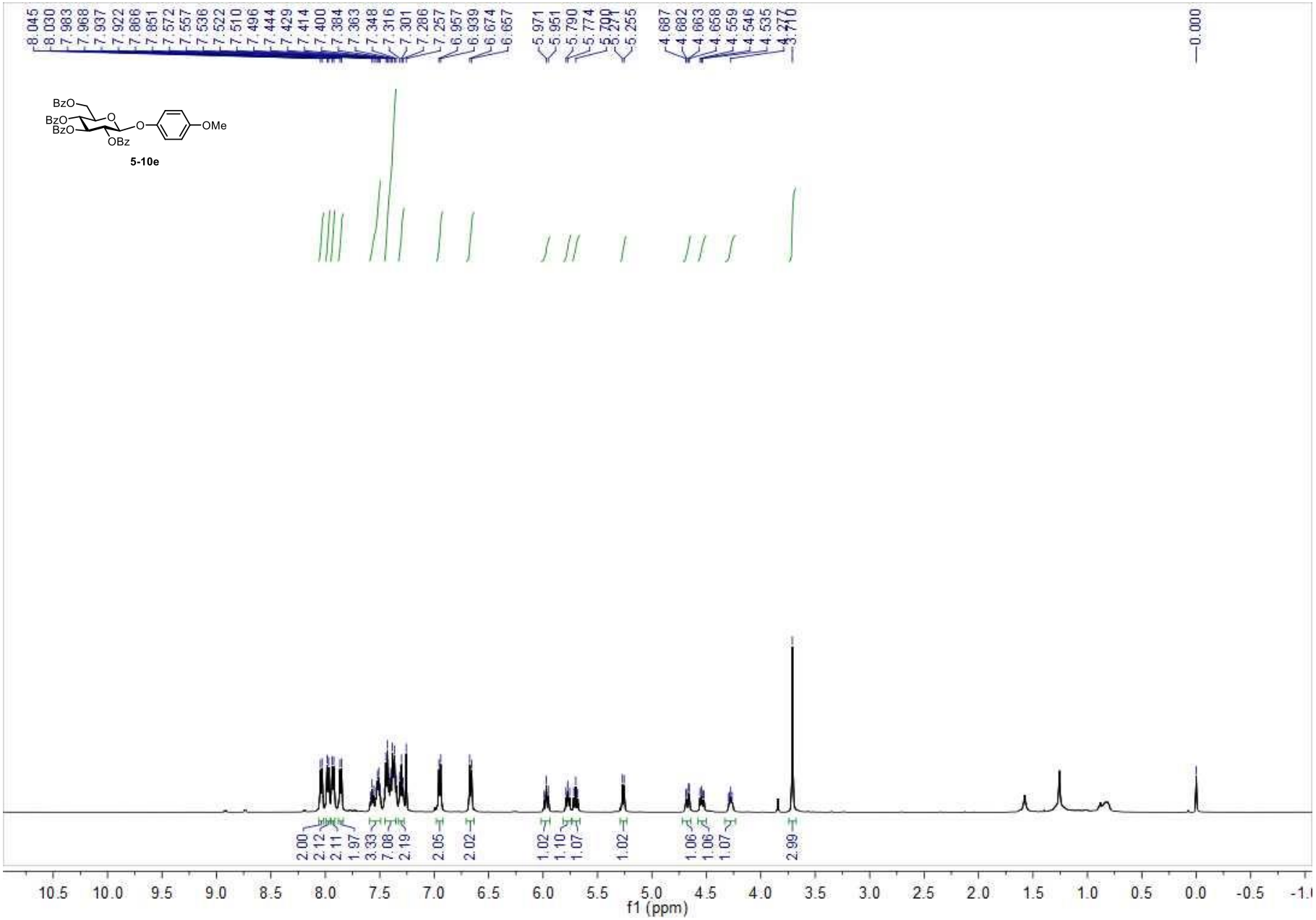
69.710
55.594
f1 (ppm)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7.536
7.522
7.510
7.496
7.444
7.429
7.414
7.400
7.384
7.363
7.348
7.316
7.301
7.286
7.257
6.957
6.939
6.674
6.657
5.971
5.951
5.790
5.774
5.271
5.255
4.687
4.682
4.663
4.658
4.559
4.546
4.535
4.277
3.710
0.000
BzO
BzO
BzO
OBz
O
O
OMe
5-10e
2.00
2.12
2.11
1.97
3.33
7.08
2.19
2.05
2.02
1.02
1.10
1.07
1.02
1.06
1.06
1.07
2.99
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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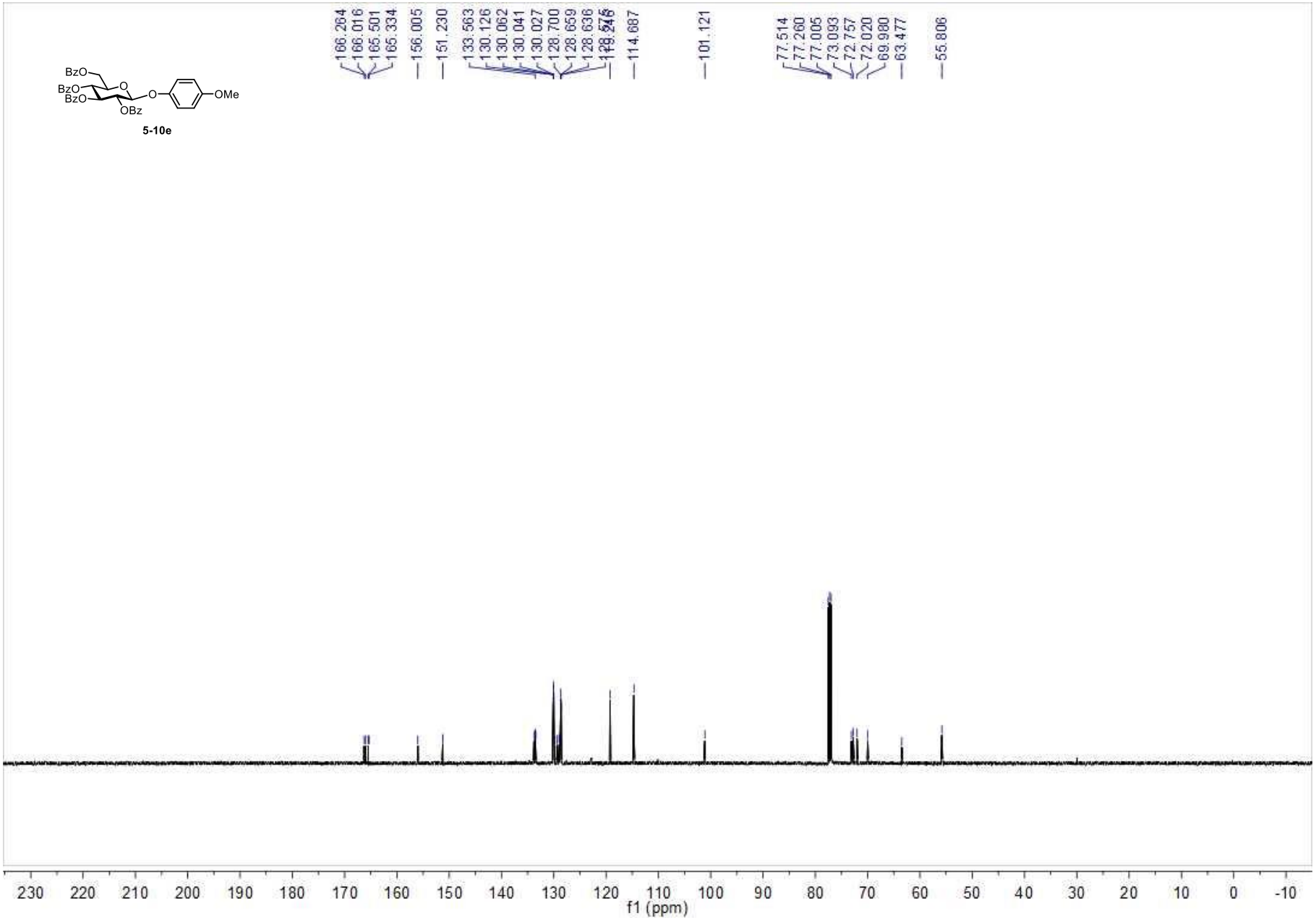
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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BzO
BzO
OBz
O
O
OMe
5-10e
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166.016
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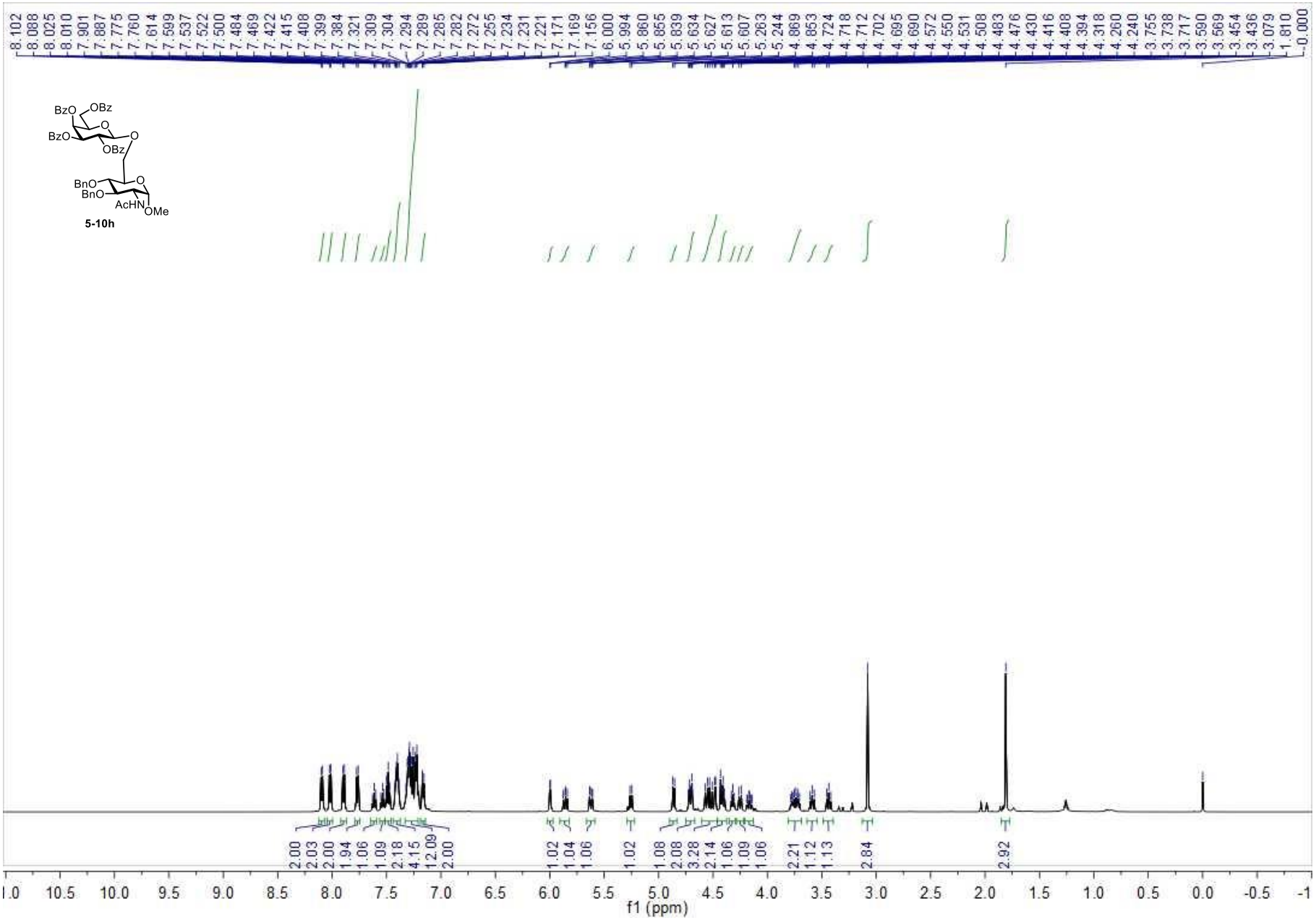
165.334
156.005
151.230
133.563
130.126
130.062
130.041
130.027
128.700
128.659
128.636
114.687
101.121
77.514
77.260
77.005
73.093
72.757
72.020
69.980
63.477
55.806
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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7.537
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7.500
7.484
7.469
7.422
7.415
7.408
7.399
7.384
7.321
7.309
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7.285
7.282
7.272
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7.231
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5.613
5.607
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5.244
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4.853
4.724
4.718
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4.483
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4.260
4.240
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3.738
3.717
3.590
3.569
3.454
3.436
3.079
1.810
0.000
BzO
OBz
BzO
O
O
OBz
BnO
BnO
O
AcHN
OMe
5-10h
2.00
2.03
2.00
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1.06
1.09
2.18
4.15
12.09
2.00
1.02
1.04
1.06
1.02
1.08
2.08
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1.06
1.09
1.06
2.21
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1.13
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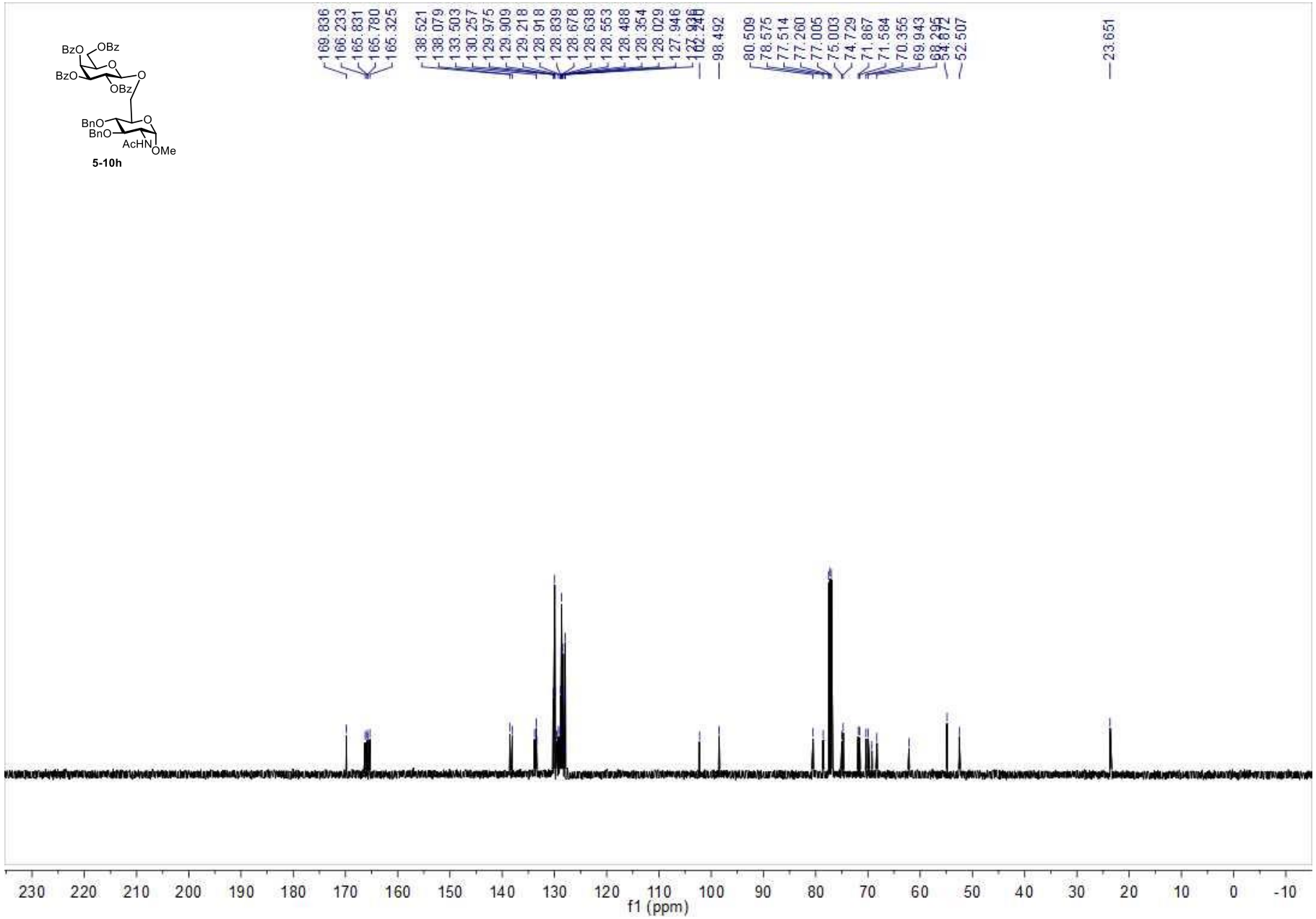
2.92
f1 (ppm)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OBz
BzO
OBz
BnO
BnO
AcHN
OMe
5-10h
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165.325
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138.079
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130.257
129.975
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129.218
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128.678
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128.553
128.488
128.354
128.029
127.946
98.492
80.509
78.575
77.514
77.260
77.005
75.003
74.729
71.867
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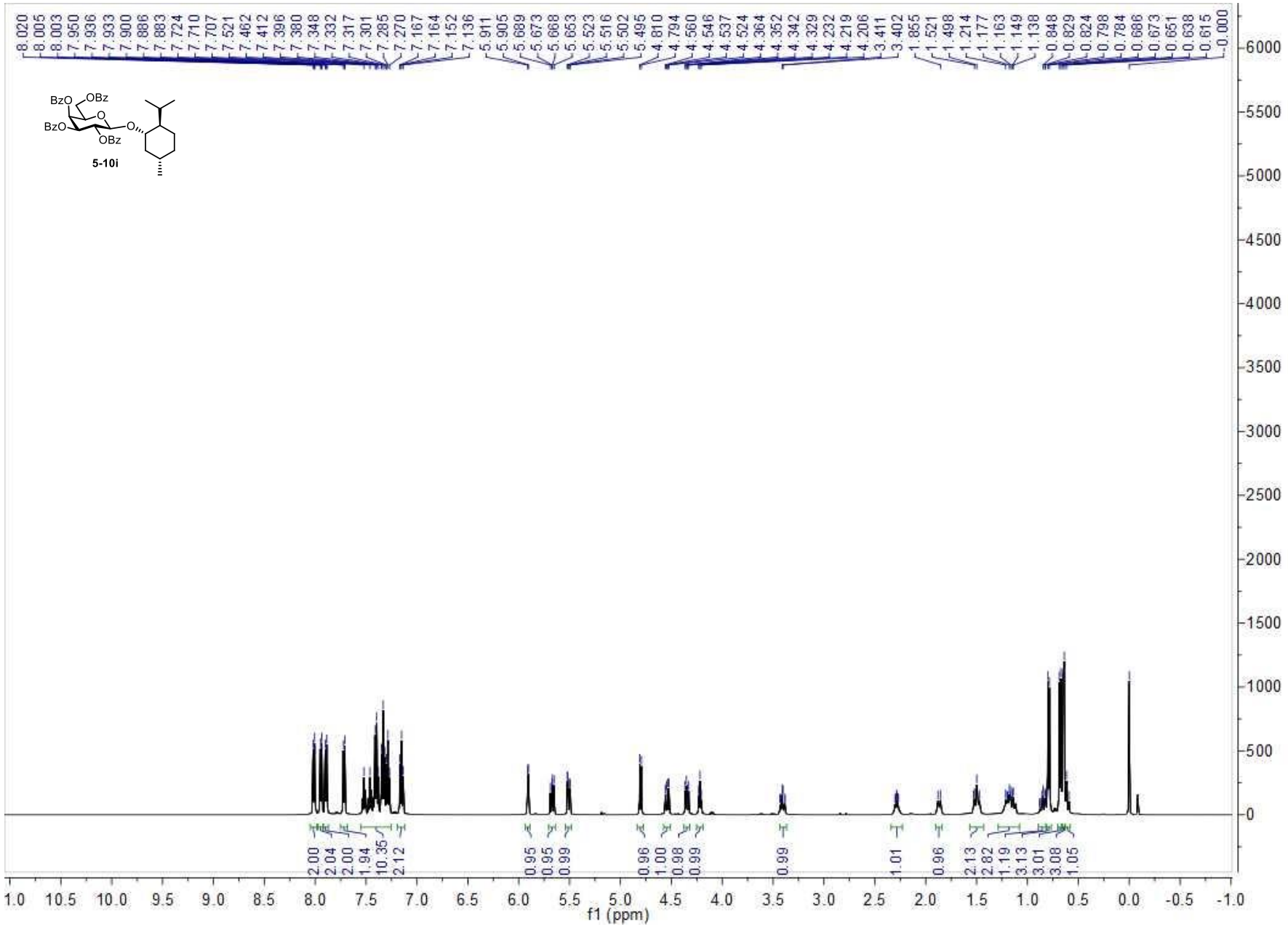
69.943
52.507
23.651
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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7.412
7.396
7.380
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7.332
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7.301
7.285
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5.905
5.689
5.673
5.668
5.653
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5.502
5.495
4.810
4.794
4.560
4.546
4.537
4.524
4.364
4.352
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4.329
4.232
4.219
4.206
3.411
3.402
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1.521
1.498
1.214
1.177
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1.149
1.138
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0.829
0.824
0.798
0.784
0.686
0.673
0.651
0.638
0.615
0.000
BzO
OBz
BzO
O
O
OBz
5-10i
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3500
3000
2500
2000
1500
1000
500
0
2.00
2.04
2.00
1.94
10.35
2.12
0.95
0.95
0.99
0.96
1.00
0.98
0.99
0.99
1.01
0.96
2.13
2.82
1.19
3.13
3.01
3.08
1.05
1.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
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6.5
6.0
5.5
5.0
4.5
4.0
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2.0
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0.0
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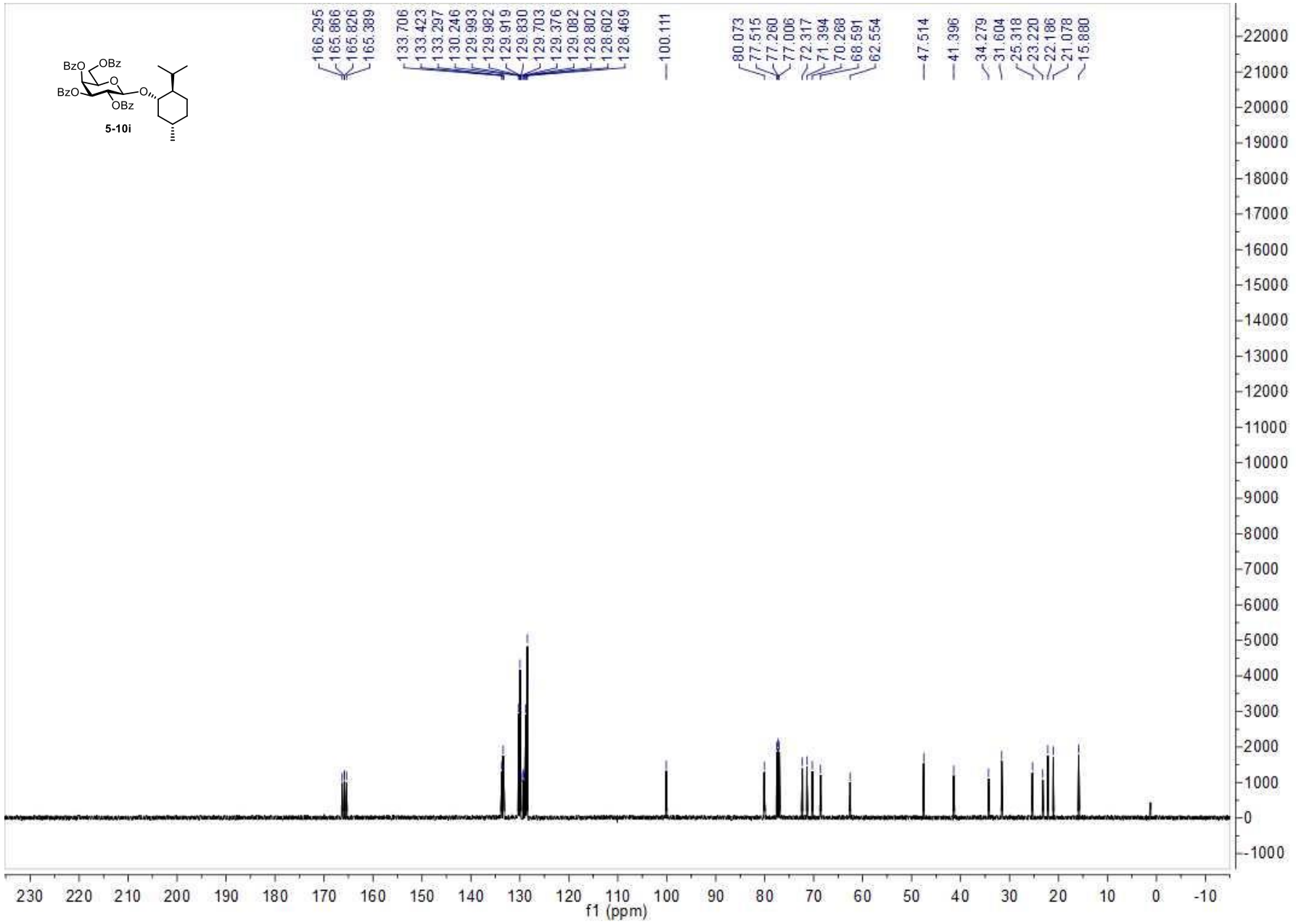
f1 (ppm)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128.602
128.469
100.111
80.073
77.515
77.260
77.006
72.317
71.394
70.268
68.591
62.554
47.514
41.396
34.279
31.604
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21.078
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OBz
BzO
OBz
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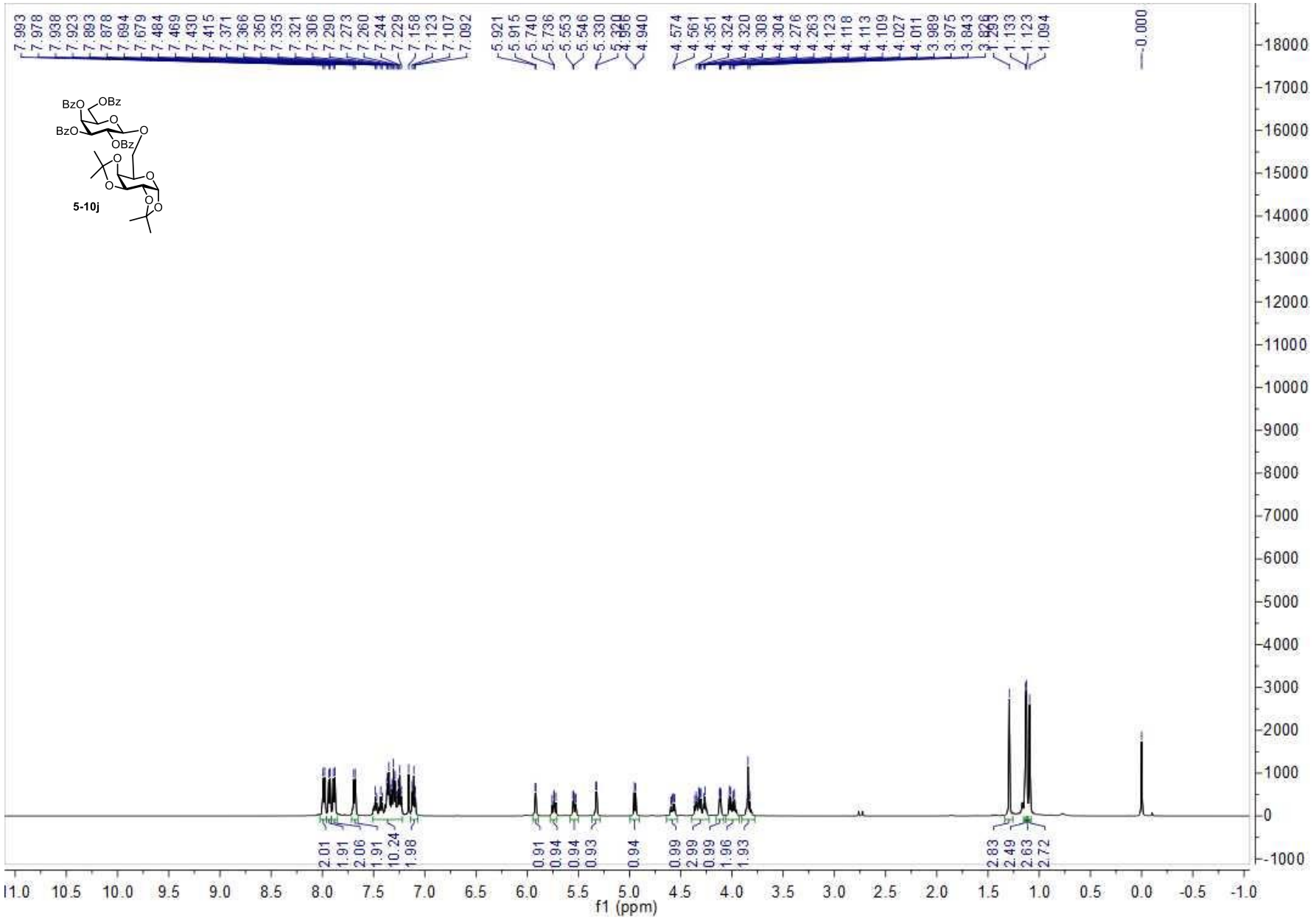
O
5-10i
f1 (ppm)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7.371
7.366
7.350
7.335
7.321
7.306
7.290
7.273
7.260
7.244
7.229
7.158
7.123
7.107
7.092
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5.915
5.740
5.736
5.553
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5.330
4.956
4.940
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4.561
4.351
4.324
4.320
4.308
4.304
4.276
4.263
4.123
4.118
4.113
4.109
4.027
4.011
3.989
3.975
3.843
3.826
1.133
1.123
1.094
0.000
BzO
OBz
BzO
OBz
5-10j
2.01
1.91
2.06
1.91
10.24
1.98
0.91
0.94
0.94
0.93
0.94
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2.99
0.99
1.96
1.93
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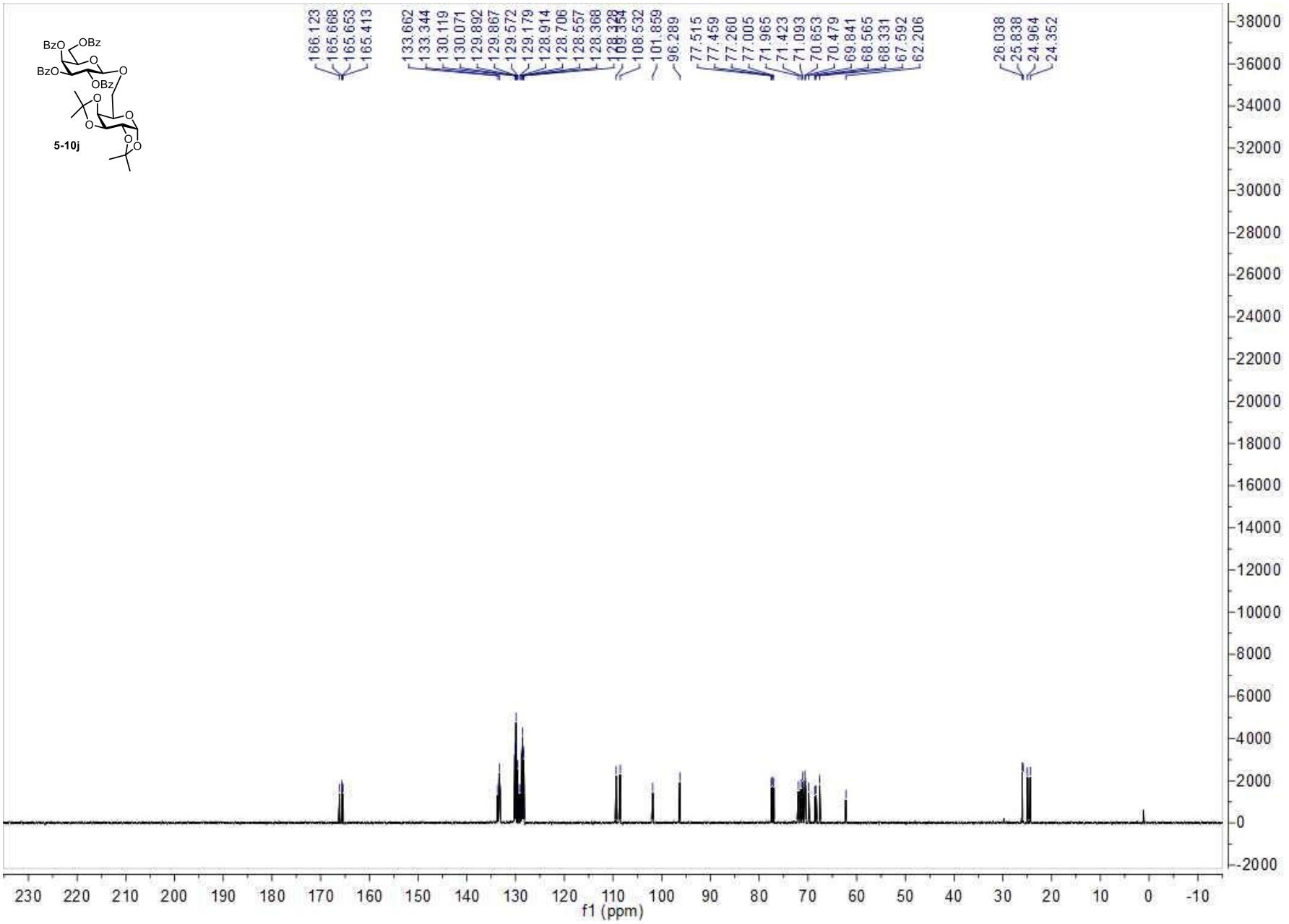
2.49
2.63
2.72
f1 (ppm)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128.368
108.532
101.859
96.289
77.515
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71.965
71.423
71.093
70.653
70.479
69.841
68.565
68.331
67.592
62.206
26.038
25.838
24.964
24.352
BzO
OBz
BzO
OBz
O
O
O
O
O
O
O
O
5-10j
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36000
34000
32000
30000
28000
26000
24000
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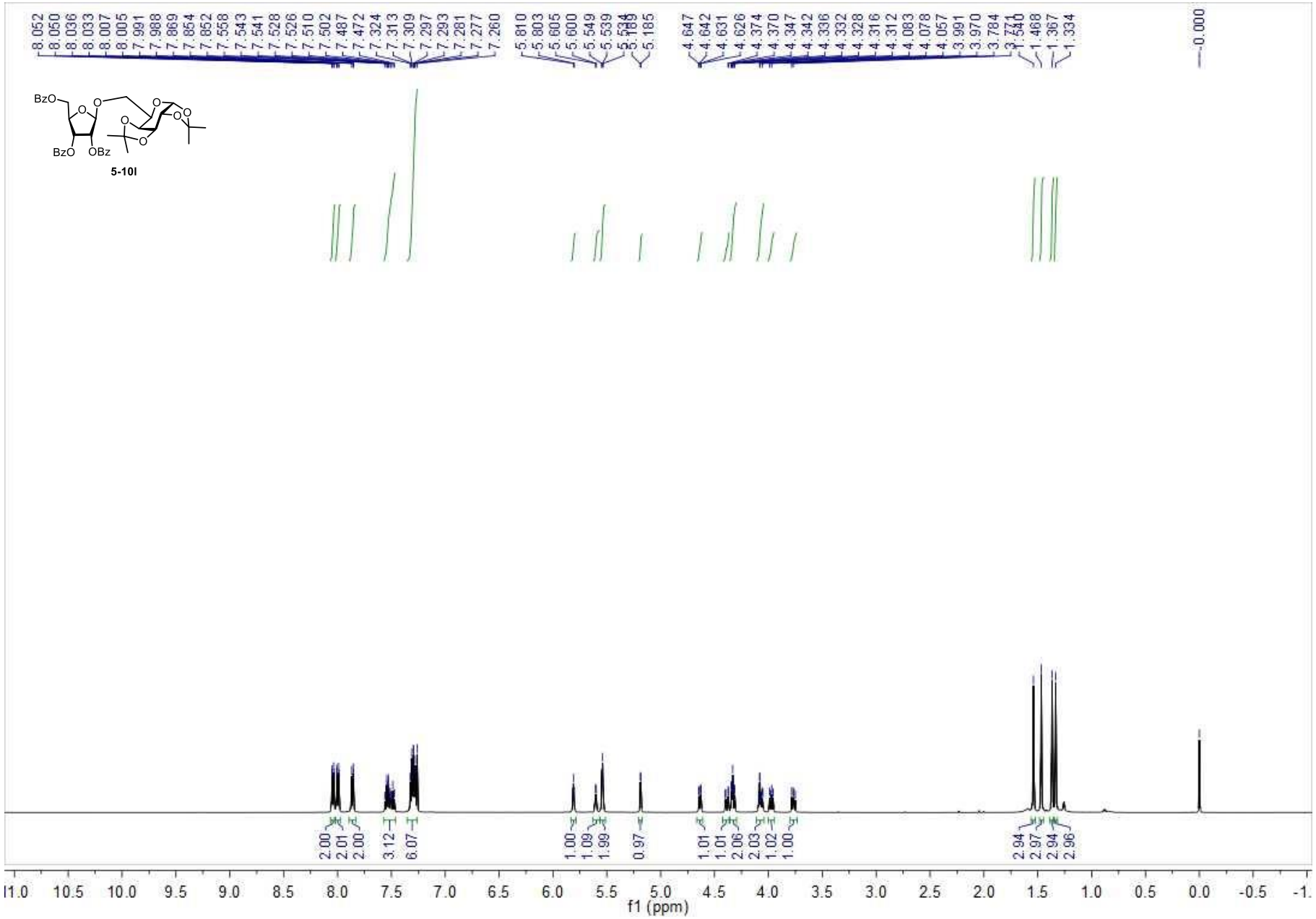
8000
6000
4000
2000
0
-2000
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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8.033
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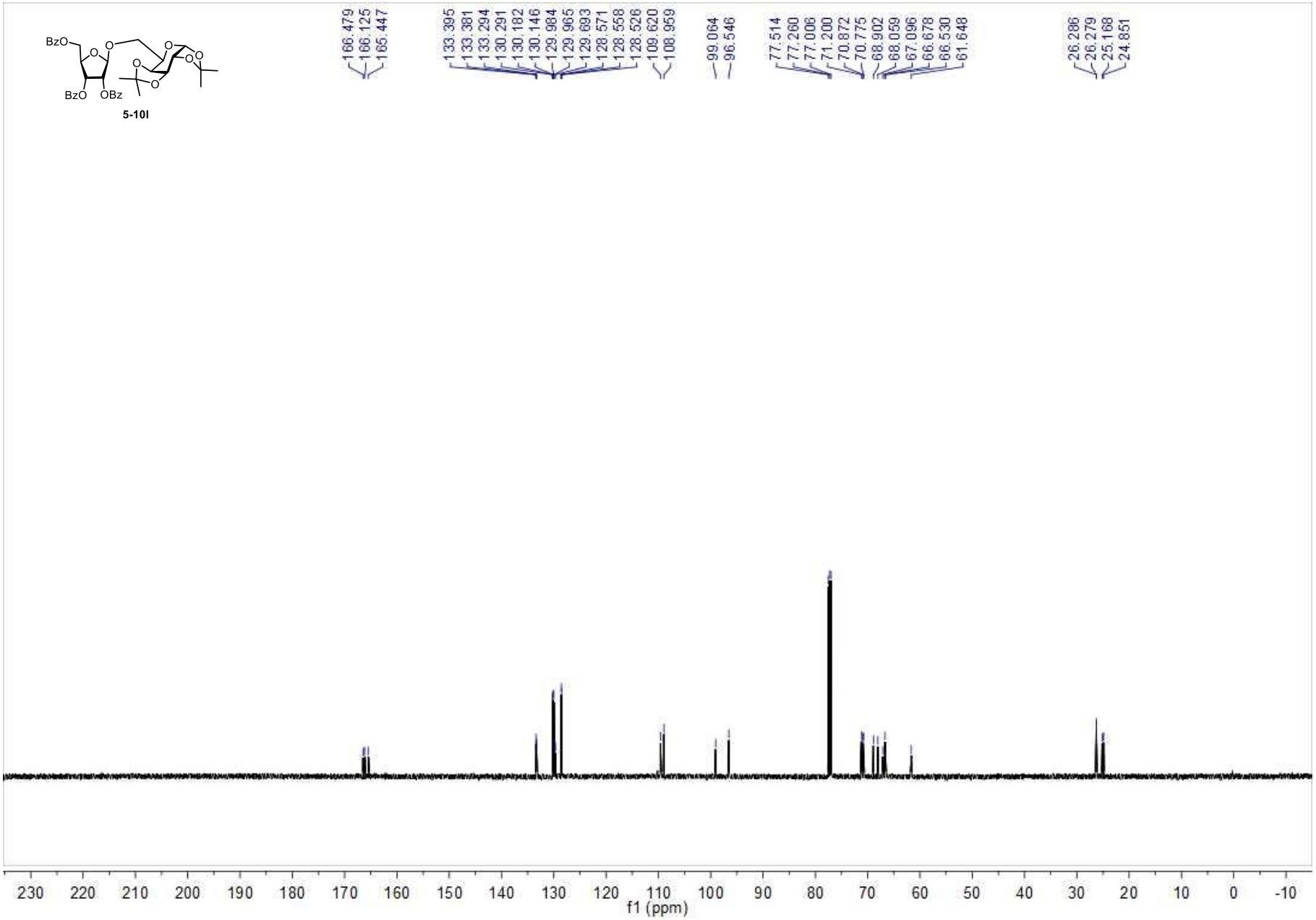
7.988
7.869
7.854
7.852
7.558
7.543
7.541
7.528
7.526
7.510
7.502
7.487
7.472
7.324
7.313
7.309
7.297
7.293
7.281
7.277
7.260
5.810
5.803
5.605
5.600
5.549
5.539
5.185
4.647
4.642
4.631
4.626
4.374
4.370
4.347
4.342
4.336
4.332
4.328
4.316
4.312
4.083
4.078
4.057
3.991
3.970
3.784
1.468
1.367
1.334
-0.000
BzO
BzO
OBz
5-10l
2.00
2.01
2.00
3.12
6.07
1.00
1.09
1.99
0.97
1.01
1.01
2.06
2.03
1.02
1.00
2.94
2.97
2.94
2.96
f1 (ppm)


BzO
BzO
OBz
5-10l
166.479
166.125
165.447
133.395
133.381
133.294
130.291
130.182
130.146
129.984
129.965
129.693
128.571
128.558
128.526
109.620
108.959
99.064
96.546
77.514
77.260
77.006
71.200
70.872
70.775
68.902
68.059
67.096
66.678
66.530
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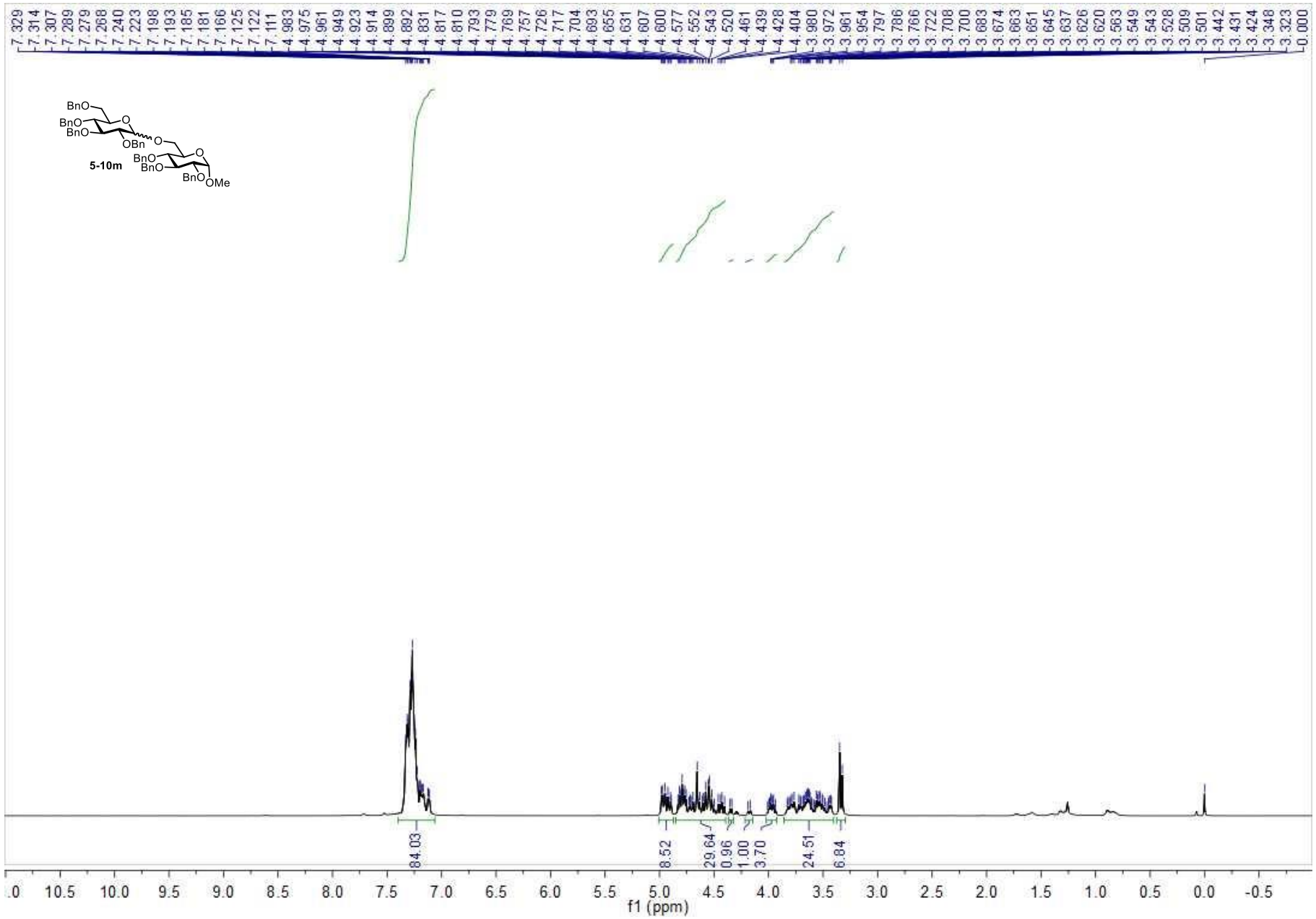
26.286
26.279
25.168
24.851
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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7.307
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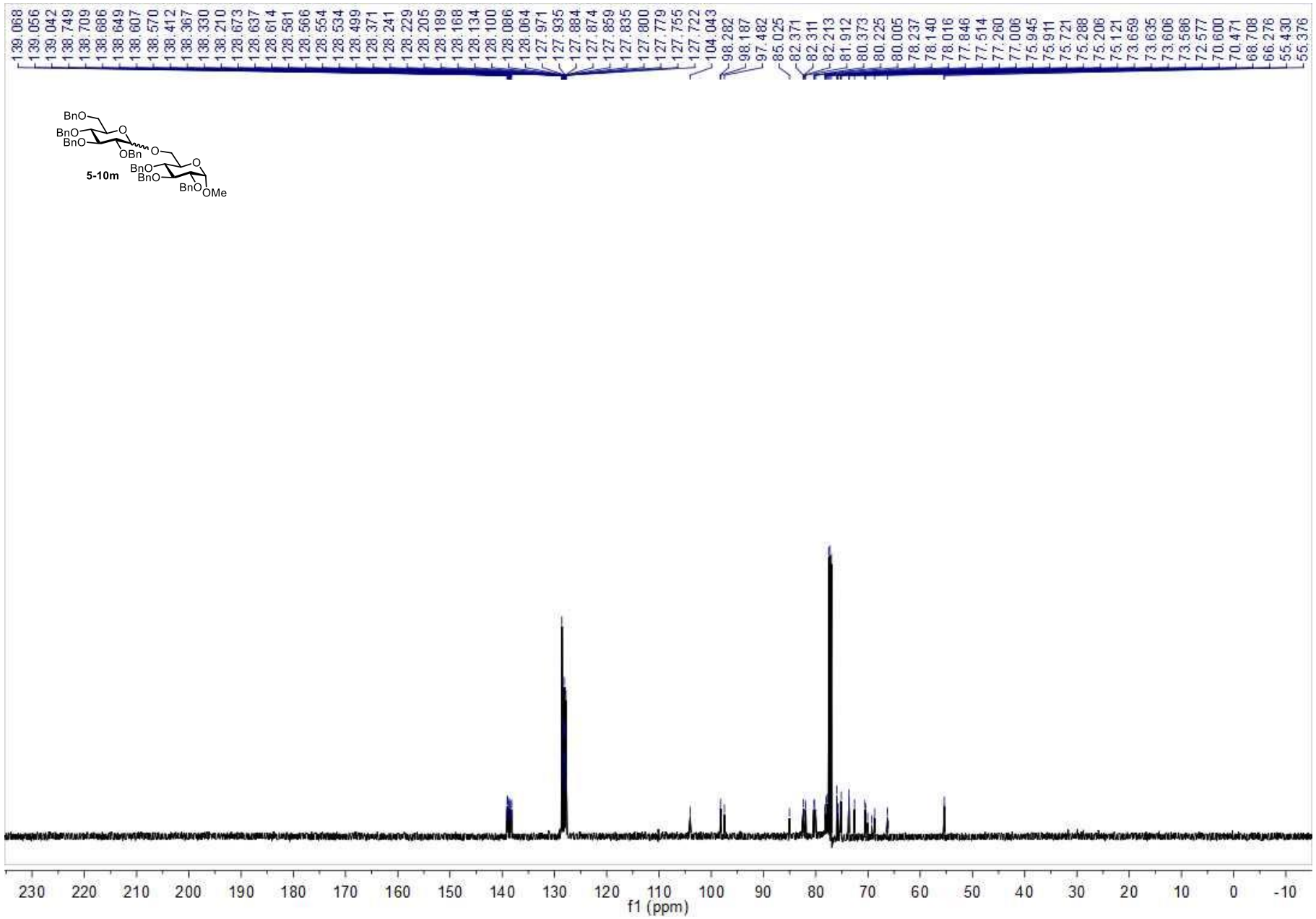
7.279
7.268
7.240
7.223
7.198
7.193
7.185
7.181
7.166
7.125
7.122
7.111
4.983
4.975
4.961
4.949
4.923
4.914
4.899
4.892
4.831
4.817
4.810
4.793
4.779
4.769
4.757
4.726
4.717
4.704
4.693
4.655
4.631
4.607
4.600
4.577
4.552
4.543
4.520
4.461
4.439
4.428
4.404
3.980
3.972
3.961
3.954
3.797
3.786
3.766
3.722
3.708
3.700
3.683
3.674
3.663
3.651
3.645
3.637
3.626
3.620
3.583
3.549
3.543
3.528
3.509
3.501
3.442
3.431
3.424
3.348
3.323
0.000
BnO
BnO
BnO
OBn
O
BnO
BnO
BnO
OMe
5-10m
84.03
8.52
29.64
0.96
1.00
3.70
24.51
6.84
f1 (ppm)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139.042
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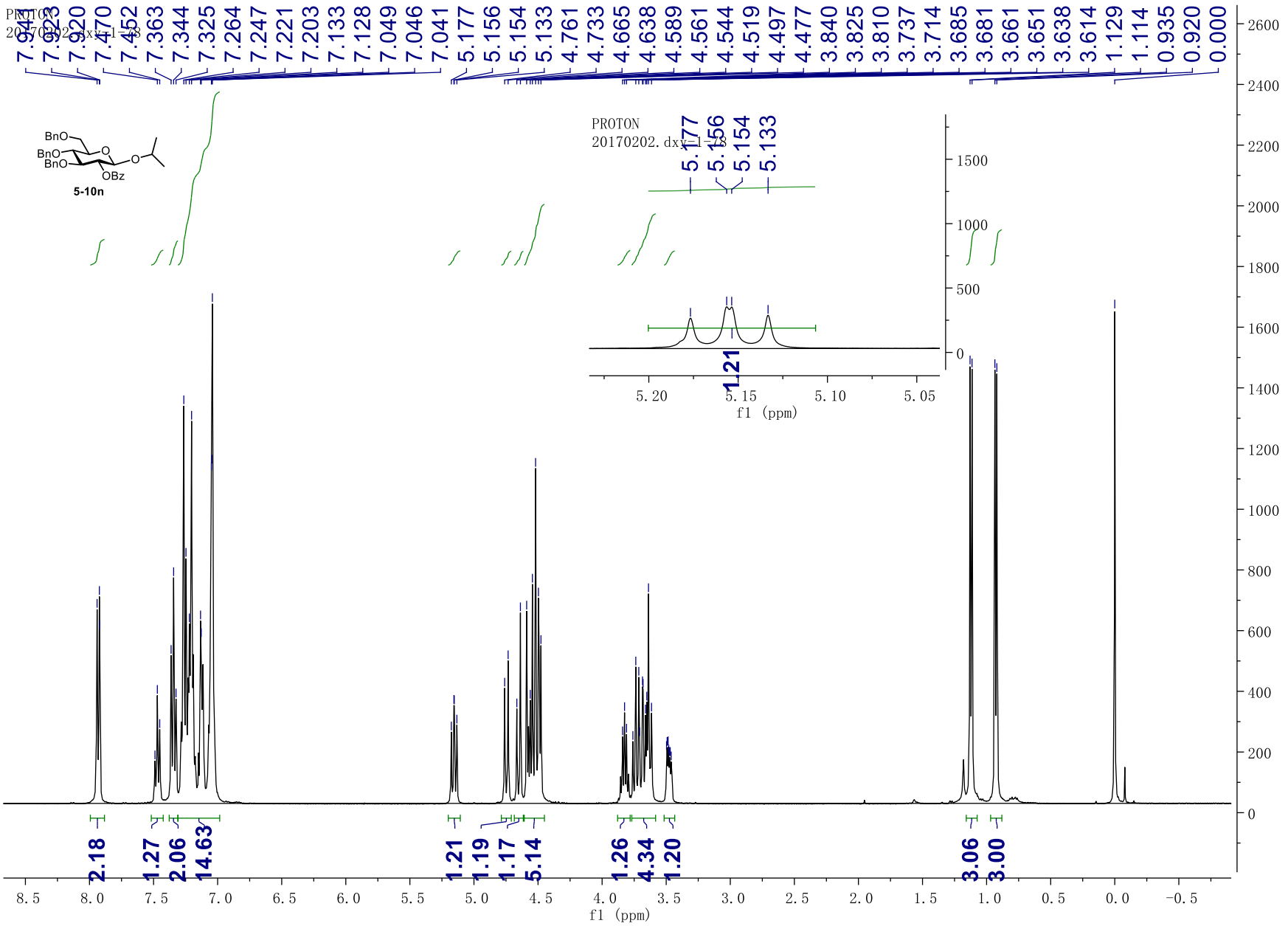
138.607
138.570
138.412
138.367
138.330
138.210
128.673
128.637
128.614
128.581
128.566
128.554
128.534
128.499
128.371
128.241
128.229
128.205
128.189
128.168
128.134
128.100
128.086
128.064
127.971
127.935
127.884
127.874
127.859
127.835
127.800
127.779
127.755
127.722
104.043
98.282
98.187
97.482
85.025
82.371
82.311
82.213
81.912
80.373
80.225
80.005
78.237
78.140
78.016
77.846
77.514
77.260
77.006
75.945
75.911
75.721
75.288
75.206
75.121
73.659
73.635
73.606
73.586
72.577
70.600
70.471
68.708
66.276
55.430
55.376
BnO
BnO
BnO
OBn
O
O
BnO
BnO
BnO
OMe
5-10m
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


PROTON
20170202.dxy-1-78
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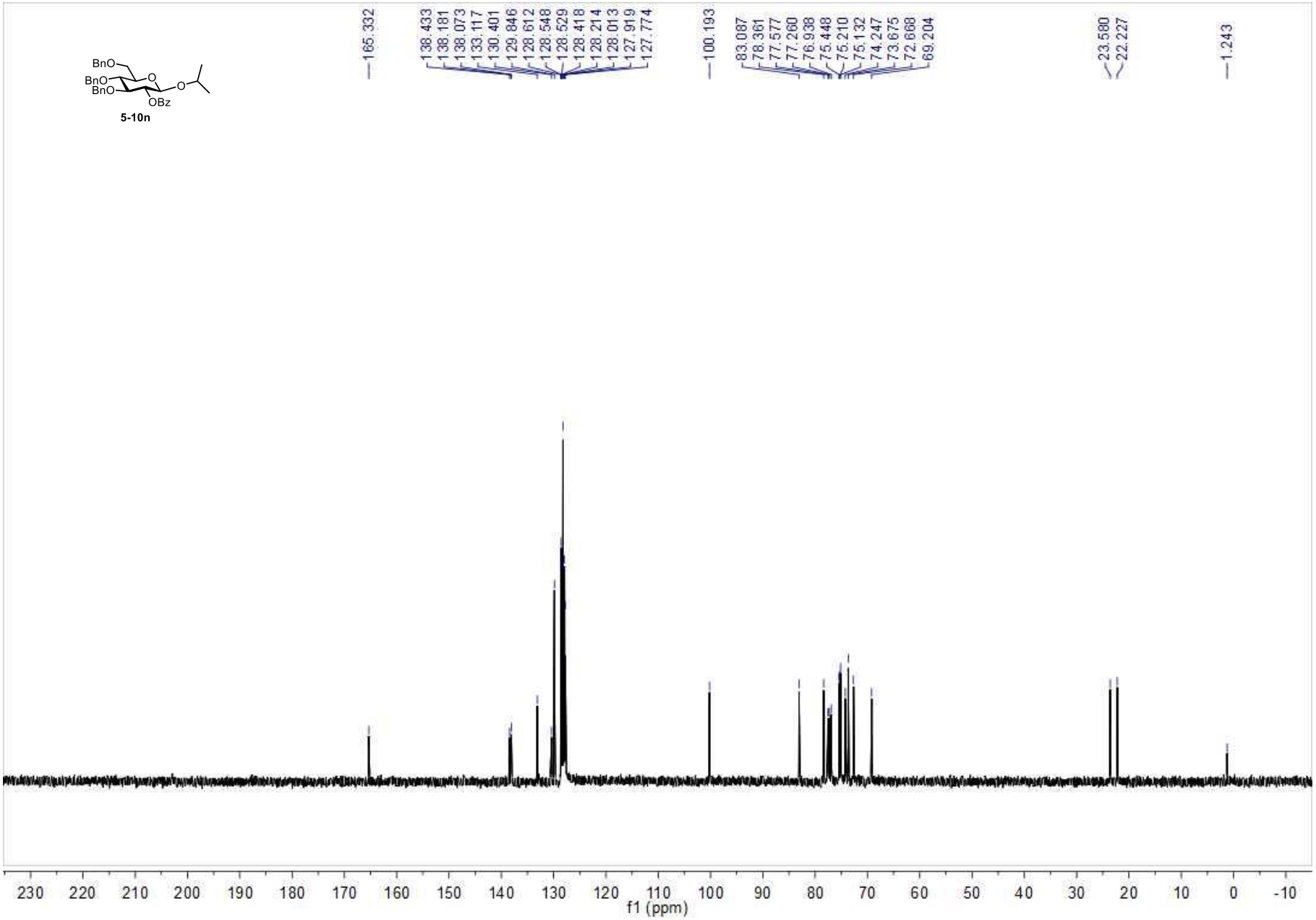
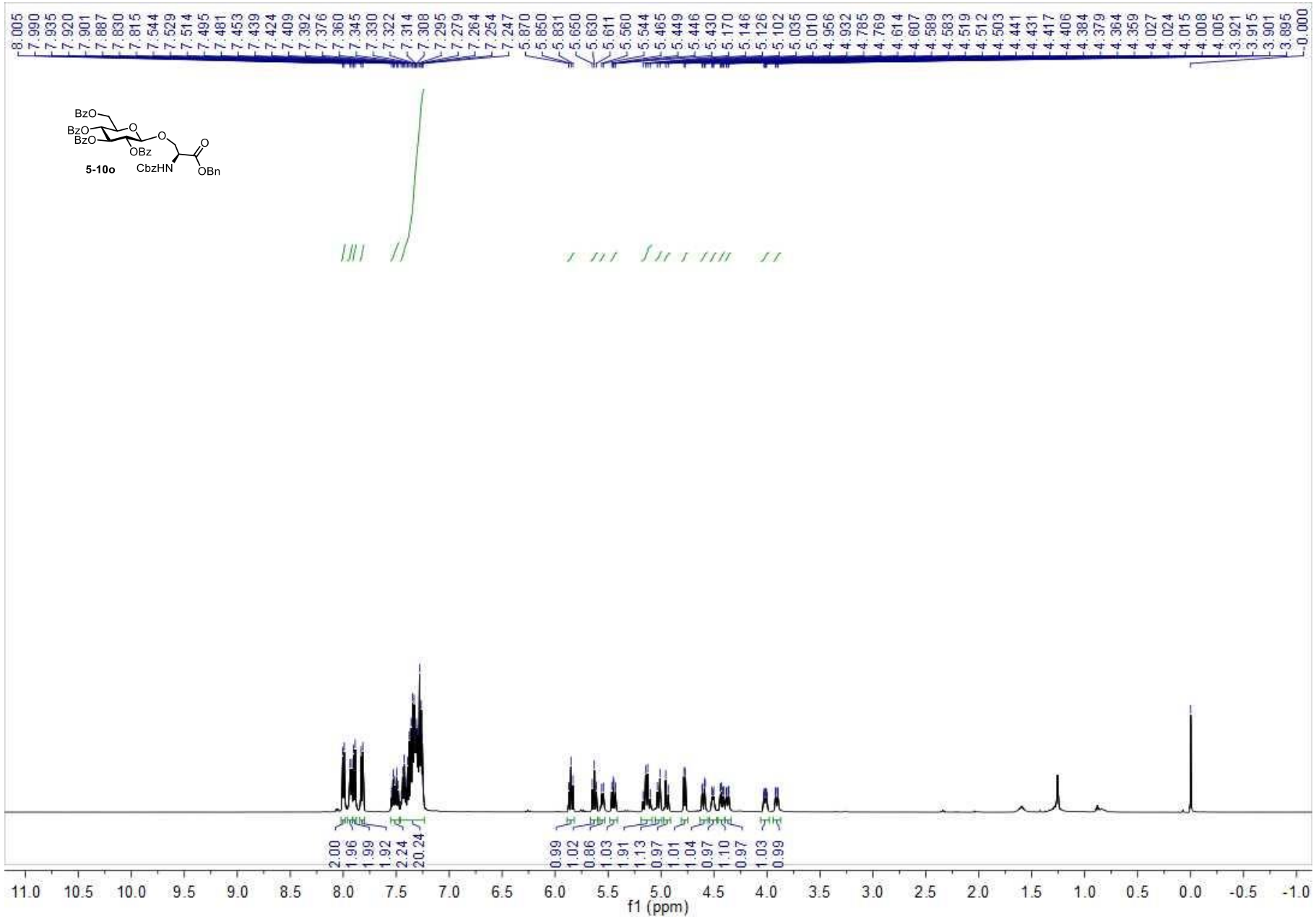
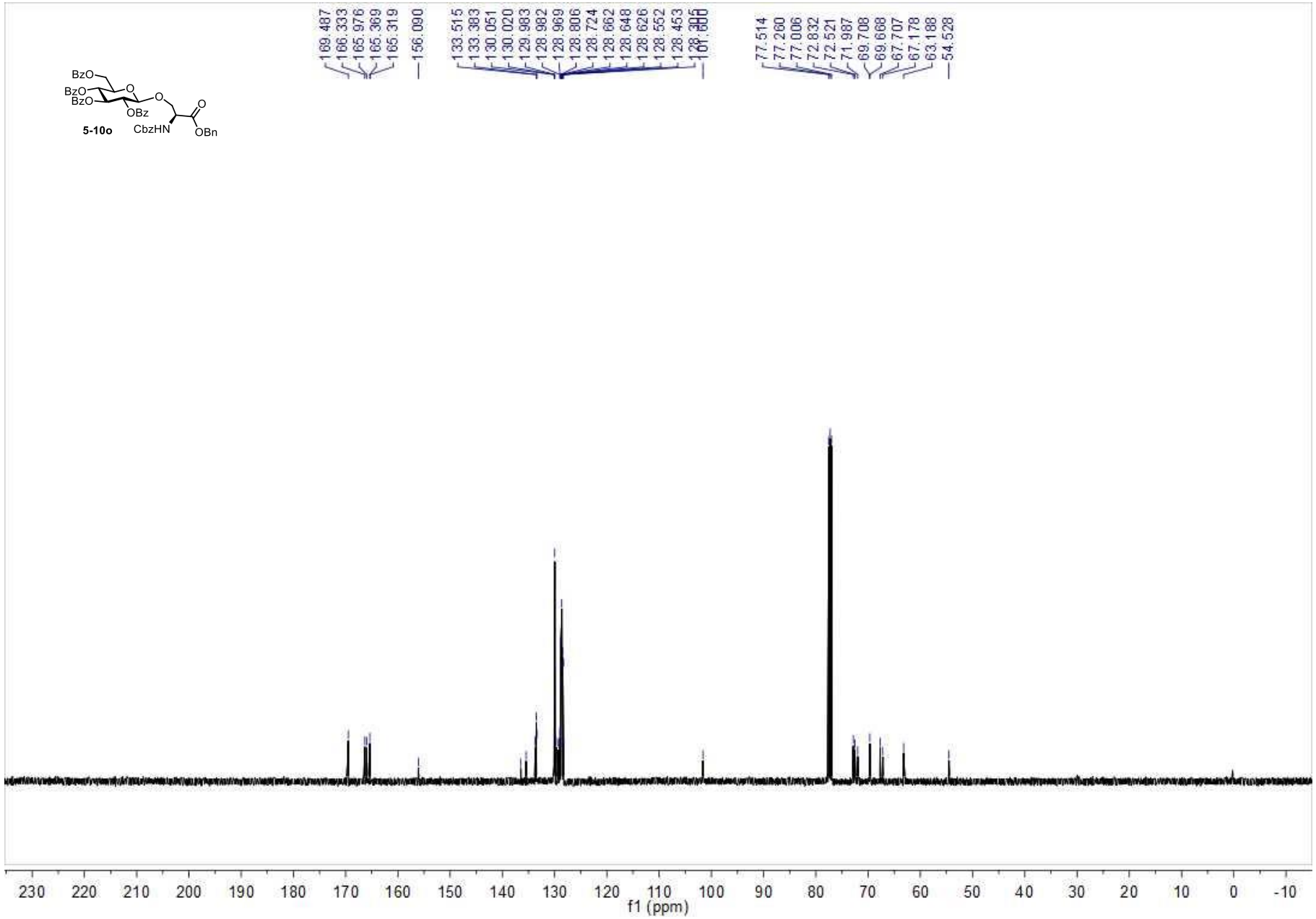
7.923
7.920
7.470
7.452
7.363
7.344
7.325
7.264
7.247
7.221
7.203
7.133
7.128
7.049
7.046
7.041
5.177
5.156
5.154
5.133
4.761
4.733
4.665
4.638
4.589
4.561
4.544
4.519
4.497
4.477
3.840
3.825
3.810
3.737
3.714
3.685
3.681
3.661
3.651
3.638
3.614
1.129
1.114
0.935
0.920
0.000
BnO
BnO
BnO
O
O
OBz
5-10n
PROTON
20170202.dxy-1-78
5.177
5.156
5.154
5.133
1.21
f1 (ppm)
2.18
1.27
2.06
14.63
1.21
1.19
1.17
5.14
1.26
4.34
1.20
3.06
3.00
f1 (ppm)


BnO
BnO
BnO
O
O
OBz
5-10n
165.332
138.433
138.181
138.073
133.117
130.401
129.846
128.612
128.548
128.529
128.418
128.214
128.013
127.919
127.774
100.193
83.087
78.361
77.577
77.260
76.938
75.448
75.210
75.132
74.247
73.675
72.668
69.204
23.580
22.227
1.243
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


8.005
7.990
7.935
7.920
7.901
7.887
7.830
7.815
7.544
7.529
7.514
7.495
7.481
7.453
7.439
7.424
7.409
7.392
7.376
7.360
7.345
7.330
7.322
7.314
7.308
7.295
7.279
7.264
7.254
7.247
5.870
5.850
5.831
5.650
5.630
5.611
5.560
5.544
5.465
5.449
5.446
5.430
5.170
5.146
5.126
5.102
5.035
5.010
4.956
4.932
4.785
4.769
4.614
4.607
4.589
4.583
4.519
4.512
4.503
4.441
4.431
4.417
4.406
4.384
4.379
4.364
4.359
4.027
4.024
4.015
4.008
4.005
3.921
3.915
3.901
3.895
-0.000
BzO
BzO
BzO
OBz
CbzHN
OBn
5-10o
2.00
1.96
1.99
1.92
2.24
20.24
0.99
1.02
0.86
1.03
1.91
1.13
0.97
1.01
1.04
0.97
1.10
0.97
1.03
0.99
11.0
10.5
10.0
9.5
9.0
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
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)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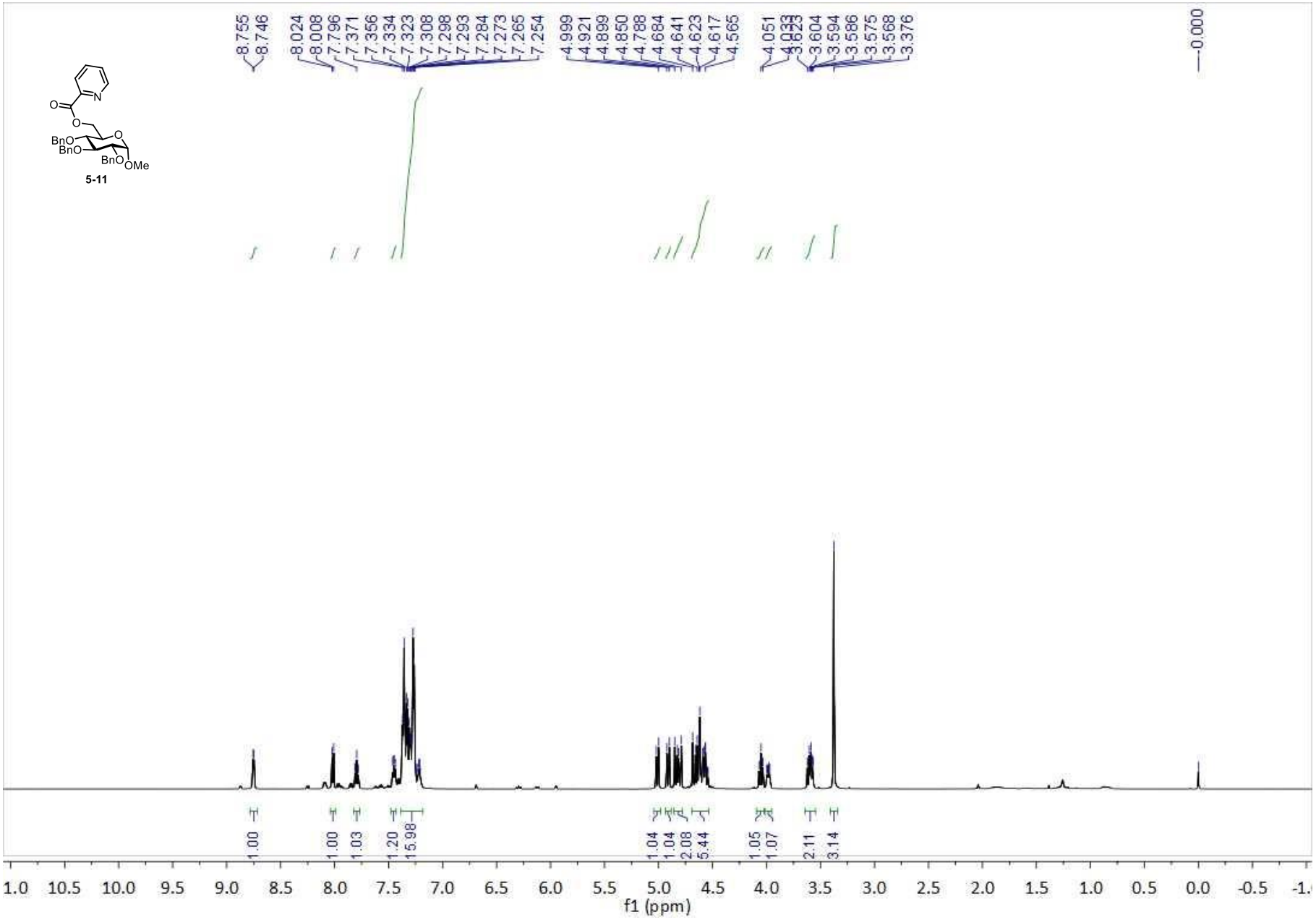
165.976
165.369
165.319
156.090
133.515
133.383
130.051
130.020
129.983
128.982
128.969
128.806
128.724
128.662
128.648
128.626
128.552
128.453
77.514
77.260
77.006
72.832
72.521
71.987
69.708
69.668
67.707
67.178
63.188
54.528
BzO
BzO
BzO
OBz
CbzHN
OBn
5-10o
f1 (ppm)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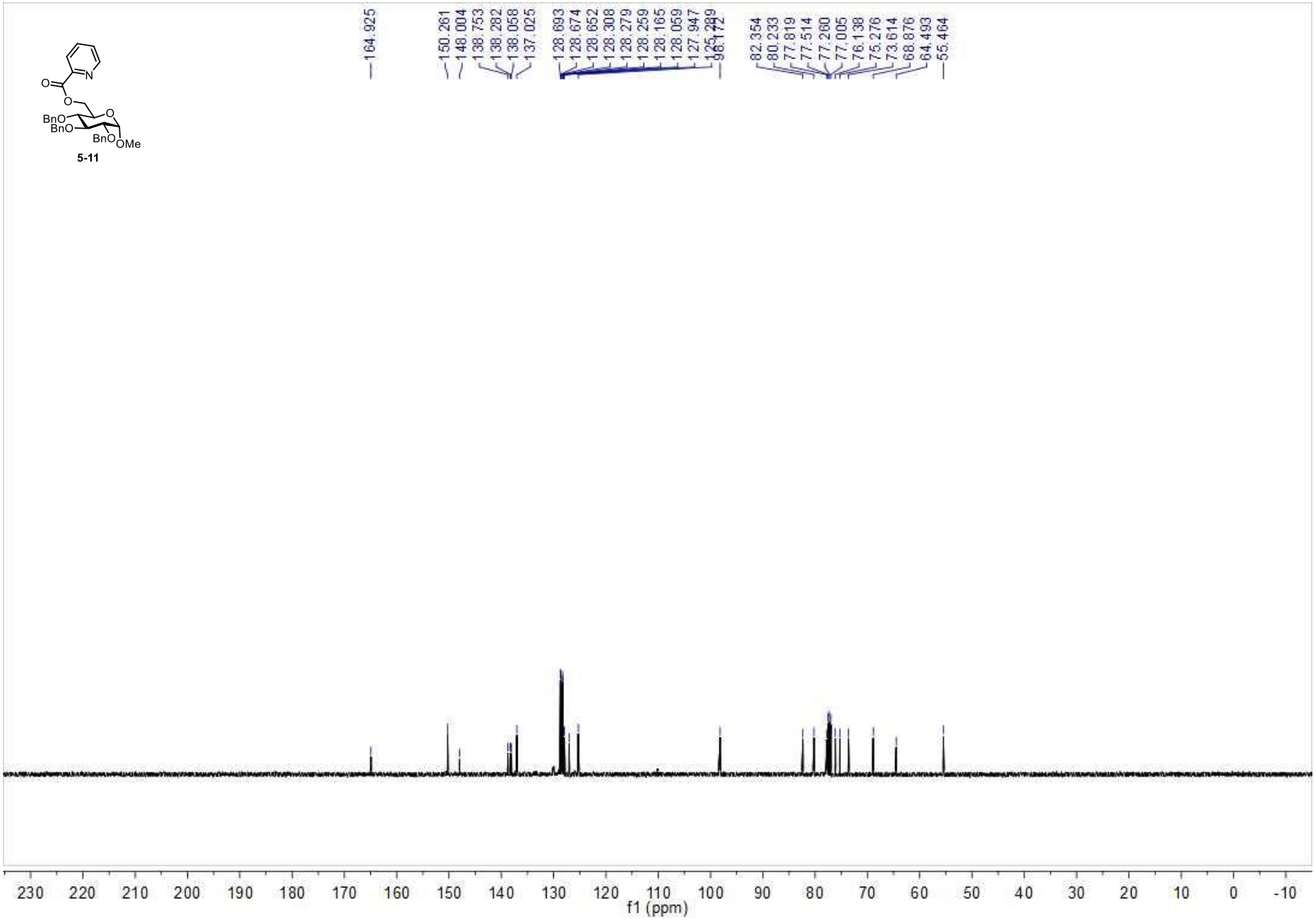
8.746
8.024
8.008
7.796
7.371
7.356
7.334
7.323
7.308
7.298
7.293
7.284
7.273
7.265
7.254
4.999
4.921
4.899
4.850
4.788
4.684
4.641
4.623
4.617
4.565
4.051
4.033
3.623
3.604
3.594
3.586
3.575
3.568
3.376
0.000
BnO
BnO
BnO
OMe
5-11
1.00
1.00
1.03
1.20
15.98
1.04
1.04
2.08
5.44
1.05
1.07
2.11
3.14
f1 (ppm)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148.004
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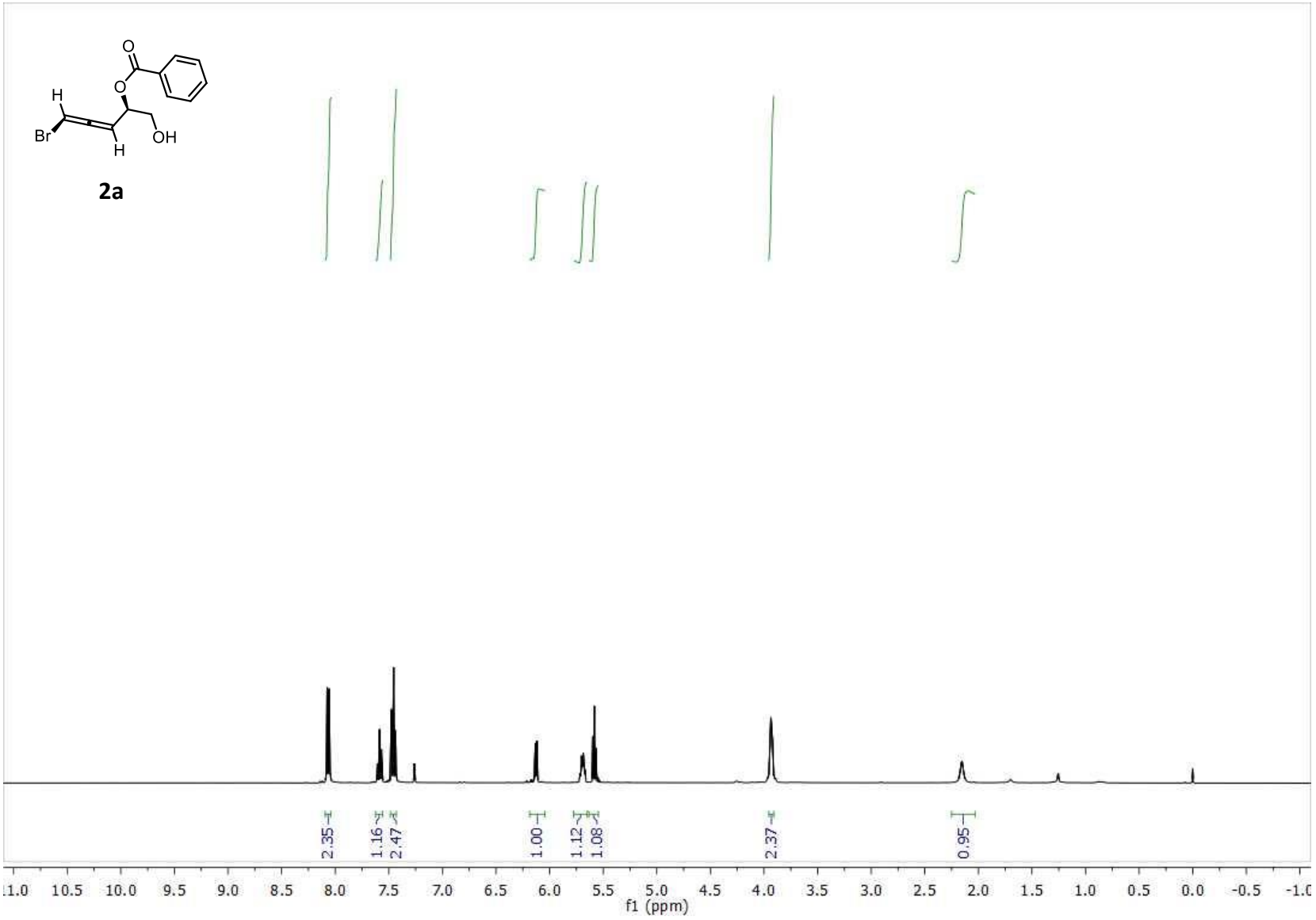
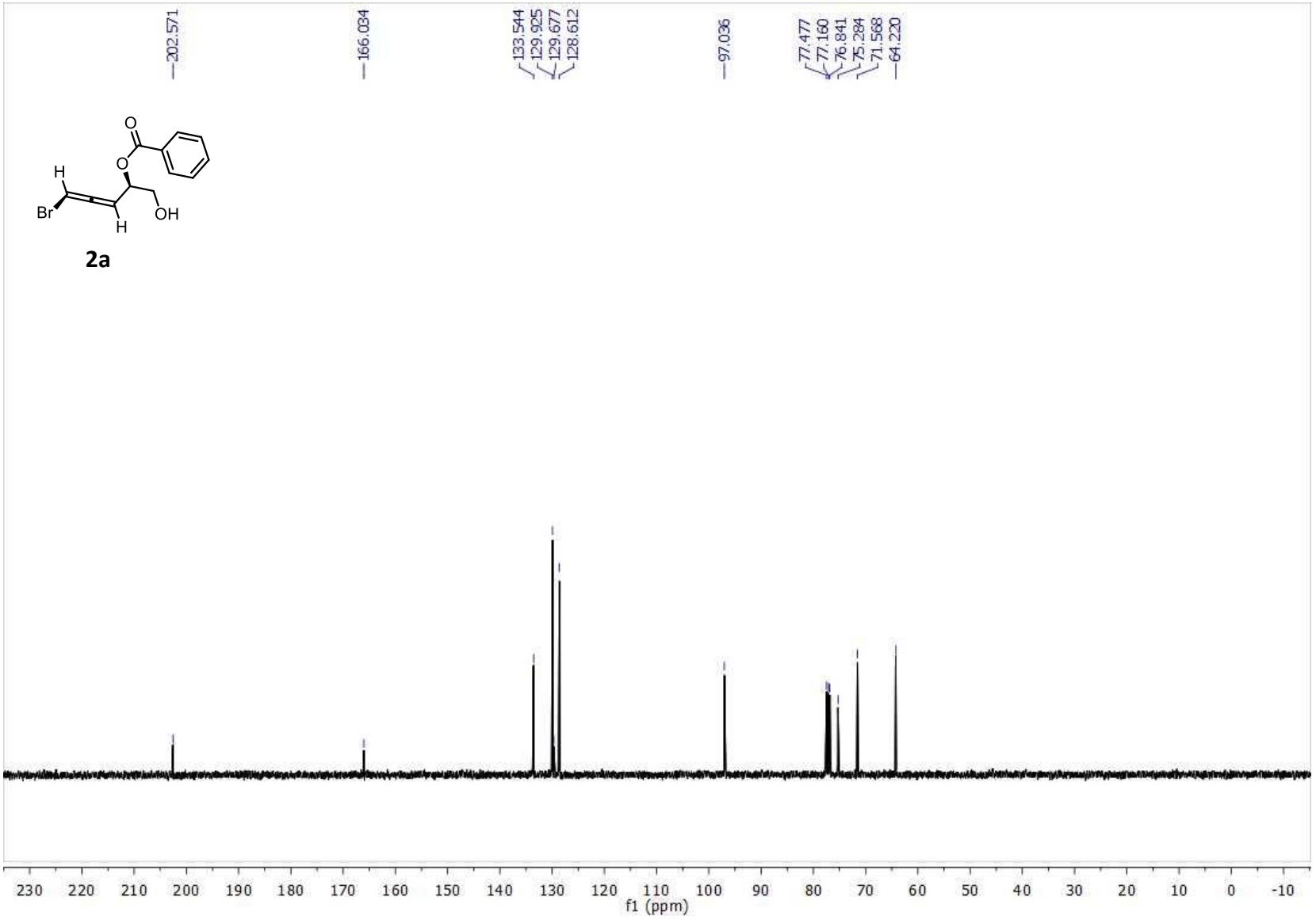
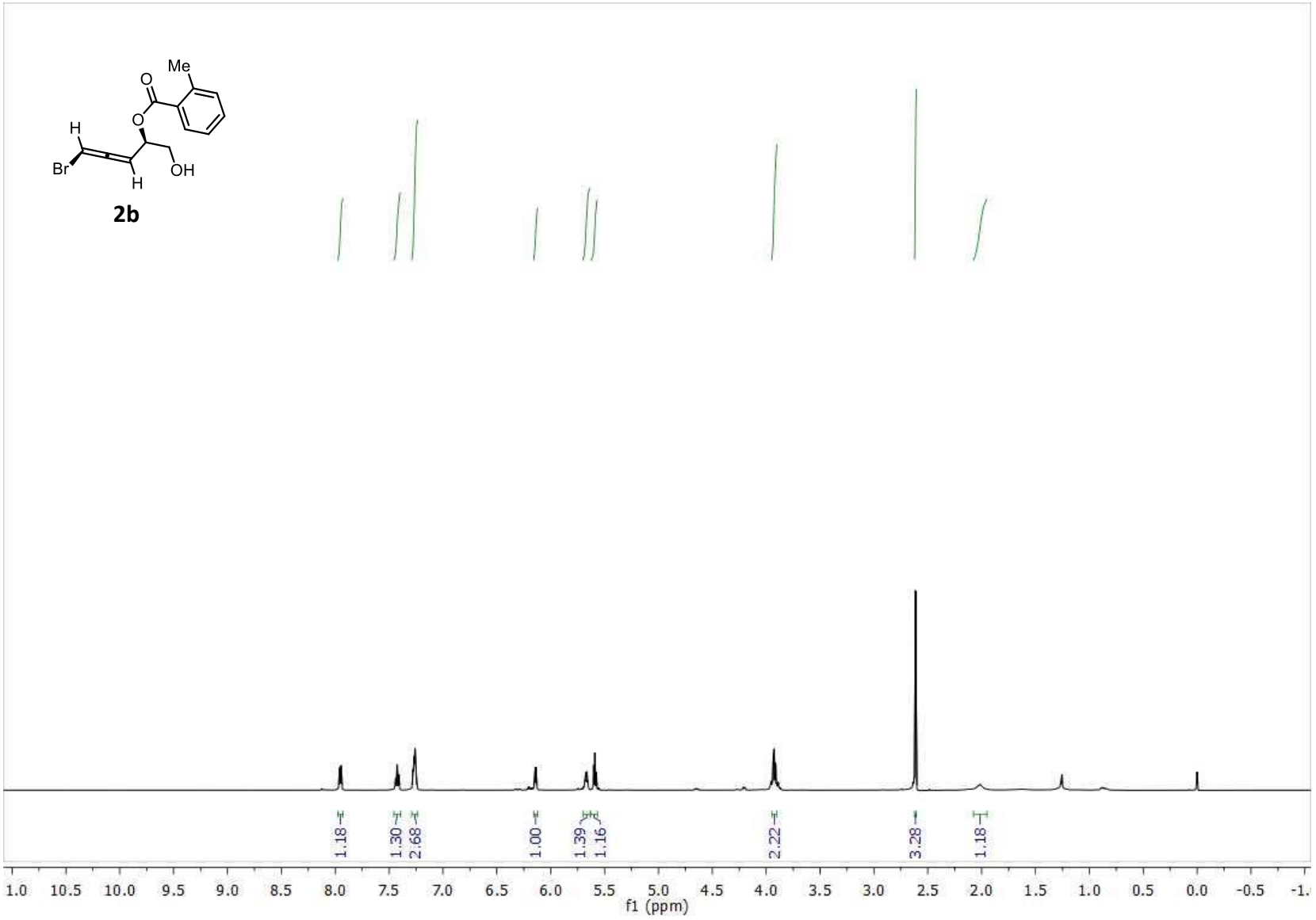
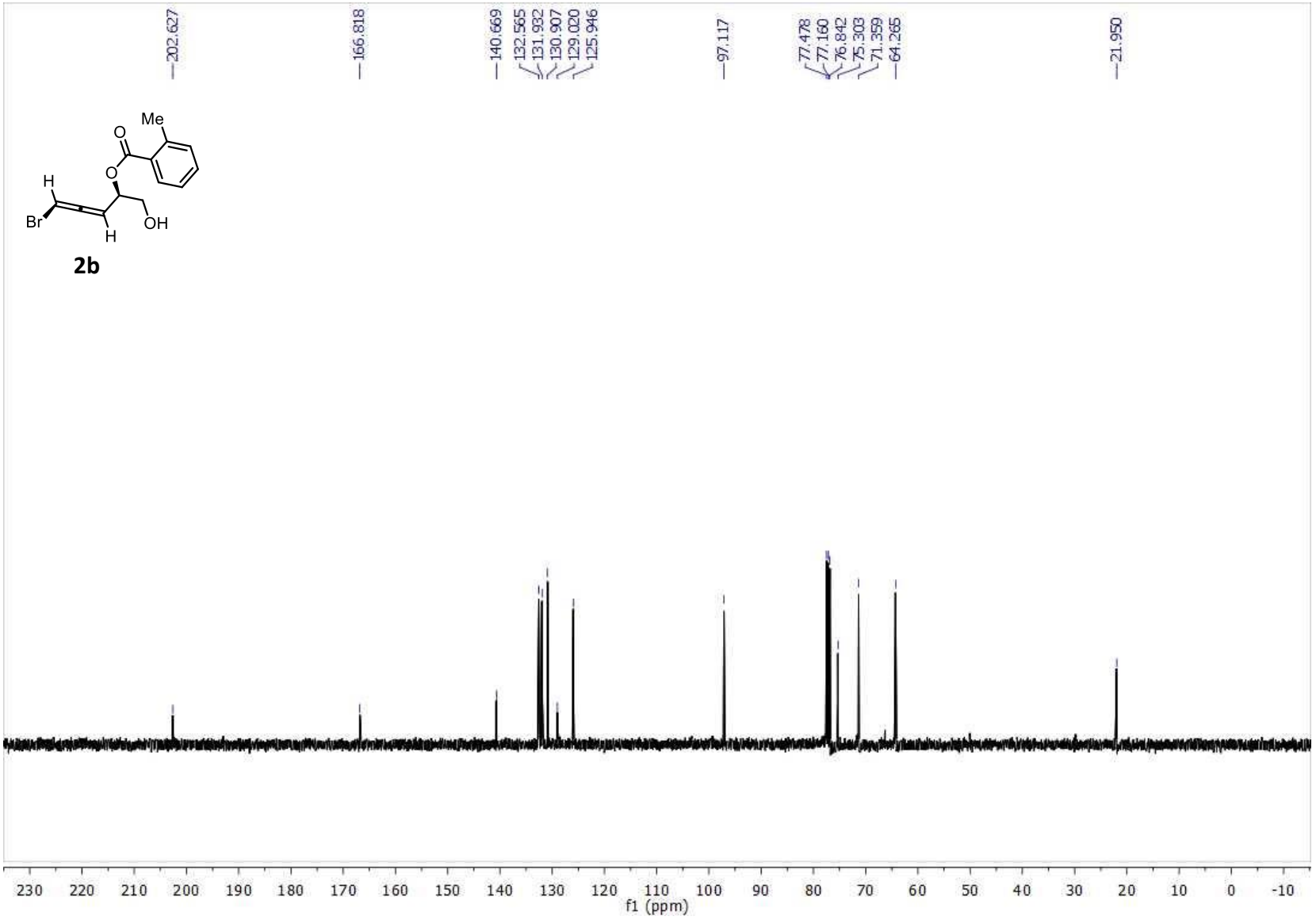
138.282
138.058
137.025
128.693
128.674
128.652
128.308
128.279
128.259
128.165
128.059
127.947
135.289
98.172
82.354
80.233
77.819
77.514
77.260
77.005
76.138
75.276
73.614
68.876
64.493
55.464
BnO
BnO
BnO
OMe
5-11
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
O
H
Br
H
OH
2a
2.35
1.16
2.47
1.00
1.12
1.08
2.37
0.95
f1 (ppm)


202.571
166.034
133.544
129.925
129.677
128.612
97.036
77.477
77.160
76.841
75.284
71.568
64.220
O
O
H
Br
H
OH
2a
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Me
O
O
H
Br
H
OH
2b
1.18
1.30
2.68
1.00
1.39
1.16
2.22
3.28
1.18
1.0 10.5 10.0 9.5 9.0 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 1.5 1.0 0.5 0.0 -0.5 -1.
f1 (ppm)


202.627
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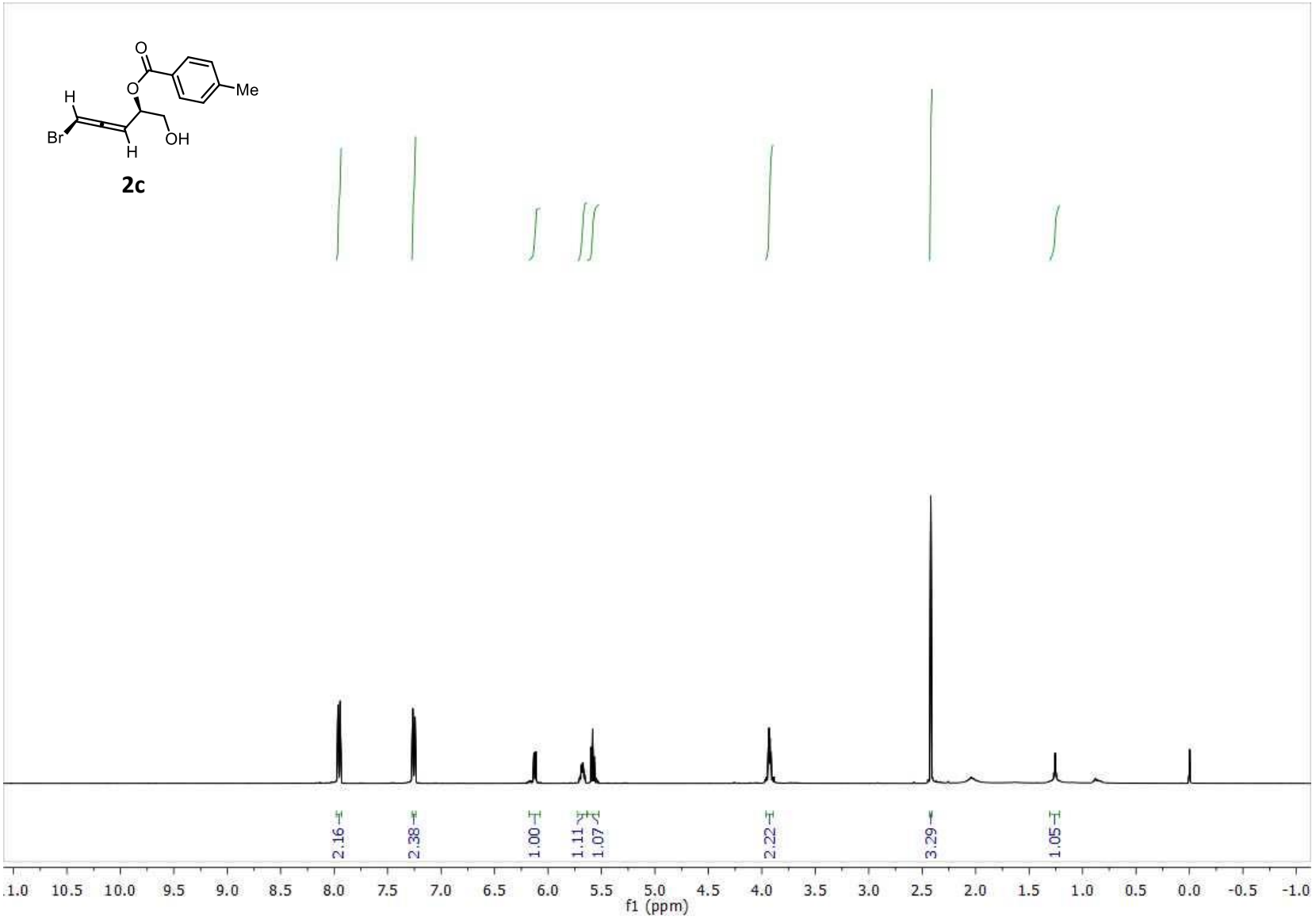
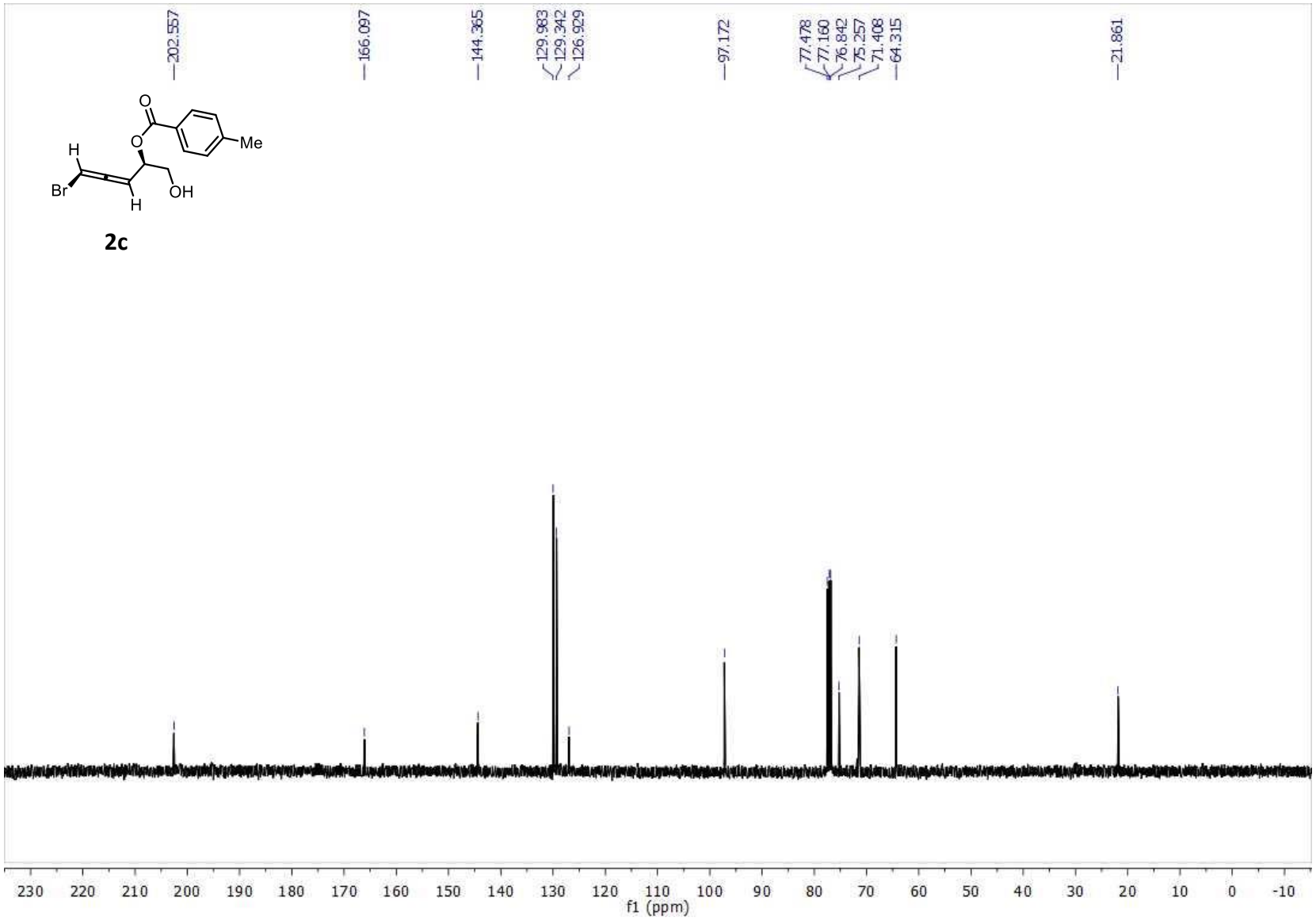
140.669
132.565
131.932
130.907
129.020
125.946
97.117
77.478
77.160
76.842
75.303
71.359
64.265
21.950
Me
O
O
H
Br
H
OH
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

2b


O
O
Me
H
Br
H
OH
2c
2.16
2.38
1.00
1.11
1.07
2.22
3.29
1.05
f1 (ppm)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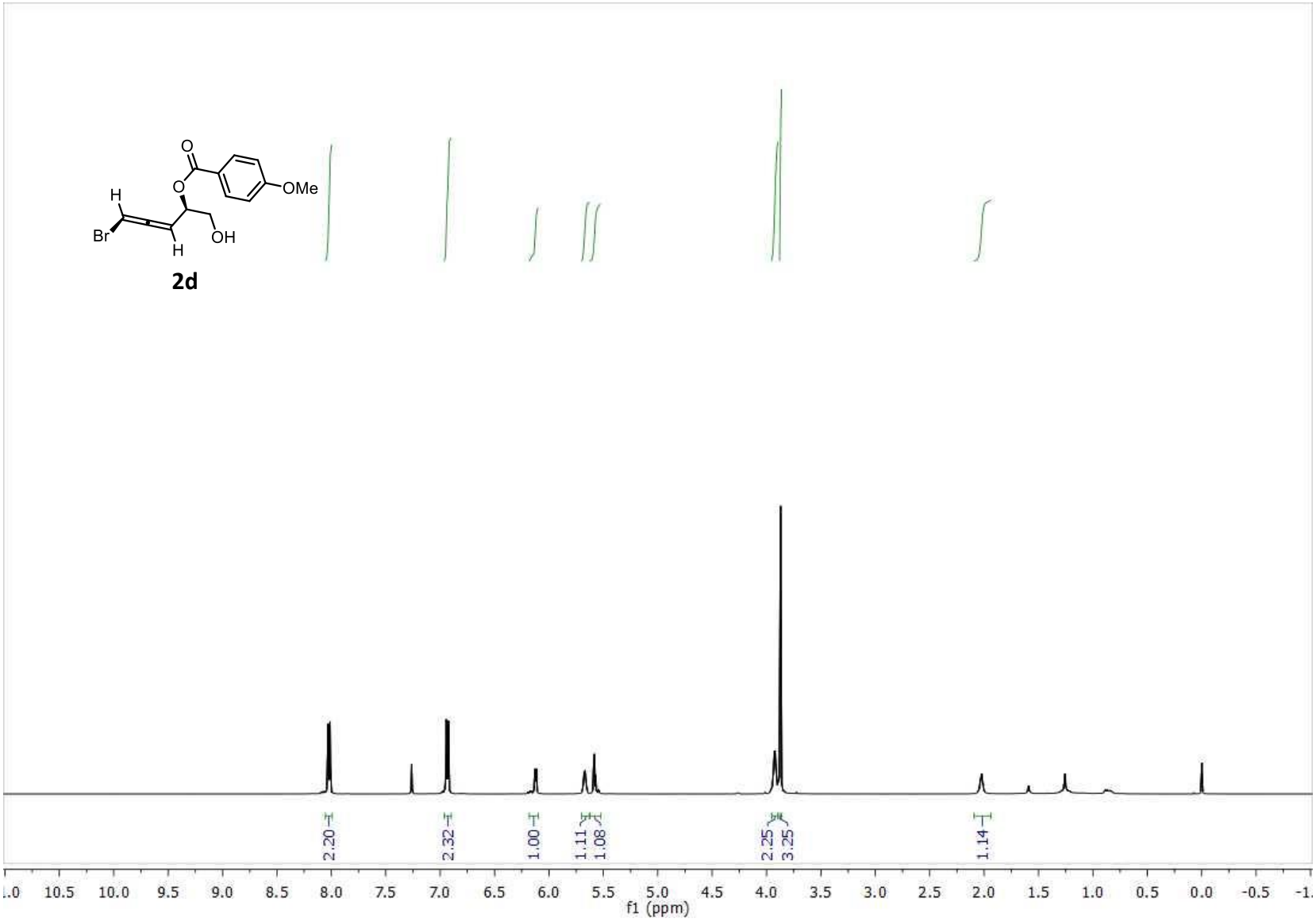
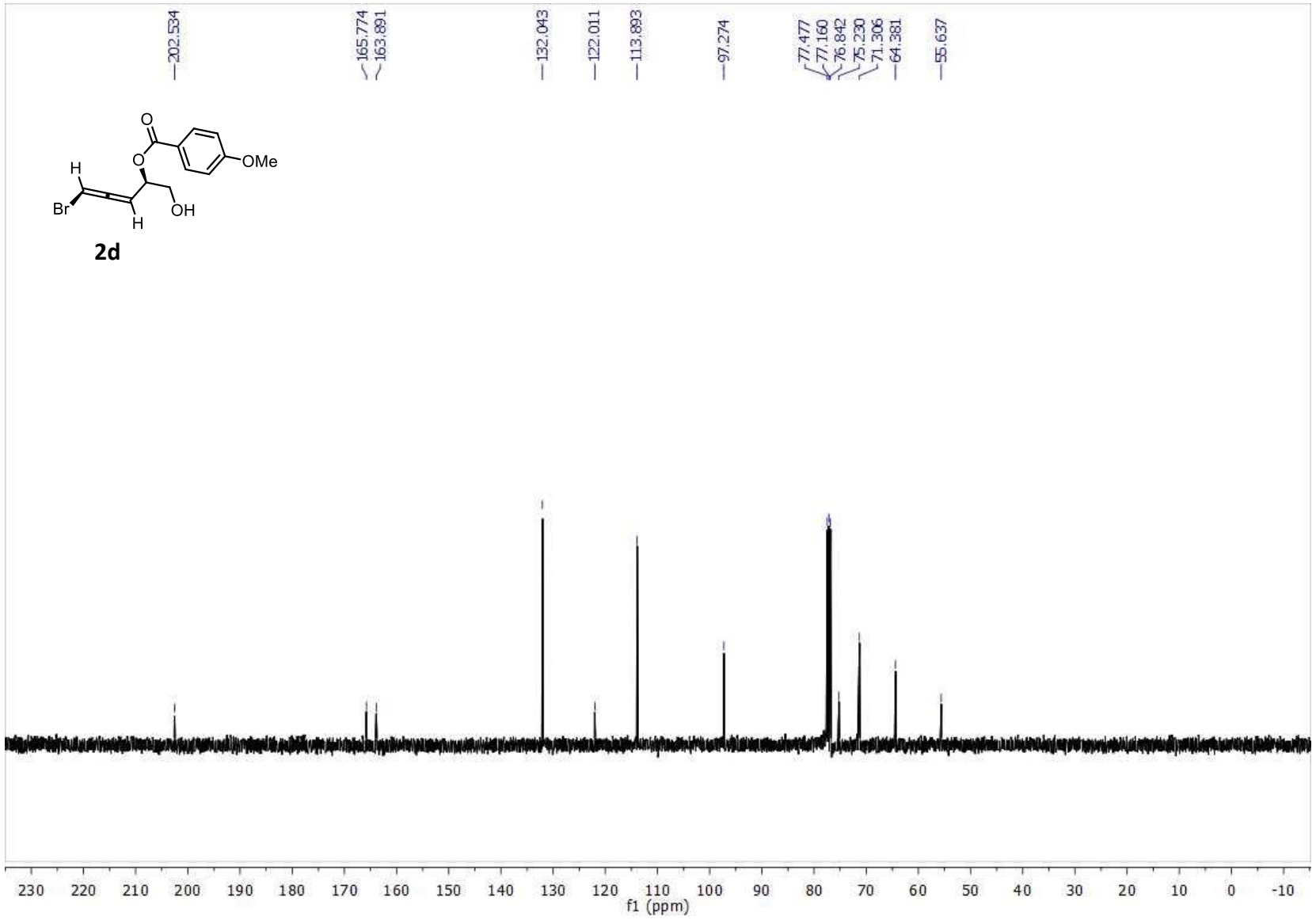
129.983
129.342
126.929
97.172
77.478
77.160
76.842
75.257
71.408
64.315
21.861
O
O
Me
H
Br
H
OH
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

2c


O
O
OMe
H
Br
H
OH
2d
2.20
2.32
1.00
1.11
1.08
2.25
3.25
1.14
f1 (ppm)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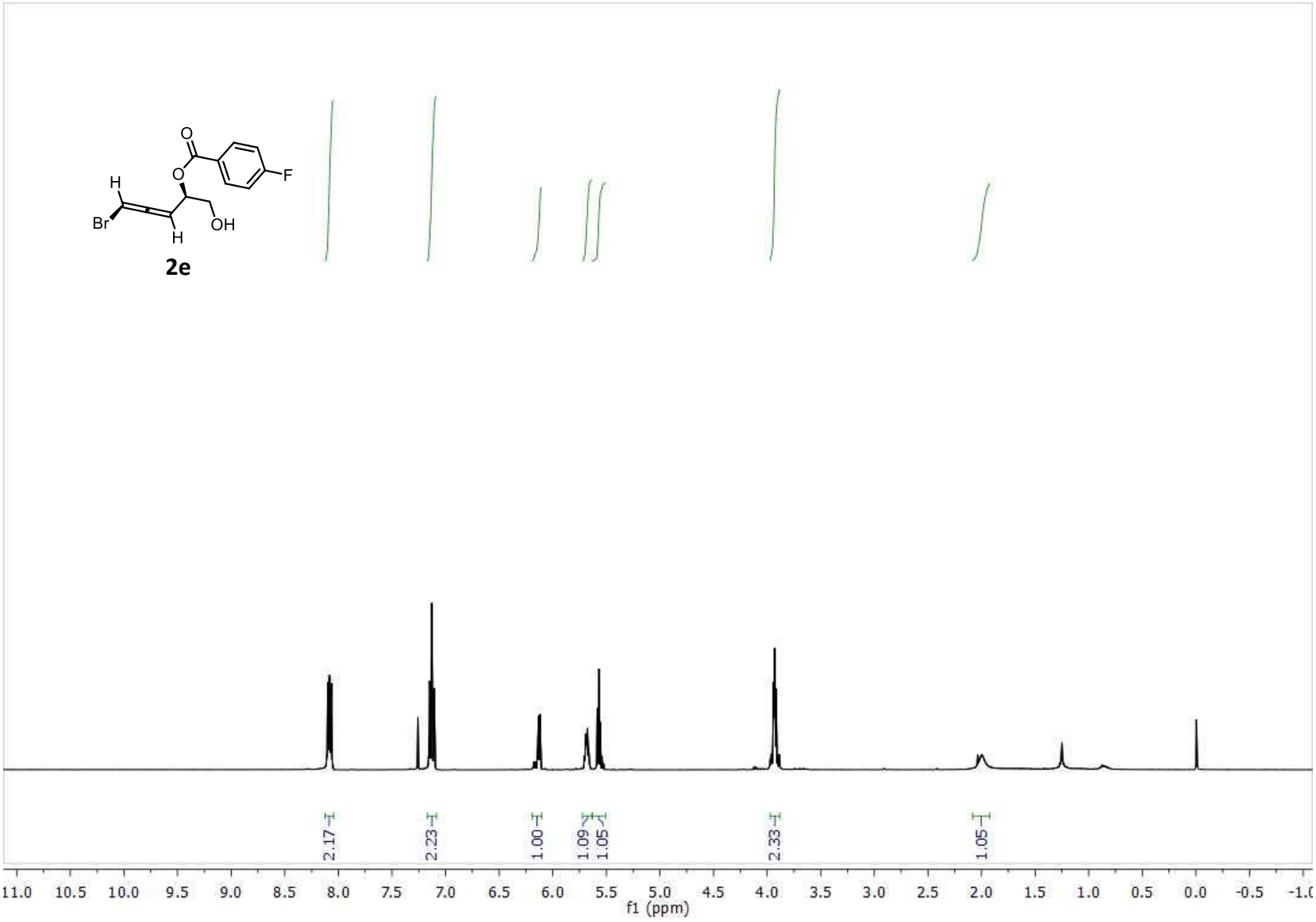
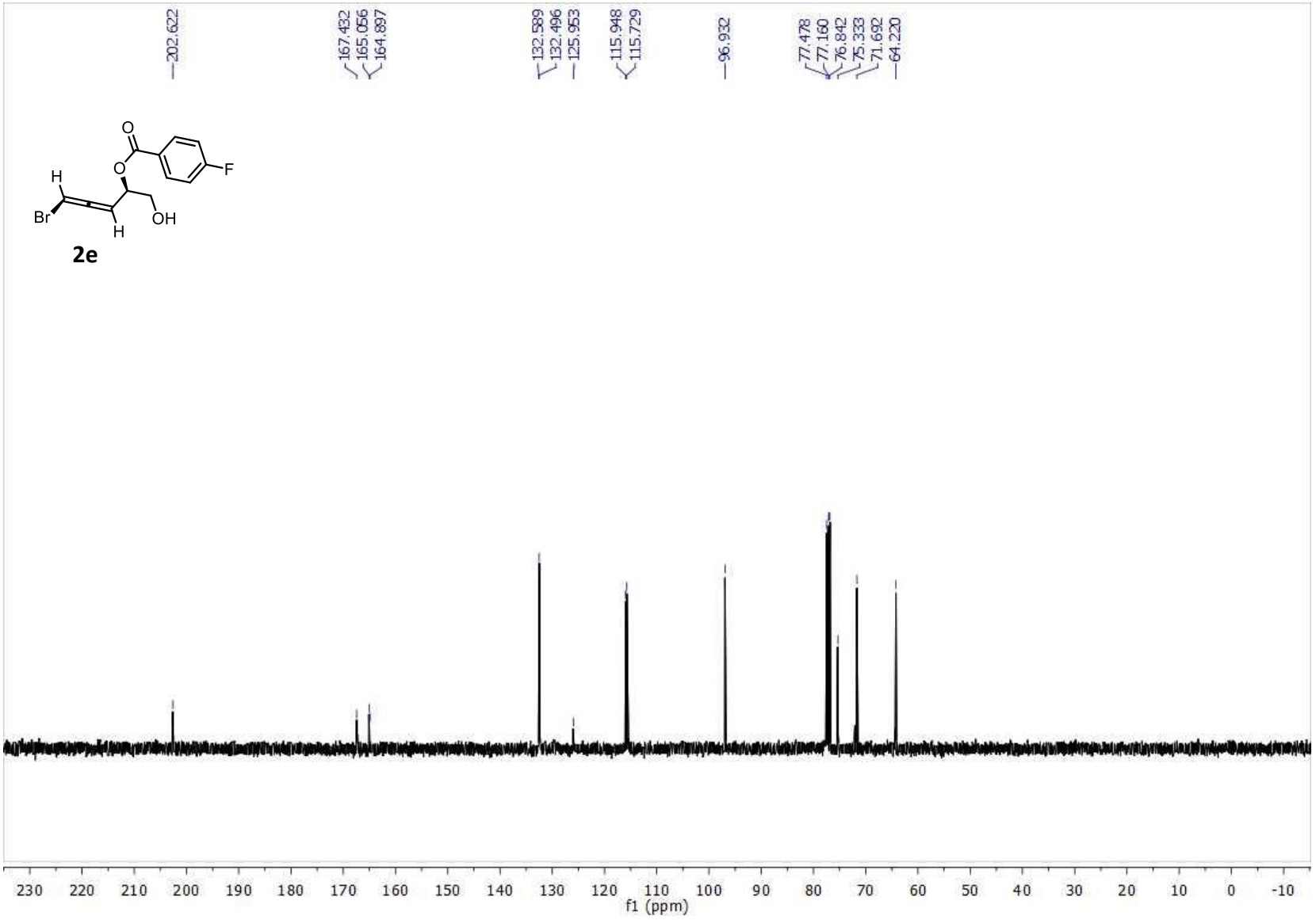
165.774
163.891
132.043
122.011
113.893
97.274
77.477
77.160
76.842
75.230
71.306
64.381
55.637
O
O
OMe
H
Br
OH
H
2d
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
O
F
H
Br
H
OH
2e
2.17
2.23
1.00
1.09
1.05
2.33
1.05
11.0 10.5 10.0 9.5 9.0 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 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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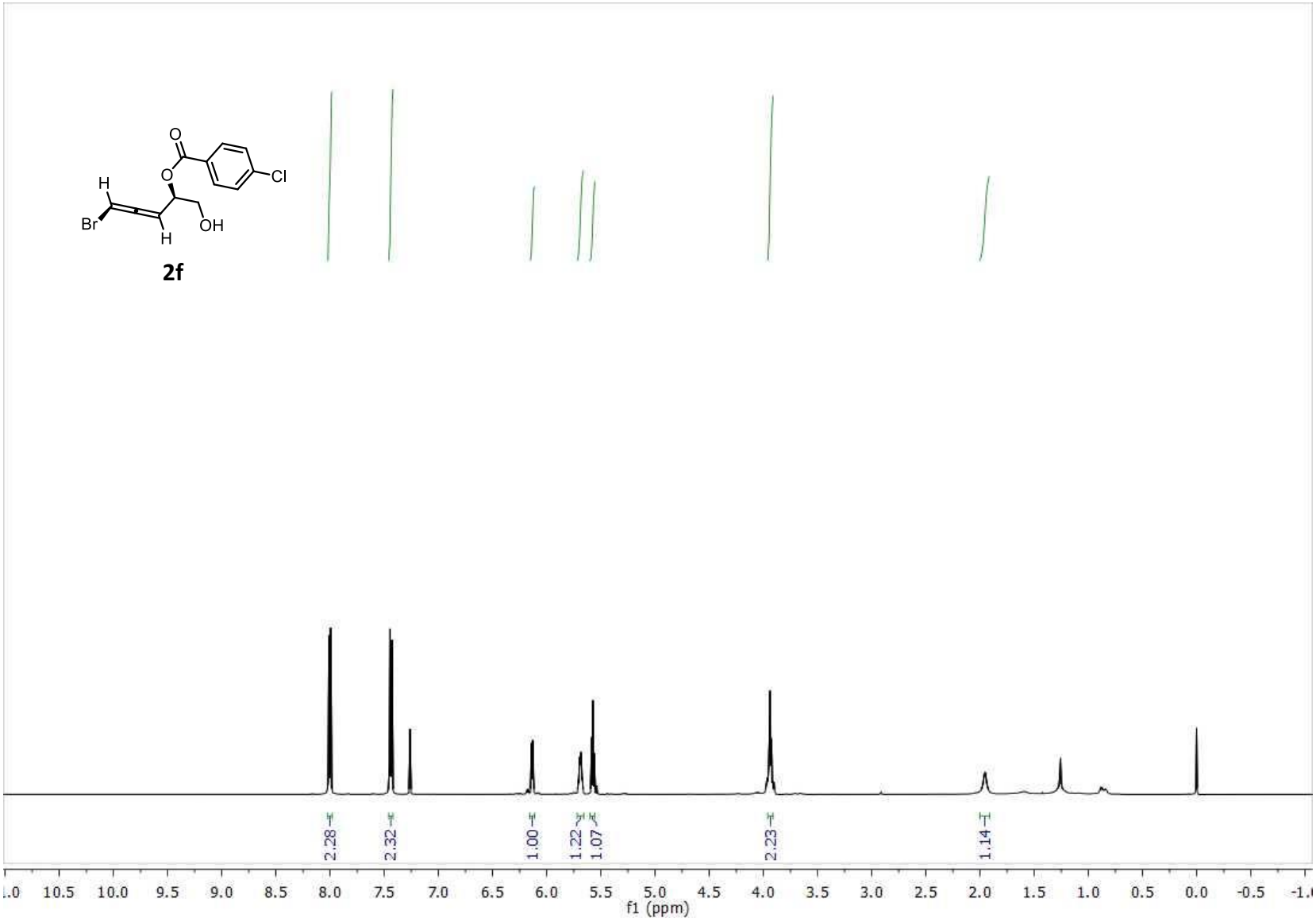
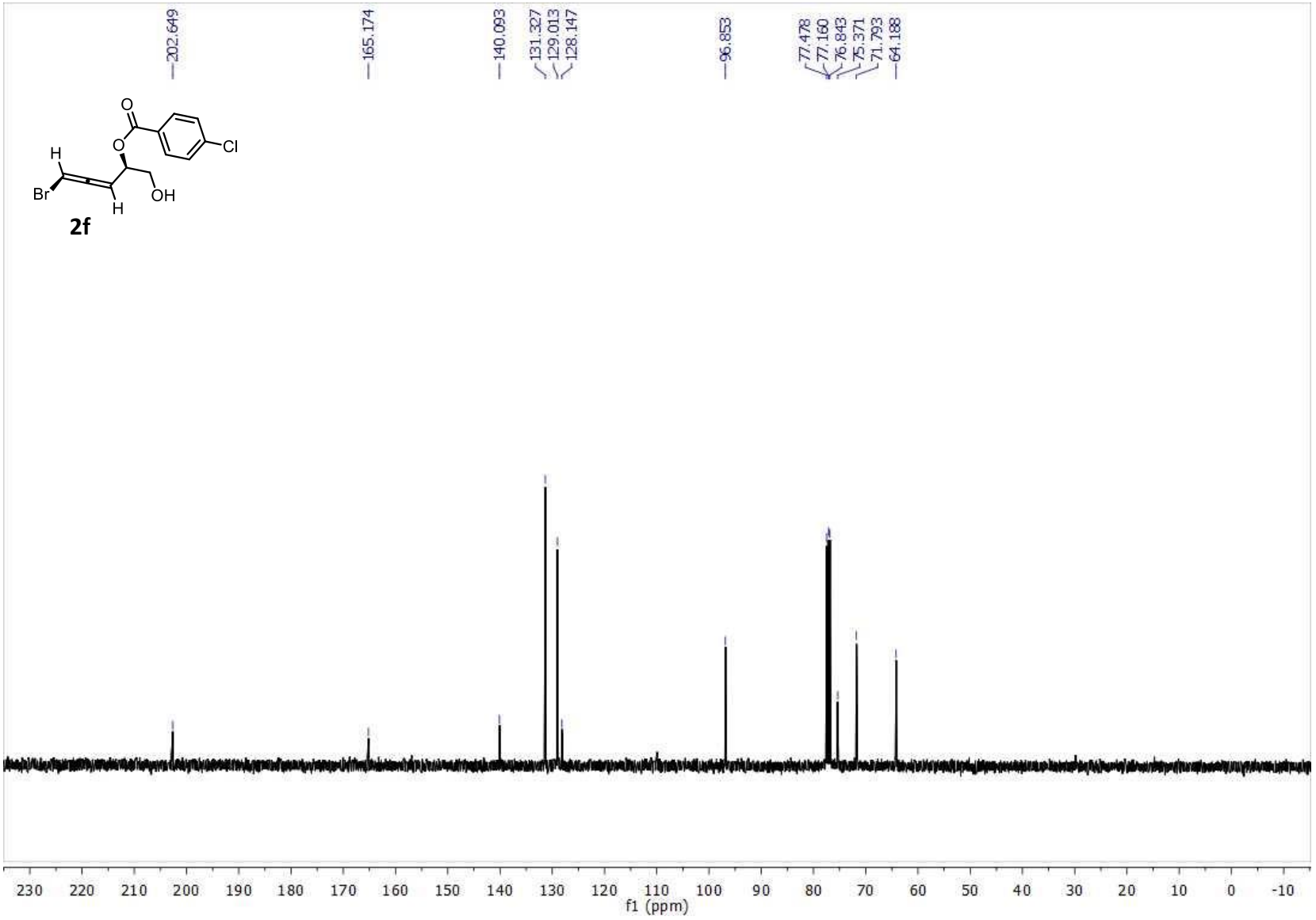
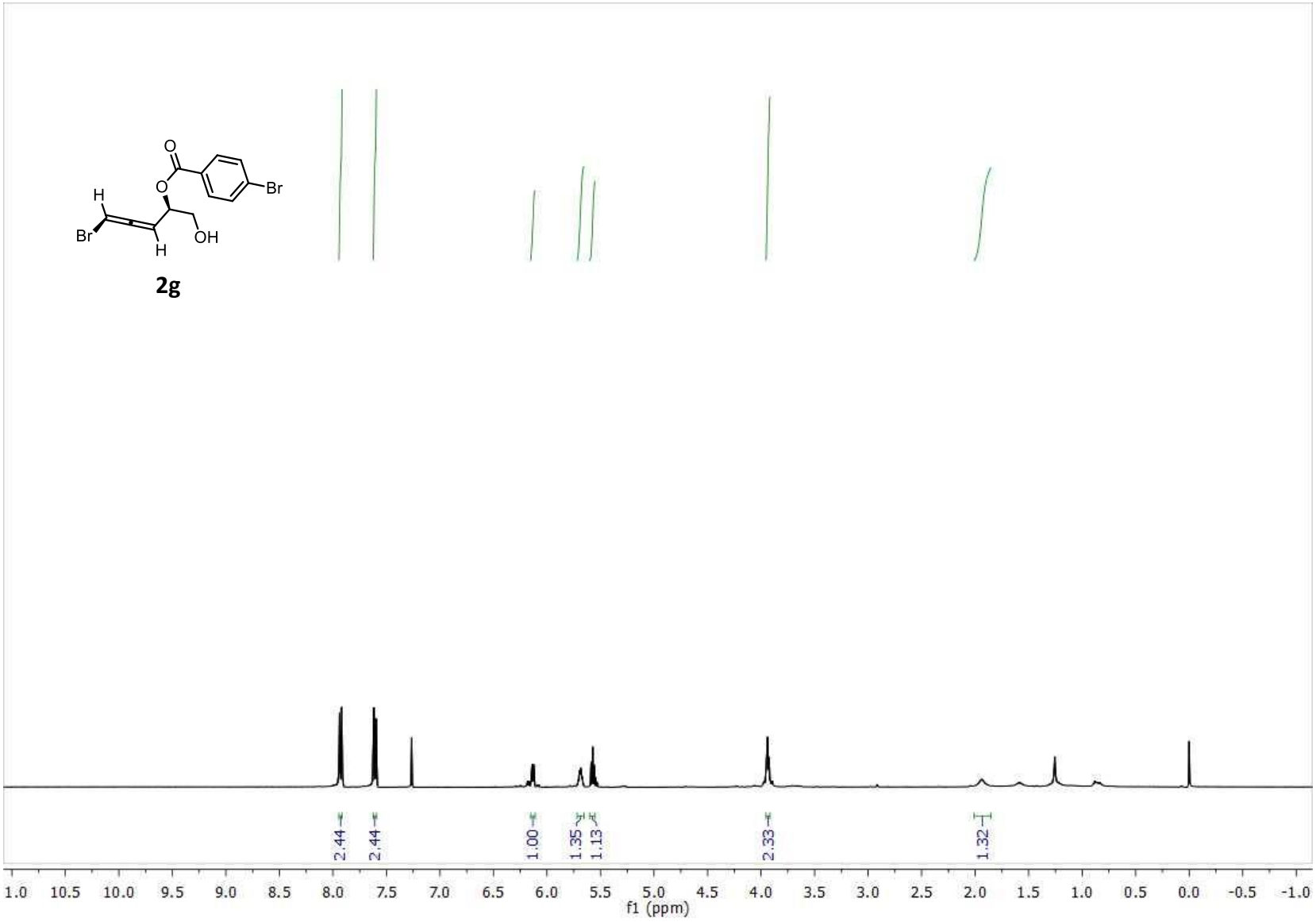
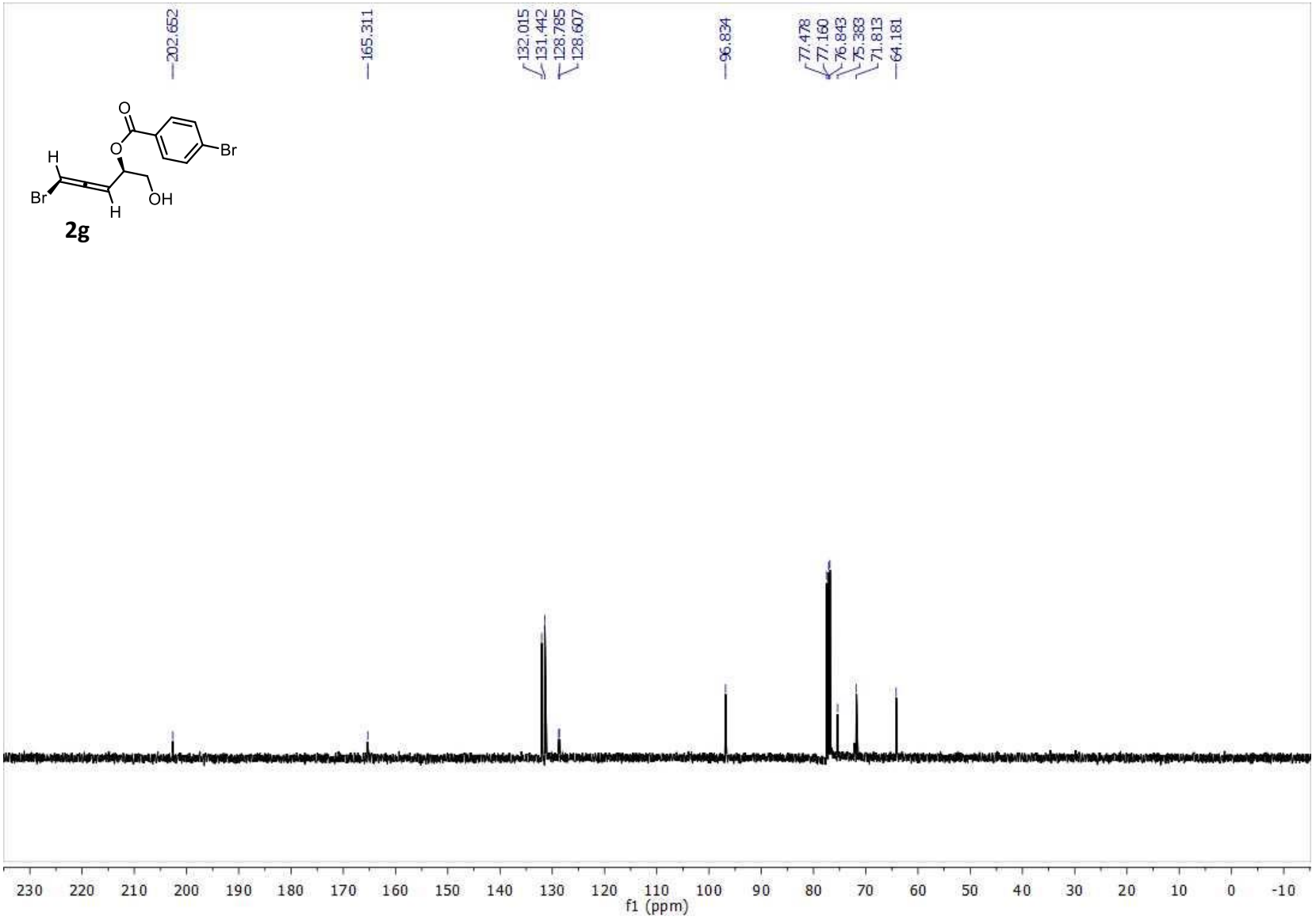
165.056
164.897
132.589
132.496
125.953
115.948
115.729
96.932
77.478
77.160
76.842
75.333
71.692
64.220
O
O
F
H
Br
H
OH
2e
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

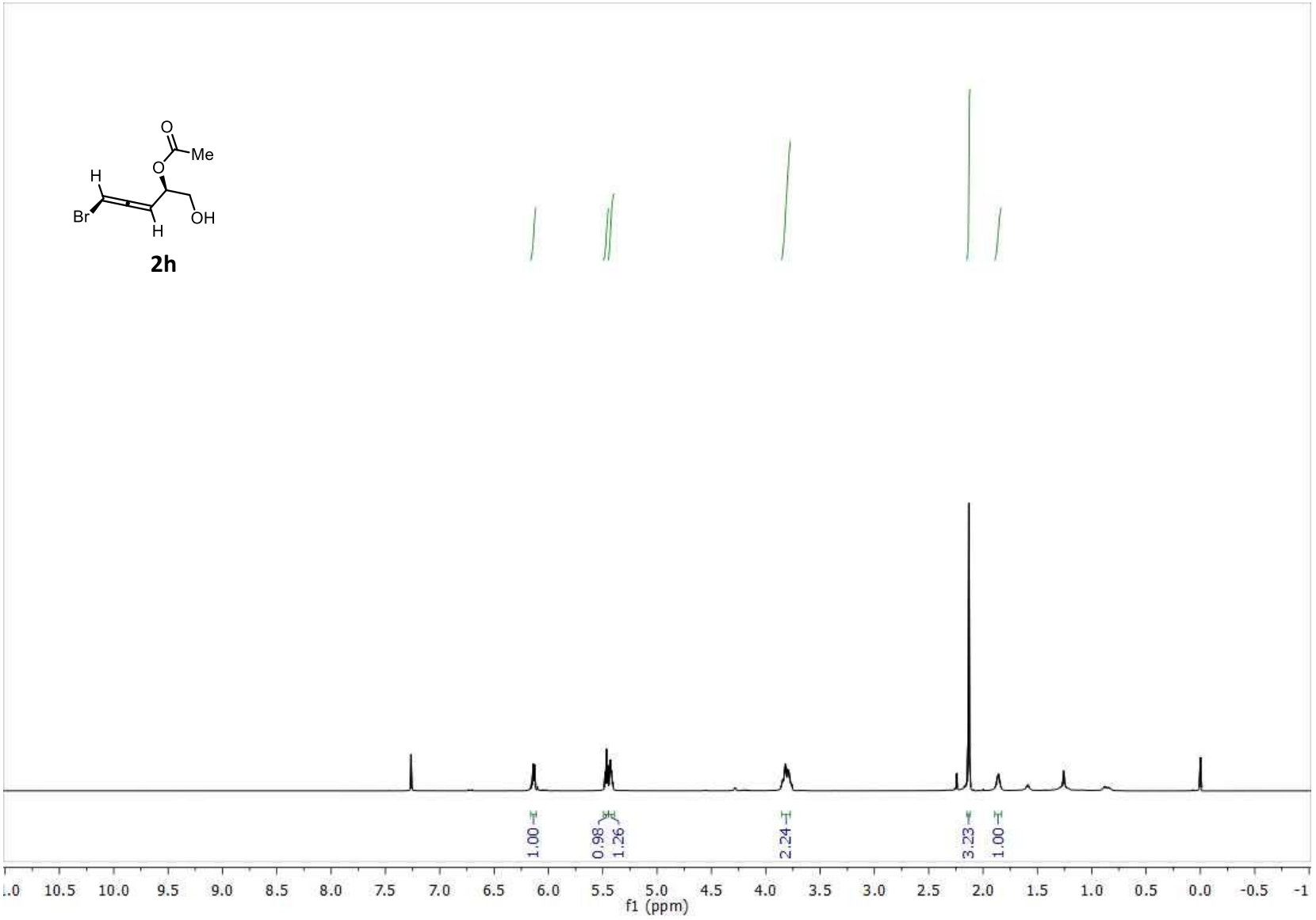

O
O
Cl
H
Br
OH
H
2f
2.28
2.32
1.00
1.22
1.07
2.23
1.14
f1 (ppm)


202.649
165.174
140.093
131.327
129.013
128.147
96.853
77.478
77.160
76.843
75.371
71.793
64.188
O
O
Cl
H
Br
OH
H
2f
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

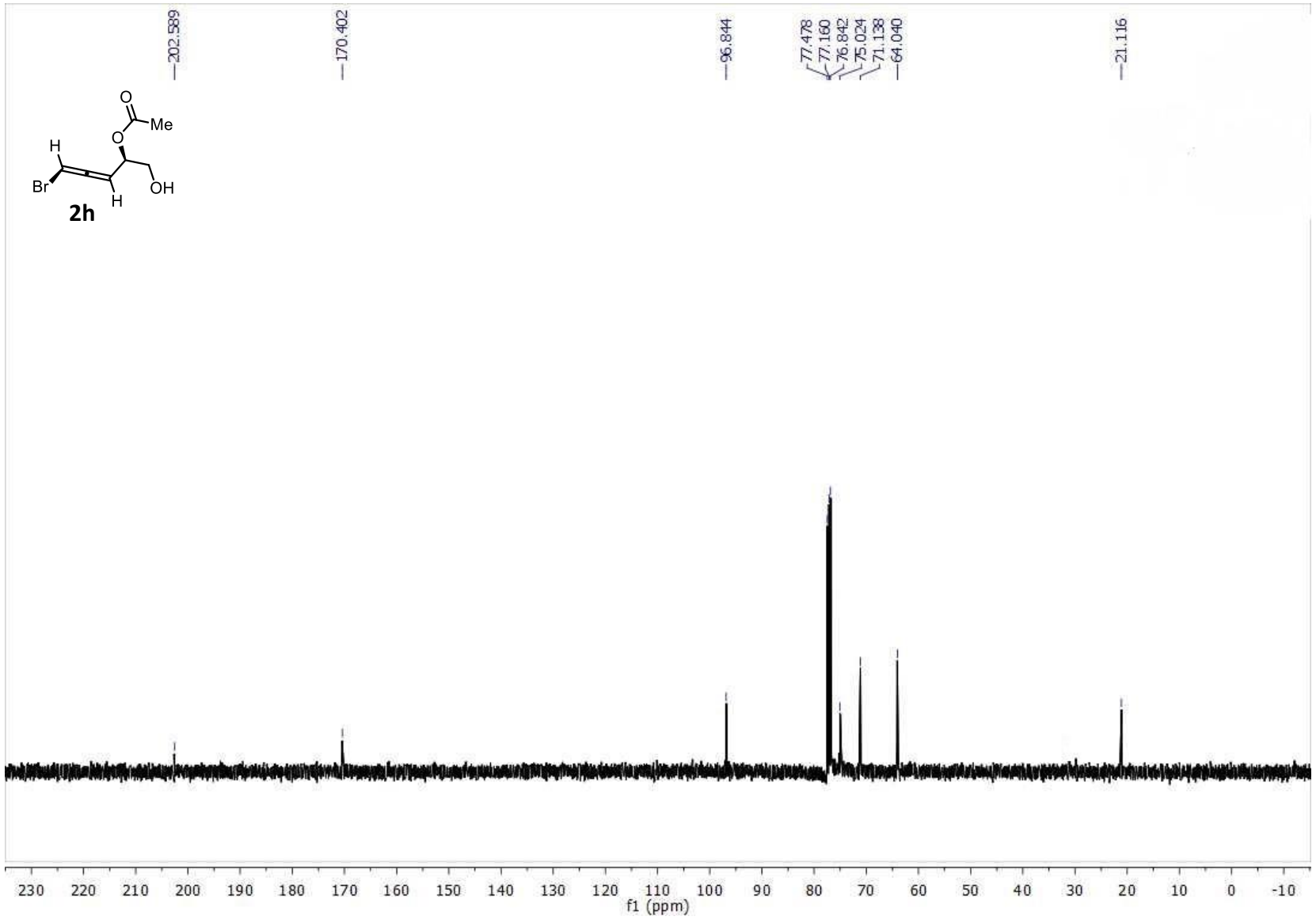

O
O
Br
H
Br
OH
H
2.44
2.44
1.00
1.35
1.13
2.33
1.32
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

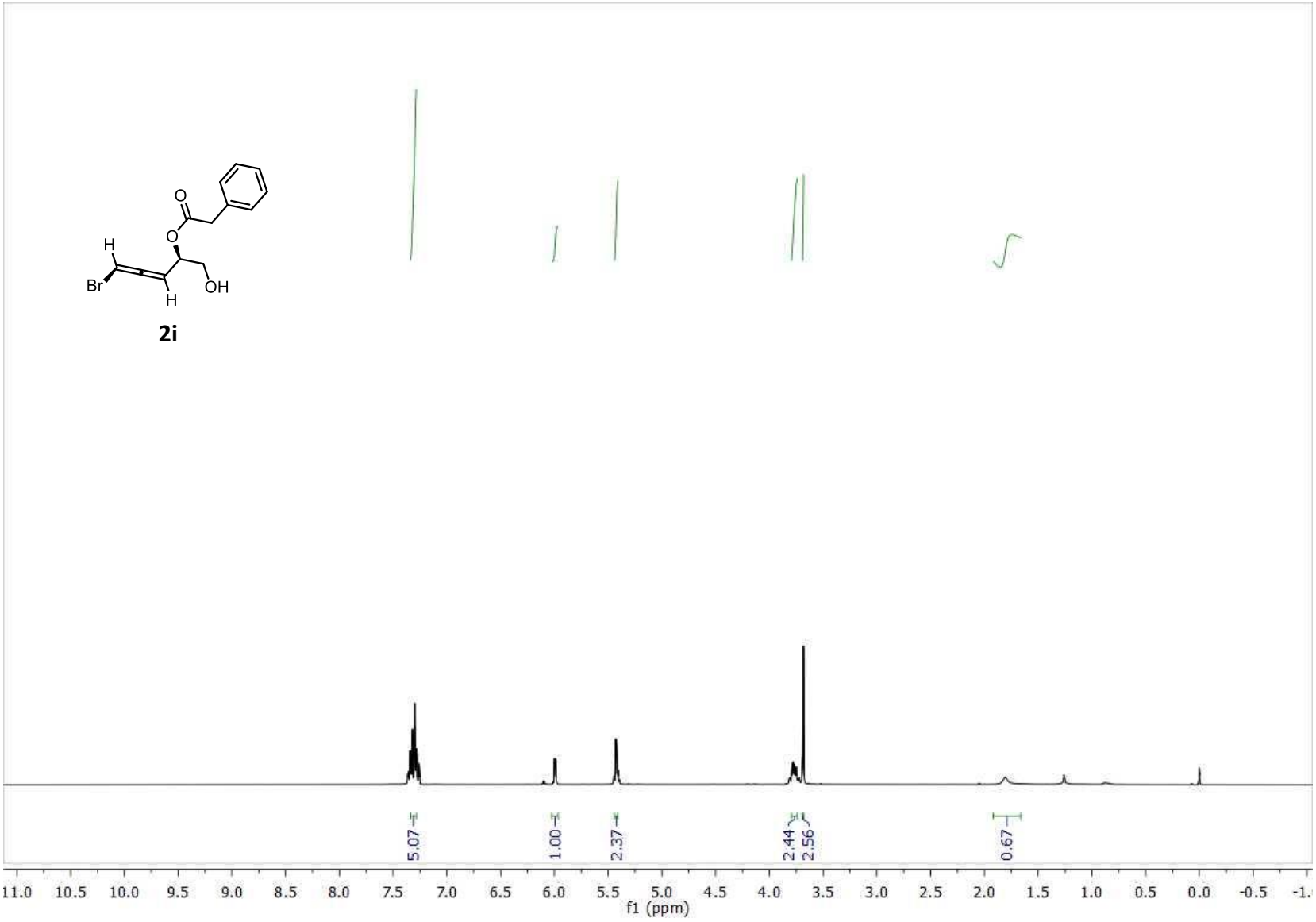
2g


202.652
165.311
132.015
131.442
128.785
128.607
96.834
77.478
77.160
76.843
75.383
71.813
64.181
O
O
Br
H
Br
OH
H
2g
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

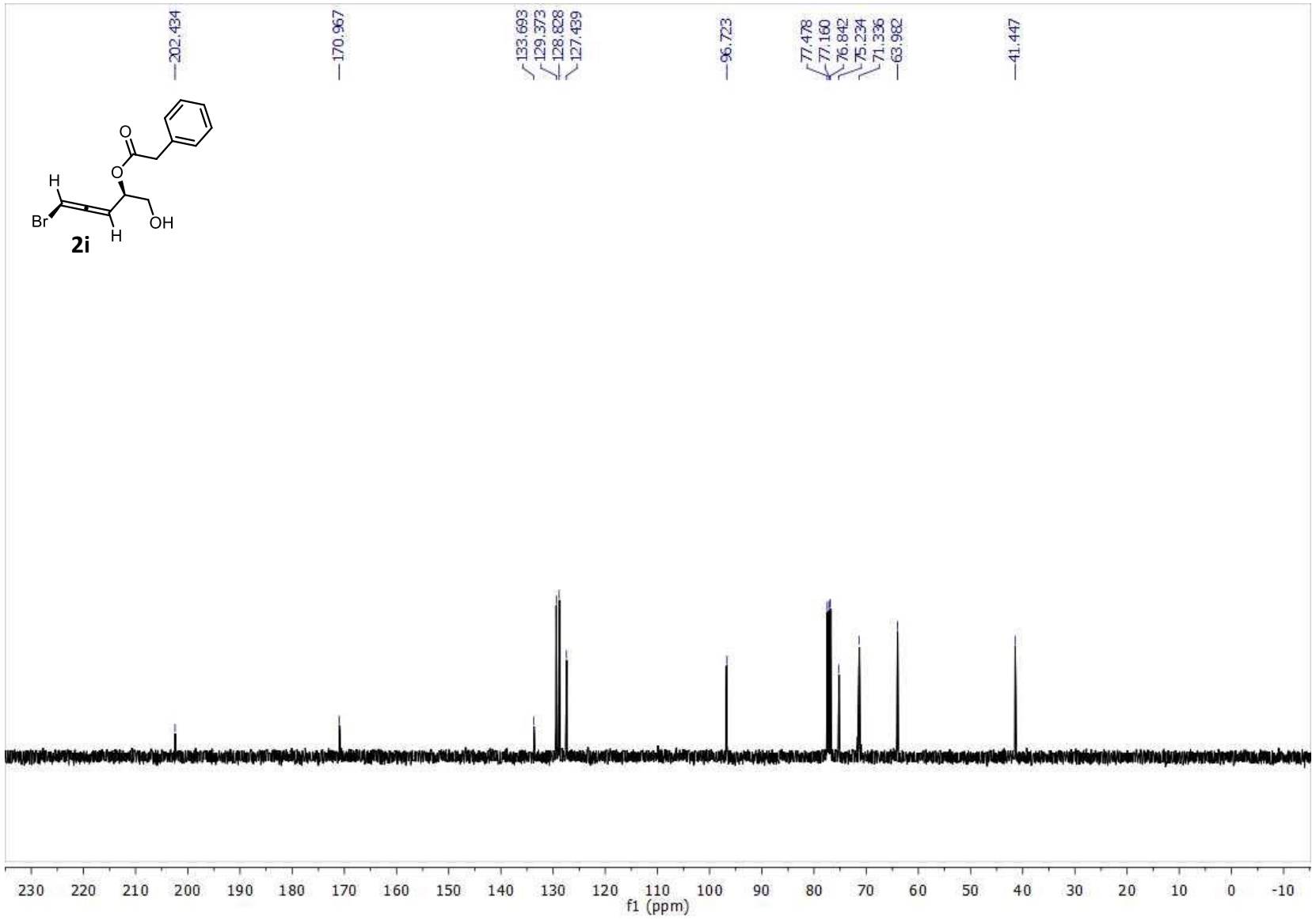


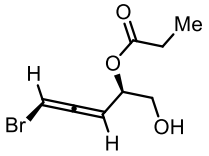
2h


202.589
170.402
96.844
77.478
77.160
76.842
75.024
71.138
64.040
21.116
O
Me
O
H
Br
H
OH
2h
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
O
H
Br
H
OH
5.07
1.00
2.37
2.44
2.56
0.67
11.0 10.5 10.0 9.5 9.0 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 1.5 1.0 0.5 0.0 -0.5 -1.
f1 (ppm)

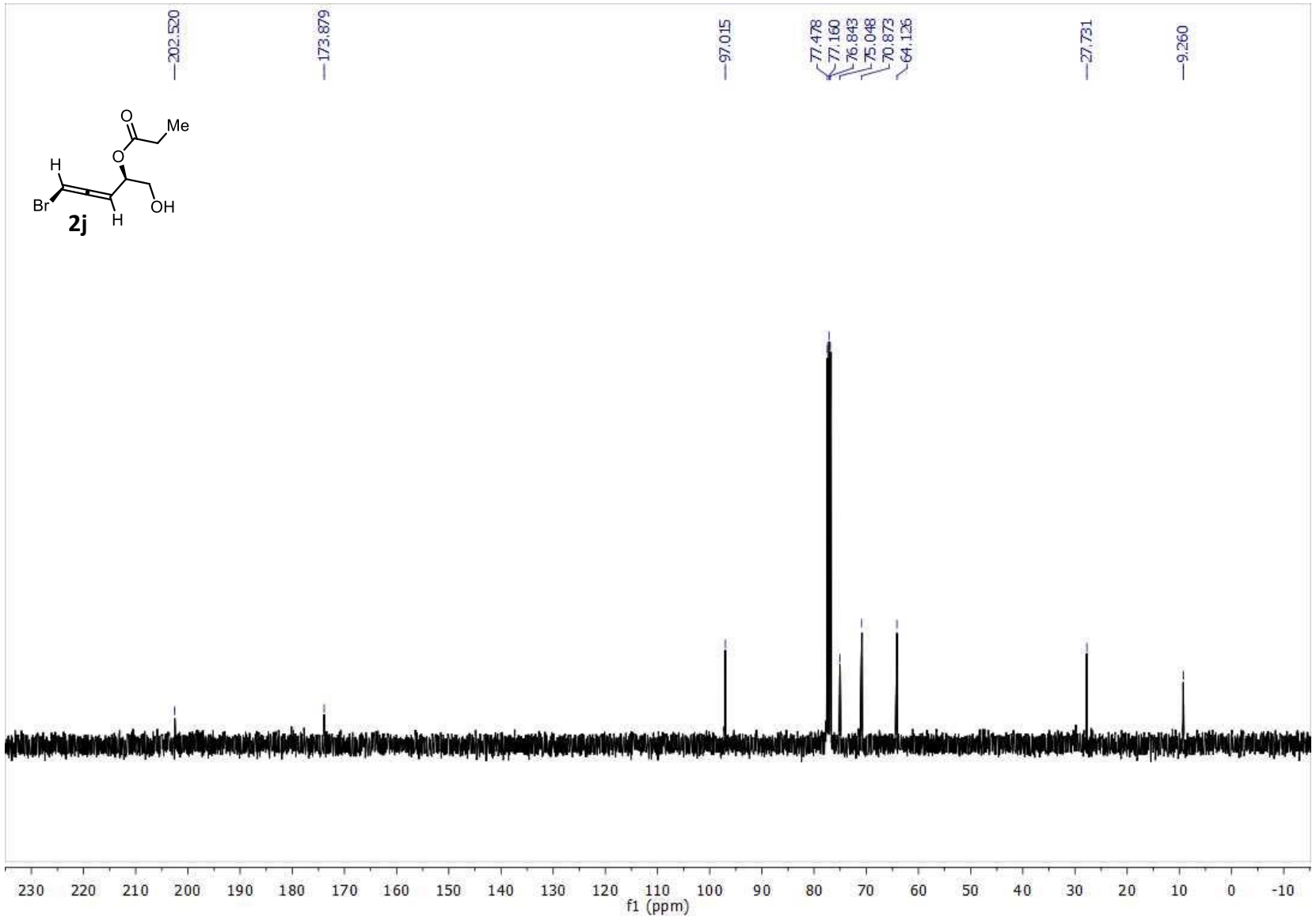
2i

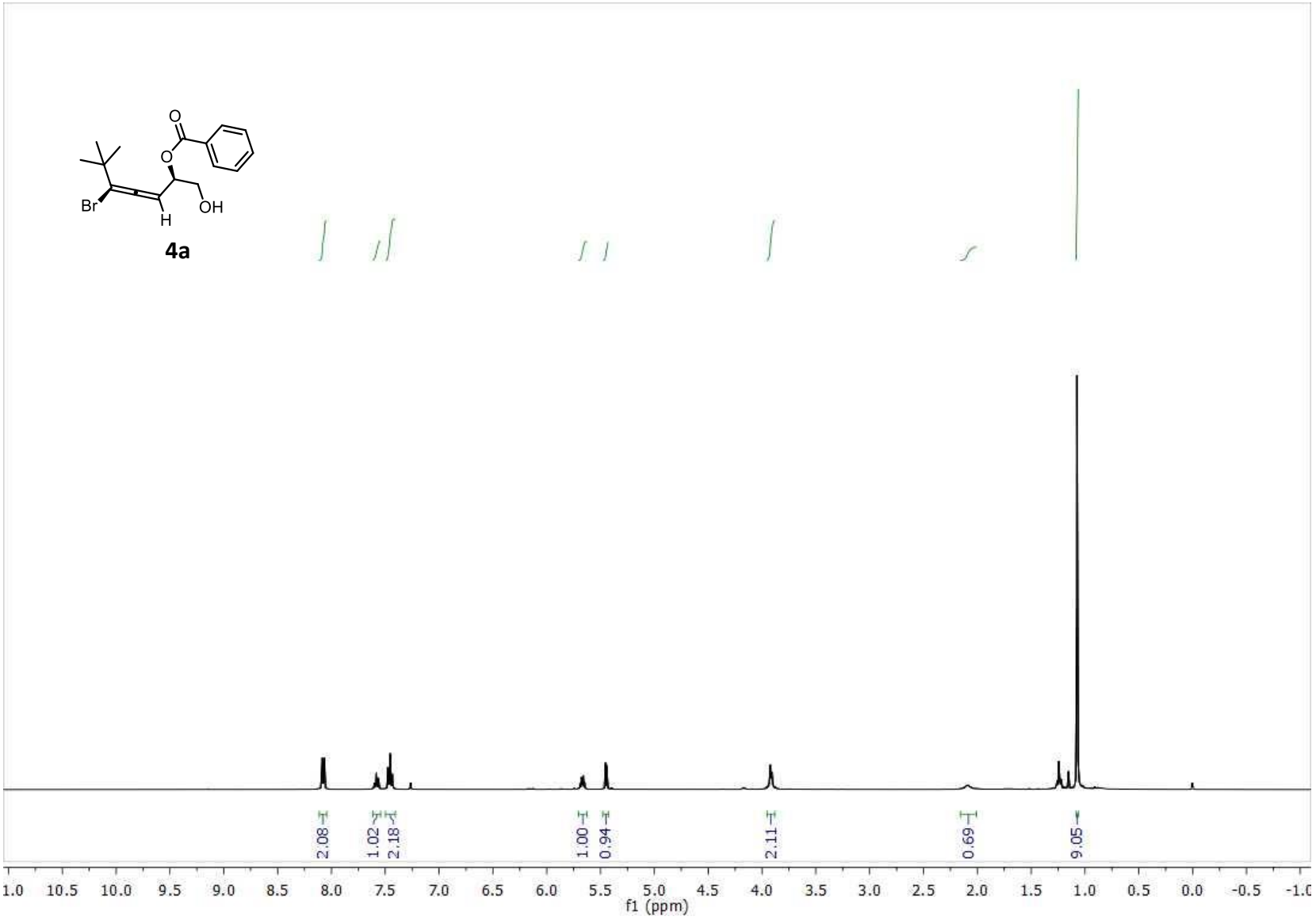

202.434
170.967
133.693
129.373
128.828
127.439
96.723
77.478
77.160
76.842
75.234
71.336
63.982
41.447
O
O
H
Br
H
OH
2i
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

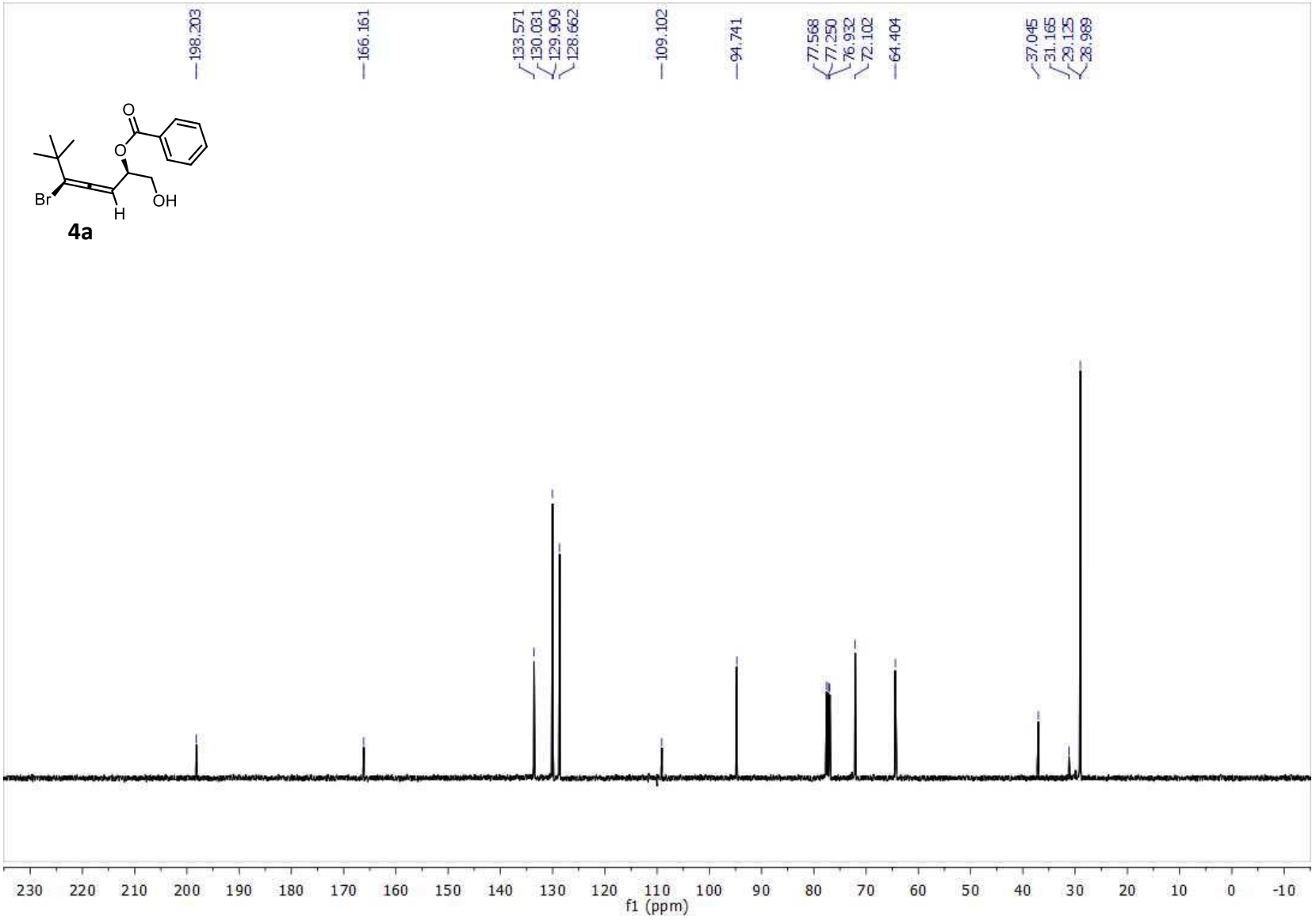

O
Me
O
H
Br
H
OH

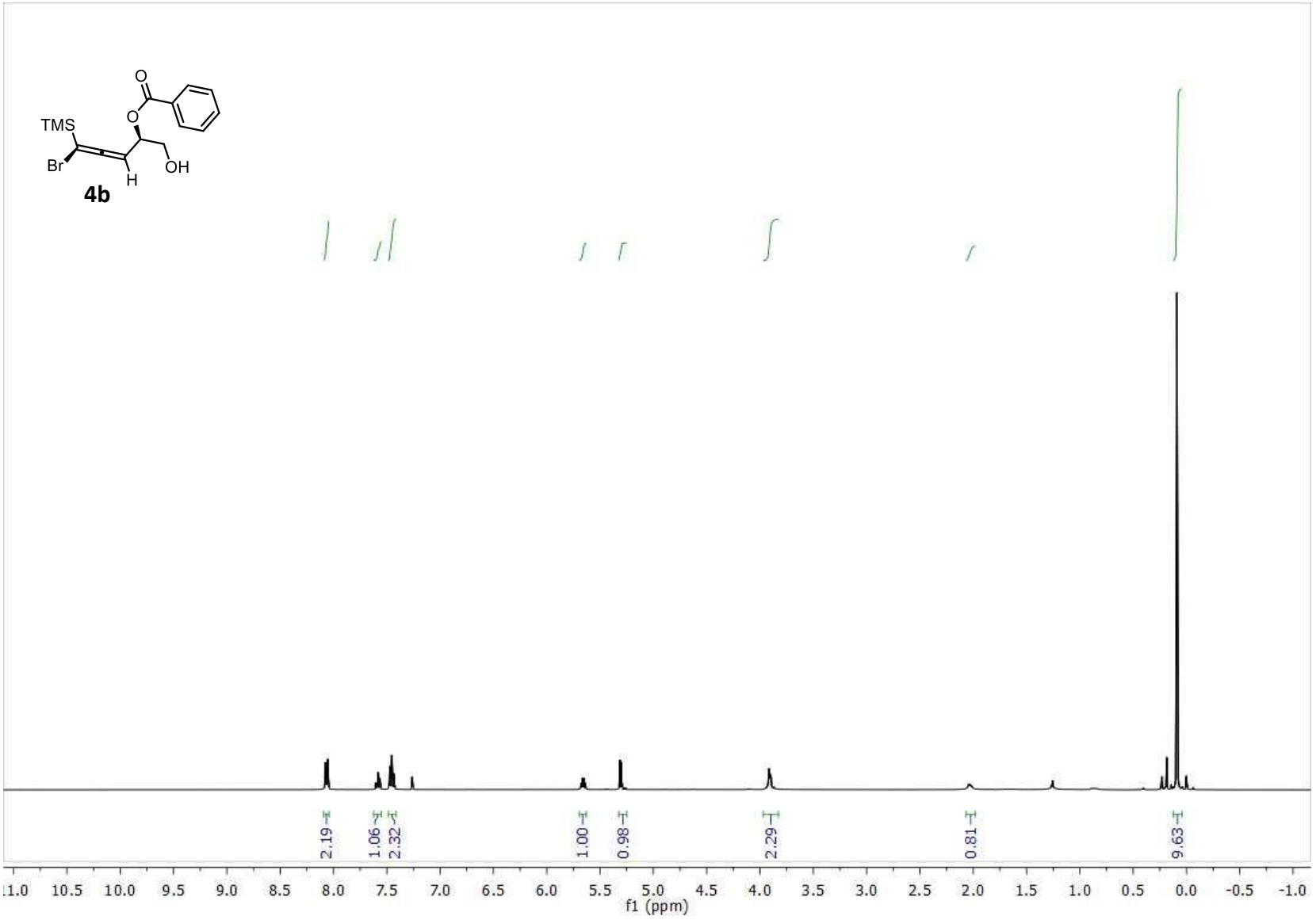
2j

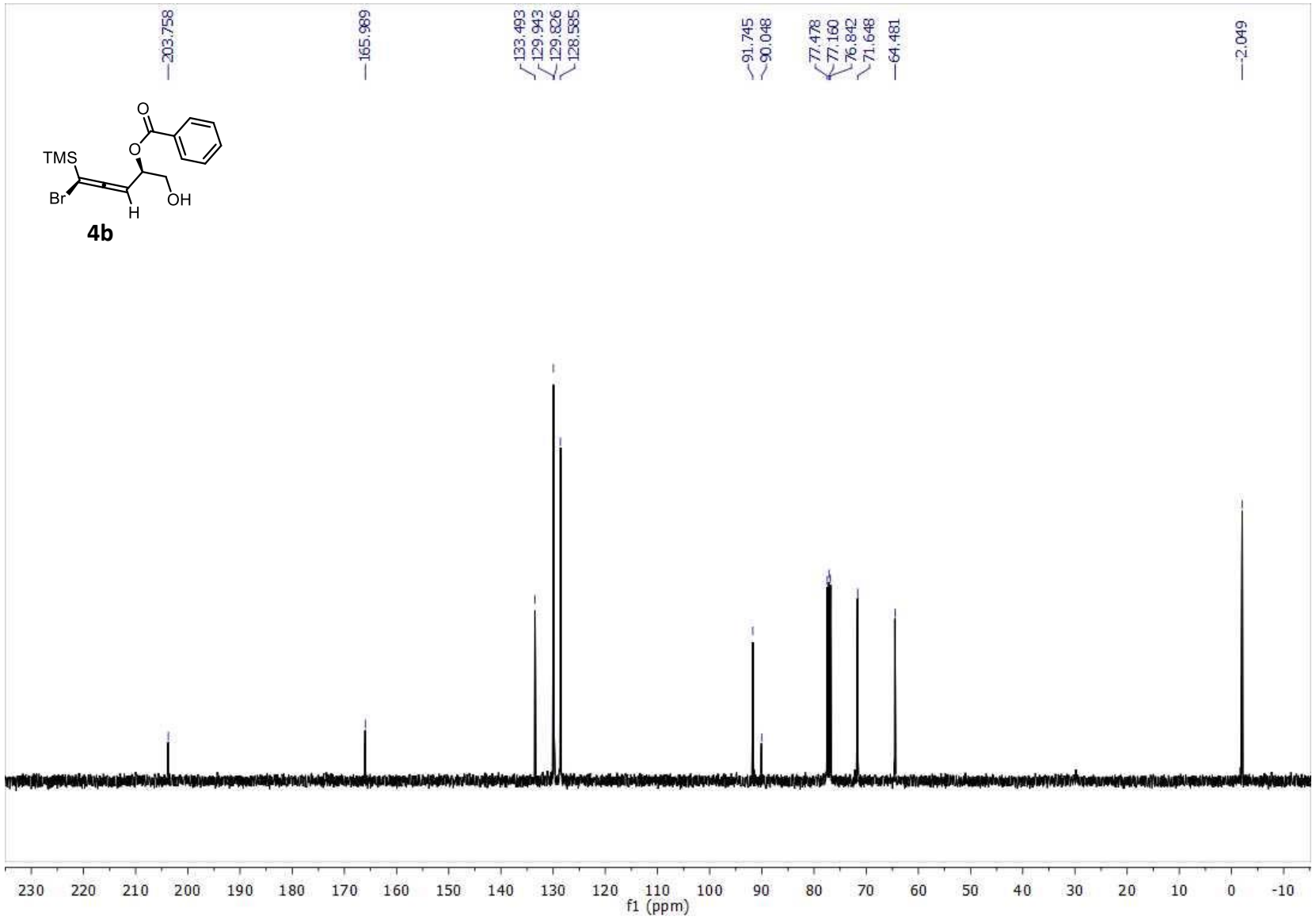
1.00
2.22
2.45
2.42
0.98
3.32
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.
f1 (ppm)


202.520
173.879
97.015
77.478
77.160
76.843
75.048
70.873
64.126
27.731
9.260
O
Me
O
H
Br
H
OH
2j
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
O
Br
H
OH
4a
2.08
1.02
2.18
1.00
0.94
2.11
0.69
9.05
1.0 10.5 10.0 9.5 9.0 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 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


198.203
166.161
133.571
130.031
129.909
128.662
109.102
94.741
77.568
77.250
76.932
72.102
64.404
37.045
31.165
29.125
28.989
O
O
Br
H
OH
4a
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


TMS
Br
H
O
O
OH
4b
2.19
1.06
2.32
1.00
0.98
2.29
0.81
9.63
f1 (ppm)


203.758
165.989
133.493
129.943
129.826
128.595
91.745
90.048
77.478
77.160
76.842
71.648
64.481
2.049
TMS
Br
H
O
O
OH
4b
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)