2016

Visible Light and Electron Transfer Chemistry for O-Glycosylation and Remote Hydroxylation

Mark Louis Spell
Louisiana State University and Agricultural and Mechanical College, mspell4@lsu.edu

VISIBLE LIGHT AND ELECTRON TRANSFER CHEMISTRY FOR *O*-GLYCOSYLATION AND REMOTE HYDROXYLATION

A Dissertation

Submitted to the Graduate Faculty of the
Louisiana State University and
Agricultural and Mechanical College
in partial fulfilment of the
requirements for the degree of
Doctor of Philosophy

in

The Department of Chemistry

by
Mark Louis Spell
B.S., University of Louisiana at Lafayette, 2011
May 2016

Dedicated to my
family and everyone
who encouraged me

ACKNOWLEDGMENTS

Throughout the process of obtaining my Ph.D. There have been several people who provided me with their help and encouragement. First, I would like to thank my advisor Professor Justin R. Ragains for mentoring me during my graduate career. I found it easy to communicate with Dr. Ragains no matter the issue. I look forward to seeing continued success from his lab.

I would also like to thank all of my committee members, Dr. George Stanley, Dr. Rendy Kartikia, Dr. Donghui Zhang and Dr. Edward Bush for their advice and availability during this process. In addition, I want to give a special thank you to the LSU faculty and staff who have played a vital part in helping me obtain my Ph.D., Importantly Mrs. Connie Davis, Dr. Thomas Weldeghioghis and Dr. Dale Treleaven. I also want to mention Dr. Rebecca Butcher who gave her time and expertise in collaborating with us on several projects.

I also would like to show my gratitude to my group members (Dr. Elizabeth Balapityia, Dr. Kyle Hollister, Xiaoping Wang, Kristina Deveaux, Rashanique Quarels, Elizabeth Kimball, Shaofu Du and Ashley Fulton) for their support, advice and most importantly their friendship. In addition, I want to give credit to a couple of undergraduates that I had the pleasure of mentoring William Schefield, and Bradley Bernard who were extremely helpful.

Finally I want to recognize my family. My amazing girlfriend Brittany Morgan who has been with me throughout this process. Your love and support in the tough times is greatly appreciated. My parents, Randy and Bonnie Spell your love, encouragement, and quality advice has been made life enjoyable. My brother Josh Spell who has been a great friend. My uncle and his fiancée C.J. Spell and Valarie Monte who have always been there for me to lean on. Without your love and support obtaining my Ph.D. would not be possible. I also want to

thank everyone from teachers to close friends who all had an impact on my life and helped make me the person I am today.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF SCHEMES

ABSTRACT

This dissertation focuses on the synthesis of dauer pheromone analogs for biological evaluation, the development of visible light promoted *O*-glycosylation methods and the development of an $Ir(ppy)_3$ catalyzed C-H hydroxylation method. Chapter 1 describes the synthesis of dauer pheromone analogs. *C.elegans* is a small nematode that enters a dauer stage when encountering unfavorable environmental conditions. The dauer stage is initiated by the nematodes chemosensation of the dauer pheromone caused by the down regulation biochemical pathways TGF-β and IGF-1. These biochemical pathways are also seen in *Homo Sapiens* and play a role in a number of biological processes. Understanding how these pathways work in *C.elegans* can give us a better understanding of how they function in humans. In order to see the effect structure has on binding to the GCPR's that initiate dauer formation a series of dauer pheromone analogs differing in chain length and degree of unsaturation were synthesized. These analogous were then tested to see there dauer inducing activity to give a structure to activity relationship.

Chapter 2 centers upon the development of an *alpha* selective glycosylation of alcohols with selenoglycosides using visible light. Selenoglycosides are highly stable glycosyl donors. There stability is useful in oligosaccharide synthesis. This stability, however, requires harsh reaction conditions to activate them. The development of a mild and easily performed *O*-glycosylation method using selenoglycosides is described here.

Chapter 3 focuses on the development of a metal free, visible light promoted O-glycosylation method using thioglycosides. Thioglycosides like selenoglycosides are commonly used in oligosaccharide synthesis. The harsh reaction conditions used to activate them has been a long standing issue in the carbohydrate community. The development of a mild, catalyst free O-glycosylation method using thioglycosides is described here. The method uses 4-methoxyphenyl-

3-butenylthioglucoside donors in the presence of easily handled and bench stable Umemoto's reagent to provide good yields of disaccharides, it is selective for the β-anomer when using the glycosyl donor with an acetate group at the 2- position, and the method is orthogonal.

Chapter 4 details the development of a C-H hydroxylation method using *fac*-$Ir(ppy)_3$ catalyst. 1-6 and 1-7-hydrogen atom transfers from unactivated aliphatics were performed with the aid of a Tz^o directing group. The resulting radical then underwent redox chemistry followed by attack of water to give hydroxylated products in moderate yield.

CHAPTER 1: SYNTHESIS AND BIOLGICAL EVALUATION OF ASCAROSIDES FOR DAUER FORMATION IN *C.ELEGANS*

1.1 Introduction

The study of model organisms can provide a deeper understanding of biology. One of these model organisms, C.elegans, was popularized by Sydney Brenner, who won the Nobel Prize in 2002 for his work on the genetics of organ development and programmable cell death in *C.elegans*.[1] *C.elegans* (shown in Figure 1.1) is a small (approximately 1mm in length in adulthood), transparent nematode.[2] This transparency allows scientists to view many biological processes

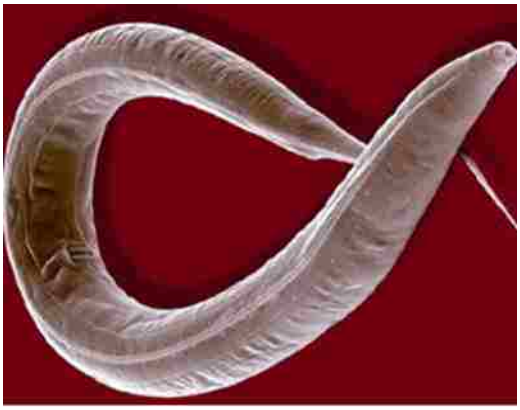


Figure 1.1 Caenorhabditis elegans[16]

associated with *C.elegans* under a microscope.[3] The nematode consists of an inner tube and outer tube with a pseudocoelom between.[4] The inner tube contains the reproductive and alimentary systems. The outer tube is comprised of the cuticle and the hypodermis, nervous and excretory system, and muscles. The pseudocoelom serves multiple functions, acting as an immune and circulatory system while facilitating intracellular signaling and nutrient dispersion.[4,5]

C.elegans is an excellent model organism. It is easy to grow and cultivate in a laboratory and feeds on bacteria.[2,6] It has a short generation time (2-3) days and life span (2-3 weeks), contains

This chapter previously appeared as [Kyle A. Hollister, Elizabeth S. Conner, Xinxing Zhang, Mark Spell, Gary M. Bernard, Pratik Patel, Ana Carolina G.V. de Carvalho, Rebecca A. Butcher, Justin R. Ragains, Ascaroside activity in Caenorhabditis elegans is highly dependent on chemical structure, 2/11/2013]. It is reprinted by permission of [Elsevier.]"

exactly 959 somatic cells (in adult hermaphrodites) and a genome size of 100Mb.[2] While it is a relatively simple organism, studies on *C.elegans* biological process can lead to a better understanding of similar process in *Homo Sapiens*. *C.elegans* has 20,000 genes compared to 23,000 in *Homo Sapiens*.[2,7] The *C.elegans* genome bears an approximately 60-80% homology to that of humans.[2,7] The similarity of *C.elegans* to other species can be seen by the higher behavioral processes it exhibits such as responding to sensory cues, learning, and memory.[2,7]

1.1.1 Life Cycle

C.elegans has a short life span (2-3 weeks) (shown in Figure 1.2) in which the worm goes through several changes.[2] The life cycle starts with an egg in the adult hermaphrodite's uterus that goes through four larvae stages (L1-L4) after fertilization and egg laying. The sexually mature adult directly proceeds L4. This life cycle is normal for *C.elegans* under favorable conditions (sufficient food supply, low population density and ideal temperatures). If these conditions change early in the *C.elegans* L1 larvae stage, chemical cues sensed by neurons in the head of the worm

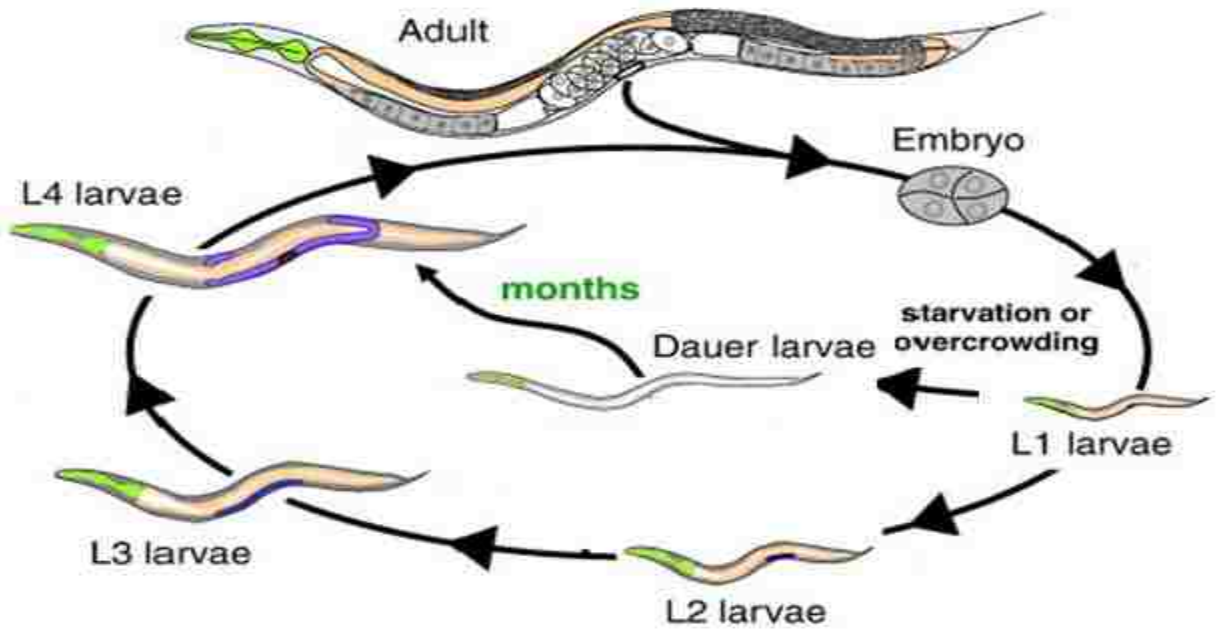


Figure 1.2: Life Cycle of C.elegans[15]

trigger a process called dauer diapause. The L1 larvae enter an alternate larva stage known as the dauer larva.[8,9] In the non-ageing dauer phase, *C.elegans* show increased longevity (they are able to survive up to 4 months compared to the typical 2-3 week life span).[9,10] The nematode is completely motionless at this stage and does not feed while it is protected from environmental factors via a tough cuticle. When environmental conditions are once again favorable, the worm senses chemical cues and responds by exiting the dauer stage and entering the L4 larvae stage in route to adulthood.[9,10]

1.1.2 Dauer Diapause

Dauer diapause is of significant importance to developmental biology. Interest in this phenomenon is due to the two pathways that regulate dauer formation: transforming growth factor beta (TGF-β) and insulin-like growth factor 1 (IGF-1).[11] These two biochemical pathways are highly conserved in higher organisms, and are known to have an effect on metabolism, growth, development, aging, they also play a role in several diseases.[12] The study of these pathways provides scientists with a better understanding of how theses biological pathways work in *Homo sapiens*, possibly leading to multiple medical advances. *C.elegans* provides an ideal platform to exam these biological pathways with no ethical concerns restricting their use.

Down regulation of (TGF-β) and (IGF-1), which trigger dauer formation, is caused by the sensory neurons located in the head of the worm that sense ascarosides excreted by the worm.[13] A series of the dauer formation-triggering ascarosides that are excreted (as determined with dauer formation assays) are shown in Figure 1.3. Five ascarosides comprise the known dauer pheromone asc-C6-MK, asc-ΔC9, asc-ωC3, IC-asc-C5 and asc-C7-PABA.[14,15,16,17] The first four ascarosides were discovered by bioassay-guided fractionation of extracts from worm cultures, and were structurally characterized with multiple techniques including NMR spectroscopy and mass

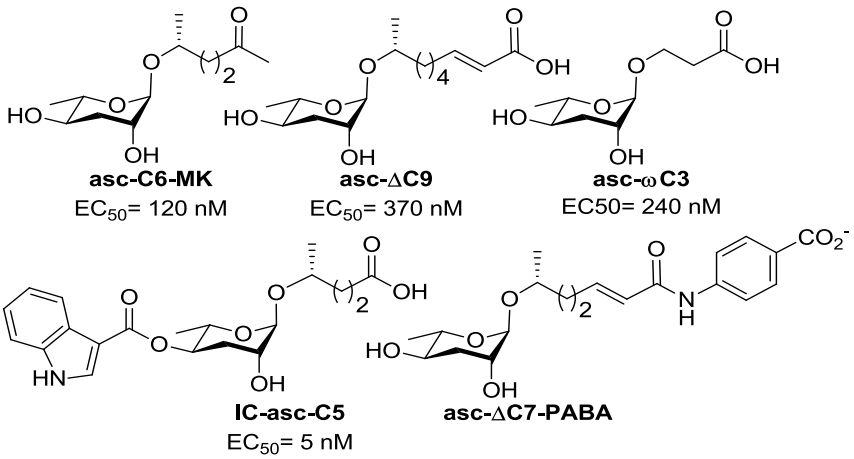


Figure 1.3: Ascaroside components of the dauer pheromone

spectrometry. These ascarosides were all shown to promote dauer formation with EC50 values of 120 nM, 370 nM, 240 nM and 5 nM, respectively. Unlike the first four ascarosides, asc-C7-PABA was discovered with comparative metabolic studies using NMR spectroscopy. As seen from the EC 50 values, IC-asc-C5 shows the highest activity for dauer formation but only up to a certain concentration at which point it starts to inhibit its own activity. While asc-ωC3 is not as potent, it works synergistically with asc-ΔC9, asc-C6-MK, and IC-asc-C5, to cause dauer formation.[15]

The ascarosides that comprise the dauer pheromone share similarities in their structure. Each ascaroside has the ascarylose sugar moiety shown in Figure 1.4. While the moiety remains the same for all the ascarosides, there is variability in the head group, fatty acid side chain and terminus group. Two of the most commonly occurring head groups are the free hydroxyl group

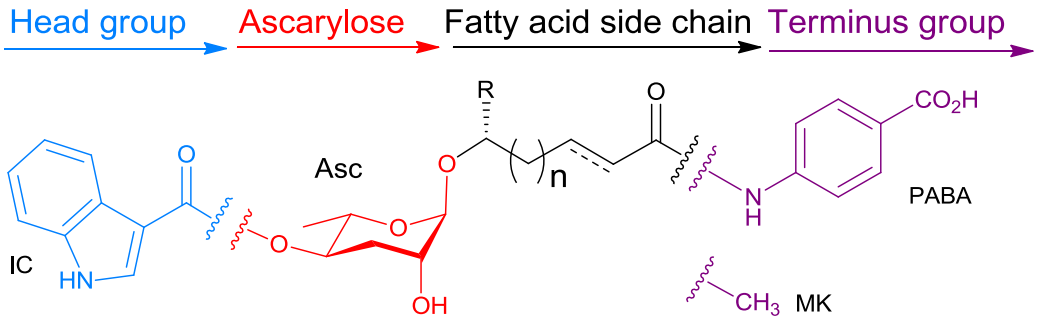


Figure 1.4: Structural components of dauer ascarosides

and indole-3-carbonyl (IC). The fatty acid side chain is linked with either a ω-linkage when R = H or a (ω-1) linkage when R = Me. In addition to the linkage, the side chain can vary in length and degree of unsaturation. The terminus groups include a carboxylic acid, methyl ketone (MK) and *para*-aminobenzonic acid (PABA) group. Variability in structure between the ascarosides can have a drastic effect on the ability to promote dauer formation as shown with the EC50 values.

Dauer formation in *C.elegans* is attributed to the chemosensation of the dauer pheromone. The dauer pheromone, is excreted constitutively.[8,9] Nematodes like *C.elegans* use several chemical cues to gather information about their environment. One of these cues is a yet- unidentified "food signal". This "food signal" gives information about food availability in the area and is an antagonist of the dauer pheromone. Dauer formation of *C.elegans* and the length of time spent in the dauer form is dependent on the balance between the dauer pheromone and this "food signal".[13]

1.1.3 IGF-1 and TGF-β Pathways

The dauer pheromone functions by binding to the G coupled protein receptors (GCPRs) in *C.elegans*. The binding occurs when the chemosensory neurons in the head of the worm are exposed to the pheromone.[18] Dauer pheromone ascarosides bind to the GCPRs to induce dauer formation as has been observed during several experimental studies.[19-25] In one study when two alpha subunits of GCPRs gpa-2 and gpa-3 were upregulated, dauer formation was observed.[19] However, when these subunits were altered, no dauer formation was seen. There are five major neurons that express the GCPRs. The neurons that mediate the chemosensation of the dauer pheromone are ADF, ASG, ASI, ASJ and ASK. Two of these neurons, ASI and ASJ, are known to down regulate the highly conserved pathways IGF-1 and TGF-β.[20] These pathways that are operative in *C.elegans*, as stated earlier, have homologs in *Homo sapiens*. There are various biological processes in which IGF-1 and TGF-β play a role and understanding of how these

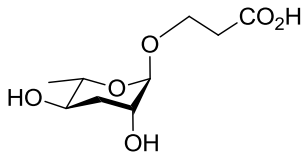
pathways work may be key to slowing the aging process and treating diseases. IGF-1 has been shown to have an effect on the aging process of different organisms. In two separate experiments wherein the IGF-1 receptor in *C.elegans* and mice were altered, the aging process was decelerated.[21] IGF-1 levels have also been shown to have an effect on cancer growth. The decrease of IGF-1 levels was shown to decrease the growth of colorectal carcinoma, breast cancer and melanoma cancer cells in one study.[22] It has also been shown that the down regulation of IGF-1 through diet correlates to a lower cancer risk.[23]

The TGF-β pathway plays a role in various diseases like cancer and Alzheimer's disease.[24] The effect of TGF-β on cancer can be as both a suppressant and promoter depending on the type of cancer.[25] In gastric and pancreatic cancer TGF-β acts as a suppressant as the shutdown of the TGF-β pathway is observed in this form of cancer. By contrast, the role as a promoter is observed in breast cancer, where the up regulation of the pathway increases tumor growth. A High concentration of TGF-β has also been seen in the blood and cerebral fluid of patients suffering from Alzheimer's disease.[24] The IGF-1 and TGF-β pathways play vital roles in biological process. Understanding how these pathways work may be key to slowing the aging process and treating diseases. Studying the effect that these pathways have on C.elegans and extrapolating the observations to higher organisms is one way of advancing this understanding. As showm the up- and down regulation of IGF-1and TGF-β play many important biological roles. Further understanding of how the biochemical pathways are up and down regulated could lead to better understanding of their biological roles. This could be performed by subjecting *C.elegans* to analogs of ascarosides know to down regulate IGF-1 and TGF-β (which result in dauer formation). Examination of the amount of dauer inducing activity of each analog could be directly correlated to that compound's ability to regulate IGF-1 and TGF-β.

1.2 Results and Discussion

Analogs of the dauer pheromone that we synthesized contain the ascarylose sugar moiety that is seen in the naturally occurring ascarosides. Our structural manipulations were made on the fatty acid side chain by varying the length and degree of unsaturation. The terminus of the side chain can also designated as a methyl ketone or carboxylic acid. In order to establish a structure-activity relationship (SAR), a variety of analogs is needed. The degree of dauer inducing activity of these analogs may hinge on the structural modification of the naturally occurring ascarosides. In order to determine the dauer-formation activity, each analog was synthesized and submitted to dauer formation assays.[26] This would show the variability in dauer inducing activity based on manipulation of the fatty acid side chain length and unsaturation. The results of these assays will tell us whether the GCPRs that bind the ascaroside are selective toward specific side chain modifications or if the ascarylose moiety itself is necessary and sufficient for activity.

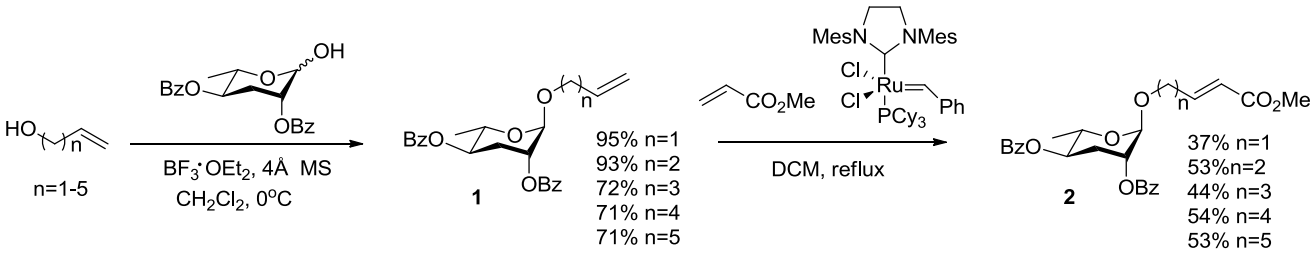
Multiple series of analogs with varying structural modifications were synthesized. The series of analogs that I synthesized are derivatives of the naturally-occurring pheromone shown in Figure 1.5. Analogs have fatty acid side chain lengths of four to eight carbons. Saturated and unsaturated analogs with carboxylic acid termini were synthesized.



asc-ω-C3
EC_{50}= 240 nM

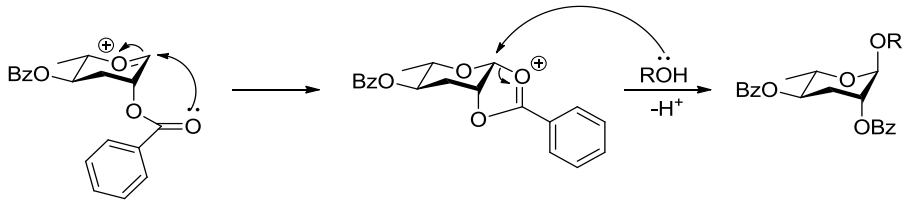
Figure 1.5 Naturally occurring ascaroside

The synthesis of each analog began with a Lewis acid-promoted glycosylation of dibenzoyl ascarylose with terminal alkene-bearing alcohols (containing one to five methylene carbons) to produce intermediate compounds represented by structure 1 (Scheme 1.1) in moderate to excellent



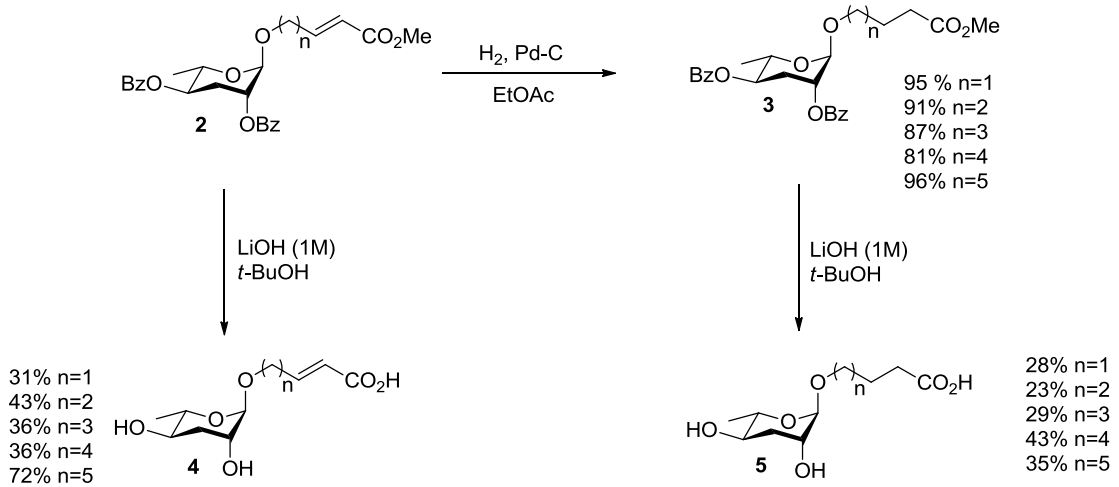
Scheme 1.1 Glycosylation and Olefin Cross Metathesis

yields. Selectivity for the desired α anomer is achieved due to the neighboring group participation shown in Scheme 1.2. The dryness of the solvent was of great importance as yields increased when using DCM dried by a solvent system compared to that of typical reagent grade solvent.



Scheme 1.2 Neighboring group participation

The glycosylated products were then subjected to olefin cross metathesis using methyl acrylate and the Grubbs catalyst to obtain intermediate 2 (Scheme 1.1). The reaction was performed in refluxing dichloromethane to increase the reactivity. In order to obtain the saturated versions of these compounds, intermediate 2 was subjected to hydrogenation using a 1 atm of hydrogen (in a balloon) with palladium on activated carbon in ethyl acetate to give intermediates 3 in high yield (Scheme 1.3). Intermediates 2 and 3 were then subjected to basic hydrolysis using 1M lithium hydroxide and *tert*-butyl alcohol to give the carboxylic acid-bearing terminus analogs 4 and 5 (Scheme 1.3). Moderate yields were obtained after purification with HPLC.



Scheme 1. 3 Completion of Analog Series

Once all of the analogs were synthesized and fully characterized by ^{1}H and ^{13}C NMR along with high resolution mass spectrometry and polarimetry, they were screened in dauer formation assays to determine the amount of dauer producing activity of each analog.[26] The assays were performed by taking a mixture of each of the synthesized ascaroside analogs at concentrations of 220 nM and 6000 nM with nematode growth media agar and heat treated *E.coli*. The mixture was poured onto a plate and allowed to set. Adult *C.elegans* then laid eggs on the set mixture which was then incubated for approximately 3 days at 25°C. After removal of the adults, this provided 50-100 larvae on each plate. The number of dauers was then determined by their small size and lack of pharyngeal pumping. The percentage of dauers formed was then determined. The concentration of the ascaroside analogs was specifically chosen. The 220 nM would help us identify potent analogs while the 6000 nM concentration would help us identify analogs with poor activity or a paradoxical inhibitory effect.

When comparing the activity of the dauer pheromone analogs to that of the naturally occurring dauer pheromones (Figure 1.6), it is clearly seen that the analogs display significantly less dauer inducing activity. The low amount of dauer inducing activity of the dauer pheromone

analogs is interesting since their structure only slightly differs from the natural dauer pheromones. The ascarosides I synthesized (asc-ωΔC4 through asc-ωΔC7) which differ from the natural ascaroside asc-ωC3 in chain length and degree of unsaturation and asc-ωC4 through asc-ωC7 which differ only in chain length all have significantly less dauer inducing activity. The only two compounds that did show some activity at the 6000 nM concentration were asc-ωC4 and asc-ωΔC5. The asc-ωC4 analog is one carbon longer than the naturally occurring pheromone and we hypothesize that its activity is due to the analog mimicking the asc-ωC3. The asc-ωΔC5 analog, however, cannot be explained so simply since it differs in chain length by two carbons and in degree of unsaturation. The activity may be due to low GCPR affinity for the unnatural ascarosides that I synthesized. This established a flag pole SAR where activity is greatly diminished if there is any deviation from the natural ascarosides, which themselves show a significant amount of dauer inducing activity. The high selectivity of the GPCRs makes sense when considering that, in nature,

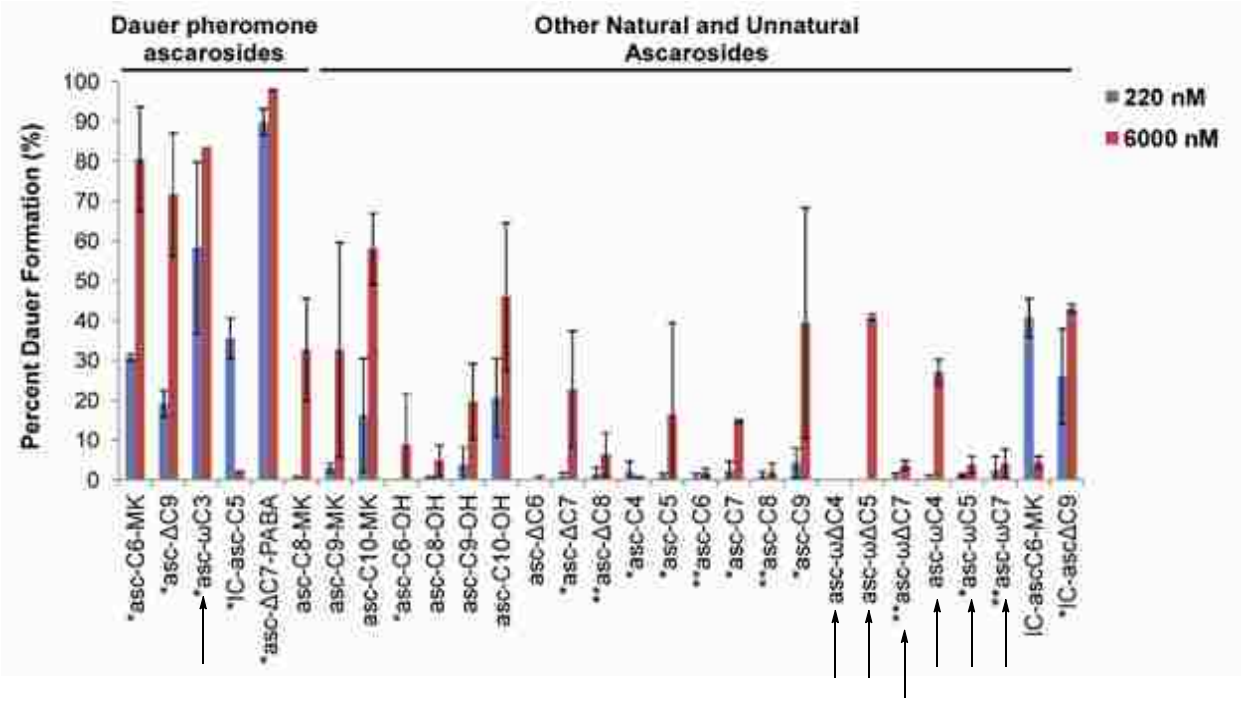


Figure 1.6 Initiation of dauer formation by ascarosides

C.elegans occupy the same habitat as other nematodes that also use ascarosides for signalling.[27] The selectivity of the GCPRs prevents cross talk from other species.

1.3 Conclusion

I synthesized multiple analogs in order to establish a structure-activity relationship. This showed the variability in dauer inducing activity based on manipulation of the fatty acid side chain length and unsaturation. The analogs I synthesized varied in chain length and degree of unsaturation. Once highly pure samples of these analogs were obtained, their dauer inducing activity was determined. None of the analogs showed any significant dauer inducing activity despite their similarites to the naturally occurring dauer pheromone ascarosides. This suggests that the G protein-coupled receptors are highly selective in what ascarosides they bind. This selectivity is beneficial to prevent species cross talk since other nematodes use similar ascarosides for signaling.

1.4 Experimental

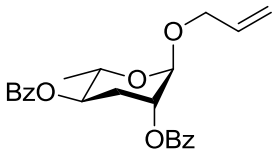
1.4.1 General Methods

Reagents were purchased from Sigma Aldrich and used as received. Flash column chromatography was performed using 60Å silica gel purchased from Sigma Aldrich. ^{1}H NMR and ^{13}C NMR spectroscopy were performed on a Bruker AV-400, DPX 400, DPX 250 and AV- 500 spectrometer. HPLC purifications were conducted with a Waters Breeze 2 system equipped with an XBridge C18 semi-preparative column (5 lm, 10 x 100 mm) with gradient runs of H_2O in CH_3CN. Mass spectra were obtained using an Agilent 6210 electrospray time-of-flight mass spectrometer. Optical rotation measurements were obtained using a JASCO P-2000 polarimeter. Analytical and preparative TLC were conducted on aluminum sheets (Merck, silica gel 60, F254). Compounds were visualized by UV absorption (254 nm) and staining with anisaldehyde. All

glassware was flame-dried under vacuum and backfilled with dry nitrogen prior to use. Deuterated solvents were obtained from Cambridge Isotope Labs. All solvents were purified according to the method of Grubbs.[1]

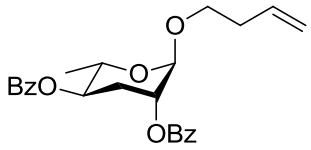
1.4.2 Experimental procedures and tabulated data

Representative procedure for Glycosylation 1 (n=1):



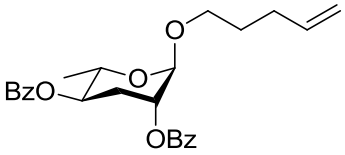
A suspension of 400 mg (1.122 mmol) dibenzoyl ascarylose, 0.12 mL (1.8 mmol) allyl alcohol and 120 mg 4Å molecular sieves in 12 mL CH_2Cl_2 was cooled to 0°C. To this suspension was added 0.61 mL (4.8 mmol) $BF_3.OEt_2$ at once. The resulting suspension was stirred at 0°C for 4 h. 12 mL saturated $NaHCO_3$ solution was then added. Upon cessation of effervescence, the aqueous layer was separated from the organic layer and then extracted with 3x10mL CH_2Cl_2. The resulting organic extracts were dried over MgSO4 and filtered to obtain 514.5 mg of oil after evaporation of solvent. Silica gel column chromatography (39 g silica gel, gradient run from 5% EtOAc in hexanes to 15% EtOAc) afforded 420.8 mg (95%) of a colorless syrup. . $[\alpha]_D^{25}$= 2.6, c 1.33; HRMS (m/z): [M+Na] calcd. For $C_{23}H_{24}O_6Na$ 419.1465, found 419.1473; ^{1}H NMR (250 MHz, Chloroform-d) δ 8.13 (d, J = 7.01, 1.5 Hz, 2H), 8.05 (d, J = 7.01, 1.5 Hz, 2H), 7.65 – 7.52 (m, 2H), 7.52 – 7.37 (m, 4H), 6.10 – 5.87 (m, 1H), 5.38 (dq, J = 17.2, 1.6 Hz, 1H), 5.31 – 5.13 (m, 3H), 4.91 (s, 1H), 4.29 (ddt, J = 12.9, 5.2, 1.5 Hz, 1H), 4.21 – 4.02 (m, 2H), 2.46 (dt, J = 14.3, 4.0 Hz, 1H), 2.26 (ddd, J = 13.8, 11.3, 3.2 Hz, 1H), 1.32 (d, J = 6.2 Hz, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 165.4, 165.3, 133.6, 133.04, 132.98, 129.8, 129.7, 129.6, 129.4, 128.2, 117.3, 95.4, 70.3, 68.0, 66.6, 29.5, 17.7.

Synthesis of 1, (n=2) glycosylation:



Started with 400 mg (1.129 mmol) dibenzoyl ascarylose (1), 0.16 mL (1.796 mmol) 3-buten-1-ol, 130 mg 3Å molecular sieves, and 0.61 mL (4.838 mmol) BF_3•OEt_2 in 12 mL CH_2Cl_2. Purified to obtain 429.8 mg (93%) of a colorless oil. $[\alpha]_D^{25}$= 8.3, c 0.4; HRMS (m/z): [M+Na] calcd. for $C_{24}H_{26}O_6Na$ 433.1622, found 433.1629; ^{1}H NMR (250 MHz, Chloroform-d) δ 8.12 (d, 7.0 Hz 2H), 8.03 (d, 7.0 Hz 2H), 7.54 (dt, J = 7.1, 3.6 Hz, 2H), 7.43 (td, J = 7.6, 4.5 Hz, 4H), 5.87 (ddt, J = 17.0, 10.2, 6.7 Hz, 1H), 5.31 – 5.15 (m, 3H), 5.10 (dd, J = 10.2, 1.9 Hz, 1H), 4.87 (s, 1H), 4.11 (dd, J = 9.8, 6.0 Hz, 1H), 3.81 (dt, J = 9.6, 6.8 Hz, 1H), 3.58 (dt, J = 9.7, 6.6 Hz, 1H), 2.41 (q, J = 6.9 Hz, 3H), 2.22 (ddd, J = 13.9, 11.3, 3.1 Hz, 1H), 1.31 (d, J = 6.2 Hz, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 165.4, 165.3, 134.6, 133.00, 132.94, 129.7, 129.6, 129.4, 128.2, 116.6, 96.1, 70.3, 66.9, 66.6, 33.8, 29.5, 17.7.

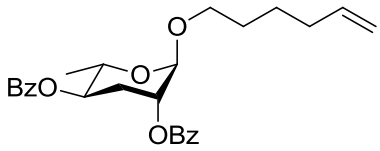
Synthesis of 1, (n=3) glycosylation:



Started with 300 mg (0.842 mmol) dibenzoylascarylose, 0.14 mL (1.3 mmol) 4-penten-1-ol, 90 mg 3Å molecular sieves, and 0.46 mL (3.6 mmol) BF_3·OEt_2 in 9 mL CH_2Cl_2. Purified to obtain 256.2 mg (72%) of a colorless oil. $[\alpha]_D^{25}$= 11.7, c 0.61; HRMS (m/z): [M+Na] calcd. For $C_{25}H_{28}O_6Na$ 447.1778, found 447.1780; ^{1}H NMR (400 MHz, Chloroform-d) δ 8.00 (d, 2H), 7.93 (d, 2H), 7.54 – 7.44 (m, 2H), 7.36 (td, J = 7.6, 5.4 Hz, 4H), 5.83 – 5.69 (m, 1H), 5.14 – 5.03 (m, 2H), 5.03 – 4.87 (m, 2H), 4.72 (s, 1H), 3.97 (dq, J = 9.5, 6.2 Hz, 1H), 3.68 (dt, J = 9.6, 6.5 Hz,

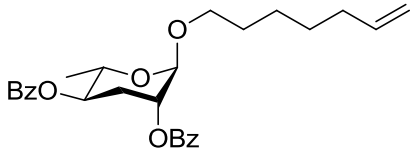
1H), 3.42 (dt, J = 9.6, 6.3 Hz, 1H), 2.31 (dt, J = 13.4, 3.9 Hz, 1H), 2.17 – 2.04 (m, 3H), 1.74 – 1.60 (m, 2H), 1.19 (d, J = 6.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 165.6, 138.0, 133.23, 133.15, 130.0, 129.9, 129.8, 129.6, 128.4, 115.0, 96.4, 70.6, 67.1, 66.7, 30.3, 29.7, 28.7, 17.9.

Synthesis of 1, (n=4) glycosylation:



Started with 300 mg (0.842 mmol) dibenzoylascarylose, 0.16 mL (1.3 mmol) 5-hexen-1-ol, 90 mg 3Å molecular sieves, and 0.46 mL (3.6 mmol) BF_3•OEt_2 in 9 mL CH_2Cl_2. Purified to obtain 262.6 mg (71%) of a colorless oil. $[\alpha]_D^{25}$= 7.7, c 0.48; HRMS (m/z): [M+Na] calcd. For $C_{26}H_{30}O_6Na$ 461.1935, found 461.1945; ^{1}H NMR (400 MHz, Chloroform-d) δ 8.11 (d, 2H), 8.04 (d, 2H), 7.64 – 7.52 (m, 2H), 7.51 – 7.42 (m, 4H), 5.84 (ddt, 1H), 5.24 – 5.12 (m, 2H), 5.10 – 4.94 (m, 2H), 4.83 (s, 1H), 4.07 (dq, J = 9.8, 6.3 Hz, 1H), 3.77 (dt, J = 9.7, 6.6 Hz, 1H), 3.52 (dt, J = 9.7, 6.4 Hz, 1H), 2.42 (dt, J = 13.6, 3.9 Hz, 1H), 2.21 (ddd, J = 13.9, 11.4, 3.2 Hz, 1H), 2.17 – 2.07 (m, 2H), 1.68 (dq, J = 9.2, 6.5, 5.6 Hz, 2H), 1.59 – 1.46 (m, 2H), 1.30 (d, J = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 165.8, 138.8, 133.5, 133.4, 130.1, 130.0, 129.8, 128.6, 114.9, 96.6, 70.8, 67.92, 67.94, 33.7, 30.0, 29.2, 25.7, 18.1.

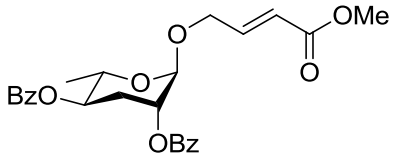
Synthesis of 1, (n=5) glycosylation:



Started with 300 mg (0.842 mmol) dibenzoylascarylose, 0.18 mL (1.3 mmol) hept-6-en-1-ol, 90 mg 3Å molecular sieves, and 0.46 mL (3.6 mmol) BF_3·OEt_2 in 9 mL CH_2Cl_2. Purified to obtain 271.8 mg (71%) of a colorless oil. $[\alpha]_D^{25}$= 5.7, c 0.48; HRMS (m/z): [M+Na] calcd. For

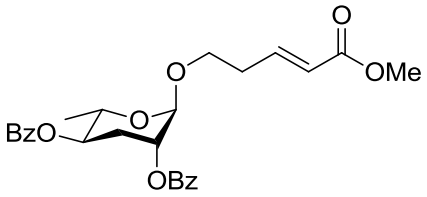
$C_{27}H_{32}O_6Na$ 475.2091, found 475.2091; ^{1}H NMR (250 MHz, Chloroform-d) δ 8.03 (d, *J* = 7.0, 1.5 Hz, 2H), 7.96 (d, *J* = 7.0, 1.4 Hz, 2H), 7.57 – 7.43 (m, 2H), 7.43 – 7.28 (m, 4H), 5.75 (ddt, *J* = 16.9, 10.1, 6.7 Hz, 1H), 5.19 – 5.02 (m, 2H), 5.02 – 4.80 (m, 2H), 4.75 (s, 1H), 3.99 (dq, *J* = 9.7, 6.2 Hz, 1H), 3.68 (dt, *J* = 9.6, 6.7 Hz, 1H), 3.43 (dt, *J* = 9.6, 6.5 Hz, 1H), 2.33 (m, 1H), 2.13 (ddd, *J* = 13.8, 11.3, 3.1 Hz, 1H), 2.01 (tdd, *J* = 7.0, 5.3, 2.2 Hz, 2H), 1.59 (dd, *J* = 13.2, 6.5 Hz, 2H), 1.47 – 1.26 (m, 4H), 1.22 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (100 MHz $CDCl_3$,) δ 178.0, 100.5, 71.0, 69.6, 68.5, 68.4, 36.1, 35.2, 30.7, 30.3, 27.3, 26.2, 18.2.

Representative procedure for cross metathesis 2 (n=1):



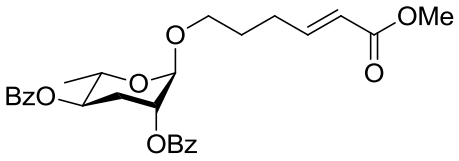
To a solution of 262.8 mg (.663 mmol) terminal alkene 1 (n=1) and 0.30 mL (3.3 mmol) of methyl acrylate in 22.2 mL CH_2Cl_2 was added 56.3 mg (66.3 μmol) Grubbs 2nd generation ruthenium catalyst at once. The resulting solution was allowed to stir at reflux for 4 h. The reaction mixture was concentrated to 167.6 mg of maroon oil. Column chromatography (12 g silica gel, gradient run from 50% DCM in hexanes to pure DCM) afford 112.4 mg (37%) of a colorless oil. $[\alpha]_D^{25}$= 4.5, c 0.5; HRMS (m/z): [M+Na] calcd. For $C_{25}H_{26}O_8Na$ 477.1531, found 477.1520; ^{1}H NMR (250 MHz, Chloroform-d) δ 8.10 (d, J = 7.25 Hz, 2H), 8.03 (d, 7.25 Hz, 2H), 7.64 – 7.51 (m, 2H), 7.51 – 7.37 (m, 4H), 7.02 (dt, J = 15.7, 4.3 Hz, 1H), 6.16 (dt, J = 15.7, 2.0 Hz, 1H), 5.32 – 5.11 (m, 2H), 4.89 (s, 1H), 4.45 (ddd, J = 16.0, 4.3, 2.1 Hz, 1H), 4.24 (ddd, J = 16.1, 4.6, 2.1 Hz, 1H), 4.13 – 3.98 (m, 1H), 3.76 (s, 3H), 2.46 (dt, J = 13.6, 4.0 Hz, 1H), 2.23 (ddd, J = 14.0, 11.3, 3.2 Hz, 1H), 1.29 (d, J = 6.2 Hz, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 166.4, 165.50, 165.46, 143.3, 133.2, 133.1, 129.8, 129.6, 129.5, 128.4, 121.0, 96.0, 70.2, 70.1, 67.0, 65.7, 51.6, 29.6, 17.7.

Synthesis of 2, n=2 cross metathesis:



Started with 429.8 mg (1.047 mmol) 1 (n=2), 0.47 mL (5.2 mmol) methyl acrylate, and 88.9 mg (104 µmol) Grubbs second generation catalyst in 36.6 mL CH_2Cl_2. Purified to obtain 258.8 mg (53%) of a colorless oil. $[\alpha]_D^{25}$= 11.2, c 0.2; HRMS (m/z): [M+Na] calcd. For $C_{26}H_{28}O_8Na$ 491.1676, found 491.1672; ^{1}H NMR (250 MHz, Chloroform-d) δ 8.09 (d, J = 7.2, 1.4 Hz, 2H), 8.02 (d, J = 7.25 Hz, 2H), 7.62 – 7.49 (m, 2H), 7.49 – 7.35 (m, 4H), 7.00 (dt, J = 15.7, 7.0 Hz, 1H), 5.94 (m, 1H), 5.28 – 5.08 (m, 2H), 4.84 (s, 1H), 4.04 (m, 1H), 3.86 (dt, J = 9.8, 6.5 Hz, 1H), 3.71 (s, 3H), 3.63 (dt, J = 9.8, 6.2 Hz, 1H), 2.62 – 2.47 (m, 2H), 2.41 (dt, J = 13.5, 4.0 Hz, 1H), 2.17 (ddd, J = 13.9, 11.4, 3.2 Hz, 1H), 1.28 (d, J = 6.2 Hz, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 166.5, 165.5, 165.4, 145.2, 133.1, 133.0, 129.73, 129.67, 129.6, 129.4, 128.3, 122.8, 96.2, 70.2, 66.8, 65.6, 51.3, 32.2, 29.5, 17.7.

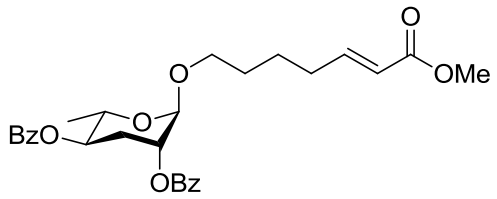
Synthesis of 2, (n=3) cross metathesis:



Started with 218.7 mg (0.515 mmol) 1 (n=3), 0.22 mL (2.6 mmol) methyl acrylate, and 51.5 mg (60.7µmol) Grubbs second generation catalyst in 18.4 mL CH_2Cl_2. Purified to obtain 110.1 mg (44%) of a colorless oil. $[\alpha]_D^{25}$= 2.7, c 0.2; HRMS (m/z): [M+Na] calcd. For $C_{27}H_{30}O_8Na$ 505.1833, found 505.1856; ^{1}H NMR (400 MHz, Chloroform-d) δ 8.11 (d, 2H), 8.05 (d, 2H), 7.63 – 7.53 (m, 2H), 7.47 (td, J = 7.5, 4.8 Hz, 4H), 7.03 (dt, J = 15.9, 6.9 Hz, 1H), 5.90 (d, J = 15.6 Hz,

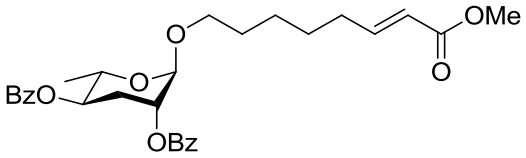
1H), 5.24 – 5.14 (m, 2H), 4.83 (s, 1H), 4.06 (dt, J = 9.5, 6.0 Hz, 1H), 3.80 (dt, J = 9.7, 6.5 Hz, 3H), 3.74 (s, 1H), 3.54 (dt, 1H), 2.48 – 2.32 (m, 2H), 2.27 – 2.15 (m, 2H), 1.85 (p, J = 6.8, 5.7 Hz, 2H), 1.30 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 165.71, 165.6, 148.6, 133.3, 133.2, 130.0, 129.9, 129.61, 128.5, 128.4, 121.4, 96.4, 70.48, 70.46, 66.9, 51.4, 29.7, 29.0, 28.0, 17.9.

Synthesis of 2, (n=4) cross metathesis:



Started with 100 mg (0.228 mmol) 1 (n=4), 0.10 mL (1.1 mmol) methyl acrylate, and 19.4 mg (22.8 µmol) Grubbs second generation catalyst in 8.4 mL CH_2Cl_2. Purified to obtain 60.6 mg (53%) of a colorless oil. $[\alpha]_D^{25}$= 4.1, c 0.48; HRMS (m/z): [M+Na] calcd. For $C_{27}H_{32}O_6Na$ 519.1989, found 519.1996. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.11 (d, *J* = 8.4, 1.6 Hz, 2H), 8.05 (d, 2H), 7.64 – 7.54 (m, 2H), 7.47 (ddd, *J* = 8.8, 7.1, 5.2 Hz, 4H), 7.01 (dt, *J* = 15.7, 7.0 Hz, 1H), 5.88 (dt, *J* = 15.6, 1.6 Hz, 1H), 5.25 – 5.13 (m, 2H), 4.83 (s, 1H), 4.06 (dq, *J* = 9.9, 6.2 Hz, 1H), 3.78 (dt, *J* = 9.8, 6.3 Hz, 1H), 3.73 (s, 3H), 3.52 (dt, *J* = 9.8, 6.1 Hz, 1H), 2.48 – 2.37 (m, 1H), 2.29 (qd, *J* = 7.1, 1.6 Hz, 2H), 2.21 (ddd, *J* = 13.5, 11.3, 3.1 Hz, 1H), 1.74 – 1.56 (m, 4H), 1.30 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0 165.7, 165.6, 149.0, 133.24, 133.16, 130.0, 129.84, 129.79, 129.6, 128.4, 121.3, 96.4, 70.5, 67.4, 66.8, 51.4, 31.9, 29.7, 28.9, 24.7, 17.9.

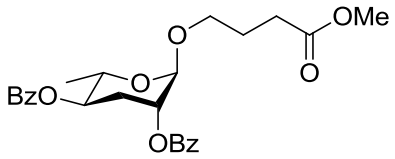
Synthesis of 2, (n=5) cross metathesis:



Started with 271.8 mg (0.6010 mmol) 1 (n=5), 0.27 mL (3.0 mmol) methyl acrylate, and 51 mg (60 µmol) Grubbs second generation catalyst in 23 mL CH_2Cl_2. Purified to obtain 163.2 mg

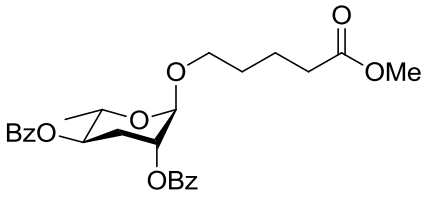
(53%) of a colorless oil. $[\alpha]_D^{25}$= 3.8, c 1.5; HRMS (m/z): [M+Na] calcd. For $C_{29}H_{34}O_8Na$ 533.2146, found 533.2157; ^{1}H NMR (250 MHz, Chloroform-d) δ 8.11 (d, J = 7.0, 1.5 Hz, 2H), 8.04 (d, J = 7.0, 1.4 Hz, 2H), 7.68 – 7.52 (m, 2H), 7.52 – 7.38 (m, 4H), 6.99 (dt, J = 15.7, 6.9 Hz, 1H), 5.85 (dt, J = 15.6, 1.6 Hz, 1H), 5.28 (s, 1H), 5.18 (ddd, J = 9.9, 5.2, 3.7 Hz, 2H), 4.82 (s, 1H), 4.05 (dq, 1H), 3.85 – 3.73 (m, 1H), 3.71 (s, 3H), 3.50 (dt, J = 9.7, 6.4 Hz, 1H), 2.42 (dt, J = 13.4, 4.0 Hz, 1H), 2.33 – 2.11 (m, 3H), 1.68 (dd, J = 11.7, 4.8 Hz, 2H), 1.50 (ddt, J = 13.8, 10.2, 5.9 Hz, 4H), 1.30 (d, J = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 165.7, 165.6, 149.3, 133.24, 133.16, 130.0, 129.9, 129.8, 129.6, 128.4, 121.0, 96.3, 70.6, 67.6, 66.7, 51.4, 32.1, 29.7, 29.7, 29.2, 27.8, 25.7, 17.9.

Representative procedure for 3 (n=1) hydrogenation:



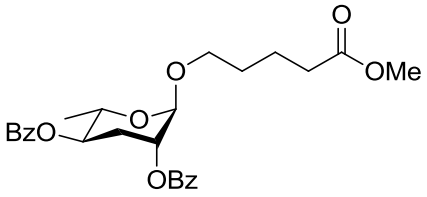
A suspension of 89.7 mg (0.197 mmol) unsaturated ester 2 (n=1) and 9.3 mg 10% palladium on activated carbon in 9ml EtOAc was vacuum purged and back filled with H_2 gas . The resulting suspension was allowed to stir at 25°C for 24 h. The reaction mixture was filtered through celite and concentrated to obtain 85.7 mg (95%) of a colorless oil that required no further purification. $[\alpha]_D^{25}$= 5.8, c 0.2; HRMS (m/z): [M+Na] calcd. For $C_{25}H_{28}O_8Na$ 479.1676, found 479.1700; ^{1}H NMR (250 MHz, Chloroform-d) δ 8.10 (d, J = 7.0, 1.4 Hz, 2H), 8.04 (d, J = 7.1, 1.4 Hz, 2H), 7.65 – 7.51 (m, 2H), 7.51 – 7.38 (m, 4H), 5.27 – 5.09 (m, 2H), 4.82 (s, 1H), 4.14 – 3.97 (m, 1H), 3.82 (dt, J = 9.8, 6.2 Hz, 1H), 3.70 (s, 3H), 3.54 (dt, J = 9.7, 6.1 Hz, 1H), 2.55 – 2.34 (m, 3H), 2.19 (ddd, J = 13.8, 11.3, 3.2 Hz, 1H), 1.99 (h, J = 6.5 Hz, 2H), 1.29 (d, J = 6.2 Hz, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 173.8, 165.6, 165.5, 133.14, 133.07, 129.8, 129.73, 129.68, 129.5, 128.3, 96.3, 70.4, 67.2, 66.7, 51.4, 33.6, 29.6, 28.8, 21.7, 17.8.

Synthesis of 3, (n=2) hydrogenation:



Started with 131.1 mg (0.2800 mmol) 2 (n=2) 13.5 mg palladium on activated carbon 10% palladium in 13.4 mL ethyl acetate. Purified to obtain 120.1 mg (91%) colorless oil. $[\alpha]_D^{25}$= 12.4, c 0.3; HRMS (m/z): [M+Na] calcd. For $C_{26}H_{30}O_8Na$ 493.1833, found 493.1826 ^{1}H NMR (250 MHz, Chloroform-d) δ 8.10 (d, 2H), 8.03 (d, J = 7.0, 1.6 Hz, 2H), 7.64 – 7.51 (m, 2H), 7.44 (ddd, J = 8.8, 6.9, 3.6 Hz, 4H), 5.27 – 5.09 (m, 2H), 4.82 (s, 1H), 4.14 – 3.99 (m, 1H), 3.78 (dt, J = 9.4, 6.0 Hz, 1H), 3.67 (s, 3H), 3.51 (dt, J = 9.7, 5.7 Hz, 1H), 2.50 – 2.31 (m, 3H), 2.20 (ddd, J = 13.9, 11.3, 3.1 Hz, 1H), 1.75 (ddt, J = 12.3, 7.9, 4.7 Hz, 4H), 1.29 (d, J = 6.2 Hz, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 173.8, 165.6, 165.5, 133.14, 133.07, 129.8, 129.7, 129.7, 129.5, 128.3, 96.3, 70.4, 67.2, 66.7, 51.4, 33.6, 29.6, 28.8, 21.7, 17.8.

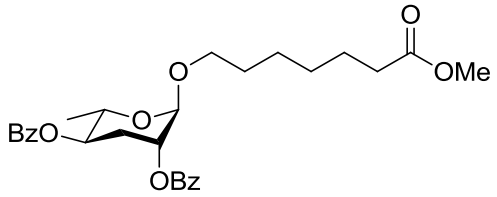
Synthesis of 3, (n=3) hydrogenation:



Started with 52 mg (0.11 mmol) 2 (n=3) 5.3 mg palladium on activated carbon 10% palladium in 5.3 mL ethyl acetate. Purified to obtain 45.5 mg (87%) colorless oil. $[\alpha]_D^{25}$= 6.1, c 0.4; HRMS (m/z): [M+Na] calcd. For $C_{27}H_{32}O_8Na$ 505.1833, found 505.1856; ^{1}H NMR (400 MHz, Chloroform-d) δ 8.11 (d, J = 7.1, 1.4 Hz, 2H), 8.04 (d, 2H), 7.58 (dddd, J = 6.9, 5.2, 2.6, 1.3 Hz, 2H), 7.46 (ddd, J = 8.7, 7.0, 5.0 Hz, 4H), 5.24 – 5.12 (m, 2H), 4.82 (s, 1H), 4.06 (dq, J = 9.6, 6.2 Hz, 1H), 3.77 (dt, J = 9.6, 6.6 Hz, 1H), 3.68 (s, 3H), 3.51 (dt, J = 9.6, 6.4 Hz, 1H), 2.47 – 2.32

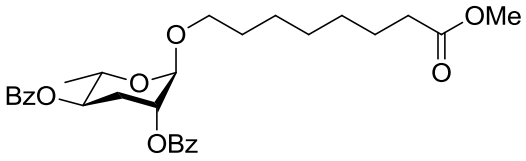
(m, 3H), 2.20 (ddd, J = 13.8, 11.4, 3.1 Hz, 1H), 1.77 – 1.62 (m, 4H), 1.45 (tt, J = 9.8, 6.2 Hz, 2H), 1.30 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 165.7, 165.6, 133.23, 133.16, 130.0, 129.9, 129.8, 129.6, 128.4, 96.4, 70.6, 67.6, 66.8, 51.5, 34.0, 29.73, 29.68, 29.2, 25.8, 24.7, 17.9

Synthesis of 3, (n=4) hydrogenation:



Started with 103.4 mg (0.208 mmol) 2 (n=4) 10.6 mg palladium on activated carbon 10% palladium in 10.6 mL ethyl acetate. Purified to obtain 84.4 mg (81%) colorless oil. $[\alpha]_D^{25}$= 2.8, c 0.3; HRMS (m/z): [M+Na] calcd. For $C_{28}H_{34}O_8Na$ 521.2146, found 521.2163; ^{1}H NMR (400 MHz, Chloroform-d) δ 8.11 (d, 2H), 8.04 (d, 2H), 7.64 – 7.54 (m, 2H), 7.52 – 7.42 (m, 4H), 5.24 – 5.12 (m, 2H), 4.82 (s, 1H), 4.06 (dq, J = 9.8, 6.3 Hz, 1H), 3.76 (dt, J = 9.7, 6.7 Hz, 1H), 3.67 (s, 3H), 3.50 (dt, J = 9.7, 6.5 Hz, 1H), 2.41 (dt, J = 13.7, 4.0 Hz, 1H), 2.34 (t, J = 7.5 Hz, 2H), 2.21 (ddd, J = 13.8, 11.4, 3.2 Hz, 1H), 1.67 (dq, J = 11.0, 7.0, 6.5 Hz, 4H), 1.41 (tdd, J = 10.6, 7.3, 4.2 Hz, 4H), 1.30 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 166.0, 165.9, 133.5, 133.4, 130.2, 130.09, 130.06, 129.8, 128.7, 96.6, 70.8, 68.0, 67.0, 51.7, 34.2, 30.0, 29.5, 29.2, 26.1, 25.1, 18.1.

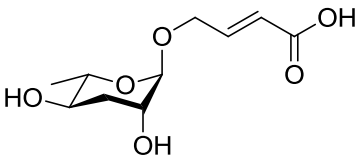
Synthesis of 3, (n=5) hydrogenation:



Started with 52 mg (0.10 mmol) 2 (n=5), 5.3 mg palladium on activated carbon 10% palladium in 5.3 mL ethyl acetate. Purified to obtain 50 mg (96%) colorless oil. $[\alpha]_D^{25}$= 4.3, c 0.2;

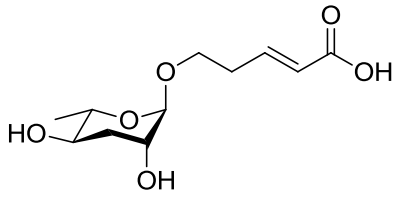
HRMS (m/z): [M+Na] calcd. For $C_{29}H_{36}O_8Na$ 535.2302, found 535.2315; ^{1}H NMR (400 MHz, Chloroform-d) δ 8.11 (d, J = 7.2, 1.4 Hz, 2H), 8.04 (d, 2H), 7.64 – 7.53 (m, 2H), 7.47 (td, J = 7.5, 5.0 Hz, 4H), 5.25 – 5.11 (m, 2H), 4.82 (s, 1H), 4.06 (dt, J = 9.6, 6.1 Hz, 1H), 3.75 (dt, J = 9.7, 6.7 Hz, 1H), 3.67 (s, 3H), 3.50 (dt, J = 9.5, 6.4 Hz, 1H), 2.42 (dt, J = 13.5, 4.1 Hz, 1H), 2.33 (t, J = 7.5 Hz, 2H), 2.27 – 2.15 (m, 1H), 1.74 – 1.60 (m, 4H), 1.47 – 1.32 (m, 6H), 1.32 – 1.23 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 165.7, 165.7, 133.24, 133.17, 130.0, 129.9, 129.8, 129.6, 128.4, 96.4, 70.6, 67.9, 66.7, 51.5, 34.1, 29.74, 29.7, 29.4, 29.1, 26.0, 24.9, 17.9.

Representative procedure for 4 (n=1) hydrolysis:



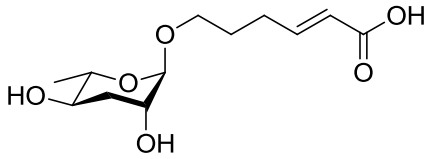
To a solution of 44.3 mg (0.0970 mmol) methyl ester **2** (n=1) in 7.8 mL of *t*BuOH was added 7.8 mL 1M LiOH at once. The resulting solution was allowed to stir at 25°C for 24 h. The solution was then acidified with 1M HCl until a pH of 3. The organic layer was then separated from the aqueous. The aqueous layer was then extracted 4 x 10 mL DCM. The combined organic layers were washed with brine, dried with Na_2SO_4 and filtered. Evaporation of solvent afforded 20.1 mg of an oil. HPLC purification on reverse phase column (gradient run pure CH_3CN to water) afforded 7 mg (31%) colorless oil. $[\alpha]_D^{25}$= -100.2, c 0.1; HRMS (m/z): [M+Na] calcd. For $C_{10}H_{16}O_6Na$ 255.0839, found 255.0841; ^{1}H NMR (400 MHz, Methanol-d4) δ 6.89 (dt, J = 15.6, 4.5 Hz, 1H), 6.04 (d, J = 15.6, 2.1 Hz, 1H), 4.57 (s, 1H), 4.34 (ddd, J = 16.0, 4.3, 2.1 Hz, 1H), 4.16 (ddd, J = 16.0, 4.7, 2.0 Hz, 1H), 3.83 (q, J = 2.6 Hz, 1H), 3.54 (dq, J = 9.9, 5.0, 4.2 Hz, 2H), 3.34 (s, 1H), 1.98 (dt, J = 13.0, 3.6 Hz, 1H), 1.80 (ddd, J = 13.4, 10.6, 3.1 Hz, 1H), 1.23 (d, J = 5.6 Hz, 3H). ^{13}C NMR (100 MHz, MeOD) δ 170.8, 144.6, 123.9, 100.2, 71.4, 69.4, 68.40, 66.7, 36.2, 18.2.

Synthesis of 4, (n=2) unsaturated hydrolysis:



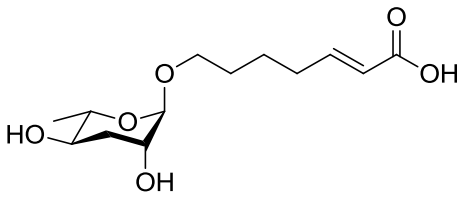
Started with 102.1 mg (0.2180 mmol) 2 (n=2) and 17.9 mL (1N) LiOH in 17.9 mL of tert-Butanol. Purified to obtain 23 mg (43%) colorless oil. $[\alpha]_D^{25}$= -53.8, c 0.3; HRMS (m/z): [M+Na] calcd. For $C_{11}H_{18}O_6Na$ 269.0996, found 269.1003; ^{1}H NMR (400 MHz, Methanol-d4) δ 6.96 (dt, J = 15.7, 6.9 Hz, 1H), 5.88 (d, J = 15.7 Hz, 1H), 4.52 (s, 1H), 3.86 – 3.72 (m, 2H), 3.54 (ddt, J = 14.9, 10.5, 5.3 Hz, 3H), 3.35 – 3.25 (m, 1H), 2.50 (q, J = 6.5 Hz, 2H), 1.94 (dt, J = 13.0, 3.8 Hz, 1H), 1.75 (ddd, J = 13.2, 10.5, 3.2 Hz, 1H), 1.22 (d, J = 5.7 Hz, 3H). ^{13}C NMR (100 MHz, MeOD) δ 170.1, 147.7, 124.4, 100.7, 71.3, 69.45, 68.44, 66.9, 36.1, 33.6, 18.2.

Synthesis of 4, (n=3) unsaturated hydrolysis:



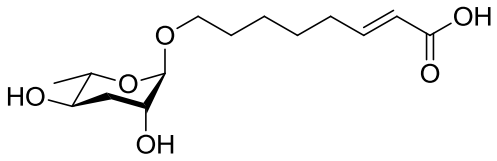
Started with 38.9 mg (0.0810 mmol) 2 (n=3) and 6.9 mL (1N) LiOH in 6.9 mL of tert-Butanol. Purified to obtain 7.5 mg (36%) colorless oil. $[\alpha]_D^{25}$= -65.5, c 0.4; HRMS (m/z): [M+Na] calcd. For $C_{12}H_{20}O_6Na$ 283.1152, found 283.1163; ^{1}H NMR (400 MHz, Methanol-d4) δ 6.97 (dt, J = 15.6, 7.0 Hz, 1H), 5.83 (dt, J = 15.6, 1.5 Hz, 1H), 4.50 (s, 1H), 3.78 (td, J = 3.1, 1.5 Hz, 1H), 3.73 (dt, J = 9.8, 6.3 Hz, 1H), 3.61 – 3.39 (m, 3H), 2.33 (qt, J = 7.1, 1.6 Hz, 2H), 2.01 – 1.90 (m, 1H), 1.83 – 1.70 (m, 3H), 1.23 (d, J = 5.9 Hz, 3H). ^{13}C NMR (100 MHz, MeOD) δ 170.4, 150.4, 123.2, 100.6, 71.1, 69.5, 68.5, 67.6, 36.2, 30.1, 29.4, 18.2.

Synthesis of 4, (n=4) unsaturated hydrolysis:



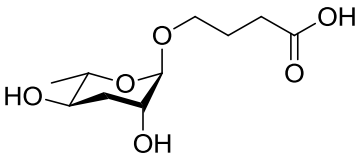
Started with 42 mg (0.082 mmol) 2 (n=4) and 7.4 mL (1N) LiOH in 7.4 mL of tert-Butanol. Purified to obtain 8.5 mg (36%) colorless oil. $[\alpha]_D^{25}$= -49.0, c 0.2; HRMS (m/z): [M-H]- calcd. For $C_{13}H_{22}O_6Na$ 273.1344, found 273.1343; ^{1}H NMR (400 MHz, Methanol-d4) δ 6.92 (dt, J = 15.6, 7.0 Hz, 1H), 5.81 (d, J = 15.6 Hz, 1H), 4.49 (s, 1H), 3.76 (td, J = 3.1, 1.5 Hz, 1H), 3.70 (dt, J = 9.9, 6.1 Hz, 1H), 3.60 – 3.38 (m, 3H), 2.25 (qd, J = 7.0, 1.6 Hz, 2H), 1.99 – 1.89 (m, 1H), 1.76 (ddd, J = 13.1, 10.9, 3.1 Hz, 1H), 1.60 (tdd, J = 11.9, 8.5, 5.3 Hz, 4H), 1.22 (d, J = 5.9 Hz, 3H). ^{13}C NMR (100 MHz, MeOD) δ 170.6, 150.5, 100.6, 71.1, 69.6, 68.5, 68.12, 49.6, 36.2, 33.0, 30.3, 26.2, 18.3.

Synthesis of 4, (n=5) unsaturated hydrolysis:



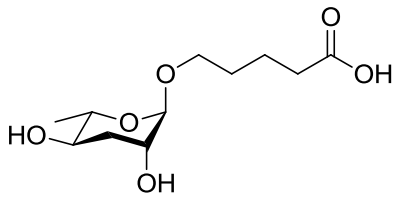
Started with 47.3 mg (0.0930 mmol) 2 (n=5) and 8.4 mL (1N) LiOH in 8.4 mL of tert-Butanol. Purified to obtain 19.1 mg (72%) colorless oil. $[\alpha]_D^{25}$= -67.1, c 0.6; HRMS (m/z): [M+Na] calcd. For $C_{14}H_{24}O_6Na$ 311.1465, found 311.1466; ^{1}H NMR (400 MHz, Methanol-d4) δ 6.95 (dt, J = 15.6, 7.0 Hz, 1H), 5.81 (dt, J = 15.6, 1.7 Hz, 1H), 4.50 (s, 1H), 3.77 (q, J = 2.8 Hz, 1H), 3.69 (dt, J = 9.7, 6.5 Hz, 1H), 3.62 – 3.47 (m, 2H), 3.43 (dt, J = 9.7, 6.2 Hz, 1H), 2.24 (qd, J = 7.1, 1.6 Hz, 2H), 1.95 (dt, J = 13.0, 3.7 Hz, 1H), 1.76 (ddd, J = 13.3, 10.8, 3.1 Hz, 1H), 1.70 – 1.57 (m, 2H), 1.57 – 1.35 (m, 4H), 1.23 (d, J = 5.8 Hz, 3H). ^{13}C NMR (100 MHz, MeOD) δ 170.5, 150.0, 122.9, 100.6, 71.1, 69.5, 68.5, 68.3, 36.13, 33.2, 30.5, 29.1, 27.1, 18.3.

Synthesis of 5, (n=1) saturated hydrolysis:



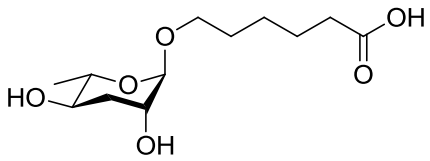
Started with 48.6 mg (0.106 mmol) 3 (n=1) and 8.5 mL (1N) LiOH in 8.5 mL of tert-Butanol. Purified to obtain 7 mg (28%) colorless oil. $[\alpha]_D^{25}$= -88.5, c 0.2; HRMS (m/z): [M+Na] calcd. For $C_{11}H_{20}O_6Na$ 257.0996, found 257.1004; ^{1}H NMR (400 MHz, Methanol-d4) δ 4.49 (s, 1H), 3.76 (tt, J = 3.9, 1.9 Hz, 1H), 3.74 – 3.68 (m, 1H), 3.60 – 3.39 (m, 3H), 2.37 (t, J = 7.3 Hz, 2H), 1.99 – 1.82 (m, 3H), 1.76 (ddd, J = 13.2, 10.9, 3.1 Hz, 1H), 1.21 (d, J = 5.9 Hz, 3H). ^{13}C NMR (100 MHz, MeOD) δ 177.8, 100.6, 71.1, 69.5, 68.5, 67.5, 36.1, 32.3, 26.4, 18.23.

Synthesis of **5**, (n=2) saturated hydrolysis:



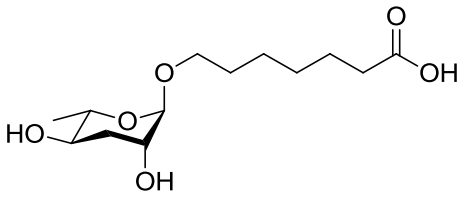
Started with 40.3 mg (0.0950 mmol) 3 (n=2) and 7.8 mL (1N) LiOH in 7.8 mL of tert-Butanol. Purified to obtain 5.8 mg (23%) colorless oil. $[\alpha]_D^{25}$= -64.8, c 0.3; HRMS (m/z): [M+Na] calcd. For $C_{11}H_{20}O_6Na$ 271.1152, found 271.1143; ^{1}H NMR (400 MHz, Methanol-d4) δ 4.50 (s, 1H), 3.77 (q, J = 2.6 Hz, 1H), 3.72 (dd, J = 9.8, 6.2 Hz, 1H), 3.62 – 3.38 (m, 3H), 2.32 (t, J = 6.7 Hz, 2H), 1.95 (dt, J = 13.0, 3.8 Hz, 1H), 1.83 – 1.76 (m, 1H), 1.76 – 1.56 (m, 5H), 1.23 (d, J = 5.9 Hz, 3H). ^{13}C NMR (100 MHz, MeOD) δ 177.8, 100.4, 70.9, 69.4, 68.3, 67.9, 36.0, 34.9, 30.1, 23.1, 18.1.

Synthesis of 5, (n=3) saturated hydrolysis:



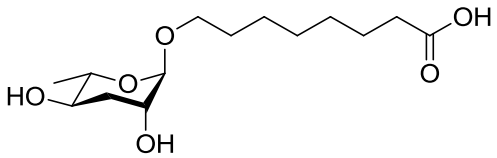
Started with 40.3 mg (0.08300 mmol) 3 (n=3) and 7.1 mL (1N) LiOH in 7.1 mL of tert-Butanol. Purified to obtain 6.3 mg (29%) colorless oil. $[\alpha]_D^{25}$= -74.9, c 0.3; HRMS (m/z): [M+Na] calcd. For $C_{12}H_{22}O_6Na$ 285.1309, found 285.1301; ^{1}H NMR (400 MHz, Methanol-d4) δ 4.50 (s, 1H), 3.76 (q, J = 2.8 Hz, 1H), 3.69 (dt, J = 9.7, 6.5 Hz, 1H), 3.53 (tdd, J = 13.9, 7.6, 3.9 Hz, 2H), 3.42 (dt, J = 9.6, 6.1 Hz, 1H), 2.29 (t, J = 7.4 Hz, 2H), 1.95 (dt, J = 13.2, 3.8 Hz, 1H), 1.77 (ddd, J = 13.3, 10.8, 3.1 Hz, 1H), 1.70 – 1.56 (m, 4H), 1.44 (ddd, J = 10.8, 8.7, 5.0 Hz, 2H), 1.22 (d, J = 5.9 Hz, 3H). ^{13}C NMR (100 MHz, MeOD) δ 178.0, 100.6, 71.1, 69.6, 68.5, 68.3, 36.2, 35.3, 30.5, 27.1, 26.1, 18.2.

Synthesis of 5, (n=4) saturated hydrolysis:



Started with 53 mg (0.11 mmol) 3 (n=4) and 9.4 mL (1N) LiOH in 9.4 mL of tert-Butanol. Purified to obtain 12.7 mg (43%) colorless oil. $[\alpha]_D^{25}$= -63.0, c 0.2; HRMS (m/z): [M-H]- calcd. For $C_{13}H_{24}O_6Na$ 275.1500, found 275.1497; ^{1}H NMR (400 MHz, Methanol-d4) δ 4.48 (s, 1H), 3.75 (td, J = 3.1, 1.4 Hz, 1H), 3.68 (dt, J = 9.7, 6.6 Hz, 1H), 3.60 – 3.45 (m, 2H), 3.41 (dt, J = 9.6, 6.2 Hz, 1H), 2.28 (t, J = 7.4 Hz, 2H), 1.99 – 1.89 (m, 1H), 1.76 (ddd, J = 13.3, 10.9, 3.1 Hz, 1H), 1.61 (ddt, J = 10.3, 7.3, 4.5 Hz, 4H), 1.47 – 1.32 (m, 4H), 1.22 (d, J = 5.9 Hz, 3H). ^{13}C NMR (100 MHz, MeOD) δ 178.0, 100.6, 71.0, 69.6, 68.5, 68.4, 36.2, 35.2, 30.7, 30.2, 27.2, 26.3, 18.3.

Synthesis of 5, (n=5) (saturated hydrolysis):



Started with 34 mg (0.066 mmol) 3 (n=5) and 6 mL (1N) LiOH in 6 mL of tert-Butanol. Purified to obtain 6.7 mg (35%) colorless oil. $[\alpha]_D^{25}$= -71.6, c 0.3; HRMS (m/z): [M+Na] calcd. For $C_{14}H_{26}O_6Na$ 313.1622, found 313.1617; ^{1}H NMR (400 MHz, Methanol-d4) δ 4.49 (s, 1H), 3.76 (td, J = 3.1, 1.5 Hz, 1H), 3.68 (dt, J = 9.7, 6.6 Hz, 1H), 3.61 – 3.45 (m, 2H), 3.42 (dt, J = 9.7, 6.2 Hz, 1H), 2.28 (t, J = 7.4 Hz, 2H), 1.98 – 1.91 (m, 1H), 1.77 (ddd, J = 13.4, 10.8, 3.1 Hz, 1H), 1.60 (qd, J = 8.2, 7.7, 5.3 Hz, 4H), 1.45 – 1.32 (m, 6H), 1.22 (d, J = 5.9 Hz, 3H). ^{13}C NMR (100 MHz, MeOD) δ 178.0, 100.5, 71.0, 69.6, 68.5, 68.4, 36.1, 35.2, 30.7, 30.3, 27.3, 26.2, 18.2.

1.5 References

1. Brenner, S.; *ChemBioChem.* **2003**, *4*, 683.
2. Hulme, S.E.; Whitesides, G.M. *Angew Chem Int Ed*. **2011**, *50*, 4774-4807.
3. Brenner, S.; *The nematode Caenorhabditis elegans*. Cold Spring Harbor Laboratory Press: Cold Spring Harbor, 1998.
4. Altun, Z. F., Introduction to *C. elegans* Anatomy. In *Wormatlas*, 2005.
5. Cheung, B. H.; Cohen, M.; Rogers, C.; Albayram, O.; de Bono, M., Experience-Dependent Modulation of C. elegans Behavior by Ambient Oxygen. *Curr. Biol.* **2005,** *15* , 905-917.
6. Brenner, S.; Wolpert, L., *My Life in Science*. BioMed: London, 2001.
7. Kaletta, T.; Hengartner, M.O. *Nature Reviews. Drug discovery*. **2006**, *5*, 387-398.
8. Golden, J.W.; Riddle, D. L. *Dev. Biol*. **1984**, *102*, 368-378.
9. Hu, P. J., Dauer. *WormBook*: *the online review of C.elegans biology*. **2007**, 1-19.
10. Klass, M.; Hirish, D. *Nature*. **1976**, *260*, 523-525.
11. (a) Vowels, J. J.; Thomas, J. H. *Genetics*. **1992**, *130*, 105-123.; (b) Thomas, J. H.; Birnby, D.A.; Vowels, J. J. *Genetics* **1993**, *134*, 1105-1117.; (c) Riddle, D. L.; Swanson, M.M.;

Albert, P. S. *Nature (London)*. **1981**, *290*, 668-671.; (d) Jia, K.; Albert, P. S.; Riddle, D. L. *Devlopment*. **2002**, *129*, 221-231.; (e) Gottlieb, S.; Ruvkun, G. *Genetics*. **1994**, *137*, 107-120.; (f) Simon, J. M.; Sterenberg, P. W. *Proc. Natl. Acad. Sci. USA*. **2002**, *99*, 1598-1603.; (G) Ren, P.E. A. *Science*. **1996**, *274*, 1389-1391.; (h) Kimura, K. D. *Science*. **1997**, *277*, 942-946.

12. Butcher, R. A.; Fujita, M.; Schroeder, F.C.; Clardy, J. *Nature chemical biology*. **2007**, *3*, 420-422.

13. Golden, J.; Riddle, D. A Pheromone Influences Larval Development in the Nematode *Caenorhabditis elegans*. *Science* **1982,** *218*, 578-580.

14. Butcher, R. A.; Fujita, M.; Schroeder, F. C.; Clardy, J. Small-Molecule Pheromones that Control Dauer Development in Caenorhabditis elegans. *Nat. Chem. Biol.* **2007,** *3*, 420-2.

15. Butcher, R.; Ragains, J.; Kim, E.; Clardy, J., A Potent Dauer Pheromone Component in *Caenorhabditis elegans* that Acts synergistically with Other Components. *Proc. Natl. Acad. Sci. U.S.A.* **2008,** *105*, 14288-14292.

16. Butcher, R.; Ragains, J.; Clardy, J. An Indole-Containing Dauer Pheromone Component with Unusual Dauer Inhibitory Activity at Higher Concentrations. *Org. Lett.* **2009,** *11*, 3100-3103.

17. Pungaliya, C.; Srinivasan, J.; Fox, B.; Malik, R.; Ludewig, A.; Sternberg, P.; Schroeder, F. A Shortcut to Identifying Small Molecule Signals that Regulate Behavior and Development in *Caenorhabditis elegans*. *Proc. Natl. Acad. Sci. U.S.A.* **2009,** *106*, 7708-7713.

18. Ward, S.; Thomson, N.; White, J.; Brenner, S. Electron Microscopical Reconstruction of the Anterior Sensory Anatomy of the Nematode *Caenorhabditis elegans*. *J. Comp. Neurol.* **1975,** *160*, 313-337.

19. Zwaal, R.; Mendel, J.; Sternberg, P.; Plasterk, R. Two Neuronal G Proteins are Involved in Chemosensation of the *Caenorhabditis elegans* Dauer-Inducing Pheromone. *Genetics* **1997,** *145*, 715-727.

20. (a) Ren, P.; Lim, c.; Johnsen, R.; Albert, P.; Pilgrim, D.; Riddle, D. Control of *C. elegans* Larval Development by Neuronal Expression of a TGF-Beta Homolog. *Science* **1996,** *274*, 1389-1391.; (b) Larsen, P.; Albert, P.; Riddle, D. Genes that Regulate Both Development and Longevity in *Caenorhabditis elegans*. *Genetics* **1995,** *139*, 1567-1583.

21. Bartke, A. Single-Gene Mutations and Healthy Ageing in Mammals. *Philos. Trans. R. Soc. B.* **2011,** *366*, 28-34.

22. Arnaldez, F.; Helman, L. Targeting the Insulin Growth Factor Receptor 1. *Hematol. Oncol. Clin. North Am.* **2012,** *26*, 527-542.

23. McCarty, M. Vegan Proteins May Reduce Risk of Cancer, Obesity, and Cardiovascular Disease by Promoting Increased Glucagon Activity. *Med. Hypotheses* **1999,** *53*, 459-485.

24. Swardfager, W.; Lanctot, K.; Rothenburg, L.; Wong, A.; Cappell, J.; Herrmann, N. A Meta-Analysis of Cytokines in Alzheimer's Disease. *Biol. Psychiatry* **2010,** *68*, 930-941.

25. Padua, D.; Massague, J. Roles of TGF-Beta in Metastasis. *Cell Res.* **2009,** *19*, 89-102.

26. Hollister, K. A.; Conner, E. S.; Zhang, X.; Spell, M.; Bernard, G. M.; Patel, P.; de Carvalho, A. C.; Butcher, R. A.; Ragains, J. R. Ascaroside Activity in Caenorhabditis elegans is Highly Dependent on Chemical Structure. *Bioorg. Med. Chem.* **2013,** *21*, 5754-69.

26. Felix, M.; Duveau, F. Population Dynamics and Habitat Sharing of Natural Populations of *Caenorhabditis elegans* and *C. briggsae*. *BMC Biol.* **2012,** *10*, 59.

CHAPTER 2: ALPHA SELECTIVE GLYCOSYLATION OF ALCOHOLS WITH SELENOGLYCOSIDES USING VISIBLE LIGHT

2.1 Introduction

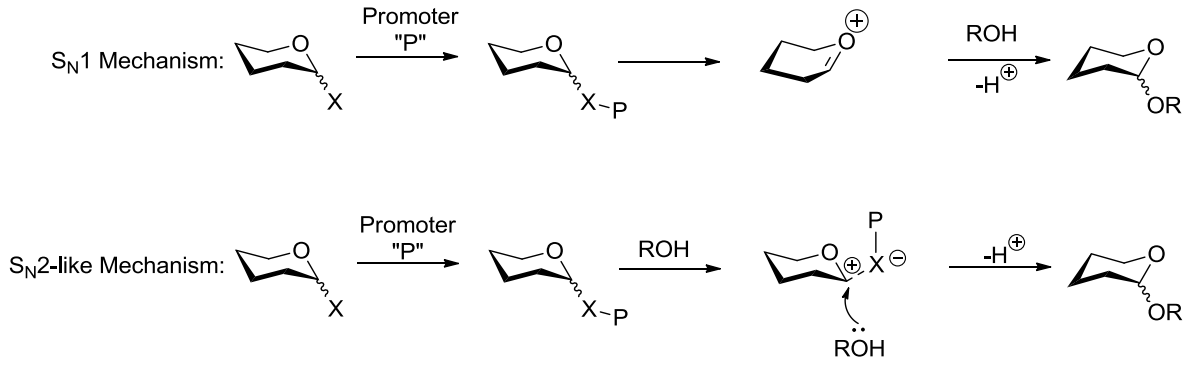
Oligosaccharides are involved in the structural modification of proteins, lipids, and secondary metabolites. They are also used as molecular recognition elements in biological processes such as cell-cell recognition, cellular adhesion, and cellular transport.[1] Developing methods to synthesize oligosaccharides would provide an efficient way to access the saccharide region of glycoproteins.[1] The synthesis of these oligosaccharides is a complex task due to the multiple glycosidic linkages in the oligosaccharides. This has led to the development of multiple glycosylation methods in attempt to address problems related to yields, stereoselectivity, mildness and orthogonality.

The stereoselective formation of the glycosidic bond is crucial to the synthesis of oligosaccharides. Glycosidic bonds are formed when a nucleophile displaces a leaving group (x) that is attached to the anomeric carbon (the carbon directly attached to the leaving group X in Scheme 2.1) of a carbohydrate donor. The glycosyl donor is the compound that "donates" the anomeric carbon and the glycosyl acceptor is the nucleophile that attaches to the anomeric carbon. If the nucleophile is an alcohol "ROH", the process is termed *O*-glycosylation. In many glycosylation methods, a promoter is also used in catalytic to stoichiometric amounts to drive the reaction forward.[2]

2.1.1 Possible Mechanisms of Glycosylation

While there are many mechanistic considerations in *O*-glycosylation two commonly proposed chemical glycosylations mechanisms are shown in Scheme 2.1. The first mechanism proceeds by a S_N1 pathway in which the glycosyl donor undergoes the loss of its leaving group

This chapter previously appeared as [Mark Spell, Xiaoping Wang, Amir E. Wahba, Elizabeth Conner, Justin Ragains, An α-selective, visible light photocatalytic glycosylation of alcohols with selenoglycosides, 4/22/2013]. It is reprinted by permission of [Elsevier.]



Scheme 2.1 General glycosylation mechanisms

(which is activated by a promoter) to form the oxacarbenium ion. This oxacarbenium ion is then attacked from either face by the glycosyl acceptor to form the glycosidic bond.[2] The second mechanism is more S_N2 like as it proceeds with inversion. The glycosyl donor undergoes the loss of its leaving group (that is activated by a promoter) to form an ion pair in which the negatively charged leaving group is in close proximity to the positively charged carbon. The glycosyl acceptor then attacks this partially positively charged carbon forming the glycosidic bond.[2] For the purposes of this dissertation, when the glycosidic C-C bond and the bond at the C_5-C_6 position are *trans* to one another it said to be in the *alpha* configuration. However, if the bonds are *cis* to one another it is in the *beta* configuration. The mechanism of the glycosylation gives us important information about the reaction. Understanding the multiple factors taking place in the mechanism can explain the stereoselectivity of the reaction.

2.1.2 Anomeric Effect

While there are multiple factors that contribute to the stereochemical outcome of glycosylation two major contributors are the "anomeric effect" (commonly observed when the system is in equilibrium) and "neighboring group" participation. The Edward-Lemieux effect ("anomeric effect") seen in Figure 2.1 is a stereoelectronic effect that describes the preference of a substituent next

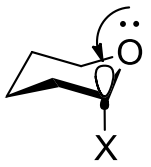
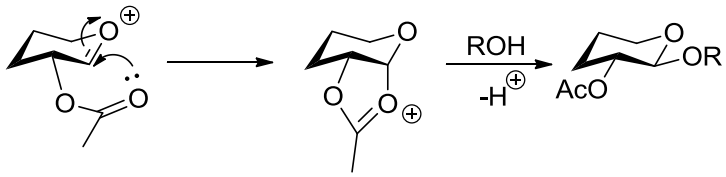


Figure 2.1 Anomeric effect

to a heteroatom (mainly oxygen) in a cyclohexane ring to be in the axial position rather than the sterically less demanding equatorial position.[3] Hyperconjugation (Figure 2.1) and the overall dipole observed are two plausible explanations for why the anomeric effect is observed. The hyperconjugation is seen between the lone pair on the oxygen in the ring and the σ* orbital of the C-X bond.[4] This hyperconjugation gives increased stability to the molecule due to electron delocalization. Substituents in the axial position also confer a reduced molecular dipole moment for the system.[4] When the substituent is in the axial position, the dipoles associated with the C-X and C-O bonds oppose each other. The opposite scenario is seen when substituents are in the equatorial position.

2.1.3 Neighboring Group Participation

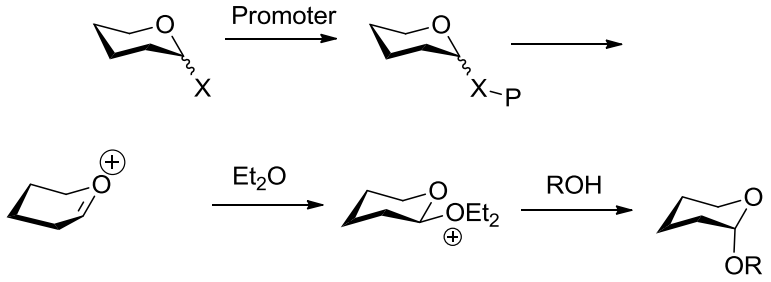
Neighboring group participation can also affect the stereochemical outcome of *O*-glycosylation. This is observed when an oxacarbenium ion is blocked from attack by a nucleophile from one face due to a protecting group (usually a carboxyl protecting group) such as acetate or benzoyl which donate a lone pair of electrons from the carbonyl oxygen to form an onium ion (Scheme 2.2).[5,6] This results in the formation of the new C-O bond in the equatorial (beta) position upon attack of alcohol.



Scheme 2.2 Neighboring group participation

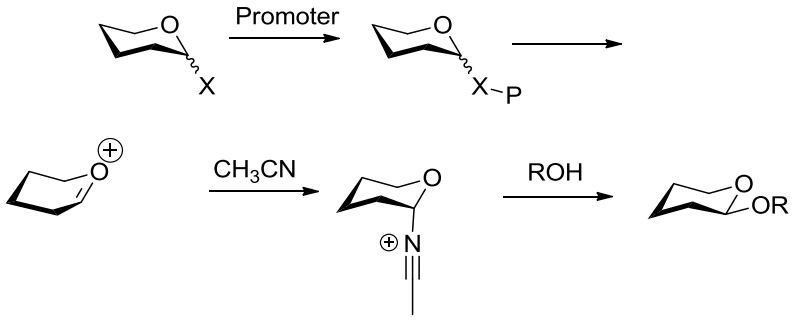
2.1.4 Solvent effects

Choice of solvent is an important factor to consider when performing an *O*-glycosylation, since the overall rate and stereochemical outcome of the reaction can be heavily influenced by the solvent (Scheme 2.3 and Scheme 2.4). Solvents of low polarity like diethyl ether and dichloromethane are commonly used while



Scheme 2.3 Effect of diethyl ether on glycosylation

polar aprotic solvents like acetonitrile and nitromethane are also common. Interaction of solvent with the oxacarbenium intermediate can have a significant effect on the stereochemical outcome



Scheme 2.4 Effect of acetonitrile on glycosylation

of a glycosylation. Acetonitrile and ether are two solvents that are known to interact with the oxacarbenium ion (shown in Scheme 2.3) influencing the glycosylation to form *beta* and *alpha* linkages respectfully.[7,8] The use of ether as solvent promotes addition of a solvent molecule via an S_N1 type pathway where ether attacks the oxonium intermediate forming a *beta* linkage (reverse anomeric effect) that is then attacked by a glycosyl acceptor (via an S_N2 pathway) to form the

alpha linkage as shown in Scheme 2.3 .[7] Acetonitrile, a polar aprotic solvent, also attacks the oxacarbenium ion forming the α-nitrilium ion that is attacked by a glycosyl acceptor to form the major β-glycoside (Scheme 2.4).[8]

2.1.5 Glycosyl donor

The overall reactivity associated with a glycosylation can be enhanced by various parameters. One of these parameters is the structure of the glycosyl donor. The protecting groups on the donor have a significant effect on the donor's reactivity due to the stability of the charged oxacarbenium intermediate that the protecting groups can perturb through electron withdrawal or release. Glycosyl donors have been placed into three categories (shown in Figure 2.2) based on

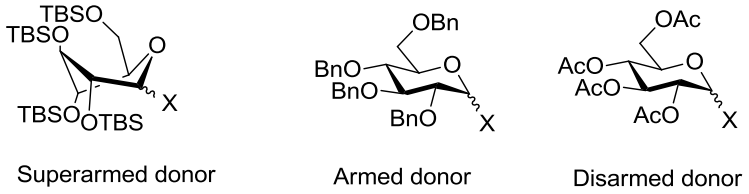
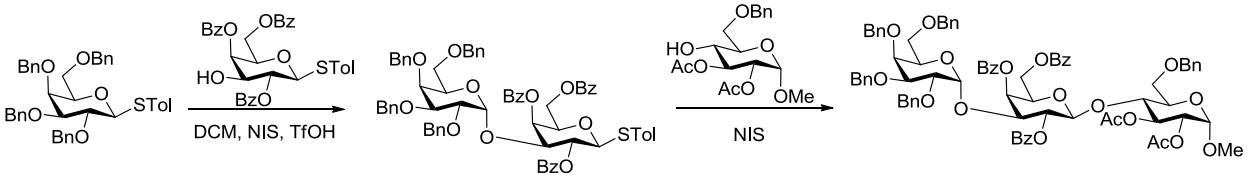


Figure 2.2 Reactivity of glycosyl donors

the nature of their protecting groups. Disarmed donors, which are the least reactive, are those with ester protecting groups. The ester groups are electron withdrawing destabilize the oxacarbenium ion. Armed donors are more reactive than disarmed donors and typically have ether protecting groups. The ether protecting groups are electron donating, providing stabilization to the oxacarbenium ion. The most reactive are the superarmed donors which have sterically demanding groups like TBS that induce twist boat conformation placing C-O bonds in an axial position. This gives increased stability to the aforementioned oxacarbenium ion through electrostatic stabilization.[9]

Glycosyl donor reactivity can also be tuned by the nature of the leaving group at the anomeric carbon.[9] Different leaving groups require different reaction conditions to promote their activation. The ability to tune the reactivity of glycosyl donors gives carbohydrate chemists the ability to perform multiple glycosylations in the same reaction flask since the order of events can be predicted based on relative donor reactivity (shown in Scheme 2.5). For example, a trisaccharide



Scheme 2.5 One pot oligosaccharide synthesis

can be formed in one pot using protecting groups (armed/disarmed donors) to control the order of events in the reaction.[9] Development of glycosyl donors that are easy to access, highly stable toward protecting group manipulation, and have a specific mild set of activation conditions are the subject of intensive investigation to further the utility of one-pot and multistep oligosaccharide synthesis.

2.1.6 Glycosyl acceptor

The reactivity of the acceptor is based largely on the nucleophilicity of the alcohol in *O*-glycosylation. In the case of an alcohol acceptor, a primary alcohol is generally more nucleophilic than a secondary alcohol. Alcohols in the equatorial position are more reactive than alcohols in the axial position, which is important to consider since protecting groups can change the conformation of the ring between $^4C_1$ and $^1C_4$ (Figure 2.3) changing the spatial orientation of the alcohol. Carbohydrate acceptors with sterically demanding protecting groups also have diminished nucleophilicity. Finally, Electron withdrawing protecting groups lower the overall reactivity of the acceptor.[9]

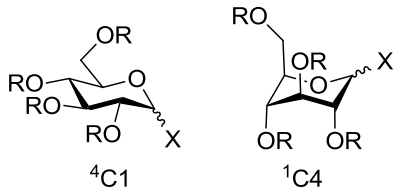
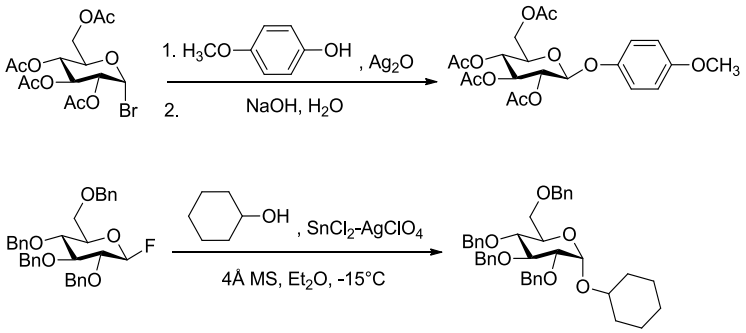


Figure 2.3 $^4C_1$ and $^1C_4$ chair conformations

2.2 Glycosylation Methods

2.2.1 Koenigs-Knorr and Glycosyl Fluorides

Glycosylation method development has been ongoing for over a century and has seen significant progress. One of the earliest methods that is still used today is the Koenigs-Knorr method.[10] The reaction is performed with glycosyl chloride and bromide donors which are activated with a halophilic Lewis acid (usually a silver or mercury salt). The activated donors then undergo a S_N2 reaction with a nucleophile (alcohol) to give an *O*-glycosidic linkage. While often useful, the Koenigs-Knorr reaction suffers from multiple disadvantages such as instability of glycosyl halides (resulting in short shelf life) and the use of stoichiometric quantities of toxic mercury and silver salts to promote the reaction.[11] The issue of instability of glycosyl halides was somewhat resolved in 1981 when Mukaiyama introduced a Lewis acid catalyzed *O*-glycosylation using glycosyl fluorides as donors (Scheme 2.6).[10,11] The stability of the carbon-fluorine bond is



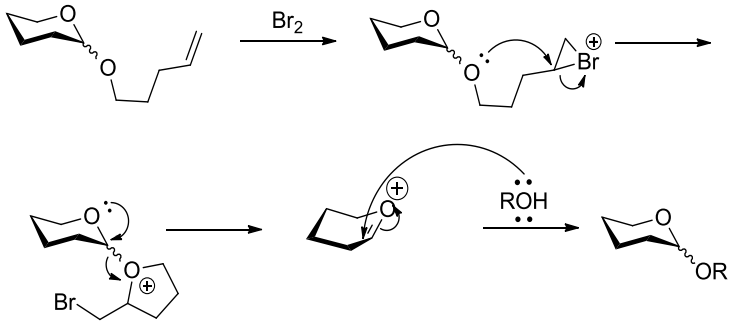
Scheme 2.6 Koenigs-Knorr and Glycosyl Fluoride Examples

the reason for the increased stability of the molecule. While the stability was a welcome

improvement, the overall reactivity of the glycosyl fluorides is significantly hampered relative to the other glycosyl halides.[10,11]

2.2.2 *n*-pentenyl glycosides

The use of n-pentenyl glycosides as glycosyl donors, pioneered by Frasier-Reid, was first reported in 1988 (Scheme 2.7). This involved glycosyl donor with an *n*-pentenyl chain which could



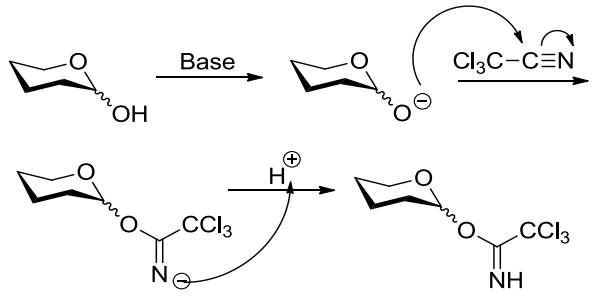
Scheme 2.7 *n*-pentenyl glycoside-based glycosylation mechanism

be activated in the presence of a halonium ion source.[12] Upon activation by the halonium ion, the lone pair of electrons on the anomeric oxygen atom cyclize resulting in a positively charged heterocyclic ring. The ring could then be displaced by the lone pair of electrons on pyran oxygen to produce an oxacarbenium ion intermediate which can then be intercepted by a glycosyl acceptor. The stability of these glycosyl donors allows them to be used in a wide variety of reaction conditions. This stability, however, is also a hindrance to this method which requires the use of harsh reagents like molecular bromine for activation.[13]

2.2.3 Trichloroacetimidates

Another approach for glycosylation first reported in the 1980s by Schmidt was the use of trichloroacetimidates as glycosyl donors. Trichloroacetimidates are activated under mild acidic conditions and are easily generated by treating hemiacetalic sugars with trichloroacetonitrile in the presence of base (Scheme 2.8).[14] Trichloroacetimidates are excellent leaving groups and can lead

to the selective formation of either *alpha* or *beta* glycosidic linkages depending on the reaction.

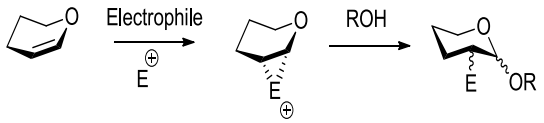


Scheme 2.8 Mechanism of Anomeric O-Alkylation.[14,15]

The mild activation conditions for trichloroacetimidates has resulted in their widespread use. However activation conditions limits the orthogonality of these glycosyl donors.

2.2.4 Glycals

The use of glycals as glycosyl donors to perform glycosylations was popularized by Danishefsky.[16,17] Glycals can be activated by electrophilic addition onto the alkene to give a reactive three membered onium or epoxide intermediate which can then be attacked by a glycosyl donor providing the glycosidic linkage (Scheme 2.9). This method has seen extensive use in the



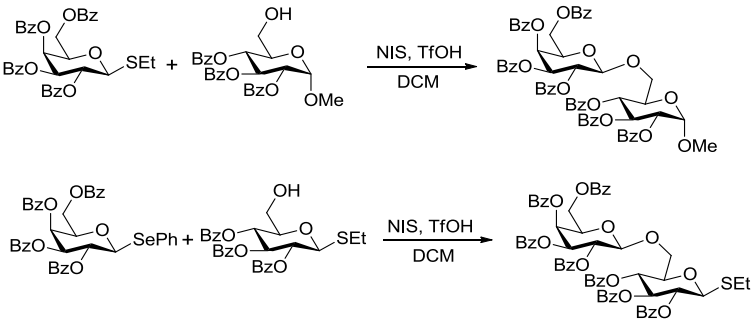
Scheme 2.9 Glycosylation with Glycals

area of stereoselective synthesis of *O*-glycosides. The harsh reaction conditions sometimes required to activate glycals limit their use in some cases.[18]

2.2.5 Chalcogenoglycosides

Chalcogenoglycosides (seleno and thioglycosides) are highly stable glycosyl donors first championed by Ferrier, Nicolaou, Pinto, and others.[19,20,21,22] High stability is afforded with both thioglycosides and selenoglycosides. The low reactivity of the thioglycosides (and

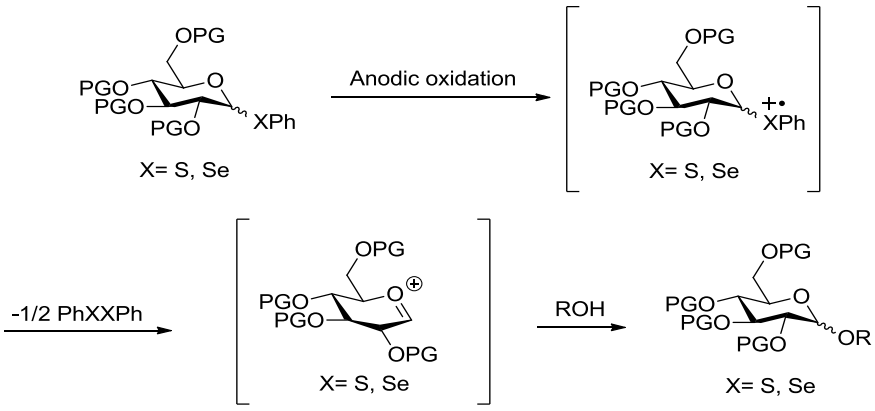
selenoglycosides) requires the use of harsh reaction conditions (toxic heavy metal ions or highly reactive and sensitive electrophiles) for their activation (Scheme 2.10).[23,24] Once these donors are



Scheme 2.10 Chalcogenoglycosides as glycosyl donors

activated, the sulfonium/selenonium ions are expelled by the lone pair of electrons on the anomeric oxygen to give the oxacarbenium ion intermediate which is then attacked by a glycosyl acceptor to give the glycosidic linkage. While the high stability of the glycosyl donors makes them appealing for multistep synthesis, the harsh conditions and highly reactive reagents required to activate them is a major concern.

An alternative route to activating chalcogenoglycosides without the use of harsh reagents is via electrochemical activation (Scheme 2.11).[25] The glycosyl donor is activated when an anode oxidizes the sulfur or selenium ion (by SET) resulting in sulfur or selenium radical cation. This



Scheme 2.11 Electrochemical glycosylation

radical cation then undergoes rapid irreversible fragmentation to give the oxacarbenium ion which then intercepts a glycosyl donor providing the glycosidic linkage.[25] This method avoids the harsh reagents used in the chemical activation of these glycosyl donors but requires specialized equipment to perform the reactions.

While this discussion is not comprehensive, it highlights some of the major issues facing the field. Solutions to some of these issues may be accomplished by taking advantage of the elimination of harsh reagents (e.g. with the electrochemical activation of chalcogenoglycosides) with the added benefit of avoiding specialized equipment. We identified visible light photochemistry as a potentially viable route to accomplishing these goals.

2.3 Visible Light Photoredox Catalysis

The utility of visible light photoredox catalysis in solving long standing organic problems was first realized by Macmillan, Yoon, Stephenson, Sanford and several others who popularized the field.[26,27,28,29,30] The ability of excited state photocatalyst to undergo single electron transfers (SET) with organic substrates gives visible light photoredox catalysis exceptional versatility in accessing radical and radical ionic intermediates. The chemistry of these intermediates, in turn, has remarkable versatility. Tris(2,2'-bipyridine) ruthenium (II) ($Ru(bpy)_3^{2+}$, (Figure 2.4) is a

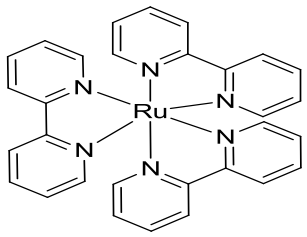


Figure 2.4 $Ru(bpy)_3^{2+}$

commonly used photocatalyst. This catalyst is promoted from its singlet ground state to its triplet Quenching Cycle excited state via absorption of a photon from a light source (*e.g.* blue LEDs λ_{max}=455nm). The resulting transfer of an electron from a molecular orbital with metal like

character to the π* orbital with ligand character is a process called metal to ligand charge transfer (MTLCT) .[31,32,33] Once in its excited state, the utility of this photocatalyst can be fully realized. It can serve dual roles as either a reducing agent ($E_{1/2}^{III/II*}$= −0.81 V vs. the saturated calomel electrode (SCE) compared to the ground state $E_{1/2}^{III/II}$ = +1.29V vs. SCE) or oxidizing agent ($E_{1/2}^{II*/I}$ = +0.77 V vs. SCE compared to $E_{1/2}^{II/I}$= −1.33 V vs. SCE) depending on the reagents that are present.[33,34] This remarkable property of $Ru(bpy)_3^{2+}$ allows it to operate under a reductive or oxidative manifold (Figure 2.5).[35] This duality of the photocatalyst gives access to bond formations

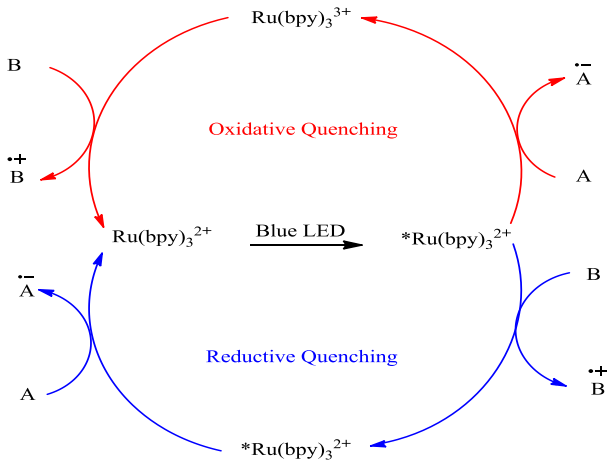


Figure 2.5 $Ru(bpy)_3^{2+}$ quenching cycle

that have been unattainable under previous methods.[35] In addition to novel bond formations, visible light photocatalysis can provide more efficient and environmentally friendly reaction methods.

2.4 Results and Discussion

Electrochemical glycosylation, as stated earlier, is a method for forming *O*-glycosidic linkages that avoids harsh reagents but requires a complicated experimental setup. The reactive intermediate formed in this electrochemical process is a selenium centered radical cation that then rapidly fragments to give an oxacarbenium ion that can then be intercepted by a glycosyl acceptor.[25] We hypothesized that the same reactive selenium radical cation intermediate can be

obtained via visible light photoredox catalysis using $Ru(bpy)_3^{2+}$. Our initial hypothesis for the reaction as seen in Figure 2.6 shows the photocatalyst being promoted to its excited state via

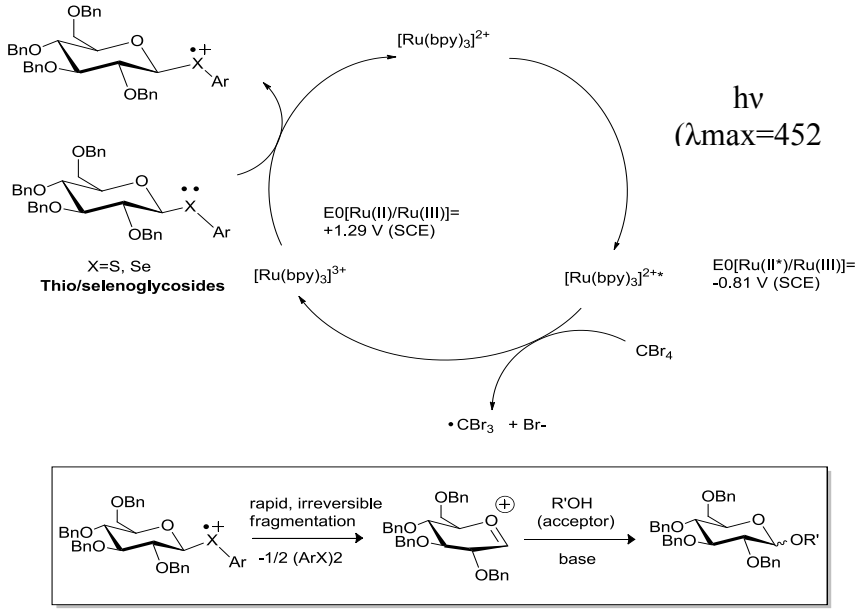
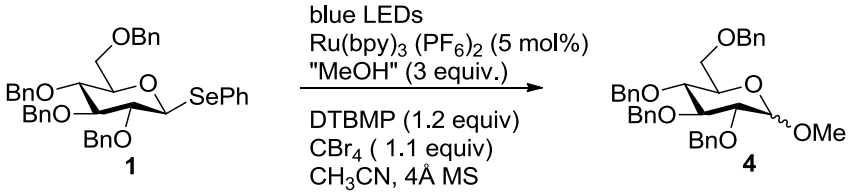


Figure 2.6 Proposed $Ru(bpy)_3^{2+}$ catalyzed visible light glycosylation

irradiation at 455nm. The excited photocatalyst then undergoes a single electron transfer to CBr_4 to provide a $Ru(bpy)_3^{3+}$ complex that can then oxidize th e selenium to provide the selenium radical cation. The initial test of this hypothesis (Scheme 2.12) was performed by irradiating a 5 mL Pyrex



Scheme 2.12 Initial test of hypothesis

reactor vial charged with **1** with Blue LEDs in the presence of 5 mol % $Ru(bpy)_3(PF_6)_2$, 1.1 equiv of the electron acceptor tetrabromomethane, and 1.2 equiv of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) as base and 3 equiv MeOH in CH_3CN resulted in complete consumption of **1** and a 75% yield of glycosylation product 4 (2.5:1 α/β) after 5 h of irradiation. Several glycosidic products

were synthesized under the same reaction conditions using the selenoglycoside donors and alcohol acceptors shown in Figure 2.7 in moderate to good yields and low selectivity.[36] In the process of

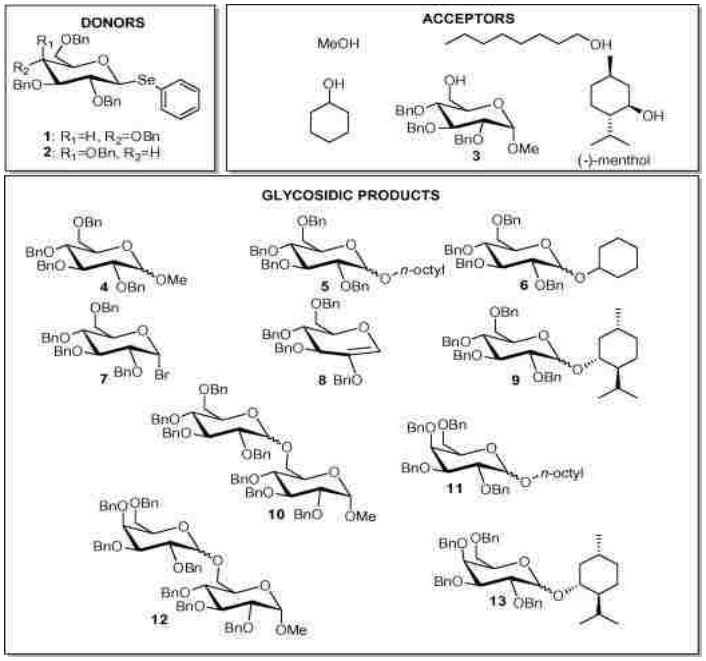
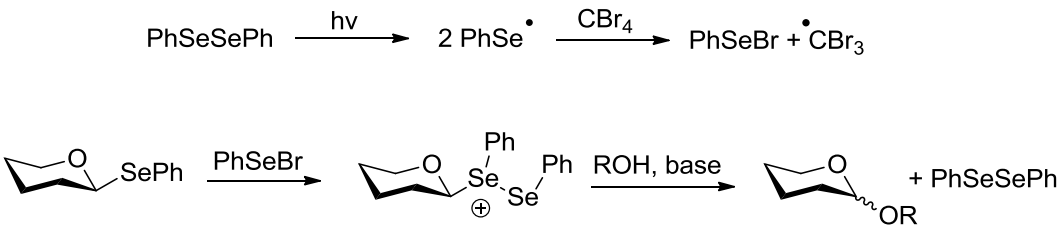


Figure 2.7 Glycosyl donors, acceptors, and glycosidic products

developing this reaction, an interesting control was performed wherein no catalyst was used. The control provided product in 30% yield although a long induction period was observed before the control provided product in 30% yield although a long inductio n period was observed before the reaction proceeded. This long induction period suggested the buildup of a species that was promoting the reaction. A common byproduct seen, whether or not the reaction is run in the presence of photocatalyst, is diphenyldiselenide, indicating that it may be important for reactivity. In an attempt to identify the species in question ^{77}Se NMR studies were performed. The presence of PhSeBr in the ^{77}Se NMR led to further mechanistic insight.

These observations led to our use of diphenyldiselenide as a promoter to accomplish glycosylation). The reactions were performed in a similar fashion to the experiments performed with $Ru(bpy)_3^{2+}$, using 5 mL Pyrex reactor vials charged with 10 mol% diphenyldiselenide, 1 equiv

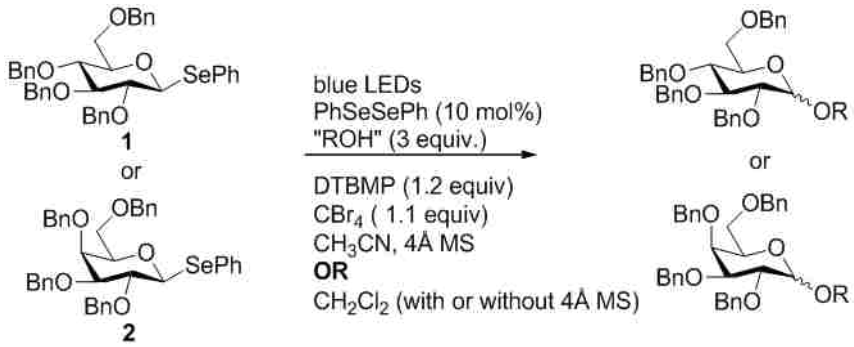
of selenoglycoside donor, 3 equiv of alcohol acceptor, 1.1 equiv CBr_4 and 1.2 equiv of DTBMP in 2 mL of solvent with blue LED irraditation.[37-41] While diphenyldiselenide gives the same product with similar reactivity and yield, the mechanism by which the reaction proceeds is obviously different (Scheme 2.13). Diphenyldiselenide undergoes Se-Se bond homolysis upon



Scheme 2.13 Proposed diphenyldiselenide promoted glycosylation pathway

irradiation with visible light to give two phenylselenyl radicals, that can then attack CBr_4 to give phenylselenyl bromide (identified in ^{77}Se NMR) and tribromomethyl radical.[16] The Selenoglycoside donor could then attack the phenylselenyl bromide to provide an onium ion that could be easily expelled following attack by the glycosyl donor via an S_N2-like exploded transition state to yield product. The feasibility of the phenylselenyl radical to abstract a bromine from CBr_4 was of concern and was studied using Gaussian 2009 calculations (6-311G** basis set). The calculations indicated a favorable process by (-9.3Kcal/mol).[42]

As shown in Figure 2.8 a variety of glycosyl products were synthesized using diphenyldiselenide as a promoter. The yields and selectivity for the reaction when performed in acetonitrile, where comparable to the $Ru(bpy)_3^{2+}$-promoted reaction. However, when the reactions were performed in DCM the yields (with the exception of 10) and selectivity improved although



Entry (α/β)	Donor	"ROH" (3 equiv)	Solvent	Irradiation time	Product yield (%)	Anomeric ratio
1	1	Cyclohexanol	CH_3CN, 4ÅMS	5 h	**6**, 65	1.5:1
2	1	(-)-Menthol	CH_3CN, 4ÅMS	10 h	**9**, 57	4:1
3	1	3	CH_3CN, 4ÅMS	8 h	**10**, 33	2:1
4	2	1-Octanol	CH_3CN, 4ÅMS	6.5 h	**11**, 65	2:1
5	2	3	CH_3CN, 4ÅMS	10.5 h	**12**, 50	3:1
6	1	1-Octanol	CH_3CN, 4ÅMS	3 days	**5**, 0	n/a
7	1	1-Octanol	CH_2Cl_2, 4ÅMS	36 h	**5**, 53	20:1
8	1	1-Octanol	CH_2Cl_2	12 h	**5**, 72	8:1
9	1	Cyclohexanol	CH_2Cl_2	12 h	**6**, 71	6:1
10	1	(-)-Menthol	CH_2Cl_2	50 h	**9**, 66	10:1
11	1	3	CH_2Cl_2	76 h	**10**, 20	4:1
12	2	1-Octanol	CH_2Cl_2	21 h	**11**, 71	4:1
13	2	(-)-Menthol	CH_2Cl_2	39 h	**13**, 55	8:1
14	2	3	CH_2Cl_2	70 h	**12**, 49	5.5:1

Figure 2.8 Diphenyldiselenide promoted glycosylations

long reaction times of up to 3 days (for disaccharide formation) were observed. The higher selectivities seen when using DCM can be attributed to the inhibition of ionic pathways commonly seen when acetonitrile is used as solvent (nitrile effect).

I have demonstrated that visible light promoted glycosylation with the promoter diphenyldiselenide is a mild and efficient method for performing *O*-glycosylations of alcohols with selenoglycoside donors in comparable yield and selectivity to the $Ru(bpy)_3^{2+}$ promoted reactions. The long induction period seen in the absence of promoter suggest that the diphenyl diselenide being built up in the reaction is actually performing the glycosylation and $Ru(bpy)_3^{2+}$ is acting only as a promoter in the formation of diphenyl diselenide. The originally proposed mechanism for the $Ru(bpy)_3^{2+}$ catalyzed reactions is, at best, a minor pathway. The PhSeSePh-promoted method provides multiple advantages over traditional glycosylation methods in being cost effective, using exceptionally mild reaction conditions and providing moderate selectivity for the *alpha* anomer especially when DCM is utilized as solvent. Diphenyldiselenide provides a much cheaper alternative to $Ru(bpy)_3(PF_6)_2$ ($4/g and $111/g, respectively) However, the overall reactivity of the reaction in DCM (at times taking days to complete) leaves room for improvement.

In an attempt to improve the reactivity of the system while maintaining the selectivity seen when using DCM as solvent, several components of the reaction were studied. The first of these components was the $Ru(bpy)_3^{2+}$ counteranion. In order to obtain the reactivity seen when running these glycosylations using $Ru(bpy)_3(PF_6)_2$ in CH_3CN the weakly coordinating BArF anion was used in place of the PF_6 anion to engender solubility in DCM (Figure 2.9).[43] Attempts to Increase the reactivity of the glycosyl donor were also made. We synthesized three new selenoglycoside donors: 4-methoxyphenylselenyl-2,3,4,6-tetra-*O*-benzyl glucopyranoside (14), 2,4-dimethoxyphenylselenyl-2,3,4,6-tetra-*O*-benzyl glucopyranoside (15), and 4-

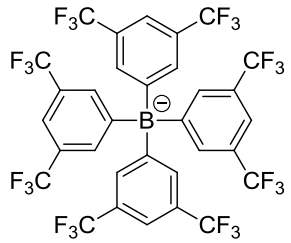


Figure 2.9 BArF anion

dimethylaminophenylselenyl-2,3,4,6-tetra-*O*-benzyl glucoside (16, Figure 2.10).[37-41,44] The electron donating groups on the phenylselenyl ring lower the redox potential. We proposed that this would allow the selenium center to undergo oxidation at a faster rate, improving the overall rate of the reaction.[37-41,44] To examine if these changes would improve the reactivity of the system,

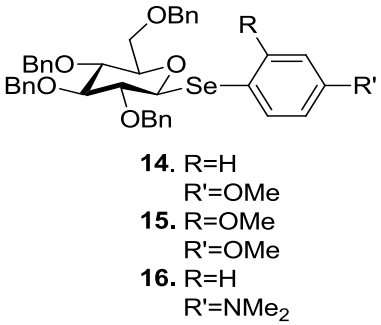
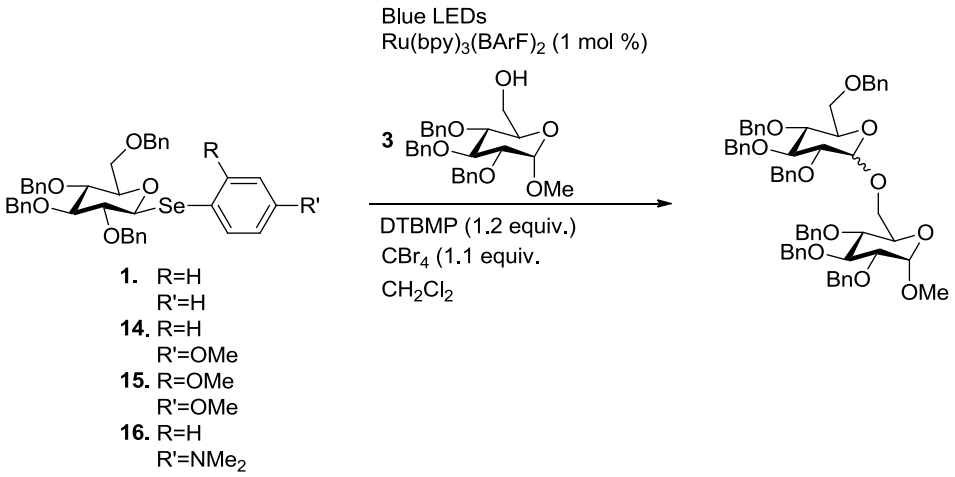


Figure 2.10 Glycosyl donors

I used the original and new selenoglycoside donors and the soluble ruthenium catalyst in conjuction with the least reactive acceptor 3 from th e previous work under similar reaction conditions (Figure 2.11). The reactions were performed in 5 mL Pyrex reactor vials charged with 1 mol % of catalyst, 1 equiv. of selenoglycoside donor, 3 equiv. of acceptor, 1.1 equiv. of CBr_4 and 1.2 equiv. of DTBMP in 2 ml of DCM and irradiated with blue LEDs.

Neither the catalyst nor the more reactive donors improved the overall reactivity of the system since long reaction times were still required (Entries 1-4). However, the conditions did provide a significant increase in yield and selectivity of the glycosylation. The improvement in

selectivity and yield was a welcome improvement, but the issue of low reactivity needed to be addressed.

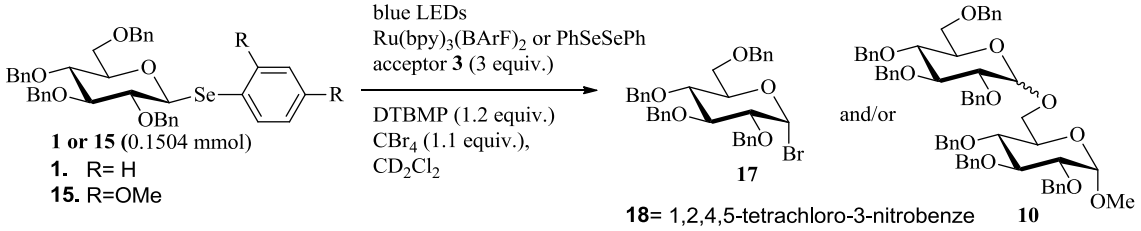


Entry	Donor	Acceptor	Solvent	Irradiation time	Yield %	Anomeric ratio (α:β)
1	1	3	CH_2Cl_2	60 h	57	5.5:1
2	14	3	CH_2Cl_2	60 h	56	5:1
3	15	3	CH_2Cl_2	60 h	78	5.5:1
4	16	3	CH_2Cl_2	60 h	74	4.5:1

Figure 2.11 Glycosylations with $Ru(bpy)_3(BArF)_2$

Having observed no improvement in reactivity using the soluble ruthenium catalyst in DCM, the possibility of catalyst decomposition over the course of the reaction was of concern. Exploring this possibility, I set up a series of small scale NMR experiments where the glycosylation was performed using the soluble ruthenium catalyst in CD_2Cl_2 in NMR tubes so that the reaction progress could be observed over time (Figure 2.12). The experiments revealed that, over the course of the reaction (3 days), the selenoglycoside starting material had not been fully consumed in the presence of 1 mol % $Ru(bpy)_3(BArF)_2$ and 3 equiv of glycosyl acceptor 3. Decomposition of the catalyst was not a factor as the catalyst could be observed in the ^1H NMR throughout the course of the reaction. However, another species that I identified as α-bromoglucoside 17 was present in small quantities (Entry 1). Identifying α-bromoglucoside as a likely intermediate in route to formation of the glycosyl product, I hypothesized that increasing

the rate at which this intermediate could react would increase the overall rate of the reaction.[45] performing the same NMR experiments with one equivalent of tetra-*n*-butylammonium bromide (TBABr), a species known to increase the rate of glycosylation with glycosyl bromide donors, provided complete consumption of the selenoglycoside starting material after three days (Entry 2), suggesting halide ion catalysis as a viable route to improving the rate of glycosylation.



Entry	Promoter	Donor	Acceptor	Additive	Comments
1	$Ru(bpy)_3(BArF)_2$ (5 mol%)	1	3	none	-incomplete consumption of 1 during irradiation period of 3 days; small quantities of 17 observed throughout irradiation period
2	$Ru(bpy)_3(BArF)_2$ (5 mol%)	1	3	1 equiv. TBABr	-complete consumption of 1 observed on the third day;small quantities of 17 observed throughout irradiation period
3	$Ru(bpy)_3(BArF)_2$ (5 mol%)	1	3	none	-complete consumption of 1 observed after 26 h in the absence of 3; signals from 17 replaced those of 1; 3 equiv. of 3 were then added and 17 was consumed in < 22h
4	$Ru(bpy)_3(BArF)_2$ (5 mol%)	1	3	1 equiv. TBABr	-complete consumption of 1 observed in < 5 h; signals from 17 replaced those of 1; 3 equiv. of 3 were then added and 17 was consumed in < 16 h
5	$Ru(bpy)_3(BArF)_2$ (5 mol%)	15	none	1 equiv. TBABr	-complete consumption of 15 observed in < 6 h; signals from 17 replaced those of 15
6	$Ru(bpy)_3(BArF)_2$ (5 mol%)	1	none	18 as internal std., 1 equiv. TBABr	-complete consumption of 1 observed in < 6 h; ~ 99 % yield of 17 based on internal standard
7	PhSeSePh (10 mol%)	1	none	18 as internal std., 1 equiv. TBABr	-complete consumption of 1 observed in < 6 h; ~ 99 % yield of 17 based on internal standard

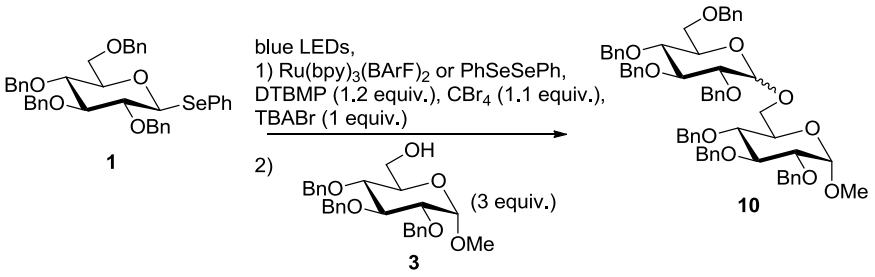
Figure 2.12 NMR experiments in CD_2Cl_2

To see how efficient the process of forming the α-bromoglucoside from the selenoglycoside starting material was, I decided to observe the formation of the α-bromoglucoside (17) in the absence of TBABr and glycosyl acceptor (Entry 3). Unexpectedly, I observed the complete conversion of the selenoglycoside starting material to the α-bromoglucoside via NMR in less than 26 hours. The addition of one equivalent of TBABr shortened this process to just under 5 hrs (Entry 4). These experiments show that the formation of α-bromoglucoside is quite efficient in the absence of acceptor. However, the rate at which the (17) is attacked still needed further investigation. This to a two-step process in which the α-bromoglucoside was generated first followed by addition of three equivalents of glycosyl acceptor with and without the addition of TBABr, resulting in the consumption of α-bromoglucoside in 22 h and 16 h, respectively (Entries 3 and 4). The rate at which the glycosylation proceeded was significantly increased compared to the previous one pot procedure that took 3 days to perform (often resulting in incomplete consumption of the selenoglycoside starting material). This suggested that bulky glycosyl acceptors like 3 inhibit the conversion of the selenoglycoside donor to the α-bromoglucoside. The increase in reactivity observed when using TBABr suggest that a bromide ion catalysis mechanism is involved. The use of more electron rich donors such as 15 in this two-step procedure provided no advantage (Entry 5). Through the course of these experiments there was no evidence to suggest that decomposition of $(Ru(bpy)_3^{2+}$ was ever a factor in the glycosylation since it was always observed in the ^1H NMR.

In order to obtain a quantitative assessment of the efficiency of the conversion of selenoglycoside donor 1 to the α-bromoglucoside, NMR experiments using 1,2,4,5-tetrachloro-3-nitrobenzene 18 was used as an internal standard indicated that the conversion is near quantitative over the course of 6 h in the presence of $Ru(bpy)_3(BArF)_2$ (Entry 6). The use of 10 mol %

diphenyldiselenide also provides a near quantitative conversion in 6h (Entry 7). With the efficiency of each system being the same, the use of diphenyldiselenide is optimal since it is inexpensive and likely the species promoting the glycosylation in either case.

Encouraged by the NMR experiments suggesting a two-step approach to increase the reactivity of the glycosylation, a series of preparative experiments were performed to optimize this approach (Figure 2.13).



Entry	Promoter	Irradiation Time stage 1), stage 2)	Additive	Yield (%, isolated), selectivity
1	$Ru(bpy)_3(BArF)_2$, 5 mol%	7h, 18h	TBABr 1 equiv.	56%, 6:1 α/β
2	PhSeSePh, 10 mol%	7h, 18h	TBABr 1 equiv.	57%, 6.5:1 α/β
3	PhSeSePh, 10 mol%	6h, 18h	TBAI, 1 equiv., no TBABr	23%, 5:1 α/β
4[a]	PhSeSePh, 10 mol%	6h, 18h	TBAI, 1 equiv., no TBABr	NA, NA
5[b]	PhSeSePh, 10 mol%	6h, 18h	TBAI, 1 equiv., no TBABr	6%, 5:1 α/β
6	PhSeSePh, 10 mol%	6h, 16h	1 equiv. TBABr added in 2nd stage	60%, 7:1 α/β
7[c]	PhSeSePh, 10 mol%	6h, 18h	2 equiv. TBABr added in 2nd stage, (3 equiv. total)	83%, 7:1 α/β
[a] TBAI was added in the second stage, after glycosyl bromide formation; rxn was kept in the dark during the second stage [b] conditions are the same is in Entry 4 except that *N,N*-diisopropylamine replaced DTBMP [c] 0.5 equiv. of glycosyl acceptor **3** used				

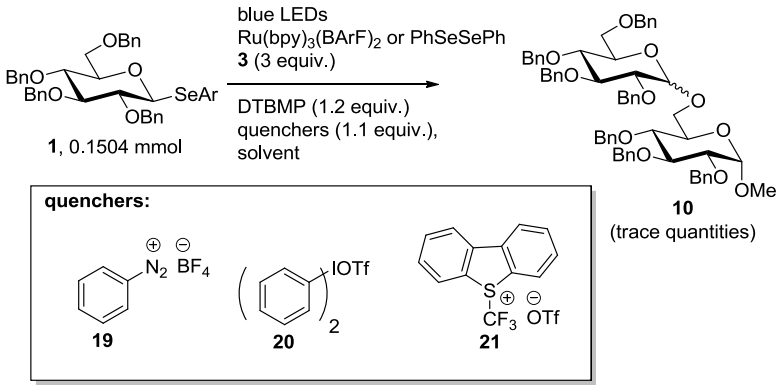
Figure 2.13 Optimization of two stage approach

The selenoglycoside donor 1 was irradiated with blue LEDs in the presence of $Ru(bpy)_3(BArF)_2$ or PhSeSePh, CBr_4, TBABr and DTBMP until glycosyl donor 1 was consumed by TLC. At this stage, the glycosyl acceptor 3 and any additives would be added to the reaction and irradiation

would continue until all bromoglucoside was consumed. The choice of $Ru(bpy)_3(BArF)_2$ vs PhSeSePh showed little difference in yield and selectivity (Entries 1 and 2) so the inexpensive PhSeSePh (which is likely the species promoting glycosylation regardless of promoter used)was used for further optimizations. The experiments required a day to complete, which is an improvement over the 3 day, one step protocol. The glycosylation experiment that I performed had used an excess of glycosyl acceptor (Entry 6) which led me to question if using the glycosyl donor in excess would be beneficial. This led to increased yield and selectivity for the reaction (Entry 7). Adding two equivalents of TBABr in the second stage of the reaction with the acceptor in excess did not increased the yield. In an attempt to further optimize this protocol, I decided to use one equivalent of tetrabutylammoniumiodide TBAI in the second stage of the reaction instead of TBABr (Entry 3). This change was made in to generate a glycosyl iodide intermediate which has been proven to have superior reactivity to the glycosyl bromides.[46] Unfortunately, all attempts at using TBAI in the second stage of the reaction provided inferior yield and selectivity. It is known that visible light can promote the decomposition of glycosyl iodides, so an experiment was conducted where light would be excluded from the second stage of the reaction (Entry 4).[47] The use of diisopropyl amine provided no advantage (entry 5). TBAI proved to be inferior to TBAB. These experiments revealed that using the glycosyl acceptor in excess while adding two additional equivalents of TBABr in the second stage of the reaction gave the optimal yields and selectivites.

The two step protocol improved the overall reactivity of the glycosylation but further improvement was still needed. In an effort to improve the reactivity, we explored the use of other oxidants than CBr_4 in the one step $Ru(bpy)_3^{2+}$ promoted reactions. By using the same one step protocol reaction conditions (Scheme 2.12) with oxidants containing weakly coordinating anions like arenediazonium tetrafluroborate 19, diaryliodonium salt 20 and Umemoto's reagent (21

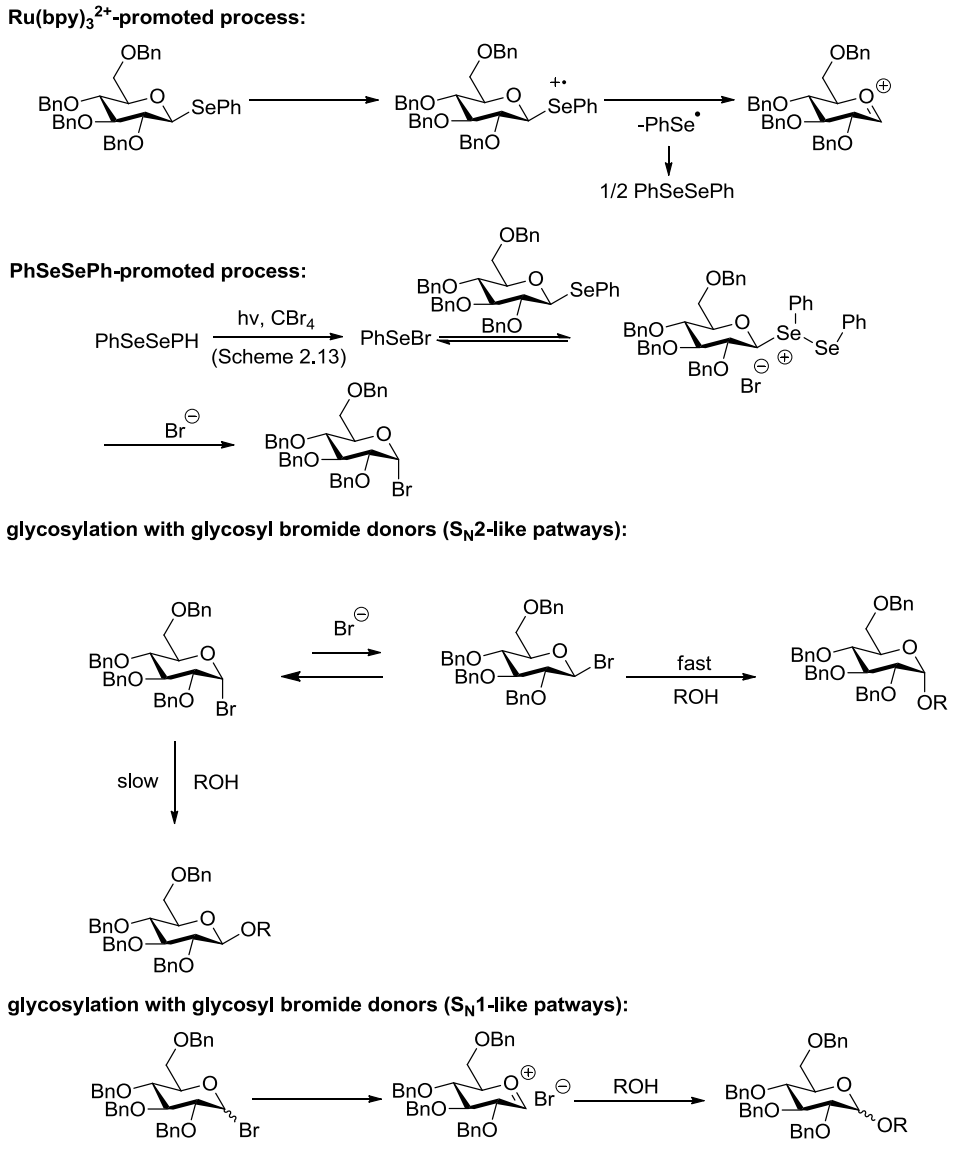
commercially available), I hoped to avoid slow reacting intermediates like the glycosyl bromide and form the oxacarbenium ion from the unstable selenium radical cations that were shown in the original proposed glycosylation (Scheme 2.14).[48] None of the oxidants provided isolatable



Scheme 2.14 Screening of alternative oxidative quenchers to CBr_4

quantities of glycosidic product while small quantities were seen in ^1H NMR spectra. This showed $Ru(bpy)_3^{2+*}$ does not play a significant role in promoting glycosylation through the proposed SET process depicted in Figure 2.6. Our previously reported $Ru(bpy)_3^{2+}$-promoted reaction involving CBr_4 may just be involved in the efficient formation of an initial amount of PhSeSePh that actually promotes the reaction. This hypothesis is supported by the long induction periods for glycosidic product formation that we often witnessed in our previous protocol.

In accordance with the data obtained and previously reported in the literature, we proposed a mechanism (Scheme 2.15) in which $Ru(bpy)_3^{2+}$ acts as an inefficent promoter for the formation of PhSeSePh, which could also be added purposely. Diphenyldiselenide undergoes Se-Se bond homolysis generating two phenylselenyl radicals that can abstract a bromine from CBr_4 resulting in PhSeBr (seen in ^{77}Se NMR) and tribromomethyl radical. Selenoglycoside donor then attacks the PhSeBr to generate an onium intermediate which is either displaced by a bromide anion providing the α-bromoglycoside intermediate and PhSeSePh or loses PhSeSePh to form the



Scheme 2.15 Revised mechanism

oxacarbenium ion and PhSeSePh which further promotes glycosylation. The glycosidic product is then formed when glycosyl acceptor attacks either the α-bromoglycoside or β-bromoglycoside which are in equilibrium, Inter conversion of these stereoisomers is facilitated by bromide anion. The selectivity for the α-anomer is due to fast reaction of acceptor with β-bromoglycoside, which is considerably more reactive than the α-bromoglycoside. The kinetics of the reaction favor the formation of α-glycosides.

It was shown that sterically demanding alcohols like glycosyl acceptor 3 inhibits the glycosylation, while addition of bromide added in the form of TBABr increases the rate. Glycosyl acceptor 3 slows the rate glycosylation by inhibiting the formation of 17. The increase in rate exhibited when using TBABr is attributed to the promotion of the key glycosyl bromide intermediate (17). The ^{1}H NMR experiment where selenoglycoside was irradiated with 3 equivalents of glycosyl acceptor 3 over the course of three days showed small quantities of α-bromoglycoside which suggest that glycosyl bromide is formed slowly followed by fast glycosylation in the presence of 3. Reaction with the α-bromoglycoside could proceed in several ways, one being an S_N2-like pathway which would give the minor β-glycoside. Another reaction route leading to both β and α-glycoside formation is via ionization to oxacarbenium ion followed by attack of a glycosyl acceptor. The low selectivities seen in CH_3CN may be attributed to ionization and nitrile attack on the oxacarbenium (nitrile effect) leading to β-glycoside formation.

It has been demonstrated by Lemieux and coworkers that halide ions catalyze reaction of α-bromoglycosides with alcohol acceptors, specifically by addition of bromide in the form of tetraethylammonium bromide.[45] The α selectivity observed in my glycosylation is attributed to the same phenomenon present in Lemieux's glycosylation. The stable and unreactive α-bromoglycosides generated in the reaction are in equilibrium with unstable but highly reactive β-bromoglycoside. The conversion between the two anomers can be facilitated by addition of bromide ions. The β-bromoglycoside, once formed, likely reacts rapidly with alcohol acceptor via a corresponding twist boat conformation (Figure 2.14) to form the α-glycoside. The observed alpha selectivity is a perfect example of the Curtin-Hammet principle wherein the unstable isomer in equilibrium with the more stable isomer proves to be the most reactive under kinetic conditions and determines product distribution.

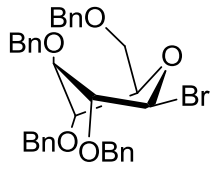


Figure 2.14 β-bromoglycoside twist boat conformation

2.5 Conclusions

I originally intended to develop a mild *O*-glycosylation method using visible light photoredox catalysis. The intial method using $Ru(bpy)_3(PF_6)_2$ in CH_3CN provided glycosylation products in reasonable yields and low selectivity. The SET process originally proposed in Figure 2.6, however, was shown to be, at best, a minor pathway in formation of glycosidic product and that the $Ru(bpy)_3(PF6)_2$ "catalyst" was simply promoting the buildup of PhSeSePh, which promotes the reaction. This was strongly supported by our inability to obtain isolable quantities of product when using other oxidants that would promote the originally proposed pathway and by obtaining similar reactivity and yields when using PhseSePh as promoter. The selectivity of the glycosylation was greatly improved when using DCM as solvent, however, the reactions took several days and often did not completely consume starting material when using glycosyl acceptor **3**. The low reactivity showed no signs of improvement by using a more soluble ruthenium catalyst or more electron rich selenoglycoside donors.

Several NMR studies gave insight suggesting that our glycosylations were proceeding via a glycosyl bromide intermediate and bulky glycosyl acceptors like acceptor **3** were inhibiting the formation of these intermediates. These findings led to a two-step protocol in which glycosyl bromide was formed first followed by glycosyl acceptor addition, which gave a significant improvement in yield and overall reaction rate of the glycosylation. Optimization of this protocol resulted in the use of glycosyl donor in excess rather than acceptor and the use of TBABr as a halide ion catalyst. The improvements provide the highest yields and selectivities that we have

observed for this glycosylation. Our studies also suggested that the glycosylation operated under a mechanistic pathway similar to the one initially proposed when using PhSeSePh as a promoter, except that the onium ion formed is displaced by bromide instead of glycosyl acceptor, giving the α-glycosyl bromide which is in equilibrium with the more reactive β-bromoglycoside (facilitated by TBABr) which is attacked by glycosyl acceptor (Scheme 2.14). The glycosyl bromide intermediates can be intercepted by a glycosyl acceptor to yield product. The selectivity for the *alpha* anomer is the result of halide ion catalysis. The experimental data demonstrate that the two step protocol using the donor in excess with TBABr provided a very mild glycosylation with good yields and selectivity. While this protocol is a significant improvement in the field of visible light promoted glycosylation, the overall reactivity needs further improvement.

2.6 Experimental and tabulated data

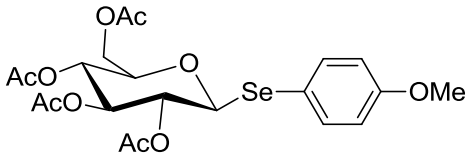
2.6.1 General methods

Tris(bipyridyl)ruthenium(II) bis(hexafluorophosphate) ($Ru(bpy)_3(PF6)_2$),[1] 1-phenylselenyl-2,3,4,6-tetra-*O*-benzyl glucopyranoside[2] and 1-phenylselenyl-2,3,4,6-tetra-*O*-benzyl galactopyranoside[3] were prepared as previously described. Flash column chromatography was performed using 60Å silica gel. ^{1}H NMR and ^{13}C NMR spectroscopy were performed on a Bruker AV-400, DPX 400, DPX 250 or Varian 500 spectrometer. Mass spectra were obtained using an Agilent 6210 electrospray time-of-flight mass spectrometer. Optical rotation measurements were obtained using a JASCO P-2000 polarimeter. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Analytical and preparative TLC were conducted on aluminum sheets (Merck, silica gel 60, F254). Compounds were visualized by UV absorption (254 nm) and staining with anisaldehyde. 5 mL Pyrex micro reaction vessels (Supelco) were used in the glycosylation reactions. All glassware

was flame-dried under vacuum and backfilled with dry nitrogen prior to use. Deuterated solvents were obtained from Cambridge Isotope Labs. All solvents were purified according to the method of Grubbs.[50]

2.6.2 Procedures and characterization

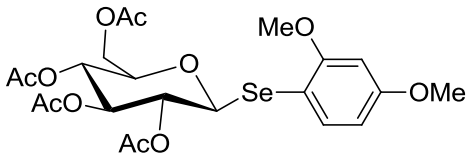
Representative procedure for the addition of phenyl selenides to 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide



To a suspension of 70.9 mg (2.92 mmol) magnesium in tertrahydrofuran 5 mL was added 0.37 mL (2.9 mmol) 4-bromoanisole dropwise. The suspension was then heated to reflux. Once all the magnesium dissolved 230.2 mg (2.916 mmol) selenium was added proportion wise to maintain a gentle reflux. Reflux was continued for 3 h before cooling to room temperature. The solution was then left open to air for 13 h. Ether 20 mL was then added and the solution was gravity filtrated followed by extraction 4× 10 mL ether. The resulting organic extracts dried over Na_2SO_4 and filtered to obtain a red oil after evaporation of the solvent. To a solution of the crude in 3 mL of ethanol was add sodium borohydride 91.9 mg (2.43 mmol) at 0°C giving a clear solution. The reaction was the warmed to room temperature and stirred for 30 min. The solution was then cooled back down to 0°C and 1.00 g (2.43 mmol) 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide was added. The solution was then warmed to room temperature and allowed to stir for 12 h. Water 4 mL was then added to quench the reaction. Upon cessation of effervescence, the aqueous layer was separated from the organic layer and then extracted with 3x10 mL Et_2O. The resulting organic extracts dried over Na_2SO_4 and filtered to obtain 1.2156 g of a pale yellow oil after evaporation of the solvent. Silica gel column chromatography (75 g silica gel, gradient run from 30% EtOAc in

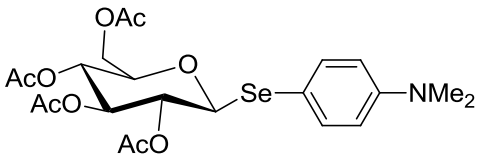
hexanes to 50% EtOAc) afforded 357.7 mg of 22 (28%) of a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.46 (d, *J* = 8.6 Hz, 2H), 6.77 (d, *J* = 8.8, 3.0 Hz, 2H), 5.11 (t, 1H), 4.98 – 4.81 (m, 2H), 4.72 (d, *J* = 10.1, 2.4 Hz, 1H), 4.11 (d, *J* = 3.6 Hz, 2H), 3.75 (d, *J* = 3.3 Hz, 3H), 3.61 (dt, *J* = 10.0, 3.5 Hz, 1H), 2.06 – 1.98 (m, 6H), 1.97 – 1.88 (m, 6H).

Synthesis of 23



Started with 354.7 mg (14.59 mmol) magnesium, 27 mL of tertrahydrofuran, 2.10 mL (14.6 mmol) 1-bromo-2,4-dimethoxybenzene, 1.152 g (14.59 mmol) selenium, 5.0 g (12.2 mmol) 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide, 460.0 mg (12.16 mmol) sodium borohydride, and 17 mL of ethanol. Purified to obtain 1.9698 g of 23 (30%) of a white solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.43 (d, 1H), 6.45 – 6.35 (m, 2H), 5.13 (t, J = 9.2 Hz, 1H), 4.96 (dt, J = 26.2, 9.4 Hz, 2H), 4.85 (d, J = 10.1 Hz, 1H), 4.15 (dd, J = 12.3, 4.9 Hz, 1H), 4.12 – 4.05 (m, 2H), 3.77 (s, 6H), 2.01 (s, 3H), 1.99 (s, 3H), 1.96 (s, 3H), 1.93 (s, 3H).

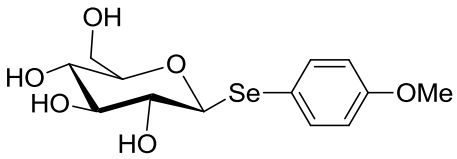
Synthesis of 24



Started with 354.7 mg (14.59 mmol) magnesium, 27 mL of tertrahydrofuran, 2.919 g (14.59 mmol), 4-bromo-N,N-dimethylaniline, 1.152 g (14.59 mmol) selenium, 5.0 g (12.2 mmol) 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide, 460.0 mg (12.16 mmol) sodium borohydride, and 17 mL of ethanol. Purified to obtain 1.2744 g of 24 (20%) of a pale yellow solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.39 (d, 2H), 6.57 (d, 2H), 5.11 (t, J = 9.3 Hz, 1H), 4.91 (dt, J = 23.8,

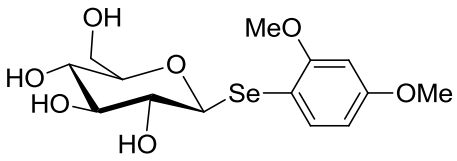
9.6 Hz, 2H), 4.68 (d, J = 10.0 Hz, 1H), 4.13 (d, J = 3.6 Hz, 2H), 3.60 (dt, J = 10.3, 3.6 Hz, 1H), 2.93 (s, 6H), 2.04 (s, 3H), 2.02 (s, 3H), 1.96 (s, 3H), 1.93 (s, 3H).

Representative procedure for Methanolysis



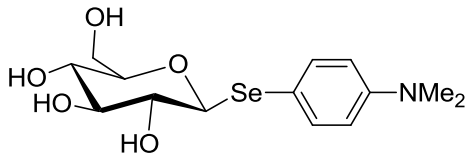
To a solution of 78.07 mg (1.509 mmol) 22 in methanol 19 mL was added 0.83 mL (0.83 mmol) 1M solution of sodium methoxide in methanol. The solution was stirred for 5 h at room temperature. Evaporation of the solvent gave a white solid that was dissolved in methanol, dried over Na_2SO_4 and filtered. Evaporation of the solvent gave 543.9 mg of (25) crude material that was used without further purification. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.56 (d, 2H), 6.79 (d, 2H), 4.67 (dd, J = 9.8, 1.5 Hz, 1H), 3.80 (dt, J = 13.9, 3.0 Hz, 1H), 3.71 (s, 3H), 3.68 – 3.60 (m, 2H), 3.38 – 3.32 (m, 1H), 3.28 – 3.15 (m, 3H).

Synthesis of 26



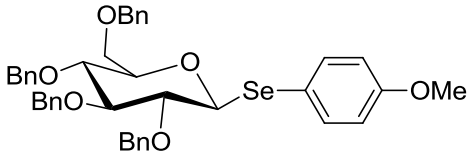
Started with 80.11 mg (1.462 mmol) 23, methanol 19 mL and 0.80 mL (0.80 mmol) 1 M solution of sodium methoxide in methanol. Worked up to obtain 627.9 mg of (26) crude material. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.48 (d, J = 8.4 Hz, 1H), 6.49 – 6.42 (m, 2H), 4.75 (d, J = 9.7 Hz, 1H), 3.76 (s, 3H), 3.75 – 3.68 (m, 4H), 3.62 (dd, J = 12.1, 4.7 Hz, 1H), 3.37 (t, 1H), 3.28 – 3.19 (m, 3H).

Synthesis of 27



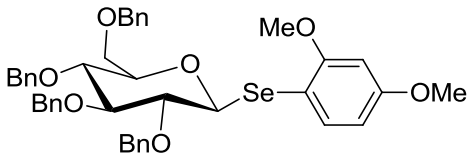
Started with 49.85 mg (0.9398 mmol) 24, methanol 12 mL and 0.52 mL (0.52 mmol) 1 M solution of sodium methoxide in methanol. Worked up to obtain 365.9 mg of (22) crude material. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.48 (d, 2H), 6.59 (d, 2H), 4.60 (d, J = 9.7 Hz, 1H), 3.80 (d, 1H), 3.66 (ddd, J = 18.6, 12.0, 5.0 Hz, 1H), 3.24 – 3.12 (m, 4H), 2.85 (s, 6H).

Representative procedure for benzylation



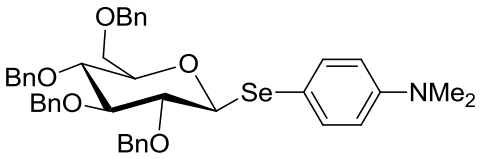
To a solution of 916.9 mg (22.93 mmol) sodium hydride in 7 mL of DMF at 0°C was added 976.1 mg (3.058 mmol) 20 in 11 mL of DMF. Benzyl bromide 2.50 mL (21.0 mmol) is was added dropwise and the solution was stirred for 13 h at room temperature. The solution was then cooled back to 0°C and 1.5 mL methanol was added to quench the reaction. The solution was then poured into 40 mL of H_2O and extracted 3× 20 mL ethyl acetate. The organic extracts where then washed with water and brine. The organic extract was then dried over Na_2SO_4, filtered and concentrated to give 1.4517 g of a pale yellow crude oil. Silica gel column chromatography (80 g silica gel, gradient run from 10% EtOAc in hexanes to 15% EtOAc) afforded 1.3526 g of (14) (62%) a pale yellow solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.60 (d, 2H), 7.40 (d, 3H), 7.35 (d, J = 4.5 Hz, 7H), 7.33 – 7.26 (m, 10H), 7.23 – 7.17 (m, 2H), 6.70 (d, 2H), 4.90 – 4.84 (m, 3H), 4.81 (d, J = 11.1 Hz, 2H), 4.74 (t, J = 10.1, 8.3 Hz, 2H), 4.64 – 4.56 (m, 3H), 3.74 (s, 3H), 3.70 – 3.58 (m, 3H), 3.50 – 3.40 (m, 2H).

Synthesis of 15



Started with 1.1301 g (28.265 mmol) sodium hydride, 10 mL of DMF, 1.4322 g (3.7686 mmol) 21 in 16 mL of DMF and 3.08 mL (25.9 mmol) benzyl bromide. Purified to obtain 1.5986 g of (15) (57%) a pale yellow solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.61 (d, J = 8.4 Hz, 1H), 7.44 – 7.39 (m, 2H), 7.37 (d, J = 4.4 Hz, 1H), 7.35 – 7.23 (m, 16H), 7.21 (d, J = 2.4 Hz, 1H), 6.41 (d, J = 2.6 Hz, 1H), 6.27 (dd, J = 8.5, 2.6 Hz, 1H), 4.92 – 4.78 (m, 5H), 4.71 (d, J = 10.0 Hz, 1H), 4.63 – 4.43 (m, 3H), 3.76 (s, 3H), 3.73 (s, 3H), 3.69 – 3.59 (m, 3H), 3.53 (t, J = 9.8, 8.3 Hz, 1H), 3.50 – 3.43 (m, 1H).

Synthesis of 16

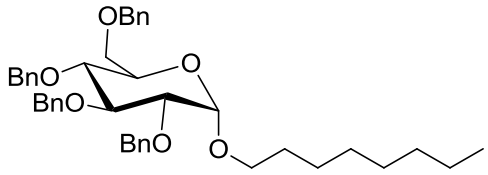


Started with 726.4 mg (18.27 mmol) sodium hydride, 6 mL of DMF, 877.6mg (2.4224 mmol) 22 in 10 mL of DMF and 1.98 mL (16.6 mmol) benzyl bromide. Purified to obtain 1.0209 g of (16) (58%) a pale yellow solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.54 (d, 2H), 7.46 – 7.40 (m, 2H), 7.40 – 7.22 (m, 16H), 7.20 (dd, J = 7.5, 2.2 Hz, 2H), 7.17 – 7.13 (m, 2H), 6.49 (d, 2H), 4.96 – 4.88 (m, 2H), 4.86 (d, J = 5.3 Hz, 1H), 4.81 (dd, J = 10.0, 3.2 Hz, 2H), 4.72 (t, J = 9.6 Hz, 2H), 4.65 – 4.57 (m, 1H), 4.53 (d, J = 11.9 Hz, 1H), 3.78 (t, J = 3.1 Hz, 3H), 3.71 – 3.56 (m, 1H), 3.49 – 3.40 (m, 2H), 2.90 (s, 6H).

General procedure for diphenyldiselenide catalyzed glycosylation

A flame dried 5 mL Pyrex reactor vial was charged with the glycosyl donor (1 equiv., 0.147 mmol), PhSeSePh (0.1 equiv., 0.015 mmol), CBr_4 (1.1 equiv., 0.165 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) (1.2 equiv., 0.180 mmol), the glycosyl acceptor (3 equiv., 0.450 mmol), 400 mg of freshly activated 4 Å molecular sieves and 2 mL of dry solvent (acetonitrile or CH_2Cl_2) under nitrogen atmosphere. The reactor vial was placed 1-2 cm away from the blue LEDs (2 strips, *vide supra* for details, were wrapped around a 250 mL beaker and irradiated from the side. Reaction progress was monitored by TLC. After consumption of the glycosyl donor, the reaction mixture was filtered through a silica gel pad to remove molecular sieves and the crude products were concentrated and then purified by silica gel chromatography.

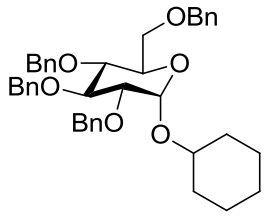
Synthesis of *n*-octyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside 5



Started with 102.2 mg (0.15 mmol) 1-phenylselenyl-2,3,4,6-tetra-*O*-benzyl glucopyranoside, 4.7 mg PhSeSePh (0.015 mmol), 54.7 mg CBr_4 (0.165 mmol), 37.0 mg 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) (0.180 mmol), 0.07 mL (0.450 mmol) 1-octanol in 2 mL of DCM. Purified to obtain 70.68 mg (72%) colorless oil in a 8:1 α:β mixture. Alpha anomer ^{1}H-NMR (250 MHz, $CDCl_3$) 0.88 (3H, t, *J*=6.8 Hz), 1.19-1.40 (10H, m), 1.53-1.67 (2H, m), 3.40 (1H, dt, *J*=9.9, 6.7 Hz), 3.55 (1H, dd, *J*=9.7, 3.5 Hz), 3.55-3.68 (3H, m), 3.72 (1H, m), 3.78 (1H, m), 3.99 (1H, t, *J*=9.2 Hz), 4.47 (2H, d, *J*=11.5 Hz), 4.61 (1H, d, *J*=12.2 Hz), 4.64 (1H, d, *J*=12.2 Hz), 4.76 (2H, m), 4.81 (1H, d, *J*=10.8 Hz), 4.83 (1H, d, *J*=10.8 Hz), 4.99 (1H, d, *J*=10.8 Hz), 7.06-7.18 (2H, m), 7.20-7.44 (18H, m); ^{13}C-NMR: (100 MHz, $CDCl_3$) 14.2, 22.8, 26.3, 29.4, 29.5, 29.5, 32.0, 68.4, 68.7, 70.4, 73.2, 73.6, 75.2, 75.8, 78.0, 80.3, 82.3, 97.0, 127.6, 127.8, 127.9, 128.0,

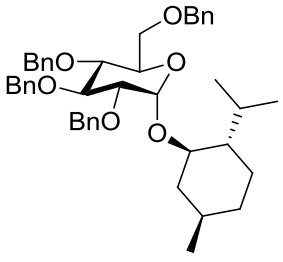
128.0, 128.1, 128.5, 128.5, 138.1, 138.4, 138.5, 139.1; HRMS *m/z* calcd for $C_{42}H_{52}NaO_6$ $(M+Na)^+$ 675.3656, found 675.3658; $[\alpha]_D^{25}$ = +38.6 (*c*= 0.46, DCM)

Synthesis of cyclohexyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside 6



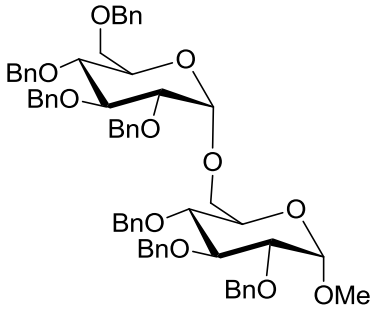
Started with 102.2 mg (0.15 mmol) 1-phenylselenyl-2,3,4,6-tetra-*O*-benzyl glucopyranoside, 4.7 mg PhSeSePh (0.015 mmol), 54.7 mg CBr_4 (0.165 mmol), 37.0 mg 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) (0.180 mmol), 0.046 mL (0.450 mmol) cyclohexanol in 2 mL of DCM. Purified to obtain 66.49 mg (71%) colorless oil in a 6:1 α:β mixture. Alpha anomer ^{1}H-NMR (400 MHz, $CDCl_3$) 1.12-1.57 (6H, m), 1.67-1.94 (4H, m), 3.55 (2H, m), 3.63 (2H, m), 3.73 (1H, dd, *J*=10.6, 3.7 Hz), 3.88 (1H, dd, *J*=10.0, 3.0 Hz), 4.00 (1H, t, *J*=9.3 Hz), 4.47, (2H, m), 4.61 (1H, d, *J*=12.2 Hz), 4.65 (1H, d, *J*=12.0 Hz), 4.73 (1H, d, J=12.0 Hz), 4.82 (2H, m), 4.95 (1H, d, *J*=2.8 Hz), 4.99 (1H, d, *J*=10.8 Hz), 7.09-7.18 (2H, m), 7.22-7.40 (18, m); ^{13}C-NMR (100 MHz, $CDCl_3$) 24.2, 24.4, 25.6, 31.4, 33.3, 68.6. 70.1, 73.0, 73.4, 75.1, 75.3, 75.6, 77.9, 80.0, 82.1, 94.7, 127.6, 127.8, 127.8, 127.9, 128.0, 128.1, 128.1, 128.2, 128.5, 128.5, 138.0, 138.3, 138.3, 139.0; HRMS *m/z* calcd for $C_{40}H_{46}NaO_6$ $(M+Na)^+$ 645.3187, found 645.3179; $[\alpha]_D^{25}$ = +52.7 (*c*= 0.63, DCM).

Synthesis of menthyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside 9



Started with 102.2 mg (0.15 mmol) 1-phenylselenyl-2,3,4,6-tetra-*O*-benzyl glucopyranoside, 4.7 mg PhSeSePh (0.015 mmol), 54.7 mg CBr_4 (0.165 mmol), 37.0 mg 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) (0.180 mmol), 70.3 mg (0.450 mmol) (-)-menthol in 2 mL of DCM. Purified to obtain 67.37 mg (66%) colorless oil in a 10:1 α:β mixture. Alpha anomer ^{1}H-NMR (400 MHz, $CDCl_3$) 0.70 (3H, d, *J*=6.9 Hz), 0.75-1.12 (9H, m), 1.20-1.40 (2H, m), 1.56-1.65 (2H, m), 2.13 (1H, d, *J*=12.0 Hz), 2.37-2.46 (1H, m), 3.35 (1H, dt, *J*=10.6, 4.3 Hz), 3.54 (1H, dd, *J*=9.8, 3.6 Hz), 3.58-3.69 (2H, m), 3.75 (1H, dd, *J*=10.5, 3.8 Hz), 3.92-3.98 (1H, m), 4.01 (1H, t, *J*=9.3 Hz), 4.46 (1H, d, *J*=10.8 Hz), 4.47 (1H, d, *J*=12.0 Hz), 4.61-4.73 (3H, m), 4.82 (1H, d, *J*=10.8 Hz), 4.83 (1H, d, *J*=10.8 Hz), 4.97 (1H, d, *J*=11.0 Hz), 5.02 (1H, d, *J*=3.6 Hz), 7.09-7.17 (2H, m), 7.21-7.37 (18H, m) ^{13}C-NMR (100 MHz, $CDCl_3$) 16.0, 21.1, 22.3, 23.1, 24.6, 31.7, 34.3, 43.0, 48.8, 68.7, 70.3, 73.2, 73.4, 75.0, 75.5, 78.1, 80.6, 81.0, 82.0, 98.6, 127.6, 127.6, 127.7, 128.0, 128.3, 128.4, 138.0, 138.3, 138.4, 138.9; HRMS *m/z* calcd for $C_{44}H_{54}NaO_6$ $(M+Na)^+$ 701.3813, found 701.3821; $[\alpha]_D^{25}$ = +92.5 (*c*= 0.25, CH_2Cl_2)

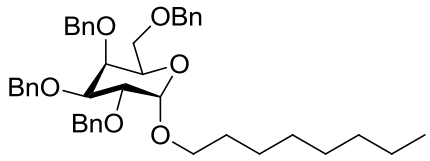
Synthesis of methyl-*O*-(2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside 10



Started with 102.2 mg (0.15 mmol) 1-phenylselenyl-2,3,4,6-tetra-*O*-benzyl glucopyranoside, 4.7 mg PhSeSePh (0.015 mmol), 54.7 mg CBr_4 (0.165 mmol), 37.0 mg 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) (0.180 mmol), 209.5 mg (0.450 mmol) glycosyl acceptor 3, 400mg 4Å MS in 2 mL of CH_3CN. Purified to obtain 49 mg (33%) colorless oil in a 2:1 α:β

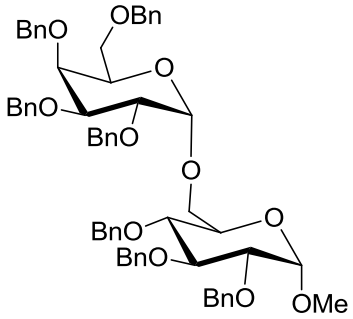
mixture. Alpha anomer ^{1}H-NMR (400 MHz, $CDCl_3$) 3.32 (3H, s), 3.40 (1H, dd, *J*=9.6, 3.6 Hz), 3.50 (2H, m), 3.58 (1H, t, *J*=9.0 Hz), 3.69-3.82 (3H, m), 3.87-3.99 (4H, m), 4.02 (1H, dd, *J*=9.3, 3.5 Hz), 4.36 (1H, d, *J*=11.8 Hz), 4.43 (1H, d, *J*=11.9 Hz), 4.51-4.60 (4H, m), 4.65-4.75 (4H, m), 4.75-4.82 (2H, m), 4.84 (1H, d, *J*=11.0 Hz), 4.93 (1H, d, *J*=11.5 Hz), 4.95 (1H, d, *J*=10.9 Hz), 4.99 (1H, d, *J*=3.6 Hz), 7.18-7.36 (35H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) 55.0, 66.4, 68.9, 69.4, 70.3, 72.5, 72.8, 73.3, 74.7, 75.0, 75.1, 75.7, 76.5, 77.2, 78.0, 78.3, 80.2, 82.1, 97.9, 97.9, 127.3, 127.4, 127.5, 127.6, 127.6, 127.7, 127.8, 127.9, 128.0, 128.2, 128.2, 128.2, 128.3, 128.3, 128.4, 128.4, 138.1, 138.2, 138.4, 138.7, 138.8, 138.9, 138.9; HRMS *m/z* calcd for $C_{62}H_{66}NaO_{11}$ $(M+Na)^+$ 1009.4497, found 1009.4490; $[\alpha]_D^{25}$ = +87.2 (*c*= 0.55, CH_2Cl_2).

Synthesis of *n*-octyl 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranoside 11



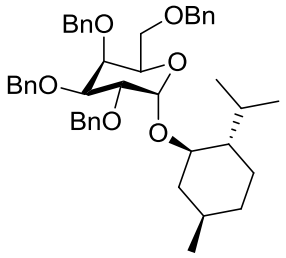
Started with 102.2 mg (0.15 mmol) 1-phenylselenyl-2,3,4,6-tetra-*O*-benzyl galactopyranoside, 4.7 mg PhSeSePh (0.015 mmol), 54.7 mg CBr_4 (0.165 mmol), 37.0 mg 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) (0.180 mmol), 0.07 mL (0.450 mmol) 1-octanol in 2 mL of DCM. Purified to obtain 66.48 mg (71%) colorless oil in a 4:1 α:β mixture. Alpha anomer ^{1}H-NMR (α-anomer, 400 MHz, $CDCl_3$) 0.88 (3H, m), 1.26 (10H, m), 1.62 (2H, m), 3.43 (1H, dt, *J*=9.9, 6.6 Hz), 3.48-3.66 (3H, m), 3.91-3.98 (3H, m), 4.03 (1H, dd, *J*=9.3, 3.6 Hz), 4.33-4.96 (9H, m), 7.20-7.40 (20H, m); ^{13}C-NMR (α-anomer, 100 MHz, $CDCl_3$) 14.1, 22.6, 26.2, 29.2, 29.4, 31.8, 68.2, 69.0, 69.2, 73.2, 73.4, 74.7, 75.1, 76.6, 79.1, 97.4, 127.4, 127.5, 127.6, 127.7, 127.7, 127.8, 127.9, 128.1, 128.1, 128.2, 128.2, 128.3, 128.3, 128.4, 138.0, 138.5, 138.7, 138.9; HRMS *m/z* calcd for $C_{42}H_{52}NaO_6$ $(M+Na)^+$ 675.3656, found 675.3660; $[\alpha]_D^{25}$ = +33.5 (*c*= 1.65, CH_2Cl_2)

Synthesis of methyl-*O*-(2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-galactopyranoside 12



Started with 102.2 mg (0.15 mmol) 1-phenylselenyl-2,3,4,6-tetra-*O*-benzyl galactopyranoside, 4.7 mg PhSeSePh (0.015 mmol), 54.7 mg CBr_4 (0.165 mmol), 37.0 mg 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) (0.180 mmol), 209.5 mg (0.450 mmol) glycosyl acceptor 3, in 2 mL of DCM. Purified to obtain 72.73 mg (49%) colorless oil in a 5.5:1 α:β mixture. Alpha anomer ^{1}H-NMR (400 MHz, $CDCl_3$) 3.29 (3H, s), 3.41 (1H, dd, *J*=9.6, 3.6 Hz), 3.46-3.55 (2H, m), 3.58 (1H, t, *J*=9.1 Hz), 3.63 (1H, m), 3.70-3.82 (3H, m), 3.88-4.00 (3H, m), 4.03 (1H, dd, *J*=9.5, 3.5 Hz), 4.36 (1H, d, *J*=11.8), 4.43 (1H, d, *J*=11.8 Hz), 4.52-4.61 (4H, m), 4.67-4.75 (4H, m), 4.77-4.82 (2H, m), 4.85 (1H, d, *J*=11.0 Hz), 4.93 (1H, d, *J*=11.2 Hz), 4.95 (1H, d, *J*=11.2 Hz), 4.99 (1H, d, *J*=3.6 Hz), 7.15-7.45 (35H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) 55.0, 66.4, 68.9, 69.7, 70.5, 72.5, 72.8, 73.3, 73.5, 74.7, 75.0, 75.1, 75.7, 76.5, 78.0, 78.2, 80.2, 82.1, 97.9, 97.9, 127.5, 127.6, 127.7, 127.8, 127.8, 127.8, 127.9, 128.1, 128.3, 128.4, 128.4, 128.5, 128.5, 138.0, 138.2, 138.4, 138.7, 138.8, 138.9; HRMS m/z calcd for $C_{62}H_{66}NaO_{11}$ $(M+Na)^+$ 1009.4497, found 1009.4490; $[\alpha]_D^{25}$ = +71.19 (*c*= 0.83, DCM).

Synthesis of Menthyl 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranoside 13



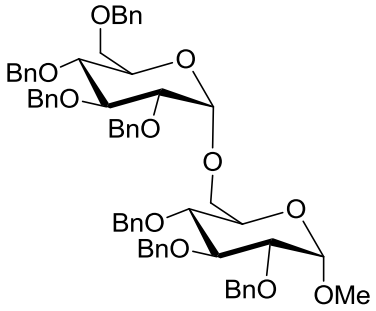
Started with 102.2 mg (0.15 mmol) 1-phenylselenyl-2,3,4,6-tetra-*O*-benzyl galactopyranoside, 4.7 mg PhSeSePh (0.015 mmol), 54.7 mg CBr_4 (0.165 mmol), 37.0 mg 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) (0.180 mmol), 70.3 mg (0.450 mmol) (-)-menthol in 2 mL of DCM. Purified to obtain 56.14 mg (55%) colorless oil in a 8:1 α:β mixture. Alpha anomer ^{1}H-NMR (500 MHz, $CDCl_3$) 0.69 (3H, *J*=6.9 Hz), 0.81 (3H, d, *J*=6.9 Hz), 0.82 (3H, d, *J*=6.0 Hz), 0.75-0.97 (2H, m), 1.02 (1H, q, *J*=12.0 Hz), 1.20-1.40 (2H, m), 1.53-1.63 (2H, m), 2.08 (1H, d, *J*=12.0 Hz), 2.41 (1H, m), 3.33 (1H, td, *J*=10.8, 4.5 Hz), 3.54 (2H, m), 3.96 (1H, dd, *J*=10.1, 2.8 Hz), 3.99 (1H, m), 4.02 (1H, dd, *J*=10.1, 3.7 Hz), 4.10 (1H, t, *J*=9.3 Hz), 4.42 (1H, d, *J*=11.9 Hz), 4.48 (1H, d, *J*=11.9 Hz), 4.57 (1H, d, *J*=11.5 Hz), 4.67 (1H, d, *J*=11.7 Hz), 4.74 (1H, d, *J*=11.8 Hz), 4.80 (1H, d, *J*=11.5 Hz), 4.81 (1H, d, *J*=12.0 Hz), 4.95 (1H, d, *J*=11.5 Hz), 5.02 (1H, d, *J*=3.7 Hz), 7.23-7.39 (20H, m); ^{13}C-NMR (125 MHz, $CDCl_3$) 16.0, 21.1, 22.3, 22.9, 24.5, 31.8, 34.3, 42.9, 48.9, 69.2, 69.3, 72.7, 73.4, 73.6, 74.7, 75.1, 79.3, 80.2, 99.3, 127.4, 127.5, 127.6, 127.7, 128.1, 128.3, 138.1, 138.8, 138.9; HRMS *m/z* calcd for $C_{44}H_{54}NaO_6$ $(M+Na)^+$ 701.3813, found 701.3832; $[\alpha]_D^{25}$ = +58.3 (*c*= 0.15, CH_2Cl_2)

General procedure for two diphenyldiselenide catalyzed glycosylation with TBAB additive

A flame dried 5 mL Pyrex reactor vial was charged with the glycosyl donor (1 equiv., 0.15-4 mmol), PhSeSePh (0.1 equiv., 0.015 mmol), CBr_4 (1.1 equiv., 0.165 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) (1.2 equiv., 0.180 mmol), TBAB (1 equiv., 0.150 mmol) and 400 mg

of freshly activated 4 Å molecular sieves and 2 mL of dry solvent of CH_2Cl_2 under nitrogen atmosphere. The reactor vial was placed 1-2 cm away from the blue LEDs (2 strips, *vide supra* for details, were wrapped around a 250 mL beaker and irradiated from the side for 6 hrs. The glycosyl acceptor (0.5 equiv., 0.0752 mmol) and TBAB (2 equiv., 0.301 mmol) was added and irradiation continued for 18 hrs Reaction progress was monitored by TLC. After consumption of the glycosyl bromide, the reaction mixture was filtered through a silica gel pad to remove molecular sieves and the crude products were concentrated and then purified by silica gel chromatography.

Synthesis of methyl-*O*-(2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside 10



Started with 102.2 mg (0.150 mmol) 1-phenylselenyl-2,3,4,6-tetra-*O*-benzyl glucopyranoside, 4.7 mg PhSeSePh (0.015 mmol), 54.7 mg CBr_4 (0.165 mmol), 37.0 mg 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) (0.180 mmol) and 400mg 4Å MS in 2 mL of DCM and irradiated for 6 hrs. 35.0 mg (0.0752 mmol) glycosyl acceptor 3 and 96.7 mg (0.300 mmol) were then added and irradiation continued for 18 hrs. Purified to obtain 60 mg (83%) colorless oil in a 7:1 α:β mixture. Alpha anomer ^{1}H-NMR (400 MHz, $CDCl_3$) 3.32 (3H, s), 3.40 (1H, dd, *J*=9.6, 3.6 Hz), 3.50 (2H, m), 3.58 (1H, t, *J*=9.0 Hz), 3.69-3.82 (3H, m), 3.87-3.99 (4H, m), 4.02 (1H, dd, *J*=9.3, 3.5 Hz), 4.36 (1H, d, *J*=11.8 Hz), 4.43 (1H, d, *J*=11.9 Hz), 4.51-4.60 (4H, m), 4.65-4.75 (4H, m), 4.75-4.82 (2H, m), 4.84 (1H, d, *J*=11.0 Hz), 4.93 (1H, d, *J*=11.5 Hz), 4.95 (1H, d, *J*=10.9

Hz), 4.99 (1H, d, *J*=3.6 Hz), 7.18-7.36 (35H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) 55.0, 66.4, 68.9, 69.4, 70.3, 72.5, 72.8, 73.3, 74.7, 75.0, 75.1, 75.7, 76.5, 77.2, 78.0, 78.3, 80.2, 82.1, 97.9, 97.9, 127.3, 127.4, 127.5, 127.6, 127.6, 127.7, 127.8, 127.9, 128.0, 128.2, 128.2, 128.2, 128.3, 128.3, 128.4, 128.4, 138.1, 138.2, 138.4, 138.7, 138.8, 138.9, 138.9; HRMS *m/z* calcd for $C_{62}H_{66}NaO_{11}$ $(M+Na)^+$ 1009.4497, found 1009.4490; $[\alpha]_D^{25}$ = +87.2 (*c*= 0.55, CH_2Cl_2).

2.7 References

1. Sznaidman, M. in *Bioorganic Chemistry*: *Carbohydrates* (ED.: S. M. Hecht), Oxford University press, New York, **1999**, 1-56.
2. Barres, F.; Hindsgaul, O. M*odern Synthetic Methods*. **1995**, *7*, 281-330.
3. IUPAC, *Compendium of Chemical Terminology*, 2nd ed. (the "Gold Book") **1997**. Online corrected version: **1996** "Anomeric Effect.
4. Cuevas, Eusebio, Juaristi, Gabriel **1995**. *The anomeric effect*. Boca Raton: CRC Press. ISBN 0-8493-8941-0.
5. Miljkovic, M.; Jokic, A.; Davidson, E.A. *Carbohyd. Res*. **1971**, 1**7**, 155-164.
6. Miljkovic, M.; Glisin, D.; Gligorijevic, M. *J. Org. Chem.* **1975**, 40, 1054–1057.
7. Lemieux, R. U. *Pure. Appl. Chem.* **1971**, 25, 527.
8. Vankar, D.; Vankar, P. S.; Behrendt, M.; Schmidt, R. R. *Tetrahedron.* **1992**, 47, 9985.
9. Haines, A. H. *Adv. Carbohydr. Chem Biochem*. **1976**, 33, 11-109. b) Moitessier, N.; Chapleur, Y. *Tetrahedron Lett*. **2003**, 44, 1731-1735.
10. (a) Koenigs, W.; Knorr, E. *Chem. Bericte*. **1901**, *34*, 957-981.; (b) Igarashi, K. *Adv. Carbohydr. Chem. Biochem.* **1997**, *34*, 243-283.; (c) Zemelen, G.; Gerecs, A. *Chem. Bericte*. **1930**, *62B*, 2720-2729.; (d) Helferich, B.; Zirner, J. *Chem. Bericte*. **1962**, *95*, 2604-2611.
11. (a) Mukiyama, T.; Murrai, V.; Shoda, S. *Chem. Lett*. **1981**, *3*, 431-432.; (b) Toshima, K. *Carbohydr. Res*. **2000**, *327*, 15-26.
12. Frasier-Reid, B.; Konradsson, P.; Mootoo, D. R.; Udodongs, U. *J. Chem. Soc. Chem. Commun*. **1988**, 823-825.
13. (a) Marra, A.; Esnault, J.; Veyrieres, A.; Sinay, P. *J. Am. Chem. Soc*., **1992**, *114*, 6354–6360.; (b) Boons, G. J.; Isles, S. *Tetrahedron Lett*. **1994**, *35*, 3593-3596.
14. Schmidt, R. R. *Angew. Chem. Int. Ed*. **1986**, *25*, 212-235.

15. (a) Schmidt, R.R.; Michel, J. *Angew. Chem*. **1980**, *92*, 763-764.; (b) Schmidt, R. R.; Michel, J. *Angew. Chem. Int. Ed.* **1980**, *19*, 731-732.

16. (a) Zhu, X. M.; Schmidt, R. R. *Angew. Chem. Int. Ed*. **2009**, *48*, 1900-1934.; (b) Schmidt, R. R.; Castro-Palomino, J. C.; Retz, O. *Pure Appl. Chem.* **1999**, *71*, 729-744.

17. (a) Lemieaux, R. U.; Levine, S. *Can. J. Chem*. **1964**, *42*, 1473.; (b) Thiem, J.; Karl, H.; Schwentner, J. *Synthesis*. **1978**, 696.; (c) Thiem, J.; Karl, H. *Tetrahedron Lett*. **1978**, *10*, 4999.; (d) Thiem, J.; Waklaffke, W. *J. Org. Chem*. **2006**, *54*, 2006-2009.

18. (a) Friesen, R. W.; Danishefsky, S. J. *J. Am. Chem. Soc*. **1989**, *111*, 6656-6660.; (b) Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc*. **1989**, *111*, 6661-6666.

19. Ferrier, R. J.; Hay, R. W.; Vethaviuasar, N. *Carbohydr. Res.* **1973**, *27*, 55-61.

20. Nicolaou, K. C.; Spitz, S. P.; Papahatiis, D. P. *J. Am. Chem. Soc*. **1983**, *106*, 2430-2434.

21. Garegg, P. J.; Henrinchson, C.; Norberg, J. C. *Carbohydr. Res.* **1983**, *116*, 162-165.

22. Mehta, S. Pinto, B. M. *Tetrahedron Lett*. **1991**, *32*, 4435-4438.

23. (a) Shiao, T. C.; Roy, R. *Top. Curr. Chem*. **2011**, *301*, 69–108.; (b) Codée, J. D. C.; Litjens, R. E. J. N.; van den Bos, L. J.; Overkleeft, H. S.; Vander Marel, G. A. *Chem. Soc. Rev*. **2005**, *34*, 769–782.; (c) Oscarson, S. *In Carbohydrates in Chemistry and Biology*; Beat, E., Hart, G. W., Sinay, P., Eds.; Wiley-VCH: Weinheim, 2000; pp 93–116.

24. (a) Valerio, S.; Iadonisi, A.; Adinolfi, M.; Ravida, A. *J. Org. Chem***. 2007**, *72*, 6097–6106.; (b) van Well, R. M.; Karkkainen, T. S.; Ravindranatha Kartha, K. P.; Field, R. A. *Carbohydr. Res*. **2006**, *341*, 1391–1397.; (c) Yamago, S.; Yamada, T.; Hara, O.; Ito, H.; Mino, Y.; Yoshida, *J. Org. Lett*. **2001**, *3*, 3867–3870.; (d) Ikeda, K.; Konishi, K.; Sano, K.; Tanaka, K. *Chem. Pharm. Bull*. **2000**, *48*, 163–165.; (e) Pinto, B. M.; Mehta, S. *J. Org. Chem*. **1993**, *58*, 3269–3276.

25. Amatore, C.; Jutand, A.; Mallet, J. M.; Meyer, G.; Sinaÿ, P. *J. Chem. Soc., Chem, Commun*. **1990**, 719.

26. (a) Nagib, D. A.; MacMillan, D. W. C. *Nature*, **2011**, *480*, 224–228.; (b) McNally,A.; Prier, C. K.; MacMillan, D. W. C. *Science*, **2011**, *334*, 1114–1117.; (c) Shih, H.-W.; Vander Wal, M. N.; Grange, R. L.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2010**, *132*, 13600–13603.; (d) Nagib, D. A.; Scott, M. E.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2009**, *131*, 10875–10877.; (e) Nicewicz, D.; MacMillan, D. W. C. *Science*. **2008**, *322*, 77–80.

27. (a) Lin, S.; Ischay, M. A.; Fry, C. G.; Yoon, T. P. *J. Am. Chem. Soc*. **2011**, *133*, 19350–19353.; (b) Lu, Z.; Shen, M.; Yoon, T. P. *J. Am. Chem. Soc*. **2011**, *133*, 1162–1164.; (c) Ischay, M. A.; Lu, Z.; Yoon, T. P. *J. Am. Chem. Soc*. **2010**, *132*, 8572–8574.; (d) Du, J.; Yoon, T. P. *J. Am. Chem. Soc*. **2009**, *131*, 14604–14605.; (e) Ischay, M. A.; Anzovino, M. E.; Du, J.; Yoon, T. P. *J. Am. Chem. Soc*. **2008**, *130*, 12886–12887.

28. (a) Wallentin, C. J.; Nguyen, J. D.; Finkbeiner, P.; Stephenson, C. R. J. *J. Am. Chem. Soc*. **2012**, *134*, 8875–8884.; (b) Tucker, J. W.; Zhang, Y.; Jamison, T. F.; Stephenson, C. R. J. *Angew. Chem., Int. Ed*. **2012**, *51*, 4144–4147.; (c) Furst, L.; Narayanam, J. M. R.; Stephenson, C. R. J. *Angew. Chem., Int. Ed*. **2011**, *50*, 9655–9659.; (d) Nguyen, J. D.;

Tucker, J. W.; Konieczynska, M. D.; Stephenson, C. R. J. *J. Am. Chem. Soc*. **2011**, *133*, 4160–4163.; (e) Dai, C.; Narayanam, J. M. R.; Stephenson, C. R. J. *Nature Chem*. **2011**, *3*, 140–145.; (f) Condie, A. G.; Gonzalez- Gomez, J.-C.; Stephenson, C. R. J. *J. Am. Chem. Soc*. **2010**, *132*, 1464–1465.; (g) Narayanam, J. M. R.; Tucker, J. W.; Stephenson, C. R. J. *J. Am. Chem. Soc*. **2009**, *131*, 8756–8757.; (h) Tucker, J. W.; Narayanam, J. M. R.; Shah, P. S.; Stephenson, C. R. J. *Chem. Commun*. **2011**, *47*, 5040–5042.

29. (a) Ye, Y.; Sanford, M. S. *J. Am. Chem. Soc*. **2012**, *134*, 9034–9037.; (b) Kalyani, D.; McMurtrey, K. B.; Neufeldt, S. R.; Sanford, M. S. *J. Am. Chem. Soc*. **2011**, *133*, 18566–18569.

30. For recent reviews, see: (a) Teply, F. Collect. Czech. *Chem. Commun*. **2011**, *76*, 859–917.; (b) Xuan, J.; Xiao, W. J. *Angew. Chem., Int. Ed*. **2012**, *51*, 2–13.; (c) Tucker, J. W.; Stephenson, C. R. J. *J. Org. Chem*. **2012**, *77*, 1617–1622.; (d) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev*. **2011**, *40*, 102–113.; (e) Yoon, T. P.; Ischay, M. A.; Du, J. *Nature Chem*. **2010**, *2*, 527–532.; (f) Zeitler, K. *Angew. Chem., Int. Ed*. **2009**, *48*, 9785–978.

31. Campagna, S.; Puntorierg, F.; Nastasi, F.; Bergamini, G.; Balzani, V. *Top. Curr. Chem*. **2007**, *280*, 117.

32. McCusker, J. K. *Acc. Chem. Res*. **2003**, *36*, 876.

33. Bock, C. R.; Connor, J. A.; Gutierrez, A. R.; Meyer, T. J.; Whitten, D. G.; Sullivan, B. P.; Nagle, J. K. *J. Am. Chem. Soc*. **1979**, *101*, 4815.

34 For conversion constants to the standard calomel electrode (SCE) see: Pavlishcuk, V. V.; Addison, A. W. *Inorg. Chem. Acta*. **2000**, *298*, 97.

35. Prier, C. K.; Rankic, A. R.; Macmillian, W. C. *Chem. Rev*. **2013**, *113*, 5322-5363.

36. Spell, M.; Wang, X.; Wahba, A.E.; Conner, E.; Ragains, J. *Carbohydrate Research*. **2013**, 369, 42–47.

37. Mehta, S.; Pinto, B.M. *J. Org. Chem.* **1993**, *58*, 3269-3276.

38. Cumpstey, I.; Crich, D. J. *Carbohydr. Chem*. **2011**, *30*, 469–485.

39. Kitagawa, I.; Yoshikawa, M.; Kobayashi, K.; Imakura,Y.; Kwang, S.; Ikenishi, Y. *Chem. Pharm. Bull*. **1980**, *28*, 296 – 300.

40. Johnsson, R.; Ohlin, M.; Ellervik, U. *J. Org. Chem*. **2010**, *75*, 8003 – 8011.

41. Chi-Rung, S.; Zheng-Hao, T.; Suvarn S. K.; Biing-Jiun, U.; Ching-Yun, H.; Shang-Cheng, H. *Angew. Chem. Int. Ed*. **2005**, *44*, 1665 –1668.

42. Conner, E. S.; Crocker, K. E.; Fernando, R. G.; Fronczek, F. R.; Stanley, G. G.; Ragains, J. R. *Org. Lett*. **2013**, *15*, 5558–5561.

43. Lin, S.; Ischay, M. A.; Fry, C. G.; Yoon, T. P. *J. Am. Chem. Soc*. **2011**, *133*, 19350.

44. (a) Reich, H. J.; Cohen, M. L.; Clark. P. S. Org. Synth. **1979**, *59*, 141. (b) Reich, H. J.; Cohen, M. L.; Clark. P. S. Org. Synth. **1988**, *6*, 533.

45. Lemieux, R. U.; Hendriks, K. B.; Stick, R. V.; James, K. *J. Am. Chem. Soc*. **1975**, 97, 4056–4062.

46. Hadd, M. J.; Gervay, J. *Carbohydrate Research*. 320, **1999**, 61–69.

47. Bickley, J.; Cottrell, J. A.; Ferguson, J. R.; Field, R. A.; Harding, J. R.; Hughes, D. L.; Kartha, K. P. R.; Law, J. L.; Scheinmannc, F.; Stachulski, A. V. *Chem. Commun*. **2003**, 1266–1267.

48. Mo, F.; Dong, G.; Zhanga, Y.; Wang, *J. Org. Biomol. Chem*. **2013**, 11, 15.

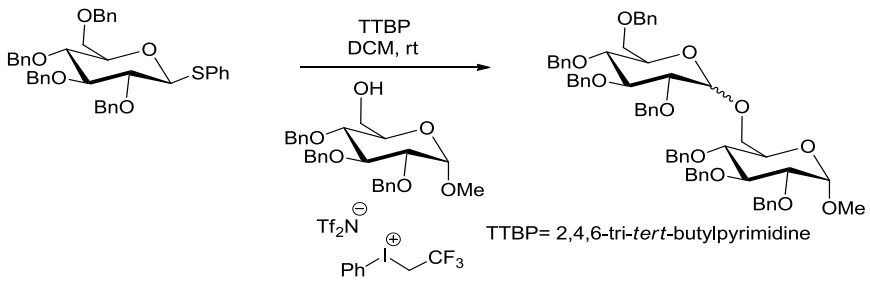
49. Zhang, Z.; Ollmann, I. R.; Ye, X. H.; Wischnat, R.; Baasov, T.; Wong, C. H. *J. Am. Chem. Soc*. **1999**, 121, 734-753.

50. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics*. **1996**, *15*, 1518.

CHAPTER 3: A METAL-FREE, VISIBLE LIGHT-PROMOTED *O*-GLYCOSYLATION WITH A THIOGLYCOSIDE DONOR

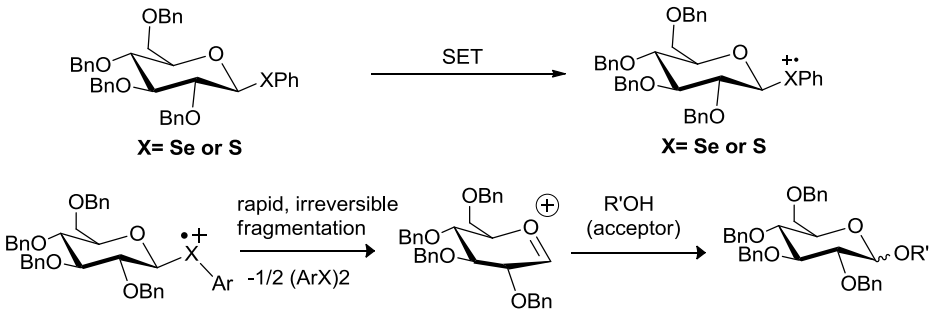
3.1 Introduction

One of the most frequently used class of glycosyl donors for performing chemical *O*-glycosylation is the thioglycosides.[1] Thioglycosides are extremely stable species (giving them a long shelf life) whose structure can be manipulated to provide a wide range of reactivity.[1] These advantages have fostered an effective methodology to form glycosidic linkages which are of significant interest to the glycoscience community.[1,2] The high stability of thioglycosides, which is arguably their greatest attribute, is also their biggest drawback, since harsh activation (strong electrophiles) are required to activate them. Strong electrophiles like NIS/HOTf, DMTST, NBS, PhSOTf, and benzenesulfonylpiperidine/Tf_2O used for activation of thioglycosides are highly reactive, unstable species, making *O*-glycosylation with thioglycosides a nontrivial task for those inexperienced in the field. By contrast, growing demand for *O*-glycosides necessitates chemical glycosylation methods that can be performed easily and requiring little skill from the experimentalist.[3] Such a method would require easily handled and bench stable reagents that can be used at ambient temperatures while providing high yields and selectivities. This provides a significant challenge to *O*-glycosylation method development that is worth addressing. Steps have been taken towards this goal, including the use gold catalysts, and iodine (III) and bismuth (V) reagents to activate the thioglycoside donors (Scheme 3.1).[4]



Scheme 3.1 A mild approach to glycosylation using an I (III) reagent with a thioglycoside

Another approach that I and others have been exploring is to irradiate with light, often visible light, to provide the energy necessary to activate thio- and selenoglycosides under easily performed, mild reaction conditions.[5] Photons emitted by a light source provide the energy of activation that is a substitute for the harsh reaction conditions described earlier. Many of these photochemical glycosylation involve a mechanism (Scheme 3.2) where a S/Se centered radical



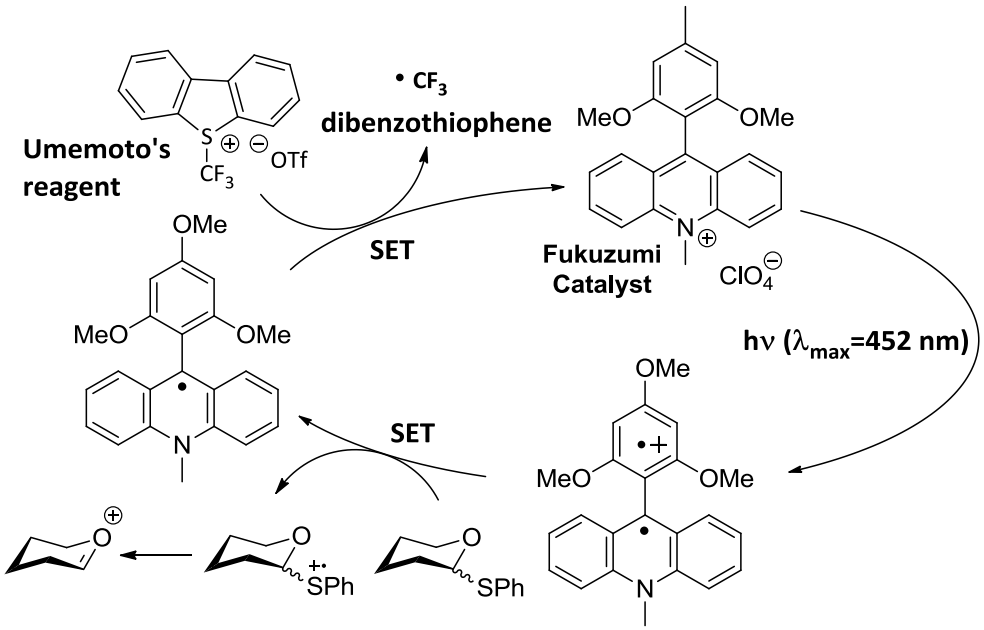
Scheme 3.2 Common mechanism for photochemical glycosylation

cation is formed as a reactive intermediate either directly or indirectly from a photoinduced electron transfer. The reactive intermediate fragments, giving the commonly-proposed oxacarbenium intermediate that can then be intercepted by a glycosyl acceptor. A recent method in which *p*-methoxyphenylthioglycosides were irradiated with visible light in the presence of an iridium photosensitizer showed some promise.[5] However, only moderate yields were seen when attempting to form difficult glycosidic linkages (a common issue in photochemical glycosylation).[5] The development of a photochemical glycosylation that is easy to perform and provides synthetically difficult glycosidic linkages is a challenge that is still being explored and which I address herein.

3.2 Results and discussion

While the studies I performed using selenoglycosides under visible light photochemical conditions to provide *O*-glycosylation was successful, the use of thioglycosides under the same

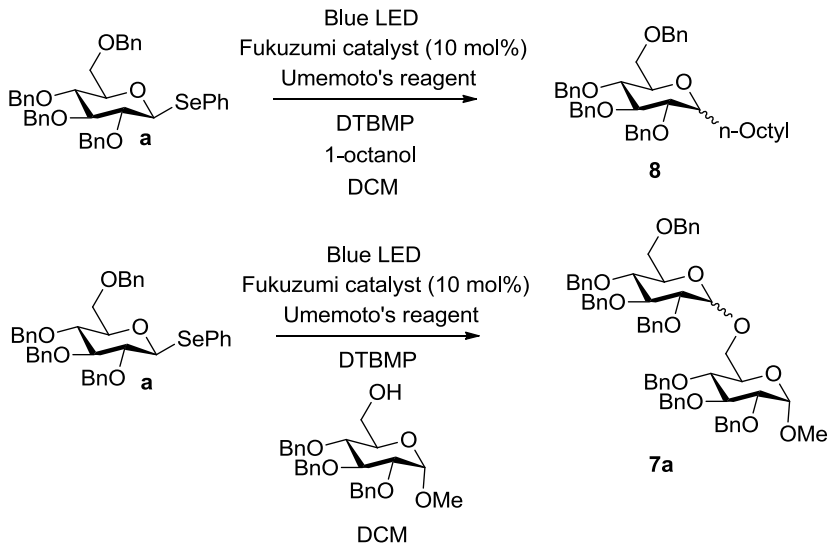
conditions provided no glycosylation.[5,6] This can be attributed to the lower reactivity of thioglycosides compared to selenoglycosides. In hopes of activating thioglycosides, the Fukuzumi catalyst was used in conjunction with a stoichiometric oxidant (Scheme 3.3). The catalyst, upon



Scheme 3.3 Proposed activation of thioglycosides using the Fukuzumi catalyst and a stoichiometric oxidant

excitation by blue light (455 nm), is converted to a strongly oxidizing species (E_{red}= 1.88V vs SCE) that could then undergo a single electron transfer from thioglycosides to provide the reactive S-centered radical cation which then undergoes fragmentation en route to the glycosidic linkage.[7] The catalyst is then regenerated by another SET to the stoichiometric oxidant. While this method showed substantial promise with selenoglycosides (Scheme 3.4), all attempts at thioglycoside activation proved unsuccessful (Scheme 3.5). This study, along with other literature reports, resulted in our conclusion that the formation of sulfur centered radical cations is a non-trivial task under visible light irradiation. With the attempts at oxidizing thioglycosides via SET from the

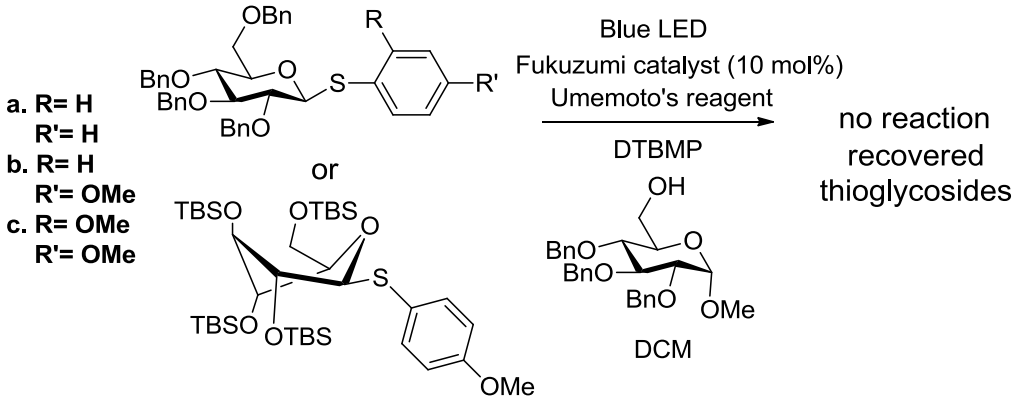
sulfur being unproductive, an alternative route at activating the thioglycosides that doesn't require



Scheme 3.4 Glycosylation of selenoglycosides using Fukuzumi catalyst

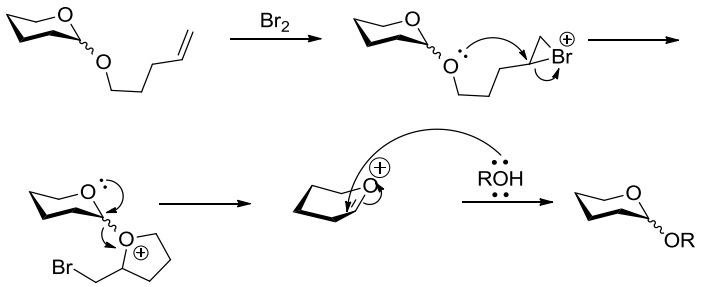
the formation of a sulfur centered radical cation was postulated.

Frasier-Reid's use of n-pentenyl glycosides was of particular interest to us (Scheme 3.6).[8] The terminal alkene of the *n*-pentenyl side chain reacts with molecular bromine forming a



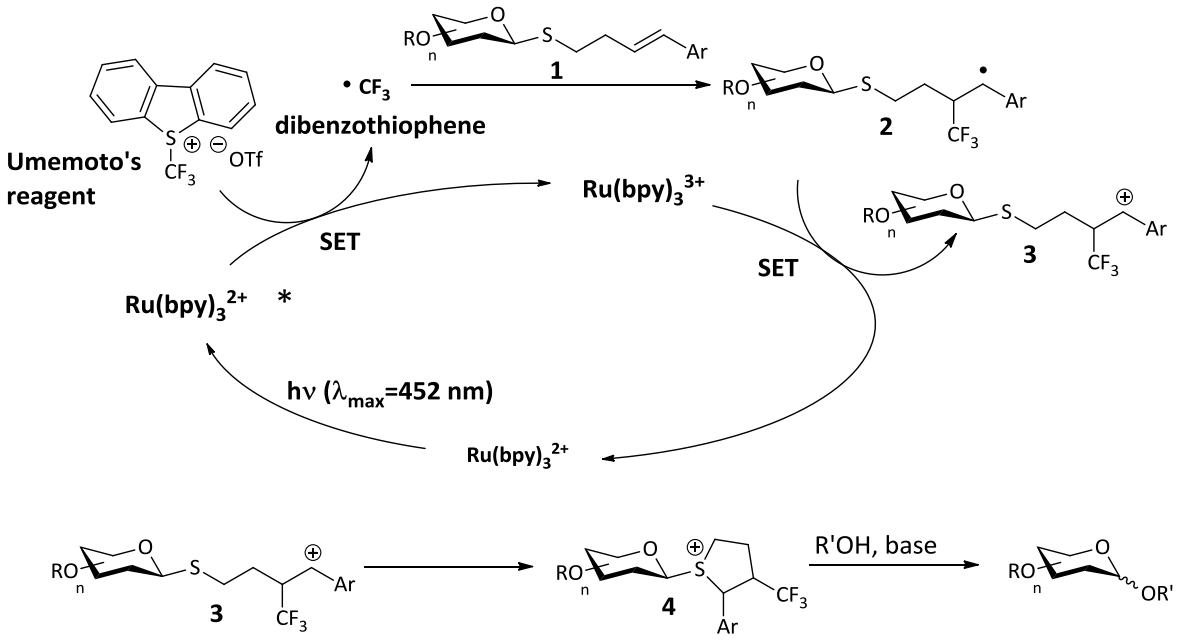
Scheme 3.5 Attempt at glycosylation of thioglycosides using Fukuzumi catalyst

bromonium ion. The glycosidic oxygen attacks the bromonium ion, changing what was once a poor leaving group into an excellent leaving group that leaves to form the oxacarbenium ion.[8] In a similar fashion, I wanted to "unburden" sulfur from a difficult SET process by capitalizing on its



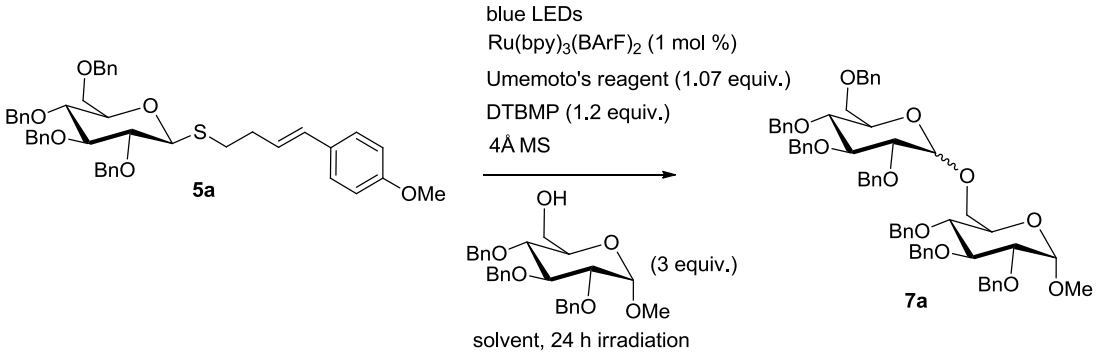
Scheme 3.6 *n*-pentenyl glycoside-based glycosylation mechanism

nucleophilicity while avoiding the unreactive glycosyl bromides commonly encountered when using *n*-pentenyl glycosides with molecular bromine. With the idea of sulfur acting as a nucleophile, I took inspiration from recent work done on the visible light photocatalytic oxytrifluromethylation of styrenes.[9] This work utilizes the reactivity of styrenes to intercept trifluromethyl radicals resulting in a benzylic radical that can then be oxidized via SET followed by nucleophilic attack of an oxygen nucleophile on the resulting carbocation. I envisioned thioglycosides containing an *S*-alkyl chain with a terminal styrene that would react similarly in the presence of trifluromethyl radicals (generated by the SET of $Ru(bpy)_3^{2+*}$ to Umemoto's reagent) ultimately resulting in a benzylic radical that would be oxidized by $Ru(bpy)_3^{3+}$ to the carbocation. The nucleophilic sulfur could then attack the carbocation and generate a good leaving group (sulfonium). The leaving group would then be expelled, giving the oxonium ion that would then be attacked by a glycosyl acceptor to provide the glycosidic linkage (Scheme 3.7). This would provide an exceptionally mild method for forming *O*-glycosidic linkages with thioglycosides that, we reasoned, could be activated in the presence of other thioglycosides, providing orthogonality. The reagents used would be stable and easily handled on a bench top ideal for non-experts unlike *n*-pentenyl which use molecular bromine and often result in unreactive glycosyl bromide intermediates.[10] The orthogonality would also provide a method to form oligosaccharides with a one-pot approach.



Scheme 3.7 Proposed mechanism for $Ru(bpy)_3^{2+}$ catalyzed glycosylation of thioglycosides

I initially decided to explore this reaction by first synthesizing thioglycosides 5a-5e which included benzyl-protected 5a, acetyl-protected 5b, and aryl- and alkylthioglycosides 5c-e.[11] The *p*-methoxy styrene used in 5a-5b was synthesized with the idea that an electron rich styrene would be more susceptible to attack by the electrophilic trifluromethyl radical than an electron deficient or electroneutral styrene. Thioglycoside 5a was subjected to the initial reaction conditions involving irradiation with blue LED's in the presence of $Ru(bpy)_3(BArF)_2$, Umemoto's reagent, DTBMP, excess acceptor 6 and 4ÅMS in DCM to give the glycosidic product 7a in 55% yield as a mixture of anomers. After this exciting result, the reaction was further studied (Figure 3.1). A solvent screen yielded no significant improvement in yield or selectivity for the reaction (Entries 1-6). With no improvement seen in the first attempts at optimization, the reaction was further explored using thioglycosides 5a-5e (Figure 3.2). Controls performed with thioglycosides 5a without light and also without Umemoto's reagent showed that the reaction depends on both to proceed (Entries 2, 3). However, a control in which no $Ru(bpy)_3^{2+}$ was used, to my surprise,



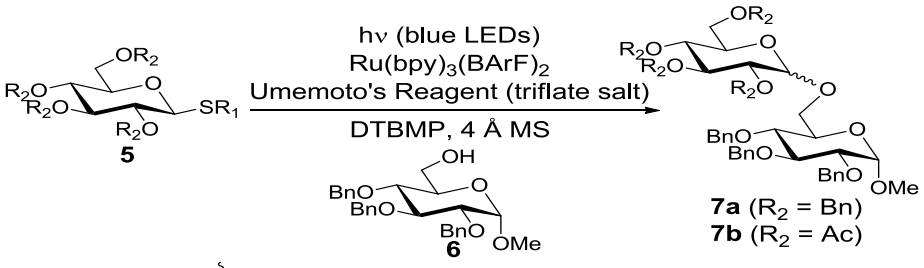
Entry	Solvent	Yield of **7a** (%)[a]	Anomeric ratio (α/β)
1	DCM	55	1.4:1
2	CH_3CN	59	1:2.3
3	DCE	60	1.2:1
4	DMF	20	3:1
5	THF	57	1.2:1
6	trifluorotoluene	55	1.4:1
7[b,d,e]	DCM	70	0.98:1
8[c,d,e]	DCM	72	1:1

a) isolated yields, b) performed at -20°C, C) performed with 0.15 equiv TEMPO, d) no catalyst and DTBMP, e) 0.5 equiv of acceptor used

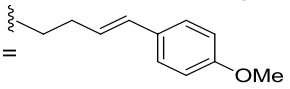
Figure 3.1 Initial screening and optimization

provided a similar yield and selectivity for formation of 7a (Entry 4), suggesting that catalyst is not needed for the glycosylation to proceed. This led me to omit catalyst in further studies. Increasing the concentration of the reaction did nothing to increase the yield of the reaction. However, using glycosyl donors in excess (rather than an excess of glycosyl acceptor 6**)** in conjunction with increasing the concentration gave a significant increase in the yield, (from 55% to 76% yield) (Entry 5). Omission of DTBMP resulted in no change to the reaction yield (Entry 6) as long as 4ÅMS were present, but when neither DTBMP nor 4ÅMS were used, the glycosylation resulted in complex mixtures and difficult purifications (data not shown). Lowering the temperature of the reaction to -20°C also resulted in no significant improvement to the reaction

(Entry 6 Figure 3.1). Interestingly, the addition of TEMPO, a common radical trapping reagent, did not shut down the reaction, providing a similar yield and selectivity to the reaction without TEMPO. This suggest that this reaction is not a radical chain process (Entry 7 Figure 3.1).



5a R_1 =



R_2 = Bn

5b R_1 = same as **5a**
R_2 = Ac

5c R_1 = 1-octyl
R_2 = Bn

5d R_1 = Ph
R_2 = Bn

5e R_1 = 2,4-diOMePh
R_2 = Bn

Entry	donor	yield (%)[a]	(α/β)
1	5a	55	1.4:1
2[b]	5a	0	N/A
3[c]	5a	0	N/A
4[d]	5a	50	1.3:1
5[d,e]	5a	76	1.1:1
6[d,e,f]	5a	75	1.6:1
7[d,e,f]	5b	0	N/A
8[d,e,f]	5c	0	N/A
9[d,e,f]	5d	0	N/A
10[d,e,f]	5e	0	N/A

Unless otherwise stated, 0.15 mmol donor **5**, 1 mol % $Ru(bpy)_3(BArF)_2$, 1.07 equiv. Umemoto's reagent, 1.2 equiv. DTBMP, 3 equiv. acceptor **6**, and 300 mg 4Å MS in 2 mL CH_2Cl_2 were irradiated for 24 h with blue LEDs. a) isolated yields b) no irradiation c) no Umemoto's reagent d) no $Ru(bpy)_3(BArF)_2$ e) 0.5 equiv. of **6**, 150 mg 4Å MS in 1 mL CH_2Cl_2 f) DTBMP omitted

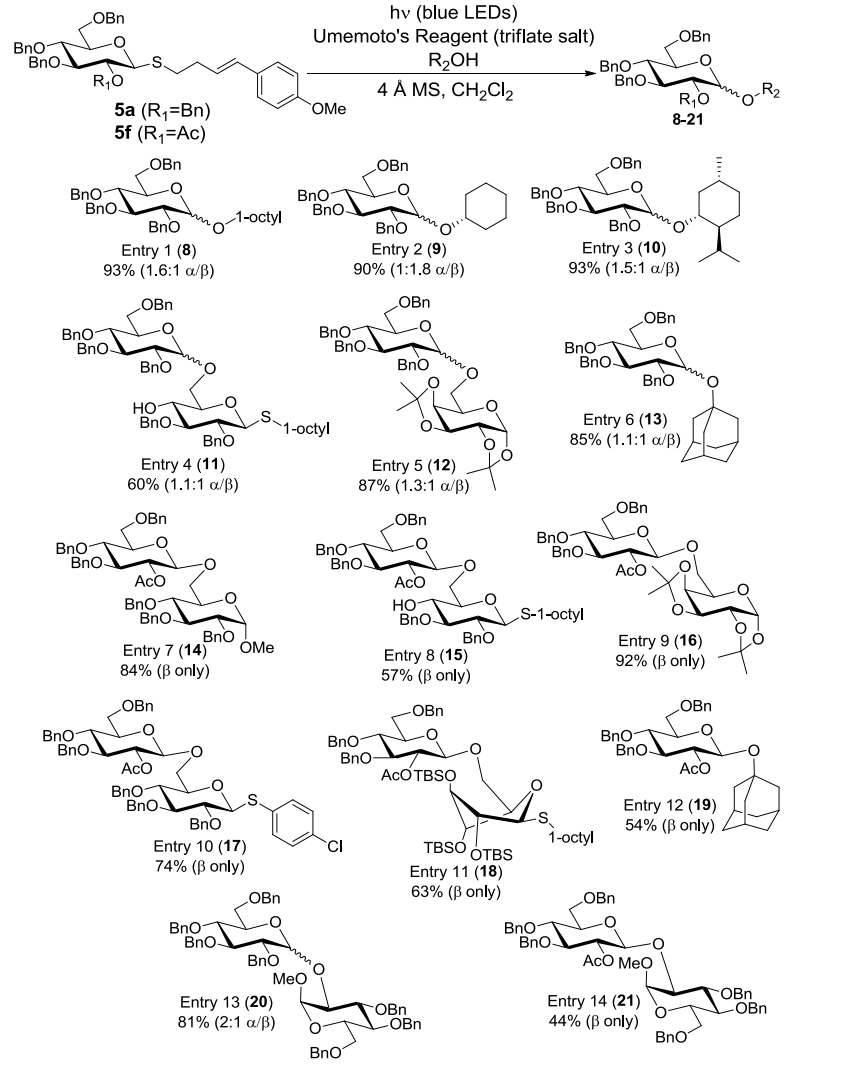
Figure 3.2 Glycosylation optimization

The optimal glycosylation conditions using no catalyst, no DTBMP, excess glycosyl donor and high concentration were used with glycosyl donors 5b-5e and acceptor 6 to test the

orthogonality of our conditions toward various thioglycosides. Orthogonality is important when forming glycosidic bonds between thioglycosides and other thioglycoside-containing alcohol acceptors. Control over which thioglycoside is activated determines the glycosidic product obtained. The selective activation of different thioglycosides could lead to an effective method to synthesize oligosaccharides in one pot. Glycosylation using the acetylated thioglycosides 5b resulted in no consumption of the glycosyl donor 5b while some decomposition of Umemoto's reagent was seen via ^{1}H NMR after 24 hrs of irradiation. This is not surprising when considering that the sulfur in 5b is far more difficult to oxidize and less nucleophilic compared to the sulfur in thioglycosides 5a and suggest that sulfur is not an innocent bystander in the incipient activation of 5a.[1,12] Thioglycosides 5c-5d were unreactive, demonstrating the orthogonality of our conditions toward various alkyl- and arylthioglycosides. Under typical conditions for thioglycoside activation, thioglycoside 5c would be considered a highly reactive donor, but it does not react under our conditions.[1] The possibility of an outer sphere SET from the sulfur in 5a in previous reactions is not likely given the facile SET oxidation of the electron rich arylthioglycosides 5e.[12]

With optimized reaction conditions for the visible light-promoted *O*-glycosylation in hand a wide range of glycosyl acceptors were screened (Figure 3.3) to probe the substrate scope of this method. The glycosylation of the structurally simple alcohol acceptors 1-octanol, cyclohexanol and (-)- menthol with glycosyl donor 5a provided high yields of glycosidic products as mixtures of anomers (Enties 1-3). The formation of more difficult disaccharide linkages was also successful using glucose and galactose-derived acceptors resulting in good yields (albeit with little stereochemical control) (Entries 4 and 5). Glycosylation of the sterically hindered tertiary alcohol acceptor 1-adamantanol also proceeded in high yield (Entry 6). The ability to form glycosidic linkages with alkylthioglycoside-bearing acceptors (Entry 4) shows that activation of

thioglycoside donor 5a in the presence of other alkylthioglycoside acceptors is possible (demonstrating the orthogonality of the method).



Unless otherwise stated, 0.15 mmol donor **5**, 1.07 equiv. Umemoto's reagent, 0.5 equiv. acceptor, and 150 mg 4Å MS in 1 mL CH_2Cl_2 were irradiated for 24 h with blue LEDs.

Figure 3.3 Glycosylation substrate scope

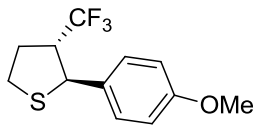
The use of thioglycoside donor 5a provided good to excellent yields of glycosidic products. However, the stereoselectivity in all cases was close to 1:1 *alpha*/*beta*. The presence of an acetate at the 2-position (thioglycoside donor 5f) provided a completely stereoselective glycosylation for the *beta* anomer due to the neighboring group participation of this group (Entry 7). This was the

case when forming simple glycosidic linkages and disaccharide linkages (galactose diacetonide, 1-octylthioglucoside and others) while continuing to show orthogonality (Enties 8-11,13, and 14). The sterically hindered 1- adamantanol was also glycosylated, providing just the *beta* anomer (Entry 12).

The formation of glycosidic product 18 (Entry 11) is of particular interest since the bulky silyl-protecting groups on the glycosyl acceptor force the compound to adopt a twist boat conformation.[13] The twist boat conformation (observed by NMR of the species) forces the oxygens on the carbohydrate moiety into a pseudoaxial position which provides stabilization of oxacarbenium ion due to electrostatic interactions.[13] The stabilization of the oxacarbenium ions of the silyl-protected glycosyl acceptor renders this species 20 times more reactive than the analogous tetrabenzyl-protected thioglycoside.[14] The fact that this highly reactive acceptor is not activated under our conditions and does not oligomerize with itself is noteworthy and is the best example of the orthogonality exhibited by this glycosylation. The conventional method to build oligosaccharides from thioglycosides in one pot is to couple them in decreasing order of glycosyl donor reactivity.[1] The most reactive species is activated first. The glycosylation I have developed could potentially remove this limitation, providing a novel way to build oligosaccharides in one pot where our photochemical approach could be used alone or in conjunction with conventional methods for thioglycoside activation. The selective activation of the thioglycoside donors like 5a/5f under my visible light promoted glycosylation conditions could also be useful in multistep synthesis of oligosaccharides.

While the glycosylation provided good to excellent yields and complete selectivity when using glycosyl donor 5f, the mechanism under which the reaction proceeds needed further investigation. When examining the crude ^{1}H NMR spectra of the glycosylation reactions,

considerable quantities of an unidentified species were present. The species was isolated along with dibenzothiophene by collecting early eluting fractions from column chromatography. Further purification using preparative thin layer chromatography provided the product as a single diastereomer (+/-)- 22 (Figure 3.4) as determined by mass spectrometry, polarimetry and



(+/-)-22

-isolated from product mixtures

Figure 3.4 Tetrahydrothiophene By-product

comparison of ^{1}H NMR coupling constants with previously reported tetrahydrothiphenes.[15] This supports a mechanistic pathway similar to that proposed in Scheme 3.7 although, $Ru(bpy)_3^{2+}$ is not involved.

It was stated early on that the addition of 0.15 equivalents of the radical trapping reagent TEMPO had no effect on the glycosylation as it proceeded in comparable yield. This suggests that the reaction does not proceed via a radical chain process but didn't rule out the possibility of radicals being present.[16] In order to further investigate the possibility of a chain process, an NMR experiment was conducted where the reaction was allowed to proceed in the presence and absence of light over a 10 hr period. The percent consumption of starting glycosyl donor 5a in the light on/light off experiment (Figure 3.5) showed that the reaction required continuous irradiation to proceed as absence of light shuts down the reaction. The experiment further corroborates that the reaction is most likely not proceeding by a radical chain process. However, the possibility of radical intermediates and short chain processes cannot be completely ruled out.[16,17]

The realization that the glycosylation does not require $Ru(bpy)_3^{2+}$ was a pleasant surprise. However, it raised the question of how the reaction is actually proceeding, mechanistically. Insight

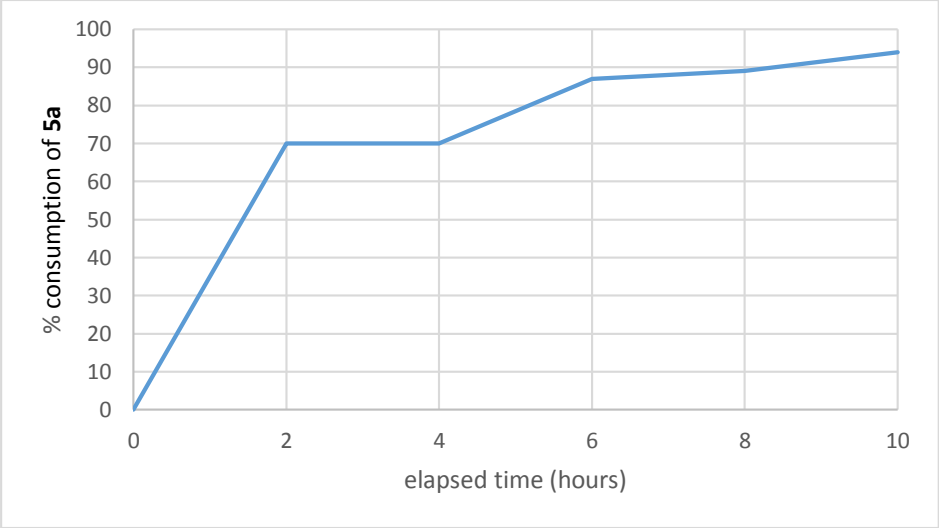


Figure 3.5 Light on/off experiment

into the mechanistic process was first realized by the observation that solutions of Umemoto's reagent and glycosyl donors 5a/b in DCM and acetonitrile produced a yellow color upon mixture that is not observed when mixing glycosyl donors 5c-e with Umemoto's reagent. The *p*-methoxystyrene terminus of glycosyl donors 5a/b was deemed necessary for color change, since a mixture of Umemoto's reagent and *p*-methoxystyrene also produced the same yellow color seen in the previous mixture. There is recent literature that shows that several synthetic transformations can be performed via activation of electron donor-acceptor complexes (EDAs also known as charge transfer complexes).[18] Theses complexes result in color change when the electron donor and acceptor are mixed together in solution and exhibit new absorbance bands as often observed by UV-vis spectrophotometry. UV-vis spectra showed that a putative EDA complex absorbance trailed well into the visible region with a measurable extinction at 455 nm (blue LED λmax= 455 nm). I obtained UV-vis spectra of mixtures of 26.6 mM Umemoto's reagent and differing concentrations of glycosyl acceptor 5a in acetonitrile (Figure 3.6). The absorbance strongly suggest the presence of an EDA complex via interaction of 5a/b and Umemoto's reagent. In order to further explore the possibility of an EDA complex a computational investigations on a model

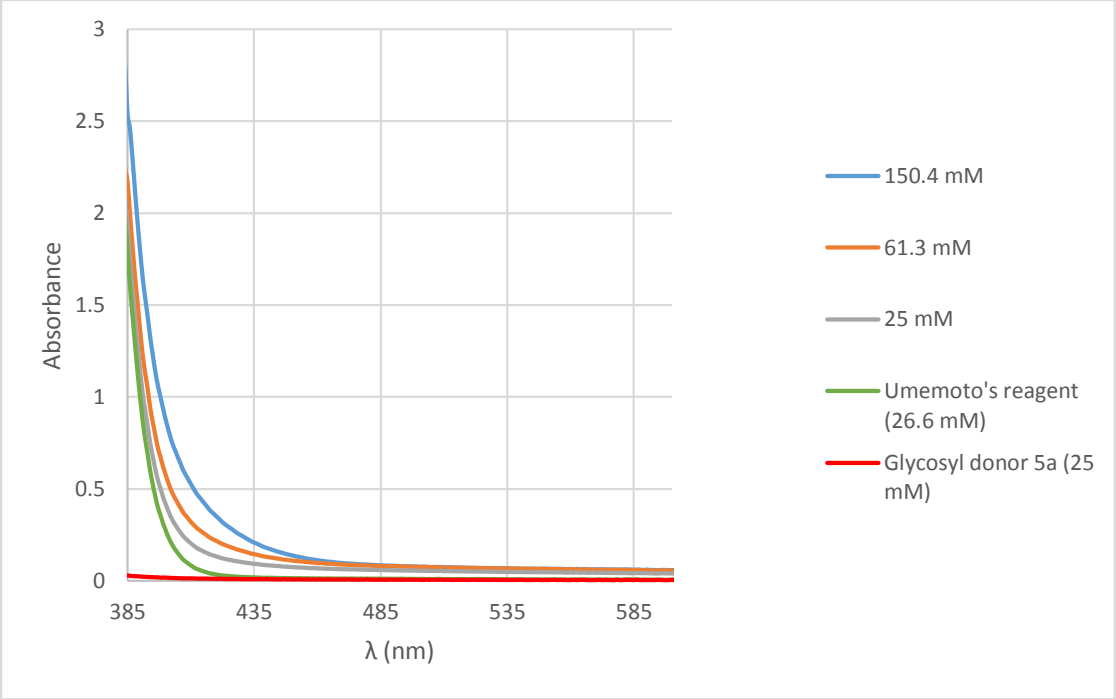


Figure 3.6 Titration experiment, evidence for EDA complex

system consisting of the complex of styrene and 4-methoxystyrene with the *S*-trifluoromethyldibenzothiophenium cation of Umemoto's Reagent (Figure 3.7). The electronic

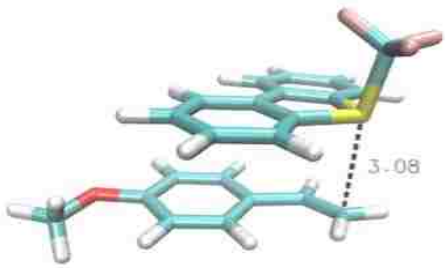
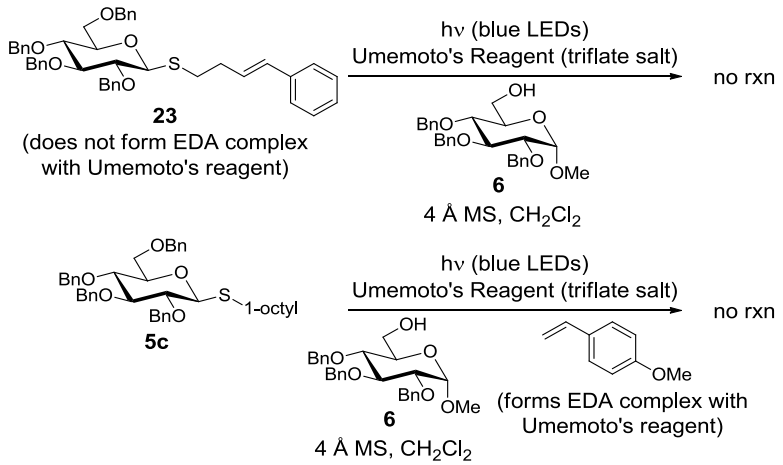


Figure 3.7 Structure of model system EDA Complex determined with DFT

structure calculations at the DFT level of theory on the ground state complex for each system showed that the charge transfer for low-lying isomers of the methoxystyrene-Umemoto's reagent complex was substanially higher (around 50%) than that of the styrene complex. The complexs all had interplanar distances around 3Å which is consitent with values reported in literature.[19] The involvement of Umemoto's reagent in the formation of EDA complexes has been shown in other

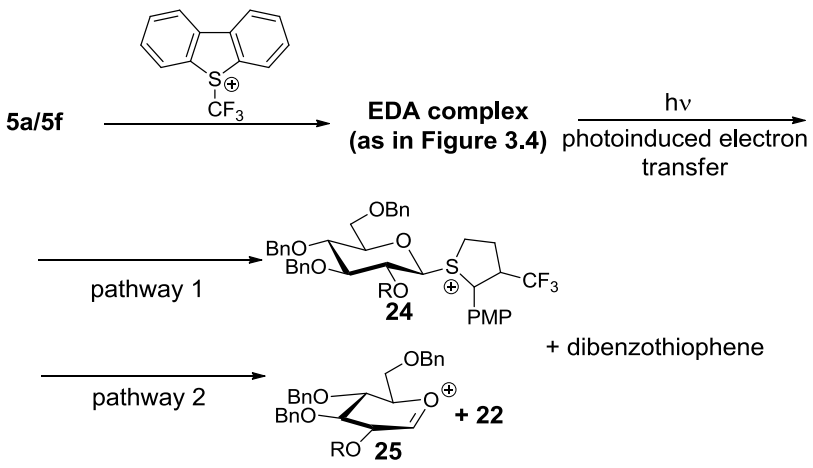
systems where it complexes with non styreneic species, further suggesting the feasibility of Umemoto's reagent in an EDA complex as a prerequisite to glycosylation.[19]

The presence of an EDA complex is strongly suggested by the data collected, however, the role, if any, of the EDA complex in the reaction mechanism was still undetermined. If the EDA complex is required for the reaction to occur, a similar glycosyl donor that does not form an EDA complex under the same reaction conditions would not be able to undergo *O*-glycosylation. Glycosyl donor 23 did not form a yellow color upon dissolution with Umemoto's reagent and showed no new absorbance in the UV-vis spectra. Thus the hypothesis was tested by performing the glycosylation with glycosyl donor 23 (Scheme 3.8). The glycosylation did not proceed, indicating that the EDA complex plays a role in the reaction mechanism. This idea was further investigated by subjecting glycosyl donor 5c to the normal reaction conditions with the addition of *p*-methoxylstyrene to the reaction mixture. Despite the formation of yellow color, the glycosyl donor 5c was not converted, suggesting that activation must occur intramolecularly.



Scheme 3.8 Role of EDA Complex in *O*-Glycosylation with 4-Aryl-3-butenylthioglucosides

The experimental and computational data suggest a mechanism shown in Scheme 3.9. The EDA complex of 5a (or 5f) is formed via π-π stacking of *p*-methoxystyrene moiety with the *S*-



Scheme 3.9 Preliminary mechanistic proposal

trifluoromethyldibenzothiophenium cation of Umemoto's reagent and absorbes a photon. The addition of trifluoromethyl and the intramolecular addition of the sulfur of 5a/5f across the styrenic double bond result in the direct formation of either 24 (pathway 1) or 25 + 22 (pathway 2) which is then intercepted by acceptor. During the conversion of EDA complex to 24/25, *S*-trifluoromethyldibenzothiophenium may undergo reduction by photoinduced electron transfer from thioglycoside sulfur to generate trifluoromethyl radical and dibenzothiophene.

3.3 Conclusion

I have developed an exceptionally mild, visible light-promoted *O*-glycosylation method using 4-methoxyphenyl-3-butenylthioglucoside donors in the presence of easily handled and bench stable Umemoto's reagent. The reaction conditions are selective for the glycosyl donors 5a/5f which were employed in the presence of other thioglycosides that proved to be orthogonal. It is strongly suggested that the reaction proceeds through a mechanism involving the EDA complex formed via interaction of glycosyl donor 5a/b and Umemoto's reagent. Alcohol acceptors ranging from primary to tertiary were used, providing moderate to high yields and complete selectivity for the *beta* anomer when using glycosyl donor 5f. This glycosylation is the mildest

visible light-promoted *O*-glycosylation method in the literature and may be useful for future attempts at synthesizing oligosaccharides due to its orthogonality.

3.4 Experimental

3.4.1 General Methods

Reagents were purchased from Sigma Aldrich and used as received. Flash column chromatography was performed using 60Å silica gel purchased from Sigma Aldrich. ^{1}H NMR and ^{13}C NMR spectroscopy were performed o n a Bruker AV-400 and AV- 500 spectrometer. Mass spectra were obtained using an Agilent 6210 electrospray time-of-flight mass spectrometer. UV-vis spectrophotometry was performed on a Varian Cary50 UV/vis spectrophotometer. Analytical and preparative TLC were conducted on aluminum sheets (Merck, silica gel 60, F254). Compounds were visualized by UV absorption (254 nm) and staining with anisaldehyde. 5 mL Pyrex micro reaction vessels (Supelco) were used in the glycosylation reactions. The triflate salt of Umemoto's reagent was used in all glycosylations. All glassware was flame-dried under vacuum and backfilled with dry nitrogen prior to use. Deuterated solvents were obtained from Cambridge Isotope Labs. All solvents were purified according to the method of Grubbs.[20]

3.4.2 Procedures and characterization

Procedure for glycosylations performed in presence of $Ru(bpy)_3(BArF)_2$

A flame-dried 5 mL Pyrex reactor vial was charged with the glycosyl donor (1 equiv., 0.150 mmol), $Ru(bpy)_3(BArF)_2$[21] (1 mol %, 1.5 μmol), 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP, 1.2 equiv., 0.180 mmol), Umemoto's reagent (1.07 equiv., 0.160 mmol), the glycosyl acceptor (3 equiv., 0.450 mmol), 300 mg of freshly activated 4 Å molecular sieves and 2 mL of dry solvent under nitrogen atmosphere. The reactor vial was placed 1-2 cm away from the light source (4W blue LEDs, 2 strips, Sapphire Blue LED Flex Strips from Creative Lighting Solutions,

were wrapped around a 150 × 75 Pyrex crystalizing dish (Figure 3.8), and irradiated from the side for 24 hours. The reaction mixture was then filtered to remove molecular sieves and the crude products were concentrated and then purified by gradient silica gel chromatography to afford a mixture of anomeric products.

Procedure for Optimized glycosylation conditions

A flame-dried 5 mL Pyrex reactor vial was charged with the glycosyl donor (1 equiv., 0.150 mmol), Umemoto's reagent (1.07 equiv., 0.160 mmol), the glycosyl acceptor (0.5 equiv., 0.0752 mmol), 150 mg of freshly activated 4 Å molecular sieves and 1 mL of dry dichloromethane under nitrogen atmosphere. The reactor vial was placed 1-2 cm away from the light source (4W blue LEDs, 2 strips, Sapphire Blue LED Flex Strips from Creative Lighting Solutions, were wrapped around a 150 × 75 Pyrex crystalizing dish, Figure S1) and irradiated from the side for 24 hours. The reaction mixture was then filtered to remove molecular sieves and the crude products were concentrated and then purified by gradient silica gel chromatography to afford a mixture of anomeric products.

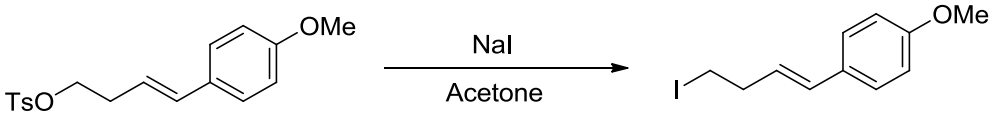
Determination of anomeric ratios

The anomeric ratio (α/β) was determined based on the integration of key resonances identified with the assistance of published ^{1}H NMR data. In the cases where spectral data was unavailable, the anomeric products were separated with silica gel chromatography or preparative TLC.

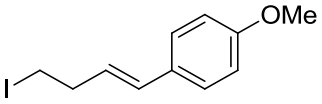
Experimental setup

Figure 3.8 Experimental setup

Synthesis of (*E*)-1-iodo-4-(4-methoxyphenyl)-3-butene

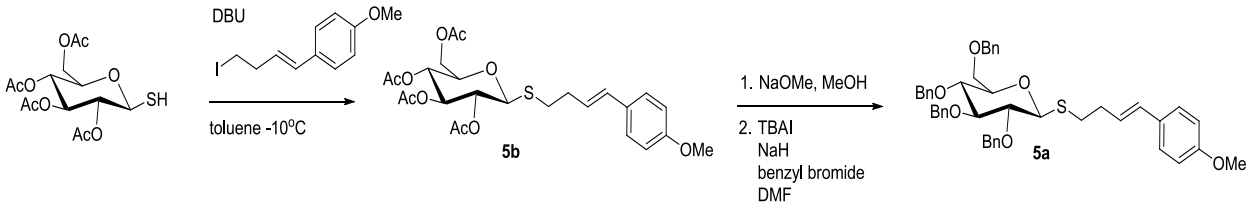


(*E*)-1-iodo-4-(4-methoxyphenyl)-3-butene

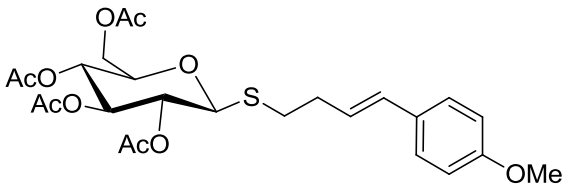


A 250 mL round bottom flask was charged with 6.00 g (18.0 mmol) of (*E*)-4-(4-methoxyphenyl)but-3-en-1-yl-*p*-toluenesulfonate[22] 10.3 g (68.7 mmol) of sodium iodide and 49 mL of acetone under nitrogen atmosphere. Reaction progress was monitored by TLC. After consumption of the tosylate (16 hrs) the solution was filtered through a pad of Celite using a fritted Buchner funnel. The filter cake was washed with pentane. The filtrate was then washed with 175 mL each of water and brine. The organic layer was then dried over Na_2SO_4, filtered and concentrated to give 4.86 g (94 % yield) of a yellow solid. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.29 (d, J = 9.0 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 6.41 (d, J = 15.8 Hz, 1H), 6.00 (dt, J = 15.7, 7.0 Hz, 1H), 3.80 (s, 3H), 3.23 (t, J = 7.3 Hz, 2H), 2.75 (qd, J = 7.1, 1.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.31, 131.88, 130.08, 127.53, 126.52, 114.22, 55.52, 37.29, 5.60. HRMS m/z Calcd for $C_{11}H_{13}IO$ $(M+H)^+$ 289.0084, found 289.0076.

Synthesis of glycosyl donors 5a and 5b



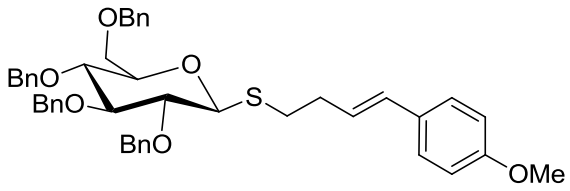
Glycosyl donor 5b ((*E*)-4-(4-methoxyphenyl)-3-butenyl β-D-1-thio-2,3,4,6-tetra-*O*-acetylglucopyranoside)



A 100 mL round bottom flask was charged with 3.70 g (10.2 mmol) of 2,3,4,6-Tetra-*O*-acetyl-1-mercapto-β-D-glucopyranosid[23] and 23 mL of toluene under nitrogen atmosphere. 1.53 mL (10.2 mmol) of 1,8-diazabicycloundec-7-ene was added to the reaction mixture at -10°C followed by 2.94 g (10.2 mmol) of (*E*)-1-iodo-4-(4-methoxyphenyl)-3-butene dissolved in 7 mL of toluene. After consumption of starting material as observed by TLC (1.5 hrs), the reaction was quenched with 36 mL of H_2O and the layers were separated. The aqueous layer was then extracted with 2 × 115 mL of DCM followed by dilution with 350 mL of DCM. The organic layer was then washed with 150 mL each of 1M H_2SO_4, saturated $NaHCO_3$, and brine. The organic layer was then dried over Na_2SO_4, filtered and concentrated to give 4.97 g of crude material. Purified by gradient silica gel chromatography 20% → 40% ethyl acetate in hexanes to give 4.65 g (87% yield) white solid. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.27 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 6.38 (d, J = 15.8 Hz, 1H), 6.05 (dt, J = 15.8, 6.9 Hz, 1H), 5.26 – 5.20 (m, 1H) , 5.07 (dt, J = 17.4, 9.7 Hz, 2H), 4.52 (d, J = 10.0 Hz, 1H), 4.25 (dd, J = 12.4, 5.0 Hz, 1H), 4.14 (dd, J = 12.4, 2.4 Hz, 1H), 3.80 (s, 3H), 3.71 (ddd,

J = 10.0, 4.9, 2.3 Hz, 1H), 2.80 (tdd, J = 20.1, 9.7, 6.0 Hz, 2H), 2.57 – 2.40 (m, 2H), 2.07 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.27, 170.78, 170.32, 169.56, 159.12, 131.15, 130.21, 127.34, 125.81, 114.12, 83.76, 76.07, 74.04, 70.02, 68.49, 62.32, 55.44, 33.43, 30.03, 20.90, 20.87, 20.77, 20.74. HRMS m/z Calcd for $C_{25}H_{32}NaO_{10}S$ $(M+Na)^+$ 547.1608, found 547.1613. $[\alpha]_D^{25}$ = -40.3 (*c*= 1, DCM).

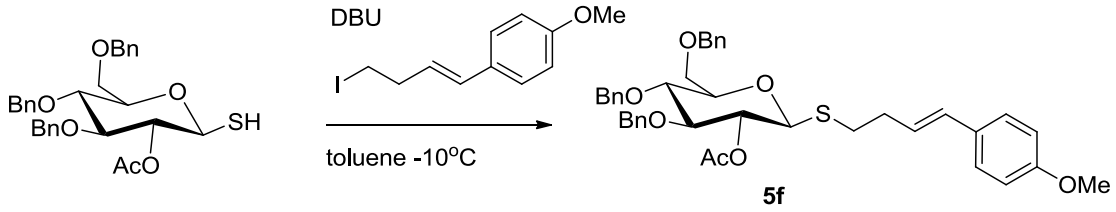
Glycosyl donor 5a ((*E*)-4-(4-methoxyphenyl)-3-butenyl β-D-1-thio-2,3,4,6-tetra-*O*-benzylglucopyranoside)



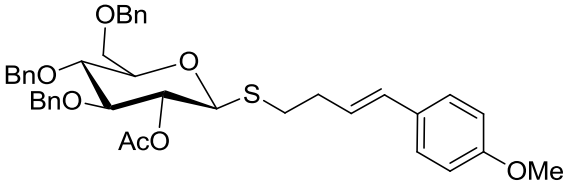
A 250 mL round bottom flask was charged with 4.65 g (8.86 mmol) of glycosyl donor 5b and 100 mL of methanol under a nitrogen atmosphere. 4.87 mL (4.87 mmol) of a 1M NaOMe solution was added via a syringe at once and the reaction was stirred for 15 hrs. The solvent was then removed giving 3.3 g of deprotected thioglucoside. 3 g of the crude product was then transferred to a 250 mL round bottom flask with 620 mg (1.68 mmol) of tetrabutylammonium iodide and 85 mL of DMF under a nitrogen atmosphere. 2.525 g (63.2 mmol) of sodium hydride (60% in mineral oil) was added to the solution at 0°C and the suspension was stirred for 30 minutes. 6.9 mL (57.8 mmol) of benzyl bromide was then added dropwise via a syringe to the suspension at 0°C. The suspension was then allowed to warm to 23°C and stir for 16 hrs. The reaction was then quenched with 60 mL of saturated ammonium chloride at 0°C followed by extraction with 2 × 65 mL Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to give 3.78 g of crude material. Purified by gradient silica gel chromatography 8% → 18% ethyl acetate in hexanes to give 3.42 g (54% yield over 2 steps) white solid. ^{1}H NMR (500

MHz, Chloroform-d) δ 7.40 – 7.20 (m, 20H), 7.17 (d, J = 7.5 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 6.37 (d, J = 15.8 Hz, 1H), 6.09 (dt, J = 15.7, 6.9 Hz, 1H), 4.92 (d, J = 10.6 Hz, 2H), 4.88 – 4.78 (m, 2H), 4.74 (d, J = 10.2 Hz, 1H), 4.64 – 4.52 (m, 3H), 4.49 (d, J = 9.7 Hz, 1H), 3.80 (s, 3H), 3.75 (dd, J = 10.9, 1.9 Hz, 1H), 3.71 – 3.65 (m, 2H), 3.65 – 3.59 (m, 1H), 3.51 – 3.39 (m, 2H), 2.95 – 2.76 (m, 2H), 2.56 (qd, J = 7.3, 1.4 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.10, 138.73, 138.41, 138.26, 138.18, 130.94, 130.47, 128.67, 128.65, 128.62, 128.60, 128.57, 128.54, 128.21, 128.19, 128.06, 128.02, 128.00, 127.98, 127.94, 127.93, 127.88, 127.80, 127.44, 127.43, 126.43, 114.14, 86.87, 85.52, 82.03, 79.35, 78.19, 75.98, 75.74, 75.28, 73.70, 69.37, 55.51, 33.84, 31.08. HRMS m/z Calcd for $C_{45}H_{48}NaO_6S$ $(M+Na)^+$ 739.3064, found 739.3073. $[\alpha]_D^{25}$ = -11.5 (*c*= 1, DCM).

Synthesis of glycosyl donor 5f



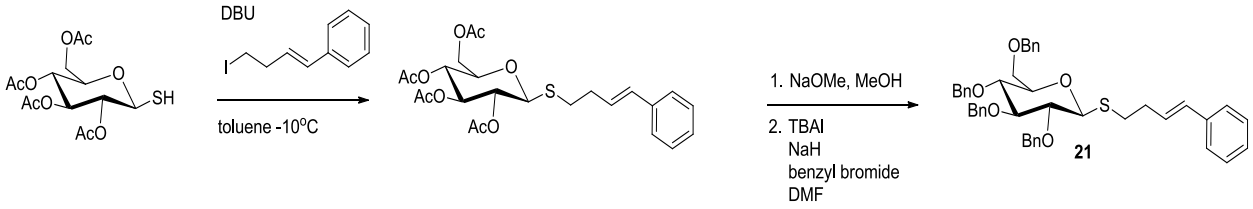
Glycosyl donor 5f ((*E*)-4-(4-methoxyphenyl)-3-butenyl β-D-1-thio-2-*O*-acetyl-3,4,6-tri-*O*-benzylglucopyranoside)



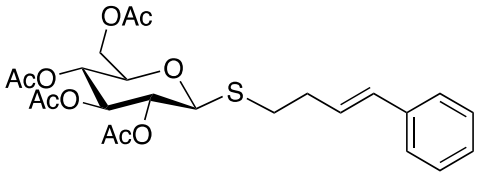
A 50 mL round bottom flask was charged with 1.803 g (3.545 mmol) 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-1-deoxy-1-mercapto-β-D-glucopyranoside[23] and 8 mL of toluene under nitrogen atmosphere. 0.54 mL (3.545 mmol) of 1,8-diazabicycloundec-7-ene was added to the reaction mixture at -10°C followed by 1.021 g (3.545 mmol) of (*E*)-1-iodo-4-(4-methoxyphenyl)-3-butene dissolved in 3 mL of toluene. After consumption of starting material as observed by TLC (2 hrs),

the reaction was quenched with 13 mL of H_2O. The solution was then extracted with 2 × 39 mL of DCM followed by dilution with 121 mL of DCM. The organic layer was then washed with 80 mL each of 1M H_2SO_4, saturated $NaHCO_3$, and brine. The organic layer was then dried over Na_2SO_4, filtered and concentrated to give 1.38 g of crude material. Purified by gradient silica gel chromatography 7% → 10% ethyl acetate in hexanes to give 992.8 mg (42% yield) white solid. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.41 – 7.22 (m, 15H), 7.19 (d, J = 3.8 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 6.35 (d, J = 15.8 Hz, 1H), 6.05 (dt, J = 16.0, 6.9 Hz, 1H), 5.09 – 5.02 (m, 1H) , 4.79 (dd, J = 11.1, 5.7 Hz, 2H), 4.68 (d, J = 11.5 Hz, 1H), 4.64 – 4.49 (m, 3H), 4.38 (d, J = 10.0 Hz, 1H), 3.78 (s, 3H), 3.76 – 3.64 (m, 4H), 3.50 (ddd, J = 9.7, 4.3, 2.0 Hz, 1H), 2.84 (ddd, J = 12.4, 8.4, 6.7 Hz, 1H), 2.76 (dt, J = 12.4, 7.5 Hz, 1H), 2.49 (dt, J = 11.1, 7.1 Hz, 2H), 1.96 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.82, 159.01, 138.34, 138.28, 138.05, 130.84, 130.40, 128.60, 128.54, 128.20, 128.03, 127.92, 127.90, 127.83, 127.75, 127.35, 126.31, 114.06, 84.53, 83.64, 79.66, 78.01, 75.37, 75.27, 73.64, 71.91, 69.03, 55.42, 33.60, 29.66, 21.14. HRMS m/z Calcd for $C_{40}H_{44}NaO_7S$ $(M+Na)^+$ 691.2700 , found 691.2710. $[\alpha]_D^{25}$ = -20.3 (*c*= 1, DCM).

Synthesis of glycosyl donor 21

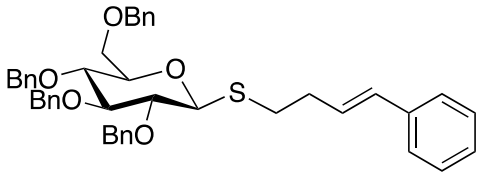


tetraacetyl-21 ((*E*)-4-phenyl-3-butenyl β-D-1-thio-2,3,4,6-tetra-*O*-acetylglucopyranoside)



A 100 mL round bottom flask was charged with 1.40 g (3.84 mmol) of 2,3,4,6-tetra-*O*-acetyl-1-mercapto-β-D-glucopyranoside[23] and 11.4 mL of toluene under nitrogen atmosphere. 0.58 mL (3.87 mmol) of 1,8-diazabicycloundec-7-ene was added to the reaction mixture at -10°C followed by 1.00 g (3.87 mmol) of (*E*)-1-Iodo-4-phenyl-3-butene[1] dissolved in 2.4 mL of toluene. After consumption of starting material as observed by TLC (2 hrs), the reaction was quenched with 15 mL of H_2O. The solution was then extracted with 2 × 45 mL of DCM followed by dilution with 135 mL of DCM. The organic layer was then washed with 36 mL each of 1M H_2SO_4, saturated $NaHCO_3$, and brine. The organic layer was then dried over Na_2SO_4, filtered and concentrated to give 3.39 g of crude material. Purified by gradient silica gel chromatography 20% → 30% ethyl acetate in hexanes to give 820 mg (43% yield) white solid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.34 (d, *J* = 7.2 Hz, 2H), 7.29 (t, *J* = 7.6 Hz, 2H), 7.21 (t, *J* = 7.2 Hz, 1H), 6.44 (d, *J* = 15.8 Hz, 1H), 6.20 (dt, *J* = 15.8, 6.9 Hz, 1H), 5.26 - 5.18 (m, 1H), 5.14 - 5.00 (m, 2H), 4.52 (d, *J* = 10.1 Hz, 1H), 4.25 (dd, *J* = 12.4, 5.0 Hz, 1H), 4.15 (dd, *J* = 12.4, 2.3 Hz, 1H), 3.72 (ddd, *J* = 10.1, 5.0, 2.4 Hz, 1H), 2.91 - 2.74 (m, 2H), 2.59 - 2.45 (m, 2H), 2.07 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.75, 170.30, 169.53, 137.39, 131.80, 128.68, 128.02, 127.40, 126.22, 83.75, 76.12, 74.05, 70.01, 68.51, 62.32, 33.41, 29.84, 20.88, 20.85, 20.75, 20.72. HRMS m/z Calcd for $C_{24}H_{30}NaO_9S$ $(M+Na)^+$ 517.1503, found 517.1499. $[\alpha]_D^{25}$ = -40.3 (*c*= 1, DCM).

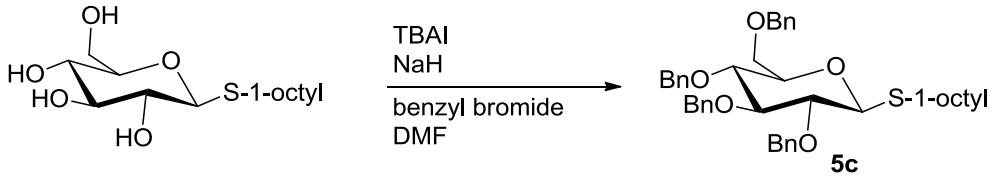
Glycosyl donor 21 ((*E*)-4-phenyl-3-butenyl β-D-1-thio-2,3,4,6-tetra-*O*-benzylglucopyranoside)



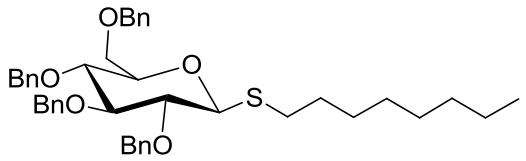
A 100 mL round bottom flask was charged with 523 mg (1.06 mmol) of tetraacetyl-21 and 13.4 mL of methanol under a nitrogen atmosphere. 0.58 mL (0.58 mmol) of a 1M NaOMe solution

was added via a syringe at once and the reaction was stirred for 15 hrs. The solvent was then removed giving the deprotected thioglucoside which was then transferred to a 100 mL round bottom flask with 78.1 mg (0.21 mmol) of tetrabutylammonium iodide and 11 mL of DMF under a nitrogen atmosphere. 316.9 mg (7.93 mmol) of sodium hydride (60% in mineral oil) was added to the solution at 0°C and the suspension was stirred for 30 minutes. 0.86 mL (7.23 mmol) of benzyl bromide was then added dropwise via a syringe to the suspension at 0°C. The suspension was then allowed to warm to 19°C and stir for 16 hrs. The reaction was then quenched with 10 mL of saturated ammonium chloride at 0°C followed by extraction with 2 × 10 mL Et_2O. The organic layer was dried over Na_2SO_4, filtered and concentrated to give 1.03 g of crude material. Purified by gradient silica gel chromatography 5% → 10% ethyl acetate in hexanes to give 456 mg (63% yield over 2 steps) white solid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.39 - 7.14 (m, 25H), 6.43 (d, *J* = 15.8 Hz, 1H), 6.24 (dt, *J* = 15.8, 6.9 Hz, 1H), 4.92 (d, *J* = 10.7 Hz, 2H), 4.86 - 4.79 (m, 2H), 4.74 (d, *J* = 10.2 Hz, 1H), 4.62 - 4.53 (m, 3H), 4.49 (d, *J* = 9.7 Hz, 1H), 3.75 (dd, *J* = 10.9, 1.9 Hz, 1H), 3.71 - 3.65 (m, 2H), 3.61 (m, *J* = 9.4 Hz, 1H), 3.50 - 3.43 (m, 2H), 2.94 - 2.80 (m, 2H), 2.59 (q, *J* = 6.7 Hz, 2H).^{13}C NMR (126 MHz, $CDCl_3$) δ 138.67, 138.35, 138.21, 138.11, 137.56, 131.52, 128.63, 128.58, 128.56, 128.54, 128.51, 128.47, 128.12, 127.98, 127.93, 127.91, 127.85, 127.80, 127.72, 127.27, 126.26, 86.81, 85.45, 81.97, 79.31, 78.14, 75.90, 75.67, 75.20, 73.64, 69.33, 33.77, 30.86. HRMS m/z Calcd for $C_{44}H_{46}NaO_5S$ $(M+Na)^+$ 709.2958, found 709.2977. $[\alpha]_D^{25}$ = -7.5 (*c*= 1, DCM).

Synthesis of glycosyl donor 5c

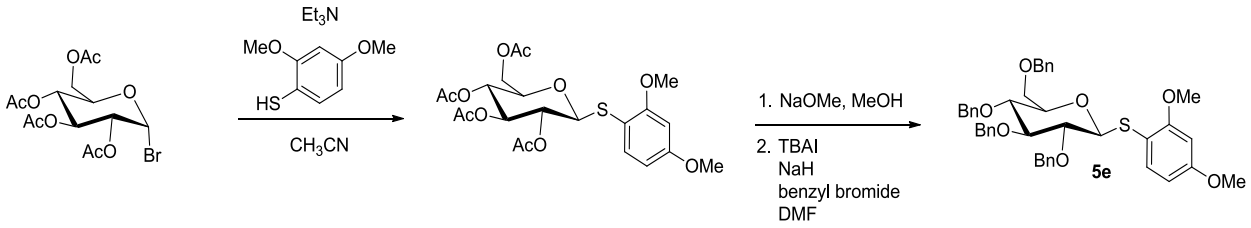


Glycosyl donor 5c (octyl β-D-1-thio-2,3,4,6-tetra-*O*-benzylglucopyranoside)

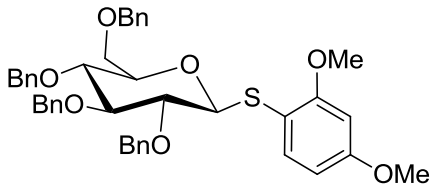


A 100 mL round bottom flask was charged with 1.07 g (3.47 mmol) of octyl β-D-1-thioglucopyranoside, 222 mg (0.600 mmol) of tetrabutylammonium iodide and 30 mL of DMF under a nitrogen atmosphere. 0.900 g (22.5 mmol) of sodium hydride (60% in mineral oil) was added to the solution at 0°C and the suspension was stirred for 30 minutes. 2.5 mL (21 mmol) of benzyl bromide was then added dropwise via a syringe to the suspension at 0°C. The suspension was allowed to warm to 23°C and stirred for 16 hrs. The reaction was then quenched with 22 mL of saturated ammonium chloride at 0°C followed by extraction with 2 × 25 mL Et_2O. The organic layer was washed with 35 mL of brine, dried over Na_2SO_4, filtered and concentrated to give 1.56 g of crude material. Purified by gradient silica gel chromatography 5% → 10% ethyl acetate in hexanes to give 1.25 g (54% yield) white solid. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.40 – 7.35 (m, 2H), 7.35 – 7.22 (m, 16H), 7.16 (dd, J = 7.5, 2.1 Hz, 2H), 4.92 (dd, J = 10.6, 5.4 Hz, 2H), 4.89 – 4.78 (m, 2H), 4.74 (d, J = 10.2 Hz, 1H), 4.63 – 4.51 (m, 3H), 4.44 (d, J = 9.7 Hz, 1H), 3.74 (dd, J = 11.0, 2.0 Hz, 1H), 3.71 – 3.64 (m, 2H), 3.65 – 3.58 (m, 1H), 3.50 – 3.39 (m, 2H), 2.82 – 2.61 (m, 2H), 1.71 – 1.59 (m, 2H), 1.46 – 1.33 (m, 2H), 1.33 – 1.18 (m, 8H), 0.88 (t, J = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.65, 138.35, 138.18, 138.13, 128.54, 128.52, 128.50, 128.45, 128.09, 127.95, 127.89, 127.88, 127.81, 127.77, 127.68, 86.79, 85.38, 81.95, 79.25, 78.09, 75.87, 75.62, 75.15, 73.56, 69.23, 31.96, 31.01, 30.04, 29.35, 29.32, 29.07, 22.80, 14.28. HRMS m/z Calcd for $C_{42}H_{52}NaO_5S$ $(M+Na)^+$ 691.3428, found 691.3457. $[\alpha]_D^{25}$ = -2.7 (*c*= 1, DCM).

Synthesis of Glycosyl donor 5e



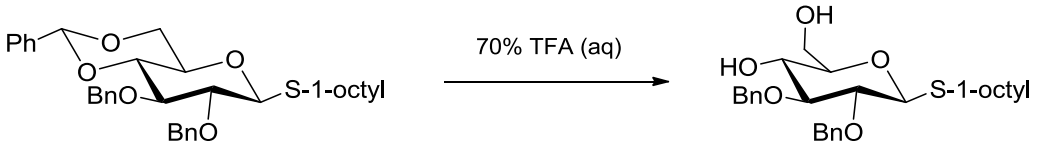
Glycosyl donor 5e (2,4-dimethoxyphenyl β-D-1-thio-2,3,4,6-tetra-*O*-benzylglucopyranoside)



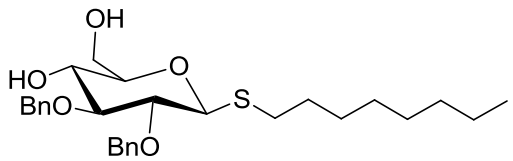
4.00 g (9.73 mmol) of α-1-bromoglucose tetraacetate was placed in a 100 mL round bottom flask and 20 mL of CH_3CN was added under a nitrogen atmosphere. 1.54 mL (10.7 mmol) of 2,4-dimethoxybenzenethiol and then 2.71 mL (19.4 mmol) of triethylamine were then added to the solution which was stirred for 16 h at 25°C. The solution was then diluted with 250 mL of DCM and washed with 3 × 350 mL water. The organic layer was then dried over Na_2SO_4, filtered and concentrated to give 4.54 g of crude material. Purified by gradient silica gel chromatography 30% → 70% ethyl acetate in hexanes to give 4.29 g (88 %) of a white solid (β–2,4-dimethoxyphenylthioglucose tetraacetate). All 4.29 g (8.57 mmol) of the product was placed in a 250 mL round bottom flask and dissolved in 94 mL of methanol under a nitrogen atmosphere. 4.71 mL (4.71 mmol) of a 1M NaOMe solution was added via a syringe at once and the reaction was stirred for 15 hrs at 25°C. The solvent was then removed resulting in 3.07 g of crude 2,4-dimethoxyphenylthioglucoside. 2.85 g of this crude product was then transferred to a 250 mL round bottom flask with 634 mg (1.72 mmol) of tetrabutylammonium iodide and 86 mL of DMF was added under a nitrogen atmosphere. 2.572 g (64.3 mmol) of sodium hydride (60% in mineral

oil) was added to the solution at 0°C and the suspension was stirred for 30 minutes. 7.0 mL (58.9 mmol) of benzyl bromide was then added dropwise via a syringe to the suspension at 0°C. The suspension was allowed to warm to 23°C and stir for 16 hrs. The reaction was then quenched with 65 mL of saturated ammonium chloride at 0°C followed by extraction with 2 × 70 mL Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to give 5.38 g of crude material. Purified by gradient silica gel chromatography 10% → 20% ethyl acetate in hexanes to give 4.79 g (81 %) white solid. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.57 (dd, J = 8.5, 1.4 Hz, 1H), 7.46 (d, J = 7.4 Hz, 2H), 7.35 – 7.25 (m, 18H), 7.22 – 7.17 (m, 2H), 6.42 (d, J = 2.6 Hz, 1H), 6.32 (dd, J = 8.5, 2.5 Hz, 1H), 4.97 (d, J = 10.1 Hz, 1H), 4.91 (d, J = 10.8 Hz, 1H), 4.87 – 4.79 (m, 2H), 4.73 (d, J = 10.1 Hz, 1H), 4.64 – 4.57 (m, 2H), 4.57 – 4.46 (m, 2H), 3.78 (s, 3H), 3.75 (s, 3H), 3.73 – 3.66 (m, 1H), 3.63 – 3.57 (m, 1H), 3.54 – 3.42 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.29, 160.00, 138.67, 138.61, 138.46, 138.26, 136.07, 128.65, 128.62, 128.58, 128.54, 128.48, 128.15, 128.05, 127.99, 127.97, 127.90, 127.67, 112.43, 105.23, 99.18, 87.05, 86.97, 81.43, 79.34, 78.10, 76.03, 75.53, 75.23, 73.65, 69.41, 55.96, 55.59. HRMS m/z Calcd for $C_{42}H_{44}NaO_7S$ $(M+Na)^+$ 715.2700, found 715.2714. $[\alpha]_D^{25}$ = -10.5 (*c*= 1.5, DCM).

Synthesis of octyl β-D-1-thio-2,3-di-*O*-benzylglucopyranoside



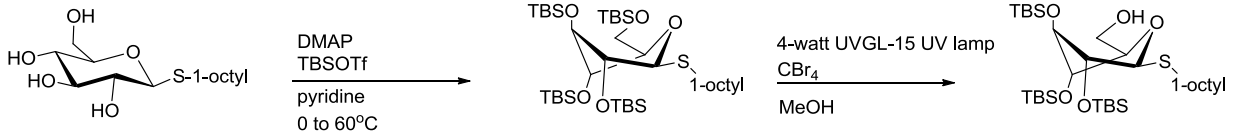
octyl β-D-1-thio-2,3-di-*O*-benzylglucopyranoside



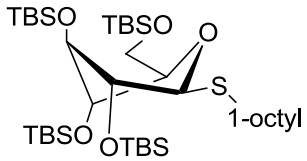
A 50 mL round bottom flask was charged with 1.1 g (1.907 mmol) of octyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-β-D-1-thioglucopyranoside,[24] 11.4 mL of 70% TFA (aq) under a

nitrogen atmosphere. The reaction was then stirred at 23°C for 2 h during which starting material was consumed. The reaction mixture was then concentrated to give 868.5 mg of crude material. Purified by gradient silica gel chromatography 5% → 40% ethyl acetate in hexanes to give 454.8 mg (49% yield) colorless oil. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.44 – 7.27 (m, 10H), 4.96 (dd, J = 10.9, 4.3 Hz, 2H), 4.72 (dd, J = 10.9, 9.1 Hz, 2H), 4.48 (d, J = 9.6 Hz, 1H), 3.87 (dd, J = 11.9, 3.5 Hz, 1H), 3.75 (dd, J = 11.9, 5.2 Hz, 1H), 3.60 – 3.54 (m, 1H), 3.52 – 3.46 (m, 1H), 3.41 – 3.36 (m, 1H), 3.33 (ddd, J = 9.1, 5.1, 3.5 Hz, 1H), 2.72 (qt, J = 12.5, 7.4 Hz, 2H), 2.19 (s, 2H), 1.71 – 1.55 (m, 2H), 1.45 – 1.34 (m, 2H) , 1.34 – 1.18 (m, 8H), 0.88 (t, J = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.59, 138.01, 128.88, 128.70, 128.66, 128.62, 128.57, 128.53, 128.22, 128.18, 128.14, 128.08, 86.12, 85.85, 81.76, 79.21, 75.62, 75.58, 70.72, 62.92, 32.00, 31.43, 30.11, 29.38, 29.37, 29.07, 22.85, 14.29. HRMS m/z Calcd for $C_{28}H_{40}NaO_5S$ $(M+Na)^+$ 511.2493 , found 511.2489. $[\alpha]_D^{25}$ = -37.8 (*c*= 1, DCM).

Synthesis of octyl β-D-1-thio-2,3,4-tri-*O*-*tert*-butyldimethylsilylglucopyranoside



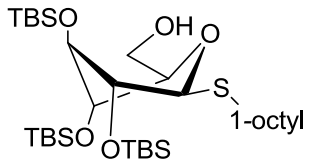
octyl β-D-1-thio-2,3,4,6-tetra-*O*-*tert*-butyldimethylsilylglucopyranoside



A 100 mL round bottom flask equipped with a reflux condenser was charged with 1 g (3.242 mmol) of octyl-β-D-thioglucopyranoside (Sigma Aldrich), 71.3 mg (0.584 mmol) of DMAP and 37 mL of pyridine under a nitrogen atmosphere. 5.36 mL (23.34 mmol) of *tert*-butyldimethylsilyl trifluoromethanesulfonate was then added to the solution at 0°C. The solution

was heated to 60°C and stirred for 24 hrs. The reaction was then allowed to cool to 23°C and quenched with 13 mL of methanol. The mixture was diluted with 110 mL of ethyl acetate followed by washing with 200 mL each of water, 1M HCl and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated to give 2.543 g of crude material. Purified by silica gel chromatography (20% ethyl acetate in hexanes) to give 2.34 g (94% yield) colorless oil. ^{1}H NMR (500 MHz, Chloroform-d) δ 4.67 (d, J = 8.0 Hz, 1H), 3.98 – 3.92 (m, 1H), 3.82 (d, J = 3.1 Hz, 1H), 3.77 – 3.70 (m, 1H), 3.62 (d, J = 8.0 Hz, 1H), 2.68 (ddd, J = 12.6, 8.0, 6.4 Hz, 1H), 2.58 (dt, J = 12.6, 7.5 Hz, 1H), 1.68 – 1.54 (m, 2H), 1.45 – 1.33 (m, 2H), 1.33 – 1.21 (m, 10H), 0.92 – 0.87 (m, 39H), 0.16 – 0.02 (m, 24H). 13C NMR (126 MHz, $CDCl_3$) δ 83.75, 83.56, 78.37, 70.24, 64.47, 32.07, 31.01, 30.09, 29.44, 29.41, 29.17, 26.30, 26.18, 26.06, 22.87, 18.57, 18.34, 18.18, 18.08, 14.31, -3.84, -3.91, -4.00, -4.18, -4.46, -4.49, -5.02, -5.04. HRMS m/z Calcd for $C_{38}H_{84}NaO_5SSi_4$ $(M+Na)^+$ 787.5009 , found 787.5005. $[\alpha]_D^{25}$ = - 9.4 (*c*= 1.1, DCM).

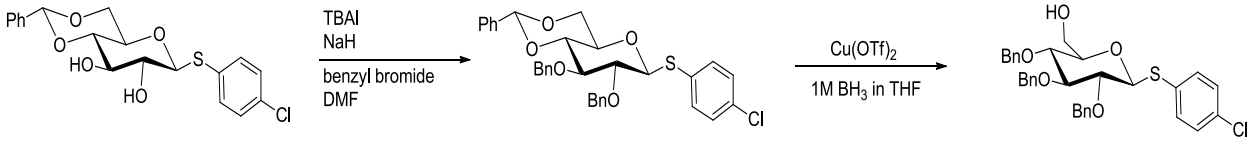
octyl β-D-1-thio-2,3,4-tri-*O*-*tert*-butyldimethylsilylglucopyranoside



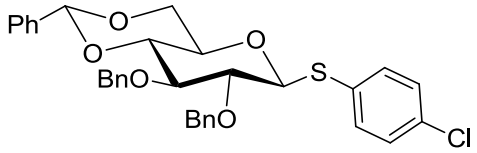
A 15 mL round bottom flask was charged with 300.0 mg (0.392 mmol) of octyl β-D-1-thio-2,3,4,6-tetra-*O*-*tert*-butyldimethylsilylglucopyranoside, 6.5 mg (20 μmol) of CBr_4 and 3.9 mL of methanol under a nitrogen atmosphere. The solution was irradiated with a 4-watt UVGL-15 UV lamp for 30 min. The reaction was then stirred at 23°C for 4 hrs and concentrated giving 220.5 mg of crude material. Purified by gradient silica gel chromatography 3% → 5% ethyl acetate in hexanes to give 169.8 mg (67% yield) colorless oil. ^{1}H NMR (500 MHz, Chloroform-d) δ 4.64 (d, J = 6.6 Hz, 1H), 3.81 (dd, J = 6.5, 3.3 Hz, 1H), 3.80 – 3.76 (m, 1H), 3.75 – 3.65 (m, 2H), 2.69

(ddd, J = 12.7, 8.0, 6.6 Hz, 1H), 2.61 (dt, J = 12.7, 7.5 Hz, 1H), 2.30 (dd, J = 7.5, 4.5 Hz, 1H), 1.68 – 1.54 (m, 2H), 1.44 – 1.33 (m, 2H), 1.34 – 1.20 (m, 10H), 0.96 – 0.80 (m, 30H), 0.17 – 0.04 (m, 18H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 85.22, 83.19, 77.50, 76.30, 71.46, 64.35, 32.04, 31.66, 30.14, 29.42, 29.40, 29.12, 26.21, 26.07, 26.04, 22.86, 18.29, 18.21, 18.12, 14.31, -4.04, -4.05, -4.11, -4.19, -4.71. HRMS m/z Calcd for $C_{32}H_{70}NaO_5SSi_3$ $(M+Na)^+$ 673.4144 , found 673.4141. $[\alpha]_D^{25}$ = -34.8 (*c*= 1, DCM).

Synthesis of 4-chlorophenyl β-D-1-thio-2,3,4-tri-*O*-benzylglucopyranoside



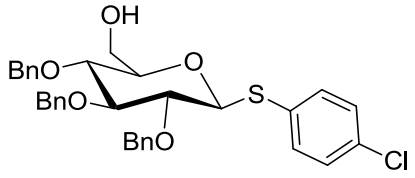
4-chlorophenyl 4,6-*O*-benzylidene-β-D-1-thio-2,3-di-*O*-benzylglucopyranoside



A 50 mL round bottom flask was charged with 500.0 mg (1.27 mmol) of 4-chlorophenyl 4,6-*O*-benzylidene-β-D-1-thioglucopyranoside,[25] 46.5 mg (0.126 mmol) of tetrabutylammonium iodide and 14 mL of DMF under a nitrogen atmosphere. 624.3 mg (15.62 mmol) of sodium hydride (60% in mineral oil) was added to the solution at 0°C and the suspension was stirred for 30 minutes. 0.37 mL (3.1 mmol) of benzyl bromide was then added dropwise via a syringe to the suspension at 0°C. The suspension was warmed to 23°C and stirred for 16 hrs. The reaction was then quenched with 10 mL of saturated ammonium chloride at 0°C followed by extraction with 2 × 11 mL Et_2O. The organic layer was washed with 50 mL of brine, dried over Na_2SO_4, filtered and concentrated to give 856 mg of crude material. Purified by gradient silica gel chromatography 10% → 20% ethyl acetate in hexanes to give 656 mg (90% yield) white solid. ^{1}H NMR (500 MHz,

Chloroform-d) δ 7.59 – 7.46 (m, 4H), 7.46 – 7.29 (m, 15H), 5.63 (s, 1H), 4.99 (d, J = 11.2 Hz, 1H), 4.87 (s, 2H), 4.82 (d, J = 11.2 Hz, 1H), 4.75 (d, J = 9.8 Hz, 1H), 4.42 (dd, J = 10.5, 5.0 Hz, 1H), 3.93 – 3.77 (m, 2H), 3.78 – 3.67 (m, 1H), 3.57 – 3.44 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.39, 138.06, 137.35, 134.42, 134.02, 131.59, 129.36, 129.21, 128.62, 128.60, 128.47, 128.37, 128.31, 128.14, 128.00, 126.17, 101.35, 88.34, 83.10, 81.62, 80.58, 76.11, 75.50, 70.46, 68.82. HRMS m/z Calcd for $C_{33}H_{31}ClNaO_5S$ $(M+Na)^+$ 597.1473 , found 597.1490. $[\alpha]_D^{25}$ = -36.6 (*c*= 0.66, DCM).

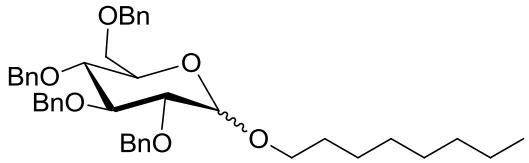
4-chlorophenyl β-D-1-thio-2,3,4-tri-*O*-benzylglucopyranoside



A 50 mL round bottom flask was charged with 950.0 mg (1.652 mmol) of 4-chlorophenyl 4,6-*O*-benzylidene-β-D-1-thio-2,3-di-*O*-benzylglucopyranoside, and 8.26 mL (8.26 mmol) of a 1M solution of borane in tetrahydrofuran under a nitrogen atmosphere. 29.9 mg (82.7 μmol) of copper (II) triflate was then added to the solution under a flow of nitrogen. The reaction was stirred for 3.5 hrs at which time 0.29 mL of triethylamine was added. 5 mL of methanol was then added dropwise into the solution (H_2 gas evolved). The mixture was concentrated to give 746 mg of crude material. Purified by gradient silica gel chromatography (10% → 30% ethyl acetate in hexanes) to give 656 mg (69% yield) white solid. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.43 (d, J = 8.5 Hz, 2H), 7.42 – 7.15 (m, 17H), 4.95 – 4.81 (m, 4H), 4.77 (d, J = 10.3 Hz, 1H), 4.66 (dd, J = 10.4, 5.6 Hz, 2H), 3.87 (ddd, J = 12.0, 6.0, 2.6 Hz, 1H), 3.78 – 3.62 (m, 2H), 3.62 – 3.53 (m, 1H), 3.50 – 3.41 (m, 1H) , 3.37 (ddd, J = 9.7, 4.6, 2.6 Hz, 1H), 1.84 (t, J = 6.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.41, 137.94, 134.18, 133.46, 132.06, 129.40, 128.75, 128.70, 128.68, 128.38, 128.27,

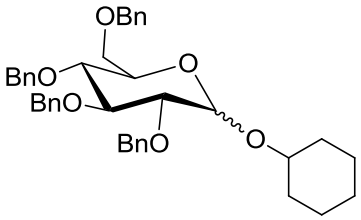
128.24, 128.20, 128.00, 127.98, 87.74, 86.70, 81.21, 79.57, 77.63, 76.05, 75.80, 75.35, 62.26. HRMS m/z Calcd for $C_{33}H_{33}ClNaO_5S$ $(M+Na)^+$ 599.1629 , found 599.1636. $[\alpha]_D^{25}$ = +3.1 (*c*= 1, DCM).

octyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside 8 [26]



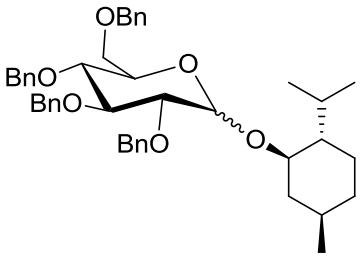
Started with 107.8 mg (0.150 mmol) of glycosyl donor 5a, 64.4 mg (0.160 mmol) of Umemoto's reagent, 11.9 µL (0.0752 mmol) 1-octanol, and 150 mg of 4Å MS in 1 mL of DCM. Purified to obtain 45.6 mg (93%) colorless oil in a 1:1 α:β mixture. Spectral data matched that previously reported in literature.[26]

cyclohexyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside 9 [27]



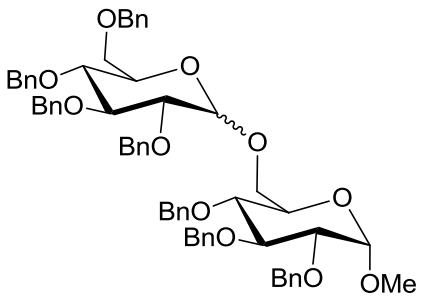
Started with 107.8 mg (0.150 mmol) of glycosyl donor 5a, 64.4 mg (0.160 mmol) of Umemoto's reagent, 7.8 µL (0.0752 mmol) cyclohexanol, 150 mg of 4Å MS, in 1 mL of DCM. Purified to obtain 42.2 mg (90%) colorless oil in a 1:1.8 α:β mixture. Spectral data matched that previously reported in literature.[27]

menthyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside 10 [27]



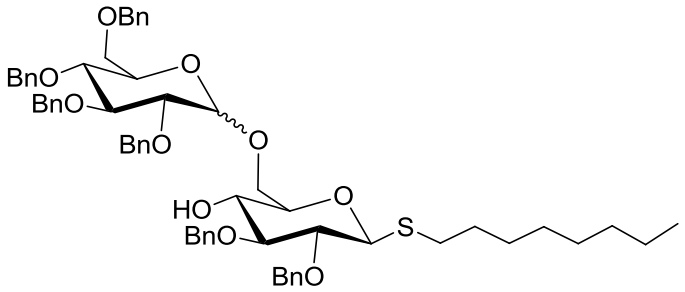
Started with 107.8 mg (0.150 mmol) of glycosyl donor 5a, 64.4 mg (0.160 mmol) of Umemoto's reagent, 11.8 mg (0.0755 mmol) (-)-menthol, 150 mg of 4Å MS, in 1 mL of DCM. Purified to obtain 38.4 mg (75%) white solid in a 1.5:1 α:β mixture. Spectral data matched that previously reported in literature.[27]

methyl-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside 7a [28]



Started with 107.8 mg (0.150 mmol) of glycosyl donor 5a, 64.4 mg (0.160 mmol) of Umemoto's reagent, 35.0 mg (0.0753 mmol) of methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside, 150 mg of 4Å MS, in 1 mL of DCM. Purified to obtain 56 mg (75%) colorless oil in a 1.6:1 (α:β) mixture. Spectral data matched that previously reported in literature.[28]

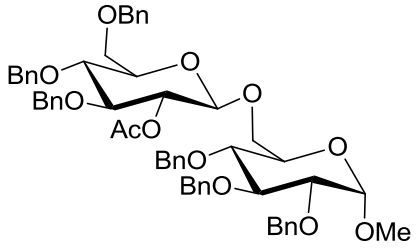
synthesis of disaccharide 11



Started with 107.8 mg (0.150 mmol) of glycosyl donor 5a, 64.4 mg (0.160 mmol) of Umemoto's reagent, 36.7 mg (0.0751 mmol) of octyl β-D-1-thio-2,3-di-*O*-benzylglucopyranoside, 150 mg of 4Å MS, in 1 mL of DCM. Purified to obtain 45.7 mg (60%) colorless oil in a 1.1:1 (α:β) mixture. α anomer ^{1}H NMR (500 MHz, Chloroform-d) δ 7.42 – 7.19 (m, 28H), 7.12 (d, J = 7.3, 2.3 Hz, 2H), 4.94 (d, J = 10.8 Hz, 1H), 4.92 – 4.74 (m, 6H), 4.69 (dd, J = 11.1, 9.4 Hz, 2H), 4.60 (d, J = 12.1 Hz, 1H), 4.50 – 4.40 (m, 2H), 3.99 – 3.90 (m, 2H), 3.83 (ddd, J = 10.2, 3.7, 2.0 Hz, 1H), 3.75 – 3.54 (m, 6H), 3.54 – 3.48 (m, 1H) , 3.46 (dt, J = 9.7, 5.0 Hz, 1H), 3.34 – 3.25 (m, 1H) , 3.11 (s, 1H), 2.71 (dt, J = 12.5, 7.2 Hz, 1H), 2.63 (dt, J = 12.5, 7.5 Hz, 1H), 1.67 – 1.51 (m, 4H , 1.40 – 1.16 (m, 10H), 0.86 (t, J = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.97, 138.54, 138.32, 138.32, 138.24, 138.09, 128.72, 128.68, 128.63, 128.60, 128.57, 128.54, 128.50, 128.20, 128.15, 128.12, 128.08, 128.04, 127.99, 127.94, 127.89, 127.80, 127.77, 97.92, 86.21, 85.37, 82.26, 81.37, 80.04, 77.69, 75.93, 75.67, 75.65, 75.17, 73.65, 73.41, 73.15, 70.55, 68.89, 68.61, 32.03, 31.03, 29.98, 29.44, 29.40, 29.08, 22.87, 14.31. HRMS m/z Calcd for $C_{62}H_{74}NaO_{10}S$ $(M+Na)^+$ 1033.4895 , found 1033.4928. $[\alpha]_D^{25}$ = +23.8 (c= 0.87, DCM). β anomer ^{1}H NMR (500 MHz, Chloroform-d) δ 7.43 – 7.19 (m, 28H), 7.16 – 7.12 (m, 2H), 4.93 (dd, J = 21.6, 10.9 Hz, 3H), 4.82 – 4.75 (m, 2H) , 4.76 – 4.67 (m, 2H), 4.60 (d, J = 12.2 Hz, 1H), 4.55 – 4.48 (m, 3H), 4.43 (d, J = 9.7 Hz, 1H), 4.13 (dd, J = 11.3, 3.3 Hz, 1H), 3.86 (dd, J = 11.3, 5.8 Hz, 1H), 3.74 – 3.63 (m, 2H), 3.63 – 3.53 (m, 3H), 3.52 – 3.40 (m, 4H), 3.40 – 3.30 (m, 1H),2.71 – 2.59 (m, 2H), 2.57 (s, 1H), 1.63 – 1.48 (m,

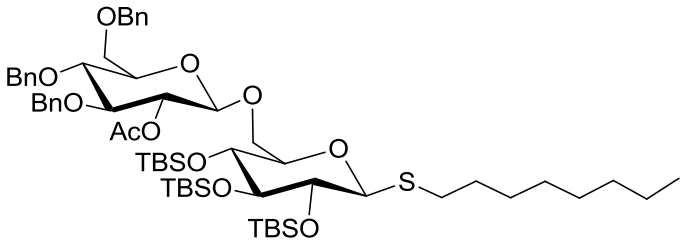
4H), 1.36 – 1.15 (m, 10H), 0.86 (t, J = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.82, 138.78, 138.62, 138.29, 138.28, 138.18, 128.79, 128.59, 128.57, 128.51, 128.40, 128.16, 128.15, 128.12, 128.11, 128.08, 128.03, 128.02, 127.99, 127.96, 127.90, 127.86, 127.82, 127.80, 103.98, 86.16, 85.55, 84.90, 82.24, 81.64, 78.82, 77.96, 75.90, 75.63, 75.58, 75.22, 75.01, 75.00, 73.70, 71.78, 69.73, 69.00, 32.03, 31.10, 29.92, 29.43, 29.12, 22.87, 14.32. HRMS m/z Calcd for $C_{32}H_{74}NaO_{10}S$ $(M+Na)^+$ 1033.4895 , found 1033.4893. $[\alpha]_D^{25}$ = - 7 (*c*= 0.58, DCM).

synthesis of disaccharide 14 [29]



Started with 100.6 mg (0.150 mmol) of glycosyl donor 5f, 64.4 mg (0.160 mmol) of Umemoto's reagent, 35 mg (0.0753 mmol) of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside, 150 mg of 4Å MS, in 1 mL of DCM. Purified to obtain 59.3 mg (84%) colorless oil. Spectral data matched that previously reported in literature.[29]

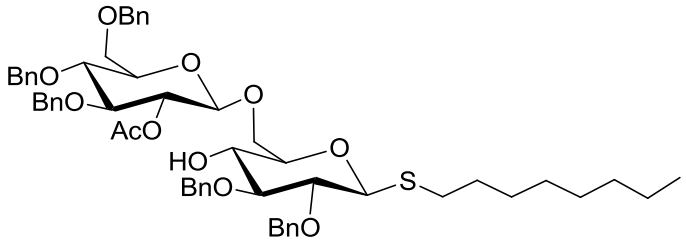
synthesis of disaccharide 18



Started with 100.6 mg (0.150 mmol) of glycosyl donor 5f, 64.4 mg (0.160 mmol) of Umemoto's reagent, 49 mg (0.0753 mmol) of octyl β-D-1-thio-2,3,4-tri-*O*-*tert*-butyldimethylsilylglucopyranoside, 150 mg of 4Å MS, in 1 mL of DCM. Purified to obtain 53.3

mg (63%) colorless oil. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.38 – 7.22 (m, 13H), 7.16 (d, J = 7.2, 2.4 Hz, 2H), 4.99 (dd, J = 9.6, 8.0 Hz, 1H), 4.77 (dd, J = 11.0, 5.5 Hz, 2H), 4.69 – 4.65 (m, 1H), 4.63 (d, J = 9.8 Hz, 1H), 4.61 – 4.52 (m, 2H), 4.53 – 4.45 (m, 2H), 3.94 (dd, J = 10.0, 5.6 Hz, 1H), 3.91 – 3.84 (m, 1H), 3.81 – 3.72 (m, 2H) , 3.72 – 3.59 (m, 4H), 3.43 (d, J = 9.9, 3.9, 1.9 Hz, 1H), 2.68 (ddd, J = 12.6, 8.0, 6.3 Hz, 1H), 2.57 (dt, J = 12.6, 7.5 Hz, 1H), 1.97 (s, 3H), 1.68 – 1.54 (m, 2H), 1.45 – 1.32 (m, 2H), 1.33 – 1.19 (m, 10H), 0.95 – 0.77 (m, 30H), 0.15 – 0.02 (m, 18H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.69, 138.41, 138.31, 138.24, 128.62, 128.58, 128.54, 128.51, 128.14, 127.98, 127.96, 127.85, 127.74, 101.54, 83.74, 83.39, 81.91, 78.13, 77.68, 77.51, 76.51, 75.25, 75.21, 75.16, 73.63, 73.38, 71.15, 68.85, 32.04, 30.78, 29.99, 29.48, 29.42, 29.17, 26.23, 26.07, 26.01, 22.85, 21.24, 18.29, 18.14, 18.03, 14.29, -3.91, -3.96, -4.07, -4.21, -4.48, -4.69. HRMS m/z Calcd for $C_{61}H_{100}NaO_{11}SSi_3$ $(M+Na)^+$ 1147.6186 , found 1147.6188. $[\alpha]_D^{25}$ = -69.6 (*c*= 2.55, DCM).

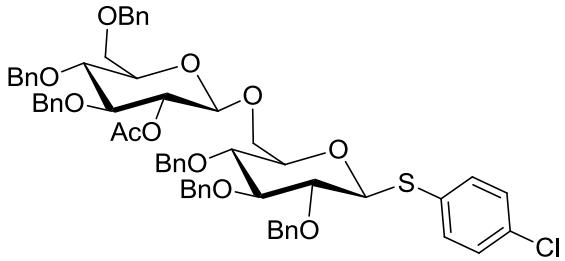
synthesis of disaccharide 15



Started with 100.6 mg (0.150 mmol) of glycosyl donor 5f, 64.4 mg (0.160 mmol) of Umemoto's reagent, 36.7 mg (0.0751 mmol) of octyl β-D-1-thio-2,3-di-*O*-benzylglucopyranoside, 150 mg of 4Å MS, in 1 mL of DCM. Purified to obtain 41.5 mg (57%) colorless oil. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.44 – 7.21 (m, 23H), 7.13 (dd, J = 7.0, 2.6 Hz, 2H), 5.02 (dd, J = 9.3, 8.0 Hz, 1H), 4.95 – 4.81 (m, 3H), 4.81 – 4.70 (m, 3H), 4.66 (d, J = 11.4 Hz, 1H), 4.61 (d, J = 12.2 Hz, 1H), 4.55 – 4.46 (m, 2H), 4.46 – 4.39 (m, 1H), 4.00 (dd, J = 11.3, 3.5 Hz, 1H), 3.82 (dd, J = 11.3, 5.0 Hz, 1H), 3.69 (q, J = 4.0, 3.1 Hz, 2H), 3.67 – 3.57 (m, 2H), 3.54 – 3.44 (m, 2H), 3.36 (ddd, J

= 9.8, 8.5, 4.4 Hz, 2H), 2.92 (s, 1H), 2.78 – 2.58 (m, 2H), 1.97 (s, 3H), 1.71 – 1.56 (m, 4H), 1.45 – 1.34 (m, 2H), 1.34 – 1.17 (m, 8H), 0.87 (t, J = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.75, 138.97, 138.31, 138.24, 137.97, 137.95, 128.67, 128.62, 128.54, 128.20, 128.12, 128.07, 128.04, 128.00, 127.94, 127.91, 100.62, 86.02, 85.44, 83.09, 81.49, 78.72, 77.84, 75.64, 75.59, 75.29, 75.24, 75.11, 73.71, 72.67, 71.66, 68.49, 67.87, 32.03, 31.04, 29.89, 29.42, 29.09, 22.86, 21.14, 14.31. HRMS m/z Calcd for $C_{57}H_{70}NaO_{11}S$ $(M+Na)^+$ 985.4531 , found 985.4543. $[\alpha]_D^{25}$ = -31.8 (*c*= 1.85, DCM).

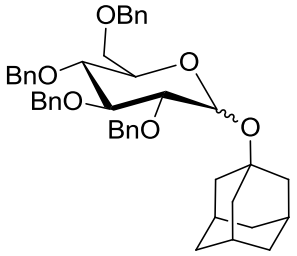
synthesis of disaccharide 17



Started with 100.6 mg (0.150 mmol) of glycosyl donor 5f, 64.4 mg (0.160 mmol) of Umemoto's reagent, 43.4 mg (0.0752 mmol) of 4-chlorophenyl β-D-1-thio-2,3,4-tri-*O*-benzylglucopyranoside, 150 mg of 4Å MS, in 1 mL of DCM. Purified to obtain 58.2 mg (74%) white solid. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.49 (d, J = 8.5, 1.8 Hz, 2H), 7.40 – 7.20 (m, 30H), 7.18 (d, J = 8Hz, 2H), 5.11 – 5.01 (m, 1H), 4.92 – 4.74 (m, 6H), 4.73 – 4.64 (m, 2H), 4.63 – 4.53 (m, 4H), 4.50 (d, J = 12.2 Hz, 1H), 4.44 (d, J = 8.0, 1.8 Hz, 1H), 4.11 (d, J = 11.1, 1.9 Hz, 1H), 3.78 – 3.59 (m, 6H), 3.56 – 3.38 (m, 4H), 1.86 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.45, 138.44, 138.29, 138.18, 138.08, 138.06, 138.01, 133.81, 133.25, 132.42, 129.39, 128.65, 128.62, 128.59, 128.57, 128.52, 128.25, 128.18, 128.02, 127.96, 127.90, 127.87, 127.85, 127.75, 101.00, 87.49, 86.67, 83.21, 80.67, 78.82, 78.14, 77.77, 77.77, 75.90, 75.54, 75.41, 75.27, 75.24, 75.18,

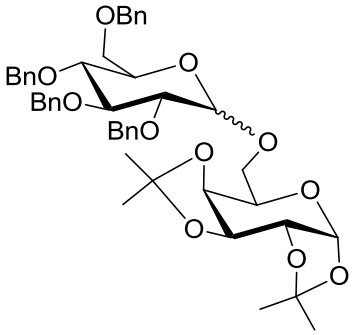
75.08, 73.70, 73.13, 68.90, 67.88, 21.07. HRMS m/z Calcd for $C_{62}H_{63}ClNaO_{11}S$ $(M+Na)^+$ 1073.3672 , found 1073.3644. $[\alpha]_D^{25}$ = -31.2 (*c*= 2.5, DCM).

1-adamantyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside 13 [30]



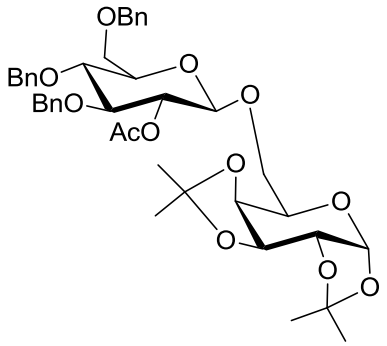
Started with 107.8 mg (0.150 mmol) of glycosyl donor 5a, 64.4 mg (0.160 mmol) of Umemoto's reagent, 11.4 mg (0.0752 mmol) of 1-adamantanol, 150 mg of 4Å MS, in 1 mL of DCM. Purified to obtain 43.3 mg (85%) colorless oil in a 1.1:1 α:β mixture. Spectral data matched that previously reported in literature.[30]

Synthesis of disaccharide 12[30]



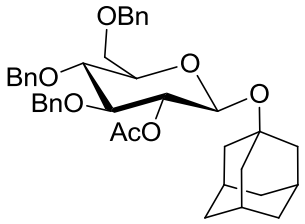
Started with 107.8 mg (0.150 mmol) of glycosyl donor 5a, 64.4 mg (0.160 mmol) of Umemoto's reagent, 19.6 mg (0.0752 mmol) of 1,2,3,4-di-*O*-isopropylidene-D-galactopyranose, 150 mg of 4Å MS, in 1 mL of DCM. Purified to obtain 51.2 mg (87%) colorless oil in a 1.3:1 α:β mixture. Spectral data matched that previously reported in literature.[30]

Synthesis of disaccharide 16[31]



Started with 100.6 mg (0.150 mmol) of glycosyl donor 5f, 64.4 mg (0.160 mmol) of Umemoto's reagent, 19.6 mg (0.0752 mmol) of 1,2,3,4-di-O-isopropylidene-D-galactopyranose, 150 mg of 4Å MS, in 1 mL of DCM. Purified to obtain 50.6 mg (92%) colorless oil. Spectral data matched that previously reported in the literature.[31]

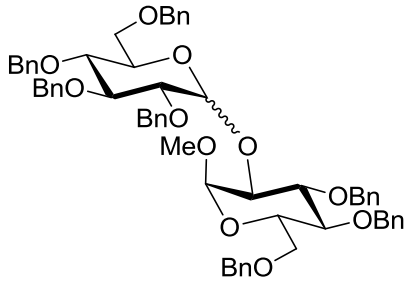
(1-adamantyl)-2-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranoside 19



Started with 100.6 mg (0.150 mmol) of glycosyl donor 5f, 64.4 mg (0.160 mmol) of Umemoto's reagent, 11.4 mg (0.0752 mmol) of 1-adamantanol, 150 mg of 4Å MS, in 1 mL of DCM. Purified to obtain 25.4 mg (54%) colorless oil. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.39 – 7.22 (m, 13H), 7.20 (dd, J = 7.6, 1.9 Hz, 2H), 4.94 (dd, J = 9.4, 7.9 Hz, 1H), 4.78 (dd, J = 11.2, 9.1 Hz, 2H), 4.73 – 4.51 (m, 4H), 3.74 (dd, J = 10.9, 2.0 Hz, 1H), 3.71 – 3.54 (m, 2H), 3.48 (ddd, J = 9.7, 5.6, 2.0 Hz, 1H), 2.20 – 2.07 (m, 3H), 1.96 (s, 3H), 1.83 (dq, J = 11.9, 2.4 Hz, 3H), 1.76 – 1.65 (m, 3H), 1.67 – 1.53 (m, 8H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.51, 138.57, 138.51, 138.22, 128.61, 128.60, 128.49, 128.21, 128.08, 128.01, 127.87, 127.80, 127.68, 94.18, 83.54, 78.54,

75.16, 75.13, 73.77, 73.62, 69.48, 42.71, 36.43, 30.85, 21.26. HRMS m/z Calcd for $C_{39}H_{46}NaO_7$ $(M+Na)^+$ 649.3136 , found 649.3123. $[\alpha]_D^{25}$ = 3.8 (*c*= 1, DCM).

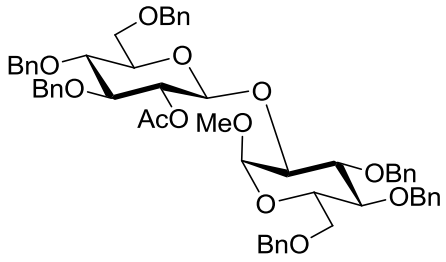
methyl-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-(1→2)-3,4,6-tri-*O*-benzyl-α-D-glucopyranoside 20



Started with 107.8 mg (0.150 mmol) of glycosyl donor 5a, 64.4 mg (0.160 mmol) of Umemoto's reagent, 35.0 mg (0.0752 mmol) of methyl-3,4,6-tri-*O*-benzyl-α-D-glucopyranoside,[13] 150 mg of 4Å MS, in 1 mL of DCM. Purified to obtain 60.0 mg (81%) colorless oil in a 2:1 (α:β) mixture. α anomer ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.40 – 7.19 (m, 27H), 7.18 – 7.06 (m, 6H), 7.00 (m, , 2H), 4.94 (ddd, *J* = 15.8, 13.1, 10.5 Hz, 4H), 4.88 – 4.74 (m, 5H), 4.71 (d, *J* = 12.2 Hz, 1H), 4.61 (d, *J* = 12.1 Hz, 1H), 4.57 – 4.41 (m, 4H), 4.32 (d, *J* = 12.1 Hz, 1H), 4.08 (td, *J* = 9.4, 7.9 Hz, 2H), 4.00 (dt, *J* = 10.3, 2.5 Hz, 1H), 3.84 (dd, *J* = 9.9, 3.4 Hz, 1H), 3.79 (ddd, *J* = 10.4, 3.9, 2.0 Hz, 1H), 3.75 – 3.55 (m, 6H), 3.53 (dd, *J* = 10.9, 3.0 Hz, 1H), 3.45 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.97, 138.91, 138.66, 138.53, 138.36, 138.18, 138.13, 128.72, 128.67, 128.63, 128.61, 128.58, 128.55, 128.51, 128.49, 128.37, 128.26, 128.24, 128.21, 128.17, 128.13, 128.08, 128.06, 128.03, 127.88, 127.85, 127.81, 127.79, 127.75, 127.70, 127.57, 96.56, 94.34, 82.36, 80.96, 79.23, 78.20, 77.80, 76.43, 75.88, 75.16, 75.06, 74.90, 73.72, 73.54, 73.04, 70.42, 70.30, 68.76, 68.30, 55.06 HRMS m/z Calcd for $C_{62}H_{66}NaO_{11}$ $(M+Na)^+$ 1009.4497, found 1009.4504. $[\alpha]_D^{25}$ = 79.4 (*c*= 0.85 , DCM). β anomer ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.42 – 7.06 (m, 35H), 5.05 – 4.95 (m, 2H), 4.93 – 4.74 (m, 4H), 4.75 – 4.56 (m, 4H), 4.50 (ddd, *J* = 19.7, 10.8, 6.3 Hz,

4H), 4.07 – 3.99 (m, 1H), 3.86 (dd, *J* = 9.8, 3.5 Hz, 1H), 3.81 (dt, *J* = 10.5, 2.8 Hz, 1H), 3.78 – 3.56 (m, 10H), 3.55 – 3.49 (m, 1H), 3.41 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.78, 138.64, 138.40, 138.31, 138.25, 138.20, 128.65, 128.58, 128.53, 128.51, 128.49, 128.39, 128.31, 128.19, 128.18, 128.16, 128.11, 128.08, 128.06, 128.02, 127.98, 127.96, 127.93, 127.88, 127.83, 127.73, 127.53, 127.47, 104.18, 99.95, 85.01, 82.26, 81.98, 78.83, 78.50, 77.97, 75.81, 75.35, 75.19, 74.94, 73.73, 73.71, 70.20, 69.01, 68.80, 55.37. HRMS m/z Calcd for $C_{62}H_{66}NaO_{11}$ $(M+Na)^+$ 1009.4497, found 1009.4522. $[\alpha]_D^{25}$ = 21 (*c*= 0.22 , DCM).

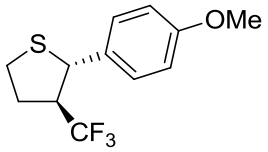
methyl-*O*-(2-acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)-(1→2)-3,4,6-tri-*O*-benzyl-α-D-glucopyranoside 21



Started with 100.6 mg (0.150 mmol) of glycosyl donor 5f, 64.4 mg (0.160 mmol) of Umemoto's reagent, 35.0 mg (0.0752 mmol) of methyl-3,4,6-tri-*O*-benzyl-α-D-glucopyranoside,[13] 150 mg of 4Å MS, in 1 mL of DCM. Purified to obtain 31.0 mg (44%) white solid as the β anomer. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.38 – 7.19 (m, 26H), 7.20 – 7.13 (m, 2H), 7.06 (dd, *J* = 6.7, 3.0 Hz, 2H), 5.11 (dd, *J* = 9.4, 8.0 Hz, 1H), 4.97 (d, *J* = 3.5 Hz, 1H), 4.87 – 4.79 (m, 2H), 4.79 – 4.72 (m, 2H), 4.70 (d, *J* = 11.3 Hz, 1H), 4.68 – 4.58 (m, 2H), 4.56 (d, *J* = 5.1 Hz, 1H), 4.55 – 4.46 (m, 2H), 4.44 (d, *J* = 10.8 Hz, 1H), 3.98 – 3.91 (m, 1H), 3.79 – 3.59 (m, 6H), 3.46 (ddd, *J* = 9.7, 4.4, 2.1 Hz, 1H), 3.36 (s, 3H), 1.63 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.55, 138.99, 138.40, 138.25, 138.17, 138.11, 137.98, 128.64, 128.62, 128.60, 128.57, 128.55, 128.52, 128.48, 128.26, 128.16, 128.10, 128.06, 128.00, 127.96, 127.93, 127.90, 127.87, 127.82, 127.79, 127.60, 127.55,

102.38, 99.73, 83.39, 81.17, 81.15, 78.07, 78.05, 75.26, 75.20, 75.18, 73.72, 73.69, 73.12, 70.07, 69.01, 68.71, 55.44, 20.86 HRMS m/z Calcd for $C_{57}H_{62}NaO_{12}$ $(M+Na)^+$ 961.4133, found 961.4145. $[\alpha]_D^{25}$ = 37.7 (*c*= 1.1 , DCM).

Tetrahydrothiophene by-product (+/-) - 22



The compound was purified from early-eluting column chromatography fractions from an *O*-glycosylation procedure using preparative TLC with hexanes as eluent. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.32 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 4.55 (d, J = 8.6 Hz, 1H), 3.79 (s, 3H), 3.19 (ddd, J = 10.8, 8.9, 6.3 Hz, 1H), 3.03 (ddd, J = 11.2, 7.1, 4.3 Hz, 1H), 2.93 (dtd, J = 9.5, 8.2, 6.4 Hz, 1H), 2.54 (dtd, J = 12.9, 6.4, 4.4 Hz, 1H), 2.30 (dtd, J = 13.1, 9.3, 7.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.02, 132.43, 129.13 (q, J= 165.06 Hz) 128.84, 113.96, 55.33 (q, J= 26.46 Hz) 55.24, 50.60, 32.25, 31.15. m/z Calcd for $C_{12}H_{14}F_3OS$ $(M+H)^+$ 263.0712 , found 263.0707.

Light on/off experiment

A reaction of donor 5a with acceptor 6 was performed at one half the scale of the typical *O*-glycosylation procedure under dry N_2 in an NMR tube using CD_3CN as solvent. Umemoto's reagent dissolved completely under these conditions (CH_2Cl_2 does not). ^{1}H NMR was recorded at 2 h intervals after periods of irradiation with blue LEDs or being kept in the dark. The experiment was conducted for a total of 10 hrs. The integration of the styrenic resonances of 5a were compared using the CD_2HCN proton signal at 1.93 ppm as an internal standard to monitor reaction progress.

Hours 0-2, 4-6 and 8-10 comprised periods of irradiation while the NMR tube was kept in the dark for hours 2-4 and 4-8 (Figure 3.9).

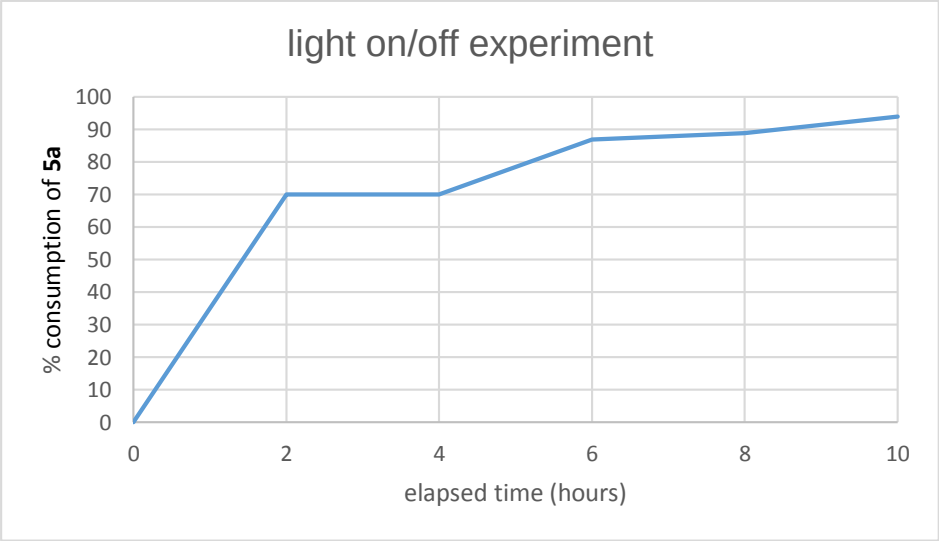


Figure 3.9 Light on light off experiment

Photograph of Yellow EDA complex Figure 3.10

Figure 3.10 Yellow EDA complex

left NMR tube: 25 mM 5a center: 26.6 mM Umemoto's reagent right: mixture of both (all are solutions in CD_3CN)

Spectrophotometry (Figures 3.11-3.15)

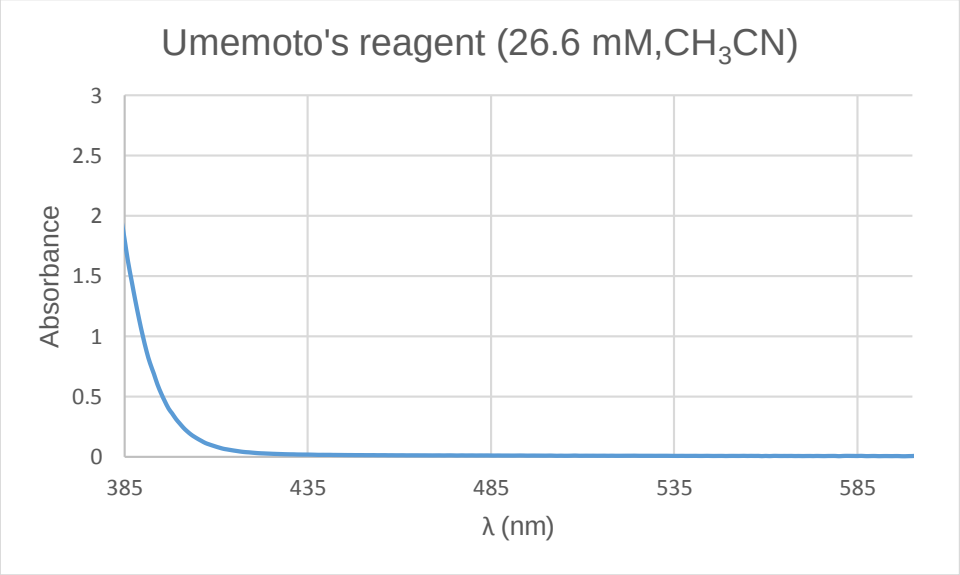


Figure 3.11 Umemoto's reagent UV-Vis

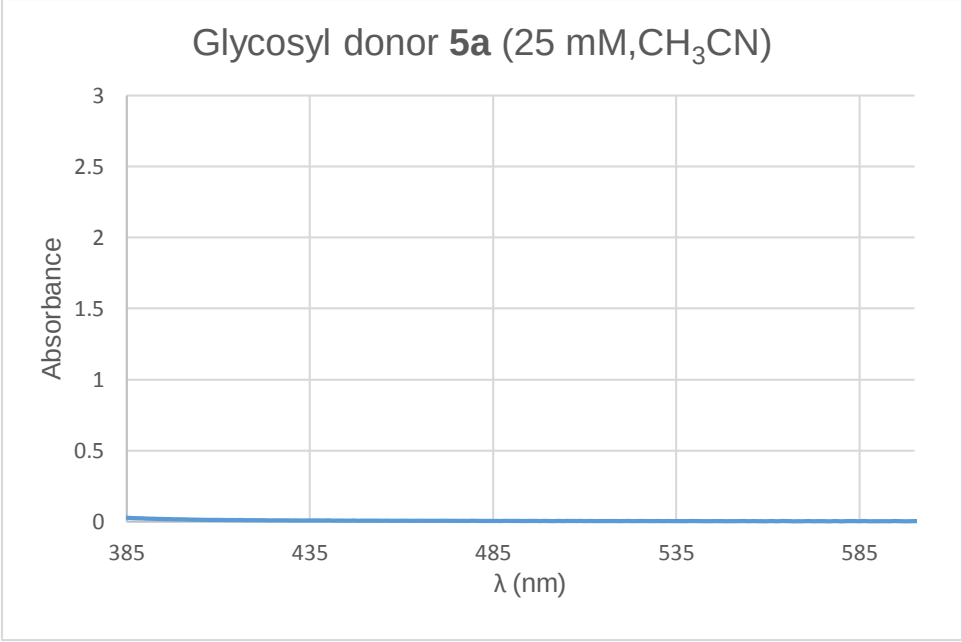


Figure 3.12 Glycosyl donor 5a UV-Vis

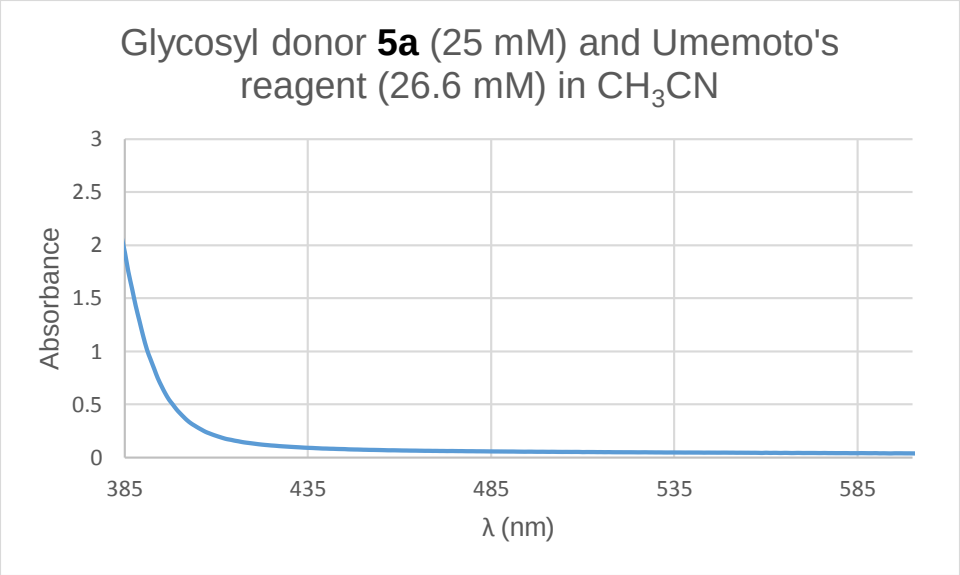


Figure 3.13 Glycosyl donor 5a and Umemoto's reagent mix UV-Vis

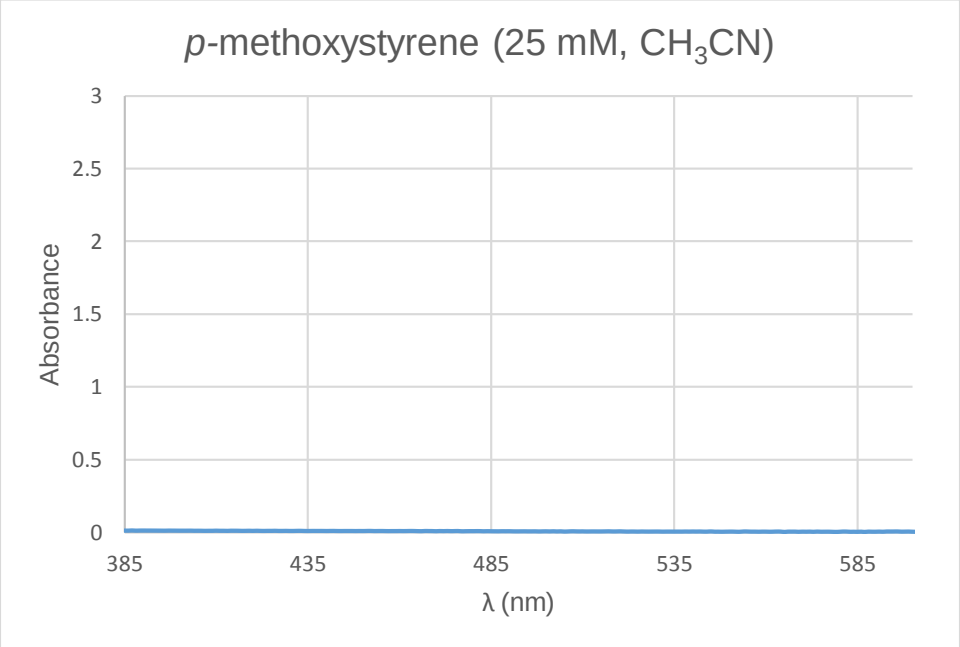


Figure 3.14 *p*-methoxystyrene UV-Vis

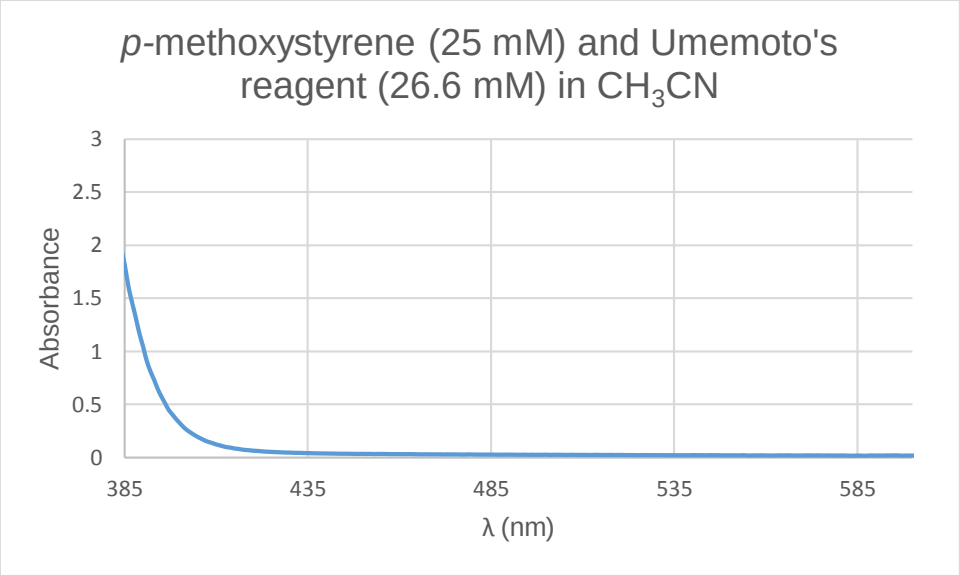


Figure 3.15 *p*-methoxystyrene and Umemoto's reagent mix UV-Vis

In order to see the effect of concentration on the formation of the charge transfer complex, a series of UV-vis spectra was obtained by varying the concentration of *p*-methoxystyrene and keeping the concentration of Umemoto's reagent steady at 26.6 mM.

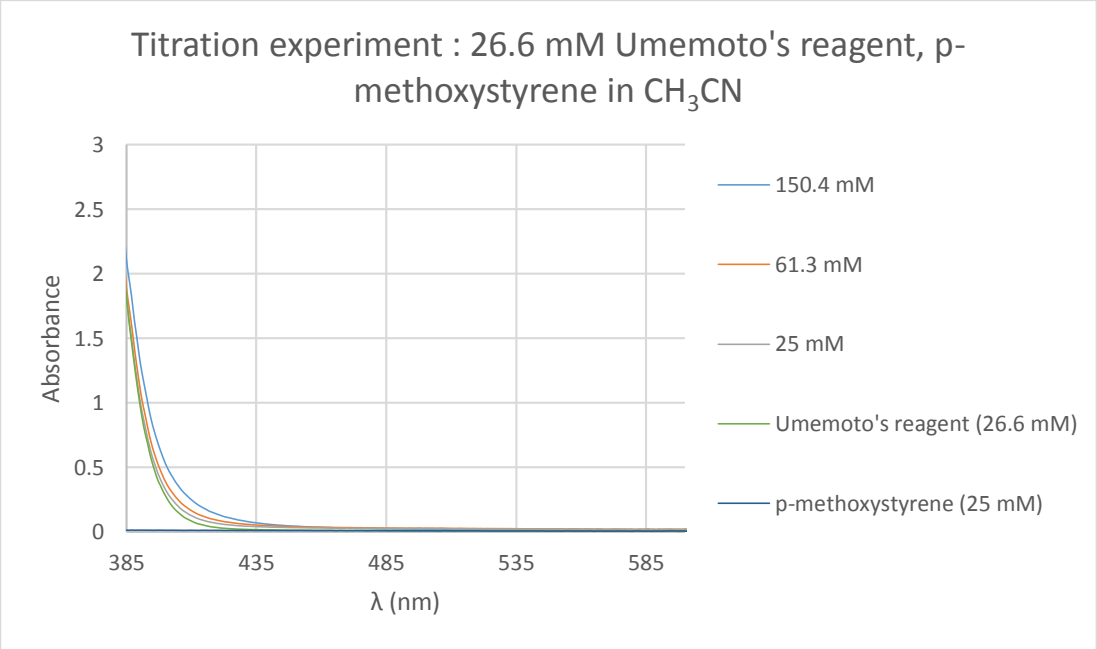


Figure 3.16 *p*-methoxystyrene and Umemoto's reagent titration experiment

In order to see the effect of concentration on the formation of the charge transfer complex, a titration was performed by varying the concentration of glycosyl donor 5a and keeping the Umemoto's reagent concentration steady at 26.6 mM in CH_3CN.

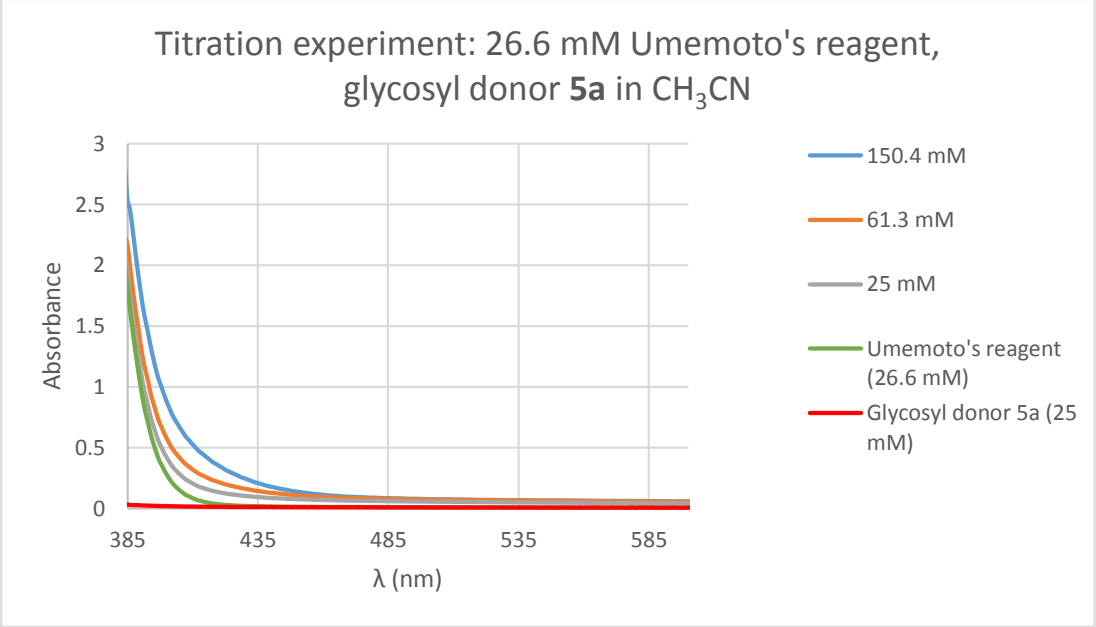


Figure 3.17 Glycosyl donor 5a and Umemoto's reagent titration experiment

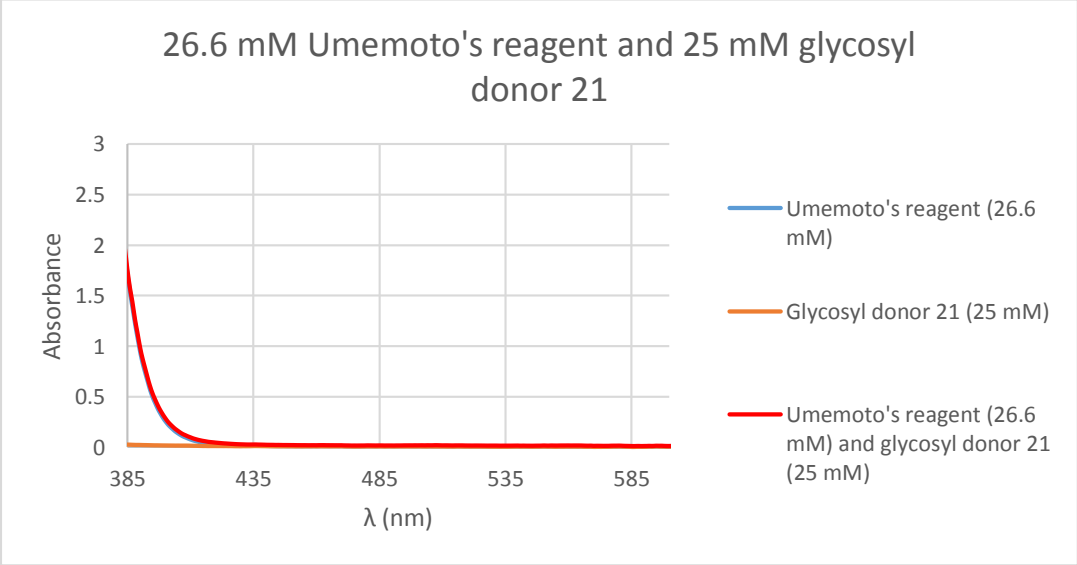


Figure 3.18 Glycosyl donor 21 and Umemoto's reagent titration experiment

3.5 References:

1. a) Codée, J. D. C.; Litjens, R. E. J. N.; van den Bos, L. J.; Overkleeft, H. S.; van der Marel, G. A. *Chem. Soc. Rev.* **2005**, *34*, 769-782. b) Shiao, T. C.; Roy, R. *Top. Curr. Chem.* **2011**, *301*, 69-108. c) Demchenko, A. V. *Synlett.* **2003**, 1225-1240. d) Koeller, K. M.; Wong, C. H. *Chem. Rev.* **2000**, *100*, 4465-4493. e) Zhang, A.; Ollmann, I. R.; Ye, X. S. *Carbohydrates in Chemistry and Biology* (Eds.: Beat, E.; Hart, G.W.; Sinaÿ, P.); Wiley-VCH: Weinheim, **2000**, pp. 93-116.

2. a) Crich, D.; Sun, S. *Tetrahedron* **1998**, *54*, 8321-8348. b) Crich, D.; Li, W. *J. Org. Chem.* **2007**, *72*, 7794-7797.

3. *Transforming Glycoscience: A Roadmap to the Future*. The National Academies Press: Washington, D.C. **2012**.

4. a) Goswami, M.; Ellern, A.; Pohl, N. L. B. *Angew. Chem. Int. Ed.* **2013**, *52*, 8441-8445.; *Angew. Chem.* **2013**, *125*, 8599-8603. b) Chu, A. H. A.; Minciunescu, A.; Montanari, V.; Kumar, K.; Bennett, C. S. *Org. Lett.* **2014**, *16*, 1780-1782. c) Adhikari, S.; Baryal, K. N.; Zhu, D.; Li, X.; Zhu, J. *ACS Catal.* **2013**, *3*, 57-60.

5. Griffin, G. W.; Bandara, N. C.; Clarke, M. A.; Tsang, W. S.; Garegg, P. J.; Oscarson, S.; Silwanis, B. A. *Heterocycles* **1990**, *30*, 939-947. b) Nakanishi, M.; Takahashi, D.; Toshima, K. *Org. Biomol. Chem.* **2013**, *11*, 5079-5082. c) Furuta, T.; Takeuchi, K.; Iwamura, M. *Chem. Commun.* **1996**, 157-158. d) Spell, M.; Wang, X.; Wahba, A. E.; Conner, E.; Ragains, J. *Carbohydr. Res.* **2013**, *369*, 42-47. e) Cumpstey, I.; Crich, D. *J. Carbohydr. Chem.* **2011**, *30*, 469-485. f) Mao, R. Z.; Guo, F.; Xiong, D. C.; Li, Q.; Duan, J.; Ye, X. S. *Org. Lett.* **2015**, *17*, 5606-5609.

6. Romero, N.; Nicewicz, D. A. *J. Am. Chem. Soc.* **2015**, *136*, 17024-17035.

7. Fukuzumi, S.; Ohkubo, K. *Org Biomol Chem*. **2014,** 32, 6059-71.

8. Frasier-Reid, B.; Konradsson, P.; Mootoo, D. R.; Udodongs, U. *J. Chem. Soc., Chem. Commun*. **1988**, 823-825.

9. Yasu, Y.; Koike, T.; Akita, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 9567-9571; *Angew. Chem.* **2012**, *124*, 9705-9709.

10. a) Mootoo, D. R.; Konradsson, P.; Udodong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583-5584. b) Kaeothip, S.; Yasomanee, J. P.; Demchenko, A. V. *J. Org. Chem.* **2012**, *77*, 291-299.

11. a) Inanaga, J.; Yokoyama, Y.; Hanamoto, T. *Tetrahedron Lett.* **1993**, *34*, 2791-2794. b) Dinkelaar, J.; De Jong, A. R.; van Meer, R.; Somers, M.; Lodder, G.; Overkleeft, H. S.; Codée, J. D. C.; van der Marel, G. A. *J. Org. Chem.* **2009**, *74*, 4982-4991.

12. Yamago, S.; Kokubo, K.; Hara, O.; Masuda, S.; Yoshida, J. I. *J. Org. Chem.* **2002**, *67*, 8584-8592.

13. Pederson, C. M.; Nørdstrom, L. U.; Bols, M. *J. Am. Chem. Soc.* **2007**, *129*, 9222-9235.

14 Pedersen, C. M.; Marinescu, L. G.; Bols, M. *Chem. Commun.* **2008**, 2465-2467.

15. Aono M.; Terao, Y.; Achiwa, K. *Heterocycles* **1995**, *40*, 249-260.

16. Cismesia, M. A.; Yoon, T. P. *Chem. Sci.* **2015**, *6*, 5426-5434.

17. a) Voica, A. F.; Mendoza, A.; Gutekunst, W. R.; Fraga, J. O.; Baran, P. S. *Nature Chem.* **2012**, *4*, 629-635. b) Hollister, K. A.; Conner, E. S.; Spell, M. L.; Deveaux. K.; Maneval, L.; Beal, M. W.; Ragains, J. R. *Angew. Chem. Int. Ed.* **2015**, *54*, 7837-7841.; *Angew. Chem.* **2015**, *127*, 7948-7952.

18. a) Arceo, E.; Jurberg, I. D.; Álvarez-Fernández, A.; Melchiorre, P. *Nature Chem.* **2013**, *5*, 750-756. b) Mattia, S.; Arceo, E.; Jurberg, I. D.; Cassani, C.; Melchiorre, P. *J. Am. Chem. Soc.* **2015**, *137*, 6120-6123. c) Kandukuri, S. R.; Bahamonde, A.; Chatterjee, I.; Jurberg, I. D.; Escudero-Adán, E. C.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2015**, *54*, 1485- 1489.; *Angew. Chem.* **2015**, *127*, 1505-1509. d) Fernández-Alvarez, V. M.; Nappi, M.; Melchiorre, P.; Maseras, F. *Org. Lett.* **2015**, *17*, 2676-2679.

19. a) Rosokha, S. V.; Kochi, J. K. *Acc. Chem. Res.* **2008**, *41*, 641-653. b) Cheng, Y.; Yuan, X.; Ma, J.; Yu, S. *Chem. Eur. J.* **2015**, *21*, 8355-8359.

20. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.

21. Lin, S.; Ischay, M. A.; Fry, C. G.; Yoon, T. P. *J. Am. Chem. Soc.* **2011**, *133*, 19350–19353.

22. Stokes, B. J.; Opra, S. M.; Sigman, M. S. *J. Am. Chem. Soc*. **2012**, *134*, 11408−11411.

23. Jana, M.; Misra, A. K. *J. Org. Chem*. **2013**, *78*, 2680−2686.

24. Ueda, Y.; Muramatsu, W.; Mishiro, K.; Furuta, T.; Kawabata, T. *J. Org. Chem*. **2009**, *74*, 8802–8805.

25. Basu, N.; Maity, S. K.; Roy, S.; Singha, S.; Ghosh, R. *Carbohydr. Res*. **2011**, *346*, 534-539.

26. Nagai, H.; Sasaki, K.; Matsumura, S.; Toshima, K. *Carbohydr. Res*. **2005**, *340*, 337–353.

27. Imagawa, H.; Kinoshita, A.; Fukuyama, T.; Yamamoto, H.; Nishizawa, M. *Tetrahedron Lett*. **2006**, *47*, 4729–4731.

28. Nokami, T.; Shibuya, A.; Tsuyama, H.; Suga, S.; Bowers, A. A.; Crich, D.; Yoshida, J. *J. Am. Chem. Soc***. 2007**, *129*, 10922–10928.

29. He, H.; Zhu, X. *Org. Lett*. **2014**, *16*, 3102–3105.

30. Chen, G.; Yin, Q.; Yin, J.; Gu, X.; Liu, X.; You, O.; Chen, Y.L.; Xiong, B.; Shen, J. *Org. Biomol. Chem*. **2014**, *12*, 9781.

31. Halcomb, R.L.; Danishefsky, S.J. *J. Am. Chem. Soc*. **1989**, *111*, 6661-6666.

CHAPTER 4: REMOTE HYDROXYLATION BY RADICAL TRANSLOCATION AND REDOX CHEMISTRY

4.1 Introduction

The biosynthesis of molecules is complex. Nature utilizes synthetic pathways that are either unattainable or difficult for synthetic chemists to duplicate in the lab. One of these pathways is the activation and functionalization of aliphatic C-H bonds.[1] Unactivated C-H bonds (like those present in alkanes) are stable bonds that are unreactive under most reaction conditions. The synthetic manipulation of unactivated C-H bonds was first reported in the 1800's.[9] The activation of the C-H bonds often required the use of harsh conditions (decomposition of the molecule) that resulted in low yields and selectivites.[2] C-H bond functionalization can be performed in high yield by mimics enzymes, however it is not a viable solution since enzyme mimickers are expensive and often are selective for a very specific C-H bond.[3] These issues have led to the development of several methods for aliphatic C-H functionalization in the past two decades providing higher yields and selectivities that may prove useful in the synthesis of complex molecules.[4]

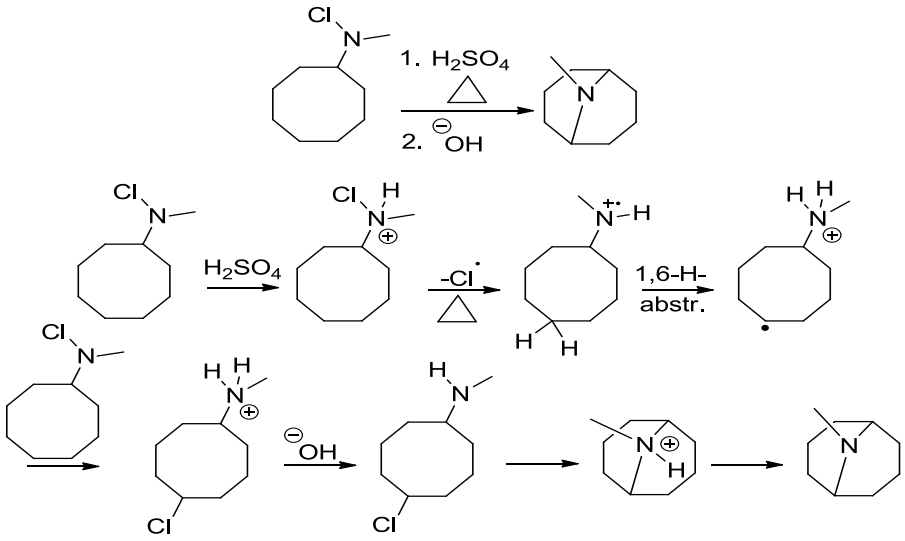
There are several advantages that can be utilized when incorporating C-H functionalization in the area of total synthesis. The typical method for building complex molecules is by performing reactions on the functional groups of the molecule to slowly build the compound while the aliphatic C-H bonds are untouched, often resulting in undesirable step-, atom- and redox-economy.[5] Synthetic efficiency is improved when using aliphatic C-H bonds as a synthetic handle rather then regarding them as unproductive bystanders.[5] The reduction of synthetic steps and overall improvement in synthetic efficiency can alleviate the cost of, and improve the production of , complex drugs.[4]

This chapter previously appeared as [Kyle A. Hollister, Elizabeth S. Conner, Mark L. Spell, Kristina Deveaux, Léa Maneval, Michael W. Beal, Justin R. Ragains, Remote Hydroxylation through Radical Translocation and Polar Crossover, 5/26/2015]. It is reprinted by permission of [John Wiley and Sons.]

Strategies used for the functionalization of aliphatic C-H bonds fall into two classes: non-directed and directed.[6,7] Non-directed C-H functionalization relies on the inherent reactivity of the C-H bond.[6] Directed C-H functionalization utilizes a specific functionality that is attached to the molecule to direct either the inner sphere of a transition metal or a metal-oxo species to a specific C-H bond.[7] Another approach to directed C-H functionalization is to install a functionality that, upon thermal, chemical, or photochemical activation, will produce a radical that abstracts hydrogen from a C-H bond lying in a remote position of the same molecule (referred to as a radical translocation event).[8]

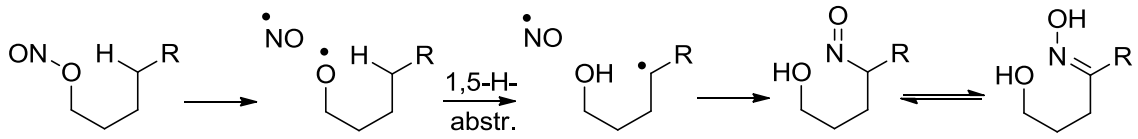
4.1.1 Literature Examples of Radical Translocation

Hofmann, Löffler, and Freytag discovered radical translocation in the late 1800s and continued to explore the area until the early 1900s.[9] The radical translocation characterizing the Hoffman-Löffer-Freytag reaction was not acknowledged until 1950 with work published by Wawzonek and Thelen (Scheme 4.1). The mechanism proposed by the authors was supported by the work of Corey and Hertler in 1960.[9]



Scheme 4.1 Wawzonek and Thelen's proposed radical translocation mechanism

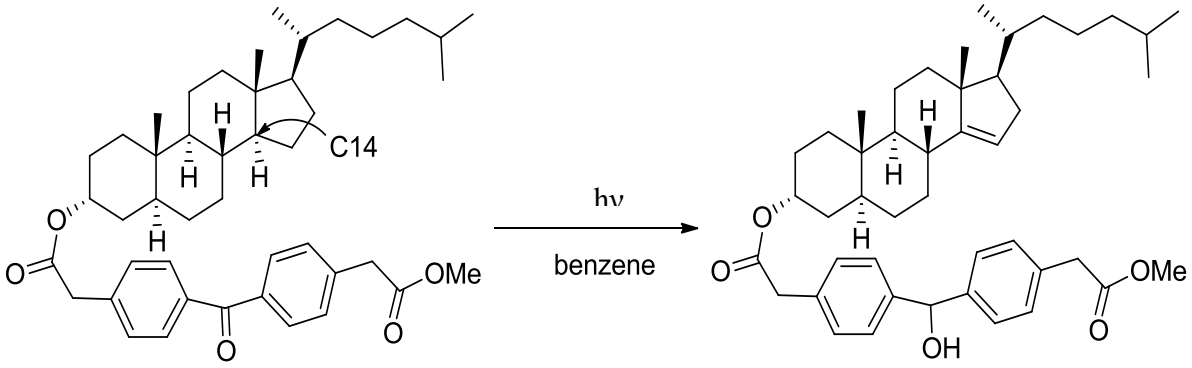
The reaction begins with protonation of the N-chloroamine with sulfuric acid followed by bond homolysis (promoted by light or heat) of the N-Cl bond. The resulting nitrogen centered radical cation abstracts a hydrogen intramolecularly (uncommon 1,6-H-abstraction) from a secondary carbon atom resulting in a secondary carbon centered radical. The radical participates in a chain process by abstracting chlorine from another substrate molecule. The subsequent base-promoted cyclization then proceeds via an S_N2 pathway. The 1,6-H abstraction is rare in comparison to the 1,5-H abstraction exemplified by Baton's nitrite ester photolysis (Scheme 4.2)



Scheme 4.2 Barton's nitrile ester photolysis

which is mechanistically similar to the Hoffman-Löffer-Freytag reaction .[10]

In the 1970s, a method of guided C-H functionalization using radical translocation was reported by Breslow and coworkers.[11] Esterification of benzophenone acids and cholestanols provided intermediates where the benzophenone triplet diradical would be orientated to abstract the hydrogen on carbon 14 of the steroid D ring (for example, Scheme 4.3) upon photochemical

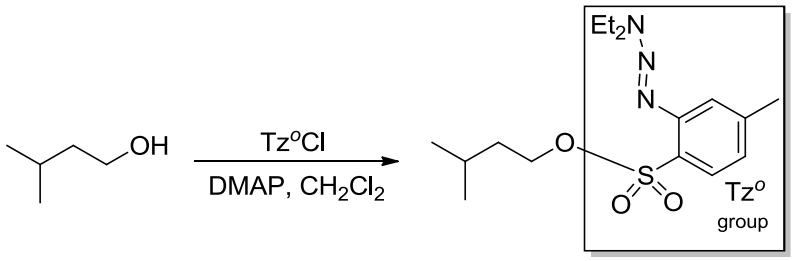


activation with UV light.[11] The selectivity of the radical translocation for the hydrogen on carbon

Scheme 4.3 Breslow's light promoted remote desaturation

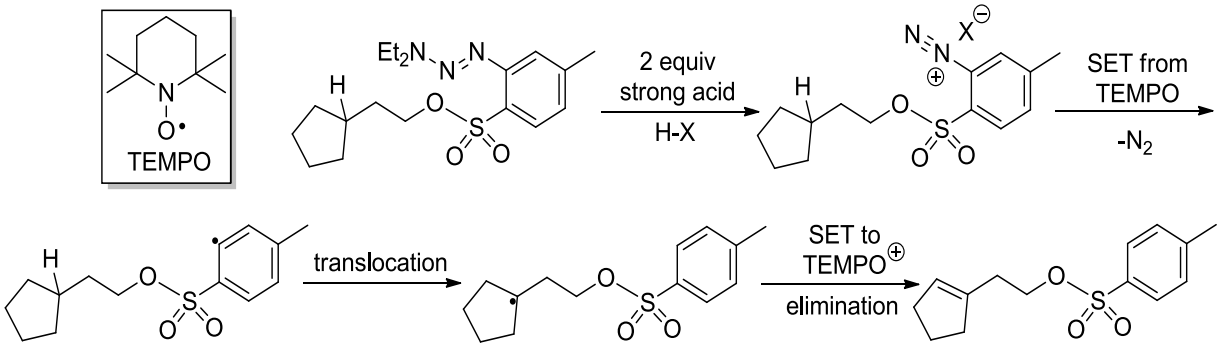
14 in this reaction was a testament to the selectivity that can be afforded with radical translocation.

A recent remote desaturation method developed by Baran and coworkers involved radical translocation as a key step.[12] Baran developed a unique aryl radical precursor termed the Tz^o group. This group is easily installed by reacting various alcohols and amines with the requisite aryl sulfonyl chloride Tz^{o}Cl (*o*-tosyl triazene sulfonyl chloride, Scheme 4.4).



Scheme 4.4 Installation of Tz^o directing group

Once the Tz^o group is installed, the resulting substrate is subjected to Baran's reaction conditions and proceeds through the proposed mechanism shown in Scheme 4.5. The reaction begins with acid-promoted liberation of aryl diazonium salt from triazene. TEMPO then reduces the redox-active aryl diazonium ion which loses N_2 providing an aryl radical that undergos an (unusual 1, 7) intramolecular hydrogen abstraction yielding a stable tertiary radical. The tertiary



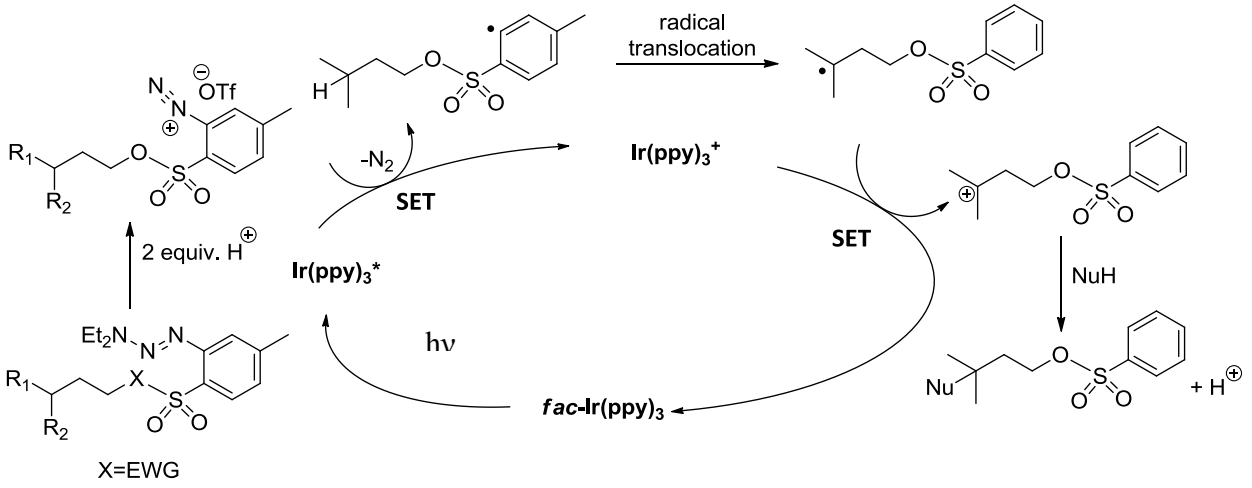
Scheme 4.5 Baran's proposed remote desaturation mechanism

radical is then oxidized to the carbocation by nitroxonium (TEMPO$^+$) followed by elimination to

provide the alkene product. The product of the reaction also bears a tosyl group that can be subsequently displaced by a nucleophile.

4.2 Results and Discussion

The development of a selective, mild and easily performed C-H functionalization method that would allow various functionalities to be added to unreactive C-H positions was desired. We belived that this could be accomplished in a similar manner to Baran's work but using photoredox catalysis (Scheme 4.6). This would involve a radical translocation followed by oxidation of the intermediate radical to the carbocation that would undergo nucleophilic attack providing different functional groups at the unreactive C-H position. Various nucleophiles such as alcohols (hydroxylation), carboxylic acids (esterification), amines (Ritter amidation) and halides among others could be explored to provide a variety of useful functionalities.



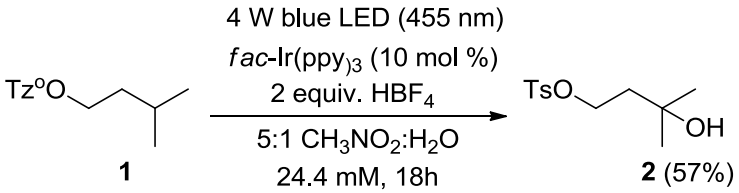
Scheme 4.6 Proposed remote functionalization

We proposed that proceeding through a favorable radical translocation from an unstable electron poor aryl radical to a more stable alkyl radical would be a facile process. Similar translocations from unreactive aryl radicals to stable alkyl radicals have been demonstrated.[6-9,12,13] The easily oxidized alkyl radical could then undergo SET oxidation under mild conditions to form

the carbocation that could be attacked by a nucleophile.[14] This proposed process is shown in Scheme 4.6.

Like Baran, we decided to use substrates containing the Tz^{o} group which, upon treatment with 2 equivalents of acid, produces an arenediazonium cation. The arenediazonium, which has a typical reduction potential (E_{red}) of -0.1 to +0.5 V vs. SCE, could then undergo a SET reduction from an excited state photocatalyst like *fac*-Ir(ppy)$_3^*$ to generate N_2 and aryl radical. The excited *fac*-Ir(ppy)$_3^*$ is an excellent reducing agent with a reduction potential E° of -1.73 vs. SCE.[15,16] The unstable aryl radical would then abstract hydrogen from the attached alkyl moiety to form a more stable alkyl radical. The alkyl radical (E_{ox}= 0-0.75 V vs. SCE) could then undergo SET oxidation from the oxidatively quenched photocatalyst (Ir(ppy)$_3^+$ E°= +0.77 V vs. SCE) regenerating catalyst and providing a carbocation that can be attacked by a nucleophile to provide product.[14,15]

Initial experimentation revealed several interesting aspects of this reaction. It was shown that the reaction required a nucleophile that does not undergo hydrogen abstraction easily with the radicals that are formed in the course of the reaction. This led to the use of water as a nucleophile in nitromethane (Scheme 4.7). As water and nitromethane are only slightly miscible, the reaction requires vigorous stirring.



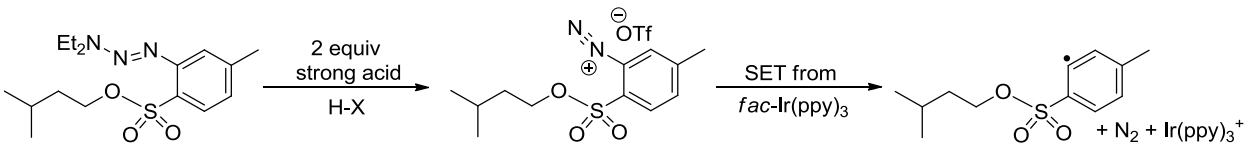
Scheme 4.7 Standard remote hydroxylation conditions

With the use of water as a nucleophile, 57% of product 2 was afforded. The Reaction was optimized (Figure 4.1). The use of *fac*-Ir(ppy)$_3$ was required for reaction as all other photocatalysts

Entry	Deviation from Std. Cond	Irradiation time (h)	% yield
1	18.5h irradiation	18	57
2	5 mol% *fac*-Ir(ppy)$_3$	18	12
3	1 mol% *fac*-Ir(ppy)$_3$	18	4
4	light excluded	18	50
5	Conc. 48.8 mM	18	40
6	Conc. 10 mM	18	57
7	TFA replaces HBF_4	18	54

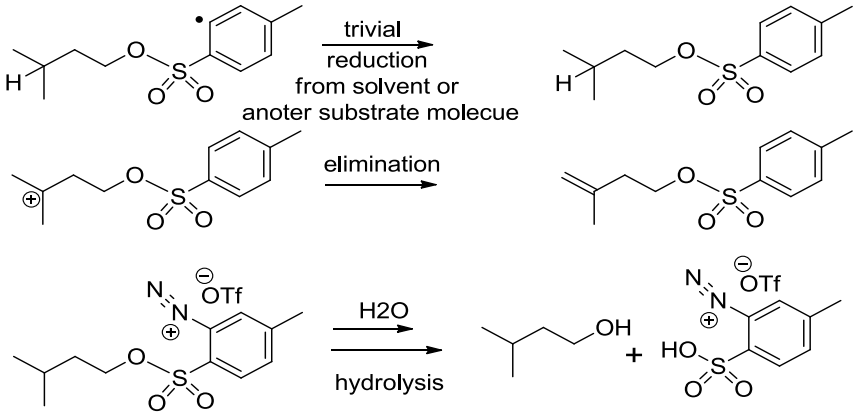
Figure 4.1 Optimization of the remote hydroxylation reaction conditions

((Ru(phen)$_3$(BArF)$_2$, Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)(PF$_6$), ethyl eosin, and Ru(bpy)$_3$(PF$_6$)$_2$) proved unproductive. The high catalyst loading of 10 mol % *fac*-Ir(ppy)$_3$ was also required to provide good yield as use of one and five mol % resulted in poor yield. The concentration of the reaction and the use of TFA in place of HBF_4 showed little effect on the yield. Interestingly, the reaction also works in the absence of light but in lower yields suggesting that ground state *fac*-Ir(ppy)$_3$ may have the ability to undergo SET reduction to substrate diazonium (Scheme 4.8). Such a process is coupled to the irreversible loss of nitrogen and energetically favorable.[17]



Scheme 4.8 Generation of diazonium by ground state *fac*-Ir(ppy)$_3$

The optimized conditions never provide product in higher than 60% yield. This is likely due to side reactions (Scheme 4.9) producing trivial reduction and elimination side products. The electron deficient diazonium formed during the reaction may also be undergoing hydrolysis thus affecting the yield (Scheme 4.9). With the optimized conditions, various substrates were screened providing yields in 31-63%. Some of the substrates screened are highlighted in Figure 4.2. The citronellol derivative underwent remote hydroxylation in 38% yield (Figure 4.2, product 4) while



Scheme 4.9 Side reactions of intermediates formed in the remote hydroxylation reaction

the benzylic Tz^{o} ester underwent hydroxylation in 63 and 56% yield (Figure 4.2 products 6 and 8). This demonstrated that the hydroxylation method was applicable to a range of substrates.

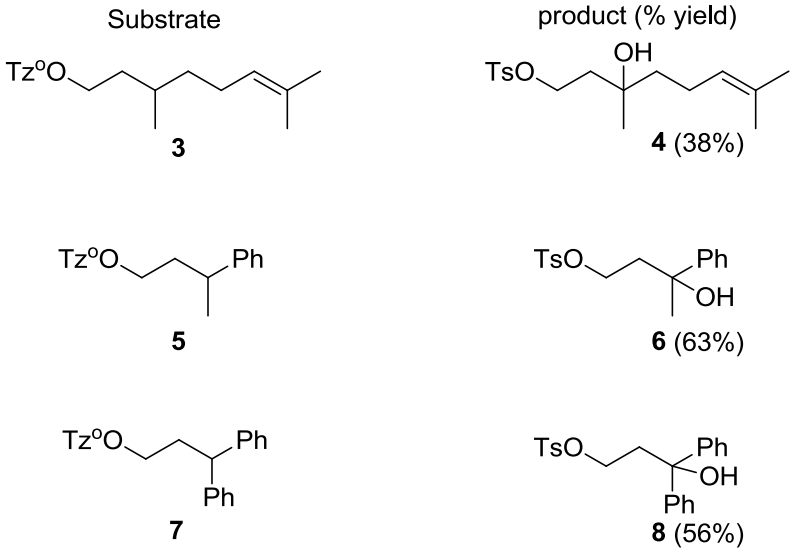
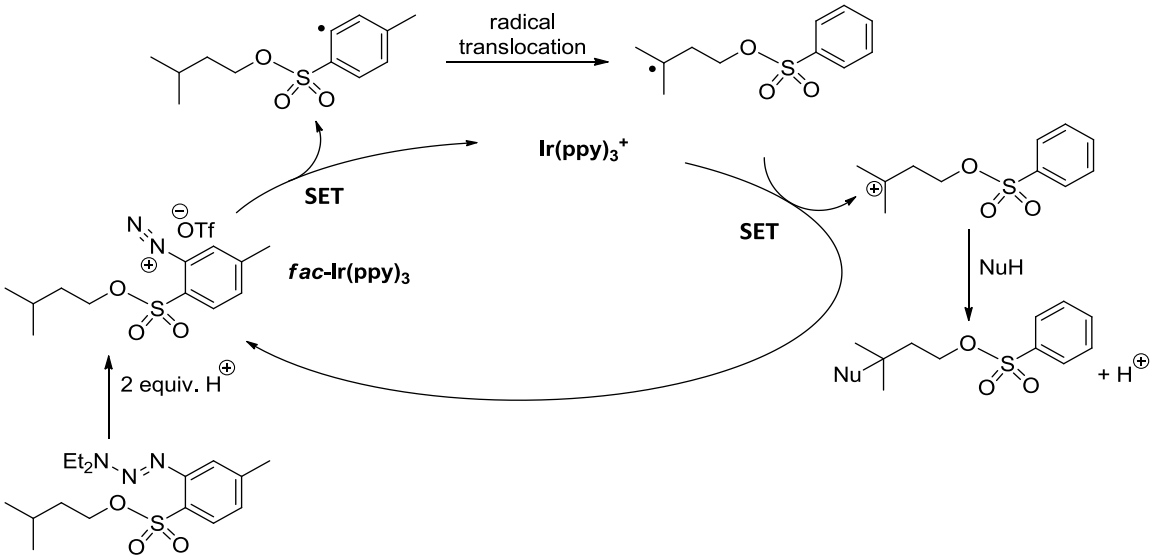


Figure 4.2 Substrate scope for remote hydroxylation

The ability of the reaction to proceed in the dark but in lower yields using substrate 1 led us to believe that light plays a limited role in the reaction. A SET from ground state *fac*-Ir(ppy)$_3$ initiating the reaction may be the major reaction pathway (Scheme 4.10). To study this hypothesis multiple substrates were submitted to the original reaction conditions (Scheme 4.7) without the light. The reaction provided product for all of the substrates in comparable yields to the irradiated



Scheme 4.10 Proposed remote hydroxylation reaction in the dark

reactions (Figure 4.3). This showed that SET by ground state *fac*-Ir(ppy)$_3$ could be sufficient for

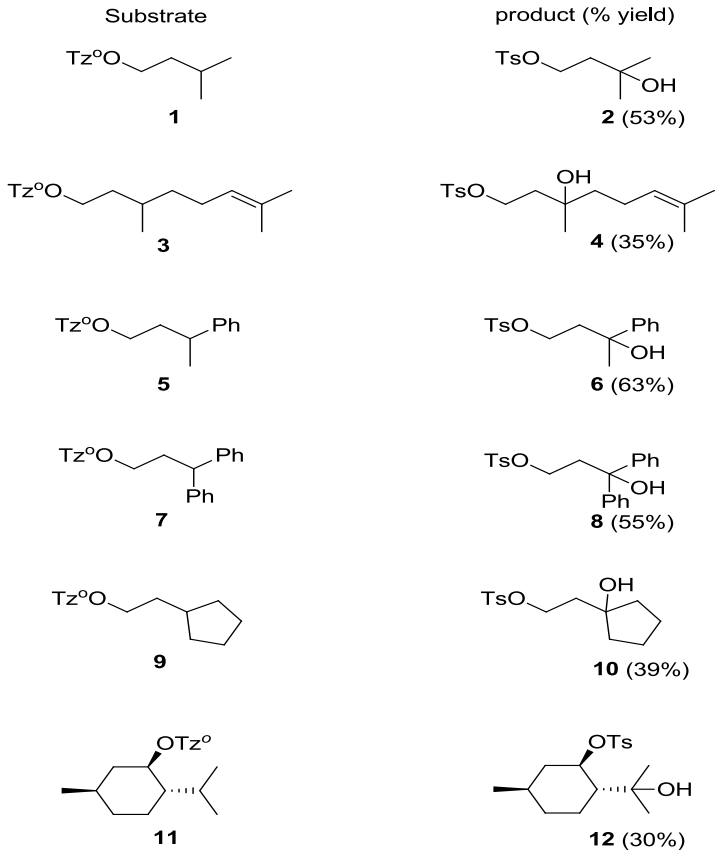


Figure 4.3 Substrate scope for light excluded remote hydroxylation

the reaction to proceed and suggests that the increase in yield when irradiating may be attributed to a minor photochemical reaction pathway that also provides product.

4.3 Conclusion

The functionalization of aliphatic C-H bonds is a challenging process perfected by nature and growing in significance in the organic synthesis community. The majority of organic molecules possess aliphatic C-H bonds and the ability to selectively functionalize them would provide a more efficient synthesis of drugs and other molecules. Previous methods for performing C-H bond functionalization required the use of expensive enzyme mimics or harsh reaction conditions. We have developed a method that helps to resolve some of these issues and proceeds under mild reaction conditions with a wide range of substrates. The reaction is efficient without the presence of light and is easily performed on a bench top.

4.4 Experimental

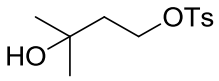
4.4.1 General methods

^{1}H NMR and ^{13}C NMR spectroscopy was conducted using a Bruker AV-400 or AV-500 spectrometer. Mass spectra were attained using an Agilent 6210 electrospray time-of-flight mass spectrometer. Optical rotation was measured using a JASCO P-2000 polarimeter. All materials were received from commercial suppliers and used without further purification. Flash column chromatography was accomplished using high purity grade 60 Å silica gel (Fluka® Analytical). Qualitative TLC was performed on aluminum sheets (Merck, silica gel, F254) and observed via UV absorption (254 nm) and staining with anisaldehyde or $KMnO_4$. Deuterated solvents were acquired from Cambridge Isotope Labs. Tz^{o}Cl and CH_3NO_2 (reagent grade, 96%) were received from Sigma-Aldrich. Unless otherwise noted, all Tz^{o} -containing compounds were synthesized according to literature procedure.[1] All reactions were carried out under an atmosphere of dry

nitrogen. Photocatalyzed remote hydroxylation reactions were conducted in round bottom flasks and irradiated with 4W blue LEDs (Creative Lighting Solutions, λmax=455 nm) which were wrapped around a beaker or crystallizing dish.

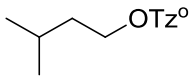
4.4.2 Procedures and characterization

Representative procedure for remote hydroxylation - synthesis of 2



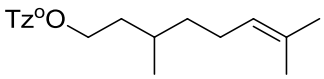
To a vigorously stirred 20°C solution of 100.0 mg (0.2929 mmol) triazene 4.5 and 19.2 mg (0.0293 mmol) fac-Ir(ppy)$_3$ in 10 mL CH_3NO_2 and 2 mL deionized H_2O was added 87 77 μL (0.59 mmol) 48% HBF_4 via gas-tight syringe. After 4 minutes, irradiation of the solution with blue LEDs (λmax=455 nm) commenced and the reaction mixture was stirred vigorously for 18.5 h. 10 mL of 5% $NaHCO_3$(aq.) was then added at once followed by 10 mL CH_2Cl_2 and the resulting layers were separated. The aqueous layer was extracted with an additional 2 x 10 mL CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and concentrated to yield 117.3 mg of a brown residue. Silica gel chromatography (gradient run from 20% EtOAc in hexanes to 30% EtOAc in hexanes) of the residue afforded 43.4 mg (57%) of a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.2 88 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 4.20 (t, J = 6.8 Hz, 2H), 2.44 (s, 3H), 1.85 (t, J = 6.8 Hz, 2H), 1.67 (br s, 1H), 1.21 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.0, 133.1, 130.1, 128.0, 69.8, 67.8, 41.8, 29.8, 21.8; HRMS (m/z) calcd for $C_{12}H_{18}NaO_4S$ $[M+Na]^+$ 281.0818, found 281.0805.

Synthesis of 1



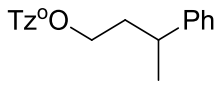
Started with 2000.0 mg (6.902 mmol) Tz^{o}Cl, 486.7 mg (5.521 mmol) isoamyl alcohol, 1349.0 mg (11.04 mmol) DMAP and 11.1 mL CH_2Cl_2. Silica gel chromatography 30 g silica gel, (gradient run from 10% EtOAc in hexanes to 20% EtOAc in hexanes) afforded 1724.3 mg (91%) of a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.1 Hz, 1H), 7.34 (s, 1H), 6.96 (d, *J* = 8.1 Hz, 1H), 4.02 (t, *J* = 6.6 Hz, 2H), 3.80 (q, *J* = 7.2 Hz, 4H), 2.36 (s, 3H), 1.66 (m, 1H), 1.48 (q, *J* = 6.7 Hz, 2H), 1.32 (t, *J* = 7.3 Hz, 3H), 1.24 (t, *J* = 7.3 Hz, 3H), 0.80 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.25, 145.05, 130.46, 125.98, 124.99, 118.35, 68.68, 49.30, 42.24, 37.58, 24.37, 22.14, 21.65, 14.48, 11.29; HRMS m/z calcd for $C_{16}H_{27}N_3NaO_3S$ $(M+Na)^+$ 364.1665, found 364.1658.

Synthesis of 3



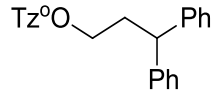
Started with 500.0 mg (1.73 mmol) Tz^{o}Cl, 0.25 mL (1.4 mmol) Citronellol, 337 mg (2.76 mmol) DMAP and 2.8 mL CH_2Cl_2. Silica gel chromatography, (20% DCM, 5% Et_2O in hexanes) afforded521 mg (91%) of a red oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.1 Hz, 1H), 7.37 (s, 1H), 7.00 (d, J = 8 Hz 1H), 5.02 (t, J= 7.2Hz, 1H), 4.13 – 3.99 (m, 2H), 3.83 (q, *J* = 7.2 Hz, 4H), 2.39 (s, 3H), 1.98-1.79 (m, 2H), 1.78-1.46 (m, 2H), 1.66 (s, 3H), 1.56 (s, 3H), 1.45-1.19 (m, 2H), 1.36 (t, 3H), 1.27 (t, 3H), 1.16 – 1.02 (m, 1H), 0.80 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.4, 145.2, 131.5, 130.7, 126.3, 125.3, 124.6, 118.5, 68.8, 49.5, 42.5, 37.0, 36.0, 29.1, 25.9, 25.5, 21.9, 19.2, 17.8, 14.7, 11.5; HRMS (m/z): $[M+H]^+$ calcd for $C_{21}H_{36}N_3O_3S$ 410.2472, found 410.2475.

Synthesis of 5



Started with 350.0 mg (1.208 mmol) Tz^{o}Cl , 0.15 mL (0.97 mmol) 3-Phenyl-1-butanol, 294.9 mg (2.414 mmol) 4-Dimethylaminopyridine and 1.9 mL of CH_2Cl_2. Silica gel chromatography, (gradient run from 8% EtOAc in hexanes to 10% EtOAc in hexanes) afforded 261.5 mg (67%) of a red oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.0 Hz, 1H), 7.39 (s, 1H), 7.20 (t, *J* = 7.4 Hz, 2H), 7.14 (d, *J* = 6.9 Hz, 1H), 7.04 (d, J = 8 Hz, 2H), 6.95 (d, *J* = 8 Hz, 1H), 3.99 (dt, *J* = 9.7, 6.0 Hz, 1H), 3.92 – 3.85 (m, 1H), 3.81 (q, *J* = 7.2 Hz, 4H), 2.81 (q, *J* = 7.2 Hz, 1H), 2.38 (s, 3H), 1.92 – 1.81 (m, 2H), 1.33 (t, *J* = 7.3 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.17 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 145.8, 145.2, 130.6, 128.5, 126.9, 126.3, 126.0, 125.1, 118.4, 68.6, 49.4, 42.4, 37.3, 35.8, 21.9, 21.8, 14.6, 11.4; HRMS (m/z): $[M+H]^+$ calcd for $C_{21}H_{30}N_3O_3S$ 404.2002, found 404.2000.

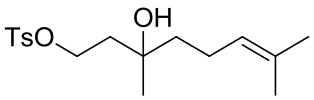
Synthesis of 7



Started with 350.0 mg (1.208 mmol) Tz^{o}Cl, 0.19 mL (0.97 mmol) 3,3-diphenyl-1-propanol, 294.9 mg (2.414 mmol) DMAP and 1.9 mL of CH_2Cl_2. Silica gel chromatography (20% DCM and 5% Et2O in hexanes) afforded 307.9 mg (68%) of a red oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 8.1 Hz, 1H), 7.38 (s, 1H), 7.20 (dd, J = 8.3, 6.7 Hz, 4H), 7.17 – 7.11 (m, 2H), 7.08 (d, J = 7.5 Hz, 4H), 6.95 (d, J = 7.8 Hz, 1H), 4.05 – 3.96 (m, 3H), 3.80 (dq, J = 13.9, 7.3 Hz, 4H), 2.40 (s, 3H), 2.34 (dt, J = 7.8, 6.2 Hz, 2H), 1.33 (t, J = 7.3 Hz, 3H), 1.24 (t, J = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.4, 91 145.3, 143.7, 130.8, 128.7, 128.0, 126.6, 126.3, 125.3, 118.6,

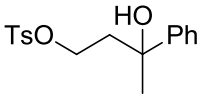
68.6, 49.5, 46.9, 42.6, 35.0, 21.9, 14.7, 11.6; HRMS (m/z) calcd for $C_{26}H_{32}N_3O_3S$ $[M+H]^+$ 466.2159, found 466.2156.

Synthesis of 4



Started with 112 mg (0.293 mmol) of 3, 19.2 mg (0.0293 mmol) of *fac*-Ir(ppy)$_3$, 77 µL (0.585 mmol) HBF_4 (48% in H_2O), and 2 mL deionized H_2O and 10 mL CH_3NO_2. Irradiated for 18 h. Silica gel chromatography, (gradient run from 10% EtOAc in hexanes to 30% EtOAc in hexanes afforded 19.3 mg (22%) of a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J = 8.5 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 5.07 (t, *J* = 7 Hz, 1H), 4.20 (tq, *J* = 5.5, 3.0 Hz, 2H), 2.45 (s, 3H), 2.00 (q, *J* = 7.7 Hz, 2H), 1.85 (q, *J* = 6.9 Hz, 2H), 1.68 (s, 3H), 1.59 (s, 3H), 1.48 – 1.42 (m, 3H), 1.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.0, 133.2, 132.5, 130.1, 128.1, 124.0, 71.9, 67.6, 42.4, 40.2, 27.1, 25.9, 22.8, 21.9, 17.9; HRMS (m/z): $[M+Na]^+$ calcd for $C_{17}H_{26}NaO_4S$ 349.1444, found 349.1443, and 5 mg (6%) of the trivial reduction product, a colorless oil. Spectral data matched that previously reported in literature.[18]

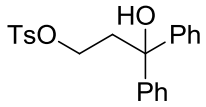
Synthesis of 6



Started with 118.0 mg (0.292 mmol) of 6, 19.2 mg (0.0293 mmol) of *fac*-Ir(ppy)$_3$, 77 µL (0.585 mmol) HBF_4 (48% in H_2O), 2 mL deionized H_2O and 10 mL of CH_3NO_2. Irradiated for 18 h. Silica gel chromatography, (gradient run from 15% EtOAc in hexanes to 30% EtOAc in hexanes afforded 59.1 mg (63%) of a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.4 Hz, 2H), 7.35 – 7.18 (m, 7H), 4.10 (dt, *J* = 10.1, 7.1 Hz, 1H), 3.95 (dt, *J* = 10.0, 6.6 Hz, 1H), 2.43 (s, 3H), 2.19 (td, *J* = 6.9, 1.9 Hz, 2H), 2.06 (s, 1H), 1.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.5,

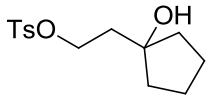
144.9, 133.0, 130.0, 128.5, 128.0, 127.1, 124.6, 73.6, 67.7, 42.5, 31.0, 21.8; HRMS (m/z): $[M+H]^+$ calcd for $C_{17}H_{21}O_4S$ 321.1155, found 321.1154.

Synthesis of 8



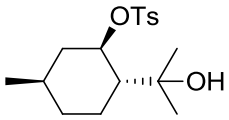
Started with 136.4 mg (0.2929 mmol) of 7, 19.2 mg (0.0293 mmol) of *fac*-Ir(ppy)$_3$, 77 µL (0.585 mmol) HBF_4 (48% in H_2O), 2 mL deionized H_2O and 10 mL CH_3NO_2. Irradiated for 18 h. Silica gel chromatography, (gradient run from 10% EtOAc in hexanes to 20% EtOAc in hexanes afforded 63.2 mg (56%) of a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.9 Hz, 2H), 7.34 – 7.16 (m, 12H), 4.08 (t, *J* = 7.3 Hz, 2H), 2.69 (t, *J* = 7.4 Hz, 2H), 2.42 (s, 3H), 2.39 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.9, 144.9, 133.0, 130.0, 128.5, 128.0, 127.4, 125.8, 77.0, 67.9, 40.7, 21.8; HRMS (m/z): $[M+Na]^+$ calcd for $C_{22}H_{22}NaO_4S$ 405.1131, found 405.1125

Synthesis of 10



Started with 107.6 mg (0.2929 mmol) 9, 19.2 mg (0.0293 mmol) *fac*-Ir(ppy)$_3$, 77 µL (0.586 mmol) HBF_4 (48% in H_2O), 2 mL millipore H_2O and 10 mL CH_3NO_2. It was irradiated for 18 h. Silica gel chromatography (14 g silica gel, gradient run from 100% hexanes to 25% ethyl acetate in hexanes) afforded 34.2 mg (41%) of a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.1 Hz, 2H), 4.24 (t, J = 6.8 Hz, 2H), 2.45 (s, 3H), 1.97 (t, J = 7.3 Hz, 2H), 1.76 (m, 2H), 1.64 (m, 4H), 1.55 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.7, 133.0, 129.8, 127.8, 80.5, 68.0, 40.0 (2C's), 39.7, 23.4 (2C's), 21.6; HRMS m/z calcd for $C_{14}H_{20}NaO_4S$ $(M+Na)^+$ 307.0975, found 307.0974, and 14.6 mg (19%) of an inseparable mixture of desaturation and reduced products (3.5:1). Spectral data matched that previously reported in literature.[12]

Synthesis of 12



Started with 120.0 mg (0.2929 mmol) 11, 19.2 mg (0.0293 mmol) *fac*-Ir(ppy)$_3$, 77 µL (0.586 mmol) HBF_4 (48% in H_2O), 2 mL millipore H_2O and 10 mL CH_3NO_2. Silica gel chromatography (14 g silica gel, 20% EtOAc in hexanes) afforded 30.0 mg (31%) of a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 4.83 (td, *J* = 10.8, 4.3 Hz, 1H), 2.56 (s, 1H), 2.43 (s, 3H), 2.20 (d, *J* = 11.8 Hz, 1H), 1.92 (m, 1H), 1.67 (m, 2H), 1.48 (m, 1H), 1.25 (s, 2H) 1.20 (s, 3H), 1.16 (s, 3H), 1.05 (qd, *J* = 13.1, 3.5 Hz, 1H), 0.88 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.00, 134.91, 130.00, 127.60, 84.66, 72.66, 52.34, 42.32, 33.99, 31.69, 28.87, 27.34, 25.86, 21.77, 21.75; HRMS m/z calcd for $C_{17}H_{26}NaO_4S$ $(M+Na)^+$ 349.1444, found 349.1446, and 19.9 mg (22%) desaturation product as a white solid. Spectral data matched that previously reported in literature.[12]

4.5 References

1. Newhouse, T.; Baran, P. S. *Angew. Chem. Int. Ed. Engl*. **2011**, 50, 3362-74.

2. White, M. C. *Science*. **2012**, 335, 807-809.

3. Breslow, R. *Acc. Chem. Res*. **1979**, 13, 170-177.

4. Gaich, T.; Baran, P. S. *J. Org. Chem*. **2010**, 75, 4657-73.

5. Gutekunst, W. R. *Chem. Soc. Rev*. **2011**, 40, 1976-1991.

6. Fujiwara, Y.; Dixon, J. A.; O'Hara, F.; Funder, E. D.; Dixon, D. D.; Rodriguez, R. A.; Baxter, R. D.; Herle, B.; Sach, N.; Collins, M. R.; Ishihara, Y.; Baran, P. S. *Nature*. **2012**, 492, 95-99.

7. (a) Ishii, Y.; Sakaguchi, S.; Iwahama, T. *Adv. Synth. Catal*. **2001**, 343, 393-427.; (b) Fokin, A. A.; Schreiner, P. R. *Chem. Rev*. **2002**, 102, 1551- 1593.; (c) Crabtree, R. H. *J. Chem. Soc., Dalton Trans*. **2001**, 17, 2437- 2450.; (d) Chen, X.; Engle, K. M.; Wang, D.

H.; Yu, J. Q. *Angew. Chem. Int. Ed. Engl*. **2009**, 48, 5094-115.; (e) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem. Eur. J*. **2010**, 16, 2654-2672.

8. Robertson, J.; Pillai, J.; Lush, R. K. *Chem. Soc. Rev*. **2001**, 30, 94-103.

9. (a) Wawzonek, S.; Thelen, P. J. *J. Am. Chem. Soc*. **1950**, 72, 2118-2120.; (b) Corey, E. J.; Hertler, W. R. *J. Am. Chem. Soc*. **1960**, 82, 1657-1668.

10. a) Barton, D. H. R.; Beaton, J. M.; Geller, L. E.; Pechet, M. M. *J. Am. Chem. Soc*. **1960**, 82, 2640. b) Barton, D. H. R.; Beaton, J. M.; Geller, L. E.; Pechet, M. M. *J. Am. Chem. Soc*. **1961**, 83**,** 4076–4083.

11. Breslow, R.; Baldwin, S.; Rechtner, T.; P. Kalicky; Liu, S.; Washburnle, W. *J. Am. Chem. Soc*. **1973**, 95, 3251-3262.

12. Voica, A. F.; Mendoza, A.; Gutekunst, W. R.; Fraga, J. O.; Baran, P. S. *Nature chemistry*. **2012**, 4, 629.

13. Chen, K.; Richter, J. M.; Baran, P. S. *J. Am. Chem. Soc*. **2008**, 130, 7247–7249.

14. Wayner, D. D. M.; McPhee, D. J.; Griller, D. *J. Am. Chem. Soc*. **1988**, 110, 132-137.

15. (a) Reckenthäler, M.; Griesbeck, A. G. *Adv. Synth. Catal*. **2013**, 355, 2727–2744.; (b) Yoon, T. P.; Ischay, M. A.; Du, J. *Nat. Chem*. **2010**, 2, 527-532.; (c) Hari, D. P.; Konig, B. *Angew. Chem. Int. Ed. Engl*. **2013**, 52, 4734-43.; (d) Hu, J.; Wang, J.; Nguyen, T. H.; Zheng, N. *Beilstein J. Org. Chem*. **2013**, 9, 1977-2001.; (e) Narayanam, J. M.; Stephenson, C. R. *Chem. Soc. Rev*. **2011**, 40, 102-13.; (f) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. *Chem. Rev*. **2013**, 113, 5322-63.; (g) Teplý, F. *Chem. Commun*. **2011**, 76, 859-917.; (h) Tucker, J. W.; Stephenson, C. R. *J. Org. Chem*. **2012**, 77, 1617-22.; (i) Xuan, J.; Xiao, W. *Angew. Chem. Int. Ed. Engl*. **2012**, 51, 6828-38.; (j) Zeitler, K. *Angew. Chem. Int. Ed. Engl*. **2009**, 48, 9785-9.

16. Galli, C. *Chem. Rev*. **1988**, 88, 765-792.

17. (a) Sahoo, B.; Hopkinson, M. N.; Glorius, F. *J. Am. Chem. Soc*. **2013**, 135, 5505-8.; (b) Verberne-Sutton, S. D.; Quarels, R. D.; Zhai, X.; Garno, J. C.; Ragains, J. R. *J. Am. Chem. Soc*. **2014**, 136, 14438-44.

18. Denmark, S. E.; Kobayashi, T.; Regens, C. S. *Tetrahedron*. **2010**, 66, 4745-4759.

APPENDIX A: COPYRIGHT RELEASES

ELSEVIER LICENSE
TERMS AND CONDITIONS

Feb 18, 2016

This is an Agreement between Mark L Spell ("You") and Elsevier ("Elsevier"). It consists of your order details, the terms and conditions provided by Elsevier, and the payment terms and conditions.

All payments must be made in full to CCC. For payment instructions, please see information listed at the bottom of this form.

Supplier	Elsevier Limited The Boulevard,Langford Lane Kidlington,Oxford,OX5 1GB,UK
Registered Company Number	1982084
Customer name	Mark L Spell
Customer address	448 West Parker blvd Apt 3 BATON ROUGE, LA 70808
License number	3812090513421
License date	Feb 11, 2016
Licensed content publisher	Elsevier
Licensed content publication	Bioorganic & Medicinal Chemistry
Licensed content title	Ascaroside activity in Caenorhabditis elegans is highly dependent on chemical structure
Licensed content author	Kyle A. Hollister,Elizabeth S. Conner,Xinxing Zhang,Mark Spell,Gary M. Bernard,Pratik Patel,Ana Carolina G.V. de Carvalho,Rebecca A. Butcher,Justin R. Ragains
Licensed content date	15 September 2013
Licensed content volume number	21
Licensed content issue number	18
Number of pages	16
Start Page	5754
End Page	5769
Type of Use	reuse in a thesis/dissertation
Intended publisher of new work	other

Portion	figures/tables/illustrations
Number of figures/tables/illustrations	All
Actual number of figures/tables/illustrations	11
Format	both print and electronic
Are you the author of this Elsevier article?	Yes
Will you be translating?	No
Title of your thesis/dissertation	I. SYNTHESIS AND BIOLGICAL EVALUATION OF ASCAROSIDES FOR DAUER FORMATION IN C.ELEGANS II. ALPHA SELECTIVE GLYCOSYLATION OF ALCOHOLS WITH SELENOGLYCOSIDES USING VISIBLE LIGHT III. A METAL-FREE, VISIBLE LIGHT-PROMOTED O-GLYCOSYLATION WITH A THIOGLYCOSIDE DONOR IV. REMOTE HYDROXYLATION BY RADICAL TRANSLOCATION AND REDOX CHEMISTRY.
Expected completion date	Apr 2016
Estimated size (number of pages)	
Elsevier VAT number	GB 494 6272 12
Price	0.00 USD
VAT/Local Sales Tax	0.00 USD / 0.00 GBP
Total	**0.00 USD**

ELSEVIER LICENSE
TERMS AND CONDITIONS

Feb 18, 2016

This is an Agreement between Mark L Spell ("You") and Elsevier ("Elsevier"). It consists of your order details, the terms and conditions provided by Elsevier, and the payment terms and conditions.

All payments must be made in full to CCC. For payment instructions, please see information listed at the bottom of this form.

Supplier	Elsevier Limited The Boulevard,Langford Lane Kidlington,Oxford,OX5 1GB,UK
Registered Company Number	1982084
Customer name	Mark L Spell
Customer address	448 West Parker blvd Apt 3 BATON ROUGE, LA 70808
License number	3812090665153
License date	Feb 11, 2016
Licensed content publisher	Elsevier
Licensed content publication	Carbohydrate Research
Licensed content title	An α-selective, visible light photocatalytic glycosylation of alcohols with selenoglycosides
Licensed content author	Mark Spell,Xiaoping Wang,Amir E. Wahba,Elizabeth Conner,Justin Ragains
Licensed content date	22 March 2013
Licensed content volume number	369
Licensed content issue number	n/a
Number of pages	6
Start Page	42
End Page	47
Type of Use	reuse in a thesis/dissertation
Portion	figures/tables/illustrations
Number of figures/tables/illustrations	All
Actual number of figures/tables/illustrations	11
Format	both print and electronic
Are you the author of this Elsevier article?	Yes

Will you be translating?	No
Title of your thesis/dissertation	I. SYNTHESIS AND BIOLGICAL EVALUATION OF ASCAROSIDES FOR DAUER FORMATION IN C.ELEGANS II. ALPHA SELECTIVE GLYCOSYLATION OF ALCOHOLS WITH SELENOGLYCOSIDES USING VISIBLE LIGHT III. A METAL-FREE, VISIBLE LIGHT-PROMOTED O-GLYCOSYLATION WITH A THIOGLYCOSIDE DONOR IV. REMOTE HYDROXYLATION BY RADICAL TRANSLOCATION AND REDOX CHEMISTRY.
Expected completion date	Apr 2016
Estimated size (number of pages)	
Elsevier VAT number	GB 494 6272 12
Price	0.00 USD
VAT/Local Sales Tax	0.00 USD / 0.00 GBP
Total	**0.00 USD**

JOHN WILEY AND SONS LICENSE TERMS AND CONDITIONS

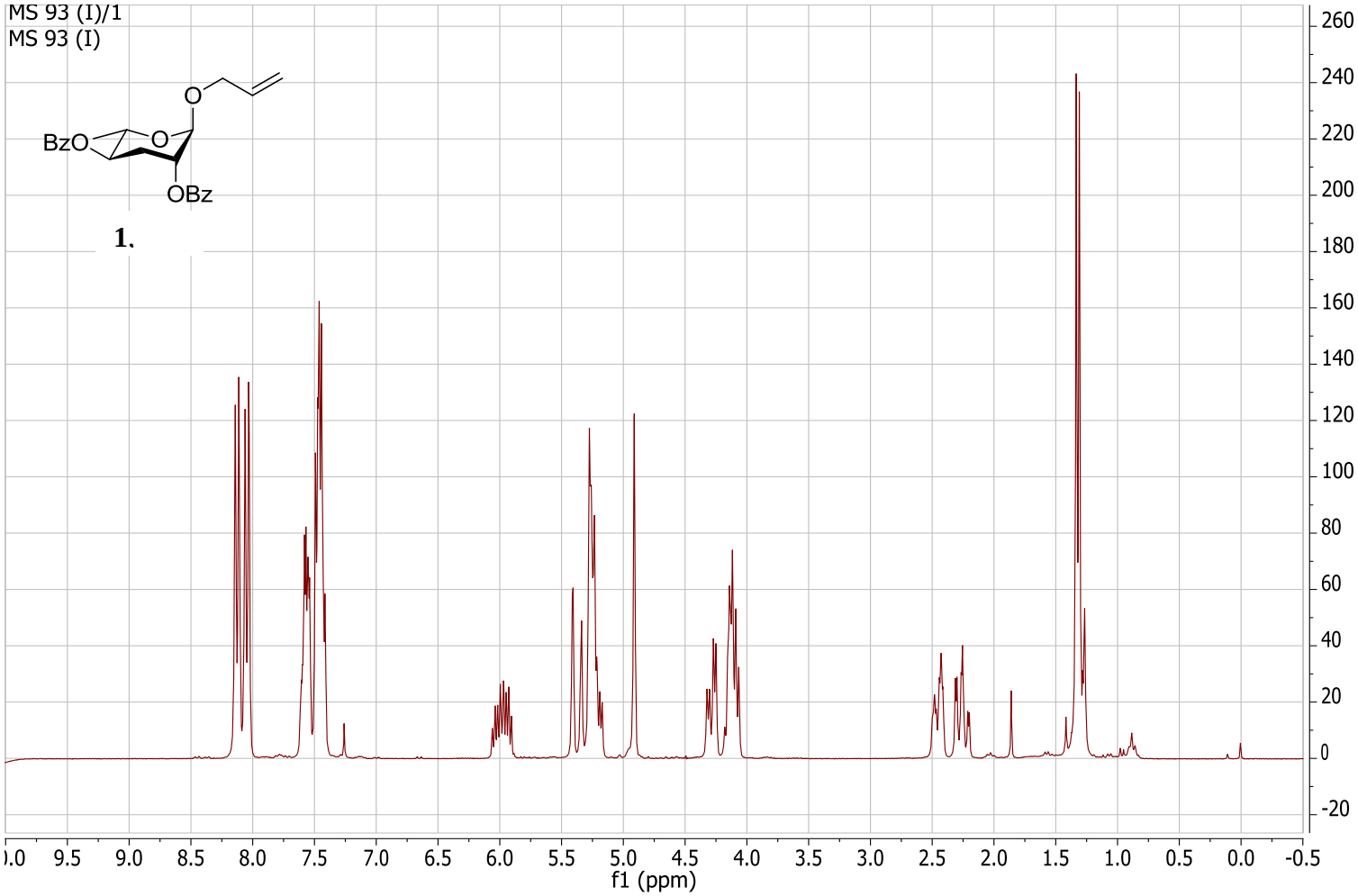
Feb 11, 2016

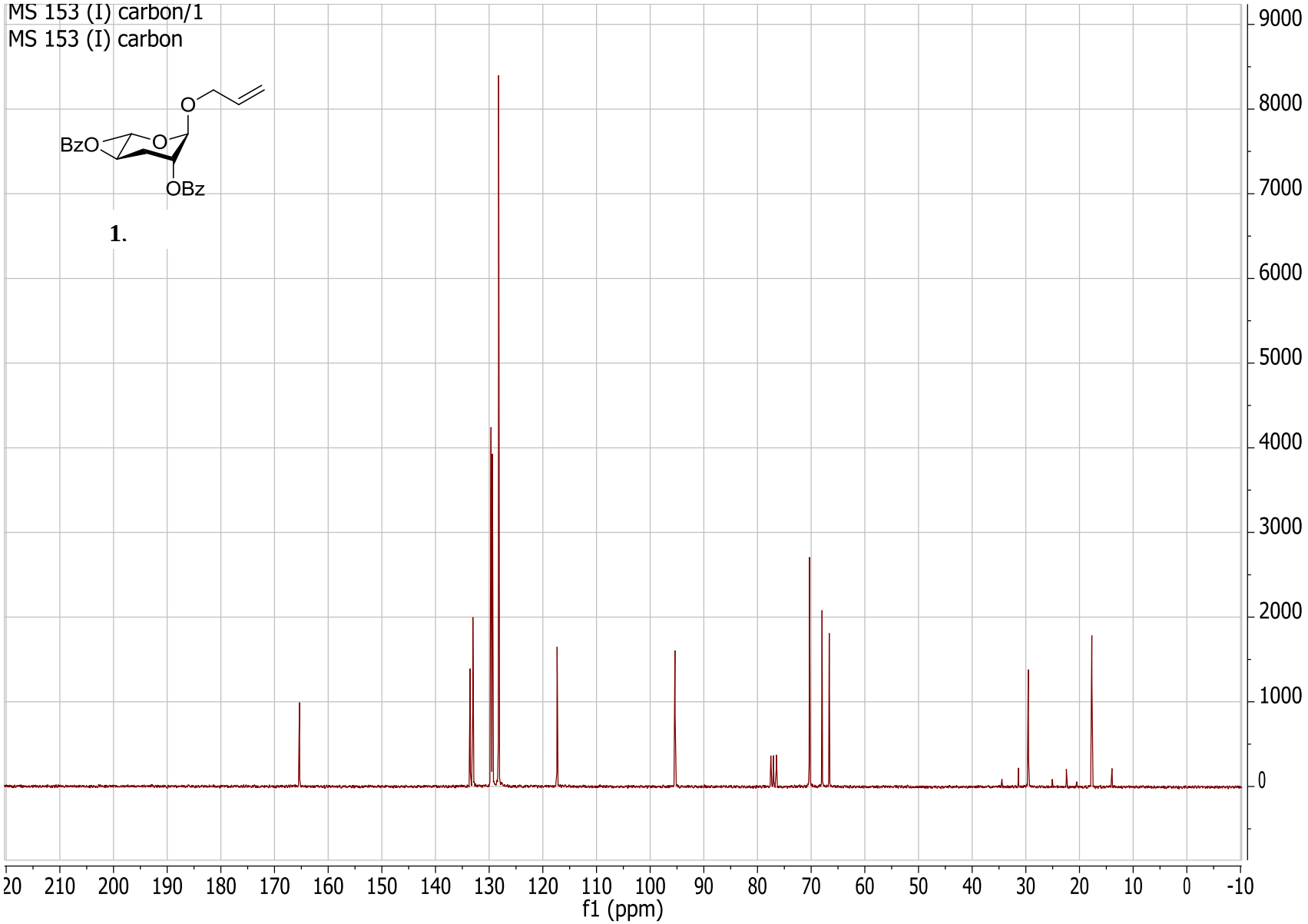
This Agreement between Mark L Spell ("You") and John Wiley and Sons ("John Wiley and Sons") consists of your license details and the terms and conditions provided by John Wiley and Sons and Copyright Clearance Center.

License Number	3805931207011
License date	Feb 11, 2016
Licensed Content Publisher	John Wiley and Sons
Licensed Content Publication	Angewandte Chemie International Edition
Licensed Content Title	Remote Hydroxylation through Radical Translocation and Polar Crossover
Licensed Content Author	Kyle A. Hollister,Elizabeth S. Conner,Mark L. Spell,Kristina Deveaux,Léa Maneval,Michael W. Beal,Justin R. Ragains
Licensed Content Date	May 26, 2015
Pages	5
Type of use	Dissertation/Thesis
Requestor type	Author of this Wiley article
Format	Print and electronic
Portion	Full article
Will you be translating?	No
Title of your thesis / dissertation	I. SYNTHESIS AND BIOLGICAL EVALUATION OF ASCAROSIDES FOR DAUER FORMATION IN C.ELEGANS II. ALPHA SELECTIVE GLYCOSYLATION OF ALCOHOLS WITH SELENOGLYCOSIDES USING VISIBLE LIGHT III. A METAL-FREE, VISIBLE LIGHT-PROMOTED O-GLYCOSYLATION WITH A THIOGLYCOSIDE DONOR IV. REMOTE HYDROXYLATION BY RADICAL TRANSLOCATION AND REDOX CHEMISTRY.
Expected completion date	Apr 2016
Expected size (number of pages)	250
Requestor Location	Mark L Spell 448 West Parker blvd Apt 3 448 West Parker blvd Apt 3 BATON ROUGE, LA 70808 United States Attn: Mark L Spell
Billing Type	Invoice

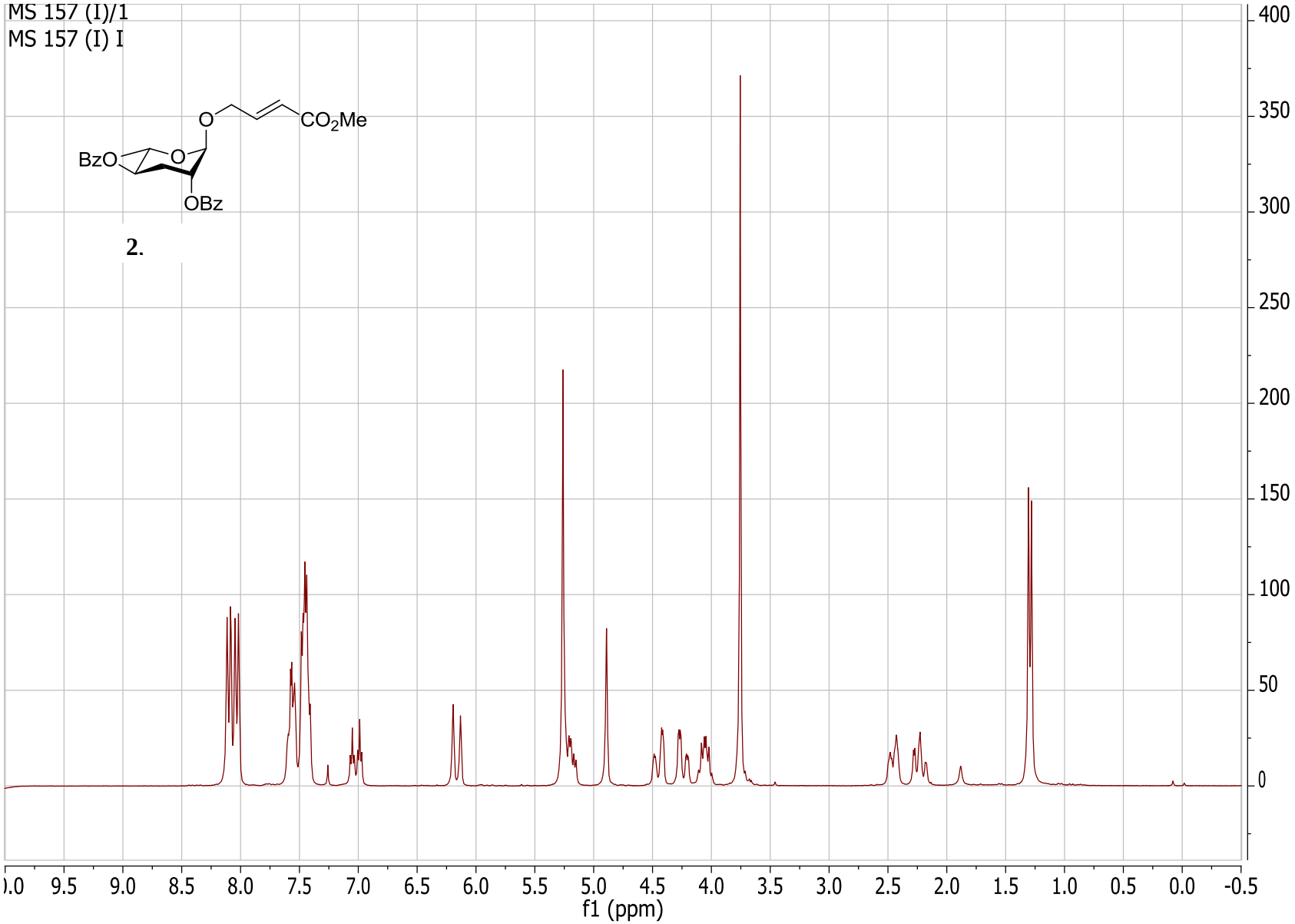
Billing Address	Mark L Spell 448 West Parker blvd Apt 3 448 West Parker blvd Apt 3 BATON ROUGE, LA 70808 United States Attn: Mark L Spell
Total	0.00 USD
Terms and Conditions	

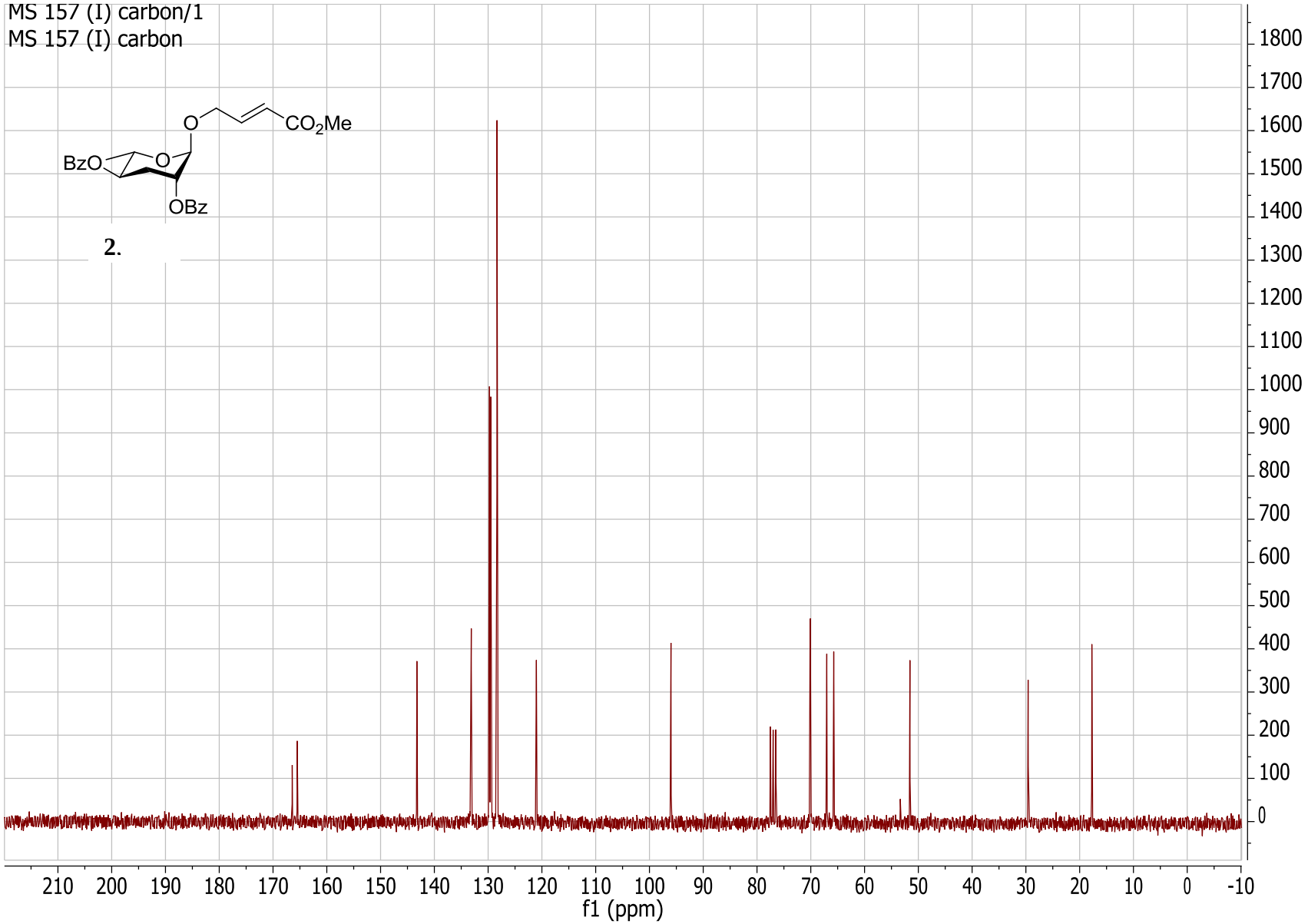
APPENDIX B: NMR SPECTRA OF COMPOUNDS FOUND IN CHAPTER 1

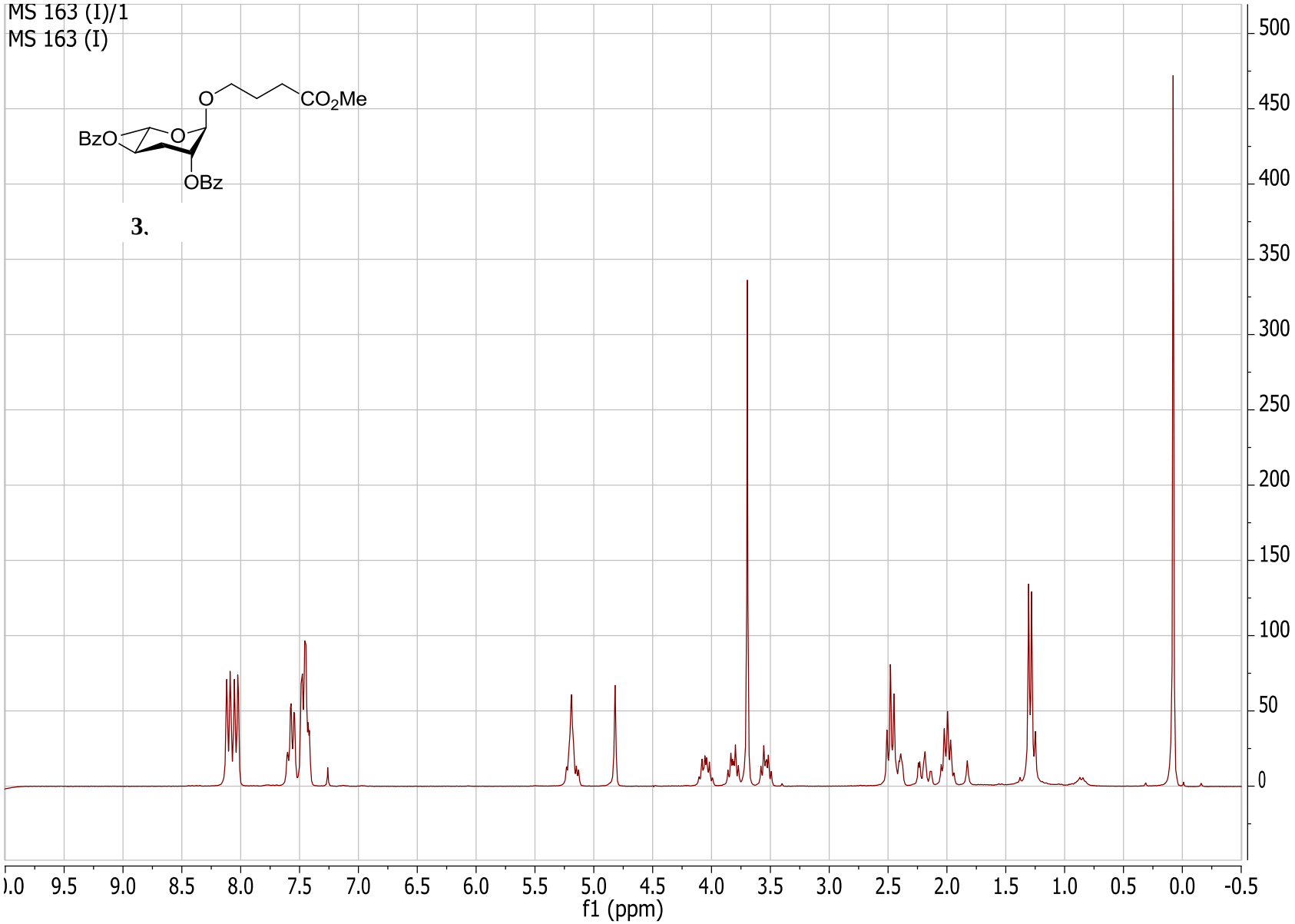


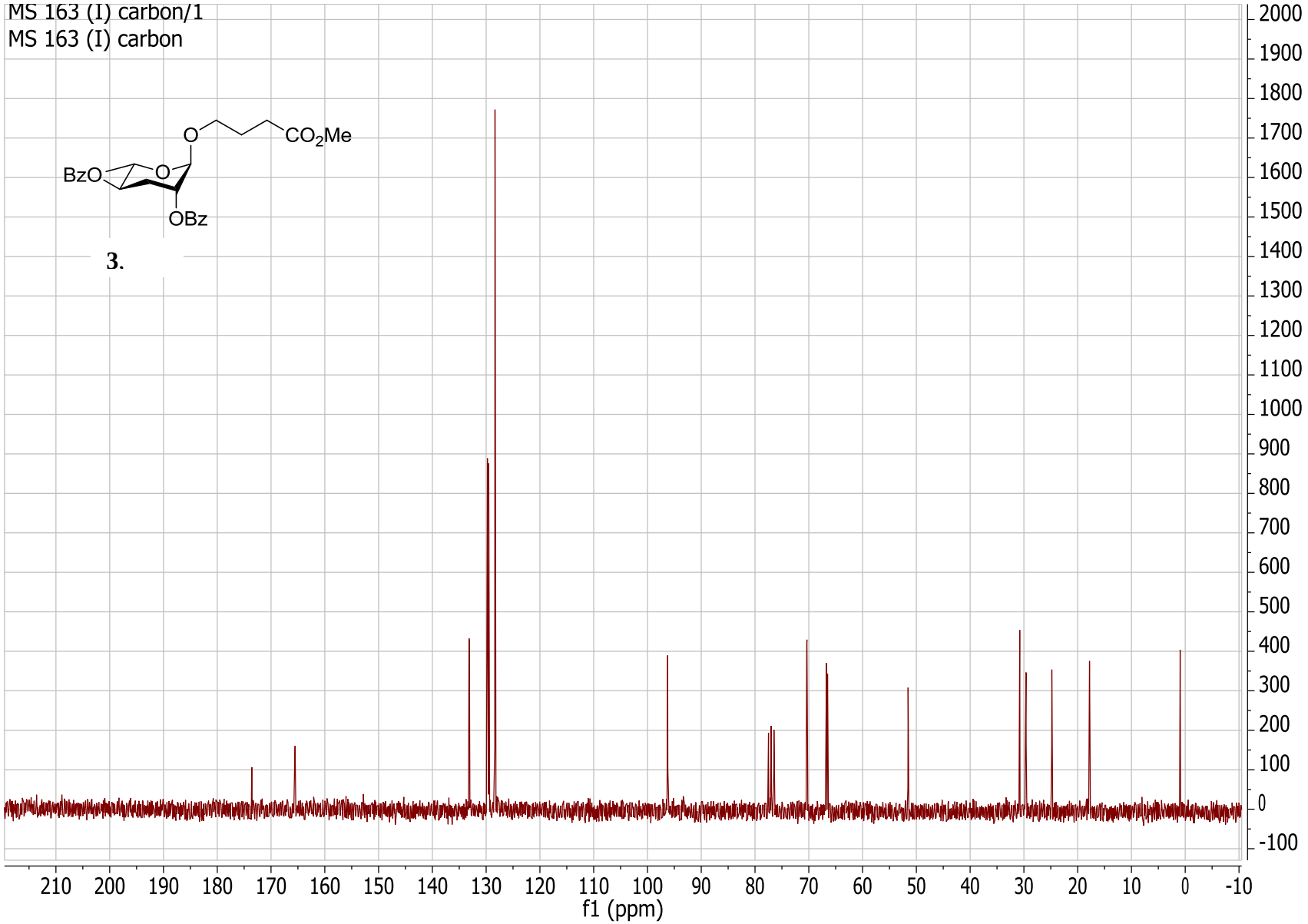

MS 153 (I) carbon/1
MS 153 (I) carbon
O
BzO
O
OBz
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

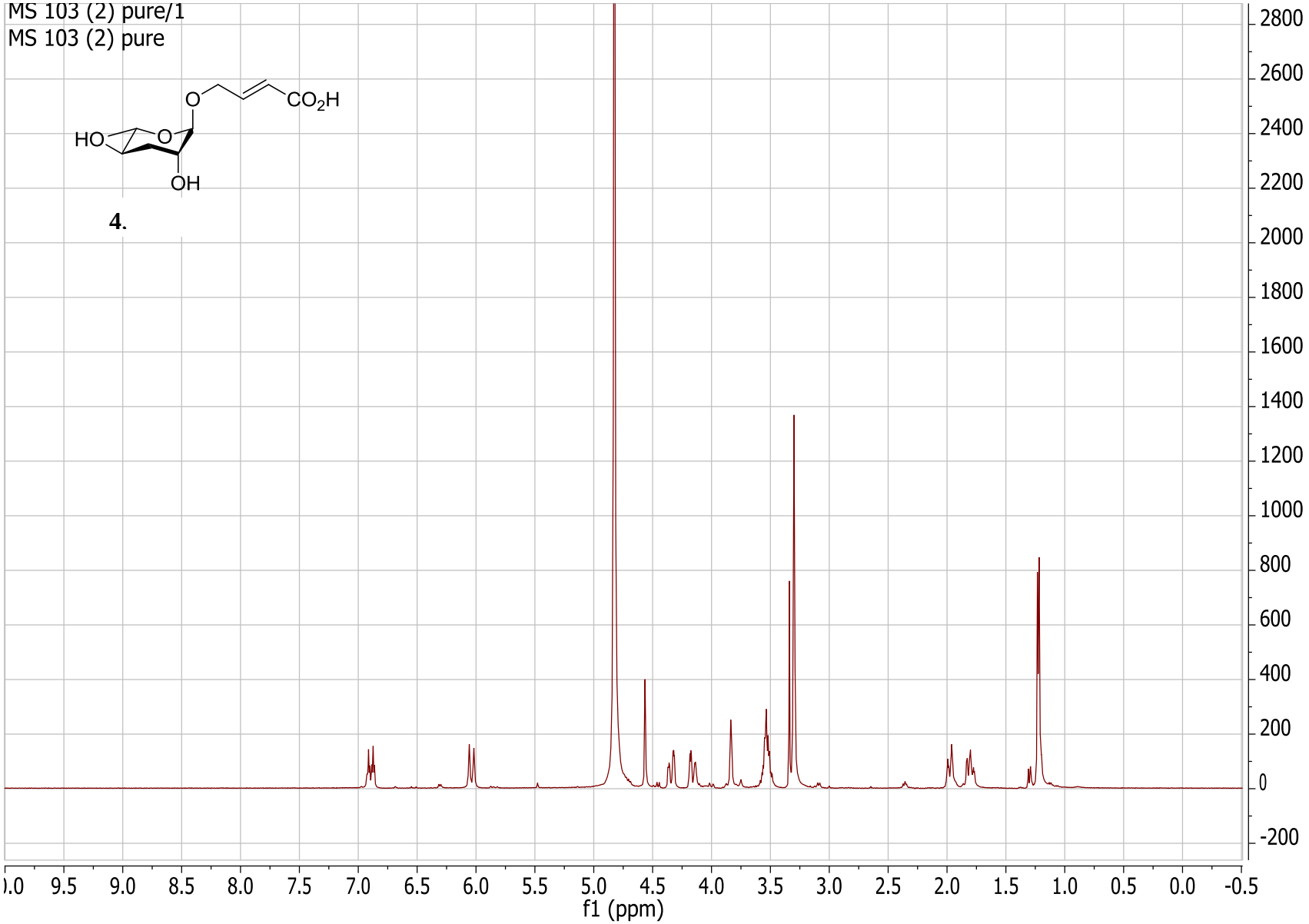
1.

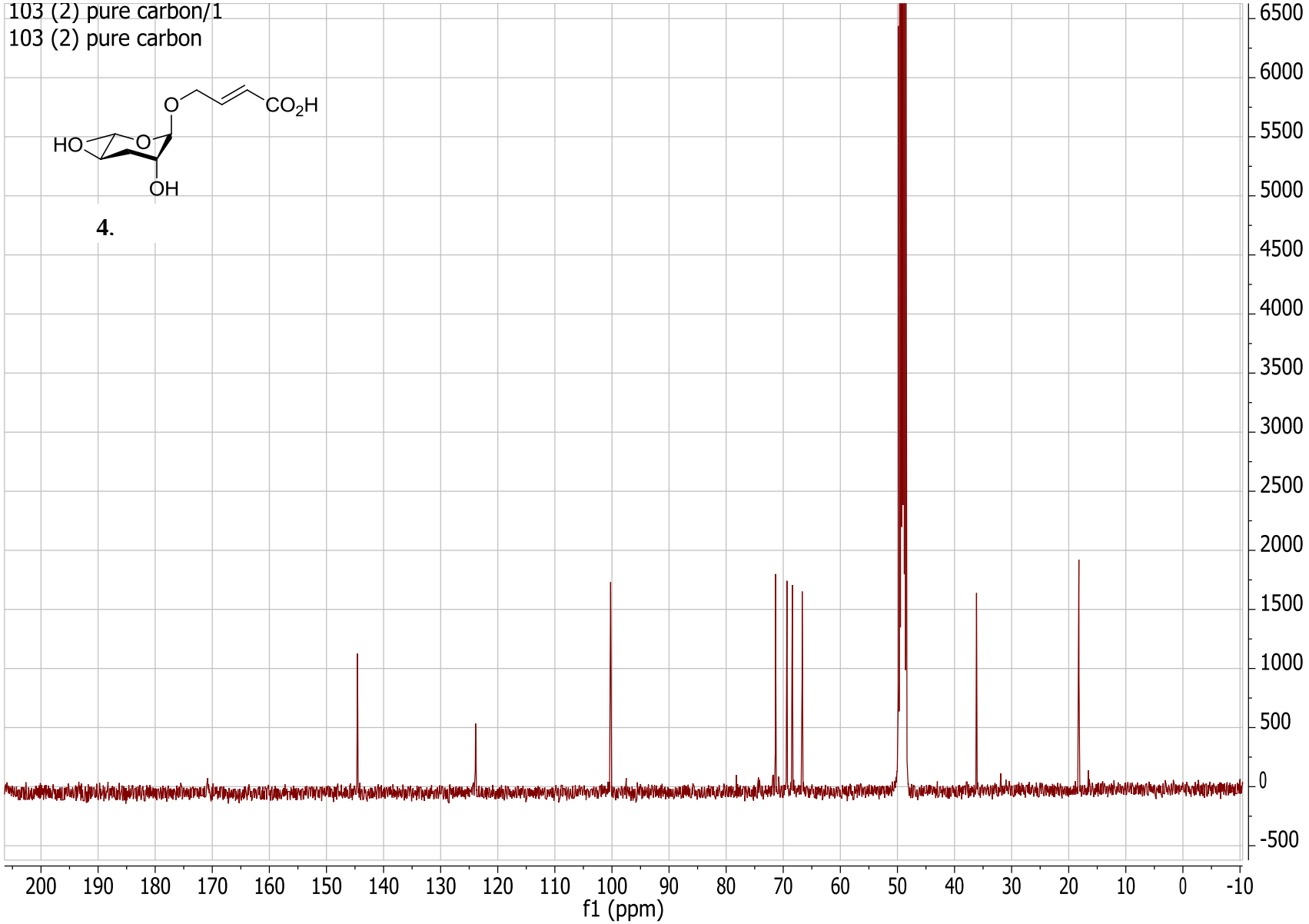

MS 157 (I)/1
MS 157 (I) I
O
CO2Me
BzO
O
OBz
2.
400
350
300
250
200
150
100
50
0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

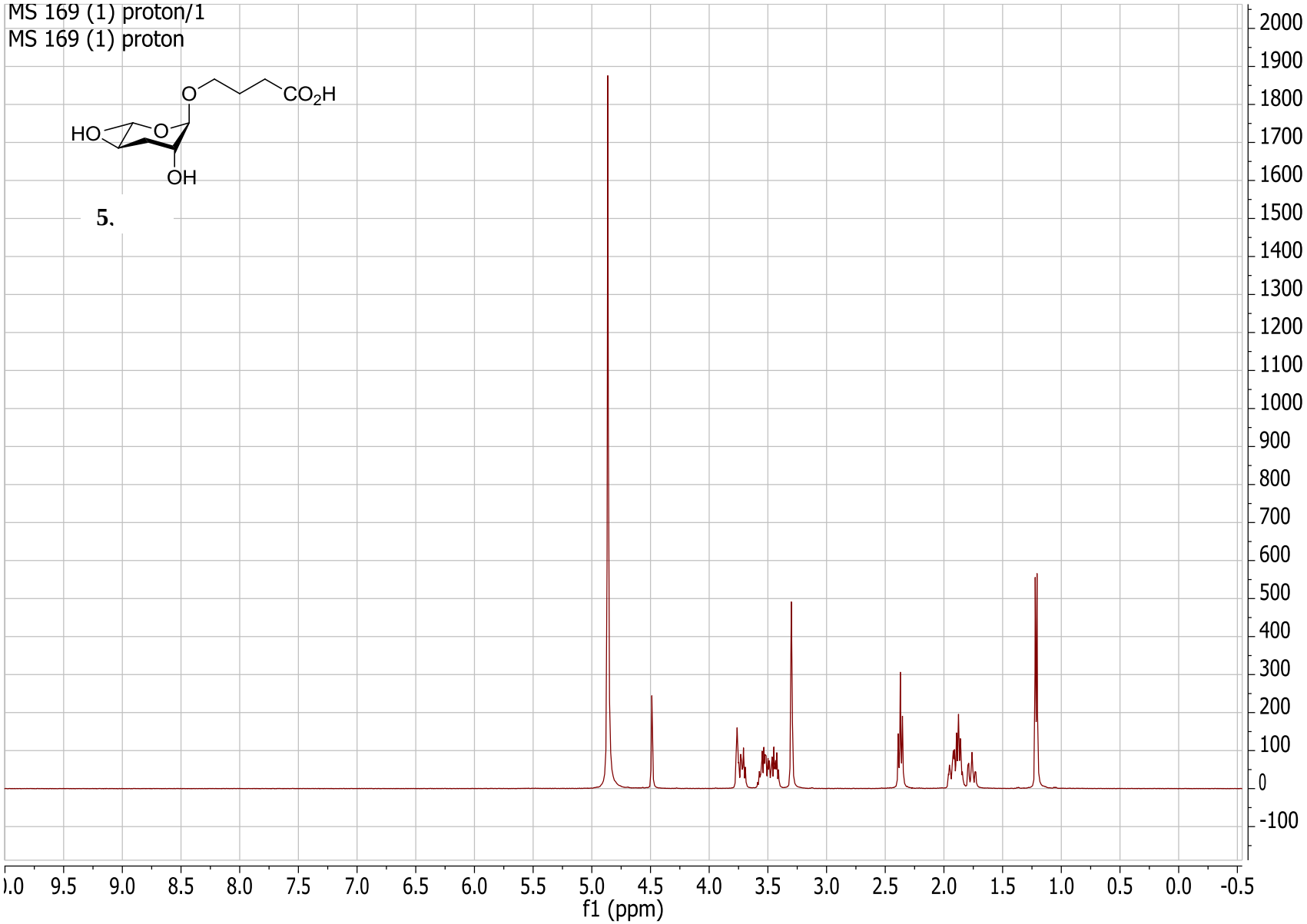

MS 157 (I) carbon/1
MS 157 (I) carbon
O
CO2Me
BzO
O
OBz
2.
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

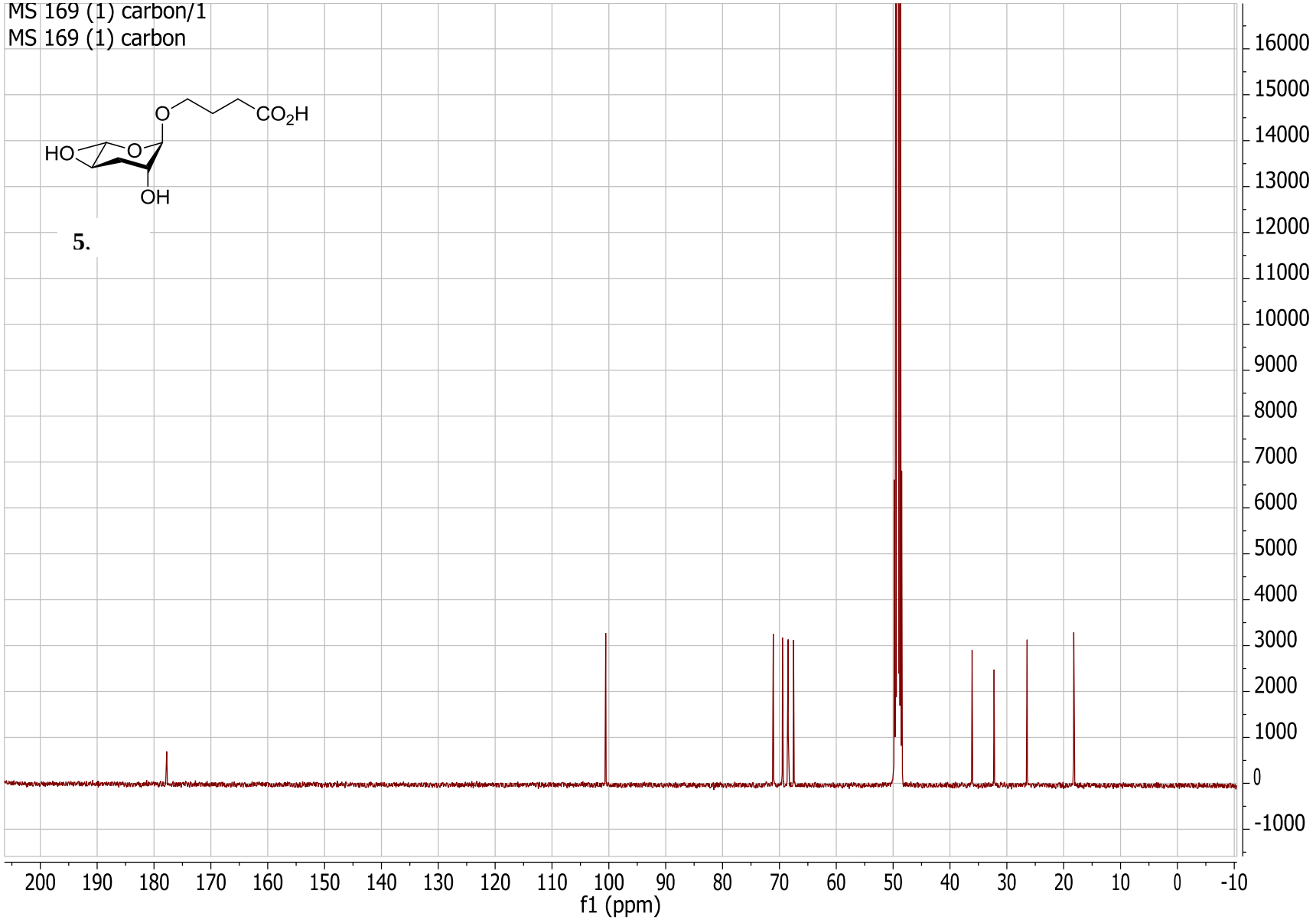

MS 163 (I)/1
MS 163 (I)
O
CO2Me
BzO
O
OBz
3.
500
450
400
350
300
250
200
150
100
50
0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

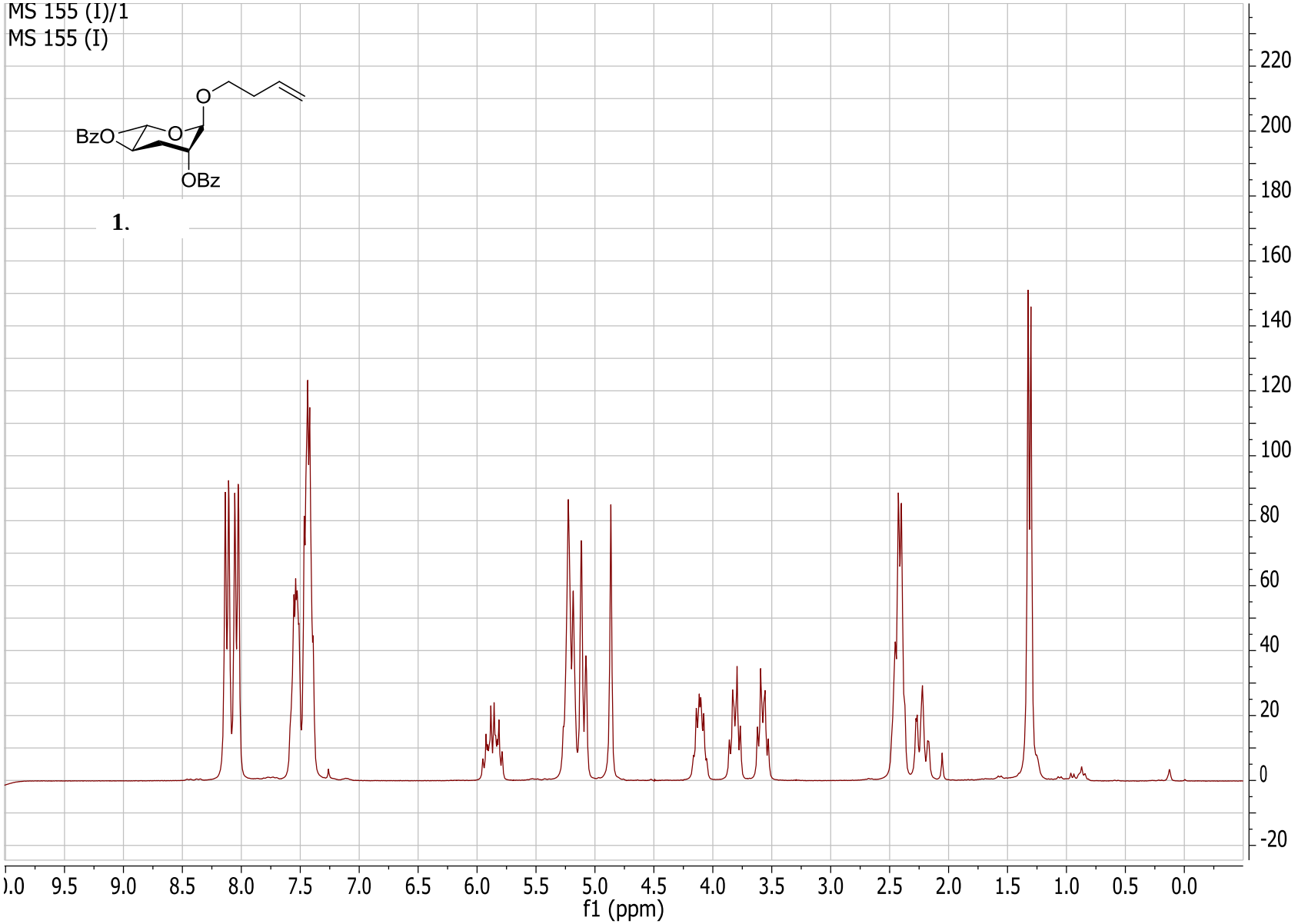

MS 163 (I) carbon/1
MS 163 (I) carbon
O
CO2Me
BzO
O
OBz
3.
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


MS 103 (2) pure/1
MS 103 (2) pure
O
CO2H
HO
O
OH
4.
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
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)

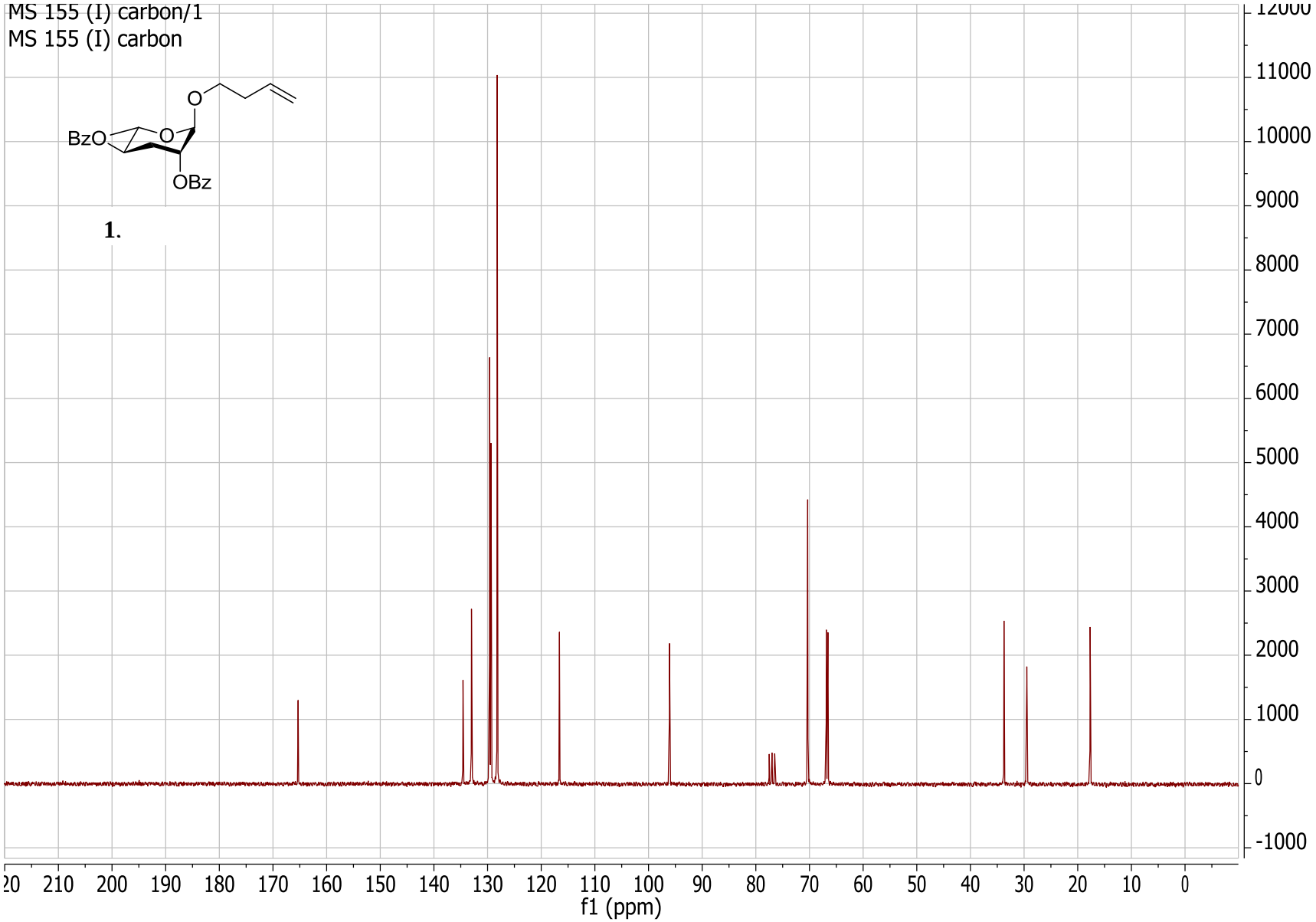

103 (2) pure carbon/1
103 (2) pure carbon
O
CO2H
HO
O
OH
4.
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

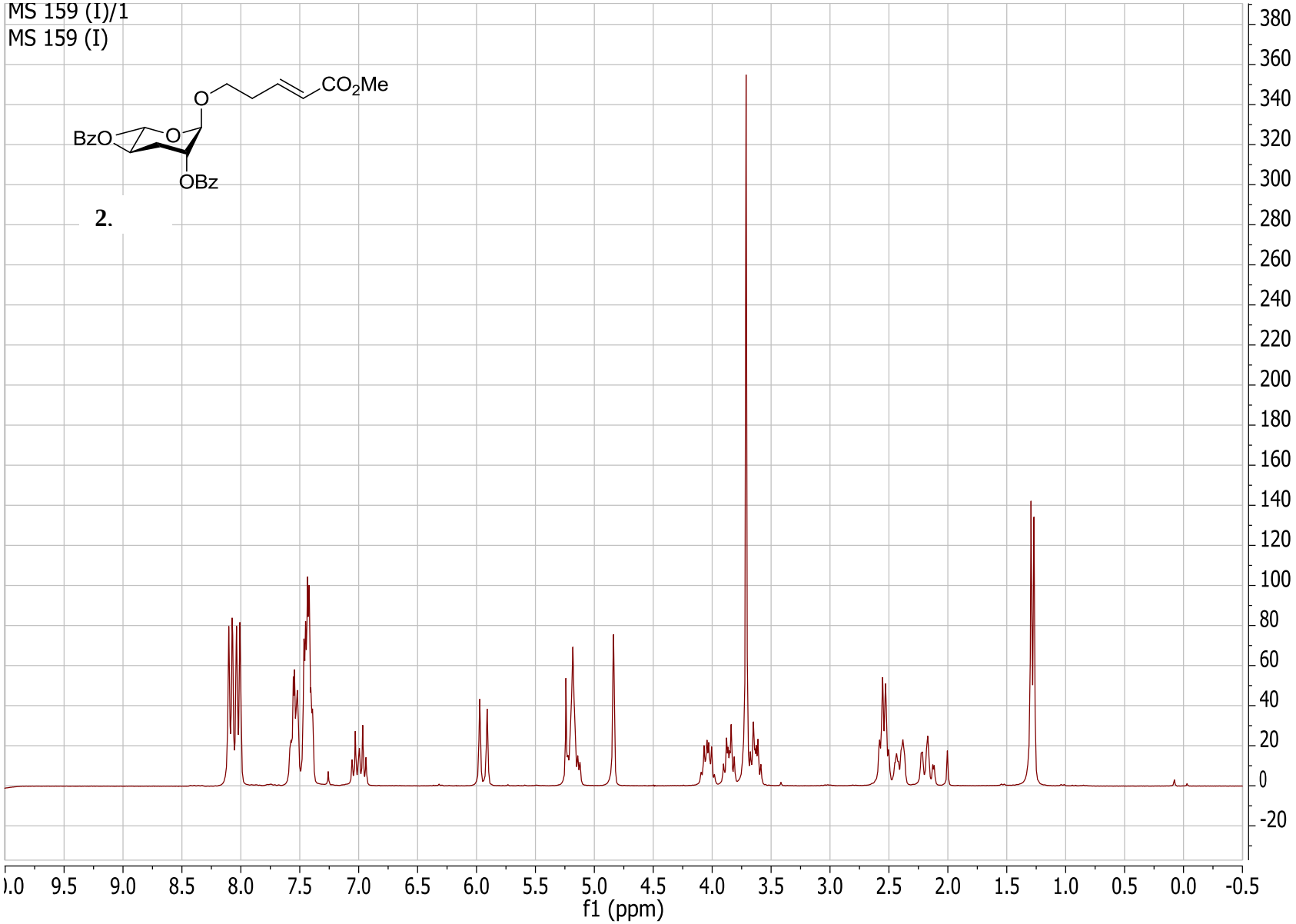

MS 169 (1) proton/1
MS 169 (1) proton
HO
O
O
CO2H
OH
5.
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

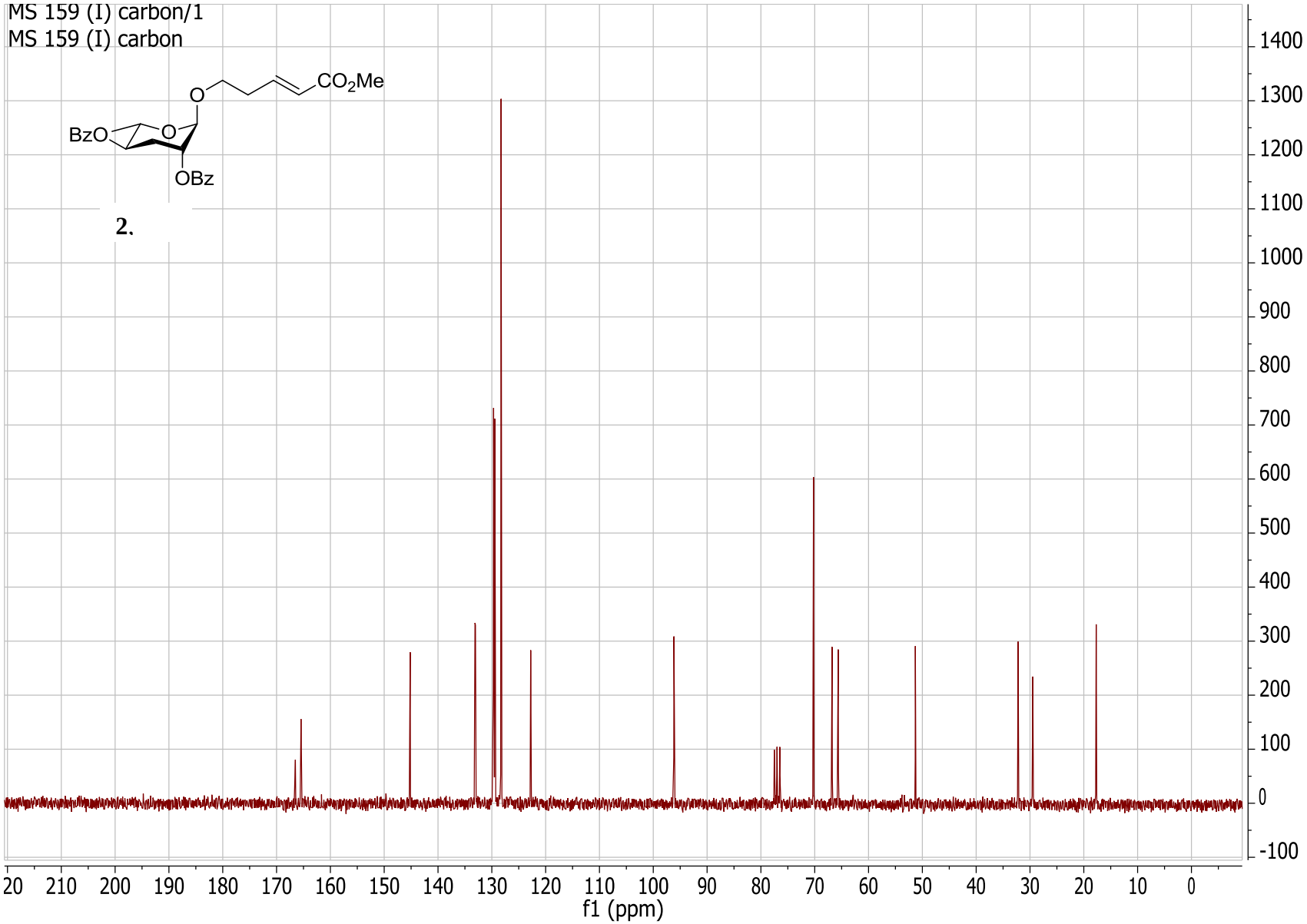

MS 169 (1) carbon/1
MS 169 (1) carbon
O
CO2H
HO
O
OH
5.
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

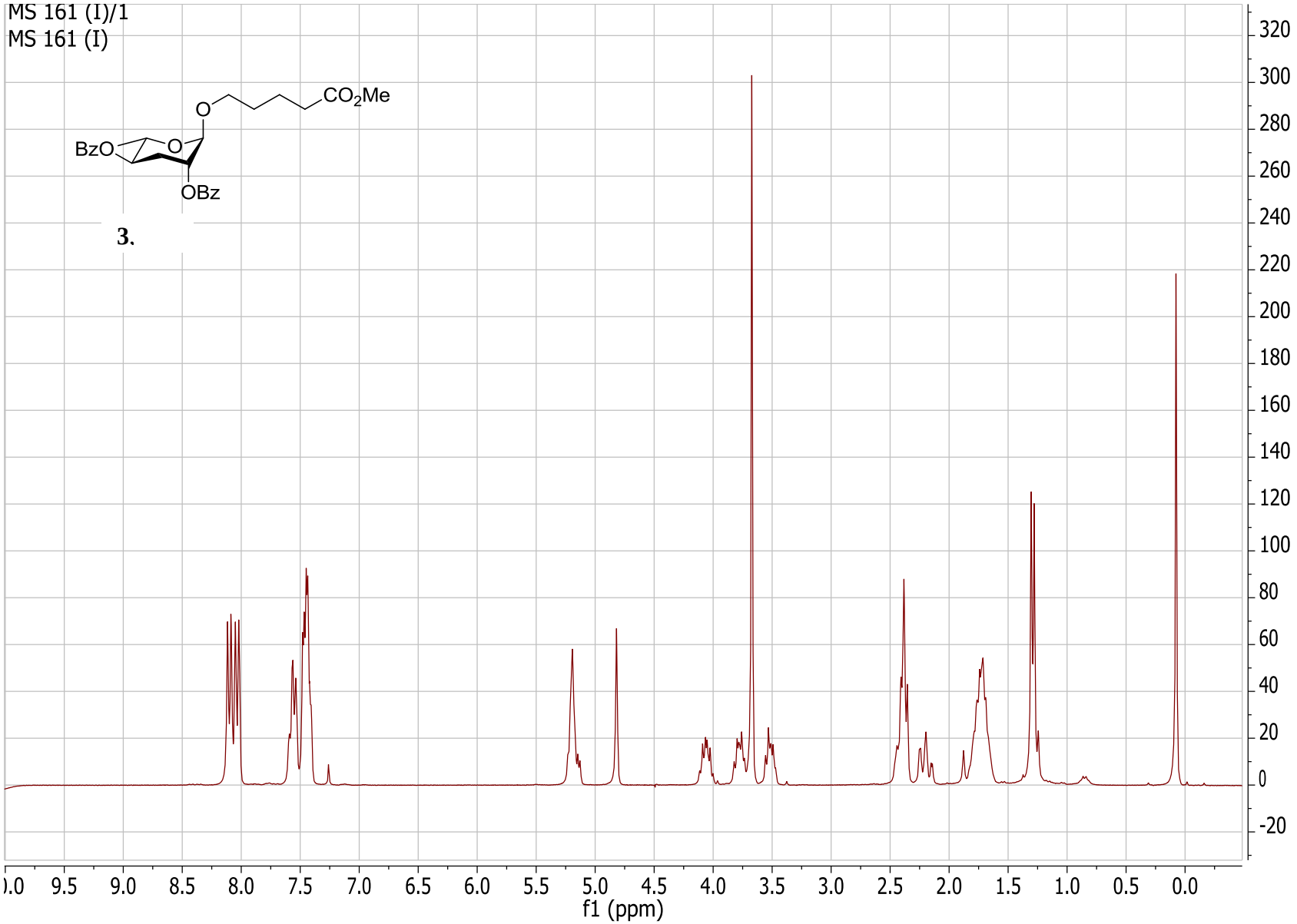

MS 155 (I)/1
MS 155 (I)
BzO
O
O
OBz
220
200
180
160
140
120
100
80
60
40
20
0
-20
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

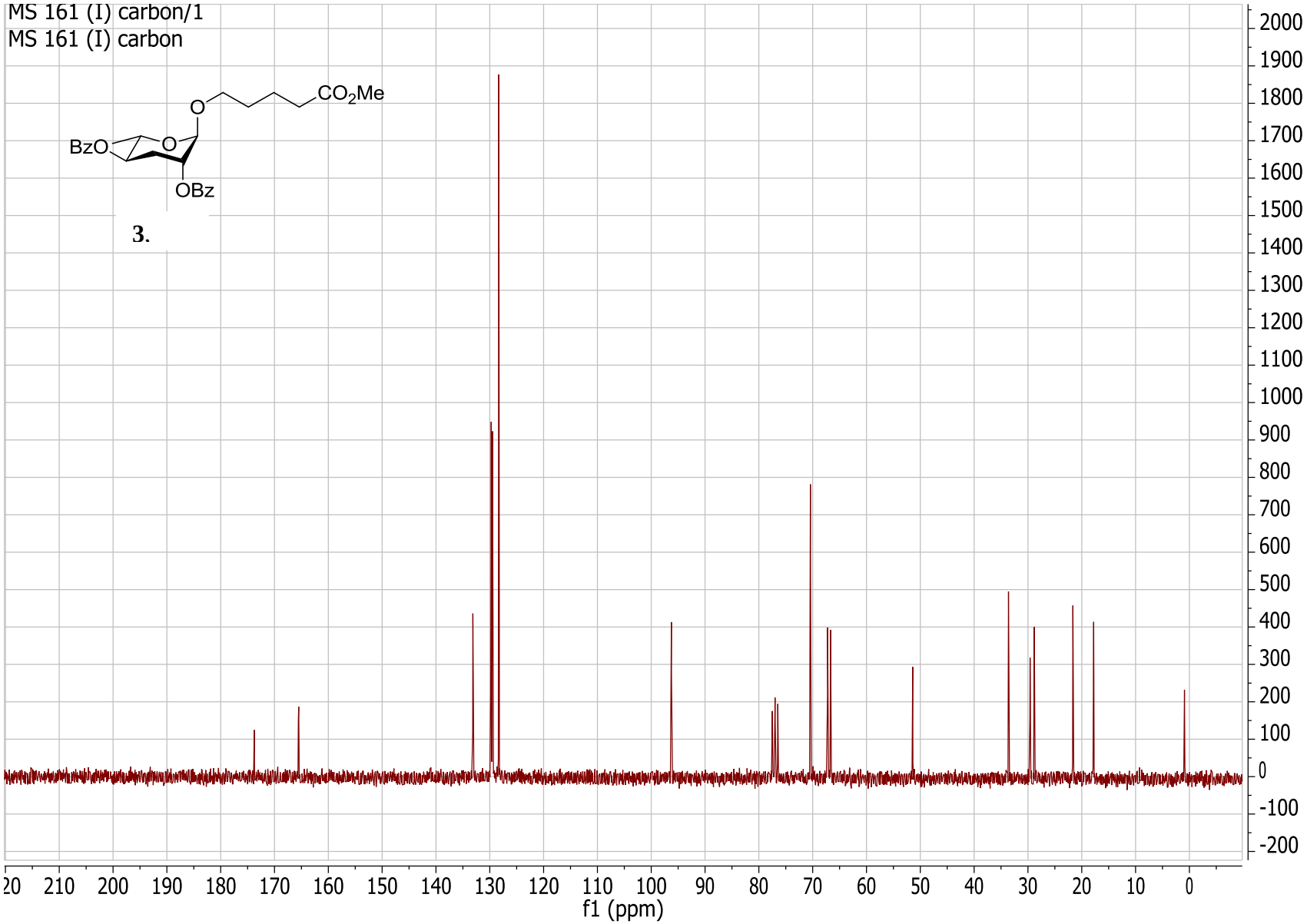
1.

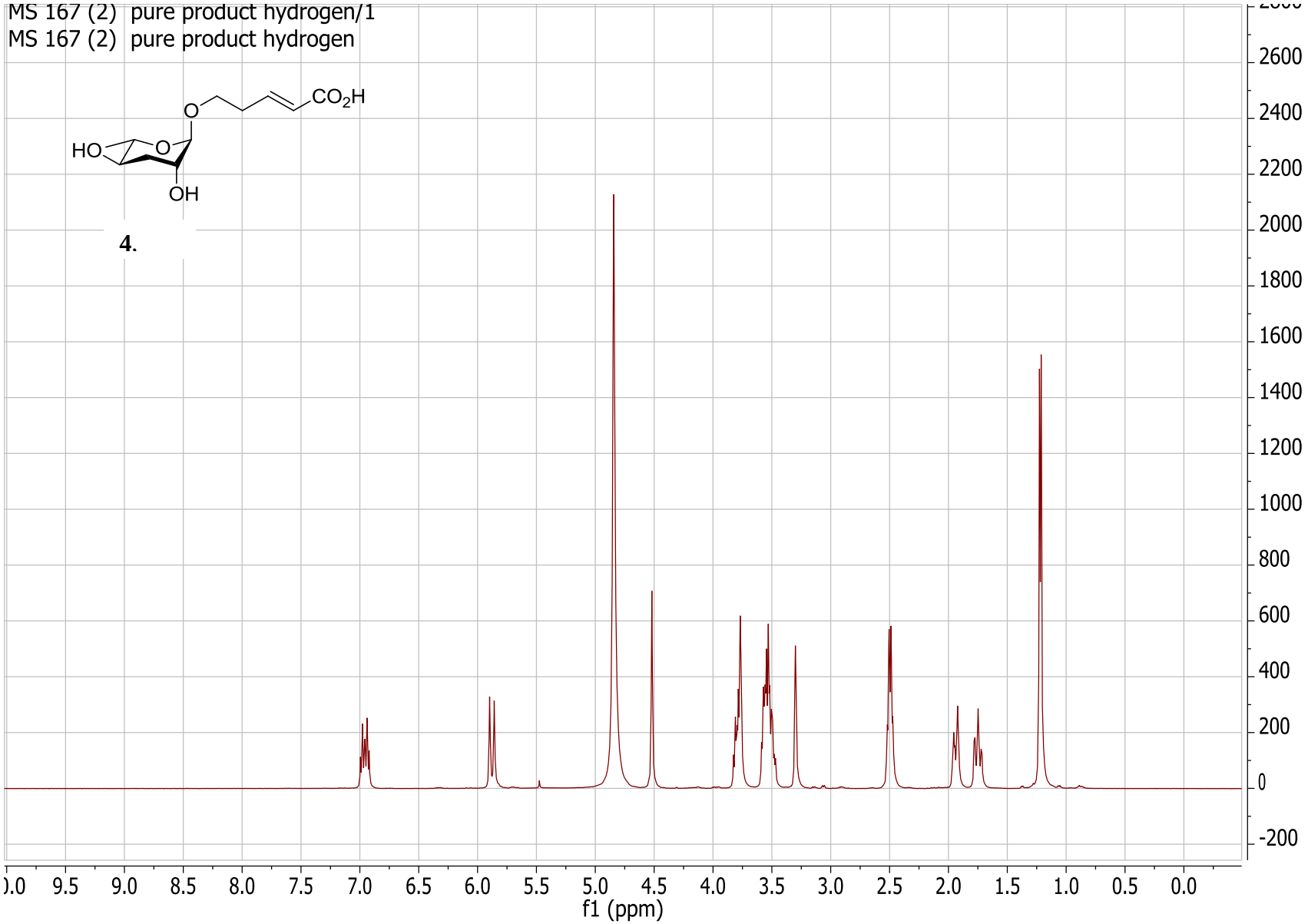

MS 155 (I) carbon/1
MS 155 (I) carbon
O
BzO
O
OBz
1.
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

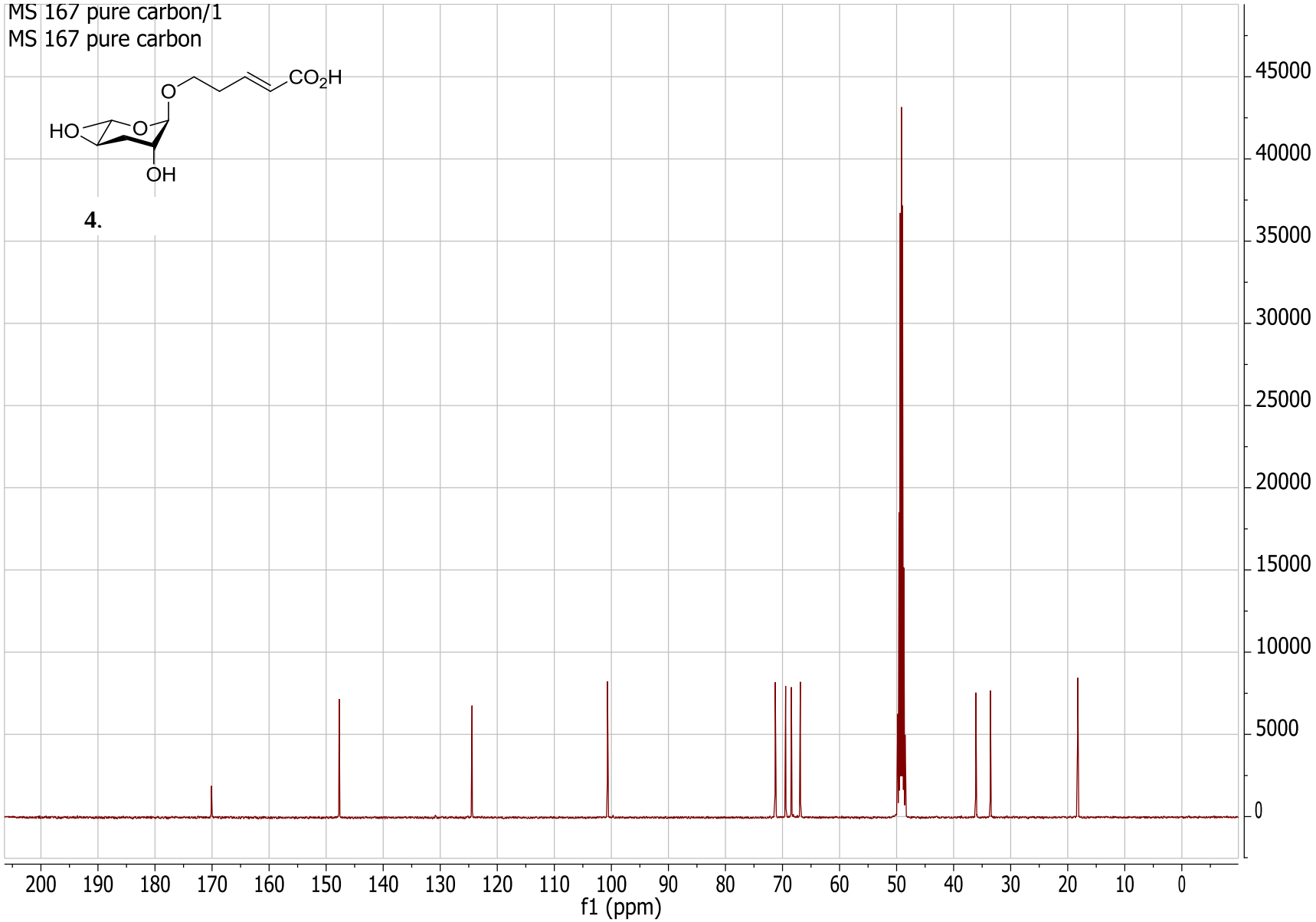

MS 159 (I)/1
MS 159 (I)
O
CO2Me
BzO
O
OBz
2.
380
360
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

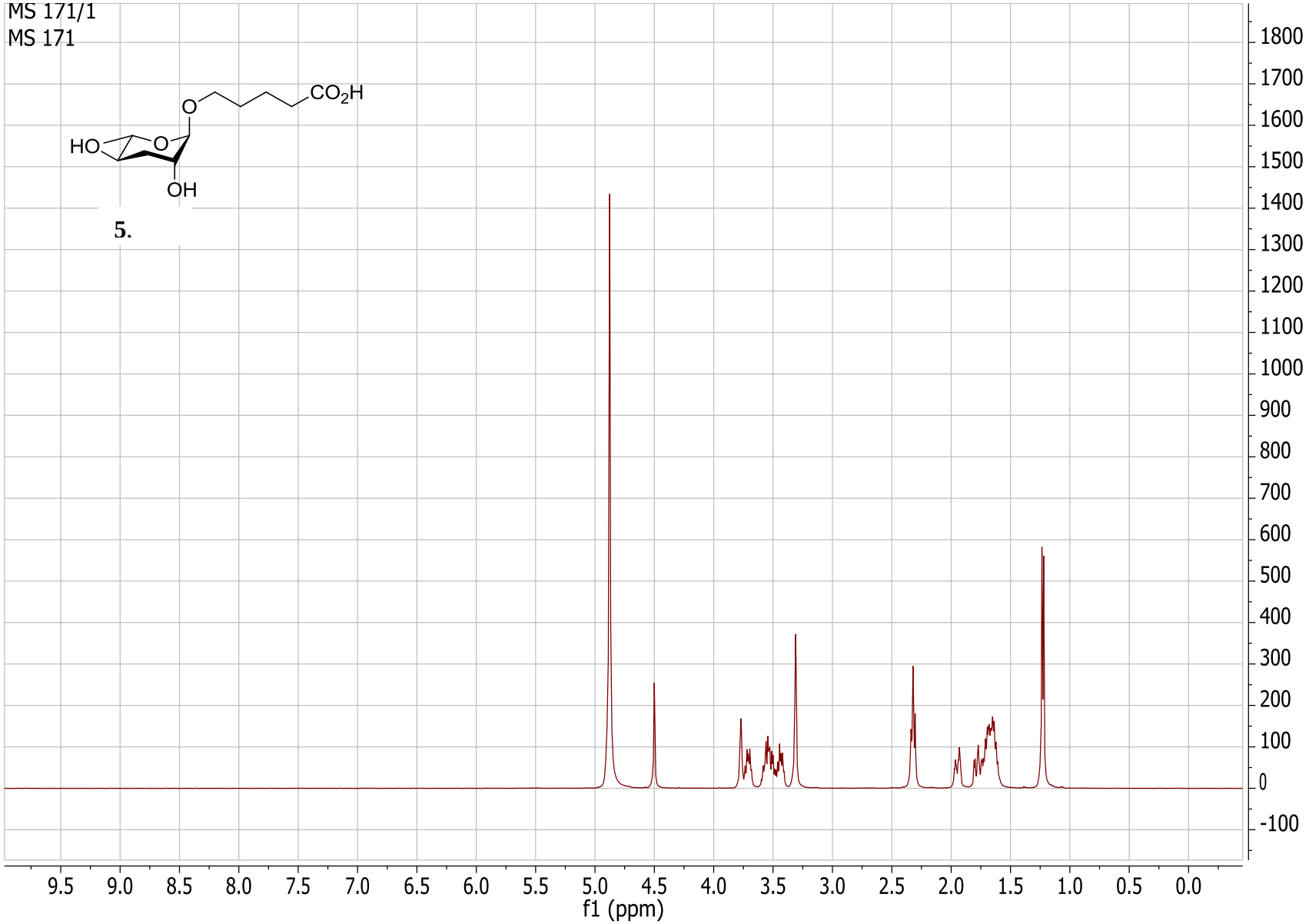

MS 159 (I) carbon/1
MS 159 (I) carbon
CO2Me
O
BzO
O
OBz
2.
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

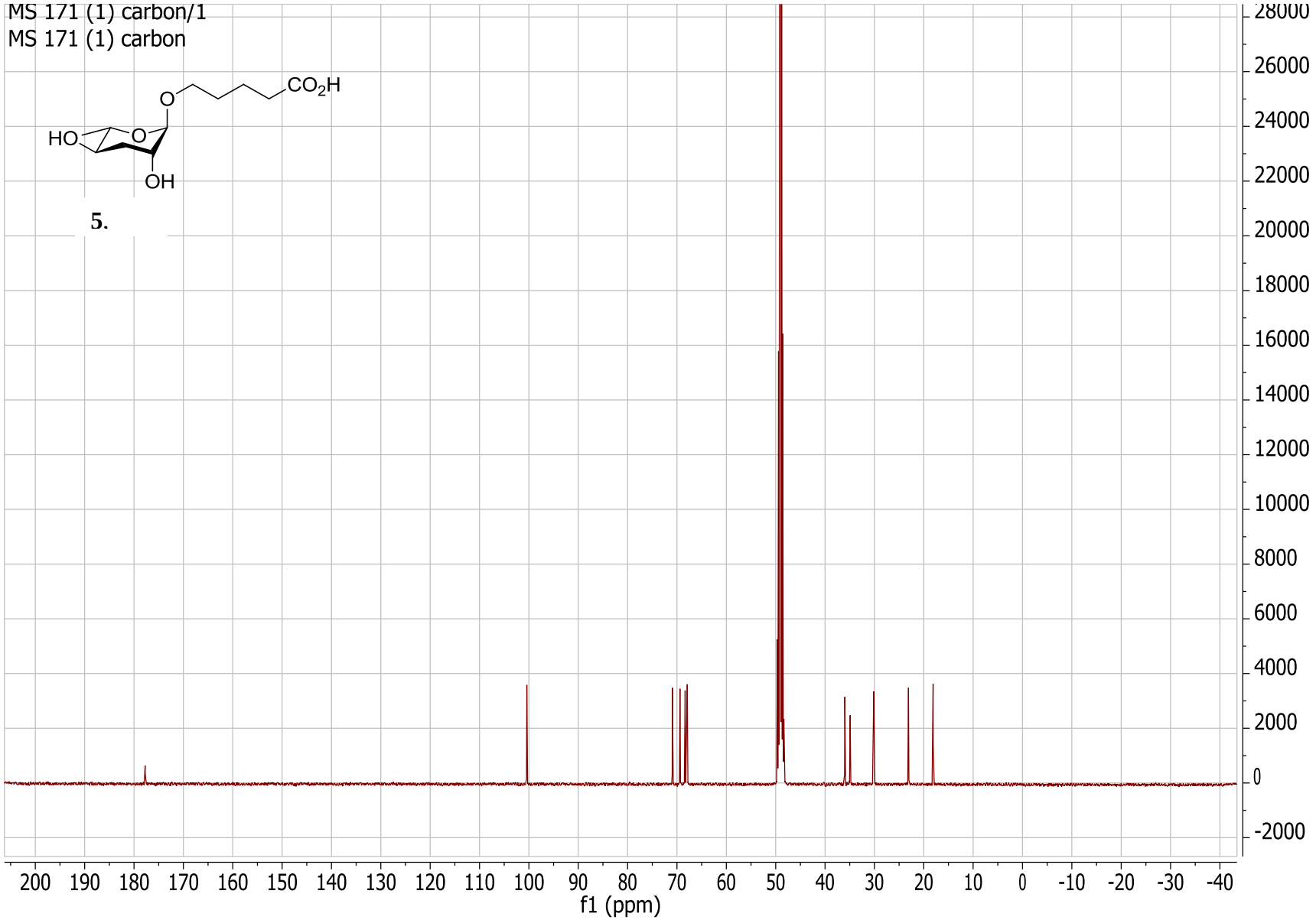

MS 161 (I)/1
MS 161 (I)
CO2Me
O
BzO
O
OBz
3.
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

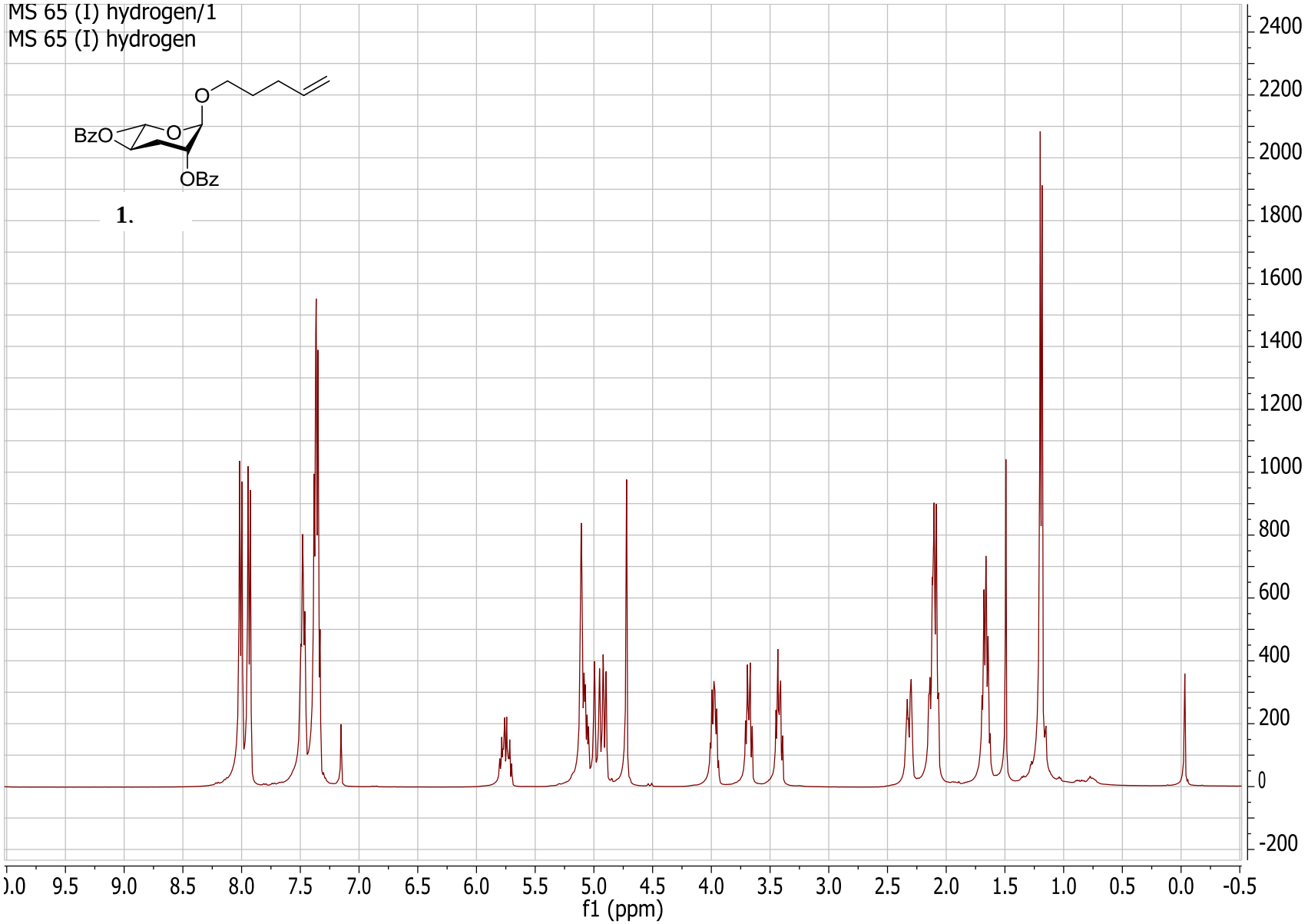

MS 161 (I) carbon/1
MS 161 (I) carbon
CO2Me
O
BzO
O
OBz
3.
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-200
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


MS 167 (2) pure product hydrogen/1
MS 167 (2) pure product hydrogen
CO2H
O
HO
O
OH
4.
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
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
f1 (ppm)

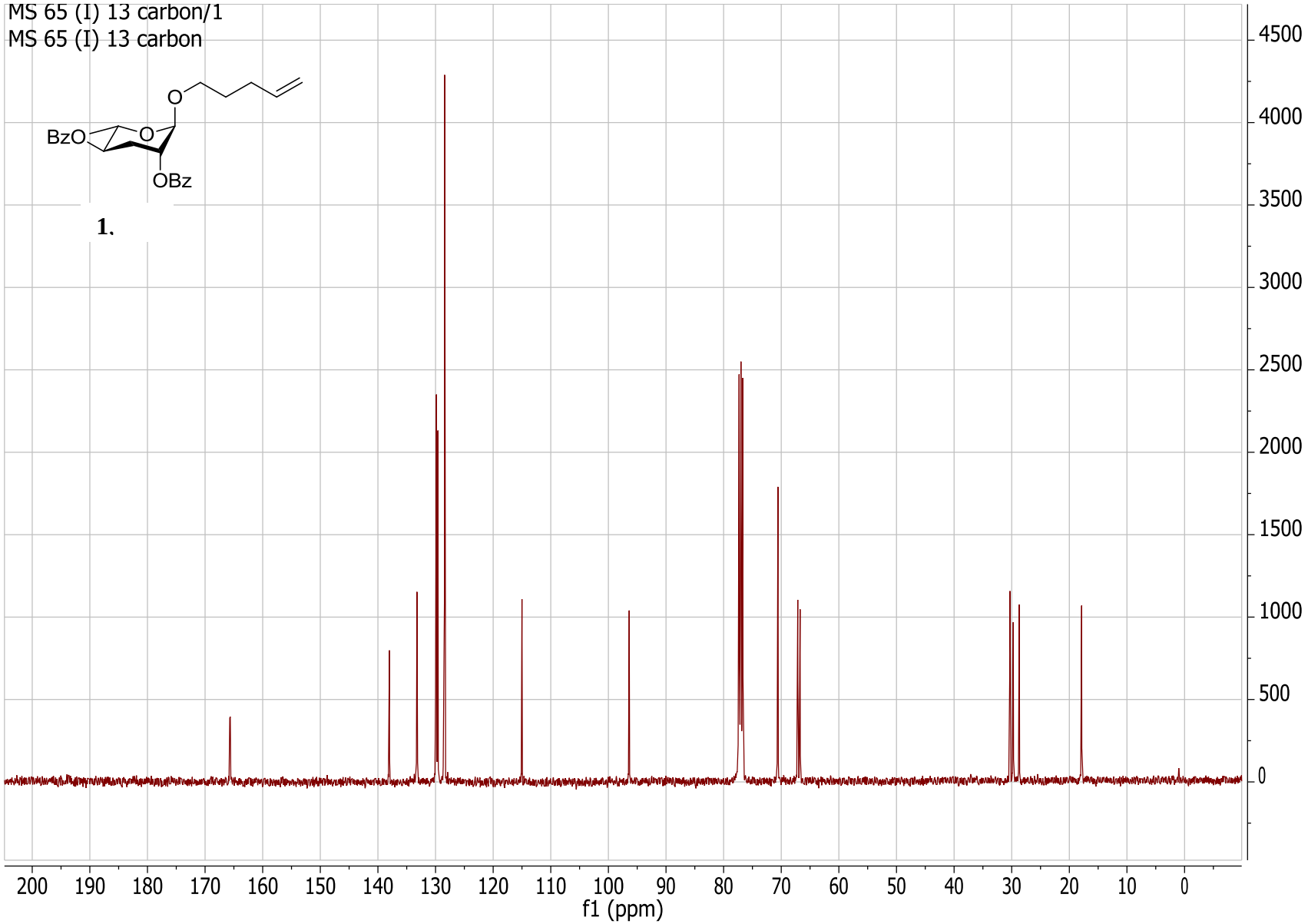

MS 167 pure carbon/1
MS 167 pure carbon
HO
O
O
OH
CO2H
4.
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


MS 171/1
MS 171
HO
O
O
OH
CO2H
5.
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
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
f1 (ppm)

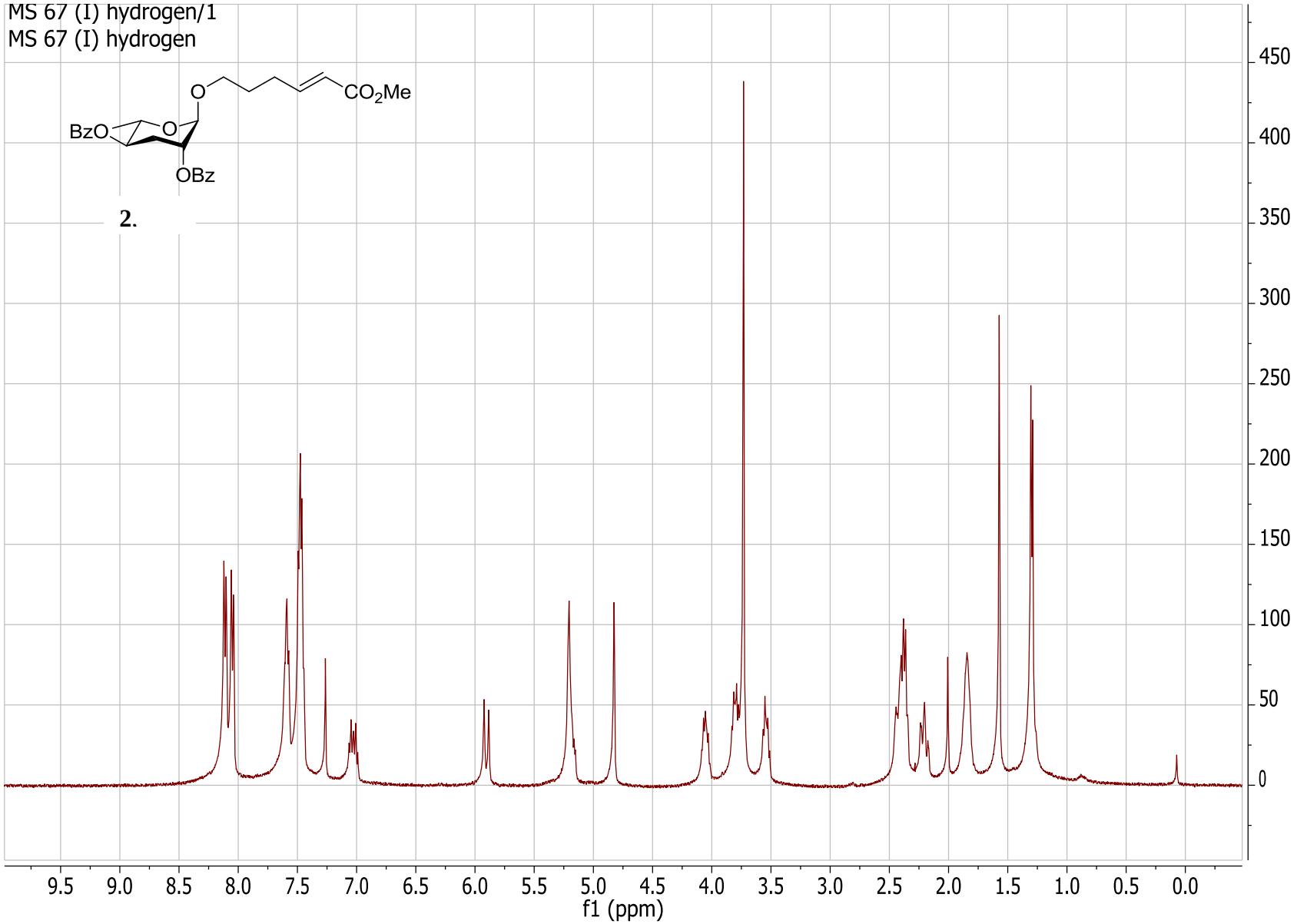

MS 171 (1) carbon/1
MS 171 (1) carbon
CO2H
O
HO
O
OH
5.
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40
f1 (ppm)

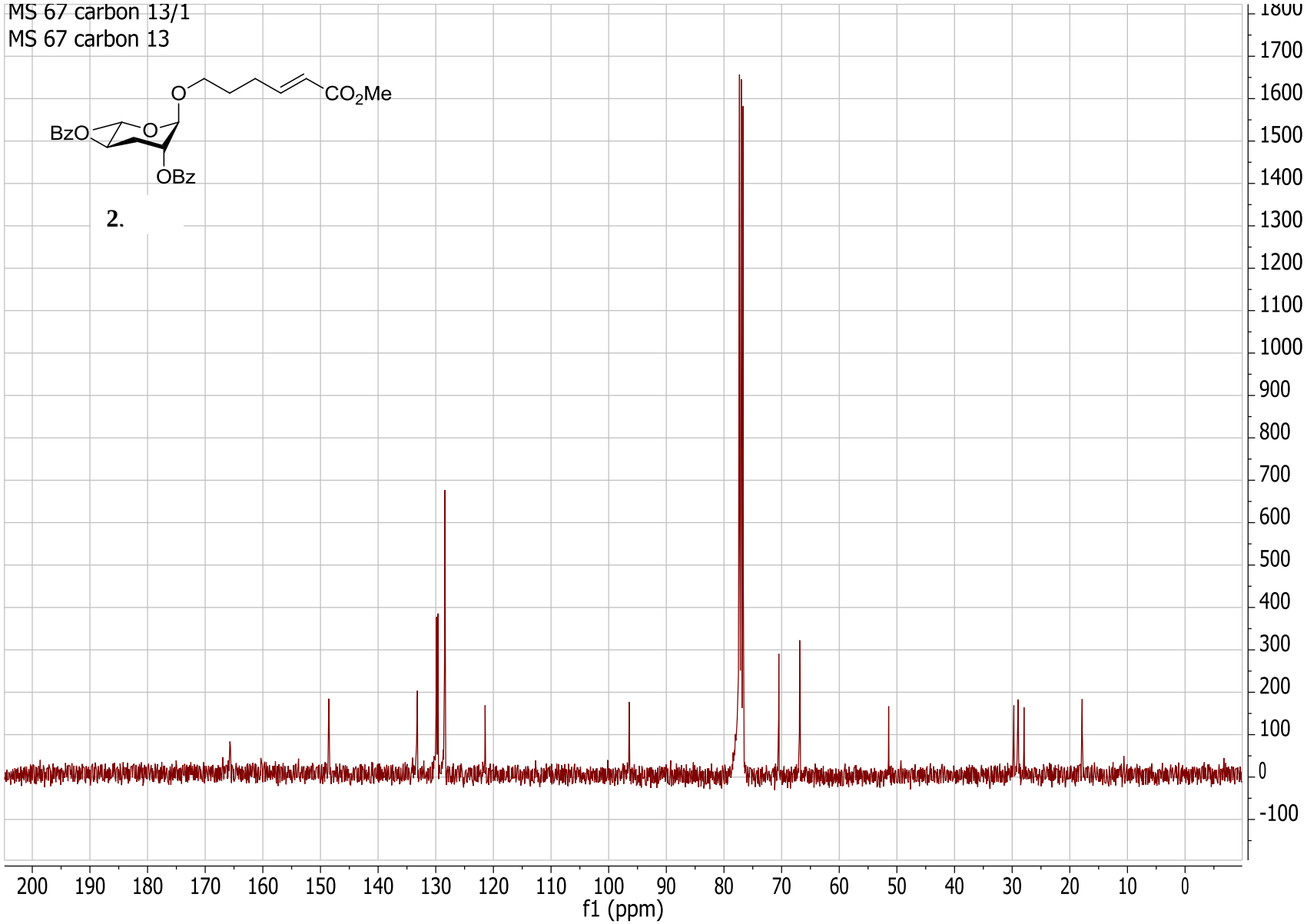

MS 65 (I) hydrogen/1
MS 65 (I) hydrogen
O
BzO
O
OBz
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

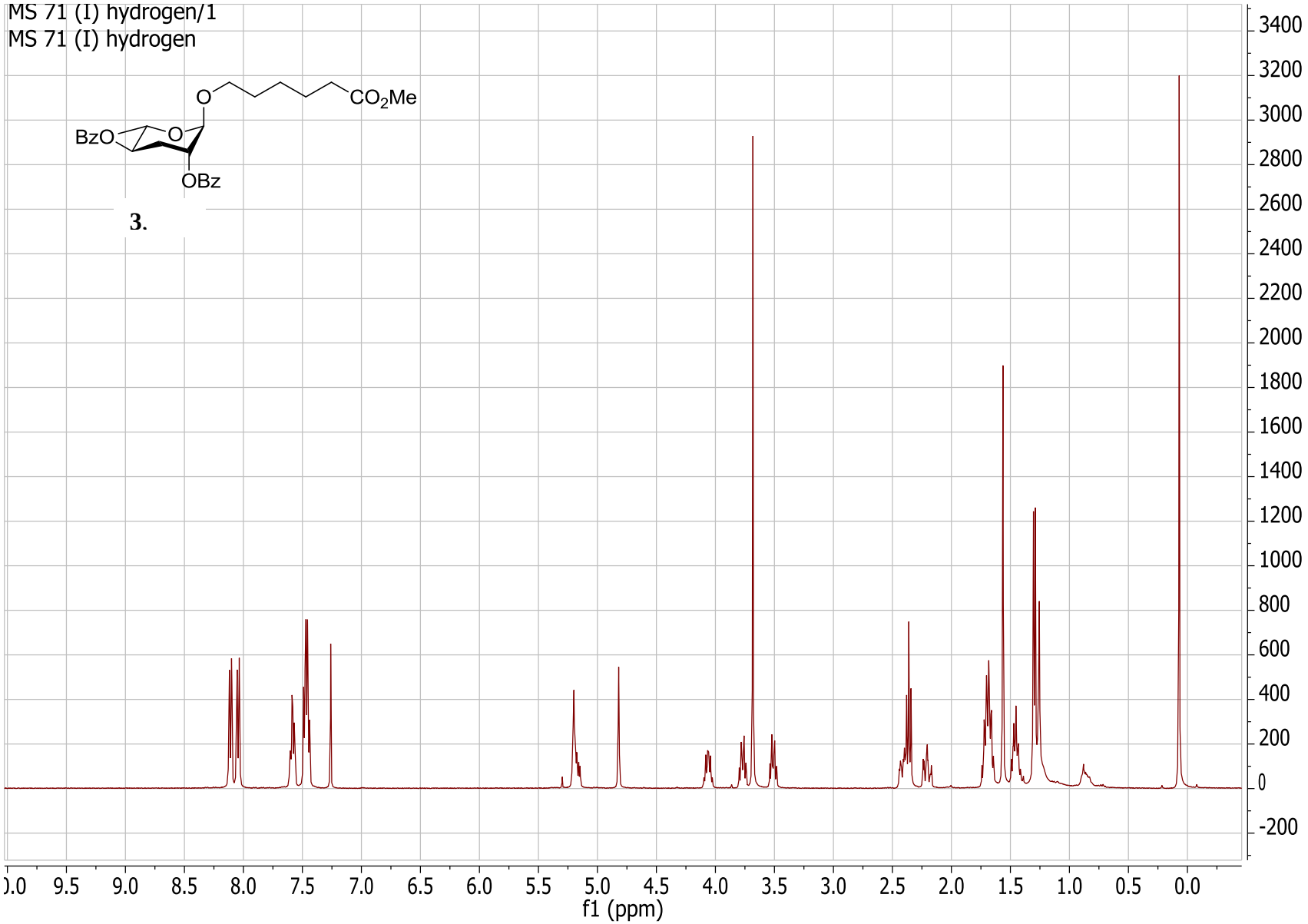
1.

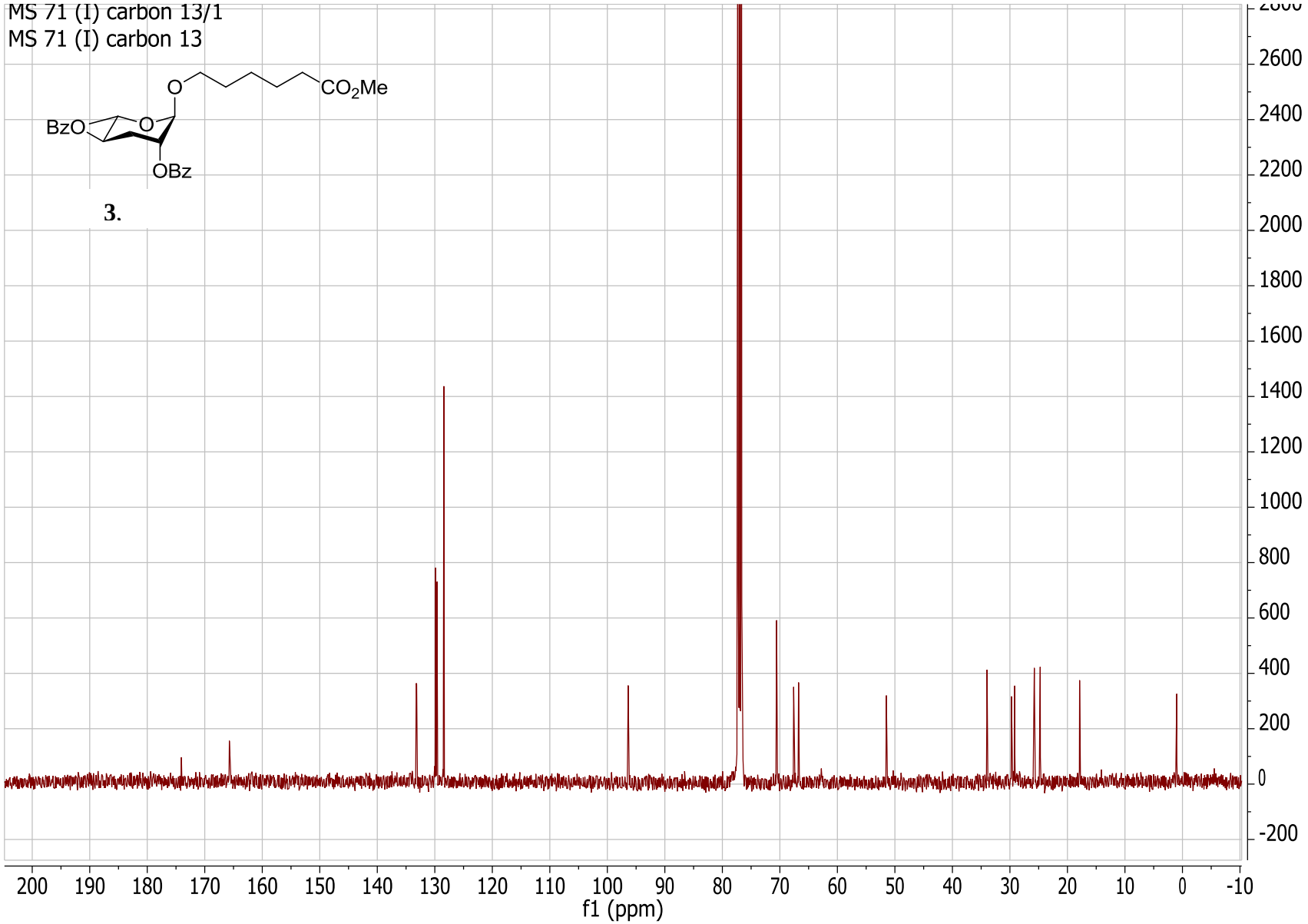

MS 65 (I) 13 carbon/1
MS 65 (I) 13 carbon
O
BzO
O
OBz
4500
4000
3500
3000
2500
2000
1500
1000
500
0
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

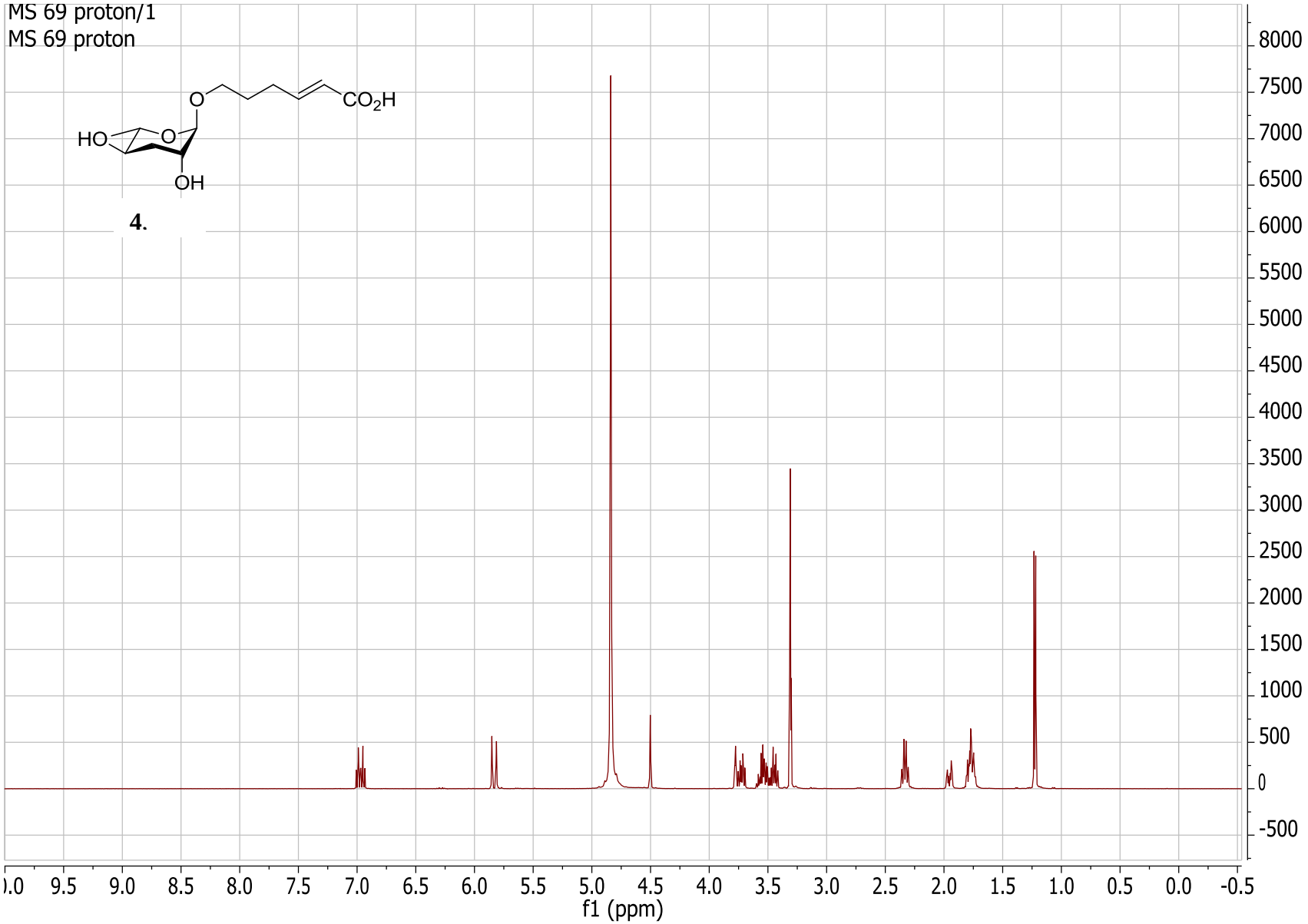
1.

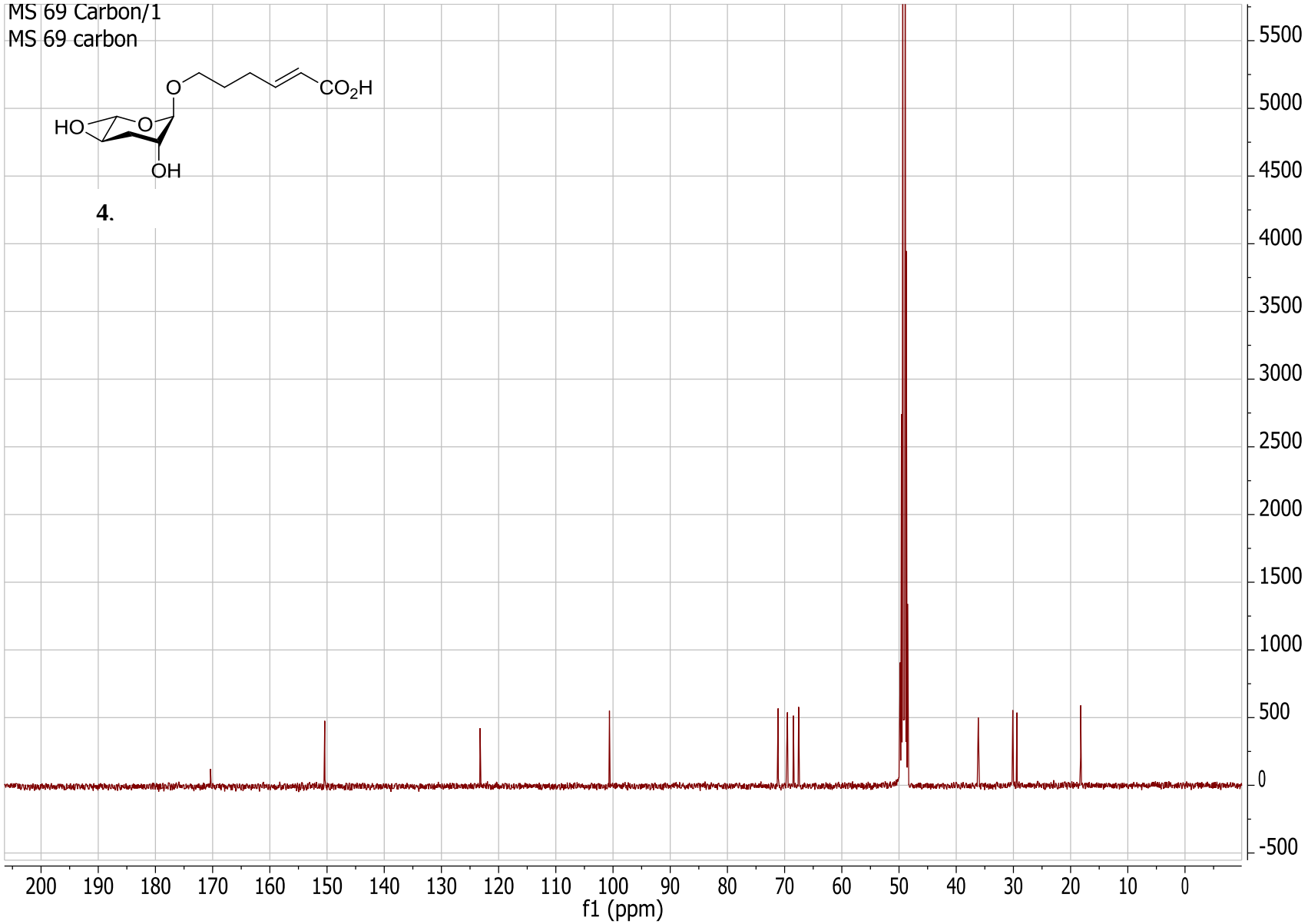

MS 67 (I) hydrogen/1
MS 67 (I) hydrogen
O
CO2Me
BzO
O
OBz
2.
450
400
350
300
250
200
150
100
50
0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

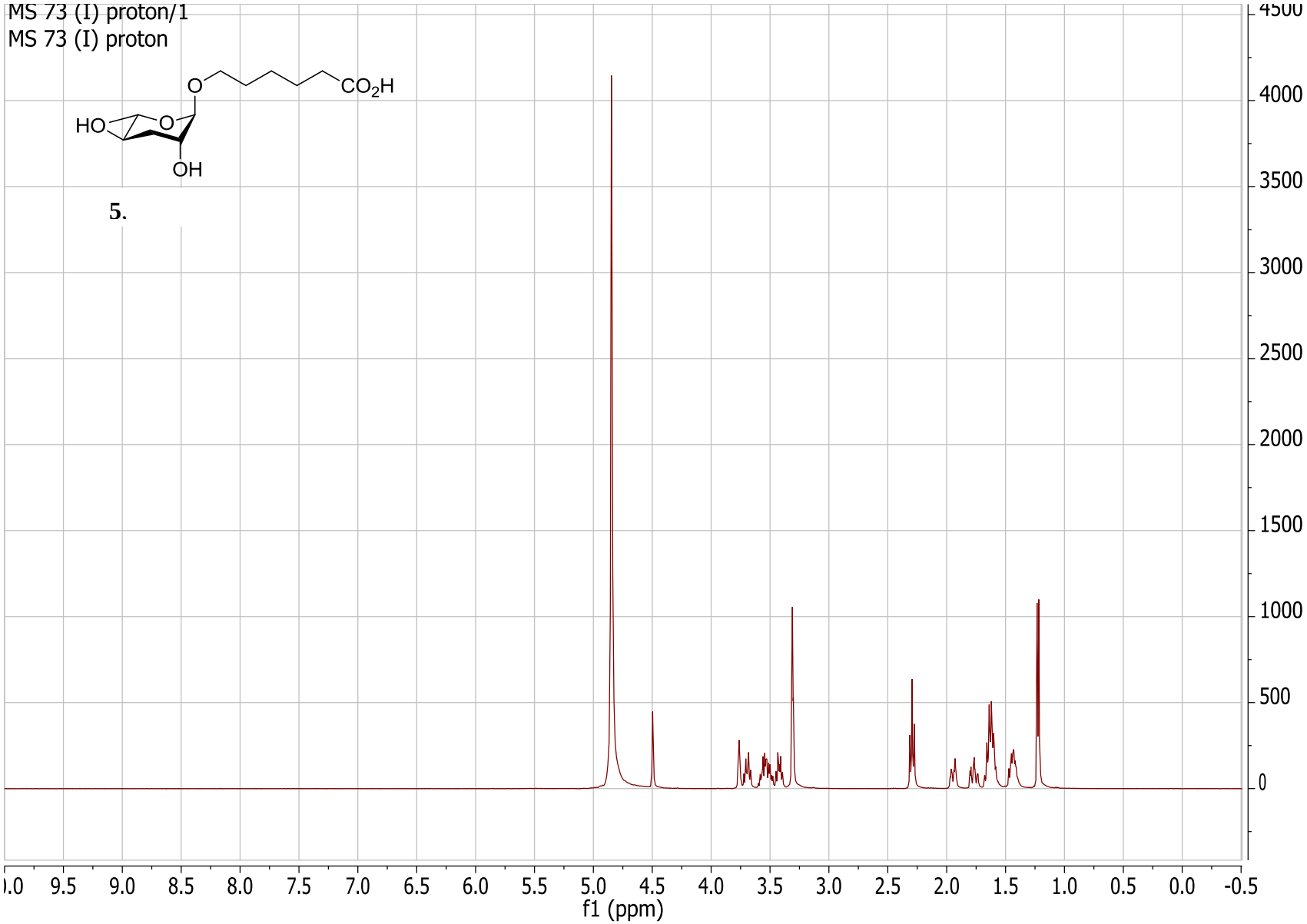

MS 67 carbon 13/1
MS 67 carbon 13
O
CO2Me
BzO
O
OBz
2.
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

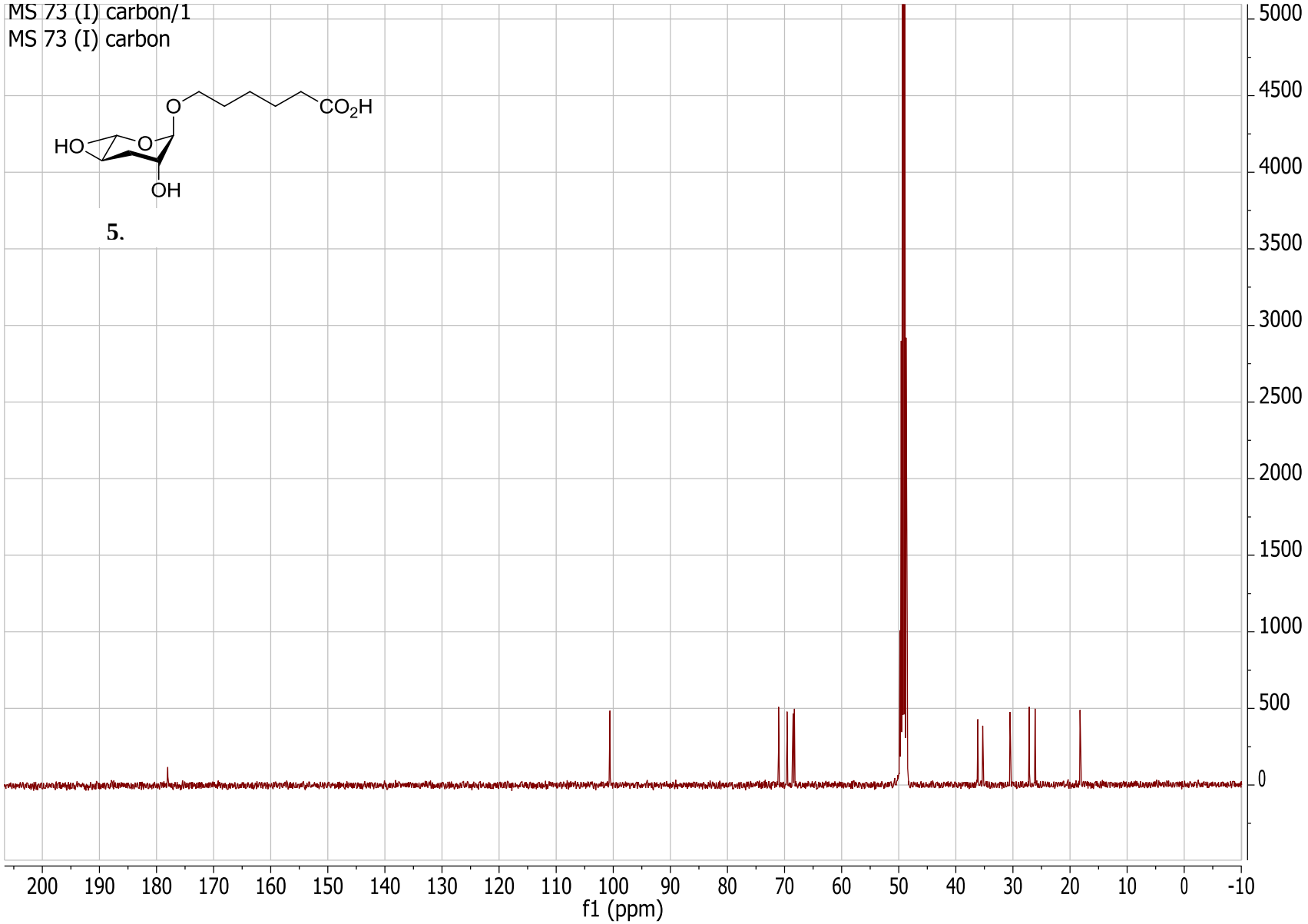

MS 71 (I) hydrogen/1
MS 71 (I) hydrogen
O
CO2Me
BzO
O
OBz
3.
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

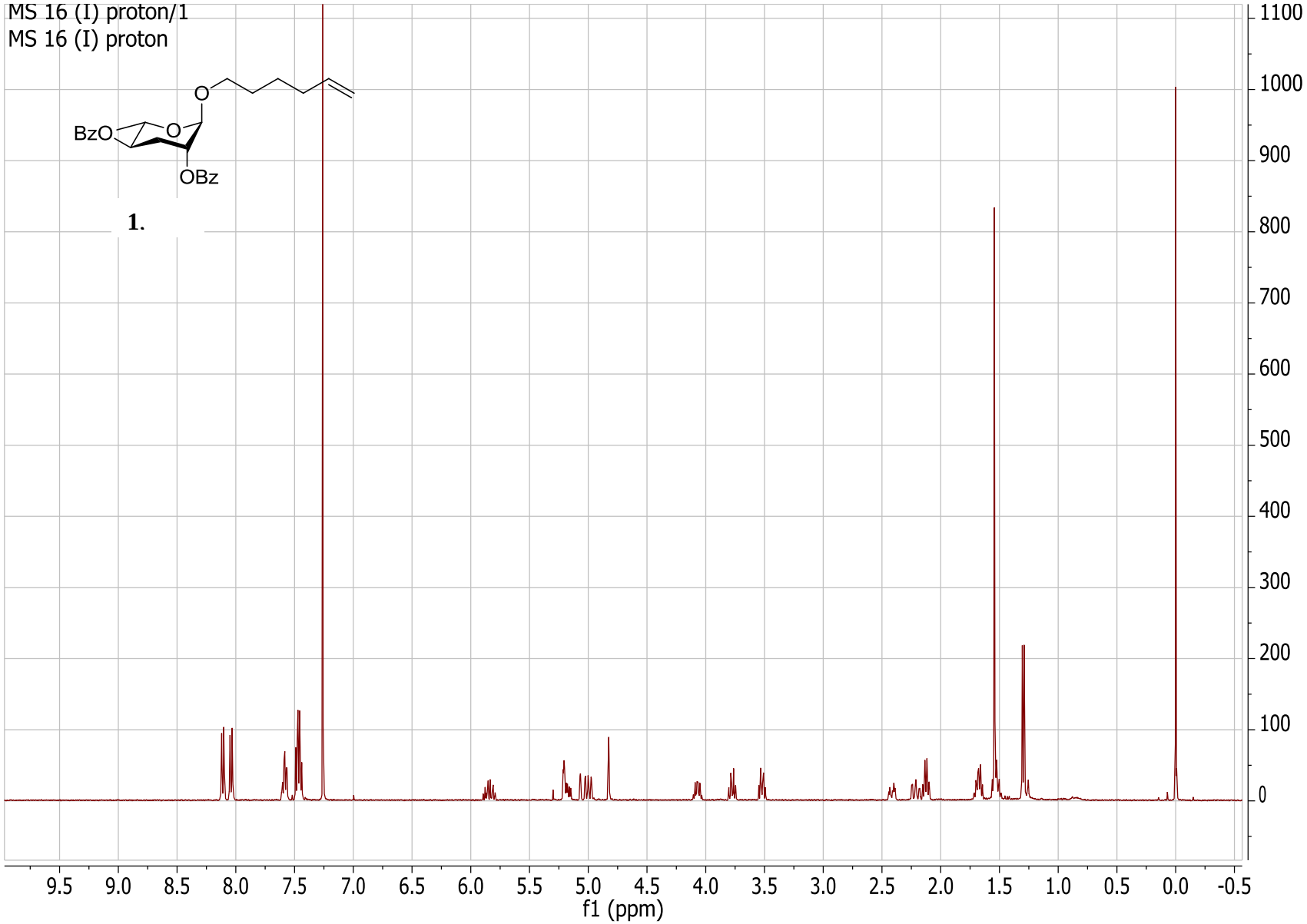

MS 71 (I) carbon 13/1
MS 71 (I) carbon 13
O
CO2Me
BzO
O
OBz
3.
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

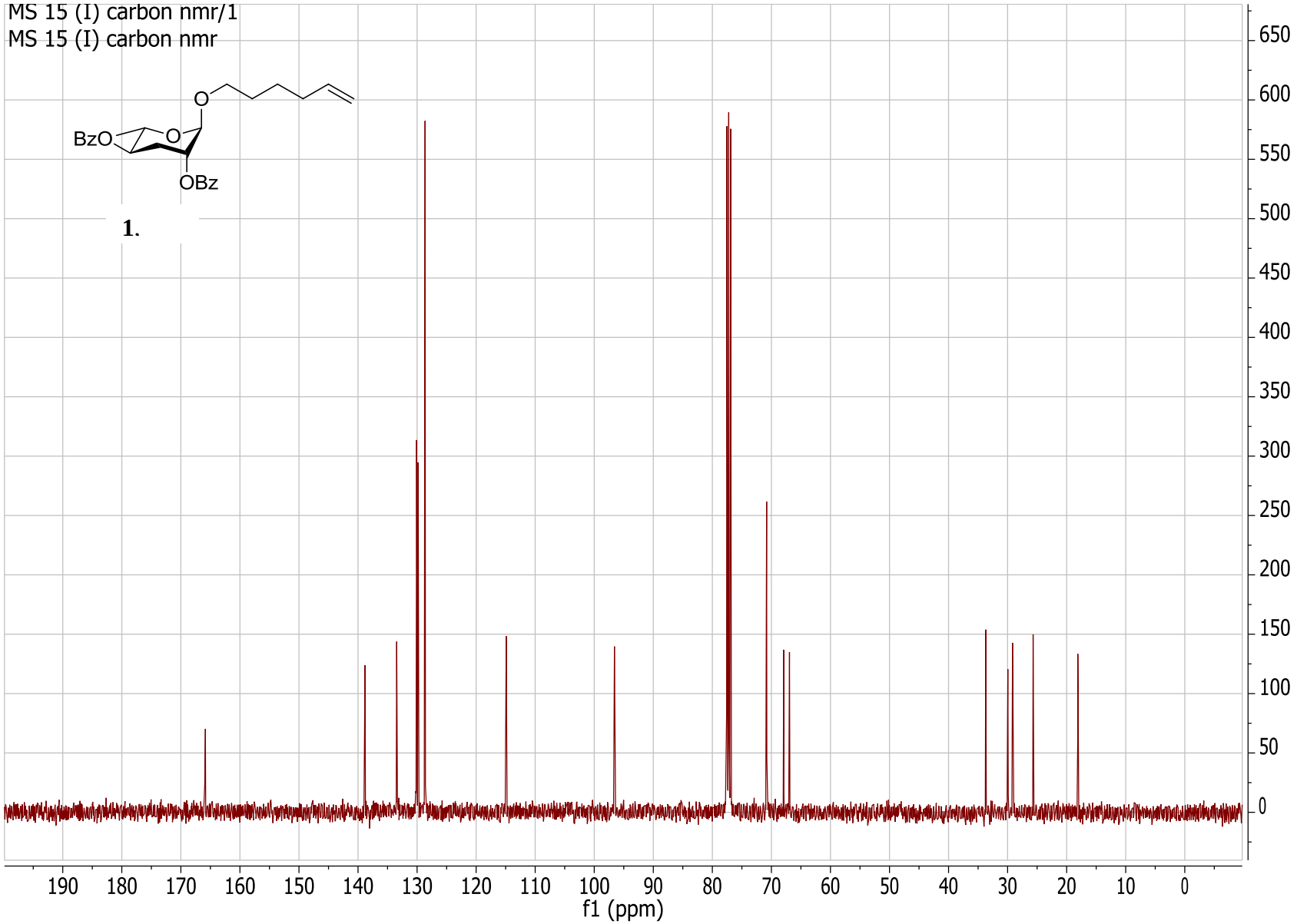

MS 69 proton/1
MS 69 proton
O
CO2H
HO
O
OH
4.
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


MS 69 Carbon/1
MS 69 carbon
O
CO2H
HO
O
OH
4.
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

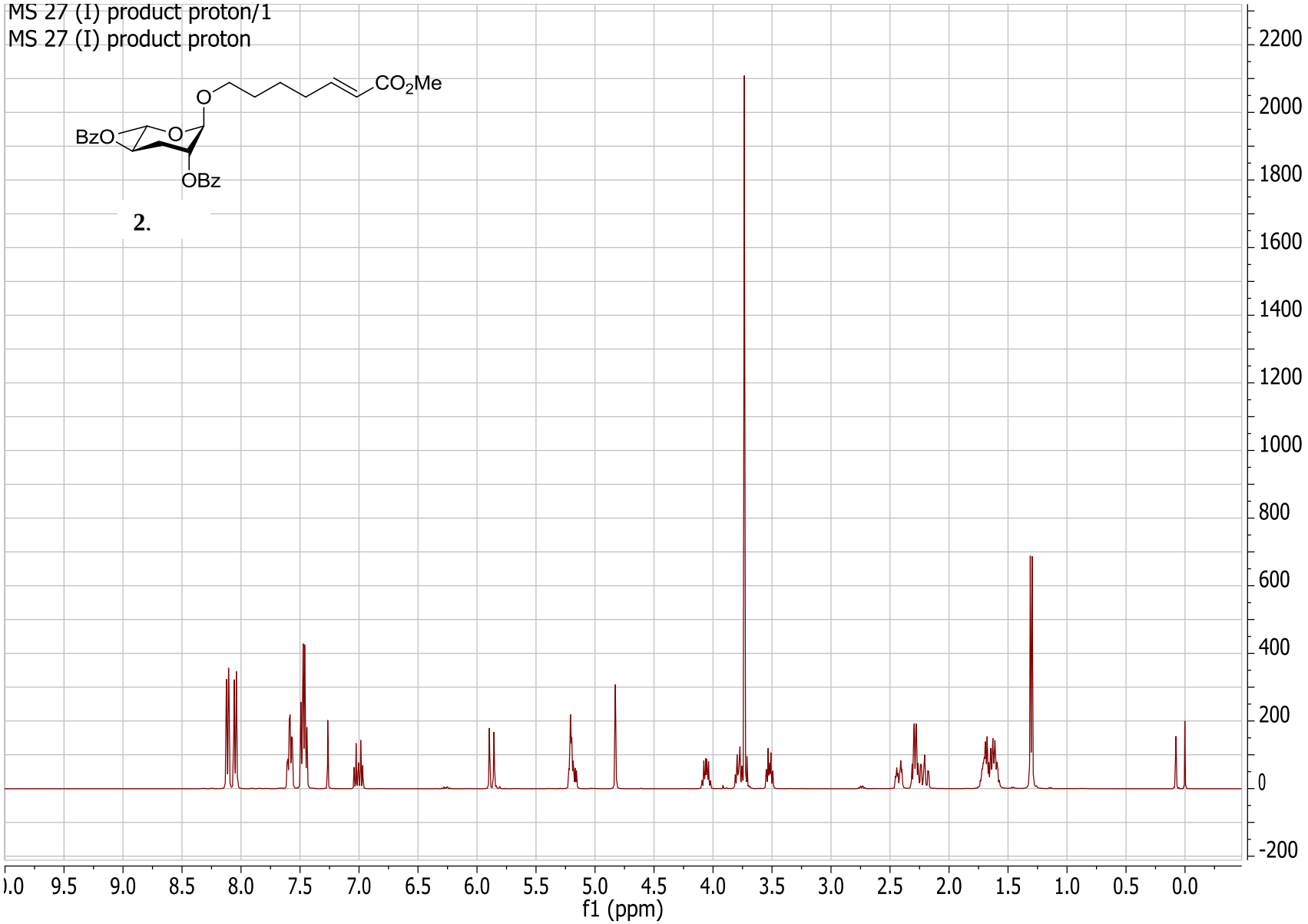

MS 73 (I) proton/1
MS 73 (I) proton
O
CO2H
HO
O
OH
5.
4500
4000
3500
3000
2500
2000
1500
1000
500
0
1.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

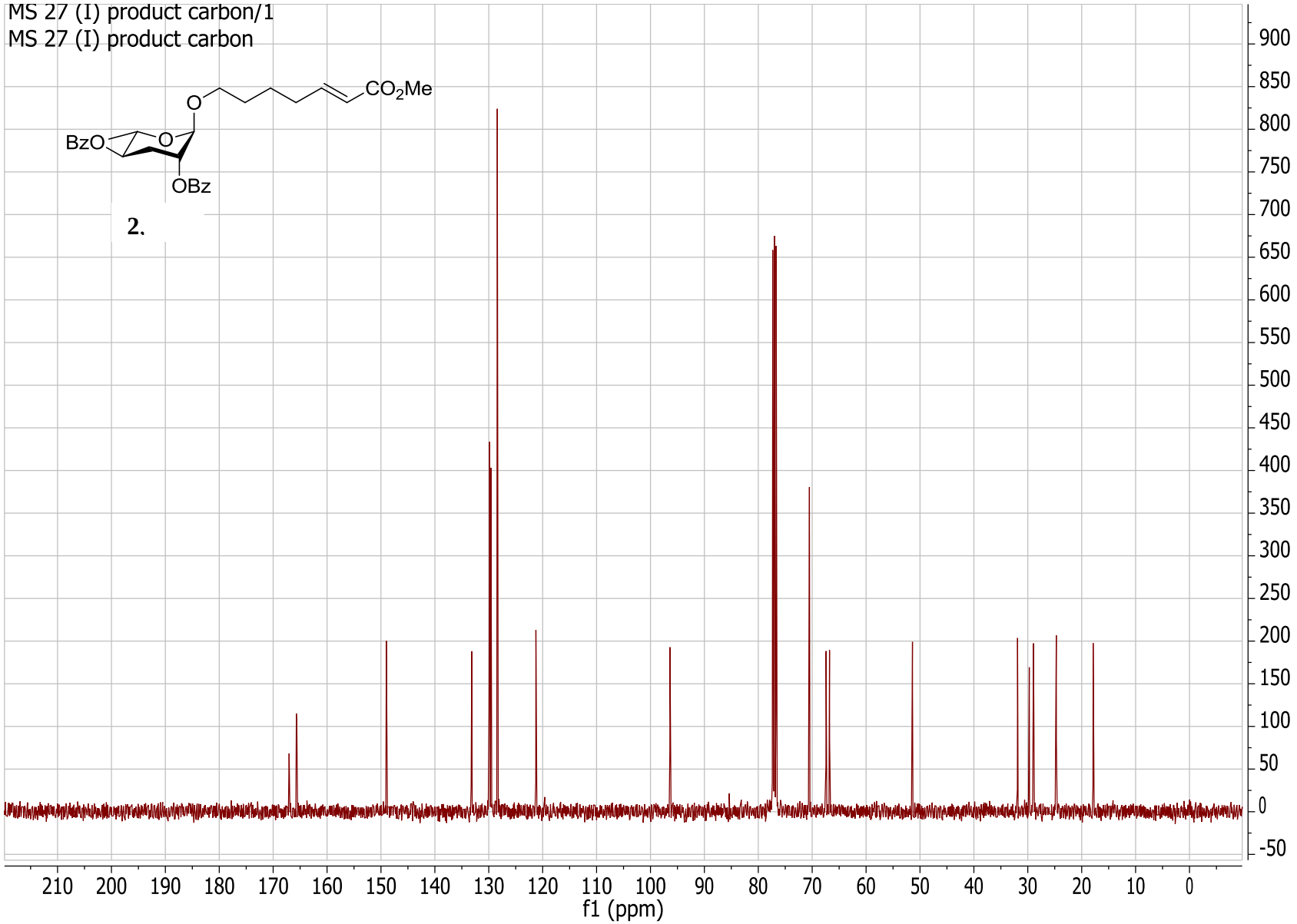

MS 73 (I) carbon/1
MS 73 (I) carbon
O
CO2H
HO
O
OH
5.
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

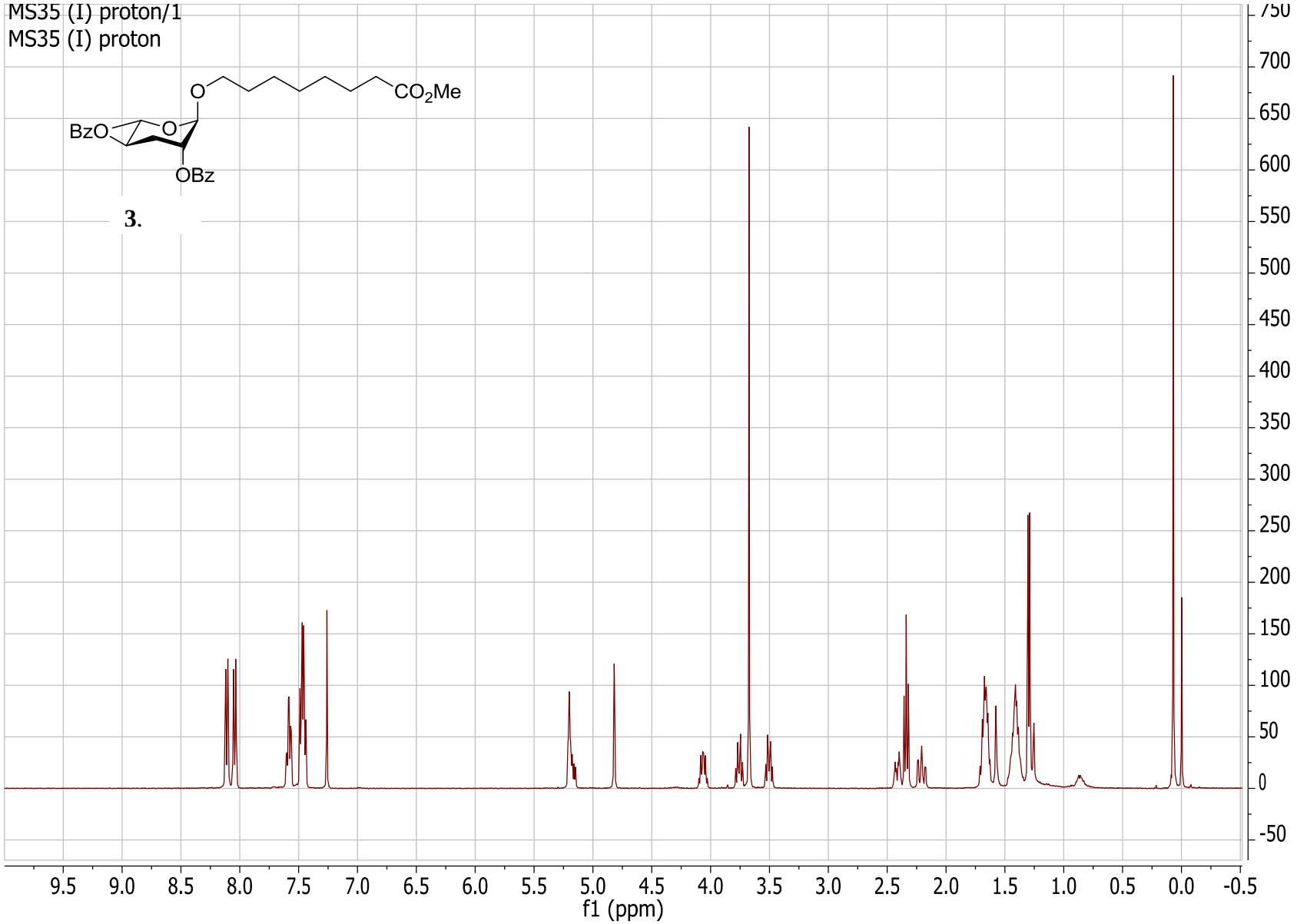

MS 16 (I) proton/1
MS 16 (I) proton
BzO
O
O
OBz
1.
1100
1000
900
800
700
600
500
400
300
200
100
0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

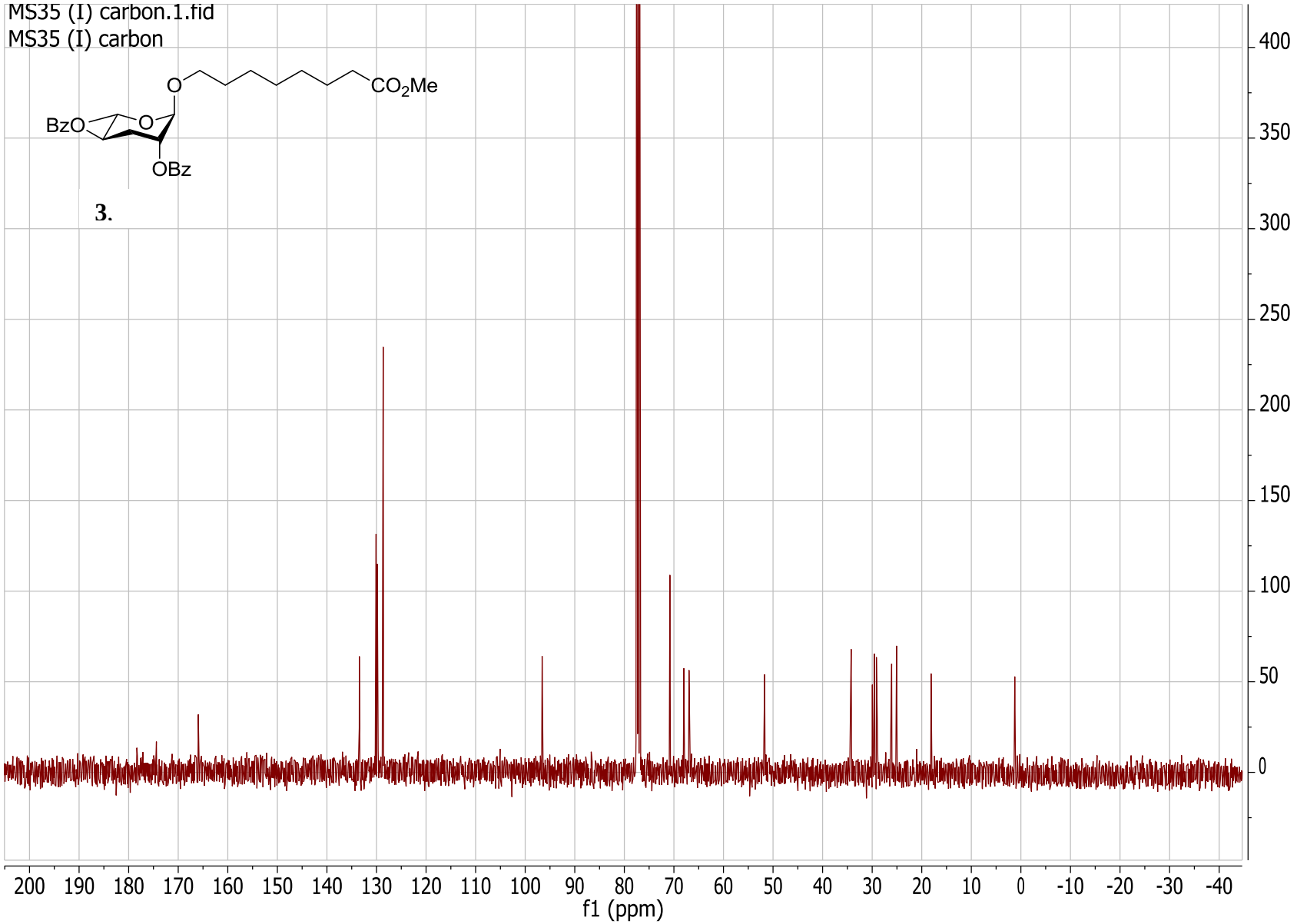

MS 15 (I) carbon nmr/1
MS 15 (I) carbon nmr
O
BzO
O
OBz
650
600
550
500
450
400
350
300
250
200
150
100
50
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

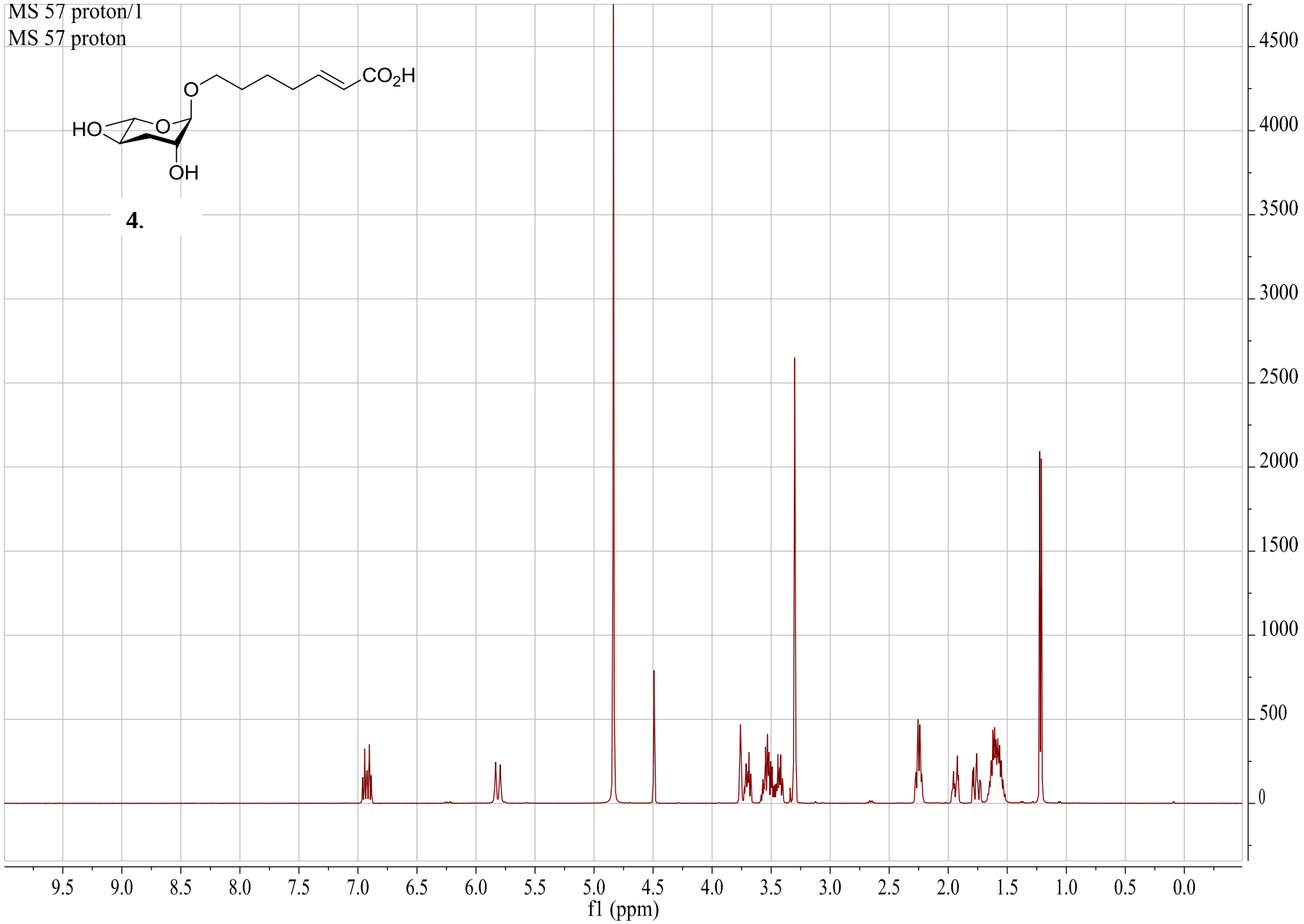
1.

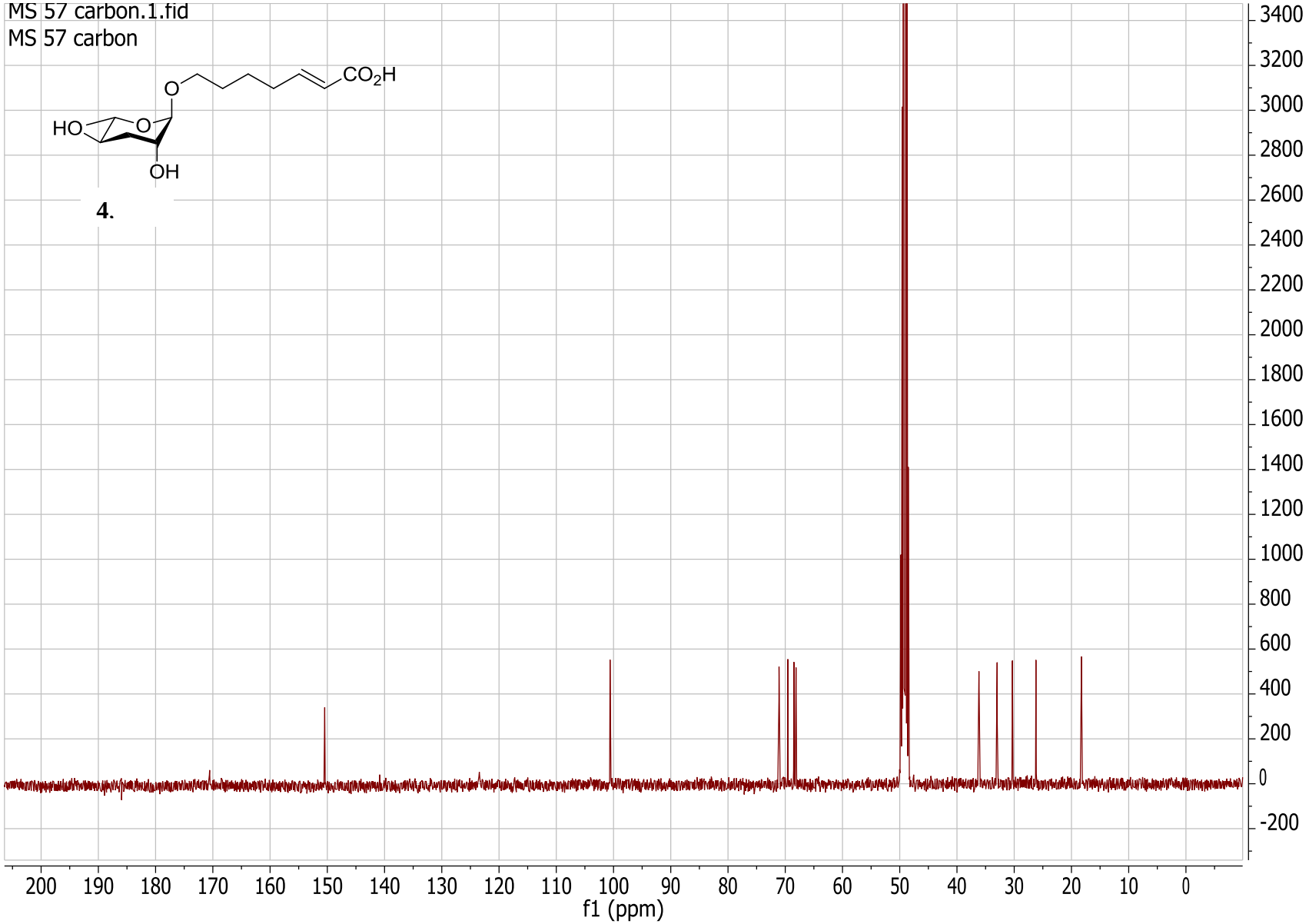

MS 27 (I) product proton/1
MS 27 (I) product proton
CO2Me
O
BzO
O
OBz
2.
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

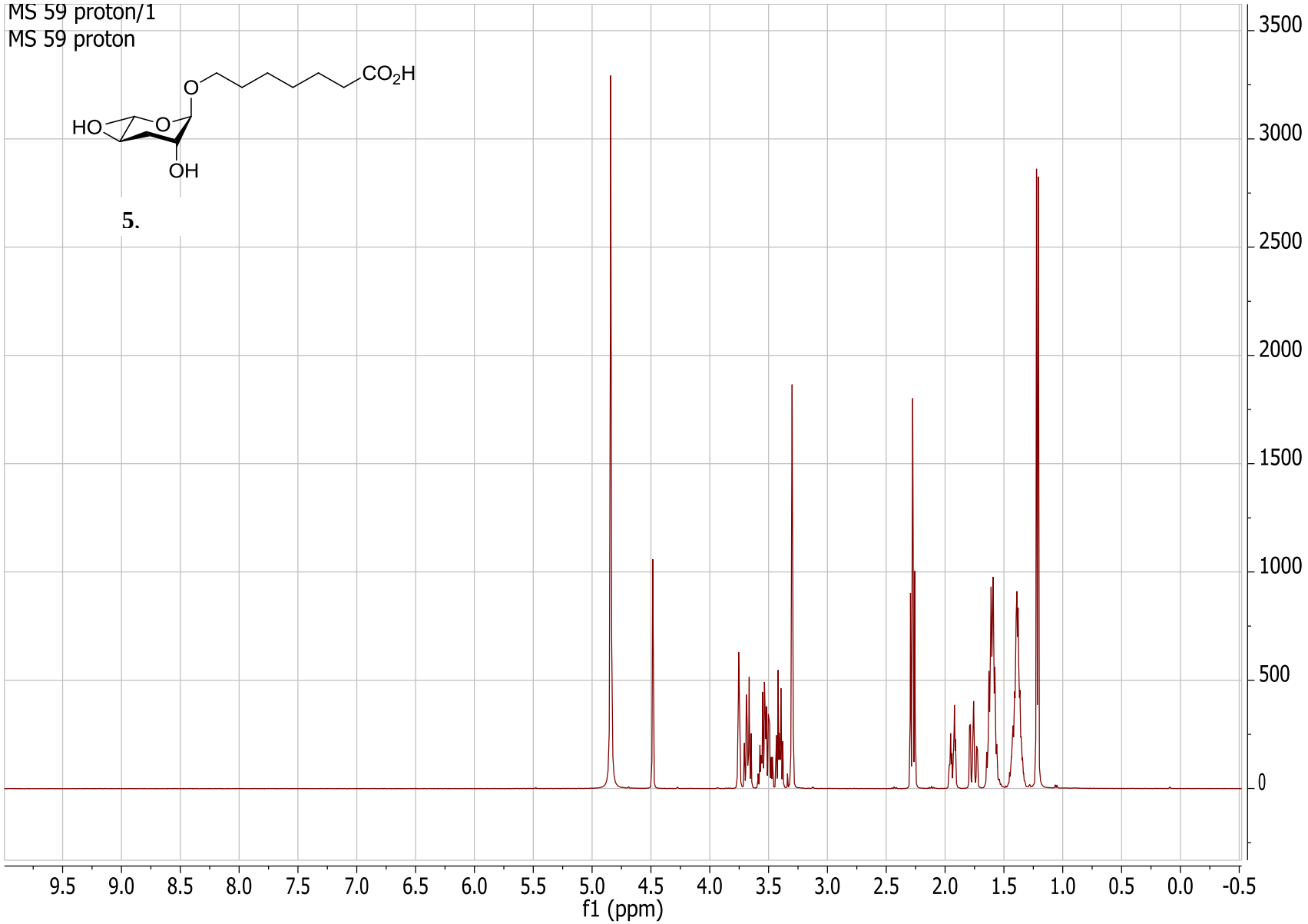

MS 27 (I) product carbon/1
MS 27 (I) product carbon
CO2Me
O
BzO
O
OBz
2.
900
850
800
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

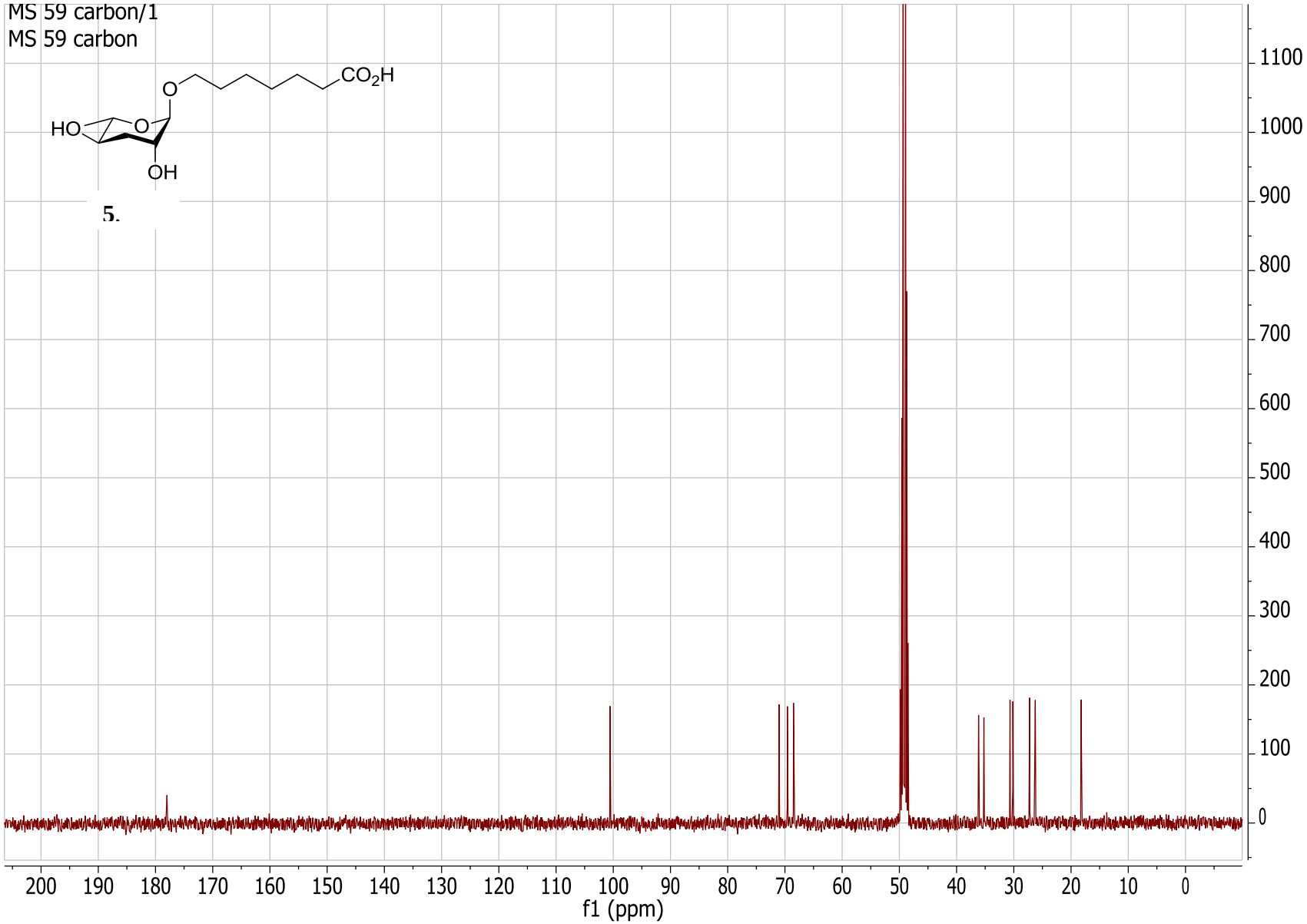

MS35 (I) proton/1
MS35 (I) proton
O
CO2Me
BzO
O
OBz
3.
f1 (ppm)

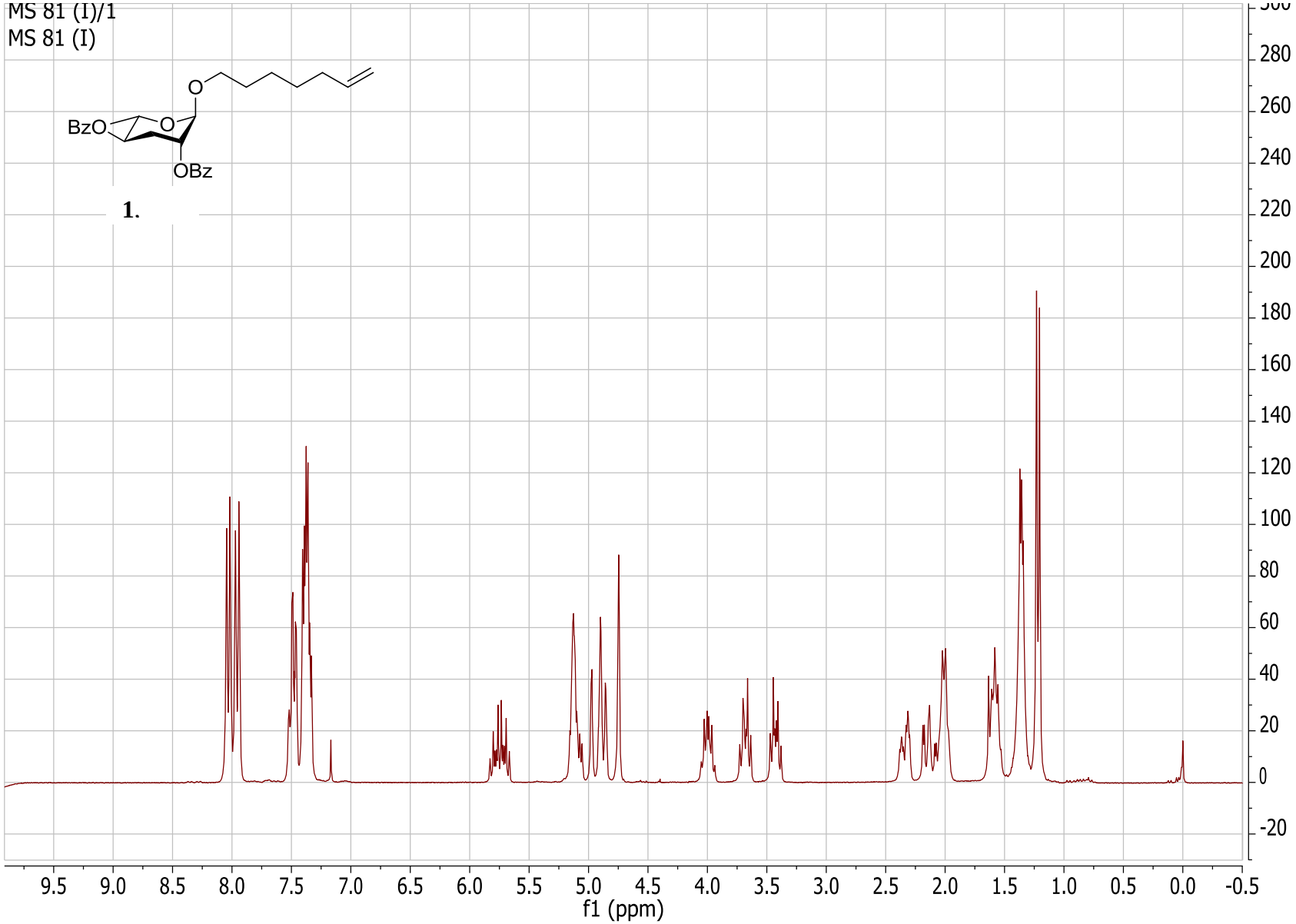

MS35 (I) carbon.1.fid
MS35 (I) carbon
O
CO2Me
BzO
O
OBz
3.
400
350
300
250
200
150
100
50
0
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40
f1 (ppm)

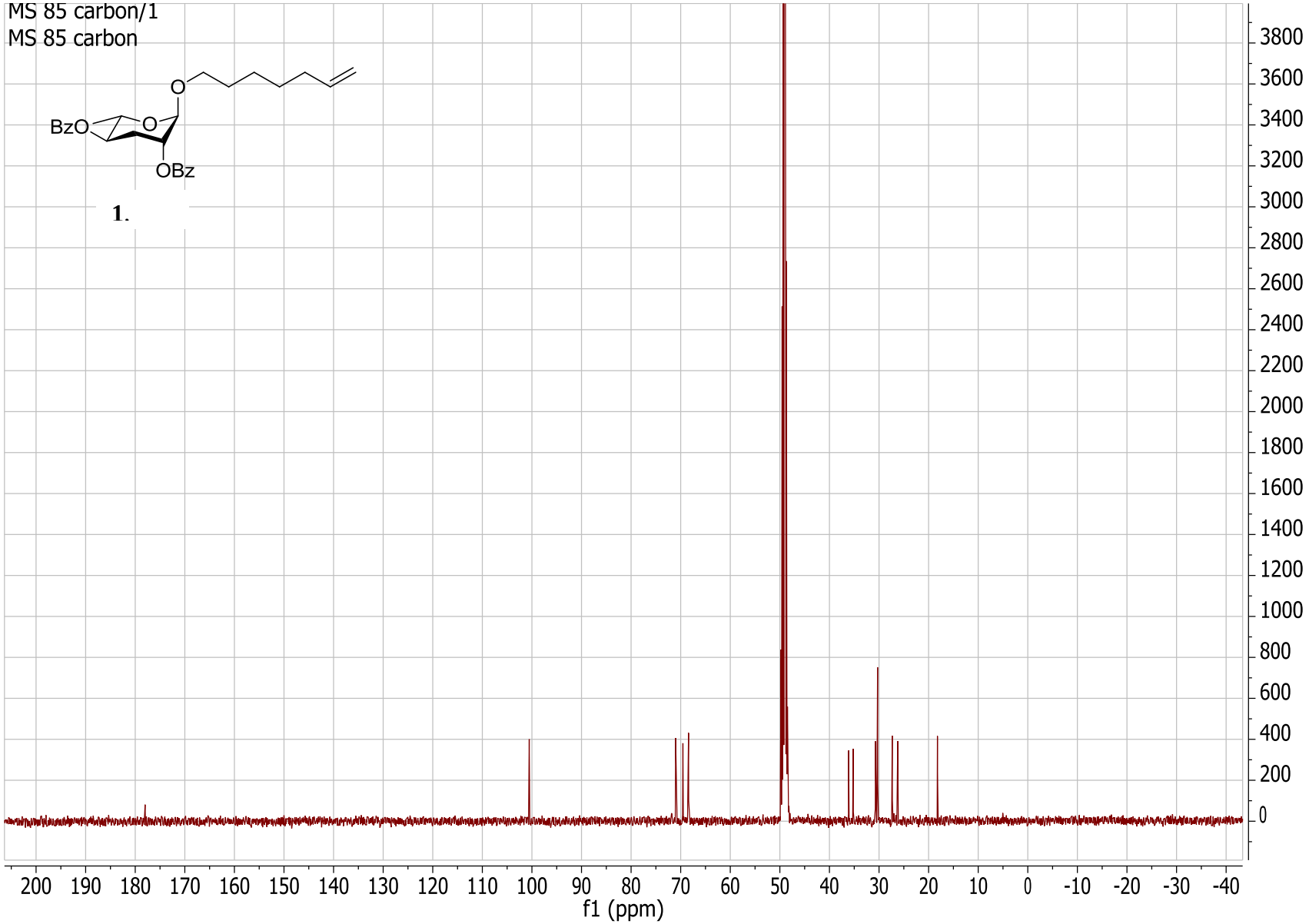

MS 57 proton/1
MS 57 proton
HO
O
O
OH
CO2H
4.
4500
4000
3500
3000
2500
2000
1500
1000
500
0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

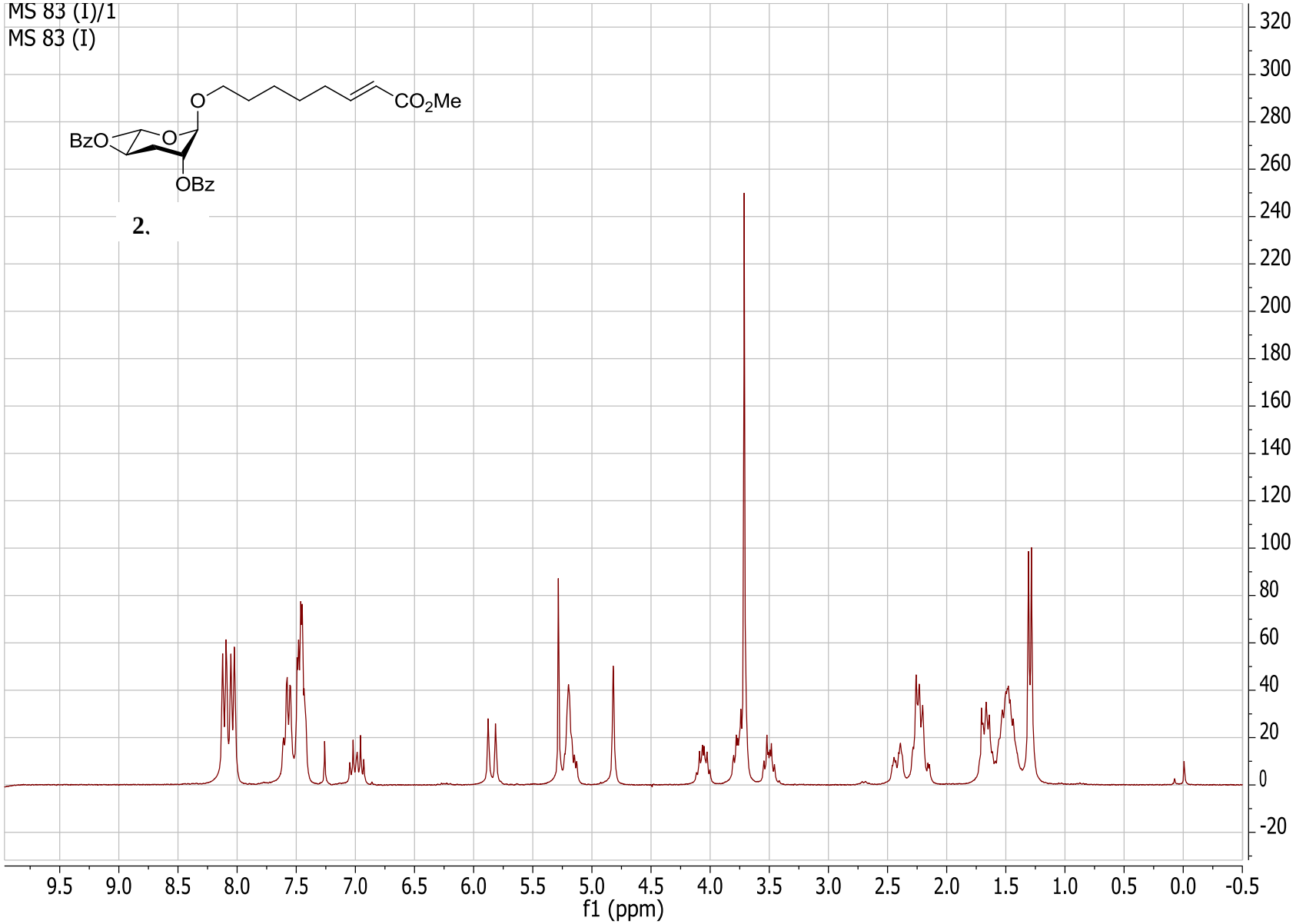

MS 57 carbon.1.fid
MS 57 carbon
CO2H
O
HO
O
OH
4.
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

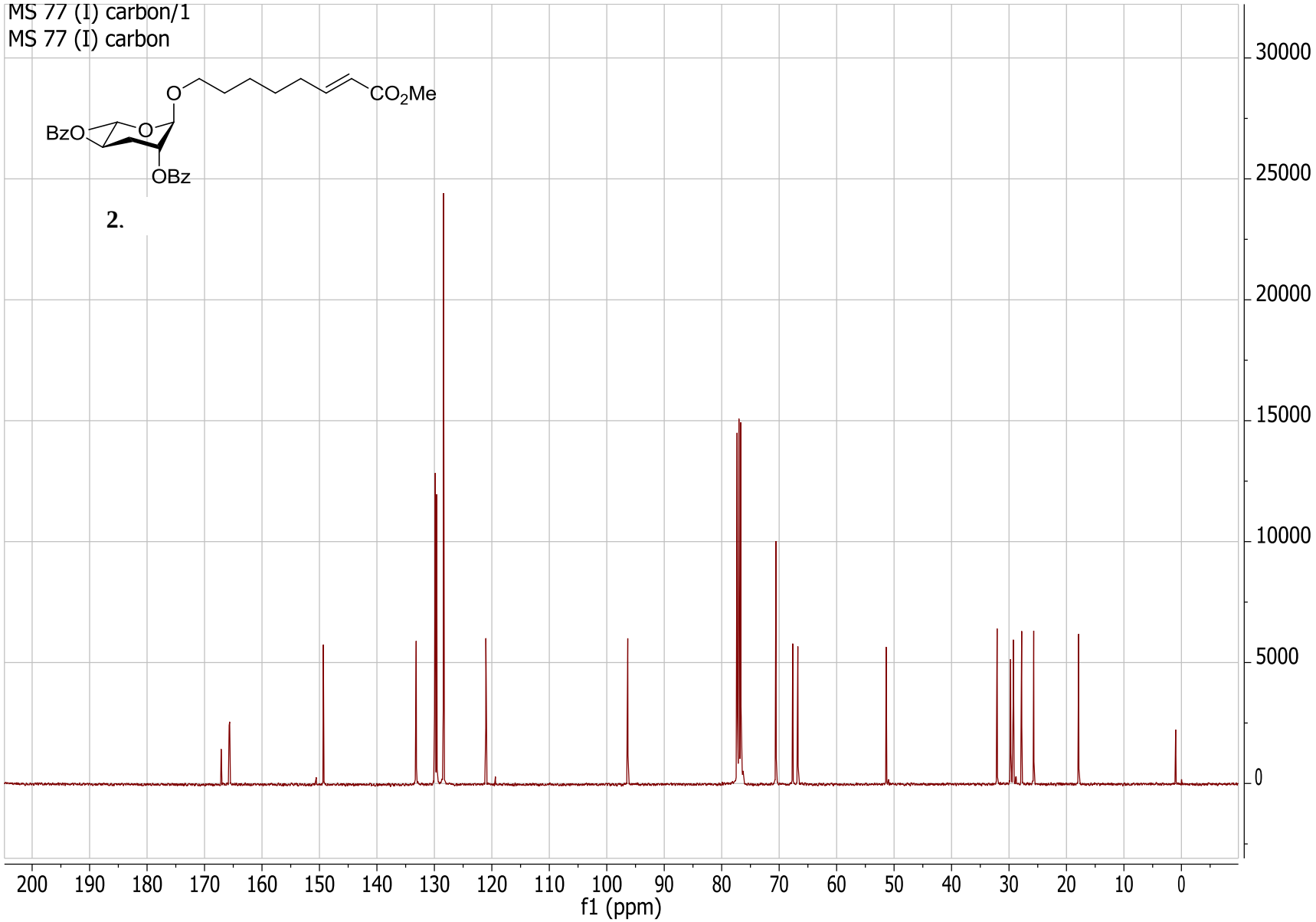

MS 59 proton/1
MS 59 proton
HO
O
O
OH
CO2H
5.
3500
3000
2500
2000
1500
1000
500
0
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

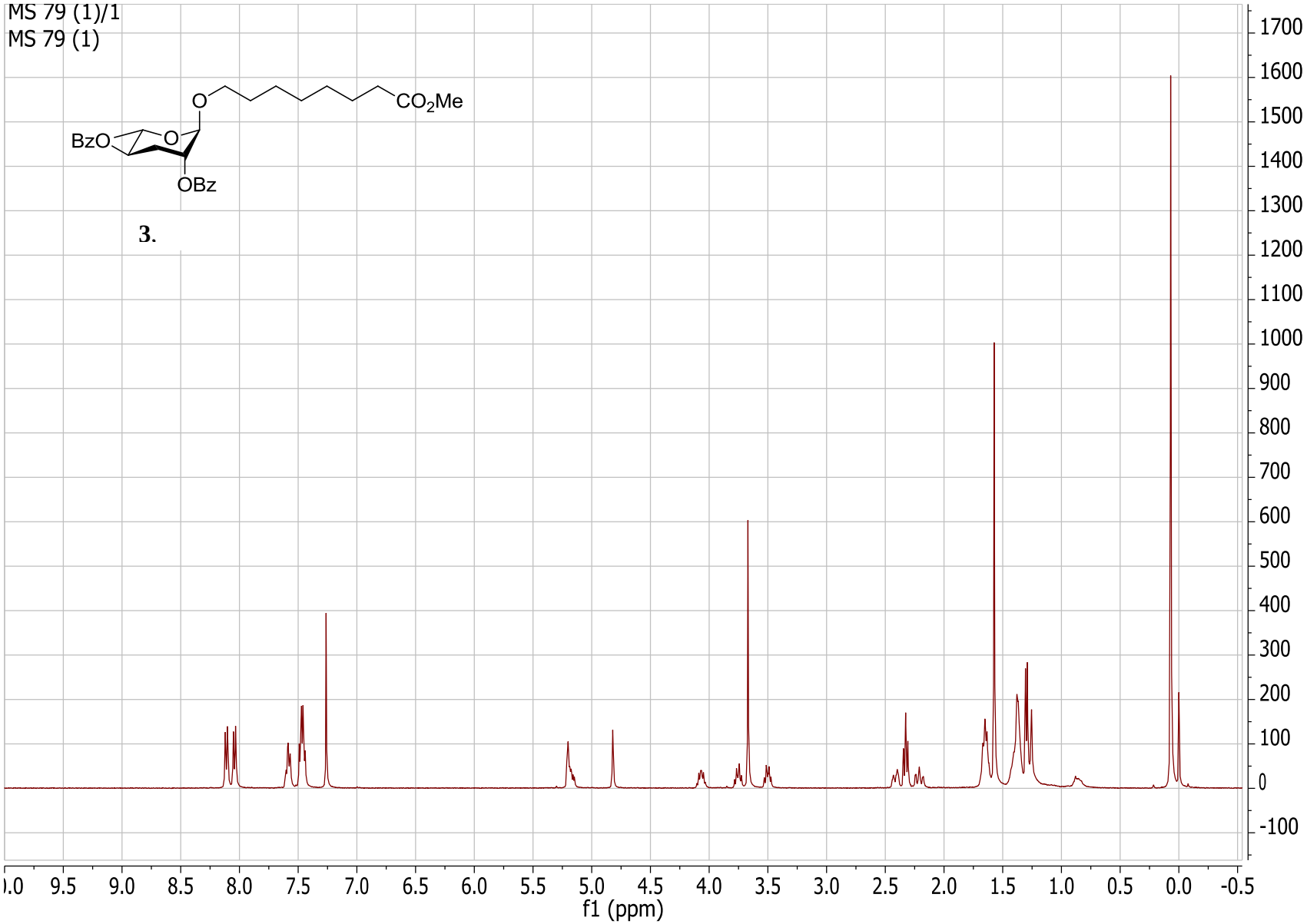

MS 59 carbon/1
MS 59 carbon
HO
O
O
OH
CO2H
5.
1100
1000
900
800
700
600
500
400
300
200
100
0
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

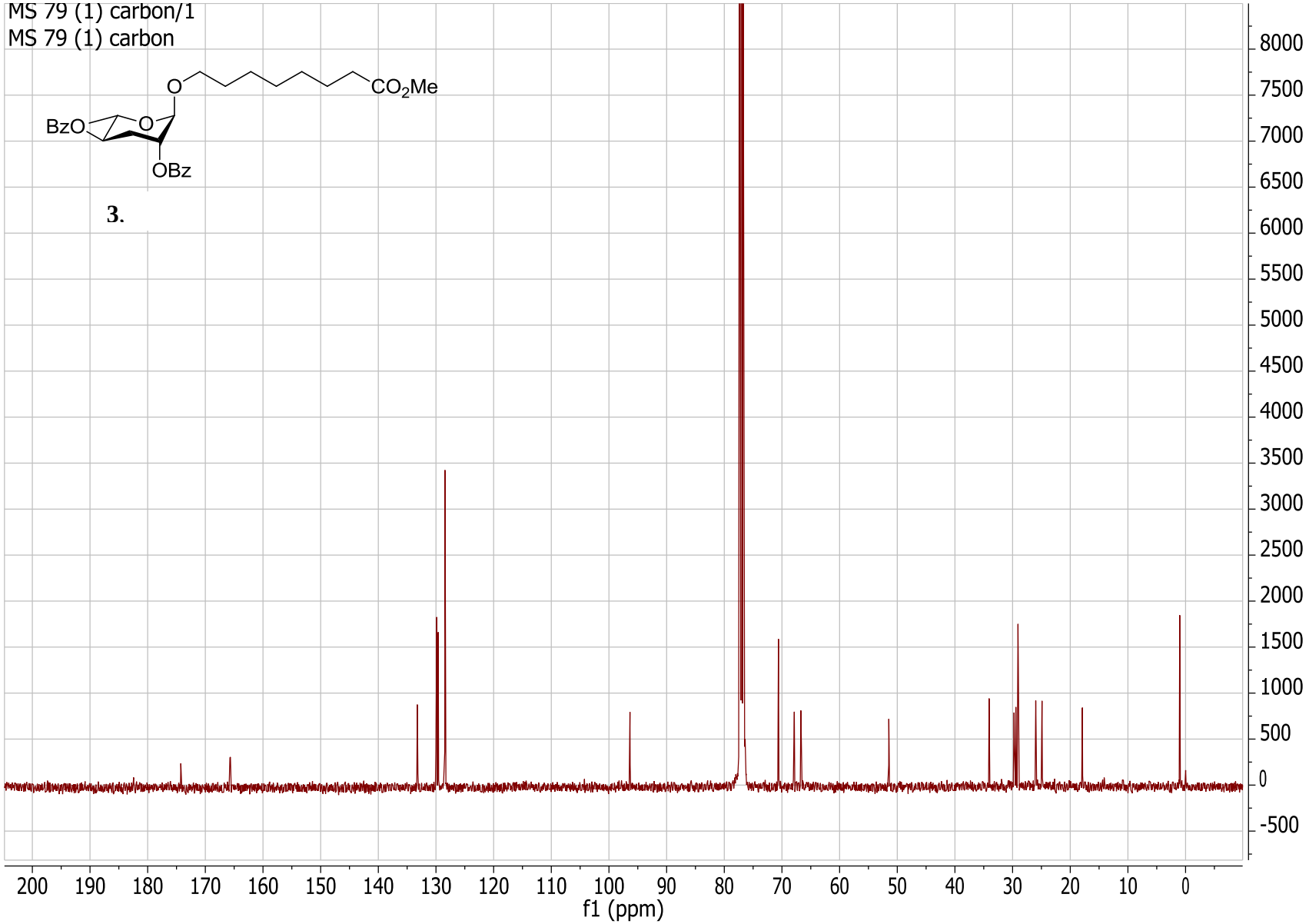

MS 81 (I)/1
MS 81 (I)
O
BzO
O
OBz
1.
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


MS 85 carbon/1
MS 85 carbon
O
BzO
O
OBz
1.
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40
f1 (ppm)

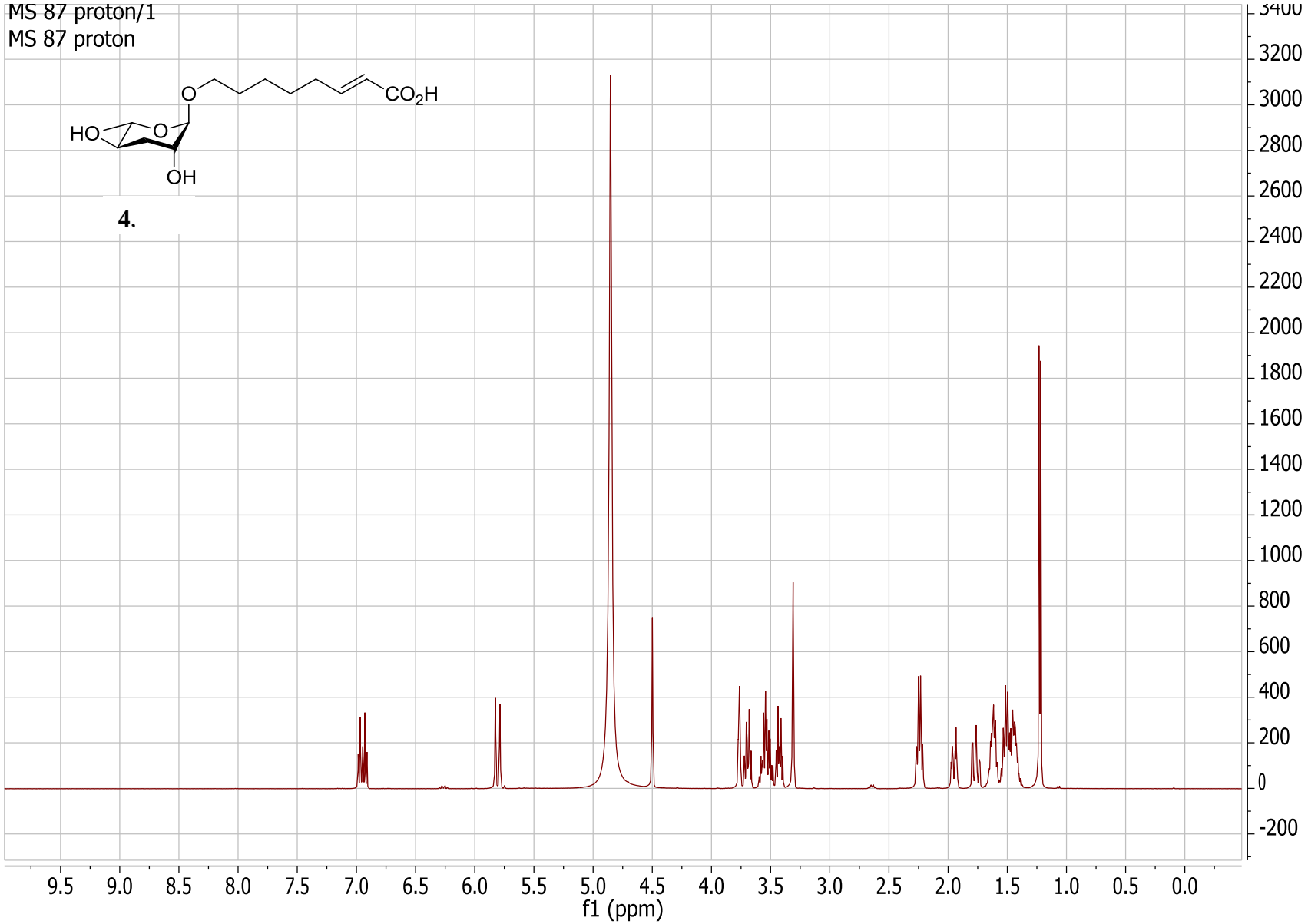

MS 83 (I)/1
MS 83 (I)
O
CO2Me
BzO
O
OBz
2.
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

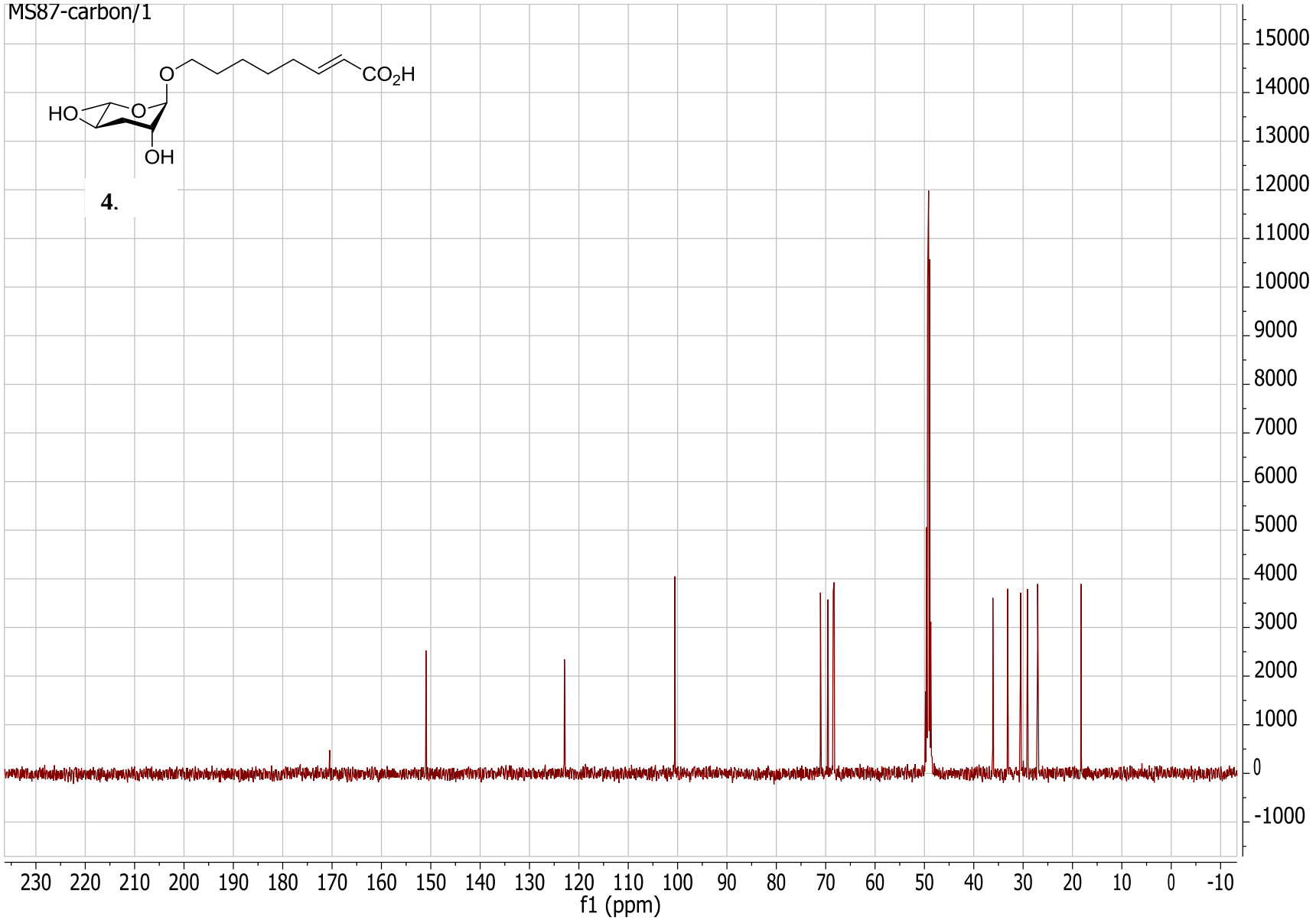

MS 77 (I) carbon/1
MS 77 (I) carbon
O
CO2Me
BzO
O
OBz
2.
30000
25000
20000
15000
10000
5000
0
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

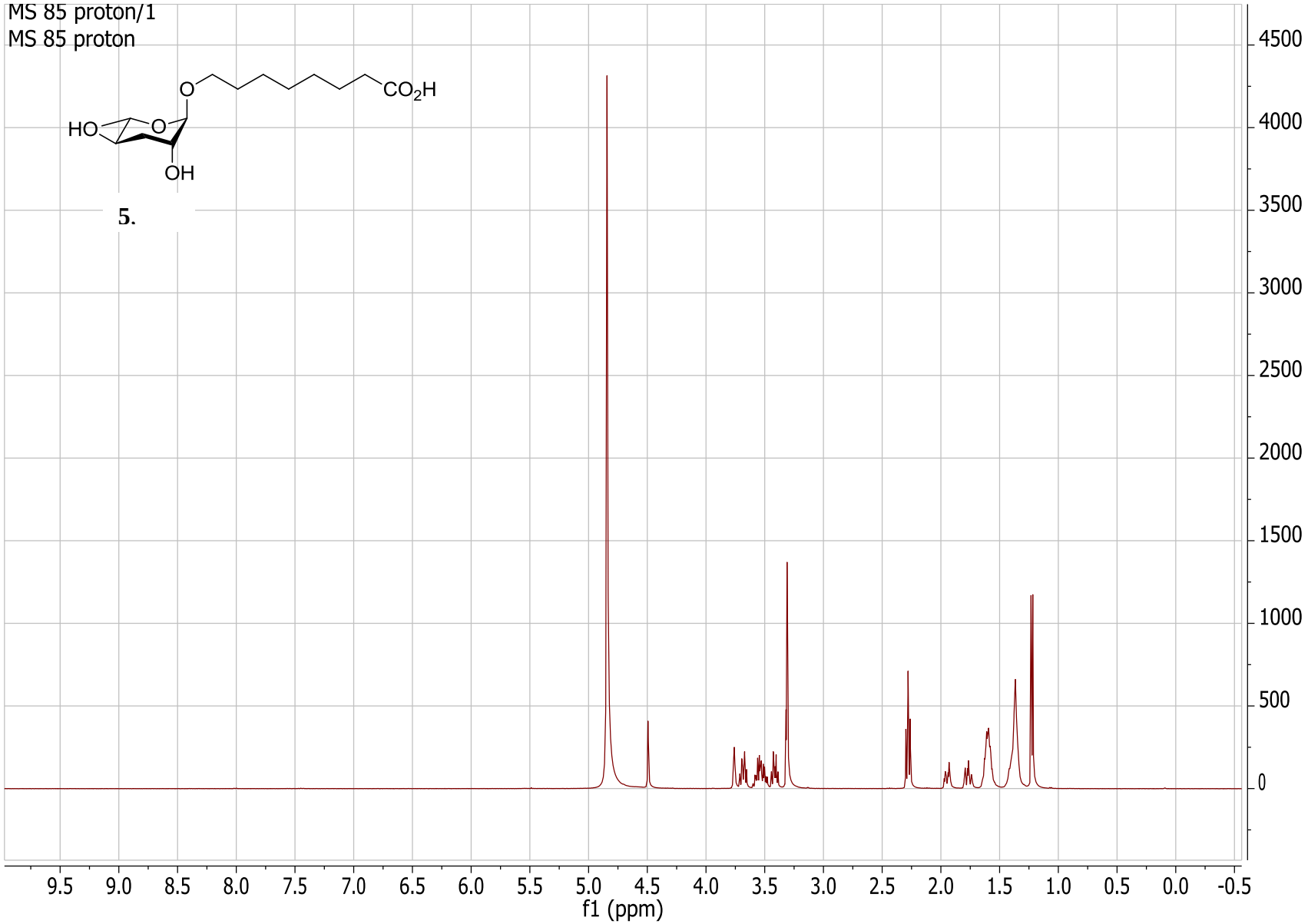

MS 79 (1)/1
MS 79 (1)
O
CO2Me
BzO
O
OBz
3.
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

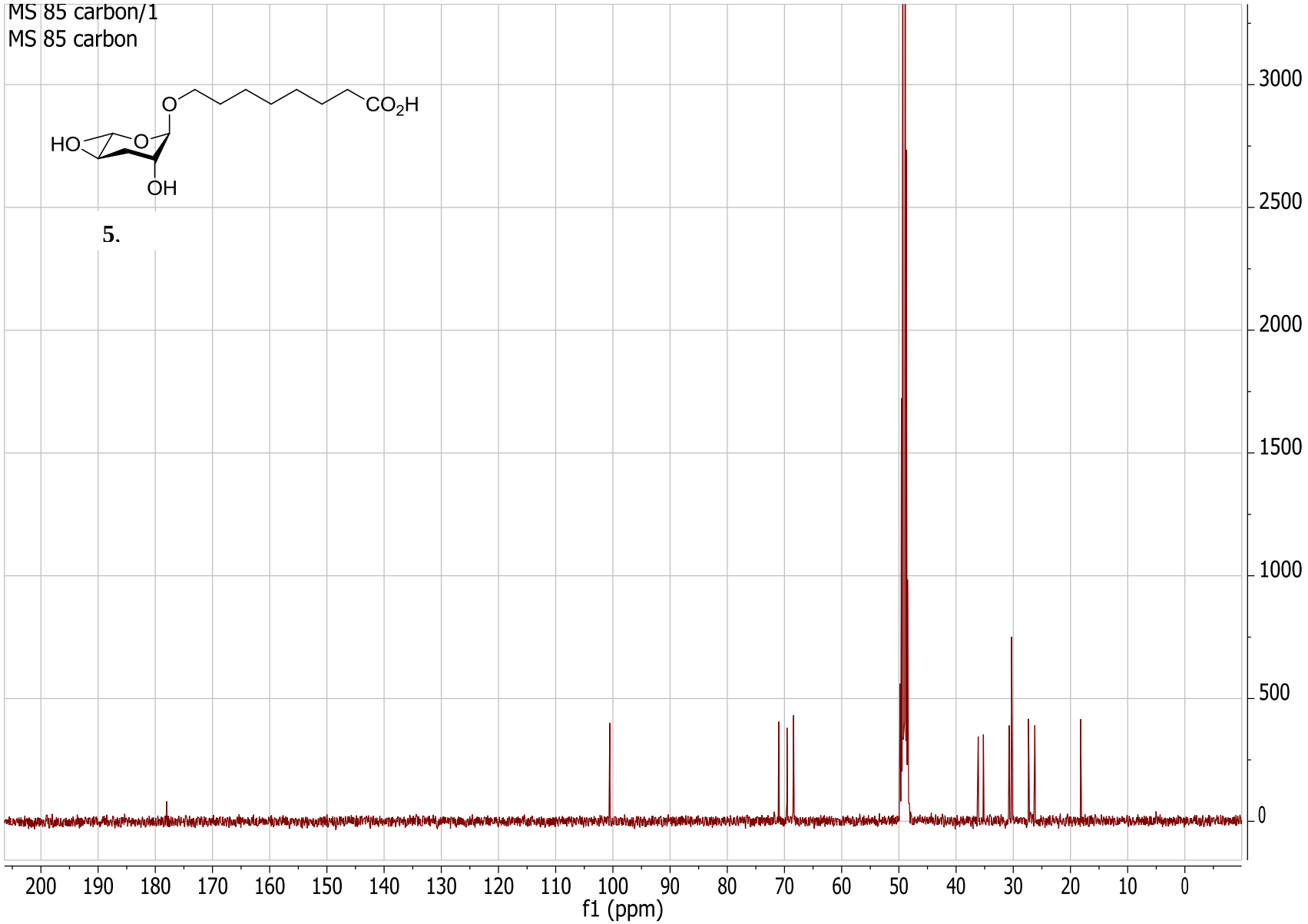

MS 79 (1) carbon/1
MS 79 (1) carbon
O
CO2Me
BzO
O
OBz
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

3.

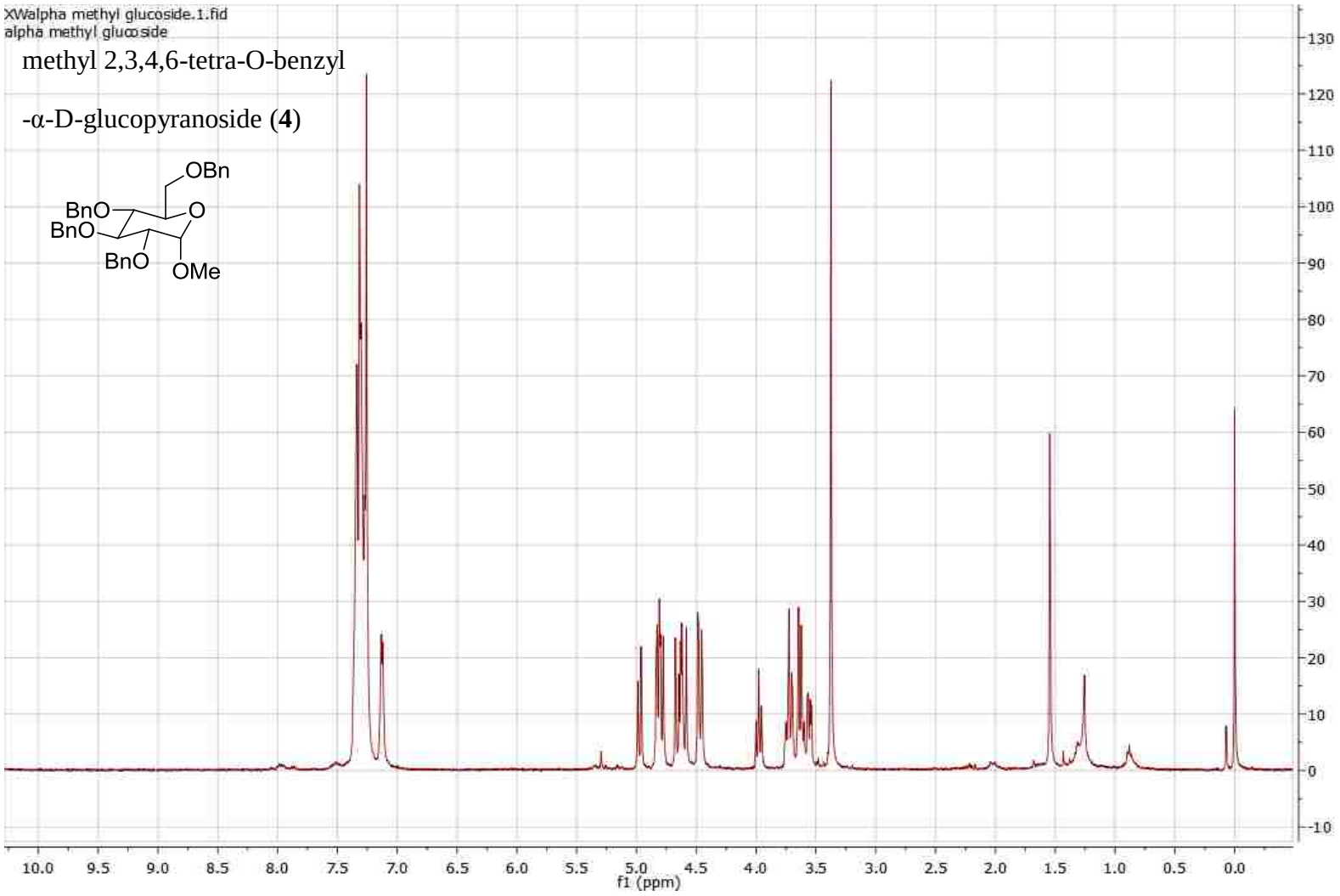

MS 87 proton/1
MS 87 proton
O
CO2H
HO
O
OH
4.
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

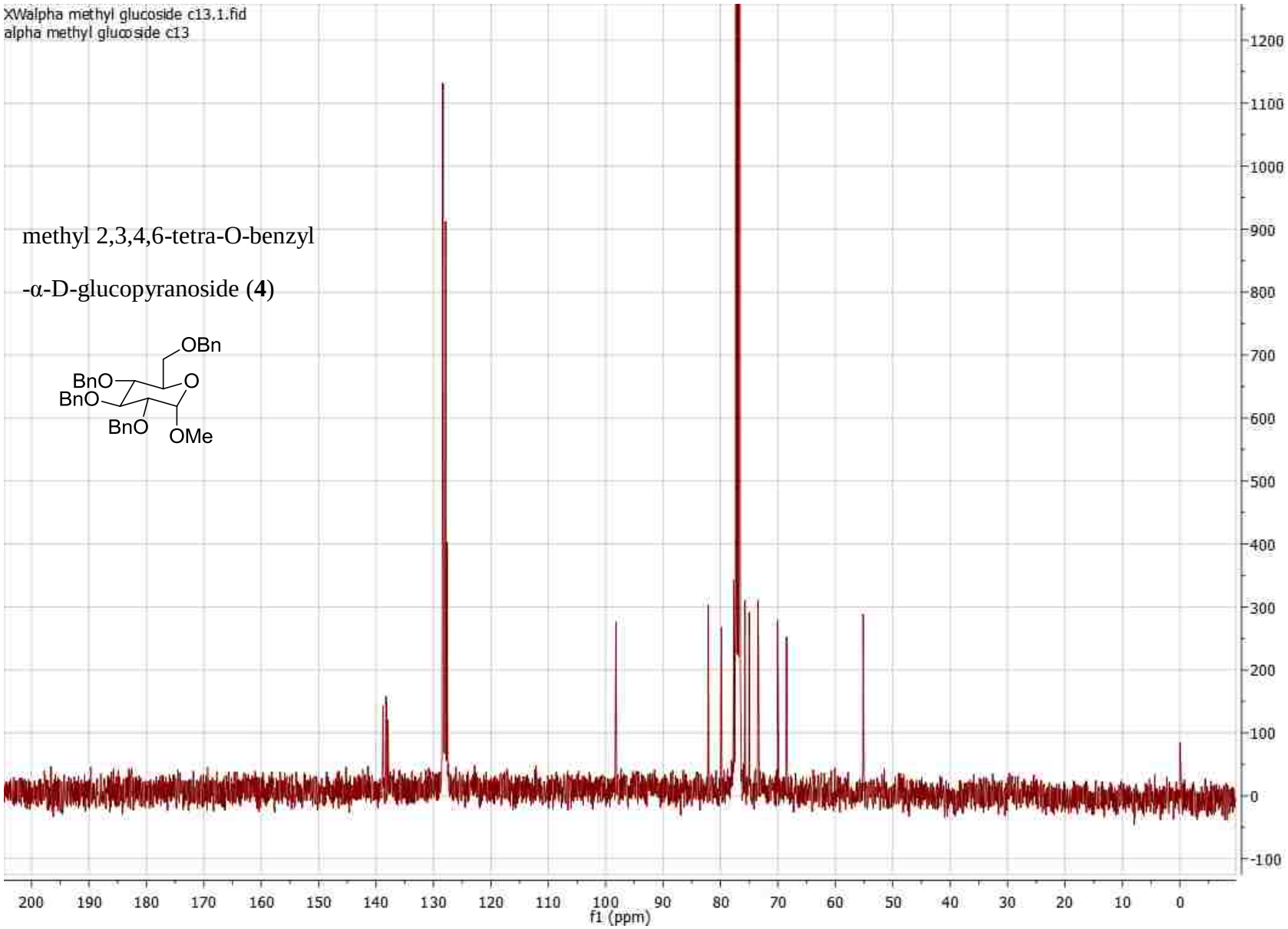

MS87-carbon/1
HO
O
O
OH
CO2H
4.
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

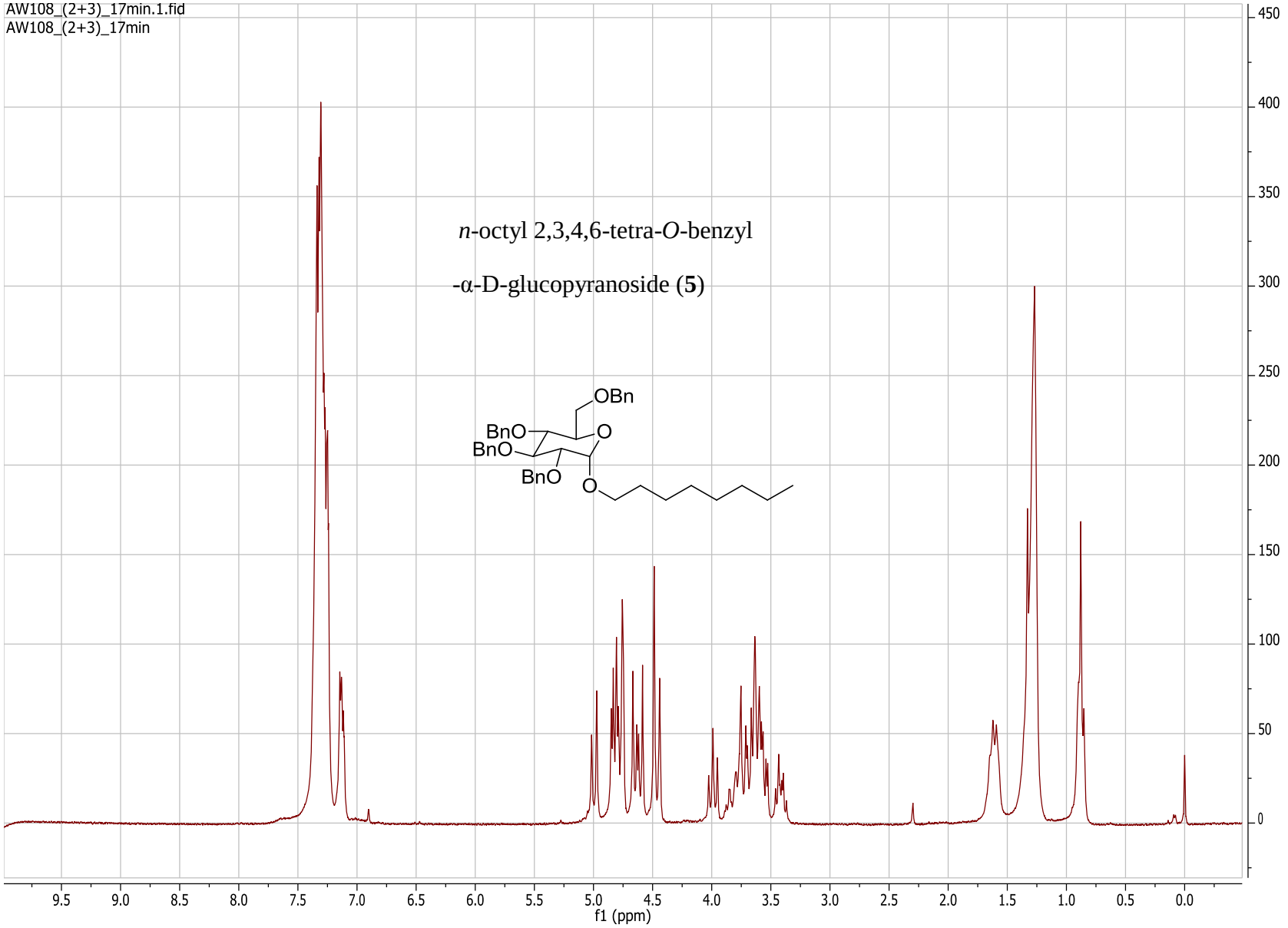

MS 85 proton/1
MS 85 proton
HO
O
O
OH
CO2H
5.
4500
4000
3500
3000
2500
2000
1500
1000
500
0
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

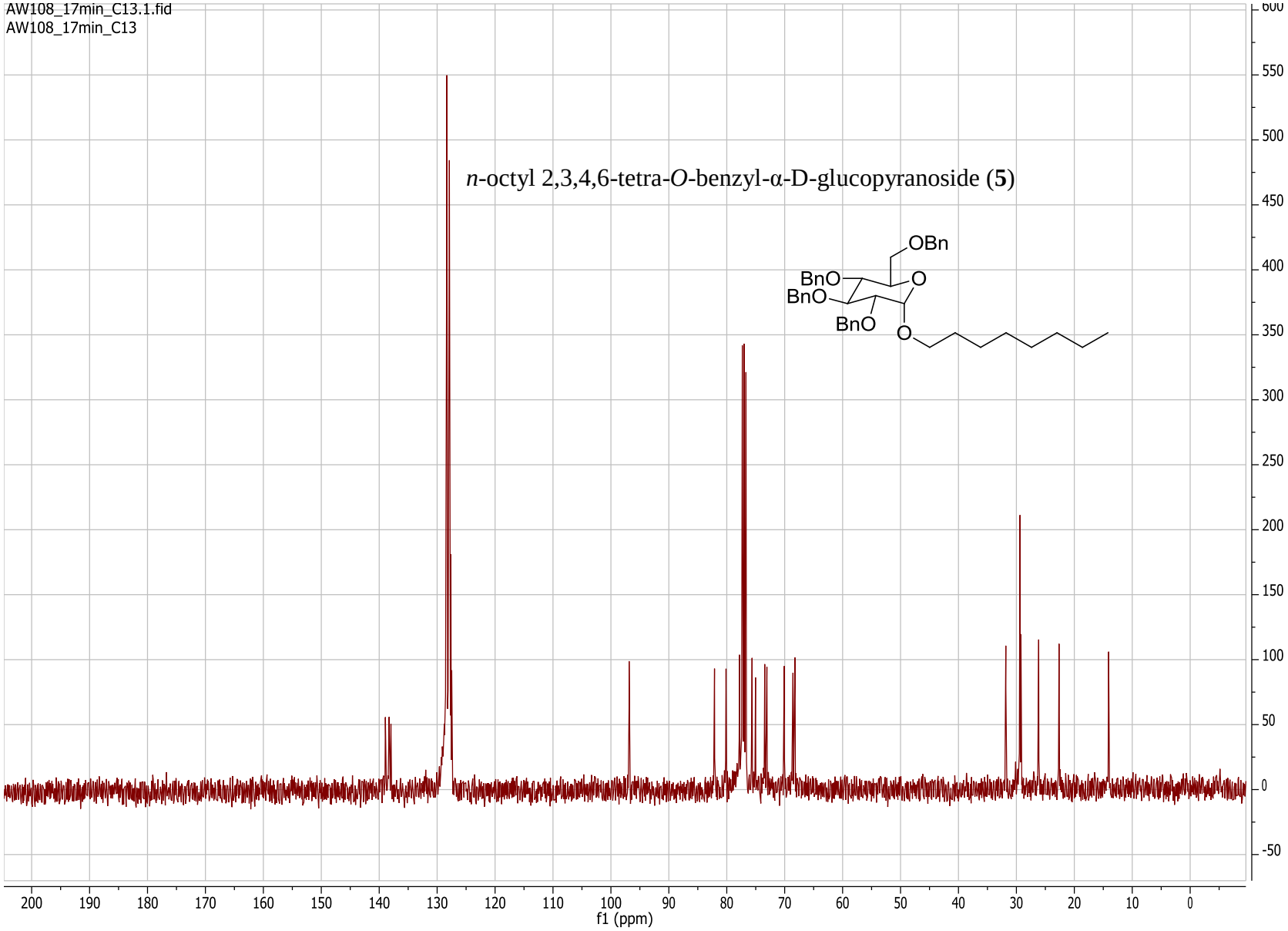

MS 85 carbon/1
MS 85 carbon
O
CO2H
HO
O
OH
5.
3000
2500
2000
1500
1000
500
0
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

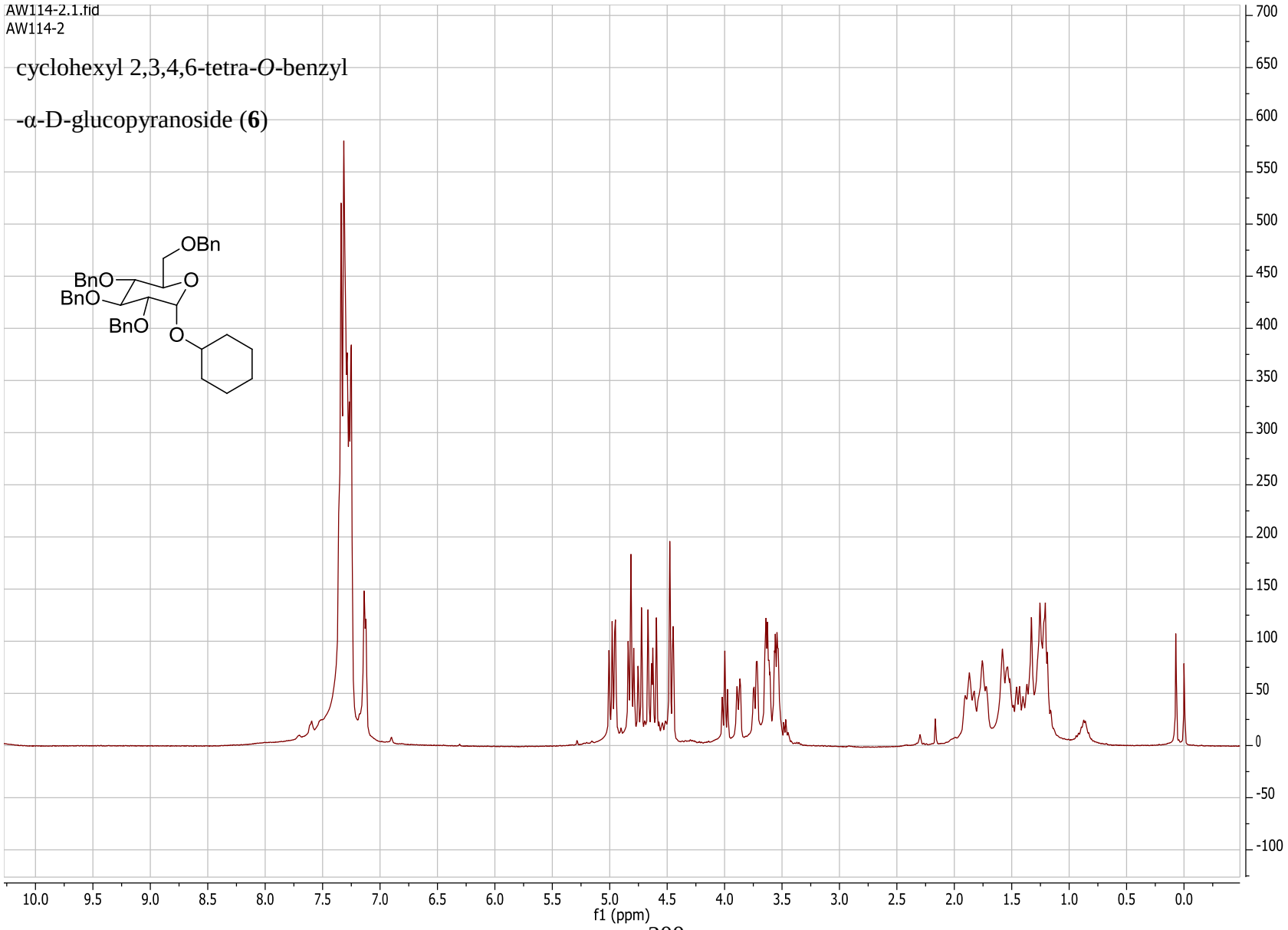
APPENDIX C: NMR SPECTRA OF COMPOUNDS FOUND IN CHAPTER 2

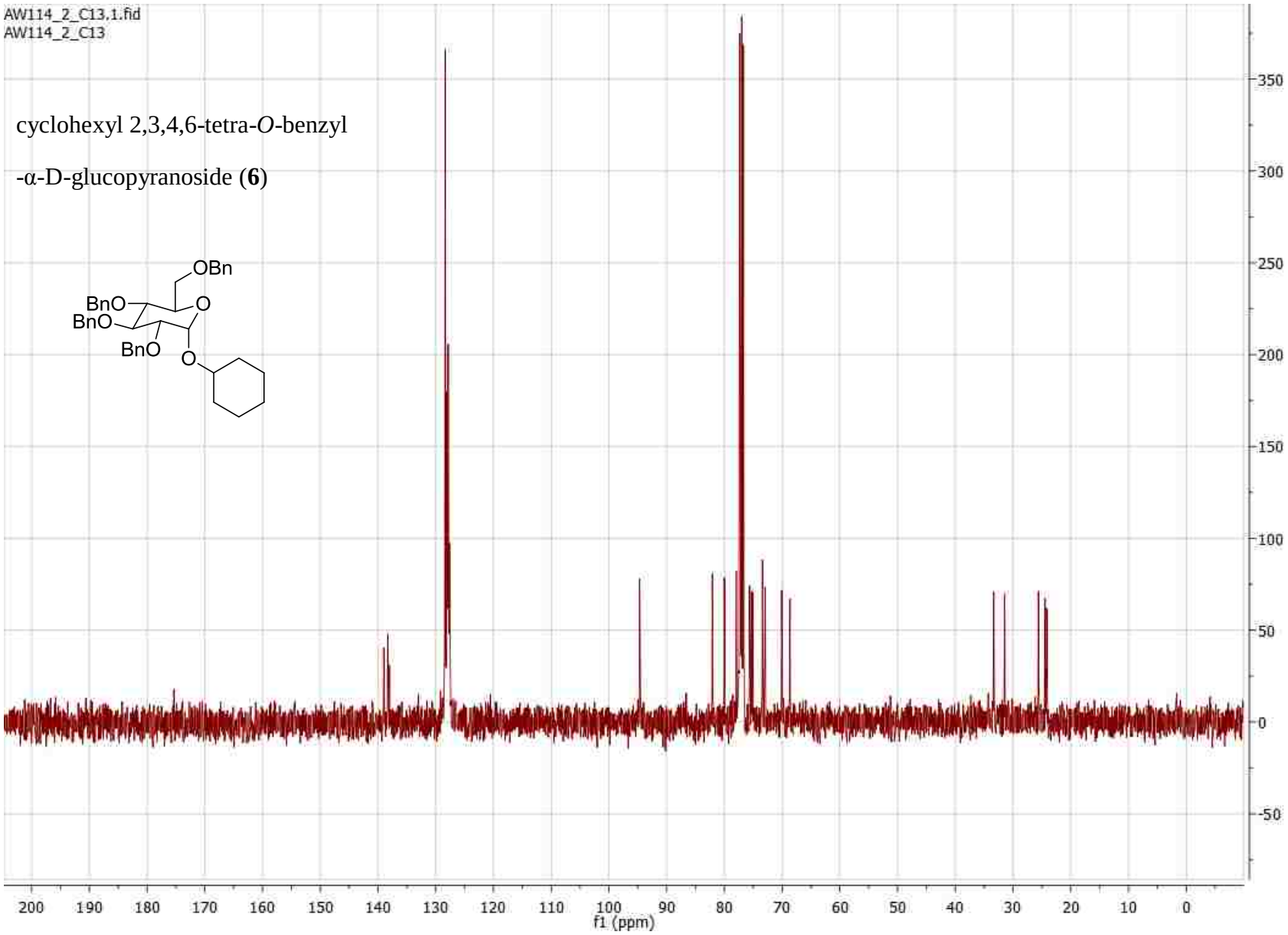


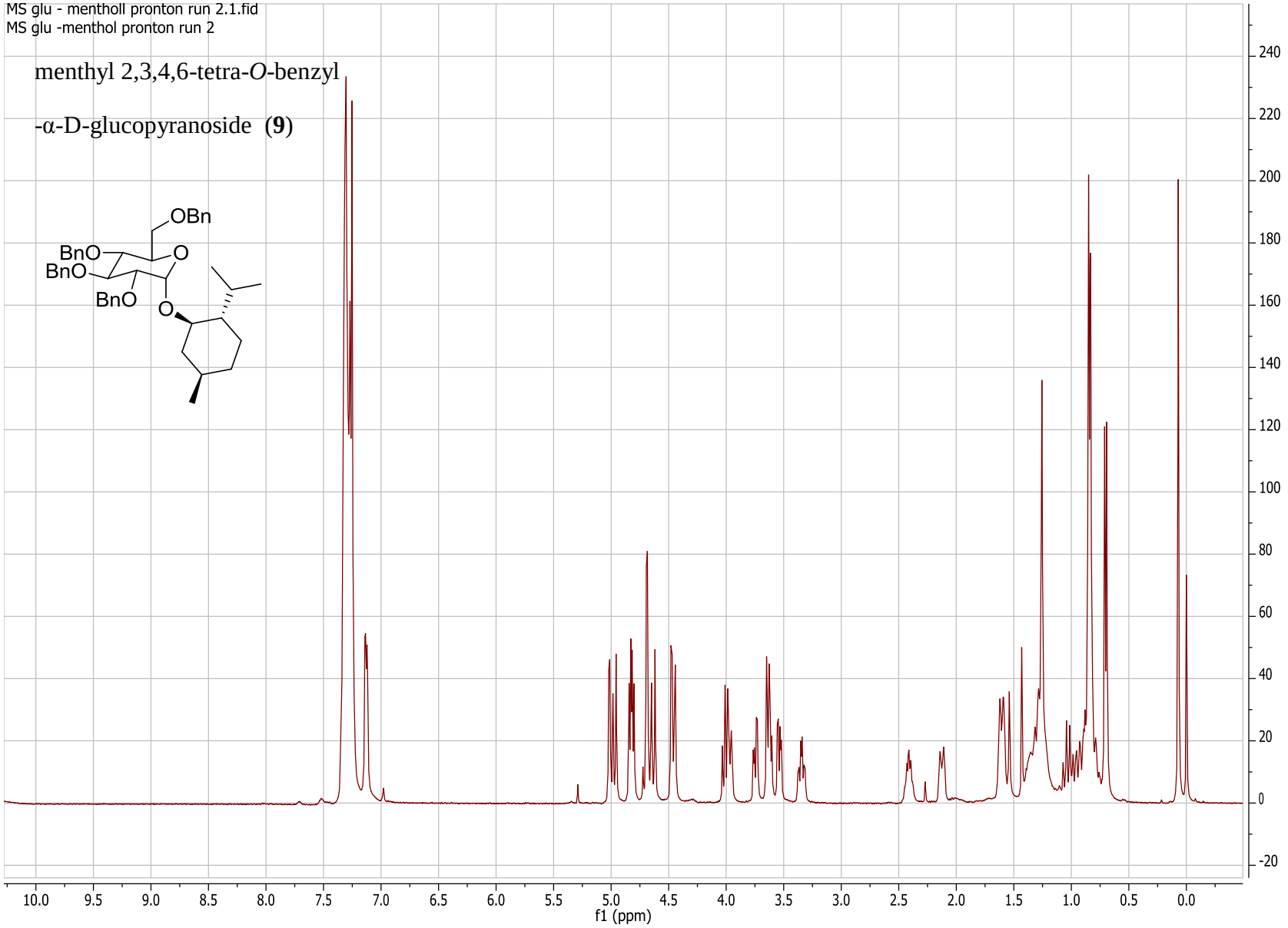

XWalpha methyl glucoside c13.1.fid
alpha methyl glucoside c13
methyl 2,3,4,6-tetra-O-benzyl
-α-D-glucopyranoside (4)
OBn
BnO
O
BnO
BnO
OMe
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

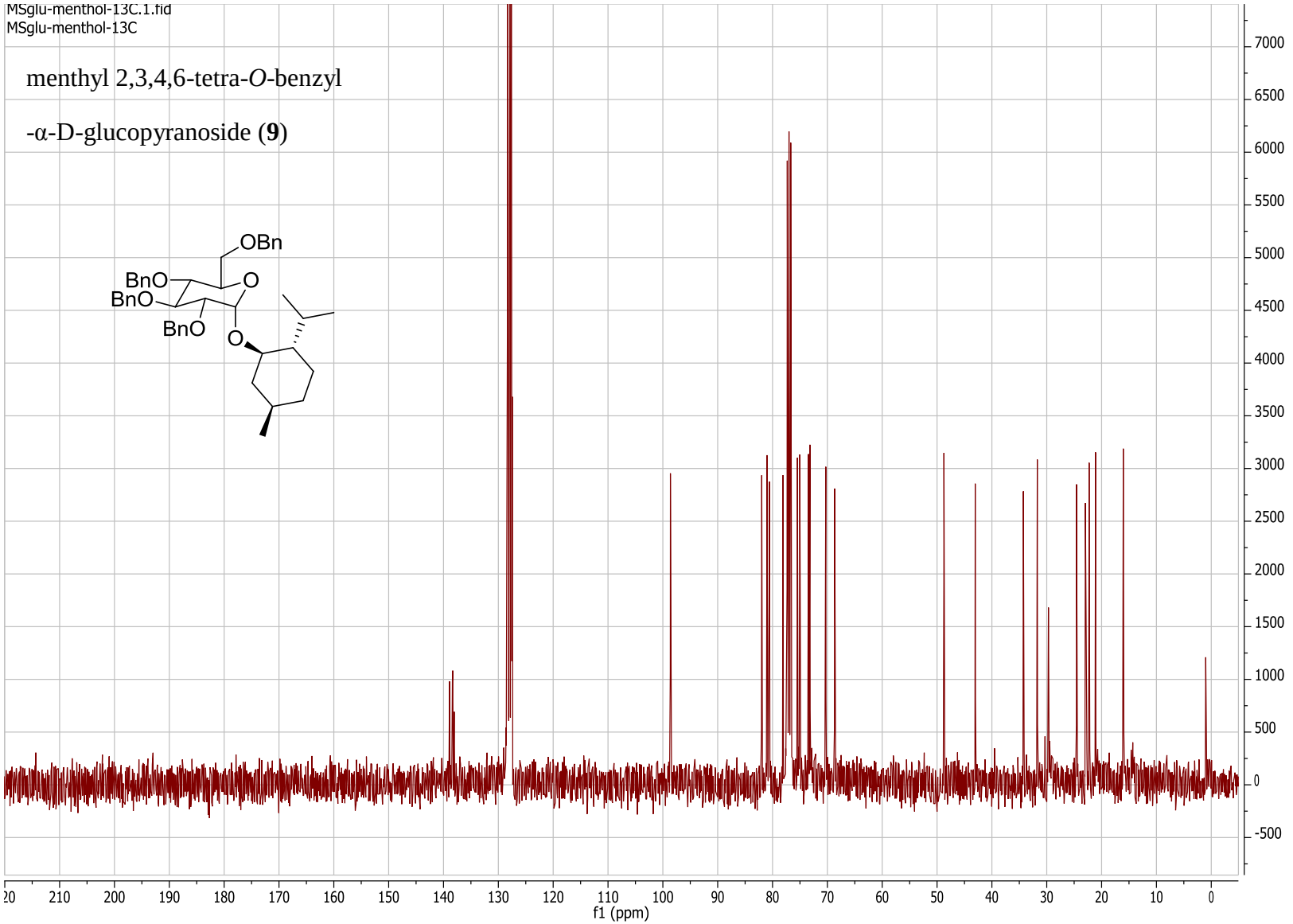

AW108_(2+3)_17min.1.fid
AW108_(2+3)_17min
n-octyl 2,3,4,6-tetra-*O*-benzyl
-α-D-glucopyranoside (**5**)
OBn
BnO
BnO
BnO
O
O
f1 (ppm)

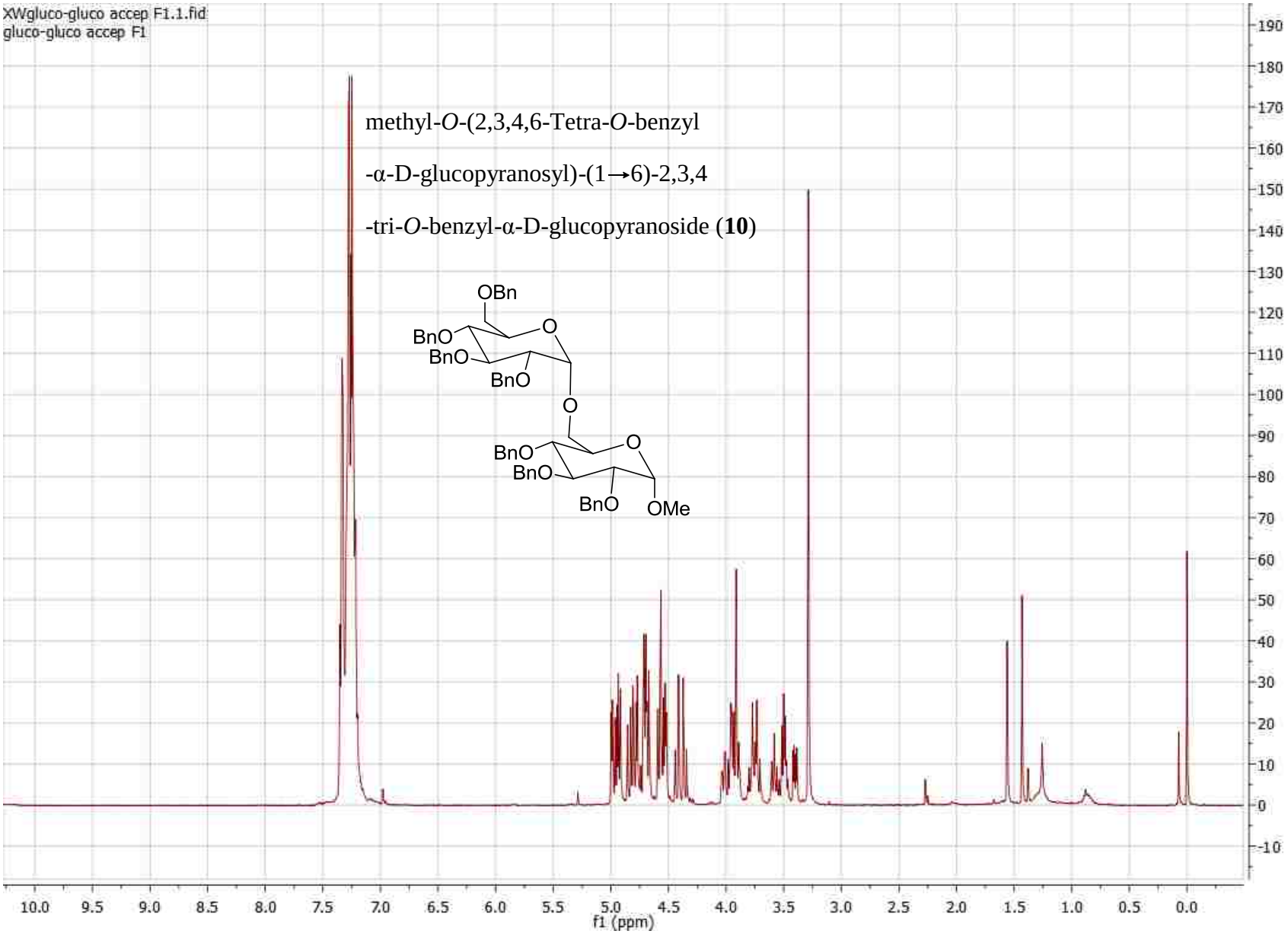

AW108_17min_C13.1.fid
AW108_17min_C13
n-octyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (**5**)
OBn
BnO
BnO
BnO
O
O
f1 (ppm)

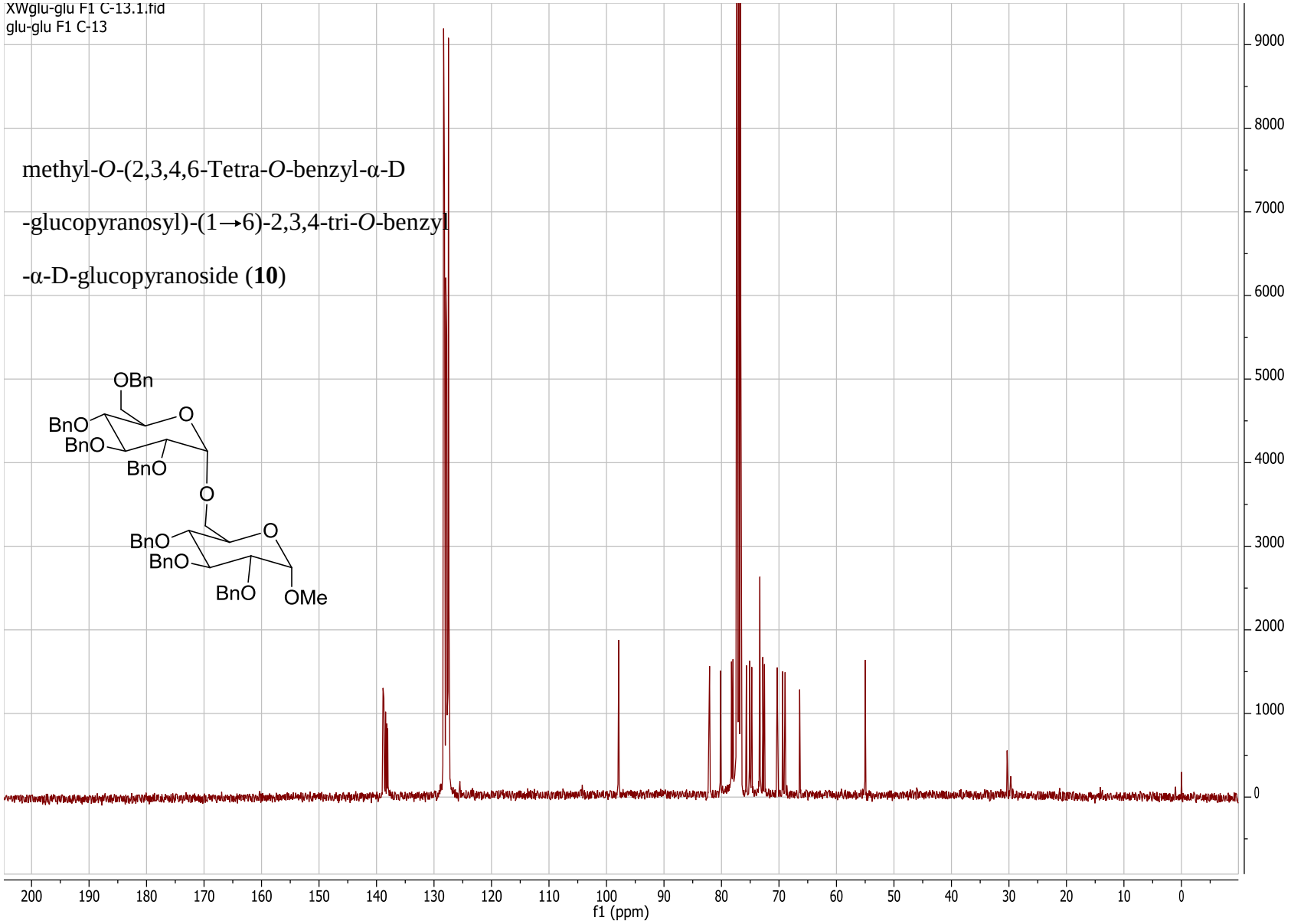

AW114-2.1.fid
AW114-2
cyclohexyl 2,3,4,6-tetra-O-benzyl
-α-D-glucopyranoside (6)
OBn
BnO
BnO
BnO
O
O
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
-100
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

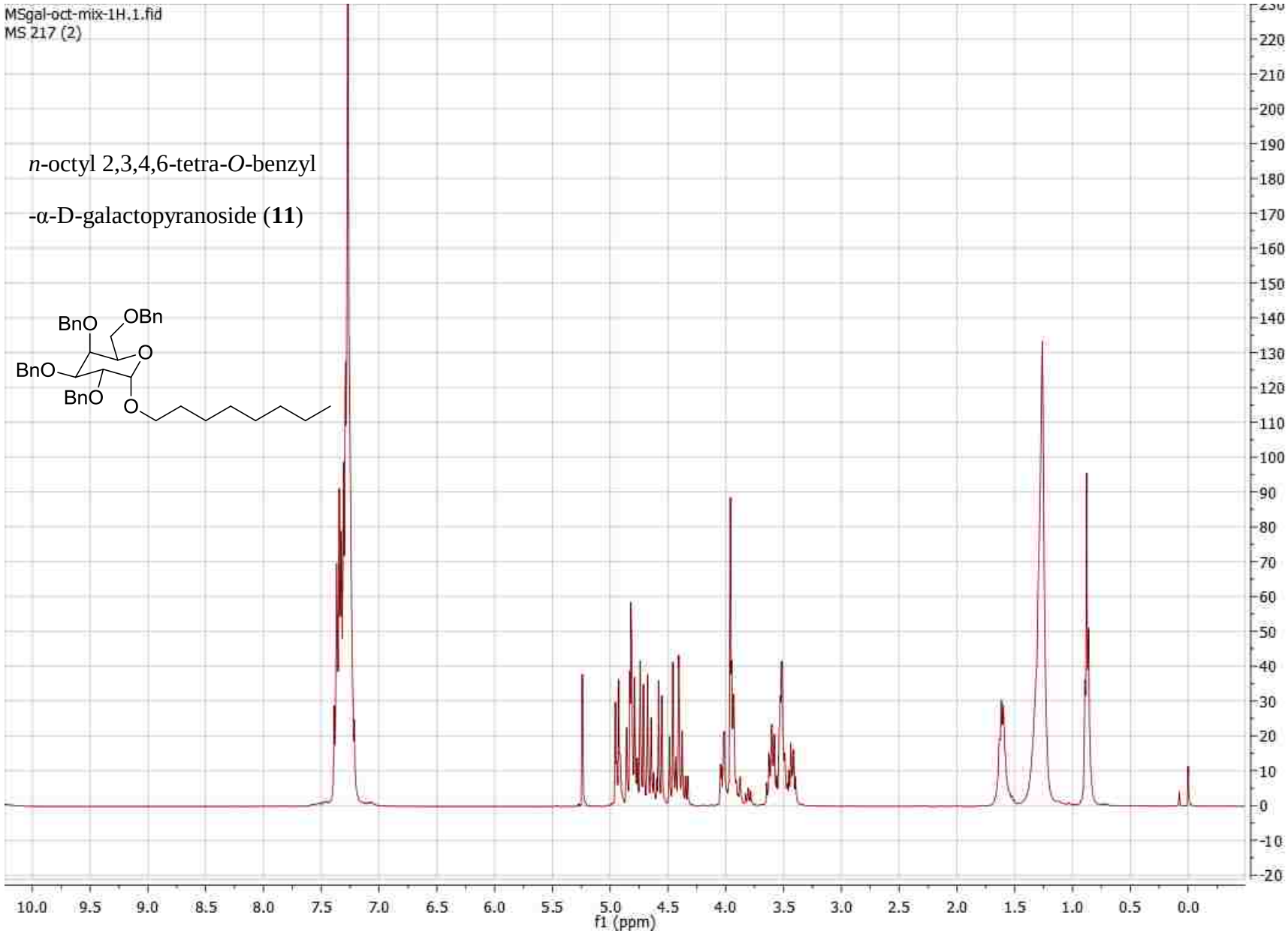

AW114_2_C13.1.fid
AW114_2_C13
cyclohexyl 2,3,4,6-tetra-O-benzyl
-α-D-glucopyranoside (6)
OBn
BnO
BnO
BnO
O
O
350
300
250
200
150
100
50
0
-50
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

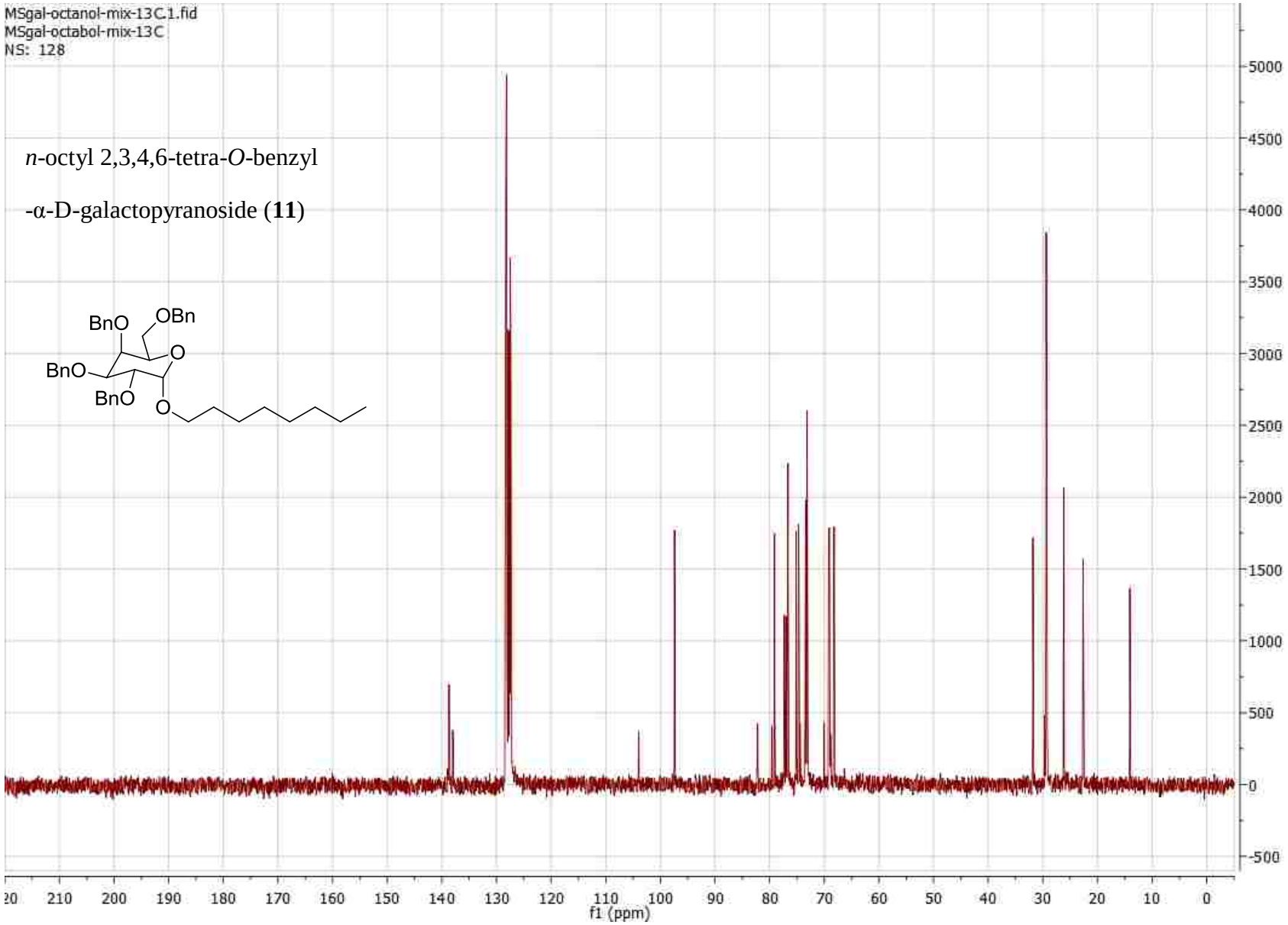

MS glu - mentholl pronton run 2.1.fid
MS glu -menthol pronton run 2
menthyl 2,3,4,6-tetra-O-benzyl
-α-D-glucopyranoside (9)
OBn
BnO
BnO
BnO
O
O
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

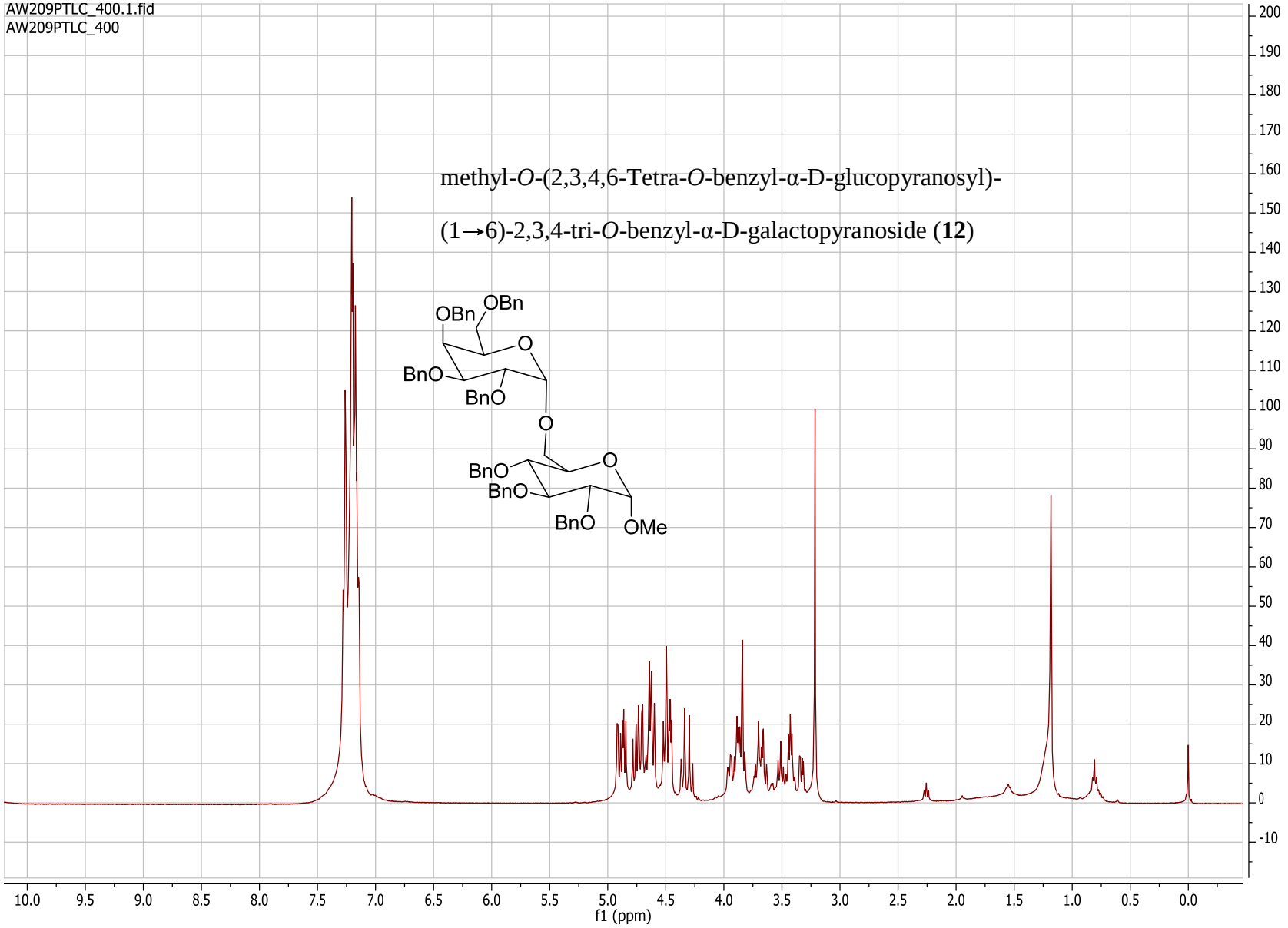

MSglu-menthol-13C.1.fid
MSglu-menthol-13C
menthyl 2,3,4,6-tetra-O-benzyl
-α-D-glucopyranoside (9)
OBn
BnO
BnO
BnO
O
O
f1 (ppm)

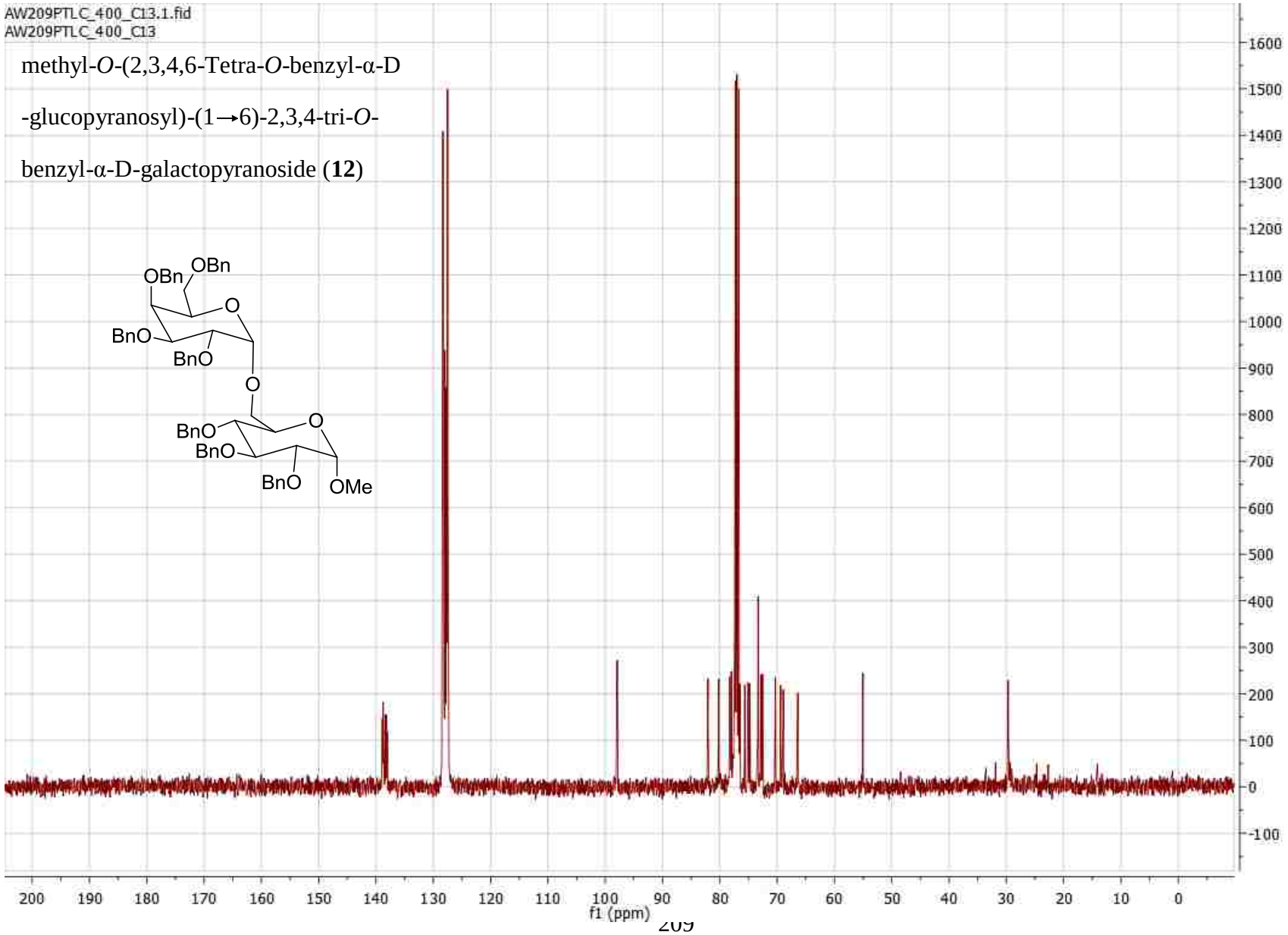

XWgluco-gluco accep F1.1.fid
gluco-gluco accep F1
methyl-O-(2,3,4,6-Tetra-O-benzyl
-α-D-glucopyranosyl)-(1→6)-2,3,4
-tri-O-benzyl-α-D-glucopyranoside (10)
OBn
BnO
BnO
BnO
O
O
BnO
BnO
BnO
OMe
f1 (ppm)

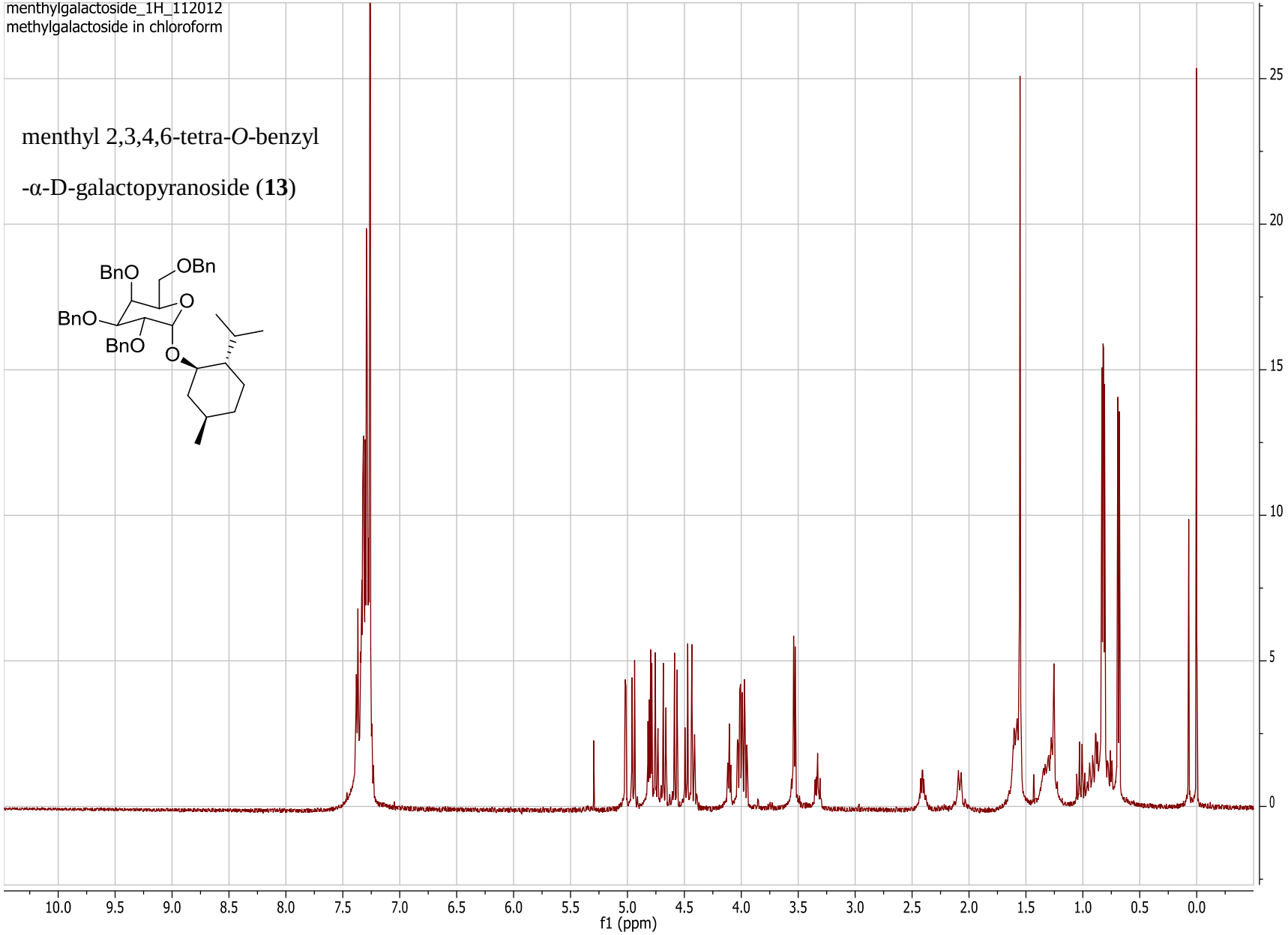

XWglu-glu F1 C-13.1.fid
glu-glu F1 C-13
methyl-O-(2,3,4,6-Tetra-O-benzyl-α-D
-glucopyranosyl)-(1→6)-2,3,4-tri-O-benzyl
-α-D-glucopyranoside (10)
OBn
BnO
BnO
BnO
O
O
BnO
BnO
BnO
OMe
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

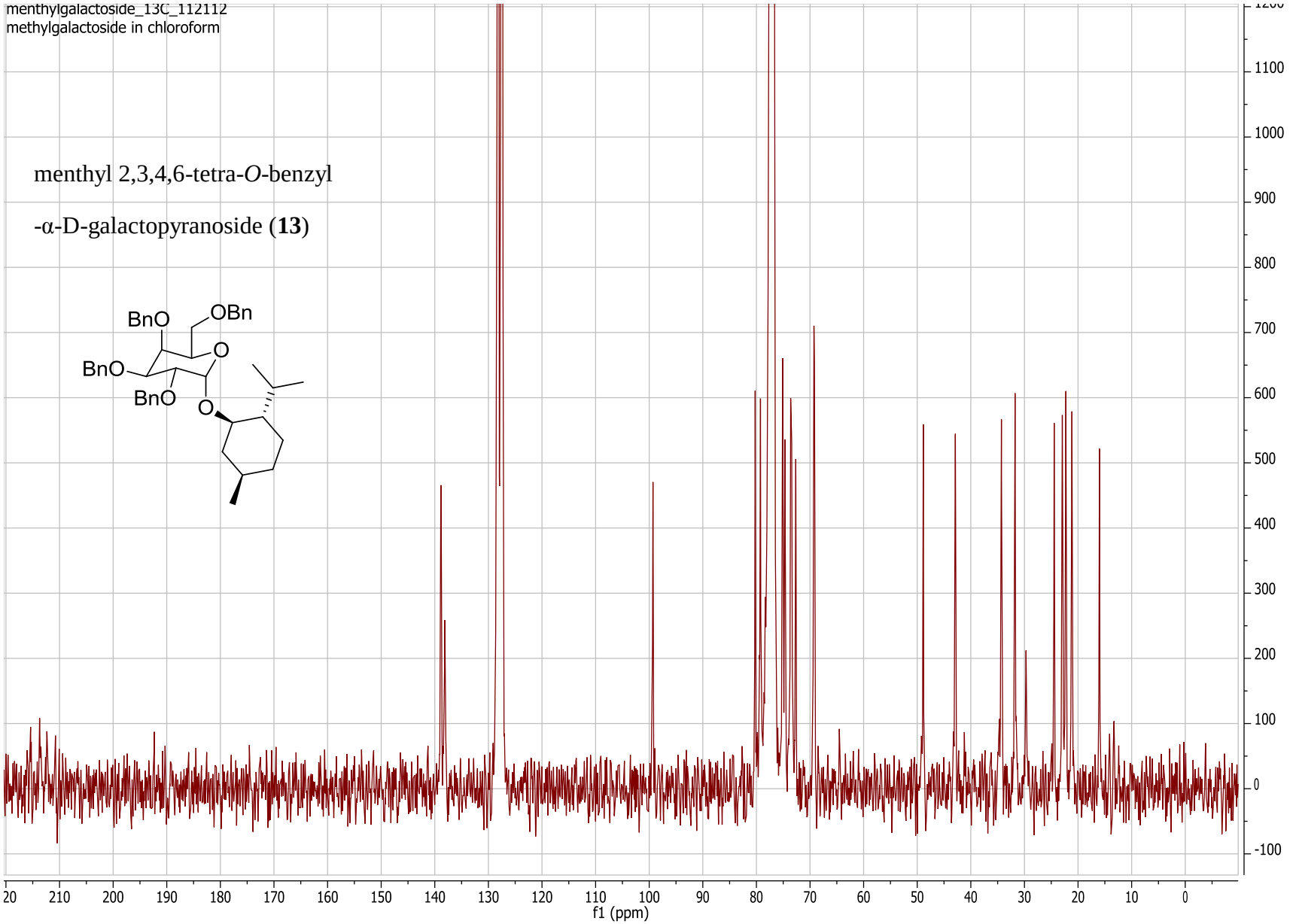

MSgal-oct-mix-1H.1.fid
MS 217 (2)
n-octyl 2,3,4,6-tetra-*O*-benzyl
-α-D-galactopyranoside (**11**)
BnO
OBn
O
BnO
BnO
O
f1 (ppm)


MSgal-octanol-mix-13C.1.fid
MSgal-octabol-mix-13C
NS: 128
n-octyl 2,3,4,6-tetra-*O*-benzyl
-α-D-galactopyranoside (**11**)
BnO
OBn
O
BnO
BnO
O
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

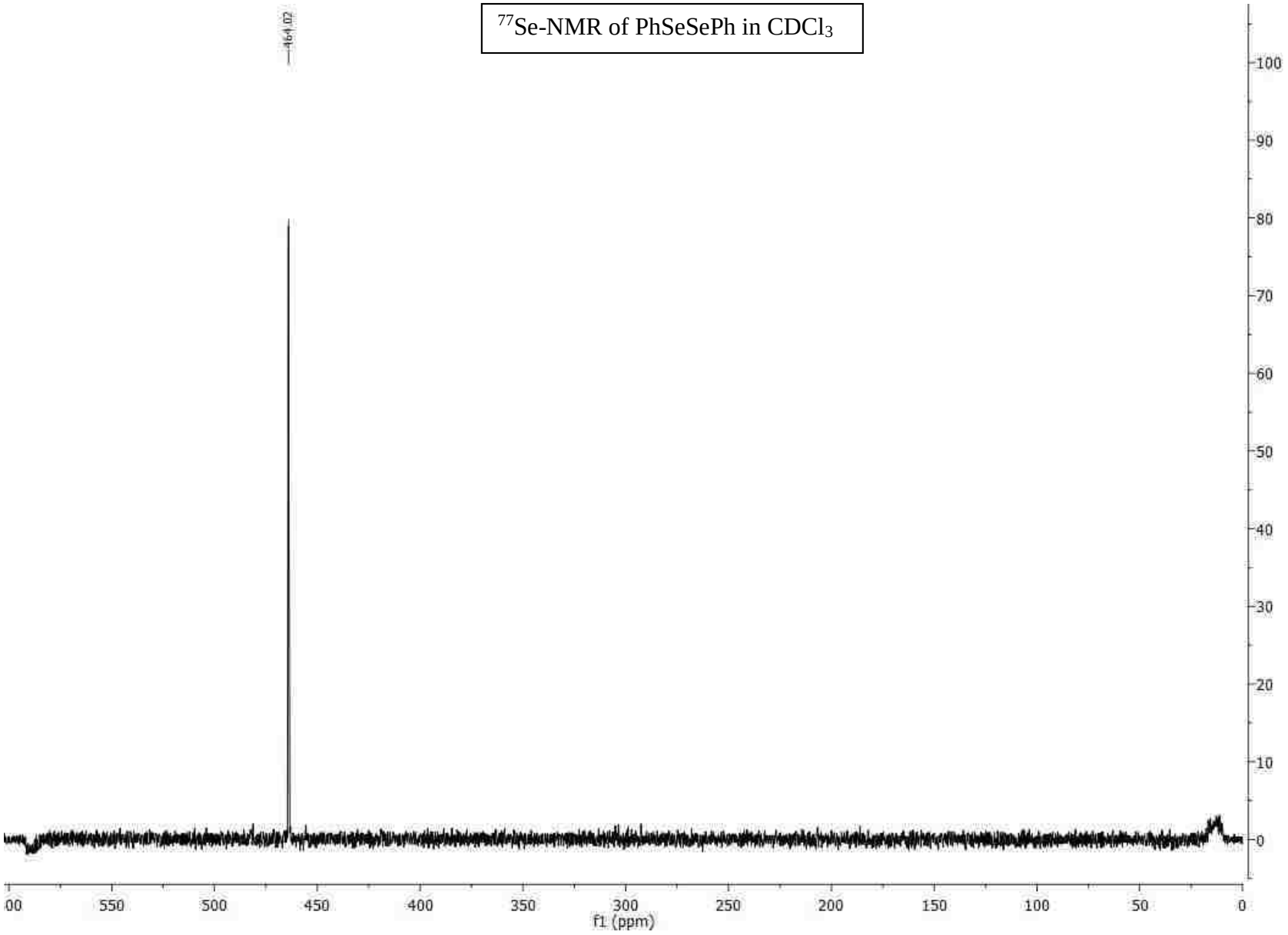

AW209PTLC_400.1.fid
AW209PTLC_400
methyl-O-(2,3,4,6-Tetra-O-benzyl-α-D-glucopyranosyl)-
(1→6)-2,3,4-tri-O-benzyl-α-D-galactopyranoside (12)
OBn
OBn
O
BnO
BnO
O
BnO
O
BnO
BnO
OMe
f1 (ppm)


AW209PTLC_400_C13.1.fid
AW209PTLC_400_C13
methyl-*O*-(2,3,4,6-Tetra-*O*-benzyl-α-D
-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-
benzyl-α-D-galactopyranoside (**12**)
OBn
OBn
O
BnO
BnO
O
BnO
O
BnO
BnO
OMe
f1 (ppm)

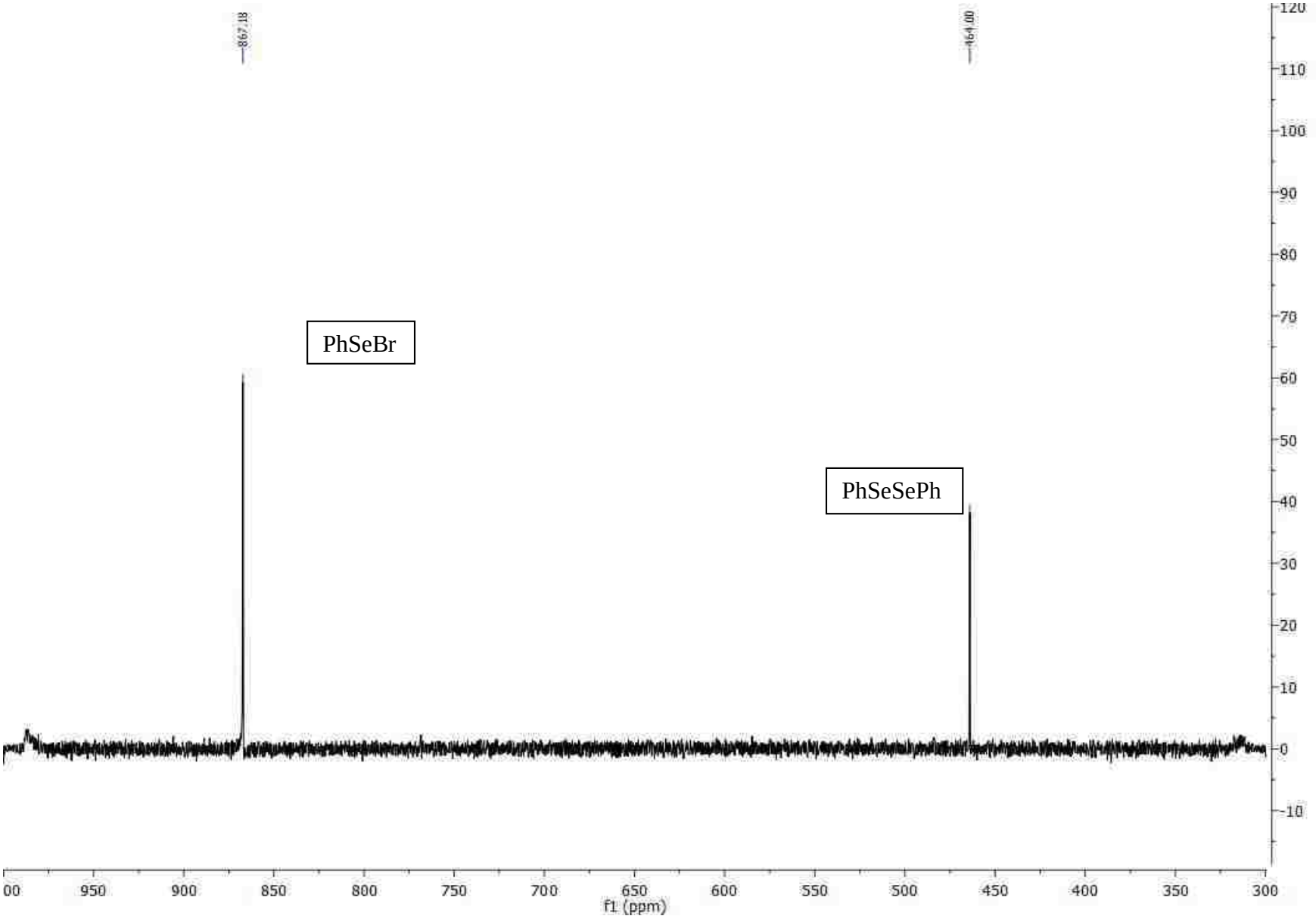

menthylgalactoside_1H_112012
methylgalactoside in chloroform
menthyl 2,3,4,6-tetra-O-benzyl
-α-D-galactopyranoside (13)
BnO
OBn
O
BnO
BnO
O
25
20
15
10
5
0
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

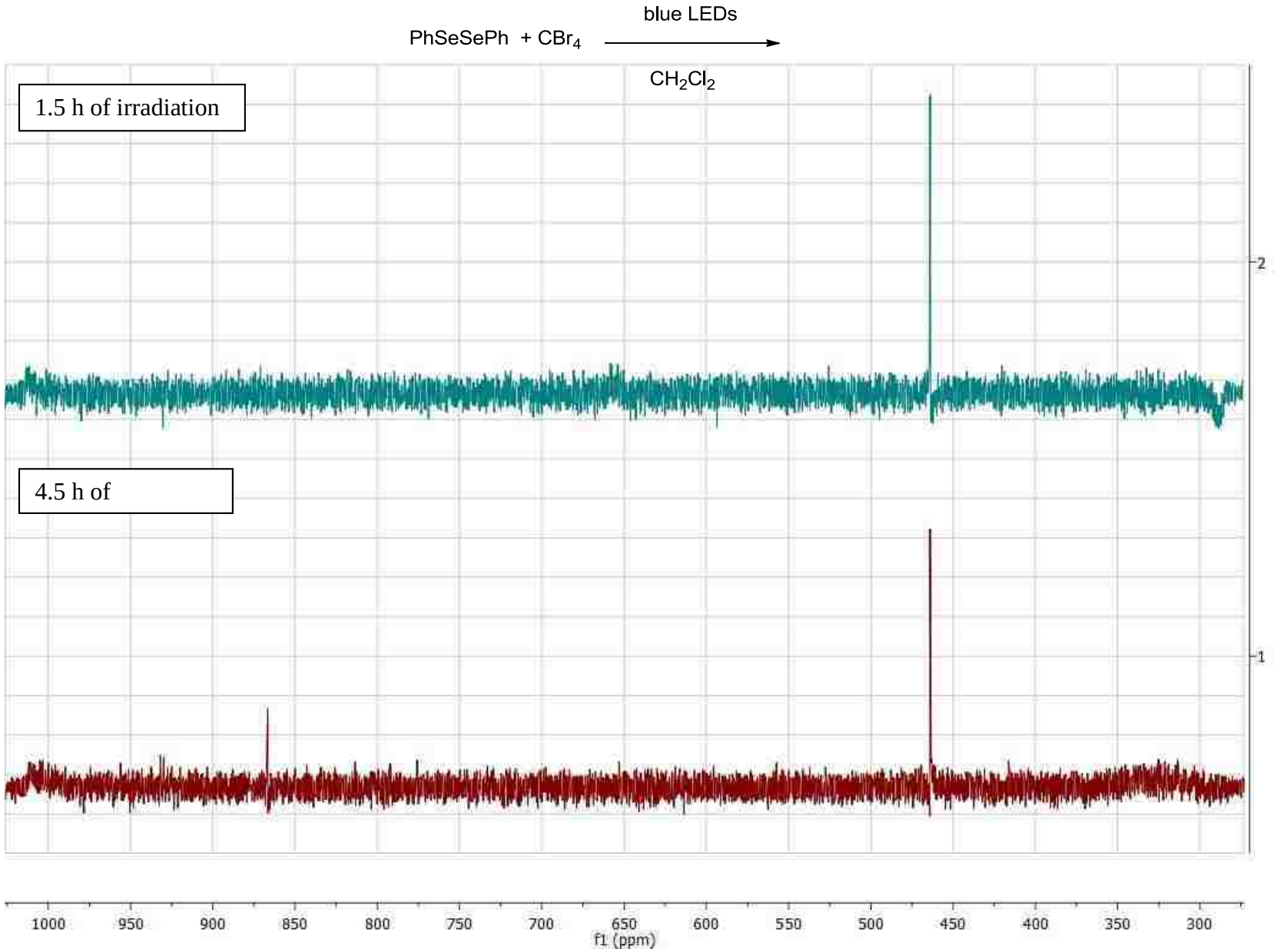

menthylgalactoside_13C_112112
methylgalactoside in chloroform
menthyl 2,3,4,6-tetra-O-benzyl
-α-D-galactopyranoside (13)
BnO
OBn
O
BnO
BnO
O
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

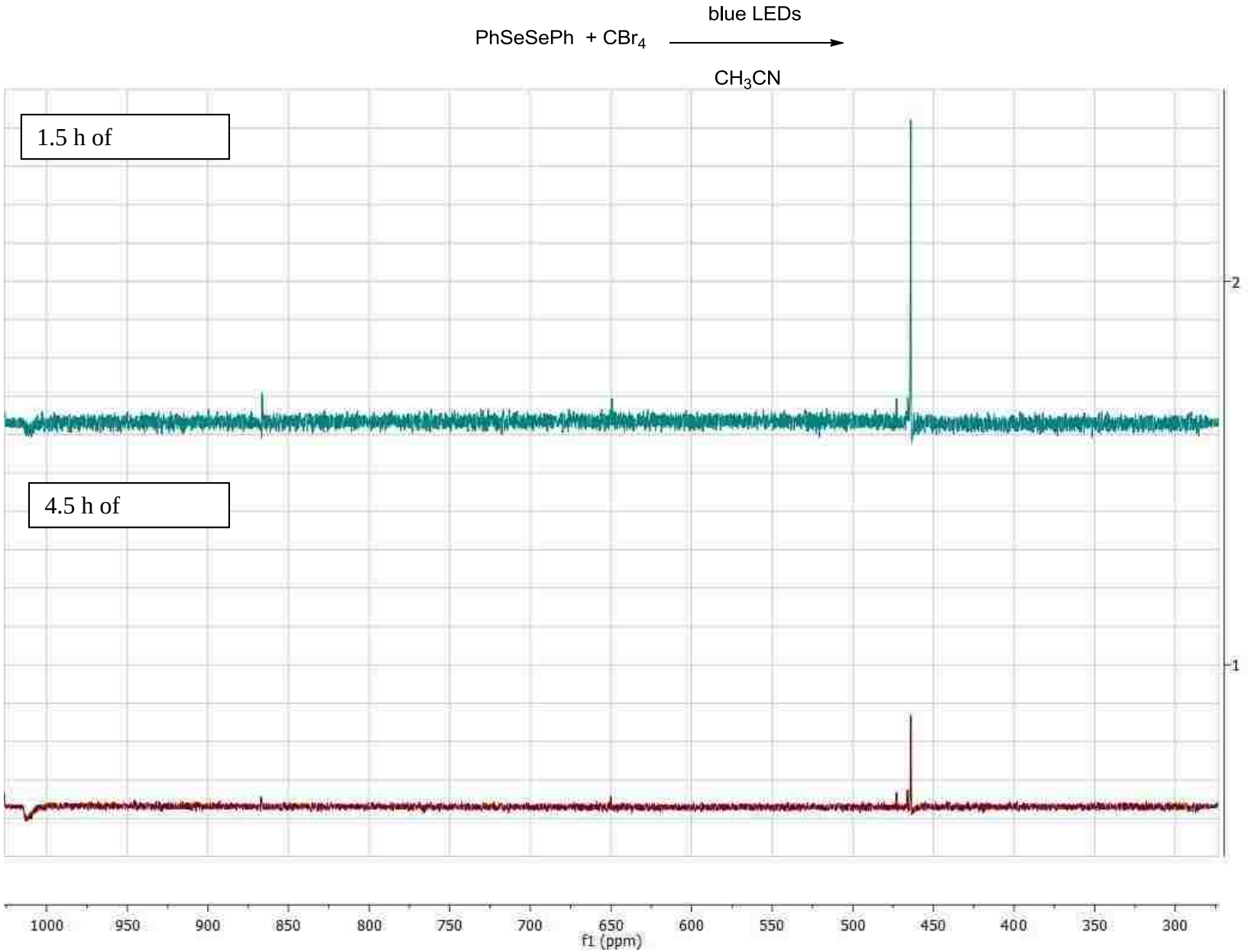
^{77}Se-NMR of PhSeSePh in $CDCl_3$



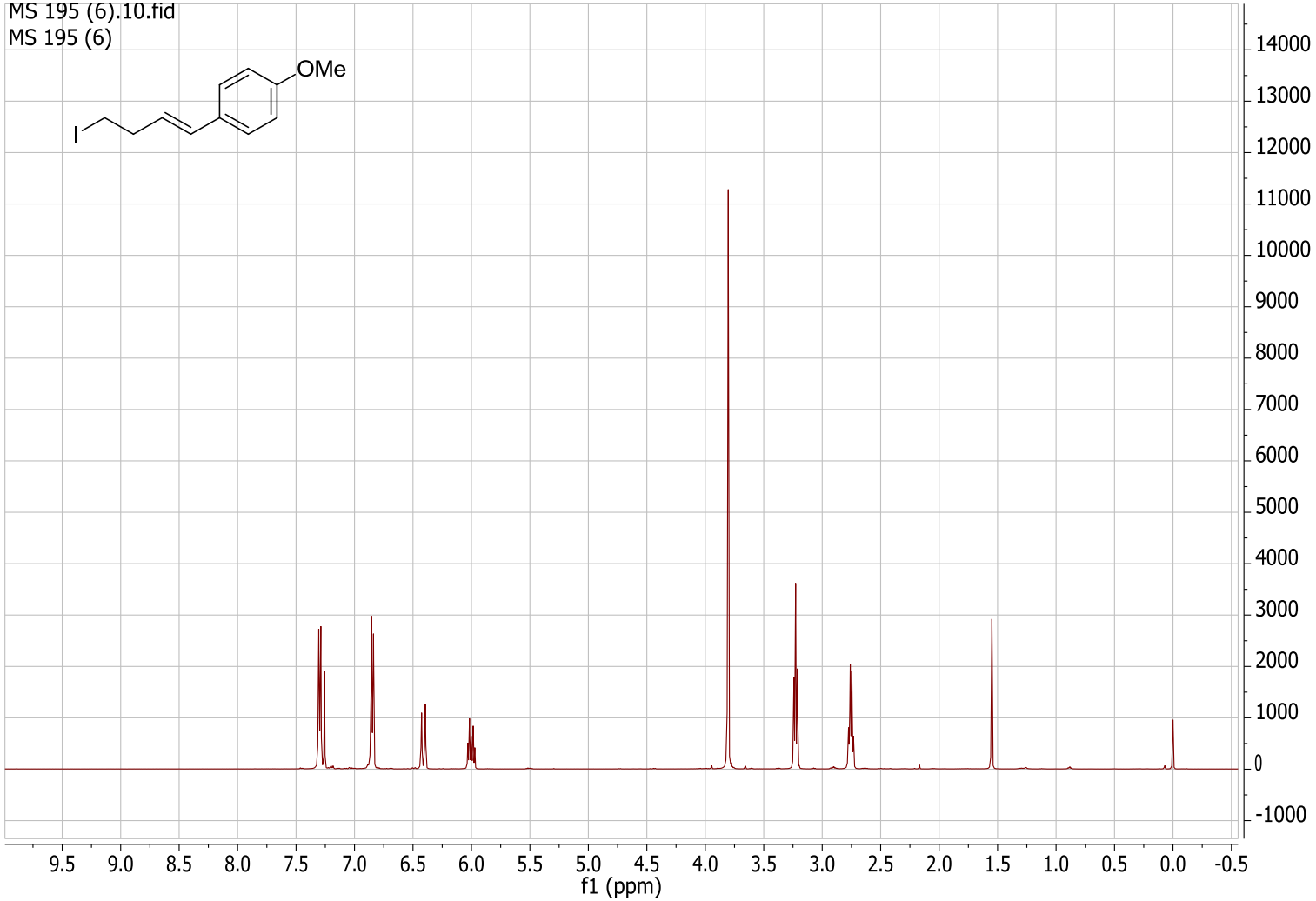
^{77}Se-NMR of a mixture of PhSeSePh and PhSeBr in $CDCl_3$

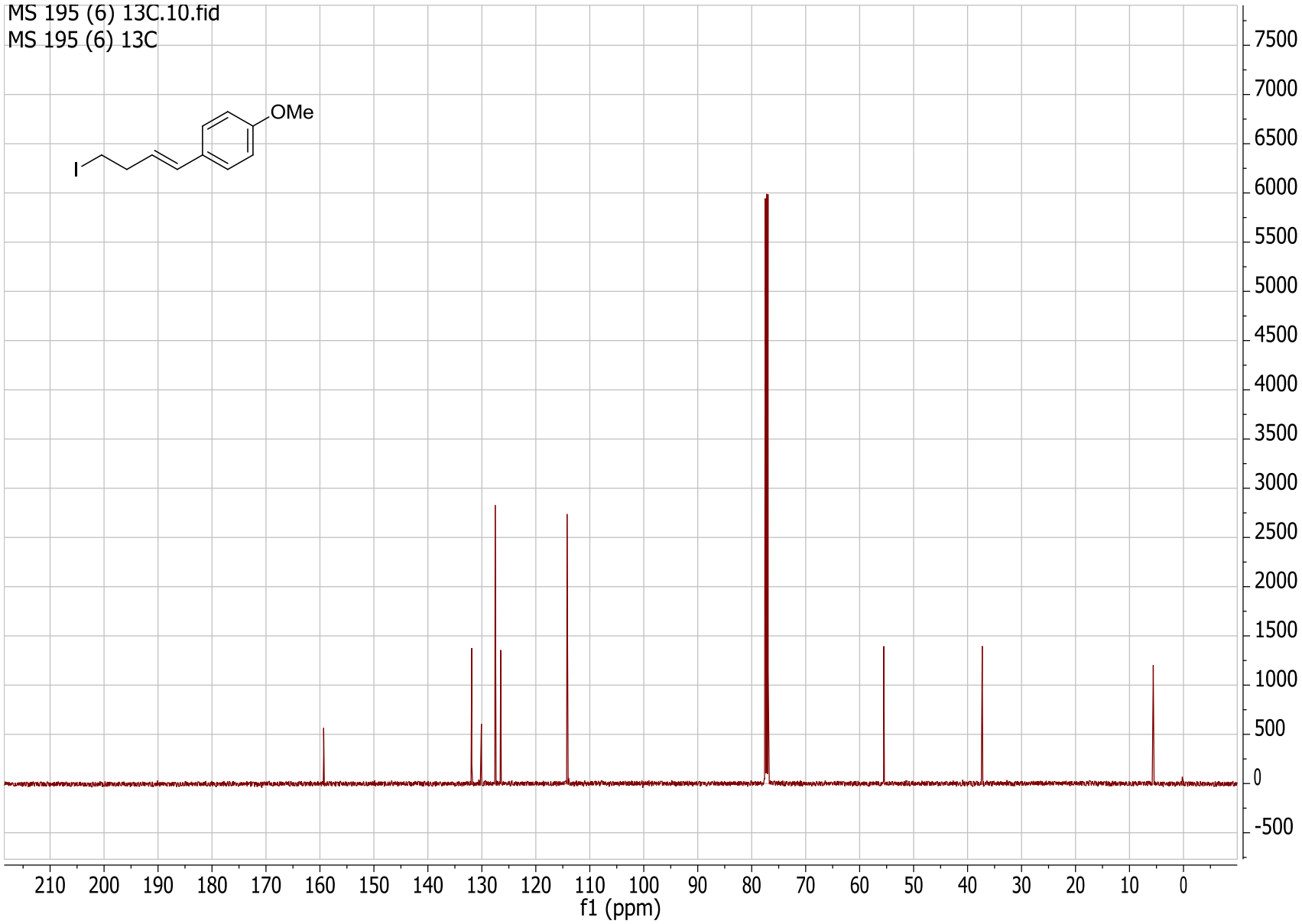


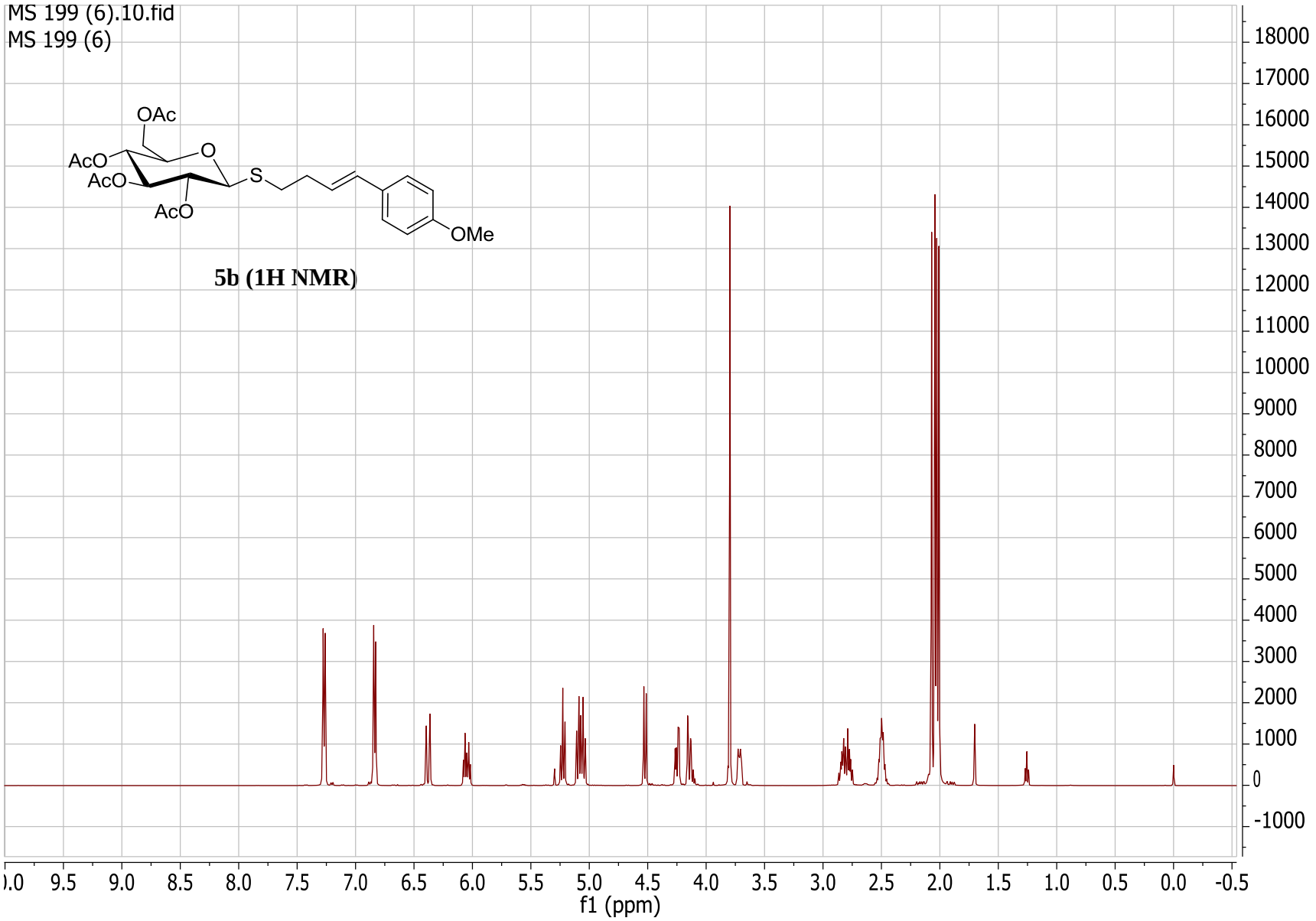

blue LEDs
PhSeSePh + CBr4
CH2Cl2
1.5 h of irradiation
4.5 h of
2
1
1000
950
900
850
800
750
700
650
600
550
500
450
400
350
300
f1 (ppm)

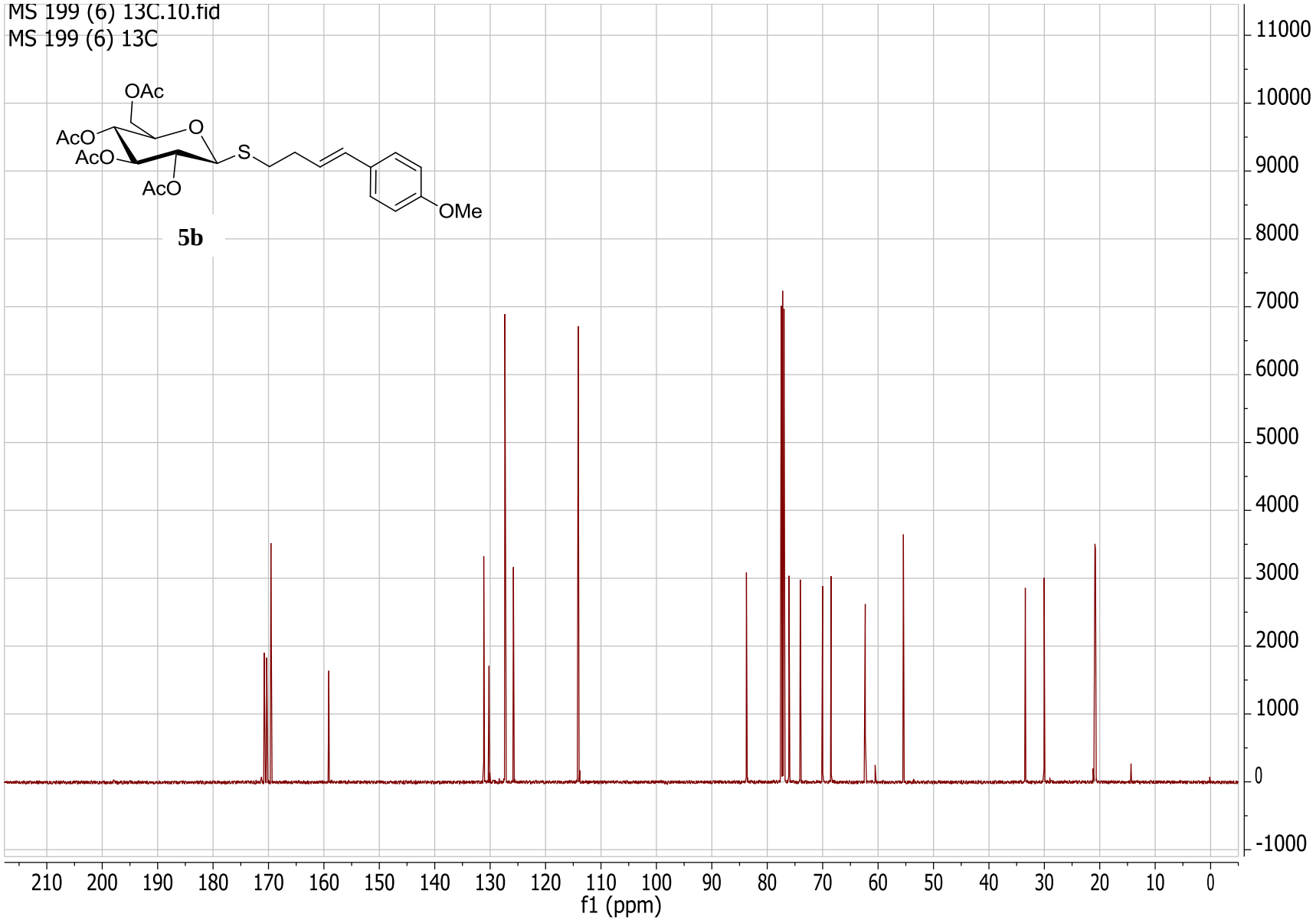

blue LEDs
PhSeSePh + CBr4
CH3CN
1.5 h of
4.5 h of
2
1
1000
950
900
850
800
750
700
650
600
550
500
450
400
350
300
f1 (ppm)

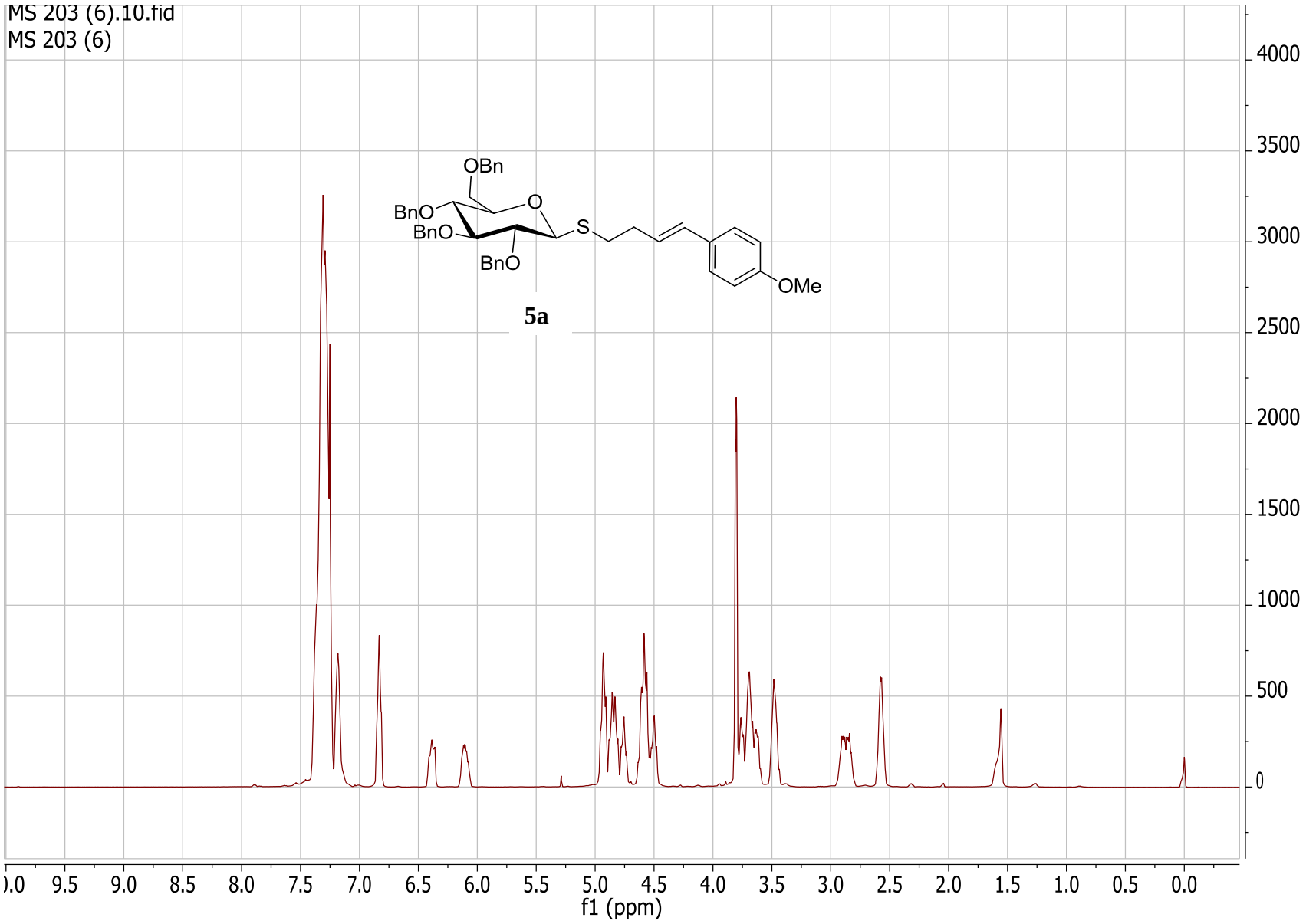
APPENDIX D: NMR SPECTRA OF COMPOUNDS FOUND IN CHAPTER 3

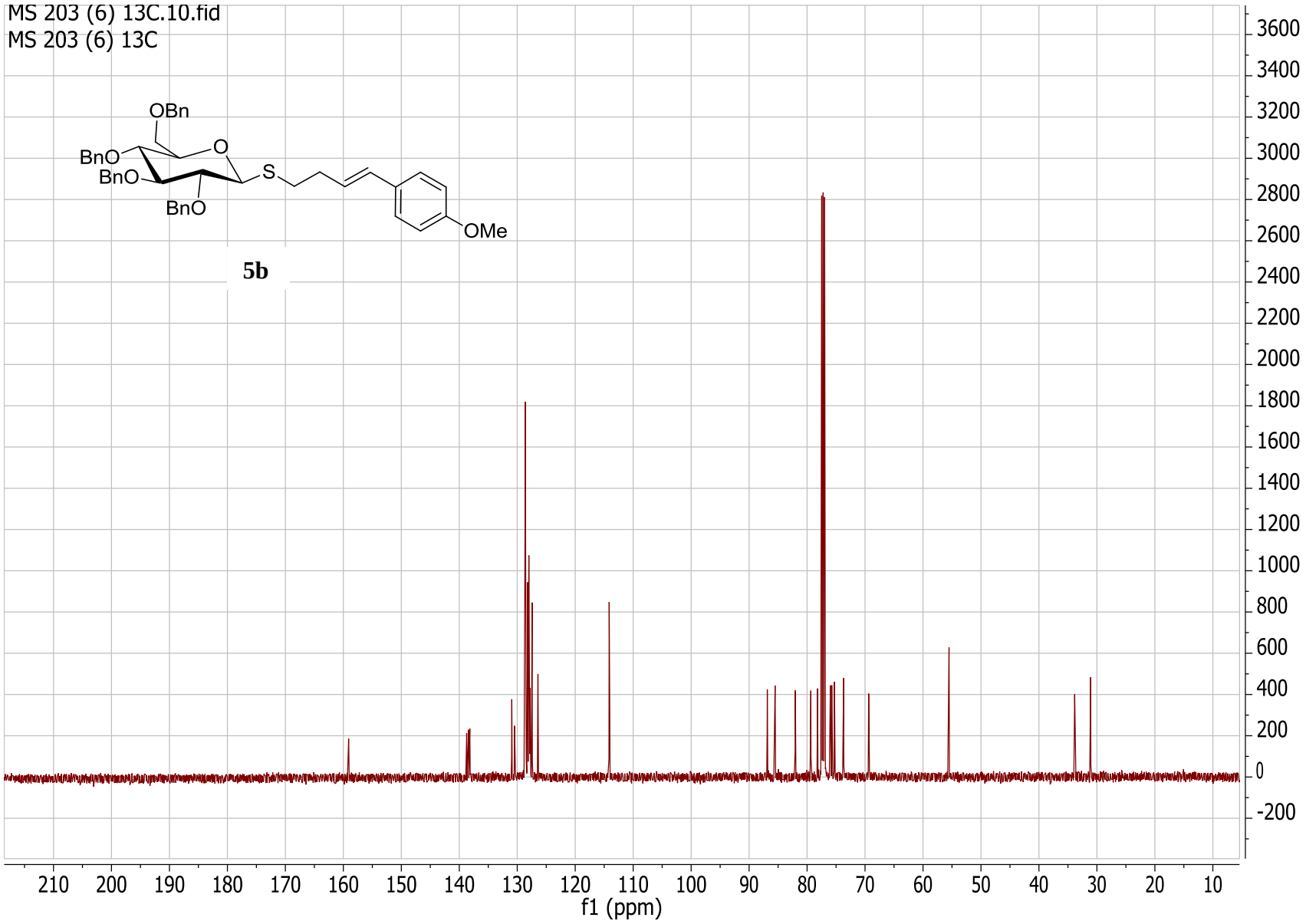


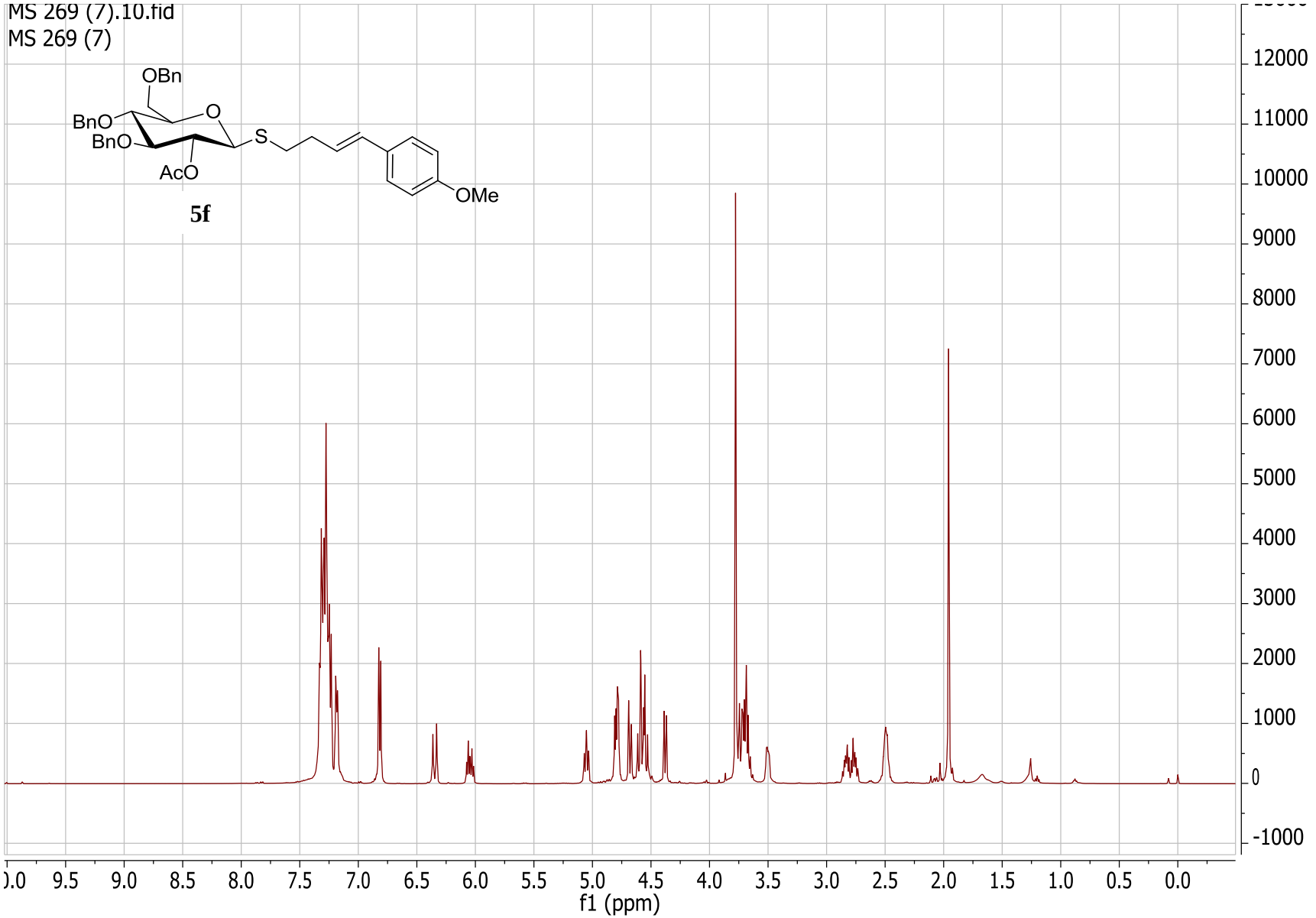

MS 195 (6) 13C.10.fid
MS 195 (6) 13C
OMe
I
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

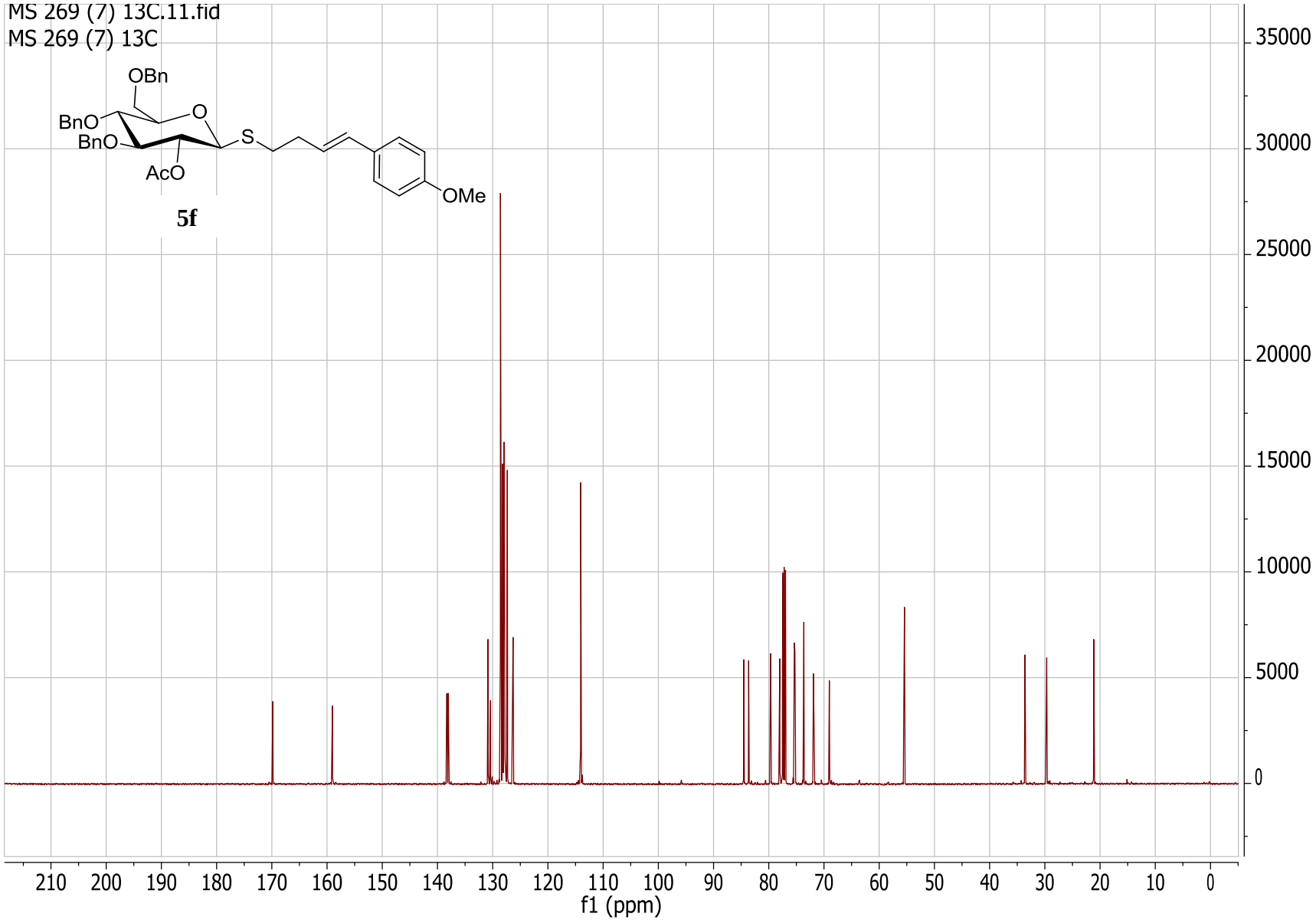

MS 199 (6).10.fid
MS 199 (6)
OAc
AcO
AcO
AcO
O
S
OMe
5b (1H NMR)
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

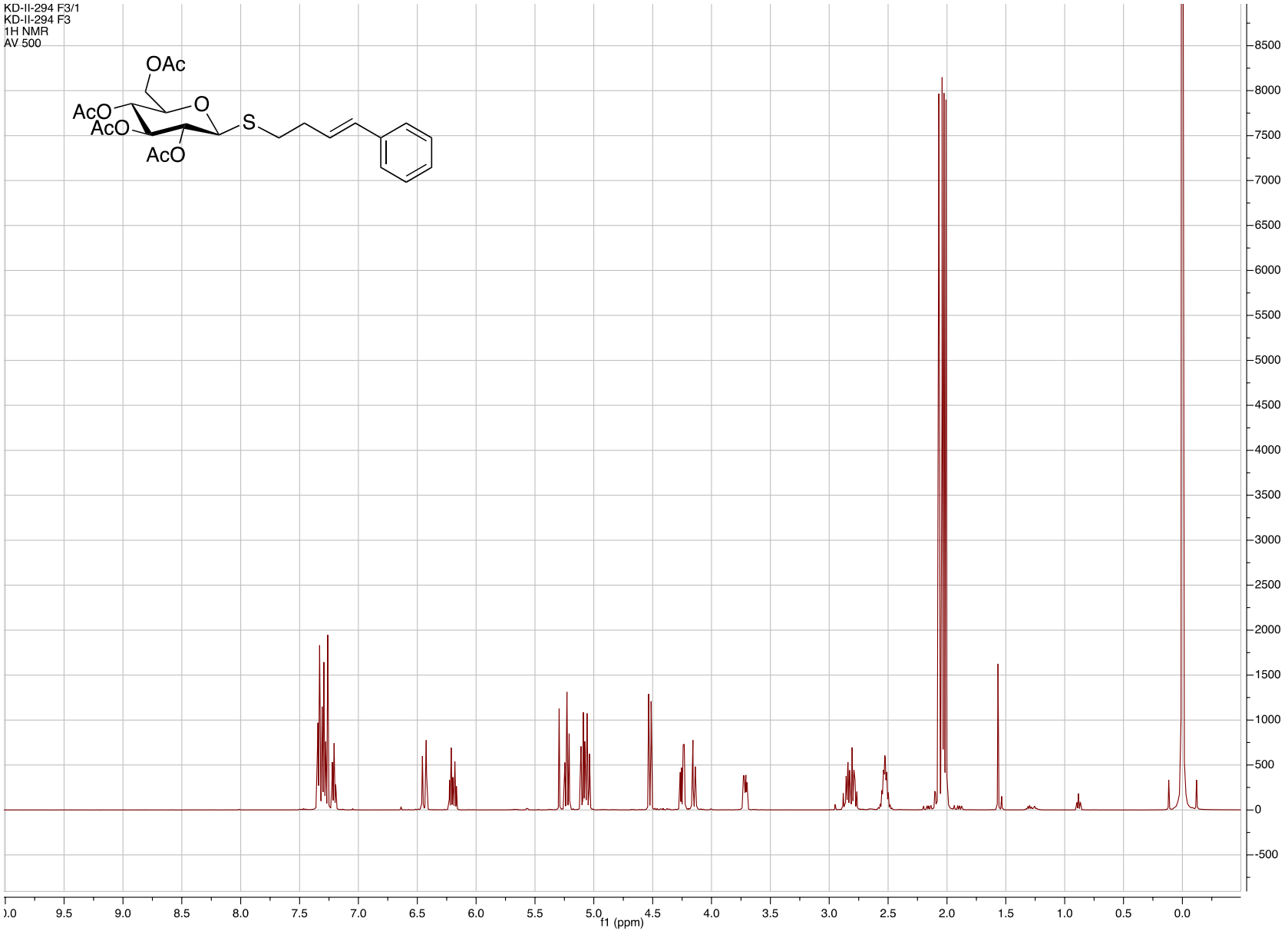

MS 199 (6) 13C.10.fid
MS 199 (6) 13C
OAc
AcO
AcO
AcO
O
S
OMe
5b
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

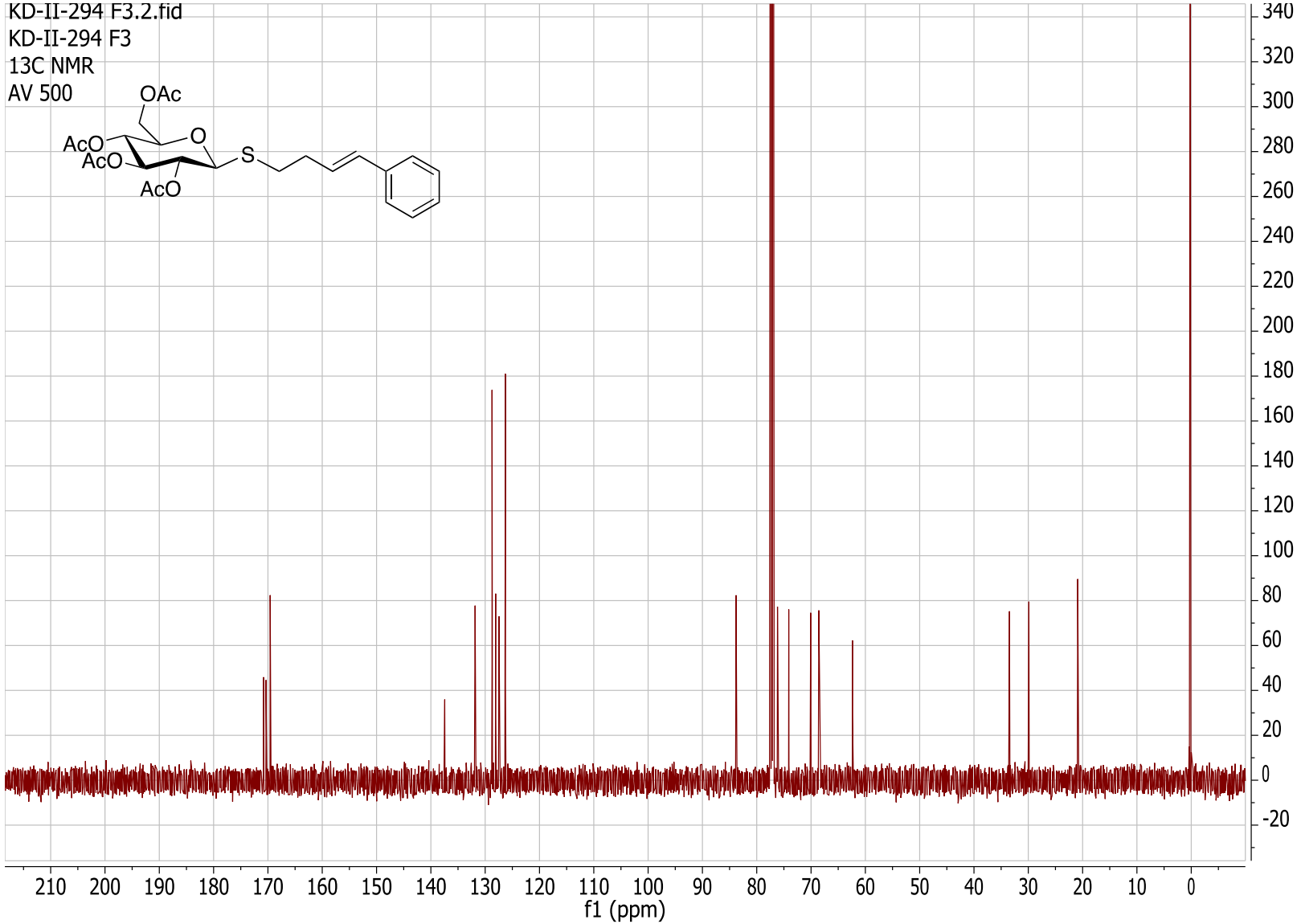

MS 203 (6).10.fid
MS 203 (6)
OBn
BnO
BnO
BnO
O
S
OMe
5a
4000
3500
3000
2500
2000
1500
1000
500
0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

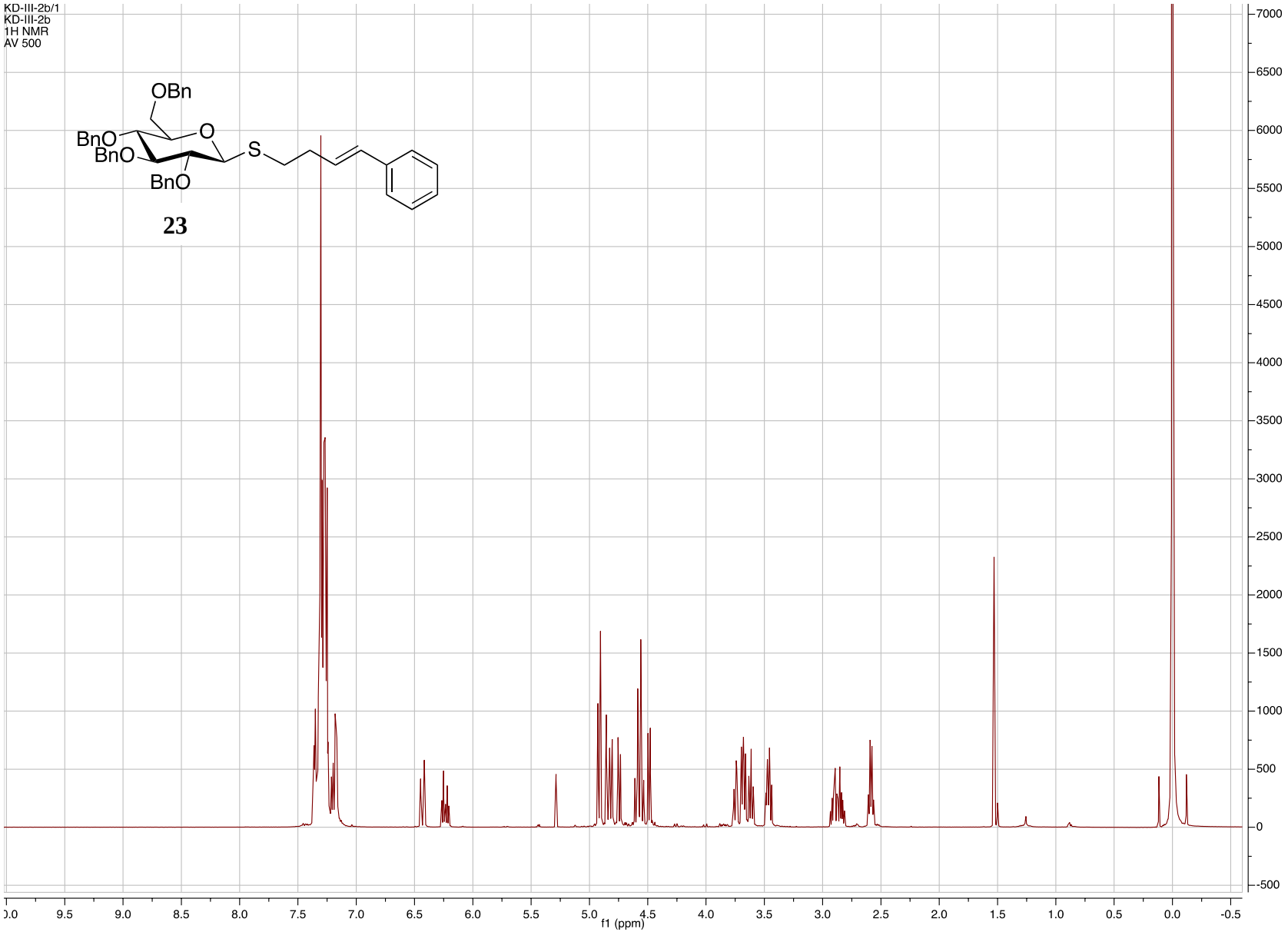

MS 203 (6) 13C.10.fid
MS 203 (6) 13C
OBn
BnO
BnO
BnO
O
S
OMe
5b
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

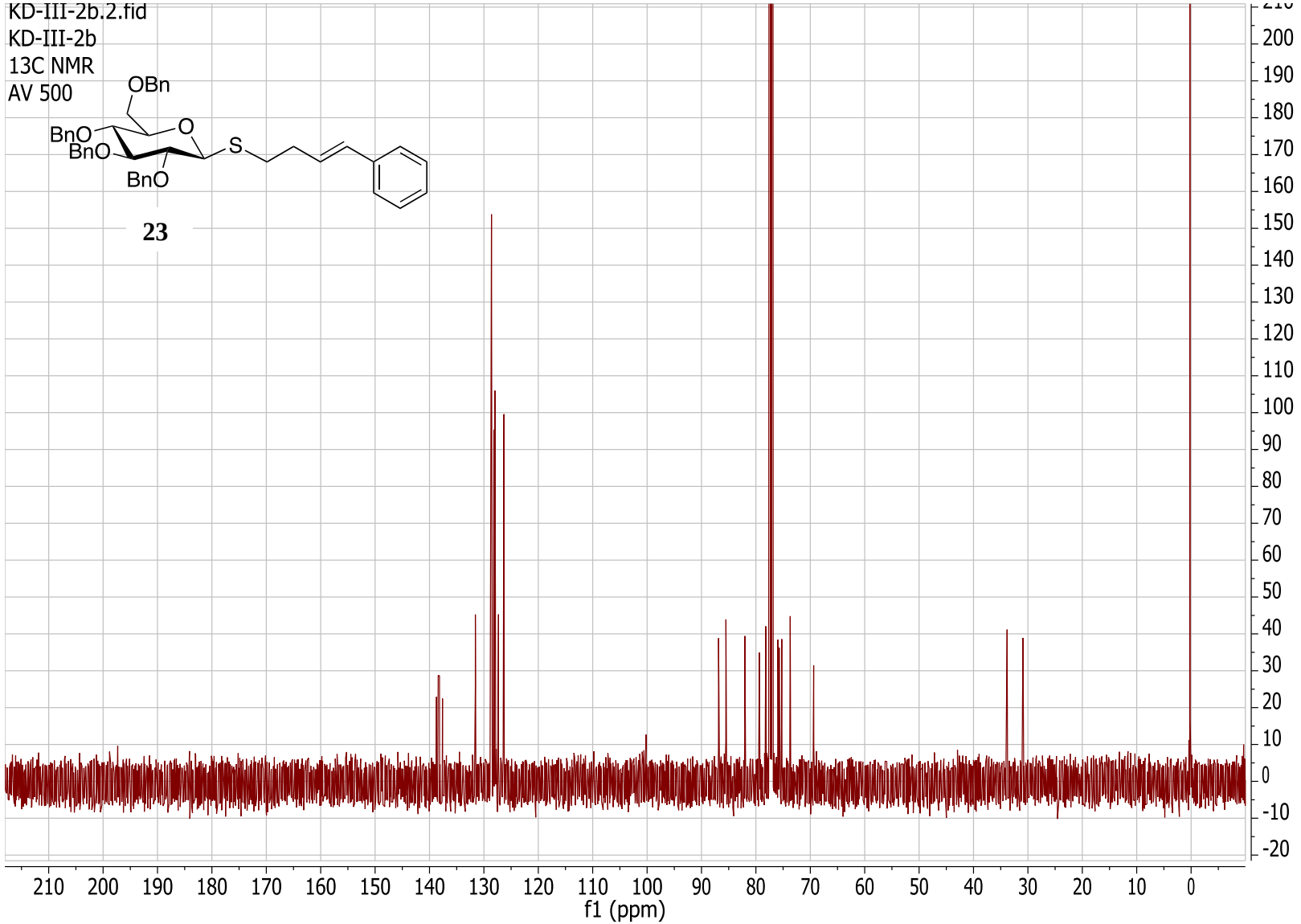

MS 269 (7).10.fid
MS 269 (7)
OBn
BnO
BnO
AcO
O
S
OMe
5f
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

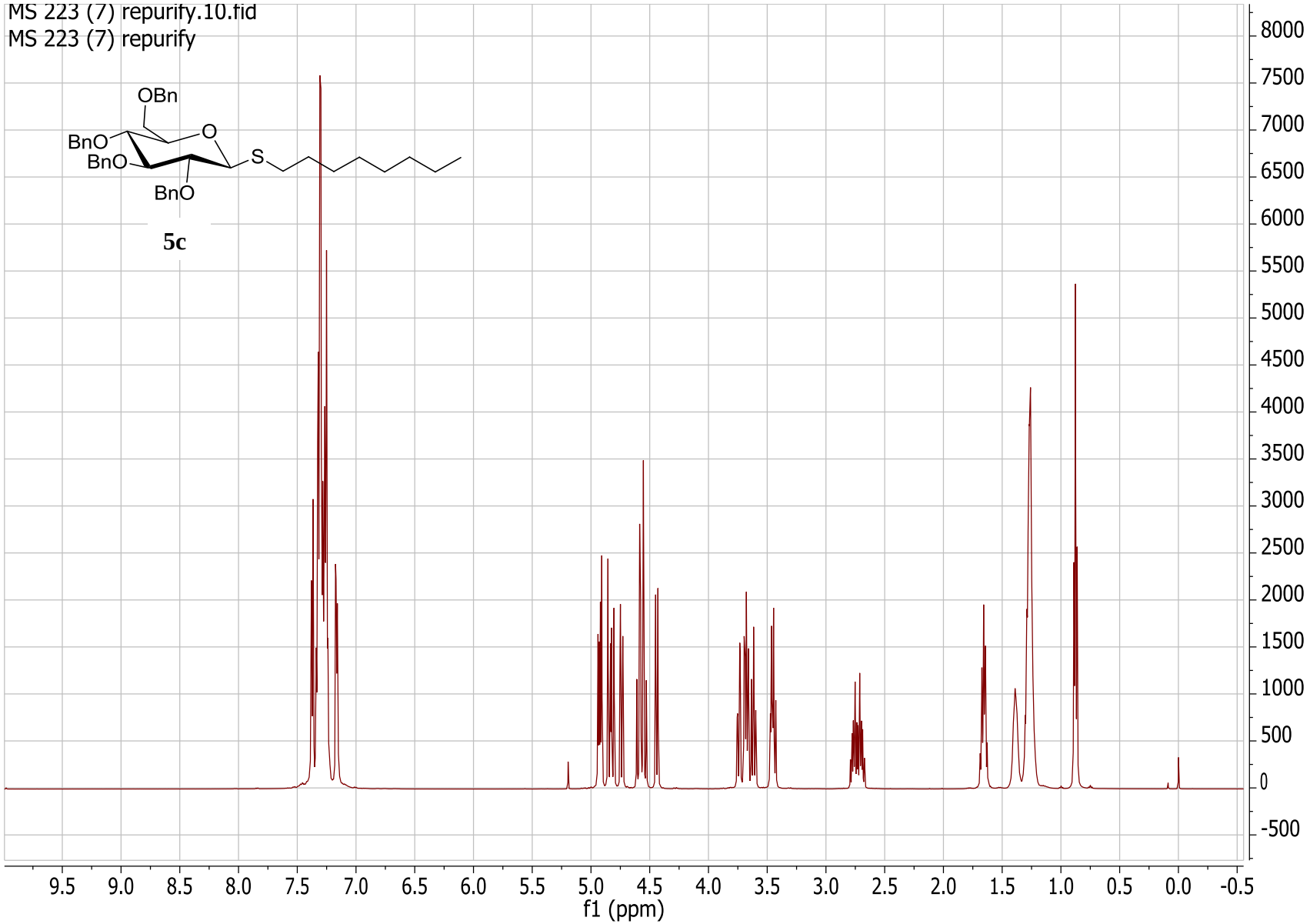

MS 269 (7) 13C.11.fid
MS 269 (7) 13C
OBn
BnO
BnO
O
S
AcO
OMe
5f
35000
30000
25000
20000
15000
10000
5000
0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

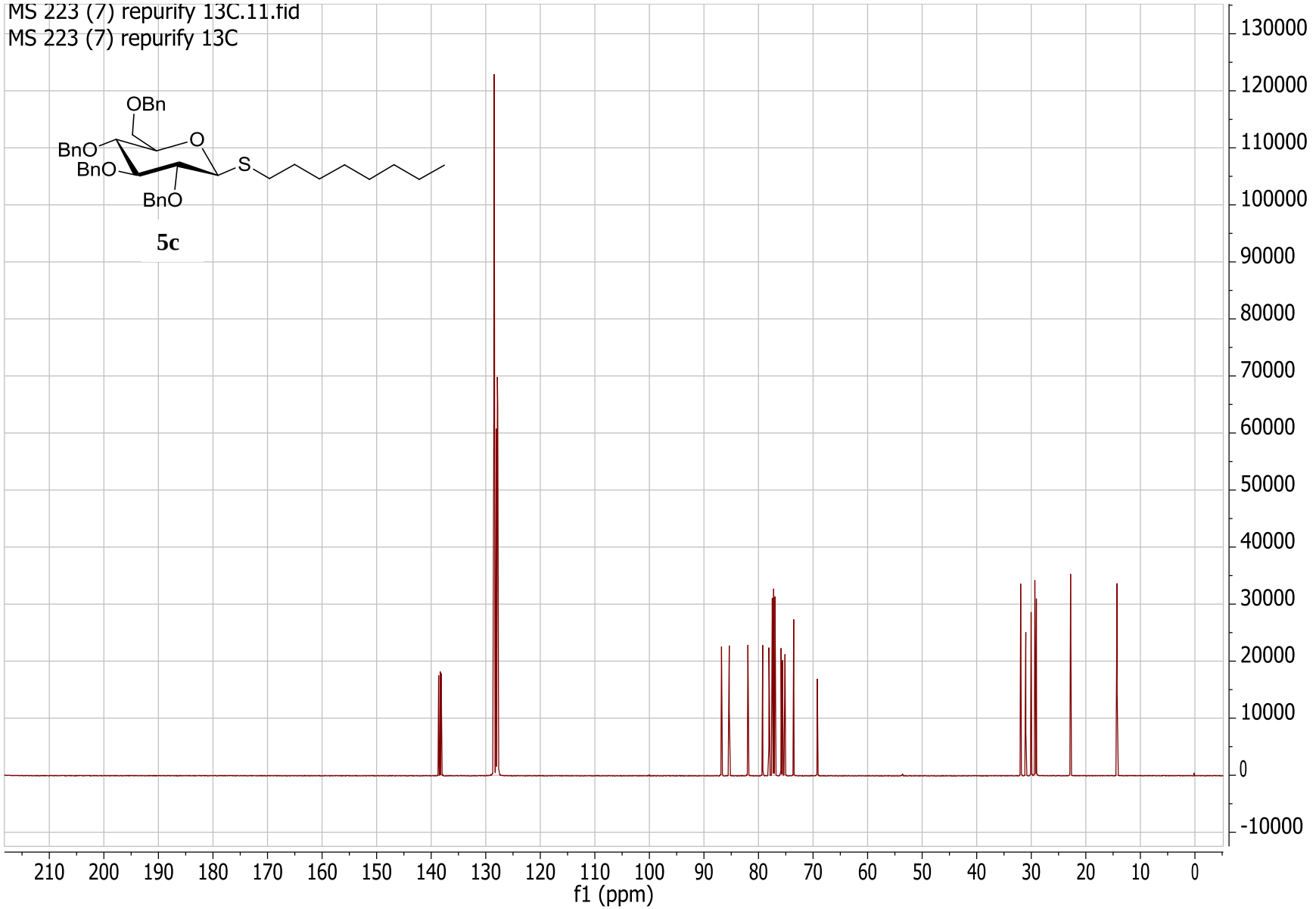

KD-II-294 F3/1
KD-II-294 F3
1H NMR
AV 500
OAc
AcO
AcO
AcO
O
S
f1 (ppm)

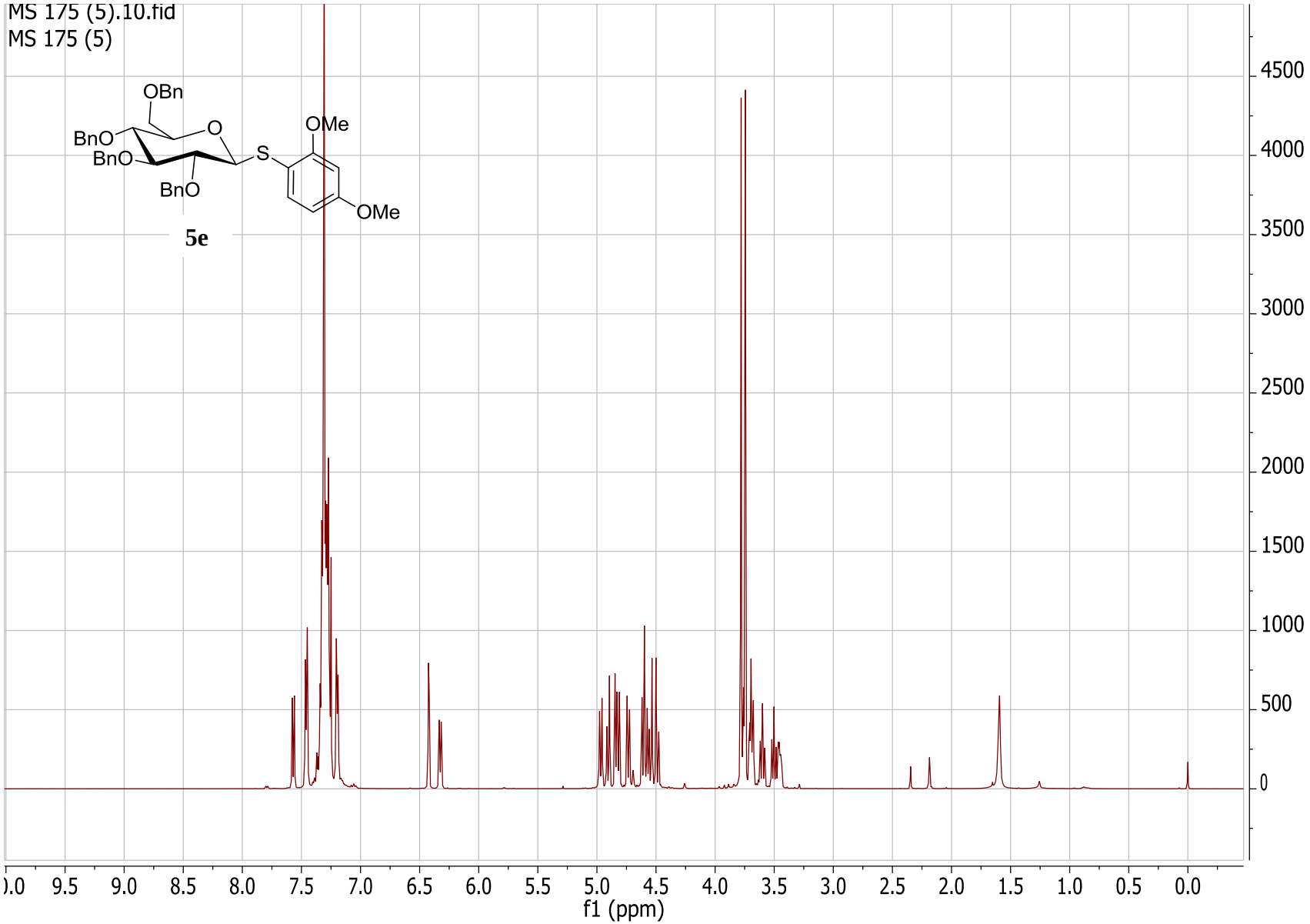

KD-II-294 F3.2.fid
KD-II-294 F3
13C NMR
AV 500
OAc
AcO
AcO
AcO
O
S
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

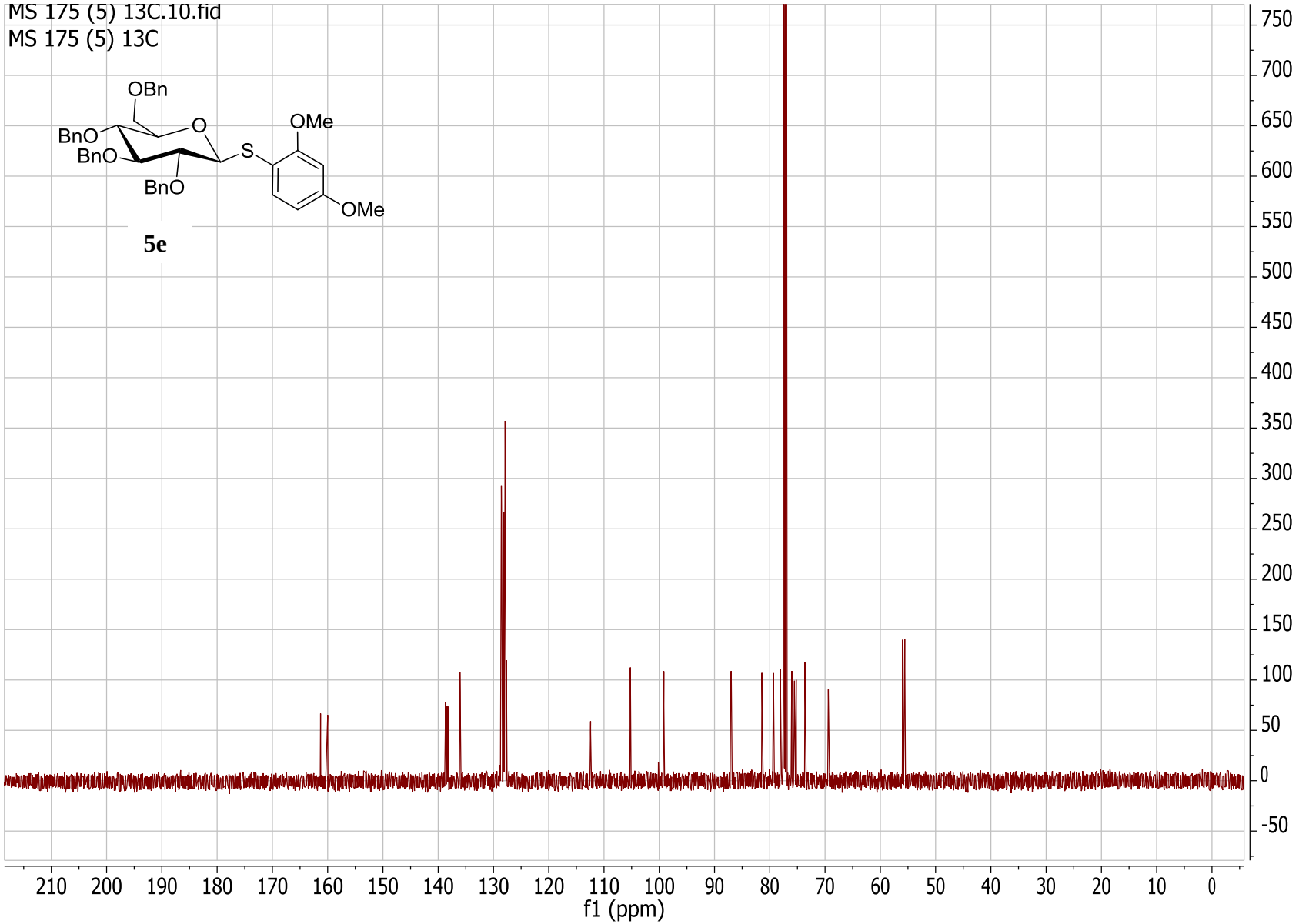

KD-III-2b/1
KD-III-2b
1H NMR
AV 500
OBn
BnO
BnO
BnO
O
S
23
f1 (ppm)

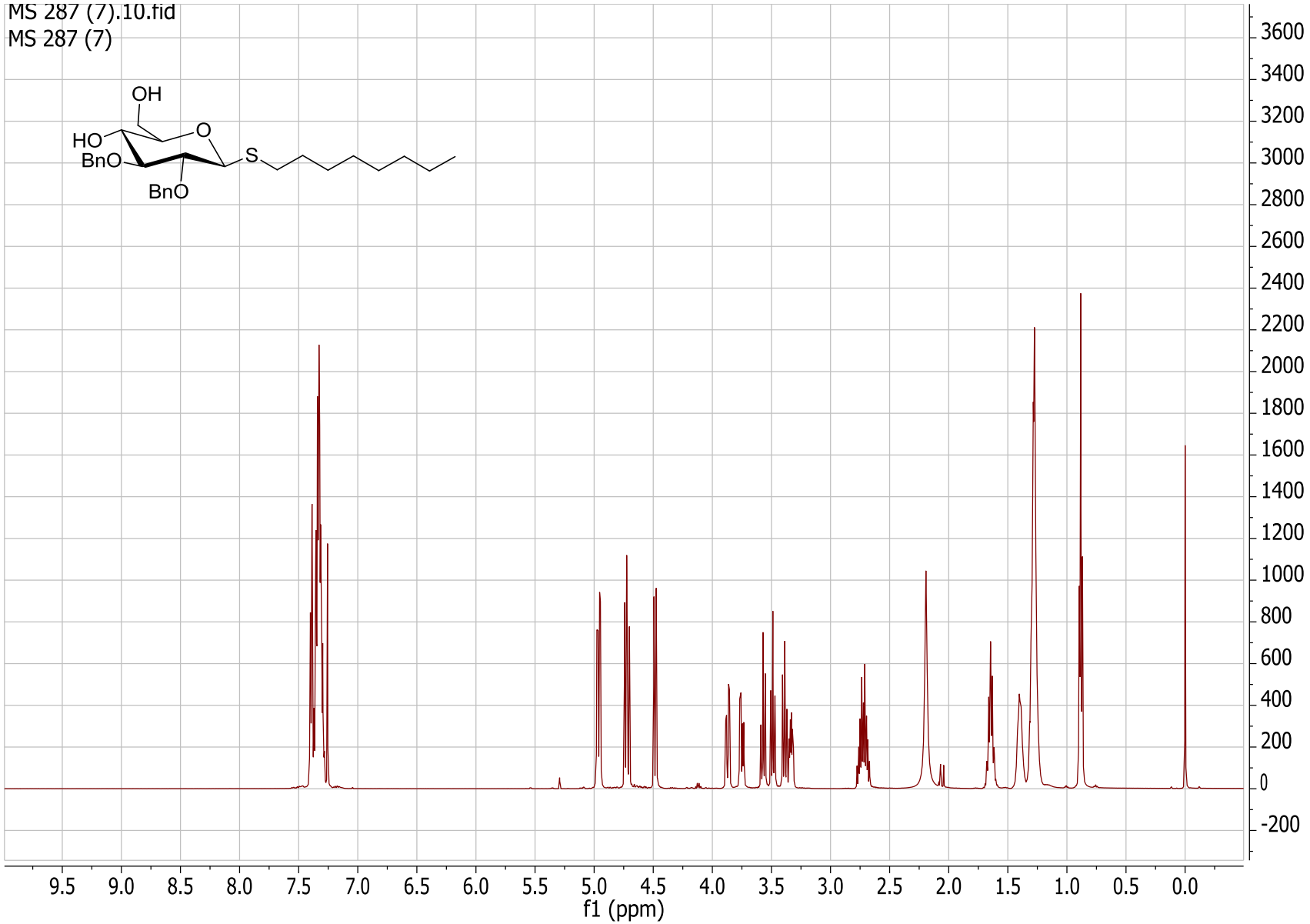

KD-III-2b.2.fid
KD-III-2b
13C NMR
AV 500
OBn
BnO
BnO
BnO
O
S
23
f1 (ppm)

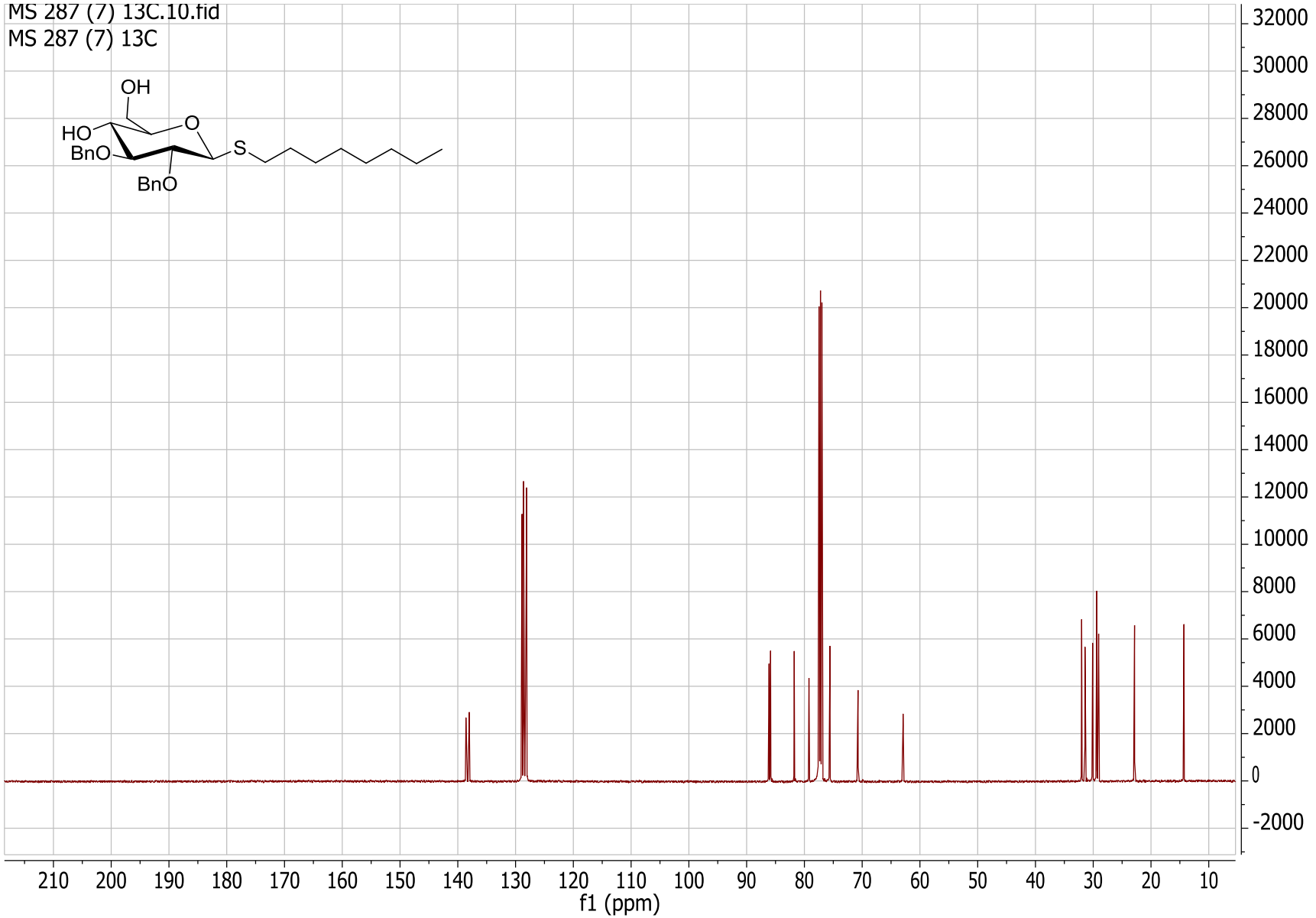

MS 223 (7) repurify.10.fid
MS 223 (7) repurify
OBn
BnO
O
BnO
S
BnO
5c
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

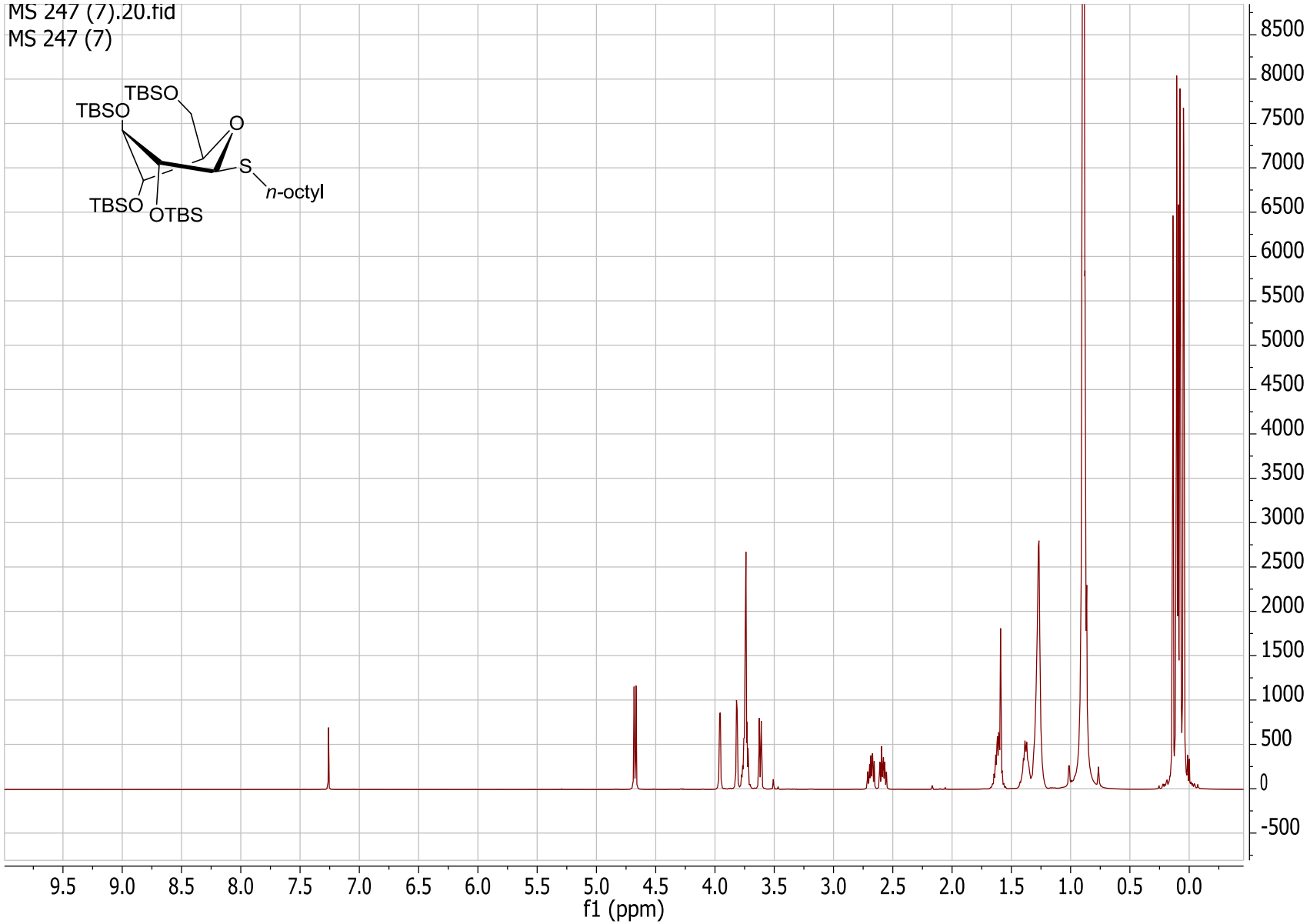

MS 223 (7) repurify 13C.11.fid
MS 223 (7) repurify 13C
OBn
BnO
O
BnO
S
BnO
5c
130000
120000
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

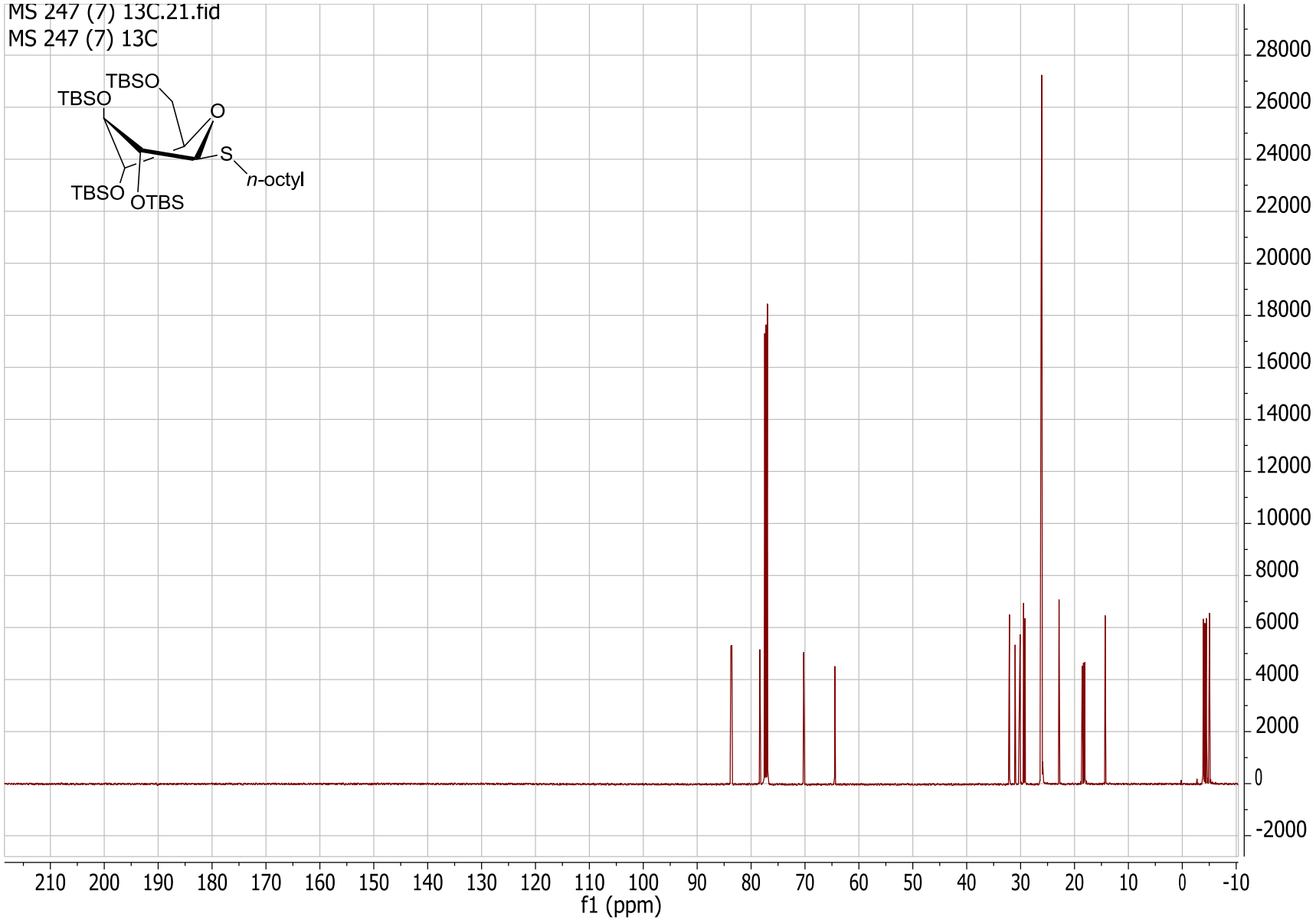

MS 175 (5).10.fid
MS 175 (5)
OBn
BnO
BnO
BnO
O
S
OMe
OMe
5e
4500
4000
3500
3000
2500
2000
1500
1000
500
0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

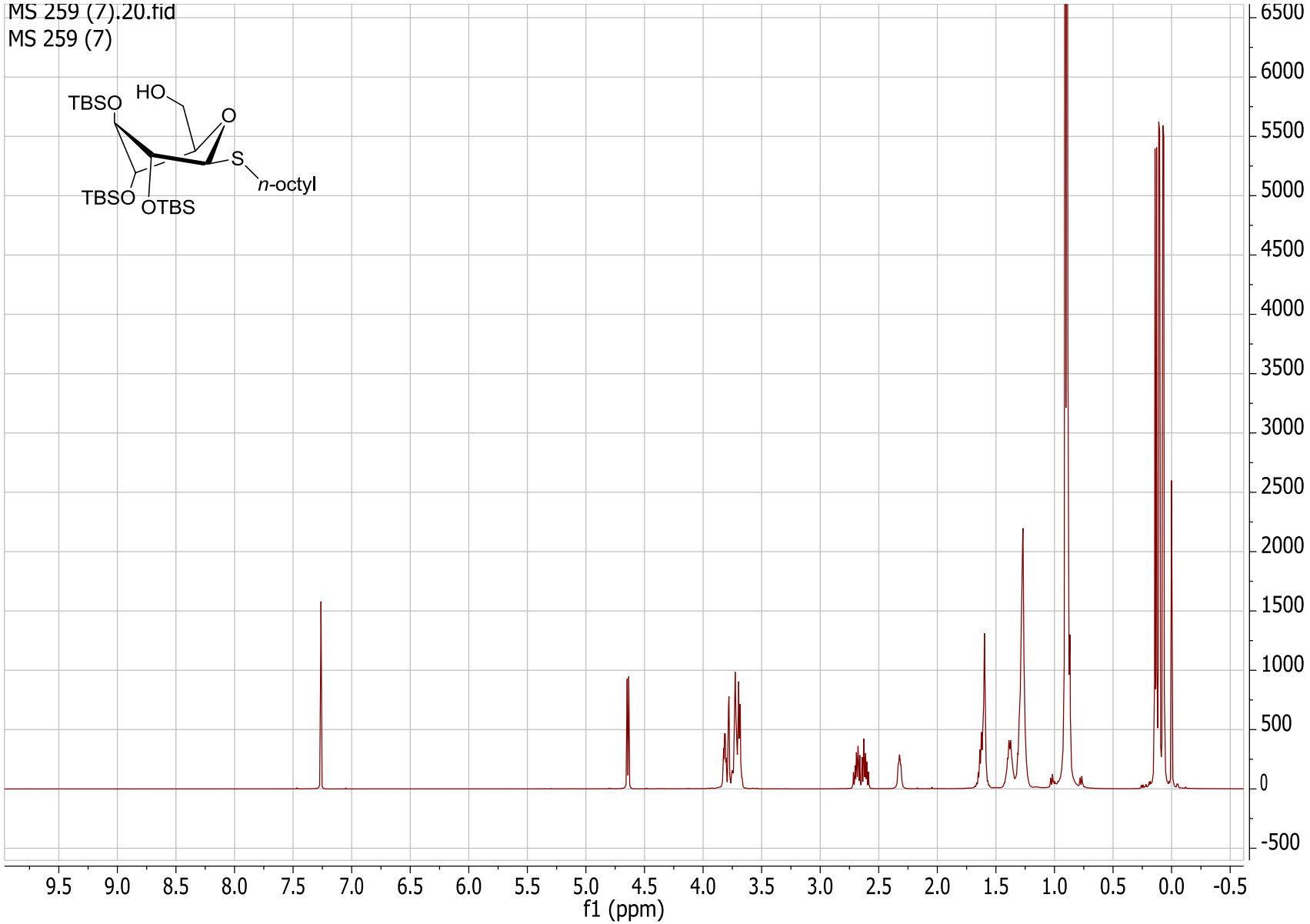

MS 175 (5) 13C.10.fid
MS 175 (5) 13C
OBn
BnO
BnO
BnO
O
S
OMe
OMe
5e
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

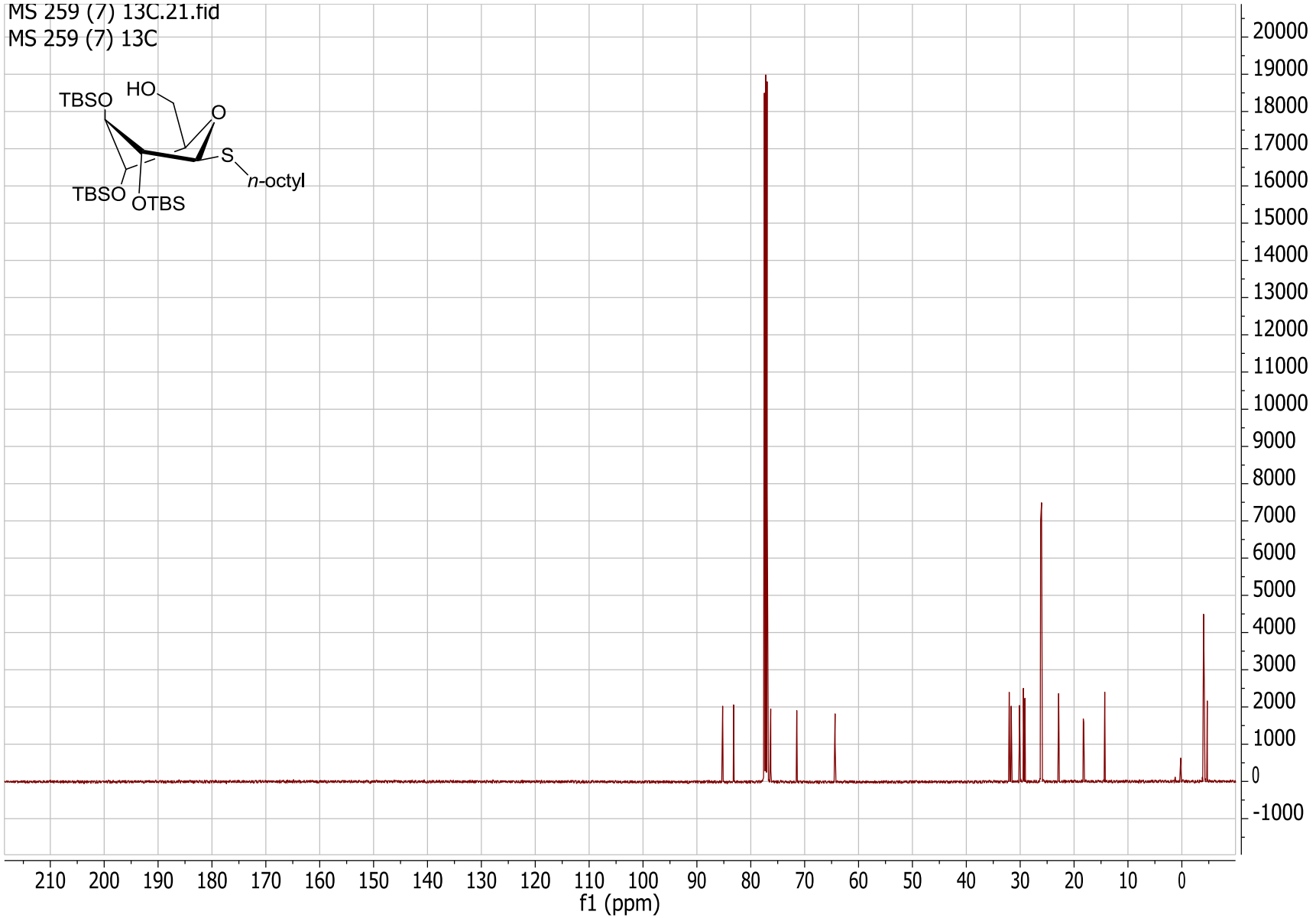

MS 287 (7).10.fid
MS 287 (7)
OH
HO
O
BnO
S
BnO
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

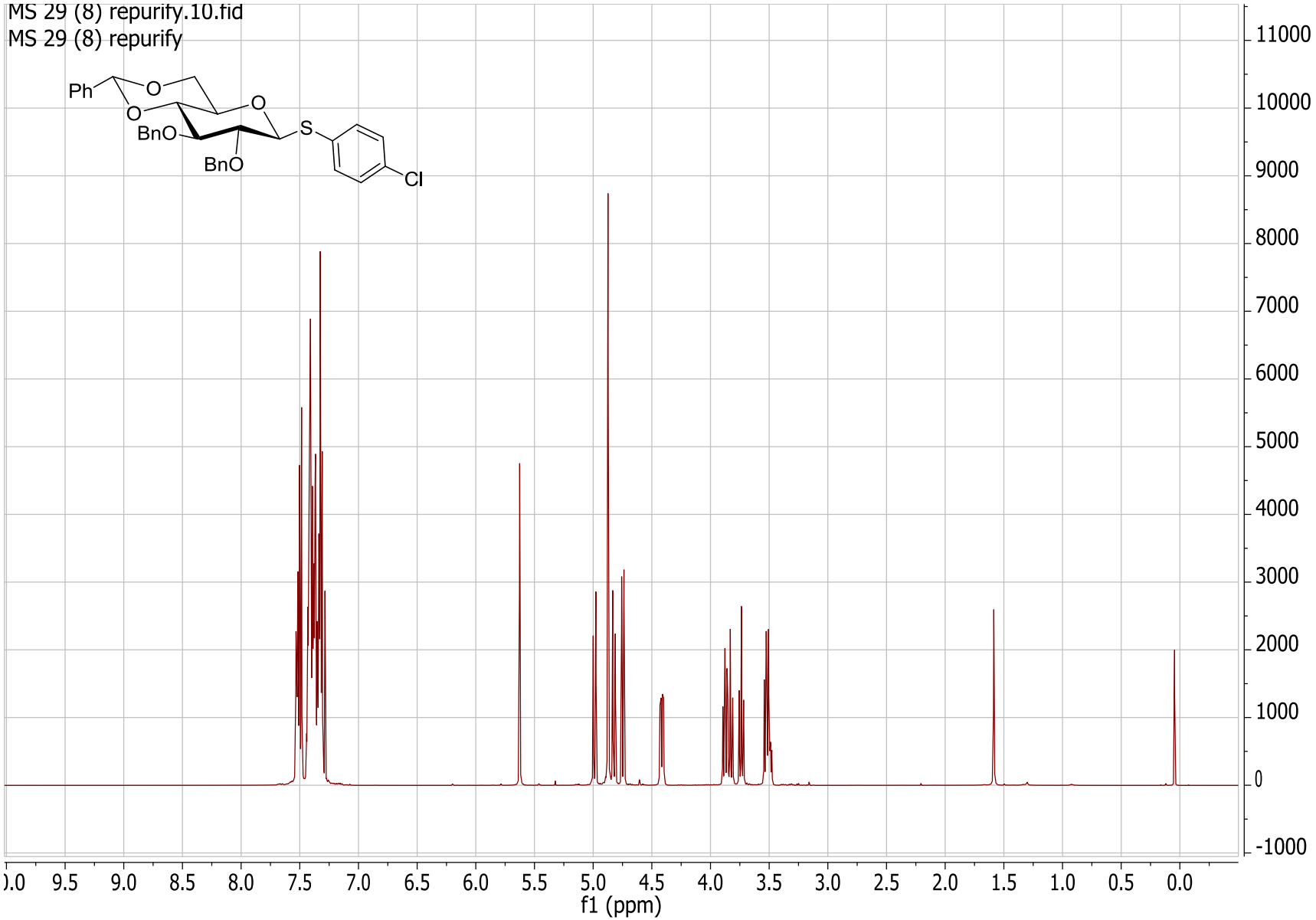

MS 287 (7) 13C.10.fid
MS 287 (7) 13C
OH
HO
O
BnO
S
BnO
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

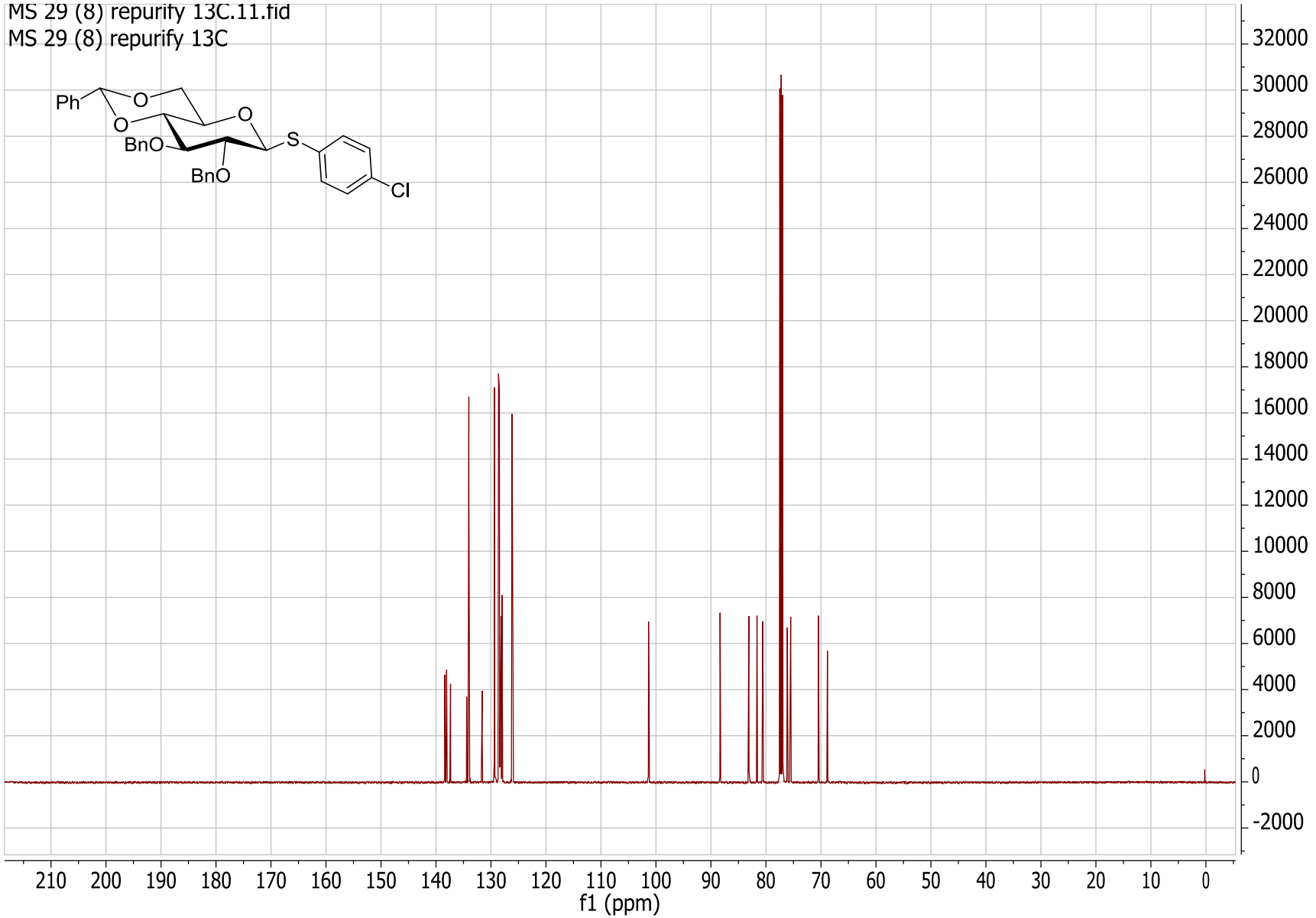

MS 247 (7).20.fid
MS 247 (7)
TBSO
TBSO
O
S
n-octyl
TBSO
OTBS
8500
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

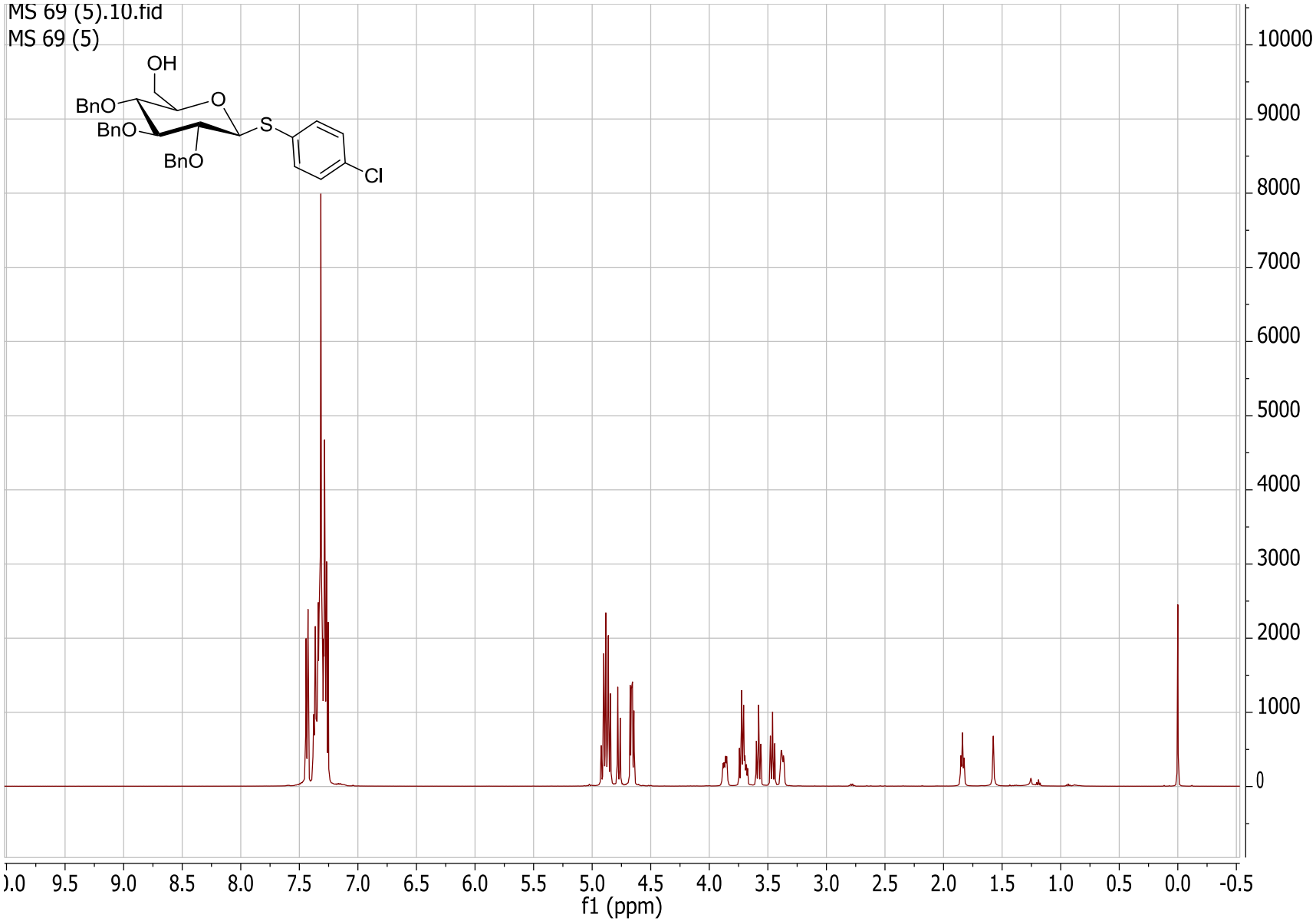

MS 247 (7) 13C.21.fid
MS 247 (7) 13C
TBSO
TBSO
O
S
n-octyl
TBSO
OTBS
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

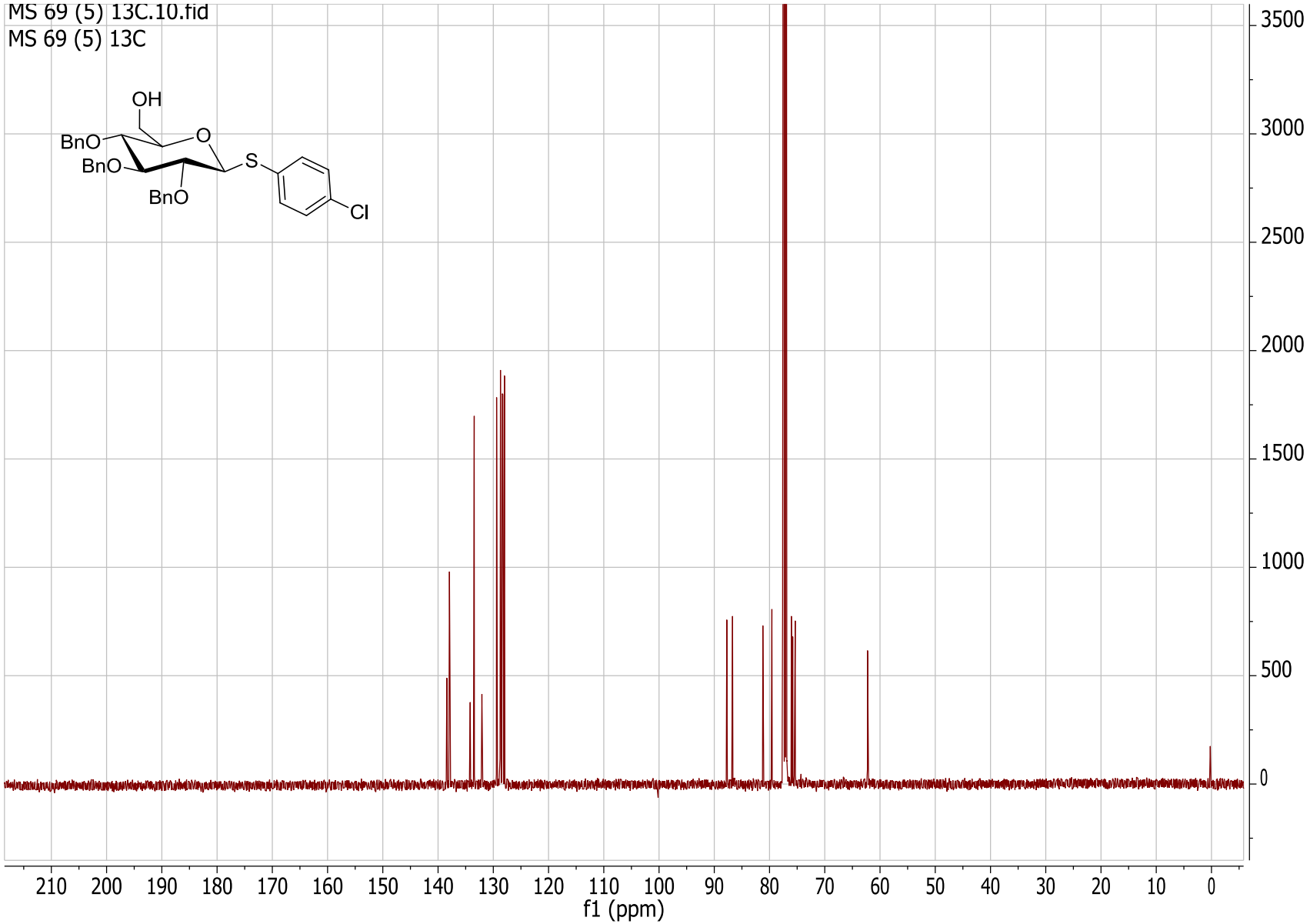

MS 259 (7).20.fid
MS 259 (7)
TBSO
HO
O
S
n-octyl
TBSO
OTBS
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

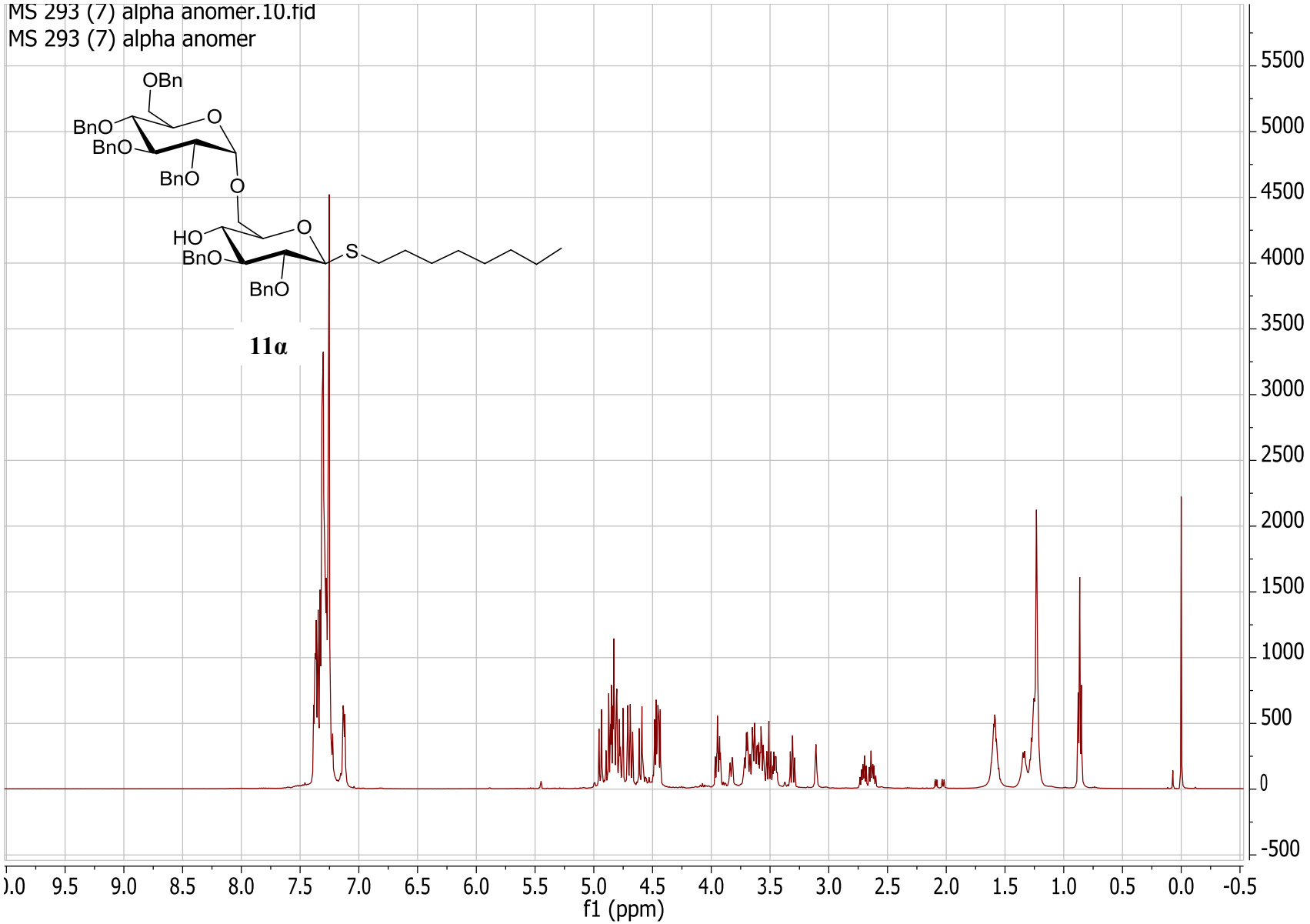

MS 259 (7) 13C.21.fid
MS 259 (7) 13C
TBSO
HO
O
S
n-octyl
TBSO
OTBS
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

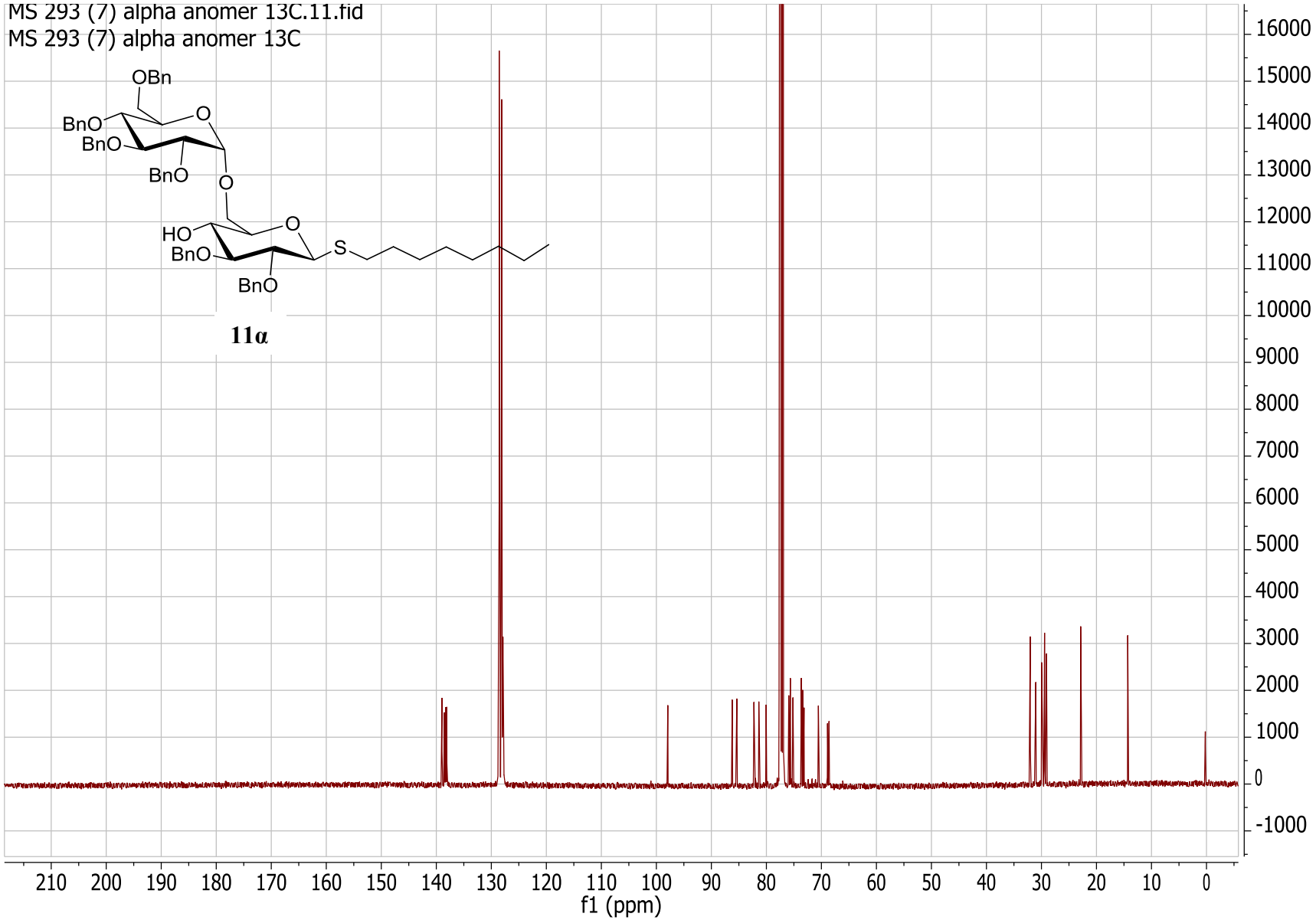

MS 29 (8) repurify.10.fid
MS 29 (8) repurify
Ph
O
O
O
BnO
BnO
S
Cl
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

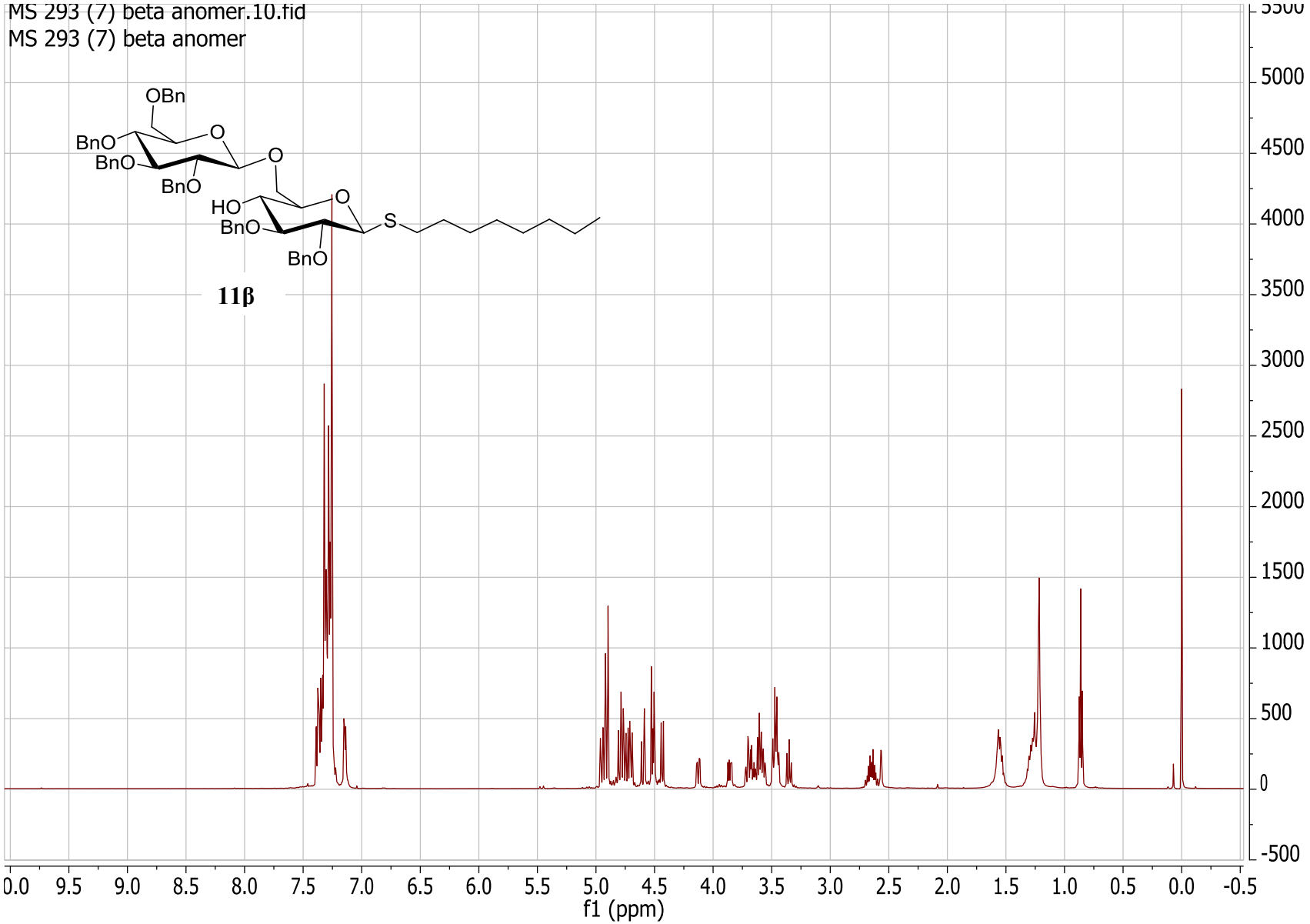

MS 29 (8) repurify 13C.11.fid
MS 29 (8) repurify 13C
Ph
O
O
O
BnO
BnO
S
Cl
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

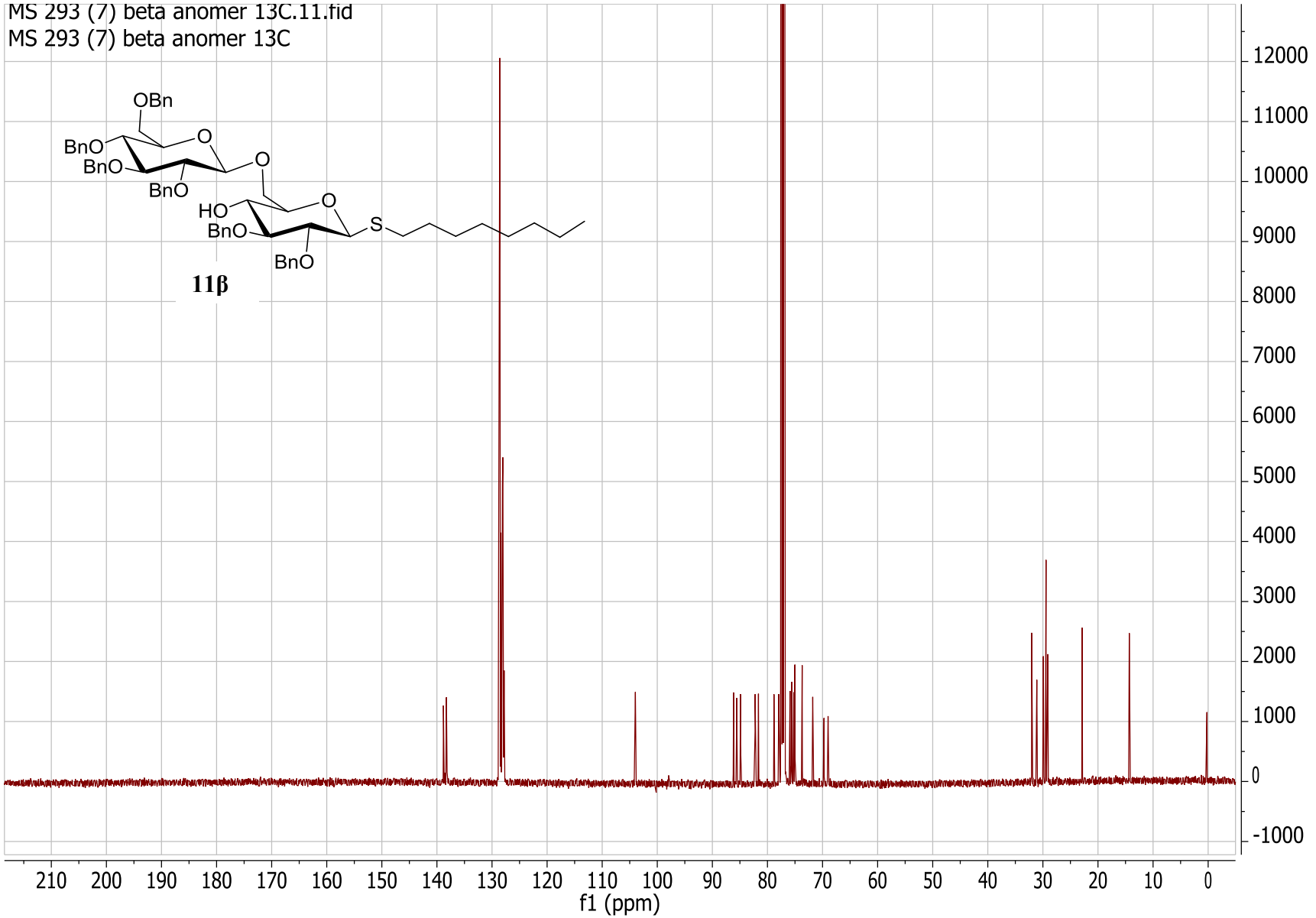

MS 69 (5).10.fid
MS 69 (5)
OH
BnO
BnO
BnO
O
S
Cl
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

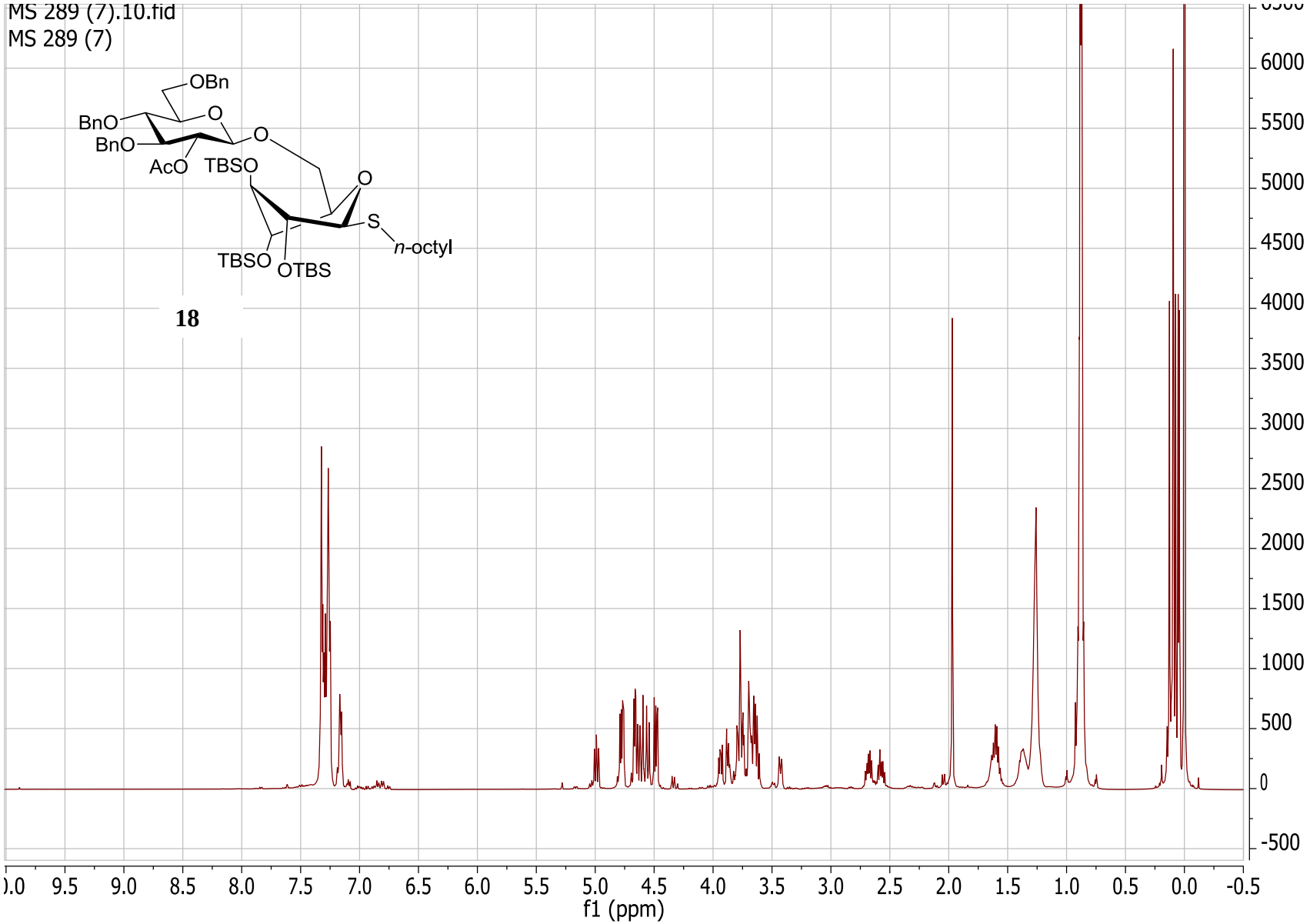

MS 69 (5) 13C.10.fid
MS 69 (5) 13C
OH
BnO
BnO
BnO
O
S
Cl
3500
3000
2500
2000
1500
1000
500
0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

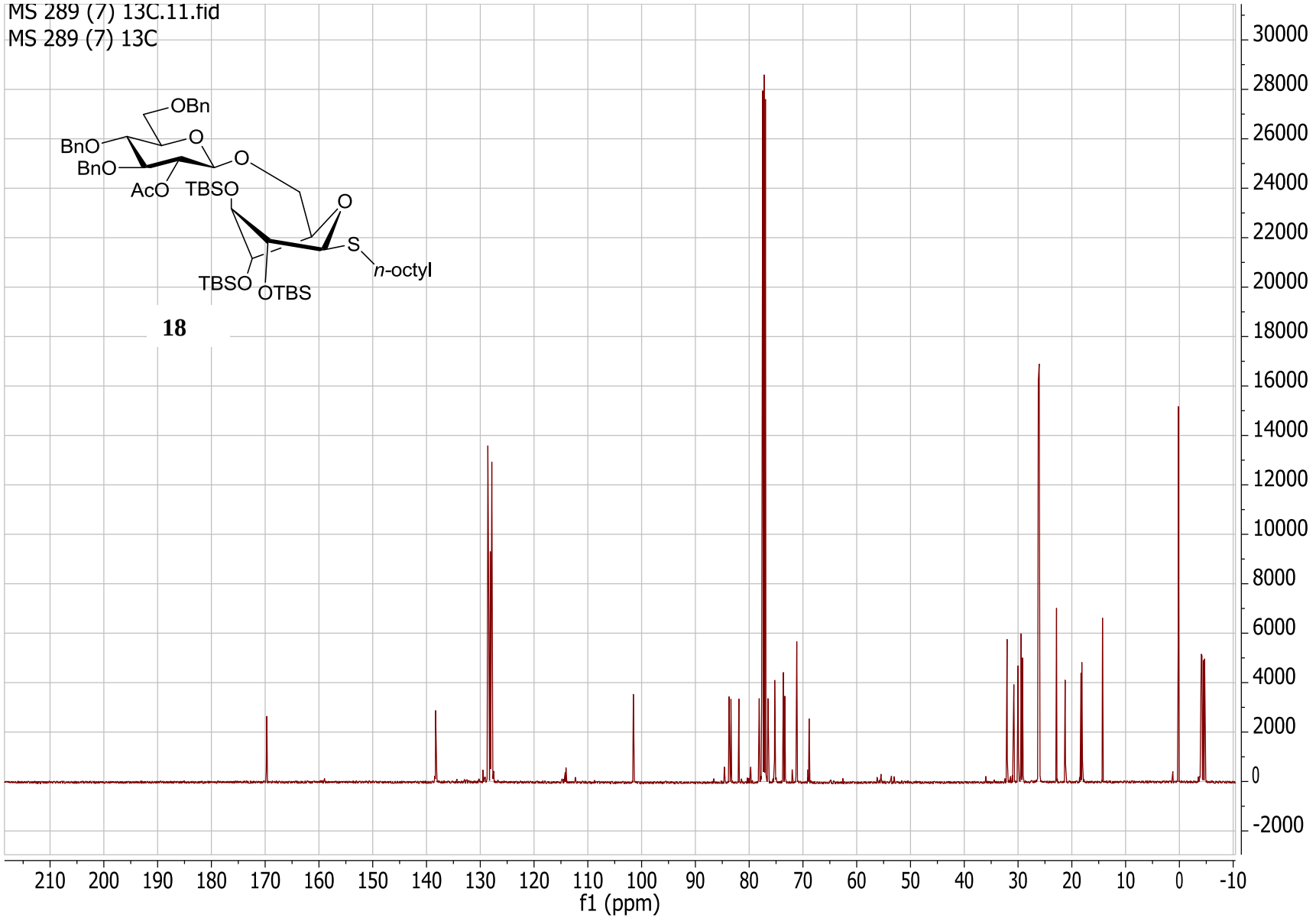

MS 293 (7) alpha anomer.10.fid
MS 293 (7) alpha anomer
OBn
BnO
BnO
BnO
O
O
HO
BnO
BnO
O
S
11α
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

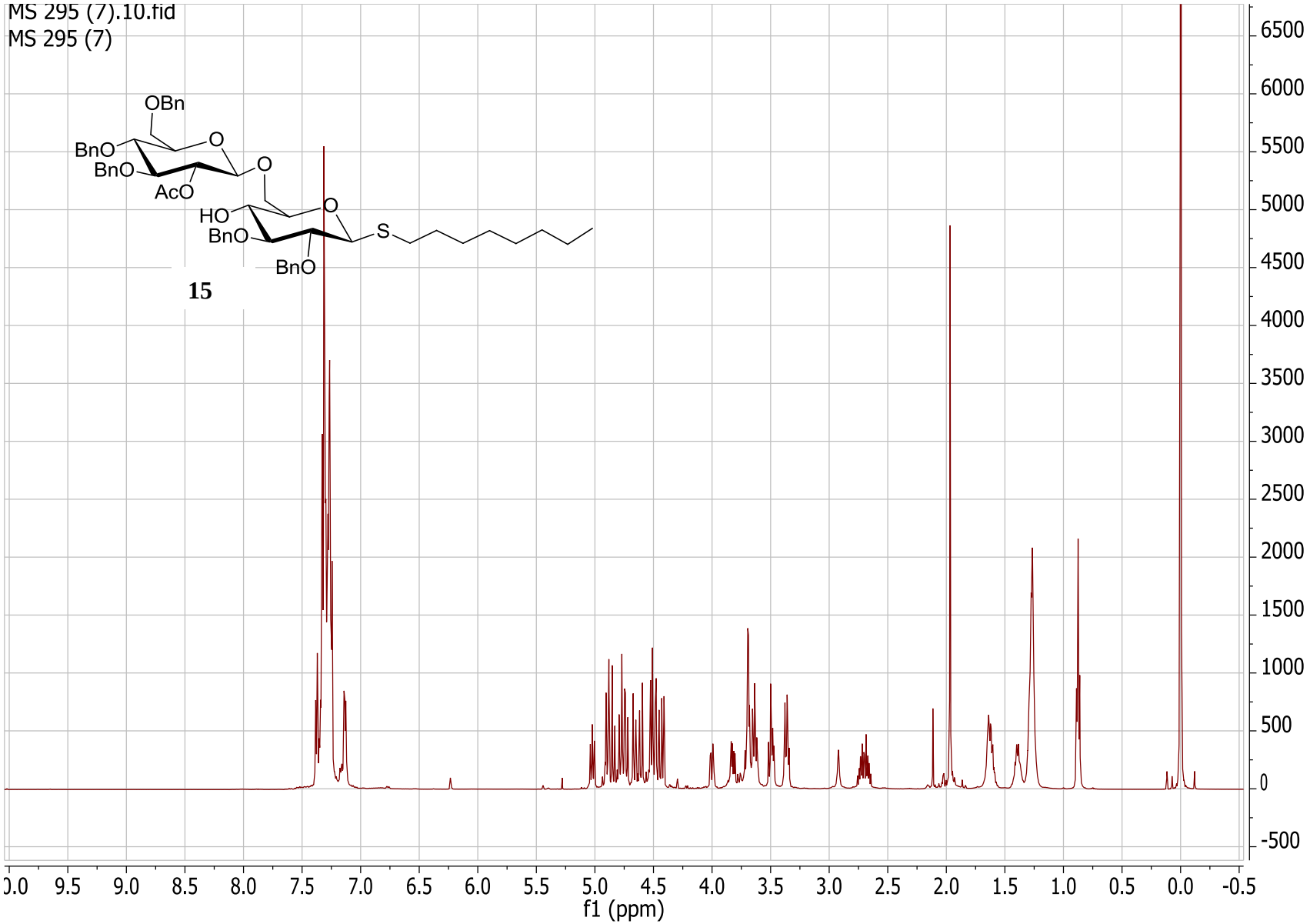

MS 293 (7) alpha anomer 13C.11.fid
MS 293 (7) alpha anomer 13C
OBn
BnO
BnO
BnO
O
O
HO
BnO
BnO
O
S
11α
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

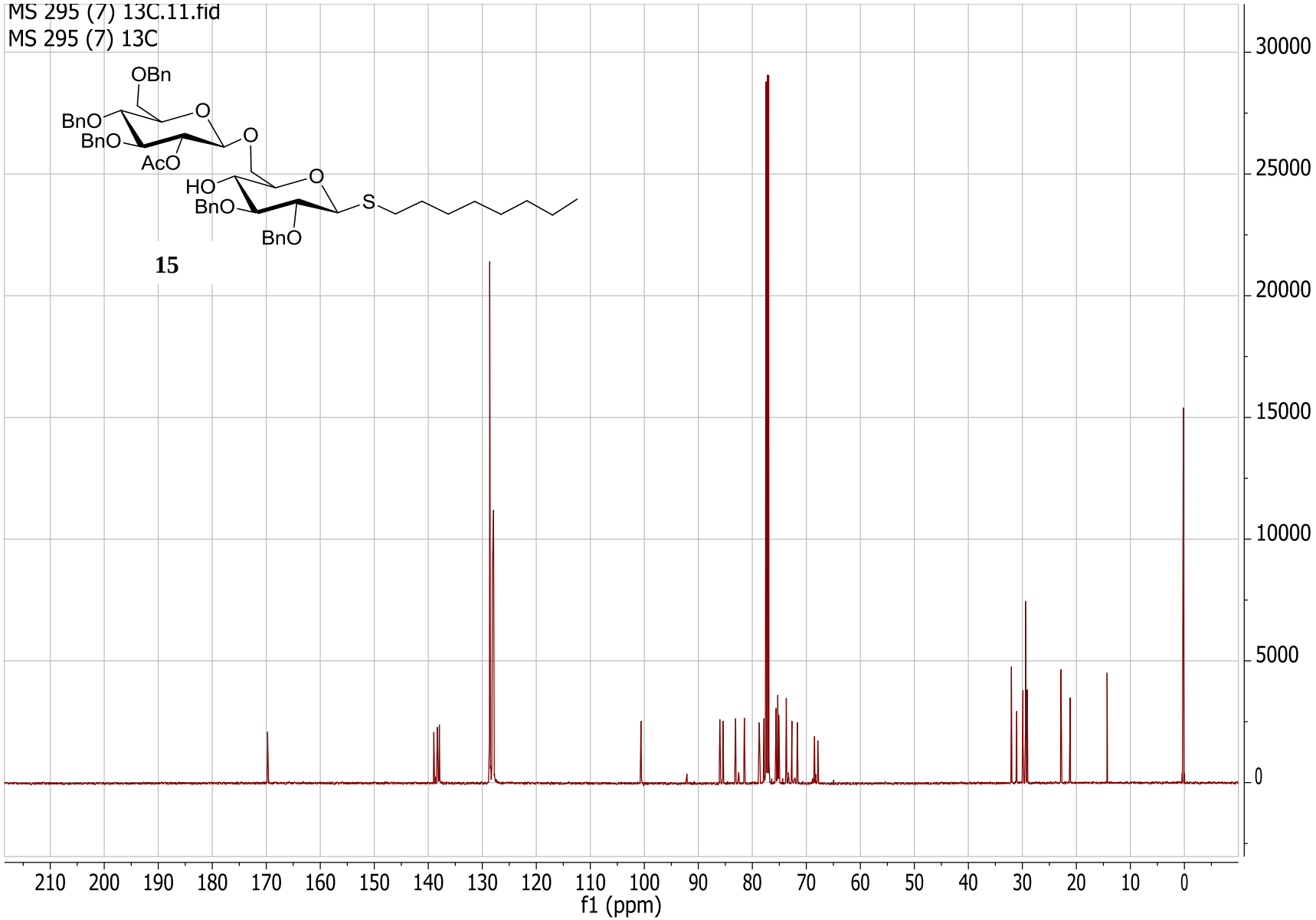

MS 293 (7) beta anomer.10.fid
MS 293 (7) beta anomer
OBn
BnO
BnO
BnO
O
O
HO
BnO
BnO
O
S
11β
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

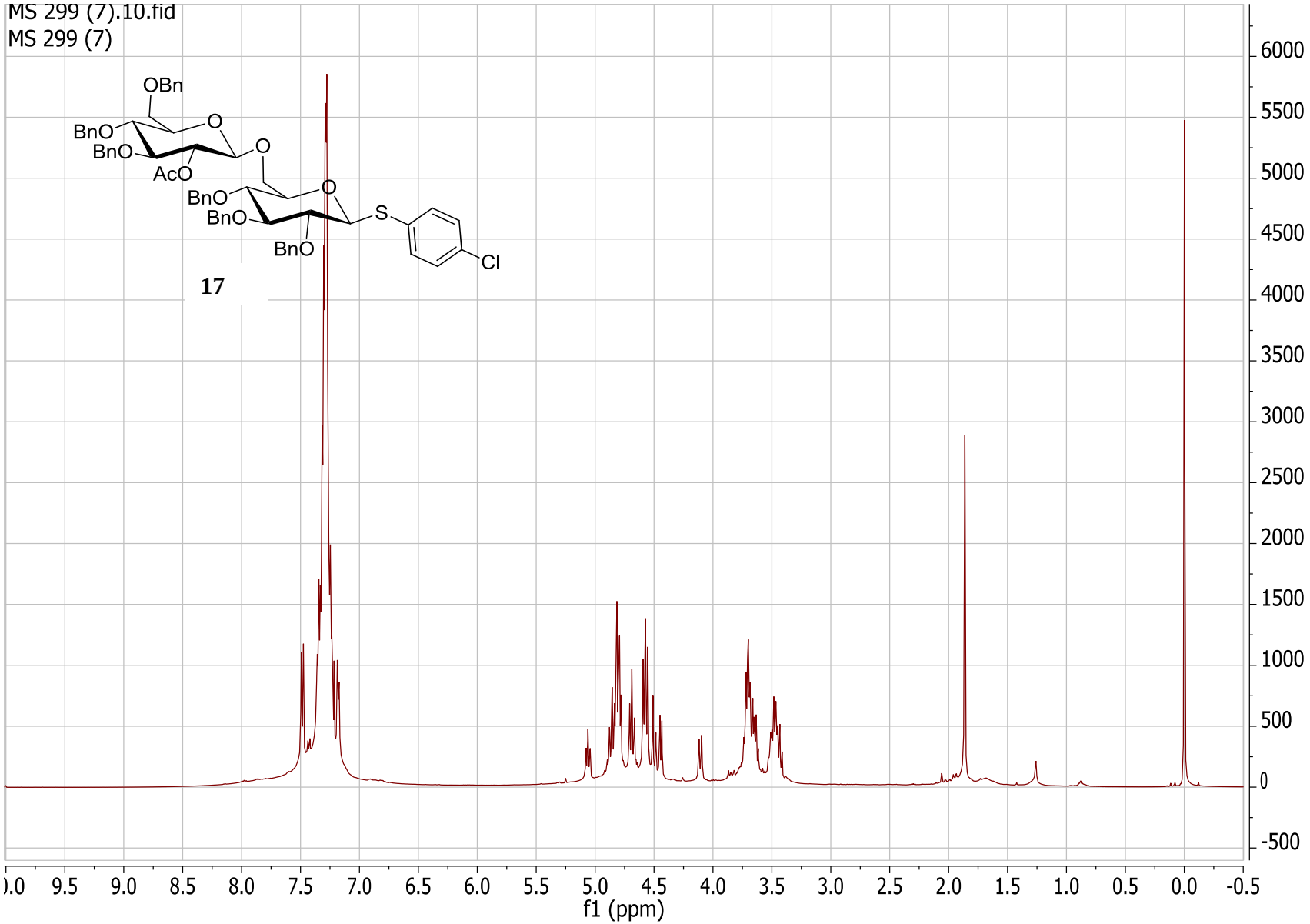

MS 293 (7) beta anomer 13C.11.fid
MS 293 (7) beta anomer 13C
OBn
BnO
BnO
BnO
O
O
HO
BnO
BnO
O
S
11β
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

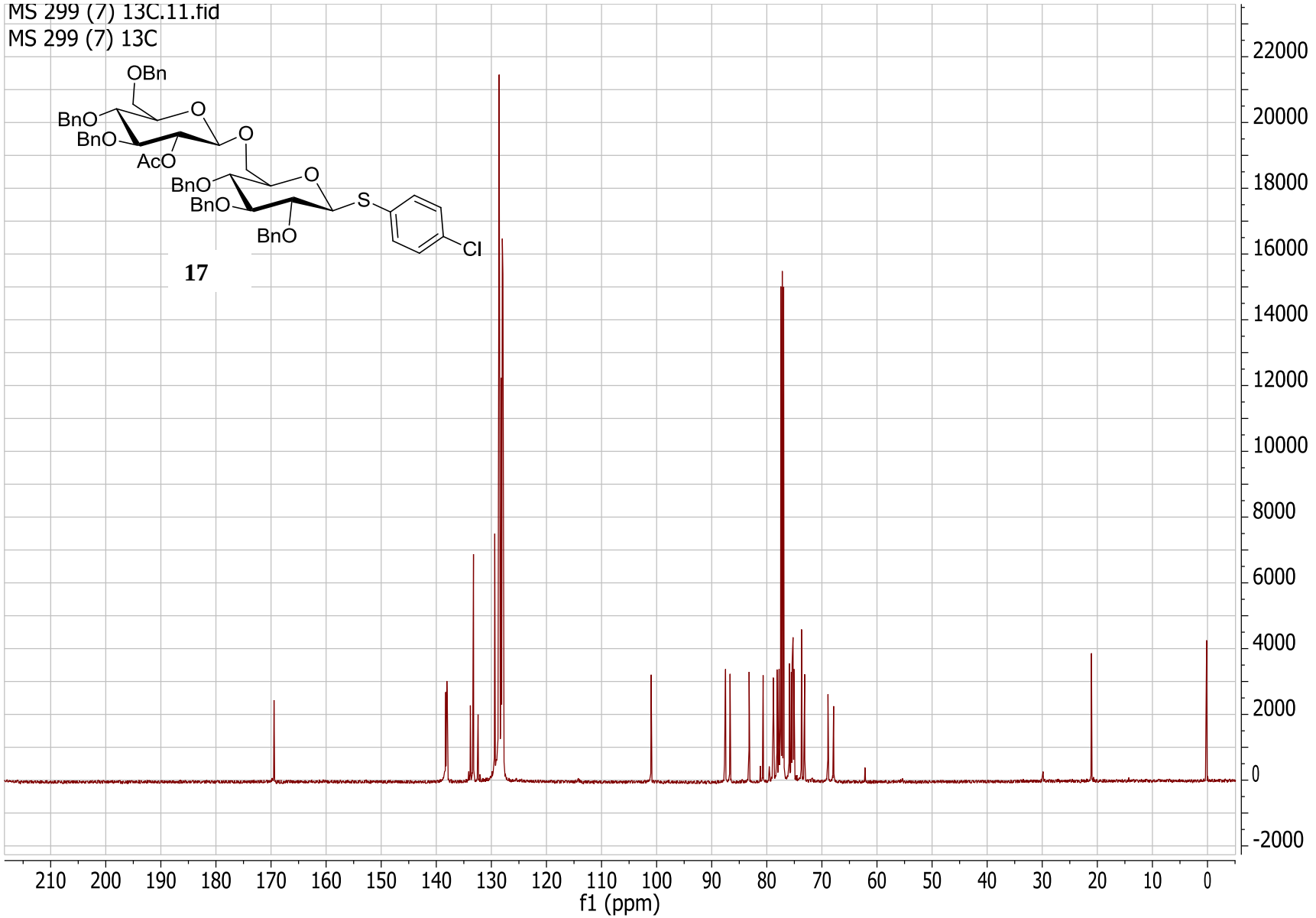

MS 289 (7).10.fid
MS 289 (7)
OBn
BnO
BnO
AcO
TBSO
TBSO
OTBS
S
n-octyl
18
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

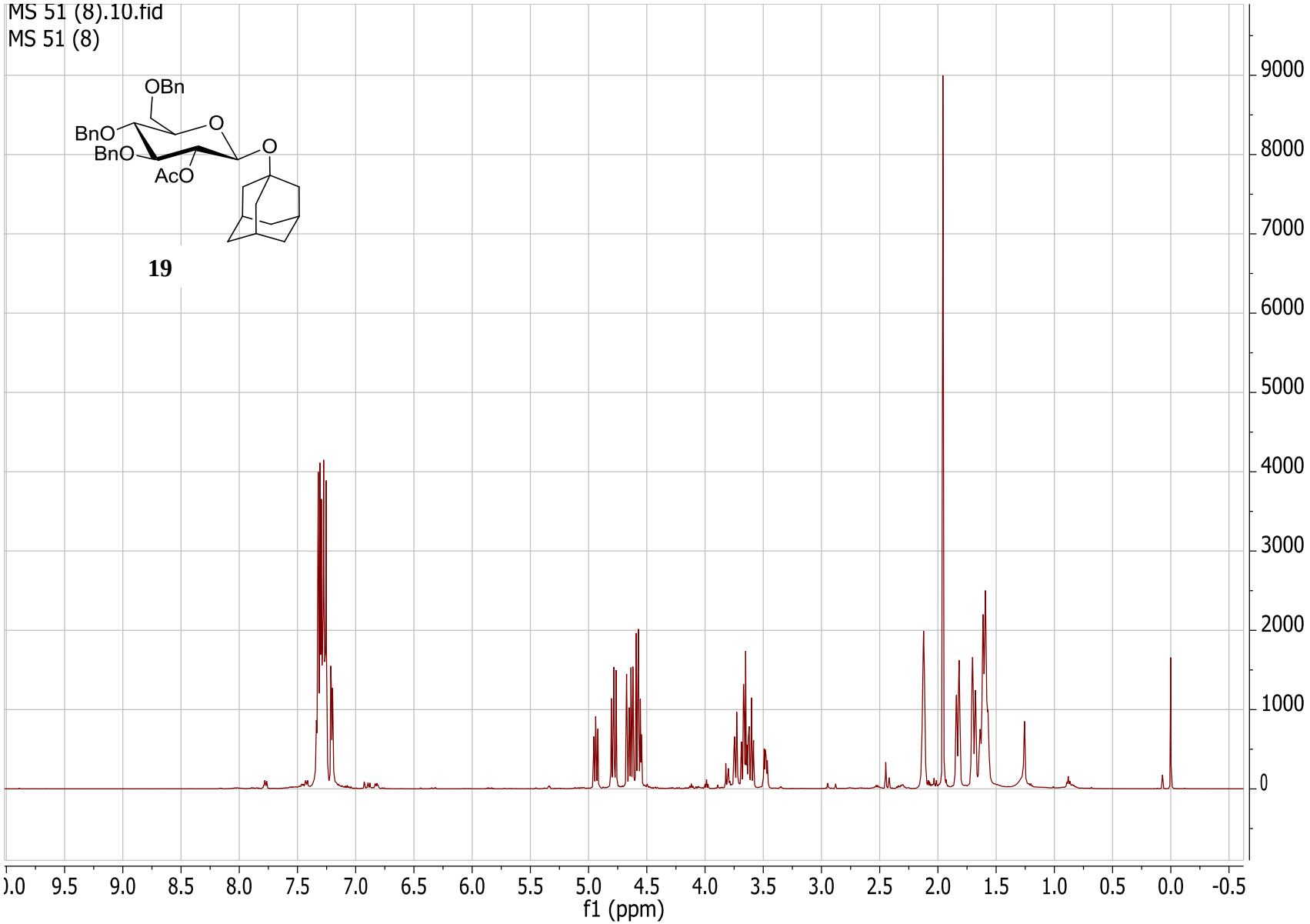

MS 289 (7) 13C.11.fid
MS 289 (7) 13C
OBn
BnO
BnO
AcO
TBSO
TBSO
OTBS
S
n-octyl
18
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

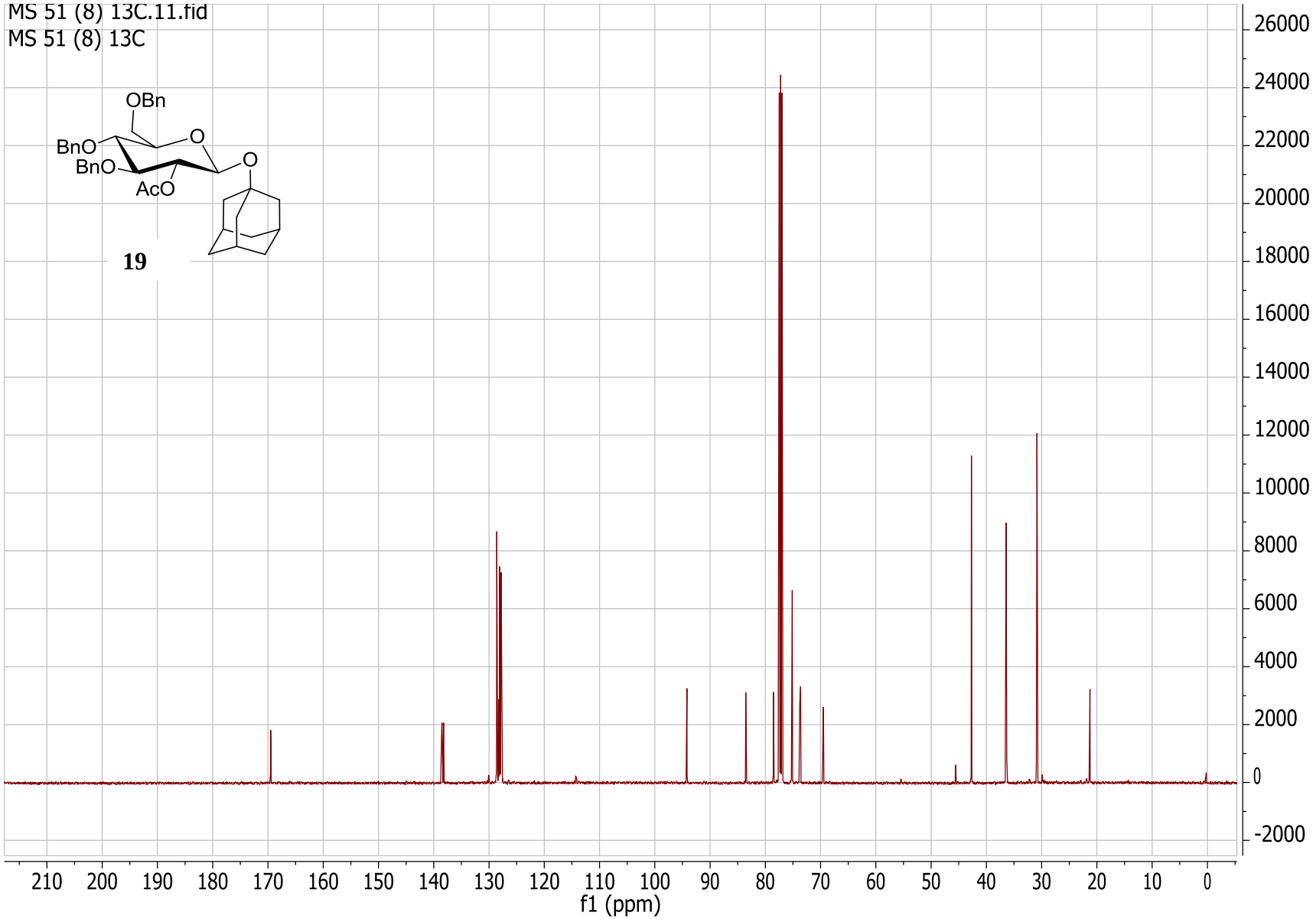

MS 295 (7).10.fid
MS 295 (7)
OBn
BnO
BnO
AcO
O
O
HO
BnO
BnO
O
S
15
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

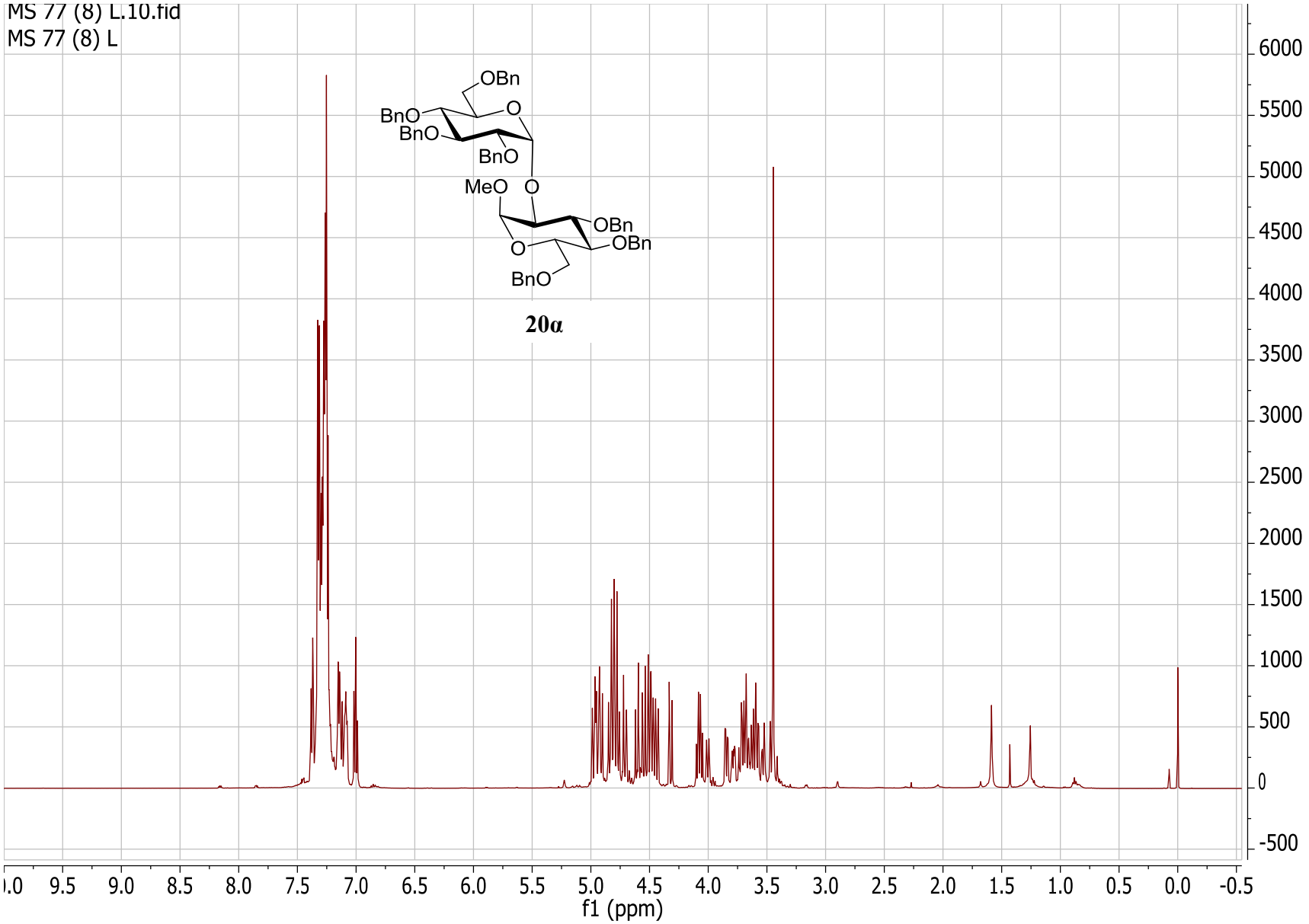

MS 295 (7) 13C.11.fid
MS 295 (7) 13C
OBn
BnO
BnO
AcO
O
O
O
HO
BnO
BnO
S
15
30000
25000
20000
15000
10000
5000
0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


MS 299 (7).10.fid
MS 299 (7)
OBn
BnO
BnO
AcO
O
O
BnO
BnO
BnO
O
S
Cl
17
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
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)

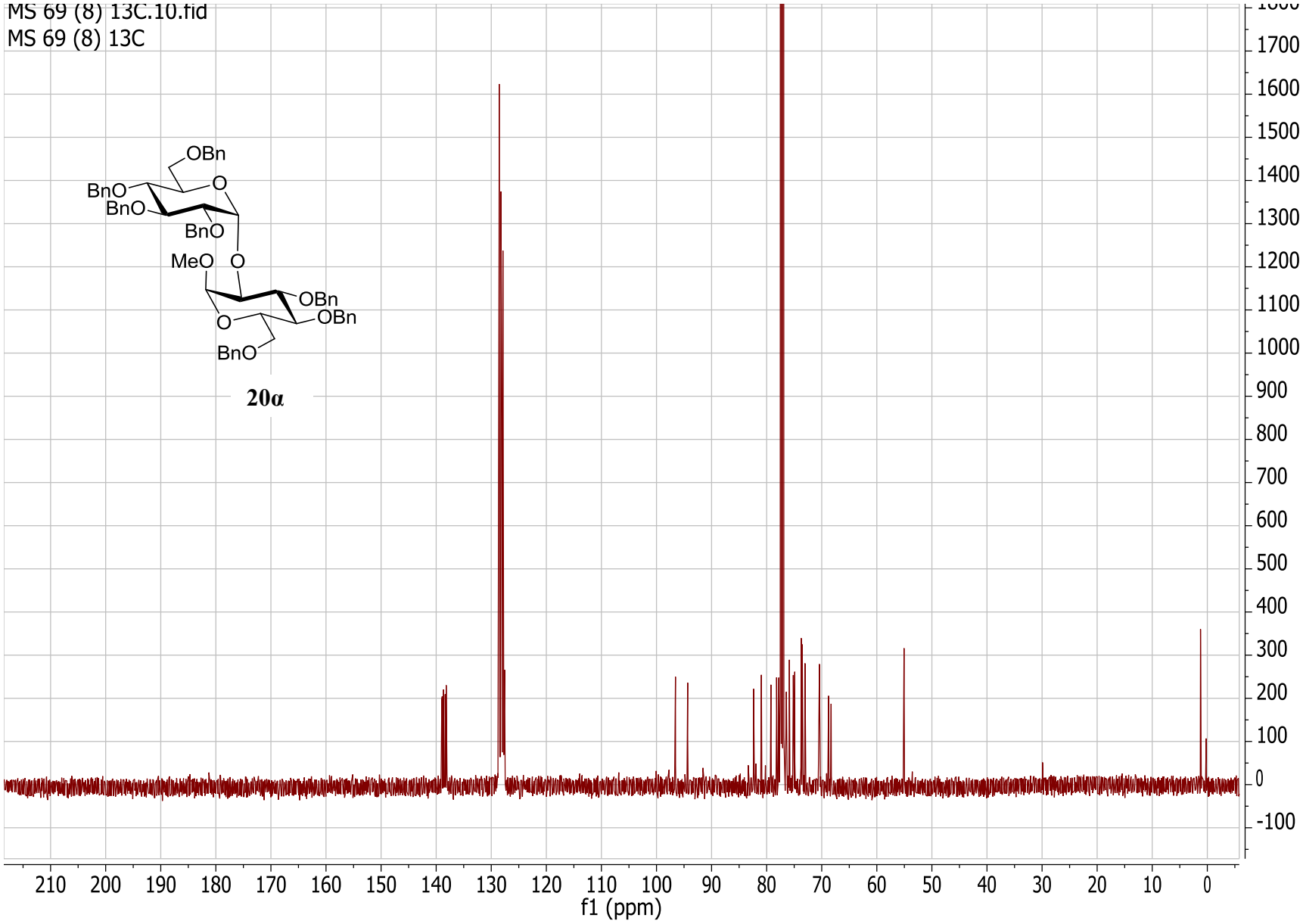

MS 299 (7) 13C.11.fid
MS 299 (7) 13C
OBn
BnO
BnO
AcO
BnO
BnO
BnO
O
O
O
O
S
Cl
17
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

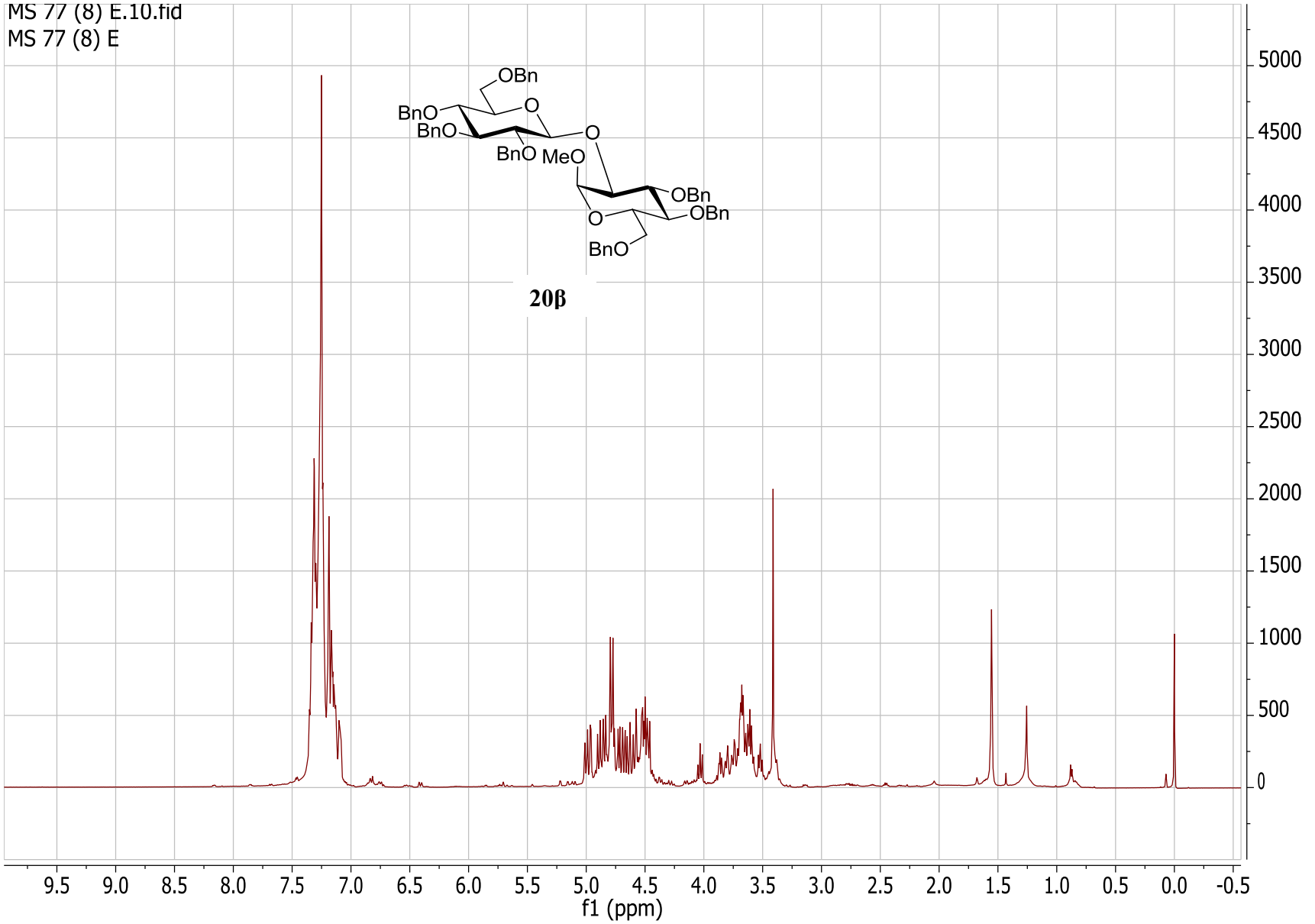

MS 51 (8).10.fid
MS 51 (8)
OBn
BnO
BnO
AcO
O
O
19
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

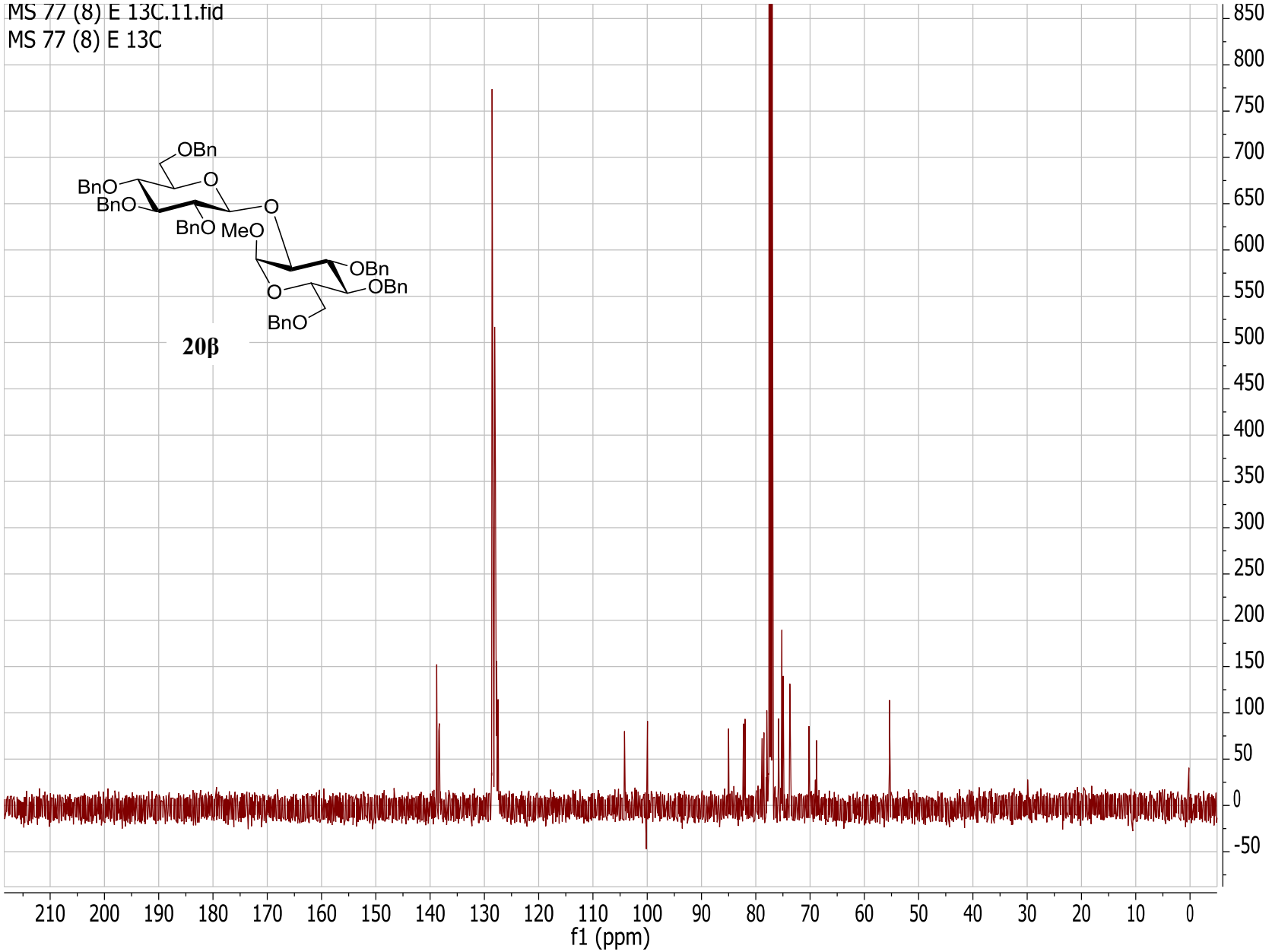

MS 51 (8) 13C.11.fid
MS 51 (8) 13C
OBn
BnO
BnO
AcO
O
O
19
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

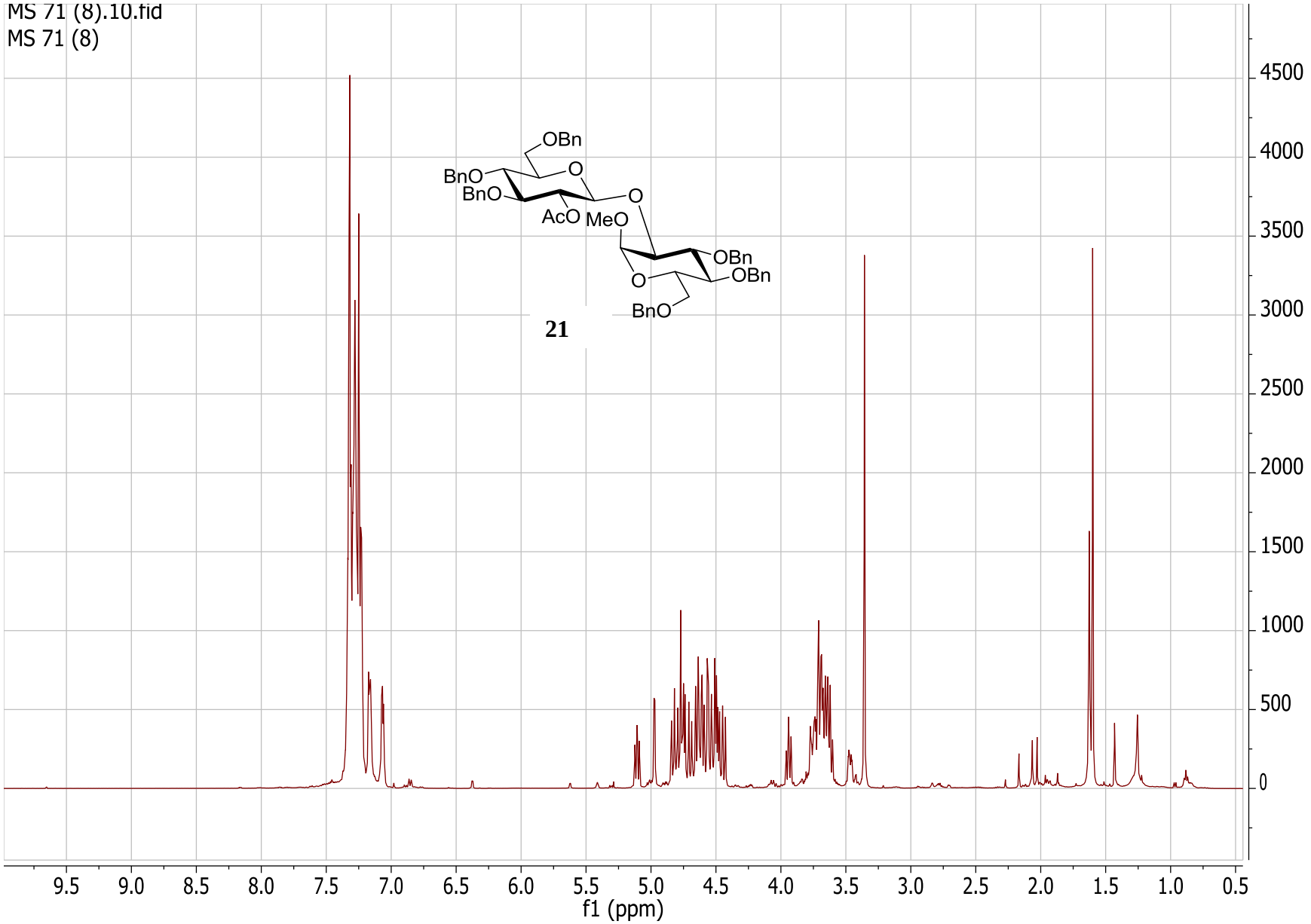

MS 77 (8) L.10.fid
MS 77 (8) L
OBn
BnO
O
BnO
BnO
MeO
O
OBn
OBn
O
BnO
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

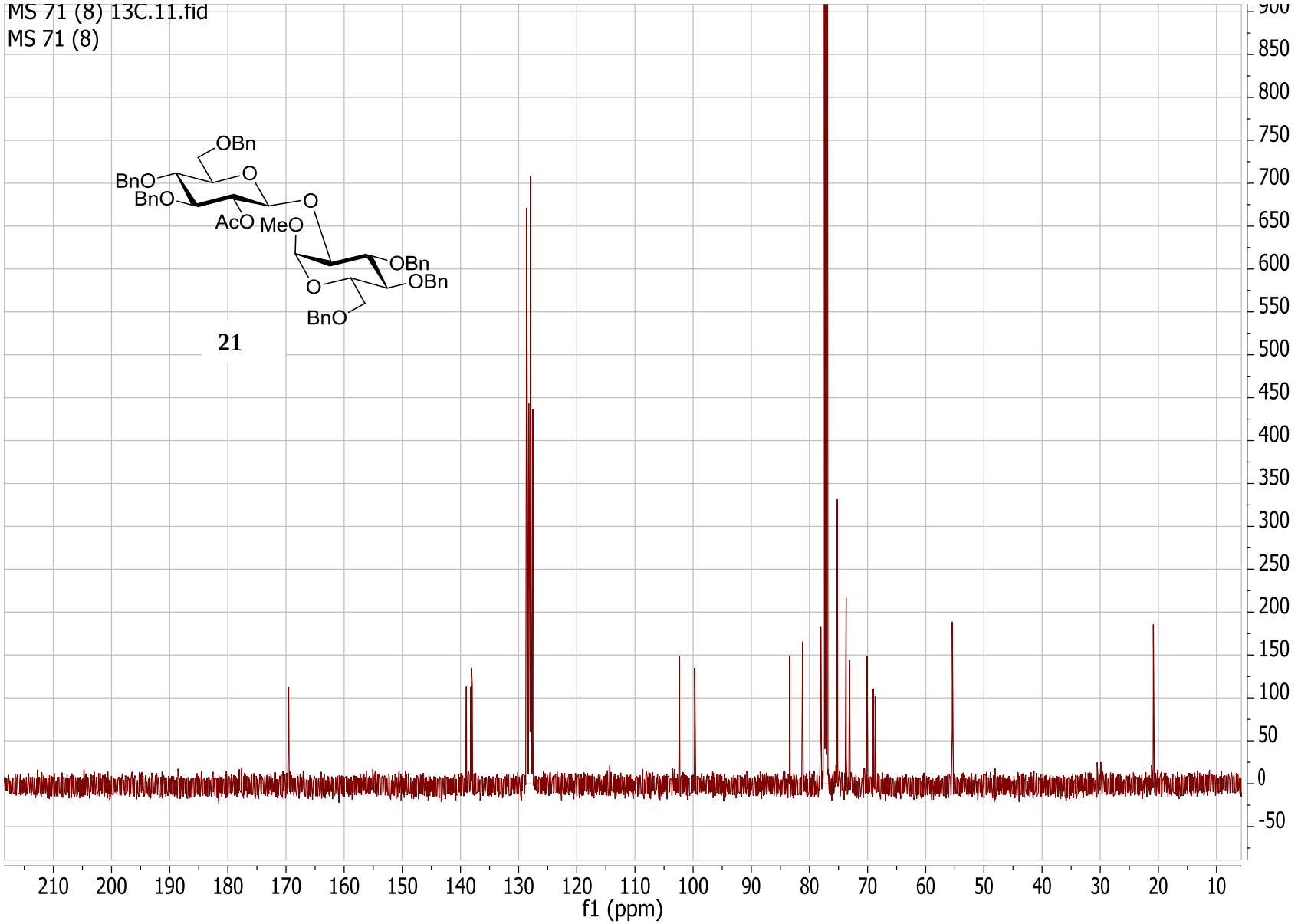
20α

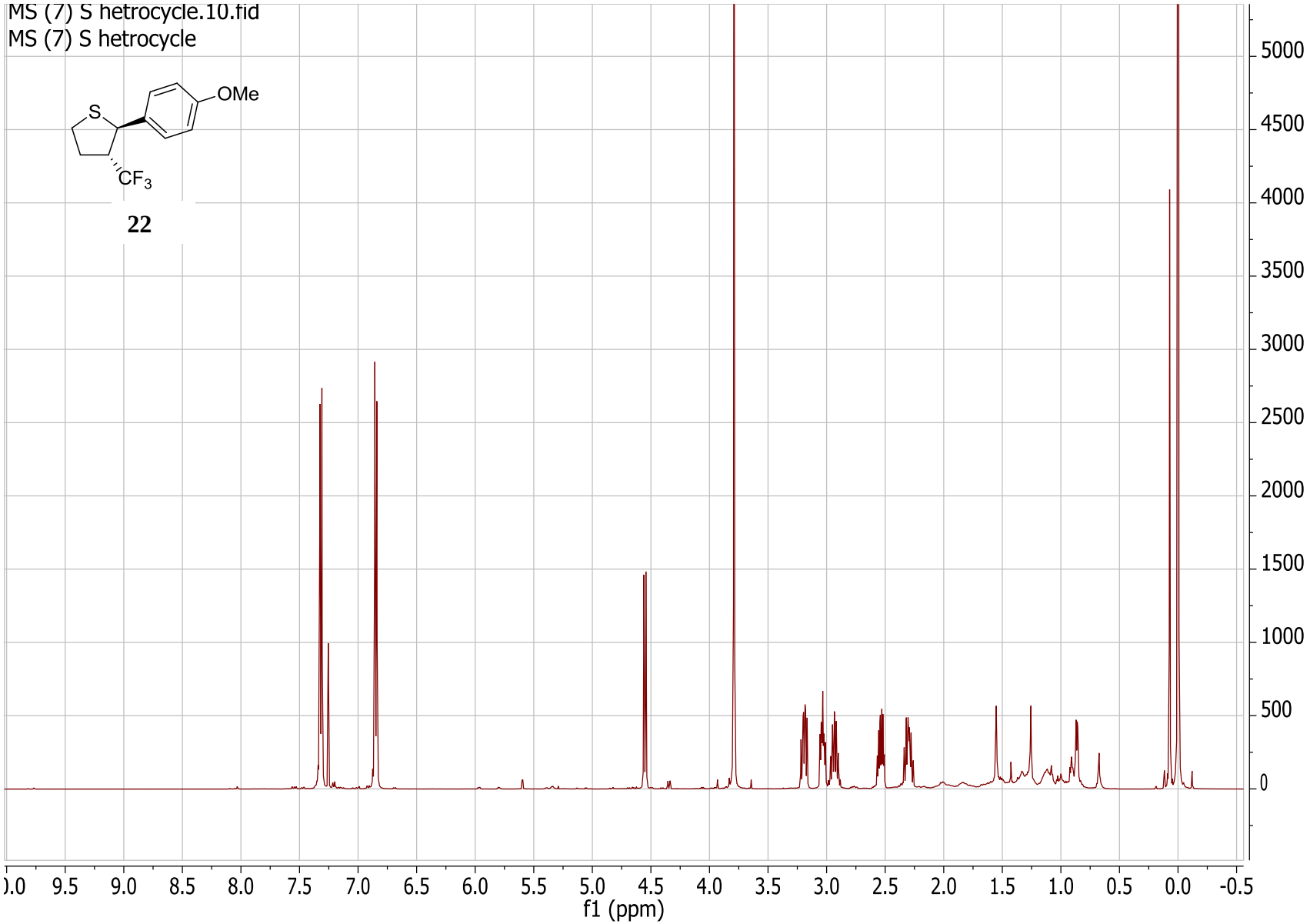

MS 69 (8) 13C.10.fid
MS 69 (8) 13C
OBn
BnO
O
BnO
BnO
MeO
O
OBn
OBn
O
BnO
20α
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

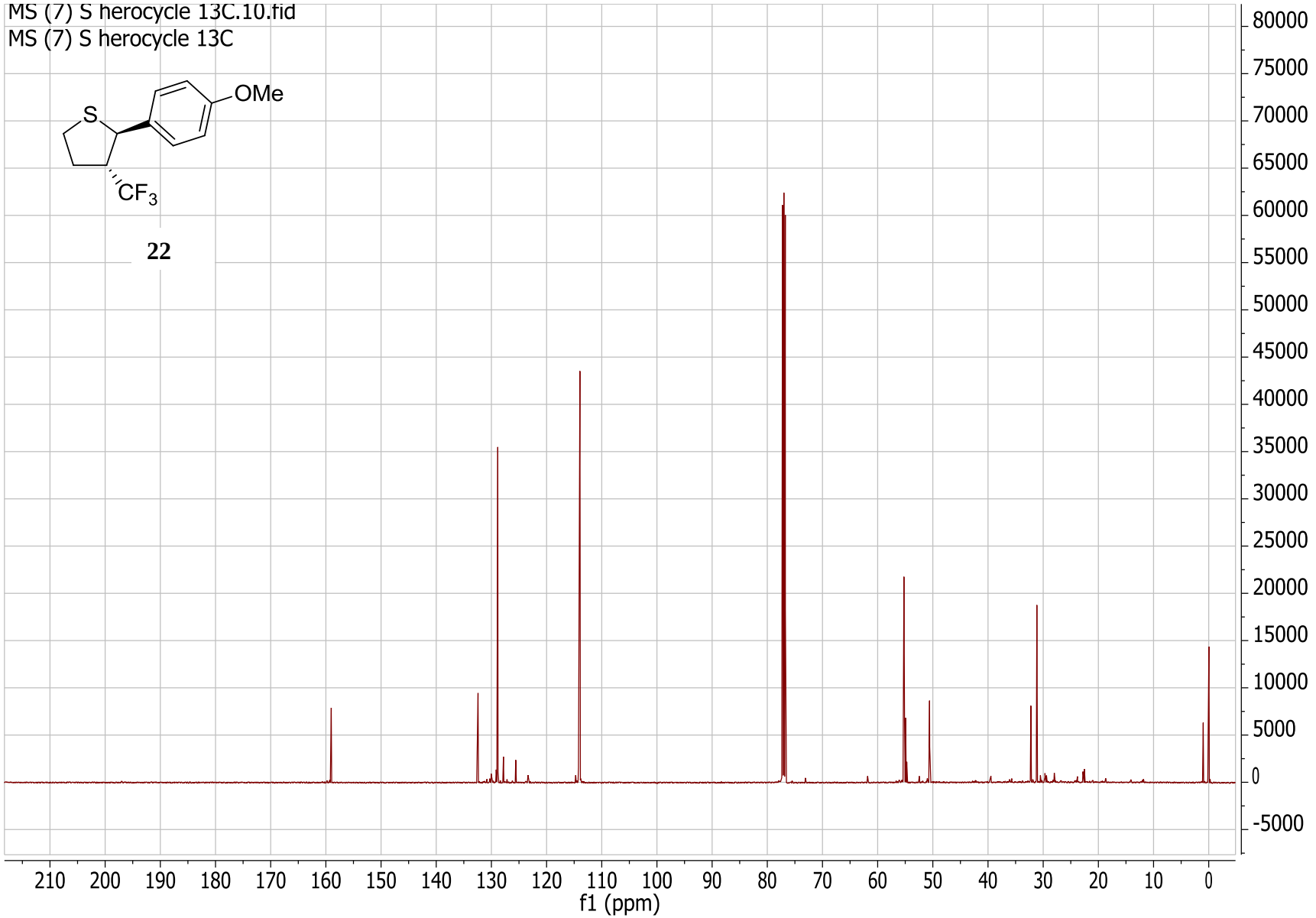

MS 77 (8) E.10.fid
MS 77 (8) E
OBn
BnO
O
BnO
O
BnO
MeO
OBn
OBn
O
BnO
20β
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


MS 77 (8) E 13C.11.fid
MS 77 (8) E 13C
OBn
BnO
O
BnO
O
BnO
MeO
OBn
OBn
O
BnO
20β
850
800
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

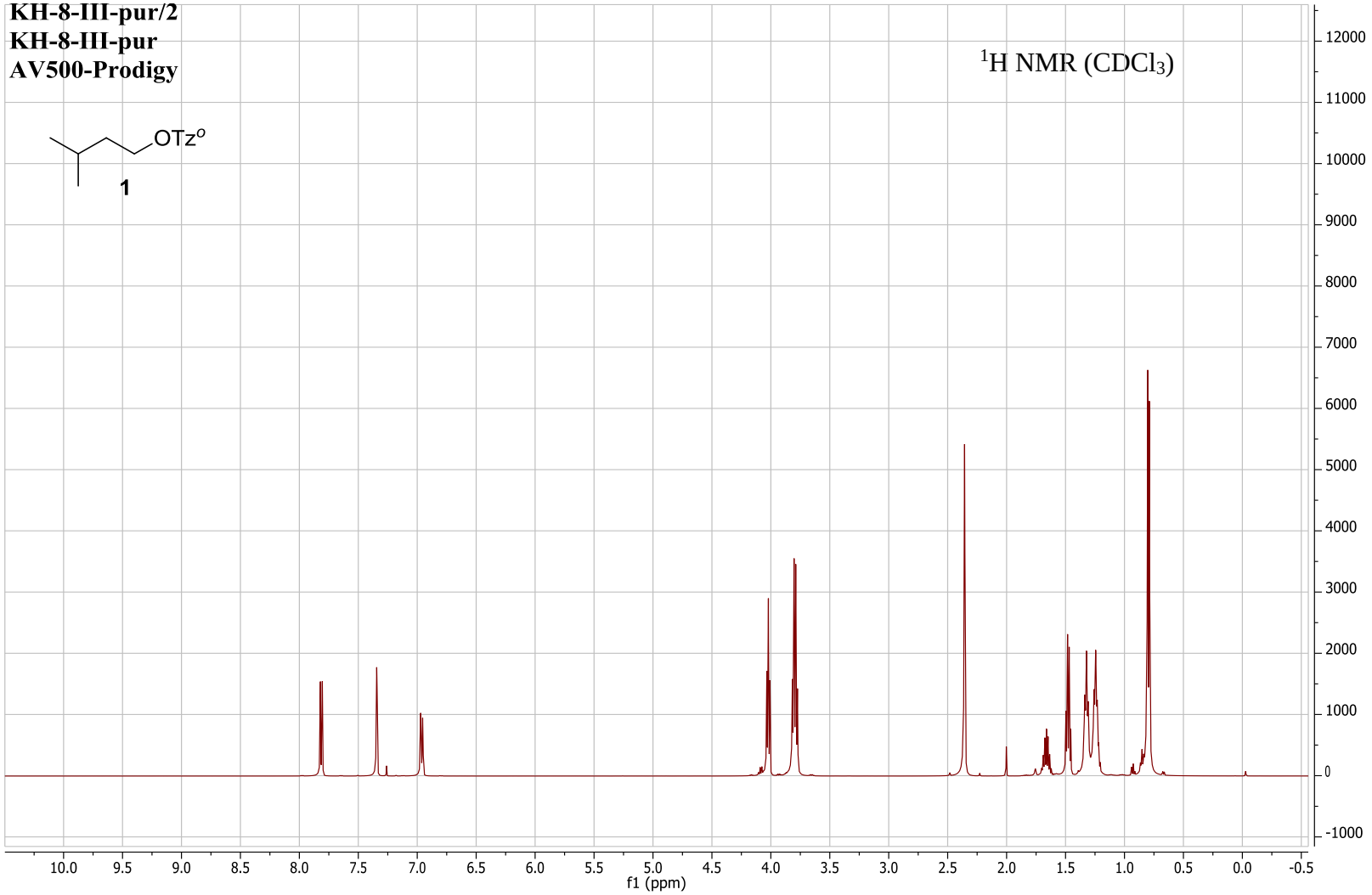

MS 71 (8).10.fid
MS 71 (8)
OBn
O
BnO
BnO
O
AcO
MeO
OBn
OBn
O
BnO
21
4500
4000
3500
3000
2500
2000
1500
1000
500
0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

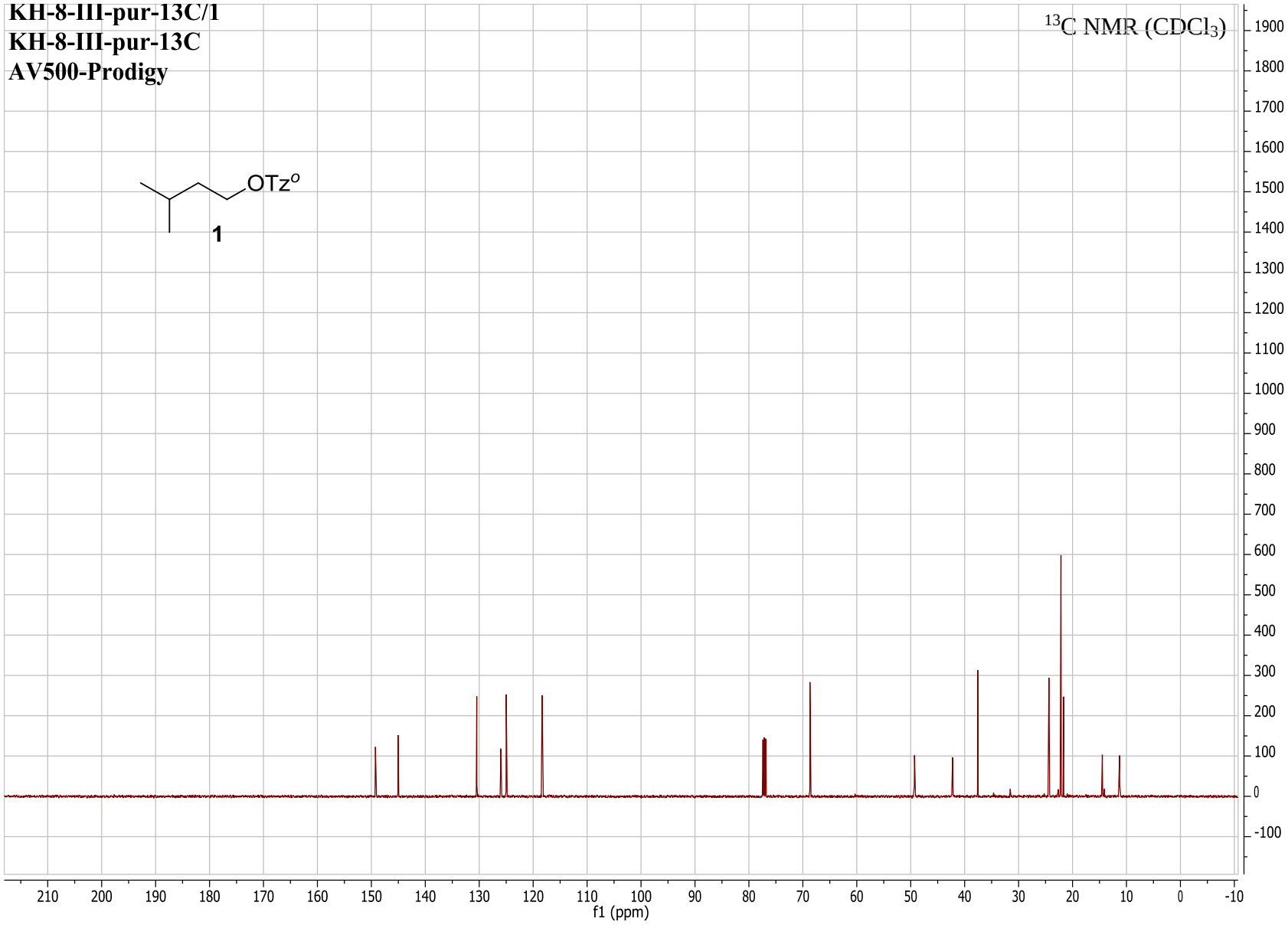

MS 71 (8) 13C.11.fid
MS 71 (8)
OBn
BnO
BnO
O
AcO
MeO
O
OBn
OBn
O
BnO
21
900
850
800
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

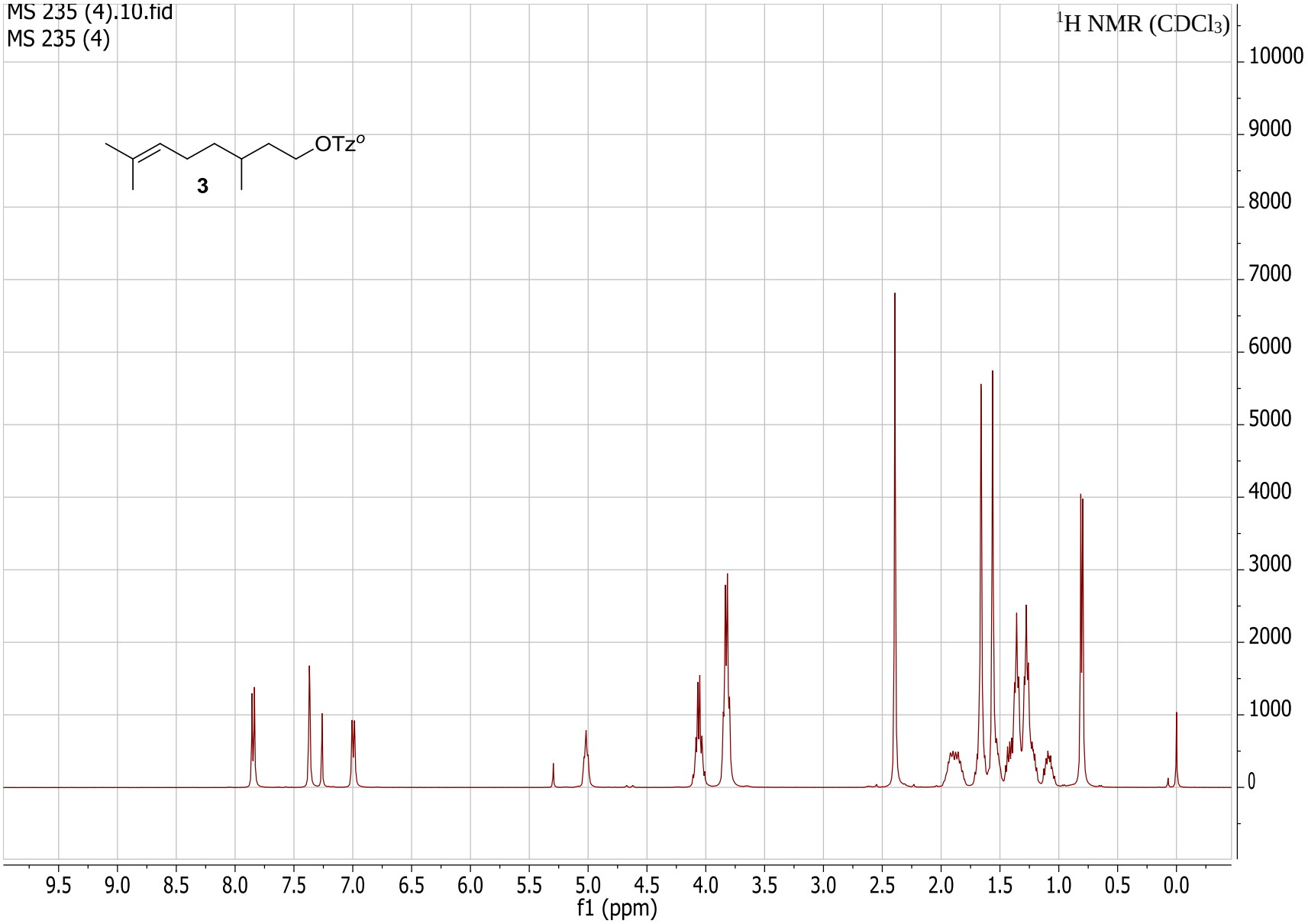

MS (7) S hetrocycle.10.fid
MS (7) S hetrocycle
S
OMe
CF3
22
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

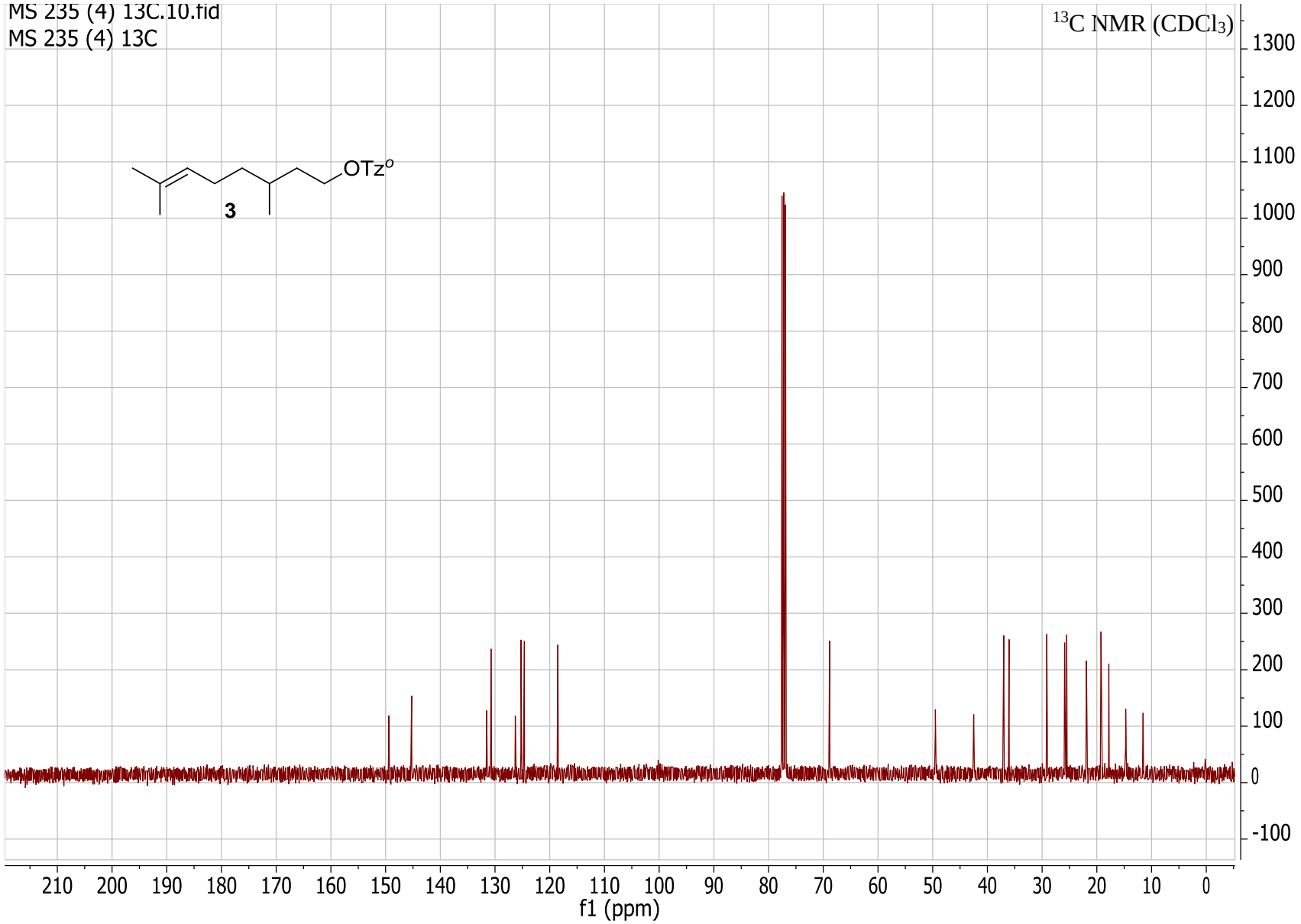

MS (7) S herocycle 13C.10.fid
MS (7) S herocycle 13C
OMe
S
CF3
22
80000
75000
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

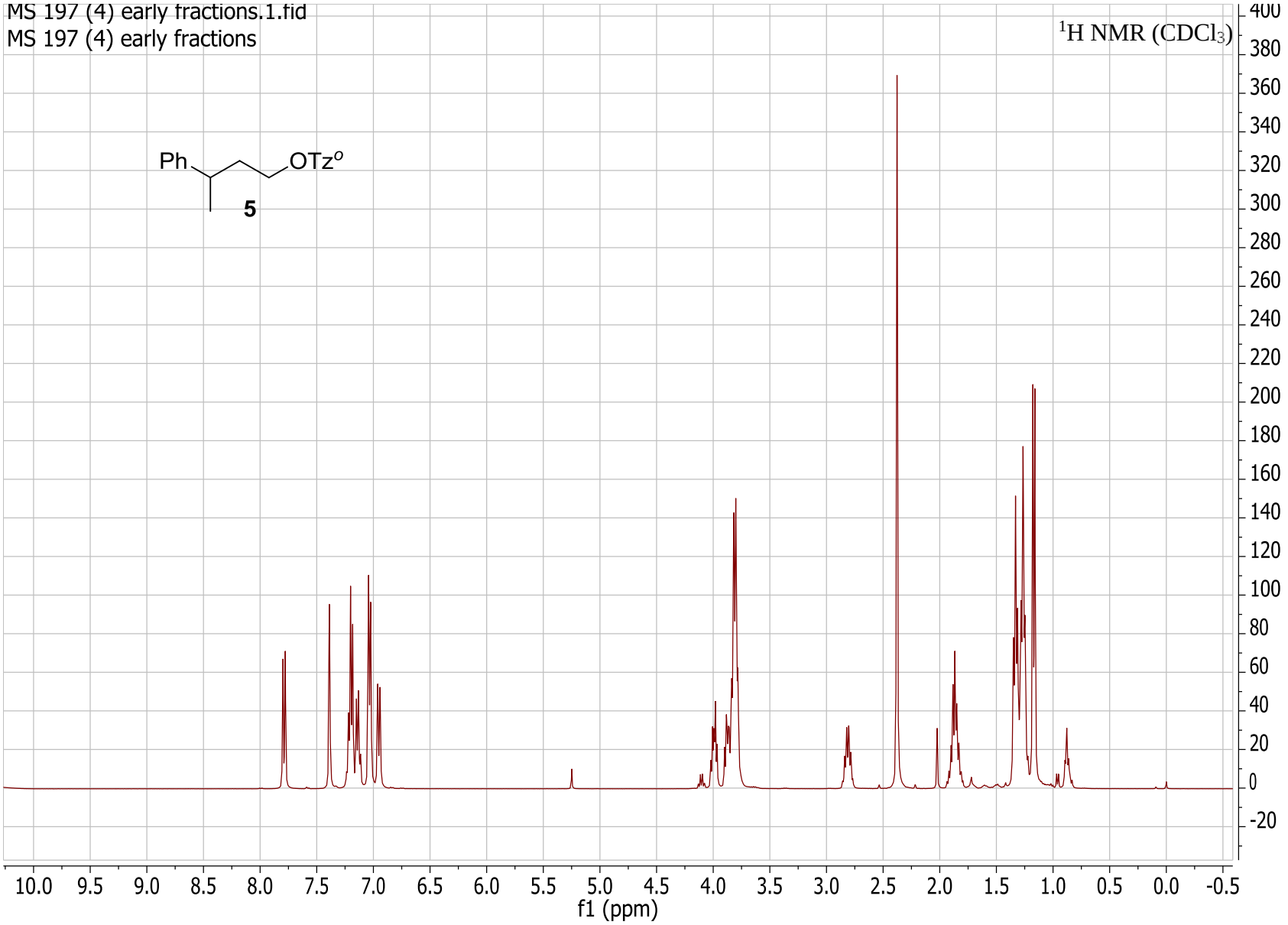
APPENDIX E: NMR SPECTRA OF COMPOUNDS FOUND IN CHAPTER 4

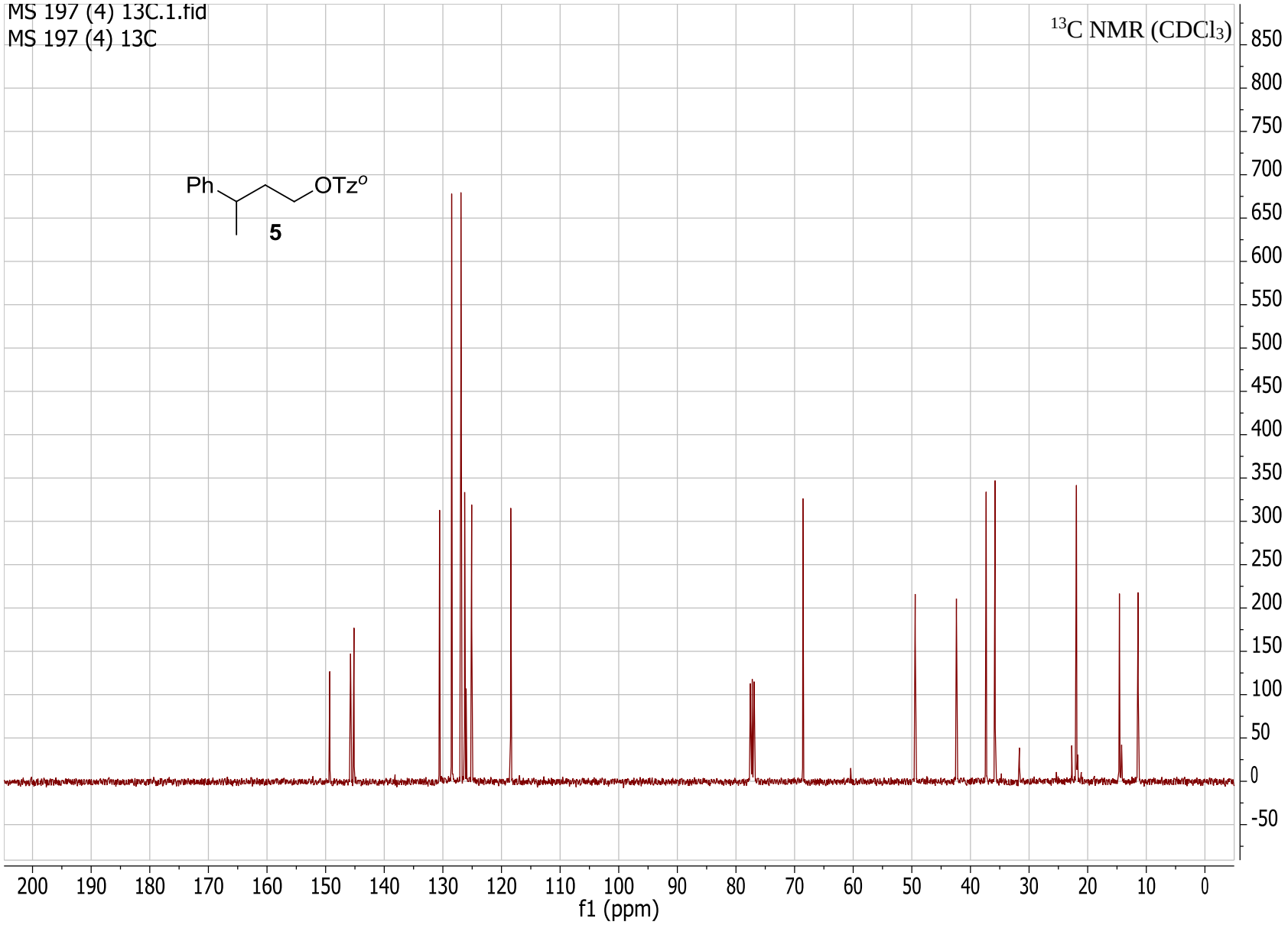


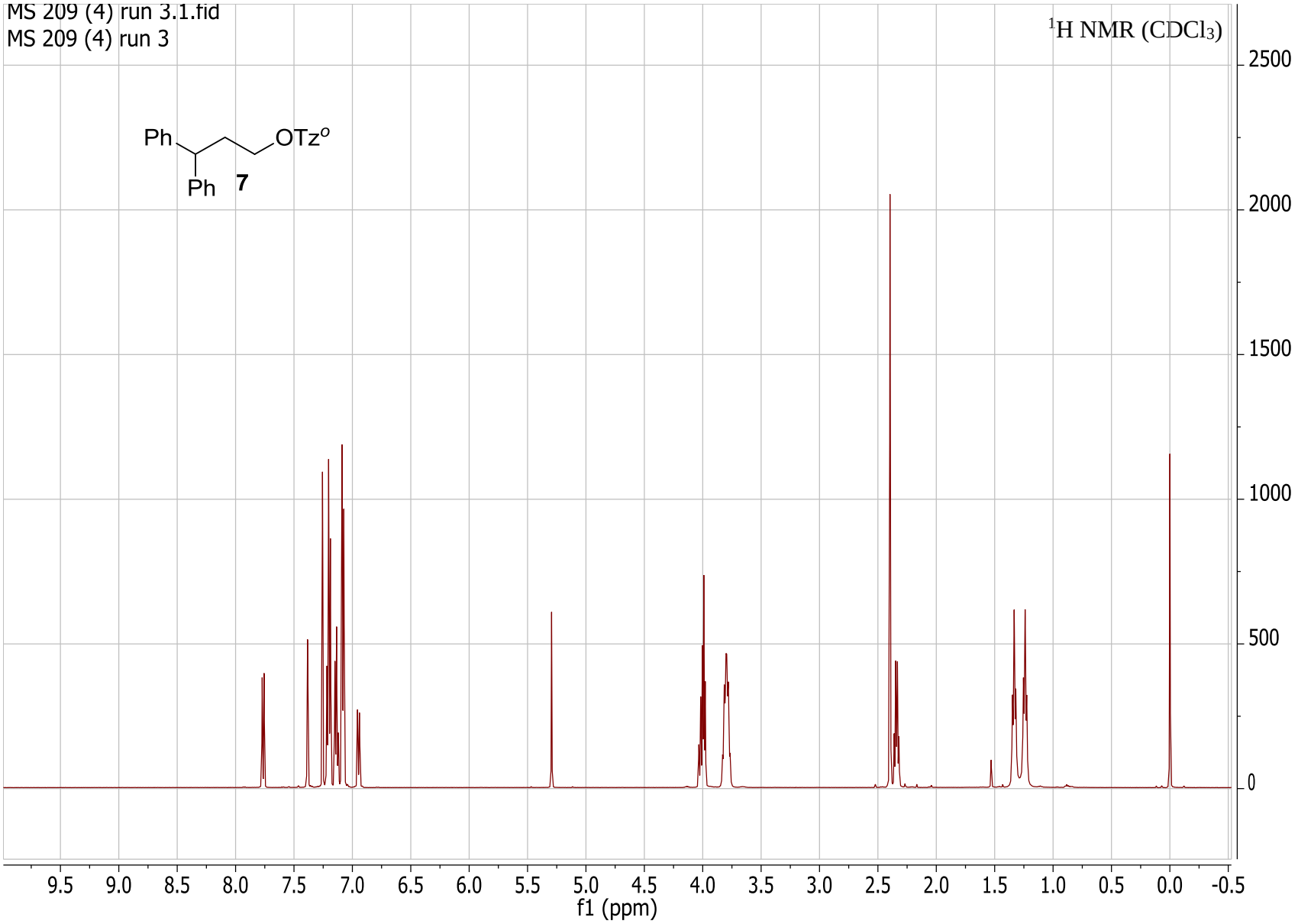

KH-8-III-pur-13C/1
KH-8-III-pur-13C
AV500-Prodigy
^{13}C NMR ($CDCl_3$)
OTz^o
1
f1 (ppm)

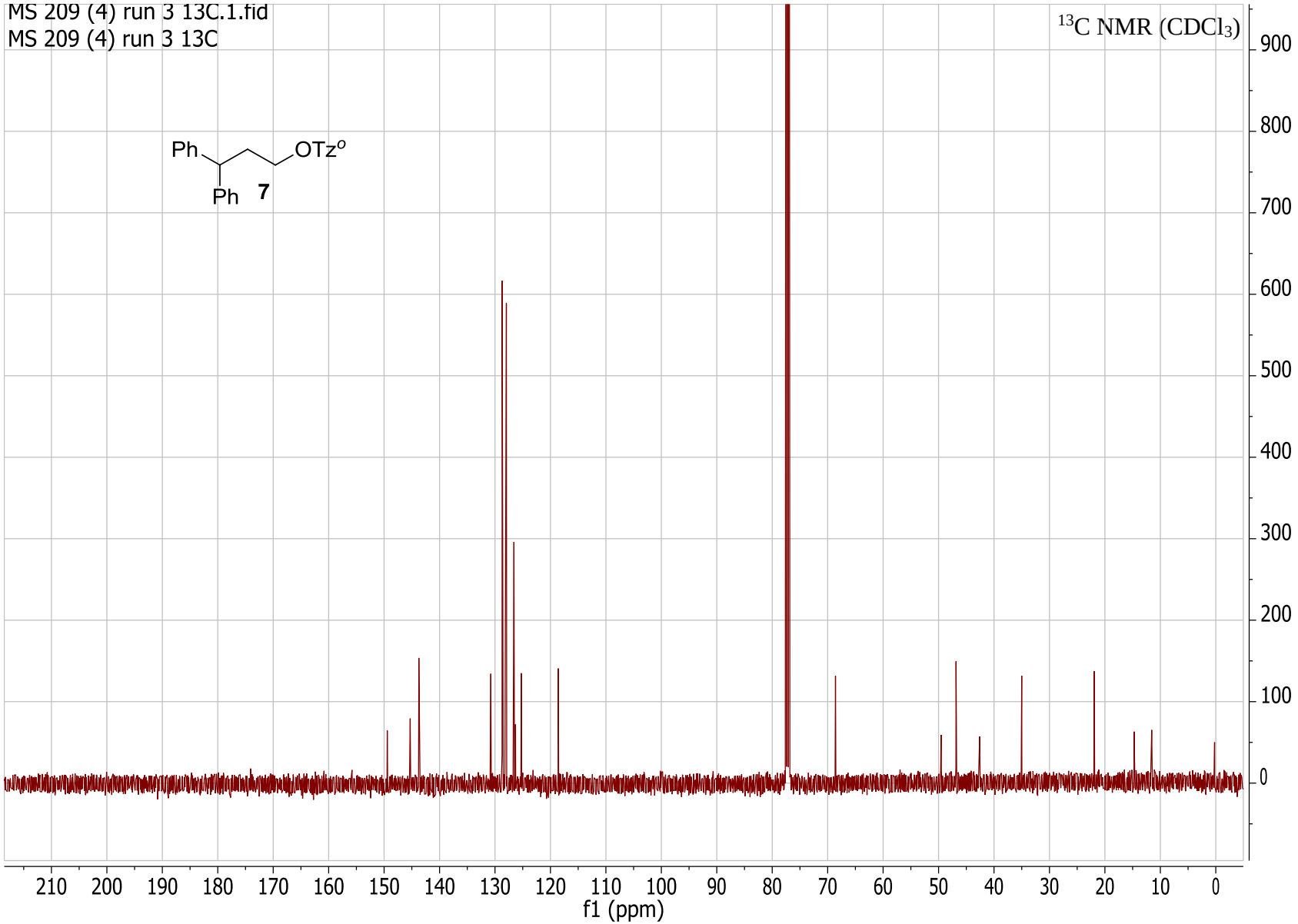

MS 235 (4).10.fid
MS 235 (4)
^{1}H NMR ($CDCl_3$)
OTz^o
3
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

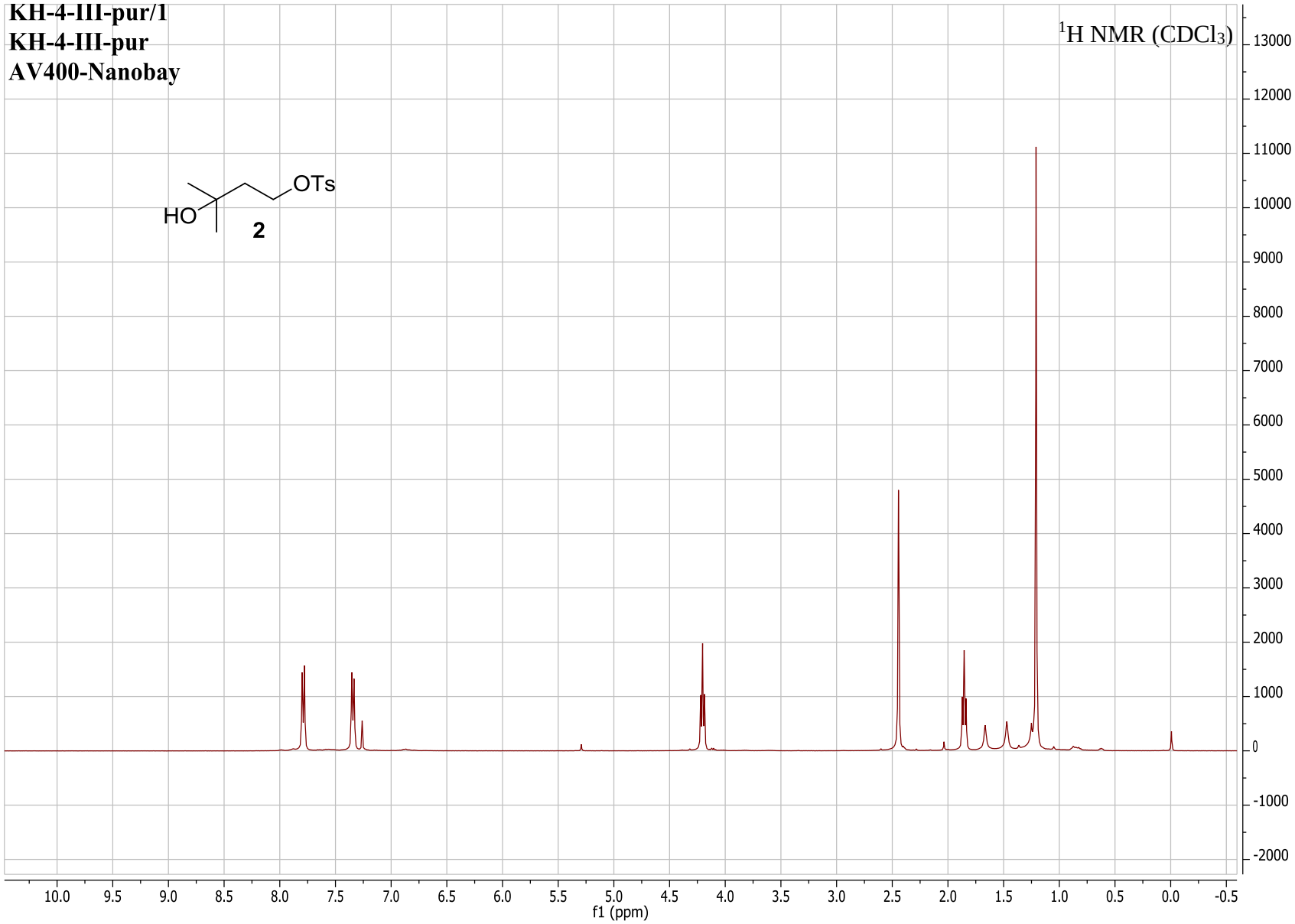

MS 235 (4) 13C.10.fid
MS 235 (4) 13C
^{13}C NMR ($CDCl_3$)
OTz^o
3
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

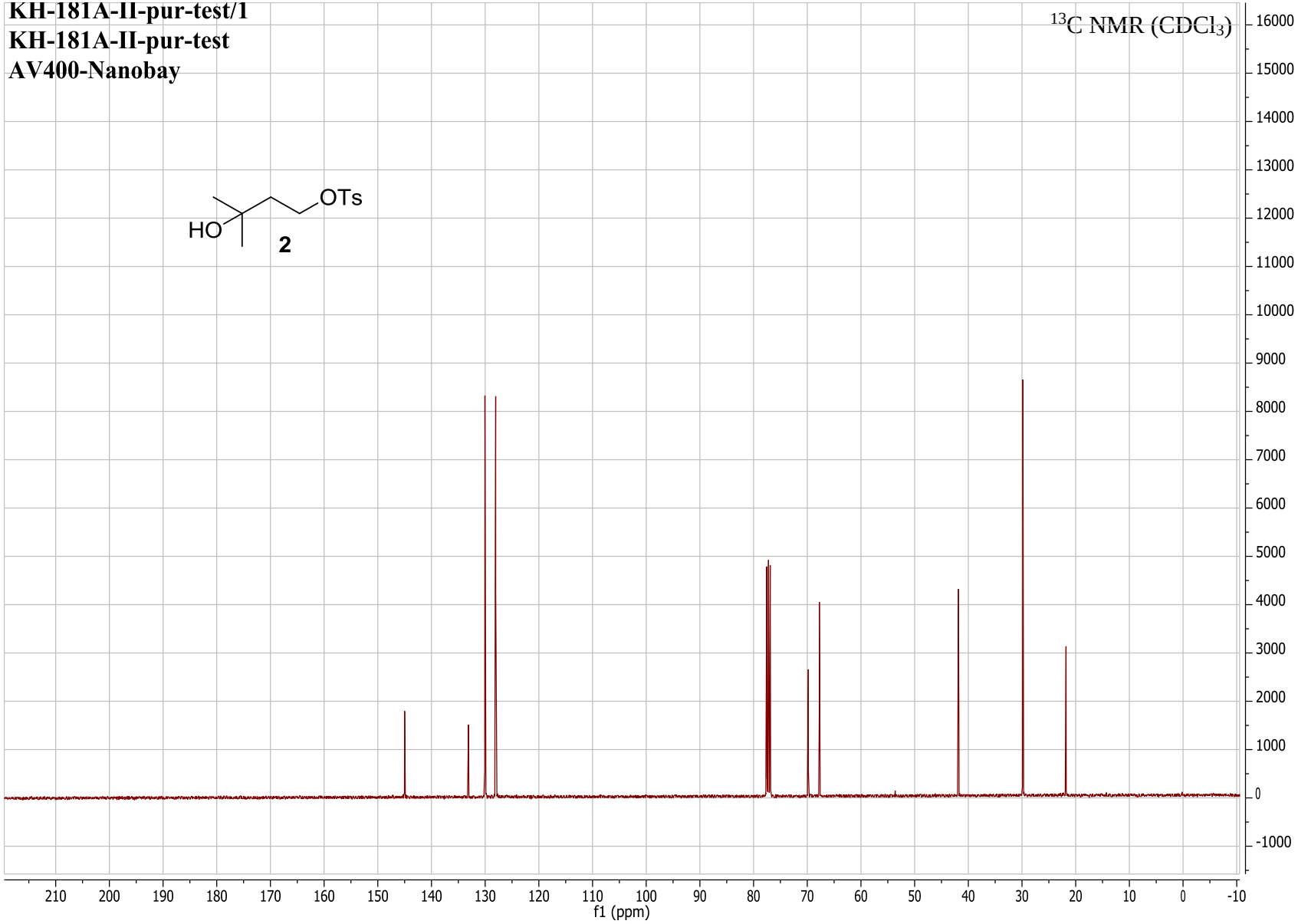

MS 197 (4) early fractions.1.fid
MS 197 (4) early fractions
^{1}H NMR ($CDCl_3$)
Ph
OTz^o
5
400
380
360
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

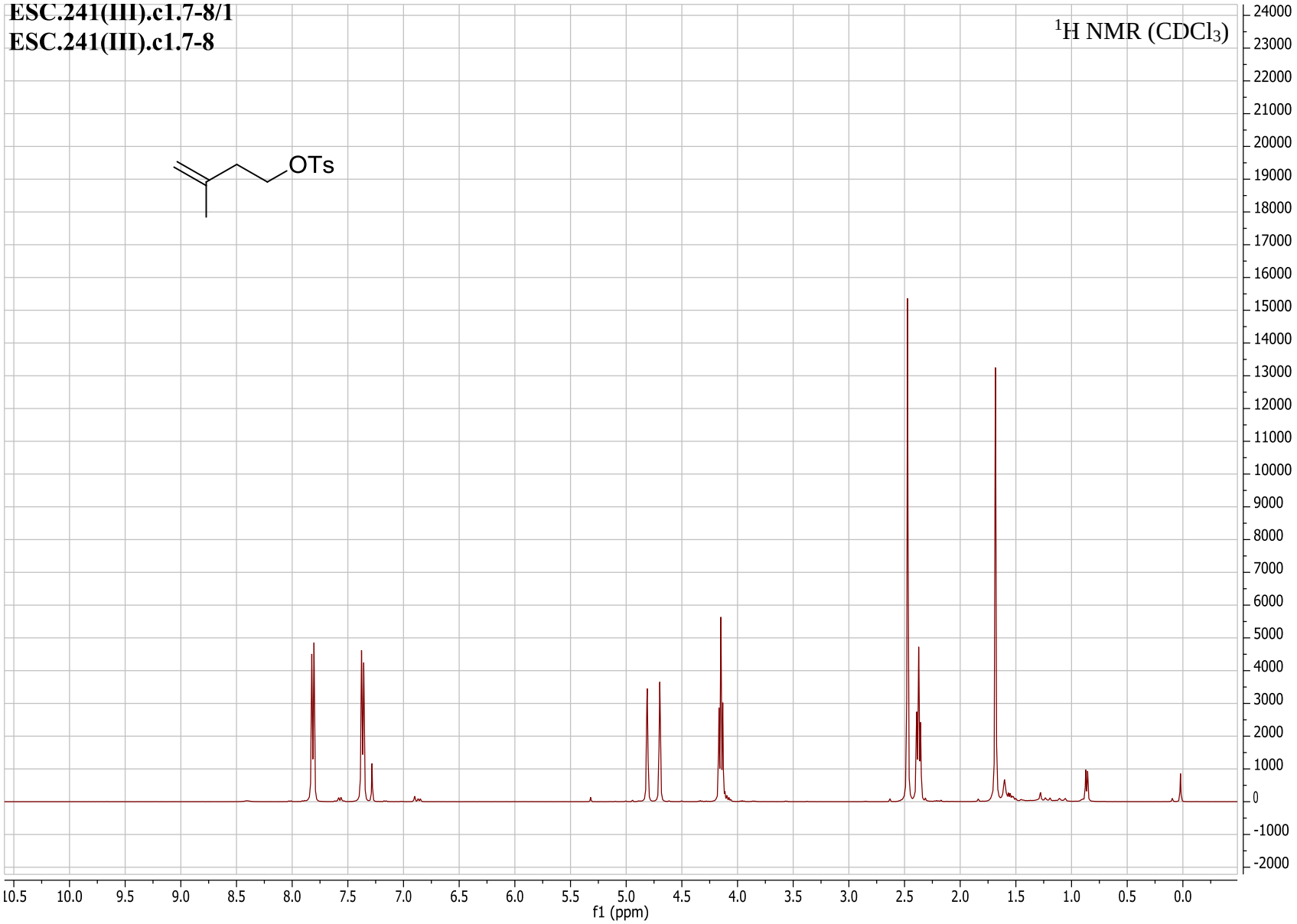

MS 197 (4) 13C.1.fid
MS 197 (4) 13C
^{13}C NMR ($CDCl_3$)
Ph
OTz^o
5
850
800
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

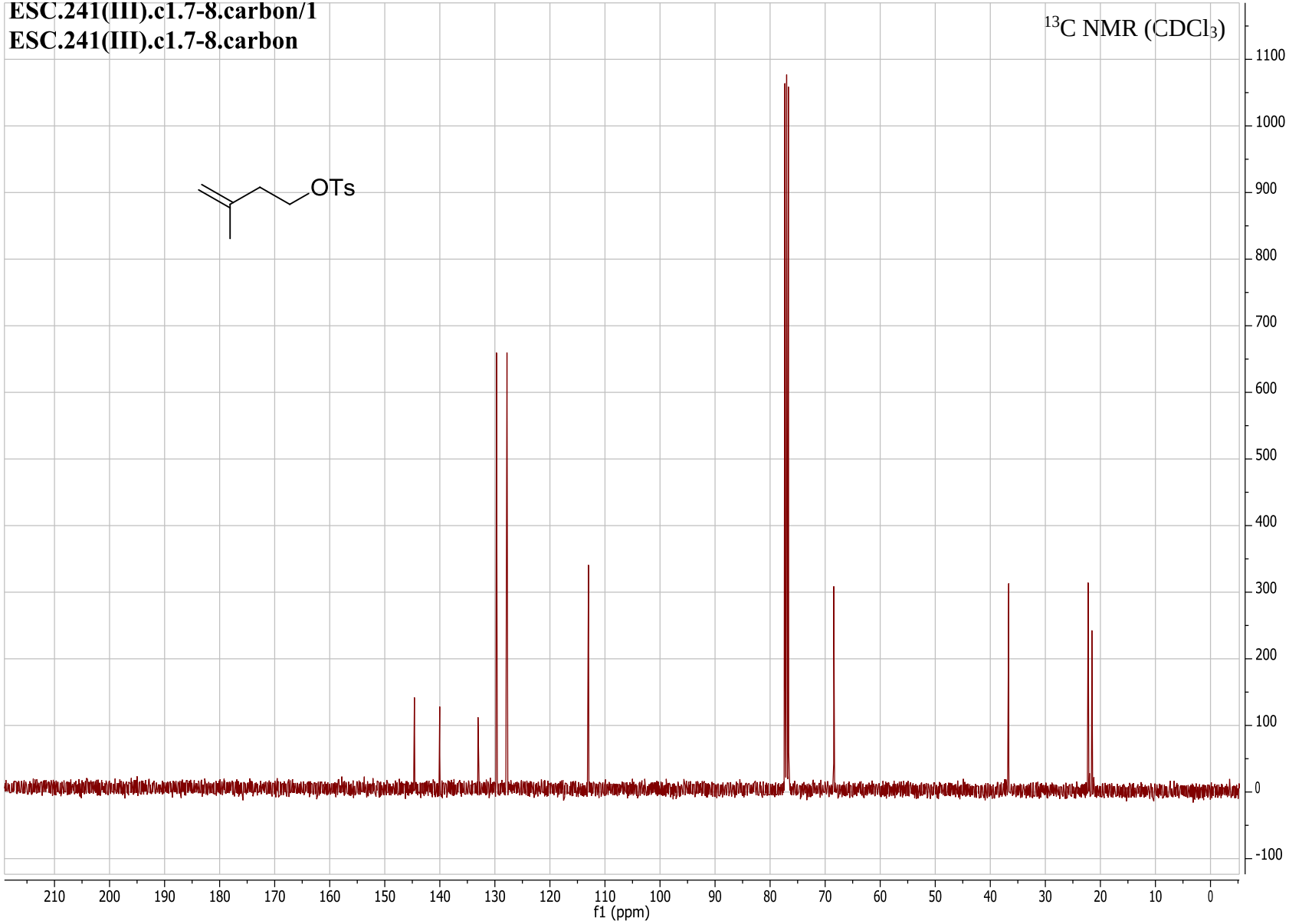

MS 209 (4) run 3.1.fid
MS 209 (4) run 3
^{1}H NMR ($CDCl_3$)
Ph
OTz^o
Ph
7
2500
2000
1500
1000
500
0
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

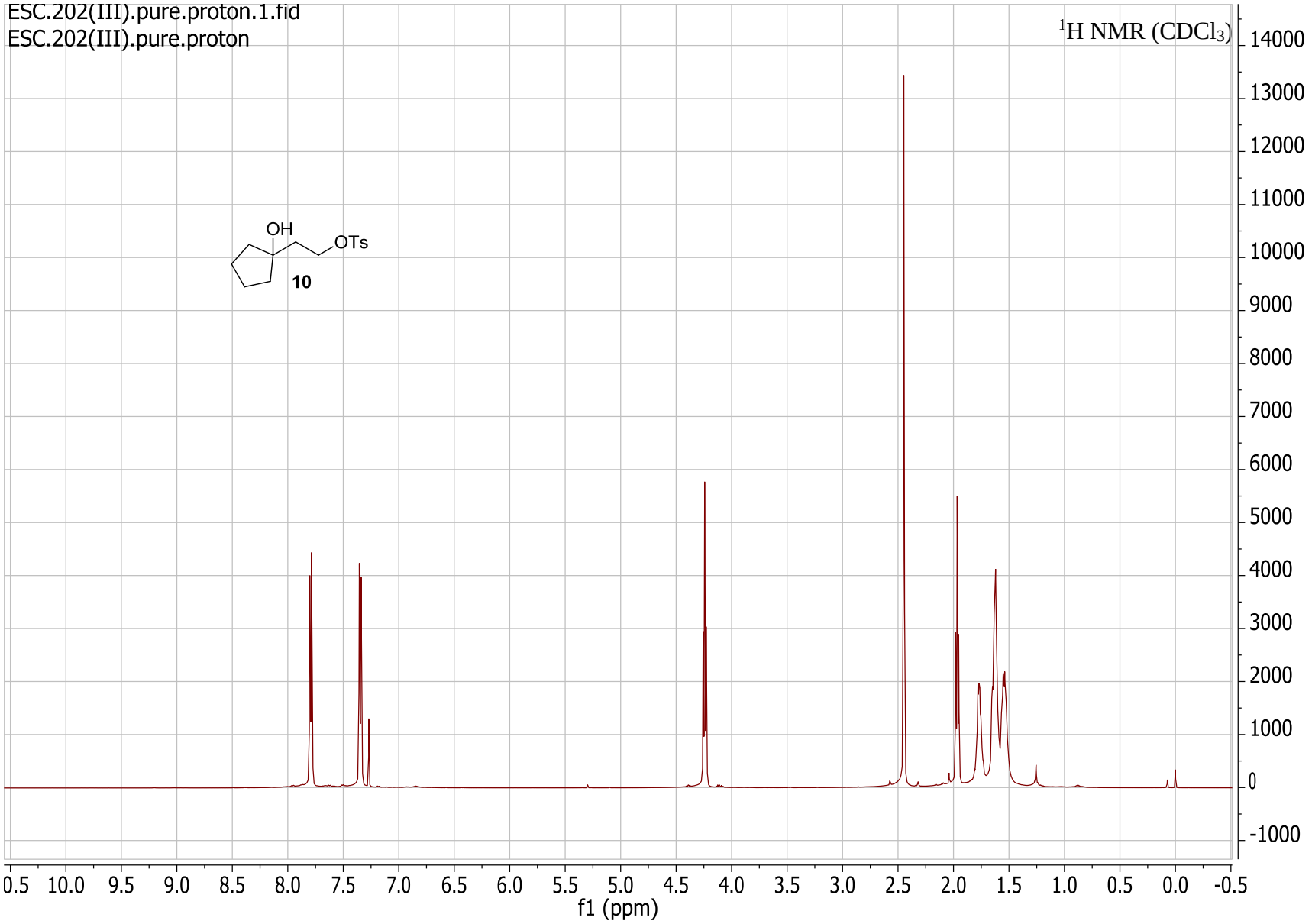

MS 209 (4) run 3 13C.1.fid
MS 209 (4) run 3 13C
^{13}C NMR ($CDCl_3$)
Ph
OTz^{o}
Ph
7
900
800
700
600
500
400
300
200
100
0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

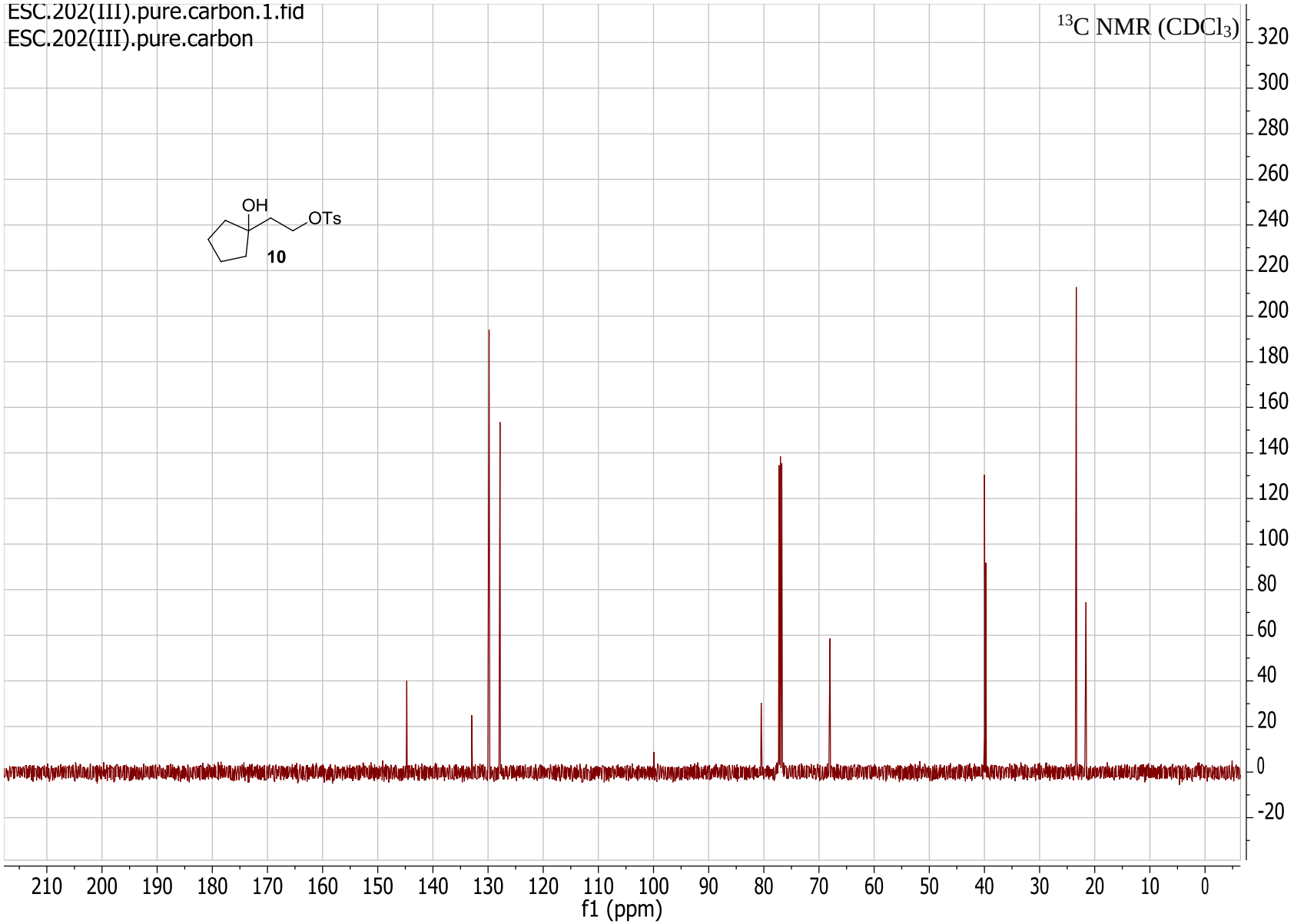

KH-4-III-pur/1
KH-4-III-pur
AV400-Nanobay
^{1}H NMR ($CDCl_3$)
OTs
HO
2
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-2000
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

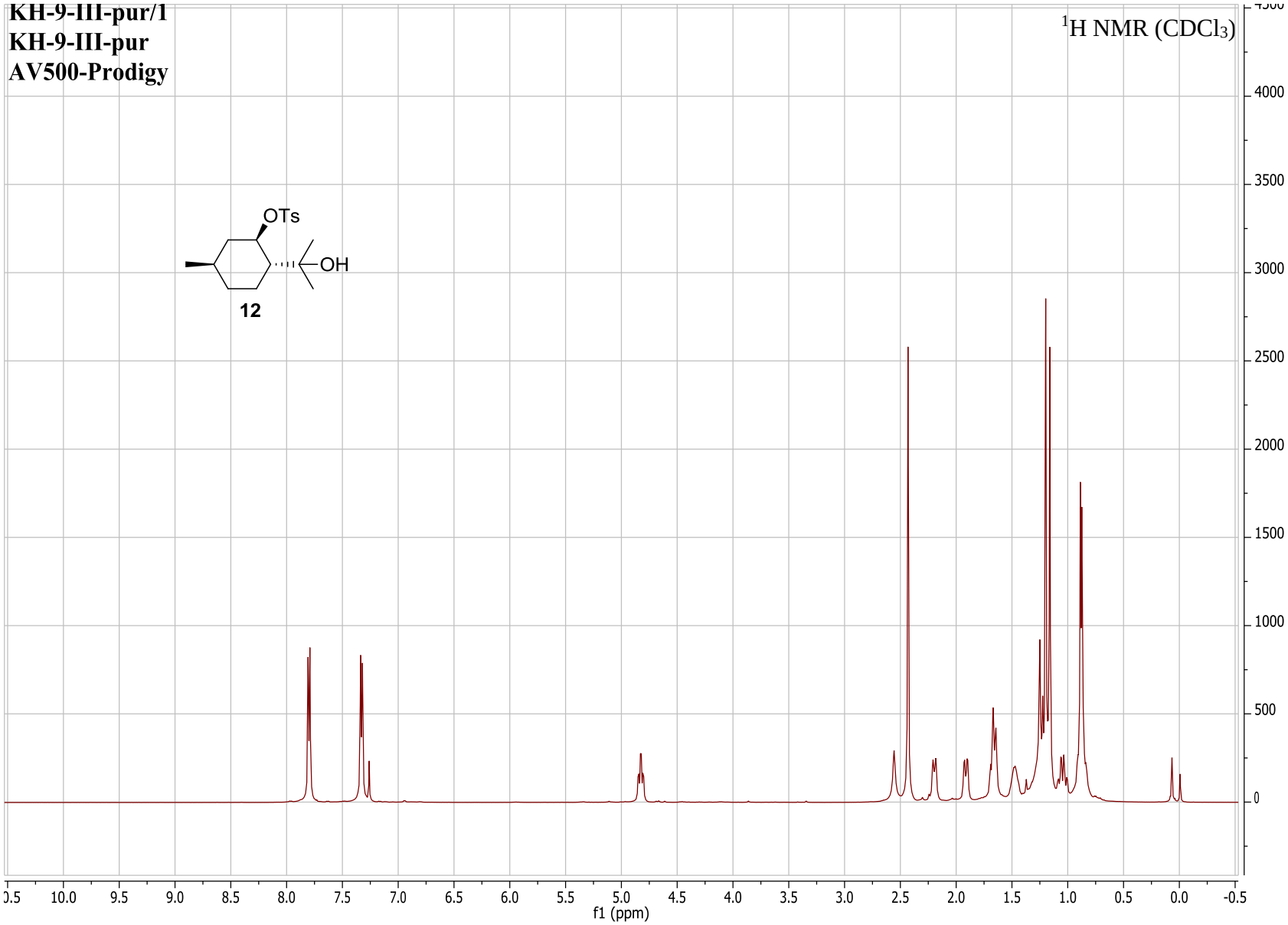

KH-181A-II-pur-test/1
KH-181A-II-pur-test
AV400-Nanobay
^{13}C NMR ($CDCl_3$)
OTs
HO
2
f1 (ppm)

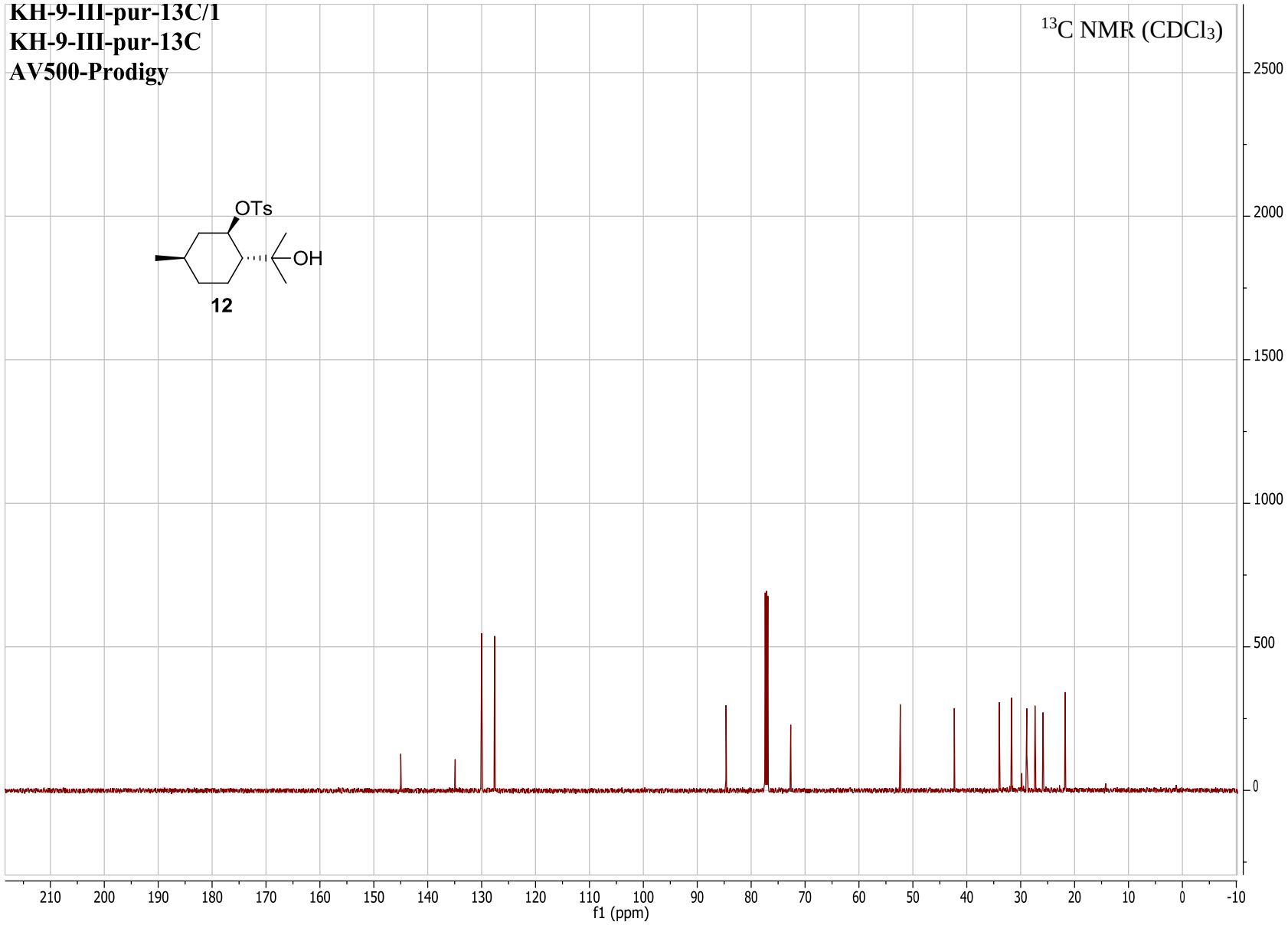

ESC.241(III).c1.7-8/1
ESC.241(III).c1.7-8
^{1}H NMR ($CDCl_3$)
OTs
f1 (ppm)

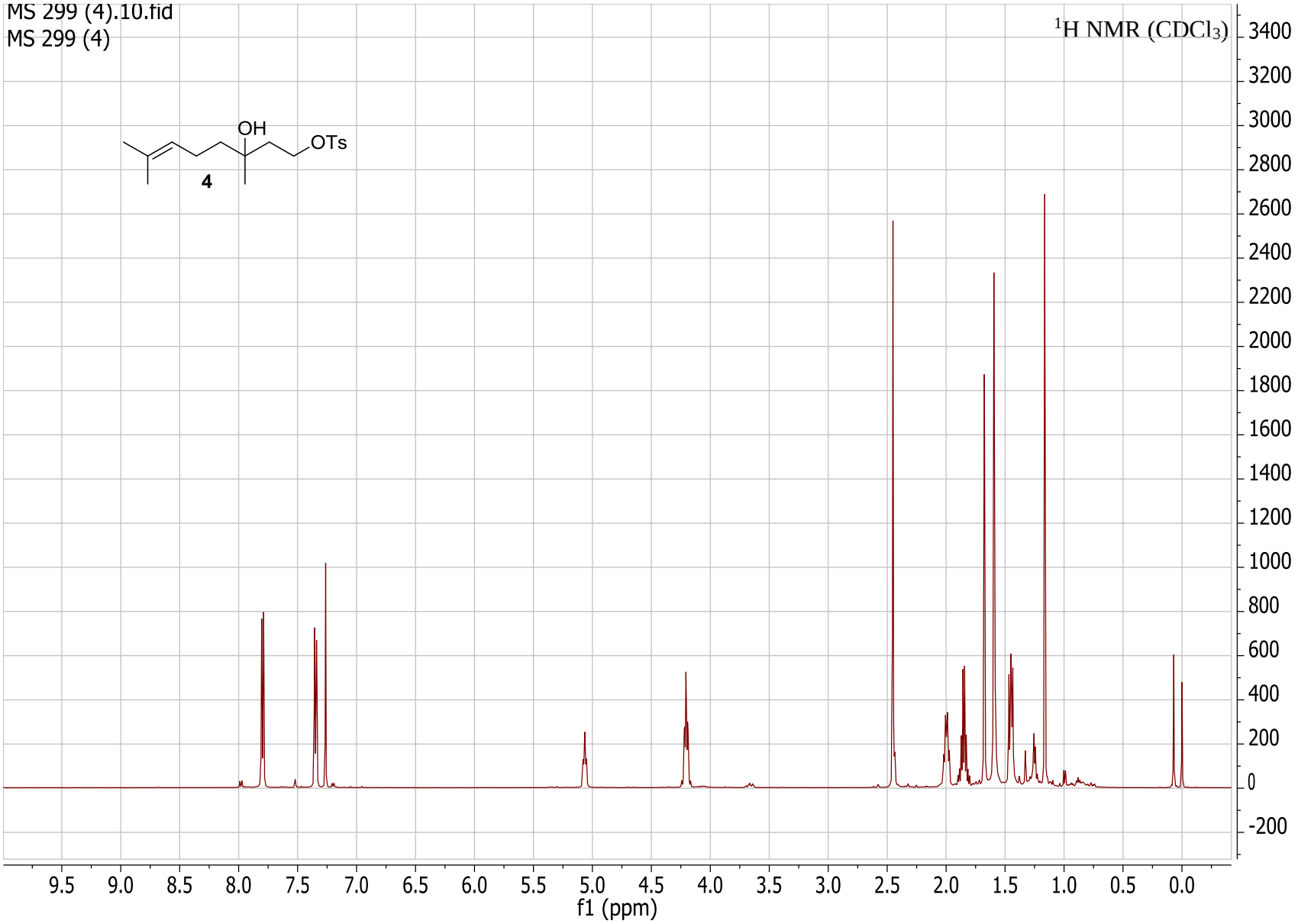

ESC.241(III).c1.7-8.carbon/1
ESC.241(III).c1.7-8.carbon
^{13}C NMR ($CDCl_3$)
OTs
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

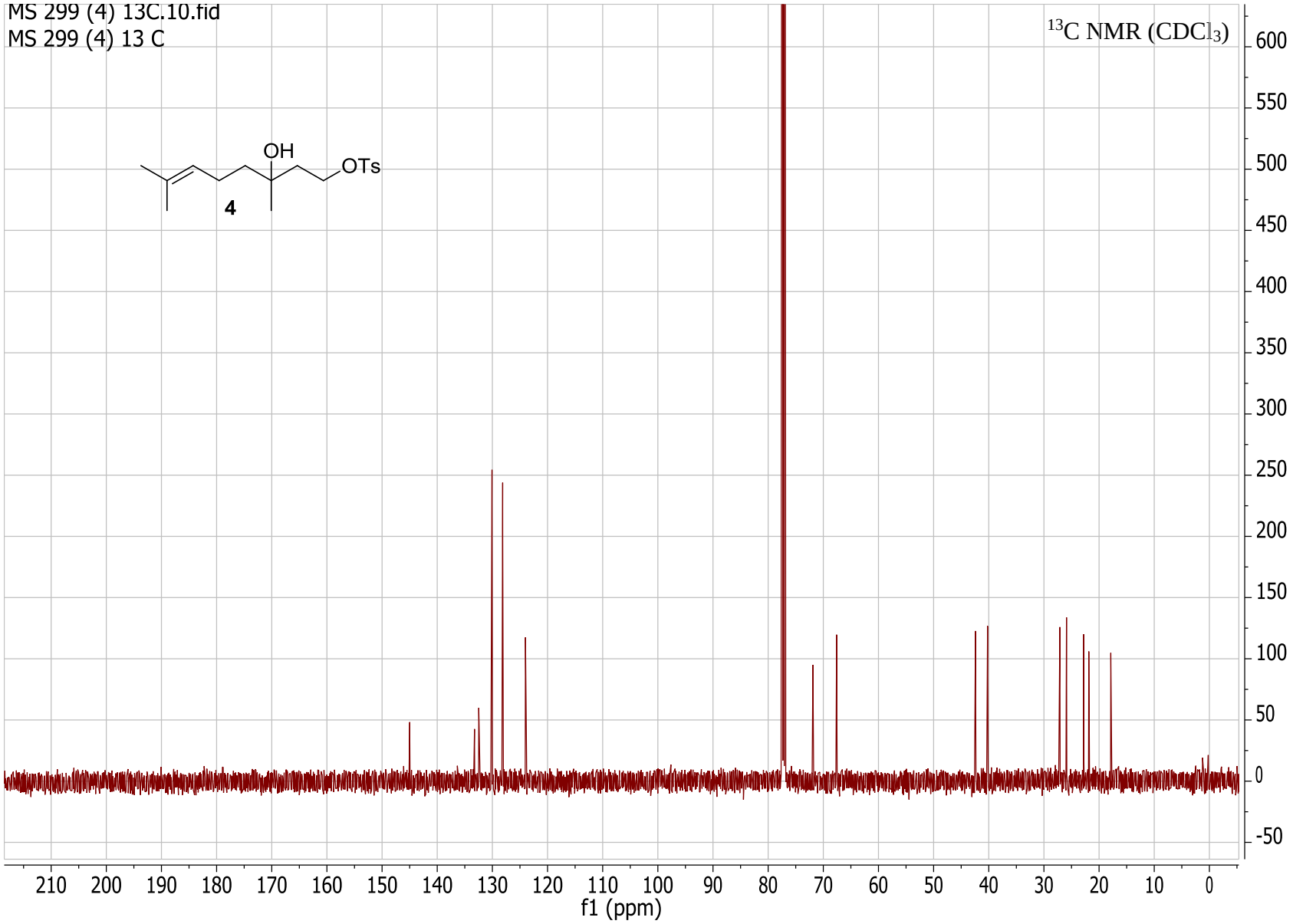

ESC.202(III).pure.proton.1.fid
ESC.202(III).pure.proton
^{1}H NMR ($CDCl_3$)
OH
OTs
10
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
0.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

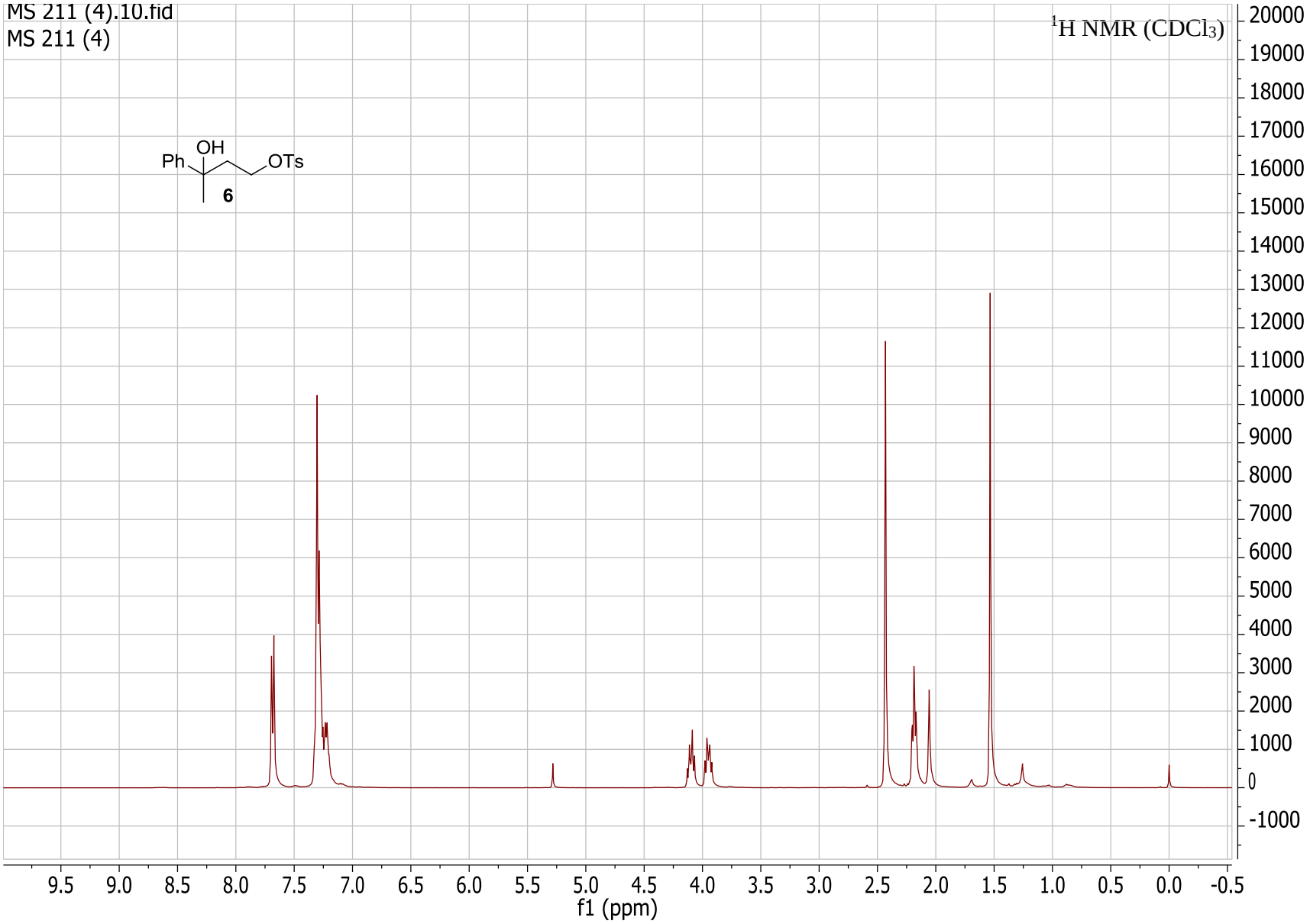

ESC.202(III).pure.carbon.1.fid
ESC.202(III).pure.carbon
^{13}C NMR ($CDCl_3$)
OH
OTs
10
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

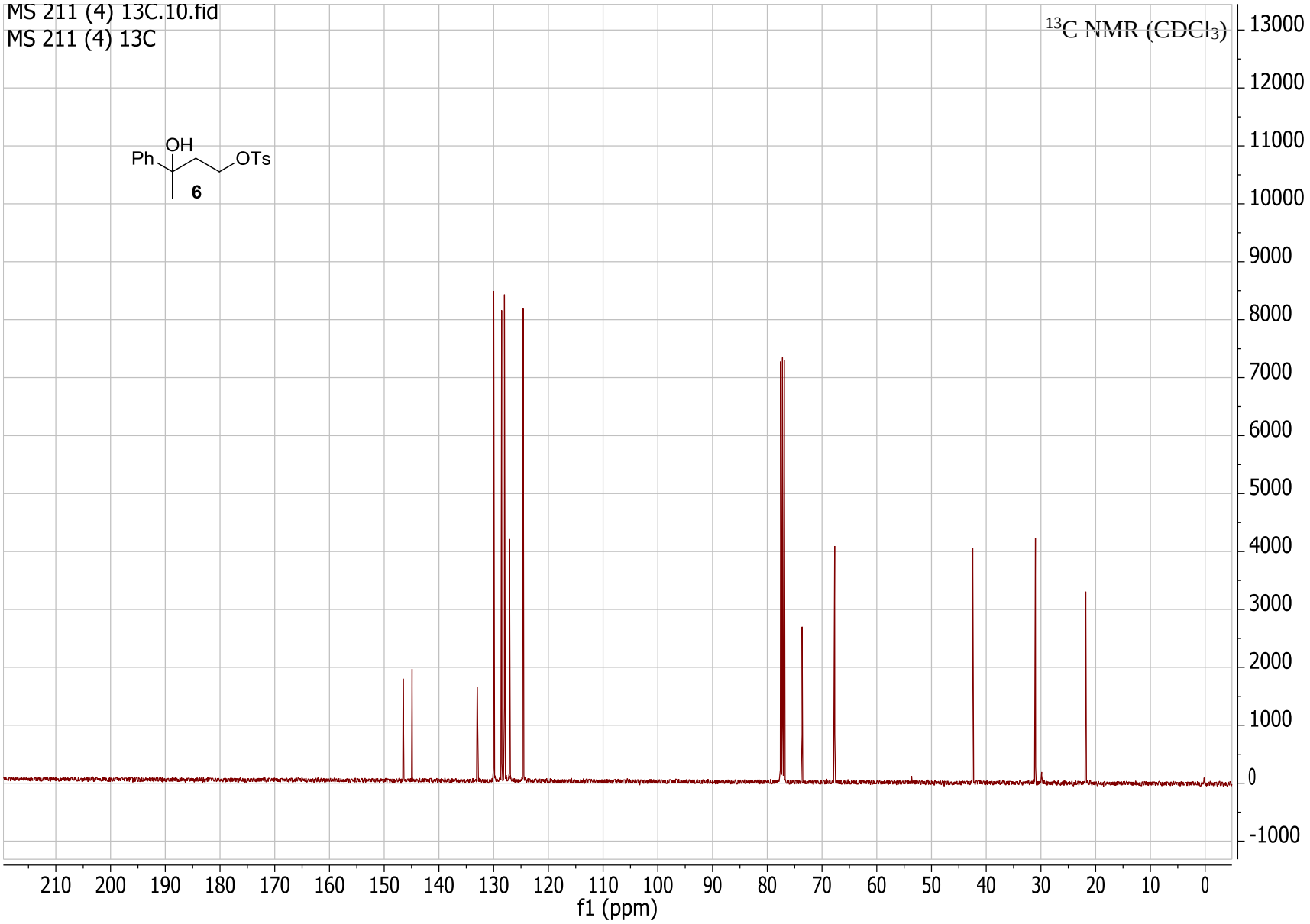

KH-9-III-pur/1
KH-9-III-pur
AV500-Prodigy
^{1}H NMR ($CDCl_3$)
OTs
OH
12
f1 (ppm)

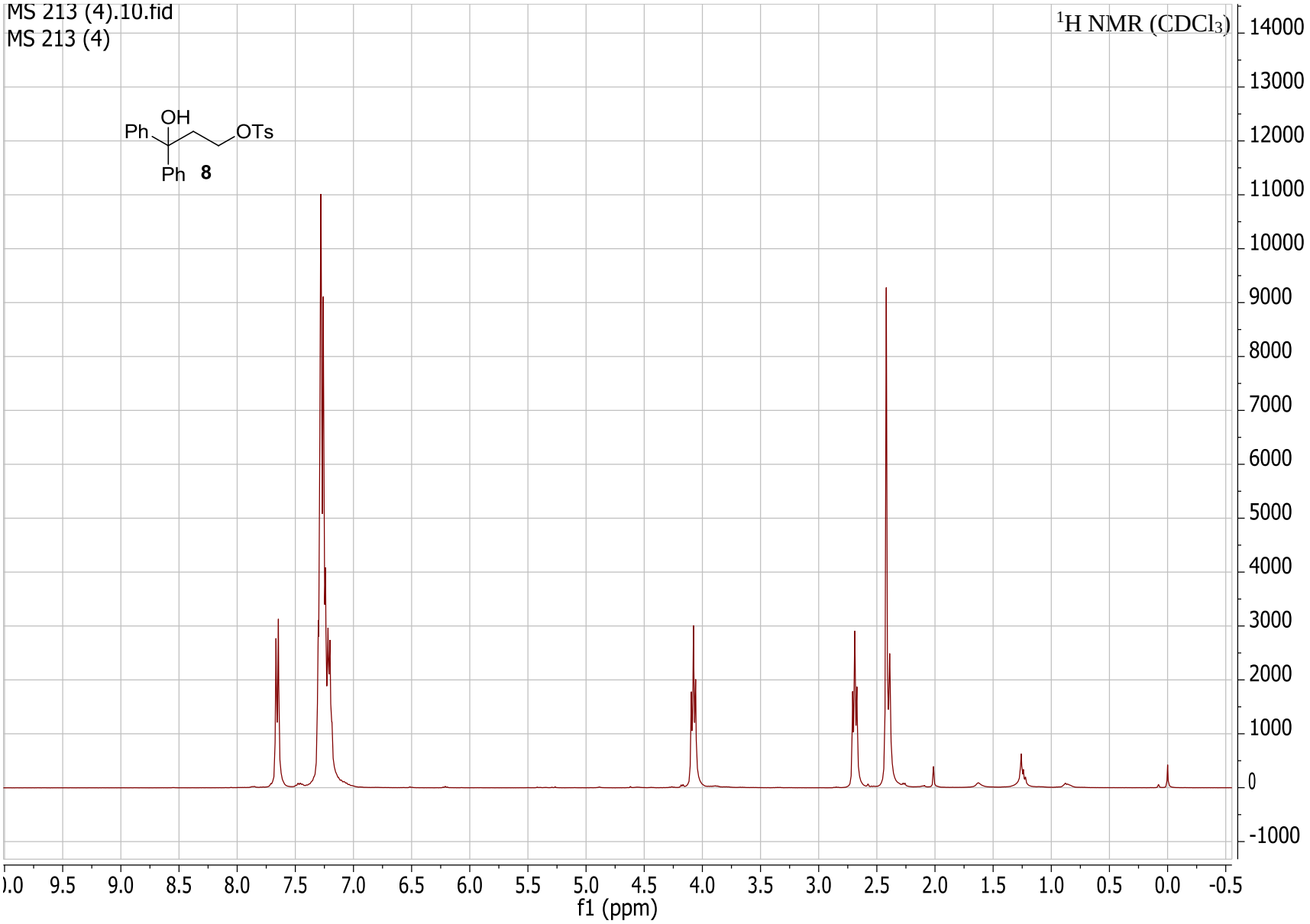

KH-9-III-pur-13C/1
KH-9-III-pur-13C
AV500-Prodigy
^{13}C NMR ($CDCl_3$)
OTs
OH
12
2500
2000
1500
1000
500
0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

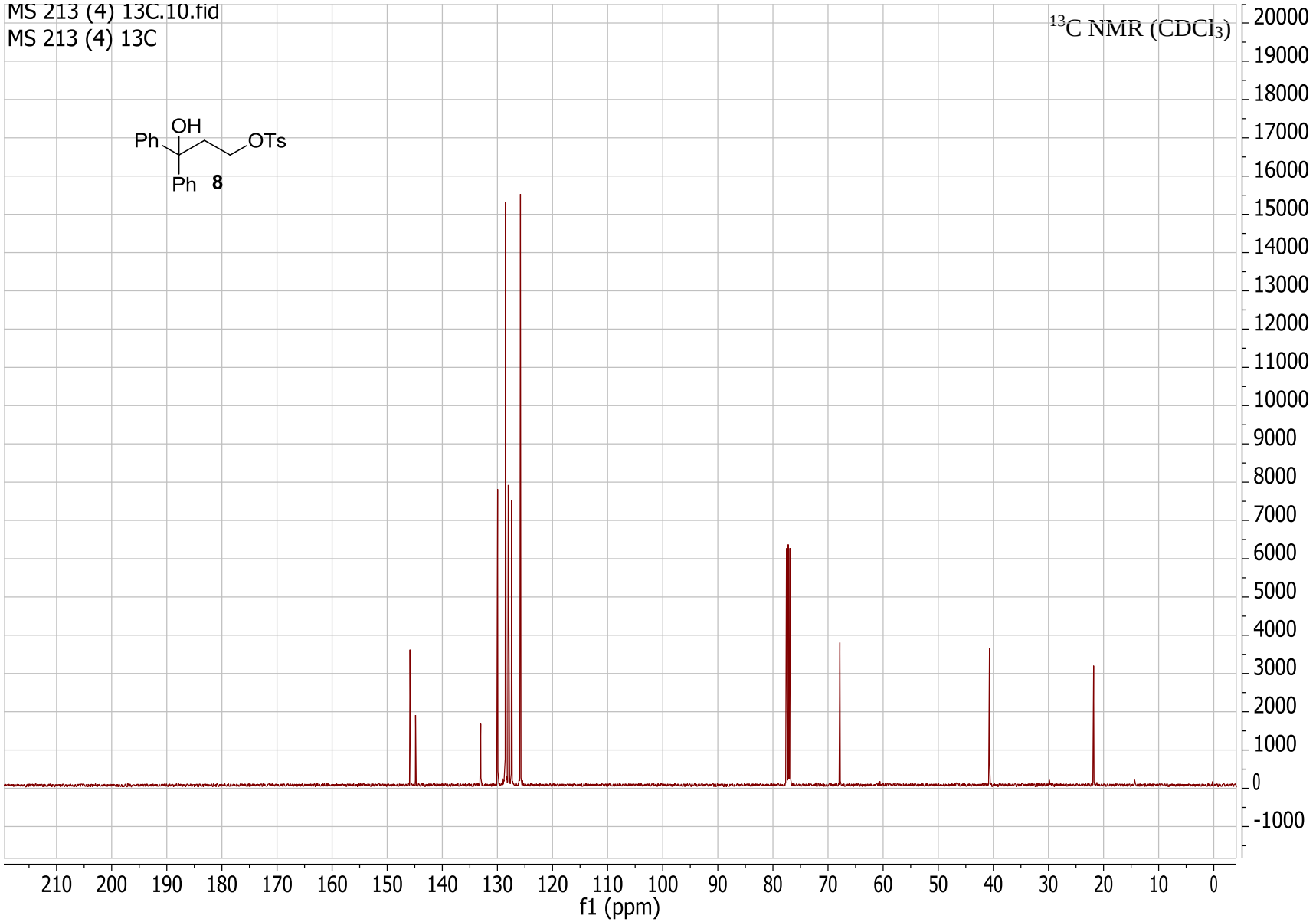

MS 299 (4).10.fid
MS 299 (4)
^{1}H NMR ($CDCl_3$)
OH
OTs
4
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


MS 299 (4) 13C.10.fid
MS 299 (4) 13 C
^{13}C NMR ($CDCl_3$)
OH
OTs
4
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


MS 211 (4).10.fid
MS 211 (4)
^{1}H NMR ($CDCl_3$)
Ph
OH
OTs
6
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
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)


MS 211 (4) 13C.10.fid
MS 211 (4) 13C
^{13}C NMR ($CDCl_3$)
Ph
OH
OTs
6
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


MS 213 (4).10.fid
MS 213 (4)
^{1}H NMR ($CDCl_3$)
OH
Ph
OTs
Ph
8
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
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)


MS 213 (4) 13C.10.fid
MS 213 (4) 13C
^{13}C NMR ($CDCl_3$)
OH
Ph
OTs
Ph
8
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

VITA

Mark Louis Spell is from the small town of Crowley Louisiana where he was born to Randy J Spell and Bonnie M Spell. After completion of his primary studies in 2007, he obtained his bachelors degree in chemistry from the University of Louisiana at Lafayette in the spring of 2011. He then decided to join the doctoral program at LSU focusing on synthetic organic chemistry and joined the research group of Dr. Justin Ragains in the fall of 2012. Mark is currently a candidate for a doctoral degree in chemistry, which will be awarded at the May 2016 commencement ceremony.