Synthesis and Characterization of Novel Atypical Sphingoid Bases

Essa M. Saied[1, 2] and Christoph Arenz[1] *

[1] Institute for Chemistry, Humboldt Universität zu Berlin, Brook-Taylor-Str. 2, 12489 Berlin, Germany.

[2] Chemistry Department, Faculty of Science, Suez Canal University, Ismailia, Egypt

* to whom correspondence should be submitted: arenzchr@hu-berlin.de

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Abstract

Sphingolipids represent an important class of eukaryotic membrane lipids. In mammals, sphingolipids are mostly characterized as derivatives of sphingosine, a long-chain 1,3-dihydroxy-2-amino alcohol. Recently, more and more atypical sphingolipids have been discovered, which are often elevated under various pathological conditions and have the potential to become biomarkers for diseases such as diabetes mellitus. The synthesis and in-depth chemical characterization of some recently discovered sphingosine bases is presented here.

1 Introduction

Sphingolipids (SL) are major components of all eukaryotic plasma membranes and characterized by hydroxyl amino alkanes, also termed long chain bases (LCB), as a core structural motif.[1-3] Key step for the synthesis of LCBs is the condensation reaction of L-serine and palmitoyl-CoA catalyzed by serine palmitoyl transferase (SPT) giving rise to C-18 3-Ketosphinganine, which is then reduced to sphinganine (also termed "dihydrosphingosine") followed by N-acylation and desaturation at the Δ4 position to form ceramides (Figure 1). The latter serves as membrane anchor for more complex SL like glycosphingolipids (GSL) or the major plasma membrane lipid, sphingomyelin (SM).[1] Under physiological conditions, about 60% of all mammalian sphingolipids contain C-18 sphingosine as core LCB. The remaining LCB differ with respect to chain length, saturation and hydroxylation and other features.[4] In other species like plants and fungi (inclucing yeast), the fully saturated 1,3,5-trihydroxyl-2-amino octadecane, phytosphingosine, is the major LCB, which also occurs in mammals, but only in rather small amounts.

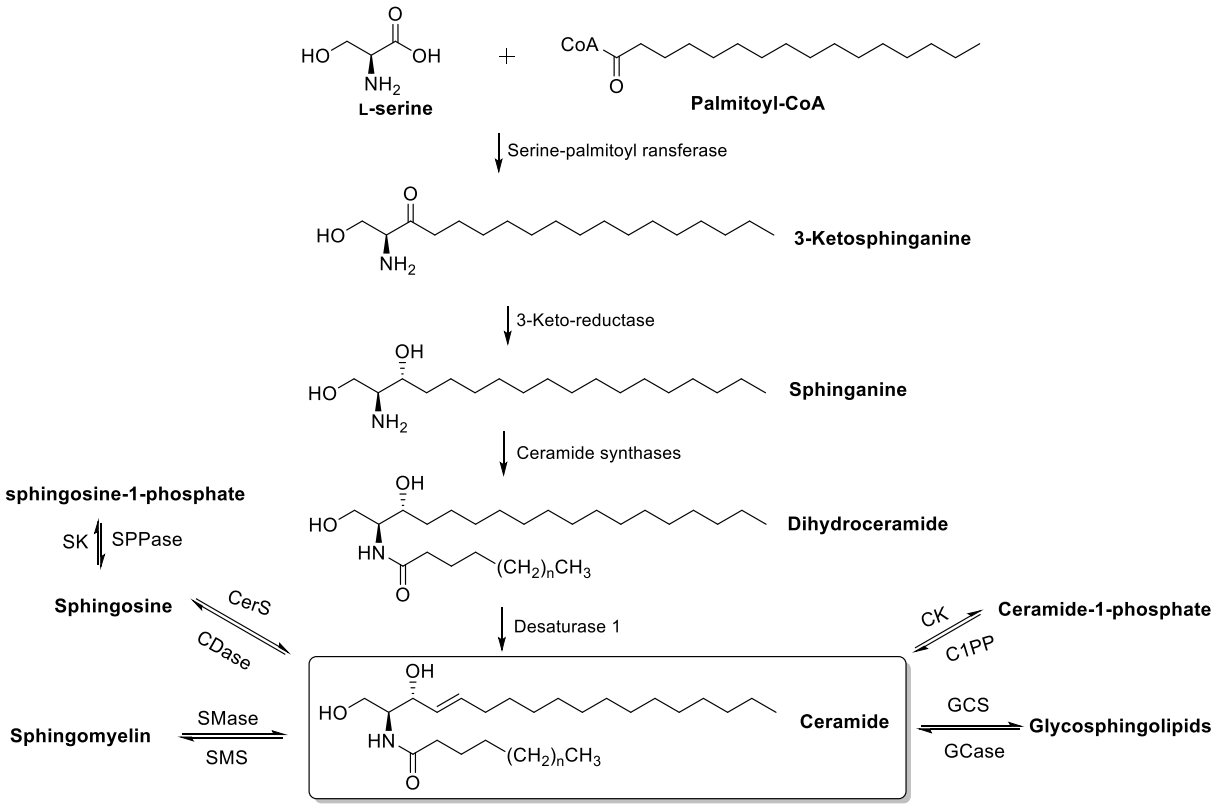


Figure 1: Metabolism of canonical sphingolipids. Various different headgroups can be added to ceramide to form different classes of complex sphingolipids. SMS, sphingomyelin synthase; SMase, sphingomyelinase; GCS, glucosyl-ceramide synthase; GCase, glucosyl ceramidase; CDase, ceramidase; CerS, ceramide synthase; CK, ceramide kinase; C1PP, ceramide-1-phosphate phosphatase; SPPase, S1P phosphatase; SK, sphingosine kinase.

In the past, the head groups and acyl chains of more complex SL have been subject to intense research, while other modifications have been much less appreciated.[4] Among the known variations to the LCB part of sphingolipids, most are introduced downstream of the SPT reaction. This is especially true for unique modifications found in some pathogenic fungi, which are the result of atypical biosynthetic pathways, catalyzed by specialized enzymes, which might provide opportunities for targeted pharmacological strategies.[5, 6] Recently, a number of LCB based on an alternative use of the enzyme serine plamitoyl transferase have come into focus.

Research in this direction has been significantly triggered by the finding that the rare inherited neuropathy HSAN1, which is linked to mutations in the SPT gene, is correlated with highly elevated levels of LCBs devoid of the primary hydroxyl group.[7, 8] The resulting deoxysphingolipids and deoxymethyl sphingolipids are elevated due to a permanent shift in substrate preference of SPT from the canonical serine to alanine or glycine, respectively. Later it was shown that these lipids are not only neurotoxic, but also elevated in other diseases without mutations in the SPT gene, like in type II diabetes mellitus.[9, 10] The mechanisms that underlie these changes in LCB composition under pathological conditions are still unknown, but subject to intense research.

SPT is a large enzyme complex consisting of the three key subunits SPTLC1, SPTLC2 and SPTLC3. SPTLC1 and SPTLC2 are essential and ubiquitously expressed,[11] while SPTLC3 expression occurs only in specific tissues.[12] SPT activity is controlled in a negative feedback mechanism through reversible phosphorylation of the two phospho-proteins, Orm1 and Orm2.[13] In yeast, another protein, Tsc3p is also required for maximal SPT activation.[14] In mammals and plants, the small subunits of SPT, ssSPTa and b are functional orthologues of Tsc3 and appear to modulate SPT activity and substrate affinity [15, 16] and recently a gain of activity mutation in ssSPTb was shown to pathologically increase C20 LCB formation in brain, leading to retinopathy and central neurodegeneration in mice.[15]

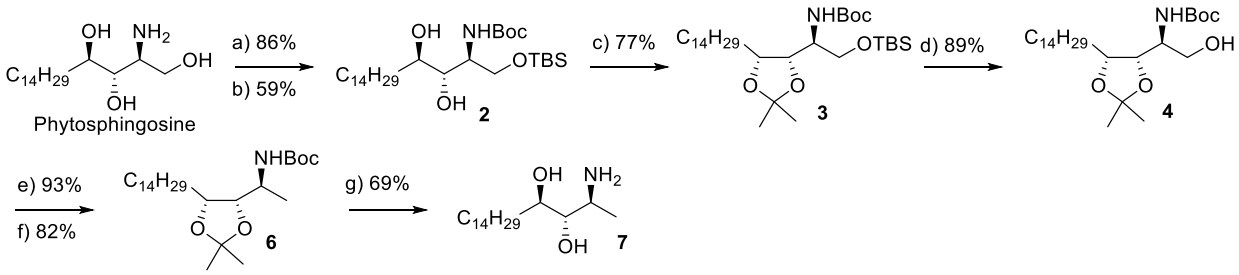
Clearly, aberrations in LCBs structure and distribution have key physiological or pathological consequences. For instance, the neurotoxicity of deoxy SL suggests their involvement in the occurrence of the frequent diabetic polyneuropathy.[9, 10, 17] Albeit, the exact molecular mechanism for the altered LCB formation in diabetes is still elusive. As LCBs derived from alanine or glycine instead of serine lack the primary hydroxyl group, formation of more complex sphingolipids via attachments of polar head groups is impossible. As a result, deoxy- and deoxymethyl SL cannot be cleared via the usual catabolic pathways due to the lack of the canonical catabolic intermediate sphingosine-1-phosphate (S1P). Recently, we have elucidated the chemical structure of 1-deoxysphingosine, the major LCB derived from an alanine instead of serine incorporation into the SPT reaction. We revealed that the primary misguided metabolic step is followed by an unexpected non-canonical introduction of the double bond. Instead of the 5E a 14Z double bond was introduced.[18] It has been found that this double bond is formed by the desaturase FADS3, which is also responsible for introduction of the 14Z double bond in sphingadienine.[19] Furthermore, the alternative catabolism of this atypical LCB by members of the cytochrome P450 family and the resulting metabolites has been elucidated.[20] Notably, the metabolic intermediates that have characterized during these studies have the potential to serve as potential biomarkers, not only for diseases like HSAN1, but may be also be highly predictive for the occurrence of neuropathy in diabetic patients.

Herein, we describe the synthesis of novel atypical sphingolipids, which have been synthesized in the course of deciphering the mechanisms of LCB and SL biosynthesis in yeast and humans. Most of these compounds have been confirmed as naturally occurring metabolites or are currently under further investigation.

2 Results and Discussion

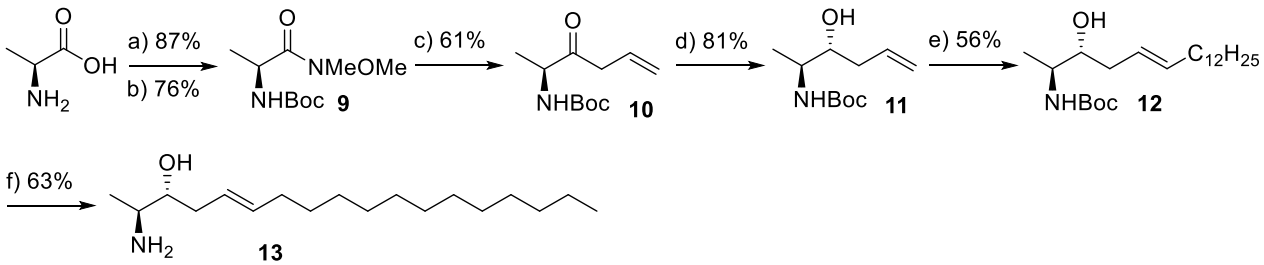
As mentioned above, phytosphingosine is the predominant LCB in plants and fungi, but also occurs in humans. In order to test, whether a deoxy-form of phytosphingosine exists, synthesis of 1-deoxysphingosine **7** was envisioned (scheme 1). Towards this end, commercial phytosphingosine was selectively N-protected using Boc-anhydride to form the intermediate **1** (not shown), which was followed by TBS-protection of the primary hydroxyl function to yield

2. Acetal protection of the remaining hydroxyl groups yielded intermediate **3**, which was treated with tert. Butyl amm0nium fluoride (TBAF) to yield **4**. The thus-deprotected primary hydroxyl group was defunctionalized after mesylation and hydride substitution to form the protected precursor **6** of the desired compound **7**. Application of this compound has been previously published.[16]



Scheme 1. **Synthesis of 1-deoxy-phytosphingosine (7)**. Reagents and conditions: a) (*t*-Boc)$_2$O, 1M NaOH, EtOH-H$_2$O, 0°C to r.t., 16h. b) TBSCl, 4-DMAP (cat.), Et$_3$N, DCM, r.t., 4h. c) 2,2-dimethoxypropane, *p*-TsOH (cat.), toluene, 90°C, 2h. d) TBAF, THF, 60°C, 1h. e) MsCl, Et$_3$N, DCM, 40°C, 1h. f) LiAlH$_4$, THF, -15°C, 1h. g) AcCl, MeOH, 0°C, 2h.

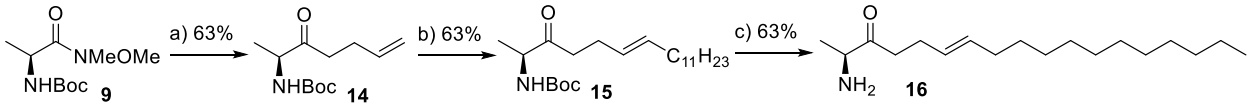
Next, we planned to synthesize 5*E*-1-deoxy-sphingosine **13**. This compound differs from the originally postulated 1-deoxy-sphingosine by a double bond, shifted by one carbon position. This synthesis was achieved by a modification of the original sphingosine synthesis developed by Garner et al. in which a protected L-serinal is modified by nucleophilic attack.[21, 22] Here, we followed an alternative strategy by Yamamoto et al.[23] The group reacted the Weinreb amide of protected L-serine with vinyl magnesium bromide to form the respective α,β unsatured ketone. Similar approaches have since then been used to synthesize SL containing modified LCB.[24-26] Moreover, 1-deoxysphingosine derivatives have been synthesized, starting from L-alanine, instead of serine.[27-29] Here, the weinreb amide of L-alanine **9** was reacted with allyl magnesium bromide to form the ketone **10** (scheme 2). Stereoselective reduction yielded **11** in excellent yield, which was subjected to olefin metathesis to form the protected precursor **12**. Deprotection of the Boc group yielded the desired compound **13.**



Scheme 2. **Synthesis of 5*E*-1-deoxy-sphingosine (13)**. Reagents and conditions: a) Boc$_2$O, 1M NaOH, dioxane, -10°C to r.t., 4h; b) Me(MeO)NH.HCl, EDCI.HCl, NMM, DCM, -15^{O}C, 2h; c) (i) Mg, 1,2-DBE, 1-allylbromide, Et$_2$O, 3h, (ii) **9**, Et$_2$O, 0°C- r.t., 3h; d) TBLAH,

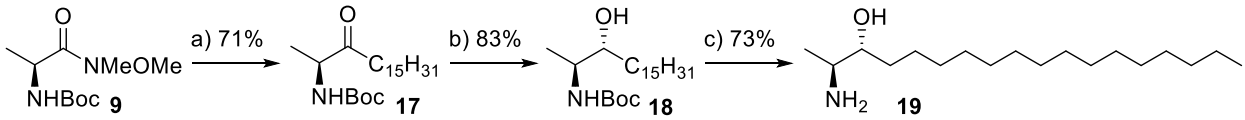
EtOH, -78°C, 2h; e) 1-tetradecene, *p*-benzoquinone (10 mol%), Grubbs 2nd generation cat.(10 mol%), DCM, 40°C, 12h; e) AcCl, MeOH, 0°C-r.t, 2h.

In the canonical SL biosynthesis, the SPT-mediated condensation step is followed by reduction of the ketone to yield sphinganine. In mammals, the desaturation takes place after N-acylation.[30] We wanted to test, whether this regime might be changed during the synthesis of deoxy-SL. As a potential intermediate, synthesis of 3-keto-6E-1-deoxy-sphingosine **16** as was envisioned (scheme 3). The synthesis was achieved starting from **9** and the desired compound **16** was achieved in three steps with a total yield of 25% (scheme 3).



Scheme 3. **Synthesis of 3-keto-6*E*-1-deoxy-sphingosine (16)**. Reagents and conditions: a) (i) Mg, 1,2-DBE, 1-butylbromide, Et_2O, 1h, (ii) **9**, Et_2O, 0°C- r.t., 2h; b) 1-tridecene, *p*-benzoquinone (10 mol%), Grubbs 2nd generation cat.(8 mol%), DCM, 40°C, 6h; c) AcCl, MeOH, 0°C-r.t, 2h.

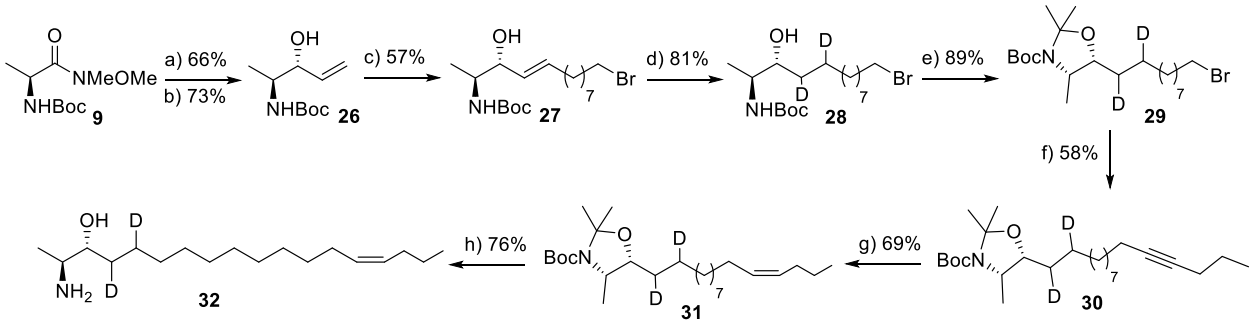
The characterization of a cell's LCB content usually follows previous saponification of all SL. Therefore, it is unknown whether the desaturation step also occurs after N-acylation or is independent from this step. A useful intermediate to follow up on this question is the 1-deoxysphinganine **19**. The latter was synthesized from **9** in three steps in very good yield (scheme 4). Instead of an unsaturated organic nucleophile, the Weinreb amide **9** was reacted with 1-bromopentadecane in the presence of metallic magnesium to form **17**. The latter was steroselectively reduced, followed by deprotection of the amino group to yield **19**.



Scheme 4. **Synthesis of 1-deoxy-sphinganine (19)**. Reagents and conditions: a) (i) Mg, 1,2-DBE, 1-bromopentadecane, THF, 3h, (ii) **9**, THF, 0°C- r.t., 2h; b) TBLAH, EtOH, -78°C, 2h; c) AcCl, MeOH, 0°C-r.t, 2h.

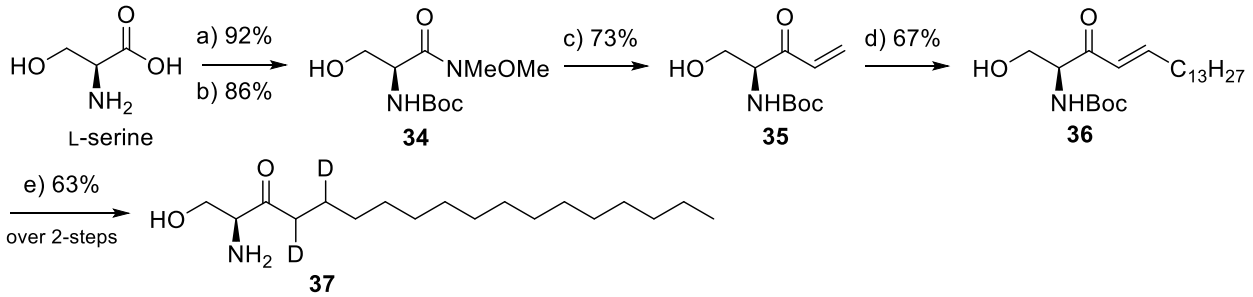
The final elucidation of the structure of 1-deoxy-sphingosine makes it a potential biomarker for diabetic retinopathy. Therefore we aimed at synthesizing a deuterated MS standard (scheme 5). Towards this end, **9** was converted into the w-bromocompound **27** followed by deuteration of the double bond to yield **28**. The latter was reacted with dimethoxy propane and the resulting

intermediate **29** was reacted with 1-pentyne in presence of tert.-BuLi. The resulting intermediate **30** was selectively converted to the Z-alkene **31** and the desired deuterated 1-deoxy-sphingosine **32** was achieved after deprotection.



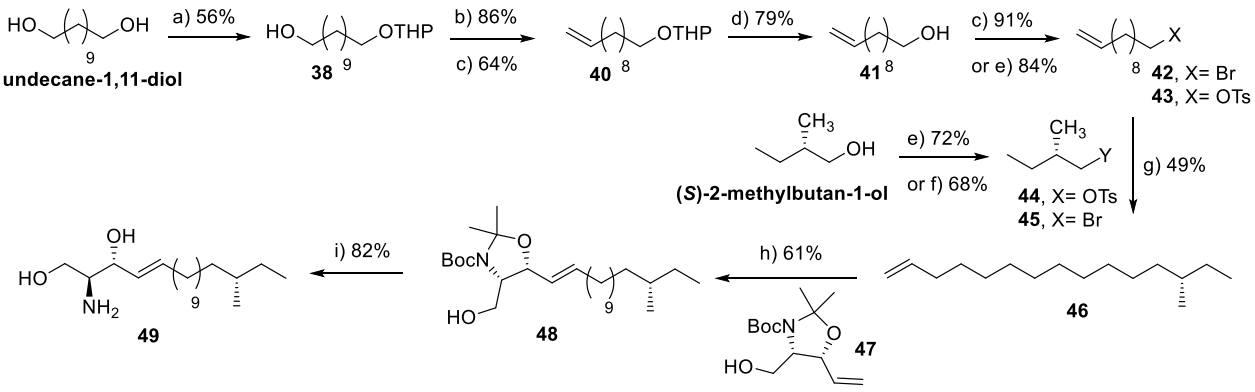
Scheme 5. **Synthesis of 14*Z*-1-deoxy-sphingosine-d_2 (32)**. Reagents and conditions: a) vinylmagnesium bromide (1M in THF), THF, -20^{O}C-r.t., 4h; b) TBLAH, EtOH, -78°C, 3h; c) 10-bromo-1-decene, *p*-benzoquinone (10 mol%), Grubbs 2nd generation cat.(10 mol%), DCM, 40°C, 12h; d) D_2, 10 % Pd/C, d-acetic acid (cat.), d-Methanol, rt, 14h; e) 2,2-dimethoxypropane, *p*-TsOH (cat.), toluene, reflux, 2h; f) (i) 1-pentyne, *tert*-BuLi, THF, -78°C, (ii) **29**, HMPA, THF, -78°C- r.t.,12h; g) H_2, Lindlar cat., EtOAc, DMF, r.t., 16h; h) AcCl, MeOH, 0°C-r.t, 2h.

Next, we wanted to synthesize an MS standard for the canonical 3-ketosphinganine. Towards this goal, L-serine was converted into the respective Boc-protected Weinreb amide **34** (scheme 6). This was followed by reaction with vinyl magnesium bromide to yield **35**, as described previously.[28] After the essential olefin metathesis, the resulting intermediate **36** was deuterated to yield the target molecule **37**.



Scheme 6. **Synthesis of 3-ketosphinganine-d_2 (37)**. Reagents and conditions: a) Boc_2O, 1M NaOH, dioxane, -10°C to r.t., 4h; b) Me(MeO)NH.HCl, EDCI.HCl, NMM, DCM, -15^{O}C, 2h; c) (i) n-BuLi, THF, -65^{O}C, 30min, (ii) vinylmagnesium bromide (1M in THF), -65°C- r.t., 6h; d) 1-pentadecene, Grubbs 2nd generation cat.(7 mol%), DCM, 40°C, 6h; e) (i) D_2, 10 % Pd/C, d-acetic acid (cat.), d-Methanol, rt, 12h, (ii) 2M HCl, THF-MeOH, reflux, 2h.

In the course of our ongoing studies, the methyl-branched LCB **49** was postulated (unpublished results). To proof this hypothesis, the target compound was synthesized as depicted in scheme 7. The long chain terminal diol **9** was protected with a single THP group as described above. Then, the resulting **38** was brominated followed by Br-elimination to yield the terminal alkene **40**. After deprotection the hydroxyl group was tosylated and reacted with the branched building block **45** in presence of metallic magnesium. The branched alkene **46** was then reacted in an olefin metathesis with the previously described intermediate **47**.[28] Final deprotection yielded the desired branched LCB **49**.



Scheme 7. **Synthesis of (16*S*)-Methyl-sphingosine (49)**. Reagents and conditions: a) DHP, PTSA (cat.), THF, 0°C-rt, 16h; b) CBr_4, PPh_3, DCM, 0°C-rt, 4h; d) PPTS (cat.), EtOH, 62°C, 2h; e) TsCl, pyridine, DCM, 0°C-rt, 16h; f) NBS, PPh_3, DCM, 0°C-rt, 2h; g) (i) **45**, Mg, THF, 30°C, 90 min, and then (ii) **43**, Li_2CuCl_4 (cat), THF, -78°C-rt, 16h; h) **47**, Grubbs 2nd generation (cat.), DCM, reflux, 12h; i) AcCl, MeOH, 0°C-rt, 2h.

3 Conclusion

Here, we have described the synthesis of several novel atypical sphingolipid LCB.

4 Experimental

4.1 General description of materials and methods

Unless otherwise specified, all reactions were carried out in oven-dried (>120°C) glassware equipped with a magnetic stir bar and a rubber septum under a positive pressure of argon. Air- or moisture-sensitive reagents were transferred to the reaction vessel under positive pressure of argon via syringe. Air and/or moisture sensitive reactions were carried out in well dried glassware under an argon atmosphere with dry, freshly distilled solvents using standard syringe-cannula/septa techniques. Reactions were run at room temperature (20-25°C) unless otherwise noted in the experimental procedure, and reported reaction temperatures refer to the external temperatures measured for the bath in which the reaction vessel was immersed. Heating was obtained through the use of a silicone oil bath. For reactions run below room temperature, the term "-78°C" refers to a bath of acetone and dry ice, "-

20°C" refers to a slurry of sodium chloride and ice-water bath, and "0°C" refers to an ice-water bath. Removal of residual solvents was accomplished by evacuation of the container for a period of 12-20 hours using a high vacuum line.

Reagents and solvents

All the commercially available reagents were purchased from Sigma-Aldrich, TCI, Fluka or Acros and used without further purification, unless otherwise specified. All the solvents were used after distillation by standard methods. The petroleum ether used throughout this study had a boiling range of 40–60°C.

Chromatography

The thin layer chromatography studies were performed on pre-coated silica gel 60-F_{254} on aluminum sheets (Merck KGaA) and spots were detected by UV illumination (254 nm), and/or spraying with 1.3% ninhydrin solution, ceric ammonium molybdate (Seebach reagent) solution (25 g $MoO_3 \cdot H_3PO_4 \cdot H_2O$, 10 g $Ce(SO_4)_2 \cdot 4H_2O$, 60 ml H_2SO_4 and 905 ml of H_2O) or $KMnO_4$ solution (1.5 g $KMnO_4$, 10 g K_2CO_3 and 1.25 ml 10% NaOH in 200 ml water) followed by heating. Preparative flash column chromatography was performed manually using glass columns of different size packed with Silica Gel 60M (0.04-0.063 mm) as stationary phase with indicated eluent systems in parenthesis following the description of purification. Solvent ratios for chromatography and R_f values are reported in v/v% ratios.

Spectroscopic Data

The structure of all synthesized compounds was confirmed with ^{1}H NMR, ^{13}C NMR, DEPT, ^{31}P NMR and MS analysis. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on Bruker AVANCE II 300, AVANCED PX 300, AVANCE 400 and Bruker ADVANCE III 500 spectrometers (^{1}H at 300, 400 or 500 MHz, ^{13}C at 75.4, 101.2 or 125.7 MHz and ^{31}P at 161.9 or 202.4 Hz) as solutions in $CDCl_3$, CD_3OD or mixtures of those at 25 °C. Chemical shifts (δ) are reported in parts per million (ppm): multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Chemical shifts are given in ppm with respect to TMS as an external standard, (^{1}H, APT, ^{13}C, δ = 0.00) with calibration against the residual solvent signal or 85% H_3PO_4 (^{31}P, δ= 0.00) as external standard. The coupling constants *J* are given in Hz.

Mass Spectroscopy

Mass spectroscopy (MS) experiments were recorded on an AGILENT 6120 UPLC–MS system consisting of an SQD (single quadrupole detector) mass spectrometer equipped with an electrospray ionization interface (ESI) in the positive and negative ion detection modes. The samples were separated on a Zorbax Eclipse Plus C18 column (particle size 1.8 µ m, 2.1 × 50 mm) using a UPLC pump at a flow rate of 0.8 ml per min with a ternary solvent system of MeOH-H_2O-HCOOH, methanol (99.9% MeOH: 0.1% HCOOH, v/v). The column was first equilibrated using a mixture of 95% mobile phase A and 5% mobile phase B, and then 10 µ l of the sample was injected. This was followed by a ramp gradient over 2 min to 95% phase B and 5% phase A, which remained until 7 min, followed by a ramp gradient back down to 95% solvent A and 5% solvent B for 1 min, and column equilibration with the same mixture for 1 min. The detection was performed in full scan mode and the major observable molecular ion and selected fragments and clusters have been reported.

(2*S*,3*S*,4*R*)-*tert*-butyl-(1,3,4-trihydroxyoctadecan-2-yl)carbamate (1)

A suspension of phytosphingosine (1.0 g, 3.15 mmol) in a mixture of ethanol (20 mL) and water (10 mL) at ambient temperature was treated with a solution of 1M NaOH (4 mL, until pH=8). After the resulting mixture was cooled to 0°C, di-*tert*-butyldicarbonate (1.1 g, 4.73 mmol) was added in portions. The resulting reaction mixture was allowed to stir at ambient temperature for 16h (as indicated by TLC analysis for complete reaction), and subsequently was quenched with 1M HCl solution (50 mL). The resulting mixture was extracted with ethylacetate (3×80 mL), and the combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to provide compound **1** as a white solid. The product was used in the next step without any further purification.

Yield: 1.53 g, (86%). R_f: 0.4 (EtOAc 100%, visualized with 1.3% ninhydrine). ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 5.46 (d, *J* = 6.7 Hz, 1 H), 3.92-3.62 (m, 5 H), 3.17 (br s, 1 H), 1.45 (s, 9 H), 1.38-1.18 (m, 26 H), 0.89 (t, *J* =6.9 Hz, 3 H). ^{13}C-NMR ($CDCl_3$, 125 MHz, ppm) δ 156.5, 80.2, 76.7, 73.0, 62.1, 53.1, 33.2, 31.9, 30.0, 29.7, 29.6, 29.3, 28.4, 25.9, 22.7, 14.1. ESI-MS *m/z* $(M+Na)^+$ 440.3.

(2*S*,3*S*,4*R*)-*tert*-butyl-1-((*tert*-butyldimethylsilyl)oxy)-3,4-dihydroxyoctadecan-2-yl)-carbamate (2)

To a stirred solution of compound **1** (1.0 g, 2.4 mmol) in dry DCM (52 mL) at 0°C under argon atmosphere was added triethylamine (385 µl, 2.75 mmol), followed by a catalytic amount of 4-(dimethylamino)-pyridine (4-DMAP, 29 mg, 10 mol%). After being stirred at the same conditions for 10 min, the resulting mixture was treated with *tert*-butyldimethylsilyl chloride (TBSCl, 0.41 g, 2.75 mmol) in portions over a period of 10 min. The resulting reaction mixture was allowed to stir at ambient temperature for 2h (as monitored by TLC analysis), before it was quenched with methanol (10 mL). The resulting mixture was diluted with DCM (100 mL), and sequentially washed with 1% HCl solution (80 mL), saturated $NaHCO_3$ solution (80 mL), and brine (80 mL). The organic phase was then dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Flash column chromatography of the obtained crude residue over silica gel using cyclohexane and ethylacetate as eluents (from 5-15% ethylacetate in cyclohexane) provided the desired product **2** as a pale yellow oil.

Yield: 0.75 g, (59%). R_f: 0.65 (cyclohexane / EtOAc 3:2, visualized with 1.3% ninhydrine). ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 5.17 (d, *J* = 7.4 Hz, 1H), 4.01 (d, *J* = 9.7 Hz, 1 H), 3.87 (br.s, 1H), 3.85-3.79 (m, 1H), 3.67-3.58 (m, 2H), 1.64-1.27 (m, 35H), 0.91 (s, 9 H), 0.89 (t, *J* = 6.8 Hz, 3H), 0.13 (s, 6 H). ^{13}C-NMR ($CDCl_3$, 125 MHz, ppm) δ 155.6, 108.2, 76.0, 73.4, 62.9, 51.7, 33.4, 32.0, 29.8, 29.7, 29.6, 29.4, 28.4, 25.9, 25.9, 22.7, 14.2, -5.5. ESI-MS *m/z* $(M+H)^+$ 532.4.

***tert*-Butyl((*S*)-2-((*tert*-butyldimethylsilyl)oxy)-1-((4*S*,5*R*)-2,2-dimethyl-5-tetradecyl-1,3-di-oxolan -4-yl)ethyl)carbamate (3)**

A stirred solution of compound **2** (700 mg, 1.32 mmol) in anhydrous toluene (7 mL) under an argon atmosphere was treated with 2,2-dimethoxypropane (650 µL, 5.3 mmol), followed by a catalytic amount of *p*-toluensulfonic acid monohydrate (*p*-TsOH, 25 mg, 10 mol%). After the resulting reaction mixture was allowed to stir under reflux for 1h (as judged by the TLC analysis, visualized with $KMnO_4$ solution), the reaction mixture was cooled to ambient temperature, diluted with ethylacetate, and carefully quenched with saturated $NaHCO_3$ solution

(100 mL). The layers were separated, and the aqueous layer was extracted with ethylacetate (3x80 mL). The organic layers were combined, washed with brine (150 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the obtained crude mixture by flash column chromatography over silica gel using petroleum ether and ethylacetate as eluents (from 0% to 2.5% ethylacetate in petroleum ether) afforded the desired product **3** as a colorless solid.

Yield: 580 mg, (77%). R_f: 0.66 (cyclohexane / EtOAc 95:5, visualized with 1.3% ninhydrine). ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 4.72 (d, *J* = 9.6 Hz, 1H), 4.10- 4.00 (m, 2H), 3.83 (dd, *J* = 9.8 Hz, 1 H), 3.74 (m, 1 H), 3.68-3.61 (m, 1H), 1.58-1.40 (m, 14H), 1.32-1.23 (m, 27H), 0.89 (s, 9 H), 0.87 (t, *J* = 6.9 Hz, 3 H), 0.05 (s, 6 H). ^{13}C-NMR ($CDCl_3$, 125 MHz, ppm) δ 155.2, 107.9, 79.5, 78.1, 75.7, 63.0, 50.9, 32.1, 29.8, 29.8, 29.7, 29.5, 28.5, 26.0, 22.8, 18.5, 14.3, -5.3. ESI-MS *m/z* $(M+H)^+$ 572.4.

tert-Butyl-((*S*)-1-((4*S*,5*R*)-2,2-dimethyl-5-tetradecyl-1,3-dioxolan-4-yl)-2-hydroxyethyl)-carbamate (4)

A solution of n-tetrabutylammonium fluoride (TBAF, 2.6 mL, 2.6 mmol, 1M solution in THF) was added dropwise to a stirred solution of compound **3** (500 mg, 0.87 mmol) in dry THF (9 mL) at ambient temperature under argon atmosphere. After the resulting reaction mixture was allowed to stir for 1h at 60°C (as monitored by TLC analysis, Cyclohexane/ EtOAc 9:1; $R_{f\ (adduct)}$= 0.7; $R_{f\ (product)}$=0.3; visualized with 1.3% ninhydrine), the solvent was removed under reduced pressure. The residue was subsequently partitioned between water (50 mL) and CH_2Cl_2 (50 mL), and the layers were separated. The aqueous layer was extracted several times with dichloromethane (3×40 mL) and the combined organic layers were washed with saturated $NaHCO_3$ solution (100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Flash column chromatography of the resultant crude residue over silica gel using petroleum ether and ethylacetate as eluents (from 20-25% ethylacetate in petroleum ether) provided compound **4** as a colorless solid.

Yield: 355 mg, (89%). R_f: 0.48 (cyclohexane / EtOAc 3:2, visualized with 1.3% ninhydrine). ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 4.95 (d, *J* = 8.6 Hz, 1H), 4.17 (m, 1H), 3.86 (m, 1H), 3.77 (m, 1 H), 3.69 (m, 1H), 1.68-1.41 (m, 14H), 1.36-1.22 (m, 27H), 0.87 (t, *J* = 6.9 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 125 MHz, ppm) δ 108.2, 78.0, 77.4, 63.9, 51.2, 32.1, 29.8, 29.8, 29.7, 29.6, 29.5, 29.3, 28.5, 27.7, 25.6, 25.4, 22.8, 14.3. ESI-MS *m/z* $(M+Na)^+$ 480.3.

(*S*)-2-((*tert*-butoxycarbonyl)amino)-2-((4*S*,5*R*)-2,2-dimethyl-5-tetradecyl-1,3-dioxolan-4-yl)-ethyl methanesulfonate (5)

To a stirred solution of compound **4** (320 mg, 0.7 mmol) in dry DCM (7 mL) at 0°C under argon atmosphere was added triethylamine (0.55 ml, 1.75 mmol), followed by dropwise addition of mesyl chloride (82 µL, 1.05 mmol) over a period of 20 min. After being stirred at 40°C for 1h (as indicated by TLC analysis for complete mesylation of adduct (cyclohexane/ EtOAc 3:2; $R_{f\ (adduct)}$= 0.48; $R_{f\ (product)}$=0.67; visualized with 1.3% ninhydrine), the reaction mixture was cooled to 0°C, and was carefully quenched with saturated NH_4Cl solution (50 mL). The resulting mixture was diluted with DCM (50 mL), and the layers were separated. The aqueous layer was extracted several times with dichloromethane (3x50 mL), and the combined

organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The obtained crude mixture was immediately purified by flash column chromatography over silica gel using petroleum ether and ethylacetate as eluents (from 10-15% ethylacetate in petroleum ether) to provide the desired product **5** as pale yellow solid. The product was used immediately in the next step.

Yield: 350 mg, (93%). R_f: 0.51 (cyclohexane / EtOAc 4:1, visualized with 1.3% ninhydrine). ESI-MS *m/z* $(M+Na)^+$ 558.2.

tert-Butyl ((S)-1-((4*S*,5*R*)-2,2-dimethyl-5-tetradecyl-1,3-dioxolan-4-yl)ethyl)-carbamate (6)

To a stirred solution of compound **5** (310 mg, 0.58 mmol) in dry THF (6 mL) at -15°C under argon atmosphere was added lithium aluminum hydride (LAH, 26.5 mg, 0.7 mmol) in portions over a period of 20 min. After the reaction mixture was allowed to stir at the same conditions for 1h (as monitored by TLC analysis, cyclohexane/EtOAc 4:1; $R_{f(adduct)} = 0.51$; $R_{f(product)} = 0.63$; visualized with 0.3% ninhydrine), an ice-cooled 10% aqueous potassium hydroxide solution (2 mL) was carefully added to quench. After the resulting mixture was stirred at ambient temperature for 1h, the white precipitate was removed by filtration through celite. The combined organic filtrates were washed with aqueous phosphate buffer (pH=7, 50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the resultant residue by flash column chromatography over silica gel using petroleum ether and ethylacetate as eluents (from 5%- 15% ethylacetate in petroleum ether) afforded the desired product **6** as colorless solid.

Yield: 210 mg, (82%). R_f: 0.63 (cyclohexane / EtOAc 4:1, visualized with 1.3% ninhydrine). ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 4.53 (d, *J* = 8.9 Hz, 1H), 4.14 (dd, *J* = 12.9, 6.4 Hz, 1H), 3.98 (t, *J* = 5.4 Hz, 1H), 3.75 (m, 1H), 1.60 – 1.41 (m, 14H), 1.34 – 1.24 (m, 27H), 1.15 (d, *J* = 6.6 Hz, 3H), 0.88 (t, *J* = 6.9 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 125 MHz, ppm) δ 155.1, 107.9, 80.6, 79.4, 77.9, 46.6, 32.1, 29.8, 29.8, 29.7, 29.5, 28.5, 25.5, 22.8, 18.0, 14.3. ESI-MS *m/z* $(M+H)^+$ 442.3.

(2*S*,3*S*,4*R*)-2-aminooctadecane-3,4-diol (7)

A stirred solution of compound **6** (140 mg, 0.32 mmol) in methanol (5mL) at 0°C was treated with acetyl chloride in dropwise (AcCl, 230 µL, 3.2 mmol). After the resulting reaction mixture was allowed to stir at ambient temperature for 2h, the resultant white solid was filtered off and subsequently washed with ice-cooled diethylether to provide the desired product as a colorless solid. The obtained crude product was further purified by flash column chromatography over silica gel using ethylacetate and isopropanol as eluents (from 0-10% isopropanol in ethylacetate) to afford compound **7** as a white solid.

Yield: 65 mg (69 %). R_f: 0.38 (EtOAc/ iso-propanol 4:1, visualized with $KMnO_4$ solution). ^{1}H NMR (MeOD, 500 MHz, ppm) δ 3.58 (dt, *J* = 9.5, 4.7 Hz, 1H), 3.40 (ddd, *J* = 16.9, 11.8, 5.9 Hz, 1H), 1.82 (t, *J* = 9.5 Hz, 1H), 1.60 –1.52 (m, 1H), 1.40–1.26 (m, 8H), 1.25 (d, *J* = 6.7 Hz, 1H), 0.89 (t, *J* = 6.8 Hz, 1H). ^{13}C NMR (MeOD, 125 MHz, ppm) δ 74.7, 72.8, 50.4, 35.3, 33.1, 30.8, 30.8, 30.7, 30.5, 26.3, 23.7, 14.4, 11.9. ESI-MS *m/z* $(M+H)^+$ 302.3.

Synthesis of (*tert*-butoxycarbonyl)-L-alanine (8)

A solution of di-*tert*-butyl dicarbonate (14.34 g, 70.72 mmol) in dioxane (120 mL) was added dropwise to a stirred solution of L-alanine (6.00 g, 67.34 mmol) in aqueous 1M NaOH (120 mL) at -10ºC. After the resulting reaction mixture was stirred for 12h at ambient temperature, the reaction mixture was washed with ethylacetate (2×150 mL) to remove excess of unreacted Boc_2O. The aqueous layer was cooled again at -15ºC and carefully acidified with a solution of 1M $KHSO_4$ to pH=2-3. The resulting mixture was subsequently extracted several times with ethylacetate (4×150 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to provide *N*-Boc-L-alanine as white solid. The product was used in the next step without further purification.

Yield: 11.4 g (87%). R_f: 0.3 ($CHCl_3$/MeOH 12:1; visualized with 1.3% ninhydrine solution). ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 5.12-5.04 (m, 1H), 4.40-4.32 (m, 1H), 1.48-1.43 (m, 12H). ^{13}C NMR ($CDCl_3$, 126 MHz, ppm): δ 177.83, 155.62, 80.46, 49.25, 28.43, 18.43. ESI-LCMS: *m/z* calcd for $C_8H_{16}NO_4$ $[M+H]^+$ 190.11; observed 190.1 [31].

Synthesis of (*S*)-*tert*-butyl-1-(*N*-methoxy-*N*-methylcarbamoyl)ethylcarbamate (9)

To a stirred solution of *N*-Boc-L-alanine (4.50 g, 23.8 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (2.6 g, 26.2 mmol) and *N*-methylmorpholine (5.2 mL, 47.6 mmol) in dry DCM (100 mL) at -10°C under an argon atmosphere, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (5 g, 26.2 mmol) was added portionwise over a period of 30 min. The resulting reaction mixture was allowed to stir for 4h at 0°C (as monitored by TLC analysis for almost complete reaction; Silica gel, EtOAc 100%; $R_{f(adduct)}$= 0.1; $R_{f(product)}$=0.56; visualized with 1.3% ninhydrine solution), and was then quenched with saturated NH_4Cl solution (200 mL). The layers were separated and the aqueous layer was extracted several times with CH_2Cl_2 (4×100 mL). The organic layers were combined, washed with saturated $NaHCO_3$ solution (120 mL), brine (120 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford compound **9** as a white solid. The product was used in the next step without any further purification.

Yield: 4.1 g (76 %). R_f: 0.42 (cyclohexane/ethylacetate 3:2, visualized with 1.3% ninhydrine). ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 5.27 (d, *J*= 6.9 Hz, 1H), 4.74-4.62 (br. m, 1H), 3.77 (s, 3H), 3.21 (s, 3H), 1.44 (s, 9H), 1.31 (d, *J*= 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 126 MHz, ppm): δ 18.80, 28.50, 32.27, 46.66, 61.75, 79.65, 155.33, 173.80. ESI-LCMS: *m/z* calcd for $C_{10}H_{21}N_2O_4$ $[M+H]^+$ 233.15; observed 233.1 [31].

Synthesis of (*S*)-*tert*-butyl -(3-oxohex-5-en-2-yl)carbamate (10)

The 1-allylmagnesium bromide was prepared as follows; Catalytic drops of 1,2-dibromoethane was added to a mixture of magnesium powder (1.84 g, 77 mmol) in anhydrous Et_2O (10mL) under an argon atmosphere at ambient temperature. The resulting mixture was stirred at the same conditions for 10 min, before it treated with a solution of 1-allylbromide (2.4 g, 19.3 mmol, 1M solution in anhydrous Et_2O). The resulting reaction mixture was allowed to stir at 35°C for 3h to afford a transparent allylmagnesium bromide solution which was used in the next step.

A freshly prepared allylmagnesium bromide solution (19.3 mmol, 20 mL) was added dropwise to a stirred solution of Weinreb amide **9** (1.3 g, 5.5 mmol) in dry diethylether (mL) under argon atmosphere at 0°C. After being stirred at the same conditions for 30 min and for additional 2h at ambient temperature (as judged by TLC analysis; Pet. ether/ EtOAc 4:1; $R_{f\ (adduct)}$= 0.2; $R_{f\ (product)}$=0.54;visualized with 1.3% ninhydrine), the reaction mixture was dropwisely added to an ice-cooled 1M HCl solution (100 mL) to quench. The resulting mixture was diluted with ethylactetate and transferred to separating funnel. The layers were separated and the aqueous layer was extracted again with ethylacetate (2x100 mL). The organic extracts were combined, washed with sat $NaHCO_3$ solution and brine solution, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to provide a brownish oil residue. Purification of the resultant crude residue with flash column chromatography over silica gel using petroleum ether and ethylacetate as eluents (0-10% ethylacetate in petroleum ether) afforded the product **10** as a white solid.

Yield: 710 mg (61 %). R_f: 0.54 (Pet. ether /EtOAc 4:1, visualized with 1.3% ninhydrine solution). ^{1}H NMR ($CDCl_3$, 500 MHz, ppm) δ 5.91 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.20 (ddd, *J* = 10.2, 2.7, 1.3 Hz, 1H), 5.16 (dq, *J* = 17.1, 1.5 Hz, 1H), 4.39 – 4.32 (m, 1H), 3.33 – 3.22 (m, 2H), 1.43 (s, 9H), 1.33 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 126 MHz, ppm) δ 207.55, 155.28, 129.94, 119.45, 79.94, 54.91, 44.14, 28.47, 17.83. ESI-MS *m/z* calcd for $C_{11}H_{20}NO_3$ $[M+H]^+$ 214.14; observed: 214.1.

Synthesis of (2*S*,3*R*)-*tert*-butyl (3-hydroxyhex-5-en-2-yl)carbamate (11)

Lithium tri-(*tert*-butoxy)-aluminum hydride (1.7 g, 6.75 mmol) was added in portionwise to a stirred solution of compound **10** (0.58 g, 2.7 mmol) in dry ethanol (6 mL) under argon atmosphere at -78°C. The resulting reaction mixture was allowed to stir at the same conditions for 2h (as judged by TLC analysis; Pet. ether/ EtOAc 4:1; $R_{f\ (adduct)}$= 0.54; $R_{f\ (product)}$=0.42;visualized with 1.3% ninhydrine), before it was quenched with ice-cooled 1M HCl solution (120 mL). The resulting mixture was allowed to warm gradually to ambient temperature and then diluted with ethylacetate (100 mL). The layers were separated and the aqueous layer was extracted with ethylacetate (2x100 mL). The combined organic extracts were washed with sat. $NaHCO_3$ solution and brine solution, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The obtained crude residue was purified by flash column chromatography over silica gel using petroleum ether and ethylacetate as eluents (10-20% ethylacetate in petroleum ether) to provide the product **11** as a pale yellow oil.

Yield: 470 mg (81 %). R_f: 0.48 (Pet. ether /EtOAc 3:2, visualized with 1.3% ninhydrine solution). ^{1}H NMR ($CDCl_3$, 500 MHz, ppm) δ 5.83 (ddt, *J* = 17.1, 10.2, 7.1 Hz, 1H), 5.17 – 5.13 (m, 1H), 5.12 (dd, *J* = 3.3, 1.5 Hz, 1H), 4.78 (br.s, 1H), 3.73 – 3.67 (m, 2H), 2.27 – 2.12 (m, 2H), 1.44 (s, 9H), 1.11 (d, *J* = 6.8 Hz, 3H).^{13}C NMR ($CDCl_3$, 126 MHz, ppm) δ 155.92, 134.83, 118.22, 79.65, 73.45, 50.42, 38.45, 28.54, 14.74. ESI-MS *m/z* calcd for $C_{11}H_{22}NO_3$ $[M+H]^+$ 216.16; observed: 214.2.

Synthesis of (2*S*,3*R*,*E*)-*tert*-butyl (-3-hydroxyoctadec-5-en-2-yl)carbamate (12)

To a stirred solution of compound **11** (210 mg, 1 mmol) and 1-tetradecene (0.8 g, 4mmol) in dry d-chloroform (5 mL) under argon atmosphere at ambient temperature was added a catalytic amount of *p*-benzoquinone (10 mol%) followed by a catalytic amount of Grubbs catalyst 2nd

generation (10 mol%). The resulting reaction mixture was allowed to stir under reflux for 12h (as monitored by TLC analysis, no change in the composition of reaction mixture, Pet. ether/ EtOAc 4:1; $R_{f\ (adduct)}$= 0.42; $R_{f\ (product)}$=0.56;visualized with 1.3% ninhydrine). The mixture was concentrated under reduced pressure and the resultant residue was purified by flash column chromatography over silica gel using petroleum ether and ethylacetate as eluents (0-10 % ethylacetate in petroleum ether) to provide the desired product **12** as colorless oil.

Yield: 210 mg (56 %). R_f: 0.56 (Pet. ether /EtOAc 4:1, visualized with 1.3% ninhydrine solution). ^{1}H NMR ($CDCl_3$, 500 MHz, ppm) δ 5.55 (dt, *J* = 13.6, 6.7 Hz, 1H), 5.44 – 5.37 (m, 1H), 4.78 (br.s, 1H), 3.74 – 3.65 (m, 1H), 3.65 – 3.60 (m, 1H), 2.22 – 2.15 (m, 1H), 2.09 (dd, *J* = 15.0, 7.2 Hz, 1H), 2.00 (dd, *J* = 14.4, 7.2 Hz, 2H), 1.44 (s, 9H), 1.37 – 1.24 (m, 20H), 1.10 (d, *J* = 6.8 Hz, 3H), 0.88 (t, *J* = 7.0 Hz, 3H).^{13}C NMR ($CDCl_3$, 126 MHz, ppm) δ 155.71, 134.83, 125.53, 79.37, 73.48, 50.15, 37.25, 32.66, 31.93, 29.68, 29.65, 29.63, 29.51, 29.44, 29.36, 29.23, 28.42, 22.69, 14.12. ESI-MS *m/z* calcd for $C_{23}H_{45}NO_3Na$ $[M+Na]^+$ 406.33; observed: 406.3.

Synthesis of (2*S*,3*R*,*E*)-2-aminooctadec-5-en-3-ol (13)

To a stirred solution of compound **12** (135 mg, 0.36 mmol) in dry methanol (4 mL) at 0°C was added dropwise acetyl chloride (260 μL, 3.6 mmol) over a period of 10 min. After being stirred at the same conditions for 30 min and for additional 2h at ambient temperature (as indicated by TLC analysis for complete deprotection), the mixture was concentrated *in vacuo*. The residue was diluted with diethylether and washed with sat. $NaHCO_3$ solution. The aqueous layer was extracted again with diethylether and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The obtained residue was purified by flash column chromatography over silica gel using isopropanol and ethylacetate as eluents (0-10% isopropanol in ethylacetate) to afford the pure product **13** as a white waxy-white solid.

Yield: 64 mg (63%). R_f: 0.45 (EtOAc/ iso-propanol 4:1, visualized with 1.3% ninhydrine). ^{1}H NMR (MeOD, 500 MHz, ppm) δ 5.58 (dd, *J* = 14.3, 7.5 Hz, 1H), 5.44 (dd, *J* = 14.6, 7.2 Hz, 1H), 3.78 – 3.72 (m, 1H), 3.26 (dd, *J* = 6.7, 2.8 Hz, 1H), 2.29 – 2.13 (m, 2H), 2.03 (dd, *J* = 13.3, 6.6 Hz, 2H), 1.42 – 1.27 (m, 20H), 1.23 (d, *J* = 6.8 Hz, 3H), 0.90 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (MeOD, 126 MHz, ppm) δ 135.37, 126.18, 71.69, 51.92, 37.68, 33.67, 33.04, 30.78, 30.70, 30.59, 30.43, 30.37, 23.77, 14.48, 11.62**.** ESI-MS: *m/z* calcd for $C_{18}H_{38}NO$ $[M+H]^+$ 284.29; observed 284.3.

Synthesis of (*S*)-*tert*-butyl-(3-oxohept-6-en-2-yl)carbamate (14)

The 1-butylmagnesium bromide solution was prepared as follows, A magnesium powder (510 mg, 21.2 mmol) was suspended in dry diethylether (2 mL) at ambient temperature under argon atmosphere and the resulting mixture was subsequently treated with drops of 1,2-diromoethane. The resulting mixture was allowed to stir at the same conditions for 10 min and then a solution of 4-bromobutene (0.71 g, 5.3 mmol, 1M in dry diethylether) was dropwisely added over a period of 10 min. The resulting reaction mixture was allowed to stir at 35ºC for 1h to afford a

transparent solution of 1-butylmagnesium bromide. The solution was used directly in the next step.

To a stirred solution of Weinreb amide **9** (0.34 g, 1.5 mmol) in dry diethylether (15 mL) under argon atmosphere at 0ºC was added dropwise a fresh solution of 1-butylmagnesium bromide (5.3 mmol, 1M in diethylether) over a period of 20 min. The resulting reaction mixture was allowed to stir at the same conditions for 30 min and for additional 2h at ambient temperature (as monitored by TLC analysis; Pet. ether / EtOAc 4:1; $R_{f\,(adduct)}$= 0.2; $R_{f\,(product)}$=0.55; visualized with 1.3% ninhydrine solution). The reaction was diluted with diethylether (100 mL) and subsequently quenched with an ice-cold 1M HCl (100mL). The layers were separated and the aqueous layer was extracted with diethylether (2x 80 mL). The organic layers were combined, washed with sat. $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the obtained residue by flash column chromatography over silica gel using petroleum ether and ethylacetate as eluents (10-15% ethylacetate in petroleum ether) afforded the desired product **14** as a white solid.

Yield: 210 mg (71 %). R_f: 0.55 (Pet. ether /EtOAc 4:1, visualized with 1.3% ninhydrine solution). ^{1}H NMR ($CDCl_3$, 500 MHz, ppm) δ 5.79 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.24 (br.s, 1H), 5.03 (ddd, *J* = 17.1, 3.2, 1.6 Hz, 1H), 4.98 (dd, *J* = 10.2, 1.4 Hz, 1H), 4.31 (p, *J* = 7.0 Hz, 1H), 2.63 (dt, *J* = 17.2, 7.5 Hz, 1H), 2.59 – 2.52 (m, 1H), 2.35 (dt, *J* = 14.0, 4.3 Hz, 2H), 1.43 (s, 9H), 1.32 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 126 MHz, ppm) δ 208.97, 155.32, 136.88, 115.68, 79.86, 55.22, 38.41, 28.47, 27.60, 17.96. ESI-MS *m/z* calcd for $C_{12}H_{22}NO_3$ $[M+H]^+$ 228.16; observed: 228.2.

Synthesis of (*S*,*E*)-*tert*-butyl -(3-oxooctadec-6-en-2-yl)carbamate (15)

A stirred solution of compound **14** (110 mg, 0.47 mmol) and 1-tridecene (0.34 g, 1.9 mmol) in dry d-chloroform (4 mL) under argon atmosphere at ambient temperature was treated a catalytic amount of *p*-benzoquinone (10 mol%) followed by a catalytic amount of Grubbs catalyst 2nd generation (8 mol%). After the resulting reaction mixture was stirred under reflux for 6h (as monitored by TLC analysis; no further change in the composition of the reaction mixture; Pet. ether/ EtOAc 4:1; $R_{f\,(adduct)}$= 0.55; $R_{f\,(product)}$=0.68;visualized with 1.3% ninhydrine), the solvent was removed under reduced pressure. The obtained residue was subjected to flash column chromatography over silica gel using petroleum ether and ethylacetate as eluents (0-10% ethylacetate in petroleum ether) to afford the desired product **15** as a waxy-white solid.

Yield: 95 mg (53 %). R_f: 0.47 (Pet. ether /EtOAc 9:1, visualized with 1.3% ninhydrine solution). ^{1}H NMR ($CDCl_3$, 500 MHz, ppm) δ 5.52 – 5.34 (m, 1H), 5.33 – 5.25 (m, 1H), 5.20 (br.s, 1H), 4.35 – 4.20 (m, 1H), 2.59 – 2.41 (m, 1H), 2.28 – 2.18 (m, 1H), 1.99 – 1.84 (m, 4H), 1.37 (s, 9H), 1.30 – 1.17 (m, 21H), 0.81 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 126 MHz, ppm) δ 209.09, 155.20, 132.01, 127.85, 79.69, 55.09, 39.17, 32.51, 31.93, 29.64, 29.52, 29.45, 29.36, 29.18, 28.35, 26.56, 22.70, 17.87, 14.13. ESI-MS *m/z* calcd for $C_{23}H_{43}NO_3Na$ $[M+Na]^+$ 404.31; observed: 404.3.

Synthesis of (*S*,*E*)-2-aminooctadec-6-en-3-one (16)

To a stirred solution of compound **15** (77 mg, 0.2 mmol) in absolute methanol (2mL) at 0ºC was dropwisely added acetylchloride (143 µL, 2 mmol) over a period of 10 min. The resulting

reaction mixture was allowed to stir at the same conditions for 30 min, gradually warm to ambient temperature, and stirred for additional 2h; during while a white solid formed. The mixture was filtered and the residue was washed several times with ice-cooled diethylether to afford a white waxy-solid of crude product. The obtained crude product was further purified by flash column chromatography over silica gel using ethylacetate and isopropanol as eluents (0-10% isopropanol in ethylacetate) to provide the final pure product **16** as a white solid.

Yield: 38 mg (67%). R_f: 0.51 (EtOAc/iso-propanol 4:1, visualized with $KMnO_4$ solution). ^{1}H NMR (MeOD, 500 MHz, ppm) δ 5.55 – 5.47 (m, 1H), 5.45 – 5.39 (m, 1H), 4.14 (q, *J* = 7.3 Hz, 1H), 2.76 – 2.69 (m, 1H), 2.66 – 2.58 (m, 1H), 2.35 – 2.27 (m, 2H), 1.98 (q, *J* = 6.6 Hz, 2H), 1.53 – 1.49 (m, 4H), 1.37 – 1.27 (m, 17H), 0.90 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (MeOD, 126 MHz, ppm) δ 206.76, 133.10, 129.15, 55.86, 39.32, 33.57, 33.07, 30.78, 30.74, 30.60, 30.46, 30.27, 27.21, 23.73, 15.66, 14.43. ESI-MS: *m/z* calcd for $C_{11}H_{36}NO$ $[M+H]^+$ 282.28; observed 282.3.

Synthesis of (*S*)-*tert*-butyl-(3-oxooctadecan-2-yl)carbamate (17)

The 1-pentadecylmagnesium bromide solution was synthesized as follows; A mixture of magnesium turnings (0.51 g, 21 mmol) in anhydrous THF (4 mL) under an argon atmosphere at ambient temperature was treated with drops of 1,2-dibromoethane. The resulting mixture was allowed to stir at the same conditions for 20 min, before it was treated dropwisely with a solution of 1-bromopentadecane (1.5 g, 5.2 mmol, in 2 mL of anhydrous THF) over a period of 20 min. The resulting reaction mixture was allowed to stir for additional 3h at 35°C to afford a transparent solution of 1-pentadecylmagnesium bromide which was immediately used in the next step.

A stirred solution of Weinreb amide derivative **9** (0.35 g, 1.5 mmol) in anhydrous THF (15 mL) under an argon atmosphere at 0°C was treated dropwisely with a freshly prepared 1-pentadecylmagnesium bromide solution (6 mL, 5.1 mmol, 1M solution in Et_2O) over a period of 10 min. After being stirred at ambient temperature for 2h (as monitored by TLC analysis; Pet. ether / EtOAc 4:1; $R_{f\ (adduct)}$= 0.2; $R_{f\ (product)}$=0.69; visualized with 1.3% ninhydrine solution), the reaction mixture was cooled again to 0°C and subsequently quenched with an ice-cold 1M HCl solution (40 mL). The resulting mixture was diluted with diethylether (50 mL), and the layer were separated. The aqueous layer was extracted with diethylether (3x50 mL), and the combined organic phases were washed with saturated $NaHCO_3$ solution (80 mL) and brine (80 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resultant crude product was purified by flash column chromatography over silica gel using petroleum ether and ethylacetate as eluents (from 5-15% ethylacetate in petroleum ether) to yield compound **17** as white solid.

Yield: 410 mg (71 %). R_f: 0.48 (Pet. ether /EtOAc 9:1, visualized with 1.3% ninhydrine solution). ^{1}H NMR ($CDCl_3$, 500 MHz, ppm) δ 5.28 (d, *J* = 6.0 Hz, 1H), 4.30 (p, J = 7.0 Hz, 1H), 2.55 – 2.40 (m, 2H), 1.62 – 1.54 (m, 2H), 1.43 (s, 9H), 1.31 (d, *J* = 7.2 Hz, 3H), 1.29 – 1.21 (m, 24H), 0.87 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 126 MHz, ppm) δ 209.79, 155.18, 79.65, 55.02, 39.21, 31.93, 29.70, 29.67, 29.60, 29.45, 29.37, 29.22, 28.35, 23.59, 22.69, 17.97, 14.13. ESI-MS *m/z* calcd for $C_{23}H_{46}NO_3$ $[M+H]^+$ 384.34; observed: 384.3.

Synthesis of (2*S*,3*R*)-*tert*-butyl (-3-hydroxyoctadecan-2-yl)carbamate 18

To a stirred solution of compound **17** (0.34 g, 0.89 mmol) in dry ethanol (2 mL) under argon atmosphere at -78ºC was added portionwise lithium tri-(*tert*-butoxy)-aluminum hydride (0.57 g, 2.2 mmol) over a period of 20 min. After the resulting reaction mixture was allowed to stir at the same conditions for 2h (as judged by TLC analysis: Pet. ether / EtOAc 4:1; $R_{f\ (adduct)}$= 0.69; $R_{f\ (product)}$=0.57; visualized with 1.3% ninhydrine solution), an ice-cold 1M HCl solution (100 mL) was added dropwise to quench the reaction. The resulting mixture was allowed to warm gradually to ambient temperature and subsequently diluted with ethylacetate (100 mL). The layers were separated and the aqueous layer was extracted again with ethylacetate (2x100 mL). The combined organic extracts was washed with sat. $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography for the obtained residue over silica gel using petroleum ether and ethylacetate as eluents (15-23% ethylacetate in petroleum ether) afforded the desired product **18** as a white solid.

Yield: 285 mg (83 %). R_f: 0.57 (Pet. ether /EtOAc 4:1, visualized with 1.3% ninhydrine solution). ^{1}H NMR ($CDCl_3$, 500 MHz, ppm) δ 4.63 (br. s, 1H), 3.77–3.53 (m, 2 H), 1.46 (s, 9H), 1.45-1.22 (m, 28H), 1.07 (d, *J* = 6.8 Hz, 3H), 0.88 (t, *J* = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 126 MHz, ppm) δ 155.78, 79.56, 74.57, 50.68, 33.62, 32.13, 29.79, 29.73, 29.58, 29.36, 28.46, 26.23, 22.68, 14.43, 14.11. ESI-MS *m/z* calcd for $C_{23}H_{48}NO_3$ $[M+H]^+$ 386.36; observed: 386.4.

Synthesis of (2*S*,3*R*)-2-aminooctadecan-3-ol 19

A solution of compound **18** (0.15 g, 0.38 mmol) in dry methanol (4 mL) at 0ºC was treated with acetyl chloride (272 μL, 3.8 mmol) in dropwise over a period of 10 min. After the resulting reaction mixture was stirred at the same conditions for 30 min and for additional 1h at ambient temperature (as controlled by TLC analysis; Pet. ether / EtOAc 3:2; $R_{f\ (adduct)}$= 0.51; $R_{f\ (product)}$=0.0; visualized with 1.3% ninhydrine solution), the solvent was removed under reduced pressure. The obtained residue was portioned between diethylether (100 mL) and sat. $NaHCO_3$ solution (90 mL). The layers were separated and the aqueous layer was extracted again with diethylether (2x80 mL). The combined organic layers was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford a white waxy solid. The crude product was further purified by flash column chromatography over silica gel using ethylacetate and isopropanol as eluents (0-10% isopropanol in ethylacetate) to provide the final product **19** as a white solid.

Yield: 84 mg (77%). R_f: 0.47 (EtOAc/ iso-propanol 9:1, visualized with 1.3% ninhydrine). ^{1}H NMR (MeOD, 500 MHz, ppm) δ 3.72 – 3.68 (m, 1H), 3.27 (qd, *J* = 6.8, 3.0 Hz, 1H), 1.53 (dt, *J* = 11.0, 8.2 Hz, 1H), 1.45 (dt, *J* = 13.6, 4.6 Hz, 2H), 1.38 – 1.27 (m, 26H), 1.22 (d, *J* = 6.8 Hz, 3H), 0.90 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (MeOD, 126 MHz, ppm) δ 71.65, 52.62, 34.00, 33.07, 30.78, 30.76, 30.72, 30.67, 30.63, 30.47, 26.97, 23.73, 14.43, 12.05. ESI-MS: *m/z* calcd for $C_{18}H_{40}NO$ $[M+H]^+$ 286.32; observed 286.3.

Synthesis of (*tert*-butoxycarbonyl)glycine (20)

A stirred solution of glycine (1.1 g, 14.8 mmol) in aqueous 1M NaOH solution (50 mL) at 0°C was treated in dropwise with a solution of di-*tert*-butyl dicarbonate (3.4 g, 16.3 mmol, in dioxane) over a period of 20 min. After the resulting reaction mixture was stirred at the same conditions for 1h and for additional 12h at ambient temperature, the solvent was removed under reduced pressure. The mixture was washed with n-hexane (50 mL) to remove the unreacted Boc_2O. The aqueous residue was cooled again to 0ºC and was carefully acidified by 1M $KHSO_4$ solution. The obtained mixture was diluted with ethylacetate (100 mL) and the layers were separated. The aqueous layer was extracted with ethylacetate (2x100 mL), and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated. The obtained crude product **20** was pure as determined by NMR- analysis and was used directly in the next step without any further purification.

Yield: 2.3 mg (89%). ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 6.78 (br.s, 1H), 3.97 (br.s, 2H), 1.45 (s, 9H). ^{13}C NMR ($CDCl_3$, 126 MHz, ppm): δ 178.23, 155.16, 80.57; 43.66, 28.36. ESI-LCMS: *m/z* calcd for $C_7H_{13}NO_4$ $[M+H]^+$ 176.09; observed 176.1.

Synthesis of *tert*-butyl (2-(methoxy(methyl)amino)-2-oxoethyl)carbamate (21)

To a stirred solution of *N*-Boc-glycine **20** (1.2 g, 6.75 mmol) in dry dichloromethane (25 mL) under argon atmosphere at -10°C was added *N*-methylmorpholine (2.3 mL, 20.3 mmol), followed by *N*,*O*-dimethylhydroxylamine hydrochloride (0.79 g, 8.1 mmol). The resulting mixture was treated at the same conditions with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.55 g, 8.1 mmol) in portionwise over a period of 30 min. After being stirred at the same conditions for 2h (as detected by TLC analysis; EtOAc 100%; $R_{f(adduct)}$= 0.1; $R_{f(product)}$=0.54; visualized with 1.3% ninhydrine solution), the reaction was quenched with sat. NH_4Cl (100 mL). The mixture was diluted with DCM and the layers were separated. The aqueous layer was extracted again with DCM (2x80 mL), and the combined organic layers were washed with sat. $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to afford a white solid of the desired product **21**. The obtained product was pure as determined by LCMS- and NMR-analysis and was directly used in the next step without any further purification.

Yield: 1.15 mg (78%). R_f: 0.54 (EtOAc 100%, visualized with 1.3% ninhydrine solution). ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 5.28 (br.s, 1H), 4.09 (br.s, 2H), 3.71 (s, 3H), 3.22 (s, 3H), 1.46 (s, 9H). ^{13}C NMR ($CDCl_3$, 126 MHz, ppm): δ 173.78, 155.23, 79.63, 61.39, 41.74, 32.42, 28.36. ESI-LCMS: *m/z* calcd for $C_9H_{19}N_2O_4$ $[M+H]^+$ 219.13; observed 219.1.

Synthesis of *tert*-butyl (2-oxoheptadecyl)carbamate (22)

1-pentadecylmagnesium bromide was synthesized as follows; A mixture of magnesium powder (0.51 g, 21 mmol) in dry THF (2 mL) under argon atmosphere was treated with a catalytic drop of 1,2-dibromoethane followed by a dropwise addition of a solution of 1-bromopentadecane (1.5 g, 5.2 mmol, 1M in dry TFH). The resulting reaction mixture was stirred under reflux for 2h to afford a transparent solution of 1-pentadecylmagnesium bromide which was used in the next step.

To a stirred solution of compound **21** (330 mg, 1.5 mmol) in dry THF (15 mL) under argon atmosphere at 0C was added dropwise a freshly prepared 1-pentadecylmagnesium bromide

solution over a period of 20 min. After being stirred for 2h at ambient temperature (as monitored by TLC analysis; Pet. ether/ EtOAc 4:1; $R_{f\ (adduct)}$= 0.19; $R_{f\ (product)}$=0.68;visualized with 1.3% ninhydrine), the reaction mixture was added in dropwise to an ice-cooled 1M HCl solution (100 mL) to quench. The resulting mixture was diluted with ethylacetate (100 mL) and the layers were separated. The aqueous layer was extracted with ethylacetate (2x100 mL), and the combined organic layers were washed with sat. $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered, and concentrated. The obtained residue was purified by flash column chromatography over silica gel using petroleum ether and ethylacetate as eluents (0-14% ethylacetate in petroleum ether) to afford compound **22** as a white solid.

Yield: 340 mg (62%). R_f: 0.47 (cyclohexane/EtOAc 9:1, visualized with 1.3% ninhydrine solution). ^{1}H NMR ($CDCl_3$, 500 MHz, ppm) δ 4.11 (br.s, 2H), 2.58 – 2.42 (m, 2H), 1.66 – 1.58 (m, 2H), 1.44 (s, 9H), 1.28 – 1.20 (m, 24H), 0.87 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 126 MHz, ppm): δ 209.52, 155.26, 79.68, 42.57, 40.12, 33.25, 29.79, 29.61, 29.59, 29.47, 29.41, 29.26, 28.56, 23.63, 22.72, 14.16. ESI-LCMS: *m/z* calcd for $C_{22}H_{43}NO_3Na$ $[M+Na]^+$ 392.31; observed 392.3.

Synthesis of (*R*)-*tert*-butyl-(2-hydroxyheptadecyl)carbamate (23)

Lithium tri-(*tert*-butoxy)-aluminum hydride (0.49 g, 1.9 mmol) was added in portionwise to a stirred solution of compound **22** (285 mg, 0.76 mmol) in dry ethanol (2 mL) under argon atmosphere at -78C. After the resulting reaction mixture was stirred at the same conditions for 3h (as detected by TLC analysis; Pet. ether/ EtOAc 4:1; $R_{f\ (adduct)}$= 0.69; $R_{f\ (product)}$=0.55;visualized with 1.3% ninhydrine), an ice-cooled 1M HCl solution (100 mL) was added in dropwise over a period of 20 min. The resulting mixture was allowed to warm to ambient temperature and was extracted with ethylacetate (3x100 mL). The combined organic extracts were washed with sat. $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the resultant residue by flash column chromatography over silica gel using petroleum ether and ethylacetate as eluents (10-20% ethylacetate in petroleum ether) afforded the desired product **23** as a white waxy-solid.

Yield: 210 mg (74%). R_f: 0.55 (cyclohexane/EtOAc 4:1, visualized with 1.3% ninhydrine solution). ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ ^{1}H NMR ($CDCl_3$, 500 MHz, ppm) δ 4.48 (br. s, 1H), 3.79 – 3.72 (m, 1H), 3.17–2.89 (m, 2H), 1.47 (s, 9H), 1.47-1.24 (m, 28H), 0.89 (t, *J* = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 126 MHz, ppm): δ 155.62, 79.55, 62.27, 43.71, 34.52, 32.63, 29.78, 29.75, 29.57, 29.39, 28.47, 26.28, 22.67, 14.11. ESI-LCMS: *m/z* calcd for $C_{22}H_{46}NO_3$ $[M+H]^+$ 372.35; observed 372.3.

Synthesis of (*R*)-1-aminoheptadecan-2-ol (24)

Acetyl chloride (305 μL, 4.3 mmol) was added in dropwise to a stirred solution of compound **23** (0.16 g, 0.43 mmol) in dry methanol (4 mL) at 0°C. The resulting reaction mixture was allowed to stir at the same conditions for 30 min and for additional 2h at ambient temperature (as monitored by TLC analysis), during while a white solid was formed. The mixture was filtrated and the residue was washed several times with ice-cooled diethylether to afford a white waxy-solid crude product. Purification of the crude product by flash column chromatography over silica gel using isopropanol and ethylacetate as eluents (0-10% isopropanol in ethyacetate) provided the final product **24** as a white solid.

Yield: 76 mg (65%). R_f: 0.39 (EtOAc/iso-propanol 10:1, visualized with 1.3% ninhydrine). ^{1}H NMR (MeOD, 500 MHz, ppm) δ 3.77 – 3.70 (m, 1H), 3.01 (dd, *J* = 12.7, 3.0 Hz, 1H), 2.75 (dd, *J* = 12.7, 9.5 Hz, 1H), 1.48 (t, *J* = 7.8 Hz, 2H), 1.43 – 1.23 (m, 26H), 0.90 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (MeOD, 126 MHz, ppm) δ 68.76, 46.09, 36.03, 33.07, 30.78, 30.72, 30.67, 30.64, 30.46, 26.40, 23.73. ESI-MS *m/z* clcd for $C_{17}H_{38}NO$ $[M+H]^+$: 272.29; observed 272.3.

Synthesis of (*S*)-*tert*-butyl-3-oxopent-4-en-2-ylcarbamate (25)

A stirred solution of compound **9** (3 g, 13 mmol) in dry THF (65 mL) under an argon atmosphere at -20°C was added dropwise a solution of vinylmagnesium bromide (45.5 mL, 45.5 mmol, 1M solution in THF); the addition rate was adjusted so as to keep the internal temperature at -20 °C and it took 45 min to complete. The resulting reaction mixture was allowed to stir at the same conditions for 30 min and for additional 3h at ambient temperature (as judged by TLC analysis; Pet. ether/ EtOAc 4:1; $R_{f\ (adduct)}$= 0.2; $R_{f\ (product)}$=0.54;visualized with 1.3% ninhydrine). The reaction mixture was added dropwisely to an ice-coold 1M HCl solution to quench; again so as to keep the temperature of solution below -10°C. The resultant mixture was diluted with ethylacetate and the layers were separated. The aqueous layer was extracted with ethylacetate (2x100 mL), and the combined organic extracts were subsequently washed with saturated $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The resultant residue was purified by flash column chromatography over silica gel using cyclohexane and ethylacetate as eluents (from 5-15% ethylacetate in cyclohexane) to afford the desired product **25** as a white solid.

Yield: 1.7 g (66 %). R_f: 0.54 (cyclohexane/ethylacetate 4:1, visualized with 1.3% ninhydrine solution). ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 6.48 (dd, *J* = 17.4, 9.9 Hz, 1H). 6.37 (dd, *J* = 17.4, 1.9 Hz, 1H), 5.88 (dd, *J* = 10.2, 1.9 Hz, 1H), 5.37 (br s, 1H), 4.54-4.67 (m, 1H), 1.44 (s, 9H), 1.33 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 126 MHz, ppm): δ 198.68, 155.23, 132.91, 130.34, 79.51, 53.20, 28.63, 18.42. ESI-LCMS *m/z* calcd for $C_{10}H_{18}NO_3$ $[M+H]^+$ 200.13; observed 200.1.

Synthesis of (2*S*,3*R*)-*tert*-butyl-(3-hydroxypent-4-en-2-yl)carbamate 26

To a stirred solution of compound **25** (1.5 g, 7.5 mmol) in anhydrous ethanol (15 mL) under an argon atmosphere at -78°C was added in portionwise lithium tri-(*tert*-butoxy)-aluminum hydride (4.8 g, 18.75 mmol); the addition rate was adjusted so as to keep the internal temperature below -65°C and it took 30 min to complete. After the resulting reaction mixture was allowed to stir at the same conditions for 3h (as judged by TLC analysis; Pet. ether/ EtOAc 4:1; $R_{f\ (adduct)}$= 0.54; $R_{f\ (product)}$=0.42;visualized with 1.3% ninhydrine), an ice-coold 1M HCl solution (100 mL) was added dropwise to quench the reaction; again so as to keep the internal temperature below -65°C and it took 30 min to complete. The resulting mixture was diluted with ethylacetate and was allowed to gradually warm to ambient temperature. The layers were separated and the aqueous layer was subsequently extracted with ethylacetate (2x 100mL). The combined organic layers were sequentially washed with saturated $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Flash column

chromatography of the resultant crude mixture over silica gel using cyclohexane and ethylacetate as eluents (from 15-25% ethylacetate in cyclohexane) afforded the desired product **26** as a white solid.

Yield: 1.1 g (73%). R_f: 0.42 (cyclohexane/ethylacetate 4:1, visualized with $KMnO_4$ solution). ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 5.85 (ddd, *J*= 17.2, 10.6, 5.5 Hz, 1H), 5.33 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.24 (dd, *J* = 10.5, 1.5 Hz, 1H), 4.76-4.62 (m, 1H), 4.23-4.16 (m, 1H), 2.85 (br. s, 1H), 1.45 (s, 9H), 1.09 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 126 MHz, ppm): δ 156.46, 136.98, 116.68, 79.89, 75.92, 50.96, 28.50, 15.46. ESI-LCMS: *m/z* calcd for $C_{10}H_{19}NO_3Na$ $[M+Na]^+$ 224.13; observed 224.1.

Synthesis of 10-bromo-1-decene

A stirred solution of 1,10-dibromodecane (7 g, 23.3 mmol) in anhydrous THF (200 mL) under an argon atmosphere was treated in portionwise with *tert*-BuOK (2.9 g, 25.6 mmol) over a period of 30 min. After being stirred at 50°C for 12h (as detected by TLC analysis; Pet. ether; $R_{f\ (adduct)}$= 0.58; $R_{f\ (product)}$=0.89; visualized with $KMnO_4$ solution), the reaction mixture was cooled to 0°C and subsequently quenched with water. The resulting mixture was diluted with diethylether, and the layers were separated. The aqueous layer was extracted with diethylether (2x100 mL), and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the obtained crude product by flash column chromatography over silica gel using petroleum ether as eluent provided the desired product 10-bromo-1-decene as colorless oil.

Yield: 3.1 g (61%). R_f: 0.84 (*n*-hexane 100%, visualized with $KMnO_4$ solution). ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 5.81 (ddt, *J* = 16.9, 10.1, 6.7 Hz, 1H), 5.04 – 4.91 (m, 2H), 3.41 (t, *J* = 6.9 Hz, 2H), 2.03 (dt, *J* = 7.6, 4.0 Hz, 2H), 1.92 – 1.78 (m, 2H), 1.49 – 1.28 (m, 10H). ^{13}C NMR ($CDCl_3$, 126 MHz, ppm): δ 139.29, 114.34, 34.20, 33.91, 32.97, 29.42, 29.14, 29.01, 28.86, 28.30.

Synthesis of (2*S*,3*R*,4*E*)-*tert*-butyl-(13-bromo-3-hydroxytridec-4-en-2-yl)carbamate (27)

A stirred mixture of aminoalcohol derivative **26** (660 mg, 3.25 mmol) and 10-bromo-1-decene (2.9 g, 13 mmol) in anhydrous d-chloroform (10 mL) under an argon atmosphere was treated with a catalytic amount of *p*-benzoquinone (10 mol%) followed by Grubbs Catalyst 2nd Generation (10 mol%, in one portion). After the resulting reaction mixture was stirred under reflux for 12 h (as detected by TLC analysis, until no further change in the composition of the reaction mixture, Pet. ether/ EtOAc 4:1; $R_{f\ (adduct)}$= 0.42; $R_{f\ (product)}$=0.51; visualized with 1.3% ninhydrine solution), the solvent was removed under reduced pressure. Flash column chromatography for the obtained residue over silica gel using cyclohexane and ethylacetate as eluents (from 10-25% ethylacetate in cyclohexane) provided the desired product **27** as a colorless oil.

Yield: 725 mg (57%). R_f: 0.51 (Pet. ether /ethylacetate 4:1, visualized with 1.3% ninhydrine solution). ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 5.70 (dtd, *J* = 15.0, 6.8, 1.1 Hz, 1H), 5.43 (dd, *J* = 15.4, 6.6 Hz, 1H), 4.10 (d, *J* = 2.4 Hz, 1H), 3.83-3.73 (m, 1H), 3.40 (t, *J* = 6.9 Hz, 2H), 2.04

(q, *J* = 7.0 Hz, 2H), 1.88 – 1.81 (m, 2H), 1.44 (s, 9H), 1.42 – 1.27 (m, 10H), 1.07 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 126 MHz, ppm): δ 156.40, 134.05, 128.57, 79.78, 75.89, 51.21, 34.16, 32.94, 32.46, 29.38, 29.25, 29.16, 28.83, 28.53, 28.28, 15.66. ESI-MS: *m/z* calcd for $C_{18}H_{35}NO_3Br$ $[M+H]^+$ 392.18; observed 392.2.

Synthesis of (2*S*,3*R*)-*tert*-butyl (13-bromo-3-hydroxytridecan-2-yl-4,5-d_2)carbamate (28)

To a stirred solution of compound **27** (660 mg, 1.7 mmol) in dry d-methanol (20 mL) under argon atmosphere at ambient temperature was added a catalytic amount of 10% Pd/C (10 mg) followed by catalytic drop of d-acetic acid. The reaction vessel was evacuated and backfilled with deuterium gas (this process was repeated 2 times) and the resulting heterogeneous reaction mixture was allowed to stir at the same conditions for 14h (as detected by HPLC analysis for complete reduction reaction). The reaction mixture was filtered through a short pad of Celite, which was rinsed several times with methanol (3x50 mL). The combined filtrates was concentrated under reduced pressure and the obtained residue was purified by flash column chromatography over silica gel using cylcohexane and ethylacetate as eluents (10-20% ethylacetate in cyclohexane) to provide compound **28** as a colorless oil.

Yield: 540 mg (81%). R_f: 0.5 (Pet. ether/ EtOAc 4:1, visualized with 1.3% ninhydrine solution). ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 4.76 (s, 1H), 3.67 (d, *J* = 15.5 Hz, 1H), 3.63 (t, *J* = 6.3 Hz, 1H), 3.40 (t, *J* = 6.9 Hz, 2H), 1.88 – 1.81 (m, 2H), 1.44 (s, 9H), 1.41 – 1.22 (m, 14H), 1.07 (d, *J* = 6.8 Hz, 3H).^{13}C NMR ($CDCl_3$, 126 MHz, ppm): δ 156.02, 79.60, 74.60, 50.73, 34.19, 33.58, 32.97, 29.77, 29.63, 29.57, 29.53, 28.88, 28.55, 28.30, 26.17, 14.50. ESI-LCMS: *m/z* calcd for $C_{18}H_{35}D_2NO_3Br$ $[M+H]^+$ 396.21; observed 396.2.

Synthesis of (4*S*,5*R*)-*tert*-butyl-5-(10-bromodecyl-1,2-d2)-2,2,4-trimethyloxazolidine-3-carboxylate (29)

To a stirred solution of compound **28** (515 mg, 1.3 mmol) in anhydrous toluene (13 mL) under an argon atmosphere was added 2,2-dimethoxypropane (0.8 mL, 6.5 mmol), followed by a catalytic amount of *p*-toluensulfonic acid monohydrate (10 mol%). After being stirred under reflux in a Dean-Stark apparatus for 2h (as judged by the TLC analysis; Pet. ether/ EtOAc 4:1; $R_{f\ (adduct)}$= 0.5; $R_{f\ (product)}$=0.78; visualized with 1.3% ninhydrine solution), the reaction mixture was cooled to ambient temperature, diluted with ethylacetate, and successfully quenched with sat. $NaHCO_3$ solution (80 mL). The mixture was transferred to separating funnel and the layers were separated. The aqueous layer was extracted again with ethylacetate (2x80 mL) and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. Flash column chromatography of the resultant crude residue over silica gel using cyclohexane and ethylacetate as eluents (0% to 10% ethylacetate in cyclohexane) provided the desired product **29** as a colorless oil.

Yield: 505 mg (89%). R_f: 0.53 (cyclohexane/EtOAc 9:1, visualized with 1.3% ninhydrine solution). ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 3.99 – 3.76 (m, 2H), 3.40 (t, *J* = 6.9 Hz, 2H), 1.88 – 1.81 (m, 2H), 1.61 – 1.45 (m, 15H), 1.45 – 1.23 (m, 14H), 1.07 (dd, *J* = 15.9, 6.2 Hz,

3H). ^{13}C NMR ($CDCl_3$, 126 MHz, ppm): δ 152.11, 151.79, 92.64, 92.19, 79.91, 79.28, 76.56, 76.35, 55.44, 55.42, 34.17, 32.97, 29.57, 29.53, 28.88, 28.70, 28.63, 28.30, 27.51, 25.12, 23.96, 14.46, 13.78. ESI-LCMS: *m/z* calcd for $C_{21}H_{38}D_2NO_3BrNa$ $[M+Na]^+$ 458.22; observed 458.2.

Synthesis of (4*S*,5*R*)-*tert*-butyl 2,2,4-trimethyl-5-(pentadec-11-yn-1-yl-1,2-d_2)oxazolidine-3-carboxylate (30)

The lithated 1-pentyne was synthesized as follows; to a stirred solution of 1-pentyne (330 μL, 3.3 mmol) in anhydrous THF (7 mL) under an argon atmosphere at -78°C was carefully added a solution of *t*-BuLi (1.8 mL, 3 mmol, 1.7M solution in pentane) in dropwise over a period of 20 min; the rate of addition was adjusted so as to keep the internal temperature below -65°C. The resulting reaction mixture was stirred at the same conditions for 2h to afford lithated 1-pentyne solution which was used directly in the next step.

A stirred solution of freshly prepared lithated 1-pentyne at -78°C was sequentially treated with hexamethylphosphoramide (870 μL, 5 mmol), followed by a dropwise addition of a solution of compound **29** (470 mg, 1.1 mmol, 0.25M solution in anhydrous THF) over a period of 20 min. After being stirred at the same conditions for 1h, and for additional 12h at ambient temperature (as monitored by TLC analysis; Pet. ether/ EtOAc 9:1; $R_{f\ (adduct)}$= 0.53; $R_{f\ (product)}$=0.64; visualized with Seebach reagent), the reaction mixture was carefully quenched with an ice-coold sat. NH_4Cl solution (80 mL). The resulting mixture was diluted with ethylacetate (80 mL) and the layers were separated. The aqueous phase was extracted again with ethylacetate, and the combined organic phases were subsequently washed with sat. $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The obtained residue was purified by flash column chromatography over silica gel using petroleum ether and ethylacetate as eluents (from 0-15% ethylacetate in petroleum ether) to afford the desired product **30** as a pale yellow oil.

Yield: 265 mg (58%). R_f: 0.48 (Pet. ether/ EtOAc 10:1, visualized with 1.3% ninhydrine solution). ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 3.93 – 3.74 (m, 2H), 2.66 – 2.27 (m, 4H), 1.78 – 1.64 (m, 2H), 1.63 – 1.46 (m, 17H), 1.44 – 1.22 (m, 14H), 1.09 (dd, *J* = 15.9, 6.1 Hz, 3H), 0.89 (t, *J*= 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 126 MHz, ppm): δ 152.12, 151.81, 92.63, 92.19, 83.67, 79.89, 79.28, 77.84, 76.57, 76.37, 55.45, 55.41, 31.58, 30.34, 29.91, 29.74, 29.71, 29.67, 29.61, 29.44, 28.71, 28.63, 28.43, 27.52, 27.36, 25.12, 23.97, 23.04, 22.73, 22.11, 14.46, 13.97, 13.78. ESI-LCMS: *m/z* calcd for $C_{26}H_{46}D_2NO_3Br$ $[M+H]^+$ 424.38; observed 424.4.

Synthesis of (4*S*,5*R*)- *tert*-butyl 2,2,4-trimethyl-5-((*Z*)-pentadec-11-en-1-yl-1,2-d_2)oxazolidine-3-carboxylate (31)

A stirred solution of compound **30** (220 mg, 0.53 mmol) in dry mixture of ethylacetate:DMF (50 mL, 95:5) under an argon atmosphere at ambient temperature was treated with a catalytic amount of Lindlar catalyst. The reaction vessel was evacuated and then backfilled with hydrogen gas (this process was repeated at least 2 times), and the resulting reaction mixture was allowed to stir at the same conditions for 16h (as monitored by HPLC analysis for complete reduction). The mixture was subsequently filtered through a pad of Celite, which was rinsed

several times with ethylacetate (3x80 mL). The combined filtrates were concentrated under *in vacuo* and the obtained residue was purified by flash column chromatography over silica gel using petroleum ether and ethylacetate as eluents (from 0-10% ethylacetate in petroleum ether) to provide the desired compound **31** as a colorless oil.

Yield: 155 mg (69%). R_f: 0.47 (Pet. ether/ EtOAc 10:1, visualized with 1.3% ninhydrine solution). ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 3 5.40 – 5.32 (m, 2H), 3.98 – 3.77 (m, 2H), 2.04 – 1.98 (m, 4H), 1.60 – 1.45 (m, 16H), 1.41 – 1.23 (m, 17H), 1.08 (dd, *J* = 16.1, 6.2 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 126 MHz, ppm): δ 152.11, 151.80, 130.25, 129.79, 92.64, 92.19, 79.90, 79.27, 76.58, 76.38, 55.47, 55.42, 31.58, 30.34, 29.91, 29.74, 29.71, 29.67, 29.61, 29.44, 28.71, 28.63, 28.43, 27.52, 27.36, 25.12, 23.97, 23.30, 23.04, 14.46, 13.96, 13.78. ESI-LCMS: *m/z* calcd for $C_{26}H_{46}D_2NO_3Br$ $[M+H]^+$ 426.39; observed 426.4.

Synthesis *of* (2*S*,3*R*,*Z*)-2-aminooctadec-14-en-4,5-*d*$_2$-3-ol (32)

To a stirred solution of compound **31** (0.12 g, 0.28 mmol) in dry methanol (3 mL) at 0°C was added dropwise acetyl chloride (200 µL, 2.8 mmol). After being stirred at the same conditions for 30 min, and for additional 90 min at ambient temperature (as monitored by TLC, visualized with $KMnO_4$ solution), the reaction mixture was concentrated under reduced pressure. The resultant residue was taken up in diethylether (50 mL) and sequentially washed with saturated $NaHCO_3$ solution (50 mL) and brine solution (80 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Flash olumn chromatography of the obtained crude product over silica gel using ethylacetate and isopropanol as eluents (from 0-10% isopropanol in ethylacetate) provided the desired product **32** as a white solid.

Yield: 62 mg (76%). R_f: 0.46 (EtOAc/ iso-propanol 4:1, visualized with 1.3% ninhydrine solution). ^{1}H NMR (MeOD, 500 MHz, ppm): δ 5.39 – 5.31 (m, 2H), 3.72 – 3.68 (m, 1H), 3.27 (qd, *J* = 6.8, 3.0 Hz, 1H), 2.06 – 1.99 (m, 2H), 1.46 – 1.28 (m, 18H), 1.22 (d, *J* = 6.8 Hz, 3H), 0.91 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (MeOD, 126 MHz, ppm): δ 131.01, 130.61, 71.59, 52.62, 30.85, 30.73, 30.63, 30.33, 30.29, 28.12, 23.95, 14.11, 12.05. ESI-LCMS: *m/z* calcd for $C_{18}H_{36}D_2NO$ $[M+H]^+$ 286.31; observed 286.3.

(*S*)-2-[(*tert*-Butoxycarbonyl)-amino]-3-hydroxypropionic acid (33)

A stirred solution of L-serine (2.5 g, 23.75 mmol) in aqueous 1M NaOH (25 mL) at -15°C was treated with a solution of di-*tert*-butyldicarbonate (6.2 g, 28.5 mmol) in dioxane (25 mL) dropwise over a period of 20 min. After being stirred at the same conditions for 1h and for additional 3h at ambient temperature, the reaction mixture was washed two times with n-hexane (2×60 mL) to remove excess of unreacted Boc_2O. The aqueous layer was then cooled to -15°C and carefully acidified with a solution of 1M $KHSO_4$ (to pH≈2-3). The resulting mixture was subsequently extracted with ethylacetate (4×80 mL), and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to provide *N*-Boc-L-serine **33** as colourless oil. The product was used in the next step without any further purification. Yield: 4.5 g (92%). R_f: 0.2 (EtOAc 100%, visualized with 1.3% ninhydrine). The spectroscopic data of the product were consistent with those reported in literature [1].

(*S*)-*tert*-butyl-1-(*N*-methoxy-*N*-methylcarbamoyl)-2-hydroxyethylcarbamate (34)

To a stirred solution of *N*-Boc-L-serine **33** (3 g, 14.6 mmol) in dry DCM (30 mL) at -15°C under argon atmosphere was added *N,O*-dimethylhydroxylamine hydrochloride (1.6 g, 16.1 mmol), followed by addition of *N*-methylmorpholine (1.8 mL, 16.1 mmol, until pH≈8-9). To the resulting mixture, 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDCI.HCl) (3.1 g, 16.1 mmol) was added portionwise over a period of 30 min. After the resulting reaction mixture was allowed to stir for 90 min at -15°C (as judged by TLC analysis, EtOAc 100%; $R_{f(adduct)}$= 0.2; $R_{f(product)}$=0.5; visualized with 1.3% ninhydrine), an ice-cold 1M HCl solution (100 mL) was carefully added to quench the reaction. The resulting mixture was subsequently diluted with CH_2Cl_2 (100 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3×80 mL). The combined organic layers were sequentially washed with saturated $NaHCO_3$ solution (100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to provide compound **34** as a white solid. The product was used in the next step without any further purification [1].

Yield: 3.1 g, (86%). R_f: 0.16 (EtOAc 100%, visualized with 1.3% ninhydrine). ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 1.44 (s, 9H), 3.22 (s, 3H), 3.77 (s, 3H), 3.80-3.82 (m, 2H), 4.79 (b.s, 1H), 5.65 (d, *J*=5.7 Hz, 1H), ^{13}C-NMR ($CDCl_3$, 125 MHz, ppm) δ 28.4, 32.2, 52.5, 61.7, 63.8, 80.2, 156.0, 171.1. ESI-HRMS *m/z* calcd for $C_{10}H_{20}N_2O_5Na$ $[M+Na]^+$ 271.1269; observed 271.1264.

(*S*)-*tert*-Butyl-(1-hydroxy-3-oxopent-4-en-2-yl)carbamate (35)

To a stirred solution of compound **34** (1.45 g, 5.9 mmol) in dry THF (30 mL) at -78°C under argon atmosphere was added dropwise a solution of n-butyllithium (*n*-BuLi, 2.1 mL, 5.3 mmol, 2.5M in hexane). The resulting mixture was stirred at the same conditions for 30 min, before a solution of vinylmagnesium bromide (14.8 mL, 14.8 mmol, 1M solution in THF) was added dropwise; the addition rate was adjusted so as to keep the internal temperature at -40°C and it took 25 min to complete. After being stirred at -40°C for 30 min, gradually warmed to ambient temperature and stirred for additional 4h (as monitored by TLC analysis), the reaction mixture was added dropwise to an ice-cold 1M HCl solution (100 mL) to quench; again so as to keep the internal temperature below -10°C and it took 30 min to complete. The resultant mixture was subsequently diluted with ethylacetate (100 mL) and the layers were separated. The aqueous layer was extracted several times with ethylacetate (4x80 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution (150 mL) and brine (150 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Flash column chromatography of the resultant crude mixture over silica gel using cyclohexane and ethylacetate as eluents (from 25-40% ethylacetate in cyclohexane) afforded compound **35** as a colorless oil.

Yield: 920 mg, (73%). R_f: 0.45 (Cyclohexane/ EtOAc 1:1, visualized with 1.3% ninhydrine). ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 6.57 (dd, *J* = 17.4, 10.5 Hz, 1H), 6.44 (dd, *J* = 17.5, 1.0 Hz, 1H), 5.93 (d, *J* = 10.5 Hz, 1H), 5.69 (br.s, 1H), 4.66 (m, 1H), 3.95 (dd, *J* = 11.6, 3.6 Hz, 1H), 3.90 (dd, *J* = 11.6, 4.2 Hz, 1H), 1.46 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz, ppm): δ 196.4, 156.1, 132.7, 130.7, 80.4, 63.6, 59.9, 28.3. ESI-MS *m/z* $(M+H)^+$ 216.1.

(2*S*,4*E*)-*tert*-Butyl -(1-hydroxy-3-oxooctadec-4-en-2-yl)carbamate (36)

To a stirred solution of compound **35** (155 mg, 0.72 mmol) in dry DCM (4 mL) under argon atmosphere was added 1-pentadecene (782 μL, 2.9 mmol), followed by a catalytic amount of Grubbs Catalyst 2nd Generation (as a solid in one portion, 7 mol%). The resulting reaction mixture was allowed to stir under reflux and was monitored by TLC analysis until no further change in the composition of the reaction mixture (6h, visualized with $KMNO_4$). The solvent was subsequently removed under reduced pressure and the resultant residue was directly purified by flash column chromatography over silica gel using cyclohexane and ethylacetate as eluents (from 20-27% ethylacetate in cyclohexane) to afford the desired product **36** as a yellow oil.

Yield: 190 mg (67%). R_f: 0.62 (cyclohexane/ethylacetate 3:2, visualized with 1.3% ninhydrine solution). ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 7.06 (dt, *J* = 15.7, 6.9 Hz, 1H), 6.27 (d, *J* = 15.7 Hz, 1H), 5.73 (br.s, 1H), 4.62 (s, 1H), 3.93 (dd, *J* = 11.5, 3.4 Hz, 1H), 3.85 (dd, *J* = 11.5, 4.5 Hz, 1H), 2.27 – 2.22 (m, 2H), 1.45 (s, 9H), 1.33 – 1.24 (m, 22H), 0.87 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz, ppm): δ 195.9, 156.4, 151.2, 126.5, 80.5, 64.5, 60.1, 32.9, 32.1, 22.8, 14.3. ESI-MS *m/z* $(M+H)^+$ 398.4.

(2*S*)-2-amino-1-hydroxyoctadecan-3-one-4,5-d_2 (37)

A stirred solution of compound **36** (100 mg, 0.25 mmol) in anhydrous d-chloroform (5 mL) under an argon atmosphere at ambient temperature was treated with a catalytic amount of 10 % Pd/C (6 mg) followed by 2-drops of d-acetic acid. After being evacuated, the reaction vessel was backfilled with deuterium gas and the resulting heterogeneous reaction mixture was allowed to stir for 16h at the same conditions. The suspension was subsequently filtered through a short pad of Celite, which was rinsed several times with chloroform (3x50 mL). The filtrates were combined and concentrated under reduced pressure to afford *N*-Boc-3-ketosphinganine-d_2 as an oily residue. The obtained residue was dissolved in methanol (15 mL) and subsequently treated with 4N HCl-THF solution (3 mL). After the resulting reaction mixture was allowed to stir under reflux for 2h (as monitored by TLC analysis; cyclohexane / EtOAc 3:2; $R_{f\ (adduct)}$= 0.62; $R_{f\ (product)}$=0.01; visualized with 1.3% ninhydrine solution), the solvent was removed under reduced pressure. The obtained residue was taken up in *n*-hexane (5 mL) and the mixture was vigorously stirred for 30 min, during while a white precipitate was formed. The obtained white precipitate was filtered off and subsequently washed with ice-cold diethylether to provide the desired product **37** as a white solid.

Yield: 46 mg (63%, over 2 steps). R_f: 0.32 (EtOAc/ iso-propanol 10:1, visualized with 1.3% ninhydrine solution). ^{1}H NMR (MeOD, 500 MHz, ppm): δ 4.18 (t, *J* = 3.8 Hz, 1H), 4.10 (dd, *J* = 12.1, 4.2 Hz, 1H), 3.98 (dd, *J* = 12.1, 3.5 Hz, 1H), 2.62 (dd, *J* = 14.1, 7.1 Hz, 1H), 1.60 (m, 1H), 1.30 (m, 24H), 0.90 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (MeOD, 126 MHz, ppm): δ 205.3, 62.2, 60.2, 33.1, 30.8, 30.7, 30.6, 30.5, 30.4, 29.9, 23.7, 14.4. ESI-MS *m/z* $(M+H)^+$ 302.4.

11-((tetrahydro-2H-pyran-2-yl)oxy)undecan-1-ol (38)

A stirred solution of 1,11-undecandiol (11.8 g, 63 mmol) in dry tetrahydrofuran (200 mL) at 0°C under argon atmosphere was treated with a catalytic amount of *p*-toluenesulfonic acid

monohydrate (PTSA) (0.95 g, 5.04 mmol, 8 mol%), followed by dropwise addition of 3,4-dihydropyran solution (5.9 mL, 69.3 mmol, 1M in dry THF). After being stirred at the same conditions for 1h, gradually warmed to ambient temperature and stirred for additional 16h (as judged by TLC analysis; cyclohexane/ EtOAc 6:4; $R_{f\ (adduct)}$= 0.36; $R_{f\ (product)}$=0.67; visualized with ceric ammonium molybdate solution), the reaction mixture was diluted with diethylether (100 mL) and carefully quenched at 0°C with saturated aqueous $NaHCO_3$ solution (150 mL). The layers were separated and the aqueous layer was extracted with diethylether (3x100 mL). The combined organic extracts was washed with brine solution (200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the obtained crude product by flash column chromatography over silica gel using cyclohexane and ethylacetate as eluents (from 18-26% ethylacetate in cyclohexane) provided compound **38** as colorless oil [2,3].

Yield: 9.6 g (56%; **note**, the di-protected diol byproduct was isolated in ~6% yield). R_f: 0.52 (cyclohexane/EtOAc 7:3, ceric ammonium molybdate solution). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 4.53 (1H, t, *J* =3.2 Hz), 3.75-3.71 (m, 2H), 3.67-3.62 (m, 2H), 3.46 (2H, t, *J* =6.5 Hz), 1.86-1.69 (m, 8H), 1.61-1.23 (m, 16H). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ 98.79, 67.61, 62.87, 62.17, 32.67, 30.64, 29.72, 29.60, 29.52, 29.49, 29.38, 29.33, 26.17, 25.67, 25.43, 19.52. MS (ESI^+) *m/z* calcd for $C_{16}H_{33}O_3$ $[M+H]^+$ 273.24; observed 273.2.

2-((11-bromoundecyl)oxy)tetrahydro-2H-pyran (39)

To a stirred solution of alcohol **38** (9.1 g, 33.52 mmol) and CBr_4 (12.2 g, 36.9 mmol) in anhydrous dichloromethane (335 mL) at 0°C under an argon atmosphere was added dropwise a solution of triphenyl phosphine (10.1 g, 38.5 mmol, 39 mL 1M in dry dichloromethane) over a period of 20 min. After the resulting reaction mixture was allowed to stir for 1h at 0°C, gradually warmed to ambient temperature, and stirred for additional 3h (as monitored by TLC analysis; Pet. ether/ EtOAc 8:2; $R_{f\ (adduct)}$= 0.37; $R_{f\ (product)}$=0.68; visualized with ceric ammonium molybdate solution), the solvent was removed under reduced pressure. The resultant oily residue was suspended in petroleum ether (100 mL) and the mixture was stirred for 30 min at ambient temperature, during while a white precipitate was formed. The mixture was filtered through a pad of Celite to remove the formed triphenylphosphonium oxide and the combined filtrates was concentrated under reduced pressure. This process was repeated several times until no further precipitate was formed. The obtained oily crude product was subsequently purified by flash column chromatography over silica gel using petroleum ether and ethylacetate as eluents (from 5-15% ethylacetate in petroleum ether) to yield compound **39** as colorless oil.

Yield: 9.64 g (86 %). R_f: 0.53 (petroleum ether /EtOAc 9:1, ceric ammonium molybdate solution). These data are in accordance with literature precedence [2,3].^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 4.59-4.56 (m, 1H), 3.92-3.86 (m, 1H), 3.76-3.69 (m, 1H), 3.54-3.49 (m, 1 H), 3.42 (t, *J*= 7.1 Hz, 2H), 3.39-3.36 (m, 1H), 1.89-1.52 (m, 8H), 1.42-1.27 (m, 16H). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ 98.96, 67.82, 62.46, 34.12, 32.89, 30.84, 29.92, 29.73, 29.61, 29.57, 28.90, 28.24, 26.37, 25.64, 19.76. MS (ESI^+) *m/z* calcd for $C_{16}H_{32}O_2Br$ $[M+H]^+$ 335.16; observed 335.2.

2-(undec-10-en-1-yloxy)-tetrahydro-2H-pyran (40)

To a stirred solution of compound **39** (9.4 g, 28.3 mmol) in anhydrous THF (280 mL) at ambient temperature under an argon atmosphere was added *tert*-BuOK (3.5 g, 31.13 mmol) in portionwise over a period of 30 min. After being stirred under reflux for 12h (as monitored by TLC analysis, cyclohexane/EtOAc 95:5; $R_{f(adduct)}$ = 0.4; $R_{f(product)}$ = 0.58; visualized with ceric ammonium molybdate solution), the reaction was cooled to room temperature and subsequently quenched with water (200 mL). The layers were separated and the aqueous layer was extracted with petroleum ether (3x100 mL). The combined organic extracts were washed with brine (200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the resultant oil by flash column chromatography over silica gel using petroleum ether and ethylacetate as eluents (from 0-9% ethylacetate in petroleum ether) provided compound **40** as colorless oil.

Yield: 4.6 g (64 %). R_f: 0.67 (Pet. ether/ EtOAc 9:1, visualized with ceric ammonium molybdate solution). ^{1}H-NMR (126 MHz, $CDCl_3$, ppm): 5.81 (ddt, *J*=16.9, 6.7, 1.3 Hz, 1H), 5.12-4.93 (m, 2H), 4.58-4.54 (m, 1H), 3.89-3.69 (m, 2 H), 3.64-3.31 (m, 2H), 2.11-1.98 (m, 2H), 1.89-1.65 (m, 2H), 1.64-1.46 (m, 6H), 1.44-1.27 (m, 12H). ^{13}C-NMR (126 MHz, $CDCl_3$, ppm): 139.17, 113.79, 98.84, 67.65, 62.24, 33.87, 30.76, 29.69, 29.56, 29.37, 29.14, 28.75, 26.24, 25.53, 19.56. ESI-MS *m/z* calcd for $C_{16}H_{31}O_2$ $[M+H]^+$: 255.23; observed 255.2.

Undec-10-en-1-ol (41)

A stirred solution of compound **40** (4.4 g, 17.1 mmol) in ethanol (85 mL) at ambient temperature was treated with a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) (0.43 g, 1.71 mmol, 10 mol%). After the resulting reaction mixture was allowed to stir under reflux for 2h (as judged by TLC analysis for almost a complete deprotection; Pet. ether/ EtOAc 9:1; $R_{f\,(adduct)}$= 0.67; $R_{f\,(product)}$=0.39; visualized with ceric ammonium molybdate solution), the solvent was removed under reduced pressure. The resultant oily residue was diluted with diethylether (100 mL) and subsequently washed with saturated $NaHCO_3$ solution (100 mL). The aqueous layer was extracted again with diethylether (3×80 mL), and the combined organic extracts were washed with brine (150 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The obtained crude product was purified by flash column chromatography over silica gel using cyclohexane and ethylacetate as eluents (from 15-20% ethylacetate in cyclohexane) to furnish compound **41** as colorless oil.

Yield: 2.3 g (79 %). R_f: 0.48 (Pet. ether/ EtOAc 4:1, visualized with ceric ammonium molybdate solution). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 5.81 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 4.99 (ddd, *J* = 17.1, 3.7, 1.6 Hz, 1H), 4.92 (ddt, *J* = 10.2, 2.3, 1.2 Hz, 1H), 3.63 (t, *J* = 6.7 Hz, 2H), 2.06-2.01 (m, 2H), 1.56 (dq, *J* = 13.4, 6.7 Hz, 2H), 1.42 – 1.26 (m, 12H). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ 139.37, 114.25, 63.21, 33.94, 32.93, 29.68, 29.55, 29.25, 29.06, 25.87. ESI-MS *m/z* calcd for $C_{11}H_{23}O$ $[M+H]^+$: 171.17; observed 171.2.

11-bromoundec-1-ene (42)

A stirred solution of 10-undecenol **41** (1.05 g, 6.15 mmol) and CBr_4 (2.25 g, 6.8 mmol) in dry dichloromethane (62 mL) at 0°C under an argon atmosphere was treated with a solution of triphenyl phosphine (1.85 g, 7.1 mmol, 7 mL 1M in dry dichloromethane) dropwise over a period of 20 min. The resulting reaction mixture was allowed to stir at the same conditions for 1h and for additional 3h at ambient temperature (as judged by TLC analysis; Pet. ether/ EtOAc 4:1; $R_{f\ (adduct)}$= 0.48; $R_{f\ (product)}$=1; visualized with $KMnO_4$ solution), before it was filtered through a pad of silica gel and rinsed subsequently with petroleum ether. The combined filtrates was concentrated under reduced pressure and the resultant oily crude product was purified by flash column chromatography over silica gel using petroleum ether as eluent to afford 11-bromoundec-1-ene **42** as colorless oil.

Yield: 1.3 g (91 %). R_f: 0.57 (Pet. ether, visualized with $KMnO_4$ solution). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 5.82 (ddt, *J* = 16.7, 6.8 Hz, 1H), 4.96 (ddd, *J* = 17.1, 3.7, 1.6 Hz, 1H), 4.93 (ddt, *J* = 10.2 Hz, 1H), 3.43 (t, *J*= 6.8 Hz, 2H), 2.14-2.05 (m, 2H), 1.96-1.88 (m, 2H,), 1.47-1.26 (m, 10H). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ 139.31, 114.32, 34.13, 33.91, 32.96, 29.57, 29.23, 29.04, 28.96, 28.47.

Undec-10-en-1-yl 4-methylbenzenesulfonate (43)

A stirred solution of 10-undecenol **41** (1.1 g, 6.25 mmol) in dry dichloromethane (16 mL) under argon atmosphere at 0^{o}C was treated with pyridine (2 mL, 25 mmol), followed by a portionwise addition of tosyl chloride (1.5 g, 7.8 mmol). After being stirred at the same condition for 1h and for additional 16h at ambient temperature (as monitored by TLC analysis; Pet. ether/ EtOAc 4:1; $R_{f\ (adduct)}$= 0.48; $R_{f\ (product)}$=0.77; visualized with $KMnO_4$ solution), the reaction mixture was diluted with CH_2Cl_2 (100 mL) and carefully quenched with saturated $NaHCO_3$ solution (100 mL). The layers were separated and the aqueous layer was extracted several times with CH_2Cl_2 (3x 80 mL). The combined organic layers were successively washed with saturated $CuSO_4$ solution (150 mL) and brine (150 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Flash column chromatography of the resultant crude product over silica gel using petroleum ether and ethylacetate as eluents (from 0-10% ethylacetate in petroleum ether) afforded the desired product **43** as white waxy solid.

Yield: 1.7 g (84 %). R_f: 0.57 (petroleum ether /EtOAc 9:1, visualized with $KMnO_4$ solution). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 4.58 (dd, *J* = 4.4, 2.8 Hz, 1H), 3.88 (ddd, *J* = 11.1, 7.0, 3.9 Hz, 1H), 3.74 (dt, *J* = 9.6, 6.9 Hz, 1H), 3.50 (ddd, *J* = 8.1, 6.5, 4.6 Hz, 1H), 3.46-3.34 (m, 3H), 1.92-1.78 (m, 3H), 1.79-1.66 (m, 1H), 1.63-1.49 (m, 6H), 1.46-1.25 (m, 12H). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ 99.01, 67.82, 62.52, 34.22, 32.97, 30.93, 29.88, 29.60, 29.57, 29.51, 28.88, 28.30, 26.36, 25.65, 19.86. ESI-MS *m/z* calcd for $C_{18}H_{28}NaO_3S$ $[M+Na]^+$: 347.17; observed 347.2.

(*S*)-2-methylbutyl 4-methylbenzenesulfonate (44)

To a stirred solution of (*S*)-2-methylbutan-1-ol (2 g, 22.4 mmol) in dry dichloromethane (45 mL) under argon atmosphere at 0^{o}C was added pyridine (7.2 mL, 89.6 mmol), followed by a portionwise addition of tosyl chloride (5.3 g,28 mmol). The resulting reaction mixture was

allowed to stir for 4h at ambient temperature (as monitored by TLC analysis; Pet. ether/ EtOAc 7:3; $R_{f\ (adduct)}$= 0.38; $R_{f\ (product)}$=0.79; visualized with ceric ammonium molybdate solution), before it was carefully quenched with saturated $NaHCO_3$ solution (100 mL). The resultant mixture was extracted with n-pentane (3x 100 mL) and the combined organic layers were washed with saturated $CuSO_4$ solution (150 mL) and brine (150 mL), dried over anhydrous Na_2SO_4, filtered and concentrated (**Caution**: temperature of rotatory evaporator shouldn't exceed 35°C). Purification of the crude product with flash column chromatography over silica gel using n-pentane and ethylacetate as eluents (from 0-9% ethylacetate in petroleum ether) afforded the desired product **44** as colorless oil.

Yield: 3.9 g (72 %). R_f: 0.53 (petroleum ether /EtOAc 9:1, ceric ammonium molybdate solution). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.82 (d, *J*= 8.5 Hz, 2H), 7.36 (d, *J*= 8.1 Hz, 2H), 3.74 (d, *J*= 6.1 Hz, 2H), 2.46 (s, 3H), 1.74-1.61 (m, 1H), 1.48-1.09 (m, 2H), 0.86 (d, *J*= 6.9, 3H), 0.82 (t, *J*= 7.5 Hz, 3H). ESI-MS *m/z* calcd for $C_{12}H_{18}NaO_3S$ $[M+Na]^+$: 265.09; observed 265.1.

(*S*)-1-bromo-2-methylbutane (45)

A stirred solution of (*S*)-2-methylbutyl 4-methylbenzenesulfonate **44** (3.1 g, 12.7 mmol) and *N*-bromosuccinimide (NBS) (2.5 g, 14 mmol) in anhydrous dichloromethane (125 mL) at 0°C under argon atmosphere was treated with a solution of triphenyl phosphine (PPh_3) (3.8 g, 14.6 mmol) in anhydrous dichloromethane (15 mL) over a period of 20 min. After the resulting reaction mixture was allowed to stir for 2h at ambient temperature (as judged by TLC analysis for almost a complete reaction, Pet. ether/ EtOAc 9:1; $R_{f\ (adduct)}$= 0.53; $R_{f\ (product)}$=1; visualized with $KMnO_4$ solution), the reaction mixture was filtered through a pad of silica gel and rinsed subsequently with n-pentane. The solvent was removed under reduced pressure (**Caution**: temperature of rotatory evaporator shouldn't exceed 25°C), and the resultant residue was subsequently purified by flash column chromatography over silica gel using n-pentane as eluent to furnish the desired compound **45** as colorless oil.

Yield: 1.3 g (68 %). R_f: 0.57 (petroleum ether, visualized with $KMnO_4$ solution). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 3.41 (dd, *J*= 9.8 Hz, 1H), 3.37 (dd, *J*= 9.8, 5.6 Hz, 1H), 1.79-1.71 (m, 1 H), 1.56-1.44 (m, 1H), 1.26 (q, *J* = 7.4 Hz, 1H) 1.02 (d, *J*= 6.7 Hz, 3H), 0.93 (t, *J*= 7.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ 41.25, 37.18, 27.63, 18.74, 11.36.

(*S*)-13-methylpentadec-1-ene (47)

The Grignard reagent of (*S*)-1-bromo-2-methylbutane **(46)** was synthesized as follows; A mixture of magnesium turnings (0.3 g, 12.5 mmol) in anhydrous THF (3 mL) under an argon atmosphere was treated with 2 drops of 1,2-dibromoethane (in order to activate the magnesium), followed by a solution of (*S*)-1-bromo-2-methylbutane (1.2 g, 8.3 mmol, in 5 mL of anhydrous THF). After the reaction had begun, the reaction mixture was allowed to stir for 90 min at 30°C to yield a transparent Grignard solution which was immediately used in the next step.

Coupling reaction: According to Effenberger and Heid [4], and Tamura and Kochi [5] with some modifications. To a stirred solution of tosylate **43** (0.9 g, 2.8 mmol) in anhydrous THF (25 mL)

under argon atmosphere at -78°C was added dropwise a catalytic amount of dilithium tetrachlorocuprate (Li_2CuCl_4) solution (1.4 mL, 0.1 M in THF). The resulting mixture was stirred for 10 min at the same conditions, before a freshly prepared Grignard solution **46** was added dropwise over a period of 20 min. After the resulting reaction mixture was allowed to stir at ambient temperature for 16 h, during while a dark solution formed, (as monitored by TLC analysis; Pet. ether/ EtOAc 9:1; $R_{f\ (adduct)}$= 0.57; $R_{f\ (product)}$=1; visualized with $KMnO_4$ solution), the reaction mixture was cooled to 0°C and successfully quenched with an ice-cold saturated NH_4Cl solution (100 mL). The resulting mixture was diluted with n-pentane (100 mL), and the layers were separated. The aqueous layer was extracted with n-pentane (3x 50mL), and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* (**Caution**: temperature of rotatory evaporator shouldn't exceed 25°C). Purification of the obtained crude mixture by flash column chromatography over silica gel using n-pentane as eluent afforded the desired product **47** as colorless oil.

Yield: 0.42 g (49 %). R_f: 0.59 (Pet. ether, visualized with $KMnO_4$ solution). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 5.82 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 4.99 (ddd, *J* = 17.1, 3.7, 1.6 Hz, 1H), 4.93 (ddt, *J* = 10.2, 2.3, 1.2 Hz, 1H), 2.07 – 2.02 (m, 2H), 1.40 – 1.25 (m, 26H), 1.17 – 1.07 (m, 6H), 0.88 – 0.83 (m, 19H). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ 139.44, 114.22, 36.81, 34.87, 34.57, 34.09, 33.99, 30.19, 29.88, 29.84, 29.78, 29.67, 29.67, 29.32, 29.12, 27.28, 19.37, 11.59, 11.56.

(4*S*,5*R*)-*tert*-Butyl-4-(hydroxymethyl)-2,2-dimethyl-5-vinyloxazolidine-3-carboxylate (48)

The titled compound was synthesized in 7 steps starting from L-serine according to our previously established route [1]. R_f: 0.5 (cyclohexane/EtOAc 6:4, visualized with 1.3% ninhydrine). ^{1}H NMR ($CDCl_3$, 500 MHz, ppm) δ 5.94-5.76 (m, 1H), 5.37-5.28 (m, 1H), 5.23-5.19 (m, 1H), 4.54-4.48 (m, 1H), 3.93-3.75 (m, 1H), 3.56 (dd, *J*= 5.8, 11.1 Hz, 1H), 3.37 (m, 1H), 1.45-1.39 (m, 6H), 1.27 (br.s, 9H). ^{13}C NMR ($CDCl_3$, 300 MHz, ppm): δ 154.39, 131.93, 119.31, 93.27, 81.32, 76.47, 63.51, 61.85, 28.49, 24.79. MS (ESI^+) *m/z* calcd for $C_{13}H_{23}NNaO_4$ $[M+Na]^+$ 280.15; observed 280.1.

(4*S*,5*R*)-*tert*-butyl -4-(hydroxymethyl)-2,2-dimethyl-5-((*S*,*E*)-13-methylpentadec-1-en-1-yl)oxazolidine-3-carboxylate (49)

To a stirred solution of compound **48** (82 mg, 0.32 mmol.) in dry dichloromethane (3 mL), under argon atmosphere, was added the cross partner **47** (0.36 g, 1.6 mmol), followed by a catalytic amount of (1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)-dichloro-(phenylmethylene) (tricyclohexylphosphine)-ruthenium, Grubbs catalyst 2nd generation, 8 mol%). After the resulting reaction mixture was allowed to stir under reflux for 12h (until the TLC analysis showed no further change in the composition of the reaction mixture; Pet. ether/ EtOAc 7:3; $R_{f\ (adduct)}$= 0.45; $R_{f\ (product)}$=0.6;visualized with 1.3% ninhydrine), the solvent was removed under reduced pressure. The resultant crude residue was subsequently purified by flash column chromatography over silica gel using cyclohexane and ethylacetate as eluents (from 20-25% ethylacetate in cyclohexane) to afford the desired product **49** as pale yellow oil.

Yield: 88 mg (61.4%). R_f: 0.48 (cyclohexane/ethylacetate 8:2, visualized with 1.3% ninhydrine). ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 5.92 – 5.84 (m, 1H), 5.63 – 5.41 (m, 1H), 4.57 (t, *J* = 6.5 Hz, 1H), 4.11 – 4.04 (m, 1H), 3.89 – 3.43 (m, 3H), 2.06 (dd, *J* = 10.3, 6.4 Hz, 2H), 1.67 – 1.46 (m, 15H), 1.42 – 1.25 (m, 21H), 1.16 – 1.07 (m, 2H), 0.87 – 0.82 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz, ppm): δ 154.59, 137.56, 123.37, 93.10, 81.36, 80.41, 63.93, 62.19, 36.79, 34.55, 32.53, 30.17, 29.85, 29.82, 29.72, 29.65, 29.60, 29.38, 28.55, 27.26, 19.37, 11.56. ESI-MS *m/z* calcd for $C_{27}H_{52}NO_4$ $[M+H]^+$: 454.39; observed 454.4.

(2*S*,3*R*,16*S*,*E*)-2-amino-16-methyloctadec-4-ene-1,3-diol (50)

A stirred solution of compound **49** (65 mg, 0.14 mmol) in absolute methanol (1.5 mL) at 0°C was carefully treated with acetyl chloride in dropwise (AcCl, 150 µL, 2.1 mmol). After the resulting reaction mixture was allowed to stir at the same conditions for 30 min and for additional 90 min at ambient temperature (as detected by TLC analysis for complete deprotection), the solvent was removed under reduced pressure. The resultant waxy residue was washed with ice-cooled diethylether and subsequently filtered off to provide the desired crude product as a colorless waxy solid. Further purification of the obtained crude product was performed by flash column chromatography over silica gel using ethylacetate and isopropanol as eluents (from 0-5% isopropanol in ethylacetate) to afford compound **50** as a white waxy solid.

Yield: 36 mg (82 %). R_f: 0.31 (EtOAc/ iso-propanol 9:1, visualized with $KMnO_4$ solution). ^{1}H NMR (MeOD, 500 MHz, ppm) δ 5.88 (ddd, *J* = 14.9, 7.2, 3.8 Hz, 1H), 5.53 – 5.47 (m, 1H), 4.34 – 4.30 (m, 1H), 3.82 (dd, *J* = 11.6, 4.0 Hz, 1H), 3.69 (dd, *J* = 11.6, 8.3 Hz, 1H), 3.23 (dt, *J* = 8.5, 4.3 Hz, 1H), 2.13 (q, *J* = 7.0 Hz, 2H), 1.48 – 1.43 (m, 2H), 1.40 – 1.30 (m, 16H), 1.20 – 1.11 (m, 2H), 0.92 – 0.87 (m, 6H). ^{13}C NMR (MeOD, 125 MHz, ppm) δ 136.54, 128.46, 70.95, 59.42, 58.54, 37.78, 35.69, 33.35, 31.10, 30.80, 30.78, 30.73, 30.63, 30.59, 30.36, 30.17, 28.19, 19.63, 11.74. ESI-MS *m/z* calcd for $C_{19}H_{40}NO_2$ $[M+H]^+$: 314.31; observed 314.3.

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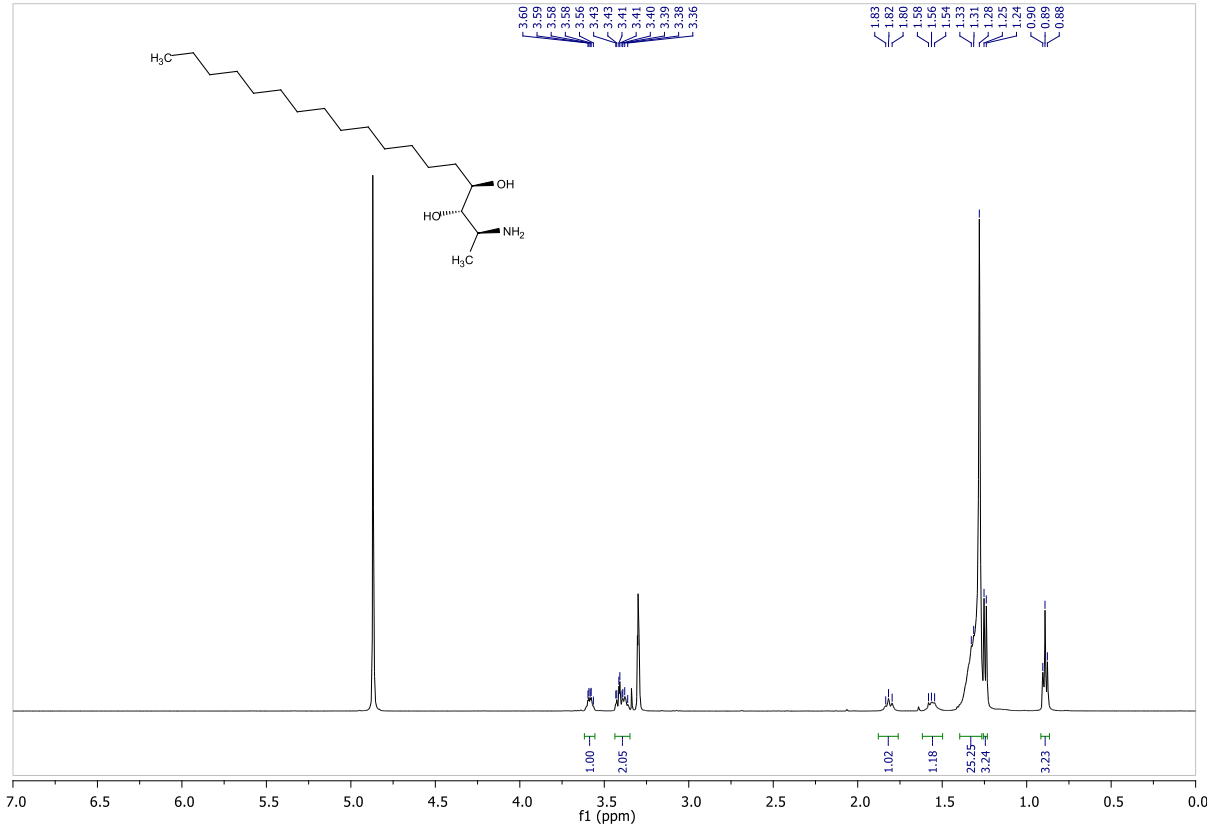
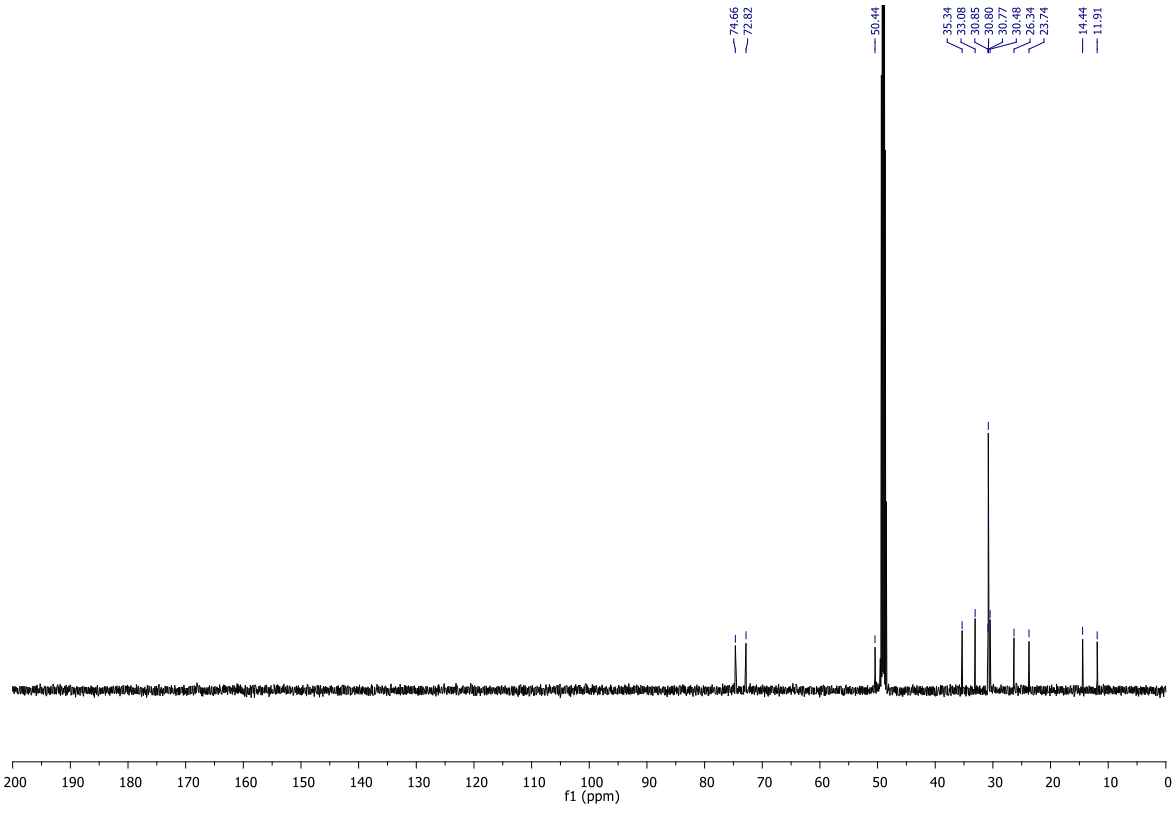
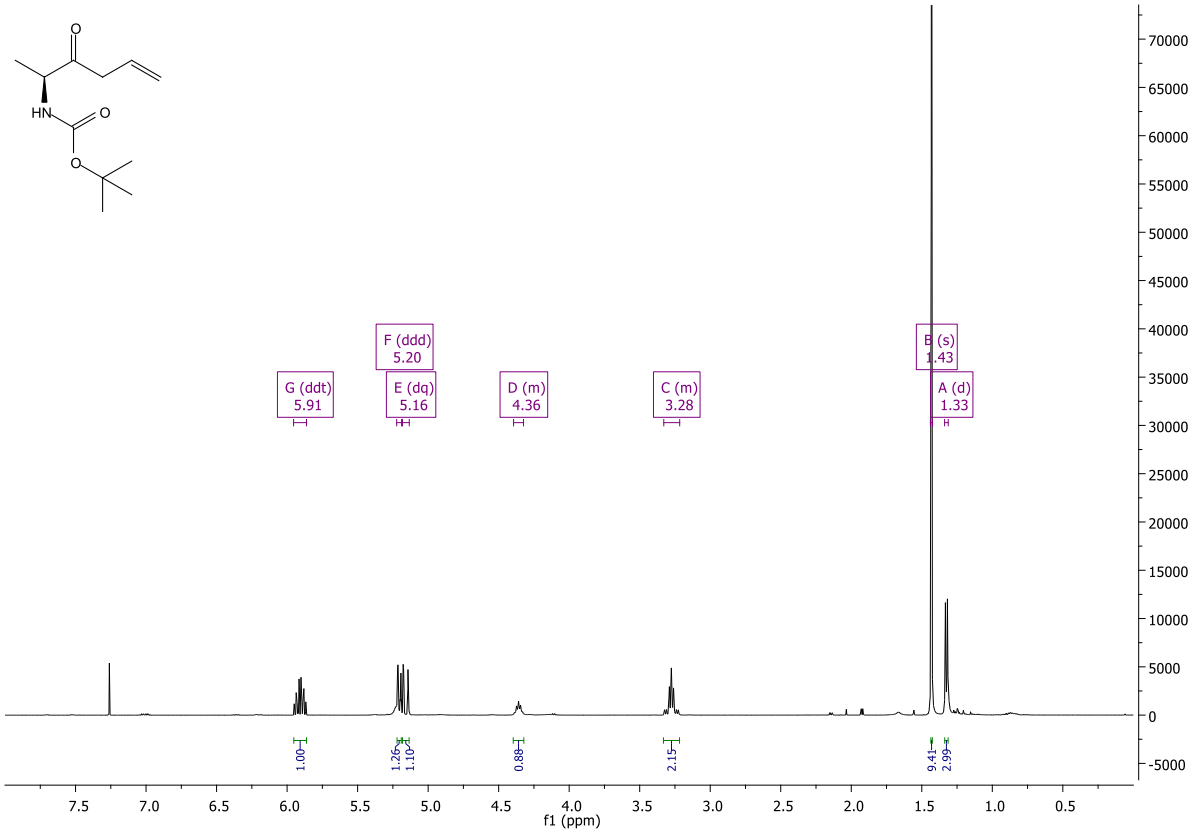
6 NMR spectra of synthesized compounds



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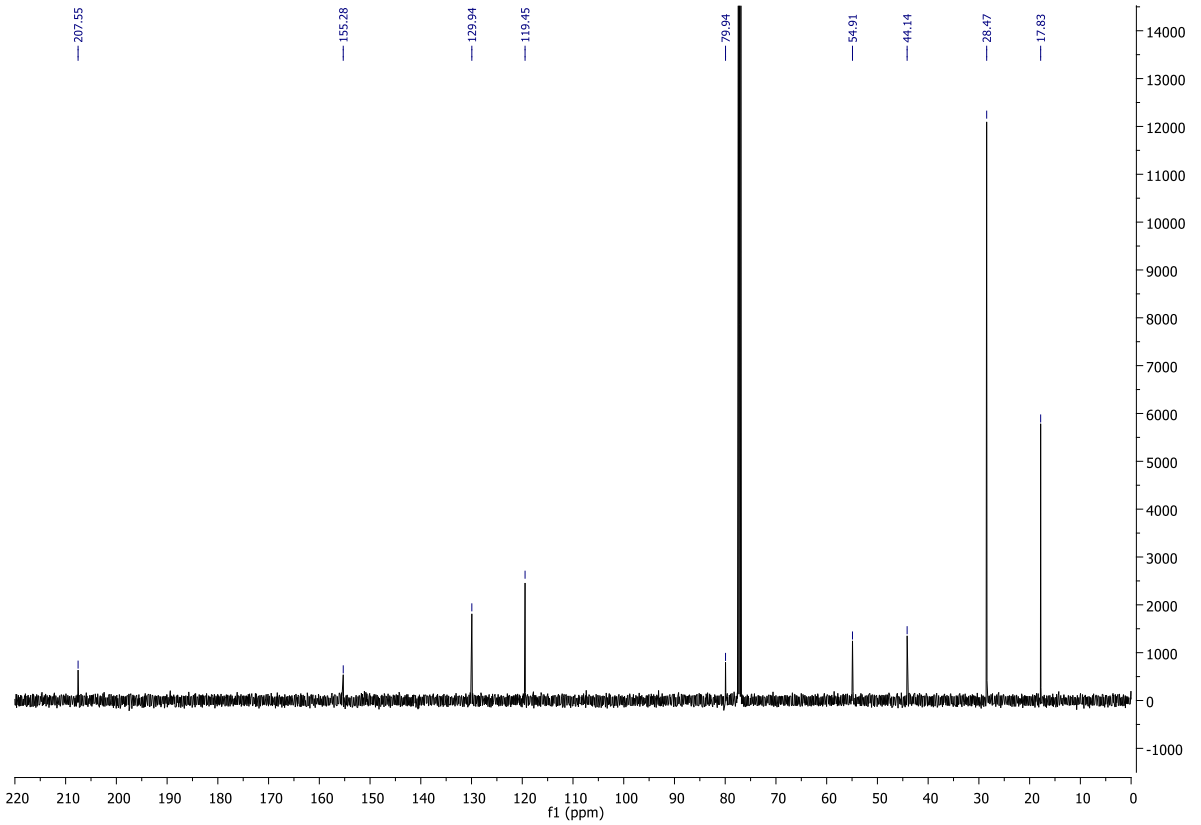
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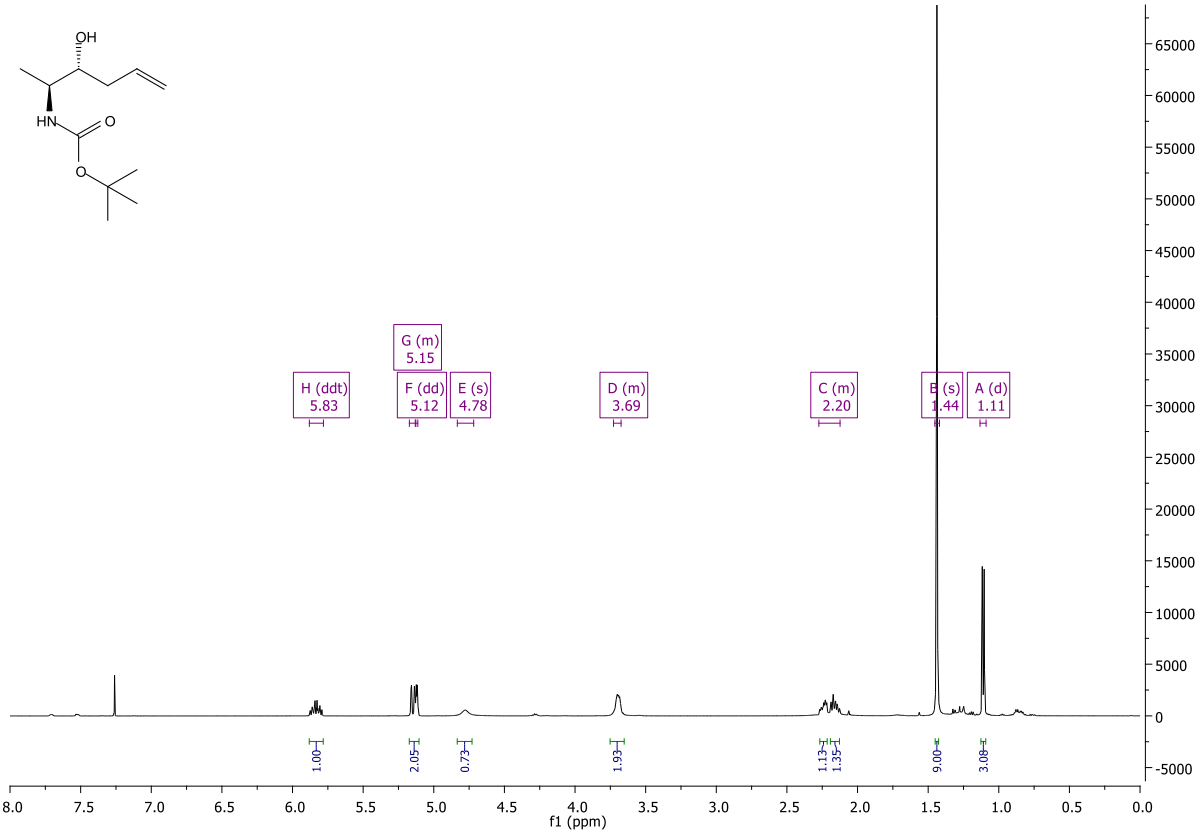
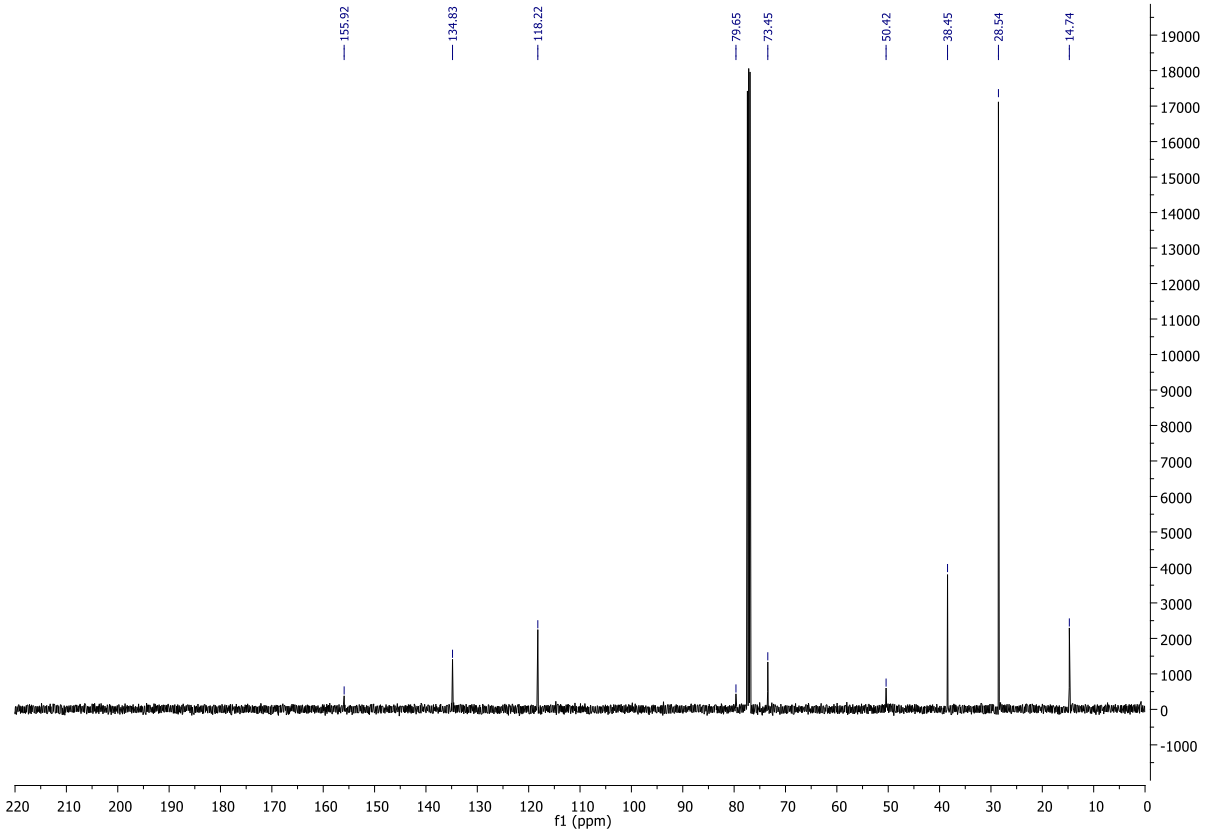
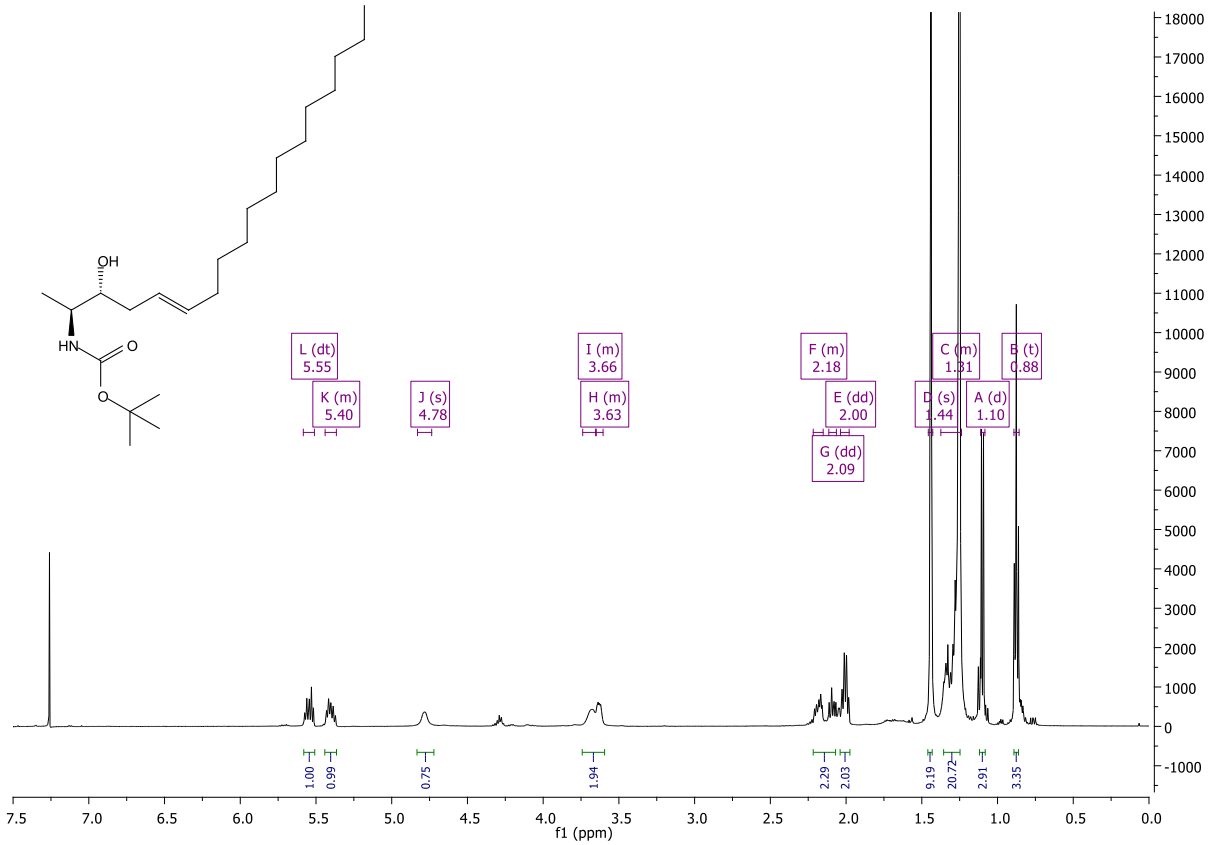
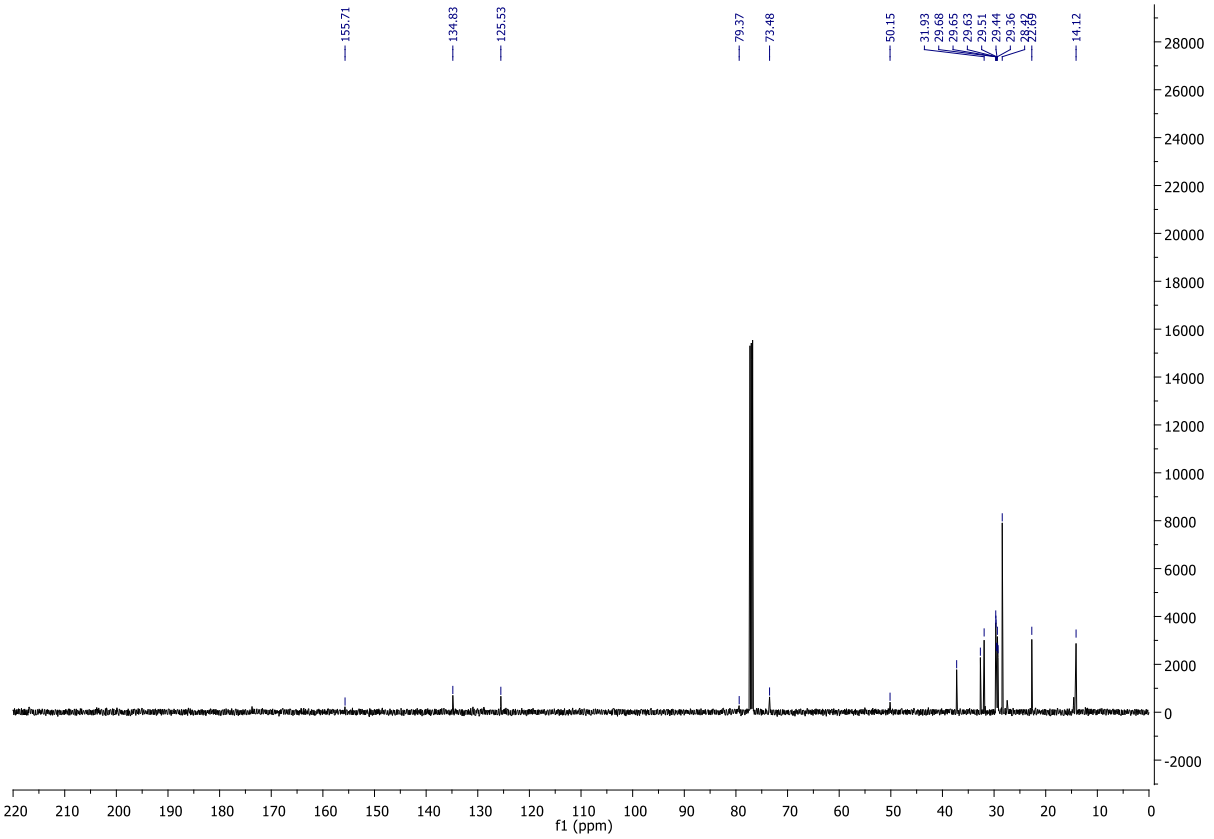
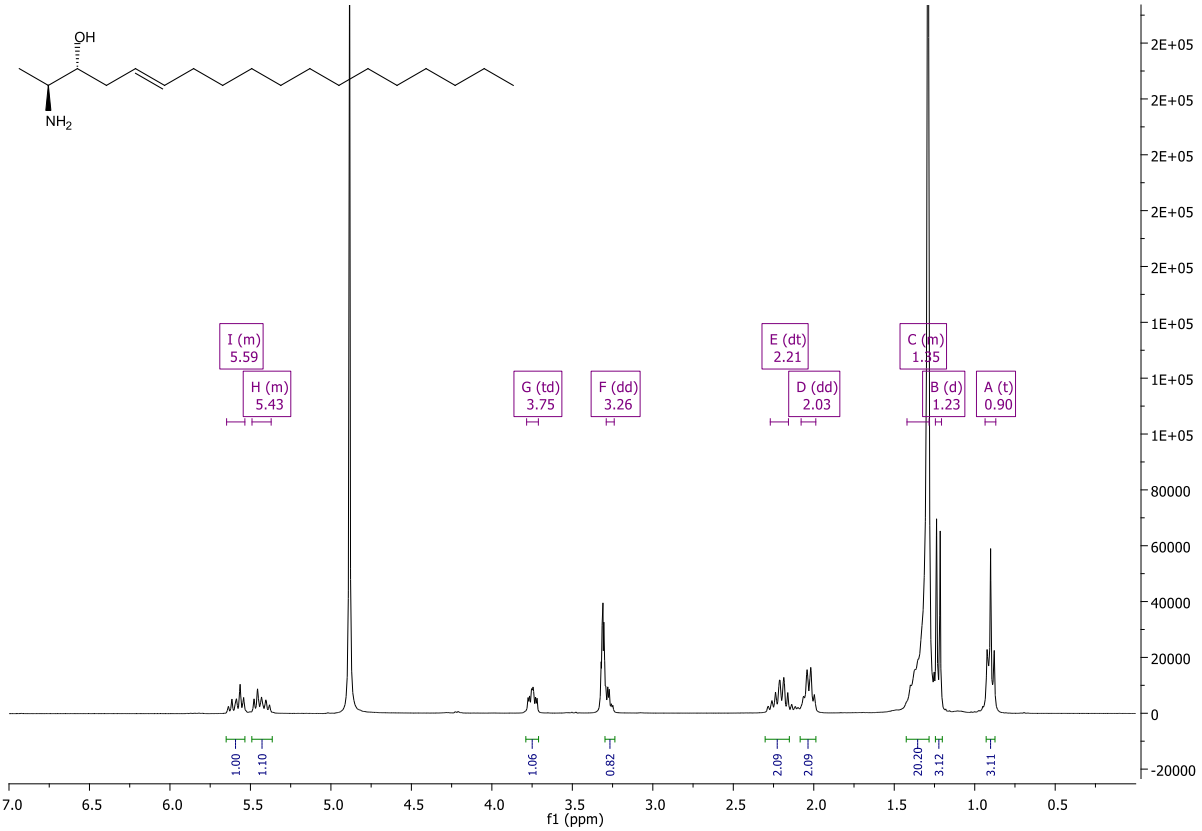
17.83
f1 (ppm)

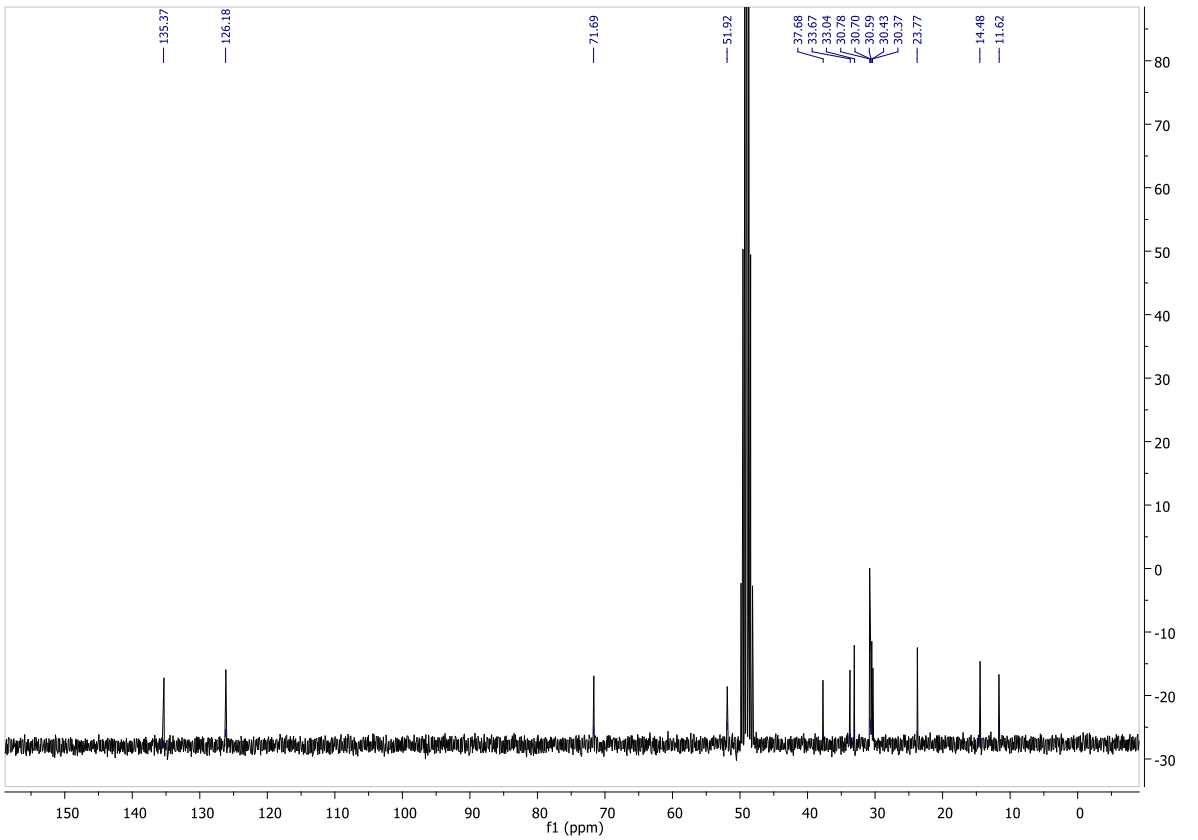

OH
HN
O
O
H (ddt) 5.83
G (m) 5.15
F (dd) 5.12
E (s) 4.78
D (m) 3.69
C (m) 2.20
B (s) 1.44
A (d) 1.11
1.00
2.05
0.73
1.93
1.13
1.35
9.00
3.08
f1 (ppm)

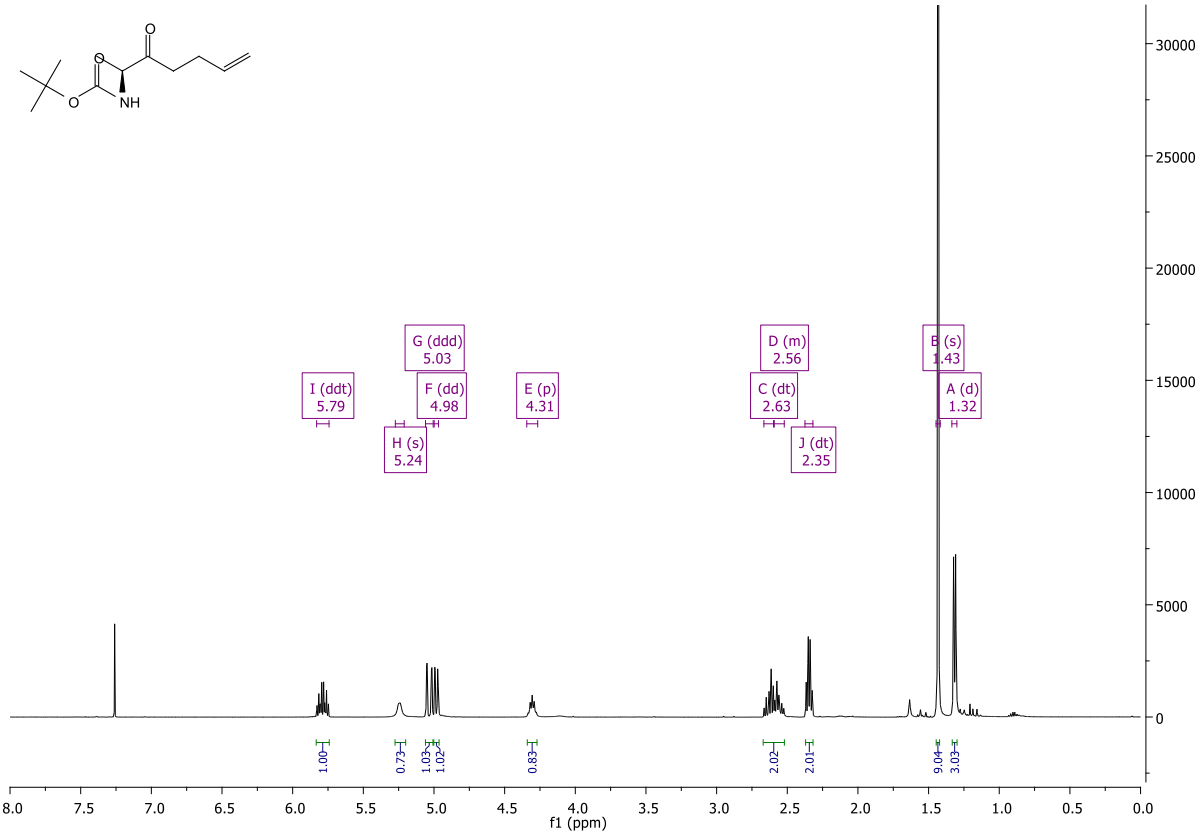

155.92
134.83
118.22
79.65
73.45
50.42
38.45
28.54
14.74
f1 (ppm)

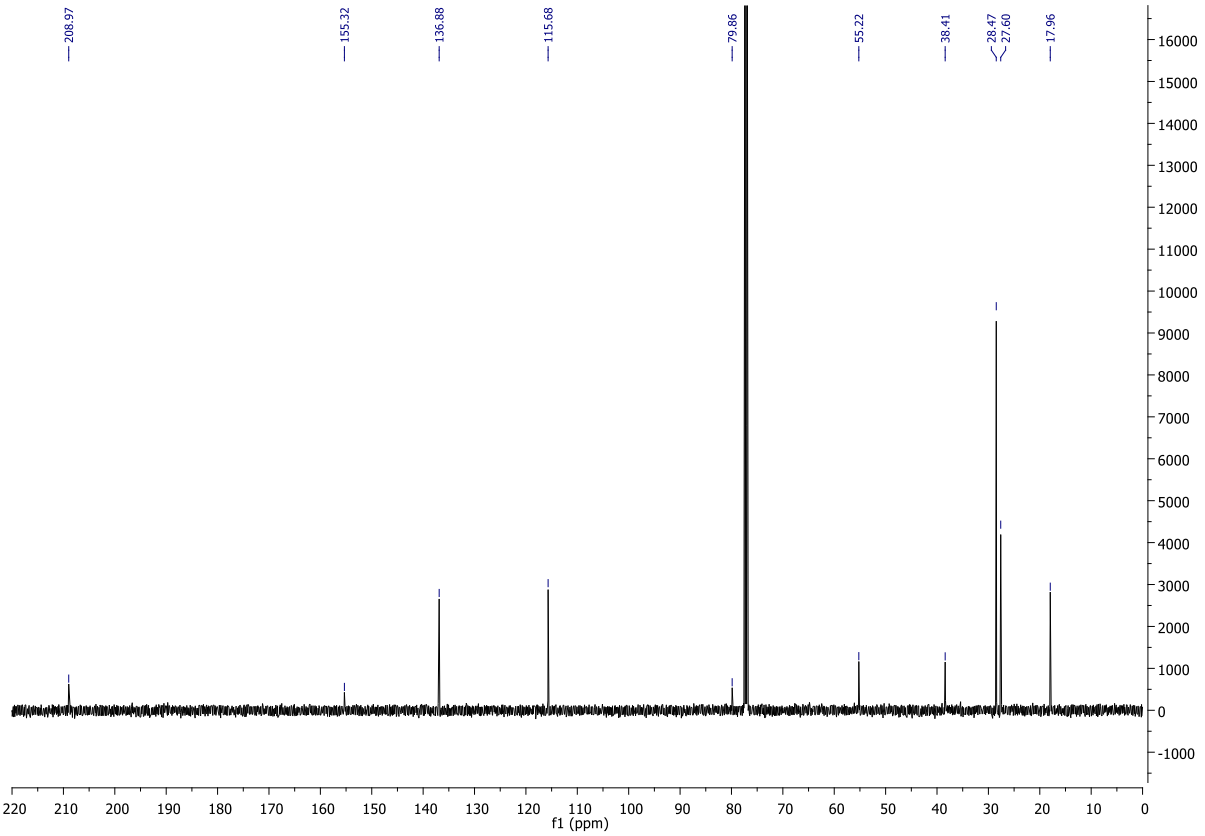

OH
HN
O
O
L (dt) 5.55
K (m) 5.40
J (s) 4.78
I (m) 3.66
H (m) 3.63
F (m) 2.18
E (dd) 2.00
G (dd) 2.09
C (m) 1.31
D (s) 1.44
A (d) 1.10
B (t) 0.88
1.00
0.99
0.75
1.94
2.29
2.03
9.19
20.72
2.91
3.35
f1 (ppm)

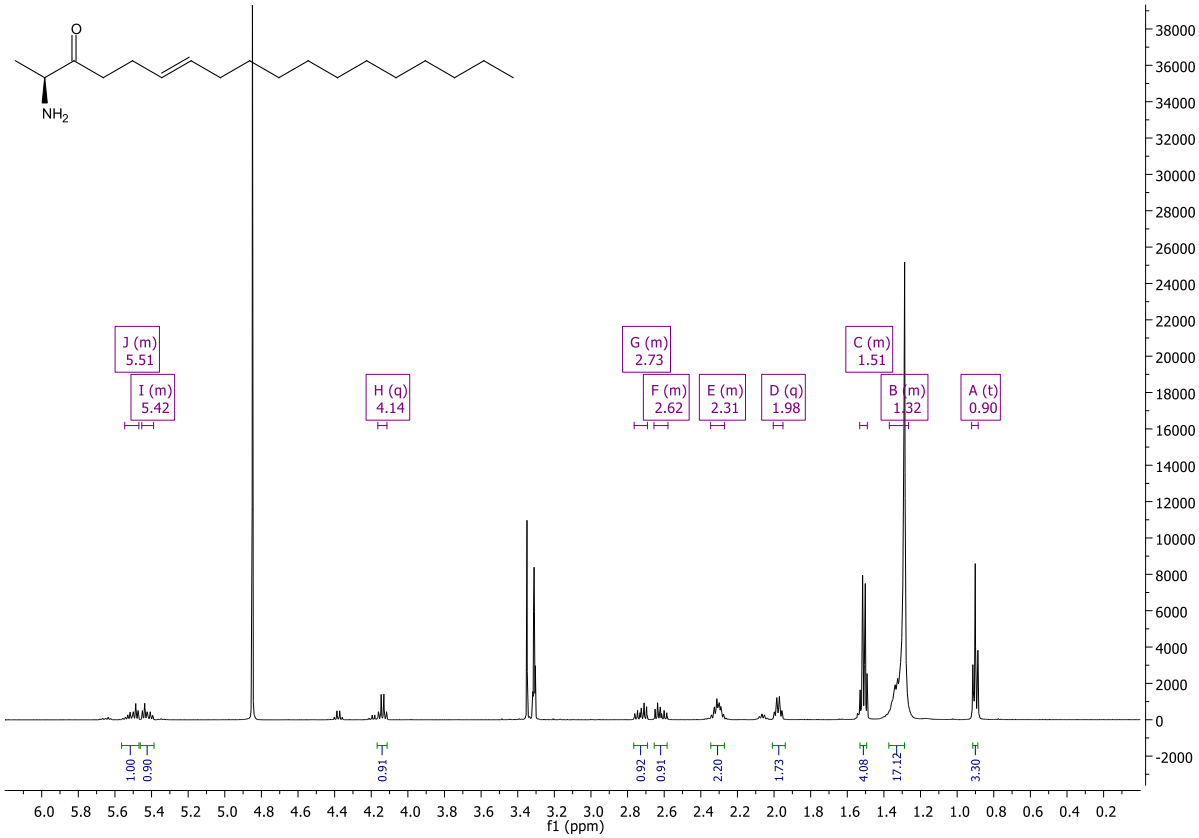

155.71
134.83
125.53
79.37
73.48
50.15
31.93
29.68
29.65
29.63
29.51
29.44
29.36
22.89
14.12
f1 (ppm)

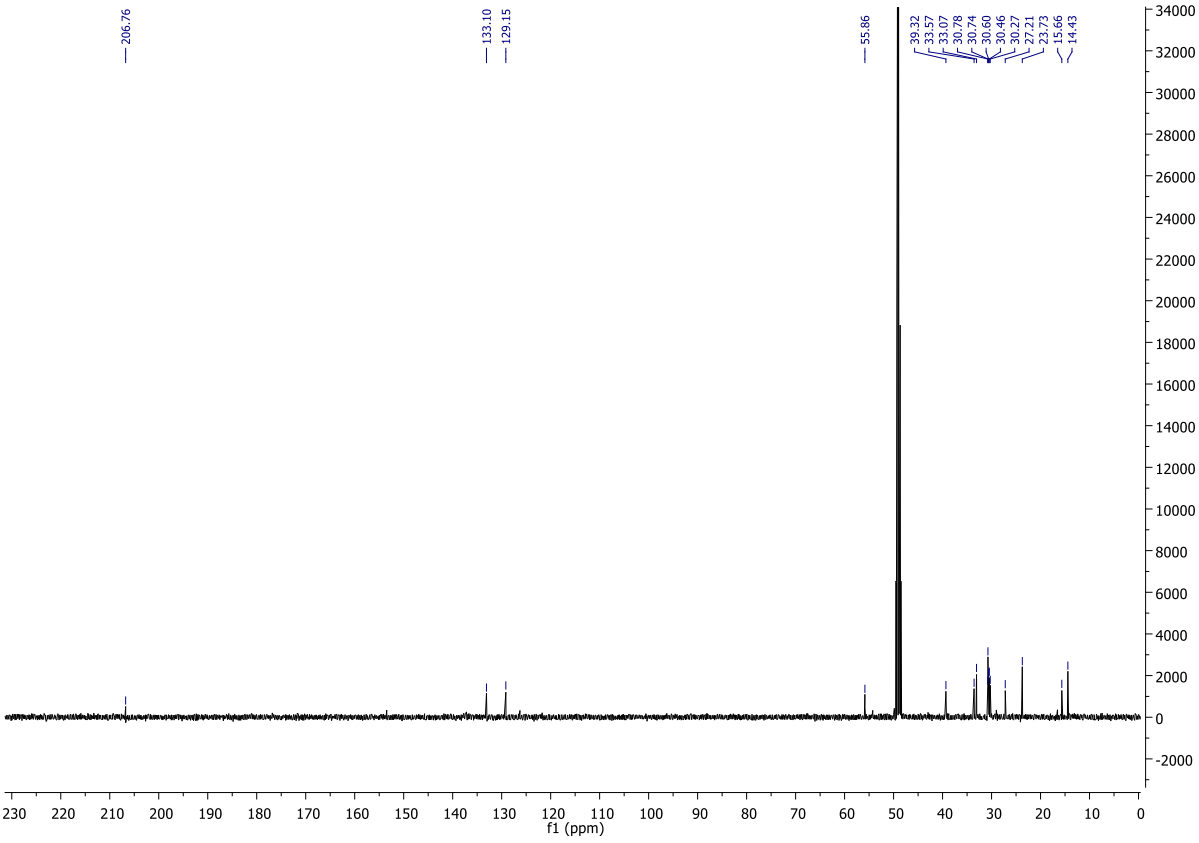

OH
NH2
I (m) 5.59
H (m) 5.43
G (td) 3.75
F (dd) 3.26
E (dt) 2.21
D (dd) 2.03
C (m) 1.35
B (d) 1.23
A (t) 0.90
1.00
1.10
1.06
0.82
2.09
2.09
20.20
3.12
3.11
f1 (ppm)

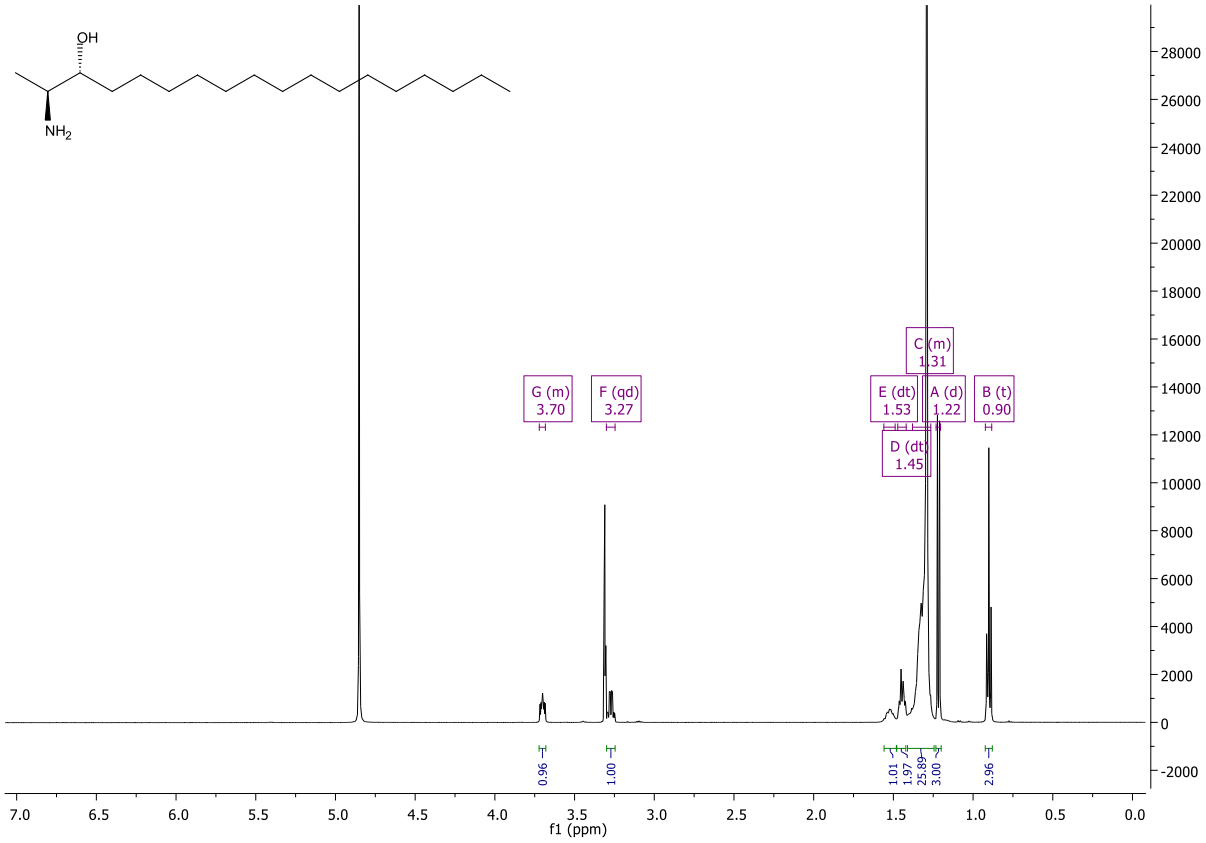

135.37
126.18
71.69
51.92
37.68
33.67
33.04
30.78
30.70
30.59
30.43
30.37
23.77
14.48
11.62
f1 (ppm)

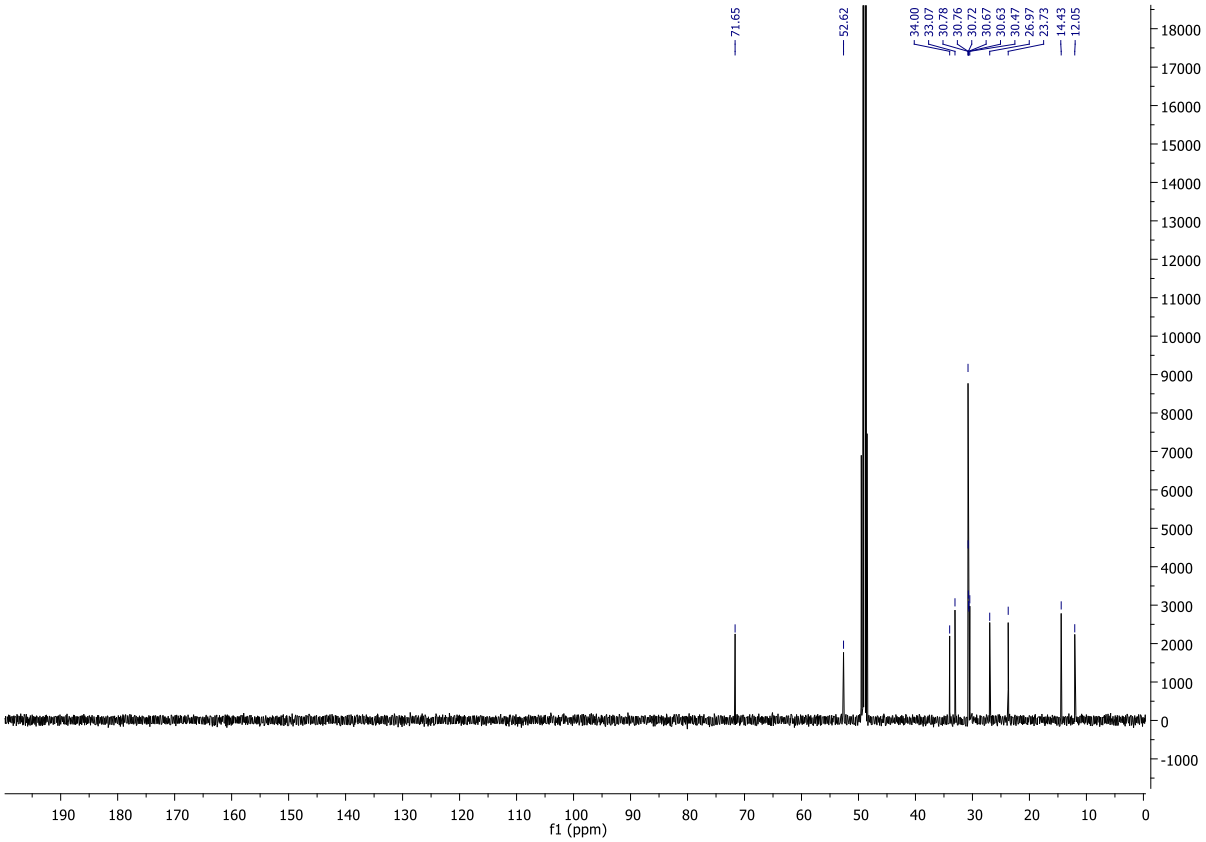

O
O
NH
O
I (ddt)
5.79
G (ddd)
5.03
F (dd)
4.98
H (s)
5.24
E (p)
4.31
D (m)
2.56
C (dt)
2.63
J (dt)
2.35
B (s)
1.43
A (d)
1.32
1.00
0.73
1.03
1.02
0.83
2.02
2.01
9.04
3.03
f1 (ppm)

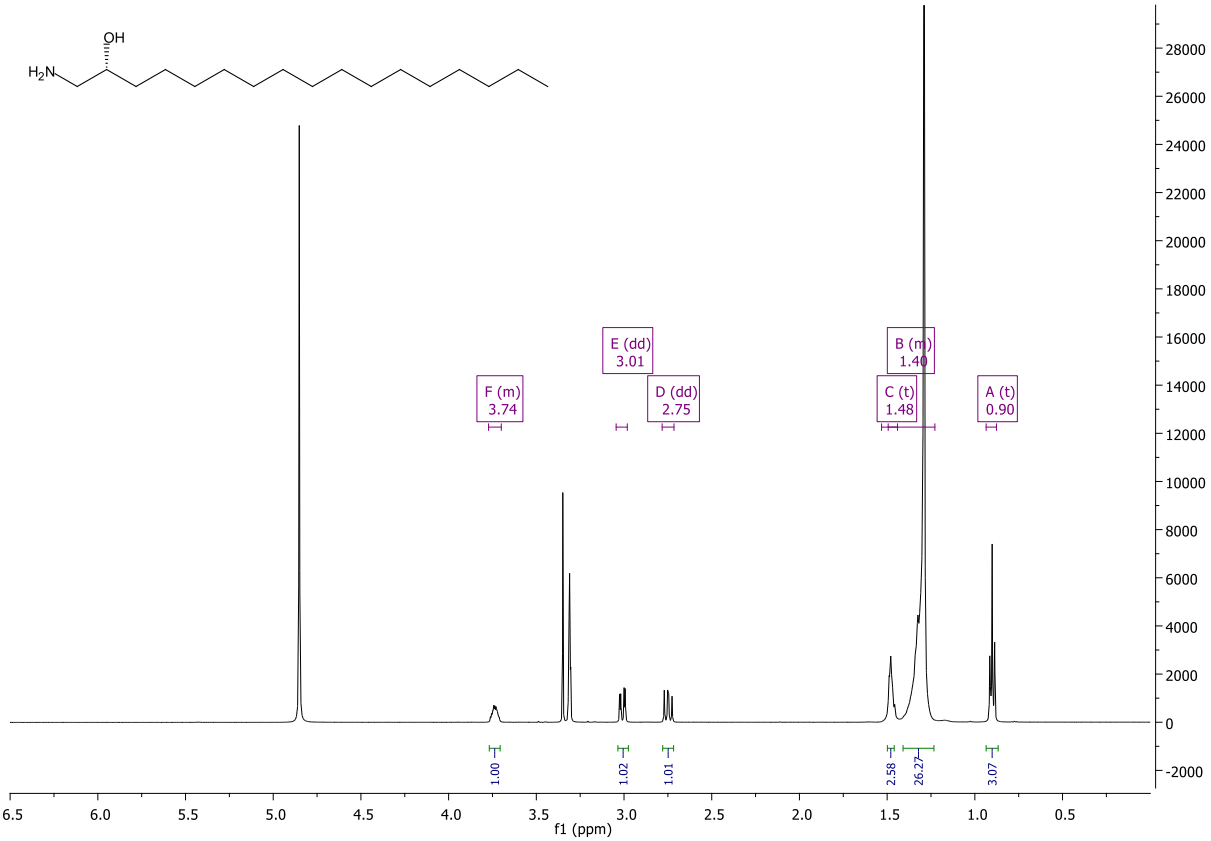

208.97
155.32
136.88
115.68
79.86
55.22
38.41
28.47
27.60
17.96
f1 (ppm)

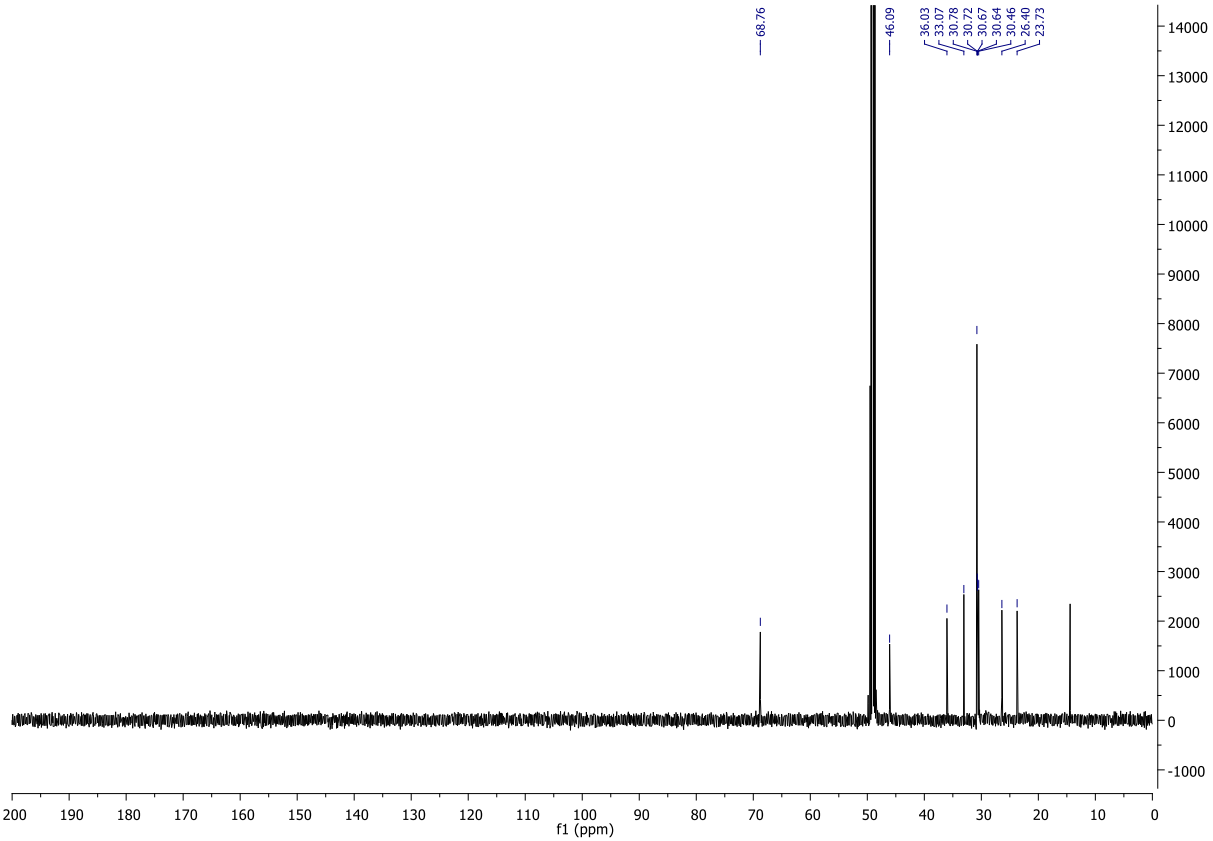

O
NH2
J (m) 5.51
I (m) 5.42
H (q) 4.14
G (m) 2.73
F (m) 2.62
E (m) 2.31
D (q) 1.98
C (m) 1.51
B (m) 1.32
A (t) 0.90
1.00
0.90
0.91
0.92
0.91
2.20
1.73
4.08
17.12
3.30
f1 (ppm)

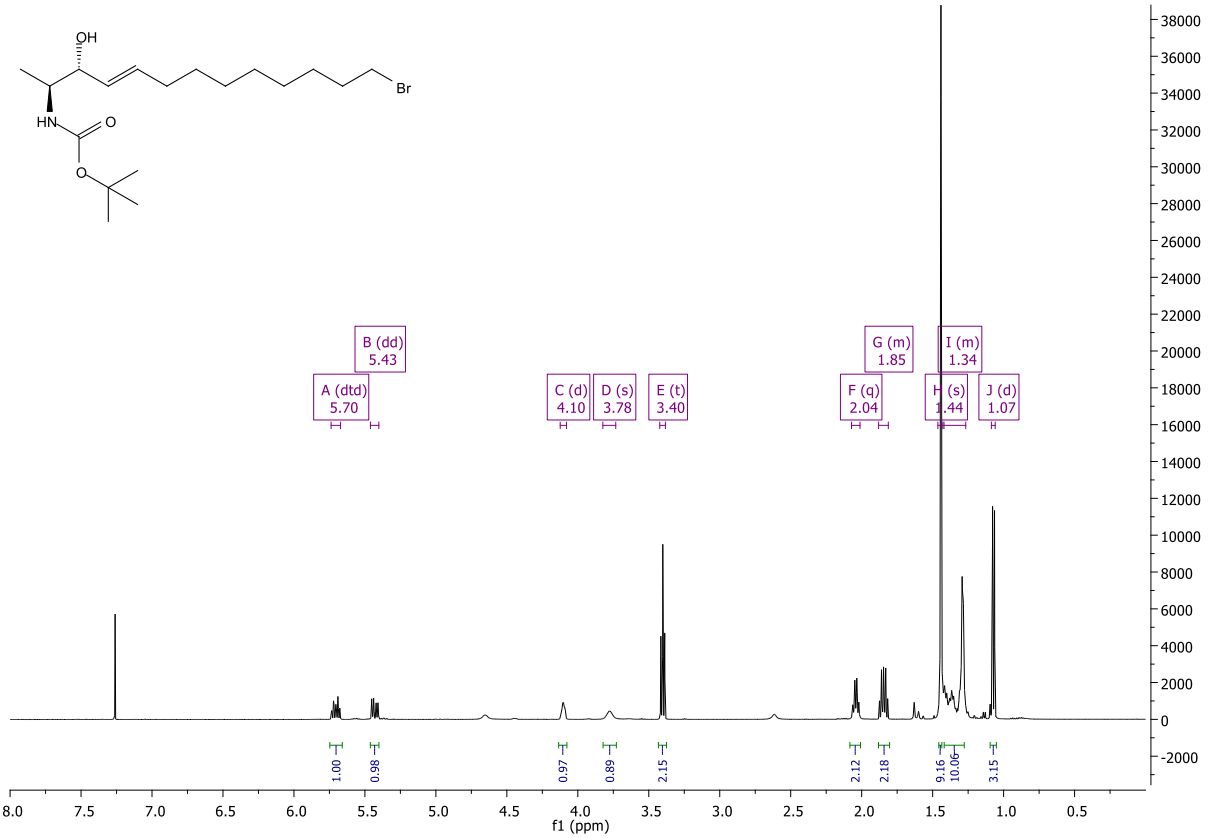

206.76
133.10
129.15
55.86
39.32
33.57
33.07
30.78
30.74
30.60
30.46
30.27
27.21
23.73
15.66
14.43
f1 (ppm)

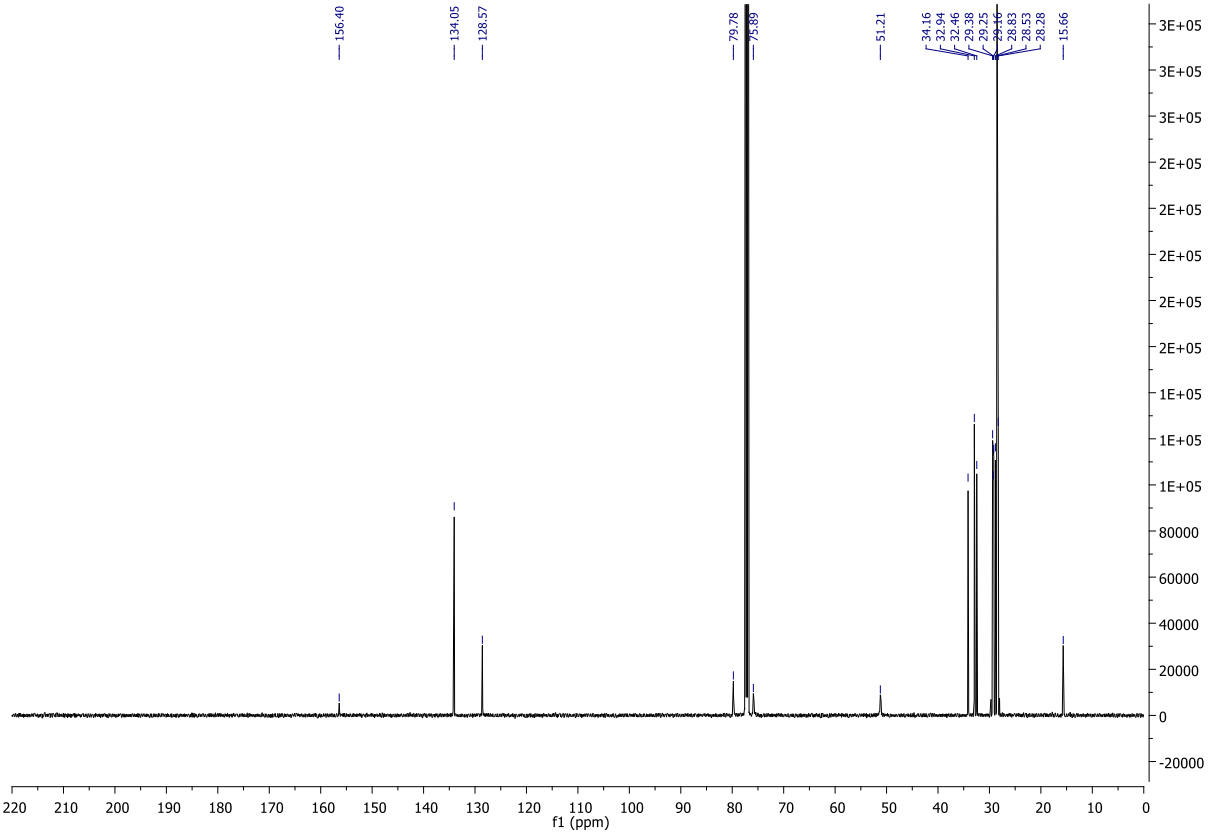

OH
NH2
G (m)
3.70
F (qd)
3.27
C (m)
1.31
E (dt)
1.53
A (d)
1.22
D (dt)
1.45
B (t)
0.90
0.96
1.00
1.01
1.97
25.89
3.00
2.96
f1 (ppm)

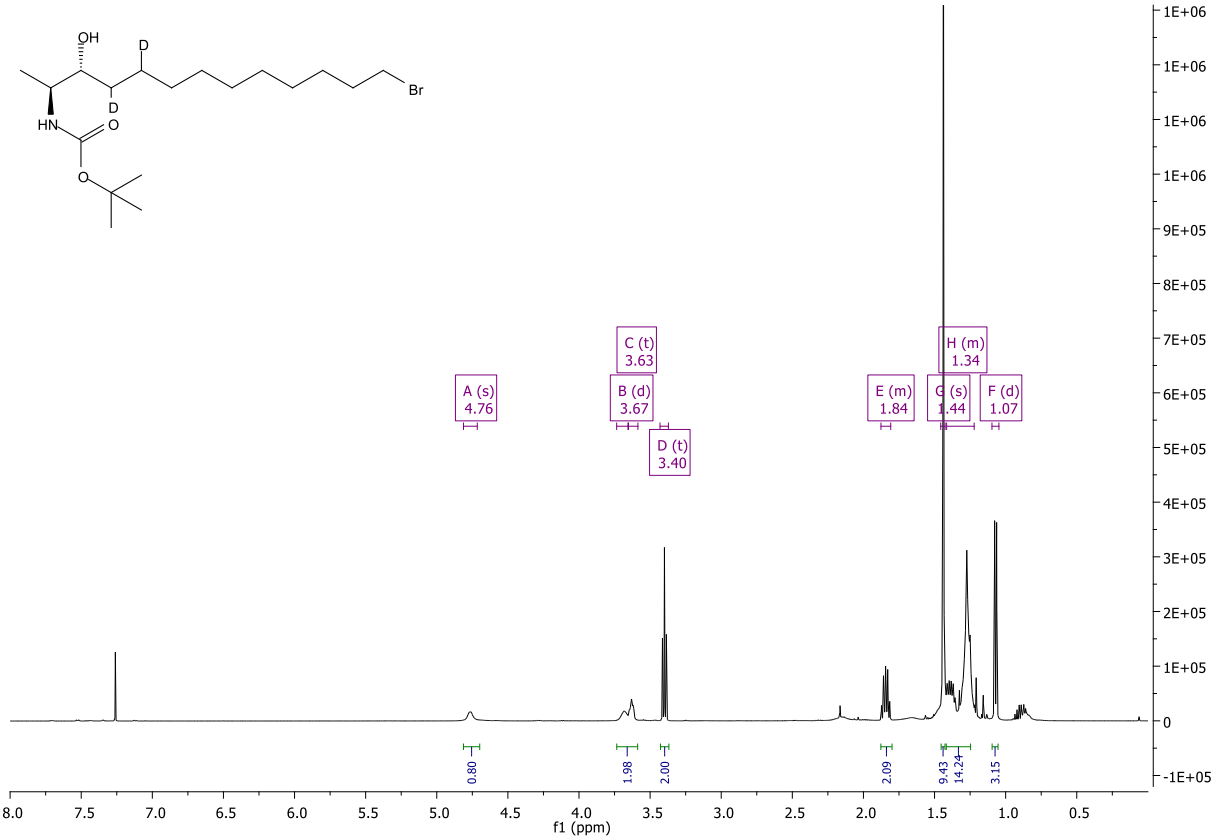

71.65
52.62
34.00
33.07
30.78
30.76
30.72
30.67
30.63
30.47
26.97
23.73
14.43
12.05
f1 (ppm)

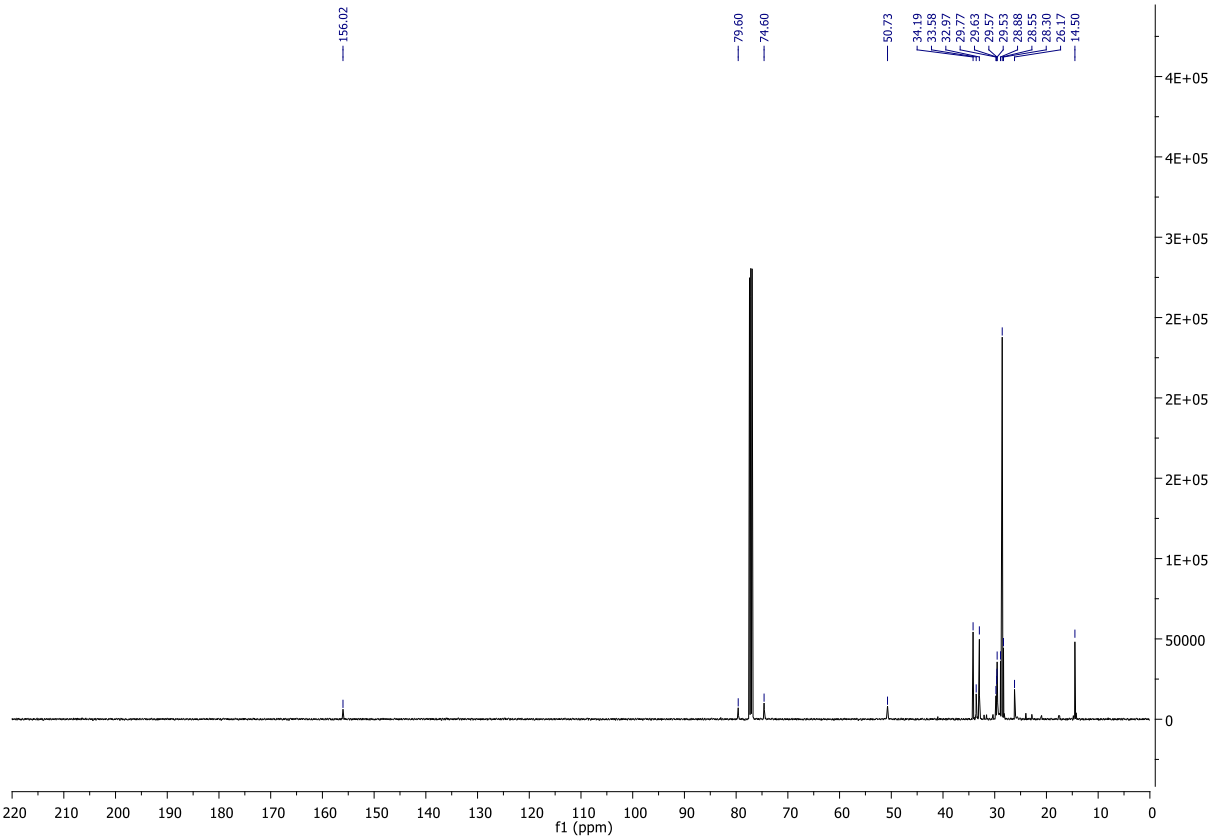

OH
H2N
F (m)
3.74
E (dd)
3.01
D (dd)
2.75
C (t)
1.48
B (m)
1.40
A (t)
0.90
1.00
1.02
1.01
2.58
26.27
3.07
f1 (ppm)

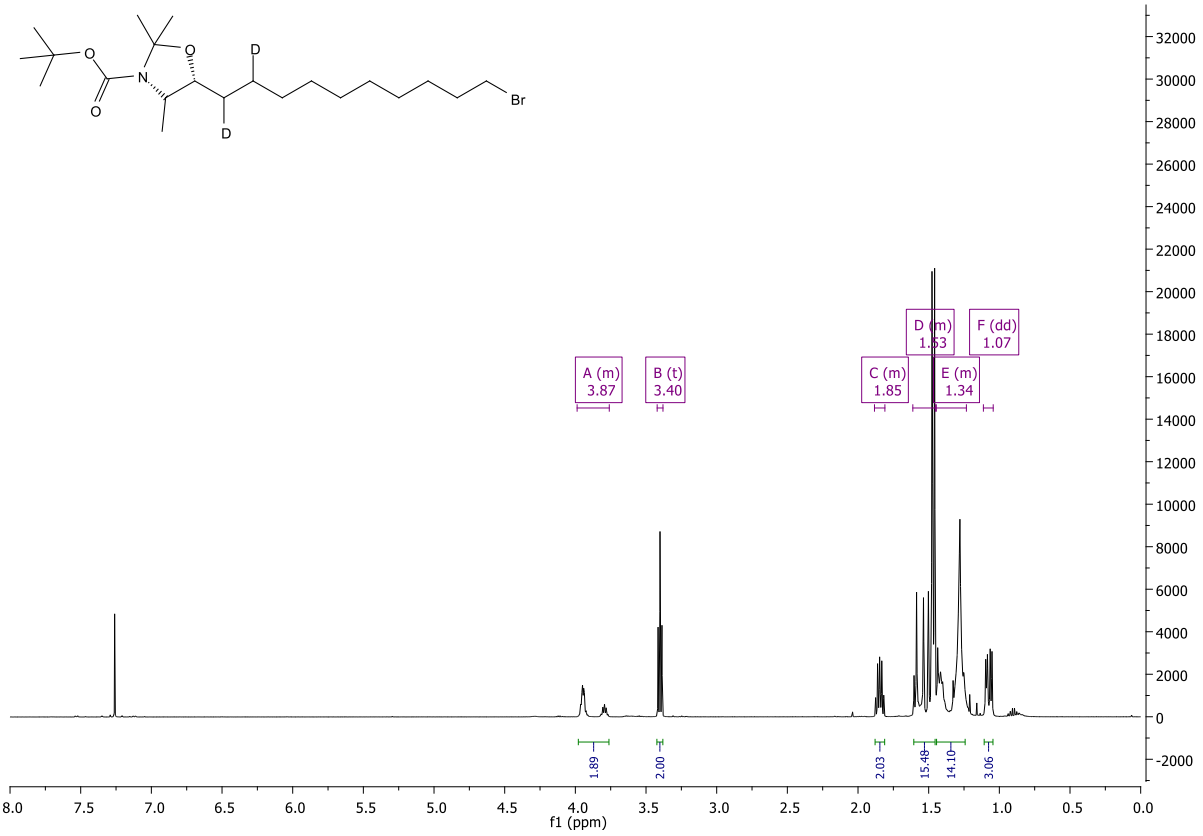

68.76
46.09
36.03
33.07
30.78
30.72
30.67
30.64
30.46
26.40
23.73
f1 (ppm)

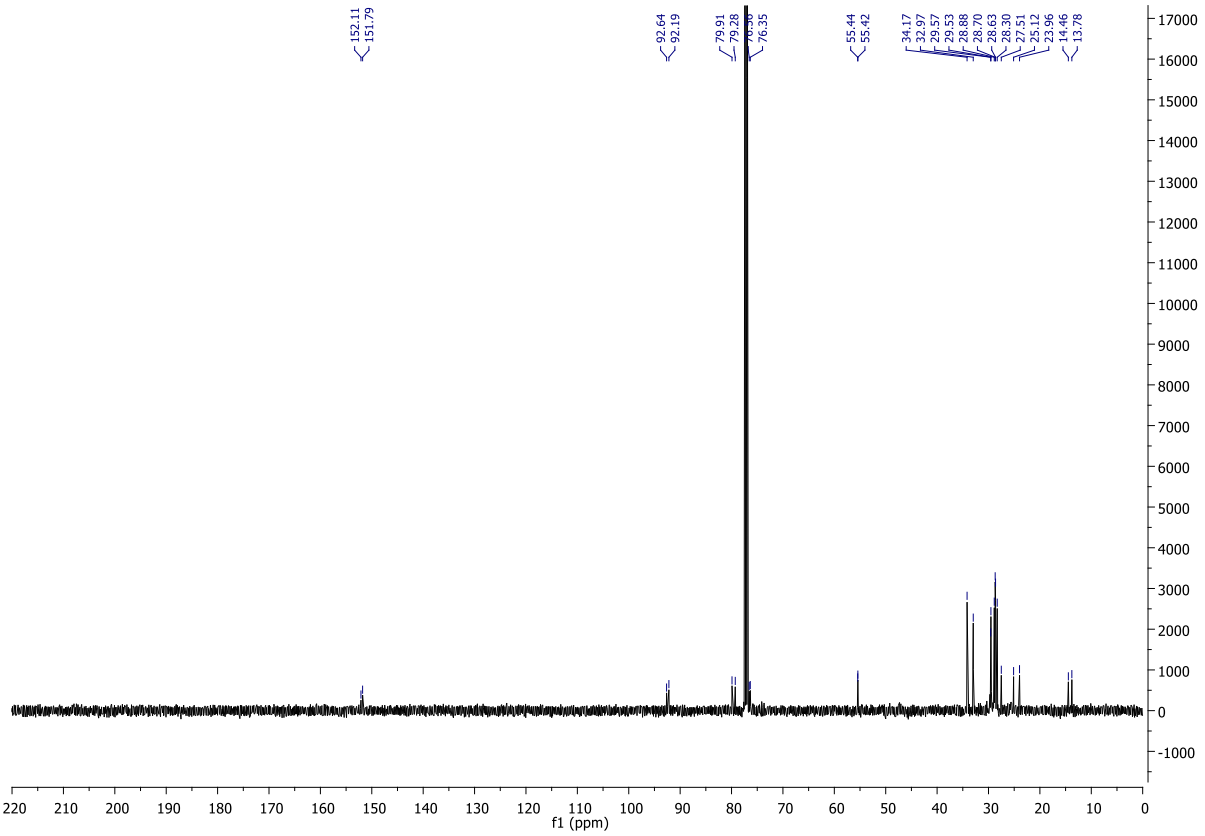

OH
HN
O
O
Br
B (dd)
5.43
A (dtd)
5.70
C (d)
4.10
D (s)
3.78
E (t)
3.40
G (m)
1.85
I (m)
1.34
F (q)
2.04
H (s)
1.44
J (d)
1.07
1.00
0.98
0.97
0.89
2.15
2.12
2.18
9.16
10.06
3.15
f1 (ppm)

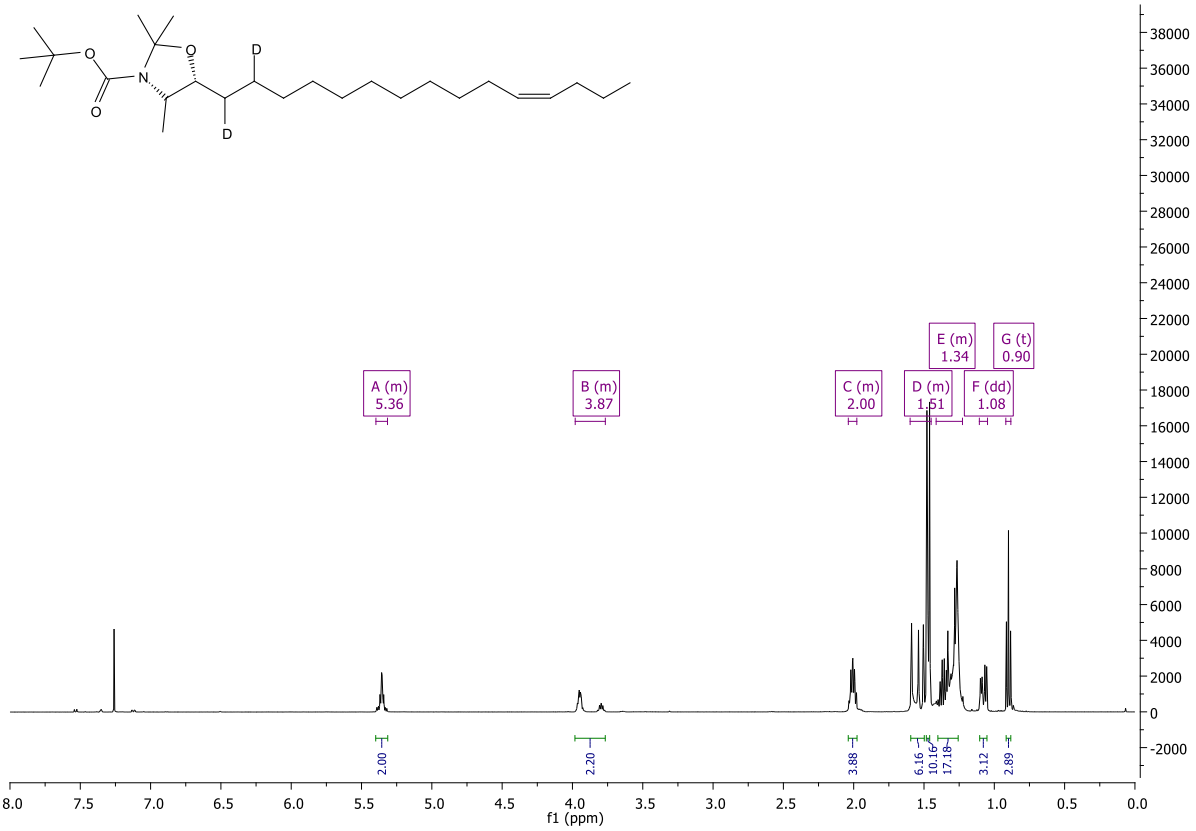

156.40
134.05
128.57
79.78
75.89
51.21
34.16
32.94
32.46
29.38
29.25
29.16
28.83
28.53
28.28
15.66
f1 (ppm)

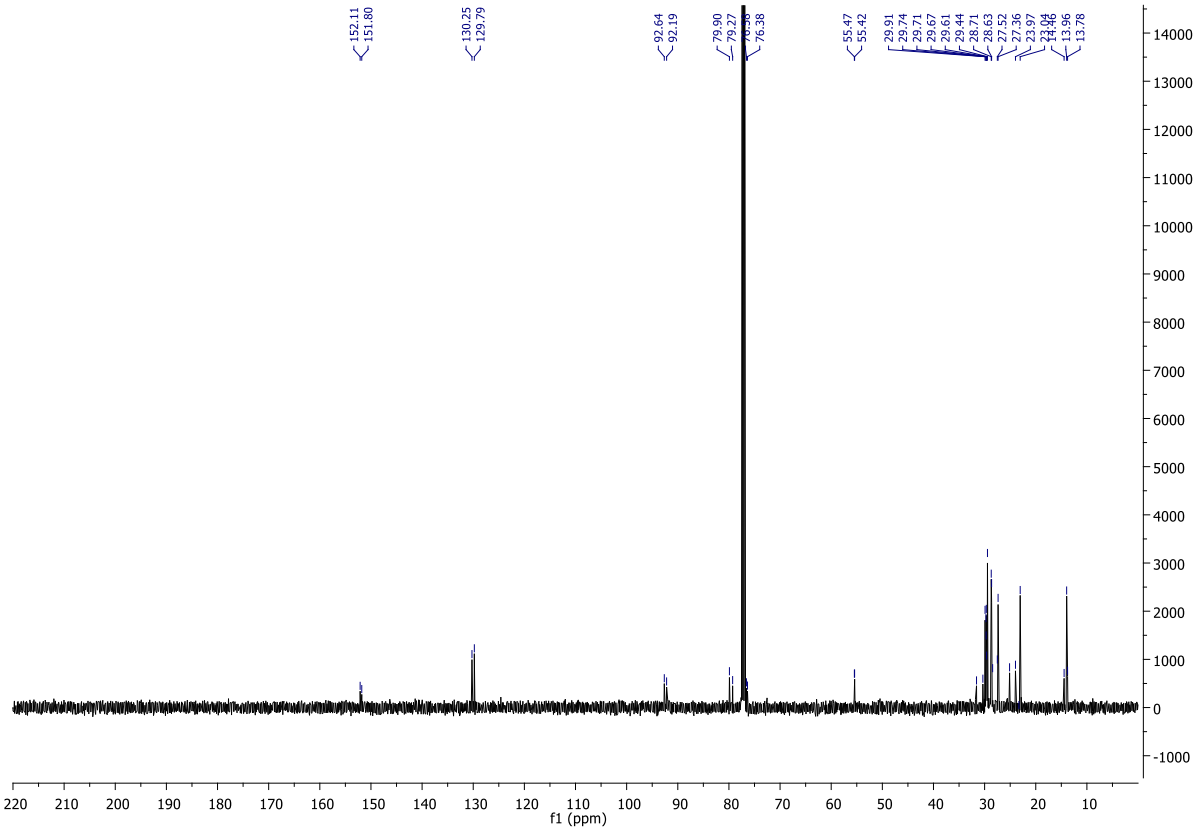

OH
D
D
HN
O
O
Br
A (s)
4.76
B (d)
3.67
C (t)
3.63
D (t)
3.40
E (m)
1.84
G (s)
1.44
H (m)
1.34
F (d)
1.07
0.80
1.98
2.00
2.09
9.43
14.24
3.15
f1 (ppm)

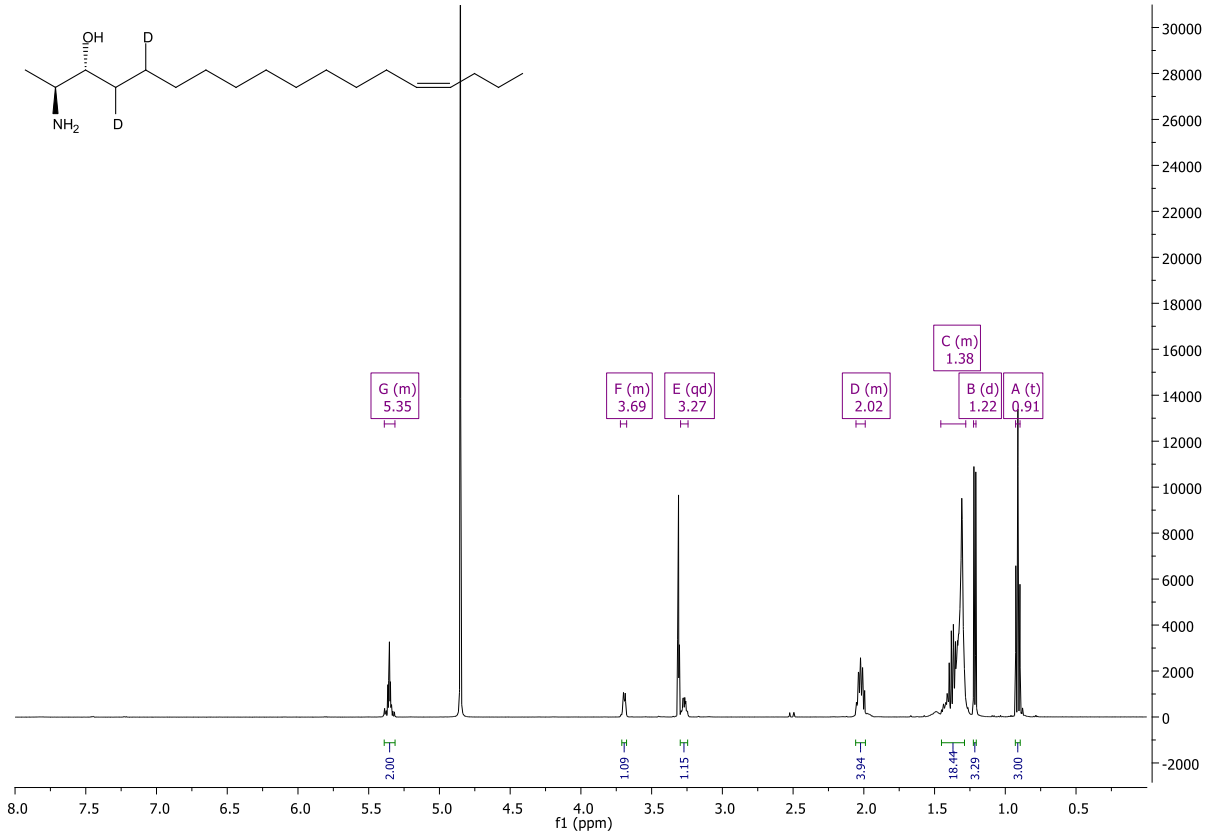

156.02
79.60
74.60
50.73
34.19
33.58
32.97
29.77
29.63
29.57
29.53
28.88
28.55
28.30
26.17
14.50
f1 (ppm)

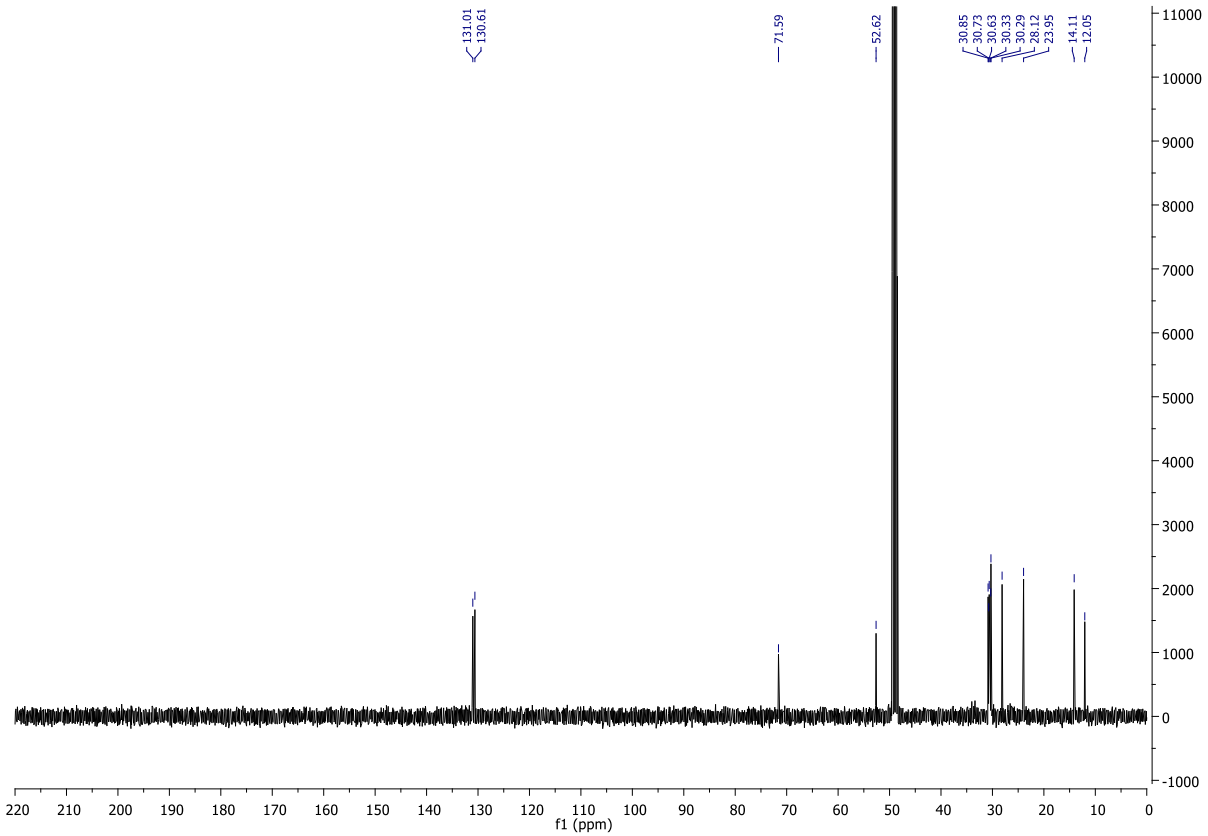

O
O
N
O
O
D
D
Br
A (m)
3.87
B (t)
3.40
C (m)
1.85
D (m)
1.53
E (m)
1.34
F (dd)
1.07
1.89
2.00
2.03
15.48
14.10
3.06
f1 (ppm)

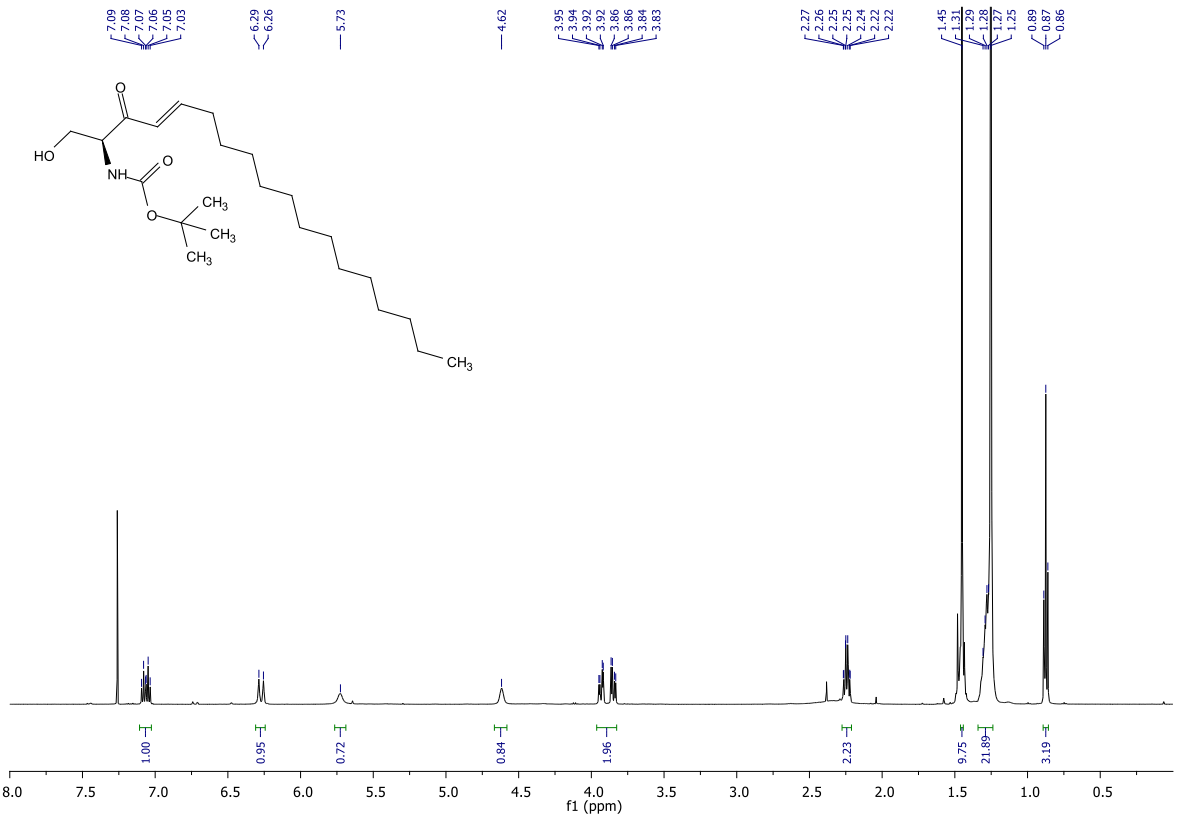

152.11
151.79
92.64
92.19
79.91
79.28
76.35
55.44
55.42
34.17
32.97
29.57
29.53
28.88
28.70
28.63
28.30
27.51
25.12
23.96
14.46
13.78
f1 (ppm)

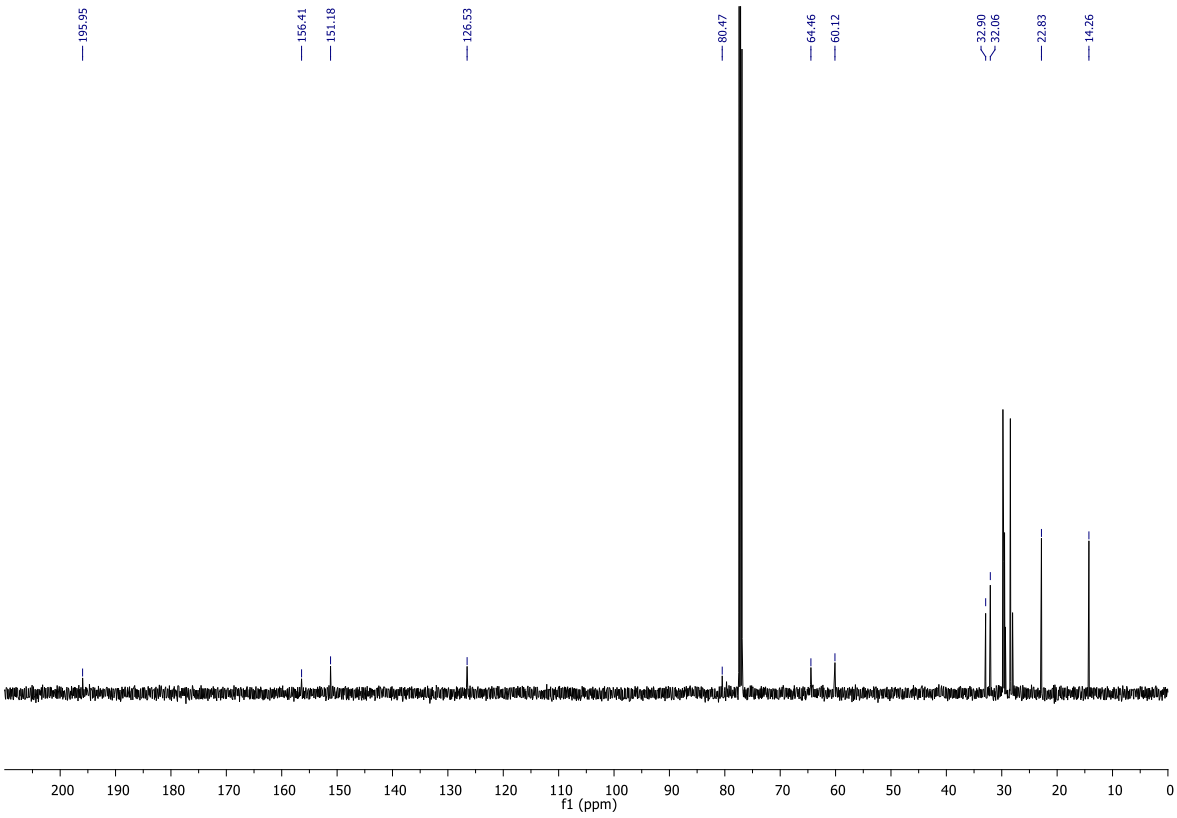

A (m)
5.36
B (m)
3.87
C (m)
2.00
D (m)
1.51
E (m)
1.34
F (dd)
1.08
G (t)
0.90
2.00
2.20
3.88
6.16
10.16
17.18
3.12
2.89
f1 (ppm)

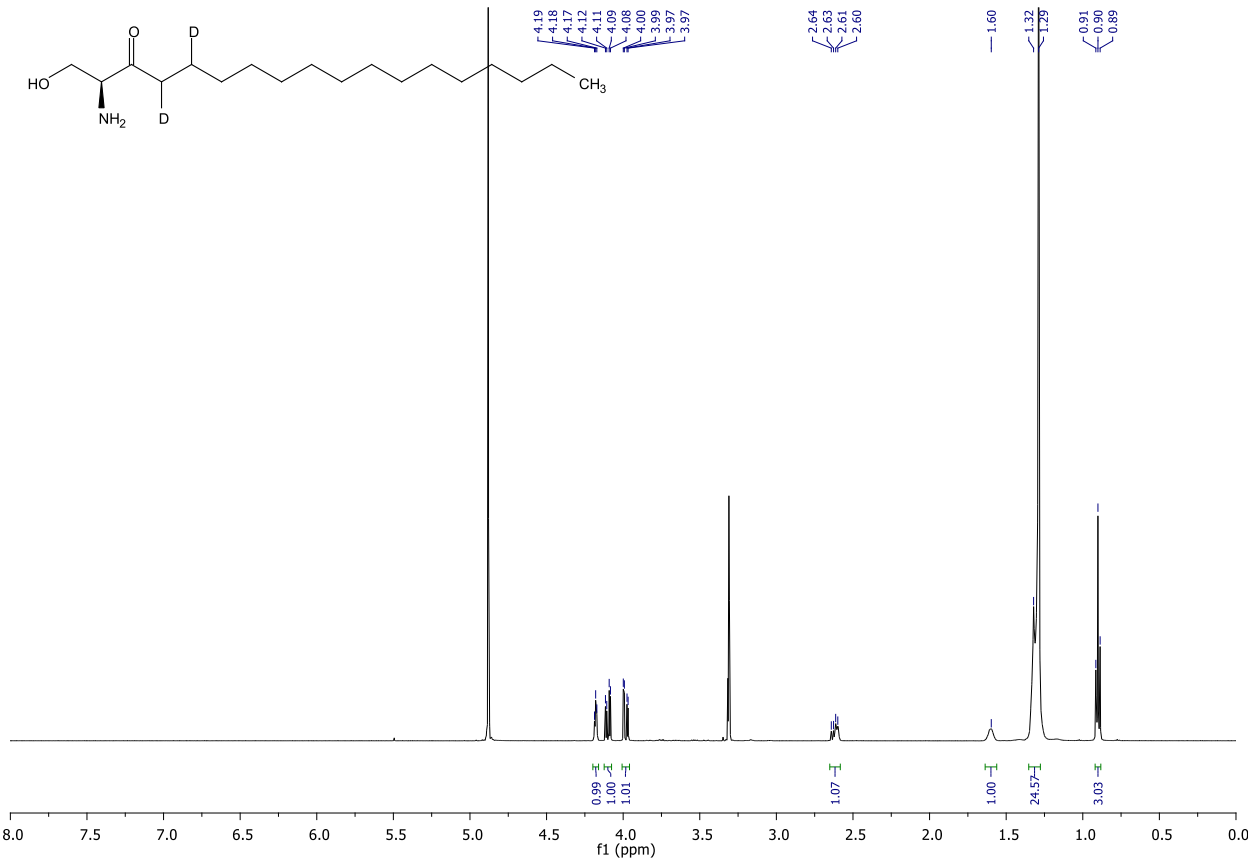

152.11
151.80
130.25
129.79
92.64
92.19
79.90
79.27
76.38
55.47
55.42
29.91
29.74
29.71
29.67
29.61
29.44
28.71
28.63
27.52
27.36
23.97
13.96
13.78
f1 (ppm)

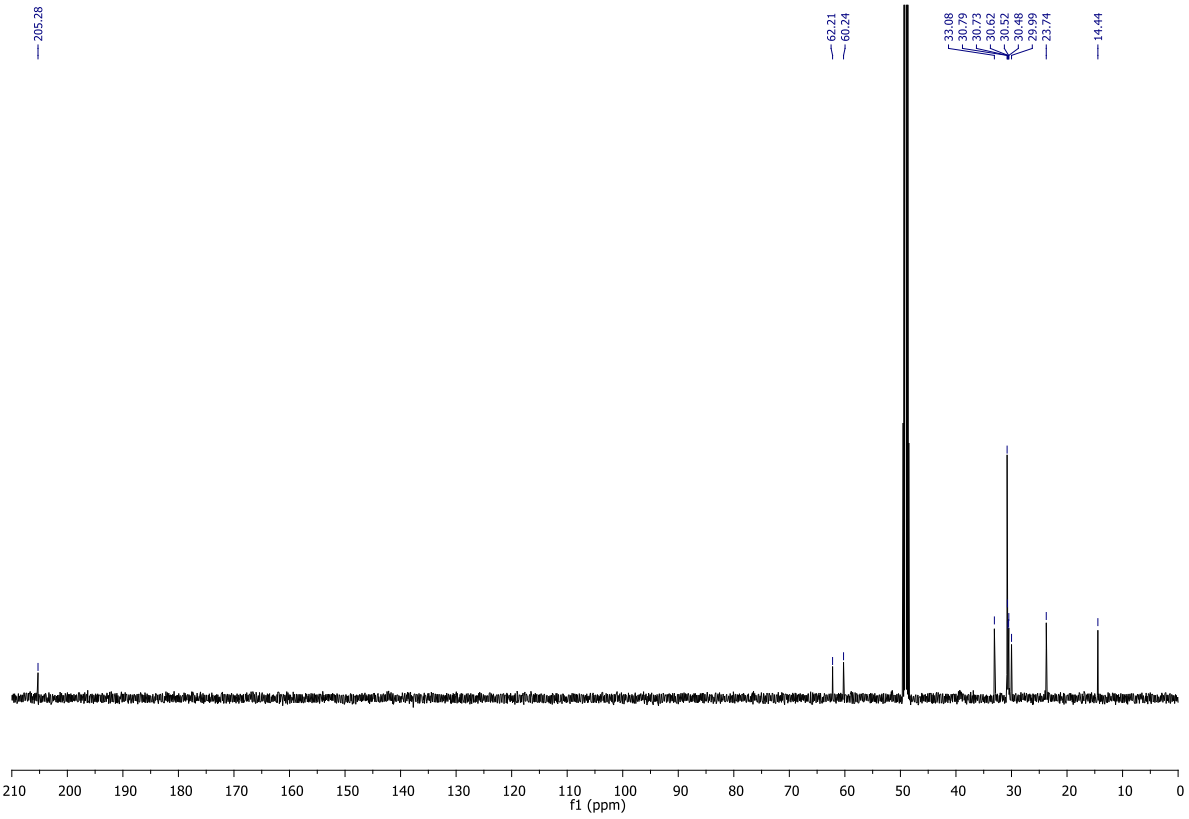

OH
D
NH2
D
G (m)
5.35
F (m)
3.69
E (qd)
3.27
D (m)
2.02
C (m)
1.38
B (d)
1.22
A (t)
0.91
2.00
1.09
1.15
3.94
18.44
3.29
3.00
f1 (ppm)

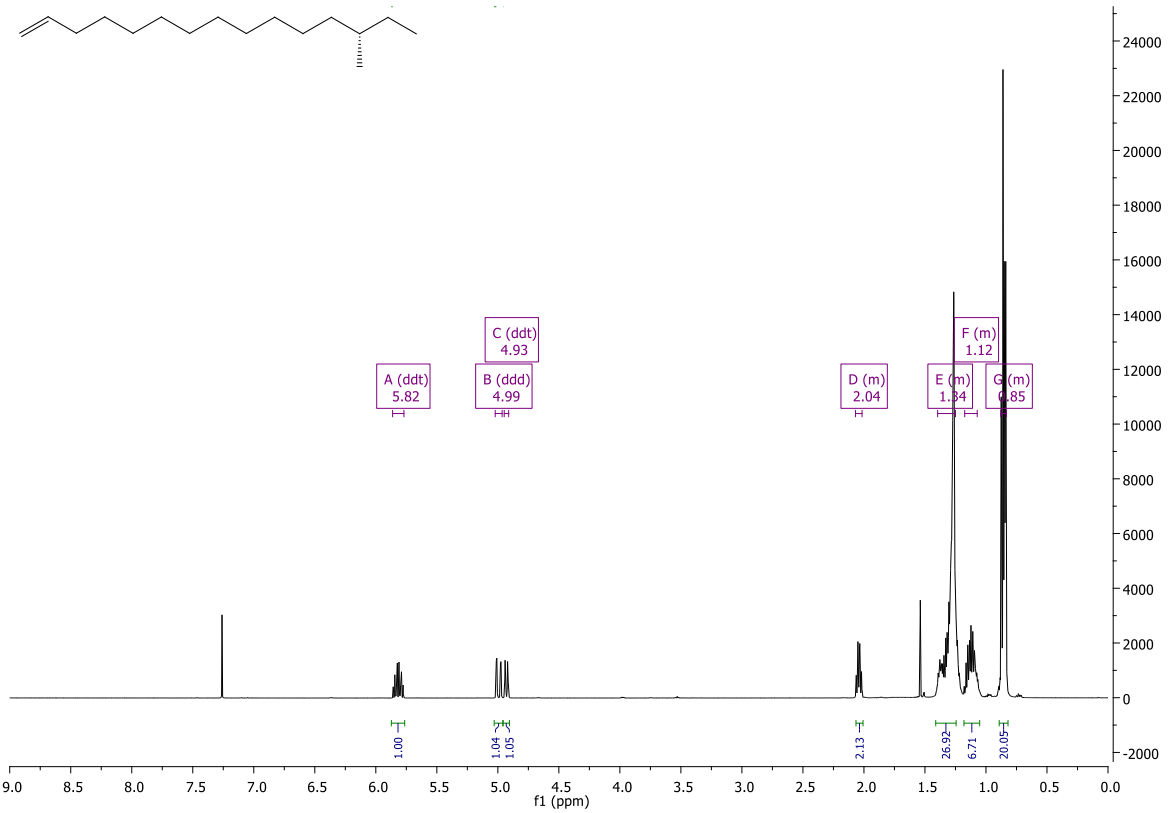

131.01
130.61
71.59
52.62
30.85
30.73
30.63
30.33
30.29
28.12
23.95
14.11
12.05
f1 (ppm)

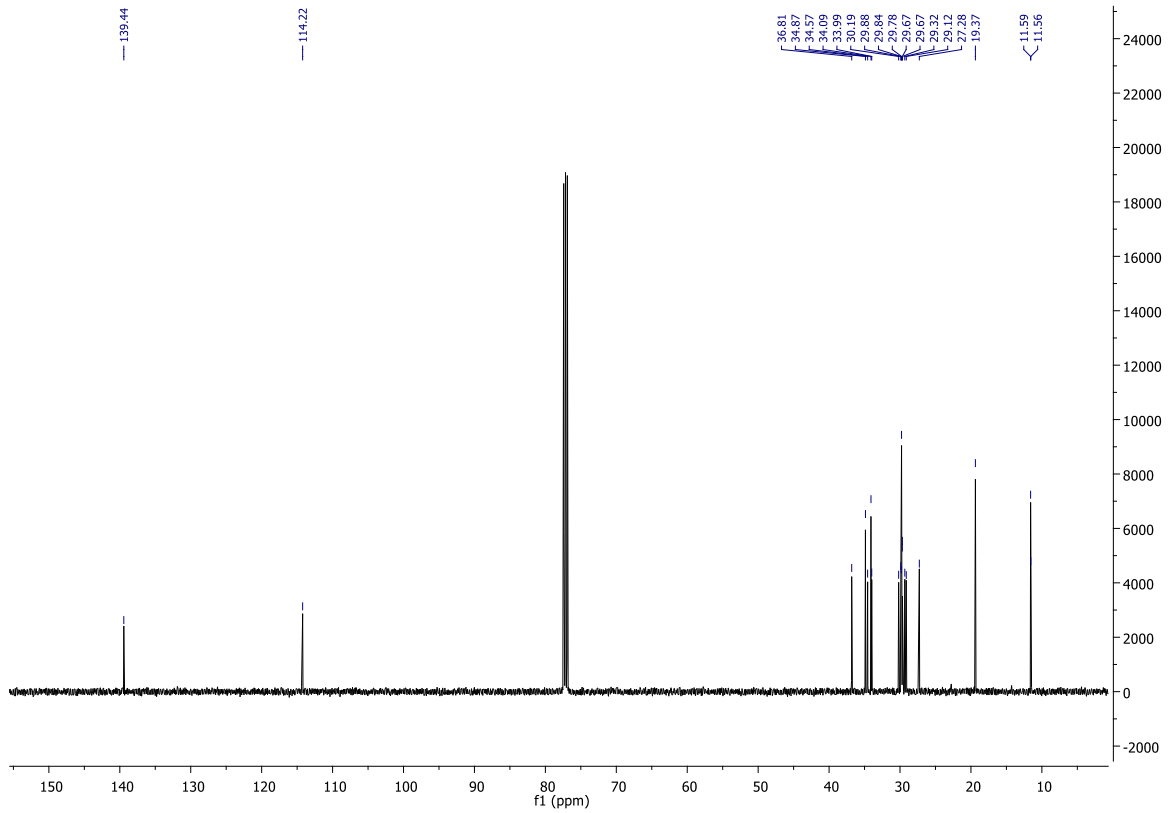

7.09
7.08
7.07
7.06
7.05
7.03
6.29
6.26
5.73
4.62
3.95
3.94
3.92
3.92
3.86
3.86
3.84
3.83
2.27
2.26
2.25
2.25
2.24
2.22
2.22
1.45
1.31
1.29
1.28
1.27
1.25
0.89
0.87
0.86
HO
NH
O
O
O
CH3
CH3
CH3
CH3
1.00
0.95
0.72
0.84
1.96
2.23
9.75
21.89
3.19
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

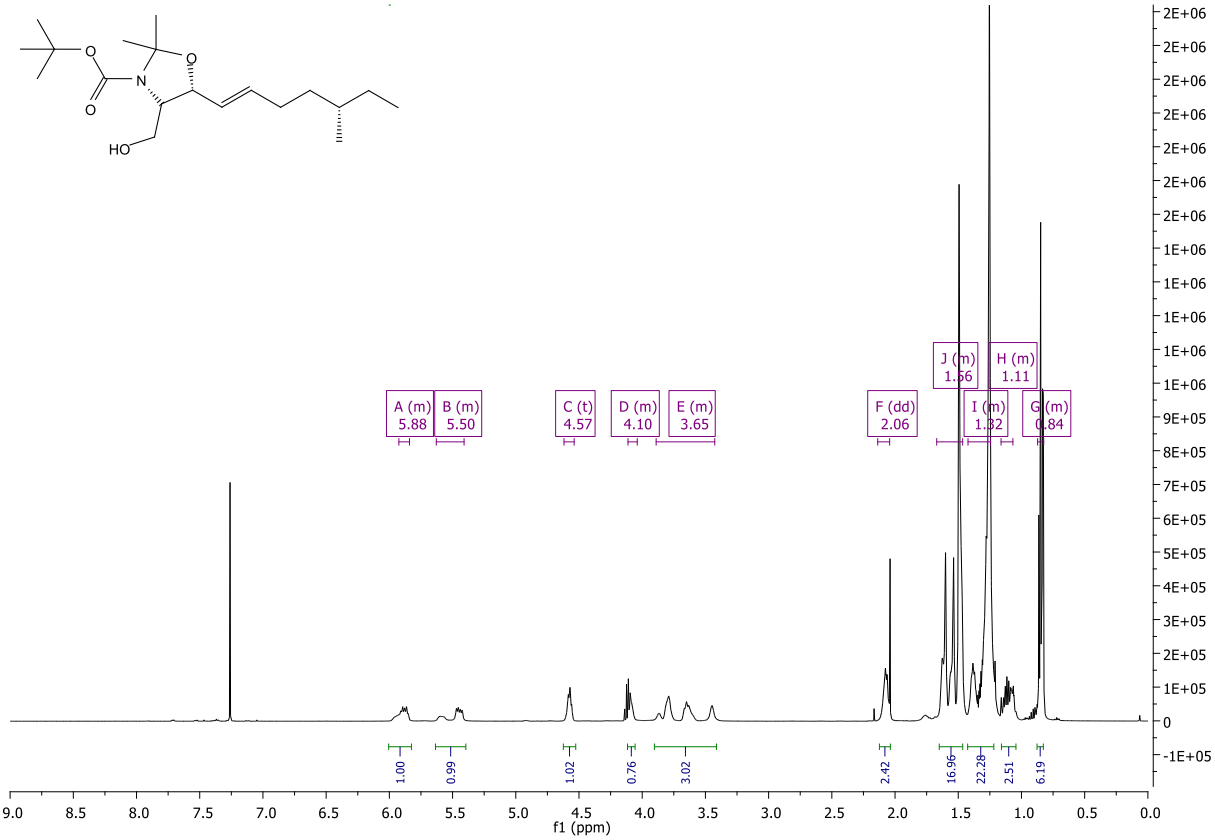

195.95
156.41
151.18
126.53
80.47
64.46
60.12
32.90
32.06
22.83
14.26
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

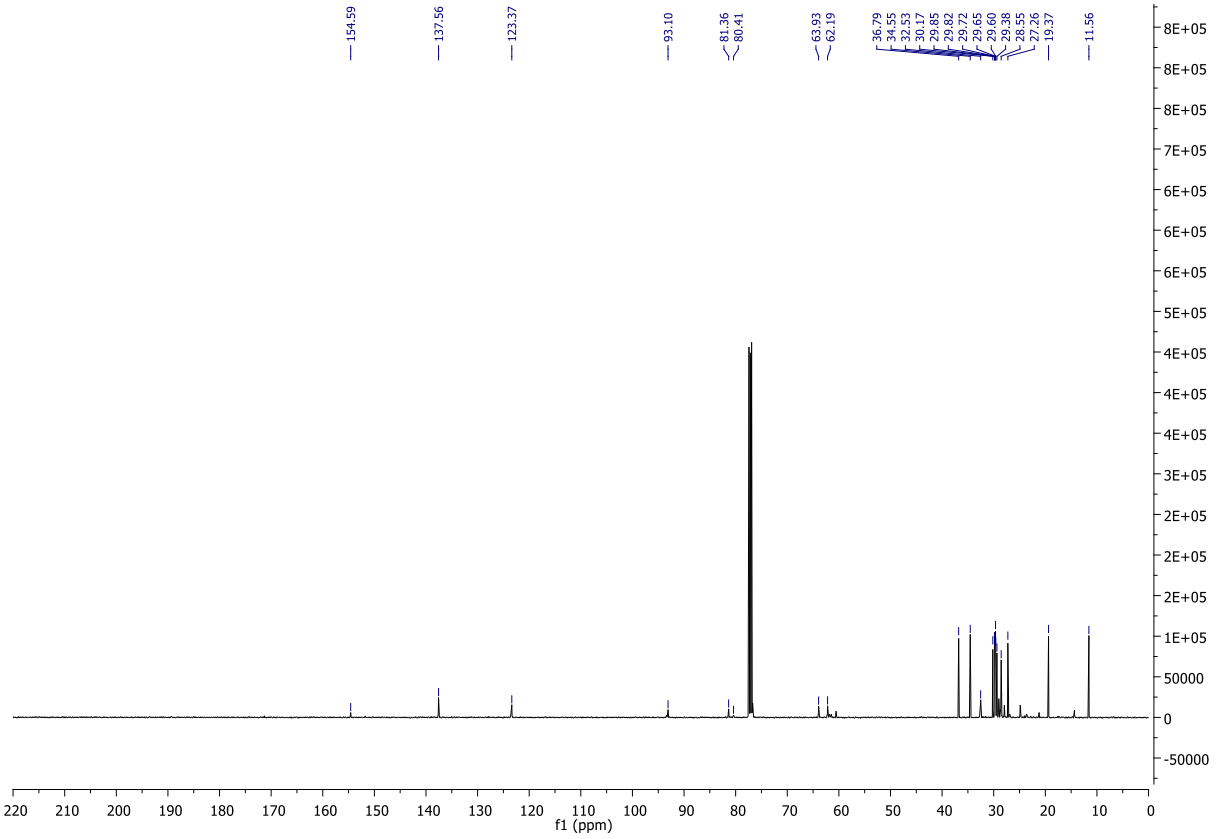

HO
O
D
NH2
D
CH3
4.19
4.18
4.17
4.12
4.11
4.09
4.08
4.00
3.99
3.97
3.97
2.64
2.63
2.61
2.60
1.60
1.32
1.29
0.91
0.90
0.89
0.99
1.00
1.01
1.07
1.00
24.57
3.03
f1 (ppm)

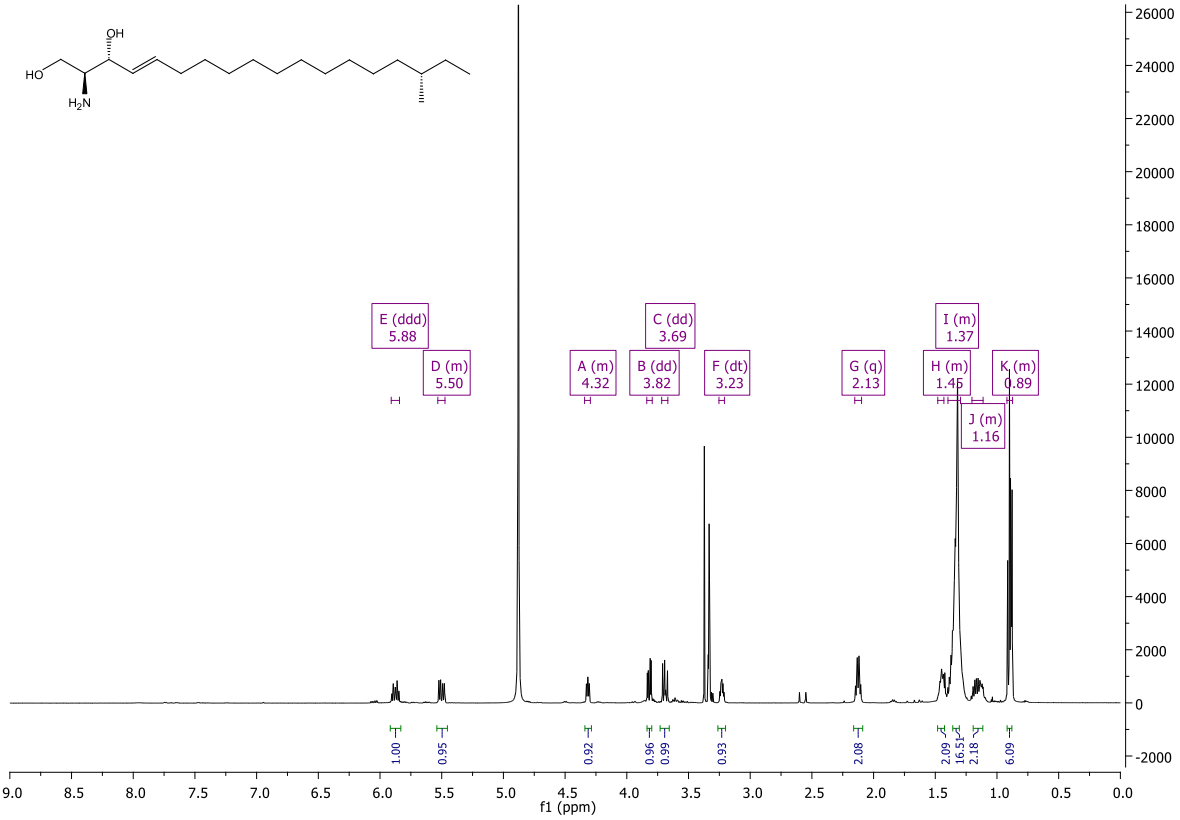

205.28
62.21
60.24
33.08
30.79
30.73
30.62
30.52
30.48
29.99
23.74
14.44
f1 (ppm)

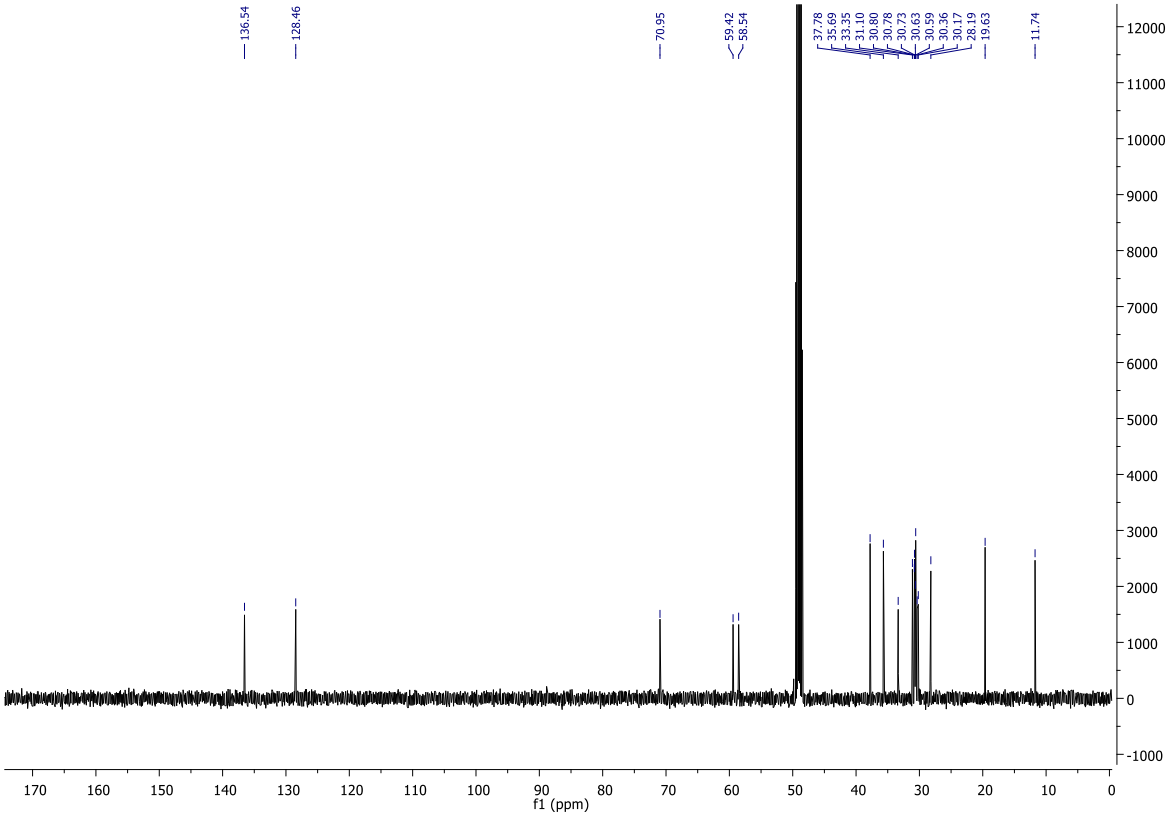

A (ddt)
5.82
B (ddd)
4.99
C (ddt)
4.93
D (m)
2.04
E (m)
1.34
F (m)
1.12
G (m)
0.85
1.00
1.04
1.05
2.13
26.92
6.71
20.05
f1 (ppm)


139.44
114.22
36.81
34.87
34.57
34.09
33.99
30.19
29.88
29.84
29.78
29.67
29.67
29.32
29.12
27.28
19.37
11.59
11.56
f1 (ppm)


A (m) 5.88
B (m) 5.50
C (t) 4.57
D (m) 4.10
E (m) 3.65
F (dd) 2.06
J (m) 1.56
H (m) 1.11
I (m) 1.32
G (m) 0.84
1.00
0.99
1.02
0.76
3.02
2.42
16.96
22.28
2.51
6.19
f1 (ppm)


154.59
137.56
123.37
93.10
81.36
80.41
63.93
62.19
36.79
34.55
32.53
30.17
29.85
29.82
29.72
29.65
29.60
29.38
28.55
27.26
19.37
11.56
f1 (ppm)


OH
HO
H2N
E (ddd) 5.88
D (m) 5.50
A (m) 4.32
C (dd) 3.69
B (dd) 3.82
F (dt) 3.23
G (q) 2.13
I (m) 1.37
H (m) 1.46
K (m) 0.89
J (m) 1.16
1.00
0.95
0.92
0.96
0.99
0.93
2.08
2.09
16.51
2.18
6.09
f1 (ppm)


136.54
128.46
70.95
59.42
58.54
37.78
35.69
33.35
31.10
30.80
30.78
30.73
30.63
30.59
30.36
30.17
28.19
19.63
11.74
f1 (ppm)