Supporting Information for:

Lipidated cyclopropenes *via* a stable 3-*N* spirocyclopropene scaffold

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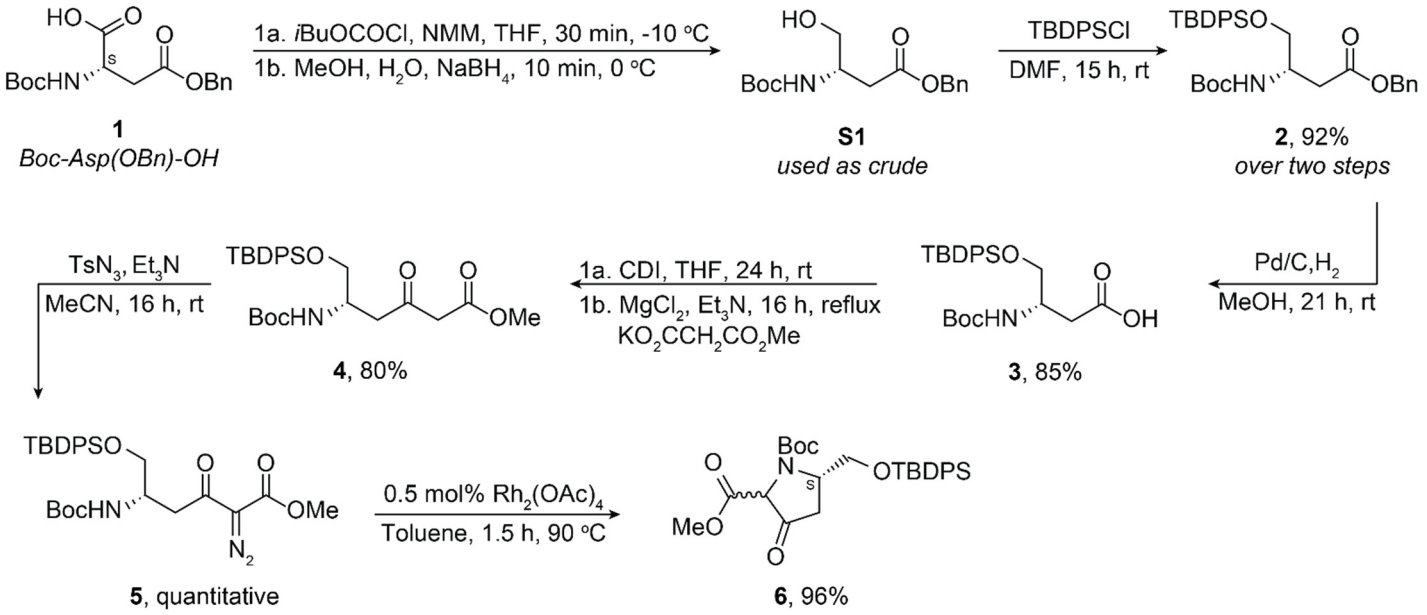
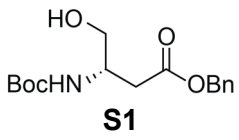
List of abbreviations

Calcd	Calculated
CDI	1,1'-Carbonyldiimidazole
CTAB	Cetyltrimethylammonium bromide
DCM	Dichloromethane
DIPEA	*N,N*-diisopropylethylamine
DMF	Dimethylformamide
DOPE	1,2-di-(9Z-octadecenoyl)-*sn*-glycero-3-phosphoethanolamine
ESI	Electrospray ionization
EtOAc	Ethyl acetate
EtOH	Ethanol
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
HMPA	Hexamethylphosphoramide
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
LAH	Lithium aluminum hydride
MeCN	Acetonitrile
MeOH	Methanol
MHz	Megahertz
MOMCl	Methoxymethyl chloride
R_f	Retention factor
R_t	Retention time
TBDPS	tert-Butyldiphenylsilane
THF	Tetrahydrofuran
TLC	Thin layer chromatography
UV	Ultraviolet

General materials and methods. All chemical reagents were of analytical grade, obtained from commercial suppliers, and used without further purification unless otherwise specified. Reactions were monitored by thin layer chromatography (TLC) on pre-coated glass TLC plates (Analtech UNIPLATE™ silica gel HLF w/ organic binder, 250 μm thickness, with UV254 indicator) or by LC/MS (Agilent LC-MSD, direct-injection mode, 1–10 μL, ESI). TLC plates were visualized by UV illumination or developed with either potassium permanganate stain ($KMnO_4$ stain: 1.5 g $KMnO_4$, 10 g K_2CO_3 and 1.25 mL of 10% NaOH dissolved in 200 mL H_2O), ceric ammonium molybdate stain (CAM stain: 12 g $(NH_4)_6Mo_7O_{24} \cdot 4H_2O$, 0.5 g $Ce(NH_4)_2(NO_3)_6$ and 15 mL of concentrated H_2SO_4 dissolved in 235 mL H_2O), or ninhydrin stain (1.5 g ninhydrin dissolved in 100 mL of 1-butanol and 3 mL of conc. AcOH). Flash chromatography was carried out using Sorbtech, 60 Å, 40–63 μm or Millipore 60 Å, 35–70 μm silica gel according to the procedure described by Still[1]. HPLC was performed using a Shimadzu HPLC (FCV-200AL) equipped with an Agilent reversed phase Zorbax Sb-Aq C18 column (Preparatory column: 4.6 × 250 mm or Analytical column: 21.2 × 250 mm) fitted with an Agilent stand-alone prep guard column. HPLC purifications were carried using solvents spiked with 0.1% TFA unless specified otherwise. NMR spectra (^1H and ^{13}C) were obtained using a 300, 400, 500, or 700 MHz Bruker spectrometer and analyzed using Mestrenova 9.0. ^1H and ^{13}C chemical shifts (δ) were referenced to residual solvent peaks. Following residual solvent peaks were chosen: (for ^1H NMR) $CDCl_3$, 7.2600 ppm; CD_3OD, 3.3100 ppm; $(CD_3)_2SO$, 2.5000 ppm (for ^{13}C NMR) $CDCl_3$, 77.1600 ppm; CD_3OD, 49.0000 ppm; $(CD_3)_2SO$, 39.5200 ppm; D_2O, 4.7900 ppm. Further, following abbreviations were used to define ^1H NMR peaks: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Low-resolution electrospray ionization (ESI) and High-resolution electrospray ionization (ESI) mass spectra were obtained at the Stony Brook University Institute for Chemical Biology and Drug Discovery (ICB&DD) Mass Spectrometry Facility with an Agilent LC/MSD and LC-UV-TOF spectrometer respectively. Synthesis for compound **15** and **16** was carried using the method recently described by us[2].

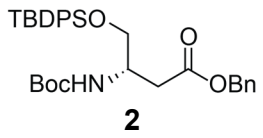
Scheme S1





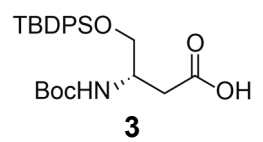
S1

S1 was synthesized based on modifications of a previously published protocol[3]. To an ice-cold solution of benzyl protected Boc-aspartic-acid (5.0 g, 15.46 mmol, 1 eq) in THF (40 mL) was added N-methyl morpholine (1.8 mL, 16.23 mmol, 1.05 eq) and the reaction mixture was stirred at the same temperature for 5 mins. To this solution was added iso-butyl chloroformate (2.4 mL, 17.00 mmol, 1.1 eq) dropwise and the reaction mixture was stirred at the same temperature for 30 mins. The reaction mixture was filtered using THF (3×20 mL) and cooled down using an ice-bath. $NaBH_4$ (0.9 g, 23.79 mmol, 1.5 eq) and water (8.0 mL) were added to this reaction mixture in one portion. After 5 mins, additional 400 mL water was added to the reaction mixture. The reaction mixture was transferred to a separatory funnel and the layers were separated using EtOAc (50 mL). The aqueous layer was further washed with EtOAc and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to obtain crude **S1** (4.97 g) which was used without further purification. MS (ESI): Calcd for $C_{16}H_{24}NO_5$ $[M+H]^+$: 310.1, found: 310.1, 254.1[M-C(CH3)3+2H]$^+$, 210.1 $[M-Boc+2H]^+$.



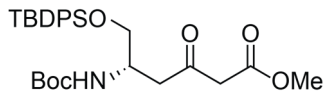
2

2 was synthesized based on modifications of a previously reported patent[4]. To a solution of crude **S1** (4.97 g) obtained from the previous step in DMF (30 mL) was added imidazole (1.64 g, 24.11 mmol, 1.5 eq) and TBDPS-Cl (3.98 g, 17.68 mmol, 1.1 eq) respectively. The reaction mixture was stirred at rt for 15 h and quenched with saturated NH_4Cl (100 mL). The crude product was extracted with EtOAc (3×30 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by flash chromatography (75 g silica, Hexanes to 5% EtOAc/hexanes (v/v)) to obtain **2** (7.8 g, 92.2% over two steps). R_f = 0.25 (6% EtOAc/Hexanes, visualized w/ UV). ^{1}H NMR (500 MHz, $CDCl_3$): δ= 7.71–7.58 (m, 4H), 7.41–7.35 (m, 6H), 5.10 (s, 2H), 4.17 (br s, 1H), 3.74 (d, *J* = 3.8 Hz, 2H), 2.74 (t, *J* = 6.2 Hz, 2H), 1.45 (s, 9H), 1.08 (s, 9H). MS (ESI): Calcd for $C_{32}H_{42}NO_5Si$ $[M+H]^+$: 548.3, found: 548.3.



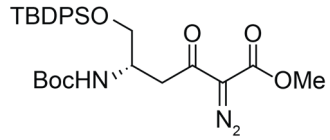
3

To a solution of **2** (7.8 g, 142.4 mmol, 1.0 eq) in MeOH (60 mL) at rt was added 10% Pd/C (160 mg) and H_2 balloon. The reaction was stirred for 15 h. Additional Pd/C (50 mg) and H_2 was supplied based on the TLC and the reaction mixture was stirred for additional 6h. Upon completion the reaction mixture was passed through a pad of celite using MeOH to remove Pd/C. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography (70 g silica, 10% EtOAc/hexanes to 30% EtOAc/hexanes (v/v)) to obtain **3** (5.54 g, 85.0%). R_f = 0.30 (5–20% EtOAc/Hexanes, visualized w/ UV). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.66–7.63 (m, 4H), 7.44–7.36 (m, 6H), 5.11 (d, *J* = 9.1 Hz, 1H), 3.73 (br s, 2H), 2.70 (d, *J* = 5.8 Hz, 2H), 1.43 (s, 9H), 1.07 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ= 177.09, 155.44, 135.66, 133.12, 133.05, 129.96, 127.91, 79.78, 65.00, 48.77, 35.95, 28.48, 26.96, 19.38. MS (ESI): Calcd for $C_{25}H_{24}NO_5Si$ $[M-H]^-$: 456.2, found: 456.2, 913.3 $[2M-H]^-$.



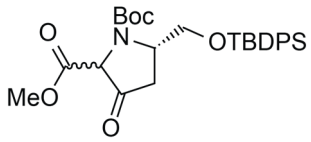
4

To a solution of **3** (12.0 g, 26.2 mmol, 1.0 eq) in THF (125 mL) at rt was added CDI (5.1 g) and the yellow reaction mixture was stirred at rt for 24h. To this activated acid was added a 24 h stirred mixture of of $MgCl_2$ (3.49 g, 36.7 mmol, 1.4 eq), Potassium 3-methoxy-3-oxopropanoate (5.73 g, 36.7 mmol, 1.4 eq), and Et_3N (5.54 mL, 4.03 g, 39.8 mmol, 1.5 eq) in THF (125 mL). The suspension was refluxed for 16 h, quenched with water, and concentrated *in vacuo* to remove THF. The reaction mixture was then diluted with DCM and 2M HCl, and stirred at rt for 15 min to dissolved the white solid. The aqueous layer was acidified to pH 1–2 using 2M HCl and extracted with DCM. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to obtain a pale-yellow oil that was purified by flash chromatography (20% EtOAc/hexanes) to obtain **4** (10.77 g, 80%) as a light-yellow oil. R_f = 0.75 (50% EtOAc/hexanes, visualized w/ UV). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.66–7.62 (m, 4H), 7.41–7.33 (m, 6H), 5.09–4.96 (m, 1H), 4.14 (br s, 1H), 3.73–3.65 (m, 5H), 3.48–3.39 (m, 2H), 2.91–2.80 (m, 2H), 1.41 (s, 9H), 1.07 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ= 201.08, 167.19, 155.07, 135.39, 135.35, 132.93, 132.85, 129.74, 127.70, 127.68, 79.15, 64.85, 52.06, 48.97, 48.38, 43.98, 28.20, 26.75, 19.12. COSY NMR (400 MHz, $CDCl_3$, attached) was obtained under the same conditions. HRMS (ESI): Calcd for $C_{28}H_{40}NO_6Si$ $[M+H]^+$: 514.2619, found: 514.2625.



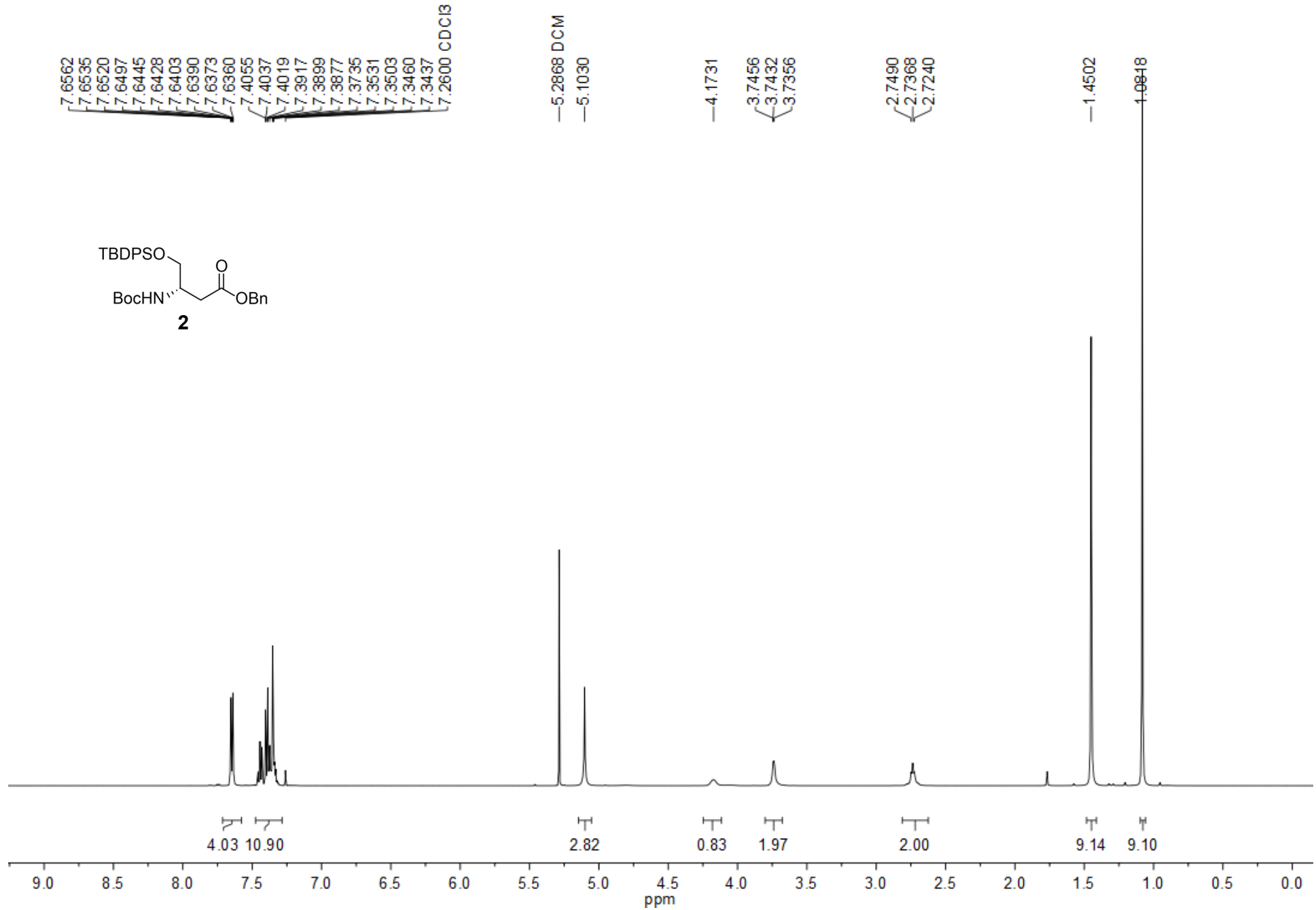
5

To a solution of β-ketoester **4** (3.13 g, 6.09 mmol, 1 eq) in MeCN (50 mL) was added tosyl azide (1.08 g, 5.48 mmol, 0.9 eq). Et_3N (2.5 mL, 1.88 g, 18.3 mmol, 3 eq) was added dropwise and the mixture was stirred at rt for 16 h. The reaction mixture was concentrated *in vacuo*, and diluted with DCM and water. The organic layer was collected and the aqueous layer was further washed with DCM. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by flash chromatography (45 g silica, 15% ethyl acetate/hexanes (v/v)) to obtain **5** as a yellow oil (3.3 g, quantitative). A separate reaction starting from 20 g of **4** also afforded **5** in 95% yield. R_f = 0.30 (10% EtOAc/hexanes, visualized w/ UV).^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.67–7.64 (m, 4H), 7.44–7.36 (m, 6H), 5.18 (d, *J* = 9.4 Hz, 1H), 4.24 (br s, 1H), 3.81–3.80 (m, 5H), 3.16 (d, *J* = 6.2 Hz, 2H), 1.44 (s, 9H), 1.10 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ= 190.73, 161.66, 155.29, 135.61, 135.59, 133.22, 133.15, 129.79, 127.75, 79.26, 76.35, 65.53, 52.21, 49.11, 41.67, 28.38, 26.92, 19.31. ^{13}C DEPT135 NMR (101 MHz, $CDCl_3$): δ= (up) 135.61, 135.59, 129.78, 127.74, 52.20, 49.11, 28.38, 26.92, (down) 65.52, 41.66. HRMS (ESI): Calcd for $C_{28}H_{38}N_3O_6Si$ $[M+H]^+$: 540.2524, found: 540.2532.



6

To a solution of **5** (3.3 g, 6.11 mmol, 1 eq) in dry toluene (40 mL) was added Rh_2OAc_4 (13.5 mg, 0.03 mmol, 0.005 eq) and the mixture was stirred at 90 °C for 1.5 h. The reaction mixture was concentrated *in vacuo* and passed through silica gel (30 g) using diethyl ether to obtain **6** as an oil that was used without further purification (3.01 g, 96.5%). R_f = 0.52 (20% EtOAc/hexanes, visualized w/ UV). ^{1}H NMR (rotamers and mixture of diastereomers 400 MHz, $CDCl_3$): δ= 7.68–7.54 (m, 4H), 7.37–7.35 (m, 6H), 4.66–4.58 (m, 1H), 4.50–4.34 (m, 1H), 4.17–3.76 (m, 3H), 3.66–3.45 (m, 2H), 2.98–2.53 (m, 2H), 1.46–1.37 (m, 9H), 1.03–1.00 (m, 9H). ^{13}C NMR (rotamers and mixture of diastereomers, 101 MHz, $CDCl_3$): δ= 203.30, 203.08, 202.65, 166.88, 166.58, 165.85, 153.24, 152.96, 152.75, 135.48, 135.43, 135.40, 135.20, 133.07, 132.96, 132.84, 132.45, 132.33, 132.20, 132.19, 129.91, 129.87, 129.82, 129.75, 129.69, 129.52, 127.86, 127.80, 127.75, 127.70, 127.53, 80.99, 80.98, 80.84, 77.16, 67.08, 66.65, 65.83, 65.76, 65.29, 65.09, 64.73, 64.70, 64.44, 54.99, 54.51, 54.43, 52.85, 52.67, 52.44, 40.86, 40.49, 40.06, 39.79, 28.16, 28.09, 28.05, 26.72, 26.58, 26.46, 19.06, 18.96, 18.85. . ^{13}C-DEPT135 NMR (rotamers and mixture of diastereomers, 101 MHz, $CDCl_3$): δ = (up) 135.62, 135.57, 135.54, 135.34, 130.05, 130.01, 129.96, 129.83, 129.65, 128.00, 127.94, 127.89, 127.84, 127.67, 67.22, 66.79, 65.90, 65.43, , 55.13, 54.64, 54.56, 52.98, 52.81, 52.57, 28.30, 28.23, 28.19, 26.86, 26.71, 26.60, (down) 65.97, 65.23, 64.84, 64.57, 40.99, 40.63, 40.20, 39.92. HRMS (ESI): Calcd for $C_{28}H_{37}NO_6SiNa$ $[M+Na]^+$: 534.2282, found: 534.2318.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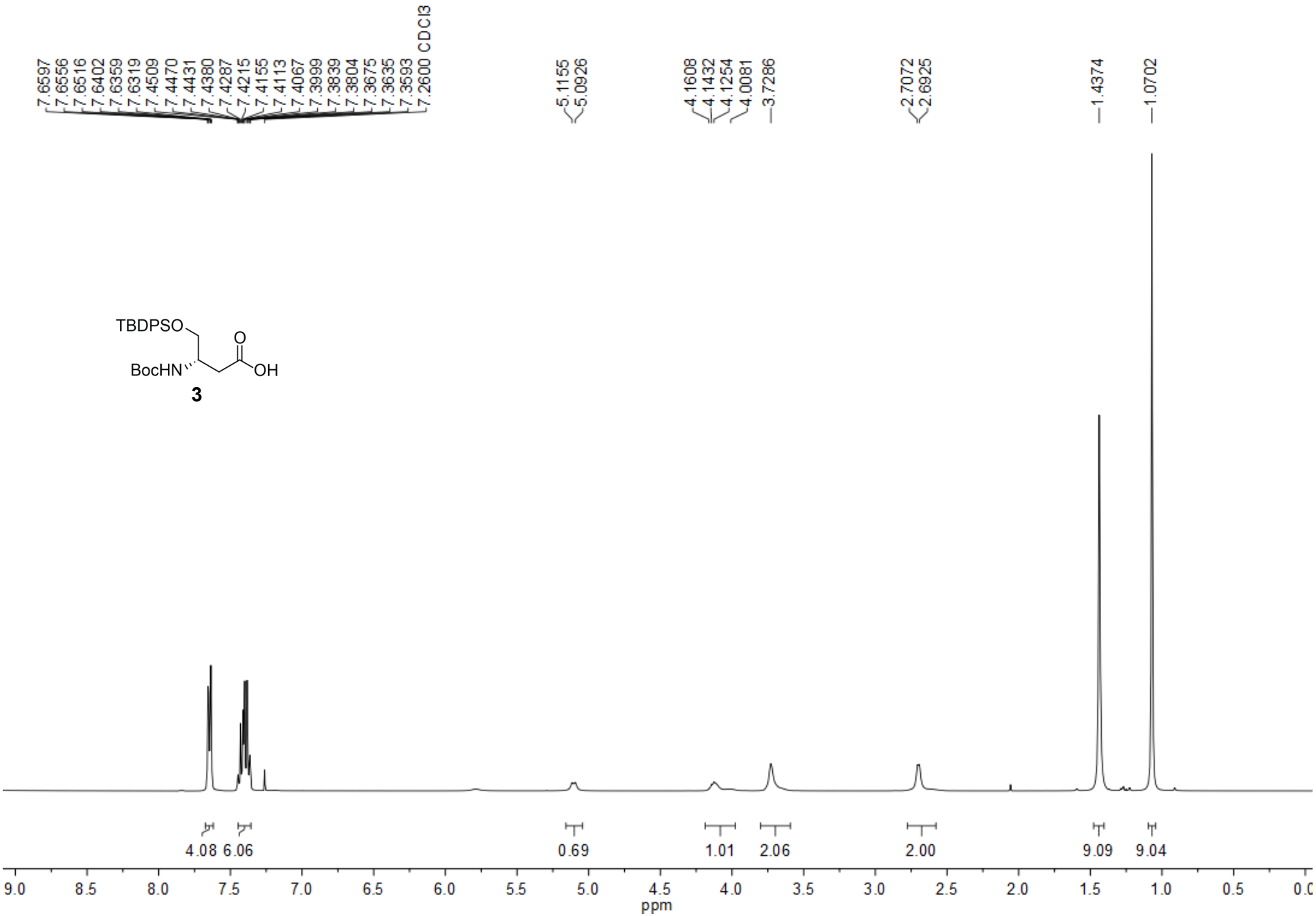
^{1}H NMR (400 MHz)



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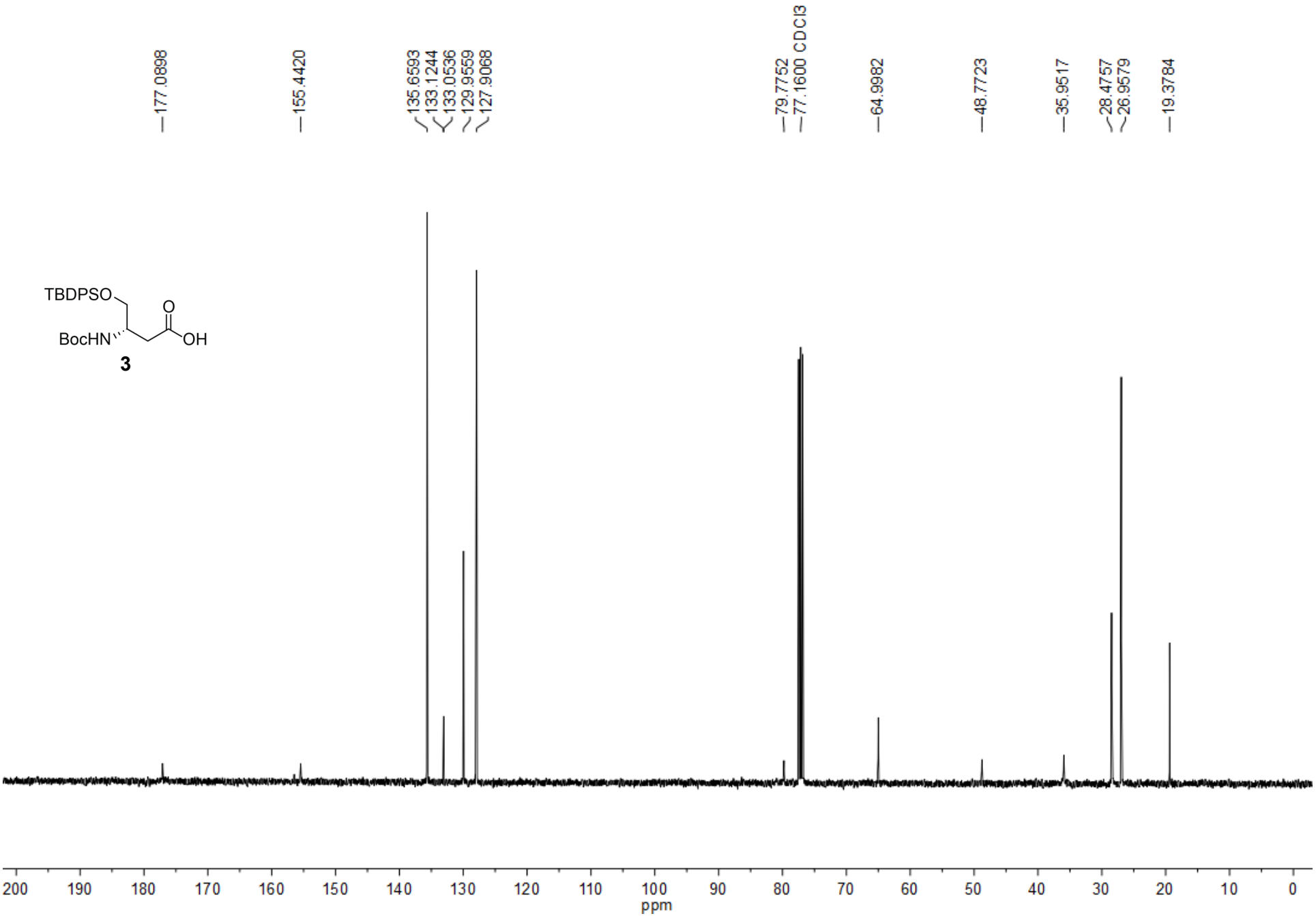

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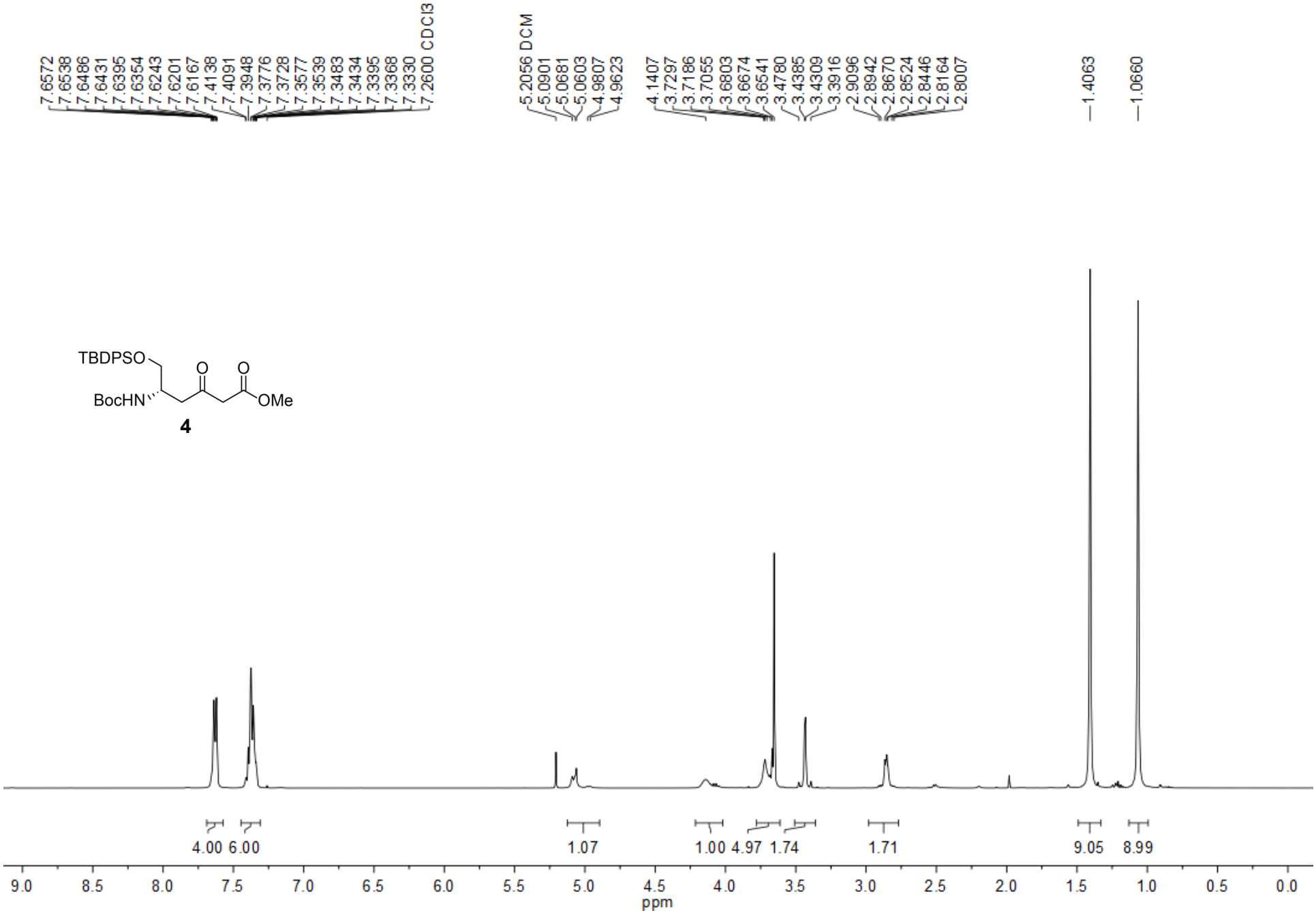

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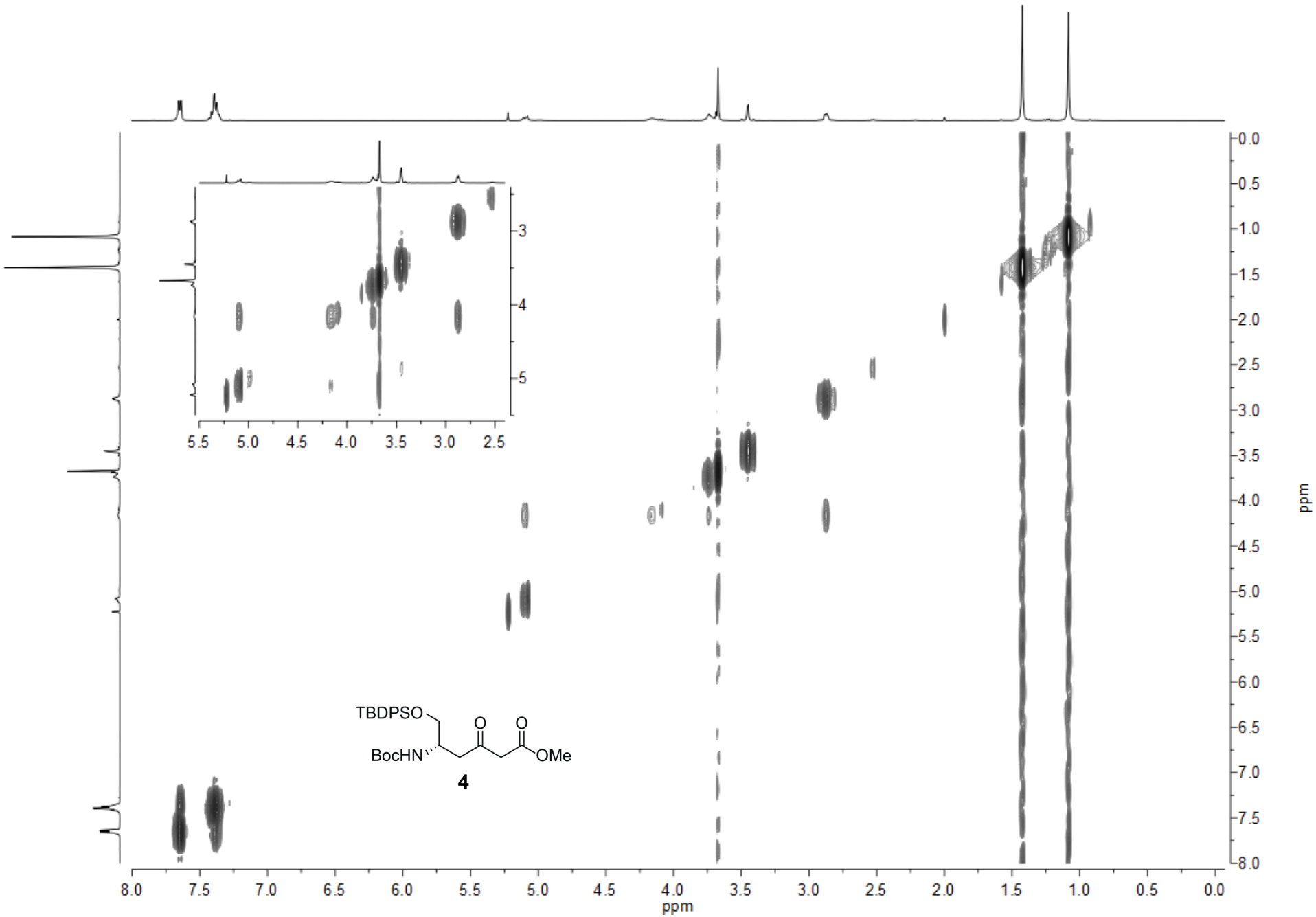

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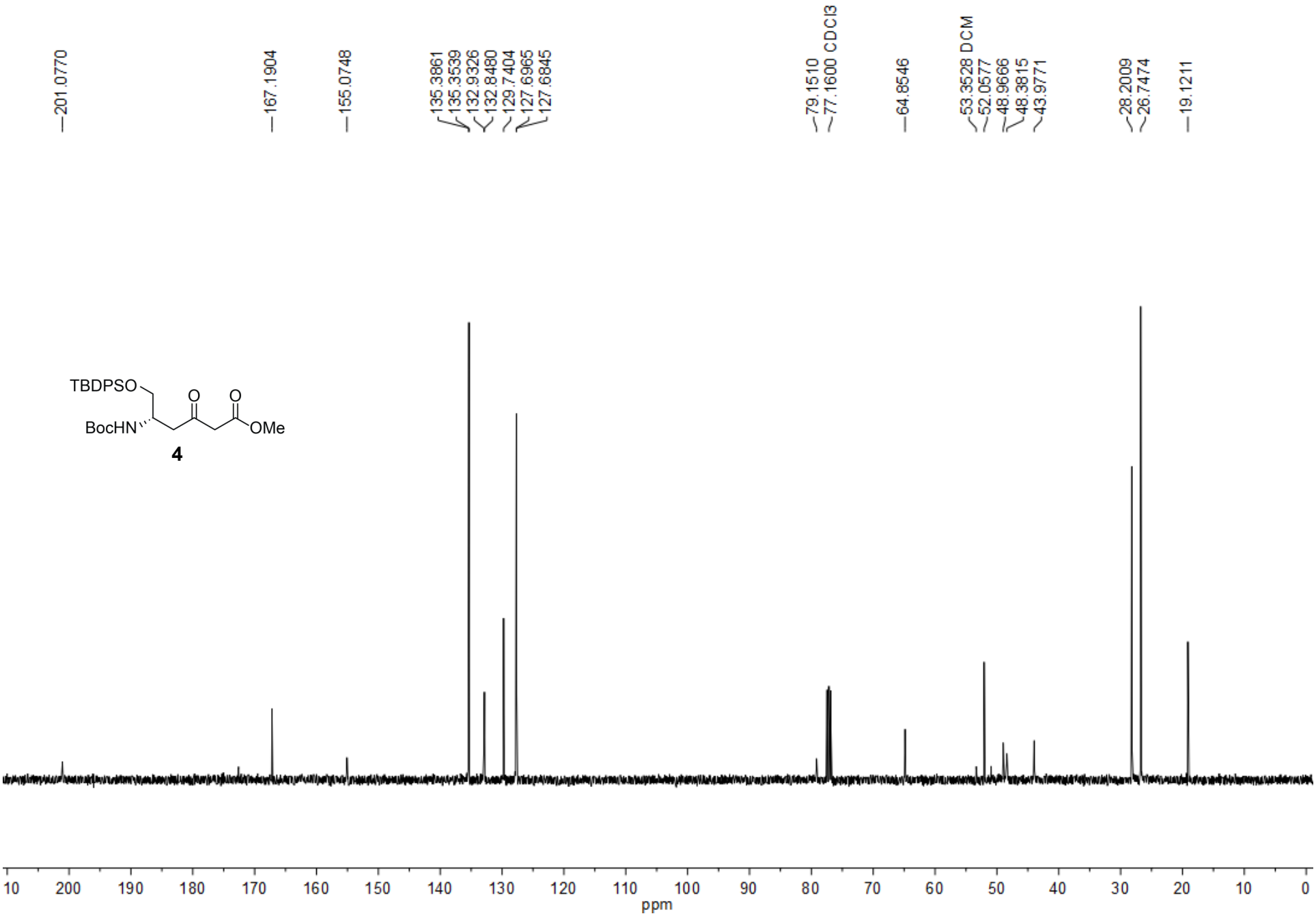

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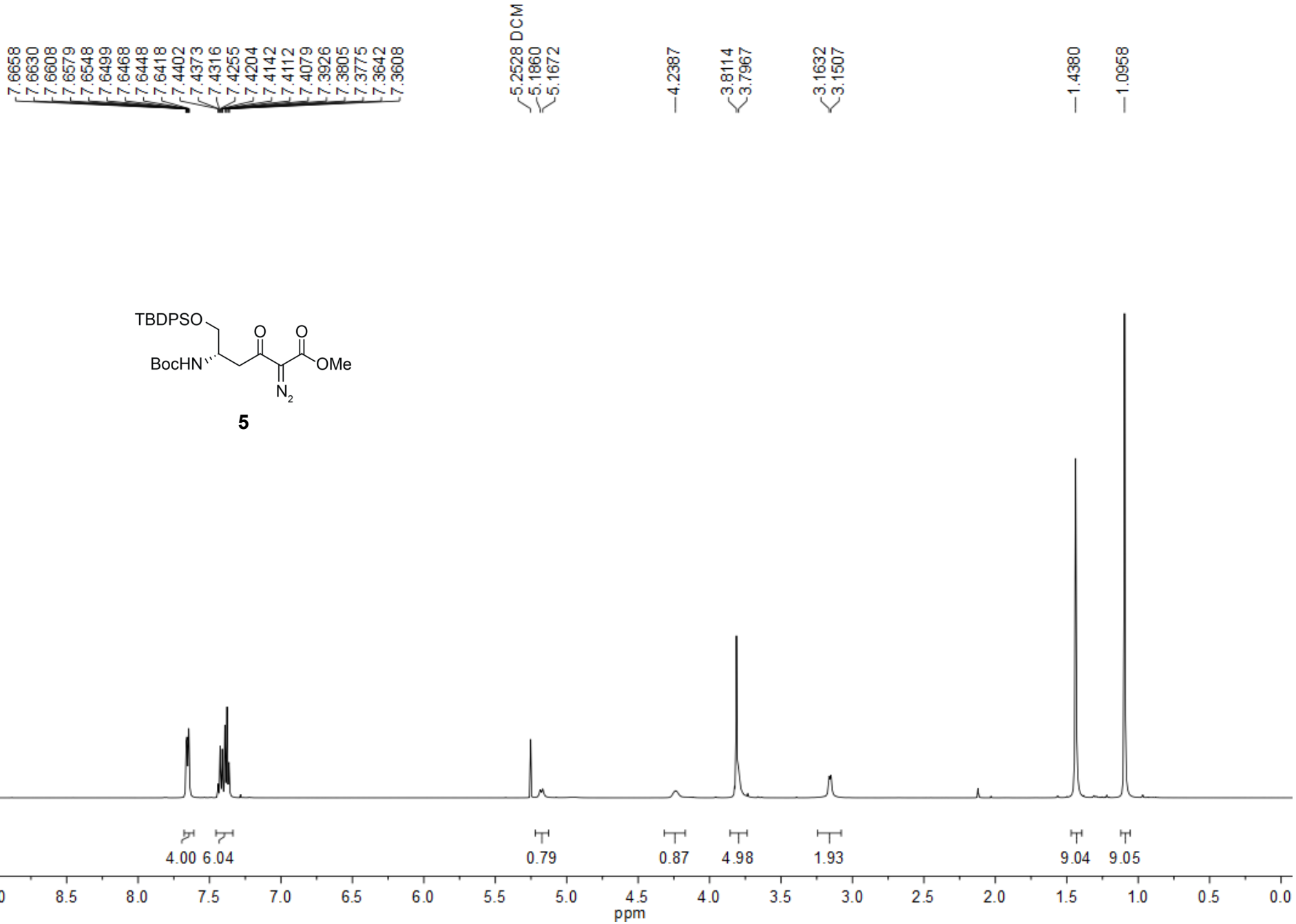

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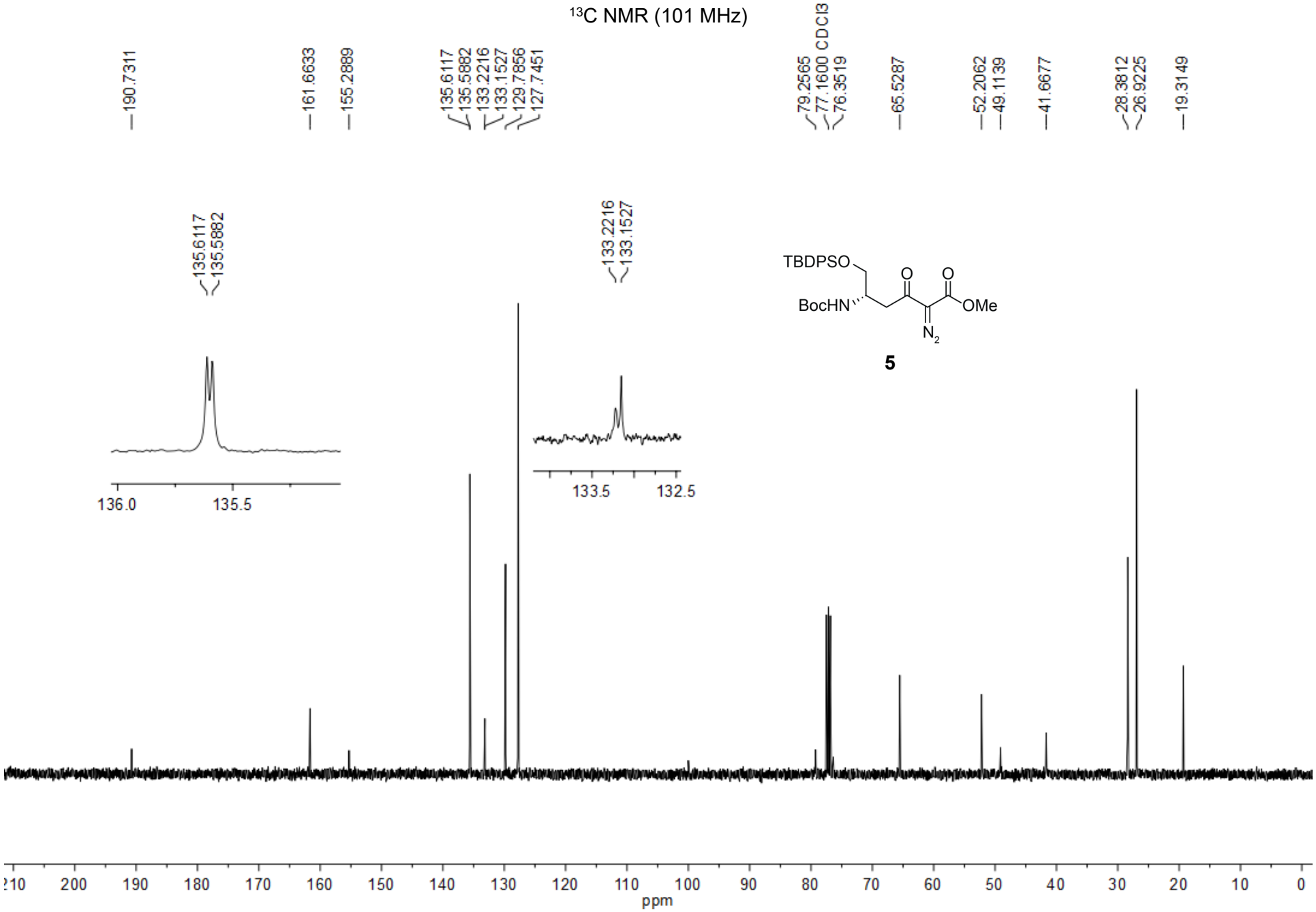
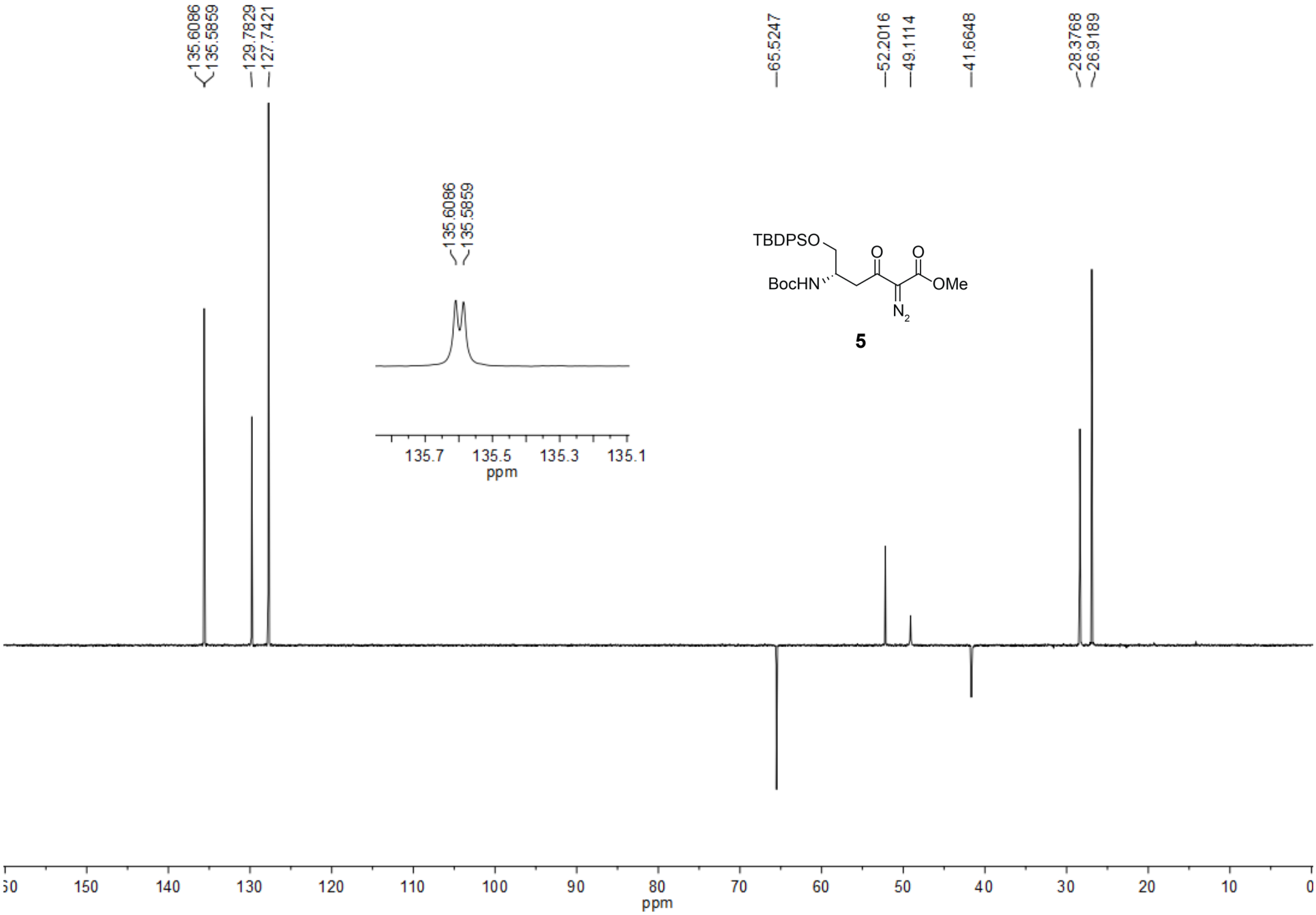
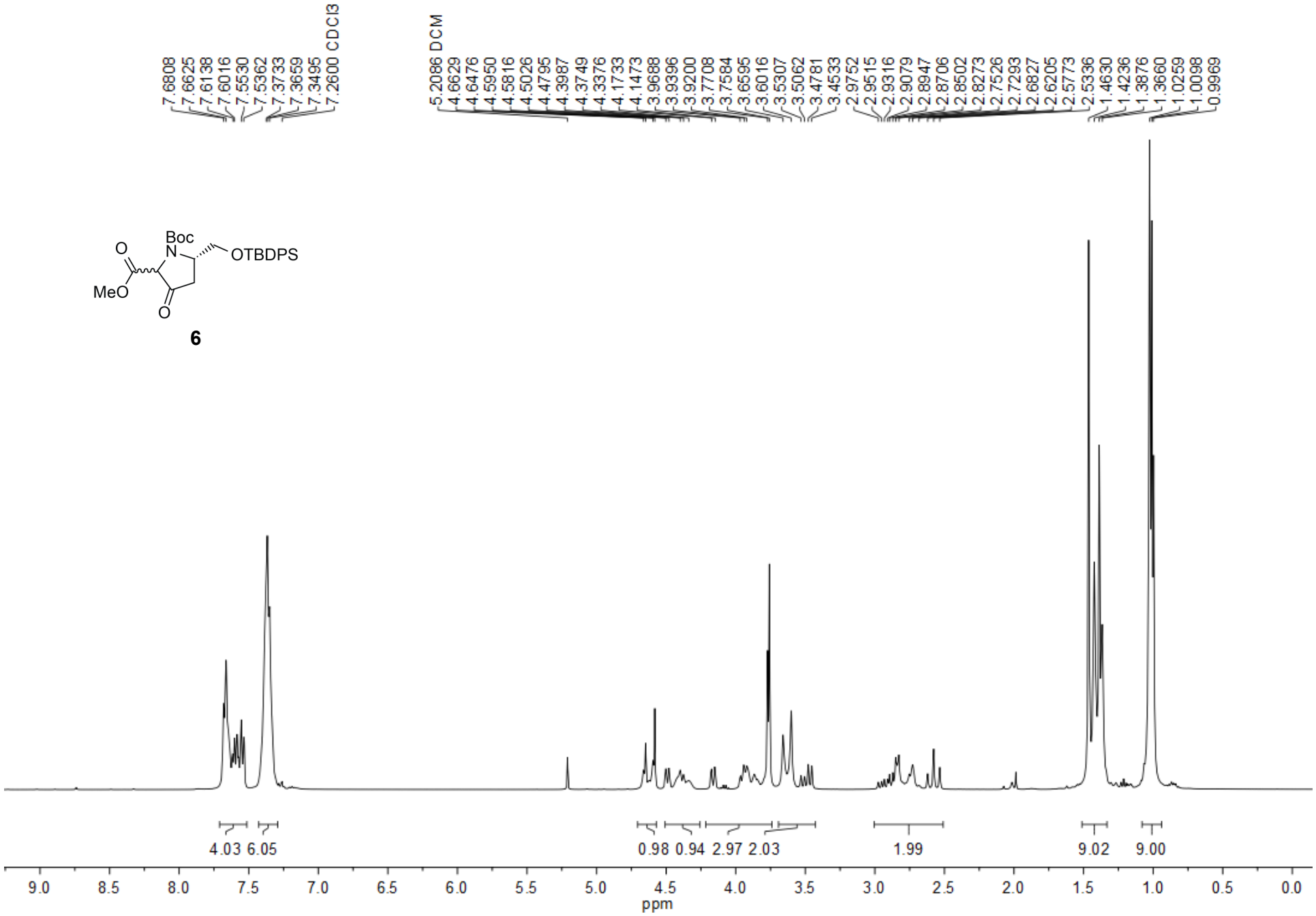


^{13}C DEPT-135 NMR (101 MHz)

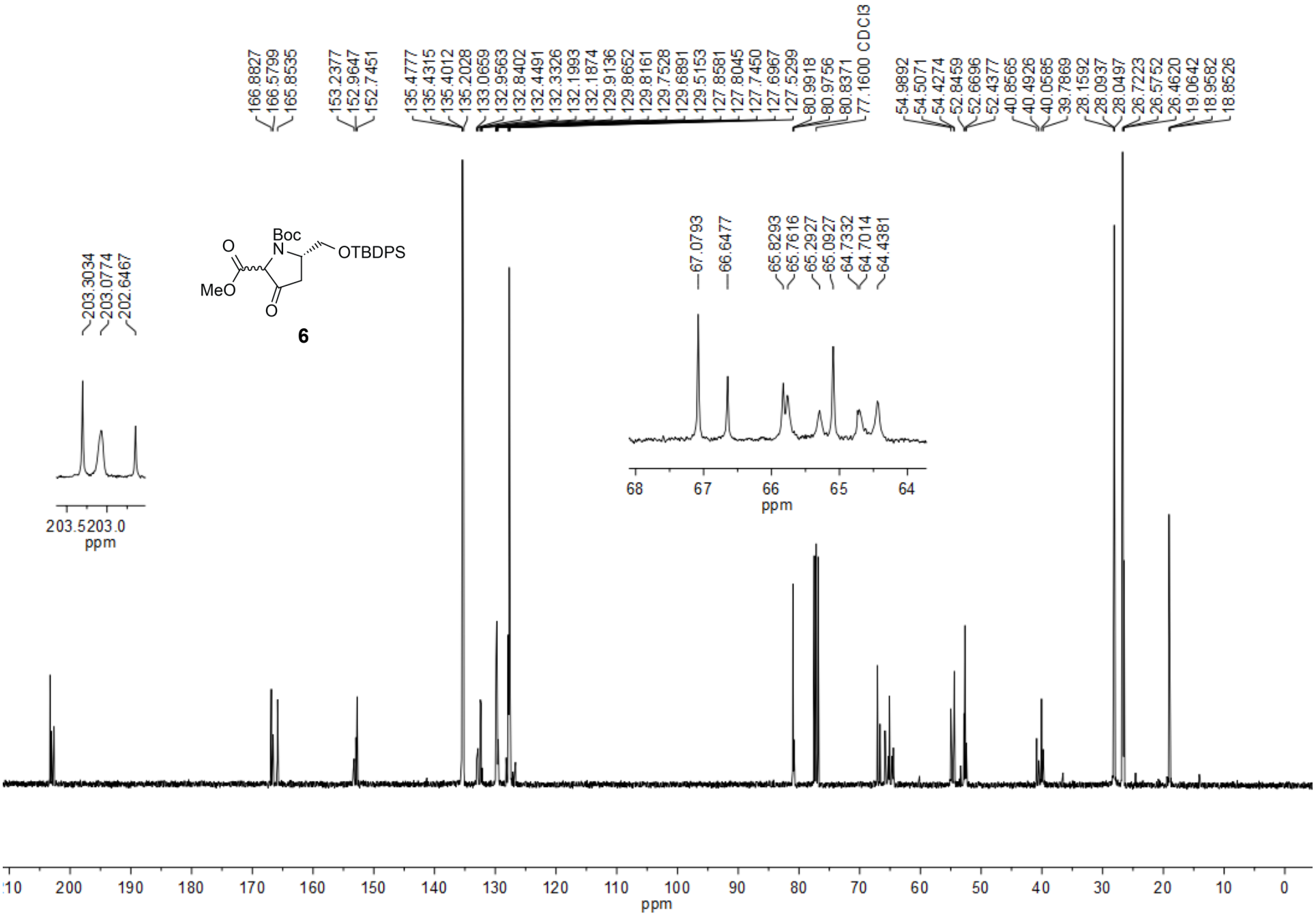


^{1}H NMR (400 MHz)



6

^{13}C NMR (101 MHz)



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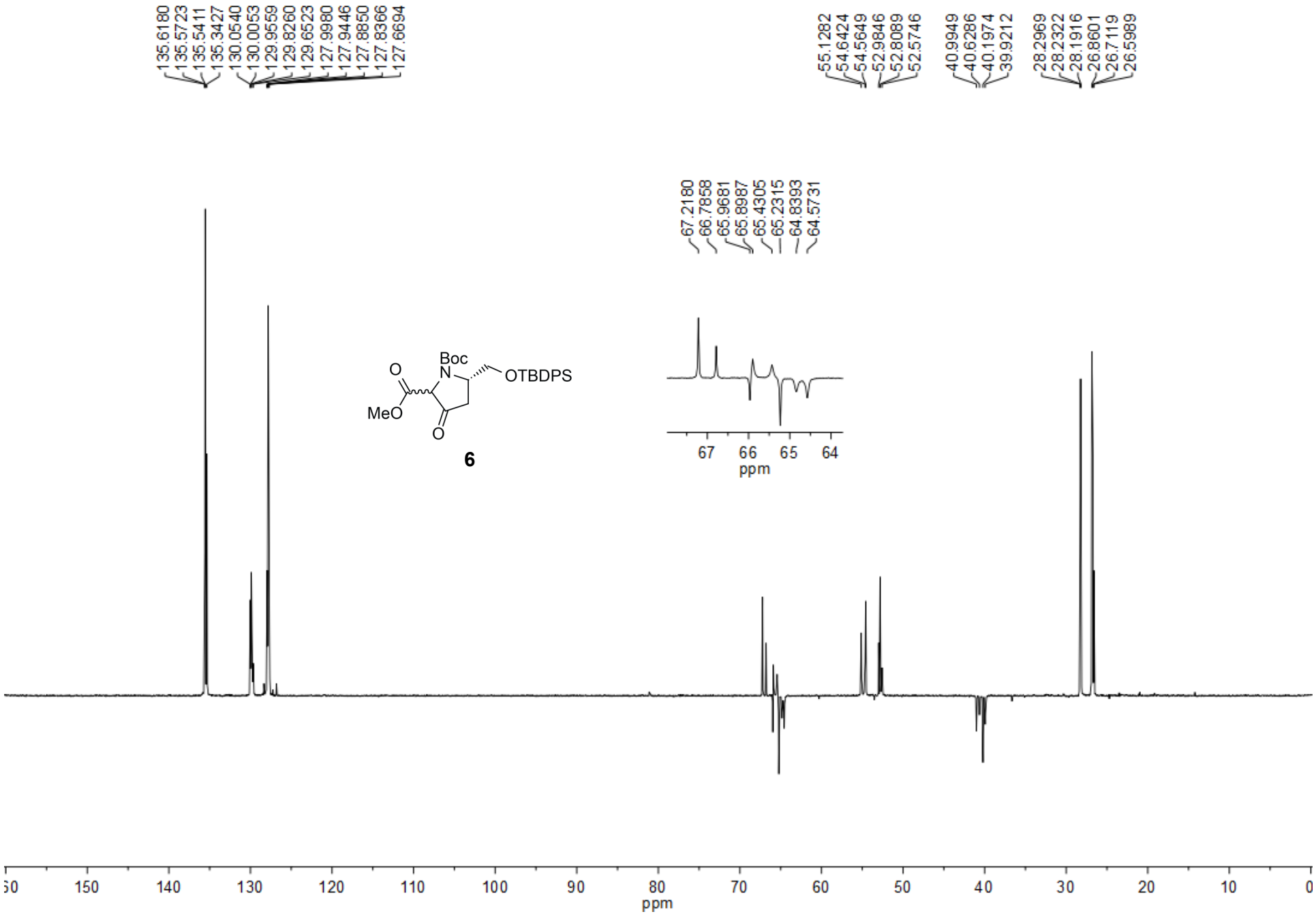
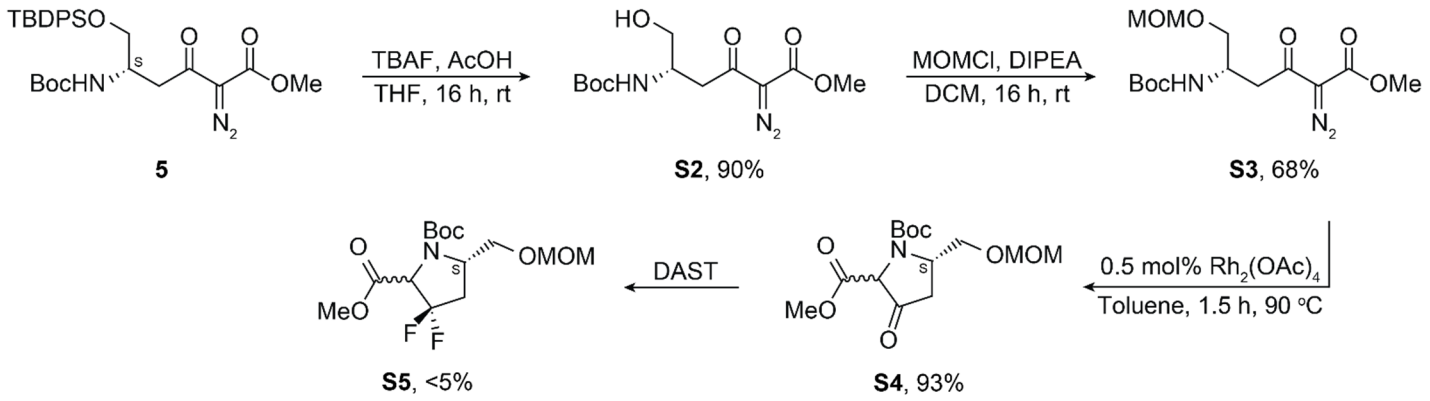
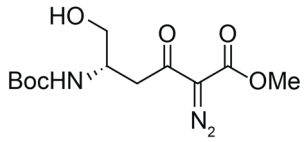


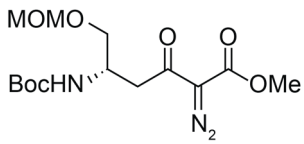
Scheme S2





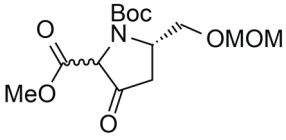
S2

To an ice-cold solution of **5** (3.51 g, 6.50 mmol, 1 eq) and acetic acid (1.57 mL, 1.65 g, 27.49 mmol, 4.0 eq) in THF (20 mL) was added 1M TBAF (20.61 mL, 20.61 mmol, 3 eq). The reaction mixture was allowed to warm to rt over 16 h and quenched by addition of saturated NH_4CO_3. The reaction mixture was concentrated *in vacuo*, and diluted with DCM and saturated NH_4CO_3. The organic layer was collected and the aqueous layer was further washed with DCM. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by flash chromatography (65 g silica, 40–75% ethyl acetate/hexanes (v/v)) to obtain **S2** as a yellow oil (1.94 g, quantitative). R_f = 0.35 (40% EtOAc/hexanes, visualized w/ UV).^{1}H NMR (400 MHz, $CDCl_3$): δ= 5.31 (d, *J* = 8.7 Hz, 1H), 4.09–4.00 (m, 1H), 3.79 (s, 3H), 3.63–3.61 (m, 2H), 3.14–2.98 (m, 2H), 1.36 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ= 191.02, 174.28, 161.81, 155.94, 79.67, 76.69, 64.64, 53.50, 52.40, 49.63, 41.53, 28.33. HRMS (ESI): Calcd for $C_{12}H_{19}N_3O_6$ $[M+Na]^+$: 324.1166, found: 324.1170.



S3

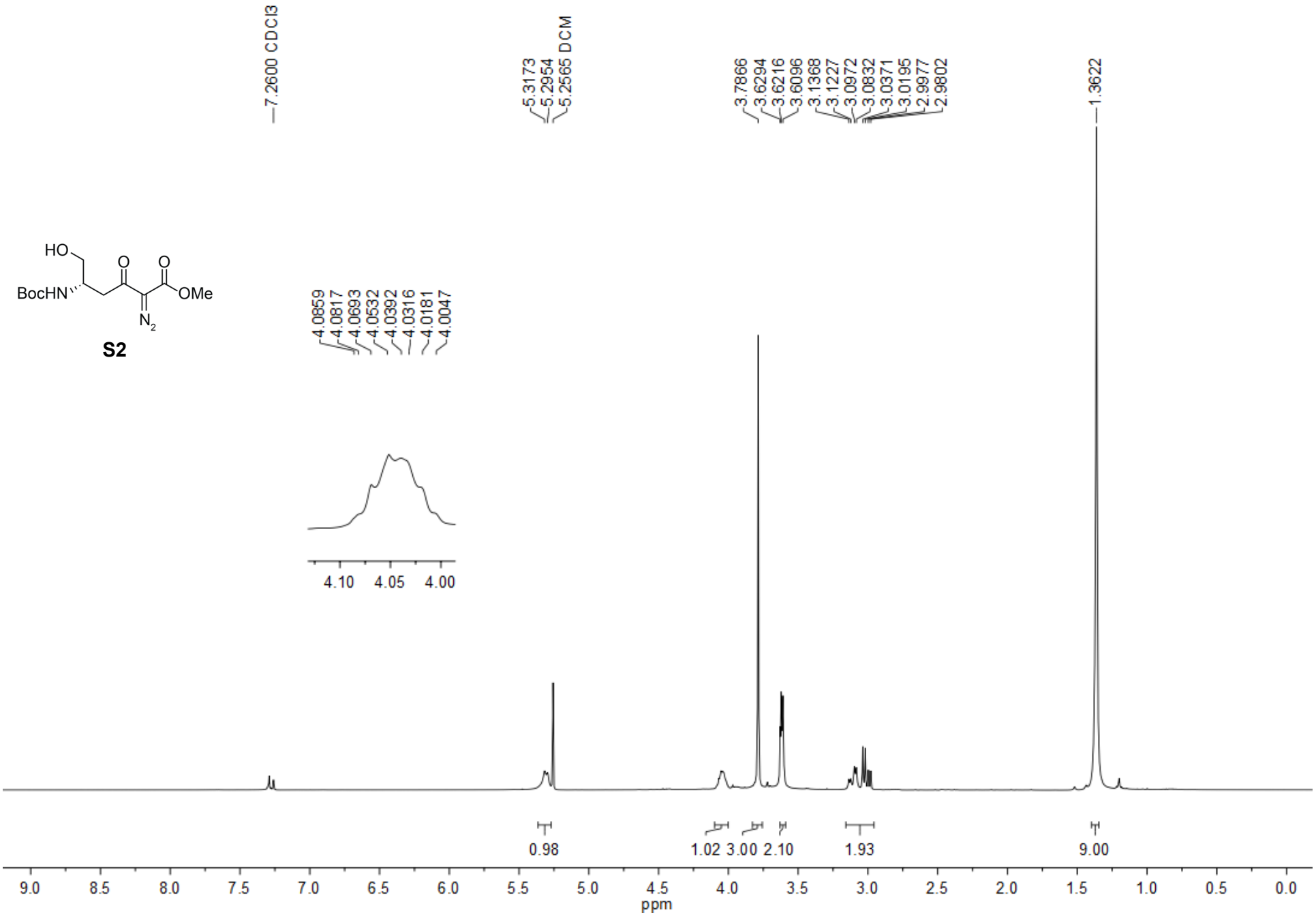
To an ice-cold solution of **S2** (460 mg, 1.53 mmol, 1 eq) in DCM (20 mL) under N_2 atmosphere was added MOM-Cl (267 mg, 232 µL, 4.98 mmol, 2.1 eq). DIPEA (1.06 mL, 858 mg, 6.12 mmol, 4 eq) was added dropwise and the reaction mixture was allowed to warm to overnight. Additional MOM-Cl and DIPEA was furnished based on TLC. Upon consumption of the starting material, the orange reaction mixture was concentrated *in vacuo* and purified by flash chromatography (30 g silica, 20% ethyl acetate/hexanes (v/v)) to obtain **S3** as an oil (361 mg, 68%). R_f = 0.35 (40% EtOAc/hexanes, visualized w/ UV).^{1}H NMR (400 MHz, $CDCl_3$): δ= 5.11 (d, *J* = 9.1 Hz, 1H), 4.48 (s, 2H), 4.12 (br s, 1H), 3.72 (s, 3H), 3.56–3.45 (m, 2H), 3.22 (s, 3H), 3.06–2.94 (m, 2H), 1.30 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ= 190.41, 161.58, 155.16, 96.48, 79.11, 76.10, 69.31, 55.17, 52.10, 47.36, 41.89, 28.18. HRMS (ESI): Calcd for $C_{14}H_{24}N_3O_7$ $[M+H]^+$: 346.1609, found: 346.1611.



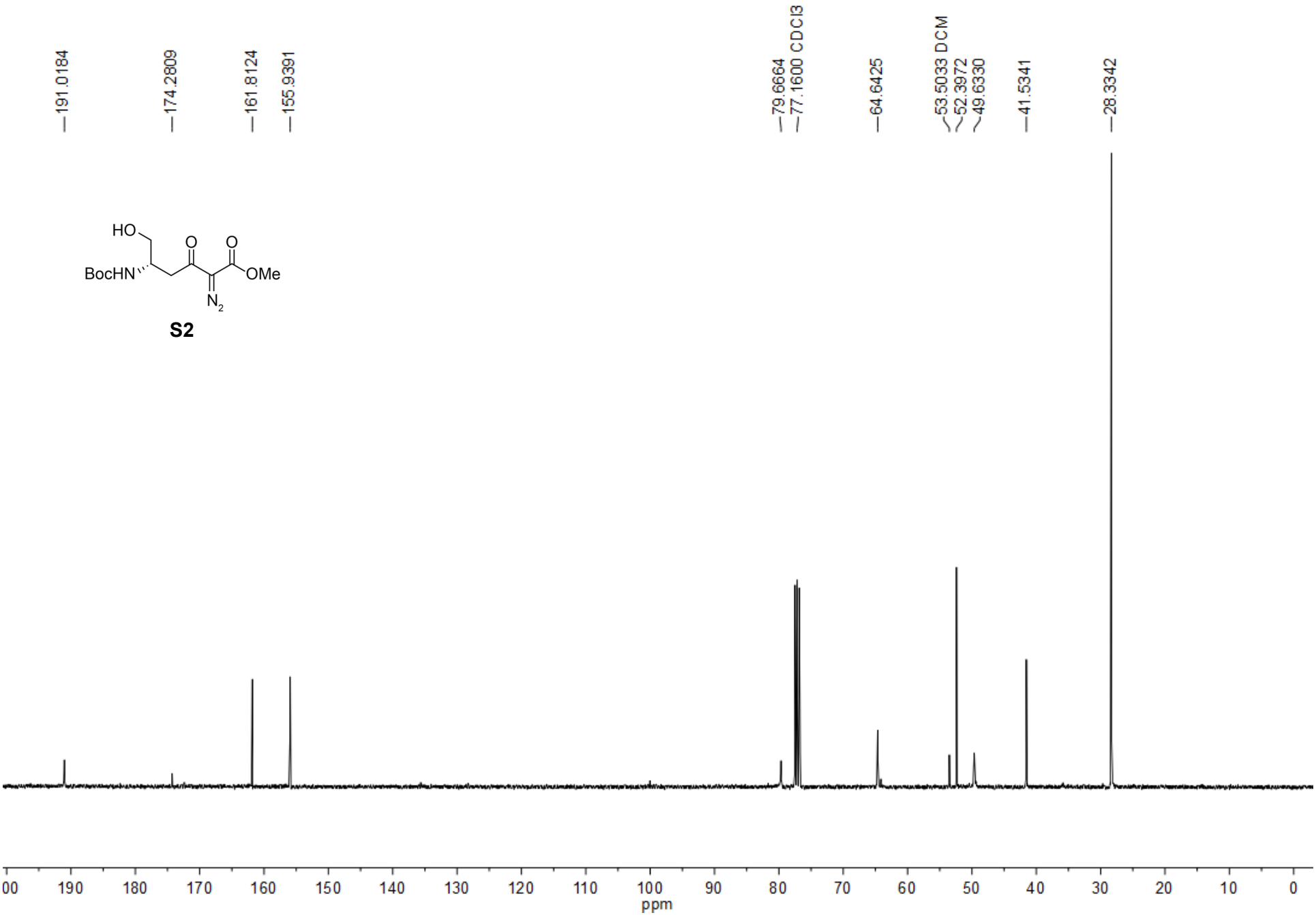
S4

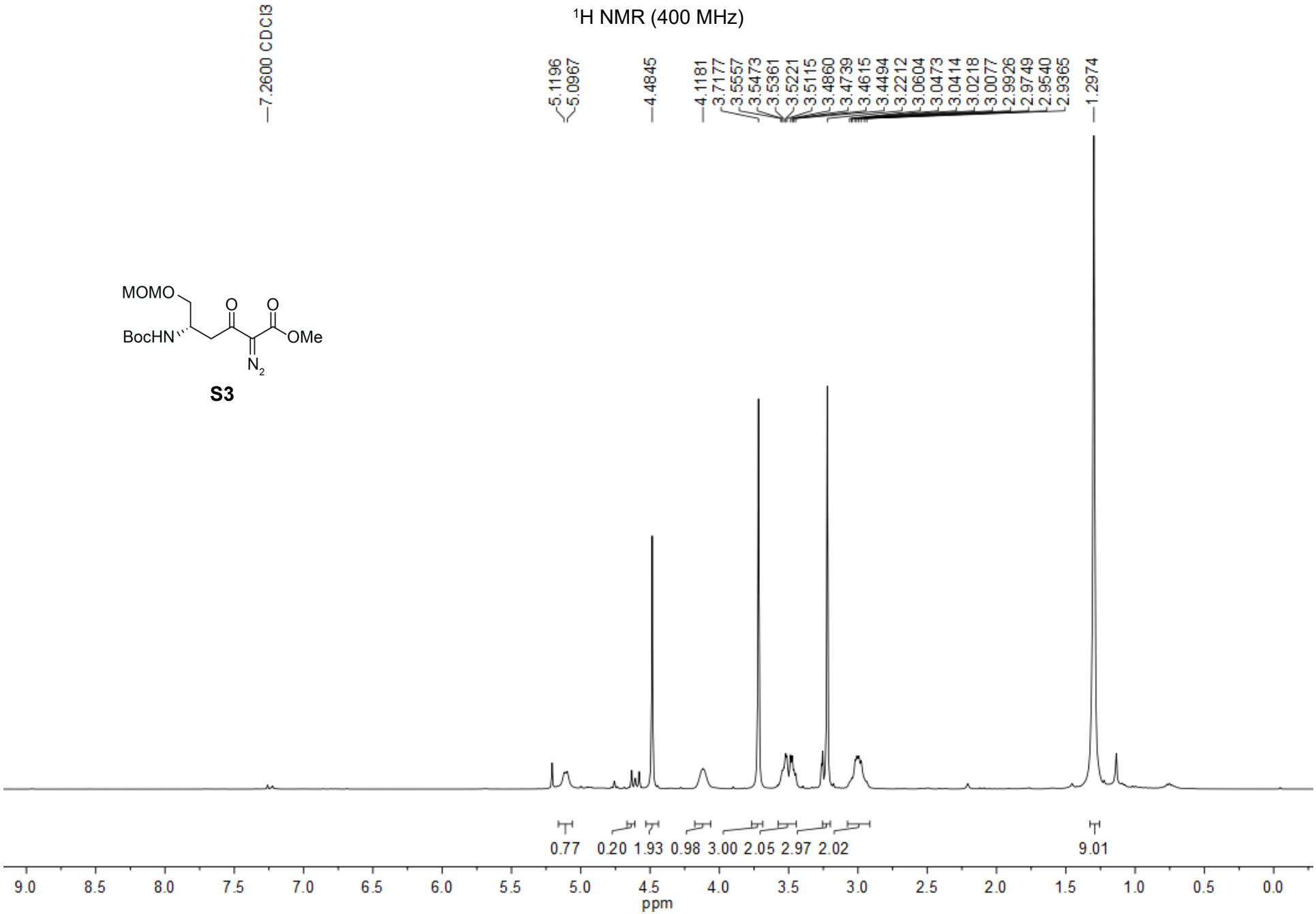
To a solution of **S3** (1.21 g, 3.5 mmol, 1 eq) in dry toluene (30 mL) was added Rh_2OAc_4 (7.8 mg, 0.018 mmol, 0.005 eq) and the mixture was stirred at 90 °C for 1.5 h. The reaction mixture was concentrated *in vacuo* and passed through silica gel (30 g) using diethyl ether to obtain **S4** as an oil that was used without further purification (1.05 g, 93.0%). R_f = 0.46 (40% EtOAc/hexanes, visualized w/ KMnO4). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 5.11 (d, *J* = 9.1 Hz, 1H), 4.48 (s, 2H), 4.12 (br s, 1H), 3.72 (s, 3H), 3.56–3.45 (m, 2H), 3.22 (s, 3H), 3.06–2.94 (m, 2H), 1.30 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ= 190.41, 161.58, 155.16, 96.48, 79.11, 76.10, 69.31, 55.17, 52.10, 47.36, 41.89, 28.18. HRMS (ESI): Calcd for $C_{14}H_{24}NO_7$ $[M+H]^+$: 318.1547, found: 318.1553.

^{1}H NMR (400 MHz)

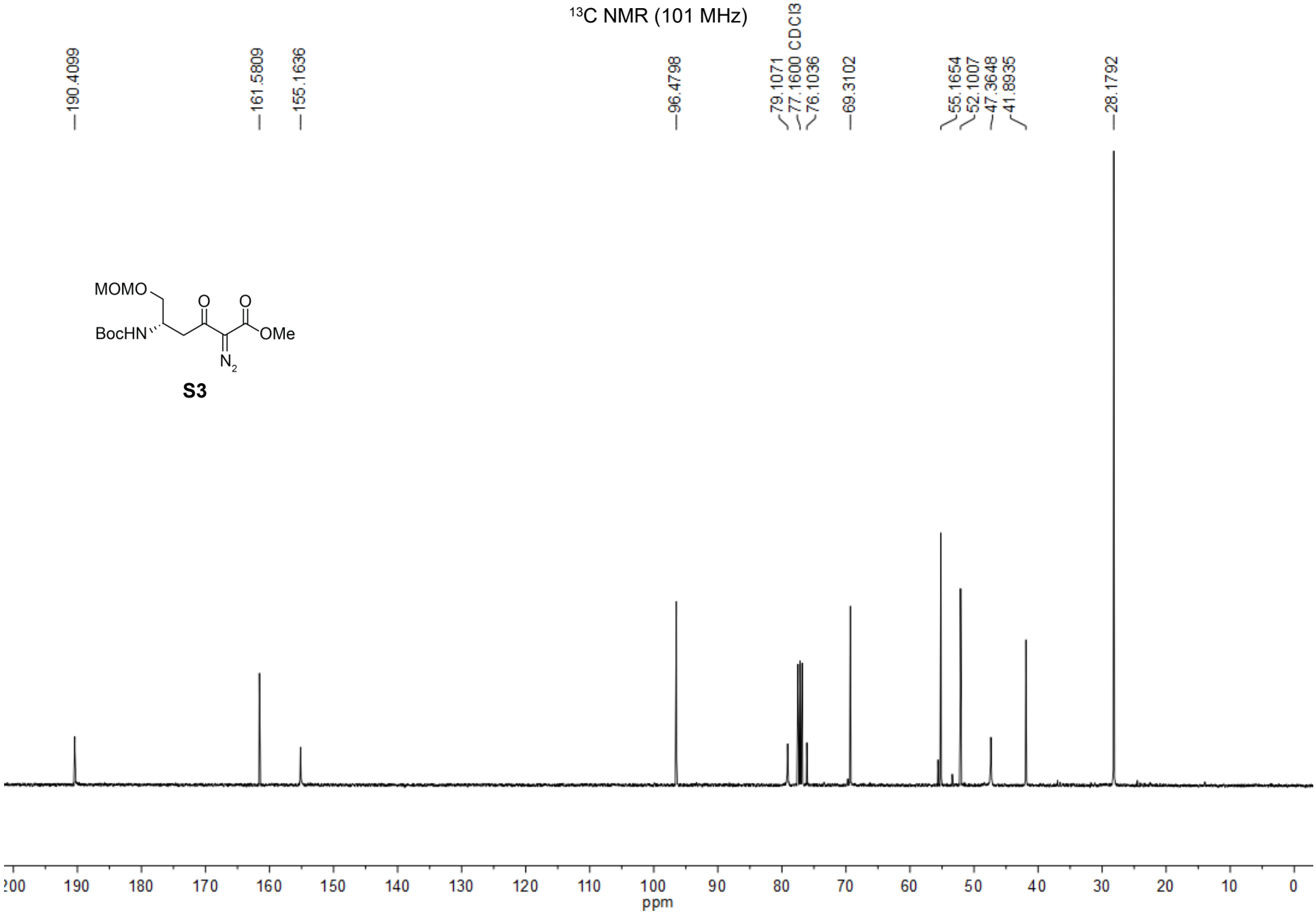


^{13}C NMR (101 MHz)



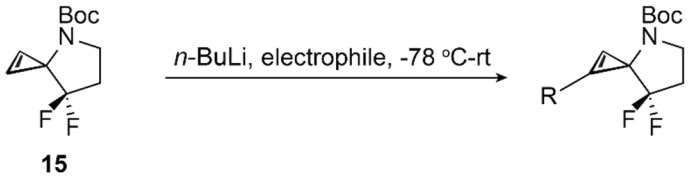

^{1}H NMR (400 MHz)
7.2600 CDCl3
5.1196
5.0967
4.4845
4.1181
3.7177
3.5557
3.5473
3.5361
3.5221
3.5115
3.4860
3.4739
3.4615
3.4494
3.2212
3.0604
3.0473
3.0414
3.0218
3.0077
2.9926
2.9749
2.9540
2.9365
1.2974
MOMO
BocHN
O
O
OMe
N_2
S3
0.77
0.20
1.93
0.98
3.00
2.05
2.97
2.02
9.01
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

^{13}C NMR (101 MHz)

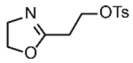
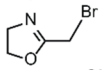
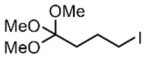


S3

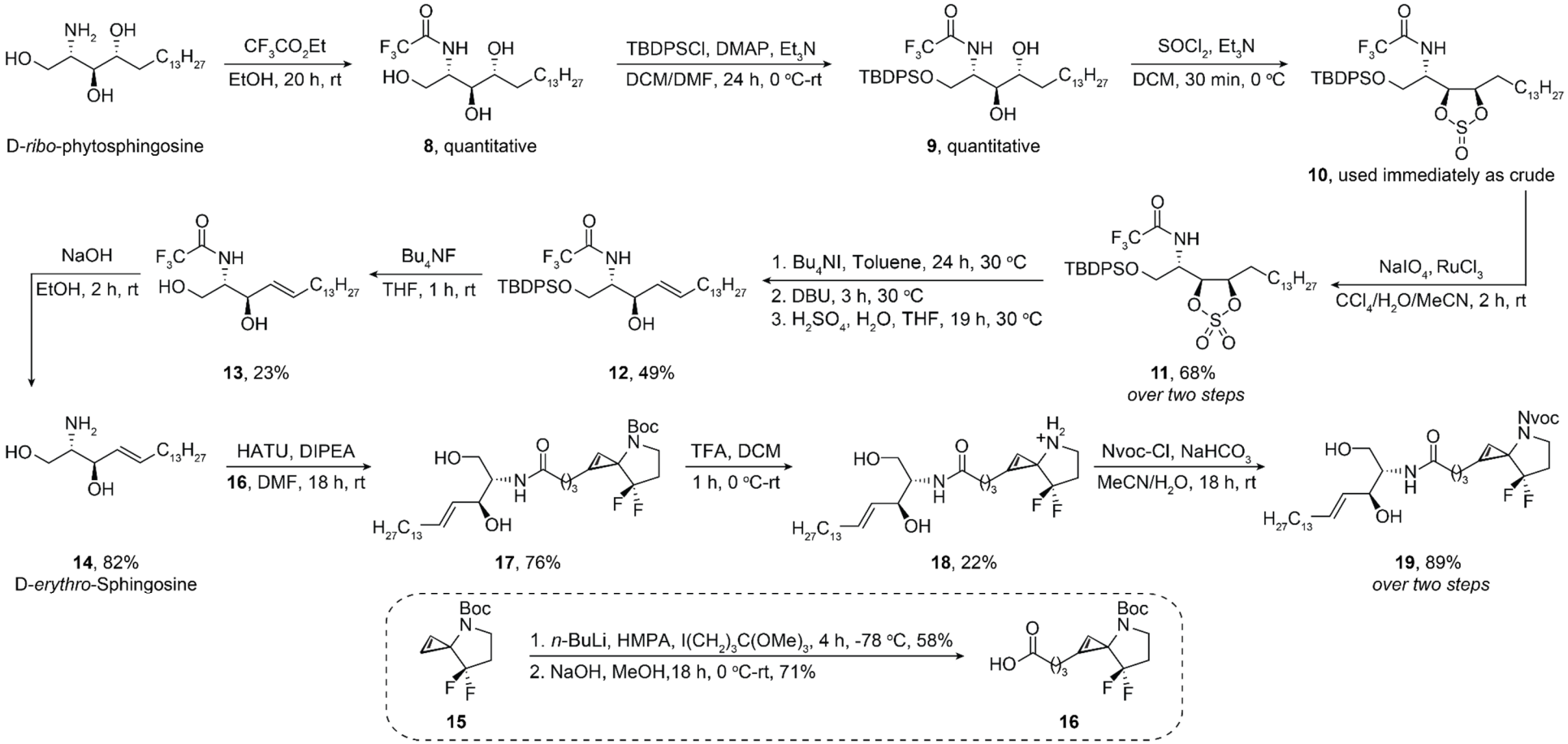
Scheme S3

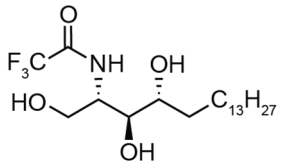


15

Electrophile	***Comment***
Paraformaldehyde, $(CH_2O)_n$	No reaction, **15** was recovered, decomposition of the electrophile
Oxirane, 	
Dihydrooxazol-, 	
Dihydrooxazol-, 	
Iodo-orthoformate, 	Complete consumption of **15**, Product formation, **R** = $(CH_2)_3CO_2Me$

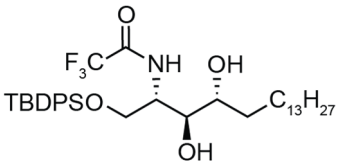
Scheme S4


D-ribo-phytosphingosine
CF3CO2Et
EtOH, 20 h, rt
8, quantitative
TBDPSCl, DMAP, Et3N
DCM/DMF, 24 h, 0 °C-rt
9, quantitative
SOCl2, Et3N
DCM, 30 min, 0 °C
10, used immediately as crude
NaIO4, RuCl3
CCl4/H2O/MeCN, 2 h, rt
11, 68%
over two steps
1. Bu4NI, Toluene, 24 h, 30 °C
2. DBU, 3 h, 30 °C
3. H2SO4, H2O, THF, 19 h, 30 °C
12, 49%
Bu4NF
THF, 1 h, rt
13, 23%
NaOH
EtOH, 2 h, rt
14, 82%
D-erythro-Sphingosine
HATU, DIPEA
16, DMF, 18 h, rt
17, 76%
TFA, DCM
1 h, 0 °C-rt
18, 22%
Nvoc-Cl, NaHCO3
MeCN/H2O, 18 h, rt
19, 89%
over two steps
1. n-BuLi, HMPA, I(CH2)3C(OMe)3, 4 h, -78 °C, 58%
2. NaOH, MeOH,18 h, 0 °C-rt, 71%
15
16



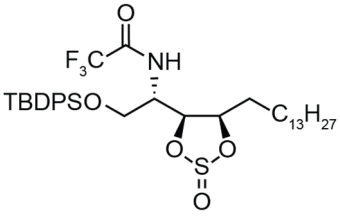
8

D-*erythro*-Sphingosine was synthesized from the commercially available D-*ribo*-Phytosphingosine by modifying the cyclic sulfate strategy by Lee et al.[5] To a solution of D-*ribo*-Phytosphingosine (1.0 g, 3.15 mmol, 1.0 eq) in EtOH (6.25 mL) was added trifluoroethyl acetate (0.575 mL, 4.82 mmol, 1.53 eq). After stirring the reaction mixture for 20 h at rt, it was poured in brine and washed with EtOAc (2×20 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by flash chromatography (70.0 g silica, 50% EtOAc/hexanes (v/v)) to obtain **8** (1.3 g, quantitative). R_f = 0.30-0.55 (50% EtOAc/hexanes, visualized w/ UV). MS (ESI): Calcd for $C_{20}H_{37}F_3NO_4$ $[M-H]^-$: 412.3, found: 412.3.



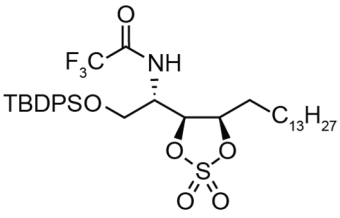
9

To an ice-cold solution of **8** (1.56 g, 3.78 mmol, 1.0 eq), DMAP (46 mg, 0.38 mmol, 0.1 eq), and Et_3N (0.78 mL, 1.48 eq) in DCM (15.0 mL) and DMF (5.46 mL) was added TBDPS-Cl (1.40 mL, 5.48 mmol, 1.45 eq). The reaction mixture was allowed to warm to rt over 24h. The reaction was diluted with EtOAc (75.0 mL) and washed with brine (2×60 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by flash chromatography (90.0 g silica, 15% EtOAc/hexanes (v/v)) to obtain **9** (2.48 g, quantitative). R_f = 0.24 (15% EtOAc/hexanes, visualized w/ UV). MS (ESI): Calcd for $C_{36}H_{56}F_3NO_4Si$ $[M-H]^-$: 650.4, found: 650.4.



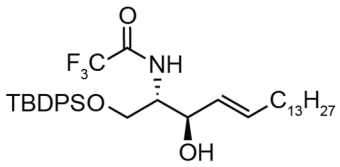
10

To an ice-cold solution of diol **9** (2.87 g, 4.40 mmol, 1.0 eq) in DCM (35.0 mL) under N_2 atmosphere was added Et_3N (2.11 mL, 15.1 mmol, 3.44 eq) and $SOCl_2$ (0.42 mL, 4.84 mmol, 1.11 eq). After stirring the reaction mixture for 30 mins it was poured into brine (70.0 mL) and extracted with EtOAc (2×80 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated to dryness *in vacuo* to obtain crude cyclic sulfite **10** (3.07 g) which was used immediately without purification. R_f = 0.5 (10% EtOAc/hexanes, visualized w/ UV). MS (ESI): Calcd for $C_{36}H_{53}F_3NO_5SSi$ $[M-H]^-$: 696.3, found: 696.3.



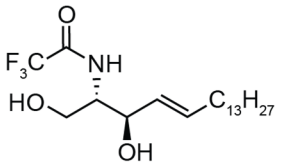
11

To a solution of the crude sulfite **10** (3.07 g, 4.40 mmol, 1.0 eq) obtained from the previous step in 1:1:1 CCl_4/H_2O/MeCN (37.0 mL) was added $NaIO_4$ (2.82 g, 13.2 mmol, 3.0 eq) and $RuCl_3$ (47 mg, 0.023 mmol, 0.05 eq) consecutively. After stirring the reaction mixture at rt for 2 h it was diluted with EtOAc (100.0 mL). The organic layer was washed with sat. $NaHCO_3$, dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by flash chromatography (90.0 g silica, 10% EtOAc/hexanes (v/v)) to obtain the sulfate **11** (2.12 g, 67.6% over two steps). R_f = 0.25 (10% EtOAc/hexanes, visualized w/ UV). MS (ESI): Calcd for $C_{36}H_{53}F_3NO_6Si$ $[M-H]^-$: 712.2, found: 712.2.



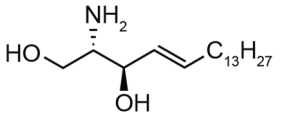
12

To a solution of the sulfate **11** (2.12 g, 2.98 mmol, 1.0 eq) in toluene (31.2 mL) was added *n*Bu_4NI (1.25 g, 3.39 mmol, 1.14 eq) and the reaction mixture was stirred at 30 °C for 24 h. DBU (0.676 mL, 4.26 mmol, 1.43 eq) was added and the reaction mixture was stirred for 2.75 h at the same temperature. To this reaction was added conc. H_2SO_4 (42 µL), H_2O (37.5 µL), and THF (0.682 mL) The reaction was stirred for 19 h. Additional 2X of conc. H_2SO_4, H_2O, and THF was added based on TLC and the reaction was shifted to 55 °C for 1.5 h. Again, based on TLC additional amount of conc. H_2SO_4 was added (reaction pH ~2-3) and the reaction was stirred at 63 °C for 1.5 h. The reaction mixture was cooled down to rt, diluted with EtOAc (100.0 mL), and washed successively with sat. $NaHCO_3$ and brine (2×80 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by flash chromatography (130.0 g silica, 4% EtOAc/hexanes (v/v)) to obtain the alkene **12** (578 mg, 48.6%). R_f = 0.15 (4% EtOAc/hexanes, visualized w/ UV). MS (ESI): Calcd for $C_{36}H_{53}F_3NO_3Si$ $[M-H]^-$: 632.2, found: 632.2.



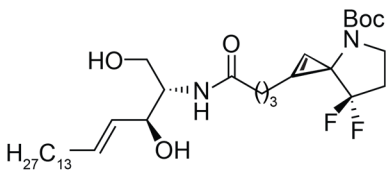
13

To a solution of the crude alkene **12** (578 mg, 0.91 mmol, 1.0 eq) in THF (13.0 mL) was added *n*Bu_4NF (1.37 mL, 1.37 mmol, 1.50 eq, 1.0 M in THF) and the reaction was stirred at rt for 1 h. The reaction mixture was concentrated *in vacuo* and immediately subjected to flash chromatography (40.0 g silica, 25% EtOAc/hexanes (v/v)) to obtain **13** containing unidentifiable minor impurity. Repeating the purification step two more times did not help in getting rid of this unknown impurity. A total of **13** (83 mg, 23%) was obtained. R_f = 0.55 (0% EtOAc/hexanes, visualized w/ UV). MS (ESI): Calcd for $C_{20}H_{35}F_3NO_3$ $[M-H]^-$: 394.3, found: 394.3.



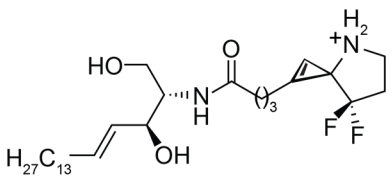
14

To a solution of the **13** (83 mg, 0.21 mmol, 1.0 eq) in EtOH (4.0 mL) was added aq. NaOH (2.0 M, 3.38 mL) and the reaction was stirred at rt for 2 h. The reaction was diluted with H_2O (5.0 mL) and extracted with EtOAc (2×5 mL). The combined organic layer was washed with brine (2×5 mL), dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by flash chromatography (10.0 g silica, 15% MeOH/DCM + .5% Et_3N (v/v)) to obtain **14** (52 mg, 82.5 %). R_f = 0.22 (15% MeOH/DCM + 0.5% Et_3N, visualized w/ UV). ^1H NMR (700 MHz, $CDCl_3$): δ= 5.75–5.71 (m, 1H), 5.43 (dd, *J* = 15.5, 6.7 Hz, 1H), 4.10 (s, 1H), 3.67 (br s, 6H), 2.89 (s, 1H), 2.02 (q, *J* = 7.2 Hz, 2H), 1.35 (p, *J* = 7.2 Hz, 2H), 1.29–1.24 (m, 20H), 0.87 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ= 134.57, 129.01, 74.31, 62.94, 56.49, 32.54, 32.05, 29.85, 29.80, 29.68, 29.60, 29.39, 22.8, 14.23. HRMS (ESI): Calcd for $C_{18}H_{38}NO_2$ $[M+H]^+$: 300.2897, found: 300.2901.



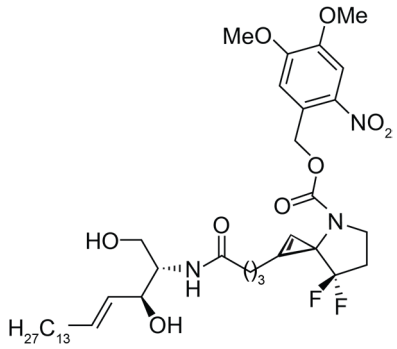
17

Compounds **15** and **16** were synthesized as recently described by us[2]. To an ice-cold solution of **16** (7.0 mg, 0.022 mmol, 1.0 eq) in dry DMF (1.0 mL) under an inert atmosphere was added DIPEA (4.6 µL, 0.026 mmol, 1.2 eq). Further, HATU (10.1 mg, 0.026 mmol, 1.2 eq) as a solution in dry DMF (0.3 mL) was added dropwise and the reaction was continued stirring at the same temperature for 30 mins. D-*erytho*-Sphingosine **14** (7.6 mg, 0.025 mmol, 1.15 eq) as a solution in dry DMF (0.3 mL) was added to this activated acid and the resulting yellowish mixture was allowed to gradually warm to rt overnight. The reaction mixture was extracted using DCM and water. The combined organic layer was dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by flash chromatography (8.0 g silica, 1% MeOH/DCM (v/v) to 10% MeOH/DCM) to obtain **17** (10.1 mg, 76.5%). R_f = 0.37 (5% MeOH/DCM, visualized w/ $KMnO_4$). ^1H NMR (500 MHz, $CDCl_3$): δ= 6.80 (s, 1H), 6.54 (br s, 1H), 5.81–5.74 (m, 1H), 5.55–5.48 (m, 1H), 4.31 (q, *J* = 4.7 Hz, 1H), 3.96–3.86 (m, 2H), 3.71–3.66 (m, 1H), 3.59–3.50 (m, 2H), 3.12 (br s, 1H), 2.67–2.56 (m, 2H), 2.38–3.23 (m, 4H), 2.07–1.98 (m, 4H), 1.69 (s, 1H), 1.40 (s, 9H), 1.36–1.35 (m, 2H), 1.27–1.25 (m, 20H), 0.87 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ= 173.07, 154.11, 134.06, 133.94, 128.97, 128.95, 127.93, 125.32, 123.01, 114.06, 103.25, 80.23, 80.20, 74.70, 74.55, 62.55, 62.51, 54.79, 50.35, 50.07, 49.78, 41.35, 35.64, 35.62, 32.44, 32.14, 32.07, 31.94, 31.75, 29.83, 29.80, 29.77, 29.65, 29.51, 29.37, 29.30, 29.27, 28.64, 24.26, 24.23, 23.01, 22.84, 14.27. COSY NMR (500 MHz, $CDCl_3$, attached) was obtained under the same conditions. HRMS (ESI): Calcd for $C_{33}H_{56}F_2N_2O_5$ $[M+H]^+$: 599.4236, found: 599.4233.



18

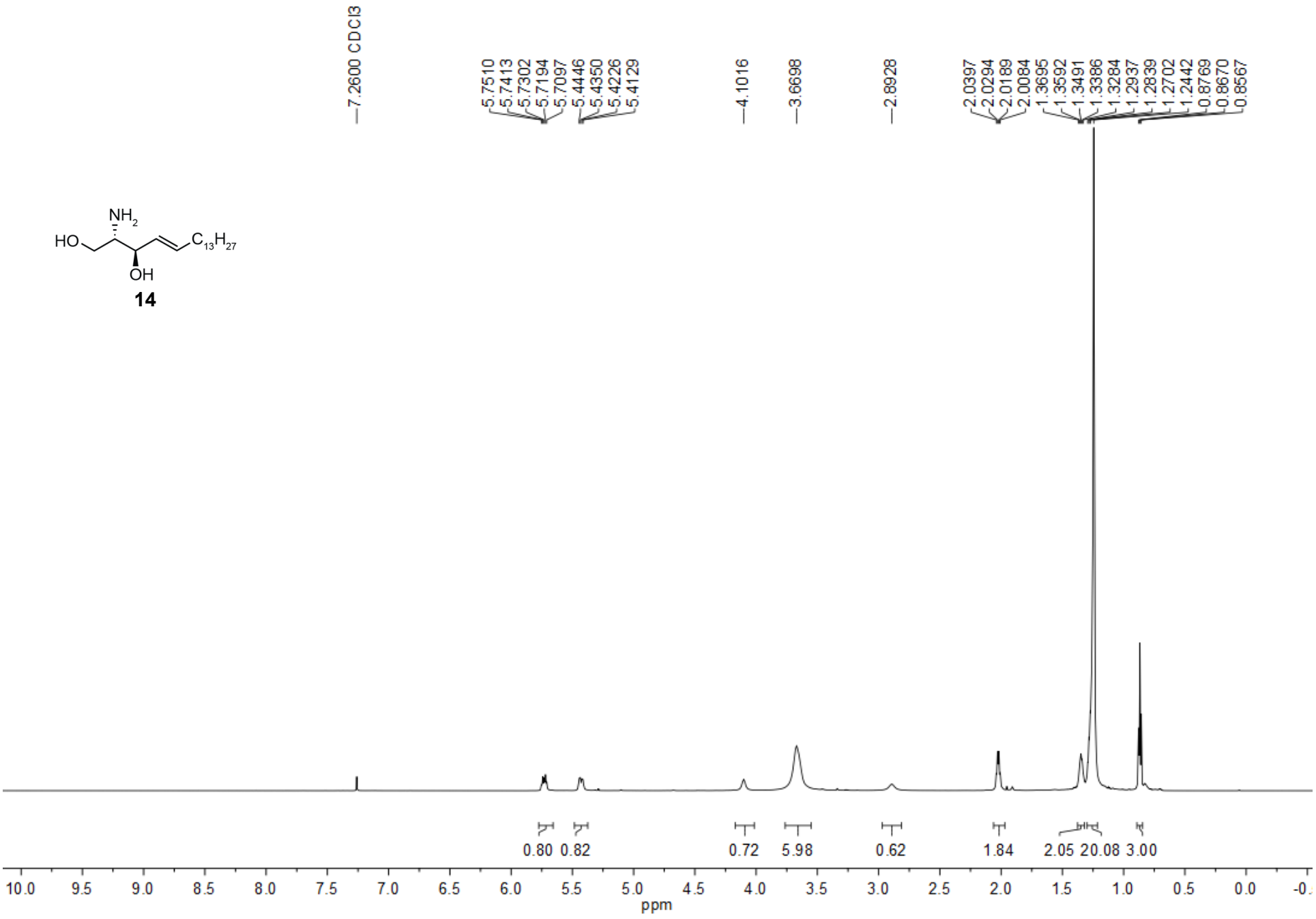
To an ice-cold solution of **17** (10.0 mg, 0.017 mmol, 1.0 eq) in DCM (2.0 mL) was added TFA (0.45 mL) and the reaction was allowed to gradually warm to rt over 1.25 h. The reaction was concentrated *in vacuo* to obtain crude **18** as a TFA salt that was used in the next step without further purification. An analytically pure sample was obtained by purifying it using analytical column on HPLC (R_t = 17.2 mins, 50–100% MeOH over 10 mins, and then 100% MeOH from 10–30 mins, flow rate = 1 mL/min). Yield = 22.0%. R_f = 0.19 (5% MeOH/DCM, visualized w/ $KMnO_4$). ^1H NMR (700 MHz, $CDCl_3$): δ= 6.91 (br s, 1H), 6.86 (br s, 1H), 5.76–5.71 (m, 1H), 5.48– 5.43 (m, 1H), 4.53–4.50 (m, 1H), 3.95–3.83 (m, 2H), 3.51–3.45 (m, 3H), 3.14 (qd, *J* = 7.3, 4.5 Hz, 1H), 2.67–2.63 (m, 4H), 2.36–2.34 (m, 2H), 2.07–2.00 (m, 5H+H_2O), 1.35–1.25 (s, 22H), 0.88 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$): δ= 53.59, 45.79, 32.08, 29.86, 29.84, 29.82, 29.78, 29.63, 29.52, 22.85, 14.29, 8.66. Peaks for tertiary and quaternary carbons were not observed. HRMS (ESI): Calcd for $C_{28}H_{49}F_2N_2O_3$ $[M+H]^+$: 499.3706, found: 499.3707.

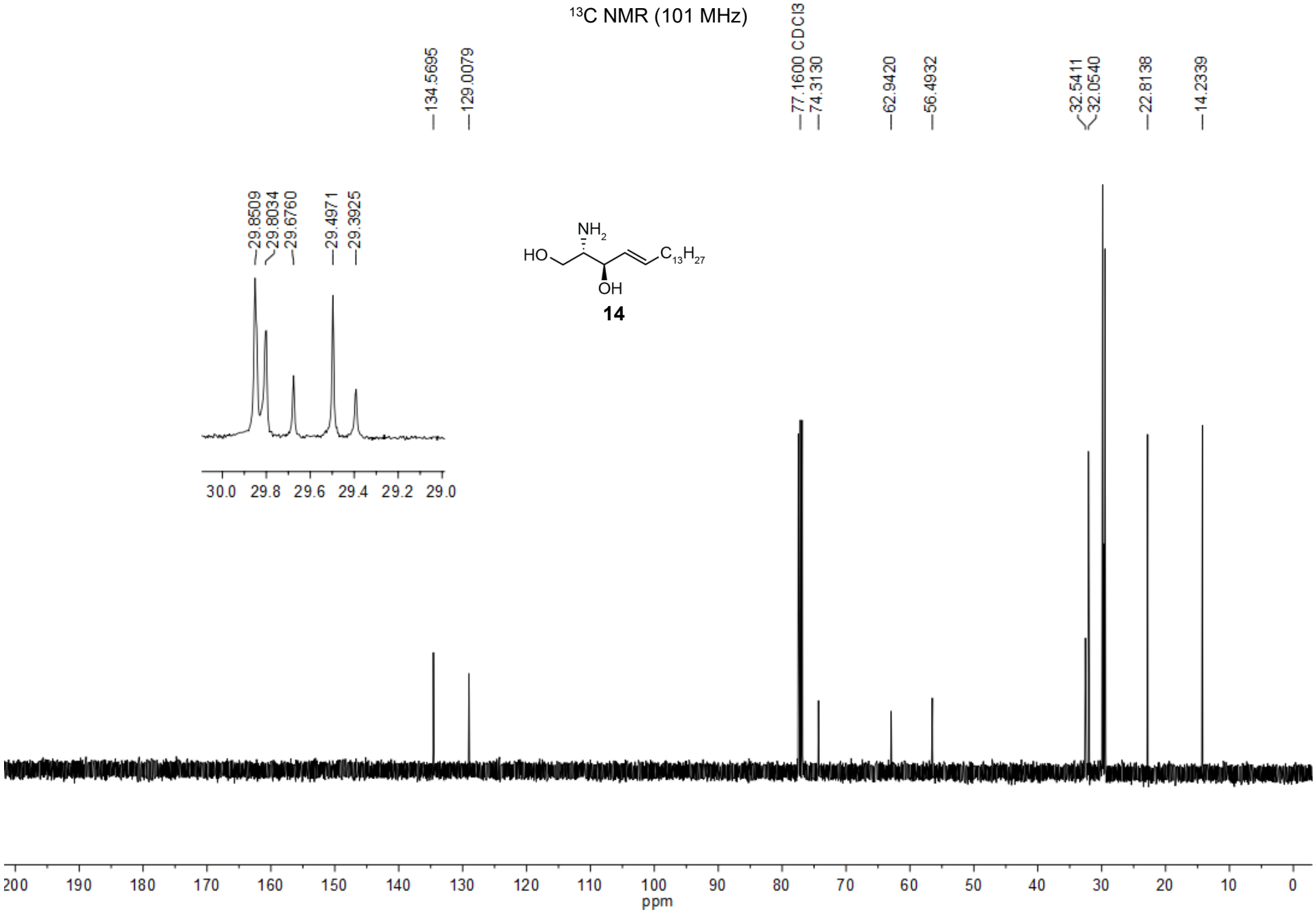


19

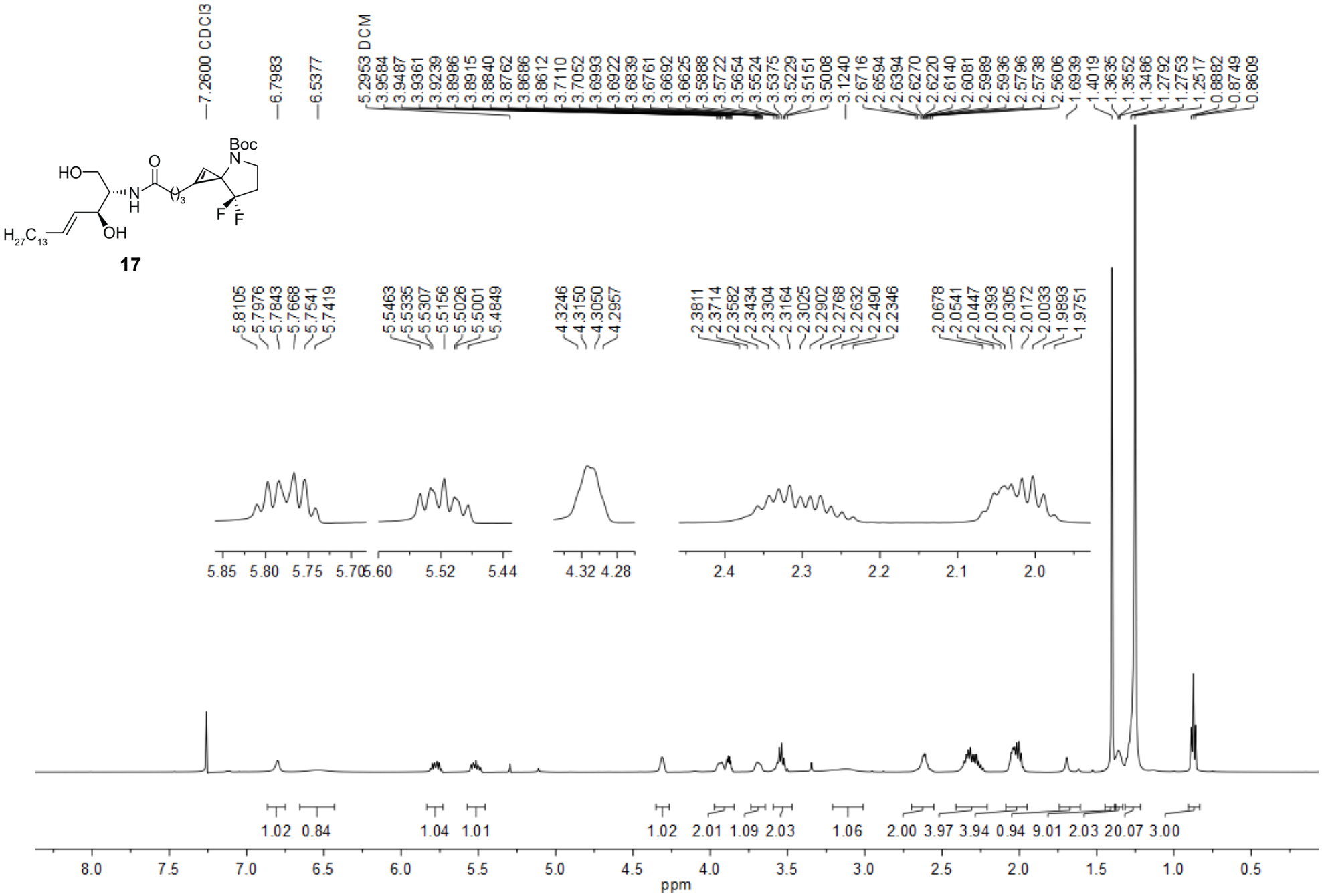
To an ice-cold suspension of crude TFA salt **18,** obtained from the previous step, in MeCN (3.0 mL) and water (1.0 mL) was added aq. $NaHCO_3$ (20 mg, 0.6 mL H_2O, reaction pH ~ 8.5). To this reaction mixture was added Nvoc-Cl (5.53 mg, 0.020 mmol, 1.2 eq) and the reaction was allowed to warm up to rt overnight under dark. The reaction was extracted using DCM and water. The combined organic layer was dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and subjected to flash chromatography (5.5 g silica, 50% EtOAc/hexanes (v/v) and then 3% MeOH/DCM) to obtain **19** (11 mg, 89% over two steps) as a yellow oil. R_f = 0.30 (5% MeOH/DCM, visualized w/ UV). ^{1}H NMR (700 MHz, $CDCl_3$): δ= 7.69 (s, 1H), 6.95 (s, 1H), 6.83 (br s, 1H), 6.61 (d, 1H), 5.79–5.74 (m, 1H), 5.53–5.49 (m, 1H), 5.40 (s, 2H), 4.31–4.29 (m, 1H), 3.96 (s, 3H), 3.95 (s, 3H), 3.91–3.88 (m, 1H), 3.69–3.63 (m, 3H), 2.62–2.61 (m, 2H), 2.41–2.31 (m, 4H), 2.04 (p, *J* = 7.7 Hz, 4H), 1.63–1.61 (d, *J* = 11.8 Hz, 1H), 1.35 (q, *J* = 7.5 Hz, 2H), 1.30–1.24 (m, 20H), 0.87 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$): δ= 173.05, 153.47, 148.45, 140.27, 133.96, 128.86, 127.20, 122.55, 110.64, 108.41, 74.83, 74.68, 63.95, 62.50, 56.57, 56.55, 54.54, 53.58, 41.27, 35.27, 32.45, 32.07, 31.93, 31.79, 29.84, 29.81, 29.78, 29.65, 29.51, 29.39, 29.27, 24.34, 22.92, 22.84, 14.28. COSY NMR (500 MHz, $CDCl_3$, attached) was obtained under the same conditions. HRMS (ESI): Calcd for $C_{38}H_{58}F_2N_3O_9$ $[M+H]^+$: 738.4136, found: 738.4142.

^{1}H NMR (700 MHz)

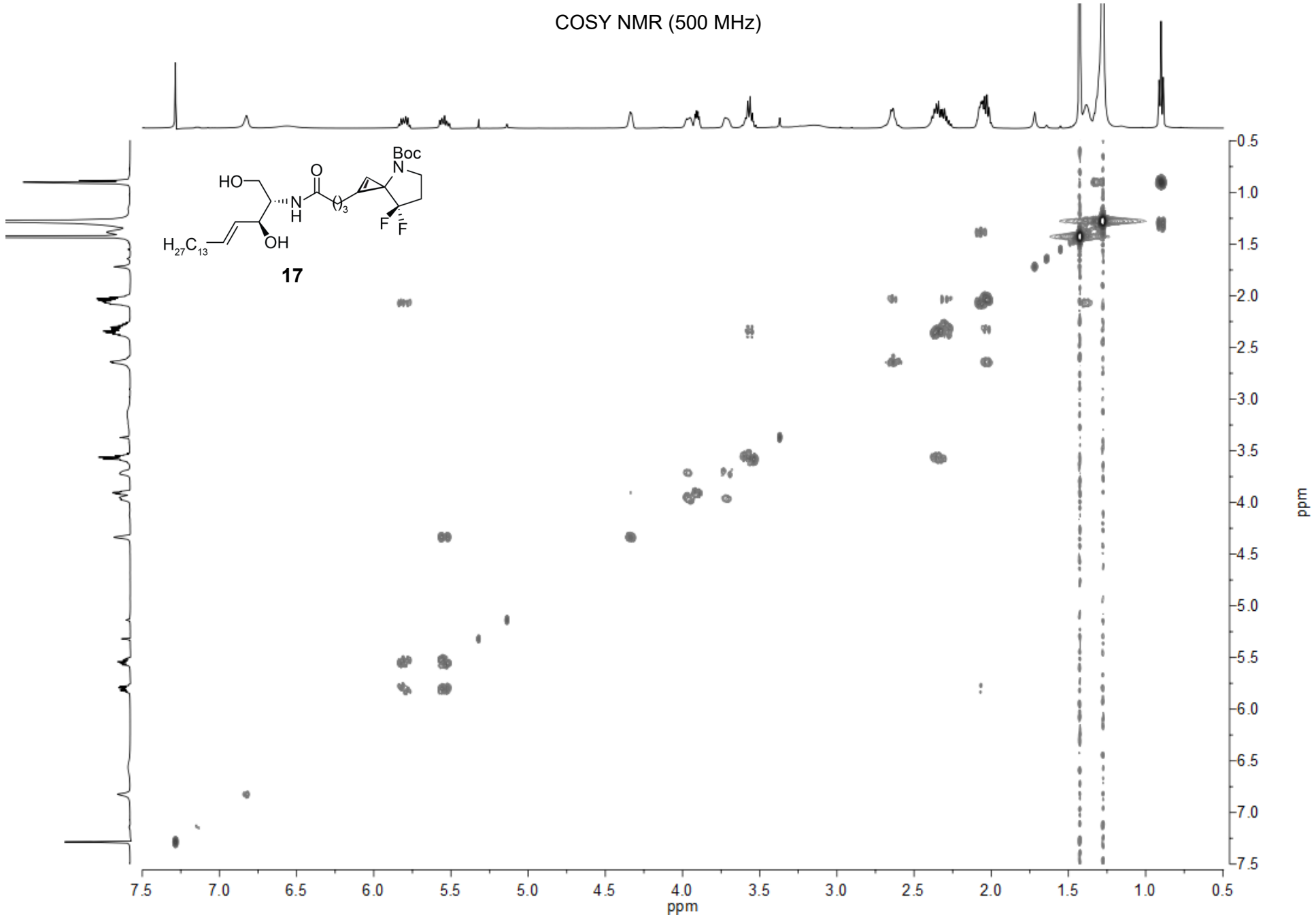



^{13}C NMR (101 MHz)
134.5695
129.0079
77.1600 CDCl3
74.3130
62.9420
56.4932
32.5411
32.0540
22.8138
14.2339
29.8509
29.8034
29.6760
29.4971
29.3925
30.0 29.8 29.6 29.4 29.2 29.0
NH2
HO
C13H27
OH
14
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

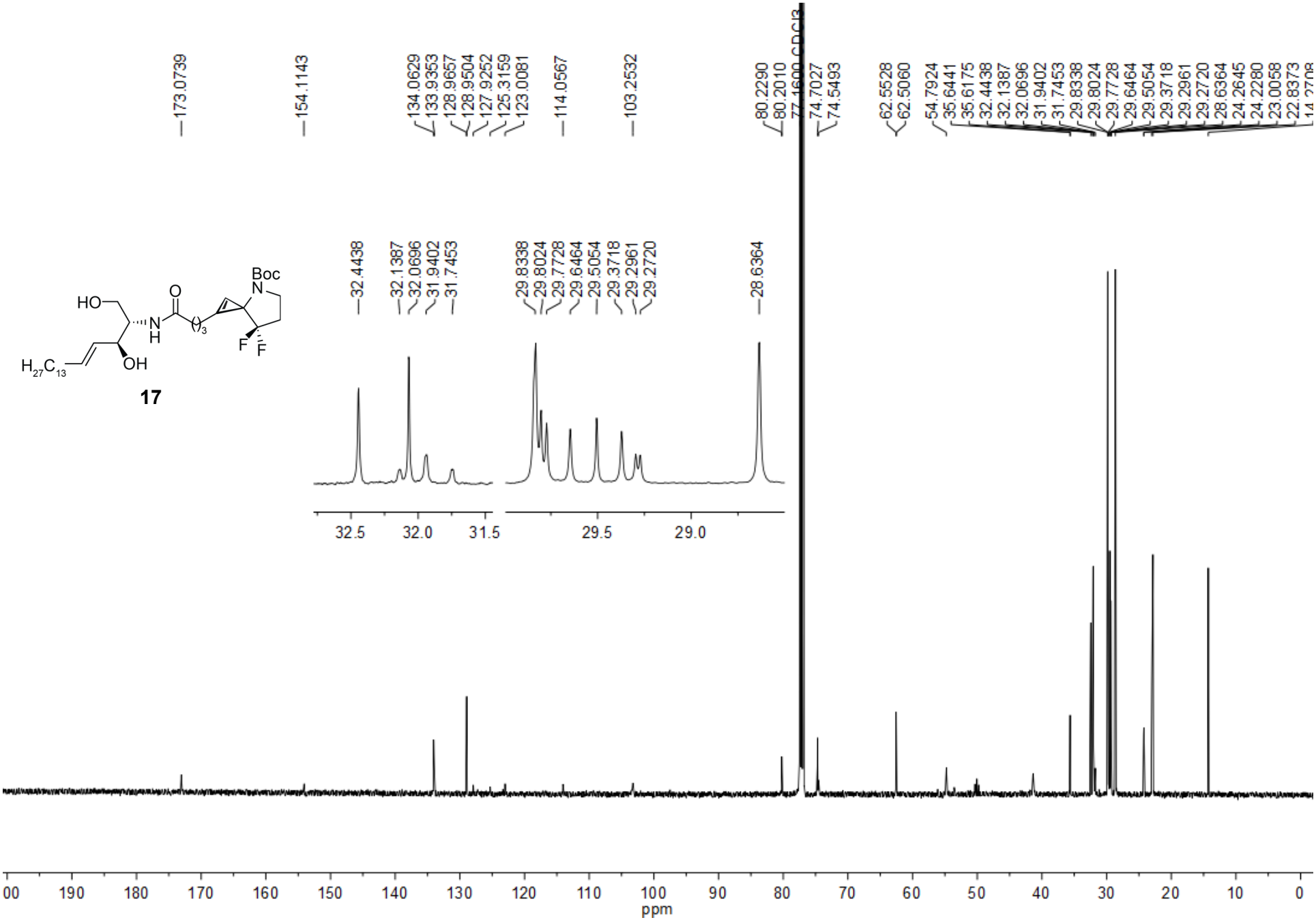
^{1}H NMR (500 MHz)



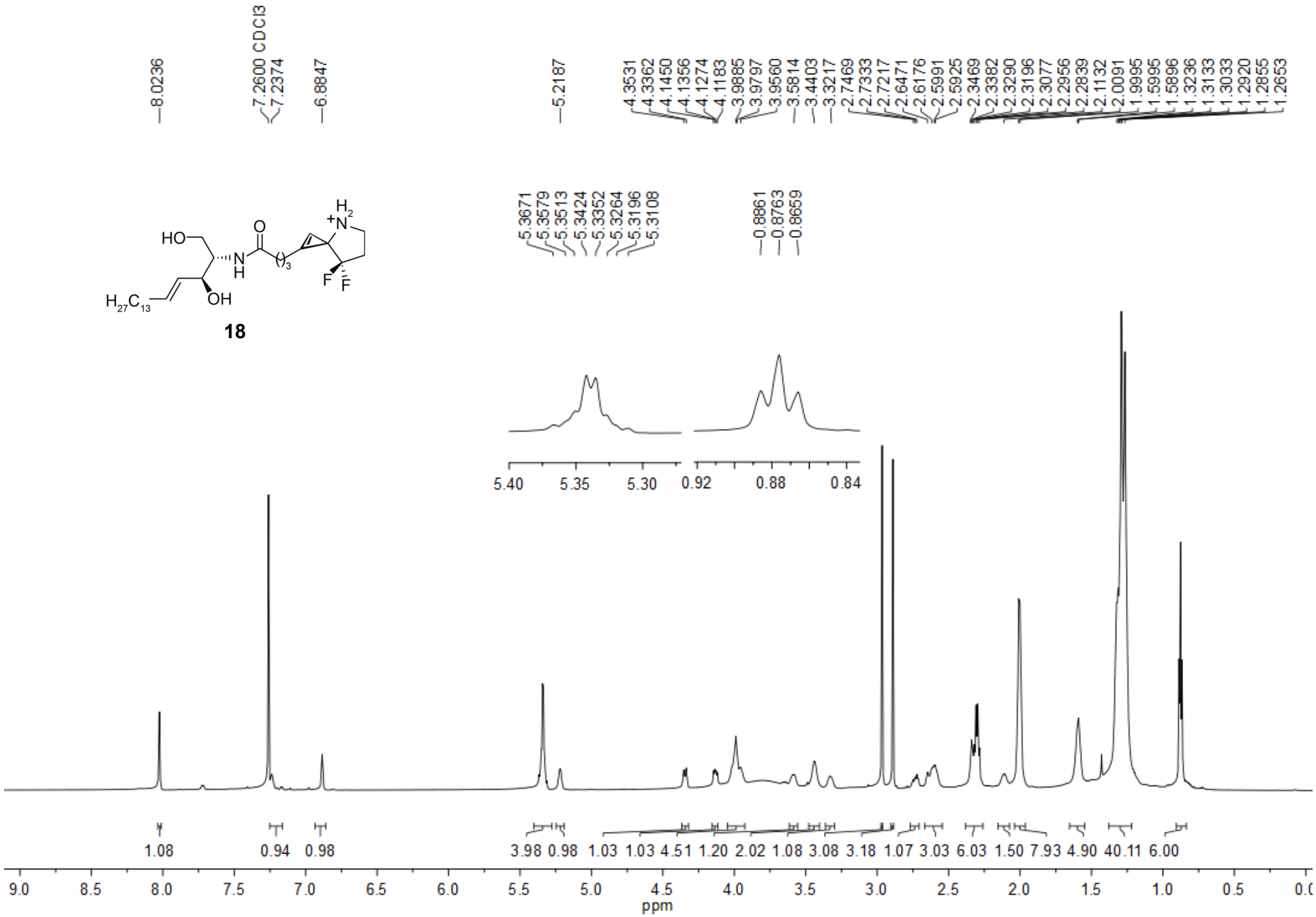
COSY NMR (500 MHz)



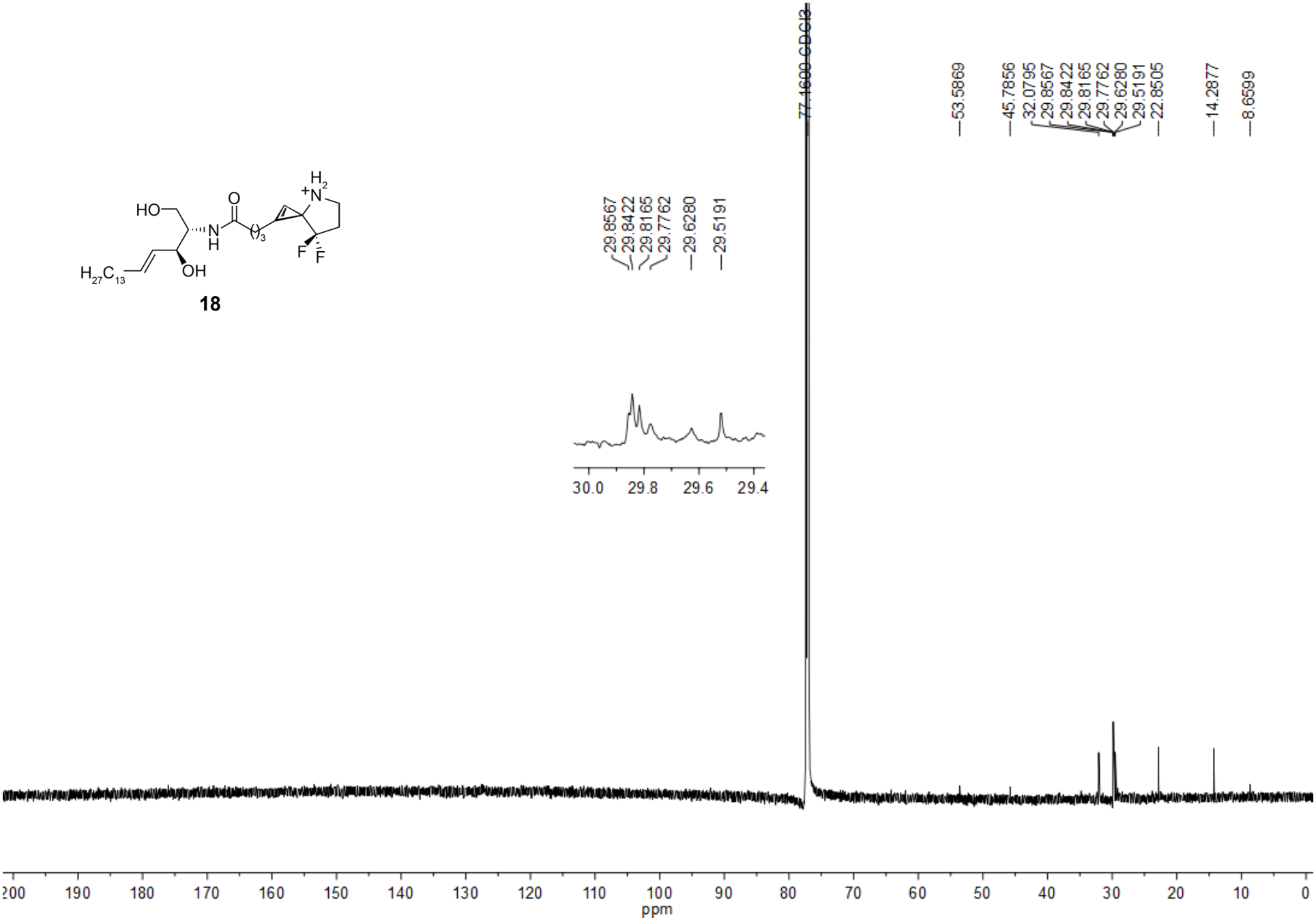
^{13}C NMR (126 MHz)



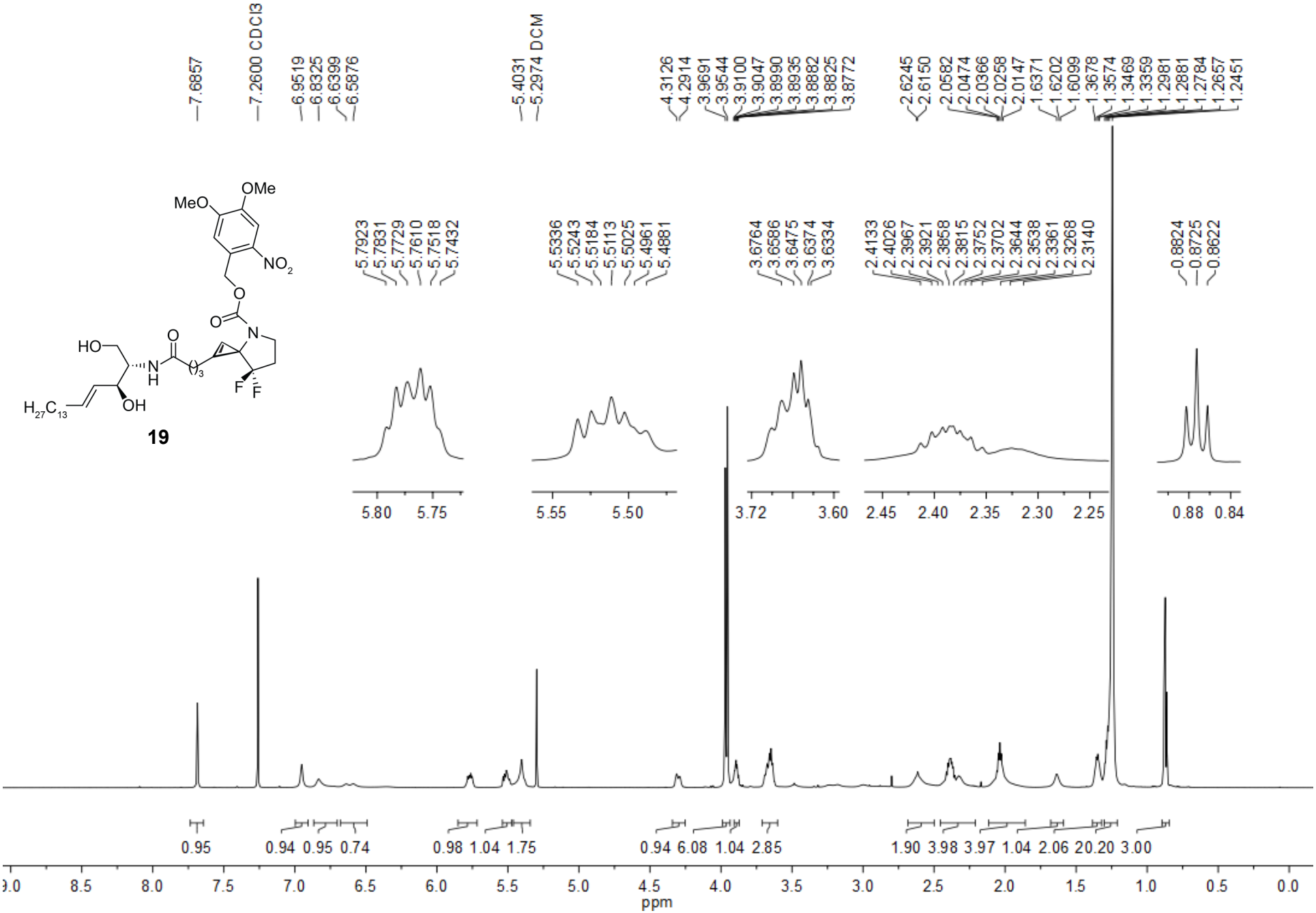
^{1}H NMR (700 MHz)



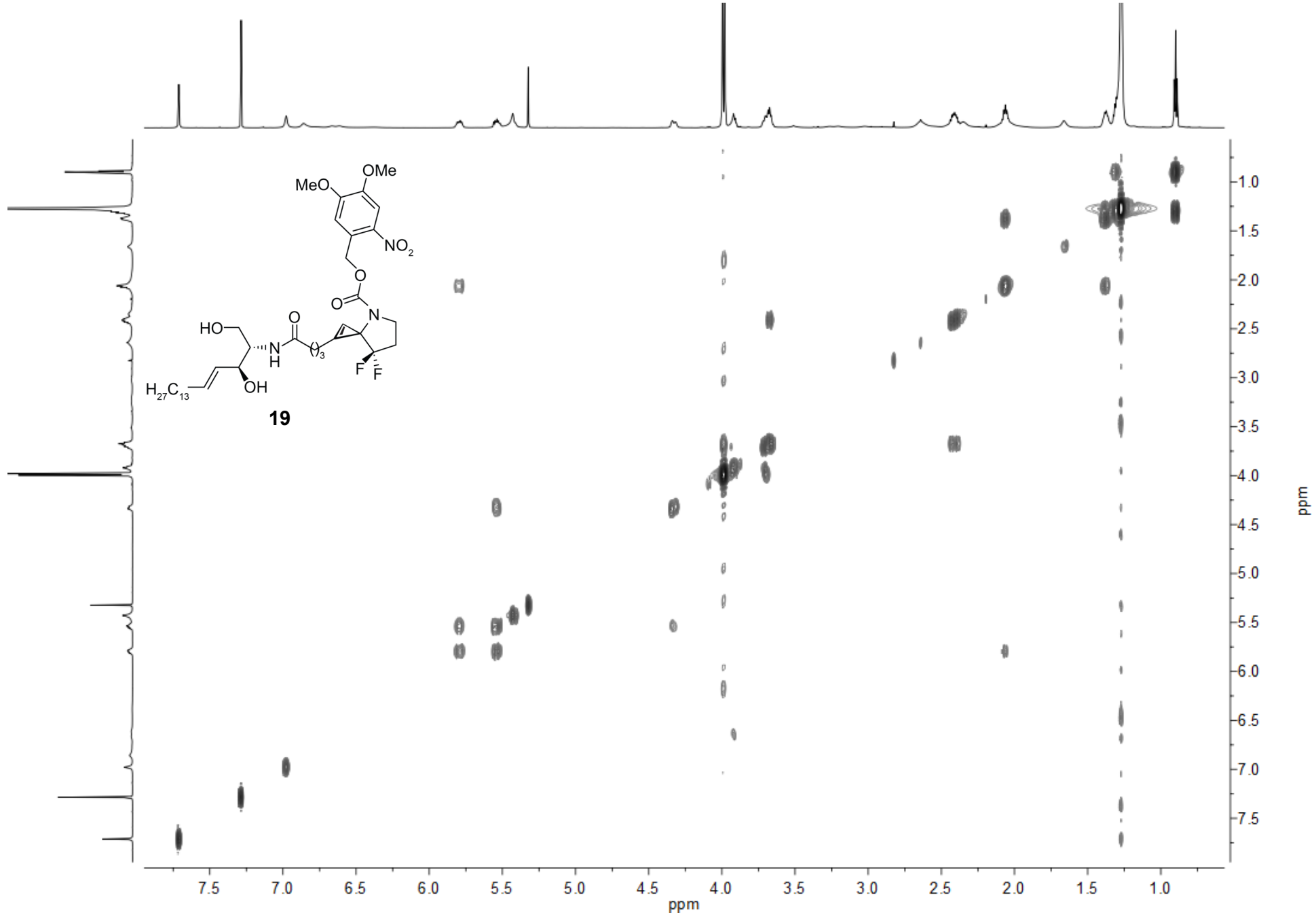
^{13}C NMR (176 MHz)



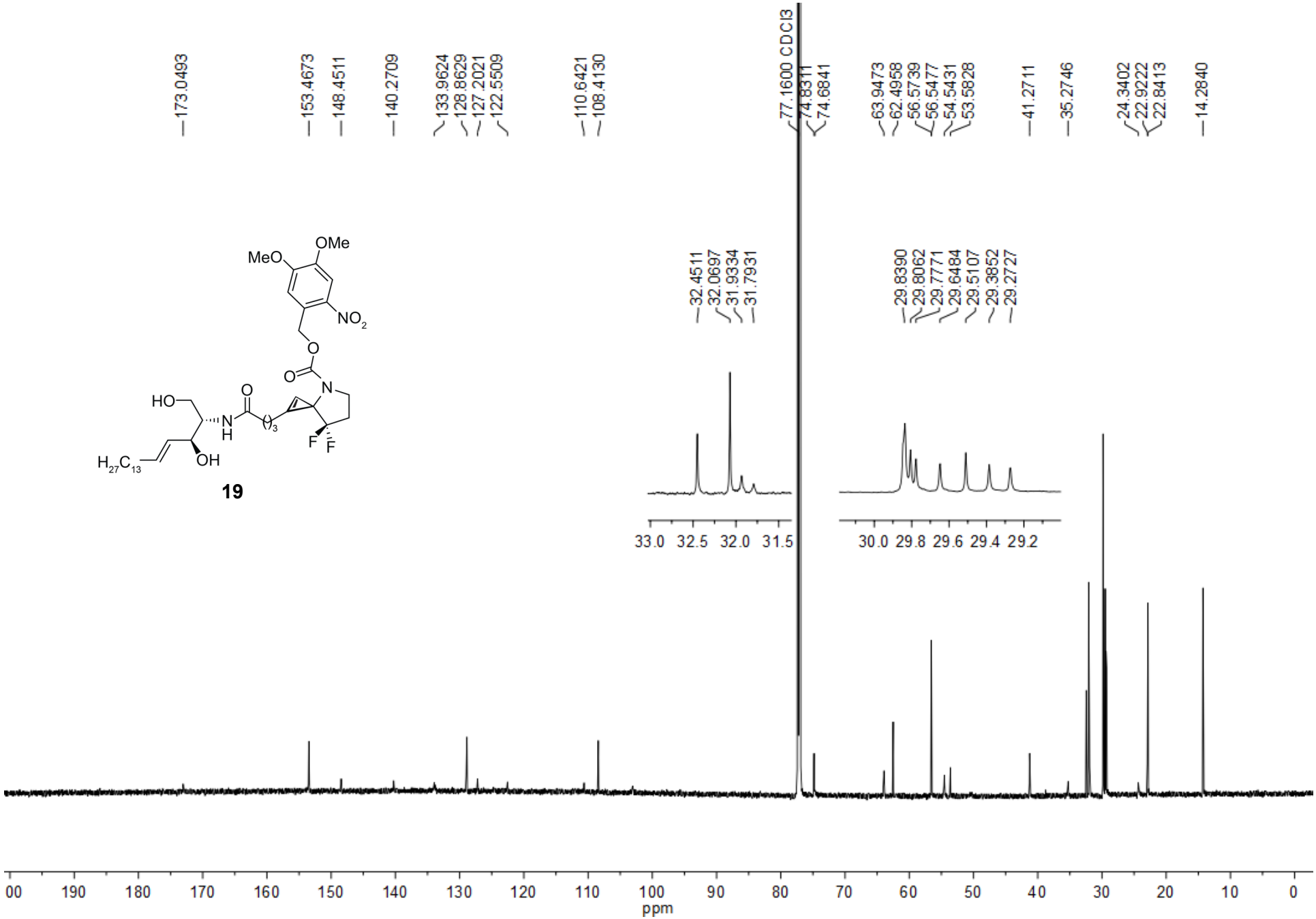
^{1}H NMR (700 MHz)



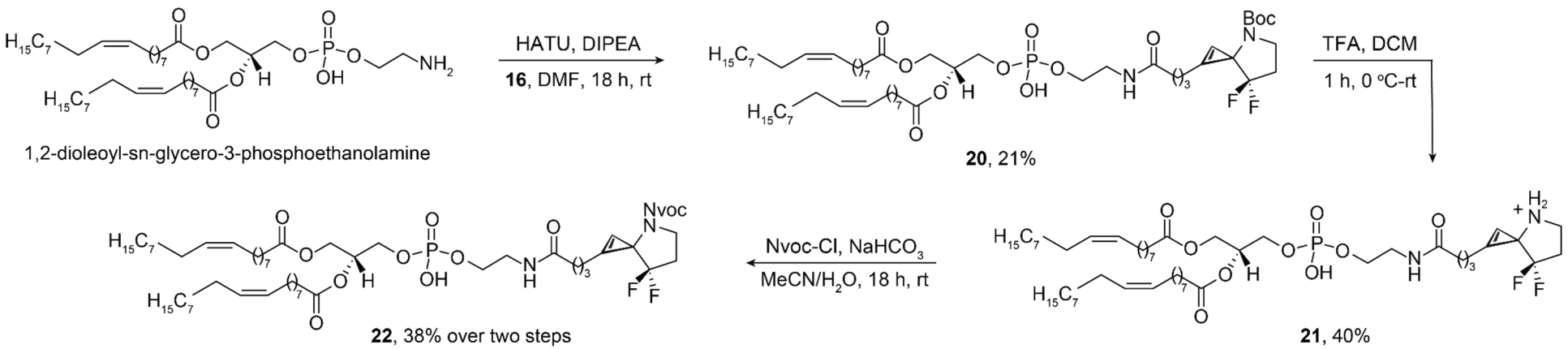
COSY NMR (700 MHz)

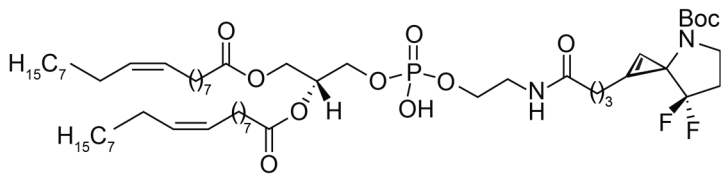


^{13}C NMR (176 MHz)



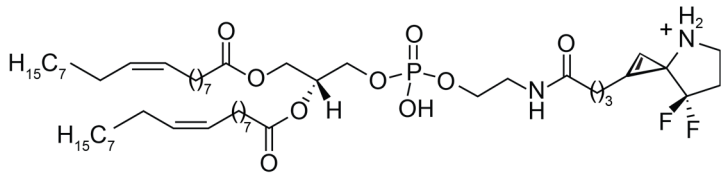
Scheme S4





20

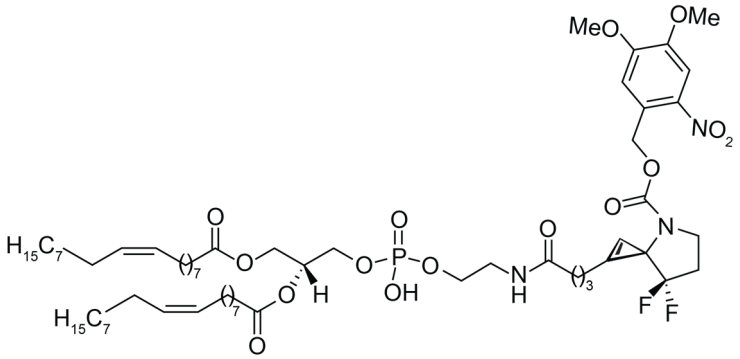
To an ice-cold solution of **16** (10.0 mg, 0.031 mmol, 1.0 eq) in dry DMF (2.0 mL) under an inert atmosphere was added DIPEA (6.8 µL, 0.038 mmol, 1.2 eq). Further, HATU (14.4 mg, 0.038 mmol, 1.2 eq) as a solution in dry DMF (0.5 mL) was added dropwise and the reaction was continued stirring at the same temperature for 30 mins. DOPE (25.8 mg, 0.035 mmol, 1.1 eq) as a solution in THF was added to this activated acid and the resulting mixture was allowed to gradually warm to rt over 48 h. The reaction mixture was extracted using DCM and water. The combined organic layer was dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by flash chromatography (30.0 g silica, 10% MeOH/DCM) to obtain **20** (10 mg, 20.8%). R_f = 0.13 (10% MeOH/DCM, visualized w/ $KMnO_4$). ^{1}H NMR (700 MHz, $CDCl_3$): δ= 7.18– 7.11 (m, 1H), 6.80 (br s, 1H), 5.34 (p, *J* = 5.8, 5.4 Hz, 4H), 5.22 (br s, 1H), 4.35 (t, *J* = 11.2 Hz, 1H), 4.12 (br s, 1H), 3.91 (br s, 2.5H), 3.54–3.48 (m, 2.5H), 3.15 (q, *J* = 7.3 Hz, 2H), 2.54 (m, 3.5H), 2.30– 2.28 (m, 7.5H), 2.00 (q, *J* = 6.6 Hz, 8H), 1.93–1.92 (m, 2H), 1.62–1.57 (m, 4H), 1.47–1.43 (m, 1H), 1.39 (s, 9H), 1.36–1.26 (m, 40H), 0.87 (t, *J* = 7.0 Hz, 6H). ^{13}C NMR (176 MHz, $CDCl_3$): δ= 173.85, 162.78, 130.14, 129.80, 129.79, 129.79, 114.04, 79.98, 70.46, 63.80, 62.89, 54.75, 46.56, 34.35, 34.18, 32.05, 29.92, 29.85, 29.69, 29.48, 29.47, 29.40, 29.38, 29.33, 29.28, 28.59, 27.38, 25.05, 24.98, 22.83, 14.27, 12.35, 8.76. HRMS (ESI): Calcd for $C_{56}H_{98}F_2N_2O_{11}P$ $[M+H]^+$: 1043.6871, found: 1043.6854.



21

To an ice-cold solution of **20** (10.0 mg, 0.009 mmol, 1.0 eq) in DCM (2.0 mL) was added TFA (0.4 mL) and the reaction was allowed to gradually warm to rt over 2 h. The reaction was concentrated *in vacuo* to obtain crude **21** as a TFA salt. One half of this reaction was purified on analytical column using HPLC (75–100% MeOH over 15 mins, flow rate = 1 mL/min) to obtain **21** (2 mg, 40 %) and the other half was used directly without further purification for next reaction. We found the HPLC purification to be extremely challenging as it required multiple rounds of purification with poor separation. ^{1}H NMR (700 MHz, $CDCl_3$): δ= 8.02 (s, 1H), 7.24 (br s, 1H), 6.88 (br s, 1H), 5.34 (p, *J* = 5.8, 5.4 Hz, 4H), 5.22 (br s, 1H), 4.34 (d, *J* = 11.8, 1H), 4.13 (dd, *J* = 12.2, 6.5 Hz, 1H), 3.99–3.96 (m, 5H), 3.58 (br s, 1H), 3.44 (br s, 2H), 3.32 (br s, 1H), 2.75–2.72 (m, 1H), 2.65–2.59 (m, 3H), 2.35–2.28 (m, 6H), 2.11 (br s, 1.5H),

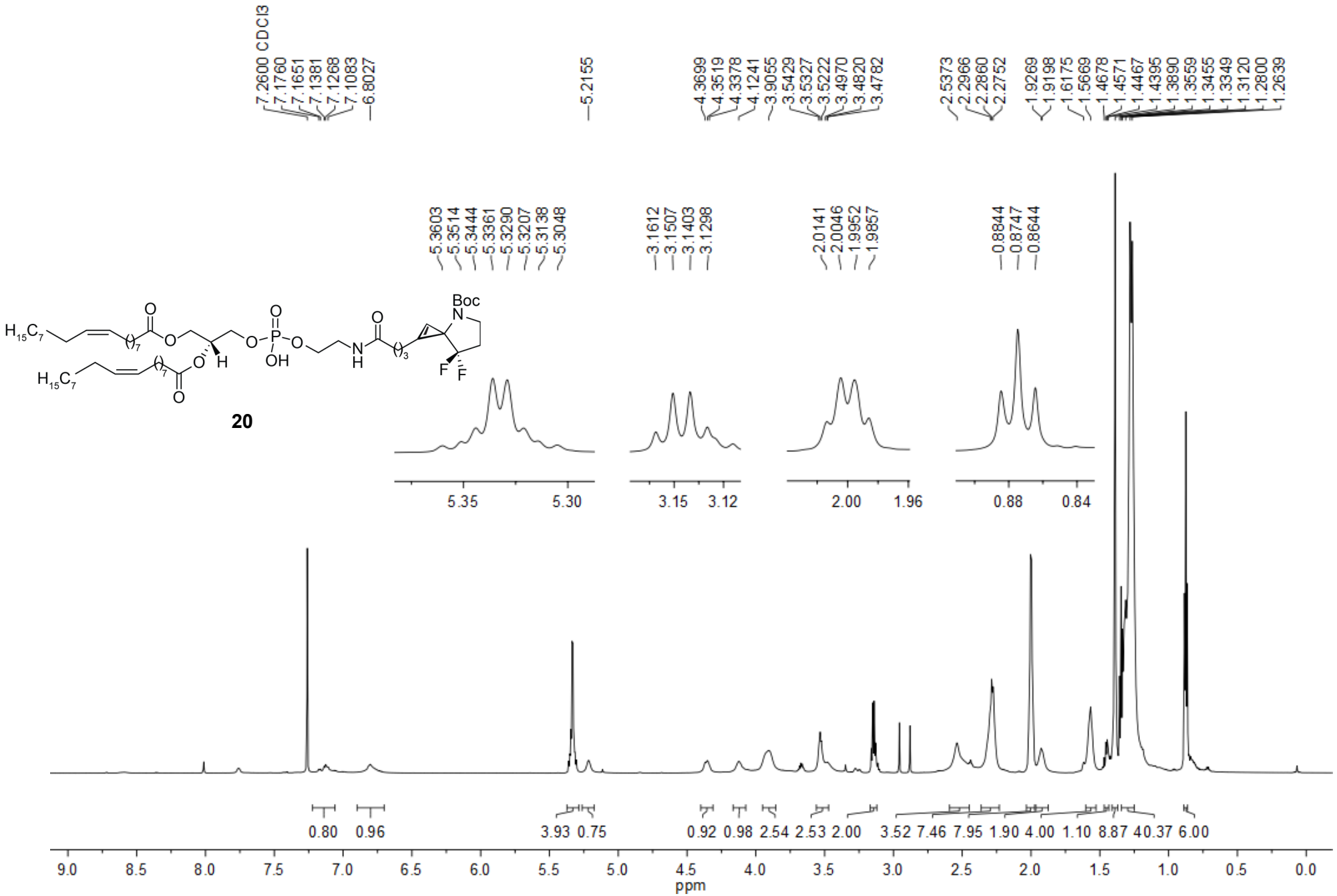
2.00 (d, *J* = 6.7 Hz, 8H), 1.59 (d, *J* = 6.9 Hz, 5H), 1.32–1.27 (m, 40H), 0.88 (t, *J* = 7.0 Hz, 6H). ^{13}C NMR (176 MHz, $CDCl_3$): δ= 173.68, 173.44, 173.31, 162.85, 130.18, 129.82, 129.80, 123.88, 119.77, 99.96, 70.01, 69.97, 65.44, 64.41, 62.34, 62.29, 40.41, 39.49, 36.74, 34.90, 34.33, 34.17, 33.63, 32.06, 31.67, 29.91, 29.88, 29.68, 29.47, 29.43, 29.37, 29.30, 29.26, 29.22, 27.37, 27.33, 25.00, 24.97, 22.83, 22.16, 22.13, 14.27. HRMS (ESI): Calcd for $C_{51}H_{89}F_2N_2O_9P$ [M+H]$^+$: 943.6347, found: 943.6329.



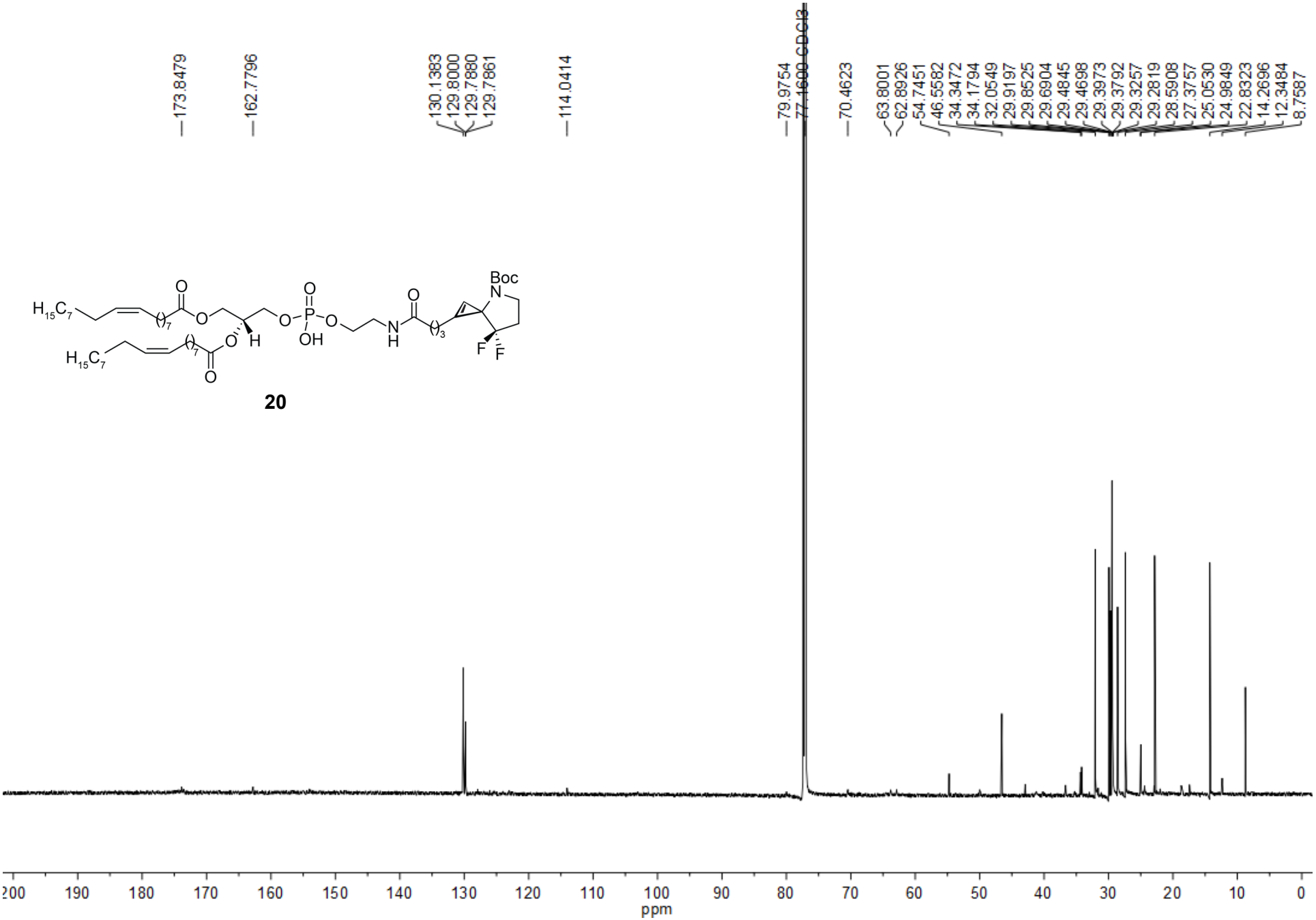
22

To an ice-cold suspension of the second half of crude TFA salt **21,** obtained from the previous step, in MeCN (3.0 mL) and water (1.0 mL) was added aq. $NaHCO_3$ (20 mg, 0.6 mL H_2O, reaction pH ~ 8.5). To this reaction mixture was added Nvoc-Cl (3.04 mg, 0.011 mmol, 1.2 eq) and the reaction was allowed to warm up to rt overnight under dark. The reaction was extracted using DCM and water. The combined organic layer was dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and subjected to HPLC purification (50–100% MeOH over 15 mins, flow rate = 1 mL/min) to obtain **22** (2 mg, 38.4% over two steps). R_f = 0.18 (10% MeOH/DCM, visualized w/ UV). HRMS (ESI): Calcd for $C_{61}H_{99}F_2N_3O_{15}P$ [M+H]$^+$: 1182.6776, found: 1182.6803.

^{1}H NMR (700 MHz)



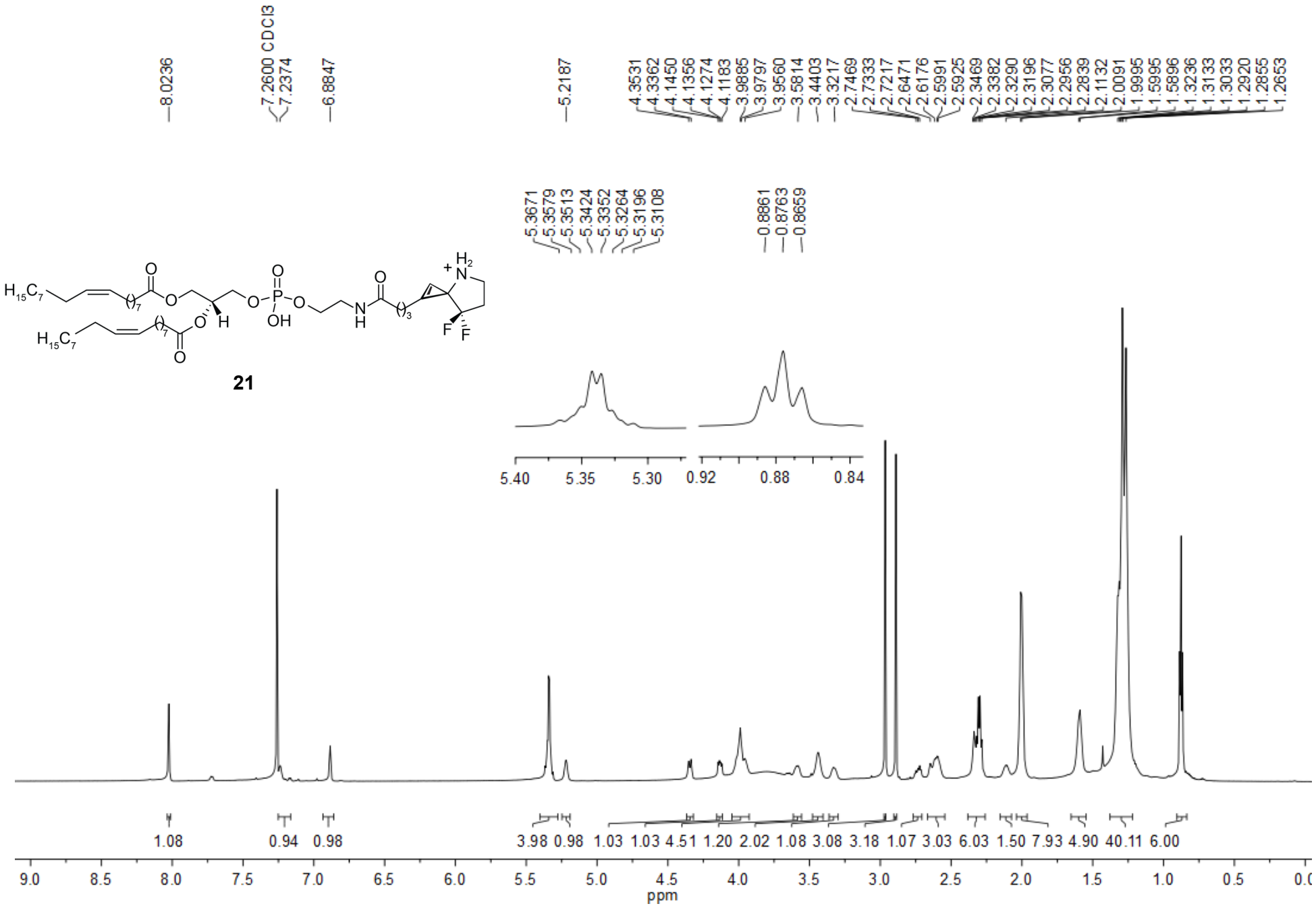
^{13}C NMR (176 MHz)



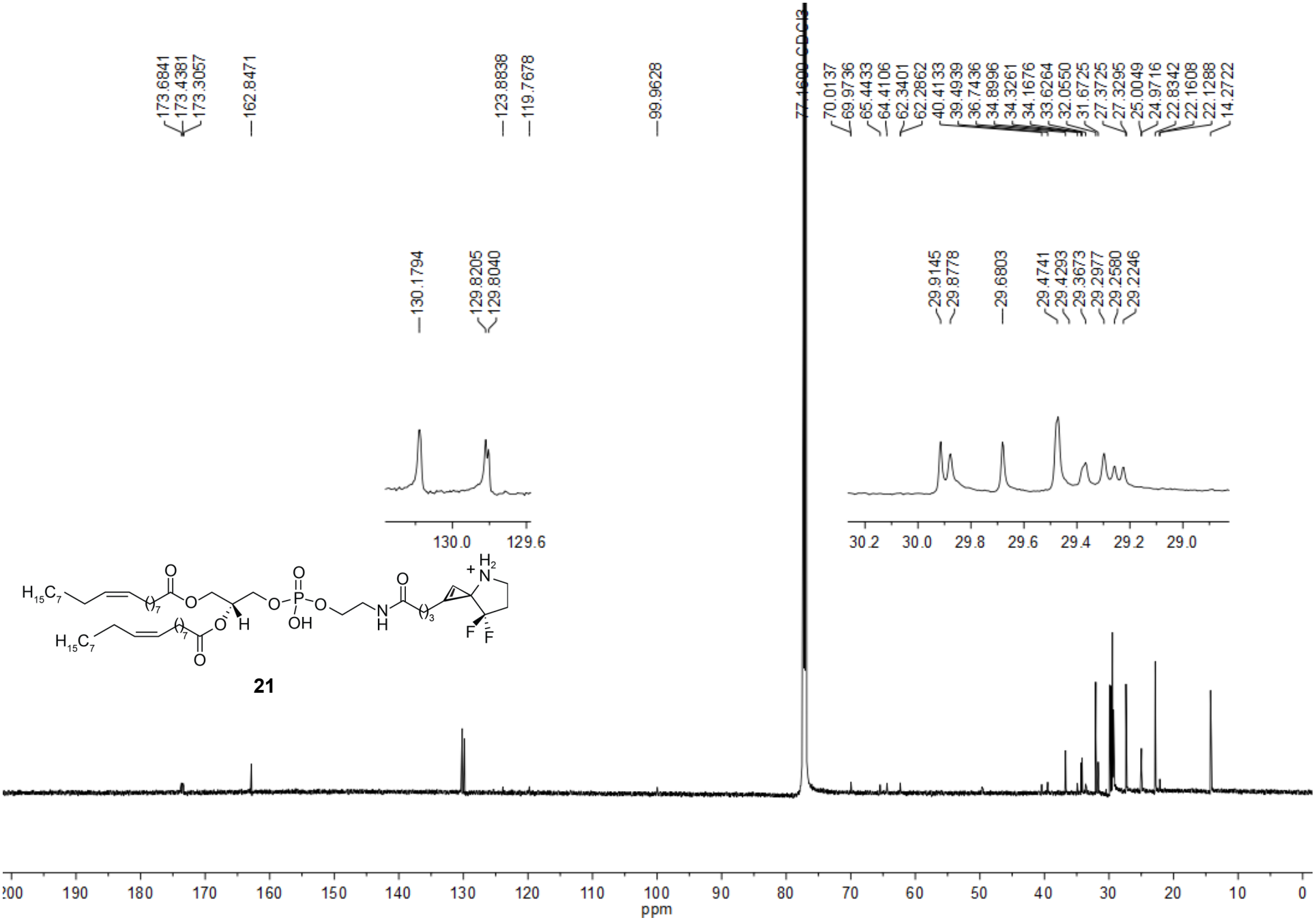
20

[S42]

^{1}H NMR (700 MHz)



^{13}C NMR (176 MHz)



21

[S44]

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