Scalable Synthesis of Cyclocitrinol

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Supporting Information

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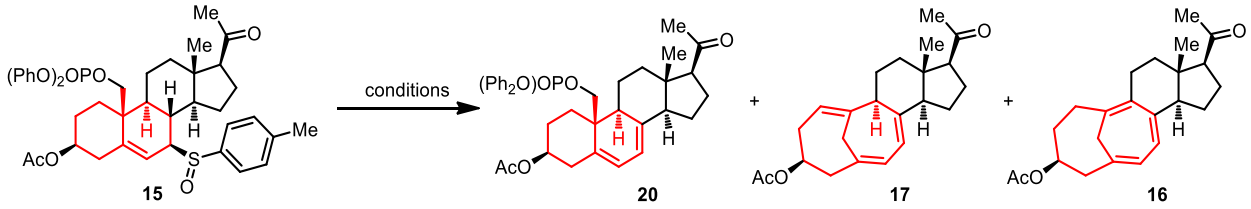
1. General experimental

All reactions utilizing air- or moisture-sensitive reagents were carried out in flame-dried glassware under an argon atmosphere, unless otherwise stated. Dry tetrahydrofuran (THF), dichloromethane (DCM), toluene (PhMe), diethyl ether (Et_2O) were obtained by passing the HPLC grade or pre-dried solvents through activated alumina columns. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin layer chromatography (TLC) with 0.15-0.2 mm pre-coated silica gel (10-40 μm) plates, using UV light as the visualizing agent or ethanolic phosphomolybdic acid and heating as developing agents. Flash chromatography was performed with silica gel (200-300 mesh) under pressure. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous material, unless otherwise stated. NMR spectra were recorded on Bruker-400 spectrometers and were calibrated using residual undeuterated solvent as an internal reference ($CDCl_3$ ^{1}H NMR δ = 7.26 ppm, ^{13}C NMR δ = 77.2 ppm; DMSO-d_6 ^{1}H NMR δ = 2.50 ppm, ^{13}C NMR δ = 39.5 ppm). The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. IR spectra were collected on Avatar 330 FT-IR spectrometer. Melting points were determined on SGW X-4 microscopic melting point apparatus and were uncorrected. Optical rotations were determined on JASCO P-1030 Polarimeter in the solvent indicated. High-resolution mass spectra were recorded on IonSpec 4.7 Tesla FTMS or Bruker Daltonics, Inc. APEXIII 7.0 TESLA FTMS.

2. Optimization of the key biomimetic cascade rearrangement.

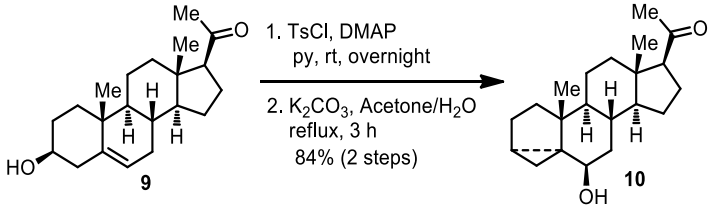
Table S1. Optimization of the key biomimetic cascade rearrangement.



entry	base (2 equiv)	solvent	temp. (°C)	concentration (mol/L)	time (h)	^{1}H NMR ratio (**20**:**17**:**16**)[a]
1	-	toluene	70	0.02	5	**16** only
2	Et_3N	toluene	70	0.02	12	81:15:4
3	DIPEA	toluene	70	0.02	12	73:19:8
4	Proton sponge	toluene	70	0.02	12	75:18:7
5	HMTA	toluene	70	0.02	12	76:18:6
6	Pyridine	toluene	70	0.02	12	33:19:48
7	DABCO	toluene	70	0.02	12	77:18:5
8	DABCO	toluene	100	0.02	5.5	0:67:33
9	DABCO	MeCN	100	0.02	2.5	0:17:83
10	DABCO	DMF	100	0.02	1.5	complex
11	DABCO	chlorobenzene	120	0.02	1.5	0:71:29
12	DABCO	*o*-DCB	120	0.02	1	0:67:33
13	DABCO	DCE	120	0.02	5	0:23:77
14	DABCO	CCl_4	120	0.02	6	0:47:53
15	DABCO	dioxane	120	0.02	1	0:57:43
16	DABCO	anisole	120	0.02	1	0:68:32
17	DABCO	toluene	130	0.02	1.5	0:77:23
18[b]	DABCO	toluene	130	0.03	2	0:70:30
19[b]	DABCO	toluene	130	0.01	2	0:80:20
20[b]	DABCO	toluene	130	0.005	2	0:84:16
21[b]	DABCO	toluene	130	0.0025	2	0:86:14
22[b]	*O*-methylquinine	toluene	130	0.0025	2	0:89:11 (57%)[c]
23[b]	*O*-methylquinidine	toluene	130	0.0025	2	0:88:12
24[b]	*O*-methylhydroquinine	toluene	130	0.0025	2	0:89:11
25[b]	*O*-methylhydroquinidine	toluene	130	0.0025	2	0:89:11
26[b]	*O*-methylcinchonidine	toluene	130	0.0025	2	0:85:15

[a]determined by ^{1}H NMR of the crude reaction mixture. [b]**15** was used as crude mixture from *m*-CPBA oxidation. [c]Isolated yield of **17** shown in parenthesis. DIPEA, diisopropylethylamine; proton sponge, 1,8-bis(dimethylamino)naphthalene; HMTA = hexamethylenetetramine; DABCO, 1,4-diazabicyclo[2.2.2]octane; DMF, *N,N*-dimethylformamide; DCB, 1,2-dichlorobenzene; DCE, 1,2-dichloroethane.

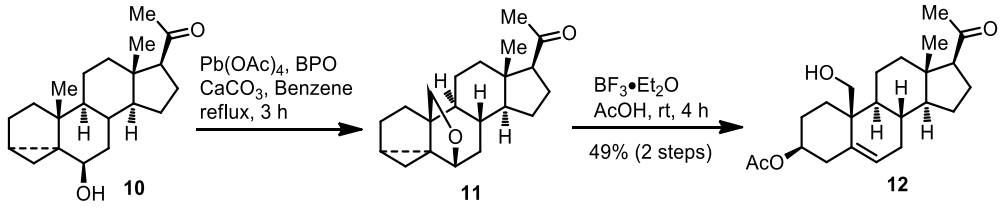
3. Experimental procedures and characterization data for compounds 10-20.



To a solution of pregnenolone **9** (10 g, 31.6 mmol, 1.0 equiv) in pyridine (80 mL) was added recrystallized TsCl (18.1 g, 94.9 mmol, 3.0 equiv) and DMAP (1.9 g, 15.8 mmol, 0.5 equiv). The reaction mixture was stirred at room temperature overnight and poured into ice water. The solid was filtered and the filtrate was washed with water and dried to give the crude tosylate, which was used in the next step without further purification.

A solution of the crude tosylate and K_2CO_3 (13.1 g, 94.8 mmol, 3.0 equiv) in acetone/H_2O (525 mL, 4:1) was refluxed for 3 h. Acetone was removed under reduced pressure and the crude product was extracted with DCM (3×100 mL). The combined organic layers were washed with brine (100 mL) and dried over Na_2SO_4. Concentration under reduced pressure afforded the crude product, which was purified by flash chromatography (SiO_2, 5:1→3:1 petroleum ether:EtOAc) to provide compound **10** (8.4 g, 84%) as a white solid and recovered pregnenolone **9** (0.6 g, 6%).

The ^1H NMR of compound **10** was in accordance with that reported in the literature.[1]



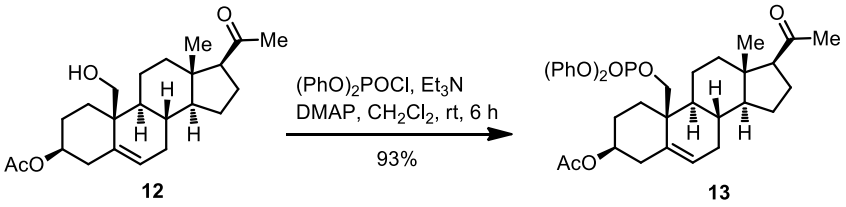
To a solution of **10** (4.0 g, 12.6 mmol, 1.0 equiv) and $CaCO_3$ (3.6 g, 31.5 mmol, 2.5 equiv) in dry benzene (640 mL) was added $Pb(OAc)_4$ (5.6 g, 12.6 mmol, 1.0 equiv) and BPO (610 mg, 2.52 mmol, 0.2 equiv). After the reaction mixture was refluxed for 1 h, $Pb(OAc)_4$ (5.6 g×2, 12.6 mmol×2, 1.0 equiv×2) and BPO (610 mg×2, 2.52 mmol×2, 0.2 equiv×2) were added in two portions every 1 h. After being refluxed for additional 2 h, the mixture was then filtered through celite and the

filtrate was washed with saturated aq. Na_2SO_3, aq. $NaHCO_3$ (5%), brine and dried over Na_2SO_4. Concentration under reduced pressure afforded the crude product, which was used in the next step without further purification.

To a solution of the crude product in 186 mL AcOH was added distilled $BF_3 \cdot Et_2O$ (80 μL, 1.26 mmol, 0.1 equiv). After stirred for 4 h at room temperature, the reaction mixture was poured into 80 mL H_2O and extracted with DCM (3×100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (SiO_2, 5:1→3:1 petroleum ether:EtOAc) to provide compound **12** (2.3 g, 49%) as a white solid.

Compound 11: TLC (petroleum ether:EtOAc, 5:1 v/v): R_f = 0.35; $[\alpha]_D^{29}$ +29.1 (*c* 0.45, $CHCl_3$);^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (d, *J* = 7.2 Hz, 1H), 3.89 (d, *J* = 4.8 Hz, 1H), 3.43 (d, *J* = 7.2 Hz, 1H), 2.52 (t, *J* = 9.0 Hz, 1H), 2.11 (s, 3H), 0.76 (dd, *J* = 4.5, 2.3 Hz, 1H), 0.69 (s, 3H), 0.30 (dd, *J* = 7.5, 4.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.5, 76.5, 70.8, 63.7, 55.9, 55.2, 47.8, 47.0, 44.7, 39.3, 35.6, 34.5, 33.5, 31.4, 23.7, 23.5, 23.0, 20.6, 15.6, 13.8, 12.7; IR (KBr): ν = 2930, 2849, 1704, 1459, 1385, 1188, 1050, 800 cm^{-1}; HRMS (ESI, *m/z*): $[M+H]^+$ calcd for $C_{21}H_{31}O_2$, 315.2319; found, 315.2319.

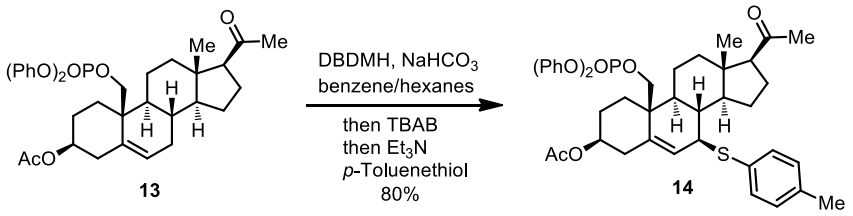
The ^{1}H NMR of compound **12** was in accordance with that reported in the literature.[2]



To a solution of **12** (6.9 g, 18.4 mmol, 1.0 equiv) in dry DCM (90 mL) was added successively Et_3N (10.2 mL, 73.6 mmol, 4.0 equiv), $(PhO)_2POCl$ (7.6 ml, 36.7 mmol, 2.0 equiv) and DMAP (0.22 g, 1.84 mmol, 0.1 equiv) at room temperature. After stirred at this temperature for 6 h, the reaction mixture was quenched with sat. aq. $NaHCO_3$ (60 mL) and extracted with DCM (3×100 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. Removal of the solvent under reduced pressure and purification by flash chromatography (SiO_2, 5:1 petroleum

ether:EtOAc) furnished compound **13** as a white solid (10.6 g, 93%).

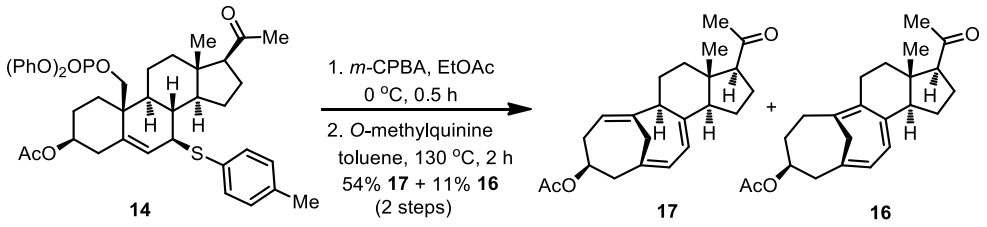
Compound 13: mp: 111.6 – 112.3 °C; TLC (petroleum ether:acetone, 4:1 v/v): R_f = 0.52; $[\alpha]_D^{25}$ – 1.9 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.26 (m, 4H), 7.24 – 7.16 (m, 6H), 5.59 (d, *J* = 4.9 Hz, 1H), 4.66 – 4.55 (m, 1H), 4.48 (dd, *J* = 10.7, 5.0 Hz, 1H), 4.19 (dd, *J* = 10.7, 4.1 Hz, 1H), 2.50 – 2.44 (m, 1H), 2.43 – 2.36 (m, 1H), 2.10 (s, 3H), 2.02 (s, 3H), 0.50 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.4, 170.5, 150.50 (d, J_{C-P} = 7.4 Hz), 150.48 (d, J_{C-P} = 7.4 Hz), 133.4, 129.8, 129.7, 127.4, 125.4, 125.3, 119.92 (d, J_{C-P} = 5.0 Hz), 119.91 (d, J_{C-P} = 5.0 Hz), 73.0, 68.4 (d, J_{C-P} = 7.1 Hz), 63.5, 57.3, 49.7, 43.9, 40.5 (d, J_{C-P} = 8.1 Hz), 38.9, 37.9, 32.5, 32.4, 31.5, 31.1, 27.6, 24.1, 22.7, 21.7, 21.3, 13.2; IR (KBr): ν = 2938, 2854, 1730, 1700, 1590, 1491, 1447, 945 cm^{-1}; HRMS (ESI, *m/z*): $[M+Na]^+$ calcd for $C_{35}H_{43}O_7NaP$, 629.2639; found, 629.2631.



A flame-dried 250 mL three-necked flask equipped with a stir bar was charged with hexanes/benzene (120 mL, 1:1) and bubbled with Ar for 15 min before **13** (3 g, 4.95 mmol, 1.0 equiv), DBDMH (0.85 g, 3.0 mmol, 0.6 equiv) and $NaHCO_3$ (2 g, 24.7 mmol, 5.0 equiv) were added. After being refluxed at 80 °C for 1 h, the reaction mixture was cooled to room temperature and TBAB (0.1 M in THF, 10 mL, 1.0 mmol, 0.2 equiv) was added. After another 1 h at room temperature, Et_3N (1.38 mL, 10.0 mmol, 2.0 equiv) and *p*-toluenethiol (1.23 g, 10.0 mmol, 2.0 equiv) were added. The reaction mixture was stirred at room temperature for 1 h and quenched with sat. aq. $NaHCO_3$ and extracted with EtOAc (100 mL). The aqueous phase was further extracted with EtOAc (3×100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, 8:1→5:1 petroleum ether:EtOAc) to furnish compound **14** as a white solid (2.9 g, 80%).

Compound 14: mp: 123.9 – 125.4 °C; TLC (petroleum ether:EtOAc, 2:1 v/v): R_f = 0.59; $[\alpha]_D^{25}$

+73.7 (*c* 0.80, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.29 (m, 4H), 7.26 – 7.15 (m, 8H), 7.09 – 7.03 (m, 2H), 5.59 (br s, 1H), 4.61 – 4.51 (m, 1H), 3.81 (dd, *J* = 11.1, 4.4 Hz, 1H), 3.43 (dd, *J* = 11.1, 3.7 Hz, 1H), 3.22 (d, *J* = 8.3 Hz, 1H), 2.49 (t, *J* = 9.3 Hz, 1H), 2.46 – 2.38 (m, 1H), 2.27 (s, 3H), 2.11 (s, 3H), 2.01 (s, 3H), 0.60 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.5, 170.6, 150.6 (d, $J_{C\text{-}P}$ = 7.4 Hz), 150.5 (d, $J_{C\text{-}P}$ = 7.4 Hz), 138.6, 135.3, 135.2, 130.0, 129.92, 129.88, 129.6, 129.1, 125.54, 125.49, 120.13 (d, $J_{C\text{-}P}$ = 4.8 Hz), 120.08 (d, $J_{C\text{-}P}$ = 4.9 Hz), 72.4, 67.1 (d, $J_{C\text{-}P}$ = 7.1 Hz), 63.2, 57.4, 50.8, 49.3, 44.9, 40.9 (d, $J_{C\text{-}P}$ = 8.4 Hz), 39.3, 37.6, 36.9, 31.7, 30.8, 27.3, 26.9, 23.4, 22.6, 21.4, 21.2, 13.6; IR (KBr): ν = 2945, 2872, 1732, 1702, 1590, 1489, 1456, 952 cm^{-1}; HRMS (ESI, *m/z*): $[M+Na]^+$ calcd for $C_{42}H_{49}O_7NaPS$, 751.2829; found, 751.2823.



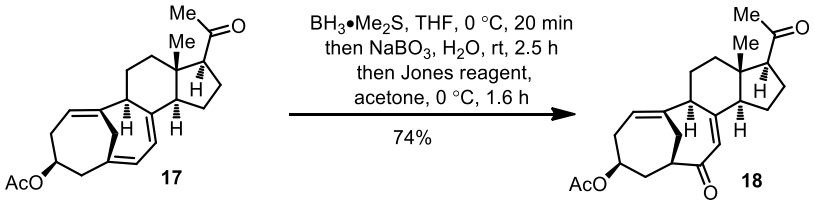
To a solution of **14** (1.0 g, 1.37 mmol, 1.0 equiv) in EtOAc (50 mL) was added 85% *m*-CPBA (0.3 g, 1.44 mmol, 1.05 equiv) at 0 °C. After stirred at this temperature for 0.5 h, the reaction mixture was quenched with sat. aq. Na_2SO_3 and the aqueous phase was extracted with EtOAc (3×40 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. Removal of the solvent under reduced pressure afforded the crude diastereomeric mixture of sulfoxides **15** which was used in the next step without further purification.

To the crude sulfoxides **15** in toluene (550 mL, 0.0025 M) was added *O*-methylquinine (0.93 g, 2.74 mmol, 2.0 equiv). After heated at 130 °C for 2 h, the reaction mixture was cooled to room temperature and concentrated in *vacuo* to afford the crude product which was purified by flash chromatography (SiO_2, 30:1 petroleum ether:EtOAc) to furnish compound **17** (0.264 g, 54%) and **16** (0.054 g, 11%) as a white solid.

Compound 17: mp: 117.8 – 120.1 °C; TLC (petroleum ether:EtOAc, 9:1 v/v): R_f = 0.35; $[\alpha]_D^{20}$

+1126.1 (*c* 0.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.61 (d, *J* = 5.4 Hz, 1H), 5.45 (d, *J* = 5.4 Hz, 1H), 4.94 (t, *J* = 6.8 Hz, 1H), 4.61 – 4.52 (m, 1H), 3.04 (d, *J* = 11.2 Hz, 1H), 2.90 (dd, *J* = 11.0, 5.4 Hz, 1H), 2.13 (s, 3H), 2.02 (s, 3H), 1.51 – 1.42 (m, 1H), 0.62 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.2, 170.1, 149.7, 143.8, 139.3, 120.3, 118.4, 115.2, 74.4, 63.7, 56.4, 52.3, 46.6, 46.1, 38.9, 35.7, 32.6, 31.5, 30.6, 23.6, 22.3, 21.4, 13.5; IR (KBr): ν = 2937, 2852, 1732, 1701, 1636, 1558, 1238, 882 cm^{-1}; HRMS (ESI, *m/z*): $[M+Na]^+$ calcd for $C_{23}H_{30}O_3Na$, 377.2087; found, 377.2088.

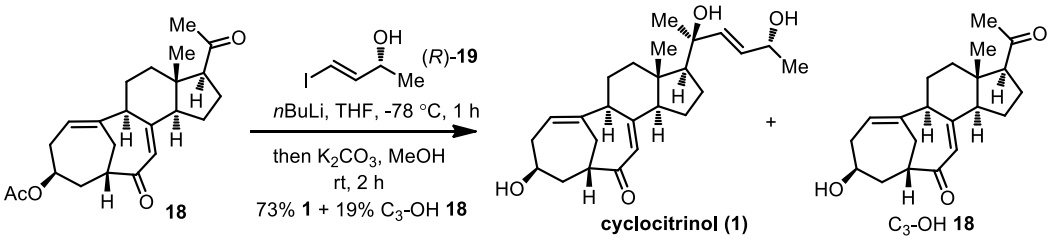
Compound 16: mp: 140.3 – 142.8 °C; TLC (petroleum ether:EtOAc, 9:1 v/v): R_f = 0.30; $[\alpha]_D^{27}$ +79.4 (*c* 0.83, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.18 (d, *J* = 6.0 Hz, 1H), 5.84 (d, *J* = 6.0 Hz, 1H), 4.29 – 4.23 (m, 1H), 2.90 (d, *J* = 9.4 Hz, 1H), 2.86 – 2.77 (m, 1H), 2.73 (t, *J* = 9.3 Hz, 1H), 2.15 (s, 3H), 2.02 (s, 3H), 1.92 – 1.76 (m, 2H), 1.67 (d, *J* = 12.6 Hz, 1H), 1.59 (d, *J* = 4.2 Hz, 1H), 1.46 (qd, *J* = 11.9, 6.4 Hz, 1H), 0.65 (d, *J* = 9.4 Hz, 1H), 0.44 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.4, 170.3, 142.4, 129.8, 122.9, 121.7, 106.9, 105.3, 73.7, 63.7, 51.8, 44.0, 41.1, 36.8, 34.8, 31.2, 30.5, 27.8, 24.5, 23.9, 23.7, 21.5, 16.6; IR (KBr): ν = 2962, 2878, 1732, 1700, 1558, 1541, 1240, 796 cm^{-1}; HRMS (ESI, *m/z*): $[M+H]^+$ calcd for $C_{23}H_{31}O_3$, 355.2268; found, 355.2267.



To a stirred solution of **17** (1.06 g, 3.0 mmol, 1.0 equiv) in dry THF (65 mL) at 0 °C was added 92% $BH_3 \cdot Me_2S$ (0.53 mL, 5.23 mmol, 1.74 equiv). After 10 min, another portion of 92% $BH_3 \cdot Me_2S$ (0.23 mL, 2.27 mmol, 0.76 equiv) was added and stirring was continued for another 10 min at the same temperature. H_2O (12 mL) was added to the reaction system, followed by $NaBO_3 \cdot 4H_2O$ (0.92 g, 6.0 mmol, 2.0 equiv), and the resulting mixture was allowed to warm to room temperature and stirred for 2.5 h. Acetone (130 mL) was then added and the reaction mixture was treated with Jones reagent (9.2 mL, 2.6 M, 24.0 mmol, 8.0 equiv) at 0 °C. After 40 min at the

same temperature, another portion of Jones reagent (2.3 mL, 2.6 M, 6.0 mmol, 2.0 equiv) was added. The reaction mixture was stirred for 1 h at 0 °C and quenched with isopropanol (50 mL). The mixture was then filtered through celite and the filtrate was concentrated in *vacuo*. The resulting residue was extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. Removal of the solvent under reduced pressure afforded the crude product which was purified by flash chromatography (SiO_2, 6:1→4:1 petroleum ether:EtOAc) to furnish compound **18** (0.82 g, 74%) as a white solid.

Compound 18: mp: 162.3 – 163.9 °C; TLC (petroleum ether:EtOAc, 2:1 v/v): R_f = 0.57; $[\alpha]_D^{25}$ +158.3 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.63 (dd, *J* = 8.0, 6.8 Hz, 1H), 5.61 (s, 1H), 4.56 – 4.47 (m, 1H), 2.87 – 2.79 (m, 2H), 2.78 – 2.68 (m, 2H), 2.59 – 2.54 (m, 2H), 2.15 (s, 3H), 2.00 (s, 3H), 0.63 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.6, 204.0, 170.0, 155.8, 145.9, 125.5, 121.8, 67.2, 63.4, 55.7, 53.6, 48.3, 46.5, 38.0, 37.5, 32.7, 31.4, 27.55, 27.53, 23.2, 22.5, 21.4, 13.8; IR (KBr): ν = 2934, 2854, 1734, 1701, 1666, 1617, 1251, 759 cm^{-1}; HRMS (ESI, *m/z*) $[M+Na]^+$ calcd for $C_{23}H_{30}O_4Na$, 393.2036; found, 393.2038.

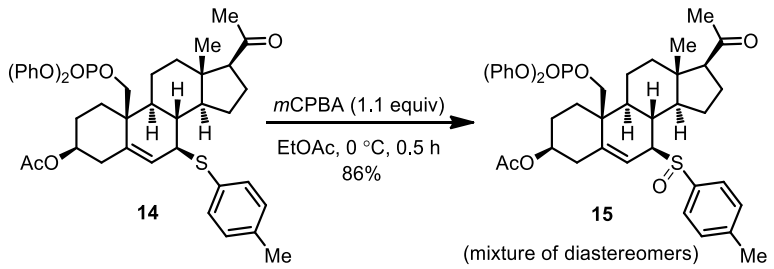


To a stirred solution of (*R*)-vinyl iodide **19** (140 mg, 0.70 mmol, 5.0 equiv) in 2 mL dry THF was added *n*-BuLi (0.62 mL, 2.26 M in hexanes, 1.4 mmol, 10.0 equiv) at -78 °C. The reaction mixture was stirred for 30 min at the same temperature before it was treated with a solution of ketone **18** (52 mg, 0.14 mmol, 1.0 equiv) in THF (2 mL) and stirred for 0.5 h until it was quenched with MeOH (6 mL). The mixture was allowed to warm to room temperature and K_2CO_3 (96 mg, 0.70 mmol, 5.0 equiv) was added. After stirring was continued for 2 h at the same temperature, the resulting mixture was concentrated and the residue was treated with sat. aq. NH_4Cl (2.5 mL) and diluted with EtOAc (10 mL). The layers were separated, and the aqueous phase was extracted with

EtOAc (3×5 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4. Removal of the solvent under reduced pressure afforded the crude product which was purified by flash chromatography (SiO_2, 2:1→1:1 petroleum ether:EtOAc to 50:1→30:1 DCM:MeOH) to furnish compound C_3-OH **18** (9 mg, 19%) and cyclocitrinol (**1**) (41 mg, 73%) as a white solid.

cyclocitrinol (1): mp: 177.5 – 179.9 °C; TLC (DCM:MeOH, 19:1 v/v): R_f = 0.32; $[\alpha]_D^{25}$ +138.2 (*c* 0.3, MeOH); ^{1}H NMR (600 MHz, DMSO-*d*$_6$) δ 5.63 (dd, *J* = 15.6, 1.3 Hz, 1H), 5.53 (dd, *J* = 8.3, 6.3 Hz, 1H), 5.49 (dd, *J* = 15.6, 5.4 Hz, 1H), 5.37 (s, 1H), 4.61 (d, *J* = 4.4 Hz, 1H), 4.57 (d, *J* = 4.6 Hz, 1H), 4.21 (s, 1H), 4.11 – 4.06 (m, 1H), 3.13 – 3.08 (m, 1H), 2.78 (dd, *J* = 12.1, 5.5 Hz, 1H), 2.33 (ddd, *J* = 13.1, 11.2, 6.3 Hz, 1H), 1.20 (s, 3H), 1.09 (d, *J* = 6.4 Hz, 3H), 0.71 (s, 3H); ^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ 204.1, 157.1, 145.7, 136.0, 130.8, 124.5, 122.0, 73.3, 66.3, 63.1, 60.1, 55.3, 53.2, 48.1, 45.9, 41.4, 38.9, 36.0, 28.9, 27.5, 27.2, 24.1, 22.3, 22.1, 14.4; IR (KBr): ν = 3396, 2948, 2871, 1645, 1616, 1367, 1030, 735 cm^{-1}; HRMS (ESI, *m/z*) $[M+H]^+$ calcd for $C_{25}H_{37}O_4$, 401.2686; found, 401.2687.

Compound C$_3$-OH 18: mp: 181.7 – 183.4 °C; TLC (petroleum ether:EtOAc, 1:1 v/v): R_f = 0.43; $[\alpha]_D^{27}$ +154.2 (*c* 0.33, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.62 – 5.55 (m, 2H), 3.55 – 3.43 (m, 1H), 2.89 (brd, *J* = 12.7 Hz, 1H), 2.81 (dd, *J* = 12.2, 5.4 Hz, 1H), 2.77 – 2.68 (m, 2H), 2.58 – 2.43 (m, 3H), 2.15 (s, 3H), 1.91 – 1.52 (m, 9H), 0.63 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.8, 205.0, 156.1, 145.6, 125.7, 122.5, 64.6, 63.6, 55.9, 53.9, 48.7, 46.7, 41.7, 38.2, 35.8, 31.6, 27.7, 27.7, 23.3, 22.6, 13.9; IR (KBr): ν = 3445, 2949, 2869, 1700, 1684, 1617, 1178, 868 cm^{-1}; HRMS (ESI, *m/z*) $[M+H]^+$ calcd for $C_{21}H_{29}O_3$, 329.2111; found, 329.2109.

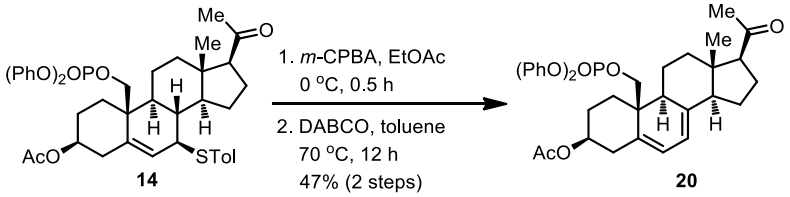


To a solution of **14** (300 mg, 0.41 mmol, 1.0 equiv) in EtOAc (10 mL) was added 85% *m*-CPBA (93 mg, 0.45 mmol, 1.1 equiv) at 0 °C. After stirred at this temperature for 0.5 h, the reaction mixture was quenched with sat. aq. Na_2SO_3 and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. Removal of the solvent under reduced pressure afforded the crude product which was purified by flash chromatography (SiO_2, 3:1→2:1→1:1 petroleum ether:EtOAc) to furnish **15**-major isomer (210 mg, 68%) and **15**-minor isomer (55 mg, 18%) as white foam.

Compound 15-minor isomer: mp 80.5 – 81.9 °C; TLC (petroleum ether:EtOAc, 2:1 v/v): R_f = 0.25; $[\alpha]_D^{24}$ +234.2 (*c* 0.92, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.15 (m, 14H), 4.89 (s, 1H), 4.53 – 4.45 (m, 1H), 4.39 (d, *J* = 4.4 Hz, 2H), 3.00 (d, *J* = 8.5 Hz, 1H), 2.42 (s, 3H), 2.13 (s, 3H), 1.99 (s, 3H), 1.49 – 1.41 (m, 1H), 1.37 – 1.30 (m, 1H), 1.16 – 1.09 (m, 1H), 1.03 – 0.95 (m, 1H), 0.59 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.8, 170.6, 150.51 (d, $J_{C\text{-}P}$ = 7.4 Hz), 150.47 (d, $J_{C\text{-}P}$ = 7.2 Hz), 145.0, 141.0, 138.3, 129.79, 129.78, 129.77, 125.4, 125.3, 124.0, 120.17 (d, $J_{C\text{-}P}$ = 5.3 Hz), 120.12 (d, $J_{C\text{-}P}$ = 5.3 Hz), 118.0, 72.1, 68.2 (d, $J_{C\text{-}P}$ = 8.0 Hz), 67.0, 62.9, 57.1, 50.4, 44.7, 40.3 (d, $J_{C\text{-}P}$ = 8.2 Hz), 39.2, 38.2, 33.3, 31.5, 30.3, 27.1, 26.5, 22.9, 22.6, 21.4, 21.3, 13.5; IR (KBr): ν = 2945, 1732, 1702, 1590, 1489, 1456, 1025, 774 cm^{-1}; HRMS (ESI, *m/z*) $[M+Na]^+$ calcd for $C_{42}H_{49}O_8NaPS$, 767.2778; found, 767.2780.

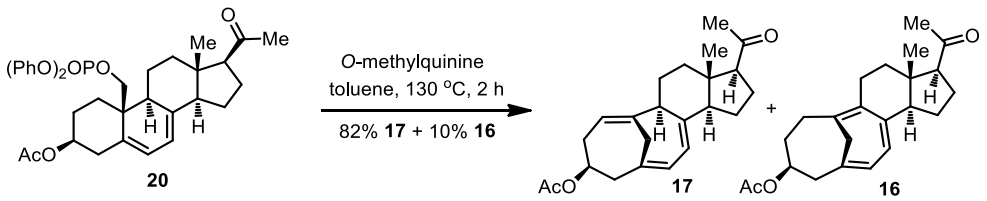
Compound 15-major isomer: mp 79.5 – 80.9 °C; TLC (petroleum ether:EtOAc, 2:1 v/v): R_f = 0.13; $[\alpha]_D^{24}$ +120.8 (*c* 1.04, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.09 (m, 14H), 5.98 (s, 1H), 4.62 – 4.54 (m, 1H), 3.66 – 3.61 (m, 1H), 3.30 (dd, *J* = 11.4, 4.3 Hz, 1H), 2.60 – 2.52 (m, 2H), 2.40 (dd, *J* = 11.4, 3.3 Hz, 1H), 2.30 (s, 3H), 2.13 (s, 3H), 2.04 (s, 3H), 1.21 – 1.11 (m, 1H), 1.10 – 1.02 (m, 1H), 0.91 – 0.81 (m, 1H), 0.63 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.8, 170.3, 150.39 (d, $J_{C\text{-}P}$ = 7.6 Hz), 150.32 (d, $J_{C\text{-}P}$ = 7.6 Hz), 143.2, 141.8, 135.5, 129.9, 129.8, 128.9, 127.1, 125.53, 125.47, 119.9 (d, $J_{C\text{-}P}$ = 4.8 Hz), 119.8 (d, $J_{C\text{-}P}$ = 5.1 Hz), 119.1, 71.8, 65.9 (d, $J_{C\text{-}P}$ = 7.3 Hz), 65.1, 62.8, 56.3, 49.4, 44.3, 40.3 (d, $J_{C\text{-}P}$ = 8.6 Hz), 38.8, 37.6, 32.3, 31.5, 29.5, 27.0, 26.9, 22.9, 22.3, 21.4, 21.3, 13.4; IR (KBr): ν = 2945, 1732, 1701, 1591, 1489, 1456, 1037, 775

cm^{-1}; HRMS (ESI, *m/z*) $[M+Na]^+$ calcd for $C_{42}H_{49}O_8NaPS$, 767.2778; found, 767.2770.



To a solution of **14** (1.0 g, 1.37 mmol, 1.0 equiv) in EtOAc (28 mL) was added 85% *m*-CPBA (0.3 g, 1.44 mmol, 1.05 equiv) at °C. After stirred at this temperature for 0.5 h, the reaction mixture was quenched with sat. aq. Na_2SO_3 and extracted with EtOAc (3×40 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. Removal of the solvent under reduced pressure afforded the crude sulfoxides **15** which was used in the next step without further purification. The crude sulfoxides obtained above were dissolved in 138 mL toluene. DABCO (307 mg, 2.74 mmol, 2.0 equiv) was added and the mixture was heated at 70 °C for 12 h. The reaction mixture was cooled to room temperature and concentrated in *vacuo* to afford the crude product which was purified by flash chromatography (SiO_2, 6:1→5:1 petroleum ether:EtOAc) to furnish compound **20** (388 mg, 47%) as a yellow solid.

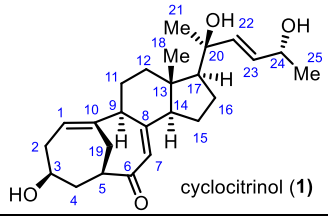
Compound 20: mp: 84.4 – 86.0 °C; TLC (petroleum ether:EtOAc, 1:1 v/v): R_f = 0.52; $[\alpha]_D^{24}$ –8.2 (*c* 0.56, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 4H), 7.22 – 7.15 (m, 6H), 5.70 – 5.65 (m, 1H), 5.32 – 5.27 (m, 1H), 4.73 – 4.63 (m, 1H), 4.34 (dd, *J* = 10.6, 4.4 Hz, 1H), 4.14 (dd, *J* = 10.6, 4.3 Hz, 1H), 2.59 (t, *J* = 8.7 Hz, 1H), 2.55 – 2.46 (m, 1H), 2.35 (t, *J* = 13.0 Hz, 1H), 2.12 (s, 3H), 2.02 (s, 3H), 0.46 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.1, 170.7, 150.67 (d, J_{C-P} = 7.6 Hz), 150.65 (d, J_{C-P} = 7.6 Hz), 140.4, 132.1, 129.89, 129.86, 125.5, 125.4, 124.3, 120.2 (d, J_{C-P} = 5.0 Hz), 120.1 (d, J_{C-P} = 5.0 Hz), 117.1, 72.0, 67.8 (d, J_{C-P} = 7.6 Hz), 63.3, 54.7, 46.0, 44.4, 41.1 (d, J_{C-P} = 7.6 Hz), 38.5, 36.8, 33.2, 31.5, 27.9, 23.2, 22.8, 22.6, 21.5, 13.3; IR (KBr): ν = 2945, 2883, 1731, 1702, 1590, 1489, 1024, 748 cm^{-1}; HRMS (ESI, *m/z*) $[M+Na]^+$ calcd for $C_{35}H_{41}O_7NaP$, 627.2482; found, 627.2482.



To a solution of **20** (20 mg, 0.033 mmol, 1.0 equiv) in toluene (13.2 mL, 0.0025 M) was added *O*-methylquinine (22.4 mg, 0.066 mmol, 2.0 equiv). After heated at 130 °C for 2 h, the reaction mixture was cooled to room temperature and concentrated in *vacuo* to afford the crude product, which was purified by flash chromatography (SiO_2, 30:1 petroleum ether:EtOAc) to furnish compound **17** (9.7 mg, 82%) and **16** (1.2 mg, 10%) as white solids.

4. NMR comparison of synthetic and natural cyclocitrinol

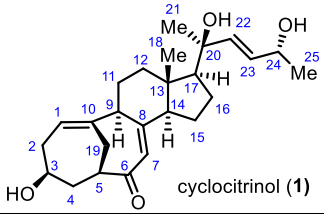
^{1}H NMR data comparison of synthetic and natural cyclocitrinol



cyclocitrinol (**1**)

Position	Natural cyclocitrinol[3] (600 MHz in DMSO-d_6)	Synthetic cyclocitrinol (600 MHz in DMSO-d_6)	Δδ
1	5.53 (dd, J = 8.7, 6.8 Hz)	5.53 (dd, J = 8.3, 6.3 Hz)	0
3	3.11 (m)	3.13 – 3.08 (m)	0
5	2.67 (m)	2.68 – 2.65 (m)	0
7	5.38 (s)	5.37 (s)	0.01
9	2.78 (dd, J = 12.4, 5.5 Hz)	2.78 (dd, J = 12.1, 5.5 Hz)	0
18	0.71 (s)	0.70 (s)	0.01
21	1.20 (s)	1.19 (s)	0.01
22	5.62 (dd, J = 15.6, 1.3 Hz)	5.63 (dd, J = 15.6, 1.3 Hz)	0.01
23	5.49 (dd, J = 15.6, 5.5 Hz)	5.49 (dd, J = 15.6, 5.4 Hz)	0
24	4.10 (m)	4.11 – 4.06 (m)	0.01
25	1.08 (d, J = 6.4 Hz)	1.08 (d, J = 6.4 Hz)	0
3-OH	4.61 (d, J = 4.5 Hz)	4.61 (d, J = 4.4 Hz)	0
24-OH	4.57 (d, J = 4.5 Hz)	4.57 (d, J = 4.6 Hz)	0

^{13}C NMR data comparison of synthetic and natural cyclocitrinol

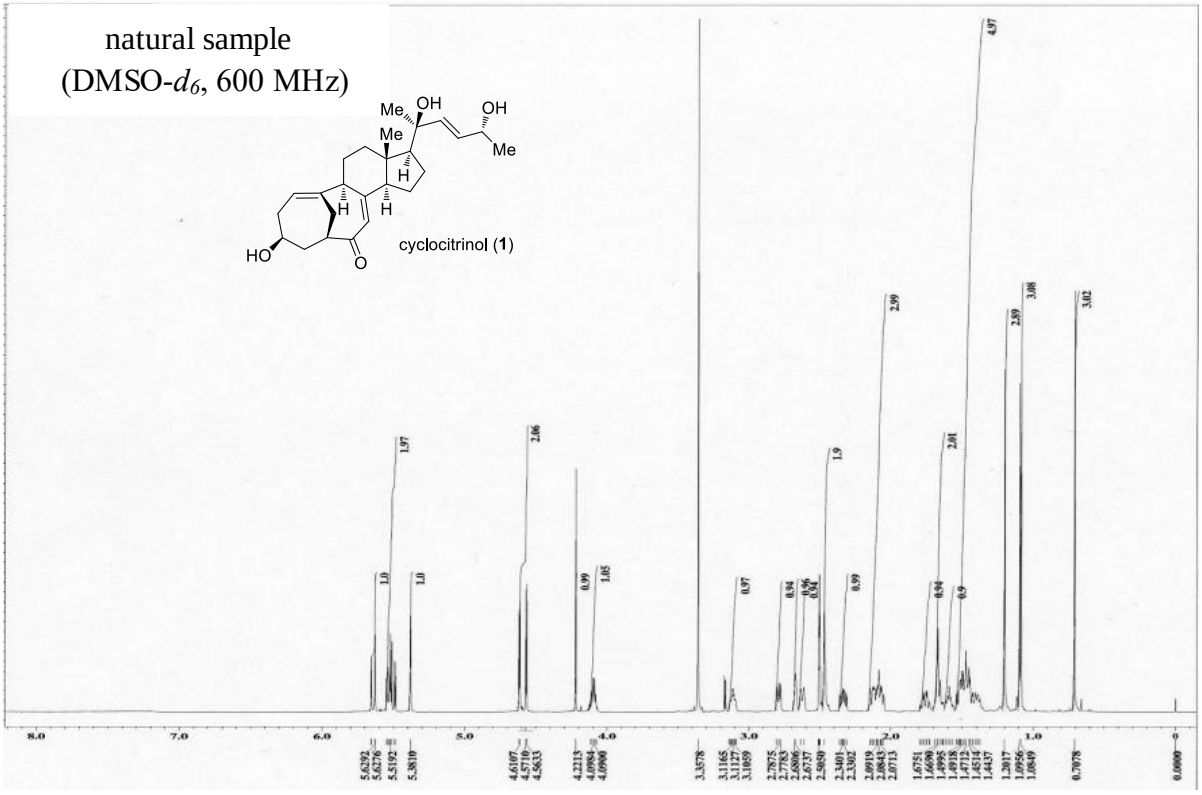


cyclocitrinol (**1**)

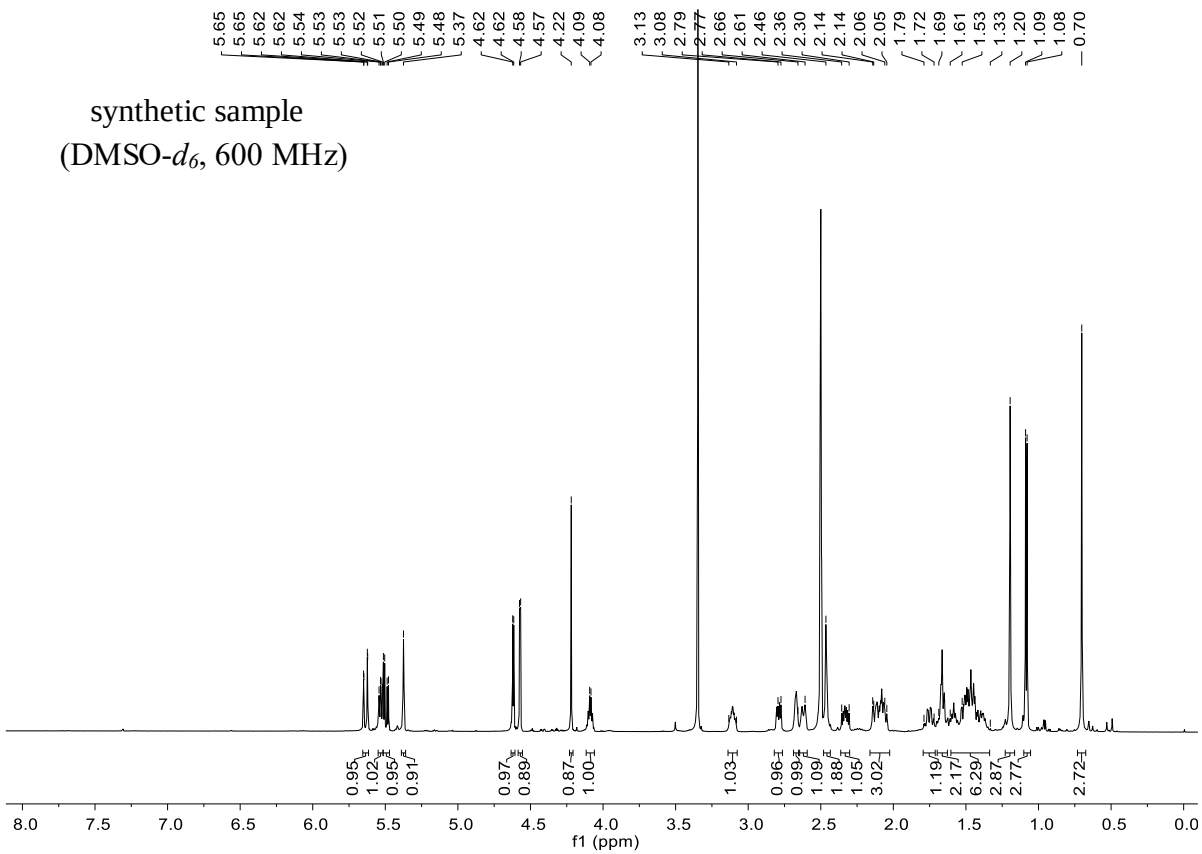
Position	Natural cyclocitrinol[3] (150 MHz in DMSO-d_6)	Synthetic cyclocitrinol (126 MHz in DMSO-d_6)	Δδ
1	121.9	122.0	0.1
2	35.9	36.0	0.1
3	63.1	63.1	0
4	41.3	41.4	0.1
5	48.1	48.1	0
6	204.1	204.1	0
7	124.5	124.5	0
8	157.1	157.1	0
9	53.2	53.2	0
10	145.7	145.7	0
11	27.5	27.5	0
12	38.8	38.9	0
13	45.9	45.9	0
14	55.2	55.3	0.1
15	22.1	22.1	0
16	22.3	22.3	0
17	60.1	60.1	0
18	14.3	14.4	0.1
19	27.1	27.2	0.1
20	73.3	73.3	0
21	28.9	28.9	0
22	136.0	136.0	0
23	130.8	130.8	0
24	66.3	66.3	0
25	24.0	24.1	0.1

NMR spectra comparison of synthetic and natural cyclocitrinol

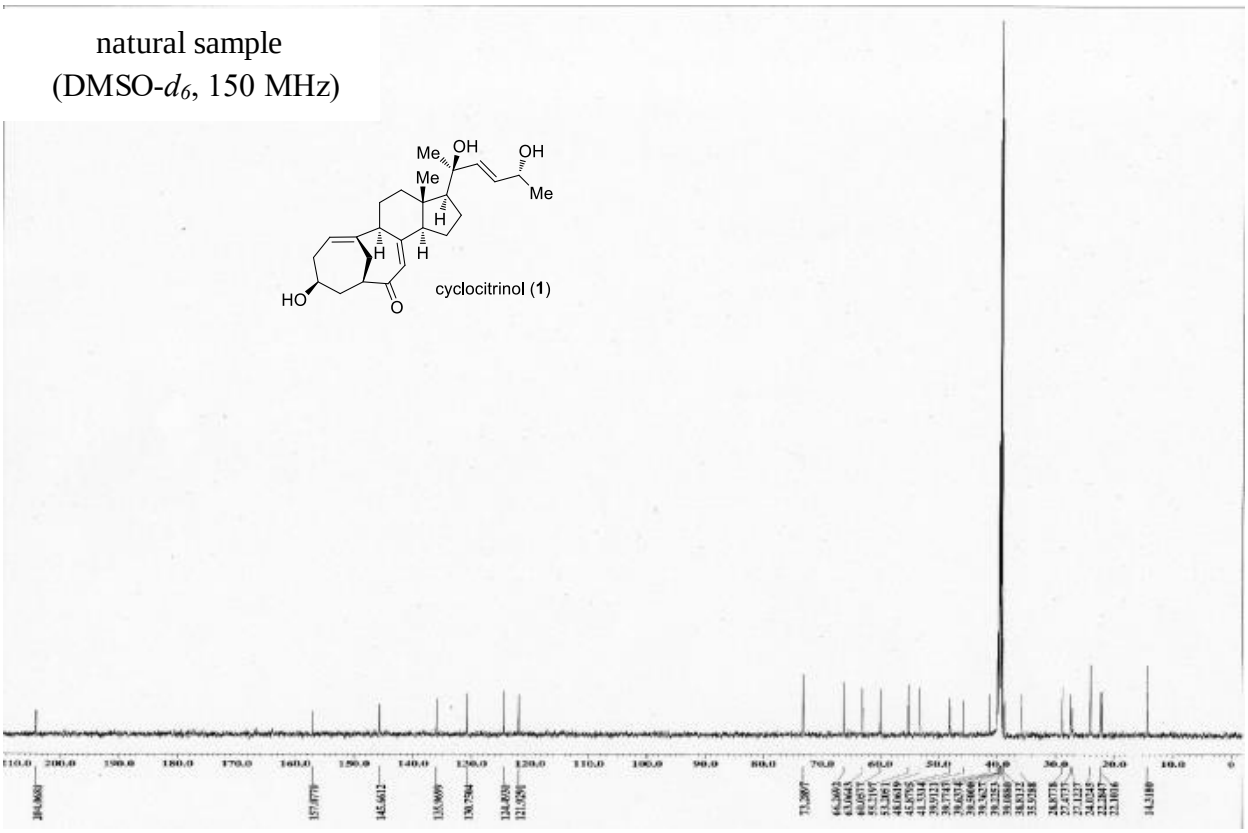
natural sample
(DMSO-d_6, 600 MHz)



synthetic sample
(DMSO-d_6, 600 MHz)

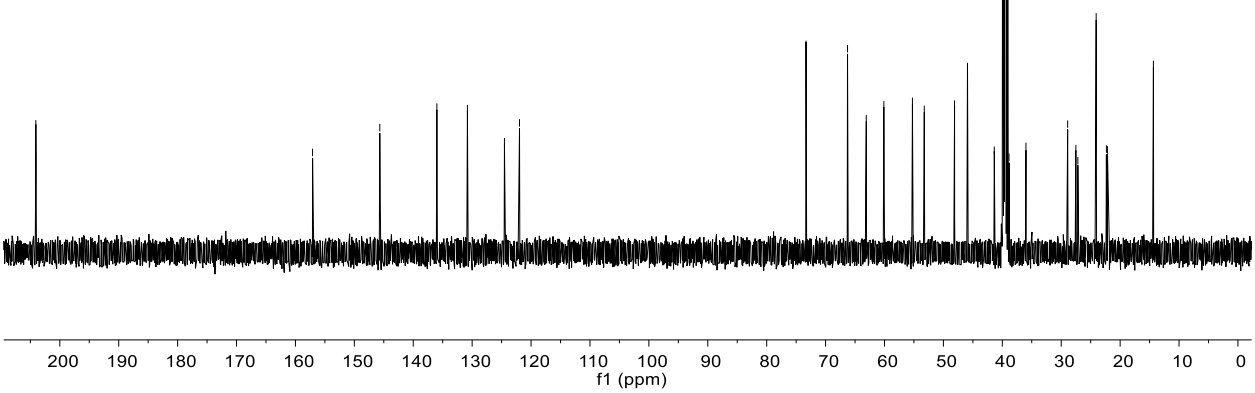


natural sample
(DMSO-d_6, 150 MHz)



204.1 157.1 145.7 136.0 130.8 124.5 122.0 73.3 66.3 63.1 60.1 55.3 53.2 48.1 45.9 41.4 38.9 36.0 28.9 27.5 27.2 24.1 22.3 22.1 14.4

synthetic sample
(DMSO-d_6, 126 MHz)



5. X-ray crystallographic data for 18

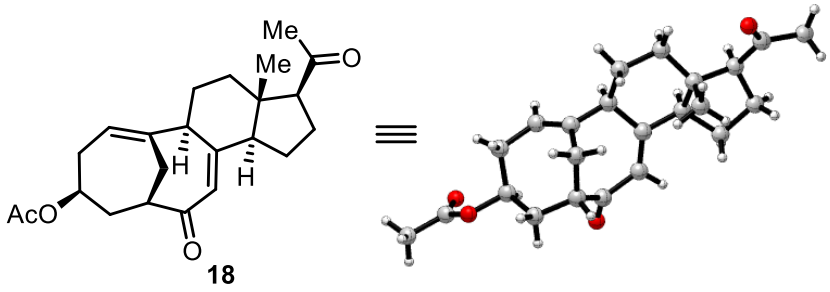


Table S2. Crystal data and structure refinement for CCDC 1837109.

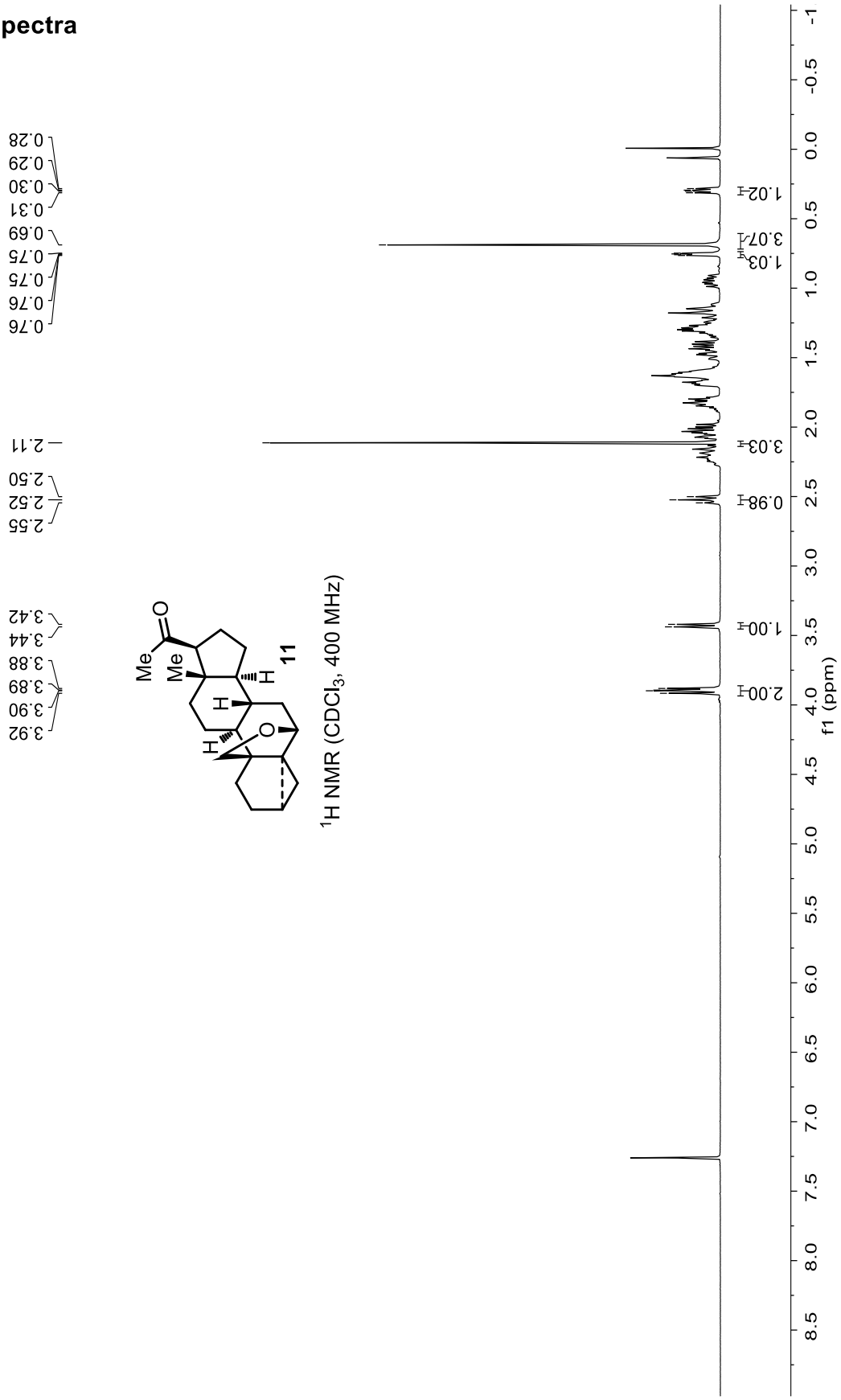
Identification code	CCDC 1837109	
Empirical formula	C23 H30 O4	
Formula weight	370.47	
Temperature	296(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 6.70030(10) Å	α= 90°.
	b = 14.5512(3) Å	β= 90°.
	c = 20.4826(4) Å	γ = 90°.
Volume	1997.00(6) $Å^3$	
Z	4	
Density (calculated)	1.232 Mg/m^3	
Absorption coefficient	0.662 mm^{-1}	
F(000)	800	
Crystal size	0.200 x 0.160 x 0.120 mm^3	
Theta range for data collection	6.456 to 66.500°.	
Index ranges	-7<=h<=7, -17<=k<=17, -24<=l<=21	
Reflections collected	16139	
Independent reflections	3452 [R(int) = 0.0287]	
Completeness to theta = 67.679°	95.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7533 and 0.6267	

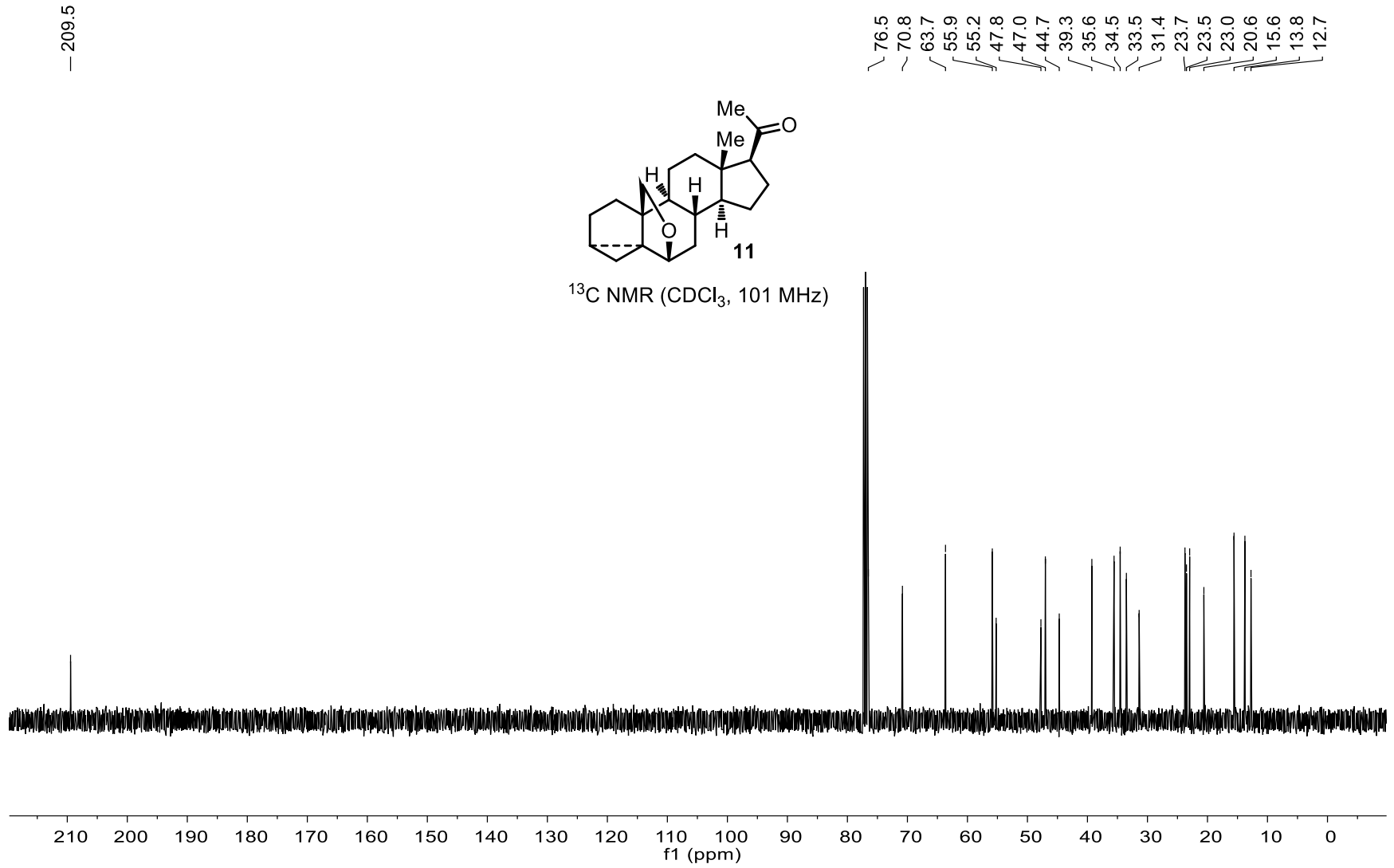
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3452 / 0 / 248
Goodness-of-fit on F^2	1.051
Final R indices [I>2sigma(I)]	R1 = 0.0374, wR2 = 0.1049
R indices (all data)	R1 = 0.0382, wR2 = 0.1059
Absolute structure parameter	0.06(6)
Largest diff. peak and hole	0.217 and -0.204 e.$Å^{-3}$

6. References

(1) Hazra, B. G.; Basu, S.; Bahule, B. B.; Pore, V. S.; Vyas, B. N.; Ramraj, V. M. *Tetrahedron* **1997**, *53*, 4909.
(2) (a) Terasawa, T.; Okada, T. *Tetrahedron* **1986**, *42*, 537; (b) Kranz, D. P.; Meier zu Greffen, A.; El Sheikh, S.; Neudoerfl, J. M.; Schmalz, H.-G. *Eur. J. Org. Chem.* **2011**, 2860.
(3) Du, L.; Zhu, T.; Fang, Y.; Gu, Q.; Zhu, W. *J. Nat. Prod.* **2008**, *71*, 1343.

7. NMR spectra




209.5
76.5
70.8
63.7
55.9
55.2
47.8
47.0
44.7
39.3
35.6
34.5
33.5
31.4
23.7
23.5
23.0
20.6
15.6
13.8
12.7
Me
Me
O
H
H
H
O
11
13C NMR (CDCl3, 101 MHz)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

7.35
7.30
7.23
7.16
5.60
5.58
4.65
4.62
4.61
4.59
4.57
4.49
4.48
4.47
4.46
4.21
4.20
4.18
4.17
2.50
2.48
2.46
2.42
2.40
2.38
2.37
2.33
2.30
2.10
2.02
0.50
4.27
6.27
0.95
1.09
1.07
0.96
1.10
1.12
1.04
2.94
3.22
2.87
f1 (ppm)
(PhO)2OPO
AcO
Me
Me
H
H
H
13
1H NMR (CDCl3, 400MHz)

209.4
170.5
150.5
150.5
150.5
150.4
133.4
129.8
129.7
127.4
125.4
125.4
125.3
125.3
119.9
119.9
119.9
119.9
73.0
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57.3
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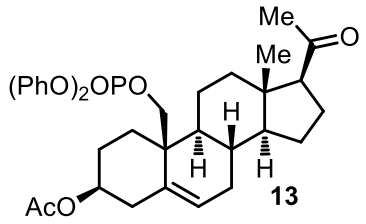
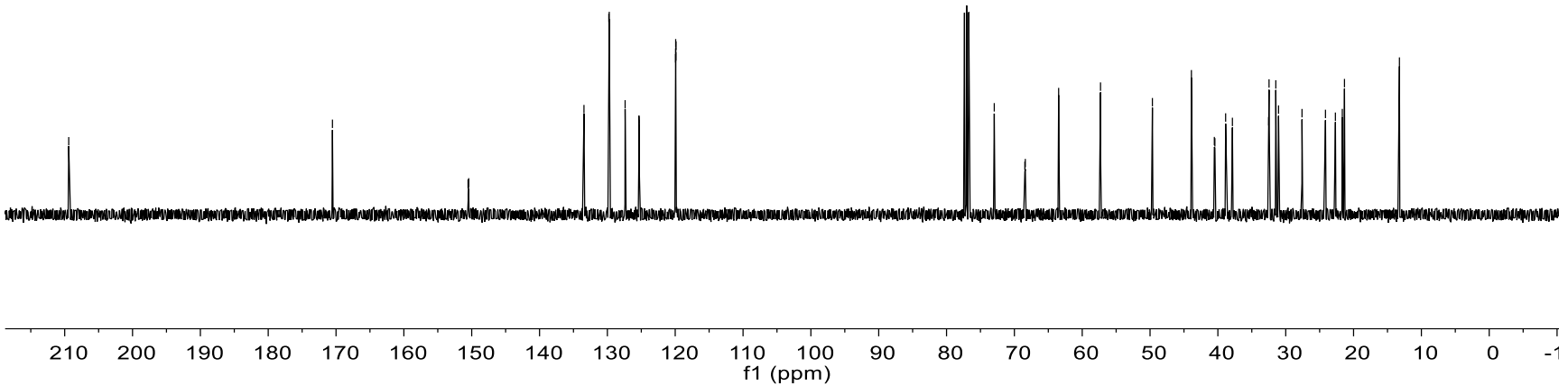
24.1
22.7
21.7
21.3
13.2

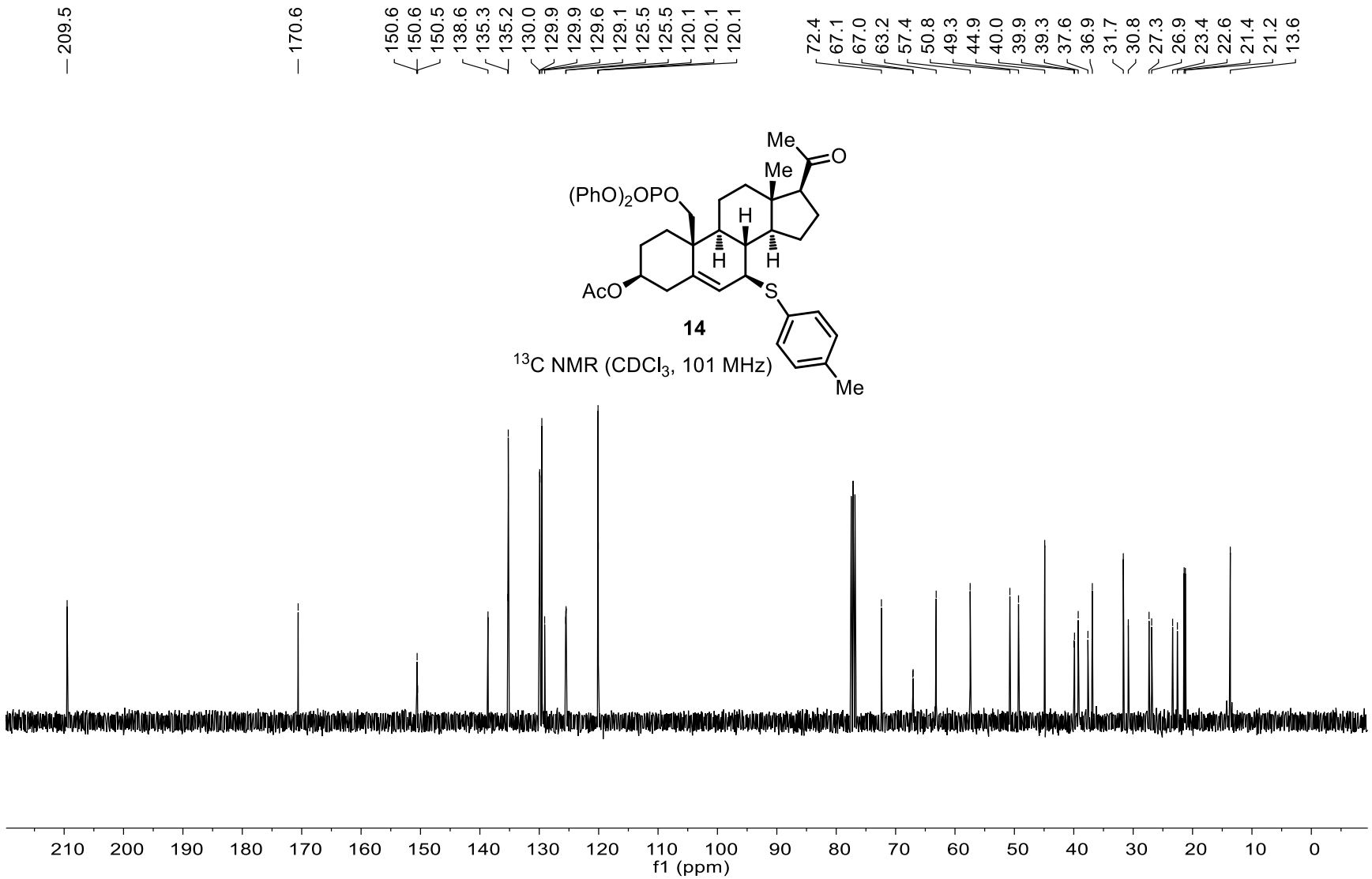


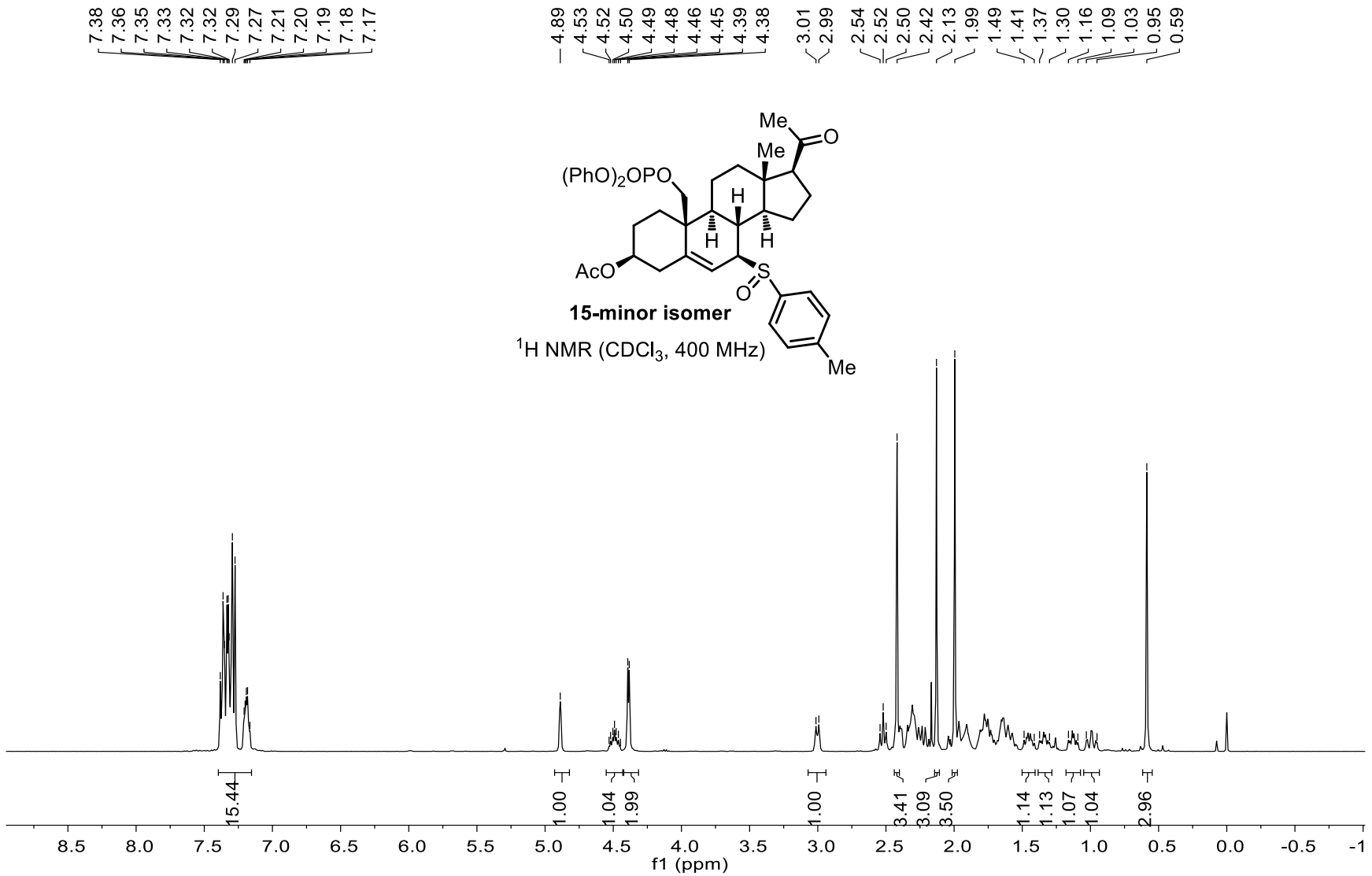
13

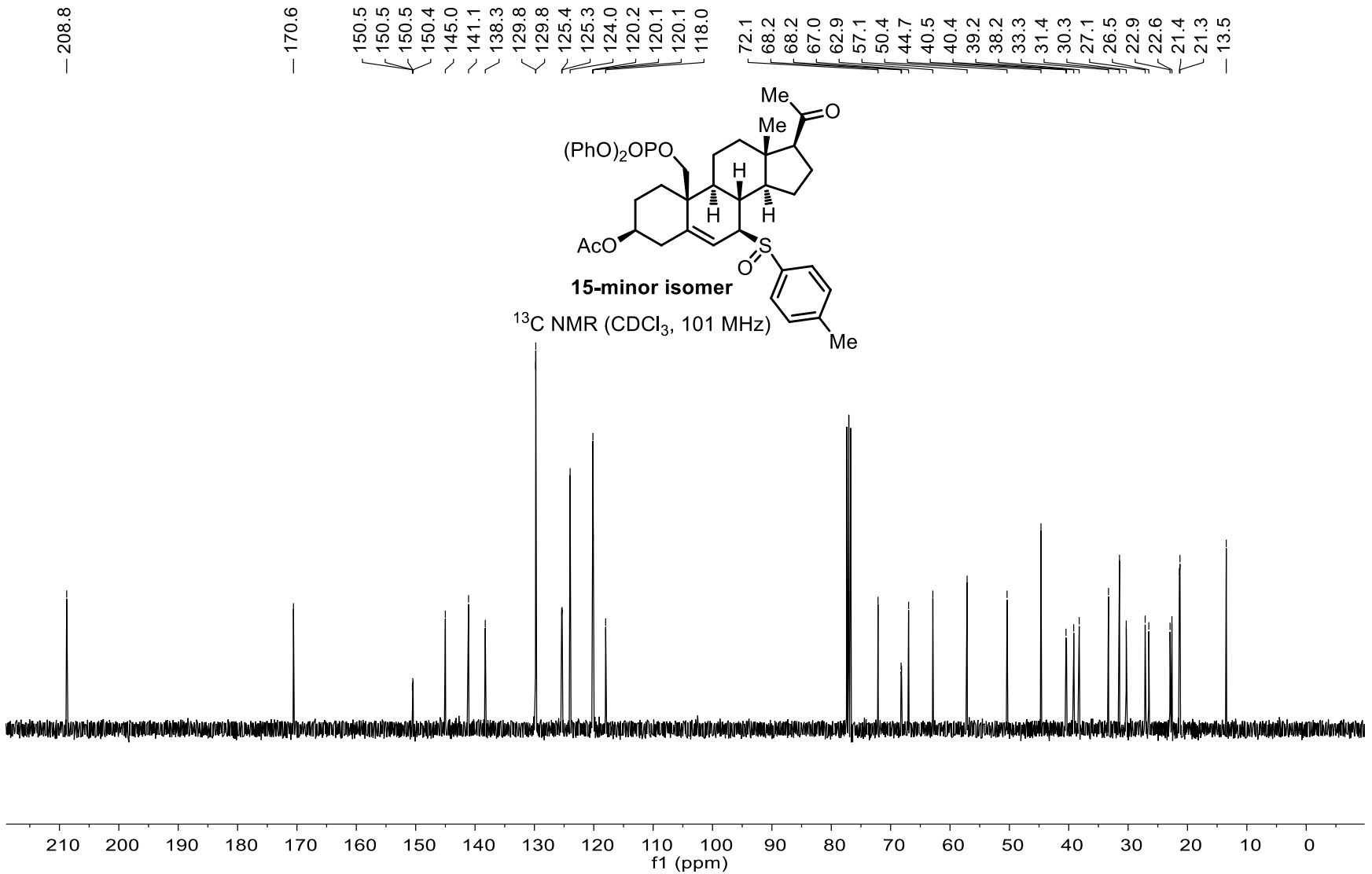
^{13}C NMR ($CDCl_3$, 101MHz)



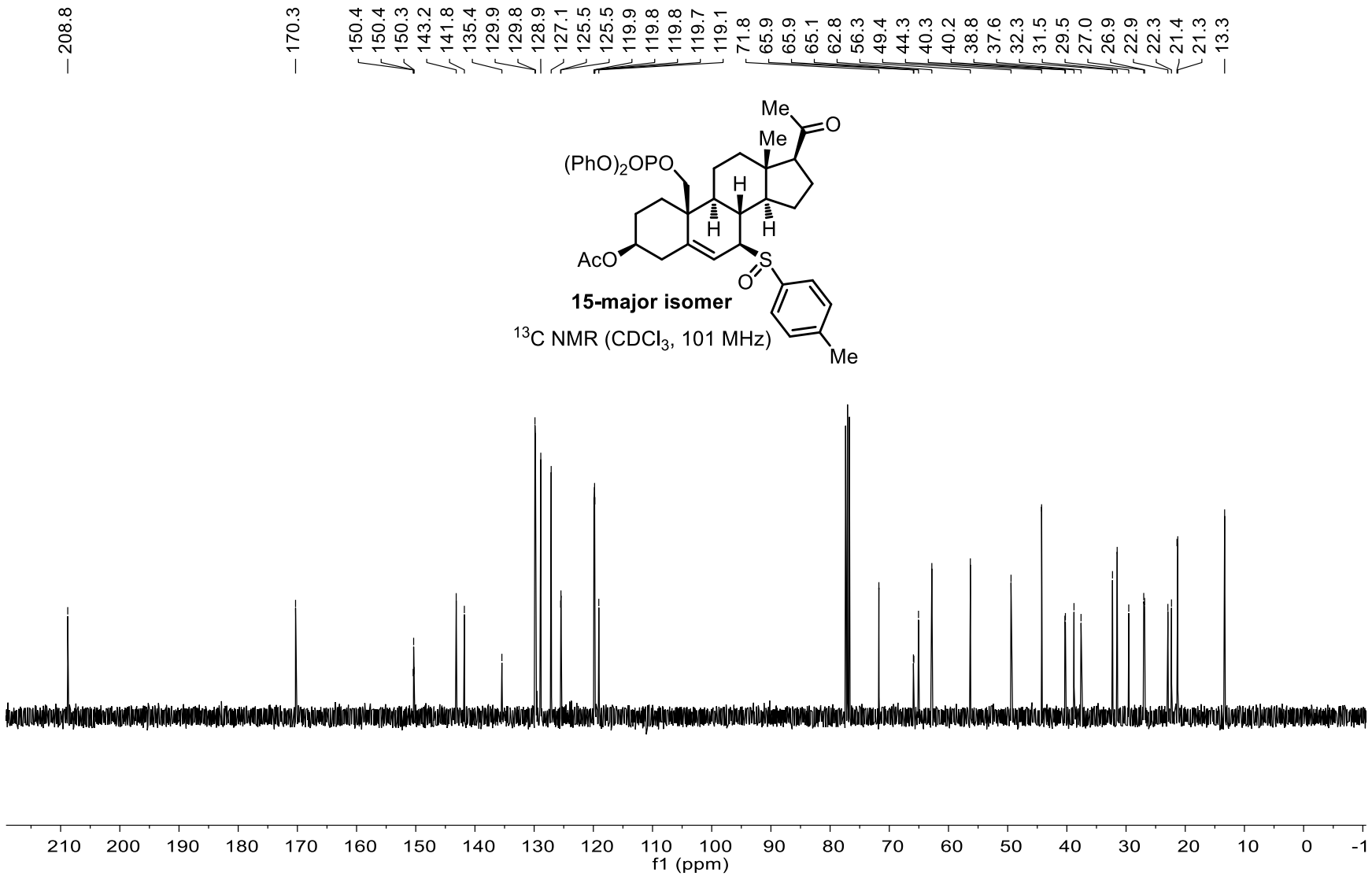
14
^{1}H NMR ($CDCl_3$, 400 MHz)
f1 (ppm)


209.5
170.6
150.6
150.6
150.5
138.6
135.3
135.2
130.0
129.9
129.9
129.6
129.1
125.5
125.5
120.1
120.1
120.1
72.4
67.1
67.0
63.2
57.4
50.8
49.3
44.9
40.0
39.9
39.3
37.6
36.9
31.7
30.8
27.3
26.9
23.4
22.6
21.4
21.2
13.6
Me
O
Me
(PhO)2OPO
H
H
H
AcO
S
Me
14
13C NMR (CDCl3, 101 MHz)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

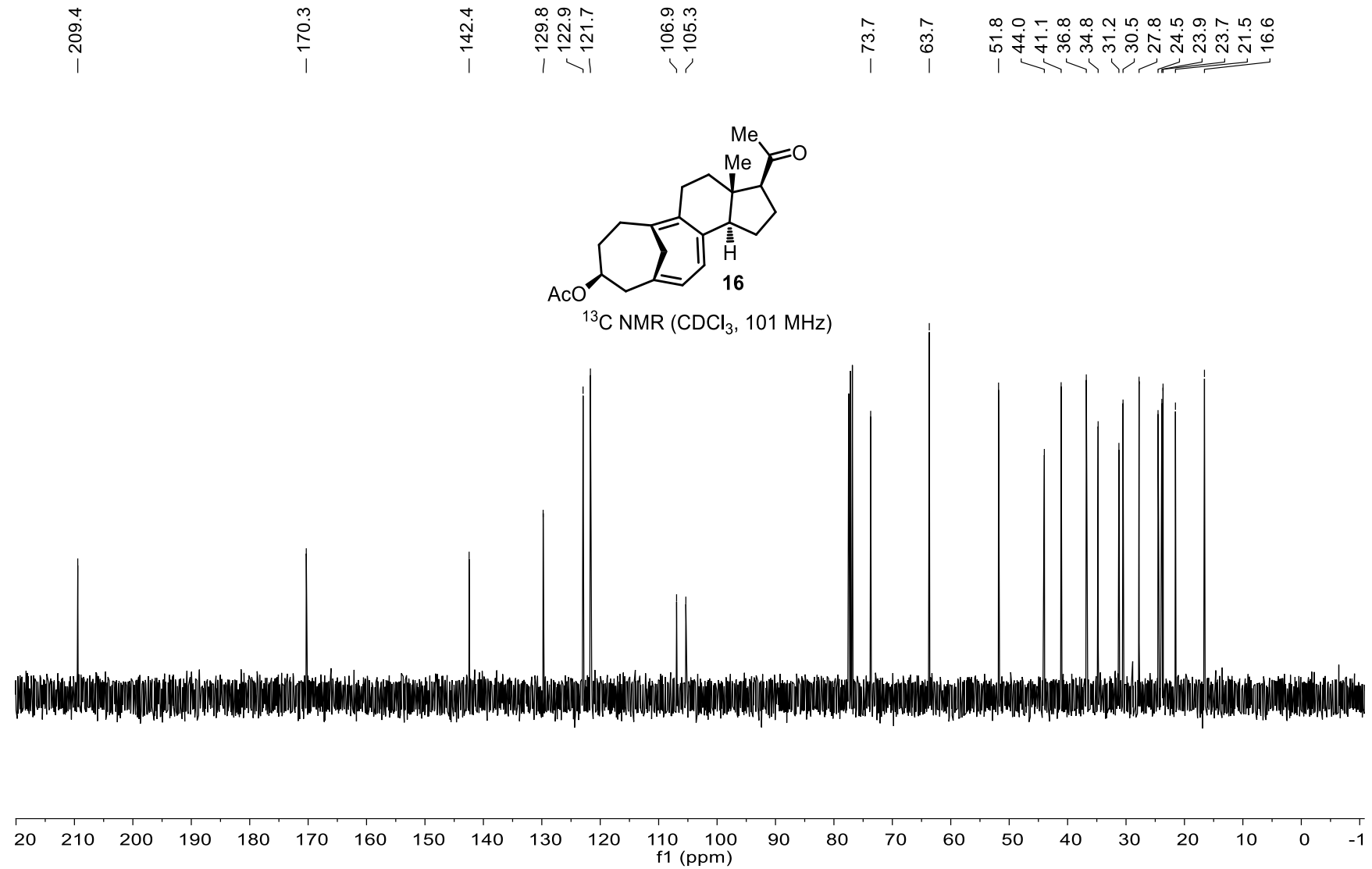

7.38
7.36
7.35
7.33
7.32
7.32
7.29
7.27
7.21
7.20
7.19
7.18
7.17
4.89
4.53
4.52
4.50
4.49
4.48
4.46
4.45
4.39
4.38
3.01
2.99
2.54
2.52
2.50
2.42
2.13
1.99
1.49
1.41
1.37
1.30
1.16
1.09
1.03
0.95
0.59
Me
O
Me
(PhO)2OPO
H
H
H
AcO
S
O
15-minor isomer
1H NMR (CDCl3, 400 MHz)
Me
15.44
1.00
1.04
1.99
1.00
3.41
3.09
3.50
1.14
1.13
1.07
1.04
2.96
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1
f1 (ppm)


208.8
170.6
150.5
150.5
150.5
150.4
145.0
141.1
138.3
129.8
129.8
125.4
125.3
124.0
120.2
120.1
120.1
118.0
72.1
68.2
68.2
67.0
62.9
57.1
50.4
44.7
40.5
40.4
39.2
38.2
33.3
31.4
30.3
27.1
26.5
22.9
22.6
21.4
21.3
13.5
Me
O
Me
(PhO)2OPO
H
H
H
AcO
S
O
15-minor isomer
13C NMR (CDCl3, 101 MHz)
Me
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

15-major isomer
^{1}H NMR ($CDCl_3$, 400 MHz)
f1 (ppm)

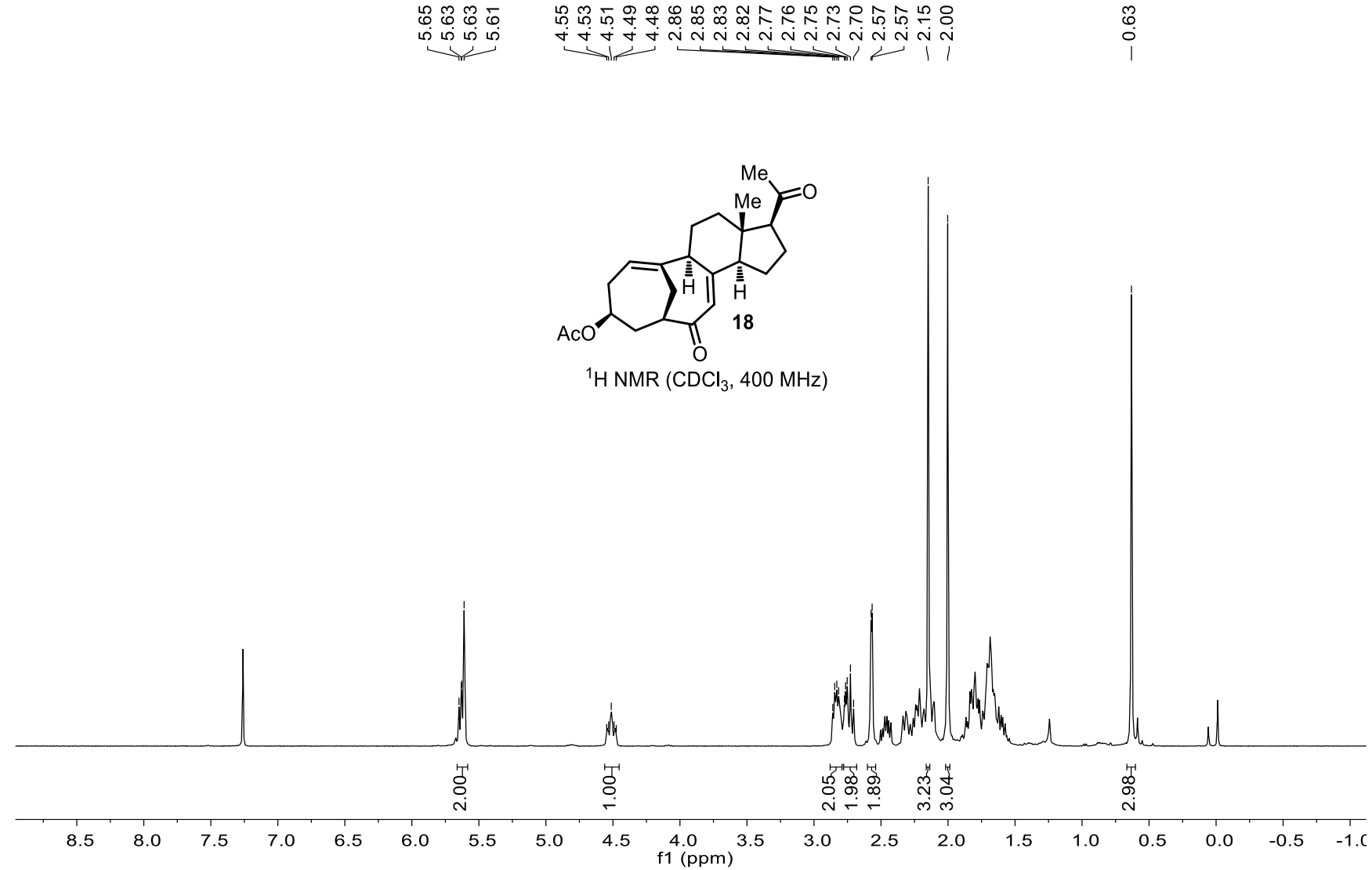

208.8
170.3
150.4
150.4
150.3
143.2
141.8
135.4
129.9
129.8
128.9
127.1
125.5
125.5
119.9
119.8
119.8
119.7
119.1
71.8
65.9
65.9
65.1
62.8
56.3
49.4
44.3
40.3
40.2
38.8
37.6
32.3
31.5
29.5
27.0
26.9
22.9
22.3
21.4
21.3
13.3
Me
O
Me
(PhO)2OPO
H
H
H
AcO
S
O
15-major isomer
13C NMR (CDCl3, 101 MHz)
Me
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
f1 (ppm)

Me
Me
H
O
AcO
16
^{1}H NMR ($CDCl_3$, 400 MHz)
f1 (ppm)


209.4
170.3
142.4
129.8
122.9
121.7
106.9
105.3
73.7
63.7
51.8
44.0
41.1
36.8
34.8
31.2
30.5
27.8
24.5
23.9
23.7
21.5
16.6
Me
Me
O
H
AcO
16
13C NMR (CDCl3, 101 MHz)
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

0.62
1.44
1.49
2.02
2.13
2.88
2.89
2.91
2.92
3.03
3.06
4.53
4.53
4.56
4.56
4.57
4.60
4.60
4.92
4.94
4.96
5.44
5.46
5.60
5.62
Me
Me
O
H
H
17
AcO
1H NMR (CDCl3, 400 MHz)
3.00
1.11
3.04
3.26
1.13
1.03
1.02
1.01
1.05
1.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

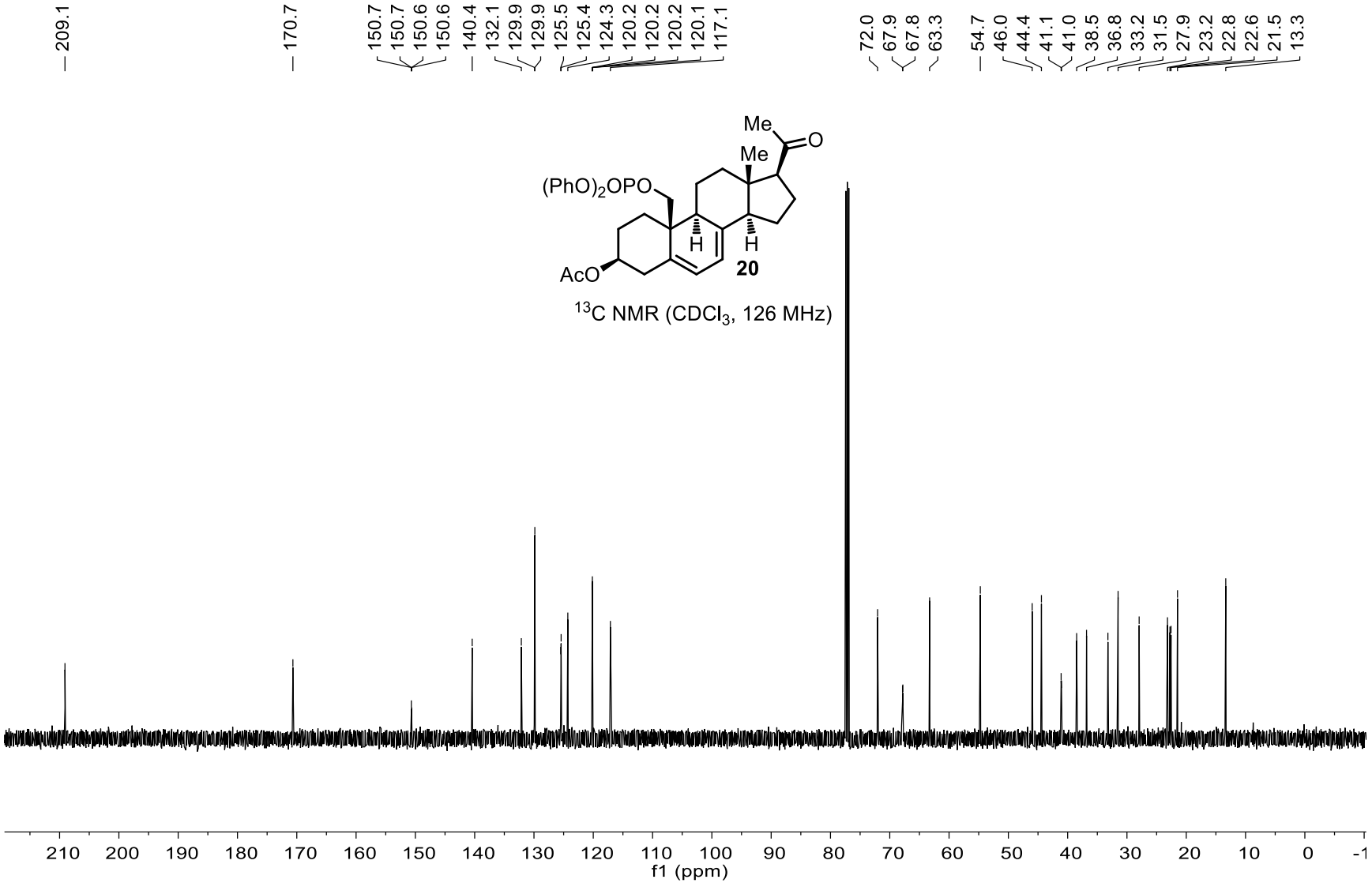
209.2
170.1
149.7
143.8
139.3
120.3
118.4
115.2
74.4
63.7
56.4
52.3
46.6
46.1
38.9
35.7
32.6
31.5
30.6
23.6
22.3
21.4
13.5
Me
O
Me
H
H
AcO
17
^{13}C NMR (CDCl$_3$, 101 MHz)
f1 (ppm)



^{1}H NMR ($CDCl_3$, 400 MHz)

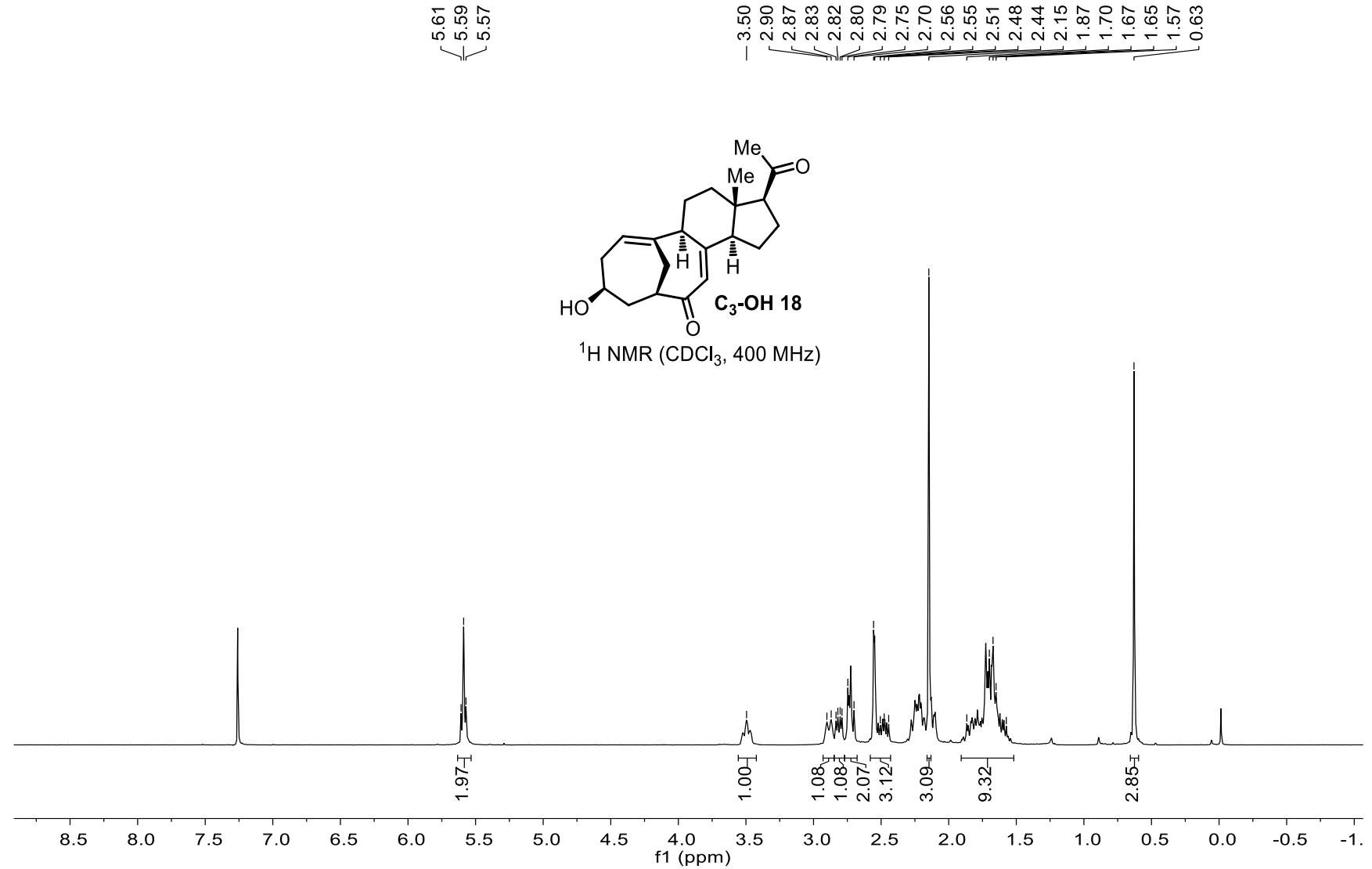
208.6
204.0
170.0
155.8
145.9
125.5
121.8
67.2
63.4
55.7
53.6
48.3
46.5
38.0
37.5
32.7
31.4
27.5
27.5
23.2
22.5
21.4
13.8
Me
O
Me
H
H
O
AcO
18
^{13}C NMR ($CDCl_3$, 101 MHz)
f1 (ppm)

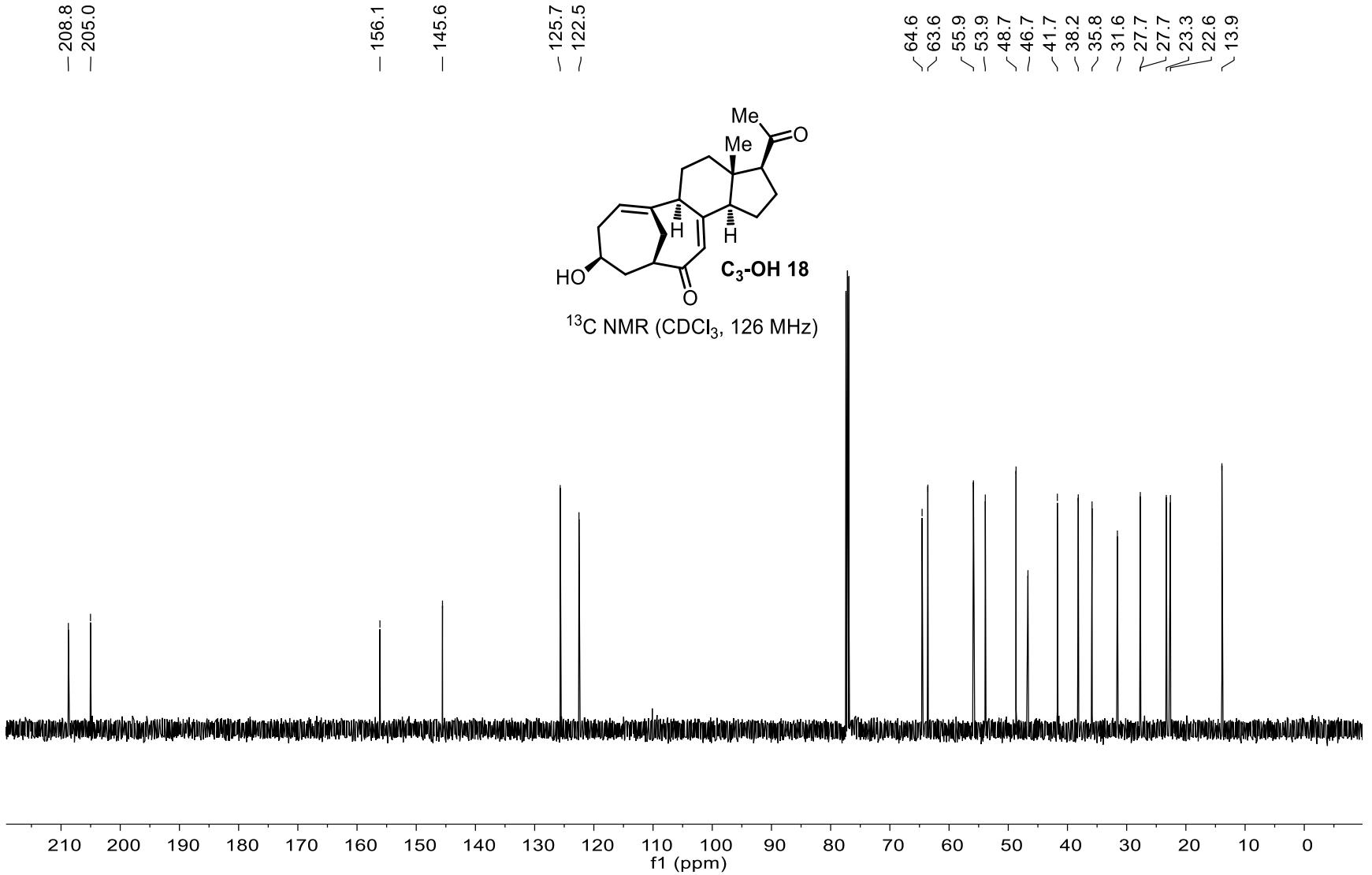
7.34
7.33
7.32
7.30
7.30
7.30
7.20
7.18
5.68
5.67
5.29
5.29
4.73
4.71
4.70
4.69
4.67
4.66
4.65
4.35
4.34
4.33
4.32
4.16
4.15
4.13
4.12
2.61
2.59
2.56
2.53
2.52
2.49
2.48
2.38
2.35
2.31
2.12
2.02
0.46
Me
Me
O
H
H
(PhO)2OPO
AcO
20
1H NMR (CDCl3, 400 MHz)
4.44
6.48
1.00
1.06
1.05
0.98
1.01
1.02
1.08
1.20
2.94
3.36
2.82
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1
f1 (ppm)


209.1
170.7
150.7
150.7
150.6
150.6
140.4
132.1
129.9
129.9
125.5
125.4
124.3
120.2
120.2
120.2
120.1
117.1
72.0
67.9
67.8
63.3
54.7
46.0
44.4
41.1
41.0
38.5
36.8
33.2
31.5
27.9
23.2
22.8
22.6
21.5
13.3
Me
O
Me
(PhO)2OPO
H
H
AcO
20
13C NMR (CDCl3, 126 MHz)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
f1 (ppm)

cyclocitrinol (1)
^{1}H NMR (DMSO-d_6, 600 MHz)
f1 (ppm)

cyclocitrinol (1)
^{13}C NMR (DMSO-d_6, 126 MHz)
f1 (ppm)
204.1
157.1
145.7
136.0
130.8
124.5
122.0
73.3
66.3
63.1
60.1
55.3
53.2
48.1
45.9
41.4
38.9
36.0
28.9
27.5
27.2
24.1
22.3
22.1
14.4


5.61
5.59
5.57
3.50
2.90
2.87
2.83
2.82
2.80
2.79
2.75
2.70
2.56
2.55
2.51
2.48
2.44
2.15
1.87
1.70
1.67
1.65
1.57
0.63
Me
Me
O
H
H
HO
O
C3-OH 18
1H NMR (CDCl3, 400 MHz)
1.97
1.00
1.08
1.08
2.07
3.12
3.09
9.32
2.85
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.
f1 (ppm)


208.8
205.0
156.1
145.6
125.7
122.5
64.6
63.6
55.9
53.9
48.7
46.7
41.7
38.2
35.8
31.6
27.7
27.7
23.3
22.6
13.9
Me
Me
O
H
H
HO
O
C3-OH 18
13C NMR (CDCl3, 126 MHz)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)