Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Practical and scalable enantioselective synthesis of (+)-majoranolide from Cyrene

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Experimental

General Procedures

Unless otherwise stated, common chemicals and solvents (HPLC-grade or reagent-grade quality) were purchased from commercial sources and used without further purification. A hot plate magnetic stirrer and PEG bath was used as the heating source in all reactions requiring heat. Aluminium plates coated with a 0.2 mm-thick layer of silica gel 60 F_{254} were used for thin-layer chromatography (TLC) analysis, and flash column chromatography purification was carried out using silica gel 60 (230–400 mesh). Proton (^{1}H) spectra were recorded at 25 °C using a 500 MHz spectrometer and proton-decoupled carbon (^{13}C{^{1}H}) NMR spectra were recorded at 125 MHz using the deuterated solvent as an internal deuterium lock. ^{1}H NMR spectra were referenced to TMS (δ 0.00 ppm) and ^{13}C{^{1}H} NMR spectra recorded in $CDCl_3$ were referenced to $CDCl_3$ (δ 77.0 ppm). High-resolution electrospray ionization mass spectra (ESI-MS) were recorded on an instrument equipped with a triple-time of flight detector.

Synthetic Procedures

(1*S*,5*R*,*E*)-3-Butylidene-6,8-dioxabicyclo[3.2.1]octan-4-one (15). A stirred solution of butanal (147 mg, 2.04 mmol) and piperidine (60 µL, 0.61 mmol) in Cyrene (5 mL) was heated to 80 °C for 2.5 h after then allowed to cool to ambient temperature. The reaction mixture was subsequently diluted with Et_2O (20 mL) and washed with sat. Na_2HCO_3 (1 × 40 mL). The aqueous layer was extracted with Et_2O (3 × 15 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 10% EtOAc/hexanes) affording **15** as light-yellow oil (206 mg, 55%); R_f 0.47 (15% EtOAc/hexanes); $[\alpha]_D^{20}$ −158 (*c* 1.2, CH_2Cl_2); IR (ATR): 2963, 1708, 1620, 1248, 1110, 988, 735 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.94 (dddd, *J* = 7.5, 7.5, 2.5, 1.7 Hz, 1H), 5.26 (s, 1H), 4.85 (br dd, *J* = 5.4, 5.4 Hz, 1H), 3.93 (ddd, *J* = 7.1, 5.4, 1.5 Hz, 1H), 3.79 (dd, *J* = 7.1, 1.0 Hz, 1H), 2.95–2.86 (m, 1H), 2.55 (br d, *J* = 16.6 Hz, 1H), 2.16–2.02 (m, 2H), 1.54–1.43 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 188.8, 144.9, 128.3, 100.8, 72.6, 68.7, 31.9, 30.1, 21.4, 13.9; HRMS (ESI) calc. for $C_{10}H_{15}O_3^+$ [M + H]$^+$, 183.1016; found 183.1016.

(1*S*,5*R*,*E*)-3-Dodecylidene-6,8-dioxabicyclo[3.2.1]octan-4-one (16). A stirred solution of dodecanal (10.01 g, 54.3 mmol) and piperidine (1.64 mL, 16.6 mmol) in Cyrene (70 mL) was

heated to 80 °C for 2.5 h then allowed to cool. The reaction mixture was diluted with Et_2O (100 mL) and washed with sat. Na_2HCO_3 (1 × 500 mL). The aqueous layer was extracted with Et_2O (3 × 100 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by dry flash chromatography (SiO_2, 5% EtOAc/hexanes), affording **16** as light-yellow solid (10.12 g, 63%); R_f 0.34 (5% EtOAc/hexanes); mp 41–44 °C; $[\alpha]_D^{20}$ −87.3 (*c* 0.79, CH_2Cl_2); IR (ATR): 2915, 1709, 1617, 1112, 911, 641 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.94 (dddd, *J* = 7.5, 7.5, 3.0, 1.4 Hz, 1H), 5.25 (s, 1H), 4.85 (ddddd, *J* = 5.5, 5.5, 1.0, 1.0, 0.7 Hz, 1H), 3.93 (ddd, *J* = 7.1, 5.5, 1.6 Hz, 1H), 3.78 (dd, *J* = 7.1, 1.0 Hz, 1H), 2.96–2.90 (m, 1H), 2.54 (br d, *J* = 16.6 Hz, 1H), 2.17–1.22 (m, 2H), 1.50–1.39 (m, 2H), 1.31–1.22 (m, 16H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 188.9, 145.3, 128.1, 100.8, 72.6, 68.6, 31.9, 31.8, 29.61, 29.59, 29.5, 29.4, 29.3, 28.13, 28.09, 22.7, 14.1; HRMS (ESI) calc. for $C_{18}H_{31}O_3^+$ $[M + H]^+$, 295.2268; found 295.2265.

(1*S*,5*R*,*E*)-3-Octylidene-6,8-dioxabicyclo[3.2.1]octan-4-one (17). The reaction of octanal (262 mg, 2.04 mmol) and piperidine (60 µL, 0.61 mmol) in Cyrene (5 mL) as for the preparation of **15** afforded **17** as a light-yellow oil (304 mg, 63%); R_f 0.43 (10% EtOAc/hexanes); $[\alpha]_D^{20}$ −111 (*c* 1.0, CH_2Cl_2); IR (ATR): 2925, 1709, 1620, 1266, 1111, 735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.94 (dddd, *J* = 7.6, 7.6, 3.0, 1.6 Hz, 1H), 5.25 (s, 1H), 4.84 (br dd, *J* = 5.4, 5.4 Hz, 1H), 3.92 (ddd, *J* = 7.2, 5.4, 1.6 Hz, 1H), 3.78 (dd, *J* = 7.2, 1.1 Hz, 1H), 2.94–2.87 (m, 1H), 2.54 (br d, *J* = 16.4, Hz, 1H), 2.16–2.04 (m, 2H), 1.51–1.40 (m, 2H), 1.34–1.20 (m, 8H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 188.8, 145.2, 128.1, 100.8, 72.6, 68.6, 31.8, 31.7, 29.3, 29.0, 28.11, 28.09, 22.6, 14.0; HRMS (ESI) calc. for $C_{14}H_{23}O_3^+$ $[M + H]^+$, 239.1642; found 239.1638.

(1*S*,5*R*,*E*)-3-Tetradecylidene-6,8-dioxabicyclo[3.2.1]octan-4-one (18). The reaction of tetradecanal (429 mg, 2.02 mmol) and piperidine (60 µL, 0.61 mmol) in Cyrene (5 mL) as for the preparation of **15** afforded **18** as a colourless solid (393 mg, 60%); R_f 0.44 (5% EtOAc/hexanes); mp 52–56 °C; $[\alpha]_D^{20}$ −84.3 (*c* 0.89, CH_2Cl_2); IR (ATR): 2914, 1709, 1616, 1111, 785, 641 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.94 (dddd, *J* = 7.5, 7.5, 3.0, 1.7 Hz, 1H), 5.25 (s, 1H), 4.84 (br dd, *J* = 5.5, 5.5 Hz, 1H), 3.93 (ddd, *J* = 7.1, 5.5, 1.7 Hz, 1H), 3.78 (dd, *J*

= 7.1, 1.1 Hz, 1H), 2.96–2.89 (m, 1H), 2.54 (br d, *J* = 16.6 Hz, 1H), 2.17–2.03 (m, 2H), 1.50–1.39 (m, 2H), 1.35–1.19 (m, 20H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 188.8, 145.2, 128.1, 100.8, 72.6, 68.6, 31.9, 31.8, 29.7, 29.63, 29.61, 29.5, 29.4, 29.3, 28.13, 28.11, 22.7, 14.1; HRMS (ESI) calc. for $C_{20}H_{35}O_3^+$ $[M + H]^+$, 323.2581; found 323.2576.

(*S*,*E*)-3-Butylidene-5-(hydroxymethyl)dihydrofuran-2(3H)-one (19). A solution of **15** (186 mg, 1.02 mmol), PTSA.H_2O (306 mg, 1.61 mmol) and 70% *m*-CPBA (274 mg, 1.11 mmol) in CH_2Cl_2 (5 mL) was stirred at ambient temperature for 2 h. The reaction was quenched by the addition of 10% *w/w* palladium on carbon (25 mg), and when the evolution of oxygen had ceased, the mixture was diluted with EtOAc (10 mL) and washed with sat. $NaHCO_3$ (50 mL). The aqueous layer was extracted with EtOAc (4 × 10 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was dissolved in THF (5 mL) and 2M HCl (5 mL) and stirred at ambient temperature for 4 h, then diluted with sat. $NaHCO_3$ solution (50 mL). The mixture was extracted with EtOAc (5 × 10 mL), the combined organic extracts, dried and concentrated under reduced pressure. The residue was purified via flash column chromatography (SiO_2, 50% EtOAc/hexanes to 60% EtOAc/hexanes) affording **19** as a light-yellow oil (108 mg, 64%); R_f 0.29 (50% EtOAc/hexanes); See Table 2 for $[\alpha]_D$; IR (ATR): 3419, 2958, 1734, 1202, 1042, 732 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.75 (dddd, *J* = 7.6, 7.6, 3.0, 3.0 Hz, 1H), 4.65 (dddd, *J* = 8.5, 5.7, 5.1, 3.1 Hz, 1H), 3.88 (dd, *J* = 12.4, 3.1 Hz, 1H), 3.65 (dd, *J* = 12.4, 5.1 Hz, 1H), 2.88 (ddddd, *J* = 16.9, 8.5, 3.0, 1.8, 1.5 Hz, 1H), 2.70 (ddddd, *J* = 16.9, 5.7, 3.1, 1.8, 1.5 Hz, 1H), 2.16 (app. dddt, *J* = 7.6, 7.6, 1.8, 1.5 Hz, 2H), 1.98 (br s, 1H), 1.52 (app. tq, *J* = 7.4, 7.4 Hz, 2H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 141.3, 125.9, 77.3, 64.5, 32.2, 26.7, 21.4, 13.8; HRMS (ESI) calc. for $C_9H_{14}O_3Na^+$ $[M + Na]^+$, 193.0835; found 193.0835.

(*S*,*E*)- 3-Octylidene-5-(hydroxymethyl)dihydrofuran-2(3H)-one (20). The reaction of **17** (249 mg, 1.05 mmol), PTSA·H_2O (240 mg, 1.26 mmol) and 70% *m*-CPBA (265 mg, 1.08 mmol) in CH_2Cl_2 (5 mL) as for the preparation of **19** afforded **20** as a yellow oil (120 mg, 51%); R_f 0.34 (40% EtOAc/hexanes); See Table 2 for $[\alpha]_D$; IR (ATR): 3414, 2926, 1743, 1218, 1010, 734 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.75 (dddd, *J* = 7.5, 7.5, 3.0, 3.0 Hz, 1H), 4.65 (dddd, *J* = 8.6, 5.6, 5.1, 3.0 Hz, 1H), 3.88 (ddd, *J* = 12.4, 6.7, 3.0 Hz, 1H), 3.65 (ddd, *J* = 12.4, 6.3, 5.2 Hz, 1H), 2.92–2.84 (m, 1H), 2.72–2.66 (m, 1H), 2.22–2.12 (m, 2H), 2.08–1.87 (m, 1H),

1.48 (tt, J = 7.1, 7.1 Hz, 2H), 1.36–1.20 (m, 8H), 0.88 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 141.6, 125.7, 77.2, 64.6, 31.7, 30.3, 29.3, 29.0, 28.1, 26.8, 22.6, 14.0; HRMS (ESI) calc. for $C_{13}H_{22}O_3Na^+$ $[M + Na]^+$, 249.1461; found 249.1457.

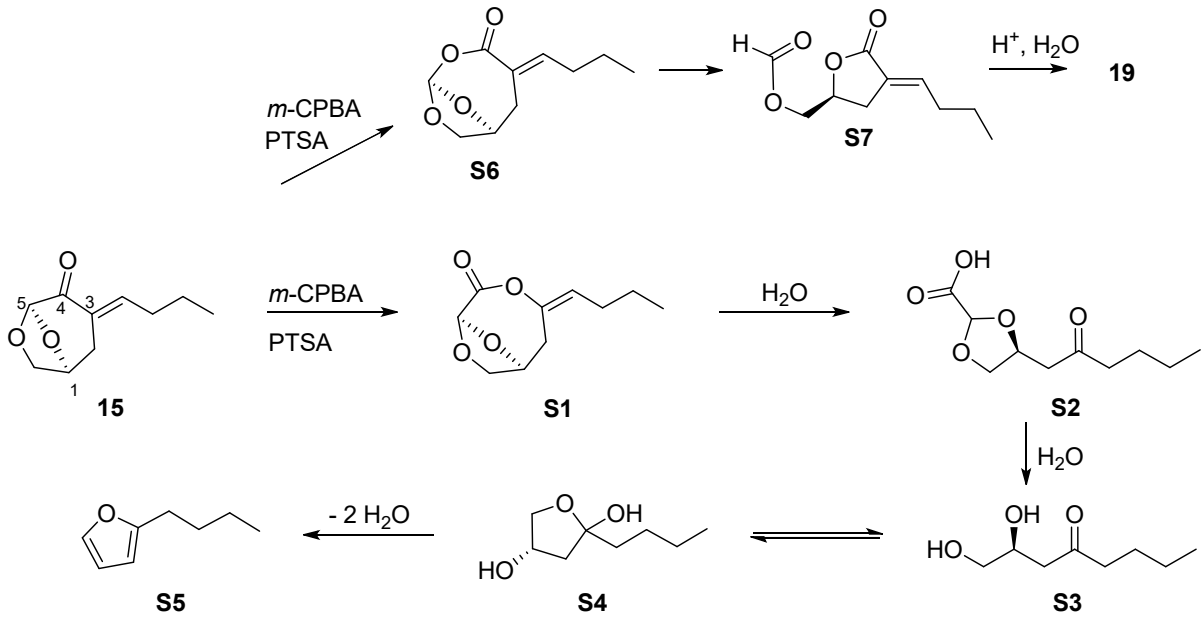
Majoranolide (1). The reaction of **18** (325 mg, 1.01 mmol), PTSA·H_2O (233 mg, 1.23 mmol) and 70% *m*-CPBA (269 mg, 1.09 mmol) in CH_2Cl_2 (5 mL) as for the preparation of **19** afforded **1** as a colourless solid (136 mg, 43%); R_f 0.32 (30% EtOAc/hexanes); mp 61–64 °C; See Table 2 for $[\alpha]_D$; IR (ATR): 3295, 2916, 1743, 1467, 1211, 1046, 706 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.75 (dddd, J = 7.5, 7.5, 3.0, 3.0 Hz, 1H), 4.65 (dddd, J = 8.5, 5.7, 5.2, 3.1 Hz, 1H), 3.88 (dd, J = 12.4, 3.1 Hz, 1H), 3.65 (dd, J = 12.4, 5.2 Hz, 1H), 2.88 (ddddd, J = 16.9, 8.5, 3.0, 1.6, 1.6 Hz, 1H), 2.69 (ddddd, J = 16.9, 5.8, 3.0, 1.9, 1.9 Hz, 1H), 2.18 (app. dddt, J = 7.5, 7.5, 1.6, 1.6 Hz, 2H), 1.82 (br s, 1H), 1.48 (app. tt, J = 7.5, 7.5 Hz, 2H), 1.34–1.20 (m, 20H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 141.6, 125.7, 77.2, 64.6, 31.9, 30.3, 29.67, 29.64 (2C), 29.62, 29.5, 29.4, 29.3 (2C), 28.1, 26.8, 22.7, 14.1; HRMS (ESI) calc. for $C_{19}H_{35}O_3^+$ $[M + H]^+$, 311.2581; found 311.2579.

Majoranolide B (2). The reaction of **16** (10.07 g, 34.2 mmol), PTSA.H_2O (7.09 g, 37.3 mmol) and *m*-CPBA 70% (9.09 g, 36.9 mmol) in CH_2Cl_2 (150 mL) as for the preparation of **19** afforded **2** as a beige solid (6.14 g, 64%); R_f 0.35 (30% EtOAc/hexanes); mp 54–59 °C; See Table 2 for $[\alpha]_D$; IR (ATR): 3300, 2915, 1743, 1467, 1215, 1037, 706 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.75 (dddd, J = 7.6, 7.6, 3.0, 3.0 Hz, 1H), 4.65 (dddd, J = 8.5, 5.7, 5.2, 3.0 Hz, 1H), 3.88 (dd, J = 12.3, 2.0 Hz, 1H), 3.65 (dd, J = 12.3, 4.9 Hz, 1H), 2.88 (ddddd, J = 16.9, 8.5, 3.0, 1.7, 1.7 Hz, 1H), 2.69 (ddddd, J = 16.9, 5.7, 3.0, 1.7, 1.7 Hz, 1H), 2.17 (app. dddt, J = 7.6, 7.4, 1.7, 1.7 Hz, 2H), 2.01 (br s, 1H), 1.47 (app. tt, J = 7.4, 7.4 Hz, 2H), 1.33–1.22 (m, 16H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 141.6, 125.6, 77.3, 64.6, 31.9, 30.3, 29.60, 29.58, 29.50, 29.4, 29.32, 29.31, 28.1, 26.7, 22.7, 14.1; HRMS (ESI) calc. for $C_{17}H_{31}O_3^+$ $[M + H]^+$, 283.2268; found 283.2261.

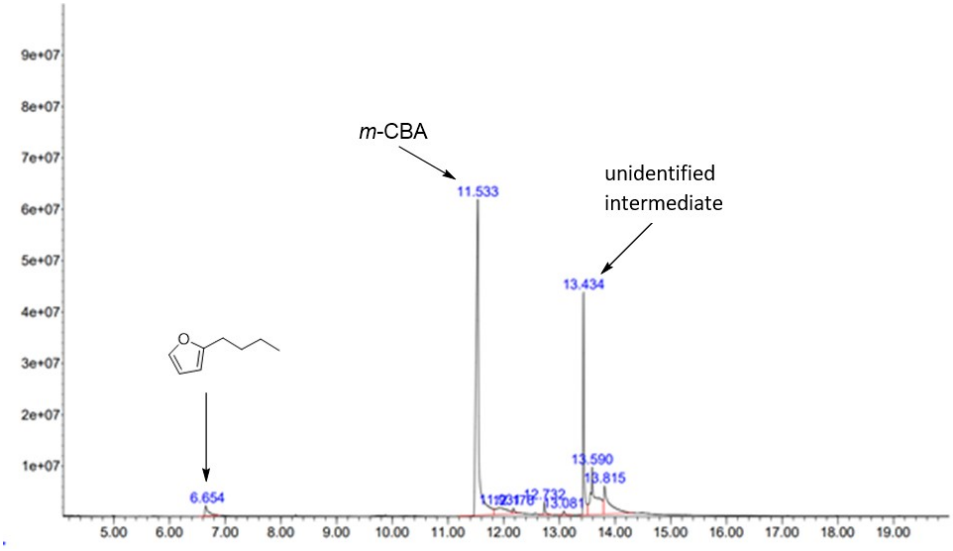
Identification of 2-butylfuran in crude mixtures from the Baeyer-Villiger reaction.

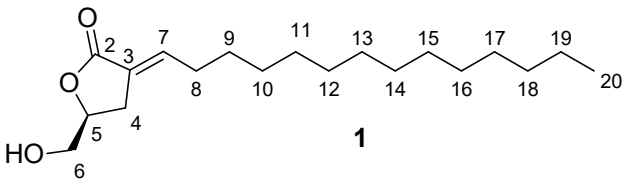
In the crude reaction mixture obtained from the oxidation of **15**, the presence of 2-butylfuran (**S5**) was observed, with the fragmentation pattern matched against the NIST 2020 database. A plausible mechanistic proposal for the formation of the furan is shown in Scheme S1. If the

reaction results in oxygen insertion into the C3-C4 bond, the formation of **S1** would be expected, which could hydrolyse to **S2** due to the acidic conditions and presence of water from the oxidant. Ketone **S2** could further hydrolyse to **S3**, then cyclise to **S4**, which could then undergo sequential dehydration reactions resulting in the furan **S5**. Furans such as **S5** are oxidatively sensitive, and react with *m*-CPBA, which was present in the reaction mixture. The isolation or preparation of these furans was not an objective in the current work, although similar compounds are found in the genus *Persea*. Further reports of this process will be published in due course. The formation of lactone **19** via oxygen insertion into the C4-C5 bond giving **S6**, rearrangement to intermediate formate ester **S7**, and then hydrolysis is also shown.

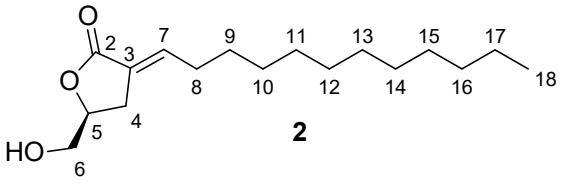


Scheme S1. Detection of furan **S5** by Baeyer-Villiger reaction on **15**.





1



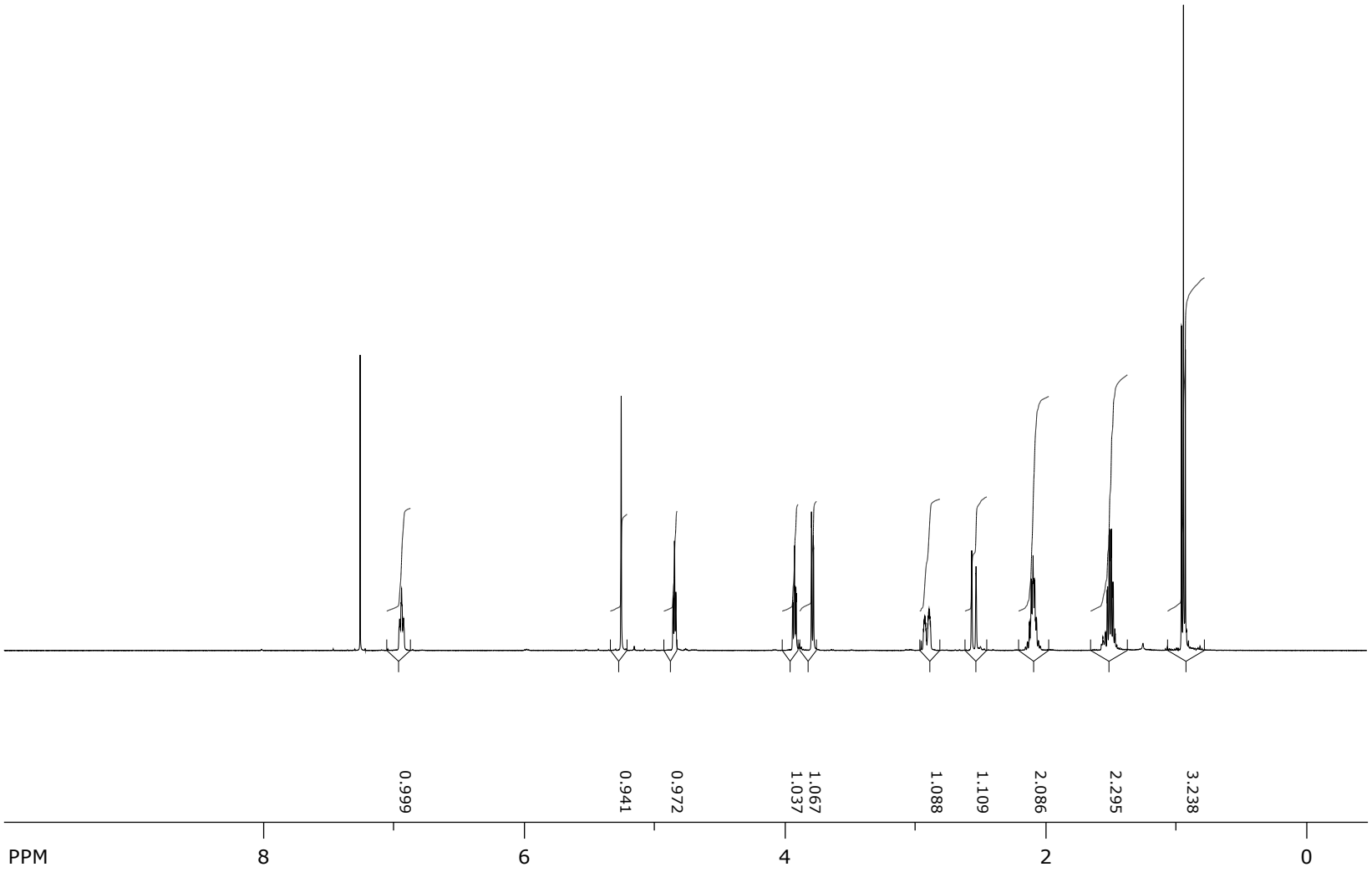
2

Table 1: Comparison of obtained NMR data of compounds **1** and **2** with NMR data found by Fraga et al.[1]

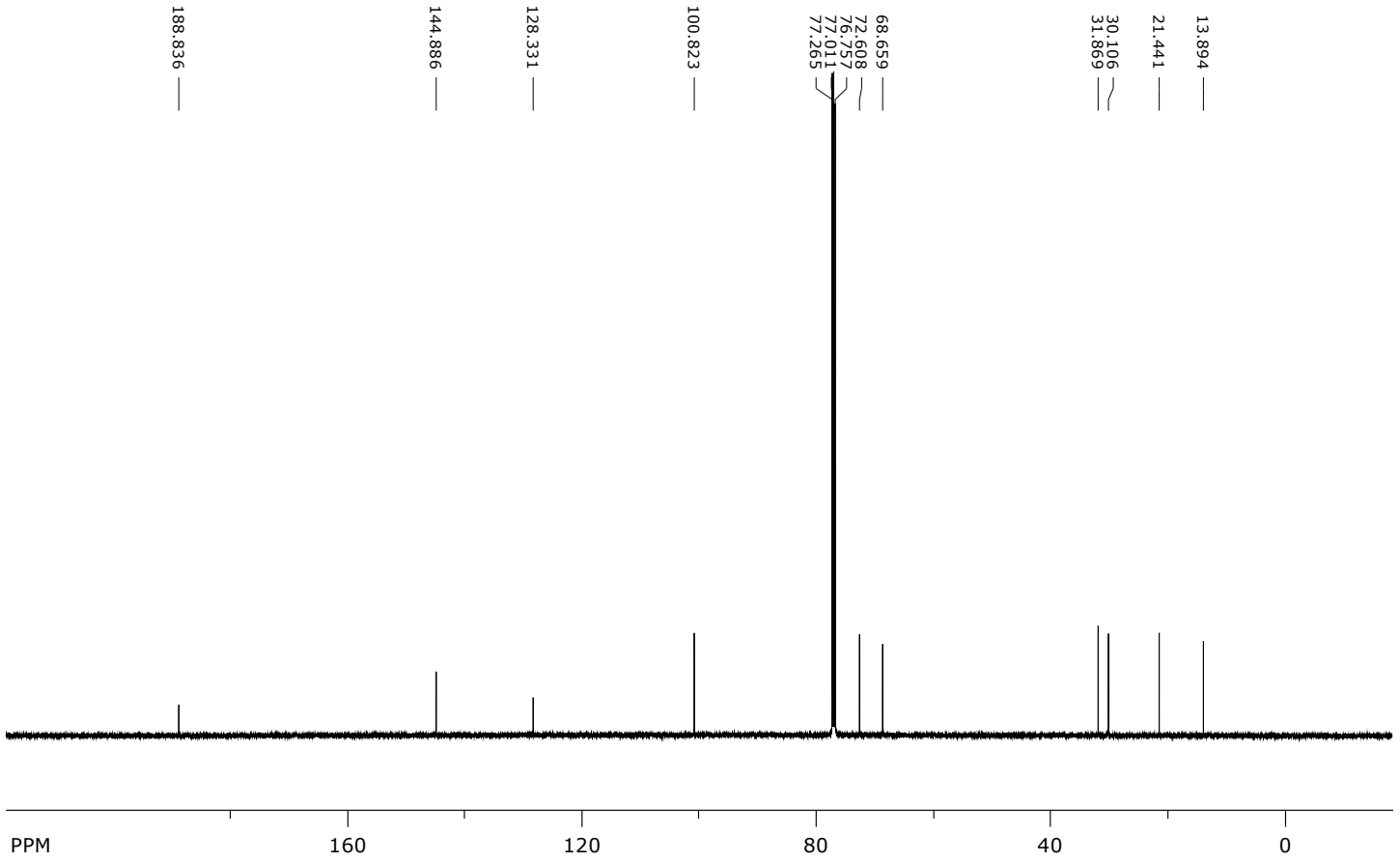
Position	(+)-Majoranolide[1]	1	(+)-Majoranolide B[1]	2
2	170.6	170.7	170.6	170.8
3	125.6	125.7	125.6	125.6
4	26.8	26.8	26.8	26.7
5	77.2	77.2	77.2	77.3
6	64.6	64.6	64.6	64.6
7	141.5	141.6	141.5	141.6
8	30.2	30.3	30.2	30.3
16	29.6	29.6	31.9	31.9
17	29.6	29.6	22.6	22.7
17	31.9	31.9	14.0	14.1
19	22.6	22.7	---	---
20	14.0	14.1	---	---

1. B. M. Fraga, C. E. Diaz, P. Bolanos, M. Bailen, M. F. Andres and A. Gonzalez-Coloma, *Phytochemistry*, 2020, **176**, 112398.

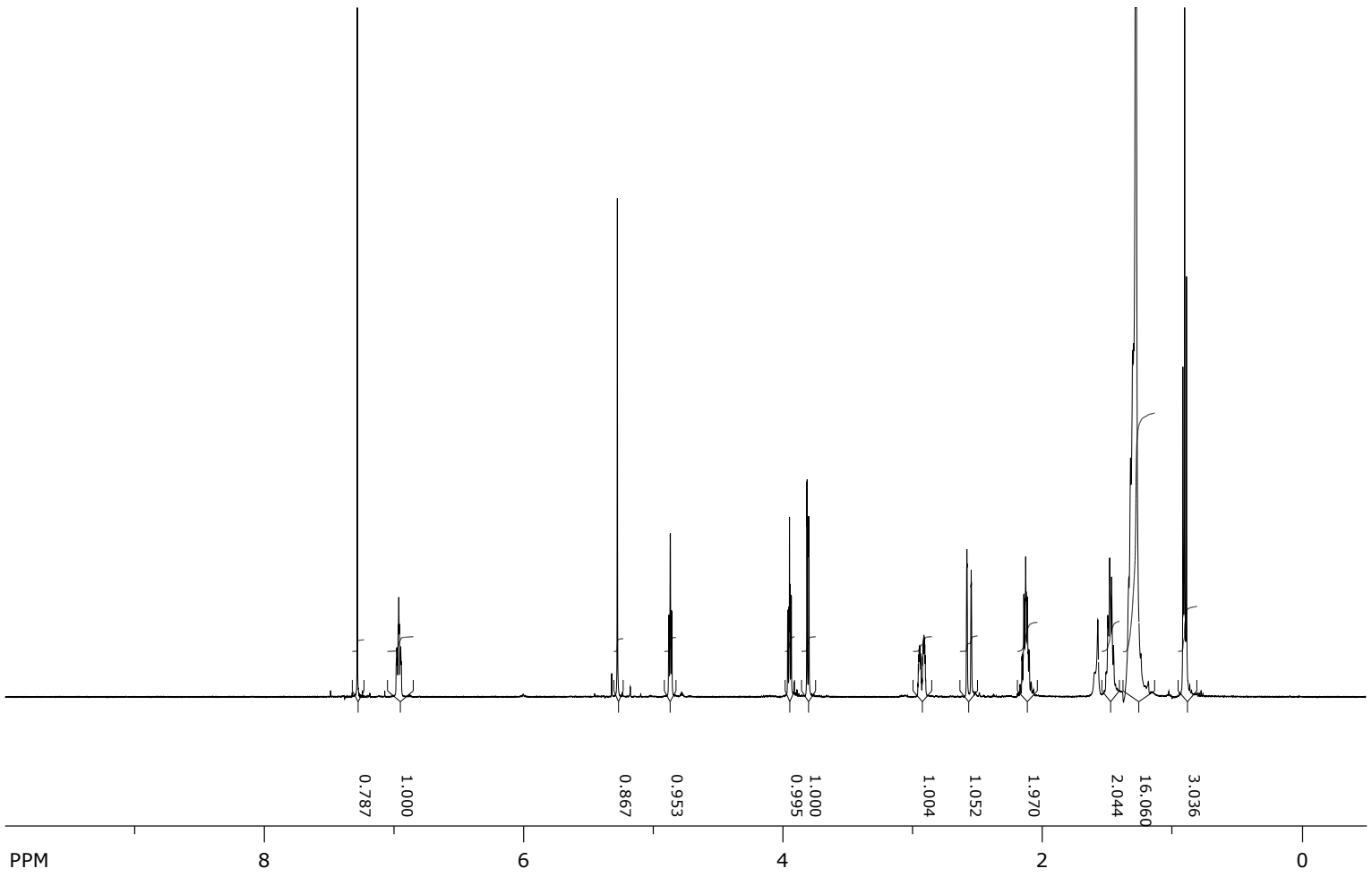
^{1}H NMR spectrum of (1*S*,5*R*,*E*)-3-butylidene-6,8-dioxabicyclo[3.2.1]octan-4-one (**15**, 500 MHz, $CDCl_3$)



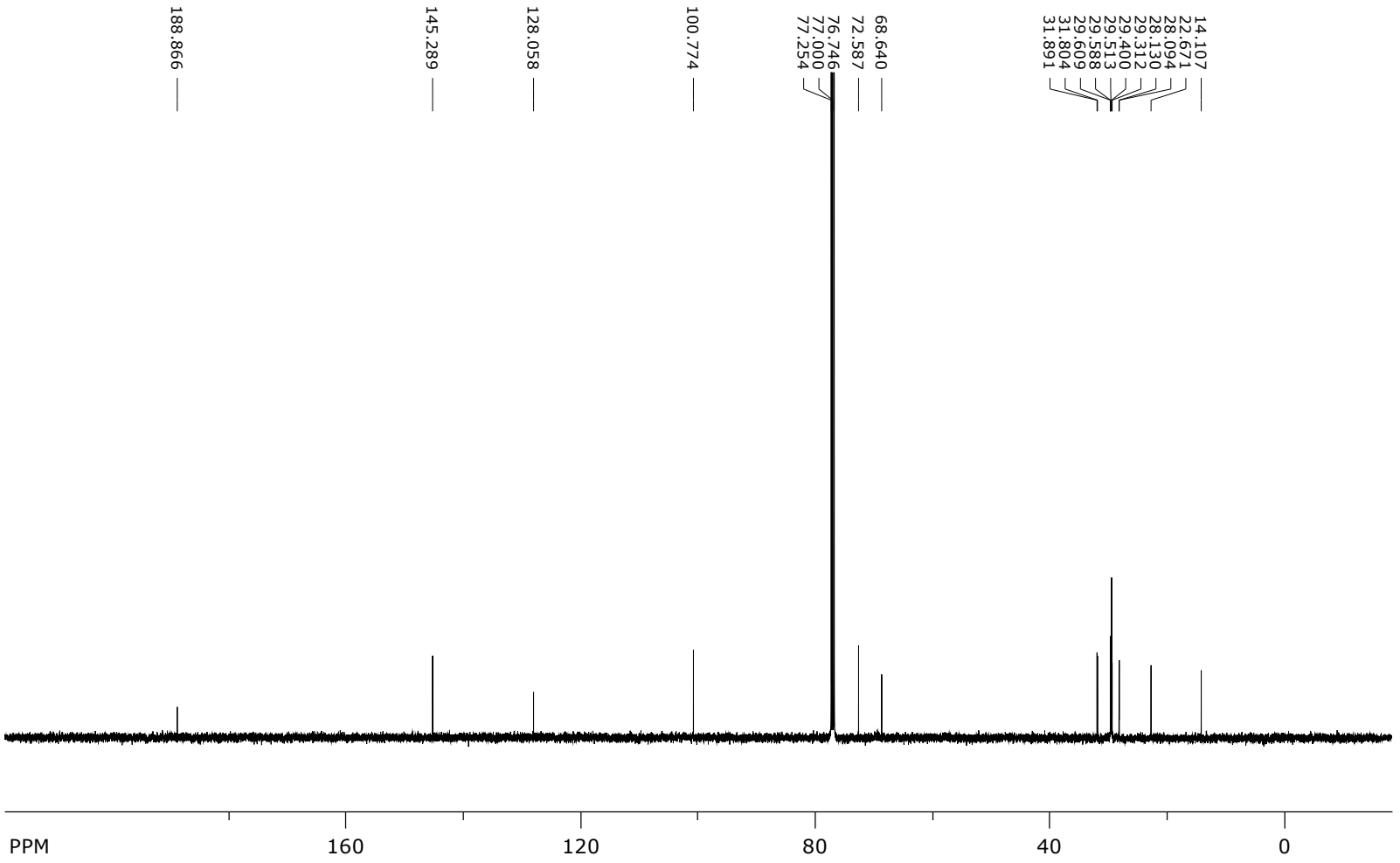
$^{13}C\{^{1}H\}$ NMR spectrum of (1*S*,5*R*,*E*)-3-butylidene-6,8-dioxabicyclo[3.2.1]octan-4-one (**15**, 125 MHz, $CDCl_3$)



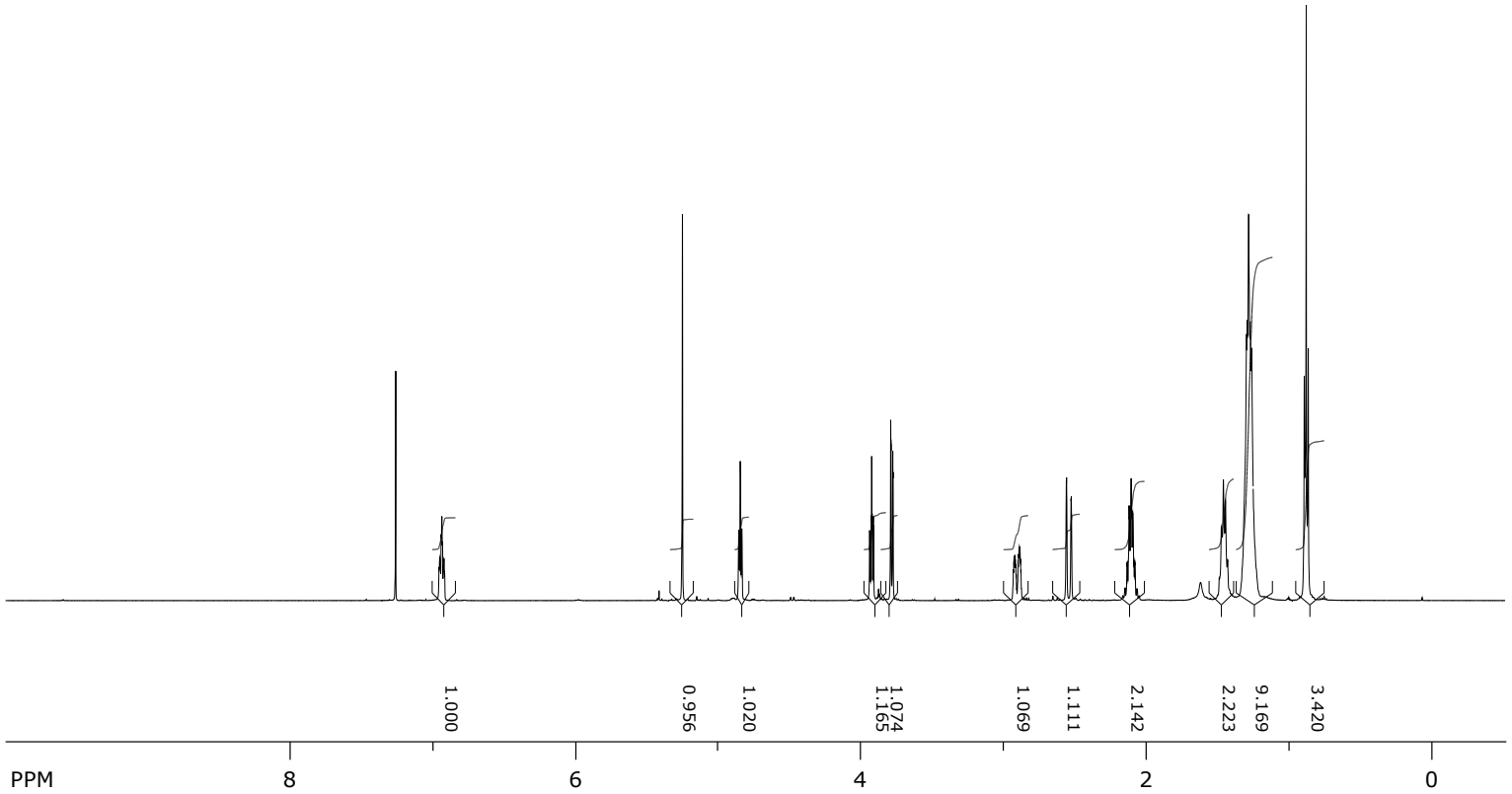
^{1}H NMR spectrum of (1*S*,5*R*,*E*)-3-dodecylidene-6,8-dioxabicyclo[3.2.1]octan-4-one (**16**, 500 MHz, $CDCl_3$)



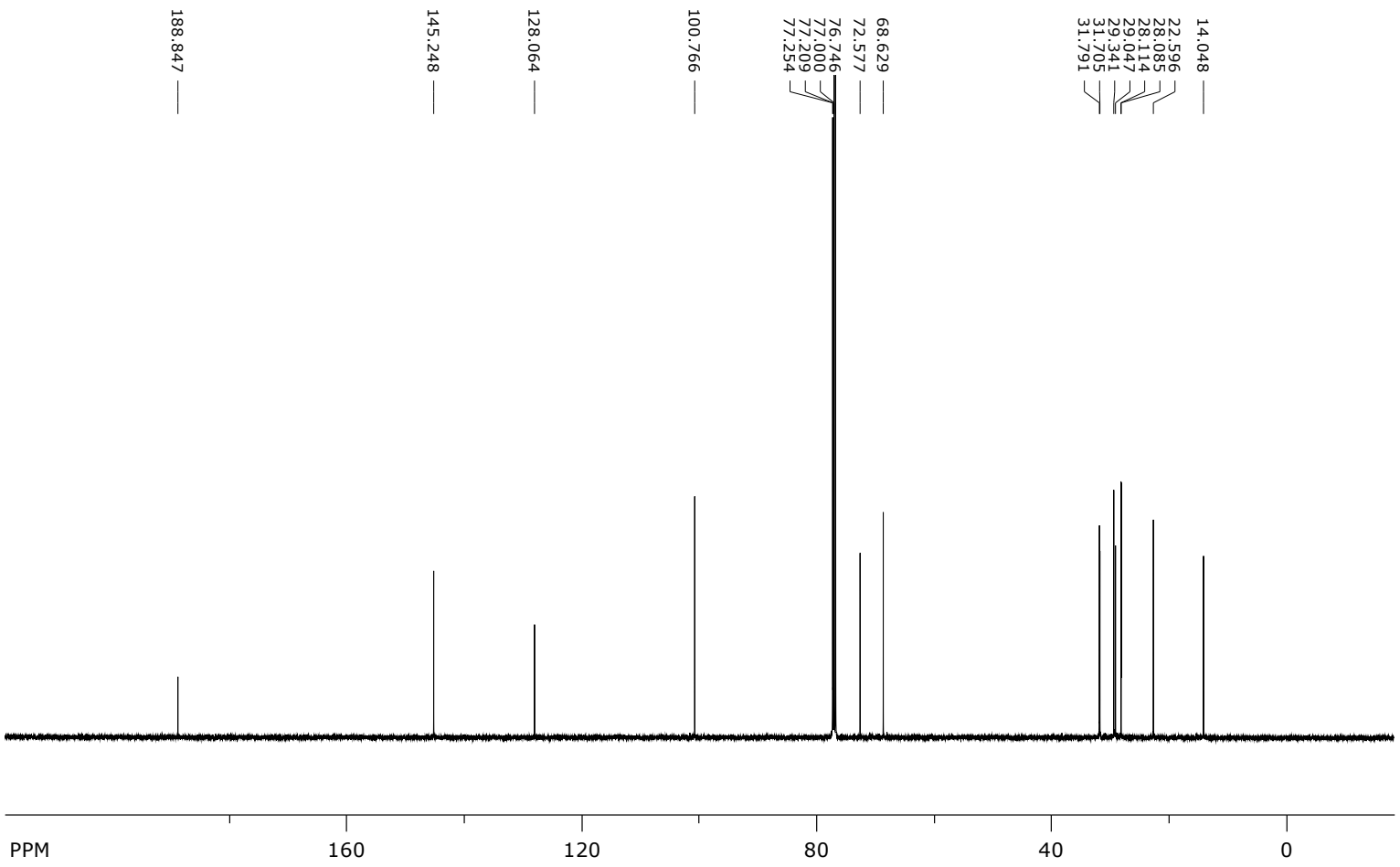
$^{13}C\{^{1}H\}$ NMR spectrum of (1*S*,5*R*,*E*)-3-dodecylidene-6,8-dioxabicyclo[3.2.1]octan-4-one (**16**, 125 MHz, $CDCl_3$)



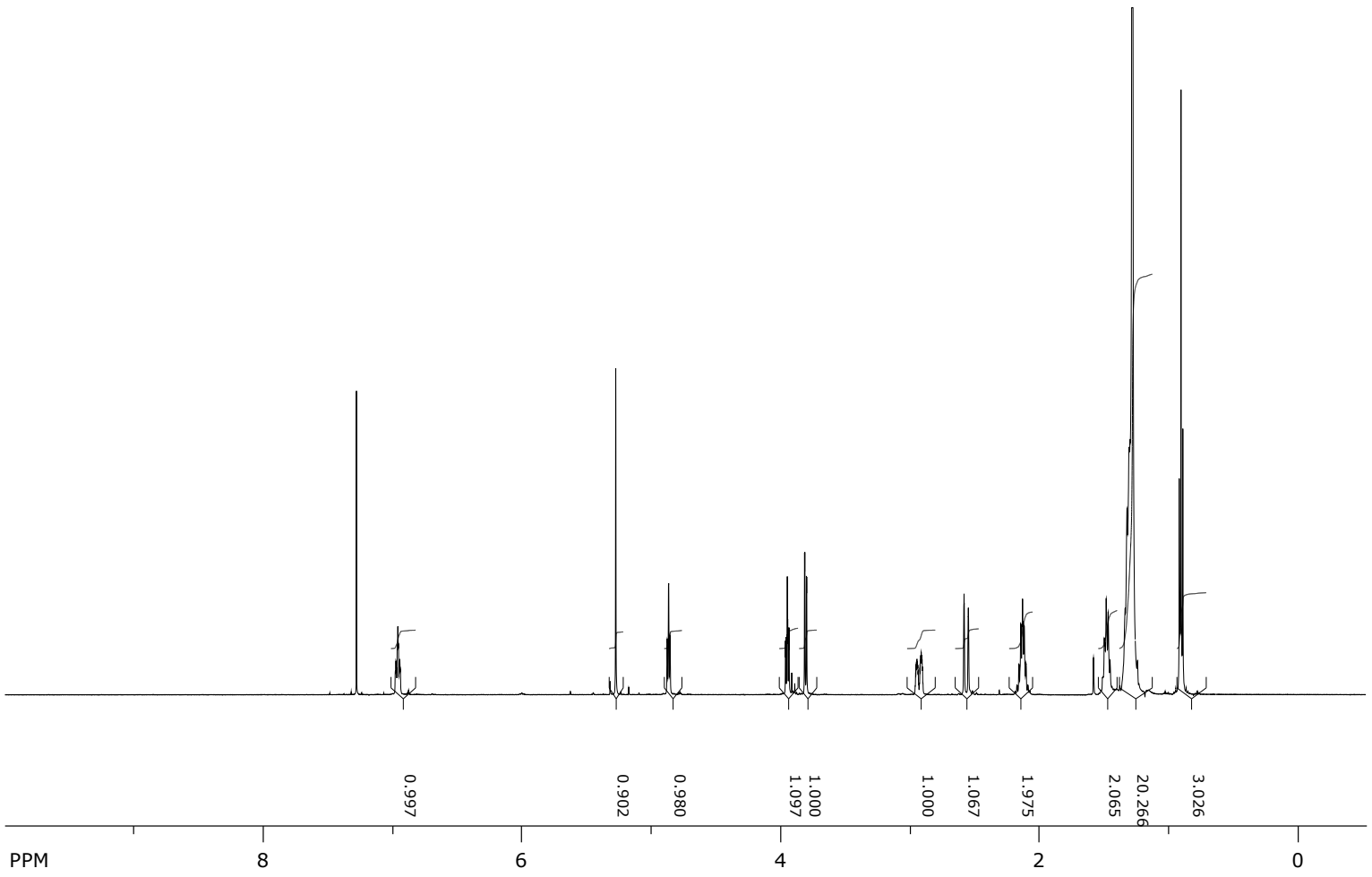
^{1}H NMR spectrum of (1*S*,5*R*,*E*)-3-octylylidene-6,8-dioxabicyclo[3.2.1]octan-4-one (**17**, 500 MHz, $CDCl_3$)



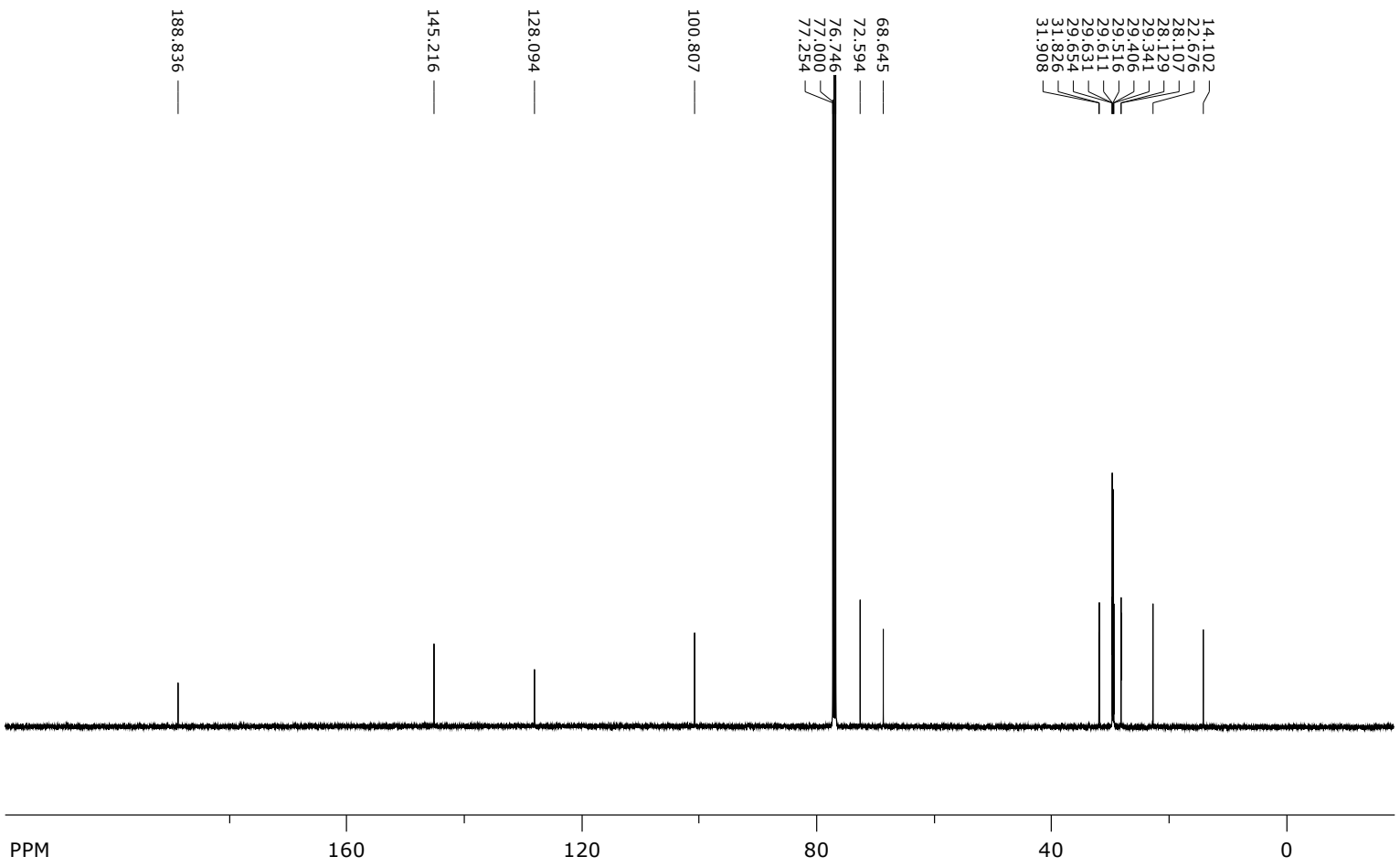
$^{13}C\{^{1}H\}$ NMR spectrum of (1*S*,5*R*,*E*)-3-octylylidene-6,8-dioxabicyclo[3.2.1]octan-4-one (**17**, 125 MHz, $CDCl_3$)



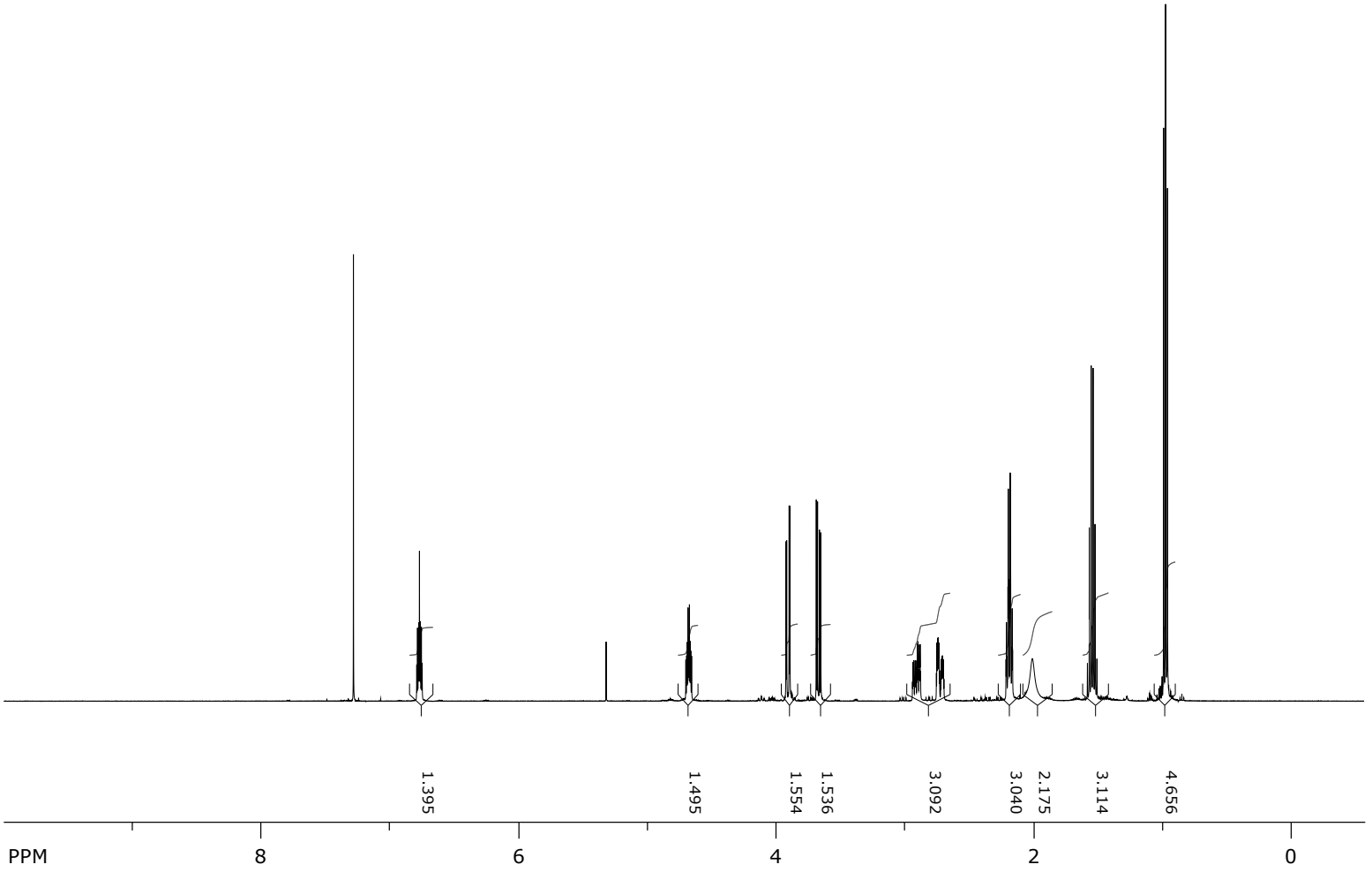
^{1}H NMR spectrum of (1*S*,5*R*,*E*)-3-tetradecylidene-6,8-dioxabicyclo[3.2.1]octan-4-one (**18**, 500 MHz, $CDCl_3$)



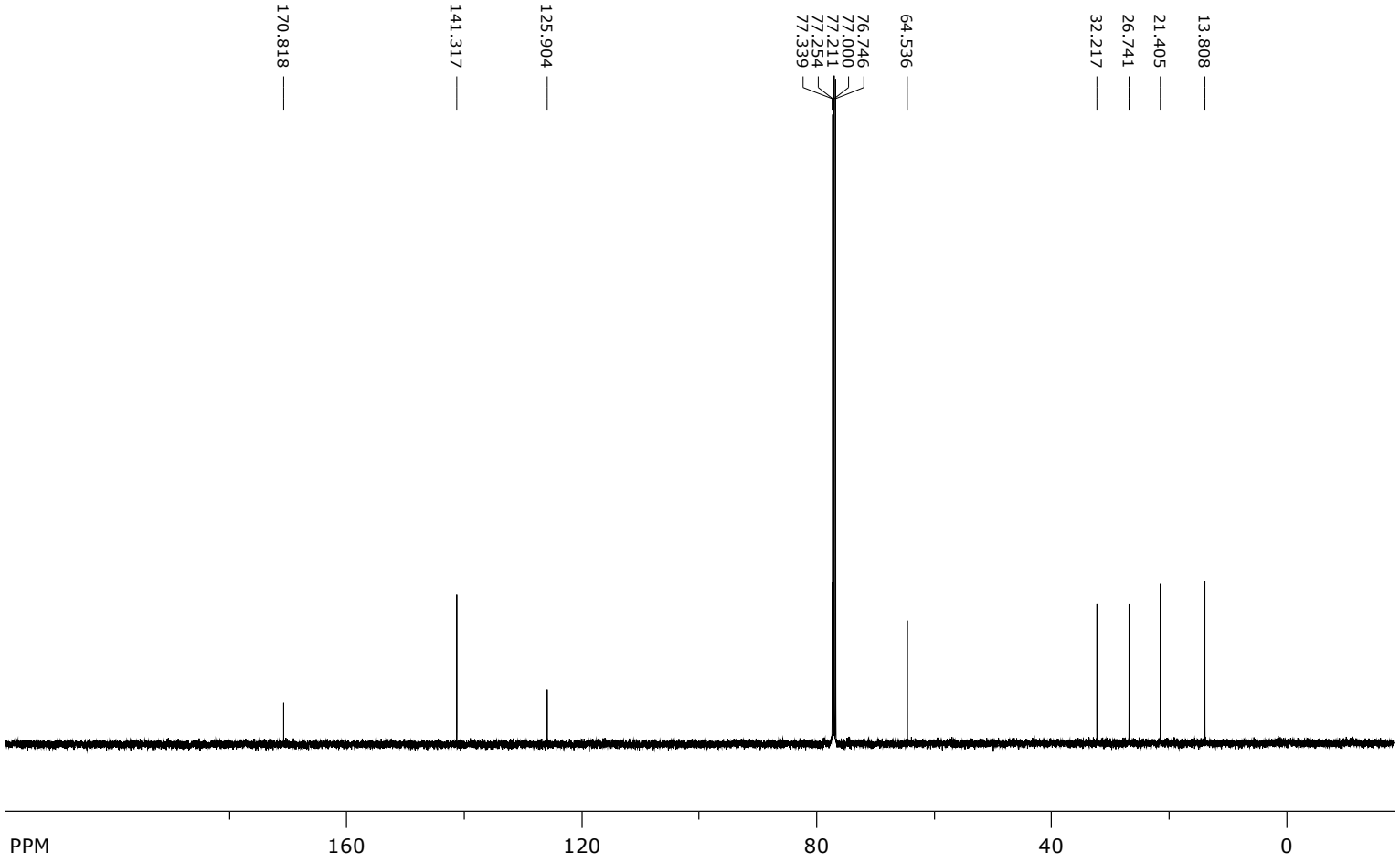
$^{13}C\{^{1}H\}$ NMR spectrum of (1*S*,5*R*,*E*)-3-tetradecylidene-6,8-dioxabicyclo[3.2.1]octan-4-one (**18**, 125 MHz, $CDCl_3$)



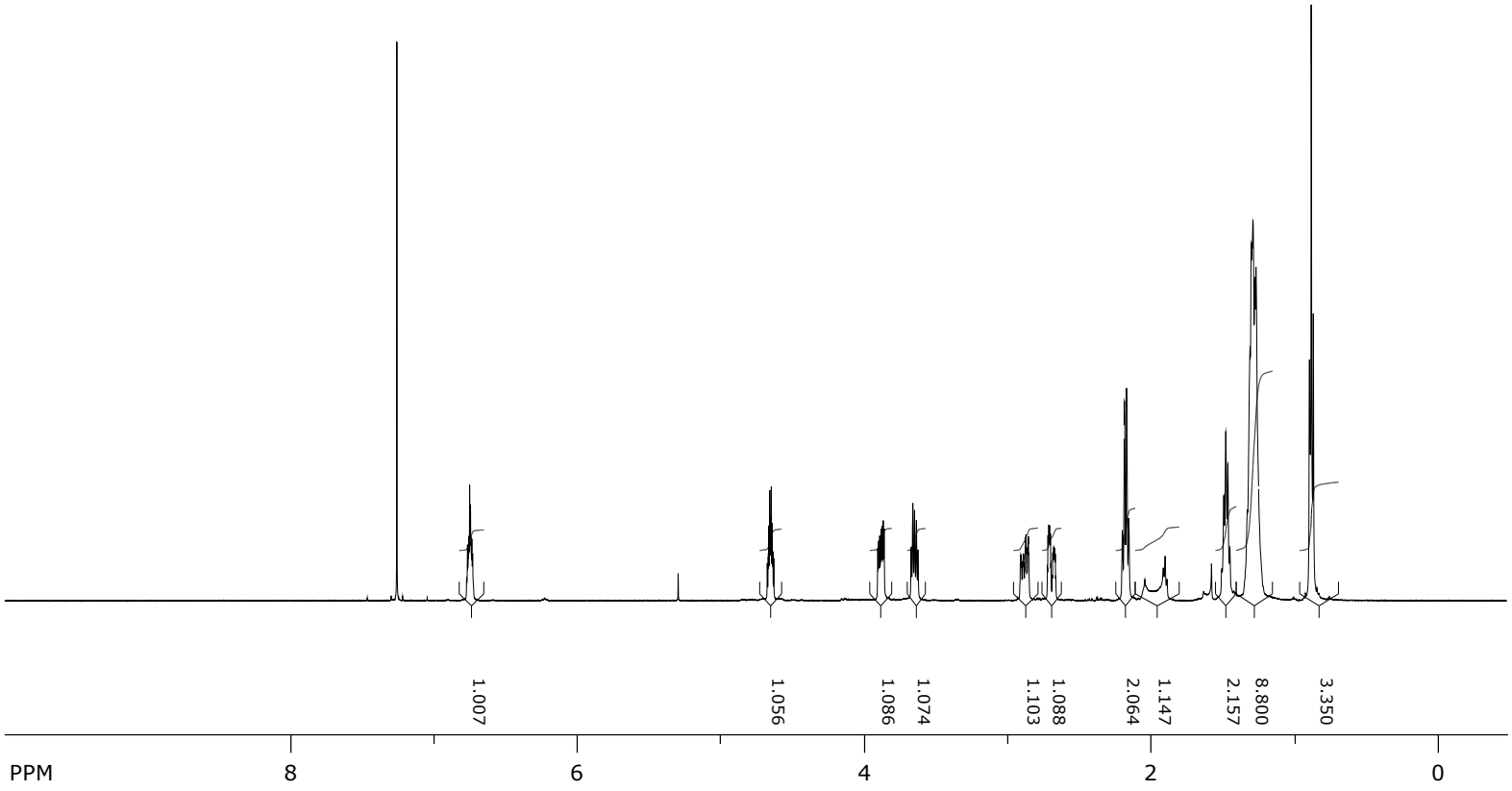
^{1}H NMR spectrum of (*S*,*E*)-3-butylidene-5-(hydroxymethyl)dihydrofuran-2(3H)-one (**19**, 500 MHz, $CDCl_3$)



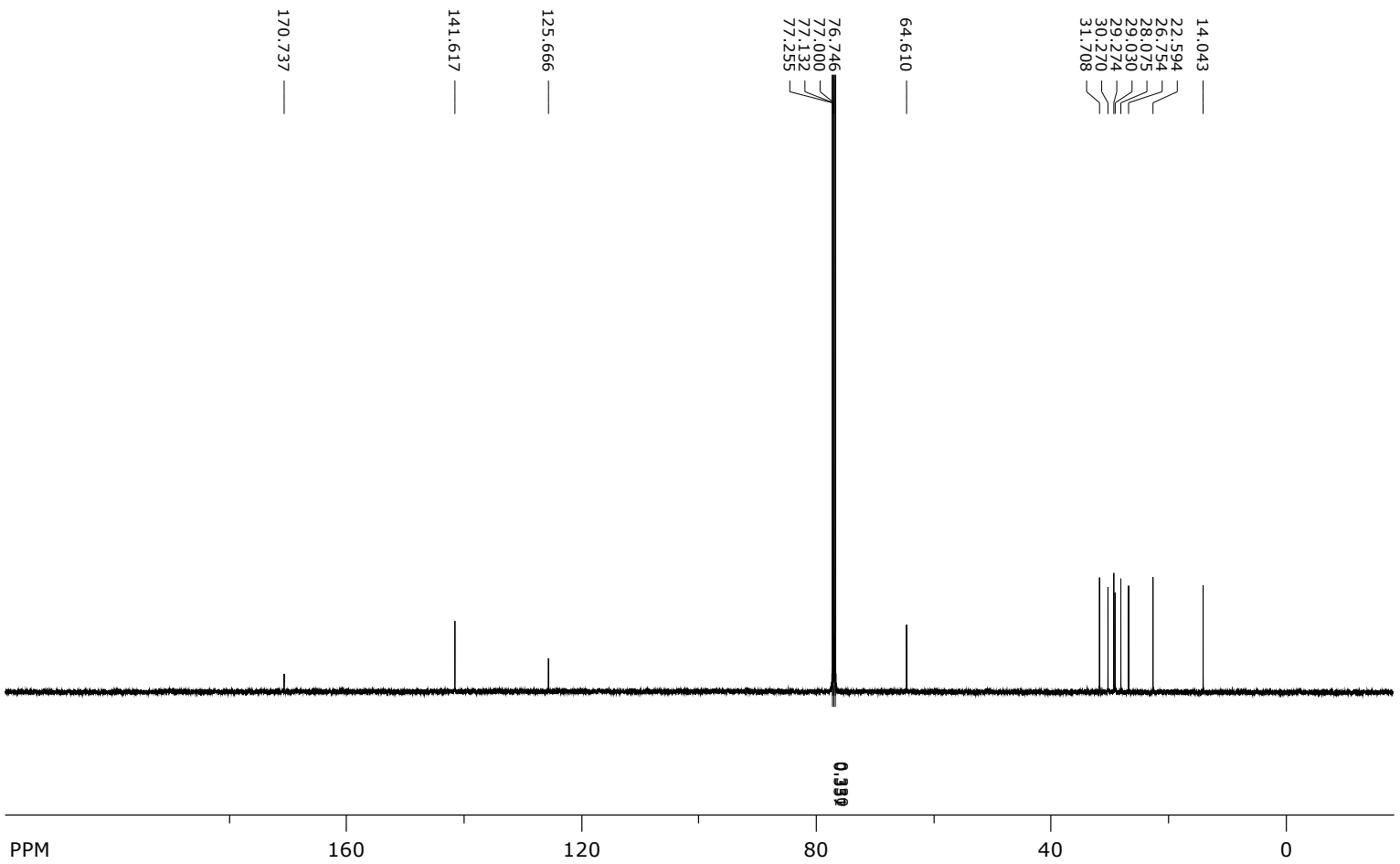
$^{13}C\{^{1}H\}$ NMR spectrum of (*S*,*E*)-3-butylidene-5-(hydroxymethyl)dihydrofuran-2(3H)-one (**19**, 125 MHz, $CDCl_3$).



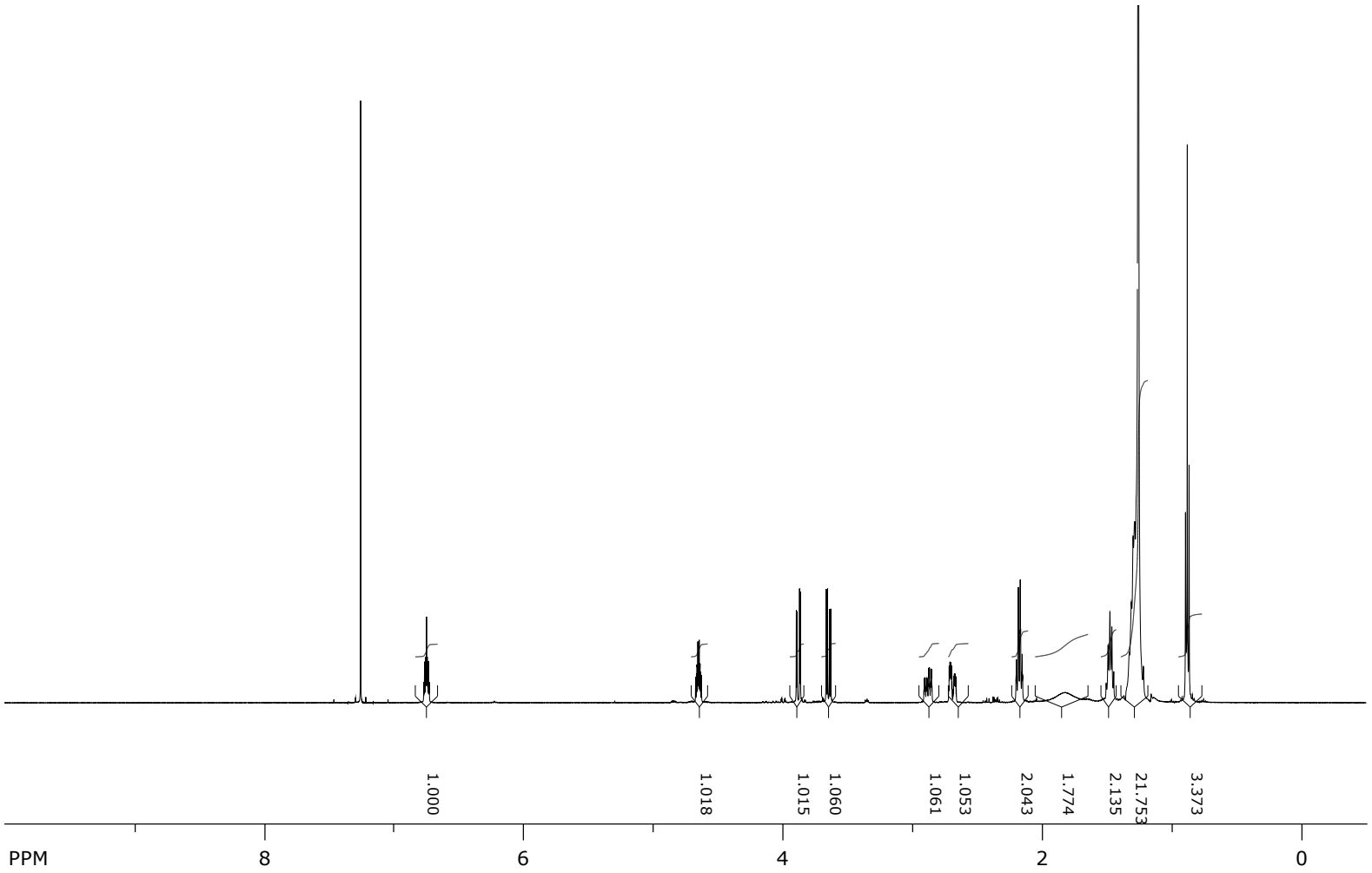
^{1}H NMR spectrum of (*S*,*E*)- 3-octylidene-5-(hydroxymethyl)dihydrofuran-2(3H)-one (**20**, 500 MHz, $CDCl_3$)



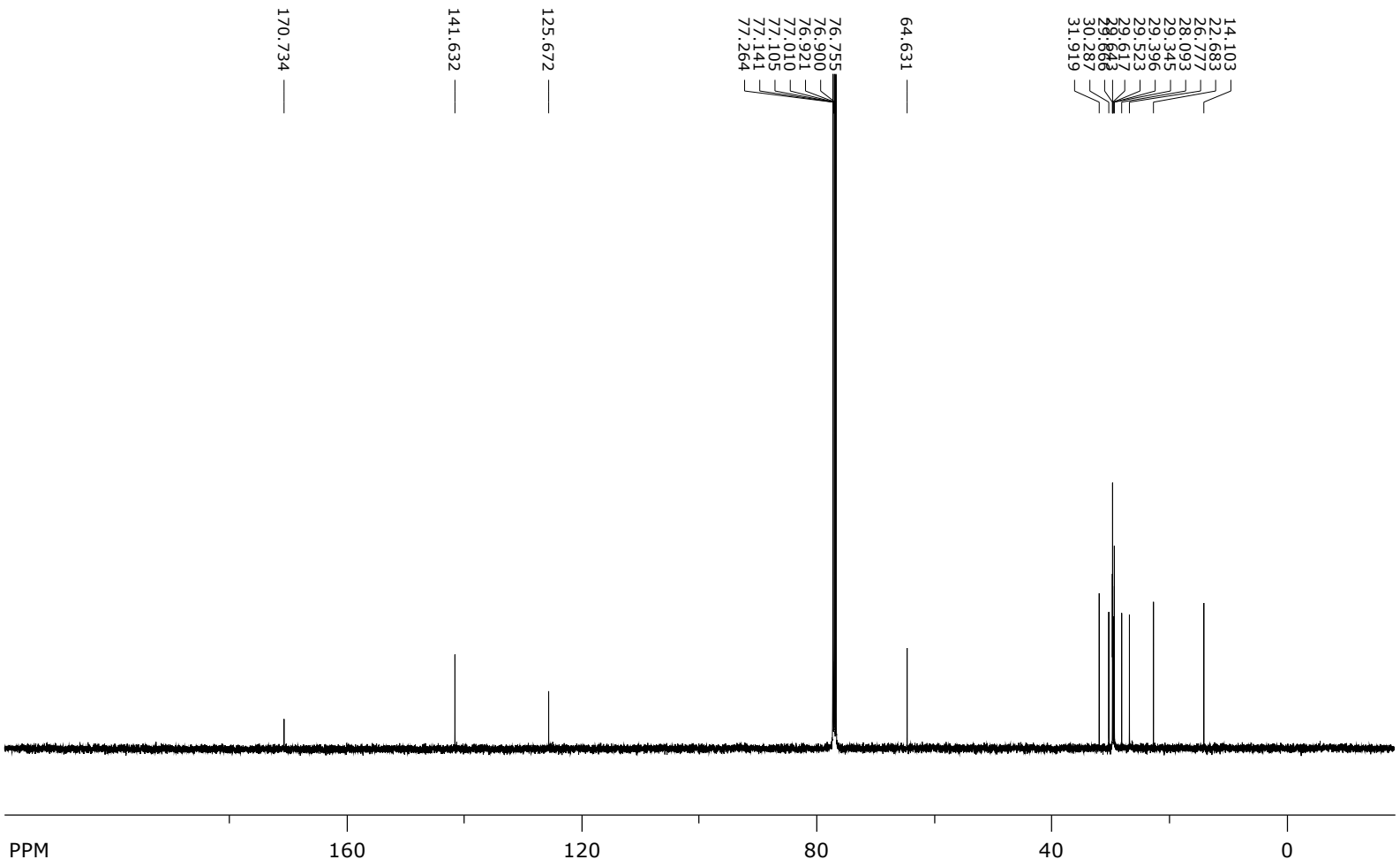
$^{13}C\{^{1}H\}$ NMR spectrum of (*S*,*E*)- 3-octylidene-5-(hydroxymethyl)dihydrofuran-2(3H)-one (**20**, 125 MHz, $CDCl_3$)



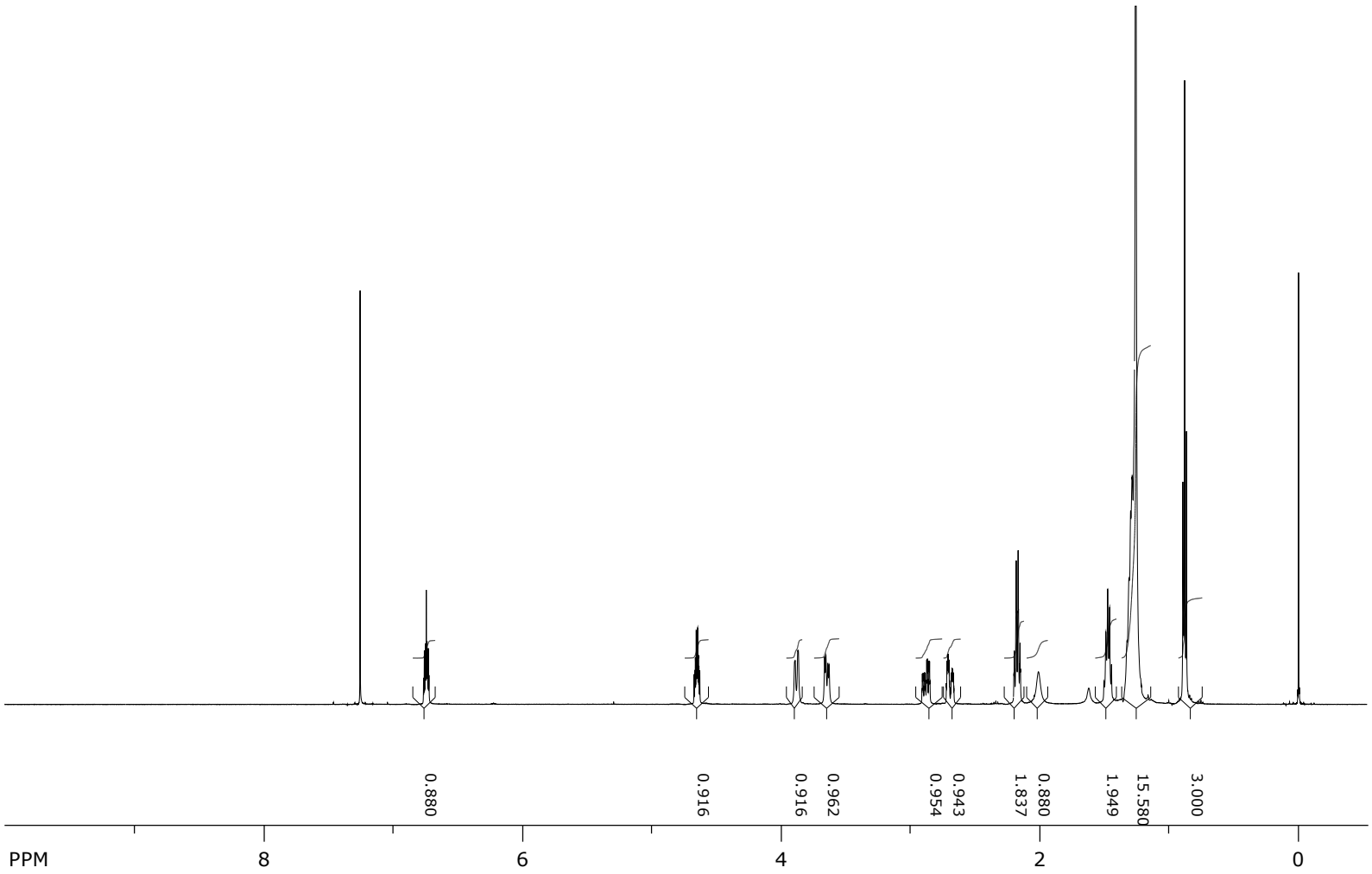
^{1}H NMR spectrum of majoranolide (**1**, 500 MHz, $CDCl_3$)



$^{13}C\{^{1}H\}$ NMR spectrum of majoranolide (**1**, 125 MHz, $CDCl_3$)



^{1}H NMR spectrum of majoranolide B (**2**, 500 MHz, $CDCl_3$)



$^{13}C\{^{1}H\}$ NMR spectrum of majoranolide B (**2**, 125 MHz, $CDCl_3$)